Stress appraisals and cellular aging: A key role for anticipatory threat in the relationship between psychological stress and telomere length

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A large body of epidemiological evidence indicates that exposure to psychological stress increases risk for disease and early mortality (Boscarino, 1997; Dube et al., 2009; Ohlin et al., 2004; Schulz and Beach, 1999; Taylor et al., 2007). There are two striking but underappreciated features of the link between psychological stress and physical disease. The first is that many different forms of stress exposure, ranging from caregiving to low socioeconomic status to trauma exposure, increase risk for disease. The second is that psychological stress increases risk for many different types of physical disease, ranging from cardiovascular, autoimmune and neurodegenerative disorders to cancer. That associations exist between different types of stress exposures and different diseases suggests that common biological and psychological mechanisms may link stress exposure and disease risk.

The types of diseases that are more common in samples exposed to psychological stress provide clues about possible common biological mechanisms underlying the association between psychological stress and disease. Individuals who experience chronic or traumatic stress tend to be at increased risk for earlier development of diseases that typically emerge later in life, the chronic diseases of aging such as cardiovascular, autoimmune and neurodegenerative disorders and cancer (Dube et al., 2009; Ohlin et al., 2004; Schulz and Beach, 1999; Taylor et al., 2007). A potential common etiological factor across these diseases is “cellular aging” or the changes that occur in cells over time across the lifespan, eventually leading them to become functionally impaired and unable to proliferate (Blackburn, 2000; Chan and Blackburn, 2004; Sahin et al., 2011).

While cellular aging is multifaceted and difficult to precisely quantify, telomeres provide one index. Telomeres are DNA–protein...
complexes that cap the ends of chromosomes and protect against damage to the DNA that encodes genetic information. Telomeres shorten with somatic cell division and with exposure to oxidative stress, and evidence supports leukocyte telomere length as both a marker and potential mechanism of cellular aging (Blackburn, 2000; Sahin et al., 2011). Across studies, short leukocyte telomere length is associated with significantly higher risk for cardiovascular, autoimmune and neurodegenerative disorders and cancer (Cawthon et al., 2003; Goronzky et al., 2006; Willeit et al., 2010). Moreover, in line with the hypothesis that cellular aging is a potential common mechanism linking psychological stress and disease, short telomere length has been observed in individuals exposed to various forms of psychological stress (Cherkas et al., 2006; Damjanovic et al., 2007; Epel et al., 2004; Kiecolt-Glaser et al., 2011; O’Donovan et al., 2011a).

Individuals differ in their psychological and biological responses to stress. In particular, an individual’s appraisal or assessment of a specific psychological stressor determines their cognitive-emotional response, which in turn influences their biological response and hence the extent to which the stressor has the potential to “get under the skin” to influence physical health (Blascovich and Mendes, 2010). According to the classic Lazarus and Folkman “Transaction Model of Stress and Coping”, individuals who perceive that a stressor exceeds their resources to cope effectively will appraise the situation as threatening and exhibit a response characterized by threat-related cognitions and emotions such as worry and fear. In contrast, individuals who perceive that they have adequate resources to cope with a stressor will appraise it as challenging and exhibit a response characterized by challenge-related cognitions and emotions such as perceived control and excitement (Lazarus and Folkman, 1984). Subsequent research has shown that biological reactions to stressors appraised as threatening differ from those appraised as challenging, and that the former are associated with more harmful physiological reactions than are the latter (Blascovich and Mendes, 2010).

The degree to which individuals appraise stressors as threatening or challenging may reflect current and prior experiences of stress in addition to specific objective characteristics of the stressor (e.g., how dangerous the situation actually is) and specific characteristics of the individual (e.g., personality). For example, exposure to traumatic stressors can heighten sensitivity to threatening stimuli (Blackburn, 2000; Felmingham et al., 2010; Pine, 2003), and the chronic stress of growing up in a socioeconomically disadvantaged family has been associated with more threatening interpretations of ambiguous social situations in adolescents (Chen et al., 2004). We propose that other forms of psychological stress, particularly chronic stress, may also influence stress appraisals and heighten sensitivity to threatening stimuli. In particular, we propose that everyday stressors will be appraised as more threatening and less challenging against a backdrop of chronic stress because chronic stress depletes psychological and biological resources that are needed to deal with life stress. Higher threat and lower challenge appraisals of daily stressors would in turn lead to repeated and prolonged activation of harmful biological stress responses, which could promote cellular aging in chronically stressed individuals. However, at present, little is known about the relationship between stress appraisals and telomere length.

In the present study, we combine analyses at the levels of acute and chronic stress by examining threat and challenge appraisals of an acute laboratory stressor in chronically stressed caregivers and non-caregiving control participants in whom we also measured leukocyte telomere length. We hypothesized that: (1) higher threat appraisals and lower challenge appraisals will be associated with shorter telomere length; (2) caregivers will perceive an acute laboratory stressor as more threatening and less challenging than controls; (3) caregivers will have shorter telomere length than controls; and (4) there will be an indirect effect of caregiver status on telomere length through altered stress appraisals.

Methods

Participants

We recruited two groups of healthy postmenopausal women, caregivers and controls, to provide a clear contrast between groups with and without chronic stress. The group exposed to chronic stress included women who were providing at least 4 h per day of care, every day, to a relative with dementia and who reported high levels of perceived stress as indexed by a score of at least 12 on the 10-item Perceived Stress Scale, which represents the population mean in women (Cohen et al., 1983). The second group of women consisted of non-caregiving controls with similar mean age and body mass index (BMI) as the caregiver group, and low levels of perceived stress. For inclusion in the study, all participants had to be non-smoking and without major or unstable medical conditions or confounding medications as assessed by self-report and by physical exam by the study physician. Additionally, all participants had to pass a chemistry screening for normal glucose, electrolytes, thyroid, liver and kidney function. In all, 63 participants (n = 34 caregivers; n = 29 controls) were recruited through flyers and posters in the community, as well as from elderly service providers in the San Francisco Bay Area, California. Of these, 51 women participated in the acute stress task and had data on telomere length. One of these 51 participants was then excluded because of being an outlier with telomere length greater than 2.5 standard deviations from the mean telomere length of the sample. Characteristics of the full sample of 63 participants in the larger study and of the subsample of 50 participants in this study are described in Table 1. There were no significant differences between the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full Sample n = 63</th>
<th>Subsample n = 50</th>
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</thead>
<tbody>
<tr>
<td>Caregivers</td>
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<td>27 (54)</td>
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<tr>
<td>Duration of caregiving</td>
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<td>5–137</td>
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<tr>
<td>Median [IQR]</td>
<td>47 [34, 62]</td>
<td>48 [36, 60]</td>
</tr>
<tr>
<td>Age: range (Mean ± SD)</td>
<td>51–79</td>
<td>51–79</td>
</tr>
<tr>
<td>BMI: range (Mean ± SD)</td>
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<td>17.7–37.5</td>
</tr>
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<td></td>
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<tr>
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<td>38 (76)</td>
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<td>12 (24)</td>
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<td>5 (10)</td>
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<td>31 (62)</td>
</tr>
<tr>
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<td>11 (22)</td>
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<tr>
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<td>8 (16)</td>
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<td>1 (2)</td>
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<tr>
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<td>0</td>
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<td>Telomere length: range</td>
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<td>0.34–1.61</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td>(0.93 ± 0.30)</td>
<td>(0.94 ± 0.27)</td>
</tr>
</tbody>
</table>

Notes. Figures refer to n (%) unless otherwise specified. Duration of caregiving refers to time since caregiving began in months.
participants and non-participants on any of the demographic variables.

Procedures
During their first visit to the laboratory, participants fasted for 10 h and then donated blood, from the non-dominant arm between 08:00 and 10:00 h for telomere length measurement. During this visit participants also provided demographic information and completed questionnaire measures of perceived stress and neuroticism. At a second visit one week later, they ate a standardized lunch at 12:00 h and then had a 1-h resting baseline period while listening to relaxing music. Following this, participants were exposed to a modified form of the Trier Social Stress Test (TSST) between 14:00 and 17:00 h, in which they were asked to give a speech about their personal strengths and weaknesses and to perform a difficult serial subtraction math task aloud (Kirschbaum et al., 1993). The phases of the modified TSST included four 5-min stressful periods, including: (1) introduction to two trained evaluative, non-responsive audience members for description of tasks; (2) a quiet period for speech preparation and completion of a questionnaire assessing anticipatory threat and challenge appraisals; (3) delivery of speech; and (4) completion of math task. All tasks were performed in front of an evaluative audience who maintained neutral facial expressions and tone of voice throughout. Participants then immediately completed a questionnaire assessing retrospective threat and challenge appraisals. At the end of the session, participants were fully debriefed. All procedures were fully approved by the University of California San Francisco Committee on Human Subjects Research and written informed consent was obtained from all participants.

Measures
Threat and challenge appraisals
A self-report questionnaire completed before the TSST assessed anticipatory threat and challenge appraisals, and an analogous questionnaire completed after the TSST assessed retrospective appraisals. The questions were based on previous work (Mendes et al., 2007b). The anticipatory threat appraisal scale included six items pertaining to cognitive (e.g., the upcoming tasks will be very demanding) and emotional (e.g., how anxious do you feel about the upcoming tasks?) appraisals of the upcoming task. The anticipatory threat appraisal scale included eight items pertaining to cognitive (e.g., I have control over how I will do on the upcoming task) and emotional (e.g., how excited do you feel about the upcoming tasks?) appraisals, posed in the future tense. The retrospective appraisal scales included parallel items asking about the participant’s experience of the TSST (e.g., the tasks were very demanding), posed in the past tense. Items were responded to on a Likert scale ranging from −4 (strongly disagree) to +4 (strongly agree). Cognitive and emotional subscales for anticipatory and retrospective threat and challenge appraisals were converted into Z scores and summed to create four scales that showed acceptable reliability as indexed by Cronbach’s alpha: anticipatory threat appraisals (α = .80); retrospective threat appraisals (α = .75); anticipatory challenge appraisals (α = .87); and retrospective challenge appraisals (α = .75).

Neuroticism
The Big Five Inventory was used to assess neuroticism (John et al., 1991). This scale comprises eight items that assess emotional stability or neuroticism (e.g., “I see myself as someone who worries a lot”). Participants rate their agreement with the items on a 5-point Likert scale ranging from 1 (“disagree strongly”) to 5 (“agree strongly”). Internal consistency for the scale was acceptable (α = .84).

Perceived stress
The 10-item Perceived Stress Scale was used to assess psychological stress experienced during the last month, including the extent to which situations were experienced as unpredictable, uncontrollable and overwhelming (Cohen et al., 1983). Participants rated the extent to which they felt or thought a particular way in the previous month on a 5-point Likert scale ranging from 0 (“never”) to 4 (“very often”). Internal consistency was high (α = .93).

Education
Participants’ educational attainment was assessed with a single item on highest level of education by degree.

Body mass index (BMI)
Weight and height were measured by trained research assistants, and BMI was calculated as weight (kg) divided by height in meters squared (m²).

Leukocyte telomere length
Blood samples were collected in 10-ml heparin tubes (Becton-Dickinson, Franklin Lakes, NJ). Leukocytes were isolated and frozen at −80°C. DNA was extracted from leukocytes by the University of California San Francisco DNA bank. Genomic DNA isolation was performed using a standardized and quality-controlled PureGene DNA isolation system (Centra Systems, Minneapolis). DNA was analyzed for telomere length using quantitative polymerase chain reaction (qPCR) (Cawthon, 2002) with modifications as described in (Lin et al., 2010).

Data analysis
To examine if acute stress appraisals were associated with age-adjusted telomere length, we used linear regression models including age in the first step and appraisals in the second step of the model. In follow-up analyses, we adjusted for potential confounding and mediating factors by including BMI, education, perceived stress and neuroticism with age in the first step of separate linear regression models with appraisals in the second step. To examine if there was a relationship between caregiver status and telomere length through altered stress appraisals, we used a series of linear regression models to assess the extent to which: (1) caregiving status was associated with stress appraisals (a pathway); (2) stress appraisals were associated with telomere length (b pathway); and (3) caregiver status was associated with telomere length without (c pathway) and with (c’ pathway) stress appraisals in the model. Because of our small sample size, we used the vce (bootstrap) command in STATA Version 11 to estimate p values and confidence intervals (CI) based on 1000 resamples for all linear regression models. Results are presented as standardized regression coefficients (β) with p values and 95% CIs. However, the overall pattern of results was similar with and without bootstrapping.
To examine the indirect path representing the change in telomere length when caregiver status is kept constant and stress appraisals are changed to the level they would be at if caregiver status changed by one unit (ab pathway), we used bias-corrected bootstrapping procedure macros in SPSS (Lockhart et al., 2011; Preacher and Hayes, 2004, 2008). These procedures allowed us to estimate the indirect effect ab as well as 95% confidence intervals for the population value of ab based on the value of ab in 20,000 resamples of our data with replacement (Preacher and Hayes, 2004, 2008). The traditional and most widely used mediation analysis technique is the causal steps approach, which specifies a series.
of requirements needed in support of a mediation model (Baron and Kenny, 1989). This approach involves no formal significance test of indirect effects (ab pathway) and our study is underpowered for the widely used Sobel test of indirect effects (Fritz and Mackinnon, 2007). Bias-corrected bootstrapping approaches to mediation analysis based on asymmetric distributions provide more accurate estimates of mediation effects (Lockhart et al., 2011; Preacher and Hayes, 2004, 2008). This approach is also in line with recent methodological advances in mediation analysis, which emphasize that an indirect effect can occur even if the relationship between the independent and dependent variables is not statistically significant (Hayes, 2009; Mackinnon and Fairchild, 2009). We used Pearson’s correlations and Student’s t-tests to examine associations between continuous variables and group differences in continuous variables respectively. Means and standard deviations (SD) are provided for continuous variable as appropriate. Apart from the bootstrapped linear regression models that were conducted with STATA 11, all other statistical analyses were performed with SPSS 18.0.

Results

Acute stress appraisals and telomere length

Higher anticipatory threat appraisals were significantly associated with shorter telomere length \( (\beta = -0.32, \ p = 0.03, 95\% \ CI [-0.19,\ -0.01]). \) However, none of retrospective threat appraisals, \( (\beta = -0.17, \ p = 0.36, 95\% \ CI [-0.17,\ 0.78]) \), anticipatory challenge appraisals \( (\beta = 0.15, \ p = 0.38, 95\% \ CI [-0.06,\ 0.16]) \), or retrospective challenge appraisals \( (\beta = 0.05, \ p = 0.77, 95\% \ CI [-0.17,\ 2.09]) \) was significantly associated with telomere length.

Participants reporting higher anticipatory threat appraisals had higher levels of perceived stress \( (r = 0.34, \ p = 0.02) \), higher retrospective threat appraisals \( (r = 0.44, \ p = 0.002) \) and lower anticipatory challenge appraisals \( (r = -0.43, \ p < 0.001) \). However, there were no significant associations between anticipatory threat appraisals and BMI, neuroticism, or retrospective challenge appraisals and no significant differences in anticipatory threat appraisals between participants with and without an advanced degree. Moreover, none of the covariates were significantly associated with telomere length in this sample. Follow-up analyses separately adjusting for perceived stress, anticipatory challenge appraisals, or retrospective threat appraisals in addition to age indicated that the relationship between anticipatory threat appraisals and telomere length was independent of these potential covariates (all \( p < 0.05 \)) (see Fig. 1).

Altered stress appraisals: a mediator of the chronic stress–telomere length relationship?

Levels of perceived stress were significantly higher in caregivers \( (Mean = 19.78, \ SD = 4.97) \) compared with controls \( (Mean = 9.18, \ SD = 4.87) \), \( t(47) = 7.49, \ p < 0.001 \). Moreover, chronically stressed caregivers anticipated that the upcoming tasks would be more threatening \( (\beta = -0.36, \ p = 0.006, 95\% \ CI [-1.04,\ -0.18]) \) than did non-caregivers. After completing the tasks, the chronically stressed women rated them as more threatening than did controls \( (\beta = -0.29, \ p = 0.03, 95\% \ CI [-0.90,\ -0.04]). \) In contrast, there were no differences between chronically stressed women and controls on either anticipatory \( (\beta = 0.15, \ p = 0.27, 95\% \ CI [-0.21,\ 0.72]) \) or retrospective \( (\beta = -0.10, \ p = 0.45, 95\% \ CI [-0.28,\ 0.63]) \) appraisals of challenge. Combined, the significant relationships between caregiver status and anticipatory threat appraisals and between anticipatory threat appraisals and telomere length are consistent with an indirect effect of caregiver status on telomere length operating through anticipatory threat appraisals (Fig. 2).

In order to examine if there was indeed a significant indirect effect of caregiver status on telomere length through anticipatory

![Fig. 2](image-url). Illustration of theoretical direct and indirect effects of caregiver status on telomere length. Numbers represent unstandardized coefficients from linear regression with 95% confidence intervals in brackets. Path \( a \) represents the significant difference between caregivers and controls in anticipatory threat appraisals. Path \( b \) represents the significant relationship between anticipatory threat appraisals and telomere length. Path \( c \) represents the non-significant difference between caregivers and controls in telomere length, and path \( c' \) represents the non-significant difference between caregivers and controls including anticipatory threat appraisals in the model. Paths \( a \) and \( b \) represent the significant indirect effect of caregiver status on telomere length through anticipatory threat appraisals. Asterisks indicate statistical significance of the path coefficients, \( \* p < 0.05, \ ns, \ non-significant. \)
threat appraisals, we employed procedures as described in the data analysis section to estimate $a$, $b$, $c$, $c'$ and $ab$ as illustrated in Fig. 2. First, we confirmed the finding that caregivers had higher anticipatory threat appraisals than controls ($a = -0.61$, $b = -0.36$, $p = 0.008$, 95% CI [0.21, 1.44]). Second, linear regression confirmed the age-adjusted association between anticipatory threat appraisals and shorter telomere length when including caregiver status in the model ($b = -0.10$, $p = -0.31$, $p = 0.04$, 95% CI [0.19, -0.01]). Third, however, although caregivers had shorter age-adjusted telomere length (Mean T/S ratio = 0.90, SD = 0.33) than controls (Mean T/S ratio = 0.98, SD = 0.19), linear regression indicated that the groups were not significantly different on telomere length ($c = 0.08$, $b = 0.14$, $p = 0.32$, 95% CI [-0.07, 0.23]). However, the effect size for this non-significant relationship between caregiver status and telomere length was markedly decreased with anticipatory threat appraisals in the model ($c' = 0.02$, $b = 0.04$, $p = 0.79$, 95% CI [-0.13, 0.17]).

Bias corrected 95% confidence intervals indicated a statistically significant indirect effect of caregiver status on telomere length through anticipatory threat appraisals ($ab_{	ext{sample}} = 0.06$, $ab_{	ext{bootstrap}} = 0.06$, 95% CI [0.01, 0.16]). In follow-up linear regression analyses, we found that anticipatory threat appraisals were significantly associated with telomere length in caregivers ($t = -0.36$, $p = 0.03$, 95% CI [-0.34, -0.02]) but not in controls ($b = -0.22$, $p = 0.08$, 95% CI [-0.02, 0.15]). Thus, although the relationship between anticipatory threat appraisals and telomere length was in the same direction in both caregivers and controls, the association between higher anticipatory threat appraisals and shorter telomere length was statistically significant only in caregivers.

Discussion

The present study provides evidence of an association between higher threat appraisals and accelerated cellular aging as indexed by shorter age-adjusted telomere length. Women who experienced higher levels of threat in anticipation of an upcoming acute stressor had significantly shorter leukocyte telomere length than those who anticipated less threat. Moreover, participants exposed to chronic stress (i.e., caregivers) appraised the acute stress tasks as more threatening than did the low-stress non-caregiving controls and there was an indirect effect of caregiver status on telomere length through anticipatory threat appraisals. In particular, women experiencing chronic psychological stress appraised a standardized stressor as more threatening, and such high threat appraisals were in turn associated with shorter age-adjusted telomere length. These data extend a growing body of research showing associations between psychological stress and telomere length by suggesting exaggerated threat anticipation as a novel psychological pathway by which different forms of stress exposure might accelerate telomere shortening.

A growing body of clinical research indicates that conditions that foster exaggerated threat perception, such as childhood adversity and post-traumatic stress disorder, are associated with short telomere length (Kiecolt-Glaser et al., 2011; O’Donovan et al., 2011a; Tyrka et al., 2009). Our data extend this work by showing that greater anticipatory threat appraisals of a standardized stressor are associated with shorter telomere length in chronically stressed caregivers and that there is an indirect effect of caregiver status on telomere length through exaggerated anticipatory threat appraisals.

One might wonder how threat appraisals, which are measured as a state-like response to specific stimuli in the lab, could be linked to a long-term health indicator like telomere length. We view threat appraisals of the standardized acute stressor as a reflection of two factors – dispositional threat sensitivity and the acute state responses to the specific tasks at hand. The dispositional threat sensitivity component is relatively stable and likely reflects variance attributable to genetic factors that have relevance for threat-related information processing, including the serotonin transporter gene (Munafo et al., 2008). However, threat sensitivity is also likely to be shaped by life experiences through epigenetic modifications, changes in brain structure and function generated through neural plasticity, and shaping of cognitive-behavioral reactions (e.g., Ellis and Boyce, 2008). Given that telomere shortening takes place over long periods of time, we believe that the relatively stable threat sensitivity component of threat appraisals is likely to be driving the association between threat appraisals and telomere length. Our proposed model is that psychological stress exposure leads to exaggerated threat sensitivity, which drives more frequent and prolonged threat perception in daily life, which in turn promotes activation of the biological stress responses that can drive telomere shortening. Thus, we view threat sensitivity as a potential mediator of the relationship between chronic stress and telomere length.

An alternative model, which is also consistent with our findings, is that anticipatory threat appraisals moderate the relationship between chronic stress and telomere length; in other words, that only the combination of chronic stress exposure and high threat appraisals is associated with accelerated telomere shortening. This model would suggest that only individuals with a high degree of threat sensitivity – as indexed by their high threat appraisals of the standardized stressor – who are also chronically exposed to high levels of stress would show accelerated telomere shortening. However, the relationship between higher anticipatory threat appraisals and shorter telomere length was significant and robust in the full combined sample even when controlling for caregiver status. Nonetheless, this and other explanations of our findings remain possible and additional research is required to compare potential models. Such research could productively examine the rate of telomere length change over time in individuals with a high degree of threat sensitivity who are either confronting a chronic life stressor such as caregiving or not confronting any major life stressors. If exposure to chronic stress is associated with increasing threat sensitivity and associated accelerations in the rate of telomere shortening over time, this would support our proposed model. If threat sensitivity remains entirely stable over time in both chronically stressed and non-chronically stressed individuals and only the chronically stressed participants with high levels of threat sensitivity show accelerated telomere shortening, this would support the alternative model. Regardless of the outcomes of such future studies, the two models and the present data overlap in the conclusion that anticipatory threat appraisals play a key role in the relationship between chronic stress and telomere length.

The present data indicate that anticipated threat is more strongly associated with shorter telomere length than threat reported retrospectively about experiences during a stressor. Previous work indicates that anticipatory threat elicits cardiovascular responses equivalent to those associated with actual exposure to threat, underlining the potential importance of anticipatory appraisals as determinants of biological stress reactivity (Waugh et al., 2010). Given the survival value associated with a strongly attuned threat-detection system, the ability to anticipate threats is a human adaptation that has considerable benefits, even if as our data suggest, it also has costs (Neuberg et al., 2011; Stein and Nesse, 2011). Moreover, while the experience and recall of stressful events is constrained by perception and memory of those events, there are no such constraints on anticipated stressors leaving them more susceptible to the influence of cognitive biases. Finally, the anticipation of threat may be the most enduring form of psychological stress because people can perceive and worry about potential threats that are in the far-distant future.
Accumulating evidence indicates that exposure to real or imagined psychological threat activates multiple biological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, and inflammatory response (Dickerson and Kemeny, 2004; Dickerson et al., 2008; Mendes et al., 2007a). The mechanisms by which greater biological stress reactivity could result in short telomere length have yet to be fully elucidated. However, repeated and prolonged activation of biological factors with telomere length. In fact, while pessimism or psychological factors with telomere length. The present research was made possible by Grants from the Division of Behavioral and Social Research at the National Institute of Aging/National Institutes of Health R56 Grant (AG030424 to ESE), K08 Grant (MH64110-01A1) and Bernard and Barbro Foundation (EHB) as well as by a Society in Science: Branco Weiss Fellowship (AOD). The CTSP CCRC and the Core Immunology Lab were supported by NIH/NCCR UCSF-CTSI Grant No. UL1 RR024131. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of funders. Furthermore, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors would like to thank the participants in this study for the time and energy that they devoted to this project as well as Peter Bacchetti, Ph.D., Josh Woolley, MD/PhD and George...
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