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Single Pulse Electrical Stimulation to identify epileptogenic cortex: Clinical information obtained from early evoked responses

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HIGHLIGHTS

- Electrodes with ERs are stronger associated with SOZ than with non-SOZ electrodes.
- Stimulating the SOZ evokes ERs that are associated with the seizure propagation area.
- ERs evoked by SPES can add information for identification of epileptic cortex.

ABSTRACT

Objective: Single Pulse Electrical Stimulation (SPES) probes epileptogenic cortex during electrocorticography. Two SPES responses are described: pathological delayed responses (DR, >100 ms) associated with the seizure onset zone (SOZ) and physiological early responses (ER, <100 ms) that map cortical connectivity. We analyzed properties of ERs, including frequencies >80 Hz, in the SOZ and seizure propagation areas.
Methods: We used data from 12 refractory epilepsy patients. SPES consisted of 10 pulses of 1 ms, 4–8 mA and 5 s interval on adjacent electrodes pairs. Data were available at 2048 samples/s for six and 512 samples/s (22 bits) for eight patients and analyzed in the time–frequency (TF) and time-domain (TD).
Results: Electrodes with ERs were stronger associated with SOZ than non-SOZ electrodes. ERs with frequency content >80 Hz exist and are specific for SOZ channels. ERs evoked by stimulation of seizure onset electrodes were associated with electrodes involved in seizure propagation.
Conclusion: Analysis of ERs can reveal aspects of pathology, manifested by association with seizure propagation and areas with high ER numbers that coincide with the SOZ.
Significance: Not only DRs, but also ERs could have clinical value for mapping epileptogenic cortex and help to unravel aspects of the epileptic network.

1. Introduction

Cortical Single Pulse Electrical Stimulation (SPES) and its responses yield information about the epileptic tissue in the brain. SPES was first described by Valentín et al. (2002) in focal refractory epilepsy patients who underwent chronic electrocorticography (ECoG) preceding surgery. The stimulation protocol consists of ten brief pulses of 1 ms and 4–8 mA amplitude with a 5 s interval given over two neighboring electrodes (Valentín et al., 2002). SPES evokes two types of responses: early responses (ERs) within 100 ms after stimulation and delayed responses (DRs) after 100 ms up to 1 s after stimulation (Valentín et al., 2002; Valentín et al., 2005a,b). SPES research has mainly focused on DRs. DRs are associated with the seizure onset zone (SOZ) and contain pathological high frequency (80–500 Hz) information. These high frequency DRs are more specific for the seizure onset zone compared to DRs in the low frequency band (<80 Hz) (van 't Klooster et al., 2011). ERs are assumed to be a physiological phenomenon originating from stimulation of cortico-cortical association fibers

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(u-fibers). ERs resemble the N1 potential in cortico-cortical evoked potentials (CCEP; general settings 0.3 ms pulses, 1 Hz, 1–15 mA, 20–70 stimuli averaged). The N1 potential provides information regarding cerebral functional connectivity (Matsumoto et al., 2005, 2007, 2012a,b; Lacruz et al., 2007; Iwasaki et al., 2010; Enatsu et al., 2012a,b). It has been suggested as a method for the identification of functional areas during surgery (Saito et al., 2014). As such, CCEPs, and ERs, may reveal regions of rich network connectivity. On the other hand, it has been shown that seizure propagation proceeds locally through neocortical cells as well as over longer distances through the deeper lying u-fibers that are stimulated by CCEP (Spencer, 1988; Alarcon et al., 1994). ERs might mirror these seizure propagation pathways, thus revealing an important aspect of the pathology of epilepsy.

We investigated ERs, including higher frequency responses above 80 Hz, evoked by stimulation out- and inside the seizure onset zone (SOZ) and analyzed their properties in the SOZ and in areas of seizure propagation, respectively. We used two approaches; analysis in the time–frequency (TF) domain of high temporal resolution data and analysis in the time-domain (TD) of high dynamic range data.

2. Methods

2.1. Patients

Data from 12 patients (5 males, mean age 19.7 years, range 8–42 years) with refractory epilepsy who underwent chronic ECoG preceding epilepsy surgery were used. All patients were admitted to the intensive epilepsy monitoring unit of the UMC Utrecht in the Netherlands in the period 2008–2012. SPES was routinely performed as a clinical protocol. SPES results were included in the medical decision making after visual inspection in line with recommendations of Valentín et al. (2002).

Monitoring time ranged from 3 to 8 days. All 12 patients underwent resective surgery of a presumed epileptic focus. Five patients had temporal, three had frontal, two had frontocentral, and two had parietal lobe epilepsy. Most patients were on multiple anti-epileptic drugs that were tapered during the registration. Patient information is summarized in Table 1.

The institutional ethical committee indicated that no explicit approval was necessary because of the retrospective character of this study, provided that data were coded and handled anonymously.

2.2. Electrocorticography data

Subdural grids and strips (Ad-Tech, Racine, Wisconsin, USA) were placed under general anesthesia, after craniotomy. The circular platinum electrodes, imbedded in silicon, had a contact surface of 4.2 mm^2 and an inter-electrode spacing of 1 cm. In two patients, additional depth electrodes were implanted with eight cylindrical contacts with 7.9 mm^2 contact surface and 5 mm inter-electrode distance. Electrode placement was based on clinical pre-operative diagnostics, covering both the suspected epileptogenic region(s) and eloquent areas. Electrode positions on the cortex were obtained by co-registration of post-implantation CT with preoperative 3D MRI images (Noordmans et al., 2002). The median number of implanted electrodes was 96 (range 88–120) per patient (Table 1).

2.3. Clinical information

Per patient a recording of a typical spontaneous clinical seizure was analyzed retrospectively by two neurologists (chosen from CF/FL/MZ). They were asked to mark independently; (1) the one electrode with the first ictal activity as the seizure onset electrode (SO-electrode), (2) all electrodes on which seizure propagation was found (SP-electrodes) within the first 30 s after initial onset. Ictal activity was defined as the first ECoG pattern consisting of rhythmic spikes, rhythmic sharp waves, recruiting gamma activity, regular or low-amplitude activity in the beta range prior to or coinciding with the clinical manifestation of the seizure (Alarcon, 1996). In case of a generalizing seizure, observers marked all electrodes showing ictal activity up to the point of generalization. Disagreement in the marked onset or propagation between two observers was solved in a consensus meeting. Additionally, a clinical SOZ area was defined, based on all recorded seizures from the total monitoring period (by FL/CF). This SOZ typically contained multiple electrodes.

2.4. Single pulse data acquisition

Single Pulse Electrical Stimulation (SPES) was performed using a manually controlled cortical stimulator (IRES 600 surgical, Micromed, Treviso, Italy). Monophasic SPES stimuli were given, ten pulses with a duration of 1 ms, separated by 5 s intervals, on pairs of adjacent electrodes. Stimulation was performed at an intensity of 8 mA and only in stimulation pairs where twitches or pain occurred the intensity was gradually reduced to as low as 4 mA. In six patients SPES was available at a high sampling rate of 2048 Hz and a hardware anti-aliasing filter of 538 Hz in a subset of 64 electrodes simultaneously (SD128, Micromed, Treviso, Italy). Subset selection was based on the monitoring result of previous days, and included the clinical SOZ. In eight patients SPES was sampled at 512 Hz (anti-aliasing filter 134 Hz) with a high dynamic range at 22 bits resolution, simultaneously in all implanted electrodes. In two patients both types of recordings were available. Data were recorded with respect to an extra-cranial reference. All recordings showed stimulus artifacts in most electrodes that needed to be dealt with. Electrodes with other artifacts were excluded from analysis.

2.5. Time–frequency processing of SPES

We used the same SPES datasets and a similar analytical approach as in our previous study on time–frequency analysis of evoked DRs (van 't Klooster et al., 2011). The aim of the current study is time–frequency analysis of evoked ERs instead of evoked DRs. To enable analysis of ERs we made the following methodological changes: (1) the time-interval of interest was changed to <100 ms, (2) time–frequency decomposition was based on Hilbert-Huang Transformation instead of Wavelet transform in order to create a higher time resolution, and (3) additional processing was required in order to obtain images similar to the Event Related Spectral Pertubation images (ERSPs) in the previous study (van 't Klooster et al., 2011). Further details are provided in the following sections.

2.5.1. Preprocessing

Time frequency (TF) analysis was done only on data sampled at 2048 Hz. Preprocessing of the data files was performed in Matlab® (The MathWorks, Natick, MA) as described in our previous study (van 't Klooster et al., 2011). Preprocessing steps included: stimulus detection, epoching of the data and re-referencing to average reference. Re-referencing was performed in order to exclude contamination of the data by frequencies above 70 Hz, mostly muscle artifacts, which could be present in the extra-cranial common reference. Epochs with interval of [−1 s:1 s] covering pre-stimulus baseline were selected. This resulted into ten epochs for each stimulated electrode pair and all recorded response electrodes.