



Review

Major depression and the biological hallmarks of aging

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ABSTRACT

Major depressive disorder (MDD) is characterized by psychological and physiological manifestations contributing to the disease severity and outcome. In recent years, several lines of evidence have suggested that individuals with MDD have an elevated risk of age-related adverse outcomes across the lifespan. This review provided evidence of a significant overlap between the biological abnormalities in MDD and biological changes commonly observed during the aging process (i.e., hallmarks of biological aging). Based on such evidence, we formulate a mechanistic model showing how abnormalities in the hallmarks of biological aging can be a common denominator and mediate the elevated risk of age-related health outcomes commonly observed in MDD. Finally, we proposed a roadmap for novel studies to investigate the intersection between the biology of aging and MDD, including the use of geroscience-guided interventions, such as senolytics, to delay or improve major depression by targeting biological aging.

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders across the lifespan. Its prevalence varies in different populations, and recent estimates suggest a 12-month and lifetime prevalence of 10.4% and 20.6%, respectively (Hasin et al., 2018). In addition to its high prevalence, it also ranks among the five most disabling disorders worldwide (Whitford et al., 2013).

The disability associated with MDD is not solely due to the burden of psychopathology. MDD is associated with a higher risk of cardiovascular, cerebrovascular disease, and metabolic disorders (Leung et al., 2012; Richmond-Rakert et al., 2021). MDD across the lifespan is a major risk factor for Alzheimer's disease and related dementia (ADRD), frailty, and decreased health span (Diniz et al., 2013; Richmond-Rakert et al., 2022; Soysal et al., 2017). Finally, MDD increases the risk of all-cause and cardiovascular-related mortality (Diniz et al., 2014b; Leung et al., 2012). Notably, these are features commonly associated with advancing chronological aging, suggesting that individuals with MDD present with, or are at higher risk for, a premature aging phenotype.

Despite robust clinical and epidemiological evidence that associates MDD with premature aging phenotypes, the underlying mechanisms are not well-understood. In this review, we aim to summarize the current

evidence suggesting that individuals with MDD across the lifespan present with cellular and molecular changes related to biological aging. We also aim to provide a novel conceptual, mechanistic framework by which MDD increases the risk of adverse health outcomes commonly associated with advanced aging.

2. The hallmarks of biological aging: implications for major depressive disorder

Biological aging (BA) is a complex process involving interconnected changes in multiple biological pathways that ultimately lead to accumulating damage in cells and tissues. Detailed reviews about processes that drive BA and the current challenges of measuring it have been previously published (Ferrucci et al., 2020; López-Otín et al., 2013). Table 1 describes commonly accepted BA hallmarks and the evidence that such processes are affected in MDD. In this review, we will focus on studies that examined individuals with MDD. When data from human studies are lacking, we will review data from animal models of depression.

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Table 1

The hallmarks of biological aging¹⁰ and the evidence of its association with major depressive disorder.

Hallmark of biological aging	Description	Evidence
Cellular senescence	Includes a state of persistent cell arrest due to telomere attrition, intracellular accumulation of lipids and glycoproteins (e.g., senescence-associated β -galactosidase, lipofuscin), telomere shortening, and activation of cell cycle control pathways (e.g., p16 ^{INK4A} and p21 genes)	††
Altered intercellular communication	Includes changes in circulating biomarkers (e.g., the SASP, inflammasome) that can act in a paracrine or endocrine fashion to convey, to different cells and tissues, information about the molecular state of a cell or tissue	††
Mitochondrial dysfunction	Includes the abnormal and unchecked production of the reactive oxygen species (ROS), mtDNA damage, loss of mitochondrial integrity	††
Deregulation of nutrient sensing	Includes the abnormal activation of the insulin and IGF-1 signaling (IIS) pathway and other nutrient sensing pathways (e.g., mTOR, AMPK, and SIRT1)	††
Epigenetic alterations	Includes histone modification, chromatin remodeling, and other mechanisms that influence gene expression without alteration of DNA sequence (e.g., microRNAs)	††
Genomic instability	Includes the accumulation of DNA damage (nuclear and mitochondrial DNA): base damage, double-strand breaks, base mismatching; and the failure of DNA repair mechanisms	†
Loss of proteostasis	Includes the accumulation of unfolded, misfolded and aggregated proteins due to reduced capacity of protein stabilization and degradation	†
Stem cell exhaustion	Includes the decline in the regenerative potential of tissues due to deficient proliferating capacity of stem cells	†

Footnote: ††: strong evidence; †: moderate evidence; †: poor or lack of evidence.

3. Cellular senescence

The accumulation of senescent cells has become one of the most widely recognized BA hallmarks. Cellular senescence is characterized by irreversible growth arrest that occurs when cells experience replicative exhaustion, oncogenic insults, cellular stress, or genomic instability (Campisi and d'Adda di Fagagna, 2007; Sharpless and Sherr, 2015). Senescent cells share common morpho-functional features, for example, enlarged cell size, accumulation of senescence-associated β -galactosidase, and lipofuscin in the cytoplasm (Gasek et al., 2021; Hernandez-Segura et al., 2018; Ogorodnik, 2021). They also show accumulation of DNA damage foci, condensed heterochromatin regions, telomere shortening, and overexpression of cell cycle regulator markers like p16 and p21 (Gasek et al., 2021; Hernandez-Segura et al., 2018; Ogorodnik, 2021). Other key characteristics of senescent cells are the incapacity to initiate pro-apoptotic pathways, relying on immune cells for tissue clearance, and changes in the cellular secretome (the senescence-associated secretory phenotype, SASP) (Deursen, 2014; Fafian-Labora and O'Loghlen, 2020).

Few studies have focused on the expression of cyclin-dependent kinases p16 and p21 in MDD. In a small post-mortem study, p21 expression in hippocampal neurons was significantly higher in older individuals with MDD than in the control group (Epp et al., 2013). This study also found that the use of antidepressants was associated with even higher p21 expression in the hippocampus. In another study, p16 mRNA expression in PBMCs was significantly higher in subjects with

MDD and significantly correlated with the severity of depressive symptoms (Teyssier et al., 2012).

3.1. Telomere attrition

Telomeres are nucleoprotein complexes at the end of chromosomes, composed of TTAGGG repeats and a 3'-rich single-stranded overhang, and are critical to the stability and integrity of DNA (Lu et al., 2013). Telomeres are shortened after each cell cycle division, and after achieving a critical threshold, it signals the cells to stop further replication and to enter into a senescent state (i.e., replicative senescence) (Aubert, 2014).

Previous studies have demonstrated the association between telomere attrition and MDD. Community-based studies showed that individuals with MDD had shorter leukocyte telomere length (LTL) compared with never-depressed control subjects (Schaakxs et al., 2015; Verhoeven et al., 2018). Longer duration of depressive episodes, the severity of depressive symptoms, and the presence of medical comorbidity are features associated with shorter LTL in MDD (Mendes-Silva et al., 2021; Schutte and Malouff, 2015; Wolkowitz et al., 2011). Telomere attrition has also been associated with higher IL-6 and oxidative stress marker levels in MDD (Wolkowitz et al., 2011). Interestingly, one longitudinal study showed that changes in the course of depressive symptoms over six years were not associated with different rates of LTL attrition (Verhoeven et al., 2016). On the other hand, young individuals who experienced incident major depressive episodes (MDE) showed a greater LTL attrition than those without incident MDE, independent of baseline telomere length (Shalev et al., 2014), suggesting that telomere attrition may be a trait-dependent phenomenon in MDD.

Despite their importance, there are several limitations in interpreting the findings showing significant telomere attrition in MDD. First, these studies focus on LTL analyses, and it is unclear how LTL is related to telomere length in brain cells. Second, neurons are terminally differentiated cells, and the functional role of neuronal telomeres is not clear. Interestingly, studies including post-mortem brain samples showed more significant telomere attrition in different brain cortical areas and oligodendrocytes in MDD (Mamdani et al., 2015; Szabadi et al., 2014), reinforcing the association between MDD and cellular senescence in the brain.

4. Altered intercellular communication

The concept of intercellular communication is very broad and can encompass almost any known physiological function. It is usually defined as the transfer of information from one cell to another through paracrine, autocrine, endocrine, or cell-to-cell contact signaling. Changes in intercellular communication processes are another common hallmark of BA and affect many overlapping pathways between aging and MDD.

4.1. Senescence-associated secretory phenotype (SASP)

One of the most important characteristics of cellular senescence is a shift in the cellular secretome profile, the senescence-associated secretory phenotype (SASP) (Fafian-Labora and O'Loghlen, 2020). Senescent cells accumulating in tissues secrete a myriad of pro-inflammatory cytokines, chemokines, extracellular matrix proteases, angiogenic factors, growth factors, cell cycle, and metabolic regulating factors (Basisty et al., 2020; Coppé et al., 2010, 2008). If senescent cells are not effectively cleared, they can accumulate, driving the increase of SASP factors expression, and their release to the systemic circulation, leading to further deleterious effects on neighboring and distant cells and tissues (Young and Narita, 2009).

Since SASP factors comprise several signaling proteins associated with inflammatory control, tissue remodeling, cell growth, cell cycle control, and metabolic regulation, the analyses of a single or few

markers may not reflect the complexity of the SASP. To address this issue, we developed and optimized a biomarker-composite index, the SASP index, to reflect the interrelated associations between distinct SASP factors into a single variable reflecting a systemic cellular senescence burden at a molecular level.

We first showed that older adults with MDD expressed higher levels of different SASP factors and had higher SASP index scores than never-depressed age-matched older adults, suggesting an increasing cellular senescence burden in MDD (Diniz et al., 2017). Additional studies using independent cohorts confirmed our initial findings and demonstrated that a higher SASP index was also associated with global cognitive impairment, specifically with executive dysfunction and slower information processing speed (Diniz et al., 2021). We further expanded our findings to show that young and middle-aged adults with MDD had higher SASP index scores than never-depressed individuals (Diniz et al., 2019). Finally, in this study, we demonstrated the relevance of somatic health parameters to the accumulation of SASP among individuals with MDD since we found a strong association between higher SASP index, higher body mass index, and higher medical comorbidity burden.

Although our initial findings indicated a clear association between SASP factors, somatic parameters, and cognitive impairment in older adults with MDD, these data did not indicate if SASP factors were associated with structural changes in brain areas related to emotional and cognitive processing. Thus, we tested if the SASP index would negatively impact brain structural changes. We found that higher SASP index scores negatively affected brain health markers and were associated with reduced cortical thickness, lower fractional anisotropy, and higher mean diffusivity measures in older adults with major depressive disorder (Diniz et al., 2017; Mendes-Silva et al., 2019). These changes were more intense in brain areas related to executive function and episodic memory performance, providing mechanistic links between abnormal SASP factors and worse cognitive performance in older adults with MDD. Interestingly, these structural brain changes have also been related to neurodegenerative changes and Alzheimer's disease pathology in older adults (Jack et al., 2014), reduced axonal integrity, and higher inflammatory activity in the brain (O'Donnell and Westin, 2011), providing potential mechanistic links between MDD and the risk of age-related neurodegenerative disorders.

Despite the evidence that SASP factors were associated with MDD across the lifespan, the prognostic significance of the SASP factors was unclear. In a recent study, we examined data from a large clinical trial of older adults with MDD and found that a higher SASP index significantly predicted lower treatment remission rates after adjusting for well-established predictors of treatment remission in this population (Diniz et al., 2022). Interestingly, none of the individual SASP factors included in the SASP index significantly predicted treatment remission in this population. Our findings suggest that the SASP index is more informative than its individual components in evaluating complex clinical and biological phenomena, in line with recent reports showing that a global phenotypic aging measure is better than its individual components for tracking longitudinal aging changes (Belsky et al., 2022, 2015).

4.2. "Inflammaging"

Inflammaging is a chronic, sterile, low-grade inflammation state throughout the body that can lead to tissue dysfunction, disease pathology, and poor disease outcomes (Ferrucci and Fabbri, 2018). Although reviewed separately, this pro-inflammatory secretory profile can be viewed as part of the SASP.

The inflammatory response and its resolution are tightly regulated processes in which the balance between pro- and anti-inflammatory systems is essential to elicit the appropriate cellular responses and resolution of the inflammatory process. In aging, however, this balance is gradually disrupted with a gradual preponderance of pro-inflammatory over anti-inflammatory markers (i.e., inflammaging) (Ferrucci and Fabbri, 2018; Franceschi et al., 2007, 2018).

In the past decades, a large bulk of evidence has demonstrated the association between MDD across the lifespan, abnormal levels of inflammatory markers, and changes in the immune response. For example, a meta-analysis showed that specific sets of cytokines preferentially upregulated in depressed individuals, including IL-6, IL-10, sIL-2R, TNF- α , IL-1 β (Kohler et al., 2017). Another study suggests that inflammation correlates with depressive episode severity and that the levels of inflammatory markers decrease after depressive episode recovery but do not reach the levels observed in never-depressed individuals (Dahl et al., 2014). Interestingly, high inflammatory markers such as IL-6 and CRP are specifically associated with physical and cognitive decline (Frank et al., 2021). Finally, low-grade inflammation has also been associated with poor treatment and health outcomes in MDD (Chamberlain et al., 2019; Strawbridge et al., 2015).

5. Deregulated nutrient sensing

Aging is accompanied by significant changes in the regulation of nutrient-sensing processes in cells and tissues. Changes include increased insulin resistance, impaired growth hormone-insulin-like growth factor 1 (IGF-1) signaling, and an imbalance between catabolic and anabolic processes (López-Otín et al., 2013). Systemic consequences of changes in nutrient sensing cascades include the increased incidence of metabolic disorders (e.g., diabetes, obesity), sarcopenia, osteoporosis, and frailty in older adults (Farr and Almeida, 2018).

Several clinical and epidemiological studies have demonstrated a potential link between MDD and deregulated nutrient sensing. Individuals with MDD have a higher prevalence and incidence of diabetes, obesity, and other metabolic disorders (Ghanei Gheshlagh et al., 2016). MDD has also been associated with a higher risk of sarcopenia and low muscle strength in middle-aged adults (Hayashi et al., 2019). Low grip strength was also an independent predictor of prevalent and incident clinically significant depressive symptoms in older adults in community-based cohort studies (Brooks et al., 2018; Carvalho et al., 2021).

Additional evidence of the association between major depression and deregulated nutrient sensing comes from studies that evaluated the markers of insulin resistance and components of the insulin signaling cascade system. The HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) is a proxy measure of insulin resistance used in clinical practice (Tahapary et al., 2022). A meta-analysis of 18 cross-sectional studies, including more than 25,000 individuals, showed a significant association between insulin resistance and major depression (Kan et al., 2013). Insulin resistance, measured by the HOMA-IR, was independently associated with the severity of depressive symptoms and mediated the association between depressive symptoms and metabolic syndrome in a large population-based cohort of Mexican-American older adults (Diniz et al., 2018a). Our group also demonstrated that older adults with MDD have lower adiponectin levels, an insulin-sensitizing hormone secreted by adipocytes, indicating higher insulin resistance in this sample (Diniz et al., 2012).

Sirtuins are important regulators of the insulin signaling cascade, improving insulin sensitivity and glucose and fatty acid metabolism (Nogueiras et al., 2012). Sirtuins are a family of conserved nicotinamide adenine dinucleotide (NAD $^{+}$)-dependent deacetylase and mono-ADP-ribosyl transferase (Sirt1–7). Their activity is regulated by the bioavailability of NAD $^{+}$, and they are involved in a broad range of cellular functions, including metabolic control, mitochondrial homeostasis, DNA repair, inflammation, autophagy, and apoptosis (Pardo and Boriek, 2020).

Reduced sirtuins activity has been implicated in accelerated aging processes and age-related medical disorders (Hall et al., 2013). Case-control studies and a genome-wide association study (GWAS), including mainly Chinese participants, showed a significant association between SIRT gene polymorphisms and MDD (Consortium, 2015; Kishi et al., 2010; Liu et al., 2019). However, these findings have not been

replicated in recent mega GWAS analyses, including more diverse samples (Howard et al., 2019). Individuals with MDD present with a significant, state-dependent reduction of mRNA levels of SIRT1, 2, and 6 in the blood (Abe et al., 2011; McGrory et al., 2018). A large study, including two independent cohorts in China, showed a significant reduction of the SIRT1 gene expression in the amygdala post-mortem among individuals with a history of MDD (Liu et al., 2019).

6. Mitochondrial dysfunction

Mitochondrial dysfunction closely correlates to cellular and organismal aging and has been implicated in many diseases like depression, diabetes, and Alzheimer's disease (AD) (Caruso et al., 2019; Lopez-Otin et al., 2016; Wang et al., 2020). Mitochondrial dysfunction during aging can occur at different levels, including defects in the biogenesis, electron transport chain, and mitochondria clearance (Webb and Sideris, 2020). Moreover, mitochondrial dysfunction directly impacts other hallmarks of aging, like deregulated nutrient sensing, genomic instability, and loss of proteostasis (Lopez-Otin et al., 2016).

The number of mitochondrial DNA copies (mtDNA-cn) is an indirect marker of mitochondrial function, where lower mtDNA-cn indicates more intense mitochondria dysfunction (Castellani et al., 2020). However, data from studies including young adults with MDD are conflicting, with studies showing a significant decrease in mtDNA-cn in MDD (Chang et al., 2015; Edwards et al., 2016), while other studies, including larger sample sizes, did not confirm the associations between MDD and mtDNA-cn (Lindqvist et al., 2018; Verhoeven et al., 2018).

Oxidative stress (OS) is a sub-product of mitochondrial function, and elevated ROS production is another marker of mitochondrial dysfunction that, if unchecked, can lead to mitochondrial, cellular, and DNA damage (Valko et al., 2007). Young and middle-aged individuals with MDD have consistently shown higher levels of OS markers (e.g., TBARS, 8-OH-DNA, protein carbonyl content) and lower levels of antioxidants (e.g., glutathione peroxidase, glutathione transferase) (Black et al., 2015). Studies focusing on older adults also showed significantly higher lipid peroxidation markers (Pomara et al., 2012) and an imbalance between oxidative stress vs. anti-oxidative stress markers in MDD (Diniz et al., 2018b) compared to non-depressed controls. Moreover, increased oxidative stress has been associated with poor response to antidepressant treatment (Lindqvist et al., 2017).

Another consequence of elevated OS is the oxidation and fragmentation of mitochondrial DNA (mtDNA). Fragmented mtDNA can escape to the cell cytosol and extracellular fluids such as the blood (i.e., circulating cell-free mtDNA, ccf-mtDNA), and ccf-mtDNA is a promising biomarker for aging, tissue damage, and cellular stress in different conditions (Kananen et al., 2022). Young adults with MDD had significantly higher ccf-mtDNA levels than non-depressed controls (Kageyama et al., 2018; Lindqvist et al., 2018). Interestingly, individuals who did not respond to antidepressant treatment with SSRIs showed a significant increase in ccf-mtDNA levels, while those who responded to treatment showed no significant changes in ccf-mtDNA levels after treatment (Lindqvist et al., 2018). Higher ccf-mtDNA has been associated with more severe depressive episodes and suicidal behaviors (Lindqvist et al., 2016). Our group investigated the association between ccf-mtDNA and MDD in older adults and found significantly higher ccf-mtDNA levels compared to never-depressed control individuals, suggesting more intense mitochondrial dysfunction in this population (Goncalves et al., 2021). Interestingly, we also found that ccf-mtDNA was significantly correlated with higher levels of IL-6, a master regulator of inflammatory response and a major component of the SASP. In a follow-up study, we also demonstrated that older adults with comorbid MDD and frailty presented significantly higher ccf-mtDNA levels (Ampo et al., 2022).

7. Epigenetic alterations

Epigenetic alterations to the genome are an important form of

control of gene expression without modifying the DNA sequence. They include DNA and histone modifications (e.g., methylation and acetylation) and post-translational control of gene expression by microRNA and other non-coding RNAs (López-Otin et al., 2013). Increasing DNA methylation rate is a consistent feature of advanced chronological aging, and several studies have developed algorithms to determine biological aging based on genome-wide methylation data (Belsky et al., 2022; Rutledge et al., 2022).

Individuals with MDD have higher global DNA methylation rates than healthy comparison subjects (Li et al., 2019). Interestingly, some genes with higher DNA methylation rates have also been affected by chronological aging, e.g., the BDNF gene (Dell'Osso et al., 2014; Januar et al., 2015). Another recent large-scale study also showed a significant correlation of gene methylation changes in the blood and in brain areas that have been involved in the MDD (e.g., anterior and rostral prefrontal cortex) (Aberg et al., 2020). Epigenome-wide association studies also show that differentially methylated genes in MDD are involved in age-related biological processes, like the control of metabolic processes and proteostasis (e.g., insulin receptor signaling, mTOR signaling biological pathways) (Zhu et al., 2019), inflammatory response (e.g., p38 MAPK pathways) (Cordova-Palomera et al., 2015), or genes that show age-dependent changes in mRNA expression (McKinney et al., 2019).

7.1. Aging clocks, brain age, and major depressive disorder

Recently, a large body of work has identified aging clocks based on different biomarkers. Ideally, these aging clocks should be easy to measure and calculate, reflect critical features of the biology of aging, be well correlated with chronological aging, and predict adverse, age-related health outcomes (Ferrucci et al., 2020; Hamczyk et al., 2020; Rutledge et al., 2022). For example, Han and colleagues, using data from a large community-based study, showed that subjects with MDD had significantly higher epigenetic aging than never-depressed subjects, with a significant dose-effect with increasing symptom severity in the overall sample and replicated in an independent dataset of post-mortem brain sample (Han et al., 2018). Another study used the GrimAge epigenetic clock to estimate the biological age, and individuals with MDD showed a biological age acceleration compared to non-depressed controls (Protsenko et al., 2021). A more recent study, using data from a large population-based cohort of young adults, showed a higher burden of psychopathology, including depressive symptoms and other internalizing disorders, was independently associated with a faster DNA-methylation pace of aging between ages 26 and 45 years (Wertz et al., 2021).

One key aspect of the biology of aging is that different organs and tissues age at different paces, and a systemic measure of biological aging may not reflect the aging process of the brain (Nie et al., 2022; Schaum et al., 2020). Thus, brain-specific biological aging clocks are needed to address if MDD was associated with accelerated brain aging (Cole et al., 2019). An early study using structural brain MRI to estimate the "brain age" showed that young and middle-aged adults with MDD had four years more estimated brain age (i.e., brain age gap) than their chronological age (Koutsouleris et al., 2014). In this work, the brain regions that were mostly predictive of age mapped to subcortical and periventricular, orbitofrontal, cerebellar, limbic, cingulate, and perisylvian regions. A study using data from the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium showed that participants with MDD had higher predicted brain age than individuals without a psychiatric diagnosis (predicted brain age difference of +1.08 (SE 0.22)), though with a small effect size (Cohen's $d=0.14$, 95% CI: 0.08–0.20) (Han et al., 2021a). In this study, the brain areas that showed the highest predicted age difference were the paralimbic, temporal, and orbitofrontal areas. Another epidemiologic study showed that subjects with MDD had higher predicted brain age than health controls (+2.78 years, Cohen's $d=0.25$, 95% CI –0.10 to 0.60) (Han et al., 2021b). In a multivariable regression model, the severity of somatic

depressive symptoms was the only variable significantly associated with higher predicted brain age in MDD. In contrast, the current use of antidepressant was associated with lower predicted brain age, suggesting a potential protective effect of antidepressant use against accelerated brain aging in MDD. Interestingly, predicted brain age was not significantly correlated with different omics-based clocks (epigenetic, transcriptomic, and metabolomic) and telomere length (with Pearson r in the range of -0.03 to 0.15), and showed a significant negative association age proteomic clock ($r = -0.24$, $p = 0.02$) in this cohort. Finally, a recent meta-analysis confirmed the association between MDD and accelerated brain aging and showed that the average estimated brain age gap was 1.12 years [0.41; 1.83] (Ballester et al., 2022). A recent study using deep learning statistical methods (i.e., DeepBrainNet) obtained robust brain-age estimates across the lifespan and better fit than other commonly used machine learning methods using minimally processed brain MRI scans (Bashyam et al., 2020). This study also showed that subjects with different neuropsychiatric disorders, including MDD, showed an accelerated brain aging pattern across the lifespan.

Interestingly, chronological age may significantly moderate the association between MDD and the brain age gap since older adults have a more significant brain age gap than younger adults (Ballester et al., 2021). This finding suggests there may be a non-linear accumulation of age-related abnormalities in the hallmarks of biological aging processes among individuals with MDD that reflects on more significant brain age gap estimates among older individuals with MDD.

8. Genomic instability

Genomic instability is driven by various factors, including environmental stressors, DNA damage and replication errors, telomere attrition, and genetic mutations (López-Otín et al., 2013). Genomic instability and damage increase with age, activating DNA damage response (DDR) mechanisms to repair and avoid further DNA damage (Yousefzadeh et al., 2021). If DDR is ineffective, several cellular fates can ensue, including apoptosis, cell cycle arrest, and cellular senescence (Schumacher et al., 2021). Individuals with MDD across the lifespan have evidence of increased levels of oxidative DNA and RNA damage (Chang et al., 2015; Czarny et al., 2015; Vieira et al., 2021). Also, individuals with MDD have more DNA double-stranded breaks following oxidative damage and reduced ability to perform DNA repair (Czarny et al., 2015).

9. Loss of proteostasis

Proteostasis is essential for maintaining cellular function, particularly following exposure to cell stress (Kaushik and Cuervo, 2015; López-Otín et al., 2013). When proteins are exposed to excessive stress, e.g., heat, pH disruption, oxidative stress, a tightly regulated network of other proteins, such as heat-shock proteins and chaperones, proteasomes, and lysosomes work to stabilize and correct the misfolded protein or degrade it (Hetz and Saxena, 2017; Pomatto et al., 2018). These cellular responses prevent the aggregation and proteotoxicity that plays a significant role in the pathogenesis of several neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Haass and Selkoe, 2007).

Very few studies have addressed abnormalities in proteostasis control in MDD. A previous study from our group identified that proteins related to biological pathways involved in controlling protein stability, dimerization activity, protein localization, and protein complex binding are abnormally regulated in older adults with MDD (Diniz et al., 2016). A post-mortem study showed the excessive activation of the unfolded protein response (UPR) in MDD (Kowalczyk et al., 2021). Finally, another study showed that abnormalities in proteostasis control are strongly associated with more significant cognitive impairment in older adults with MDD (Diniz et al., 2015).

10. Stem cell exhaustion

Stem cells are essential to maintaining tissue homeostasis and regenerative responsiveness to injuries owed to their unique ability to self-renew and differentiate into mature tissue-specific subtypes (Oh et al., 2014). Since they persist throughout life, stem cells are particularly susceptible to an age-associated decline in number, proliferative, and differentiation capacity. Intrinsic, e.g., DNA damage, mitochondrial dysfunction, and extrinsic stressors, e.g., reactive oxygen species, can impair a tissue-specific stem cell niche environment, leading to the accumulation of cellular damage and induction of senescence over time (Duscher et al., 2014; Oh et al., 2014). A functional consequence is a depletion of fully functional stem cell populations, diminishing tissue repair and regenerative capacity, which are essential for proper organ functioning and survival.

Evidence supporting a clear mechanistic link between stem cell exhaustion and MDD is lacking, especially in humans. However, studies with animal models of depression have shown decreased neurogenesis in which neural stem cells (NSC) and neural progenitor cells (NPC) show limited ability to proliferate and differentiate into new neurons in mice (Berger et al., 2020; de Andrade et al., 2013; Pham et al., 2003). Interestingly, many different factors compromising the ability of neural stem cells to proliferate and differentiate into functional neurons have been associated with the pathophysiology of depression. For example, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and the nerve growth factor (NGF), which play an essential role in NSC niche maintenance and cellular differentiation (Numakawa et al., 2017), have consistently shown reduced levels in individuals with MDD across the lifespan. They have also been associated with worse treatment response and cognitive impairment in MDD (Diniz et al., 2014a; Molendijk et al., 2014). Despite the evidence from animal models suggesting that MDD is linked with changes in NSC biology, current methodological challenges to quantifying and evaluating the function of NSC in humans *in vivo* hinder the ability to understand their role in the pathophysiology of MDD.

A few studies evaluated the impact of MDD on circulating progenitor cells in humans, focusing on endothelial progenitor cells (EPC). A study including middle-aged individuals with MDD showed a significant reduction in the circulating levels of mature ($CD34^+/\text{VEGFR2}^+$) and immature ($CD34^+/CD133^+/\text{VEGFR2}^+$) EPCs (Dome et al., 2009). These results were replicated in another study that showed the link between lower EPC count and higher inflammatory cytokine levels (Yang et al., 2011). The authors hypothesized that the lower EPC count in MDD could represent a mechanistic link between endothelial dysfunction, vascular disease, and the development of major depressive episodes, a condition known as vascular depression (Aizenstein et al., 2016). However, a recent study including a younger cohort of individuals with MDD did not find a significant difference between depressed and non-depressed individuals (Liou et al., 2021).

11. An integrative model linking abnormalities in biological aging and MDD

As reviewed above, robust evidence suggests that many pathophysiological abnormalities observed in MDD are in tandem with abnormalities in processes associated with the BA hallmarks. However, these studies have not been consistently framed from a life-course developmental perspective nor the biology of aging or geroscience perspectives. The geroscience framework suggests that identifying and targeting biological processes related to biological aging can ideally prevent or delay the onset or progression of multiple chronic diseases and adverse age-related health outcomes typically observed in older adults (Kennedy et al., 2014).

Within the geroscience framework, the association between abnormalities in biological hallmarks of aging and MDD can be viewed from two main perspectives. First, they can be viewed as having a causal role

in MDD. Although there is evidence that high levels of inflammatory markers, mostly CRP and IL-6, or immunoinflammatory challenges (e.g., IFN- γ treatment for hepatitis C) are associated with the development of depressive symptoms and MDD, these findings are not universal (Au et al., 2015; Beratis et al., 2005; Verduijn et al., 2015). There is no evidence that drugs with potent anti-inflammatory or immunomodulatory effects can single-handedly treat a major depressive episode in the general population (Köhler et al., 2014). Other biological aging hallmarks, like telomere attrition over time, are not consistently associated with changes in depressive symptoms severity or trajectory (Verhoeven et al., 2016), despite a robust cross-sectional association between them. There is even less evidence to indicate that any hallmark of biological aging is causally linked with MDD from human studies. To that end, if abnormalities in the hallmarks of biological aging were causal to MDD, we would expect an abrupt increase in the incidence and prevalence of MDD among older adults, but this is not supported by epidemiological studies (Buchtemann et al., 2012). In fact, the incidence and prevalence of MDD peak in young adulthood and decrease with older age. Therefore, the literature evidence so far does not provide evidence for the perspective that abnormalities in the hallmarks of biological aging are antecedent to MDD onset and can be causally linked with MDD.

An alternative perspective is that the abnormalities in the hallmarks of biological aging are secondary to the emergence of MDD across the lifespan. Independent of the etiological factors that lead to MDD in an individual, its presence triggers a myriad of downstream, deleterious abnormalities in several biological processes, many of them related to the hallmarks of biological aging. The persistence of these biological abnormalities over time can lead to gradual changes in cellular response mechanisms in the brain and the peripheral tissues, creating a state of heightened biological vulnerability and reduced resilience demonstrated via a diminished capacity to deal with novel or ongoing endogenous and exogenous systemic or brain-specific stressors, which can be independent of the primary MDD etiopathological mechanisms. Furthermore, if these biological abnormalities remain unchallenged or are not promptly resolved (e.g., due to the persistence of MDD, recurrent depressive episodes, and treatment resistance, among others), they can accumulate over time, leading to a positive feedback loop, decreasing systemic resilience and increasing the biological vulnerability to endogenous and exogenous stressors, in a process called homeostenosis or reduced adaptive homeostasis capacity (Davies, 2016; Epel, 2020; Khan et al., 2017).

The reduced adaptive homeostatic capacity due to the accumulation of biological aging abnormalities in MDD can manifest clinically by the observed risk of age-related adverse health outcomes (e.g., higher rates of multimorbidity, frailty, cognitive impairment, and dementia) or even MDD-specific phenomena like increased rates of recurrence and relapse, worse treatment response, the severity of depressive symptoms and associated disability. Within this perspective, the abnormalities on the hallmarks of biological aging are factors contributing to and mechanistically linked to the emergence of a premature aging phenotype in MDD across the lifespan.

MDD, behavioral and social processes, and biology of aging: This review has focused on the intersection between the MDD and the abnormalities in hallmarks of biological aging. However, we do acknowledge other possible theoretical frameworks by which MDD may contribute to a premature aging phenotype, specially via behavioral and social processes. When MDD occurs at its peak prevalence during young adulthood, the illness derails the healthy transition from adolescence to adulthood, interferes with educational attainment, diminishes work life, income, and wealth, reduces social connectedness, increases social isolation, and disrupts health behaviors necessary for healthy aging, such as physical activity. All of these are known as social hallmarks of accelerated aging (Crimmins, 2020). Moreover, many of these social and behavioral processes have been associated with abnormalities in hallmarks of biological aging, in particular an elevated pro-inflammatory status, independently of the presence of MDD or other psychiatric

disorders (Ahmadian et al., 2020; Lam et al., 2021; Shankar et al., 2011; Vingeliene et al., 2019). Therefore, testing how social and behavioral processes can modify the associations between MDD and the biological hallmarks of aging will bring greater explanatory precision and translational power.

12. Future directions

The conceptualization of many biological changes observed in MDD from a geroscience perspective is novel and brings many new unanswered questions. First, is there a hierarchy of changes among the hallmarks of biological aging, acting in a cascade fashion? How do these changes impact and interact with each other? Are abnormalities in one hallmark of biological aging linked to specific adverse MDD outcomes, or are they broadly associated with any adverse outcomes in MDD? Are elevated aging hallmarks specific to MDD, or are they shared by other mental disorders that peak in early adulthood and are commonly comorbid with MDD (Caspi et al., 2020)? This set of questions highlights the importance of well-powered studies, including the simultaneous measurement of multiple hallmarks of biological aging, depressive symptoms, and diverse health outcomes relevant to aging in a diverse study sample followed longitudinally with repeated measures for an empirical lifespan approach.

Many studies of the hallmarks of aging reviewed here have reported on older adults, but because MDD incidence peaks in early adulthood and declines in older adulthood, more studies should assess the hallmarks of aging in young-adult MDD patients. Studies of national register medical record datasets (Plana-Ripoll et al., 2022; Richmond-Rakert et al., 2022, 2021) can also be helpful by documenting to what extent patients diagnosed with MDD tend to be the same patients later diagnosed with age-related diseases and whether MDD poses a specific risk for diseases with known inflammatory etiology versus equivalent risk for all age-related diseases.

Second, should interventions focusing on the modulation of abnormalities on hallmarks of biological aging improve mental health treatment outcomes or mitigate the risk of long-term adverse events in this population? In fact, physical exercise significantly improves cellular senescence markers (Englund et al., 2021; Valente et al., 2021) and has shown a significant benefit as an adjuvant for MDD treatment and prevention (Bellon et al., 2021; Lee et al., 2021). Lithium carbonate, a drug long used for treating recurrent and treatment-resistant depressive episodes, has also shown a potential effect on clearing senescent cells, improving cellular senescence markers, and modulating SASP factors (Fang et al., 2022; Squassina et al., 2016; Viel et al., 2020). The development of senolytic drugs, which can clear senescent cells (Kirkland and Tchkonia, 2020; Partridge et al., 2020), also offers a promise that their use as adjuvants to antidepressant treatment can ameliorate the abnormalities in the hallmarks of biological aging in MDD, improving treatment response rates and reducing the risk of age-related adverse health outcomes in this population. Finally, it will be important to include measures of hallmarks of aging and outcomes in randomized clinical trials of MDD and other psychiatric disorders to evaluate if and how currently available psychiatric treatment can impact age-related biological processes and related adverse health outcomes.

Third, are there moderators of the association between the abnormalities in the hallmarks of biological aging and adverse outcomes in MDD? To respond to this question, studies need to address whether potential demographic (e.g., chronological age), biological (e.g., biological sex, gut microbiota), and social determinants of health (e.g., educational status, race, socio-economic status, social isolation) moderate or mediate the association between MDD, abnormalities in the hallmarks of biological aging, and adverse health outcomes.

All of the above issues will need to be addressed, as will growing heterogeneity between individuals in terms of MDD, related clinical conditions, and rate of biological aging in late life, to develop a precision geroscience approach to MDD.

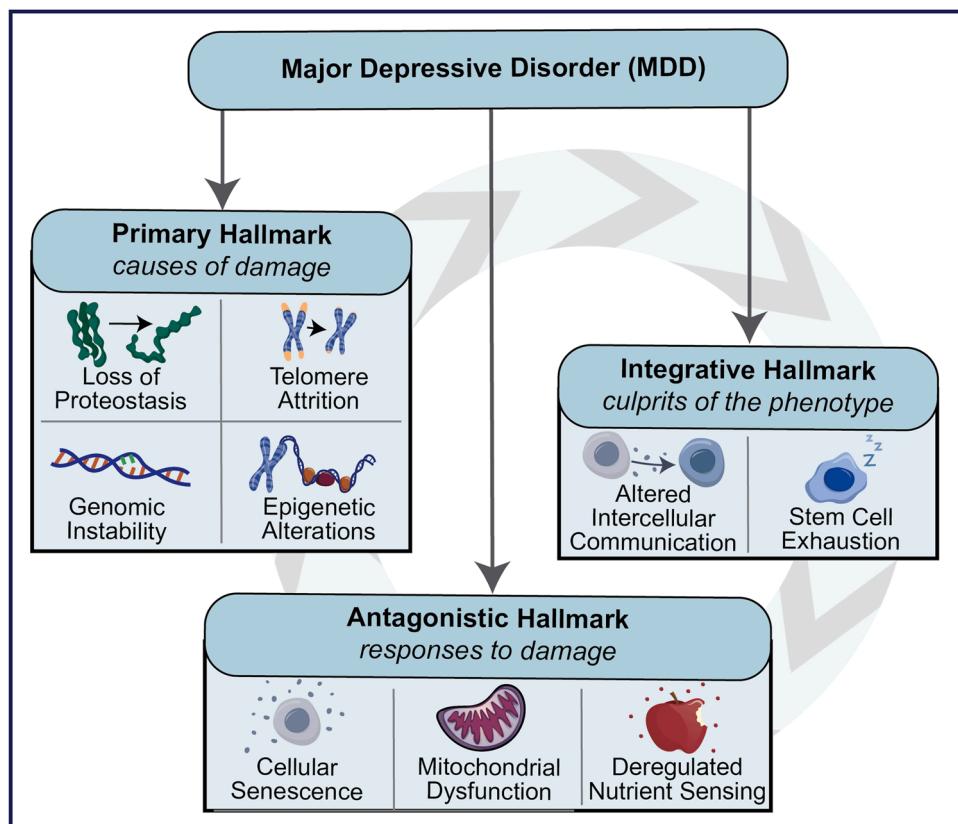


Fig. 1. Hallmarks of biological aging in MDD. Footnote: Major depressive disorder can show changes in many different hallmarks of biological aging.

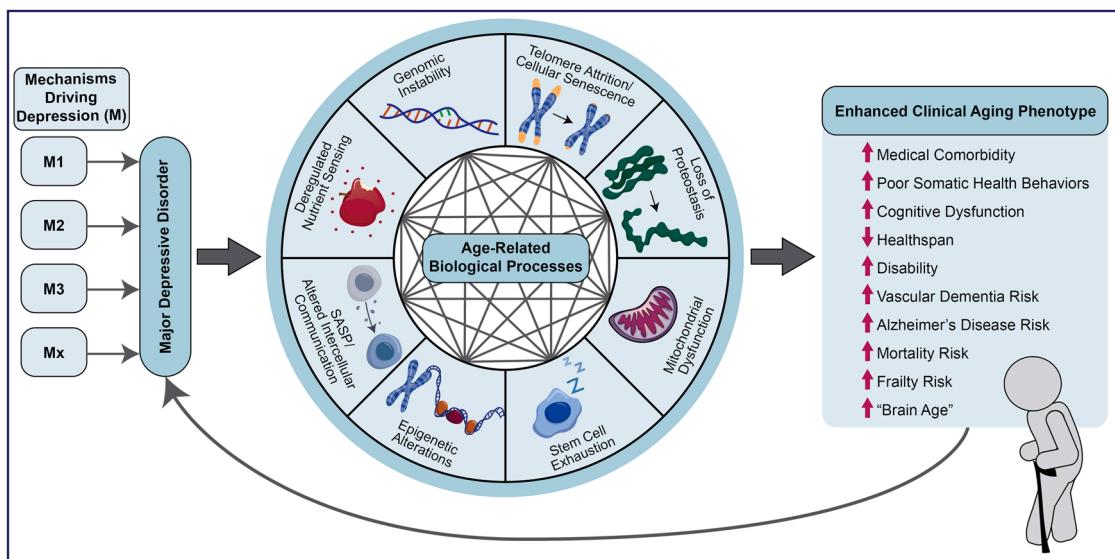


Fig. 2. Mechanistic model linking the hallmarks of biological aging with adverse health outcomes in MDD. Footnote: Major depressive disorder (MDD) triggers abnormalities in many hallmarks of biological aging which can be independent of the primary etiological mechanisms of the MDD. It is not clear how MDD triggers the dysregulation of different hallmarks of biological or what is the cascade or hierarchy of changes. However, once these biological processes are activated, they may work in concert and interact among themselves leading to a self-perpetuating deleterious cycle of damage accumulation and diminished resilience to endogenous and exogenous insults (i.e., homeostasis). If this deleterious cycle remains unchecked, it can manifest clinically as different adverse health outcomes commonly observed among individuals with MDD.

Such an approach will shed light on how MDD (and probably other psychiatric disorders) negatively affect the hallmarks of biological aging, both in the brain and systemically, lead to a premature aging phenotype in individuals with a history of MDD across the lifespan, and help identify novel therapeutic targets and approaches to mitigate the

long-term disability and adverse health outcomes associated with MDD (Fig. 1, Fig. 2).

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Conflicts of interest

All authors have no conflict of interest to report.

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