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Topical review

Assessment of small fibers using evoked potentials

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HIGHLIGHTS

- Small-fiber evoked potentials can assess nociceptive pathways.
- A flat tip mechanical stimulator can elicit reliable pinprick-evoked potentials.
- Cool-evoked potentials can assess non-nociceptive pathways for cooling.
- New methods are useful to document sensitization of the nociceptive system.
- Small-fiber evoked potentials may be useful in the diagnosis of neuropathic pain.

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ABSTRACT

Background and purpose: Conventional neurophysiological techniques do not assess the function of nociceptive pathways and are inadequate to detect abnormalities in patients with small-fiber damage. This overview aims to give an update on the methods and techniques used to assess small fiber (Aδ- and C-fibers) function using evoked potentials in research and clinical settings.

Methods: Noxious radiant or contact heat allows the recording of heat-evoked brain potentials commonly referred to as laser evoked potentials (LEPs) and contact heat-evoked potentials (CHEPs). Both methods reliably assess the loss of Aδ-fiber function by means of reduced amplitude and increased latency of late responses, whereas other methods have been developed to record ultra-late C-fiber-related potentials. Methodological considerations with the use of LEPs and CHEPs include fixed *versus* variable stimulation site, application pressure, and attentional factors. While the amplitude of LEPs and CHEPs often correlates with the reported intensity of the stimulation, these factors may also be dissociated. It is suggested that the magnitude of the response may be related to the saliency of the noxious stimulus (the ability of the stimulus to stand out from the background) rather than the pain perception.

Results: LEPs and CHEPs are increasingly used as objective laboratory tests to assess the pathways mediating thermal pain, but new methods have recently been developed to evaluate other small-fiber pathways. Pain-related electrically evoked potentials with a low-intensity electrical simulation have been proposed as an alternative method to selectively activate Aδ-nociceptors. A new technique using a flat tip mechanical stimulator has been shown to elicit brain potentials following activation of Type I A mechano-heat (AMH) fibers. These pinprick-evoked potentials (PEP) have a morphology resembling those of heat-evoked potentials following activation of Type II AMH fibers, but with a shorter latency. Cool-evoked potentials can be used for recording the non-nociceptive pathways for cooling. At present, the use of cool-evoked potentials is still in the experimental state. Contact thermodes designed to generate steep heat ramps may be programmed differently to generate cool ramps from a baseline of 35 °C down to 32 °C or 30 °C. Small-fiber evoked potentials are valuable tools for assessment of small-fiber function in sensory neuropathy, central nervous system lesion, and for the diagnosis of neuropathic pain. Recent studies suggest that both CHEPs and pinprick-evoked potentials may also be convenient tools to assess sensitization of the nociceptive system.

Conclusions: In future studies, small-fiber evoked potentials may also be used in studies that aim to understand pain mechanisms including different neuropathic pain phenotypes, such as cold- or touch-evoked allodynia, and to identify predictors of response to pharmacological pain treatment.

Implications: Future studies are needed for some of the newly developed methods.

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Abbreviations: AMH, Aδ-mechano-heat receptor; CHEP, contact heat-evoked potential; CMH, C-mechano-heat receptor; EEG, electroencephalogram; GBO, gamma band oscillation; ISI, interstimulus interval; LEP, laser evoked potential; PEP, pinprick-evoked potentials; SEP, somatosensory evoked potential; SNR, signal-to-noise ratio.

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1. Introduction

Peripheral neuropathy represents an increasing healthcare problem worldwide. It includes neuropathy due to, *e.g.*, diabetes, HIV, and chemotherapy. In patients with small-fiber neuropathy, neuropathic pain is a common and disabling feature. Neuropathic pain is characterized by pain in the territory of the injured nerve(s) and abnormal sensory function with negative (*e.g.*, sensory loss) and/or positive (*e.g.*, hypersensitivity) signs [1,2]. Standard neurophysiological testing such as nerve conduction studies and somatosensory evoked potentials (SEPs) are useful to assess somatosensory large fibers and the dorsal columns and to demonstrate fiber damage along these pathways. However, these techniques do not assess the function of the nociceptive pathways and are inadequate to detect abnormalities in patients with small-fiber damage that is related to neuropathic pain [3]. Quantitative sensory testing with assessment of cold and warm detection and pain thresholds, quantification of sudomotor activity, and skin biopsy with intraepidermal nerve fiber density estimation are used to diagnose small-fiber neuropathy. In addition, evoked potentials related to pain and small fibers serve as a non-invasive functional method to assess the nociceptive system. Neuropathic pain is also a common complication of other lesions and diseases of the somatosensory nervous system, *e.g.*, peripheral nerve injury, stroke, and spinal cord injury, in which assessment of the small fibers and the spinothalamic tract is important. This overview aims to give an update on the methods and techniques used to assess small-fiber function using evoked potentials. First, we will outline the well-established methodologies of heat-evoked potentials used in research and clinical settings including laser evoked potentials (LEPs) and contact-heat evoked potentials (CHEPs). Second, we will describe new methods like mechanically and cold-evoked potentials to assess small fibers. Finally, we will address newly developed techniques and recommendations that may be used in future studies.

2. Small-fiber evoked potentials

Evoked brain potentials appear as transient changes in the ongoing electroencephalogram (EEG). These changes are time locked to a sensory event, such as a nociceptive heat stimulus, and reflect increased synchronized postsynaptic activity in populations of cortical neurons. Due to the small amplitude, the detection of these responses relies on across-trial averaging procedures. The ongoing EEG activity that is unrelated or not time locked to the stimulus onset should ideally be cancelled out when repeating the stimuli, while it should preserve evoked activity, which is assumed constant and unaffected by averaging procedures. Evoked potentials consist of a series of voltage polarity changes and appear as peaks or deflections in the average waveform reflecting neural activity arising from several temporally overlapping sources. They are classified according to their relative timing to the stimulus onset (latency), their polarity (negative and positive), and their magnitude (amplitude). Evoked potentials exhibit high temporal resolution and are thus suitable to detect and characterize neuronal processes.

3. Peripheral Aδ- and C-fibers

Brief noxious stimuli activate Aδ- and C-nociceptors. These distinct fiber classes can be differentiated by conduction velocity [4], heat thresholds [5,6], and distribution density [7]. C-fibers exhibit a slow conduction velocity in the range of 0.5–2.5 m/s [4,6] compared to the faster conducting Aδ-fibers (4–30 m/s) [8,9]. Due to these differences, the Aδ-input will reach the central projections earlier than the C-fiber-derived input. The perceived sensation following activation of Aδ-fibers is of a pricking, sharp, and stinging character and termed "first pain", while that associated with C-fibers is of a burning and diffuse character and termed "second pain" due to its delayed occurrence compared to the Aδ-fiber response [10–13]. The Aδ-fibers or mechano-heat A-fibers (AMHs) can be subdivided into two distinct populations [5,14]: Type I AMHs are responsive only to intense long-duration heat stimuli (>53 °C), but are excited more easily by mechanical stimuli, exhibit high conduction velocities, and thus are involved in the first pain sensation to mechanical stimuli. Type II AMHs are responsive to short low-threshold heat stimuli (approximately 46–47 °C) and exhibit slower conduction velocities and may be involved in first pain to heat [14–17]. Furthermore, Ringkamp et al. (2001) showed that Type II AMHs are sensitive to capsaicin in contrast to Type I AMHs [16]. C-fibers or mechano-heat C-fibers (CMHs) respond to heat stimuli in a way similar to that of Type II AMHs [5] and are sensitive to capsaicin [18–20]. Distinct from the CMH nociceptors, there is a population of C-warm fibers with a slightly lower heat threshold and a lower distribution density in the skin [4,21,22].

4. Thermal nociceptive stimuli and heat-evoked potentials

The synchronous and concomitant activation of Aδ- and C-nociceptors using either contact or radiant heat allows the recording of heat-evoked brain potentials. LEPs are currently considered to be the best tool for assessing nociceptive pathways in