PTSD and Accelerated Aging

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PTSD and Accelerated Aging

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For hundreds of years, scientists have recognized that the human body is highly sensitive to the external environment. In the mid-1800s, Claude Bernard, who is credited with being among the first to develop and apply scientific methods of experimentation to the study of physiology, suggested that the external environment could alter the "milieu intérieur" (interior environment; Bernard, 1974), the predecessor to the concept of physiological homeostasis. Since that time, a broad research basis has been established focused on understanding how stress, life adversity, and other aspects of the external environment get "under the skin" and lead to poor physical health (e.g., McEwen, 2012). More recently, investigators have suggested that aspects of the intra-individual environment, such as psychiatric symptoms, may impact physiology directly and be as important as the external environment, if not more so, in predicting subsequent health outcomes (e.g., Schnurr & Green, 2004).

This idea has received recent attention in PTSD literature, as there is evidence that PTSD is associated with premature development of physical health problems, ranging from metabolic and cardiovascular diseases, to cognitive decline, to premature death (e.g., Ahmadi et al., 2011; Wolf, Bovin, et al., 2016; Yaffe et al., 2010). Early development of these age-related conditions is thought to provide evidence that PTSD is associated with premature aging such that the stress of PTSD symptoms leads to an accelerated pace of cellular aging relative to chronological aging. The goal of this article is to provide readers with a guide to the growing empirical literature concerning PTSD-related accelerated aging and to the methodologies used to study it.

Miller and Sadeh (2014) were among the first to put forth a comprehensive theory of PTSD-related accelerated aging (see also Williamson, Porges, Lamb, & Porges, 2015 and Lohr et al., 2015 who contributed complementary papers concerning mechanisms of PTSD-related accelerated aging). They highlighted the PTSD symptoms (e.g., sleep disturbance, emotional arousal) that would be expected to most strongly contribute to cellular aging, and they suggested mechanisms (e.g., epigenetics) and biological systems (e.g., oxidative stress, hypothalamic-pituitary-adrenal axis [HPA] dysfunction) that might contribute to this. Their focus on potential epi/genetic markers of cellular aging was strongly influenced by groundbreaking discoveries in understanding the genetics of aging, as described below.

Up until quite recently, much of the genetic work focused on accelerated aging in PTSD used telomeres as the marker of cellular age. Telomeres are areas of deoxyribonucleic acid (DNA) repeats found at the ends of chromosomes (Blackburn, 2005). As a function of cell division, these repeat DNA sequences become shorter with age, suggesting that telomeres may index accelerated aging when they are shorter than would be expected based on chronological age. Epel and colleagues have developed a large body of groundbreaking research in this area and have shown that many forms of stress, ranging from life adversity to psychological stress to metabolic stress, can influence telomere length (see Epel, 2009 for an excellent introduction and review). Several studies have suggested that PTSD and/or trauma exposure are also associated with shortened telomere length, as summarized in a comprehensive literature review of telomere length and psychiatric disorders by Lindqvist et al. (2015). Collectively, such research has been critical for introducing the genetics of aging literature into the PTSD field.

However, important recent work has called into question whether telomeres can serve as a valid marker of cellular age specifically. Two articles that are required reading for anyone interested in telomere research are Müezzinler, Zaineddin, and Brenner (2013) and Barrett, Iles, Dunning, and Pooley (2015).

Continued on page 2

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Continued from cover

Müezzinler and colleagues reviewed the literature on the association between telomere length and chronological age and found that, on average, this association was quite small (r ~ .30); this should raise doubt about the use of telomeres to index cellular age specifically. Barrett et al. reviewed the literature on telomere length and disease and highlighted a number of sources of measurement error in telomere length estimates, including variation in the laboratory techniques used for determining estimates, batch effects, and intra-individual variation (see also Martin-Ruiz et al., 2015 and Cunningham et al., 2013 for empirical evaluations of telomere length-related measurement error). Given these concerns, it is possible that telomere length may be a much more general and inexact indicator of physiological stress and ill health rather than a highly specific marker of cellular aging.

More recently, DNA methylation (DNAm) research has provided evidence of a superior metric of cellular age. Methylation is one form of epigenetic regulation that is sensitive to the environment (see Szyf, 2013 for an accessible review); it is a physical process that affects gene transcription without altering the sequence of DNA. Two independent research groups (Horvath, 2013; Hannum et al., 2013) developed algorithms using DNAm data that were strongly predictive of chronological age (both r = .96). Horvath (2013) developed a *DNAm age* index, which he referred to as the "epigenetic clock," based on 353 DNAm loci across the genome that showed consistent evidence of association with chronological age in 51 tissue types and over 80 datasets (i.e., a multi-tissue DNAm age algorithm). Hannum et al. (2013) developed a DNAm age algorithm from whole blood, which subsequently replicated in other tissues, and was based on methylation levels at 71 loci. The two algorithms are based on largely nonoverlapping loci. These studies paved the way for research focused on the factors that influence cellular aging and on the health consequences of accelerated aging. History may later show that this work reflects a significant turning point in understanding the genetics of aging.

Two recent studies evaluated the health consequences of accelerated DNAm age and have been critical for establishing the external validity of these indices of cellular age. Specifically, across multiple, large epidemiological samples, Marioni, Shah, McRae, Ritchie, et al. (2015) were the first to show that accelerated Horvath DNAm age was cross-sectionally (though not longitudinally) associated with poorer performance on cognitive, motor, and lung function tasks, and Marioni, Shah, McRae, Chen, et al. (2015) showed that Horvath and Hannum et al. advanced DNAm age estimates were associated with increased odds for mortality. Together, these two studies provided much needed evidence that DNAm age and, more importantly, differences between DNAm age estimates and chronological age were capturing meaningful variability in age-related biological processes.

With respect to the effects of trauma and PTSD on DNAm age, the first study to evaluate this was Boks et al. (2015). This was a longitudinal study of 96 Dutch Veterans pre- and post-deployment which surprisingly suggested that trauma exposure was associated with greater Horvath DNAm age over time while PTSD was associated with reduced DNAm age over time. Before this can be interpreted as indicative of accelerated and decelerated aging, respectively, it is important to note that chronological age was not factored into these estimates and, as a result, neither was the difference between DNAm age estimates relative to chronological age.

Our work (Wolf, Logue, et al., 2016) addressed this concern by examining the influence of PTSD severity across the lifespan on Horvath and Hannum et al. DNAm age estimates that were residualized for chronological age (i.e., positive residuals reflect DNAm age estimates that are advanced relative to chronological age). We showed, in contrast to Boks et al., that PTSD was cross-sectionally associated with advanced Hannum et al. DNAm age. This study also provided additional evidence of the external validity of accelerated DNAm age by showing that it was associated with decline in the integrity of a region of the corpus callosum—the genu—that is particularly sensitive to the effects of aging and, through this decline, linked to poorer performance on tests of executive function and working memory.

In addition, work by Zannas et al. (2015) and Simons et al. (2016) has broadened our understanding of the kinds of psychological stress that are associated with accelerated DNAm age. Specifically, Zannas et al. found that general life stressors were associated with accelerated Horvath DNAm age, although no effect for PTSD was observed in that study. Simons et al. suggested that financial stress was associated with accelerated Hannum et al. DNAm age. The work by Zannas et al. was critical in that the study also used gene expression methodologies to demonstrate that many of the loci included in the Horvath DNAm age script were responsive to glucocorticoid signaling and/or located in glucocorticoid response elements. This provided a critical piece of evidence to support the theory that HPA axis reactivity is one biological mechanism of epigenetic accelerated aging (Miller & Sadeh, 2014). Much more work is needed to identify other biological mechanisms that alter DNAm age among those with PTSD.

Another line of research suggestive of PTSD-related accelerated aging is found in studies showing that PTSD is associated with premature development of age-related health conditions. There is a robust literature linking PTSD to cardiovascular disease (see Kubzansky & Koenen, 2009 for a review), so this section highlights a select number of recent studies that are particularly novel. For example, Vaccarino et al. (2013) used the twin design to demonstrate that among Vietnam-era twin pairs who were discordant for PTSD, the incidence of cardiovascular disease was about double in the PTSD+ twin, suggesting strongly that PTSD may play a causal role in the development of cardiovascular disease. Ahmadi et al. (2011) demonstrated that those with coronary artery disease were at increased risk for death if they also had PTSD, suggesting that PTSD amplifies cardiac-related mortality risk. Roy, Foraker, Girton, and Mansfield (2015) found that PTSD was prospectively associated with new incident heart disease among a large Veteran epidemiological sample. Finally, our group recently demonstrated that Veterans with PTSD under age 40 had a greater prevalence of metabolic syndrome in comparison to an epidemiological sample of the same age (Wolf, Bovin, et al., 2016). Moreover, our study was the first to show that PTSD longitudinally predicted increasing metabolic risk over time and to address the important question of whether the associations between PTSD and metabolic syndrome might be bidirectional (only a unidirectional association from PTSD to metabolic syndrome was supported by the results of Wolf, Bovin, et al., 2016).

A much smaller body of research has evaluated PTSD and dementing disorders. One study of U.S. Department of Veterans Affairs (VA) healthcare users found that Veterans with PTSD had more than twice the risk of developing dementia as those without the disorder

(Yaffe et al., 2010). The study did not directly address the question of whether dementia among those with PTSD occurred at an earlier age relative to those without PTSD. Related work suggests that PTSD chronicity (e.g., having severe PTSD for a long period of time) is associated with reduced cortical thickness in prefrontal and temporal brain regions, even after controlling for age-related effects (Lindemer, Salat, Leritz, McGlinchey, & Milberg, 2013). Our own research has suggested that at least some of this effect might be related to metabolic syndrome as a potential mechanism linking PTSD to age-independent reductions in cortical thickness (Wolf, Sadeh, et al., 2016). Taken together, these studies provide initial evidence that PTSD-related accelerated aging may be manifested in cognitive and neuronal decline, although longitudinal research is needed to evaluate this concern comprehensively.

The complementary lines of research highlighted in this article collectively provide evidence that PTSD is associated with accelerated aging and that this is reflected in an array of metrics ranging from genetics to physical health diagnoses. This line of work reflects a shift from thinking about the neurobiology of PTSD to thinking about the neurobiological and medical consequences of the disorder. As such, it may also mark a new research focus aimed at identifying who is at risk for specific PTSD-related morbidities and in the development of interventions to prevent or reverse premature morbidity and mortality. It also raises questions regarding the capacity of existing evidence-based treatments for PTSD to reduce the risk of premature negative health outcomes and, if so, through what biological mechanisms. More research is needed to address these questions as it is clear that the potential individual and societal benefits of such work are substantial.

FEATURED ARTICLES

Ahmadi, N., Hajsadeghi, F., Mirshkarlo, H. B., Budoff, M., Yehuda, R., & Ebrahimi, R. (2011). **Post-traumatic stress disorder, coronary atherosclerosis, and mortality.** *American Journal of Cardiology, 108*, 29-33. doi:10.1016/j.amjcard.2011.02.340 Post-traumatic stress disorder (PTSD) is associated with increased risk of multiple medical problems including myocardial infarction. However, a direct link between PTSD and atherosclerotic coronary artery disease (CAD) has not been made. Coronary artery calcium (CAC) score is an excellent method to detect atherosclerosis. This study investigated the association of PTSD to atherosclerotic CAD and mortality. Six hundred thirty-seven veterans without known CAD (61 ± 9 years of age, 12.2% women) underwent CAC scanning for clinical indications and their psychological health status (PTSD vs non-PTSD) was evaluated. In subjects with PTSD, CAC was more prevalent than in the non-PTSD cohort (76.1% vs 59%, p = 0.001) and their CAC scores were significantly higher in each Framingham risk score category compared to the non-PTSD group. Multivariable generalized linear regression analysis identified PTSD as an independent predictor of presence and extent of atherosclerotic CAD (p <0.01). During a mean follow-up of 42 months, the death rate was higher in the PTSD compared to the non-PTSD group (15, 17.1%, vs 57, 10.4%, p = 0.003). Multivariable survival regression analyses revealed a significant linkage between PTSD and mortality and between CAC and mortality. After adjustment for risk factors, relative risk (RR) of death was 1.48 (95% confidence interval [CI] 1.03 to 2.91, p = 0.01) in subjects with PTSD and CAC score >0 compared to subjects without PTSD and CAC score equal to 0.

FEATURED ARTICLES *continued*

With a CAC score equal to 0, risk of death was not different between subjects with and without PTSD (RR 1.04, 95% CI 0.67 to 6.82, p = 0.4). Risk of death in each CAC category was higher in subjects with PTSD compared to matched subjects without PTSD (RRs 1.23 for CAC scores 1 to 100, 1.51 for CAC scores 101 to 400, and 1.81 for CAC scores ≥400, p <0.05 for all comparisons). In conclusion, PTSD is associated with presence and severity of coronary atherosclerosis and predicts mortality independent of age, gender, and conventional risk factors.

Barrett, J. H., Iles, M. M., Dunning, A. M., & Pooley, K. A. (2015). **Telomere length and common disease: Study design and analytical challenges.** *Human Genetics, 134*, 679-689. doi:10.1007/s00439-015-1563-4 Telomeres, the repetitive sequences that protect the ends of chromosomes, help to maintain genomic integrity and are of key importance to human health. The aim here is to give an overview of the evidence for the importance of telomere length (TL) to the risk of common disease, considering the strengths and weaknesses of different epidemiological study designs. Methods for measuring TL are described, all of which are subject to considerable measurement error. TL declines with age and varies in relation to factors such as smoking and obesity. It is also highly heritable (estimated heritability of ~40 to 50 %), and genome-wide studies have identified a number of associated genetic variants. Epidemiological studies have shown shorter TL to be associated with risk of a number of common diseases, including cardiovascular disease and some cancers. The relationship with cancer appears complex, in that longer telomeres are associated with higher risk of some cancers. Prospective studies of the relationship between TL and disease, where TL is measured before diagnosis, have numerous advantages over retrospective studies, since they avoid the problems of reverse causality and differences in sample handling, but they are still subject to potential confounding. Studies of the genetic predictors of TL in relation to disease risk avoid these drawbacks, although they are not without limitations. Telomere biology is of major importance to the risk of common disease, but the complexities of the relationship are only now beginning to be understood.

Boks, M. P., van Mierlo, H. C., Rutten, B. P. F., Radstake, T. R. D. J., De Witte, L., Geuze, E., . . . Vermetten, E. (2015). **Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder.** *Psychoneuroendocrinology, 51*, 506-512. doi:10.1016/j.psyneuen.2014.07.011 Several studies have reported an association between traumatic stress and telomere length suggesting that traumatic stress has an impact on ageing at the cellular level. A newly derived tool provides an additional means to investigate cellular ageing by estimating epigenetic age based on DNA methylation profiles. We therefore hypothesise that in a longitudinal study of traumatic stress both indicators of cellular ageing will show increased ageing. We expect that particularly in individuals that developed symptoms of post-traumatic stress disorder (PTSD) increases in these ageing parameters would stand out. From an existing longitudinal cohort study, ninety-six male soldiers were selected based on trauma exposure and the presence of symptoms of PTSD. All military personnel were deployed in a combat zone in Afghanistan and assessed before and 6 months after deployment. The Self-Rating Inventory for PTSD was used to measure the presence of PTSD symptoms, while exposure to combat trauma during deployment was measured with a 19-item deployment

experiences checklist. These groups did not differ for age, gender, alcohol consumption, cigarette smoking, military rank, length, weight, or medication use. In DNA from whole blood telomere length was measured and DNA methylation levels were assessed using the Illumina 450K DNA methylation arrays. Epigenetic ageing was estimated using the DNAm age estimator procedure. The association of trauma with telomere length was in the expected direction but not significant ($B = -10.2$, $p = 0.52$). However, contrary to our expectations, development of PTSD symptoms was associated with the reverse process, telomere lengthening ($B = 1.91$, $p = 0.018$). In concordance, trauma significantly accelerated epigenetic ageing ($B = 1.97$, $p = 0.032$) and similar to the findings in telomeres, development of PTSD symptoms was inversely associated with epigenetic ageing ($B = -0.10$, $p = 0.044$). Blood cell count, medication and premorbid early life trauma exposure did not confound the results. Overall, in this longitudinal study of military personnel deployed to Afghanistan we show an acceleration of ageing by trauma. However, development of PTSD symptoms was associated with telomere lengthening and reversed epigenetic ageing. These findings warrant further study of a perhaps dysfunctional compensatory cellular ageing reversal in PTSD.

Epel, E. S. (2009). **Psychological and metabolic stress: A recipe for accelerated cellular aging?** *Hormones, 8*, 7-22. Chronic stress can affect human health through a myriad of behavioral and biochemical pathways. This review focuses on some key hormonal and metabolic pathways that appear important today. In modern society, we are faced with excessive psychological stress, as well as an epidemic of overeating, and the two together appear to have synergistic effects. Chronic stress can lead to overeating, co-elevation of cortisol and insulin, and suppression of certain anabolic hormones. This state of metabolic stress in turn promotes abdominal adiposity. Both the direct stress response and the accumulation of visceral fat can promote a milieu of systemic inflammation and oxidative stress. This biochemical environment appears to be conducive to several cell aging mechanisms, mainly dampening telomerase and leading to telomere length (TL) shortening and cell senescence. Immune cell telomere shortness is linked with many chronic disease states and earlier mortality. In this way, chronic stress may influence a variety of diseases through a biochemical cascade leading to immune cell senescence. Certain psychological temperaments at high risk of this stress cascade (mainly anxiety prone), gene-environment interactions, and potential interventions for interrupting the stress-aging cascade are discussed.

Hannum, G., Guinney, J., Zhao, L., Zhang, L., Hughes, G., Sadda, S., . . . Zhang, K. (2013). **Genome-wide methylation profiles reveal quantitative views of human aging rates.** *Molecular Cell, 49*, 359-367. doi:10.1016/j.molcel.2012.10.016 The ability to measure human aging from molecular profiles has practical implications in many fields, including disease prevention and treatment, forensics, and extension of life. Although chronological age has been linked to changes in DNA methylation, the methylome has not yet been used to measure and compare human aging rates. Here, we build a quantitative model of aging using measurements at more than 450,000 CpG markers from the whole blood of 656 human individuals, aged 19 to 101. This model measures the rate at which an individual's methylome ages, which we show is impacted by gender and genetic variants. We also show that differences in aging rates help explain epigenetic drift and are reflected in the transcriptome. Moreover, we show how our aging model is upheld in other human tissues and reveals an advanced aging rate in tumor tissue. Our model highlights specific components of the aging process and provides a quantitative readout for studying the role of methylation in age-related disease.

Horvath, S. (2013). **DNA methylation age of human tissues and cell types.** *Genome Biology, 14*, R115. doi:10.1186/gb-2013-14-10-r115 *Background:* It is not yet known whether DNA methylation levels can be used to accurately predict age across a broad spectrum of human tissues and cell types, nor whether the resulting age prediction is a biologically meaningful measure. *Results:* I developed a multi-tissue predictor of age that allows one to estimate the DNA methylation age of most tissues and cell types. The predictor, which is freely available, was developed using 8,000 samples from 82 Illumina DNA methylation array datasets, encompassing 51 healthy tissues and cell types. I found that DNA methylation age has the following properties: first, it is close to zero for embryonic and induced pluripotent stem cells; second, it correlates with cell passage number; third, it gives rise to a highly heritable measure of age acceleration; and, fourth, it is applicable to chimpanzee tissues. Analysis of 6,000 cancer samples from 32 datasets showed that all of the considered 20 cancer types exhibit significant age acceleration, with an average of 36 years. Low age-acceleration of cancer tissue is associated with a high number of somatic mutations and *TP*53 mutations, while mutations in steroid receptors greatly accelerate DNA methylation age in breast cancer. Finally, I characterize the 353 CpG sites that together form an aging clock in terms of chromatin states and tissue variance. *Conclusions:* I propose that DNA methylation age measures the cumulative effect of an epigenetic maintenance system. This novel epigenetic clock can be used to address a host of questions in developmental biology, cancer and aging research.

Lindemer, E. R., Salat, D. H., Leritz, E. C., McGlinchey, R. E., & Milberg, W. P. (2013). **Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF veterans and the impact of comorbid TBI.** *Neuroimage: Clinical, 2*, 601-611. doi:10.1016/j.nicl.2013.04.009 Posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) in military personnel is increasing dramatically following the OEF/OIF conflicts and is associated with alterations to brain structure. The present study examined the relationship between PTSD and cortical thickness, and its possible modification by mTBI, in a 104-subject OEF/OIF veteran cohort ranging in age from 20 to 62 years. For each participant, two T1-weighted scans were averaged to create high-resolution images for calculation of regional cortical thickness. PTSD symptoms were assessed using the Clinician Administered PTSD Scale (CAPS) and scores were derived based on the previous month's symptoms ("current") and a Cumulative Lifetime Burden of PTSD (CLB-P) reflecting the integral of CAPS scores across the lifetime. Mild TBI was diagnosed using the Boston Assessment of TBI-Lifetime (BAT-L). Results demonstrated a clear negative relationship between current PTSD severity and thickness in both postcentral gyri and middle temporal gyri. This relationship was stronger and more extensive when considering lifetime burden (CLB-P), demonstrating the importance of looking at trauma in the context of an individual's lifetime, rather than only at their current symptoms. Finally, interactions with current PTSD only and comorbid current PTSD and mTBI were found in several regions, implying an additive effect of lifetime PTSD and mTBI on cortical thickness.

Lindqvist, D., Epel, E. S., Mellon, S. H., Penninx, B. W., Révész, D., Verhoeven, J. E., . . . Wolkowitz, O. M. (2015). **Psychiatric disorders and leukocyte telomere length: Underlying mechanisms linking mental illness with cellular aging.** *Neuroscience and Biobehavioral Reviews, 55*, 333-364. doi:10.1016/j.neubiorev.2015.05.007 Many psychiatric illnesses are associated with early mortality and with an increased risk of developing physical diseases that are more typically seen in the elderly. Moreover, certain psychiatric illnesses may be associated with accelerated cellular aging, evidenced by shortened leukocyte telomere length (LTL), which could underlie this association. Shortened LTL reflects a cell's mitotic history and cumulative exposure to inflammation and oxidation as well as the availability of telomerase, a telomere-lengthening enzyme. Critically short telomeres can cause cells to undergo senescence, apoptosis or genomic instability, and shorter LTL correlates with poorer health and predicts mortality. Emerging data suggest that LTL may be reduced in certain psychiatric illnesses, perhaps in proportion to exposure to the psychiatric illnesses, although conflicting data exist. Telomerase has been less well characterized in psychiatric illnesses, but a role in depression and in antidepressant and neurotrophic effects has been suggested by preclinical and clinical studies. In this article, studies on LTL and telomerase activity in psychiatric illnesses are critically reviewed, potential mediators are discussed, and future directions are suggested. A deeper understanding of cellular aging in psychiatric illnesses could lead to re-conceptualizing them as systemic illnesses with manifestations inside and outside the brain and could identify new treatment targets.

Lohr, J. B., Palmer, B. W., Eidt, C. A., Aailaboyina, S., Mausbach, B. T., Wolkowitz, O. M., . . . Jeste, D. V. (2015). **Is post-traumatic stress disorder associated with premature senescence? A review of the literature.** *American Journal of Geriatric Psychiatry, 23*, 709-725. doi:10.1016/j.jagp.2015.04.001 *Objective:* Post-traumatic stress disorder (PTSD) has major public health significance. Evidence that PTSD may be associated with premature senescence (early or accelerated aging) would have major implications for quality of life and healthcare policy. We conducted a comprehensive review of published empirical studies relevant to early aging in PTSD. *Method:* Our search included the PubMed, PsycINFO, and PILOTS databases for empirical reports published since the year 2000 relevant to early senescence and PTSD, including: 1) biomarkers of senescence (leukocyte telomere length [LTL] and pro-inflammatory markers), 2) prevalence of senescence-associated medical conditions, and 3) mortality rates. *Results:* All six studies examining LTL indicated reduced LTL in PTSD (pooled Cohen's *d* = 0.76). We also found consistent evidence of increased pro-inflammatory markers in PTSD (mean Cohen's *d*s), including C-reactive protein = 0.18, Interleukin-1 beta = 0.44, Interleukin-6 = 0.78, and tumor necrosis factor alpha = 0.81. The majority of reviewed studies also indicated increased medical comorbidity among several targeted conditions known to be associated with normal aging, including cardiovascular disease, type 2 diabetes mellitus, gastrointestinal ulcer disease, and dementia. We also found seven of 10 studies indicated PTSD to be associated with earlier mortality (average hazard ratio: 1.29). *Conclusion:* In short, evidence from multiple lines of investigation suggests that PTSD may be associated with a phenotype of accelerated senescence. Further research is critical to understand the nature of this association. There may be a need to re-conceptualize PTSD beyond the boundaries of mental illness, and instead as a full systemic disorder.

Marioni, R. E., Shah, S., McRae, A. F., Chen, B. H., Colicino, E., Harris, S. E., . . . Deary, I. J. (2015). **DNA methylation age of blood predicts all-cause mortality in later life.** *Genome Biology, 16*, 25. doi:10.1186/s13059-015-0584-6 *Background:* DNA methylation levels change with age. Recent studies have identified biomarkers of chronological age based on DNA methylation levels. It is not yet known whether DNA methylation age captures aspects of biological age. *Results:* Here we test whether differences between people's chronological ages and estimated ages, DNA methylation age, predict all-cause mortality in later life. The difference between DNA methylation age and chronological age (Δ_{age}) was calculated in four longitudinal cohorts of older people. Meta-analysis of proportional hazards models from the four cohorts was used to determine the association between Δ_{age} and mortality. A 5-year higher Δ_{age} is associated with a 21% higher mortality risk, adjusting for age and sex. After further adjustments for childhood IQ, education, social class, hypertension, diabetes, cardiovascular disease, and *APOE* e4 status, there is a 16% increased mortality risk for those with a 5-year higher Δ_{age}. A pedigree-based heritability analysis of Δ_{age} was conducted in a separate cohort. The heritability of Δ_{age} was 0.43. *Conclusions:* DNA methylation-derived measures of accelerated aging are heritable traits that predict mortality independently of health status, lifestyle factors, and known genetic factors.

Marioni, R. E., Shah, S., McRae, A. F., Ritchie, S. J., Muniz-Terrera, G., Harris, S. E., . . . Deary, I. J. (2015). **The epigenetic clock is correlated with physical and cognitive fitness in the Lothian Birth Cohort 1936.** *International Journal of Epidemiology, 44*, 1388-1396. doi:10.1093/ije/dyu277 *Background:* The DNA methylation-based 'epigenetic clock' correlates strongly with chronological age, but it is currently unclear what drives individual differences. We examine cross-sectional and longitudinal associations between the epigenetic clock and four mortality-linked markers of physical and mental fitness: lung function, walking speed, grip strength and cognitive ability. *Methods:* DNA methylation-based age acceleration (residuals of the epigenetic clock estimate regressed on chronological age) were estimated in the Lothian Birth Cohort 1936 at ages 70 (n = 920), 73 (n = 299) and 76 (n = 273) years. General cognitive ability, walking speed, lung function and grip strength were measured concurrently. Cross-sectional correlations between age acceleration and the fitness variables were calculated. Longitudinal change in the epigenetic clock estimates and the fitness variables were assessed via linear mixed models and latent growth curves. Epigenetic age acceleration at age 70 was used as a predictor of longitudinal change in fitness. Epigenome-wide association studies (EWASs) were conducted on the four fitness measures. *Results:* Cross-sectional correlations were significant between greater age acceleration and poorer performance on the lung function, cognition and grip strength measures (r range: −0.07 to −0.05, P range: 9.7×10^{-3} to 0.024). All of the fitness variables declined over time but age acceleration did not correlate with subsequent change over 6 years. There were no EWAS hits for the fitness traits. *Conclusions:* Markers of physical and mental fitness are associated with the epigenetic clock (lower abilities associated with age acceleration). However, age acceleration does not associate with decline in these measures, at least over a relatively short follow-up.

Miller, M. W., & Sadeh, N. (2014). **Traumatic stress, oxidative stress and post-traumatic stress disorder: Neurodegeneration and the accelerated-aging hypothesis.** *Molecular Psychiatry, 19*, 1156-1162. doi:10.1038/mp.2014.111 Post-traumatic stress disorder (PTSD) is associated with elevated risk for a variety of age-related diseases and neurodegeneration. In this paper, we review evidence relevant to the hypothesis that chronic PTSD constitutes a form of persistent life stress that potentiates oxidative stress (OXS) and accelerates cellular aging. We provide an overview of empirical studies that have examined the effects of psychological stress on OXS, discuss the stress-perpetuating characteristics of PTSD, and then identify mechanisms by which PTSD might promote OXS and accelerated aging. We review studies on OXS-related genes and the role that they may have in moderating the effects of PTSD on neural integrity and conclude with a discussion of directions for future research on antioxidant treatments and biomarkers of accelerated aging in PTSD.

Müezzinler, A., Zaineddin, A. K., & Brenner, H. (2013). **A systematic review of leukocyte telomere length and age in adults.** *Ageing Research Reviews, 12*, 509-519. doi:10.1016/j.arr.2013.01.003 *Objective:* To provide a systematic review of the relationship between age and leukocyte telomere length (LTL) in adults. *Methods:* Relevant studies were identified by a systematic search of Medline, EMBASE and ISI Web of Knowledge databases. Key data, such as age and LTL, were extracted from the studies along with correlation coefficients and yearly attrition rates where available. Obtained data were used to calculate weighted means and correlation coefficients. *Results:* Overall, 124 cross-sectional studies and 5 longitudinal studies were identified. A statistically significant inverse correlation between mean age and mean LTL across cross-sectional studies was observed for both absolute ($r = -0.338$, $p < 0.0001$) and relative LTL ($r = -0.295$, $p = 0.0088$). From mean LTL and ages, a yearly telomere loss of 24.7 base pairs (BP)/year was estimated by weighted linear regression. Weighted means of within study correlation of age and TL and yearly telomere loss rate estimates from cross-sectional studies were also in a similar order of magnitude (–0.380 and 21.91 BP/year). The few longitudinal studies reported somewhat higher mean telomere loss rates (between 32.2 and 45.5 BP/year). *Conclusion:* While a decrease of LTL with age is out of question, data on variation of the decrease according to sex, age and other potential determinants especially from longitudinal data are still sparse.

Roy, S. S., Foraker, R. E., Girton, R. A., Mansfield, A. J. (2015). **Posttraumatic stress disorder and incident heart failure among a community-based sample of US veterans.** *American Journal of Public Health, 105*, 757-763. doi:10.2105/AJPH.2014.302342 We investigated the association between posttraumatic stress disorder (PTSD) and incident heart failure in a community-based sample of veterans. We examined Veterans Affairs Pacific Islands Health Care System outpatient medical records for 8248 veterans between 2005 and 2012. We used multivariable Cox regression to estimate hazard ratios and 95% confidence intervals for the development of heart failure by PTSD status. Over a mean follow-up of 7.2 years, veterans with PTSD were at increased risk for developing heart failure (hazard ratio [HR] = 1.47; 95% confidence interval [CI] = 1.13, 1.92) compared with veterans without PTSD after adjustment for age, gender, diabetes, hyperlipidemia, hypertension, body mass index, combat service, and military service period. Additional predictors for heart failure included age (HR = 1.05; 95% CI = 1.03, 1.07), diabetes (HR = 2.54; 95% CI = 2.02, 3.20), hypertension (HR = 1.87; 95% CI = 1.42, 2.46), overweight (HR = 1.72; 95% CI= 1.25, 2.36), obesity (HR =3.43; 95% CI = 2.50, 4.70), and combat service (HR = 4.99; 95% CI = 1.29, 19.38). Ours is the first large-scale longitudinal study to report an association between PTSD and incident heart failure in an outpatient sample of US veterans. Prevention and treatment efforts for heart failure and its associated risk factors should be expanded among US veterans with PTSD.

Simons, R. L., Lei, M. K., Beach, S. R. H., Philibert, R. A., Cutrona, C. E., Gibbons, F. X., & Barr, A. (2016). **Economic hardship and biological weathering: The epigenetics of aging in a U.S. sample of black women.** *Social Science & Medicine, 150*, 192-200. doi:10.1016/j.socscimed.2015.12.001 *Background:* Past research has linked low socio-economic status (SES) to inflammation, metabolic dysregulation, and various chronic and age-related diseases such as type 2 diabetes, coronary heart disease, stroke, and dementia. These studies suggest that the challenges and adversities associated with low SES may result in premature aging and increased risk of morbidity and mortality. *Objective:* Building upon this research, the present study investigates various avenues whereby low income might accelerate biological aging. *Methods:* Structural equation modeling and longitudinal data from a sample of 100 Black, middle-aged women residing in the United States was used to investigate the effect of income on a recently developed epigenetic measure of biological aging. This measure can be used as a "biological clock" to assess, at any point during adulthood, the extent to which an individual is experiencing accelerated or decelerated biological aging. *Results:* Low income displayed a robust association with accelerated aging that was unaffected after controlling for other SES-related factors such as education, marital status, and childhood adversity. Further, our analyses indicated that the association between income and biological aging was not explained by health-related behaviors such as diet, exercise, smoking, alcohol consumption, or having health insurance. Rather, in large measure, it was financial pressure (difficulty paying bills, buying necessities, or meeting daily expenses) that accounted for the association between low income and accelerated aging. *Conclusions:* These findings support the view that chronic financial pressures associated with low income exert a weathering effect that results in premature aging.

Vaccarino, V., Goldberg, J., Rooks, C., Shah, A. J., Veledar, E., Faber, T. L., . . . Bremner, J. D. (2013). **Post-traumatic stress disorder and incidence of coronary heart disease: A twin study.** *Journal of the American College of Cardiology, 62*, 970-978. doi:10.1016/j.jacc.2013.04.085 *Objectives:* The aim of this study was to determine whether post-traumatic stress disorder (PTSD) is associated with coronary heart disease (CHD) using a prospective twin study design and objective measures of CHD. *Background:* It has long been hypothesized that PTSD increases the risk of CHD, but empirical evidence using objective measures is limited. *Methods:* We conducted a prospective study of middle-aged male twins from the Vietnam Era Twin Registry. Among twin pairs without self-reported CHD at baseline, we selected pairs discordant for a lifetime history of PTSD, pairs discordant for a lifetime history of major depression, and pairs without either condition. All underwent a clinic visit after a median follow-up of 13 years. Outcomes included clinical events (myocardial infarction, other hospitalizations for CHD and coronary revascularization) and

quantitative measures of myocardial perfusion by [^{13}N] ammonia positron emission tomography, including a stress total severity score and coronary flow reserve. *Results:* A total of 562 twins (281 pairs) with a mean age of 42.6 years at baseline were included in this study. The incidence of CHD was more than double in twins with PTSD (22.6%) than in those without PTSD (8.9%; $p < 0.001$). The association remained robust after adjusting for lifestyle factors, other risk factors for CHD, and major depression (odds ratio: 2.2; 95% confidence interval: 1.2 to 4.1). Stress total severity score was significantly higher (+95%, $p = 0.001$) and coronary flow reserve was lower (-0.21, $p = 0.02$) in twins with PTSD than in those without PTSD, denoting worse myocardial perfusion. Associations were only mildly attenuated in 117 twin pairs discordant for PTSD. *Conclusions:* Among Vietnam-era veterans, PTSD is a risk factor for CHD.

Williamson, J. B., Porges, E. C., Lamb, D. G., & Porges, S. W. (2015). **Maladaptive autonomic regulation in PTSD accelerates physiological aging.** *Frontiers in Psychology, 5*, 1571. doi:10.3389/fpsyg.2014.01571 A core manifestation of post-traumatic stress disorder (PTSD) is a disconnection between physiological state and psychological or behavioral processes necessary to adequately respond to environmental demands. Patients with PTSD experience abnormal oscillations in autonomic states supporting either fight and flight behaviors or withdrawal, immobilization, and dissociation without an intervening "calm" state that would provide opportunities for positive social interactions. This defensive autonomic disposition is adaptive in dangerous and life threatening situations, but in the context of every-day life may lead to significant psychosocial distress and deteriorating social relationships. The perpetuation of these maladaptive autonomic responses may contribute to the development of comorbid mental health issues such as depression, loneliness, and hostility that further modify the nature of cardiovascular behavior in the context of internal and external stressors. Over time, changes in autonomic, endocrine, and immune function contribute to deteriorating health, which is potently expressed in brain dysfunction and cardiovascular disease. In this theoretical review paper, we present an overview of the literature on the chronic health effects of PTSD. We discuss the brain networks underlying PTSD in the context of autonomic efferent and afferent contributions and how disruption of these networks leads to poor health outcomes. Finally, we discuss treatment approaches based on our theoretical model of PTSD.

Wolf, E. J., Bovin, M. J., Green, J. D., Mitchell, K. S., Stoop, T. B., Barretto, K. M., . . . Marx, B. P. (2016). **Longitudinal associations between post-traumatic stress disorder and metabolic syndrome severity.** *Psychological Medicine, 46*, 2215-2226. doi:10.1017/S0033291716000817 *Background:* Post-traumatic stress disorder (PTSD) is associated with elevated risk for metabolic syndrome (MetS). However, the direction of this association is not yet established, as most prior studies employed cross-sectional designs. The primary goal of this study was to evaluate bidirectional associations between PTSD and MetS using a longitudinal design. *Method:* A total of 1355 male and female veterans of the conflicts in Iraq and Afghanistan underwent PTSD diagnostic assessments and their biometric profiles pertaining to MetS were extracted from the electronic medical record at two time points (spanning ~2.5 years, $n = 971$ at time 2). *Results:* The prevalence of MetS among veterans with PTSD was just under 40% at both time points and was significantly greater than that for veterans without PTSD; the prevalence of MetS among those with PTSD was also elevated relative to age-matched population estimates. Cross-lagged panel models revealed that PTSD severity predicted subsequent increases in MetS severity ($\beta = 0.08$, $p = 0.002$), after controlling for initial MetS severity, but MetS did not predict later PTSD symptoms. Logistic regression results suggested that for every 10 PTSD symptoms endorsed at time 1, the odds of a subsequent MetS diagnosis increased by 56%. *Conclusions:* Results highlight the substantial cardiometabolic concerns of young veterans with PTSD and raise the possibility that PTSD may predispose individuals to accelerated aging, in part, manifested clinically as MetS. This demonstrates the need to identify those with PTSD at greatest risk for MetS and to develop interventions that improve both conditions.

Wolf, E. J., Logue, M. W., Hayes, J. P., Sadeh, N., Schichman, S. A., Stone, A., . . . Miller, M. W. (2016). **Accelerated DNA methylation age: Associations with PTSD and neural integrity.** *Psychoneuroendocrinology, 63*, 155-162. doi:10.1016/j.psyneuen.2015.09.020 *Background:* Accumulating evidence suggests that posttraumatic stress disorder (PTSD) may accelerate cellular aging and lead to premature morbidity and neurocognitive decline. *Methods:* This study evaluated associations between PTSD and DNA methylation (DNAm) age using recently developed algorithms of cellular age by Horvath (2013) and Hannum et al. (2013). These estimates reflect accelerated aging when they exceed chronological age. We also examined if accelerated cellular age manifested in degraded neural integrity, indexed via diffusion tensor imaging. *Results:* Among 281 male and female veterans of the conflicts in Iraq and Afghanistan, DNAm age was strongly related to chronological age (*rs* ~.88). Lifetime PTSD severity was associated with Hannum DNAm age estimates residualized for chronological age ($\beta = .13$, $p = .032$). Advanced DNAm age was associated with reduced integrity in the genu of the corpus callosum ($\beta = -.17$, $p = .009$) and indirectly linked to poorer working memory performance via this region (indirect $\beta = -.05$, $p = .029$). Horvath DNAm age estimates were not associated with PTSD or neural integrity. *Conclusions:* Results provide novel support for PTSD-related accelerated aging in DNAm and extend the evidence base of known DNAm age correlates to the domains of neural integrity and cognition.

Wolf, E. J., Sadeh, N., Leritz, E. C., Logue, M. W., Stoop, T. B., McGlinchey, R., . . . Miller, M. W. (2016). **Posttraumatic stress disorder as a catalyst for the association between metabolic syndrome and reduced cortical thickness.** *Biological Psychiatry, 80*, 363-371. doi:10.1016/j.biopsych.2015.11.023 *Background:* Metabolic syndrome (MetS), defined by a constellation of cardiometabolic pathologies, is highly prevalent among veterans, especially veterans with posttraumatic stress disorder (PTSD), and poses a major risk for adverse health outcomes, including neurodegeneration and mortality. Given this, we evaluated 1) the association between MetS and neural integrity, indexed by cortical thickness; 2) the relationship between PTSD and MetS; and 3) whether PTSD was associated with cortical thickness indirectly through MetS. *Methods:* The sample consisted of 346 US military veterans (89.3% male; 71.4% white) who deployed to Iraq, Afghanistan, or both. Neuroimaging data were available for 274 participants. *Results:* In whole-brain analyses, MetS was negatively associated with cortical thickness in two left and four right hemisphere regions, as follows: bilateral temporal lobe, including temporal pole,

fusiform gyrus, and insula, and extending into occipital cortex (left hemisphere) and orbitofrontal cortex (right hemisphere); bilateral precuneus, posterior cingulate, calcarine, and occipital-parietal cortex; and right rostral anterior cingulate cortex and central sulcus/postcentral gyrus. Path models showed that PTSD predicted MetS ($\beta = .19$, $p < .001$), which was associated with reduced cortical thickness ($\beta = -.29$ to $-.43$, all $p < .001$). *Conclusions:* Results from this young veteran sample provide evidence that PTSD confers risk for cardiometabolic pathology and neurodegeneration and raise concern that this cohort may be aging prematurely and at risk for substantial medical and cognitive decline. This study highlights the need to identify the molecular mechanisms linking PTSD to MetS and effective interventions to reduce PTSD-related health comorbidities.

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K. E., Neylan, T., . . . Marmar, C. (2010). **Posttraumatic stress disorder and risk of dementia among US veterans.** *Archives of General Psychiatry, 67*, 608-613. doi:10.1001/archgenpsychiatry.2010.61 *Context:* Posttraumatic stress disorder (PTSD) is highly prevalent among US veterans because of combat and may impair cognition. *Objective:* To determine whether PTSD is associated with the risk of developing dementia among older US veterans receiving treatment in the Department of Veterans Affairs medical centers. *Design:* A stratified, retrospective cohort study conducted using the Department of Veterans Affairs National Patient Care Database. *Setting:* Department of Veterans Affairs medical centers in the United States. *Participants:* A total of 181 093 veterans 55 years or older without dementia from fiscal years 1997 through 2000 (53 155 veterans with and 127 938 veterans without PTSD). *Main Outcome Measures:* During the follow-up period between October 1, 2000, and December 31, 2007, 31 107 (17.2%) veterans were ascertained to have newly diagnosed dementia according to International Classification of Diseases, Ninth Revision, Clinical Modification codes. *Results:* The mean baseline age of the veterans was 68.8 years, and 174 806 (96.5%) were men. Veterans with PTSD had a 7-year cumulative incident dementia rate of 10.6%, whereas those without had a rate of 6.6% ($P < .001$). With age as the time scale, Cox proportional hazards models indicated that patients with PTSD were more than twice as likely to develop incident dementia compared with those without PTSD (hazard ratio, 2.31; 95% confidence interval, 2.24-2.39). After multivariable adjustment, patients with PTSD were still more likely to develop dementia (hazard ratio, 1.77; 95% confidence interval, 1.70-1.85). Results were similar when we excluded those with a history of head injury, substance abuse, or clinical depression. *Conclusions:* In a predominantly male veteran cohort, those diagnosed as having PTSD were at a nearly 2-fold-higher risk of developing dementia compared with those without PTSD. Mechanisms linking these important disorders need to be identified with the hope of finding ways to reduce the increased risk of dementia associated with PTSD.

Zannas, A. S., Arloth, J., Carrillo-Roa, T., Iurato, S., Röh, S., Ressler, K. J., . . . Mehta, D. (2015). **Lifetime stress accelerates epigenetic aging in an urban, African American cohort: Relevance of glucocorticoid signaling.** *Genome Biology, 16*, 266. doi:10.1186/s13059-015-0828-5 *Background:* Chronic psychological stress is associated with accelerated aging and increased risk for aging-related diseases, but the underlying molecular mechanisms are unclear.

FEATURED ARTICLES *continued*

Results: We examined the effect of lifetime stressors on a DNA methylation-based age predictor, epigenetic clock. After controlling for blood cell-type composition and lifestyle parameters, cumulative lifetime stress, but not childhood maltreatment or current stress alone, predicted accelerated epigenetic aging in an urban, African American cohort (n=392). This effect was primarily driven by personal life stressors, was more pronounced with advancing age, and was blunted in individuals with higher childhood abuse exposure. Hypothesizing that these epigenetic effects could be mediated by glucocorticoid signaling, we found that a high number (n=85) of epigenetic clock CpG sites were located within glucocorticoid response elements. We further examined the functional effects of glucocorticoids on epigenetic clock CpGs in an independent sample with genome-wide DNA methylation (n=124) and gene expression data (n=297) before and after exposure to the glucocorticoid receptor agonist dexamethasone. Dexamethasone induced dynamic changes in methylation in 31.2 % (110/353) of these CpGs and transcription in 81.7 % (139/170) of genes neighboring epigenetic clock CpGs. Disease enrichment analysis of these dexamethasone-regulated genes showed enriched association for aging-related diseases, including coronary artery disease, arteriosclerosis, and leukemias. *Conclusions:* Cumulative lifetime stress may accelerate epigenetic aging, an effect that could be driven by glucocorticoid-induced epigenetic changes. These findings contribute to our understanding of mechanisms linking chronic stress with accelerated aging and heightened disease risk.

ADDITIONAL CITATIONS

Bernard, C. (1974). *Lectures on the phenomena of life common to animals and plants* (H. E. Hoff, R. Guillemin, & L. Guillemin, Trans.). Springfield, IL: Charles C Thomas. This classic text includes Bernard's writing on basic physiology and the influence of the environment on this. It includes a description of the milieu intérieur.

Blackburn, E. H. (2005). **Telomeres and telomerase: Their mechanisms of action and the effects of altering their functions.** *FEBS Letters, 579*, 859-862. doi:10.1016/j.febslet.2004.11.036 This paper describes the biology of telomeres, including their structure and function. It also describes factors that influence these parameters.

Cunningham, J. M., Johnson, R. A., Litzelman, K., Skinner, H. G., Seo, S., Engelman, C. D., . . . Boardman, L. A. (2013). **Telomere length varies by DNA extraction method: Implications for epidemiologic research.** *Cancer Epidemiology, Biomarkers & Prevention, 22*, 2047-2054. doi:10.1158/1055-9965.EPI-13-0409 This empirical paper compares telomere length estimates as a function of DNA extraction method. It shows substantial differences across methods that might contribute to variance across studies.

Kubzansky, L. D., & Koenen, K. C. (2009). **Is posttraumatic stress disorder related to development of heart disease? An update.** *Cleveland Clinic Journal of Medicine, 76*, S60-S65. doi:10.3949/ccjm.76.s2.12 This manuscript reviews the literature on PTSD-related cardiovascular disease and suggests possible pathways between the two. It also includes a discussion of the limits of our understanding of this pathway based on current research.

ADDITIONAL CITATIONS *continued*

Martin-Ruiz, C. M., Baird, D., Roger, L., Boukamp, P., Krunic, D., Cawthon, R., . . . von Zglinicki, T. (2015). **Reproducibility of telomere length assessment: An international collaborative study.** *International Journal of Epidemiology, 44*, 1673-1683. doi:10.1093/ije/dyu191 This empirical paper compared telomere length estimates as a function of laboratories and laboratory methods. They found evidence of major differences in estimates across laboratories.

McEwen, B. S. (2012). **Brain on stress: How the social environment gets under the skin.** *Proceedings of the National Academy of Sciences of the United States of America, 109*, 17180-17185. doi:10.1073/pnas.1121254109 This review paper describes multiple mechanisms linking stress to brain structure and function. These include the role of glucocorticoid signaling and growth factors on epigenetic processes, among others. The paper integrates these basic biological processes with the broader construct of allostasis.

Schnurr, P. P., & Green, B. L. (2004). **Understanding relationships among trauma, post-traumatic stress disorder, and health outcomes.** *Advances in Mind-Body Medicine, 20*, 18-29. This review article describes comorbidity between trauma, PTSD, and physical health disorders and discusses a variety of mechanisms that might link these. Potential mediators described include biological (e.g., HPA axis), behavioral (health and illness behaviors), psychological (PTSD comorbidity), and cognitive (e.g., biased attention) processes.

Szyf, M. (2013). **The genome- and system-wide response of DNA methylation to early life adversity and its implication on mental health.** *Canadian Journal of Psychiatry, 58*, 697-704. This comprehensive review describes the influence of multiple forms of early life adversity on DNA methylation and psychiatric symptoms. It includes a basic biological primer on DNA methylation and describes the functional and adaptive role of DNA methylation.

Acknowledgements

This work was supported by a Presidential Early Career Award for Scientists and Engineers (PECASE) to Erika Wolf and administered through the United States Department of Veterans Affairs Office of Research & Development (award # PECASE 2013A).