

Emotional pain modulation: an effect of emotion, attention or empathy for pain?

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Abstract

In this study it was explored whether pain perception is influenced by emotion, attention and / or empathy for pain using somatosensory-evoked potentials (SEPs). It was expected that valence effects will be found on the early negative peak of the SEP (N1) and attention effects were found on the later positive peak (P2). Furthermore, effects of arousal and empathy for pain can be expected, but the temporal characteristics of arousal and empathy for pain were not clear. Two stimulus intensities, painful and nonpainful, and three emotional conditions, pain-related, neutral and pleasant, were used. Nineteen students participated in the experiment (ten males, mean age 20.8). Emotional and neutral pictures (in total 120) of the IAPS and pain-related pictures from previous experiments were used. For N1, significant main effects of intensity and electrode were found. For P2, significant main effects of emotion and intensity were found, with highest amplitudes for neutral pictures. For both N1 and P2, activity was larger for painful stimuli. Electrophysiological source analysis shows that activity is found in SI/SII, multisensory cortex and ACC, with highest activation for painful conditions. This experiment showed that emotional pictures captured attention and therefore less attention was focused on the pain.

Introduction

Recently, the interest in the influence of emotion on pain is growing. Since the introduction of the gate control theory of pain (Melzack & Wall, 1965), the focus has changed from a one-to-one relationship between stimulus characteristics and pain perception to the multidimensional experience pain is (Melzack, 1999; 2001). The definition of pain also clarifies that pain is more than just potential tissue damage. The International Association for the Study of Pain (IASP) defines pain as: 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Tracey & Mantyh, 2007). The 'objective' presence or potential for, tissue damage is defined as nociception (Rainville, 2002). Because of the subjectivity of pain, it can be expected that pain perception is modulated by many factors within the brain. For example, the effects of emotion and attention on pain were extensively studied (de Wied & Verbaten, 2001; Kenntner-Mabiala, Andreatta, Wieser, Muhlberger & Pauli, 2008; Villemure & Bushnell, 2002).

Although there has been published a number of papers with respect to modulation of pain experiences, Electroencephalographic (EEG) papers with respect to this topic are rare. EEG studies revealed information about the temporal characteristics of pain perception in the cortex. In most studies, the activation in different brain regions evoked by stimulation was used to study pain. These somatosensory evoked potentials (SEPs) bring out the direct change in activation after stimulation. Studies showed that the waveform of pain SEPs consists of a negative peak at 100-240 ms (N1 / N2) and a positive peak at 200-390 ms (P2 / P3) (Christmann, Koeppe, Braus, Ruf & Flor, 2007; Kakigi, Watanabe & Yamasaki, 2000; Kanda et al., 2002; Zaslansky, Sprecher, Katz, Rozenberger, Hemli & Yarnitsky, 1996a; Zaslansky, Sprecher, Tenke, Hemli & Yarnitsky, 1996b). These characteristics were not found when the stimulation was not painful and it can therefore be stated that these brain activations are related to pain (Kakigi et al., 2000). The early negative peak is thought to be mainly influenced by stimulus intensity (Christmann et al., 2007), while the later positive peak is thought to be influenced by emotional-motivational aspects of pain (Chen, 2001; Zaslansky et al., 1996a). Imaging techniques such as functional Magnetic Resonance Imaging (fMRI) increased the knowledge about brain regions involved in pain perception and have mapped the so-called ' pain matrix' in the brain. According to Chen (2001), Peyron, Laurent & Garcia-Larrea (2000), Rainville (2002) and Schnitzler and Proner (2000) the most important brain regions involved the processing of pain are the primary

somatosensory cortex (SI), the secondary somatosensory cortex (SII), the insula, the thalamus and the anterior cingulate cortex (ACC). SI and SII are thought to be involved in the sensory-discriminative dimension of pain (Chen, 2001; Peyron et al., 2000; Rainville, 2002; Schnitzler et al., 2000; Treede, Kenshalo, Gracely & Jones, 1999), whereas affective, cognitive and motivational elements of pain are thought to be processed in ACC and thalamus (Chen, 2001; Petrovic & Ingvar, 2002; Peyron et al., 2000; Price, 2000; Rainville, 2002; Schnitzler et al., 2000; Tracey, 2005; Treede et al., 1999). The insula is stated to have a wide variety of functions in both the sensory-discriminative and affective-motivational dimension of pain (Peyron et al., 2000; Schnitzler et al., 2000; Tracey, 2005; Treede et al., 1999). Research also shows a relationship between SEPs and brain regions involved in pain. Christmann et al. (2007) found that BOLD effects in SI, SII and ACC corresponded with the SEP components found. Other researchers used source analysis and found the following relationships between SEPs and brain locations: early activation originated from SI (< 110 ms post stimulus) and SII (< 160 ms) and a late source was located in the cingulated region (200 – 300 ms) (Bromm & Chen, 1995; Tarkka & Treede, 1993). In this study, the effect of emotional modulation on pain processing in the brain was examined using somatosensory-evoked potentials (SEPs). Literature shows four possible explanations for the emotional modulation of pain: an influence of valence, arousal, attention and empathy for pain. In the section below, the different explanations are examined and hypotheses for the present study are presented.

Research shows that emotion influences pain processing (Villemure et al., 2002). In the last decade, the emotion-pain research focused mostly on the emotional priming theory (Lang, 1995). According to this theory, two emotional systems can be active: the appetitive and the aversive system. Activation of one of the two is influenced by valence (pleasant/appetitive – unpleasant/aversive) and the level of activation is influenced by the degree of arousal: the higher the degree of arousal, the higher the level of activation of the brain and the body. According to Barry, Clarke, McCarthy, Selikowitz & Rushby (2005) arousal is defined as: ‘the current energetic level of the organism’. If one of these systems is activated (through emotional pictures, odors, films, etc), processing of a subsequent similarly valenced stimulus is processed more thoroughly. This means that evoked negative emotions lead to a more thorough processing of painful stimulation. The International Affective Picture System (IAPS) (Lang, Bradley &

Cuthbert, 2005) is convenient for this type of research. The IAPS consists of a standardized set of pictures systematically varied on the two major dimensions of emotion: valence and arousal (Lang, 1995). Most of the pain research in recent years supported the emotional priming theory: overall, negative emotions lead to lower pain thresholds and positive emotions lead to higher pain thresholds (de Wied et al., 2001; Kenntner-Mabiala & Pauli, 2005; Meagher, Arnau & Rhudy, 2001; Rainville, Bao & Chrétien, 2005; Rhudy, McCabe & Williams, 2007; Rhudy, Williams, McCabe, Rambo & Russell, 2006; Zelman, Howland, Nichols & Cleeland, 1991). Previous SEP research on pain and emotion showed that the negative valence leads to higher amplitudes for painful stimulation on N1 of the SEP (Kenntner-Mabiala et al., 2005). According to Tarkka et al. (1993), Bromm et al. (1995) and Christmann et al. (2007), activation is associated with activity in SI and SII. Not only valence, but also arousal contributes to pain perception. According to the emotional priming theory and research on emotional modulation of pain, the level of arousal only influences the magnitude of effect for the negative or positive state someone is in (Lang, 1995; Rhudy, Williams, McCabe, Russell & Maynard, 2008).

Previous research on the influence of emotion on pain perception showed that also arousal can have a distinct effect on pain perception (Kenntner-Mabiala, Gorges, Alpers, Lehmann & Pauli, 2007). In this study, the effect of music on pain perception was examined. Fast music was found to be more arousing and higher pain ratings were found for fast music; no significant effects of the emotional valence the music induced were found. This research showed that higher levels of arousal independently can lead to lower pain thresholds.

Although valence and arousal are the two dimensions of emotion and are most likely to influence pain perception through emotional modulation, emotion can also influence pain perception because of the distracting properties of emotional materials (Meagher et al., 2001; Rhudy & Meagher, 2000, 2003). Previous studies showed that emotional pictures (unpleasant or pleasant and scoring high on arousal) were processed more thoroughly than neutral pictures (low in arousal) (Cuthbert, Schupp, Bradley, Birbaumer & Lang, 2000; Lang, 1995; Schupp, Cuthbert, Bradley, Hillman, Hamm & Lang, 2004). According to Keil, Bradley, Hauk, Rockstroh, Elbert & Lang (2002) and Schupp et al. (2004), emotional pictures are motivationally relevant and therefore automatically demand attention. Kenntner-Mabiala et al. (2005) found that the P260 amplitudes were diminished for positive and negative pictures, showing the largest amplitude for neutral pictures. Most experiments showed an effect of attention on later positive components (>

200 ms) (Yamasaki, Kakigi, Watanabe & Hoshiyama, 2000), indicating a change in activation for ACC (Kenntner-Mabiala et al., 2005; Legrain, Guérit, Bruyer & Plaghki, 2002). Kenntner-Mabiala et al. (2008) state that this effect was caused by the level of arousal of the pictures.

Two experiments by de Wied et al. (2001) showed the content of the emotional cue can also have an influence on pain processing. Participants seeing pictures of people in pain had low pain thresholds; in contrast, negative pictures without a painful element seemed to have the same effect on pain thresholds as neutral pictures. According to Preston and de Waal (2002), perception of emotion activates the neural mechanisms that are responsible for the generation of emotions, described as the perception action model. This can also be the case for observing pain or 'empathy for pain' (Fan & Han, 2008; Singer, Seymour, O'Doherty, Kaube, Dolan & Frith, 2004; Ushida et al., 2008). The recent growing neuroscientific research on empathy for pain contributes to the knowledge about the effects of observed pain on brain areas involved in actual pain. From research on empathy for pain, it is clear that seeing someone else in pain activates the brain regions involved in the emotional-motivational aspects of pain: the ACC, insula and thalamus (Botvinick, Jha, Bylsma, Fabian, Solomon & Prkachin, 2005; Fan et al., 2008; Jackson, Brunet, Meltzoff & Decety, 2006; Jackson, Meltzoff and Decety, 2005; Morrison & Downing, 2007; Morrison, Lloyd, di Pellegrino & Roberts, 2004; Singer et al., 2004). But, researchers also found activation in the SI during processing of pain of others (Bufalari, Aprile, Avenanti, Di Russo & Aglioti, 2007). Not many researchers have examined the effects of empathy for pain on pain processing yet. Godinho, Magnin, Perchet and Garcia-Larrea (2006) found that pictures showing physical pain content enhanced SEP amplitudes in comparison to unpleasant pictures without reference towards pain. The effect was found later than 270 ms. Valeriani et al (2008) showed that observation of needle penetration reduced the N1/P1 component of the SEP, indicating effects of empathy for pain on SI and SII. The effects were explained by the competitive influence of the observed pain stimuli and painful stimulation. So, both Godinho et al. (2006) and Valeriani et al. (2008) found effects of empathy for pain on SEPs, but the temporal characteristics remain a topic for discussion.

In this study, SEPs were used to examine the effects of valence, arousal, attention and empathy for pain on the cortical processing of pain. Emotional pictures were varied on valence, arousal and pain-related content. Three emotional picture conditions were used: pain-related

(unpleasant), neutral and pleasant. In contrast to other studies on emotional modulation of pain (Godinho et al., 2006; Kenntner-Mabiala et al., 2005; 2008), also pain-related and pleasant pictures varied significantly on arousal. According to Kanda et al. (2002), it is important to randomize stimulus intensities for reliable pain research. Therefore in this study, nonpainful and painful electrical stimuli were used. Furthermore, it is interesting to examine if the effects of emotion only influence painful stimuli or also nonpainful stimuli. Kenntner-Mabiala et al. (2005; 2008) used the same paradigm and found larger amplitudes for painful stimuli on both N1 and P2. Furthermore, in both studies, an effect of emotion on N1 is only found for painful stimuli.

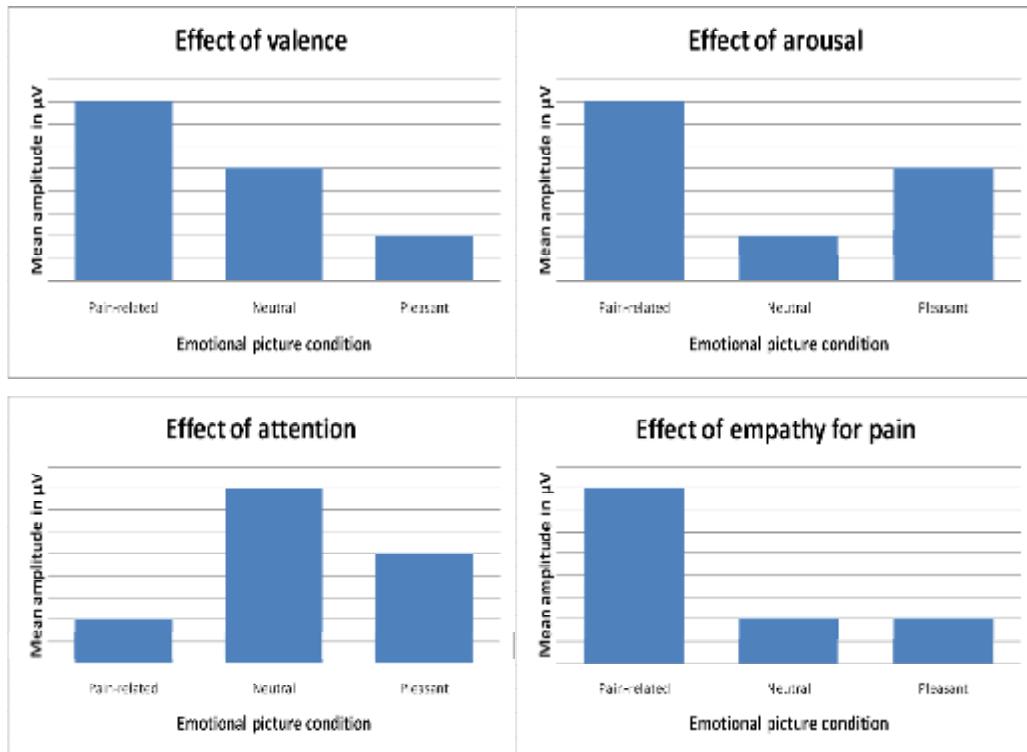


Figure 1. The four hypotheses in diagrams.

In figure 1, the four hypotheses are displayed. If pain perception is influenced by valence, effects were expected on N1 with highest amplitudes for pain-related pictures and lowest for pleasant pictures, which is associated with activation from SI and SII. For attention, effects were expected on P2 with highest amplitudes for neutral pictures and lowest for pain-related pictures, associated with activation in ACC (Christmann et al., 2007; Kenntner-Mabiala et al., 2005; 2008). The literature was ambiguous on the effects of arousal and empathy for pain. In the case of arousal,

highest amplitudes were expected for pain-related pictures and lowest amplitudes for neutral pictures. If empathy for pain has an influence on pain perception, highest amplitudes were expected for pain-related pictures and low amplitudes are expected for neutral and pleasant pictures. Finally, if pain processing is not modulated by emotion, attention or empathy for pain, SEP amplitudes were expected to be the same for the different emotional conditions. It was hypothesized that only painful stimulation was modulated on N1. Previous studies by Kenntner-Mabiala et al. (2005; 2008) showed that the attention effects on P2 were present for both painful and nonpainful stimuli.

Methods

Participants

Twenty students of the University of Twente participated in the study. One participant was excluded because of knowledge of the pictures used in the experiment. Of the other nineteen participants ten were male. The mean age was 20.8 (range 18 to 25 years). The participants were recruited on the University of Twente. Most of the students were first- and second year Social Science students and they received credits for participation; seven subjects participated voluntarily. None of the participants had a neurological or psychiatric history or recent symptoms. Furthermore, they had normal or corrected-to-normal vision, were free of pain and used no pain medication at the time of the experiment. The study was approved by the ethics committee of the Radboud University (Nijmegen) and the University of Twente. All the participants were right-handed.

Visual stimuli

In total, 120 pictures were used in the experiment, of which 40 had a neutral content, 40 were pleasant and 40 were used in the pain-related category. 84 of the pictures were selected from the International Affective Picture System. The IAPS does not consist of sufficient pictures consisting physical pain, therefore 36 pictures from other researchers were used. Nine were used from the study of Ogino, Nemoto, Inui, Saito, Kakigi and Goto (2006), which are pictures consisting arms and hands pricked with needles. Also, 27 pictures from a study of Jackson, et al. (2006) were used. These pictures present right hands and feet in painful situations (i.e. foot in glass, foot in fire, hand between car door, etc.). The 36 pictures from other experiments were first validated in two pretests to establish valence and arousal levels and pain-relatedness.

After picture selection, two sets of 120 pictures were validated in a pilot experiment. Each set consisted of 40 pain-related pictures, 40 pleasant pictures and 40 neutral pictures selected from the IAPS (Lang et al., 2005) and pictures from previous experiments by Jackson et al. (2006) and Ogino et al. (2006). In total, 204 participants (62 male, mean age 20.7 years (SD = 3.7)) participated in the second pretest. A group of 100 participants evaluated the first picture set and 104 participants rated the second picture set on valence and arousal. In this experiment, the pictures were only rated on one scale by a participant to overcome interscale effects. Furthermore, some participants rated the pictures on inverted scales. The second picture set was

chosen because the three subsets differ more on valence and arousal. Below, the mean scores for the used picture set are presented.

Table 1. *Mean scores and standard deviations for the three subsets.*

	Arousal (SD)	Valence (SD)
Pain-related	7.31 (0.45)	2.00 (0.39)
Neutral	2.84 (0.56)	5.06 (0.46)
Pleasant	5.09 (0.86)	7.19 (0.71)

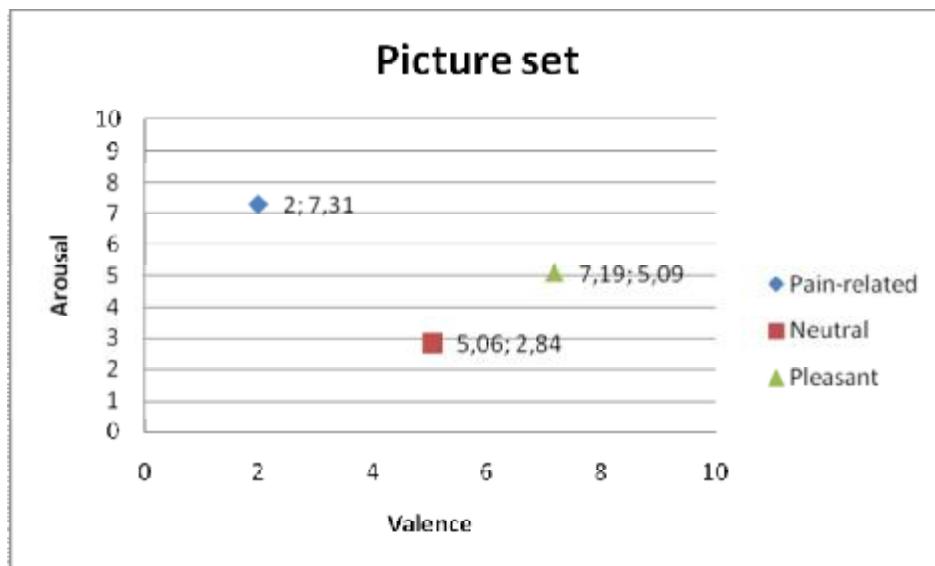


Figure 2. Diagram of the picture set; mean scores for the subsets are shown.

The three emotional picture conditions vary significantly on both valence (pain and neutral: $t = 31.9, p < 0.001$; pain and pleasant: $t = -40.5, p < 0.001$; neutral and pleasant: $t = -15.9, p < 0.001$) and arousal (pain and neutral: $t = -39.4, p < 0.001$; pain and pleasant: $t = 14.4, p < 0.001$; neutral and pleasant: $t = -13.9, p < 0.001$).

Electrical stimuli

The Constant Current Stimulus Generator (2005.101) from the Radboud University in Nijmegen was used to generate electrical stimuli. During the experiment, two types of electrical stimuli were used: nonpainful (below pain threshold) and painful (above pain threshold). Nonpainful and painful stimuli differed in number of pulses: in the nonpainful condition 1 pulse was used and in

in the painful condition the same pulse was sent out 5 times. Pulse duration for both conditions was 2 ms and time between pulses for the painful condition was 5 ms. Before the experiment, the value used in the experiment was decided using the five electrical stimuli and the Visual Analogue Scale (VAS) scale. A series of stimuli were presented, starting with 0.1 mA and heightened in steps of 0.1 mA until pain tolerance level (VAS 10) was reached. Sensation level (mean: 0.5 mA), pain threshold (mean: 1.0mA) and pain tolerance level (mean: 4.2 mA) were established for every participant. The value used during the experiment was set on 75% between the pain threshold and pain tolerance level. The mean electrical strength used in the experiment is 3.6 mA which participants rated 7.5 on VAS; well above pain threshold. On average, the nonpainful stimulus used in the experiment was rated 4.1 on VAS; below pain threshold. After the experiment, the painful stimulus was rated 6.9 on VAS and the nonpainful stimulus was rated 3.0 on VAS. Clearly, the electrical stimuli used in the experiment were respectively below and above pain threshold.

Task and procedure

After arrival in the experiment room, the participant received information about the experiment and signed the informed consent. The participant was asked about medicine use or recent pain experience. Participants experiencing pain or using pain medicine would be excluded from the study. After that, the participant filled in the Annett Handedness Inventory (Annett, 1970) and the Thayer mood scale. Before determination of the sensation level, pain threshold and pain tolerance level, the participant was informed about the EEG measurement and the Constant Current Stimulus Generator. The skin of the left forearm was smoothed and cleaned to reduce impedance. The electrodes for the electrical stimuli were filled with conducting gel and attached to the arm using tape (impedance levels were below 30 kOhm). Then, pain levels were established and the EEG electrodes were attached. After that, the experiment was started in Presentation. In figure 3, the sequence of events on every trial is presented. The interstimulus interval (ISI) was varied, to avoid anticipation as much as possible.

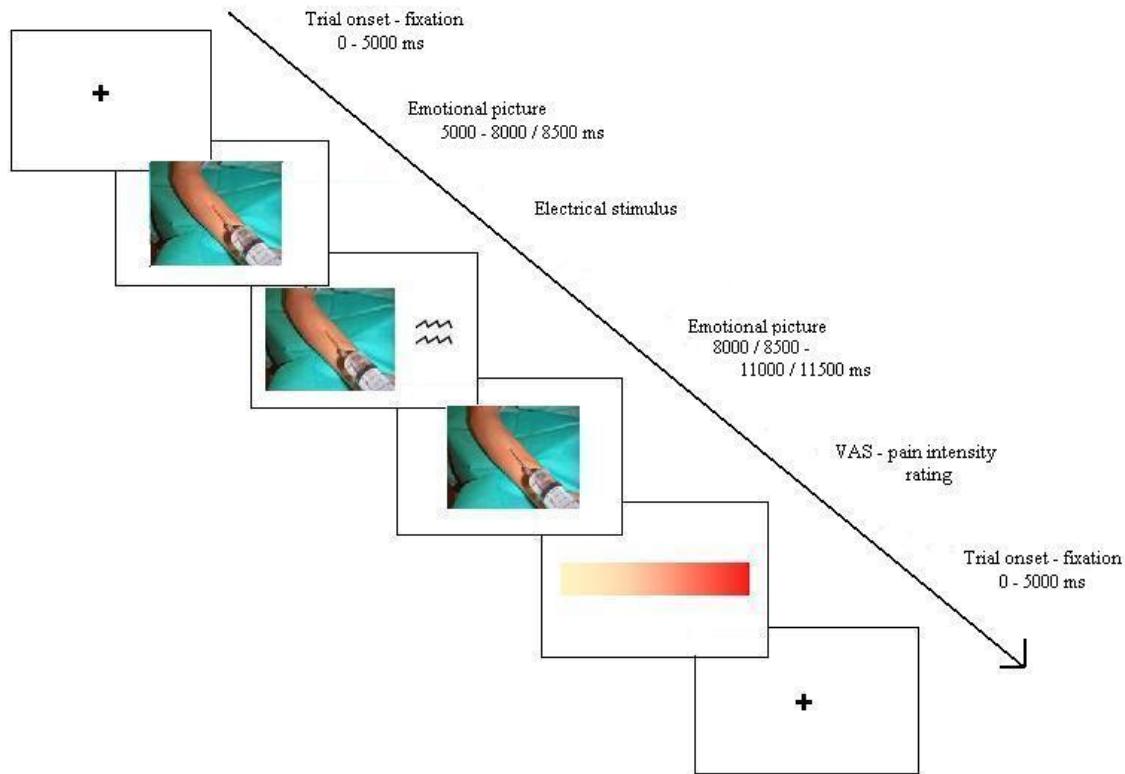


Figure 3. At the beginning of each trial, a fixation cross appeared on the middle of the screen for 5000ms. Then, the picture (S1) was presented. After that, between 3000ms and 3500ms, the electrical stimulus (S2) was given. In the mean time, the picture stayed on the screen, for another 3000ms. After the picture, the VAS was presented and the participants had to rate the pain intensity. Then, the next trial started and the fixation cross was presented again.

Table 2. The six conditions of the experiment.

Electrical stimuli		
Emotional pictures	<i>Painful</i>	<i>Nonpainful</i>
	<i>Pain-related</i>	<i>Pain-pain</i>
	<i>Neutral</i>	<i>Neutral-pain</i>
<i>Pleasant</i>		
<i>Pleasant-pain</i>		
<i>Pleasant-nonpain</i>		

The 120 pictures were presented in four blocks of 30 pictures and 30 electrical stimuli. The electrical stimuli were equally divided over the different emotional pictures. For each of the six conditions, 20 trials were presented. In every block, 15 of the electrical stimuli were above pain

threshold and 15 were below pain threshold. After each block, the participant had a three minute break and impedance was checked. In total, the experiment took about two hours; over 1 hour of preparation and determination of pain values, 30 minutes for the actual experiment and 20 minutes of breaks and impedance checks. After the experiment, the pain levels were checked again and another Thayer mood scale was filled in. The participants were asked how they experienced the experiment; problems and other information were logged.

Data acquisition

A Pentium IV 3.00 Ghz computer was used with 1 GB RAM and 128MB video memory. The screen had a resolution of 1024 x 768, 32 bit, 70 Hz and 96 dpi. The subjects sat at about 63 cm from the screen.

Continuous EEG was recorded from an electrode cap. Impedance at all recording electrodes was less than 10 kOhm. For the EEG measures, 61 channels were placed according to the international 10-20 system. In addition, three bipolar channels were used to record heart rate, horizontal and vertical eye movements. To measure vertical EOG, the electrodes were placed above and below the left eye; horizontal EOG was measured with electrodes placed to the left and right external canthus. The ground electrode was located on the forehead. EEG was measured with a sampling rate of 500Hz. Signals higher than 200Hz were cutoff and were not recorded. For each stimulus, visual and electrical, a digital code was sent to the continuous EEG, allowing offline segmentation and averaging of the raw EEG data.

Data analysis

Electrophysiological data

Data were processed using Brain Vision Analyzer (version 1.05). Epochs were created from the continuous EEG from 100 ms prior to the electrical stimulus and 500 ms poststimulus and were baseline corrected with reference to the mean baseline interval (-100 to 0 ms). Furthermore, trials were excluded using automatic (maximal allowed voltage step: 100 μ V, minimal and maximal allowed amplitude: 120 μ V, lowest allowed activity 0.5 μ V, interval length: 100 ms) and ocular correction (vertical EOG: 120 μ V, horizontal EOG: 60 μ V). No participant was excluded on the basis of these corrections. For the nineteen participants, 7.24 % of the trials were excluded. After exclusion of trials, the data was averaged across each condition for each participant. Time

windows of 40 ms (+- 20 ms) of the Grand Averages were centered on the maxima of effects. Electrodes for further analysis were selected using previous literature on pain SEPs (Chen, 2001; Godinho et al., 2006; Kenntner-Mabiala et al., 2005, 2008; Zaslansky, 1996a, 1996b) and by visual inspection. For N1, the average amplitude of the time window 120-160 ms was used in the analysis. Furthermore, the average amplitude of the time window of 260-300 ms for P2 was selected. Both time windows were also found in previous studies (Chen, 2001; Kenntner-Mabiala et al., 2005, 2008; Zaslansky et al., 1996a, 1996b). It was decided to include the electrodes FCz, Cz, C3, C4 and PCz in the analysis. Three-way repeated measures ANOVA (intensity x emotion x electrode) was used; the electrodes with largest amplitudes on N1 and P2 were used for further analysis on emotion and intensity effects. An alpha level of .05 was used for all the statistical tests.

Electrophysiological source analysis

After the creation of grand averages for the six different conditions, the data were exported to Brain Electrical Source Analysis (BESA) to determine the contribution and level of activation of different brain areas for different time windows. Also, an overall grand average including all the six conditions was created to find an overall solution for the data. The global field power (GFP), a measure of changes in electric field strength, was used to identify the different processes contributing to the signal. Furthermore, previous research was used to support the locations found (Beauchamp, Argall, Bodurka, Duyn & Martin, 2004; Chen, 2001; Peyron et al., 2000; Rainville, 2002; Schnitzler et al., 2000). For every identified process two symmetrical dipoles were placed. The first time window was set on 62-92 ms, the second selected time window was 128-154 ms and the third time window was set on 182-202 ms. In the time window from 62 to 300 ms (including P2), the model explained 99.1% of the activation for all the conditions together. This model is applied to the six conditions to examine the amount of activation from the found locations for every condition. Principal component analysis was used to examine if the contribution of the different processes is the same for the six conditions.

Results

Electrophysiological data

A three-way repeated measures ANOVA was used to examine the effects of intensity (painful, nonpainful), emotion (pain-related, neutral, pleasant) and electrode (FCz, C3, Cz, C4, PCz) on cortical SEP amplitudes for N1 (120-160 ms) and P2 (260 – 300 ms). Figure 2 shows the Grand Average for painful and nonpainful stimuli. For the N1, highest amplitudes were found at C4. In figure 4, the mean amplitudes at C4 for painful and nonpainful are shown. For further analysis, C3 and C4 were included to examine effects of intensity, emotion and hemisphere. P2 had the highest amplitudes at the central sites: Cz, FCz and CPz; amplitude at Cz was highest and was used for further analysis. In figure 4 and 5, mean amplitudes at Cz for painful and nonpainful stimuli are displayed.

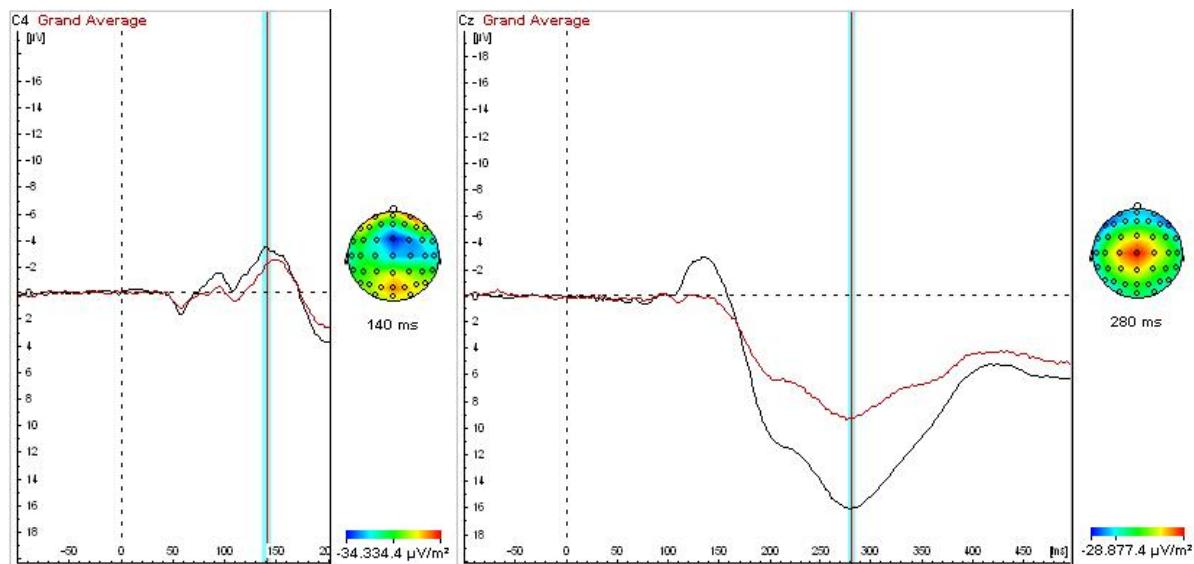


Figure 4. Mean amplitudes and CSD map at C4 on 140 ms for painful (black) and nonpainful (red) stimuli.

Figure 5. Mean amplitudes and CSD map at Cz on 280 ms for painful (black) and nonpainful (red) stimuli.

In the sections below, the effects for N1 at C3 and C4 and the effects for P2 at Cz are summed.

N1

The N1 amplitudes were higher for painful than for nonpainful stimuli, $F(1, 19) = 9.3, p < 0.007$. An effect of hemisphere was found, $F(1, 19) = 5.2, p < 0.035$, with the highest negative peak at C4 ($p < 0.004$). Effects of emotion were not significant $F(2, 38) = 3.1, p < 0.061$, but

showed a tendency towards higher amplitudes for the pain-related condition and lower for the pleasant condition. No interaction effects of emotion and intensity were found $F(2, 38) = 0.6, p < 0.515$. In figure 6 and 7, the amplitudes at C4 for painful and nonpainful stimuli for the three emotional conditions are displayed.

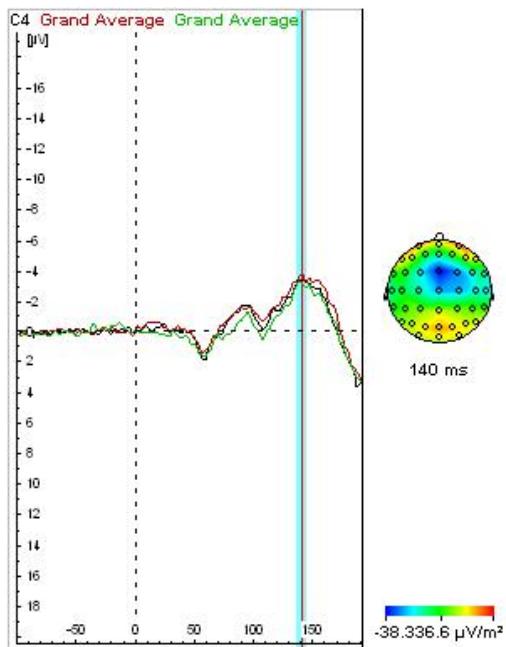


Figure 6. Grand Averages at C4 for painful stimuli for the three emotional conditions: pain-related (red), neutral (black) and pleasant (green).

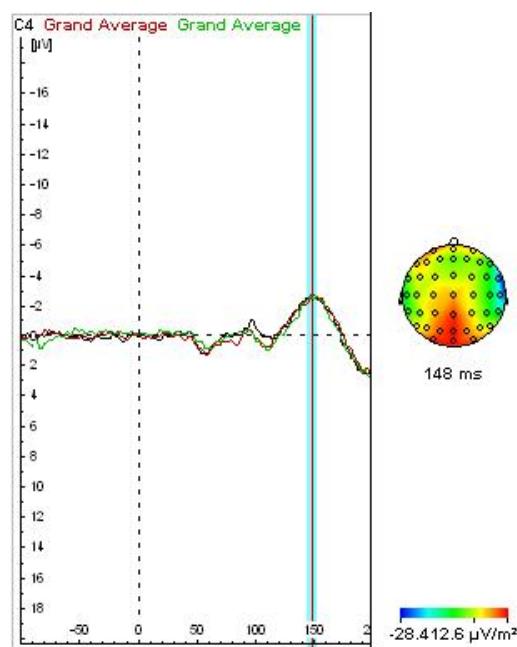


Figure 7. Grand Averages at C4 for nonpainful stimuli for the three emotional conditions: pain-related (red), neutral (black) and pleasant (green).

P2

For P2 amplitudes, an effect of intensity was found, $F(1, 19) = 62.1, p < 0.001$, with higher amplitudes for painful than for nonpainful stimuli. Furthermore, an effect of emotion was found, $F(2, 38) = 6.1, p < 0.009$, with larger amplitudes for the neutral condition in comparison with the pleasant ($p < 0.001$) and pain-related condition ($p < 0.023$). In figure 8 and 9, the Grand Averages for the three emotional conditions in the painful and nonpainful condition are displayed. In figure 10, the mean P2 amplitudes for the three emotional conditions are shown. No intensity x emotion effects were found, $F(2, 38) = 0.3, p < 0.683$.

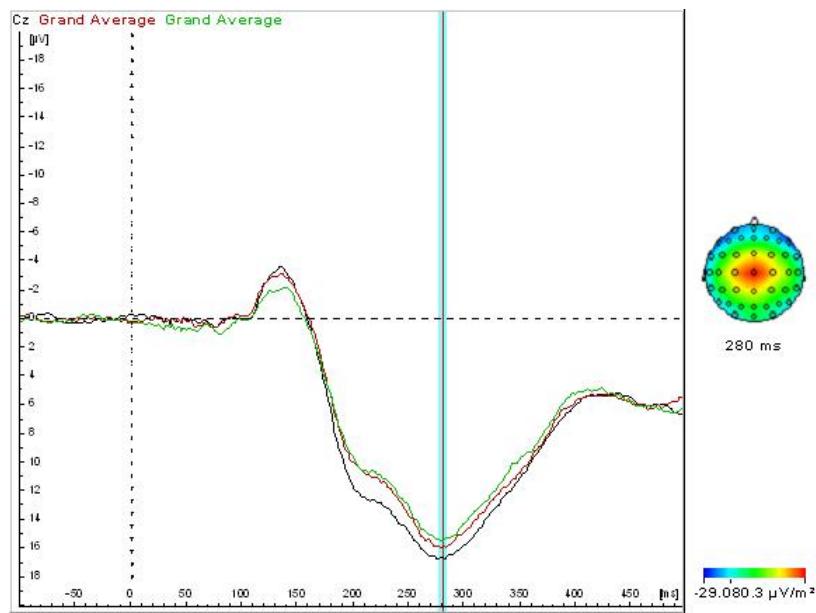


Figure 8. Grand Averages at Cz for painful stimuli for the three emotional conditions: pain-related (red), neutral (black) and pleasant (green).

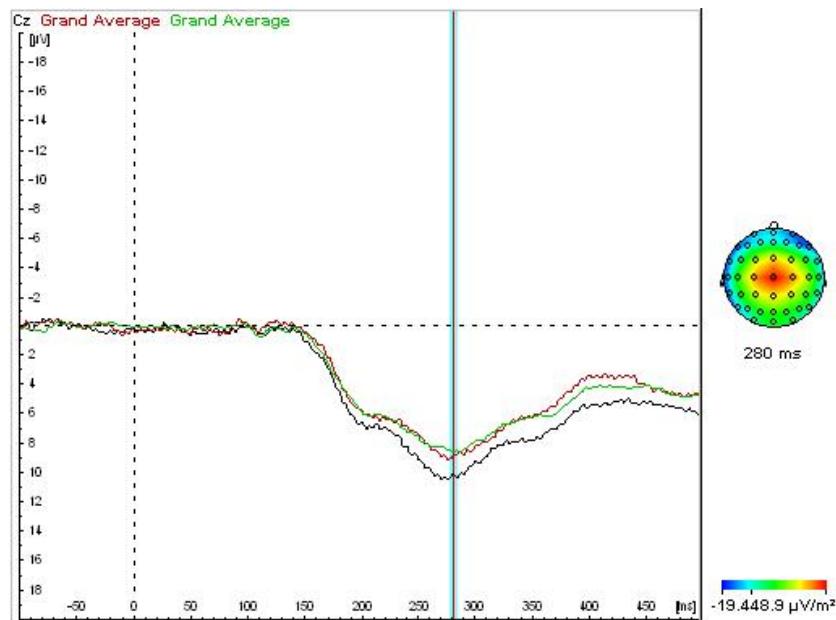


Figure 9. Grand Averages at Cz for nonpainful stimuli for the three emotional conditions: pain-related (red), neutral (black) and pleasant (green).

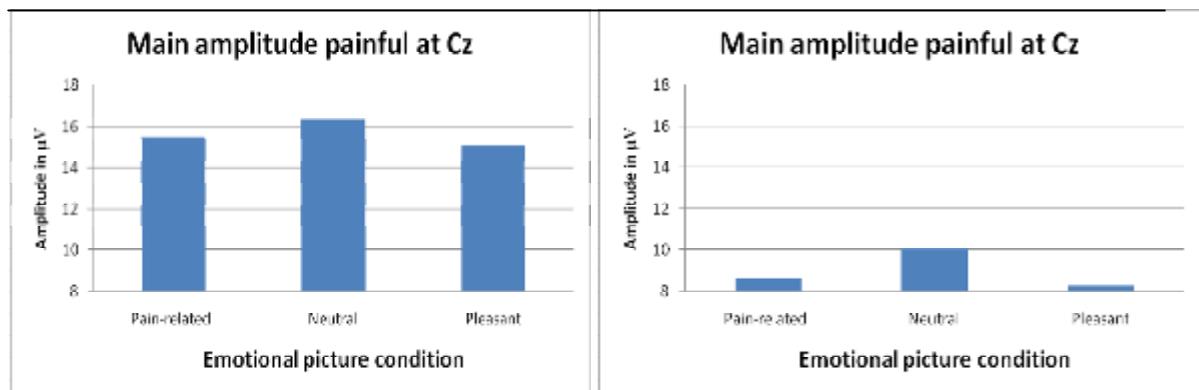


Figure 10. Mean P2 amplitude at Cz for painful and nonpainful stimuli for the three emotional conditions.

Electrophysiological source analysis

Grand Average SEPs were exported to BESA and an overall solution for the six conditions was established. The GFP was used to find the temporal characteristics of the different processes. Furthermore, the PCA were used to decide the number of processes and locations that contribute to the solution. In figure 11, the PCA for the six conditions from -100 ms to 500 ms is displayed. Three main sources were found, which means that three pairs of sources can explain the largest part of activation.

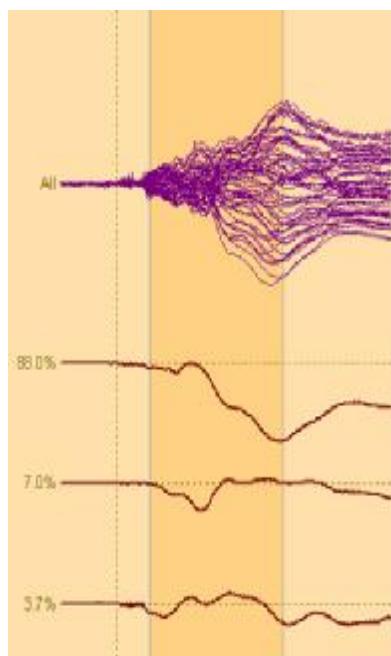


Figure 11. Principal component analysis (PCA) for the six conditions together. Three main sources were found.

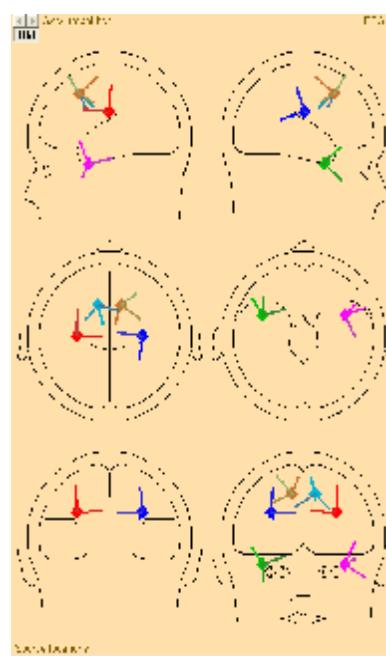


Figure 12. Regional sources found for the six conditions together. The red and (dark) blue locations represent SI/SII, the pink and green locations represent the multisensory cortex and the brown and light blue locations represent the ACC.

The solution found for the overall grand average consisted of three pairs of symmetrical locations. For the first time window (62-92 ms), the location was identified on the somatosensory cortices; a combination of activation in SI and SII. Activation was found to be higher for the right hemisphere, because of stimulation of the left forearm. In the second time window (128-154 ms), activity emerging from the multi-sensory cortex was found. In the last time window (182-202 ms), activation emerged from central/frontal sites indicating activation from ACC. The model explains 99.1% of the variance for the time window from 62 to 300 ms. In figure 12, the regional sources are displayed.

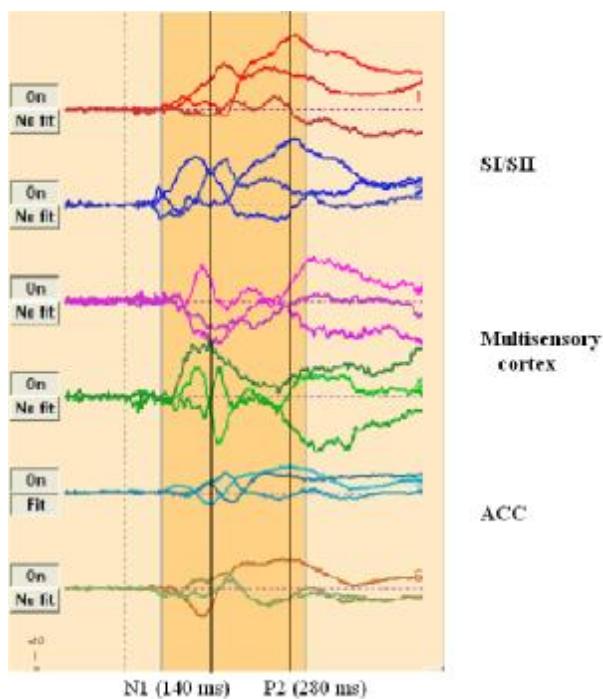


Figure 13. Source waveforms for all the conditions.

In figure 13, the source waveforms are displayed. As can be seen, activity on N1 was mainly from SI/SII and the multisensory cortex. The amplitude of P2 consisted of activation from all three sources: SI/SII, multisensory cortex and ACC.

The solution described above and presented in figures 11, 12 and 13 was used for the six different conditions. In order to compare the results found for the different conditions, it is important that the PCA is stable for the conditions; the number of components and the contribution of the different components should be the same. For this solution, that was the case.

Three components were found and the contribution of the different components was comparable for the conditions: first component 89.3 - 91.0 %, second component 4.8 - 6.4 % and the third component 2.5 - 3.4 %

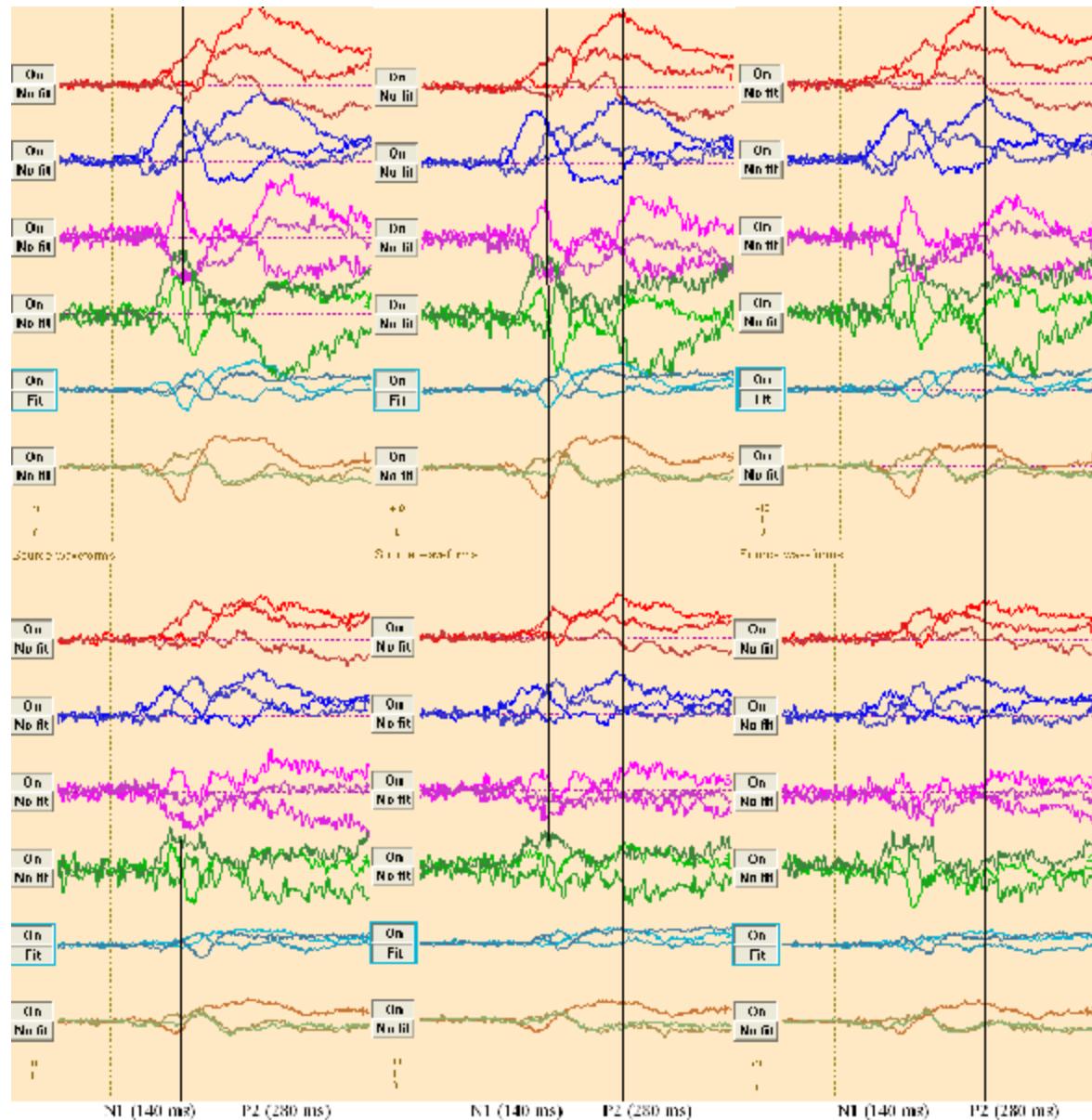


Figure 14. Source waveforms for the painful (above) and nonpainful (below) neutral (first), pain-related (second) and pleasant (third) conditions.

In figure 14, the source waveforms for the six different conditions are displayed. The difference between painful and nonpainful conditions is clear. For the painful stimuli, activation from SI/SII, the multi-sensory cortex and ACC was higher. In the painful conditions considerable activation from ACC was already present around 140 ms. For the different emotional picture conditions, no obvious differences were found for N1 or P2.

Discussion

In the present experiment, we examined the effect of emotion on pain processing. Four hypotheses were introduced to account for the influence of emotion on pain perception: pain can be influenced by valence, arousal, attention and empathy for pain. In the case of valence, effects were expected on N1 with highest amplitudes for pain-related pictures and lowest for pleasant pictures, which is associated with activation from SI and SII. It was expected that only painful stimulation would modulated by valence on N1. If pain perception was influenced by attention, effects were expected on P2 with highest amplitudes for neutral pictures and lowest for pain-related pictures, associated with activation in ACC (Christmann et al., 2007; Kenntner-Mabiala et al., 2005; 2008). Previous studies by Kenntner-Mabiala et al. (2005; 2008) showed that the attention effects on P2 were found for both painful and nonpainful stimuli. Expected effects of arousal and empathy for pain were not as clear. In the case of arousal, highest amplitudes were expected for pain-related pictures and lowest amplitudes for neutral pictures. Finally, if empathy for pain has an influence on pain perception, highest amplitudes were expected for pain-related pictures and low amplitudes were expected for neutral and pleasant pictures. For arousal and empathy for pain, it was not clear which component of the SEP would be influenced. The hypotheses were tested using three emotional picture conditions: pain-related, neutral and pleasant, and two stimulus intensities: painful and nonpainful.

For both N1 and P2, a main effect of intensity was found, with higher amplitudes for painful stimuli. Kenntner-Mabiala et al. (2005; 2008) found the same results. For N1, the highest amplitude was found at C4; source analysis showed that activation in SI/SII was earlier on the right side, which can be explained by the electrical stimulation of the left forearm. A significant effect of hemisphere was found, with higher negative amplitudes at C4. For P2, the highest amplitudes were found on central electrodes.

For P2, an effect of attention on pain perception was found. The pleasant and pain-related conditions showed lowest amplitudes for electrical stimuli. Yamasaki et al. (2000) already showed that distraction leads to lower amplitudes on N240-P340. But, this effect was not pain specific and was also found for nonpainful stimulation. Studies by Kenntner-Mabiala et al., (2005; 2008) found the same results: attention effects for P2 for both painful and nonpainful

stimuli. In the later study (Kenntner-Mabiala, 2008), it was stated that the attentional modulation influenced pain intensity in SI. In the present study, it was found that P2 consisted of activation from SI/SII, multisensory cortex and ACC. The activation from the multisensory cortex was caused by the combination of tactile and visual stimuli. As mentioned previously, SI/SII and ACC are important in respectively the sensory-discriminative and motivational-emotional processing of pain (Chen, 2001; Christmann et al., 2007).

The effect of attention can be explained by the fact that emotional pictures are motivationally relevant and automatically demand attention (Cuthbert et al., 2000; Rhudy & Meagher, 2001; 2003; Schupp et al, 2004). From previous studies, it is clear that emotional pictures (scoring high on arousal and high or low on valence) were processed more thoroughly and slow wave negativity was more pronounced (up to five seconds) than for neutral pictures (Cuthbert et al, 2000; Schupp, Cuthbert, Bradley, Cacioppo, Ito & Lang, 2000). Also, Lang (1995) showed that voluntary viewing time for emotional pictures was much longer than for neutral pictures: about 4 seconds for neutral pictures and more than 7 seconds for pleasant and unpleasant pictures. This means that probably fewer resources were available for processing pain in the pain-related and pleasant condition (Cuthbert et al., 2000). Coull (1998) and Portas, Rees, Howesman, Josephs, Turner & Frith (1998) stated that in the case of sustained attention, which emotional pictures generated, adequate levels of arousal are necessary to sustain attention. In the present study, the degree of arousal was high enough for emotional pictures, but not for neutral pictures to sustain attention. Also Kenntner-Mabiala et al. (2005; 2008) stated that this effect was caused by the degree of arousal of the pictures. In the present study, the degree of arousal was significantly different for pain-related and pleasant pictures, but the P2 amplitude was the same. The results showed that emotional pictures, varying in arousal, all distract attention away from the pain, in comparison to neutral pictures. There are two possible explanations for this effect. It is possible that pictures need to evoke a certain degree of arousal to sustain attention. Another explanation is that arousal and valence both play a role in the attention capturing properties of emotional material.

In the present study, no attention instructions were given to the participants and no trials without picture presentation were used in the experiment. Therefore, it could be stated that attention was not modulated in the present experiment. Kenntner-Mabiala et al. (2008) showed that for emotional pictures and pain, emotional pictures distract attention away from the pain

even when participants were told to focus on pain intensity or pain unpleasantness. Also for those cases, P2 amplitudes remained highest for the neutral condition. This shows that emotional pictures automatically capture attention.

Since P2 consisted of activation from SI/SII and ACC, it can be stated that both the sensory-discriminative and emotional-motivational aspects of pain could have been influenced by attention. The ACC has many functions, one of them being switching between attention resources and processing the emotional aspects of pain (Chen, 2001; Peyron et al., 2000; Villemure et al., 2002; Treede et al., 1999). Therefore, it remains difficult to conclude which brain regions and which part of pain perception was influenced by attention in the present study. Furthermore, since attentional modulation was not limited to pain in the present study, it can be stated that the attentional effects were not pain specific.

For N1, no effect of emotion is found. The results showed an effect of valence, with the highest amplitudes for the pain-related condition, middle amplitudes in the neutral condition and lowest amplitudes for the pleasant condition, but the effects were not significant. Previous studies did find significant effects of valence for N1 (Kenntner-Mabiala et al., 2005; 2008). A possible explanation is that the emotional pictures in this experiment were not strong enough to elicit emotion. In the present study, pictures of people in pain were used, while in most other pain experiments pictures of mutilation and attack were used in the unpleasant condition (i.e. de Wied et al., 2001; Godinho et al., 2006) It is quite possible that these pictures are more arousing and unpleasant than pictures of people in day-to-day pain. Also, as previously stated by Rhudy et al. (2008), the content of the pictures could be relevant. Mutilation and attack scenes are more threatening than hurting a foot or hand. More studies are needed to establish these difficulties. Furthermore, other studies discussed the diminishing effects of presenting the electrical stimulus during the presentation of the picture; the picture distracts attention away from the pain (Rhudy & Meagher, 2001; Kenntner-Mabiala et al., 2005). It is possible that effects of valence were found if the electrical stimulus was presented after the emotional picture. Source analysis showed that, as expected, N1 represented activation in SI/SII and the processing of stimulus intensity. It also showed that also activation from ACC was already present around 140 ms, which is earlier than stated in the literature (Chen, 2001; Christmann et al., 2007). No influence of arousal on pain perception was found. Kenntner-Mabiala et al. (2007) did find an effect of arousal

independent of valence, but in that study music was used to induce emotion instead of pictures, which could elicit different effects. In previous research on emotional pain modulation using emotional pictures, effects of arousal on pain perception were only found as dependent of valence (Rhudy et al., 2008). In other words, valence influences of the activation one of the brain systems from the motivational priming theory and arousal only influence the magnitude of that activation. In the present study, no effects of arousal nor valence were found. Therefore, the emotional priming theory was not supported.

Also, no effects of empathy for pain were found. Much more research has to be conducted on empathy for pain and being in pain. The present results showed that it is important for future researchers to also include a pleasant category in the experiment. For example, the diminishing amplitude found for N1 for the pain-related condition by Valeriani et al. (2008) can also be explained by distraction effects instead of effects of empathy for pain. Godinho et al. (2006) found effects of empathy for pain on late components (> 300 ms) of the SEP. In the present study, the focus was on N1 and P2 of the SEP; later components were not included in the study. It is possible that later components will be influenced by empathy for pain. As mentioned previously by Godinho et al. (2006) these later effects of empathy for pain could be caused by effects of memory; the pain is remembered in the context of the pain-related picture and is remembered more painful. Further studies are needed to establish these effects. In the present study, the action perception model was not supported.

There are a couple of limitations of the experiment. The reliability of lab pain for studying the influence of emotion on pain can be discussed. Experiencing pain in an experimental setting is very different from experiencing pain in daily life. The intense affective reaction is very different (Peyron et al., 2000). Experiencing pain in daily life can cause higher arousal levels, such as stress and fear. In that case, it is not clear if emotional material can still distract attention away from the pain. Therefore, it is difficult to generalize the results found to daily pain experience.

In relation to that, also predictability of the painful stimulus can play a role in pain perception. From previous research, it is clear that predictable and unpredictable painful stimuli are processed differently (Carlsson, Andersson, Petrovic, Petersson, Öhman, & Ingvar, 2006; Legrain et al., 2002). Although the pain-related stimuli were delivered at different times during the picture (after 3000-3500 ms), the stimuli still were predictable. Carlsson et al. (2006) found

that attention was more focused on pain during unpredictable stimulation. If stimulation is predictable, attention towards the pain declines. This means that attention during predictable stimuli will easier focus on the emotional pictures presented during the experiment and therefore, in the case of emotional and motivationally relevant pictures, attention remained focused on the emotional pictures and was distracted away from the pain. Since pain in daily life is unpredictable, emotional modulation can be less effective because the pain will attract more attention. Unpredictable stimuli had strongest effects on the brain regions involved in the emotional processing of pain (Carlsson et al., 2006).

This study showed that attention influenced the P2 amplitude in both the painful and nonpainful condition. P2 consisted of activation from SI/SII, multisensory cortex and ACC. Emotional material, whether it is positive or negative and pain-related, distracts attention away from the painful and nonpainful stimuli. There are limitations to the generalization of the results to daily life: studies on predictability and the emotional aspects of pain showed that unpredictable pain in daily life could produce a more pronounced emotional reaction and will capture more attention. It is questionable whether emotional pictures capture enough attention to distract attention away from the pain.

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