ATTENTIONAL MODULATION OF SOMATOSENSORY PROCESSING DURING THE ANTICIPATION OF MOVEMENTS ACCOMPANYING PAIN: AN EVENT-RELATED POTENTIAL STUDY

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Abstract

Attending to pain-relevant information is crucial to protect us from physical harm. Behavioral studies have already suggested that during anticipation of pain somatosensory input at the body location under threat is prioritized. However, research using daily life cues for pain, especially movements, is lacking. Furthermore, no studies have looked at cortical processing associated with somatosensory processing during threatened movements. The current study aims to investigate whether movements accompanying pain automatically steer attention towards somatosensory input at the threatened location, affecting somatosensory evoked potentials. Healthy volunteers were cued to perform movements with the left or the right hand, and one of these movements could be accompanied by pain on the moving hand. During movement anticipation, a task-irrelevant tactile stimulus was presented to the threatened or pain-free hand to evoke SEPs. During anticipation of movements accompanying pain, the N120 component was increased for tactile stimuli at the threatened relative to the hand without pain. Moreover, the P200 SEP was enhanced during anticipation of movements accompanying pain relative to movements without pain, irrespective of which hand was stimulated. These findings show that the anticipation of pain-accompanying movements may affect the processing of somatosensory input, and that this is likely to be driven by attentional processes.

Perspective

This article shows that the anticipation of pain-related movements automatically biases attention towards stimuli at a pain-related location, as measured by somatosensory evoked potentials. The present study provides important new insights in the interplay between pain and attention, and its consequences at the cortical level .

Key words

Attention, bias, pain, SEP, movement

Introduction

The ability of pain to capture and direct attention allows quick initiation of adaptive responses that may eliminate the pain or its source to protect the organism from further harm [10]. However, it is important that not only pain, but also cues predicting pain, are able to guide attention [35]. Since pain is often initiated or exacerbated by the performance of specific movements, such motor actions typically qualify as cues for pain [42,43]. Performing as well as anticipating movements accompanying pain has been shown to evoke fear [29,30]. In line with the fear-avoidance model [43], we propose that movements accompanying pain might heighten attending to the body part where pain is expected. For instance, a person with chronic low back pain leaning forward to pick up an item from the floor, is likely to attend more strongly to the back to be able to quickly detect and respond to potential signals of harm, and this might result in enhanced somatosensory processing in the back. However, whereas pain often occurs during movement in real life, anticipating a painful situation (i.e. a movement accompanying pain) can modulate somatosensory attention to a threatened body part.

There is some behavioral evidence, though, that experimentally induced anticipation of pain results in enhanced processing of somatosensory input at to the body location where pain is expected, indicating heightened attending to that location [9,36]. For example, a number of studies have shown that participants threatened with pain on one hand perceived innocuous tactile stimuli at that hand earlier than tactile stimuli on the other hand [39,41]. These findings have been suggested to reflect an “attentional bias” towards body locations where pain is expected [36]. However, the behavioral indicators used in these studies are not entirely free from alternative explanations such as response strategies, because the stimuli to which responses were measured were task-relevant, making it difficult to infer genuine attentional effects [13]. Moreover, it has not been investigated whether such anticipatory effect on somatosensory attention can be obtained by movements accompanying pain.

The aim of the current study was therefore to investigate whether movements accompanying pain enhance somatosensory attention to the body part under threat, and whether somatosensory evoked potentials (SEPs) can inform us about such increased attention to tactile stimuli. Healthy volunteers were cued to perform either a hand movement threatened with the administration of a painful stimulus, or with an innocuous stimulus at the moving hand. During anticipation of the movement, a tactile stimulus was applied at either the threatened or the hand without pain, to evoke SEPs. These stimuli were completely task-irrelevant, meaning that effects could not be confounded by non-perceptual processes such as response strategy [13,36]. Importantly, several studies have already shown that the magnitude of SEPs is sensitive to attentional modulation [11,16,17,45]. Moreover, since these stimuli are task-irrelevant and participants are not motivated to attend to them, attentional modulations of the SEPs are most likely to be due to pain expectations.

We hypothesize that during the anticipation of pain-accompanying hand movements, but not movements without pain, SEPs to tactile stimuli will be enhanced when these stimuli are presented at the threatened hand as compared to the non-threatened hand.

Method

Participants. Forty healthy volunteers (12 men) were recruited through the online recruiting system for research participants of Ghent University. To limit potential sensory differences between the two hands due to handedness, only right-handed participants were recruited. Participants' mean score on the Edinburgh Handedness Inventory was 77.92 (*SD*=20.69). Moreover, only individuals without neurological disorders were allowed for participation in the study. One participant reported only after the experiment that she suffered from attention deficit hyperactivity disorder (ADHD) and was therefore excluded from the analyses. Analyses were thus performed on 39 participants. The mean age of the remaining participants was 23.31 (range 17-49). The participants took part in the experiment in exchange for a monetary reward and were not informed about the goals of this study before the start of the experiment. To avoid that only participants without fear of pain would be recruited for the experiment, the use of painful stimuli in the study was not mentioned during recruitment. However, the painful nature of the stimuli was disclosed when the participants arrived at the experiment. Participants were told that they were free to not participate or to terminate the experiment at any time should they so desire. All participants agreed to continue with the experiment and signed an informed consent. The study protocol was approved by the local ethical committee and was performed according to the ethical standards laid down in the declaration of Helsinki.

Materials. This experiment was programmed using the Tscope 5 library package, in the programming language C [34]. Two resonant-type tactors (C-2 TACTOR, Engineering Acoustics, Inc., Florida [38]) were used to administer vibrotactile stimuli (200 ms) to the metacarpals of both hands. Both the amplitude and the frequency were controlled by means of a self-developed software program. The tactors were attached directly to the skin surface using double-sided tape rings and were driven by a custom-built device. To prevent any interference from environmental noise, participants were asked to wear earplugs. Prior to the start of the experiment, the perceived stimulus intensities at each tactor location were individually matched. In order to accomplish this, a standardized matching procedure was used for each participant [38]. First, a tactile reference stimulus (Power = 0.04 watts) was presented on the left hand, followed by a tactile stimulus at the other hand. Participants then had to verbally report whether the intensity was lower than, higher than, or equal to the intensity of the reference stimulus. The amplitude of the tactor on the right hand was varied until it was reported that the subjective intensity of each stimulus was perceived as being equal to the subjective intensity of the stimulus on the left hand. As a result, all participants received the exact same stimulus at the left hand. Only the stimulation at the right hand differed slightly. This method was opted for to maintain comparable stimulus intensities, since different intensities may influence the SEP latencies and amplitudes [19]. Two different frequencies were used during the experiment. For the tactile stimulus that was provided *before* movement execution, and served to evoke SEPs, the frequency was set to 200 Hz. The tactile stimulus that was applied *during* the movement, and served as a (neutral) conditioning stimulus, had a higher frequency (300 Hz). This decision was made in line with the results of a pilot study we conducted, showing that movements may suppress the perception of tactile stimuli (i.e. sensory suppression [22,38]). Note that no SEPs were recorded in response to these stimuli during movement execution.

The painful electrocutaneous stimuli (ES, bipolar; 50Hz; 200 ms; instantaneous rise and fall time) were delivered by means of a Constant Current Stimulator (DS5, Digitimer Ltd, Hertfordshire, UK) with two lubricated Medcat surface electrodes (1cm diameter). These electrodes were placed in the middle of the base of metacarpal 2 and attached directly to the skin surface using double-sided tape rings. Participants were first presented with an ES of low amplitude (0.5 mA) to prevent the initial surprise effect to affect the evaluation of the stimulus. After this, the participants were presented with the same stimulus and were motivated to choose an intensity that they evaluated as unpleasant as possible but that they were still willing to receive during the experiment. By evaluating the unpleasantness, we aimed to create a stimulus reflecting the affective-motivational dimension of pain, as this dimension is typically the main driver of attentional processes [10,35]. Each time the participant pressed a button to increase the intensity, the amplitude was elevated in steps of 0.5 mA. Going back to a lower intensity was not possible. An optical sensor box was used to record the movement onset.

Design and Procedure. Participants were asked to take place in front of a computer screen and to place their hands on the sensor box (figure 1). The study consisted of 2 similar phases. In the first part of the experiment, the *learning phase,* the participants were familiarized with the experiment and learned that moving one hand was associated with a painful stimulus and moving the other hand was associated with a non-painful stimulus. The assignment of which hand movement was associated with the painful stimulation was counterbalanced across participants. In the second phase, the *experimental* phase, brain responses to tactile stimuli during movement anticipation were measured.

In the *learning* phase, each trial started with the presentation of a fixation cross (500 ms), followed by the presentation of a cue (the Dutch words for "LEFT", "RIGHT" or "STOP") in the middle of the screen. This cue was presented on a screen with a random duration between 2250 and 3250 ms. This cue indicated which hand was required to perform the movement (i.e. either the left hand, the right hand or no movement at all. Participants were asked to refrain from moving until this cue disappeared from the screen. If participants answered before the cue had disappeared, the Dutch words for "TOO FAST" were presented in red in the middle of the screen for 1000 ms, followed by the next trial. The movement consisted of releasing the corresponding hand from the detector of the sensor box and to press a button placed 20 centimeters further. Importantly, participants learned that the execution of a movement with the hand under threat of pain was combined in 25% of the cases with the administration of a painful ES on the corresponding hand. In the other 75% of the cases the threatened hand received no stimulation. Similarly, the hand that was not under threat of pain received a non-painful tactile stimulus during movement in 25% of the cases, with no stimulation in the rest of the trials (75%). The association which hand was associated with which stimulus type was made clear both by verbal instructions and experience, which is known to cause more fear than mere experience [12]. The stimulation was presented shortly after releasing the sensorbox. The next trial started 1500 ms after pressing the button. In total, this learning phase consisted of 24 trials.

The *experimental phase* was very similar as the learning phase. However, during the presentation of the cue (i.e., during movement anticipation), a tactile stimulation was administered between 1000 and 1500 ms after cue onset (figure 1). This stimulation was presented on one of the two hands for 200 ms, and had a frequency of 200 Hz. The SEPs evoked by this stimulation were recorded. To make sure that the participants were not motivated to attend to the tactile stimulus, they were instructed that this stimulation was irrelevant for the task, and that they therefore could ignore this stimulation. Movements were still presented with a sensory stimulus (tactile or electrocutaneous) in 25% of the cases to maintain the association. There were in total 672 trials, 112 trials for each condition. Non-movement trials (i.e. "STOP" trials) were included in the design to check whether movement may contribute to the SEP amplitudes. These trials were excluded from the main analysis. The design of the study was thus a 2 (type of cue: pain-accompanying movement vs movement without pain) x 2 (stimulation location: pain-related location vs location without pain) design, with the ERP amplitudes evoked by the tactile stimulus during anticipation as the dependent variable.

[figure 1 about here]

Questionnaires. After the experiment, participants were asked to fill out a self-made questionnaire to evaluate the successfulness of the conditioning phase and whether their expectations and fear for the stimulus could potentially drive the effect. Participants were asked to report about their pain experience ('How painful did you find the electrocutaneous stimuli?'), how unpleasant they rated the stimulus ('How unpleasant did you find the electrocutaneous stimuli?'), and their expectations and fear ('To what extent did you expect that the right/left hand movement cue would be followed by a painful stimulus?' and 'To what extent were you afraid that the right/left hand movement cue would be followed by a painful stimulus?') on an eleven-point numerical rating scale (anchored 0 = not at all and 10 = very strongly [41]. Also, they were asked to fill out a Dutch version of the Pain Vigilance and Awareness Questionnaire (PVAQ), which is a valid and reliable questionnaire that evaluates the participants' dispositional attention and vigilance for pain sensations [28]. This questionnaire contains 16 items (e.g., I pay close attention to pain) which participants are asked to rate a scale from 1 ("never") to 5 ("always").

EEG recording and analyses. EEG was recorded continuously using a Biosemi ActiveTwo recording system at a sampling rate of 2,048 Hz from 64 active electrodes, placed according to the international 10/20 setting. EEG signals were referenced online to the active Common Mode Sense (CMS) and passive Driven Right Leg (DRL) ground electrodes. Bipolar electrodes were placed respectively above and below the left eye and next to the outer left and right canthi to record eye movements. Electrode contact was checked by the offset values (i.e. running average of voltage at each electrode), which were kept between -50 and 50 µV at all electrodes.

EEG data were analyzed off-line using Brainvision Analyzer 2.1 (Brain Products GmbH, Munich, Germany). First, signals were re-referenced to the right and left mastoids, band-pass filtered between 0.1 and 30 Hz and epoched from -200 ms to 500 ms. Prior to averaging, artifacts due to eye blinks were automatically corrected by means of the Gratton et al. algorithm [21]. Next, an automatic artifact rejection was applied including a gradient check (maximum allowed voltage step: 50 µV/ms within 200 ms before and after the locked event), a minimum/maximum amplitude check (-75 µV and 75 µV respectively), and a low activity check (0.5 µV within an interval length of 100 ms). Since we were not interested in left/right hand differences, data from the stimulation of the left hand were flipped as if they were received on the right hand. Data were then averaged to obtain, for each participant, four waveforms in response to stimuli applied to: (i) the pain-related hand while anticipating a movement with the pain-free hand (NoPain cue-Pain location), (ii) the pain-free hand while anticipating a movement with the pain-free hand (NoPain cue-NoPain Location), (iii) the pain-related hand while anticipating a movement with the pain-related hand (Pain Cue-Pain Location), (iv) the pain-free hand while anticipating a movement with the pain-related hand (Pain Cue-NoPain Location). Based on the literature [2,4,20], and on visual inspection of the data, two components were clearly identified: an earlier negative component around 120 ms with a topography contralateral to the stimulated hand and a later positive component around 250 ms located centrally. Note that components were identified on the basis of a collapsed localizer that was created by averaging the waveforms of the four different conditions at the relevant electrodes [27]. This average waveform peaked at 127 and 248 ms for the N120 and P200 component respectively. Similar to previous studies, the earlier component of the averaged waveform was centered around electrodes C3, C5, FC3, FC5 [2,4,20] (figure 2). The latter positive component had a central topography around electrodes FCz and Cz [2] (figure 3). To further explore these components for each condition, mean area amplitudes were exported from the abovementioned electrodes. Mean amplitude was selected to quantify the components because it is an unbiased measure [26]. A time frame between 102 and 152 ms, and 178 and 318 ms centered around the peak of the collapsed localizer was selected for data extraction of the different conditions [27] based on timeframe widths used in earlier studies [14,33]. All statistical analyses were conducted with SPSS Statistics 22 on the exported mean area amplitudes. Data were analyzed by means of a 2 (type of cue: pain-accompanying movement vs movement without pain) x2 (stimulation location: pain-related location vs pain-free location) repeated measures analysis of variance (ANOVA). Post-hoc testing was conducted only after significant interactions. Multiple comparisons were adjusted by means of a Bonferroni Correction.

To evaluate the relationship between the SEPs and the questionnaires, the indexes of the interactions were calculated as the differences of the mean values under the curves ($M_{\text{NoPainCue\_PainLoc}} - M_{\text{PainCue\_PainLoc}}$) – ($M_{\text{NoPainCue\_NoPainLoc}} - M_{\text{PainCue\_NoPainLoc}}$) for both components and correlated with the participants' reported amounts of fear, pain expectations, and scores on the PVAQ scale.

Results

Self-report data. Participants selected an average intensity of 2.91 mA (*SD*= 1.5, range = 1.5 – 8.0 mA) for the ES and rated these stimuli as painful (*M*= 6.61, *SD*= 1.44) and unpleasant (*M*=7.39, *SD*= 1.71). Furthermore, they reported that they expected more pain before performing a pain-accompanying movement (*M*= 7.25, *SD*= 1.20) compared to the neutral movement (*M*=0.77, *SD*=1.06), *t*(38)=25.793, *p*<0.001, *d*= 4.13. Similarly, the participants also reported to experience more fear when they had to perform a pain-accompanying movement (*M*= 7.14, *SD*= 2.14) compared to the neutral movement (*M*=0.87, *SD*=1.45), t(38)=17.27 *p*<0.001, *d*= 2.76, indicating a successful manipulation. Finally, the mean score on the PVAQ was 36.56 (*SD*= 12.20), which is comparable to the scores for this population in previous studies [40,41].

ERP data

N120. The N120 was larger for the collapsed movement trials (*M*=-1.25, *SD*=1.75) than for non-movement trials (*M*=-0.59, *SD*=1.72), *t*(38)=-3,80 *p*<0.001, *d*= 0.18. This suggests that movements may enhance SEP amplitudes compared to no-movement trials. Next, the 2x2 (cue type x stimulus location) ANOVA revealed a significant main effect of cue, *F*(1,38)=11.92, *p*=0.001, *d*= 0.55, and a significant main effect of stimulus location, *F*(1,38)=4.16, *p*=0.048, *d*= 0.33. Moreover, the analysis revealed a significant cue x location interaction, *F*(1,38)=5.43, *p*=0.025, *d*= 0.37 (see figure 2). Further t-tests revealed when stimulating at the pain-threatened location, responses were larger when the participants were cued to perform a pain-accompanying movement compared to a pain-free movement (*t*(38)=-3.80; *p*=0.004, *d*= 0.31). With regard to tactile SEPs at the pain-free location, there was no difference between a pain-accompanying movement and the movement without pain (*t*(38)=.93; *p*=0.821, *d*= 0.15). When anticipating a pain-accompanying movement, t-tests revealed larger amplitudes at the threatened location compared to the pain-free location (*t*(38)=-2.80; *p*=0.031, *d*= 0.45). No difference in tactile SEPs between the locations was found when anticipating a movement without pain (*t*(38)=-.416; *p*=0.990, *d*= 0.07).

P200. A t-test comparing no-movement trials (*M*=4.49, *SD*=2.74) and collapsed painful and pain-free movement trials (*M*=3.72, *SD*=2.64) suggested also an effect of movement anticipation, *t*(38)=-2.78, *p*=0.008, *d*= 0.45. Next, the 2x2 repeated measures ANOVA revealed a significant main effect of cue, *F*(1,38)=12.55, *p*=0.001, *d*= 0.57, but no main effect of stimulus location, *F*(1,38)=1.43, *p*=0.239, *d*=0.19. Furthermore, no significant interaction was found, *F*(1,38)=1.01, *p*=0.321, *d*=0.16 (see figure 3). SEPs were larger when anticipating a pain-accompanying movement than when anticipating the movement without pain, regardless of whether the tactile stimulus was presented at the pain-related or the pain-free location.

Correlations. When correlating the SEP amplitudes and the participants' rates of pain and unpleasantness, no correlations reached significance (all p>.05). Similarly, the PVAS scores did not correlate significantly with the N120 amplitudes(r=.30, p=.067) or the P200 amplitudes (r=.11, p=.459).

[figures 2 and 3 about here]

Discussion

The current study described cortical responses to tactile stimuli while anticipating pain-accompanying movements versus movements without pain. It was hypothesized that the SEPs to tactile stimuli presented at the threatened body location would be enhanced, as compared to SEPs to tactile stimuli presented on the pain-free body location, but only when anticipating a pain-accompanying movement. In line with the hypothesis, the results indicated that a pain-accompanying movement influenced the amplitude of the SEP evoked by a tactile stimulus.

The analysis on the amplitude of the earlier and negative component, the N120, showed a significant interaction between the type of anticipated movement (pain-accompanying versus pain-free) and the stimulus location, with larger amplitudes when stimulating at the pain-related as compared to the location without pain, but only when anticipating a pain-accompanying movement. The negative earlier wave, which is thought to originate from the secondary somatosensory cortex [1,3] is typically larger for attended than unattended stimuli [18]. Note, however, that the study by García-Larrea, and colleagues [18] describes differential explanations for the N120 and the N140 SEP. Specifically, the earlier component would reflect an exogenous attentional process and the latter an endogenous attentional process, whereas the N120 in the current study could only be explained by endogenous processes. However, it is possible that the difference explanations might also be the result of differences in somatosensory stimulation (i.e. electrical versus vibrotactile). The results of the current study may thus indicate that when participants are preparing a pain-accompanying movement, attention towards the threatened body part is heightened, resulting in enhanced cortical responses to somatosensory input at that body part. More specific, the expectation of pain probably resulted in vigilance towards pain-related information, guiding attention towards the pain-relevant body location [36], as described in the fear-avoidance model [24]. These results are in line with previous behavioral studies regarding attentional bias towards pain-related body location [10,37,41]. However, the current study substantially extends these earlier findings by revealing, for the first time, cortical processes involved in this attentional bias and using movements as a signal for pain. Moreover, the current methodology allows the exclusion of non-attentional interpretations such as response strategies with regard to the somatosensory inputs, as in previous studies with behavioral measurements of attentional bias [13,36]. The current study resembles better daily life situations than previous studies in two ways. First, threat of pain was induced by movements, which are typical cues for pain, in daily life and clinical situations [44]. Second, somatosensory inputs were task-irrelevant, and participants were not instructed to actively allocate attention to these stimuli.

For the second component, the P200, the results indicated that when anticipating a pain-accompanying movement, tactile stimuli elicited a larger response than when anticipating a movement without pain. Interestingly, and in contrast to the N120, this effect occurred regardless of the location at which tactile stimuli were presented. Similar as the N120, the P200 SEP has been suggested to be dependent on the participants' mental processes, such as cognitions and expectations [14]. Moreover, this component is suggested to reflect a more detailed and complex cognitive or emotional processing of the stimulus, such as memory or stimulus evaluation [23.32]. Indeed, cues that signal threat may induce a larger P2 component (a positive peak around 200 ms, similar as the P200) compared to no-pain cues [45]. The P200 may thus reflect the participants' fearful state when anticipating pain. Also, similar as the N120 component, the P200 component has shown to be modulated by attention [14,15,23]. Moreover, the current effect occurred irrespective of the location of the stimulus. This corresponds to earlier findings in the literature (e.g. the review on cortical responses to nociceptive stimuli [25]), where the P2 amplitude seems to reflect broad general attention, but not selective spatial attention [5,6,7,8]. In sum, it might well be that the P200 SEP reflects an unspecific effect of threat, and maybe even a heightened state of awareness, or arousal.

The ERP results did not correlate with self-reported fear and expectation of pain during the experiment, nor with dispositional vigilance or awareness for pain. This may be somewhat surprising considering that it is well known that individuals who expect or fear pain tend to scan their body for threats [24]. However, it is plausible that the measures used in this study were not sufficiently specific or sensitive to detect individual differences in the experimental context. For example, it is possible that probing the fear of pain after each trial rather than once at the end of the experiment would have been a more appropriate measure [31].

To our knowledge, this study is the first to use SEPs to investigate an attentional bias towards a pain-related location when preparing for pain-accompanying movements. In summary, we have shown that the anticipation of a pain-accompanying movement may affect the processing of task-irrelevant somatosensory input, and that this is likely to be driven by attentional processes. Based on the results of the current study, it can be suggested that anticipating a pain-accompanying movement elicits two different processes: first an attentional bias towards somatosensory input at the threatened location, as reflected in the N120 component, and second, a threat-induced and location-unspecific bias towards all incoming somatosensory input, as reflected in the P200 component. The present study provides important new insights in the interplay between pain, attention and movements, and its consequences at a cortical level. Moreover, the current paradigm may be useful in the study of somatosensory processing in clinical populations, such as patients suffering from unilateral musculoskeletal pain disorders.

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Figures

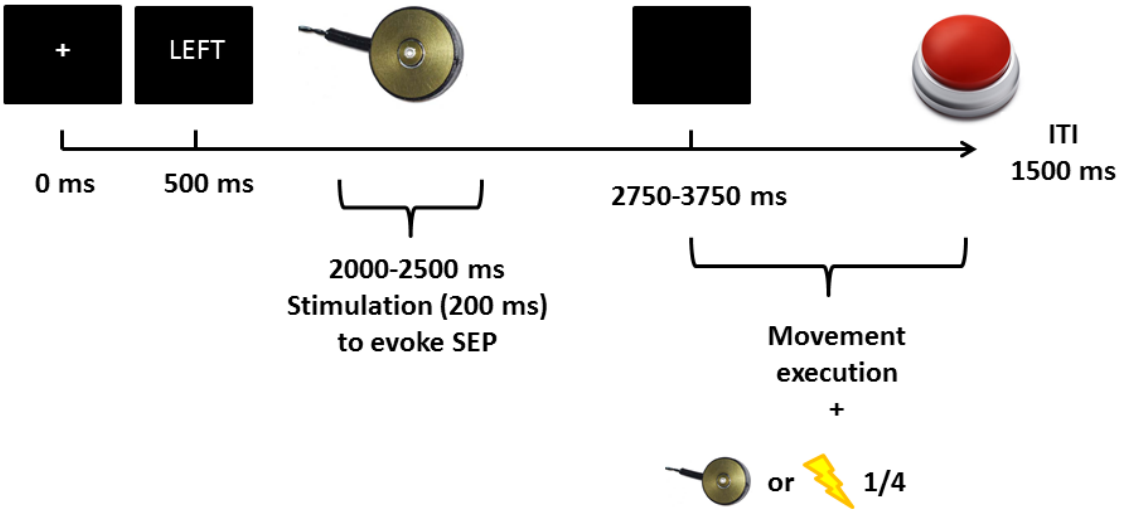

Figure 1. Design of the experiment . Each trial started with the presentation of a fixation cross (500 ms), followed by the presentation of a cue. Participants were instructed to respond to the disappearance of the cue. During the presentation period of this cue, a tactile stimulus was presented on the left or right hand. As soon as the cue disappeared, participants had to press the button of the response box as fast as possible.

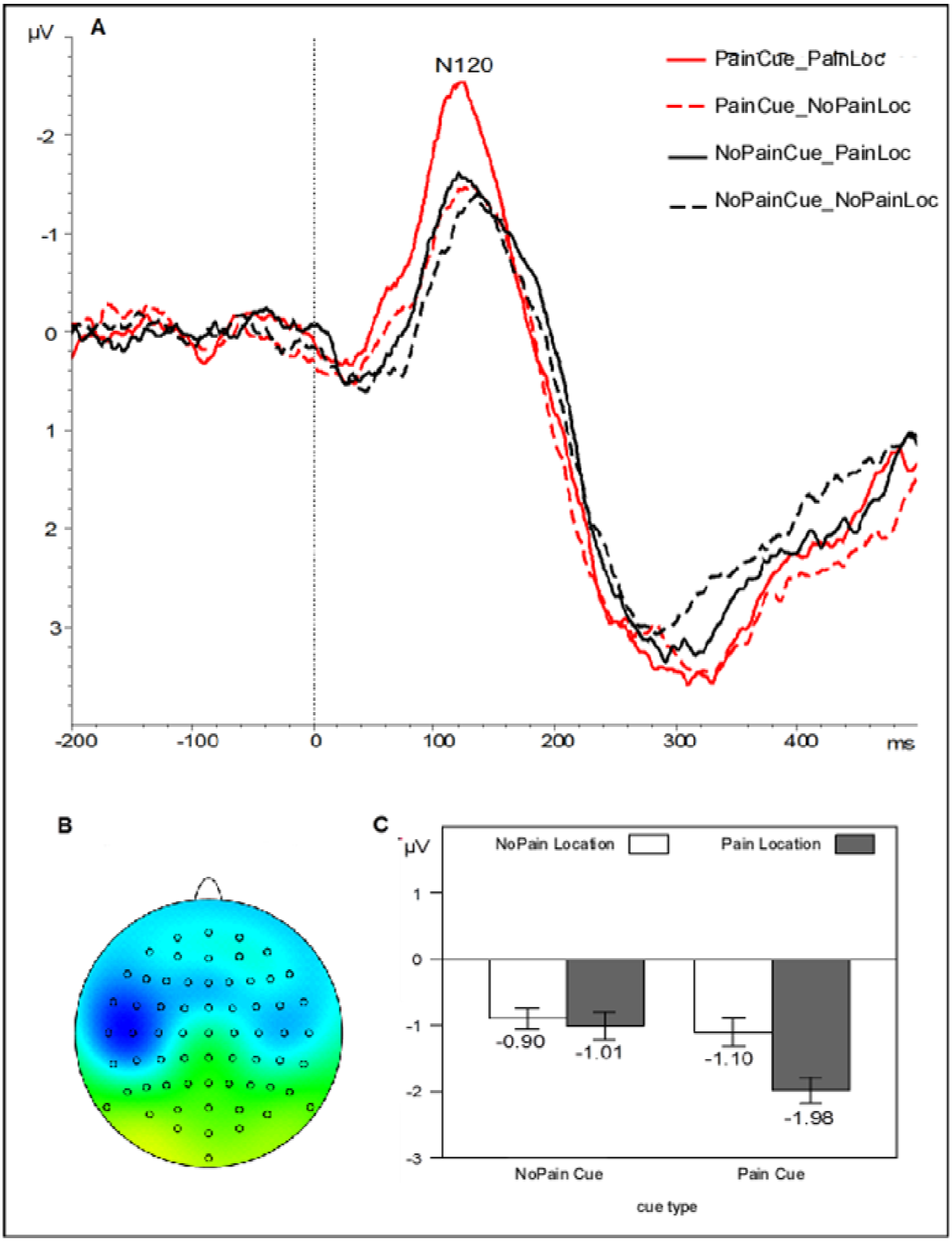

Figure 2. N120 results. A) Grand average N120 SEP, recorded at a representative electrode position (C5) for the 4 different conditions. B) Mapping view of the grand average at 127 ms after stimulus onset C) Bar graphs of the mean amplitudes and standard errors of each condition.

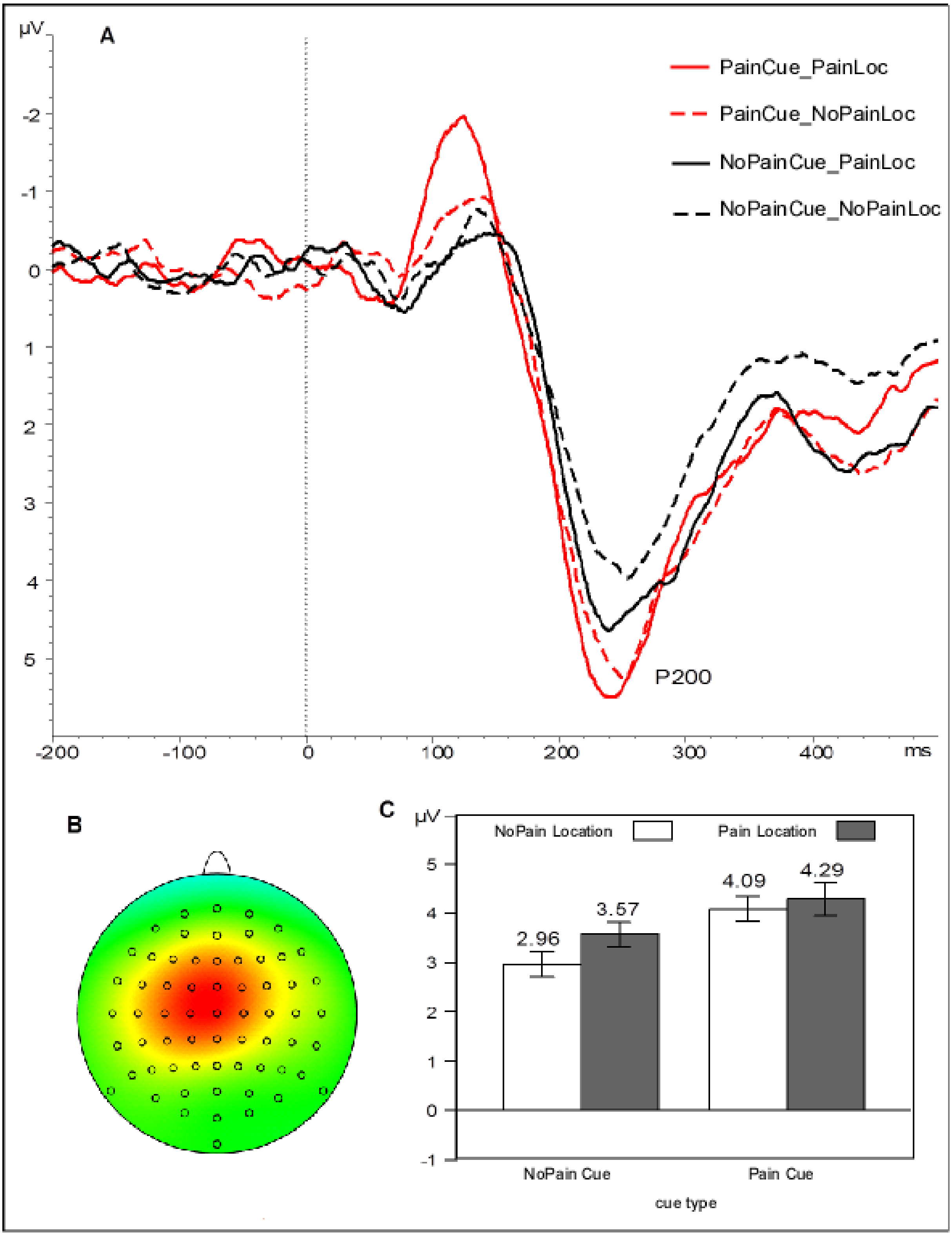

Figure 3. P200 results. A) Grand average P200 SEP, recorded at a representative electrode position (Cz) for the 4 different conditions. B) Mapping view of the grand average at 248 ms after tactile stimulus onset. C) Bar graphs of the mean amplitudes and standard errors of each condition.