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When spikes are symmetric, ripples are not: Bilateral spike and wave above 80 Hz in focal and generalized epilepsy

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HIGHLIGHTS

- Scalp ripples can be used as an additional tool to lateralize the epileptic focus in secondary bilateral synchrony.
- In idiopathic generalized epilepsy scalp ripples are recordable and show an anterior dominance.
- To differentiate focal patients with secondary bilateral synchrony from patients with idiopathic generalized epilepsy scalp ripples are not useful.

ABSTRACT

Objective: To evaluate scalp ripples distribution in secondary bilateral synchrony as a tool to lateralize the epileptic focus and to differentiate focal from generalized epilepsy.
Methods: Seventeen EEG recordings with bilateral synchronous discharges of focal (focal group-FG: 10) and generalized (generalized group-GG: 7) epilepsy patients were selected for spikes and ripples marking; the spike-normalized ripple rate was calculated in each hemisphere (right/left – anterior/posterior) and a ripple-dominant hemisphere (the one with the highest rate) was identified. Concordance in FG between the ripple dominant hemisphere and the hemisphere of clinical lateralization was evaluated. The ripple-dominant/ripple-nondominant spike-normalized ripple rate ratio was studied to compare groups.
Results: In FG the hemisphere of clinical lateralization and the ripple-dominant hemisphere were 100% concordant. In GG only 3/7 patients showed ripples (vs 10/10 FG), all with anterior dominance. No difference in hemisphere ripple dominance between groups was found.
Conclusions: Ripples in secondary bilateral synchrony help to lateralize the epileptic focus but do not help to differentiate between focal and generalized epilepsy. This is the first report of visually identified ripples in idiopathic generalized epilepsy.
Significance: Ripples confirm the clinical lateralization of the epileptic focus in secondary bilateral synchrony but cannot distinguish between focal and generalized epilepsy.

1. Introduction

Bilateral synchronous spike and wave activity can be found on the scalp EEG of patients with focal and generalized epilepsy. The expression "secondary bilateral synchrony" (SBS) (Tukel and Jasper, 1952) implies that in focal epilepsy the generalized synchronous spike and wave discharge is triggered by an epileptic

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discharge in a localized area of the brain, whereas "primary bilateral synchrony" refers to a discharge triggered by bilateral subcortical-cortical interactions. On scalp EEG, secondary and primary bilateral synchrony can look similar; many studies tried to find differences by investigating specific features of the standard frequency EEG, such as time difference in interictal epileptiform discharges (IEDs) between hemispheres (Gotman, 1981; Kobayashi et al., 1992) and spike and wave morphological features (Tukel and Jasper, 1952; Blume and Pillay, 1985), but it remains still challenging for clinicians to distinguish on the basis of standard EEG if there is a focality or not.

The neurophysiological basis of SBS is still not completely understood. The thalamic (Penfield and Jasper, 1954) and callosal connections (Musgrave and Gloor, 1980; Gotman, 1981) are thought to have a role in the propagation of the discharge from the cortical foci. Diffuse encephalopathy (Gloor, 1969) and multiple foci (Blume and Pillay, 1985) were suggested to facilitate bisynchronous epileptic discharge. To differentiate between patients with focal and generalized epilepsy is fundamental regarding the medical therapeutic options and regarding surgery in pharmacoresistant patients (Engel et al., 2003). In the last decade, studies on frequencies above the standard scalp EEG range (0.1–70 Hz) opened a promising research area. Scalp ripples (>80 Hz) have been recorded in generalized epilepsy (Kobayashi et al., 2010, 2015), and are emerging as a new biomarker of the seizure onset zone (SOZ) in focal epilepsy, being more specific markers than interictal spikes (Andrade-Valenca et al., 2011; Melani et al., 2013). These findings, as demonstrated earlier in intracranial EEG studies (Jirsch et al., 2006; Urrestarazu et al., 2007; Jacobs et al., 2008, 2010; Wu et al., 2010; Akiyama et al., 2011), suggest a potential role of scalp HFOs in identifying an epileptic focus in patients affected by focal epilepsy.

Our goal is to determine if fast oscillations, namely ripples, could lateralize the origin of SBS. We also aim to assess if ripples could be recorded on an adult population of patients affected by IGE and if their distribution in bilateral synchronous IEDs differ between IGE and focal epilepsy patients.

2. Methods

2.1. Patient selection

From January 2011 all patients admitted in the EEG-telemetry Unit of the Montreal Neurological Hospital had one EEG recording sampled at 1000 Hz which was performed during the second night of telemetry. These EEGs are collected in a database from which we selected consecutive recordings of patients affected by focal or generalized epilepsy with predominantly bilateral synchronous spike and wave activity on a previous scalp EEG recording.

Patients were divided into two groups: focal group (FG), with focal epilepsy, and generalized group (GG), with generalized epilepsy. The diagnosis was made based on clinical, neurophysiological and neuroimaging data by attending staff physicians. Exclusion criteria were unclear diagnosis, severe encephalopathy, artefacts interfering with the scoring of ripples, or absence of IEDs in the EEG recording sampled at 1000 Hz.

2.2. Recording methods

EEGs were obtained using the Harmonie monitoring system (Stellate, Montreal, QC, Canada), with a 300 Hz low pass filter and a 1000 Hz sampling rate. Electrodes were placed according to the 10–20 system and recorded with CPz as reference; a bipolar anterio–posterior montage was used for review (Fp1-F3, F3-C3, C3-P3, P3-O1, Fp1-F7, F7-T3, T3-T5, T5-O1, and symmetrically in the right hemisphere).

The analysis in each patient was made during 30 min of N2 and N3 sleep, manually scored according to AASM 2.0 (Berry et al., 2012) by an electrophysiologist with board certification in sleep medicine.

To equalize as much as possible IED duration throughout all the patients (as it is known that HFOs on scalp EEG occur most often at the time of IEDs – Melani et al., 2013) we applied this criterion: for each EEG we analyzed the first consecutive 10 min of the N2 and N3 sleep and if 10 IEDs (see "marking of IEDs and fast oscillations" section) were present we also selected for the ripple analysis the following consecutive 20 min of N2 and N3 sleep (this was valid for all patients included in the FG and for two patients in the GG); if there were less than 10 IEDs in the first 10 min we further selected, in the same night recording, N2 and N3 sleep EEG sections where IEDs were identified (with a duration of a few minutes around each IED) to reach a total time of 30 min per patient.

Sleep recordings were chosen because they: (1) present less movement artefacts, (2) have higher ripple rate (Staba et al., 2004; Bagshaw et al., 2009; Dümpelmann et al., 2015) and (3) show higher incidence of SBS (Blume and Pillay, 1985). We excluded from the analysis sections with arousals, awakenings and artefacts. When selecting sections, we also excluded 5 s before and after each major artefact seen in the unfiltered EEG. Channels with a considerable amount of artefacts interfering with ripple identification were also excluded.

To minimize the effects of seizure on the EEG we analyzed only recordings at least 2 h before and after a clinical seizure (electrographic seizures were not considered, but they were excluded from the analysis).

2.3. Marking of IEDs and fast oscillations

We applied a similar methodology for ripple marking as described in our previous scalp EEG papers (Andrade-Valenca et al., 2011; Melani et al., 2013). IEDs were identified using a bipolar montage with 10s/page time scale, and an amplification of 7.50 μV/mm. Spikes, sharp waves, spikes and slow waves complexes, polyspikes and polyspikes and slow wave complexes were marked. The mark was made from the beginning of the negative or positive deflection to the return at baseline in all channels where IEDs were identified. If consecutive IEDs were present, without a background activity interval, we considered the event as a single IED (Fig. 1). Considering the diffuse IED distribution in our patients, we selected for further analysis all channels for the period of the longest IED identified in the bipolar montage (Fig. 1).

Ripples (>80 Hz) were then marked with the IED marking invisible. We used a high-pass filtering at 80 Hz and a low-pass filtering at 200 Hz; a finite-impulse response filter was applied to minimize ringing. Ripples were defined as at least four consecutive fast oscillations (> 80 Hz and < 200 Hz) that clearly stand out of the background.

After the EEGs were reviewed twice by one reviewer, each mark was cross-checked by a second reviewer. In ambiguous cases, a consensus was reached by both reviewers.

2.4. Artefact identification

A three-step analysis was carried out in order to avoid contamination with artefacts: (1) we excluded from the analysis all the channels with malfunctions or continuous artefacts (Andrade-Valenca et al., 2011) and in the channels selected for analysis we excluded each visible artefact (muscle, electrodes artefacts) on the raw EEG at 10 s/page time scale prior to beginning the ripple analysis; (2) we took the morphology of the oscillations into