Published in final edited form as:
Arch Gen Psychiatry. 2008 November ; 65(11): 1275–1284. doi:10.1001/archpsyc.65.11.1275.

Major Depressive Disorder is Associated with Altered Functional Brain Response During Anticipation and Processing of Heat Pain

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Abstract

Context—Chronic pain and depression are highly comorbid 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 (fMRI) data were collected during an event-related factorial experimental pain paradigm. Painful and non-painful 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—15 (12 F) young adults with current MDD and 15 (10F) 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 fMRI signal change to anticipation and processing of painful versus non-painful temperature stimuli.

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

Conclusion—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 ability to modulate negative affective states in MDD, which is a core characteristic of this disorder.

Introduction

Chronic pain and depression are common and often overlapping syndromes. Over 75% of patients with depression experience chronic or recurring pain [1]. Similarly, 30-60% of chronic

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pain patients report significant depressive symptoms [2]. Understanding the neurobiological basis of this relationship is important because the presence of comorbid pain contributes significantly to poorer outcomes and increased cost of treatment in MDD [3]. However, despite the close relationship between clinical pain and depression, the neural basis of altered pain processing in patients with major depressive disorder (MDD) is poorly understood.

Anticipation of future events is an important component of emotion processing [4]. Negative anticipatory biases not only affect acute emotional experiences [5], but also play an important role in the development and maintenance of MDD and chronic pain disorders [6]. Current cognitive models of MDD posit that depressed individuals negatively bias their expectations, perceptions and memories [7-9 10]. Such negative biases may account for the development of passive coping styles that promotes helplessness, and therefore the maintenance of depression [7, 10-12]. Depressed individuals exhibit more passive response styles, such as lack of control, rumination and helplessness [13], which have been associated with longer and more severe episodes of depression [14, 15], as well as with enhanced emotional impact of chronic and experimental pain [16, 17].

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 [18]. Related studies, which have examined experimental pain processes in currently depressed patients, [19-21] 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 MDD subjects show an affective bias (i.e., increased emotional reactivity) when they experience experimental pain [22, 23], although some find increased thermal pain thresholds in depression (e.g.,24 but see [22] for discussion). 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 (i.e., pain), which biases individuals towards 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 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 (CON) subjects with no lifetime history of MDD (or other psychiatric illness). We hypothesized that MDD relative to CON 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.

Materials and Methods

Subjects

Fifteen unmedicated (no pharmacological treatments > 30 days), currently depressed subjects (12F, mean age ± SD: 24.5±5.5) were recruited via flyers and internet bulletin boards (see Table 1 for detailed description). Each individual fulfilled diagnostic criteria for MDD according to a structured clinical interview for DSM IV (SCID-P) [25], which was administered by a board certified psychiatrist (SCM). Participants completed the Beck Depression Inventory (BDI-2) [26] to establish the severity of current depressive symptoms. Ten out of fifteen subjects were naïve to psychotropic medication. As well as meeting criteria for current MDD, seven of the MDD individuals also met criteria for lifetime (but not current) comorbid depressive and/or anxiety disorders. Specifically, three MDD subjects (one male) met criteria for past but not

current dysthymia, two female MDD subjects met criteria for past but not current PTSD, one female MDD subject met criteria for past but not current generalized anxiety disorder and panic disorder and one female MDD subject met criteria for past but not current dysthymia and panic disorder. Fifteen medically healthy comparison (CON) subjects (10F, mean age 24.3±5.0) with no history of psychiatric disorders according to a structured clinical interview for DSM IV (SCID-P) [25] and no first-degree relatives with psychiatric disorders were matched to the MDD subjects for age ($t(28)=0.1$, $p=0.92$) and level of education ($t(28)=0.4$, $p=0.69$). 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; 6) had a history of current or past chronic pain condition. Written informed 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 chi-square showed that the groups were not significantly different in their gender distributions ($\chi^2=0.682$, p=n.s.). All but one MDD subject completed the Pain Catastrophizing Scale (PCS) [16] which is a self-report 13-item questionnaire that evaluates three separate dimensions of catastrophizing: magnification (e.g. “I wonder whether something serious may happen”), rumination (e.g. “I can’t seem to keep it out of my mind”) and helplessness (e.g. “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 Illness Cognition Questionnaire (ICQ), for instance, that assess “helplessness” associated with chronic illness [27].

Paradigm Design (see Figure 1)

We used two different types of temperature stimuli (i.e., moderately painful heat and non-painful warmth), two different cognitive contexts (i.e., fixation and continuous performance task (CPT)) and examined brain behavior during two temporal phases (i.e., stimulus anticipation and stimulus administration). CPT was used to engage subjects in a measurable, low cognitive load, controlled experimental probe. This task entailed pressing LEFT button when subjects saw a circle and RIGHT button whenever they saw a square on the screen. Visual stimuli were presented at a rate of 0.5Hz. The two stimulation intensities (i.e., moderately painful heat and non-painful warmth) were individualized to each participant prior to scanning in order to establish similar perceptual intensity between groups. Stimuli were presented in a pseudo-random and counterbalanced order using a $9cm^2$ thermode (Medoc TSA-II, 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) MDD: painful - 46.4 ± 0.6°C, non-painful - 38.9 ± 0.2°C; 2) CON: painful - 46.9 ± 0.6°C, non-painful - 38.9 ±0.2°C. Painful ($p=0.08$, $t(28)=1.8$) and non-painful ($p=0.59$, $t(28)=0.54$) temperatures were not statistically different between the groups. Since painful temperatures were only ~0.5°C higher in MDD than in CON participants, 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 non-painful warm stimulus whenever the color of the shape changed to GREEN. Subjects were told that they would feel several painful and non-painful stimuli. Subjects’ performance on the CPT, including reaction times (RT) and percent correct, were scored and compared between the groups. Lack of differences between the groups in percent correct and RTs would suggest similar attentional engagement and psychomotor reactivity, respectively, both of which are compromised in MDD [28]. The effects of the CPT were regressed out by the linear contrasts of interests (see below). Main effects of CPT are shown in Supplementary Material.

fMRI Protocol

Four fMRI runs (for a total of 952 brain volumes) sensitive to blood oxygenation level-dependent (BOLD) contrast [29] were collected for each subject using 3.0 Tesla GE scanner (T2* weighted echo planar imaging, TR=2000 ms, TE=32ms, flip angle= 90, FOV=23cm, 64×64 matrix, 30 2.6-mm 1.4-mm gap axial slices, 238 scans) while they performed the above paradigm. FMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a high-resolution T1-weighted image (FSPGR, TR=8ms, TE=3ms, TI=450 ms, flip angle=12, FOV=25cm, 172 sagital slices, 1×0.97×0.97 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 eight task-related regressors (Figure 1): 1) Anticipation of painful stimuli with CPT (**A1**); 2) Anticipation of painful stimuli without CPT (**B1**); 3) Anticipation of non-painful stimuli with CPT (**C1**); 4) Anticipation of non-painful stimuli without CPT (**D1**); 5) Processing of painful stimuli with CPT (**A2**); 6) Processing of painful stimuli without CPT (**B2**); 7) Processing of non-painful stimuli with CPT (**C2**); 8) Processing of non-painful stimuli without CPT (**D2**). Eight additional regressors were included in the model as nuisance regressors: two cue regressors (to signal an upcoming temperature stimulus), one outlier regressor to account for physiological and scanner noise, each individual's white matter regressor to account for activation that is not spatially specific, three 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-half maximum of 4mm was applied to the voxel-wise percent signal change data to account for individual variation in the anatomical landmarks. Data from each subject were normalized to Talairach coordinates [31].

Primary contrasts between regression coefficients from the AFNI program 3dDeconvolve were entered into two-sample t-tests. We examined activation differences between the groups for: 1) Pain Anticipation (i.e., [(A1+B1)-(C1+D1)], Figure 1), and 2) Pain Stimulation (i.e., [(A2 +B2)-(C2+D2), Figure 1]. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false positive areas of activation [32]. Based on the whole brain analysis, an *a priori* voxel-wise probability of $p<0.05$ in a cluster of 512 μL resulted in an *a posteriori* cluster-wise probability of $p <0.05$. Since amygdala consistently shows abnormal activity in MDD [33] and plays important role in pain [34]and anticipatory processes [35]we performed region of interest (ROI) analyses in the amygdala for the above linear contrasts using Talairach-defined bilateral masks for the amygdalae [31]. Due to small volume correction, a cluster of at least 128 μL in the amygdala during the ROI analysis was considered significant. The average percent signal in the amygdala was extracted from each individual subject's data using the group functional mask that survived this threshold/cluster method. This activation was then correlated with the three dimensions of PCS (i.e., helplessness, rumination, ramification) to examine whether amygdala activity was predicted by passive coping styles. Correlations were performed separately for each group and corrected for multiple comparisons using Bonferoni's method. The between-group differences in the strength of these correlations was tested by contrasting the Fisher Z transform of the correlation values in each group; this allowed testing whether relationship between amygdala activation and passive coping styles is specific to MDD. Furthermore, in order to examine whether activation of dorsolateral prefrontal cortices (dlPFC) and PAG during painful stimulus was related to recruitment of pain modulatory systems [36-38] the average percent signal in these areas was extracted from each individual subjects' data using the group functional mask that survived whole brain threshold/ cluster method and correlated with subject' average post-scan ratings of pain intensity and

unpleasantness. All post-hoc statistical analyses were performed with SPSS 12.0 (SPSS. Inc, Chicago, IL).

Results

Behavioral Measures

Performance on the CPT—There was no significant difference between the groups in RT or percent correct (Table 2) suggesting that both MDD and CON individuals showed similar engagement in the experimental paradigm.

Behavioral Ratings between fMRI runs—Subjects reported the average intensity and unpleasantness of the painful and non-painful stimuli following each functional run (Figure 2). All subjects rated high temperatures as painful, and low temperatures as non-painful. The MDD and CON groups did not differ in their ratings of the intensity and unpleasantness of painful heat, or in their ratings of the intensity of non-painful warmth (p's > 0.2, t's(28) < 1.2). The MDD relative to the CON subjects rated non-painful warm stimuli as slightly more unpleasant (p=0.04, t(28)= 2.15), a finding which is consistent with our previous observations of the increased affective bias in MDD at non-painful temperatures [22].

fMRI Results

Pain Anticipation—Table 3 (upper section) shows significant group differences in BOLD signal during the anticipation of pain, i.e., anticipation of painful heat versus anticipation of non-painful warmth. Whole brain analyses revealed that MDD compared to CON subjects showed increased activity in several brain regions including, right anterior insular region (AI), left AI/inferior frontal gyrus, bilateral dorsal anterior cingulate cortex (ACC), right dorsolateral prefrontal cortex (DLPFC), several clusters in the left DLPFC, as well as clusters in the temporal and occipital lobes. CON compared to MDD subjects 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 MDD versus CON subjects during anticipation of painful heat relative to anticipation of non-painful warmth.

Pain Stimulation—Table 3 (lower section) shows significant group differences in BOLD signal during painful stimulation, i.e., painful-heat versus non-painful warmth. A whole brain analysis revealed that MDD compared to CON subjects showed increased BOLD activation in the left parahippocampal gyrus and occipital cortex, whereas CON compared to MDD subjects showed increased BOLD signal in several regions within DLPFC, right rostral ACC, periaqueductal gray (PAG), a cluster in the temporal lobe, precuneus and cerebellum (Figure 3b). ROI analysis in the amygdala showed increased right amygdala activation in MDD versus CON subjects for the painful heat versus non-painful warmth comparison.

Brain-Behavior Correlations—To examine whether amygdala activation was related to passive coping styles in MDD, we correlated percent signal change within the amygdala with the helplessness, rumination and ramification dimensions of PCS (see Methods). Significant positive correlations were observed in the MDD group between greater helplessness scores and greater activity in the right amygdala during the anticipation of pain (r=0.65, p = 0.014) (Figure 4a). After correcting for multiple comparisons, there was a trend for correlations between rumination subscale and amygdala activation during anticipation (r=0.63, p=0.017), as well as helplessness (r=0.62, p=0.019) and rumination (r=0.59, p=0.029) subscales and amygdala activation during pain to be significant. In comparison, none of these correlations were significant in the CON group (-0.27<r's<0.25, p's >0.34). Furthermore, significant

between-group difference was found in the strength of correlations between helplessness and amygdala activation only during anticipation of pain (p=0.012).

To examine whether activation within bilateral DLPFC and PAG during pain stimulation was related to recruitment of pain modulatory systems, we correlated percent signal changes within these areas with subjects' post-scan ratings of temperature stimuli (see Methods). We found significant inverse correlation between percent signal change within right DLPFC and subjects' post-scan ratings of pain intensity in the MDD (r=-0.6, p=0.019), CON (r=-0.64, p=0.012) and in the combined groups (r=-0.57, p=0.001) (Figure 4b). Correlations between left DLPFC and PAG and subjects' intensity ratings or between bilateral DLPFC and PAG and subjects' unpleasantness ratings did not reach statistical significance in MDD, CON or the combined groups (p's > 0.08).

Comment

Three main results were observed. First, increased activation of the amygdala, anterior insular region and ACC was observed during pain anticipation in MDD subjects, suggesting that depressed individuals experience increased affective processing even before they actually experience painful 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, MDD subjects 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 MDD [22, 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 (reviewed in [10]). The increased activation within amygdala, AI and ACC in MDD subjects during anticipation of pain found here is consistent with this cognitive model, and may represent a neural correlate of hypervigilant monitoring [42] 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, i.e., feelings and motivations associated with changes in the body's physiological condition and with the autonomic responses and behaviors that occur in order to restore an optimal balance [44, 45]. Moreover, evidence from rodents and non-human 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 "emotional salience" network that is active during undirected mental activity [47], 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, MDD subjects 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 [44, 48, 49]. Increased AI activation during anticipation of pain in our MDD subjects 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 [50]. Thus, in much the same way that MDD individuals 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 [51] and catastrophizing [52]. For example, a lack of controllability during painful stimulation was associated with increased amygdala activity in healthy human subjects [53]. Likewise, unsolvable cognitive problems that induce a state of learned helplessness in humans are associated with increased amygdala activity [54]. Furthermore, in fibromyalgia patients, passive attitudes toward pain are significantly associated with activity in extended amygdala [52]. Exaggerated activation of the amygdala in our MDD patients during anticipation of pain was significantly predicted by a measure of helplessness towards pain in these patients and this relationship was specific to the MDD patients. Acute antidepressant treatments can significantly diminish resting metabolism and functional activation within amygdala towards negative emotional stimuli and the amount of decrease can predict relapse [55, 56]. 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 [57, 58], 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 [57, 59] and/or attentional diversion to a secondary task [60, 61] consistently show increased activation within 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 [58, 62]. Furthermore, regions of the lateral and medial prefrontal cortex play important role in emotion regulation, showing increasing activation as a function of the emotion and pain suppression process (e.g., reappraisal) (reviewed in [37, 39]) or placebo analgesia [36]. In the current study, all of these structures were significantly more activated in healthy compared to MDD subjects during actual pain experience, supporting maladaptive response within pain- and emotion-modulatory circuits in MDD. Furthermore, right DLPFC activation during pain experience in our study showed significant negative correlation with average subjective pain intensity ratings, suggesting that decreased activation of this structure during painful stimulation in MDD might be related to maladaptive cortical pain modulation in this disorder. These findings are consistent with ineffective emotional regulation [63-66] and altered endogenous opioid neurotransmission on mu-opioid receptors in MDD [67]. Deficient endogenous pain modulation has been implicated in chronic and functional pain disorders, including fibromyalgia [68 69], chronic tension-type headache [70], irritable bowel syndrome [71] and central post-stroke pain [72]. Deficient endogenous pain modulation is one of the possible mechanisms leading to sensory allodynia in chronic pain disorders, i.e., when stimuli that are normally perceived as non-painful become painful [73]. In our study, groups were matched on the perceived intensity of non-painful and painful stimuli, i.e., the sensory experience of thermal stimuli was not different between the groups. However, as we observed previously [22], MDD subjects demonstrated

"emotional allodynia", i.e., experiencing non-painful warm stimuli as unpleasant. In fact, a recent study showed that this concept also applies to fibromyalgia patients who rated non-painful 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 MDD patients is due to ineffective functioning of these systems or a side 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 MDD compared to healthy control subjects in our study. This finding is consistent with the notion of competing cognitive networks [75] and prior observations in MDD patients [76, 77]. In addition this region appears responsive to treatment in MDD [76, 77] and can predict prognosis in mild cognitive impairment [78]. Future studies need to examine the role of the posteromedial cortex in pain-depression comorbidity.

Our results are in direct agreement with our own psychophysical observations [22] 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 chronic pain patients with history of depression [81, 82], as well as increased affective processing in comorbid chronic pain and depression [20], these results suggest that depression has profound acute, as well as chronic effects on the emotional behavior and brain circuitry. Therefore, even acute changes in the affective state of an individual may significantly influence interoceptive state, which then affectively biases behaviors and feelings towards environmental stimuli. Therapeutic interventions directed towards 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 MDD and CON groups, further studies confirming our results would aid in generalizing the present findings. Future studies examining brain responses to pain stimulation and anticipation in MDD patients of greater diversity without chronic pain and in patients with co-morbid 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 MDD patients (i.e., older vs. younger age, many vs. few comorbidities and prior episodes, earlier vs. later age of 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 anterior insular region, 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.

Acknowledgements

This study was supported by Barrow Neurological Foundation (IAS and ADC), by the National Institute of Mental Health (MH080003; MH077205; IAS), by the National Association for Research in Schizophrenia and Depression (NARSAD) (IAS, ANS and SCM), and by the UCSD Center of Excellence for Stress and Mental Health (MPP and ANS); authors demonstrate no financial or conflict of interest in connection with this work; Dr. Strigo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Lepine JP, Briley M. The epidemiology of pain in depression. HumPsychopharmacol 2004;19(Suppl 1):S3–S7.
2. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. ArchInternMed 2003;163(20):2433–2445.
3. Gameroff MJ, Olfson M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. The Journal of clinical psychiatry 2006;67(8):1232–1239. [PubMed: 16965201]
4. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biological psychiatry 2003;54(5):504–514. [PubMed: 12946879]
5. Kirsch I. Response expectancy as a determinant of experience and behavior. American Psychologist 1985;40(11):1189–1202.
6. Boersma K, Linton SJ. Expectancy, fear and pain in the prediction of chronic pain and disability: a prospective analysis. European journal of pain (London, England) 2006;10(6):551–557.
7. Beck, AT. Depression: clinical, experimental and theorietical aspects. Hoeber Medical Division, Harper & Row; New York: 1967.
8. Beck AT. Cognitive Models of Depression. Journal of Cognitive Psychotherapy: An International Quarterly 1987;1(1):5–37.
9. Abramson LY, Metalsky GI, Alloy LB. Hopelessness Depression: A Theory-Based Subtype of Depression. Psychological Reviews 1989;96(2):358–372.
10. Alloy LB, Abramson LY, Whitehouse WG, Hogan ME, Tashman NA, Steinberg DL, Rose DT, Donovan P. Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins. Behaviour research and therapy 1999;37(6): 503–531. [PubMed: 10372466]
11. Beck, AT.; Rush, AJ.; Shaw, BF.; Emery, G. Cognitive therapy of depression. Guilford Press; New York: 1979.
12. Teasdale JD, Lloyd CA, Hutton JM. Depressive thinking and dysfunctional schematic mental models. The British journal of clinical psychology / the British Psychological Society 1998;37(Pt 3):247–257. [PubMed: 9784882]
13. Seligman, ME. Depression and learned helplessness. In: Friedman, RJ.; Katz, MM., editors. The psychology of depression: Contemporary theory and research. Winston-Willey; Washington, D.C.: 1974.
14. Nolen-Hoeksema S, Parker LE, Larson J. Ruminative coping with depressed mood following loss. Journal of personality and social psychology 1994;67(1):92–104. [PubMed: 8046585]
15. Just N, Alloy LB. The response styles theory of depression: tests and an extension of the theory. Journal of abnormal psychology 1997;106(2):221–229. [PubMed: 9131842]
16. Sullivan M, Bishop S, Pivik J. The Pain Catastrophizing Scale: Develompent and Validation. Psychol Assess 1995;7:524–532.
17. Sullivan MJ, D'Eon JL. Relation between catastrophizing and depression in chronic pain patients. JAbnormPsychol 1990;99(3):260–263.
18. Abler B, Erk S, Herwig U, Walter H. Anticipation of aversive stimuli activates extended amygdala in unipolar depression. J Psychiatr Res. 2006
19. Derbyshire SW, Jones AK. Cerebral response to pain in two depressed patients. DepressAnxiety 1998;7(2):87–88.

20. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum 2005;52 (5):1577–1584. [PubMed: 15880832]
21. Bar KJ, Wagner G, Koschke M, Boettger S, Boettger MK, Schlosser R, Sauer H. Increased Prefrontal Activation During Pain Perception in Major Depression. Biological psychiatry. 2007
22. Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP. Increased affective bias revealed using experimental graded heat stimuli in young depressed adults: evidence of “emotional allodynia”. Psychosomatic medicine. 2008
23. Bar KJ, Brehm S, Boettger MK, Boettger S, Wagner G, Sauer H. Pain perception in major depression depends on pain modality. Pain 2005;117(12):97–103. [PubMed: 16061323]
24. Dworkin RH, Clark WC, Lipsitz JD. Pain responsivity in major depression and bipolar disorder. Psychiatry Res 1995;56(2):173–181. [PubMed: 7667442]
25. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. ArchGenPsychiatry 1992;49(8):624–629.
26. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. Journal of personality assessment 1996;67(3):588–597. [PubMed: 8991972]
27. Smith TW, Christensen AJ, Peck JR, Ward JR. Cognitive distortion, helplessness, and depressed mood in rheumatoid arthritis: a four-year longitudinal analysis. Health Psychol 1994;13(3):213–217. [PubMed: 8055856]
28. Ottowitz WE, Dougherty DD, Savage CR. The neural network basis for abnormalities of attention and executive function in major depressive disorder: implications for application of the medical disease model to psychiatric disorders. Harvard review of psychiatry 2002;10(2):86–99. [PubMed: 11897749]
29. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. ProcNatlAcadSciUSA 1990;87(24):9868–9872.
30. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. ComputBiomedRes 1996;29(3):162–173.
31. Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain. Thieme; New York: 1988.
32. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn ResonMed 1995;33(5):636–647.
33. Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 2005;48(2):175–187. [PubMed: 16242399]
34. Neugebauer V. The amygdala: different pains, different mechanisms. Pain 2007;127(12):1–2. [PubMed: 17118556]
35. Nitschke JB, Sarinopoulos I, Mackiewicz KL, Schaefer HS, Davidson RJ. Functional neuroanatomy of aversion and its anticipation. Neuroimage 2006;29(1):106–116. [PubMed: 16181793]
36. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 2004;303 (5661):1162–1167. [PubMed: 14976306]
37. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 2003;126(Pt 5):1079–1091. [PubMed: 12690048]
38. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueductal gray in humans. JNeurosci 2002;22(7):2748–2752. [PubMed: 11923440]
39. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci 2005;9(5):242–249. [PubMed: 15866151]
40. Pinerua-Shuhaibar L, Prieto-Rincon D, Ferrer A, Bonilla E, Maixner W, Suarez-Roca H. Reduced tolerance and cardiovascular response to ischemic pain in minor depression. JAffectDisord 1999;56 (23):119–126.
41. Suarez-Roca H, Pinerua-Shuhaibar L, Morales ME, Maixner W. Increased perception of post-ischemic paresthesias in depressed subjects. JPsychosomRes 2003;55(3):253–257.

42. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 1998;280(5364):747–749. [PubMed: 9563953]
43. Whalen PJ, Shin LM, Somerville LH, McLean AA, Kim H. Functional neuroimaging studies of the amygdala in depression. Seminars in clinical neuropsychiatry 2002;7(4):234–242. [PubMed: 12382206]
44. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. NatRevNeurosci 2002;3(8):655–666.
45. Mayer EA, Naliboff BD, Craig AD. Neuroimaging of the brain-gut axis: from basic understanding to treatment of functional GI disorders. Gastroenterology 2006;131(6):1925–1942. [PubMed: 17188960]
46. Mesulam MM, Mufson EJ. Insula of the old world monkey. III: Efferent cortical output and comments on function. JComp Neurol 1982;212(1):38–52. [PubMed: 7174907]
47. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27(9):2349–2356. [PubMed: 17329432]
48. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. NatNeurosci 2004;7(2):189–195.
49. Gray MA, Harrison NA, Wiens S, Critchley HD. Modulation of emotional appraisal by false physiological feedback during fMRI. PLoS ONE 2007;2(6):e546. [PubMed: 17579718]
50. Paulus MP, Stein MB. An insular view of anxiety. BiolPsychiatry 2006;60(4):383–387.
51. Amorapanth P, LeDoux JE, Nader K. Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus. Nature neuroscience 2000;3(1):74–79.
52. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 2004;127(Pt 4):835–843. [PubMed: 14960499]
53. Salomons TV, Johnstone T, Backonja MM, Davidson RJ. Perceived controllability modulates the neural response to pain. J Neurosci 2004;24(32):7199–7203. [PubMed: 15306654]
54. Schneider F, Gur RE, Alavi A, Seligman ME, Mozley LH, Smith RJ, Mozley PD, Gur RC. Cerebral blood flow changes in limbic regions induced by unsolvable anagram tasks. The American journal of psychiatry 1996;153(2):206–212. [PubMed: 8561200]
55. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biological psychiatry 2006;59(9):816–820. [PubMed: 16460693]
56. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. Annals of the New York Academy of Sciences 1999;877:614–637. [PubMed: 10415674]
57. Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;120(12):8–15. [PubMed: 16364549]
58. Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. ProgBrain Res 2000;122:245–253.
59. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia--imaging a shared neuronal network. Science 2002;295(5560):1737–1740. [PubMed: 11834781]
60. Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125(Pt 2):310–319. [PubMed: 11844731]
61. Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. Pain 2004;109(3):399–408. [PubMed: 15157701]
62. An X, Bandler R, Ongur D, Price JL. Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. JComp Neurol 1998;401(4):455–479. [PubMed: 9826273]
63. Davidson RJ, Irwin W, Anderle MJ, Kalin NH. The neural substrates of affective processing in depressed patients treated with venlafaxine. AmJPsychiatry 2003;160(1):64–75.

64. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. AmJPsychiatry 1999;156(5):675–682.

65. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. BiolPsychiatry 2003;54(5):515–528.

66. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, Niehaus L, Boeker H, Northoff G. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biological psychiatry 2008;63(4):369–376. [PubMed: 17888408]

67. Kennedy SE, Koeppe RA, Young EA, Zubieta JK. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. Archives of general psychiatry 2006;63(11): 1199–1208. [PubMed: 17088500]

68. Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. Pain 2005;118(12):215–223. [PubMed: 16202520]

69. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci 2007;27(37):10000–10006. [PubMed: 17855614]

70. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain 1997;13(3):189–196. [PubMed: 9303250]

71. Wilder-Smith CH, Schindler D, Lovblad K, Redmond SM, Nirkko A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. Gut 2004;53(11):1595–1601. [PubMed: 15479679]

72. Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, Conrad B, Tolle TR. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [11C] diprenorphine PET study. Pain 2004;108(3):213–220. [PubMed: 15030940]

73. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55 (3):377–391. [PubMed: 17678852]

74. Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci 2007;25(12): 3576–3582. [PubMed: 17610577]

75. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van EDC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. ProcNatlAcadSciUSA 2005;102(27): 9673–9678.

76. Fu CH, Williams SC, Brammer MJ, Suckling J, Kim J, Cleare AJ, Walsh ND, Mitterschiffthaler MT, Andrew CM, Pich EM, Bullmore ET. Neural responses to happy facial expressions in major depression following antidepressant treatment. The American journal of psychiatry 2007;164(4): 599–607. [PubMed: 17403973]

77. Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, Andrew CM, Pich EM, Williams PM, Reed LJ, Mitterschiffthaler MT, Suckling J, Bullmore ET. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Archives of general psychiatry 2004;61(9):877–889. [PubMed: 15351766]

78. Petrella JR, Prince SE, Wang L, Hellegers C, Doraiswamy PM. Prognostic value of posteromedial cortex deactivation in mild cognitive impairment. PLoS ONE 2007;2(10):e1104. [PubMed: 17971867]

79. Walsh T. Pain Correlates of Depressed Mood in Young Adalts. Pain research & management 1998;3 (3):135–144.

80. Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. Pain 2003;106(12):101–108. [PubMed: 14581116]

81. Conner TS, Tennen H, Zautra AJ, Affleck G, Armeli S, Fifield J. Coping with rheumatoid arthritis pain in daily life: within-person analyses reveal hidden vulnerability for the formerly depressed. Pain 2006;126(13):198–209. [PubMed: 16904829]

82. Tennen H, Affleck G, Zautra A. Depression history and coping with chronic pain: a daily process analysis. Health Psychol 2006;25(3):370–379. [PubMed: 16719609]

83. van Puymbroeck, CM.; Zautra, A.; Harakas, P. Chronic pain and depression: Twhin burdens of adaptation. In: Steptoe, A., editor. Depression and physical illness. Cambridge University Press; Cambridge, UK: 2006. p. 145-164.

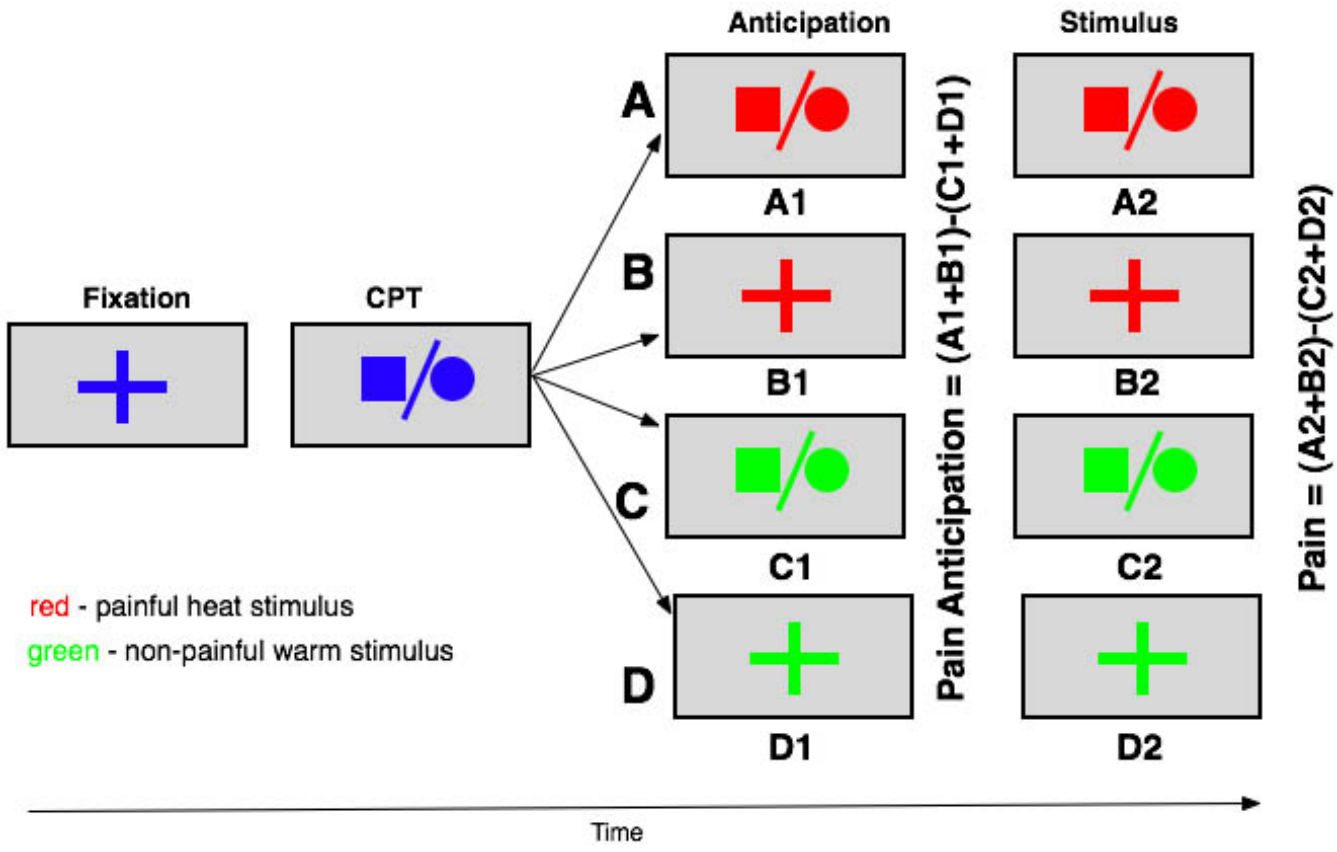

Figure 1. Experimental Paradigm

All subjects completed the paradigm in the scanner. In order to ensure similar engagement between the groups, subjects were asked to engage in the continuous performance task (CPT) [circle - LEFT, square - RIGHT button, 1 trial / 2 secs]. The stimuli change color (red - anticipate pain, green - anticipate warmth, 4-8 seconds) for the *anticipation condition*. The *stimulus condition* consists of a hot-painful or warm-non-painful stimulus for 5 seconds. The four experimental conditions are: **A.** Painful heat stimulus is given during CPT; **B.** Painful heat stimulus is given alone; **C.** Non-painful warm stimulus is given during CPT; **D.** Non-painful warm stimulus is given alone. There are two regressors of interest for each task condition **(anticipation: A1, B1, C1, D1)** and **(stimulus: A2, B2, C2, D2)**. Two linear contrasts of interest were obtained: [(A1+B1)-(C1+D1)] to examine group differences during pain anticipation; and [(A2+B2)-(C2+D2)] to examine group differences during painful stimulation.

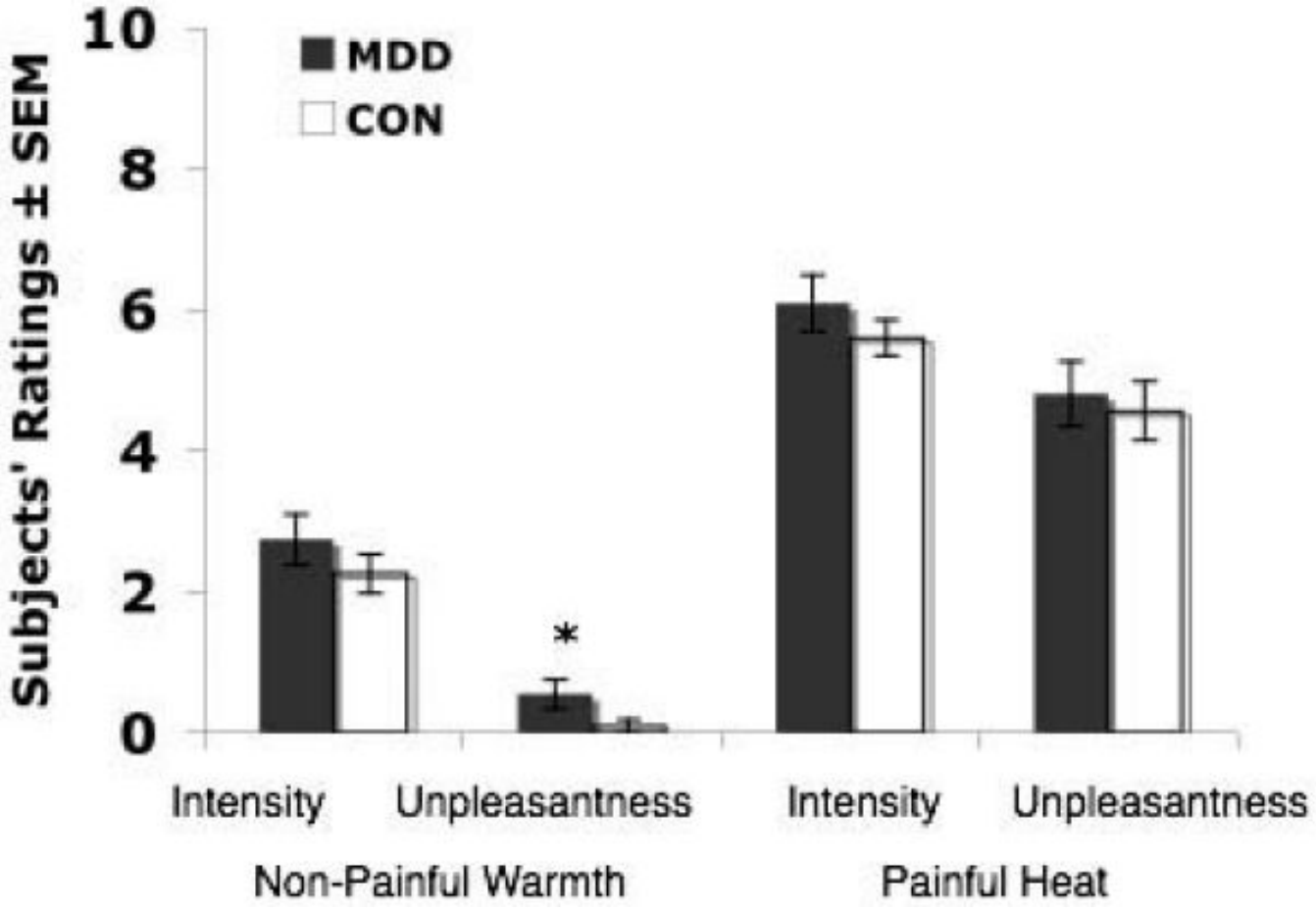

Figure 2. Average Post-Scan Subjects' Ratings of Temperature Stimuli

Subjects reported the average intensity and unpleasantness of non-painful heat and non-painful warm stimuli following each functional run to ensure similar perceptual ratings between the groups. The intensity of painful and non-painful temperatures was rated on two separate 11-point Likert scales (see Methods). No significant group differences in the subjective ratings of painful heat intensity, painful heat unpleasantness, and non-painful warm intensity were observed (p's > 0.2). MDD subjects reported higher unpleasantness ratings to non-painful warm stimuli (p=0.03).

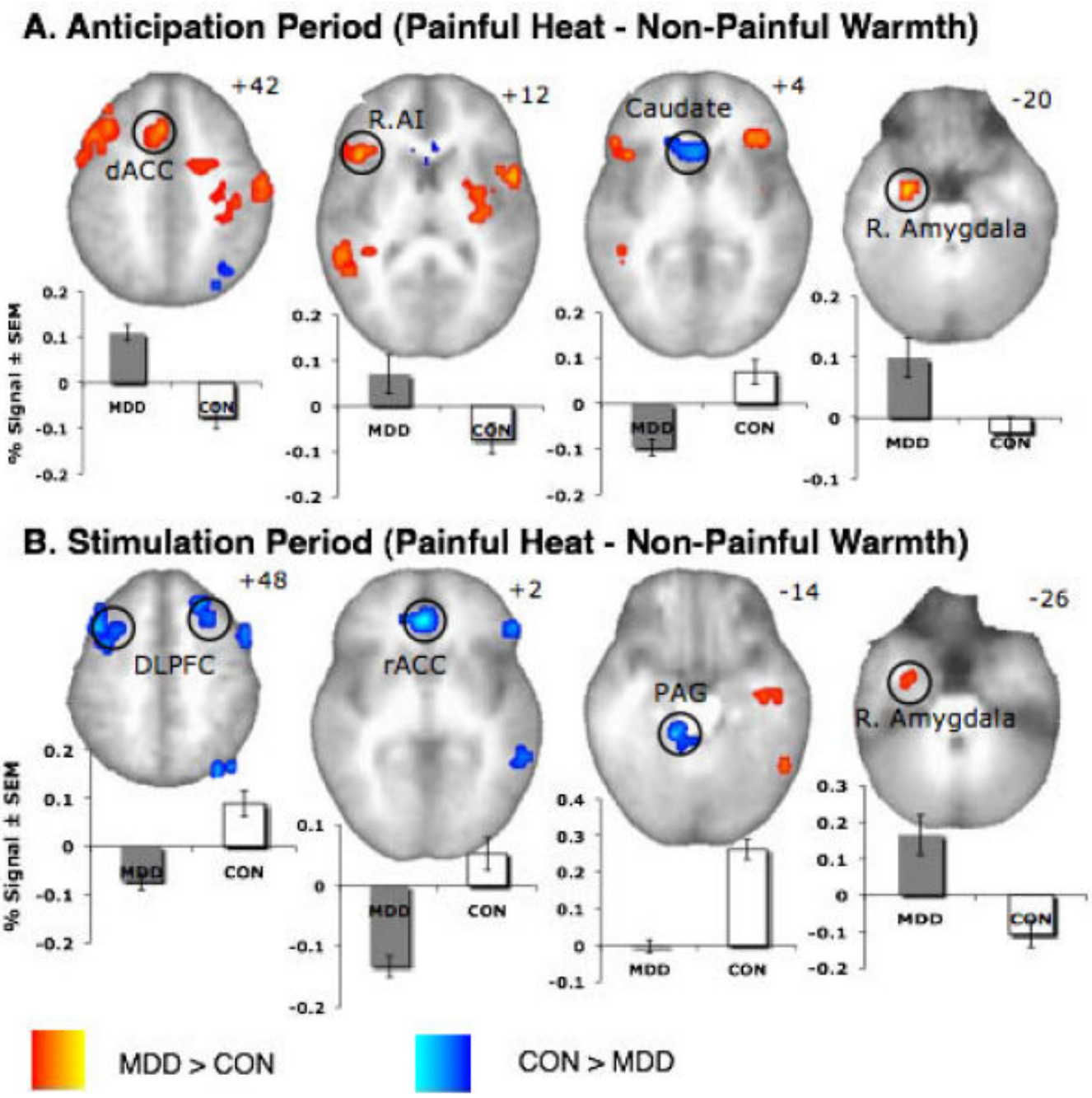

Figure 3. Significant Group Differences during Anticipation (A) and Stimulation (B) Periods

Bar graphs show % BOLD changes for the (Painful Heat - Non-painful warmth) contrast for MDD and CON groups. C.f. Table 2 for details. Images are shown in neurological orientation. dACC- dorsal anterior cingulate cortex, R. AI - right anterior insular region, DLPFC - dorso-lateral prefrontal cortex, PAG - periaqueductal grey

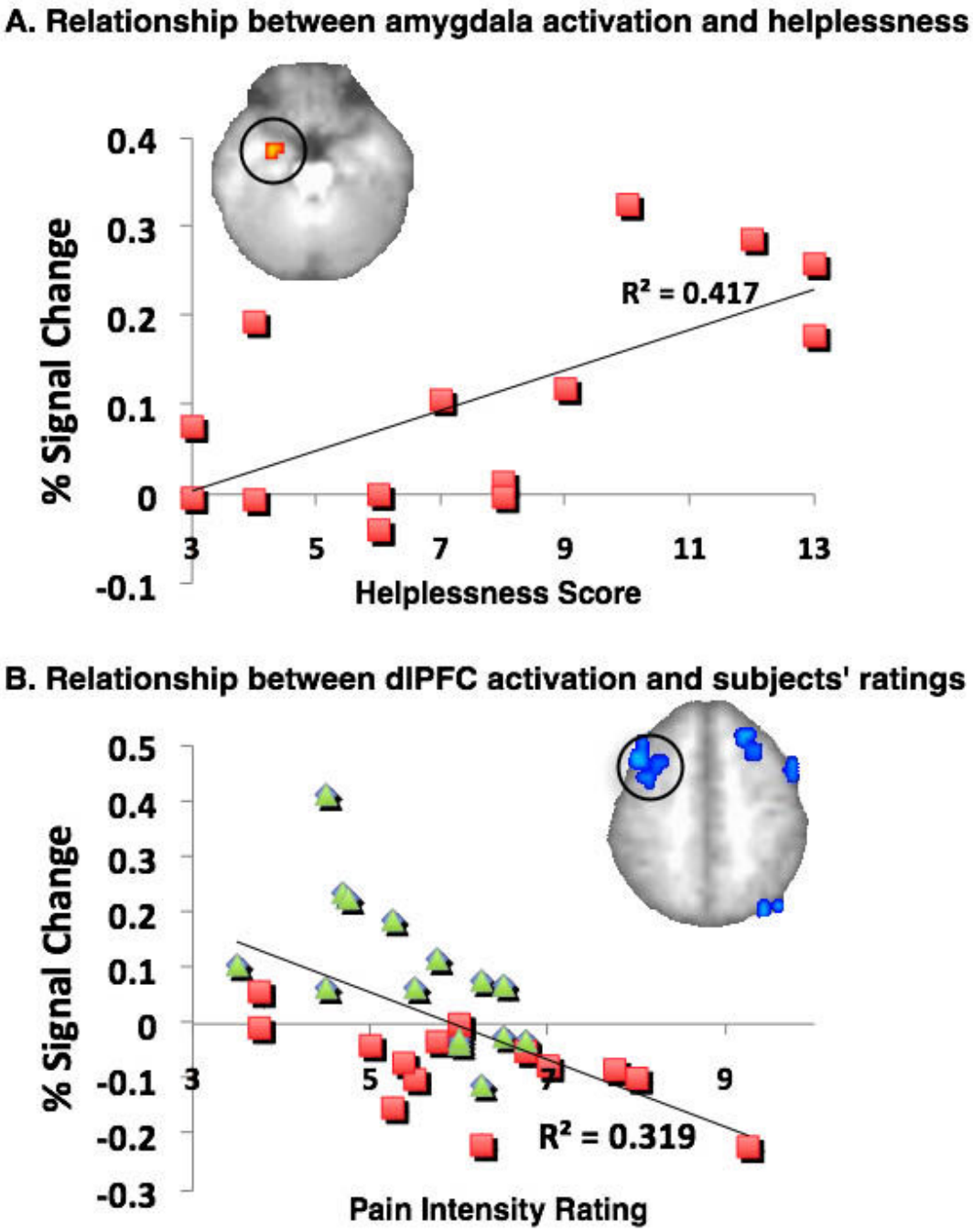

Figure 4. Brain-behavior Correlations

A) Right amygdala showed significantly higher BOLD signal change in MDD versus CON individuals during pain anticipation (c.f. Table 2 for details). Extracted % signal changes within amygdala showed significant positive correlation with helplessness scores in MDD subjects during pain anticipation ($r = 0.65$, $p < 0.05$), which was specific to this disorder; B) Right dorso-lateral prefrontal cortex (DLPFC) showed lower BOLD signal change in MDD versus CON individuals during pain experience (c.f. Table 2 for details). Extracted % signal change within right DLPFC showed significant negative correlation with post-scan subjects' ratings of pain intensity in MDD, CON and in the combined group ($r's > 0.5$, $p's < 0.05$).

Arch Gen Psychiatry. Author manuscript; available in PMC 2009 June 26.

Table 1

Patients Characteristics

ID	Sex	Age	MDD Onset	# Lifetime MDD Episodes	BDI-II	Diagnosis (DSM-IV)
1	F	20	18	3	25	MDD
2	F	19	17	2	15	MDD
3	F	19	16	3	22	MDD[1]
4	F	18	17	3	33	MDD[1]
5	F	19	16	3	18	MDD
6	M	29	13	3	43	MDD[4]
7	F	21	13	5	23	MDD
8	F	25	15	8	32	MDD[23]
9	F	24	12	9	26	MDD[34]
10	F	28	25	2	24	MDD
11	M	34	28	1	34	MDD
12	F	35	31	12	26	MDD[4]
13	M	20	18	6	30	MDD
14	F	28	11	4	26	MDD[4]
15	F	22	14	3	40	MDD

MDD = major depressive disorder; BDI-II = Beck Depression Inventory II; Comorbid lifetime (not current) diagnosis of: (1) post-traumatic stress disorder (PTSD), (2) general anxiety disorder (GAD), (3) panic disorder (PD), (4) Dysthymia;

Table 2

Subjects' Performance

	% Correct ± SEM		t-test	Reaction Times ± SEM		t-test
	MDD	CON	(p val)	MDD	CON	(p val)
CPT	92.2±2.6	97.1±1.1	1.7(0.1)	742.3±22	709±15.3	1.2(0.2)
Anticipate non-painful warmth	93±2.1	95.3±1.4	0.9(0.4)	749.5±31.9	711.3±19	1.0(0.3)
Non-painful warmth	91.6±2.7	94.8±2	0.9(0.4)	733.5±24.4	712±21.4	0.7(0.5)
Anticipate painful heat	92.8±2.6	96±1.6	1.0(0.3)	729.4±26.8	708.9±20.2	0.6(0.6)
Painful heat	93.9±2	97.1±1.5	1.3(0.2)	759.1±25.2	720±23.1	1.1(0.3)
Average	92.7±2	96.1±1.4	1.3(0.2)	742.8±25.4	712.3±18.6	1.0(0.3)

Table 3

Group Differences in Brain Activation

Brain Region	Talairach Coordinates			Volume μL	T-val
	X	Y	Z		
Pain Anticipation					
MDD > CON					
Right AI	44	22	9	832	4.3
Left AI/IFG	-32	20	16	640	4.0
Right ACC (dorsal)	10	17	41	704	3.6
Left ACC (dorsal)	-18	-2	42	768	3.5
Right DLPFC/MFG	45	12	38	2688	4.9
Left DLPFC/IFG	-34	2	21	5312	5.6
Left DLPFC/MFG	-26	33	26	832	3.7
Left IFG	-33	29	4	576	4.3
	-46	17	-7	576	3.6
Left Somatomotor/Motor	-35	-29	42	1152	5.0
	-53	-16	40	832	4.2
	-27	-20	45	512	2.9
Right STG	44	-41	13	1984	6.5
Right MTG	52	-39	-1	1280	4.3
Right Amygdala[$]	25	-2	-20	192	3.1
Visual (BA 19)	18	-55	-8	576	4.0
CON > MDD					
Right Caudate	6	22	4	1472	5.4
Right Precuneus	1	-61	34	1024	3.4
Left Precuneus	-4	-70	19	640	4.5
	-29	-69	27	3008	4.4
Ventral brainstem	4	-13	-17	512	3.2
Right PCC (BA 30)	-4	-50	21	512	3.6
Pain stimulation					
MDD > CON					

Pain stimulation					
Right Amygdala/Uncus[$]	28	-1	-28	256	2.7
Left Parahippocampal gyrus	-40	-10	-16	512	4.5
Visual (BA 19)	-51	-50	-20	512	4.0
CON > MDD					
Right ACC (rostral)	4	38	2	896	4.1
	11	41	14	640	3.5
Right DLPFC	33	11	47	2304	4.0
Left DLPFC	-44	7	45	512	3.4
	-47	35	5	512	3.9
Left SFG	-18	25	51	640	3.9
	-22	18	46	512	3.4
Left MTG	-54	-42	-1	512	3.3
Left Precuneus	-34	-70	39	1472	3.8
	-47	-51	35	896	3.6
Right PAG	10	-34	-12	704	5.6
Right Brainstem/Cerebellum	12	-38	-24	704	3.7

[$]ROI analysis; IFG - inferior frontal, MFG - medial frontal, SFG - superior frontal, MTG - medial temporal gyrus;