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Preliminary communication

Adverse childhood experiences and leukocyte telomere maintenance in depressed and healthy adults



Stephen H. Chen^a, Elissa S. Epel^b, Synthia H. Mellon^c, Jue Lin^d, Victor I. Reus^b,
Rebecca Rosser^b, Eve Kupferman^b, Heather Burke^b, Laura Mahan^b,
Elizabeth H. Blackburn^d, Owen M. Wolkowitz^{b,*}

^a Department of Psychology, Wellesley College, Wellesley, MA, USA

^b Department of Psychiatry, University of California, San Francisco (UCSF), School of Medicine, 401 Parnassus Avenue, San Francisco, CA 94143, USA

^c Department of OB-GYN and Reproductive Sciences, UCSF School of Medicine, San Francisco, CA, USA

^d Department of Biochemistry and Biophysics, UCSF School of Medicine, San Francisco, CA, USA

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ABSTRACT

Background: Adverse childhood experiences (ACEs) are associated with poor physical and mental health outcomes in adulthood. Adverse childhood experiences are also associated with shortened leukocyte telomere length (LTL) in adults, suggesting accelerated cell aging. No studies have yet assessed the relationship of ACEs to LTL in individuals with major depressive disorder (MDD), despite the high incidence of antecedent ACEs in individuals with MDD. Further, no studies in any population have assessed the relationship of ACEs to the activity of telomerase, the major enzyme responsible for maintaining LTL, or the relationship between telomerase and LTL in individuals with ACEs.

Methods: Twenty healthy, unmedicated adults with MDD and 20 healthy age-, sex- and ethnicity-matched controls had ACEs assessed and had blood drawn for LTL and peripheral blood mononuclear cell (PBMC) resting telomerase activity.

Results: In healthy controls, greater ACE exposure was associated with shorter LTL ($p < .05$) but was unassociated with telomerase activity. In MDD, however, the opposite pattern was seen: greater ACE exposure was unrelated to LTL but was associated with increased telomerase activity ($p < .05$) and with a higher telomerase:LTL ratio ($p = .022$).

Limitations: Study limitations include the small sample size, a single timepoint assessment of telomerase activity, and the use of retrospective self-report to assess ACEs.

Conclusions: These results replicate prior findings of shortened LTL in healthy adults with histories of multiple ACEs. However, in MDD, this relationship was substantially altered, raising the possibility that activation of telomerase in ACE-exposed individuals with MDD could represent a compensatory response to endangered telomeres.

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1. Introduction

Serious adverse childhood experiences (ACEs) are remarkably prevalent, with between 52% and 64% of individuals in the United States experiencing at least one serious ACE before the age of 18 and between 6.2% and 12.5% of individuals experiencing four or more serious ACEs before that age (Anda et al., 2006; Felitti et al., 1998). ACEs are associated with increased risk of adult physical and mental disease and with shortened life expectancy (Anda et al., 2010; Brown et al., 2009; Chapman et al., 2004). The mechanisms underlying this increased risk are unknown, but one possibility is

that ACEs are associated with premature biological aging. An emerging measure of biological age at the cellular level is the length of telomeres in circulating leukocytes. Shorter leukocyte telomere length (LTL) is associated with earlier onset or elevated risk of several common diseases of aging (Andrews et al., 2009; Epel et al., 2006).

Telomeres are deoxyribonucleic acid (DNA)–protein complexes found at the ends of linear chromosomes that cap and protect the genome from damage. Telomere shortening can occur with repeated cell division as well as with chronic exposure to cytotoxic stressors such as oxidative stress and inflammation (O'Donovan et al., 2011b; Von Zglinicki, 2002), and telomere length may provide a biomarker for assessing an individual's cumulative exposure to, or ability to cope with, stressful conditions (Epel et al., 2004; Kotschal et al., 2007). Telomere shortening can be counteracted

* Corresponding author. Tel.: +1 415 476 7433; fax: +1 415 502 2661.

E-mail address: Owen.Wolkowitz@ucsf.edu (O.M. Wolkowitz).

or reversed by telomerase, an enzyme that elongates telomeres (Blackburn and Collins, 2011). However, the amount of telomerase in most somatic cells is insufficient to maintain telomere length indefinitely (Beyne-Rauzy et al., 2005; Kotrschal et al., 2007), and when telomeres reach a critically short length, cells become susceptible to senescence and apoptosis (Price et al., 2013; Epel et al., 2006).

Shortened LTL has been associated with psychiatric illness, such as anxiety and depressive disorders (Hartmann et al., 2010; O'Donovan et al., 2011a; Simon et al., 2006), and accelerated LTL shortening has been demonstrated in adults with ACEs (Kiecolt-Glaser et al., 2011; Tyrka et al., 2010; Price et al., 2013). Despite the high prevalence of both ACEs and poor health outcomes in MDD, no studies have assessed the relationship of ACEs to LTL in individuals with major depressive disorder (MDD). Further, the role of peripheral blood mononuclear cell (PBMC) telomerase activity (TA) has not been well characterized in stressed and psychiatrically ill individuals, nor in individuals with histories of ACEs.

This study examined LTL and TA in healthy unmedicated adults with MDD and in well-matched healthy controls. We hypothesized that graded exposure to ACEs would be associated with diminished LTL in both groups. We did not hypothesize specific TA changes or telomerase:LTL ratios that would be associated with graded exposure to ACEs due to the lack of prior data.

2. Methods

2.1. Participants

This study was approved by the University of California San Francisco Committee on Human Research. Participants gave informed consent to participate and were reimbursed for their participation.

Twenty subjects with MDD and 20 healthy controls (individually matched on age \pm 3 years, gender and ethnicity) participated and completed all procedures. The individuals with MDD and 18 of the controls have been described in other publications using different measures and testing different hypotheses (Wolkowitz et al., 2012). MDD diagnoses were made using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) and verified through clinical interview with a Board-certified psychiatrist. Depressed subjects were required to have a minimum rating of 17 on the 17-item Hamilton Depression Rating Scale (Hamilton, 1960). Healthy controls were required to have no present or lifetime history of any DSM-IV Axis I diagnosis. All subjects were medically healthy, as assessed by physical examination, vital signs and standard laboratory screening tests. All subjects were free of acute illnesses at the time of testing. For at least 6 weeks prior to participation, no subjects had received vaccinations, immunizations, psychotropic medications, or other medications thought to affect LTL, TA, oxidative stress or inflammation (except prn short-acting sleep medication, up to 3 times per week, but none within one week of the study visit). Subjects with lifetime diagnoses of bipolar or psychotic illness or with diagnoses of alcohol or substance abuse within the preceding six months were excluded, as were subjects with symptoms of PTSD in the past month. Other comorbid anxiety diagnoses were permitted within the MDD group if MDD was considered the primary diagnosis.

2.2. Procedures

Subjects were admitted as outpatients to the UCSF Clinical Translational Science Institute at 8:00 am following a 12-h

overnight fast (except for water). After subjects rested quietly, an indwelling intravenous catheter was placed for blood drawing.

2.2.1. Assays

LTL assay procedures were adapted from the published original method (Cawthon, 2002). Whole blood was drawn into lavender top EDTA Vacutainer tubes, and buffy coat was saved for LTL assay. High molecular weight DNA was extracted from frozen whole blood using commercially available reagents (Puregene, Genra Systems, Qiagen, Valencia, CA). DNA quality and quantity were assessed with a nanodrop spectrophotometer and random samples were also assessed by agarose gel electrophoresis. The T (telomeric) and S (single copy gene) values of each sample were determined by quantitative polymerase chain reaction (PCR) using the following primers: tel1b [59-CGGTTT(GTTTGG)5GTT-39] and tel2b [59 GGCTTG(CCTTAC)-5CCT-39] for T and hbg1 [59 GCCT-CTGACACAACCTGTGTTCACTAGC-39] and hbg2 [59 CACCAACTT-CATCCACGTTACC-39] for S (human beta-globin). Genomic DNA from HeLa cells was used as the reference to quantify the T and S values relative to the reference DNA sample by the standard curve method. All PCRs were carried out on a Roche Lightcycler 480 real-time PCR machine with 384-tube capacity (Roche Diagnostics Corporation, Indianapolis, IN). The telomere thermal cycling profile consisted of: cycling for T (telomeric) PCR: denature at 96 μ C for 1 s, anneal/extend at 54 μ C for 60 s, with fluorescence data collection, 30 cycles; cycling for S (single copy gene) PCR: denature at 95 μ C for 15 s, anneal at 58 μ C for 1 s, extend at 72 μ C for 20 s, 8 cycles; followed by denature at 96 μ C for 1 s, anneal at 58 μ C for 1 s, extend at 72 μ C for 20 s, hold at 83 μ C for 5 s with data collection, 35 cycles. Blood samples from MDD participants and their matched controls were assayed in the same batch. The inter-assay coefficient of variation (CV) for telomere length measurement was 4%.

Blood for PBMC TA determination was collected in Cell Preparation Tubes (Becton-Dickinson, Franklin Lakes, NJ, USA, Vacutainer CPT), which contain a Ficoll separation gradient. Blood processing procedures have been described in detail previously (Wolkowitz et al., 2012). Telomerase activity was assayed with the telomere repeat amplification protocol (TRAP). TA assay was optimized on the basis of the commercially available kit TRAPeze (Chemicon, Temecula, CA, USA). Telomerase activity is defined as 1 unit = the amount of product from one 293T cell/10,000 PBMC's. Blood samples from MDD participants and their matched controls were assayed in the same batch. Inter-assay CV of PBMC telomerase activity was 6.8%.

2.3. Ratings

Subjects reported depressive symptoms over the preceding week using the Quick Inventory of Depressive Symptoms Scale (QIDS; Rush et al., 1996). Subjects reported on ACEs using the self-administered 8-item Adverse Childhood Experiences scale (Felitti et al., 1998). This scale has been well-validated (Anda et al., 2010) and assesses history of personal abuse, neglect, and household dysfunction. Scores range from zero (no history of ACEs) to eight (all eight types of ACEs). Sleep quality was assessed with the Insomnia Severity Index (Morin et al., 2011). Subjective socioeconomic status was measured using a 10-rung ladder version of the MacArthur Scale of Subjective Social Status (Adler et al., 2000).

All variables were screened for normality, and non-normal distributions were natural log-transformed. Independent sample *t*-tests and chi-square tests were used to compare groups on demographic variables, including age, gender, ethnicity, socioeconomic variables (e.g., education), exercise activity, tobacco and alcohol use, and insomnia. Age was significantly associated

with telomere length ($r = -.52, p < .05$) among depressed individuals but not among controls ($r = -.07, p = .78$). In the control group only, effects were found between gender and telomere length (telomere length was longer in males; $r = .51, p < .05$), and between age and telomerase activity ($r = -.63, p < .01$).

3. Results

MDD and control groups did not significantly differ in age, sex, ethnicity, educational level, socioeconomic status, or alcohol or tobacco use. Individuals with MDD reported more difficulties with insomnia ($t(22.8) = -4.89, p = .000$), compared to healthy controls, but sleep was not associated with LTL or TA, in either group.

As expected, individuals with MDD reported a higher severity of depressive symptoms on the QIDS than healthy controls ($t(17.5) = -11.64, p = .000$) as well as a greater number of ACEs ($M = 3.90, SD \pm 2.05, t(38) = -3.04, p = .004$). Among individuals with MDD, 65% had ACE scores of ≥ 4 (out of a maximum score of 8), compared to 25% of the controls ($\chi^2(1, n = 40) = 14.07, p < .001$). As reported previously with a subset of this sample (Wolkowitz et al., 2012), individuals with MDD had higher TA than healthy controls ($t(36) = -2.53, p = .016$) and did not have significantly shorter leukocyte telomeres than controls. Finally, controlling for age and gender, individuals with MDD had increased TA:LTL ratios compared to healthy controls ($F = 6.06, p = .02$).

Partial correlations examined associations between ACEs and LTL controlling for participants' age and gender. Among healthy controls, ACEs were significantly inversely correlated with LTL ($r = -.61, p < .05$) (Fig. 1a) but were not significantly correlated with TA ($r = -.22, p > .10$) (Fig. 2a) or with the TA:LTL ratio ($r = .12, p > .10$). By contrast, among individuals with MDD, ACEs were not significantly correlated with LTL ($r = -.13, p > .10$) (Fig. 1b), but were positively correlated with TA ($r = .58, p < .05$) (Fig. 2b), and the TA:LTL ratio ($r = .60, p < .01$).

4. Discussion

We replicated previous findings of shortened LTL in healthy non-depressed individuals with extensive ACEs (Kiecolt-Glaser et al., 2011; Tyrka et al., 2010; Price et al., 2013), but found a distinctly different pattern in healthy unmedicated individuals with MDD. Specifically, greater exposure to ACEs was correlated

with significantly shorter LTL among the healthy controls but not among the MDDs. By contrast, greater exposure to ACEs was significantly correlated with increased TA in the individuals with MDD but not in healthy controls. Likewise, greater exposure to ACEs was associated with greater TA:LTL ratios in the individuals with MDD but not in the healthy controls.

To our knowledge, no study has previously examined the relationship between ACEs and LTL in individuals with MDD, despite the fact that histories of ACEs are common in adults with MDD (Anda et al., 2006), and no study has yet examined the relationship between ACEs and TA in any population. The present findings suggest that ACEs may be an important factor to consider in studies of LTL and may explain some of the variability reported across studies (Price et al., 2013; Shalev et al., 2012; Shalev et al., 2013).

The mechanisms by which ACEs, at least in non-MDD individuals, come to be associated with shortened LTL are not known, and it is unknown if a causal relationship exists. However, there are multiple pathways through which early adversity may become "biologically embedded" throughout the lifespan (Shalev et al., 2013; Shalev, 2012), including excessive oxidative stress and inflammation (Tyrka et al., 2013; Fagundes et al., 2013; Danese and McEwen, 2012) and dysfunction of the HPA and noradrenergic stress response systems (Heim et al., 2008).

Our overall findings may be best explained by the balance between TA and LTL. Specifically, the increased TA observed among individuals with MDD may reflect a compensatory response that maintains LTL or mitigates telomere shortening, as previously hypothesized (Wolkowitz et al., 2011; Damjanovic et al., 2007). This mechanistic explanation might be consistent with prior pre-clinical and human studies that indicate upregulation of TA in response to cell damage (Baek et al., 2004; Mattson et al., 2001), and a preferential elongation by telomerase of shorter telomeres (Britt-Compton et al., 2009). Finally, the associations between ACEs and increased TA:LTL ratios in the MDD subjects are consistent with several recent studies that also indicate higher ratios in other unhealthy or high-risk conditions (Damjanovic et al., 2007; Kroenke et al., 2012). Higher TA relative to LTL could indicate greater telomere endangerment, requiring greater telomerase activation in an attempt to maintain telomere homeostasis.

This putative compensatory telomerase response is absent in the controls, who exhibit LTL shortening but no TA in proportion to their history of ACEs. It is unknown why telomerase activation did not accompany shorter leukocyte telomeres in the healthy

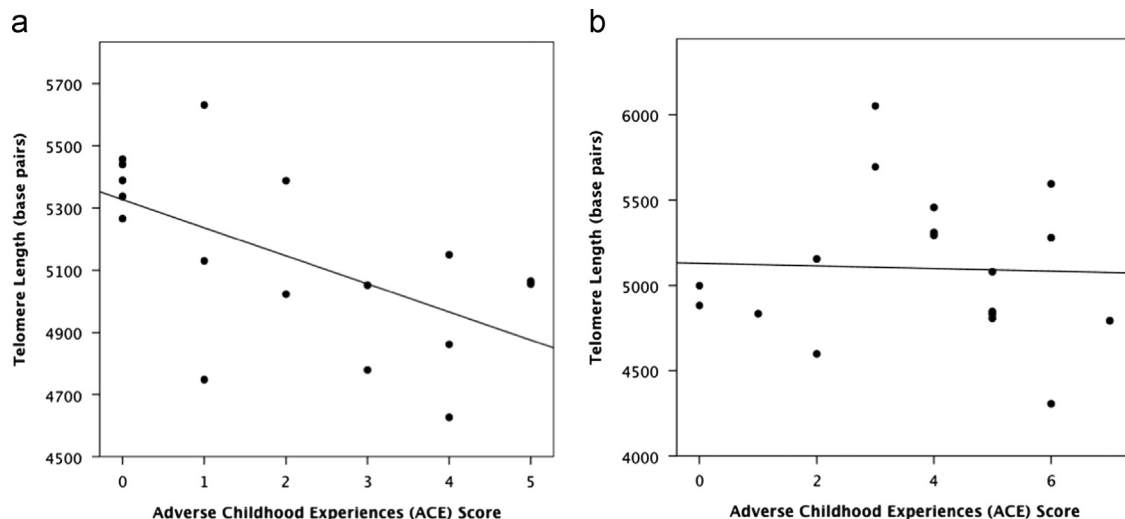


Fig. 1. Associations between adverse childhood experiences and leukocyte telomere length in non-depressed individuals ($r = -.61, p < .05$) (a) and individuals with major depressive disorder ($r = -.13, p > .10$) (b). (a) Non-depressed Healthy Controls and (b) Major Depressive Disorder.

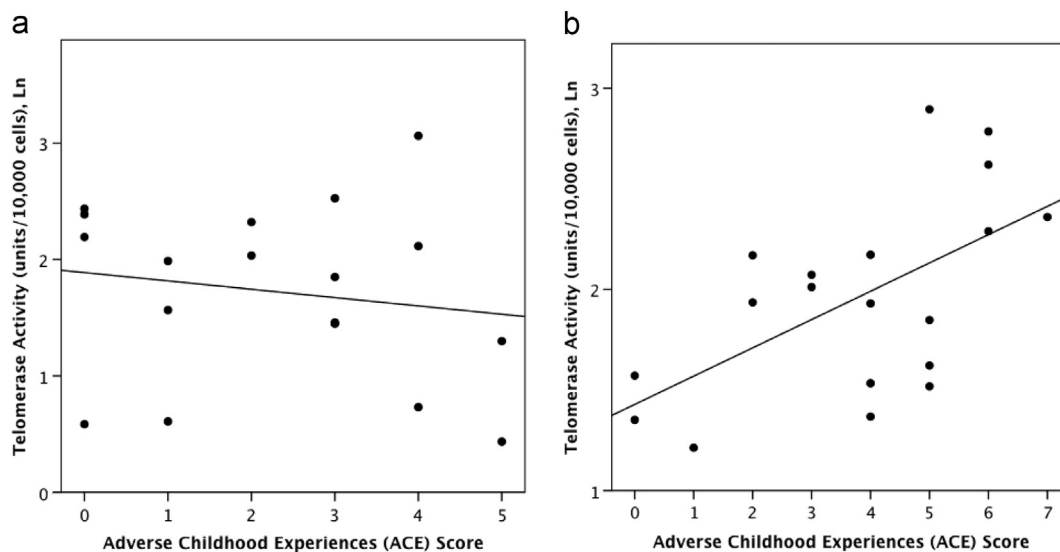


Fig. 2. Associations between adverse childhood experiences and peripheral blood mononuclear cell telomerase activity in non-depressed individuals ($r = -.22$, $p > .10$) (a) and individuals with major depressive disorder ($r = .58$, $p < .05$) (b). (a) Non-depressed Healthy Controls and (b) Major Depressive Disorder

controls. It is possible that additional biochemical alterations seen in MDD (e.g., NF κ B activation, oxidative stress, and inflammation) contribute to telomerase activation (Schiavone et al., 2013; Yamagiwa et al., 2006). Larger studies with prospective designs will be needed to further assess issues of mediation and causality.

Strengths of the present study include the use of well-screened and characterized subjects who were medically healthy and who had been off of psychoactive and other interfering medications for a minimum of 6-weeks before participation. Another strength was the assessment of both telomere length and telomerase activity at the same time in the same subjects. Limitations include the small sample size, and the use of only single timepoint TA assessment. Whereas LTL is a relatively stable marker, TA can change more quickly (Epel et al., 2010). Another limitation is the significant mean difference in ACE scores in the control and MDD groups, calling into question whether the different findings in the two groups are related to diagnosis vs. level of antecedent ACE. Future studies utilizing flow cytometry with cell separation will be needed to assess whether changes in average LTL are due to changes on a per-cell basis or due to a redistribution of leukocyte subpopulations (Lin et al., 2010). Finally, ACEs were assessed through retrospective self-reports, which may be subject to bias (Hardt and Rutter, 2004).

5. Conclusions

The present data are the first to relate ACEs to TA in any population and the first to relate ACEs to LTL in individuals with MDD. These data highlight biological sequelae of early life psychological and physical trauma and suggest that these sequelae may differ in depressed vs. non-depressed individuals. ACE-related alterations in cell aging in certain populations might also contribute to, and help explain, the excess medical morbidity and early mortality seen in adults with histories of multiple ACEs. In addition, given recent findings suggesting that parent–child relationships may play a key role in the associations between childhood adversity and telomere length (Asok et al., 2013; Brody et al., 2014), interventions promoting secure attachment relationships among children exposed to adversity (Ghosh Ippen et al., 2011; Lieberman et al., 2005) can also be examined for long-term biological benefits.

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Conflict of interest

EHB, JL and ESE were co-founders of a company providing telomere length measures.

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