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HOT TOPICS

Epigenetic aging in psychiatry: clinical implications and therapeutic opportunities

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Patterns of accelerated aging have been reported in severe psychiatric disorders and are hypothesized to underlie many poor health outcomes, including higher rates of chronic medical conditions, a steeper age-related decline in functioning and cognitive abilities, increased morbidity, and premature mortality. Nevertheless, features of accelerated aging are not found in all patients, with substantial heterogeneity even within the same clinical diagnosis. Therefore, exploring its biological mechanisms and clinical implications and identifying subgroups of patients presenting with accelerated aging may allow for focused strategies aimed at counteracting these mechanisms and ultimately prevent complications.

Different biomarkers have been investigated to explore accelerated aging in psychiatric disorders, most notably telomere length, oxidative stress, and DNA methylation (DNAm). The latter can be used to estimate the so-called "epigenetic age", a biomarker based exclusively on DNAm levels at multiple CpG sites which has been suggested to strongly predict morbidity and lifespan in multiple populations. Of note, a significant acceleration of epigenetic aging has recently been associated with many age-related conditions and psychiatric disorders. Importantly, while there are multiple epigenetic aging markers available, the strongest associations with mental illnesses have been found for the newer, second-generation clocks focused on biological (rather than chronological) aging variables and mortality, such as the "PhenoAge" (based on clinical measures of phenotypic age) and "GrimAge" (based on DNAm surrogates of plasma proteins linked to age-related conditions, smoking pack-years, sex, and age).

The drivers and clinical implications of this accelerated epigenetic aging in psychiatric disorders are slowly being uncovered. Accelerated GrimAge, for instance, has been previously associated with all-cause mortality, time-to-death, time-to-coronary heart disease, time-to-cancer, and many physiological signs of aging in the general population [1]. In bipolar disorder, we have recently found significant associations between GrimAge acceleration and cognitive impairment, functional decline, and earlier age of illness onset [2], emphasizing important clinical and cognitive implications of epigenetic aging in this condition. The same epigenetic clock has also been recently associated with lifetime trauma, posttraumatic stress disorder, and cortical atrophy in brain areas associated with emotion and threat regulation [3]. Moreover, across many studies, one of the strongest predictors of accelerated epigenetic aging is smoking [2], which is supported by evidence of smoking-induced increased morbidity and aging effects in clinical and non-clinical populations.

Of relevance, as a dynamic and potentially modifiable alteration, epigenetic aging may be explored as a target for the development of novel treatment strategies. Indeed, many available treatments for psychiatric disorders have been shown to present anti-aging effects in vitro and in vivo, as seen in telomere length-elongating properties for many of them. Mood stabilizers and antipsychotics are also known to modulate DNA methylation levels [4] and epigenetic enzymes (such as histone deacetylases), suggesting potential (yet unexplored) protective effects against epigenetic aging acceleration. All in all, developing anti-aging strategies to prevent (or reverse) accelerated epigenetic aging, which has been recently achieved in healthy controls by pharmacological and lifestyle interventions [5, 6], may provide novel opportunities for reducing morbidity and prevent premature mortality in psychiatric patients.

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AUTHOR CONTRIBUTIONS

CNCL contributed to the design, conceptualization, and writing of the first draft of the manuscript. GRF contributed to the design, conceptualization, and writing/

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CONFLICT OF INTEREST

The authors declare no competing interests.

ADDITIONAL INFORMATION

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