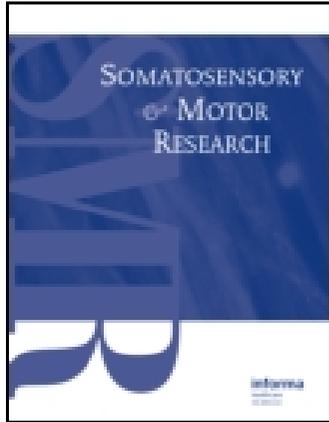


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Responses to tonic heat pain in the ongoing EEG under conditions of controlled attention

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ORIGINAL ARTICLE

Responses to tonic heat pain in the ongoing EEG under conditions of controlled attention

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Abstract

To confirm the existence of an ongoing electroencephalogram (EEG) pattern that is truly suggestive of pain, tonic heat pain was induced by small heat pulses at 1 °C above the pain threshold and compared to slightly less intense tonic non-painful heat pulses at 1 °C below the pain threshold. Twenty healthy subjects rated the sensation intensity during thermal stimulation. Possible confounding effects of attention were thoroughly controlled for by testing in four conditions: (1) focus of attention directed ipsilateral or (2) contralateral to the side of the stimulation, (3) control without a side preference, and (4) no control of attention at all. EEG was recorded via eight leads according to the 10/20 convention. Absolute power was computed for the frequency bands delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–11 Hz), alpha2 (11–14 Hz), beta1 (14–25 Hz), and beta2 (25–35 Hz). Ratings were clearly distinct between the heat and pain conditions and suggestive for heat and pain sensations. Manipulation of attention proved to be successful by producing effects on the ratings and on the EEG activity (with lower ratings and lower EEG activity (theta, beta1, 2) over central areas for side-focused attention). During pain stimulation, lower central alpha1 and alpha2 activity and higher right-parietal and right-occipital delta power were observed compared to heat stimulation. This EEG pattern was not influenced by the manipulation of attention. Since the two types of stimuli (pain, heat) were subjectively felt differently although stimulation intensities were nearby, we conclude that this EEG pattern is clearly suggestive of pain.

Keywords

EEG, experimental pain, ongoing EEG, tonic pain, visuospatial attention

History

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Introduction

Tonic experimental pain stimuli resemble clinic pain more closely than brief phasic pain stimuli, because in contrast to phasic pain stimuli, clinically relevant pain rarely lasts only for a few seconds or even less than a second. Pain normally lasts for minutes to hours or even longer. Therefore, tonic stimulation paradigms seem to be better apt to research pain in more natural circumstances.

A fair number of studies have already investigated responses in the ongoing electroencephalogram (EEG) to various tonic pain stimuli. Frequently, the cold pressor test (CPT) was applied as a model for tonic pain (Chen et al. 1989, 1998; Chen and Rappelsberger 1994; Ferracuti et al. 1994; Chang et al. 2002b). Cutaneous and muscle pain were also used (Veerararn and Stohler 1992; Chang et al. 2001a, 2001b, 2002a, 2002c) and were induced by injecting capsaicin or hypertonic saline. Frequent effects of tonic pain on the EEG were higher beta activity and lower alpha activity, when

compared to the baseline. In most CPT, but usually not in capsaicin and hypertonic saline pain paradigms, an increase in delta activity was often found. Changes in theta activity were also observed, but more inconsistently.

These results cannot unequivocally be attributed to pain as a distinct perceptual modality compared to non-pain sensations because the two qualitatively different perceptual conditions were regularly confounded with substantial differences in stimulus intensity: cool or lukewarm water was used as non-painful control condition for painfully cold water and isotonic saline as non-painful stimulus in the cutaneous and muscle pain models. Therefore, the question has remained unanswered whether it was the noxious quality of pain or the enormous increase in stimulus intensity, which was responsible for the reported EEG changes.

Chang et al. (2002a) were aware of this problem and, therefore, made use of an aversive auditory stimulus as the control condition. This stimulus matched their experimental muscle pain in subjective arousal and unpleasantness as well as in maximum intensity. The result of this comparison was a decrease in alpha activity during the muscle pain condition. The stimuli they used were, however, of completely different physical natures.

Huber et al. (2006) tried a different solution to the same problem. To limit intensity differences as far as possible, they

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used not only a baseline condition, but added an intense non-pain control stimulus. It was induced with the same type of heat stimulation as the pain stimulus and was, moreover, very similar in intensity to it. Their non-pain control stimulus—supposed to be felt as intense heat—was set at 0.3 °C below the pain threshold and their pain stimulus at 1 °C above the pain threshold, with the stimulation protocol being according to the tonic heat pain model (THPM) by Lautenbacher et al. (1995). Thus, the two stimuli should differ unequivocally in the perceptual qualities evoked, one being perceived as not painful and the other as painful, while at the same time being very similar in intensity. The authors found substantially different EEG patterns when comparing baseline and both conditions with intense heat stimulation, but no differences between the latter two conditions. Therefore, they could not confirm any truly pain-specific changes in the EEG.¹

In the study by Huber et al. (2006), the heat (control) stimulation that was meant to be below the pain threshold was in some cases nevertheless rated as painful, which might be the reason for the finding of no significant difference in the EEG between the heat (control) and the pain conditions. The balance between keeping the stimulation intensities of the non-painful and painful conditions as close as possible and still preserving the step in perceptual quality should be optimized in the present study. As already suggested by Huber et al., the temperature of the non-painful heat (control) condition was set lower this time, at a slightly higher distance to the threshold, to guarantee non-painfulness throughout. A temperature difference of −1.0 °C relative to the pain threshold was used in the present study instead of −0.3 °C as in Huber et al.

Since attention is known to influence nociception and central pain processing (Bushnell et al. 1985; Honoré et al. 1995; Legrain et al. 2002; Villemure and Bushnell 2002), we found it again necessary to control for attentional processes in the present EEG experiment. Differently to Huber et al. (2006), we used visual attentional control tasks instead of auditory ones this time to examine whether potential modulatory effects of attention on central pain processing generalize across sensory modalities.

Methods

Subjects

Participants were recruited via notice boards in the University of Bamberg or by personal contact. Subjects with any acute or chronic mental or physical diseases were excluded before the experiment. The remaining sample consisted of 20 subjects (mean age = 23.3 years, SD = 3.3 years): 10 male (mean age = 24.5 years, SD = 3.4 years) and 10 female (mean age = 22.0 years, SD = 2.8 years). None of the participants was under any medication during the experiment and the preceding week. Eight female participants took hormonal contraceptives. Furthermore, participants were asked not to consume alcohol on the day of the experiment or the evening before. Habitual smokers were instructed not to refrain from smoking too long before the experimental session, in order to prevent influences of nicotine deprivation on nociception.

The study was approved by the ethics committee of the University of Bamberg and written informed consent was obtained from all subjects.

Experimental design and protocol

The experiment was divided into 16 blocks resulting from combinations of the three factors “stimulation intensity” (“tonic painful heat” or “tonic non-painful heat”), “visual attentional control” (“focus of attention ipsilateral to stimulation”, “focus of attention contralateral to stimulation”, “focus of attention without side preference”, or “no control of attention”), and “stimulation side” (thermal stimulation on the “left” or on the “right” thigh).

The factor “stimulation side” became necessary to ensure that the Peltier thermode could be moved after each block to another part of the skin, which had not been stimulated before. There would not have been sufficient sites for stimulation on only one thigh. Additionally, the factor guaranteed that the variation between an ipsilateral and a contralateral focus of attention was not confounded with variation between the left and the right body side.

The 16 experimental blocks that resulted from the described 2 × 4 × 2 within-factors design were divided into two experimental sessions. They took place on two separate days, starting at the same time in the afternoon. The split into two sessions became necessary, as the procedures would have lasted for nearly 4 h if they had all been conducted in a single session, which might have resulted in confounding effects of declining vigilance. Influences of circadian rhythms were minimized by scheduling the sessions for all participants only in the afternoon.

In both sessions, four experimental blocks with thermal stimulation on the right thigh were followed by four blocks with stimulation on the left thigh. The sequences of the two stimulation intensity conditions and the four visual attentional control conditions were pseudo-randomized in a way that these conditions were distributed evenly over the two sessions. The same resulting sequence of conditions was used for each participant.

During both sessions, the subjects were seated in an upright chair in front of a computer screen. The first session started with a standardized general introduction to the procedures of the experiment. Afterwards, the subjects filled out several psychological questionnaires, which will not be presented in this paper. The completion of the questionnaires

Table I. Overview of the experimental protocol.

Session 1	Session 2
General introduction	
Questionnaires ^a	
	Attaching of the EEG leads
	Heat pain threshold right thigh
	Introduction to the pain rating scale
Familiarization period	
	Four experimental blocks on the right thigh
	Heat pain threshold left thigh
	Four experimental blocks on the left thigh

^aNot further reported in this paper.

lasted 15 min and was necessary only once; thus, it was not part of the second session (see Table I for a schematic overview of the experimental protocol).

In both sessions, after attaching the EEG leads, the subjects' heat pain threshold was assessed on their right thigh; subsequently, they were instructed in the use of the pain rating scale. During the next 6 min of the first session, subjects were allowed to familiarize themselves with the experimental setting. This phase was not necessary in the second session.

The following protocol was identical for both sessions: four experimental blocks with thermal stimulation were conducted on the right thigh. Each block lasted for 370 s; within the first 10 s the temperature was raised from 37 °C to the stimulation temperature. Stimulation was continued over the subsequent 6 min (see Figure 1).

During the four blocks, the experimenter stayed in an adjacent observation room, controlling the experimental apparatus. The participants were monitored via an audio-video system and could be contacted via intercom. Between blocks the experimenter moved the thermode to an adjacent site on the thigh. After completing the first four blocks, the heat pain threshold was assessed on the left thigh followed by four experimental blocks as described above for the right thigh.

The subjects were instructed to focus on the center of the computer screen. During the first 55 s of each minute of thermal stimulation, moving arrows were displayed. The direction of motion was different according to the attentional control conditions described below. In conditions of "no attentional control", the subjects were blindfolded. Pain intensity was rated verbally in the last 5 s of each minute after a verbal cue was given by the experimenter and a visual cue was displayed on the screen. In the "no attentional control condition", the visual cue was omitted (see Figure 1 for the order of events in 1 min). During the blocks with attentional control, the optokinetic stimulation paused 6 times for the pain ratings to take place, whereas the thermal stimulation always continued without interruption also while the ratings were given.

After each block, the participants completed a questionnaire about their mood and psychosomatic functioning, which will not be reported on further.

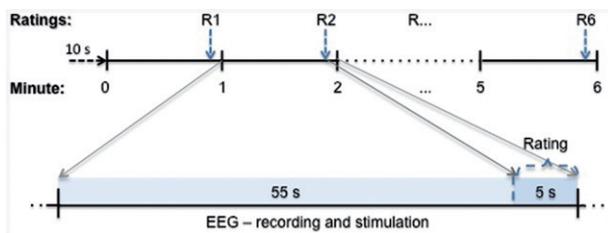


Figure 1. Schematic representation of the protocol of stimulation. Top: Entire stimulation block of 370 s. During the first 10 s the temperature of the Peltier thermode increases to the final stimulation temperature. In the following 6 min of stimulation pain intensity is rated during the last 5 s of each minute epoch. Bottom: One minute epoch of stimulation; during the first 55 s of each minute EEG samples are taken and attentional control is active, during the last 5 s ratings were given.

Measurement of heat pain threshold and tonic thermal stimulation

A thermal sensory analyzer (TSA 2001 produced by Medoc, Ramat-Yishai, Israel) was used for heat induction. The apparatus included a Peltier thermode with a 3 cm × 3 cm stimulation surface, which was attached to the participant's dorsal thigh with an elastic band.

The *heat pain threshold* was assessed using a method of adjustment. Starting from a baseline temperature of 35 °C the participants up-regulated the temperature by pressing the right button of a computer mouse. When the right button was constantly pressed, the temperature increased by a rate of 0.5 °C/s. The participants could down-regulate the temperature in a similar manner by pressing the left button. They were asked to adjust a temperature which they perceived as barely painful. There was one familiarization trial and thereafter six experimental trials; the mean value of the last five of those was used as the participant's heat pain threshold estimate.

Before each experimental block, the Peltier thermode was relocated to a new position on the participant's thigh. For that purpose, both dorsal thighs were subdivided into six stimulation areas of comparable size. One site on each thigh was used for obtaining the pain threshold, a second one for the adaption period (on the right thigh only), and four further sites on each thigh for the respective four experimental blocks. No site was stimulated twice during one session.

The *tonic thermal stimulation* consisted of small heat pulses (oscillations between two temperature levels) with a repetition frequency of 30 pulses/min. It was designed according to the THPM by Lautenbacher et al. (1995). The maximum temperature of these pulses was set either 1 °C above ("tonic painful heat") or 1 °C below the individual pain threshold ("tonic non-painful heat"). The pulse amplitude was 1.3 °C in both conditions.

In each experimental block, the temperature started from a baseline of 37 °C, then rose to the maximum with a rate of change of 0.5 °C/s. Once the target temperature was reached, the temperature began to oscillate for the rest of the block with a rate of change of 4.0 °C/s and at a frequency of 30 pulses/s. After 370 s the temperature returned to the baseline. The subjects were instructed to notify the experimenter in case their tolerance threshold was reached, so that the temperatures could be lowered in steps of 0.3 °C. This was possible without having to terminate the stimulation.

Pain ratings

The subjects rated sensation intensity verbally during the last 5 s of each minute in the experimental blocks. This resulted in six ratings per block, as there were 6 min of stimulation in each block. For the ratings, a numerical scale was used, which was anchored with 0 "no sensation", 5 "barely painful", and 10 "extremely intense pain". Accordingly, non-painful sensations should be indicated by numbers below 5 and painful sensations by a number of 5 or higher. The rating interval was signaled by appearance of the numerical scale on the computer screen and additionally by a verbal cue of the experimenter. During conditions with no attentional control, in which the subjects were blindfolded, only the verbal cue

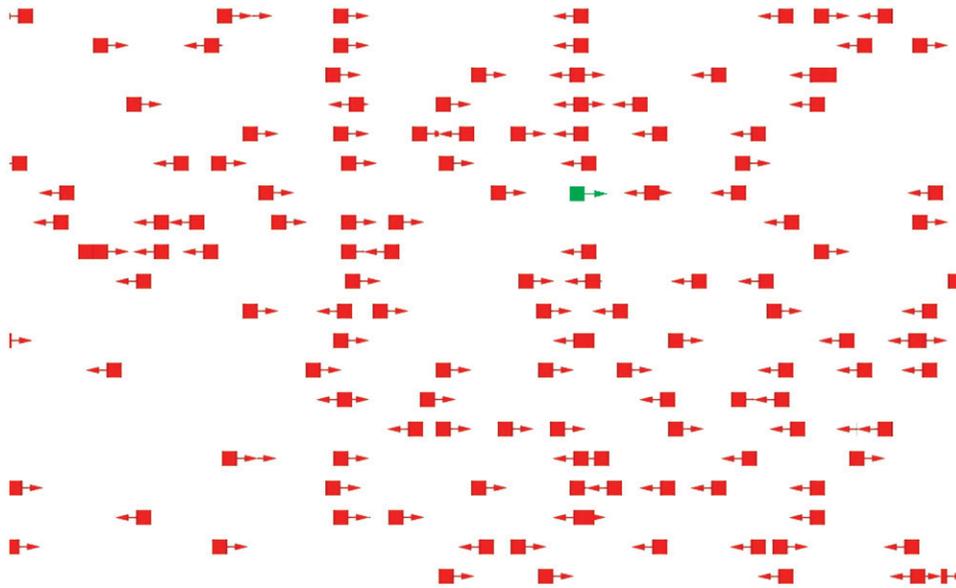


Figure 2. Screenshot of optokinetic stimulation for the condition “attentional control without a side preference”; one arrow among the red arrows having its color changed from red to green. Color intensity of red and green arrows was identical.

was given. The rating procedure was practiced during the familiarization period.

Attentional control

Attentional control conditions were incorporated into the experiment in order to allow for generalization of the EEG findings over various defined states of attention.

There were a total of four attentional conditions, three conditions of control of attention and a fourth condition where attention was not controlled.

In the attentional condition of “no control of attention”, the participants were instructed to keep their eyes closed and they additionally wore blindfolds.

The conditions with control of attention should allocate the subjects’ visuospatial focus of attention to different sides, either corresponding to the side of thermal stimulation (ipsilateral) or not (contralateral); in a third condition the visuospatial focus of attention remained unclear. These conditions were designed according to optokinetic stimulation. Optokinetic stimulation had been developed for the treatment of patients with visual neglect in order to produce robust and ongoing re-allocations of spatial attention towards the side that is ignored by the patients. During this stimulation, a number of visual stimuli are moving at a common speed towards the side that is ignored by the neglect patient. This is usually the left side. The stimulation has been found to be very effective in allocating visuospatial attention to the direction of the movement (Mattingley et al. 1994).

According to this paradigm, horizontally moving red arrows were displayed on the 19” screen in front of the participants during the first 55 s of each minute of an experimental block (see Figure 2) (the final 5 s of each minute were reserved for the ratings). The arrows were sized 32×14 pixels and moved 60–180 pixels/s on 30 lines. In the conditions with attention focused on a specific side (ipsi- or contralateral to the thermal stimulus), the arrows moved either from the left side of the screen to the right side or from the

right side to the left side—allocating the subject’s attention either to the left or right half of the visual field. This would correspond either to the side ipsilateral or contralateral to the thermal stimulation on the thigh.

In the condition with attentional control but without side preference, the arrows moved concurrently in both directions. This procedure was designed to capture attention without inducing clear attentional side preferences. Figure 2 displays a screenshot of the simulation in the third condition, showing that half of the arrows moved to the left while the other half moved to the right.

To ensure that participants were really paying attention to the visuospatial presentation on the screen, we added a simple monitoring task. Some of the moving arrows changed color from red to green within the screen half before the final destination. There were 19–21 color changes per experimental block of 6 min. At the end of each 6-min block, participants were asked to report the number of counted color changes.

EEG recording and data processing

Eight recording electrodes were affixed according to the 10/20 convention (see Figure 3 for their positions) using the ECI Electro-Cap Electrode System (Electro-Cap International, Eaton, Ohio, USA). The cap was available in two sizes and could be chosen according to each participant’s head size. Two referential electrodes were connected to the earlobes and a ground electrode to the forehead above the nasion. The electrooculography (EOG) was recorded for detection of eye movement artifacts with electrodes in the horizontal axis, one next to each orbit. Electrode impedance was controlled to be lower than $9 \text{ k}\Omega$ in each lead.

The EEG signals were recorded and processed by a Sigma Plpro (SIGMA Medizin-Technik, Gelenau, Germany) with the amplifier DB 36. The band-pass filter was set from 0.2 Hz (12 dB/octave) to 300 Hz (48 dB/octave) and the EEG signals were A/D converted with a sampling rate of 512 Hz. A 50 Hz notch filter was used.

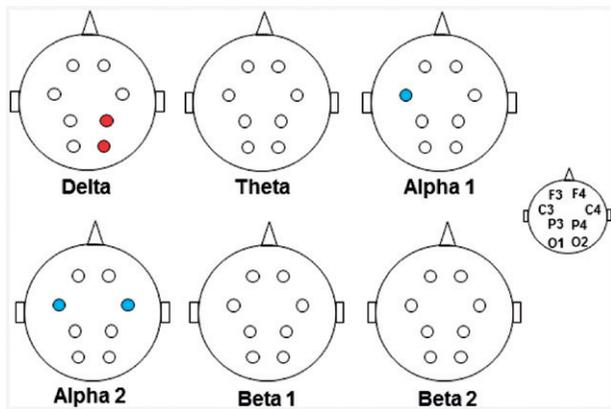


Figure 3. Significant main effects of stimulation intensity on the ongoing EEG separated into six frequency bands. Higher (lower) EEG activity during pain condition when compared to the non-painful heat condition was observed in the Delta band (in the Alpha bands) at the electrodes of the frequency bands that are marked as significant.

Three 2-s long artifact-free epochs of each minute of stimulation were taken for analysis. The criteria for the selection were no eye movements registered by the EOG and no apparent disturbances or irregularities in the EEG signal on visual inspection. Furthermore, no epoch was taken from the last 5 s of a recording minute, as the pain ratings were given during this time.

Spectral analysis was performed by use of Fast Fourier Transform. Absolute power spectra were calculated, separately for each electrode, for the frequency bands delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–11 Hz), alpha2 (11–14 Hz), beta1 (14–25 Hz), and beta2 (25–35 Hz). The absolute power spectra of the three epochs of each minute were averaged to form single values for each minute. Further analysis could then be conducted for each minute of stimulation.

Statistical analysis

Analyses of variance (ANOVA) with repeated measurement were conducted separately for each frequency band and each electrode as well as for pain ratings as dependent variables. These analyses included four within-subject factors, namely: (i) *stimulation intensity* (“tonic non-painful heat” and “tonic heat pain”), (ii) *visuospatial attentional control* (“focus of attention directed ipsilateral” to the pain stimulus, “focus of attention directed contralateral” to the pain stimulus, “attentional control without a side preference”, and “no control of attention”), (iii) *stimulation side* (“left” and “right” thigh), and (iv) *time* (six levels, one for each minute of stimulation); and one between-group factor *sex*.

Since our main interest was the effect of the stimulation intensity, we will focus on this main effect as well as on the interaction effects including the factor *stimulation intensity*. In addition, the main effect of the factor *visuospatial attentional control* will shortly be addressed, but mainly when interacting with the factor *stimulation intensity* because we were only prepared to test hypotheses about the effect of attention on pain-related changes and not about the effect of attention in general.

Paired *t*-tests were performed to specify the effects that were found in the ANOVAs (*post hoc*). For descriptive statistics, mean and standard deviation were computed. The alpha-value was set at 0.05 throughout the testing.

Results

Heat pain threshold

The heat pain thresholds were determined for both thighs separately and served later in the study to tailor the supra- and sub-threshold thermal stimulation individually for each person and body side. For female and male participants, the mean values were 43.8 °C (SD = 2.0) and 44.0 °C (SD = 1.5) on the left thigh and 44.3 °C (SD = 1.6) and 44.9 °C (SD = 1.3) on the right thigh, respectively.

Effects of the stimulation intensity

Effects on the pain rating

The main effect of the factor *stimulation intensity* on the pain rating was highly significant ($F(1,18) = 75.63$, $p < 0.001$). During stimulation with “tonic non-painful heat” the mean rating was 3.2 (SD = 0.9), whereas it was significantly higher at 6.0 (SD = 0.9) during stimulation with “tonic heat pain”. Thus, the two conditions of stimulation intensity were clearly felt as distinct with regard to their subjective intensity.

The mean value for the condition supposed to produce non-painful heat sensations was, furthermore, well below the scale modulus of 5, which should be used to describe a barely painful sensation. In contrast, the condition supposed to be painful produced a mean rating well above the modulus of 5. These findings suggest that the intended change in sensation quality from non-painful to painful did occur on a regular basis. However, there were individual exceptions to this general finding, which did not conform to our predictions: 22.3% of the ratings during the pain condition were rated as being not painful, whereas 17.3% of the ratings in the heat condition were rated as being painful.

Despite that, there was clearly much more “pain sensation” and much more “heat sensation” in the corresponding conditions.

Effects on the EEG

The factor *stimulation intensity* yielded a significant effect on the EEG activity for the frequency bands alpha1, alpha2, and delta at four electrode sites (C3, C4, P4, and O2). In summary, delta power significantly increased under painful heat in comparison to tonic non-painful heat (at electrodes P4 and O2) whereas alpha power significantly decreased (in alpha1 (at C3) as well as in alpha2 (at C3 and C4)). The leads with significant changes (power increase during pain is marked in red whereas a decrease in power is marked in blue) are displayed in Figure 3. The findings are detailed in the following.

Increases in delta power. At electrode P4 the mean of the absolute delta power was $11.18 \mu\text{V}^2$ (SD = 2.6) under non-painful stimulation and significantly increased to $11.70 \mu\text{V}^2$ (SD = 2.75) under painful stimulation ($F(1,18) = 10.61$, $p < 0.01$). The mean of the absolute delta power at O2 was

19.90 μV^2 (SD = 8.28) under non-painful stimulation and significantly increased to 20.82 μV^2 (SD = 9.12) under painful stimulation ($F(1/18) = 5.40$, $p < 0.05$).

Decreases in alpha power. In the frequency band alpha1, a significant main effect of stimulation intensity was found at C3 ($F(1/18) = 6.55$, $p < 0.05$). The mean of the absolute power was 10.41 μV^2 (SD = 8.02) under non-painful heat stimulation and decreased to 9.63 μV^2 (SD = 6.92) under pain stimulation. The frequency band for alpha2 also decreased from non-painful to painful stimulation at two sites. At electrode C3 the mean power under heat stimulation was 5.92 μV^2 (SD = 4.15), while it was 5.16 μV^2 (SD = 3.39) under pain stimulation. This difference was highly significant ($F(1,18) = 8.61$, $p < 0.01$). The mean power at C4 was 5.52 μV^2 (SD = 3.53) under the heat condition and with 5.03 μV^2 (SD = 2.75) significantly lower in the pain condition ($F(1/18) = 5.47$, $p < 0.05$).

Effects of the attentional control

The control of attention appeared necessary to allow for generalization of the EEG comparisons between pain and heat over various states of attention.

Pain rating

The main effect of focus of attention on the pain ratings was highly significant ($F(3,54) = 16.85$, $p < 0.001$). Paired *t*-tests showed that ratings did not differ between “attentional control without a side preference” ($M = 4.9$, $SD = 2.2$) and “no control of attention” ($M = 4.9$, $SD = 2.3$) with $p = 1.00$. The ratings during “focus of attention directed ipsilateral” ($M = 4.1$, $SD = 2.1$) were significantly lower ($p < 0.01$) than during “focus of attention directed contralateral” ($M = 4.5$, $SD = 2.1$) and the ratings of both conditions with focused attention towards one body side were significantly lower than those in the conditions of “attentional control without a side preference” and “no control of attention” (all $p < 0.05$). This means that a specific focus of spatial attention produced lower pain ratings, whereby the attentional focus directed ipsilateral to the pain stimulation resulted in even lower ratings than the attentional focus directed contralateral to the pain stimulation.

The interaction effect of *stimulation intensity* with *attentional control* was not significant ($F(3,54) = 1.72$, $p = 0.18$). This implies that the effect the attentional control conditions had on the ratings did not depend on whether the stimulation was painful or not. This also means that the effect of stimulation intensity was independent from the mode of attentional control. In other words, our attentional conditions did have an influence on the intensity ratings, however, not specifically for pain, but also for non-painful sensations.

EEG results

We found a significant main effect ($p < 0.05$) for the factor *visuospatial attentional control* on the EEG activity at several frequency bands and electrode sites. As *post hoc* tests revealed, EEG activity (alpha2 and beta1, 2) significantly increased during focused attention (ipsi- and contralateral) compared to “attentional control without a side preference”²

at occipital and parietal areas; whereas the activity (theta and beta1, 2) decreased in more central areas.

However, most importantly, these effects of attention on EEG activity did not interact with stimulus intensities (all values of $p > 0.05$). No significant interaction effect of control of attention with stimulation intensity could be found at any electrode/frequency band. Accordingly, the observed intensity effects of tonic heat stimulation on the EEG were not dependent on attentional conditions.

In summary, the attentional control conditions were effective experimental manipulations, considering the changes in pain ratings and EEG activity, but we could not observe any modulatory impact on the intensity-related effect, neither for the pain ratings nor for the EEG.

Discussion

In the present study, intense non-painful heat was compared to heat pain on their effects on the ongoing EEG. To provide evidence for pain-indicative changes, we compared two stimuli, which were close in sensory intensity but different in perceptual quality, namely, in painfulness. During tonic heat pain a pattern of lower central alpha power and higher right-occipital and right-parietal delta power was observed in the ongoing EEG, when compared to tonic non-painful heat. We will discuss these findings in detail below.

Correspondence with earlier studies

Lower alpha power was frequently found in other studies as well, usually over the parieto-occipital part of the brain, for example, by Ferracuti et al. (1994) and Chang et al. (2002b) during the CPT, by Chang et al. (2001a, 2001b) during capsaicin-induced muscle pain, and by Chang et al. (2002a) when capsaicin-induced muscle pain was compared to aversive auditory stimulation. Lower alpha1 activity in comparison to the baseline was also observed by the preceding study of Huber et al. (2006), who, like the authors of the present study, used the THPM by Lautenbacher et al. (1995).

With regard to the *increased delta power* that we observed during painful stimulation, previous findings are much more inconsistent. Whereas several studies did not find changes in delta power during painful stimulation, others did. It seems that the type of pain induction method is of relevance. When using tonic thermal pain (e.g., the cold pressor task, tonic heat pain), most studies seem to find an increased delta power during pain (Ferracuti et al. 1994; Chen et al. 1998; Russ et al. 1999; Stevens et al. 2000; Chang et al. 2002b; Huber et al. 2006) in accordance with our study. Nevertheless, there are also several exceptions with studies not finding increased delta power during tonic thermal pain stimulation (Backonja et al. 1991; Dowman et al. 2008; Shao et al. 2012). Moreover, when using capsaicin or hypertonic saline-induced pain to study EEG changes during pain, most studies failed (with one exception (Le Pera et al. 2000)) to observe delta power changes during pain (Veerasarn and Stohler 1992; Chang et al. 2001a, 2001b, 2002a, 2002c). Thus, higher delta power has almost never been observed in studies using muscular or intradermal pain, but predominantly—with a few exceptions—in studies using tonic thermal pain.

In contrast to the present findings, some prior studies have also observed *higher beta power* during CPT and during capsaicin-induced pain (e.g., Backonja et al. 1991; Veerasarn and Stohler 1992; Chang et al. 2002c), and also during tonic heat stimulation (Huber et al. 2006).

Altogether, there is substantial overlap of the present findings with those of earlier studies—especially with regard to changes in alpha power—although our stimulus control condition made use of stimulation intensities much closer to the pain range than most previous studies have.

Are the EEG changes suggestive of pain?

The applied stimuli were all of the same type of physical energy; the stimulation intensities of the non-painful and painful heat stimuli differed only minimally in intensity. Therefore, the observed difference in the EEG between these two stimulus conditions can be mainly attributed to the change in perceptual quality from non-painful to painful. Of course, one cannot completely exclude that even the minimal differences in intensity still had an effect on the changes in the EEG. In order to prove a truly pain-specific EEG pattern, identical forms of physical stimulation leading to different perceptual qualities are required, which might be produced by devices like the “thermal grill” (Bouhassira et al. 2005). We are nevertheless confident that the change in perceptual quality from no-pain to pain is mostly responsible for the observed changes in EEG activity, given that the intensity difference was only very small. These EEG changes we observed during pain were not influenced by manipulations of attention. Thus, we conclude that the EEG pattern of higher right-occipital and right-parietal delta power and lower central alpha power is related to acute human pain.

As stated above, the observed change in alpha power during painful stimulation is a robust finding that previous studies have also repeatedly found. Analyses of Dowman et al. (2008) suggest that this lower central alpha power during pain at the central electrodes might be associated with pain-related activation in the “primary somatosensory cortex (SI) [...] and the somatosensory association areas located in the parietal operculum and insula” (p. 1202).

As stated above, the findings regarding changes in delta power are much less consistent than the findings regarding alpha power. It is possible that an increase in delta power was mainly observed during tonic thermal pain stimulation but not in studies using muscular or intradermal pain because the finding of higher delta power might not be specific for pain but related to unspecific effects of thermal stimulation (e.g., clear onset, predictable course, better subjective control). Instead, it might be related only to pain induced by stimuli targeting superficially located nociceptors and reflect a characteristic of superficial pain compared to deep tissue pain. Moreover, the underlying neurophysiology of the increase in delta power during pain is still unclear. Generally, an increase in delta power is considered to reflect processes of cortical inhibition (Pizzagalli 2007). Ferracuti et al. (1994) found a diffuse increase of delta power over both hemispheres, including P4 and O2 as in the present study, with an emphasis over frontal regions. They hypothesized that the increase might reflect an attempt to inhibit nociceptive

processing. According to our findings, this inhibition has to be thought of as a mechanism that is not related to attention, just like the diffuse noxious inhibitory controls/conditioned pain modulation (DNIC/CPM; Moont et al. 2010, 2011). Ferracuti et al. (1994) furthermore pointed out that it might be stress related. Chen et al. (1989) interpreted their finding of increased delta activity as being linked to the stress component of pain as well.

Attentional control

By controlling the subjects’ attentional focus, we intended to control, as far as possible, for the influence of cerebral processes, which inevitably evolve in studies on the sensory and perceptual effects of stimuli and which might interact with the processing of heat and pain stimuli. The manipulation of visuospatial attention itself was successful in regards to changes in pain ratings and EEG activity. Stimulation ipsilateral to the focus of attention was perceived as less intense than stimulation contralateral to the focus of attention. This is consistent with Naveteur et al. (2005) who used ipsilateral and contralateral eye orientation.

However, the opposite effect has also been reported with the perceived intensity of a painful stimulus increasing when it is presented ipsilateral to a visual cue that immediately precedes it compared to contralateral stimulation (e.g., Van Ryckeghem et al. 2011). Reasons for these seemingly contradictory findings might be the different length of painful stimulation (tonic (here) vs. phasic), the required maneuver used to direct spatial attention (mainly passive viewing (here) vs. participation in response-requiring tasks), or the type of required behavioral response (counting and memorizing the number of stimuli (here) vs. immediate evaluation of each visual stimuli on a trial-to-trial basis). One or more of these factors might be relevant moderators when studying the effects of visuospatial attention with ipsi- or contralateral focus on pain processing.

Besides the difference between ipsi- and contralateral attentional focus we found that both conditions were perceived as less intense than stimulation during “attentional control without a side preference” and “no control of attention”. Accordingly, clear spatial foci of attention proved to be effective in reducing pain intensity, no matter whether the attentional focus coincided with the site of pain stimulation or not.

This is a very common result: Piira et al. (2006), who compared a stimulus focusing task, a distraction task, and a control condition in children, also found that pain ratings during both tasks were lower than in the control condition. Distraction from the pain stimulus has frequently been reported to increase pain threshold and/or pain tolerance and sometimes to decrease perceived pain intensity when compared to no distraction (Johnson and Petrie 1997; Johnson et al. 1998; Dunckley et al. 2007; Dahlquist et al. 2010; Hoffman et al. 2011; Weiss et al. 2011). Interestingly, doing seemingly the opposite, that is, focusing on pain stimuli has been found to have similar effects, at least in subgroups of people (Blitz and Dinnerstein 1971; Baron et al. 1993; Logan et al. 1995; Keogh et al. 2000; Michael and Burns 2004; Roelofs et al. 2004).

In summary, our data suggests that developing and maintaining a long-term spatial focus of attention seems to consume so much attentional resources that the exact spatial focus of attention (whether it is focused ipsi- or contralateral) is not decisive to lower processing of tonic pain. Interestingly, we also found that participants made more errors in counting and memorizing the color changes during the focused visuospatial attention conditions (regardless of whether focused ipsi- or contralateral) compared to the “no-focus” condition. Thus, developing and maintaining a long-term spatial focus of attention not only captures attentional resources that are relevant for pain processing but also for other cognitive processes (like memory processes).

We also found an effect of attentional control on EEG activity. Both conditions of focused attention (ipsi- and contralateral) led to different EEG activity compared to the “attentional control without a side preference”. Ipsi- and contralateral conditions led to higher EEG activity (alpha and beta power) in occipital and parietal areas and reduced EEG activity (mainly theta) over central areas. Most importantly, however, our attentional task did not change the critical features of the reported EEG pattern due to pain (alpha power decrease and delta power increase). Since no significant interaction effect on the ongoing EEG was found between attentional control and stimulation intensity, the reported main effects of stimulation intensity on the EEG were apparently not influenced by the manipulation of attention.

Limitations

Investigating pain effects on the ongoing EEG by comparison with control stimulation far below the pain level, as it has been done previously, confounds the change in perceptual quality of interest, that is, from non-painful to painful, with big changes in sensory intensity. Therefore, we developed stimulation paradigms with stimulation close to the pain level to control for this factor. Our first approach by Huber et al. (2006) included a control condition, which bore the high risk of leading to painful experiences. This time, our paradigm appeared improved in this respect. The two stimulation intensities for heat and pain, which were separated physically by 2 °C, resulted in clearly distinct ratings on the pain scale (0–10), with the pain stimulus being rated approximately 2.8 points higher than the heat stimulus. Furthermore, the mean value of the ratings for “non-painful heat” in the present study never rose above the modulus of 5, which was designated as being “barely painful”. In contrast, in the study of Huber et al., the mean ratings increased after 4 min of “non-painful” stimulation (10 min total stimulation) above the scale value designated as the pain threshold. Unfortunately, also in the present study, around 20% of the ratings were above 5 for pure heat stimulation and below 5 for pain stimulation, suggesting that there was still a slight confusion of conditions. Although this is still not ideal, it is the best possible we could achieve with our strategy and to our knowledge also the best control of the intensity confound that has been done so far. In future studies additional control conditions should be added to “heat pain” and “strong heat”. By adding two more temperature levels, one 2 °C lower than our non-painful heat and one 2 °C higher than our painful

heat, the difference of 2 °C across the pain threshold could be compared to the same intensity differences below and above the pain threshold. The extensive control of attentional influences, which led to very long sessions in the present study, prevented that from happening this time.

Conclusion

In the present study, heat pain—when compared to intense non-painful heat—produced an increase in right-parietal and right-occipital delta power and a decrease in central alpha power. This result was obtained while potentially confounding attentional processes were well controlled for. Given that this decrease in alpha power during pain has been repeatedly shown—also when applying other pain induction methods—we feel confident that the decrease in alpha power (and possibly also the increase in delta power) is an EEG response that is suggestive of acute pain.

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Declaration of interest

The authors would like to state that there are no conflicts of interest regarding this work.

Annotations

1. It has to be acknowledged that even when selecting temperatures that are very close in intensity but also differ in their perceptual quality (pain vs. no-pain), one cannot exclude that possible changes are mainly due to intensity differences and do not reflect exclusively the change in quality from “no-pain” to “pain”. In order to prove a truly pain-specific EEG pattern, identical forms of physical stimulation leading to different perceptual qualities are required, which might be produced by devices like the “thermal grill”.
2. The blindfolded condition “no control of attention” was not included in the EEG analysis given that the lack of visual input makes it difficult to compare it with the other conditions. Thus, leaving the visuospatial attentional control once completely inactivated—as intended—was bought by a general lack of activation of the visual system, which was helpful to assess the efficacy of the visuospatial attentional control on pain but hampered the study of EEG changes.

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