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EEG responses to tonic heat pain

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Abstract The aim of the present study was to characterize the EEG response pattern specific for tonic pain which is an experimental pain model resembling clinical pain more closely than phasic pain. Tonic experimental pain was produced by a series of heat pulses 1°C above pain threshold over 10 min. A series of heat pulses 0.3°C below pain threshold and a constant temperature of 37°C served as non-painful heat control and as baseline condition, respectively. The level of attention was experimentally manipulated by instruction and by a distraction task. Twenty male, pain-free subjects had to rate the sensation intensity and sensation unpleasantness during thermal stimulation. Furthermore, a German version of the McGill Pain Questionnaire was to be filled out after tonic painful heat stimulation. The EEG was recorded via 10 leads according to 10/20 convention. Power density was calculated for the usual frequency bands. The ratings showed that tonic painful heat was experienced clearly distinct from tonic non-painful heat. An EEG response pattern emerged characterized by a rather generalized increased delta² activity, a left-biased fronto-temporally diminished theta activity, a fronto-temporal decrease in the alpha¹ activity and a left-sided temporal increase in the beta¹ activity. This observation agrees well with the findings of others. However, there was no evidence in our data that these EEG changes are

specific to tonic heat pain as opposed to changes observed during tonic non-painful heat stimulation. Accordingly, the repeatedly reported EEG patterns are also likely to be produced by other forms of strong somatosensory stimuli and to be not specific for pain.

Keywords Experimental pain · EEG

Introduction

Experimental pain has extensively been used in the recent past as a tool for investigating the physiological and psychological factors involved in processing pain under controlled conditions. The insights obtained for better understanding of clinical pain are also numerous (Apkarian et al. 2005; Lautenbacher and Fillingim 2004).

However, clinical pain is rarely brief or exactly timed. Even acute pain due to injuries lasts normally from minutes to hours and does not resemble phasic experimental pain, which has often been used as stimulation paradigm. Brain responses to phasic pain can be assessed easily by evoked brain potentials. If phasic pain is not modelling clinical pain sufficiently as regards duration, more tonic forms of experimental pain are required. Numerous models have been developed (Arendt-Nielsen and Lautenbacher 2004). Whereas brain imaging studies have appeared to make good use of these tonic pain models, methods such as EEG have not yet been able to describe unequivocally the brain activity due to tonic pain (Bromm and Lorenz 1998; Chen 2001). How did this happen?

A few EEG-changes have been repeatedly observed during processing of tonic pain: increase in delta power, rare change in theta power, decrease in alpha power and increase in beta power. These findings could be obtained by a variety of physical stressors. Whereas cold-pressor pain has been mainly used (Backonja et al. 1991; Chang et al. 2002a; Chen and Rappelsberger 1994; Chen et al. 1989, 1998; Ferracuti et al. 1994), injections of capsaicin

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into the skin (Chang et al. 2001a) and into the muscle (Chang et al. 2001b) as well as of hypertonic saline into the muscle (Chang et al. 2002b) have also been applied. Chang et al. (2004) compared experimental tonic skin and muscle pains directly with the result that besides considerable similarities in EEG patterns, tonic muscle pain resulted into a stronger beta² activity.

These results have been obtained with consistency and even allow for generalization across physical stressors. The stage appears to be set for further progress. However, there are still doubts as to the specificity of the described EEG changes for pain (Bromm and Lorenz 1998). The EEG patterns might simply be due to sensory processing in general and to all cognitive and affective processes linked to sensory processing. The lack of clear answers to this questions is partly a consequence of the methods used for pain induction, which do not allow for sufficient experimental control.

Using the cold-pressor test, either no control conditions (Chen 1989; Chen and Rappelsberger 1994; Chang et al. 2002a) or control conditions with physically and subjectively enormous differences to the tonic cold pain conditions (Backonja et al. 1991; Chen et al. 1998; Ferracuti et al. 1994) were put into effect. Similarly, tonic experimental pains induced by injections of capsaicin or hypertonic saline were controlled by injections of vehicle or isotonic saline, which constituted hardly comparable types of stimulation (Chang et al. 2001a, b, 2002b). Conditions with strong differences in stimulus intensities were compared, which were different in many respects besides the fact that one stimulus was painful and the other was not.

Chang et al. (2002b) were aware of this limitation and designed a study, allowing for comparing two types of strong stimuli, unpleasant auditory stimulation and muscle pain. The two stimuli could even be matched with respect to the level of unpleasantness and arousal. The frequently observed reduction in alpha¹ activity was found to be specific to muscle pain. This undermined the argument that the reduction of alpha observed in many pain studies was a variant of event-related desynchronisation (ERD, Pfurtscheller 1992), which occurs for a short time after onset of internal and external stimulation of many kinds.

In the present study we tried to add to this line of reasoning. In contrast to Chang et al. (2002b), who used a perfectly different stimulus modality and activated distinctively different sensory cortex areas, we aimed at comparing the differences in EEG patterns obtained during strong but still not painful heat stimulation and during just painful heat stimulation. The difference in physical intensity between conditions should be as small as possible with the decisive difference being a change in perceptual quality from non-painful to painful.

Attention is the psychological description of the selectivity of the brain. It determines which brain activity prevails at a given time. Of course, attentional processes are influenced by pain and influence pain in a variety of ways (Bushnell et al. 2004). Focusing on pain

or distraction from pain control how much pain is experienced (Lautenbacher et al. 1998). So far, in the EEG studies on the effects of tonic experimental pain, attention has been scarcely controlled by experimental manipulation. In the present study we manipulated attention by instruction and induced active distraction by a mental task.

Methods

Subjects

Young healthy, right-handed male volunteers were recruited from the university community. Individuals suffering from any acute and chronic disease were excluded after a physical investigation and an interview. All subjects were studied drug-free, were paid for participation and gave written informed consent before participating in the study. The experimental protocol was approved by the ethics committee of the medical school of the University of Marburg. Two subjects had to be excluded because of missing data; the remaining sample consisted of 20 young male, healthy, right-handed volunteers, aged from 20 to 32 years (mean = 26.9, years, SD = 3.3). Complete EEG recordings were obtained from all 20 subjects. None of them had signs of abnormal EEG records.

General experimental procedure

Sessions took place in a sound-attenuated room with dimmed luminescence. Subjects were seated comfortably in an upright chair. At the beginning of each session subjects were instructed in a standardized way about the general procedure. After fixation of EEG leads and recording of 5 min of resting EEG activity, which allowed for screening for pathological EEG patterns, the individual pain thresholds of the subjects were determined. Thereafter, subjects were familiarized with the pain ratings and questionnaires. This was followed by a period of 10 min of adaptation to the experimental setting (see Fig. 1a).

The session itself consisted of nine experimental blocks of 10 min each, with intervals of 5 min between blocks (see Fig. 1a). The nine blocks resulted from a combination of the two experimental factors “stimulation” and “attention” with three levels each. The three levels of “stimulation” were (S1) tonic painful heat, (S2) tonic non-painful heat and (S3) baseline. The levels of “attention” were (A1) attention focused, (A2) attention defocused and (A3) no control of attention. The nine resulting experimental conditions were presented in the same randomized sequence to all subjects. During the experimental blocks subjects were asked to close their eyes and they wore eye caps in addition. Ratings were given verbally during this time.

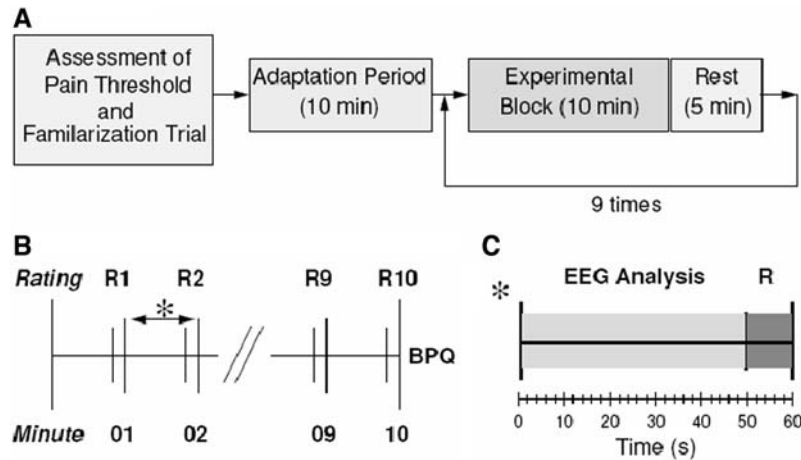


Fig. 1 Schematic representation of the study. **a** First, the pain thresholds were assessed and familiarization trials were conducted, an adaptation period followed. Then, the nine experimental blocks, resulting from the combination of the three levels of thermal stimulation (tonic painful heat, tonic non-painful heat, baseline) with the three levels of attentional control (attention focused, attention defocused, no control of attention) were run. **b** Each experimental block lasted for 10 min and at the end of each minute

of stimulation sensation intensity and sensation unpleasantness were rated. A German version of the McGill Pain Questionnaire, the Berner Pain Questionnaire (BPQ), had to be filled out after experimental blocks with tonic painful heat stimulation. **c** EEG analysis was performed on 3-s periods from the first 50 s whereas the ratings were obtained during the last 10 s of each minute of stimulation

Pain ratings and questionnaire

During those experimental blocks, which included thermal stimulation, the subjects rated intensity and unpleasantness of sensation during the last 10 s of each minute (see Fig. 1b). The rating interval was always signalled by acoustic cues. Intensity and unpleasantness were assessed by means of a numerical scale. The numerical scale for intensity of sensation ranged from 0 to 100 with the scale anchors, “no sensation” = 0, “barely painful” = 50 and “extremely intense pain” = 100. Accordingly, all non-painful sensations should be indicated by ratings smaller than 50 and all painful ones by ratings greater than 50. The numerical scale for unpleasantness of sensation was marked with the scale anchors: “no sensation” = 0, “barely unpleasant sensation” = 50 and “extremely unpleasant sensation” = 100. At the end of the three experimental blocks, which involved tonic heat pain, the subjective pain responses were assessed in addition by a German version of the McGill Pain Questionnaire (MPQ, Melzack 1975) called the Berner Pain Questionnaire (BPQ, Radvalla et al. 1987).

Thermal stimulation

Thermal stimuli were administered by means of a temperature controlled contact thermode with a stimulation surface of $1.6 \times 3.6 \text{ cm}^2$. The thermode mounted on an articulated arm (which enables the thermode to be swivelled flexibly) was attached to the left volar forearm, which was supported by a bolster. The contact pressure was held at 0.4 N/cm^2 . The apparatus PATH Tester MPI 100 (Phywe, Göttingen) was described in detail by Galfe et al. (1990).

Each tonic heat stimulus consisted of a series of small heat pulses with a constant frequency of 30 pulses/min and an amplitude of 1.3°C (Lautenbacher et al. 1995). In the experimental blocks with tonic painful heat the pulses were tailored to have a peak temperature of 1°C above the individual pain threshold and in the experimental blocks with tonic non-painful heat of 0.3°C below the individual pain threshold. Stimulation was constantly on for 10 min during experimental blocks with tonic thermal stimulation. Baseline stimulation was achieved by setting the temperature for the 10 min at 37°C , considered as neutral.

Stimulation sites varied between experimental blocks. The volar forearm therefore was divided into a medial and a lateral part, which were again subdivided into a distal, a middle and a proximal part. Stimulation varied between the six sites in a way, that prevented painful stimulation occurring twice at the same site.

Since tonic thermal stimulation was tailored to the individual pain thresholds, heat pain thresholds were assessed by means of an adjustment procedure (see Fig. 1a). Subjects were asked to adjust a temperature starting from 37°C , using heating and cooling buttons, until they obtained a level which was barely painful. Following a familiarization trial, there were six trials and the average of the last five trials was used to constitute the threshold estimate. Thresholds were assessed twice to guarantee reliability, once at the lateral proximal site and once at the medial distal site. Finally, the two threshold estimates were averaged.

Attentional control

Three levels of attention were put into effect: attention focused, attention defocused and no control of attention.

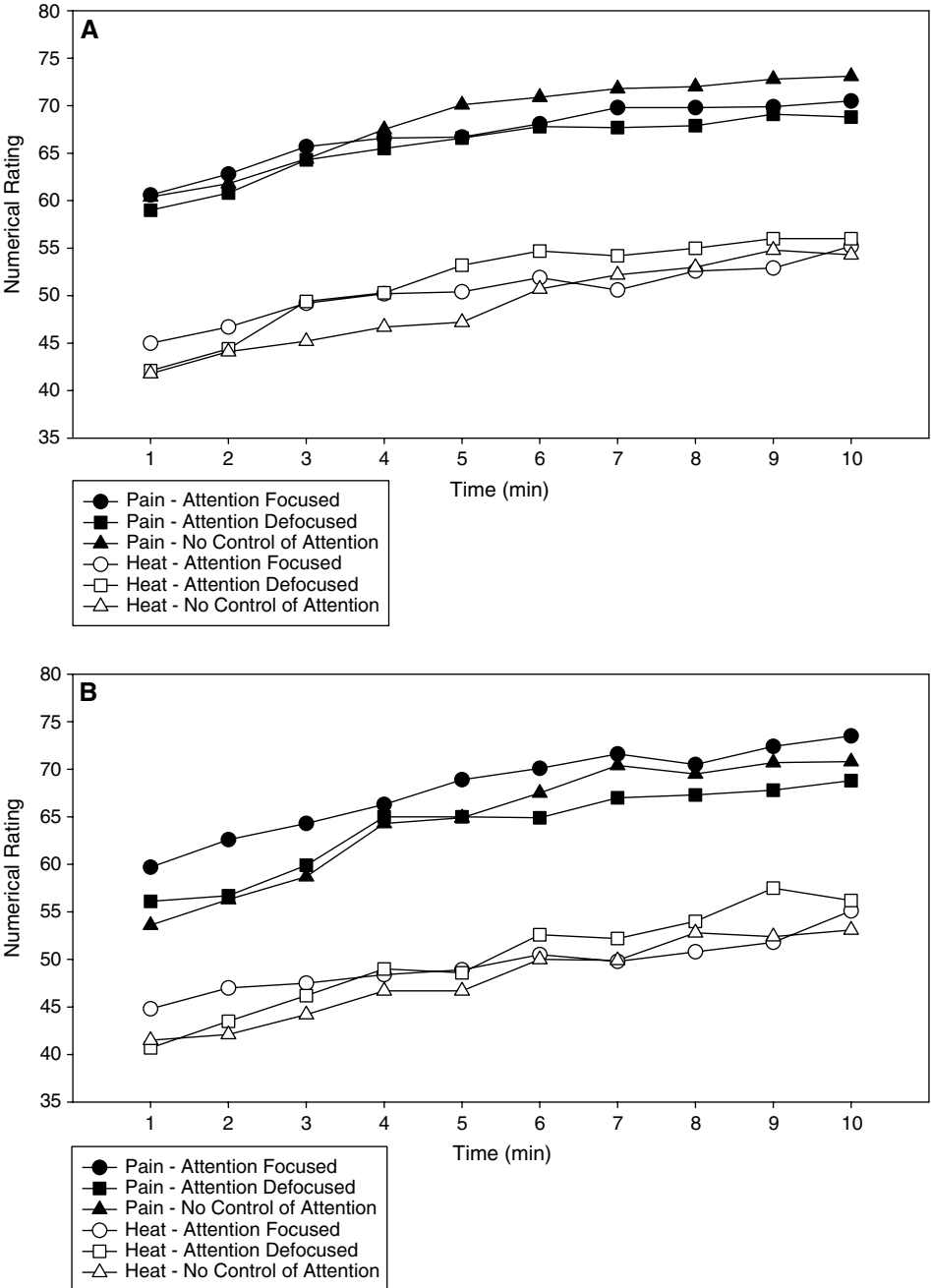
For the condition “attention focused” the subjects were instructed to focus attention on the respective site of stimulation and on the sensations perceived there. For the condition “attention defocused” subjects were required to monitor a sequence of two distinct acoustic signals (440 or 880 Hz of frequency , 80 dB of amplitude, 750 ms of duration), which were played through ear-phones. (The subjects wore the ear-phones during each experimental block, either for administration of the distraction task or for further improving noise insulation.) The repetition of the same signal was the target stimulus whereas the alternation between the two signals was the non-target stimulus. The subjects were instructed to respond to the target stimulus by pressing a

key as quickly as possible. For the condition “no control of attention” the subjects were instructed to concentrate on whatever they wanted to. Since instructions cannot guarantee definite defocusing from pain, subjects were required to engage in additional sensory and motor processing in the condition with distraction although the many processes might have resulted in confusion as regards the effect of attentional control of pain.

EEG recording and data processing

EEG recording electrodes were affixed at frontal (F3, F4), central (C3, C4), temporal (T3, T4), parietal (P3,

Fig. 2 Mean numerical ratings for sensation intensity (a) and sensation unpleasantness (b) during tonic thermal stimulation (black: tonic painful heat, white: tonic non-painful heat; circles: attention focused, squares: attention defocused, triangles: no control of attention)



P4) and occipital (O1, O2) loci for both hemispheres according to the international 10/20 convention. Referential electrodes were bilaterally connected to the two earlobes and then averaged. Impedance was controlled to be less than 3 k Ω in each lead. Two electro-oculographic leads were recorded for vertical and horizontal eye blink control.

EEG signals were amplified by a Madaus-Schwarzer (ES-16000, Munich) EEG amplifier. The band pass filters were set to 1–70 Hz (6 dB/octave). EEG data were A/D converted with a sampling rate of 172 Hz and stored for off-line analysis on magnetic tapes. Two reviewers independently examined the raw EEG data and only artefact-free 3-s epochs, on which the two could agree, were used for analysis. Only artefact-free 3-s epochs during the first 50 s of each minute were taken (see Fig. 1c). Spectral analysis with Fast Fourier Transform was performed using a software package custom written in our laboratory. Absolute power spectra were calculated from zero to 86 Hz (step size 0.3364 Hz) and the power densities ($\mu\text{V}^2/\text{Hz}$) for delta² (2–4 Hz), theta (4–8 Hz), alpha¹ (8–10 Hz), alpha² (10–12 Hz) and beta¹ (12–16 Hz) were determined (Walter 1968). In order to eliminate any contamination by slow eye movements and muscle potentials we used the following approach (Lopes da Silva 1993). Since slow eye movements are reflected in the slowest frequency band (0–1.5 Hz), we excluded the delta¹ band. In order to avoid artefacts by muscle potentials, which we might have missed during visual examination, we did not consider the beta² band; electromyographic activity, which normally occurs at frequencies between 30 and 60 Hz, can produce changes in signal power below 20 Hz.

Statistical analysis

Analyses of variance for repeated measurements were conducted. All designs included three factors, which were “stimulation”, “attention” and “time”. However,

the levels of the factor “stimulation” differed between analyses. For the numerical ratings of sensation intensity and sensation unpleasantness the factor “stimulation” included only two levels (S1 = tonic painful heat, S2 = tonic non-painful heat) because no ratings were obtained during baseline stimulation, resulting in a 2 \times 3 \times 10 factorial design. For each EEG lead (F3, F4, C3, C4, T3, T4, P3, P4, O1, O2) and each frequency band (delta², theta, alpha¹, alpha², beta¹) a separate analysis of variance was computed. There were two types of analyses, one including all three levels of stimulation (S1 = tonic painful heat, S2 = tonic non-painful heat, S3 = baseline; 3 \times 3 \times 10) and others including always only two levels of stimulation (2 \times 3 \times 10) to specify the potential effect of stimulation in the first type of analysis. The second type allowed for comparing all stimulation levels in pairs with each other. Since the effects of tonic thermal stimulation on the EEG responses is the focus of interest, and since an inflation of statistical tests is to be avoided, main and interaction effects not including the factor “stimulation” were not detailed. There was one exception to the three-factorial type of design. The effect of attention on the BPQ was assessed by an analysis of variance for repeated measurements with only one factor because the pain questionnaire was used only after conditions with tonic painful heat. To control for multiple comparisons, the alpha level was set to 0.01 throughout.

Results

Subjective data

The mean of heat pain thresholds was 44.1 $^{\circ}\text{C}$ (SD=1.21). Fig. 2 shows the effects of tonic thermal stimulation on the numerical ratings of sensation intensity and sensation unpleasantness. There was a highly significant effect of the factor “stimulation” both

Fig. 3 Mean (+SD) scores in the Berner Pain Questionnaire (BPQ) for sensations rated after tonic painful heat stimulation (*black*: attention focused, *white*: attention defocused, *grey*: no control of attention). Scores include the Pain Rating Index for the sensory component (PRI-S), the affective component (PRI-A), the evaluative component (PRI-E), the miscellaneous component (PRI-M) and for all components added up (PRI-T) as well as the Present Pain Index (PPI)

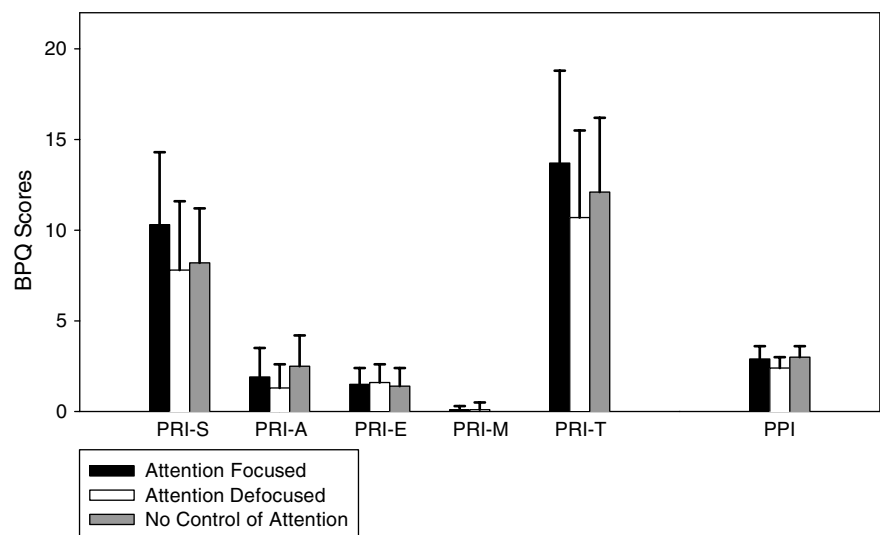


Table 1 *F*- and *P*-values for the main and interaction effects in the analyses of variance with the factors “stimulation”, “attention” and “minute” in the 3×3×10 factorial designs for EEG power density

	Delta ²		Theta		Alpha ¹		Alpha ²		Beta	
	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
Locus: F3										
Stimulation	20.88	<0.001	9.00	0.001	7.55	0.002	0.00	0.998	1.46	0.245
Time	9.15	<0.001	4.75	<0.001	0.65	0.749	2.0	0.043	2.75	0.005
Attention	3.49	0.041	0.09	0.910	7.27	0.002	0.97	0.388	0.83	0.442
Stimulation × Time	0.96	0.503	1.76	0.029	1.35	0.157	1.5	0.087	0.97	0.493
Stimulation × Attention	0.91	0.461	0.22	0.926	1.87	0.126	0.13	0.971	0.71	0.591
Locus: F4										
Stimulation	20.6	<0.001	6.81	0.003	8.06	0.001	0.29	0.751	2.95	0.064
Time	9.07	<0.001	4.69	<0.001	0.45	0.905	2.73	0.005	2.74	0.005
Attention	3.82	0.031	0.24	0.791	10.23	<0.001	2.43	0.102	2.64	0.085
Stimulation × Time	0.94	0.535	1.28	0.197	0.94	0.530	1.35	0.155	0.78	0.724
Stimulation × Attention	1.26	0.292	0.11	0.979	1.92	0.115	0.21	0.931	0.43	0.789
Locus: C3										
Stimulation	10.28	<0.001	0.3	0.743	3.3	0.048	0.51	0.604	0.08	0.927
Time	6.69	<0.001	1.85	0.062	0.61	0.788	3.27	0.001	1.64	0.108
Attention	11.75	<0.001	0.95	0.394	4.17	0.023	3.01	0.061	0.08	0.921
Stimulation × Time	1.25	0.222	1.18	0.276	1.39	0.133	0.76	0.752	1.47	0.098
Stimulation × Attention	1.96	0.109	0.56	0.691	1.41	0.240	0.24	0.916	0.99	0.416
Locus: C4										
Stimulation	8.86	0.001	0.43	0.651	5.84	0.006	2.60	0.087	0.44	0.647
Time	6.42	<0.001	2.65	0.007	1.53	0.141	2.48	0.011	2.03	0.039
Attention	8.4	0.001	1.56	0.224	5.4	0.009	1.65	0.205	1.83	0.174
Stimulation × Time	1.13	0.319	1.33	0.167	1.59	0.061	0.9	0.574	0.84	0.654
Stimulation × Attention	2.14	0.084	0.99	0.419	1.45	0.224	0.46	0.762	0.2	0.936
Locus: P3										
Stimulation	9.74	<0.001	0.21	0.809	3.61	0.037	1.97	0.153	0.6	0.556
Time	3.42	0.001	1.57	0.129	0.36	0.953	1.38	0.201	0.74	0.668
Attention	7.01	0.003	0.87	0.425	2.57	0.090	0.35	0.706	0.93	0.403
Stimulation × Time	1.11	0.340	1.31	0.177	1.19	0.270	0.89	0.595	0.82	0.675
Stimulation × Attention	1.98	0.105	0.95	0.441	0.82	0.519	1.19	0.322	0.89	0.477
Locus: P4										
Stimulation	5.8	0.006	0.26	0.770	2.15	0.130	0.8	0.455	0.13	0.880
Time	2.47	0.011	2.26	0.020	1.25	0.268	0.67	0.736	1.18	0.312
Attention	7.14	0.002	0.55	0.581	3.56	0.038	0.36	0.699	0.52	0.597
Stimulation × Time	0.78	0.723	1.78	0.026	1.49	0.092	0.78	0.726	1.07	0.379
Stimulation × Attention	2.24	0.072	0.5	0.736	0.7	0.596	0.49	0.746	0.42	0.793
Locus: T3										
Stimulation	9.16	0.001	11.87	<0.001	6.43	0.004	0.26	0.769	5.71	0.007
Time	0.81	0.609	3.59	<0.001	1.37	0.206	2.73	0.005	10.68	<0.001
Attention	2.88	0.069	0.48	0.625	3.98	0.027	2.87	0.069	0.23	0.798
Stimulation × Time	1.06	0.387	1.45	0.106	1.01	0.448	0.73	0.779	2.19	0.004
Stimulation × Attention	0.5	0.736	0.61	0.656	1.25	0.298	0.51	0.730	0.87	0.488
Locus: T4										
Stimulation	12.59	<0.001	2.63	0.085	9.87	<0.001	3.02	0.061	3.06	0.059
Time	1.34	0.219	3.27	0.001	0.52	0.859	3.6	<0.001	4.69	<0.001
Attention	6.38	0.004	2.82	0.072	8.76	0.001	2.44	0.100	0.72	0.492
Stimulation × Time	1.35	0.154	1.06	0.397	0.79	0.715	0.88	0.606	1.81	0.023
Stimulation × Attention	0.74	0.567	0.25	0.907	1.59	0.187	0.19	0.941	0.93	0.452
Locus: O1										
Stimulation	2.64	0.084	0.3	0.739	3.18	0.053	0.28	0.760	1.49	0.239
Time	1.35	0.215	0.273	0.273	1.7	0.093	0.82	0.598	1.33	0.225
Attention	1.54	0.227	0.34	0.715	1.07	0.353	0.1	0.905	0.37	0.690
Stimulation × Time	0.93	0.547	1.49	0.089	1.12	0.328	1.09	0.363	1.04	0.417
Stimulation × Attention	2.93	0.026	1.17	0.329	0.49	0.741	0.55	0.697	0.7	0.597
Locus: O2										
Stimulation	1.7	0.197	0.42	0.660	3.01	0.061	0.32	0.731	1.79	0.180
Time	1.07	0.391	2.25	0.021	1.6	0.120	0.58	0.812	0.73	0.684
Attention	6.48	0.004	0.14	0.870	2.35	0.109	0.02	0.977	0.68	0.513
Stimulation × Time	0.61	0.891	2.3	0.002	1.14	0.316	0.86	0.623	1.28	0.197
Stimulation × Attention	1.31	0.272	1.19	0.321	0.5	0.734	0.43	0.785	0.51	0.727

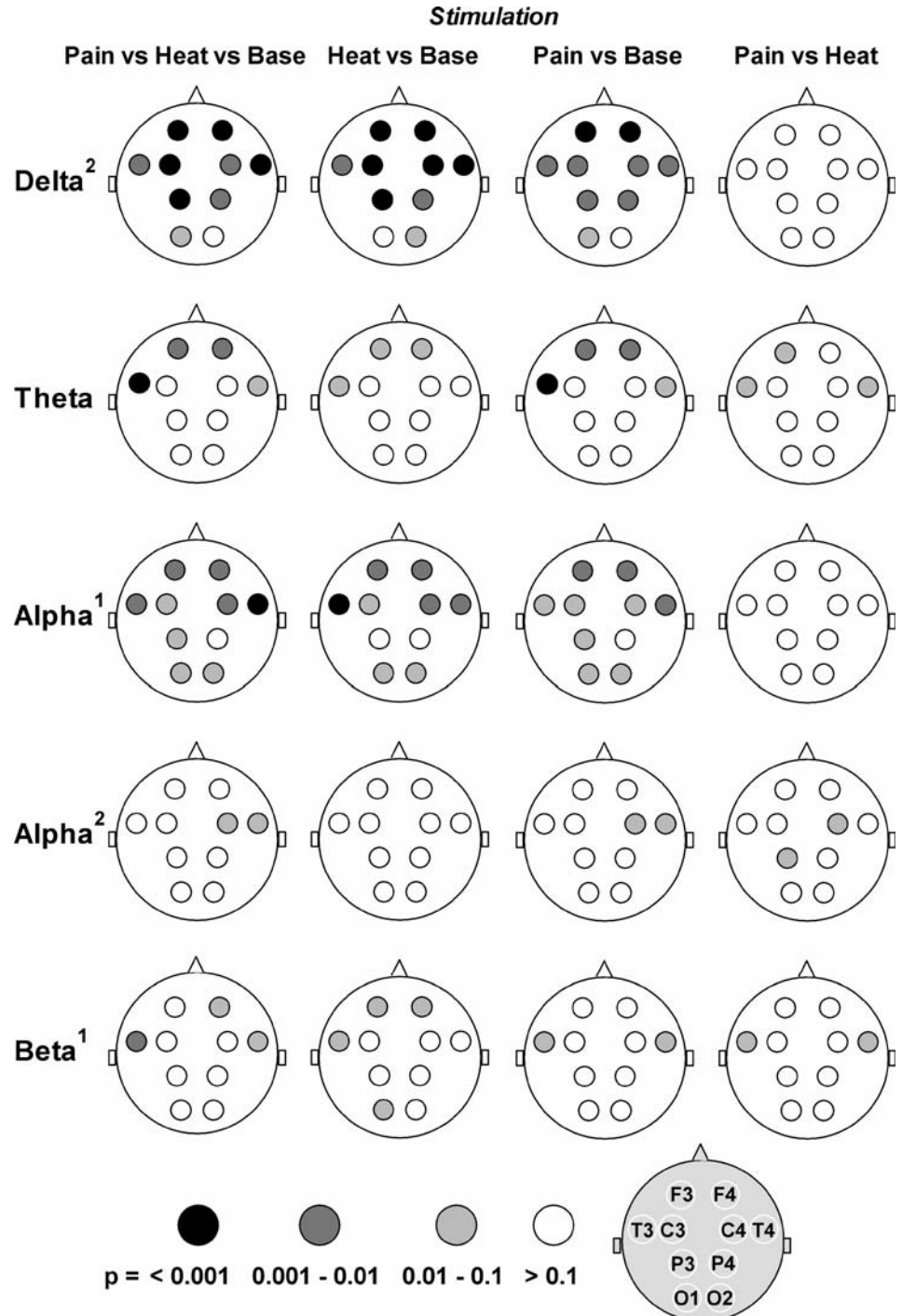
Degrees of freedom (*df*) of *F*-values are 2/38 for Stimulation and Attention, 9/171 for Time, 18/342 for Stimulation × Time and 4/76 for Stimulation × Attention through out the table except for Alpha¹ in F3, where the *df* values are 2/36, 9/162, 2/36, 18/324 and 4/72, respectively, due to missing data

for sensation intensity (df 1/19, $F=42.28$, $P<0.001$, see Fig. 2a) and for sensation unpleasantness (df 1/19, $F=46.73$, $P<0.001$; see Fig. 2b), with the conditions designated as tonic painful heat leading to ratings of approximately 15 scale units higher than those designated as tonic non-painful heat. According to this finding, the conditions were clearly separated regarding their subjective strength. Unfortunately, the ratings for sensation intensity were just above 50 after the fourth minute in the blocks with non-painful heat, suggesting

that in the course of stimulation, faintly painful sensations developed even in this condition.

There was a highly significant effect of the factor “time” both for sensation intensity (df 9/171, $F=10.13$, $P<0.001$, see Fig. 2a) and for sensation unpleasantness (df 9/171, $F=17.86$, $P<0.001$; see Fig. 2b), based on an approximate increase in ratings of 10 scale units in the course of tonic thermal stimulation. This trend appeared almost linear with some tendency to level off at the end of stimulation.

Fig. 4 P -values for the main effects of the factor “stimulation” with the three levels (tonic painful heat = “Pain”, tonic non-painful heat = “Heat”, baseline = “Base”) in the analyses of variance for EEG power density. Column 1 shows the comparison of all three levels ($3\times 3\times 10$ factorial design of analysis) whereas columns 2–4 show comparisons of always two levels only ($2\times 3\times 10$ factorial designs of analysis)



The effect of our attentional manipulation seemed limited because no significant main and interaction effects could be established including the factor “attention” on the numerical ratings of sensation intensity (see Fig. 2a). However, there was a significant interaction “attention” × “stimulation” ($df = 3/57, F = 2.44, P < 0.001$) for the ratings of sensation unpleasantness (see Fig. 2b). It appeared that attention focused on pain led throughout to higher ratings of sensation unpleasantness but only in the condition with tonic painful heat. The efficacy of our attentional manipulation was also corroborated by the BPQ. The pain rating index (PRI) indicated significant effects for the sensory component

(PRI-S; $df = 2/19, F = 6.93, P = 0.003$). The same was true for the Present Pain Index (PPI); $df = 2/19, F = 6.83, P = 0.003$). The PRI for the affective component (PRI-A) and the total score (PRI-T) approached significance. The PRI-S was higher for attention focused on pain compared to attention defocused and to no control of attention. The PPI was lowest for attention defocused from pain compared to attention focused and to no control of attention (Fig. 3).

In sum, our manipulation of stimulation and attention led to subjective states distinct enough regarding their painfulness to have had good chance to be mirrored in the EEG-responses.

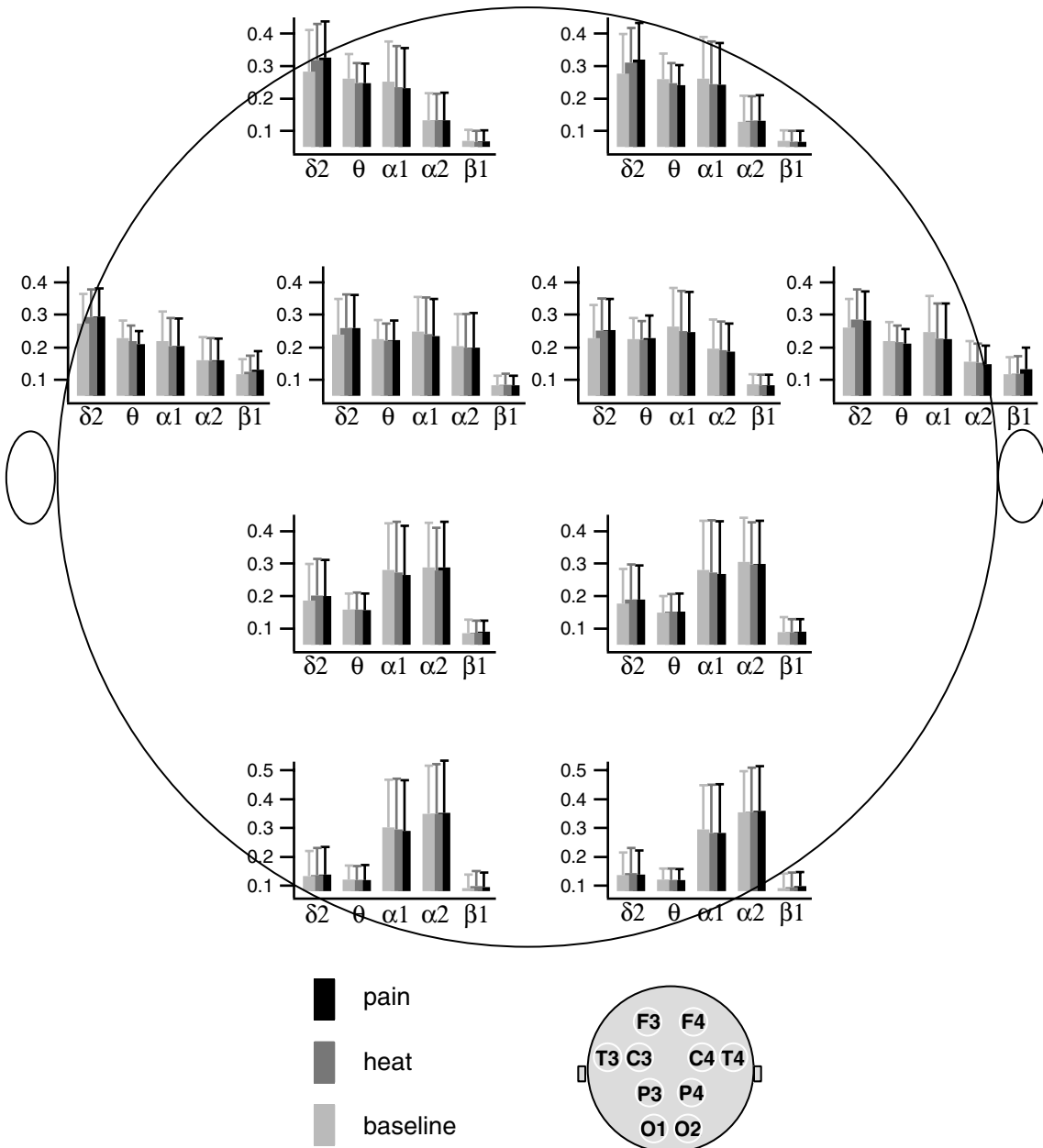


Fig. 5 Topographical distribution of mean (+SD) power densities in each frequency band separated according to the levels of stimulation (*black*: tonic painful heat = “Pain”, *dark grey*: tonic

non-painful heat = “Heat”, *light grey*: “Baseline”) averaged over the three levels of attentional control and over 10 min of stimulation

EEG responses

For the EEG responses the significant effects were too numerous to be described in detail in the text. Detailed descriptions of the results of the analyses of variance are given in Table 1 and in Figs. 4 and 6.

The factor “stimulation” produced significant effects for power density in the δ^2 frequency band in all EEG leads except in the two occipital ones. This was due to increases in the two conditions with tonic painful and

tonic non-painful stimulation compared to baseline. The significance was preserved when each of the two conditions with tonic stimulation was compared separately to baseline. However, the significance of differences was completely lost when the condition with tonic painful heat was compared to the condition with tonic non-painful heat (see Table 1; Figs. 4, 5).

Theta changes were obvious only in the two frontal leads and the left temporal one in the form of decreases in power density. The significant decrease was produced by tonic painful heat only. Again, no difference in power density was found when the two conditions with tonic thermal stimulations were compared (see Table 1; Figs. 4, 5).

The factor “stimulation” produced significant effects for power density in the α^1 frequency band in the frontal and temporal EEG leads when all three levels of stimulation were compared. The power density of α^1 decreased in these cases. The effects of stimulation when the tonic non-painful heat and when the tonic painful heat were both compared to baseline appeared similar. Again, no significant differences were obtained when comparing the two conditions with tonic thermal stimulation (see Table 1; Figs. 4, 5).

Besides a trace of left temporal (T3) increase in power density for the β^1 frequency band as a general effect of tonic thermal stimulation, no further significant EEG responses to tonic stimulation were observed (see Table 1; Figs. 4, 5).

The described effects of stimulation on the EEG responses appeared very stable over time because the interaction effects “stimulation” \times “time” were hardly significant. Only two out of 50 tests on this interaction passed the level of significance. In O2 the decrease of power density in theta under tonic stimulation developed only at the end of the 10 min period of stimulation. The left temporal increase (T3) in power density of β^1 due to tonic thermal stimulation already reported also developed only at the end of the 10 min period of stimulation (see Table 1; Fig. 6a).

The described effects of stimulation on the EEG responses appeared perfectly independent of the level of attention because none of the 50 tests on the interaction effect “stimulation” \times “attention” passed the level of significance. This was the more surprising as attention influenced the subjective experience of pain and exerted general effects on the EEG, a discussion of which is outside the scope of the present report (see Table 1; Fig. 6b).

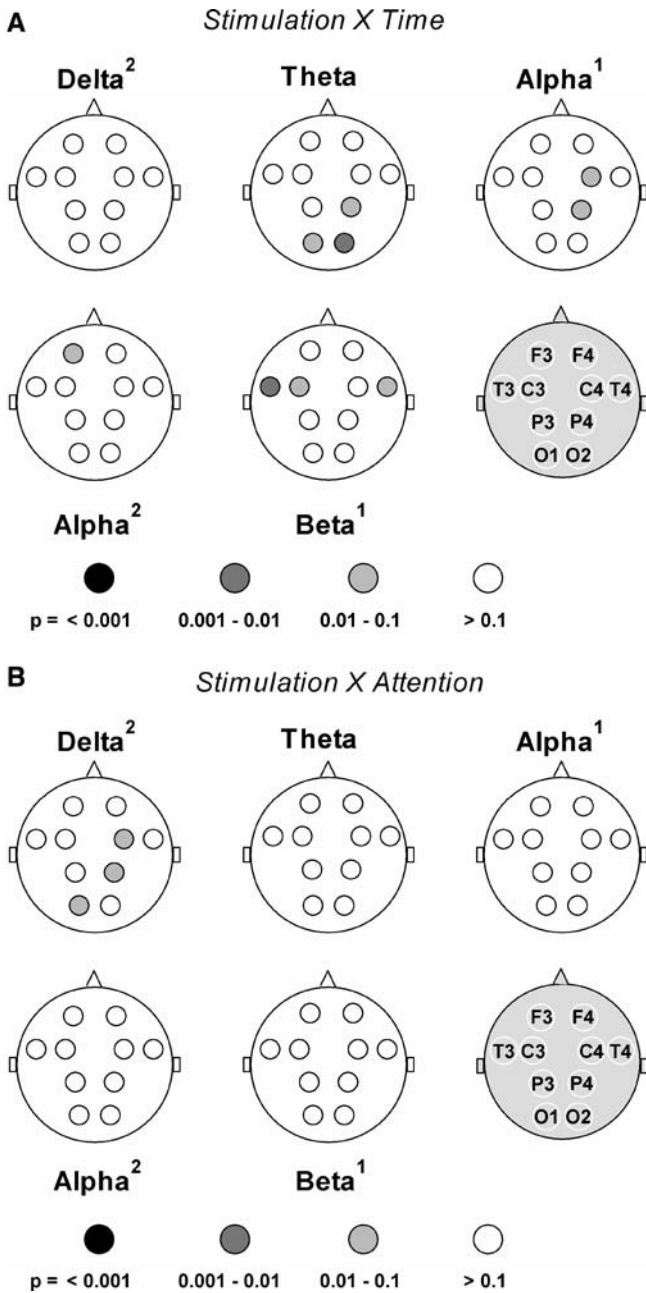


Fig. 6 P-values for the interaction effects of the factors “stimulation” and “time” (a) and of the factors “stimulation” and “attention” (b) in the analyses of variance ($3 \times 3 \times 10$ factorial design of analysis) for EEG power density

Discussion

In this study we investigated the effects of tonic heat pain on subjective and EEG responses as compared to tonic non-painful heat and to a baseline condition. We observed (1) during tonic thermal stimulation a pattern of EEG responses characterized by a rather generalized increased δ^2 activity, a left-biased fronto-temporally

diminished theta activity, a fronto-temporal decrease in the alpha¹ activity and a left-sided temporal increase in the beta¹ activity but we found (2) no evidence that these changes are specific to tonic heat pain and not like the changes observed during tonic non-painful heat stimulation. The EEG patterns were not affected by our attentional manipulations, with attention focused on pain and distracted from pain, which proved to be effective as regards the subjective experience of pain, and largely did not vary over time, suggesting a marked stability of brain activity while processing tonic thermal stimulation.

First, we discuss the degree of correspondence of our EEG response patterns with patterns observed in earlier studies. Chen et al. (1989) observed, as we also did, an increase in delta and beta¹ power density but, in contrast to our data, no changes in theta and alpha activity. In a later study, in which again the cold-pressor test was used, Chen and Rappelsberger (1994), however, found a reduction of theta and alpha amplitude. In a further study of the same group (Chen et al. 1998), in which the findings were similar in many respects to our data, the use of the cold-pressor test led to an increase in theta amplitudes, which contrasts with their former observation and with ours, of a theta activity decrease. Alpha¹ reduction as seen in our study was also reported in other studies, in which the cold-pressor test was used (Backonja et al. 1991; Chang et al. 2002a; Ferracuti et al. 1994). The decrease of alpha¹ activity appeared to be a rather transient phenomenon induced by the cold-pressor test whereas the reduction was stable under tonic heat stimulation in the present study. Decrease in alpha² activity was seen in some (Chang et al. 2002a; Ferracuti et al. 1994) but not all studies (Backonja et al. 1991) and not in ours. Our observation of an increase in delta² power density has also been preceded by similar reports from others (Chang et al. 2002a; Ferracuti et al. 1994). In sum, given the reported variability of the EEG patterns found in studies, in which the cold pain was used as tonic pain model, our results accord well with other findings.

Is there now a difference to tonic pain models, which made use of injection of capsaicin or hypertonic saline? Reduction of alpha¹ and alpha² activity as well as augmentation of beta² activity were found after injection of algogenic substances into the muscle (Chang et al. 2001a, b, 2004). This suggests that also tonic chemical pain models induce EEG patterns similar to those obtained by application of tonic cold pain and tonic heat pain.

The main question in the present study was of whether the observed EEG responses, which were in good accord with the EEG patterns seen in earlier studies, were specific to pain. We cannot give a positive answer. The EEG responses evoked in a condition designated as non-pain control, in which temperatures below pain threshold were used, were strikingly similar to the EEG responses, which were elicited in the pain condition, in which temperatures above pain threshold

were administered. The two conditions were physically separated by 1.3°C and subjectively by approximately 15 scale units on a numerical scale from 0 to 100. We used deliberately a non-pain control condition closest possible to the pain condition to avoid confounding differences between pain and non-pain with huge differences in stimulation intensity. Unfortunately, our tonic non-painful heat stimulation produced after 4 min numerical ratings suggestive of faint pain sensations likely due to some kind of sensitization and was not ideal in this respect. (In future studies a slightly lower stimulation intensity for the non-pain control condition is therefore warranted.) However, if this potential change in perceptual quality had induced an EEG pain pattern into the non-pain control condition during the course of stimulation, significant interactions between the factor “stimulation” and “time” should have been found more often than was the case. This also means that the similar EEG patterns in the pain and non-pain conditions did not differ between the early and late epochs of stimulation, an assumption, which was confirmed in additional analyses. We assume that the better explanation still is that strong somatosensory stimulation induces EEG response patterns quite similar to those induced by pain stimulation and that pain specificity has not yet been proven.

Chang et al. (2001a, b) were already quite aware that part of the EEG changes observed after injections of algogenic substances are not specific to pain because they found similar changes after injections of control substances, which did not trigger pain at all. However, they concluded that the remaining EEG pattern differences between the conditions with algogenic and control substances can be pain-specific. Given that the conditions differed also markedly as regards the intensity of sensation, further investigation is justified.

Cerebral nociception never does occur without concurrent additional brain activities, which may affect in turn nociception. We tried to control for these additional brain activities by setting experimentally the stage for an influence with established relevance; This is attentional control. Our attentional manipulations (focused, defocused and uncontrolled attention), which were, as often observed, moderately effective as regards the subjective experience of pain, did not change the EEG responses to tonic heat stimulation. The latter finding suggest that the observed EEG patterns are stable and general. Since attention was not a variable of interest in its own right and since the number of tests were already substantial, the corresponding main effects of attention were not considered in detail.

In sum, we observed a pattern of EEG responses (i.e. changes in power density in the classical frequency bands) to tonic heat pain, which were very similar to EEG patterns found in earlier studies by use of other types of tonic pain. However, the attempt to verify the pain specificity of this pattern by comparing with tonic non-painful heat stimulation, failed.

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