Towards non-invasive multi-unit spike recordings: Mapping 1 kHz EEG signals over human somatosensory cortex

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HIGHLIGHTS

- Non-invasive detection of 1 kHz SEP components.
- Low-noise amplifier custom-made for high-frequency recordings.
- Time–frequency analysis and spatial characterization of somatosensory evoked high-frequency components.

ABSTRACT

Objective: Scalp-derived human somatosensory evoked potentials (SEPs) contain high-frequency oscillations (600 Hz; ‘sigma-burst’) reflecting concomitant bursts of spike responses in primary somatosensory cortex that repeat regularly at 600 Hz. Notably, recent human intracranial SEP have revealed also 1 kHz responses (‘kappa-burst’), possibly reflecting non-rhythmic spiking summed over multiple cells (MUA; multi-unit activity). However, the non-invasive detection of EEG signals at 1 kHz typical for spikes has always been limited by noise contributions from both, amplifier and body/electrode interface. Accordingly, we developed a low-noise recording set-up optimised to map non-invasively 1 kHz SEP components.

Methods: SEP were recorded upon 4 Hz left median nerve stimulation in 6 healthy human subjects. Scalp potentials were acquired inside an electrically and magnetically shielded room using low-noise custom-made amplifiers. Furthermore, in order to reduce thermal Johnson noise contributions from the sensor/skin interface, electrode impedances were adjusted to 6 kΩ. Responses averaged after repeated presentation of the stimulus (n = 4000 trials) were evaluated by spatio-temporal pattern analyses in complementary spectral bands.

Results: Three distinct spectral components were identified: N20 (<100 Hz), sigma-burst (450–750 Hz), and kappa-burst (850–1200 Hz). The two high-frequency bursts (sigma, kappa) exhibited distinct and partially independent spatiotemporal evolutions, indicating subcortical as well as several cortical generators.

Conclusions: Using a dedicated low-noise set-up, human SEP ‘kappa-bursts’ at 1 kHz can be non-invasively detected and their scalp distribution be mapped. Their topographies indicate a set of subcortical/cortical generators, at least partially distinct from the topography of the 600 Hz sigma-bursts described previously.

Significance: The non-invasive detection and surface mapping of 1 kHz EEG signals presented here provides an essential step towards non-invasive monitoring of multi-unit spike activity.

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1. Introduction

Somatosensory evoked human EEG responses contain contributions in different temporal and spectral domains. The early low-frequency thalamic (P16) and cortical (N20) peaks are overlapped by smaller high-frequency contributions (around 600 Hz; up to a few hundreds of nanoVolt peak-to-peak; Cracco and Cracco, 1976; MEG correlates: Curio et al., 1994; Hashimoto et al., 1996). These repetitive spike-like wavelets, designated here as ‘sigma-burst’, represent the opportunity to record and monitor non-invasively highly synchronized and rapidly repeating population spikes generated possibly by cuneothalamic and thalamocortical relay cells, cortical bursting pyramidal cells, and fast-spiking
inhibitory interneurons (overview: Curio, 2004): Early observations of these wavelets were interpreted as volume-conducted far-field potentials generated in diencephalic structures (Cracco and Cracco, 1976); later studies identified the location of sigma-burst components in area 3b of human primary somatosensory cortex (Curio et al., 1994; Hashimoto et al., 1996). While low-frequency EEG and MEG (<100 Hz) are mainly generated by postsynaptic mass excitation (Okada et al., 1997), it was proposed that high-frequency EEG/MEG reflects spiking activity (Curio et al., 1994). This hypothesis is supported by simultaneous macroscopic high-frequency EEG and invasive single-cell micro-recordings in awake macaque monkeys (Baker et al., 2003) which have shown that the macroscopic sigma-burst is coincident with synchronous spike bursts of neurons in the primary somatosensory cortex. Furthermore, non-invasive characterization of sigma-burst generators revealed a typical somatotopic arrangement (Curio et al., 1997), nonlinear recruitment with increasing stimulus intensity (Klostermann et al., 1998), nonlinear refractory behaviour with increasing stimulus frequency (Klostermann et al., 1999a), and a distinct amplitude modulation by slight natural or benzodiazepine induced vigilance fluctuations (Gobelé et al., 2000; Haueisen et al., 2000). Furthermore, subcortical sigma-burst components were identified in EEG (Gobelé et al., 2003) and in intrathalamic recordings from tremor patients with ‘deep brain’ electrodes (Klostermann et al., 1999b, 2002). Also burst components linking lower (200 Hz) and upper (600 Hz) frequency domains were characterized (Haueisen et al., 2001), as well as differential modifications of bursts and low-frequency SEP components during sensorimotor interactions (Gobelé et al., 2003). Moreover, clinical studies showed burst alterations in basal ganglia disease, multiple sclerosis, and schizophrenia (Waberski et al., 2004).

Notably, fast oscillations are not limited to the sigma-burst range. In particular, oscillations at and above 1 kHz were found intrathalaminically in patients with Parkinson’s disease (Klostermann et al., 2002; Hanajima et al., 2004), reflecting locally restricted near-field activity. Oscillations faster than sigma-bursts have been observed also epidurally in spinal cord and dorsal column nuclei measurements (Insola et al., 2008, 2010), and at the cortical level in epileptic patients fitted with subdural electrodes (Sakura et al., 2009). Thus, while there is ample evidence from invasive measurements for oscillations in the kHz range, their stable detection at the scalp appears to be hindered by noise. Accordingly, we developed a non-invasive recording approach (Scheer et al., 2011) optimised for the 1 kHz range (‘kappa’-burst). Here, we show both, time-domain and spectral SEP features, and demonstrate that sigma- and kappa-bursts express specific scalp voltage patterns, pointing to partially different cortical and subcortical generators.

2. Methods

SEP measurements were performed in six healthy subjects, inside an electrically and magnetically shielded room (Vakuumschmelze AK3b). Sintered Ag/AgCl ring electrodes were placed using a fabric cap with holders at positions according to the 10/20 system. For three subjects 29 EEG electrodes were distributed over the scalp; for the other three subjects 10 electrodes were used, focused over the pericentral primary sensorimotor areas bilaterally. The reference was placed on the nasion, and ground on Fz. The impedances at all electrode–skin interfaces were carefully prepared using standard abrasive paste until for all electrodes values at or below 1 kΩ were achieved; impedance stability below 1 kΩ was checked and confirmed repeatedly during all measurements. During the recordings the subject was comfortably resting on a bed in a relaxed position. A constant-current square wave electrical stimulus of 200 μs width, 5–8 mA (1.5× motor threshold) and 4.3 Hz repetition rate was applied transcutaneously to the median nerve at the left wrist. Data were acquired using a bandwidth of 0.16–2000 Hz (total gain 10000, ADC rate 5 kHz, resolution 20 bits). We utilised a low-noise custom-made amplifier, with a white noise level of 4.8 nV/√Hz (Scheer et al., 2006). Noise spectra were obtained with the amplifier input connected either to ground or to the relaxed subject without stimulation, using an FFT analyzer (Agilent model 35670A) connected to the amplifier analog output. The data analysis was performed on averages of about 5000 trials in order to isolate stimulus-locked low-amplitude response components. Stimulus artifacts were removed in single-trials in each channel by cubic interpolation from −5 to +5 ms around the stimulus onset. Trials exceeding three times the average standard deviation in the frequency range 200–2000 Hz were rejected. Frequency analysis by means of S-Transform (Stockwell et al., 1996) was performed to identify distinct spectral components, and the obtained time–frequency representations were normalized with respect to the prestimulus (−40 to −10 ms) mean power at each frequency bin thereby rendering visible wide power variations in the spectral range spanning from near-DC to 2 kHz (hardware anti-aliasing frequency low-pass filter). The averaged signal was filtered in three distinct frequency bands (sigma, kappa1, kappa2) as determined from the S-Transform power distribution. In these individually determined frequency bands, scalp map voltage distributions allowed to characterize the spatiotemporal evolution of different evoked patterns in the subjects fitted with 29 electrodes. The analysis was performed with Fieldtrip Toolbox (Oostenveld et al., 2011) for Matlab.

The filter and S-Transform impulse response were tested using artificial signals. Thereby, possible artifact contributions could be excluded; in particular, filter ringing around the stimulus event was avoided by the cubic interpolation.

3. Results

For the analysis a “signal window” was defined (10–50 ms post-stimulus) as well as a “baseline window” (−40 to −10 ms). For each subject the power spectral density of the averaged signal (Fig. 1) of all channels was determined for the two windows in order to individually delineate the corner frequencies for the bandpass filtering. In all subjects increases in power spectral density were observed in the N20 range (up to 200 Hz), in the sigma range (400–900 Hz) and, additionally, further distinct components at and also above 1 kHz. Subjects 1 and 4 expressed a prominent component at 1400 Hz, subjects 2, 3, 5 and 6 at 1200 Hz.

In agreement with previous studies, a sigma-burst band was defined between 400 and 800 Hz, and two bands were added for the components at and above 1 kHz (bandpass corner frequencies for each subject are reported in Table 1). In order to prevent overlap between different components these separation bands were optimized for each subject. We present raw data referenced to the nose electrode.

To better localize these components in the temporal domain a frequency analysis was performed (Fig. 2a) by means of S-Transform (Stockwell et al., 1996), which allowed to identify three distinct frequency ranges with increased amplitude, slightly different for each subject (Table 1); the corresponding time curves of a representative pericentral channel contralateral to the stimulated median nerve are displayed in Fig. 2b.

Fig. 3 exhibits the corresponding time evolution of characteristic voltage scalp maps so that a spatiotemporal assessment of the high-frequency somatosensory evoked potential (hf-SEP) becomes possible. Exploratory analysis showed that while the improved sensitivity achieved here permitted to identify and map high-frequency components at and above 1 kHz, further increases of SNR...
would be required to warrant a stable inverse multi-source reconstruction; accordingly, in the following topographic descriptions are reported that can be obtained from the available spatio-temporal characterisation of the hf-SEP as shown in Figs. 2 and 3.

In the full-band traces two low-frequency peaks were identified, P16 (onset ranging from 15.0 to 16.8 ms) with a widely distributed monopolar scalp pattern and N20 (from 19.2 to 21.8 ms) with a typical dipolar pattern (data not shown), consistent with a deep thalamic P16 and a cortical area 3b N20 generator.

In the sigma-band (400–800 Hz) two main components were encountered, an early monopolar one (onset from 12.2 to 15.4 ms), showing two or three peaks with interpeak intervals of about 1.8 ms, and a later dipolar component (similar to the N20 map) with onset from 18.8 to 21.8 ms featuring four to five peaks (interpeak intervals 1.6 ± 0.13 ms, mean ± s.d.), thereby reproducing the typical spatiotemporal sequence of a leading thalamic sigma-burst generator and a trailing cortical source (Gobbelé et al., 2000).

In the kappa-band (800–2000 Hz) the early onset monopolar pattern indicated a subcortical deep radial source, pointing towards C4-CP4 and starting between 11.8 and 14.6 ms. The inter-peak-interval (IPI) across all subjects for the major peaks is IPI = 1.12 ± 0.1 ms (mean ± s.d.). Around 20 ms this component became more focal over the somatosensory area contralateral to the stimulus, lasting until between 21.4 and 23.4 ms. Based on

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**Table 1**

Filters settings for each subject.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sigma band (Hz)</th>
<th>Kappa1 band (Hz)</th>
<th>Kappa2 band (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td>450–750</td>
<td>850–1150</td>
<td>1250–2000</td>
</tr>
<tr>
<td>Subject 2</td>
<td>400–700</td>
<td>800–1000</td>
<td>1100–2000</td>
</tr>
<tr>
<td>Subject 3</td>
<td>400–700</td>
<td>800–1150</td>
<td>1250–2000</td>
</tr>
<tr>
<td>Subject 4</td>
<td>500–850</td>
<td>900–1050</td>
<td>1120–2000</td>
</tr>
<tr>
<td>Subject 5</td>
<td>450–700</td>
<td>800–1100</td>
<td>1200–2000</td>
</tr>
<tr>
<td>Subject 6</td>
<td>450–750</td>
<td>810–1050</td>
<td>1150–2000</td>
</tr>
</tbody>
</table>

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Fig. 1. Power spectra of the averaged SEP signal from three subjects with 29 electrodes (left side) and three subjects with 10 electrodes (right side), computed either in the time window 10–40 ms post-stimulus (coloured curves), or in the prestimulus baseline window (black curves; –40 to –10 ms). The horizontal bars specify the filter settings for the sigma (red), kappa1 (green), and kappa2 (magenta) for each subject, as outlined in Table 1.
the spatial pattern analysis two parts in the kappa band can be dis-
tinguished: kappa1 (800–1150 Hz) and kappa2 (1100–2000 Hz). Fig. 3a demonstrates the pattern stability in the kappa1-band with a repetition period of 1 ms corresponding to a frequency of 1 kHz. Specifically, the alternation between a focal monopolar and a narrowly spaced tripolar pattern points to a superficial and complex (radial and tangential) multi-source generator structure. No repeating pattern was identified for the kappa2 band (Fig. 3, lower plot); notably, there was always an alternation between a monopolar and a more complex pattern, but here the temporal binning is not a perfect divider of one main periodicity. Similar results were observed for all subjects with individually slightly varying different spatiotemporal patterns.

Thus, while the sigma-burst can be interpreted by two (mono-
polar and dipolar) sources, the kappa components apparently have more complex origins (Fig. 4). Both sigma and kappa wavelets have their onset around 13 ms, corresponding to a deep radially oriented component with a monopolar scalp pattern. In contrast, the cortical kappa band generators were evidently more complex than the superficial sigma source in area 3b, possibly reflecting spike activities from multiple generators in the primary somato-
sensory hand area with different soma and/or axon orientations.
4. Discussion

The present data demonstrate the possibility to increase the sensitivity of non-invasive EEG recordings by minimizing the various sources of noise in the high-frequency range. To this end, we recorded median nerve SEP in an electromagnetically shielded environment, employed a dedicated custom-made low-noise preamplifier, and optimized the electrode–skin impedances. This combination enabled the detection and even mapping of neuronal evoked components in the kiloHertz frequency range non-invasively.

Scalp mappings of hf-SEP reveal that the kappa component at and above 1 kHz exhibits more than one repeating spatial pattern and can be observed also after the N20 peak; notably, at identical latencies patterns clearly different from the sigma burst were observed suggesting that the kappa-band provides additional information. All SEP parameters, such as onset time, wavelet duration, time evolution, and voltage distribution on the scalp, consistently indicate the detectability of several kappa-generators in subcortical as well as intracortical structures.

Subcortical pre-synaptic and intracortical post-synaptic hf-SEP components have been implicated in numerous studies, showing different dependence on stimulus parameters like single vs double pulses (Klostermann et al., 2000) or stimulation frequency (Klostermann et al., 1999a). In particular, cortically applied kynurenic acid (blocking glutamatergic receptors) selectively reduced the later high-frequency (postsynaptic) cortical burst responses in piglet primary somatosensory cortex (Ikeda et al., 2002) without affecting the earlier (presynaptic) subcortical components. The origin of the subcortical components is ascribed to cuneothalamic fibers (12–15 ms) and action potential barrages in fibers of thalamo-cortical projection cells (15–18 ms). The origin of the cortical late (post N20) burst oscillations has been suggested as linked to GABAergic inhibitory cells (Hashimoto et al., 1996; Swadlow et al., 1998); notably, bursts are not affected by modified GABAergic inhibition after lorazepam (Restuccia et al., 2002b) or tiagabine (Restuccia et al., 2002a). Dosage, however, appears critical because higher lorazepam levels can delay later burst peaks (Haueisen et al., 2000). The acetylcholinesterase inhibitor rivastigmine increased selectively later burst wavelets between 18 and 28 ms; interestingly, pyramidal chattering cells can be cholinergically activated whereas ACh does not modify the firing rate of fast-spiking GABAergic interneurons (Restuccia et al., 2003).

Measurements obtained in patients with Deep Brain Stimulation (DBS) intrathalamic electrodes distinguished a thalamic very fast component at 1 kHz from a later cortical component at around 600 Hz (Klostermann et al., 1999b, 2002). This distinction is robustly supported by invasive concomitant local-field potential (LFP) and single unit recordings (Hanajima et al., 2004) showing a neat match between neuronal spikes and oscillations. Moreover, such kiloHertz “kappa band” contributions have been detected after median nerve stimulation in the somatosensory cortex in epilepsy patients who underwent long-term subdural electrode monitoring (Sakura et al., 2009) and in resting state recording in extremely localized cortical regions (Usui et al., 2010), as well as in epidural measurements at lower structures such as the spinal cord and dorsal column nuclei (Insola et al., 2008, 2010).
The presence of such a fast firing rate can be understood in the face of firing properties, e.g., of thalamic cells capable to discharge at high frequencies (800–1000 Hz) during spindle oscillations (Steriade et al., 1993). This confirms the kiloHertz range as a natural response mode, which is not artificially driven by the electric stimulation. Alternately, even if cellular burst displayed interspike intervals of 2–3 ms (Hanajima et al., 2004), they could contribute to some, but not necessarily to all peaks of a 1 kHz SEP component; thus, multiple burst generators working at shifted phases could superimpose (Klostermann, 2005).

The present non-invasive recordings cannot specify the cellular origin of the kappa oscillations. Nevertheless, different spatial patterns before and after the N20 peak were identified for the kappa band. While inverse multi-source reconstructions are not stable given the present signal-to-noise ratio one can detect a contrast between an initial well defined monopolar pattern (typical for a subcortical radial source, such as deep thalamocortical fibers) and a later circumscribed tripolar (maybe even more complex) kappa-burst pattern (arguing for multiple superficial cortical sources); this matches comparably narrow focal hf-SEP patterns as described also in invasive (epidural) recordings (Sakura et al., 2009).

5. Conclusion

Extremely low-amplitude (few tens of nanoVolts) oscillatory somatosensory evoked EEG signals at and above 1 kHz, previously detected only using implanted electrodes in patients, can be measured with scalp electrodes in healthy human subjects using a dedicated low-noise amplifier and low electrode impedances. This non-invasive approach now enables the recording and analysis of such hf-signals from any subject rather than only from Parkinson or epilepsy patients carrying implanted electrodes for diagnostic or therapeutic reasons and can enable further steps towards non-invasive monitoring of multi-unit spike activity.

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