Induction of Depressed Mood Disrupts Emotion Regulation Neurocircuitry and Enhances Pain Unpleasantness

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Background: Depressed mood alters the pain experience. Yet, despite its clear clinical relevance, little is known about the cognitive and neural mechanisms underlying this phenomenon. We tested an experimental manipulation to unravel the interaction between depressed mood and pain. We hypothesized that dysregulation of the neural circuitry underlying emotion regulation is the mechanism whereby pain processing is affected during depressed mood.

Methods: Using functional magnetic resonance imaging, we compared the effects of sad and neutral cognitive mood inductions on affective pain ratings, pain-specific cognitions, and central pain processing of a tonic noxious heat stimulus in 20 healthy volunteers.

Results: The increase in negative pain-specific cognitions during depressed mood predicted the perceived increase in pain unpleasantness. Following depressed mood induction, brain responses to noxious thermal stimuli were characterized by increased activity in a broad network including prefrontal areas, subgenual anterior cingulate cortex, and hippocampus, as well as significantly less deactivation when compared with pain responses in a neutral mood. The participants who reported the largest increase in pain unpleasantness after the sad mood induction showed greater inferior frontal gyrus and amygdala activation, linking changes in emotion regulation mechanisms with enhancement of pain affect.

Conclusions: Our results inform how depressed mood and chronic pain co-occur clinically and may serve to develop and translate effective interventions using pharmacological or psychological treatment.

Key Words: Cognitions, depressed mood, emotion regulation, fMRI, pain

Pain and depression have been reciprocally linked in many experimental and clinical studies. Chronic pain is more likely in individuals with a history of depression (1) and depression exacerbates the burden of painful diseases (2). Pain lends itself well to experimental investigation. Thus, depressed patients (without chronic pain) have altered prefrontal activity compared with healthy control subjects during brief noxious stimulation (3,4). Moreover, in patients with chronic pain, symptoms of depression correlate with amygdalar and anterior insular activity during experimental pain (5) and medial prefrontal cortex activation during disease-relevant experimentally induced pain (6). These recent studies support a general hypothesis of dysfunctional emotion regulation during pain perception. However, these patients exhibit significant comorbidity and enduring structural or functional changes that may confound experimental studies (7,8). For better controlled experiments, negative cognitive mood induction procedures allow us directly to manipulate mood. Although acute, these mood modulations have been used frequently in psychology (e.g., [9]) to investigate cognitive processes relevant to chronic mood states (10). While negative mood inductions can worsen affective pain ratings (11–14), the mechanisms underlying such modulation of pain perception are not yet established.

It is has been suggested that maladaptive thought processes may mediate changes in pain perception in the context of depressed mood (15). Specifically, catastrophizing thoughts (i.e., negative pain-related cognitions) are amplified in depressed individuals (16) and depressed patients exhibit deficient emotion regulation when exposed to negatively valenced stimuli (4,17,18); hence, we hypothesized that central pain processing during depressed versus neutral mood would be characterized by altered activity in the dorsolateral and/or ventrolateral prefrontal cortex (dlPFC, vlPFC) and increased amygdala activation, reflecting ineffective emotion regulation. Finally, we predicted that the level of activity in these regions during painful stimulation in the sad condition would influence individual differences in pain unpleasantness scores.

Accordingly, we used a well-established negative or sad mood induction procedure and a matching neutral procedure for experimental comparison (19). Healthy volunteers received a tonic painful stimulus after undergoing each mood induction inside the functional magnetic resonance imaging (fMRI) scanner. This allowed an experimental test of hypotheses based on cognitive theories of pain-mood interactions. Noxious stimuli, rated for pain unpleasantness, and mood reinforcers were given (Figure 1). We hypothesized that the effects of an induced depressed mood compared with a neutral mood would be: 1) an increase in negative pain-related thoughts (i.e., catastrophizing [20]), 2) an increase in the perceived unpleasantness of the pain, and 3) neural evidence of disruption of normal emotion regulation.

Methods and Materials

Participants

Twenty-seven pain-free, nondepressed, right-handed volunteers were recruited. Invitations were sent to university students asking for healthy volunteers who were not suffering from any

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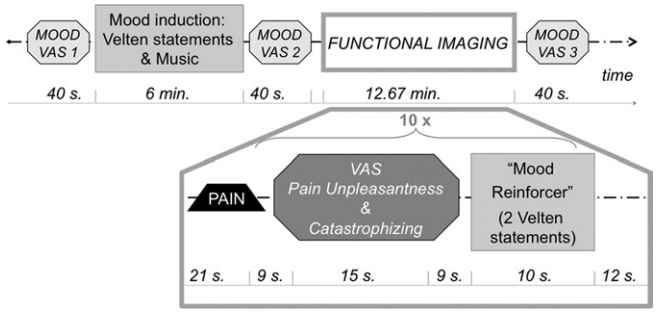

Figure 1. Design and timing of the experimental runs. In each run, participants started by rating their current mood on visual analogue scales (mood VAS: "At this moment I feel sad/happy" rated from not at all [0] to extremely [10]). The two separate scales were integrated into a composite depressed mood score for analysis. Participants then underwent a mood induction procedure by Velten statements accompanied by mood-congruent music after which they re-rated their mood. A third mood rating followed the functional imaging. During functional imaging, participants received 10 repeats of the following sequence. The 21-second heat-pain was followed by a VAS for pain unpleasantness (not at all [0] to intensely unpleasant [10]) and a VAS for in vivo catastrophizing thoughts (e.g., "I worry about when the pain will end" anchors: not at all [0] to all the time [10]). Then, two mood-congruent Velten statements were presented that served as mood reinforcers, and finally, the sequence was concluded by a 12-second long rest. Each participant underwent two runs, the order of presentation of mood inductions being counterbalanced across participants. VAS, visual analogue scale.

pain condition, psychiatric disorder, or taking daily painkillers or antidepressants. The study received local Research Ethics Committee approval (number C02.283) and conformed to the guidelines of the 1996 Declaration of Helsinki. The analysis was conducted on a group of 20 volunteers (mean age: 28, range 19–41; 11 male/9 female; Beck Depression Inventory-II [BDI-II] mean: 5.74 ± SD 5.48) as postscanning exclusion criteria were met by 7 participants (Supplement 1). To exclude those with a current depressive episode, participants completed the BDI-II (21) and a short interview based on DSM-IV criteria (22) if the BDI-II score was above 12. No participant needed exclusion on this basis. Negative affectivity was measured before the scanning procedure with the short form of the neuroticism scale of the Eysenck Personality Questionnaire, which is highly associated with anxiety (23).

Experimental Design

All participants underwent both a negative and a neutral mood induction in the scanner, each followed by a scanning session (Figure 1) (within-subjects design, runs presented in counterbalanced order across participants, with participants attributed to groups in a pseudorandomized way, 11 participants receiving the order neutral-sad and 9 sad-neutral; this slight imbalance was due to postscanning exclusion criteria).

The mood induction procedure consisted of reading Velten-type statements (24) while listening to mood-congruent music via headphones (19). Velten-type neutral and sad statements, matched for number of words (e.g., "Cherries are fruits" vs. "I feel worthless") were adapted from previous studies (24,25). The mood induction used 49 different statements presented each for 8 seconds, in white writing on a black background, in a set order. While presenting the sad mood induction statements, sad music (Prokofiev's "Russia Under the Mongolian Yoke") was played at half speed (25,26). The largo movement from Dvorak's "Symphony from the New World" was played with the neutral mood induction statements (27). Participants were not told which type of mood they should be experiencing (28). As the effects of mood inductions are of short duration (19), a "mood reinforcer" was presented between each painful stimulus. Two mood-congruent Velten-type statements presented for a total of 10 seconds without music (the first one a repeat from the mood induction, the second one a new statement) served as mood reinforcers. This was followed by a 12-second rest period (Figure 1).

Participants were deemed to have experienced a sad mood induction if they achieved a greater than 40% increase in depressed mood scores and a concomitant less than 20% change (negative or positive) in the neutral mood manipulation (details regarding the mood ratings can be found in Supplement 1). To ensure a robust mood manipulation, these criteria were more conservative than some of those described previously (see Clark [19] for a review).

Pain Procedure

Two series of 10 tonic heat stimuli (21 sec each) were applied on a patch of skin of the left forearm, pretreated with capsaicin .075% (Axsain, Zeneus Pharma, United Kingdom). The painful stimulus was calibrated to an intensity rating of 6.5 (on a numerical rating scale of 0–10 with 0 = no pain, 1 = just painful, to 10 = extremely painful) at baseline, before the first run. The same temperature was applied in both runs. Pain unpleasantness ratings plus catastrophizing ratings were recorded as shown in Figure 1. The difference between what was meant by pain intensity (sensory-discriminative rating) and pain unpleasantness (affective rating) was explained as in previous studies (29) (further details regarding the pain stimuli and pain scoring during the runs can be found in Supplement 1).

fMRI Image Acquisition

Functional images were acquired using a 3 Tesla Siemens/Varian Inova magnetic resonance system (Varian, Inc., Palo Alto, California). The collection parameters are detailed in Supplement 1.

Data Analysis

Behavioral Data. A depressed mood composite score was created, consisting of a mean of the ratings on the sad and (inverted) happy visual analogue scale {[(10 − happy) + sad]/2}. This score was computed for each participant at three time points in both mood conditions. Repeated-measures analyses of variance (ANOVAs) were conducted on the depressed mood scores, with the within-subjects factors of time (at three time points since the mood induction: t0, t + 6, t + 20) and mood (sad/neutral mood induction) as between-subjects factors (Figure 2A). Post hoc *t* tests assessed the significance levels of the changes over time in each mood separately. The difference of the depressed mood scores between the two runs (ratings in sad mood − ratings in neutral mood) was calculated at *t* + 6 (immediately after the mood induction). To exclude an effect of group (order of mood inductions neutral-sad vs. sad-neutral) on the mood ratings at t + 6, an ANOVA was conducted on these measures, with mood as within-subjects factor and group as between-subjects factor.

Individual means and standard deviations of pain unpleasantness and in vivo catastrophizing ratings were calculated for each condition. Separate ANOVAs were conducted on each measure, with mood as within-subjects factor and group as between-subjects factor. One participant was excluded from the analysis of the catastrophizing data, as he was an outlier in the difference of his ratings between moods (>2 SD). Then, post hoc compar-