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Negative fateful life events in midlife and advanced predicted brain aging

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ABSTRACT

Negative fateful life events (FLEs) such as interpersonal conflict, death in the family, financial hardship, and serious medical emergencies can act as allostatic stressors that accelerate biological aging. However, the relationship between FLEs and neuroanatomical aging is not well understood. We examined 359 men (mean age 62 years) participating in the Vietnam Era twin study of aging (VETSA) to determine whether negative midlife FLEs are associated with advanced brain aging after controlling for physical, psychological, and lifestyle factors. At two different time points, participants were assessed for negative FLEs, health and well-being, general cognitive ability, socioeconomic status, depression, and ethnicity. Participants underwent a magnetic resonance imaging examination, and T1-weighted images were processed with FreeSurfer. Subsequent neuroanatomical measurements were entered into the Brain-Age Regression Analysis and Computation Utility software (BARACUS) to predict brain age. Having more midlife FLEs, particularly relating to interpersonal relationships, was associated with advanced predicted brain aging (i.e., higher predicted brain age relative to chronological age). This association remained after controlling for the significant covariates of alcohol consumption, cardiovascular risk, adult socioeconomic status, and ethnicity.

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1. Introduction

It has been hypothesized that chronic exposure to prolonged stressful situations can result in biological weathering and premature aging (Geronimus, 2013; Geronimus et al., 2010). Stress has been shown to exert a disruptive effect on biological systems resulting in oxidative stress, mitochondrial damage, immunosenescence, endocrinosenescence, as well as epigenetic modifications of the sympathetic nervous system, hypothalamic-pituitary-adrenal axis, immune system, and other metabolic processes (Cole, 2014; Jenny, 2012; Jenny et al., 2012). Adverse circumstances such as economic hardship, low education, and community disadvantage have been associated with various chronic, age-related diseases such as type 2 diabetes, coronary heart disease, stroke, and dementia (Fraga et al., 2015; Gruenewald et al., 2009; Hemingway et al., 2003; Koster et al., 2006; Loucks et al., 2007, 2009, 2010; Robertson et al., 2015; Smith et al., 2011). Cumulative lifetime stress, but not childhood or recent stress, has been shown to accelerate epigenetic (DNA methylation based) aging in an urban, African-American cohort (Zannas et al., 2015). Furthermore, a study of African-American middle-aged women of low socioeconomic status (SES) showed advanced biological aging as determined by leukocyte telomere length (Simons et al., 2016). Interestingly, this effect was predominately influenced by everyday financial pressure over other factors such as diet, exercise, smoking, alcohol consumption, and having health insurance, suggesting that certain types of psychological distress can significantly accelerate biological aging. What remains to be determined is if exposure to these negative fateful life events (FLEs) in midlife is related to brain aging, and if this effect is associated with SES and/or ethnicity.

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Many studies have characterized normal brain aging and pathologically advanced aging in dementias. The most common metric of normal brain aging is gross brain volume reductions of 0.2%–0.5% per year (Enzinger et al., 2005; Ezekiel et al., 2004; Fotenos et al., 2005; Hedman et al., 2012; Scahill et al., 2003). Cortical volume reductions of around 0.5% per year are found across the brain surface in most regions (Fjell et al., 2014). There is, however, considerable interindividual variability in the magnitude of brain changes with age; the degree of brain aging can be adversely affected by poor physical and mental health. Cardiovascular risk factors such as hypertension, diabetes, and obesity have been shown to be associated with advanced brain aging (Leritz et al., 2011; Ronan et al., 2016). Regarding mental health, FLEs and stress are highly associated with depression, and depression has been associated with reductions in hippocampal volume (Schmaal et al., 2016) and cortical thickness within the orbitofrontal cortex, cingulate, insula, and temporal lobes (Schmaal et al., 2017). Furthermore, a retrospective study of 1271 older adults found that 78% of dementia patients had a stressful life event before the onset of dementia compared to 55% for control subjects (Tsolaki et al., 2010). How FLEs affect people in late middle age with and without mild cognitive impairment (MCI) or at high genetic risk of dementia (i.e., apolipoprotein E4 [*APOE-ε4*] allele carrier) is yet to be assessed. Therefore, examining the association between FLEs and advanced brain aging needs to take into account physical and mental health factors that are thought to adversely affect neuroanatomy.

With computational advancement, quantifying healthy brain aging has evolved from retrospective correlative analysis to several predictive models of brain aging. One model (Liem et al., 2017) combines measures of cortical thickness, cortical surface area, and subcortical volumes to calculate a predicted brain age. The mean absolute prediction error of this model is 4.29 years, which is similar to other models of predicted brain age (Cole et al., 2015, 2017; Franke et al., 2010). More importantly, the difference between predicted brain age and chronological age (predicted brain age difference [PBAD]) was shown to be sensitive to cognitive impairment; that is, higher PBAD was associated with worse objective cognitive impairment (Liem et al., 2017). Predictions were resilient to head motion artifacts and generalizable to other data sets, although differences in scanner, sequence, and head coil may still influence estimates of predicted brain age. This model has been made publicly available in an easy-to-use application called Brain-Age Regression Analysis and Computation Utility Software (BARACUS).

The aims of this project were to investigate the extent to which negative FLEs are associated with advanced predicted brain aging in a group of late-middle-aged men as assessed by magnetic resonance imaging and PBAD using BARACUS (Liem et al., 2017). Considering the findings that lifetime stress accelerates epigenetic aging (Zannas et al., 2015) and telomere length reduction (Simons et al., 2016), we hypothesized that higher total FLE scores would be associated with a brain age greater than chronological age. We also sought to identify whether FLEs concerning relationships, finances, and/or health would be associated with advanced PBAD. We hypothesized that financial stress would be a significant factor based on previous findings in middle-aged African-American women (Simons et al., 2016). Finally, we tested the relationship between FLEs and PBAD after controlling for covariates. We hypothesized that the relationship between FLEs and PBAD would be influenced by physical health complications, ethnicity, and/or SES. We also sought to delineate the effect of FLEs on brain aging from potential confounding factors, namely neuroanatomical changes due to traumatic brain injury (TBI), MCI, or genetic risk for Alzheimer's disease based on *APOE-ε4* status.

2. Material and methods

2.1. Participants

Participants in the Vietnam Era twin study of aging (VETSA) magnetic resonance imaging (MRI) cohort (Kremen et al., 2010) were recruited from the Vietnam Era twin registry, a nationally distributed sample of male-male twin pairs who served in the United States military at some point between 1965 and 1975 (Goldberg et al., 2002; Tsai et al., 2013). Participants have similar health and lifestyle characteristics to American men in their age range (Schoenborn and Heyman, 2009). Although all VETSA participants are veterans, most (~80%) did not experience combat situations. The present study included 359 participants aged 61.8 years (2.6 standard deviation [SD]; 56.5–65.6 range) at time of MRI scan, who were predominantly white (87.7%) and did not have a neurological disorder. The study was conducted under local institutional review board supervision at the participating institutions, and all participants provided signed informed consent.

2.2. Fateful life events

Participants were asked to tally a list of life-changing events over the past 2 years based on an extension of the Holmes-Rahe Stress Inventory (Holmes and Rahe, 1967). We extracted negative FLEs spanning the domains of relationships, finance, and health (see Box 1) from the universally negative adverse events indicated in the Psychiatric Epidemiology Research Interview Life Event Scale (Dohrenwend et al., 1978, 1980). To get a more comprehensive measure of FLEs, we aggregated these data with those from the same measure collected 5 years previously in the first wave of the VETSA. Thus, the summed events represent stressful midlife events occurring during the first 2 and last 2 years of the 7 years. Within one month of completing this self-report, participants underwent an MRI exam and a supervised assessment to collect relevant covariates.

2.3. Covariates

2.3.1. Physical health

Through a series of questions regarding a history of myocardial infarctions, cardiac procedures, and angina, participants were assessed as being at risk of cardiovascular disease or not as previously described (Xian et al., 2010). To determine if there was a history of TBI, participants were asked, "Have you ever had a severe head injury that was associated with loss of consciousness or confusion?" A reported head injury that was severe enough to be categorized as a TBI required at least one of the following criteria: had any loss of consciousness, resulted in confusion/memory loss, required medical attention, required hospitalization, involved any post-traumatic amnesia, and/or included any "early" or "late" seizures. Participants were also asked about daily alcohol consumption, whether they currently smoked, and were measured for height and weight to calculate body mass index (BMI = weight[kg]/height^2[m]).

2.3.2. Cognitive ability

General cognitive ability (GCA) was assessed using the 100-item multiple-choice Armed Forces Qualification Test (Uhlaner and Bolanovich, 1952). The test is highly correlated with other tests of GCA, such as Wechsler adult intelligence scale (r = 0.84) (Uhlaner and Bolanovich, 1952).

2.3.3. Depressive symptoms

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale, a questionnaire designed

to measure depressive symptomatology during the past week (Radloff, 1977). The total Center for Epidemiologic Studies Depression Score is the sum of all 20 questions (ranging from 0 to 80).

2.3.4. Apolipoprotein E4

The *APOE*-ε4 allele is the major risk allele for Alzheimer's disease. Participants were divided into ε4+ and ε4-groups. *APOE* genotyping was performed as previously described (Lyons et al., 2013).

2.3.5. Mild cognitive impairment

We employed a battery of neuropsychological tests to diagnose participants with MCI, a risk factor for dementia, according to the Jak-Bondi approach as previously described (Granholm et al., 2017; Jak et al., 2009; Kremen et al., 2014). Briefly, participants were neurocognitively assessed across the domains of episodic memory (three measures), executive functioning (four measures), attention and working memory (four measures), verbal language skills (three measures), visuospatial skills (three measures), and processing speed (four measures). Individuals were classified as having MCI if they showed impairment (1.5 SD below normative data) on two measures within a domain. Validation of the diagnosis is provided by evidence that higher scores on a validated Alzheimer's disease polygenic risk score were associated with significantly increased odds of having MCI (Logue et al., 2018) in this sample.

2.3.6. SES and ethnicity

We determined childhood SES according to the Hollingshead four-factor index of socioeconomic status (Hollingshead, 1975), which is based on a weighted combination of educational attainment and occupation. Childhood SES was the average of parents' SES if the mother was employed, or just father SES if the mother was a homemaker. The average of a twin pair's scores was used. Adults' SES is that of the participant at time of MRI assessment (average age 62 years). Ethnicity was categorized as either non-Hispanic white or not.

2.4. Magnetic resonance imaging acquisition and analysis

T1-weighted images providing high anatomical detail were acquired on 3T scanners at University of California, San Diego (UCSD) and Massachusetts General Hospital. At UCSD, images were acquired on a GE 3T Discovery 750× scanner (GE Healthcare, Waukesha, WI, USA) with an eight-channel-phased array head coil. The imaging protocol included a sagittal 3D fast-spoiled gradient echo T1-weighted image (echo time = 3.164 msec, repetition time = 8.084 msec, inversion time = 600 msec, flip angle = 8°, pixel bandwidth = 244.141, field of view = 25.6 cm, frequency = 256, phase = 192, slices = 172, and slice thickness = 1.2 mm). At Massachusetts General Hospital, images were acquired with a Siemens Tim Trio, (Siemens USA, Washington, D.C.) with a 32-channel head coil. The imaging protocol included a 3D magnetization-prepared rapid gradient echo T1-weighted image (echo time = 4.33 msec, repetition time = 2170 msec, inversion time = 1100 msec, flip angle = 7°, pixel bandwidth = 140, field of view = 25.6 cm, frequency = 256, phase = 256, slices = 160, and slice thickness = 1.2 mm).

As described in our prior work (Eyler et al., 2012), raw image files were processed using an in-house pipeline written in MATLAB and C++ by the UCSD Center for Multimodal Imaging and Genetics. Data were qualitatively assessed and images with severe scanner artifacts or excessive head motion were either rescanned where possible or excluded from the analysis (approximately 3%). T1-weighted structural images were corrected for gradient distortions (Jovicich et al., 2006) and B1 field inhomogeneity (Sled et al., 1998). Subcortical segmentation and surface-based cortical parcellation were performed using FreeSurfer version 5.3 (surfer.nmr.mgh.harvard.edu) as previously described (Fischl, 2012). Inaccuracies in automated segmentations were manually corrected by trained neuroimaging analysts. All images required some form of manual editing to ensure the correct classification of the pial and white matter surfaces, with particular attention given to the orbitofrontal cortex, the temporal lobes, meninges, and transverse and superior sagittal sinuses. Problematic segmentations/parcellations were reviewed by consensus with three neuroimaging analysts. Ten images were unable to be corrected and were excluded from this investigation to obtain the final total of 359 participants.

2.5. Predicted brain age and predicted brain age difference

To predict brain age, we used BARACUS v0.9.4, available at https://github.com/BIDS-Apps/BARACUS (Liem et al., 2017; https://zenodo.org/record/826543#.WjF5Ft-nE2x). BARACUS uses linear support vector regression models to predict brain age derived from each individual's FreeSurfer statistics. Specifically, vertex-wise cortical metrics were derived from the fsaverage4 standard space for cortical thickness (n = 5124 vertices) and surface area (n = 5124 vertices), and subcortical segmentation metrics were derived from the aseg.stat file for subcortical volume (n = 66 regions of interest). We used the BIDS-mode docker on Ubuntu 16.04 using the default database (Liem2016_OCI_norm), which is trained on 1166 subjects with no objective cognitive impairment (566 female/600 male, mean age 59.1 years, SD 15.2, range 20–80 years). The PBAD was calculated by subtracting the chronological age from the predicted brain age (referred to as the "stacked-anatomy" brain age in BARACUS). Therefore, a positive PBAD is indicative of brain age that is estimated to be older than one's chronological age.

2.6. Statistical analyses

All statistical analysis was performed using R (R Core Team, 2017). All continuous measures were z-scored before analysis,

Box 1. Negative fateful life events

Over the last 24 months, have you experienced the following events?

Relationships
- Separation from your spouse due to marital/work problems
- Divorce
- Spouse died
- Miscarriage/still birth
- Child died
- Other family member died
- A "falling out" of a close personal relationship
- Close friend died

Finances
- A major decrease in income
- Laid off/fired
- Difficulties paying regular bills
- A foreclosure of a mortgage or loan

Health
- An illness or injury that kept you in bed a week or more, or sent you to the hospital
- An illness or injury that was less serious than above
- Health worse than a year ago

Table 1
Fateful life events (FLEs) and demographics

Variable	Total (n = 359)	Low 0–2 FLEs (n = 170)	Moderate 3–5 FLEs (n = 147)	High 6 + FLEs (n = 42)	Sig. Test
Age, y	61.8 (2.6)	62.0 (2.5)	61.9 (2.7)	60.5 (2.3)	0.004 (H<L,M)
Smoker (%)	67 (18.7)	35 (20.6)	29 (19.7)	3 (7.1)	0.123
Drinks/day	0.95 (1.69)	1.18 (2.04)	0.78 (1.37)	0.59 (0.81)	0.522
Cardiometabolic risk (%)	37 (10.8)	16 (9.8)	13 (9.4)	8 (20.0)	0.137
Body mass index	29.07 (4.35)	28.81 (4.38)	29.05 (4.25)	30.14 (4.50)	0.209
APOE-ε4 carrier (%)	87 (24.2)	44 (25.9)	34 (23.1)	9 (21.4)	0.767
MCI diagnosis (%)	55 (15.7)	24 (14.5)	24 (16.6)	7 (17.9)	0.810
Depressive symptoms	6.70 (7.57)	5.38 (6.13)	6.79 (7.66)	11.74 (10.16)	<0.001 (L<M<H)
Traumatic brain injury (%)	98 (28.0)	38 (22.9)	44 (31.0)	16 (38.1)	0.086
GCA percentile score	63.5 (21.7)	66.8 (21.2)	60.9 (21.2)	59.5 (24.0)	0.123
Childhood SES	33.38 (11.32)	33.71 (11.78)	33.15 (10.88)	32.85 (11.09)	0.867
Adult SES	42.25 (10.77)	41.64 (11.16)	42.34 (10.10)	44.43 (11.41)	0.322
White ethnicity (%)	315 (87.7)	151 (88.8)	130 (88.4)	34 (81.0)	0.359
Fateful life events total	3.06 (2.17)	1.36 (0.77)	3.72 (0.80)	7.60 (1.36)	<0.001 (L<M<H)
Relationships	1.11 (1.15)	0.51 (0.64)	1.41 (1.03)	2.48 (1.58)	<0.001 (L<M<H)
Finances	0.70 (1.10)	0.22 (0.47)	0.76 (0.90)	2.40 (1.68)	<0.001 (L<M<H)
Health	1.25 (1.18)	0.62 (0.73)	1.55 (1.07)	2.71 (1.31)	<0.001 (L<M<H)

Continuous variables are given as mean (SD), categorical variables are shown as count (%). Data are displayed with three subgroup for illustrative purposes only; all subsequent regression analysis was conducted using the total scores (continuous measure). Statistical differences between groups were assessed using nlme for continuous normal data and lme4 for categorical data with twin relatedness as a random factor, significance set at $p < 0.05$. General cognitive ability (GCA) was assessed using the Armed Forces Qualification Test. Depression was measured using the Center for Epidemiologic Studies Depression Scale (CES-D).
Key: APOE-ε4, apolipoprotein E4 allele carrier; MCI, mild cognitive impairment; SES, socioeconomic status.

and significance was set at $p < 0.05$ (two-tailed). A generalized linear model assessed the prevalence of FLEs between the two time points of data collection controlling for the Poisson distribution. To reduce the influence of large positive skew of the initial total FLEs (skew = 2.08, kurtosis = 6.81), we Winsorized extreme outliers to three SDs (i.e., total FLEs maximum = 9). This approach transformed 3% (n = 11) of the sample to give a more normal distribution (skew = 1.04, kurtosis = 0.91), and the minimal mean absolute error (MAE = 0.11) indicated that the transformation remained a good fit to the data. For consistency, we also Winsorized the three domain scores to three SDs (i.e., maximum FLEs for relationships, finance, and health domains = 5 each) with similar results.

To illustrate how demographic covariates differ with increasing FLEs, participants were split into three groups: low (0–2 FLEs), moderate (3–5 FLEs), and high (≥6 FLEs). Statistical differences between FLE groups were assessed using the R package nlme version 3.1–131 (Pinheiro et al., 2017) for continuous normal data, and lme4 version 1.1–14 (Bates et al., 2015) for categorical data. The relatedness of twin pairs was set as a random effect.

To test the goodness of fit of the BARACUS predicted brain age to the actual chronological age, we calculated the MAE. We also performed a linear mixed model using nlme to check the relationship between PBAD and chronological age. This included scanner as a fixed effect and twin relatedness as a random effect. All subsequent linear mixed models were run in nlme version 3.1–131 (Pinheiro et al., 2017) using FLE as a continuous rather than categorical measure. We tested the relationships between FLEs and PBAD controlling for MRI scanner (one per site) and treating the relatedness of twin pairs as a random effect. First, we examined the direct relationship between the three FLE domains of relationships, finance, and health on PBAD. Next, we examined this relationship while controlling for covariates. Nonsignificant covariates were removed in a backward elimination process.

3. Results

3.1. Fateful life events and covariates

The prevalence of FLEs between the first (mean total FLEs = 1.62, SD 1.77) and second time points (mean total FLEs = 1.56, SD 1.62) was slightly but significantly reduced [$\beta = 0.09$, standard error (SE) 0.021, $z(354) = 4.10$, $p < 0.001$]. Combined, the mean total FLEs was 3.06 (SD 2.17; Table 1). When comparing low (0–2), moderate (3–5) to high (≥6) FLE groups, the prevalence of FLEs in the domains of relationships, finances, and health significantly increased (Table 1). There was a significant increase in depressive symptoms between the low, medium, and high FLE groups (mean score for low = 5.38; moderate = 6.79; and high = 11.74; Table 1). Compared to the low FLE group, the high FLE group showed a trend for reduced smoking ($p = 0.054$) and increased prevalence of TBI ($p = 0.055$). The high FLE group was also younger than the other groups ($p = 0.004$). All subsequent analyses were performed using FLEs as a continuous measure.

3.2. Fateful life events and brain aging

The mean predicted brain age was 63.9 years (SD 5.9, range 35.2–74.4, Fig. 1). Testing the goodness of fit of the BARACUS predicted brain age to the chronological age, MAE = 5.13. The mean PBAD was +2.3 years (5.8 SD, range -21.1 to 14.8), which was significantly different from chronological age [$\beta = -0.11$, SE 0.022, $t(134) = -4.90$, $p < 0.001$] but still remains within the mean absolute prediction error for BARACUS (±4.29 years).

We first examined the direct relationship between FLEs and PBAD. The number of FLEs was positively associated with PBAD [$\beta = 0.13$, SE 0.052, $t(134 = 2.57$, $p = 0.011$; Fig. 2]. Examining this effect for each FLE domain individually (relationships, finance, or health) showed that PBAD was not significantly associated with financial events [$\beta = 0.06$, SE 0.052, $t(132) = 1.174$, $p = 0.242$] or health events [$\beta = 0.05$, SE 0.050, $t(132) = 0.964$, $p = 0.337$]; there was a trend for an association with relationships [$\beta = 0.10$, SE 0.051, $t(132) = 1.96$, $p = 0.0526$]. Based on the Akaike information criterion (AIC), the model with total FLE (AIC = 990) had the better fit to the data than with each domain separately (AIC = 1002) and was used as the sole FLE measure going forward.

Next, all the covariates were added to the model and nonsignificant measures were removed in a backward elimination process. BMI, diagnosis of MCI, *APOE*-ε4 status, childhood SES, history of TBI, depression severity, smoking status, and GCA were each removed from the model in that order. Cardiovascular risk ($\beta = 0.47$) and alcohol consumption ($\beta = 0.16$) were significantly positively correlated with PBAD; white race/ethnicity ($\beta = -0.61$) and adult SES ($\beta = -0.17$) were negatively correlated with PBAD. That is, those with

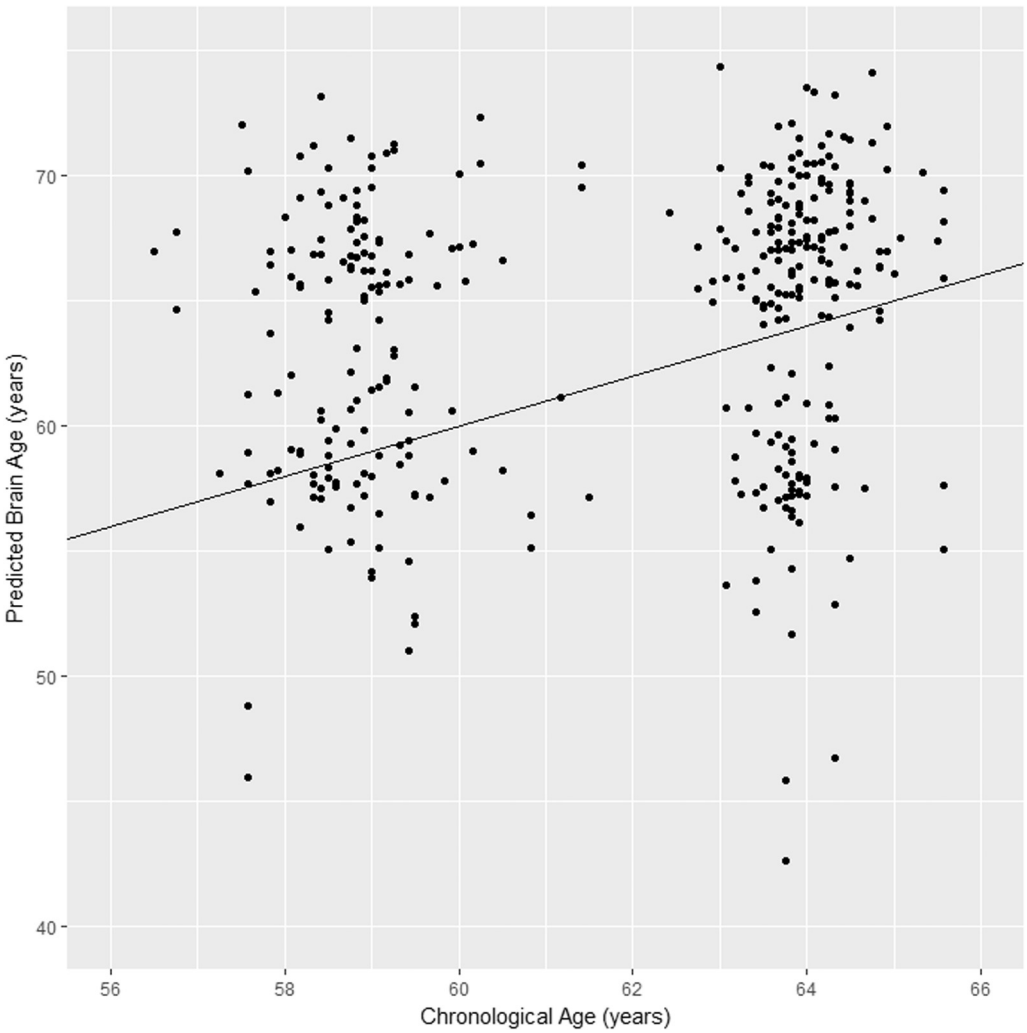

Fig. 1. Chronological age versus predicted brain age. The reference line shows where chronological age equals predicted brain age. The predicated brain age difference is calculated by subtracting the chronological age from the predicted brain age. Points above the reference line are positive predicted brain age differences indicative of accelerated brain aging. Mean absolute prediction error of this model is 4.29 years.

greater cardiovascular risk, more alcohol consumption, lower adult SES, and whose race/ethnicity was other than non-Hispanic white had older predicted brain age than chronological age. After controlling for these covariates, FLEs remained significantly positively associated with PBAD [$\beta = 0.14$, SE 0.054, $t(106) = 2.57$, $p = 0.011$] and improved the fit of the model (AIC = 866). Thus, when all significant covariates are taken into account, on average one FLE is associated with an increase in PBAD by 0.37 years.

To check that extreme outliners did not disproportionally influence these findings, five subjects with a PBAD < -15 years were removed and the analyses were repeated. Total FLEs remained positively associated with PBAD [$\beta = 0.13$, SE 0.051, $t(131) = 2.59$, $p = 0.011$], and the association with the relationship domain was significant [$\beta = 0.11$, SE 0.050, $t(129) = 2.57$, $p = 0.026$]. After adding covariates into the model, total FLEs remained positively associated with PBAD [$\beta = 0.11$, SE 0.053, $t(103) = 2.09$, $p = 0.039$], and the same covariates remained significant and associated in the same direction.

Although chronological age was not considered an *a priori* covariate of interest, the initial analysis (Table 1) showed that participants with six or more FLEs were significantly younger than those with less FLEs. Accordingly, we ran a post-hoc analysis of the full model including chronological age as a covariate. FLEs remained significantly positively associated with PBAD [$\beta = 0.11$, SE 0.053, $t(105) = 2.14$, $p = 0.034$], the same covariates remained significant and associated in the same direction, and age was a significant covariate ($\beta = -0.22$).

4. Discussion

We showed here that FLEs in midlife are associated with advanced predicted brain aging, although the nature of that relationship is complex. When all significant covariates are taken into account, on average one FLE is associated with an increase in PBAD by 0.37 years. Those with more alcohol consumption, greater cardiovascular risk, lower adult SES, and whose race/ethnicity was other than non-Hispanic white had older brain age than chronological age. However, not all factors were associated with advanced predicted brain age: BMI, childhood SES, MCI, *APOE* status, TBI, smoking, depressive symptoms, and general cognitive ability could all be dropped from the statistical model. Thus, only some factors that reflect greater allostatic load and are frequently associated with elevated levels of stress were associated with advanced predicted brain aging. Importantly, the association between FLEs and PBAD remained significant after controlling for the covariates that were significantly associated with PBAD. In other words, FLEs were still associated with PBAD even after accounting for multiple

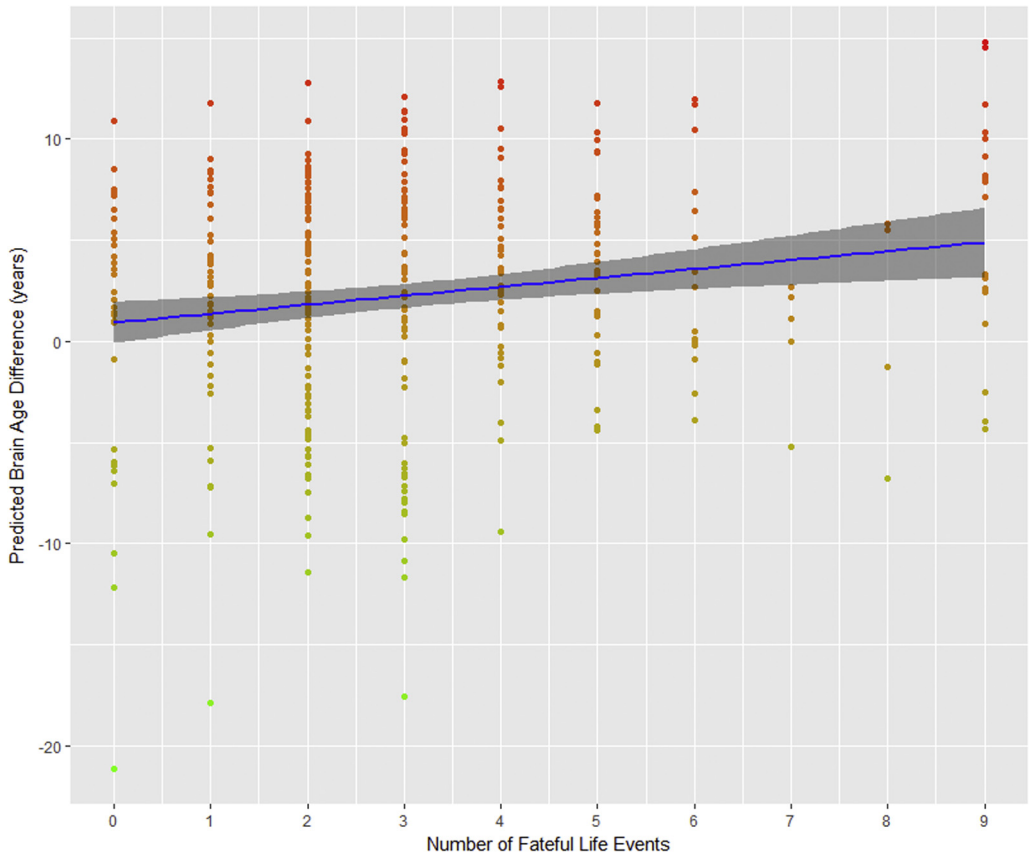

Fig. 2. Fateful life events and predicted brain age difference. Each data point represent an individual participants' predicted brain age difference with respect to the number of fateful life events they have experienced. The blue line denotes the linear model trend with 95% confidence interval. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

medical, cognitive, genetic, and psychosocial factors. Taken together, these results are consistent with the idea that there is some additional psychological stress response to FLEs that has a negative impact on brain aging.

Our findings extend previous investigations into FLEs and other indices of accelerated biological aging. Simons et al. (2016) showed in African-American middle-aged women that stressful life events were associated with accelerated telomere shortening, particularly with regard to financial stress. Minority race/ethnicity was associated with advanced predicted brain aging in our sample. However, we showed here that PBAD was positively correlated with total FLEs predominantly within the domain of interpersonal relationships but not financial FLEs. In addition to sex differences, the key life events may have been different in these two samples. There is also evidence that cumulative life stress is associated with accelerated epigenetic aging (Zannas et al., 2015). Thus, there appears to be strong evidence that adverse events are associated with multiple manifestations of accelerated aging, including aberrant genetic/epigenetic modifications and accelerated structural brain aging.

A post-hoc analysis found that chronological age was also a significant covariate. We posit that this is the result of several FLEs occurring earlier in midlife that do not reoccur later in life, such as the death of family members or divorce/separation. However, a reduction in these midlife FLEs in late life does not preclude the increase in other events, particularly health-related FLEs. While this investigation focuses on the effect of FLEs on the brain in midlife, future research should examine the frequency of FLEs across difference stages of life and their effect on brain health.

A diagnosis of MCI was not associated with advanced predicted brain aging and did not influence the relationship between FLEs and PBAD in the present study. Liem et al. (2017) created composite neuropsychological domain scores for adults ages 19–82. They defined cognitive impairment as mild if a domain score was between 1 and 2 SDs below normative means and major if a domain score was more than 2 SDs below normative means. Worse objective cognitive impairment was associated with higher PBAD. The difference in results between the two studies might be due to differing definitions of cognitive impairment or the very different age compositions of the sample or the fact that ours was a male-only sample. Participants in the Liem et al. study ranged in age from 18 to 82 years, and it is likely that those with MCI or dementia were older. If brain age changes accelerate with MCI or dementia, it could increase differences from noncognitively impaired individuals. Liem et al. did not examine MCI subtypes but that could also affect the results. We found partial consistency with the results of Liem et al. in that post-hoc analysis showed that individuals with nonamnestic, but not amnestic, MCI had significantly more advanced predicted brain age than noncognitively impaired participants. MCI or MCI subtype was not a significant predictor of PBAD when the other covariates were included in the model. The goal of Liem et al. was not to examine FLEs, so they did not include the covariates used in the present study. Future investigations aimed at training BARACUS with different samples may be useful for understanding brain structure trajectories and cognitive decline in later life, as well as to differentiate based on the sex of the participant.

Several studies highlight the neurodegenerative cellular processes associated with prolonged stress. Exposure to stress shifts

immune system gene expression, increasing expression of proinflammatory genes and decreasing expression of antiviral processes and antibody synthesis-associated genes (Cole, 2014). This chronic elevation of inflammation has been linked to tissue damage, dysregulated metabolic processes, and increased risk for chronic and age-related conditions (Cole, 2014; Maggio et al., 2006). It has been proposed that such accumulation of DNA damage in neurons leads to the activation of several repair processes that, if impaired, result in further accumulation of DNA damage leading to cellular senescence, apoptosis, neurodegeneration, and premature brain aging (Coppede and Migliore, 2010). Cumulative lifetime stress burden has also been associated with accelerated epigenetic aging via glucocorticoid signaling (Zannas et al., 2015). These studies may provide possible molecular mechanisms linking FLEs with advanced predicted brain aging.

Neuroimaging-based age predictions represent an evolving biomarker of deviations in brain development and aging, which provide several advantages. First and foremost, PBAD is a simple, single composite score that can act as a putative biomarker representing complex interactions that may not be fully captured in the traditional analysis of multiple regions of interest. In the clinic, a predicted brain age may help provide an easily understandable metric for informing patients of their brain health relative to their age. In clinical trials, PBAD would be useful for improving study design and recruitment, such as nonrandomized arm allocation using models specific to the investigation. These include measuring early brain development (Brown et al., 2012; Dosenbach et al., 2010), risk of schizophrenia or borderline personality disorder (Koutsouleris et al., 2014), predicting cognitive impairment (Liem et al., 2017), and conversion to Alzheimer's disease (Gaser et al., 2013).

The simplicity of the PBAD can also be problematic. Using a general measure of brain age inhibits the ability to identify specific locations or magnitude of pathology being observed or the characteristic topology of a given disorder. A counterargument to this limitation is that PBAD indexes deviations in the brain structure network as a whole rather than in delineated locations. Finally, while PBAD is useful in a number of contexts (development, aging, cognition), what it is actually indexing remains an open empirical question. Considering these algorithms are developed from cross-sectional data, at any given age, one would expect a normal distribution of morphometric variation that could be due to neurological insult, congenital conditions (e.g., type 1 diabetes), psychological insult, or simply normal heterogeneity. To this end, researchers should be more circumspect in the interpretation of this new biomarker, discussing the deviations in predicted brain age rather than interpreting advanced predicted brain age as reflecting an "older brain". To better characterize what is being measured, future neuroimaging-based age predictions might benefit by incorporating other physiological measures such as electroencephalography and magnetoencephalography as well as combining with molecular and cellular age prediction assessments such as telomere and methylation approaches.

4.1. Limitations

Limitations to this investigation warrant discussion. As this study involves late-middle-aged predominately white men of a narrow age range, these results may not be applicable to women or other ethnic groups. However, it is noteworthy that our findings of advanced predicted brain aging with midlife FLEs is in line with findings in African-American middle-aged women (Simons et al., 2016). Also, it can be advantageous to have people of similar chronological age, as in our study, so as to obtain a "snapshot" of brain aging at a specific life stage, namely late midlife before the increase in prevalence of dementia. In addition, although PBAD is often considered to be a result of longitudinal changes in brain structure, the cross-sectional nature of the study and the training set preclude interpretations about change over time. For instance, it is possible that characteristics of advanced brain age were present before experiencing midlife FLEs. Future analysis of the VETSA longitudinal data will be able to compare those whose brain age is accelerating from those who are stable and observe possible differential correlates of these two patterns. Finally, we do not discount the influence of early life events and childhood trauma on advanced brain aging in later life, and future research should examine the relationships between early and recent FLEs on brain aging.

Our assessment of FLEs also has limitations. On two occasions, separated by 5 years, we asked participants to recall FLEs over the past 2 years. Although it would be preferable to have asked participants to recall events over the past 5 years to reduce the gap in this epoch, we prioritized the validity of accurately recalling events over a 2-year period rather as a trade-off against reduced recall accuracy over a longer period. At the individual level, participants with excessive FLEs at the first time point had resolved them 5 years later, whereas participants with excessive FLEs at the second time point had few FLEs 5 years previously. Thus, many FLEs would have been unaccounted for if we used data from only one of the 2-year periods. It is also relevant to note that while we scored divorce, separation from spouse due to marital/work problems, and a "falling out" of a close personal relationship as FLEs in line with the original Psychiatric Epidemiology Research Interview Life Event Scale (Dohrenwend et al., 1978, 1980), future research would benefit by explicitly including problems with a wider range of interpersonal relationships.

5. Conclusion

In middle age, cardiovascular risk factors, low adult SES, alcohol consumption, and ethnicity were significantly associated with advanced predicted brain age. Even after controlling for these factors, individuals who had higher levels of major life events showed signs of advanced predicted brain aging. Although post-hoc analysis showed that nonamnestic, but not amnestic, MCI was also associated with advanced predicted brain aging, this association did not hold up after controlling for these other factors. It remains to be determined whether the influence of midlife FLEs and other factors on brain age may change with increasing chronological age.

Disclosure statement

AMD is a founder and holds equity in CorTechs Laboratories, Inc., and also serves on its Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. All other authors report no potential conflicts of interest.

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