Commentary

Biological Psychiatry: GOS

The Complex Relationship Between Early-Life Stress and Cellular Aging

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There is a well-established link between early-life stress (ELS) and an increased risk for psychiatric illness later in life, but less is known about the biological processes underlying this relationship. Not everyone subjected to ELS goes on to develop significant psychiatric symptoms in adulthood, suggesting that there are biological and environmental protective factors that may mitigate the effects of ELS on psychiatric sequelae or that there are other factors increasing the risk. Accelerated biological aging may be a link between stress and somatic as well as psychiatric symptom manifestations (1). One of the candidate biomarkers for this is leukocyte telomere length (LTL), an index of one aspect of accelerated cellular aging or biological age. LTL may serve as a cumulative measure of the number of cell divisions and degree of exposure to oxidative stress. Shorter LTL has been associated with old age somatic disorders, such as cardiovascular disease, cancer, and Alzheimer's disease, but also with a wide array of psychiatric disorders, with a possible dose-response relationship, meaning that individuals with greater symptom severity or longer illness duration tend to have the shortest telomeres (2). Childhood adversities have also been associated with short LTL later in life in most but not all studies (3). Despite a growing number of studies linking ELS to cellular changes, there are also several caveats in this field of research, including challenges in teasing apart the effects of ELS from those of lifestyle factors also known to be associated with shortened LTL.

The effects of ELS on LTL are complex and could be moderated by genetic predisposition (4) as well as timing (3) and duration of the stressor (5), just to name a few factors. In the current issue of *Biological Psychiatry: Global Open Science*, Ridout *et al.* (6) add more complexity to this issue. In a validated model of ELS in nonhuman primates called variable foraging demand (VFD), Ridout *et al.* (6) examined the relationship between ELS and adult LTL. In contrast with most of the literature, they found that nonhuman primates exposed to conditions of ELS had longer LTL in adulthood. In the VFD model, nursing monkeys are subjected to varying conditions of access to food, which is thought to disrupt maternal–infant attachment, leading to an unpredictable rearing environment and stress. Nonhuman primate models hold certain advantages over human studies in the field. The former study design can inherently control for several potential confounders, including baseline genetic differences in LTL, socioeconomic status, and diet. The findings by Ridout *et al.* (6) of an association between ELS and longer LTL in adulthood challenge us to think even deeper about the relationship between stress and cellular aging. As argued for by the authors, these findings may in fact be consistent with a compensatory model of telomere lengthening as an adaptive response to stress exposure. Longitudinal studies in humans show that while most people experience shortening of telomeres over time, some individuals instead display lengthening of telomeres (7). Although the mechanisms for such telomere elongation in some individuals are not fully understood, they may involve recruitment of telomerase, the major telomere lengthening enzyme (2). Both animal and human studies suggest that telomerase activity increases after acute stress exposure, perhaps as a compensatory response to protect telomeres from critical shortening due to oxidative stress and other cell damaging factors (2). Moreover, some studies have reported greater telomerase activity in clinical depression and stress-related conditions (2), which could also reflect a compensatory response to stressors. One caveat, however, is that several studies in both psychiatric and nonpsychiatric cohorts reported elevated telomerase activity in combination with shorter LTL, suggesting that recruitment of telomerase in the face of stress may sometimes be a futile compensatory effect, insufficient to fully counteract telomere shortening (2). However, the possible involvement of telomerase activation in the study by Ridout *et al.* (6) is not known because telomerase was not specifically assessed in this study.

The effects of stress on telomere shortening are likely dynamic and may depend on timing (3) or chronicity of the stressor (5), as well as the presence or absence of various resiliency factors, including strong social connections and healthy lifestyle choices (Figure 1) (7). One large-scale study found that early life traumatic events (e.g., physical abuse or having parents with substance abuse) predicted shorter LTL later in life, whereas financial problems (e.g., paternal unemployment or relocation due to financial difficulties) did not (8), suggesting that the effects of ELS on telomere shortening may also be contingent on the nature of the stressor. Although an exact translation of the VFD model into a human setting might be difficult to achieve, one might argue that conditions in the VFD model more closely resemble unstable living conditions of financial hardships rather than situations of physical abuse and more acute traumatic events. While it is indeed possible that the findings by Ridout *et al.* (6) of longer LTL in the VFD group reflect a compensatory biological response to ELS, it is also possible that this particular type of stressor did in fact not result in telomere attrition, while some other types of stressors might have.

Ridout *et al.* (6) further tested the relationship between plasma glucagon-like peptide 1 (pGLP-1) and LTL. Interestingly, they reported that higher adolescent levels of this brain-gut peptide in nonhuman primates were associated with longer

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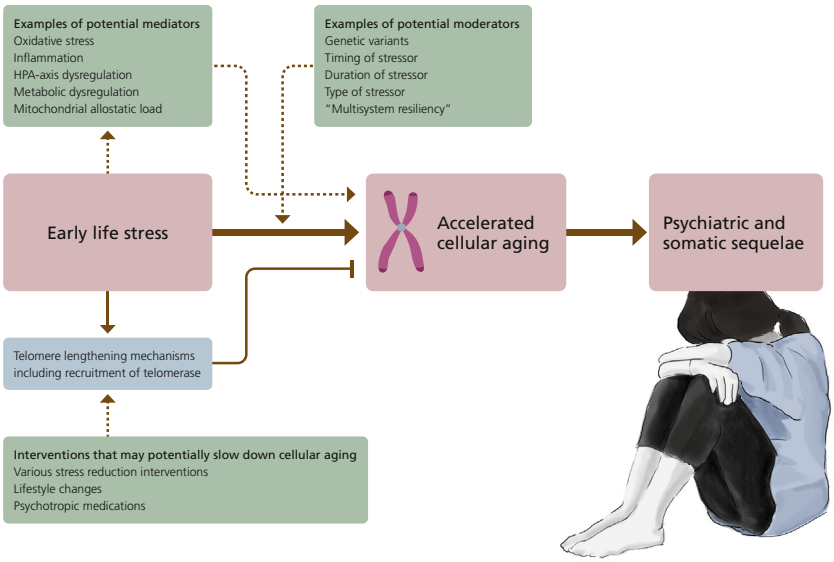

Figure 1. A tentative model of the relationship between early-life stress, cellular aging, and psychiatric and somatic sequelae, and examples of factors mediating and moderating this relationship. Stress may lead to accelerated cellular aging via various mechanisms including, but not limited to, oxidative stress, inflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, metabolic dysregulation, and mitochondrial allostatic load [as further reviewed in (1,2)]. The relationship between early-life stress and cellular aging may be moderated by several factors, e.g., genetic variants associated with serotonin and dopamine pathways (4) as well as timing, duration, and type of stressor (3,5,8). Moreover, "multisystem resiliency," an index comprising psychological stress resilience, social connections, and healthy lifestyle factors, may be a protective factor (7). Telomerase activation protects against telomere shortening. Several small-scale intervention studies suggest that both pharmacological and non-pharmacological interventions can increase telomerase activity [reviewed in (2,10)]. There are some studies, both in animals and in humans, suggesting that stress may lead to a compensatory telomerase increase (2), although it is not currently clear if this compensatory response is successful or futile in protecting against critical telomere shortening.

telomere length in adulthood, independent of ELS and body mass. This positive correlation between pGLP-1 and LTL adds to the growing body of evidence linking metabolic alterations to cellular aging. For instance, short LTL has been cross-sectionally associated with obesity, dyslipidemia, hyperglycemia, and metabolic syndrome (9). There are several potential mechanisms that could explain how GLP-1 relates to telomere shortening, including its effects on insulin sensitivity, feeding, inflammation, apoptosis, and oxidative stress. These mechanisms are known to influence cellular aging (2) and could link greater GLP-1 with longer LTL and should thus be investigated in future studies.

While the findings by Ridout *et al.* (6) are provocative and an important contribution to the published literature, they also raise several critical questions. One outstanding research question is the extent to which different indicators of biological aging—LTL, mitochondrial biomarkers, epigenetic aging and brain imaging markers, to name a few—relate to each other and to what extent they are actually causal and/or vulnerability factors rather than a consequence of psychopathology (1). To answer this question, we need longitudinal studies and predictive models taking several different biomarkers into account (1). Another important issue is how these observational or preclinical findings can be used in developing novel methods for treatment and diagnostics in clinical psychiatry. A more detailed understanding of which factors moderate and mediate the relationship between stress, biological alterations, and morbidity could help us identify novel targets for interventions before pathology arises (1). As reviewed elsewhere (1,10), there are also several small-scale studies linking various biomarkers of biological aging to antidepressant treatment response to both pharmacological and nonpharmacological interventions. Though interesting and potentially clinically meaningful, these findings need to be replicated in larger studies before these biomarkers are ready for clinical prime time. In summary, the article by Ridout *et al.* (6) is an important contribution in furthering our understanding of the biological mechanisms underlying risk and resilience in the face of ELS, and future studies should carefully consider these and other findings when exploring the clinical relevance of this research field.

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Article Information

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