# Exploration of nociceptive cortical processing with steady-state evoked potentials

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## Introduction

Studies have shown that the periodic repetition of a stimulus induces, at certain stimulation frequencies, a sustained electro-cortical response of corresponding frequency, referred to as steady-state evoked potentials (SSEPs)[1]. Using infrared laser stimulation, we recently showed that SSEPs can be used to explore nociceptive cortical processing[2]. Here, we implemented a novel approach to elicit such responses, using a periodic intra-epidermal electrical stimulation of cutaneous Aδ-nociceptors (Aδ-SSEPs). Using a wide range of frequencies (3, 7, 13, 23 vs. 43 Hz), we compared the scalp topographies and the temporal dynamics of these Aδ-SSEPs to the Aβ-SSEPs elicited by non-nociceptive transcutaneous electrical stimulation, as well as to the transient event-related potentials (Aδ- and Aβ-ERPs) elicited by the onset of the 10-s stimulation trains, which were applied to the left and right hand.

## Methods

- EEG: 64 scalp electrodes, 1,000 Hz sampling-rate
- 9 participants
- Two types of stimulation: Aδ stimulus vs. Aβ stimulus

  - **Aδ stimulus:** nociceptive intra-epidermal electrical stimulation of the hand dorsum (sensory territory of the superficial radial nerve)[3,4].

  - **Aβ stimulus**: non-nociceptive transcutaneous electrical stimulation of the superficial radial nerve at the level of the wrist.

  - Stimulus intensity : Aδ stimulus: 0.24 ±0.03 mA
    Aβ stimulus: 1.13 ±0.41 mA
    (2x detection threshold to a single 0.5 ms pulse)[4]

- Two sites of stimulation: right hand vs. left hand.
- Five stimulation frequencies: 3, 7, 13, 23 and 43 Hz.
- Five stimulation blocks
  Each block consisted in 10 trains of electrical pulses lasting 10 s, modulated at the corresponding stimulation frequency, and separated by a 10 s ITI.
- After each stimulation train
  Subjects were asked to report the intensity of perception using a numerical rating scale (NRS: 0-10).

1. Regan, D. (Ed), 1989. Human brain electrophysiology. Evoked potentials and evoked magnetics fields in science and medicine. Elsevier, New-York.

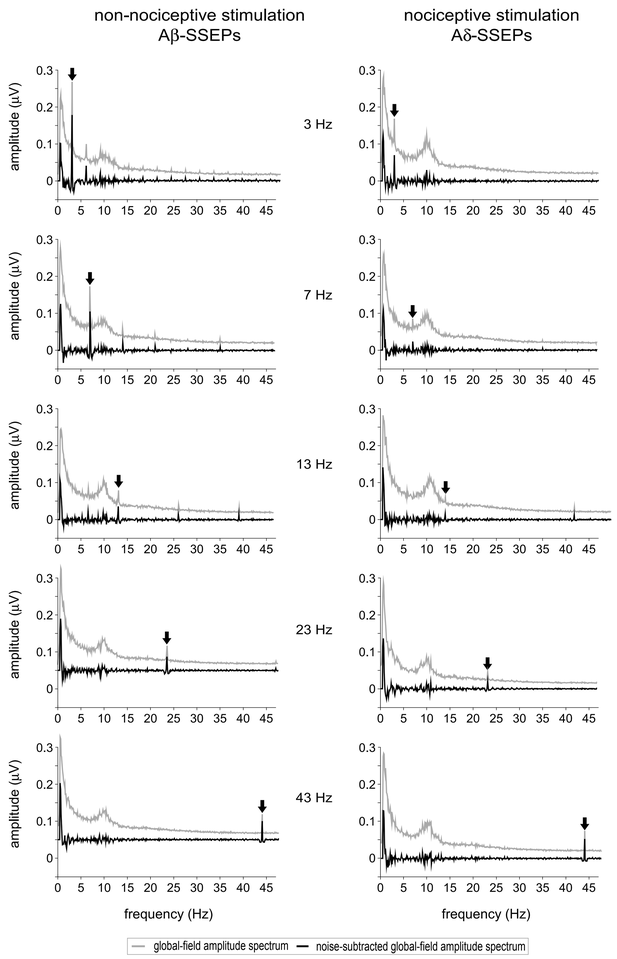
2. Mouraux, A., Iannetti, G.D., Colon, E., Nozaradan, S., Legrain, V., Plaghki, L., 2011. Nociceptive steady-state evoked potentials elicited by rapid periodic thermal stimulation of cutaneous nociceptors. Journal of Neuroscience 31, 6079-6087.

3. Inui, K., Tran, T.D., Hoshiyama, M., Kakigi, R., 2002. Preferential stimulation of Aδ fibers by intra-epidermal needle electrode in humans. Pain 96, 247-252.

4. Mouraux, A., Iannetti, G.D., Plaghki, L., 2010. Low intensity intra-epidermal electrical stimulation can activate Aδ-nociceptors selectively. Pain 150, 199-207.

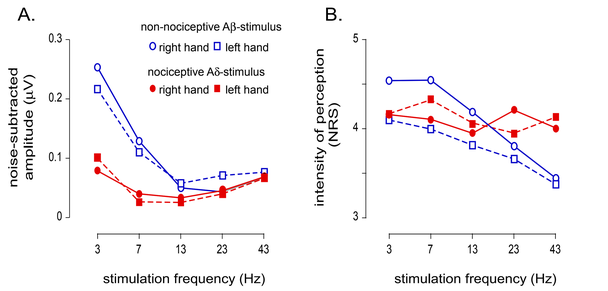
## Results

### Steady-state evoked potentials (SSEPs)



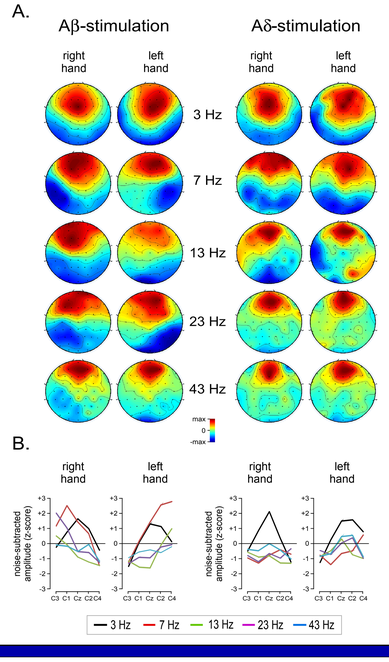

Consistent SSEPs were obtained for all stimulus types, stimulus locations and stimulation frequencies. After subtraction of the surrounding frequency bins to account for residual background noise, the magnitude of both non-nociceptive Aβ-SSEPs and nociceptive Aδ-SSEPs, averaged across all scalp channels was signicantly greater than zero (all t >2.42, p <0.04).

### Effect of stimulation frequency




**A.** The magnitude of both Aβ- and Aδ-SSEPs was dependent on the frequency of stimulation, being greater at low and high frequencies of stimulation. **B.** For non-nociceptive Aβ stimulation, low-frequency stimulation was perceived as more intense than high-frequency stimulation. In contrast, frequency of stimulation had little or no effect on the intensity of perception elicited by Aδ-stimulation.

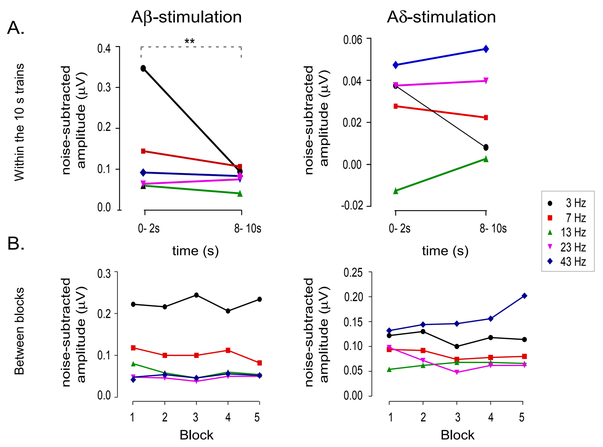
### Scalp topographies of Aβ- and Aδ-SSEPs




**A. At 3 Hz**, the scalp topographies of Aβ- and Aδ-SSEPs were very similar, maximum over fronto-central regions and symmetrically distributed over both hemispheres. **At >3 Hz**, the scalp topographies of Aβ-SSEPs were maximal over the contralateral hemisphere, whereas the scalp topographies of Aδ-SSEPs were symmetrically distributed over both hemispheres, and maximal over fronto-central regions.

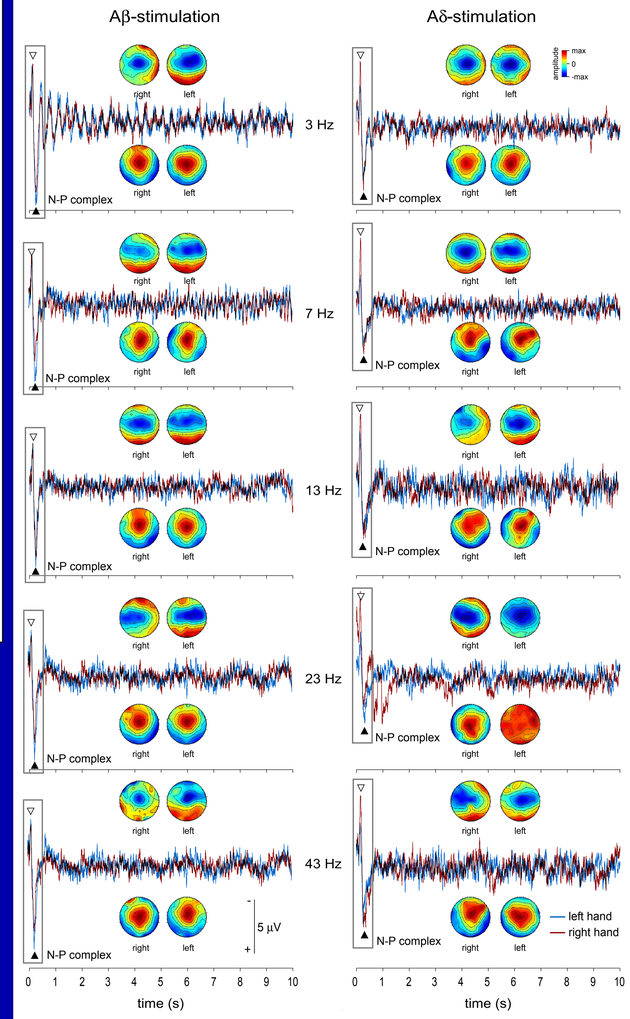
**B.** For all stimulation frequencies except 3 Hz, the scalp topographies of Aβ-SSEPs were significantly lateralized. Such a hemispheric lateralization was not found for Aδ-SSEPs.

### Temporal dynamics of Aβ- and Aδ-SSEPs




**A.** For all stimulation frequencies, the magnitude of Aδ-SSEPs remained constant throughout the 10-s train. The magnitude of Aβ-SSEPs remained also constant, except when stimulating at 3 Hz. **B.** The magnitude of both Aδ and Aβ-SSEPs was largely unaffected by stimulus repetition across blocks.

### Event-related potentials (ERPs)




The onset of both the Aβ and Aδ stimulation trains elicited a clear ERP consisting of a late negative and positive wave, whose scalp topographies were maximal at the scalp vertex. **For all stimulation frequencies > 3 Hz**, no later ERPs could be identified within the 10-s average waveforms. In contrast, when **non-nociceptive Aβ stimuli were applied at 3 Hz**, the average waveforms appeared to be composed of a succession of ERPs, whose magnitude decayed rapidly as a function of time.

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## Conclusion

Our result show that **consistent nociceptive SSEPs** can be obtained by the selective, rapid and periodic **intra-epidermal electrical stimulation** of nociceptive free nerve endings, using a wide range of frequencies (3-43 Hz). **At 3 Hz**, the topographies of Aβ- and Aδ-SSEPs were both maximal at the vertex, and resembled that of the late P2 wave of transient ERPs, suggesting activity originating from the **same neuronal populations**. The magnitude of 3 Hz Aβ-SSEPs also show marked habituation, suggesting that these responses were mainly related to unspecific, attention-related processes. In contrast, **at frequencies >3 Hz**, the topographies of Aβ- and Aδ-SSEPs were markedly different. Aβ-SSEPs were maximal over the contralateral parietal region, while Aδ-SSEPs were maximal over midline frontal regions, thus indicating an **entrainement of distinct neuronal populations**. Furthermore, the responses showed no habituation, suggesting more obligatory and specific stages of sensory processing.