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Does Late-Life Depression Accelerate Aging?

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Depression in older adults occurs in the context of biological aging that contributes to the clinical symptoms, biomarkers, and the course of the disease.[1] Neurobiology of aging and late-life mental disorders share features of increased cellular senescence, inflammation, and reduced mitochondrial function. In addition, serious mental disorders (SMDs), including major depression, 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, even after controlling for suicide.[1] Patients with late-life depression (LLD) are also at increased risk for developing somatic diseases that are typically associated with advanced age, such as cardiovascular diseases, metabolic syndrome, immune dysregulation, and dementia.[1] The causes of this are likely multifactorial, including genetic predisposition, biological changes associated with early-life adversity, and multiple lifestyle factors. Lifestyle factors, while important, do not fully explain the increased mortality and morbidity in these individuals, and consequently, "accelerated biological aging" is increasingly being seen as an intrinsic factor in mental disorders.[2-3] This observation takes LLD and SMDs out of the realm of "mental disorders" or brain diseases, but rather points to the whole-body multisystem disorders that are present with psychological symptoms.[3] Understanding these underlying mechanisms should offer novel preventative and therapeutic opportunities to improve physical and mental health and increase the lifespan of older adults. However, it remains unclear whether these markers are causally related to depression, or simply coexist with mental disorders. Below, we discuss several potential biomarkers that have been linked to greater morbidity- and mortality in LLD and other mental disorders, including the novel marker proposed by Mastrobattista, Diniz and colleagues.[4]

TELOMERE LENGTH

Telomere length (TL) determinations, generally in peripheral leukocytes (LTL), are the most widely studied markers of biological aging in SMDs.[2]

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Telomeres, which cap DNA strands, protect chromosomes from damage and replicative senescence.[2] Most studies have replicated findings of LTL shortening in chronic psychological stress and major depressive disorder (MDD)[3] Increases in inflammation and oxidative stress and stress hormones are prime candidates for the causal processes.[2] 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, points to a toxic cellular milieu, or both[2,5]

DNA METHYLATION AND EPIGENETIC CLOCKS

More recently described markers, based on methylation of the genome, may provide even stronger estimates of biological age.[6] 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.[7] Advanced epigenetic age is associated with many serious medical illnesses and predicts mortality better than chronological age alone.[8] Several different measures of epigenetic aging (termed "clocks") are strongly associated with chronological age and certain illnesses and mortality, each has specific properties and meanings. For example, the Horvath clock was the first developed[7] 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. Han et al used a newer DNA methylation algorithm that examined virtually the entire 28 million CpG sites to assess epigenetic aging in MDD[8] and found a set of 80,000 CpG sites that revealed a modest but significant acceleration of EpiAge in MDD. Pathway analysis of the top CpG sites associated with epigenetic aging in MDD implicated neurogenesis, neuron differentiation, and regulation of neuron death.[8]

While telomere length and epigenetic clocks significantly correlate with chronological age and predict disease and mortality, they are independent from each other.[9] However, both TL and methylation are affected by the environment and lifestyle behaviors (e.g., sleep, diet, smoking, and exercise), which has logistic implications for clinical use and the interpretation of the results.[9]

IMMUNOSENESCENCE AND INFLAMMAGING

Aging-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.[10] While chronic low-level inflammation has repeatedly been demonstrated in MDD and other SMDs,[1,2] its role in accelerating biological aging and its utility as a biomarker of biological aging have yet to be adequately studied.

MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction may reflect, and perhaps also play a role in, accelerated biological aging, and is being studied in mental disorders.[4] The relationships between mitochondrial dysfunction and its associated consequences of impaired oxidative metabolism, especially in SMD's, are complex and remain incompletely understood. As Mastrobattista, Diniz et al. stated in their article "when damaged, mitochondria elicit a stress response by releasing various proteins and peptides known as mitokines."[4,11] Mitochondrial dysfunction and the release of mitokines have also been associated with abnormal regulation of apoptosis and increased oxidative stress markers that contribute to accelerated aging associated with MDD.[4,11] As the article in this issue summarizes, "there is accumulating evidence that growth differentiation factor 15 (GDF-15) plays a significant role in biological aging and the development of age-related diseases. GDF-15 is involved in biological pathways relevant to aging, such as energy homeostasis, stress response, and inflammatory regulation."[4,11,12] GDF-15 is shown to be a pleiotropic molecule, and its biological effects are probably

dependent on different biological contexts as well as chronological age."[4,11,12]

In this issue of the Journal, Mastrobattista, Diniz, and colleagues provide another example of a potential biomarker of accelerated aging by studying circulating levels of the GDF-15 in 393 older adults with MDD in association with depression severity, physical comorbidity burden, age of onset of first depressive episode, and cognitive performance. The primary hypothesis for the study was that higher GDF-15 levels would be observed in depressed participants compared to nondepressed controls, and associated with higher severity of depressive symptoms, a higher burden of physical comorbidity, older age of onset of first depressive episode, and poorer cognitive performance. The authors found that depressed older adults had significantly higher GDF-15 serum than the nondepressed controls. Among depressed individuals, those with high GDF-15 had higher levels of comorbid physical illness, lower executive cognitive functioning, and a higher likelihood of having late-onset depression. Thus, these results support the role of GDF-15 as a marker of age-related biological changes that can serve as a biological pathway between depression and accelerated biological and cognitive aging.

The current evidence points to the greatest value of biomarkers of aging in their clinical utility. Among the most important questions is whether biological aging in mental disorders can be decelerated with appropriate interventions.[2,13] Behavioral and lifestyle interventions can likely attenuate the pace of certain types of biological aging.[13] Preliminary evidence also suggests that certain pharmacological therapies may delay biological aging.[13,14] At this time, the use of aging biomarkers for clinical purposes may not be helpful, due to the differences in assay techniques, lack of normative ranges, and lack of knowledge about the effect of covariates. However, biomarker testing may be useful in longitudinal tracking within individuals to assess the trajectories of these markers and possibly to indicate whether therapeutic interventions are effective in reversing biological aging.

With progress in our understanding of the role of biomarkers of biological aging, with a new focus on subcellular components and processes in addition to neurotransmitters, we may move from the current belief that mental disorders are brain disorders to a broader concept of the multisystem biological imbalance including biochemical system disturbances (e.g., glucocorticoids, inflammation, oxidative stress) that can broaden our view of therapeutic modalities for achieving emotional well-being. Future research may lead us beyond the pure consensus and phenomenology-based diagnostic system that is the currently used DSM-5TR diagnostic and statistical manual[15] that guides our clinical and research practices and overlooks broad biological underpinnings of psychiatric pathology and limits our therapeutic approaches. With this conceptual switch, a new understanding of a "Whole person" approach to the healing of psychiatric disorders can make more sense, and hopefully, be more successful than all presently narrowly brain-focused somatic (e.g., psychotropic drugs, various brain stimulation techniques), and psychotherapeutic modalities. This scientific direction can revolutionize the care for older adults with mental disorders, and address the multifaceted neurobiology of aging.

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DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

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