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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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Contents

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

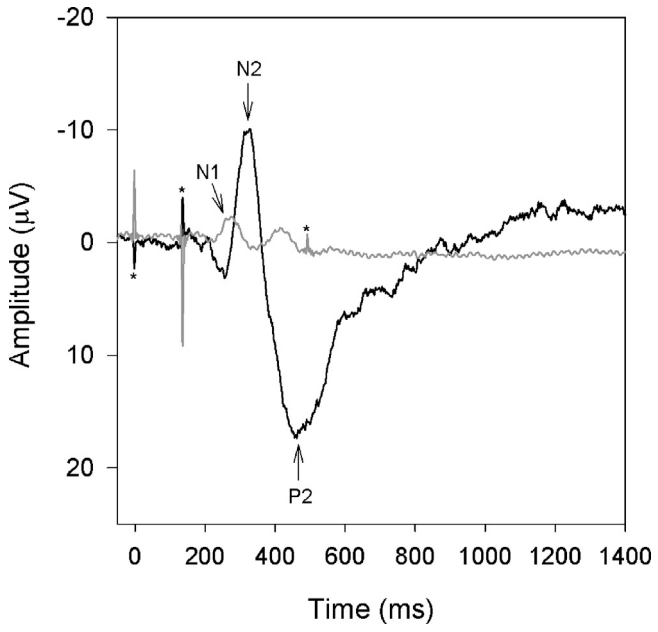

Fig. 1. Grand averages of CHEPs following stimulation of the left dorsal hand in 22 healthy subjects. The black trace shows the main N2–P2 response from the vertex position (Cz–A2), and the light-grey trace shows the N1 response recorded from a central–frontal montage (C4–Fz). Arrows indicate N1, N2, and P2 peaks. Asterisks indicate CHEP stimulation artefacts.

patients with neuropathic pain [3,23] and have been used to study nociceptive processing for decades [17]. Several types of lasers are available, but in most studies, the CO_2-laser, which was the first type used in the context of pain-related evoked potentials [24], has been used [25]. With a wavelength of 10.6 μm, the energy of the CO_2-laser is absorbed in the most superficial layers of the skin where the somatosensory nociceptors are located. The solid-state lasers, such as the Thulium or Neodymium lasers use a shorter wavelength (1–2 μm), resulting in steeper heat ramps and thus a more synchronized activation [26]. The deeper skin penetration may also be advantageous in order to reduce skin burns related to laser stimulation, which is more commonly seen with CO_2-lasers [27]. Lasers exhibit the advantage of very fast temperature rise times (>1000 °C) to produce highly synchronous and direct activation of cutaneous nociceptors. See [28,29] for a review of different types of lasers and their utilities.

CHEPs have been introduced more recently as a reliable method to study nociceptive pathways [30,31], and the method is now widely used in both clinical and basic research. Contact heat has the advantage of stimulating a large cutaneous area, thereby activating a large amount of nociceptors [32]. In addition, contact heat stimuli can be precisely controlled [28], have temperature rise times (nominally 70 °C/s) sufficient to elicit evoked potentials [15,31,32], and they require fewer safety precautions than laser stimulation (*e.g.*, approved room, no safety goggles) [33]. For review of the use of CHEPs in basic science and clinical use, see [34].

4.1. Aδ-fiber-related late responses

LEPs and CHEPs comprise a number of waves that are time locked to the stimulus onset. The most prominent component consists of a large biphasic negative–positive complex (N2–P2) maximal at the vertex. This response, occurring subsequent to laser stimuli at approximately 236 ms (N2) and 315 ms (P2) when stimulating the dorsal hand [25] and following contact heat approximately 100 ms later, is referred to as the late response (Fig. 1). Numerous studies have demonstrated that the late response is related to Aδ-fiber activity [35–39]. The main N2–P2 complex is preceded by a smaller negative wave (N1) with a latency of approximately 170 ms (following laser stimuli to the dorsal hand) [38] that overlaps in time and space with the N2 component and is described to have a distribution that is maximal over the temporal area contralateral to the site of stimulation [40]. Recently, Hu et al. (2010) proposed that the N1 is better recorded at the central–frontal area [41]. Due to the small amplitude of the N1 response, the clinical utility is limited [42]. The P2 component displays a central and wide distribution at the vertex similar to the N2 component, which in addition also extends bilaterally from the vertex [38].

In most studies of CHEPs and LEPs, a limited number of electrodes are applied to the scalp in order to record responses to noxious stimuli. Source analysis methods (dipolar modelling) have been used to gain information about the underlying generators. In short, multi-channel (20–128 electrodes) EEG recordings are used to estimate localization and activity of the sources of the scalp responses [32,43]. It has convincingly been shown that the secondary somatosensory cortex (SII) and the insular and the anterior cingulate cortical areas are major contributors to the late response [43–45]. The anterior cingulate cortex (ACC) has been described as a significant source to the late responses, especially the P2 component [43]. Whether the primary sensory cortex (SI) contributes to the late response remains unclear. Most studies have found the SI to be unrelated to CHEP and LEP responses [32,44–47], whereas others also suggest an SI activation [48,49].

4.2. C-fiber-related ultralate responses

Despite the concomitant activation of Aδ- and C-fibers from noxious stimuli and despite the fact that the subjects report the perception of both Aδ-fiber-related first pain and delayed C-fiber-related second pain, only evoked potentials with latencies compatible with Aδ-fibers are recorded [50,51]. Bromm et al. (1983) showed, as the first group, that ultralate responses with a latency of approximately 1260 ms could be recorded by suppressing the Aδ-fiber activity using a preferential block of the superficial radial nerve [52], and this finding has been repeated more recently [53–55]. Other experimental techniques have been reported to activate C-fibers selectively (see [29] for review). These techniques include (1) a stimulus intensity below the Aδ-fiber threshold (between 40 and 46 °C) so that the skin temperature only reaches the threshold of C-nociceptors and C-warm fibers [6,22,56,57] and (2) narrowing the stimulation area yielding selective C-fiber activation [58–60] because C-fibers have a higher skin density distribution than Aδ-fibers [7]. Pathological conditions exist with the loss of Aδ-fibers and hence the loss of the late response [61]. Lankers et al. (1991) demonstrated ultralate responses in a patient with heredity motor and sensory neuropathy Type 1 affecting myelinated fibers with preservation of C-fibers [62].

Less is known about CHEPs related to C-fibers. Granovsky et al. (2005) reported that heat stimuli at low intensity (41 °C) evoked a warm sensation and C-fiber-related CHEPs [63]. However, this finding could not be replicated [64], thus questioning the utility of CHEPs to demonstrate C-fiber-related responses. In a recent study, it was demonstrated that ultralate C-fiber-related CHEPs could be recorded following an A-fiber blockade in 6 out of 21 healthy subjects increasing to 13 out of 22 subjects when the blockade was combined with capsaicin [55].

LEP ultralate responses have been reported with a latency of approximately 700–1150 ms [5,6,52,54,58,65], although longer latencies (1000–1500 ms) have also been described [59]. This is compatible with results using CHEPs where ultralate responses with latencies >800 ms were identified [55]. Interestingly, after blockade of Aδ-fibers, responses with latencies in the range between the latencies of Aδ- and C-fibers were recorded, suggesting

release of Aδ-fibers with slower conduction velocity than normally recorded with CHEPs after blockade of faster conducting fibers [55].

The morphology of ultralate responses resembles that of the late response [6,39] with similar scalp distributions [47,60]. In addition, source analysis studies have shown that similar dipole configurations could produce both late and ultralate responses [22,66]. Therefore, it is likely that late and ultra-late responses share common generators. It has been suggested that due to a refractory period of these generators following Aδ-input, the later arriving C-fiber input does not elicit an ultralate response due to the generators being in a state of transient refractory and a first come, first served effect [51,67]. However, Mouraux et al. (2004) questioned this hypothesis and demonstrated that the second of two consecutive stimuli could elicit a response unaffected by the proposed refractory period [68]. Thus, this hypothesis may not solely explain why ultralate responses are only visible without concomitant Aδ-fiber activity. Other hypotheses have been discussed. First, it has been proposed that the C-fiber afferent volley may be inhibited by the preceding Aδ-fiber volley at the spinal level [69]. This may conflict with the sensation of first and second pain following a noxious heat stimulus [68]. Second, it has been proposed that the large latency jitter due the variable conduction velocities associated with C-fibers [8] may result in insufficient synchronization to elicit C-fiber related responses [39]. In summary, C-fibers elicit reliable ultralate responses only when Aδ-fiber activation is avoided or when the preceding afferent volley, *i.e.*, the Aδ-fiber volley, is blocked, but the reason for this is still not fully understood.

4.3. Comparisons of LEPs and CHEPs – general concepts

Although there seems to be a general agreement that both of these methods are suitable for activating nociceptive pathways and the scalp topographies of CHEPs and LEPs are very similar, suggesting that the same cerebral dipoles are activated [32], some important differences should be considered when comparing the results obtained with the two different methods. The heat ramp of the stimulus (time from baseline to peak temperature) using the contact heat evoked potential stimulator is in the order of 200–250 ms [15,26,30,64]. Therefore, contact heat results in a slower increase of the skin temperature and hence a slower heat transmission from the skin surface to the nociceptive nerve endings than radiant heat stimuli. This may explain why CHEP latencies are generally longer compared to latencies obtained by laser stimulation [15,32,64,70], although CHEP latencies within the normal range of those of LEPs [25] have also been reported [63]. In accordance with this notion, Iannetti et al. (2004) showed that a laser stimulus of shorter duration and a steeper heat ramp caused a shortening of latency [71]. One disadvantage of the CHEPS is that the thermode is in direct contact with the skin, with the possibility of concomitant activation of low threshold mechano-sensitive fibers, which may modulate the spinal transmission of nociceptive information [29,72]. However, Valeriani et al. (2002) showed that only nociceptive inputs are involved in the heat-evoked potentials from contact heat [32]. In addition, the rigid and planar surface of the thermode may limit their usability at some cutaneous areas.

4.4. LEPs and CHEPs – methodological considerations

Due to the risk of burn injuries, laser stimuli cannot be applied to the same spot twice. Regarding safety precautions, laser stimulation requires safety goggles to protect the cornea of both the examiner and the patient. Since more than 100 papers have been published using LEPs [25], guidelines are available for its use and normal values have been published [25]. In this regard, only limited normative data on CHEP variables are available, and a recent study showed a systematic shift in CHEP amplitude and latency over a 6-month interval in 60 healthy subjects [73]. Recently, methodological papers have been published concerning the use of CHEPs. Variations in the thermode application pressure have been shown not to influence the N2 latency, amplitude, or the heat pain threshold [74]. A habituation effect in terms of reduced amplitudes has been shown using a fixed thermode position due to receptor fatigue [75,76], and it is recommended to vary the thermode position following each stimulus [34]. In a recent study, no reproducible CHEPs could be identified in two out of 22 healthy subjects using a fixed thermode position, most likely due to repeated stimulation of the same skin area [77], although these issues were not encountered in other comparable studies [15,63]. In general, a peak temperature of approximately 51 °C is used. This temperature is regarded as safe and should not induce superficial skin burns. In most studies, a baseline temperature of 32–35 °C has been preferred, but in two recent publications, the effect of increasing the baseline temperature has been evaluated [78,79]. By increasing the baseline to 42–45 °C, Kramer et al. (2012) showed that both the CHEP amplitude and the heat pain intensity were increased, most likely due to a more synchronized response caused by the shortening of the stimulus or shorter heat ramp [78,79]. In addition, the increase in baseline temperature also improved the sensitivity of CHEPs in patients with spinal cord injury (SCI) [79]. The same group could demonstrate an improved N1 response by increasing the baseline temperature without inducing more pain [79]. The N1 response has been suggested to be more directly related to the nociceptive input [41,80]. The low signal-to-noise (SNR) can be improved by performing advanced signal processing and single-trials analysis [41,79] which may improve the clinical utility of the N1 response (see Section 9).

5. Electrically evoked potentials

Despite the usefulness and feasibility of contact and radiant heat as tools to induce pain and the recording of heat-evoked potentials, both methods have their limitations as pointed out in Section 4. Epidermal electrical stimulation has been proposed as an alternative method to selectively activate Aδ-nociceptors [34,81,82]. With this technique, Mouraux et al. (2010) could demonstrate that with low-intensity stimulation, *i.e.*, below twice the perceptual threshold, reliable brain potentials, the so-called electrically evoked pain-related somatosensory evoked potentials [34] could be recorded in healthy subjects [81]. Importantly, the epidermal stimulation was only nociceptive-selective at low stimulus intensities, since activation of non-nociceptive Aβ-fibers was evident at higher intensities [81]. This technique may serve as an alternative tool to assess nociceptive pathways in future studies. See [34] for comparisons of thresholds and stimulation intensities of different electrodes used for activation of nociceptive fibers.

6. Pinprick-evoked potentials

Mechanical stimuli excite a mixture of non-nociceptive Aβ-fibers and nociceptive Aδ-fibers. Although this dual activation exists, a new technique using a flat tip mechanical stimulator has recently been shown to elicit brain potentials following activation of Type I AMH fibers (responsive to noxious mechanical stimuli) [83]. In healthy subjects, pinprick-evoked potentials (PEPs) were reliably recorded from the vertex position with a morphology resembling those of heat-evoked potentials following activation of Type II AMHs. With a shorter latency (*N*: approximately 100 ms) this could be compatible with a conduction velocity of the fast Type I AMH nociceptors. Due to the increase in the *N*-amplitude following capsaicin sensitization, this suggests that PEPs may be useful to assess experimental mechanical hyperalgesia. In a patient with a selective lesion of the spinothalamic tract and unilateral

deficit of thermoreception and nociception, both PEPs and LEPs were reduced in amplitude at the same (affected) side, whereas the SEP response was normal on both sides, suggesting the same projection pathway for both modalities (PEPs and LEPs) [83]. This recent finding suggests that PEPs could add useful and relevant information and serve as a complementary tool to LEPs and CHEPs in both experimental and clinical settings.

7. Contact cool-evoked potentials

Whereas LEPs and CHEPs have been used as objective laboratory test to assess the pathways mediating thermal pain, no such test exists for the non-nociceptive pathways for cooling. This sensory modality is conveyed by Aδ- and C-fibers [84]. The sensitivity to dynamic stimuli (cooling with 1 °C/s) is high; differences of about 1 °C can be reliably detected in the face and on the hands in healthy subjects [85]. Neurophysiologic testing of the cold pathway may be useful, since changes in cool detection and/or the presence of cold allodynia are early and relatively frequent signs in low back pain and neuropathic pain [86,87]. In some cases, perhaps even more important, is the simple advantage over heat pain that cool stimulation typically does not evoke any pain, while this type of stimulation is still a test for small-fiber function.

At present, the use of cool-evoked potentials is still in the experimental state. A major obstacle to test this sort of stimulation in a larger number of subjects or patients is the lack of commercially available reliable devices that meet the technical demands to produce constant cool temperature ramps over a wider temperature range. Previous studies have used custom-made devices and recorded biphasic brain responses with latencies of about 200–300 ms (negativity) and 400–550 ms (positivity) [88]. For the time being, contact thermodes designed to generate steep heat ramps may be programmed differently to generate cool ramps. Recent attempts included cool ramps from a baseline of 35 °C down to 32 °C or to 30 °C, which yielded cool-evoked potentials with the biphasic vertex potential, coding the intensity when different temperature steps (1.5, 3.0, 5.0 °C) were applied [89]. The EEG recording setup is the same as for LEPs and CHEPs with the N1 component visible at contralateral temporal leads (frontal reference) and the main response at Cz (ear or mastoid reference). Future studies are needed to evaluate whether cool evoked potentials are useful to document functional impairment of small fibers or central projection pathways in patients.

8. Modulating effects of small-fiber evoked potentials

CHEP and LEP responses are modulated by attentional and cognitive effects [9,39,40,90,91]. It has been suggested that the early N1 response is not affected by attentional focus [40], although a modulating effect on the N1 response in addition to the N2 response has also been reported [92,93].

Sensitizing agents, such as capsaicin (the pungent ingredient in hot chili peppers), has been widely used in human experimental pain models [94]. Acute topical capsaicin application is known to induce primary hyperalgesia to heat due to activation of transient receptor potential vanilloid (TRPV1) receptors expressed by nociceptors on Aδ- and C-fibers [16,19,95–98]. Allodynia and hyperalgesia to heat and mechanical stimuli and hypoesthesia to cold develop in the primary area, whereas only allodynia and hyperalgesia to mechanical stimuli develop in the surrounding secondary area [19,99–102], although heat hyperalgesia in the secondary area has also been suggested [103]. In agreement with the clinical expression of heat allodynia, acute application of topical capsaicin has been shown to reduce late CHEP latencies and to increase contact heat-evoked pain compatible with sensitization of Aδ-fibers [77]. Ultralate CHEPs consistent with C-fiber sensitization have also been recorded in a subset of healthy subjects following capsaicin application both without and with Aδ-fiber blockade [55]. In contrast, a recent CHEP study by Roberts et al. (2011) did not find any significant changes in latencies or amplitudes following acute capsaicin application [104]. In LEP studies, topical capsaicin at doses that produced clinical signs of sensitization with heat hyperalgesia and allodynia either did not change or reduced laser-evoked pain with reduced LEP amplitudes in some studies [56,105–108], while no change or delay in LEP latencies have also been reported [105–107]. The reasons for the differential effect of capsaicin on LEPs and CHEPs are at present largely unknown, but may be due to the different time courses of sensitization and desensitization following acute application of the substance and variable timing of testing procedures. Prolonged topical application of low-concentration capsaicin has been shown to reduce epidermal nerve fibers and expectedly attenuate heat pain sensitivity [109] and LEPs [81,95,110].

In a recent study examining pinprick-evoked potentials (PEPs), an increase in *N*-amplitude was found following capsaicin sensitization, suggesting that PEPs may a convenient tool to assess experimental mechanical hyperalgesia [83].

9. Novel analysis techniques

So far, this review has focused on the typical recording and analyzing approach, *i.e.*, across-trial averaging of a relatively large number of trials in the time domain. As described in Section 2, the background noise should ideally cancel out during the averaging process and only the response synchronized to the stimulus should be preserved. Traditionally, the analysis has been carried out using visual inspection of the LEP and CHEP responses (N1, N2, P2 peak amplitudes and latencies). Although this method is standard and has been widely used for decades, this approach suffers from some limitations and drawbacks. First, in cases where no apparent peaks can be identified visually in averaged waveform, due to low SNR or where the response is attenuated, the amplitudes and latencies may be regarded as missing values or given an arbitrary zero value [41,110,111]. In situations with questionable detectability, the assignment of an amplitude as zero value may overestimate a deficit in clinical studies, or in case of experimental modulation, overestimate a given effect. This would systematically result in an apparently increased sensitivity, but reduced specificity. Second, visual inspection in principle, with or without discarding "missing responses" induces a bias related to the subjective choice of the signal by the observer. This problem can be avoided by application of automated single trial analyses, where an algorithm tailored for the expected responses with respect to, *e.g.*, time window and shape of the response, automatically detects and measures the evoked potential for each stimulus response [112]. The across-trial variability of the response by means of latency and amplitude could be used as additional "jitter parameter" for pathological changes under certain conditions like peripheral neuropathies or central demyelinating disease. This information is lost in the conventional approach. More recently, these single-trial analysis methods have been refined by advanced noise subtraction based on wavelet filtering and multiple linear regression, to increase the SNR of single-trials LEP and CHEP responses, especially the early N1 component, and to provide a more accurate estimation of the single-trail CHEP and LEP parameters [41,79,112]. The sensitivity of this novel approach has recently been demonstrated in patients with a dysfunction of the nociceptive system [111], suggesting that this automated approach could reliably complement the more conventional approach. However, more clinical and experimental studies are needed in order to demonstrate the effectiveness and additional clinical value of this novel approach. At

present, a second important obstacle that seems to prevent these novel analysis methods from being implemented as standard clinical procedures is the relatively time consuming procedure.

Many studies using both radiant and contact heat have suggested that the amplitude of CHEP and LEP responses correlate well with the stimulus intensity and the perceived pain perception [31,37,40,64,76,113–115]. However, the amplitude of the late as well as ultra-late responses and the perceived pain perception have also been shown to be dissociated under certain circumstances [30,54,58].

With repeated laser stimulation with a constant interstimulus interval (ISI), a decrement of LEP amplitude is expected [116,117]. However, with random and unpredictable ISI, the response magnitude is less affected by the preceding stimulus [68]. These observations suggest 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 [117,118]. Recently, it has been demonstrated that a neurophysiological phenomenon known as gamma band oscillations (GBO) could predict the amount of the subjective pain perception, which was not affected by saliency [119,120]. These brief responses occur shortly following the nociceptive stimulus at frequencies between 30 and 100 Hz, are not phase-locked like standard evoked potentials, and typically cancel each other out in standard averaging procedures. Pain-related GBOs may be an important tool in future studies, since they seem to be closer related to the subjective perception of pain than the amplitude of standard LEP or CHEP. Open questions are whether they are truly specific for nociception, and whether they mirror pain perception over time or serve as a brief "label" for the initial nociceptive perception. Finally, the reproducibility needs to be determined on single subject level before application to the clinical context.

10. Clinical implications

Small-fiber evoked potentials are a useful way to detect and document conduction abnormalities of the nociceptive systems from the periphery to the cortex [42,121]. In particular, LEPs are well studied and accepted as a sensitive and reliable diagnostic tool for assessing small-fiber function in sensory neuropathy, and usually show a good correlation with heat-pain hypoesthesia and intraepidermal nerve fiber density [121]. The assessment of the spinothalamic tract in CNS lesions is another application, and CHEPs have also been used to assess the dermatomal sensory function corresponding to spinal cord segments in, *e.g.*, spinal cord injured patients [122,123]. The ability of the small-fiber evoked potentials to identify lesions in the nociceptive system is also highly relevant for the diagnosis of definite neuropathic pain, in which a diagnostic test confirming a relevant lesion or disease is necessary [1]. Small-fiber evoked potentials may thus be useful in the diagnosis of neuropathic pain, and LEPs have a level-A recommendation for assessing the function of the Aδ-fiber subcortical pathways in patients with neuropathic pain [23]. Small-fiber evoked potentials have also been used in studies that aim to understand pain mechanisms (*e.g.*, [124–127]) and to identify different pain phenotypes in the same underlying disease [127,128]. As an example, partial preservation and desynchronization of LEPs are shown to increase the probability of allodynia in patients with neuropathic pain [125–127]. CHEPs have also proven useful to identify predictors of response to pharmacological pain treatment [129].

11. Conclusions

With the recent developments of the various stimulation techniques to assess small fibers, we now have the possibility to objectively assess different sensory functions and document differential sensory loss. Recent methods, in particular CHEPs and pinprick-evoked potentials, also seem to be able to document sensitization in addition to decreased function of the nociceptive system [34]. Therefore, the hope is that small-fiber evoked potentials can be used to demonstrate pathophysiological mechanisms of different neuropathic pain phenotypes, such as cold- or touch-evoked allodynia in addition to the conventional use. It is also likely that we will see more studies related to the diagnosis, pain phenotyping, and identification of predictive factors of the response to pain treatment. Despite some limitations of the applicability of the different methods for routine clinical use described in this review, small-fiber evoked potentials have demonstrated to be useful in addition to somatosensory evoked potentials for the comprehensive assessment of the somatosensory nervous system.

Conflict of interest

No conflict of interest declared.

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