Clinical Neurophysiology 127 (2016) 143–149

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Relationships between interictal epileptic spikes and ripples in surface EEG

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ARTICLE INFO

Article history:
Accepted 16 April 2015
Available online 7 May 2015

Keywords:
Electroencephalography
Epilepsy
Non-invasive EEG
Ripples
Spikes
High frequency oscillations

HIGHLIGHTS

- 64% of the ripples start before the spike starts.
- Spikes with ripples are on average shorter, and have higher amplitude and slope.
- Ripples in surface EEG have a smaller spatial spread than spikes.

ABSTRACT

Objective: Ripples (80–250 Hz) have been shown to be a more specific biomarker for the epileptogenic zone than epileptic spikes in intracranial EEG and even surface EEG. Ripples often co-occur with spikes. We investigated the spatiotemporal relation between spikes and ripples, and differences between spikes that do and do not co-occur with ripples.
Methods: We marked 50 time points with spikes in bipolar surface EEG during NREM sleep in patients with focal or multifocal epilepsy. We marked ripples that occurred with spikes and calculated parameters relating spikes and ripples: the duration, amplitude and slope of spikes, the timing of the start of ripples and spikes and the proportion of overlap.
Results: In total 219 ripples and 5995 individual spikes were marked in 31 patients. Spikes with ripples were on average shorter, had higher amplitude and higher slope than spikes without ripples. 64% of ripples started before spikes started. Spikes occurred on 13 (5–26) channels per patient, and ripples on 3 (0–14) channels, which were also spike channels.
Conclusion: Ripples precede rather than follow spikes, so ripples are unlikely to result from spikes.
Significance: Ripples and spikes seem not one-on-one coupled, but certain states of the brain can accommodate both.

1. Introduction

High frequency oscillations (HFOs, >80 Hz) in invasive intracranial recordings are newly proposed biomarkers for the brain area that generates seizures (Zijlmans et al., 2012; Jacobs et al., 2012; Bragin et al., 1999). HFOs are more specific for defining the epileptogenic zone than spikes (Jacobs et al., 2009). In line with this finding, they seem to be more related to disease activity (Zijlmans et al., 2009, 2011) and possibly predict outcome after epilepsy surgery (Jacobs et al., 2010; Van't Klooster et al., 2015).

HFOs between 80 and 250 Hz, called ripples, can also be found in the non-invasive surface electroencephalogram (EEG). This increases the population for whom HFO analysis is available, beyond the small group of drug-resistant focal epilepsy patients who are candidates for surgery with intracerebral electrodes. Reports describe 50–100 Hz activity in ictal recordings (Kobayashi et al., 2004, 2009), ripples in interictal EEG in adults with focal epilepsy (Andrade-Valenca et al., 2011; Melani et al., 2013; Zelmann et al., 2013), in children with continuous spike and wave in slow-wave sleep (Kobayashi et al., 2010), and idiopathic partial epilepsy (Kobayashi et al., 2011). A recent study showed that interictal surface ripples decrease after treatment

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http://dx.doi.org/10.1016/j.clinph.2015.04.059
1388-2457/

with ACTH in children with West Syndrome (Kobayashi et al., 2015). Co-occurrence of ripples with epileptic spikes is reported in 44–64% of all ripples in intracranial and surface recordings (Melani et al., 2013; Andrade-Valenca et al., 2011; Urrestarazu et al., 2007; Jacobs et al., 2009; Wang et al., 2013). Ripples co-occurring with a spike are more related to the seizure onset zone than ripples without a spike (Wang et al., 2013).

There seems to be a relation between ripples and spikes, but so far no study addressed this important aspect in detail. Knowledge about this relation could help to get insight into the mechanisms of ripple generation and the clinical relevance of the coupling between ripples and spikes. Our goal was to further investigate the relationship between ripples and epileptic spikes in non-invasive surface EEG. The two main research questions were: Are there differences between spikes that show and those that do not show a ripple at the same time? What is the temporal and spatial relation between spikes and ripples?

2. Methods

2.1. Patients

We included adult patients with focal or multifocal epilepsy who were admitted to the EEG-telemetry unit of the Montreal Neurological Hospital, and showed more than one epileptic spike or sharp wave per minute during N2 or N3 sleep. Patients who only showed polyspikes were excluded because of the difficulty in assessing the relationship between the ripple and the spike. We consecutively included patients from September 2014 back in time until more than a total number of 200 ripples were marked, a number which we thought was sufficient to assess spike-ripple relationship. All patients gave informed consent in agreement with the Research Ethics Board of the Montreal Neurological Institute and Hospital.

2.2. EEG recording, data selection and event marking

Recordings were performed with the Harmonie system (Stellate, Montreal, Canada) with electrodes placed according to the 10–20 EEG system, with additional zygomatic and F9/F10, T9/T10 and P9/P10 electrodes and FCz as reference. The low pass filter was set at 300 Hz and the sampling frequency at 1000 Hz. We used the recording of the second night after admission. Typically the whole night (9 pm–9 am) was recorded. We selected epochs of N2 and N3 sleep. Sleep stages were marked according to the American Academy of Sleep Medicine (AASM) criteria (Berry et al., 2012) by one reviewer and checked and discussed with a second reviewer.

We manually marked 50 consecutive time points with spikes in each patient in N2 or N3 sleep, starting at the first sleep cycle of that night. Epochs within two hours before or after a seizure were excluded. The first 50 time points with spikes were marked (Fig. 1, vertical lines); they usually occurred in the first sleep cycle, but could extend beyond. The length of the epochs therefore differed per patient, because it depended on the spike rate. The spikes were marked in a bipolar montage with a 15 s/page time scale and a 10 μV/mm amplitude scale. Spikes were marked on the individual channels as well, to allow for comparison with ripples on specific channels (Fig. 1, horizontal lines). Only isolated spikes were marked: spikes occurring within 1 s from a marked spike were excluded, as were spikes including artefacts.

Subsequently, ripples were manually marked in a 400 ms time window around each spike in a bipolar montage with an 80 Hz finite impulse response (FIR) high pass filter, at a 1.5 s/page time scale and a 1 μV/mm amplitude scale. Ripples were marked by one reviewer and checked and discussed with a second reviewer. We defined a ripple as at least four oscillations above 80 Hz, which were clearly distinct from the background EEG. We did not use a maximum number of oscillations or maximum duration because surface EEG ripples are generally short. Ripples with irregular frequency or amplitude morphology were suspicious to be artefacts and were therefore not marked.

2.3. Data analysis

All statistics were calculated with IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered significant.

2.3.1. Spike characteristics

We determined the amplitude, duration, and slope of the first and second half-wave of each spike (Fig. 2). Since spikes are positive or negative in the bipolar montage, we refer to the first and second half-wave (FHW and SHW) instead of the ascending and descending slope. Spikes with a ripple on the same channel at the same time were considered as co-occurring. Differences in the characteristics between spikes with and without ripples were investigated with the Mann Whitney U test. We recalculated the statistics in a second way to assess the robustness of our results. (1) We recalculated statistics with a maximum of seven ripples per patient, to reduce the influence of patients with many ripples. This number was chosen as it was the average number of ripples per patient. (2) We recalculated statistics with the same number of spikes with and without ripple, because the original number of spikes without ripples was much higher than the number of spikes with ripples.

2.3.2. Temporal relation between spikes and ripples

We marked the start and end of each spike and ripple. The start of a spike was defined as the beginning of the steep phase preceding the apex, and the end as the end of the steep phase following the apex. The start and end of a ripple were defined as the start and end of the first and last oscillations that stood out from baseline (Fig. 2). We measured the difference in time between the start of the ripple and the start of the accompanying spike and tested significance with the Mann Whitney U test. Also, we measured the percentage of time during which a ripple was present before the spike, on the FHW, on the SHW and after the spike (Fig. 2). Differences were examined with the Kruskal Wallis test and post hoc pairwise comparisons.

As a second step, we investigated if the ripple and spike relation is time-locked for spikes of a given channel. We averaged all spikes with ripples on individual channels, if at least five of those spikes with ripples existed on that channel. The trigger point of the average was the apex of the spike.

2.3.3. Spatial relation between spikes and ripples

We determined the number of channels that showed spikes and that showed ripples in each patient and tested the difference with a Wilcoxon Signed Rank test. We specifically looked at the ripples that occurred at the same time as spikes, but on a different channel, because these can cause a difference in spatial distribution between ripples and spikes. We calculated the difference in duration between ripples with and without a spike on the same channel with a Mann Whitney U test.

3. Results

3.1. Patients

We included 31 patients with focal or multifocal epilepsy to reach a total number of 219 ripples (Table 1). The average age of