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The role of white matter in personality traits and affective processing in bipolar disorder

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Introduction

Bipolar disorder (BD) is a serious mental illness with significant functional and social consequences for both the affected individuals, their relatives, and the general society (1, 2). Alongside affective disturbances, cognitive deficits are core features of BD that often persist during the euthymic and acute phase of BD (3–6). In particular, BD has been associated with poor performance on tests of visuomotor speed, verbal and visual memory, sustained attention and executive functioning (5–10). Individuals with BD also exhibit deficits in processing affective information which are reflected by attentional biases towards negative stimuli (11–14). In agreement with these findings a number of studies have detected structural abnormalities in brain regions such as the fronto-limbic and cingulate cortices which are involved in both cognitive functions and affective processing (15–29).

Personality traits influence mood and cognition (30, 31). Individuals with BD have elevated neuroticism scores and report lower extraversion (32), score higher on novelty-seeking scales, and lower on persistence scales compared with healthy controls (33–35). Reduced self-directedness and harm avoidance have also been reported (36, 37). Notably, neuroticism has been linked to negative affect and increased reactivity to negative events, and both extraversion and agreeableness are associated with positive affect, less mood variability and reduced reactivity to negative stimuli (38–41). There is evidence that personality traits such

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Conflict of interest

Drs Bauer, Wu, Ouyang, Meyer, Mwangi, Spiker, Zunta-Soares and Huang have no conflicts of interest

Contribution

DS, GZS and JCS designed the study, wrote the protocol and collected the data. IB, AH, MJW, BM organized and analyzed the data, and IB wrote the first draft of the manuscript. TDM provided substantial input with respect to the clinical variables. HH and BM provided advice regarding analyses and interpretation of the DTI data. All authors contributed to the interpretation of the data, and have approved the final manuscript.

as harm avoidance and empathy are associated with differences in white matter (WM) integrity (42–47). Of relevance for the current study are findings from two studies investigating WM correlates of psychopathy traits and neuroticism in male inmates and a non-clinical population. Those studies showed a positive link between increased neuroticism and psychopathy-related traits (e.g. lying, manipulateness, egocentricity), and reduced WM integrity in the uncinate fasciculus, the forceps minor, the corona radiata, the superior longitudinal fasciculus, and the inferior fronto-occipital fasciculus (48, 49). No published study has, however, investigated the association between WM and personality traits in BD.

Similarly, the relationship between cognitive functioning and personality in BD is largely unexplored. To the authors' knowledge the only published paper focusing on this topic found that, in patients with BD, cyclothymia and irritability were associated with better processing speed, working memory, reasoning and problem solving (31). By contrast, healthy controls with high irritability scores performed more poorly on tasks of attention and social cognition. Thus, in BD, certain personality traits may lead to negative mood symptoms, while, to a certain extent, “facilitating” neurocognitive functioning. An earlier study focused on cognition and symptoms dimensions such as negative symptoms, depression in non-affective psychosis (50). In line with Russo et al.'s results, the authors found a U-shaped association between mania and executive functions which may indicate that a certain amount of mania may boost cognitive abilities.

Diffusion tensor imaging (DTI) offers a unique insight into the microstructural characteristics of white matter pathways connecting to different cortical regions. DTI explores the white matter (WM) microstructure by using parameters such as fractional anisotropy (FA), mean diffusivity (MD), axial (AD) and radial (RD) diffusivity (51, 52). These indices provide essential information on the type of biological mechanisms underlying potential WM alterations (53, 54). In particular AD has shown to be altered following axonal damage, while RD is more sensitive to demyelination and axonal degeneration (55, 56). Adults with BD typically display decreased FA coupled with decreased RD and MD values within the retrolenticular part of the internal capsule, the superior and anterior corona radiata, and the corpus callosum (57, 58). Similar abnormalities have been found in the hippocampus, thalamus and caudate nucleus (54). Reduced FA values have also been observed in tracts connecting amygdala, anterior and subgenual cingulate cortex (24, 59). AD and RD have been shown to be altered in the commissural (corpus callosum) and projection tracts (thalamic radiation) and in pathways connecting subgenual, supragenual, and posterior areas of the cingulate cortex (56, 60, 61). Increased RD values were also observed in the association tracts of BDI patients when compared to their unaffected relatives and healthy controls (62).

Only a small number of studies have investigated the relationship between DTI metrics and cognitive abilities in BD. In our previous study we found that a BD sample including individuals with BDI, BDII and BD NOS performed poorly on verbal fluency tasks and exhibited large clusters of altered FA, RD and MD values in the internal capsule, the superior and anterior corona radiata, and the corpus callosum (57). In this study increased FA values in the left inferior fronto-occipital fasciculus and the forceps minor correlated positively with verbal fluency scores (57). Further, RD and MD parameters in the

corticospinal tract and the superior corona radiata correlated negatively with memory scores. Another study showed a positive correlation between problem solving scores and FA in the thalamic radiation and fornix (60). Decreased FA values in the internal capsule, the right uncinate fasciculus, and the corpus callosum were coupled with decreased accuracy in set shifting and risk taking tasks (63). Further, individuals with BDI were found to have reduced FA values in the uncinate fasciculus, increased fronto-limbic functional connectivity when exposed to fear stimuli, and slowed response times to affective stimuli during an attention control task (64). In sum, alterations in WM properties may contribute to the difficulties in disengaging attention away from positive stimuli (65) and focus on negative stimuli (66–68) observed in BD.

Given the dearth of research in this area, we decided to investigate: 1. whether there are DTI alterations in WM tracts underlying affective processing in adults with BD compared to healthy controls (HC); 2. whether WM FA values correlate negatively with personality factors which are discussed as risk factors for BD (e.g. neuroticism), and correlate positively with personality traits which may increase resilience (e.g. extraversion).; and 3. whether WM FA values correlate positively with performance on a task of affective processing.

Based on the available evidence we expected to find: 1) reduced FA values in the corticospinal tract, the superior longitudinal fasciculus (SLF), the inferior fronto-occipital fasciculus (IFOF), and the forceps minor in adults with BD compared with HC; 2.) a positive correlation between FA values and performance in the AGN task; 3). a negative correlation between FA values and neuroticism scores, and 4). a positive correlation between FA values and personality traits such as openness, extraversion and consciousness. Given the preliminary nature of this study we could not predict whether correlations would differ in strength or direction between BD and HC. For all these analyses we will focus on WM FA values of tracts found to be altered when comparing HC and BD. Further, we predicted that adults with BD would present with altered DTI parameters, a different personality structure, and have stronger attentional bias toward affective material compared to HC.

Materials and methods

Participants

The sample included 24 healthy controls and 38 adults with BDI (HC: 29.47±2.23 years, 15 females; BDI: 32.44±1.84 years, 20 females). Patients were recruited from inpatient and outpatient clinics of the University of North Carolina at Chapel Hill (UNC). Ten individuals with BDI were euthymic, 19 depressed, 3 manic, 1 hypomanic and 4 in mixed mood state at the time of testing. Healthy subjects were recruited through local media advertisements and flyers posted in public areas. All patients met the DSM-IV-R criteria for BDI. 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) (69), which was administered to all participants by a psychiatrist or trained research assistant. Individuals with BDI and healthy controls had no history of substance abuse in the previous 6 months and no current medical problems. Healthy controls (HC) with a history of any Axis I disorder in first-degree relatives prior to the start of the study were excluded. Current mood state was evaluated by trained research staff via the

Montgomery-Åsberg Depression Rating Scale (MADRS)(70) and the Young Mania Rating Scale (YMRS)(71). All female participants underwent a urine pregnancy test and urine drug screen to exclude pregnancy and illegal drug use. Subjects suffering from chronic, cardiovascular and neurological disorders or taking medications for these conditions were excluded. The study protocol was approved by the local Institutional Review board and informed consent was obtained from all the participants.

Personality

Personality traits were assessed using the 44-item Big Five Inventory (BFI: (72)). This self-report questionnaire measures five personality traits: extraversion (e.g. “is talkative”), agreeableness (e.g. “is helpful and unselfish with others”), conscientiousness (e.g. “does a thorough job”), neuroticism (e.g. “worries a lot”), and openness (e.g. “has an active imagination”) (73). Participants are asked to rate a list of characteristics on a five-point Likert scale (1 = disagree strongly to 5 = agree strongly). Each trait is scored by adding the appropriate items together. BFI shows high convergent validity with other self-report personality scales (74) and Cronbach’s alpha reliability scores range from 0.716 to 0.88 (75).

Cognitive assessment

To estimate participants’ premorbid general intelligence we used the Wechsler Abbreviated Scale of Intelligence (WASI) (76, 77). Participants were then administered the Affective Go/No-Go paradigm (AGN) and the Rapid Visual Processing (RVP) of the computerized Cambridge Neurocognitive Test Automated Battery (CANTAB - <http://www.cantab.com>) (78). The selection of this cognitive battery was based on its well-established sensitivity to cognitive impairment in psychiatric disorders (79, 80).

The AGN task evaluates the effect of the emotional valence of words on the participant’s ability to identify the target valence (positive or negative) and to inhibit a response to the non-target valence with the target and non-target valences switching across trials. Participants are presented with positive (e.g., joyful, warmth, courage) and negative (e.g., mistake, hopeless, burden) words in a counterbalanced manner, and instructed to respond to either happy or sad stimuli depending on the task condition. The primary outcome measures of this study are the mean latencies to correct trials and the number of commission errors (false positives) across the positive and negative conditions.

The Rapid Visual Processing (RVP) task is a non-emotional analogue of the AGN task selected to assess attention and information processing abilities. This task was selected to control for general differences in attention that could potentially impair performance in the AGN task. Participants are presented with sequences of digits from 2 to 9 and instructed to press on a response pad when they see the target sequence of numbers (e.g. 2–4–6). The main outcome measures were the mean response time to correct target sequences (mean latency) and the total number of commission errors.

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=2mm, imaging matrix=128×104, voxel size= 2mm, b-value =1000 sec/mm². Two non-diffusion weighted scans (b-value =0 s/mm²) were acquired prior to the acquisition of 30 diffusion weighted scans (each containing 80 slices). To correct for eddy currents we used the first b0 image as a template.

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 threshold of 0.3. The "DTIfit" routine implemented in FSL was then used to fit the diffusion tensor to each voxel thus creating voxel-wise maps of FA, AD, RD and MD.

Voxelwise statistical analysis of data was carried out using Tract-Based Spatial Statistics (TBSS) within FSL. All subject's FA data were affine-registered to MNI152 space using the FSL nonlinear registration tool FNIRT. The mean FA image was created and optimized to create a mean FA skeleton to represent common tracts among all individuals. Individual subjects' FA data was projected onto this skeleton. Voxelwise statistics across subjects (adjusted for gender and age) were carried out on each point of the FA skeleton using permutation-based nonparametric testing (RANDOMISE - as implemented in FSL), using 5000 permutations [40] to compare differences between BD patients and HC. A false discovery rate (FDR) correction was used to correct the threshold for multiple comparisons and the minimum threshold of statistical significance was set at $p < 0.001$. Based on the results of the voxel-wise analyses, we superimposed significant clusters containing > 5 voxels on the Johns Hopkins University (JHU)-ICBM-DTI-81 WM labels atlas and extracted FA, RD, MD and AD values for each participant.

Statistical analyses

The analyses presented in this paper are based on data from a subset of the participants who took part in our previous study focusing on DTI and cognition (57). In the current study we selected individuals diagnosed with BD Type I and examined the relationship between their DTI findings, personality, and affective processing using the CANTAB cognitive battery. Statistical analyses were performed using IBM SPSS statistics (Version 21.0). Normality assumptions were examined. Where appropriate, outliers were winsorised and log, square root or reciprocal transformations applied to achieve normality. One-way ANOVAs and chi-square (χ^2) analyses were used to compare demographic and clinical differences between groups. Separate multivariate analyses of variance (MANOVA) were performed to find group differences in: 1. DTI measures (FA, RD, AD and MD values extracted from each significant cluster containing > 5 voxels as stated in the previous section); 2. Big Five

Inventory scores; and 3. mean latencies and number of errors in the AGN and RVP tasks. Analyses focusing on AGN and RVP variables included “Age” as a covariate. Demographic and cognitive results were considered to be statistically significant at a Bonferroni-adjusted *p-value* .05. Pearson’s correlation coefficients were calculated to explore the relationship between AGN measures (accuracy and reaction times), the five traits of the BFI, and FA values in WM tracts found to be altered in BD compared to HC. P-values for Pearson’s correlation analyses were adjusted for multiple comparisons by using false discovery rate (FDR) correction (81). P-values ranging from .05 to .10 were considered to be statistical trends. To assess the significance of the difference between relevant correlations in BD and HC we first used Fisher’s z-transformations, and then determined if the difference between values was smaller or greater than the statistical threshold ($p=.05$; $z=1.96$) (82).

Results

Group characteristics

Demographics and clinical features for BDI and HC are reported in Table 1. There was no significant difference in age and gender between the two groups. Years of education and the pre-morbid IQ (WASI) were significantly reduced in BDI patients compared to HC (Education: $p=.003$, WASI: $p=.008$). As might be expected individuals with BDI scored higher on mood rating scales (e.g. YMRS, MADRS) than HC and displayed reduced global functioning in the GAF scale.

Personality traits

14 HC and 22 individuals with BDI completed the BFI questionnaire. A MANOVA was used to compare personality trait scores between BDI and HC resulting in a highly significant main effect of group (Pillai’s Trace=.626, $F(5,30)=10.063$, $p<.001$). The univariate F tests showed that BDI and HC differed in terms of agreeableness [$F(1,34)=4.58$, $p=.04$, $\eta^2=.119$], conscientiousness [$F(1,34)=13.33$, $p=.001$, $\eta^2=.282$], and neuroticism [$F(1,34)=47.77$, $p<.001$, $\eta^2=.584$]. Compared to HC, BDI scored lower on the agreeableness and conscientiousness scale, while they achieved higher scores in the neuroticism scale. There was no statistically significant difference in mean extraversion and openness scores between the two groups. (Table 1).

Cognitive performance

Statistical analyses of the number of commission errors retrieved significant results (Pillai’s Trace =.129, $F(2, 58)=4.279$, $p=.018$, $\eta^2=.129$) and showed differences in the number of errors to positive [$F(1,59)=6.828$, $p=.011$, $\eta^2=.104$] and negative stimuli in the AGN task between BD and HC [$F(1,59)=8.444$, $p=.005$, $\eta^2=.125$]. *Post-hoc* analyses showed that individuals with BD committed a greater number of commission errors in the AGN task than HC ($p=.05$). Mean response latencies to positive and negative stimuli in the AGN task were comparable across groups. There was no group difference in mean latency and mean number of false alarms in the RVP task ($p>.05$) (Table 2).

To control for general differences in attention that could potentially impair performance in the AGN task, we re-ran the analyses for the AGN measures using RVP reaction times and

accuracy as covariates. Results remained significant [Pillai's trace=.118, $F(2, 56)=3.748$, $p=.03$, $\eta^2=.118$] for both the number of total commission errors to positive [$F(1, 57)=5.54$, $p=.022$, $\eta^2=.089$] and negative stimuli [$F(1, 57)=7.255$, $p=.009$, $\eta^2=.113$].

DTI metrics

Individuals with BD exhibited reduced FA and increased RD and MD values in all major WM tracts. The largest clusters (> 10 voxels) with abnormal FA values were located within the right corticospinal tract, the left superior longitudinal fasciculus, the left inferior fronto-occipital fasciculus and the forceps minor. Increased RD values were found within the right corticospinal tract and the fronto-occipital fasciculus bilaterally. There was no statistically significant difference in DA values scores between BD and HC. By superimposing these results on the JHU-ICBM-DTI-81 atlas, clusters with reduced FA were found to be located in the right retrolenticular portion the internal capsule. Clusters with increased RD were situated in the body of the corpus callosum, right and left superior corona radiate, the corticospinal tract and the left internal capsule. Increased MD values were found in the body of the body of corpus callosum (Figure 1).

Personality traits and AGN performance

In BD neuroticism scores correlated negatively with mean latency to positive stimuli ($r=-.567$, FDR-corrected $p=.03$). After FDR correction there were statistical trends towards a negative correlation between neuroticism and mean latency to negative stimuli ($r=-.433$, $p=.08$), and a positive correlation between neuroticism and commission errors to positive stimuli ($r=.404$, $p=.09$). Interestingly, although not significant, the correlation between neuroticism and latencies to positive stimuli was negative in HC too ($r=-.165$, $p=.58$, Figure 2). Comparing the correlations between BD and HC, however, did not reveal any statistically significant significances ($z=-1.26$, $p=.104$). The positive correlation between neuroticism and the total number of commission errors to negative stimuli was positive in HC too but not significant after correction ($r=.564$, $p=.15$). Correlations between AGN measures and the other BFI traits did not approach significance.

Correlations between DTI metrics, personality and AGN performance

Pearson's coefficients of correlation were calculated to explore the relationship between FA values in WM tracts found be altered in BDI compared to HC, BFI scores, and performance in the AGN task. In HC, FA values in the left SLF correlated positively with mean latency to positive stimuli ($r=.901$, $p=.01$). Similarly, correlations between FA values in both the left SLF and IFOF and mean latency to negative stimuli were positive and statistically significant (SLF: $r=.842$, $p=.02$; IFOF $r=.827$, $p=.02$). In BD, all these correlations were not significant (left SLF and latency to positive stimuli: $r=-.062$, $p=.89$; left SLF and mean latency to negative stimuli: $r=.061$, $p=.81$; IFOF and mean latency to negative stimuli: $r=.542$, $p=.11$). The differences between correlations in BD and HC were statistically significant (IFOF: $z=3.187$, $p=.001$; SLF: $z=2.416$, $p=.008$ respectively).

Discussion

The purpose of the current study was to examine personality traits and affective processing alongside WM integrity in adults with BDI. Whole-brain TBSS analyses found FA alterations in the right corticospinal tract, the left superior longitudinal fasciculus (L-SLF), the left inferior fronto-occipital fasciculus (IFOF-L) and the forceps minor. Altered RD values were found within the right corticospinal tract (CST) and the IFOF bilaterally. These results are consistent with the current literature (81) and confirm the results of our previous study - from which the current subset of BDI participants was selected (57) – that detected clusters with reduced FA and abnormal RD and MD values that were predominantly located in the retrolenticular part of the internal capsule, the superior and anterior corona radiata (SCR, ACR), and the corpus callosum.

Markers of tissue water diffusivity such as RD provide essential information on the nature of the microstructural changes observed in BD (61, 82). Such changes may be due to reduced integrity of the axonal wall (83) and demyelination (55, 84–86). Few studies have examined AD and RD and little is, therefore, known about changes in these indices in individuals with BD. In a previous study middle-aged individuals with BD were found to be characterized by lower AD and RD in the left internal capsule, the left ILF, and in the cortico-spinal tract when compared to HC (87). The authors hypothesized that this could be due to axonal damage based on previous evidence showing that temporal lobe surgery leads to tissue swelling and altered AD values (88). Another study comparing pediatric and adult BD populations found an age effect across all DTI parameters in the left internal capsule, with young BD patients displaying reduced FA values and, similarly to our study, increased RD values in the internal capsule when compared to adult BD individuals (89). This finding was associated with reduced myelination. Considering all these findings together, one could speculate that abnormalities in RD are more common in adults with BD and result from delayed brain maturation. However, given the cross-sectional nature of all these studies it is unclear whether RD abnormalities are vulnerability markers of BD and/or lead to the clinical and cognitive symptoms observed in pediatric BD.

The current findings provide valuable insight into the relationship between the integrity of WM pathways and the deficits in cognitive processing observed in BD. Indeed, the internal capsule and the corona radiata are important WM nodes that facilitate the transfer of sensorimotor and cognitive information between the brain stem, the thalamus, and the fronto-striatal circuit (29, 90) (87). Further, tracts connecting to the corpus callosum, such as the fornix minor, mediate the transfer of interhemispheric information, which is crucial for higher order cognitive functions, and the corpus callosum has been shown to exhibit morphological abnormalities in mood disorders (91, 92).

In terms of affective processing, individuals with BDI exhibited similar reaction times than HC but their response accuracy was reduced. This result suggests that BDI participants may have not been able to compensate for the distraction effect of affective stimuli. In line with previous studies showing increased brain activation during conditions of emotional distractibility in BD (93, 94), one could speculate that the recruitment of neural resources needed to suppress affective stimuli reduced their attentional capacity and led to reduced

accuracy on the AGN task. The lack of group differences in performance in the RVP task suggests that there are no general attentional deficits in BDI compared to HC, and this further confirms evidence that the neuropsychological performance of patients with BD may be impaired by dysregulations in affect processing, rather than alterations in high-order cognitive functions such as attention and working memory.

Further, our prediction that neuroticism scores would correlate with performance in the AGN task was only partially met. Indeed, in BDI, elevated neuroticism scores were linked to faster reaction times with mean latency to positive stimuli, but this correlation was not statistically significant in HC. Furthermore, the difference in correlations between HC and BD was not significant. These findings may suggest that the link between cognition and neuroticism differs between HC and BD. Support for this hypothesis comes from a previous study showing that while in HC irritability – a facet of neuroticism – correlated negatively with attention, in BD, high irritability was associated with faster processing speed (31). Therefore, the faster response times could indicate increased “impulsivity” or high responsiveness to emotional stimuli in patients with BD. Further, since neuroticism has been linked to increased focus on negative stimuli and increased stress responsiveness (95), one could speculate that neuroticism may contribute to the “negative affective bias” typically observed in BD. However, given the small sample size, these findings may not provide an optimal description of the link between neuroticism and cognition. The current findings should, therefore, be considered preliminary, and need to be replicated with a larger sample.

Our findings also show important links between WM integrity, personality and affective processing in BD. Besides confirming our hypothesis that BD individuals would present a different personality profile and AGN performance than HC, we found significant correlations between FA values, AGN measures and neuroticism scores. In particular, the positive correlations between mean latencies to affective stimuli and FA values in the left SLF and IFOF were more pronounced in HC than BD. These results are compelling for a number of reasons. The WM tracts included in our analyses are known to underlie both affective processing and cognitive control. Indeed, the SLF is a pathway that connects frontal to parieto-temporal regions and has been reported to be altered in individuals with psychotic features (59). The corpus callosum connects to the fronto-limbic network and is essential for the explicit and implicit processing of emotional stimuli, along with attentional control and emotional dysregulation (59). The negative correlation between FA and neuroticism is consistent with previous findings showing a link between altered DTI metrics in the fronto-cingulate and limbic regions and neuroticism (96–98). There is also evidence of an association between abnormal DTI metrics in the cingulum-hippocampus tracts and increased anxiety scores (99). It is intriguing that the expected significant relationship between FA values and neuroticism was observed in HC but not in BD. A similar dissociation was found in Motzkin et al.’s study where anxiety and FA in the right uncinate fasciculus was present in HC but not in psychopaths. The authors suggested that this could be due to an inefficient connectivity between limbic/frontal regions and inefficient integration and processing of affective information (100).

Equally intriguing is that the positive correlations between increased mean latencies to affective stimuli and elevated FA values in the left SLF and IFOF were observed in HC but

not in BDI. Considering that patients with BDI were overall faster but less accurate than HC, this finding supports the hypothesis of reduced brain connectivity and information processing. In other words, WM integrity in these tracts may be essential for individuals to perform optimally on a timed task. For instance, by “slowing down” individuals can minimize variations in attention, fatigue and motivation while having the time to be accurate in the task. Our results have to be interpreted with caution and warrant replication in a larger sample. Indeed only a subset of HC and BD completed the BFI. Thus, the reported correlations between DTI, cognition and neuroticism scores were based on a small sample size. Further, we focused our analyses on a small number of WM tracts and selected FA values as an estimate of WM integrity.

One of the strengths of the current study is the use of tasks from a validated and standardized computerized cognitive battery (CANTAB) previously used in samples with psychiatric disorders (78) and the Big Five Inventory as a questionnaire based on a well validated model of personality (101) with strong predictive validity (102, 103) and interrater agreement (104). A potential confounder is that the majority of our BD participants took one or more psychotropic medications. Indeed, psychotropic medications have been associated with structural changes in the fronto-limbic and hippocampal regions (105–107) and differences in cognitive performance (108, 109). Furthermore, this study included patients with BD in different mood phases. Meta-analyses and empirical studies found that individuals in the acute BD phase present with significant deficits in processing speed, learning and memory, and attention (79, 110). Given that the MADRS scores of our BD sample revealed the presence of depressive symptoms of mild intensity; one could argue that current mood may have impaired performance in the AGN and RVP tasks and potentially personality assessment. Additionally, AD and RD values are known to vary according to levels of water diffusivity and may be affected by shift of water from extracellular space that are not related to mental health conditions (87). Future studies should therefore investigate intra-individual variations in AD and RD across BD mood phases.

In conclusion, our findings provide preliminary evidence of the association between neuroticism, affective processing and WM integrity in adults with BDI. The reported attentional bias toward affective stimuli along with the distinct personality traits (increased neuroticism, decreased agreeableness and consciousness), and changes in integrity observed in relevant WM tracts appear to be closely connected and may serve as markers of vulnerability to BD.

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Figure 1.

Mean fractional anisotropy (FA), radial diffusivity (RD) and mean diffusivity (MD) values in the right retrolenticular part of the internal capsule (IC-R-ret), the corpus callosum (CC-body), the left CP, the right and left superior corona radiata (SCR-R and SCR-L) of individuals with BD-I (right of the box pair) and HC (left of the box pair). Tracts are labeled with reference to the JHU ICBM-DTI-81 white matter labels atlas. L and R denote the left and right hemisphere. *FDR-corrected $p < .05$; **FDR-corrected $p < .01$.

Figure 2. Scatterplots showing the relationship between Neuroticism scores and AGN reaction times to positive stimuli in HC (left figure) and BDI (right figure).

Table 1

Demographic and clinical characteristics of the sample. Abbreviations: BD: Bipolar Disorder; GAF: Global Assessment of Functioning; HC=Healthy Controls; MADRS: Montgomery–Åsberg Depression Rating Scale, YMRS: Young Mania Rating Scale, WASI: Wechsler Abbreviated Scale of Intelligence.

Group	N (HC/BD)	HC	BD	Mean (SD)	F/X ²	p
Gender Male/female, N	24/38	9/15	15/20		.6	.31
Age (years)	24/38	29.47±2.23	32.44±1.84		1.03	.31
Education Years	22/38	16.59±2.404	14.24±2.48		12.86	.001
WASI Full Scale IQ	22/36	117.95±13.13	108.59±12.13		7.66	.008
Current Mood State	0/37		10 euthymic 19 depressed 3 manic 1 hypomanic 4 mixed			
YMRS	23/37	.35±.57	6.3±5.78		24.05	.001
MADRS	22/38	.23±1.07	17.66±12.38		43.09	.001
GAF	24/38	93.33±3.99	58.29±10		266.76	.001
MEDICATION Medicated/Total	24/36	0/24	12/36 (2 lithium, 2 anticonvulsants, 2 antidepressants, 2 antipsychotics, 2 benzodiazepines, 2 stimulants)			
Age of onset of mood disorders (years)	0/34		21.56±5.95			
Lifetime number of mood episodes	0/33		57.57±36.47			

Table 2

Demographic and clinical characteristics of the sample. Abbreviations: GAF: Global Assessment of Functioning, MADRS: Montgomery–Åsberg Depression Rating Scale, YMRS: Young Mania Rating Scale, BFI: Big Five Inventory; WASI: Wechsler Abbreviated Scale of Intelligence, WRAT: Wide Range Achievement Test.

Group	N (BD/HC)	Healthy Controls (HC)	Bipolar Disorder (BD)	F/X ²	p
AGN RT Negative Stimuli	24/38	520.26±54.41	523.36±74.46	0.12	.012
AGN RT Positive Stimuli	24/38	508.58±51.78	507.79±84.99	0.14	.906
AGN Commissions negative	24/38	2.27±1.744	4.62±3.46	8.44	.005
AGN Commission positive	24/38	2.77±1.93	5.26±4.03	6.83	.011
RVP RT	24/38	395.61±87.12	418.75±86.13	.85	.361
RVP false positive	24/38	1.00±1.14	1.76±2.85	1.38	.246
BFI Extroversion	14/22	29.29±3.29	26.02±7.74	2.21	.146
BFI Agreeableness	14/22	34.36±3.37	29.95±7.18	4.58	.040
BFI Conscientiousness	14/22	34±4.61	26.68±6.52	13.33	.001
BFI Neuroticism	14/22	17.57±3.30	30.91±6.70	47.77	.001
BFI Openness	14/22	38.64±3.65	38.52±8.65	.002	.961