



# Facilitation dynamics of late somatosensory evoked potentials after sural nerve stimulation



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## HIGHLIGHTS

- Electrical sural nerve train stimuli significantly facilitate late somatosensory evoked potentials.
- The magnitude of this facilitation was inversely related to the within train interstimulus interval.
- Train stimuli may constitute a novel tool to investigate cerebral synaptic plasticity.

## ABSTRACT

**Objective:** Somatosensory evoked potentials (SSEPs) could be suitable for elucidating the properties of synaptic potentials (SPs). Two experiments were designed for this purpose.

**Methods:** 1st experiment: the sural nerve was stimulated in 13 subjects with single or trains of 3 stimuli (1 Hz or 0.4 Hz), the within train interstimulus interval (ISI) was stepwise extended from 2 to 10 ms. Cz' against Fz, time interval 500 ms. 2nd experiment: Gating was investigated in a paired stimulus paradigm with intervals of 0.7, 1, 2, 5 s in 15 subjects after single and train stimuli (ISI 3 ms) with equal stimulus and recording positions.

**Results:** 1st experiment: N1-P1, P1-N2a, and P2-N2b but not N37-P40 displayed a significant gain in amplitude following train stimuli compared with single stimuli. Significantly larger N1-P1 amplitude values were observed with 0.4 Hz stimulus repetition compared with 1.0 Hz. Short ISIs of 2–4 ms led to higher N1-P1 amplitudes than obtained with longer ISIs of 7–10 ms. 2nd experiment: recovery of the habituated N1-P1 amplitude was complete when the 2nd of 2 stimuli followed after 2 s.

**Conclusions:** SSEP vertex potential amplitudes (especially N1-P1) recorded after train stimuli presumably reflect the decay dynamics of excitatory postsynaptic potentials. Recovery of the habituated N1 (2nd experiment) was complete within 2 s.

**Significance:** Our study may be relevant to study properties of excitatory synaptic potentials in diseases of the central nervous system such as e.g. epilepsy or migraine.

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## 1. Introduction

Evoked potentials (EPs) constitute easily observable phenomena that may give insight to the underlying cerebral processes. Lesion location and cognitive processes have been studied in detail by EP analysis (Yamada et al., 2004; Kotchoubey, 2006; Polich, 2007). In contrast to early components of EP that reflect the information propagation from the periphery to the cortex, late EP have been used to study the information processing within the central

nervous system. This can be achieved with a high level of time resolution by way of studying late components of EP. Therefore, these have been intensively used in the fields of cognitive psychology and in neuropsychiatric disease states. The exact sources for these late evoked potentials have not been definitively clarified (Valeriani et al., 2001). The N1 component is thought to reflect the perceptual resource in early sensory information processing (Kok, 1997). Part of the later potentials have been attributed in part e.g. to cognitive events. As EP consist of synaptic field potentials, they may contain information about the basic synaptic events that contribute to their generation. There have almost no attempts been done in the past to make use of this EP information content with respect to synaptic potentials (SPs). Late EP components could be especially suitable for elucidating the properties of the underlying

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excitatory and inhibitory SPs, since they embody information on action potential generation within cerebral neuronal loops. Somatosensory EP (SSEP) may be superior to auditory or visual EP for this purpose, due to the fact that a whole sensory nerve may be repetitively and completely excited within brief time intervals. This allows defined information quanta to be delivered in a stepwise manner. Thereby, the summation behaviour of SP arriving at cortical target neurones should become accessible in surface recordings. Previously, we have shown that SSEPs can be amplified compared to single stimuli by way of electrical train stimuli with very short within train interstimulus intervals (ISIs) in the range of few milliseconds (Zakharova and Kornhuber, 2013). This augmentation was similarly present for all SSEP components, i.e. N20, N1, and N2, respectively. When ISI-values were increased from 2 ms up to 10 ms, facilitation was less strong, presumably due to the SP decay dynamics. It is not known whether SSEP responses to foot afferents would behave in a similar way like shown for arm afferents. In fact, several differences exist between the SSEP derived from arms and legs. The early SSEP components from arm and leg afferents differ in their polarity, being negative after arm nerve stimulation (N20) and positive after leg nerve stimulation (P40). N2 is represented by a single component when arm nerves are stimulated, while it usually divides into 2 components, namely N2a and N2b, after leg nerve stimulation. Furthermore, there are known differences in function between arms and legs that might be accompanied in differences in the cortical sensory or sensory-motor signal processing. Such differences might be associated with differences in the SSEP-behaviour when stimulus parameters are varied. Therefore, in the present study SSEP were recorded after stimulation of a leg nerve, i.e. the sural nerve.

Furthermore, in our previous investigation SSEP amplitudes were dependent on the stimulus frequency, indicating influences of refractoriness (Zakharova and Kornhuber, 2013). In the present study, recovery from refractoriness was addressed by way of a paired stimulus paradigm.

## 2. Material and methods

### 2.1. 1st experiment

Thirteen healthy adult subjects (6 females, age 25–48 years) were included in the first experiment after they had given their informed consent in accordance with the Helsinki Declaration. Subjects were in a comfortable supine position. They were asked to keep eyes open and to fix a given point at the ceiling. First, they were made familiar with the different electrical stimuli. Compound sensory action potentials were recorded 4 cm caudal to the lateral malleolus against a reference 4 cm distal to this position after stimuli over the right sural nerve. The stimulus intensity was stepwise increased until no further gain in amplitude was seen. Ten to twenty percent of current intensity was added to this maximum level. Such supramaximum electrical 0.2 ms rectangular stimuli were delivered lateral to the Achilles tendon as either single or trains of 3 stimuli at a repetition rate of 1 Hz or 0.4 Hz. Stimulus intensities were between 9 and 12 mA. For train stimuli, the following within train interstimulus intervals (ISI in ms) were investigated: 2, 2.5, 3, 3.5, 4, 5, 6, 7, 10. Recordings were obtained over Cz' against Fz with the mastoid ipsilateral to the stimulus as the ground position. Electrode impedances were kept below 5 k $\Omega$ . EEG-signals were sampled at 4000 Hz after band-pass filtering (0.05–50 Hz) 50 ms before and 450 ms following stimulus onset. Thirty single traces were averaged. For each experimental condition, 2 average curves were taken in order to judge reproducibility. An average curve containing a total of 60 single curves was derived from both these curves. This final average curve was used to eval-

uate latency values of P40, N1, N2a, and N2b. Furthermore, amplitude values were measured on screen for N37-P40, N1-P1, P1-N2a, and P2-N2b. These amplitude values are referred to as P40, N1, N2a, and N2b, respectively.

A detailed perceptual rating of the different stimulation conditions was not done, mainly in order not to influence the state of relaxedness of the subjects. Nevertheless, a general comment on subjective perception of the different stimulation conditions was obtained at the end of each session. All subjects perceived train stimuli as stronger than single stimuli. The unpleasantness of the trains increased together with the ISI value. The stimulus repetition rate (0.4 vs. 1 Hz) did not have major influence on the subjective stimulus perception.

### 2.2. 2nd experiment

Fifteen healthy adult subjects (5 females, age 25–62 years) were included into the 2nd selective averaging experiment. Stimulus site and recording conditions were essentially the same as in the 1st experiment. Stimuli were delivered as trains of 3 stimuli (ISI 3 ms). Pairs of these stimuli with intervals (in s) of 0.7, 1.0, 2.0, or 5.0 were repeated 30 times. Thereby, each pair was separated by a recovery time interval of 10 s. Recording positions, band-pass filtering and recorded time window were the same as in the 1st experiment. Thirty single traces were selectively averaged for the 1st of the 2 stimuli (curve A), and for the 2nd of 2 stimuli (curve B) separately. Like in the 1st experiment, the 2 average curves (i.e. separate average curves for curves A and B) were taken in order to judge reproducibility. A final average curve containing 60 single traces derived from both these curves was used to evaluate amplitude and latency values of P40, N1, N2a, and N2b. The ratio was formed by dividing N1 amplitudes obtained in curve B by those in curve A in order to judge recovery from refractoriness.

Friedman's ANOVA was used to test for statistical significance. Post hoc analysis was done with Wilcoxon's test. It is well known that late EP components are influenced by attention (Kida et al., 2004) and vigilance (Tsumoto et al., 1972; Cauller and Kulics, 1988). As our experiments were performed in the morning in a state of vigilance and during the same session, these factors of influence do not seem to be pivotal for our results.

## 3. Results

Typical recordings as obtained during the 1st experiment are shown in Fig. 1. The early SSEP component, i.e. P40, did not show any difference in amplitude and latency values when single or train stimuli were used at different within train interstimulus intervals (n.s.; Fig. 2). By way of contrast, the N1-amplitude values critically depended on the stimulus parameters (Fig. 3). After train stimuli, N1-amplitudes were significantly larger than after single stimuli ( $p < 0.001$ , stimulus repetition rate 0.4 Hz, Wilcoxon's test;  $p < 0.05$ , stimulus repetition rate 1 Hz, Friedman test;  $p$  values  $< 0.05$  except for the ISI = 6 ms condition (n.s.), stimulus repetition rate 1 Hz; Wilcoxon's test). In the 0.4 Hz stimulus repetition condition, this effect depended on the within train ISI. Thus, with the smaller ISIs of 2–4 ms, the gain in N1 amplitudes relative to single stimuli was in the range of 2–2.5fold and significantly larger than with longer ISI values of 7 or 10 ms, which were 1.8 or 1.6fold larger as compared with single stimuli ( $p$  values varied from 0.009 for ISI = 2.5 ms vs. ISI = 10 ms to 0.037 for ISI = 4 ms vs. ISI = 7 ms; Wilcoxon test). When stimulus repetition was increased, the gain in N1-amplitudes decreased. Following the lower repetition rate of 0.4 Hz, N1-amplitudes were always significantly higher as compared to the faster stimulus repetition rate of 1.0 Hz, both after single stimuli and after train stimuli ( $p$  at

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