Association of Major Depressive Disorder With Altered Functional Brain Response During Anticipation and Processing of Heat Pain

Irina A. Strigo, PhD; Alan N. Simmons, PhD; Scott C. Matthews, MD; Arthur D. (Bud) Craig, PhD; Martin P. Paulus, MD

Context: Chronic pain and depression are highly co-morbid conditions, yet little is known about the neurobiological basis of pain processing in major depressive disorder (MDD).

Objective: To examine the neural substrates underlying anticipation and processing of heat pain in a group of unmedicated young adults with current MDD.

Design: Functional magnetic resonance neuroimaging data were collected during an event-related factorial experimental pain paradigm. Painful and nonpainful heat stimuli were applied to the left volar forearm while different color shapes explicitly signaled the intensity of the upcoming stimulus.

Setting: University brain imaging center.

Patients: Fifteen (12 female) young adults with current MDD and 15 (10 female) healthy subjects with no history of MDD were recruited and matched for age and level of education. The Structured Clinical Interview for DSM-IV was administered to all participants by a board-certified psychiatrist.

Main Outcome Measure: Between-group differences in blood oxygen level–dependent functional magnetic resonance neuroimaging signal change to anticipation and processing of painful vs nonpainful temperature stimuli.

Results: Subjects with MDD compared with healthy controls showed (1) increased activation in the right anterior insular region, dorsal anterior cingulate, and right amygdala during anticipation of painful relative to nonpainful stimuli, (2) increased activation in the right amygdala and decreased activation in periaqueductal gray matter and the rostral anterior cingulate and prefrontal cortices during painful stimulation relative to nonpainful stimulation, and (3) greater activation in the right amygdala during anticipation of pain, which was associated with greater levels of perceived helplessness.

Conclusions: These findings suggest that increased emotional reactivity during the anticipation of heat pain may lead to an impaired ability to modulate pain experience in MDD. Future studies should examine the degree to which altered functional brain response during anticipatory processing affects the ability to modulate negative affective states in MDD, which is a core characteristic of this disorder.

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hhibit more passive response styles, such as lack of control, rumination, and helplessness, which have been associated with longer and more severe episodes of depression, as well as with enhanced emotional impact of chronic and experimental pain.

Consistent with this conceptualization, human imaging studies have shown that MDD is associated with abnormally increased activation within an emotion-processing network that includes the extended amygdala and prefrontal cortex during the anticipation of negative images. Related studies that have examined experimental pain processes in currently depressed patients provide preliminary evidence that MDD is associated with functional alterations of emotion-processing circuitry during the perception of pain. Additionally, recent findings by our group and others suggest that subjects with MDD show an affective bias (ie, increased emotional reactivity) when they experience experimental pain, although some found increased thermal pain thresholds in depression. Despite these findings, little is known about the degree to which anticipatory pain processing is altered in MDD or whether certain types of coping styles contribute to these changes. Clarifying the relationship between heightened anticipation of negative events (ie, pain), which biases individuals toward helplessness and depression, and its underlying neural substrates helps to develop a mechanistic insight of why being depressed makes one susceptible to chronic pain and/or why comorbid pain worsens the course of depression.

In this functional magnetic resonance neuroimaging (fMRI) study, we examined the neural systems involved in the anticipation and processing of heat pain in a group of young individuals with current MDD and a matched group of healthy control subjects with no lifetime history of MDD (or other psychiatric illness). We hypothesized that subjects with MDD relative to control subjects would show increased emotional reactivity to anticipatory cues, as evidenced by increased activation of emotion-processing brain areas. We further hypothesized that a passive response style would underlie heightened anticipatory reactivity to negative stimuli in MDD.

**Subiects**

Fifteen unmedicated (no pharmacological treatments > 30 days), currently depressed subjects (12 female, mean [SD] age, 24.3 [5.0] years) were recruited via flyers and Internet bulletin boards (Table 1). Each individual fulfilled diagnostic criteria for MDD according to a structured clinical interview for DSM-IV, which was administered by a board-certified psychiatrist (S.C.M.). Participants completed the Beck Depression Inventory II to establish the severity of current depressive symptoms. Ten of 15 subjects were naive to psychotropic medication. As well as meeting criteria for current MDD, 7 of the individuals with MDD also met criteria for lifetime (but not current) comorbid depressive and/or anxiety disorders. Specifically, 3 subjects with MDD (1 male) met criteria for past but not current dysthymia, 2 female subjects with MDD met criteria for past but not current post-traumatic stress disorder, 1 female subject with MDD met criteria for past but not current generalized anxiety disorder and panic disorder, and 1 female subject with MDD met criteria for past but not current dysthymia and panic disorder. Fifteen medically healthy comparison subjects (10 female, mean [SD] age, 24.3 [5.0]) with no history of psychiatric disorders according to a structured clinical interview for DSM-IV (Structured Clinical Interview for DSM-IV) and no first-degree relatives with psychiatric disorders were matched to the subjects with MDD for age (t sub=0.1; P = .92) and level of education (t sub=0.4; P = .69). Subjects were excluded from the study if they (1) met DSM-IV criteria for lifetime alcohol or substance dependence; (2) fulfilled DSM-IV criteria for alcohol or substance abuse within 30 days of study participation; (3) were experiencing active suicidal ideation; (4) had a lifetime history of bipolar or psychotic disorder; (5) had clinically significant comorbid medical conditions, such as cardiovascular and/or neurological abnormality; or (6) had a history of current or past chronic pain condition. Written in-

**Table 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Subject No./ Sex/Age, y</th>
<th>Age at MDD Onset, y</th>
<th>No. of Lifetime MDD Episodes</th>
<th>BDI-II Score</th>
<th>Diagnosis (DSM-IV)</th>
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<td>3</td>
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<td>8</td>
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</tr>
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<td>15/F/22</td>
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<td>3</td>
<td>40</td>
<td>MDD</td>
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</table>

Abbreviations: BDI-II, Beck Depression Inventory II; MDD, major depressive disorder.

a Comorbid lifetime (not current) diagnosis of posttraumatic stress disorder.
b Comorbid lifetime (not current) diagnosis of dysthymia.
c Comorbid lifetime (not current) diagnosis of general anxiety disorder.
d Comorbid lifetime (not current) diagnosis of panic disorder.

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formed consent was obtained from each individual following a detailed description of the study, which was approved by the University of California San Diego institutional review board. A χ2 test showed that the groups were not significantly different in their sex distributions (χ2=0.682; P = .41). All but 1 subject with MDD completed the Pain Catastrophizing Scale (PCS), which is a self-report, 13-item questionnaire that evaluates 3 separate dimensions of catastrophizing: magnification (eg, “I wonder whether something serious may happen”), rumination (eg, “I can’t seem to keep it out of my mind”), and helplessness (eg, “There is nothing I can do to reduce the intensity of pain”). We used this PCS to assess helplessness since it is specific to pain experience, unlike the Illness Cognition Questionnaire, for instance, which assesses helplessness associated with chronic illness.

PARADIGM DESIGN

We used 2 different types of temperature stimuli (ie, moderately painful heat and nonpainful warmth) and 2 different cognitive contexts (ie, fixation and continuous performance task [CPT]) and examined brain behavior during 2 temporal phases (ie, stimulus anticipation and stimulus administration) (Figure 1). The CPT was used to engage subjects in a measurable, low cognitive load, controlled experimental probe. This task entailed pressing the left button when subjects saw a circle and the right button whenever they saw a square on the screen. Visual stimuli were presented at a rate of 0.5 Hz. The 2 stimulation intensities (ie, moderately painful heat and nonpainful warmth) were individualized to each participant prior to scanning to establish similar perceptual intensity between groups. Stimuli were presented in a pseudorandom and counterbalanced order using a 9-cm2 thermode (TSA-II; Medoc, Ramat-Yishai, Israel), which was securely fastened to each subject’s left volar forearm. Each temperature was presented 20 times. The following average temperatures (mean [SD]) that resulted in similar ratings of intensity of thermal stimuli were used: (1) subjects with MDD: painful, −46.4 (0.6)°C; nonpainful, −38.9 (0.2)°C and (2) controls: painful, −46.9 (0.6)°C; nonpainful −38.9 (0.2)°C. Painful (P = .08; tSD = 1.8) and nonpainful (P = .59; tSD = 0.54) temperatures were not statistically different between the groups. Because painful temperatures were only about 0.3°C higher in subjects with MDD than in controls, the observed differences in brain activation were probably not due to differences in physical attributes of the stimuli. Subjects were cued to an upcoming painful stimulus whenever the color of the shape changed to red and to an upcoming nonpainful warm stimulus whenever the color of the shape changed to green. Subjects were told that they would feel several painful and nonpainful stimuli. Subjects’ performance on the CPT, including reaction times (RTs) and percentage correct, was scored and compared between the groups. Lack of differences between the groups in percentage correct and RTs would suggest similar attentional engagement and psychomotor reactivity, respectively, both of which are compromised in MDD.26 The effects of the CPT were regressed out by the linear contrasts of interest with MDD completed the Pain Catastrophizing Scale (PCS), which is a self-report, 13-item questionnaire that evaluates 3 separate dimensions of catastrophizing: magnification (eg, “I wonder whether something serious may happen”), rumination (eg, “I can’t seem to keep it out of my mind”), and helplessness (eg, “There is nothing I can do to reduce the intensity of pain”). We used this PCS to assess helplessness since it is specific to pain experience, unlike the Illness Cognition Questionnaire, for instance, which assesses helplessness associated with chronic illness.

IMRI PROTOCOL

Four IMRI runs (for a total of 952 brain volumes) sensitive to blood oxygenation level–dependent (BOLD) contrast29 were collected for each subject using a 3.0-T scanner (GE Medical Systems, Milwaukee, Wisconsin) (T2*-weighted echo planar imaging, repetition time = 2000 milliseconds, echo time = 32 milliseconds, flip angle = 90°, field of view = 23 cm, 64 × 64 matrix, thirty 2.6-mm slices with a 1.4-mm gap, 238 scans) while he or she performed the experimental paradigm. Functional MRI acquisitions were time-locked to the onset of the task. During the same experimental session, a high-resolution T1-weighted image (fast spoiled gradient-recalled echo sequence, repetition time = 8 milliseconds, echo time = 3 milliseconds, inversion time = 450 milliseconds, flip angle = 12°, field of view = 25 cm, 172 sagittal slices, 1.0 × 0.97 × 0.97 mm3 voxels) was obtained for anatomical reference.

STATISTICAL ANALYSIS

All imaging data were analyzed with the Analysis of Functional Neuroimages (AFNI) software package.30 Preprocessed time-series data for each individual were analyzed using a multiple regression model consisting of 8 task-related regressors (Figure 1): (1) anticipation of painful stimuli with the CPT (A1); (2) anticipation of painful stimuli without the CPT (B1); (3) anticipation of nonpainful stimuli with the CPT (C1); (4) anticipation of nonpainful stimuli without the CPT (D1); (5) processing of painful stimuli with the CPT (A2); (6) processing of painful stimuli without the CPT (B2); (7) processing of nonpainful stimuli with the CPT (C2); and (8) processing of nonpainful stimuli without the CPT (D2). Eight additional regressors were included in the model as nuisance regressors: 2 cue regressors (to signal an upcoming temperature stimulus), 1 outlier regressor to account for physiological and scanner noise, each individual’s white matter regressor to account for activation that is not spatially specific, 3 movement regressors to account for residual motion (in the roll, pitch, and yaw directions), and regressors for baseline and linear trends to account for signal drifts. A Gaussian filter with a full width at half maximum of 4 mm was applied to the voxel-wise percentage of signal change data to account for individual variation in the anatomical landmarks. Data from each subject were normalized to Talairach coordinates.

Primary contrasts between regression coefficients from the AFNI program 3DDeconvolve were entered into 2-sample t tests. We examined activation differences between the groups for (1) pain anticipation (ie, [A1 + B1] − [C1 + D1]) (Figure 1) and (2)
Activation of the dorsolateral prefrontal cortex (DLPFC) and periaqueductal gray matter (PAG) during painful stimulus was related to recruitment of pain modulatory systems. The average percentage of signal in these areas was extracted from each individual subject’s data using the group functional mask that survived the whole-brain threshold/cluster method and correlated with subjects’ average postscan ratings of pain intensity and unpleasantness. All post hoc statistical analyses were performed with SPSS 12.0 (SPSS Inc, Chicago, Illinois).

**BEHAVIORAL MEASURES**

**Performance on the CPT**

Subjects reported the average intensity and unpleasantness of painful heat and nonpainful warm stimuli following each functional run to ensure similar perceptual ratings between the groups. The intensity of painful and nonpainful temperatures was rated on 2 separate 11-point Likert scales (see "Methods" section in the text). No significant group differences in the subjective ratings of painful heat intensity, painful heat unpleasantness, and nonpainful warm intensity were observed ($P > .20$). Subjects with major depressive disorder (MDD) reported higher unpleasantness ratings to nonpainful warm stimuli ($P = .04$). CON indicates control subjects.

**FMRI RESULTS**

**Pain Anticipation**

Table 3 (upper section) shows significant group differences in BOLD signal during the anticipation of pain (ie, anticipation of painful heat vs anticipation of nonpainful warmth). Whole-brain analyses revealed that subjects with MDD compared with control subjects showed increased activity in several brain regions, including the right anterior insular region (AI), left AI/inferior frontal...
gyrus, bilateral dorsal anterior cingulate cortex (ACC), right DLPFC, and several clusters in the left DLPFC, as well as clusters in the temporal and occipital lobes. Control subjects, compared with subjects with MDD, showed increased activity in the right caudate, bilateral precuneus, right posterior cingulate cortex, and ventral brainstem (Figure 3A). The ROI analysis in the amygdala showed increased right amygdala activation in subjects with MDD vs control subjects during anticipation of painful heat relative to anticipation of nonpainful warmth.

Pain Stimulation

Table 3 (lower section) shows significant group differences in BOLD signal during painful stimulation (ie, painful heat vs nonpainful warmth). A whole-brain analysis revealed that subjects with MDD compared with control subjects showed increased BOLD activation in the left parahippocampal gyrus and occipital cortex, whereas controls compared with subjects with MDD showed increased BOLD signal in several regions within the DLPFC, right rostral ACC, PAG, and a cluster in the temporal lobe, precuneus, and cerebellum (Figure 3B). The ROI analysis in the amygdala showed increased right amygdala activation in subjects with MDD vs control subjects for the painful heat vs nonpainful warmth comparison.

Brain-Behavior Correlations

To examine whether amygdala activation was related to passive coping styles in MDD, we correlated percentage of signal change within the amygdala with the helplessness, rumination, and ramification dimensions of the PCS. Correlations between the left DLPFC and PAG and subjects’ postscan ratings of temperature stimuli (see “Methods” section). We found significant inverse correlation between percentage of signal change within the right DLPFC and subjects’ postscan ratings of pain intensity in the MDD ($r=-0.6; P=.02$), control ($r=-0.64; P=.01$), and combined groups ($r=-0.57; P=.001$) (Figure 4B). Correlations between the left DLPFC and PAG and subjects’ intensity ratings or between bilateral DLPFC and PAG and subjects’ unpleasantness ratings did not reach statistical significance in the MDD, control, or combined groups ($P$ values >.08).

**Table 3. Group Differences in Brain Activation**

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<tr>
<th>Brain Region</th>
<th>Talairach Coordinate</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>Volume, $\mu$L</th>
<th>$t$ Value</th>
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<tr>
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</table>

*Region of interest analysis.

Abbreviations: ACC, anterior cingulate cortex; AI, anterior insular region; BA, Brodmann area; CON, control; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus, L, left; MDD, major depressive disorder; MFG, medial frontal gyrus, MTG, medial temporal gyrus; PAG, periaqueductal gray matter; PCC, posterior cingulate cortex; R, right; SFG, superior frontal gyrus; STG, superior temporal gyrus.

**COMMENT**

Three main results were observed. First, increased activation of the amygdala, AI, and ACC was observed during pain anticipation in subjects with MDD, suggesting that depressed individuals experience increased affective processing even before they actually experience pain-
ful stimuli. Second, greater right amygdala activation during pain anticipation in MDD was associated with greater levels of perceived helplessness, which was specific to this disorder. Third, for the same perceived intensity of painful stimulation, subjects with MDD seemed to show maladaptive activation of a neural network that is involved in pain and emotion modulation.39 Taken together, these findings extend previous research describing affective biasing of the pain experiences in MDD22,23,40,41 and are consistent with the conceptualization of MDD as a disorder of abnormal anticipatory processing and hypervigilance. These findings may also suggest that altered functional responses within a specific neural network during anticipatory processing in MDD may lead to an impaired ability to modulate not only the experience of pain but also negative affective states.

To our knowledge, this is the first study to examine the neural correlates of anticipatory pain processing in young, unmedicated individuals with current MDD. Cognitive models of depression suggest that depressed individuals negatively bias their expectations, thereby creating conflict with the environment.10 The increased activation within the amygdala, AI, and ACC in subjects with MDD during anticipation of pain found herein is consistent with this cognitive model and may represent a neural correlate of hypervigilant monitoring42 of negative information in MDD.43 Both the ACC and insula receive afferent information via the lamina I homeostatic pathway.44 According to recent neuroanatomical and neuroimaging evidence, this pathway subserves all homeostatic emotions, including pain (ie, feelings and motivations associated with changes in the body’s physiological condition and with the autonomic responses and behaviors that occur to restore an optimal balance).44,45 Moreover, evidence from rodents and nonhuman primate studies describes strong anatomical connections between the insula and both the amygdala and ACC.46 Related functional neuroimaging evidence shows that the AI, ACC,
and amygdala are also the main nodes within the “emotional salience” network that is active during undirected mental activity, further indicating that these structures are directly involved in homeostatic processing. Inappropriately large responses within the brain’s homeostatic and emotional salience network to a stressor or upcoming pain suggest an exaggerated experience of emotional distress or affective biasing in MDD, even before the actual painful stimulation occurs. Interestingly, subjects with MDD showed increased affective biasing during anticipation of pain even though the perception of pain intensity was not different. This suggests that the difference between the expected and the actual body state, or the interoceptive error signal, may be higher in MDD. Neuroanatomical and functional neuroimaging evidence shows that the AI plays a major role in detecting the mismatch between cognitive and interoceptive states, reflecting subjects’ awareness of the perceived (and not the actual) interoceptive state. Increased AI activation during anticipation of pain in our subjects with MDD is consistent with the idea that the awareness of the interoceptive state during anticipation of impending pain is heightened in MDD. This heightened awareness of the interoceptive state creates a mismatch between the observed and expected body state similar to the ideology behind anxiety disorders. Thus, in much the same way that individuals with MDD have a maladaptive interpretation of the environmental cues, they also may have impaired interoception.

Cognitive coping styles play an important role in the anticipation and processing of negative emotional information, and the amygdala is directly involved in these processes. Specifically, the amygdala has been linked to passive coping strategies, such as helplessness and catastrophizing. For example, a lack of controllability during painful stimulation was associated with increased amygdala activity in healthy human subjects. Likewise, unsolvable cognitive problems that induce a state of learned helplessness in humans are associated with increased amygdala activity. Furthermore, in patients with fibromyalgia, passive attitudes toward pain are significantly associated with activity in the extended amygdala. Exaggerated activation of the amygdala in our subjects with MDD during anticipation of pain was significantly predicted by a measure of helplessness toward pain in these subjects and this relationship was specific to the subjects with MDD. Acute antidepressant treatments can significantly diminish resting metabolism and functional activation within the amygdala toward negative emotional stimuli, and the amount of decrease can predict relapse. Although speculative, the mechanistic relationship between helplessness and amygdala activation found in our study may suggest that the therapeutic effects of cognitive therapy directed toward reducing passive cognitions in depression may be grounded in the effects of therapy on amygdala functioning.

When dealing with pain, cortical and subcortical modulatory systems are normally activated, which are aimed to elicit adaptive behaviors to stressful exposures. Our findings suggest that MDD is associated with a heightened alarm signal during anticipation of pain. Nevertheless, despite this heightened alarm signal in MDD, the brain shows ineffective or maladaptive recruitment of pain- and emotion-modulatory pathways during the experience of pain. Studies that have examined the mechanisms of pain and emotion modulation using, for instance, placebo and/or attentional diversion to a secondary task consistently show increased activation within the rostral ACC. This region of the ACC is connected to PAG, which, in turn, is one of the main nodes of the endogenous pain-inhibitory circuits. Furthermore, regions of the lateral and medial prefrontal cortex play an important role in emotion regulation, showing increasing activation as a function of the emotion- and pain-suppression process (eg, reappraisal) or placebo analgesia. In the current study, all of these structures were significantly more activated in healthy subjects compared with subjects with MDD during actual
Deficient endogenous pain modulation is one of the possible mechanisms leading to sensory allodynia in chronic pain disorders (ie, when stimuli that are normally perceived as nonpainful become painful).73 In our study, groups were matched on the perceived intensity of nonpainful and painful stimuli (ie, the sensory experience of thermal stimuli was not different between the groups). However, as we observed previously,22 subjects with MDD demonstrated “emotional allodynia” (ie, experiencing nonpainful warm stimuli as unpleasant). In fact, a recent study showed that this concept also applies to patients with fibromyalgia, who rated nonpainful muscle sensation as unpleasant or emotional.74 It is plausible that the decreased activation within the brain’s pain- and emotion-modulation circuitry observed in our subjects with MDD is due to ineffective functioning of these systems or an adverse effect of emotional allodynia. Further studies should examine how decreased activation of endogenous pain/emotion regulatory systems relates to experience of emotional allodynia and whether compromised pain modulation contributes to high vulnerability to chronic pain in depression.

We also observed decreased activation within bilateral precuneus and posterior cingulate cortex in subjects with MDD compared with healthy control subjects in our study. This finding is consistent with the notion of competing cognitive networks75 and prior observations in patients with MDD.76,77 In addition, this region appears responsive to treatment in MDD76,77 and can predict prognosis in mild cognitive impairment.78 Future studies need to examine the role of the postero medial cortex in pain-depression comorbidity.

Our results are in direct agreement with our own psychophysical observations22 of increased emotional reactivity to painful stimuli in young depressed adults without comorbid chronic pain condition. Considering increased pain affect to experimental pain in students with increased and/or induced depressive moods,79,80 increased affective biasing to daily pain in patients with chronic pain with a history of depression,81,82 and increased affective processing in comorbid chronic pain and depression,83 these results suggest that depression has profound acute, as well as chronic, effects on emotional behavior and brain circuitry. Therefore, even short-term changes in the affective state of an individual may significantly influence interoceptive state, which then affectively biases behaviors and feelings toward environ-

mental stimuli. Therapeutic interventions directed toward supporting and restoring interoceptive/homeostatic functioning, by building resilience, for example, have been relatively successful in comorbid depression and chronic pain conditions.83

We would like to acknowledge that our findings are based on a mixed sample of relatively modest size. Although we observed large statistical differences between the MDD and control groups, further studies confirming our results would aid in generalizing the present findings. Future studies examining brain responses to pain stimulation and anticipation in subjects with MDD of greater diversity without chronic pain and in subjects with comorbid chronic pain and MDD, as well as in older medicated depressed adults, would aid in clarifying the relationship between pain and depression. Specifically, future studies should examine how different subpopulations of subjects with MDD (ie, older vs younger age, many vs few comorbidities and prior episodes, earlier vs later age at MDD onset) respond to anticipation and receipt of experimental pain.

In summary, using pain as a probe of emotional circuitry, we have shown that unmedicated young adults with recurrent MDD and without comorbid chronic pain conditions show increased affective bias during aversive anticipation in several brain regions, including the AI, ACC, and amygdala, and decreased response during pain experience in regions responsible for cortical and subcortical pain modulation. The anticipatory brain response may indicate hypervigilance to impending threat, which may lead to increased helplessness and maladaptive modulation during the experience of heat pain. This mechanism could in part explain the high comorbidity of pain and depression when these conditions become chronic. Future studies that directly examine whether maladaptive response to pain in MDD is due to emotional allodynia, maladaptive control responses, lack of resilience, and/or ineffectual recruitment of positive energy resources will further our understanding of pain-depression comorbidity.

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Correspondence: Irina A. Strigo, PhD, Department of Psychiatry, University of California San Diego, 3350 La Jolla Village Dr, Bldg 13, MC 9151-B, La Jolla, CA 92161 (istrigo@ucsd.edu).

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Additional Information: The eFigure and eTable are available at http://archgenpsychiatry.com.
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Correction
In the Original Article by Strigo et al titled “Association of Major Depressive Dis-
order With Altered Functional Brain Response During Anticipation and Processing of Heat Pain,” published in the November issue of the Archives (2008;65[11]:1275-
1284), there was an error in the Funding/Support section. It should have said that Drs Paulus and Simmons were supported by the University of California San Diego Center of Excellence for Stress and Mental Health, not Drs Paulus and Strigo.