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Neural Functioning in Major Depressive Disorder

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Major Depressive Disorder (MDD) is one of the most prevalent and costly of all psychiatric disorders. MDD has been found to be responsive to a diverse set of brain-based interventions, including antidepressant medications and electroconvulsive therapy, strongly implicating anomalous neural functioning in its pathogenesis. Neuroimaging studies have yielded important information about depression-associated abnormalities both in resting-state brain activation and in neural responsivity to emotional stimuli, findings that promise to lead to a more comprehensive understanding of the development and maintenance of this disorder.

Because depression involves a diminished ability to regulate the experience of negative affect, attempts to understand the neural underpinnings of this disorder have focused on neural systems implicated in the experience and regulation of emotion. Although investigators have documented anomalous function of at least a dozen brain structures in MDD (Seminowicz et al., 2004), researchers have focused in particular on the roles of the amygdala and the dorsolateral prefrontal cortex (DLPFC).

It is clear from a decade of research that the amygdala is involved in the perception and experience of negative affect, and in directing attention to personally salient stimuli. Investigators using positron emission tomography (PET) have found elevated baseline amygdala activity in depressed individuals that returns to normal levels following successful

pharmacotherapy (Drevets, Bogers, & Raichle, 2002). Moreover, there is also now a large literature documenting that depressed persons show heightened amygdala activity in response to self-relevant negative stimuli. In fact, Hamilton and Gotlib (2008), recently demonstrated that this increased amygdala activation during the encoding of negative information may function to enhance their memory for this material, thereby maintaining their negative mood.

In contrast to this heightened limbic activation in MDD, researchers have documented that depression is characterized by low levels of activity in brain regions involved in executive control, most consistently in the DLPFC. This pattern of findings is consistent with the view that MDD is characterized by an inability to inhibit the processing of negative material. Indeed, investigators have demonstrated that MDD is associated with attenuated DLPFC activation, both at rest and in response to affective stimuli (e.g., Hooley et al., 2005).

Thus, depression is associated with functional abnormalities of brain structures that are critically involved in the experience and regulation of emotion. More specifically, whereas limbic structures such as the amygdala are overactive in depression, the DLPFC, which scientists have postulated exerts cognitive control over the experience of emotion, is less active in MDD, suggesting a reciprocal relation between these sets of structures. Indeed, researchers are now examining explicitly the nature of the relation between limbic and cortical structures in depression with the goal of developing a more comprehensive formulation of neural dysfunction in this disorder. Exciting findings from studies using deep brain electrical stimulation (Mayberg et al., 2005) and real-time neurofeedback (Hamilton et al., 2008) suggest that the normal reciprocal relation between the limbic system and dorsal cortical structures is altered in depression such that limbic over-activity inhibits activation in dorsal structures, reducing their ability to regulate limbic activation (see Figure 1). It is critical that investigators continue to

examine the functional relations among structures implicated in MDD, with the goal of developing more effective approaches to the prevention and treatment of this debilitating disorder.

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Figure Captions

Figure 1. Schematic of a neural model of depression emphasizing the dominance of limbic activity in the reciprocal relation between the limbic system and the dorsal cortex.

