Lack of association between epigenetic aging acceleration and oxidative stress in bipolar disorder

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Aims

Bipolar disorder (BD) has been associated with accelerated epigenetic aging, but the mechanisms underlying this acceleration are unknown. We aimed to investigate the potential role of oxidative stress in this process.

Methods

Euthymic BD patients (n = 93) and matched healthy controls (n = 40) were enrolled for this analysis. Samples were analyzed for genome-wide DNA methylation levels using the EPIC BeadChip (Illumina) and assessed for epigenetic age and 'epigenetic aging acceleration' using the Horvath calculator. Oxidative stress markers thiobarbituric acid reactive substances (TBARS), protein carbonyl content (PCC), total antioxidant capacity and 8-oxo-2'-deoxyguanosine (8-oxo-dG) were assessed in peripheral blood with commercial kits. Groups showing slower (negative acceleration residual) or accelerated aging (positive acceleration residual) were compared in controls and patients by univariate analyses. Binary logistic regressions were also performed to check for the combined effects of the markers and covariates on the likelihood that participants would show a slower or accelerated epigenetic aging.

Results

Table 1. Demographic data

	Healthy controls	BD patients	P-value
N	40	93	
Age, mean ± SD	35.5 ± 10.3	36.6 ± 10.8	0.570[a]
Sex (M/F)	13/27	26/67	0.598[b]
Ethnicity (NH/H/U)	31/8/1	72/20/1	0.816[b]
BMI, median (IQR)	29.3 (9.8)	30.8 (10.4)	0.315
MADRS, median (IQR)	0 (0)	9 (15)	
YMRS, median (IQR)	0 (1)	4 (9)	
GAF, median (IQR)	90 (4)	51 (22)	

[a]Independent t-test; [b]Chi-Square test.

Table 2. Oxidative stress markers in patients with bipolar disorder compared to healthy individuals

	t	df	P	Mean difference	95% CI of the difference	
					Lower	Upper
TBARS (µM)	0.21	122	0.8	-0.02879	-0.2931	0.2356
Protein Carbonyl (nmol/ml)	1.48	99	0.1	-0.002515	-0.0058	0.00083
Total antioxidant capacity (mM)	1.567	125	0.1	-0.3387	-0.7664	0.00083
8-oxo-dG (nM)	1.506	128	0.1	-0.4577	-1.059	0.1437

TBARS - thiobarbituric acid reactive substances; 8-oxo-dG - 8-oxo-2'-deoxyguanosine)

Results (cont.)

In a multiple linear regression, TBARS, PCC, antioxidant capacity, and 8-oxo-dG significantly predicted epigenetic aging acceleration in the whole sample ($F(4,89) = 3.227$, $p = 0.016$, $R^2 = 0.127$), but not when the analysis was performed within each group (controls – $F(4,26) = 1.766$, $p = 0.166$, $R^2 = 0.214$; patients – $F(4,58) = 1.344$, $p = 0.265$, $R^2 = 0.085$). Similarly, binary logistic regression models were not statistically significant in controls ($X^2(6)=8.956$, $p=0.176$) or in patients ($X^2(7)=3.502$, $p=0.835$).

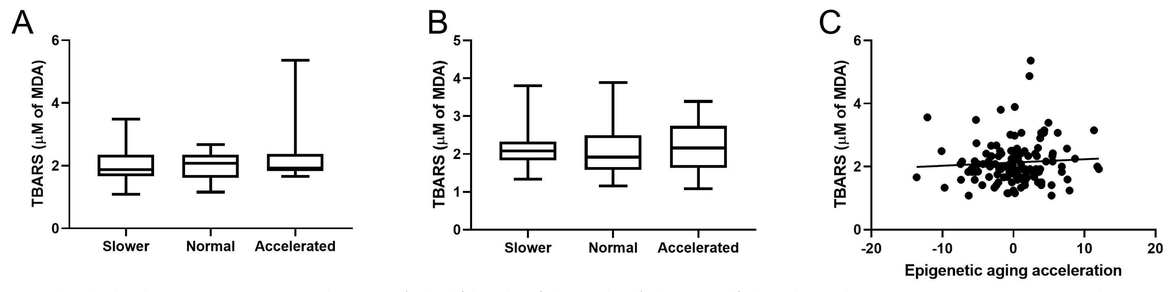

Figure 1. Thiobarbituric acid reactive substances (TBARS) levels. A) Controls; B) Patients; C) Correlation between epigenetic aging acceleration and TBARS levels in the whole sample.

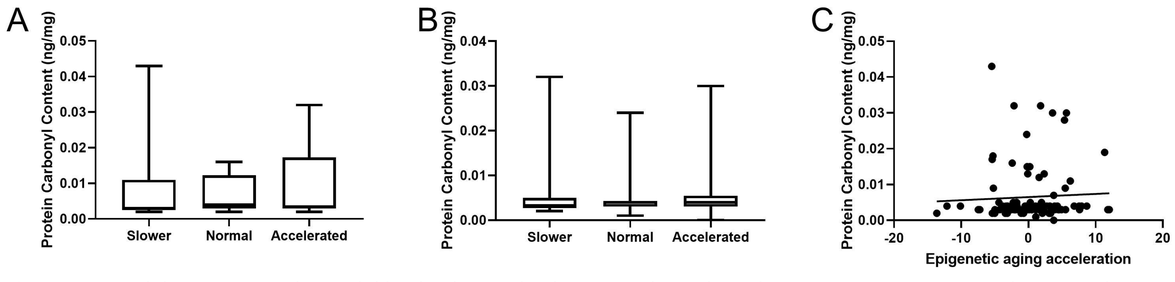

Figure 2. 8-oxo-2'-deoxyguanosine (8-oxo-dG) levels. A) Controls; B) Patients; C) Correlation between epigenetic aging acceleration and TBARS levels in the whole sample.

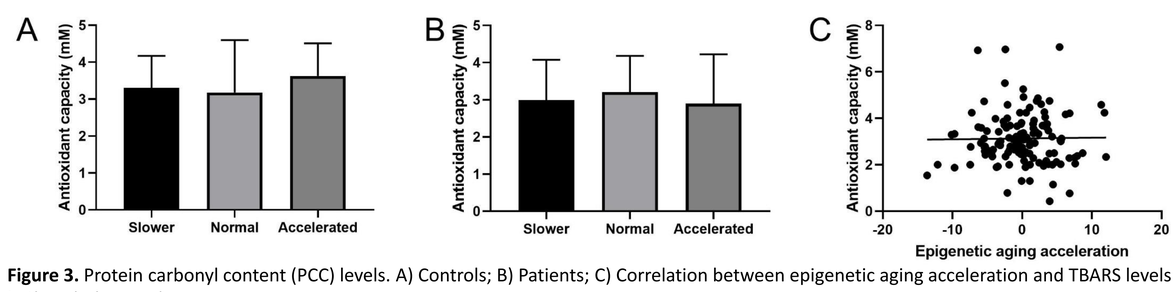

Figure 3. Protein carbonyl content (PCC) levels. A) Controls; B) Patients; C) Correlation between epigenetic aging acceleration and TBARS levels in the whole sample.

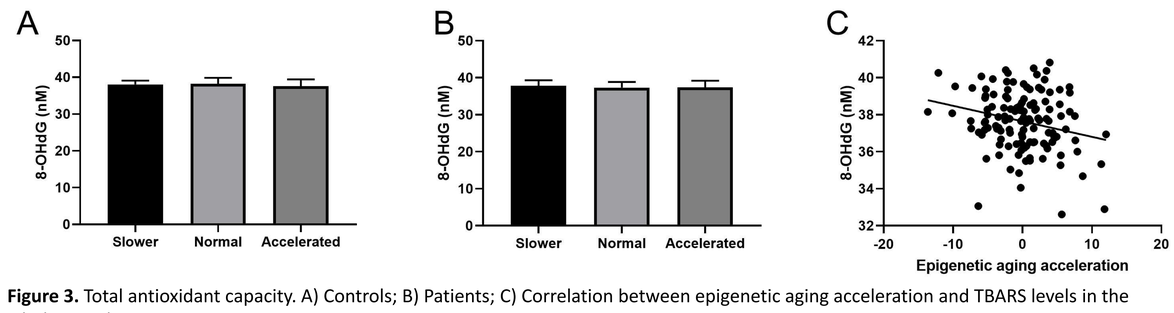

Figure 3. Total antioxidant capacity. A) Controls; B) Patients; C) Correlation between epigenetic aging acceleration and TBARS levels in the whole sample.

Conclusion

We did not find major influences of oxidative stress on epigenetic aging acceleration in patients or controls. Epigenetic aging is thought to result from a chronic exposure to stress, inflammation, and many other aging-inducing stimuli, which may not be captured by an acute assessment of oxidative stress markers.

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