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Cortico-limbic response to personally challenging emotional stimuli after complete recovery from depression

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Abstract

People vulnerable to depression are at increased risk of relapse if they live in highly critical family environments. To explore this link, we used neuroimaging methods to examine cortico-limbic responding to personal criticisms in healthy participants and participants with known vulnerability to major depression. Healthy controls and fully recovered participants with a past history of major depression were scanned while they heard praising, critical, and neutral comments from their own mothers. Prior to scanning, the formerly depressed and the control participants were indistinguishable with respect to self-reported positive, negative, or anxious mood. They also reported similar mood changes after being praised or criticized. However, formerly depressed participants responded to criticism with greater activation in the amygdala and less activation in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) than did controls. During praise and neutral commentary, amygdala activation was comparable in both groups, although lower levels of activation in the DLPFC and ACC still characterized formerly depressed participants. Vulnerability to depression may be associated with abnormalities in cortico-limbic activation that are independent of mood state and that remain even after full recovery. Criticism may be a risk factor for relapse because it activates the amygdala and perturbs the affective circuitry that underlies depression.

Keywords: Expressed emotion; fMRI; Vulnerability markers; Amygdala; Anterior cingulate cortex; Prefrontal cortex

1. Introduction

Recovery from an episode of major depression is often slow. Nonetheless, most patients eventually experience remission. In some cases, mild, sub-clinical symptoms may remain; in other cases, the recovery will be complete with no residual symptoms and a full return to the former level of functioning (Boland and Keller, 2002). However, even after clinical improvement, people who have experienced depression are at increased risk of relapse or recurrence (Burcusa and Iacono, 2007) especially if they live in highly critical family environments (Butzlaff and Hooley, 1998). This suggests that trait vulnerability markers of depression may exist even after full clinical recovery. Here, we investigate cortico-limbic responses to critical commentary to determine whether altered

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neurobiological responding to criticism is associated with a past history of depression.

Despite the high prevalence of mood disorders, their underlying neuropathology is still poorly understood. Current models of depression implicate widespread functional interactions between neocortical, limbic, and subcortical brain regions in the pathogenesis of affective illness (Mayberg et al., 1997; Drevets, 2000; Davidson et al., 2002). Altered functioning in these systems is supported by imaging data that have highlighted neural networks underlying emotional processing deficits related to mood disorders. For example, Mayberg et al. (1999) have suggested a cortico-limbic model that includes ventral, dorsal and rostral compartments(Mayberg et al., 1999). A number of frontal brain regions, including the dorsolateral and dorsomedial prefrontal cortex, the dorsal anterior cingulate (dACC), posterior cingulate and the ventral prefrontal cortex, insula, and subgenual anterior cingulate have been shown to be associated with the cognitive, somatic and affective disturbances associated with depression.

Compared with healthy controls, currently depressed individuals show decreased activation in the dorsolateral prefrontal cortex (DLPFC; Buchsbaum et al., 1997; Drevets et al., 1997; Mayberg et al., 1997; Keedwell et al., 2005a; Siegle et al., 2007). Activation in the DLPFC has also been shown to be decreased when non-depressed individuals are exposed to a sad mood induction (Gemar et al., 1996; Baker et al., 1997; Liotti et al., 2000). Anterior cingulate activity is also dysfunctional in depression (Mayberg et al., 1999; Seminowicz et al., 2004; Pizzagalli et al., 2006). This region, which is functionally quite heterogenous, has been parcellated into a cognitive and an affective subdivision based on distinct afferent and efferent projection systems. The affective subdivision encompasses ventral (rostral, subcallosal, and subgenual) areas of the ACC and has extensive connections with limbic and paralimbic regions including the amygdala (Devinsky et al., 1995; Drevets et al., 1997). Emotional tasks are thought to activate the affective division (Whalen et al., 1998; Mayberg et al., 1999; Davidson et al., 2002). In contrast, cognitive tasks such as the classic Stroop test activate the cognitive subdivision of the ACC (Bush et al., 1998; Mayberg et al., 1999). The cognitive subdivision of the ACC involves more dorsal regions and has connections with brain regions such as the DLPFC, posterior cingulate, and parietal cortex (Devinsky et al., 1995; Mayberg et al., 1999; Davidson et al., 2002).

Dorsal regions of the ACC have been shown to be hypoactive in depression (Davidson et al., 2002). In contrast, greater rostral cingulate activity has been associated with better response to pharmacological treatments and ECT (Mayberg et al., 1997) as well as to the antidepressant effects of sleep deprivation (Wu et al., 1999). Deep brain stimulation of the subgenual ACC has also been shown to improve clinical symptoms in treatment refractory-patients (Mayberg et al., 2005).

Other key findings concern the amygdala. Drevets (1999) has suggested that this limbic region is hyperactive in people who are depressed. Although group differences between controls and depressed patients were not reported by Abercrombie and colleagues (Abercrombie et al., 1998), these investigators did find that right amygdalar glucose metabolism was positively correlated with the level of dispositional negative affect reported by the depressed participants. Siegel and colleagues (2002, 2007) have reported increased and sustained amygdalar responses to emotional stimuli (words) in medicated and unmedicated depressed patients compared with never depressed controls. Moreover, bilateral amygdala response to valenced words has been linked to increased recall of negative self-referent information in remitted patients exposed to a sad mood challenge (Ramel et al., 2007). This suggests the amygdala may play a role in mood-congruent memory in depression.

The disinhibition of the amygdala system may be linked to a failure of inhibition from integrative cortical structures such as the DLPFC (Davidson, 2000; Drevets, 2003). Increased limbic activity in response to emotional stimuli has been linked to decreased DLPFC activity during cognitive tasks; there also appears to be a decreased functional relationship between these brain structures in depressed patients (Siegle et al., 2007). For some patients, increased tonic amygdala activity could lead to decreased DLPFC function (Siegle et al., 2002). In other cases, there may be a failure to effectively recruit the DLPFC, leading to a failure to inhibit limbic activity.

Although neuroimaging studies suggest that depression involves disruptions in limbic-cortical pathways, (Drevets, 1999; Mayberg et al., 1999; Siegle et al., 2006), the extent to which activity in these pathways normalizes after full recovery from depression is unexplored. Certainly, there is reason to believe that vulnerability factors may be evident in clinically remitted patients. Liotti, Mayberg, and colleagues (Liotti et al., 2002) exposed currently depressed, remitted and never depressed participants to a sad mood provocation. They then used PET to examine cerebral blood flow abnormalities in the three groups. When in a sad mood, the remitted depressed patients showed patterns of brain activity that were more like those found in currently depressed patients as opposed to never depressed healthy participants.

Clinical remission may still involve the presence of sub-clinical symptoms, however. This raises the question of the extent to which vulnerability markers for depression may be found in people who have a past history of the