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Measuring spike strength in patients with continuous spikes and waves during sleep: Comparison of methods for prospective use as a clinical index

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HIGHLIGHTS

- Assessment of epileptiform EEG activity in the patients with continuous spikes and waves during sleep (CSWS) needs new objective measures.
- Strength of epileptiform spikes during sleep offers a method complementary to previously used spike index.
- Spatial integration over multiple electrodes during steady NREM sleep renders the measures of spike strength stable enough for clinical use.

ABSTRACT

Objective: To compare methods of estimating spike strength as a potential index in the assessment of continuous spikes and waves during sleep (CSWS).
Methods: Spikes were searched and averaged automatically from pre- and postoperative EEGs of ten patients with CSWS who underwent corpus callosotomy (eight) or resective epilepsy surgery (two). From the most prominent spike, we measured peak amplitude and root mean square (RMS) over ±150 ms window around the peak. In order to compensate for spatiotemporal instability of spikes, the cumulative amplitude and RMS were computed from the highest quartile of electrodes (Ampl-Q and RMS-Q, respectively). The stability of parameters was studied by comparing two ten minute epochs during the first hour of NREM sleep, as well as by analyzing overnight variation of indices in further ten patients with CSWS. The Ampl-Q and RMS-Q were compared between pre- and postoperative recordings.
Results: All four measures, amplitude, RMS, Ampl-Q and RMS-Q, were correlated with each other and highly dependent on NREM/REM-sleep stage and arousals. Expectedly, Ampl-Q and RMS-Q had the greatest intra-individual stability. The amplitude had up to 71% intra-individual variation making it unhelpful for clinical use. Ampl-Q and RMS-Q were comparable in assessing change following surgical treatment.
Conclusions: Computing an integrated RMS over multiple electrodes during steady NREM sleep offers a stable and reliable parameter for evaluating the strength of spikes in CSWS.
Significance: Analyzing spike strength with RMS-Q may offer a clinically useful, supplementary index for EEG monitoring of CSWS where spike index has been of limited value.

1. Introduction

Epilepsy with continuous spikes and waves during sleep (CSWS) is a pediatric epileptic encephalopathy, which is characterized by abundant spike-and-wave discharges during slow wave sleep and eventually seizures (Patry et al., 1971; Tassinari et al., 2000, 2009; Loddenkemper et al., 2011). Electrographic diagnosis of CSWS is commonly defined by estimating the amount of spiking (a.k.a. spike index, SI) in the sleep EEG. Different threshold values from 25% to classical 85% of the NREM sleep have been used (Patry et al., 1971; Tassinari et al., 2000; Inutsuka et al., 2006; Van Hirtum-Das et al., 2006; Scheltens-de Boer, 2009; Saltik et al., 2005; Sánchez

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Fernández et al., 2012). Treatment of CSWS is challenging (Inutsuka et al., 2006; Aeby et al., 2005; Kramer et al., 2009; Loddenkemper et al., 2009; Liukkonen et al., 2010; Peltola et al., 2011; Veggiotti et al., 2012), and it is further complicated by difficulties in assessing treatment response. Several methodological studies have devised, optimized and tested semiautomatic tools for calculating SI (Chavakula et al., 2009, 2013; Larsson et al., 2009, 2010b; Nonclercq et al., 2012; Peltola et al., 2012; Sánchez Fernández et al., 2012). However, during the course of CSWS, it is uncommon to find a direct correlation between SI and clinical parameters, such as cognitive and behavioral impairments or seizure frequency (Morikawa et al., 1985; Hommet et al., 2000; Sánchez Fernández et al., 2012). Hence, there is an obvious need for developing EEG-based measures that could capture aspects of epileptiform activity other than the temporally cumulating number of spikes measured by SI.

One straightforward and often implicitly estimated EEG feature is the strength, or magnitude, of the epileptic spikes. Using spike strength as a measure gains support from earlier studies reporting how reduction in discharge propagation and/or in the spike amplitude after medical or surgical treatment correlates with a favorable outcome (Larsson et al., 2010a; Peltola et al., 2011). Physiologically, the spike amplitude is considered to express the strength of the epileptic source by combining both the spatial extent and the density of synchronously acting neuronal networks. Such a measure is mechanistically distinct from SI, which reflects the firing activity of neurons involved in the epileptic network irrespective of how strongly and/or widely each individual spike is recruiting the cortical networks. (Cooper et al., 1965; Kobayashi et al., 2005; Tao et al., 2005; Cosandier-Rimélé et al., 2008).

There are several technical paradigms to measure spike strength from multichannel EEG, and better understanding of their characteristics, especially of the stability and sensitivity is essential before introducing the measure into clinical studies. The present study was set out to compare four technical paradigms: Two paradigms measured only the EEG channel with highest spike (peak amplitude and root mean square (RMS)). The other two measures were integrated amplitude and RMS over the highest quartile of channels (Ampl-Q and RMS-Q, respectively), in order to find a balance between spatial specificity of the measure and spatiotemporal variability of the spike propagation.

2. Methods

2.1. Patients

The first part of this study was based on previously published 13 patients with epileptic encephalopathy with CSWS and structural etiology who underwent epilepsy evaluation and surgery during 1991–2005 at the Helsinki University Central Hospital (data set 1) (Peltola et al., 2011). The diagnosis of epileptic encephalopathy with CSWS was based on continuous spike-and-waves occupying at least 85% of NREM sleep in the overnight video-EEG combined with developmental regression, with or without clinical epileptic seizures. These criteria are consistent with the definition of ILAE Task Force on Classification and Terminology (Engel, 2006). The SI was estimated visually by counting the discharge free episodes of minimum duration of ten seconds in the overnight EEG. All patients had either uni- or multifocal bilaterally propagated CSWS preoperatively.

For the present study, we included those ten patients for whom both pre- and postoperative digital EEG recordings were available. Eight of these patients had undergone corpus callosotomy and two focal resections. The EEG and clinical details of the patients are summarized in Supplementary Table S1. Eight patients (numbers 1–5, 7–9 in Supplementary Table S1) had cognitive benefit and over 90% reduction of seizures postoperatively.

In the second part of this study, we analyzed ten EEGs of nine patients with CSWS in whom the whole night recording was available (data set 2). Four of the patients had structural etiology. The recordings were selected randomly from the database of the Epilepsy Unit of the Helsinki University Central Hospital among the patients with suspected or previously diagnosed CSWS between 2006 and 2010. The EEG and clinical details of the patients are summarized in Supplementary Table S2.

2.2. EEG

The EEG data was recorded at 200 Hz with a Telefactor® by using 26–35 scalp electrodes placed according to the International 10–20/10–10 system. The data was viewed and analyzed with the Brain Electrical Source Analysis software version 5.3 (BESA, MEGIS GmbH, Gräfelfing, Germany) (Scherg et al., 2002; Bast et al., 2004). Two epochs of ten minutes during the first hour of NREM sleep were selected randomly from the preoperative EEG (data set 1, Fig. 1A) and one epoch from the postoperative EEG without controlling the stage of NREM sleep. The EEG analysis of the data set 2 was made over the whole night recording.

2.2.1. Spike search

The most prominent spike focus was identified, and the signal was filtered with a 2 Hz forward low-cut filter (6 dB/oct) and 40 Hz zero-phase high-cut filter (24 dB/oct; both filters are built-in functions of BESA® software). A representative typical spike with a fast rise time and high amplitude was chosen for an index spike ("template") for the spatiotemporal pattern search as described earlier (Larsson et al., 2009; Peltola et al., 2012; Bast et al., 2004). Spike search was done using the virtual average montage over all channels with a correlation percentage of 60%. This montage is a standard option in BESA® software, based on estimating the voltage at defined locations of a sphere using spherical spline interpolation from the original EEG signal. Duration of time window for averaging was ± 150 ms around the peak of the largest spike. Baseline was defined from the first 50 ms of the averaging window.

For the data set 1, three different spike averages were computed from the first ten minute epoch of the preoperative EEG data: two averages containing only half of the spike matches, either even or odd spikes, and an average of all spike matches. Only one spike average which included all spike matches was computed from the second ten minute epoch of the preoperative data and from the postoperative data.

For the data set 2, we examined the temporal variation of spike metrics from time series computed by averaging consecutive spikes using a sliding window over the whole night sleep. Akin to the analysis of dataset 1, each individual spike magnitude was first calculated from the ± 150 ms window around the peak of the largest spike. In order to further assess the stability of measures, we computed time courses of averages using different numbers of consecutive spikes (n = 1, 5, 9, 49, and 499).

The average spike epochs were viewed in a virtual Laplacian montage of 27 electrodes (built in function in BESA® software) and exported as ASCII files into Excel 2010® for further analysis.

2.3. Measures of spike strength

We employed four measures of spike strength, two based on single channel, and two based on the combination of channels that together accounted for the highest quartile of spike strength. The latter measures, Ampl-Q and RMS-Q, were introduced to find compensation to the commonly observed spatiotemporal variation of spikes on amplitude related parameters.