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Electrical stimulation for cortical mapping reduces the density of high frequency oscillations

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KEYWORDS
Refractory epilepsy;
Electrical stimulation;
Ripple;
Fast ripple

Summary
Background: High frequency oscillations (HFOs, 80—500 Hz) are EEG biomarkers for epileptogenic areas. HFOs are also indicators of disease activity as HFO rates increase after reduction of antiepileptic medication. Electrical stimulation (ES) can be used for diagnostic purposes as well as therapy in patients with refractory epilepsy. This study investigates the occurrence and changes of HFOs during ES in patients with refractory epilepsy.
Objective: Analysis of the effects of ES using intracranial ES on the occurrence of epileptic HFOs.
Methods: Patients underwent ES for diagnostic purposes. Ripples (80—200 Hz) and fast ripples (200—500 Hz) were visually marked in a baseline EEG segment prior to ES, after each period of ES as well as after the end of ES. In patients in whom ES triggered a seizure a pre- and postictal segment was marked. Rates of HFOs were compared for the different time periods using a Spearman's correlation and Wilcoxon rank sum test ($p < 0.05$).
Results: 12 patients with 911 EEG channels were analyzed. Ripple ($r = -0.42$, $p < 0.001$) as well as fast ripple ($r = -0.21$, $p < 0.001$) rates decreased significantly over the course of stimulation. This phenomenon was not focal over the seizure onset or neighboring contacts but even observed over distant contacts.

Abbreviations: ES, electrical stimulation; FR, fast ripple; HFO, high frequency oscillations; SOZ, seizure onset zone; SPS, single pulse stimulation.

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Conclusions: ES resulted in a gradual decrease of HFO-Rates over time. The decrease of HFOs was not limited to SOZ areas. If HFOs are considered as markers of disease activity the reduction in HFO-rates as a result of intracranial ES has to be interpreted as a reduction of disease activity.

Introduction

Epilepsy is one of the most common neurological diseases with a prevalence of 0.5—1%. First line treatment are antiepileptic drugs, but despite the development of many new drugs over the recent years, 30% of all patients remain to have seizures and are thus classified as medically refractory (Kwan and Brodie, 2000). For these patients epilepsy surgery to remove the epileptogenic tissue is the most promising treatment for seizure freedom (Picot et al., 2008). A precise identification of epileptogenic tissue is crucial for successful epilepsy surgery and in some patients intracranial electrodes are placed during the presurgical investigation to record EEG directly from the cortical surface. These electrodes can also be used for electrical stimulation which serves the purpose to identify eloquent as well as epileptic areas (Gloor, 1975; Lee et al., 2010). The stimulation of eloquent brain areas results in an interruption of region specific functions such as speech (Gloor, 1975; Gallentine and Mikati, 2009; Lesser et al., 1987). Epileptic tissue reacts to stimulation with the occurrence of epileptic after-discharges and sometimes provoked epileptic seizures (Haag et al., 2008; Schulz et al., 1997). The value of electrical stimulation for the localization of epileptic tissue is however still a matter of debate as some authors point out that the application of high voltages will lead to epileptic reactions outside the primary epileptic focus (Halgren et al., 1983) On the contrary some lesional regions are so severely changed that they show no epileptic reaction anymore (Cherlow et al., 1977). Despite numerous presurgical investigations epilepsy surgery is not an option for all patients, as in some the epileptogenic region overlaps with eloquent areas, multiple foci occur or the focus remains unclear. As a result, in the last years electrical stimulation has received new attention as a therapeutic tool. Multicentre trials indicated that both deep brain stimulation and seizure focus stimulation can result in decreased seizure frequency in patients with refractory epilepsy (Fisher et al., 2010; Morrell, 2011). Electrical stimulation most likely modulates neuronal activity by interrupting synaptic integration and affecting synchronization and can thus lead to both increased inhibition and excitation. Inconsistent results of diagnostic and therapeutic studies reflect the dependency of the brain reaction on stimulation parameters such as pulse width and frequency as well as on the localization of stimulation and the underlying pathology. Little is known about the mechanisms of actual effect of stimulation on epileptic networks.

High frequency oscillations (HFO) have been increasingly recognized as markers of epileptogenic areas during the past years (Jacobs et al., 2012). They can be identified using clinical intracranial electrodes and are divided by frequency into ripples (80—200 Hz) and fast ripples (200—500 Hz). HFOs are mainly generated over brain areas which are part of the seizure onset zone (SOZ) (Crepon et al., 2010; Chatillon et al., 2013; Jacobs et al., 2008). Moreover, removal of HFO generating brain areas correlated with a seizure free postsurgical outcome (Wu et al., 2010; Akiyama et al., 2011). There is also evidence that HFO rates have a value in measuring epileptic disease activity. In rodents, HFOs are more frequent in those animals which have a higher seizure frequency (Bragin et al., 2004). In epileptic patients, HFOs are more common after reduction of antiepileptic medication (Zijlmans et al., 2009) and in patients with highly compared to less epileptic lesions (Kerber et al., 2013). HFOs have therefore been used to evaluate whether specific interventions result in increased or decreased epileptogenicty of the underlying cortex (Bechstein et al., 2012).

It is known that single pulse stimulation SPS, which is based on repetitive very short stimuli, can be used for localization of epileptic areas and can evoke distinct HFOs which have a high localization value for the SOZ ('t Klooster et al., 2011). These results from SPS can however not be transferred to other stimulation settings. For clinical EEG mapping, e.g., higher frequency stimulation is more commonly used. No studies so far exist which address changes of HFOs in the stimulated brain areas during electrical stimulation with 50—60 Hz, even if this would be a way to assess neuromodulation in the epileptic brain caused by this type of stimulation. The present study aims to investigate systematic changes in the amount of HFOs during the period of diagnostic stimulation either for functional mapping or to obtain information about epileptic regions.

Methods

Patient recruitment and clinical information

All patients which were implanted with intracranial electrodes between 2004 and 2009 at the Epilepsy Center in Freiburg were considered for this study. Inclusion criteria were (i) Chronic EEG recording with a sampling rate of at least 1024 Hz, (ii) Stimulation study for diagnostic mapping of functional and epileptic areas. Exclusion criteria were (i) application of emergency antiepileptic medication directly prior or during the stimulation (ii) exclusive language mapping of only 1—5 EEG contacts. All patients gave informed consent to participate in this study. The study was approved by the local ethics committee.

Electrode locations, stimulation protocols and duration of the implantation and recording were solely based on the clinical decision of the attending physician and neurophysiologist and thus independent of this study. Information on the localization of the SOZ and all other clinical details of the patients were retrieved from patient records and reports. Surgical outcome was classified after Engel after a minimum of 12 months following the surgery (Engel, 1993). All