## Title

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Short communication

# Association of dimensional psychological health measures with telomere length in male war veterans

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ABSTRACT

*Background:* Several psychiatric disorders may be characterized by peripheral telomere shortening. However, it is unclear whether telomere shortening is associated with these psychiatric disorders per se or, rather, with underlying dimensional parameters that are often, but not necessarily, associated with them. We explored the association between dimensional psychopathological measures and telomere length (TL) in granulocytes among veterans independent of psychiatric diagnosis.

*Methods:* Seventy-six combat-exposed male veterans (41 psychiatrically healthy, 18 with Posttraumatic Stress Disorder [PTSD] and 17 with concomitant PTSD and Major Depressive Disorder [MDD]) had TL assayed. Assessments included Clinician-Administered PTSD Scale (CAPS), Beck Depression Inventory-II (BDI-II), Early Trauma Inventory (ETI), Symptom Checklist-90-R Global Severity Index (SCL-90-GSI), Perceived Stress Scale (PSS) and Positive and Negative Affect Schedule (PANAS). Correlations were corrected for age, BMI, antidepressants and ethnicity.

*Results:* Across subjects, TL was negatively correlated with early trauma ($p<0.001$), global psychopathological severity ($p=0.044$) and perceived stress ($p=0.019$), positively correlated with positive affect ($p=0.026$), not significantly correlated with symptom severity of PTSD, depression or negative affect. Across these dimensions, early trauma and positive affect were associated with TL after excluding subjects with somatic illnesses.

*Limitations:* The study was cross-sectional with a moderate sample size and only male combat-exposed subjects.

*Conclusions:* These preliminary findings suggest that early trauma, severity of perceived stress and general psychopathological symptoms are more closely associated with shorter TL than is the severity of core diagnostic symptoms of PTSD or MDD, whereas positive affect is associated with longer TL. Larger-scale studies should assess TL associated with specific psychiatric dimensions, apart from only categorical psychiatric diagnoses, to develop more specific biologically-relevant endophenotypes.



## 1. Introduction

War veterans are at an increased risk of developing certain psychiatric and physical disturbances (Hoge et al., 2008, Thomas et al., 2010, Tansey et al., 2012). Several of these disturbances (e.g. Major Depressive Disorder [MDD], Posttraumatic Stress Disorder

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[PTSD], cardiovascular diseases, metabolic disturbances, cognitive decline, cirrhosis, infectious diseases) may be associated with clinical and cellular/molecular evidence of accelerated aging (Calado and Young, 2012; Lindqvist et al., 2015). Peripheral telomere shortening has been proposed as a relevant and easily obtained measure of ageing-related cellular pathology (Blasco, 2005; Wolkowitz et al., 2011; Lindqvist et al., 2015), and peripheral telomere length (TL) shortening has been associated in other studies and populations with poor physical and mental health outcomes (Blackburn, 2010).

Psychiatric disorders such as MDD (Wolkowitz et al., 2011), schizophrenia (Yu et al., 2008), bipolar disorder (Elvsashagen et al., 2011) and PTSD (O'Donovan et al., 2011) may be associated with short peripheral telomeres, at least in certain patients, although the findings are mixed (Wolkowitz et al., 2011; Darrow et al., 2015; Lindqvist et al., 2015; Teyssier et al., 2012). However, it is not clear whether the telomere shortening is associated with these psychiatric diagnoses per se or, rather, with underlying psychological parameters that are often, but not necessarily, associated with these psychiatric diagnoses. For example, high levels of chronic psychological distress, dispositional tendencies towards pessimism and having experienced early childhood adversities have been associated with accelerated telomere shortening, in both patients with psychiatric disorders (O'Donovan et al., 2011; Wolkowitz et al., 2011) and healthy people (Epel et al., 2004; O'Donovan et al., 2009; Shalev et al., 2013b).

A better understanding of cell aging correlates, combined with trans-diagnostic psychological parameters, could potentially lead to the development of more specific mental health and physical health interventions and more appropriate prevention strategies for high-risk populations, as well as to a better delineation of possible psychobiological and behavioral endophenotypes. Beyond the studies reviewed above, the objective of the present study was to assess, in combat stress-exposed individuals, which dimensions of psychological health, irrespective of categorical psychiatric diagnoses (i.e. PTSD or PTSD with comorbid MDD), are associated with TL.

## 2. Methods

### 2.1. Ethical statement

The Institutional Review Boards of Icahn School of Medicine at Mount Sinai (ISMMS; New York, NY), the James J. Peters Veterans Administration Medical Center (JJPVAMC; Bronx, New York), New York University Medical Center (NYU; New York, NY), and the University of California, San Francisco, Medical Center (UCSF; San Francisco, CA) approved this study. Study participants gave written informed consent to participate. Participants were compensated for their participation. The study was conducted in accordance with the provisions of the Helsinki Declaration.

### 2.2. Recruitment procedures and study participants

One hundred and three Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) veterans were recruited by NYU and ISMMS/JJPVAMC. Subjects were recruited from the Mental Health Services of the Manhattan, Bronx and Brooklyn Veterans Affairs Medical Centers, other regional VA medical centers, Veterans Service Organizations, National Guard, reservist agencies and organizations and from the general community. Recruitment methods included flyers, in-person presentations, media advertisements, internet postings (e.g. Craigslist) and referral from clinicians. Criteria for inclusion were: (a) having served in war zones; (b) current age between 20 and 60; (c) males; and (d) proficient in the English language. Exclusion criteria included: (a) history of alcohol dependence within the past 8 months; (b) history of drug abuse or dependence (except nicotine dependence) within the past year; (c) lifetime history of any psychiatric disorder with psychotic features, bipolar disorder, or obsessive-compulsive disorder; (d) those who were currently exposed to recurrent trauma or have been exposed to a traumatic event within the past 3 months; (e) prominent suicidal or homicidal ideation; (f) neurologic disorder or systemic illness affecting central nervous system function; (g) history of anemia or recent blood donation in the past 2 months; (i) subjects who were not stable for at least 2 months on psychiatric medication, anticonvulsants, antihypertensive medication or sympathomimetic medication; (j) subjects who were classified with a moderate or severe traumatic brain injury (TBI) on the Ohio State University TBI Identification Method–Short Form; and finally (k) subjects who experienced loss of consciousness for greater than 10 min.

All study participants experienced combat theater traumas described in criterion A of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV PTSD diagnostic criteria (2000), whether or not they met the remaining diagnostic criteria for PTSD. The 103 combat-exposed male subjects were recruited for a larger overall study examining biomarkers of PTSD, as diagnosed by DSM-IV criteria. Of these, a subsample of all subjects ($N=77$) who had TL assayed were included in the present report; 26 potential subjects were excluded due to inadequate blood samples. Of the included 77 subjects, 36 participants had current diagnoses of combat-related PTSD; 17 of these subjects with PTSD had additional comorbid diagnoses of MDD. The other 41 subjects had no current DSM-IV axis I disorder. One of the individuals with PTSD had hepatitis; this individual was excluded from the subsequent analyses, leaving 76 subjects to constitute the final study sample. To establish psychiatric diagnoses, Structured Clinical Interview for DSM-IV disorders (SCID) (First, 1997) were conducted by Doctoral level psychologists, and were audio recorded and calibrated weekly with a senior clinician. Some of the study participants had comorbid somatic diseases, which were controlled and clinically stable, including mild asthma or allergies ($n=5$), diabetes ($n=2$), stable angina ($n=2$), hypertension ($n=9$) and prostate cancer ($n=1$). Some of the study participants were taking medications including statins ($n=2$), non-steroidal anti-inflammatory drugs (NSAIDs) ($n=5$), antidepressants ($n=13$), analgesics ($n=1$), antibiotics ($n=1$) and hormone drugs. ($n=1$). A listing of medication use and medical comorbidities is presented in Table 1. Since antidepressant use was common and may be associated with telomere maintenance or telomerase activity (Lindqvist et al., 2015; Bersani et al., in press), it was used as a covariate.

### 2.3. Psychiatric and psychological assessment measures

Current and lifetime combat-related PTSD symptom severity was assessed with the Clinician-Administered PTSD Scale (CAPS). Depression symptom severity was assessed with the self-rated Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). Exposure to early life trauma was evaluated using the Early Trauma Inventory (ETI)–Self Report Short Form (Bremner et al., 2007). An assessment of global psychopathological severity was evaluated with the Symptom Checklist-90-R Global Severity Index (SCL-90-GSI) (Derogatis, 1992). The Perceived Stress Scale (PSS) (Cohen et al., 1983) was used to measure the perception of psychological stress in the past month. Positive and negative affects were assessed with the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988).

**Table 1**
Demographic and clinical characteristics across all participants.

| | |
|---|---|
| **Participants (*n*)** | *76* |
| **Age (years, mean ± SD)** | *34.64 ± 9.17* |
| **Years of education (mean ± SD)** | *14.79 ± 2.44* |
| **Gender** | *All males* |
| **PTSD diagnosis (total *n*)** | *35* |
| **PTSD sole diagnosis (*n*)** | *18* |
| **Comorbid PTSD and MDD diagnoses (*n*)** | *17* |
| **Current smokers (*n*)** | *11* |
| ***Medications*** | |
| **Taking statins (*n*)** | *2* |
| **Taking NSAIDs regularly (*n*)** | *5* |
| **Taking antidepressants (*n*)** | *13* |
| **Taking antibiotics (*n*)** | *1* |
| **Taking hormone drugs for prostate cancer (*n*)** | *1* |
| **Taking analgesics** | *1* |
| ***Concomitant somatic diseases*** | |
| **Mild asthma or allergies** | *5* |
| **Diabetes** | *2* |
| **Stable angina** | *2* |
| **Clinical hypertension** | *9* |
| **Prostate cancer** | *1* |
| ***Ethnicity*** | |
| **Hispanic (*n*)** | *35* |
| **Non-Hispanic (*n*)** | *42* |
| ***Biological measures*** | |
| **Telomere length (T/S ratio) (mean ± SD)** | *1.19 ± 0.19* |
| **BMI (mean ± SD)** | *29.98 ± 4.50* |
| ***Clinical measures*** | |
| **CAPS total current (mean ± SD)** | *33.36 ± 34.70* |
| **CAPS total lifetime (mean ± SD)** | *47.45 ± 42.76* |
| **BDI-II (mean ± SD)** | *14.18 ± 12.58* |
| **ETI total score (mean ± SD)** | *6.55 ± 4.86* |
| **PANAS Positive Scale (mean ± SD)** | *30.30 ± 9.23* |
| **PANAS Negative Scale (mean ± SD)** | *21.13 ± 9.51* |
| **SCL-90-R GSI (mean ± SD)** | *0.89 ± 0.85* |
| **PSS (mean ± SD)** | *2.43 ± 0.91* |

SD: standard deviation; PTSD: post-traumatic stress disorder; MDD: major depressive disorder; NSAID: non-steroidal anti-inflammatory drug; BMI: body mass index; CAPS: clinician-administered PTSD scale; BDI-II: Beck depression inventory-II; ETI: early trauma inventory; PANAS: positive and negative affect schedule; SCL-90: symptom checklist-90-R; PSS: perceived stress scale.

### 2.4. Blood sampling and telomere length measurement

Blood was drawn in the morning after a night of fasting into 10 ml EDTA Lavender Top (LTT) tubes. Peripheral blood mononuclear cells (PBMCs) were purified whole blood using standard Ficoll gradient centrifugation method. Granulocytes were prepared from the red blood pellets after Ficoll separation of the PBMCs by lysing in three volumes of ACK lysis buffer (QIAgen, cat #158902). The cells were left in ACK lysis buffer at room temperature for 10 min with inversion every 2 min. The cells were spun at 400 g for 10 min in a Sorvall Legend RT tabletop centrifuge at 10 °C. The cell pellets were washed twice with 10 ml of cold DPBS (Invitrogen, cat # 14040-133) and spun at 400 g for 10 min at 10 °C. After the second wash, the cell pellets were resuspended in 5 ml of DPBS, aliquoted into 5 of 1.5 ml eppendorf tubes, spun at 7000 rpm for 5 min at 4 °C, and, finally, were stored at −80 °C for batch DNA purification. DNA was purified using QIAamp blood mini kit (cat# 51106) based on the manufacture's manual and quantity were assessed with a nanodrop spectrophotometer. The TL measurement assay was adapted from the published original method (Cawthon, 2002) as reported elsewhere (Epel et al., 2004). The same reference DNA was used for all PCR runs. The inter-assay coefficient of variation (CV) for telomere length measurement was 4%. Details of the method can be found in (Lin et al., 2010).

### 2.5. Statistical analyses

All tests were 2-tailed with an alpha=0.05. ETI total score, PANAS Negative Scale, SCL-90-R GSI subscales were non-normally distributed; thus they were transformed using Ln or Blom transformation (if not normalized by Ln transformation). Pearson partial correlation was used to test correlations between TL and the assessment scales, correcting for age, body mass index (weight in kilograms divided by the square of height in meters; BMI), ethnicity and antidepressant use because of their reported associations with telomere maintenance. Smoking data were only available for a subset of the subjects, and when this variable was additionally entered as a covariate, the main results did not change substantially. Among the clinical assessments, all the variables significantly associated with TL by Pearson partial correlation were inserted in a linear regression analysis with TL as a dependent variable. The associations were reported as standardized $\beta$ coefficients and their $p$-values.

## 3. Results

Demographic and clinical characteristics of the subjects are presented in Table 1. Across all subjects, controlling for age, BMI, ethnicity, and antidepressants, TL was significantly negatively correlated with ETI total score ($r=-0.428$; $p<0.001$), SCL-90-GSI ($r=-0.240$; $p=0.044$) and PSS ($r=-0.277$; $p=0.019$) (Fig. 1), significantly positively correlated with PANAS positive scale ($r=0.263$; $p=0.026$) (Fig. 1) and not significantly correlated with PANAS negative scale ($r=-0.140$; $p=0.241$), BDI-II ($r=-0.079$; $p=0.512$), CAPS current ($r=-0.072$; $p=0.550$) or lifetime ($r=-0.073$; $p=0.544$) subscales and MDD ($r=0.049$; $p=0.682$) or PTSD ($r=-0.076$; $p=0.524$) diagnoses. Adding smoking as an additional covariate (in subjects for whom smoking data were available) did not change the significance of the correlations.

Given their significant association with TL, measures of ETI, SCL-90-GSI, PSS and PANAS positive were inserted as independent variables in a linear regression analysis with TL as criterion. The model explained 24.4% of the variability of the data ($R$-squared=0.289; adjusted $R$-squared=0.244). The ETI and PANAS positive were independently associated with TL, so that more severe early traumas (standardized $\beta$ coefficient=−0.470; $p<0.001$) and higher levels of positive affect (standardized $\beta$ coefficient=0.294; $p=0.030$) were associated with TL even when controlling for the presence of other variables. More details are given in Table 2. An additional regression model in which age, BMI, ethnicity and antidepressant use were also inserted as independent variables led to similar results.

The conditions of asthma/allergies, diabetes, hypertension and angina, as well as the use of statins, NSAIDs and antidepressants, were not significantly associated with TL. Excluding the participant with prostate cancer from the analyses did not change the significance of any of the results. Finally, when we excluded all the individuals with concomitant somatic disorders from the analyses, the association of TL with ETI and PANAS remained significant, while the association of TL with SCL-90-GSI and PSS became non-significant.

## 4. Discussion

To our knowledge, this is the first study investigating the association between leukocyte TL and dimensional psychological

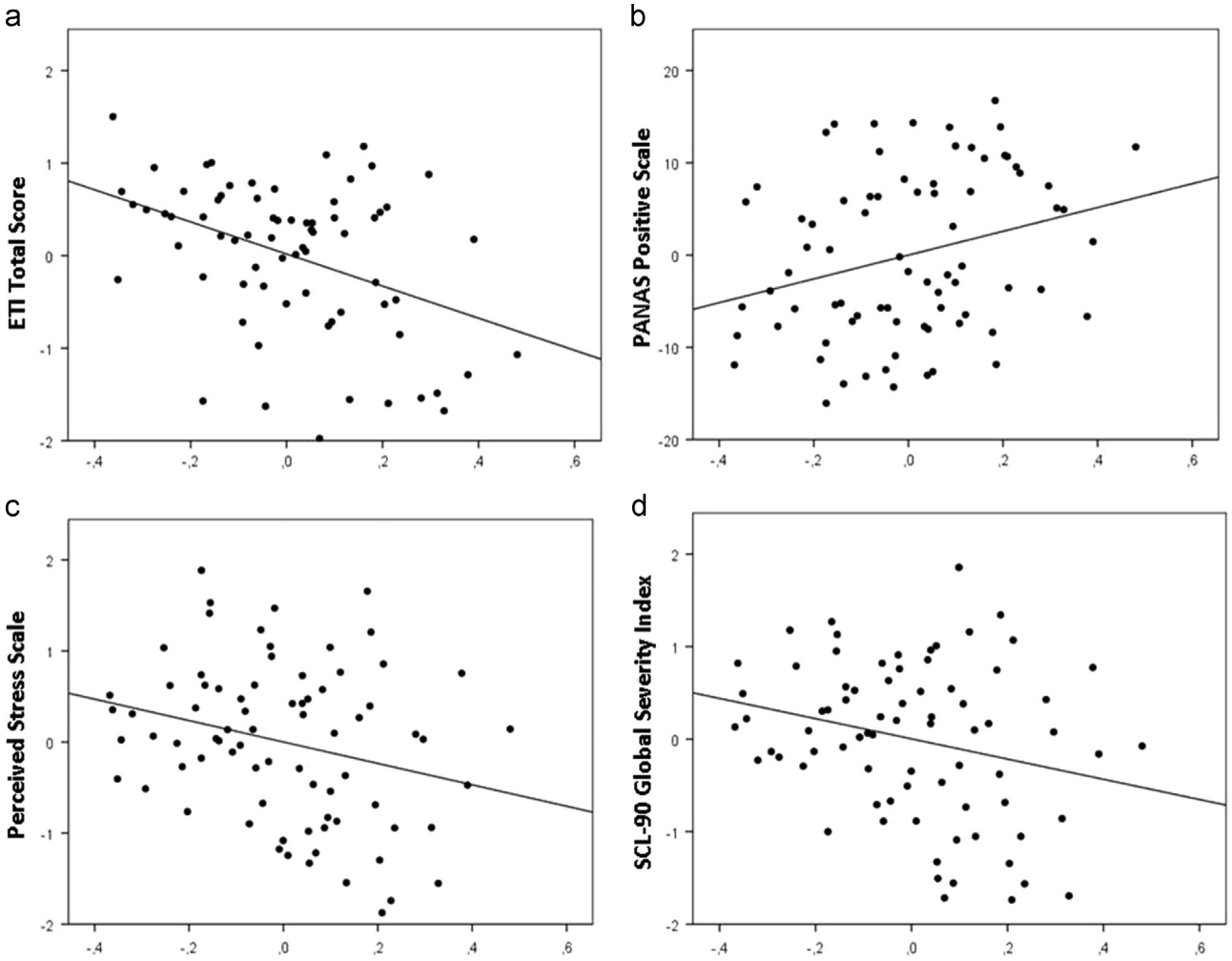


**Fig. 1.** Significant correlations between telomere length (TL) and (a) Early Trauma Inventory total score ($r=-0.428$; $p<0.001$), (b) Positive and Negative Affect Schedule – positive scale ($r=0.263$; $p=0.026$), (c) Perceived Stress Scale ($r=-0.277$; $p=0.019$) and (d) Symptom Checklist-90-R Global Severity Index ($r=-0.240$; $p=0.044$). *X*-axes refer to residual values of TL (T/S ratio) in all graphs, and the *Y*-axis refers to residual values of the assessment scales (after covarying age, BMI, antidepressants and ethnicity).

**Table 2**
Linear regression analysis.

| | Standardized $\beta$ coefficient | *P* | Confidence Interval | |
|---|---|---|---|---|
| | | | *Lower limit* | *Upper limit* |
| **Dependant variable (telomere length)** | | < 0.001 | 0.993 | 1.620 |
| **ETI total score** | −0.470 | < 0.001 | −0.164 | −0.054 |
| **SCL-90-R GSI** | 0.226 | 0.338 | −0.052 | 0.148 |
| **PSS** | −0.213 | 0.349 | −0.141 | 0.050 |
| **PANAS Positive Scale** | 0.294 | 0.030 | 0.001 | 0.012 |

ETI: early trauma inventory; PANAS: positive and negative affect schedule; SCL-90: symptom checklist-90-R; PSS: perceived stress scale.

and psychiatric measures in a sample of combat-exposed war veterans independent of psychiatric diagnosis. The results of the present research indicate that early childhood adversities (ETI total score), subjective perception of psychological stress (PSS) and global psychopathological severity (SCL-GSI) were negatively correlated with TL, while a positive affective state (PANAS positive scale) was positively correlated with TL. Negative affect on the PANAS was negatively but non-significantly correlated with TL. On the other hand PTSD and MDD diagnoses as well as the clinical scales that rated the severity of core symptoms of PTSD and MDD (CAPS and BDI-II) did not show any significant associations with TL. Therefore, our results suggest that ratings of the global degree of perceived stress and psychological measure severity as well as the magnitude of early traumatic experiences are associated with cellular senescence in male veterans to a greater degree than are the core symptoms of MDD and PTSD per se. In addition, positive affect (PANAS positive scale) was associated with relatively longer TL, although it is not known if positive affect represents a cellular "protective factor" potentially contributing to the maintenance of an enhanced telomere homeostasis or if it is an epiphenomenon. Notably, multiple regression analysis revealed that early adverse trauma and positive affect were the two dimensions that remained independently correlated with TL when all four dimensions were considered simultaneously in the same model. Similarly, early trauma and positive affect remained associated with TL after excluding from the analyses all subjects with somatic illnesses, while the association of TL with general psychopathology and perceived stress became non significant (possibly due to the smaller sample size).

Associations between TL, early traumatic experiences, affect and perceived stress have been found in some, but not all, previous studies focused on different populations including healthy adults (mainly females), healthy children and patients with psychiatric disorders (Epel et al., 2004; O'Donovan et al., 2009; O'Donovan et al., 2011; Wolkowitz et al., 2011; Price et al., 2013; Shalev et al., 2013b; Lindqvist et al., 2015; Cai et al., 2015). In particular, a recent meta-analysis revealed a significant negative

correlation between perceived stress ratings and TL (Schutte and Malouff, in press). Our data are also consistent with many studies showing an inverse correlation between childhood adversity across different populations (Price et al., 2013), and, in particular, with a study showing that childhood adversity accounted for much of the variance in telomere shortening in individuals with PTSD (O'Donovan et al., 2011); specifically, after adverse childhood adversities were controlled for, PTSD diagnosis no longer had a significant relationship with TL (O'Donovan et al., 2011). However, one study failed to detect a significant correlation between adverse childhood events and TL in military PTSD (Zhang et al., 2014). Finally, one other prior study examined cross-sectional relationships between TL and psychopathological measures in war veterans and found, as we did, no significant correlations between TL and CAPS or BDI ratings (Jergovic et al., 2014). Our findings contribute and add to this field of investigation by reporting data about trans-diagnostic dimensional psychological health measures.

Our results highlight the importance of examining broad dimensions of psychological health, stress or early exposure to trauma, in addition to more traditional diagnosis-based measures, in studies of behavioral and other correlates of TL. Studies suggest that a range of cellular/molecular mechanisms may mediate the relationship of mental and physiological processes with TL, including hypothalamic–pituitary–adrenal axis dysregulation, increased oxidative stress, immune dysregulation and chronic antigen stimulation (Epel et al., 2004; Blackburn, 2010; Wolkowitz et al., 2011; Shalev et al., 2013a; Lindqvist et al., 2015). Notably, these biological mechanisms are not specifically seen in any single DSM-defined psychiatric disorder, but rather may represent common elements of several disparate DSM-defined psychiatric disorders (Wolkowitz et al., 2011; Lindqvist et al., 2015). In this context, we find potential in the recently developed Research Domain Criteria (RDoC) (Insel et al., 2010) and believe that future studies should investigate a trans-diagnostic RDoC-like approach for correlational fit with TL, in addition to the standard DSM-driven approach.

### 4.1. Strengths and limitations

One of the strengths of the present study is that the sample was clinically very well-characterized. All study participants (independent of psychiatric diagnosis) had been exposed to combat-related trauma, allowing us to control for the non-specific effects of serving in the military and experiencing combat trauma. However, including only combat-exposed individuals limits generalizability to non-combat people. An additional strength of this study is its sample of relatively young veterans, since age-related illnesses can pose significant confounds in studies of psychiatric disorders in older subjects. Limitations of the present study include (i) our use of an all male study sample (i.e. the results may not be applicable to women) and (ii) a moderate sample size. (iii) Since this was a cross-sectional study based on single time-point blood and behavioral measurements, we cannot assess any temporal/causal relationships or variability in the measures over time. In addition, as it was a single time point measure, we were not able to assess moment-to-moment variability in the psychological measures. (iv) Most of the assessment measures relied on subjective report or recall. (v) These preliminary analyses did not assess specific between-group differences in TL between individuals with PTSD, MDD and healthy controls. These will be examined later in a larger sample of subjects because the present sample size, while sufficient for assessing dimensional relationships in the overall group, was not sufficient for reliably assessing between-group differences.

## 5. Conclusion

It is not known whether there is a causal relationship between peripheral TL changes and the psychological health measures we investigated, and, if so, whether therapeutically ameliorating negative affect and general psychiatric pathology is capable of affecting TL (Verhoeven et al., 2014). To the extent this can happen, our findings raise the possibility that one approach to protecting combat-exposed veterans' cellular health may involve integrated psychosocial, psychotherapeutic and behavioral interventions to increase stress management skills and to develop an adaptive resiliency towards a more optimistic and positive engagement with the environment.

To summarize, our data (i) extend the association between TL and early traumatic experiences, perceived stress and aspects of positive affect previously obtained in other populations (Epel et al., 2004; O'Donovan et al., 2009; O'Donovan et al., 2011; Zalli et al., 2014) to a sample of male war veterans, and (ii) preliminarily indicate that broad dimensional psychological health measures may bear a closer relationship to TL than do symptom severity ratings specifically related to PTSD or MDD categorical diagnoses. Studies on larger samples are planned by our research team in order to assess whether between-diagnostic group differences in TL exist between veterans with PTSD, MDD or no psychiatric diagnosis and whether similar relationships are seen in women veterans.

## Author disclosure

### *Contributors*

All authors contributed to design the study, develop hypotheses, write the protocol, write and/or proof read the manuscript, and approve the final paper. In addition, the following individuals also undertook additional responsibilities:

Rachel Yehuda, Janine Flory, Clare Henn-Hasse, Linda M. Bierer, Duna Abu-Amara and Charles Marmar oversaw recruitment of subjects, behavioural ratings and phenotyping of subjects, blood collection and processing. In addition, Linda M. Bierer was responsible for clinical care and evaluation of the subjects including evaluating laboratory results and medical exclusions. In addition, Duna Abu-Amara was responsible for overall administrative structuring and managing the study. In addition, Charles Marmar was the co-PI of the study, secured funding, interfaced with the funders (Department of Defense) and coordinated methodology across all sites.

Iouri Makotine, Synthia H. Mellon, Jue Lin and Elizabeth H. Blackburn were responsible for biological sample collection, preparation, processing, conducting assays, interpreting results and for writing parts of the manuscript related to assay methodology

Francesco Saverio Bersani, Daniel Lindqvist, Elissa S. Epel, Michelle Coy, Victor I. Reus, Owen M. Wolkowitz guided hypotheses development, provided the theoretical background for the study, managed the literature searches, the statistical analysis, wrote the first draft of the manuscript and finalized the ultimate paper.

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## References

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders fourth edition (DSM-IV). American Psychiatric Press, Washington.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio.

Bersani, F.S., Lindqvist, D., Mellon, S.H., Penninx, B.W., Verhoeven, J.E., Révész, D., Reus, V.I., Wolkowitz, O.M., 2015. Telomerase activation as a possible mechanism of action for psychopharmacological interventions. Drug. Discov. Today. http://dx.doi.org/10.1016/j.drudis.2015.06.016 (in press).

Blackburn, E.H., 2010. Telomeres and telomerase: the means to the end (Nobel lecture). Angew. Chem. Int. Ed. Engl. 49, 7405–7421.

Blasco, M.A., 2005. Telomeres and human disease: ageing, cancer and beyond. Nat. Rev. Genet. 6, 611–622.

Bremner, J.D., Bolus, R., Mayer, E.A., 2007. Psychometric properties of the early trauma inventory-self report. J. Nerv. Ment. Dis. 195, 211–218.

Cai, N., Chang, S., Li, Y., Li, Q., Hu, J., Liang, J., Song, L., Kretzschmar, W., Gan, X., Nicod, J., Rivera, M., Deng, H., Du, B., Li, K., Sang, W., Gao, J., Gao, S., Ha, B., Ho, H. Y., Hu, C., Hu, J., Hu, Z., Huang, G., Jiang, G., Jiang, T., Jin, W., Li, G., Li, K., Li, Y., Li, Y., Li, Y., Lin, Y.T., Liu, L., Liu, T., Liu, Y., Liu, Y., Lu, Y., Lv, L., Meng, H., Qian, P., Sang, H., Shen, J., Shi, J., Sun, J., Tao, M., Wang, G., Wang, G., Wang, J., Wang, L., Wang, X., Wang, X., Yang, H., Yang, L., Yin, Y., Zhang, J., Zhang, K., Sun, N., Zhang, W., Zhang, X., Zhang, Z., Zhong, H., Breen, G., Wang, J., Marchini, J., Chen, Y., Xu, Q., Xu, X., Mott, R., Huang, G.J., Kendler, K., Flint, J., 2015. Molecular signatures of major depression. Curr. Biol. 25, 1146–1156.

Calado, R., Young, N., 2012. Telomeres in disease. F1000 Med. Rep. 4, 8.

Cawthon, R.M., 2002. Telomere measurement by quantitative PCR. Nucleic Acids Res. 30, e47.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.

Darrow, S.M., Verhoeven, J.E., Révész, D., Lindqvist, D., Penninx, B.W., Delucchi, K.L., Wolkowitz, O.M., Mathews, C.A., 2015. Are psychiatric disorders associated with shorter telomeres? A meta-analysis involving 14,827 persons. Biol. Psychiatry. Rev.

Derogatis, L.R., 1992. The Symptom Checklist-90-revised, NCS Assessments. Minneapolis.

Elvsashagen, T., Vera, E., Boen, E., Bratlie, J., Andreassen, O.A., Josefsen, D., Malt, U.F., Blasco, M.A., Boye, B., 2011. The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder. J. Affect. Disord. 135, 43–50.

Epel, E.S., Blackburn, E.H., Lin, J., Dhabhar, F.S., Adler, N.E., Morrow, J.D., Cawthon, R. M., 2004. Accelerated telomere shortening in response to life stress. Proc. Natl. Acad. Sci. USA 101, 17312–17315.

First, M.B., 1997. Structured Clinical Interview for DSM-IV axis I disorders. American Psychiatric Press, Washington.

Hoge, C.W., Castro, C.A., Messer, S.C., McGurk, D., Cotting, D.I., Koffman, R.L., 2008. Combat duty in Iraq and Afghanistan, mental health problems and barriers to care. US Army Med. Dep. J., 7–17.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167, 748–751.

Jergovic, M., Tomicevic, M., Vidovic, A., Bendelja, K., Savic, A., Vojvoda, V., Rac, D., Lovric-Cavar, D., Rabatic, S., Jovanovic, T., Sabioncello, A., 2014. Telomere shortening and immune activity in war veterans with posttraumatic stress disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 54, 275–283.

Lin, J., Epel, E., Cheon, J., Kroenke, C., Sinclair, E., Bigos, M., Wolkowitz, O.M., Mellon, S., Blackburn, E., 2010. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. J. Immunol. Methods 352, 71–80.

Lindqvist, D., Epel, E., Mellon, S., Penninx, B.W., Révész, D., Verhoeven, J.E., Reus, V.I., Lin, J., Mahan, L., Hough, C., Rosser, R., Bersani, F.S., Blackburn, E.H., Wolkowitz, O.M., 2015. Psychiatric disorders and leukocyte telomere length: underlying mechanisms linking mental illness with cellular aging. Neurosci. Biobehav. Rev. 55, 333–364.

O'Donovan, A., Epel, E., Lin, J., Wolkowitz, O., Cohen, B., Maguen, S., Metzler, T., Lenoci, M., Blackburn, E., Neylan, T.C., 2011. Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. Biol. Psychiatry 70, 465–471.

O'Donovan, A., Lin, J., Tillie, J., Dhabhar, F.S., Wolkowitz, O.M., Blackburn, E.H., Epel, E.S., 2009. Pessimism correlates with leukocyte telomere shortness and elevated interleukin-6 in post-menopausal women. Brain Behav. Immun. 23, 446–449.

Price, L.H., Kao, H.T., Burgers, D.E., Carpenter, L.L., Tyrka, A.R., 2013. Telomeres and early-life stress: an overview. Biol. Psychiatry 73, 15–23.

Schutte, N.S., Malouff, J.M., 2015. The relationship between perceived stress and telomere length: a meta-analysis. Stress. Health. http://dx.doi.org/10.1002/smi.2607 (in press).

Shalev, I., Entringer, S., Wadhwa, P.D., Wolkowitz, O.M., Puterman, E., Lin, J., Epel, E. S., 2013a. Stress and telomere biology: a lifespan perspective. Psychoneuroendocrinology 38, 1835–1842.

Shalev, I., Moffitt, T.E., Sugden, K., Williams, B., Houts, R.M., Danese, A., Mill, J., Arseneault, L., Caspi, A., 2013b. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. Mol. Psychiatry 18, 576–581.

Tansey, C.M., Raina, P., Wolfson, C., 2012. Veterans' physical health. Epidemiol. Rev. 35, 66–74.

Teyssier, J.R., Chauvet-Gelinier, J.C., Ragot, S., Bonin, B., 2012. Up-regulation of leucocytes genes implicated in telomere dysfunction and cellular senescence correlates with depression and anxiety severity scores. Plos One 7, e49677.

Thomas, J.L., Wilk, J.E., Riviere, L.A., McGurk, D., Castro, C.A., Hoge, C.W., 2010. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Arch. Gen. Psychiatry 67, 614–623.

Verhoeven, J.E., Revesz, D., Wolkowitz, O.M., Penninx, B.W., 2014. Cellular aging in depression: permanent imprint or reversible process?: An overview of the current evidence, mechanistic pathways, and targets for interventions. Bioessays 36, 968–978.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54, 1063–1070.

Wolkowitz, O.M., Reus, V.I., Mellon, S.H., 2011. Of sound mind and body: depression, disease, and accelerated aging. dialog- Clin. Neurosci. 13, 25–39.

Yu, W.Y., Chang, H.W., Lin, C.H., Cho, C.L., 2008. Short telomeres in patients with chronic schizophrenia who show a poor response to treatment. J. Psychiatry Neurosci. 33, 244–247.

Zalli, A., Carvalho, L.A., Lin, J., Hamer, M., Erusalimsky, J.D., Blackburn, E.H., Steptoe, A., 2014. Shorter telomeres with high telomerase activity are associated with raised allostatic load and impoverished psychosocial resources. Proc. Natl. Acad. Sci. USA 111, 4519–4524.

Zhang, L., Hu, X.Z., Benedek, D.M., Fullerton, C.S., Forsten, R.D., Naifeh, J.A., Li, X., Li, H., Benevides, K.N., Smerin, S., Le, T., Choi, K., Ursano, R.J., 2014. The interaction between stressful life events and leukocyte telomere length is associated with PTSD. Mol. Psychiatry 19, 855–856.