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Non-invasive single-trial detection of variable population spike responses in human somatosensory evoked potentials

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HIGHLIGHTS

- Low-noise 8-channel SEP permit single-trial detection of cortical population spikes even in an electromagnetically noisy clinical environment.
- Single-trial amplitudes of low-frequency SEPs and σ-bursts are shown to vary significantly.
- Thus, the variability of population spikes in the human somatosensory cortex can be traced non-invasively in a clinical setting.

ABSTRACT

Objective: Somatosensory evoked potentials (SEPs) around 600 Hz ('σ-bursts') are correlates of cortical population spikes. Recently, single-trial σ-bursts were detected in human scalp EEG using 29-channel low-noise recordings in an electromagnetically shielded room. To achieve clinical applicability, this study aimed to establish a protocol using only 8 EEG channels in an unshielded environment and to quantify the variability of σ-bursts.
Methods: Median nerve SEPs were recorded in 10 healthy subjects using a custom-built low-noise EEG amplifier. A detection algorithm for single-trial σ-bursts was trained as combination of spatio-temporal filters and a non-linear classifier. The single-trial responses were probed for the presence of significant increases of amplitude and variability.
Results: Single-trial σ-burst detection succeeded with Detection Rates and Positive Predictive Values above 80% in subjects with high SNR. A significant inter-trial variability in the amplitudes of early low-frequency SEPs and σ-bursts could be demonstrated.
Conclusions: Single-trial σ-bursts can be detected on scalp-EEG using only 8 EEG channels in an electromagnetically disturbed environment. The combination of dedicated hardware and detection algorithms allows quantifying and describing their variability.
Significance: The variability of population spikes in the human somatosensory cortex can be traced non-invasively in a clinical setting.
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1. Introduction

Non-invasive electroencephalography during peripheral nerve stimulation provides functional information about central stimulus processing. In particular, the clinically established low-frequency EEG (<100 Hz) mainly reflects cortical postsynaptic potentials, i.e., the input of neuronal computation (Okada et al., 1997). In contrast, somatosensory evoked potentials (SEPs) contain an additional oscillatory high-frequency EEG burst (≈600 Hz), denoted here as 'σ-burst', which is concomitant with the first cortical low-frequency component (the post-synaptically generated 'N20' for median nerve stimulation) and can be isolated by high-pass filtering above 400 Hz (Cracco and Cracco, 1976; Eisen et al., 1984). Simultaneous macroscopic subdural SEP and microscopic cortical single-cell recordings in behaving non-human primates revealed that this σ-burst is synchronous (Baker et al., 2003) and co-variable (Telenczuk et al., 2011) with cortical single-cell spike

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bursts. Hence, σ-bursts can be regarded as a non-invasively accessible correlate of cortical population spikes, hereby complementing the information content of the established low-frequency EEG and providing access to the very output of neuronal computation, i.e., spikes.

Commonly, to increase the SNR, the average EEG response to multiple peripheral nerve stimuli is calculated, hereby presuming an invariable 'static' sequence of SEP-waves. This technique allowed to localize the generator of σ-bursts to the primary somatosensory cortex (S1) and to thalamocortical radiation fibers (Curio et al., 1994; Gobbele et al., 1998; Ritter et al., 2008) and revealed valuable physiologic information about the changes of burst-amplitude during sleep, sedation and in certain diseases (for a review: Curio, 2004). However, averaging across trials precludes studying the single-trial variability of SEPs, which is a key feature of a functional description of mechanisms underlying the temporal variability in somatosensory processing.

Recently, we demonstrated the feasibility of single-trial σ-burst detection (Waterstraat et al., 2015a) combining low-noise EEG amplifiers and optimized offline analysis (Waterstraat et al., 2015b). In that pilot study, EEG was recorded from 29 low-impedance (<1 kΩ) scalp electrodes during electric median nerve stimulation (4.3 stimuli/s) in four subjects using a custom-built low-noise EEG amplifier in an electromagnetically shielded environment. In two subjects, Detection Rate (DR) and Positive Predictive Value (PPV) reached values at or above 90% whereas the performance of the detector declined in parallel with the lower SNR in the two remaining subjects. While these results were promising, practical problems limit a widespread implementation of this approach: (1) commercially available EEG amplifiers do not offer the required low-noise characteristics; (2) preparing 29 scalp EEG electrodes to reach impedances below 1 kΩ is time-consuming and challenging to obtain in patient recordings; and (3) an electromagnetically shielded recording environment is not regularly available for clinical recordings. Thus, it remains an open question whether the pilot results can validated under simpler conditions with quicker preparation.

Accordingly, here we investigate the feasibility of single-trial σ-burst detection using a custom-built CE-certified 8-channel low-noise EEG amplifier (Scheer, 2013) in a standard hospital environment. As an additional and novel study goal, we exploit the increase in SNR as compared to commercially available EEG equipment to characterize the extent of trial-to-trial variability attributable to σ-bursts (i.e., population spikes).

2. Methods

2.1. EEG recordings

EEG was recorded from 3 female and 7 male healthy subjects, with a mean age of 35 ys (range 22–56 ys). Measurements were performed using a custom-built CE-certified low-noise EEG amplifier (Scheer, 2013) with a set of 8 Ag/AgCl-plated ring electrodes on the scalp and reference at the nose. The electrode placement was chosen to preferentially cover areas above the left pre- and post-central cortex. Careful preparation of the EEG electrodes ensured impedances around 1 kΩ (max. 2 kΩ), which was checked repeatedly between the recording sessions and corrected if necessary; thereby minimizing the contribution of thermal Johnson–Nyquist noise originating at the electrode–skin interface. The EEG was digitized at a sampling frequency of 10 kHz (analogue band-pass 0.016-5000 Hz) and with a precision of 24 bit. SEPs were evoked by electric median nerve stimulation (cathode proximal) at the right wrist of each subject without considering handedness. The intensity of the rectangular stimulus (0.2 ms duration, 4 stimuli/s) was set to 1.5 × motor-threshold so that a thumb twitch was visible for every stimulus. Subjects were placed on a comfortable chair in upright position. They were instructed to keep their eyes open, blink rarely, relax their jaw muscles, and to avoid any movements. For an independent study, 30 min of resting-state EEG was recorded from each subject before starting the electric stimulation of the median nerve. These data, however, were not used for the present article. The subsequent actual SEP recordings consisted of three 10 min blocks so that approximately 7200 trials were recorded in each subject. Overall – including preparation (15–20 min), recording of resting-state EEG (30 min), SEP measurements (30 min), and short breaks between the blocks – the procedure required 90–100 min. The complete study protocol was approved by the local Ethics Committee and all subjects gave written informed consent for their participation.

The time interval containing the stimulus artifacts (−9 ms to 2 ms) was interpolated using monotone cubic Hermite spline interpolation to prevent the prominent stimulus artefact from dominating the results of the subsequent analysis steps and to prevent ringing of the applied digital filters. Outlier segments of the recordings were identified by the deviation of their linear spectral density (LSD) from baseline. Channel Fz was chosen for this procedure based on the propensity of frontal channels to be contaminated by EMG activity. The baseline LSD was defined by a fit of an exponential function to the median LSD of non-overlapping blocks of 1 s duration, estimated using Welch's average periodogram method (Welch, 1967). Subsequently, the Euclidian distance between each block-wise LSD and baseline LSD was determined. The outlier-threshold was assessed visually from the histogram of Euclidian distances and all segments above threshold were rejected from further analysis.

EEG data were band-pass filtered utilizing Butterworth IIR-filters (500–900 Hz). The filter order was chosen as the lowest order guaranteeing a maximal loss of 3 dB in the pass-band and a minimal attenuation of 8 dB in the stop-band, with a transition width between these bands of 10% of the respective cut-off frequency (Rabiner and Gold, 1975).

2.2. Spatial filtering

Each EEG electrode records the activity of a multitude of neurons. However, only a minority of these neurons contribute to the activity of interest; hence, it is desirable to 'focus' the EEG by a spatial filter maximizing the contribution of cortical regions involved in the generation of σ-bursts. Here, we applied Canonical Correlation Average regression (CCAr; Fedele et al., 2013; Waterstraat et al., 2015b), a variant of Canonical Correlation Analysis (CCA), to maximize the correlation of single trials with their respective average in the 14–25 ms post-stimulus segments, hereby amplifying the contribution of phase-locked evoked activity in these segments of the spatially filtered EEG.

2.3. Analysis of single-trial amplitude and variability

Standard SEP analysis involves averaging across multiple stimulus responses to increase the SNR. This approach, however, neglects potential response variability, which can be a false assumption for any dynamic neural generator. Accordingly, we aimed to quantify the amplitude variability of wideband single-trial responses after being decomposed in the time–frequency plane and spatially filtered with the CCAr-filter corresponding to the highest canonical correlation.

For time–frequency analysis we adopted the S transform (Stockwell et al., 1996), combining globally referenced phases and optimally progressive spectral and temporal resolution. Specifically, the discrete S transform algorithm developed by Brown et al.

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