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

Chantal Berna, Siri Leknes, Emily A. Holmes, Robert R. Edwards, Guy M. Goodwin, and Irene Tracey

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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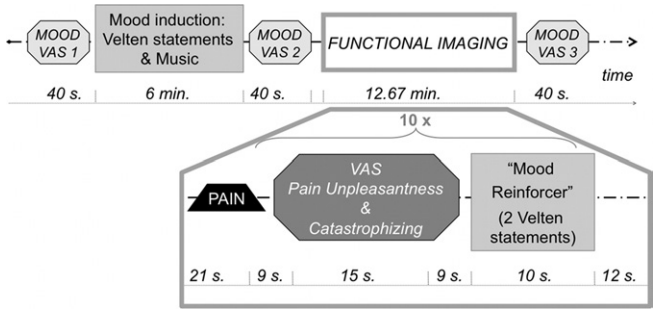

Figure 1. Design and timing of the experimental runs. In each run, participants started by rating their current mood on visual analogue scales (mood VAS: "At this moment I feel sad/happy" rated from not at all [0] to extremely [10]). The two separate scales were integrated into a composite depressed 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-

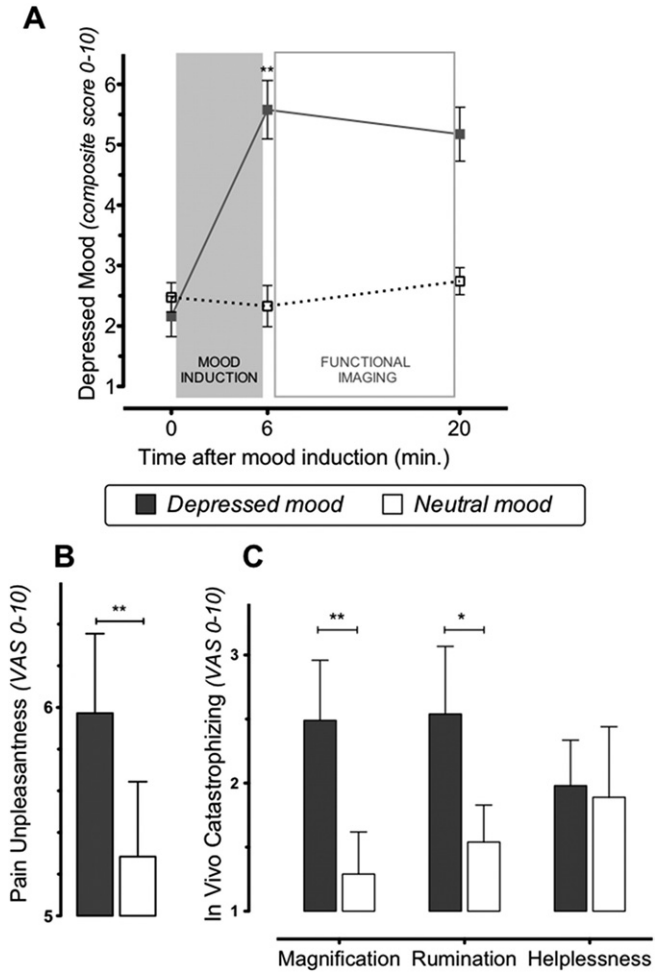

Figure 2. Psychophysical results. **(A)** Mean ratings of depressed mood before and after the mood inductions, as well as at the end of the experiment. Composite score: 0 = not sad at all and extremely happy; 10 = extremely sad and not happy at all. **(B)** Mean pain unpleasantness ratings in both mood conditions on a VAS ranging from not unpleasant at all (0) to intensely unpleasant (10). **(C)** Average frequency of in vivo catastrophizing in both mood conditions for each of the three subscales on a VAS: not at all (0) to all the time (10). Error bars indicate SEM, *$p < .05$, **$p < .01$). VAS, visual analogue scale.

isons of the subscales of the in vivo catastrophizing ratings between the two mood conditions were performed using paired two-tailed *t* tests.

Stepwise linear regressions were conducted to test the explanatory power of the model, namely that the difference in mood would predict the difference in catastrophizing and subsequently the difference in pain unpleasantness between the two runs.

A median split was performed on participants according to the difference in their pain unpleasantness ratings between the two runs. These groups' baseline measures were compared with independent sample *t* tests and a chi-square test for gender.

Imaging Data. Imaging data were analyzed in a multistage process using FEAT (fMRI Expert Analysis Tool; FMRIB, Oxford, United Kingdom, http://www.fmrib.ox.ac.uk/fsl). Preprocessing was conducted along standard procedures in FEAT (Supplement 1). At the first level, statistical analysis was carried out using a general linear model approach. For each participant, the regressors of interest were the painful stimuli and the mood reinforcers. The rating periods were excluded as regressors of no interest. The baseline consisted of two 9-second and one 12-second rest periods (Figure 1). Contrast images were calculated for the painful stimuli (vs. baseline) and the mood reinforcers (vs. baseline) separately for the depressed and neutral mood conditions. These contrast images were then used for mixed-effects group analyses (30), calculating statistically significant increases or decreases in blood oxygenation level-dependent (BOLD) signal in response to the stimuli for both mood conditions, in addition to paired *t* tests comparing the mood conditions (depressed/neutral). Additionally, the functional contrast (deactivation during pain in the neutral mood > baseline) was used as a mask to restrict a paired *t* test (pain depressed > neutral) to the areas significantly deactivated in the neutral mood. The *Z* statistic images from the group analysis were thresholded at $Z > 2.3$, with a cluster threshold of $p < .05$. This cluster-based significance thresholding procedure includes a multiple-comparisons correction.

Furthermore, the median percentage of signal changes in prefrontal regions of interest (ROIs) relevant to emotion regulation was extracted, using a small spherical mask (6.36-mm radius) centered on the peak voxel from the group functional activation map of the paired *t* test (pain in the depressed > neutral mood): left dlPFC (Montreal Neurological Institute x, y, z coordinates in mm: −24, 22, 44), orbitofrontal cortex (OFC) (−45, 40, −14), and vlPFC, more specifically the inferior frontal gyrus (IFG) (−56, 14, 6). The median signal changes from these prefrontal ROIs (left dlPFC, OFC, IFG) during the depressed mood run were then used in a linear regression on the dependent variable "difference in pain unpleasantness between the two moods". Additionally, an ROI analysis was performed for the amygdala. Since this structure did not show an increased activation in our main functional contrasts, the peak voxel reported by Strigo *et al.* (4) lying within the 80% probability map from the Harvard-Oxford subcortical structural atlas (25, −2, −20) was used to draw a small spherical mask, allowing to extract the median percentage of signal change from the right amygdala. This peak coordinate was inverted for the left amygdala (−25, −2, −20).

Results

Behavioral Results

Twenty participants completed both pain-testing sessions in the fMRI scanner and achieved the targeted mood effects after the cognitive mood inductions. One participant failed to report mood ratings at the end of the neutral run. There were no significant differences on the BDI-II or the neuroticism scores between the groups undergoing the mood induction in either order (all $t < 1$, $p > .50$).

The depressed mood ratings were significantly affected by the type of mood induction ($F = 20.75$, $df = 1.18$, $p < .001$), by time relative to the mood induction ($F = 21.31$, $df = 2.36$, $p < .001$), and by the interaction of these two parameters ($F = 20.51$, $df = 2.36$, $p < .001$). The negative mood score increased after the sad mood induction relative to the neutral induction and stayed elevated to the end of the experimental window (differences in the sad mood run: between t0 and t + 6: $t = 7.08$, $df = 19$, $p < .001$; between t + 6 and t + 20: $t < 1$, ns) (Figure 2A). Mood ratings at time t + 6 were affected only by the type of mood induction ($F = 31.84$, $df = 1.18$, $p < .001$) but not by the order of presentation or by an interaction ($F < 1$, $df = 1.18$). Similarly,

mood ratings at t + 20 were only affected by the type of mood induction ($F = 15.16$, $df = 1.17$, $p = .001$; order of presentation: $F = 1.62$, $df = 1.17$, $p = .22$; interaction $F < 1$, $p > .5$).

The painful stimuli, which were calibrated for a pain intensity of 6.5 out of 10 (Supplement 1), were rated as significantly more unpleasant in the depressed (M = 5.97, SD = 1.71) than neutral mood condition (M = 5.28, SD = 1.61, $F = 7.7$, $df = 1.18$, $p = .01$) (Figure 2B), with no effect of the order of presentation of the mood inductions or interaction ($F < 1$ $df = 1.18$). Overall, participants reported more catastrophizing thoughts in the depressed mood than in the neutral one (depressed: M = 2.30, SD = 1.92 vs. neutral: M = 1.66, SD = 1.42, $F = 9.76$, $df = 1.17$, $p = .006$), with no effect of order of mood induction procedures or interaction ($F < 1$ $df = 1.17$). The mood effect on catastrophizing was significant on the magnification ($t = 3.34$, $df = 18$, $p = .004$) and rumination ($t = 2.36$, $df = 18$, $p = .03$) subscales but not on the helplessness subscale ($t < 1$, $df = 18$) (Figure 2C).

Stepwise linear regression showed that the model: depressed mood → increase in catastrophizing → increase in pain unpleasantness, explained 34% of the variability in the difference of pain unpleasantness ratings ($F = 4.11$, $df = 2.18$, $p = .04$).

Imaging Data: Whole-Brain Analysis

Significant activation during pain (compared with rest) was observed in a broad network of cerebral regions (Figure 3, red), including bilateral thalamus, insula, prefrontal cortex and contralateral somatosensory areas during both depressed and neutral conditions. In striking contrast, the pattern of simultaneous deactivations revealed a marked and obvious qualitative difference between depressed and neutral conditions. In the depressed mood condition, there was no significant deactivation at all. In the neutral condition, a network including the bilateral precuneus, bilateral S1, and medial temporal lobe was deactivated (Figure 3, blue). A paired t test confirmed a statistical difference in deactivation patterns (Figure S1 and Table S2 in Supplement 1).

Quantitative increases in BOLD signal in response to pain and mood reinforcers in the depressed compared with neutral conditions were investigated using a mixed effects paired t test group contrast. For pain, this revealed increased activation in the subgenual anterior cingulate cortex (sACC), the left IFG, the left OFC, the left dlPFC, the left posterior insula, the left hippocampus, the left thalamus, the left middle temporal gyrus, the left precuneus, and the left caudate, as well as the

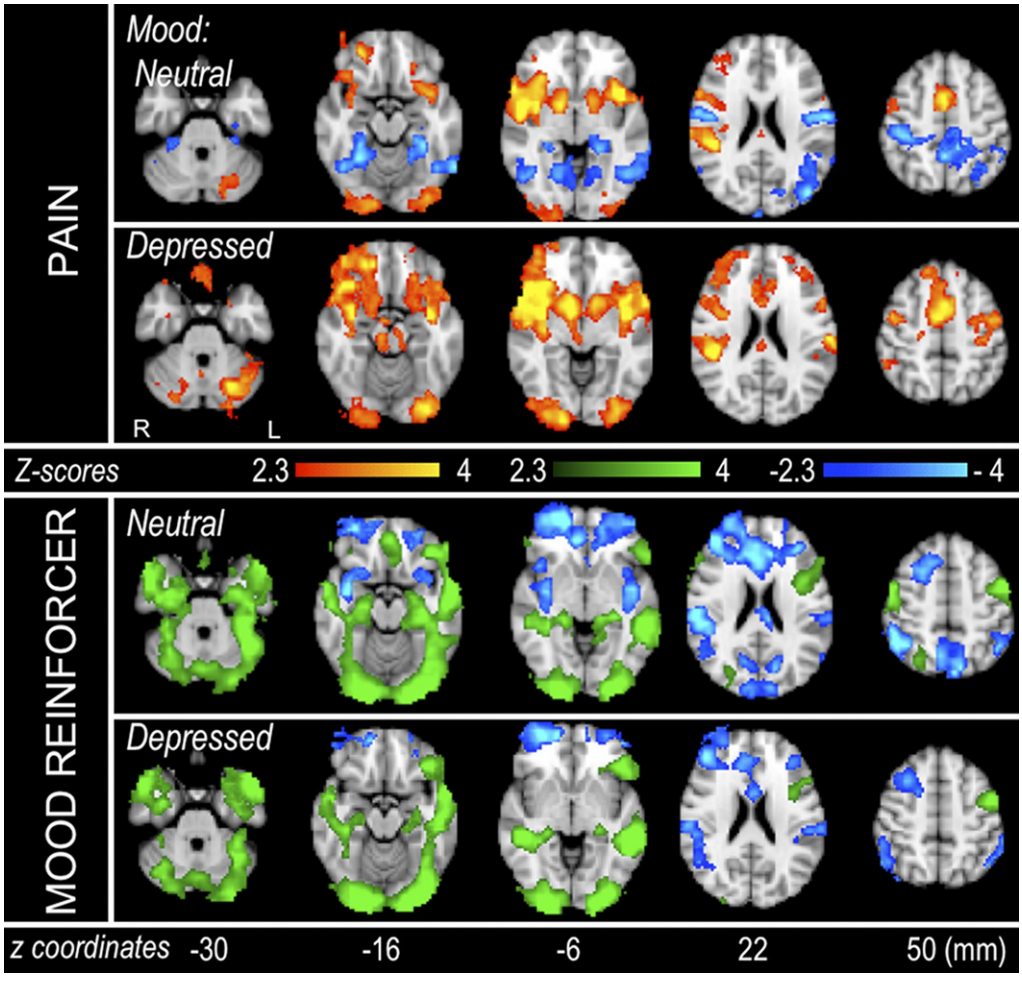

Figure 3. Significant activations and deactivations during pain (red-blue, top) and the mood reinforcers (green-blue, bottom), each separately compared with rest. Note the lack of significant deactivations in the pain contrast in the depressed mood. Group fMRI data of 20 participants, plotted on the average MNI 152 brain. The *Z* coordinates shown below are on the MNI system in millimeters. The scales for *Z* test scores are shown in the middle. fMRI, functional magnetic resonance imaging; MNI, Montreal Neurological Institute.

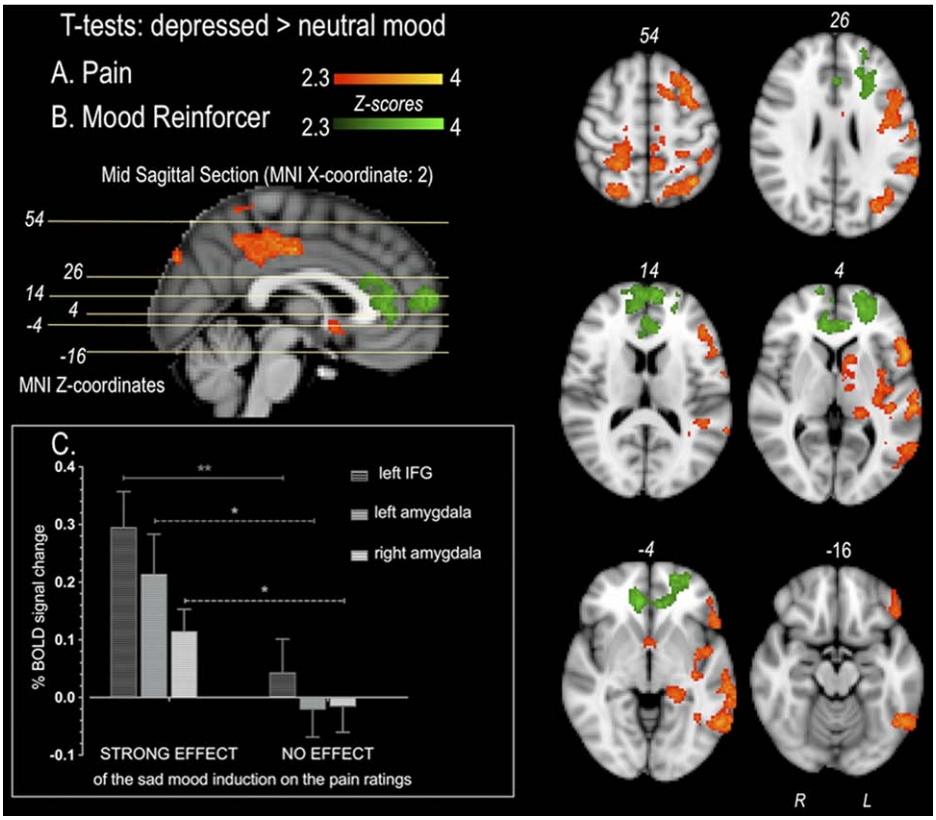

Figure 4. Paired *t* tests between (depressed > neutral) run for pain **(A**, red**)** and the mood reinforcers **(B**, green**)** are shown on the left. Below, the analysis of the ROIs during pain in the depressed mood is presented **(C)**. The % BOLD signal activity change in the left inferior frontal gyrus and both amygdalae during pain in the depressed mood are plotted, showing differences between the strong versus no pain unpleasantness modulation group. Error bars indicate SEM, $*p < .05$, $**p < .01$. BOLD, blood-oxygenation level dependent; IFG, inferior frontal gyrus; L, left hemisphere; MNI, Montreal Neurological Institute; R, right hemisphere; ROI, region of interest.

bilateral supramarginal gyri (Figure 4A; Table S3 in Supplement 1).

For the mood reinforcer condition, brain activity for depressed mood compared with neutral was increased in the rostral anterior cingulate cortex (ACC) and perigenual ACC, as well as the ventromedial prefrontal cortex and the OFC (Figure 4B; Table S4 in Supplement 1). These areas are consistent with previously reported neural correlates of perceiving sad stimuli (31). The fact that there was no other activation suggests that the Velten statements were well matched between the two mood inductions/reinforcers.

The opposite *t* test (neutral > depressed) provided no significant results for the pain contrast and a unique confluent activation in the left inferior temporal gyrus for the mood reinforcer contrast (Figure S2 and Table S5 in Supplement 1).

Imaging Data: Exploring Neural Activity Changes That Explain Behavioral Variance

A linear regression revealed that the magnitude of the difference in pain unpleasantness ratings between the sad and the neutral mood correlated with the left dlPFC ($ß = -.65$, $p = .002$) and at trend level with the left IFG activity ($ß = .44$, $p = .06$) but not with the left OFC activity ($ß = .23$, $p = .32$) (Figure S3 in Supplement 1). The activity in these prefrontal areas explained 58% of the variability in the difference between reported pain unpleasantness in depressed versus neutral mood (Figure 5). When adding the difference in catastrophizing and mood ratings to this model, 69% of the variance in the pain ratings could be explained.

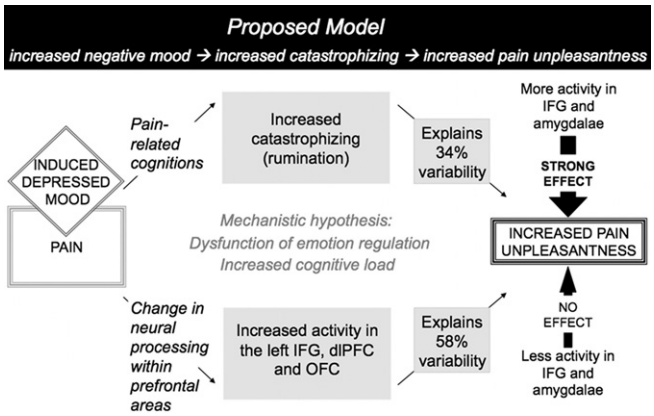

Figure 5. Synopsis of findings and proposed model. At a cognitive level, pain experienced in an induced depressed mood leads to more negative pain-related thoughts (catastrophizing). The concurrent prefrontal neural correlates are represented below. The contribution to explaining the difference in affective pain ratings of these elements is reported to the right. Finally, in terms of outcome, the differences in the emotion regulation areas between the participants showing a strong versus no pain modulation by the mood manipulation are shown. dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; OFC, orbitofrontal cortex.

To explore these associations further, a median split divided participants according to the strength of the modulation of pain unpleasantness by the mood manipulation (strong modulation: M = 1.52, SD = .75; weak or no modulation: M = −.17, SD = .42, called no modulation group). The strong and no pain modulation groups did not differ significantly on any baseline measure or pain intensity ratings during the calibration of the stimulus (Table S1 in Supplement 1). The pain unpleasantness ratings did not differ between these two groups during the neutral mood, but the group showing strong modulation reported more pain unpleasantness in the depressed mood compared with the no modulation group (Table S1 in Supplement 1). Those participants who showed the strong effect had higher activation in the left IFG ($p = .009$) and both amygdalae (left $p = .01$, right $p = .04$) during pain in the depressed mood than those participants with no modulation (Figure 4C; Table S1 in Supplement 1).

Finally, activity in the left IFG correlated significantly with activity in the left amygdala during pain in the depressed mood only (depressed mood: $r = .54$, $p = .014$; neutral mood: $r = .30$, $p = .21$, difference between the two correlation strengths ns).

Discussion

A sad cognitive mood induction had the predicted effects on reported depressed mood, increased the frequency of negative thoughts about the tonic pain stimulus, and increased its subjective unpleasantness. A stepwise linear regression analysis supported the hypothesis that depressed mood increases pain-related thoughts (catastrophizing), so increasing the unpleasantness of the painful experience, implying if not proving directionality. Compared with neutral mood, depressed mood increased the BOLD fMRI signal to pain in nociceptive afferent areas and in cortico-subcortical structures involved in emotional processing and regulation and also reduced deactivations (otherwise found in neutral mood). Participants experiencing the highest effect on pain unpleasantness had higher activation in the left IFG and both amygdalae in response to noxious stimuli during depressed mood.

Mood Induction, Pain Affect, and Cognitions

Pain was rated as more unpleasant after the sad mood induction, when compared with the neutral mood induction. This supports our hypothesis that depressed mood increases pain and is consistent with earlier findings (11,13,14) (Figure 2B). Furthermore, depressed mood was associated with increases in negative pain-related cognitions (catastrophizing), suggesting a mechanism for this effect (Figure 5). The proposed model explained 34% of the variability in the difference in affective pain ratings. While this might seem modest, only a few behavioral measures were collected. In this respect, our findings were of similar magnitude to those reported previously (32). Furthermore, when including measures of prefrontal activity in the regression analysis, 69% of the variability in affective pain ratings could be explained. The model we propose is consistent with a clinical model of pain in which negative affectivity exacerbates a vicious cycle of negative pain-related cognitions and distress and drives subsequent increases in the perception and impact of pain (33). The mood manipulation specifically affected the worry-related subscales of the in vivo catastrophizing scale (magnification and rumination) (Figure 2C). This is interesting given the emphasis on rumination as a driving process in depression (34) and recent cognitive models of chronic pain, which have also highlighted worry as an important maintaining factor (35).

Neuroimaging Findings

Increased Activation during Pain in Depressed Mood. The areas that showed increased activity during tonic pain in the depressed mood included the left insula, thalamus, hippocampus, IFG, dlPFC, OFC, and the sACC (Figure 4A). The thalamus and the insular cortex are part of the afferent nociceptive network (36). The sACC is commonly activated during negative mood (31) and appears to be a key area for depression (37). Increased activity in the sACC has only rarely been reported in fMRI studies of pain (e.g., [38]). It has been suggested that this region responds selectively to negative emotional processing of personally relevant material; acute exogenous experimental stimuli may not meet this criterion (39). This argument is also supported by the depression-related increase in activity in the hippocampal formation. This region is known to be involved in anxiety-induced hyperalgesia (40) and nocebo-induced hyperalgesia (41). Furthermore, the hippocampus is connected with the sACC (42), and these structures have been proposed to be part of a dysfunctional limbic-frontal circuitry in major depression (43).

Activations in Areas Relevant to Emotion Regulation. Given recent findings in depressed patients (4), we hypothesized that depressed mood would impair emotion regulation of pain affect. When presented with an aversive stimulus, different types of automatic or voluntary cognitive processes can help the individual to cope emotionally. The prefrontal cortex is highly involved in these emotion regulation processes (44). Effortful modulation is thought to be predominantly underpinned by lateral structures (vlPFC, dlPFC), while automatic emotion regulation appears to be mostly mediated by medial structures; however, some structures, such as the dorsal ACC and the OFC, are shared by the two systems (45).

We found that both the activity in the dlPFC and IFG during the negative mood was correlated with measured differences in affective pain ratings between the two mood conditions but in opposite ways (Figure S3 in Supplement 1). Increased activity in the left dlPFC predicted a smaller difference in pain unpleasantness between the two moods, consistent with activation related to successful downregulation of pain unpleasantness. However, the left IFG activity was positively correlated with the difference in pain unpleasantness ratings. The IFG peak coordinate in this study is located posterior to the vlPFC region previously implicated in the downregulation of pain due to perceived control over the stimulus (46,47). In fact, our peak activation closely corresponds to the area within the vlPFC, which has been identified in studies of cognitive reappraisal of sad emotion and alternatively named IFG or vlPFC (17,48–51). Wager *et al.* (49) have suggested that two separate paths originate from this functional area: the first one, linked to the nucleus accumbens, is involved in generating positive reappraisal, while the second one, connected to the amygdala, is thought to generate or enhance negative appraisals.

Supporting this notion, activity in the amygdala and the IFG was significantly correlated during pain in the depressed mood. Furthermore, results from the median split analysis showed that the participants with the greatest increase in pain unpleasantness during depressed mood also showed significantly higher amygdala activation during this condition (Figure 4C). This suggests that the IFG, a structure that could exert positive reappraisal, instead underpinned either ineffective or detrimental emotion regulation during depressed mood. This notion is supported by the Wager *et al.* (49) findings and by a recent study of emotional and attentional pain modulation, which similarly identified the

IFG as a modulator in the emotional process (52). The latter study also provided strong evidence against the notion that a mood modulation was merely a hidden attentional manipulation.

Our fMRI results show that in a depressed mood, volunteers increased activity in areas involved in emotional appraisal. Furthermore, despite the left-sided pain stimulation used in this study, a majority of the emotion regulation circuitry recruited seemed lateralized to the left hemisphere (Figure 4A). Nevertheless, this potential lateralization was not tested formally, as lateralization of emotional processing was not the focus of this study and investigating this debated topic would require a more specific design (53).

Depressed Mood Affects Deactivations During Pain. No significant task-induced deactivations (54–56) were observed during pain in the depressed mood condition (Figure 3). Areas that were more deactivated in the neutral than the depressed mood (Figure S1 in Supplement 1) included the left angular gyrus and the bilateral precuneus and posterior cingulate. This lack of deactivation could be linked to changes in the default mode network during the negative mood, as previously demonstrated (57). While the rest periods in this study were too short to allow a proper analysis of resting state networks, previous research has suggested that depressed mood states are associated with increased cognitive load (58).

In conclusion, the fact that mood and cognition can influence pain perception at a neural level suggests that interventions to modify these processes may indeed be useful to reduce pain. Such insights about mood and cognition will be critical for the development of better treatments for chronic pain, both psychological (such as cognitive behavior therapy) and pharmacological.

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Professor Goodwin reports receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Eisai, Lundbeck, and Servier; holding shares in P1Vital; and serving on advisory boards for AstraZeneca, Bristol-Myers Squibb, Janssen Cilag, Lilly, Lundbeck, P1Vital, Sanofi-Aventis, Servier, and Wyeth. Professor Goodwin has also served as an expert witness for Lilly and Servier. The other authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

1. Bair MJ, Robinson RL, Katon W, Kroenke K (2003): Depression and pain comorbidity: A literature review. *Arch Intern Med* 163:2433–2445.
2. Geisser ME, Roth RS, Theisen ME, Robinson ME, Riley JL 3rd (2000): Negative affect, self-report of depressive symptoms, and clinical depression: Relation to the experience of chronic pain. *Clin J Pain* 16:110–120.
3. Bar KJ, Wagner G, Koschke M, Boettger S, Boettger MK, Schlosser R, *et al.* (2007): Increased prefrontal activation during pain perception in major depression. *Biol Psychiatry* 62:1281–1287.
4. Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP (2008): Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. *Arch Gen Psychiatry* 65:1275–1284.
5. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ (2005): The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum* 52:1577–1584.
6. Schweinhardt P, Kalk N, Wartolowska K, Chessell I, Wordsworth P, Tracey I (2008): Investigation into the neural correlates of emotional augmentation of clinical pain. *Neuroimage.* 40:759–766.
7. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, *et al.* (2004): Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 24:10410–10415.
8. Campbell S, MacQueen G (2006): An update on regional brain volume differences associated with mood disorders. *Curr Opin Psychiatry* 19:25–33.
9. Williams JM, Barnhofer T, Crane C, Beck AT (2005): Problem solving deteriorates following mood challenge in formerly depressed patients with a history of suicidal ideation. *J Abnorm Psychol* 114:421–431.
10. Goodwin AM, Williams JMG (1982): Mood-induction research—its implications for clinical depression. *Behav Res Ther* 20:373–382.
11. Loggia ML, Mogil JS, Bushnell MC (2008): Experimentally induced mood changes preferentially affect pain unpleasantness. *J Pain* 9:784–791.
12. Villemure C, Slotnick BM, Bushnell MC (2003): Effects of odors on pain perception: Deciphering the roles of emotion and attention. *Pain* 106: 101–108.
13. Rainville P, Bao QVH, Chretien P (2005): Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain* 118:306–318.
14. Zelman DC, Howland EW, Nichols SN, Cleeland CS (1991): The effects of induced mood on laboratory pain. *Pain* 46:105–111.
15. Sharp TJ (2001): Chronic pain: A reformulation of the cognitive-behavioural model. *Behav Res Ther* 39:787–800.
16. Geisser ME, Robinson ME, Keefe FJ, Weiner ML (1994): Catastrophizing, depression and the sensory, affective and evaluative aspects of chronic pain. *Pain* 59:79–83.
17. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ (2007): Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci* 27:8877–8884.
18. Beauregard M, Paquette V, Levesque J (2006): Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Neuroreport* 17:843–846.
19. Clark DM (1983): On the induction of depressed mood in the laboratory: Evaluation and comparison of the Velten and musical procedures. *Adv Behav Res Ther* 5:27–49.
20. Edwards RR, Smith MT, Stonerock G, Haythornthwaite JA (2006): Pain-related catastrophizing in healthy women is associated with greater temporal summation of and reduced habituation to thermal pain. *Clin J Pain* 22:730–737.
21. Beck AT, Steer RA, Brown GK (1996): *Manual for the Back Depression Inventory-II*. San Antonio, TX: Psychological Corporation.
22. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59(suppl 20):22–33; quiz 34–57.
23. Eysenck SBG, Eysenck HJ, Barrett P (1985): A revised version of the psychoticism scale. *Pers Individ Dif* 6:21–29.
24. Velten E Jr (1968): A laboratory task for induction of mood states. *Behav Res Ther* 6:473–482.
25. Richell RA, Anderson M (2004): Reproducibility of negative mood induction: A self-referent plus musical mood induction procedure and a controllable/uncontrollable stress paradigm. *J Psychopharmacol* 18:94–101.
26. Clark DM, Teasdale JD (1985): Constraints on the effects of mood on memory. *J Pers Soc Psychol* 6:1595–1608.
27. Au Yeung C, Dalgleish T, Golden A-M, Schartau P (2006): Reduced specificity of autobiographical memories following a negative mood induction. *Behav Res Ther* 44:1481–1490.
28. Seibert PS, Ellis HC (1991): A convenient self-referencing mood induction procedure. *Bull Psychon Soc* 29:121–124.
29. Price DD, McGrath PA, Rafii A, Buckingham B (1983): The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 17:45–56.
30. Beckmann CF, Jenkinson M, Smith SM (2003): General multilevel linear modeling for group analysis in fMRI. *Neuroimage* 20:1052–1063.

31. Phan KL, Wager T, Taylor SF, Liberzon I (2002): Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16:331–348.
32. Rhudy JL, Williams AE, McCabe KM, Russell JL, Maynard LJ (2008): Emotional control of nociceptive reactions (ECON): Do affective valence and arousal play a role? *Pain* 136:250–261.
33. Vlaeyen JWS, Linton SJ (2000): Fear-avoidance and its consequences in chronic musculoskeletal pain: A state of the art. *Pain* 85:317–332.
34. Nolen-Hoeksema S (2000): The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *J Abnorm Psychol* 109: 504–511.
35. Eccleston C, Crombez G (2007): Worry and chronic pain: A misdirected problem solving model. *Pain* 132:233–236.
36. Tracey I, Mantyh PW (2007): The cerebral signature for pain perception and its modulation. *Neuron* 55:377–391.
37. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, *et al.* (1999): Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *Am J Psychiatry* 156:675–682.
38. Bingel U, Schoell E, Herken W, Buchel C, May A (2007): Habituation to painful stimulation involves the antinociceptive system. *Pain* 131:21–30.
39. Vogt BA (2005): Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 6:533–544.
40. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, *et al.* (2001): Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci* 21:9896–9903.
41. Kong J, Gollub RL, Polich G, Kirsch I, Laviolette P, Vangel M, *et al.* (2008): A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. *J Neurosci* 28:13354–13362.
42. Johansen-Berg H, Gutman DA, Behrens TEJ, Matthews PM, Rushworth MFS, Katz E, *et al.* (2008): Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex* 18:1374–1383.
43. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, *et al.* (2004): Limbic-frontal circuitry in major depression: A path modeling metanalysis. *Neuroimage.* 22:409–418.
44. Tucker DM, Luu P, Pribram KH (1995): Social and emotional self-regulationa. *Ann N Y Acad Sci* 769:213–240.
45. Phillips ML, Ladouceur CD, Drevets WC (2008): A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry* 13:833–857.
46. Kalisch R, Wiech K, Critchley HD, Seymour B, O'Doherty JP, Oakley DA, *et al.* (2005): Anxiety reduction through detachment: Subjective, physiological, and neural effects. *J Cogn Neurosci* 17:874.
47. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ (2006): Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *J Neurosci* 26:11501–11509.
48. Dolcos F, McCarthy G (2006): Brain systems mediating cognitive interference by emotional distraction. *J Neurosci* 26:2072–2079.
49. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN (2008): Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59:1037–1050.
50. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE, *et al.* (2004): For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23:483–499.
51. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME (2005): Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biol Psychiatry* 57:210–219.
52. Villemure C, Bushnell MC (2009): Mood influences supraspinal pain processing separately from attention. *J Neurosci* 29:705–715.
53. Wager TD, Phan KL, Liberzon I, Taylor SF (2003): Valence, gender, and lateralization of functional brain anatomy in emotion: A meta-analysis of findings from neuroimaging. *Neuroimage* 19:513–531.
54. Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, Houdé O, *et al.* (2001): Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull* 54:287–298.
55. McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR (2003): A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci* 15:394–408.
56. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, *et al.* (1997): Common blood flow changes across visual tasks. II. Decreases in cerebral cortex. *J Cogn Neurosci* 9:648–663.
57. Harrison BJ, Pujol J, Ortiz H, Fornito A, Pantelis C, Yucel M (2008): Modulation of brain resting-state networks by sad mood induction. *PLoS ONE* 3:e1794.
58. Wegner DM, Erber R, Zanakos S (1993): Ironic processes in the mental control of mood and mood-related thought. *J Pers Soc Psychol* 65:1093–1104.