Amygdala reactivity to emotional faces predicts improvement in major depression

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Behavioral studies suggest that emotional reactivity in depressed persons predicts subsequent symptom reduction. Using functional magnetic resonance imaging in a prospective study, we show that greater amygdala activation to emotional facial expressions among depressed patients predicts symptom reduction 8 months later, controlling for initial depression severity and medication status. Functional magnetic resonance imaging may thus be used as a method to identify neural markers in depressed patients at risk for poor outcome. *NeuroReport* 16:1267–1270 © 2005 Lippincott Williams & Wilkins.

Key words: Affect; Amygdala; Depression; Imaging; Psychiatric outcome

INTRODUCTION

Depression is associated with abnormalities in frontal and limbic neural circuits including the amygdala [1], which is more strongly activated at rest and in response to emotional stimuli in depressed patients than in controls [1–4]. Individual differences in response to emotional stimuli can predict subsequent treatment outcome. For example, behavioral, cognitive, and autonomic studies of depressed patients have demonstrated that individuals who are more reactive to emotional stimuli exhibit greater symptomatic improvement than do individuals who show little emotional reactivity [5,6]. Because the amygdala is engaged in the processing of emotional stimuli, we hypothesized that greater amygdala activation during a depressive episode would predict greater improvement in depressive symptomatology over the course of the episode. To test this hypothesis, we conducted a prospective study of 16 individuals diagnosed with major depressive disorder (MDD). Participants viewed emotional and neutral faces in a gender discrimination task as they underwent functional magnetic resonance imaging (fMRI) during a depressive episode at Time 1 (T1). We examined the relationship between degree of amygdala activation at T1 and improvement in level of depressive symptomatology an average of 8 months later at Time 2 (T2).

MATERIALS AND METHODS

Study participants: Sixteen adults diagnosed with MDD, on the basis of the Structured Clinical Interview for DSM Axis I (SCID-I) [7], participated in this study. Interrater reliability for diagnoses of MDD was excellent (κ=1.00, [8]). All participants (1) were between the ages of 18 and 60; (2) had no reported history of brain injury, psychotic ideation, social phobia, panic disorder, mania, or substance abuse within the past 6 months; (3) had no behavioral indications of possible impaired mental status; and (4) had no physical fMRI counterindications. Individuals diagnosed with comorbid panic disorder or social phobia were excluded. Nine of the participants were taking antidepressant medications, but all participants met DSM-IV criteria for current MDD. Severity of depressive symptoms was assessed using the Beck Depression Inventory [9] (BDI) at T1 (mean BDI score=25.1; sd=11.33; range: 10–45) and again at T2 approximately 8 months later (mean interval: 8.2 months; sd=2.37 months; range: 3–13 months; T2 mean BDI score=21.7; sd=9.71; range: 6–39). Informed consent was obtained from all participants.

Behavioral procedures: Participants viewed blocked presentations of pictures of emotional (happy, sad, angry, fearful), neutral, and scrambled faces used in previous studies [8,10] in a sex-discrimination task. Blocks of 10 faces from each of the six categories (fear, angry, sad, happy, neutral, and scrambled) were presented at a rate of 3 s per face. Each category was presented three times, for a total of 30 novel face images. Two different stimuli orders were created and counterbalanced across participants.

Functional magnetic resonance imaging procedures: Whole-brain imaging data were acquired on a 3 T MRI Signa LX Horizon Echospeed (8.2.5 systems revision, G.E. Medical Systems, Fairfield, Connecticut, USA) using structural and functional imaging parameters, and preprocessing methods described in detail elsewhere [11]. Briefly,

functional images were acquired using a gradient echo T2*-weighted spiral scan (TR=3 s, TE=30 ms, flip angle=83°, FOV=24 cm, matrix=80 × 80), smoothed (8 mm full-width at half maximum), normalized (gray-matter SPM99 template), and preprocessed using SPM99.

Data analysis: Voxel-wise fixed-effects contrast analyses [12] were performed at the single-participant level and random effects analyses [13] were conducted at the group-level. Analyses were based on contrasts between each of the emotional conditions and the neutral face condition. To evaluate the extent to which brain activation is correlated with symptom improvement, a random-effects multiple regression model was calculated for each emotion condition into which BDI scores at T2 were entered, using BDI scores at T1 as a covariate to control for concurrent depression severity effects on brain activation levels [14,15]. In addition, to control for use of medication, medication status (medication taken vs. not taken) was entered as another covariate.

Analyses of the amygdala as the *a priori* region of interest were conducted with significance levels set at $p<0.05$ (uncorrected) and a 40-voxel extent threshold, reducing the probability of a false-positive error per pixel to an estimated $p=0.0005$ (extrapolated from Forman and colleagues [16]). The amygdala was defined by way of an automated method for generating region of interest masks [17]. Whole-brain analyses were conducted with significance levels set at $p<0.001$ (uncorrected) and a 10-voxel extent threshold. All coordinates are represented in MNI (Montreal Neurological Institute) space.

RESULTS

Behavioral data: Partial correlations were conducted to evaluate the relationship between BDI scores and behavioral responses to emotional facial expressions. Depression severity at T1 (controlling for medication use) was not significantly correlated with reaction times to any of the face stimuli, nor were reaction times predictive of BDI scores at T2 (controlling for BDI at T1 and for medication use). Thus, results for the fMRI data are not confounded with behavioral responses.

Functional magnetic resonance imaging data: In the amygdala, the magnitudes of activation at T1 correlated significantly and negatively with BDI scores at T2 (i.e. greater activation at T1 was associated with lower levels of depressive symptoms at T2) for sad, happy, and fearful facial expressions (Table 1, Fig. 1).

Outside the amygdala, 15 activations at T1 correlated with improved BDI scores at T2, and only two activations correlated with worsened BDI scores at T2 (Table 2). Correlation clusters associated with improved T2 BDI scores were localized across a wide network of cortical and subcortical regions, and were observed in all emotion

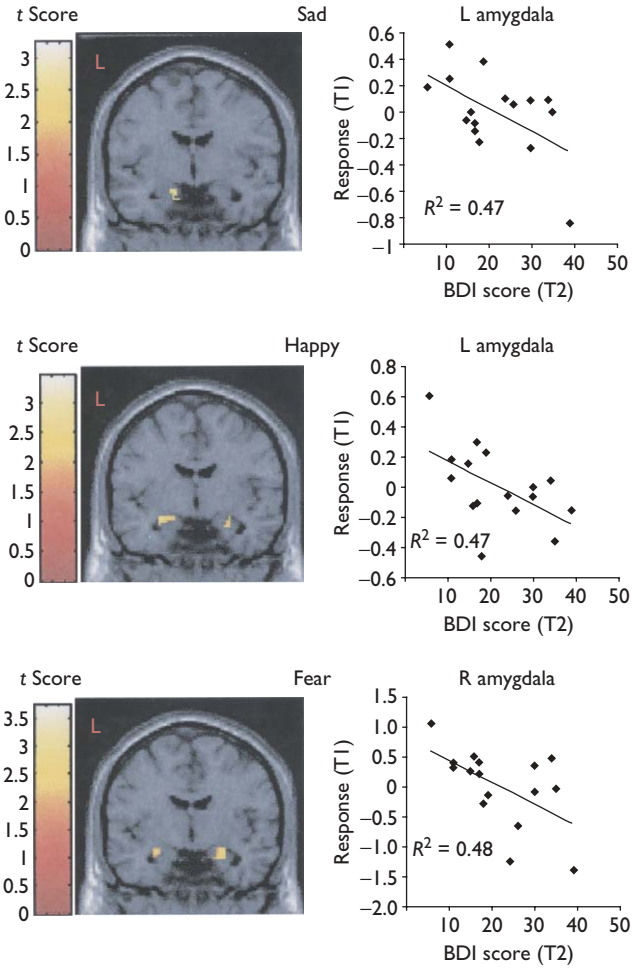

Fig. 1. Amygdala activation across individuals at Time 1 (T1) correlated with Beck Depression Inventory (BDI) symptom improvement at Time 2 (T2). Left column shows projections of significant clusters onto coronal images. Right column shows scatterplots depicting fitted and adjusted responses for the maximally significant voxel. Squared correlation coefficients are based on partial correlations, controlling for BDI scores at T1 and medication use.

Table 1. Correlation clusters within the amygdala in which magnitude of activation at Time 1 was associated with improved (lower) Beck Depression Inventory scores at Time 2.

Emotion condition	Cluster size	*Z* score	*p* Value	*X*	*Y*	*Z*
Sad	96	2.69	0.004	−8	−10	−20
Happy	49	2.82	0.002	30	0	−18
	53	2.69	0.004	−20	−10	−12
Fear	93	2.98	0.001	30	0	−18
	45	2.13	0.017	−28	−6	−16

Cluster size refers to the number of significant voxels. *Z*-value refers to the *Z*-transformed *t*-statistic for the maximally significant voxel within a cluster. Coordinates of that voxel are given in MNI space.

Table 2. Whole-brain locations of correlation clusters in which magnitude of activation at Time 1 (T1) was correlated with Beck Depression Inventory (BDI) scores at Time 2.

Condition	Cluster size	*Z* score	*X*	*Y*	*Z*	Location
T1 activation correlated with poorer (higher) BDI scores						
Sad	49	4.15	64	−32	18	R superior temporal gyrus (BA 42)
Happy	—	—	—	—	—	
Angry	—	—	—	—	—	
Fear	10	3.85	22	8	−38	R superior temporal gyrus (BA 38)
T1 activation correlated with improved (lower) BDI scores						
Sad	24	3.85	14	−66	28	R precuneus
	16	3.64	62	−16	−12	R middle temporal gyrus (BA 21)
	15	3.49	18	−22	2	R thalamus, ventral posterior lateral nucleus
Happy	14	4.09	−12	40	−28	L orbital gyrus (BA 11)
	16	4.08	36	−88	24	R superior occipital gyrus (BA 19)
	15	4.07	62	−54	8	R superior temporal gyrus (BA 22)
	29	3.97	48	−62	46	R inferior parietal lobule, (BA 40)
	30	3.92	30	−10	−2	R putamen, lentiform nucleus
	11	3.88	36	−92	22	R superior occipital gyrus (BA 19)
	19	3.78	18	−10	−26	R parahippocampal gyrus (BA 28)
Angry	14	3.71	−42	−28	62	L postcentral gyrus (BA 3)
	19	3.51	−60	−60	16	L superior temporal gyrus (BA 22)
	15	3.39	14	−60	26	R precuneus (BA 31)
Fear	10	3.44	−2	60	24	L medial frontal gyrus (BA 10)
	11	3.42	−62	−60	16	L superior temporal gyrus (BA 22)

Cluster size refers to the number of significant voxels. *Z*-value refers to the *Z*-transformed t-statistic for the maximally significant voxel within a cluster. All significance levels are $p < 0.001$ (uncorrected). Coordinates of that voxel are given in MNI space. L=left hemisphere, R=right hemisphere, BA=Brodman's area.

conditions, although the largest number of activations (seven) was associated with happy facial expressions. The distribution of these clusters was strongly left-lateralized for angry and fearful facial expressions (54 of 69 voxels; 78%), and strongly right-lateralized for sad and happy facial expressions (175 of 189 voxels; 93%). Correlation clusters associated with worsened T2 BDI scores were exclusively right-lateralized and located within the superior temporal gyrus for sad and fearful facial expressions.

DISCUSSION

This is the first study to show that amygdala reactivity to emotional facial expressions in a sample of MDD participants predicted the degree of symptom improvement 8 months later. Whole-brain analyses revealed additional regions in which activation was associated with subsequent symptom improvement. The finding that the largest number of such activations occurred for happy facial expressions is consistent with prior behavioral studies reporting that greater reactivity to positive stimuli during a depressive episode is associated with greater symptom improvement [5,6]. Considered collectively, these findings underscore the importance of focusing on responsivity to positive, as well as negative, stimuli in depression.

Some of the regions detected in whole-brain analyses have previously been associated with treatment response to depression. Anterior cingulate activation to sad faces predicting symptom reduction is consistent with a report that anterior cingulate activation to negative pictures at baseline predicted 8-week treatment response to venlafaxine [18]. Thalamic activation to sad faces predicting symptom improvement is consistent with a report that administration of fluoxetine was associated with enhanced thalamus activation in response to sad facial expressions at baseline and reduced activation after 8 weeks of treatment [19]. Parietal lobule activation to happy facial expressions predicting improvement in BDI scores is consistent with previous reports that changes in parietal blood-flow predict recovery from depression [20], and that stimulation of the parietal cortex in healthy individuals is associated with reduction in negative mood [21].

To date, only three fMRI studies have investigated the association between patterns of brain activation in depressed patients and changes in depressive symptoms. Of these, two were based on dynamic changes across pre-treatment and post-treatment scans [3,19], and neither of these studies reported data from baseline scans that predicted subsequent symptomatic improvement. A third study [18] reported that baseline activation of the anterior cingulate (but no other regions) of depressed patients in response to negative pictures predicted short-term treatment response to venlafaxine (consistent with our study). All three of these studies used 8-week intervals as pre-treatment to post-treatment comparisons, compared with our interval of 8 months. Clinically, of course, longer-term outcomes yield the most salient information.

Previous fMRI studies of treatment-related brain changes assessed groups of patients who received a common treatment, such as selective serotonin reuptake inhibitors or selective serotonin/norepinephrine reuptake inhibitors [3,19]. In contrast, our study sample consisted of both unmedicated participants and participants who were taking a broad range of antidepressants. We view the fact that we controlled statistically for the effects of medication in our analyses as a strength of the study, because the predictive effects of brain activation during episode were obtained across various treatment modalities and, thus, are more likely to generalize to the population of individuals with MDD. Certainly, however, delineating the effects of medication on neural functioning of depressed individuals, particularly in the absence of diagnostic improvement, is

an important task for future research. We also controlled for depression severity, because Drevets *et al.* [15] and Abercrombie *et al.* [14] have found that depression severity is positively correlated with amygdala activity. It is important to note that both medication and depression severity may affect amygdala habituation [22,23], subjective experience, and emotion perception [24]. Consequently, future studies should examine explicitly the effects of medication status and depression severity on these measures, and should also add assessor-based measures of depression severity, such as the Hamilton Rating Scale for Depression [25].

Finally, most previous clinical neuroimaging studies have used fMRI to demonstrate differences between healthy and diseased brains in a number of psychiatric conditions. The present study underscores the promise of this technology in identifying individuals within a specific psychiatric disorder who have better or worse long-term prognosis. Thus, individuals who show little amygdala activation to emotional stimuli during a depressive episode may require additional, or different, treatment options than do depressed persons who show robust activation. Indeed, the present results indicate that emotional reactivity captured with fMRI is a better predictor of long-term symptomatic outcome than is a behavioral index (reaction time to emotional faces at T1), and that fMRI can be used to identify individual differences in brain–behavior relationships among depressed individuals that may have direct consequences for the course of this disorder. Future work should delineate the specificity with which brain activation in depressed persons predicts improvement. In particular, it will be important to examine whether greater neural activation during nonemotional cognitive or sensory–motor tasks is as strong a predictor of improvement in depressive symptomatology as is affective responsiveness.

CONCLUSION

Using fMRI and a sex-discrimination task, we report that individual differences in amygdala activation to emotional, relative to neutral, facial expressions during a depressive episode predict symptom improvement 8 months later. In the amygdala and multiple other brain regions, greater activation in response to emotional facial expressions was associated with greater symptom improvement. fMRI can delineate individual differences in brain activation levels that can identify depressed individuals who are at risk for poor outcome, allowing clinicians to develop individualized treatment strategies.

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