Epigenetic GrimAge acceleration in bipolar disorder

Camila Nayane de Carvalho Lima, Giselli Scaini, Valeria A. Cuellar, Consuelo Walss-Bass, Jair C. Soares, Joao Quevedo, Gabriel R. Fries
Faillace Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center, Houston

Introduction

Bipolar disorder (BD) has been previously associated with functional impairment and accelerated epigenetic aging.

In this study, we assessed whether the acceleration of one biomarker of biological aging as measured by the GrimAge clock is associated with functioning in patients with BD and controls.

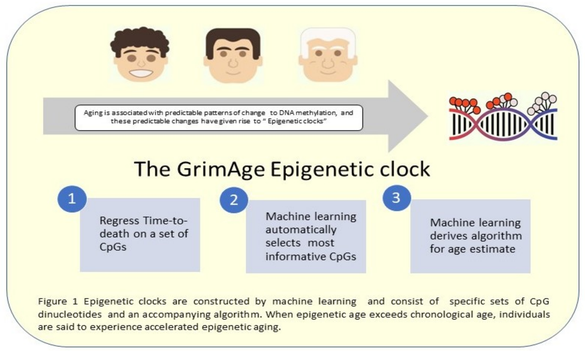


Figure 1 Epigenetic clocks are constructed by machine learning and consist of specific sets of CpG dinucleotides and an accompanying algorithm. When epigenetic age exceeds chronological age, individuals are said to experience accelerated epigenetic aging.

Materials and methods

Sample: Patients with BD and controls.

DNA methylation: Whole blood genome-wide DNA methylation levels were measured with the Infinium EPIC BeadChip (Illumina).

Epigenetic age estimates were calculated using an online tool (dnamage.genetics.ucla.edu/).

Data were analyzed using Spearman correlations and linear regression analysis, with a significance level set at 0.05.

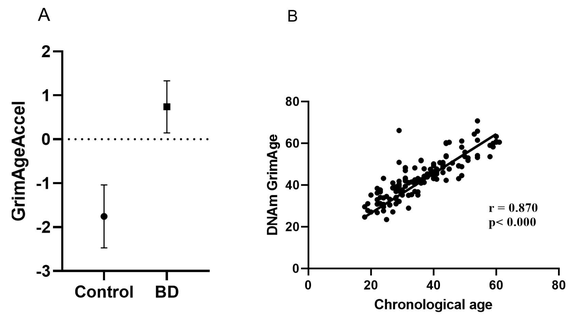
Results

Table 1. Sample demographics

	Bipolar disorder (n=90)	Controls (n=40)	*p*-value
Age (years), mean (SD)	36.92 (11.25)	35.45 (10.29)	0.500†
Sex (%)			
Female	73.3	67.5	0.496‡
Male	26.7	32.5	
Race/ethnicity (%)			
Non-Hispanic White or	37.8	20.0	0.108‡
Caucasian	14.4	20.0	
Hispanic or Latino	32.2	50.0	
Black or African American	14.4	10.0	
Others	1.2		
Missing			
Smoking status (%)			
Yes	27.8	2.5	**0.001**‡
No	67.8	97.5	
Missing	4.4		
Education categorical (%)			
Elementary school grade (1 to	4.4	2.5	0.247‡
12)	20.0	5	
High school	31.1	32.5	
Part college	32.2	52.5	
Graduated college	12.3	7.5	
Graduated professional			

†Mann–Whitney test, ‡Chi-square test.

Figure 2. Differences in GrimAgeAccel between patients with BD and controls



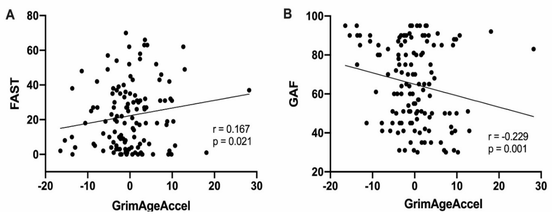
A) Scatterplot illustrating the significant and positive correlation between GrimAge (epigenetic age, in years, predicted based on surrogate biomarkers for blood plasma proteins related to morbidity and mortality and cigarette smoking) and chronological age (years). Analysis was performed by Pearson correlation coefficient. B) Higher GrimAge acceleration (GrimAgeAccel) in patients with bipolar disorder (BD). Bars represent mean ± standard error. GrimAge acceleration was calculated by regressing the predicted GrimAge to the chronological age of the subjects and using the residuals as an estimate of the difference between them. Negative and positive values represent younger and older GrimAges compared to their chronological

Table 2. Linear regression analyses of clinical variables and GrimAge acceleration in bipolar disorder (outcome: GrimAgeAccel)

Predictor	Outcome (GrimAgeAccel)	β	95% CI	*p*-value
Length of Illness	Unadjusted	0.077	-0.041, 0.194	0.199
	Adjusted for age, sex and race	0.222	0.063, 0.380	0.007
	Multivariable-adjusted†	0.143	0.021, 0.265	0.022
Medication status	Unadjusted	-2.215	-6.935, 2.505	0.354
	Adjusted for age, sex and race	-1.714	-6.581, 3.152	0.486
	Multivariable-adjusted†	-4.454	-8.037, -0.871	0.016
Comorbidities total	Unadjusted	0.471	0.040, 0.903	0.033
	Adjusted for age, sex and race	0.471	0.022, 0.920	0.040
	Multivariable-adjusted†	0.316	-0.032, 0.664	0.075
Any comorbid substance abuse or dependence	Unadjusted	3.000	0.681, 5.319	0.012
	Adjusted for age, sex and race	2.829	0.425, 5.233	0.022
	Multivariable-adjusted†	2.484	0.595, 4.374	0.011

†Adjusted for age, sex, race, smoking status, and blood cell counts. GrimAgeAccel: DNAm GrimAge acceleration. b: unstandardized beta is the regression coefficient of the respective variable from the regression model as stated above. Significant p-values (<0.05) are bolded.

Figure 3. Association between GrimAgeAccel and functioning status



A) Scatterplot illustrating the significant and positive correlation between Functioning Assessment Short Test (FAST) total scores and GrimAge acceleration. B) Negative correlation between Global Assessment of Functioning (GAF) total scores and GrimAge acceleration. Analyses were performed by Spearman's rho correlation.

Conclusions

Epigenetic aging, as measured by the lifespan predictor GrimAge, is accelerated by comorbid substance use and longer length of illness in BD, with a protective effect of medication. Moreover, this acceleration may contribute to functional decline in patients with BD.

Acknowledgments

This study was funded by the UTHealth Consortium on Aging through the UTHRO Endowment for Healthy Aging Geriatric Studies for Junior Faculty Program, by the UTHealth Center for Clinical and Translational Sciences (CCTS), and the Louis A. Faillace, MD Department of Psychiatry and Behavioral Sciences at UTHealth. GRF is funded by the National Institute of Mental Health (NIMH, 5K01MH121580).

Literature cited

Fries GR, Zamzow MJ, Andrews T, Pink O, Scaini G, Quevedo J. Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications. Neurosci Biobehav Rev. 2020;112:107-116.

Contact information

Gabriel.R.Fries@uth.tmc.edu
@FriesGabriel