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BSc Biology Thesis:

The Role of Estrogen on Verbal Memory and Learning in Menopause

Author: Sofia Teixeira
Student number: S5096081
Department: University of Groningen, Faculty of Science and Engineering
Course: Bachelor's Thesis Life Sciences (WBBY901-05)
Supervisor: Robbert Havekes (r.havekes@rug.nl)
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1. Abstract

Verbal memory and learning impairments are common cognitive symptoms that menopausal women experience, often leading to the need for treatment. The decline in estrogen levels during menopause has been linked to these changes. Given estrogen's various neuroprotective effects and the widespread presence of estrogen receptors throughout the brain, estrogen supplementation shows significant potential as a treatment option. This thesis investigates how changes in estrogen levels during menopause affect cognitive functions and the neurobiological mechanisms involved, aiming to improve clinical approaches for managing these cognitive symptoms. A large focus is given to describing verbal memory and learning impairments, the effects of menopausal hormone therapy (MHT) and the role of estrogen on hippocampal synaptic plasticity. The reviewed literature suggests that the menopausal decline in verbal memory and learning is linked to decreased nuclear ERα levels in the hippocampal CA1 region, reducing synaptic plasticity. Estrogen therapy (ET) can mitigate these effects within a critical period by preserving ERα levels. Decreased estrogenic neuroprotection is also disrupted in menopause and may influence memory. Psychosocial and biological factors can also contribute to these deficits. Future research should focus on therapies that enhance hippocampal synaptic plasticity and estrogen's neuroprotective actions. Treatment strategies should also address modifiable non-hormonal factors. This paper concludes that menopause-related complaints should be addressed through a holistic and adaptable approach to reflect individual variations.

2. Introduction

Menopause is an important milestone in adult female aging, marking the end of the reproductive period. It occurs due to the cessation of egg production by the ovaries, which promotes a cascade of hormonal changes ultimately culminating in the termination of menstruation (Takahashi & Johnson, 2015). Worldwide, the majority of women enter natural menopause between 49 and 52 years of age (Morabia & Costanza, 1998). As menopause refers to the point in time where there has been an absence of spontaneous menses for a 12 month period (Harlow et al., 2012) rather than a duration of time, the term 'menopausal transition' (MT) is often used to describe the transition from the regular reproductive period to menopause. This period usually lasts 4 to 10 years, and may also be referred to as perimenopause (Harlow et al., 2012). In perimenopause, ovarian function fluctuates, resulting in oscillating levels of estrogen (see Figure 1), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as well as menstrual irregularity (Gatenby & Simpson, 2023). Despite these fluctuations, as oocyte production gradually stops, estrogen production generally declines while LH and FSH levels typically rise (Takahashi & Johnson, 2015; Santoro et al., 2020). The postmenopausal stage describes the remainder of the female lifespan, where estrogen stabilizes at low levels (see Figure 1), while LH and FSH remain high (Hall, 2015). These hormonal changes are thought to be the cause of the variety of symptoms that menopausal women experience, and may hold the key to developing treatment options that can enhance quality of life following the reproductive period.

As the body experiences significant endocrine changes, various symptoms of menopause arise, both in peri- and postmenopausal women. Individuals often report vasomotor symptoms, including night sweats and hot flashes, which may persist in postmenopause (Hamoda et al., 2020). Sleep disturbances and insomnia are often common, and affect quality of life (Constantine et al., 2016). Cognition is also impacted by the menopausal transition, leading to increased forgetfulness and difficulty concentrating (Sullivan Mitchell & Fugate Woods, 2001). Perimenopausal women often struggle with remembering words, numbers and events, misplacing objects, becoming easily distracted and losing their train of thought (Sullivan Mitchell & Fugate Woods, 2001). Together these symptoms can be categorized as brain fog, which Maki and Jaff (2022) define as "the constellation of cognitive symptoms experienced by women around the menopause, which most frequently manifest in memory and attention difficulties". While some memory difficulties may resolve in the postmenopausal period (Greendale et al., 2009), quality of life is affected by the deficits seen in perimenopausal stage (Greendale et al., 2020), highlighting the need for treatment and, if possible, prevention options. Furthermore, studies have shown that both surgical and natural menopause at earlier ages are associated with long-term negative effects on cognition (Ryan et al., 2014; Guo et al., 2025), linking menopause (at extreme ages) to a higher risk of cognitive impairment and dementia. This further emphasizes the importance of developing therapies to conserve cognitive function during female aging.

In order to treat and prevent the cognitive decline associated with menopause, it is imperative to understand the neurobiological mechanisms underlying it. The brain fog evidenced in the menopausal transition suggests a hormonal basis to changes in cognition (Maki and Jaff, 2022). In particular, estrogen, known to have

neuroprotective effects (Wise, 2002), has been implicated in the changes in memory seen in the menopausal transition. Studies have shown that removal of the ovaries, characterized by a large reduction in estrogen levels, leads to a decline in verbal learning and memory (Sherwin, 1988), as well a heightened risk for cognitive impairment and dementia (Rocca et al., 2007; Rocca et al., 2011). Both of these effects can be reversed by reversed by estrogen treatment (Sherwin, 1988; Rocca et al., 2007; Rocca et al., 2011). Additionally, this steroid plays a crucial role in signaling within the brain. This is evident from the widespread presence of estrogen receptors throughout various brain regions, including key areas that regulate memory processes, such as the hippocampus (Rettberg et al., 2014). Given the relationship between estrogen and cognitive function, along with the insights gained from hormone therapy, understanding the molecular mechanisms by which the decline in estrogen during menopause affects cognitive abilities will be essential for optimizing hormone supplementation therapies.

One particular aspect that requires attention are verbal memory and learning difficulties. These types of deficits are one of the most prominent cognitive symptoms of menopause (Hogervorst et al., 2021; Maki and Jaff, 2022) and among the largest sources of complaints in menopausal women (Sullivan Mitchell & Fugate Woods, 2001). Furthermore, research has shown that performance on verbal memory tests are negatively correlated to the severity of the complaint (Weber & Mapstone, 2009; Drogos et al., 2013), highlighting the importance of addressing patients' complaints and creating safe treatment options to alleviate this decline. Thus, this thesis will investigate how estrogen affects verbal memory and learning in women during the menopausal transition and the postmenopausal phase, along with the neurobiological mechanisms driving these changes.

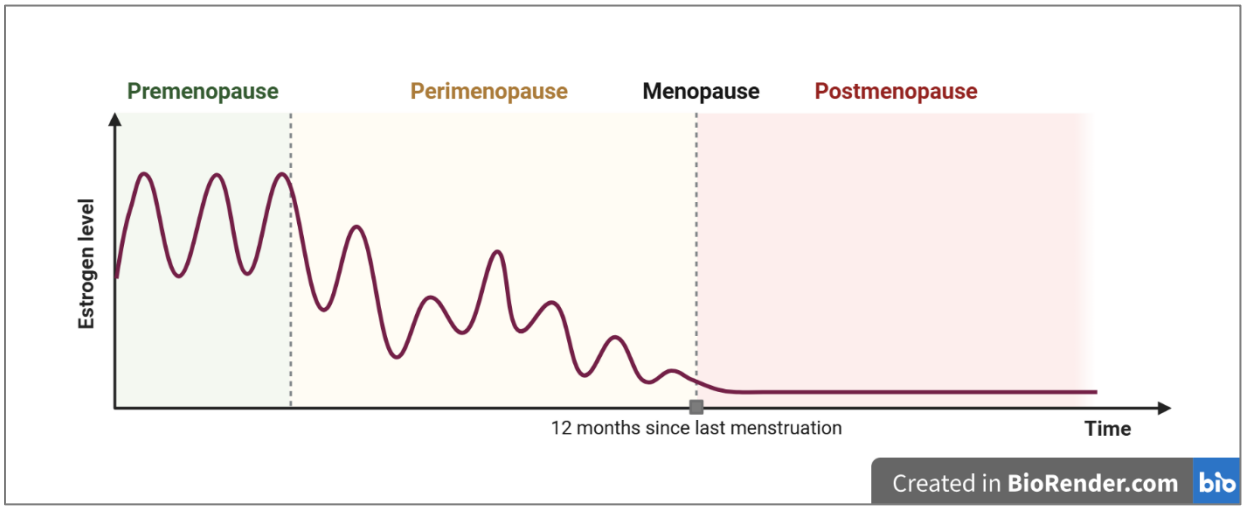

Figure 1. Estrogen levels throughout the menopausal transition (MT). In the premenopausal stage (green), estrogen fluctuates regularly with every menstrual cycle. Once perimenopause begins (yellow), estrogen fluctuates more erratically with a general decreasing tendency. After menopause (black), estrogen stabilizes at low levels in the postmenopausal period (red). Created in https://BioRender.com.

3. Verbal Memory and Learning in Menopause

3.1. The Effect of Natural Menopause on Verbal Memory and Learning

Many studies indicate a worsening of verbal memory and learning as one of the most prominent cognitive alterations during the MT (Hogervorst et al., 2021; Maki and Jaff, 2022). In 2009, Greendale et al. assessed verbal memory using the East Boston Memory Test (EBMT) in menopausal women and found that perimenopause disturbed verbal episodic memory. This effect was subtle and was characterized by a learning impairment: while pre- and postmenopausal individuals had improved EBMT scores over repeated testing, perimenopausal participants did not. The fact that improvement resumed post-menopause, is further indication that the lack of improvement seen in perimenopause was related to the MT rather than chronological age. Another 14 -year long longitudinal study examining 403 women from pre- to postmenopausal stages, found a worsening of verbal memory performance over the MT, which was independent of normal age-related decline (Epperson et al., 2013). In this study, the primary effect of menopausal stage on immediate and delayed verbal recall was further highlighted by a lack of an effect on processing speed, which can affect many cognitive measures, including verbal recall. The authors did not determine whether this decline persisted in postmenopause, as participants were not well accompanied into this stage. Consistent with these findings, Kilpi et al. (2020) found that menopause modestly negatively impacted immediate and delayed verbal episodic memory, when accounting for chronological age, learning effects and socioeconomic confounders. Similarly to Epperson et al. (2013), whether the decrease in verbal memory was persistent or transient could not be detected. However, there were no decreases in practice effects, contrary to previous research (Greendale et al., 2009). Recent research sought to compare menopause-related cognitive decline between women with and without HIV. While the majority of women did not experience clinically significant declines, up to 11% displayed clinically significant worsening in verbal memory and learning in the transition from pre- to early perimenopause and to postmenopause, indicating cognitive vulnerability in a subset of women (Maki et al., 2021). Scores for both measures were decreased and the chance of cognitive impairment increased for both groups. While the heightened odds of memory impairment resolved in the post-menopausal period, for learning, this raise was sustained across the MT and after. The frequency of testing may have inhibited changes from the early to late perimenopausal period from being detected. Measures between HIV-positive and HIV-negative women were largely comparable, with few differences between the groups (Maki et al., 2021).

To summarize, most menopausal women maintain a normal range of memory/cognitive function (Maki et al., 2021). Nevertheless, age-independent verbal memory and learning impairments are frequent (Epperson et al., 2013; Kilpi et al., 2020), likely due to an impairment in learning abilities (Greendale et al., 2009; (Maki et al., 2021). These issues begin in perimenopause and often resolve themselves post-menopause, only persisting for some women (Greendale et al., 2009).

3.2. The Effect of Induced Menopause on Verbal Memory and Learning

Menopause may also be medically-induced by the surgical removal of the ovaries (medically termed oophorectomy or ovariectomy), chemotherapy, radiation therapy, and other medications that suppress ovarian function. It manifests as an abrupt termination of menstruation, and is characterized a sudden drop in estrogen levels (Hamoda & Sharma, 2023). Research has shown that inducing menopause results in an acute decrease of verbal memory (Sherwin, 1988). Elderly women with unilateral oophorectomy (with or without hysterectomy) scored lower on immediate recall and delayed word recall tests, compared to the control group (individuals who underwent natural menopause) (Zhou et al., 2011). Nappi et al. (1999) reproduced these observations by subjecting participants to the Serial Learning Test, which examines verbal memory. This test considers both primacy (PS1) and recency (PS2) effects, reflecting long- and short-term memory, respectively. Women who underwent ovariectomy in experienced lower PS2 scores, compared to individuals undergoing a natural physiological menopause. PS1 score did not differ across the groups. Furthermore, the authors demonstrated an effect of age at the time of surgery and years since the procedure on the severity of this decline. PS2 scores were positively correlated to age at menopause in the surgical group (see Figure 2C); i.e. women performed better when surgery occurred later in life. Short-term memory performance was also negatively correlated to years since surgery (see Figure 2D), indicating a worsening of verbal memory over time (Nappi et al., 1999). A 2014 study (Bove et al., 2014) confirmed these findings. Here, earlier age at surgical menopause was associated with a steeper decrease in verbal memory, as shown in Figure 2A. In line with these results, a shorter reproductive period – calculated by subtracting age of menarche from age of final menstrual period (FMP) – was also correlated to a larger decline in verbal memory.

In short, surgical menopause reflects these same changes, albeit at a steeper and faster decline, particularly before the natural age of FMP. This effect increases the earlier menopause is induced (Nappi et al., 1999; Bove et al., 2014). Given the verbal memory and learning deficits that both natural and surgical menopause can cause in women, which lead to various complaints and negatively impact quality of life (Greendale et al., 2020), it is important to understand the underlying reasons for these changes. This knowledge could assist researchers and clinicians in developing effective therapies to improve quality of life.

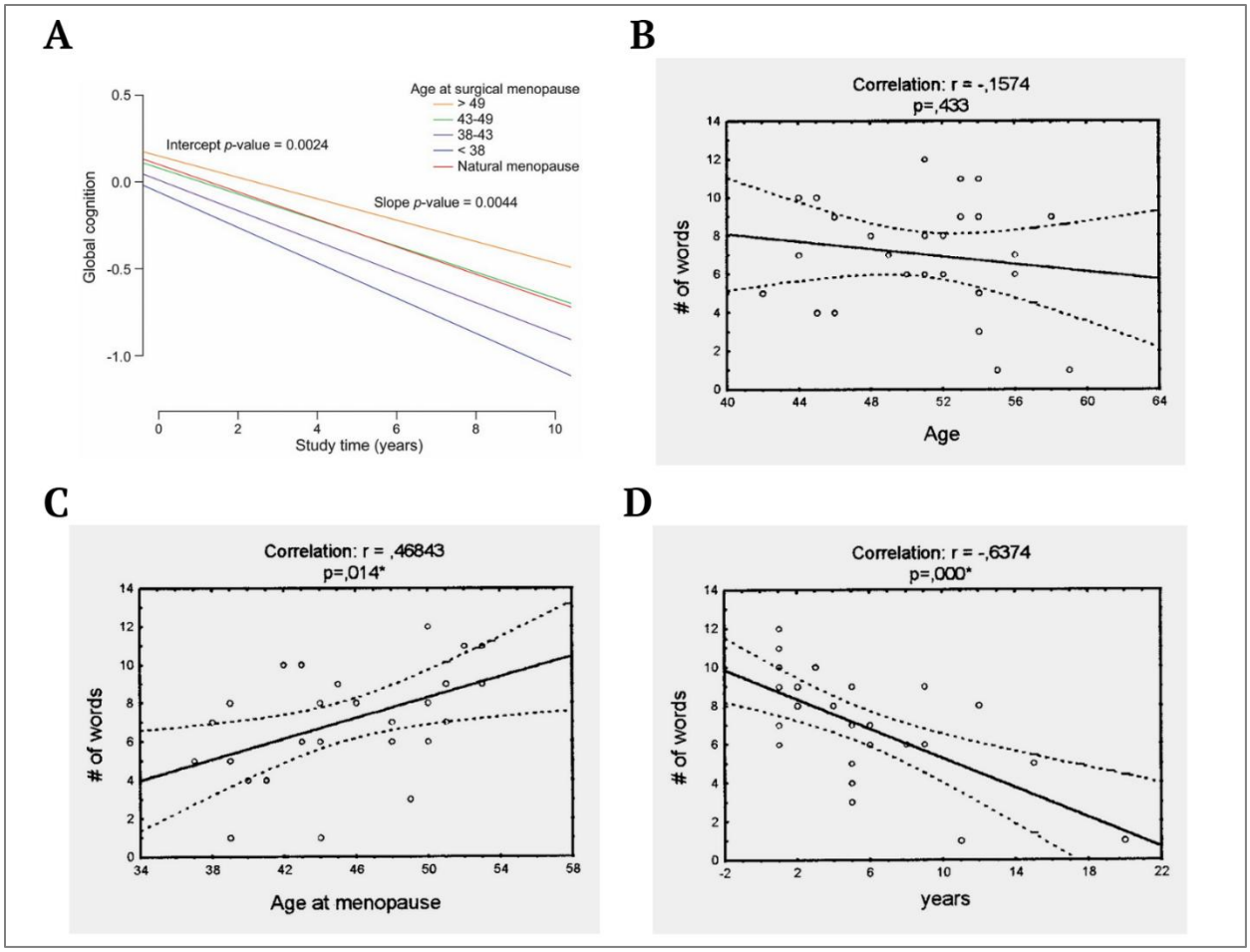

Figure 2. Natural and surgical menopause impair verbal memory. A) *Earlier age at surgical menopause is associated with steeper slope of cognitive decline*. X-axis depicts the years since the study began and y-axis represents the change in global cognitive performance, including verbal memory, since the baseline registered at the start of the study. Adapted from *Bove et al., 2014*. B) *Age is not associated with short-term verbal memory performance*. X-axis depicts the number of words recalled in the Serial Learning Test, measuring recency effects (PS2). Y-axis depicts age at the time of the study. Adapted from *Nappi et al., 1999*. C) *Age at surgical menopause is negatively correlated to short-term verbal memory performance*. X-axis depicts the number of words recalled in the Serial Learning Test, measuring recency effects (PS2). Y-axis depicts age at surgical menopause. Adapted from *Nappi et al., 1999*. D) *Years since surgical menopause is negatively correlated to short-term verbal memory performance*. X-axis depicts the number of words recalled in the Serial Learning Test, measuring recency effects (PS2). Y-axis depicts years since surgical menopause. Adapted from *Nappi et al., 1999*.

4. Estrogen in Menopause and its Relation to Verbal Memory and Learning Deficits

4.1. Evidence for the Influence of Estrogen on Menopausal Memory Decline

Developing treatment strategies to address memory decline during the MT requires an understanding of its source. In general, one of the largest measurable changes during and after menopause are hormonal levels. This has led researchers to propose a causal role in the cognitive outcomes associated with menopause. Estrogen, in particular, has been the main attention of multiple studies as it has been shown to have memory-protective effects. Estrogens have many actions in the brain, including promotion of neuronal growth and synapse formation (McEwen, 2001; McEwen, 2002). Additionally, brain regions important for episodic memory, such as the hippocampus and prefrontal cortex, are dense in estrogen receptors, further solidifying estrogen's influence in verbal memory and learning (McEwen, 2001; McEwen, 2002). Thus, the changes in estrogen, and therefore protective action, in peri and post-menopause would explain the decline in verbal memory and learning that many women experience. This explains why these declines often resolve postmenopausally (Maki et al., 2021). Moreover, estrogen's beneficial action in the brain, may also explain why women are reported to have a higher risk of developing Alzheimer's disease, compared to men (Beam et al., 2018). Considering that verbal memory and learning are the most commonly impaired cognitive functions in menopause (Hogervorst et al., 2021; Maki and Jaff, 2022), and that these functions are largely diminished in AD (Atri, 2019), it is plausible that the estrogen changes in menopause may contribute to the higher rates of AD in women. Indeed, studies have demonstrated that both natural and induced menopause heighten the risk of developing cognitive impairment and dementias, among them AD (Ryan et al., 2014; Guo et al., 2025), further supporting this link.

Additional evidence for the role of estrogen in cognitive changes in menopause has been provided by Kilpi et al., 2020 where reproductive hormones were also examined. Here, the authors found that both FSH and LH were negatively correlated to immediate and delayed verbal episodic memory performance. While estrogen levels were not recorded in this research, it is known that the FSH and LH rises throughout and after the MT, likely due to decreases in estrogen, and therefore a loss of negative feedback (Hall, 2015). The association of these hormones with performance provides a compelling argument that the drop in estrogen may be responsible for these deficits (Kilpi et al., 2020). Furthermore, findings of a Swedish longitudinal study indicated that women with a normal weight (body mass index or BMI 18.5—25) declined more rapidly in verbal (episodic) memory performance, compared to overweight and obese individuals (BMI>25) (Thilers et al., 2010). Considering that, following menopause, estrogen production occurs mainly in the adipose tissue, women with higher BMIs present larger amounts of estradiol and estrogen (Cauley et al., 1989; Rannevik et al., 2008). As such, the authors suggested that higher estrogen levels in overweight women may have had a protective effect, resulting in a less pronounced cognitive decline.

As discussed in the previous chapter, surgically-induced menopause leads to an abrupt decline in estrogen (Hamoda & Sharma, 2023) and a more pronounced detrimental effect on verbal memory and learning, compared to the gradual decline observed in natural menopause (Sherwin, 1988; Zhou et al., 2011). Younger ages at menopause, and shorter reproductive periods worsened this effect (Nappi et al., 1999; Bove et al., 2014). Together, these findings provides clear evidence of the role of estrogen in menopausal changes to verbal memory and learning, suggesting that longer exposure is beneficial to these functions. Moreover, removal of the ovaries has been linked to cognitive impairment and dementia. According to Rocca et al. (2007), unilateral and bilateral oophorectomy were both associated with a higher chance of developing cognitive impairment or dementia, which increased with earlier age of induced menopause. Bove et al. (2014), showed that surgical menopause was associated with a faster cognitive decline and an increased presence of neuritic plaques, a marker of AD pathology. The findings of these studies seem to suggest that increased exposure to estrogen throughout life protects cognition and acts to prevents neurodegeneration.

Altogether, it is clear that estrogen plays a critical role in maintaining cognitive function, including verbal memory and learning, and that the decline of estrogen seen throughout menopause contributes to the impairments that many women experience.

4.2. Menopausal Hormone Therapy

Following the link between estrogen and menopause, there is a great interest in determining whether menopausal hormone therapy (MHT), in particular estrogen therapy (ET), could help in alleviate menopausal symptoms. Some research has demonstrated a positive effect of ET in women who underwent natural menopause. Shaywitz et al. (2003) evaluated the effect conjugated equine estrogens (CEE) on verbal memory and oral reading in midlife postmenopausal women (aged 32.8 to 64.9 years) and found that treatment improved performance in both measures. Similar results were found in a study by Joffe et al. (2006) examining ET in perimenopausal and early postmenopausal women (aged 40 to 60). Verbal memory and learning was assessed using the California Verbal Learning Test (CVLT) and the Wechsler Memory Scale-Revised (WMS-R) tests. Estradiol-treated participants demonstrated a greater improvement in verbal recall, with a 43% reduction in perseverative errors on the CVLT, compared to the placebo group, which exhibited a 9% decline in errors (Joffe et al., 2006).

Contrastingly, many studies have also observed neutral, or even harmful effects of ET. In a study analyzing 20-week estradiol treatment in women aged 70 or older, a variety of cognitive measures were obtained, including verbal memory. No differences were found between treatment groups in any of the measures, though a non-significant trend was observed where participants in the placebo group displayed a larger improvement in the CVLT total verbal memory score (Almeida et al., 2006), indicating a potential negative impact of ET. Similar results were obtained by Yaffe et al. (2006), who examined the effects of 2-year estradiol treatment in women who were at least 5 years into postmenopause (aged 60 to 80 years). Compared to the control group, treatment did not improve performance in any of the cognitive measurements, including verbal memory. Furthermore, the Women's Health Initiative Study of Cognitive Aging (WHISCA) study assessed both combined estrogen and

progesterone treatment (CEE/MPA) and estrogen treatment alone (CEE), in late postmenopausal women (aged 66-82). CEE/MPA decreased verbal memory performance, while CEE alone had no effect (Resnick et al., 2004). This research was ancillary to the WHIMS study, which found that CEE/MPA increased the risk of dementia, while CEE did not (Shumaker, 2004). This is similarity is clinically relevant as research shows that verbal memory and learning deficits are a good predictor of later incidence of dementia (Tierney et al., 2005; Blacker et al., 2007).

In light of these conflicting findings, the 'critical timing' hypothesis, also referred to as the 'critical window' or 'critical period' hypothesis, was proposed. According to this theory, the effect of estrogen treatment depends on when it is initiated. When hormone use is initiated near the age of the FMP (within 5 years) its effects may be beneficial to cognition. After this period, the effects of MHT are likely neutral or even detrimental to mental performance (Sherwin, 2009; Maki, 2013). This is schematically represented in Figure 3. Findings by Greendale et al. (2009) reflect this hypothesis. Here the effects of former and current hormone use on cognitive performance were also evaluated. The authors found that hormone supplementation prior to the FMP was correlated to enhanced baseline verbal memory, whereas current hormone use indicated worse EBMT performance compared to premenopausal women. Nevertheless, there is a large amount of mixed evidence regarding this hypothesis, including research indicating a harmful influence of hormone use (Maki, 2013). As such, many authors do not recommend MHT for treating cognitive complaints or preventing cognitive decline at any age in natural menopause (Hogervorst et al., 2021; Maki and Jaff, 2022).

In cases of surgically induced menopause, there is a stronger support for the beneficial effects of estrogen supplementation. In the 80's, it was demonstrated that women undergoing MHT (treatment consisted of estrogen, androgen or a combination of both), scored higher on verbal memory tests compared to the placebo group (Sherwin, 1988). Later on, Rocca et al. (2007) showed that ET prevented an increased risk of cognitive impairment or dementia in surgically-induced women when treatment lasted until at least age 50. In another study, hormone replacement therapy (HRT) was also correlated to a reduced decline in verbal (episodic) memory (Bove et al., 2014). A longer HRT duration was also found to be associated with a more gradual decline, suggesting that it attenuated some of the negative impact of early oophorectomy. Interestingly, Bove et al. (2014) discovered that this association disappeared when HRT was initiated beyond 5 years after surgical menopause, highlighting the time constraints of estrogen neuroprotection, as described in the critical timing hypothesis.

In summarize, MHT and ET research has provided even more convincing evidence for the role of estrogen depletion in menopause-related cognitive decline. While there are conflicting descriptions of the effects of MHT in naturally menopausal women are, there is a general consensus that a critical period may modulate the influence of ET. In the case of surgical menopause, estrogen supplementation up until the age of natural FMP is believed to be beneficial (Hogervorst et al., 2021; Maki and Jaff, 2022). The benefits and limitations of estrogen can be better understood by exploring its mechanistic action in the brain. This will provide an explanation for the existence of the critical period and assist in optimizing MHT.

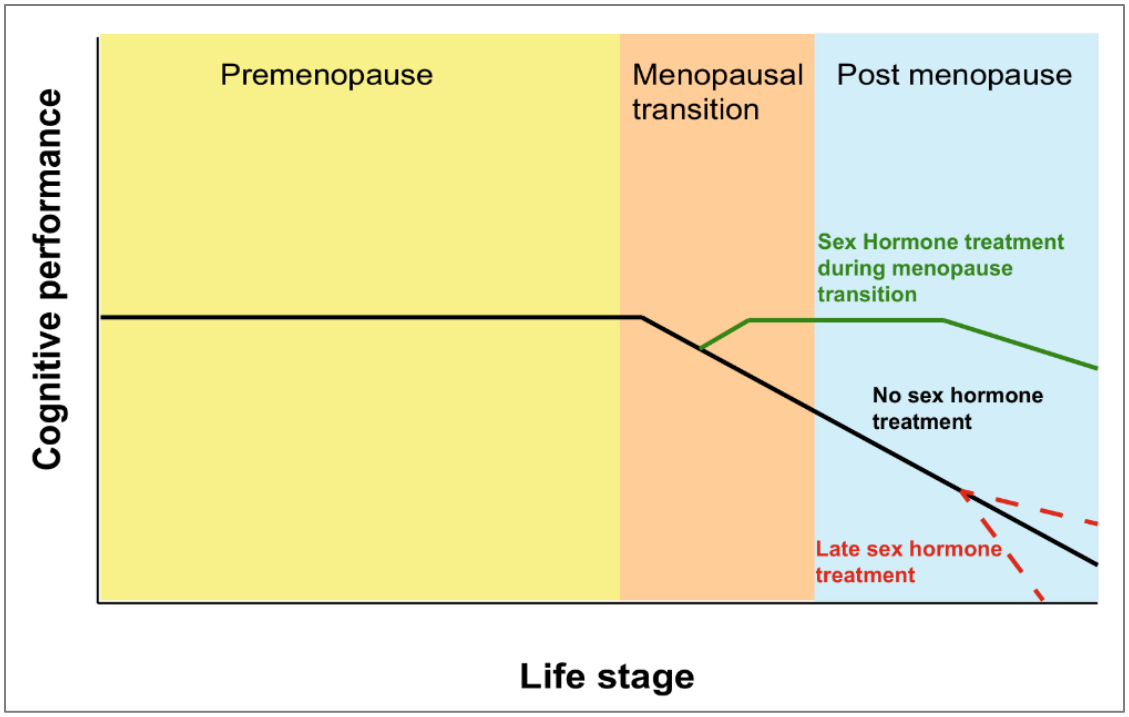

Figure 3. Effect of initiating menopausal hormone therapy (MHT) at different life stages on cognitive performance. In premenopause (yellow), cognitive performance, including verbal memory and learning, remains stable. Once the menopausal transition (MT) begins, performance begins to decline. If MHT is initiated at this stage (orange), then cognition (green line) recovers, only suffering late in postmenopause (blue). If there is no hormone treatment, performance keeps declining steadily. MHT initiated late in the postmenopausal stage likely negatively influences cognitive performance (red dashed line), including verbal memory and learning. Taken from *Russel et al., 2019*.

5. Estrogen's Action in the Brain

5.1. Estrogen Signaling and Hippocampal Synaptic Plasticity

Estrogen's ability to modulate synaptic plasticity in the hippocampus was first discovered in the 1990s (Gould et al., 1990; Woolley et al., 1990), and is thought to be one of the main mechanisms underlying its positive effects on memory and learning. Since then, research has focused on estrogen receptors (ER) as the key mediators of these effects. Classical estrogen receptors alpha (ERα) and beta (ERβ), which may be located in the nucleus or cell membranes, are particularly relevant as they are largely expressed in areas important for memory processes, such as the hippocampus and the prefrontal cortex (PFC) (Taxier et al., 2020). ERα, specifically, has been largely associated with modulating synaptic plasticity and cognitive function, with emphasis on its activity in the hippocampus. In mouse models, ERα activation via 17β-Estradiol treatment leads to increased dendritic spine density in the CA1 region of the hippocampus, which is accompanied by improved performance in learning tasks (Phan et al., 2011; Phan et al., 2012). Additionally, Wang et al. (2018) showed that female rodents have higher synaptic levels of membrane ERα in this region. Long-term potentiation (LTP), a form of synaptic plasticity crucial for learning, in the CA1 was also found to be dependent on these receptors, via activation of ERK1/2 and Src signaling kinases. In agreement with this, injections of a selective ERα antagonist in the dorsal hippocampus were found to induce memory loss in female mice, which was associated with an increased phosphorylation of ERK1/2 (Rinaudo et al., 2022).

ERβ and G-Protein-Coupled Estrogen Receptor (GPER1), another membrane estrogen receptor, have also been implicated in memory processes. While their mechanisms are not as well understood, these receptors have been linked to modulating hippocampal synaptic plasticity. In knockout models, ERβ knockout mice (ERβKO) experienced learning and memory impairments, as well as decreased hippocampal CA1 LTP (Rissman et al., 2002, Day et al., 2005). Further research by Liu et al. (2008) demonstrated that ERβ activation modulates hippocampal synaptic plasticity. In this study, use of a selective ERβ agonist resulted in increased levels of synaptic proteins, such as PSD-95, synaptophysin and the AMPA-receptor subunit GluR1, and CREB phosphorylation. Congruently, ERβ activation also increased dendritic branching as well as mushroom spine density, and heightened LTP in the CA1. The mice administered with the selective ERβ agonist also performed better on hippocampus-dependent memory tasks. Elevated LTP and synaptic proteins were not seen in ERβKO mice (Liu et al., 2008). Similarly, GPER1 specific agonist G1 was found to induce stimulate synaptic plasticity in the CA3 region of the hippocampus by promoting brain-derived neurotrophic factor (BDNF) release (Briz et al., 2015). Further GPER1 agonist and antagonist studies provided more evidence for the role of this receptor by demonstrating the presence of GPER1-specific pathways. Kumar et al. (2015) found that G1 increased CA3-CA1 synaptic transmission to a similar extent of an estrogen agonist, 17β-estradiol-3-benzoate (EB), in female ovariectomized mice. Furthermore, prior treatment with GPER1 antagonist G15 prevented the EB-induced synaptic enhancement, while G1 occluded it. In this study, selective agonists for ERα and ERβ were also tested. However, these only produced modest increases, suggesting a larger role for GPER1 in mediating estrogen's

effects on synaptic transmission and plasticity and, which were facilitated by ERK signaling (Kumar et al., 2015). Later, Clements et al. (2023) described a novel GPER1 pathway where G1 dose-dependently increased synaptic transmission in the CA1, via NMDA receptor activation and ERK signaling, independent of PI3K. In addition, the LTP induced by G1 required synaptic insertion of GluA2-lacking AMPA receptors, and was inhibited by G15 treatment.

In general, estrogen's memory-enhancing effects are thought to be mediated by both nuclear ERα/β, as well as through membrane receptor ERα/β and GPER1 activation. The nuclear receptors dimerize upon activation and bind directly to segments of DNA called estrogen responsive elements (ERE) to promote gene transcription. On the other hand, the membrane receptors initiate protein kinase signaling cascades, among them mitogen-activated protein kinase (MAPK) signaling, which in turn lead to the activation of transcription factors. Ultimately, both pathways culminate in the expression of genes that stimulate synaptic plasticity, such as BDNF and PSD95, depicted in Figure 4 (Braan et al., 2022; Sato et al., 2023). Together these studies provide compelling support for the role of estrogen receptor activation in enhancing memory and learning by promoting synaptic plasticity in hippocampal CA1 and CA3 regions.

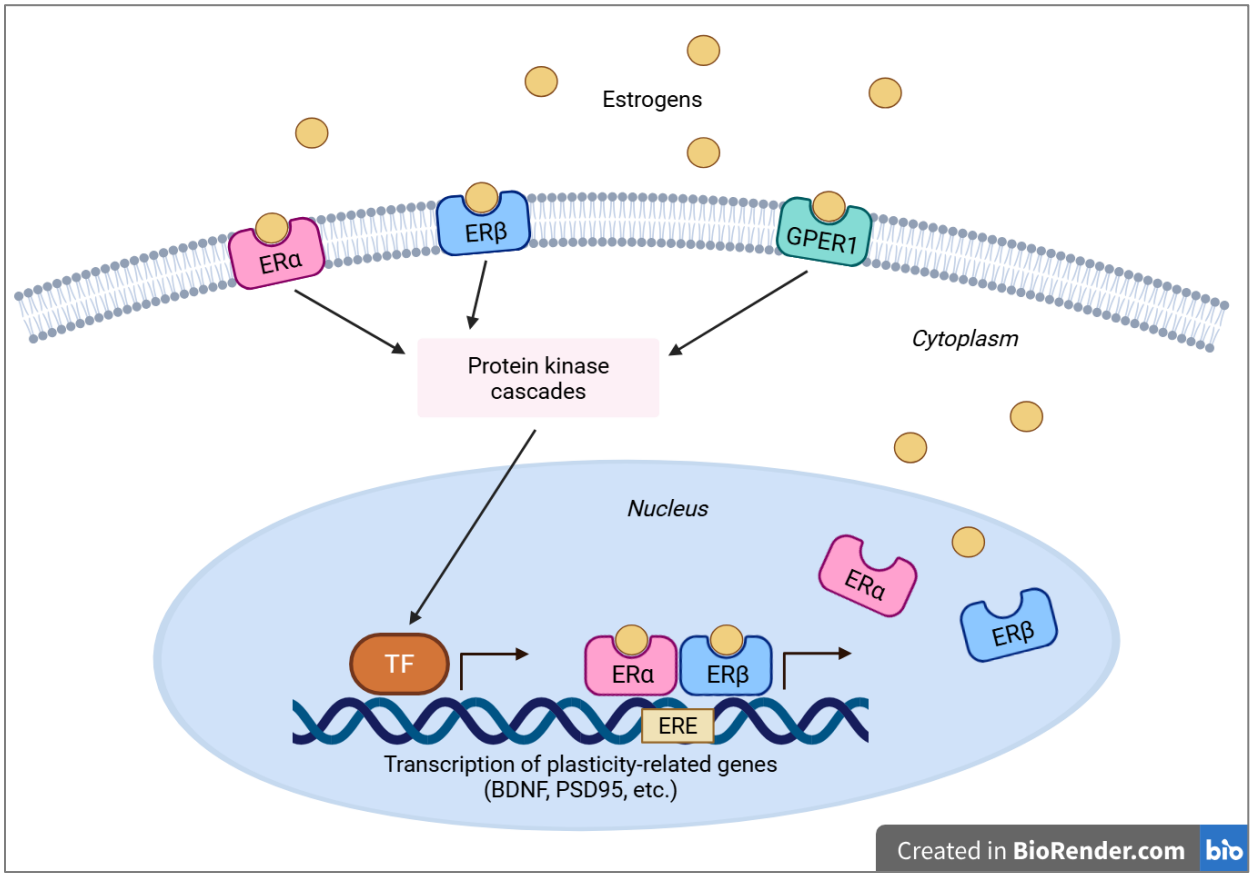

Figure 4. Estrogen signaling mediates increased synaptic plasticity. Estrogen binds to membrane estrogen receptors α (ERα) and β (ERβ) and G-protein coupled estrogen receptor 1 (GPER1) activating protein kinase cascades, which lead to transcription factor-induced of genes related to synaptic plasticity. Alternatively, estrogen binds to nuclear ERα/β, which then

dimerize and bind to estrogen response elements (ERE), leading to gene transcription. Adapted from *Braan et al, 2022*. Created in https://BioRender.com.

5.2. Neurobiological Changes in Menopause and Estrogen Therapy

In menopause, estrogen levels drop sharply and stabilize at low levels. Animal models have demonstrated that this hormonal decline affects memory and learning. In 1990, it was shown that removing circulating estrogen by removal of the ovaries led to a reduction in spine density in CA1 pyramidal cells of the hippocampus in female rats (see Figures 5A and 5B). This effect was not seen in the CA3 or the dentate gyrus (DG) and was blocked by estradiol treatment (Gould et al., 1990). In accordance, Wallace et al. (2006) found that this ovariectomy-induced decline in hippocampal CA1 dendritic spine density was associated with impaired performance on memory tests, as shown in Figures 5C and 5D. These effects are likely to be a result of a reduction in hippocampal CA1 estrogen receptors caused by estrogen deprivation following menopause (Daniel, 2013). Interestingly, while both ERα and ERβ have been shown to decrease in this region following ovariectomy (Adams et al., 2002; Mehra et al., 2005; Waters et al., 2011), only ERα becomes unresponsive to ET in aged rats (Adams et al., 2002; Waters et al., 2011). Later rodent studies have observed additional receptor-specific effects of estrogen loss, leading researchers to propose that hippocampal loss of ERα, specifically, may be a mechanism underlying not only menopausal memory deficits, but also the timing-dependent effects of ET outlined by the critical period hypothesis (Daniel, 2013).

Zhang et al. (2009) demonstrated that hormone deprivation following ovariectomy significantly decreased ERα in the CA1, without affecting ERβ. In the same year, Bohacek and Daniel (2009) demonstrated that initiating ET immediately after ovariectomy increased hippocampal ERα, but not ERβ, protein levels. Contrastingly, treatment initiated 5 months after removal of the ovaries produced no effect. Similarly, Rodgers et al. (2010) observed that 40-day estradiol treatment, initiated immediately after ovariectomy, caused a rise in hippocampal ERα and improved memory performance. While there were no effects on ERβ, ERα levels remained elevated 8 months post-treatment. More recently, Baumgartner et al. (2021) showed that short-term estradiol treatment increases levels of nuclear ERα in the hippocampus of ovariectomized rats, even after the end of treatment. In this study, ET also upregulated gene expression and protein levels of BDNF. Together, these studies provide compelling evidence that reduced hippocampal ERα levels are responsible for the diminished synaptic plasticity seen in menopause and may be reversed with estrogen supplementation within a critical period.

The mechanism by which ERα levels decrease in the hippocampus has been investigated by Zhang et al. (2011). Here, the researchers found that timely ET prevented the degradation of ERα in the CA1 stimulated by long-term ovarian hormone deprivation. According to this study, estrogen deprivation promotes an interaction of ERα with the E3 ubiquitin ligase C terminus of Hsc70-interacting protein (CHIP). This interaction results in proteasomal degradation of ERα, which is prevented by estradiol treatment when initiated close to ovariectomy, as the ERα-CHIP link is not enhanced in this condition. When treatment was initiated 10 weeks

after removal of the gonads, ERα levels could not be restored. The conclusion to be drawn hers is that if ET is not initiated within the critical window, the perhaps permanent loss of ERα in the CA1 is so profound that the positive effects mediated by this receptor will not be significant (Zhang et al., 2011; Daniel, 2013). Once ERα levels are upregulated, its effects are likely to be long-term, even beyond the critical window, as they can be activated by endogenously synthesized estrogens (Kretz et al., 2004) and through ligand-independent mechanisms (Hall et al., 2001).

In summary, decreasing CA1 hippocampal ERα levels provide a possible explanation for menopausal memory deficits, as well as the timing-dependent effects of ET (Daniel, 2013). According to this model, estrogen deficiency induced by menopause decreases ERα levels in the CA1 by promoting its degradation, which leads to diminished synaptic plasticity, ultimately contributing to the verbal memory and learning deficits seen in the MT. Should ET be initiated within the critical period, ERα levels and their beneficial effects are maintained and can later be activated even in the absence of gonadal estrogen. In the absence of (timely) ET, ERα will degenerate until a potentially irreversible point is reached where the brain is no longer sensitive to their action.

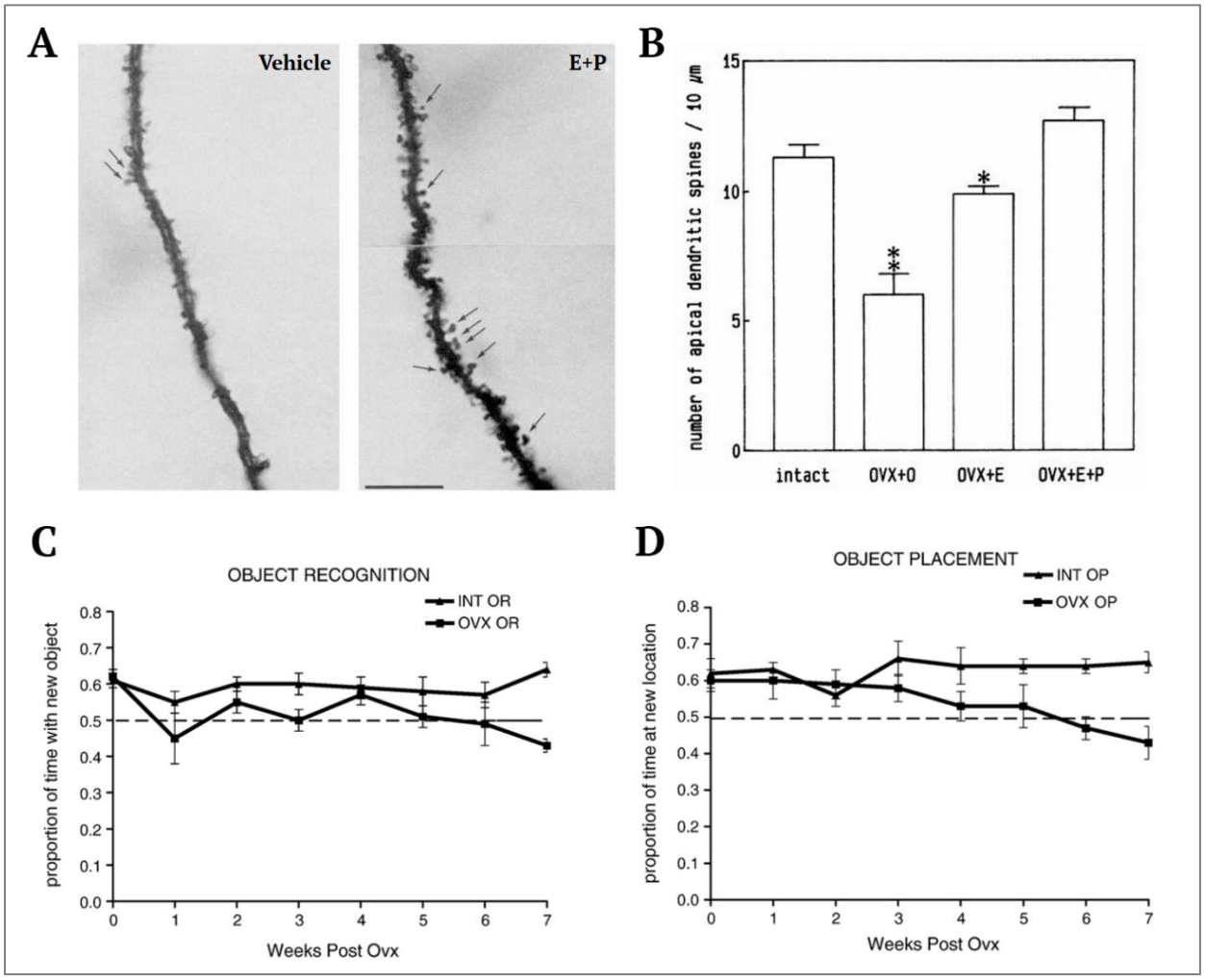

FIGURE 5: Ovariectomy causes decreased hippocampal CA1 dendritic spine density and memory performance, which can be prevented by estrogen treatment. A) *Effect of hormone treatment on spine density in ovariectomized rats*. Photomicrograph montage of apical dendrites from CA1 pyramidal cells of ovariectomized rats treated with vehicle or combined estradiol and progesterone (E+P). Scale bar, 10 pm. Rats treated with E+P have significantly more dendritic spines than in vehicle group, as seen by the number of pronounced heads (arrows). Adapted from *Gould et al., 1990*. B) *Effect of ovariectomy and hormone treatment on spine density*: Number of dendritic spines/ 10 pm dendrite obtained from the apical portion of the CA1 pyramidal cell dendritic tree. Ovariectomized rats (OVX) have significantly lower spine density compared to intact females (**). Dendritic spine density in ovariectomized individuals is also significantly different (*) between estradiol (OVX+E) treatment and combined estradiol and progesterone treatment (OVX+E+P). Intact and ovariectomized females on estradiol treatment (OVX+E) did not differ in spine density. Adapted from *Gould et al., 1990*. C) *Effect of ovariectomy object recognition in female rats*. Exploration ratio of ovariectomized (OVX OR) and intact (INT OR) is depicted. Week 0 represents performance before ovariectomy. Dashed line at 0.5 indicates equal time spent exploring new and old objects. Ovariectomy (OVX) was significantly associated with a decline in performance. Adapted from *Wallace et al, 2006*. D) *Effect of ovariectomy object placement in female rats*. Exploration ratio of ovariectomized (OVX OP) and intact (INT OP) is depicted. Week 0 represents performance before ovariectomy. Dashed line at 0.5 indicates equal time spent exploring objects at the new and old location. After week 2, ovariectomized rats could no longer discriminate between locations. Adapted from *Wallace et al, 2006*.

6. Discussion & Conclusion

6.1. Main Findings

Verbal memory and learning difficulties are significant cognitive symptoms of menopause, often leading to complaints among menopausal women (Sullivan Mitchell & Fugate Woods, 2001), and pose a need for treatment options. As such, the objective of this thesis was to explore the impact of estrogen on verbal memory and learning during menopause, with a focus on underlying neurobiological mechanisms that can be exploited to treat these deficits. This paper found that while many menopausal women maintain normal cognitive function, verbal memory impairments are common, stemming from deficits in learning ability beginning in perimenopause (Maki et al., 2021). These issues can persist post-menopause for some women, with surgical menopause causing a more rapid decline (Bove et al., 2014). Estrogen plays a vital role in maintaining cognitive function, including verbal memory and learning. Its depletion during menopause significantly contributes to cognitive decline, with mixed findings on the effects of menopausal hormone therapy and estrogen therapy. Regardless, there is a consensus that early estrogen supplementation can be beneficial (Hogervorst et al., 2021; Maki and Jaff, 2022). Animal research showed that estrogen likely enhances memory through nuclear and membrane estrogen receptors (ERα/β and GPER1). These receptors promote gene transcription and signaling pathways that support hippocampal synaptic plasticity (Braan et al., 2022; Sato et al., 2023). The estrogen deficiency-induced decline of nuclear ERα levels in the CA1 region of the hippocampus provides a plausible mechanistic basis for the verbal memory and learning deficits in menopause, depicted in Figure 6. ET within the critical period may help mitigate these effects, while delayed treatment leads to declines in receptor sensitivity (Daniel, 2013).

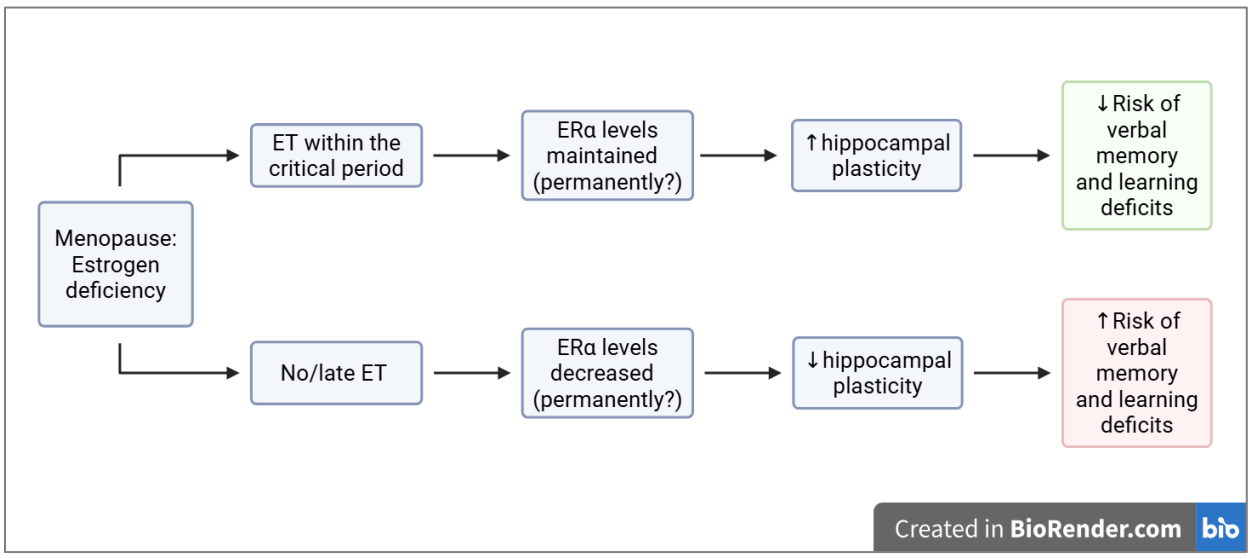

Figure 6. Estrogen therapy initiation modulates the risk of verbal memory and learning deficits through ERα levels and hippocampal synaptic plasticity. Estrogen administered within the critical period (top) maintains estrogen receptors

α (ERα) levels which maintain hippocampal synaptic plasticity, leading to a lowered risk of verbal memory and learning deficits. Alternatively, a lack of or late administration of estrogen treatment (bottom) leads to a decrease in ERα levels and hippocampal synaptic plasticity, which increases the risk of verbal memory and learning deficits. Adapted from *Daniel, 2013*. Created in https://BioRender.com.

6.2. General Neuroprotective Effects of Estrogen

Estrogen's role in enhancing hippocampal synaptic plasticity is vital for improving and sustaining memory performance during menopause. However, estrogen also displays general neuroprotective effects in the brain, that may beneficially influence verbal memory and learning. For example, estrogen has been shown to have anti-inflammatory effects, inhibiting pro-inflammatory cytokines and reducing microglial activation (Arevalo et al., 2014; Russell et al., 2019). This reduces cognition-harming neuroinflammation and helps maintain a healthy environment for neuronal function. Estrogens also enhance mitochondrial function and bioenergetics by promoting glucose metabolism, ATP production in neurons and mitochondrial biogenesis (Russell et al., 2019). These actions support cognitive processes by maintaining energy homeostasis in the brain. Furthermore, it has antioxidant properties, reducing the production of reactive oxygen species and enhancing the activity of various antioxidant enzymes. These properties protect neurons from oxidative damage, promote DNA repair and prevent impaired cognitive function (Behl et al., 1997; Lee & McEwen, 2001; Bustamante-Barrientos et al., 2021). Interestingly, increased oxidative stress and reduced mitochondrial activity are characteristics of many neurodegenerative diseases (Starkov, 2008). In addition to upregulating BDNF, estrogen also influences the expression of other neurotrophic factors such as insulin-like growth factor 1 (IGF-1) and nerve growth factor (NGF), which aid in neuronal growth and survival (Lee & McEwen, 2001; Arevalo et al., 2014; Bustamante-Barrientos et al., 2021). Lastly, estrogen increases cerebral blood flow by increasing vasodilation and promoting nitric oxide pathways, ensuring optimal oxygenation and nutrient delivery to memory-related brain regions, which is crucial for cognitive functioning (Maki & Resnick, 2000; Bustamante-Barrientos et al., 2021).

Many of these neuroprotective mechanisms are disrupted during menopause, which may contribute to the observed decline in verbal memory and learning (Bustamante-Barrientos et al., 2021). Future research should explore whether targeting these mechanisms could help alleviate the deficits in verbal memory and learning associated with menopause.

6.3. Additional Factors Influencing Cognition in Menopause

Declining estrogen levels significantly influence the verbal memory and learning deficits that occur during menopause. However, additional psychosocial and biological factors also shape cognitive trajectories during the MT, resulting in variation among menopausal women. Cognitive reserve is a particularly important factor that can affect cognitive outcomes. It refers to the brain's ability to compensate for and recover from age-related changes or damage caused by disease. This capacity can be enhanced through engaging in cognitively stimulating activities (Savarimuthu & Ponniah, 2024). Women who have higher education levels, intellectually stimulating jobs, and actively participate in cognitive or social activities often possess greater cognitive

reserves. As a result, they may be more resilient to hormonal and neurodegenerative effects, leading to milder memory and learning deficits during menopause (Duval et al., 2024).

Psychosocial factors, such as mental health, social support, and mood changes, are known to influence cognitive function and memory processes. Menopause, in particular, is often associated with increased vulnerability to anxiety and depression, which can result in impaired attention and memory (Santoro et al., 2020). Additionally, chronic stress may lead to hippocampal atrophy and memory dysfunction, largely due to elevated cortisol levels (Conrad et al., 2017). Sleep disturbances are also common symptom of menopause, often caused by hot flashes, night sweats, and insomnia (Takahashi & Johnson, 2015). These disturbances can also impact cognitive function. Generally, poor quality and insufficient sleep can impair memory consolidation, encoding, and long-term recall. Furthermore, disrupted sleep patterns can exacerbate mood disorders and fatigue, further deteriorating memory (Pearson et al., 2023).

Other individual differences, such as genetics, lifestyle, comorbidities, and socioeconomic status, can also influence verbal memory and learning. Women with genetic polymorphisms linked to estrogen receptor expression, synaptic plasticity, or neurodegenerative diseases, for example the APOE-ε4 allele, which is linked to an increased risk of Alzheimer's disease, may experience steeper declines (Riedel et al., 2016). Lifestyle factors, including diet and physical activity, have long been recognized for their impact on brain health and likely affect cognition in menopausal women (Grindler & Santoro, 2015; Yelland et al., 2023). Comorbidities, for example severe obesity, are often associated with decreased cognitive performance and can exacerbate memory deficits during menopause (Blümel et al., 2025). Common examples that affect midlife women include hypertension, obesity, diabetes, and metabolic syndrome (Harlow & Derby, 2015). Finally, women with lower socioeconomic status may face reduced access to healthcare and increased stress, which can negatively impact memory performance (Avila-Rieger et al., 2022).

Overall, considering these non-hormonal factors will offer a more comprehensive approach to addressing complaints related to verbal memory and learning during menopause. This understanding can help clinicians decide on the appropriateness of estrogen supplementation on an individual basis. Healthcare providers may recommend addressing these modifiable factors alongside or in lieu of hormone therapy, offering a more personalized approach to preserving memory performance in menopausal women.

6.4. Conclusion

In conclusion, this research validates the concerns of menopausal women by demonstrating that a significant portion experience a decline in verbal memory during both natural and surgical menopause. This decline likely stems from learning impairments that occur during the perimenopausal phase but may improve after menopause. Hormone therapy, particularly estrogen supplementation, can help address these complaints, maintaining premenopausal memory performance. However, the benefits of hormone therapy are only observed when treatment begins close to the onset of menopause, supporting the existence of a critical period for MHT.

Evidence from animal models suggests that memory decline induced by ovariectomy may be linked to a decrease in nuclear ERα levels in the hippocampal CA1 region due to estrogen deficiency. This reduces the activation of estrogen signaling pathways that are essential for promoting synaptic plasticity in this area. In rats, ET within the critical period has been shown to maintain CA1 ERα levels and hippocampal synaptic plasticity following removal of the ovaries. While this research offers a reasonable explanation for the memory deficits observed during menopause, as well as the timing-dependent effects of MHT, it is challenging to determine if these findings are applicable to humans. It is especially difficult to assess the causes of verbal memory and learning deficits, as these cannot be easily tested in rodents. A limitation of this thesis is that, in animal studies, alternative types of memory performance, such as spatial and working memory, are being evaluated as proxies for verbal memory in women. This complicates the process of translating findings from animals to humans. Nevertheless, the existence of a critical period for initiating ET in both ovariectomized rodents and menopausal women suggests a shared mechanism between the two species, likely involving hippocampal CA1 ERα levels, as discussed in this paper.

Additionally, other neuroprotective effects of estrogen, such as its anti-inflammatory and antioxidant properties, improved cerebral blood flow, and enhanced mitochondrial function, may also be disrupted during menopause, further impacting verbal memory and learning. Furthermore, various psychosocial and biological factors, including genetic polymorphisms, (mental) comorbidities, lifestyle differences, and cognitive reserve, can also influence verbal memory and learning. Therefore, this thesis recommends that future research should focus on therapies that target the neuroprotective actions of estrogen, alongside its effects on hippocampal synaptic plasticity. Many of the non-hormonal factors affecting verbal memory and learning are modifiable and should thus be incorporated into treatment strategies alongside ET. The key conclusion to be drawn from this paper is that menopausal complaints should be addressed through a holistic and customizable approach that reflects the natural variability present in the affected demographic.

7. Declaration of Artificial Intelligence use

In this thesis, Artificial Intelligence (AI) was used in compliance with the University of Groningen's guidelines on AI for students of the Biology cluster. These can be found by accessing https://brightspace.rug.nl/ (Student Portal > Study Info > Students > FSE Students > Biology > General Information > Guidelines on AI). A broader overview can also be found here: https://www.rug.nl/about-ug/organization/quality-assurance/education/artificial-intelligence-ai/?lang=en.

The following models were used:

Scite (https://scite.ai/): For brainstorming and constructing an outline.

ChatGPT-4 (https://chat.openai.com): For brainstorming.

Grammarly 2025 (https://www.grammarly.com/): For restructuring self-written text, correcting spelling and grammar mistakes.

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