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Recording human cortical population spikes non-invasively – An EEG tutorial

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HIGHLIGHTS

- We present an approach to single-trial analysis of high-frequency SEP – non-invasive markers of cortical population spikes.
- The relevant noise budget mainly consists of amplifier noise and thermal electrode noise.
- Optimized spatio(-temporal) filtering is a key-step of the off-line analysis.
- All critical steps, from recordings to tailored analysis, are explained in detail.
- Source codes are provided as supplementary material online.

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ABSTRACT

Background: Non-invasively recorded somatosensory high-frequency oscillations (sHFOs) evoked by electric nerve stimulation are markers of human cortical population spikes. Previously, their analysis was based on massive averaging of EEG responses. Advanced neurotechnology and optimized off-line analysis can enhance the signal-to-noise ratio of sHFOs, eventually enabling single-trial analysis.
Methods: The rationale for developing dedicated low-noise EEG technology for sHFOs is unfolded. Detailed recording procedures and tailored analysis principles are explained step-by-step. Source codes in Matlab and Python are provided as supplementary material online.
Results: Combining synergistic hardware and analysis improvements, evoked sHFOs at around 600 Hz ('σ-bursts') can be studied in single-trials. Additionally, optimized spatial filters increase the signal-to-noise ratio of components at about 1 kHz ('κ-bursts') enabling their detection in non-invasive surface EEG.
Conclusions: sHFOs offer a unique possibility to record evoked human cortical population spikes non-invasively. The experimental approaches and algorithms presented here enable also non-specialized EEG laboratories to combine measurements of conventional low-frequency EEG with the analysis of concomitant cortical population spike responses.

1. Introduction

The brain generates electric potential oscillations ranging from 0.05 to 1000 Hz (Buzsaki, 2006; Hanajima et al., 2004; Klostermann et al., 2002). Notably, the capability to detect spikes defines a striking contrast between invasive (microscopic) and non-invasive (macroscopic) recordings. While the latter are dominated by low-frequency (<200 Hz) summed postsynaptic potentials reflecting neuronal input (Okada et al., 1997), invasive electrodes can

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provide direct access also to the very output of neuronal computation – spikes. This micro/macro gap, however, has been narrowed gradually over the last years by combining special physiological paradigms with neuro-technological advances.

High-frequency EEG (hf-EEG; >400 Hz), as evoked by conventional electric peripheral nerve stimulation, represents highly synchronized population spikes as verified by invasive microelectrode and simultaneous epidural macroelectrode recordings in non-human primates (Baker et al., 2003; Telenczuk et al., 2011). These bursts of somatosensory high-frequency oscillations (sHFOs) can be recorded non-invasively by EEG and MEG above the somatosensory cortex in healthy humans after median nerve stimulation (Curio, 2004; Ozaki and Hashimoto, 2011).

Here, we present a stepwise approach, from optimized recordings to novel data analysis of sHFOs. After a short overview of key neurophysiological findings and technical limitations we provide practice-oriented explanations on data acquisition and subsequent analysis, focusing on algorithms for multivariate feature extraction, illustrated by examples which demonstrate both advantages and limitations. Matlab and Python source codes are provided as supplementary material online (https://github.com/neurophysics).

2. Physiology of sHFOs

First noted as a few small notches superimposed on the N20 peak of somatosensory evoked potentials (SEP) following median nerve stimulation (Cracco and Cracco, 1976), sHFOs at about 600 Hz, here denoted as 'σ-burst', were subsequently co-localized with the N20 in the primary somatosensory cortex (Curio et al., 1994; Hashimoto et al., 1996), exhibiting a somatotopic arrangement (Curio et al., 1997). Nonlinear recruitment at increasing stimulus intensity (Klostermann et al., 1998) and analysis of short-term variability (Klostermann et al., 2001) led to a marked distinction between sHFOs and the underlying low-frequency response. Source reconstruction studies revealed early thalamic (pre-synaptic) and late cortical (post-synaptic) burst components (Gobbele et al., 2004; Haueisen et al., 2000, 2001; Nakano and Hashimoto, 1999; Ritter et al., 2008). In agreement with this division, in various experimental protocols the first part of the burst remained mostly stable in power and timing, in contrast with the high variability of the later part of the sigma-burst (for a review: Ozaki and Hashimoto, 2011). Importantly, sHFOs are greatly decreased during non-REM-sleep in a majority of subjects (Halboni et al., 2000; Yamada et al., 1988). Additionally, slighter changes of vigilance and attention modify sHFOs as well (Gobbele et al., 2000; Klostermann et al., 2001).

Also pathophysiological burst alterations were identified, e.g., in patients with Parkinson's disease (Inoue et al., 2001; Mochizuki et al., 1999), cervical dystonia (Inoue et al., 2004), cortical myoclonus (Alegre et al., 2006), mitochondriopathy (Liepert et al., 2001), epilepsy (Kubota et al., 2004; Mochizuki et al., 1999; Restuccia et al., 2007), migraine (Coppola et al., 2005; Sakuma et al., 2004), schizophrenia (Norra et al., 2004; Waberski et al., 2004) and multiple sclerosis (Gobbele et al., 2003; Rossini et al., 1985).

Simultaneous invasive microelectrode and epidural macroelectrode recordings in non-human primates confirmed that σ-bursts are non-invasive correlates of population spike bursts: Single-cell action potentials in the somatosensory cortex preferably align with the peaks of the macroscopic σ-burst (Baker et al., 2003). Furthermore, single-neuron spiking patterns show congruence with subaverages of macroscopic epidural σ-bursts (Telenczuk et al., 2011). Several neuronal populations are discussed as contributing to σ-bursts (Curio, 2004): The early pre-synaptic component is ascribed to thalamocortical fibers arriving in Brodmann area 3b while the later component relates to transsynaptically activated cortical neurons, possibly comprising burst-discharging pyramidal cells and/or GABAergic feedforward interneurons.

Notably, sHFOs are not limited to the σ-burst range. Recordings obtained in patients using thalamic macroelectrodes could distinguish fast components at 1 kHz (Klostermann et al., 1999, 2002), which are synchronous to the preferred firing times of thalamic single neurons as assessed by simultaneous microelectrode recordings (Hanajima et al., 2004). Interestingly, SEP components at and above 1 kHz could be detected non-invasively at the scalp as well (Scheer et al., 2011), and their spatiotemporal features allow for the definition of a distinct 'κ-burst' (Fedele et al., 2012).

3. Outline of sHFO measurement protocol

A critical first step is to consider the technical prerequisites to measure sHFOs. The importance of this step is illustrated by a comparison of the range of amplitudes that has to be dealt with: the peak-to-peak amplitude of σ-bursts is about 10–20-fold smaller than the traditional low-frequency SEP. These themselves are about 50–100 times smaller than the amplitude of an occipital alpha-wave, and for clinical usage of low-frequency SEP averaging of at least 500 responses is recommended (Cruccu et al., 2008). Additionally, conventional recording technology is not optimized to record data in the frequency range of sHFOs. While since the first description of sHFOs (Cracco and Cracco, 1976) conventional biomedical technology has been used regularly, only recent studies (Fedele et al., 2012; Scheer et al., 2009; Waterstraat et al., 2012) have shown that specialized recording technology can substantially increase the SNR of high-frequency EEG recordings. In the following, we describe the recording protocol to measure sHFOs, discuss how to safely interpolate the stimulus artifacts, identify spectral bands of interest and perform band-pass filtering. Subsequently, approaches to spatial filtering of the recordings are presented. We conclude by illustrating a showcase example.

4. Technical prerequisites

The reliable detection of sHFOs at the scalp is limited by the SNR. Systematic characterization of EEG noise sources has isolated three main contributions (Scheer et al., 2006): (i) biological background activity, (ii) impedance-dependent thermal noise at the skin-electrode interface, and (iii) electronic noise of the recording system. Fig. 1 contrasts the power spectrum obtained with a conventional EEG recording system with one from a custom-made optimized low-noise setup: In traditional EEG bands (<100 Hz) biological background activity dominates the power spectrum with its characteristic $1/f$-trend. In contrast, noise-power in the high-frequency range is mainly composed of thermal and electronic noise. The root mean square (rms) noise floor ($\mathrm{nf}_{\mathrm{rms}}$) of the recording system can be calculated as follows

$$\mathrm{nf}_{\mathrm{rms}} = \sqrt{\mathrm{BW}} \cdot \sqrt{e^2_{\mathrm{amplifier}} + e^2_{\mathrm{thermal}}}, \tag{1}$$

where BW (in Hz) is the frequency bandwidth of the analysis, $e_{\mathrm{amplifier}}$ (in $\mathrm{nV}/\sqrt{\mathrm{Hz}}$) is the input noise of the EEG amplifier and e_{thermal} (in $\mathrm{nV}/\sqrt{\mathrm{Hz}}$) is the thermal Johnson–Nyquist noise (Johnson, 1928; Nyquist, 1928) at the electrode–skin interface which is determined as:

$$e_{\mathrm{thermal}} = \sqrt{4kTR}, \tag{2}$$

with k being the Boltzmann's constant in J/K, T the absolute temperature in K and R the real part of the impedance in Ω. Considering an amplifier noise of $4.8\,\mathrm{nV}/\sqrt{\mathrm{Hz}}$ (J-FET input technology), an impedance of 1 kΩ at 37 °C and a 100 Hz wide band-pass, the resulting noise floor is 63.4 $\mathrm{nV}_{\mathrm{rms}}$. Thus, assuming a Gaussian distribution, the noise is statistically confined (at 99.9% of the cumulative distribution function) to a peak-to-peak amplitude of 391.7 nV. In