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Reduced white matter integrity and verbal fluency impairment in young adults with bipolar disorder: A diffusion tensor imaging study

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ABSTRACT

Background: Clinical evidence shows that bipolar disorder (BD) is characterized by white matter (WM) microstructural abnormalities. However, little is known about the biological mechanisms associated with these abnormalities and their relationship with cognitive functioning.
Methods: 49 adult BD patients ((M ± SD): 29.27 ± 7.92 years; 17 males, 32 females; 34 BD-I, 10 BD-II, and 5 BD-NOS) and 28 age-matched normal subjects ((M ± SD): 29.19 ± 7.35 years; 10 males and 18 females) underwent diffusion tensor imaging (DTI) imaging. DTI metrics were computed using whole-brain tract-based spatial statistics (TBSS) as part of the FMRIB Software Library. Measures of WM coherence (fractional anisotropy - FA) and axonal structure (mean, axial and radial diffusivity – MD, AD and RD) were employed to characterize the microstructural alterations in the limbic, commissural, association and projection fiber tracts. All participants performed the Brief Assessment of Cognition for Affective disorders (BAC-A).
Results: BD patients performed poorly on verbal fluency tasks and exhibited large clusters of altered FA, RD and MD values within the retrolenticular part of the internal capsule, the superior and anterior corona radiata, and the corpus callosum. Increased FA values in the left IFOF and the forceps minor correlated positively with verbal fluency scores. Altered RD parameters in the corticospinal tract and the forceps minor were associated with reduced visuomotor abilities.
Conclusions: The reported verbal fluency deficits and FA, RD and MD alterations in WM structures are potential cognitive and neural markers of BD. Abnormal RD values may be associated with progressive demyelination.

1. Introduction

Bipolar disorder (BD) is a devastating illness with significant functional and social consequences for both affected individuals and their relatives (Geddes and Miklowitz, 2013; Mathers et al., 2008). In BD the alternation of periods of euphoria and periods of depression is accompanied by significant cognitive impairment that persists during the euthymic and acute phases (APA, 2002; MacQueen et al., 2001; Bora et al., 2009; Quraishi and Frangou, 2002). In particular, BD patients have been shown to present with deficits in visual motion perception (O'Bryan et al., 2013), visuomotor speed, visual and verbal memory, sustained attention (Bora et al., 2009; Quraishi and Frangou, 2002; Goldberg et al., 1993; Albus et al., 1996; Martínez-Arán et al., 2004; Martínez-Arán et al., 2004) and conceptual reasoning (Ryan et al., 2012).

Microstructural abnormalities in white matter (WM) fiber tracts connecting to the limbic-striatal, cingulate, thalamus, corpus callosum and prefrontal regions have been observed in children, adolescents and adults with BD (Adler et al., 2006; Adler et al., 2004; Benedetti et al., 2011; Frazier et al., 2007; Beyer et al., 2005; Liu et al., 2010; Nortje et al., 2013; Mahon et al., 2009). The corpus callosum and thalamic radiation of middle-aged and drug-naïve BD populations showed abnormal axial (AD) and radial diffusivity (RD)

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values (Oertel-Knöchel et al., 2014; Barysheva et al., 2013; Lagopoulos et al., 2013). Increased RD values have been observed in the cingulum, the superior and inferior uncinated fasciculus, the corpus callosum and the internal capsule of BD I patients when compared to their unaffected relatives and healthy controls (Emsell et al., 2013a). Another study found similar abnormalities in the hippocampus, thalamus and caudate nucleus (Canales-Rodríguez et al., 2013). The reduction in WM integrity observed in BD has been linked to processes of demyelination, cerebral hypoperfusion, neuroinflammation and reduced mitochondrial metabolism (Canales-Rodríguez et al., 2013; Mahon et al., 2010) but there is little empirical evidence supporting either of these biological hypotheses.

Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique that enables visualization of the WM fibers, and characterization of microstructural changes based on the degree of water diffusion at a voxel and regional level. Traditional metrics derived from DTI are fractional anisotropy (FA) and mean, axial and radial diffusivity (MD, AD and RD). FA represents the proportion of water diffusion parallel to the axons compared to that perpendicular to the axons. AD and RD estimate water diffusivity along and across the axons, and MD is a linear combination of AD and RD where $MD = (AD + 2*RD)/3 = 1/3*AD + 2/3*RD$. While a decrease in FA in projection fibers such as the thalamic radiation and the posterior corona radiata has been associated with disruptions in the overall WM organization, FA abnormalities in association tracts (e.g. longitudinal fasciculus) and commissural fibers (corpus callosum) have been linked to poor intra- or interhemispheric connectivity (Heng et al., 2010). Further, findings from animal studies indicate that increased AD values may reflect axonal injury, and that RD values increase as a result of demyelination processes (Song et al., 2003; Song et al., 2002; Song et al., 2005).

To date only a limited number of studies has investigated the relationship between DTI metrics and cognitive functioning in BD. A recent publication found WM alterations in the corpus callosum and the anterior thalamic radiation bilaterally in middle-aged BD I patients when compared to healthy controls (Oertel-Knöchel et al., 2014). Notably, the authors found a positive correlation between problem solving abilities and FA, MD and RD values in the thalamic radiation and fornix in BD but not in the HC group. In another study middle-aged BD I patients showed decreased FA values in the internal capsule, the right uncinate fasciculus and the corpus callosum along with decreased accuracy in set shifting and risk taking tasks (Linke et al., 2013). In adolescents with BD I reduced mean FA values in fiber tracts connecting to fronto-temporal and cingulate regions were associated with psychomotor retardation on the Trail Making Test (Kafantaris et al., 2009). These findings show a link between WM abnormalities and reduced visuomotor processing speed and executive functions. It is, however, unclear whether this relationship is specific to BD I or represents a trait marker of the bipolar illness. Further, considering that the brain morphology changes considerably over the lifespan (Yap et al., 2013; Wu et al., 2014; Brenhouse and Andersen, 2011), it is difficult to compare the results of these studies as they included adolescents and middle-aged adults. Another potential confounding factor is related to the type of cognitive tests employed in previous studies as they may not be suitable for assessing cognition in BD.

Thus, the purpose of this study is to elucidate the relationship between WM integrity and cognitive functioning in young adults by using multiple parameters of WM integrity and the Brief Assessment of Cognition in Affective Disorder (BAC-A) – a well-validated cognitive battery designed specifically for BD (Keefe et al., 2014). Based on previous findings we expected to find WM abnormalities in the BD group when compared to HC. We also predicted to find positive correlations between indices of WM integrity and memory, visuomotor processing and executive scores, as these cognitive domains have been found to be impaired in BD.

2. Materials and methods

2.1. Participants

The sample included 49 adult BD patients (M ± SD: 29.10 ± 7.86 years; 19 males, 30 females; 34 BD-I, 10 BD-II, and 5 BD-NOS) and 28 age-matched healthy controls (HC) (M ± SD: 29.03 ± 7.34 years; 9 males and 19 females). Patients were recruited from inpatient and outpatient clinics of the University of North Carolina at Chapel Hill (UNC). HC were recruited through local media advertisements and flyers posted in public areas. All patients met the DSM-IV-R criteria for BD. The diagnosis of BD among patients and the absence of mental disorders among controls were ascertained by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I) (First et al., 2012), which was administered to all participants by an independent psychiatrist or trained research assistant. The interview also included the Montgomery–Åsberg Depression Rating Scale (MADRS) (Williams and Kobak, 2008) and the Young mania Rating Scale (YMRS) (Young et al., 1978). Functional impairment was evaluated using the Global Assessment of Functioning (GAF) which is Axis V of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). Participating BD patients and HC were aged between 18 and 48 years, had no history of substance abuse in the previous 6 months and no current medical problems. 41 of the 49 BD participants took psychotropic medication at the time of enrollment. HC with a history of any Axis I disorder in first-degree relatives and use of psychoactive medication less than 2 weeks prior to the start of the study were excluded. All female participants underwent a urine pregnancy test and urine drug screen to exclude pregnancy and illegal drug use. Subjects suffering from chronic medical issues including cardiovascular and neurological disorders were excluded. The study protocol was approved by the local Institutional Review board and informed consent was obtained from all the participants.

2.2. Imaging data acquisition and image processing

All imaging was performed on a 3T Siemens Allegra scanner at the UNC imaging facility. Whole-brain diffusion-weighted images were acquired using a spin echo-planar imaging protocol. Image acquisition parameters included: repetition time = 9200 ms, echo time = 79 ms, slice thickness = 2 mm, imaging matrix = 128 × 104, voxel size = 2 mm, b-value = 1000 s/mm^2. Two images without gradient loading (b-value = 0 s/mm^2) were acquired prior to the acquisition of 30 directions (each containing 80 slices) with uniform gradient loading (b0 = 1000 s/mm^2). To correct for eddy currents we used the first b0 image as a template. In addition to diffusion-weighted images we also acquired T1-weighted structural images for the purpose of anatomical localization.

2.3. DTI processing

The FMRIB's Diffusion Toolbox (FDT) within FSL (http://www.fmrib.ox.ac.uk/fsl) was used to preprocess diffusion weighted images and correct for eddy current distortions. FA maps of both BD and control subjects were affine and then non-linearly registered to an MNI template. FA images were created by fitting a tensor model to the raw diffusion data using the DTIFIT Reconstruct Diffusion Tensor tool. Brain Extraction Tool (BET) was used to remove non-brain tissue from images of the brain with a fractional intensity