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SHORT COMMUNICATION

Laterality and temporal distribution of seizures in patients with bitemporal independent seizures during a trial of responsive neurostimulation

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Summary We describe seizure laterality and temporal seizure patterns in six subjects with bilateral temporal lobe epilepsy (bTLE) implanted with bilateral hippocampal depth electrodes and the NeuroPace RNS™ system over 84 consecutive days. Seizures were disproportionate in laterality in three subjects and disproportionate in time for two subjects. Clustering of seizures did not clearly affect laterality. Some but not all subjects with bTLE displayed nonrandom temporal or lateral clustering of seizures.
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Introduction

Epilepsy is a common neurological condition, with a lifetime prevalence of 0.5—1%. Approximately 2/3 of patients with epilepsy will achieve seizure control with antiepileptic medications; 1/3 are possible candidates for epilepsy surgery. Patients with unilateral mesial temporal lobe epilepsy (mTLE) are among the best surgical candidates, however there is substantial evidence from pathological, imaging, and electroencephalographic (EEG) studies that mTLE is often a bilateral disease, and 14—23% of patients show independent seizure onsets from both mesial temporal regions (So et al., 1989; Hirsch et al., 1991). These patients are generally not suitable surgical candidates.

Independent bitemporal seizure onset is largely determined by EEG monitoring. Because the duration of EEG monitoring is limited, these studies are prone to sampling bias. The number of seizure recordings needed to assure unilateral seizure onset is debated, and depends both on the proportion of seizures from each temporal lobe and tendency to cluster seizures from one temporal lobe as a result of short interseizure interval or other factors (Blum, 1994; Todorov et al., 1994; Haut et al., 1997, 2002; Choi et al., 2006).

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Table 1 Characteristics of subjects.

Subject	Gender	Age	Age of seizure onset	Etiology	MRI	History of intracranial monitoring prior to RNS?	Previous epilepsy surgery?	Previous VNS?
1	F	25	2	Febrile seizures	Bilateral MTS	No	No	No
2	F	42	15	Febrile seizures	Bilateral MTS	Yes	No	No
3	F	34	23	Meningo-encephalitis	None	No	No	No
4	M	50	21	Unknown	Left MTS	No	No	Yes
5	F	26	9	Meningo-encephalitis	None	Yes	No	Yes
6	M	34	8	Post-traumatic	Bilateral MTS and bilateral encephalomalacia	Yes	No	Yes

MTS = MRI findings characteristic of mesial temporal sclerosis.

We studied six subjects with known independent bitemporal seizure foci and chronically implanted depth electrodes as part of the NeuroPace RNS™ system trial. Our primary objective was to describe the probabilistic temporal and laterality patterns of seizure onset in patients with independent bitemporal seizure onsets using this unique data set of long-term ambulatory intracranial electroencephalography. A secondary objective was to explore the effect of interseizure interval (ISI) on the laterality of next seizure.

The results have direct implications for the presurgical evaluation of patients with refractory temporal lobe epilepsy.

Methods

Study design

This was a retrospective study of a consecutive series of subjects with independent, bitemporal onset seizures and chronically implanted hippocampal depth electrodes who were enrolled in the NeuroPace RNS™ System trial at Oregon Health & Science University or Swedish Medical Center. The RNS™ neurostimulator and depth electrodes were implanted at least 20 weeks prior to the 84-day data evaluation period of this study to eliminate any influence of immediate postoperative changes.

Subjects

Bilateral independent temporal lobe seizures were confirmed in all subjects by standard presurgical evaluation prior to RNS™ implantation. Three subjects had long term scalp EEG recordings only and three subjects had both scalp and intracranial EEG monitoring (Table 1). Subject characteristics are summarized in Table 1. All subjects had four contact depth electrodes stereotactically implanted along the longitudinal axis of each hippocampus. Depth electrode placement was confirmed by co-registration of pre-implant MRI and post-implant CT imaging.

Enrollment criteria for the RNS™ study required that subjects were 18—70 years of age and had medically refractory localization-related epilepsy (disabling simple partial, complex partial or secondarily generalized seizures) defined as lack of response to two or more antiepileptic medications. They had on average three or more disabling seizures per month for the three months prior to study entry and were on stable antiepileptic medication for 12 weeks prior to enrollment. Subjects were excluded from participation if they had primary generalized epilepsy, psychogenic nonepileptic events or substantial psychiatric disease in the year prior to enrollment, a clinically significant or unstable medical condition or progressive central nervous system disease.

ECoG data

Subjects used a data transmitter daily to upload four, 90 s ECoGs to a secure central data repository: the Patient Data Management System (PDMS). ECoGs were automatically stored for each seizure containing low-voltage fast activity or rhythmic sharp activity that continued for at least 30 s and was distinct from the ECoG background activity, based on pre-defined parameters that had been optimized over the preceding 20 weeks and that remained unchanged throughout the 84-day data evaluation period. Seizures were detected and ECoGs stored regardless of clinical symptoms. A specific clinical seizure could be marked and stored by the subject or caregiver by swiping a magnet over the device at the time of the event.

Definition and identification of seizures

All ECoG data stored by the RNS over the 84-day data evaluation period were reviewed by two board certified electroencephalographers (DS and MS). Determination of whether an ECoG pattern represented a seizure and laterality of each seizure was by consensus. Most of the recorded seizures were similar in morphology to those observed during patient-reported seizures. Conservative criteria were applied so that repetitive focal spiking and short duration events (<10 s) were not recorded as seizures. Each identified seizure was described by date and time of onset, and laterality of seizure onset. Interseizure interval (ISI) was determined by calculating the time interval between seizure recordings on PDMS.

Data analysis

We assessed the probability that observed seizures were random samples from subjects with equal likelihood of seizures from either side using a binomial test. To assess whether the laterality sequence of seizures was random, we used the nonparametric run test on each subject's series of seizures. Temporal distribution of seizures was assessed by testing the fit of the distribution of time intervals between seizures to an exponential distribution with a Kolomogorov Smirnov test (Ogburn and Brown, 2003).

The relationship between interseizure interval (ISI) and laterality of seizure pairs was descriptive in nature due to the