Neural Responses to Sad Facial Expressions in Major Depression Following Cognitive Behavioral Therapy

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Background: Affective facial processing is an important component of interpersonal relationships. The neural substrate has been examined following treatment with antidepressant medication but not with psychological therapies. The present study investigated the neural correlates of implicit processing of sad facial expressions in depression pretreatment and posttreatment with cognitive behavioral therapy (CBT).

Methods: The patient group consisted of 16 medication-free subjects (mean age 40 years) with a DSM-IV diagnosis of acute unipolar major depression, and the comparison group were 16 matched healthy volunteers. Subjects participated in a prospective study with functional magnetic resonance imaging (fMRI) at weeks 0 and 16. During the fMRI scans, subjects performed an affect recognition task with facial stimuli morphed to display varying intensities of sadness. Patients received 16 sessions of CBT. Functional magnetic resonance imaging data were analyzed for the mean activation and differential response to variable intensity (load-response) of facial affect processing.

Results: During an acute depressive episode, patients showed elevated amygdala-hippocampal activity relative to healthy individuals. Baseline dorsal anterior cingulate activity in patients showed a significant relationship with subsequent clinical response.

Conclusions: These data provide further support for elevated amygdala activity in depression and suggest that anterior cingulate activity may be a predictor of treatment response to both pharmacotherapy and CBT.

Key Words: Amygdala, anterior cingulate, cognitive behavioral therapy, depression, fMRI, sad facial expressions

Major depression is characterized by impairments in affect, behavior, and cognition. Cognitive behavioral therapy (CBT) considers the interrelationship of each factor in the maintenance of depression and attempts to intervene in the vicious cycle of low mood, social withdrawal, and negative thinking style (1). Cognitive behavioral therapy and pharmacotherapy are both effective treatments for acute depressive episodes with comparable response rates (2), and there is some evidence that CBT may have greater efficacy than antidepressant medications in preventing a relapse (3,4). However, the neurobiological mechanisms of CBT are poorly understood.

Neuroimaging studies of depression have largely focused on pharmacological treatments (5). In resting state studies, antidepressant therapy has been associated with decreased limbic activity and increases in dorsal cortical activity (6–9). Using experimental tasks to more directly engage affective processing, functional magnetic resonance imaging (fMRI) studies have reported excessive amygdala activation to negatively valenced stimuli in acutely depressed patients (10–13), which normalizes following antidepressant treatment (10,12). Identifying neurobiological predictors of clinical response is an important potential of longitudinal neuroimaging studies. Of particular note is the anterior cingulate cortex, as its strength of activation during an acute episode has been associated with an improved clinical response to antidepressant therapy (6–9,11,12).

Few studies have conducted psychotherapy treatment trials in depression with serial neuroimaging assessments (14,15). Initial studies examined interpersonal psychotherapy (IPT), a time-limited therapy with a focus on individual relationships and social networks (16). Martin *et al.* (15) observed greater posterior cingulate and basal ganglia activation following 6 weeks of IPT, while Brody *et al.* (14) reported decreases in activation in the anterior cingulate and right prefrontal cortices and increases in the insula and temporal regions after 12 weeks of therapy. Few consistencies are evident from these data, although patient clinical response rates and timeframes of the follow-up scans differed substantially. More recently, there have been two prospective trials with CBT (17,18). In a resting state positron emission tomography (PET) study, Goldapple *et al.* (17) found increased activity in the dorsal anterior cingulate and hippocampus and decreased activity in the prefrontal cortices following CBT, an inverse pattern of response to that observed with antidepressant treatment. However, no regions at the pretreatment scan were reported as showing an association with clinical response. In an fMRI study, Siegle *et al.* (18) focused on baseline predictors of treatment response to CBT. In response to negative adjectives, attenuated activity in the subgenual anterior cingulate and increased activity in the right amygdala were associated with an improved clinical outcome following CBT. Neural effects of CBT though were not described, as subjects did not have a follow-up scan.

In the present study, patients with unipolar depression underwent magnetic resonance imaging (MRI) scans during an acute episode and following CBT, and healthy volunteers had the same scans at the same time points. Subjects performed an fMRI task as reported with a separate group of patients who received treatment with antidepressant medication (12). The task

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sought to engage implicit processing of sad facial expressions, as impairments in affective processing are evident in depression and may contribute to interpersonal difficulties (19,20).

A key neuropsychological impairment in depression is a mood-congruent processing bias in which ambiguous or positive events are experienced as negative (1). With emotional facial expressions, patients in an acute depressive episode show a negative bias, as they tend to misperceive happy faces as being neutral and neutral faces as being sad (20). A persistence of such a bias during clinical remission is associated with vulnerability for future episodes (21). The neural circuitry is postulated to consist of a core system responsible for initial visual processing of facial features and an extended system for processing additional features, such as emotional expressions (22). Core regions include the fusiform face area in the occipitotemporal cortex, which shows a selective engagement for faces, and the superior temporal sulcus, which is responsive to mouth and eye movements, while the extended system for affective processing includes the amygdala, which is reactive to stimuli of high emotional salience (22). Affective evaluation of facial expressions appears to occur initially at an implicit level (23) prior to explicit judgments of the type or intensity of affect (24), and attentional processing of affective judgments modulates amygdala activity (25).

We expected that patients in an acute depressive state would show greater amygdala activation relative to healthy control subjects (10,12,13). Our hypothesis of the effect of CBT on amygdala activity was more provisional. Following antidepressant therapy, attenuation of abnormally elevated amygdala activity has been observed (10,12), but changes in its activity have not been reported following treatment with IPT or CBT (14,15,17,18). As a neural marker of treatment response, anterior cingulate activation during the acute depressive episode has consistently been associated with patient outcome with pharmacotherapy (6–9,11,12) and reported with CBT (18). If anterior cingulate activity is a marker of clinical response irrespective of the treatment modality, we also expected an association with clinical improvement with CBT.

Methods and Materials

Subjects

The study was approved by the Institute of Psychiatry and South London and Maudsley (SLAM) National Health Services (NHS) Ethics Research Committee. Seventeen participants (14 women) meeting DSM-IV criteria for major depressive disorder by Structured Clinical Interview for DSM-IV (SCID) (26) and clinical interview with a psychiatrist were recruited through local newspaper advertisements. Inclusion criteria were an acute episode of major depressive disorder, unipolar subtype (27), and a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (HRSD) (28). Exclusion criteria were a history of neurological trauma resulting in a loss of consciousness, a current neurological disorder, history of diabetes or medical disorder, other Axis I disorder including an anxiety disorder, or history of substance abuse within 2 months of study participation. All patients were free of psychotropic medication for a minimum of 4 weeks at recruitment (8 weeks for fluoxetine) and remained medication-free throughout the treatment. Sixteen depressed patients (13 women; mean age 40.0 years [SD = 9.4]) completed the study, as one subject had a geographical relocation shortly following the initial scan. Sixteen age, gender, and IQ-matched healthy comparison subjects with HRSD scores less than 8 (13 women; mean age 39.2 years [SD = 9.3]) and no history of any psychiatric disorder, neurological disorder, or head injury resulting in a loss of consciousness were recruited by advertisement from the local community (Table 1). All participants provided written, informed consent.

Table 1. Demographic and Clinical Characteristics of the Sample

	Healthy Control Subjects (n = 16)	Depressed Patients (n = 16)
Mean Age	39.2 years (9.3)	40.0 years (9.4)
Gender M:F	3:13	3:13
Mean Duration of Current Episode	NA	1.64 years (range .2–4 years)
Mean Number of Treatment Trials for Current Episode	NA	.13 (range 0–1 trials)[a]
Number of Previous Episodes	NA	.63 (range 0–2)[b]
Mean Age of Onset	NA	33.8 years (range 18–53 years)
Mean IQ		
Full	123.8 (10.9)	116.6 (16.4)
Verbal	121.1 (12.2)	115.8 (19.3)
Performance	122.3 (11.7)	114.4 (14.1)
Mean HRSD Score		
Week 0	.3 (.7)	20.9 (1.9)
Week 16	.6 (1.2)	6.4 (5.2)
Mean BDI Score		
Week 0	2.9 (3.9)	38.0 (11.7)
Week 16	2.0 (2.3)	14.5 (15.4)

Mean values and standard deviations are presented in parentheses, unless otherwise stated.

BDI, Beck Depression Inventory; F, female; HRSD, Hamilton Rating Scale for Depression; IQ, intelligence quotient; M, male; NA, not applicable.

[a]Three patients had medication treatment trials for their current episode.

[b]Four patients had treatment trials with antidepressant medication for previous depressive episodes.

Treatment

Patients received 16 sessions of CBT with experienced therapists (C.D., H.S., or B.S.). All sessions were audiotaped and/or reviewed in supervision to ensure the CBT followed the standard format (1) and that the therapists met the required level of competency (3). Patient progress was monitored regularly with the Beck Depression Inventory (29) and at baseline and following the course of CBT with the HRSD (28).

Experimental Design

The first neuroimaging session served to acquire a structural MRI for neuroradiological examination and to familiarize subjects with the scanning environment. The additional sessions consisted of fMRI scans of 60 to 90 min total duration at baseline or week 0 and upon study completion after 16 weeks. Each session consisted of a number of paradigms, including the same sad faces task in our fluoxetine treatment study (12) as the final task to prevent any residual effects of a possible negative mood state (30).

Implicit Sad Facial Affect Recognition Task

Ten faces from a standardized series (31) were morphed to represent three intensities of sadness: low, medium, and high. Facial stimuli and baseline trials (crosshair fixation point) were presented in random order in an event-related fMRI design on a neuro-optimized 1.5 Tesla IGE LX System (Maudsley Hospital, SLAM NHS Trust, London, United Kingdom). For each facial trial,

subjects were asked to indicate the gender of the face (male or female) by lateral movement of a joystick (Table 4 in Supplement 1); no hand movement was required in the baseline trials. A full description of the MRI acquisition details is presented in Supplement 2.

fMRI Data Analysis

Factorial effects of interest were identified with a 2 × 2 analysis of variance (ANOVA) model (12): main effect of group (patients vs. healthy control subjects at both time points), main effect of time (week 0 vs. week 16), and a group × time interaction for each measure of mean overall activation, i.e., response elicited between baseline trials and all facial trials, and facial processing load-response, i.e., the linear trend between facial trials at low, medium, and high intensities of sadness (described in full in Supplement 1).

As we expected greater amygdala activity at baseline in patients relative to control subjects, the main effect of group at week 0 was also examined at a threshold of $p = .05$ corrected for multiple comparisons, which revealed greater right amygdala activity in patients compared with control subjects. Interaction effects in the right amygdala were examined by extraction of the activity of this functional region of interest for each group at weeks 0 and 16.

To identify brain regions associated with within-group symptomatic response at baseline, the percentage change in HRSD score for each patient after 16 weeks of treatment was regressed onto the mean overall and linear load-response activity at week 0. Percentage reduction in HRSD was used as a measure of clinical improvement because there were no significant correlations in depression severity at baseline and at follow-up (measured by HRSD).

Results

Clinical Responses

All 16 patients completed the full treatment course of CBT (Table 1). Their mean HRSD showed a decrease of 69.5% (SD = .2) ($F = 118.45$, $df = 1,15$; $p < .001$). Thirteen patients (81.2%) met a 50% decrease in HRSD criteria for a full clinical response, although only 9 (56.3%) of the 16 patients met criteria for full remission with a final HRSD ≤7.

Table 2. Interaction Effect of Group by Time in Mean Overall Activity

Cerebral Region	BA	Cluster Size (Voxels)	Talairach Coordinates (mm) x	y	z
Cingulate Gyrus					
Anterior	24/32	439	−12	29	8
			−11	26	40
Middle	33/24	125	−14	−2	24
			−13	−1	28
	31/24	22	22	−9	35
			21	−13	45
Posterior	31	33	17	−34	40
Middle Frontal Gyrus	8	13	−25	26	40
			−25	26	45
Superior Frontal Gyrus	8	37	3	30	45
			0	29	50
		46	−11	28	45
			−16	28	50
Inferior Parietal Cortex	40	116	29	−48	40
			23	−39	45
Precuneus	7	171	10	−53	40
			17	−36	50

BA, approximate Brodmann area.

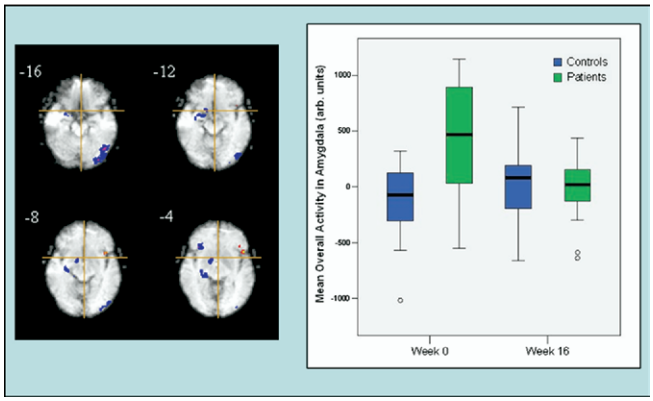

Figure 1. Two-dimensional representative slices are presented for the main effect of group at week 0, revealing greater right amygdala activity in patients relative to control subjects (extending from Talairach coordinates [x, y, z] [27, −7, −16] to [13, −5, −8]). Additional effects were evident in the parahippocampal gyrus, putamen, and inferior occipital cortex. Transverse views are presented in radiological convention with the right side of the brain on the left, extending from z-coordinates of −16 to −4 in standard Talairach coordinates. The box plot illustrates the mean overall activity in the right amygdala in the patient and control groups at both time points. Patients showed greater activity in the right amygdala relative to control subjects at the week 0 scan, but there was no significant difference between groups at the week 16 scan. Arbitrary units refer to the average regional values of the voxel statistics contained within the region of interest, which are the coefficients of the linear model normalized by their standard errors and are dimensionless statistics.

fMRI Data

Interaction Effect of Group by Time. In mean overall activity, there was a significant interaction effect in the right amygdala extending into the hippocampus (Talairach coordinates [x, y, z] [27, −7, −16] to [13, −5, −8], cluster size 58 voxels; $F = 11.26$, $df = 1,30$; $p < .002$; effect size .27), while there were no significant main effects of group ($F = .19$, $df = 1,30$; $p = .67$) or time ($F = .10$, $df = 1,30$; $p = .76$). Patients showed greater mean overall activity relative to control subjects ($p < .006$) at baseline, and post hoc analyses revealed a significant increase in amygdala-hippocampal activity in control subjects from weeks 0 to 16 ($F = 5.01$, $df = 1,15$; $p < .04$; effect size .25), as well as a significant decrease in patients ($F = 7.04$, $df = 1,15$; $p < .02$; effect size .32), such that there was no significant difference between the groups at the follow-up scan ($t = 1.69$, $df = 15$, $p = .11$) (Figure 1).

An interaction effect was also observed in the anterior cingulate (Brodmann area [BA] 24, 32) extending to the superior frontal gyrus (BA 8), posterior cingulate gyrus (BA 31), inferior parietal cortex (BA 40), and precuneus (BA 7). Post hoc analysis indicated that the patient group showed a reduced overall activation in these regions relative to the healthy control group at baseline ($t = 3.04$, $df = 15$, $p < .008$) and a significant increase following CBT ($F = 14.87$, $df = 1,15$; $p < .002$; effect size .50) to a level comparable with the baseline activity level in the healthy control group at baseline ($t = -.36$, $df = 15$, $p = .73$) but greater than that at the follow-up scan ($t = -2.48$, $df = 15$, $p < .03$) (Figure 2, Table 2).

In linear load-response activity, significant interaction effects

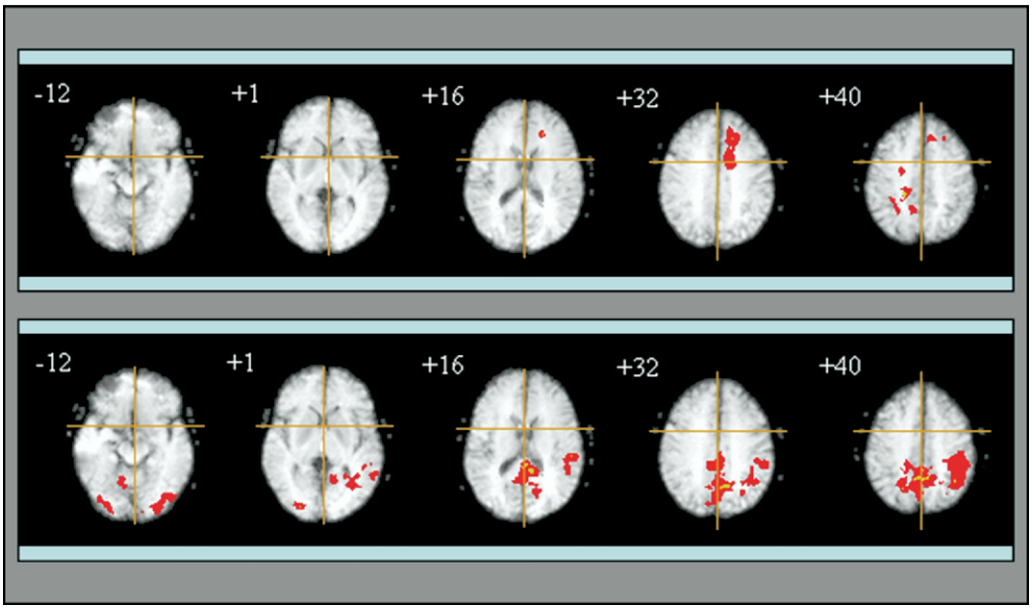

Figure 2. Group by time interaction effects were found for overall activity (top panel) in the anterior cingulate (BA 24, 32), extending to the superior frontal gyrus (BA 8), posterior cingulate gyrus (BA 31), inferior parietal cortex (BA 40), and precuneus (BA 7), which showed reduced activity in patients relative to control subjects at baseline and a significant increase at the follow-up scan. In linear load-response activity (bottom panel), the fusiform and lingual gyri (BA 19), left lateral temporal (BA 21, 22, 37) and inferior parietal (BA 40) cortices, posterior cingulate cortex (BA 23, 30, 31), precuneus (BA 7), and cerebellum showed a greater response in patients relative to control subjects at baseline, which decreased following CBT. Transverse views are presented in radiological convention with the right side of the brain on the left, extending from z-coordinates of −12 to +40 in standard Talairach coordinates. BA, Brodmann area; CBT, cognitive behavioral therapy.

were observed in the fusiform and lingual gyri (BA 19), left lateral temporal (BA 21, 22, 37) and inferior parietal (BA 40) cortices, posterior cingulate cortex (BA 23, 30, 31), precuneus (BA 7), and cerebellum. In these regions, post hoc analysis showed a significantly greater load-response activity in depressed patients at baseline relative to healthy control subjects (t = -5.17, df = 15, $p < .001$), which decreased following CBT (F = 25.64, df = 1,15; $p < .001$; effect size .63) to a level comparable with the load-response in the healthy control group at baseline ($t = -.17$, df = 15, p = ns) (Figure 2, Table 3).

Correlation of Clinical Response and Cerebral Activity. Significant associations between clinical response and mean overall activation were found in two regions: a cluster extending from the right inferior frontal gyrus to the insula (centroid [x, y, z] = [31, 16, 8]; 512 voxels) (r^2 = .62, $p < .001$)) and the left putamen/globus pallidus (−19, −6, 6; 823 voxels) (r^2 = .80, $p <$ .001). Both regions showed significant negative correlations indicating that patients with the greatest clinical improvement following CBT had the lowest mean activity in these regions at baseline during an acute depressive episode (Figure 3).

A significant positive association between clinical outcome and linear load-response activity was evident in the left inferior frontal gyrus (BA 44) (−47, 17, 16; 798 voxels) (r^2 = .48, $p <$ .003), as patients with the greatest clinical response showed the highest linear load-response in this region at baseline. The inverse relationship was observed in a cluster that encompassed the following regions: anterior cingulate (BA 32) (2, 32, 38; 173 voxels), right middle frontal (BA 9) (36, 22, 32; 576 voxels), right insula/inferior frontal gyrus (33, 7, −1; 1153 voxels), and putamen (31, 11, 8; 296 voxels) (r^2 = .85, $p < .001$). These regions showed significant negative correlations such that patients with the greatest clinical improvement had the lowest linear load-response activity at baseline (Figure 3; Supplements 3 and 4). Logistic regression analysis indicated that load-response activity in this region predicted clinical remission. Clinical remission was correctly predicted in six of seven patients (85.7%), and residual symptoms were correctly predicted in eight of nine patients (88.9%) (χ^2 = 4.19, df = 1, p = .04). These correlations were not confounded by initial depression severity, as no regions showed a significant relationship with baseline HRSD score.

Main Effects of Group and Time. The main effect of group revealed regional cortical and limbic differences between groups, which reflected the neural pathways associated with sad facial processing (22), while a main effect of time was observed in posterior cortical, subcortical, and limbic regions (Tables 5 and 6 in Supplement 5).

Discussion

During an acute depressive episode, sad facial processing was associated with excessive amygdala activity. Increased amygdala activity is a well-reported feature of unipolar depression (10–13,32,33) and may be related to depression severity (33). Amygdala activation appears to normalize following antidepressant medication (10,12), but this has not been reported following treatment with IPT or CBT (14,15,17), although resting state scans may not sufficiently engage the amygdala (25). With the present task, we observed normalization of amygdala-hippocampal activity following CBT. As the analysis though was derived from a region of interest that showed an initial difference between patients and control subjects, there is a potential confound by regression-to-the-mean effects. In the absence of a patient-control group, it is not possible to wholly refute a regression-to-the-mean effect.

Additional group by time interaction effects were evident in the dorsal anterior cingulate extending to the parietal cortex. In

Table 3. Interaction Effect of Group by Time in Linear Load-Response

Cerebral Region	BA	Cluster Size (Voxels)	Talairach Coordinates (mm)		
			x	y	z
Posterior Cingulate Gyrus	30/31	956	−9	−59	8
			−2	−63	28
	23	31	−4	−27	24
			−5	29	28
Middle Temporal Gyrus	37/21	30	−56	−54	−4
			−56	−55	1
	21	71	−48	−54	8
Superior Temporal Gyrus	42/22	177	−49	−25	8
			−50	−38	20
Inferior Parietal Cortex	40	938	−44	−37	24
			−37	−45	50
Precuneus	7	983	−1	−55	32
			5	−55	45
Fusiform Gyrus	18	235	−29	−84	−16
			−31	−85	−12
	18	134	32	−82	−16
			33	−87	−12
Inferior Occipital Gyrus	18	98	−26	−90	−8
			−36	−89	−1
		139	27	−92	−8
			27	−89	4
Lingual Gyrus	19	128	−15	−58	1
			−10	−57	4
Cerebellum		506	−33	−57	−37
			−37	−77	−20
		855	34	−52	−36
			35	−59	−16
		158	−8	−91	−28
			−10	−92	−20
		102	12	−59	−16
			14	−63	−12

BA, approximate Brodmann area.

these regions, depressed patients showed an increase in overall activity following CBT, while healthy control subjects had decreased activity at the follow-up scans. The dorsal anterior cingulate cortex is engaged by a number of tasks, including response selection (34) and error monitoring (35), which perhaps elicit an underlying function in modifying behavioral responses to avoid a loss of reward or negative outcomes (36). Abnormalities in anterior cingulate morphology (37–40) and activity (12,41–43) are commonly observed in depression. Cognitive behavioral therapy explicitly addresses patient thought processes, decisions, and actions that contribute to their depressive state (1). Although we found a decrease in anterior cingulate activity following treatment with fluoxetine using the same task (12), most studies have reported increased dorsal anterior cingulate activity following pharmacological therapy (8,14) or CBT (17). Its activity may reflect a neural state marker of depression, perhaps indicating improvement in neurocognitive responses following therapy.

Interaction effects in overall activity extended into the superior frontal gyrus, inferior parietal cortex, and precuneus. Depressed patients showed greater activity to sad faces following CBT treatment, while healthy control subjects had reduced activity in these regions at the follow-up scan. The superior frontal gyrus is implicated in visuospatial attention (44) and the inferior parietal cortex and precuneus in visuospatial working memory (45), each components of the affective facial processing task. Again, the effects of CBT contrast with those associated with pharmacotherapy, as reduced overall activity was observed in the inferior parietal cortex and precuneus following treatment with fluoxetine (12).

In linear load-response activity, treatment effects were evident in both the core and extended neural components of affective facial processing (22). At baseline, patients showed an exaggerated load-response to sad faces, which was reduced following CBT to a level comparable with control subjects. The initial visual analysis of facial features is mediated in the core regions of the fusiform and lingual gyri, whose activity is modulated by the intensity of affective facial expressions (46). The main processing of affective expressions is located in cortical and limbic regions, which form the extended processing streams (22). In the present study, the effects of CBT were limited to cortical regions, namely lateral temporal and inferior parietal cortices, while the treatment effects of fluoxetine included cortical as well as limbic-subcortical regions, which showed an enhanced linear load-response following antidepressant medication (12). Goldapple *et al.* (17) also observed reciprocal cortical-limbic changes in response to CBT, which contrasted with the effects of pharmacological treatments (8). Following CBT, they found decreased activity in the inferior temporal and parietal regions and increased activity in the hippocampal region. However, we did not observe any significant treatment effects of CBT in limbic-subcortical regions with implicit processing of sad faces.

Our other main hypothesis was an association between anterior cingulate activity and clinical response. Elevated anterior cingulate activity in acutely depressed individuals has shown a significant relationship with treatment response to antidepressant medication (6–9,11,12). In the present study, we examined whether neural activity at baseline, prior to the initiation of treatment, would be predictive of subsequent clinical response to CBT. We found a significant relationship with linear load-response activity in the dorsal anterior cingulate region, which distinguished patients who showed a greater improvement with CBT.

This region of the anterior cingulate cortex is engaged by tasks of high demand involving a potential loss of reward or a negative outcome (36). The significant relationship suggests that there is a resilience of activity during an acute depressive episode in those patients who subsequently show the most clinical improvement. Comparison of the patient subgroups with the healthy control group revealed that patients with the greatest improvement showed the most similar pattern of activation to healthy control subjects. Moreover, it was the pattern of activation rather than an absolute increase in overall activity that was predictive of treatment response.

Of the studies that have examined the predictive association of neural activity during an acute depressive episode with patients' subsequent clinical response, the relationship has been of both increases (7,11,47) and decreases (9,18,48) in anterior cingulate activity. These reports have included a variety of neuroimaging tasks, in particular resting state (7,48), continuous performance tasks (9,47), and negative stimuli (11,18). However, few studies have presented the associations as a comparison with matched healthy individuals (6,9). From our observation, we suggest that the distinction may be between patients who fail to show a good clinical treatment effect and those patients who are subsequent responders to treatment and may be more comparable to healthy control subjects in their neural responses.

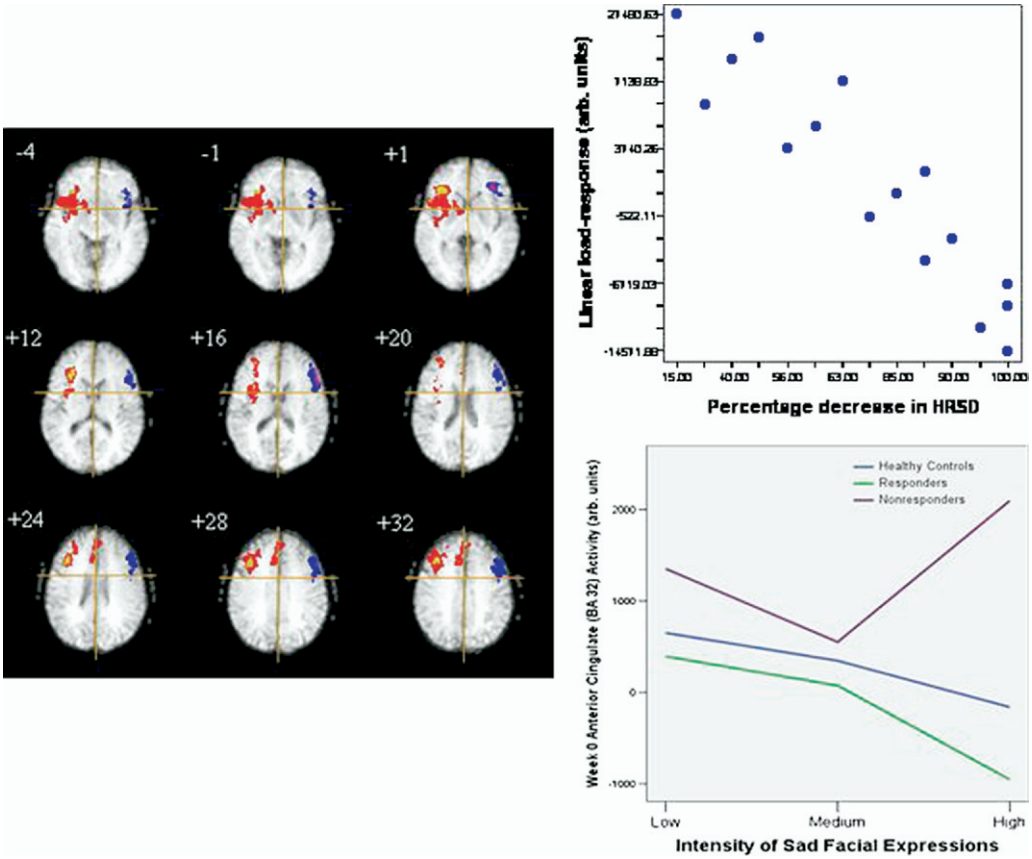

Figure 3. Brain correlates of symptomatic response. Regions in which linear load-response activity at week 0 was predictive of patient clinical response at week 16. The anterior cingulate (BA 32), right middle frontal (BA 9) and right insula/inferior frontal cortices, and putamen showed a significant negative correlation with clinical response. Patients with the greatest clinical improvement following CBT showed the lowest load-response activity in these regions (colored in red). Top graph shows relationship between load-response activity and clinical response measured as percentage decrease in HRSD score from weeks 16 to 0. Bottom graph shows activation for each intensity of facial expression in the anterior cingulate cortex for the healthy control subjects and the patients divided into good responders (>50% decrease in HRSD) and poor responders (≤50% decrease in HRSD). The inverse pattern was found in the left inferior frontal cortex (BA 44) as patients with the greatest clinical response had the highest linear load-response in this region at baseline (colored in green). BA, Brodmann area; CBT, cognitive behavioral therapy; HRSD, Hamilton Rating Scale for Depression.

More recently, there have been reports of an association between amygdala activity during an acute episode and clinical response (9,18,32), demonstrating positive (18,32) as well as negative (9) relationships. In the present study, we did not observe a significant association between baseline amygdala activity and clinical outcome. Several factors may account for the discrepancies, including task design and sample characteristics. In particular, Siegle *et al.* (18) noted a correlation in amygdala activity to high levels of self-reported ruminations, which was not specifically examined in our patient group.

The main effect of group revealed both increased and decreased regional activations in patients, which included cortical and limbic-subcortical areas involved in affective facial processing (22). The combination of relative responses is in contrast to the group effect observed in our fluoxetine treatment study in which patients showed a greater overall activity relative to healthy control subjects (12). The analysis of the main effect of group implicates neural regions that show a trait-like response. However, the main effect was confounded by effects of medication in the previous study (12). In the present report, patients were medication-free at both time points, and their differences highlight possible effects of antidepressant medication on neural responses.

A major limitation of the present study is sample bias, as there is likely a large element of patient self-selection for treatment with a psychological therapy or antidepressant medication. As well, the specificity of the effects of CBT cannot be distinguished from the effects of illness severity or the supportive aspects of frequent contact with expert therapists because the comparison group did not include placebo treatment or another form of psychotherapy. In the fMRI contrasts, we examined mean overall activity as a measure of the average neural response to all the intensities of the sad facial expressions. The experimental face conditions though were not matched for visual content or response requirements with the control condition, which consisted of viewing a crosshair fixation without any selection responses. An alternative control condition could have included scrambled facial expressions and required a motor response. However, we sought to capture the neural responses to affective processing of the intensity of the sad facial expressions with the linear load-response activity measurement. Yet, this measurement may also be an approximation, as the neural load-response may not necessarily be linear with increasing affective intensity. With the combination of these contrasts, our intention was to make the best estimates of the neural responses given these limitations. Moreover, the same stimuli were used at both scan

sessions, which may have contributed to habituation and reduced neural responses.

In summary, these findings extend similar observations with pharmacological treatments, suggesting that amygdala activity may be a marker of depressive state and provide further support for anterior cingulate activity as a neural predictor of treatment response in depression.

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Supplementary material cited in this article is available online.

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