Commentary

Biological signatures of brain aging and accelerated aging by early life threat

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Understanding aging, and the factors that affect its pace, is becoming increasingly relevant. Humans live considerably longer than just a few decades ago and the world's population is ageing at a highest pace than ever. However, this marked increase in longevity has not been paralleled by a suppression of the deterioration processes characteristic of old age; the debilitating effects of aging have just been postponed (1). Aging typically encompasses physiological deterioration, worsening the quality of life, and driving chronic diseases and mortality. Thus, ameliorating the aging process is, today, a particularly critical challenge for biomedicine.

So far, progress in tackling biological aging has been hindered by a limited understanding of the molecular and cellular mechanisms emerging with ageing in specific organs and cell types. In addition, very little is known about how specific molecular changes relate to the decline or preservation of specific functional and biological changes. This gap of knowledge is particularly noteworthy in the brain, mainly due to the high degree of complexity of cell types in microcircuits and long-range connectivity. In this issue of *Biological Psychiatry*, the report by Skukla *et al*. (2) represents a major step forward in mapping age-related molecular changes in specific cortical cell-types and advancing insights on how those molecular changes may relate to alterations in cognition and anxiety.

A large number of animal and human studies have highlighted a particular susceptibility of the prefrontal cortex to experience structural and functional alterations with aging. Prefrontal cortex-dependent executive functions –such as working memory- progressively deteriorate with age. In addition, age-related alterations in brain microstructure, including decreases in cortical thickness, are most noticeable in frontal regions (3). However, the underlying mechanisms of this vulnerability are unclear. Former work has highlighted pathways involved in the excitation/inhibition (E/I) balance and regulation of prefrontal network dynamics as potential contributors to brain aging (4).

In their study, Skukla *et al*. (2) examine gene transcriptomic changes within specific neuronal cell-types in the frontal cortex of C57BL/6 mice aged either 2 or 22 months. Using standard behavioral tasks, the authors confirmed that older mice show higher levels of anxiety-like behaviors and deficits in the performance in working memory tasks. Gene expression profiles were analyzed through RNAseq followed by neuroinformatics and validated by fluorescent in situ hybridization. Cell-type specificity was achieved by applying laser capture microscopy to separately dissect four cell types that, together, orchestrate E/I balance in cortical microcircuits: i) excitatory pyramidal cells, and three types of inhibitory GABAergic neurons expressing ii) vasoactive intestinal peptide (VIP), iii) somatostatin or iv) parvalbumin.

Importantly, the age-associated molecular profiles obtained from about 14,000 mapped genes were unique for each of the four cell types examined. In particular, pyramidal neurons showed the highest vulnerability with age, displaying the most robust upregulated metabolic and downregulated synaptic changes. At the other end, parvalbumin neurons showed the lowest vulnerability, while somatostatin- and VIP-expressing cells displayed intermediate intrinsic levels of resilience. In a canonical microcircuit parvalbumin-expressing GABAergic neurons target the pyramidal cells perisomatic region, regulating excitatory output. Thus, these results provide a potential molecular explanation for functional E/I neuronal imbalances occurring with aging.

To understand the underpinnings of this variability in cellular vulnerability better, the authors examined markers of neuronal vulnerability related to mitochondrial function and metabolism. Pyramidal but not GABAergic neurons, showed increased expression of neuronal vulnerability markers implicated in oxidative stress [i.e., the oxidation resistance-1 (*Oxr1*) and the ryanodine receptor-3 (*Ryr3*) genes]. In addition, in line with the proposed contribution of mitochondrial dysfunction to stress and senescence (5), expression levels of a gene marker of mitochondrial dynamics (*Opa1*) was reduced with age in pyramidal cells while enriched in interneurons. These results strongly highlight mitochondrial homeostasis as a plausible contributor to the differential susceptibility to aging observed in 'vulnerable' pyramidal neuros versus more 'resilient' interneurons.

In their attempt to link age-related molecular changes with behavior, Skukla *et al*. (2) reported an interesting overlap between the molecular pathways associated with anxiety and cognition. They further identified a pleiotropic contribution of gene expression specifically in somatostatin interneurons with both behavioral dimensions. This shared molecular contribution to both anxiety and cognition provides a potential biological explanation for previously reported evidence linking high anxiety with cognitive impairments (6). Although the study identified as well an overlap in changes in gene expression between these behavioral dimensions and those of aging, the fact that behavioral changes occurred with age did not allow disentangling specific molecular signatures linking ageing with behavioral alterations beyond those related to anxiety and cognition.

Despite the strengths of this study in dissecting cell-type dependent molecular aging signatures, several notes of caution should be raised. The first warning is related to statements in title and discussion, where causality is somehow implied. The associations between gene expression and behavioral changes described in the report remain correlational. A second point relates to the use of inbred –as opposed to outbred– animals. Given the importance of genetics for aging and longevity (7), the absence of genetic variation may have biased the results towards a particular, single genotype. A

further point for consideration is that life experiences, known to influence aging processes (8), were not included in the study.

Interestingly, aspects related to the last two points were integrated by Sumner et al (9) in a report that assessed potential factors that affect the speed of aging at youth. While genetic variation was implicitly included, as the study was performed in humans, the contribution of life experiences was explicitly examined here. Importantly, instead of focusing in an old-age population, the authors dealt with the concept of accelerated biological aging at a younger age; i.e., during childhood and adolescence. Specifically, the study exploited the important distinction between chronological and biological age, and examined the impact of early life adversity (ELA) on accelerated aging at young age. In line with recent advances in the field, biological aging was established as epigenetic age and it was determined from genome-wide DNA methylation (DNAm) analyses. To calculate potential deviations in the pace of aging, they regressed DNAm age on chronological age. In addition, they assessed pubertal stage through self-reporting methods. Previous studies, mostly using telomere length and mitochondrial DNA copy number, have reported accelerating effects of ELA and biological or mental aging (10). However, a key point here is that instead of considering all sorts of adverse experiences as a whole, this study explored potential differences in the impact of 'threatening' versus 'deprivation' experiences.

For the formulation of their hypothesis, Sumner et al (9) were inspired by the "life history theory" from the field of evolutionary biology. According to this theory, natural selection has shaped developmental mechanisms for organisms to adopt biobehavioral strategies that optimize survival and reproduction over the life cycle. Thus, in high-mortality (i.e., dangerous) environments, organisms should have an accelerated maturation and invest in early reproduction. This strategy has been shown to accelerate aging and shorten lifespan. In contrast, in the face of scarcity, a slow life history strategy, involving slower maturation and delayed timing of sexual development and reproduction, should be favored. Consequently, Sumner et al (9) hypothesized that threat-related ELA (such as exposure to violence or physical abuse) may be a particular risk factor to trigger accelerated aging in terms of both epigenetic age and pubertal onset.

In the study, children and adolescent (age range: 8-16 years; sample size: 247 children) were recruited from a community with wide variability in ELA exposure, that was estimated through interviews and self-reports of both children and caregivers. Subsequently, the authors created threat and deprivation exposure composites following strict criteria. Then, DNAm was analyzed from saliva samples and pubertal stage established through a self-report method. Data analyses included linear regression, bootstrapping and sensitivity analyses in which several relevant covariates (i.e., sex, race, family

poverty) were considered. Strikingly, in line with their hypothesis, only threat was associated with accelerated biological aging; the higher the threat exposure, the higher the epigenetic age acceleration. Deprivation, instead, was only associated with pubertal stage. Epigenetic age, thus, appears as a plausible biomarker for specific ELA types at youth. Given that epigenetic alterations are seemingly reversible, therapies targeting epigenetic modifications may help rectifying the negative fate of early life threats and promote healthy aging.

These remarkable findings link evolutionary thinking with societal influences on biological fate. Although they should be replicated, ideally in longitudinal studies and including richer characterization of adversity and biobehavioral phenotypes, they represent a potential mechanism for the differential biological trajectories programmed by specific ELA types. However, they also raise several questions such as what are the signals that mediate the identified threat-induced epigenetic changes; or whether and how the identified epigenetic modifications relate to biological aging. It will also be important to connect the described global DNAm changes with their corresponding transcriptomic profile. In fact, the field can greatly benefit from combining approaches in Skukla et al. (2) and Sumner et al (9) studies, linking peripheral markers of aging with cell-type specific understanding of molecular and functional adaptations taking place in specific brain circuits.

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The author has no conflicts of interest to declare.

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