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Bipolar patients with vascular risk display a steeper age-related negative slope in inhibitory performance but not processing speed: A preliminary study

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Abstract

Objective—Bipolar disorder (BD) is associated with cognitive deficits, yet little is known about associations between cognition, vascular risk (VR) and age in this population. This study investigated whether BD patients with VR demonstrate stronger apparent age-related decline in inhibitory performance and processing speed (PS).

Methods—A full medical history was obtained for 34 euthymic BD and 41 healthy comparison (HC) individuals. The Delis-Kaplan Executive Functions Color Word Interference Subtests was administered to all participants to assess for inhibitory performance (condition 3) and PS (condition 1 and 2). VR positive (VRPos) and VR negative (VRNeg) groups were created based on the presence of one or more VR factors.

Results—VRPos-BD participants demonstrated significantly worse inhibitory performance with older age, while age and inhibition were not significantly related in the VRPOS-HC group or in those who were VRNeg. The same was not true for PS.

Conclusion—BD patients with VR may also be at risk for greater decline in inhibitory performance, but not PS, with age. Longitudinal studies are needed to further investigate the contributions of VR to cognitive decline among older BD patients.

Keywords

Bipolar disorder; Vascular risk; Cognitive aging; Inhibition

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Objective

Alterations in cognitive performance have received considerable attention in BD, and studies have documented deficits in executive functioning (EF) and processing speed (PS) compared to psychiatrically healthy samples (1, 2). Recent evidence has suggested the possibility of altered age-related cognitive decline among those with BD compared to those without mental illness. Cross-sectional studies have found that BD participants display a steeper negative slope of age-related changes in cognitive performance compared to healthy comparison (HC) groups (3). However, the few longitudinal studies that have followed BD patients across time have not demonstrated differential trajectories of cognitive change (4). Given that BD patients present a heterogeneous cognitive profile, ranging from normal performance to severe global deficits (5), it is possible that certain sub-groups of patients are more at risk for accelerated age-related cognitive decline.

Potential sub-groups may be identified by examining the large number of medical co-morbidities in BD. As a group, patients are at a higher risk for developing cardiovascular disease and typically possess greater vascular risk (VR) burden (6). Studies investigating the impact of vascular burden on cognition in BD have demonstrated greater deficits among those with burden compared to those without (7), though less is known about how VR relates specifically to EF and PS among patients. Given that VR also predicts future cognitive decline in populations without mental illness (8), including those at risk for Alzheimer's disease, it is possible that BD individuals with VR may experience greater cognitive impairments associated with age than those without VR factors.

The objective of this cross-sectional study was to investigate whether those with and without VR would show differential relationships of age to EF and PS in a sample of BD and HC participants. We hypothesized that BD individuals possessing VR factors would demonstrate a stronger association between older age and poorer cognitive performance than those without VR factors.

Methods

Thirty-four euthymic BD and 41 age- and education-comparable psychiatrically healthy comparison (HC) participants were enrolled in the Bipolar Aging study, described elsewhere (9). A full medical and substance use history was obtained. To compute medication load, low (1) and high (2) values were assigned for antipsychotics, mood stabilizers, antidepressants and anxiolytics based on dosage and duration of use. These values were summed across medication type to represent a unique medication load variable for each BD participant (10). Participants were administered the Delis-Kaplan Executive Functions Color Word Interference test. Executive functioning was assessed with the Inhibition (condition 3) subtest (11). A composite processing speed score was created by averaging the color naming (condition 1) and word reading (condition 2) subtests. Higher raw scores (in seconds) indicate worse performance.

Vascular risk groups

VR factors of interest included: 1) hypertension (HTN), 2) atrial fibrillation 3) history of cardiovascular disease (CVD), 4) transient ischemic attack or stroke, 5) diabetes, and 6) current smoking. Individuals were considered hypertensive if they reported a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or were taking a prescription for antihypertensive medications. VR positive (VRPos) and VR negative (VRNeg) groups were created based on the presence of one or more VR factors for each individual (12).

Among the BD sample, VRPos (n = 17) and VRNeg (n = 17) groups did not differ in age ($t(32) = 0.24$; $p = 0.81$), education ($t(32) = -0.87$; $p = 0.40$), gender ($\chi^2(1) = 0.15$; $p = 0.70$), illness duration ($t(32) = 0.38$, $p = 0.71$) or lifetime number of manic ($t(32) = 1.12$; $p = 0.27$) and depressed ($t(32) = -0.51$; $p = 0.62$) episodes. Of those BD individuals in the VRPos group, 58.8% possessed 1 risk factor (n = 10; 70% smoking, 10% HTN, 10% CVD, 10% diabetes), 35.5% possessed 2 risk factors (n=6; 33% HTN + smoking, 33% HTN + diabetes, 33% HTN + CVD), and 5.9% possessed 3 risk factors (n=1; HTN + diabetes + smoking). Among the HC sample, VRPos (n = 13) and VRNeg (n = 28) groups did not differ in age ($t(39)= 1.50$; $p = 0.14$), education ($t(39) = -0.56$; $p = 0.57$) or gender ($\chi^2(1) = 1.2$; $p = 0.27$). Of those HC individuals in the VRPos group, 100% possessed one VR factor (n = 13; 54% smoking, 38% HTN, 8% CVD). Thus, although VRG group membership proportions are equivalent across both diagnostic groups, the BD group in this sample appears to have greater vascular burden. Further, smoking status was the most common risk factor present among the VRpos groups, but did not significantly differ between diagnostic groups (BD = 9, HC = 7; $\chi^2(1) = 1.46$, $p = 0.22$).

Statistical analyses

All continuous variables were centered before performing statistical analyses. Independent sample T-tests were utilized to determine diagnostic group (DG) and VR group (VRG) differences in quantitative demographic variables. A Chi-squared analysis investigated DG differences in gender and VRG membership. Bivariate correlations investigated the relationship between medication load and cognitive performance (EF and PS). A linear regression examined associations between DG, age and VRG. In particular, two-way DG-age, DG-VRG, and VRG-age as well as three-way DG-Age-VRG interaction terms were included in the model to assess for differential age relationships to inhibitory performance and PS in the VR and diagnostic groups. Follow-up group-wise correlations examined the nature of any observed significant interactions.

Results

BD (mean age: 46.39; age range: 31–67; 73% female) and HC (mean age: 48.69; age range: 31–68; 58% female) participants did not significantly differ in age, gender, education, or proportion in each VRG.

With regard to EF, the regression model revealed a main effect of age and VRG, indicating that older age and the possession of one more VR factors predicted worse inhibitory performance. These main effects were qualified by a significant 3-way DG-age-VRG

interaction (t(71)= 2.27; $p = 0.03$), such that VRPos-BD participants demonstrated significantly worse inhibitory performance with older age (r(15) = 0.60; $p = 0.01$) while age and inhibition were not significantly related in the VRPos-HC (r(11) = −0.08; $p = 0.80$) group or in those who were VRNeg (BD: r(15) = 0.31, $p = 0.23$; HC: r(26)= 0.36, $p = 0.06$; See Figure 1). Illness duration, but not number of mood episodes, was significantly correlated with both age and inhibition in the VRPos-BD group. Exploratory Sobel test indicated that including illness duration in the model did not change the relationship between age and inhibition (Sobel statistic = −1.32, $p = 0.20$). Medication load was not related to age or inhibitory performance (r(32) = −0.03, $p = 0.87$) or PS (r(32) = −0.10, $p = 0.60$) in the whole BD sample. The full model investigating the impact of age, VRG and DG on processing speed was not significant.

Conclusions

The aim of this preliminary study was to determine the relationship of vascular risk to age-related cognitive deficits in a small sample of BD and HC participants. Among the whole sample, older age and the possession of one or more VR factors was associated with worse inhibitory performance. A significant three-way interaction revealed that only among BD individuals who possessed VR factors was there a significant negative association between age and inhibitory performance. These associations were not present for PS. The results of this study suggest that those individuals who are diagnosed with BD and who possess one or more VR factors may be at a higher risk of steeper age-related decline in EF, but not PS, than those who are psychiatrically and/or medically healthy.

These findings confirm previous reports of worse inhibition with older age and VR, and extend these findings to demonstrate these relationships in BD patients. Further, these results suggest that there is a sub-group of BD patients, characterized by their VR, which exhibits a stronger association between older age and worse inhibitory performance. Importantly, this relationship is present in relatively cognitively intact middle-aged BD patients, suggesting that perhaps VR is an early predictor of premature or accelerated cognitive decline in this population. Previous investigations in BD and other psychiatric populations have suggested the possibility of a cerebrovascular compensatory mechanism that may be engaged prior to the onset of cognitive impairment (9). Thus, it is possible that those BD patients with VR are more vulnerable to executive dysfunction compared to their medically healthy BD peers because they are less able to recruit the extra cerebrovascular resources necessary to prevent future cognitive decline. Future longitudinal studies are required to investigate the presence of an accelerated trajectory of cognitive decline in BD patients with VR.

This investigation is not without its limitations. The cross sectional design does not allow us to make causal conclusions about the relationship between VR in BD and age on cognition, nor does it allow us to confirm the presence of an accelerated rate of cognitive decline. Although studies have demonstrated an effect of medication on cognition (13), medication load was not related to either inhibition or age in our BD sample. However, it should be noted that this study was not designed to disentangle the effects of medication type (i.e., lithium vs. anti-psychotics). Our efforts to recruit euthymic participants may have restricted our sample to individuals exhibiting less illness severity, potentially influencing the

variability in vascular health and the generalizability of these findings. Smoking status accounted for a large proportion of VRPos group membership. It is possible that the effects of cigarette ingredients or nicotine drive the observed relationships. Although our exploratory Sobel test did not support illness duration as a potential mediator of the observed relationships, future studies designed to disentangle overlapping contributions of illness duration and age on cognition is warranted. Finally, individuals in the BD VRPos group were more likely to possess more than one VR factor than the individuals in HC VRPos group. Thus, despite equivalent proportions of VRG membership across diagnostic groups, the BD VRPos group appears to have a greater vascular burden, which may underlie this group's uniquely strong association between age and inhibitory performance.

Nevertheless, the novel results of this study suggest that there may be a sub-group of BD patients that experience a differential trajectory of age-related executive dysfunction. Future longitudinal studies are required to determine whether this sub-group of individuals experience an accelerated trajectory of decline.

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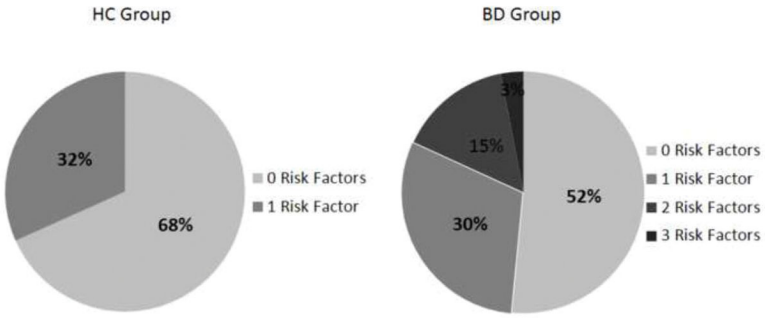

Figure 1.
Pie chart describing the number of risk factors present within each diagnostic group. BD = bipolar disorder; HC = healthy comparison.

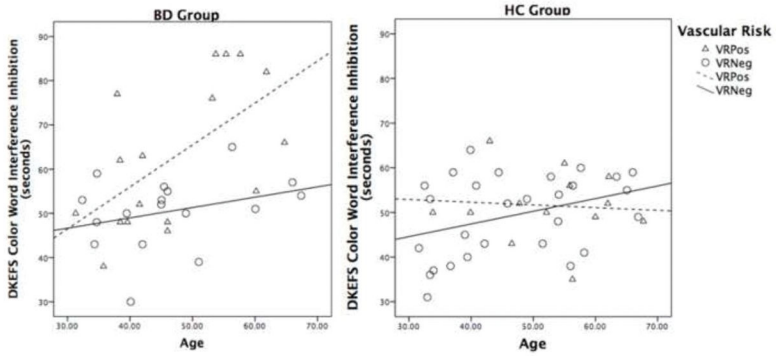

Figure 2.

Scatter plots demonstrating vascular group [Vascular risk positive (VRPos) *vs.* vascular risk negative (VRNeg)] differences in the relationship between age and inhibitory performance in bipolar (BD) and comparison (HC) participants.

Table 1

Demographic and clinical characteristics of participants

	Mean (SD)			
	BD	**HC**	**t or χ^2**	***p***
Age	46.4 (10.39)	48.69 (11.16)	−0.74	0.46
Education	15.75 (2.05)	15.12 (2.12)	1.30	0.20
Gender	F: 73%	F: 58%	1.85	0.17
Vascular risk group (VRG)	VRGPos: 48%	VRGPos: 32%	2.59	0.16
PANSS	41.30 (7.0)			
HAM-D	5.45 (3.76)			
YMRS	1.18 (1.44)			
Lifetime # of manic episodes	6.03 (6.5)			
Lifetime # of depressed episodes	15.77(22.01)			
Illness duration	27.58 (11.30)			

Note: PANSS = Positive and Negative Syndrome Scale; HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; SD = standard deviation; BD = bipolar disorder; HC = healthy control; VRGPos = vascular risk positive group; Degrees of freedom for t-tests = 4..

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Table 2

Main effects and interactions of associations between diagnostic group, vascular group and age on inhibition and processing speed.

Main Effects									
	DG			**VR**			**age**		
	β	**t**	***p***	**β**	**t**	***p***	**β**	**t**	***p***
Inhibition	−6.38	−2.62	0.01*	−7.40	−3.03	0.003*	0.351	3.02	0.004*
PS	7.07	1.56	0.12	−9.19	−2.03	0.05*	−0.20	−0.94	0.35
Two-way interactions									
	DG × age			VG × age			DG × VG		
	β	t	*p*	β	t	*p*	β	t	*p*
Inhibition	−0.48	−2.06	0.04*	−0.19	−0.80	0.43	10.45	2.14	0.04*
PS	−0.65	−1.51	0.14	0.47	1.10	0.27	−13.50	−1.50	0.14
Three-way interactions									
	DG × VG × age								
	β			t			*p*		
Inhibition	1.060			2.28			0.026*		
PS	1.32			1.54			0.13		

*$p \leq 0.05$;

Note. DG = diagnostic group; VG = vascular group; PS = processing speed; β = unstandardized coefficients; t = t-statistic; p = p-value; degrees of freedom for all t-statistics = 67.