



Reduced heat pain thresholds after sad-mood induction are associated with changes in thalamic activity

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ARTICLE INFO

Article history:

Received 5 June 2008

Received in revised form 15 October 2008

Accepted 27 October 2008

Available online 5 November 2008

Keywords:

Pain perception threshold
Major depression
Mood induction
fMRI

ABSTRACT

Negative affective states influence pain processing in healthy subjects in terms of augmented pain experience. Furthermore, our previous studies revealed that patients with major depressive disorder showed increased heat pain thresholds on the skin. Potential neurofunctional correlates of this finding were located within the fronto-thalamic network. The aim of the present study was to investigate the neurofunctional underpinnings of the influence of sad mood upon heat pain processing in healthy subjects. For this purpose, we used a combination of the Velten Mood Induction procedure and a piece of music to induce sad affect.

Initially we assessed heat pain threshold after successful induction of sad mood outside the MR scanner in *Experiment 1*. We found a highly significant reduction in heat pain threshold on the left hand and a trend for the right. In *Experiment 2*, we applied thermal pain stimuli on the left hand (37, 42, and 45 °C) in an MRI scanner. Subjects were scanned twice, one group before and after sad-mood induction and another group before and after neutral-mood induction, respectively. Our main finding was a significant group × mood-induction interaction bilaterally in the ventrolateral nucleus of the thalamus indicating a BOLD signal increase after sad-mood induction and a BOLD signal decrease in the control group. We present evidence that induced sad affect leads to reduced heat pain thresholds in healthy subjects. This is probably due to altered lateral thalamic activity, which is potentially associated with changed attentional processes.

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1. Introduction

The complex sensory experience of pain involves cognitive, behavioural and emotional aspects which are closely interrelated. A model for the interaction between different components has been proposed, which involves a dual pathway of affective pain processing (Price, 2000). In addition to direct activation by the spinothalamic pathway, a corticolimbic pathway may play a role in integrating sensory pain characteristics with information from other sensory systems as well as learning and memory. This adds a cognitive aspect regarding the long-term consequences to affective pain processing. In addition, it has been pointed out that direct pathways from the thalamus to the amygdala and related structures may exist (Price, 2000). The interrelation between emotion and pain is multifactorial and there is strong experimental evidence that emotion modulates pain perception in healthy subjects as well as in patients with psychiatric disorders (Bär et al., 2006; Jochum et al., 2006).

Several experimental approaches assessed the influence of emotion on pain in healthy subjects. Positive as well as negative emotion

induction by affective material like pictures produces differential pain processing (Meagher, Arnau, & Rhudy, 2001). Willoughby, Hailey, Mulkana, and Rowe (2002) presented evidence that healthy subjects had significantly lower tolerance times in the cold-pressor task and higher pain catastrophizing scores after negative sad-mood induction. Pain catastrophizing is defined as a set of negative emotional and cognitive processes during the experience of pain, which characterizes pain as awful, horrible and unbearable. In the study of Willoughby et al. (2002), it was assessed by administering the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995). Furthermore, it was shown that viewing depressive statements reduces cold-pressor tolerance while viewing elation statements enhances pain tolerance (Zelman, 1991).

In our previous studies with depressed patients, we could observe that patients with major depressive disorder showed hypoalgesia for thermal or electrical pain on the skin (Bär et al., 2005). By means of fMRI, we tested the neurofunctional underpinnings of this type of hypoalgesia for thermal pain and observed a relative hyperactivation in a fronto-thalamic brain network (Bär et al., 2007).@@

To further elucidate the influence of emotional states upon pain processing, we investigated the neurofunctional correlates of the interaction between sad affect and thermal pain in healthy subjects.

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We investigated at first pain thresholds after sad-mood induction and under neutral control condition in healthy controls outside the MR scanner (*Experiment 1*). Thereafter, we investigated brain activations by means of fMRI before and after sad-mood induction (*Experiment 2*). Based on our previous findings in depressive patients during pain processing and fMRI (Bär et al., 2007), we predicted that sad affect will have an influence on heat pain with regards to BOLD signal in prefrontal and thalamic structures.

Otherwise, we hypothesized that brain areas which are considered to play a pivotal role in the affective dimension of pain (Rainville, Duncan, Price, Carrier, & Bushnell, 1997), such as the anterior cingulate cortex or insular cortex (IC), would additionally show an altered activation pattern.

2. Methods

2.1. Subjects and experimental design

Forty healthy female subjects between 19 and 37 years of age ($M = 25.4$, $S.D. = 7.3$) participated in this study. All subjects were right-handed, according to the modified version of Edinburgh Handedness Inventory (Oldfield, 1971) and had no history of a psychiatric or neurological illness. They were recruited from the local community and provided an informed consent that was approved by the Ethics Committee of the Medical Faculty of the Friedrich Schiller University.

Two weeks before *Experiment 2* (fMRI investigation), all subjects were randomly assigned to one of the two groups (sad or neutral-mood induction) and their pain thresholds were assessed before and after mood induction to test the effect of sad mood on pain threshold.

Afterwards, subjects who experienced a decrease in mood valence (as assessed using the Self-Assessment Manikin (SAM), an affective rating system devised by Lang, 1980) were included in the fMRI sad-mood group as well as the rest of the subjects with neutral-mood induction condition in the control group. Thus, 16 female subjects matched for age were assigned to both groups, respectively. Two subjects in the group with sad-mood induction were excluded from the final fMRI analysis due to excessive movement and image artefacts.

2.2. Mood induction procedure for Experiments 1 and 2

To induce sad and neutral emotional states, the modified Velten Mood Induction Procedure (MIP) was used. The Velten MIP is amongst the most widely used techniques for studying affective influences upon cognition and behaviour (Velten, 1968), and it has demonstrated effectiveness in altering subjective emotional states (Frost & Green, 1982). During the MIP, participants were exposed to a series of 21 self-referent sad-mood statements, which were presented two times and subjects had to read the statements aloud. While reading the statements, participants were asked to attempt to experience the mood suggested by the statements (e.g. "Life is a heavy burden."). Additionally, to facilitate the mood induction procedure, participants were presented individually tailored music during MIP (Sutherland, Newman, & Rachman, 1982). To increase the impact of sad MIP, subjects were asked to bring a piece of music before the experiment, which they thought would put them into a sad mood (Westermann, Spies, Stahl, & Hesse, 1996).

In contrast, for the neutral procedure, participants were exposed to a series of 21 neutral statements (e.g. "An orange is a citrus fruit."), which was similarly presented as the sad statements. Mozart's *Piano concerto No. 21 in C Major* was chosen for all subjects as neutral music. The whole mood-induction procedure lasted approximately 12 min.

To assess affective changes during the experiment, participants were asked to rate the amount of MIP on the dimensions of valence and arousal using the SAM, an affective rating system devised by Lang (1980). In this system, ratings of valence are indicated by five graphical representations of facial expressions ranging from a severe frown (most sad = -4) to a broad smile (most positive = +4). For arousal, the manikin varies from a state of low to high agitation (9 represents a high rating and 1 represents a low rating).

For *Experiments 1* and *2*, the SAM ratings were filled out before and immediately after negative and neutral MIP.

2.3. Procedures for the assessment of the individual pain threshold (*Experiment 1*)

Thermal pain thresholds (TPT) were determined by an ascending method of limits, using a 9 cm² contact thermode (TSA-2001; Medoc, Israel) with a temperature increase of 0.5 °C/s (baseline temperature: 32.0 °C; maximal temperature: 53.0 °C). This has been previously described in our studies (Bär, Greiner, Letsch, Kobele, & Sauer, 2003). The thermode was attached to the left as well as right volar wrist. To determine thermal pain thresholds, subjects were asked to read and follow the written instruction: "When thermal perception becomes painful, press the stop button immediately." After three learning trials, five tests were performed and averaged.

2.4. Statistical analysis (*Experiment 1*)

For statistical analyses, SPSS for Windows (version 14.0) was used. A univariate analysis of variance (ANOVA) with a between-subjects factor group (sad and neutral-mood group) and within-subjects factor treatment (before and after mood induction) was used to uncover differences of dimension of valence with additional within-subjects factor side for heat pain threshold. Since groups were matched for age and sex, no covariates were used.

2.5. Procedures for the delivery of noxious thermal stimuli during fMRI scanning (*Experiment 2*)

A Peltier-type thermal stimulator (TSA-2001; Medoc, Israel) was used to deliver thermal pain stimuli at 37–45 °C during the pain experiments. The fMRI-compatible nonferrous thermode (3 cm × 3 cm surface) was fixed on the subject's volar surface of the left forearm with a Velcro belt. We stimulated the left instead of the right forearm due to the results of the effect of mood-induction procedure on pain threshold, which we tested outside the scanner in *Experiment 1*.

The thermode was equipped with a 12 m cable and was controlled with commercial software (COVAS; Medoc) on a personal computer from outside the scanner room (Davis, Kwan, Crawley, & Mikulis, 1998; Kwan, Crawley, Mikulis, & Davis, 2000; Peyron et al., 1999).

The experimental procedure was carried out in a block design with parametric variation of the thermode temperature in two runs. In the first run, all subjects were stimulated without mood induction. Subsequently, all subjects underwent the mood-induction procedure with sad or neutral stimuli and were scanned for the second time immediately (a few seconds after the end of MIP and SAM rating) afterwards.

All stimuli were initiated from a baseline resting temperature of 32 °C (OFF condition). The three ON conditions included 37, 42, and 45 °C with a fixed presentation order. Each ON condition consisted of eight blocks with a thermal stimulation length of 10 s and additionally approximately 3 s for ramp up and down. At the beginning of the ON phase, the thermode temperature was increased from 32 °C to the experimentally predefined pain level at a ramp rate of 10 °C/s and at the end of the ON phase it was decreased to 32 °C at the same rate. We limited the duration of the ON phase to 10 s to reduce head motion-related artifacts and to limit potential individual adaptation. The inter-stimulus interval was approximately 10.5 s. The total duration of the scanning procedure was about 10 min for each run. During the scanning procedure, subjects were asked to relax, keep their eyes closed and concentrate on the sensation of the left arm.

2.6. Image acquisition

Functional data were collected on a 1.5 T Siemens Magnetom Vision whole body system (Siemens, Erlangen, Germany) equipped with a head volume coil. Foam pads and a firm chin strap were used for positioning and immobilization of the subject's head within the headcoil.

T₂-weighted images were obtained using a gradient-echo EPI sequence (TR = 2700 ms, TE = 60 ms, flip angle = 90°) containing 24 contiguous transversal slices of 5 mm thickness covering the entire brain. Matrix size was 64 × 64 pixels with in-plane resolution of 3.44 mm × 3.44 mm and a field view of 220 mm. A series of 2 × 228 whole-brain volumes were acquired in two runs, with the first three images being discarded in order to obtain steady state tissue magnetization.

High-resolution anatomical T₁-weighted volume scans were obtained in sagittal orientation (TR = 15 ms, TE = 5 ms, flip angle = 30°, FOV = 256 mm, matrix = 256 × 256, number of sagittal slices = 192) with a slice thickness of 1 mm and in-plane resolution of 1 mm × 1 mm.

2.7. Image processing and statistical analysis

For image processing and statistical analyses, we used the SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm>). The 450 EPI scans were corrected for differences in time acquisition by sinc interpolation, realigned at the first image and normalized to the Montreal Neurological Institute (MNI, Montreal, Canada) reference brain. The data were smoothed with a Gaussian kernel (10 mm, full-width at half-maximum) and subsequently analyzed voxel-wise within the GLM to calculate statistical parametric maps of *t*-statistics for condition-specific effects. Prior to this analysis, the data were high-pass filtered with a cutoff period of 128 s and corrected for serial correlations choosing the AR (1) model.

Additionally, to control for the potential confound of the subjects' movement during thermal stimulation, individual movement parameters were entered as covariates into the design matrix as estimated during the realignment step.

A fixed effect model at a single-subject level was performed to create images of parameter estimates, which were then entered into a second-level analysis.

During the second-level RFX analysis, a two-way ANOVA design matrix within SPM5 was set up with the within-subjects factor treatment (before and after MIP) and the between-subjects factor group (sad and neutral condition). To reveal brain areas associated with sad mood and thermal pain, individual contrast images for the 45° condition were entered into the two-way ANOVA.

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