Neuroimaging and Depression

Current Status and Unresolved Issues

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ABSTRACT—*Major depression is among the most debilitating, prevalent, and recurrent of all psychiatric disorders. Over the past decade, investigators have examined the neural mechanisms associated with this disorder. In this article we present an overview of neuroimaging research that has assessed the structure and functioning of the amygdala, subgenual anterior cingulate cortex, and dorsolateral prefrontal cortex in major depression. We then describe results of studies that have attempted to elucidate the nature of the relations among these brain structures. The picture that emerges from these investigations is one in which heightened activity in limbic structures that underlie the experience and expression of emotion dampens activation in dorsal cortical structures that are involved in affect regulation, reducing their ability to influence limbic activation. We conclude by highlighting unresolved issues concerning the roles of these structures in depression and their relation to specific symptoms of this disorder.*

KEYWORDS—*depression; neuroimaging; fMRI; amygdala; ACC; DLPFC*

Major Depressive Disorder (MDD) is among the most prevalent of all psychiatric disorders. MDD is characterized by sad mood and/or a loss of interest or pleasure in almost all daily activities, as well as by several associated symptoms such as weight loss or gain, sleep disturbance, psychomotor agitation or retardation, fatigue, and concentration difficulties. Depression is both widespread, with up to 20% of the general population experiencing at least one episode of depression during their lifetime, and recurrent, with a relapse rate of over 80%. This high prevalence and recurrence of depression, combined with its significant personal and societal costs, makes it imperative that we identify and elucidate factors that are involved in the onset and maintenance of MDD and in recovery from this disorder.

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Over the past 15 years, investigators have used neuroimaging techniques to examine the neural substrates of depression. In this review, we briefly summarize findings from this work, emphasizing key regions of the brain that have been implicated in MDD. We then discuss these findings in the context of an integrative formulation of the neural substrates of depression. We conclude by highlighting important unresolved issues in this field and by suggesting directions for future research that will help to add specificity and breadth to neural models of depression.

DEPRESSION AND THE BRAIN

Even before the advent of structural and functional neuroimaging research on MDD, there were strong indications that neural abnormalities play a crucial role in depression. Foremost among these is the fact that depressive disorders are responsive to a diverse set of brain-based interventions. In addition to showing positive outcome following drug treatment, for example, a significant subset of depressed individuals also respond favorably to electroconvulsive therapy, in which seizure-inducing current is applied to the temples, as well as to surgeries that sever neural fiber tracts or destroy brain regions that are postulated to be involved in the maintenance of depression.

The specific symptoms that make up the syndrome of MDD also implicate the functioning of particular brain structures. Depression is primarily a disorder of emotion and its regulation; indeed, hallmark symptoms of depression are pervasive sad mood and an inability to inhibit the processing of negative information, exacerbating the experience of negative affect. Over the past decade, neuroscientists examining the "emotion circuitry" of the brain have documented the involvement of the limbic system, a complex of structures including the amygdala, hippocampus, insula, and parts of the anterior cingulate cortex (ACC), in the experience and expression of emotional states (see Davidson et al., 2002, for a review). Among these structures, the amygdala and the ventral (i.e., bottom) aspect of the ACC, most often referred to as the subgenual ACC, have received the most attention from investigators interested in depression. Whereas the amygdala has been shown to play a prominent role in

emotionally mediated attention, in assigning emotional significance to stimuli, and in remembering emotionally significant events (see Phelps, 2008, this issue), the subgenual ACC appears to mediate subjective experience of emotion and emotional reactions to stimuli, particularly stimuli associated with reward seeking. These two structures are involved directly in the *experience* and *processing* of emotion, but investigators have also examined cortical structures, most notably the dorsolateral prefrontal cortex (DLPFC), that appear to be involved in the *regulation* of emotion in depression and in cognitive control. In the sections below, we briefly summarize empirical work examining the amygdala, subgenual ACC, and DLPFC in depressed individuals.

AMYGDALA

Studies of amygdala volume in depression have yielded inconsistent findings. We recently conducted a meta-analysis of these studies and found no aggregate difference in amygdala volume between depressed and healthy individuals. We did find, however, that amygdala volume decreases significantly with increasing number of depressive episodes; depression history, therefore, may be an important variable to consider in future neuroimaging studies. Studies using positron emission tomography (PET) to examine neural activity have found elevated baseline amygdala activity in depression that is positively correlated with depressive severity (e.g., Drevets, Bogers, & Raichle, 2002). In addition to being characterized by elevated baseline amygdalar activity, depressed persons have also been found to exhibit greater amygdala reactivity to emotional stimuli, particularly negatively valenced stimuli, than do controls (e.g., Fales et al., in press; Sheline et al., 2001). Although some investigators have also found abnormal amygdala responsivity to positively valenced stimuli in depressed individuals, these effects are found infrequently and are less consistent in their direction, with one study showing increased amygdala response to happy faces (Sheline et al., 2001) and another reporting decreased amygdala reactivity to positive words (Canli et al., 2004).

SUBGENUAL ACC

A small number of studies have reported decreased volume in the subgenual ACC associated with depression (e.g., Drevets et al., 1997). Investigators examining resting state activity in the subgenual ACC of depressed individuals have found decreased activity in this region (e.g., Drevets et al., 2002; Drevets et al., 1997). Interestingly, Drevets (1999) presented a simulation that adjusted estimates of activity in the subgenual ACC to compensate for the volume loss in this structure associated with depression and found that the volume-adjusted activity estimates indicated *increased* subgenual ACC activity in this disorder. This formulation is consistent with Kegeles et al.'s (2003) finding of a decrease in subgenual ACC metabolism following the administration of fenfluramine—an agonist of serotonin with antidepressant effects—to depressed individuals. Kegeles et al. also found the magnitude of the metabolic subgenual ACC decrease to be positively correlated with alleviation of depressive symptoms. Consistent with the results of these studies, Gotlib et al. (2005) found depressed individuals to exhibit greater subgenual ACC activation than did controls in response to emotional faces. Moreover, Siegle, Carter, and Thase (2006) showed that those depressed persons who eventually improve with cognitive-behavior therapy have less subgenual ACC reactivity to affective words than do depressed individuals who do not improve.

DLPFC

Given the high levels of rumination in depression that may reflect difficulties in cognitive control, investigators have hypothesized that depression is characterized by low levels of activity in the DLPFC (e.g., Mayberg et al., 1999). Indeed, although there is little evidence of structural anomalies in the DLPFC in depression, remarkably consistent findings regarding abnormalities of function in this region have been reported. Several investigators have reported lower resting-state DLPFC activity in depressed than in healthy individuals (e.g., Gonul, Kula, Bilgin, Tutus, & Oguz, 2004; Mayberg et al., 2005). Studies examining the neural bases of induced depressive relapse through depletion of tryptophan—an amino acid that is a necessary precursor to serotonin—have reported that individuals who relapse have lower DLPFC activity during relapse than do individuals who do not relapse (Bremner et al., 1997). Consistent with these findings, researchers have found depressed individuals to exhibit less DLPFC reactivity to affective stimuli than do healthy controls. Hooley, Gruber, Scott, Hiller, and Yurgelun-Todd (2005), for example, showed that, unlike their non-disordered counterparts, depressed individuals failed to activate the DLPFC while listening to taped criticism from their mothers. Schaefer, Putnam, Benca, and Davidson (2006) extended these findings to positive affect, reporting diminished reactivity of the DLPFC in depressed participants in response to both erotica and positive emotion faces.

CONCLUSIONS, UNRESOLVED ISSUES, AND FUTURE DIRECTIONS

This brief review has shown that, perhaps not surprisingly, there are functional abnormalities of neural structures implicated in the experience, expression, and regulation of emotion in depression; most consistently, the amygdala and subgenual ACC appear to be overactive in MDD, and the DLPFC underactive. Given the patterns of anatomical connectivity among these structures, it is unlikely that they are expressing abnormality independently of one another. A challenge for future work,

therefore, is to identify the patterns of functional connectivity that characterize the depressive neural network. Investigators working from a neural systems perspective have begun to examine functional connectivity in depression. Mayberg et al. (2005), for example, assessed the neural consequences of modulating activity in the subgenual ACC by implanting and activating stimulating electrodes near this structure (deep brain stimulation) in depressed patients who were unresponsive to conventional forms of therapy. They found, in addition to marked clinical improvement in several patients, that stimulation near the subgenual ACC in such patients attenuated the pre-existing overactivity in this structure and resulted in increased activity in the previously underactive DLPFC. This reciprocal relation between dorsally situated cortical structures and limbic structures in depression has also been documented in functional neuroimaging studies. Siegle, Steinhauer, Thase, Stenger, and Carter (2002), for example, found an inverse relation between amygdala and DLPFC activation in depressed individuals in response to affective words.

This pattern of activity is consistent with a neural model developed by Helen Mayberg, who proposed that the normal reciprocal relation between the limbic system and dorsal cortical structures is imbalanced, or skewed, in depression. Mayberg essentially describes a vicious circle in which hyperactivation in limbic structures like the subgenual ACC and amygdala dampens activation in dorsal structures, reducing the ability of the latter to regulate limbic activation (see Fig. 1 for a simple schematic of this model). It is also important to note, however, that recent work suggests that network abnormalities in depression are not limited to interactions between the limbic system and dorsal cortical structures. For example, Greicius et al. (2007) found that the "default mode network," a complex of cortical and subcortical structures that is proposed to mediate internally generated thought processes, extends to include the subgenual ACC in depression. Moreover, in our laboratory we are finding that when depressed individuals successfully encode negative information, there is increased correlation, relative to that found in never-depressed participants, between activity in the amygdala and activity in the hippocampus, a structure that is vital in the encoding of information. This amygdala–hippocampus synchrony appears to facilitate memory for negative material; indeed, the degree of synchrony predicts individual differences in subsequent memory for negative, but not positive or neutral, material in depressed individuals. Further research is needed both to continue to delineate patterns of functional connectivity among neural structures in depression and to begin to map the anatomical foundations of those patterns using techniques like diffusion tensor imaging that make it possible to detect and assess the integrity of pathways connecting brain structures.

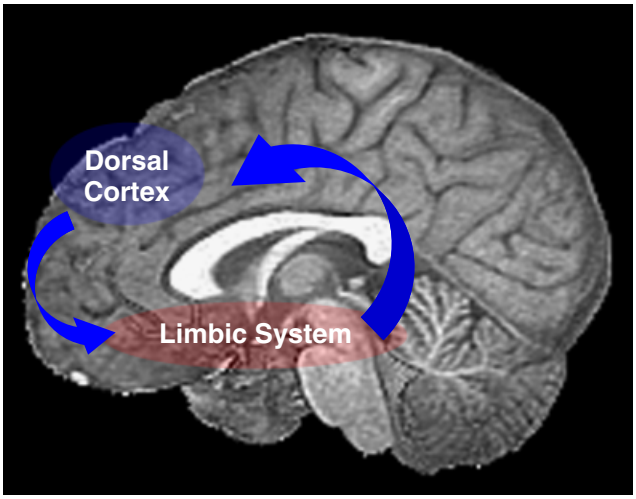

Fig. 1. Schematic of a neural model of depression emphasizing the dominance of limbic activity in the reciprocal relation between the dorsal cortex, which includes the dorsolateral prefrontal cortex (DLPFC); and the limbic system, which includes the amygdala, hippocampus, insula, and parts of the anterior cingulate cortex (ACC).

Another critical task for future research is to elucidate the roles played by functional and structural anomalies in the onset and maintenance of depression and in recovery from this disorder. Although the research we have described above indicates that the amygdala, subgenual ACC, and DLPFC are functionally and, in some cases, structurally aberrant in depression, we know relatively little about *how* these anomalies are related to MDD. In beginning to examine this question, researchers have assessed temporal relations between neural activity and symptoms of depression, examining whether neural abnormalities are present after symptomatic improvement, whether they precede the onset of depression, and whether they are associated with the subsequent course of depression. For example, the increased activity in the amygdala and subgenual ACC and the decreased activity in the DLPFC that is present during the depressive episode appears to normalize following successful treatment (e.g., Drevets et al., 2002; Mayberg et al., 1999; Mayberg et al., 2005; Schaefer et al., 2006); suggesting that functional disturbances in these structures are simply correlates of a depressive episode. Two recent findings from our laboratory raise questions about this conclusion, however. First, studying a sample of remitted depressed individuals in an induced sad mood, we found that elevated amygdala activation during encoding predicts increased recall of negative self-referent words (Ramel et al., 2007). Second, young girls at elevated risk for depression because of a family history of the disorder but who have not themselves had a depressive episode exhibit pronounced amygdala activation when experiencing induced sadness and when attempting to regulate that sadness (see Fig. 2). These findings indicate that, in individuals who are vulnerable to developing depression, sad mood may provide the context for the increased amygdala activation that has been found to characterize depressive episodes.

In interpreting the results of such studies, however, it is important to recognize that elucidating the timing of neural

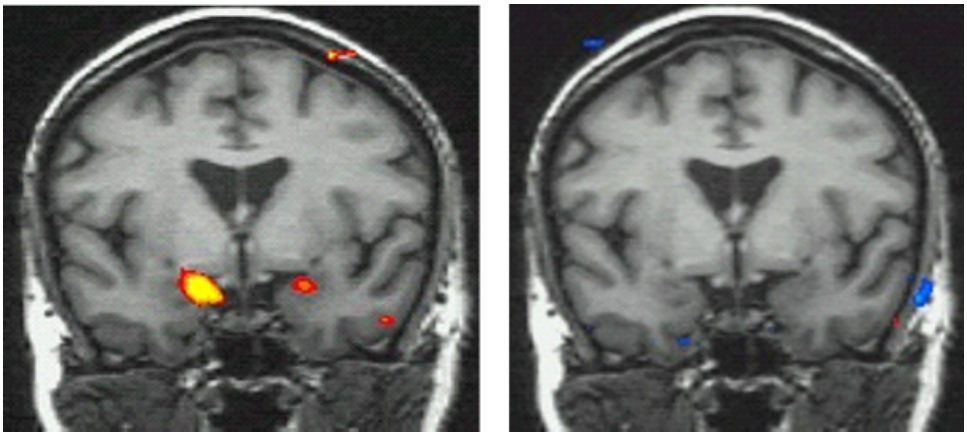

Fig. 2. Amygdala activation during the experience of sad mood in young girls at high risk (left) and low risk (right) of developing depression.

abnormalities in depression does not necessarily illuminate their role in the disorder. That is, anomalies can be present in a disordered state (and, indeed, may precede the onset of a disorder) without being involved in its development. Parsing this literature, therefore, is going to be a difficult endeavor. Adding to this complexity are studies reporting seemingly contradictory findings. For example whereas greater amygdala reactivity to affective stimuli during a depressive episode has been found to predict a subsequent decrease in symptoms (e.g., Canli et al., 2005), symptomatic improvement in depression has also been found following deactivation of the subgenual ACC both with deep brain stimulation (Mayberg et al., (2005) and, in our laboratory, through neurofeedback (i.e., presenting real-time visual feedback in the scanner to modulate ACC activity). It may be, therefore, that although the amygdala and subgenual ACC have both been found to be more active in depressed than in nondepressed participants, they have different temporal relations with the expression of depressive symptoms.

These results concerning the temporal relation between neural activation and depression and the role of neural dysfunction in depression are complex and do not cohere to tell as clear a story as we would like. Above all, they underscore the fact that "depression" refers to a heterogeneous group of disorders that are not carved at their neurobiological joints in the *DSM-IV*. Perhaps the most pressing task for future research, therefore, is to begin more explicitly to conceptualize depression subtypes and symptom profiles that are related systematically to specific neural functional and structural abnormalities, and to explore more precisely how these neural abnormalities are related to the behavioral, cognitive, and affective symptoms of depression. We believe it is only through such an effort that significant progress can be made in elucidating and understanding neural aspects of depressive disorders.

Recommended Reading

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