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Different seizure-onset patterns in mesiotemporal lobe epilepsy have a distinct interictal signature

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HIGHLIGHTS

- We analyzed the interictal signature of the two most common temporal lobe seizure-onset patterns.
- Despite interindividual variability, both seizure-onset patterns show distinct interictal epileptiform discharge morphology.
- This suggests that spike morphology is a marker of the underlying mechanisms of seizure generation.

ABSTRACT

Objective: Experimental research demonstrated that distinct underlying mechanisms go along with different seizure-onset patterns on EEG. These different mechanisms may reflect different tissue abnormalities which, we hypothesize, could also be reflected in morphological differences in the interictal epileptic and background EEG activity.
Methods: We searched our database of intracranial EEG recordings for mesiotemporal lobe epilepsy patients with either predominant low-voltage fast activity (LVF) or periodic spiking (PS). Interictal epileptiform discharges (IEDs) were characterized by the spike/polyspike amplitude, the amplitude of the post-spike slow wave, and the associated low-frequency and high-frequency power increases. The EEG background was assessed with the root mean square amplitude, the distribution of the instantaneous amplitude relative to the root mean square value, and the power spectral density.
Results: We identified 18 patients with predominant LVF or PS. IEDs in PS were 1.7-times sharper as determined by the high-frequency power increase than IEDs in LVF. In contrast, IEDs in LVF had a 1.2-times higher post-spike slow wave amplitude, and a 1.5-times larger low-frequency power content than IEDs in PS. There was no difference in rates of IEDs/HFOs, spike amplitude, HFO co-occurrence, and EEG background.
Conclusions: We demonstrated an association between the morphology of IEDs and the type of the seizure-onset pattern in mesiotemporal lobe epilepsy.
Significance: Our findings therefore suggest that IED morphology is a marker of the underlying mechanisms of seizure generation.

1. Introduction

Different seizure-onset patterns (SOP) have been described in intracranial EEG. A recent meta-analysis demonstrated the variety of SOPs in focal epilepsy, and concluded that low-voltage fast activity (LVF) is overall the most common, whereas high-amplitude low-frequency periodic spiking (PS) is the most prevalent in mesiotemporal lobe epilepsy (mTLE) (Singh et al., 2015). In a large series of patients with refractory focal epilepsy due to different pathologies, our group identified seven different intracerebral SOPs (Perucca et al., 2014). Except for PS, observed only in the mesiotemporal lobe, and delta brush, rare and occurring exclusively in focal cortical dysplasia, the remaining SOPs were neither specific to brain pathologies nor brain regions (Perucca et al.,

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2014). It therefore seems that distinct epileptogenic lesions can adopt the same mechanisms underlying seizure generation.

In TLE, the two most frequently described SOPs are LVF and PS (Perucca et al., 2014; Spencer et al., 1992a, 1992b; Engel, 1993; Park et al., 1996; Spanedda et al., 1997; Velasco et al., 2000; Wennberg et al., 2002). Various studies of the last years suggested differences between both SOPs regarding neurophysiological, neuropathological, clinical, and neuroimaging properties: PS shows a more focal rather than regional seizure onset, slower spread to the contralateral mesiotemporal structures, greater neuronal loss in the resected hippocampal tissue, and a better surgical outcome than LVF (Perucca et al., 2014; Spencer et al., 1992b; Park et al., 1996; Velasco et al., 2000; Wennberg et al., 2002; Schuh et al., 2000; Ogren et al., 2009). Also, a structural MRI study demonstrated that the extent of extra-hippocampal structural alterations differs between the two patterns: PS primarily involves the hippocampus, but LVF also involves the lateral temporal and orbitofrontal cortices (Memarian et al., 2015). Moreover, it is known for many years that both have different underlying mechanisms: PS seems to result from neuronal hypersynchronization in combination with increased inhibition, whereas LVF is associated with increased local neuronal firing due to either disinhibition or hyperexcitation (Babb and Crandall, 1976; Babb et al., 1987; Engel, 1990). Recent studies in animal models of mTLE showed that the LVF pattern mainly results from the synchronous activity of γ-aminobutyric acid-releasing cells, whereas the PS pattern reflects principal neuron firing via glutamatergic mechanisms (Salami et al., 2015; Shiri et al., 2015). In line with these findings, it was demonstrated that specific high frequency oscillation (HFO) patterns are associated with these two types of SOPs: ripples (>80 Hz), which are thought to reflect summated inhibitory postsynaptic potentials generated by pyramidal cells in response to inhibitory interneuron firing, predominate during LVF seizures, and fast ripples (>250 Hz), which are believed to mirror the hypersynchronous bursting of principal (glutamatergic) cells, predominate during PS seizures (Levesque et al., 2012).

Because of the increasing evidence suggesting different underlying pathophysiological mechanisms for LVF and PS in mTLE, we hypothesized that the interictal patterns [interictal epileptiform discharges (IEDs), HFO rates, and background activity] present in patients showing either SOP might show differences as well. This study aimed to determine whether specific SOPs have a distinct interictal epileptic and background signature. The answer to this question might be of importance when considering, for instance, antiepileptic drug therapy tailored to the underlying epileptic mechanisms. We studied subjects with mesiotemporal seizure-onset only; this in order to avoid a potential influence of localization, and compared the two most common encountered SOPs in mTLE, LVF and PS.

2. Materials and methods

2.1. Patient selection

Patients were selected from our database of intracranial EEG recordings performed with a 2000 Hz sampling rate, acquired during work-up for epilepsy surgery in patients with pharmacoresistant focal epilepsy between November 2004 and April 2015. We selected all patients with uni- or bilateral mTLE (lesional or non-lesional) who had one predominant (>75%) SOP of either LVF or PS in a minimum of three clinical seizures during the continuous intracerebral EEG recording. LVF was defined as a clearly visible low voltage rhythmic activity over 10 Hz preceded or not by one spike-and-wave complex (Velasco et al., 2000; Memarian et al., 2015). PS was defined as a periodic continuous or discontinuous medium to high-voltage spiking activity at 0.5–2 Hz lasting over 5 s (Perucca et al., 2014; Spencer et al., 1992b; Velasco et al., 2000).

Forty-nine patients with an epileptic generator in the mesiotemporal lobe structures were identified. Nineteen patients met exclusion criteria. The remaining 30 patients had one or the other pattern of interest during their seizures, but in 12 neither LVF nor PS predominated, i.e. none was present in >75% of the total number of seizures recorded. Therefore, we ended with 18 subjects with a clear-cut predominant LVF ($n = 8$) or PS ($n = 10$) pattern.

This study was approved by the Review Ethics Board at the Montreal Neurological Institute and Hospital. All patients signed a written informed consent prior to study participation.

2.2. Intracerebral EEG recordings

Stereo-EEG (SEEG) electrodes were implanted stereotactically using an image-guided system. Electrode locations were determined by either per-implantation CT co-registered with a pre-implantation MRI using Statistical Parametric Mapping 8 software ($n = 8$), the information from the reconstructed planned position of the electrodes from the Neuronavigation System ($n = 6$), per-implantation MRI ($n = 2$) or post-explantation MRI ($n = 2$). Intracerebral electrode positions were tailored for each patient. The EEG signal was high pass-filtered at 0.1 Hz, low-pass filtered at 500 Hz, and sampled at 2000 Hz. EEG were recorded using the Harmonie EEG system (Stellate, Montreal, QC, Canada).

2.3. Selection of interictal segments

IEDs and HFOs with frequencies ranging from 80 to 500 Hz were evaluated in intracerebral channels inside the seizure-onset zone (defined by the clinical neurophysiologist interpretation at the time of stereo-EEG investigation). A 10-min interictal segment was selected for each patient during NREM sleep, with no clinical seizure 12 h before or 6 h after it. Asymptomatic EEG seizures had to be absent in the 2 h before and after the selected segment. The first suitable segment fulfilling these criteria, which was obtained at least 72 h after electrode implantation was used for analysis. In the same interictal segments, we marked periods with no IEDs to define the interictal EEG background. In each patient, 30 s of EEG activity with no IEDs were marked as six blocks of 5 s. The blocks were selected consecutively if possible. This background was used in two ways, as a reference against which to compare the IEDs amplitude and power, and to compare background characteristics in the LVF and PS groups.

2.4. Assessment of IEDs and HFOs

Bipolar montages from one s-EEG electrode contact to the neighboring contact were used. IEDs were visually identified in the intracerebral EEG channels of the seizure-onset zone by one board certified electrophysiologist who was blinded to the type of SOP. We evaluated only isolated IEDs, defined as having a minimum inter-IED distance of 1 s. The marking was performed in the channel of the seizure-onset zone showing the highest IED amplitude, as assessed in a referential montage. A maximum of three different IED sets was marked for each patient. The IEDs were marked as events with duration, including the post-spike slow wave if present. The rate of IEDs was computed in each patient combining all the IED subsets' rates during the 10-min interictal segment.

Ripples (>80 Hz) and fast ripples (>250 Hz) were visually marked in the same channel identified for the marking of IEDs inside the seizure-onset zone – using also a bipolar montage – by one scorer who was blinded to the type of SOP during the first 5 min of the interictal EEG segments (for further information of