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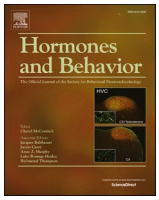

The neuroanatomy of menopause☆

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ABSTRACT

Sex hormones are known to affect brain structure. Given that menopause is marked by a significant decline in female sex hormones, there might be structural brain alterations around menopause. The aim of this article is to provide a narrative review on what we know today with respect to links between brain anatomy and menopause, while also considering potential effects of menopausal hormone therapy (MHT). The review is focused on neuroimaging studies analyzing the macro-anatomy or micro-anatomy of the human brain as based on structural magnetic resonance imaging (MRI) or diffusion tensor imaging (DTI). Out of the 32 studies reviewed here, 22 studies revealed at least some findings that suggest beneficial effects of estrogen. However, overall, findings are rather mixed pointing to both beneficial and adverse effects (or to no effects at all). The nature of the effects seemed to be unrelated to the spatial scales applied, the morphometric measures obtained, and the brain tissues targeted. Nevertheless, there were some intriguing effects in terms of the study design: Cross-sectionally, there seemed to be a trend for beneficial effects in small-scale studies and for adverse effects in large-scale studies. Longitudinally, there seemed to be a trend for beneficial effects in purely observational studies and for beneficial as well as adverse effects in controlled clinical trials. With particular respect to MHT, early treatment (short after the onset of menopause) might be more beneficial than later treatment. However, overall, data are insufficient to draw final conclusions and further research is required.

1. Introduction

Sex hormones are known to affect brain structure, which has been vividly demonstrated in association with the menstrual cycle, pregnancy, and postpartum (reviewed in Dubol et al., 2021; Luders et al., 2022; Rehbein et al., 2020). Therefore, similar brain alterations may occur during menopause, a period marked by a significant decline in female sex hormones, specifically estrogen and progesterone (reviewed in Burger et al., 2002; Hall, 2015). There is a wealth of studies suggesting that menopause changes brain function (reviewed in Barth et al., 2015; Brinton et al., 2015; Comasco et al., 2014; Georgakis et al., 2016; Jacobs and Goldstein, 2018; Low and Anstey, 2006), but research with particular focus on brain structure has been relatively sparse, at least until a few years ago (reviewed in Lu et al., 2023; Ramli et al., 2023; Rehbein et al., 2020). Moreover, existing studies revealed conflicting results with respect to the affected brain region as well as brain tissue (gray matter vs. white matter vs. cerebrospinal fluid), and also the spatial scale of effects (global vs. regional vs. local). Perhaps even more surprising, studies disagree with respect to the nature of the effect (adverse vs. beneficial) of menopause and menopausal hormone replacement on brain structure.

The aim of this article is to provide a narrative review on what we know today with respect to links between brain anatomy and menopause, while also considering potential effects of exogenous hormones in pre-, peri-, and postmenopausal women. To keep the review as concise as possible, it is focused on neuroimaging studies analyzing the macro-anatomy or micro-anatomy of the human brain as based on structural magnetic resonance imaging (MRI) or diffusion tensor imaging (DTI). Studies on menopause and/or hormonal treatments which did not put their primary focus on measures derived using structural imaging or only in conjunction with other kinds of neuroimaging, such as functional MRI (fMRI), resting-state fMRI, arterial spin labeling fMRI, positron

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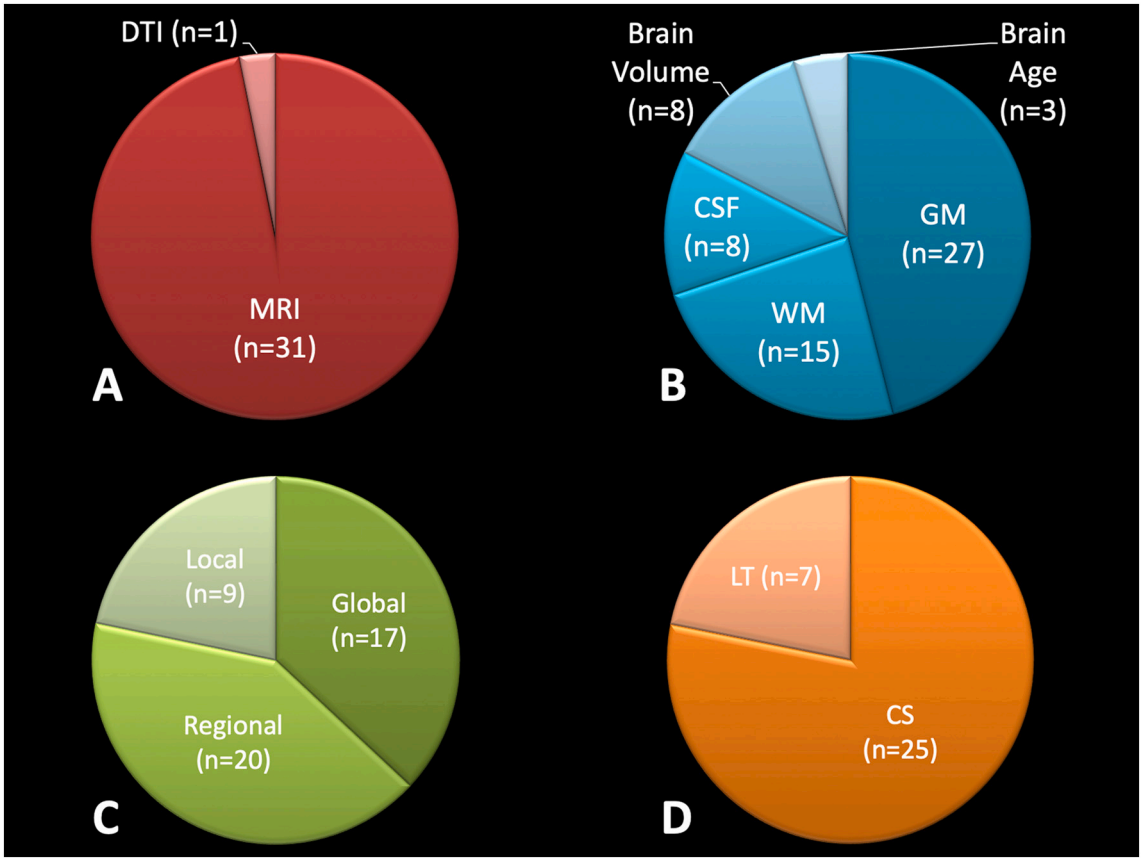

Fig. 1. Study-specific Characteristics. Panel A: Different imaging modalities (MRI = magnetic resonance imaging; DTI = diffusion tensor imaging). Panel B: Different targets (GM = gray matter; WM = white matter; CSF = cerebral spinal fluid). Panel C: Different spatial scales. Panel D: Different study designs (CS = cross-sectional; LG = longitudinal).

emission tomography, or ultrasound (e.g., Baek et al., 2019; Ficek-Tani et al., 2023; Guo et al., 2024; Kim et al., 2024; Liu et al., 2021; Mosconi et al., 2017a; Mosconi et al., 2017b; Mosconi et al., 2018; Sato et al., 2023; Testo et al., 2024; Thurston et al., 2023; Zhang et al., 2022) were omitted. Similarly, studies which were conducted in the framework of clinical conditions and/or using patients or individuals with risk factors, dysfunctions or specific genotypes (e.g., Cote et al., 2023; Eberling et al., 2004; Juutinen et al., 2024; Khan et al., 2014; Li et al., 2023; Lorefice et al., 2023; Moon et al., 2024; Myers et al., 2024; Rahman et al., 2020; Saleh et al., 2023; Schelbaum et al., 2021; Vaidya et al., 2024; Wang et al., 2014) were excluded.

Altogether, the review includes 32 studies (Albert et al., 2017; Ambikairajah et al., 2020; Barth et al., 2024; Boccardi et al., 2006; Coker et al., 2014; Cook et al., 2002; de Lange et al., 2020b; Eberling et al., 2003; Erickson et al., 2005; Erickson et al., 2010; Ghidoni et al., 2006; Goto et al., 2011a; Goto et al., 2011b; Greenberg et al., 2006; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2018; Kim et al., 2023; Kling et al., 2020; Lord et al., 2008; Low et al., 2006; Lu et al., 2018; Luders et al., 2024; Moir et al., 2023; Nabulsi et al., 2023; Pintzka and Haberg, 2015; Raz et al., 2004; Resnick et al., 2009; Seitz et al., 2019; Than et al., 2021; Zhang et al., 2021; Zhang et al., 2016), written in English and published in peer-reviewed scientific journals.

Studies either focused on (pre-, peri, post-) menopause[1] per se and/or explored the effects of menopausal hormone therapy. Of note, there is a lot of heterogeneity in regards to the nomenclature of "pre-", "peri-", and "post-"menopause (Ambikairajah et al., 2022). Since this review is not intended to re-define or evaluate the study-specific use of these terms, we report the terms as mentioned in the respective article. Similarly, studies have used different terms to describe hormonal interventions in the framework of menopause, which also is a by-product of changing nomenclature over time (e.g., hormone therapy, hormone replacement therapy, menopausal hormone therapy, estrogen therapy, or estrogen replacement therapy). To simplify things, we will use "menopausal hormone therapy" (or "MHT") throughout the review, except for one study which also included premenopausal women who received hormonal replacements (de Lange et al., 2020b); here we use "hormonal replacement therapy (or "HRT").

2. Different imaging modalities and different brain tissues targeted

The neuroimaging studies included here were based on structural MRI or DTI analyses. These kinds of analyses provide information about the brain's macro- and micro-structure. Thus, when directed at examining brain anatomy during menopause and/or menopausal hormone therapy, they can provide insights into potentially degenerative or neuroprotective effects of estrogens or progesterone. Out of the 32 studies, 31 were based on structural MRI and only 1 on DTI (see Fig. 1, panel A). The majority of studies (n = 27) examined attributes of gray matter (Albert et al., 2017; Ambikairajah et al., 2020; Barth et al., 2024; Boccardi et al., 2006; Coker et al., 2014; de Lange et al., 2020; Eberling et al., 2003; Erickson et al., 2005; Erickson et al., 2010; Ghidoni et al., 2006; Goto et al., 2011a; Goto et al., 2011b; Greenberg et al., 2006; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2018; Kim et al., 2023; Lord et al., 2008; Low et al., 2006; Lu et al., 2018; Pintzka and Haberg, 2015; Raz et al., 2004; Resnick et al., 2009; Seitz et al., 2019;

[1] The review does not differentiate between natural and surgical menopause due to a lack of available information for some of the studies.

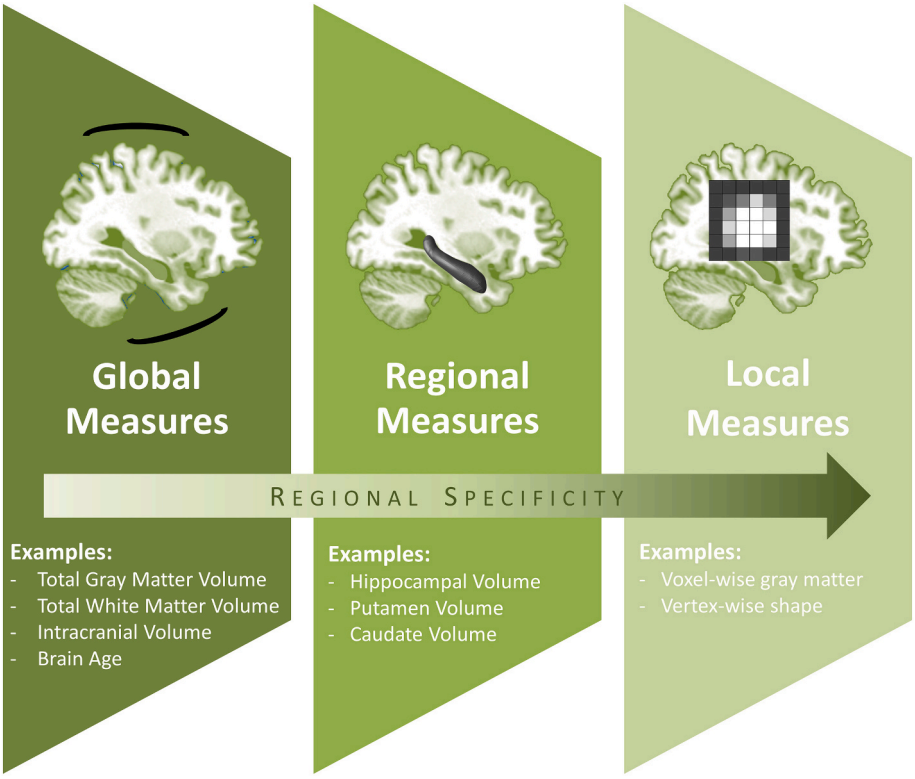

Fig. 2. Spatial Scales of Structural Measures and Findings. Global measures capture large-scale effects. Regional measures capture effects for so-called regions of interest; they are smaller in scale than global measures but larger than local measures. Local measures capture fine-grained (voxel-wise or vertex-wise) effects across the brain or for a region of interest.

Than et al., 2021; Zhang et al., 2021; Zhang et al., 2016). Fifteen studies examined attributes of white matter (Barth et al., 2024; Coker et al., 2014; Cook et al., 2002; Erickson et al., 2005; Ghidoni et al., 2006; Greenberg et al., 2006; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2023; Kling et al., 2020; Low et al., 2006; Moir et al., 2023; Nabulsi et al., 2023; Raz et al., 2004; Than et al., 2021), and eight studies analyzed CSF (Coker et al., 2014; Cook et al., 2002; Erickson et al., 2005; Greenberg et al., 2006; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2023; Resnick et al., 2009). In addition, eight studies analyzed brain volume (Ambikairajah et al., 2020; Coker et al., 2014; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2023; Moir et al., 2023; Resnick et al., 2009; Than et al., 2021) and three studies analyzed brain age (Barth et al., 2024; de Lange et al., 2020b; Luders et al., 2024). For an overview of studies in regards to their focus, see Fig. 1 (panel B).

3. Different spatial scales and different morphometric measures obtained

The existing studies differ in terms of the regional specificity of their morphometric approach, which in turn determines the spatial scale of their findings ranging from global, to regional, to local (Fig. 2).

Global measures offer a good starting point to explore if there are any differences between groups or changes over time at all. However, as the name implies, global measures are severely limited in their spatial sensitivity and unlikely to produce any significant findings if effects are spatially restricted. Global measures were examined in 17 studies, focusing on total brain volume (Ambikairajah et al., 2020; Coker et al., 2014; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2023; Moir et al., 2023; Resnick et al., 2009; Than et al., 2021); total gray and white matter volume (Coker et al., 2014; Ghidoni et al., 2006; Greenberg et al., 2006; Kim et al., 2023; Low et al., 2006; Than et al., 2021); total CSF volume, including total ventricular volume, ventricular CSF, sulcal CSF, or non-ventricular CSF, respectively[2] (Coker et al., 2014; Cook et al., 2002; Greenberg et al., 2006; Kantarci et al., 2016; Kantarci et al., 2018; Kim et al., 2023; Resnick et al., 2009); total white matter hyperintensities / lesions, including total deep white matter or periventricular white matter hyperintensities / lesions, respectively[3] (Barth et al., 2024; Coker et al., 2014; Cook et al., 2002; Greenberg et al., 2006; Kantarci et al., 2016; Kantarci et al., 2018; Kling et al., 2020; Low et al., 2006; Moir et al., 2023; Than et al., 2021), characteristics of white matter microstructure (Nabulsi et al., 2023), as well as brain age (Barth et al., 2024; de Lange et al., 2020b; Luders et al., 2024).

For greater specificity, regional measures – often obtained in so-called region-of-interest (ROI) analyses – may be obtained as a follow-up to global effects (or even to local effects), but also conducted independently. Regional analyses were conducted in 20 studies and directed at the volume (or subvolumes) of the hippocampus (Albert et al., 2017; Ambikairajah et al., 2020; Barth et al., 2024; Coker et al., 2014; Eberling et al., 2003; Erickson et al., 2005; Erickson et al., 2010; Goto et al., 2011b; Greenberg et al., 2006; Lord et al., 2008; Low et al., 2006; Pintzka and Haberg, 2015; Raz et al., 2004; Resnick et al., 2009; Seitz et al., 2019; Zhang et al., 2021); amygdala (Erickson et al., 2010; Lord et al., 2008; Low et al., 2006; Zhang et al., 2021); or cerebellum (Ghidoni et al., 2006), just to name a few (for additional regions, see Coker et al., 2014; Erickson et al., 2010; Ghidoni et al., 2006; Greenberg

[2] Strictly speaking, these measures could also be considered regional. However, to keep things simple and also to discriminate these measures from region-of-interest measures (see next paragraph), we list them here as global.

[3] See previous footnote.

Table 1
Imaging modality, brain tissue, spatial scale, and brain measures (cross-sectional studies).

Study	Imaging [Brain Tissue] Spatial Scale	Brain Measures
(Eberling et al., 2003)	MRI [gray matter] regional	– regional volumes and subvolumes (whole, anterior, and posterior hippocampus)
(Erickson et al., 2005)	MRI [gray matter, white matter, and CSF] regional + local	– voxel-wise gray matter within the anterior hippocampus – voxel-wise gray matter across the brain – voxel-wise white matter across the brain – voxel-wise CSF across the brain
(Boccardi et al., 2006)	MRI [gray matter] local	– voxel-wise gray matter across the brain
(Ghidoni et al., 2006)	MRI [gray matter and white matter] global + regional	– total gray matter volume – total white matter volume – regional volumes (frontal, temporal, parietal, occipital lobes, and cerebellum)
(Greenberg et al., 2006)	MRI [gray matter, white matter, and CSF] global + regional	– total gray matter volume – total white matter volume – total ventricular CSF volume – total non-ventricular CSF volume – total white matter lesions volume – regional volumes (hippocampus, caudate, and putamen)
(Low et al., 2006)	MRI [gray matter and white matter] global + regional	– total gray matter volume – total white matter volume – total WMHI volume – regional volumes (hippocampal and amygdala) – various measures of brain atrophy (see original publication)
(Lord et al., 2008)	MRI [gray matter] regional	– regional volumes (hippocampus and amygdala)
(Resnick et al., 2009)	MRI [gray matter and CSF] global + regional	– total brain volume – total ventricular volume – regional volumes (hippocampus and frontal lobe)
(Erickson et al., 2010)	MRI [gray matter] regional	– regional volumes (hippocampus, amygdala, and caudate)
(Goto et al., 2011a)	MRI [gray matter] local	– voxel-wise gray matter across the brain
(Goto et al., 2011b)	MRI [gray matter] regional	– regional volumes (hippocampus)
(Pintzka and Haberg, 2015)	MRI [gray matter] regional + local	– regional volumes (hippocampus) – vertex-wise shape of the hippocampus
(Zhang et al., 2016)	MRI [gray matter] local	– voxel-wise gray matter across the brain
(Kim et al., 2018)	MRI [gray matter] local	– voxel-wise gray matter across the brain
(Lu et al., 2018)	MRI [gray matter] local	– voxel-wise gray matter across the brain
(Seitz et al., 2019)	MRI [gray matter] regional	– regional volumes (dorsolateral prefrontal cortex, inferior parietal lobule, anterior cingulate cortex, hippocampus, and parahippocampus)
(Ambikairajah et al., 2020)	MRI [gray matter] global + regional	– total brain volume – regional volumes (hippocampus[1])
(de Lange et al., 2020a, 2020b)	MRI [gray matter[2]] global	– brain age
(Than et al., 2021)	MRI [gray matter and white matter] global + regional	– total brain volume – total gray matter volume – total white matter volume – total WMHI volume – various regional volumes (see original publication)
(Zhang et al., 2021)	MRI [gray matter] regional	– various regional volumes (see to original publication)
(Kim et al., 2023)	MRI [gray matter, white matter, and CSF] global + local	– total brain volume – total gray matter volume – total white matter volume – total CSF volume – voxel-wise gray matter across the brain
(Moir et al., 2023)	MRI [gray matter[3] and white matter] global	– total brain volume – total WMHI / white matter lesions volume
(Nabulsi et al., 2023)	DTI [white matter] global	– total diffusivity indices (FA, MD, RD, AD, OD, ICVF, and ISOVF)
(Barth et al., 2024)	MRI [gray matter and white matter] global + regional	– two different brain ages[4,5] – total WMHI volume – regional volumes (hippocampus)
(Luders et al., 2024)	MRI [gray matter[6] and white matter[6]] global	– brain age[7]

AD = Axial Diffusivity; CSF = Cerebrospinal Fluid; DTI = Diffusion Tensor Imaging; FA = Fractional Anisotropy; ICVF = Intracellular volume fraction; ISOVF = Isotropic volume Fraction; MRI = Magnetic Resonance Imaging; MD = Mean Diffusivity; OD = Orientation Dispersion; RA = Radial Diffusivity; WMHI = White Matter Hyperintensities.
[1] Left and right volumes combined.
[2] Only to calculate brain age.
[3] Only to calculate total brain volume.
[4] Estimated based on gray matter.
[5] Estimated based on white matter.
[6] Only to calculate brain age.
[7] Estimated based on gray matter and white matter.

et al., 2006; Kantarci et al., 2018; Raz et al., 2004; Resnick et al., 2009; Seitz et al., 2019; Than et al., 2021; Zhang et al., 2021).

Finally, local measures – either obtained as a follow-up to global / regional analyses or examined in independent analyses – capture effects with a very high regional specificity across the entire brain, and sometimes also within a region of interest (Albert et al., 2017; Erickson et al., 2005; Pintzka and Haberg, 2015). Local analyses were conducted in 9 studies and directed at voxel-wise gray matter (Albert et al., 2017; Boccardi et al., 2006; Erickson et al., 2005; Goto et al., 2011a; Kim et al., 2018; Kim et al., 2023; Lu et al., 2018; Zhang et al., 2016) and vertex-wise shape (Pintzka and Haberg, 2015). For an overview of studies in regards to their spatial scale, see Fig. 1 (panel C).

Table 1 (cross-sectional studies) and Table 2 (longitudinal studies) provide details on the studies included in this review with respect to the imaging modality (i.e., MRI or DTI), the brain tissue considered (i.e., gray matter, white matter, or CSF), the spatial scale of the analysis (i.e., global, regional, or local), as well as the specific measures obtained (e.g., voxel-wise gray matter).

4. Different study designs and different effects revealed

Cross-sectional studies collect data from a population at a specific

Table 2
Imaging modality, brain tissue, spatial scale, and brain measures (longitudinal studies).

Study	Imaging Modality [Brain Tissue] Spatial Scale	Brain Measures
(Cook et al., 2002)	MRI [white matter and CSF] global + regional	– total deep WMHI volume – total periventricular WMHI volume – total ventricular CSF volume – total sulcal CSF volume – regional deep WMHI volume (anterior / posterior brain) – total periventricular WMHI volume (anterior / posterior brain) – regional ventricular CSF volume (anterior / posterior brain) – total sulcal CSF volume (anterior / posterior brain)
(Raz et al., 2004)	MRI [gray matter and white matter] regional	– regional volumes (prefrontal, fusiform, pericalcarine and entorhinal cortex, and hippocampus)
(Coker et al., 2014)	MRI [gray matter, white matter, and CSF] global + regional	– total brain volume – total lesion volume – total white matter lesion volume – total gray matter lesion volume – total basal ganglia lesion volume – total ventricular CSF volume – regional volumes (frontal lobe and hippocampus)
(Kantarci et al., 2016)	MRI [gray matter, white matter, and CSF] global	– total brain volume – total ventricular volume – total WMHI volume
(Albert et al., 2017)	MRI [gray matter] regional + local	– regional volumes (hippocampus) – voxel-wise gray matter within the hippocampus
(Kantarci et al., 2018)	MRI [gray matter, white matter, and CSF] global + regional	– total brain volume – total ventricular volume – total WMHI volume – various regional volumes (see original publication)
(Kling et al., 2020)	MRI [white matter] global	– total WMHI volume

CSF = Cerebrospinal Fluid; MRI = Magnetic Resonance Imaging; WMHI = White Matter Hyperintensities.

point in time, which allows establishing group differences (e.g., between postmenopausal women with and without MHT) and correlations (e.g., correlations between brain anatomy and the duration of MHT). In contrast, longitudinal studies collect data from the same sample(s) over an extended period of time, which allows establishing causality (e.g., changes in brain anatomy due to MHT), in addition to any group differences and correlations. Out of the 32 studies, 25 were cross-sectional and seven were longitudinal in nature (see Fig. 1, Panel D).

Table 3 (cross-sectional studies) and Table 4 (longitudinal studies) provide an overview of the studies included in this review with respect to the study (sub)samples, the significant effects,[4] as well as the implications of the effect in terms of beneficial versus adverse.[5] With respect to the sample and when indicating if individuals underwent MHT, we make a distinction between "unopposed" (estrogen only), "combined" (estrogen and progesterone), and "unspecified" for the cross-sectional studies. For the longitudinal studies, we added detailed information (if

[4] For studies that examined the effects of menopause, together with the effects of menarche and reproductive span, only the outcomes pertaining to menopause and reproductive span are included.

[5] These opposing terms are solely used for the sake of clarity and simplicity. Increases in gray matter, for example, are interpreted as "beneficial", decreases in gray matter as "adverse". We acknowledge that such labels do not fully capture the complexity or context-dependent nature of the present findings.

Table 3
Sample composition, significant effects, and implications (cross-sectional studies).

Study	Sample	Significant Effects	Implications
(Eberling et al., 2003)	$n = 13$, postmenopausal F with MHT (unopposed) $n = 46$, postmenopausal F w/o MHT $n = 38$, M	Volume of the right hippocampus: - F with MHT > F w/ o MHT - F with MHT > M Volume of the anterior hippocampus: - F with MHT > F w/ o MHT - F with MHT > M Volume of the right anterior hippocampus: - F with MHT > F w/ o MHT - F with MHT > M Volume of the left anterior hippocampus: - F with MHT > M	↑ Beneficial effects of estrogen
(Erickson et al., 2005)	$n = 16$, postmenopausal F with current MHT (unopposed and combined) $n = 14$, postmenopausal F with past MHT (unopposed and combined) $n = 13$, postmenopausal F w/o MHT	Gray matter in the anterior hippocampus: - F w/o MHT < F with MHT Age-related loss of gray matter in the anterior hippocampus: - F w/o MHT > F with MHT Gray and white matter in various brain regions: - F w/o MHT < F with MHT Age-related loss of gray matter in various brain regions: - F w/o MHT > F with MHT Correlation with MHT duration: - The longer, the more gray and white matter in various brain regions. CSF in various brain regions: - F w/o MHT > F with MHT	↑ Beneficial effects of estrogen / progesterone
(Boccardi et al., 2006)*	$n = 16$, postmenopausal F with current MHT (unopposed) $n = 7$, postmenopausal F with past MHT (unopposed) $n = 17$, postmenopausal F w/o MHT	Gray matter in various brain regions: - F w/o MHT < F with MHT - F with current MHT < F with past MHT	↑ Beneficial effects of estrogen
(Ghidoni et al., 2006)*	$n = 16$, postmenopausal F with current MHT (unopposed) $n = 7$, postmenopausal F with past MHT (unopposed) $n = 17$,	Volume of total gray matter: - F w/o MHT < F with MHT Volumes of parietal, occipital, and cerebellar gray matter:	↑ Beneficial effects of estrogen

(continued on next page)

Table 3 (*continued*)

Study	Sample	Significant Effects	Implications
	postmenopausal F w/o MHT	- F w/o MHT < F with MHT	
(Greenberg et al., 2006)	$n = 41$,[1] F with MHT (unopposed and combined) $n = 51$,[2] F w/o MHT $n = 33$, M	Volume of total gray matter: - F w/o MHT > F with MHT - F w/o MHT > M Volume of non-ventricular CSF: - F w/o MHT < F with MHT Volume of the left and right putamen: - F w/o MHT > M	↓ Adverse effects of estrogen / progesterone
(Low et al., 2006)	$n = 80$, postmenopausal F w/o MHT $n = 64$, postmenopausal F with current MHT (unspecified) $n = 69$, postmenopausal F with past MHT (unspecified)	[no significant group differences in global or regional brain measures] [no significant correlations between the duration of HRT and global or regional brain measures]	→ No clear implication with respect to the effects of estrogen / progesterone
(Lord et al., 2008)	$n = 16$, postmenopausal F with current MHT (unopposed) $n = 10$, postmenopausal F with past MHT (unopposed) $n = 15$, postmenopausal F w/o MHT $n = 15$, M	Volume of the right hippocampus: - F with current MHT > F w/o MHT - F with current MTH > F with past MHT Volume of the left and right hippocampus: - F with current MHT > M Correlation with MHT duration: - The longer, the smaller the total (left and right combined) volume of the hippocampus ǂ	↑ Beneficial effects of estrogen (except for the outcome marked with ǂ)
(Resnick et al., 2009)**	$n = 436$, postmenopausal F with MHT (combined) $n = 257$, postmenopausal F with MHT (unopposed) $n = 710$, postmenopausal F with placebo	Volumes of the frontal lobe: - F with MHT (pooled: combined + unopposed) < F with placebo - F with MHT (unopposed) < F with placebo Volumes of the hippocampus: - F with MHT (pooled: combined + unopposed) < F with placebo	↓ Adverse effects of estrogen / progesterone
(Erickson et al., 2010)	$n = 62$, postmenopausal F with current MHT (unopposed and combined) $n = 37$, postmenopausal F w/o MHT	Volume of the left and right hippocampus: - F with MHT (initiated <1 years after menopause) > F w/o MHT - F with MHT (initiated >1 year after menopause) = F w/o MHT Correlation with time between menopause and MHT initiation: - The less time, the larger the volume of the left and right hippocampus.	↑ Beneficial effects of estrogen / progesterone
(Goto et al., 2011a)***	$n = 51$,[3] premenopausal F $n = 120$, postmenopausal F $n = 46$[3] (59; 49; 17), F in their 40s (50s; 60s; 70s) $n = 85$ (80; 63; 13) M in their 40s (50s; 60s; 70s)	Gray matter in the left and right hippocampus: - premenopausal F > postmenopausal F Gray matter in the left and right hippocampus: - F in their 40s (3 at menopause) > F in their 50s (51 at menopause)	↑ Beneficial effects of estrogen / progesterone
(Goto et al., 2011b)***	$n = 46$[3] (59; 49; 17), F in their 40s (50s; 60s; 70s) $n = 85$ (80; 63; 13), M in their 40s (50s; 60s; 70s)	Volume of the left and right hippocampus: - F in their 40s > F in their 50s - M in their 60s > M in their 70s	↑ Beneficial effects of estrogen / progesterone
(Pintzka and Haberg, 2015)	$n = 80$, postmenopausal F with MHT (unopposed and combined MHT) $n = 80$, postmenopausal F w/o MHT	Volume of the right hippocampus: - F with MHT > F w/o MHT Shape of the right hippocampus (CA1 subfield and subiculum): - F with MHT > F w/o MHT	↑ Beneficial effects of estrogen / progesterone
(Zhang et al., 2016)**	$n = 420$, postmenopausal F with MHT (combined) $n = 254$, postmenopausal F with MHT (unopposed) $n = 691$, postmenopausal F with placebo	Gray matter in various brain regions: - F with MHT (pooled: combined + unopposed) < F with placebo - F with MHT (unopposed) < F with placebo	↓ Adverse effects of estrogen / progesterone
Kim et al., 2018)	$n = 20$, pre-menopausal F[4] $n = 20$, postmenopausal F[4]	Gray matter in various brain regions: pre-menopausal F > postmenopausal F Correlation with estradiol level: The higher, the more gray matter in various brain regions	↑ Beneficial effects of estrogen / progesterone (especially estrogen)
(Lu et al., 2018)	$n = 32$, pre-menopausal F $n = 25$, perimenopausal F w/o MHT	Gray matter in various brain regions: - pre-menopausal F > perimenopausal F	↑ Beneficial effects of estrogen / progesterone
(Seitz et al., 2019)	$n = 33$, premenopausal F $n = 29$, perimenopausal F w/o MHT $n = 32$, postmenopausal F w/o MHT $n = 99$, M	Volume of the dorsolateral prefrontal cortex, inferior parietal lobule, anterior cingulate cortex, and hippocampus: - premenopausal F > M postmenopausal F > M	→ No clear implication with respect to the effects of estrogen / progesterone
(Ambikairajah et al., 2020)+	$n = 735$, pre-menopausal F $n = 4337$,	Total volume of the brain: - pre-menopausal F < postmenopausal F	↓ Adverse effects of estrogen / progesterone (except for the

(*continued on next page*)

Table 3 (*continued*)

Study	Sample	Significant Effects	Implications
	postmenopausal F w/o MHT	Total volume of the hippocampus (left and right combined): - pre-menopausal F < postmenopausal F Age-related loss of total brain volume: - pre-menopausal F < postmenopausal F ǂ Correlation with menopause onset: - The later, the smaller the total brain volume and the total hippocampus volume. Correlation with reproductive stage duration: - The longer, the smaller the brain volume.	outcome marked with ǂ)
(de Lange et al., 2020a, 2020b)[+]	n = 8878, pre- and postmenopausal F with HRT (unspecified) and w/o HRT	Correlation with cumulative estrogen exposure (based on age at menarche, age at menopause, time since menopause, body mass index, duration of HRT): - The higher, the older the brain.	↓ Adverse effects of estrogen / progesterone (especially estrogen)
	n = 11,139, pre- and postmenopausal F w/o HRT n = 5546, pre- and postmenopausal F with HRT (unspecified)	Brain age: - pre- and postmenopausal F w/o HRT < pre- and postmenopausal F with HR	
(Zhang et al., 2021)	n = 54, premenopausal F n = 45, early menopausal women w/o MHT	Volume of the left and right amygdala: - premenopausal F > early menopausal F	↑ Beneficial effects of estrogen / progesterone
(Than et al., 2021)	n = 230, pre-/peri-menopausal F n = 1827, postmenopausal F with MHT (unspecified) and w/o MHT n = 2165, M	Age-related loss of total brain volume: - pre-/peri-menopausal F < post-menopausal F with and w/o MHT - M < F Age-related loss of total gray matter volume: - pre-/peri-menopausal F < post-menopausal F with and w/o MHT - M < F Age-related loss of total white matter volume: - M < F Age-related gain of WMHI volumes: - pre-/peri-menopausal F < post-menopausal F with and w/o MHT	↑ Beneficial effects of estrogen / progesterone (except for the outcome marked with ǂ)

Table 3 (*continued*)

Study	Sample	Significant Effects	Implications
		Age-related gray matter loss in various brain regions: - pre-/peri-menopausal F < post-menopausal F with and w/o MHT Age-related gray matter loss in the left and right putamen: - pre-/peri-menopausal F > post-menopausal F with and w/o MHT ǂ	
(Kim et al., 2023)	n = 20, menopausal F with MHT (unopposed and combined) n = 21, menopausal F w/o MHT[2]	Gray matter in various brain regions: - menopausal F with MHT > menopausal F w/o MHT Correlation with MHT duration: - The longer, the more gray matter in the angular gyrus and hypothalamus Correlation with progesterone levels: - The higher, the less gray matter within the inferior frontal gyrus and angular gyrus ǂ	↑ Beneficial effects of estrogen / progesterone (except for the outcome marked with ǂ)
(Moir et al., 2023)	n = 19, early-onset menopausal F w/o oral MHT n = 16, later-onset menopausal F w/o oral MHT	WMHI volumes: - early-onset menopausal F > later-onset menopausal F	↑ Beneficial effects of estrogen / progesterone
Nabulsi et al., 2023)[+]	n = 3033, postmenopausal F with MHT (n=300, unopposed and n=90, combined) n = 5093, postmenopausal F w/o MHT	Age-related loss in various diffusivity indices: - F w/o MHT < F with MHT - F with combined MHT < F with unopposed MHT	↓ Adverse effects of estrogen / progesterone (especially estrogen)
(Barth et al., 2024)[+]	n=12,012, postmenopausal F w/o MHT n = 1153, postmenopausal F with current MHT (unspecified) n = 6681, postmenopausal F with past MHT (unspecified)	Brain age: - F w/o MHT < F with MHT Volume of the left hippocampus: - F w/o MHT > F with MHT Brain age: - F w/o MHT < F with current MHT Volume of the left and right hippocampus: - F w/o MHT > F with current MHT Correlation with the duration of MHT: - The longer, the older the brain. - The longer, the smaller the left and right hippocampus.	↓ Adverse effects of estrogen / progesterone
(Luders et al., 2024)[+]	n = 1006, postmenopausal F with MHT	Correlation with the onset of menopause:	↑ Beneficial effects of

(*continued on next page*)

Table 3 (*continued*)

Study	Sample	Significant Effects	Implications
	(unspecified) and w/o MHT	- The later, the younger the brain. Correlation with the duration of the reproductive span: - The longer, the younger the brain.	estrogen / progesterone

F = Females; HRT = Hormonal Replacement Therapy; M = Males; MHT = Menopausal Hormone Therapy; n.s. = not significant; WMHI = White Matter Hyperintensities; *,**,***overlapping samples.

[+] samples based on UK Biobank.

[1] There was no information on menopausal status, but the mean age was 70±6 years.

[2] There was no information on menopausal status, but the mean age was 71±6 years.

[3] There was no information on MHT.

[4] No hormones were taken for one month before assessment.

available) on type of estrogen and dosage as well as timing of MHT and duration.

With respect to the nature of the reported effects, note that a negative effect of menopause corresponds to a positive effect of estrogen / progesterone. Thus, to make it easier to grasp the heterogeneity (or homogeneity) across studies, we list all effects as pertaining to the presumed effect of estrogen and/or progesterone (see last columns in Tables 3-4). For example, a significant group difference indicating more brain tissue in pre-menopausal women than in postmenopausal women will be interpreted as a beneficial effect of estrogen and/or progesterone. Similarly, a significant group difference indicating more brain tissue in postmenopausal women with MHT than in postmenopausal women without MHT will be interpreted as a beneficial effect of estrogen (in case of unopposed MHT) or of estrogen and/or progesterone (in case of combined or unspecified MHT).

Out of the 32 studies, 22 contain at least some findings that suggest beneficial effects of estrogen (Albert et al., 2017; Ambikairajah et al., 2020; Boccardi et al., 2006; Cook et al., 2002; Eberling et al., 2003; Erickson et al., 2005; Erickson et al., 2010; Ghidoni et al., 2006; Goto et al., 2011a; Goto et al., 2011b; Kantarci et al., 2018; Kim et al., 2018; Kim et al., 2023; Kling et al., 2020; Lord et al., 2008; Lu et al., 2018; Luders et al., 2024; Moir et al., 2023; Pintzka and Haberg, 2015; Raz et al., 2004; Than et al., 2021; Zhang et al., 2021). In contrast, 14 studies contain at least some findings that suggest adverse effects (Ambikairajah et al., 2020; Barth et al., 2024; Coker et al., 2014; de Lange et al., 2020a; Greenberg et al., 2006; Kantarci et al., 2016; Kim et al., 2023; Lord et al., 2008; Low et al., 2006; Nabulsi et al., 2023; Resnick et al., 2009; Seitz et al., 2019; Than et al., 2021; Zhang et al., 2016). Three studies (Coker et al., 2014; Low et al., 2006; Seitz et al., 2019) reported null effects and as such do not have clear implications, one way or the other. Note, the total number of studies pertaining to beneficial, adverse, and no effects is larger than 32, because some studies reported effects that point to both beneficial and adverse effects (Ambikairajah et al., 2020; Kantarci et al., 2018; Kim et al., 2023; Lord et al., 2008; Than et al., 2021). The arrows in Tables 3-4 indicate the dominant directions of the observed effects. It might also be worth pointing out that there was some overlap across studies in terms of samples analyzed; for details see footnotes in Tables 3-4.

5. General discussion

The aim of this review was to summarize existing neuroimaging studies and their outcomes in the framework of menopause, including MHT. Taken together, the studies reviewed here seem to provide preliminary evidence that menopause causes significant changes in brain structure or, at least, is significantly related to alterations in brain structure. Likewise, similarly to menopause, MHT appears to exert a measurable influence on brain anatomy.

5.1. What is the nature of the observed effects?

Twenty-two out of the 32 studies reviewed (69 %), contain at least some findings that suggest beneficial effects of estrogen. Even though this is the majority of studies, some studies also reported adverse effects, yet others reported null effects. Interestingly, the study-specific effects (or lack thereof) seemed to be unrelated to the spatial scale applied in the respective study, the morphometric measures obtained, and the brain tissues targeted.[6] Similarly, the study design (cross-sectional vs. longitudinal) did not seem to systematically alter the nature of the effect, but the following observations seem worth mentioning: With respect to the outcomes of the cross-sectional studies, it appears that large scale-studies tend to reveal negative effects, while smaller scale studies revealed positive effects, albeit there are exceptions and, as mentioned above, some studies (even if independently conducted and varying in sample size and composition) were based on overlapping samples (i.e., from the UK Biobank). With respect to the outcomes of the longitudinal studies, purely observational studies (Cook et al., 2002; Raz et al., 2004) seem to indicate beneficial effects of estrogen, while the controlled clinical trials revealed both, beneficial effects (Albert et al., 2017; Kantarci et al., 2016; Kantarci et al., 2018; Kling et al., 2020) and adverse effects of estrogen (Kantarci et al., 2016; Kantarci et al., 2018), sometimes even within the same study.

5.2. What are possible reasons for discrepancies in findings?

The observed lack of a clear effect direction (beneficial vs. adverse) is somewhat surprising given that other hormone-related events (e.g., menstrual cycle, pregnancy, or postpartum) have revealed more conclusive (albeit not unequivocal) findings (Dubol et al., 2021; Luders et al., 2022; Rehbein et al., 2020). Studying menopause, however, faces additional challenges.

For example, women typically enter menopause between the ages of 45 and 55, with the average age being around 51. However, it is possible to enter menopause as early as the late thirties or as late as the early sixties, and the effect of declining estrogen levels may have substantially different effects in the brain of a healthy woman in her forties and a woman in her sixties who suffers from various medical conditions (hypertension, type-2 diabetes, etc.).

Moreover, the rate by which estrogen declines may be more or less steep, with some women maintaining regular menstrual cycles up until the last menses (suggesting maintained estrogen levels), and others suffering vasomotor symptoms (suggesting declining estrogen levels) for years before they reach menopause. In addition to these natural variations, estrogen levels are heavily affected by surgical procedures (oophorectomy, hysterectomy, etc.).

Finally, the relatively common use of hormonal IUDs or progestogen-only contraceptives in premenopausal women makes it difficult in general for women themselves to know if and when they have reached menopause. This may lead to involuntary inaccuracies with respect to the age at menopause, as reported by participants when undergoing MHT and/or participating in research studies. With respect to the latter, the aforementioned issues related to the nomenclature surrounding menopause could be another contributing (albeit probably only minor) factor.

5.3. Is there evidence in support of the critical window theory?

The "Critical Window" theory suggests that MHT only has

[6] There was only one DTI study (all others were based on MRI), so we cannot draw any conclusion on the impact of the imaging modality.

Table 4
Sample composition, hormonal treatment, significant effects, and implications (longitudinal studies).

Study	Sample	Estrogen (and Progesterone)	MHT (and Age)	Significant Effects	Implications
(Cook et al., 2002)	*n* = 3, postmenopausal F with MHT (unopposed) *n* = 3, postmenopausal F with MHT (combined) *n* = 9, postmenopausal F w/o MHT	Type: n/a Dosage: n/a	Timing: n=4 started MHT before start of study, n=2 started MHT during study Duration: n/a Age: 61–86 years at enrolment	Increase in the volume of the ventricles: - F w/o MHT > F with MHT Increase in the volume of the anterior ventricles: - F w/o MHT > F with MHT Increase in the volume of the posterior ventricles: - F w/o MHT > F with MHT	↑ Beneficial effects of estrogen
(Raz et al., 2004)	*n* = 7, postmenopausal F with MHT (unopposed) *n* = 5, postmenopausal F with MHT (combined) *n* = 9, postmenopausal F w/o MHT	Type: CEE Dosage: n/a	Timing: n=12 started MHT before start of study, n=3 started during study, n=3 stopped during study Duration: n/a Age: mean 63.58 years	Decrease in the volumes of the lateral prefrontal cortex, fusiform cortex, entorhinal cortex, and prefrontal white matter: - F w/o MHT > F with MHT	↑ Beneficial effects of estrogen
(Coker et al., 2014)[1]	*n* = 127, postmenopausal F with MHT (unopposed) *n* = 229, postmenopausal F with MHT (combined) *n* = 241, postmenopausal F w/o MHT (placebo – group 1) *n* = 132, postmenopausal F w/o MHT (placebo – group 2)	Type: CEE (or CEE + MPA) Dosage: CEE 0.625 mg /day (or CEE 0.635 mg + MPA 2.5 mg /day)	Timing: most started MHT at enrolment but some had MHT before); follow-up at 1.4 years (unopposed) or 3 years (combined) after MHT Duration: 6.2 years* for (unopposed) or 5.2 years* (combined) *on average, as trial was stopped early Age: 65-79 years	[no significant group differences in global or regional brain measures]	→ No clear implication with respect to the effects of estrogen / progesterone[3]
(Kantarci et al., 2016)[2]	*n* = 29, postmenopausal F with MHT (combined – group 1) *n* = 30, postmenopausal F with MHT (combined – group 2) *n* = 36, postmenopausal F w/o MHT (placebo)	Type: - group 1: CEE + P - group2: 17ß-estradiol + P Dosage: - group 1: 0.45 mg CEE + 200 mg P - group 2: 59 µg 17ß-estradiol + 200 mg P	Timing: MHT started at enrolment, 5-36 months after last menses; follow-up at 18, 36 and 48 months Duration: 48 months Age: 42-56 years	Increase in the volume of the ventricles: - F with MHT (combined –CEE) > F w/o MHT	↓ Adverse effects of estrogen / progesterone
(Albert et al., 2017)	*n* = 33, postmenopausal F with MHT (unopposed – group 1) *n* = 21, postmenopausal F (unopposed – group 2) *n* = 21, postmenopausal F w/o MHT (placebo)	Type: 17ß-estradiol Dosage: - group 1: 1 mg 17ß-estradiol for 1 month followed by 2 mg 17ß-estradiol for 2 months - group 2: 1 mg 17ß-estradiol for 3 month	Timing: MHT started at enrolment, ≥1 year past last menses; follow-up at 3 months Duration: 3 months Age: 42-56 years	Increase of gray matter in the posterior hippocampus: - F with MHT (unopposed – 2 mg estradiol) > F w/o MHT	↑ Beneficial effects of estrogen
(Kantarci et al., 2018)[2]	*n* = 20, postmenopausal F with MHT (combined – group 1) *n* = 22, postmenopausal F with MHT (combined – group 2) *n* = 33, postmenopausal F w/o MHT (placebo)	Type: - group 1: CEE + P - group2: 17ß-estradiol + P Dosage: - group 1: 0.45 mg CEE + 200 mg P - group 2: 59 µg 17ß-estradiol + 200 mg P	Timing: MHT started at enrolment, 5-36 months after last menses; follow-up at 18, 36 and 48 months Duration: 48 months Age: 42-56 years	Decrease in the volumes of the superior and middle frontal gyrus: - F with MHT (combined -estradiol) < F w/o MHT Increase in WMHI volumes: - F with MHT (combined – CEE) > F w/o MHT	↑ Beneficial effects of estrogen (estradiol) / progesterone ↓ Adverse effects of estrogen (CEE) / progesterone
(Kling et al., 2020)[2]	*n* = 23, postmenopausal F with MHT (combined – group 1) *n* = 24,	Type: - group 1: CEE + P - group2: 17ß-estradiol + P	Timing: MHT started at enrolment, 5-36 months after last menses; follow-up at 18, 36 and 48 months	Correlation with increases in WMHI: - the smaller, the larger the increase in estrone (but no link with	↑ Beneficial effects of estrogen (estrone) / progesterone

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Table 4 (*continued*)

Study	Sample	Estrogen (and Progesterone)	MHT (and Age)	Significant Effects	Implications
	postmenopausal F with MHT (combined – group 2) $n = 31$, postmenopausal F (placebo)	Dosage: - group 1: 0.45 mg CEE + 200 mg P - group 2: 59 µg 17ß-estradiol + 200 mg P	Duration: 48 months Age: 42-56 years	estradiol) (in F with MHT)	

CEE = Conjugated Equine Estrogen, MHT = Menopausal Hormone Therapy, MPA = Medroxyprogesterone Acetate; P= Progesterone; WMHI = White Matter Hyperintensities; n/a = not available

[1] Overlapping sample with two cross-sectional studies (Resnick et al., 2009; Zhang et al., 2016).

[2] Overlapping samples.

[3] However, see adverse cross-sectional outcomes by Resnick et al. (2009) and Zhang et al. (2016) in overlapping sample (Table 3).

neuroprotective effects when initiated around menopause (Marder and Sano, 2000; Resnick and Henderson, 2002). The premise is that estrogen has protective and beneficial effects primarily in healthy cells, whereas it might be less beneficial – perhaps even harmful – in damaged or stressed cells e.g., due to aging (Brinton, 2008). Out of the four longitudinal studies that provided information on the timing of MHT in relation to the onset of menopause, one study included exclusively postmenopausal women who were without menses for at least one year (Albert et al., 2017). This study reported positive effects of MHT, but conclusions are somewhat limited by the relatively short duration of the study (3 months). Three other studies (Kantarci et al., 2016; Kantarci et al., 2018; Kling et al., 2020) reported that the last menses occurred between 5 and 36 months before enrolment, thus including a mix of peri- and postmenopausal women. These three studies reported beneficial effects of estrogen, albeit one (Kantarci et al., 2018) also reported adverse effects in addition. While the duration of these studies was longer (48 months), the studies were based on overlapping samples. Therefore, the current review does not provide any conclusive evidence for (or against) the "Critical Window" theory. However, it might be worth mentioning that the aforementioned adverse effect was observed when MHT was based on conjugated equine estrogen (CEE), rather than estradiol (Kantarci et al., 2018). Nevertheless, there is also a study that reported beneficial effects of CEE-based MHT compared to no MHT (Raz et al., 2004). So, regardless of whether there is a critical window or not, it remains to be established if the type of estrogen used for MHT plays a significant role in comparison to not administering MHT.

6. Conclusions and implications for future research

The studies reviewed here seem to provide preliminary evidence that menopause and MHT affect brain structure. Notwithstanding, overall, findings are mixed ranging from positive, to negative, to no effects. This discrepancy in findings is unsettling and more research is clearly needed. Aside from chronological age, individual rates of estrogen decline and levels (as discussed in Section 5.2) as well as MHT timing and estrogen type (as discussed in Section 5.3), MHT duration and hormonal dosage may have a modulating impact on brain preservation. So, future studies might want to systematically alter (or at least control for) these factors. Moreover, they should consider expanding the time frame when brain measures are obtained covering peri-menopause (i.e., after the last regular period) and post-menopause (i.e., after period absence for 12 consecutive months), ideally after establishing a reference / baseline at pre-menopause (i.e., before the last regular period). That baseline scan should be acquired consistently across women in reference to the onset of peri-menopause or menopause to ensure comparability. All this is extremely challenging because a woman's age is no reliable predictor for when pre-menopause will end; it is merely a rough estimator. Similarly, it is impossible to predict the duration of peri-menopause for each woman; the average duration is around four years but inter-individual variability is high. A possible solution could be to scan hundreds (or thousands) of women at a certain age (e.g., 45 years) and acquire follow-up scans for those who will indeed enter peri-menopause (and menopause, respectively) within the targeted time frames (e.g., within one year for peri-menopause and within five years for menopause). However, given that this kind of systematic prospective research is very challenging (and cost-intense), other short-term studies, preferably using randomized controlled clinical trials, will continue to be an invaluable source of information.

CRediT authorship contribution statement

Eileen Luders: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Inger Sundström Poromaa:** Writing – review & editing, Writing – original draft, Conceptualization. **Florian Kurth:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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