HHS Public Access

Author manuscript

Psychosom Med. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Psychosom Med. 2016 September ; 78(7): 772–775. doi:10.1097/PSY.0000000000000373.

Psychiatric Disorders, Morbidity, and Mortality: Tracing Mechanistic Pathways to Accelerated Aging

Janice K. Kiecolt-Glaser, PhD and **Stephanie J. Wilson, PhD**

Ohio State Institute for Behavioral Medicine Research (JKK and SJW) and the Department of Psychiatry and Behavioral Health (JKK), The Ohio State University College of Medicine, Columbus, Ohio, USA

Abstract

A recent meta-analysis published in Psychosomatic Medicine provides convincing evidence that certain psychiatric populations have shorter telomeres than nonpsychiatric controls, in accord with the strong evidence linking psychiatric disorders with premature mortality. After addressing the clinical significance of shorter telomeres, this editorial describes mechanistic pathways that lead to telomere shortening. Additionally, two other novel methods for measuring biological markers of accelerated aging are briefly discussed, DNA methylation and cellular senescence based on $p16^{INK4a}$; these innovative approaches could be used to confirm and extend our understanding of psychiatric patients' increased health and mortality risks.

Keywords

psychiatric disorder; telomere; mortality; DNA methylation; p16INK4a; inflammatory response

Psychiatric patients have a greater risk for premature all-cause mortality than the general population. Epidemiological studies show that the life expectancy for all major psychiatric diagnoses is reduced by 7–24 years (1). Indeed, psychiatric illness takes a toll as great or greater than the 8–10 year difference exacted by heavy smoking (1).

Highlighting one potential mechanistic pathway to premature mortality, the excellent meta-analysis from Darrow and colleagues (2) provides convincing evidence that certain psychiatric populations have shorter telomeres than nonpsychiatric controls. Other recent meta-analyses have only addressed depression and telomere length, but these authors show that the effects are broader; depressive disorders, anxiety disorders, and post-traumatic stress disorder (PTSD, one of the anxiety disorders), had relatively larger effect sizes than psychotic and bipolar disorders. Psychiatric patients are more likely to have poorer health behaviors including smoking, poor diets, sedentary lifestyles, and greater alcohol/drug use compared to nonpsychiatric populations, but the differences in telomere length persist even after adjusting for these factors (2). Accordingly, Darrow et al. suggest that the differences may be mediated by accelerated cellular aging.

Address correspondence to Janice K. Kiecolt-Glaser, Ph.D., Institute for Behavioral Medicine Research, Ohio State University College of Medicine, 460 Medical Center Drive, Columbus, OH 43210, USA.

In this commentary we first address the clinical significance of shorter telomeres, and then we explore mechanistic pathways that lead to telomere shortening. We end by highlighting two other novel biological markers of accelerated aging that could be used to confirm and extend our understanding of psychiatric patients' increased health and mortality risks.

Telomeres and health

Telomeres have clinical significance for health: a growing literature has linked shorter telomeres with a range of negative outcomes from poor health behaviors to mortality (3). Though telomeres typically shorten over the lifespan, chronological age accounts for less than 10% of the variance in human telomere length (3). Accordingly, telomeres predict mortality and aging-related disease incidence independent of chronological age. For example, in a sample of people ages 60 or older, the mortality rate from infectious disease was more than eight times higher among those with shorter telomeres than those with longer telomeres, and heart disease deaths occurred more than three times as often in the former than the latter (4). Even after adjusting for age and other key risk factors including BMI, substance use, physical activity, blood pressure, and cholesterol levels, telomere shortening predicted all-cause mortality in a Danish population-wide study (5). Likewise, telomere shortening has been associated with the occurrence of many common age-related morbidities including dysregulated immune function, cancers, diabetes, and multiple aspects of cardiovascular disease (3, 6).

Conversely, reductions in inflammation and/or oxidative stress may affect telomere length. In a randomized controlled trial, four months of omega-3 supplementation significantly reduced both inflammation and oxidative stress and simultaneously lengthened leukocyte telomeres (7). Other researchers have also shown that telomeres can grow under certain conditions (8–12).

In addition to explaining the route from psychiatric disorders to mortality, telomere shortening may also exacerbate the vulnerability of psychiatric patients to premature death. For example, although depressive symptoms were associated with increased mortality and a shorter disease-free survival time among bladder cancer patients at diagnosis, patients who had both higher depressive symptoms and short telomeres had a four-fold increased mortality risk (13).

Mechanistic pathways to telomere shortening

Telomeres can be maintained or lengthened by telomerase, an intra-cellular enzyme that adds telomeric DNA to shortened telomeres (3). Telomere length is also regulated in part by exposure to proinflammatory cytokines and oxidative stress (3, 14, 15). Inflammation triggers T-cell proliferation, one known cause of telomere shortening (3). Oxidative stress promotes telomere erosion during cellular replication, and thus leukocyte telomere shortening reflects the joint burden of inflammation and oxidative stress. Inflammation and oxidative stress are both heightened in anxiety and depressive disorders (16, 17).

Many psychiatric disorders have shared genetic underpinnings (2). Comparing across the individual diagnoses that were most strongly associated with telomere shortening in Darrow

and colleagues' (1) analysis — the anxiety disorders (including PTSD) and depressive disorders— reveals a common phenomenology: an exaggerated inflammatory reactivity to stressors. The ability to minimize inflammatory responses to stressful encounters influences the burden that stressors place on an individual. Larger, more frequent, or more persistent stress-related changes in inflammation would have negative consequences for health, including a greater inflammatory impact on telomeres.

Prior depression may sensitize individuals such that they become more responsive to subsequent stressors and have a greater risk for future depressive symptomatology (18, 19). Depression and anxiety can play a sensitizing role in the promotion of stress-related inflammatory responses as well (20–22). Early life stress is associated with shorter telomeres, and early adversity also amplifies inflammatory responsiveness (22, 23).

Psychiatric illness is complex, and inflammation may only contribute to increased morbidity and mortality in subpopulations. For example, about a third of depressed patients have inflammatory values that are noticeably higher than the majority of nondepressed comparison subjects (16). Thus, inflammation clearly plays an important role in substantial subpopulations and undoubtedly contributes to telomere shortening in those subgroups, but other pathways also contribute to the excess psychiatric-related morbidity and mortality. Below we briefly describe two other promising markers that have strong relationships with chronological age; these markers provide additional avenues for understanding the heightened morbidity and mortality associated with psychiatric illness.

DNA methylation (DNAm)

Epigenetic changes in DNA methylation (DNAm) can give rise to heritable changes in gene expression (24). Indeed, DNAm can change across the lifespan, providing a molecular mechanism through which social and behavioral factors are translated into health outcomes (24). For example, the differences in DNA methylation in identical twins rise with age, a phenomenon termed "epigenetic drift" (25).The development of two DNAm age algorithms that are reliably related to chronological age has provided new tools to investigate questions related to accelerated aging (26, 27). DNAm age correlates highly with chronological age ($r \geq 0.96$ for both algorithms); Hannum's algorithm is based on blood samples, while Horvath has shown the replicability of his algorithm across cell types, tissues, and organs (26, 28). Although both the Hannum and Horvath DNAm age algorithms show strong relationships with chronological age, they have just 6 overlapping loci and 11 overlapping genes (26, 27, 29).

DNAm age predicts accelerated age-related decline and early mortality. Individuals with higher levels of epigenetic aging relative to their actual age had a higher mortality risk (30). Data from a large population-based cohort of German older adults linked epigenetic aging acceleration with frailty (31). Other researchers showed that greater age acceleration was associated with poorer cognition, lung function, and grip strength measures (30).

Stressors can provoke persistent changes in DNA methylation (32, 33). For example, cumulative lifetime stress in an urban, African American cohort predicted accelerated

epigenetic aging (34). In a longitudinal study of deployed military personnel, traumatic stress was associated with accelerated epigenetic aging (35). Lifetime PTSD severity was associated with accelerated DNAm age estimates compared to chronological age; furthermore, advanced DNAm age in this cohort was also linked with neural changes and had indirect relationships with working memory performance (29). What is more, early life social stressors like low SES can predispose individuals to develop greater proinflammatory responses to biological and behavioral stimuli, reflecting epigenetic DNAm influences on stress reactivity and proinflammatory cytokine production (36).

Cellular senescence: $p16^{INK4a}$

The expression of $p16^{INK4a}$ in peripheral blood T-cells provides another human aging biomarker. Increasing exponentially with chronological age, $p16^{INK4a}$ expression rises nearly 10-fold over 60 years in humans; in contrast, telomere length decreases less than twofold over the same interval (37). A key effector of cell senescence and a cell cycle inhibitor that controls stem cell dynamics, $p16^{INK4a}$ actively influences aging (38). Greater $p16^{INK4a}$ expression is associated with higher IL-6, smoking and smoking history, and sedentary behavior (37). In genetic mouse models, $p16^{INK4a}$ inactivation has attenuated cellular senescence and slowed premature aging (38).

In conclusion, understanding the increased morbidity and mortality in psychiatric populations is important. Aging reduces telomere length, alters DNA methylation patterns, and heightens $p16^{INK4}$. A broader analysis of the key pathways through which psychiatric illness accelerates biological aging and age-related diseases is an important future direction that may help identify new avenues for intervention.

Acknowledgments

Work on this paper was supported in part by NIH grants CA172296, CA186720, and CA186251, as well as a Pelotonia Postdoctoral Fellowship from the Ohio State University Comprehensive Cancer Center.

References

1. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014; 13:153–160. [PubMed: 24890068]
2. Darrow SM, Verhoeven JE, Révész D, Lindqvist D, Penninx BWJH, Delucchi KL, Wolkowitz OM, Matthews CA. The association between psychiatric disorders in telomere length: A meta-analysis involving 14,827 persons. Psychosom Med. in press.
3. Blackburn EH, Epel ES, Lin J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. Science. 2015; 350:1193–1198. [PubMed: 26785477]
4. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet. 2003; 361:393–395. [PubMed: 12573379]
5. Rode L, Nordestgaard BG, Bojesen SE. Peripheral Blood Leukocyte Telomere Length and Mortality Among 64 637 Individuals From the General Population. Jnci-Journal of the National Cancer Institute. 2015:107.
6. von Kaenel R, Malan NT, Hamer M, Malan L. Comparison of Telomere Length in Black and White Teachers From South Africa: The Sympathetic Activity and Ambulatory Blood Pressure in Africans Study. Psychosom Med. 2015; 77:26–32. [PubMed: 25469684]

7. Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Hwang BS, Glaser R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. Brain Behav Immun. 2012; 26:988–995. [PubMed: 22640930]
8. Epel ES, Merkin SS, Cawthon R, Blackburn EH, Adler NE, Pletcher MJ, Seeman TE. The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men. Aging (Milano). 2009; 1:81–88.
9. Aviv A, Chen W, Gardner JP, Kimura M, Brimacombe M, Cao XJ, Srinivasan SR, Berenson GS. Leukocyte Telomere Dynamics: Longitudinal Findings Among Young Adults in the Bogalusa Heart Study. Am J Epidemiol. 2009; 169:323–329. [PubMed: 19056834]
10. Nordfjall K, Svenson U, Norrback KF, Adolfsson R, Lenner P, Roos G. The individual blood cell telomere attrition rate is telomere length dependent. PLoS Genet. 2009; 5:e1000375. [PubMed: 19214207]
11. Ehrlenbach S, Willeit P, Kiechl S, Willeit J, Reindl M, Schanda K, Kronenberg F, Brandstatter A. Influences on the reduction of relative telomere length over 10 years in the population-based Bruneck Study: introduction of a well-controlled high-throughput assay. Int J Epidemiol. 2009; 38:1725–1734. [PubMed: 19666704]
12. Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. Telomere Length Trajectory and Its Determinants in Persons with Coronary Artery Disease: Longitudinal Findings from the Heart and Soul Study. Plos One. 2010; 5:e8612. [PubMed: 20072607]
13. Lin J, Blalock JA, Chen M, Ye YQ, Gu J, Cohen L, Cinciripini PM, Wu XF. Depressive Symptoms and Short Telomere Length Are Associated with Increased Mortality in Bladder Cancer Patients. Cancer Epidemiology Biomarkers & Prevention. 2015; 24:336–343. [Article].
14. De Meyer T. Telomere Length Integrates Psychological Factors in the Successful Aging Story, But What About the Biology? Psychosom Med. 2011; 73:524–527. [PubMed: 21873590]
15. Verhoeven JE, van Oppen P, Puterman E, Elzinga B, Penninx BWJH. The Association of Early and Recent Psychosocial Life Stress With Leukocyte Telomere Length. Psychosom Med. 2015; 77:882–891. [PubMed: 26374947]
16. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: Depression Fans the Flames and Feasts on the Heat. Am J Psychiatry. 2015; 172:1075–1091. [PubMed: 26357876]
17. Hovatta I, Juhila J, Donner J. Oxidative stress in anxiety and comorbid disorders. Neurosci Res. 2010; 68:261–275. [PubMed: 20804792]
18. Jim HS, Small BJ, Minton S, Andrykowski M, Jacobsen PB. History of major depressive disorder prospectively predicts worse quality of life in women with breast cancer. Ann Behav Med. 2012; 43:402–408. [PubMed: 22167580]
19. Monroe S, Harkness K. Life Stress, the "Kindling" Hypothesis, and the Recurrence of Depression: Considerations from a Life Stress Perspective. Psychol Rev. 2005; 112:417–445. [PubMed: 15783292]
20. Fagundes CP, Glaser R, Hwang BS, Malarkey WB, Kiecolt-Glaser JK. Depressive symptoms enhance stress-induced inflammatory responses. Brain Behav Immun. 2013; 31:172–176. [PubMed: 22634107]
21. Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006; 163:1630–1632. [PubMed: 16946190]
22. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology. 2010; 35:2617–2623. [PubMed: 20881945]
23. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav Immun. 2013; 27:8–12. [PubMed: 22771426]
24. Needham BL, Smith JA, Zhao W, Wang X, Mukherjee B, Kardia SLR, Shively CA, Seeman TE, Liu Y, Roux AVD. Life course socioeconomic status and DNA methylation in genes related to stress reactivity and inflammation: The multi-ethnic study of atherosclerosis. Epigenetics. 2015; 10:958–969. [PubMed: 26295359]
25. Bocklandt S, Lin W, Sehl ME, Sanchez FJ, Sinsheimer JS, Horvath S, Vilain E. Epigenetic predictor of age. PLoS One. 2011; 6:e14821. [PubMed: 21731603]

26. Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, Klotzle B, Bibikova M, Fan JB, Gao Y, Deconde R, Chen M, Rajapakse I, Friend S, Ideker T, Zhang K. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell. 2013; 49:359–367. [PubMed: 23177740]
27. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013; 14:R115. [PubMed: 24138928]
28. Horvath S, Erhart W, Brosch M, Ammerpohl O, von Schoenfels W, Ahrens M, Heits N, Bell JT, Tsai P-C, Spector TD, Deloukas P, Siebert R, Sipos B, Becker T, Roecken C, Schafmayer C, Hampe J. Obesity accelerates epigenetic aging of human liver. Proc Natl Acad Sci U S A. 2014; 111:15538–15543. [PubMed: 25313081]
29. Wolf EJ, Logue MW, Hayes JP, Sadeh N, Schichman SA, Stone A, Salat DH, Milberg W, McGlinchey R, Miller MW. Accelerated DNA methylation age: Associations with PTSD and neural integrity. Psychoneuroendocrinology. 2016; 63:155–162. [PubMed: 26447678]
30. Marioni RE, Shah S, McRae AF, Chen BH, Colicino E, Harris SE, Gibson J, Henders AK, Redmond P, Cox SR, Pattie A, Corley J, Murphy L, Martin NG, Montgomery GW, Feinberg AP, Fallin MD, Multhaup ML, Jaffe AE, Joehanes R, Schwartz J, Just AC, Lunetta KL, Murabito JM, Starr JM, Horvath S, Baccarelli AA, Levy D, Visscher PM, Wray NR, Deary IJ. DNA methylation age of blood predicts all-cause mortality in later life. Genome Biol. 2015; 16:25. [PubMed: 25633388]
31. Breitling LP, Saum K-U, Perna L, Schoettker B, Holleczek B, Brenner H. Frailty is associated with the epigenetic clock but not with telomere length in a German cohort. Clinical Epigenetics. 2016:8. [PubMed: 26807160]
32. Houtepen LC, Vinkers CH, Carrillo-Roa T, Hiemstra M, van Lier PA, Meeus W, Branje S, Heim CM, Nemeroff CB, Mill J, Schalkwyk LC, Creyghton MP, Kahn RS, Joels M, Binder EB, Boks MPM. Genome-wide DNA methylation levels and altered cortisol stress reactivity following childhood trauma in humans. Nature communications. 2016:7.
33. Vinkers CH, Kalafateli AL, Rutten BPF, Kas MJ, Kaminsky Z, Turner JD, Boks MPM. Traumatic stress and human DNA methylation: a critical review. Epigenomics. 2015; 7:593–608. [PubMed: 26111031]
34. Zannas AS, Arloth J, Carrillo-Roa T, Iurato S, Roeh S, Ressler KJ, Nemeroff CB, Smith AK, Bradley B, Heim C, Menke A, Lange JF, Brueckl T, Ising M, Wray NR, Erhardt A, Binder EB, Mehta D. Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. Genome Biology. 2015:16. [PubMed: 25622821]
35. Boks MP, van Mierlo HC, Rutten BPF, Radstake TRDJ, De Witte L, Geuze E, Horvath S, Schalkwyk LC, Vinkers CH, Broen JCA, Vermetten E. Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. Psychoneuroendocrinology. 2015; 51:506–512. [PubMed: 25129579]
36. Saban KL, Mathews HL, DeVon HA, Janusek LW. Epigenetics and social context: implications for disparity in cardiovascular disease. Aging and disease. 2014; 5:346–355. [PubMed: 25276493]
37. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Ibrahim JG, Thomas NE, Sharpless NE. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. Aging Cell. 2009; 8:439–448. [PubMed: 19485966]
38. Martin N, Beach D, Gill J. Ageing as developmental decay: insights from p16(INK4a). Trends in Molecular Medicine. 2014; 20:667–674. [PubMed: 25277993]