BRIEF REPORTS

Activation in Dorsolateral Prefrontal Cortex in Response to Maternal Criticism and Praise in Recovered Depressed and Healthy Control Participants

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Background: *High family levels of expressed emotion reliably predict relapse in patients with schizophrenia and mood disorders; however, the neural mechanisms linking expressed emotion and relapse are unexplored. Dysfunctional activity in the dorsolateral prefrontal cortex (DLPFC) has been implicated in the pathophysiology of depression. Functional magnetic resonance imaging (fMRI) was used to assess focal activation changes in DLPFC in response to a novel psychosocial challenge stimulus developed from the expressed emotion construct.*

Methods: *Healthy control subjects and fully remitted unipolar depressed participants completed blood oxygen level–dependent fMRI while they heard their own mothers making critical and praising comments about them.*

Results: *Relative to control subjects, participants with a history of depression failed to activate DLPFC when they heard critical remarks. There were no differences between the two groups in their DLPFC responses to maternal praise.*

Conclusions: *Even if fully well at the time of testing, participants with a known vulnerability to depression respond differently to the psychosocial challenge of being criticized. These findings might have implications for our understanding of vulnerability to depression and to depressive relapse.*

Key Words: Depression, mood challenge, fMRI, expressed emotion, dorsolateral prefrontal cortex

Criticism is an all too frequent aspect of interpersonal life and can be regarded as a naturally occurring and common form of social threat (Hooley and Gotlib 2000). In general, healthy individuals handle criticism without adverse consequences. This is less true for people who are vulnerable to depression. Although no empirical evidence directly links criticism to the etiology of depression, considerable evidence attests to the significance of criticism with respect to psychiatric relapse. Criticism from a close relative has been demonstrated to be a reliable psychosocial predictor of relapse in unipolar depressed patients (Butzlaff and Hooley 1998).

Most of what is known about the link between criticism and relapse comes from empirical research conducted with the expressed emotion construct. Expressed emotion is a measure of the family environment that reflects the degree of criticism, hostility, and emotional over-involvement that characterizes the close family members of a psychiatric patient (see Leff and Vaughn 1985). The most important element of expressed emotion is criticism. Patients diagnosed with schizophrenia, mood disorders, and other psychopathologic conditions are at significantly higher risk of later relapse if they live with family members who are critical of them (Butzlaff and Hooley 1998); however, the mechanisms by which a psychosocial event like criticism can culminate in a biobehavioral outcome like symptom relapse are far from clear. More specifically, the functional neuroanatomic consequences of exposure to criticism remain unexplored.

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Several models of the neurobiology of depression acknowledge the role of psychosocial stressors (Post 1992; Siever and Davis 1985). The dorsolateral prefrontal cortex (DLPFC) is a brain region that has been implicated in the interaction of cognitive and emotional processing and is well placed to subserve mechanisms mediating the impact of external experience on the limbic system. For example, during negative mood states, the DLPFC is associated with sustained attention to the external environment, and it is the main target of limbic–cortical activity associated with mood state changes (Liotti and Mayberg 2001). Positron emission tomography and functional magnetic resonance imaging (fMRI) studies of depression have shown abnormal blood flow in multiple prefrontal regions, consistently showing decreased activity in DLPFC (see Drevets 1998 for a review). Moreover, successful antidepressant treatment is associated with increases in activation of DLPFC (Kennedy et al 2001). There is also evidence of anatomic differences in prefrontal cortex in patients with mood disorders (Rajkowska 2000), which might account for some of the functional differences that have been observed. On the basis of these findings, we hypothesized that the DLPFC might be dysfunctional in its response to affective stimuli in patients who suffer from depression.

This study describes a new affective challenge paradigm that integrates psychosocial risk factor research with neuroimaging. We used fMRI to explore focal activation changes in fully remitted unipolar depressed patients and healthy control subjects. Participants were exposed to a novel, interpersonally based emotion provocation task that was theoretically derived, personally meaningful, and ecologically valid. The emotion provocation task involved subjects hearing audiotapes of critical and praising remarks made about them by their own mothers.

Methods and Materials

Participants

Sixteen right-handed individuals (aged 20–30 years) were recruited into the study. Nine participants (five women, four men; aged 23.9 ± 2.6 years [mean ± SD]) were control subjects

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with no history of Axis I disorder based on a structured clinical interview (SCID; First et al 1997). In addition, seven participants (all women; aged 25.7 ± 2.3 years) who had a past history of one or more episodes of major depression diagnosed by an experienced clinical interviewer according to DSM-IV criteria (American Psychiatric Association 2000) were also recruited. These study groups did not differ with respect to their mean age [$t(14) = -1.48$, ns]. At entry to the study, participants with a past history of depression were fully remitted and had been completely well for a minimum of 5 months (mean = 35 months, range = 5–109 months). Their mean Beck Depression Inventory score (Beck et al 1961) was 1.6 (SD = 1.2). Two participants were currently taking antidepressant medications, two participants had taken antidepressants in the past (7 and 30 months previously), and three participants had no history of pharmacologic treatment. Written informed consent was obtained from all participants after a detailed description of the study, which was approved by the Harvard University Committee on the Use of Human Subjects. Mothers also provided informed consent. This was recorded on audiotape, before the taping of the maternal comments.

Mood Challenge

Subjects participated in a neuroimaging session during which they completed an fMRI scan while listening to audio-taped speech of their own mothers making specific comments about them. In the criticism condition, each mother discussed aspects of her son's or daughter's behavior that particularly bothered the mother. In the praise condition, each mother talked about aspects of her offspring's behavior that the mother especially liked.

Mothers made self-contained statements that lasted for 30 sec. During the scan, participants heard these comments over nonferrous, gradient damping headphones, in the context of a blocked design. Each scanning epoch began with a 30-sec rest period, followed by 30 sec of criticism (or praise), another rest period, another 30 sec of criticism (or praise), and then another rest period. Each subject underwent two scanning epochs; thus, each subject heard two 30-sec segments of each type of commentary. Half of the subjects heard the critical comments first, followed by the praise. For the remaining subjects, the order was reversed. Only one type of affective comment was included within a scanning epoch (i.e., two critical or two praise remarks; no commingling of comment type occurred within an epoch). Subjects heard each comment once only, and subjects did not hear any of the maternal comments before the scanning. There were a total of two comments of each type (criticism or praise) within a given scanning epoch. Examples of praising and critical maternal comments (with names changed to protect confidentiality) are provided for illustration:

"Stephanie, one thing that I really like about you is your smile and this is because your whole face lights up. Your eyes twinkle and your skin is so radiant. This has been true since the time that you were small. Whether you were three or twenty-three or twenty-seven now it is just one of the things that is so radiant, like the light is really coming through you. This is one of the things that I have always liked about you and I think other people do too."

"Jessica, one thing that bothers me about you is the style of clothing you wear. It seems like most of your wardrobe is old and shapeless and poorly fitting. The newer things you buy tend to be rather extreme in style, either wide-legged pants or tight skirts, neither of which is very flattering. I wish you'd spend a little more money on yourself and get some good advice on style. Better yet, I'd wish you'd take my advice on style."

Scan Acquisition

Scanning was performed on a GE Signa 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, Wisconsin) retrofitted with a whole-body, echo planar coil by using a circular surface coil placed at the left side of the head. A T1-weighted sagittal image was used to localize a plane parallel to the anterior commissure–posterior commissure line, and high resolution magnetic resonance images were acquired in the axial plane of study to assist in localization of the neuroanatomic region of interest (ROI) (Gruber et al 2002). Functional images were collected every 3 sec with a gradient echo pulse sequence (echo time = 40 msec, repetition time = 3000 msec, flip angle = 75°, slice thickness = 7 mm, 128 × 64, field-of-view = 20). Motion correction software, which corrects for both in-plane rotational and translational motion, was applied before data analyses (DART; Maas 1997). Data that exceeded 1° or 1 mm in either the rotational or translational plane were excluded from the analyses.

The ROIs included both the left and right DLPFC in areas corresponding to Brodmann's areas 46 and 10. Boundaries were defined on the basis of recognizable landmarks by a neuroanatomist, blind to diagnostic group, with three anatomic atlases as reference (Damasio 1995; Damasio and Damasio 1989; Kretschmann and Weinrich 1992). The DLPFC ROIs were selected on the basis of two coronal slices that included the largest visible portion of the DLPFC. The ROIs were placed as superior and as lateral as possible without including cerebrospinal fluid. These placements were made adjacent to and slightly medial to the principal sulcus by a trained rater with high interrater reliability ($\kappa = .89$). The left ROI was approximately centered around the Talairach coordinates −50, 50, 4; the right ROI was approximately centered around coordinates 51, 49, 4 (Talairach and Tournoux 1993).

The ROI was outlined on the cortical region of interest and comprised four pixels, each 3 mm × 3 mm. This method of localization and analysis is a sensitive method of detecting cortical activation between two regions in situations in which there is an a priori hypothesis and a specific brain ROI (Constable et al 1998). Given the importance of reliably assessing these precise localizations, a single investigator who had completed formal reliability training completed all of the ROI measurements.

Data Analysis

Measures of signal intensity were derived by averaging the magnetic resonance signal measured in all pixels in the DLPFC for each time point during the activation period. The signal was then normalized to each subject's baseline average, derived from the mean of the first seven images, and converted into a metric representing the percent change in magnetic resonance signal from baseline. The first seven scans acquired during the initial baseline scan, but after the acquisition of six dummy scans, were included in the baseline measure. Signal responses were averaged for the two activation periods.

Results

Mood Challenge: Behavioral Effects

Participants were asked to report on their mood with the Positive and Negative Affect Schedule (PANAS; Watson et al 1988) at regular intervals during the experimental protocol. The PANAS contains 10 positive (e.g., interested, proud) and 10 negative (e.g., ashamed, irritable) mood descriptors. Each item is rated on a 1–5 scale (1 = very slightly or not at all; 5 = extremely). As expected, after hearing praise, there was a significant increase in subjects' positive mood compared with baseline [means = 35.5 vs. 38.2, $t(15) = 2.16$, $p = .024$, one-tailed]. In addition, after hearing criticism, there was a significant increase in subjects' negative mood from baseline [means = 12.3 vs. 14.1, $t(15) = 2.37$, $p = .016$, one-tailed]. Hearing praise did not significantly change negative mood (means = 12.31 at baseline and 12.31 after praise), and hearing criticism did not significantly impact positive mood (means = 35.5 at baseline and 36.2 after criticism).

Mood Change in Control Subjects Versus Remitted Depressed Patients

Ratings of the maternal comments by a panel of independent assessors ($n = 10$) who were blind to group status revealed no differences between the mothers of the control subjects and the mothers of the recovered depressed participants in terms of how strongly critical or praising their comments were. Despite this, remitted depressed participants showed a greater increase in negative mood after hearing criticism than the control participants did [3.29 vs .67, $t(14) = 1.83$, $p = .045$, one-tailed]. There was also a nonsignificant trend for control participants to show a greater increase in positive mood after hearing praise than was characteristic of the remitted depressed participants [4.22 vs .71, $t(14) = 1.45$, $p =. 085$, one-tailed].

Activation Changes in Response to Criticism and Praise

Changes in activation in DLPFC were examined in the remitted depressed participants and in the healthy control subjects. Because our remitted depressed subjects were all right-handed women ($n = 7$), for these analyses we restricted the control group to include only right-handed women ($n = 5$). There was no difference in the mean ages of the female control subjects and the female participants with remitted depression (24.0 vs. 25.7 years, respectively). Moreover, this combined sample of 12 participants showed similar elevations in PANAS positive mood after hearing praise (35.4 at baseline and 38.1 after praise) and similar elevations in negative mood after criticism (12.2 at baseline and 14.0 after criticism) to those found in the full ($n = 16$) sample. Functional magnetic resonance imaging analyses did not adjust for medication status.

A group × condition × hemisphere repeated measures analysis of variance revealed a significant main effect of condition (praise vs. criticism) on activation in DLPFC [$F(1,10) = 7.7$, $p = .02$, $\eta^2 = .44$], with a greater overall activation occurring after hearing praise than after hearing criticism (mean percent signal change = .51 for praise and .21 for criticism). There was no significant main effect of hemisphere and no condition × hemisphere interaction. There was, however, a significant group × condition interaction [$F(1,10) = 10.5$, $p = .009$, $\eta^2 = .51$]. Post hoc Newman-Keuls tests revealed that whereas control participants showed similar levels of activation when hearing both praise and criticism from their mothers (mean percent signal change for praise = .40, for criticism = .45, $p = .75$), recovered depressed participants showed significantly more DLPFC activation when they heard praise and less DLPFC activation when they heard criticism from their mothers (means = .62 for praise and −.03 for criticism, $p = .008$). Moreover, although recovered depressed participants and healthy control subjects did not differ in DLPFC activation when hearing praise ($p = .35$), this was not so for criticism. As can be seen in Figure 1, when they were exposed to maternal criticism, healthy control subjects showed activation of DLPFC. In contrast, remitted depressed participants responded to criticism with a decrease in activation in DLPFC ($p = .008$). These findings occurred in the absence of any significant differences in how strongly praising or how strongly criticizing the maternal comments that they heard had been rated.

Discussion

This preliminary study suggests that people with a known vulnerability to depression, even when they are not depressed, respond differently than control subjects when they are confronted with an affective challenge. After being criticized by their mothers, fully remitted depressed participants showed a greater increase in negative mood, along with a significant failure to activate DLPFC compared with healthy control subjects. No significant differences between the control subjects and the remitted depressed participants were noted with respect to activation in response to hearing praise, however. The failure of the recovered depressed participants to activate DLPFC during criticism is especially striking because these participants had been depression-free for almost 3 years and had Beck Depression Inventory scores that were very similar to those of the never-depressed control subjects.

The findings of this study add to the literature examining changes in regional cerebral blood flow in response to mood challenge. Liotti et al (2002) exposed healthy, depressed, and remitted unipolar depressed patients to short autobiographic "sad scripts" that were designed to provoke a state of sadness. Interestingly, sadness provocation in the remitted patients resulted in regional cerebral blood flow decreases in pregenual anterior cingulate and medial orbitofrontal cortex that were not apparent in the healthy control subjects. Liotti et al propose that these represent sites of vulnerability in unipolar depression. Our finding of decreased activation in DLPFC in response to being challenged by criticism is based on a different but complementary challenge paradigm and provides further support for the idea that abnormalities in selected prefrontal and subcortical neural pathways are associated with vulnerability to depression.

This study has several limitations. The number of subjects who completed the imaging paradigm is relatively small, and our measures of blood oxygen level–dependent activation rely on limited brain regions consisting of four pixels selected from a single coronal slice. It is therefore possible that the tissue volume sampled within the DLPFC is not reflective of the region as a whole. Because sampling methods were reliable across diagnostic groups, however, the changes in signal intensity seem to indicate prefrontal response differences between depressed and control subjects, even if they are of a focal nature. Of course, whether such differences are indicative of vulnerability to de-

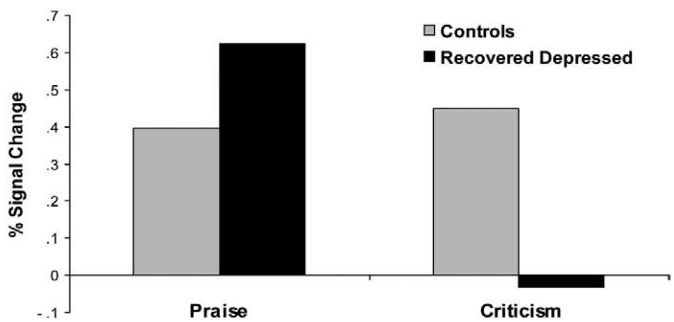

Figure 1. Dorsolateral prefrontal cortex activation to praise and criticism.

pression or are due to other factors (e.g., neuroticism, personality traits) that are associated with vulnerability to depression is not known.

This is the first study to combine critical commentary and functional neuroimaging to examine the pathophysiology of depression. Although preliminary, our findings raise the possibility that vulnerability to depression might be characterized by a failure to engage prefrontal cortex in response to a personally significant psychosocial threat. One recent model (Miller and Cohen 2001) suggests that the prefrontal cortex might send bias signals to other areas of the brain that then facilitate the expression of task-appropriate goals. Hypoactivation in certain regions of prefrontal cortex might be linked to a failure to override other more automatic responses that might then lead to more marked negative mood states (see Davidson et al 2002). The findings of this study provide a potentially important link between interpersonal experience and the neurobiology of affective stimuli and represent a first step toward understanding the well-replicated link between criticism and relapse in major depression.

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