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Steeper slope of age-related changes in white matter microstructure and processing speed in bipolar disorder

Sheena I. Dev, M.S.^{1,2,3}, Tanya T. Nguyen, Ph.D.^{2,4}, Benjamin S. McKenna, Ph.D.², Ashley N. Sutherland, M.A.^{1,2}, Hauke Bartsch⁵, Rebecca J. Theilmann, Ph.D.⁵, and Lisa T. Eyler, Ph.D.^{1,2,3}

¹Research Service, Veterans Affairs San Diego Healthcare system, San Diego, California

²Department of Psychiatry, University of California, San Diego

³San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California

⁴VA San Diego Healthcare System, Mental Illness Research, Education, and Clinical Center (MIRECC), San Diego, California

⁵Department of Radiology, University of California, San Diego

Abstract

Objectives—Bipolar disorder (BD) is associated with compromised white matter (WM) integrity and deficits in processing speed (PS). However, few studies have investigated age relationships with WM structure and cognition to understand possible changes in brain health over the lifespan. This investigation explored whether BD and healthy comparison (HC) participants exhibited differential age-related associations with WM and cognition, which may be suggestive of accelerated brain and cognitive aging.

Design—Cross-sectional study.

Setting—University of California San Diego and the Veterans Administration San Diego Healthcare System.

Participants—33 euthymic BD and 38 HC participants.

Measurements—Diffusion tensor imaging was acquired as a measure of WM integrity, and tract-specific fractional anisotropy (FA) was extracted utilizing the Johns Hopkins University probability atlas. PS was assessed with the Number and Letter Sequencing conditions of the Delis-Kaplan Executive Function System Trail Making Test.

Correspondence should be addressed to: Sheena I. Dev., M.S. Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive (151B), La Jolla, CA 92016, Ph: (858) 534-9667; F: (858) 534-9054; sdev25@gmail.com.

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Results—BD participants demonstrated slower PS compared to the HC group, but no group differences were found in FA across tracts. Multiple linear regressions revealed a significant group-by-age interaction for the right uncinate fasciculus, the left hippocampal portion of the cingulum and for PS, such that older age was associated with lower FA values and slower PS in the BD group only. The relationship between age and PS did not significantly change after accounting for uncinate FA, suggesting that the observed age associations occur independently.

Conclusions—Results provide support toward future study of the accelerated aging hypothesis by identifying markers of brain health that demonstrate a differential age association in BD.

Keywords

Bipolar; Aging; white matter; processing speed; DTI

Objective

Bipolar disorder (BD) is a disabling mental illness characterized by alternating manic, depressive, and remitted mood states. Advancements in the pharmacological treatment of mood symptoms have contributed to the longevity of patients living with the disorder; however, our understanding of the physical health and cognitive outcomes of an aging BD population is limited. It has been hypothesized that BD patients may exhibit a more rapid, or accelerated, trajectory of age-related decline compared to their psychiatrically healthy counterparts (HCs). BD patients show increased rates of metabolic syndrome, cardiovascular disease, and neurodegenerative disorders—conditions typically associated with aging—at an earlier age (1,2). However, cognitive and brain aging in BD has been relatively understudied.

Decreased white matter (WM) integrity appears to be a key pathophysiological feature of BD. Diffusion tensor studies investigating micro-structural WM alterations in BD have consistently demonstrated widespread reductions in fractional anisotropy (FA; (3,4)). The uncinate fasciculus (UF;(5,6)) and superior longitudinal fasciculus (SLF; (7,8)) appear to be especially vulnerable to WM pathology in BD. Reduced FA in both the UF and the SLF have also been noted in longitudinal studies of normal aging, suggesting that these tracts are vulnerable to age-related decline (9,10). Taken together, these studies suggest that the pathophysiology of both aging and BD are independently associated with reduced integrity of the SLF and UF. Thus, it is reasonable to suggest that older BD patients may be impacted by processes related to both aging and psychiatric illness, though it is unclear to what extent each impacts brain and cognitive health.

Despite the rich literature implicating WM alterations in BD, only a small handful of studies have investigated the trajectory of WM alterations over the lifespan and have yielded mixed results. One recent cross-sectional study, using probabilistic tractography, reported a stronger negative association between age and WM integrity in the corpus callosum of BD patients than HCs (11). However, other studies have found no evidence of differential age associations with WM integrity (12), though small sample sizes and short follow-up periods may have limited the statistical power. It should be noted that studies investigating age-associations with WM to date have done so using whole brain probabilistic tractography or TBSS methodologies to identify components of fiber tracts common to all individuals within

the sample (13,14). However, psychiatric populations have been shown to display greater variability in cognitive performance (15); thus, it is possible that a similar degree of heterogeneity exists among WM microstructure in BD. As such, a region-of-interest (ROI) based analysis of WM tracts may be a more useful technique to adequately capture tract variability within BD.

Similarly, cognitive impairment has been well characterized in BD. Processing speed (PS) is a domain particularly vulnerable in this population (16) and declines with normal aging (17); thus, it is of interest when considering trajectories of cognitive decline in bipolar disorder. Most studies investigating age-related cognitive decline in BD have found no differential cognitive trajectories between BD patients and HCs (12,18), though many of these studies did not use validated neuropsychological tests to assess cognition or did not examine PS specifically. However, one study investigated age associations with cognition utilizing a comprehensive neuropsychological battery and revealed that only Trail Making Test A exhibited steeper age-related decline with age in BD (19). It should be noted that the BD sample in this study consisted of individuals across the spectrum of mood states, making it difficult to determine whether this association would remain significant during more stable phases of the disorder. Nevertheless, it provides some indication that BD patients may experience a more rapid trajectory of decline in PS. More studies utilizing comprehensive neuropsychological testing in euthymic samples are needed to determine whether age-related changes occur above and beyond state-related changes.

The mixed results could suggest that only some BD patients experience a more rapid trajectory of decline in these domains. Thus, identifying disease markers that impact these trajectories is an imperative first step in mitigating functional decline in aging BD patients. Variables related to illness chronicity may be associated with future decline in cognitive performance and brain structure. Greater number of manic episodes, depressive episodes, and prior psychiatric hospitalizations have been linked to deficits in verbal memory, executive function, PS and attention (20) as well as decreases in grey matter volume across several cortical and subcortical brain regions (21). Similarly, greater number of mood episodes is associated with greater WM lesions in male BD patients. Taken together, these studies suggest that greater chronicity of illness in BD may contribute to worse outcomes in brain structure and function over time.

Thus, more studies are needed to disentangle the effects of the aging process on WM structure and cognition, the inter-relationship between brain and cognitive age-related trajectories, and the contributions of illness chronicity to observed trajectories in BD patients. To do this, an ROI-based methodology may be most appropriate to investigate these associations in specific tracts of interest. Given the mounting evidence of group differences reported in the literature, the UF and SLF are two such candidate tracts in which differential age associations may be observed.

The goal of this study was to explore whether BD patients and HCs exhibit differential age-related associations with WM microstructural integrity and cognition, perhaps suggestive of accelerated brain and cognitive aging. We hypothesized that 1) BD patients would demonstrate a steeper negative age-related slope of FA in bilateral UF and SLF WM tracts

compared to HCs; 2) BD patients would demonstrate a steeper positive slope in PS compared to HCs; and 3) BD individuals with greater symptom chronicity (e.g., greater number of manic episodes) would demonstrate the strongest age associations between WM and cognition. In addition, we were interested in examining the inter-relationships among age, cognition, and WM tract integrity. Given that BD with psychosis has been associated with worse cognition (22) and alterations in brain structure and function (23,24), we also explored whether there were any group differences in PS or FA between BD patients with (PBD) and without (NPBD) psychosis that might better explain our results.

Methods

Participants

Thirty-three euthymic BD and 38 age- and education-matched HC participants were enrolled in the study. Given the *a priori* nature of the age analysis, significant attempts were made to recruit relatively equivalent numbers of BD and HC participants within the following age bins: 30–39 (BD n=9, HC n=8); 40–49 (BD n=13, HC n=11); 50–59 (BD n=6, HC=12); 60–69 (BD n=5, HC n=7). Inclusion and exclusion criteria as well as clinical rating scales utilized to determine remitted mood state have been described elsewhere (25). All procedures were approved by the University of California, San Diego and San Diego Veterans Affairs Healthcare System Institutional Review Boards. Written informed consent was obtained by all participants. Demographic and clinical rating information are presented in Table 1.

Medical History and Neuropsychological Testing

A full medical and substance (including alcohol) use history was obtained. The Framingham Stroke Risk profile (26) was administered as a self-report measure of vascular risk burden. To compute medication load, low (“1”) and high (“2”) values were assigned to prescribed psychiatric medications based on dosage and duration of use. These values were summed to represent a medication load value for each BD participant (27).

All participants were administered the Delis-Kaplan Executive Function System Trail Making Test (D-KEFS; (28)). A PS composite score was computed for each participant by averaging the raw scores of the Number Sequencing and Letter Sequencing conditions.

Imaging Data Acquisition and Processing

All participants were scanned at the UCSD Center for Functional Magnetic Resonance Imaging using a research-dedicated 3T GE Discovery MR750 whole-body imaging system with an 8-channel head coil. A high resolution T1-weighted anatomical scan was acquired using a fast spoiled gradient echo pulse sequence (TE=4ms, flip angle= 90°, 1mm³ resolution). A 51 direction diffusion tensor imaging scan was acquired axially for the whole brain (TE/TR=70ms/9,700ms, in-plane resolution=2.5mm × 2.5mm, slice thickness=2.5mm, b-value=1000s/mm²). Two volumes with no diffusion encoding (b0) in alternate phase encoding directions were utilized to correct for nonlinear distortions due to field inhomogeneities.

Pre-processing of DTI images included correction of subject motion while in the scanner and image distortion in the diffusion-weighted volumes due to eddy currents, magnetic susceptibility artifacts, and scaling differences. Images were then resampled to a 1mm³ voxel resolution using linear interpolation. FA and axial and radial diffusivities were calculated using standard formulas by fitting a tensor model to raw diffusion data (29). As FA is calculated from the three eigenvalues that also compose axial and radial diffusivity, we chose to focus our analyses only on FA to avoid concerns of multiple testing. FA maps were then registered to standard MNI space. To address partial volume effects (30), FA maps were thresholded (>0.20) to increase the probability that only voxels within WM tracts were included in subsequent analyses. The Johns Hopkins University (JHU; (31)) WM probability atlas was then utilized to extract ROI FA masks of bilateral UF and SLF. Additional masks of the anterior thalamic radiation, corticospinal tract, hippocampal portion of the cingulum, cingulate portion of the cingulate, forceps major, forceps minor, inferior fronto-occipital fasciculi, and inferior longitudinal fasciculi were also available in this atlas and investigated in exploratory analyses. Mean FA values within each tract ROI were extracted and transferred to SPSS for statistical analysis.

Statistical Analysis

All variables were checked for normality and independent sample t-tests or Chi-squared tests were used to determine group differences in demographic variables. Among the BD sample only, t-tests were employed to determine group differences in FA between PBD (n=20) and NPBD (n=11) participants.

A priori linear regressions were performed with group and age on FA values in bilateral UF and SLF (hypothesis 1) and PS (hypothesis 2). Importantly, the group-by-age interaction was assessed in all models. Subsequent exploratory analyses applied the same regression model in all remaining WM tracts available in the JHU atlas.

Next, we examined the inter-relationship of age, FA, and PS in the BD group by first examining whether these were related to each other using Pearson correlations. Given the observed associations, we tested whether accounting for FA decreased the association between age and PS using Sobel's test.

Finally, linear regressions were performed only in the BD group to investigate the impact of both age and measures of illness chronicity (hypothesis 3) on those variables in which a significant group-by-age interaction was observed in the prior analyses. The interactions between age and illness chronicity were included in the models. Variables of illness chronicity included number of manic episodes, number of depressive episodes and time spent in psychiatric hospitalization. All hypothesis tests were 2-tailed and p-values were considered significant at $p<0.05$.

Results

Group comparisons

Groups were comparable on age, education, gender, systolic blood pressure, and stroke risk (Table 1). The BD group performed significantly slower on the composite PS score

($t(68)=2.55$; $p=0.013$). There were no observed group differences in FA for any of the *a priori* WM tracts of interest (all p 's >0.28). Exploratory analyses also revealed no significant group differences in FA in additional tracts available (all p 's >0.08 , see Supplementary Table A). Among the BD sample, patients with a history of psychotic symptoms exhibited higher FA than those without ($t(31)=-2.18$; $p=0.04$) in the right corticospinal tract only. There were no significant differences between PBD and NPBD participants in the FA of any other tracks or in PS.

White matter microstructure and age

Our *a priori* regression models revealed a group-by-age interaction in the right UF only ($t(68)=2.83$, $p=0.006$). This remained significant even after Bonferroni corrections for four *a priori* regions were applied ($p<0.01$). Group-wise correlations further investigating this interaction revealed that older age was significantly related to lower right UF FA for the BD group only ($r(31)=0.40$, $p=0.02$). There was no significant relationship between age and FA in the HC group. See Table 2 and Figure 1.

Analyses investigating group-by-age interactions in our eight exploratory WM tracts also revealed a significant interaction in the hippocampal region of the left cingulum bundle (CH; $t(68)=2.82$; $p=0.006$). Group-wise correlations further elucidated a similar relationship to that found in the right UF: older BD patients exhibited lower FA values than their younger counterparts ($r(31)=-0.42$; $p=0.01$) while there was no significant relationship between age and FA in the HC group. Medication load was not related to either age or right UF or left CH FA in the BD group. See Supplemental Table B.

Processing speed and age

Our analysis investigating differential effects of age on PS also revealed a significant group-by-age interaction ($t(68)=-1.96$, $p=0.05$). Group-wise correlations indicated that older age was associated with slower PS in the BD group only ($r(31)=0.41$, $p=0.02$). There was no significant relationship between age and PS in the HC group. See Table 2 and Figure 1. Medication load was not related to PS in the BD group.

Age, FA, and processing speed relationships in BD

Considering the observed group-by-age interactions in the right UF and PS, indicating negative associations with age only in the BD group, we examined how these findings were related. Within the BD group, right UF FA was negatively correlated with PS ($r(32)=-0.40$, $p=0.02$). Therefore, we tested whether accounting for right UF FA would significantly diminish the relationship between age and PS. Sobel's test was not significant (Sobel's statistic=0.51; $p=0.41$), suggesting that the negative relationships with age for the two measures, right UF FA and PS, are independent phenomena. PS was not correlated ($r(31)=-0.28$, $p=0.12$) with left CH FA in the BD group, so the correlation of PS with age in the BD group could not be explained by the association of this tract's FA with age.

Symptom chronicity and age in BD

Across all three variables of symptom chronicity, no significant age-by-chronicity interactions were detected in the right UF, left CH and PS composite score. Thus, the

observed age associations were not stronger among those BD with greater chronicity of illness. See Supplemental Table C.

Conclusions

This study explored the relationship of age to WM microstructure and PS in a sample of euthymic BD and HC participants to determine whether BD individuals display greater age-related reduction in brain structure and cognition. Although BD patients exhibited significantly slower PS than HCs, no group differences in FA were found in the WM tracts investigated in this study. Nevertheless, older age in the BD group was significantly associated with lower UF and CH FA as well as slower PS, while these relationships with age were not significant in HCs. Further, UF FA did not account for the relationship seen between age and psychomotor speed, indicating that age-related decline in WM microstructure and cognitive speed may occur independently of one another. The results of this study suggest that individuals with BD may experience greater age-related decline in brain and cognitive health compared to normal aging.

These findings are consistent with other studies indicating that WM integrity and PS are vulnerable to BD pathology, and expand upon this literature by suggesting that age may *differentially* impact WM structure and cognition in BD. To date, only one other cross-sectional study has demonstrated a differential age-related reduction in FA in BD, present in the corpus callosum. It appears that multiple, though perhaps not all, WM tracts may be differentially vulnerable to the effects of age in BD. Our results also complement the work of Lewandowski, Sperry (19), which demonstrated that BD individuals across all mood states exhibit a steeper rate of age-related decline in PS, and extend upon their findings to suggest that this phenomenon may be observed during remitted states. Although large-scale longitudinal studies are required to truly establish accelerated age-related decline in WM microstructure and cognition in BD, the results of our study and those before us are critical in identifying potential candidate markers of brain and cognitive health to follow over time. In addition, our results, from a sample that ranged in age from 30–69, also emphasize that age relationships are important to examine in studies of BD, even when the goal is simply to compare those with and without the disorder. We did not find a main effect of diagnosis on WM microstructural integrity, but this was likely due to the observed interaction with age.

Studies investigating the neuropsychological effects of WM abnormalities have consistently demonstrated an association between widespread reductions in FA and slower PS in both HC (32,33) and BD samples (34). Thus, the relationship between reduced right UF FA and slower PS seen in the present study is consistent with an expected neuropsychological outcome of WM pathology. However, tract-specific investigations of the UF have suggested that this tract may play a more important role in integrating emotionally relevant information with memory and executive functioning processes (35), and the UF has been linked to risk taking behaviors in BD (36). In this context, it is not surprising that accounting for variance in right UF FA did not significantly change the relationship between age and PS within the BD group. It is possible that age-related decline seen in both the right UF and in PS are occurring simultaneously, yet independently, and do not share a common etiological

pathway. Future studies are required to determine how age-related WM pathology may mediate cognitive decline in this population.

Stronger age-FA or age-PS relationships were not observed among those with a more severe lifetime presentation (i.e., greater symptom chronicity) of the disorder. This argues against some models of neuroprogression in BD, which postulate that the progressive decline seen in the disorder is primarily due to the cumulative burden amassed over a lifetime of mood episodes (37). Our results suggest that the stronger age association with FA and cognition identified in our BD sample cannot be better explained by the cumulative impact of illness burden (i.e., wear and tear from factors associated with the illness, such as medication effects, stress of manic episodes, and poor healthcare and lifestyle behaviors) and may be a result of specific pathophysiological changes related to bipolar disorder (i.e., rather than an acceleration of “normal aging”) that may lead to an altered aging trajectory. Prospective studies specifically designed to disentangle the effects of chronological age and illness chronicity are required to fully understand their relative contributions to decline in BD.

The lack of group differences in FA between psychotic and non-psychotic BD patients in either the RUF or LCH suggests that these age relationships are not likely driven by psychotic symptoms. However, it is possible that another subgroup of patients may exhibit a steeper age-related decline or that BD individuals display a non-linear trajectory of cognitive and brain changes across the lifespan. Indeed, our group has recently demonstrated a stronger relationship between age and inhibition in those BD individuals with vascular risk (38), and post-hoc analysis of the current data indicate that the stronger age relationships observed in BD group may be driven by the 30–39 age bin (data not shown). Future studies investigating BD subgroups and non-linear trajectories will better disentangle these relationships.

Several limitations to the present study should be acknowledged. The cross-sectional nature of the study does not allow us to directly test the presence of accelerated aging in this psychiatric population. Our modest sample size may have limited our ability to detect statistical significance, though it should be noted that we were able to detect medium to large effect sizes (adjusted R^2 's range from 0.09 to 0.2). Although we consider conditions 1 and 2 of the D-KEFS Trail Making Test as an index of PS, it is possible that these tasks capture additional processes, including fluid cognition (i.e., executive functions; (39)). Indeed, other studies investigating PS in BD often utilize symbol-digit coding, which may rely on graphomotor speed and visual scanning efficiency (40). Thus, it should be noted that PS deficits in BD reported across studies may not be referring to the same construct and likely do not reflect a “pure” PS cognitive process. Further, despite our significant attempts to recruit an equivalent number of BD and HC participants within each decade age bin, our strict inclusion/exclusion (i.e., few co-morbidities, MRI safe, etc.) criteria made it difficult to fill the older age bins for the BD group. This imbalance may contribute to the lack of group differences detected in our samples. Finally, our sample was restricted to individuals with remitted mood symptoms, limiting the range of illness severity and the generalizability of our findings to larger BD samples across varying symptom presentations. However, the study of euthymic samples allows investigators to form conclusions about brain-behavior relationships that persist during stable phases of the disorder.

Nevertheless, our study provides novel support toward future study of the accelerated aging hypothesis by identifying markers of brain health that demonstrate a differential age association in BD. We have set the stage for future large-scale longitudinal investigations of age-related declines over time. Specifically, our results suggest that the microstructural integrity of the right uncinate fasciculus and the left hippocampal portion of the cingulate, as well as the processing speed cognitive domain in bipolar disorder may be more sensitive to the effects of age than among comparison participants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Scatter plot demonstrating the interaction of group [Bipolar (BD) vs. Healthy Control (HC)] and age on the Fractional Anisotropy (FA) of the right uncinate fasciculus ($t(3) = 2.83$, $p = 0.006$) and on processing speed composite score (in seconds; $t(3) = -1.96$, $p = 0.05$). Higher processing speed composite score indicates slower performance.

Table 1

Demographics and clinical characteristics of participants.

	BD (n = 33)	HC (n = 38)	t or χ^2	p	Cohen's d
	Mean (SD)	Mean (SD)			
Age	46.26 (9.97)	48.82 (10.80)	-1.03	.30	0.25
Sex (% female)	73%	55%	2.32	.13	
Education	15.81(2.05)	15.20 (2.06)	1.27	.21	0.30
HAM-D Total	4.47 (3.82)				
YMRS Total	1.18 (1.4)				
PANSS Positive	9.53 (1.65)				
PANSS Negative	9.70 (2.52)				
Number of Manic Episodes	5.71 (5.61)				
Number of Depressive Episodes	13.30 (17.75)				
Psychiatric Hospitalization	< 3 months (30%)				
Systolic Blood Pressure	119.46 (13.13)	116.05 (12.46)	1.21	.27	0.30
Framingham Stroke Risk	4.45 (4.11)	3.00 (2.46)	1.80	.08	0.43
PS Composite Score	33.09 (12.69)	27.28 (6.62)	2.55	.01*	0.58
Right UF FA	.36 (.03)	.36 (.02)	-.48	.64	0.03
Left UF FA	.33 (.02)	.34 (.02)	-1.1	.28	0.5
Right SLF FA	.38 (.02)	.38 (.02)	.19	.85	0.02
Left SLF FA	.40 (.02)	.40 (.03)	-.34	.73	0.00

*Note.** $p < .05$; degrees of freedom for t-tests = 69;

HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; PANSS = Positive and Negative Syndrome scale; PS = processing speed; UF = uncinate fasciculus; SLF = superior longitudinal fasciculus; FA= fractional anisotropy.

Main effect, interaction and Pearson correlation terms relating FA in *a priori* white matter tracts and processing speed composite score to diagnostic group and age.

Table 2

	Main Effect of Group				Main Effect of Age				Group by Age Interaction				Group-wise correlations with age	
	β	t	p	r_{sp}^2	β	t	p	r_{sp}^2	β	t	p	r_{sp}^2	BD	HC
Right UF FA	-0.08	-2.59	0.01 *	0.09	-0.001	-2.58	0.01 *	0.10	0.002	2.83	0.006 *	0.12	-.40 (.02 *)	.21 (.21)
Left UF FA	0.02	0.63	0.53	0.01	0.000	-0.81	0.42	0.01	0.000	-0.21	0.73	0.001	-.14 (.42)	-.24 (.14)
Right SLF FA	-0.01	-0.52	0.61	0.004	-0.001	-1.78	0.08	0.04	0.000	0.57	0.57	0.005	-.35 (.05 *)	-.18 (.28)
Left SLF FA	0.000	0.00	0.99	0.00	-0.00	-1.99	0.05	0.05	0.000	.146	0.88	0.00	-.40 (.02 *)	-.30 (.07)
PS	12.44	1.23	0.22	0.02	0.51	3.24	0.00 **	0.13	-0.41	-1.96	0.05 *	0.05	.41 (.02 *)	.21 (.21)

Note:

* p .05

** p .001;

FA = fractional anisotropy; UF = uncinate fasciculus; SLF = superior longitudinal fasciculus; PS = processing speed; BD = bipolar disorder; HC = healthy controls; β = unstandardized beta coefficient; t = t-statistic; r = Pearson correlation coefficient; r_{sp}^2 = semi-partial correlation squared; Degrees of freedom for regression = 3; Degrees of freedom for correlation = 32 (BD group) and 37 (HC group).