

Changes in the Brain During Menopause: A Comprehensive Review

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Author Bio

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Abstract

Menopause is a natural physiological transition marked by fluctuations in hormone levels in the body, resulting from a decline in ovarian function and eventual ovulation cessation, not a complete halt in ovarian production, which is closely tied to menstruation (World Health Organization, 2022). Not only is it a physiological change, but it's also considered a neurological change, as indicated by key symptoms that appear, such as cognitive decline, sleep disturbances, and altered mood (Thomas, 2021). These symptoms are all related to lobes and regions in the brain. In previous years, there has been various in-depth scientific research into menopause and changes in the brain, which has provided valuable insights for this review article. The objective of this paper is to explore the relationship between menopause and neurological changes, emphasizing the impact of hormonal fluctuations on cognitive decline, sleep disturbances, and mood alterations, and providing a foundation for holistic interventions that prioritize women's well-being during this natural life transition.

Keywords: Neuroscience, menopause, brain, hormones, ovaries, cognitive behavioral therapy, cognitive impairment, vasomotor symptoms, mood swings, estrogen

Introduction

Menopause is the phase in women's life when they experience the permanent cessation of menstrual periods, which is also commonly known as "the change of life" (Johns Hopkins Medicine). The decline in ovarian production marks the end of a woman's reproductive ability, which usually is when a woman hasn't had any menstruation for a consecutive year. In the United States, around 1.3 million women undergo menopause annually, with the typical onset between the ages of 51 and 52. Even though some women start to experience early menopause between the ages of 40 and 45. The ages of onset may differ among different races and ethnicities as previous research suggested. For example, Black women usually experience menopause 8.5 months earlier than White women (Meissner, 2022).

Menopause is often accompanied by vasomotor symptoms (VMS), such as hot flashes, night sweats, heart palpitations, and fluctuations in blood pressure. The primary explanation for the emergence of these symptoms during menopause is the impact of hormonal fluctuations on the mechanisms governing blood pressure and temperature regulation. Interestingly, the causes of hot flashes are probably neurovascular, meaning they occur when alterations happen in the segment of the nervous system responsible for circulation. Experts theorize that hot flashes emerge from modifications in the brain region responsible for regulating body temperature (Nall, 2023). These episodes may be triggered by a sudden decrease in estrogen, which is a key hormone that plays a role in maintaining cognitive well-being, bone health, cardiovascular system function, and various vital physiological processes (Nichols, 2023). However, the majority of people know estrogen for its role in female reproductivity (Nall, 2023).

The fluctuations in estrogen levels have a significant impact on various brain regions that could be the leading cause of vasomotor symptoms. If estrogen levels rise or decline abnormally, the hypothalamus cannot regulate body temperature correctly, which directly results in the occurrence of hot flashes. Inactivation of the brainstem, which is the connection point of the brain and spinal cord, could be the reason for sleep disturbances during menopause for women. In addition, the amygdala is part of the

limbic system that acts as the emotional center and controls explicitly fear and anxiety. The inefficiency of estrogen may increase neuronal excitability, thus there will be several mood swings (Thomas, 2021). As estrogen level falls, women are likely to experience a growing sense of forgetfulness, also known as mental "fogginess". Interestingly, low estrogen levels are also associated with the decline in gray matter volume, which is found to have an impact on Alzheimer's Disease and other forms of dementia such as vascular dementia (LCMC Health, 2023). This topic is significant because menopause is one point along the continuum of women's life stages, marking the conclusion of their reproductive years (World Health Organization, 2022).

Discussion

Hormonal Influence on Brain Changes

The menopausal transition is closely linked to subtle cognitive decline. The impacts vary from classical nuclear actions to nonclassical membrane-mediated effects, estrogen traditionally regulates gene transcription through its interaction with nuclear receptors. The brain is closely connected to the reproductive system and women's ovaries via the HPG axis (hypothalamus pituitary-gonadal), which is responsible for releasing ovarian hormones and regulating reproductive activity (Nielsen and Herrera, 2017).

According to a multi-modality neuroimaging study of women at different menopause transition stages (pre-, peri-, post-), menopause transition demonstrates a significant impact on the structure, connectivity, and metabolic characteristics of the female brain during the hormonal and neurological changes of the midlife. By scanning and using neuroimaging techniques in the brains of more than 160 women between 40 and 65 who were in different stages of the menopause transition (MT), the researchers examined the blood flow, structure, metabolism, and function. The brain regions responsible for cognitive functions are the most affected at all ages. However, it's crucial to note that it's hard to draw the boundary between changes from aging or menopause, which could be a focus for future menopause research (Mosconi et al., 2021).

The rapid alteration of neuronal and pituitary cell excitability triggers pathways like cyclic adenosine monophosphate and mitogen-activated protein kinase. This influences the function of receptors such as kainate, G-protein coupling, calcium channels, and calcium ion entry, offering neuroprotection against damage caused by excitotoxins and free radicals (Conde et al., 2021). In the realm of estrogen, there are 3 common types: Estrone (E1), Estradiol (E2), and Estrinol (E3). Estradiol (E2), crucial during the menopausal transition, exhibits the highest affinity for intracellular estrogen receptors and binds strongly to the membrane-associated G protein-coupled receptor known as GPR30/GPER1. This hormonal shift during menopause, however, shows limited evidence of varying the risk of developing Parkinson's disease. Estradiol's impact extends to cognitive aging, quality of sleep, and mood stability, with associations found in multiple neuropsychiatric disorders, such as Alzheimer's Disease, schizophrenia, and depression. Evidence suggests that E2 plays a significant role in protecting dopaminergic neurons, with potential implications for Parkinson's disease. Furthermore, research links estrogens to cognitive aging through three factors: the cholinergic system, the dopaminergic system, and mitochondrial dysfunction. The cholinergic system's correlation with cognitive aging is supported by reduced cholinergic acetyltransferase activity. This hypothesis of the cholinergic system's correlation with cognitive aging also arises from Alzheimer Disease's treatment, particularly the FDA-approved acetylcholinesterase inhibitors. These drugs function to elevate synaptic acetylcholine levels and promote cholinergic signaling overall. Multiple literature studies have pointed out the significance of the dopaminergic system for cognitive aging (Russell et al., 2019). Its significance is evident in diseases like Huntington's disease and Parkinson's disease, where imbalances correlate with cognitive abnormalities (Brown and Marsden, 1988). Poor cognitive performance has been suggested by brain imaging scans such as Positron Emission Tomography (PET) that in individuals carrying the Huntington's disease mutation, there is a correlation between the level of striatal dopamine receptor binding and cognitive performance, where reduced binding is associated with poorer performance (Lawrence et al., 1988). Unlike the cholinergic and dopaminergic hypothesis, the mitochondrial aging hypothesis proposes that as mitochondria age, increased mitochondrial DNA Damage results in elevated reactive oxygen species,

leading to decreased mitochondrial activity and signs of aging. Applied to cognitive aging and Alzheimer's disease, it links elevated reactive oxygen species for neurofibrillary tangles and Alzheimer's hallmarks. Alzheimer's progression involves reduced brain glucose uptake, which shifts from aerobic to anaerobic metabolism, together with changes in glucose utilization preceding clinical symptoms. Mitochondrial dysfunction precedes age-related cognitive deficits. Studies on estrogen's effects reveal decreased glycolytic gene expression in irregularly cycling animals, resulting in a shift toward mitochondrial function, fatty acid uptake, and ketone metabolism (Russell et al., 2019).

Psychological and Cognitive Effects

Individuals with objective cognitive impairments on neuropsychological assessments while maintaining their ability to perform daily life activities independently, are known to live with Mild Cognitive Impairment (MCI). Common symptoms are having difficulty memorizing, learning, concentrating, and making decisions. The incidence of Mild Cognitive Impairment (MCI) was 4.5% among 6,376 postmenopausal women observed over 5.4 years in the Women's Health Initiative Memory Study (WHIMS). However, there has been limited research on the connection between MCI and menopausal factors. Cognitive functioning in postmenopausal stages exhibited a trend toward decreased performance when compared to pre- and perimenopausal phases, especially in domains such as verbal delayed memory and executive functions (cognitive control and supervisory attentional system). These cognitive domains are believed to be more responsive to fluctuations in estrogen levels. The Study of Women's Health Across the Nation (SWAN) assessed a group of 2,362 American women for four years through the repeated administration of neuropsychological tests, which is significant due to its great contribution to the understanding of women's health in areas such as menopausal transition, hormonal changes, cardiovascular health, psychological well-being. Women's performance on both immediate and delayed memory assessments during both early and late perimenopausal phases didn't exhibit any improvement with repeated testing. Likewise, Kilpi et al. conducted research involving 2,411 middle-aged women in the United Kingdom, confirming a decline in processing speed and immediate and delayed verbal

episodic memory during the perimenopausal phase. Furthermore, alterations in verbal episodic memory performance exhibited correlations with follicle-stimulating hormone and luteinizing hormone levels. Follicle-stimulating hormone (FSH) is produced by the pituitary gland at the base of the brain, and is released mainly for sexual development and reproduction. As a result, it impacts the functioning of both ovaries and testes (Cleveland Clinic, 2023). Overall, the menopausal transition has a profound impact on the female brain, impacting brain structure and function from hormonal fluctuations to cognitive decline.

Interventions and Therapies

Currently, many methods of interventions could be used to reduce menopause-related symptoms. Among them, are hormone replacement therapy (HRT), cognitive behavior therapy (CBT), and antidepressants which will be discussed in this review paper (Mayo Clinic, 2023).

Hormone Replacement Therapy (HRT), also known as postmenopausal hormone therapy or menopausal hormone therapy (MHT), is a broad term used to describe unopposed estrogen in women who have had a hysterectomy and the combined estrogen-progestin in women with an intact uterus, necessitating progestin to prevent estrogen-related endometrial hyperplasia. This medical approach is utilized to supplement a woman's diminished natural estrogen and progesterone hormones during and after menopause. This treatment is often suggested by healthcare professionals to relieve common symptoms that occur during this transition such as hot flashes and vaginal dryness. Additionally, it's employed to address long-term physiological changes, such as osteoporosis (bone loss), associated with the decline in estrogen and progesterone levels (National Cancer Institute, 2023). To alleviate menopause-related symptoms, conventional hormone replacement therapy (HRT) involves using both estrogen and progesterone components to mimic the natural hormones produced by the ovary. There are various types of estrogen therapies available, including those that are naturally occurring in the human ovary such as estradiol and estriol (Harrison and Shanahan, 2023). Still, HRT has its downsides and limitations for certain populations. If patients encounter blood clots, cancer (e.g., breast, uterine, or ovarian), heart, liver, gallbladder disease, heart attack, known or suspected pregnancy, stroke,

or unexplained vaginal bleeding, a professional may recommend avoiding HRT (WebMD Editorial Contributors, 2023). Some of the common downsides are hot flashes, night sweats, weight changes, osteoporosis, mood changes, gastrointestinal (GI) symptoms, vaginal and menstruation change, and more. Discussing with the healthcare professionals regarding the patient's prescription before using HRT is vital. This conversation should address anticipated side effects, strategies for mitigation, and procedures to follow if the patient encounters unforeseen side effects (Cancer Net, 2023).

Other non-hormone therapies aim to address the emotional challenges experienced during menopause and related issues, such as Cognitive behavioral therapy (CBT). It is a common form of psychotherapy where the patient collaborates with a mental health counselor in a structured manner. CBT's objective is to enhance patients' awareness of pessimistic thought patterns, enabling them to gain a clearer perspective on challenging situations and develop more efficient responses (Mayo Clinic, 2019). To help people cope with stressors from menopause, CBT manages problematic hot flashes and night sweats. According to a study in 2018 by Hardy et al., 124 women aged 45 to 60 who were experiencing a minimum of 10 episodes of hot flashes and night sweats were randomly divided into two groups. One group was asked to use a booklet of CBT self-guided techniques to cope with their symptoms, while the other group of participants had no treatment waitlist control. The group that used the booklet showed an improved sense of well-being compared to the other group. By breaking negative thought patterns, people who incorporate CBT into their approach may find relief from symptoms of depression and anxiety. Incidentally, CBT could help people who suffer from sleep disruptions sleep better during perimenopause and menopause. Despite the advantages of CBT, there are some disadvantages as well. For example, attending CBT sessions consistently takes up a lot of time. Because of CBT's organized format, it might be a good choice for individuals with more sophisticated mental health requirements or learning challenges. Other critics contend that as CBT primarily deals with present concerns and concentrates on particular issues, it may not explore potential root causes of mental health conditions, such as a distressing childhood (The CBT Clinic).

The final intervention that will be introduced in this review article is antidepressant medications, which is highly recommended for people with hot flashes who cannot take estrogen. There are different types of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). SSRIs and SNRIs are the class of medications prescribed most often for treating depression and hot flashes that are common for menopause. As the first-line treatment for depression, they provide comparable benefits to other medications while minimizing safety concerns and side effects (Rush, 2022). A comprehensive review reveals that these medications (SNRIs and SSRIs) lead to a substantial decrease in both the frequency and intensity of hot flashes. For instance, desvenlafaxine (a type of SNRI) demonstrated a remarkable 62% reduction in hot flash occurrences, equivalent to seven fewer incidents daily, and an overall 25% decrease in their severity (Stubbs et al., 2017). SSRIs function by inhibiting the reabsorption of serotonin by the bloodstream, resulting in elevated serotonin levels in the brain, which can enhance depression. It's important to note that SSRIs enhance the brain's existing serotonin supply rather than stimulating increased production, so they cannot boost the low levels of serotonin in the body (DiGiacinto and Fink, 2023). Nonetheless, the side effects of SSRIs and SNRIs should be taken into consideration when prescribing them. SNRIs have the potential to increase blood pressure, requiring regular blood pressure monitoring (Weer et al., 2013). Due to the varying side effects and effectiveness of SSRIs and SNRIs, if one of these medications proves ineffective or poorly tolerated, an alternative drug can be prescribed (Ferguson, 2001). Notably, patients should avoid combining MAOIs with other antidepressants such as SSRIs, as this combination can lead to serotonin syndrome, a condition that can be life-threatening (Laban and Saadabadi, 2023).

Conclusion

Based on various research conducted or studied about menopause and the brain, menopause, marking the permanent cessation of menstrual periods, occurs around ages 51-52 in the U.S., with an annual occurrence of 1.3 million women undergoing this significant transition. Vasomotor symptoms (VMS) like hot flashes, night sweats, and blood pressure

fluctuations arise from hormonal shifts impacting temperature and blood pressure regulation together with menopause. Research indicates a correlation between estrogen decline (hormonal fluctuations) and alterations in gray matter volume, potentially linking menopause to cognitive disorders such as dementia. Furthermore, the menopausal transition is connected to cognitive decline, and neuroimaging studies reveal its impact on the brain structure, connectivity, and metabolic characteristics of the female brain. Interventions for menopause-related symptoms involve Hormone Replacement Therapy (HRT), Cognitive Behavioral Therapy (CBT), and antidepressant medications like SSRIs and SNRIs, each offering advantages but implications at the same time to symptom management. Understanding the interconnection between hormonal changes, cognitive decline, and effective interventions is crucial for supporting women's overall well-being. Despite the effectiveness of current treatments/interventions for treating menopause-related symptoms, these methods entail risks for occurrence or complications after the surgery. As a result, future research may concentrate on reducing the effects of menopause and minimizing associated complications for intervention options. Ongoing research in the field of menopause aims to deliver enhanced therapies for health across communities and healthcare settings.

References

- V. (2023, June 16). YouTube. Retrieved December 3, 2023, from <https://www.sciencedirect.com/topics/neuroscience/hypothalamic-pituitary-gonadal-axis>
- V. (2023, June 16). YouTube. Retrieved December 3, 2023, from https://www.uptodate.com/contents/depression-treatment-options-for-adults-beyond-the-basics?topicRef=2167&source=see_link#H446121025
- Amin, S. (n.d.). Vasomotor Symptoms of Menopause: Causes, and More. Healthline. Retrieved December 3, 2023, from <https://www.healthline.com/health/menopause/vasomotor-symptoms-of-menopause#causes>
- Amin, S. (2022, September 14). What to Know About Racial Disparities in Menopause. Healthline. Retrieved December 3, 2023, from <https://www.healthline.com/health/menopause/racial-disparities>

- Begum, J. (2023, October 11). Menopause and HRT: Hormone Replacement Therapy Types and Side Effects. WebMD. Retrieved December 3, 2023, from <https://www.webmd.com/menopause/menopause-hormone-therapy>
- Cognitive behavioral therapy. (2019, March 16). Mayo Clinic. Retrieved December 3, 2023, from <https://www.mayoclinic.org/tests-procedures/cognitive-behavioral-therapy/about/pac-20384610>
- Costa, L. (n.d.). Menopause and cognitive impairment: A narrative review of current knowledge. NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8394691/>
- Do SSRIs and SNRIs reduce the frequency and/or severity of hot flashes in menopausal women. (n.d.). PubMed. Retrieved December 3, 2023, from <https://pubmed.ncbi.nlm.nih.gov/28649145/>
- Ferguson, J. M. (n.d.). SSRI Antidepressant Medications: Adverse Effects and Tolerability. NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC181155/>
- Follicle-Stimulating Hormone (FSH): What It Is & Function. (2023, January 23). Cleveland Clinic. Retrieved December 3, 2023, from <https://my.clevelandclinic.org/health/articles/24638-follicle-stimulating-hormone-fsh>
- Hormone Replacement Therapy - StatPearls. (2023, February 20). NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/books/NBK493191/>
- How estrogen levels in women protect brain function. (2023, March 1). LCMC Health. Retrieved December 3, 2023, from <https://www.lcmchealth.org/blog/2023/march/how-estrogen-levels-in-women-protect-brain-funct/>
- Introduction to Menopause. (n.d.). Johns Hopkins Medicine. Retrieved December 3, 2023, from <https://www.hopkinsmedicine.org/health/conditions-and-diseases/introduction-to-menopause>
- Menopausal Hormone Therapy and Cancer - NCI. (2023, September 25). National Cancer Institute. Retrieved December 3, 2023, from <https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/mht-fact-sheet>
- Menopause. (2022, October 17). World Health Organization (WHO). Retrieved December 3, 2023, from <https://www.who.int/news-room/fact-sheets/detail/menopause>
- Menopause. (2022, October 17). World Health Organization (WHO). Retrieved February 24, 2024, from <https://www.who.int/news-room/fact-sheets/detail/menopause>
- Menopause - Diagnosis and treatment. (2023, May 25). Mayo Clinic. Retrieved December 3, 2023, from <https://www.mayoclinic.org/diseases-conditions/menopause/diagnosis-treatment/drc-20353401>
- Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. (2021, June 9). NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8190071/>
- Menopause – NHS inform. (2022, November 29). NHS inform. Retrieved December 3, 2023, from <https://www.nhsinform.scot/healthy-living/womens-health/late-years-around-50-years-and-over/menopause-and-post-menopause-health/menopause>
- Monoamine Oxidase Inhibitors (MAOI) - StatPearls. (2023, July 17). NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/books/NBK539848/>
- Perez, A. (n.d.). SSRIs (Selective Serotonin Reuptake Inhibitors): What Are They? Healthline. Retrieved December 3, 2023, from <https://www.healthline.com/health/depression/selective-serotonin-reuptake-inhibitors-ssris#how-they-work>
- Pros & Cons of CBT Therapy | The CBT Therapy Clinic – Nottingham – West Bridgford. (n.d.). cbt therapy nottingham. Retrieved December 3, 2023, from <http://www.thecbtclinic.com/pros-cons-of-cbt-therapy>
- The Role of Estrogen in Brain and Cognitive Aging. (2019, July 30). NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6694379/>

Sahakian, B. (n.d.). The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease. PubMed. Retrieved December 3, 2023, from <https://pubmed.ncbi.nlm.nih.gov/9679785/>

Side Effects of Hormone Therapy. (n.d.). Cancer. Net. Retrieved December 3, 2023, from <https://www.cancer.net/navigating-cancer-care/how-cancer-treated/hormone-therapy/side-effects-hormone-therapy>

'Subcortical dementia': the neuropsychological evidence. (n.d.). PubMed. Retrieved December 3, 2023, from <https://pubmed.ncbi.nlm.nih.gov/2969464/>

Thomas, L. (2021, September 27). How Does Menopause Affect the Brain? News Medical. Retrieved December 3, 2023, from <https://www.news-medical.net/health/How-Does-Menopause-Affect-the-Brain.aspx>

Thomas, L. (2021, September 27). How Does Menopause Affect the Brain? News Medical. Retrieved December 3, 2023, from <https://www.news-medical.net/health/How-Does-Menopause-Affect-the-Brain.aspx>

Weber, M. T. (2013, June 14). Cognition and mood in perimenopause: A systematic review and meta-analysis. NCBI. Retrieved December 3, 2023, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830624/>

Wilson, D. R., & Nichols, H. (n.d.). Estrogen: Functions, uses, and imbalances. Medical News Today. Retrieved December 3, 2023, from <https://www.medicalnewstoday.com/articles/277177>