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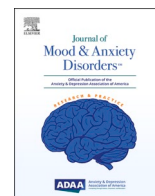

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PTSD and alcohol use disorders predict the pace of cellular aging☆

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ABSTRACT

Advanced epigenetic age is associated with psychopathology and may help to explain the link between psychopathology and physical health morbidity and mortality. Using a longitudinal sample of 171 trauma-exposed Veterans, we modeled the rate of change in epigenetic age across two time points (averaging 5.58 years apart) using two epigenetic age algorithms (GrimAge and Horvath) and tested associations with posttraumatic stress disorder (PTSD), alcohol use disorder (AUD), and depression. Results showed that PTSD ($\beta = .199$) and AUD ($\beta = .186$) were associated with a quickened *pace* of epigenetic aging over time ($ps < .021$). Results replicate and extend prior work and offer foundational support for identifying interventions that slow the pace of biological aging among those with psychopathology.

1. Introduction

Epigenetic approaches to quantifying human cellular aging have improved our ability to identify risk for accelerated aging and early onset of age-related diseases and mortality. DNA methylation (DNAm) data from a single timepoint can demonstrate that biological age (e.g., "epigenetic age" aka "DNAm age") is "advanced" relative to chronological age but cannot tell us whether the pace of aging is changing (accelerating or decelerating). A range of psychiatric symptoms and diagnoses, including posttraumatic stress disorder (PTSD) and disorders of the internalizing and externalizing spectra [1–3], are cross-sectionally associated with advanced epigenetic age (per Horvath [4]) and shortened time-to-death ("GrimAge" [5]). Although few in number, studies exploring these associations longitudinally have found evidence of associations between PTSD symptom severity and advanced (relative to chronological age) epigenetic age over time [6,7]. Estimates of advanced epigenetic age, even when analyzed longitudinally, provide only a snapshot of biological age at a given time and, thus, are distinct from the estimated *pace* or rate of epigenetic aging over time (i.e., the difference in epigenetic age estimates across time relative to the number of intervening years). Two studies have evaluated associations between the *pace* of epigenetic aging and psychopathology. In the first, Wolf et al. [1] reported that PTSD avoidance and numbing symptoms and alcohol use disorders at baseline were associated with an accelerated pace of epigenetic aging (per the Horvath algorithm) over the course of approximately two years. A more recent study found that, among 171 children and adolescents, stressful life events predicted an accelerated rate of change in Horvath estimated epigenetic aging over the course of approximately two years, and that this accelerated pace was associated with depressive symptoms at follow-up after adjusting for baseline symptoms [8]. Analysis of the pace of epigenetic aging is necessary to investigate if this form of cellular age is changing compared to the expected change based on the passage of time.

2. Methods

2.1. Participants and procedures

A total of 174 Veterans completed a longitudinal study focused on PTSD and accelerated aging over two assessments separated by 5.58 years, on average. Demographics for this group are provided in Table 1 (see also, Supplementary Materials). This report is based on a subset (*n* = 171) with DNAm data.

The study protocol included self-report surveys, structured diagnostic interviews, neurocognitive evaluation, physiological measurements, and a blood draw to obtain epi/genetic and other biomarker data. Written informed consent was obtained. All diagnoses were based on either the 4th or 5th edition of the *Diagnostic and Statistical Manual (DSM),* whichever was prevailing at Time 1 (T1; see Supplementary Materials). Current PTSD (past 30 days) diagnosis was assessed using the Clinician Administered PTSD Scale (CAPS) [9]. Comorbid major depressive (MDD) and alcohol use disorders (AUD) were determined via administration of the Structured Clinical Interview for *DSM-IV* or *DSM-5* (SCID; 2 individuals were missing these diagnoses) [10]. Participants were compensated for participation and *all procedures were approved by the local institutional review board.*

DNA was extracted from whole blood and genotyped using the Illumina HumanOmni2.5–8 BeadChip. DNAm data were obtained using the Illumina Infinium MethylationEPIC BeadChip, with individuals assigned to chip so that chips were balanced for sex, PTSD case/control status, and time points. Additional information relating to genotype and DNAm quality control methods are described in the Supplementary Materials, as are the procedures for estimating proportional white blood cell types and calculating GrimAge, Horvath DNAm age, smoking pack years, and ancestry principal components (PCs; 2 individuals were missing PCs). Additional blood was drawn into 10 ml EDTA tubes, centrifuged, and plasma was then aliquoted and frozen at −80 °C. These samples were later shipped to an affiliate lab where a variety of metabolic assays were obtained (see Supplementary Materials) for use in follow-up analyses examining the potential confounding effects of metabolic dysregulation and inflammation, as studies have shown associations between accelerated epigenetic age and biomarkers of metabolic pathology and inflammation [11].

2.2. Data analysis

We computed the rate of DNAm age change per year for the Horvath and GrimAge epigenetic age estimates per the following formula: [(T2 DNAm Age – T1 DNAm Age)/# of intervening years]. The use of two time points to directly model the pace of epigenetic aging is distinct from recently developed epigenetic "pace" clocks (e.g., DunedinPACE [12]), which estimate pace from single time point of DNAm data. Our longitudinal approach provides an estimate of the change in epigenetic age per calendar year. Values greater than 1 indicate that the pace of epigenetic aging exceeds what is expected per year, while values less than 1 indicate the pace of epigenetic aging is slower than expected. We calculated the correlation between the two rate variables.

We next conducted two multiple regressions predicting the rate of change in epigenetic aging (one for each rate variable). T1 PTSD, MDD, and AUD diagnoses were included as predictors in each model, covarying for T1 age, sex, the top three ancestry PCs, DNAm smoking score, and white blood cell type proportions. Because we conducted two models, we adjusted the *p*-value threshold for significance using a Bonferroni correction (i.e., $p < .025$). For models with significant effects for any psychiatric diagnosis, we conducted follow-up regressions which additionally covaried for T1 metabolic pathology, C-reactive protein (CRP), education, and the *DSM* version used to derive diagnoses to see if these better accounted for associations attributable to psychiatric diagnoses. Additional follow-up analyses also evaluated whether change in diagnostic status of any of the psychopathology variables across the two assessment points was associated with the rate of DNAm age change. All models were conducted in SPSS v. 26.

3. Results

On average, participants' epigenetic age increased by 0.84 (range: −2.61 to 4.57; 95 % CI: 0.69–1.0) and 0.87 (range: −3.96 and 4.58; 95 % CI:.75 to.98) years, per the Horvath and GrimAge algorithms, respectively, for every intervening year between assessments. The two rate variables were not significantly associated with each other ($r = .039$, $p = .61$).

3.1. Predictors of the pace of epigenetic aging

PTSD at T1 was associated with an increased pace of epigenetic aging over time per the Horvath algorithm (β = .199, 95 % CI:.065 to.780, $p = .021$; Table 1; Fig. S1) while AUD at T1 was associated with an increased pace of epigenetic aging per the GrimAge algorithm (β = .186, 95 % CI:.081 to.761, $p = .015$; Table 1; Fig. S2). The association between PTSD and the Horvath rate variable remained significant when additionally controlling for T1 metabolic pathology, CRP, education, and SCID/CAPS version (ps ≤.026). Likewise, the association between AUD and the rate of epigenetic aging per GrimAge remained significant when additionally controlling for these same covariates (ps ≤.017). These associations also remained significant when we eliminated PCs from the model to maximize the sample size, given that 2 individuals were

Table 1

Participant Characteristics and Regression Results Predicting the Rate of Change in Horvath and GrimAge-defined Epigenetic Age.

Variable at T1	*M* (SD)	*n* (%)	Horvath Rate			GrimAge Rate		
			B	β	p	B	β	p
Age	59.6 (12.14)		-.010	-.114	.204	-.002	-.034	.680
Sex (male)		149 (85.6)	-.067	-.021	.797	-.223	-.095	.213
PC1	-.002 (.03)		-3.062	-.080	.358	-1.41	-.040	.621
PC2	-.007 (.01)		9.537	.104	.228	-2.200	-.032	.688
PC3	.001 (.01)		-2.126	-.028	.742	4.107	.072	.360
Smoking DNAm	4.43 (27.61)		-.001	-.021	.808	.002	.058	.466
CD8-T	.08 (.05)		.113	.005	.956	.706	.042	.615
CD4-T	.17 (.06)		1.545	.092	.287	**3.985**	**.315**	**<.001**
NK	.04 (.02)		-4.658	-.105	.229	3.659	.110	.173
B cell	.05 (.03)		**-8.825**	**-.213**	**.015**	4.540	.146	.070
Mono	.09 (.03)		2.681	.065	.444	2.986	.096	.219
PTSD DX		85 (48.9)	**.423**	**.199**	**.021**	-.068	-.043	.589
MDD DX		38 (21.8)	-.424	-.166	.053	.058	.030	.699
AUD DX		24 (13.8)	.116	.038	.641	**.421**	**.186**	**.015**

Note. Significant effects are shown in bold font. PC = ancestry principal component; DNAm = DNA methylation, NK = natural killer, PTSD = posttraumatic stress disorder; MDD = major depressive disorder; AUD = alcohol use disorder; DX = diagnosis.

missing PCs. Associations did not appear to be driven by multi-collinearity amongst the psychiatric diagnoses given that PTSD was not strongly related to AUD ($r = .182$, $p = .018$) or MDD ($r = .345$, $p < .001$); nor were AUD and MDD related to each other ($r = .031$, $p = .693$). In follow-up analyses exploring the effects of change in psychiatric diagnostic status on the rate of DNAm age acceleration, new effects emerged for AUD. Specifically, ongoing AUD diagnosis and new onset AUD diagnosis at T2 (versus negative for AUD at both timepoints) was associated with an increased pace of epigenetic aging per the Horvath algorithm ($\beta = .250$, 95 % CI:.237 to 1.102, $p = .003$; Supplementary Table 2). There was no evidence that change in PTSD or MDD diagnoses across time was associated with the rate of DNAm age acceleration (Supplementary Table 2).

4. Discussion

In this trauma-exposed veteran cohort, we found that PTSD and AUD at baseline were associated with an accelerated pace of epigenetic aging over time, per the Horvath and GrimAge algorithms, respectively. This association persisted when accounting for the effects of common trauma-related psychiatric comorbidity and other potential confounds for pace of epigenetic aging: metabolic pathology and inflammation [11, 13], education [14], and smoking [15]. In addition, ongoing AUD over time and new onset AUD was associated with increased pace of the Horvath algorithm, raising the possibility that the effect of AUD on epigenetic aging is cumulative and becomes more apparent with greater chronicity of the condition. Though associations were not consistent across the two epigenetic clocks examined, this is commonly observed (e.g., [1,16]) and may reflect that each clock is sensitive to different aspects of cellular aging, after accounting for the shared effects of age and intervening time. This interpretation is consistent with the observation that the correlations between these DNAm age estimates tend to be modest (at best) after residualizing the estimates for chronological age [16]. The point estimates for the mean pace of epigenetic aging overall were somewhat less than expected (.84–.87 of a year), though the confidence intervals for these estimates included 1.0 (i.e., aging one year per the DNAm age algorithms for every intervening year). This suggests that the epigenetic clock generally kept pace with this period of intervening time. These average pace estimates are similar to those previously reported in the literature [e.g.,.76; 1]. That said, we do not necessarily expect that the pace of biological aging will be a constant for every developmental stage of life. For example, there is evidence that the rate of biological aging is accelerated for chronologically older people compared to younger people [12]). Therefore, the average rates in our sample (.84 and.87) reflect the mean of rate estimates across all ages in the cohort and over this period of intervening time. The range of each rate variable (-2.61 to 4.57 for GrimAge and -3.96 to 4.58 for Horvath) may reflect age-dependent variability. Future work using larger and more age diverse samples should conduct follow-up analyses stratified by age to address this question.

The association between PTSD and an increased pace of epigenetic aging (per the Horvath clock) replicates findings previously obtained by our group in a distinct and much younger (M_{age} 32.84) sample of veterans [1] and extends recent work showing a similar association between stress and pace of cellular aging among a community youth (M_{age} 12.50) sample [8]. The sample size in this study ($n = 171$) is very similar to the sample sizes in the two known existing longitudinal studies of epigenetic age pace referenced above ($n = 179$ and $n = 171$, respectively), though future work would benefit from larger cohorts. Additionally, the association between AUD and increased pace of epigenetic aging (per the GrimAge clock) extends prior work demonstrating cross-sectional associations between externalizing psychopathology symptoms and advanced GrimAge [2]. The clinical significance of this finding is particularly noteworthy given converging evidence pointing to the likely additive effects of both the psychological stress accompanying AUD and the biological stress of alcohol consumption specifically

on epigenetic aging [17–20]. The consistency of findings across samples differing in age and psychological presentations raises the possibility that psychological stress increases risk for faster biological aging across the lifespan. This speaks to the need for interventions that may slow or reverse the pace of biological aging.

Longitudinal approaches are essential for disentangling the extent to which epigenetic aging is a correlate versus a consequence of trauma-related psychopathology. They can also provide critical information concerning the pathophysiological mechanisms that connect accelerated cellular aging to numerous adverse health outcomes [21]. Additional studies are needed to determine if the pace of epigenetic aging can be slowed through pharmacological or behavioral interventions in order to mitigate risk for premature morbidity and mortality.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.xjmad.2023.100026.

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