Neurophysiologie Clinique 51 (2021) 517—523

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ORIGINAL ARTICLE

The N13 spinal component of somatosensory evoked potentials is modulated by heterotopic noxious conditioning stimulation suggesting an involvement of spinal wide dynamic range neurons

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Received 5 May 2021; accepted 3 September 2021
Available online 28 October 2021

KEYWORDS
Experimental pain;
Pain;
Spinal cord;
Wide dynamic range neurons

Abstract
Objectives: Although somatosensory evoked potentials (SEPs) after median nerve stimulation are widely used in clinical practice, the dorsal horn generator of the N13 SEP spinal component is not clearly understood. To verify whether wide dynamic range neurons in the dorsal horn of the spinal cord are involved in the generation of the N13 SEP, we tested the effect of heterotopic noxious conditioning stimulation, which modulates wide dynamic range neurons, on N13 SEP in healthy humans.

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https://doi.org/10.1016/j.neucli.2021.09.001
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Methods: In 12 healthy subjects, we performed the cold pressor test on the left foot as a heterotopic noxious conditioning stimulus to modulate wide dynamic range neurons. To verify the effectiveness of heterotopic noxious conditioning stimulation, we tested the pressure pain threshold at the thenar muscles of the right hand and recorded SEPs after right median nerve stimulation before, during and after the cold pressor test.
Results: The cold pressor test increased pressure pain threshold by 15% (p = 0.04). During the cold pressor test, the amplitude of the N13 component was significantly lower than that recorded at baseline (by 25%, p = 0.04).
Discussion: In this neurophysiological study in healthy humans, we showed that a heterotopic noxious conditioning stimulus significantly reduced N13 SEP amplitude. This finding suggests that the N13 SEP might be generated by the segmental postsynaptic response of dorsal horn wide dynamic range neurons.
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Introduction

Although Aβ-fibre-mediated somatosensory evoked potentials (SEPs) after median nerve stimulation are widely used in clinical practice [7,25], the neuronal generator of the N13 SEP spinal component is not clearly understood [13,17]. Previous studies identified the dorsal column and cuneate nucleus as possible N13 SEP generators [29]. Subsequently, surface and direct recordings during spinal surgery showed that N13 SEP reaches maximal amplitude at the entry zone of cervical roots V-VII and reverses polarity when recorded with prevertebral or anterior neck surface electrodes [5,9,10,11,19]. Desmedt and Cheron then suggested that this transverse N13-P13 dipole reflects the postsynaptic activity of a fixed generator located in the lower cervical cord [5]. Therefore, N13 SEP may reflect the segmental postsynaptic response of wide dynamic range (WDR) neurons in laminae IV-V of the dorsal horn [5,23]. WDR neurons receive convergent input from nociceptors and tactile receptors and provide a major contribution to pain sensation [2].

In animal experiments, heterotopic noxious conditioning stimulation activates the diffuse noxious inhibitory control that, via a spinal-bulbar-spinal loop involving the subnucleus reticularis dorsalis, inhibits WDR neurons [16]. Although many studies have investigated the diffuse noxious inhibitory control in humans, due to the complexity of the descending modulation influence on human pain perception, expert opinion has recommended the term "conditioned pain modulation" to describe the psychophysical paradigm in which a heterotopic noxious stimulus affects a painful test stimulus [16,21] and replicates the diffuse noxious inhibitory control inhibiting the WDR neurons [14].

Spinal low-threshold mechanoreceptive neurons related to Aβ-fibres are not affected by the conditioned pain modulation phenomenon [2,6,27]. Therefore, evidence that the Aβ-fibre mediated N13 SEP originates from spinal WDR neurons could be provided by demonstrating N13 SEP sensitivity to heterotopic noxious conditioning stimulation.

More reliable information on whether N13 SEP is generated by the segmental postsynaptic response of dorsal horn WDR neurons might be useful to support the use of N13 SEP for assessing dorsal horn excitability in experimental and clinical pain conditions.

In this neurophysiological study in healthy humans, we aimed to verify whether heterotopic noxious conditioning stimulation affects N13 SEP, which would support the hypothesis that this spinal SEP component is mediated by WDR neurons. To do so, we recorded N13 SEP before, during and after cold pressor test-induced conditioned pain modulation in healthy humans.

Methods

Participants

We consecutively enroled 12 healthy subjects (mean age 26.7 years, 5 males) without chronic pain disorders, symptoms or signs of peripheral or central nervous system disorders or other medical conditions, drug intake in the past two weeks, jet lag, irregular working hours, sleep restrictions in the last week, or past drug abuse. Participants were asked to refrain from caffeine, nicotine and alcohol for at least 8 h before their arrival at the laboratory.

This study was approved by the local institutional review board (REF.CE 4789—2018) and performed in accordance with the Declaration of Helsinki for the involvement of humans in experimental studies. Written informed consent was obtained from all participants.

Experimental procedures

To investigate whether heterotopic noxious conditioning stimulation modulates N13 SEP, we collected median nerve SEP and psychophysical measures during three sessions: before (T0), during (T1), and 60 min after (T2) the cold pressor test (Fig. 1).

All subjects underwent a pilot experimental session to familiarise themselves with the technical procedures. This session included immersion of the left foot in an ice water bath (around 6—7 °C) until pain perception was reported, SEP recording after electrical stimulation of the right median nerve at the wrist (one block of 500 trials) and pressure pain threshold assessment. In all experimental procedures, the laboratory temperature remained stable (20—25 °C).

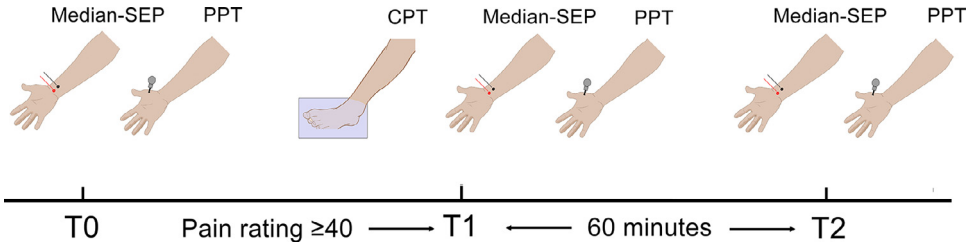

Figure 1 Experimental design. Somatosensory evoked potentials after right median nerve stimulation (median SEP) and pressure pain threshold (PPT) at the thenar muscles were collected before, during, and 60 min after the cold pressor test (CPT) on the left lower limb.
The duration of the N13 SEP and PPT sessions corresponded to 10 and 4−5 min. After a pause of 5 min, the T1 session started with the CPT; as soon as pain perception was rated as at least 40 (about 2−4 min) the N13 SEP recording started. Eventually, the time interval between the end of the T0 N13 SEP recording session and the beginning of the T1 N13 SEP recording session was about 15 min.

Cold pressor test

The cold pressor test consisted of immersing the left foot in an ice water bath (around 6−7 °C) [16]. Water temperature was monitored with an electronic probe thermometer. The investigator ensured that water temperature remained around 6−7 °C, by adding ice to water as needed. With the participant lying supine, the investigator put the subject's left foot in the cold water. At T0, the subject did not have the foot immersed in the tub, but the positions of the spine, leg and knee were the same as at T1 and T2. The only allowed movement was raising the foot for a few centimetres, sufficient to permit the immersion, or to remove the foot from the tub. Subjects were asked to quantify pain perception by using a numerical rating scale (NRS) ranging from 0 to 100. As soon as pain perception during the cold pressor test was rated as at least 40 (0−100 NRS) we recorded the second SEP block (T1). At the end of T1 SEP recording, we stopped the cold pressor test and subjects provided a global rating of perceived pain during the cold pressor test (0−100 NRS). To verify the effectiveness of the heterotopic noxious conditioning stimulation in the WDR inhibition, we tested the pressure pain threshold on the thenar muscle of the right hand across the three time points, immediately after the N13 SEP recording. The pressure pain threshold was measured with a pressure gauge device (FDN200, Wagner Instruments, USA) with a probe area of 1 cm^2 (probe diameter of 1.1 cm) that exerted forces up to 20 kg/cm^2, corresponding to 2000 kPa.

SEP recording

SEPs were recorded after electrical stimulation of the right median nerve at the wrist (electrical pulse duration: 0.1 ms; frequency: 4 Hz; high-pass filter at 3 Hz, low-pass filter at 2 KHz; analysis time base: 50 ms). The cathode was placed 2 cm proximal to the wrist crease and the anode was placed on the wrist crease. Intensity was set at the threshold for evoking muscle twitch in the median nerve muscles of the hand (10.4 ± 1.2 mA). For median nerve stimulation and SEP recordings we used silver cup electrodes with a 10 mm cup diameter.

Three blocks of 500 trials were collected, superimposed to evaluate reproducibility, and averaged. Muscle artefacts were avoided by making the subject as comfortable as possible. Subjects were instructed to lie on an examination couch at rest in a supine position. Automatic artefact rejection was used to eliminate occasional high-amplitude artefactual transients.

SEP recording electrodes were placed according to International Federation of Clinical Neurophysiology guidelines (IFCN) [4]. In order to monitor the input to the spinal cord, the peripheral N9 component was recorded with the surface electrode over Erb's point bilaterally, within the angle formed by the posterior border of the clavicular head of the sternocleidomastoid muscle and the clavicle, 2−3 cm above the clavicle. The N13 component was recorded with the posterior spinal cervical electrode located over the sixth cervical spinous process, with the anterior cervical electrode as a reference on the skin surface of the supra-glottal region on the midline. N20 and P25 components were recorded with a parietal scalp electrode (CP3) placed according to the 10−20 international system of EEG electrode placement, with the reference at Fz. During the three time points of the experimental session, electrode impedance was kept below 5000 Ω; the electrodes were kept in the same position during the experimental session. We measured peak latency and amplitude of the N9, N13, N20, and P25 components according to IFCN guidelines [4]. SEP measures were analysed offline by two investigators who were unaware of the time points (T0-T1-T2).

Statistical analysis

All data had a normal distribution as assessed by the Shapiro-Wilk normality test. We investigated the differences between amplitude and latency of the different SEP components (i.e., N9, N13, and N20) and the related amplitude ratios (N13/N9, N13/N20, N20/N9) across the three time-points with one-way repeated measures analysis of variance (ANOVA), using the Greenhouse-Geisser correction and Dunnett's multiple comparisons test. Pearson correlation was used to verify the correlation between N13 amplitude and pressure pain threshold value. In the text and in the Tables, results are reported as mean±SD. A corrected p-value <0.05 was considered statistically significant.

Results

All participants tolerated the entire procedure and reported that the electrical stimulation of the median nerve was not painful.

In all subjects, the cold pressor test induced a pain perception of at least 40 (0—100 NRS) in a time range of 2—4 min after foot immersion. The mean pain rating associated with the cold pressor test was 70.8 ± 1.4, as assessed by 0—100 NRS.

The ANOVA of the pressure pain threshold showed a significant effect across the three time points (F (1.772, 17.72) = 5.000; Geisser-Greenhouse's epsilon = 0.8860; $p = 0.02$). The ANOVA of the N13 SEP amplitude showed a significant effect across the three time points (F (1.357, 14.92) = 8.220; Geisser-Greenhouse's epsilon = 0.6783; $p = 0.007$). The multiple comparison test showed that at T1, pressure pain threshold was significantly higher (by 15%) and N13 SEP amplitude lower (by 25%) than at T0 ($p = 0.04$). At T2, pressure pain threshold and N13 SEP amplitude did not significantly differ to those at T0 (Fig. 2; Table 1).

Between T0 and T1 the N13/N9 ratio was decreased (by 41%, from 0.95 to 0.39), indicating a reduced spinal responsiveness, whereas the N20/N9 ratio was unchanged (0.92 vs. 0.75), indicating unchanged cortical responsiveness to Aβ-fibre input; the N13/N20 ratio decreased (by 44%, from 2.1 to 0.92), supporting a selective inhibitory effect of the heterotopic noxious conditioning stimulation paradigm on spinal vs. cortical processing of the same peripheral inputs (Table 2).

The N13 latency and the other SEPs variables (N9, N20, P25) did not change across the three time points.

We did not find any correlation between cold pressor test-induced changes in pressure pain thresholds and N13 amplitude (Pearson r=—0.1; $p = 0.68$).

Discussion

In this neurophysiological study in healthy humans, we showed that heterotopic conditioning noxious stimulation reduced the amplitude of the N13 SEP, thus supporting the hypothesis that this spinal component is sensitive to a conditioned pain modulation effect. This finding indicates that the N13 SEP might reflect the segmental postsynaptic response of dorsal horn WDR neurons.

In our study, we used the cold pressor test as heterotopic noxious conditioning stimulation. The cold pressor test is commonly used in human studies since it results in a stronger effect than heat stimulation through a thermode [1,24].

In line with human studies investigating the conditioned pain modulation [16], we compared our outcome variables before and during the heterotopic noxious conditioning stimulation. We recorded N13 SEP during and 60 min after the cold pressor test, since we assumed maximum effect during the heterotopic noxious conditioning stimulation and a presumed discontinuation effect after 60 min, based on previous studies [12,22].

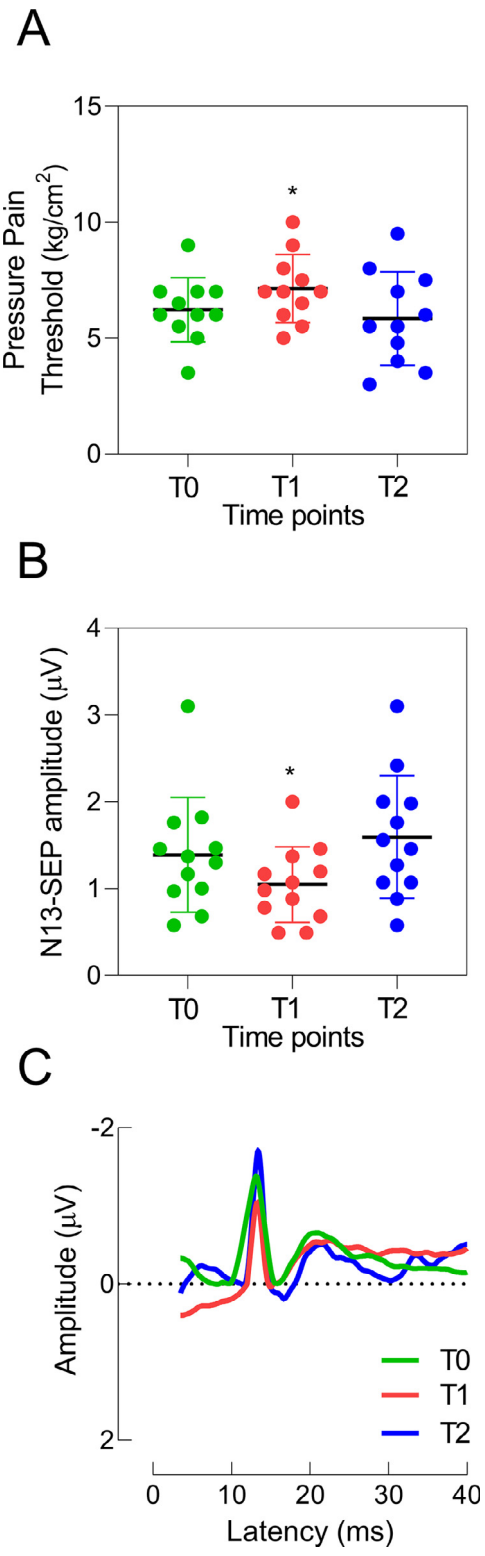

Figure 2 Cold pressor test modulation of pressure pain threshold and N13 SEP. Scatterplots with mean ± standard deviation representing the pressure pain threshold and the N13 SEP amplitude changes across the three timepoints (A and B). C. Grand-average of N13 SEP recordings across the three time points. *$p = 0.04$.

Table 1 Somatosensory evoked potentials variables.

SEPs	T0	T1	p*	T2	p**
N9 latency (ms)	9.75±0.92	9.83±0.86	0.37	9.88±0.83	0.15
N9 amplitude (μV)	2.64±1.67	3.32±1.55	0.14	3.01±1.31	0.67
N13 latency (ms)	12.79±1.1	12.36±1.19	0.18	12.62±1.21	0.68
N13 amplitude (μV)	**1.39±0.68**	**1.04±0.43**	**0.04**	1.62±0.78	0.08
N20 latency (ms)	19.1 ± 1.15	19.27±1.72	0.83	19±1.32	0.82
P25 latency (ms)	21.81±1.65	21.9 ± 2.07	0.96	21.56±1.59	0.48
N20-P25 amplitude (μV)	3.76±1.74	4.29±3	0.80	3.7 ± 2.37	0.92
PPT (kPa)	**610.7 ± 135.8**	**699.8 ± 143.9**	**0.04**	573.2 ± 197.1	0.59

Data are expressed as Mean ± SD; T0: baseline; T1: during the cold pressor test; T2: after 60 min the cold pressor test; *by Dunnett's multiple comparisons test (T0-T1); **by Dunnett's multiple comparisons test (T0-T2); PPT: pressure pain threshold.

To verify that the cold pressor test was effective in inducing conditioned pain modulation, we assessed how this test modulated remote nociceptive signal processing by measuring the pressure pain threshold at the contralateral thenar muscles. We found that during the cold pressor test (T1) the pressure pain threshold increased, thus suggesting that this heterotopic noxious conditioning stimulation effectively modulated pain processing remotely, plausibly affecting WDR neuron excitability [15,20]. Sixty minutes after the cold pressor test (T2), the pressure pain threshold was similar to that at baseline (T0), indicating discontinuation of the heterotopic noxious conditioning stimulation effectiveness. Accordingly, we found that during the cold pressor test (T1) the amplitude of the N13 SEP was lower than that at baseline (T0); after 60 min (T2) the N13 SEP amplitude returned to baseline amplitude (T0) (Fig. 3). These findings indicate that the heterotopic noxious conditioning stimulation, inhibiting the WDR neurons, reduced the N13 SEP amplitude.

The N13 SEP reflects the response of dorsal horn neurons to stimulation of collateral branches of somatosensory ascending pathways [18]. Peripheral N9 SEP and cortical N20-P25 SEP did not parallel N13 amplitude modifications across the three time points of the experiment. The unchanged N9 SEP indicates that the peripheral input to the spinal cord remained stable. The cortical SEP components are generated in the primary somatosensory cortex by large myelinated fibres whose collaterals activate WDR cells in the dorsal horn, and thus they are not affected by modifications of the neurons generating N13 SEP [4]. These findings therefore provide evidence of altered signal processing in the dorsal horn during the cold pressor test.

We found that cold pressor test-induced changes of N13 SEP and pressure pain threshold were not correlated. This finding may reflect a different contribution of the descending modulatory systems on these two variables. The cold pressor test we used in our experiments probably activates a complex descending modulatory system of pain pathways, including the modulatory effect on WDR neurons. In

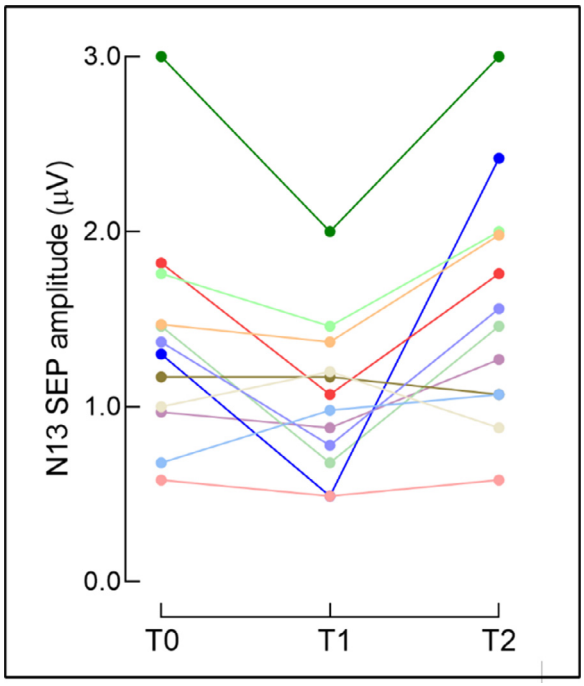

Figure 3 Individual N13 SEP amplitude changes. Each dot represents individual N13 SEP amplitude across the three conditions (T0 before cold pressor test; T1 during cold pressor test; T2 60 min after cold pressor test).

Table 2 Ratios of the somatosensory evoked potentials variables.

Ratio	T0	T1	p*	T2	p**
Amplitude ratio N13/N9	0.95±0.94	0.39±0.27	0.03	0.71±0.4	0.9
Amplitude ratio N13/N20	2.1 ± 1.9	0.92±0.37	0.06	1.5 ± 0.9	0.85
Amplitude ratio N20/N9	0.92±1.61	0.75±1.09	0.94	0.53±0.5	0.94

Data are expressed as Mean ± SD; T0: baseline; T1: during the cold pressor test; T2: after 60 min the cold pressor test; *by Dunnett's multiple comparisons test (T0-T1); **by Dunnett's multiple comparisons test (T0-T2).

our participants the effect of the cold pressor test on the pressure pain threshold may therefore reflect the complex balance between all the different descending modulatory systems of the pain pathways, as well as the contribution of attention, emotion and expectation [16].

Although the N13 SEP modulation we found probably reflects the effect of the heterotopic noxious conditioning stimulation on WDR neurons, we cannot exclude that different dorsal horn neurons might participate in N13 SEP generation. This hypothesis is indirectly supported by our finding of relatively mild N13 amplitude change. Interneurons account for 99% of all neurons in the spinal dorsal horn [8]. Hence, WDR neurons and dorsal horn interneurons might concur in N13 SEP generation.

Our data show the previously unreported finding that N13 SEP amplitude reflects WDR neuron excitability. WDR neurons lie in the dorsal horn of the spinal cord, predominantly in lamina V. They are a convergence point for high- and low-threshold somatosensory input conveyed by Aα and Aβ afferents carrying non-noxious stimuli, and thinly myelinated Aδ and unmyelinated C fibres transmitting thermal and noxious stimuli [26, 28]. WDR neuron projections ascend the spinothalamic tract, a major pain pathway to the brain. They are strategic sites where various types of excitatory and inhibitory influences converge, and play an essential role in nociception. WDR neurons are primarily involved in spinal plasticity mechanisms, with increased activity after central sensitization [26]. Central sensitization, consisting of increased responsiveness of central nervous system nociceptive neurons to their normal or subthreshold afferent input (https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Centralsensitization), is one of the key mechanisms contributing to chronic pain. Its potential mechanisms include long-term potentiation in the dorsal horn, descending facilitation via a brainstem loop and a reduction in descending inhibition [28].

Our data showing that N13 SEP reflects the excitability of WDR neurons in the dorsal horn indirectly support the use of N13 SEP in the assessment of dorsal horn excitability during central sensitization. Dorsal horn-mediated N13 SEP might be therefore used to detect central sensitization in human clinical trials and demonstrate how different medications affect central sensitization. Since most analgesic drugs failed phase II and phase III trials [3], the use of N13 SEP in preliminary pharmacological trials might facilitate the selection of the most promising drug candidates for chronic pain.

Limitations

In our experiments, we did not include a control experimental condition, e.g. a condition with immersion of the foot in tepid water with similar timing. Although a control condition may account for possible distracting effects, we believe that given the nature of the N13 SEP circuitry, non-specific, distracting effects have probably a negligible effect on N13 SEP amplitude.

Although the time interval between T0 and T1 recordings was shorter (about 15 min, Fig. 1) than that between T1 and T2 (60 min), we believe that the N13 SEP changes between T0 and T1 sessions cannot reflect habituation, given that short-latency responses such as N13 SEP, mediated by oligosynaptic circuit, do not probably undergo significant habituation at this time course.

Admittedly, the N13 SEP has a low amplitude and requires several hundred stimulus repetitions to be detected above noise level. This limitation may affect its usefulness for assessing rapid changes in WDR neuron excitability. The relatively low amplitude of N13 SEP and the mild amplitude decrease during cold pressor test also prevents reliable use of this SEP component for assessing dorsal horn excitability changes at single subject level.

Another possible limitation is that the N13 SEP can be elicited by median, ulnar or radial nerve stimulation, but not by segmental cutaneous stimulation. However, a dorsal horn SEP component can be recorded after stimulation of lower limbs (N22 SEP), thus allowing investigation of central sensitization also in the lower limbs. The N13 SEP investigation might be therefore relevant to investigating either global widespread WDR neuron excitability changes (as hypothesized in fibromyalgia) or to signal processing changes for distal limb inputs (as in painful diabetic neuropathy).

Conclusions

In this neurophysiological study in healthy humans, we showed that heterotopic noxious conditioning stimulation activating descending modulatory system and modulating WDR neurons excitability reduces N13 SEP amplitude, thus probably indicating that this spinal SEP component is generated by the segmental postsynaptic response of dorsal horn WDR neurons to large-fibre inputs. Our findings might be useful to support the use of N13 SEP in the assessment of dorsal horn excitability during central sensitization.

Declaration of Competing Interest

The authors declare no conflict of interest regarding this work, which has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No [777,500]. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. The statements and opinions presented here reflect the author's view and neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained therein. www.imi-paincare.eu; www.imi.europa.eu

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