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FULL-LENGTH ORIGINAL RESEARCH

Single-neuron correlate of epilepsy-related cognitive deficits in visual recognition memory in right mesial temporal lobe

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Abstract

Objective: Impaired memory is a common comorbidity of refractory temporal lobe epilepsy (TLE) and often perceived by patients as more problematic than the seizures themselves. The objective of this study is to understand what the relationship of these behavioral impairments is to the underlying pathophysiology, as there are currently no treatments for these deficits, and it remains unknown what circuits are affected.

Methods: We recorded single neurons in the medial temporal lobes (MTLs) of 62 patients (37 with refractory TLE) who performed a visual recognition memory task to characterize the relationship between behavior, tuning, and anatomical location of memory selective and visually selective neurons.

Results: Subjects with a seizure onset zone (SOZ) in the right but not left MTL demonstrated impaired ability to recollect as indicated by the degree of asymmetry of the receiver operating characteristic curve. Of the 1973 recorded neurons, 159 were memory selective (MS) and 366 were visually selective (VS) category cells. The responses of MS neurons located within right but not left MTL SOZs were impaired during high-confidence retrieval trials, mirroring the behavioral deficit seen both in our task and in standardized neuropsychological tests. In contrast, responses of VS neurons were unimpaired in both left and right MTL SOZs. Our findings show that

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neuronal dysfunction within SOZs in the MTL was specific to a functional cell type and behavior, whereas other cell types respond normally even within the SOZ. We show behavioral metrics that detect right MTL SOZ-related deficits and identify a neuronal correlate of this impairment.

Significance: Together, these findings show that single-cell responses can be used to assess the causal effects of local circuit disruption by an SOZ in the MTL, and establish a neural correlate of cognitive impairment due to epilepsy that can be used as a biomarker to assess the efficacy of novel treatments.

KEYWORDS

cognitive deficits, memory, single neuron, temporal lobe epilepsy

1 | INTRODUCTION

Millions of people worldwide suffer from temporal lobe epilepsy (TLE),[1] and cognitive deficits are a significant comorbidity in these patients.[2] These deficits, especially those that affect memory and executive function, are perceived by many patients as more burdensome than the seizures themselves.[3,4] A better understanding of the underlying neural mechanisms is needed so that treatments for these deficits can eventually be developed.

Cognitive dysfunction is present during interictal periods[5] and may persist even after successful treatment of seizures by medication.[6,7] This suggests that cognitive dysfunction may be related not only to ongoing seizure-related activity, but also to permanent damage to brain circuits. Cognitive deficits in mesial temporal lobe (MTL) epilepsy are often specific to certain kinds of memory—in particular, declarative memories such as recognition memory[8]—whereas semantic memory is comparatively less affected.[2] Cognitive deficits can be present in the absence of structural abnormalities as judged by magnetic resonance imaging (MRI) or postoperative pathology,[9] and responses measured within the epileptic zone can be the same as those measured in nonepileptic MTL to cognitive tasks as assessed using intracranial electroencephalography.[10] The specificity of the behavioral deficits and normal electrophysiological response at the aggregate level of field potentials indicate that the underlying dysfunction might be restricted to a small subset of cells or circuits. If so, this would indicate the possibility that novel pharmacological or electrical treatments that target functionally specific types of neurons could rescue certain cognitive functions.

The type of cognitive deficit a given patient suffers from depends on the location of the seizure onset zone (SOZ) in the brain.[11] However, whether this is due to neural dysfunction within the SOZ, hijacking of normal brain circuitry within the local affected area, and/or perturbed remote processes through network effects remains unknown.[3,12] To establish a link between behavioral performance and specific neural mechanisms, we performed intracranial recordings from single neurons in the hippocampus and amygdala of human patients with TLE. We quantified responses of visually selective (VS), animal responsive (AR), and memory selective (MS) cells. The rationale for focusing on these cells is their prominence in studies of human cognition,[13,14] making it important to establish whether their response is affected by epilepsy. VS/AR cells are tuned to the identity of visual stimuli and include concept cells,[15] category cells,[16,17] face cells,[18] and animal cells.[17] MS cells contribute to declarative memory by signaling whether a stimulus has been seen before,[16,19] and if so, the strength of the memory.[20]

Key Points

- Patients with temporal lobe epilepsy often suffer from cognitive deficits whose neural mechanisms are poorly understood
- We recorded from single neurons in the human medial temporal lobe from patients with intractable epilepsy
- Cells signaling memory strength had lower selectivity if located within a right-hemisphere MTL SOZ
- Patients with a right MTL SOZ performed worse on our visual recognition task as assessed by shape of the behavioral ROC curve but not accuracy

2 | MATERIALS AND METHODS

2.1 | Subjects and electrophysiology

Subjects (27 female, 35 male, age = 37 ± 15 years) who underwent depth electrode implantation in the MTL to localize their seizures (Table S1) provided informed consent to

participate in this institutional review board-approved study. Methods for electrophysiological recording procedures,[21,22] spike sorting,[23] and electrode localization[21] are as previously described. Briefly, we localized electrode locations by merging the postoperative MRI/computed tomographic scans onto the preoperative MRI scan of each patient, which in turn is registered to the MNI152 atlas brain.[21] Here, we only consider recordings located in either the amygdala or anterior hippocampus, jointly referred to as the MTL (Figure 1A). The mean waveform (shape of the extracellular spike) of each neuron is the average of all waveforms of all spikes of that unit. The trough-to-peak time was based on the mean waveform and is defined as the time from the first negative peak to the first positive peak after the trough. For plotting, waveforms were normalized so that their peak waveform was equal to −1.

2.2 | Task

Briefly (see Faraut et al.[21] for details), subjects first viewed 100 novel images (Figure 1B, top). After a break, subjects then viewed another series of images (50 of which were identical to those seen before, 50 were new) and indicated for each whether they had seen it before (familiar) or not (novel) together with a three-level confidence rating (Figure 1B, bottom).[21] All images shown belonged to one of five visual categories (depending on the task variant; animal was always a category, with the others varying, see Table 2 in Faraut et al.[21]).

2.3 | Receiver operating characteristic curve shape analysis

We computed the behavioral receiver operating characteristic (ROC) curve of each session using the ROC MATLAB Toolbox.[24] We quantified the shape (the asymmetry relative to the antidiagonal) of the ROC curves by the slope of a straight line fitted to the z-transformed ROC (zROC slope). A slope of =1 or <1 indicates a symmetric or asymmetric ROC curve, respectively. The zROC slope is an assessment of whether subjects relied on recollection (slope < 1) or not (slope = 1).[25]

2.4 | Selection of neurons and statistics

The terms "neuron" and "cell" are used interchangeably. We used all 100 trials of the recognition block to identify VS, AR, and MS neurons. A cell qualified as an MS neuron if its firing rate in the 200–1700-ms window following stimulus onset differed significantly between correctly recognized familiar and novel trials regardless of visual category (two-tailed bootstrap test, $p < .05$).[16] A cell qualified as a VS neuron if its firing rate in the same window differed as a function of the visual category of the images shown (1 × 5 analysis of variance [ANOVA], $p < .05$).[16] Finally, a cell qualified as an AR neuron if its response to animal pictures in the same time window was significantly higher than the baseline firing rate[17] (t-test, $p < .05$). All post hoc comparisons were corrected for multiple comparisons using Tukey's honestly significant difference test, and the reported p-values are after correction.

2.5 | SOZ identification

The location of the SOZ was determined based on the clinical workup for each patient available at the time of completion of invasive intracranial monitoring (Table S1). For each neuron recorded (all of which were in the MTL), we determined whether it was located within an MTL SOZ depending on whether a particular patient had an SOZ in that hemisphere of the MTL. For example, if a neuron was recorded from the right MTL, and the subject had a right MTL SOZ, the neuron was categorized to be "within the SOZ." If a neuron was recorded from the left MTL of the same subject, that neuron was "outside the SOZ." All neurons recorded in subjects with bilateral MTL SOZs were considered to be inside the SOZ, and all MTL neurons recorded in subjects with extratemporal SOZs were considered to be outside of an MTL SOZ. No neurons located within extratemporal SOZs were analyzed.

2.6 | Selectivity analysis

To quantify the selectivity of a neuron, we calculated the effect size metric ω^2 for each cell as previously defined.[16] We used the firing rate in the 200–1700 ms poststimulus windows as the response.

2.7 | MS neurons and confidence

We pooled the three levels of confidence into two groups: a high confidence (++, responses of 1 or 6) and a low confidence (+, responses of 2–4) group. We did not analyze medium confidence trials separately. There were two types of MS cells: those firing most to familiar stimuli (old > new) and those firing most to novel stimuli (new > old; Figure 2A–D shows examples). We refer to the type of trial (old or new) to which a cell responds the most and least as the preferred and nonpreferred category, respectively. Prior work shows that confidence modulates the response of MS cells primarily in the preferred trials.[16] For analysis of the mean response across all cells (Figure 3C), we calculated the mean response across all MS cells for four groups of trials: high and low confidence preferred trials, and high and low confidence

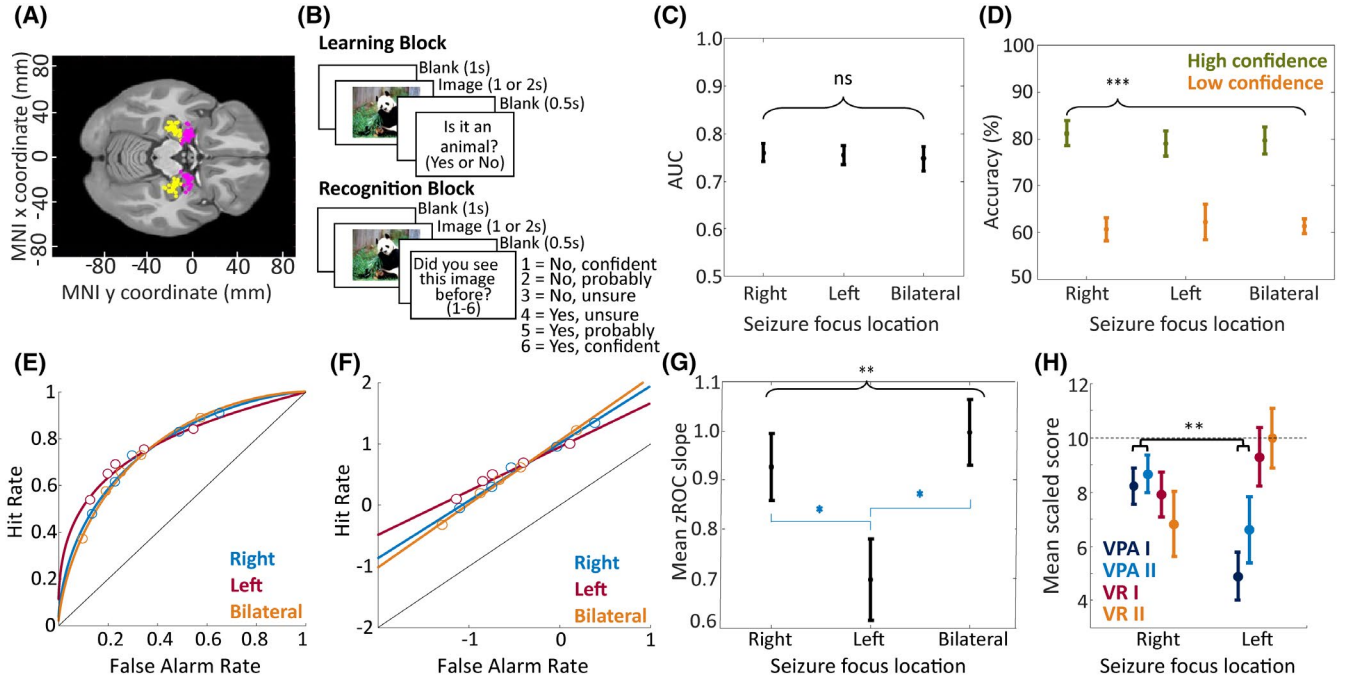

FIGURE 1 Electrode locations, memory recognition task, and behavior. (A) Electrode placement in Montreal Neurological Institute (MNI152) space. Axial ($z = -16$) plane shows the electrode locations from which we recorded at least one neuron in the amygdala (pink) and the hippocampus (yellow). Each dot is one microelectrode bundle. (B) The memory recognition task consisted of a learning and a recognition block. During learning, 100 unique novel images were shown, each followed by a control question. Following a delay period, a subset of 50 of the images shown during learning were shown intermixed with another set of 50 novel and unique images (100 trials). After each image, subjects were asked to indicate whether they had seen the image and with what confidence on a scale of 1–6. All images shown belonged to one of five visual categories (e.g., vehicles, food, people, houses/buildings, animals, with 20 instances chosen from each category). (C) Accuracy as quantified by area under the curve (AUC) of the behavioral receiver operating characteristic (ROC) curves shown in panel E did not differ significantly between the groups (one-way analysis of variance [ANOVA], $p = .93$). (D) Accuracy (percentage correct) as a function of confidence and SOZ group. Accuracy differed as a function of confidence but did not differ significantly between the two groups (2×3 ANOVA, high/low vs. SOZ laterality; main effect high vs. low confidence $p < 10^{-10}$, no significant main effect of SOZ group [$p = .99$] and no significant interaction [$p = .79$]). (E) Average behavioral ROC curves of subjects with right, left, and bilateral mesial temporal lobe SOZs. Gray line indicates chance. (F) *Z*-transformed ROC (zROC) version of the ROC curves shown in C for the three subject groups. Gray line indicates chance. (G) Average zROC slopes across all sessions of each group. Subjects with a left-sided SOZ had significantly lower zROC slopes compared to those with unilateral right or bilateral SOZs (one-way ANOVA; 1×3 ANOVA, $p = .0068$; post hoc pairwise comparisons [honestly significant difference], $p = .021$ and $p = .011$, respectively). (H) Mean scaled scores for Wechsler Memory Scale verbal paired associates (VPA) and visual reproduction (VR) tests, separately for patients with a right-sided versus left-sided SOZ. Patients with a left-sided SOZ had significantly lower VPA scores compared to those with a right-sided SOZ (2×2 ANOVA, test version immediate/delayed vs. SOZ laterality; main effect of SOZ side, $p = .007$). Patients with a right-sided SOZ had significantly lower VR scores compared to those with left-sided SOZs (2×2 ANOVA, test version vs. SOZ laterality; main effect of SOZ side, $p = .033$). A scaled score of 10 is the mean of the age-corrected control group (dashed line). Error bars are SEM. $^*p < .05$, $^{**}p \leq .01$, $^{***}p \leq .001$. ns, not significant

nonpreferred trials. We only included neurons with five or more trials for each group. We normalized the firing rate of each neuron by dividing by the average firing rate of the neuron throughout the whole task.

2.8 | Neuropsychology

Memory scores for 51 patients were available from preoperative neuropsychological assessment (Table S2). We analyzed immediate and delayed recall scores from the visual reproduction (VR) and verbal paired associates (VPA) subtests of the Wechsler Memory Scale (WMS). We included scores from all available WMS versions (R, III, and IV), using age-corrected scaled scores (mean = 10, SD = 3). Scaled score conversion was conducted using tables in the WMS-III and IV test manuals. For WMS-R, the manual was used to convert raw scores to age corrected *z*-scores, which were then transformed to scaled scores.

2.9 | Sclerosis ratings

Preoperative MRI scans were scored by epilepsy neurosurgeons (A.N.M. and T.A.V.) for the extent of sclerosis in the mesial temporal lobe[26,27] on a scale of 0–3 (0 = no evidence

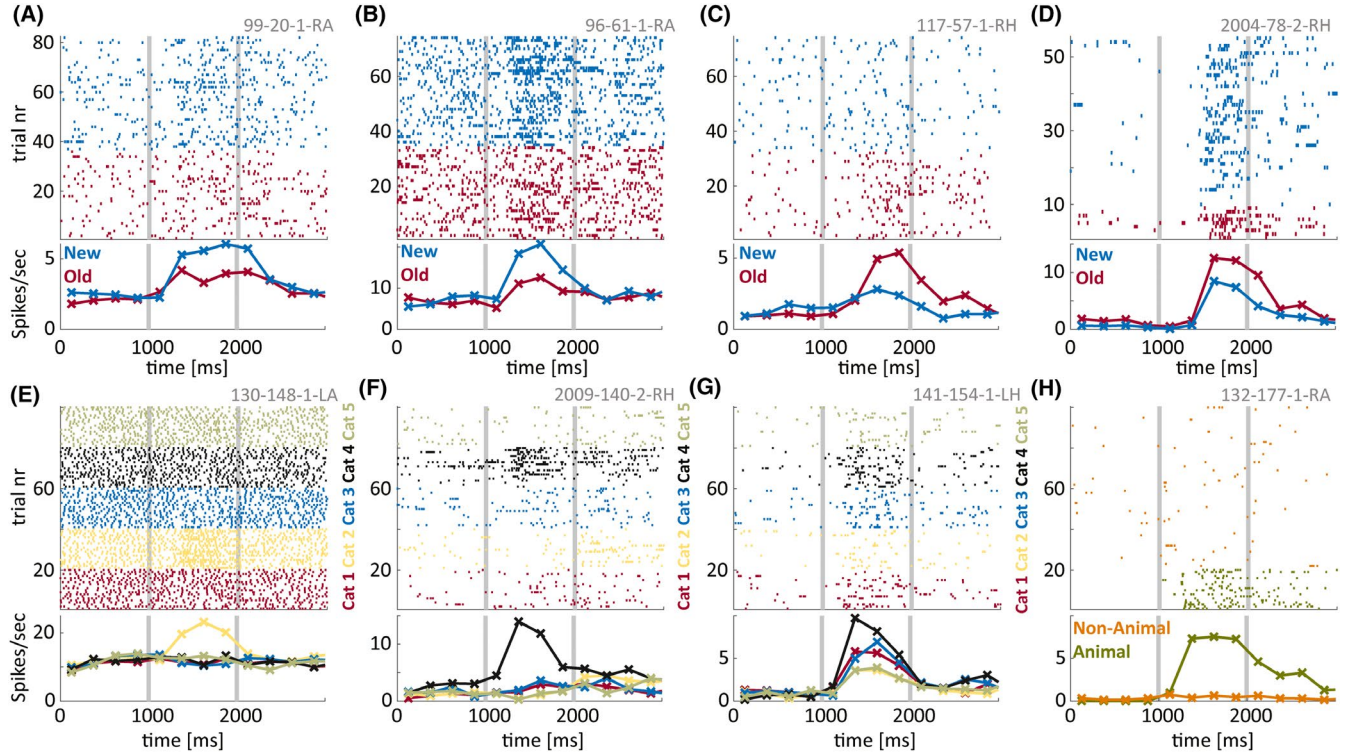

FIGURE 2 Single-neuron examples of the cell types analyzed. (A–D) Memory selective neurons. Shown are only correct trials. Shown are both examples of cells that fire more for new compared to old stimuli (A, B) as well as vice versa (C, D). (E–G) Visually selective cells, some with simple selectivity (E, F) and others with more complex tuning (G). (H) Animal responsive neuron. Notation: Stimulus onset is at $t = 1000$ ms. Color denotes stimulus category as indicated by colored text. Each neuron is labeled at the top right (in gray text) with the session ID, channel number, cell number, and brain region (R/L is right/left, A/H is amygdala/hippocampus)

of sclerosis, 1 = mild, 2 = moderate, 3 = severe sclerosis). We utilized imaging-based ratings rather than pathology so that we could include as many patients as possible, given that a significant fraction of patients did not undergo surgical resection.

3 | RESULTS

3.1 | Electrophysiology and behavior

We recorded from 1973 neurons in the amygdala and hippocampus across 92 sessions in 62 patients[16,21] while they performed a visual recognition memory task (Figure 1A,B). Thirty-seven patients had an MTL SOZ (left hemisphere, $n = 12$; right hemisphere, $n = 17$; bilateral, $n = 8$; see Table S1). Thirty-five patients who did not have an MTL SOZ only provide recordings from outside of the SOZ and were not considered in the behavioral analysis. Thirty-five percent of all recorded neurons were located inside an MTL SOZ. The proportion of cells within the SOZ was significantly higher in the hippocampus (38%, $n = 314/819$) than the amygdala (33%, $n = 378/1154$; χ^2 [1, $N = 1973$] = 6.56, $p = .01$).

We assessed whether the accuracy by which subjects discriminated between new and old stimuli differed as a function of SOZ location. A 2 × 3 repeated measures ANOVA (two levels of confidence in three patient groups [left, right, or bilateral MTL SOZ]) revealed that accuracy was significantly greater for high-confidence trials (F[1, 101] = 56.84, $p < .001$), but there was neither a significant difference between groups nor an interaction (Figure 1C,D; see Table 1 for statistics). To examine the extent to which subjects relied on episodic recollection,[28,29] we used the degree of asymmetry of the ROC curve (zROC slope) as a metric. Significant asymmetry, which is indicative of episodic recollection, was only evident in the subjects with a left-hemisphere MTL SOZ (Figure 1E–G; zROC slope mean = .70 ± .08 [SE]; $n = 14$ sessions, t-test vs. 1 for left SOZ, t[13] = −3.64, $p = .003$, $d = .92$). zROC slopes differed significantly among the three groups (Table 1; Figure 1F,G), with significantly lower zROC values for the left MTL SOZ group compared to the groups with right-lateralized SOZ (95% confidence interval [CI] = −1.06 to −.074, $p = .021$) and bilateral SOZ (95% CI = .15–1.29, $p = .011$). This indicates that subjects with a left MTL SOZ retained their ability to engage episodic recollection, whereas the others did not. The area under the curve (AUC) of the ROC did not differ significantly among the three groups (Figure 1E; F[2, 51] = .07, $p = .99$). This analysis indicates that the laterality of the SOZ impacted

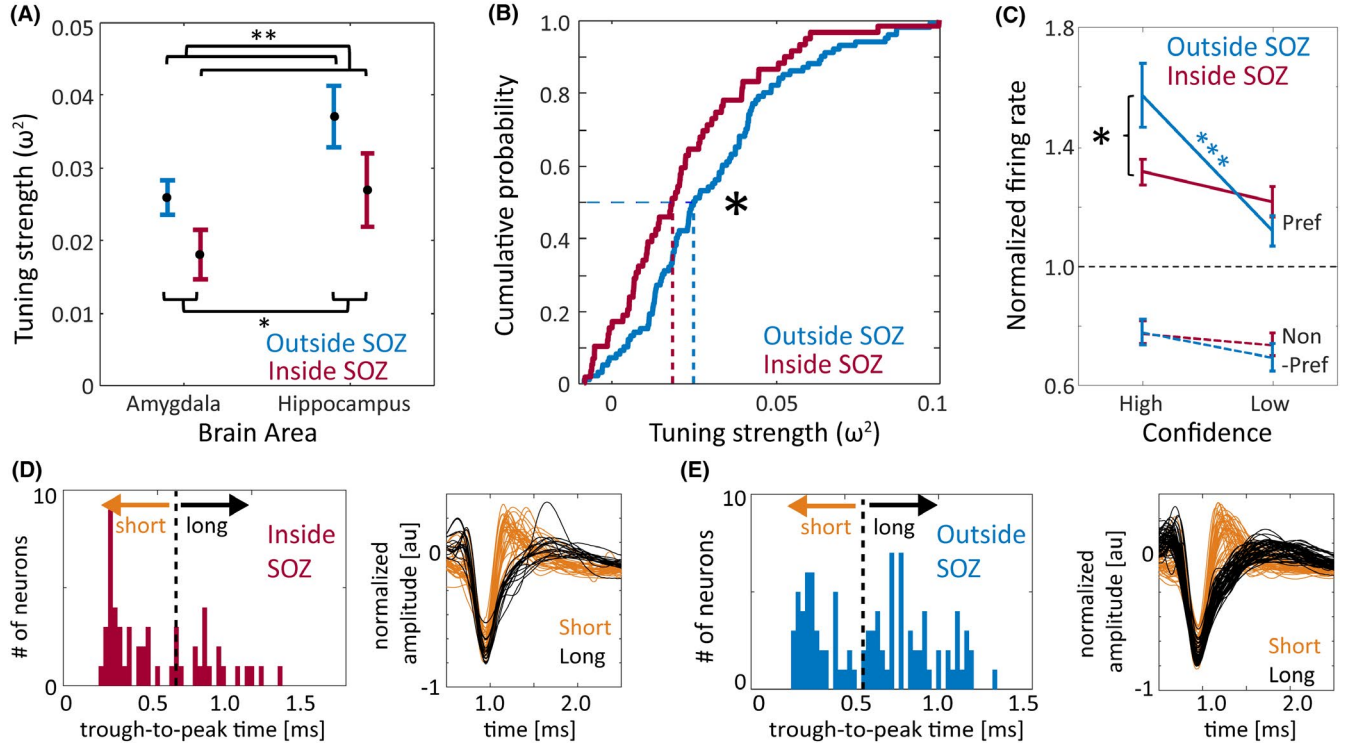

FIGURE 3 Memory selective (MS) neurons inside the seizure onset zone (SOZ) are less selective. (A) Strength of tuning of MS cells as quantified by ω^2 as a function of brain area and location relative to the SOZ. MS cell tuning was significantly different as a function of SOZ ($p = .021$) and brain area ($p = .010$), with no significant interaction between the two. (B) Cumulative distribution function of ω^2 values of MS neurons shows shift of distribution due to location with respect to SOZ (two-tailed Kolmogorov–Smirnov test, $p = .033$). (C) Normalized firing rates of MS neurons as a function of confidence and preferred stimulus of the cell (Preferred is solid lines; Non-Preferres is dashed lines). (D, E) Extracellular waveforms of MS cells recorded within (D) and outside (E) the SOZ. Shown are a histogram of the trough-to-peak widths (left) and the mean waveforms (right). Waveforms are divided into a short and a long group, with a threshold of .6 ms (black dotted line). * $p < .05$, ** $p \leq .01$, *** $p \leq .001$

the extent to which subjects utilized episodic recollection but not the accuracy of recognition.

3.2 | MS neurons

Of 1973 neurons, 159 were MS cells (8%, significantly above chance, $p < 10^{-8}$, Bernoulli; Figure 2A–D shows examples). The proportions of MS cells recorded from the amygdala and hippocampus were similar (9%, $n = 77/819$ vs. 7% $n = 82/1154$, respectively; $\chi^2[1, N = 1973] = 3.40$, $p = .065$). One hundred (63%) MS cells were outside the SOZ (from 47 sessions), and 59 (37%) were inside the SOZ (from 25 different sessions). The proportion of MS cells within the SOZ was similar in the amygdala (35%, $n = 29/82$) and the hippocampus (39%, $n = 30/77$; $\chi^2[1, N = 159] = .22$, $p = .64$). The proportions of cells that qualified as MS cells were not significantly different when comparing neurons recorded from outside (7.8%, $n = 100/1281$) and inside the SOZ (8.5%, $n = 59/692$; $\chi^2[1, N = 1973] = .31$, $p = .58$). Also, the proportions of MS cells were higher than expected by chance both outside and inside the SOZ (7.8% and 8.5%, respectively, significantly larger than chance at $p < 10^{-4}$ and $p < 10^{-5}$, respectively; Bernoulli). Together, this confirms that MS cells existed with similar proportions both inside and outside the SOZ.

Pyramidal neurons are frequently lost inside the SOZ. We therefore examined the shape of the extracellular waveforms of the MS cells, with wider and shorter waveforms indicative of putative pyramidal and inhibitory neurons.[16] The proportion of MS cells with long waveforms (>.6 ms, an established threshold[16,30]) was significantly lower for MS cells located within the SOZ (Figure 3D,E; 34% vs. 57%; $n = 18/53$ vs. 56/98, for inside vs. outside, respectively; $\chi^2[1, N = 151] = 7.4$, $p = .007$; eight cells were excluded from this analysis because the waveform was not available). This finding is compatible with a loss of putative pyramidal cells inside the SOZ.

We first examined whether the extent to which the response of MS cells changed between novel and familiar stimuli (quantified using the ω^2 effect size metric) differed as a function of recording location (Figure 3). A 2 × 2 ANOVA revealed significant main effects of SOZ location ($F[1, 155] = 5.42$, $p = .021$) and brain area ($F[1, 155] = 6.74$,

TABLE 1 Summary of all analysis of variance results

	df	*F*	*p*
Accuracy (AUC) ##			
Confidence rating (high, low)**	1101	56.84	<.001
Group (left, right, bilateral)	2101	.01	.99
Confidence × group	2101	.24	.79
zROC slope ##			
Group (left, right, bilateral)**	246	5.57	.007
MS cells (ω^2)			
Location in SOZ (inside, outside)*	1155	5.42	.021
Brain area (amygdala, hippocampus)*	1155	6.74	.013
SOZ × brain area	1155	.09	.76
MS cells mean firing rate			
Location in SOZ (inside, outside)	1368	.54	.46
Stimulus (preferred, not preferred)**	3368	66.31	<.001
SOZ × stimulus*	3368	3.50	.015
VS cells (ω^2)			
Location in SOZ (inside, outside)	1362	.01	.32
Brain area (amygdala, hippocampus)	1362	1.00	.91
SOZ × brain area	1362	1.36	.24
AR cells (ω^2)			
Location in SOZ (inside, outside)	1294	.21	.64
Brain area (amygdala, hippocampus)	1294	1.01	.32
SOZ × brain area**	1294	7.95	.005
MS cells (ω^2), laterality			
Location in SOZ (inside, outside)	1155	2.22	.14
Hemisphere (right, left)	1155	1.86	.17
SOZ × laterality**	1155	8.80	.003
VS cells (ω^2), laterality			
Location in SOZ (inside, outside)	1362	3.11	.08
Hemisphere (right, left)	1362	2.2	.14
SOZ × laterality	1362	1.36	.12
AR cells (ω^2), laterality			
Location in SOZ (inside, outside)*	1189	4.54	.034
Hemisphere (right, left)	1189	.77	.38
SOZ × laterality	1189	.04	.84
VPA (neuropsychology) ##			
Recall time (immediate/delayed)*	116	6.545	.021
Group (left/right MTL)*	116	4.868	.042
Time × group	116	2.909	.107
VR (neuropsychology) ##			
Recall time (immediate/delayed)	119	.145	.647
Group (left/right MTL)	119	2.796	.111
Time × group	119	3.040	.097
MS cells (ω^2), laterality (no sclerotic cells)			
Location in SOZ (inside, outside)	1104	1.29	.26
Hemisphere (right, left)	1104	1.89	.18
SOZ × laterality*	1104	8.80	.018
MS cells (ω^2, no sclerotic cells)			
Location in SOZ (inside, outside)*	1155	4.59	.035
Brain area (amygdala, hippocampus)*	1104	6.8	.011
SOZ × brain area	1155	.55	.46

Rows marked by ## show behavioral results, whereas all unmarked rows show neuronal results.

Abbreviations: AR, animal responsive; AUC, area under the curve; MS, memory selective; MTL, mesial temporal lobe; SOZ, seizure onset zone; VPA, verbal paired associates; VR, visual reproduction; VS, visually selective; zROC, *z*-transformed receiver operating characteristic.

*$p < .05$; **$p < .01$.

$p = .013$), with no significant interaction (see Table 1 for statistics; Figure 3A). Post hoc tests corrected for multiple comparisons indicated that MS cell selectivity was higher in neurons outside versus inside the SOZ ($F[1] = 5.42$, $p = .020$), and higher in the hippocampus versus the amygdala ($F[1] = 5.4$, $p = .0094$). Comparing the distribution of ω^2 values across all MS neurons as a further post hoc comparison reveals a significant shift of the distribution to lower selectivity values in the SOZ (Figure 3B; two-tailed Kolmogorov–Smirnov [KS] test, $D = .23$, $p = .033$).

Memory strength as assessed by declared confidence modulates the response of MS cells to their preferred stimulus (novel or familiar).[16] We thus examined whether the response of MS cells (mean firing rate in a 1.5-s window starting 200 ms after stimulus onset) was affected by the SOZ. To do so, we pooled cells according to their preferred and nonpreferred stimulus ("Pref" and "Non-Pref"), and split the preferred and nonpreferred trials into high (++) and low (+) confidence trials (52 and 42 MS cells from outside and inside the SOZ, respectively, had enough trials to be included in this analysis). We used a 2 × 4 repeated measures ANOVA, with the first independent variable indicating neuron location (relative to SOZ), the second indicating the trial type (Pref++, Pref+, Non-Pref+, Non-Pref++), and the dependent variable as the mean firing rate. This revealed a significant interaction between recording location and trial type (Table 1 shows statistics; note that of interest here is only the interaction). Post hoc pairwise tests corrected for multiple comparisons revealed a significantly higher normalized

firing rate for neurons outside relative to inside the SOZ only during high confidence Pref trials (Figure 3C; 1.57 ± .76 Hz vs. 1.31 ± .29 Hz, respectively, 95% CI = .004–.51; $p = .043$). This effect was due to a significantly higher firing rate for high compared to low confidence trials for preferred trials for neurons outside but not inside the SOZ (95% CI = .21–.70, $p < 10^{-6}$ for outside SOZ; 95% CI = −.17 to .37, $p = .95$ for inside the SOZ; see Figure 3C). In response to nonpreferred stimuli, MS neurons both outside and inside the SOZ significantly reduced their firing rate relative to baseline for low and high confidence trials (see Figure 3C, dotted lines; paired t-test, outside SOZ: $t[51] = -6.73$, $p < 10^{-7}$, $d = .69$ and $t[51] = -5.08$, $p < 10^{-5}$, $d = .92$; inside SOZ: $t[41] = -6.62$, $p < 10^{-7}$, $d = .88$ and $t[41] = -5.80$, $p < 10^{-6}$, $d = 1.00$, for low and high confidence, respectively). This analysis shows that MS cells located within the SOZ were less effective at differentiating between novel and familiar stimuli.

3.3 | VS neurons

We next examined the response of the 366 VS cells (Figure 2E,F shows examples; 19%, significantly above chance, $p < 10^{-15}$, Bernoulli). The proportion of VS neurons was similar in the amygdala (19%, $n = 223/1154$) and the hippocampus (17%, $n = 143/819$; $\chi^2[1, N = 1973] = 1.10$, $p = .29$). Two hundred forty-seven VS neurons were located outside an MTL SOZ (52 sessions, 173 amygdala, 74 hippocampus), and 119 were located inside an MTL SOZ (31 sessions, 50 amygdala, 69 hippocampus). We quantified the selectivity of VS cells using the effect size metric ω^2. A 2 × 2 ANOVA revealed that the response of VS cells did not differ significantly as a function of location relative to the SOZ or brain area, nor was there a significant interaction (Figure 4A; Table 1 shows statistics).

Lastly, we asked the same question for AR neurons[17] (Figure 2H shows an example). We identified 298 AR neurons (15%, significantly above chance, $p < 10^{-15}$, Bernoulli). AR neurons were more common in the amygdala (17%, $n = 193/1154$) compared to the hippocampus (13%, $n = 105/819$; $\chi^2[1, N = 1973] = 5.69$, $p = .017$), as expected.[17] One hundred ninety were outside and 108 (36%) were inside the SOZ. A 2 × 2 ANOVA revealed no significant effects of location relative to SOZ or brain area (Figure 4B), but a significant interaction ($F[1, 294] = 7.95$, $p = .005$). Post hoc tests corrected for multiple comparisons indicated that in the amygdala, AR neurons outside the SOZ had significantly higher selectivity than those inside the SOZ (Figure 4B, left; 95% CI = −.058 to −.0002, $p = .048$). Also, when only considering AR neurons outside the SOZ, those in the amygdala had significantly higher selectivity compared to those in the hippocampus (95% CI = .0044–.063, $p = .017$). Together, this result shows that AR neurons located in the amygdala were less selective for animals if they were located inside the SOZ.

3.4 | Laterality

Behaviorally (Figure 1), having an SOZ in the right MTL impacted performance in our task. We thus next compared selectivity of MS, VS, and AR cells separately for both hemispheres (right vs. left MTL). For MS cells ($n = 159$), a 2 × 2 ANOVA revealed a significant interaction between SOZ location and laterality ($F[1, 155] = 8.80$, $p = .0034$; Table 1 shows statistics; Figure 5A). Post hoc tests corrected for multiple comparisons indicated that this was due to significantly lower selectivity of cells located within a right hemisphere SOZ (Figure 5A; 95% CI = −.031 to −.0048, $p = .0024$), with no difference between the two groups in the left hemisphere (95% CI = −.010 to .022, $p = .77$). The same 2 × 2 ANOVA revealed no significant effects for VS cells (Figure 5B; Table 1 for statistics). AR neurons in the amygdala exhibited greater selectivity outside relative to inside the SOZ (Figure 5C), with no significant effects of laterality or an interaction.

To further assess our patient cohort, we next analyzed select verbal and visual memory scores from WMS: immediate (I) and delayed (II) recall from the VPA and VR subtests. Patients with both right and left SOZs had significantly lower VPA scores compared to the normative distribution (Figure 1F; VPA I: right, $t[8] = -5.46$, $p < .0001$, $d = .60$; left, $t[8] = -2.5$, $p = .017$, $d = 1.65$; VPA II: right, $t[8] = -1.95$, $p = .05$, $d = .46$; left $t[8] = -2.71$, $p = .013$, $d = .82$). A 2 × 2 repeated measures ANOVA comparing recall time (immediate vs. delayed) and SOZ side (right vs. left) revealed significantly reduced VPA scores in left SOZ relative to right SOZ patients (Figure 1F; $p = .042$) and a significant difference for recall time ($p = .021$), but a nonsignificant interaction (Table 1 shows statistics). On the VR subtest, only right-sided SOZ patients scored significantly below the normative distribution (7.55 ± .61; Figure 1F; VR I: $t[10] = -2.6$, $p = .01$, $d = .75$; VR II: $t[10] = -2.76$, $p = .01$, $d = .77$), whereas left-sided SOZ patients' VR scores fell within the normal distribution (VR I: $t[9] = -.65$, $p = .27$, $d = .19$; VR II: $t[9] = 0$, $p = .50$, $d = 0$). A 2 × 2 repeated measures ANOVA revealed marginally but not significantly poorer VR performance in patients with right-sided SOZ than in patients with left-sided SOZ (7.55 ± .61 vs. 9.65 ± .75; Table 1).

3.5 | Sclerosis

We considered whether the degree of hippocampal sclerosis as assessed by visual inspection of the MRI was related to the selectivity of MS cells within the SOZ. The average sclerosis

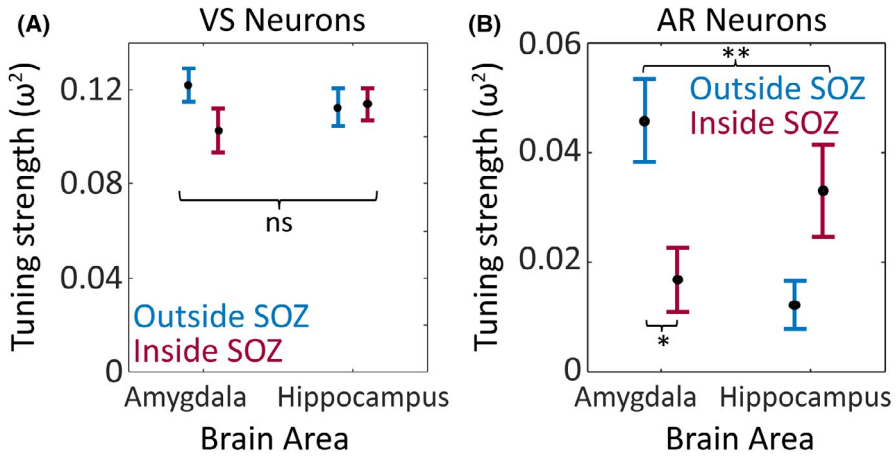

FIGURE 4 Selectivity of visually selective (VS) cells does not differ significantly with location relative to the seizure onset zone (SOZ), whereas animal responsive (AR) neurons in the amygdala are less selective inside SOZ. (A) Strength of tuning of VS cells as a function of brain area and location with respect to SOZ. There were no significant main effects ($p = .91$) nor an interaction ($p = .24$) of the ω^2 of VS neurons when comparing SOZ versus brain area (2×2 analysis of variance [ANOVA]), with a post hoc test also confirming this for brain area ($p = .91$) and outside versus inside SOZ ($p = .32$). (B) Strength of tuning of AR cells as a function of brain area and location with respect to SOZ. A 2×2 ANOVA between brain area and location relative to SOZ revealed a significant interaction ($p = .0051$), but no significant main effects. Error bars are SEM. *$p < .05$, **$p \leq .01$. ns, not significant

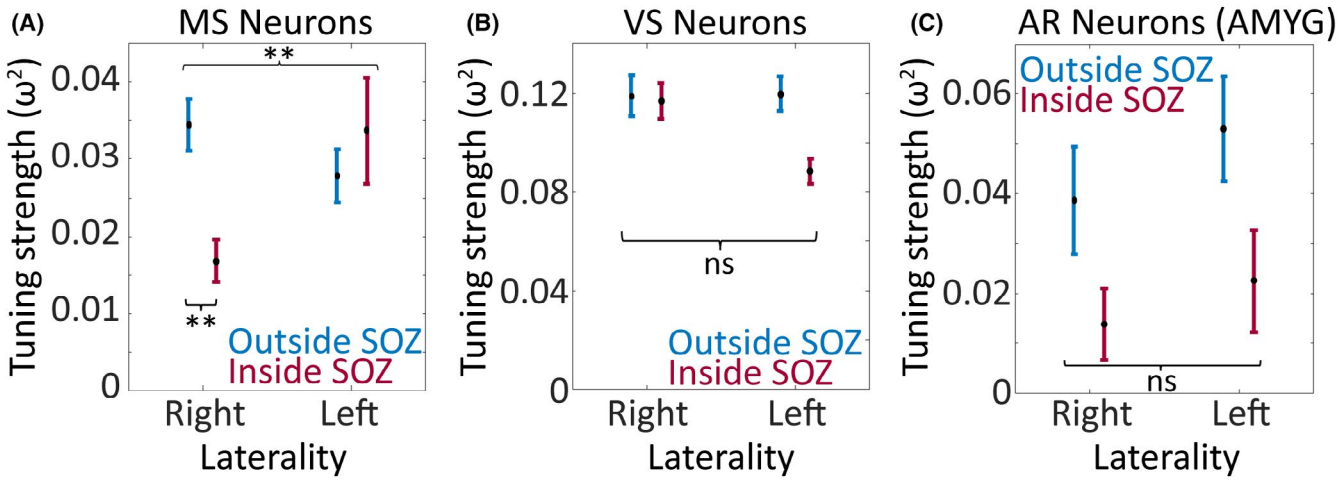

FIGURE 5 Selectivity of neurons as a function of hemisphere and seizure onset zone (SOZ) location. (A) Strength of tuning of memory selective (MS) cells as a function of hemisphere and SOZ location. There was a significant interaction between outside/inside SOZ and right/left hemisphere ($p = .0034$, 2×2 analysis of variance), with a post hoc test showing a significant difference of selectivity in the right hemisphere between outside versus inside the SOZ ($p = .0024$), but not on the left ($p = .77$). (B, C) Strength of tuning of visually selective (VS) and animal responsive (AR) cells. There were no differences between right and left hemispheres for both VS neurons, nor for AR neurons in the amygdala (AMYG). Error bars are S.E.M. **$p \leq .01$. ns, not significant

scores of the right and left hemisphere SOZ groups were not significantly different ($\chi^2 = 1.145$, $p = .766$). The degree of sclerosis was not significantly correlated with the ω^2 of all MS cells ($r = -.11$, $p = .20$) or the ω^2 of MS cells separated by location: left SOZ ($r = -.094$, $p = .75$), left non-SOZ ($r = -.11$, $p = .47$), right SOZ ($r = .14$, $p = .44$), or right non-SOZ ($r = -.18$, $p = .23$). Lastly, we repeated our 2×2 ANOVA analysis for the subset of MS cells from areas with no sclerosis (score = 0). Results were quantitatively similar (see Table 1). Together, this analysis indicates that the degree of sclerosis does not explain the loss of selectivity of MS cells within the SOZ nor of cells in the right hemisphere.

4 | DISCUSSION

Our data reveal cell-type-specific dysfunction during a visual recognition memory task: cells that signal memory strength

(MS cells) responded abnormally if located within a right MTL SOZ, whereas VS cell responses were independent of location relative to the MTL SOZ. MS cell responses were specifically impaired for high-confidence retrieval decisions, a type of memory that is sensitive to MTL damage.[25,31] Behaviorally, patients with an SOZ in their right MTL were less likely to engage episodic recollection when deciding whether they had seen a stimulus before (as shown by zROC differences), but this did not result in a reduction in the overall accuracy by which they answered the new/old question (as indicated by no differences in the AUC of the behavioral ROC curves). This behavioral finding is coherent with our neuronal finding, which was also specific to the right MTL. In the context of formal models of memory,[28,29,32] our findings indicate that an SOZ in the right MTL selectively disrupts recollection rather than familiarity (dual-process models) or that it reduces the variance but not the mean of the familiarity signal (single-process models). Together, these findings link behavioral deficits in recognition memory to TLE-related neuronal dysfunction, thereby revealing a cell-type-specific neuronal and behavioral deficit in the same task.

Our findings indicate that differences in neuronal tuning due to TLE were only apparent for specific types of cells in specific locations (MS cells in the right MTL) and when viewed from the point of view of a specific behavior. Additionally, a role of the MTL that has attracted interest is the amygdala's response when viewing animals,[17] including AR cells in the amygdala that respond to animals.[17] We found that the tuning of amygdala AR cells was impaired if located within the SOZ. The response of VS cells was not impaired, a finding that is of interest because it has been argued that VS cells, which are common in the human MTL, are a reflection of the abstract semantic knowledge of the subject.[33] MS neurons have longer response latencies compared to VS neurons.[16] Given the anatomy and connectivity of the temporal lobe, this indicates that the response of VS cells mirrors that of upstream areas,[34] whereas the response of MS cells likely reflects the outcome of computational processes performed by the MTL.

The right and left MTL are thought to be engaged differentially by different forms of memories, with the left more engaged for verbal memory and the right for visual memory.[35] However, this dichotomy is complex and poorly understood. For example, although surgical resection of the right MTL often results in no noticeable deficits[36] in standard clinical tests, electrical stimulation of the right but not left MTL white matter can improve memory.[37] Here, we show that the response of MS cells located within the right but not left MTL SOZ is reduced. This finding thus offers a neurophysiological correlate that is specifically sensitive to right MTL damage.

Neuropsychological tests are frequently used to establish a preoperative cognitive baseline and to help localize the SOZ. Compatible with prior work,[36,38–40] analysis of WMS scores of our patients indicated that patients with right MTL SOZs had marginally weaker visual memory (VR subtest) and significantly stronger verbal memory (VPA subtest) in comparison to patients with a left MTL SOZ. Identifying deficits due to an SOZ in the right MTL has been shown to be relatively unreliable using these measures,[41] compatible with our weak difference in the VR scores. In contrast, in our task we find reliable effects of an SOZ in the right MTL both behaviorally and neuronally.

Future work is needed to investigate several caveats and limitations of our study. First, what is the effect of SOZs located outside of the MTL (which we did not investigate here) on category and memory signals within the MTL? One hypothesis is that an SOZ in the anterior lateral temporal lobe would impair category but not memory signals due to the impact on semantic encoding. Second, what is the relationship between our findings and interictal discharges (IEDs)? Although IEDs are generally rare, their occurrence is correlated with impaired memory[42–44] and they transiently entrain neurons within the MTL.[45] It remains an open question whether the selective impairment of MS but not VS cells can be explained by selective entrainment of these neurons by IEDs. Third, memory-related gamma-band and other electrophysiological activity is impaired within the SOZ.[46–49] One hypothesis is that the reduced MS cell activity we document here gives rise to these population-level phenomena. Fourth, our assessment of the degree of sclerosis is based on MRI, leaving open the question of whether sclerosis levels as evaluated histologically are related to the extent of MS cell response deficits. Fifth, our study compared neurons according to the side of the brain they were recorded in, leaving open the question of whether the differences we found were due to language dominance or laterality. Given the high correlation between the two, a substantially larger dataset will be required to answer this. Sixth, the comparison of MS cells was across subjects rather than paired within-subject. Seventh, do the functional cell types we investigated map onto known molecular cell types? If so, this would indicate the feasibility of specific targeting.

Finally, we hypothesize that the identified cells with impaired responses are part of the circuitry impaired by TLE. Of broad scientific interest is the causal manipulation that a focal SOZ offers for investigation of neural mechanisms. Identifying impaired signals within an SOZ might offer a general methodology to test the causal effects of disrupting a specific circuit in a particular area for a given behavior. The broader translational significance of this work is that it establishes a neural correlate of cognitive impairment due to epilepsy, which can now be used as a biomarker to assess the efficacy of novel treatments such as targeted electrical stimulation or pharmacological treatments.

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CONFLICT OF INTEREST

The authors report no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

Conceptualization: Ueli Rutishauser; Software: Nand Chandravadia and Ueli Rutishauser; Data Curation: Seung J. Lee, Danielle E. Beam, Nand Chandravadia; Investigation: Seung J. Lee, Danielle E. Beam, Andrea G. P. Schjetnan, Lynn K. Paul, Nand Chandravadia, Ueli Rutishauser; Resources: Chrystal M. Reed, Jeffrey M. Chung, Ian B. Ross, Taufik A. Valiante, Adam N. Mamelak; Writing–Original Draft: Seung J. Lee, Danielle E. Beam, Lynn K. Paul, Adam N. Mamelak, Ueli Rutishauser; Writing–Review & Editing: Andrea G. P. Schjetnan, Chrystal M. Reed; Funding Acquisition: Ueli Rutishauser; Supervision: Ueli Rutishauser, Adam N. Mamelak, Taufik A. Valiante.

DATA AVAILABILITY STATEMENT

This dataset is available on the Open Science Framework in the standardized Neurodata Without Borders format (https://doi.org/10.17605/OSF.IO/HV7JA).[50]

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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