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Changes of EEG synchronization during low-frequency electric stimulation of the seizure onset zone

Kaspar Schindler[a,*], **Christian E. Elger**[a], **Klaus Lehnertz**[a,b,c]

[a] *Klinik für Epileptologie, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany*
[b] *Helmholtz-Institut für Strahlen- und Kernphysik, University of Bonn, Nussallee 14-16, 53115 Bonn, Germany*
[c] *Interdisciplinary Center for Complex Systems, University of Bonn, Römerstr. 164, 53117 Bonn, Germany*

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Summary
Purpose: To assess whether EEG synchronization changes during short-term low-frequency electrical stimulation of the seizure onset zone.
Methods: In 10 patients (34 ± 11 years) with pharmaco-resistant epilepsy the seizure onset zone (9 temporal lobe, 1 frontal lobe) was electrically stimulated at 1 Hz for 5 min via intracranial electrodes. Bipolar stimuli were applied and four pulse widths (0.05, 0.1, 0.5, and 1.0 ms) were tested. Stimulation amplitudes were held fixed at 1 mA for strip electrodes and at 2 mA for depth electrodes. Changes of EEG synchronization were assessed by the eigenvalue dynamics of the cross-correlation matrix computed from a 2.5 s sliding window.
Results: 37 stimulations were performed. We observed EEG desynchronization in 49% (18/37), an increase of EEG synchronization in 27% (10/37) and an EEG pattern with no significant change of synchronization in 24% (9/37). EEG synchronization most frequently occurred when stimulating with a pulse width of 0.5 ms. In a patient with bilateral independent seizure onsets stimulation effects on EEG synchronization were different for each side. In the patient with the shortest duration of temporal lobe epilepsy, stimulation triggered periodic epileptic spikes phase-locked to stimulation. One patient experienced an aura during stimulation, which did not evolve into a seizure, and in one patient a sub-clincial seizure occurred.
Discussion: Low-frequency stimulation of the seizure onset zone is associated with different changes of EEG synchronization and its effects depend on the widths of the stimulation pulses. It may be an appropriate stimulation technique for long-term studies assessing whether synchronized or desynchronized brain dynamics prevent seizure occurrence.

* Corresponding author at: c/o Klaus Lehnertz, Klinik für Epileptologie, Sigmund-Freud-Str. 25, 53105 Bonn, Germany.
Tel.: +49 228 2871 5864; fax: +49 228 2971 6294.
E-mail address: kaspar.schindler@gmail.com (K. Schindler).

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1. Introduction

Seizure freedom is the single most important factor improving health-related quality of life (Birbeck et al., 2002) and is correlated with a reduction of mortality rate (Sperling et al., 1999). However, only 60—70% of epilepsy patients become seizure-free under drug therapy (Kwan and Brodie, 2000) and another 15—20% following epilepsy surgery or alternative treatment methods. Approximately 20% of epilepsy patients continue to suffer from recurrent seizures with currently established therapies (Crawford, 2000). Therefore new approaches to treat patients suffering from refractory epilepsy are needed.

One such recently introduced approach has been referred to as low-frequency electric cortical stimulation of the ''epileptic focus'' (Chkhenkeli et al., 2004; Yamamoto et al., 2006).

This approach to electric brain stimulation in epilepsy patients has several advantages compared to other procedures (Theodore and Fisher, 2004). When directly stimulating the epileptogenic cortex that has been individually delineated during pre-surgical evaluation, there is no need to implant further electrodes into presumably normal brain tissue. Electrode implantations always carry the risk of permanent tissue damage and in two recent long-term follow-up studies, where stimulation electrodes had been targeted at the thalamus, seizure rates dropped before electrical stimulation was actually initiated (Andrade et al., 2006; Lim et al., 2007). One plausible explanation for this observation is that structural damage due to inserting the electrodes was responsible for the beneficiary effect. Another practical advantage of using low-frequency rather than high-frequency stimulation is the lower power consumption, which would increase the life-time of the battery of a permanently implanted stimulation device. In addition, low power consumption could make possible the use of smaller batteries, which might be implanted closer to the stimulation targets. This would reduce the length of the stimulation electrodes and possibly decrease the rate of hardware-related complications like lead fractures (Hamani and Lozano, 2006).

A further rationale for using low-frequency stimulation are the results of a recent randomised clinical trial, in which slow repetitive transcranial magnetic stimulation (TMS) was applied in patients with refractory epilepsy due to malformations of cortical development. Low-frequency TMS was followed by a significantly decreased number of seizures for at least 2 months in the group of treated patients (Fregni et al., 2006). Given the advantages mentioned above, we consider direct low-frequency electric stimulation of epileptogenic cortex to be a promising new therapy and here we set out to further investigate its effects. However, compared to previous studies of other groups (Chkhenkeli et al., 2004; Yamamoto et al., 2006) we define our stimulation target as the ''seizure onset zone'' and not the ''epileptic focus''. The latter term is difficult to define in practice and furthermore may misleadingly imply that the epileptogenic tissue is focal, i.e., anatomically located in a small and clearly circumscribed area. This concept has long been debated (Engel, 1987). Other models that conceptualise the epileptic brain as consisting of different ''zones'', one of them the ''seizure onset zone'', have since been developed (Rosenow and Lüders, 2001). The notion of ''zones'' instead of a ''focus'' expresses better the clinical and experimental evidence, that even in so-called ''focal'' epilepsy, there are pathophysiological changes in functionally connected and spatially extended neuronal networks. In order to better understand the basics of epilepsy it is thus advisable to complement classical reductionistic investigations on the subcellular and cellular level with studies of the emergent activity of larger neuronal networks (McCormick and Contreras, 2001). An important corollary in the present context is, that electric stimulation of only a part of these epileptogenic neuronal networks could — due to their functional connections — modify network activity and influence seizure expression or occurrence (Spencer, 2002; Cooke and Bliss, 2006). A central methodological part of the study presented here is the application of a powerful, genuinely multivariate technique recently advanced and introduced to the field of EEG analysis (Müller et al., 2005; Schindler et al., 2007a, 2007b). This technique allows one to assess the interdependence of multi-channel EEG signals, which is necessary to characterize the influence of focal brain stimulation on the emergent activity of large neuronal networks.

But how should network activity be modified? At present, this is not clear, but recent experimental evidence implicates that electric stimulation adjusted to increase EEG synchronization could turn out to exert anticonvulsive effects during the pre-seizure period (Mormann et al., 2003) or may promote seizure termination (Topolnik et al., 2003; Schindler et al., 2007a, 2007b). Therefore the objective of this study was to assess whether short-term low-frequency electric stimulation of the seizure onset zone may change and specifically increase EEG synchronization.

2. Methods

2.1. Patients

Ten consecutive patients (mean age: 34 ± 11 years, range: 16—46 years), who suffered from pharmaco-resistant epilepsy (mean duration: 24 ± 10 years, range 10—35 years) and underwent invasive pre-surgical evaluation at our clinic were included in the study after they had given written informed consent. Exclusion criteria were the need for other medical electric stimulation devices (e.g. cardiac pacemaker implants) and/or pregnancy. Electric stimulation was always performed after data acquisition for pre-surgical evaluation had been finished. The study protocol had previously been approved by the ethics committee of the University of Bonn. Clinical information about the patients is given in Table 1.

2.2. EEG recordings

EEG signals were recorded intracranially by strip-, grid- or depth electrodes (all manufactured by AD-TECH, Wisconsin, USA). Using a Stellate Harmonie recording system (Stellate, Montreal, Canada; amplifiers constructed by Schwarzer GmbH, München, Germany) EEG signals were sampled at 200 Hz, i.e., at a sampling interval $\Delta t = 5$ ms, band-pass filtered between 0.1—70 Hz, and A/D converted at 16 bit resolution. For analysis only bipolar derivations between nearest neighbour electrode contacts were used, in the following denoted by $\mathrm{EEG}_i(t)$, where i runs over all channels. The terms ''channel'' and ''bipolar derivation'' are used synonymously here. In the case of square grid electrodes only the bipolar derivations along one dimension (perpendicular to the attachment points of the connecting wires) were included.