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Accelerated Aging in Serious Mental Disorders

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Abstract

Purpose of Review: Clinical, epidemiological and biological evidence raise the possibility that serious mental disorders (SMD's) are associated with accelerated biological aging. To the extent this is true, SMD's should not simply be considered in terms of mental illness or brain dysfunction, but also as "whole body" and multi-system illnesses, or else as conditions with significant somatic concomitants.

Recent Findings: The concept of accelerated biological aging in SMD's is supported by reports of accelerated changes in certain biomarkers normally associated with the aging process.

Summary: We define and discuss several proposed biological aging markers that have been examined in SMD's, we review the most recent findings, and we conclude with opinions regarding the merits and meanings of these markers, their usefulness in understanding and treating SMD's, and remaining questions and future directions in this area of research.

Keywords

Serious mental disorders; Aging; Biological aging; Telomeres; Epigenetics

1. INTRODUCTION

Serious mental disorders (SMD's) are associated with an increased risk of medical illnesses and premature mortality from natural causes, with lifespans up to 25 years shorter than the general population [1]. Although lifestyle and socioeconomic factors play a role, the psychiatric condition itself may be an independent risk factor, even after excluding death by suicide [1]. The particular medical illnesses that are more frequent in SMD's are those that are more commonly seen with advanced age, such as cardiovascular disease and others. This has raised the possibility that SMD's are associated with accelerated biological aging. Whereas chronological age is measured by the passage of time, biological age is defined

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physiologically and functionally and is more closely associated with disease processes and mortality.

2. PROPOSED MARKERS OF BIOLOGICAL AGING IN PSYCHIATRY

2.1 Telomere Length

Telomere length (TL) determinations, generally in peripheral leukocytes (LTL), are the most widely studied markers of biological aging in SMD's. Telomeres, which cap DNA strands, protect chromosomes from damage and replicative senescence [2]. Telomeres shorten with repeated mitoses as well as with chronic exposure to oxidation, inflammation and possibly to the stress hormones, cortisol and catecholamines, unless acted upon by the telomere-lengthening enzyme, telomerase, or by alternative telomere-lengthening mechanisms [2]. When telomeres critically shorten, cells undergo replicative senescence or apoptosis or become genomically unstable. Telomere length inversely tracks chronological age, as LTL's shorten at an average rate of approximately 25–30 base pairs per year, and the correlation between LTL and chronological age has been reported as −0.30 [3]. Shortened LTL is associated with, and longitudinally predicts, poor physical health and is significantly correlated with all-cause mortality [4–6]. Most studies have replicated findings of LTL shortening in chronic psychological stress and in SMD's (especially major depressive disorder - MDD) [2,5,7–8], but the "toxic ingredients" of stress and SMD are unknown. Increases in inflammation and oxidative stress and stress hormones are prime candidates [2,8–13]. Because these biochemical factors can, themselves, be associated with physical disease and decreased life span, it is uncertain whether LTL shortening directly relates to health and age-associated outcomes, or rather, serves as a proxy or "canary in a coal mine," informing on a toxic cellular milieu [2,14], and these possibilities are not mutually exclusive [15]. In any event, it is possible that LTL shortening has pathophysiologic significance in its own right [2,14].

Further complicating interpretation of telomere shortening in SMD's is the question of which comes first. Studies on within-person longitudinal relationships between LTL and certain psychiatric symptoms (mainly symptoms of depression and anxiety), which could suggest a causal direction, have provided so far contrasting findings [16–21]. While it is intuitive to assume that stress and SMD's eventuate in shortened telomeres, it is also possible that (a) shortened telomeres are a risk factor for developing certain SMD's [22–25], and (b) shortened telomeres and SMD's both arise from common antecedents [15,26] such as environmental factors, or common genetic underpinnings. For example, first episode, never-medicated depressed adolescents already show significant LTL shortening [23], as do never-depressed girls at high risk for developing depression [27]. Indeed, familial risk for MDD [27] or bipolar disorder (BD) [28] are reportedly associated with reduced LTL, although a recent cohort study showed that genetic risk for MDD, BD and schizophrenia was not associated with shorter LTL [29]. Telomere length is partly heritable, with estimates of 64% at baseline and 28% for rates of attrition [30], but heredity interacts with the environment in predicting TL [15]. Several GWAS studies have identified single nucleotide polymorphisms (SNPs) showing associations with LTL [31–37]; one study found that a specific genetic variation of TERT (rs2736100), the catalytic subunit of telomerase, was

associated with certain types of clinical depression [38], but this was not replicated by Michalek et al. [39], who instead found that a variant in the TERC gene (rs10936599), coding for the RNA component of telomerase, predicted increased risk for childhood-onset MDD, albeit accounting for only 3% of the variance. Moreover, several recent reports have not shown significant associations between genetic predisposition to shorter LTL and the risk of clinically significant depression [40–41], including the largest study yet completed (N=67,306) [42]. Thus far, failures in replication, as well as issues of population stratification and limitations of the candidate gene approach in general, make any specific genetic association to psychiatric syndromes highly speculative.

2.2 Epigenetic Aging

More recently described markers, based on methylation of the genome, may provide even stronger estimates of biological age [43]. Age-associated site-specific methylation changes occur with surprising regularity across individuals and in some cases across tissues. Assessing such changes at specific 5'-C-phosphate-G-3' (CpG) sites can indicate "DNA methylation age" or "epigenetic age" (EpiAge). Correlations between EpiAge and chronological age are remarkably high, with correlations of up to 0.96 [44]. Advanced epigenetic age is associated with many serious medical illnesses and predicts mortality better than chronological age alone [45]. Several different measures of epigenetic aging (termed "clocks") have been developed. While each is strongly associated with chronological age and certain illnesses and mortality, each has specific properties and meanings. The Horvath clock was the first developed [44] and is based on methylation patterns of a set of 353 CpG's (out of 21,369 examined) that was "trained" on predicting chronological age and then validated in independent samples; it was found to not only accurately predict chronological age, but to be more strongly associated with biological aging parameters. Soon thereafter, the Hannum clock was developed, based on a largely non-overlapping set of 71 CpG's [46]. The Horvath clock assesses "intrinsic epigenetic aging" (IEAA), which is irrespective of cell or tissue type (and specifically controls for differences in leukocyte subpopulations), whereas the Hannum clock assesses "extrinsic epigenetic aging" (EEAA), which incorporates information about leukocyte sub-populations that also change with aging. Han et al used a newer DNA methylation algorithm that examined virtually the entire 28 million CpG sites to assess epigenetic aging in MDD [47] and found a set of 80,000 CpG sites that revealed a modest but significant acceleration of EpiAge in MDD. Notably, pathway analysis of the top CpG sites associated with epigenetic aging in MDD implicated neurogenesis, neuron differentiation and regulation of neuron death [47]. The only study to examine blood-based epigenetic aging in BD found no overall difference in EpiAge, although accelerated EpiAge was reported in the older BD subjects in that study [48]. Studies in schizophrenia mainly did not show show accelerated EpiAge in blood or brain samples [49–52]. Epigenetic aging has been more extensively studied in PTSD or lifetime stress. Lifetime stress in urban African-Americans was associated with accelerated EpiAge, possibly secondary to glucocorticoid activation [53]. Individuals exposed to combat trauma showed accelerated EpiAge, but, paradoxically, those who developed PTSD showed an attenuation of this acceleration [54–55]. Perhaps related to this paradox, cases of PTSD showed EpiAging in direct proportion to ratings of resiliency [56], possibly secondary to compensatory processes such as telomerase activation [54]. In a

separate study, overall lifetime PTSD severity was not associated with EpiAge changes, but the lifetime severity of the cluster of PTSD symptoms related to hyper-arousal was associated with an acceleration of EpiAge [57]. A recent meta-analysis found that lifetime PTSD symptom severity was associated with advanced Hannum (but not Horvath) EpiAge [58], but a later longitudinal study found that baseline PTSD symptoms of avoidance and numbing predicted subsequent accelerated EpiAge by the Horvath, but not the Hannum, clock [59].

While TL and these epigenetic clocks all significantly correlate with chronological age and predict disease and mortality [6], they are independent from each other [60], and their mediators likely differ, with TL mostly affected by repeat mitoses, inflammation and oxidative stress [2], and certain epigenetic clocks possibly affected by glucocorticoids, age-related variations of methylcytosine or increasing age-related entropy of the methylome [53,61–63] and, in the case of the Hannum clock, inflammation [64–65]. Interestingly, TERT, which is generally associated with longer TL, may paradoxically confer higher IEAA [66]. Nonetheless, both TL and methylation are affected by the environment and lifestyle behaviors (e.g., sleep, diet, smoking and exercise) [26,62,67], which has obvious clinical implications.

Other recently introduced epigenetic clocks also correlate strongly with chronological age, but they more strongly predict disease and mortality; however, these promising new measures have yet to be examined in SMD's. Methylation profiles of these latter clocks were developed specifically to predict lifespan and health span rather than chronological age alone. These clocks were trained on, in addition to age, clinical laboratory measures ("phenotypic age") that generally change with aging and that predict illness and mortality (e.g., albumin, creatinine, glucose, C-reactive protein, white blood cell count and others), called "DNAm PhenoAge" [68], or on a selection of plasma proteins that have previously been associated with mortality or morbidity (e.g., plasminogen activator inhibitor-1 [PAI-1], cystatin C, leptin and others) as well as on methylation changes related to cigarette smoking history, called "DNAm GrimAge" [67]. This latter clock reportedly strongly predicts time-to-death. Of note, several of the factors implicated in DNAm GrimAge are also associated with shortened LTL [69].

At this early stage of investigation, caution must be exercised in interpreting findings of epigenetic aging in SMD's, because of the small sample sizes and/or small effect sizes or hazard ratios in several of the studies [67], various technical challenges, uncertain interpretations of the different measures of EpiAge (and their modest inter-correlations [67]), and inadequate deep phenotyping of the subjects [65]. In particular, use of psychotropic or other medications, or the presence of comorbid medical or psychiatric conditions or tobacco/substance use, could instill major confounds into many of these studies.

2.3 Emerging Markers of Accelerated Aging

2.3a Mitochondria—Mitochondrial dysfunction may reflect, and perhaps also play a role in, accelerated biological aging [70–71] and is being studied in certain SMD's. The relationships between telomere shortening and other indices of aging, such as mitochondrial

dysfunction and its associated consequences of impaired oxidative metabolism, especially in SMD's, are complex and remain incompletely understood [19,70,72–81]. The literature may be inconsistent in part because mitochondrial status is variably defined by parameters of structure, copy number and function, which can change in relationship to each other over time [76,79] and can differ in different cellular subtypes [82–83], and because one mitochondrial parameter in particular, mitochondrial DNA copy number, may bear an "inverted-U"-shaped relationship with cellular health [72,84–85]. Evidence for a causal mechanistic connection between TL and age-associated mitochondrial parameters exists in both directions [86–92]. The relationship between mitochondrial parameters and EpiAge is also of interest. D'Aquila et al [93] performed methylation analyses on CpG sites in candidate genes associated with mitochondria quality control and identified two genes (RAB32; RHOT2), confirmed by replication, that regulated mitochondrial aging. Interestingly, higher methylation levels in RHOT2 predicted greater disability in the subject population.

2.3b Immunosenescence/ Inflammaging—Ageing-associated systemic, low-grade inflammation, termed "inflammaging," is characterized by chronically increased levels of inflammatory cytokines and acute phase reactants and may underlie the progression of pathological senescence processes, including those in the brain [94–96]. While chronic low level inflammation has repeatedly been demonstrated in MDD and various other SMD's (at least in a subset of such patients) [97], its role in accelerating biological aging and its utility as a biomarker biological aging [98–102] have yet to be adequately studied in SMD's. A novel biological aging marker called "IMM-AGE" takes into consideration the relative abundance of 33 immune cell subsets that are consistently associated with age as well as with the function of these cells to express certain genes and to produce and react to cytokines [103]. This measure, which has yet to be assessed in SMD's, reportedly correlates with overall survival more than 500-fold better than does than the Horvath EpiAge clock and may be more accurate for assessing overall all-cause mortality risk.

3. CONCLUSION

The landscape of SMD's is changing, with a new focus on subcellular components and processes in addition to neurotransmitters. To the extent accelerated biological aging occurs in SMD's, the scope of their pathophysiology broadens considerably, and they might no longer be framed as only "mental disorders" or even brain diseases, but rather as whole-body, multi-system illnesses (or at least as illnesses with substantial somatic comorbidity), of which the psychiatric presentation is just the most readily observable pathology [8,104]. This should lead to improved targeting of specific underlying pathologies ("personalized medicine").

Challenges in appraising the significance of these biomarkers include:

- Elucidating the relevance of peripheral blood biomarkers to the brain and other somatic cells;
- Understanding whether the biomarkers have diagnostic specificity, or rather, are related to underlying trans-diagnostic physiological processes, including those

suggested by the NIMH Research Domain Criteria (RDoC) [105]; inflammation, oxidative stress and glucocorticoids seem particularly relevant to several of the markers reviewed here [13,96,106–109];

- Differentiating “accelerated” from “premature” aging [110];
- Clarifying whether the biomarkers are causally related to the aging process or merely epiphenomena.

Biological aging is likely a multi-faceted process, not easily quantifiable by a single biomarker [111–112]. The analogy of the six blind men describing an elephant as a snake, a tree trunk, a broad leaf, etc., seems especially pertinent in defining biological aging. Already, we are seeing different calibrating tools that measure different aspects of aging, such as TL, mitochondrial functioning, immune activation, epigenetic aging and others. With the advent of powerful ‘omics tools, massive amounts of data can be collected and “trained” against different markers (e.g., chronological age, disability, disease, clinical lab test values, time to death, etc.), to provide different types of information.

Perhaps the greatest value of biomarkers of aging is their therapeutic utility. Among the most important questions is whether biological aging in SMD’s can be decelerated with appropriate interventions [2,113–114]. Behavioral and lifestyle interventions can likely attenuate the pace of certain types of biological aging [115–117]. Preliminary evidence also suggests that certain pharmacological therapies may retard biological aging [113], although few prospective, double-blind trials have yet been conducted. In our opinion, cross-sectional testing of aging biomarkers for clinical purposes is not “ready for prime time,” due to differences in assay techniques, lack of normative ranges and lack of knowledge about the effect of covariates. If anything, biomarker testing may be useful in longitudinal tracking within individuals to assess trajectories of these markers and possibly to indicate whether therapeutic interventions are called for and are effective [43,118–119]. In all, we expect that understanding aging markers in SMD’s will accelerate our diagnostic and therapeutic approaches to these conditions and help clarify their pathophysiologies.

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KEY BULLET POINTS:

- Biological aging differs from chronological aging and is more closely related to serious age-related illnesses and mortality.
- Serious mental illnesses may be characterized by accelerated biological aging.
- Accelerated biological aging may contribute to increased illness and mortality in individuals with serious mental illnesses.
- Telomere shortening, epigenetic changes, glucocorticoids and “inflammaging” may contribute to accelerated biological aging.
- Lifestyle as well as pharmacological interventions may have the potential to decelerate the pace of biological aging.