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Small sharp spikes as EEG markers of mesiotemporal lobe epilepsy

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HIGHLIGHTS

- Mesial temporal lobe epilepsy, a common type of focal epilepsy, often lacks scalp EEG correlates.
- Small sharp spikes on EEG were time-locked to hippocampal discharges recorded on intracranial electrodes.
- Small sharp spikes can be EEG markers of mesiotemporal lobe epilepsy rather than normal variants.

ABSTRACT

Objective: Mesial temporal lobe epilepsy (mTLE) is the most common type of focal epilepsy, but often lacks scalp EEG correlates. We ask if hippocampal epileptiform discharges that are characteristic of mTLE are associated with small sharp spikes (SSS) recorded on scalp EEG. SSS are considered benign waveforms, so are not currently used as markers of epilepsy.
Methods: To determine if there is a relationship between SSS and hippocampal discharges, simultaneous scalp and hippocampal depth electrode EEGs were recorded from 27 patients being evaluated for possible mTLE. Scalp EEG waveforms were assessed at the time of hippocampal discharges identified on intracranial hippocampal depth electrodes.
Results: 15 of 27 patients had SSS on scalp EEG that were time locked to hippocampal epileptiform discharges measured intracranially. These hippocampal spikes tended to have overlying high frequency oscillations and to co-localize with a seizure onset zone, suggesting that they were pathological discharges.
Conclusions: There is a tight coupling between a subset of pathological hippocampal discharges and SSS.
Significance: SSS can be scalp EEG markers of mTLE rather than normal EEG variants.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most common focal epilepsy (Asadi-Pooya et al., 2016; Stern and Engel Jr., 2015). It classically presents with focal seizures with aura, automatisms, impaired awareness, and sometimes progression to generalized convulsive seizures. However, the diagnostic evaluation of patients with mTLE can be prolonged and imperfect because pathological hippocampal activity cannot consistently be identified on scalp EEG (Koessler et al., 2015; Ramantani et al., 2016). This can lead to a misdiagnosis of non-epileptic psychogenic seizures; while the prevalence of this misdiagnosis is unknown, the mortality and morbidity can be substantial if seizures are undertreated (Beghi and Cornaggia, 2002; van den Broek, 2004).

A subset of hippocampal discharges manifest on the scalp EEG as large amplitude sharp waves after propagating to lateral temporal neocortical areas. Here we ask if a different population of scalp EEG waveforms is correlated with hippocampal discharges, specifically testing the hypothesis that some hippocampal spikes manifest as small sharp spikes (SSS) on the scalp EEG. SSS, sometimes referred to as benign epileptiform transients of sleep or benign sporadic sleep spikes, are small in amplitude (less than 50 μV), brief in duration (less than 50 ms), have a field over the temporal area, are usually found independently over both hemispheres, and are most easily detected in early sleep. They are typically considered benign normal variants (White et al., 1977), although

Abbreviations: mTLE, mesial temporal lobe epilepsy; SSS, small sharp spikes; HFO, high-frequency oscillations.

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several authors suggest they might be markers of epilepsy (Hughes and Gruener, 1984; Mothersill et al., 2012; Saito et al., 1987). If SSS on the scalp EEG are associated with hippocampal interictal spikes, then SSS may be an EEG marker for mesiotemporal epilepsy.

2. Materials and methods

2.1. Subjects

Data were collected from a retrospective review of simultaneous scalp and intracranial EEG recordings in 27 patients undergoing phase II monitoring at the University of Chicago Adult Epilepsy Center for medically intractable temporal lobe epilepsy. All patients who met the following criteria were included: (1) the monitoring was conducted between January 2014 and November 2017, (2) at least one depth electrode targeted the hippocampus from an occipital approach, (3) hippocampal epileptiform discharges were recorded, (4) scalp EEG was simultaneously recorded. Written informed consent was provided through a process approved by the University of Chicago Institutional Review Board.

2.2. Simultaneous scalp and intracranial EEG

Scalp electrodes were placed in the international 10–20 arrangement with supplementary sub-temporal electrodes F9, T9, F10, T10 from the 10–10 system, and mastoid electrodes M1, M2. The configuration of intracranial electrodes varied among subjects, but all had at least one depth electrode (Integra Life Sciences Corporation, Plainsboro, NJ) that was inserted through an occipital burr hole targeting the hippocampus; in 13 subjects bilateral hippocampal depth electrodes were placed. Additional intracranial subdural strip or depth electrodes, when present, were placed through one burr hole over the temporal lobe and in a minority of patients through an additional frontal or parietal burr hole. In none of the subjects was a craniotomy performed. Locations of the electrodes were estimated based on post-implantation CT scans co-registered with pre-implantation MRI scans (Brang et al., 2016). Signals were acquired at 1 kHz using a Natus Neurolink EEG amplifier (Natus Neurology Incorporated, Middleton, WI). Intracranial electrodes were recorded with an FCz reference. The scalp and intracranial EEG was typically viewed using a common average referential montage, in which the average reference was constructed using all the scalp electrodes except Fp1, Fp2, M1, and M2; none of the intracranial electrodes were included in the average.

For each patient, two-hour EEG segments during drowsiness and sleep were reviewed. Hippocampal spikes were visually identified on hippocampal depth channels, and the pattern of scalp EEG activity in the same time window was assessed by two experienced EEG readers (NPI, JXT) as either containing a small sharp spike, or not containing one. For this study small sharp spikes were defined by sharp, negative deflections with an amplitude less than 50 μV that lasted less than 50 ms and were found in one or more temporal scalp EEG channels; the duration and amplitude of a subsequent positive deflection, if present, was not considered in the assessment. Discrepancies were resolved by consensus.

To determine what fraction of small sharp spikes were associated with hippocampal spikes, we reviewed a one-hour scalp EEG segment in patients during drowsiness and sleep from a different night than the initial assessment. Small sharp spikes were identified on scalp EEG without reference to the intracranial recordings. SSS were counted only in hemispheres in which a

Table 1
Summary of findings in 27 patients. Abbreviations. SSS – small sharp spike, HFO – high frequency oscillation.

Patient #	SSS with hippocampal spike?	HFO associated?	Seizure localization	Side of Electrode
1	No	n/a	L hippocampal	Left
2	R: Yes L: No	Yes	Independent bilateral hippocampal	Bilateral
3	Yes	Yes	R hippocampal	Right
4	No	n/a	L hippocampal	Left
5	R: Yes L: No	Yes	R hippocampal	Bilateral
6	Yes	Yes	R hippocampal	Right
7	No (SSS delayed 30–60 msec)	n/a	Independent L hippocampal, L parietal	Left
8	R: Yes L: Yes	R: Yes L: Yes	R hippocampal	Bilateral
9	No	n/a	Independent bilateral hippocampal	Bilateral
10	No	n/a	L hippocampal	Left
11	No	n/a	Independent bilateral hippocampal	Bilateral
12	Yes	Yes	L temporal	Left
13	Yes	Yes	R hippocampal	Right
14	R: Yes L: Yes	R: Yes L: Yes	Independent bilateral hippocampal	Bilateral
15	R: Yes L: No	Yes	R hippocampal	Bilateral
16	Yes	No	L hippocampal	Left
17	No	n/a	R hippocampal	Bilateral
18	Yes	Yes	R lateral temporal	Right
19	No	n/a	Independent bilateral hippocampal	Bilateral
20	R: Yes L: No	Yes	Independent bilateral hippocampal	Bilateral
21	No	n/a	L mesial anterior temporal lobe	Left
22	No	n/a	bilateral mesial temporal onset	Bilateral
23	No	n/a	Bilateral hippocampal	Bilateral
24	R: Yes L: No	Yes	R hippocampal	Bilateral
25	No	n/a	R hippocampal	Right
26	Yes	Yes	R hippocampal	Right
27	Yes	Yes	R hippocampal interictal activity (no seizures recording during phase II recording)	Right