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A Review of the Effects of Major Depressive Disorder on Biological Brain Aging

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ABSTRACT

Major Depressive Disorder (MDD), or clinical depression, is a serious and common mood disorder that affects 5% of the world population. Despite its prevalence, the underlying mechanisms of depression are not fully understood. In recent years, advances in genetic research have provided new insights into the biological and neural basis of depression and its potential connection to chronological aging, a natural process that occurs over the human lifespan. Despite their distinct nature, depression and chronological aging have been linked in several studies, suggesting continued research in this important area. This review explores fundamental knowledge of clinical depression, including its leading causes, symptoms, and current treatments. It will also examine the genetic and biological overlaps between depression and aging, including the role of genetic factors, biological systems, and processes such as inflammation and oxidative stress. And finally, it will discuss potential treatments for depression that also target shared symptoms in aging and the unique challenges associated with diagnosing and treating depression in an older population. This review aims to provide a comprehensive overview of the current understanding of the relationship between depression and chronological aging and to highlight the need for MDD to be viewed, studied, and treated as a multi-system disorder that interacts with major biological functions of the human body.

Introduction

Major Depressive Disorder is one of the most common mental health conditions with a multitude of causes, including genetic predisposition, childhood development, brain chemistry, and stressful life events (Cleveland Clinic, 2022). The understanding of the disorder has evolved significantly throughout medical history, especially as its prevalence surged due to the continuous development of healthcare and public awareness.

In contemporary research, the relationship between MDD and chronological brain aging has emerged as a compelling area of investigation in both neuroscience and psychiatry. Studies have uncovered intriguing connections suggesting that the disorder may accelerate the aging process fo the brain, leading to significant alterations. Notably, research shows various diseases of aging, such as cardiovascular diseases, metabolic syndromes, and dementia are often comorbid with depression.

Understanding the interplay between MDD and chronological brain aging is crucial not only for examining the pathophysiology of depression but also for information therapeutic interventions and preventive strategies. Targeted treatments can be developed to both alleviate depressive symptoms and imtigate the detrimental edffects of depression on brain health and cognitive function.

Major Depressive Disorder (MDD)

Major or clinical depression is marked by persistent feelings of sadness, hopelessness, and loss of interest or pleasure in activities ((Sawchuk, 2022)). While it is a chronic condition, it often presents in episodes (likely

more than one) that last several weeks or months (Cleveland). Because genetic factors, environmental factors, and brain chemistry and structural changes are all significant contributors to MDD, it is crucial to overview research in each area to gain a more holistic understanding of the disorder.

One of the key challenges in depression research is understanding the interplay between genetic and environmental factors contributing to the onset and course of the disorder. A growing body of evidence suggests that genetic factors play a significant role in the development of depression, with several genes associated with increased risk. Family and twin studies suggest that the heritability of the disorder may be up to 40% and even higher for severe depression (Levinson & Nichols, n.d.). This is also reflected in clinical care with the significant increase in genetic testing to inform the choice of psychiatric medications (Lebowitz, 2019). However, it is also clear that environmental factors such as trauma and stressful life events influence the development and severity of the disorder. Research have consistently associated stressful events with the onset of depression, with changing levels of stress playing a significant role over the course of the disorder (Shapero et al., 2014). The interaction between genetic and environmental factors is complex and not yet fully understood, and further research is needed to clarify the relative contributions of each.

One of the main approaches used to study the genetics of MDD is genome-wide association studies (GWAS). While the multigenetic nature of the disorder impedes pinpointing its heritable component, these studies have identified several genetic variants that are associated with an increased risk for depression. After a meta-analysis of the data from more than 800,000 individuals and further analysis of an independent sample of approx. 1.3 million individuals, 87 gene variants were associated with MDD, including genes and gene pathways related to synaptic structure and neurotransmission (Howard et al., 2019).

On the other hand, environmental factors that contribute to MDD can range from early-childhood trauma to sudden changes in life, including but not limited to childhood abuse, chronic stress/injuries, social nonconformity, death of a close relative, addictive substance abuse, and destructive life habits. Because of the complexity of gene-environment interactions that contribute to MDD and the greatly varying stress resilience of individuals, the environmental factors of clinical depression is difficult to study and often case-specific (Zhao et al. 2021). However, as it is definitive that the life experiences of individuals influence their susceptibility to depression and their ability to recuperate from it, understanding these factors is an important step in developing effective preventative and treatment strategies for the disorder.

In earlier research, neurotransmission and brain chemistry is was the most fundamental area of investigation. Studies show that an insufficiency of neurotransmitters such as serotonin, dopamine, and norepinephrine may lead to the development of depression. This hypothesis has been largely supported by the action of antidepressants, which elevant the levels of these neurotransmitters and consequently alleviate depressive symptoms (Delgado, n.d.). Serotonin, which helps to regulate sleep, appetite, and mood, is the most extensively studied in depression research. Dopamine influences motivation and the individual perception of reality, playing a significant role in the brain's reward system. Similarly, norepinephrine also helpts to determine motivation and reward. Disruptions in the levels of these important neurotransmitters are associated with increased risk of depression and suicide, distorted thinking characterized by delusions, substance abuse, and anxiety (Harvard, 2022).

In more recent years, research on functional and structural changes in the brain in depression pathology have emerged. Clinical studies demonstrate that depression symptoms are associated with synaptic loss and functional connectivity deficits in brain regions that regulate mood and cognition, suggesting a definitive link between MDD and neuronal atrophy (Holmes et al., 2019). Synapses are essential for communication between neurons, and synaptic abnormality is associated with various psychiatric disorders such as MDD, Alzheimer's, Parkinson's, and Huntington's (Albin et al., 2018). As a single neuron may require thousands of synaptic contacts with other neurons, a decrease in their connection and impairments of neuroplasticity contribute to the pathophysiology of mood and neurodegenerative disorders. Recovery could occur if appropriate plasticity is induced through psychotherapy, medicine, and other methods such as electroconvulsive therapy (ECT), which

induces neuroplasticity through synaptogenesis, neurogenesis, and other mechanisms (Rădulescu et al., 2021). In addition to synaptic structure, the identification of neural and biochemical system alterations in the brain is also one key area of investigation. Using neuroimaging techniques such as fMRI and PET scans, researchers have identified several brain regions that appear to be altered in individuals with MDD. These regions are involved in the regulation of mood, emotions, and memory, and both structural and functional abnormalities contribute to depression. Cortical abnormalities including the prefrontal cortex, anterior cingulate cortex, and the anterior subdivision of the insula, and subcortical limbic brain regions such as the amygdala, hippocampus, and the dorsomedial thalamus are highly implicated in depression. Decreased metabolism in the cortical regions of depressed individuals and decreased volume of subcortical regions are highly implicated in depression. Recent research has revealed that some antidepressant medications may reverse neurodegeneration in these critical areas (Pandya et al., 2012). While the significance of such abnormalities is not yet fully understood, treatments can be designed to target and correct the malfunction of these brain regions.

All these theories are valid to some extent in explaining the pathophysiology of depression, however, the clincal and etiological heterogeneity of the disorder makes it difficult to determine a unified hypothesis. Depression is highly variable both across different patients and the course of the disease, which demands that psychological and biological approaches to depression treatment are tailored for individual patients and stages fo disease (Hasler, 2010).

Biological Brain Aging

Biological aging is the leading risk factor for age-associate diseases, having its effects on cells, vasculature, and gross morphology (Peters, 2006). It plays an especially significant role in neurodegenerative diseases, and is reflected in significant changes in brain size, structure, and cognition (Zia et al., 2021). Biological brain aging involves multiple system, making it imperative to investigate the many biochemical pathways that play different roles in the process.

Aging leads to certain physical changes in the brain, such as a decline in brain volume and weight. This particularly affects the frontal cortex, and is attributed to neuronal cell death, change in neuronal volume, and alterations in synaptic plasticity (Zia et al., 2021). While dendritic sprouting may compensate for cell death, they are insufficient in age-associated neurodegenerative diseases due to a more significant loss of dendritic synapses (Peters, 2006). White matter, found in subcortical tisseus of the brain, also deteriorates with age and leads to white matter lesions that cause functional issues. Alongside physical changes, cognitive changes such as decline in memory and behaviours also mark biological brain aging. An increased risk of vascular pathology such as strokes contribute to cognitive impairment and the development of dementia (Zia et al., 2021). This aging process is closely associated with disorders like Alzheimer's disease (AD), where dementia is a prominent diagnostic feature (Peters, 2006). Furthermore, neurotransmitters such as dopamine and serotonin also decline with age, impacting cognitive and motor functions. These neurotransmitter pathways degenerate and synapses and receptors are inhibited with increasing age, which are again implicated in neurogenesis and neuroplasticity (Zia et al., 2021).

Environmental factors are also significant in the biological aging process. A healthy diet, phsyical exercise, and intellectual engagement have all been shown to delay age-related structural and functional impairements (Peters, 2006). These protective factors improve cognitive function and reduce risk of diseases comorbid with age through mechanisms such as increased blood flow, neurogenesis, and synaptic plasticity (Zia et al., 2021).

Biological brain aging is a multifaceted process influenced by various molecular mechanisms and environmental factors. Understanding its nature is crucial for developing interventions to mitigate age-related cognitive decline, and promoting protective factors hold promise for reducing the risk of neurodegeneration.

Correlations Between MDD and Brain Aging

Researchers have begun to examine more closely the association between increased risk for neuropsychiatric disorders and extended lifespan, suggesting mechanistic links between biological aging and neurodegerative disorders (Sibille, 2013). MDD and aging are both associated with a variety of physical and mental changes, and emerging research suggests that they may interact in complex ways. Previously, because aging presents an inherent vulnerability to physiological changes such as cognitive decline, these symptom-like conditions are often attributed to old age. However, recent age-by-disease biological models bridges the gap between "normal" brain aging and its connection to age-related diseases (Sibille, 2013). Furthermore, research on the structural and functional changes of the brain in clinical depression and chronological aging reveals significant overlaps and similarities between the two conditions (Carroll, 2002). Examining the interactions between both processes brings together basic research on aging with the investigation of neuropsychiatric disorders, highlighting a need for extensive future research.

In recent studies, biological overlaps and similar genes found in molecular aging and brain disorders have proposed a closely intertwined relationship between these processes. In a study of depression and anxiety involving 811 depression patients and 319 healthy controls, scientists found that individuals diagnosed with depression had a degree of epigenetic change indicative of an older age. This finding was then replicated in post-mortem brain tissues, where a higher epigenetic aging were found in the brains of deceased MDD patients. Depressed individuals in this study were biologically older by 8 months than the controls, and in some severe cases, their biological age were 10-15 years older than their chronological age (Han et al., 2018). More detailed research has observed similar age and disease changes for numerous genes, suggesting that normal brain aging may promote aspects of disease-related mechanisms. This phenomenon is especially clear in the case of MDD, as its associated biological pathways overlap with those frequently implicated in aging processes such as stress and inflammation (Carroll, 2002). Consequently, mitigating factors that delay age-dependent trajectories may promote resiliency against neurodegenerative disorders as well. In one study, a broad survey of age-related and disease-related genes reports a large over-representation of neurological-related genes within biological aging. Furthermore, the observed effects of aging on gene expression are greater than 90% in brain disorder-related directions – only 4% of those genes are non-age-regulated (Sibille, 2013). In depression specifically, most related genes were frequently age-regulated, again shwing evidence of the correlation between MDD effects and the increased age of genes (Douillard-Guilloux et al., 2013).

Investigation of brain-derived neurotrophic factor (BDNF) and BDNF-related genes strongly supports the interaction between age and disease. BDNF is a signalling neuropeptide that affects learning, memory, and the proper functioning of neuronal cells through the regulation of synaptic plasticity (Autry & Monteggia, 2012). Changes in its expression are associated with both biological aging and the pathogenesis of depression as it mediates significant atrophy and structural changes in the brain. Reduced BDNF levels and functions have not only been implicated in multiple brain-related disorders (MDD, Alzheimer's, Huntington's, etc.) but also with increasing age (Autry & Monteggia, 2012). Similarly, evidence shows that subjects affected with depression have decreased BDNF levels/signalling in specific areas of the brain compared to controls. For example, a study analyzing the gene expression dataset in the amygdala found a strong positive correlation between age and the effects of depression. Its examination of a postmortem cohort of 21 women with MDD and 21 age-matched controls supports the association of MDD with robust gene expression changes (specifically BDNF) that occur during biological brain aging. There is a definite link between the age-related decrease in BDNF levels and further age-related decreases in BDNF gene expression in MDD subjects (Douillard-Guilloux et al., 2013).

In addition to specific genes, biological systems such as the hypothalamic-pituitary-adrenal (HPA) axis are important subjects of research vital in our understanding of molecular functions and neuropsychiatric disorders. As a major component in the homeostatic response and a stress-regulating system, the HPA axis is a

crucial part of psychological resilience and its implications in mood disorders. Overactivation of the HPA axis is involved in both MDD and schizophrenia, often leading to cognitive dysfunction and reduced mood (Mikulska et al., 2021). HPA axis dysregulation can be caused by several pathways, including chronic stress-induced prolonged activation, which plays a key role in the pathophysiology of MDD, genetic predispositions, and dysfunction of closely tied body systems (Gaffey et al., 2016). As its function changes during the course of aging, disturbances in its regulation have been correlated with a higher risk for mood disorders.

Examining other key processes in biological aging such as inflammation and oxidative stress, it has been well-established that they play an important role in neurodegenerative disorders. Chronic inflammation and the accumulation of free radicals in the body – which interact with each other to form a positive feedback loop, contribute to the development of many age-related diseases such as Alzheimer's and Parkinson's (Doig, 2018). Similarly, emerging studies propose that they may also be vital in the progression of MDD and are highly involved in the pathogenesis of the disorder. As previous evidence suggests, depression is a neuroprogressive disorder with accelerated aging and higher risks of age-related diseases (Bakunina et al., 2015). Neuroprogression is a stage-related process of neurodegeneration, includes apoptosis, reduced neurogenesis, reduced neuronal plasticity, and increased autoimmune responses (Ruiz et al., 2018). As evidence of this progression, increased inflammatory signature and oxidative stress markers have been reported in the blood of depressed patients (Lopresti et al., 2014). After further meta-analyses and post-mortem studies, molecular signs of these two processes have been identified, and the association between depression and oxidative stress has been confirmed (Palta et al., 2014). Although the molecular pathways in relation to MDD are not yet understood, it is clear that aging and depression overlap in many major biological functions.

As seen from previous overviews and analyses, biological aging and neurodegenerative disorders such as depression share similar characteristics and overlap in areas of genetics, chemical signalling, systems, and biological processes. However, it is important to understand the heterogeneous impact of age and disease on biological pathways and cellular functions. In many cases of the elderly, these changes and dysregulations may actually be appropriate and not a significant indicator of the correlation between normal aging and depression. Consequently, there is often an under-report of MDD cases in older populations as patients believe their symptoms are products of age-related physical and mental decline.

Aging represents an intrinsic vulnerability to cognitive decline and neurodegenerative disorders, and it is necessary to process additional factors that alter expected biological trajectories to further understand the mechanisms of disease onset. Instead of identifying changes in individual genes and functions, examining moderators that displace individuals from "regular" trajectories is more critical.

Promoting Resilience and Exploring Treatment Options

Successful aging and resilience are crucial concepts in current society with unprecedented population aging (Huisman et al., 2017). Taking into account the relationship and complex interactions between depression and biological aging, scientists have begun to stress the importance of taking a holistic approach to promote resilience. Due to the fact that traditional perspectives conceptualize depression as a lack of resilience, few studies have investigated it as part of the MDD research (Laird et al., 2019). Moreover, as mentioned previously, the early phases of neuropsychiatric disorders and general age-related morbidity result in elders under-reporting symptoms. Consequently, research on resilience in that population is scarce (Sibille, 2013). Surfacing research that simultaneously examines MDD and biological aging has revealed novel perspectives on disease mechanisms, shedding light on the many potential preventative strategies and therapeutic methods.

The evident MDD pathological association with disease comorbidities commonly seen with advanced age suggest that discovering new pathological mediators in clinical depression is crucial in future treatment development (Wolkowitz et al., 2011). In addition to genetic predispositions and epigenetic modifications, the investigation of mediators such as neuronal atrophy, HPA axis alterations, oxidative stress, and inflammation

help scientists to understand the contributors of accelerated biological aging. In one particular model, depression is characterized by enhanced destructive mediators and insufficient restorative ones (Wolkowitz et al., 2011). Novel treatments would aim to reduce the destructive processes and enhance the protective or restorative ones, improving resilience to both depressive and late-life medical symptoms.

The unique challenges that come with the depression-aging interlinkage would make treating MDD in the context of aging difficult. However, interest in this direction of research has surged as improving resilience in depression and aging is a critical area that holds promise for enhancing mental health outcomes in older adults. By understanding the complexities associated with depression in aging populations, identifying effective interventions, and considering the impact of comorbidities and environmental moderators, strategies can be developed to promote resilience and well-being in older adults with depression.

Conclusion

Research on MDD and biological aging continues to evolve, with ongoing investigations focusing on the biological mechanisms, psychological and environmental factors, and immune dysregulation involved in these complex conditions. There are many potential next steps that would allow for a deepened understanding of these areas, and further examination is necessary for the development of new interventions.

Studies should continue to explore the impact of comorbidities in depression and aging, such as chronic medical conditions, cognitive impairment, and functional limitations, which can complicate the management of MDD. Further investigation could focus on the impact of comorbidities on the diagnosis, treatment, and outcomes of depression in older populations. Additionally, the impact of age-related changes (brain structure, cognitive decline, etc.) on depression should also be researched to reveal how MDD trajectory and progression are influenced in elders. While inspecting these biological functions, the role of social and environmental factors including social support and caregiving must be considered. Despite the complications external moderators would bring, further research would help scientists to develop integrated approaches to manage depression in the presence of other health conditions.

Parallel to understanding more about both conditions, investigating novel and effective interventions should be another priority. Research could focus on identifying and evaluating treatments that are specifically tailored for older depressive adults, or on exploring innovative methods that may prove to be practical. Traditional interventions may include examining the effectiveness of different types of psychotherapy, antidepressant medications, and non-pharmacological approaches in older populations. Some innovative preventions may include transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), virtual reality-based therapies, and other emerging approaches. To develop treatments that are culturally sensitive and inclusive, researchers should remember to address health disparities and diversity in depression and aging populations, with the investigation of factors such as race, ethnicity, gender, sexual orientation, and socioeconomic status.

Emerging esearch in the field of depression and aging can continue to redefine MDD as a multisystem disorder rather than one confined to the brain. An improved understanding of the complexities and connections between depression and biological aging would contribute to improved prevention and treatment of a more broadly defined depressive syndrome.

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