Telomere Shortening and Mood Disorders: Preliminary Support for a Chronic Stress Model of Accelerated Aging

Naomi M. Simon, Jordan W. Smoller, Kate L. McNamara, Richard S. Maser, Alyson K. Zalta, Mark H. Pollack, Andrew A. Nierenberg, Maurizio Fava, and Kwok-Kin Wong

Background: *Little is known about the biological mechanisms underlying the excess medical morbidity and mortality associated with mood disorders. Substantial evidence supports abnormalities in stress-related biological systems in depression. Accelerated telomere shortening may reflect stress-related oxidative damage to cells and accelerated aging, and severe psychosocial stress has been linked to telomere shortening. We propose that chronic stress associated with mood disorders may contribute to excess vulnerability for diseases of aging such as cardiovascular disease and possibly some cancers through accelerated organismal aging.*

Methods: *Telomere length was measured by Southern Analysis in 44 individuals with chronic mood disorders and 44 nonpsychiatrically ill age-matched control subjects.*

Results: *Telomere length was significantly shorter in those with mood disorders, representing as much as 10 years of accelerated aging.*

Conclusions: *These results provide preliminary evidence that mood disorders are associated with accelerated aging and may suggest a novel mechanism for mood disorder-associated morbidity and mortality.*

Key Words: Aging, bipolar, major depressive disorder, mood disorder, stress, telomere

Excess medical morbidity and mortality have been clearly associated with bipolar disorder (BPD; Kupfer 2005) and particularly with major depressive disorder (MDD), including elevated rates of diseases of aging such as cardiovascular disease and possibly cancer, even after adjustment for differences in health-related behaviors such as smoking and exercise (Evans et al 2005; Everson-Rose and Lewis 2005; Gump et al 2005; Penninx et al 1998; Wassertheil-Smoller et al 2004). Little is known about the biological mechanisms underlying this excess risk, however.

"Stress" may be conceived of as a challenge or threat to homeostasis, which generally induces a stress response as an attempt to restore homeostasis. Depression has been conceptualized as a dysregulated activation of the generalized stress response (Chrousos 1998; Raison and Miller 2003). Chronic activation of stress response mediators, although adaptive in the short term, can result in chronic "wear and tear" to tissues or organ compartments (Chrousos 1998); McEwen (2003) has elegantly modeled mood and anxiety disorders as chronic stresses with chronic biological adaptations that result in long-term biological damage.

Telomeres are specialized nucleoprotein complexes at the ends of linear chromosomes that function to "cap" chromosomal termini and prevent end-to-end recombination and thus serve a critical role in the maintenance of chromosomal integrity (Blackburn 2000, 2001). In normal human cells, telomerase levels are insufficient to maintain telomere length resulting in progressive attrition with each cell division; thus, metered loss of telomeres can serve as a cellular mitotic clock that ultimately limits the number of cell divisions and cellular life span. Increased cellular turnover in the presence of stress-related oxidative damage further exacerbates accelerated telomere shortening and ultimately causes replicative senescence and organ degeneration because stem and precursor cells can no longer replicate and maintain homeostasis. Evidence suggests that telomere driven replicative senescence of cells may be primarily a cellular stress response (von Zglinicki et al 2005), but little is known about the activation of the telomere-shortening response by organismal stress. Accelerated telomere shortening has already been linked to increased rates of cancer and aging in animal models (Wong and DePinho 2003); however, although physiologic stresses have been clearly linked to biological measures of accelerated aging (Toussaint et al 1998), little is known about the impact of chronic psychologic stress. Consistent with our hypotheses, Epel and colleagues (2004) recently demonstrated that the chronicity and perceived severity of psychosocial stress (caring for a chronically ill child) was directly associated with accelerated telomere shortening.

In this study, we propose that chronic stress associated with mood disorders results in accelerated organismal aging due to stress-related oxidative damage to cells; thus, we hypothesize that individuals with chronic MDD or BPD will have shorter telomeres than age matched nonpsychiatrically ill control subjects. Evidence for accelerated aging would offer a novel potential mechanism for the excess morbidity and mortality associated with mood disorders.

Methods and Materials

Telomere Study Sample Selection

The sample comprised 88 individuals: 15 with MDD and no lifetime anxiety disorder, 15 with BPD with a current comorbid *Diagnosis and Statistical Manual* (4th ed., DSM-IV) anxiety disorder, 14 with BPD and no anxiety, and 44 age-matched control subjects. Psychiatric diagnoses were established with the

From the Department of Psychiatry (NMS, JWS, AKZ, MHP, AAN, MF), Massachusetts General Hospital and Harvard Medical School; Department of Medical Oncology (KLM, RSM, K-KW), Dana Farber Cancer Institute; and Center for Human Genetic Research (JWS), Massachusetts General Hospital, Boston, Massachusetts.

Address reprint requests to Naomi M. Simon, M.D., M.Sc., Associate Director, Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Simches Research Building, 185 Cambridge Street, Suite 2200, Boston, MA 02114; NSIMON@Partners.org.

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Table 1. Sample Characteristics

Diagnosis	Full Sample (n = 88)	Control (n = 44)	Full Mood Sample (n = 44)	MDD (n = 15)	Bipolar no Anxiety (n = 14)	Bipolar plus Anxiety (n = 15)
Age years (mean ± SD)	50.8 ± 8.0	50.5 ± 8.36	51.1 ± 7.7	50.3 ± 7.5	51.5 ± 8.2	51.6 ± 7.8
Gender n (%) female	40 (45)	19 (43.2)	21 (47.7)	8 (53.3)	6 (42.9)	7 (46.7)
Ethnicity[a] n (%) Caucasian	80 (93)	41 (93.2)	40 (93.0)	14 (100.0)	13 (92.9)	13 (86.7)
Lifetime smoking,[b] n (%) yes	27/73 (37)	13/44 (29.6)	14/29 (48.3)	2/9 (22.2)	6/10 (60)	6/10 (60)
Duration of illness,[c] years (mean ± SD)	N/A	N/A	31.8 ± 11.2	25.7 ± 12.1	36.7 ± 11.8	33.5 ± 6.3

MDD = major depressive disorder.
[a]Ethnicity data was missing for 2 patients.
[b]Smoking data was available only for a subset (83%) of the patient sample and are presented accordingly.
[c]$p < .05$ in analysis of variance of duration of illness in three mood groups.

Structured Clinical Interview for DSM-IV (SCID-IV; First 1994), and DNA was collected for a genetic study of mood disorders at Massachusetts General Hospital (MGH; see Simon et al 2003). Data regarding age, race, and the presence or absence of lifetime smoking were collected concurrent with sample collection. All patients had provided informed consent that allowed future DNA analyses to be performed, and the Institutional Review Board at MGH approved all study procedures for the study. The oldest 15 patients with BPD plus anxiety were selected; then patients were age matched to each other in sets of three (across diagnosis) within 6 years.

In addition, each patient was age matched within 4 years to a control (see demographics in Table 1) from 300 DNA samples in the Healthy Volunteer Specimen Bank (HVS) at the Harvard Medical School—Partners Healthcare Center for Genetics and Genomics. Healthy volunteers had also signed informed consent specifically allowing future DNA analyses. A thorough medical history and physical exam was performed to exclude all active diseases and current medication use and to obtain information such as lifetime tobacco use (yes or no). Specifically, participants were asked whether they had ever been diagnosed with or treated for depression or anxiety and were excluded if they responded in the affirmative.

Telomere Length Assessment Methods

DNA was extracted from leukocytes. Telomere length was assessed with standard quantitative Telomere Southern blot analyses (Bodnar et al 1998). To improve quantification of the gel results, in addition to exposure to autoradiographic film (Kodak Biomax-ER, Rochester, New York), the radioactive signal from the gels was quantified using a phosphor-imager (Fuji imaging system, FLA 2000, New York, New York). Fuji Film Image Reader Version 1.4E software (Fuji, New York, New York) was then used to draw a grid object (25 boxes) over each lane from 24 to 2.5 kb, allowing quantification of pixel density for each box. Molecular weight size standards were used to calibrate the molecular weight associated with each box for each individual gel. The mean optical density (OD) was then calculated using the following formula: mean OD box position = Σ (OD_i * box position)/Σ (OD_i), and the box corresponding to the mean OD was then compared with the kb size standard ladder for the gel to determine the mean terminal restriction fragment (TRF) size for that sample.

Statistical Methods

Statistical analyses were performed with STATA 8.0 (STATA Corporation). Univariate analyses consisted of t tests for continuous measures, analysis of variance for telomere length among mood subgroups, and Fisher's Exact test for dichotomous variables (e.g., gender). Linear multiple regression analyses were used with telomere length as the dependent variable to allow adjustment for covariates for age, gender, and smoking. Data were stratified by gender in follow-up analyses.

Results

There was no significant difference in age or gender among the four groups (Table 1). Telomere length did not differ between the three mood disorder groups (Table 2; Figure 1), and thus the mood groups were combined for analyses. The variances of the telomere length data in the patient versus control samples were not significantly unequal (F test of homogeneity of variances). Telomere length was significantly shorter in the combined mood disorder group (n = 44) than control subjects (n = 44: t = 3.16, p = .002; mean difference 660 base pairs [bp]: Table 2) and remained so after adjustment for linear age and gender as covariates in a linear regression analysis of telomere length [mood disorder $\beta = -.65$, $t = -3.11$, $p = .003$; linear age $\beta = -.01$, $t = -1.03$, $p = .3$, gender $\beta = .04$; $t = .17$, $p = .9$: overall model $F(3,84) = 3.66$, $p = .016$, adjusted $R^2 = .08$], and after the addition of lifetime smoking history [mood disorder $\beta = -.84$, $t = -3.47$, $p = .001$: overall model $F(4,68) = 3.83$, $p = .007$, adjusted $R^2 = .13$]; smoking itself was not predictive of telomere length (smoking $\beta = .36$, $t = 1.4$, $p = .17$), although smoking data were incomplete (17% missing).

In follow-up analyses stratified by gender with adjustment for age and smoking, mood disorder was significantly predictive of shorter telomere length for both men [mood disorder $\beta = -.83$, $t = -2.27$, $p = .029$: overall model $F(3,35) = 2.11$, $p = .12$, adjusted $R^2 = .08$] and women [mood disorder $\beta = -.96$, $t = -2.79$, $p = .009$: overall model $F(3,30) = 3.28$, $p = .034$, adjusted $R^2 = .17$].

To ensure that our findings were not overly influenced by

Table 2. Mean Telomere Length by Diagnosis

Diagnosis	n	Telomere Length (kb) Mean (SD)	Range (kb)
Full Sample	88	7.31 (1.03)	5.61–10.30
Control	44	7.64 (1.10)	5.69–10.30
Any Mood Disorder	44	6.98 (.84)	5.61–8.73
Major Depressive Disorder	15	6.87 (.89)	5.61–8.31
Bipolar, No Anxiety	14	6.96 (.81)	5.89–8.73
Bipolar plus Anxiety	15	7.10 (.86)	5.61–8.31

Mean represents the sample mean (the group mean of the individual mean telomere lengths measured by telomere southern analyses), and range represents the upper and lower limits for individual participant's mean telomere lengths within each subsample.

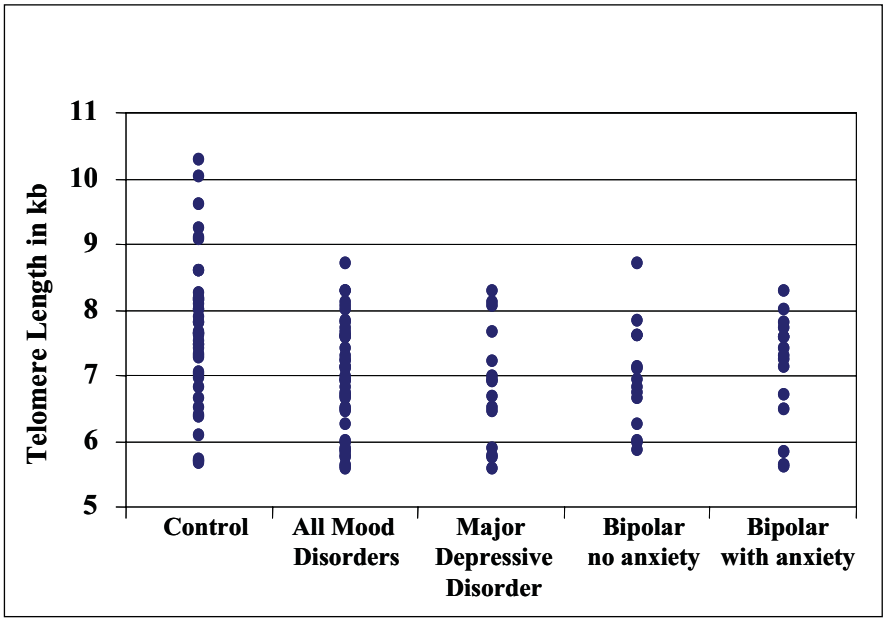

Figure 1. Patients with mood disorders have shorter telomere lengths than age-matched control subjects. A scatter plot of the mean telomere length for each study participant is displayed. The y axis represents telomere length in kilobases. The x axis represents the control group and the combined mood disorder groups, as well as the three separate diagnostic categories that comprised the combined mood disorder group. Each filled circle represents the value for an individual study participant (with some overlap).

outliers, we reran our regression analysis (with covariates for age, gender, and lifetime smoking) eliminating the six controls whose telomere lengths exceeded the longest patient telomere length (and thus all control telomere lengths > 9.0 kb): mood disorder remained significantly associated with shorter telomere length (mood disorder $\beta = -.58$, $t = -2.94$, $p = .005$), further supporting the robustness of our findings. Furthermore, we examined the unadjusted linear effect of age in our control sample to allow comparison with other studies of normal human telomere length changes with age and found a 31-bp decrease in mean telomere length per year ($\beta = -.031$, $t = -1.57$, $p = .125$), consistent with effects seen in prior studies (Iwama et al 1998; Valdes et al 2005); however, this effect did not achieve statistical significance in our sample selected for relatively older age.

Discussion

Our study provides preliminary evidence that mood disorders are associated with accelerated telomere shortening, a measure of accelerated aging. As such, our results suggest a novel mechanistic explanation contributing to the excess aging-related morbidity and mortality seen in mood disorders. Substantial evidence supports the association of MDD with abnormalities in stress related biological systems, such as the hypothalamic–pituitary–adrenal (HPA) axis and inflammatory responses (Glaser and Kiecolt-Glaser 2005; O'Brien et al 2004; Pariante and Miller 2001; Raison and Miller 2003). These dysregulated stress response systems could provide a basis for telomere shortening and accelerated aging seen in our study.

In support of our model of detrimental physiologic downstream effects of chronic mood disorder, breast cancer has been linked to chronic depression with severe episodes, with initial onset at least 20 years before breast cancer diagnosis (Jacobs and Bovasso 2000). Perhaps the strongest cancer data are in the elderly, a time of already shortened telomeres due to aging: Penninx and colleagues (1998) reported a hazard ratio of 1.88 (95% confidence interval 1.13–3.14) for new onset cancer diagnoses over 3.8 years of prospective follow-up in chronically depressed individuals aged 71 and older.

Accelerated telomere shortening has been reported in another disease of aging, cardiovascular disease: adults aged 40–55 years with myocardial infarctions (MIs) had significantly shorter telomeres (approximately 300 bp) than control subjects, using the telomere Southern methodology (Brouilette et al 2003). These data support a role of biological aging in coronary heart disease and are of particular interest given the elevated rates of cardiovascular disease documented with MDD, even though the specificity of this effect is still being determined (Everson-Rose et al 2004; Gump et al 2005; Wassertheil-Smoller et al 2004). Nonetheless, there is some variability in estimates of the linear effect of age on telomere length in humans, including rates of loss of 27 bp per year (Valdes et al 2005), 41 bp per year (Iwama et al 1998), and 59 bp per year (Rufer et al 1999), and our own (nonsignificant) estimate of 31 bp per year. Even conservatively choosing the highest normal yearly age-related shortening (Rufer et al 1999), however, our finding of mood disorder–associated telomere shortening of 660 bp represents upward of 10 years of accelerated aging and is greater than that reported with premature MI or for caretaker stress (mean reduction 550 bp; Epel et al 2004).

Because of the pilot nature of our study, we were unable to control for all potential confounders, such as trauma or stressful life event exposure, medication use, or subjective levels of stress. In addition, because there was no structured psychiatric interview of the control subjects, it is possible that some patients with mood or anxiety disorders were included in the control sample; however, such misclassification would be expected to attenuate rather than magnify the true case–control difference. Power was limited by our relatively small sample size, which also prevented the use of additional matching factors. The role of race and socioeconomic status on telomere length remains to be elucidated; our sample was predominantly Caucasian, and this may limit generalization to other groups. Furthermore, although a prior study has supported an association of obesity with shorter telomeres (Valdes et al 2005), we did not have obesity data available and thus cannot determine its potential role as a confounder of the mood disorder effect. Finally, it remains unknown whether similar differences in telomere length compared with age-matched control subjects might be present in individuals early in the course of mood disorder; longitudinal

studies examining telomere lengths over time in individuals, although difficult, would be more definitive.

Our study is the first to demonstrate accelerated telomere shortening in mood disorders, or in any chronic psychiatric disorder, and suggests that chronic mood disorders contribute to acceleration of aging processes. Although future studies are needed to establish a direct link between accelerated telomere shortening in mood disorders and the development of medical disorders, confirmation of our suggestive data could open new avenues of research into accelerated aging as a mechanism contributing to the poorly understood and undertreated issue of MDD and medical comorbidity (Evans et al 2005; Everson-Rose and Lewis 2005; Gump et al 2005; Penninx et al 1998; Wassertheil-Smoller et al 2004) and may potentially reveal novel pathways for intervention to reduce the detrimental effects of MDD. These initial findings linking accelerated telomere shortening with mood disorders further suggest the intriguing possibility that antioxidants or antiinflammatory agents could aid in prevention of stress-related diseases of aging for individuals with mood disorders. Significantly more work is needed before these hypotheses are confirmed.

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