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Subcortical volumes differentiate Major Depressive Disorder, Bipolar Disorder, and remitted Major Depressive Disorder

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ABSTRACT

Subcortical gray matter regions have been implicated in mood disorders, including Major Depressive Disorder (MDD) and Bipolar Disorder (BD). It is unclear, however, whether or how these regions differ among mood disorders and whether such abnormalities are state- or trait-like. In this study, we examined differences in subcortical gray matter volumes among euthymic BD, MDD, remitted MDD (RMD), and healthy (CTL) individuals. Using automated gray matter segmentation of T1-weighted MRI images, we estimated volumes of 16 major subcortical gray matter structures in 40 BD, 57 MDD, 35 RMD, and 61 CTL individuals. We used multivariate analysis of variance to examine group differences in these structures, and support vector machines (SVMs) to assess individual-by-individual classification. Analyses yielded significant group differences for caudate ($p = 0.029$) and ventral diencephalon (VD) volumes ($p = 0.003$). For the caudate, both the BD ($p = 0.004$) and the MDD ($p = 0.037$) participants had smaller volumes than did the CTL participants. For the VD, the MDD participants had larger volumes than did the BD and CTL participants ($ps < 0.005$). SVM distinguished MDD from BD with 59.5% accuracy. These findings indicate that mood disorders are characterized by anomalies in subcortical gray matter volumes and that the caudate and VD contribute uniquely to differential affective pathology. Identifying abnormalities in subcortical gray matter may prove useful for the prevention, diagnosis, and treatment of mood disorders.

1. Introduction

Mood disorders are among the most prevalent and severe of all psychiatric disorders (Kessler et al., 2005; WHO, 2012). Whereas both Major Depressive Disorder (MDD) and Bipolar Disorder (BD) are characterized by the presence of depressive episodes, BD is also associated with manic or hypomanic episodes. Because BD often presents clinically as a depressive episode, patients experiencing this disorder can be misdiagnosed as MDD, leading to inappropriate treatment and prolonged distress (Singh and Rajput, 2006). We know little about neurobiological differences between BD and MDD (de Almeida and Phillips, 2013), which limits effective prevention, diagnosis, and treatment of these disorders.

Subcortical gray matter structures are involved in cognitive processing and emotion generation and regulation (Lindquist et al., 2012; Ochsner et al., 2012); not surprisingly, therefore, investigators have implicated anomalies in these structures in mood disorders (Savitz and Drevets, 2009). More specifically, individuals diagnosed with mood disorders have been found to be characterized by structural and functional abnormalities in the amygdala, hippocampus, caudate and putamen, pallidum, nucleus accumbens, and thalamus (Savitz and Drevets, 2009; Hamilton et al., 2012).

Using meta-analytic methods, Kempton et al. compared regional brain volumes in MDD and BD participants and found that the caudate, corpus callosum cross-sectional area, putamen, pallidum,

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and hippocampus are smaller in MDD than in BD (Kempton et al., 2011). Importantly, these results were limited to common brain regions previously studied in both MDD and BD, and are susceptible to biases resulting from a wide range of participant inclusion criteria and neuroimaging and statistical methods across studies. Moreover, the broad comparisons of MDD versus BD did not account for heterogeneous disease states, including influences from BD I and BD II, euthymic, manic, hypomanic and depressed BD, and current and remitted MDD. Finally, Kempton et al.'s results may be confounded by differences in illness severity between MDD and BD. It is important, therefore, that investigators directly compare MDD and BD individuals in different states with comparable illness history.

To date, few studies have examined differences in brain structure between individuals diagnosed with MDD and BD. The results of these studies indicate that, compared to MDD, BD is associated with greater deep white matter hyperintensities (Dupont et al., 1995; Silverstone et al., 2003), reduced fractional anisotropy of the left superior longitudinal fasciculus (Versace et al., 2010), decreased habenula volume (Savitz et al., 2011), reduced cortical thickness in caudal middle frontal cortex, inferior parietal cortex, and precuneus (Lan et al., 2014), and increased thalamic volume (Dupont et al., 1995). In addition, Redlich et al. found clusters of reduced gray matter that spanned the hippocampal formation, amygdala, putamen, insula, and temporal pole in depressed BD compared to MDD individuals, and a cluster in anterior cingulate that was reduced in MDD compared to depressed BD individuals (Redlich et al., 2014).

Recently, investigators have begun to examine characteristics of MDD and BD that may persist beyond the clinical episode of depression or mania. For example, researchers have found that individuals with BD who are currently in remission exhibit impairment on tests of visuospatial recognition memory (Rubinsztein et al., 2000). Similarly, in a review of studies of cognitive impairment in individuals who had recovered from MDD, Hasselbach et al. (2011) found that in 9 of 11 of these studies remitted depressed participants exhibited impaired performance on at least one neuropsychological test (Hasselbalch et al., 2011). Researchers have also found that individuals continue to experience impairment in social and occupational functioning following remission of MDD or BD (e.g., Fagiolini et al., 2005; Romera et al., 2010). Importantly, investigators have documented abnormalities in regional brain volumes in individuals who have remitted from MDD and BD. For example, individuals with euthymic BD have lower metabolic rates than do healthy controls and depressed BD individuals (Yildiz et al., 2001). Similarly, individuals with remitted MDD have smaller total and posterior hippocampal volumes than do healthy controls (Neumeister et al., 2006; for review see Lorenzetti et al., 2009). Understanding temporary (i.e., state) vs. enduring (i.e., trait) characteristics of affective disorders will facilitate the identification of targets for prevention and treatment. This is particularly important for MDD and BD, given that improved characterization of remitted MDD and euthymic BD may allow for greater differentiation of these topographically similar states and help to avoid maladaptive consequences of misdiagnosis (Singh and Rajput, 2006).

In this study we directly compare, for the first time, subcortical volumetric differences between individuals diagnosed with BD who are currently euthymic and individuals diagnosed with MDD. In addition, to examine the state versus trait nature of volumetric anomalies in mood disorders, we included a sample of individuals with remitted Major Depression (RMD), in addition to a group of healthy (CTL) individuals. We used FreeSurfer's automated segmentation to assess regional subcortical gray matter volumes of the accumbens area, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, and ventral diencephalon (VD; including hypothalamus). To assess the relation of volumetric abnormalities to the severity of impairment in data-to-day functioning across disorders, we related these volumes to individuals' level of global functioning (Global Assessment of Functioning [GAF]; Endicott et al., 1976). Finally, we used support vector machines (SVMs) to examine whether identified abnormal volumes can be used to classify participants on an individual-by-individual basis (Cortes and Vapnik, 1995).

We hypothesized that MDD individuals would have smaller volumes than would BD and CTL individuals in the regions identified in Kempton et al.'s meta-analysis, including caudate, pallidum, putamen and hippocampus. In addition, based on Redlich et al.'s findings with currently depressed BD individuals (Redlich et al., 2014), we hypothesized MDD-related reductions in amygdala relative to BD individuals. Although Kempton et al. did not find significant differences between BD and CTL participants in these regions, Redlich et al. found BD-related abnormalities that spanned hippocampus, amygdala, caudate, putamen, and thalamus; thus, we hypothesized that BD individuals would be distinguishable from CTLs in these regions. We also hypothesized that volumes of the RMD participants would fall between those of MDD and BD, and MDD and CTL participants. Finally, we hypothesized that using SVMs, the identified abnormal regions would successfully classify the MDD versus BD and both the MDD and BD versus CTL groups.

2. Materials and methods

2.1. Participants and clinical information

Participants were 193 individuals: 40 diagnosed with BD (Bipolar I Disorder, all currently euthymic); 57 diagnosed with MDD; 35 diagnosed with past but not current MDD (RMD); and 61 CTLs. All individuals participated in studies at Stanford University in which MRI data were acquired. The Structured Clinical Interview for DSM was administered by trained interviewers to all participants in order to obtain DSM-IV-TR Axis I diagnoses (First et al., 2004). Our team of interviewers have demonstrated high inter-rater reliability in our samples for these diagnoses ($\kappa s > 0.9$; e.g., Levens and Gotlib, 2010; Victor et al., 2011; Johnson et al., 2012). No participant met diagnostic criteria for substance or alcohol abuse or dependence within six months prior to MRI scanning. CTL individuals did not meet diagnostic criteria for any current psychiatric disorder or past mood disorder. Interviewers also assessed level of global functioning, using the GAF scale (Endicott et al., 1976) and number of lifetime Major Depressive episodes (MDEs) and lifetime manic episodes. Scores on the GAF scale range from 1 to 100 (lowest to highest level of functioning), indexing individuals' level of occupational, psychological, and social functioning. Participants in all four groups were assessed with the GAF; relating this measure to volumetric abnormalities might offer insight into how such abnormalities are related to the day-to-day functioning of individuals with affective disorders. Written informed consent was obtained from each participant; the Stanford University Institutional Review Board approved the study.

2.2. MRI data acquisition

All data were collected using the same 1.5 T magnetic resonance imaging (MRI) system and no major scanner upgrades that would influence SPGR images were undertaken. Further details are included in the Supplemental Information.