



Published in final edited form as:

J Trauma Stress. 2018 October ; 31(5): 676–686. doi:10.1002/jts.22325.

Posttraumatic Stress Disorder Symptoms, Temperament, and the Pathway to Cellular Senescence

Samantha L. Connolly^a, Tawni B. Stoop^b, Mark W. Logue^{b,c}, Esther Hana Orr^{d,e}, Immaculata De Vivo^{d,e}, Mark W. Miller^{b,c}, and Erika J. Wolf^{b,c}

^aPsychology Service, VA Boston Healthcare System, Boston, Massachusetts

^bNational Center for PTSD at VA Boston Healthcare System

^cDepartment of Psychiatry, Boston University School of Medicine

^dChanning Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

^eDepartment of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Abstract

Traumatic stress is thought to be associated with shortened telomere length (TL) in leukocytes, an age-related marker of increased risk for cellular senescence, though findings to date have been mixed. This study assessed associations between PTSD symptom severity, temperament, and TL in a sample of 453 white, non-Hispanic middle-aged, trauma-exposed male and female veterans and civilians. Given prior work suggesting an association between PTSD and accelerated cellular age, we also examined associations between TL and an index of accelerated cellular age derived from DNA methylation data (“DNAm age”). Analyses revealed that, controlling for chronological age, PTSD was not directly associated with TL, but rather, this association was moderated by age ($\beta = -.14, p = .003, R^2 = .02$). Specifically, PTSD severity evidenced a stronger negative association with TL among relatively older participants (> 55 years). In a subset of veterans with data pertaining to temperament ($n = 150$), positive emotionality, and specifically, a drive towards achievement ($\beta = .26, p = .002, R^2 = .06$), were positively associated with TL. There was no evidence of an association between age-adjusted TL and accelerated DNAm age. Collectively, these results indicate that older adults may be more vulnerable to the negative health effects of PTSD, but that traits such as achievement, resilience, and psychological hardiness may be protective. Findings underscore the importance of identifying reliable biomarkers of cellular aging and senescence and of determining the biological mechanisms that contribute to stress-related disease and decline.

Posttraumatic stress disorder (PTSD) has been associated with a number of poor health outcomes including metabolic syndrome, cardiovascular disease, and premature death (Boscarino, 2004; Wolf et al., 2016a). Lohr et al. (2015) suggested that such associations

Correspondence concerning this article should be addressed to Erika Wolf, Ph.D., VA Boston Healthcare System, 150 S. Huntington Ave. (116B-2), Boston, MA, United States. erika.wolf@va.gov. Corresponding author pre-publication: Samantha Connolly, Ph.D., VA Boston Healthcare System. Samantha.connolly@va.gov.

were evidence of a link between PTSD and cellular senescence, a condition in which cells are no longer able to divide and proliferate, often conceptualized as an index of cellular aging (Campisi & Fagagna, 2007). In the case of PTSD, the chronic biological toll associated with emotional and physiological reactivity and disturbed sleep may promote cellular senescence and lead to early onset of age-related disease (Miller & Sadeh, 2014; Lohr et al., 2015; Wolf & Schnurr, 2016). As such, it is important to study biomarkers relevant to cellular senescence and disease risk among those with PTSD.

One index of cellular integrity is telomere length (TL) assessed in leukocytes. Telomeres are DNA-protein complexes at the end of chromosomes that protect against DNA damage and preserve chromosomal integrity (Blackburn, 1991) by preventing protein coding DNA sequences from being truncated during cell division. Telomeres are comprised of multiple repeat DNA sequences; in the process of cell division, the complete DNA repeat sequence is not fully replicated, leading to loss of DNA and telomere shortening with each cell division (Campisi & Fagagna, 2007). This is mediated by inflammatory and oxidative stress processes (Fougère et al., 2016), which have also been linked to PTSD (Miller, Lin, Wolf, & Miller, 2017; Miller et al., 2018). TL may be further influenced by compositional changes in leukocytes as a result of chronic and traumatic stress (Boeck et al., 2016; Karabatsiakos et al., 2014). Telomere degradation is one major cause of cellular senescence (von Zglinicki, 2002). Although TL has genetic determinants, such as the genes *TERT* and *TERC* (Armanios, 2009), environmental factors such as chronic stress also appear to play a significant role (Epel et al., 2009).

Multiple studies have demonstrated relationships between traumatic stress and shorter TL (Li et al., 2017b). PTSD has been associated with shorter TL among male veterans (Jergovi et al., 2014; Zhang et al., 2014), though this effect is not uniform. The opposite direction of effect was reported by Boks et al. (2015) among Dutch male soldiers, and at least one study found no relationship between PTSD diagnosis and TL among veterans, but did demonstrate associations between trauma exposure and shortened telomeres (Bersani et al., 2016). PTSD has been linked to shorter TL among female rape survivors (Malan et al., 2011) and female nurses (Roberts et al., 2017), although null findings were reported within a mixed-sex sample of former child laborers (Küffer et al., 2016). A relationship between PTSD and shortened TL was also found in a clinical sample of civilian men and women (O'Donovan et al., 2011). A recent meta-analysis reported an association between retrospectively reported childhood trauma and shortened TL in adulthood (Li et al., 2017a). Studies of population samples have reported associations between PTSD and shorter TL (Ladwig et al., 2013; Shalev et al., 2014), with a possible dose-dependent effect reported by Ladwig et al. such that telomeres were shorter among those with full compared to partial PTSD diagnoses. These findings raise the possibility that greater PTSD symptom severity may be associated with more pronounced cellular changes.

The studies of PTSD and TL that are based on clinical samples with a high prevalence of PTSD have generally been limited by small samples and a focus on relatively young cohorts, i.e., between 47–120 participants, mean age between 22–45 years (Malan et al., 2011; O'Donovan et al., 2011; Jergovi et al., 2014; Zhang et al., 2014; Boks et al., 2015; Bersani et al., 2016; Roberts et al., 2017). Further, these studies have often assessed PTSD using

self-report checklists instead of clinician-administered diagnostic interviews (Ladwig et al., 2013; Zhang et al., 2014; Boks et al., 2015; Bersani et al., 2016). Therefore, one aim of this study was to assess the relationship between PTSD and TL utilizing a clinician-administered PTSD interview within a well-characterized, large (3–4 times that of prior clinical studies of PTSD and TL) sample with a high prevalence of PTSD and significant variability in participant age. This latter point is important given the potential cumulative burden of the effects of PTSD over time (Lindemer et al., 2013) as well as evidence that shortening telomeres may cause greater chromosomal instability with advancing age (Harris et al., 2006; Rius-Ottenheim et al., 2011).

Studies have not yet examined how heterogeneity in posttraumatic psychopathology might alter associations between PTSD and TL. There is substantial variability in patterns of posttraumatic psychopathology, and temperament may underlie individual differences in its expression (Miller, 2003; Miller et al., 2004, 2007; Wolf et al., 2012). Specifically, temperament profiles characterized by high levels of negative emotionality (NEM; i.e., neuroticism) and low levels of positive emotionality (PEM; i.e., positive affect) tend to be associated with PTSD comorbidity in the internalizing domain (e.g., depression and anxiety) while temperament profiles characterized by high levels of NEM and disinhibition (e.g., impulsivity) are associated with PTSD comorbidity in the externalizing domain (e.g., substance use disorders and cluster B personality disorders; Miller et al., 2003, 2004, 2007; Sellbom & Bagby, 2009; Forbes et al., 2010; Rielage et al., 2010; Wolf et al., 2012). It is unknown how individual differences in temperament might relate to TL in a sample with substantial PTSD symptoms. In other populations, pessimism and increased sensitivity to stress have been linked to shortened TL (Epel et al., 2004; O'Donovan et al., 2009), suggesting that low PEM and high stress reactivity (a facet of NEM) might be similarly associated with shortened TL among those with PTSD.

Given this, the primary aim of this study was to investigate associations between PTSD symptoms, temperament, and TL in a large sample of trauma-exposed veterans and their trauma-exposed partners. We hypothesized that PTSD symptoms would be inversely associated with TL and that NEM and PEM would be inversely and positively associated with TL, respectively. We further hypothesized that associations between PTSD and TL would be strongest among older participants in the sample, given that: (a) the effects of chronic PTSD symptoms were expected to demonstrate a cumulative negative effect over time; and (b) telomeres, would be expected to be more sensitive to the pathological effects of PTSD among older, more vulnerable individuals (Harris et al., 2006; Rius-Ottenheim et al., 2011).

A second aim of this study was to shed light on the utility of TL as an index of accelerated cellular age. Prior research has traditionally conceptualized the effects of stress on TL as an index of an accelerated aging process. However, it is not evident that telomeres are sufficient indices of cellular age, given that correlations between TL and chronological age are modest at best (ranging from .20 – .30; Müezziner et al., 2013). Comparatively, DNA methylation (DNAm) metrics of cellular age have recently been established that show vastly superior associations with chronological age (i.e., in the realm of $r = .96$; Hannum et al., 2013; Horvath, 2013). These metrics of cellular age are referred to as “DNAm age” and are based

on a weighted algorithm of DNAm levels at specific loci from across the human genome. The Horvath DNAm age index is a multi-tissue cellular age predictor while the Hannum DNAm age index was developed in whole blood. Both can be compared against chronological age to index a spectrum of accelerated to decelerated cellular aging. Three recent studies, including a meta-analysis and an evaluation of a subset of the current participants, found that DNAm age was strongly correlated with chronological age ($r \approx .90$) and that PTSD symptoms were associated with accelerated Hannum DNAm age [edited out for blind review]. Given this, we also examined the association between DNAm age and TL, controlling for chronological age in both variables.

Method

Participants

This sample was derived from two research studies with identical assessment procedures. One study included veterans who screened positive for PTSD. The second study included veterans and their cohabitating partners, all of whom were trauma-exposed, for a combined initial sample of 852 [edited out for blind review]. Within this sample, 42 participants were excluded for not fully completing the protocol and an additional 24 were excluded due to unsuccessful blood draws. Twenty-five participants were enrolled in both protocols and therefore data were only included from one study, resulting in a baseline sample of 761 participants. Within this sample, 729 endorsed being exposed to a traumatic life event, as measured by the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). Four hundred ninety-one participants within this subset had valid genotype data and were confirmed to be of white non-Hispanic ancestry based on principal components (PC) analysis; see Supplementary Materials. DNAm was obtained from white, non-Hispanic participants because this was the largest ancestrally homogenous subsample and because of concerns relating to ancestry-related differences in DNAm (Barfield et al., 2014). DNAm data were available for 466 participants, and telomere estimates were available for a subset of $n = 453$, the final sample for this study.

The mean age at the time of the blood draw and PTSD assessment was 52.49 years (SD: 10.78, range: 23 – 75). The sample was 65.1% male and 65.9% were veterans. 90.5% of veterans were male and 92.0% of partners were female. The majority (60%) met *DSM-IV* criteria for a lifetime diagnosis of PTSD, as determined by the CAPS, and 39% had current PTSD. Temperament analyses were conducted in a subset of 150 veterans who completed the Brief Form of the Multidimensional Personality Questionnaire (MPQ-BF; Patrick et al., 2002) as part of the veteran-only study. See Table 1 for additional demographic information.

Procedure

Participants were recruited from multiple sources, including an institution-generated registry list of local veterans, recruitment database of veterans who had previously expressed interest in research in our center, clinician referrals, and flyers posted throughout the hospital. As detailed above, participants in the veterans-only study were screened by telephone for PTSD using the PTSD Checklist (PCL; Weathers et al., 1993), adhering to *DSM-IV* diagnostic criteria. Participants from the veteran and partners study were screened by telephone to

determine if the veteran was trauma-exposed and cohabitating with an intimate partner. At the data analysis stage, as detailed above, we eliminated any subjects who did not report trauma exposure; thus, all participants in these analyses, including partners, were trauma-exposed. Participants in both the veteran-only and couple study completed a blood draw and underwent psychiatric diagnostic interviewing and self-report measures during a 3–4 hour initial session, with a subset of participants returning to complete measures during a second session as needed. The MPQ-BF was administered in the veteran-only study. We also obtained information pertaining to physical health comorbidities that were present within the six months before or after the date of the study assessment for a subset of veterans in the sample with available health data from the local electronic medical record. All participants provided written informed consent and the study was reviewed and approved by the [IRB name edited out for blind review.]

Measures

PTSD symptoms were assessed using the CAPS (Blake et al., 1995), a widely used structured diagnostic interview assessing the frequency and intensity of the 17 symptoms of PTSD as per *DSM-IV* criteria. Each item was rated on a 0–4 scale for frequency and 0–4 scale for intensity. Frequency and intensity scores for all items were summed and the two scales were added together to create a total PTSD symptom severity score. PTSD diagnoses were determined using the *DSM-IV* algorithm; symptoms were deemed present if frequency ≥ 1 and intensity ≥ 2 (Weathers et al., 1999). The CAPS interviews were conducted by Masters and PhD level psychology trainees and professionals and videotaped to assess reliability of interview administration and scoring. Approximately 30% of recorded interviews were scored by an independent rater, resulting in an intraclass correlation coefficient for lifetime PTSD symptoms of $r = .97$. Cronbach's alpha in this sample was .90 [Edited out for blind review]. The CAPS total score has been shown to have excellent reliability and validity (Weathers et al., 2001). Trauma exposure was assessed using the Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000). This self-report measure assesses lifetime exposure to 22 potentially traumatic experiences, inclusive of childhood trauma (*DSM-IV* PTSD Criterion A1), as well as peritraumatic fear, helplessness or horror (*DSM-IV* PTSD Criterion A2). The number of times each event was experienced was rated on a 7-point scale (“never” to “more than 5 times”); we totaled the number of different types of traumas experienced for use in analyses. The TLEQ has demonstrated good reliability and validity with respect to PTSD diagnoses (Kubany et al., 2000). Temperament was measured using the MPQ-BF (Patrick et al., 2002), a 155-item true/false self-report questionnaire assessing three well-established higher order temperament domains: PEM, NEM, and constraint (i.e., the opposite of disconstraint; CON). MPQ-BF Higher-Order scales subsume 11 Primary Trait scales. Well-being, Social Potency, Social Closeness, and Achievement contribute to PEM, Stress Reaction, Alienation, and Aggression contribute to NEM, and Control, Harm Avoidance, and Traditionalism contribute to CON. The MPQ-BF is a well-validated measure derived from the 276-item MPQ through an iterative process of factor analysis and item selection (Tellegen & Waller, 2008). Cronbach's alpha cannot be computed for the Higher-Order scales that were the primary focus of analysis as they are weighted factor scores derived from the Primary Trait scales (Patrick et al., 2002).

Genotyping and DNAm

Peripheral, non-fasting blood samples were collected and DNA was extracted from buffy coat, with genotyping derived from the Illumina HumanOmni 2.5⁻⁸ microarray. Methods for calculating the ancestry-based principal components (PCs) from common single nucleotide polymorphisms, estimating proportional white blood cells directly from the DNAm data using the Houseman et al. (2012) and Jaffe and Irizarry (2014) methods, and for computing the Horvath (2013) and Hannum et al. (2013) DNAm age estimates are provided in [edited out for blind review; also see Supplementary Materials].

Telomere Length Measurement

Average relative TL was assessed using Real-Time Quantitative PCR (qPCR) (Cawthon, 2002) at the [edited out for blind review], by determining the copy-number ratio between telomeric repeats and a single-copy (36B4) reference gene (T/S Ratio, $-dCt$). The T/S ratio represents the average TL across all chromosomes in a cell population and was calculated per participant by subtracting the average 36B4 threshold cycle (Ct) value from the average telomere Ct value. See Supplementary Materials for a detailed description of these methods. TL was multiplied by a constant of 100 in the current analyses to improve interpretability of results.

Data Analysis

We first investigated the association between chronological age and TL via correlation. We then tested the relationship between accelerated aging as measured in DNAm data and TL using regression. To do so, we computed DNAm age residuals from a regression in which DNAm age estimates were regressed on chronological age, in accordance with prior work (Horvath et al., 2013; Marioni et al., 2015). Over-predicted DNAm age estimates are captured by positive DNAm age residuals and reflect advanced estimated age compared to chronological age (i.e., accelerated cellular age). It is expected that those with accelerated DNAm age would also have shorter TL. In contrast, negative DNAm age residuals reflect under-predicted age compared to chronological age (i.e., decelerated aging). In separate regressions, Horvath and Hannum DNAm age residuals were entered into a regression predicting TL while also controlling for age, estimated white blood cell proportions (CD4 and CD8 T-cells, natural killer cells, B cells, and monocytes), the top 2 PCs, and sex. We did not evaluate associations between DNAm age residuals and PTSD as that work has already been reported on for a subset of participants included in this study (reference edited for blind review).

Next, we conducted a linear regression investigating associations between age and lifetime PTSD symptoms in the prediction of TL. Sex and total number of unique traumas were included as covariates in the model and the effects of age and lifetime PTSD symptoms (grand mean centered) were included as main effects. In a second step of the equation, the interaction between these two centered variables was entered. Follow-up analyses controlled for white blood cell count proportional estimates and population substructure as potential confounds. This analysis was then rerun substituting lifetime PTSD diagnosis for symptom scores.

In follow-up analyses based on a subset of veterans with available electronic medical record data, we examined if physical health comorbidities might be associated with TL. The following variables (Supplementary Table 1) were entered into an equation predicting TL, controlling for age and sex: hyperlipidemia, hypertension, type 2 diabetes, and cardiovascular disease ($n = 219$). In order to maximize sample sizes, cigarette use data (available for $n = 309$) and body mass index (available for $n = 133$) were evaluated in separate regressions. Supplementary analyses were also conducted to examine whether PTSD symptoms (alone or in interaction with age) predicted the estimated white blood cell proportions. Each type was tested in a separate regression analysis with the following terms included as predictors: age, sex, number of unique traumas, PTSD symptoms, and the age \times PTSD symptoms interaction term.

Finally, we conducted additional regression analyses predicting TL within the subset of participants with MPQ-BF data. In the first regression, the first step entered age, sex, total trauma count, and lifetime PTSD symptoms and the second step added raw scores on the three MPQ-BF Higher-Order personality domains: PEM, NEM, and CON. A follow-up regression probed the relative contribution of the four PEM lower-order scales (Well-being, Social Closeness, Achievement, and Social Potency) in predicting TL, given that PEM emerged as a significant predictor in the first regression. This analysis followed the same approach as that for higher-order MPQ-BF scales except that only the four lower-order PEM scales were included in the second step. Finally, potential interactions between age and PEM, NEM, and CON were tested in three separate regressions. Sex, total number of unique traumas, and lifetime PTSD symptoms were controlled for, and age and the personality variable of interest (grand mean centered) were included as main effects in the first step. The centered interaction between age and each personality variable was entered in the second step. Standardized beta values are reported for all regressions in reference to the T/S ratio.

Results

Associations between Chronological Age, DNA Methylation Age Residuals, and TL

Chronological age was weakly but significantly correlated with TL ($r = -.247, p < .001$), and it was included as a covariate in all subsequent models. Neither the Hannum nor Horvath DNAm age residuals were significantly associated with TL when tested in separate regression equations controlling for chronological age (β s $< |-.09|, ps > .10$). Effects remained nonsignificant for both Hannum and Horvath DNAm residuals as predictors of a residualized TL variable, in which TL was first regressed on chronological age and the residuals from the equation were utilized as the dependent variable (β s $< |-.02|, ps > .10$). Consistent with previously published findings from our group, there was a strong correlation between DNAm and chronological age within this sample ($r = .90, p < .001$).

PTSD Symptoms and TL

The regression yielded no main effect of lifetime PTSD symptoms on TL (Table 2). However, a significant interaction emerged between age and lifetime PTSD symptoms in association with TL ($\beta = -.14, t(450) = -3.01, p = .003$) and explained a significant proportion of the variance ($R^2 = .02, F(5,450) = 8.97, p < .001$; Table 2). When

additionally controlling for white blood cell count estimates and population substructure, this interaction remained significant ($\beta = -.16$, $t(447) = -3.49$, $p = .001$, $R^2 = .02$, $F(12,447) = 5.35$, $p < .001$; Supplementary Table 2). Follow-up analyses detailed in the Supplementary Materials revealed no significant associations between PTSD (alone or in interaction with age) and the white blood cell estimates; Supplementary Table 3. Figure 1 depicts the nature of the interaction effect and suggests that the association between PTSD symptoms and reduced TL was greater for relatively older subjects (for the purpose of Figure 1, age was split at the sample median of 55 years). When this analysis was rerun substituting lifetime PTSD diagnosis for symptom scores, the same pattern of results emerged, in that PTSD diagnosis was not a significant independent predictor of TL but a significant interaction was found between PTSD diagnosis and age ($\beta = -.17$, $t(450) = -2.16$, $p = .032$, $R^2 = .01$, $F(4,450) = 8.22$, $p < .001$). The findings of both interactions remained significant ($ps < .027$) when controlling for the following, none of which were significant predictors of TL (smallest $p = .273$): current and lifetime diagnosis of depression and alcohol abuse or dependence, current and lifetime depressive symptom scores, current and lifetime alcohol abuse or dependence symptom scores, and antidepressant usage (details available from corresponding author upon request). In follow-up analyses conducted within subsets of the sample, none of the physical health variables were significantly associated with TL, controlling for age and sex (smallest $p = .131$): (Supplementary Table 4).

Temperament and TL

Investigation of associations between temperament and TL found that controlling for age, sex, number of different traumas, and lifetime PTSD symptoms in step 1, inclusion of PEM, NEM, and CON in step 2 of the model improved model fit ($R^2 = .05$, $F(7,149) = 4.29$, $p < .001$; Table 3). A positive association emerged between PEM and TL ($\beta = .17$, $t(149) = 2.17$, $p = .032$). NEM and CON were not associated with TL ($\beta s < .15$, $ps > .07$). In follow-up analyses, no significant interactions emerged between age and PEM, NEM, or CON in predicting TL ($\beta s < .12$, $ps > .10$).

To better characterize the association between PEM and TL, we re-ran this analysis with the four PEM subscales (Achievement, Well-being, Social Potency, and Social Closeness) as predictors of TL. Age, sex, total trauma count, and lifetime PTSD symptoms were included in the first step. This analysis revealed that Achievement was significantly associated with telomere length ($\beta = .26$, $t(150) = 3.11$, $p = .002$) and that inclusion of the four PEM subscales in the second step added incremental variance to the prediction of TL ($R^2 = .06$, $F(4,140) = 4.21$, $P < .001$; Table 4). Results were unchanged ($\beta = .26$, $p = .002$) when excluding four participants for invalid response profiles as determined by established MPQ-BF validity scale cut-points (Patrick et al., 2002). Findings remained significant ($ps < .003$) when controlling for the following, none of which were significant predictors of TL (smallest $p = .165$): current and lifetime diagnosis of depression and alcohol abuse or dependence, current and lifetime depressive symptom scores, current and lifetime alcohol abuse or dependence symptom scores, and antidepressant usage.

Discussion

It is critical to identify reliable biomarkers of cellular aging and to determine the biological mechanisms that may contribute to stress-related disease and physical health decline. In a large sample of trauma-exposed male and female veterans and civilians with a high prevalence of PTSD, lifetime PTSD symptoms were associated with shorter TL but only among participants who were relatively older (> 55 years). These results suggest that as telomeres shorten naturally with age, they are more vulnerable to the chronic effects of traumatic stress, and thus an association between PTSD and TL emerges. Results complement findings that older adults (> 70 years) with insomnia are more susceptible to telomere shortening relative to younger adults (Carroll et al., 2016) and that individuals > 55 show accentuated TL shortening when confronted with a biological stressor, such as chemotherapy (Unryn et al., 2006).

Although effect sizes were small in magnitude in the current study, they were comparable to those reported in other papers focused on psychiatric stress and TL (β s between $-.10$ – $-.14$); Ladwig et al., 2013; Roberts et al., 2017; Shalev et al., 2014). Findings emphasize the particular vulnerability of older adults to the negative effects of PTSD and raise the possibility that older age may be a risk factor for PTSD-associated health disparities. This conclusion is supported by analyses conducted in a subset of participants which showed that physical health comorbidities were not associated with TL; thus while older adults may have more physical health conditions, this did not seem to account for the contribution of PTSD to TL. Aging could signal a greater underlying “multi-system vulnerability” (Puterman & Epel, 2012) that allows for the negative health correlates of PTSD to be expressed. These results may lead to advances in identifying those at risk for premature cellular senescence and developing methods to mitigate this process. Promoting effective coping strategies, social connection, and health behaviors among younger veterans with PTSD may prevent premature cellular senescence. Our finding of moderation of the association between PTSD symptoms and TL may also help to explain inconsistent patterns of association in the literature (Boks et al., 2015; Bersani et al., 2016; Küffer et al., 2016). Estimates of TL among younger cohorts of PTSD patients may not evince associations apparent in cohorts of older subjects. The biological correlations between senescence and PTSD may differ by age, and different types of pharmacological interventions may be warranted for these groups. Longitudinal studies are necessary to evaluate these possibilities more thoroughly.

Psychological Resilience

Results from a subsample of veterans suggested a potential protective association between positive emotionality (PEM), particularly a drive towards achievement, and TL. Achievement is defined by traits and behaviors such as personal motivation and drive, a strong work ethic, persistence, and willingness to engage in challenging and demanding tasks (Tellegen & Waller, 2008). Achievement may be a component of the broader construct of resilience, typically defined as an adaptive response to stress or adversity as mediated by positive personality style, cognitions, and coping behaviors (Connor & Davidson, 2003; Herrman et al., 2011). The most widely used and well-validated measure of resilience, the Connor-Davidson Resilience Scale (Connor & Davidson, 2003), includes items that assess

high personal standards and persistence, which overlap conceptually with the construct of achievement. PTSD and resilience tend to be inversely and strongly related to each other (Davidson et al., 2012) and this raises the possibility that resilience may be a protective factor against premature TL shortening. Indeed, one study found that multisystem resiliency (defined by positive emotional and social traits and adaptive health behaviors) was associated with longer TL among individuals with major depression (Puterman et al., 2013). Furthermore, resiliency moderated associations between depression and shorter TL, such that associations between depression and TL were only evident in those with less resilience (Puterman et al., 2013). We were under-powered to evaluate a potential three-way interaction (i.e., PTSD severity \times Age \times Achievement) to examine if achievement served to buffer the association between PTSD and TL among older adults in the sample given that analyses pertaining to temperament were conducted in a smaller subset of veterans. Future research in larger samples is needed to examine the hypothesis that achievement buffers the negative health effects of PTSD in older veterans. Still, these results suggest that efforts to increase resilience and psychological hardiness among those with PTSD may be a useful adjunctive approach to treatments designed to reduce PTSD symptoms.

Cellular Senescence versus Accelerated Aging

TL was weakly associated with chronological age in this sample, consistent with prior systematic reviews of the literature (Müezzinler et al., 2013), and TL was not significantly correlated with DNAm, in keeping with prior findings of weak associations between these two biomarkers (Chen et al., 2017; Marioni et al., 2016). In contrast, the DNAm age estimates were strongly associated with chronological age. The differential strengths of association between chronological age and TL versus DNAm age estimates contributes to concerns about the utility of TL as a marker for cellular age or age acceleration specifically. Lowe, Horvath, and Raj (2016) suggested that TL is related to cellular senescence, but not cellular aging. They found that cells continued to age over time, as measured by DNAm estimates, despite the use of experimental methods to prevent cellular senescence via telomere shortening. They went on to suggest that there is a clear distinction between the processes of cellular aging and senescence; namely that cellular aging is an inevitable process based on the passage of time, while cellular senescence refers to the pathogenic effects of biological mechanisms such as oxidative stress and inflammation. TL shortening can be considered an indicator of movement in the direction of cellular senescence, the endpoint of this biological process. Further research examining the underlying cellular processes represented by shortened TL is needed to clarify the role of this important, but perhaps often mischaracterized biomarker.

Study Limitations

Study limitations include its cross-sectional design, which prevents causal conclusions concerning the impact of PTSD or temperament on TL. In addition, most of the veterans in the sample were male and most of the civilians were female, which limits the generalizability of results and makes it difficult to disaggregate sex from veteran status. With regards to TL measurement, the qPCR method is based on a T/S ratio relative to the reference sample and not an absolute value. Therefore, the current data cannot be directly compared to another study without using statistical tools to correct for batch effects. This

study also did not examine the role of oxidative stress and inflammation in telomere shortening, an important extension of this work given PTSD and personality have been associated with pro- and anti-inflammatory signaling (Vedhara et al., 2015; Lindqvist et al., 2014) and oxidative stress (Atli et al., 2016). Furthermore, we did not isolate the specific white blood cell types that the DNA was extracted from and therefore cannot address potential differences in TL due to PTSD-related changes in leukocyte composition (Boeck et al., 2016; Karabatsiakos et al., 2014). However, there were no significant associations between any estimated white blood cell type and TL, or with PTSD symptoms, suggesting that white blood cell types likely did not confound the PTSD/TL effects. Analyses pertaining to temperament were limited to 150 veterans who were 89% male, which more substantially limits generalizability of these results. All participants were of white, non-Hispanic ancestry and additional research is necessary to determine if results are replicated in other ancestral populations. Finally, while we examined some somatic variables that could contribute to shortened TL among older adults, these data was only available for a subset of the sample, and other health variables may also be pertinent; these are limitations of the work.

Conclusion

Results of this study, representing one of the largest clinical examinations of the relationship between PTSD and TL, underscore the particular vulnerability of older adults to the deleterious effects of PTSD and highlight the importance of addressing PTSD symptoms within this population. This study also suggests potential protective effects of temperament styles marked by positive affect, tenacity, and a strong personal drive. Thus, efforts to enhance these traits may be associated with improved biological and psychological resilience. That TL was only modestly correlated with chronological age and that age-adjusted TL was not significantly associated with DNAm indices of accelerated aging raises doubt about the conceptualization of TL as an index of accelerated aging specifically. Additional research is needed to determine how shortened TL and accelerated DNAm age may be differentially associated with negative health outcomes commonly associated with PTSD and what, if any, mechanistic role each biomarker may play in linking PTSD to disease and physical health decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Research reported in this publication was supported in part by the National Institute on Aging of the National Institutes of Health award R03AG051877 and 3R03AG051877-02S1 to EJW and by National Institute on Mental Health award RO1 MH079806 to MWM. This work was also supported in part by Merit Review Award Number I01 CX-001276-01 to EJW from the United States (U.S.) Department of Veterans Affairs (VA) Clinical Sciences R&D (CSR) Service, and by a Presidential Early Career Award for Scientists and Engineers (PECASE 2013A) to EJW as administered by U.S. Department of VA Office of Research and Development. This work was also supported by a U.S. Department of VA CSR Merit Review award 5I01CX000431-02 and by U.S. Department of VA Biomedical Laboratory Research & Development Program award 1I01BX002150-01, both to MWM. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the U.S. Department of Veterans Affairs, or the United States Government.

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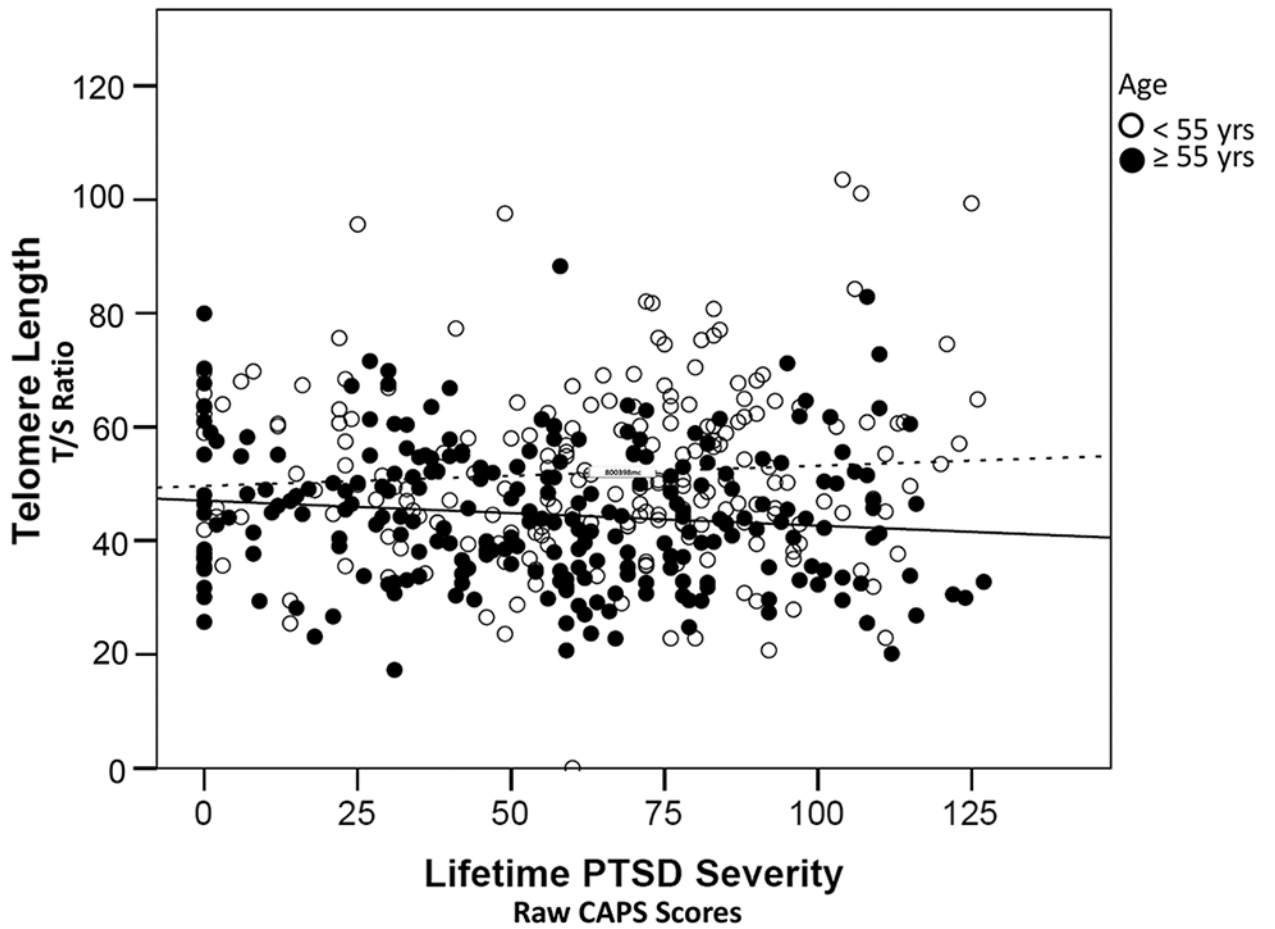


Fig. 1. The figure shows the unstandardized association between PTSD symptom severity as measured by the CAPS and leukocyte telomere length (T/S ratio, multiplied by a constant of 100 for ease of interpretability) as a function of the median age of the sample. PTSD symptom severity is associated with shorter telomeres among the relatively older participants in the sample.

Table 1.

Participant Characteristics

	Full Sample (<i>N</i> = 453)			Temperament Analysis Subsample (<i>n</i> = 150)		
	<i>M</i>	<i>SE</i>	%	<i>M</i>	<i>SE</i>	%
Age (years)	52.49	10.78		51.04	11.15	
Veteran Status			69.5			100
Female			34.9			10.7
White, non-Hispanic			100			100
Current PTSD dx			39.1			59.3
Lifetime PTSD dx			59.8			79.3
Lifetime depression dx			55.5			59.1
Lifetime alcohol abuse or dependence dx			61.4			78.0
Antidepressant use			39.3			38.0
Lifetime PTSD symptom severity	59.55	31.33		71.67	24.89	
Current PTSD symptom severity	39.32	28.62		55.32	24.18	
Num. diff. traumas	9.81	4.13		10.97	3.74	
PEM T-score				38.40	11.44	
NEM T-score				60.92	8.81	
CON T-score				43.88	8.69	

Note. PTSD = posttraumatic stress disorder. Lifetime and current PTSD symptoms = Lifetime and current symptom scores on the Clinician Administered PTSD Scale (CAPS). Num. diff. traumas = number of different traumas as measured by the Traumatic Life Events Questionnaire (TLEQ). PEM= positive emotionality, NEM= negative emotionality, CON= constraint, as measured by the Brief Form of the Multidimensional Personality Questionnaire (MPQ-BF).

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Table 2.

Regression Examining Demographic Variables, Trauma, and Lifetime PTSD Symptoms as Predictors of TL

	Unstd. <i>B</i>	SE	Std. β	<i>R</i> ²
Step 1				.073 ***
Age	-.321	.062	-.242 ***	
Sex	-3.02	1.40	-.101 *	
Num. diff. traumas	.132	.174	.038	
PTSD symptoms	-.010	.023	-.022	
Step 2				.018 ***
Age \times PTSD symptoms	-.006	.002	-.138 **	

Note. TL = telomere length; Unstd. *B* = unstandardized beta; SE = standard error; Std. β = standardized beta; Num. Diff. Traumas = number of different traumas as measured by the Traumatic Life Events Questionnaire (TLEQ); PTSD = posttraumatic stress disorder. PTSD symptoms = lifetime symptom score on the Clinician Administered PTSD scale (CAPS). Age and PTSD symptoms were centered on their means.

* $p < .05$,

** $p < .01$,

*** $p < .001$.

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Table 3.

Regression Examining Temperament Factors as Predictors of TL

	Unstd. <i>B</i>	SE	Std. β	<i>R</i> ²
Step 1				.126**
Age	-.421	.108	-.310***	
Sex	-6.89	3.89	-.141	
Num. Diff. Traumas	.213	.323	.053	
Lifetime PTSD symptoms	.009	.049	.014	
Step 2				.048***
PEM	.148	.069	.167*	
NEM	.129	.073	.148	
CON	.099	.088	.092	

Note. TL = telomere length; Unstd. *B* = unstandardized beta; SE = standard error; Std. β = standardized beta; Num. Diff. Traumas = number of different traumas as measured by the Traumatic Life Events Questionnaire (TLEQ); PTSD = posttraumatic stress disorder; Lifetime PTSD symptoms = lifetime symptom score on the Clinician Administered PTSD Scale (CAPS). PEM = positive emotionality; NEM = negative emotionality; CON = constraint, as measured by the Brief Form of the Multidimensional Personality Questionnaire (MPQ-BF).

* $p < .05$,

** $p < .01$,

*** $p < .001$.

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Table 4.

Regression Examining Facets of Positive Emotionality as Predictors of TL

	Unstd. <i>B</i>	SE	Std. β	R ²
Step 1				.129***
Age	-.428	.108	-.314***	
Sex	-6.57	3.89	-.134	
Num. Diff. Traumas	.282	.318	.071	
Lifetime PTSD symptoms	.010	.049	.017	
Step 2				.062***
Well-being	-.213	.390	-.052	
Social Potency	.080	.408	.017	
Achievement	1.09	.351	.259**	
Social Closeness	.096	.461	.018	

Note. TL = telomere length; Unstd. *B* = unstandardized beta; SE = standard error; Std. β = standardized beta; Num. Diff. Traumas = number of different traumas as measured by the Traumatic Life Events Questionnaire (TLEQ); PTSD = posttraumatic stress disorder. Lifetime PTSD symptoms= lifetime symptom score on the Clinician Administered PTSD scale (CAPS).

* $p < .05$,

** $p < .01$,

*** $p < .001$.

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