Hippocampal interictal epileptiform activity disrupts cognition in humans

Jonathan K. Kleen, PhD
Rod C. Scott, MD, PhD
Gregory L. Holmes, MD
David W. Roberts, MD
Melissa M. Rundle, BA
Markus Testorf, PhD
Pierre-Pascal Lenck-Santini, PhD
Barbara C. Jobst, MD

Correspondence to
Dr. Jobst:
Barbara.C.Jobst@hitchcock.org

ABSTRACT

Objective: We investigated whether interictal epileptiform discharges (IED) in the human hippocampus are related to impairment of specific memory processes, and which characteristics of hippocampal IED are most associated with memory dysfunction.

Methods: Ten patients had depth electrodes implanted into their hippocampi for preoperative seizure localization. EEG was recorded during 2,070 total trials of a short-term memory task, with memory processing categorized into encoding, maintenance, and retrieval. The influence of hippocampal IED on these processes was analyzed and adjusted to account for individual differences between patients.

Results: Hippocampal IED occurring in the memory retrieval period decreased the likelihood of a correct response when they were contralateral to the seizure focus ($p < 0.05$) or bilateral ($p < 0.001$). Bilateral IED during the memory maintenance period had a similar effect ($p < 0.01$), particularly with spike-wave complexes of longer duration ($p < 0.01$). IED during encoding had no effect, and reaction time was also unaffected by IED.

Conclusions: Hippocampal IED in humans may disrupt memory maintenance and retrieval, but not encoding. The particular effects of bilateral IED and those contralateral to the seizure focus may relate to neural compensation in the more functional hemisphere. This study provides biological validity to animal models in the study of IED-related transient cognitive impairment. Moreover, it strengthens the argument that IED may contribute to cognitive impairment in epilepsy depending upon when and where they occur. *Neurology*® 2013;81:18–24

GLOSSARY

CI = confidence interval; **DMTS** = delayed-match-to-sample task; **GEE** = generalized estimating equations; **IAT** = intracarotid amobarbital testing; **IED** = interictal epileptiform discharges; **OR** = odds ratio; **TLE** = temporal lobe epilepsy.

Temporal lobe epilepsy (TLE) is the most common focal epilepsy in adults, and is associated with memory impairment,[1,2] which affects psychosocial functioning and quality of life.[3] These deficits are attributed to etiologic changes in the hippocampus such as cell death and synaptic reorganization.[4] However, dynamic factors such as interictal abnormalities evident on EEG may impart an independent contribution to neuropsychological outcome.[5]

Interictal epileptiform discharges (IED) in the cortex, detected with routine scalp EEG recordings, are associated with transient cognitive impairment.[6–12] By extension, it is likely that IED in the mesial temporal lobes may affect cognition given the role of these structures in learning and memory. One study[13] showed a 6% decline in working memory performance related to mesial temporal IED. However, as demonstrated in previous studies of cortical IED,[9,10] the degree of cognitive impact could have been underestimated since the authors did not consider 1) the precise timing of the IED within the memory task trials and 2) the specific components involved in memory processing.

Using a rodent model of TLE,[14] we recently found that hippocampal IED were related to considerable decrements in short-term memory retrieval but not memory encoding or maintenance. Therefore, the cognitive impact of IED in the hippocampus may be substantially more important than previously documented. We performed a translational study to assess the hypothesis that

spontaneous hippocampal IED can dynamically disrupt short-term memory processes in patients with epilepsy.

METHODS **Patients.** Ten patients with refractory seizures participated in the study. All had depth electrodes implanted into the hippocampus for intracranial epilepsy surgery evaluation of the seizure focus. Patients were monitored in the Peter D. Williamson Epilepsy Unit at the Dartmouth-Hitchcock Epilepsy Center between 2009 and 2011. Demographics and clinical characteristics are listed in the table.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Committee for the Protection of Human Subjects at Dartmouth College. Written consent was obtained for data collection from all participants or their durable power of attorney.

Equipment. Depth electrodes were inserted via a posterior stereotactic neurosurgical approach, extending from the occipital cortex anteriorly through the longitudinal axis of the hippocampus. Electrode placement was confirmed with coregistration of postoperative CT to preoperative MRI (figure 1A). Electrodes were verified within the hippocampus. The anterior-most contact was within or close to the amygdala. Of note, no IED occurred in isolation in the amygdala. Cognitive testing began 3–5 days following the implantation of electrodes when pain was significantly controlled and antiepileptic medications had been withdrawn to induce seizures.

Cognitive task. We sought to assess short-term memory because it has been established as a hippocampal-dependent function.[15] For this purpose we used the Sternberg task,[16] which incorporates distinct short-term memory processes to perform delayed information recall. Patients performed up to 120 trials in a daily testing session with breaks between every 30 trials to avoid fatigue. For each trial (figure 2), a group of consonant letters (the "List") was displayed for 2 seconds on a computer screen. A delay of 6 seconds followed, during which the patient fixated on a dot in the middle of the screen. A single consonant letter (the "Test") was then shown on the screen for 2 seconds. The patients were instructed to respond with a left mouse click ("Yes") if they believed that the Test letter was in the previous group (figure 2A), and with a right mouse click ("No") if not (figure 2B). There was an intertrial interval of 3 seconds followed by a "+" sign displayed before the next trial commenced. To minimize anticipatory responding, the delay intervals and intertrial intervals were made variable by adding a jitter of ±200 milliseconds. Approximately 20% of trials were "Lure" trials, which did not require working memory. These consisted of repeated vowels (figure 2C) and were used for stimulus control to ensure patients were attending to the task. To ensure that patients were able to perform the task, patients performing below 65% cutoff for accuracy were excluded a priori. All 10 patients included in the analyses herein averaged above this cutoff. An additional 3 patients were excluded due to poor attention or lack of understanding the task. Patients did not participate in the study on days when they had a seizure.

Task software and hardware interface. Letter sequences were randomly generated using custom MATLAB software (The Mathworks, Inc., Natick, MA), and integrated into the Presentation program (Neurobehavioral Systems, Inc., Albany, CA). Task events and patient responses were synchronized with EEG data collected with equipment from Grass Technologies (West Warwick, RI) and exported afterward for further analysis.

Table	Patient information[a]										
Patient	Age, y	Age at onset, y	Handed-ness	IQ	Language dominance	Memory dominance	Hippocampal depths	Seizure focus	Resection	MRI findings	Pathology
1	41	20	L	126	L	R > L	B	L	None	Normal	NA
2	51	21	R	98	L	R	B	L	L TLE	L temporal cortex EM	MTS, scar tissue
3	45	24	R	76	L	R	B	R	R TLE	Normal	↓ Neuron density, gliosis
4	48	22	R	75	B	B	B	L	L AHE	L MTS	MTS, cortical dysplasia
5	55	49	R	NA	L	L	B	R	R AHE	Normal	MTS
6	32	25	R	69	B	NA	B	L	L TLE	Normal	Normal
7	22	5	R	89	B	B	L	L	L TLE	L MTS	MTS
8	56	5	R	71	L	R	B	L	None	R MTS	NA
9	49	25	L	67	L	NA	B	L > R	None	B posterior cortex MF	NA
10	41	1	R	56	L	R	B	L	L TLE	L MTS	NA
A	62	8	R	66	B	R	B	R	None	R MTS	NA
B	23	1	R	71	L	NA	L	NA	None	Normal	NA
C	26	12	R	44	NA	NA	B	L	L TLE	Normal	Normal

Abbreviations: AHE = selective amygdalohippocampectomy; B = bilateral; EM = encephalomalacia; MF = malformation; MTS = mesial temporal sclerosis; NA = not available; TLE = temporal lobe epilepsy.

[a] Individual patient characteristics are listed, including age, handedness, IQ (full-scale), language and memory dominance from the intracarotid amobarbital testing (Wada) test, hippocampal depth electrode placements, seizure focus laterality, resection outcome, MRI findings, and pathology findings. Evidence of right- or left-sided mesial temporal sclerosis on imaging or pathology did not produce large enough groups for reliable statistical analysis of lesion laterality influences. The high number of patients with differing language and memory dominance is not uncommon among patients requiring intracranial monitoring due to conflicting preoperative findings.[21] Patients A-C were not included in the study due to inability to perform the Sternberg task (see Methods).
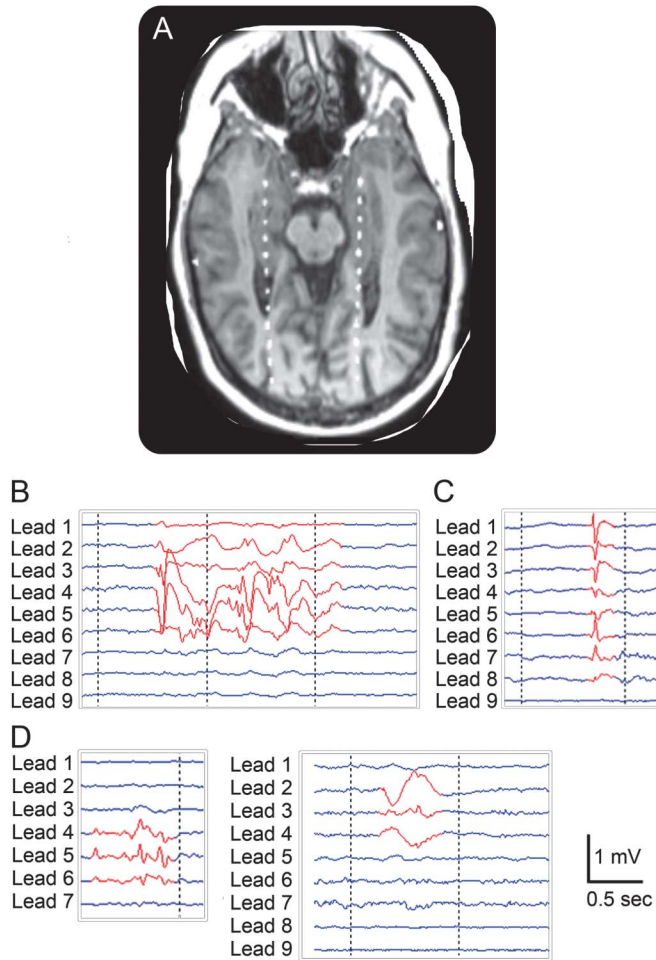
(A) Bilateral depth electrodes visualized by coregistered MRI and CT imaging. From anterior to posterior, contacts are located in the amygdala, hippocampal formation, lateral ventricles, white matter, and occipital cortex. (B) EEG signals illustrate a type 1 IED: repetitive spike-wave complex. From top to bottom, the depth-EEG signals shown are from contacts oriented from anterior to posterior, as illustrated in (A) (i.e., lead 1 is most anterior). (C) Type 2 IED: single spike or spike-wave. (D) Type 3 IED: shown are 2 examples of IED that did not show classical spike or spike-wave morphology. The left panel illustrates aberrant rhythmic activity, while the right panel shows a broad-based high-amplitude sharp wave.

Analysis methods and statistics. Data processing utilized custom software written in MATLAB. IED were detected manually with a graphical user interface by a board-certified clinical neurophysiologist (B.C.J.). The reviewer was blinded to all Sternberg trial information and was shown only continuous stretches of EEG traces from the depth electrodes. The voltage amplitude (i.e., gain) and time scale displayed on the software interface during IED detection remained constant across all patients to further prevent observer bias. The temporal duration and the number of EEG leads involved were documented for each IED. IED were classified into 3 subtypes (figure 1, B–D). Subtype 1 consisted of repetitive, high-amplitude interictal spike-wave complexes including polyspikes. Subtype 2 consisted of high-amplitude isolated interictal spikes. Subtype 3 consisted of atypical epileptiform activity that did not have a classical spike or spike-wave morphology but was considered abnormal and epileptiform. Most often this represented rhythmic, low-amplitude sharp theta/alpha activity or high-amplitude broad-based sharp waves. IED were also classified according to laterality, meaning

whether they occurred ipsilateral or contralateral to the seizure focus, or bilaterally. Subtype classification and randomly selected spike markings were reviewed by a second blinded reviewer (G.L.H.) to assure consistency. Interrater reliability was greater than 95%.

Based on our previous rodent study,[14] 3 stages of short-term memory processing were inferred in the task a priori: encoding (time window from 2 seconds before to 2 seconds after the List presentation onset), maintenance (the subsequent 4-second window), and retrieval (4-second window immediately prior to the patient's response). IED were classified according to whether or not they fell within these epochs during the Sternberg trials (e.g., retrieval IED were those that occurred within the 4-second window preceding the patient's response). IED that overlapped with multiple epochs (e.g., encoding and maintenance) were analyzed with separate tests for each epoch.

Statistical analyses were performed in STATA 11 (StataCorp LP, College Station, TX) and in SPSS (version 20; Chicago, IL). Correlations were obtained with Pearson or Spearman tests depending upon data distributions. Logistic regression was performed using generalized estimating equations (GEE) to account for within-individual correlation, test the effect of potential confounders, and adjust for uneven data (patients each performed between 30 and 480 trials). This multivariable regression method was used to investigate whether the presence and timing of IED during trials affected the likelihood of correct responses. GEE enabled a single analysis for each time epoch by using multiple factors (e.g., IED laterality and IED subtype) as covariates, minimizing the number of statistical tests used. Reaction time data were compared between trials with and without IED using a paired t test on log-transformed values following within-patient averaging to adjust for differing numbers of trials between patients.

RESULTS **Accuracy.** Sternberg task performance averaged 86% correct across patients overall, ranging from 67% to 98%. We investigated whether an IED in a given trial produced transient cognitive impairment by decreasing the likelihood of giving a correct response answer in that trial. We used reaction time as a covariate given its relation to accuracy (see Reaction time section).

Laterality of IED. During the retrieval epoch (figure 3), IED that were contralateral to the seizure focus (odds ratio [OR] 0.544; 95% confidence interval [CI] 0.336–0.883; $p < 0.05$) and bilateral IED (OR 0.645; 95% CI 0.501–0.830; $p < 0.001$) decreased the likelihood of a correct response, while ipsilateral IED did not (OR 1.090; 95% CI 0.855–1.391). In the encoding epoch, ipsilateral (OR 0.913; 95% CI 0.559–1.489), contralateral (OR 0.723; 95% CI 0.346–1.513), or bilateral (OR 0.810; 95% CI 0.357–1.838) IED did not influence accuracy. In the maintenance epoch, bilateral IED decreased the likelihood of a correct response (OR 0.557; 95% CI 0.386–0.805; $p < 0.01$), but not IED that were ipsilateral (OR 1.165; 95% CI 0.807–1.683) or contralateral (OR 1.071; 95% CI 0.659–1.743). It should be noted that according to intracarotid amobarbital testing (IAT), only one patient had memory dominance ipsilateral to the seizure focus (table). All other patients had memory dominance on the contralateral side or comparable test scores bilaterally.

The laterality analyses were repeated by designating IED as left or right hemisphere instead of ipsilateral or contralateral to the seizure focus. The results for
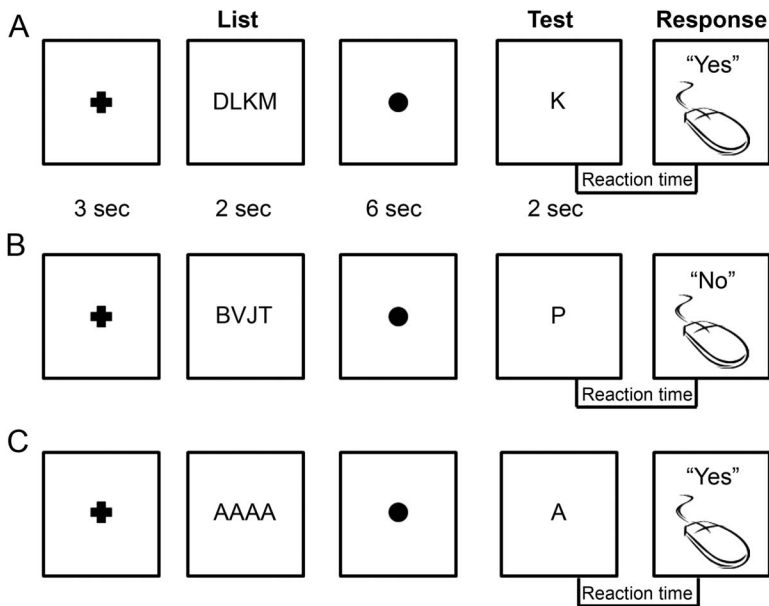
(A) Sternberg trial in which the Test letter is in the previous List sequence. During the intertrial interval (3 seconds), a cross is displayed, followed by the List sequence (2 seconds). A fixation dot is then shown (6 seconds), after which the Test letter is displayed (2 seconds). A correct response in this case would be a left mouse click ("Yes"). (B) A Sternberg trial in which the Test letter is not in the previous List sequence. A correct response in this case would be a right mouse click ("No"). (C) A Lure trial in which the List is always "AAAA" and the Test letter is always "A." The patient must simply respond with a left mouse click ("Yes") as soon as the Test letter is shown.

left- and right-sided IED were similar to ipsilateral and contralateral IED, respectively, likely since most patients had left-sided seizure foci (see table). Specifically, right-sided IED during the retrieval period decreas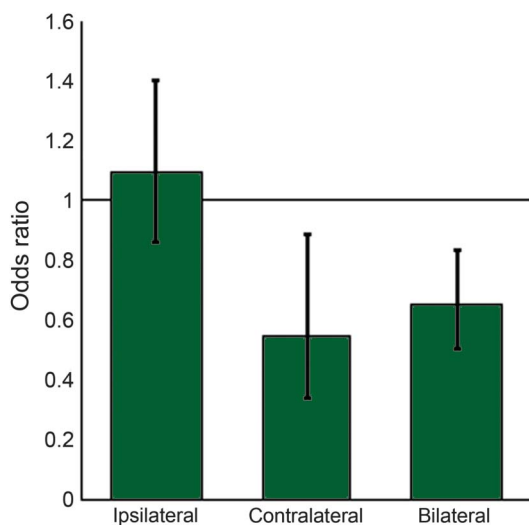ed the likelihood of a correct answer (OR 0.623; 95% CI 0.411–0.945; $p < 0.05$), while left-sided IED did not (OR 1.167; 95% CI 0.928–1.468).

Without laterality taken into account, IED that occurred during memory encoding (OR 1.054; 95% CI 0.723–1.535), maintenance (OR 0.973; 95% CI 0.730–1.298), or retrieval (OR 1.135; 95% CI 0.874–1.476) did not influence the likelihood of a correct response. Multiple IED in a trial, including IED that overlapped with multiple epochs, did not decrease the likelihood of a correct response.

IED subtypes. Separating IED into subtypes revealed that both type 1 (OR 0.542; 95% CI 0.296–0.992; $p < 0.05$) and type 3 IED (OR 0.776; 95% CI 0.604–0.998; $p < 0.05$) decreased the likelihood of a correct response when they fell in the retrieval period. The mean duration (in seconds) of type 1 IED in the memory maintenance epoch further decreased the likelihood of a correct response (OR 0.300; 95% CI 0.138–0.656; $p < 0.01$), but not during encoding (OR 0.364; 95% CI 0.204–1.793) or retrieval (OR 1.016; 95% CI 0.488–2.114). There were no other effects of the individual IED subtypes on encoding, maintenance, or retrieval. To control for multiple comparisons, we then carried out multivariable regression for each epoch using subtype, laterality, and reaction time as independent covariables. The results confirmed the significant results reported above for IED subtype and laterality influences, and showed that these variables covaried with each other.

IED correlations. The total number of IED in a given Sternberg session was not related to overall accuracy in that session (Spearman rho = −0.50, $p = 0.14$), nor was it related to IQ or other neuropsychological measures in the California Verbal Learning Test ($p > 0.05$).

Reaction time. The time between Test letter presentation and the patient's response (i.e., reaction time) was shorter for correct trials compared to incorrect trials ($p < 0.001$). Lure trials had shorter reaction times than both correct and incorrect trials ($p < 0.001$ for both). Average reaction times were 1.42 seconds in correct trials, 1.76 seconds in incorrect trials, and 0.76 seconds in Lure trials. The placement of the Test letter in the List sequence (first through fourth place) was significantly related to reaction time ($p < 0.001$), but not significantly related to accuracy (OR 0.785; 95% CI 0.570–1.080). Reaction times were longer for trials where the Test letter was in the List (see figure 2A) compared to trials where it was not in the List (see figure 2B; $p < 0.001$), though there was no significant difference in accuracy (OR 1.385; 95% CI 0.661–2.902).

The transient impact of IED on reaction time was analyzed only among correct trials to control for the influence of accuracy. If IED occurred during the retrieval period, the reaction time was similar to trials without any IED during this epoch ($p = 0.324$; figure 4). This lack of difference in reaction time between trials with and
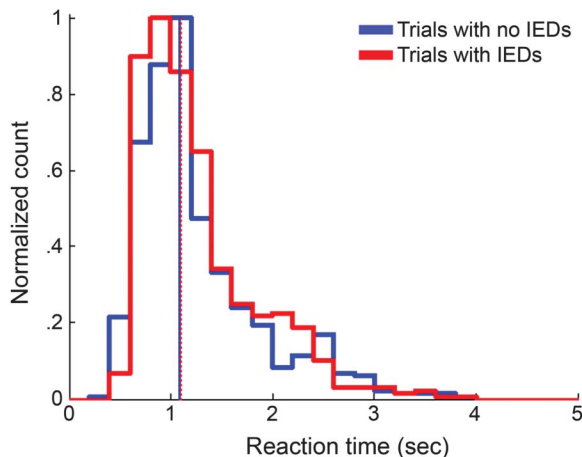
Predicted odds ratios are shown for the influence of interictal epileptiform discharges that were ipsilateral or contralateral to the seizure focus, or bilateral. Error bars indicate 95% confidence intervals. Contralateral and bilateral spikes during retrieval significantly decreased the likelihood of responding correctly during a trial.

Figure 4 Reaction time in trials with and without interictal epileptiform discharges

The figure shows histograms of the relative frequencies of reaction time in trials without interictal epileptiform discharges (IED) (thick solid blue line) and trials with IED (thick solid red line). The median reaction time was not significantly different between trials without IED (1.085 seconds; solid blue vertical line) and trials with IED (1.100 seconds; dotted red vertical line).

without IED was consistent regardless of IED laterality or subtype.

DISCUSSION We show that hippocampal IED may be associated with greater decrements in memory performance than previously reported,[13] depending on their timing and location. We also provide the first clinical translation of IED-associated transient cognitive impairment findings across species, from a rodent model[14] to patients with epilepsy.

Neuropsychological test scores have been used to indirectly investigate whether IED relate to poorer cognitive outcomes by correlating performance with the cumulative number of IED in a given period. These types of studies have produced mixed findings.[17–19] We showed no relation between the number of IED in a session and session accuracy, but there was a transient effect of an IED in a given trial. We attributed this to the concept put forth by some prior studies[9,10] that an IED has to be in the right place at the right time to produce cognitive impairment. Hippocampal IED in any period outside of maintenance and retrieval (on a short-term memory task) may be inconsequential and would not support a correlation between IED frequency and accuracy. Future investigations of IED-induced cognitive impairment must account for the timing of IED to reveal their full consequence.

The laterality of IED influenced whether cognitive impairment was observed. A classic study on transient cognitive impairment due to cortical IED[6] reported the lateralization of IED-induced impairments, with left-sided IED producing verbal task impairments and right-sided IED producing spatial task impairments. The Sternberg task involves combinations of letters,

implying a possible verbal memory component. However, right-sided IED significantly affected cognitive performance while left-sided IED did not. Another potential explanation for the strong effect of right- but not left-sided IED may relate to the majority of our patients having a left-sided seizure focus. Faulty unilateral hippocampal circuitry may have resulted in a shift of memory workload to the right (or contralateral) side over time,[20] consistent with variations in memory dominance laterality as reflected by our IAT results.[21] Other researchers have corroborated this concept by showing increased activation in the hemisphere contralateral to the seizure focus.[22] Thus, in the vast majority of patients, IED in the left (or ipsilateral) hemisphere would have little to no effect while right-sided (or contralateral) IED would compromise the compensatory networks. Bilateral IED would affect both hemispheres with additional memory circuits, and would therefore affect additional functions such as memory maintenance, as seen here. Indeed, they prominently disrupted both maintenance and retrieval processes in this study, similar to previous findings on cognitive impairment with bilateral hippocampal stimulation.[23] Laterality of IED in our previous rat study[14] did not influence accuracy. However, rats have questionable lateralization of function and show bilateral lesions after pilocarpine.

Although this study translates a number of our animal findings,[14] type 2 events, which were similar in morphology to the IED in our rodent model, did not predict impairments here. On the other hand, type 1 and type 3 events did affect accuracy, consistent with a prior study that reported a greater impact of spikes with a "larger breadth of field" than small-amplitude focal spikes on scalp EEG in humans.[8] The vulnerability of rats to focal interictal spikes may be a matter of species or due to a shorter amount of time (weeks to months) between pilocarpine epilepsy induction and the testing period. Patients in the current study had been diagnosed with epilepsy decades earlier (see table), perhaps allowing their brains to compensate for small-amplitude, focal IED.[20]

Hippocampal IED did not affect reaction time in this study, whereas hippocampal interictal spikes increased response latency (a similar measure) in the animal study. However, a previous study[13] also showed that hippocampal IED do not affect reaction time in humans. It is likely that species and task differences account for the discrepancy.

Indeed, the neural networks involved for the Sternberg task are likely different from those governing the delayed-match-to-sample task (DMTS) in the animal study. DMTS has a prominent hippocampal-dependent component according to lesion studies in rats.[24] The hippocampus is also implicated in processing the Sternberg task[25]; however, it involves the prefrontal cortex and multiple other substrates in the limbic system.[26] Both tasks require a component of short-term memory function that

is hippocampal-dependent, and both were affected by IED in the retrieval period. Likewise, neither task was affected by IED during the encoding period, in contradiction to the effects of cortical IED.[10,11] This process-specific vulnerability across species may relate to the intricate intrahippocampal circuits involved in memory recall,[27,28] while memory encoding may be buffered by other cortical structures such as the prefrontal cortex[29] or perhaps lingering representation in primary sensory areas. Thus, assessing the full impact of IED on cognition requires consideration of the characteristics of both the cognitive task and the IED themselves.[8,11]

More patients may have allowed better assessment of whether neural plasticity was truly involved in redirecting memory function to supplemental (e.g., contralateral) brain networks, and whether IED in these networks truly compromised this compensation. We were also limited in that we used only one cognitive task to assess hippocampal function, which may have been considerably verbal in nature. Furthermore, it did not allow adjustment of memory load, which can relate to the degree of hippocampal recruitment.[30] Moreover, it is unclear whether IED-associated disruption during such a specific memory task relates to clinically relevant dysfunction.

Recurrent seizures are the cornerstone of epilepsy and the focus of its treatment, while IED are not currently incorporated into treatment strategies. Instead they are usually considered a harmless biomarker that assists in the diagnosis of epilepsy. Our study demonstrates that bilateral IED and IED contralateral to the seizure focus are probably the most clinically relevant to memory impairment and warrant attention. However, treatment options are limited. Pharmacologic treatment to reduce IED is a hotly debated topic,[31] particularly since antiepileptic drugs impart their own cognitive side effects.[32,33]

Our previous findings in an animal model have been generally translated to patients in the current study. Thus we surmise that future studies of IED-associated cognitive impact can be probed with animal research. This study thereby encourages and facilitates future investigations into IED-induced effects and whether attenuating them might improve the lives of patients.

AUTHOR CONTRIBUTIONS

Dr. Kleen: study design, data acquisition, statistical analysis, study coordination, data interpretation, writing the manuscript. Dr. Scott: study design, statistical analysis, data interpretation, writing the manuscript. Dr. Holmes: study design, study coordination, data interpretation, writing the manuscript. Dr. Roberts: study design, data interpretation, writing the manuscript. M.M. Rundle: data acquisition, data interpretation, writing the manuscript. Dr. Testorf: data acquisition, data interpretation, writing the manuscript. Dr. Lenck-Santini: study design, data acquisition, study coordination, data interpretation, writing the manuscript. Dr. Jobst: study design, data acquisition, study coordination, data interpretation, writing the manuscript.

ACKNOWLEDGMENT

DISCLOSURE

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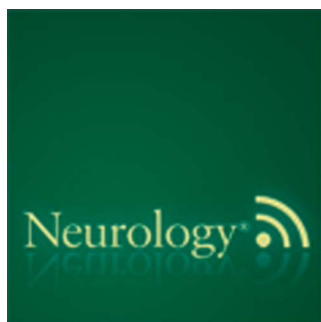
Depressive symptoms and white matter dysfunction in retired NFL players with concussion history (See p. 25)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the July 2, 2013, issue of *Neurology*. In the second segment, Dr. Christopher Giza talks with Dr. John Hart about his paper on depressive symptoms and white matter dysfunction in retired NFL players. Dr. Adam Numis then reads the e-Pearl of the week about ice cream headache. In the next part of the podcast, Dr. Alberto Espay focuses his interview with Drs. Ron Postuma and Brad Boeve on clinicopathologic correlations in 172 cases of REM sleep behavior disorder with and without a coexisting neurologic disorder. Disclosures can be found at www.neurology.org.

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