

Decreased frontal regulation during pain anticipation in unmedicated subjects with major depressive disorder

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Major depressive disorder (MDD) is characterized by impaired processing of negative information, possibly due to dysfunction in both, the bottom-up emotional network and top-down modulatory network. By acquiring functional magnetic resonance imaging (fMRI) on a pain-anticipation task, we tested the hypothesis that individuals with MDD would show increased negative biasing that may be associated with reduced frontal connectivity. Thirty-one (15 females) unmedicated young adults with current MDD and 22 (11 females) healthy subjects with no history of MDD were recruited. Groups did not differ significantly in age, race, level of education, marital status or gender distribution. fMRI data were collected during an event-related pain-anticipation paradigm, during which subjects were cued to anticipate painful heat stimuli of high or low intensity. All temperature stimuli were applied to each subject's left forearm. We found that relative to healthy comparison subjects, participants with MDD showed significantly stronger responses to high versus low pain anticipation within right ventral anterior insula (AI), but overlapping response within right dorsal AI, which correlated positively with the depression symptoms severity in the MDD group. Functional connectivity analyses showed increased functional connectivity between dorsal insula and posterior thalamus and decreased functional connectivity between dorsal insula and the right inferior frontal gyrus in the MDD compared with the non-MDD group. Our results demonstrate that unmedicated individuals with current MDD compared with healthy never-depressed subjects show both differential and overlapping response within AI during anticipation of pain. Furthermore, the overlapping insular response is less regulated by frontal brain systems and is more subservient to affective processing regions in the posterior thalamus in MDD. These results support and provide functional validation of the co-occurring enhanced 'bottom-up' and attenuated 'top-down' processing of salient, unpleasant emotional information in MDD.

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Introduction

Individuals with major depressive disorder (MDD) focus more on negative stimuli,^{1,2} and are less easily distracted from negative emotion processing.^{3–6} Recent evidence suggests that MDD also interferes with anticipatory processing,^{7,8} and increased negative biasing has been observed following anticipation of aversive images^{9,10} or pain¹¹ in MDD.

This negative biasing in MDD is thought to be influenced by: (1) increased 'bottom-up' response to emotional stimuli and (2) decreased 'top-down' modulation of emotion.^{12–15} Using experimental pain, we have previously found that unmedicated individuals with MDD, in comparison with healthy volunteers, showed enhanced activation within amygdala, anterior insula (AI) and anterior cingulate cortex during anticipation of painful heat versus non-painful warmth and decreased activation within dorsolateral prefrontal cortex during actual pain experience.¹¹ This is consistent with increased bottom-up processing during pain anticipation and decreased top-down control during pain experience. Influential models of MDD suggest that negative biasing in this disorder is probably due to a combination of both of these

processes,^{13,16} yet limited experimental data mechanistically links these notions. In addition, one of the main findings in our prior work was demonstration of 'emotional allodynia' in the MDD subjects, whereby stimuli that were not perceived as painful were rated as highly unpleasant by the depressed participants. Therefore, it is possible that the differences in the perceived affect of temperature stimuli in MDD and non-MDD subjects could have potentially influenced the observed group differences in brain activation during anticipation and processing of pain in our prior work. Deciphering affective biasing from group effects is needed in order to understand the mechanisms underlying negative anticipation in MDD.

Recent evidence suggests that the AI region has an important role in emotional anticipation by acting as an integrator of physiological, cognitive and emotional experiences.^{17–19} Individuals with MDD consistently show increased activation within insula during processing and anticipation of negative emotional events.^{11,20–23} Recent imaging data suggest functional subdivisions within the AI, whereby dorsal anterior portion is more involved in cognitive processing and show strong functional connections with the

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dorsal attentional stream, whereas ventromedial aspects of the insula relate more to emotional processing and show strong functional connections with amygdala.^{24,25} We have also recently shown the evidence of functional reorganization within AI in MDD, whereby emotion-related region of depressed subjects overlapped with pain-processing insular region in healthy controls.²⁶

The aim of this study was to use functional magnetic resonance imaging (fMRI) together with a validated cued pain-anticipation paradigm²⁷ in order to build on our prior evidence of dysfunctional anticipatory processes^{8,11} and functional reorganization within insula cortex in MDD.²⁶ Specifically, we directly tested the hypothesis that unmedicated individuals with MDD would show negative anticipatory biasing towards pain, which will be associated with maladaptive preparatory response within the insula, that would be related to both increased bottom-up (that is, thalamic) and decreased top-down (that is, prefrontal) response in the MDD. We aimed to directly test the current hypothesis by: (1) controlling for subjective negative biasing between the groups and (2) examining both contrast and connectivity effects.

Materials and methods

Subjects. Thirty-one unmedicated subjects with current MDD (15 females and 16 males) and twenty-two healthy subjects who never had MDD (non-MDD) (11 females and

11 males) gave written informed consent to participate in this study, which was approved by the University of California San Diego Human Research Protection Program and Veterans Affairs San Diego Healthcare System Research and Development Committee. Healthy control subjects were comparable to MDD participants on age ($t(51) = 0.35$, $P = 0.72$), race ($\chi^2 = 0.091$, $P = 0.993$), education ($t(51) = 1.0$, $P = 0.30$), and gender (Yates corrected $\chi^2 = 0.03$, $P = 0.87$) (Table 1). Subjects were recruited by using fliers at the University of California San Diego clinics, internet sites (for example, Craigslist), local papers and the word of mouth, and there was no overlap with our previously published sample.¹¹

To establish current and past psychiatric diagnoses, each subject underwent a Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders (DSM)-IV,²⁸ which was administered by trained interviewers. Diagnosis was verified by consensus with a board certified Psychiatrist (SCM). The Beck Depression Inventory-2²⁹ was administered to quantify current depressive symptom severity. Subjects were excluded from the study if they: (1) used psychotropic medication within the last 30 days; (2) fulfilled DSM-IV criteria for alcohol/substance abuse or dependence within 30 days of study participation; (3) fulfilled DSM-IV criteria for lifetime bipolar or psychotic disorder; (4) had ever experienced a head injury; (5) had clinically significant comorbid medical conditions, such as cardiovascular and/or neurological abnormality, or any active serious medical

Table 1 Demographics, clinical and psychological variables

	22 Non-MDD		31 MDD		Stats	
	Mean	s.d.	Mean	s.d.	t/χ^2	P
<i>Demographic variables</i>						
Gender	11 F	11 M	15 F	16 M	0.03	0.86
Age (years)	26.8	8.7	27.6	7.8	0.35	0.72
Education (years)	15.2	1.3	14.7	1.8	1.0	0.30
Marital status						
Married/living with partner	N=4		N=4		2.4	0.30
Single	N=18		N=24			
Separated/divorced	N=0		N=3			
Race						
African American	N=2		N=3		0.84	0.36
Asian	N=5		N=7			
Caucasian	N=10		N=13			
Other	N=5		N=8			
<i>Clinical variables</i>						
Age of MDD onset			22	7		
Number of previous episodes			2	1		
Comorbid diagnosis						
Posttraumatic stress disorder			N=3			
Generalized anxiety disorder			N=2			
Panic disorder			N=4			
Social phobia			N=2			
<i>Psychological variables</i>						
Beck Depression Inventory-2	1.1	1.9	25.5	8.4	13.0	<0.01
Post-scanner ratings ^a						
Low pain anticipation ^b	1.5	0.4	1.6	0.3	0.19	0.8
High pain anticipation	4.3	0.7	4.4	0.6	0.14	0.9
Low pain intensity ^c	1.5	0.4	2.0	0.3	0.92	0.4
Low pain unpleasantness ^c	1.3	0.4	1.6	0.3	0.55	0.6
High pain intensity	4.8	0.6	5.4	0.5	0.91	0.4
High pain unpleasantness	4.6	0.6	4.6	0.6	0.02	1.0

Abbreviations: F, females; M, males; MDD, major depressive disorder; Non-MDD, never-depressed controls.

^aMissing data in two MDD subjects. ^bScale range from 0 to 5. ^cScale range from 0 to 10 (see text for details).

problems requiring interventions or treatment; (6) had a history or current chronic pain disorder; (7) had irremovable ferromagnetic material; (8) were pregnant or claustrophobic; and (9) were left-handed. All female subjects were scanned during the first 10 days of their menstrual cycle.

Experimental pain paradigm. A validated cued pain-anticipation paradigm was used³⁰ (Supplementary Figure 1s). Briefly, the paradigm had two temporal conditions (anticipation and stimulus), with the former having three stimulus conditions (anticipation of either high pain, low pain or uninformed pain) and the latter having two stimulus conditions (high pain stimulation or low pain stimulation). Thermal stimuli, experienced as moderately (6 s; 47.5 °C; rise/fall rate 10 °C s⁻¹) and mildly (6 s; 45.5 °C; rise/fall rate 10 °C s⁻¹) painful to the subject, were delivered in a pseudo-random and counterbalanced order through a 9-cm² thermode (Medoc TSA-II, Ramat-Yishai, Israel) securely fastened to the subject's left volar forearm. Before scanning, subjects were pre-tested with several non-painful and painful temperature stimuli to ensure that temperatures were well tolerated. In the scanner, subjects were presented with a BLUE cross and were cued to anticipate 'high pain' if the color of the cross changed to RED, to anticipate 'low pain' if the color of the cross changed to GREEN and to anticipate 'uninformed pain' (either high or low pain) if the color of the cross changed to YELLOW (50% probability). Subjects were instructed that during the task they would receive several thermal heat stimulations that produce high and low pain sensations. A total of 28 (14 high pain and 14 low pain) temperatures were delivered. High temperatures were preceded by the high anticipatory cue (that is, cross changed from BLUE to RED) seven times and by the uninformed cue (that is, cross changed from BLUE to YELLOW) seven times. Likewise, low temperatures were preceded by low anticipatory cue (that is, cross changed from BLUE to GREEN) seven times and by the uninformed cue seven times.

Post-task questionnaire. To measure the subjective experience of the task, subjects completed a post-task questionnaire. The following variables were measured: (1) anticipatory anxiety (from 0—'not at all' to 5—'extremely anxious'); (2) perceived pain intensity (0—'no pain sensation' to 10—'extreme pain sensation'); and (3) perceived pain unpleasantness (from 0—'no unpleasantness' to 10—'extreme unpleasantness').

fMRI protocol. Two fMRI runs (412 brain volumes per run) sensitive to blood oxygenation level-dependent contrast were collected for each subject using 3.0 Tesla GE Signa EXCITE scanner (GE Healthcare, Milwaukee, WI, USA) (T2*-weighted echo planar imaging, TR = 1500 ms, TE = 30 ms, flip angle = 90, FOV = 23 cm, 64 × 64 matrix, 30 2.6-mm 1.4-mm gap axial slices) while they performed the paradigm described above (Supplementary Figure 1s). The fMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a high-resolution T1-weighted image (FSPGR, TR = 8 ms, TE = 3 ms, TI = 450 ms, flip angle = 12, FOV = 25 cm, 172 sagittal slices,

256 × 256 matrix, 1 × 0.97 × 0.97 mm³ voxels) was obtained for anatomical reference.

fMRI statistical analysis. All imaging data were analyzed with the Analysis of Functional NeuroImages software package.³¹ Preprocessed time-series data for each individual were analyzed using a multiple regression model corrected for autocorrelation consisting of three anticipation-related and two stimulus-related regressors, convolved with empirically derived HRF (http://afni.nimh.nih.gov/pub/dist/doc/program_help/waver.html), labeled as the Cox special. Anticipation-related regressors modeling the entire anticipation period consisted of: (1) anticipation of moderately painful heat stimulation, that is, high pain anticipation and (2) anticipation of mildly painful heat stimulation, that is, low pain anticipation. Because the uninformed cue did not contribute to our understanding of the specific mechanism of interest, this condition was modeled as a regressor of no interest in the current report, and a separate manuscript is being prepared that will explicitly examine the uninformed pain cue in a bigger sample. Stimulus-related regressors consisted of: (1) application of moderately painful heat, that is, high pain stimulation and (2) application of mildly painful heat, that is, low pain stimulation. Six additional regressors were included in the model as nuisance regressors: one outlier regressor to account for physiological and scanner noise (that is, the ratio of brain voxels outside of 2 s.d. of the mean at each acquisition), 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. To reduce the false positives induced by cross correlations of the time-series data were fit using the Analysis of Functional NeuroImages program 3dREMLfit. A Gaussian filter with a full-width half maximum of 4 mm 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.³² The primary contrast between regression coefficients for the high versus low pain anticipation was entered into one-sample *t*-test to examine within-group brain response to pain anticipation, as well as a two-sample *t*-test to examine between-group differences in brain response to pain anticipation. A threshold adjustment method based on Monte Carlo simulations was used to guard against identifying false-positive areas of activation.³³ Based on the whole-brain analysis using a 4-mm Gaussian filter, an *a priori* voxel-wise probability of $P < 0.05$ in a cluster of 768 mm³ resulted in an *a posteriori* cluster-wise probability of $P < 0.05$ (see Supplementary Information for further detail). The average percent signal changes only from clusters that survived this threshold/cluster method were extracted and used for exploratory *post-hoc* correlations. To verify task effects, the whole-brain activations within and between groups were also examined for high pain to low pain and are reported in the Supplementary Information. All *post-hoc* statistical analyses were performed with PASWStatistics 18.0 (IBM, Chicago, IL, USA).

Functional connectivity analysis. We used functional connectivity method introduced by Fox *et al.*³⁴ and a form

of psychophysiological interaction method introduced by Friston *et al.*³⁵ and adapted for the Analysis of Functional NeuroImages (<http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html>). Data were preprocessed as above with minor modifications aimed at removing nonspecific physiological signals (see Supplementary Information for details). Individual time courses in these processed raw signal data sets were extracted for the seed region of interest within right AI (rAI) (from the high versus low pain-anticipation conjunction map) and the psychophysiological interaction regressors were created for each subject (see Supplementary Information for details). Dorsal rAI was chosen as a seed because of our aim to show that despite overlapping activation within this region during the anticipation of pain in both groups, dorsal rAI was still differentially utilized within a larger network in the MDD group. A multiple linear regression model as above was run thereafter to examine connectivity of the seed region during high versus low pain anticipation. Interaction time course was used as regressor of interest. The resulting correlation coefficient for the time course of interest was calculated for each voxel. This provided correlation maps for the time course in the seed region within rAI and the time course from all other brain voxels as a function of pain anticipation. The Fisher's *z* transforms of these correlation maps were then warped to conform to the Talairach atlas³⁶ to allow for group comparisons of the Fisher's *z* transforms in rAI during high–low pain anticipation using independent two-sample *t*-tests. This assessed differences in functional connectivity in rAI during high versus low pain anticipation between MDD and non-MDD groups.

Results

Clinical measures. As indicated in Table 1, MDD subjects had significantly higher Beck Depression Inventory-2 scores consistent with moderate depressive symptoms. MDD subjects reported an average of two lifetime major depressive episodes. Non-MDD subjects had no history of MDD or other current or lifetime Axis-I psychiatric disorders. Among the MDD subjects, three male subjects met criteria for posttraumatic stress disorder, four males for panic disorder, two males for generalized anxiety disorder and two males for social phobia.

Post-task questionnaires. Subjects' ratings of their experience during the task are shown in Table 1. Repeated-measures analysis of variance with temperature (low and high) as a within-subject factor and group (MDD and non-MDD) as a between-subject factor showed no significant effect of group for either anticipatory anxiety ($F(1, 29) = 0.035$; $P = 0.892$), pain intensity ($F(1, 29) = 1.12$; $P = 0.30$) or pain unpleasantness rating ($F(1, 28) = 0.078$; $P = 0.781$). As expected, there was highly significant effect of temperature (or temperature cue), whereby high temperature resulted in higher rating of anticipatory anxiety ($F(1, 49) = 57.9$; $P < 0.000$), pain intensity ($F(1, 49) = 100.1$; $P < 0.000$) and pain unpleasantness ($F(1, 48) = 73.783$; $P < 0.000$). No significant group by temperature interactions were observed (anticipatory anxiety: $F(1, 49) =$

0.02 ; $P = 0.965$; pain intensity: $F(1, 49) = 0.12$; $P = 0.73$; and pain unpleasantness: $F(1, 48) = 0.227$; $P = 0.636$).

fMRI results

High versus low pain anticipation. Task effects (Figure 1a): Tables 2 and 3 show significant activation during high versus low pain anticipation in non-MDD and MDD subjects, respectively. Both groups showed significantly increased activation within bilateral insula, several areas within prefrontal and temporal cortices, as well as the cerebellum and decreased activation within parahippocampal gyrus.

Group effects (Figure 1a): Table 4 shows significant between-group differences in brain activation during high versus low pain-anticipation contrast. MDD relative to non-MDD subjects showed increased activation within right ventral AI, left middle frontal gyrus, left cingulate and left superior temporal gyrus, whereas they showed decreased activation within right dorsolateral prefrontal and right orbitofrontal cortices.

Conjunction: In order to examine in more detail pain anticipation-related insula activation, we performed conjunction analyses (Figure 1b). Both groups showed significant activation within dorsal rAI during high versus low pain anticipation, yet activation within the MDD group was more ventral and posterior. The area within dorsal AI of significant overlap between the two groups showed positive correlation with the Beck Depression Inventory-2 scores in the MDD group ($\rho = 0.40$; $P < 0.05$). This area was used as a seed for functional connectivity analyses in order to examine differences in recruited networks between the two groups.

Functional connectivity results. Using the dorsal rAI time series during high versus low pain anticipation from the conjunction map (see above) as a seed, four regions showed significant between-group differences in functional connectivity (Figure 2a, Table 5). Compared with healthy controls, right posterior thalamus and right middle prefrontal cortex (MPFC) showed increased connectivity, whereas right inferior frontal gyrus (rIFG) and cerebellum showed decreased connectivity during anticipation of pain in the MDD group.

Exploratory brain-behavior correlations. Prior literature by our group and others has shown that pain-related dorsolateral prefrontal cortex activation shapes pain experience.^{11,37,38} We therefore performed exploratory correlations between the strength of connectivity between dorsal AI and rIFG with the post-scan subjective pain rating (averaged across low and high pain) in both groups. Because both of the stimulations used in this study were painful and unpleasant (see Table 1), averaging across low and high pain was an optimal available proxy to the subjective experience in our subjects. A significant negative correlation was observed in the non-MDD group, whereby those subjects with the strongest connections between dorsal insula and rIFG during anticipation of pain provided the lowest pain intensity ($\rho = -0.43$; $P < 0.05$) and pain unpleasantness ($\rho = -0.41$; $P = 0.05$) rating (Figure 2b). Interestingly, this relationship was not evident in the MDD group who showed nonsignificant relationship between dorsal insula

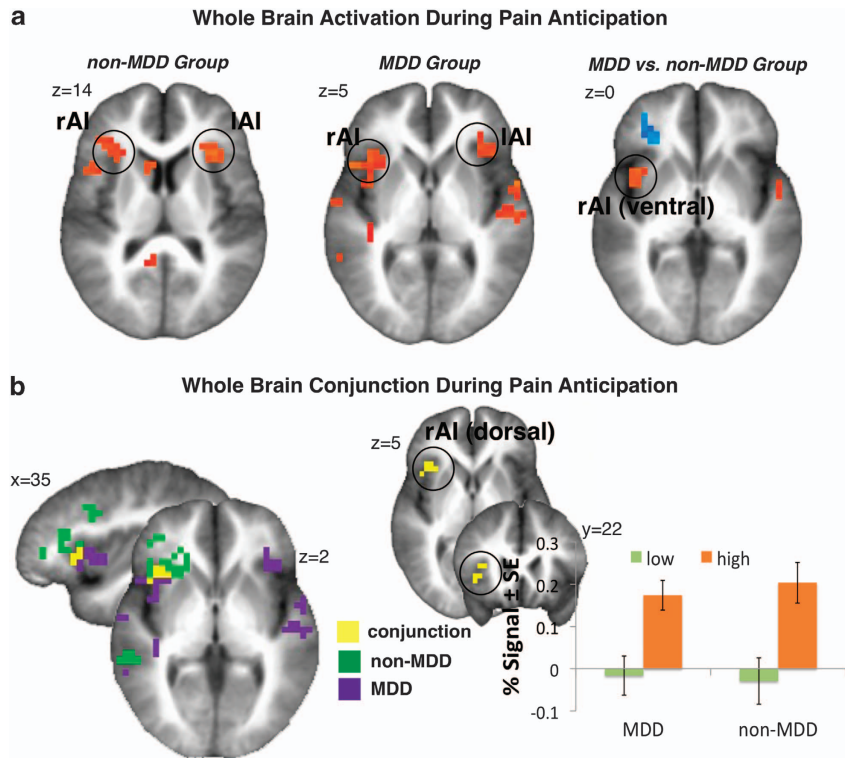


Figure 1 Whole-brain significant task effects. (a) Significant whole-brain analysis of high versus low pain anticipation in the non-MDD (left), MDD (middle) and between-group contrast (right) showed increased bilateral dorsal AI activation in both groups and increased activation within ventral portion of the rAI in MDD (see Tables 2–4 for further details). (b) Whole-brain conjunction of high versus low pain anticipation in MDD (purple) and non-MDD (green) groups showed significant overlap (yellow) in right dorsal AI (x/y/z: 37/21/5, 512 mm³). Bar graphs indicate percent signal change within right dorsal AI during anticipation of low and high pain in MDD and non-MDD group. Left = Right. Non-MDD, healthy, never-depressed controls.

Table 2 High–low pain anticipation: non-MDD group whole brain

Brain region	Volume	x	y	z	Stat
<i>High > low pain anticipation</i>					
R. insula/IFG (BA 45)	5184	32	28	6	2.66
L. insula (BA 13)	1216	-35	21	14	2.53
R. IFG (BA 9)	1792	48	15	24	2.68
R. MFG (BA 9)	1408	41	12	34	2.72
R. IPL (BA 40)	2752	53	-46	32	2.61
L. cingulate (BA 23)	1472	-1	-38	24	2.63
R. MTG (BA 22)	1216	54	-38	3	2.68
R. STG (BA 22)	1024	48	-19	-5	2.52
R. caudate	768	11	9	11	2.83
Cerebellar vermis	768	-3	-29	-12	2.84
L. cerebellar tonsil	896	-38	-46	-37	2.45
<i>Low > high pain anticipation</i>					
R. parahippocampal gyrus	832	26	-30	-13	2.73
L. precentral gyrus	768	-49	-13	31	2.46

Abbreviations: BA, Brodmann area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L., left; MFG, medial frontal gyrus; MTG, medial temporal gyrus; non-MDD, never-depressed controls; R., right; STG, superior temporal gyrus.

and rIFG connectivity and pain intensity ($\rho = 0.17$; $P = 0.35$), as well as pain unpleasantness ($\rho = 0.07$; $P = 0.65$) rating. Furthermore, the between-group difference in the strengths of these correlations was significant for pain intensity ($z = -2.16$; $P < 0.05$) and approached significance for pain unpleasantness ($z = -1.72$; $P = 0.08$) rating. We also explored whether anticipatory insula activation, and the

Table 3 High–low pain anticipation: MDD group whole brain

Brain region	Volume	x	y	z	Stat
<i>High > low pain anticipation</i>					
R. insula (BA 13)	2688	37	16	5	2.62
L. insula (BA 13)	1920	-38	18	10	2.66
L. IFG (BA 47)	960	-37	26	2	2.95
R. precentral gyrus	768	55	-12	10	2.39
L. precentral gyrus	832	-57	-5	6	2.45
R. thalamus	960	3	-11	18	2.48
R. STG (BA 22)	2688	45	-29	-1	2.64
L. STG (BA 21)	1472	-54	-17	0	2.64
L. culmen (BA 30)	1216	-9	-32	-7	2.61
<i>Low > high pain anticipation</i>					
R. parahippocampal gyrus	960	39	-25	-22	2.41

Abbreviations: BA, Brodmann area; IFG, inferior frontal gyrus; L., left; MDD, major depressive disorder; R., right; STG, superior temporal gyrus.

connections between dorsal insula and thalamus, as well as dorsal insula and MPFC, related to subjective pain experience (both average and the difference in the perceived pain were examined). None of these correlations were significant ($-0.25 < \rho < 0.25$; $P > 0.05$).

Discussion

One of the main findings of our study was that during anticipation of high pain compared with anticipation of low

Table 4 High–low pain anticipation: between-group differences whole brain

Brain region	Volume	x	y	z	Stat
MDD > non-MDD					
R. ventral anterior insula	832	40	6	3	2.45
L. MFG (BA 8)	832	-18	31	38	2.45
L. cingulate gyrus (BA 31)	1216	-20	-36	23	2.56
L. STG (BA 22)	896	-52	-1	-3	2.59
Non-MDD > MDD					
R. MFG (BA 47) (dlPFC, OFC)	1472	32	37	-2	2.46
R. MFG (BA 9, dlPFC)	896	43	12	34	2.61

Abbreviations: BA, Brodmann area; dlPFC, dorsolateral prefrontal cortex; L., left; MDD, major depressive disorder; MFG, medial frontal gyrus; non-MDD, never-depressed controls; OFC, orbitofrontal cortex; R., right; STG, superior temporal gyrus.

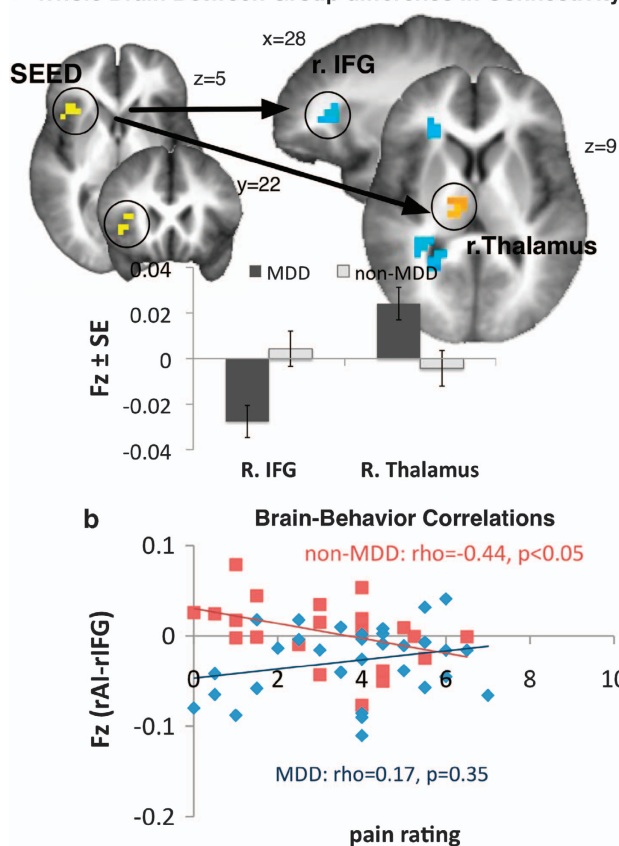
a Whole Brain Between Group difference in Connectivity

Figure 2 Whole-brain functional connectivity with dorsal insula. (a) Whole-brain between-group difference in functional connectivity using right dorsal AI (from the conjunction map) as a seed region (left) showed stronger rAI–rIFG connectivity in the non-MDD group and stronger rAI–thalamus connectivity in the MDD group during high versus low pain anticipation (see Table 5 for details). Bar graphs indicate Fisher's z transformations of the r values (F_z). (b) Significant negative correlation was found between the strength of functional connectivity between right dorsal AI and rIFG and subjective pain experience in the non-MDD group (red), whereby those subjects with strongest connections between rAI and rIFG during anticipation of pain provided lowest pain intensity ($\rho = -0.43$; $P < 0.05$) and pain unpleasantness ($\rho = -0.41$; $P = 0.05$) (not shown) rating. This relationship was not evident in the MDD group (blue) who showed nonsignificant relationship between rAI–rIFG connectivity and pain intensity ($\rho = 0.17$; $P = 0.35$), as well as pain unpleasantness ($\rho = 0.07$; $P = 0.65$) (not shown) rating. Furthermore, the between-group difference in the strengths of these correlations was significant for pain intensity ($z = -2.16$; $P < 0.05$) and approached significance for pain unpleasantness ($z = -1.72$; $P = 0.08$) rating.

Table 5 Functional connectivity with rAI: between-group differences whole brain

Brain region	Volume	x	y	z	Stat
MDD > non-MDD					
R. posterior thalamus	576	10	-16	7	2.2
R. medial prefrontal cortex	576	0	45	38	2.3
MDD < non-MDD					
R. IFG	768	25	29	10	2.4
R. cerebellum	1152	29	-56	-41	2.4
	576	15	-79	-36	2.3

Abbreviations: IFG, inferior frontal gyrus; L., left; MDD, major depressive disorder; non-MDD, never-depressed controls; rAI, right anterior insula; R., right.

pain, the rAI activation differed in MDD compared with healthy subjects who never had MDD. We found that ventral insula was more strongly activated by the MDD group during anticipation of pain, whereas both groups similarly activated the dorsal insula. Furthermore, we found that despite similar recruitment of the dorsal insula by both groups, this region showed positive correlation with depressive symptom severity and stronger connectivity with posterior thalamus in our MDD subjects. Conversely, in the non-MDD group, dorsal insula was more strongly connected to the IFG, and the strength of this connection was inversely related to subjective pain experience in these subjects. Taken together, these results provide functional validation for the co-occurring enhanced 'bottom-up' and attenuated 'top-down' processing of salient, unpleasant emotional information in MDD.¹³

Besides segregated anatomical regions within the insular cortex,^{39,40} several lines of evidence also clearly show that the insula is subdivided into several functional domains.¹⁷ In addition, meta-analyses based on published fMRI and positron emission tomography studies suggest that even within AI, that is, a region just anterior to the central sulcus of the insula, the processing of emotionally laden stimuli is represented in several regions.^{26,41} Studies that examine cognitive aspects of emotional processing (for example, appraisal) find the peak coordinates in more dorsal aspects,^{26,41} whereas studies that examine more visceral response associated with emotional experience (for example, heart rate and galvanic skin response) find the peak coordinates in more ventral aspects of the AI.⁴² This ventral insula is thought to integrate emotionally salient information from all sensory modalities with subcortical homeostatic control centers (amygdala and hypothalamus)^{17,19,43,44} and is also the site of insular co-activation with the amygdala and pregenual anterior cingulate.^{25,42,45,46} Therefore, increased activation within ventral insula in MDD during anticipation of pain found here is consistent with increased visceral response to salient cues in this disorder,¹³ and more intense affective experience.⁴⁵

We also found that dorsal AI was similarly active between the two groups during anticipation of heat pain in our study. This dorsal insula is more involved in cognitive processing.^{18,26,41,45,47–49} Although both groups activated this region similarly, several results in the current study point to differential utilization of this region by the two groups. First, this warning signal was related to greater depressive

symptomology in the MDD group, potentially, underlying increased hopelessness that can follow ineffective coping with salient cues in depressed individual.⁵⁰ Second, this region showed differential connectivity. Specifically, we found that dorsal insula was more strongly connected to the rIFG in healthy volunteers than in our MDD subjects. This pattern of connectivity in healthy subjects is consistent with several recent functional^{24,25,45,47,51} and anatomical⁴⁶ studies. For example, Peltz *et al.*⁵¹ found that during pain, right dorsal insula is connected with the prefrontal cortex, whereas Deen *et al.*²⁵ found that during resting state, dorsal aspects of the rAI are connected with the rIFG. This is also consistent with Cauda *et al.*²⁴ who found that dorsal insula is working together with the attentional network, which is critical for cognitive control of emotion, and the rIFG is a key factor in this network,⁵² and with Cerliani⁴⁶ who found that dorsal insula has strong anatomic connections with the IFG. Taken together, these findings suggest that healthy, never-depressed subjects showed adaptive emotional response during pain anticipation, whereby they engaged frontal control network as evidenced by increase in connectivity between dorsal insula and rIFG in order to modulate the unpleasant experience of the upcoming pain. This adaptive and effective mechanism or 'healthy' pain anticipation is further supported by our exploratory correlations, whereby significant negative relationship between the strength of this connection and subjective pain experience was observed only in the non-MDD subjects. Although biases in retrospective recalls cannot be ruled out, these findings are in direct agreement with prior literature^{37,53,54} and suggest that through greater frontal regulation healthy volunteers can modulate their subjective pain experience. This potential top-down control mechanism was diminished in our MDD group who employed different resources to regulate their subjective experience.

In the MDD group, the right posterior thalamus showed increased connectivity with dorsal insula. Specifically, this region lied within the medial dorsal nucleus and spanned from ventromedial to the pulvinar nuclei in the anterior-posterior direction. MDD has been associated with abnormalities within thalamus,^{55–57} particularly, within mediodorsal thalamus⁵⁸ and pulvinar.¹³ The region of the thalamus observed in our study is known to project to the anterior agranular insula^{40,59} and to the anterior cingulate⁴⁴ and is highly interconnected with the amygdala.⁶⁰ The pulvinar shows similar anatomical connections to amygdala^{61,62} and the anterior cingulate.⁶³ These connections are believed to relay salient emotional information about the environment to the limbic system.⁶⁴ Strong functional connections between the AI and the thalamus⁶⁵ are consistent with the cytoarchitecture and paralimbic emotional salience processing.⁶⁶ Therefore, the heightened connectivity between dorsal insula and the thalamus during anticipation of pain in MDD points to increased bottom-up emotional response to aversive stimulation in this disorder. This fits recent findings showing that increased activation within rAI and this region of the thalamus was modulated by anxiety sensitivity during threat anticipation.⁶⁷ Increased connectivity between dorsal insula and dorsal MPFC observed in the MDD group further strengthens this interpretation. Specifically, recent reviews of functional neuroimaging studies on fear conditioning attributed

activation within MPFC to conscious appraisal of threat⁶⁸ or expression of fear and anxiety.⁶⁹ Therefore, increased connectivity between dorsal insula and MPFC in the MDD subjects during pain anticipation observed here was likely related to the initial response formation to the pain cue. Alternatively, increased bottom-up (that is, thalamic) response in MDD could, in part, be counterbalanced by greater top-down response within MPFC; this could potentially explain the lack of significant between-group difference in dorsal insula in our study. Taken together, the co-occurrence of the increased bottom-up and reduced top-down regulation during anticipation of pain that we observed here may underlie heightened somatic complaints⁷⁰ and increased negative biasing⁷¹ in MDD.

This study had several limitations. Although the sample size is moderately large for an imaging study, a larger sample may help with the differentiation of functional subregions within the insula. Furthermore, we used brief experimental heat pain as a model for inducing acute pain and distress. Even though insula has an integral role in both acute and chronic stress and pain conditions,^{20,72,73} further studies are needed to determine generalizability of these findings to more chronic situations. Importantly, the experimental paradigm was designed to focus on the neural process during cued anticipation of pain and to compare this neural process on both contrast and connectivity levels between the groups. Although using explicit cuing and contrasting two painful stimuli minimized possible group differences in expectation biases, fear conditioning⁷⁴ and/or learning, their contribution cannot be completely ruled out. Related to these concerns is also the fact that a cue influences the subsequent stimulus appraisal. Therefore, because of the known temporal biasing effects in depression, the interpretation of the pain findings in the current paradigm must not be overgeneralized to cases of uncued pain. Furthermore, we opted not to use in scanner ratings of subjective pain experience. Although implementation of a behavioral measure within the task could have potentially strengthened our interpretations, preparing to and making decisions about pain may also interfere with neural process of emotional anticipation.⁷⁵ In addition, although prior research has shown that average within- and post-scan pain ratings do not differ significantly,⁷⁶ retrospective ratings are subject to several types of response bias (for example, averaging and forgetting), which very well may differ between MDD and non-MDD subjects. The use of retrospective ratings could also have contributed to the lack of significant correlations between AI activation and subjective pain experience in our study. However, considering that the neural process, and also the subjective emotional experience, may not necessarily be reflected by observable behavior, we focused on the neural process of pain anticipation in the current design. Finally, we selected a group of non-medicated younger adults in this study to allow for as few confounds in understanding the underlying neural substrates in relation to depression. However, this may limit the generalizability of this sample to complicated, aging or medicated samples.

In summary, our data show increased ventral AI activation during pain anticipation in unmedicated subjects with MDD. This result is consistent with prior work describing maladaptive anticipatory response to salient emotional cues in this

disorder. Furthermore, our functional connectivity data demonstrate the co-occurrence of the increased 'bottom-up' and decreased 'top-down' neural response during pain anticipation in MDD. These connectivity results provide mechanistic validation for several influential models of MDD.^{13,16,77} Taken together, our findings improve understanding of how MDD may affect 'mind-body' connections and increase vulnerability for developing pain-related conditions.⁷⁸

Conflict of interest

The authors declare no conflict of interest.

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