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The implications of war captivity and long-term psychopathology trajectories for telomere length

Zahava Solomon[a,b], Noga Tsur[a,b,*], Yafit Levin[b], Orit Uziel[c,d], Meir Lahav[c,d,e], Avi Ohry[d]

[a] I-Core Research Center for Mass Trauma, Tel-Aviv University, Israel
[b] Bob Shapell School of Social Work, Tel Aviv University, Tel Aviv, Israel
[c] The Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva, Israel
[d] Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel
[e] Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

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ABSTRACT

Background: Previous findings have demonstrated the link between trauma, its psychopathological aftermath and cellular aging, as reflected in telomere length. However, as long-term examinations of psychopathology following trauma are scarce, very little is known regarding the repercussions of depression and PTSD trajectories of psychopathology for telomeres. The current study examined the implications of war captivity and depression/PTSD trajectories on telomere length.

Methods: Ninety-nine former prisoners of war (ex-POWs) from the 1973 Yom Kippur War were evaluated for depression and PTSD at 18, 30, 35 and 42 years after the war. Data on leukocyte telomere length of ex-POWs and 79 controls was collected 42 years after the war.

Results: Ex-POWs had shorter telomeres compared to controls (Cohen's $d = .5$ indicating intermediate effect). Ex-POWs with chronic depression had shorter telomeres compared to those with delayed onset of depression (Cohen's $d = 4.89$), and resilient ex-POWs (Cohen's $d = 3.87$), indicating high effect sizes. PTSD trajectories were not implicated in telomere length (Partial eta$^2 = .16$ and $p = .11$).

Conclusion: The findings suggest that the detrimental ramifications of war captivity are extensive, involving premature cellular senesces. These findings further point to the wear-and-tear effect of long-term depression, but not PTSD, on telomere length. Explanations for the findings are discussed.

1. Introduction

Individuals exposed to trauma are at a high risk for the early development of chronic health conditions and illnesses, such as chronic pain (see Sharp and Harvey, 2001), gastrointestinal health problems (e.g., irritable bowel syndrome, ulcer; see Pacella et al., 2013), autoimmune diseases (O'Donovan et al., 2015), cardiovascular morbidity (Beristianos et al., 2014), and early mortality (see Lohr et al., 2015). Given that these deleterious health outcomes are considerably more common in later life, it is suggested that trauma may result in premature aging (Lohr et al., 2015).

Over the past decade, leukocyte telomere length has emerged as a significant indicator of cellular aging. Telomeres are repetitive TTAGGG sequences located at the chromosomal ends, which confer genomic stability (de Lange, 2002). At each cell division, telomeres progressively shorten, denoting an inverse correlation between telomere length and human age. Apart from normal aging, leukocyte telomere shortening is also correlated with life events, external stressors and lifestyle, such as chronic illness, disability (e.g., Zhai et al., 2006), nutrition and smoking (see Lin et al., 2012). Thus, augmented telomere erosion has emerged as a robust indicator of the human biological age, and a significant marker of cellular senescence.

One of the most horrific man-made traumas, which may result in premature aging, is war captivity. Captivity often entails the ongoing infliction of pain and suffering through torture, combined with the deprivation of basic needs. Former prisoners of war (ex-POWs) have also been shown to suffer from poorer health, such as higher rates of diabetes, blood pressure (Solomon et al., 2014), chronic pain (Amris and Williams, 2015), and early mortality (Solomon et al., 2014). Although these deleterious health ramifications may indicate premature aging, to the best of our knowledge, telomere length has never been examined in this population. The first aim of this study is to examine whether ex-POWs have shorter telomeres compared to a group of controls.

* Corresponding author at: I-Core Research Center for Mass Trauma, Bob Shapell School of Social Work, Tel Aviv University, P.O.B. 39040, Ramat Aviv, Tel-Aviv 69978, Israel.
E-mail address: nogatsur@gmail.com (N. Tsur).

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The traumatic experience of captivity is further manifested in its resulting debilitating psychological and psychiatric sequelae. Two of the most significant psychopathological outcomes are PTSD (Solomon et al., 2012) and depression (Engdahl et al., 2006), which may prevail separately or together, in comorbid sequelae (Ginzburg et al., 2010). These psychopathological ramifications of trauma are considered chronic stressors, which have been linked to an increased risk of cardiovascular and inflammatory disorders (McFarlane, 2010; O'Donovan et al., 2015), mitochondrial dysfunction (Bersani et al., 2016b) and premature aging (McFarlane, 2010). Indeed, findings from the last two decades have established the understanding that not only the exposure to stressors, but also the psychopathological ramifications, are linked to telomere shortening.

Findings regarding the link between depression and telomere length are quite robust, demonstrating an association between the two (Zhang et al., 2014). Although some studies have not supported this association (e.g., Needham et al., 2015; Schaakxs et al., 2015), two recently conducted meta-analyses have found a significant correlation between depression and shortened telomere length (Ridout et al., 2016; Schutte and Malouff, 2015). While these findings point to the significance of depression for telomere length, they did not refer to depression following trauma. To the best of our knowledge, only one study has examined the association between telomere length and depression subsequent to trauma. While telomere length has been significantly correlated with global psychopathological severity, it was not correlated to depression symptom severity (Bersani et al., 2016a).

Examinations of the association between PTSD and telomere shortening are more limited, demonstrating contradictory findings. Some findings have indicated that individuals with PTSD tend to have shorter telomeres compared to controls (Jergović et al., 2014; Zhang et al., 2014), especially when following multiple traumas in childhood (O'Donovan et al., 2011). Additionally, a recent meta-analysis of studies comparing leukocyte telomere length among individuals with psychopathology and healthy controls, revealed significant shorter telomeres among individuals with PTSD (Darrow et al., 2016). However, two recent studies have not supported this association, but rather implied a positive association, with longer telomeres among individuals with PTSD (Küffer et al., 2016), and an increase in telomere length among individuals who developed PTSD symptoms (Boks et al., 2015). These studies were not included in the meta-analysis conducted by Darrow et al. (2016) due to technical (publication date) and methodological matters, respectively. Furthermore, the study conducted by Küffer et al. (2016) used buccal cell telomeres, and not leukocyte telomere length, as in all other reports. Taken together, although the majority of the findings point to a link between PTSD and telomere length, it seems that this link is less established compared to the link between depression and telomeres. The second aim of this study is to examine whether the psychopathological aftermath of war captivity, as reflected in depression and PTSD, are implicated in telomere length.

Notwithstanding, long-term psychopathology following trauma is highly heterogeneous and labile, with symptoms waxing and waning over time (Blank, 1993). Variations in the course of psychopathology may have adverse effects on the wear-and-tear process, and therefore may be implicated differently in the acceleration of telomere shortening. Research has identified a number of characteristic PTSD trajectories following exposure to trauma, namely: chronic, delayed, recovered and resilient (Bonanno and Mancini, 2012; Solomon et al., 2012). To the best of our knowledge, only one study examined the implications of psychopathology for telomere length along more than two repeated assessments (Shalev et al., 2014). The results indicated that men between the ages of 11–38 who have reported psychopathology (either PTSD or depression, not necessarily related to trauma) at more time-points had shorter telomeres compared to men who reported psychopathology in fewer time-points. While these findings support the long-term effect of psychopathology on telomere length, they have not accounted for the divergent effect of depression or PTSD, or their specific course, i.e., trajectory.

The current study presents a prospective examination of the long-term effect of PTSD and depression on telomere length, over three decades. This study is part of a large-scale longitudinal study of war and captivity (see Solomon et al., 2012), in which ex-POWs were assessed 18, 30, 35, and 42 years after the war. We hypothesize that exposure to stress in captivity and a longer duration of psychopathology will be implicated in shorter telomere length. Specifically, we will examine (a) whether ex-POWs have shorter telomeres compared to controls, and (b) whether PTSD and depression trajectories (both, none or only one of them) are implicated in telomere length.

2. Methods

2.1. Participants and procedure

The present study is part of a prospective longitudinal study on the implications of war and captivity with assessments at four time points: 1991 (T1), 2003 (T2), 2008 (T3) and 2015 (T4) (for full details, see Solomon et al., 2012). Of the 240 soldiers captured during the 1973 Yom Kippur War: 164 participated in T1, 144 in T2 (10 could not be located/refused, four had died, and six could not participate due to mental deterioration), and 183 in T3 (29 could not be located/refused, 20 had died, and six could not participate due to mental deterioration). Furthermore, 74 ex-POWs from the original sampling list, who did not participate previously, were added at T3. Finally, 158 ex-POWs agreed to participate at T4 (8 could not be located, 36 refused, 5 were living abroad, 30 had died, 2 could not participate due to physical condition, and 3 could not participate due to mental deterioration). As in every longitudinal design, attrition and, in some cases, addition is inherent. PTSD and depression questionnaires were administered at all four waves of measurement. Telomere data were collected only at T4. Analyses were conducted only among ex-POWs with telomere data who participated in all 4 assessments (n = 99). Demographic information of ex-POWs is presented in Table 1.

The control group was recruited from a central hospital in Israel, and consisted of 79 healthy participants, who were past members of the military but were not held captive. This group consisted of 41 women and 33 men. No difference was found between men and women in telomere length (men's mean telomere length was 6.05 with 1.78 standard deviation, and women's mean telomere length was 6.13 with 1.58 standard deviation). Their age ranged between 65 and 85 years (mean of 75.4 with 6 standard deviation) and they were matched to the ex-POWs group in age.

2.2. Measures

2.2.1. PTSD Inventory

PTSD Inventory (PTSD-I; Solomon et al., 1993) was used to assess PTSD symptoms at all four time-points. Ex-POWs indicated the fre-

Table 1
Demographic characteristic of ex-POWs.

	Torture survivors
Age (M, SD)	63.6, 3.7 (range: 61–77)
Years of education (M, SD)	14, 3.7 (range: 6–25 years)
Family status	
Married	85 (85.86%)
Single	1 (1.01%)
Divorced	12 (12.12%)
Widowed	1 (1.01%)
Number of children[c] (M, SD)	3.1, 1.62
Income [d] (M, SD)	3.61, 1.22
	74 (74.7%) report of mean income or above
Physical exercising regularly	62 (62.6%)
Smoking on a regular basis	21 (21.2%)

quency of items reflecting the DSM-IV symptoms of PTSD (intrusion, numbing/avoidance, hyper-arousal) (American Psychiatric Association, 1994), which was the standard at the time the research was conducted. Items are scored on a four-point Likert scale, ranging from a frequency of (1) *least* to (4) *greatest*. The PTSD-I has strong reliability and convergent validity when compared with diagnoses based on structured clinical interviews (Solomon et al., 1993). This is a well-validated screening tool with high internal consistency. In the current study, the internal consistency was high at T1, T2, T3 and T4 (α = .95, α = .92, α = .93, α = .9, respectively). Ex-POWs and veterans were considered to have PTSD symptoms if they met the DSM-IV-TR criteria by endorsing at least one symptom of intrusion, at least three symptoms of numbing/avoidance, and at least two hyper-arousal symptoms and criterion F (functional impairment) (American Psychiatric Association, 1994).

2.2.2. Depression

Depression was assessed at all four time-points using the 6-item depression subscale of the Symptom Checklist-90 (SCL-90; Derogatis, 1977). Respondents were asked to indicate how frequently they experienced each symptom over the last two weeks on a 5-point scale ranging from 'not at all' to 'extremely'. We found high internal consistency in this study (α = .91, α = .91, α = .93, α = .9, respectively). The presence of clinical symptom levels was defined using a cutoff score of .73, which is based on norms for psychiatric outpatients (Derogatis, 1977).

2.3. Measurements of telomere length

Average telomere length was assessed at T4, and measured by Southern blott (as described in Uziel et al., 2007). Genomic DNA was extracted (ArchivePure; 5-prime) according to the manufacturer's instructions and quantified (NanoDrop; Thermo). DNA, 5 mg, was digested for 16 h with *RSA*I and *HINF*I (TeloTAGGG length assay; Roche). The digested DNA was separated by gel electrophoresis (0.6% agarose), de-purinated by HCl 0.25 M, denatured with alkaline denaturing solution (NaOH 0.5 M, NaCl 1.5 M) and then neutralized (Tris 0.5 M, NaCL 3 M). Subsequently, the DNA was capillary-transferred onto a positively charged whatman nylon membrane (Roche) for 16 h. The DNA was then UV-cross-linked (120 mJ) to the membrane and incubated for 16 h with DIG-labeled TL probe $(CCCTAA)_4$. The membrane underwent washes as follows: twice in Stringent wash buffer I (2× SSC, 0.1% SDS) for 5 min at RT, twice in Stringent wash buffer II (0.2× SSC, 0.1% SDS) for 15 min at 50 °C, in 1× maleic acid buffer (supplied by the TeloTAGGG length assay kit; Roche) for 5 min, in blocking solution (kit) for 30 min at RT, in Anti-DIG-AP solution for 30 min at RT, twice in washing buffer (kit) for 15 min at RT and finally in detection solution (kit) for 5 min at RT. The membrane was then applied with ~40 drops of CSPD substrate and exposed to a sensitive film for 1.5 h. After development, the film was scanned and quantified by the Quantity One software (Versadoc; BioRad). To calculate telomere length, each signal was segmented and its intensity was measured. Telomere length was calculated according to the following equation:

$$\frac{\sum (\mathrm{OD}_i)}{\sum (\mathrm{OD}_i / L_i)}$$

where OD_i is the chemiluminescent signal and L_i is the length of the telomere at position *i*.

2.4. Analytic strategy

First, the descriptive statistical information about telomere length is presented, including mean, standard deviation, minimum and maximum values, kurtosis and skewness – to ensure there is no violation of the assumption of normality, as well as a critical assessment of outliers. Secondly, in order to assess whether and how BMI should be controlled, in the following analyses we assessed the role of BMI in PTSD, depression, and telomere length. Next, we compared ex-POWs and controls in their telomere length, while controlling for age. Finally, we assessed the long-term implications of PTSD and depression in telomere length. For this purpose, we examined the differences between the trajectories of PTSD and depression regarding telomere length.

3. Results

3.1. Descriptive information of telomere length

The maximum value for the telomeres' length was 9.90 kilo base pairs (kb) and the minimum was 2.50, with a mean of 5.32 (SD = 1.5). Preliminary analyses were performed to ensure that there was no violation of the assumption of normality. Descriptive information for telomeres' variables were examined by histograms, skewness and kurtosis values, as well as by a critical assessment of any outliers for possible exclusion from analyses or necessary adjustments. The data were then checked using recommended skew values of less than 2 and kurtosis values of less than 7. Skew values between 2 and 3 and kurtosis values less than 10 were considered moderately non-normal (Curran et al., 1996). Although all variables were in the recommended acceptable range for skewness (0.74) and kurtosis (−0.4), we identified six outliers in the telomeres' lengths, signified by large gaps in the histogram and a *Z* score greater and lower than 3.33 (long telomeres ranged from 8 to 9.90 and shorter telomeres ranged from 2.5 to 3.2, while most of the sample ranged between 3.7 and 6.5, as reflected in the mean value). Since the outliers did not change the values of the kurtosis and skewness significantly, they were not addressed.

3.2. BMI, PTSD, depression, and telomere length

To assess whether and how BMI should be included as a covariate in the following analyses, we examined whether BMI was related to PTSD, depression, and telomere length. The continuous BMI did not correlate with telomere length in ex-POWs (r = −.05, p = .38), as no differences were found between ex-POWs with normal and abnormal BMI (i.e., categorical BMI) in telomere length ($t(84)$ = .74, p = .46). Next, we found that while the continuous BMI did not correlate with PTSD or depression, when using categorical BMI, the levels of PTSD in T2 ($t(94)$ = 1.89, p = .05), and depression at all 4 measurements (t ranges 2.99, p = .005 to 2.301, p = .02) were implicated in different categorical BMI levels. In other words, ex-POWs with abnormal BMI reported higher depression at all 4 measurements and higher PTSD at T2, compared to those with normal BMI scores. Hence BMI was controlled for as a categorical measure throughout all of the analyses that included depression and PTSD trajectories.

3.3. Differences between ex-POWs and controls in telomeres' length

The difference between the average lengths of telomeres between the ex-POWs and the controls, while controlling for their age, was statistically significant ($F(1,171)$ = 6.13, p = 0.01, Partial eta^2 = .05). The mean length of the telomeres of the ex-POWs (M = 5.38 SD = 1.54) was shorter than those of the controls (M = 6.12 SD = 1.52). No effect was found for age between groups ($F(1,171)$ = .05, p = .83, Partial eta^2 = .00). Since there were few predictors, the partial eta squared was not reliable. Therefore, we calculated the Cohen's effect size (calculation according to Hedges and Olkin, 1985, p. 86). We found that Cohen's d was intermediate (Cohen, 1988) which enters into the zone of desired effect sizes (Cohen's d = 0.48 CI 95% 0.183, 0.783).

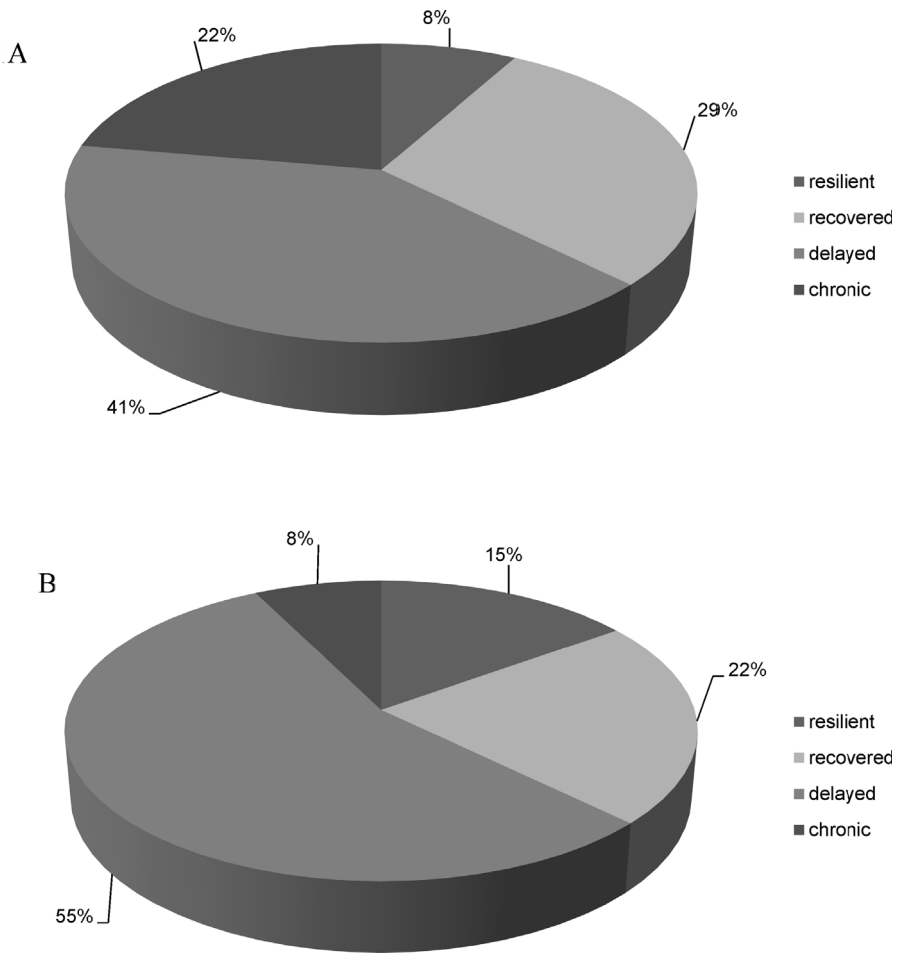

Fig. 1. Prevalence of posttraumatic stress disorder (PTSD) and depression trajectories among former prisoners of war (ex-POWs). (A) Frequencies of PTSD trajectories among ex-POWs. (B) Frequencies of depression trajectories among ex-POWs.

3.4. The longitudinal trajectories of PTSD and depression among ex-POWs

Using data from the four waves of measurement, we were able to identify the various trajectories of PTSD and depression, separately. Specifically, four subgroups of trajectories were identified for PTSD: (a) "chronic PTSD" – individuals who endorsed PTSD at all four waves of measurement; (b) "delayed onset" – individuals who did not report PTSD in previous waves of measurement, but did suffer from PTSD at one or more of a later measurement; (c) "recovery" – individuals who reported PTSD in one or more of the previous waves of measurement but not in one or more of the later waves; and (d) "resilience" – individuals who did not report PTSD in any of the four waves of measurement. Next, four subgroups of trajectories were identified for depression in the same manner, including: (a) "chronic depression"; (b) "delayed onset of depression"; (c) "recovery" and (d) "resilience".

The prevalence of PTSD trajectories and depression trajectories among the ex-POWs can be found in Fig. 1. The results showed that there were 47 ex-POWs with a resilient PTSD trajectory, 5 with chronic PTSD, 46 with delayed PTSD, and 1 with a recovered trajectory of PTSD. For the depression trajectories, there were 30 who were resilient, 15 with chronic depression, 53 with delayed depression, and 1 who had recovered. Due to the small numbers, we combined the resilient and recovery trajectories of both depression and PTSD.

3.5. The relationships between PTSD trajectories and telomeres

To examine whether PTSD trajectories were associated with different lengths of telomeres, one-way analysis of variance was conducted (one-way ANCOVA), while controlling for categorical BMI and age. This analysis revealed that the different trajectory groups were not significantly different from each other ($F(2,94) = 2.2$, $p = .11$, Partial eta$^2 = .16$). Furthermore, there were no significant effects for BMI ($F(2,94) = .26$, $p = .6$), and age ($F(2,94) = 1.7$, $p = .2$) (see Fig. 2).

3.6. The relationship between depression trajectories and telomeres

To examine whether depression trajectories predict significantly different levels of telomeres, one-way ANCOVA was conducted, while controlling for categorical BMI and age. Significant differences were found ($F(2,94) = 5.22$, $p = .007$, Partial eta$^2 = .1$). A post hoc Bonferroni test revealed that ex-POWs with a chronic depression trajectory (M = 4.29, SD = .37) had shorter telomeres compared to ex-POWs with resilient depression (M = 5.6, SD = .2) and compared to ex-POWs with a delayed depression trajectory (M = 5.4, SD = .26) (see Fig. 2). Next, we calculated the effect sizes of the different comparisons presented. We found that Cohen's d for the difference between chronic and resilient groups (Cohen's $d = 4.89$, CI 95% 3.711–6.084) and between chronic and delayed groups (Cohen's $d = 3.87$, CI 95% 3.002–4.736) were large effect sizes (Cohen, 1988). No other differences were found in this analysis. BMI ($F(1,94) = .26$, $p = .6$), and age ($F(1,94) = 1.7$, $p = .2$), were not significant in this model.

4. Discussion

The findings of this study demonstrate that ex-POWs have shorter telomeres compared to controls. The unique cohort in this study

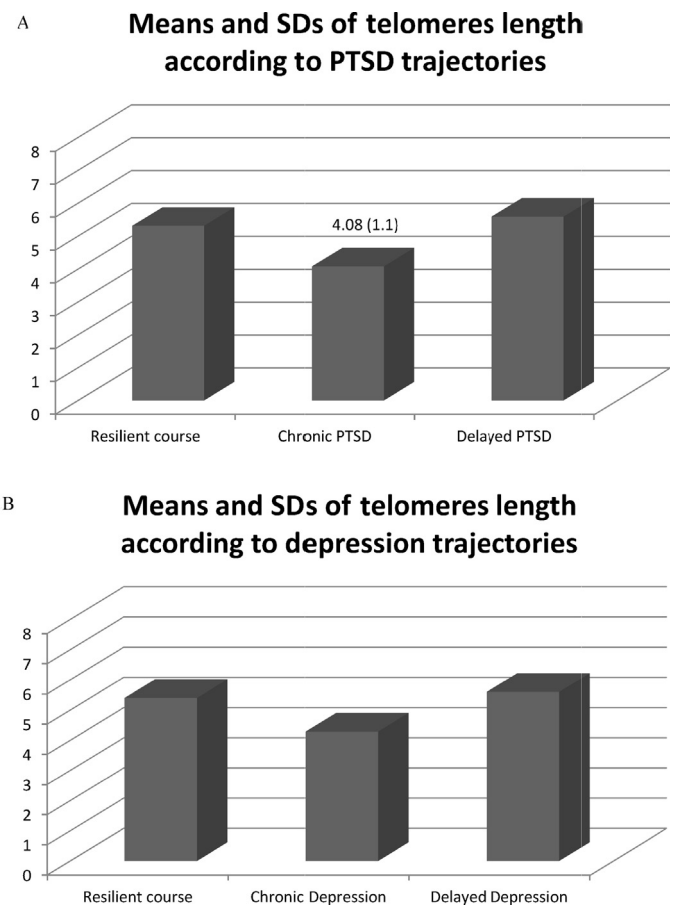

Fig. 2. (A) Means and SDs of telomere length in PTSD trajectory groups. *Notes*: Labels of each column are presented as follows: M(SDs). The statistical difference was not significant between the groups. (B) Means and SDs of telomere length in depression trajectory groups. *Notes*: Labels of each column are presented as follows: M(SDs). The statistical difference was significant between the groups of chronic depression and the two other groups.

enabled an examination of the implications of longitudinal PTSD and depression trajectories on telomere length, and we found that long-term depression, but not PTSD, was implicated in shorter telomere length.

Captivity entails ongoing exposure to extreme stressors for extended periods of time. During that time, ex-POWs encounter severe man-made brutality, demonstrated in physical and psychological torture, including starvation, humiliation, isolation, and other tactics that provoke emotional and physical pain and suffering (Solomon et al., 2012). In support of our first research hypothesis, the current findings indicate that ex-POWs exhibited shorter telomeres compared to controls. This finding is in line with previous studies that have documented the implications of trauma on telomere length (e.g., Shalev and Belsky, 2016). While the majority of these studies examined childhood trauma (see Shalev et al., 2013), findings have also demonstrated that childhood trauma interacts with stress occurring during adulthood (Kiecolt-Glaser et al., 2011), and that stress during adulthood may also be directly implicated in telomere length (e.g., Epel et al., 2010).

The current study was based on longitudinal data derived from 42 years of follow-up. This enabled us to identify four longitudinal psychopathology trajectories, and examine their implications for later telomere length. Our findings indicated that depression trajectories are implicated in telomere length. In support of our second research hypothesis, and in line with previous findings (see Ridout et al., 2016; Schutte and Malouff, 2015), this finding demonstrated the link between depression and telomere length. Furthermore, this finding demonstrated that ex-POWs who suffered from a chronic course of depression had shorter telomeres compared to ex-POWs with a delayed onset of depression, and resilient ex-POWs. Compared to the delayed onset trajectory, which exemplifies ex-POWs who did not suffer from depression in the first assessments, the chronic trajectory exemplifies ex-POWs who suffered from depression at all four time points, demonstrating the longest duration of depression. According to a recent review by Lindqvist et al. (2015), although the majority of the evidence points to shorter telomeres among individuals who suffer from depression, findings regarding the dose–response association between depression and telomere length are inconclusive. The current study points to the dose–response association of depression and telomere length in means of duration (course over time) of psychopathology. While Shalev et al. (2014) found that the duration of internalized disorders (including, but not limited to depression) was implicated in telomere length (Hartmann et al., 2010) did not find a significant association between duration or symptom severity and telomere length. A large cohort study conducted by Verhoeven et al. (2014), however, found that both currently depressed and remitted groups showed shorter telomeres compared to controls. Although these findings may indicate a long-lasting imprint of depression (Verhoeven et al., 2014), it may also indicate that shortened telomeres precede depression, manifesting in cellular sensitivity (Lindqvist et al., 2015). To the best of our knowledge, this is the first study to document the long-term implications of depression trajectories for telomeres, pointing to the significance of the course of psychopathology, and not only illness duration, for depleting psychological and physical resources.

According to the 'allostatic load' model, chronic stress, such as long-term depression, burdens the psychological and physiological resources that are dedicated to maintaining homeostasis. Short-term stressors demand survival-promoting reactions, implicated in the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system (Rohleder et al., 2010). While efficient for surviving short-term stressors, when facing chronic stressors, the repeated activation of the stress response burdens the body's normal functioning, causing 'allostatic load' (McEwen, 1998). This 'wear and tear' of the allostatic systems leads to an increased risk of cardiovascular and inflammatory disorders as well as premature aging (McFarlane, 2010), also demonstrated in telomere length (Zalli et al., 2014). In line with this inquiry, the current prospective longitudinal examination of psychopathology following trauma supports the wear-and-tear effect of long-term depression on telomere length (see Ridout et al., 2016; Schutte and Malouff, 2015). Another different, yet somewhat related explanation refers to differential susceptibility (Belsky and Pluess, 2009) or sensitivity/responsivity (Boyce and Ellis, 2005; Del Giudice et al., 2011) in relation to the external environmental context. According to this perspective, individuals differ in their level of plasticity in the face of external context (Belsky and Pluess, 2009) and biological reactivity to stressors (Boyce and Ellis, 2005). Hence, it is possible that the chronic trajectory exemplifies individuals who are more susceptible to stressors in the environment and are therefore more affected biologically by long-term allostatic load, as demonstrated in telomere length.

Nevertheless, contrary to our hypothesis, the findings demonstrated that PTSD trajectories were not implicated in telomere length. Previous findings regarding the link between PTSD and telomere length are mainly cross-sectional, with only one longitudinal examination which demonstrated that an increase in PTSD symptoms was implicated in longer telomeres (Boks et al., 2015). Furthermore, other studies have documented increased telomerase activity (the enzyme that lengthens telomeres) (Epel et al., 2010) in response to stressors, thus pointing to a possible compensatory mechanism in the face of acute (Epel et al., 2010) and chronic (Beery et al., 2012) stress. An important question then arises as to why depression, and not PTSD, was implicated in telomere length, and how can this difference be explained?

It has been suggested that depression and PTSD affect telomere length due to their mutual association with increased oxidative stress (Wolkowitz et al., 2010) and with a pro-inflammatory milieu (see

Zhang et al., 2014). However, the biological mechanisms of PTSD and depression are complicated, with findings pointing to divergent processes. That is, studies have documented different activities of the HPA axis, mainly observed as hypoactivity in PTSD (Yehuda et al., 2005), and hyper-reactivity in depression following trauma (Heim et al., 2000). These divergent processes are also implicated in different cortisol regulatory processes (Sriram et al., 2012). Diverse biological mechanisms of PTSD and depression have also been expressed in reports of basal glucocorticoid levels; with elevated levels observed in depression, and reduced levels observed in PTSD (Burke et al., 2005). These biological manifestations have been suggested to mediate the association between exposure to stress and oxidative stress (Wolkowitz et al., 2010), thus providing possible biological traces to explain the divergent implications of PTSD and depression for telomeres.

One can also speculate that the differential findings for PTSD and depression are associated with the somatic symptomatology of these two phenomena. First, both PTSD and depression may involve sleep problems, such as insomnia (American Psychiatric Association, 2013), but only depression may entail hypersomnia (Soehner et al., 2014), a much less studied phenomenon. To the best of our knowledge, the impact of hypersomnia on telomere length has never been examined, yet recent findings point to its implications for significant health deterioration (Choi et al., 2016). Second, while both PTSD and depression may entail hypervigilance and an exaggerated startle response, or psychomotor agitation (respectively; American Psychiatric Association, 2013), only depression may depict psychomotor retardation, fatigue or loss of energy. Indeed, telomere length has been found to be associated with reduced activity level (Latifovic et al., 2016). Finally, one central symptom criteria of depression, but not PTSD, is significant weight change (5%), or change in appetite. As body weight has been found to affect telomere length (Rode et al., 2014), it may also shed light on the mechanisms underlying the current findings. Indeed, our findings demonstrated that PTSD and depression trajectories are implicated in different BMI categories. However, the findings also demonstrated that BMI did not contribute significantly to the association between PTSD nor to depression and telomeres. Therefore, these speculative explanations deserve further examination.

From a psychological standpoint, depression is associated with significant loss, from the loss of loved ones, to the meltdown of core values, as well as the loss of parts of the self (Solomon et al., 1993). While PTSD involves a specific external event that threatened the individual (or someone else) (American Psychiatric Association, 2013), in depression, this external affair is internalized–imposing a negative attitude about the self and the world (Beck et al., 1979). As a result, the depressed individual experiences a sense of worthlessness, guilt, and/or inability to experience pleasure (American Psychiatric Association, 2013). Although these unique characteristics of depression have not been examined in regards to telomere length, they have been significantly correlated with physical health (e.g., Katon, 2003). Consequently, depression entails a withdrawal of the individual's energy and resources, which is often combined with excessive thoughts of death. Psychologically speaking, these characteristics reflect emotional enervation, or mental senesces, which in the current findings are also linked to cellular senesces, i.e., telomere length.

The findings of this study should be considered in light of its limitations. Most importantly, it should be considered that the number of chronic and recovered PTSD trajectory participants was very small (5 and 1, respectively). Therefore, it is possible that the insignificant results regarding the implications of PTSD trajectories for telomere length are due to the small sample size and the distribution amongst the trajectory groups. Future studies should use larger samples, with better trajectory group distribution. Furthermore, as medication use was not obtained from participants, we could not control for its possible effect on telomere length. Other limitations relate to assessment. The current study used self-report measures to assess PTSD and depression. Although these were based on well-established questionnaires (Derogatis, 1977; Solomon et al., 1993), other methods, including clinical interviews are recommended for future studies. Also, several telomere measurement methods are commonly reported in the literature. In this study, we used Southern Blot, which is considered the gold standard for telomere length measurement. Another popular method is the quantitative PCR (Q-PCR). Since Southern Blot is considered more accurate due to molecular sequencing of telomeres, which are comprised of hexamers of TTAGGG repeats, it is suggested that Q-PCR may be considered as a valid method only when used to analyze very large cohorts of samples. Nonetheless, one should consider that variability in measurement methods might have affected the results. Finally, another reservation stems from the attrition rate, a well-recognized setback in prospective studies. As the current study spans over four decades, with a long gap between the first two assessments, this shortcoming is unavoidable. Finally, since telomere length was only measured at T4, it was impossible to account for its longitudinal changes.

With these limitations in mind, the findings of the present study illuminate the long-term cellular aging consequences of trauma and its sequelae. These findings point to the close link between psychological and physiological human processes, and the need to further elucidate our understanding of their underlying mechanisms. Future studies should expand upon the longitudinal fluctuations of PTSD and depression and their implications for telomere length. Further, in depth examination of the shared and divergent biological, behavioral and affective manifestations of PTSD and depression is needed, and their potential role in clarifying the association between long-term psychopathology and premature aging, as demonstrated in telomere length.

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Conflicts of interest

None declared.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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