



**THE MENOPAUSAL BRAIN:
EFFECTS OF ESTROGEN DEPLETION
ON COGNITION**

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Abstract

Menopause is a major reproductive-related event in a woman's life, occurring naturally at around the age of fifty years. Accompanying menopause is a drastic decrease in estrogen levels. Estrogen receptors are present throughout the human brain: e.g., in regions such as the hippocampus and prefrontal cortex, both involved in cognition. Given that about half of the world's population is female, it is important to examine if and how cognition is affected by the menopausal estrogen depletion, both at the level of public health, and at the individual level. Studies within the field show diverse results due to a wide range of methodology among studies. Behavioral studies foremost point towards a potential estrogenic effect on verbal short- and long-term memory. Structural and functional neuroimaging, together with animal studies, mainly show structural and functional alterations in the hippocampus and prefrontal cortex that may be related to changes in estrogen levels. Taken together, this thesis reviews estrogenic effects on different cognitive functions, as well as structural and functional changes in the brain in relation to the menopausal estrogen depletion.

Keywords: menopause, estrogen depletion, estradiol, hormonal therapy, cognition

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1. Introduction

Just as the first menstrual period is a major reproductive-related event in a woman's life, menopause is, too. While the former signals the starting point of fertility, the latter signals the end, when a woman no longer can reproduce. Menopause is the result of reproductive aging and can be defined retrospectively, as twelve months after a woman has had her final menstrual period (FMP: Soules et al., 2001). While the onset of menopause is highly individual, natural menopause in general occurs around the age of fifty years (Morabia & Costanza, 1998). Menopause can also be surgically induced if, due to medical reasons, women experience surgery where the ovaries are removed (i.e., oophorectomy: Woods & Mitchell, 2004).

Following menopause, a drastic permanent decline in ovarian steroid hormone secretion (e.g., estrogens and progesterone) will occur (Soules et al., 2001). Estrogens and progesterone are the main female sex hormones and together they have a major impact on the female reproductive system (Martini, Nath, & Bartholomew, 2018). Estrogen levels are low throughout childhood and rise when women reach puberty. During reproductive life, estrogen levels fluctuate in relation to phases of menstrual cycles, until they permanently decline after menopause (Catenaccio, Mu, & Lipton., 2016).

Estrogens are widely recognized for their involvement in female sex characteristics and reproductive capacity (Rettberg, Yao, & Brinton, 2014), such as maintaining function of reproductive glands and organs, initiating repair of the uterine wall (the endometrium) after menstrual bleeding, increasing sexual drive, and maintaining female secondary sex characteristics (e.g., body hair distribution and location of adipose tissue deposits: Martini et al., 2018). Other known estrogenic actions, not directly related to reproduction, include stimulating growth of muscles and bones (Martini et al., 2018), and promoting dilation of blood vessels, which may protect against cardiovascular disease (White & Porterfield, 2013).

Related to reproduction, estrogen receptors (ERs) can be found in organs and tissues such as the uterus, ovaries, breasts, hypothalamus, and pituitary gland. ERs are also found in other tissues and organ systems in the body that are not directly related to reproduction (Engler-Chiurazzi, Brown, Povroznik, & Simpkins, 2017). For example, ERs are distributed throughout the brain (Hara, Waters, McEwen, & Morrison, 2015). They are present in regions such as the hippocampus, cerebral cortex, midbrain, brain stem (McEwen, 2001), amygdala, cerebellum (McEwen & Alves, 1999), and frontal lobes (Sherwin, 2006). Estrogens are known to influence several aspects of brain structure and function (Sherwin, 2006). Structural

changes have, for example, been observed in the rat hippocampus (Woolley & McEwen, 1993) and monkey prefrontal cortex (PFC: Tang et al., 2004).

Both the hippocampus and frontal lobes are involved in human cognitive processes, leading to the question whether menopausal estrogen depletion affects cognitive functions in women. Cognition can be defined as the ability to take in, process, and make use of information. According to Sherwin (2003), cognition includes functions such as attention, memory, learning, language processing, and problem solving.

About half of the world's population is female. During the last centuries, female life expectancy has increased. The average age of menopause has not, meaning that many women now spend one-third of their lives in a state where their reproductive capacity has ceased and estrogen levels are low (Genazzani, Pluchino, Luisi, & Luisi, 2007). Given that women tend to outlive men, over half of the aging population will be women (Engler-Chiurazzi et al., 2017). At the time of life when women go through menopause, they are usually otherwise healthy, and the other organ systems in their bodies generally still work properly (Soules et al., 2001). It is a critical public health issue to understand the physiological impacts of female sex hormones (Engler-Chiurazzi et al., 2017). As of today, it is still not known exactly how cognition is affected by the permanently low estrogen levels that follow menopause. This topic is thus interesting and important both at the level of public health and at an individual level.

The main focus of this thesis will be menopause and associated hormonal changes. The main aim is to examine the effects of estrogen depletion on cognition. This will be addressed by examining both behavioral and neuroscientific aspects. First, there will be an overview of the key anatomical and neuroendocrine characteristics of the female reproductive cycle, including estrogen production and function. This will be followed by a description of the menopausal transition. Finally, the relationship between estrogen and cognition, together with effects of estrogen depletion on cognition during and after menopause, will be presented and discussed.

The role of other menopause-related hormones (e.g., progesterone) will not be examined in detail. Also, since menopause is the focus of the thesis, hormonal changes taking place in adolescence or during the menstrual cycle will not be discussed. Cognitive deficits associated with pathological conditions (e.g., Alzheimer's) that are also associated with aging will likewise not be included.

2. The neuroendocrine system

The nervous system and the endocrine system are the two main communication systems in the human body (Vander, Sherman, & Luciano, 2001). They share a common goal of maintaining homeostasis (balance) in the body through controlling and coordinating bodily processes (Martini et al., 2018).

The central nervous system (CNS: i.e., the brain and the spinal cord) mainly communicates through electrical impulses within neurons, and the release of chemical neurotransmitters from axons of presynaptic neurons to the dendrites of postsynaptic neurons. The release of neurotransmitters occurs in the synaptic cleft, where the axon of the presynaptic neuron and the dendrite of the postsynaptic neuron are close to each other. Neurotransmitters that are released but not picked up by the postsynaptic neuron will quickly be broken down and recycled. This type of communication therefore does not directly affect tissues far away from the synaptic cleft (Martini et al., 2018).

Like the CNS, the endocrine system communicates through the secretion of chemical messengers. The chemical messengers of the endocrine system are called hormones, and they are released into the bloodstream by endocrine cells in the body (Martini et al., 2018). Once hormones reach their target tissues, they bind to specific receptors (Gazzaniga, Heatherton, & Halpern, 2016). By using the bloodstream for transport, hormones can affect targets far away in the body (Martini et al., 2018). Communication within the endocrine system is usually slower than the rapid CNS communication (Gazzaniga et al., 2016).

The endocrine system and the CNS together form the neuroendocrine system (McCartney & Marshall, 2014), where neurons of the brain affect hormonal secretion of endocrine glands (Fink, 2012). Related to female reproduction, the most important organs of the neuroendocrine system are the hypothalamus, pituitary gland, and ovaries (Hall, 2014), together forming the hypothalamic-pituitary-ovarian axis (i.e., the female reproductive axis: White & Porterfield, 2013).

2.1. The female reproductive axis

Female reproductive function is regulated by the hypothalamus. The anterior lobe of the pituitary gland forms an extension from the inferior hypothalamus. Although the hypothalamus and anterior pituitary gland are closely situated, they do not have a neural connection (McCartney & Marshall, 2014). Instead, there is a network of blood vessels forming a direct connection between them: the hypophyseal portal system. This vascular system brings blood directly from the hypothalamus to the anterior pituitary gland without passing the heart, ensuring it will not mix with the general circulation (Martini et al., 2018).

The hypothalamic neurons secrete gonadotropin-releasing hormone (GnRH) that is picked up by the hypophyseal portal system and brought to the anterior pituitary gland. The endocrine cells in this region are surrounded by blood vessels, making it easy for GnRH to work on them (Martini et al., 2018).

GnRH is secreted in pulses. Pulse frequency and amplitude (amount secreted per pulse) varies across the female menstrual cycle. This variation is controlled by circulating estrogens and progesterone that affect neurons in the hypothalamus. While progesterone decreases GnRH pulse frequency, estrogens increase it. GnRH stimulates endocrine cells of the anterior pituitary gland to produce and release two types of gonadotropins: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The pulse frequency of GnRH decides which of the two peptide hormones are to be released. LH and FSH regulate activities of the gonads (ovaries in women) and are involved in stimulating the ovaries to secrete estrogens. The reproductive axis is dependent on feedback from the ovaries: for example, in the form of estrogen secretion (Martini et al., 2018).

2.1.1. Physiology of the female reproductive system. The most important organs of the female reproductive system are the vagina, uterus, two uterine tubes, and two ovaries (Martini et al., 2018). The uterus is a small, hollow muscular organ from which menstrual bleedings originate, and where the fetus is held during pregnancy. The uterine tubes lead from the uterus to the ovaries, being placed on each side of the uterus. The main functions of the ovaries are the production and maturation of immature egg cells (oocytes) and secretion of female sex hormones (e.g., estrogen: Vander et al., 2001).

Through regular cyclic changes in the reproductive system, the female body prepares itself for fertilization and pregnancy (Barrett, Barman, Boitano, & Brooks, 2010). These cyclic changes are controlled by hormones (e.g., estrogens) of the hypothalamic-pituitary-ovarian axis, and consist of two separate, but closely coordinated cycles, on average lasting twenty-eight days: the ovarian cycle and uterine cycle (Martini et al., 2018). Together, the ovarian and uterine cycles are sometimes referred to as the menstrual cycle.

A brief description of the physiology of the ovarian cycle will be provided due to its involvement in estrogen production, described in later section. The uterine cycle mainly consists of structural changes of the endometrium, resulting in menstrual bleeding (Martini et al., 2018).

2.1.1.1. The ovarian cycle. At birth, ovaries together contain about two to four million oocytes, placed within individual follicles. No further oocytes are produced after birth, and the existing ones will gradually be depleted throughout life, both through natural breakdown

and ovulation (egg release). When women reach puberty and begin to ovulate, the number of ovarian oocytes will already have decreased to about 400,000 (Vander et al., 2001).

The ovarian cycle consists of two phases separated by ovulation: the follicular (preovulatory) phase and the luteal (postovulatory) phase. Beginning with the follicular phase, hypothalamic GnRH stimulates the pituitary gland to secrete FSH. This stimulates follicles (and oocytes) to grow. At around day five of the cycle, one of the growing follicles becomes dominant (i.e., will later be released in ovulation) and the rest degenerate. Granulosa cells and thecal cells are now formed on the inside of the growing dominant follicle. Thecal cells produce androstenedione, which is absorbed by the granulosa cells and converted to estrogens. When estrogen levels rise, GnRH pulse frequency increases and LH is released. The oocyte within the dominant follicle will subsequently develop further. At around day fourteen, estrogen levels reach their highest point and GnRH pulse frequency further increases, resulting in an LH surge. The follicular wall erupts and the oocyte is released (ovulated) into the uterine tube. This marks the end of the follicular phase and the start of the luteal phase (Martini et al., 2018).

In the beginning of the luteal phase, the empty follicle degenerates. Stimulated by LH, an endocrine structure containing cholesterol will be created in its place: the corpus luteum. Synthesized within the corpus luteum, progesterone is the primary luteal phase hormone, while estrogens are present in small doses. If the ovulated oocyte does not get fertilized, the corpus luteum degenerates after about twelve days, marking the end of the luteal phase. Both estrogen and progesterone levels fall considerably, and a new cycle begins (Martini et al., 2018).

2.2. Estrogens

There are three types of naturally occurring estrogens in women: estrone, estradiol, and estriol (Barrett et al., 2010). Estradiol is the predominant and most potent estrogen type during the reproductive years, except for during pregnancy when estriol temporarily becomes the primary estrogen. In postmenopausal women, estrone is the predominant type (Paramanik, 2016).

Estrogens are synthesized from the steroid hormone androstenedione. Through the enzyme aromatase, estrone and estriol can be synthesized directly from androstenedione. In the biosynthesis of estradiol, androstenedione first needs to be converted to testosterone, which can be converted to estradiol (Martini et al., 2018). Estrogen can be synthesized in the liver, intestines, skin, muscle, breasts, and brain (Birzniece et al., 2006). The main production and secretion of estrogens occur in the ovaries (in the follicular granulosa cells and corpus

luteum) and the placenta (i.e., during pregnancy: Barrett et al., 2010). During the follicular phase of the ovarian cycle, granulosa- and thecal cells are formed in the dominant follicle. Thecal cells have several LH receptors, and LH stimulates the thecal cells to convert cholesterol to androstenedione. Androstenedione is then absorbed by granulosa cells (which have several FSH receptors). FSH enhances granulosa cell aromatase activity, which in turn is used to convert androstenedione to testosterone and later estradiol (Barrett et al., 2010).

There are two types of well-known estrogen receptors (ERs) in humans: ER-alpha ($ER\alpha$) and ER-beta ($ER\beta$: Engler-Chiurazzi et al., 2017). These receptors are usually found within the cell (i.e., intracellular receptors). When activated by estrogens, ERs translocate from the cytoplasm (intracellular fluid) of the cell into the cell nucleus (kernel) where they bind to deoxyribonucleic acid (DNA) and regulate gene expression and activity. Estrogen action is not limited to DNA binding (Paramanik, 2016). Both $ER\alpha$ s and $ER\beta$ s have been found on cell membranes (Almey, Milner, & Brake, 2015), together with another type of ER: G-protein coupled ER 1 (GPER1). Binding to these receptors occurs at the membrane of the cell instead of inside it (Engler-Chiurazzi et al., 2017). This causes an increase of calcium ions (Ca^{2+}) in the cell, activating the production of further messengers (Almey et al., 2015).

Estrogens act in both genomic (involving nuclear activation and changes in expression of genes) and non-genomic ways (do not require changes in gene transcription: Wise, Dubal, Wilson, Rau, & Liu, 2001). Genomic effects are usually slower in onset (minutes to hours) and longer in duration (the effect persists after the steroid disappears from the tissue). Non-genomic effects are usually rapid in onset (seconds to minutes) and shorter in duration (the effect does not persist after the steroid disappears: McEwen, Coirini, & Schumacher, 1990).

2.2.1. Estrogen actions in the brain. Within the brain, estradiol is mainly synthesized in neurons, either from testosterone or cholesterol. Estradiol can be synthesized in astrocytes (type of neuroglia: i.e., nonneural cells within the brain), too (Li, Cui, & Shen, 2014). Besides estrogen production in the brain, peripheral estrogen (produced in the ovaries) also affects the brain, being able to cross the blood-brain barrier (BBB: Catenaccio et al., 2016). The BBB forms a protecting barrier between the CNS and the blood. Bacteria and other unwanted molecules from peripheral tissues are prevented from entering the neural tissue in the brain, while certain small molecules can diffuse through the barrier (Gazzaniga, Ivry, & Mangun, 2014).

ERs are not only widely distributed throughout different brain regions: they are also present in almost all cell types in the CNS. There are ERs within blood vessels, in neurons, and in neuroglial cells such as oligodendrocytes (which create myelin around axons),

astrocytes (which form the BBB), and microglia (which remove damaged cells: Engler-Chiurazzi et al., 2017). ERs are located in different neural locations such as synaptic terminals, dendrites, dendritic spines (i.e., small bulges localized along the dendrites, forming sites of synaptic contact), and axons (Hara et al., 2015).

Evidence indicates that estrogens not only promote growth of new and existing neurons (Lee & McEwen, 2001) but also prevent cell death within the CNS. Estrogen may inhibit generation (i.e., production) and prevent action of neurotoxic (harmful) agents in the brain (McEwen, 2001). Estrogen alters neuronal structure and enhances functional plasticity of neural synapses (Wise et al., 2001), which can be seen in changes in dendritic structure and synapses in the rat hippocampus (Woolley & McEwen, 1993) and monkey PFC (Tang et al., 2004). Neural plasticity refers to structural changes in the brain in response to either intrinsic (hormonal) or extrinsic (experience or sensory stimulation) factors. Plasticity is thought to be the underlying basis for learning and memory function (Brinton, 2009), and may include changes in synaptic interactions, such as strengthening of synapses (Gazzaniga et al., 2014). Long-term strengthening of synapses is called long-term potentiation (LTP), which occurs from repeated interaction between a presynaptic neuron and a postsynaptic neuron. Resulting from LTP, the postsynaptic neuron will more likely respond to a future stimulus (Gazzaniga et al., 2014). Brinton (2009) argues that since plasticity and synaptic connectivity may underlie learning and memory, neuroplastic changes caused by estrogen should be seen in performance, too.

Estrogen action is complex. There is some evidence that women show fluctuations in cognitive performance related to changes in endogenous (i.e., synthesized in the body) estrogen levels during the menstrual cycle (Engler-Chiurazzi et al., 2017). This indicates that menopausal estrogen depletion also may affect cognition.

3. The physiology of menopause

During the Stages of Reproductive Aging Workshop (STRAW: Harlow et al., 2012), it was agreed upon that the adult female life can be divided into three broad phases: reproductive phase, menopausal transition, and postmenopausal phase. During the reproductive phase, women usually have regular menstrual cycles. By the end of the reproductive phase, some women notice subtle changes in their menstrual cycles: a sign of the upcoming menopausal transition. The menopausal transition involves physiological changes in the body and lasts until the FMP, when women enter the postmenopausal stage (Harlow et al., 2012).

3.1. The menopausal transition

Due to ovulation and oocyte depletion throughout life, a relatively small number of follicles remain in the ovaries (Harlow et al., 2012). Less ovarian feedback (e.g., estrogens) will thus be sent to the hypothalamus and pituitary gland. The early follicular phase FSH levels will increase more than usual, leading to enhanced follicular recruitment and accelerated follicular depletion (Hall, 2007). Menstrual cycle length tends to shorten by seven days or more during this early menopausal transition (Harlow et al., 2012).

During the late transition, length of menstrual cycles varies, and women typically go through periods of no menstrual bleedings for sixty days or more (Harlow et al., 2012). Estrogen levels can both increase and fluctuate greatly, leaving out the LH surge, leading to an increased failure to ovulate. When ovulation ceases, there is a radical decrease in ovarian estradiol and progesterone production and secretion (Hall, 2007). The few follicles that might remain in the ovaries are thought to be less sensitive to FSH and LH. When FSH and LH cannot stimulate follicles to grow, estrogen and progesterone levels drop, and the woman can no longer reproduce (White & Porterfield, 2013).

Levels of estradiol continue to fall until about two years after the FMP, when they finally stabilize (Harlow et al., 2012). The main production of estrogens no longer occurs in the ovaries but instead in peripheral adipose (fat) tissue, where androgens are converted to estrogens. Estrone is the estrogen type most frequently produced in adipose tissue and therefore becomes the main circulating estrogen type (White & Porterfield, 2013).

According to White and Porterfield (2013), women can suffer from several symptoms around menopause, many associated with low estrogen levels. Common examples are vaginal dryness, accelerated bone loss, cardiovascular disease, vasomotor symptoms (hot flashes and night sweats), fatigue, and depression. To alleviate menopausal symptoms, hormonal therapy (HT) is commonly prescribed during or after the menopausal transition (Gleason et al., 2015). HT usually involves either unopposed estrogen (estrogen alone) or opposed estrogen (estrogen + progestins: i.e., the synthetic form of progesterone). Because progesterone is important for protecting the endometrium, women who have not undergone hysterectomy (i.e., removal of the uterus) usually receive opposed HT (Navarro-Pardo, Holland, & Cano, 2018). The most common estrogen types in HT are estradiol (E^2 : the most prevalent estrogen type in the CNS prior to menopause) or conjugated equine estrogens (CEE) where the main form is estrone (Dunkin et al., 2005).

It is now known that menopause brings changes in peripheral tissues of the body and that estrogen is involved in maintaining and altering neural structures of the hippocampus and

PFC. These systems and the cognitive and behavioral processes reliant on them may also be affected by the estrogen depletion following menopause. According to Mitchell and Woods (2001), about sixty percent of women state that they experience problems with memory during the menopausal transition. In the next section, menopausal estrogen depletion will be examined in relation to structural and functional changes in the brain, together with associated changes in cognition.

4. Estrogen and cognition

Cognition refers to higher-order neural processing, usually followed by a behavioral outcome, in response to stimuli (Engler-Chiurazzi et al., 2017). Studies on estrogen depletion, or HT, in relation to different cognitive functions will now be presented. Many of the published articles lack definitions of terms and therefore a glossary is provided in Appendix A. Because several studies focus on learning and memory, they will briefly be defined here.

Learning can be defined as the acquisition of new information, whereas memory can be defined as the ability to use the acquired information over time. Gazzaniga et al. (2014) state that learning is the process in which we obtain new information about the world or ourselves. When we learn something new, memories are created. Usually, memories are sorted into categories based on how long they persist. Sensory memory is information (of most we are not aware of) obtained from our senses and lasts for milliseconds to seconds (Gazzaniga et al., 2014). Short-term memory and working memory last for seconds to minutes and have limited capacities of around seven items (Miller, 1956). The primary difference between the two is that working memory extends short-term memory. Information in working memory can be acted upon, manipulated, and processed; that in short-term memory is simply maintained, through repetition. Long-term memory lasts for days to years and can be divided into declarative and nondeclarative. The former includes episodic memory (subjective experiences and contextual knowledge) and semantic memory (facts about the world and language knowledge). For the most part, we have conscious access to declarative memories and can tell others about them. Nondeclarative memories cannot be verbally reported: e.g., motor skills (Gazzaniga et al., 2014).

Memories can further be sorted based on if they are verbal or non-verbal in origin. Short-term verbal memory consists of a verbal stimulus that is held in memory for a couple of seconds, whereas long-term verbal memory is the ability to recognize the same word or phrase for an extended period. The same principle can be applied to non-verbal memory such

as visual memory and spatial memory (the ability to remember where in space something is located: Sherwin, 2003).

Memory processing occurs in stages of encoding, storage, and retrieval. When information is acquired, it is encoded into neural representations and later consolidated (i.e., stabilized over time) in long-term memory. When we want to access the stored information, we retrieve the memory (Gazzaniga et al., 2014). Memory is thus a system that both stores and retrieves information obtained through our senses (Sherwin, 2003).

Due to limited space of the thesis, only some studies will be described in detail. When appropriate, brief explanations of specific cognitive tests will be provided, while others are described in Appendix A. For clarity, some studies use the terms pre- and perimenopausal. According to Soules et al. (2001), premenopausal refers to the reproductive phase, while perimenopause refers to a timeframe beginning with the menopausal transition and ending one year after the FMP.

Because of the nature of studies in this area (e.g., multiple cognitive functions assessed within single studies), it is difficult to sort studies based on cognitive abilities. Instead, following the precedent set by Navarro-Pardo et al. (2018), studies will be sorted according to study design. When possible, similar studies will come together. First, longitudinal observational studies will be presented, followed by cross-sectional observational studies, intervention studies, and neuroimaging studies.

4.1. Longitudinal observational studies

In longitudinal (cohort) studies, the same group of participants is followed over an extended time. Cognition, together with estrogen levels or menopausal stage is assessed on several occasions to examine how menopausal stage and estrogen levels relate to cognition.

Fuh, Wang, Lee, Lu, and Juang (2006) studied cognitive functions during the menopausal transition in 495 women. All participants were premenopausal at the start of the study, and no one used HT. Participants completed the same cognitive tasks twice, eighteen months apart. Cognition was assessed in terms of long-term verbal memory (recall fifteen words after fifteen minutes' delay), visual recognition memory (view seventy figures and later answer whether figures have been shown before), verbal fluency, attention, and cognitive flexibility. By the time of the second assessment, 114 participants had gone from premenopausal to perimenopausal. After controlling for age differences, education, and baseline performance, the only significant difference in performance between groups was that the premenopausal group performed better on verbal fluency. Fuh et al. argue that the menopausal transition might not affect any other cognitive functions than verbal fluency, but

also mention the short timeframe of the study as a limitation. Potential negative effects of estrogen depletion on cognition might not be visible during this stage of the menopausal transition. According to Harlow et al. (2012), estrogen levels continue to fall during the first two years after the FMP.

In a five-year study by Meyer et al. (2003), changes in verbal working memory during the menopausal transition were examined in 803 women. Participants were either pre- or perimenopausal at baseline, with a varying grade of change in menopausal status throughout the study. Through annual assessments, Meyer et al. (2003) concluded that a natural menopausal transition is not related to changes in verbal working memory as measured by Digit Span Backward (DSB).

In a study extending over fifteen years, Epperson, Sammel, and Freeman (2013) examined changes in verbal short- and long-term memory during the menopausal transition in 403 women. All participants were premenopausal at baseline, and almost everyone was postmenopausal by the end of the study. Through annual blood samples (to measure estradiol levels) and cognitive assessments, Epperson et al. found that immediate and delayed (twenty minutes) recall on a verbal memory test (in which participants read a list of sixteen words, and later were asked to recall the words) declined significantly from the premenopausal to the postmenopausal stage. A decline in delayed recall was evident already during the early menopausal transition, whereas immediate recall did not decline until the postmenopausal stage. Estradiol levels were not significantly related to task performance.

4.2. Cross-sectional observational studies

In cross-sectional observational studies, women are placed into groups either based on current menopausal stage or whether they use HT. Participants are assessed on cognitive functions once and the results compared to the results of women of different menopausal stages.

In a study by Luetters et al. (2007), 1657 women were categorized as premenopausal, early perimenopausal, late perimenopausal, or postmenopausal. After adjusting for age, race, and education, no significant relation between menopausal stage and cognitive test performance on either immediate or delayed (ten minutes) verbal episodic memory (assessed through a paragraph recall task) or verbal working memory (DSB) was found. Estradiol levels were not related to cognitive performance. In line with Luetters et al., Henderson, Guthrie, Dudley, Burger, and Dennerstein (2003) failed to find a significant relation between estrogen levels or menopausal status and either immediate or delayed (five minutes) recall for episodic verbal memory (measured by a word recall task).

Verghese et al. (2000) assessed cognitive abilities in women with a history of hysterectomy with bilateral oophorectomy (H-BSO: i.e., surgically induced menopause) that was ($n=10$) or was not ($n=25$), treated with unopposed CEE. The authors found HT to be related to better verbal short- and long-term memory (free recall of words) but not attention.

Duff and Hampson (2000) compared cognitive abilities between HT and non-HT users. Ninety-six postmenopausal women in the ages 45-65 years participated. Length of treatment, dosages, and type of estrogen varied in the HT group. Compared to non-HT users, HT was associated with better performance on verbal working memory tasks such as DSB and Digit Ordering (i.e., say the numbers between one and ten in random order without repeating or missing digits), and a Spatial Working Memory task. No significant results were found for forward Digit Span, used as a control task measuring verbal short-term memory. According to Duff and Hampson (2000), the forward Digit Span task does not require manipulative functions mediated by the PFC the same way working memory tasks do.

Maki, Zonderman, and Resnick (2001) studied postmenopausal women in the ages 50-89 years, comparing cognitive functions of women currently ($n=103$) on HT (length of treatment, type, and dosage varied) and women who never had used HT ($n=81$). No significant differences were found between HT users and non-users for verbal working memory and attention (as measured by Digit Span), mental rotation ability, or short-term nonverbal memory (participants are shown a line drawing and later asked to draw it from memory). HT was significantly associated with better short- and long-term verbal memory. HT users were significantly younger than non-users, but the results were still significant after adjusting for age (Maki et al., 2001).

Grigorova and Sherwin (2006) failed to find any significant differences in cognitive abilities such as verbal working memory, attention, and cognitive flexibility in thirty-seven postmenopausal women (mean age = 65 years) that either were or were not using HT. Users took either opposed or unopposed estrogen. Type and dosage were not reported.

4.3. Intervention studies

Intervention studies examine whether cognition is affected by either HT (in peri- or postmenopausal women), or induced estrogen depletion (in premenopausal women). Most of these studies are randomized controlled trials. First, HT studies are presented, followed by estrogen depletion studies and animal studies.

4.3.1. Hormonal therapy. Several ancillary studies are based on the Women's Health Initiative Hormone Therapy (WHIHT) study. Postmenopausal women ($N=27500$) in the ages 50-79 years enrolled the study, of which the aim was to examine if HT could prevent coronary

heart disease in postmenopausal women. Participants were randomized to receive either opposed CEE, unopposed CEE (if no uterus), or placebo (The Women's Health Initiative Study Group, 1998). The opposed HT-trial was cancelled after 5.2 years due to increased risk for heart disease, stroke, and breast cancer compared with placebo (Writing Group for the Women's Health Initiative Investigators, 2002). The unopposed HT-trial was cancelled after 6.8 years due to increased risk for stroke (The Women's Health Initiative Steering Committee, 2004).

In the ancillary Women's Health Initiative Memory Study (WHIMS), 4500 postmenopausal women (mean age = 69 years) from the WHIHT study participated (Shumaker et al., 1998). By the time of the WHIHT cancellation, both opposed and unopposed HT was found to be significantly associated with an increased risk for cognitive decline, compared to placebo (Espeland et al., 2004; Rapp et al., 2003). A magnetic resonance imaging (MRI) study was conducted on 1403 participants from WHIMS. On average, MRI was conducted three and 1.4 years after the opposed and unopposed HT trials ended, respectively. Both opposed and unopposed HT were associated with lower hippocampal and frontal lobe volumes, compared to placebo. Baseline MRI was not included in the study (Resnick et al., 2009).

Yet another ancillary study included 2304 women in the ages 66-84 years. Cognitive functions such as verbal short- and long-term memory, non-verbal short-term memory, verbal fluency, verbal working memory, attention, and mental rotation were examined in relation to HT (Resnick et al., 2004). By the time of the WHIHT cancellation, HT was found to have a negative impact on verbal memory and a slight positive impact on non-verbal short-term memory, compared to placebo. Other cognitive domains were not affected (Resnick et al., 2006).

The results from the WHIHT and ancillary studies have been widely discussed. It has been argued that the detrimental impacts of HT seen in these studies may be due to initiation of HT several years beyond FMP (Navarro-Pardo et al., 2018). According to Navarro-Pardo et al. (2018), neurons might become less sensitive to estrogens with increasing age. They further argue that late initiation of HT may not reverse neural loss and dysfunction that could have occurred between the FMP and HT initiation.

To examine if HT had adverse effects in younger women, too, another ancillary study was conducted, including 1326 women aged between 50-55 years at HT initiation. About seven years after the WHIHT cancellation, cognition was assessed over the phone. Compared to placebo, HT was neither associated with risks nor benefits for cognitive functions (short-

and long-term verbal memory, attention, cognitive flexibility, verbal fluency, and verbal working memory: Espeland et al., 2013).

In a study by Gleason et al. (2015), 693 postmenopausal women with the mean age of fifty-three years enrolled. On average, participants had had their FMPs 1.4 years prior to the start of the study. Women were randomized into four years of treatment with either cyclical opposed oral CEE, cyclical opposed transdermal E², or placebo. Cognitive functions such as verbal short- and long-term memory, attention, verbal working memory, cognitive flexibility, and verbal fluency were assessed at baseline and yearly. In line with the study by Espeland et al. (2013), no HT-related effects on cognition were found.

In a ten-week randomized study, seventeen postmenopausal women received transdermal E² or placebo. Cognitive assessments were made at baseline and at the end of the treatment period. Compared to placebo, estrogen did not have a significant effect on executive functions, attention, verbal short- and long-term memory, or short- and long-term non-verbal memory (Dunkin et al., 2005).

Shaywitz et al. (2003) did a cross-over study on sixty postmenopausal women aged 32-65 years, with a mean of 3.2 years since the FMP. In cross-over studies, participants receive one type of treatment during a set period of time, and later they are crossed over to another type of treatment. Each participant serves as their own control. In this study, participants were randomized to either twenty-one days of unopposed oral CEE or placebo. They then underwent a washout period of fourteen days where no treatment was given. A washout period is used to ensure that any hormones associated with previous treatment will disappear from the body. After the washout period, participants received the other treatment-type for twenty-one days. After each treatment period, cognitive abilities such as verbal fluency, verbal short- and long-term memory, and mental rotation were assessed, of which verbal memory performance was significantly better during HT compared to placebo.

Sherwin (1988) did a cross-over study involving forty women who recently underwent an H-BSO, after which estrogen levels rapidly decline. Participants were randomized to receive either E² + testosterone, E² alone, testosterone alone, or placebo through monthly intramuscular injections for three months. For a subsequent washout month, all participants received placebo, and were then again randomized into another treatment condition for three months. HT was significantly associated with better verbal short-term memory (Digit Span forward) and verbal long-term memory (paragraph recall task) compared to placebo, regardless of HT formulation. Blood samples confirmed that estrogen levels were lower during placebo than HT. During the washout month, estrogen levels, together with test

performance, declined for all participants. Sherwin (1988) attributes the testosterone-related cognitive benefits to the involvement of testosterone in estradiol synthesis, where testosterone is converted to estradiol.

In another study, Phillips and Sherwin (1992) enrolled women who recently had undergone an H-BSO. Nineteen women with the mean age of forty-eight years were randomized to receive either monthly injections of E² for three months or placebo. Baseline and follow-up assessments were made. Short- and long-term verbal memory for paired associates stayed the same over time for the HT group and decreased for the placebo group. Immediate paragraph recall (short-term verbal memory) scores increased over time with HT and stayed the same for placebo. No significant results were found for Digit Span, delayed paragraph recall (long-term verbal memory), or short- or long-term visual memory (participants are shown a design and later asked to draw it from memory). Phillips and Sherwin argue that estrogen may affect verbal but not non-verbal memory.

4.3.2. Estrogen depletion. Estrogen depletion can be induced using a GnRH agonist (GnRHa). During the first week of GnRHa administration, ovarian steroid hormone secretion usually increases due to increased gonadotropin release. After a longer GnRHa administration, GnRH receptors in the anterior pituitary gland downregulate. Secretion of gonadotropins is inhibited, resulting in postmenopausal estrogen levels by the second to fourth week of GnRHa administration (Berman et al., 1997). GnRHa is commonly used for medical purposes (see e.g. Sherwin & Tulandi, 1996). Because it mimics menopausal estrogen depletion, it is sometimes used to model menopause in studies.

Sherwin and Tulandi (1996) studied nineteen premenopausal women with a mean age of thirty-four years who needed to receive a GnRHa due to medical reasons. After receiving the GnRHa for twelve weeks, participants were randomized to receive either GnRHa + CEE or GnRHa + placebo for eight weeks. Blood samples and cognitive assessments were done at baseline, after twelve weeks of GnRHa, and after eight weeks of add-back condition. Estrogen and progesterone levels decline after the use of a GnRHa, and during the add-back condition, HT (or placebo) is given to enhance levels of the given hormone. Estrogen levels, together with immediate and delayed paragraph recall, significantly decreased after twelve weeks of GnRHa. After the eight-week add-back condition, performance for immediate and delayed paragraph recall and paired associate immediate recall (verbal short-term memory) significantly increased for the group receiving HT compared to placebo. No significant results were found for delayed paired associate recall, short- or long-term non-verbal memory, or Digit Span (Sherwin & Tulandi, 1996).

In a study by Schmidt et al. (2013), a GnRHa was used to depress estrogen and progesterone levels in twenty-three healthy young women. All participants underwent three conditions: GnRHa for twelve weeks, GnRHa + transdermal E² for five weeks, and GnRHa + progestins for five weeks. The order of the two add-back conditions was randomized, separated by one to two weeks of washout. No significant differences were found between baseline and GnRHa treatment for verbal short- and long-term memory, verbal fluency, or attention. Mental rotation performance was significantly better in the GnRHa + E² condition compared to the GnRHa condition. Blood samples were not drawn. It is therefore possible that the GnRHa failed to suppress estrogen levels.

4.3.2.1. Animal studies. A common way of modelling human menopause is to perform ovariectomy (OVX: i.e., surgical removal of the ovaries) on female rats (Zárate, Stevnsner, & Gredilla, 2017). Like humans, rats have reproductive cycles that become irregular during middle age and later cease. Unlike postmenopausal women, female rats enter a state of chronically high estradiol levels (Morrison, Brinton, Schmidt, & Gore, 2006). By performing an OVX on the rat, estradiol levels fall considerably, mimicking the human postmenopausal stage (Engler-Chiurazzi et al., 2017).

Experiments on OVX rats have shown that, as estradiol levels decline after surgery, hippocampal dendritic spine density also declines. When injecting E², the effects are reversed and dendritic spine density increases, together with formation of new synapses (Woolley & McEwen, 1993). In line with Woolley and McEwen, Sandstrom and Williams (2001) found E² injections in OVX rats to be related to improvement in memory retention on a water maze task compared to placebo. Since the experimental procedure by Woolley and McEwen was followed in detail, Sandstrom and Williams attribute their findings to increased dendritic spine density and synapse formation. Sandstrom and Williams emphasize that this only is an indication of a possible relationship between memory and changes in hippocampal dendritic spine density.

There is evidence for estrogen-related enhancement of dendritic spine density in the dorsolateral PFC (DLPFC) of OVX monkeys (Tang et al., 2004). In a study on OVX monkeys, E² (compared to placebo) enhanced performance on a delayed response test of spatial working memory. This test is commonly used in monkeys and requires activation of the DLPFC (Rapp et al., 2003).

4.4. Imaging studies

The MRI study by Goto et al. (2011) is one of only a few human studies examining structural changes in the hippocampus, related to menopausal status. Examining 171 women, the

authors found significant bilateral reduction in hippocampal gray-matter volume in postmenopausal, compared to premenopausal women. Comparing women in their fifties (fifty-one of fifty-nine women were postmenopausal) with women in their forties (three of forty-six women were postmenopausal), they found a significant bilateral hippocampal gray-matter volume reduction in the former group. In contrast, comparing hippocampal volumes between men in their forties and fifties, they found no significant differences. Neither were significant differences in hippocampal volume observed between women in their fifties and sixties, or between women in their sixties and seventies. Goto et al. conclude that menopause is associated with structural hippocampal changes. These results contradict those of a similar study by Sullivan, Marsh, and Pfefferbaum (2005), failing to find significant hippocampal volume differences between pre- ($n=17$) and postmenopausal women ($n=27$). Among the postmenopausal women, eleven used HT. Hippocampal volume did not differ between HT users and non-users.

Eberling et al. (2003) used MRI to examine hippocampal volume in postmenopausal women who either were ($n=13$) or were not ($n=46$) on HT. HT users (of whom most took unopposed CEE) showed significantly larger right anterior hippocampal volumes compared to non-users. Lord, Buss, Lupien, and Pruessner (2008) also examined hippocampal volume in relation to HT. Forty-one postmenopausal women participated, of whom sixteen were current HT users, ten past users, and fifteen HT-naïve (i.e., never used HT). Unopposed CEE was the most common treatment among users. Current users showed significantly larger right hippocampal volumes compared to past users and HT-naïve participants. As the past HT users were significantly older than the current users and HT-naïve participants, age was controlled for during analyses. Among current HT users, a negative correlation between hippocampal volume and duration of HT was found. Longer duration was associated with smaller hippocampal volume, suggesting that long-term HT use might be harmful. Some participants had over twenty years of HT use. Lord et al. argue that HT use creates constant estrogen levels, which are not seen during reproductive life, because estrogen levels fluctuate with menstrual cycles.

In a recent MRI study, Albert et al. (2017) examined how different dosages of unopposed oral E^2 affect hippocampal volume in postmenopausal women in the ages 51-75 years. Participants were randomized to receive either 1 mg E^2 , 2 mg E^2 , or placebo daily for three months. MRI was conducted at baseline and after the treatment period. A dosage of 2 mg was significantly associated with greater bilateral posterior hippocampal gray-matter volume, compared to 1 mg and placebo.

Erickson et al. (2005) did a cross-sectional MRI study involving forty-three postmenopausal women above the age of fifty-five who were either HT-naïve or current or past users of HT. Among past and current users, unopposed CEE was most common, and the average length of HT was around twelve years. While no differences in gray-matter volume were found between past and current HT users, HT (including past and current users) was associated with greater gray-matter volumes in frontal (superior, middle, and inferior frontal gyri) and temporal (anterior hippocampal) brain regions. Erickson et al. conclude that estrogens may have a protecting role on brain tissue, especially in age-sensitive areas.

In a cross-sectional functional MRI (fMRI) study by Berent-Spillson et al. (2010), HT-naïve women and long-term (10+ years) users who initiated HT (CEE) within two years of the FMP were assessed during a non-verbal working memory task. No difference in performance was found between groups, but HT users showed greater task-related activation in brain regions such as the frontal cortex (bilateral superior frontal gyri), parietal cortex, insula, hippocampus, and cingulate. A positive correlation was found between task performance and brain activity and the authors concluded that early initiated long-term postmenopausal HT might benefit non-verbal working memory.

Another cross-sectional fMRI study was conducted by Maki et al. (2011). Thirty-four women with a mean age of sixty years participated, of which some were HT users, and some had never been on HT. Users had initiated HT during perimenopause. During the recognition phase of a verbal long-term memory test (after twenty minutes' delay, participants were asked to indicate whether they had seen a word during the encoding phase), HT users showed higher activation in the left hippocampus and lower bilateral parahippocampal gyri activation than HT-naïve participants. This was significantly associated with better test performance. The authors argue that early initiation of HT is beneficial.

In a more recent cross-sectional fMRI study, Jacobs et al. (2016) examined menopausal status in relation to cognition and brain activity. One hundred women aged 45-55 years were categorized as premenopausal, perimenopausal, or postmenopausal. While in the scanner, participants performed a verbal memory encoding task (two words are shown at the same time, and the participant must quietly form a sentence including both words). During retrieval, participants were asked if they remembered seeing particular words during the encoding phase. No difference in verbal memory performance was found, but postmenopausal women showed decreased activity in the left hippocampus during encoding compared to pre- and perimenopausal women. This was independent of age. Lower endogenous estradiol levels

were related to decreased left hippocampal activity. Higher estradiol levels and greater encoding-related brain activity were related to better memory retrieval.

Smith et al. (2006) and Persad et al. (2009) used similar study designs. Both were randomized cross-over fMRI studies examining the effect of HT on neural circuitry in a spatial (i.e., non-verbal) working memory task and a verbal memory task, respectively. In both studies, ten postmenopausal women with a mean of 6.9 years since FMP were randomized to receive either opposed oral E² or placebo for four weeks. A washout month followed, after which participants crossed over to the other treatment for four weeks. fMRI was conducted at the end of each treatment phase during a non-verbal working memory task and a verbal memory task, respectively. Smith et al. did not find a treatment-related effect on non-verbal working memory performance, but HT was associated with enhanced bilateral PFC activation during the task. Smith et al. discuss whether increased activation indicates increased effort needed in HT users to maintain task performance. However, increased task-related brain activity has been seen in younger people, too, during this type of task. Younger people usually show more right hemispheric activation, while bilateral activation usually is seen in older people. In Smith's study, participants in general showed bilateral activation. Persad et al. used a Levels of Processing (LOP) paradigm to measure episodic verbal memory processes. Beginning with an encoding phase, participants were asked to decide whether letters were upper- or lowercase (shallow processing) and whether words were abstract or concrete (deep processing). After twenty minutes' delay, participants were asked if they had seen specific words during encoding. There were no differences in performance between treatments, but HT was significantly associated with increased activation in left and medial areas of the PFC, dorsal anterior cingulate, posterior cingulate, and left parietal cortex during deep processing encoding. Brain activation for the recognition phase was never analyzed due to relatively low recognition rate.

Davison et al. (2013) included thirteen postmenopausal women (1-5 years since FMP) in the age range 45-55 in their study. Participants were randomized to receive either opposed oral E² or placebo for twenty-six weeks and underwent fMRI scanning at baseline and after the treatment phase while doing a mental rotation task and a verbal fluency task. No treatment-related differences in task performance or brain activity were found. The verbal fluency task used was weak in that participants received a letter and were then supposed to quietly come up with words beginning with that letter. They were told to not repeat the same word more than once, and every time they came up with a word they were to press a button. Usually during this kind of task, participants are told to say the words out loud. In this study,

it is not possible to know if participants pressed the button even if they did not come up with words or if they sometimes accidentally repeated the same words.

In a cross-over fMRI study, Shaywitz et al. (1999) examined the role of estrogen on verbal and non-verbal working memory tasks. Thirty-six postmenopausal women in the ages 33-61 (mean months since FMP = 34,3) were randomized to receive either unopposed oral CEE or placebo for twenty-one days. Participants then underwent a washout period of fourteen days, followed by a cross-over to the other condition for twenty-one days. fMRI was conducted at the end of each treatment phase during working memory tasks. During the verbal working memory task, five pronounceable nonsense words were shown sequentially for four seconds each, followed by an empty screen for twenty seconds. Participants were then asked to indicate which two out of four nonsense words had been shown. Compared to placebo, HT was associated with increased activity in inferior parietal lobule and superior frontal gyri. During the non-verbal task, HT was associated with increased activity in the right superior frontal gyrus compared to placebo. No difference in performance between HT and placebo was observed. The authors argue that the alterations in brain activation seen in this study in relation to HT may demonstrate estrogen effects that are not yet possible to detect by behavioral measures.

Joffe et al. (2006) included eleven peri- and postmenopausal women in the ages 40-60 in their study. Participants randomly received either unopposed transdermal E² or placebo for twelve weeks. At baseline and after the treatment period they underwent an fMRI scan while performing a verbal memory task and a spatial working memory task. During recall (recognition of words read outside the scanner) on the verbal memory task, HT was associated with increased activation in inferior and medial frontal regions. For the spatial working memory task, HT was associated with greater bilateral frontal and posterior cingulate/parietal region activation. No difference in performance was observed.

In an fMRI study by Dumas, Kutz, Naylor, Johnson, and Newhouse (2010), twenty postmenopausal women with mean age of sixty (mean years since FMP = 11) participated. They were randomly assigned to receive either unopposed oral E² or placebo for three months. Participants underwent fMRI scanning at baseline and at the end of the treatment period while performing a N-back sequential letter task (to measure verbal working memory). This task requires participants to actively manipulate and update information in working memory. In the more difficult conditions, there is higher working memory load. During the more difficult conditions, HT was significantly associated with increased activity in the left frontal regions (including superior and middle frontal gyri), right middle frontal gyrus, and

precuneus compared to placebo. Performance was not affected by treatment. A negative correlation between performance and activity in the right precuneus was found, where increased activity was related to worse performance. The authors argue that this may mean that women treated with HT had to try harder to perform well on the task.

In a pilot cross-over fMRI study involving sixteen postmenopausal women in the ages 45-55, Berent-Spillson et al. (2015) found a ninety-day treatment with unopposed oral E² to be significantly associated with increased activation in the left PFC during deep encoding in a verbal LOP task, compared to placebo. Since the left PFC is involved in verbal processing, the authors argue that increased activation might indicate more effective encoding. Women in the HT group tended to remember more words from the verbal task compared to placebo, but the difference in number of words recalled was not statistically significant. For a visual working memory task, no differences were found between HT and placebo, either in brain activity or task performance.

In a cross-over fMRI study, Girard et al. (2017) examined the relationship between HT and brain activity during a task-switch paradigm that requires the use of executive functions. Twelve postmenopausal women in the ages 48-55 were randomly assigned to receive either sequential (mimics hormonal fluctuations during the menstrual cycle) opposed E² or placebo for two months. Participants then crossed over to the other treatment for two months. fMRI was conducted at the end of each treatment period. No cognitive benefits were found for HT over placebo, but HT users showed increased task-related activity in the right DLPFC, ventrolateral PFC, and anterior cingulate cortex (ACC). During HT, activity in the DLPFC was related to higher task-switching performance. The authors suggest that the neurofunctional differences between HT and placebo, despite lack of behavioral differences, may reflect hormonal effects not yet detectable through behavioral measures.

Berman et al. (1997) performed a positron emission tomography (PET) study on eleven women with mean age of thirty-five. To depress steroid hormonal levels, participants received a GnRHa. All participants underwent three conditions: GnRHa (about eight weeks), GnRHa + unopposed transdermal E² (about four weeks), and GnRHa + progestins (about four weeks). In between both add-back conditions, there was a washout week where only GnRHa was administered. Participants underwent PET scanning three times each (at the end of treatment periods), performing the Wisconsin Card Sort Task (WCST). In the GnRHa condition, little or no activation of the DLPFC was shown during the WCST, even though this brain region usually is highly active during the task. Despite lack of DLPFC activation, participants performed well. In hormonal add-back conditions, DLPFC was active.

Craig et al. (2007) did an observational fMRI study involving fifteen premenopausal women in the ages 26-47 receiving a GnRHa for eight weeks due to subsequent surgery. Fifteen women on a waiting list were used as controls. Blood samples and fMRI were conducted at baseline (during the late follicular phase: i.e., high estradiol levels) and after the treatment period. While in the fMRI scanner, participants performed a verbal episodic memory task involving encoding and retrieval (word recognition). During encoding, participants that had received GnRHa showed less activation in the left inferior frontal gyrus, ACC, and bilateral medial frontal gyrus by the time of the second assessment, compared to baseline. These changes were not evident in the control group. No retrieval-related differences in brain activity were found, but the GnRHa group performed significantly worse on word recognition during the second assessment, compared to baseline. During a follow-up study, women were assessed post-surgery (did not receive GnRHa any more). Estrogen levels, encoding-related brain activity, and performance on word recognition were back to baseline levels, suggesting that the changes caused by estrogen depletion were reversible (Craig et al., 2008).

5. Discussion

The focus of this thesis has been menopausal-related hormonal changes, specifically estrogen depletion. The main aim was to examine the effects of estrogen depletion on cognition, mainly by addressing behavioral and neuroscientific aspects.

Animal studies provide a unique opportunity to study estrogen action on the cellular level, which due to the invasive nature is not possible in humans. Studies on OVX rats (Woolley & McEwen, 1993) and monkeys (Tang et al., 2004) have provided evidence for a relationship between estrogen depletion and decreased dendritic spine density in the hippocampus and DLPFC. E² treatment increases dendritic spine density and synapse number, mediating changes in plasticity. Since plasticity may be the underlying basis for cognitive functions such as learning and memory (see Page 9), this neurophysiological evidence from animal studies indicates that estrogen depletion should affect cognition. Estrogen-related structural changes have been connected to changes in cognition in rats (Sandstrom & Williams, 2001) and monkeys (Rapp et al., 2003) by using hippocampal- and DLPFC-dependent tasks, respectively. However, animal studies always raise a problem whether findings can be transferred to humans.

Only two studies have examined human hippocampal volume in relation to menopausal status. Sullivan et al. (2005) had a relatively small sample size and did not find

any significant results. Goto et al. (2011) found a bilateral reduction in hippocampal gray-matter volume in postmenopausal compared to premenopausal women. Given that aging affects the brain, it is important to separate structural changes due to normal aging from those that may follow estrogen depletion. According to Conrad and Bimonte-Nelson (2010), age-related cognitive decline can involve structural changes in the brain: e.g., alterations in dendritic structure. Reduction in gray-matter volume does not necessarily involve a decrease in neural number but may result from changes in dendritic structure, suggesting that the findings of Goto et al. may result from normal aging. After all, postmenopausal women are generally older. A strength of the study by Goto et al. is the inclusion of men in the study. While women in their fifties (majority postmenopausal) showed reduced hippocampal gray matter compared to women in their forties (majority premenopausal), the same pattern was not observed in men. It can be speculated whether men and women age differently, but the study design partly helps rule out aging as the sole explanation of hippocampal gray-matter loss in postmenopausal women. Animal studies further back up the results because both in the animal studies and in the study by Goto et al., structural changes in the hippocampus were observed following estrogen depletion.

It can be speculated upon whether there are other potential causes that may underlie the structural hippocampal changes observed after menopause: e.g., stress. Stress-related structural changes of hippocampal dendrites have previously been observed in animal studies (see e.g. Watanabe, Gould, & McEwen, 1992). It is reasonable to assume that animals find it stressful to undergo an OVX, after which decreased dendritic spine density has been observed. Women may similarly find it stressful to undergo an H-BSO, not only because the thought of having a surgery can be scary, but also because the surgery will put an end to the chance of future pregnancies. A natural menopause likewise marks the end of fertility, which some women may find difficult to accept. In addition, bodily changes occur around the time of menopause (see Page 10). Even if these bodily changes are not visible to others, women undergoing them are probably highly aware of them. In today's society, looks are important, and youth is desired and rewarded. Menopause is a sign of aging, which is another reason why women might find it stressful to go through menopause. Goto et al., did not include assessments of stress levels in the study. This is something that would be interesting to see in future studies.

While HT studies do not examine estrogen depletion *per se*, they can still provide insight into the relationship between estrogen and brain structure and, by extension, cognition. Compared to non-users, HT users have significantly larger right hippocampal (Eberling et al.,

2003), right anterior hippocampal (Lord et al., 2008), bilateral anterior hippocampal (Erickson et al., 2005), or bilateral posterior hippocampal volume (Albert et al., 2017). HT has been related to greater gray-matter volume in frontal (including PFC) and temporal regions outside the hippocampus (Erickson et al., 2005). In some studies, HT negatively affected brain structure: e.g., Resnick et al. (2009) found a relationship between HT and decreased hippocampal and frontal lobe volumes. As this was an ancillary study to the WHIHT, the results may be due to a late (relative to FMP) initiation of HT, which may be harmful (see Page 15). This MRI study was conducted several years after participants quit using HT. Lord et al. (2008) found HT duration to be related to decreased hippocampal volume, but some participants in the study had used HT for more than twenty years, which can be considered a long time. Out of all these studies, only the ones by Albert et al. (2017) and Resnick et al. (2009) were controlled trials, while the rest were cross-sectional. To sum up, late initiation and long duration of HT may have negative impact on hippocampal structure. Besides that, MRI studies generally found evidence for a positive HT-related effect on brain structure, mainly evident in the hippocampus, but also in frontal regions, in line with animal studies. According to Sherwin (2006), the hippocampus and frontal regions are involved in verbal memory and working memory. Cognitive functions reliant on them should also be affected by estrogen.

Among behavioral studies, the most commonly observed estrogenic effect on cognition is the relation to verbal memory. Several studies found estrogen to enhance short- and long-term verbal memory (e.g., Epperson et al., 2013; Maki et al., 2001; Phillips & Sherwin, 1992; Shaywitz et al., 2003; Sherwin, 1988; Sherwin & Tulandi, 1996; Verghese et al., 2000). Others found no effect on short-term verbal memory (Duff & Hampson, 2000), long-term verbal memory (Fuh et al., 2006), or both (Espeland et al., 2013; Henderson et al., 2003; Luetters et al., 2007). One study even found estrogen to have a negative impact on verbal short- and long-term memory (Resnick et al., 2006). Only in one of these studies, the relationship between cognition and menopausal phases was assessed (Epperson et al., 2013). The rest examined the relationship between HT and cognition. Epperson et al. found a decline of verbal memory associated with the postmenopausal stage. These findings do not mean *per se* that estrogen depletion is related to impairments in verbal memory. As a matter of fact, estrogen levels were not significantly associated with verbal memory performance, implying that something else may underlie the postmenopausal memory impairment. Since age was adjusted for in the analysis, memory impairment was likely due to something else. For example, sleep deprivation has been found to negatively affect cognitive functions such as

verbal memory (see e.g. Drummond et al., 2000). Women commonly experience night sweats during or after menopause (see Page 10). This could possibly lead to disrupted and impaired sleep, and in the long run: sleep deprivation. In Epperson's study, sleep quality was not controlled for. It is therefore possible that impairments in verbal memory occurred because of such coexisting effects caused by estrogen depletion.

Studies that found HT-related effects on verbal memory differed in study design. The samples of some studies consisted of women about to undergo an H-BSO (Phillips & Sherwin, 1992; Sherwin, 1988) or had a history of one (Verghese et al., 2000). An H-BSO will disrupt the system in a sudden way, compared to the gradual changes occurring during natural menopausal transition. According to Engler-Chiurazzi et al. (2017), the nature of menopause (natural or surgical) might affect cognitive outcomes. There is some evidence that oophorectomy at an earlier age than natural menopause is related to increased risk for cognitive impairment (Rocca et al., 2007). In the H-BSO studies, HT was found to positively affect cognition. If cognition is more negatively affected by surgically induced menopause than natural menopause, positive HT-related effects on cognition observed in the H-BSO studies may, in part, result from this. It is possible that HT has a greater effect on cognition following a greater cognitive decline. This would in turn cause greater cognitive differences between women who use HT and women who do not use HT or receive placebo, compared to what is seen after a natural menopause. Due to the removal of the uterus during H-BSO, women subsequently receive unopposed HT (estrogen only). This may affect cognition differently than opposed HT (estrogen plus progestins). For example, animal studies have shown that when animals initially received treatment with estrogen, positive cognitive effects were observed. When adding progestins to the treatment, the positive effects were reversed (see e.g. Bimonte-Nelson, Francis, Umphlet, & Granholm, 2006). In that way, unopposed HT would possibly be more favorable for cognition.

Not all studies found a relationship between estrogen and verbal memory. While Fuh et al. (2006) did not find estrogen to affect verbal memory, they failed to include postmenopausal women (i.e., estrogen depletion had most likely not yet occurred). Since Espeland et al. (2013) instead assessed cognition about seven years after participants stopped using HT, potential benefits of HT likely were gone by the time of assessment. The study was ancillary to the criticized WHIHT, just like the one that found estrogen to have a negative impact on verbal memory (Resnick et al., 2006).

In an fMRI study, Craig et al. (2007) examined verbal memory after GnRH α administration (estrogen depletion) and found decreased activation in the left inferior frontal

gyrus, anterior cingulate, and bilateral medial frontal gyri during encoding compared to baseline. Even though no changes in brain activity were found during the recognition task, performance significantly declined post-GnRHa. When participants no longer received the GnRHa, estrogen levels, encoding-related brain activity, and task performance were back to baseline levels (Craig et al., 2008). This provides evidence for a negative impact of estrogen depletion on neural activity and cognition. Jacobs et al. (2016) found decreased encoding-related activity in the left hippocampus in postmenopausal women (who also had lower estrogen levels), compared to pre- and perimenopausal women. Performance on the recognition task was not affected. Other studies have found HT, compared to placebo, to be related to greater activation in the left PFC (Berent-Spillson et al., 2015; Persad et al., 2009), medial PFC, dorsal anterior cingulate, posterior cingulate, and left parietal cortex (Persad et al., 2009) during encoding. Performance on recognition tasks was not affected.

During retrieval (i.e., recognition), HT-related effects have been observed as increased activity in inferior and medial frontal regions (Joffe et al., 2006) without subsequent effect on performance. Maki et al. (2011) did not examine activation patterns in the frontal lobes but found a HT-related effect during retrieval as increased left hippocampal activity and decreased bilateral parahippocampal gyri activity, both associated with better performance.

Altogether, fMRI studies show estrogen-related alterations in hippocampal and frontal lobe (especially PFC) activity during encoding and retrieval on verbal memory tasks. Three studies found increased/decreased brain activity to be related to better/worse performance respectively. Other studies found changes in brain activity without subsequent effects on performance. According to Jacobs et al. (2016), compared to younger adults, older adults typically show alterations in PFC and hippocampal activity during verbal encoding. Results from the fMRI studies presented above can be interpreted as age-related. However, participants in the study by Craig et al. (2007) were relatively young (26-47 years), and Jacobs et al. included age as a covariate in all analyses. Craig et al. (2008) found brain activity, together with task performance, to return to baseline levels after participants no longer received a GnRHa. Studies by Persad et al. (2009) and Berent-Spillson et al. (2015) were cross-over studies, making women their own controls. Thus, age less likely caused the observed changes in functional brain activity.

In most behavioral studies, no performance-related estrogen effect on verbal working memory was found (e.g., Espeland et al., 2013; Grigorova & Sherwin, 2006; Maki et al., 2001; Meyer et al., 2003), a pattern also observed in neuroimaging studies. Changes in task-related brain activity were commonly found. During verbal working memory tasks, HT-

related increase in brain activity has been observed bilaterally in inferior parietal lobules and superior frontal gyri (Shaywitz et al., 1999), left side frontal regions (including superior, and middle frontal gyri), right middle frontal gyrus, and precuneus (Dumas et al., 2010). Dumas et al. simultaneously found a negative correlation between performance and activity in the right precuneus. Taken together, performance on verbal working memory tasks was generally not affected by HT, while HT seems to impact functional brain activity, most frequently observed in the left superior frontal gyrus.

A similar pattern was found for non-verbal working memory. While task performance was not affected by HT, alterations in brain activity were observed. Greater activity was observed in regions such as the bilateral PFC (Smith et al., 2006), right superior frontal gyrus (Shaywitz et al., 1999), bilateral frontal cortex, bilateral posterior cortex (Berent-Spillson et al., 2010; Joffe et al., 2006), insula, hippocampus, and cingulate (Berent-Spillson et al., 2010). In contrast to HT-related functional alterations in the left superior frontal gyrus during verbal working memory tasks, HT-related functional alterations during non-verbal working memory tasks were most frequently observed in the right superior frontal gyrus.

From a behavioral view, estrogen does not seem to affect executive functioning. No relationship was found between estrogen and cognitive flexibility performance (Espeland et al., 2013; Fuh et al., 2006; Grigорова & Sherwin, 2006), which can be accounted for as an executive function. Estrogen-related changes in brain activity have been observed, for example during the WCST. The WCST normally activates the DLPFC, but Berman et al. (1997) found no task-related activation of the DLPFC following a GnRHa (estrogen depletion). Subsequent HT treatment lead to normal task-related brain activity. HT has been found to be related to increased activity in the right DLPFC, bilateral ventrolateral PFC, and ACC during a task-switching paradigm (Girard et al., 2017). Estrogen thus seems to impact DLPFC (especially right DLPFC) activity during tasks requiring the use of executive functions.

Functional neuroimaging studies show varying results. While estrogen commonly was found to alter functional brain activity, only a subset of studies found performance-related effects. Changes in brain activity without notable changes in cognition can be interpreted in several ways. Greater brain activity can be interpreted either as beneficial (more effective encoding in memory-related tasks: Berent-Spillson et al., 2015) or compensatory (more effort is required to maintain the same level of task performance: Smith et al., 2006). Others have argued that these findings may depend on subtle estrogen-related changes in cognitive capacity that cannot be detected with behavioral assessments (Shaywitz et al., 1999). Bringing

structural and functional neuroimaging results together, estrogen-related structural and functional changes are most frequently observed within the hippocampus and PFC.

Even if mental rotation was found to be positively related to estrogen in one study (Schmidt et al., 2013), several others found no relationship (e.g., Davison et al., 2013; Maki et al., 2001; Resnick et al., 2006; Shaywitz et al., 2003). Apart from one study (Fuh et al., 2006), no relationship between verbal fluency and estrogen was found either on performance (e.g., Gleason et al., 2015; Shaywitz et al., 2003), or brain activity (Davison et al., 2013). In one study, estrogen was found to be related to better non-verbal short-term memory (Resnick et al., 2006), while others found no relation (Maki et al., 2001; Phillips & Sherwin, 1992; Sherwin & Tulandi, 1996). Non-verbal long-term memory was not related to estrogen (Fuh et al., 2006; Phillips & Sherwin, 1992; Sherwin & Tulandi, 1996); neither was attention (e.g., Espeland et al., 2013; Grigороva & Sherwin, 2006; Resnick et al., 2006).

Altogether, evidence from behavioral studies indicates that estrogen exerts its greatest effect on verbal short- and long-term memory. Neuroimaging studies provide evidence of estrogen-related structural changes in hippocampal and to some degree PFC gray-matter volume. Task-related functional alterations have been observed in the hippocampus and PFC. These findings converge with neurophysiological evidence from animal studies, where estrogen was found to alter dendritic spine density in the hippocampus and DLPFC.

Related to dendritic spines, LTP is, as previously described, thought to underly learning and memory. According to Gazzaniga et al. (2014), an important underlying mechanism behind LTP is the influx of CA^{2+} into the postsynaptic neuron (dendritic spine), subsequently causing changes that influence synapse strength. When estrogen binds to membrane ERs, CA^{2+} will increase in the cell (see Page 8). Since ERs are located on dendritic spines, it can be speculated upon whether estrogen may be involved in enhancing LTP by, when binding to its receptors, inducing CA^{2+} inflow into the postsynaptic neuron. This way estrogen may possibly enhance cognitive functioning.

Sellers, Raval, and Srivastava (2015) have proposed that by increasing spine density, estradiol primes neurons to respond to subsequent stimuli with greater efficacy. They explain that without subsequent stimulus, new spines will eventually be eliminated. In the presence of subsequent stimulus, spines will persist and a long-term increase in synaptic connectivity occur. This may help to reinforce the consolidation of a behavior. That is, estradiol, together with subsequent stimulus, will create long-term changes in neuroplasticity. If, like in animals, estrogen affects spine density in the human hippocampus and PFC, it can be argued that practice (or the use) of cognitive tasks (or abilities) after HT administration would lead to

long-term changes in neuroplasticity, since new spines would persist. This may explain the estrogen-related behavioral changes in short- and long-term verbal memory observed throughout this thesis. In daily life, we commonly behave in similar ways as required in tasks included in verbal memory assessments. Many of us retell stories that other people have told us, which can be compared to the paragraph recall task where participants are told to retell a story of five sentences. Even if we use other cognitive abilities frequently, cognitive assessments used to measure them may not be designed so as tasks resemble the way cognitive abilities are used in daily life.

Even if patterns of estrogen-related effects on cognition has been observed in the thesis, diverse results are still present. This may in part be due to the wide range of methods used in the field. Different types and doses of HT are commonly mixed within the same study, without taking into account that they may affect cognition differently. It has recently been observed that 2 mg/day of E² enhances cognition, while 1 mg/day does not (see Page 19). Another common mistake is to include women with different menopausal nature (surgical and natural), without intending to examine differences among the two. Since women undergoing oophorectomy usually do so at a younger age than natural menopause, their reproductive periods are shorter. Georgakis et al. (2016) have proposed that differences in lifetime cumulative endogenous estrogen exposure (as measured by length of reproductive period: i.e., time between first menstrual period and FMP) may affect cognition. Evidence of a positive relationship between a longer reproductive period (longer timeframe of exposure to endogenous estrogen) and cognitive function (e.g., learning and verbal memory) has previously been provided (Heys et al., 2011). Other issues are the wide range of cognitive tests used in studies, and the lack of definitions of terms in research articles.

Throughout this thesis, studies on HT have been used as a way of examining if, and how, estrogen affects cognition. However, the aim of the thesis was not to examine how HT affects cognition, but to examine how estrogen depletion affects cognition. The choice to include HT studies may be regarded as a limitation of the thesis. Another way could have been to only include studies examining the relationship between estrogen depletion and cognition. The decision to include HT studies was partly based on how HT commonly is used to examine menopausal cognitive changes. By using HT, randomization and experimental designs can be implemented in studies. This is otherwise not possible within the field: except when a GnRHa is used. By including HT studies, a wider range of research was available. A relatively small number of studies examine how cognition (together with underlying brain structure) is affected by estrogen depletion. Including HT studies in the thesis has helped

provide further insight into the relationship between estrogen and cognition. However, as argued by Georgakis et al. (2016), exogenous hormone exposure (e.g., HT) may affect the brain differently than endogenous exposure.

When interpreting results of research within this field, individual differences (e.g., underlying brain health) that likely exist among women need to be considered. Some women are likely better able to compensate for estrogen loss, while others may be more vulnerable. The complex nature of menopause adds yet another challenge in interpreting results. Changes in cognition may, for example, not be caused by estrogen depletion *per se* but lie in changes in the ratio among estrogen types that occur during the menopausal transition. Also, due to the complicated interplay among hormones, it is not possible to conclude that changes in cognition that have been observed throughout this thesis are caused by estrogen alone. Other hormonal changes associated with menopause (enhanced FSH levels, decreased progesterone levels, changes in GnRH administration) may in part account for menopausal-related cognitive changes. In such, a limitation of the thesis is that focus mainly was placed on estrogen. An investigation of the relationship between cognition and other menopausal-related hormones could possibly have been included. However, by focusing mainly on estrogen, a more throughout review could be provided, and more details included.

6. Conclusion

The primary conclusion of this thesis is that estrogen depletion appears to have negative effects on cognition; the effects are most clearly noted with respect to verbal short- and long-term memory. Throughout this thesis, estrogen depletion has not only been observed to be associated with impairments in cognitive performance, but also with changes in underlying brain structure and function, mainly evident in the hippocampus and PFC. Menopause is complex, and future research is needed to determine if the observed effects result from estrogen depletion alone, or if other factors are involved.

Due to the lack of such studies, more research needs to be conducted focusing specifically on the relationship between menopausal estrogen depletion and structural changes in the brain. It would be of further interest to place more focus on estrogen depletion rather than HT: i.e., to conduct more studies examining the relation between estrogen depletion and cognition, and estrogen depletion and brain activity. As discussed, it would also be interesting to see studies where assessments of stress levels are included. Clear definitions of terms need to be provided in future research articles, together with the use of a uniform classification of menopausal stages. In this, the STRAW-guidelines may be useful. Finally, there are several

studies that do not assess estradiol levels even when examining how, for example, cognition is affected by estrogen depletion. I recommend that estradiol levels should be assessed in future studies. Without assessing estrogen levels, it is not possible to know if estrogen depletion has even occurred. Therefore, there is a clear benefit of doing so.

This thesis provides a comprehensive overview of what the field currently looks like, including current knowledge, problems with research, and challenges commonly faced when conducting research on the menopausal brain and the effects of estrogen depletion on cognition. By understanding if and how estrogen depletion affects cognition, we may better be able to prevent or alleviate this type of menopausal symptom. Just by knowing what is happening to themselves, women may better be able to cope with cognitive changes that may, and probably do, follow menopausal estrogen depletion.

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Appendix A

Glossary

Attention	The ability to focus one's awareness on a given stimulus, thought, or action, and ignore irrelevant stimuli, thoughts, or actions (Gazzaniga et al., 2014).
Cognitive flexibility	The ability to flexibly shift attentional focus, perspective, or response behavior (Diamond, 2006).
Digit Span (backward)	Starting with a string of three digits, participants are asked to immediately repeat digits in the reverse order from which they were presented. After each successful round, a new string is presented, containing an increasing number of digits (Wechsler, 1945).
Digit Span (forward)	Starting with a string of four digits, participants are asked to immediately repeat digits in the same order they were presented. After each successful round, a new string is presented, containing an increasing number of digits (Wechsler, 1945).
Executive functions	The ability to use our goals, knowledge, and perceptions to select thoughts and actions from several possible options, making it possible to plan for the future and make purposeful decisions (Gazzaniga et al., 2014).
Mental rotation	The ability to imagine what an object will look like if it undergoes rotation from its original position (Provost, Johnson, Karayanidis, Brown, & Heathcote, 2013).

N-back sequential letter task	A test of verbal working memory. A sequence of letters is shown. Participants are to decide whether the present letter matches a letter presented 1-, 2-, or 3 letters back in the sequence. Working memory load increases with increasing numbers back (Dumas et al., 2010).
Paired associates task	A test of verbal short- and long-term memory. Ten word pairs are presented, and when later presented with one of the words, participants are asked to recall the paired word (Sherwin & Tulandi, 1996).
Paragraph recall task	Tests verbal short- and long-term memory. A short paragraph of about five sentences is presented. Participants are later asked to recall the paragraphs (Sherwin & Tulandi, 1996).
Spatial Working Memory task	Ten pairs of colored dots are hidden under individual flaps. Participants are asked to lift two flaps at a time to find matching pairs of colored dots. They are supposed to find all ten pairs in as few choices as possible (Duff & Hampson, 2000).
Task-switch paradigm	Participants are shown a letter, and based on the color of the letter, they are supposed to either indicate if the letter is a vowel or consonant, or lower- or uppercase. This task requires a constant switch between tasks (Girard et al., 2017).
Verbal fluency	The ability to form and express words in line with required criteria. Fundamental for normal social functioning (Wysokiński et al., 2010).

Water maze task

Used in rodent studies to test spatial navigational learning and memory. A round pool filled with black water is used. An escape platform is hidden under the surface, and extra maze cues are placed in the room. By dropping the animal in different locations, memory is tested (Sandstrom & Williams, 2001).

Wisconsin Card Sort Task

A test of abstract reasoning and problem solving, that also involves working memory. Participants are asked to sort cards based on color, shape, or number. Rules change throughout the task without noticing the participant, but feedback is given after each move (Berman et al., 1997).