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Traumatic Stress and Accelerated Cellular Aging: From Epigenetics to Cardiometabolic Disease

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Abstract

Purpose of review—The aim of this paper is to review the recent literature on traumatic stress-related accelerated aging, including a focus on cellular mechanisms and biomarkers of cellular aging and on the clinical manifestations of accelerated biological aging.

Recent findings—Multiple lines of research converge to suggest that PTSD is associated with accelerated aging in the epigenome, and the immune and inflammation systems, and this may be reflected in premature onset of cardiometabolic and cardiovascular disease.

Summary—The current state of research paves the way for future work focused on identifying the peripheral and central biological mechanisms linking traumatic stress to accelerated biological aging and medical morbidity, with an emphasis on processes involved in inflammation, immune functioning, oxidative stress, autonomic arousal, and stress responding. Ultimately, such work could help reduce the pace of biological aging and improve health and wellness.

Keywords

traumatic stress; PTSD; accelerated aging; epigenetic clock; inflamm-aging; immunosenescence

Introduction

It has long been recognized that traumatic stress is associated with physical health decline. Early writings (from 1871) on this phenomenon are found in the work of Dr. Jacob Mendez Da Costa [1], who studied over 300 soldiers from the American Civil War with striking cardiac and respiratory symptoms, which Da Costa referred to as “irritable heart.” The same symptoms were later referred to as “soldier’s heart” and documented in substantial detail among veterans of World War I. Specifically, in 1916, Mackenzie [2] and Rudolf [3] described a condition in which military members became “exhausted,” and exhibited shortness of breath, heart pain, rapid heartbeat, and elevated pulse. Many were deemed too ill to return to the military and sent to hospitals to convalesce for extended periods of time. Both MacKenzie [2] and Rudolf [3] doubted that the condition was due to an organic heart

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defect or disease. Rather, they surmised that the heart was affected by stress-related "strain on the nervous system," and the impact of the nervous system on the circulatory system, i.e., "nervous instabilities of the circulation" [3, pg. 799]. Neither author dismissed the symptoms as anxiety, but rather reflected on the mechanisms by which traumatic stress might lead to these cardiovascular symptoms and long-term disability. With a prescient understanding of the genetic contribution to traumatic stress and its health correlates (discussed below), Rudolf [3] further opined: "The conclusion seems to be that in very many cases the patient has always had a circulation that is unstable, and any factor such as nerve strain may in these predisposed individuals lead to an exaggeration of the instability" (pg. 801).

In this manuscript, we provide a contemporary view of the effects of traumatic stress on cardiac health and discuss recent evidence for a link between PTSD and accelerated aging. We first briefly review recent literature concerning evidence for a link between PTSD and cardiometabolic and cardiovascular disease and refer readers to prior reviews [4–7] for more detailed description of these associations. We propose that premature onset of traumatic stress-related health conditions is a clinical manifestation of an underlying accelerated aging process. We focus the majority of the review on discussion of biological/cellular indicators of accelerated aging and their possible contributions to the link between posttraumatic stress disorder (PTSD) and pre-mature onset of cardiovascular and cardiometabolic disease. We discuss both genetic and epigenetic indices of traumatic stress-related accelerated aging, highlight on-going questions and debate in the literature, and suggest future research endeavors that may help to resolve a variety of issues and questions that limit the field at present.

Traumatic Stress and Premature Metabolic and Cardiovascular Decline

PTSD has been associated with a number of metabolic and cardiovascular disorders, with many studies suggesting that this relationship is independent of chronological age. Recent studies support associations between PTSD and risk for metabolic syndrome [8–12]—a condition defined by co-occurring obesity, hypertension, lipid abnormalities, and elevated blood sugars [13]. Estimates from both epidemiological and clinical samples suggest that the prevalence of metabolic syndrome is approximately 40% among those with PTSD [8, 10•, 11•], which is up to twice that of age-matched individuals without PTSD [10•]. In one of the few longitudinal studies of PTSD and metabolic syndrome, we recently demonstrated in a large, national sample of male and female veterans returning from the wars in Iraq and Afghanistan that PTSD symptom severity was associated with increasing metabolic syndrome severity over the course of approximately 2.5 years [11•]. Further, in an independent sample of predominately male veterans deployed to the same wars, we found that PTSD severity was cross-sectionally associated with metabolic syndrome severity and through this, linked with widespread bilateral decreases in cortical thickness [12]. Other studies have also found evidence of an association between metabolic syndrome and decreased neural integrity [14] and related to this, associations between metabolic syndrome and age-independent reductions in cognitive functioning [15]. These findings raise the possibility that metabolic syndrome could be a risk factor for accelerated aging in the brain. This parallels research suggesting that PTSD may be associated with accelerated aging as

reflected in pre-mature cognitive decline [16], dementia [17], and reduced cortical thickness [18]. This association is discussed in detail in this issue by Mohlenhoff et al. [19] in a review which posits that poor sleep among PTSD patients may account for cognitive deficits via inflammatory pathways and amyloid protein build-up in the brain.

Metabolic syndrome greatly increases the risk for cardiovascular disorders, and consistent with this, there is substantial evidence of associations between PTSD and a variety of cardiovascular diseases. This includes heart disease and heart failure [20–23], hypertension [24], stroke and/or myocardial infarction [25, 26], and chronic obstructive pulmonary disease [27]. Based on these associations, we [4] and others [28] have suggested that it may be appropriate to consider PTSD as a risk factor when deciding which patients require early screening for cardiometabolic pathology.

The working hypothesis regarding the link between PTSD and cardiometabolic/cardiovascular disease is that the stress of trauma-related symptoms leads to the premature development of these conditions [11•, 29, 30••]. However, it is also possible that the associations between PTSD and cardiovascular and cardiometabolic disorders are at least partially influenced by underlying genetic risk. This could occur in a number of different ways. One possibility is that genetic variation could jointly raise the risk for both PTSD and cardiometabolic disorders. Consistent with this, Sumner et al. [31] found that genome-wide risk for PTSD was correlated with genome-wide risk for coronary artery disease, with somewhat weaker evidence for shared genetic risk across PTSD and body mass index and insulin levels. Using an alternate methodology, Pollard et al. [32] found overlap between the candidate genes previously associated with PTSD and the candidate genes previously associated with cardiovascular disease and type 2 diabetes. Moreover, that study found overlap in the upstream genes (e.g., *TNFα,* involved in inflammation) that regulated both PTSD- and cardiovascular-associated genes, as well as overlap in their gene targets (e.g., the NfκB complex, also involved in inflammation). This suggests that the genetic link between PTSD and cardiovascular disorders is likely mediated by common genetic effects on the inflammation and immune systems [32]. Consistent with this, Breen et al. [33] found that gene networks critical for immune system functioning were associated with PTSD in gene expression data from two samples of military veterans. Collectively, these studies provide further evidence of a genetic basis, perhaps mediated by inflammation, to the link between PTSD and cardiovascular/metabolic disorders.

A second, non-mutually exclusive hypothesis concerning the role of genetics in PTSD and cardiovascular/metabolic disease comorbidity is that genotype may moderate this association such that individuals with greater genetic risk may be more apt to develop one of these health conditions given PTSD. We recently demonstrated that genome-wide risk for obesity operated in just this way. Specifically, we found that the association between PTSD and metabolic syndrome was amplified among individuals with the greatest genome-wide polygenic risk for obesity [34]. Further, we showed that this same index of obesity genetic risk also interacted with the severity of metabolic syndrome features to predict decreased cortical thickness in the left rostral middle frontal gyrus, an area of the brain previously shown to be critical for regulation of both affect and eating-related behaviors [35]. Thus, increased risk for metabolic syndrome among PTSD patients is likely to be multiply

determined, with both main and interactive effects of genetic risk and trauma-related psychiatric symptoms.

Biological Mechanisms of Accelerated Aging

We propose that PTSD-related pre-mature onset of health disorders is but the outward sign of accelerated aging and that studies that seek to understand this phenomenon must study the cellular mechanisms underlying it (Figure 1). Key questions in this line of inquiry have to do with our ability to determine: (a) which biological processes are true *mechanisms* of cellular aging versus *biomarkers* of a distinct mechanism; (b) the extent to which accelerated cellular aging represents a simple increase in the pace of the canonical processes that govern aging, as opposed to a discrete pathological aging process; (c) the biological systems that influence accelerating aging and serve as the link between traumatic stress and accelerated aging; (d) the reliability across, and interplay between, different indicators of accelerated cellular aging; and (e) the influence of chronological age on accelerated cellular aging and whether the impact of various stressors on cellular age is dependent on critical windows in development, or on other demographic factors such as ethnicity. We next review biological markers of accelerated aging, in the epi/genome and immune/inflammatory systems and discuss how the questions raised above might guide future research.

Traumatic Stress and Accelerated Cellular Aging in the Epi/genome

Two epi/genetic metrics of accelerated cellular aging have received the majority of the attention in the literature to date. Telomeres, which are repeat DNA sequences at the ends of chromosomes that protect chromosomal integrity by preventing coding regions of the genome from being truncated during cell division, have been shown to shorten with age (i.e., with each cell division unless otherwise replenished [36]). A variety of biological processes, including inflammation and oxidative stress, prompt cell division [37] and cause telomeres to shorten. A number of environmental and individual pathogenic factors have been associated with age-adjusted telomere shortening [38, 39••] and this has often been interpreted as an index of accelerated aging [40]. For example, a recent meta-analysis of associations between psychiatric disorders (including PTSD) and leukocyte telomere length reported an overall significant effect suggestive of shorter telomere length among psychiatric patients [41]. Results also raised the possibility (with somewhat weaker evidence) that this effect was greater in PTSD studies (compared to studies examining other forms of psychopathology) and older (versus younger) samples. The most recent PTSD/telomere literature continues to suggest mixed results across samples (see, for example, Roberts et al. [42], who reported that PTSD diagnosis was associated with shorter telomere length among female nurses vs. Bersani et al. [43] who found no effect for PTSD among male veterans, but did report an effect for early trauma exposure).

Numerous concerns have been raised about telomeres as a metric of accelerated aging. First, there is evidence that methodological variability contributes to differences in the precision of telomere length estimates [44]. Second, on average, telomeres tend to show a relatively weak magnitude of association with chronological age ($r \approx .30$; [45]) and this poses problems for conceptualizing telomere length estimates as markers of cellular age specifically. Related to

this, Lowe, Horvath, and Raj [46] proposed that telomeres may not be a marker for cellular aging, but rather, an index of cellular senescence (i.e., when cells are no longer able to divide), a process which Lowe et al. suggested is conceptually and biologically distinct from aging. Third, a recent meta-analysis concerning the relationship between stress and telomere length found that while stress was significantly associated with age-adjusted telomere length, the effect was small in magnitude, there was evidence of publication bias in the literature, and when this was corrected for, the association between stress and telomere length was no longer significant [47]. Collectively, these concerns raise questions about the use of telomere length estimates to index aging or accelerated aging and suggest that they may be more useful in understanding the causes and consequences of cellular senescence.

More recently, DNA methylation (DNAm) data have been used to index cellular age and accelerated age. There is ample evidence of a strong association between DNAm patterns across the epigenome and chronological age [48] and two prominent algorithms, referred to as *DNAm age*, have emerged for estimating cellular age from DNAm data. Horvath [49••] identified 353 DNAm loci (in or near 353 different genes) that were combined into a weighted score to predict chronological age with a correlation of $r = .96$ across many different types of tissues, ranging from blood and brain to liver and kidney. At about the same time, Hannum et al. [50••] developed a DNAm age estimate using whole blood DNAm levels at 89 loci (in the "all data" model; the final model was based on a subset of 71 probes), which was also found to be associated with chronological age at $r = .96$. These DNAm age estimates are thought to index the "*epigenetic clock*" and while they both show strong associations with chronological age, there is still sufficient variability in each estimate at the individual level to examine how they deviate from chronological age. This is typically operationalized by regressing estimated DNAm age (using either the Hannum or Horvath algorithm) on chronological age and saving the residuals from this equation to index cellular age that deviates from chronological age. Positive residuals (i.e., when DNAm age is over-predicted relative to chronological age) can be conceptualized as capturing accelerated aging while negative residuals (i.e., under-predicted DNAm age) reflect decelerated aging. This is a useful framework for conceptualizing the residuals but it is important to remember that, in truth, the residuals exist along a single dimension that spans positive and negative values.

Accelerated DNAm age, primarily based on the Horvath algorithm, has been associated with a variety of diseases and health outcomes including cancer [51], HIV- [52] and Alzheimer's-related [53] neurocognitive impairment, Parkinson's disease [54] and shortened time to death [55, 56••, 57]. Five studies (Table 1) have evaluated the associations between trauma and/or PTSD and accelerated DNAm age using the Horvath and/or Hannum algorithms. Boks et al. [58] modeled change in Horvath DNAm age immediately pre/post warzone deployment in a small sample of male Dutch military veterans and found that military trauma predicted increased DNAm age while change in PTSD over time was negatively associated with change in DNAm age. The relationship between DNAm age and chronological age was not factored into those analyses. Zannas et al. [59] reported no association between trauma or PTSD with Horvath DNAm age adjusted for chronological age, but did find evidence of an association between daily life stressors and accelerated Horvath DNAm age; this effect was stronger among relatively older subjects in this predominately black, female civilian sample with substantial trauma histories. Wolf et al.

[60••, 61] reported that PTSD symptoms were associated with accelerated Hannum DNAm age in two distinct samples of predominately male military veterans with substantial PTSD symptoms. Specifically, Wolf et al. [60••] found that in a relatively young sample of veterans (average age in early 30s), lifespan PTSD symptoms predicted accelerated Hannum DNAm age and accelerated Hannum DNAm age was associated with decreased performance on tests of working memory and executive functioning via reduced white matter integrity in a region of the corpus callosum (the genu) critical for connectivity across the right and left prefrontal cortices; no effects for the Horvath algorithm were evident in that sample. In a follow-up study, Wolf et al. [61] found that lifetime PTSD hyperarousal symptoms (i.e., insomnia, concentration problems, anger, hypervigilance, exaggerated startle) were associated with accelerated Hannum DNAm age among veterans with an average age in their mid-50s. Additionally, veterans in that study with accelerated Hannum DNAm age at baseline were at increased risk for all-cause mortality during the 6.5 year medical record study review period.

Given these mixed patterns of results across studies and the variability in findings across the two algorithms, Wolf et al. [62] conducted a meta-analysis of over 2000 subjects and nine cohorts contributing to the Psychiatric Genomics Consortium PTSD Epigenetics Workgroup [63] and found that lifetime PTSD symptom severity and childhood trauma (when assessed with a particularly sensitive self-report instrument) were associated with accelerated Hannum DNAm age. No trauma or PTSD-related effects emerged for the Horvath index. Collectively, the nascent literature to date provides greater support for an association between PTSD and accelerated aging in DNAm using the Hannum index of epigenetic age, though it remains unclear what biological processes might link PTSD to accelerated Hannum DNAm age. However, as not all studies have employed both the Hannum and Horvath algorithms, it is difficult to determine if there is truly specificity between PTSD and the Hannum algorithm. As well, the explanation for differential patterns of effects across the two highly correlated [60••] age algorithms is unclear. It is possible that the Hannum index is more sensitive to PTSD-related biological factors found in blood, given that this index was developed in whole blood. The Horvath index, in contrast, is a multi-tissue age predictor and perhaps it is less sensitive to blood-specific factors that impact DNAm. Additional research is needed (discussed below) to determine how these algorithms differ from each other at a mechanistic level.

Traumatic Stress and Inflammation and Immune Response

Other potential biological indices of cellular aging include the functioning and efficiency of the immune and inflammatory systems. The immune system tends to become less adaptive with advancing age, as indicated by poorer response to vaccinations, and loss of acquired immunity to pathogens. This condition has been labeled "*immunosenescence*" and can be operationalized using the ratio of CD4 to CD8 T-cells [64, 65]. When this ratio is very low (i.e., < 1), this can be a sign of a reduced number of naïve T-cells in favor of an increased number of differentiated memory T-cells, which can lead to a senescent T-cell phenotype, shortened telomeres, and increased inflammation [66]. Low CD4/CD8 T-cell ratios have been shown to predict mortality over the course of 4 years among older adults [65]. The inflammation system also undergoes age-related changes. "*Inflamm-aging*" [67] is the term

used to describe age-related increases in chronic low levels of inflammation, which can be indicated by increased pro-inflammatory cytokines, and reduced natural killer and monocyte efficacy [68•, 69]. Decreased innate immune response in the context of increased inflammation has been associated with a variety of age-related diseases [68•] and as such, the integrity of the immune and inflammation systems may serve as a good index of cellular aging and accelerated aging.

There is evidence to suggest that PTSD is associated with diminished immune response and increased number of late stage/differentiated T-cells. Aiello et al. [70•] showed that PTSD was associated with lower CD4/CD8 T-cell ratios and a greater number of late-stage (relative to naïve) T-cells. These results were obtained in a sample of 85 adults with extensive community trauma histories and analyses controlled for chronological age, suggesting that PTSD might be accelerating this age-related immune process. A similar pattern of results was obtained by Sommershof et al. [71], who found reductions in naïve $CD3^+$ and $CD8^+$ T-cells and increases in late stage $CD3^+$ and $CD8^+$ T-cells in a relatively small sample of PTSD cases compared to controls. PTSD-related immune system aberrations could help explain the link between PTSD and autoimmune disorders [72]. While there is scant literature concerning PTSD and immune system functioning, there is relatively more research examining associations between PTSD and inflammation. We recently reviewed the role of PTSD-associated inflammation in accelerated aging and neurocognitive decline [73] and refer readers to that publication for more in depth discussion of this topic. The general pattern of results across that line of research provides support for associations between PTSD and C-reactive protein [74, 75, 76•], TNFα [76•, 77], IL-6 [77], and IL-1β [77]. Additionally, a growing body of evidence suggests that PTSD is cross-sectionally associated with impaired endothelial functioning as measured by circulating markers of endothelial cell integrity [76•], and direct observation of nitric oxide-related vascular reactivity in the brachial artery [78]. There is also preliminary evidence that PTSD predicts increasing endothelial cell dysfunction over time [76•]. We suspect that associations between PTSD and dysregulated immune and inflammation processes may be a function of a broader multisystem accelerated aging process.

Potential Mechanisms linking Traumatic Stress to Accelerated Aging

One reason that we hypothesize that the functioning of the immune/inflammation systems may be particularly related to cellular aging is because markers of these systems show associations with accelerated Horvath and Hannum DNAm age. Specifically, robust associations between estimated white blood cell counts and accelerated DNAm age have emerged across studies, such as a negative relationship between CD4 T-cell counts and accelerated Hannum DNAm [55, 60••, 61–62]. There is also preliminary evidence for an association between Horvath epigenetic age acceleration (adjusted for white blood cell counts) and increased C-reactive protein as well as between Hannum epigenetic age acceleration (in an index combined with white blood cell counts, see below) and increased C-reactive protein [78]. However, the interpretation of these associations is not yet clear. These correlations could suggest that reductions in the integrity of the immune and inflammation systems drive accelerated aging in DNAm (or vice versa), or the convergence of these metrics of cellular aging could be due to a distinct and more basic biological

process. Related to this, Chen et al. [55], Quach et al. [79], and Horvath et al. [80] combined data from DNAm age and white blood cell counts to create a new index of immune system aging in blood. They showed that this new metric out-performed other age-adjusted DNAm age estimates in predicting important outcomes, such as time until death [55], and a variety of cardiometabolic measures [79]. Though chronological age was regressed out of this combined metric of DNAm age and immune system age, one concern about this approach was that the immune system components used to form this index were selected on, and weighted by, their univariate associations with chronological age (in a separate dataset). This could have the effect of masking multivariate associations between the immune parameters and chronological age or otherwise introducing a form of criterion contamination by enhancing the immune components that are known to be age-related and then finding, perhaps not surprisingly, that they predict age-related disease and decline. Longitudinal studies with estimated white blood cell counts and DNAm age estimates measured repeatedly over time are needed to fully understand the association between immune system functioning and accelerated epigenetic aging and to determine which index is the most useful for measuring biological age, predicting meaningful outcomes, and tracking response to intervention. Likewise, such work could help inform our understanding of differences that emerge across the Horvath and Hannum age calculators, with respect to their associations with disease and other pathogenic factors, such as traumatic stress.

There are numerous other potential mechanisms that might link PTSD to accelerated cellular aging and premature cardiometabolic outcomes, and a detailed review of each would require a much longer article, but we will briefly note them here. First, Zannas et al. [59] showed that the loci included in the Horvath DNAm age algorithm were disproportionately located in or near glucocorticoid response elements and that a substantial percentage of the Horvath loci showed dynamic changes in DNAm (and that genes near these probes showed changes in transcription) in response to the glucocorticoid dexamethasone. This suggests that epigenetic aging could be influenced by activation of the biological stress response system, which also contributes to cardiometabolic pathology [29]. Second, oxidative stress could contribute to accelerated aging [30••, 73]. Free radicals form as part of the cellular response to pathogens and give rise to inflammation, which, if not countered by anti-oxidants, promotes oxidative stress. Prolonged oxidative stress damages cell membranes and cellular functioning, leading to decreased efficacy of the immune system [81], and immunosenescence. A third possibility is that autonomic system dysregulation, as manifested by enhanced sympathetic reactivity (e.g., heart rate reactivity, heart rate variability, blood pressure) or failure of the parasympathetic nervous system to quell such reactivity could accelerate aging [82] and lead to cardiometabolic pathology [29, 82]. For example, a recent study found that PTSD symptom severity predicted increased negative-affect related autonomic arousal, which in turn, was associated with worse endothelial functioning [83], a potential biomarker of cellular aging. Collectively, these (and other) biological systems and processes likely exert transactional effects on cellular aging and increase risk for early-onset disease through broad dysregulation across a number of inter-related systems.

Directions for Future Research

Given this, we propose research that could be useful for identifying the biological mediators of accelerated aging and testing interventions to slow its pace. Rodent cellular age predictors have been developed recently [84•, 85] and these could prove useful for pinpointing the biological mechanisms of accelerated DNAm age, for studying the effects of acute and chronic stress on DNAm age, and for examining the influence of developmental critical periods on cellular aging. Mouse models could also allow for the interrogation of transgenerational effects of stress and trauma on cellular aging in subsequent generations. The use of mouse models has already suggested that hormones and diet impact epigenetic age in mice as measured by mouse epigenetic clock algorithms [84•]; specifically, ovariectomized mice had significantly increased epigenetic age, and F1 offspring fed a high-fat diet showed accelerated epigenetic aging in the liver (with effects exacerbated if the F0 maternal generation was fed a low-fat diet). This same research group also reported that the human-derived Horvath DNAm age algorithm failed to accurately predict chronological age when applied to DNAm data from mice [84•]. These differences may be a function of technical challenges in defining epigenetic clock sites across species, and/or differential associations between DNAm and aging across species [84•].

Future research could also extend the study of PTSD-related accelerated DNAm from peripheral blood samples to central tissue. Lu et al. [86] identified genetic predictors of DNAm age in multiple post-mortem brain regions and these findings carry implications for understanding mechanisms of accelerated aging. Future PTSD brain bank studies could use similar methodology to evaluate mechanisms of PTSD-related accelerated aging in the brain. Specifically, using *in situ* hybridization and immunohistochemistry, RNA and protein expression of candidates genes implicated in PTSD- and HPA-axis functioning (e.g., *CRF*, *FKBP5*, *NR3C1, SKA2*) [87–91], oxidative stress (*RORA*, *ALOX12*) [30••, 92••, 93], and inflammation (*TNFα*, *CRP*) [32, 74–77], could be compared across brain regions (in both neurons and glia) and the periphery. To discern which cellular elements drive the hypothesized effects on DNAm age, fluorescence activated cell sorting (FACS) could be used to interrogate differential methylation status of the loci in the age algorithms, and reactive oxygen species (ROS) levels, in glia compared to neurons across brain regions. Finally, new and powerful approaches such as Drop-seq, which allows for the sequencing and analysis of genes in a single cell [94], would enable highly parallel analysis of single cells by RNA-seq in order to identify other putative biological candidates across distinct neuronal and glial subtypes. These complementary approaches will be essential in furthering an understanding of the mechanisms of altered cellular aging and its role in PTSD.

Outside of human postmortem approaches, human induced pluripotent stem cell (iPSC) technologies offer a unique approach towards modeling the contribution of genetic factors to neuropsychiatric disorders, and provide access to patient-specific cells [95]. Recent work has described a novel reprogramming approach using neuronal microRNAs to directly convert human fibroblasts to mature neuronal subtypes, and retain many markers of cellular age including Horvath DNAm age estimates and telomere length [96]. These approaches have allowed investigators to generate neurons from healthy donors of different ages, and confirm that the epigenetic age of the reprogrammed neurons emulates the chronological age of the

donor [96]. Future work could combine neuronal reprogramming approaches with DNAm editing technologies [97], in which neurons from individuals with PTSD could be epigenetically edited (methylated or demethylated) in vitro at specific CpG loci, and the subsequent effect of these “edits” on readouts of cellular age could be queried. The use of directly reprogrammed neurons as a model of neuronal aging would have wide-ranging potential for identifying biomarkers, and studying the mechanisms underlying cellular aging in individuals with PTSD.

There is preliminary evidence that healthy diet, moderate alcohol use, exercise, and educational attainment may be protective against accelerated aging [79] and these are logical behavioral targets for intervention. It is unknown if successful PTSD treatment (e.g., psychotherapy) might have a far reaching effect on reducing the pace of cellular aging, but the addition of DNAm data to clinical trials could begin to address this question. From a pharmacological perspective, antioxidant compounds could be evaluated for efficacy in preventing or reversing accelerated cellular age. Promising antioxidant compounds include the mitochondria-targeted antioxidant SS31, which has been shown to protect neurons from neurotoxins *in vitro* [98], and L-carnitine, which crosses the blood brain barrier (BBB) [99], reduces oxidative stress damage in brain tissue, and has shown promising results across a number of functional outcomes in human studies [100–102]. Related to this, given that BBB degradation may result, in part, from substantial peripheral inflammation related to both PTSD and metabolic pathologies [103, 104], intriguing targets for intervention include pharmacological agents involved in BBB integrity. For example, adenosine has been shown to enhance gliosis, inflammation, and BBB permeability secondary to sleep loss [105, 106]. Research in rodent models has shown that antagonism of the adenosine receptor A_{2A} is able to reverse sleep-restriction induced increases in BBB permeability [105], suggesting another potential approach for reversing accelerated aging.

Conclusions

The research reviewed in this article underscores the importance of early identification of accelerated aging. All signs suggest that once this process is underway, it exacts a multi-system toll and may perpetuate an increasing array of pathological biological responses. The field is wide open for studying if targeted interventions can reduce the pace of the epigenetic clock. The research reviewed in this article highlights the importance of studying the neurobiological health consequences of traumatic stress, as opposed to only focusing on the neurobiology of PTSD, and of distinguishing the clinical manifestations of accelerated aging (i.e., medical morbidity) from the cellular processes underlying it. Ultimately, having a clear, biological definition of accelerated aging will help in the identification of the relationships between multiple biological indicators of cellular aging across peripheral and central tissues. This will advance the lessons learned from the early writings on soldier’s heart [1–3] and improve the health and wellness of present day trauma survivors.

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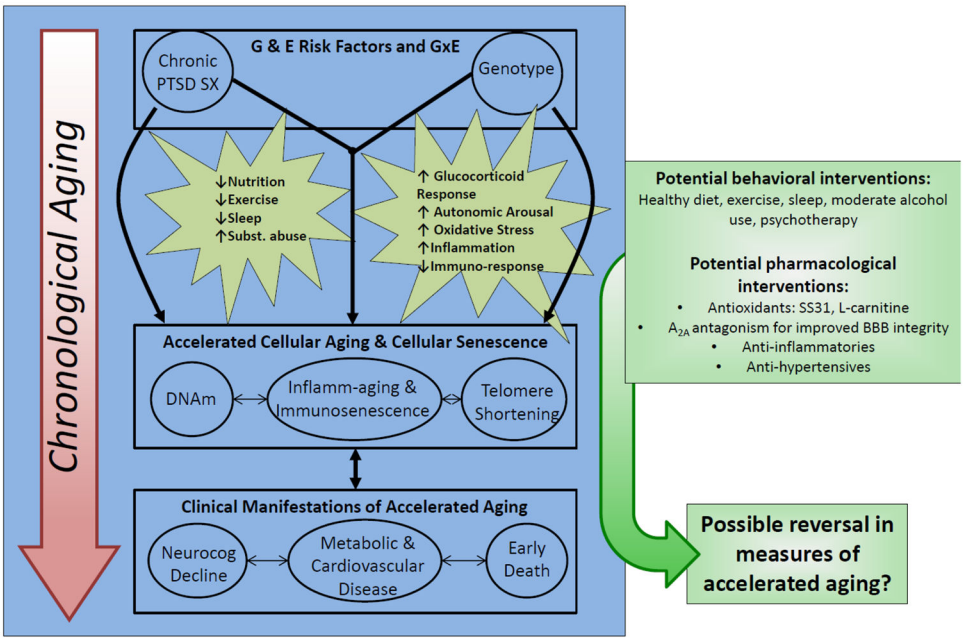

Figure 1.

The figure shows a conceptual model of the hypothesized associations between PTSD, genetic risk, interrelated indicators of accelerated cellular aging and cellular senescence, and clinical manifestations of accelerated aging, which are also likely to be interrelated. The figure shows that all of these processes occur in the context of chronological aging and it also lists hypothesized targets for research aimed at identifying the mechanisms of cellular aging and reducing the pace of biological aging.

G = genetic; E = environmental; PTSD = posttraumatic stress disorder; DNAm = DNA methylation; neurocog = neurocognitive; BBB = blood brain barrier.

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Table 1

Summary of Studies to Date Evaluating Associations between Trauma, PTSD, and DNAm Age Measures

Author	Method	Sample Size & Description	Stress Variables	Hannum Effect	Horvath Effect
Boks et al., 2015 [58]	Longitudinal	96 Dutch male soldiers pre & post deployment	Combat trauma; childhood trauma; & PTSD sev	NE	*Combat*: + DNAm age from pre-to-post *Childhood trauma*: NS *Δ PTSD*: - DNAm age from pre-to-post
Zannas et al., 2015 [59]	X-sectional	392 mostly female, African American urban community members	Cumulative personal life stressors; childhood trauma; & PTSD sev	NE	*Life Stressors*: + DNAm age compared to chron age *Childhood Trauma*: NS *PTSD*: NS
Wolf et al., 2016 [60]	X-sectional	281 mostly male, mostly white US veterans of wars in Iraq/ Afghanistan	Latent lifespan PTSD sev & lifetime trauma exposure	*Trauma*: NS *PTSD*: + DNAm age compared to chron age	NS
Wolf et al., in press [61]	X-sectional	339 mostly male, white, non-Hispanic mixed-era US veterans	Lifetime trauma exposure; lifetime PTSD sev; lifetime PTSD sx cluster sev	*Trauma*: NS *Total PTSD sx*: NS *PTSD Hyperarousal sx*: + DNAm age compared to chron age	NE
Wolf et al., 2017 [62]	X-sectional meta-analysis	2,186 participants from 9 cohorts, spanning sex, race, and military status	Lifetime trauma exposure; childhood trauma exposure; current and lifetime PTSD dx & current and lifetime PTSD sev	*Lifetime Trauma*: NS *Childhood Trauma*: + DNAm age compared to chron age (when assessed with specialized measure) *Current & Lifetime PTSD dx*: NS *Current PTSD sev*: NS *Lifetime PTSD sev*: + DNAm age compared to chron age	NS

Note. X = cross; PTSD = posttraumatic stress disorder; sev = severity; sx = symptom; dx = diagnosis; chron = chronological; NE = not evaluated; NS = not significant; DNAm = DNA methylation