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The neuroscience of depression: Implications for assessment and intervention

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ABSTRACT

Major Depressive Disorder (MDD) is among the most prevalent of all psychiatric disorders and is the single most burdensome disease worldwide. In attempting to understand the profound deficits that characterize MDD across multiple domains of functioning, researchers have identified aberrations in brain structure and function in individuals diagnosed with this disorder. In this review we synthesize recent data from human neuroimaging studies in presenting an integrated neural network framework for understanding the impairments experienced by individuals with MDD. We discuss the implications of these findings for assessment of and intervention for MDD. We conclude by offering directions for future research that we believe will advance our understanding of neural factors that contribute to the etiology and course of depression, and to recovery from this debilitating disorder.

Introduction

Major Depressive Disorder (MDD) is a prevalent psychiatric disorder characterized by significant role impairment, suicide risk, economic burden, and the largest number of years lived with disability in the US (US Burden of Disease Collaborators, 2013). Almost 20% of Americans will experience a major depressive episode in their lifetime (Hirschfeld, 2012); moreover, up to 80% of these individuals will have multiple depressive episodes (Bulloch, Williams, Lavorato, & Patten, 2014). Given its high prevalence, recurrence, and enormous personal and societal costs, it is not surprising that the World Health Organization projects that MDD will be the single most burdensome disease in the world in this century (Moussavi et al., 2007).

In this review, we synthesize multimodal neuroimaging data that inform the diagnosis and intervention of MDD, taking into consideration recent advances in the nosology and treatment of depression. With respect to diagnosis, we specifically consider the advantages of addressing the heterogeneity of MDD by integrating a dimensional Research Domain Criteria (RDoC) approach in evaluating neuroimaging characteristics of depression. In terms of intervention, we review recent research demonstrating the neural effects of the most evidence-based interventions, of rapid-acting antidepressants (e.g. ketamine), and the regional and global effects of targeting neural networks.

According to the Diagnostic and Statistical Manual-Fifth Edition (DSM-5), a diagnosis of MDD requires a persistent disturbance of mood (sadness, and/or in children, irritability) or a loss of interest or pleasure in virtually all activities, in addition to at least four of the following symptoms: sleep disturbance, guilt, loss of energy, impaired concentration, change in appetite, psychomotor agitation or retardation, and suicidal ideation (American Psychiatric Association, 2013). Given these varied symptoms, it is not surprising that depression is a heterogeneous disorder; indeed, each of these symptoms has specific risk factors, severities, and trajectories (Fried, Nesse, Zivin, Guille, & Sen, 2013). Further, both MDD and its individual symptoms often co-occur with other psychiatric disorders (Curry et al., 2014); they also manifest differently both across developmental stages (Dekker et al., 2007) and between males and females (Goodwin & Gotlib, 2004). This heterogeneity and comorbidity has posed significant challenges for the diagnosis and treatment of depression and has hindered our ability to predict long-term outcome of MDD. Although investigators and clinicians

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have made significant advancements in identifying depressive symptoms and in managing MDD with multimodal pharmacological and psychological treatments, there are wide variations in the efficacy and tolerability of interventions (Perlis, 2014), and problems related to symptom relapse and medication non-adherence (Sato & Yeh, 2013). Further, despite the well-documented burden of MDD, we do not yet understand the pathophysiology of this disorder.

In attempting to address this issue, researchers have begun to examine psychobiological aspects of MDD in the context of RDoC. For example, in order to advance our understanding of the pathophysiology and outcome of MDD, investigators have attempted to deconstruct depression along unitary psychopathological dimensions, such as anhedonia (Downar et al., 2013) or negative affect (Vrieze et al., 2014). In a recent review, Dillon et al. (2014) related anhedonic behavior to deficits in psychological functions that rely heavily on dopamine signaling, especially cost/benefit decision-making and reward learning, influenced negatively both by acute threats and chronic stress. Other studies have documented shared characteristics between MDD and other disorders associated with blunted or negative affect, such as schizophrenia, by focusing on similar reduced expressive behaviors measured by computerized acoustic analysis of speech (Cohen, Najolia, Kim, & Dinzeo, 2012). Although these are recent efforts, these dimensions of depression may aid in predicting treatment outcome. Researchers have also characterized cognitive impairments associated with depression. For example, Gotlib and Joormann (2010) noted that depressed individuals have been found consistently to be characterized by difficulties with inhibition of negative information and deficits in working memory, ruminative responses to negative mood states and life events, and the inability to use positive stimuli to regulate negative mood.

Importantly, recent advances in brain imaging have allowed researchers to augment studies of cognitive and behavioral impairments in MDD with an examination of neural circuit-level mechanisms that may underlie these difficulties (Foland-Ross & Gotlib, 2012). Specifically, neuroimaging studies have documented structural and functional neural characteristics critical to the pathogenesis of MDD (see Hamilton, Chen, & Gotlib, 2013 for a recent review). These studies have also demonstrated that anomalies in distributed, integrated neural networks that involve multiple brain regions, linked structurally and functionally, underlie the disturbances in cognitive functioning that have been documented in MDD (Sacher et al., 2012). Only recently, however, have researchers begun to examine explicitly the nature of the relation between clinical and neural network markers of MDD at various points during the onset and course of the disorder, and to use neural characteristics to predict treatment outcome. We believe that neuroimaging is a promising tool for elucidating the pathogenesis of MDD; it is a safe, noninvasive procedure that is ideally suited for simultaneously identifying aberrant behavior, brain structure, and brain function in MDD. Indeed, with neuroimaging, we can bridge a clinical assessment of depressive symptoms with an examination of brain abnormalities to advance our understanding of the pathophysiology of MDD.

We have three broad goals in this review. We describe anomalies in neural structure and function in adults and youth with MDD and discuss the implications of these abnormalities, first, for the assessment of depression, and second, for approaches to intervention with this disorder. Finally, we offer directions for future research that we believe will advance our understanding of biological factors that are implicated in the etiology and course of MDD, and in recovery from depression. We begin by presenting a brief review of neural aspects of unipolar depression and their implications for assessment of MDD.

How the neuroscience of depression can inform assessment

Researchers have consistently documented impairments in emotional functioning and emotion regulation in MDD (Gotlib & Joormann, 2010). Moreover, these difficulties have been found to predict the early onset (Klein et al., 2013) and the recurrence of depressive episodes (Lewinsohn, Allen, Seeley, & Gotlib, 1999), suggesting that impairments in specific domains of emotional functioning reflect stable vulnerabilities that place individuals at increased risk for experiencing recurrent episodes of MDD. Neuroimaging studies have complemented these clinical findings, documenting aberrant structure, function, and connectivity in brain regions that subserve these aspects of emotion and emotional regulation. Specifically, investigators have reported structural anomalies in MDD in the amygdala and hippocampus, and functional abnormalities in the subgenual anterior cingulate cortex (sgACC), dorsolateral prefrontal cortex (DLPFC), amygdala, and ventral striatum in MDD (Sacher et al., 2012). Further, there is growing recognition that depressed individuals are characterized by abnormalities in the anatomical and functional connections among these brain regions (Hamilton et al., 2013). In the following sections we describe these neural aberrations in depressed individuals, their relation to the clinical syndrome of MDD, and their implications for assessment of depression. Key findings from this section are summarized in Table 1.

Structural neuroimaging in MDD

Researchers using structural magnetic resonance imaging (MRI) have reported abnormalities in specific brain regions in depressed individuals. Using such tools as manual volumetry, voxel-based morphometry (VBM), and cortical thickness, investigators have documented differences in neural structure between individuals with depression and healthy controls, primarily involving depression-related reductions in brain regions important for the generation and regulation of emotion. Meta-analyses that have pooled structural neuroimaging data in depressed individuals have consistently identified focal gray matter volumetric reductions in the rostral anterior cingulate cortex (rACC; Bora, Fornito, Pantelis, & Yücel, 2012), hippocampus (Cole, Costafreda, McGuffin, & Fu, 2011), striatum and, more broadly, basal ganglia (Bora, Harrison, Davey, Yücel, & Pantelis, 2012), insula (Liu et al., 2014), subregions of the prefrontal cortex (PFC; Kempton et al., 2011), and amygdala (Sacher et al., 2012), although reports of decreased amygdala volume in depressed individuals are less consistent in medicated samples (Hamilton, Siemer, & Gotlib, 2008). Trait-specific structural differences between depressed and nondepressed individuals have been reported as relative thickening in MDD the temporal pole, caudate, and posterior cingulate, thinning of the medial PFC (Van Eijndhoven et al., 2013), and reduced volumes in the anterior insula (Takahashi et al., 2010) and the left anterior cingulate (Caetano et al., 2006). Larger gray matter volume in the bilateral amygdala, hippocampus, and dorsolateral PFC have been found in first-degree relatives of patients with MDD, suggesting a mechanism of risk for MDD. The most consistent state-dependent structural finding is reduction in hippocampal volume (Arnone et al., 2013).

Through inhibitory connections with other subcortical structures, the hippocampus is involved in the appraisal and regulation of stress and in the generation of emotion. Indeed, investigators have demonstrated that gray matter reductions in hippocampal volume are associated with an increased number of depressive episodes (Videbech & Ravnkilde, 2004), and with greater symptom severity and longer illness duration (Cheng et al., 2010), including longer durations during which depressive episodes went untreated