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Tract-based analysis of white matter integrity in psychotic and nonpsychotic bipolar disorder

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ABSTRACT

Background: At least 50% of individuals with bipolar disorder (BD) present with psychosis during their lifetime. Psychotic symptoms have sometimes been linked to specific genetic and phenotypic markers. This study aims to explore potential differences between bipolar disorder subtypes by measuring white matter integrity of the brain and relationships with clinical measures.

Methods: Diffusion tensor imaging and clinical measures were acquired from 102 participants, grouped as psychotic bipolar disorder (PBD) (n=48), non-psychotic bipolar disorder (NBD) (n=24), and healthy controls (n=30). We utilized a powerful, automated tool (TRACULA: Tracts Constrained by Underlying Anatomy) to analyze the fractional anisotropy (FA) and mean diffusivity (MD) of 18 white matter tracts.

Results: Decreased FA in numerous tracts was observed in bipolar disorder groups compared to healthy controls: bilateral cingulum-cingulate gyrus bundles, corticospinal tracts, and superior longitudinal fasciculi as well as the right hemisphere cingulum-angular bundle. Only left uncinate fasciculus FA differed between PBD and NPBD groups. We found no group differences in MD. Positive symptoms correlated with FA in the superior (inversely) and inferior (directly) longitudinal fasciculi. Negative symptoms directly correlated with mean FA of the corticospinal tract and cingulum-angular bundle.

Limitations: Neurotropic, mood-stabilizing medication prescribed for individuals with BD may interact with measures of white matter integrity in our BD participants.

Conclusion: Our results indicate decreased white matter coherence in BD. Minimal differences in white matter FA between PBD and NPBD participants suggest related underlying neurobiology.

1. Introduction

Bipolar disorder has a lifetime prevalence of 1–3%, and generally presents with disabling mood episodes of depression and mania (American Psychiatric Association, 2013). Additionally, at least 50% of those with bipolar disorder have experienced psychosis in their lifetime (Coryell et al., 2001). Psychotic bipolar disorder (PBD) is of special interest, as it shares symptomatic overlap with schizophrenia (Coryell et al., 2001), is prevalent at increased rates in families with schizophrenia (Kendler, 1993), and shares chromosomal linkage on the 13q31-32, 22q12 and 2p11-q14 genes with schizophrenia (Goes, 2007; Park et al., 2004; Potash et al., 2003). In addition, compared to individuals with nonpsychotic bipolar disorder (NBD), those with PBD are more likely to have been hospitalized, to have attempted suicide, to have neurocognitive impairment, and to have a history of substance related disorders (Glahn et al., 2007; Goes, 2007; Martinez-Aran et al., 2008). These findings have suggested that PBD and NBD may represent two distinct biological subtypes of the illness. Neuroimaging studies comparing these bipolar disorder subgroups have also shown differences in regional brain size (Sarrazin et al., 2015; Strasser et al., 2005; Mamah et al., 2016) and functional connectivity (Anticevic et al., 2013). There have however been no prior studies comparing structural connectivity between PBD and NBD.

Understanding brain connectivity in bipolar disorder has become of increasing interest in recent years. Histological studies of the brains of bipolar disorder patients have found fewer oligodendrocytes (Vostrikov et al., 2007) and decreased myelin (Regenold et al., 2007) relative to a healthy population. Results of neuroimaging studies of white matter size in bipolar disorder have been variable with regard to the neuroanatomical locations affected (Kempton et al., 2008; Mahon et al., 2010); however, reductions in total (Vita et al., 2009) and callosal (Arnone et al., 2008) white matter volume have often been

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reported. Diffusion imaging studies in bipolar disorder have shown variable results. Most studies have found decreased fractional anisotropy (FA) in a range of white matter tracts (Mahon et al., 2010; Nortje et al., 2013; Sexton et al., 2009), including the corpus callosum (Yurgelun-Todd et al, 2007), and in frontal and temporal regions (Adler et al., 2004; Beyer et al., 2005; Bruno et al., 2008). While clinical heterogeneity may account for some of the differences of findings across studies, variability in imaging parameters and analyses methods likely also contribute to the observed differences. For example, while FA is the most commonly evaluated metric in diffusion imaging studies, several studies have also included mean diffusivity (MD) in the investigation of structural connectivity in bipolar disorder (Benedetti et al., 2011; Canales-Rodríguez et al., 2014). In addition, a range of methods are available for processing diffusion images, including region-of-interest (ROI), voxel-based and tract-based spatial statistics (TBSS) approaches (Soares et al., 2013). ROI-based analysis requires a priori delineation of white matter tracts, which can be challenging for smaller tracts (Mukherjee et al., 2008), while voxel-based methods can be complicated by inaccuracies with registration algorithms using tensor datasets (Mukherjee et al., 2008) and have been shown to be very sensitive to differences in processing parameters (Jones et al., 2005). Tractography is a three-dimensional modeling approach to represent neural tracts using data collected by diffusion imaging. Advantages of tractography are that it is sensitive to tract-specific differences in diffusion metrics that may be obscured by normalization to standard space, and therefore allows for more readily interpretable effect sizes of tract-specific abnormalities. Existing tractography studies in bipolar disorder have indicated decreased FA in multiple white matter tracts (Sarrazin et al., 2015; Toteja et al., 2014). Recently, TRACULA (TRActs Constrained by UnderLying Anatomy), an automated probabilistic tractography toolbox within Freesurfer (Yendiki et al., 2011), was used to segment 18 major white matter tracts in bipolar disorder and showed decreased FA particularly in the superior longitudinal fasciculus (Sprooten et al., 2016).

Our current study uses TRACULA to investigate white matter tract integrity in psychotic and nonpsychotic subgroups of bipolar disorder patients. We hypothesize that there would be a differential pattern of white matter tract abnormalities across the two subgroups, with psychotic patients having more tracts affected and to a greater degree. We analyze measures of fractional anisotropy and mean diffusivity, to better characterize potential neuropathology underlying diffusion abnormalities. Finally, we will investigate the relationship of tract integrity to clinical symptoms.

2. Materials and methods

2.1. Subjects

Participants gave written informed consent prior to participation, and all study protocols were approved by the Institutional Review Board at the Washington University School of Medicine in St. Louis, MO. Imaging data was acquired from 102 individuals, who were divided into three diagnostic groups: healthy controls (n =30), psychotic bipolar participants (n =48) and non-psychotic bipolar participants (n =24). All groups were recruited from the St. Louis area community, and all clinical participants were outpatients. Bipolar (BP) participant patients were required to meet DSM-IV criteria for Bipolar I Disorder and were classified as psychotic BP if the participant had a psychotic event over the course of their lifetime, as assessed via the Structured Clinical Interview for the DSM (SCID). All psychotic events were reported to have occurred during manic episodes. Refer to Table 1 for demographic information. Participants were excluded, prior to scanning, from the control group if they had lifetime history of Axis I psychotic or mood disorders. Participants were also excluded from participation if they met DSM-IV criteria for substance dependence or severe/moderate abuse in the past 6 months, were at the time of

Table 1
Demographics Information.

	Control	Psychotic bipolar	Non-Psychotic bipolar
Number of participants	30	48	24
Age	26.09	25.20	26.15
Handedness			
Right	29	44	21
Left	1	4	3
Sex			
Male	16	20	8
Female	14	28	16
Race			
Black	17	13	2
White	13	29	18
Asian	0	1	2
Hispanic	0	3	0
> 1 Race	0	2	2
Symptoms			
Average SAPS[a]	.07	1.35	.42
Hallucination Subscale	0	.39	0
Delusion Subscale	.07	.96	.42
Average SANS[b]	2.43	4.18	3.42
Flat Affect Subscale	.10	.59	.71
Alogia Subscale	.07	.16	.13
Anhedonia Subscale	.47	1.31	1.04
Amotivation Subscale	.73	1.24	.92
Attention Subscale	1.07	.88	.63
Young Mania Rating Scale	N/A	5.91	4.88
Lifetime history of abuse or dependence[c]			
Alcohol	4	22	12
Cannabis	0	17	6
Stimulant	0	1	0
Opioid	0	2	0
Cocaine	0	6	0
Hallucinogen	0	2	1
Polysubstance	0	2	0
Psychotropic medication (%)			
Typical Neuroleptic	0	3 (6.3)	0
Atypical Neuroleptic	0	30 (62.5)	6 (25.0)
SSRI	0	24 (50.0)	10 (41.7)
Other Antidepressants[d]	0	12 (25.0)	7 (29.2)
Stimulant	0	4 (8.3)	3 (12.5)
Mood Stabilizer[e]	0	32 (66.7)	18 (75.0)
Benzodiazepines	0	20 (41.7)	6 (25.0)
Anticholinergic	0	8 (16.7)	2 (8.3)
None	30 (100.0)	6 (12.5)	1 (4.2)
DSM-IV diagnoses (SCID)			
Bipolar I	0	48	24
Bipolar II	0	0	0
MDD[f]	0	0	0
Schizophrenia	0	0	0
Schizoaffective	0	0	0
Anxiety Disorder[g]	0	25	11
OCD	0	3	2
None	30	0	0

[a] Maximum possible score on the Structured Assessment of Positive Symptoms (SAPS) is 16.
[b] Maximum possible score on the Structured Assessment of Negative Symptoms (SANS) is 20.
[c] Other than for nicotine use disorder, participants did not meet criteria for a use disorder in the last 6 months.
[d] Refers to antidepressants other than selective serotonin reuptake inhibitors (SSRI).
[e] Mood stabilizers included Lithium, Tegredol/Carbamazepine, Depakote/Divalproex, Trileptal/Oxcarbazepine, Topomax/Topiramate, and Lamictal/Lamotrigine.
[f] Major Depressive Disorder.
[g] Includes generalized anxiety disorder, specific and social phobias, panic disorder, and PTSD.