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Depressive Symptoms Predict Change in Telomere Length and Mitochondrial DNA Copy Number Across Adolescence

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Abstract

Objective—Several studies have found associations between a diagnosis or symptoms of major depressive disorder and markers of cellular aging and dysfunction. These investigations, however, are predominantly cross-sectional and focus on adults. In the present study, we used a prospective longitudinal design to test the cross-sectional association between depressive symptoms in adolescents and telomere length (TL) as well as mitochondrial DNA copy number (mtDNA-cn).

Method—121 adolescents (Mean age=11.38, SD=1.03; 39 percent male) were followed for approximately two years. At baseline and follow-up, participants provided saliva for DNA extraction, from which measures of TL and mtDNA-cn were obtained. Depressive symptoms were obtained via the Children's Depression Inventory.

Results—There was no association between depressive symptoms and markers of cellular aging at baseline; however, depressive symptoms at baseline predicted higher rates of telomere erosion (β=−.201, p=.016) and greater increases in mtDNA-cn (β=.190, p=.012) over the follow-up period. Markers of cellular aging at baseline did not predict subsequent changes in depressive symptoms. Furthermore, including number of stressful life events did not alter these patterns of findings.

Conclusion—These results indicate that depressive symptoms *precede* changes in cellular aging and dysfunction, rather than the reverse.

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Keywords

depression; adolescence; cellular aging; telomeres; mitochondrial DNA copy number

Introduction

The association between mental and physical health is well documented; increasing evidence indicates that difficulties such as major depressive disorder (MDD) and related symptoms are associated with increased morbidity and mortality[1]. One mechanism underlying this association may be accelerated cellular aging; that is, experiences of depression may set into motion a physiological cascade that affects cellular processes, including telomere length (TL) and mitochondrial DNA copy number (mtDNA-cn). These physiological markers may play a causal role in mental health difficulties, or they may be epiphenomenal.

Findings concerning associations between TL and MDD are mixed. A recent meta-analysis found a significant negative association between TL and depressive disorders[2]. Further, severity of depression is significantly related to TL[3]. Adults with both current and past MDD or with clinically significant depressive symptoms have shorter TL than do adults with no history of MDD[2–4]. Few studies have examined the prospective association between depressive symptomatology and change in TL. One study found that participants with current or remitted anxiety or depressive disorders had shorter TL than did control subjects across both baseline and 6-year follow-up timepoints[5]; these authors found further that changes in symptoms over 6 years did not track with changes in TL. Two studies support the formulation that MDD precedes accelerated telomere erosion. MDD significantly predicted greater shortening of TL relative to healthy controls over the course of two years[6]. In addition, depressive symptoms were linked prospectively to telomere erosion in younger adults[7]; more specifically, higher levels of depressive symptoms at baseline predicted greater decreases in TL over 12 years. In contrast, two studies found no association between MDD and TL over time: There was no relation between TL and MDD over a 3-month longitudinal study[8], or in an 11-year study of older women (57 to 64 years)[9]. The equivocal nature of these findings underscores the fact that we still have much to learn about the nature of the relationship between depression and TL.

Whereas TL has received considerable attention in relation to MDD, we know much less about another putative biological marker of cellular dysfunction: mitochondrial DNA copy number (mtDNA-cn). Mitochondria are organelles responsible for cellular energy production that contain multiple copies of their own, free-floating DNA[10]. As previously noted, increased oxidative stress has been shown to be associated with aberrations in mtDNA-cn; the mechanism proposed to underlie this relation is an adaptive response to stress in which biogenesis of mitochondria increases[11].

Both TL and mtDNA-cn are considered markers of cellular aging[12]; mice exposed to stress exhibited greater mtDNA-cn and decreased TL relative to unstressed, age-matched, control mice[13]. Investigators have posited that processes involved in TL and mtDNA are co-regulated[14]; unfortunately, few studies have assessed both mtDNA and TL within the same

sample. Moreover, the directional nature of the association between depressive symptoms and cellular dysfunction is not clear; it has been posited that mitochondrial dysfunction may exacerbate or even play a causal role in depression[15]. While some studies with adults have found no relation between mtDNA-cn and depression[16–19], others have found that depression is characterized by reduced mtDNA counts[20,21], while still other investigations have found that depression is associated with increased mtDNA counts[14,22,23]. Moreover, TL and mtDNA may not be linked in their changes related to depression. For example, one study found that high levels of depressive symptomatology were associated with decreased TL over 10 years, but not with changes in mtDNA[17].

The vast majority of studies in this area have focused on the relation between depression and cellular aging in adults. Given that the median age of MDD onset is in young adulthood[24], studying longitudinal patterns prior to most individuals' first MDD episode reduces the likelihood of having associations influences by recurrent MDD. In the present study, we attempted to examine the relation between depressive symptomatology and mtDNA-cn and TL in adolescents. We also examined fluctuations in levels of TL and mtDNA-cn over time, and tested whether changes in these markers of cellular aging predicted severity of depressive symptoms. Finally, given that TL has been found to be adversely affected by stress-responsive systems, such as HPA-axis activity, increased oxidative stress, increased inflammation, and a dysregulated autonomic nervous system[25], we covaried for levels of the number of stressful life events experienced by participants, testing whether stress exposure would explain levels of both depressive symptoms and cellular aging[14,26].

Method

Participants

We used flyers and local media to recruit adolescents between 9 and 13 years of age on the basis of having experienced a range of early life adversity (e.g., to avoid having a very low-stress community sample). The mean age of the sample in the present study at baseline (Wave 1) was 11.38 years (SD=1.03); 39% of participants were male and 54% identified as white. We recruited only participants who were eligible to complete a neuroimaging scan (neuroimaging data are not included in this report). The study was approved by the Stanford University Institutional Review Board; participants and their parents gave assent and informed consent, respectively.

Participants were screened for initial inclusion/exclusion criteria through a telephone interview; potentially eligible individuals were then invited to the laboratory for in-person interviews and assessments. Inclusion criteria were that children be between 9–13 years of age and proficient in English. Exclusion criteria were factors that would preclude a neuroimaging scan (e.g., metal implants, dental braces), a history of major neurological or medical illness, severe learning disabilities that would make it difficult for participants to understand the study procedures and, for female participants, the onset of menses. Girls and boys were selected to not differ in pubertal stage; consequently, boys were older than girls. Pubertal status was assessed via self-report Tanner staging[27].

Participants returned to the lab approximately two years after the initial assessment (Wave 2; M=1.97 years, SD=0.34). At Wave 1, 211 participants had complete data with both depressive symptom scores and saliva; at the time we gave samples to the assaying lab at Wave 2, 122 participants had data with both depressive symptom scores and saliva data (of the original 211 participants, 43 did not return to the study after completing Wave 1 and 48 contributed samples after the cutoff date for these analyses). The present study, participants were included if they contributed saliva samples that yielded usable data across both time points, resulting in a final sample size of 121 participants (47 boys; 74 girls) with both depressive symptoms and saliva samples at both time points.

Procedure

At Waves 1 and 2, participants attended laboratory sessions with a caregiver, during which they completed questionnaires, provided saliva samples, and completed other assessments not included in the present study (e.g., neuroimaging scans). Participants were compensated for their time.

Measures

Children's Depression Inventory – Short Form—Participants reported on their symptoms of depression using 10-item CDI Short Form (CDI-S), which was developed to assess depressive symptomatology in children ages 8 to 17 years[28]. The original CDI and the CDI-S yield comparable results[28]. Responses to the CDI-S were scored on a 3-point scale, from 0 (*occurs once in a while*) to 2 (*occurs frequently*); we summed the 10 items to compute a total score. In this sample, the internal consistency of the CDI-S was acceptable (α=.74).

Stressful Life Events—At the initial assessment, children were interviewed about their lifetime exposure to 30 types of stressful events using a modified version of the Traumatic Events Screening Inventory for Children (TESI-C[29]). For more information about our protocol see[30–32]. Only stressors rated by the panel as being above a "mild stressor" were included. For the purposes of the present analyses, to compute life stress we summed the number of stressful events reported in the child's life from birth up to the time of the baseline assessment.

Cellular Markers

Genomic DNA was purified from 500 μl of saliva collected in the Oragene DNA Kit (DNA Genotek, Kanata, ON, Canada) with the DNA Agencourt DNAdvance Kit (cat. no. A48705; Beckman Coulter Genomics, Brea, CA, USA) according to the manufacturer's instruction. DNA was quantified by Quant-iT PicoGreen dsDNA Assay Kit (cat. no. P7589; Life Techonologies, Grand Island, NY, USA) and run on 0.8% agarose gels to check the integrity. DNA samples were stored at −80 °C. Parameters for the assaying of TL and mtDNA are presented in Supplement 1, available online.

Data Analysis

Cellular aging variables were examined for normality and outliers. One TL value was beyond 3 SD from the mean and was winsorized to the next closest value; no further transformations were conducted. We examined the association between depression scores and markers of cellular aging (i.e., TL and mtDNA-cn, examined independently) both cross-sectionally and longitudinally, covarying baseline age, pubertal stage, and sex. Given the potential for number of stressful life events to be relevant to models, this variable was included as an additional covariate following the initial model. In addition, for the longitudinal models, we included the additional covariates of baseline cellular aging and the length of the interval between the baseline and follow-up assessments. We computed a slope to examine change in cellular aging markers {(Wave 2–Wave 1 values)/(Wave 2–Wave 1 age)}. We used hierarchical linear ordinal least squares regression to examine the association between depression scores, treated linearly, and markers of cellular aging, over and above the effects of the covariates. In addition, we used the general linear model to confirm effects using a group-based approach to conceptualizing depression, with a cutoff score of ≥3 on the CDI-S used as a screening cutoff for elevated depression likelihood[33]. Effect sizes are reported below.

We additionally performed Benjamini-Hochberg multiple comparisons correction at a false discovery rate of 5% for all primary models. For details, see Table S1 and Supplement 1, available online.

Results

Participant Characteristics

Demographic and clinical characteristics of the sample are presented in Table 1.

Cross-Sectional Associations Between Depression and Cellular Aging

We first examined whether depression scores predicted TL assessed at the same wave, controlling for age, pubertal stage, and sex. The full model was not significant ($F(4,118)=1.37$, $p=.250$, $R^2=.044$): depression scores did not predict variance in TL over and above the effect of the covariates ($\beta=-.011$, $t(118)=-0.12$, $p=.903$, $\Delta R^2<.001$). Similar results were obtained for mtDNA-cn. Again, the full model was not significant ($F(4,118)=1.55$, $p=.191$, $R^2=.050$): depression scores did not predict variance in mtDNA-cn over and above the effect of the covariates ($\beta=-.067$, $t(118)=-0.73$, $p=.464$, $\Delta R^2=.004$). The inclusion of stressful life events in the model did not change the patterns of results, and in neither model did stressful life events significantly predict TL or mtDNA-cn.

Longitudinal Associations Between Depression and Cellular Aging

Next, we examined whether depression scores at Wave 1 predicted *change* in markers of cellular aging over a two-year period. The full model was significant ($F(6,113)=6.54$, $p<.001$, $R^2=.26$): depression scores predicted significant variance in change in TL over and above the effect of sex, pubertal stage, age at baseline, length of follow-up, and baseline TL ($\beta=-.201$, $t(113)=-2.44$, $p=.016$, $\Delta R^2=.04$). Further, including baseline life stress did not modify this association, and the effect of depression in the model was not attenuated by its

inclusion (β=−.239, t(112)=−2.75, p=.007, ΔR^2=.05). As can be seen in Figure 1A, higher depression scores predicted faster TL shortening over adolescence.

We then conducted this analysis examining mtDNA-cn. Again, the full model was significant (F(7,113)=10.46, p<.001, R^2=.39): depression scores predicted significant variance in change in mtDNA-cn over and above the effect of sex, pubertal stage, age at baseline, length of follow-up, and baseline mtDNA-cn (β=.190, t(114)=2.54, p=.012, ΔR^2=.04). Further, including baseline life stress did not modify this association; the effect of depression was not attenuated by its inclusion (β=.214, t(113)=2.72, p=.008, ΔR^2=.04). As can be seen in Figure 1B, higher depression scores predicted greater increases in mtDNA-cn over adolescence. TL measures were correlated significantly at the two waves (r(118)=.60, p<.001), but measures of mtDNA-cn were not (r(119)=.17, p=.064).

We also used a group-based approach to examine the associations between depression and change in cellular aging, comparing children who reported scores on the CDI-S of 3 or above (n=40) with children who reported scores of 2 or below (n=81). In an analysis of covariance (ANCOVA) with baseline age, pubertal stage, sex, number of stressful life events, follow-up duration, and baseline TL levels as covariates, depression group was significantly associated with TL slope (F(1,113)=4.68, p=.033, partial η^2=.04). Children with scores above the depression cutoff had significantly greater telomere erosion than did children with scores below the cutoff (M=−0.007, SE=0.001 vs. M=−0.003, SE=0.001; Cohen's d=−0.40). Similarly, in the ANCOVA conducted on Wave 2 mtDNA-cn with baseline age, pubertal stage, sex, number of stressful life events, follow-up duration, and baseline mtDNA-cn as covariates, depression group was significantly associated with mtDNA-cn slope (F(1,114)=5.84, p=.017, partial η^2=.05). Children with scores above the depression cutoff had significantly greater change in mtDNA-cn than did children with scores below the cutoff (M=6.79, SE=1.56 vs. M=2.10, SE=1.07; d=0.41).

Next, we tested a reverse directionality model to examine whether baseline TL and mtDNA-cn predicted change in depressive symptoms over and above sex, pubertal stage, age at baseline, length of follow-up, and baseline depression scores. Neither TL (β=.008, t(116)=1.08, p=.281, ΔR^2=.01) nor mtDNA-cn (β=−.060, t(116)=−0.73, p=.467, ΔR^2=.003) at baseline significantly predicted change in depressive symptoms over the course of the follow-up period. Including stressful life events did not change the pattern of associations.

Lastly, we examined whether changes in depressive symptoms over the period were associated with changes in TL and mtDNA-cn. After covarying for sex, pubertal stage, age at baseline, length of follow-up, baseline depression scores, and baseline cellular aging, change in depressive symptoms was not a significant predictor for either telomere erosion (β=−.035, t(112)=−0.36, p=.723, ΔR^2=.001) or mtDNA-cn change (β=.152, t(113)=1.74, p=.084, ΔR^2=.002).

Discussion

In this study we examined the prospective association between depression and changes in TL and mtDNA-cn in a sample of 121 children and young adolescents. Perhaps not

surprising given the mixed evidence regarding the associations between depression and cellular aging, we found that depressive symptoms were not associated cross-sectionally with either marker of cellular aging. There were, however, prospective associations between depressive symptomatology at baseline and both telomere erosion and increases in mtDNA-cn. In contrast, there was no association between baseline TL or mtDNA-cn and changes in depressive symptoms. These findings indicate that depressive symptoms may be causally related to changes in cellular aging. Although findings of prior research on cellular aging and depression have been mixed, meta-analyses have yielded a significant correlation between TL and depression[2,3], though these studies are primarily cross-sectional and thus have not examined the temporal nature of this association. Our findings examining the prospective association between depressive symptomatology and change in cellular aging are consistent with previous findings that the duration of participants' longest episode of depression predicted mtDNA count, and that shorter TL was significantly associated with earlier age of onset of individuals' most severe depressive episode[22].

Gotlib et al. found that healthy girls with a maternal history of depression had shorter TL than did their age-matched peers, suggesting that shorter TL portends depression[34]. It is important to note, however, that this study was cross-sectional and operationalized 'nondepressed' as not meeting diagnostic criteria for MDD. Given the present findings in an independent sample of young boys and girls, it appears that examining elevated levels of depressive symptoms is important in gaining a more comprehensive understanding of the association between depression and TL, as subclinical variations in depressive symptoms predict changes in cellular aging.

Previous studies have reported both higher[14,22,23] and lower[21,35] mtDNA-cn counts associated with depression. Far fewer studies have examined the relation between mtDNA-cn and psychopathology than is the case with TL. mtDNA-cn was positively correlated with anxiety, but not with depression, in a sample of individuals age 13–17 years[18], suggesting specificity in the association with mtDNA-cn. Our findings that there was no cross-sectional association between depressive symptoms and mtDNA-cn adds to the growing number of studies examining this association, and adds a prospective lens that supports the formulation that depression symptoms precede changes in mtDNA-cn.

Differences between our findings and those of previous investigations may be due in part to study design, source of the DNA, methods for assessing depression, and age of our participants. For example, we used a prospective longitudinal design to examine the temporal nature of the relation between depressive symptoms and changes in cellular aging, rather than assessing simpler cross-sectional associations between these constructs. We also examined TL and mtDNA-cn from DNA extracted from saliva, and it is possible that cell type influences these markers[19]. We assessed depressive symptomatology on a continuum, given formulations that depression is not best represented as a taxon[36]. Nevertheless, given evidence that diagnosed depression is associated with shorter TL[37], it will be important in future research to examine the issue of the relation between cellular aging and depression assessed as a binary vs. a continuous construct.

Both stress and depression have been found in previous research to be associated with shortened TL[38]; our analyses indicate that depressive symptoms predicted TL over and above the effects of stress, which was not a significant predictor in cross-sectional or longitudinal analyses. The interaction of stress and MDD is likely to be complex[39]; indeed, in a previous study, significant associations between stress and shortened TL were attenuated by controlling for depression status of the participants[40].

While documenting the temporal association is important for establishing the potential for causality, we are unable to provide insight into the mechanism of such effects. However, depression has been implicated in chronic activation of the sympathetic nervous system, and in increased blood glucose levels[41]. Chronically elevated glucose levels have been shown to damage mitochondrial function, producing effects such as reduced quality control in mtDNA replication and increased reactive oxygen species (ROS) production[12]. In turn, evidence from in vitro studies indicates that increased circulation of ROS has been shown to shorten TL[42], and to increase mtDNA-cn by damaging existing mitochondria and triggering replication[43]. Cross-species research is most likely to be able to inform our understanding of causal and mechanistic processes regulating the relation between cellular aging and depressive symptoms.

We should note two limitations of this study, in addition to the possibility of cell type influencing the generalizability to other studies. First, we focused on depressive symptoms assessed with the CDI-S. Examining symptoms of other disorders that are associated with TL and/or mtDNA-cn will be important in determining the specificity and boundary conditions of the present findings. Second, while we found no evidence that stressful life events predicted change in cellular aging markers, we cannot rule out the possibility that intervening stressful events played a role in leading to patterns reported in this study. Given evidence of stress-generation in depression[44], this remains a possible pathway to explain the link between depression and aging processes. As a related point, while this sample has been previously characterized on the basis of type, severity, and timing of stressful experiences[30,45], its generalizability is not known.

Despite these limitations, the present study is important in demonstrating that depressive symptoms predict the rate of cellular aging in children and young adolescents. It will be important in future work to examine factors that may buffer individuals from experiencing accelerated cellular aging. For instance, one study found that lifestyle factors such as frequency of exercise and social support networks, termed ‘multi-system resiliency,’ were positively associated with longer telomeres and, conversely, that shortened telomeres were associated with depression only in individuals with lower levels of multisystem resiliency[46]. Environmental factors that have been associated with the onset of depression have also been found to moderate risk related to cellular aging. For example, high-risk children whose parents were high in parental responsiveness had shorter TL than did their high-risk peers whose parents were less responsive[47]. If replicated, these findings suggest that preventing depression will have long-term health benefits through reducing rates of telomere erosion and increases in mtDNA-cn.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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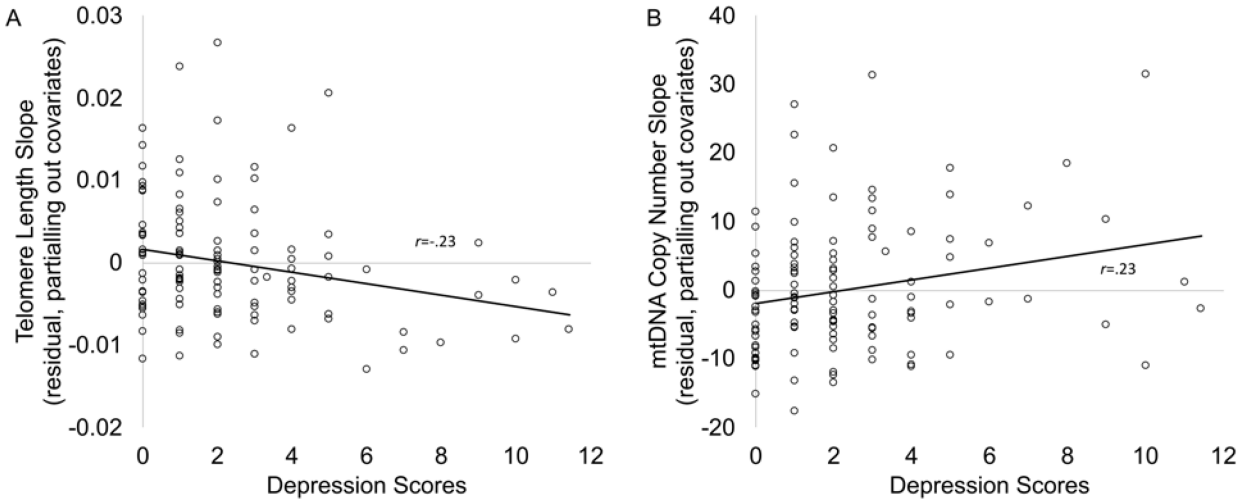

Figure 1. Depressive Symptoms and Changes in Cellular Aging Markers

Note: *Depressive symptoms predict change over adolescence in (A) telomere length and (B) mitochondrial DNA copy number. These changes are found over and above the covariates of sex, age at baseline, pubertal status at baseline, follow-up duration, number of stressful events reported, and baseline levels of cellular aging. mtDNA = mitochondrial DNA.*

Table 1:

Sample Demographic and Clinical Characteristics (N=121)

Variable	M (SD) or %
Age Wave 1	11.38 (1.03)
Pubertal Stage Wave 1	2.14 (0.77)
Sex (Percent Male)	39%
Race/Ethnicity[a,b]	
White	47%
Black/African American	8%
Hispanic	10%
Asian	12%
One than one race	13%
Other	8%
Not provided	1%
Family Income[a,b]	
Less than $25,000	7%
$25,001–$75,000	17%
$75,001–$150,000	34%
More than $150,000	35%
“Don’t know”	4%
Not provided	3%
Stressful Life Events at Baseline	3.92 (2.82)
Depression Score Wave 1	2.29 (2.51)
Telomere Length Wave 1	1.50 (0.25)
mtDNA-cn Wave 1	513.29 (176.94)
Age Wave 2	13.35 (1.05)
Telomere Length Wave 2	1.39 (0.26)
mtDNA-cn Wave 2	600.68 (231.34)

Note: mtDNA-cn = mitochondrial DNA copy number.

[a]Data concerning race/ethnicity were obtained from a diagnostic interview with the children and do not treat race and ethnicity separately.

[b]Values do not add to 100 due to rounding