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Evoked versus spontaneous high frequency oscillations in the chronic electrocorticogram in focal epilepsy

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HIGHLIGHTS

- SPES elicits SOZ-specific fast ripples in patients, even in absence of spontaneous HFOs.
- The SOZ is characterized by similar percentages of evoked and spontaneous HFOs.
- SPES cannot disentangle pathological from physiological ripples in functional areas.

ABSTRACT

Objective: Spontaneous high frequency oscillations (HFOs; ripples 80–250 Hz, fast ripples (FRs) 250–500 Hz) are biomarkers for epileptogenic tissue in focal epilepsy. Single pulse electrical stimulation (SPES) can evoke HFOs. We hypothesized that stimulation distinguishes pathological from physiological ripples and compared the occurrence of evoked and spontaneous HFOs within the seizure onset zone (SOZ) and eloquent functional areas.
Methods: Ten patients underwent SPES during 2048 Hz electrocorticography (ECoG). Evoked HFOs in time–frequency plots and spontaneous HFOs were visually analyzed. We compared electrodes with evoked and spontaneous HFOs for: percentages in the SOZ, sensitivity and specificity for the SOZ, percentages in functional areas outside the SOZ.
Results: Two patients without spontaneous FRs showed evoked FRs in the SOZ. Percentages of evoked and spontaneous HFOs in the SOZ were similar (ripples 32:33%, $p = 0.77$; FRs 43:48%, $p = 0.63$), but evoked HFOs had generally a lower specificity (ripples 45:69%, $p = 0.02$; FRs 83:92%, $p = 0.04$) and higher sensitivity (ripples 85:70%, $p = 0.27$; FRs 52:37%, $p = 0.05$). More electrodes with evoked than spontaneous ripples were found in functional (54:30%, $p = 0.03$) and 'silent' areas (57:27%, $p = 0.01$) outside the SOZ.
Conclusions: SPES can elicit SOZ-specific FRs in patients without spontaneous FRs, but activates ripples in all areas.
Significance: SPES is an alternative for waiting for spontaneous HFOs, but does not warrant exclusively pathological ripples.

1. Introduction

Epilepsy is one of the most common neurological disorders, with a prevalence of 4–10 per 1000 persons per year and an incidence of 50–70 per 100,000 persons per year (Sander, 2003). One third of people with epilepsy suffer from refractory epilepsy, meaning that their seizures are not sufficiently controlled with the use of, often multiple, anti-epileptic drugs (AEDs). In people with focal epilepsy, surgery is a curative alternative (Lesser et al., 2010). Delineation of the margins of the epileptic focus is of great importance for the success of the surgery, as well as mapping out neighboring eloquent regions to refrain from harming neurological

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function. Long-term intra-cranial electrocorticography (ECoG) monitoring is performed to ensure optimal mapping of both regions before surgery (Nair et al., 2008; Enatsu and Mikuni, 2016).

The location of the patient's seizure onset EEG rhythm (seizure onset zone, SOZ) is considered the gold standard for the epileptic focus in the long-term ECoG, but waiting for seizures can prolong the pre-surgical monitoring period, causing stress and increased complication risks (Leijten et al., 2006; Lesser et al., 2010). Inter-ictal epileptiform activity can be used as a surrogate marker to define the region of cortex that should minimally be removed to render the patient seizure-free, the so-called epileptogenic zone, which includes the SOZ (Carreño and Lüders, 2008 Inter-ictal high frequency oscillations (HFOs, >80–500 Hz), visible when the ECoG is recorded at >2000 Hz sampling rate, have been shown to be better inter-ictal predictors of the SOZ than epileptiform spikes (Jacobs et al., 2008). HFOs can be subdivided into ripples (80–250 Hz) and fast ripples (FRs, 250–500 Hz). Spontaneous FRs are presumed to be truly pathological and highly specific for the epileptogenic zone as removal of tissue generating them is associated with seizure freedom (Jacobs et al., 2010a; van 't Klooster et al., 2015). FRs are thought to be generated by small patches of synchronized clusters of hyper-connected neurons, and are considered a relatively focal phenomenon, which can be easily missed (Jiruska et al., 2010; Jefferys et al., 2012). Ripples occur more frequently than FRs and are seen in the majority of patients. Unfortunately spontaneous ripples are found over larger areas, so their clinical value is debated (Jacobs et al., 2008; Kerber et al., 2014; van 't Klooster et al., 2015). They occur both pathologically and physiologically, as they are found in healthy animal models and are associated with mesio-temporal memory consolidation (Kucewicz et al., 2014) and occipital visual processing in humans (Nagasawa et al., 2012). Post-resection ripples were found in the non-resected sensorimotor cortex during intra-operative recordings in patients who achieved seizure freedom (van Klink et al., 2014). This lack of sensitivity for FRs and lack of specificity for ripples hampers the clinical implementation of HFOs in epilepsy surgery practice.

We previously showed that HFOs can be evoked by single pulse electrical stimulation (SPES) (van 't Klooster et al., 2011). The SPES protocol consists of runs of 10 brief (1 ms) pulses stimulating over neighboring pairs of all electrodes. Delayed evoked responses occurring about >100–1000 ms after stimulation resemble inter-ictal epileptiform discharges (Nayak et al., 2014) and are considered pathological (Valentín et al., 2002, 2005a,b). These delayed responses also contain evoked HFOs, that are specific for the SOZ (van 't Klooster et al., 2011). It is unknown how evoked HFOs relate to spontaneous occurring HFOs. SPES could help to distinguish pathological from physiological ripples. We hypothesized that delayed responses to SPES are particularly provoked in the epileptogenic network, with the advantage that its stimulus-locked ripples would be truly pathological. This way SPES could provide a valid tool to obtain on demand information about the SOZ, instead of waiting for spontaneous events – be it seizures or inter-ictal events, to shorten the monitoring period or for use during intra-operative ECoG tailored epilepsy surgery. We wanted to compare inter-ictal spontaneous HFOs to evoked HFOs, especially ripples, with respect to their ability to correctly identify the SOZ and their occurrence in functionally eloquent areas.

2. Methods

2.1. Patients

We selected patients with focal refractory epilepsy who underwent long-term subdural ECoG monitoring to determine the SOZ preceding epilepsy surgery of whom SPES results, recorded at 2048 Hz sampling rate, were analyzed in a previous study (van 't Klooster et al., 2011). We excluded patient in whom no SOZ was found or no spontaneous ECoG data was available at 2048 Hz. Patients were admitted for 5–7 days to the Intensive Epilepsy Monitoring Unit of the University Medical Centre of Utrecht, The Netherlands, between 2008 and 2010. During these days, seizures were recorded, the SPES protocol was performed, and functional areas were identified with 50 Hz direct cortical stimulation. The conventional visually analyzed SPES results (Valentín et al., 2002) were available during clinical decision making, but HFOs, neither spontaneous nor evoked, were not. Patients were on (multiple) antiepileptic drugs that were tapered throughout the monitoring period.

Data were retrospectively collected and handled coded and anonymously according to the guidelines of the institutional ethical committee.

2.2. Electrocorticography

Chronic electrocorticography was performed with subdural electrodes that were placed directly on the cortex. Subdural grids and strips consisted of platinum circular electrodes embedded in silicone, had a 4.2 mm^2 contact surface, an inter-electrode distance of 1 cm. In one patient, also depth electrodes were implanted consisting of eight cylindrical contacts with 7.9 mm^2 contact surface and a 5 mm inter-electrode distance (Ad-Tech, Racine, WI, USA). Multiple subdural grids and strips were implanted making sure to cover the brain areas suspected for epileptic activity or eloquent areas in the affected hemisphere.

ECoG recordings required a high sample rate of 2048 Hz (hardware anti-aliasing filter of 538 Hz) in order to capture HFOs. We used an EEG system capable of recording either 128 channels at a regular sampling rate of 512 Hz, but only 64 channels at 2048 Hz (MicroMed, Veneto, Italy). When the clinical recording included more than 64 electrodes a selection was made that targeted the clinical seizure onset zone as found during earlier recording days.

2.3. Single pulse data acquisition

SPES was performed using a manually controlled cortical stimulator (IRES 600, Micromed). Ten monophasic single pulse stimuli of 1 ms width and at a frequency of 0.2 Hz were administered to pairs of adjacent electrodes. This was done while systematically proceeding lengthwise over the electrodes, thus covering the whole of the selected grids. Typically an intensity of 8 mA was used, but in case of twitches or pain the intensity was lowered to as low as 4 mA. A completed SPES protocol data set consists of all stimulated electrode pairs $\times$ 10 stimuli $\times$ maximal 64 recorded electrodes.

2.4. Evoked HFO analysis

The assumption is that delayed responses can occur in epileptic tissue regardless of the anatomical site of stimulation (Valentín et al., 2002). We used the evoked HFO results as reported in a previous study (van 't Klooster et al., 2011). In summary, the analysis of evoked HFOs consists of four steps; (1) Automated preprocessing of the data in average reference montage resulting in 10 epochs of [−1s: +1s] around the stimulus for each pair of stimulated electrodes. (2) A Morlet wavelet based time–frequency analysis was performed in the frequency range 10–520 Hz (settings: sliding window of 685 samples with 50% overlap, frequency resolution 1 Hz, two oscillation parameters 3 and 0.5). The ten epochs were summed in the power spectrum (dB). (3) Event related spectral perturbations (ERSP) images were calculated,