



Research paper

Pattern recognition of magnetic resonance imaging-based gray matter volume measurements classifies bipolar disorder and major depressive disorder



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ABSTRACT

Background: Bipolar Disorder (BD) cannot be reliably distinguished from Major Depressive Disorder (MDD) until the first manic or hypomanic episode. Consequently, many patients with BD are treated with antidepressants without mood stabilizers, a strategy that is often ineffective and carries a risk of inducing a manic episode. We previously reported reduced cortical thickness in right precuneus, right caudal middle-frontal cortex and left inferior parietal cortex in BD compared with MDD.

Methods: This study extends our previous work by performing individual level classification of BD or MDD in an expanded, currently unmedicated, cohort using gray matter volume (GMV) based on Magnetic Resonance Imaging and a Support Vector Machine. All patients were in a Major Depressive Episode and a leave-two-out analysis was performed.

Results: Nineteen out of 26 BD subjects and 20 out of 26 MDD subjects were correctly identified, for a combined accuracy of 75%. The three brain regions contributing to the classification were higher GMV in bilateral supramarginal gyrus and occipital cortex indicating MDD, and higher GMV in right dorsolateral prefrontal cortex indicating BD.

Limitations: This analysis included scans performed with two different headcoils and scan sequences, which limited the interpretability of results in an independent cohort analysis.

Conclusions: Our results add to previously published data which suggest that regional gray matter volume should be investigated further as a clinical diagnostic tool to predict BD before the appearance of a manic or hypomanic episode.

1. Introduction

Bipolar disorder (BD) is a leading cause of disability worldwide (Mathers et al., 2008) and is associated with significant risk of suicide and other medical morbidity and mortality (Baldessarini et al., 2010; Schneider et al., 2001). BD is often misdiagnosed as Major Depressive Disorder (MDD) for several reasons: the presentation of major depressive episodes (MDEs) in these conditions is very similar; hypomanic or manic symptoms may occur years after initial depressive symptoms

(Culpepper, 2014); and patients with BD may under-report severity of manic/hypomanic symptoms. One study found that the mean time interval between first mood episode and a correct diagnosis of BD is greater than 10 years (Lish et al., 1994). Failure to diagnose BD can lead to prescription of antidepressants without mood stabilizers, which may trigger manic symptoms, increasing the risk of social and occupational impairment (Nasrallah, 2015). Some data suggest that usual antidepressants also may not be as effective at treating the bipolar depression (Sachs et al., 2007). It would therefore be clinically valuable to

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identify biomarkers that improve diagnostic discrimination of BD from MDD prior to the first manic episode.

Noninvasive structural neuroimaging using Magnetic Resonance Imaging (MRI) is routinely available in clinical settings, and is less expensive, more reliable, and less burdensome to patients compared to other imaging modalities, such as Positron Emission Tomography or functional MRI (fMRI). Many studies have used structural MRI (sMRI) to identify morphological abnormalities in BD (including type 1, type 2 and not otherwise specified (NOS) patients) (Hanford et al., 2016b) and MDD (Zhang et al., 2016). Larger gray matter volume (GMV) was found in MDD compared to healthy volunteers (HV) in thalamus, cuneus, and superior frontal gyrus, while smaller GMV was found in insula and middle frontal gyrus (Peng et al., 2016b). Studies in BD patients have found lower cortical thickness values in BD compared to HV in frontal and limbic areas (Eker et al., 2014; Oertel-Knochel et al., 2015). MRI scans obtained before the first episode in individuals at high risk (HR) of developing mood disorders reveal thinner cortex in HR participants who went on to develop MDD compared to those who did not (Papmeyer et al., 2015). Children of BD parents have been found to have reduced cortical thickness compared to healthy controls, even when asymptomatic (Hanford et al., 2016c).

Potential structural brain differences between BD and MDD populations also have been investigated. We found less cortical thickness in right precuneus, right caudal middle-frontal cortex and left inferior parietal cortex in BD compared with MDD (Lan et al., 2014). Others found smaller GMV in BD compared with MDD in right anterior frontal gyrus and middle cingulate gyri (Cai et al., 2015). A recent meta-analysis found that MDDs have smaller GMV than BD when compared to HV in dorsolateral prefrontal cortex and hippocampus, although MDD and BD patients similarly exhibited lower GMV values compared to HV in medial prefrontal cortex, cingulate, and insula (Wise et al., 2016). Other analyses have found comparably lower/thinner cortical thickness in both groups compared to HV in temporal lobe (Niu et al., 2017). MDD, BD, and schizophrenia patients were found to share lower GMV values compared to HV in 88% of regions where the groups differed in a 4-group ANCOVA, although BD and schizophrenia patients showed white matter integrity alterations not seen in MDD (Miao Chang, 2017). A limitation of past studies comparing MDD and BD has been the inclusion of medicated patients, and of subjects in different mood states. Lithium is reported to increase gray matter density (Giakoumatos et al., 2015), and antidepressants confer neuroprotective effects in cell culture and in mouse models (Hunsberger et al., 2009), and promote neurogenesis and process extension in humans (Boldrini et al., 2009), which could mitigate gray matter loss.

In recent years, machine learning (an application of computer science that allows programs to learn from data sets and perform tasks such as pattern classification without direct user input), has been applied to structural brain imaging data in Alzheimer's disease (Zeifman et al., 2015), schizophrenia (Castro et al., 2014), obsessive compulsive disorder (Hoexter et al., 2013) and autism spectrum disorder (Zhou et al., 2014). It has also been applied to structural brain imaging data to identify MDD patients and to predict which patients would be treatment responders with an accuracy of 89% (Patel et al., 2016), and to predict the onset of MDD in healthy adolescents with an accuracy of 70% (Foland-Ross et al., 2015). Machine learning has also been used to classify Bipolar Type I from Bipolar Type II with up to 94% accuracy using Diffusion Tensor Imaging (DTI) data combined with neuropsychiatric measurements (Wu et al., 2016), and to classify pediatric BD compared to healthy volunteers with up to 79% accuracy (Mwangi et al., 2015).

Our work adds to a growing body of literature attempting to distinguish BD and MDD (Cardoso de Almeida and Phillips, 2013) by applying machine learning methods to cortical thickness or voxel-based morphometry (VBM) data. Previous studies have classified MDD and BD subjects with accuracies of 92.1% (Jie et al., 2015), 74.3% (Fung et al., 2015), 79.3% (Redlich et al., 2014), and 69.1% (Rive et al., 2016).

We sought to use brain-wide VBM gray matter volume measurements and machine learning, specifically Support Vector Machine (SVM), to discriminate MDD and BD patients in a cohort of 26 MDD and 26 BD patients. Participants were in a MDE and were antidepressant and mood-stabilizer-medication-free for at least 2 weeks at the time of scanning. Medications like SSRIs and lithium can produce neuron process extension, angiogenesis, and neurogenesis, and can enlarge gray matter (Giakoumatos et al., 2015; Boldrini et al., 2009). Next to nothing is known about the offset of such trophic effects of psychotropic medications and given the burden of untreated major depression, a 2-week drug-free period was considered reasonable.

2. Methods and materials

2.1. Participants

Twenty-six patients with DSM-IV BD (15 with Bipolar Type-I, 11 with Bipolar Type-II), and 26 age/sex-matched patients with DSM-IV MDD were included in this study. Patients were initially assessed by experienced masters or doctoral level psychologists using the Structured Clinical Interview for Axis I disorders (SCID-I/P) (First et al., 1995), followed by psychiatric interview with an experienced research psychiatrist. Final diagnoses were made by consensus in a conference where research psychiatrists and psychologists reviewed all available information. All patients also had a current 17-item Hamilton Depression Rating Scale (HDRS-17) score of 16 or greater (Hamilton, 1960) or a Quick Inventory of Depressive Symptomatology-Self Rated version (QIDS-SR) score ≥ 16 (Rush et al., 2003). Patient ages ranged from 20 to 60 years. Patients taking psychotropic medication at the time of enrollment ($n = 1/26$ MDD, $1/26$ BD), and whose depression was not responding adequately, were tapered off medications and completed a washout of ≥ 2 weeks prior to scanning. No participants were receiving fluoxetine or depot antipsychotics at the time of enrollment. Short-acting benzodiazepines were permitted in small doses. The Young Mania Rating Scale (YMRS) (Young et al., 1978) was used to assess manic symptoms. Four subjects did not have HAM-17 scores, so for these subjects Montgomery-Åsberg Depression Rating Scale (MADRS) scores (Montgomery and Asberg, 1979) were converted to HAM-17 scores (using the ID-QUIDS conversion table <http://www.ids-qids.org/index2.html#table5>) in order to evaluate an effect of depression severity on SVM classification. For all participants, exclusion criteria included (i) medical condition that may affect brain integrity assessed by physical examination, medical history, review of systems, and screening laboratory tests, including blood dyscrasias, lymphomas, hypersplenism, endocrinopathies, renal failure or chronic obstructive lung disease, multi-system autoimmune disorders, autonomic neuropathies, peripheral vascular disease, or malignancy, (ii) positive urine toxicology screen, (iii) positive pregnancy test or planned pregnancy, and (iv) alcohol or substance use disorder within the previous six months. This is a secondary analysis of pooled MRI data from patients recruited between May 2007 and April 2016. Twenty out of 52 subjects were from as-yet unpublished studies and the rest were included in earlier reports (Chhetry et al., 2016; Gray et al., 2013; Lan et al., 2013; Miller et al., 2013; Parsey et al., 2010). The Institutional Review Board of the New York State Psychiatric Institute approved all studies from which subjects were gathered, and all participants gave written informed consent.

A total pool of 59 BD and 58 MDD patients had potentially usable data for this analysis. Although all subjects were imaged on the same scanner, two different pulse sequences and head coils were employed in this sample, as described below. As both of these factors can affect GMV measurements (Focke et al., 2011) and were found to impact GMV measurements in our sample (see Supplemental materials S1), subjects were matched on both pulse sequence and head coil to prevent them from influencing the classifier's performance. Since GMV measurements are also affected by sex and age (Peng et al., 2016a), subjects were

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