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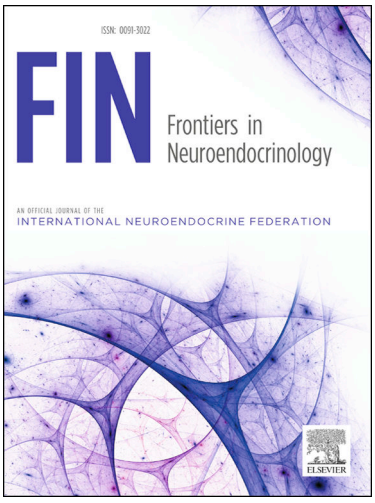

Review article

"Estrogens and human brain networks: A systematic review of structural and functional neuroimaging studies"

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Title:

"Estrogens and Human Brain Networks: A Systematic Review of Structural and Functional Neuroimaging Studies"

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Abstract

Estrogen fluctuations during the menstrual cycle, puberty, postpartum, or in the menopausal transition are associated with cognitive, affective, and behavioral effects. Additionally, estrogens are essential in hormonal contraception, menopausal hormone therapy, or gender-affirming hormone therapy. This systematic review summarizes findings on the role of estrogens for structure, function, and connectivity of human brain networks. We searched PubMed, Web of Science, and ScienceDirect for neuroimaging articles assessing estrogens published since 2008. We included 54 studies (N = 2,494 participants) on endogenous estrogen, and 28 studies (N = 1740 participants) on exogenous estrogen conditions. Estrogen-related changes were reported for emotion, reward, memory, and resting-state networks, and in regional white and gray matter, with a particular neural plasticity in the hippocampus and amygdala. By examining study designs, imaging measures, and analysis methods, this review highlights the role of neuroimaging in advancing neuroendocrine and neurocognitive research, particularly promoting brain health for women and individuals with ovaries.

Keywords: Estrogens; Neuroimaging; Menstrual cycle; Menopause; Puberty; Hormonal contraceptives; Systematic review

1. Introduction

As sex hormones, estrogens profoundly impact the nervous system, acting on cognitive, affective, and behavioral functions (Galea et al., 2017; Cui et al., 2013; McEwen, 2002). Estrogens fluctuate in both females and males, particularly starting at puberty. In females, menstrual cycles, pregnancy and postpartum, as well as the menopausal transition, may pose additional periods of estrogen fluctuations. During these fluctuations around an individual's mean, females exhibit increased prevalence of affective disorders (Amiel Castro et al., 2021; Freeman et al., 2006; Kundakovic et al., 2017; Maeng & Milad, 2015; Kundakovic and Rocks, 2022). Endogenous estrogens can offer neuroprotective properties throughout the lifespan (Dubal and Wise, 2002; McEwen, 2001), and may be essential for a healthy aging process (Zsido et al., 2019). Additionally, the administration of estrogens through hormonal contraception (HC), menopausal hormone therapy (MHT), and gender-affirming hormone therapy (GAHT) accentuates the need for a more comprehensive understanding of how different forms of estrogens affect the human brain in health and disease.

Estrogens, in their various forms (cf. *Fig. 1A*), differ in their hydroxyl groups, molecular structure, synthesis sites, and binding affinities, affecting potency and actions (Fuentes and Silveyra, 2019). In humans, there are four different types of natural estrogen, which consist of an aromatic A ring and either one (estrone, E1; with an additional ketone group), two (17β-estradiol, E2), three (estriol, E3), or four (estetrol, E4) hydroxyl groups (Stanczyk & Archer, 2023; Fuentes & Silveyra, 2019). While E2 is the most potent estrogen type and is the primary type in females of reproductive age ("estradiol"), E1 is most prominent during and after the menopausal transition (Barha et al., 2010; Hall, 2015). The estrogens E3 and E4 are primarily synthesized during pregnancy, by the fetoplacental unit (Stanczyk et al., 2024; Stanczyk & Archer, 2023). The onset of puberty is marked by the initiation of pulsatory gonadotropin releasing hormone (GnRH) secretion, leading to an increase in cyclic ovarian function through the promotion of sex steroid production (Abreu & Kaiser, 2016). Here, E2 rises during the follicular phase, peaks during ovulation, and shows a secondary surge in the mid-luteal phase followed by a sharp decline prior to menstruation (Bernal and Paolieri, 2022; cf. *Fig. 1B*). Simultaneously fluctuating is progesterone (P4), another ovarian sex hormone, that peaks in the mid-luteal phase. These endogenous fluctuations are dampened by HCs, which most frequently comprise ethinyl-estradiol (EE) and a progestin. As the latter is the central component for suppression of the pulsatory GnRH release, and thus of the hypothalamic-pituitary-gonadal feedback loop, some HCs are progestin-only preparations (POPs; Pletzer et al., 2023). However, adding the estrogenic component can enhance this suppression and alter symptoms and side effects (Stanczyk et al., 2013). While EE is by far the most commonly used estrogen in HC (Fruzzetti et al., 2024), E2 and E2 valerate, which have different pharmacodynamics, are also used (Lacasse et al., 2022; for reviews of HC pharmacology, see Hampson, 2023; Kuhl, 2005).

During and after the menopausal transition, E2 levels drop following the depletion of ovarian follicles (Hall, 2015). Here, MHT, previously also referred to as hormone replacement therapy, is sometimes used to reduce adverse effects of this depletion, by partially restoring E2 levels (Armeni et al., 2021; Harper-Harrison et al., 2024). The therapy can utilize naturally derived conjugated equine estrogens (CEE), which include a mixture of estrogens and P4, with the most prevalent estrogen being E1 (Ruan and Mueck, 2022). Alternatively, synthetically created E2 is commonly prescribed as an MHT which may have similar to better risk outcomes and protective effects of cognitive decline compared to CEE (Graham et al., 2022). In addition, exogenous estrogens are applied within the scope of feminizing therapy, a form of GAHT for transgender women, which typically includes E2 in combination with a testosterone antagonist (Tordoff et al., 2022). In transgender men, in contrast, a gonadal

suppression of estrogen production is combined with a testosterone agent (Tordoff et al., 2022).

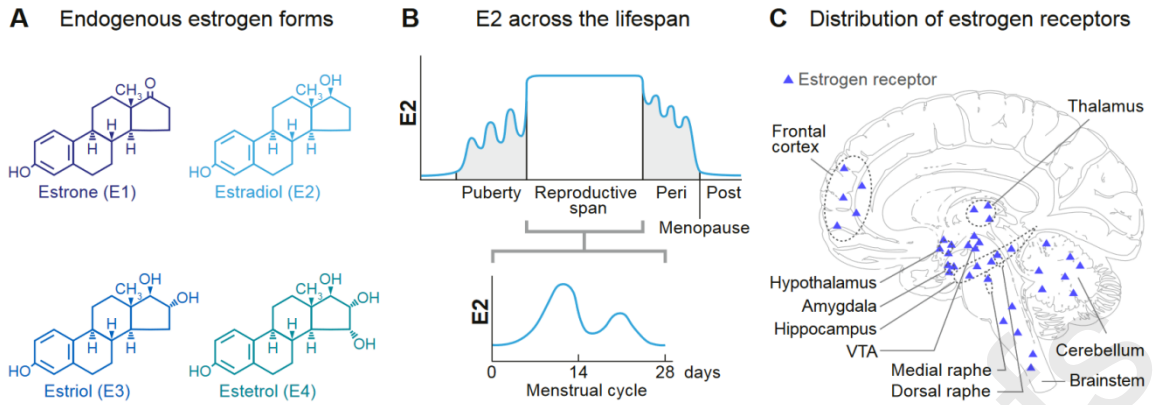

Fig. 1. Molecular structure, temporal dynamics, and brain receptor distribution of estrogens. (A) Endogenous estrogen types and their chemical structure. Adapted from Fuentes, N., Silveyra, P., 2019. Estrogen receptor signaling mechanisms, in: Advances in Protein Chemistry and Structural Biology. Elsevier, pp. 135–170. https://doi.org/10.1016/bs.apcsb.2019.01.001. (B) Estradiol (E2) concentrations vary throughout life, rising in puberty, peaking in the fertile years, and declining during the menopausal transition. Puberty and menopause are marked by fluctuating E2 levels, while the menstrual cycle during the fertile years features two E2 peaks. Adapted from Hoffmann, J.P., Liu, J.A., Seddu, K., Klein, S.L., 2023. Sex hormone signaling and regulation of immune function. Immunity 56, 2472–2491. https://doi.org/10.1016/j.immuni.2023.10.008. (C) Estrogen receptors (ERs) are widely distributed in the brain, with the highest density in the frontal cortex, cerebellum, brainstem, and subcortical areas. Adapted from Barth, C., Villringer, A., Sacher, J., 2015. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front. Neurosci. 9. https://doi.org/10.3389/fnins.2015.00037

Exogenous estrogens mimic certain functions of their endogenous counterparts, such as inhibiting the hormonal feedback loop, but they also exhibit differential effects, for instance due to binding affinity (Stanczyk et al 2013). Additionally, endogenous and exogenous estrogen action may depend on genetic variants of enzymes such as catechol-o-methyltransferase (COMT) or cytochrome P450 (CYP; Gravelsins et al., 2021; Chabi & Sleno, 2022). Therefore, it remains unclear whether subsequent changes in the brain stem from independent exogenous estrogen action, the suppression of endogenous estrogens, or the interaction between the two. While measuring endogenous estrogens is common practice, assessing exogenous hormones has been challenging but adequate methodology has recently become available, thus offering an exciting opportunity to shed light on this dynamic relationship (Stanczyk, 2024; Beltz and Moser, 2020).

In humans, neuroimaging has been a critical tool to elucidate connections between brain and behavior. Prior reviews have explored how ovarian hormones impact brain structure and function during the menstrual cycle (Beltz and Moser, 2020; Dubol et al., 2021), HC (Toffoletto et al., 2014; Brønnick et al., 2020; Montoya and Bos, 2017), MHT (Comasco et al., 2014), and GAHT (Kranz et al., 2020). Estrogen receptors (ERs) are widely distributed in the brain (cf. *Fig. 1C*), such as in the forebrain, brain stem, cerebellum, and subcortical regions, with a high receptor expression in hippocampus (HPC) and amygdala (Barth et al., 2015). Furthermore, estrogens can exhibit genomic as well as non-genomic actions (for more extensive reviews on the molecular basis, see Lokuge et al., 2010; Pickar et al., 2015; McEwen, 2001). Understanding estrogen's influence across brain networks, especially in central processing hubs like the HPC and amygdala, aids in grasping its wide-ranging effects (Peper et al., 2011).

Encompassing current available data on brain structure, function, and connectivity, this systematic review aims to evaluate the association between estrogen levels and brain networks. We explore human estrogen research on endogenous hormone fluctuations, and on exogenous estrogens, as used in HCs, MHT, and GAHT. Additionally, we aim to discern how different study designs, such as dense within-subject sampling studies and randomized-controlled trials (RCTs), contribute to this understanding. With this systematic review of neuroendocrine and neurocognitive research on estrogens, we seek to enhance the understanding of ovarian hormone fluctuations on the central nervous system throughout the lifespan, which is essential for advancing brain health for women, individuals with ovaries, and those administered estrogens.

2. Methods

This systematic review aligns with the Preferred Reporting Items for Systematic and Meta-Analyses (PRISMA) statement (Page et al., 2021, Moher et al., 2009) and was preregistered in Open Science Framework (OSF; https://osf.io/ztx78).

2.1 Inclusion and exclusion procedure

We developed a search strategy for the identification of human neuroimaging studies on the impact of estrogens on brain networks, in endogenous and exogenous estrogen conditions. Eligibility was assessed based on a three-stage procedure, detailed below. Electrophysiology studies were excluded. Patient studies were excluded, except for studies with a focus on healthy participants that also included clinical subgroups.

Identification. PubMed, ScienceDirect and Web of Science were searched on September, 14th, 2023. Five categories of keywords were used, including "brain" and "human" as mandatory. The additional three categories encompassed a variety of keywords related to the method, hormone and outcome of interest, using AND/OR statements according to Boolean syntax. For "method of interest", all neuroimaging-related words, including common methods and their abbreviations, were used (e.g., "neuroimaging", "fMRI", "PET", "tractography"). The category "hormone of interest" contained common types of endogenous and exogenous estrogens and their typical context of application (e.g., "estriol", "gender affirming", "contraception"). The category "outcome of interest" contained "pathway", "path", "network", and "connectivity". Keywords were defined as being included anywhere throughout the article, not necessarily limited to the title or abstract, to enhance search sensitivity (for all keyword combinations, and for explicit search query strings, see *Supplementary Material SM1*). From the retrieved studies, articles were removed *before screening* if they 1) were published before 2008, 2) were not written in English, or 3) were identified as records other than original research articles (such as reviews, editorial letters, book chapters, etc.), in a stepwise manner. Following the search, all articles were collated, and duplicates were removed. The following steps (screening, final selection) were performed by two independent reviewers (authors L.R. and K.H.), who subsequently compared their assessments and consulted two additional independent authors (E.M. and J.S.) in any case of ambiguity.

Screening. First, both reviewers screened the titles and abstracts, and assessed them against the inclusion criteria. Records were excluded if 1) the abstract did not include at least one keyword of each of the categories "hormone of interest", "outcome of interest" and "method of interest", or if the title or abstract revealed that 2) a non-human sample was used, or 3) none of the following neuroimaging methods was applied: structural or functional magnetic resonance imaging (sMRI or fMRI), positron emission tomography (PET), diffusion tensor imaging (DTI), diffusion weighted imaging (DWI), tractography, single photon emission computed tomography (SPECT), or optical imaging. Reasons for exclusion were recorded and discussed amongst all authors. Full texts of all remaining articles were retrieved.

Eligibility and inclusion. Both reviewers examined the full texts, and evaluated their eligibility according to the following criteria: 1) inclusion of an objective estrogen assessment, 2) independent examination of the estrogen association, 3) analysis of a brain network, and 4) focus on cognitive or affective domains. More specifically, studies needed to measure and account for estrogen levels statistically, enabling independent statements on associations with neuroimaging outcomes. As such, studies were excluded if they reported exogenous estrogen intake or endogenous estrogen levels for group assignment only (e.g., "pre- vs. perimenopause" according to serum E2, or "before vs. after gender-affirming hormone therapy") without an analysis of how current estrogen levels relate to the outcome measure. Regarding the brain network criterion, a brain network could be defined as structurally or functionally connected, such that studies were considered eligible if they comprised analyses of structural or functional connectivity measures, task- or resting-state-related activation, or gray matter (GM) and white matter (WM) architecture, in multiple areas. As such, studies which defined specific a-priori regions of interest (ROIs) were excluded if they focused on the activation of a single ROI only. Here, amygdala and HPC were specific exceptions, as they are key network processing hubs that are rich in estrogen receptors (cf. *Fig. 1C*). Thus, findings on estrogen-related plastic changes in these regions were considered particularly relevant. The last criterion excluded studies without a neurocognitive or -affective focus, such as articles on somatic or metabolic aspects, as these were considered beyond the scope of our review. In the final step, the reference lists of all selected studies and relevant reviews were screened for additional studies. A forward citation search of all selected articles was conducted. To ensure completeness and actuality of this systematic review, the systematic search procedure was repeated, filtering all three databases for articles published since the first search (date of second database search: September, 4th, 2024). *Fig. 2* delineates this procedure, from identification to inclusion.

2.2 Data extraction and synthesis

The following information was extracted from each of the articles, if available: *study* (authors, year of publication, title, journal), *sample characteristics* (sample size, subgroups, age mean/median/range, sex, gender if available), *main research question, network of interest* (regions of interests, ROI/ whole brain analysis), *assessments* (e.g., one or multiple time points, between-/within subjects comparisons, pre- vs. post-treatment,...), *estrogen measure* (type and time point), *estrogen measurement* (biological specimen material, type of assay, manufacturer, sensitivity/ intra- or inter-assay coefficient of variance), *neuroimaging measures* (acquisition details, statistical analyses), *behavioral measures* (task/ questionnaires), and *results* (main neuroimaging outcome, estrogen association with neuroimaging parameters, significant behavioral effects). The extracted information was collated into a table, categorized according to study design, for endogenous (Table 1) and exogenous (Table 2) estrogen studies separately.

2.3 Study quality assessment

Quality assessment tools developed by the National Heart, Lung, and Blood Institute (NHLBI 2021) were used for controlled interventions (14 items), observational/cross-sectional (14 items), and case-control studies (12 items). For case reports, the respective critical appraisal criteria (8 items) developed by the Joanna Briggs Institute (JBI; Moola et al., 2020) were used. Items of respective lists were scored with 0, 0.25, 0.5, 0.75, and 1 to account for small differences between the studies and to provide a fine-grained quality assessment. A quality assessment score was calculated by summing across items. Quality assessment was performed by one author.

3. Results

3.1 Literature screening and study selection

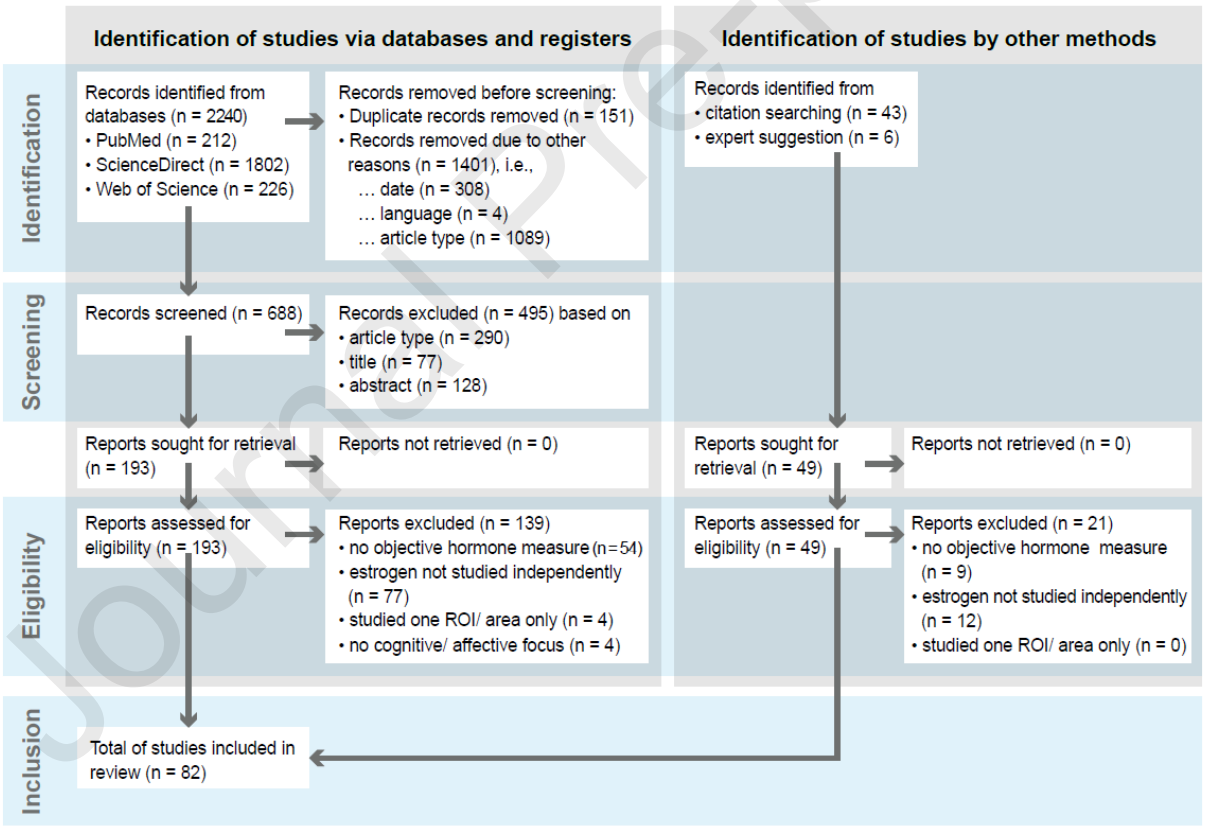

Fig. 2. PRISMA flowchart of study identification, screening, eligibility check, and final inclusion. Numbers are the sums of the results of both systematic procedures (first search September 2023, second search September 2024). Adapted from: Page, M.J., Moher, D., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al. 2021. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ n160. https://doi.org/10.1136/bmj.n160

Our initial search returned 2240 articles. After cross-checking and deletion of duplicates, 688 studies passed the initial selection. Following the screening process, our final selection included 82 studies. *Fig. 2* delineates the PRISMA flowchart. For detailed information on sample size and estrogen methodology per category of study design, see *Supplementary Material SM2*, and for a timeline of all inclusions, see *Supplementary Material SM3.*

3.2 Overview and characteristics of included studies

Of the included studies, 54 focused on endogenous estrogen conditions and 28 focused on conditions with exogenously administered estrogens. The category "endogenous" contained 29 menstrual cycle studies, 14 puberty studies, 1 pregnancy/ postpartum study, and 8 menopausal transition studies. In addition, 2 studies investigated the role of diurnal sex steroid fluctuations in a dense-sampled male participant (Grotzinger et al., 2024; Murata et al., 2024). Three menstrual cycle studies included a dense-sampled naturally cycling (NC) female with an additional follow-up after initiation of an HC, such that they are included in both results tables (*Table 1* and *Table 2*; Mueller et al., 2021; Pritschet et al., 2020; Taylor et al., 2020). All of the endogenous studies used structural and/or functional MRI to obtain their neuroimaging outcome variables, and assessed E2 levels as the estrogen measure. One menstrual cycle (Heller et al., 2024), and two menopause studies (Schroeder et al., 2024; Testo et al., 2024) determined E1 levels, additionally. In total, the endogenous estrogen category contained 2,494 participants with estrogen level assessments. Of the remaining exogenous studies, 9 studied users of HCs, 4 studied females during or after the menopausal transition with previous or experimental MHT use, and 5 studied GAHT in transgender individuals. As all of the included HC studies used oral contraceptives (OCs), we will from now on refer to them as OC studies, accordingly. Ten RCTs made up an additional category of studies, which manipulated E2 levels experimentally, with between- or within-subjects control conditions. Of those, eight were conducted in participants of reproductive age, and two in females during or after the menopausal transition. In two RCTs as well as in all but one MHT studies, PET or SPECT was used. All other studies employed MRI techniques. In all exogenous estrogen studies, E2 levels were assessed, except for one study on MHT (Brown et al., 2024) which only measured levels of the E2 metabolite estrone-1-glucuronide (E1G). One OC study additionally assessed EE levels (Brouillard et al., 2023). Together, the exogenous estrogen studies included 1,740 participants with estrogen level assessments.

3.3 Puberty

Of the 14 puberty studies, eight compared endogenous gonadal hormone fluctuations in male and female adolescents at one time point, in a cross-sectional design (Campbell et al., 2022; Cservenka et al., 2015; Herting et al., 2012; Ladouceur et al., 2019; Op de Macks et al., 2011; Peper et al., 2009; Poon et al., 2019; Stoica et al., 2019), of which two assessed E2 levels in females only (Ladouceur et al., 2019; Op de Macks et al., 2011). Three studies assessed adolescents of both sexes longitudinally (Herting et al., 2014; Ho et al., 2020; Nguyen et al., 2019), of which one assessed E2 levels in both sexes (Nguyen et al., 2019). The remaining three studies included female participants only, of which one added a longitudinal follow-up (Op de Macks et al., 2016), and two dichotomized participants into an early- and a late-puberty group, based on E2 levels (Goddings et al., 2012; Klapwijk et al., 2013). Of all studies, three studied emotion networks, four studied reward networks, three investigated the role of E2 in GM, four examined WM architecture, and three studies specifically focused on structural GM changes of the amygdala.

Emotion networks. During an emotion conflict task, occipital activation was positively associated with E2 levels in females, while activation in cerebellar and cingulate regions was negatively associated with E2 levels in males (Cservenka et al., 2015). In two studies sharing the same sample of female adolescents, social as compared to basic emotion processing was accompanied by a positive association of E2 levels with left anterior temporal cortex activation (Goddings et al., 2012), and with the coupling of the dorsomedial prefrontal cortex (PFC) and the temporo-parietal junction (Klapwijk et al., 2013).

Reward networks. In female adolescents, E2 levels were found to be positively correlated with reward-related activation in the dorsal striatum, dorsolateral PFC (dlPFC) and medial PFC, in a probabilistic decision-making task (Op de Macks et al., 2011), and with caudate activation during reward cue processing (Ladouceur et al., 2019). In addition, an interaction effect was reported between E2 levels and reward-related activation, such that female adolescents with higher E2 took fewer risks, accompanied by decreased nucleus accumbens (NAcc) activation (Op de Macks et al., 2016). For reward-related functional connectivity, E2 correlated positively with NAcc connectivity with putamen (Ladouceur et al., 2019), but negatively with NAcc connectivity with left dlPFC and bilateral anterior cingulate cortex (ACC; Poon et al., 2019).

Gray matter architecture. In female adolescents studied in a cross-sectional design, E2 was found to be negatively associated with GM density in prefrontal, parietal and middle temporal areas, but positively associated with GM density in middle frontal gyri (MFG), inferior temporal gyri (ITG), and middle occipital gyri (Peper et al., 2009). In addition, E2 levels exhibited negative associations with global GM volume. This finding on GM volume was in line with another cross-sectional study, in which higher E2 levels, in interaction with low executive function scores, were associated with reduced GM volume of the right posteromedial cortex, again, in a female sample (Stoica et al., 2019). However, in a longitudinal study with a 2-year follow-up, females with lower E2 levels showed more robust GM volume decreases over time, indicating a positive relationship (Herting et al., 2014).

White matter architecture. In addition to the GM changes, the two-year longitudinal study of Herting et al. (2014) found female adolescents with lower E2 levels to show larger WM volume increases over time. A modulating role of E2 also on WM microstructural integrity was indicated by Stoica et al. (2019), who found higher E2 levels to be associated with lower fractional anisotropy (FA) in the right inferior fronto-occipital fasciculus. In another cross-sectional study of both sexes, higher E2 was associated with FA in a sex-dependent manner, i.e., with higher FA in the thalamus and superior frontal gyrus (SFG) in males, and with lower FA in the right angular gyrus and superior longitudinal fasciculus in females (Herting et al., 2012). Conflictingly, one study found no significant association between female adolescents' E2 levels and longitudinal WM diffusion changes in any of the ten WM tracts examined (Ho et al., 2020).

Amygdala. Findings on associations between longitudinal changes in E2 levels and amygdalar volume were conflicting. Of the three longitudinal studies, one reported decreases in right amygdalar volume in female adolescents with both low E2 and low testosterone levels, and a positive association between high E2 levels and right amygdalar volume (Herting et al., 2014). The other two, however, found no direct association between E2 levels and amygdalar volume (Campbell et al., 2022; Nguyen et al., 2019). While the first of these two studies found no interaction effect between E2 and age (Campbell et al., 2022), the second revealed that E2 had an indirect influence on amygdalar-cortical structural covariance. Specifically, it mitigated age-related changes in the association of amygdalar volume and cortical thickness in the left pre-supplementary motor area, posterior cingulate cortex, and retrosplenial cortex (Nguyen et al., 2019).

3.4 Reproductive years

A total of 49 studies investigated estrogen associations in participants of reproductive age. Of the 29 menstrual cycle studies, 19 assessed endogenous hormone fluctuations in multiple NC females, in a within-subjects design (Alonso-Alonso et al., 2011; Andreano & Cahill, 2010; Bayer et al., 2014; Dan et al., 2019; Hagemann et al., 2011; Hidalgo-Lopez et al., 2020; Hidalgo-Lopez et al., 2021; Hidalgo-Lopez & Pletzer, 2021; Hjelmervik et al., 2014; Jacobs et al., 2015; Joseph et al., 2012; Konrad et al., 2008; Lisofsky et al., 2015; Pletzer et al., 2018; Pletzer et al., 2019; Rizor et al., 2024; Syan et al., 2017; Weis et al., 2008; Zsido et al., 2023), while 3 studies compared cycle phases in a between-subjects design, assessing each female only once (Hwang et al., 2015; Wang et al., 2020a; Wang et al., 2020b). Of these, five studies included a subgroup of male participants, without E2 assessments (Dan et al., 2019; Hagemann et al., 2011; Hjelmervik et al., 2014; Hwang et al., 2015; Weis et al., 2008). Seven studies (Arélin et al., 2015; Barth et al., 2016; Fitzgerald et al., 2020; Heller et al., 2024; Mueller et al., 2021; Pritschet et al., 2021; Taylor et al., 2020) used a dense-sampling approach with one participant, comprising of 25 to 32 scans (mean: 29.6 scans) across one to two menstrual cycles (mean: 40 days). Parallel to the female participant scanned on 30 consecutive days (Fitzgerald et al., 2020; Mueller et al., 2021; Pritschet et al., 2020; Taylor et al., 2020), two studies analyzed data of a dense-sampled male participant (N=30 scans; Grotzinger et al., 2024; Murata et al., 2024). A similar dense-sampling approach was also used in the included pregnancy and postpartum paper, in which one female underwent an MRI session at 26 time points, from preconception to nine months postpartum (Pritschet et al., 2024). Of the OC studies, six assessed subgroups of OC-users and NC females at one time point (Brouillard et al., 2023; Peper et al., 2013; Petersen et al., 2014; Petersen et al., 2015; Sharma et al., 2020; Sharma et al., 2021), while three assessed each group repeatedly, i.e., multiple cycle and OC pill phases (De Bondt et al., 2013a; De Bondt et al., 2013b; De Bondt et al., 2015). Of the eight RCTs conducted in premenopausal females, three used an E2 administration (Bayer et al., 2018; Conjaerts et al., 2023; Joue et al., 2022), two applied a combined OC (Hidalgo-Lopez et al., 2023; Wen et al., 2023), and three suppressed gonadal hormone production with a GnRH antagonist (GnRHa; Borgstedt et al., 2022; Fisher et al., 2017; Wei et al., 2021), of which two included male participants as well (Conjaerts et al., 2022; Joue et al., 2022). Of all studies conducted in participants during the reproductive years, eight investigated emotion networks, four studied reward networks, five assessed memory networks, and three studied verbal or semantic processing. Fourteen studies explored resting state networks (RSNs), while eight examined GM, five assessed WM architecture, and twelve studies set a specific focus on HPC, or amygdala.

Emotion networks. A menstrual cycle study of NC females found a negative association between E2 levels and hypothalamus activation during negative and neutral images, as well as between E2 and overall amygdala activation, across menstrual cycle phases. Changes in HPC or amygdala activation from the follicular to the luteal phase, however, were not related to E2 (Andreano & Cahill, 2010), which was in line with another menstrual cycle study (Bayer et al., 2014). In contrast, a menstrual cycle study on task-related activation during the viewing of high or low arousing pictures found a blunted response to arousal in the right amygdala, hypothalamus, and HPC, under high as compared to low E2 conditions of the follicular phase, which remained after accounting for P4 levels. In a subsample of females with major depressive disorder, this pattern was absent (Jacobs et al., 2015). This was corroborated by another emotion perception study with conditions of amusement and sadness. Here, E2 was positively correlated with prefrontal-parietal connectivity during sadness in the mid-follicular phase, but negatively correlated with putamen-ACC connectivity and amygdalar connectivity during amusement in the late luteal phase (Dan et al., 2019). In two RCTs, mood regulation changes were investigated after chronic E2 suppression via GnRHa administration using repeated injections (3.6 mg goserelin; Wei et al., 2021), or an implant (3.75 mg leuprorelin; Fisher et al., 2017). The first RCT, conducted in healthy females and females with premenstrual dysphoric disorder (PMDD), found greater resting regional cerebral blood flow (rCBF) in the orbitofrontal cortex, medial PFC, subgenual cingulate cortex, ITG and superior temporal gyri (STG) after E2 add-back (via 0.1 mg transdermal E2 daily), as compared to P4 add-back (via 200 mg vaginal P4 twice per day). In PMDD patients, both E2 and P4 add-back led to an rCBF decrease in the cingulate cortex, which was absent in healthy participants (Wei et al., 2021). The second RCT, conducted in healthy females only, reported that E2 level decreases in response to GnRHa administration (3.6 mg goserelin) were accompanied by increases in depressive symptoms, which were not mediated by functional connectivity changes (Fisher et al., 2017).

Two studies investigated E2-modulated changes in networks activated during fear conditioning and extinction. In NC females, E2 levels were associated with activation in the amygdala, insula, cingulate cortex, HPC, and hypothalamus, dependent on the conditioning phase. Activation in these areas was most elevated in females with high E2 levels (Hwang et al., 2015). In an RCT with administration of a single dose of E2 (2 mg) after fear conditioning and prior to fear extinction, E2 levels were positively associated with activation in precuneus and ventromedial PFC, as well as negatively correlated with task-based functional connectivities in the default mode network (DMN) and somatomotor network (SMN), during early and late extinction learning, in both NC and OC-using females (Wen et al., 2021). However, groups differed in connectivity patterns, such that OC users showed stronger positive associations of E2 with resting state functional connectivity in DMN and SMN, 10 minutes after extinction learning, as well as stronger negative associations of E2 with task-based functional connectivity during extinction retention on the next day (Wen et al., 2021).

Reward networks. In an RCT with administration of two doses of E2 valerate (6 mg in males, 4 mg in females) prior to a reinforcement learning task, E2 levels were positively associated with activation in areas of the mesocorticolimbic pathway in response to reward prediction errors in both sexes (Joue et al., 2022). Another between-subjects menstrual cycle study assessed frontostriatal connectivity in NC females, independent of a reward task (Wang et al., 2020a). Here, the correlation between E2 levels and connectivity of dlPFC and substantia nigra was positive in females in the mid-luteal phase, but negative in the late follicular phase, in parallel with changes in measures of behavioral inhibition (Wang et al., 2020a). In a study of NC females undergoing task-based fMRI with a visual food processing paradigm, the E2 increase from the early to the late follicular phase was inversely correlated with activation in the fusiform gyrus, in fasting but not in fed participants (Alonso-Alonso et al., 2011). Another study involving males and female OC users and non-users found no association between E2 levels and either frontostriatal WM integrity or performance in a delay discounting task (Peper et al., 2013).

Memory networks. Two studies in NC females used a verbal N-back working memory task, of which one found a positive correlation between E2 levels and activation in the left insula and precentral gyrus, in the late luteal, as compared to the early follicular phase (Joseph et al., 2012), while the other study found no significant associations with activation in any of the frontostriatal ROIs (Hidalgo-Lopez and Pletzer, 2021). Three studies explored the role of E2 levels in brain activation during memory tasks with emotional stimuli. In a study of OC users and non-users performing an emotional picture N-back task, E2 exhibited positive associations with activation in the right SFG, superior parietal lobule, precentral gyrus, and left precuneus for positive stimuli, and with activation in the left SFG, left ACC, and right postcentral gyrus for negative stimuli, across groups (Sharma et al., 2021). However, in another study with a similar sample and task, no associations were found between E2 levels and brain activation, for any of the stimuli or within any of the groups (Sharma et al., 2020). An RCT in premenopausal females (18-35 years) assessed the effects of E2 valerate administration (0-12 mg) on activation and functional connectivity during an emotional encoding task (Bayer et al., 2018). Here, the increase in E2 levels was found to be negatively correlated with right precuneus activation, and positively correlated with HPC activation. Furthermore, E2 exhibited a negative association with precuneus-brainstem functional connectivity (Bayer et al., 2018).

Verbal and semantic processing. Three menstrual cycle studies utilized verbal non-memory tasks. During synonym generation, a positive association between E2 levels and left PFC activation emerged, which was strongest in the luteal phase (Konrad et al., 2008). During a word-matching task, E2 levels were negatively correlated with task-related interhemispheric inhibition, resulting in reduced functional cerebral asymmetries during the follicular phase (Weis et al., 2008). Lastly, during a verbal fluency task, an observed reduction in HPC activation from the pre-ovulatory to the luteal phase was correlated with the interaction of E2 and P4, but not with E2 alone (Pletzer et al., 2019).

Resting state networks. Several studies of resting state functional connectivity reported differences between sexes (Hjelmervik et al., 2014), between cycle phases (Arélin et al., 2015; Petersen et al., 2014; Pritschet et al., 2020), between hormonal stages of OC use (Petersen et al., 2014), as well as after placebo-controlled E2 treatment (Conjaerts et al., 2023; Hidalgo-Lopez et al., 2023). However, other studies reported relative stability of RSNs across the menstrual cycle (De Bondt et al., 2015; Hjelmervik et al., 2014; Syan et al., 2017), and during hormonal stages of OC use (De Bondt et al., 2015). Although some studies found no significant association between E2 levels and functional connectivity in NC females (Arélin et al., 2015; Hjelmervik et al., 2014), or in OC users (Petersen et al., 2014), other studies did. For example, Wang et al. (2020b) identified positive associations between E2 levels and functional connectivity of the medial PFC and intraparietal lobule (Wang et al., 2020b). In another study, E2 correlated positively with functional connectivity in the left amygdala, right motor cortex, and bilateral somatosensory cortices, in the late luteal phase (Syan et al., 2017). In these two studies, E2 also exhibited negative associations with functional connectivity between ITG and thalamus in the DMN, across cycle phases (Wang et al., 2020b), as well as with functional connectivity of the bilateral entorhinal cortices, in the follicular phase (Syan et al., 2017). Furthermore, the strength (Wang et al., 2020b) and number of functional connections (Syan et al., 2017) were found to be increased in high-E2 as compared to low-E2 phases in the menstrual cycle. Findings on E2-modulated RSN changes were further supported by two RCTs. The first found decreased functional connectivity of the left amygdala with areas like the bilateral lingual gyrus in males, as well as increased functional connectivity between right HPC and left ACC in females, after administration of an E2 gel (2 mg; Conjaerts et al., 2023). The second RCT assessed the effects of one treatment cycle of a combined OC (30 mg EE and 0.15 mg levonorgestrel) and reported within-network connectivity increases in the DMN, as well as decreases in salience network (SN) and dorsal attention network (DAN). In addition, E2 was associated with increases in effective connectivity between parts of the DMN, SN, and executive control network (ECN), which were positively associated with an observed OC-induced mood deterioration (Hidalgo-Lopez et al., 2023). In another menstrual cycle study by the same authors, peri-ovulatory E2 levels were found to be associated with a right-to-left lateralization shift of network connectivity, with increased effective connectivity between the left insula and ECN, and a decoupling of the DMN into anterior and posterior parts (Hidalgo-Lopez et al., 2021). Similar resting state data of NC females was also used in a study employing a multimodal analysis approach, which revealed distinct outcomes for different analyses. Here, group independent component analysis (ICA) revealed decreased DMN intrinsic connectivity in the luteal phase, while seed-based functional connectivity analyses resulted in increased connectivity between the putamen and dorsomedial thalamus. Notably, both findings correlated positively with E2 levels (Hidalgo-Lopez et al., 2020). This is further corroborated by a dense-sampling single-subject study by Pritschet et al. (2020), in which rising E2 levels were accompanied with an overall increased functional coupling of eight RSNs, mainly driven by ovulation. Here, E2 levels were more strongly associated with the within-network rather than the between-network integration, and preceded efficiency of the DMN and DAN (Pritschet et al., 2020). Parallel data of a dense-sampled male participant revealed comparable associations between E2 levels and functional coherence in multiple RSNs, with the strongest association emerging for the DAN (Grotzinger et al., 2024). Two studies utilized the same female resting state data set as Pritschet et al. (2020). The first focused on cerebellar networks and revealed a negative association between E2 levels and within-network integration in different cerebral networks with cerebellar hubs (Fitzgerald et al., 2020). The second used dynamic community detection methods and revealed cycle-related transient reorganizational changes along the menstrual cycle, as well as a correlation between E2 levels and network flexibility in a variety of RSNs (Mueller et al., 2021). In a 1-year follow-up of the same female participant who was now using OC, the modulating role of E2 in within-network integration was replicated (Pritschet et al., 2020), while the large-scale reorganization was absent (Mueller et al., 2021). De Bondt et al. (2015) investigated functional connectivity changes in NC females during the follicular and luteal phase, and in OC users during the active and inactive pill phase. Here, E2 was positively associated with DMN functional connectivity in the inferior parietal lobule, in the luteal phase, as well as positively correlated with precuneus and MFG functional connectivity of the DAN, across conditions in both groups (De Bondt et al., 2015).

Gray matter architecture. While three studies found no associations between E2 and GM volume or cortical thickness across the menstrual cycle (Hagemann et al., 2011; Pletzer et al., 2018; Rizor et al., 2024), apart from the HPC, one study reported positive correlations between E2 and GM volume of the left parahippocampal cortex

(PHC), MFG, and cerebellum (Lisofsky et al., 2015). In a dense-sampled male participant, E2 was positively correlated with total brain volume, total GM volume, and cortical thickness, with all three measures showing significant decreases from morning to evening (Murata et al., 2024). Similar decreases were found in a pregnant female, longitudinally, in which E2 levels were associated with significant decreases in cortical and subcortical GM volume, cortical thickness, and total brain volume, across gestation, with only partial recovery during postpartum (Pritschet et al., 2024). In addition, two studies compared NC and OC-using females and reported OC-related cortical thinning in parts of the DMN and SN (Petersen et al., 2015), as well as volumetric increases in clusters of the frontal, fusiform and cingulate gyri (De Bondt et al., 2013a). However, the only significant association with E2 was a negative correlation with ACC thickness, observed in NC females during the luteal phase (De Bondt et al., 2013a).

White matter architecture. One study found no WM volume changes, neither across the menstrual cycle, nor between cycle-matched assessments in males (Herting et al., 2011). This was supported by the finding that WM volume, other than GM volume, was rather stable in the dense-sampled male participant (Murata et al., 2024). This stability was absent in the dense-sampled pregnant female, which, across gestation, exhibited significant WM volume increases, which were positively correlated with E2 levels (Pritschet et al., 2024). For WM diffusion parameters, an OC study reported greater mean diffusivity (MD) in the fornix, in OC users as compared to non-users, which was negatively correlated with E2 levels across groups (De Bondt et al., 2013b). A study on NC females also reported FA changes across the cycle, which, however, were uncorrelated with E2 (Rizor et al., 2024).

Hippocampus. Two RCTs reported a positive association between E2 levels and HPC connectivity, such that E2 suppression via a GnRHa implant decreased HPC-cingulate functional connectivity in a female sample (Fisher et al., 2017), while administration of E2 valerate increased HPC functional connectivity in female, but not male participants (Conjaerts et al., 2023). In contrast, endogenous E2 levels were not correlated with HPC functional connectivity in a dense-sampled female, across five consecutive weeks (Arélin et al., 2015). However, in the same female, E2 levels were positively correlated with FA in the HPC, which peaked before ovulation (Barth et al., 2016). This was corroborated by another menstrual cycle study conducted at four time points, which found decreases in hippocampal MD paralleling rising E2 levels (Lisofsky et al., 2015). This decrease was strongly correlated with an increase in GM volume of the bilateral HPC (Lisofsky et al., 2015). In three studies, such a menstrual cycle-related increase in total HPC volume was found to be positively correlated with E2 (Heller et al., 2024; Pletzer et al., 2018; Zsido et al., 2023). One study reported a similar positive association for E1 levels (Heller et al., 2024). In the latter, both estrogens were associated with decreased positive and increased negative affect, with this association being mediated by HPC volume increases only for positive affect (Heller et al., 2024). Contrary to the aforementioned findings, an RCT in which estrogen secretion was suppressed via a GnRHa implant (3.6 mg goserelin), only a non-significant decrease in HPC volume was observed (Borgsted et al., 2022). One study reported the opposite correlation pattern, showing that E2 levels of OC non-users were inversely correlated with bilateral HPC volume, compared to both past and current users (Brouillard et al., 2023).

In addition to total HPC volume, several studies investigated volumetric changes of different subfields of the HPC and mediotemporal lobe (MTL). Here, different subfields were found to exhibit differential association patterns with ovarian hormones. More specifically, PHC volume was found to be positively correlated with E2 levels (Lisofsky et al., 2015; Zsido et al., 2023), while perirhinal cortex and subiculum volume correlated with P4, and the interactions of both hormones correlated with cornu ammonis 1 (CA1) volume (Zsido et al., 2023). In the female that was densely sampled during pregnancy and postpartum, E2 levels were positively associated with non-linear decreases in CA1 and CA2/3 volumes, and linear increases in PHC volume, while total HPC volume remained rather stable (Pritschet et al., 2024). The complexity of this subfield-dependent plasticity of the MTL was further corroborated by an RCT in which E2 levels after E2 administration exhibited a linear relationship with activation in a right posterior HPC cluster, but a U-shaped relationship in a medial cluster of the left posterior HPC (Bayer et al., 2018).

One study assessed HPC activation during a spatial navigation task and found that E2 alone, as well as in interaction with P4, was associated with increased HPC activation in the early follicular phase. Additionally, the interaction of E2 and P4, as well as P4 alone, was associated with increased caudate and dlPFC activation, accompanied by decreased HPC activation in the luteal phase (Pletzer et al., 2019). This was interpreted as a boost of HPC activation by E2, which opposes a P4-driven down-regulation of the HPC via a boost of frontostriatal activation (Pletzer et al., 2019).

Amygdala. Two RCTs assessed amygdalar functional connectivity after exogenous E2 manipulation. The first found that administration of a single E2 dose led to decreases in amygdalar resting state functional connectivity

in males, but not females (Conjaerts et al., 2023). This negative association was supported by the second RCT in a female sample, which reported an increase in functional connectivity of amygdala and right temporal cortex, subsequent to decreased E2 secretion resulting from a GnRHa implant (Fisher et al., 2017). This is in contrast to the menstrual cycle study conducted by Syan et al. (2017) reported earlier, in which E2 levels were positively correlated with amygdalar resting state functional connectivity during the luteal phase.

3.5 Menopausal transition

A total of 14 studies assessed associations between estrogens and brain parameters in females during or after the menopausal transition. All eight endogenous estrogen studies assessed participants only once. Three studies compared females before, during and after the menopausal transition with (Jacobs et al., 2016; Jacobs et al., 2017), or without (Berent-Spillson et al., 2012) a male subgroup. Two studies compared premenopausal females with females during (Liu et al., 2021), or after the menopausal transition (Ballard et al., 2023). Three studies analyzed only one group, either during (Zsido et al., 2019) or after the menopausal transition (Schroeder et al., 2024; Testo et al., 2024). Of the six exogenous estrogen studies, four assessed females after the menopausal transition, who were either on a prior estrogenic MHT (Brown et al., 2023; Compton et al., 2008), or were assessed before and after an experimental graded E2 infusion (Ottowitz et al., 2008a; Ottowitz et al., 2008b). Two studies administered E2 during (Thomas et al., 2014), or after (Berent-Spillson et al., 2015) the menopausal transition, in a randomized controlled manner. Eight of the studies focused on memory networks, one investigated the reward circuitry, and three studied RSNs. In addition, there was one study each on HPC and amygdala connectivity.

Memory networks. One study reported a positive correlation between E2 and visual memory retention, across groups of menopausal transition, but without an effect of menopausal status (Berent-Spillson et al., 2012). An RCT in females after the menopausal transition reported no changes in visual memory-related activation subsequent to a 90 day E2 intervention (1 mg oral E2 daily; Berent-Spillson et al., 2015). While these two studies indicate a relative independence of visual working memory from E2 levels, for verbal long-term memory, their results differed. Berent-Spillson et al. (2012) reported negative correlations between E2 levels and task-related activation in the left PHC, temporal pole, inferior frontal cortex, and parietal cortex, and positive correlations with verbal fluency, across the menopausal transition. Furthermore, the RCT of Berent-Spillson et al. (2015) found E2-induced increases in left PFC activation and decreases in HPC activation, without effects on memory performance. This finding was corroborated by a study assessing verbal N-back working memory, which revealed a decrease in task-related HPC deactivation, alongside with an increase in dlPFC activation and dlPFC-HPC connectivity, as a function of menopausal status (Jacobs et al., 2017). This decrease in HPC deactivation was strongly associated with the decline in E2 levels observed during the menopausal transition (Jacobs et al., 2017). In a similar study on verbal long-term memory, the menopausal E2 decline was associated with encoding-related increases in functional connectivity between the bilateral HPC, while E2 was positively correlated with memory performance (Jacobs et al., 2016). A similar positive association between verbal long-term memory performance and E2 levels was also found in two other studies (Zsido et al., 2019; Schroeder et al., 2024). The first used a multimodal structural network approach and found positive associations with memory network covariance in females across the lifespan, with an additional association between low E2 levels and low memory performance, in a female midlife subsample (aged 35-55 years; Zsido et al., 2019). The second study involved postmenopausal females only, and found positive associations between E2 levels and encoding-related activation in the left SFG and inferior frontal gyrus (IFG), and the bilateral ITG, as well as negative associations between E2 levels and recognition-related activation in the right SFG (Schroeder et al., 2024). Furthermore, this study assessed the role of E1, and found positive associations with encoding-related activation in the left insula and precentral gyrus, right SFG, and the bilateral STG and postcentral gyri (Schroeder et al., 2024). In a study employing a task-based fMRI sequence with an associative memory task, postmenopausal females, with or without estrogenic MHT use after bilateral ovarian removal, as well as premenopausal females and females with spontaneous menopause were assessed. Here, urinary levels of an estradiol metabolite (estrone-3-glucuronide; E1G) were found to be correlated with activation in the right posterior lateral HPC and memory performance, across groups (Brown et al., 2024). In contrast to the findings outlined above, a SPECT study in females after the menopausal transition, with or without long-term estrogenic MHT use, found no correlation between E2 levels and neither hippocampal serotonin receptor availability nor verbal or general memory performance (Compton et al., 2008).

Reward networks. In an RCT, females during the menopausal transition (mean 8.7 months after last menses) were administered a sequential E2 and P4 intervention (2 mg 17β-estradiol and 100 mg P4 for 21 days) to study activation during a monetary reward task. Here, E2 levels were positively correlated with reward-related activation in the lateral and ventromedial PFC, bilateral amygdala-HPC complex, right caudate, and left ventral putamen, as well as negatively correlated with reward anticipation response time (Thomas et al., 2014).

Resting state networks. A cross-sectional study assessed resting state functional connectivity of E2-sensitive areas in a postmenopausal sample. Here, E2 levels were positively associated with functional connectivity between the anterior and posterior divisions of the parahippocampal gyrus, as well as between anterior parahippocampal gyrus and precuneus (Testo et al., 2024). Another study supported changes during resting state fMRI before females enter postmenopause, as it found increases in regional homogeneity in the left MFG and middle cingulate gyrus in females during the menopausal transition, which were negatively correlated with E2 levels (Liu et al., 2021). In a cross-sectional study on cerebellar RSNs with respect to hormone-sleep interactions during different reproductive stages, higher E2 levels and sleep quantity predicted lower Crus-I-to-dlPFC connectivity, across groups, whereby late postmenopausal stage, as compared to pre- or early postmenopausal stage, was of additional predictive value (Ballard et al, 2023). Additionally, higher E2 levels were correlated with functional connectivity between cerebellar lobule V and M1, and predicted higher cognitive and motor performance (Ballard et al, 2023).

Hippocampus. A combined FDG-PET and fMRI study in females after the menopausal transition assessed changes in HPC connectivity after a graded E2 infusion over 24 hours (0.1 ug/kg/hr for the first, 0.135 ug/kg/hr for second 12 hours). Here, the greatest increase in prefrontal cerebral glucose consumption was observed in the right SFG and MFG, both of which varied significantly with regional cerebral glucose consumption of the right HPC, indicating a potential stimulatory effect on effective connectivity within the prefrontal-HPC circuitry (Ottowitz et al., 2008b).

Amygdala. Ottowitz et al. (2008a) conducted an additional analysis of amygdalar-cortical network connectivity after the graded E2-infusion, using the same data set as described for hippocampal effective connectivity. Here, an additional significant covariation of regional cerebral glucose consumption was found for right amygdala and several temporal cortex regions, indicating similar stimulatory effects of E2 on amygdalar regions (Ottowitz et al., 2008a).

3.6 Transgender individuals

Of the five studies conducted in transgender individuals, three compared transgender women and men with cisgender individuals in a longitudinal design (Kranz et al., 2017; Nota et al., 2017; Spies et al., 2016). One study compared only transgender men and cisgender women (Soleman et al., 2016) and one study investigated transgender women after GAHT washout and after GAHT reintroduction (Schneider et al., 2019). Of the transgender studies, one investigated networks of emotion networks, three investigated RSNs, and one focused on WM diffusion parameters.

Emotion networks. In a study that explored neural activation during the viewing of emotional pictures in transgender men and cisgender women, E2 levels were not correlated with activation, neither for brain regions with nor without observed group differences (Soleman et al., 2016).

Resting state networks. None of the transgender studies reported a significant association between functional connectivity and E2 levels (Nota et al., 2017; Schneider et al., 2019; Spies et al., 2016). However, GAHT-induced changes in functional connectivity were found in transgender women, with increases in thalamic connectivity and decoupling of the subcallosal and medial frontal cortex, after 60 days (Schneider et al., 2019), as well as with increases in supramarginal gyrus connectivity strength, after 4 months (Spies et al., 2016).

White matter architecture. One study collected DWI data at baseline, as well as at 4 weeks and at 4 months after introduction of GAHT. The GAHT-induced decrease in E2 levels observed in transgender men was positively correlated with MD in the right corticospinal tract and middle cerebellar peduncle, the right cerebral peduncle, fornix, internal capsule, superior cerebellar peduncle, and the sagittal striatum, after 4 weeks of GAHT (Kranz et al., 2017). After 4 months of GAHT, these associations were absent, and E2 was negatively associated with FA in multiple WM structures (e.g., corpus callosum), instead. Additionally, natural E2 fluctuations were found to be negatively correlated with FA changes in ciswomen (Kranz et al., 2017).

4. Discussion

This systematic review collected information from 2008 to 2024 including 82 peer-reviewed studies that assess estrogen associations with human brain networks. Overall, the collected evidence supports a significant role of estrogens in shaping brain network architecture in both endogenous and exogenous estrogen conditions, as evidenced by structural and functional neuroimaging. Studies on adolescence (14 articles) mainly used task-based fMRI approaches and found endogenous E2 levels to be positively correlated with activation in occipital,

temporal, and prefrontal regions during emotion processing (Cservenka et al., 2015; Goddings et al., 2012; Klapwijk et al., 2013), as well as to have a modulating role on prefrontal-striatal activation and connectivity during reward processing (e.g., Ladouceur et al., 2019; Op de Macks et al., 2016). In addition, findings indicated an association of E2 levels with WM and GM development, though findings on longitudinal associations with amygdalar volume were conflicting (Campbell et al., 2022; Nguyen et al., 2019). The majority of studies (49 articles) focused on the reproductive years. Here, dense-sampling single-subject studies indicated E2 levels to be associated with complex reorganizations of network connectivity along the menstrual cycle (Arélin et al., 2015; Fitzgerald et al., 2020; Pritschet et al., 2020; Mueller et al., 2021) or along stages of OC use (Pritschet et al., 2020; Mueller et al., 2021), as well as of GM and WM architecture along the menstrual cycle (Barth et al., 2016; Heller et al., 2024; Taylor et al., 2020), across gestation and postpartum (Pritschet et al., 2024), and along diurnal hormone fluctuations in males (Grotzinger et al., 2024; Murata et al., 2024). Furthermore, the summarized findings showed that the HPC (e.g., Heller et al., 2024; Lisofsky et al., 2015; Zsido et al., 2023) and the amygdala (e.g., Conjaerts et al., 2023; Fisher et al., 2017) are particularly sensitive to E2 fluctuations. Studies conducted around the menopausal transition (14 articles) mainly reported a modulating role of E2 on verbal episodic and working memory (e.g., Berent-Spillson et al., 2012; Jacobs et al., 2017; Schroeder et al., 2024), while visual working memory was largely unaffected (Berent-Spillson et al., 2015; Berent-Spillson et al., 2012). Here, menopause-related E2 decreases were linked to decreased task-related HPC deactivation, as well as to increased dlPFC activation and HPC-PFC connectivity (Jacobs et al., 2017), while administration of E2 was related to increases in PFC-HPC connectivity (Ottowitz et al., 2008b). Lastly, the studies conducted in transgender individuals (5 articles), which mostly utilized observational study designs with participants on a diverse range of GAHT agents, observed complex GAHT-induced reorganizations in RSNs, which were largely independent of E2 levels (Nota et al., 2017; Spies et al., 2016; Schneider et al., 2019).

4.1 Exploring complexity of estrogen action: Insights from the hippocampus

The HPC, with its widespread cortical and subcortical connections implicated in numerous functional domains beyond memory processing, exemplifies the complexity of research on estrogen action in the human brain *in vivo*. The studies reviewed here demonstrate a profound plasticity of the HPC along the menstrual cycle (Barth et al., 2016; Heller et al., 2024; Lisofsky et al., 2015; Pletzer et al., 2018; Taylor et al., 2020; Zsido et al., 2023). Some studies reported positive associations between E2 levels and overall HPC volume (Heller et al., 2024; Lisofsky et al., 2015; Pletzer et al., 2018; Zsido et al., 2023), and with dynamic changes in HPC microstructural integrity (Barth et al., 2016; Lisofsky et al., 2015). These results are corroborated by a large body of animal research on E2-modulated structural and behavioral changes along the estrous cycle (Kundakovic and Rocks, 2022; Rocks et al., 2022; Duarte-Guterman et al., 2015; Jaric et al., 2019; cf. *Fig. 1C*). However, in an RCT reviewed here, gonadal suppression was not significantly associated with hippocampal volume decreases (Borgsted et al., 2022). This observation might be linked to the discovery that hippocampal subfields and adjacent MTL regions are differently affected. Notably, a different RCT revealed a U-shaped pattern between E2 levels and volumetric changes of certain hippocampal subfields, rather than linear relations, suggesting that E2 might exert stimulating effects only within physiological ranges (Bayer et al., 2018). This is in line with rodent studies that indicate beneficial effects of estrogen treatments on mood regulation or memory performance are dependent on sex, dosage, and site (Barker & Galea, 2008; Sinopoli et al., 2006; for review of estrogenic actions on HPC, see Sheppard et al., 2019; Frick et al., 2018; Hillerer et al., 2019). Here, rodent studies can serve as models that distinguish the underlying mechanisms of endogenous and exogenous estrogens based on the ability to precisely determine and select ovarian status, manipulate E2 dose, as well as route and timing of administration (Lacasse et al., 2022). Combined with rodent studies, the findings reviewed here do therefore have important clinical implications, especially under conditions in which endogenous E2 levels decrease, such as during the menopausal transition, when E2 administration might be considered in order to improve mood (Wharton et al., 2012). Here, research on the timing of MHT onset has shown that MHT might exert neuroprotective effects when initiated early, but can lead to adverse cognitive and cardiovascular outcomes when initiated later in the menopausal transition (Rocca et al., 2011; Manson & Kaunitz, 2016). Despite re-analysis and contextualization of the results of the Women's Health Initiative study by Manson et al. (2020), negative perceptions of MHT continue to influence public opinions and prescribing practices to women and individuals who had or have ovaries (Langer et al., 2020). This line of work calls for nuanced consideration, especially in clinical translation. In summary, most studies report rapid changes in the structure and connectivity of widespread brain networks, associated with E2 levels. The accumulating evidence (cf. *Fig. 2*) highlights the significance of advocating for a sex-specific perspective in neuropsychiatry, given the prevalent sex differences observed in many diseases. As our comprehension for estrogen action in the human brain *in vivo* deepens, the field emerges as a promising area of research for both the healthy and disrupted aspects of affect and cognition, serving as a potential bridge to understanding the neurobiology of many psychiatric conditions.

4.2 Limitations: study heterogeneity and estrogen focus

We address two noteworthy limitations of this review: the heterogeneity of included studies, as well as the sole focus on estrogen. First, the heterogeneity of study designs, outcome measures, analysis methods, and sample sizes made comparisons across studies challenging. We found valuable insights on endogenous estrogen action in proof-of-concept dense-sampling studies of single participants (based on 3 individuals), which offer a close approximation to subtle menstrual cycle changes, but are naturally limited in sample size (Arélin et al., 2015; Barth et al., 2016; Fitzgerald et al., 2020; Heller et al., 2024; Mueller et al., 2021; Pritschet et al., 2020; Taylor et al., 2021). Cross-sectional studies in larger samples, such as currently applied in some of the reviewed puberty (Campbell et al., 2022; Nguyen et al., 2019) and transgender studies (Kranz et al., 2017; Spies et al., 2016), can improve generalizability, albeit often with limited individual phenotyping. Moving forward, research could be strengthened by incorporating precision neuroimaging studies that emphasize a personalized medicine approach, tailored to specific research questions. Second, this review focused on estrogen action, although E2 acts in synergy with other sex hormones, as demonstrated by studies reporting interacting effects of E2 with P4 (e.g., Sharma et al., 2021; Zsido et al., 2023), or testosterone (e.g., Goddings et al., 2012; Herting et al., 2014). Acknowledging this complexity, we report significant P4 and testosterone findings of included studies in *Table 1* and *Table 2*. Due to our exclusion criteria, studies solely exploring synergistic hormone effects might have been initially excluded, while still adding value to the understanding of the hormonal modulation of neuroimaging parameters. Nonetheless, we highlight that a thorough and objective examination of estrogens is crucial to unravel their contributions to the brain's structural and functional architecture.

4.3 Perspectives: Recommendations for studying estrogen effects

It is important to acknowledge that our understanding of E2 action in the human brain largely stems from the extensive research conducted on animals, highlighting the mutual interdependence of these approaches. Technical innovation such as the use of ultra-high field MRI has led to enhanced signal-to-noise ratios and improved image quality (Kabasawa, 2022), and the recent shift from enzyme-linked immunosorbent assay variants to liquid chromatography-mass spectrometry/mass-spectrometry (LC-MS/MS) has concurrently increased study sensitivity (Conklin and Knezevic, 2020). Within the scope of the latter, the biological material is relevant. Estrogen levels in both saliva and blood were considered in this review. First, while saliva offers greater accessibility, the sensitivity of most commonly used ELISA kits of salivary estrogens is lower compared to P4 (Choe et al., 1983, Schmalenberger et al., 2021). When applicable with experimental design and cost, LC-MS/MS offers high sensitivity (Frederiksen et al., 2020; Faupel-Badger et al., 2010). Thus, the decision on whether to use saliva or serum estrogen samples is highly dependent on the research question. Furthermore, placebo-controlled RCTs with baseline and post-intervention hormone measures in healthy controls may provide potent insights into brain changes that are a direct result of changes in estrogen levels, considering the non-independence of exogenous administration from baseline endogenous hormone levels. Notably, only one study on exogenous estrogen conditions, namely an OC study, has distinguished between endogenous and exogenous estrogen levels, specifically between E2 and EE (Brouillard et al., 2023). The omission of exogenous EE measurements may lead to an incomplete and biased evaluation of the effect of suppressed endogenous levels that may be misattributed to exogenous hormones (Hirschberg, 2022), but recent research is moving towards its inclusion (Kimmig et al., 2023). A challenge with the interpretation of resting state fMRI studies has been highlighted in a multimodal analysis study, which found heterogeneous results for different analysis approaches, prompting a discussion of the significance of individual parameters (Hidalgo-Lopez et al., 2020). Weighing technical progress with these difficulties, we propose the following recommendations for future research. First, estrogen levels should be assessed during the day of the scan. Next, LC-MS/MS should be used to measure E2 levels, and, when feasible and relevant, EE levels, to disentangle endogenous and exogenous hormone effects. Lastly, the neuroimaging outcome measures and analysis methods (Hidalgo-Lopez et al., 2020), as well as the modeling approach of brain-hormone relationships (Bayer et al., 2018; Zsido et al., 2023) should be carefully selected and, ideally, preregistered on an open science platform (Foster and Deardorff, 2017). In addition, insights from other research fields enrich discoveries in cognitive neuroscience, promoting an interdisciplinary perspective that advances our understanding of the role of estrogens in the human brain, both in health and clinical contexts. For instance, in breast cancer research (Rossouw et al., 2013), treatments involve selective estrogen receptor modulators like tamoxifen or selective estrogen receptor degraders like fulvestrant, both of which mitigate estrogen fluctuations (Grizzi et al., 2020; Russo et al., 2006). This area of research thus introduces a complementary framework, providing an opportunity to delve into novel dimensions in understanding actions of estrogens in the brain.

5. Conclusions

Evidence from human neuroimaging studies including endogenous and exogenous estrogen measures suggests that estrogen levels are associated with structural, functional and connectivity measures of emotion processing, reward, memory, and resting state networks, as well as with regional GM and WM properties. Studies focusing on the amygdala and HPC, two brain regions which are central hubs in human cognitive and emotional processing, have deepened our understanding of the complexity of these associations. In order to advance neuroendocrine and neurocognitive research, we suggest to systematically integrate objective assessments of different sex hormone levels, account for individual variations in designated study designs, and investigate the effects of estrogen independently as well as in synergy with other sex hormones. The feasibility of such experimental approaches in humans has been demonstrated by previous proof-of-concept work applying dense within-subject sampling including deep individual cognitive and psychological phenotyping, as well as by double-blind RCTs. Though, historically, hormonal fluctuations have been used to justify the exclusion of females from studies, recent rodent research has refuted the damaging misconception that female hormonal fluctuations are inherently more variable than male (Levy et al., 2023). The many landmark studies highlighted in this review emphasize a more nuanced perspective, and encourage the need for precision imaging in women's health (Jacobs, 2023). Understanding hormonal transitions furthers not only basic science of estrogen action (Rocks et al., 2022), but also reinforces a personalized medicine approach for brain health of women and individuals with ovaries (Miller et al., 2015). Recognizing and embracing rather than disregarding this neurobiological complexity is key (see Galea et al., 2023; Galea and Parekh, 2023). This is particularly evident given the essential role of estrogens for mood, cognition, blood pressure, inflammation, and aging (Wharton et al., 2012; Barha and Galea, 2010; Caroccia et al., 2016; Nadkarni and McArthur, 2013; Brinton et al., 2015), highlighting the importance of understanding estrogen actions in the interplay of the human body and brain.

Glossary

ACC - anterior cingulate cortex

CEE - conjugated equine estrogen(s)

CA1/2/3 - cornu ammonis 1, 2, or 3

COC - combined OC

COMT - catechol-o-methyltransferase

CYP - cytochrome P450

DAN - dorsal attention network

dlPFC - dorsolateral PFC

DMN .- default mode network

DTI - diffusion tensor imaging

DWI - diffusion weighted imaging

E1 - estrone

E1G - estrone-3-glucuronide

E2 - 17β-estradiol/ estradiol

E3 - estriol

E4 - estetrol

ECN - executive control network

EE - ethinyl estradiol

ER - estrogen receptor

FA - fractional anisotropy

FDG -fluorodeoxyglucose

fMRI - functional MRI

GAHT - gender-affirming hormone therapy

GM - gray matter

GnRH(a) - gonadotropin releasing hormone (antagonist)

HC - hormonal contraception/ contraceptive

HPC - hippocampus

ICA - independent component analysis

ITG - inferior temporal gyrus

LC-MS/MS - liquid chromatography-mass spectrometry

M1 - primary motor cortex

MD - mean diffusivity

MFG - middle frontal gyrus

MHT - menopausal hormone therapy

MRI - magnetic resonance imaging

MTL - mediotemporal lobe

NAcc - nucleus accumbens

NC - naturally cycling

OC - oral contraception/ contraceptive

P4 - progesterone

PET - positron emission tomography

PFC - prefrontal cortex

PHC - parahippocampal cortex

PMDD - premenstrual dysphoric disorder

POP - progestin-only preparation

PRISMA - Preferred Reporting Items for Systematic and Meta-Analyses

rCBF - regional cerebral blood flow

RCT - randomized controlled trial

ROI - region of interest

RSN - resting state network

SFG - superior frontal gyrus

SM - supplementary material

sMRI - structural MRI

SN - salience network

SPECT - single photon emission computed tomography

STG - superior temporal gyrus

WM - white matter

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Table 1 Endogenous estrogen studies

Study	Sample characteristics	Aim of the study, pathway/ network	Study design, methods, variables	Estrogen measure	Findings
Puberty					
Campbell et al. (2022)	N=297 adolescents; n=137 females (X_{age}=14.08 y., range: 10.2-16.9 y.); n=160 males (X_{age}=14.06 y., range: 10.2-17.0 y.)	How do sex hormones influence AMY volume during puberty, controlling for age and androgen receptor gene? ROIs: bilateral AMY, nine AMY subregions	sMRI (T1-weighted; 3T); generalized additive mixed models of AMY volumes including sex hormones (E2, free testosterone); ANOVAs; androgen receptor genotyping in n=197	serum E2, RIA ("Beckman Coulter", Sen: 2.2 pg/mL, intra-assay CV: 7.4%)	females: no interaction of testosterone or E2 with age on AMY (sub)volumes; males: interaction of testosterone and age on total AMY, divisions of the basolateral nucleus, and cortical and medial nuclei volumes (the latter: mediated by androgen receptor sensitivity); no interaction with E2
Cservenka et al. (2015)	N=44 adolescents, X_{age}=13.28 y. (range: 10-15 y.); n=22 females (X_{age}=13.47 y.); n=22 males (X_{age}=13.10 y.); E2 assessed in n=41	Are there age- and sex-related effects on emotional conflict-related brain activation, controlled for pubertal status? Emotion processing areas	task-based fMRI (3T): modified emotional conflict task; correlation analyses of age, sex, and gonadal hormones (E2, total testosterone) with task-induced brain activation	serum E2, RIA ("Beckman Coulter", Sen: 2.2 pg/mL, intra-assay CV: 6.9%)	age negatively correlated with task-related activation (e.g., MFG, OFC); sex differences in task-related brain activation (e.g., right IFG, right middle occipital gyrus); females: E2 positively correlated with activation in occipital regions; males: E2 negatively correlated with activation in cerebellar/ cingulate regions

Goddings et al. (2012)	N=42 female adolescents, X_{age}=12.5 y. (range: 11.1-13.7 y.); dichotomized into early (N=21) and late puberty (N=21); E2 assessed in n=39	How do pubertal status, sex hormones, and age impact neural correlates of social emotion? Social emotion/ mentalizing network	task-based fMRI (1.5T): social emotion/ mentalizing task; regression analyses of whole-brain BOLD and hormones (E2, DHEA, testosterone); repeated measures ANOVAs	saliva E2, ELISA ("Salimetrics", intra-assay CV: <7%)	E2 and testosterone positively associated with task-related left ATC activation during social vs. basic emotion processing; no difference between puberty groups; negative correlation between age and task-related left dmPFC activation

Herting et al. (2012)	N=77 adolescents (age range: 10-16 y.);
	
	n=39 females (X_{age}=13.4 y.);
	
	n=38 males (X_{age}=13.3 y.);
	E2 assessed in n=25 females (X_{age}=13.9 y.) and n=30 males (X_{age}=13.8 y.)
		How do sex, pubertal status, and sex hormones influence WM microstructure, when controlling for age?
		
		Whole-brain
			DTI (3T); regression analyses to reveal WM differences for age, sex, and pubertal status (=ROIs); ROI-based and whole-brain voxel-wise multiple regression analyses of WM microstructure and hormones (E2, testosterone)	serum E2, RIA ("Beckman Coulter", Sen: >2.2 pg/mL, intra-assay CV: 7.4%)	females: E2 predictive of lower FA (e.g., right AG, SLF); testosterone predictive of higher FA (e.g., PCG); negative relation of pubertal status and FA in SFG;
					
					males: positive relation of pubertal status and FA in SFG; testosterone predictive of higher FA (IFG, SFG) and MD (SFG), E2 predictive of higher FA (e.g., thalamus, SFG)

Herting et al. (2014)	N=126 adolescents; n=63 females (X_{age}=11.83 y., range: 10-12 y.); n=63 males (X_{age}=12.89 y., range: 12-14 y.); t1: baseline; t2: 2y. follow-up (n=57	How do E2 and testosterone relate to changes in (sub)cortical brain volumes in adolescents and how does this relation develop over time? Whole-brain and ROIs: HPC,	sMRI (MPRAGE; 3T); total GMV and WMV; subcortical GMVs of ROIs; LMEs including age, sex, pubertal stage, and hormones (E2 in females, testosterone in both sexes); linear growth trajectories	serum E2 per visit, RIA ("Siemens", Sen: 2.71 pg/mL)	females: lower E2 levels associated with robust GMV decreases and WMV increases over time; females with lower/ higher testosterone and E2 show decreased/ increased right AMY volume

	females, n=49 males); E2 assessed in females only	AMY, caudate, thalamus			over time; males: larger total GMV; larger increase in WMV and larger left thalamus; lower testosterone associated with greater left AMY volume; higher testosterone associated with decreased WMV over time; both: low testosterone associated with increased caudate GMV
Ho et al. (2020)	N=80 adolescents; n=51 females ($\bar{X}_{age}$=11.14 y. at t1, $\bar{X}_{age}$=12.93 y. at t2); n=29 males ($\bar{X}_{age}$=11.90 at t1, $\bar{X}_{age}$=13.88 y. at t2); t1 = baseline; t2 = 2y. follow-up; E2 assessed in females only	Are longitudinal changes in pubertal sex hormones associated with longitudinal changes in WM during puberty? 10 WM tracts	DWI (3T); analysis of FA, MD, RD and AD; fixed effect linear regression models with sex and longitudinal change in hormones (E2 in females, testosterone in both sexes) on FA changes in WM tracts	saliva E2 per visit ("Salimetrics", Sen: 0.1 pg/mL; intra-assay CV: 8.1% at 3.8 pg/mL)	females: testosterone change positively associated with FA changes in six major WM tracts and with AD in left CG; E2 change positively associated with FA in left uncinate fasciculus, and with AD in left CG, only when uncorrected for testosterone; no associations of E2 change and RD or MD; males: no associations between WM changes and change in testosterone levels
Klapwijk et al. (2013)	N=42 female adolescents, $\bar{X}_{age}$=12.5 y.; E2 assessed in n=32, dichotomized into early	How does puberty relate to connectivity in a mentalizing brain network? Emotion processing	task-based fMRI (1.5T): social emotion paradigm; voxel-wise PPI analysis for FC between social brain regions;	saliva E2, ELISA ("Salimetrics", Sen: 1-32 pg/mL, intra-	increased FC between dmPFC and left ATC in late versus early puberty; positive association

	(N=15) and late puberty (N=17) group	areas: dmPFC, TPJ, ATC, pSTS	partial correlation analyses with hormones (E2, DHEA, testosterone)	assay CV: 1.8%)	between E2 levels and FC between dmPFC and right TPJ during social versus basic emotion processing
Ladouceur et al. (2019)	N=79 adolescents; n=47 females (X_{age}=11.52 y.); n=32 males (X_{age}=12.54 y.); E2 assessed in females only	To what extent is reward-related striatal activation and cortico-striatal FC linked to pubertal status and sex hormone levels? Reward circuit: striatum, medial PFC, INS	task-based fMRI (3T): reward cue processing task; seed (NAcc)-based fMRI analyses; generalized PPI; linear regression models with hormones, per sex (DHEA and testosterone in both, E2 in females only)	pooled saliva E2 (3 samples across 3 weeks), ELISA ("Salimetrics", intra-assay CV on average 2.23 %)	females: higher E2 levels associated with reduced task-related bilateral caudate activation, and with increased FC between NAcc and putamen when processing reward cues; testosterone associated with FC between NAcc and rostral ACC clusters and between NAcc and anterior INS; males: no hormone-activation associations

Nguyen et al. (2019)	N=152 children and adolescents; n=65 females; n=87 males:
	
	t1: n=30 females; n=51 males; X_{age}= 11.91 y. (range: 6.09-18.13 y.);
	
	t2: n=28 females; 36 males; X_{age}= 12.27 y. (range: 6.80-19.48 y.);
	
	t3: n=20 females; n=38
		Does E2 regulate the structural relationship between the AMY and the cortex (cortico-amygdalar structural covariance), across development?
		
		Whole-brain and AMY
			sMRI (T1- and T2-weighted; 1.5T); structural covariance of whole-brain CT and bilateral AMY; LMEs with E2 as fixed effect; mediation and moderation analyses; cognitive test battery for association with AMY structural covariance; participants with 1-3 visits every 2 years	pooled saliva E2 (2 samples per visit), ELISA ("Salimetrics", intra-assay CV: 4.1%)	with age: change from positive to negative structural covariance between AMY and left pre-SMA, PCC and left retrosplenial cortex; high E2 associated with reduced age effects;
					age interacts with E2-related cortico-AMY structural covariances on cognitive tests;
					
					no significant associations

	males; X_{age}=13.99 y. (range: 9.09-22.10 y.)				between E2 and CT or AMY volume
Op de Macks et al. (2011)	N=40 adolescents; n=30 females (X_{age}=12.9 y.); n=14 males (X_{age}=13.4 y.); E2 assessed in females only	How do pubertal sex hormones influence risk-taking behavior and reward-related brain processes in adolescents? Reward circuit: NAcc, striatum	task-based fMRI (3T): probabilistic decision-making task ("Jackpot gambling task"); whole-brain and ROI analyses with regressors for hormones (E2, DHEA, testosterone), for sexes separately	pooled saliva E2 (6 samples, 2 consecutive days); *no type of assay/ manufacturer/ sensitivity information*	both sexes with similar risk-taking behavior and brain activation; testosterone positively correlated with ventral striatal activation in both, but more robust in males than females; females: E2 positively associated with dorsal striatum, dlPFC and medial PFC activation, at a lower threshold
Op de Macks et al. (2016)	N=58 female adolescents, X_{age}=12.4 y. (n=23 11y.-olds; n=19 12y.-olds; n=16 age 13y.-olds), with two visits; E2 assessed in n=56	What is the relation between pubertal sex hormones, risk-taking behavior, and reward-related brain processes in adolescents with a narrow age range? Reward circuit: NAcc, medial OFC	task-based fMRI (3T): modified probabilistic decision-making task ("modified Jackpot gambling task"); whole-brain and ROI-based analyses; regression analyses and mediation analyses of task-related activation, behavior, and hormones (E2, testosterone)	pooled saliva E2 (2 samples on different days), ELISA ("Salimetrics", Sen: 0.1 pg/ml, intra-assay CV: 6.3%)	no direct relation between E2 and risk-taking behavior; indirect relation: females with higher E2 show increased NAcc activation during decreased risk-taking behavior; higher testosterone levels associated with increased risk-taking behavior, mediated by heightened activation in medial OFC
Peper et al. (2009)	N=78 adolescents (age range: 10.0-14.9 y.); n=41 females (X_{age}= 12.2 y.); n=37	What is the relation between pubertal sex hormones and brain structure in adolescents?	sMRI (1.5T; T1-weighted); VBM analyses for GM and WM density; linear regression analyses of relation between	pooled urinary E2 (2 samples on different days), ELISA ("Abbott Architect", Sen: 150	females: global GMV negatively associated with E2; E2 negatively correlated with GM density in prefrontal (e.g.,

	males (X_{age}= 11.6 y.)	Cortical GM and WM	hormones (E2, testosterone) and TBV, GMV, WMV, and cerebellar volume	pmol/L, intra-assay CV: 5%)	IFG), parietal (e.g., AG), and middle temporal areas; E2 positively correlated with GM density in MFG, ITG, and middle occipital gyrus; males: global GMV positively associated with testosterone
Poon et al. (2019)	N=67 adolescents (age range: 12-14y.), X_{age}=12.51; n=31 females; n=36 males; t1: questionnaires + interview; t2: tasks + hormones; t3: fMRI session (t2+ [2-6] weeks)	What are the associations between pubertal sex hormones and neural reward processing in adolescents? Reward circuit: ACC, vmPFC, dmPFC, dlPFC	task-based fMRI (3T): reward task; ROI-based and whole-brain voxel-wise analyses; seed-based FC analyses with seed in bilateral NAcc, and hormones (E2, testosterone) as predictors	saliva E2 at t2, ELISA ("Salimetrics", Sen: 0.1 pg/ml)	higher testosterone levels associated with lower bilateral dlPFC activation; no further associations of testosterone or E2 with activation or of testosterone and FC; E2 levels negatively associated with FC of left NAcc with left dlPFC and bilateral ACC
Stoica et al. (2019)	N=55 children and adolescents (age range: 7-18 y.), X_{age}=13.7; n=34 females; n=21 males; E2 assessed in n=30 female and n=18 males	What are the structural GM and WM neural correlates of executive functions in adolescents, accounting for E2? Whole-brain	sMRI (T1-weighted; 1.5T) and DTI (1.5T); surface-based morphometry analyses of cortical volumes; FA analyses of WM tracts; questionnaires on executive functions	pooled saliva E2 (2 samples), RIA (*no manufacturer/ sensitivity information)*	high E2 levels associated with lower FA in right inferior fronto-occipital fasciculus; high E2 levels and low executive function scores associated with reduced GM in right posteromedial cortex and lower FA in right inferior fronto-occipital fasciculus

Menstrual cycle (MC)					
Alonso-Alonso et al. (2011)	N=9 females, $\bar{X}_{age}$=26.2 y., early FP vs. late FP	How do E2 levels affect the brain's response to food stimuli, under different prandial states? ROIs: AMY, FFG, HPC, IFG, INS, NAcc	task-based fMRI (3T): viewing food vs. non-food stimuli in different prandial states (fasted vs. fed); whole-brain and ROI-based analyses; correlation analyses of brain activation and change in E2	serum E2 per visit, access CLIA ("Beckman Coulter", Sen: 20 pg/mL)	late FP: increased IFG and fusiform gyri activation for food stimuli; E2 change (late-early FP) inversely correlated with fusiform gyrus activation in fasted condition
Andreano & Cahill (2010)	N=17 females, $\bar{X}_{age}$=20.88 y. (range: 18-27 y.), early FP vs. mid-LP	How do high E2 and P4 levels affect the response to negatively arousing images? Emotional arousal areas: AMY, HPC, HPT	task-based fMRI (3T): viewing of negatively arousing vs. neutral images; ROI-based analyses of valence and MC phase; regression analyses of brain activation and hormones (E2, P4)	saliva E2 per visit, ELISA ("Salimetrics", intra-assay CV < 10%); E2 levels similar for FP and LP (!)	mid-LP: increased AMY and HPC activation for negative vs. neutral images, effects driven by high P4 rather than high E2 levels; E2: overall negative relation with AMY activation (univariate analysis), negative correlation with HPT during negative/ neutral encoding
Arélin et al. (2015)	N=1 female, age: 32 y., with 32 scans over two consecutive cycles	Do subtle E2 and P4 changes impact the functional architecture of the female brain? Whole-brain and ROI: bilateral dlPFC, sensorimotor cortex	MRS (3T) and rs-fMRI (3T); EC mapping with whole-brain and seed-based analyses; correlation analyses of EC and hormones levels (E2, P4)	serum E2 per visit, ECLIA ("Roche", intra-assay CV: 3.2 – 6%)	no association between E2 and EC values; only P4 associated with EC values (HPC and bilateral sensorimotor cortex, as well as dlPFC)

Barth et al. (2016)	*same subject as in Arélin et al. (2015)*, based on 30 scans	Do subtle E3 and P4 changes impact WM integrity of the HPC? Whole-brain and ROI: bilateral HPC	sMRI (MPRAGE, 3T) and DWI (3T); correlation analyses of changes in hippocampal FA and GMV and hormones (E2, P4)	*cf. Arélin et al. (2015)*	E2 levels positively correlated with hippocampal FA, with peak FA shortly before ovulation
Bayer et al. (2014)	N=23 females, $\bar{X}_{age}$=26 y. (range: 19-33 y.), early FP vs. LP (not necessarily one consecutive cycle)	Do E2 and P4 modulate performance and activation during memory tasks with emotionally arousing information, valence-specifically? Emotional arousal areas: AMY, HPC, ACC, superior medial frontal cortex	task-based fMRI (3T): emotional enhancement of memory task (EEM) with in-scanner encoding of arousing (positive/ negative) vs. neutral stimuli; retrieval 24h later (recognition performance); correlation analyses of brain activation and hormones (E2, P4)	pooled saliva E2 (3 samples per visit), ELISA ("IBL", Sen: 0.3 pg/ml)	FP with greater activation in anterior HPC, LP with greater activation in left AMY, for all emotional items; activational shift for positive EEM: FP with ACC and posterior HPC activation, LP with AMY activation; E2 change (from FP to LP) negatively correlated with change in HPC activation, for positive stimuli (uncorrected only); performance differences according to valence of emotional items
Dan et al. (2019)	N=40 adults; n=20 females (X_{age}=24.45 y., range: 21-29 y.), mid-FP vs. late LP; n=20 males (X_{age}=23.75 y, range: 19-29 y.), assessed once; E2	How do MC phases modulate behavioral and neural sex differences in emotion processing? Emotion processing areas: AMY, OFC, dmPFC,	task-based fMRI (3T): emotion perception task (ROI-based activational analyses) and emotion experience task (ROI-ROI FC analyses); correlation analyses of FC measures and hormones (E2, P4)	serum E2 per visit, sandwich immunoassay ("Advia Centaur", *no sensitivity information*), samples partly a day before or after the MRI	FP: E2 positively correlated with right inferior parietal to left inferior frontal FC during sadness; LP: reduced FC of putamen-vlPFC and putamen-dmPFC, compared to males; higher E2

	assessed in females only	putamen, calcarine gyrus			with weaker FC of putamen to dmPFC and ACC, and of AMY connections with OFC and calcarine gyrus; no correlations with FC strength during sadness
Fitzgerald et al. (2020)	N=1 female, age: 23 y., assessed for 30 consecutive days	How do subtle changes in E2 and P4 alter functional cerebellar networks at rest? 6 cerebral networks with hubs in cerebellum	rs-fMRI (3T); graph theory metrics for network topology, edgewise regression analyses of cerebellar coherence and hormones (E2, P4)	serum E2 daily, LC-MS/MS ("BRAC", Sen: 1 pg/ml, intra-assay CV < 5%)	edgewise regression analyses: robust negative associations of cerebellar coherence with P4, only sparse positive associations with E2; graph theory metrics: negative associations of E2 with global efficiency in some cerebellar networks (DAN, VAN, and SMN)
Hagemann et al. (2011)	N=15 adults; n=7 females (age range: 21-31 y.), menses vs. OP vs. mid-LP (vs. next menses in 50% of participants); n=7 males (age range: 23-37 y.), cycle-matched; E2 assessed in females only	Are there MC-related short-term changes in brain volume? Whole-brain GM, WM and CSF volumes	sMRI (1.5T, T1-weighted), twice per visit (to increase SNR); partitioning into GM, WM, CSF and background; ANCOVA with parameters for sex and time points; females: correlation analyses for volumetric changes in OP vs. menses (with E2), and for mid-LP vs. menses (with P4)	serum E2 per visit; *no type of assay information/ manufacturer/ sensitivity information*; ovulation confirmation by repeated ultrasound	OP vs. menses: GMV increase, with corresponding CSF volume loss, not correlated with E2 or P4 levels; WM unaffected; Mid-LP vs. menses: P4 significantly correlated with (non-significant) relative GM and CSF volume change; males: no WM, GM or CSF changes, no hormone correlations

Heller et al. (2024)	N=1 female with a history of irregular MCs, age: 30 y., with 25 scans over 5 consecutive weeks	Do endogenous fluctuations in sex hormones impact HPC morphology and cognition, beyond the regular MC? Bilateral HPC	sMRI (MPRAGE; 3T); HPC segmentation; positive and negative affect; cubic regression curve estimators for longitudinal changes of hormones, HPC volume and affect; correlations and post-hoc mediation regression analyses to relate affect to hormones (E1, E2, P4, LH), and to fluctuations in bilateral HPC volume	serum E1, RIA ("Roche", *no sensitivity information*), and E2, ECLIA ("Roche", Sen: 5 pg/mL, intra-assay CV: <5%); ovulation confirmed by urinary and serum LH test	MC length of 53 days (study spanned 20 FP days, 2 OP days, and 3 LP days; E1 and E2 positively correlated with bilateral HPC volume, positive, and negative affect; increased estrogen levels associated with decreased positive and increased negative affect, but only association with positive affect mediated by HPC volume changes; positive affect inversely, and negative affect positively correlated with bilateral HPC; HPC volume not correlated with P4
Hidalgo-Lopez et al. (2020)	N=60 females, $\bar{X}_{age}$=25.4 y., menses/early FP vs. pre-OP vs. mid-LP	Why did prior MC studies on rs-FC yield inconsistent results? RSNs with ROIs: HPC, caudate, putamen	rs-fMRI (3T); multimodal approach including 4 analyses, taking into account cycle phase and hormones (E2, P4): 1) group-independent ICA 2) EC 3) ALFF 4) seed-based analyses;	pooled saliva E2 (2-4 samples per visit), ELISA ("Salimetrics", *no sensitivity information*); ovulation confirmed by urinary test	LP: decreased intrinsic connectivity of right AG and DMN (1), increased EC of HPC (2), increased ALFF for caudate (3), increased putamen-thalamic FC (4); pre-OP: increased fronto-striatal (right caudate-right MFG) connectivity (4);

			1) whole-brain, 2)-4) based on ROIs		positive correlation of E2 levels with ICA connectivity strength (1) and putamen-thalamus-FC (4); neither E2 nor P4 associated with caudate and HPC findings;
Hidalgo-Lopez et al. (2021)	N=60 females, $\bar{X}_{age}$=25.36 y., *cf. Hidalgo-Lopez et al. (2020)*	How does effective connectivity change along the MC? RSNs: DMN (ROIs: PCC, AG, mPFC), ECN (ROIs: SMG, MFG), SN (ROIs: ACC, anterior INS)	rs-fMRI (3T); spectral DCM to assess between- and within-network effectivity (efferent connectivity); LMEs for within-subject effects of hormones (E2, P4)	*cf. Hidalgo-Lopez et al. (2020)*	early FP: increase right lateralization of connectivity from SN and DMN; increased integration within DMN/ between DMN and ECN, recruitment of SN by parietal ECN; pre-OP: lateralization shift with increased connectivity of left INS with ECN, and decoupling of right MFG-PCC and DMN, associated with rising E2 levels; mid-LP: lateralization shift; right INS recruiting frontal regions (driven by P4)
Hidalgo-Lopez & Pletzer (2021)	N=39 females, $\bar{X}_{age}$=24 y., menses/early FP vs. pre-OP vs. mid-LP	How do activation and connectivity of frontostriatal structures during a verbal working memory task change along the MC? Whole-brain and ROIs: bilateral dlPFC,	task-based fMRI (3T): verbal N-back working memory tasks (0-back with non-lures/targets, 2-/ 3-back with non-lures, lures and targets); per ROI: EC eigenvalues for activation, seed-to-voxel connectivity maps for FC (for each task	pooled saliva E2 (2 samples per visit), *cf. Hidalgo-Lopez et al. (2020)*	mid-LP: increased dlPFC and putamen activation; decreased FC between left striatum and inferior frontal/parietal areas as well as increased FC between dlPFC and visual cortices and

		putamen, caudate	condition); linear-mixed effects models of hormones (E2, P4)		between striatum and somatomotor cortices for targets; increased FC between bilateral dlPFC and posteromedial structures for lures; pre-OP: negative inter-hemispheric FC between fronto-parietal areas for lures; P4: better predictor for FC changes than E2
Hjelmervik et al. (2014)	N=31 adults; n=16 females (X_{age}=23.25 y.), FP vs. LP vs. menses; n=15 males (X_{age}=23.13 y.), cycle-matched; E2 assessed in females only	Is rs-fMRI stable in females or does it change along the MC? Four fronto-parietal RSNs: left and right dorsal, ventral and anterior network (from combined ICA and PCA procedure)	rs-fMRI (3T); per network: ANOVAs with sex and MC phase; multiple regression models per cycle phase with regressors for hormones (E2, P4, and interaction) in female participants; intra-class correlation analyses for retest-reliability	pooled saliva E2 (2 samples per visit), luminescence assay (*no manufacturer/ sensitivity information*)	no main effect of cycle phase or interaction effect of cycle phase and sex on rs-FC; main effect of sex: females with higher FC in left cerebellum for the right dorsal network, and in left MFG, bilateral precuneus and right IPL for the anterior network; sex difference not independent of TBV
Hwang et al. (2015)	N=85 adults; n=48 females: n=32 NC with high (n=16, X_{age}=23.0 y.) or low E2 levels (n=16, X_{age}=23.4 y.) after median split, n=16 OC users (X_{age}=23.6 y.);	How are sex, E2, and OC use associated with the fear network during fear conditioning and extinction? Areas of the fear circuit: AMY, INS, ACC, PCC, HPC, HPT	task-based fMRI (3T): ROI-based analyses of activation; Day 1: habituation, fear conditioning and early extinction recall test (conditioned stimulus: lamp pictures, unconditioned	serum E2 (*no type of assay/ manufacturer/ sensitivity information*)	high-E2 NC: greater middle CC and ACC activation as compared to low E2 or males; low E2 and OC groups with more similar brain activations than high E2 group;

	n=37 males (X_{age}=29.8 y.); E2 assessed in NC females only		stimulus: mild electric shock); Day 2: extinction recall test; analyses of group differences in activation; regression analyses of E2 in NC females		NC: E2 differentially correlated with areas of the fear extinction network along phases of conditioning and early and late extinction recall (e.g., ACC, OFC, medial CC, AMY, HPT, INS)
Jacobs et al. (2015)	N=24 females, age range: 43-50 y., early FP ("low E2") vs. late FP ("high E2"); n=13 healthy (X_{age}=45.2 y.); n=11 recurrent, remitted MDD (X_{age}=47.4 y.)	How does E2 modulate activation within cortical and subcortical regions of the stress circuit, in healthy females and in females with MDD? Stress circuit: AMY, HPT, HPC, mPFC	task-based fMRI (3T): visual stress challenge: viewing positive (high arousing) vs. negative (low arousing) vs. neutral pictures; paired *t*-tests, ANOVAs and ANCOVAs accounting for P4 levels; mood, anxiety and depression inventories	serum E2 per visit, IRMA ("DiaSorin", Sen: 20–4800 pg/ml, precision: 12–21%)	healthy: early to late FP with decrease in activation in right AMY, left HPC, and bilateral HPT, remained after correcting for P4; MDD: greater anxiety and depression; no differences between early and late FP; endocrine downregulation of stress circuit observed in healthy group missing in MDD
Joseph et al. (2012)	N=8 females, X_{age}=25 y. (range: 18-38 y.), early FP vs. late FP	How does E2 affect the neural substrates of working memory? Working memory areas	task-based fMRI (1.5T): verbal N-back working memory task (0-, 1-, and 2-back trials); ANOVAs for each ROI (derived from 2- vs. 0-back load contrasts); correlation analyses of signal change and change in E2 levels	serum E2 per visit, CLIA ("Immulite 1000", Sen: 15 pg/mL, intra-class CV: 5–8%)	early FP: greater bilateral cerebellum and tectum/pineal body activation, greater 2-back activation in cerebellar vermis and right INS; late FP: E2 change positively correlated with left INS and PCG signal change, error increase associated with

					decreased right cerebellar and increased left middle frontal cortex activation
Konrad et al. (2008)	N=24 adults; n=12 females (X_{age}=30.8 y.), early FP vs. mid-LP; n=12 males (X_{age}=33.2 y.), assessed once; overall age range: 23-45 y.	How are semantic networks affected by sex, MC, and sex hormones? Semantic processing areas	task-based fMRI (3T): synonym generation task during and after fMRI; *t*-tests of within-group-, ANOVAs of between-group activation patterns in ROIs activated across groups; regression analyses of activation and hormones (E2, P4, testosterone)	serum E2 levels per visit, ECLIA ("Roche", *no sensitivity information*)	females: E2 levels and left PFC activation weakly correlated in early FP, but strongly correlated in mid-LP; P4 and left PFC correlated in both phases; males: greater activation in left MFG and PCG; males more similar with females in mid-LP than in early FP; weak correlation of left PFC and E2 or P4; both groups: positive correlation of left PFC and testosterone; no behavioral differences
Lisofsky et al. (2015)	N=21 females, $\bar{X}_{age}$=26.8 y., early FP vs. late FP v. OP vs. LP	How do brain structure and function covary with E2 and P4 levels along the MC? Whole-brain and ROI: HPC	sMRI (T1-weighted, MPRAGE; 3T), rs-fMRI and DTI (3T); whole-brain VBM analyses of GM; whole-brain FC maps; MD; cognitive test battery; correlation analyses of whole-brain GM density and E2 levels	plasma E2 per visit, ELISA ("Millipore", *no sensitivity information*); ovulation confirmed by urinary test	late vs. early FP: increase in GMV of bilateral posterior HPC, decrease in hippocampal MD without water content changes; increase in thalamic GMV; E2 positively associated with GMV in left PHC, MFG and right cerebellum; late FP (vs. early FP and vs. LP): higher FC between bilateral

					HPC and bilateral SPL; no behavioral differences between phases
Mueller et al. (2021)	*Same sample as in Fitzgerald et al. (2020), Pritschet et al. (2020), & Taylor et al. (2020),* i.e., single dense-sampled female (age: 23 y.) for 30 consecutive days	To which extent do sex hormones modulate connectivity within and between large-scale functional brain networks over time? Nine RSNs	rs-fMRI (3T); analyses of functional brain network connectivity over time via dynamic community detection techniques; correlation analyses of network flexibility values and hormones (E2, P4); 1-year follow-up after COC-intake (*cf. Table 2*)	*cf. Fitzgerald et al. (2020)*	four core communities identified: visual, default mode, control (TPN) and somatomotor-attention core; 85% of nodes stable across MC, but ovulatory window with changes in community structure within DMN (i.e., increased DMN connectivity), E2 positively correlated with DMN, limbic network, SN/VAN, TPN, somatomotor network and subcortical network
Pletzer et al. (2018)	N=55 females, $\bar{X}_{age}$=25.67., menses/early FP vs. pre-OP vs. mid-LP; pooling data from two fMRI-studies with similar MC time windows	Are findings on MC-related changes in regional GMVs replicable in a study of sufficient power? ROIs: HPC, basal ganglia (putamen/ pallidum), INS, MFG	sMRI (T1-weighted, MPRAGE; 3T); local GMV from VBM analyses; LMEs with first model of "cycle", and second model with "E2" for effects in pre-OP, and with "E2" and "P4" for effects in mid-LP	saliva E2, ELISA ("Salimetrics", sensitivity: 1pg/mL); ovulation confirmed by urinary test	pre-OP: E2-dependent pre-ovulatory increase in GMV of bilateral HPC; mid-LP: P4-dependent increase in GMVs of right basal ganglia; no significant cycle-dependent changes or hormone associations in left basal ganglia, bilateral INS or MFG

Pletzer et al. (2019)	N=36 females, X_{age}=25.36 y., menses/early FP vs. pre-OP vs. mid-LP	How do MC changes affect brain activation and connectivity patterns underlying cognition? ROIs: HPC, putamen, caudate and dlPFC	task-based fMRI (3T): spatial navigation and verbal fluency task; ROI-to-ROI FC analyses of dlPFC's inter-hemispheric connectivity and FC with subcortical areas; LMEs for cycle phase and hormones	pooled saliva E2 (3 samples per visit), ELISA ("Salimetrics", Sen: 1pg/mL)	pre-OP: increased HPC activation in both tasks, decreased connectivity of dlPFCs; mid-LP: increased caudate and dlPFC activaction in both tasks, decoupling of dlPFC and decreased left HPC activation; change in HPC activation correlated with E2 (spatial navigation) and interaction of E2 and P4 (both tasks); change in caudate/dlPFC correlated with P4 and its interaction with E2 (spatial navigation); no behavioral differences between phases
Pritschet et al. (2020)	*Same sample as in Fitzgerald et al. (2020), Mueller et al. (2021), & Taylor et al. (2020),* i.e., single dense-sampled female (age: 23 y.) for 30 consecutive days	To which extent do fluctuations in sex hormones alter intrinsic RSNs? 8 RSNs: DMN, DAN, SMN, SN, TPN, VN, FCN, limbic network	rs-fMRI (3T); correlation analyses of time-lagged and -synchronous associations of hormones (E2, P4) and rs-fMRI measures (whole brain-FC; edgewise connectivity; graph theory: global efficiency, participation coefficient); vector autoregressive models and regression analyses;	*cf. Fitzgerald et al. (2020)*	time-synchronous: increased coupling (FC) with rising E2 levels, mainly driven by ovulation; time-lagged: edgewise connectivity and hormone levels of both prior days are associated (positively at lag day 1, negatively at lag day 2); time-lagged topology associations: E2 more strongly associated with

			1-year follow-up after COC-intake (*cf. Table 2*)		within- (global efficiency) than with between-network integration (participation coefficient), i.e., recent E2 levels precede efficiency in DMN and DAN; P4 associated with reduced coherence across the whole brain
Rizor et al. (2024)	N=30 females, $\bar{X}_{age}$=28.0 y. (age range: 18-29 y.), menses vs. OP vs. mid-LP (not necessarily one consecutive cycle)	Are fluctuations of HPG hormones (E2, P4, LH, FSH) associated with changes in WM microstructure, GMV, CT, and TBV? Whole-brain and region-specific	sMRI (MPRAGE; 3T) and QTI (3T); ANOVAs & post-hoc *t*-tests for session-specific effects; Bayesian hierarchical regression models on relationship between hormones (E2, P4, LH, FSH), and whole-brain vs. region-specific WM diffusion parameters, CT, and volumetric measures (TMV, tissue volume, CSF)	serum E2 per visit, LC-MS/MS ("Shimadzu"; Sen: 0.002-20 ng/mL, intra-assay CV: 2.1%); ovulation confirmed via urinary test	whole-brain WM diffusion parameters: E2 uncorrelated with mean size of isotropic diffusivity and FA, but positively correlated with variation in isotropic diffusivity size, μFA, and mean squared anisotropy; no credible relationships between E2 and region-specific WM diffusion parameters (P4 and FSH only); no credible relationships between E2 and whole-brain or region-specific CT (P4 and FSH only); no credible relations of E2 with TBV, tissue volume (P4 only), or CSF volume (P4 only)

Syan et al. (2017)	N=25 females, X_{age}=27.4 y. (age range: 16-45 y.), mid-FP vs. late LP	To what extent does rs-FC correlate with sex hormone levels? 6 RSNs: DMN, SN, FPN, VN, MPLN, SMN	rs-fMRI (3T); correlation analyses of hormones (E2, P4, allopregnanolone, DHEA-S) and FC (seed-based FC and group ICA); clinical questionnaires	serum E2 per visit, ELISA ("ALPCO Diagnostics", intra-assay CV: 10.4%)	no difference in FC between phases, but increased correlations of hormones levels with FC in late LP (47 correlation patterns) compared to mid-FP (9 correlation patterns); mid-FP: E2 negatively correlated with FC of bilateral ERCs (MPLN); late LP: E2 positively correlated with FC between left AMY, bilateral somatosensory and right M1 (SMN, MPLN)
Taylor et al. (2020)	*Same sample as in Fitzgerald et al. (2020), Mueller et al. (2021) & Pritschet et al. (2020),* i.e., single dense-sampled female (age: 23 y.) for 30 consecutive days	Do variations in sex hormone levels over time impact MTL morphology with subregion resolution? MTL: CA1, CA2/3, dentate gyrus, PRC, ERC, PHC, subiculum	sMRI (MPRAGE and T2-weighted; 3T); linear regression models of hormones (E2, P4) and GMV of bilateral subregion/ whole-brain; 1-year follow-up after COC-intake (*cf. Table 2*)	*cf. Fitzgerald et al. (2020)*	no significant associations between E2 levels and GMV in MTL subregions; P4 positively associated with GMV in CA2/3 and PHC, and negatively associated with GMV in PRC; neither E2 nor P4 associated with whole HPC volume or anterior/ posterior HPC volumes
Wang et al. (2020a)	N=49 females, X_{age}=22.86 y. (range: 19-28 y.);	Are sex hormones associated with the behavioral inhibition/ activation	rs-fMRI (3T); rs-FC analyses; BIS/BAS scale; ROI-to-whole-brain analyses of FC and hormones	saliva E2 per visit, ELISA ("DRG International", *no sensitivity information*);	E2 negatively associated with regional activity in VTA (IFG, STG, SPL), and substantia nigra

	n=25 in late FP (X_{age}=22.52 y.), n=24 in mid-LP (X_{age}=23.21 y.)	(BIS/BAS) system and its dopaminergic pathways? Whole-brain and ROIs: substantia nigra, VTA	(E2, P4); correlation analyses of BIS/BAS performance and hormones	relative E2 as (E2-P4)/P4	(IOG, IPL, ITG, SPL); E2 and FC of substantia nigra and dlPFC positively correlated in females with high P4, but negatively in females with low P4; similar associations of E2 and BIS scores
Wang et al. (2020b)	*Same sample as in Wang et al. (2020a)*	Do MC-related sex hormone fluctuations affect self-referential mental performance and its neural correlates? DMN (ROIs: PCC/ precuneus, mPFC, IPL, ITG, medial dorsal thalamus)	rs-fMRI (3T); ROI-to-ROI-FC of 7 DMN seeds; correlation analyses with total and relative hormones (E2, P4); measures of self-awareness and positive/ negative affect	*cf. Wang et al. (2020a)*	across phases: E2 negatively correlated with ITG-thalamus FC; relative E2 with marginally positive correlation with FC of mPFC and left IPL; LP vs. FP: ITG-thalamus FC overall greater; opposite effects on DMN by P4 (negative correlation with mPFC-ITG); higher relative P4 (in LP) accompanied by decreased DMN (less self-referential), not correlated with E2
Weis et al. (2008)	N=28 participants; n=14 females (X_{age}=26.83 y., range: 21-38 y.), FP vs. menses; n=14 males (X_{age}=27.39 y., range: 24-39 y.), assessed	Which role do sex hormones play in MC-related changes in interhemispheric inhibition, during verbal processing?	task-based fMRI (3T): word-matching task (with right vs. left visual field/ right vs. left response hand); ANOVAs and PPI-analyses of task-related changes; regression analyses of hormones (E2, P4)	serum E2 per visit, ECLIA (*no manufacturer/ sensitivity information*)	left IFG ("left hemispheric language area") activated in both sexes; menses: inhibitory influence of left hemisphere on right hemisphere, resulting in

	twice; E2 assessed in females only	Whole-brain and ROI: left IFG	and regions identified in PPI analyses (right IFG)		pronounced lateralization; E2 negatively correlated with strength of interhemispheric inhibition, resulting in reduced functional cerebral asymmetries during FP
Zsido et al. (2023)	N=27 females, age range: 18-35 y., menstrual vs. pre-OP vs. OP vs. post-OP vs. mid-LP vs. pre-menstrual (n=20 with all 6 time points)	How do sex hormone fluctuations shape structural brain plasticity in the MTL? MTL subregions: HPC (CA1, CA2, CA3, subiculum, dentate gyrus), PHC, PRC, ERC	sMRI (7T; MP2-RAGE), MTL segmentation into subregions for bilateral volume calculations; LMEs with subregion volumes and hormones (E2, P4, FSH, LH); control analyses with CBF, CSF and PCG volume	serum E2, LC-MS/MS (*no manufacturer/ sensitivity information*)	E2 levels positively associated with total HPC volume, PHC and CA1 volume; E2 and P4 interaction positively associated with CA1 volume; P4 positively associated with subiculum and perirhinal area 35, and negatively associated with CA1 volume
Pregnancy/ Postpartum					
Pritschet et al. (2024)	N=1 female, age: 38 y., with n=26 scans, pre-pregnancy (4 scans), first trimester (4 scans), second trimester (6 scans), third trimester (5 scans), postpartum (7 scans; last at 9 months postpartum)	How does the brain change throughout gestation/ postpartum, along with fluctuations in sex steroid levels? Whole-brain cortical and subcortical regions, and MTL: CA1, CA2/3, dentate gyrus, PRC,	sMRI (MPRAGE and T2-weighted; 3T) and DSI (3T); generalized additive models of CT, cortical/ subcortical GMV, and TBV; GMV of hippocampal/ MTL subfields; WM tractography (quantitative anisotropy); correlation analyses with hormones (E2, P4)	serum E2 daily, LC-MS/MS ("BRAC", Sen: 1.0 pg/mL, intra-assay CV: <5%)	across gestation: decreases in cortical and subcortical GMV, CT, and TBV, which slightly recovered postpartum; parallel increases in WM integrity across gestation; GMV and WMV changes associated with rises in E2 and P4;

		ERC, PHC, subiculum			MTL: non-linear decreases in CA1, CA2/CA3, and linear volumetric decrease in PHC, associated with E2 levels; no changes in other subfields/ total hippocampal body
Menopausal transition/ Post-menopause (MP)					
Ballard et al. (2023)	N=79 females, $\bar{X}_{age}$=59.15; n=15 pre-MP ($\bar{X}_{age}$=41.00 y., range: 35-49 y.); n=18 early post-MP ($\bar{X}_{age}$=56.17 y., range: 47-62 y.); n=35 late post-MP ($\bar{X}_{age}$= 68.94 y., range: 52-86 y.); t1: cognitive testing, hormones, actigraphy; t2: fMRI session (mean: t1+37.7 days)	How do hormone-sleep interactions affect cognitive and motor performance, as well as cerebellar-frontal network connectivity? Cerebellar frontal networks: Crus I-dlPFC, lobule V-M1	rs-fMRI (3T); ROI-to-ROI FC analyses with seeds in dlPFC and M1; overnight sleep monitoring via actigraphy after t1 for sleep quality; battery of cognitive and motor tasks; ANOVAs and multivariate multiple linear regression models for the role of hormones (E2, P4, testosterone), MP status and sleep on FC/ behavior	saliva E2 at t1, ELISA ("Salimetrics", Sen: 0.1 pg/mL, intra-assay CV: 0.15)	higher E2 and sleep efficiency, as well as higher E2 and sleep quality predict lower FC of Crus I-dlPFC; E2 positively correlated with FC of lobule V to M1; E2 and sleep quantity interaction correlated with highest cognitive composite score; E2 and Crus I to dlPFC FC correlated with higher cognitive composite score; E2 scores predicted cognitive/ motor scores
Berent-Spillson et al. (2012)	N=54 females (age range: 42-61 y.); n=15 pre-MP; n=12 peri-MP; n=32 post-MP; *no*	Are differences in cognitive function attributable to MP? Episodic verbal and visual	task based fMRI (3T): episodic verbal/ visual working memory tasks; ANOVAs; correlation analyses with hormones (E2,	serum E2, CLIA ("Bayer", *no sensitivity information*)	E2 negatively correlated with activation of left inferior frontal cortex, temporal pole, PHC, and parietal cortex during verbal but

	further age information	working memory areas	FSH); MP natural/ after hysterectomy		not visual memory tasks; E2 positively correlated with phonemic/ semantic fluency and visual memory retention; groups: menopausal stage only relevant for verbal memory
Jacobs et al. (2016)	N=186 adults; n=92 females, with n=32 pre-MP (X_{age}=49.1 y., range: 46-53 y.), n=29 peri-MP (X_{age}=49.8 y., range: 47-55 y.), n=31 post-MP (X_{age}=50.5, range: 46-54 y.); n=94 males (X_{age}= 50.2, range: 45-55 y.)	How do sex and gonadal steroid levels affect episodic memory circuits in early midlife? Episodic memory areas: vlPFC, HPC, PPC	task based fMRI (3T): verbal encoding task, with post-scan retrieval; PPI analyses with seeds in left HPC/ vlPFC; linear regression analyses of hippocampal PPI and E2; correlation analyses of activation/ performance and hormones (E2, FSH, P4, testosterone)	serum E2, LC-MS/MS ("BRAC", Sen: 1.0 pg/mL, intra-assay CV: <5%)	females: decline in E2 with MP staging, associated with increase in left-right hippocampal connectivity, such that post-MP females show greater encoding-related connectivity of bilateral HPC; males: greater FC in vlPFC and between vlPFC & bilateral IPL; better retrieval related to activation in dorsal/posterior vlPFC; higher E2 related to better memory retrieval
Jacobs et al. (2017)	N=141 adults (age range: 46-53 y.); n=69 females, with n=26 pre-MP (X_{age}=49.3 y.), n=23 peri-MP (X_{age}=49.6 y.), n=20	How do sex and MP status impact regional and network-level changes in working memory during midlife? Verbal working memory areas: HPC, dlPFC,	sMRI, task-based fMRI (3T): verbal N-back task; ANOVAs of task-related activation for MP groups; PPI analyses with seed in dlPFC; FC analyses; linear regression analyses of brain activation and hormones (E2,	serum E2, LC-MS/MS („BRAC", Sen: 1.0 pg/mL, intra-assay CV: <5%)	task-related deactivation of HPC in all groups across menopausal transition: task-related increases in dlPFC activation, decrease in HPC deactivation and increase in task-related FC

	post-MP (X_{age}=50.1 y.); n=62 males (X_{age}=49.3 y.)	inferior parietal cortex	FSH, P4, testosterone)		between left dlPFC and bilateral HPC; decline in E2 and P4 strongly associated with decreased HPC deactivation along aging; males: greater activation in dlPFC
Liu et al. (2021)	N=45 females; n=20 pre-MP (X_{age}=36.7 y.), assessed in early FP; n=25 peri-MP (X_{age}=50.76 y.)	Does spontaneous regional brain activation in females during their menopausal transition differ from that of pre-MP females? Whole-brain	rs-fMRI (3T); regional homogeneity maps; two-sample *t*-tests for group differences/ correlation analyses regarding E2 levels, regional homogeneity, anxiety/ depression scores	serum E2, CLIA ("Advia Centaur", *no sensitivity information*)	peri- vs. pre-MP: increased regional homogeneity in left MFG and middle CG, and in right posterior cerebellum; peri-MP: left MFG and left middle CG regional homogeneity negatively correlated with E2 and anxiety/ depression scores
Schroeder et al. (2024)	N=199 post-MP females, X_{age}=59.28 y. (range: 48-67 y.)	Are post-MP estrogen levels related to performance and brain activation during a memory task? Whole-brain	task-based fMRI (3T): California verbal learning test (encoding, recall, & delayed recall); linear regression analyses of hormones (E1, E2) and brain activation; correlation analyses of estrogen-correlated eigenvectors and memory/ depression/ anxiety	serum E1 and E2, LC-MS/MS (Sen: 1.0 pg/mL, intra-assay CV: 8.1%); E2 levels below threshold in n=16	E2: positively associated with encoding-related activation in left IFG, left SFG, and bilateral ITG, and memory performance, and negatively associated with recognition-related activation right SFG; E1: positively associated with encoding-related activation in left INS and PCG, right SFG, and bilateral STG and postcentral gyri; negative associations of depression/ anxiety and areas

					estrogens were related with
Testo et al. (2024)	N=88 post-MP females, X_{age}=56.33 y. (range: 51-60 y.)	How does E2 affect FC between E2-sensitive areas, after MP? ROIs: bilateral HPC, anterior and posterior divisions of PHG, precuneus	sMRI (T1-weighted; 3T) and rs-fMRI (3T); ROI-to-ROI regression analyses to assess E2 effect on FC; exploratory regression analyses of FC, including time since final menstrual period; neuropsychological battery	E2, RIA (sensitivity: 2 pg/mL); *no manufacturer information*; E1 assessed, but not further discussed	years since final menstrual period not associated with E2 levels, but with increased FC between regions of left and right PPC, and of right PPC and right lateral PFC; E2 levels associated with enhanced FC of left PHG anterior division with precuneus and with right PHG posterior division
Zsido et al. (2019)	N=974 adults; n=473 females (X_{age}=50.10 y., range: 20-78 y.), with female midlife subgroup (age range: 35-55 y.); n=501 males, (X_{age}=51.24 y., range: 19-79 y.); E2 assessed in n=390	Does E2 mitigate the negative association of VAT with structural brain networks and cognitive health? Whole-brain and verbal episodic memory areas	sMRI (T1-weighted, MPRAGE) and abdominal MRI (3T); verbal episodic memory test; regression analyses of E2 and memory network covariance and of VAT and memory network covariance with E2 as moderator	serum E2, ECLIA ("Roche", Sen: 5.01 pg/ml), E2 subgroups (low/high) by means of median split	E2 positively correlated with memory network covariance in age-adjusted females; in both sexes: VAT associated with stronger negative association of aging and network covariance; E2 associated with a reduction of this negative association (in females); female midlife subgroup: low E2 levels associated with lower memory network covariance and worse memory performance
Other studies					

Grotzinger et al. (2024)	N=1 male, age: 26 y., assessed for 30 consecutive days; *parallel to dense-sampled female of Pritschet et al. (2020)*; scan schedule: day 1-20: morning; day 11-20: morning and evening; day 21-30: evening	How do diurnal hormone fluctuations relate to changes in functional brain networks? How do hormone-brain associations differ compared to the densely sampled female (in *Pritschet et al., 2020*)? Whole-brain	sMRI (MPRAGE; 3T) and rs-fMRI (3T); FC analyses similar to female participant, (*cf. Pritschet et al., 2020, for edgewise sensitivity analyses and network parcellation*); two-way ANOVAs of hormones (E2, testosterone, cortisol) and retrieved networks; correlation analyses with hormones	serum E2 daily, LC-MS/MS ("BRAC", Sen: 1 pg/mL, intra-assay CV: <5%)	diurnal fluctuations of all 3 hormones linked to changes in functional coherence; strongest association with DAN; E2 associated with increased coherence in all networks but the subcortical network in both female & male (SMN in female only); testosterone with varied associations in both; relationships between hormones (E2, testosterone) & whole-brain coherence replicated and exaggerated in male
Murata et al. (2024)	*Same sample as in Grotzinger et al. (2024)*, i.e., single dense-sampled male (age: 26 y.) for 30 consecutive days	How do diurnal hormone fluctuations relate to changes in brain morphology? Whole-brain and MTL subregions: HPC (CA1, CA2, CA3, subiculum, dentate gyrus), PHC, PRC, ERC	sMRI (MPRAGE and T2-weighted; 3T); *for scan schedule cf. Grotzinger et al. (2024)*; *t*-tests & multivariate regressions for role of day time; correlation analyses of hormones (E2, testosterone, cortisol) and TBV, GMV, CT, CSF, and ventricle size	*cf. Grotzinger et al. (2024)*	from morning to evening: global increases in CSF and ventricle size; decreases in TBV, total GMV, and CT; strongest GMV decrease: parietal & occipital regions; volumetric decreases in right HPC, brainstem, and cerebellum; stable WMV; E2, testosterone and cortisol positively associated with TBV, total GMV, and CT;

					no association of hormones and HPC subfield volumes

Note. Retrieved and included studies on endogenous estrogen effects sorted by study design. Note that one study (Hwang et al. 2015) comprises an exogenous estrogen group, as E2 levels were available only for the NC subgroup. *ACC* anterior cingulate cortex, *AD* axial diffusivity, *AG* angular gyrus, *ALFF* amplitude of low frequency fluctuations, *AMY* amygdala, *ANCOVA* analysis of covariance, *ANOVA* analysis of variance, *ATC* anterior temporal cortex, *CA* cornu ammonis, *CBF* cerebral blood flow, *CC* cingulate cortex, *CG* cingulum, *CLIA* chemiluminescence immunoassay, *CMN* centromedial nucleus, *CRUS I* posterior cerebellum crus I, *CSF* cerebrospinal fluid, *CT* cortical thickness, *CV* coefficient of variance, *DAN* dorsal attention network, *DCM* dynamic causal modelling, *DHEA(-S)* dehydroepiandrosterone (sulfate), *dlPFC* dorsolateral prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex, *DMN* default mode network, *DSI* diffusion spectrum imaging, *DTI* diffusion tensor imaging, *DWI* diffusion weighted imaging, *E2* 17beta-estradiol, *EC* eigenvector centrality, *ECLIA* electrochemiluminescence immunoassay, *ECN* executive control network, *EEM* emotional enhancement of memory, *ELISA* enzyme-linked immunosorbent assay, *ERC* entorhinal cortex, *FA* fractional anisotropy, *FC* functional connectivity, *FCN* frontal control network, *FFG* fusiform gyrus, *fMRI* functional magnetic resonance imaging, *FP* follicular phase, *FPN* frontoparietal network, *FSH* follicle stimulating hormone, *GM(V)* gray matter (volume), *GnRHa* gonadotropin-releasing hormone antagonist, *HPC* hippocampus, *HPG* hypothalamic-pituitary-gonadal (axis), *HPT* hypothalamus, *ICA* independent component analysis, *ICPP* idiopathic central precocious puberty, *IFG* inferior frontal gyrus, *INS* insula, *IOG* inferior occipital gyrus, *IPL* inferior parietal lobule, *IRMA* immunoradiometric assay, *ITG* inferior temporal gyrus, *LC-MS/MS* liquid chromatography-mass spectrometry, *LD* longitudinal diffusivity, *LH* luteinizing hormone, *LME* linear mixed-effects model, *LP* luteal phase, *M1* primary motor cortex, *MC* menstrual cycle, *MD* mean diffusivity, *MDD* major depressive disorder, *MEIA* microparticle enzyme immunoassay, *MFG* middle frontal gyrus, *MP* menopause/menopausal, *mPFC* medial prefrontal cortex, *MPLN* meso-paralimbic network, *MP(2)RAGE* magnetization prepared (2) rapid gradient echo, *MRS* magnetic resonance spectroscopy, *MTL* mediotemporal lobe, *MTR* magnetization transfer ratio, *NAcc* nucleus accumbens, *OC* oral contraceptive, *OFC* orbitofrontal cortex, *OP* ovulatory phase, *P4* progesterone, *PCA* principal component analysis, *PCC* posterior cingulate cortex, *PCG* precentral gyrus, *PFC* prefrontal cortex, *PHC* parahippocampal cortex, *PPC* posterior parietal cortex, *PPI* psychophysiological interaction, *PPP* peripheral precocious puberty, *PRC* perihinal cortex, *pSTS* superior temporal sulcus, *PTSD* Posttraumatic Stress Disorder, *QTI* q-space trajectory imaging, *RD* radial diffusivity, *RIA* radioimmunoassay, *ROI* region of interest, *rs (-fMRI/-FC)* = resting-state (-fMRI/-FC), *RSN* resting state network, *Sen* (assay) sensitivity, *SFG* superior frontal gyrus, *SLF* superior longitudinal fasciculus, *SMG* supramarginal gyrus, *SMN* somatomotor network, *sMRI* structural magnetic resonance imaging; *SN* salience network, *SNR* signal-to-noise ratio, *SPL* superior parietal lobule, *SPM* statistical parametric mapping, *STG* superior temporal gyrus, *t* time point, *TBV* total brain volume, *TPJ* temporo-parietal junction, *TPN* temporo-parietal network, *VAN* ventral attention network, *VAT* visceral adipose tissue, *VBM* voxel-based morphometry, *vlPFC* ventrolateral PFC, *VMHC* voxel-mirrored homotopic connectivity, *VN* visual network, *VTA* ventral tegmental area, *WM(V)* white matter (volume)

Table 2 Exogenous estrogen studies

Study	Sample characteristics	Aim of the study; pathway/ network	Study design, methods, variables	Estrogen measure	Findings
Hormonal contraception (HC)					

Brouillard et al. (2023	N=180; n=139 females: n=62 current COC users (X_{age}=26.3 y.), n=37 past users (X_{age}=27.6 y.), early FP or pre-OP, n=40 never users (X_{age}=26.1 y.), early FP or pre-OP; n=41 males (X_{age}=26.3 y.)	How do endogenous and exogenous sex hormones affect structural correlates of fear circuitry, and what are the current or long-term effects of COC use? Fear circuitry: AMY, HPC, HPT, anterior INS, dorsal and rostral ACC	sMRI (MPRAGE; 3T); surface-based GMV and CT; analyses of associations between brain morphology and endogenous hormones (E2, P4, testosterone; in all groups) and exogenous EE and progestin androgenicity (in current COC users)	saliva E2 and EE, LC-MS/MS ("Sciex"; Sen: 0.3 pg/mL for E2, 0.11 mg/mL for EE)	never vs. past COC users: thicker right anterior INS, independent of cycle phase; low vs. high EE dose: smaller GMV in right anterior INS, left vmPFC, and left dorsal ACC; never users: E2 inversely correlated with bilateral HPC; males: larger GMV of bilateral vmPFC (vs. current users) and dorsal ACC (vs. females)
De Bondt e al. (2013a)	N=30 females, X_{age}= 21.7 y. (range: 18-28 y.); n=15 NC (X_{age}=21.1 y.), FP vs. LP; n=15 monophasic COC (X_{age}=22.3 y.), active vs. inactive pill phase	How do COC use and MC phase change regional GMV, in relation to hormone levels? Whole brain cortical and subcortical GM	sMRI (MPRAGE; 3T); VBM analyses for local GMV; correlation analyses with hormones (E2, P4, FSH, LH), for groups and phases separately	plasma E2 per visit, ECLIA ("Roche"; *no sensitivity information*)	FP vs. LP: GMV increased in ACC, left CG, INS, MTG right MFG; decreased in SFG; LP: strong negative correlation between E2 levels and GMV of ACC; active vs. inactive pill: decreased GMV in postcentral gyrus, caudate and left MFG; COC vs. NC: phase-dependent increases in GMV in bilateral FFG, right MFG/SFG, CG
De Bondt e al. (2013b)	*Same sample as in De Bondt et al. (2013a)*	How do COC use and MC phase affect WM, in relation to	DTI (3T); fiber tractography for tract reconstruction; FA and MD of reconstructed tracts;	*cf. De Bondt et al. (2013a)*	COC vs. NC: higher MD in fornix, across cycle phases and in LP; different

		hormone levels? ROIs: corpus callosum, bilateral CG, fornix and corticospinal tracts	correlation analyses of DTI measures and hormones (E2, P4, FSH, LH)		E2 levels only in LP; E2 and LH negatively correlated with fornix MD
De Bondt e al. (2015)	N=37 females; n=18 NC (X_{age}=24.5 y.), early FP vs. peri-OP vs. LP; n=19 monophasic COC users (X_{age}=23.3 y.), active vs. inactive pill phase	How do hormonal stages of MC and COC use affect RSNs? DMN, ECN	rs-fMRI (3T); ICAs; paired/ two-sample t-tests for within-/ between-group comparisons; correlation analyses of hormones (E2, P4, FSH, LH), imaging data and premenstrual symptoms	*cf. De Bondt et al. (2013a);* ovulation confirmed by urinary test	between groups/ hormonal stages: relative stability of DMN and ECN; LP: E2 positively correlated with FC in IPL (in ECN), of precuneus-MFG (in DMN); COC: positive correlation of posterior DMN FC and premenstrual symptoms
Mueller et al. (2021), follow-up results (part 2)	N=1 female, age: 23 y., assessed for 30 consecutive days after COC onset	Were prior findings of MC-related changes in RSNs specific to intrinsic hormone dynamics?	*cf. Mueller et al. (2021); Table 1 (Endogenous estrogen findings)*; 0.02 mg EE + 0.1 mg levonorgestrel (suppressing P4) as COC	*cf. Mueller et al. (2021); Table 1 (Endogenous estrogen findings)*	replication of same four core communities identified for RSNs in NC condition; no replication of reorganization events, suggesting absence of MC-related RSN reorganization under hormonal disruption
Peper et al. (2013)	N=40 participants (age range: 18-25 y.); n=20 females (X_{age}=21.0 y.): n=16 OC users, at the last day of withdrawal, n=4 NC, on day 7 of menses; n=20	How do sex hormones affect the integrity of frontostriatal WM and delay discounting behavior?	DTI (3T) and MTR (3T); analyses of myelination and integrity (FA, MD, LD, RD) of WM tracts; delay discounting task; correlation analyses of WM,	saliva E2, ELISA ("DRG"; intra-assay CV: 11%, 4%, and 2%, at 10, 140, and 900 pmol/L)	across groups: impulsive delay discounting behavior associated with higher MD and lower FA in frontostriatal tract; E2 not associated with frontostriatal WM integrity or

	males ($\bar{X}_{age}$=21.9 y.)	WM tracts involving PFC and striatum	performance and hormones (E2, testosterone)		delay-discounting performance in any of the groups (males, NC/ OC females); males: higher testosterone associated with higher RD in frontostriatal tract
Petersen et al. (2014)	N=91 females; n=45 NC: n=20 in early FP, n=25 in LP; n=46 COC users: n=24 in active, n=22 in inactive pill phase; *no age information*	Do NC females and females on OCs differ in their resting state activity? DMN, ECN	rs-fMRI (3T); ICA and FC analyses; ANOVAs of FC and hormonal stage (FP, LP, active OC, inactive OC); correlation analyses of network time courses (of DMN and ECN) and hormones (E2, P4); COC: monophasic, combined E2 and progestin pill	pooled saliva E2 (2 samples, before and after scanning), ELISA ("Salimetrics"; Sen: 0.1 pg/mL)	FP vs. LP: increased FC of anterior DMN (left AG) and ECN (ACC); FP vs. active COC: increased FC with anterior DMN-left AG, ECN with bilateral ACC and left MFG, FP vs. inactive COC: increased FC anterior DMN-right caudate, inactive vs. active COC: increased FC with ECN in left MFG; no correlation of FC with E2 or progesterone
Petersen et al. (2015)	N=90 females; n=46 NC: n=21 in early FP, n=25 in late LP; n=44 COC users: n=22 in active, n=22 in pill phase; *no age information*	Do oral contraceptives alter cortical thickness and the volume of subcortical regions? Regions of DMN (PCC, MTC, PHC, HPC), and SN (ACC, AMY, INS, SMG, OFC)	sMRI (T1-weighted; 3T); quantitative morphometric analysis of CT; post-hoc subgroup comparisons of brain morphometry; correlation analyses of hormones (E2, P4) and brain morphometry	*cf. Petersen et al. (2014)*	COC: thinner left caudal ACC, PCC, left INS, and left and right lateral OFC; FP and LP vs. active COC: increased thickness of PCC; FP vs. active/inactive COC: increased thickness of left/right OFC;

					E2 and left OFC thickness positively correlated in NC (uncorrected threshold)
Pritschet et al. (2020), follow-up results (part 2)	*Same sample as in Mueller et al. (2021), and Taylor et al. (2020),* i.e., single dense-sampled female (age: 23 y.) for 30 consecutive days, after COC onset	Were prior findings of MC-related changes in global efficiency specific to intrinsic hormone dynamics?	*cf. Pritschet et al. (2020); Table 1 (Endogenous estrogen findings);* 0.02 mg EE + 0.1 mg levonorgestrel (suppressing P4) as COC	*cf. Pritschet et al. (2020); Table 1 (Endogenous estrogen findings)*	replication of finding that intrinsic network dynamics are partially driven by recent E2 states; both in NC and under COC, E2 most strongly associated with global efficiency in DMN and DAN (within-network connectivity), peaking during ovulation
Sharma et al. (2020)	Part 1 (MRI): N=75 females, X_{age}=19.6 y.; n=48 NC, in early FP, pre-OP or LP; n=27 COC users in active pill phase (with pubertal or adult onset); Part 2 (Stress test): N=140 females, X_{age}=19.1 y.; n=82 NC; n=58 COC users	Are there structural, functional, or behavioral differences between females using OCs since adolescence or adulthood, and NC females? Emotional working memory and stress areas: bilateral INS, and whole-brain analyses	sMRI (MPRAGE; 3T), DTI (3T) and task-based fMRI (3T): emotional picture N-back working memory task; Trier social stress test (and cortisol); VBM analyses of total GM and WM; analyses of relation of brain activation and OC use duration (regression) and hormones (correlations; E2, P4); whole-brain FA	saliva E2 per part, ELISA ("Salimetrics", Sen: 5.49-19.08 pg/mL, intra-assay CV: <15%)	COC vs. NC: decreased GMV (right putamen), increased WMV (e.g., right putamen, right AMY, left HPC), increased FA in left HPC, increased activation for negative stimuli (e.g., right IFG and INS); pubertal vs. adult COC onset: decreased cortisol response after stress test, differences in task-related activation (e.g., increased left fusiform gyrus activity for positive cues); no correlations of E2 and brain

					activation in any group
Sharma et al. (2021)	N=74 females, X_{age}=19.6 y.; n=48 NC, in early FP, pre-OP or LP; n=26 COC users; analyses across participants, controlling for COC use	How do sex hormones influence brain activation in a positive and negative emotional working memory task? Emotional working memory areas	task-based fMRI (3T): emotional picture N-back working memory task; whole-brain multiple-regression analysis of brain activity and hormone levels; depression scores	*cf. Sharma et al. (2020);* E2-to-P4 ratio for measure of free estrogenic activity	positive stimuli elicited reward-related, negative corticolimbic activation; E2 positively correlated with right SFG, SPL and precentral gyrus and left precuneus activation for positive, and with left SFG and ACC, and right postcentral gyrus activation for negative stimuli; E2 modulated anterior areas (P4: posterior)
Taylor et al. (2020), follow-up results (part 2)	*Same sample as in Mueller et al. (2021), and Pritschet et al. (2020),* i.e., single dense-sampled female (age: 23 y.) for 30 consecutive days, after COC onset	Were prior findings of MC-related changes in MTL structure specific to intrinsic hormone dynamics? MTL: CA1, CA2/3, dentate gyrus, PRC, ERC, PHC, subiculum	*cf. Taylor et al. (2020);* *Table 1 (Endogenous estrogen findings);* 0.02 mg EE + 0.1 mg levonorgestrel (suppressing P4) as COC	*cf. Taylor et al. (2020);* *Table 1 (Endogenous estrogen findings)*	GMV in CA2/CA3 reduced in COC condition; P4-dependent volumetric changes of CA2/CA3, and PHC, observed in NC, were abolished after P4 suppressio (only P4 and PRC still negatively correlated); E2 associated with CA2/CA3 volume under P4 suppression conditions only
Menopausal hormone therapy (MHT)					

Brown et al. (2023)	N=72 females, X_{age}=47.03 y.; n=31 post-MP with BSO (age range: 35-55 y.): n=16 ERT users (X_{age}=44.75 y.), n=15 ERT non-users (X_{age}=46.53 y.); n=25 pre-MP (X_{age}=43 y., range: 33-51 y.); n=16 spontaneous MP (X_{age}=56.06 y., range: 47-59 y.)	Are associative memory changes present in females with BSO? Do these changes resemble those of females in spontaneous MP? Associative memory areas: HPC, frontal cortex	task-based fMRI (3T): associative memory task (novel vs. repeated face-name pairs); ROI-based and multivariate partial least squares analyses; correlation analyses with levels of sex hormone metabolites (E1G: estrone-3-glucuronide; PdG: pregnanediol glucuronide)	urinary E1G, (ELISA, *no type of manufacturer/ sensitivity information*)	ERT users: larger right posterior lateral HPC activation, compared to non-users and spontaneous MP females; ERT users: different network-level activational pattern than non-users and spontaneous MP females; across groups: E1G levels weakly positively correlated with right lateral posterior HPC activation and memory task accuracy
Compton et al. (2008)	N=34 post-MP females; n=17 ERT-naive (X_{age}=65 y.); n=17 long-term oophorectomized, ERT-using (X_{age}=62 y., mean of 14 years of ERT use)	How does long-term estrogen therapy affect cortical 5-HT_{2A} serotonin receptor availability? Memory-related areas: CC, HPC, MTC, STC, frontal cortex, occipital and parietal lobes	SPECT (selective 5-HT_{2A} receptor ligand I-5-I-R91150) and sMRI (MPRAGE; 1.5T); mean eBP in ROIs, adjusted for WM and GM (from VBM); correlation analyses of eBP and E2; verbal & general memory; intelligence tests	serum E2 (*no type of assay/ manufacturer/ sensitivity information*)	ERT users: higher 5-HT_{2A} receptor binding (not significant after correction for multiple comparison), mean HPC receptor binding negatively correlated with memory; ERT-naive: higher mean and right HPC receptor binding; no correlation of eBP or behavioral scores with E2 levels or length of ERT use
Ottowitz et al. (2008a)	N=7 post-MP females, X_{age}=64.2 y. (range: 48-76 y.;	How do E2 levels affect covariance of AMY	[^{18}F]FDG-PET and sMRI (T1-weighted; 1.5T); glucose binding:	serum E2 at baseline and at 24hrs, two-site monoclonal	during E2 infusion: significant covariance of

	at least 1 year from MP), being MHT-non-users; scanned at baseline and after 24 hours of E2 infusion	activation with other areas of the brain, pre- and post-MP? AMY-cortical network connectivity	voxel-wise whole-brain covariate analyses of AMY CMRglc; graded E2 infusion: 0.1 ug/kg/hr (first 12hrs), followed by 0.135 ug/kg/hr	non-isotopic system ("Abbott AxSYM", Sen: 20 pg/mL)	right AMY CMRglc with activity in three temporal cortex regions; right AMY CMRglc covaried with right medial and superior frontal gyri only during E2 infusion
Ottowitz et al. (2008b)	N=11 post-MP females, *cf. Ottowitz et al. (2008a) for age, MP status, and sampling information*	Is connectivity between HPC and PFC enhanced by E2 infusion in post-MP females? HPC-PFC connectivity	*cf. Ottowitz et al. (2008a) for FDG-PET and E2 infusion;* subtraction analyses of CMRglc for ROIs; seed-based FC (HPC, PFC); stacked models of effective connectivity	*cf. Ottowitz et al. (2008a)*	after E2 infusion: overall greatest CMRglc increase in right SFG and MFG; relative to the right SFG, the right HPC and MFG were sites of CMRglc covariance; best model of regional interactions across E2 change: path from right SFG modulates right HPC, that in turn projects to MFG
Transgender/ Gender affirming hormone therapy (GAHT)					
Kranz et al. (2017)	Baseline (t1): N=77 adults: n=44 transgender individuals: n=15 TW (X_{age}=28.07 y.), n=29 TM (X_{age}=26.79 y.); n=33 cisgender individuals: n=18 CW (X_{age}=25.78 y.), n=15 CM (X_{age}=28.6 y.); t2: GAHT + 4 weeks (n=12 TW, n=26 TM, n=6 CW, n=2 CM);	How does hormone treatment affect WM microstructure in transgender individuals, as compared to cisgender individuals?	DWI (3T); voxel-wise analysis of WM tracts: MD and FA; ANOVAs to compare individual difference maps between time points (t3-t1, t2-t1) between groups; transgender individuals with various GAHT treatments; correlation analyses of MD	plasma E2 per visit; *no type of assay/ manufacturer/ sensitivity information*	TW: increased E2 levels with time; TM at 4 weeks post-GAHT: E2 change positively correlated with MD changes in right corticospinal tract and middle cerebellar peduncle, and left cerebral peduncle, fornix/stria

	t3: GAHT + 4 months (n=15 TW, n=28 TM, n=12 CW, n=13 CM)		and FA maps with hormone levels (E2, testosterone)		terminalis, internal capsule, superior cerebellar peduncle, and sagittal striatum; TM at 4 months post-GAHT: absence of prior E2 correlations; E2 changes now negatively correlated with FA of multiple WM structures (e.g., corpus callosum); CW: E2 levels negatively correlated with FA changes (e.g., external capsule, fornix/stria terminalis, corpus callosum
Nota et al. (2017)	Baseline (t1): N=73 adults; n=34 transgender individuals: n=14 TW (med. age: 21 y., range: 18-44 y.), n=22 TM (med. age: 21 y., range: 18-43 y.); n=37 cisgender individuals: n=20 CW (med. age: 23 y., range: 19-34 y.), n=17 CM (med. age: 28 y., range: 20-34 y.); t2: GAHT + 4 months (n=13 TW, n=21 TM)	Is FC in transgender individuals sex-typical or sex-atypical before and after starting with GAHT? DMN, SN, left and right working memory network	rs-fMRI (3T); ICA analyses of rs-FC; ANOVAs and post-hoc *t*-tests of activation with hormones (E2, testosterone); clinical questionnaires; control for endogenous hormones: GnRHa (gonadal suppression) for 8 weeks prior to baseline, then: GnRHa and GAHT (E2 patches in TW; testosterone gel + letrozol in TM)	serum E2, ELISA ("PerkinElmer", Sen: 20 pmol/L); TW/ TM with E2 per visit, CW/ CM with E2 at baseline only	across groups: similar patterns for DMN, SN, and working memory network; TM & TW: no FC changes between baseline and 4 months post-GAHT onset; CM vs. CW: greater FC in caudate nucleus (right working memory network), not associated with E2 levels

Schneider et al. (2019)	N=18 TW (X_{age}=40.2 y., at least 1 year post-GAS); t1: GAHT washout + 30 days; t2: GAHT reintroduction + 60 days	How does E2 affect rs-fMRI of the SMC and basal ganglia following surgical hypogonadism in TW? Striatum, SMC, thalamus	rs-fMRI (3T); seed-based and whole-brain activation analyses; group-MVPA; multiple regression analyses of changes in rs-FC and E2; anxiety/ depression inventories	serum E2 per visit, ECLIA ("Roche", Sen: 5.0 pg/mL, intra-assay CV: 5.7%)	GAHT: increase in FC of left thalamus with left SMC and left putamen; with E2 change: subcallosal cortex with greatest signal change; decoupling of subcallosal cortex and medial frontal cortex; no association of changes in E2 levels and changes in rs-FC
Soleman et al. (2016)	*Subsample of Nota et al. (2017):* N=40 adults; n=21 TM with gonadal suppression for 8 weeks (X_{age}= 22.6 y., range: 17.5-43.3 y.); n= 19 CW (X_{age}=25.8 y., range: 18.8-42.7 y.)	How does gonadal suppression in TM affect emotion processing? Whole-brain and emotion processing areas: AMY, HPC, INS, ventral striatum, superior temporal and orbitofrontal lobe	task-based fMRI (3T): rating positive vs. negative vs. neutral images; seed-based and whole-brain activation analyses; regression analyses with hormones (E2, LH, FSH); *cf. Nota et al. (2017), for gonadal suppression*	*cf. Nota et al. (2017)*	CW significantly older than TM (!); TM after gonadal suppression: less activation in superior temporal lobe during positive affective pictures; no differences for negative affective images; no hormonal correlations with activation of ROIs, but with areas outside (for LH and FSH), without group differences; no correlation of activation with E2 levels
Spies et al. (2016)	Baseline (t1): N=134 adults; n=57 transgender individuals: n= 24 TW (X_{age}=30.25 y.), n=33 TM (X_{age}=26.79 y.); n=77 cisgender individuals: n= 44	How do sex steroids influence rsFC related to empathy? RSN clustered by SMG	rs-fMRI (7T) per visit; seed-based analyses of activation and FC; neuropsychological tests; correlation analyses of FC and hormones (E2, testosterone);	*cf. Kranz et al. (2017)*	TW: weakest FC in SMG of all groups; E2 increase from baseline to 4 months post-GAHT associated with assimilation of connectivity

	CW ($\bar{X}_{age}$=26.16 y.), n= 33 CM ($\bar{X}_{age}$=27.48 y.); t2: GAHT + 4 weeks (n=15 TW, n=20 TM); t3: GAHT + 4 months (n=15 TW, n=20 TM)	transgender individuals with various medications			strength to that of the other groups; FC change over transition not associated with E2 or questionnaire outcomes, but rather with changes in empathy; TM: no significant change in this SMG network across transition
Randomized -controlled trials (RCT)/ other					
Bayer et al. (2018)	N=125 females, $\bar{X}_{age}$=26 y. (range: 18-35 y.), assigned to E2 or placebo intervention; Day 1: menses onset; first dose of E2/placebo (evening); Day 2: second dose of E2/ placebo (morning) + memory encoding; Day 3: memory retrieval; E2 assessed in N=123	In humans, does 17β-estradiol enhance HPC plasticity in a dose-dependent or U-shaped relationship? How about other emotion processing areas? Whole-brain and ROIs: HPC, AMY	task-based fMRI (3T): emotional memory task (encoding neutral and negative pictures); retrieval and arousal rating; linear and quadratic regression models, and connectivity analyses with predictor "increase in salivary E2 from day 1 to day 2"; mood ratings; intervention: E2 valerate, 5 groups: 0 (placebo), 2, 4, 6, or 12 mg	pooled saliva E2 (2 samples per visit), luminescence assay ("IBL", Sen: 0.3 pg/mL); n=90 with additional serum E2 at t1 and t2, ELISA ("IBL", Sen: 10.6 pg/mL)	linear association of E2 increase (from day 1 to day 2) with activation in right posterior HPC, but U-shaped association with activity in a medial cluster of left posterior HPC, indicating that relationship depends on the HPC subregion; E2 without modulation of AMY, but negative association with right precuneus activation for negative vs. neutral pictures and precuneus-brainstem connectivity (in exploratory whole-brain analyses)

Berent-Spillson et al. (2015)	N=29 post-MP females (X_{age}=51.52 y., range: 45-55 y.); n=16 E2 (X_{age}=51.81 y.); n=13 P4 (X_{age}=51.15 y.) t1: baseline; t2: after first 90-day intervention period (E2/P4 or placebo); t3: after second 90-day intervention (vice versa)	How do exogenously administered E2 or P4 affect visual and verbal cognitive functioning? Episodic verbal and visual working memory areas: PFC, HPC	task-based fMRI (3T): episodic verbal memory and visual working memory tasks, in n=25 only; whole-brain and ROI-based analyses; depression inventory; intervention: 1mg oral E2 or n=200mg P4; with 12-week washout between hormone vs. placebo	serum E2, CLIA ("Bayer"; *no sensitivity information*)	E2 (vs. placebo): increased left PFC and decreased right HPC activation in verbal memory task, but similar performance; P4 (vs. placebo): increased left PFC and right HPC activation in visual working memory; E2 and P4 groups with similar performance in both tasks
Borgsted et al. (2022)	N=60 females (med. age: 22.4 y., range: 18.4-37.2 y.); n=31 GnRHa; n=29 placebo; t1: early FP (baseline: PET + MRI + depression inventory); t2: post-intervention (follow-up MRI and depression inventory; missing in n=3)	How does GnRHa affect HPC volume compared to placebo and is this structural change associated with GnRHa-induced E2 decrease or depressive symptoms increase? HPC	[^{11}C]DASB-PET; sMRI (MPRAGE; 3T); linear regressions of changes (t2-t1) in HPC volume, SERT binding potential, and E2; multiple linear regressions for changes within-GnRHa group; additional LMEs; intervention: GnRHa implant (ZOLADEX; 3.6mg goserelin) vs. placebo (saline)	serum E2 per visit, ECLIA ("Roche", Sen: 0.04, and 78.9 nmol/L); change in E2 (t2-t1; analyzed in GnRHa group)	GnRHa vs. placebo: non-significant decrease in HPC volume; GnRHa group: HPC volume positively associated with E2 change, if adjusted for baseline SERT levels, but not if adjusted for SERT change; no association between HPC volume and depressive symptoms, adjusted for E2 change; no HPC volume mediation of the association between E2 change and depressive symptoms

Conjaerts et al. (2023)	N=227 adults (age range: 18-40 y.); n=111 females (early FP); n=116 males; 4 groups: E2 gel + intranasal OXT (n=26 males, n=25 females); placebo gel + intranasal OXT (n=31 males, n=33 females); E2 gel + intranasal placebo (n=32 males, n=27 females); placebo gel + intranasal placebo (n=27 males, n=26 females)	What are the effects of exogenous E2 and OXT and their interactions on rs-FC in healthy adults? bilateral HPC, AMY; DMN (medial PFC, PCC, left and right lateral parietal regions)	sMRI (3T) and rs-fMRI (T1-weighted; 3T); whole-brain seed-to-voxel analysis (AMY, HPC); ANOVAs with hormones as covariates (E2, P4, OXT, testosterone); intervention: E2 ("Estramon", 2 mg) vs. placebo gel (2 mg ultrasonic gel), followed (gel + 3 hrs) by intranasal OXT (24 IU) vs. placebo; MRI 35 min later	serum E2, pre- and post-treatment (same day); *no type of assay/ manufacturer/ sensitivity information*	males: single OXT or E2 treatment with decreased rs-FC between left AMY and e.g., bilateral lingual gyrus; combined OXT and E2 treatment with increased rs-FC; females: single OXT or E2 treatment with increased rs-FC between right HPC and left ACC; combined treatment with opposite effect
Fisher et al. (2017)	N=58 females; n=29 GnRHa ($\bar{X}_{age}$=23.2 y.); n=29 placebo ($\bar{X}_{age}$=25.4 y.); t1: mid-LP (baseline), t2: follow-up at t1 + 17.8 days (mean; GnRHa group), or in FP (placebo group)	How does GnRHa treatment affect rs-FC brain networks involved in mood regulation and major depression? Mood- and depression-related areas: AMY, HPC, ACC, PCC, dorsal and median raphe	rs-fMRI (3T); ROI-based FC analyses; ANCOVAs; structural equation models of rs-FC changes, depressive symptoms, and E2; intervention: GnRHa implant (3.6 mg goserelin) vs. placebo (saline injection)	serum E2 per visit, *no type of assay/ manufacturer information* (Sen: 0.04-78.9 nmol/l)	GnRHa group: increase in depressive symptoms from t1 to t2 positively associated with AMY-right temporal cortex rs-FC and negatively with HPC-CG rs-FC; negative association between change in E2 and change in depressive symptoms from t1 to t2; mediation of this association by rs-FC changes not statistically significant
Hidalgo-Lopez et al. (2023)	N=34 females; n=17 COC ($\bar{X}_{age}$=25.5 y.); n=17 placebo ($\bar{X}_{age}$=24.5 y.);	How does COC treatment affect directed connectivity of RSNs	sMRI (T1-weighted; 3T) and rs-fMRI (3T); 11 ROIs of RSNs; spectral dynamic causal modeling; parametric	serum E2 per visit, ECLIA ("Roche"; *no sensitivity information*)	COC vs. placebo treatment: reduced E2 levels from t1 to t2; within-network connectivity increased in

	t1: early FP of pre-treatment cycle (no COC); t2: last week of treatment cycle (15-21 days after administration onset)	compared to placebo treatment, and how does this relate to mood symptoms? RSNs: DMN, SN, ECN	empirical bayes; intervention: COC pill (ethinyl E2 30 mg + 0.15mg levonorgestrel) vs. placebo pill, administration onset at first day of menses		DMN, decreased in SN and ECN; increased effective connectivity from dorsal ACC (SN) to medial nodes of the DMN, and right AG (posterior DMN) to posterior ECN; stronger effective connectivity between ECN and SN; increased connectivities positively associated with COC-induced mood deterioration
Joue et al. (2022)	N=131 adults; n=68 E2: n=33 females (X_{age}=25.8 y.), n=35 males (X_{age}=25.9 y.); n=63 placebo: n=31 females (X_{age}=26.4 y.), n=32 males (X_{age}=26.1 y.); t1: pill administration (females: early FP); t2: pill administration + fMRI	Are there organizational sex effects beyond activational E2 effects in the DA system? Dopaminergic system: substantia nigra/VTA, NAcc, caudate, ACC, vmPFC	task-based fMRI (3T): reinforcement learning task; questionnaires; computational modeling; ANOVAs; intervention: E2 valerate pill ("Progynova 21 UTA"; 2 x 6 mg for males, 2 x 4 mg for females) vs. placebo pill (mannitol and silicon dioxide)	pooled saliva E2 (3 samples per visit), luminescence immunoassay ("IBL"; *no sensitivity information*)	increased E2 levels associated with greater activity related to reward prediction errors in the mesocorticolimbic pathway (substantia nigra/VTA, NAcc, caudate, ACC, ventromedial and medial PFC); females vs. males: overall greater ACC activation; greater bilateral NAcc activation only for placebo group; smaller learning rate in females, and in females and males with E2 administration; circulating E2 with more extensive effects

					on activation than sex
Thomas et al. (2014)	N=13 peri-MP females, X_{age}=52.3 y. (mean of 8.7 months after last period); within-subjects counter-balanced (E2+P4 vs. placebo); t1: baseline; t2: day 39 within 1st intervention period (E2+P4 or placebo); t3: day 39 within 2nd intervention period (vice versa)	Does sequential 17β-estradiol plus P4 modulate reward-related brain activity? Reward circuit: ventral striatum (caudate, putamen), vmPFC	task-based fMRI (1.5T) at t2 and t3: monetary reward task; *t*-tests of drug effects on neural activation; regression analyses of brain activation and E2; intervention: sequential 17β-estradiol for 21 days (2mg daily) plus oral P4 (100 mg daily) from day 12-21, vs. placebo, with 7 days wash-out period	plasma E2 before study and per visit, RIA (*no manufacturer information*; Sen: 11 pmol/L, intra-assay CV <5%)	E2 levels positively correlated with reward-related areas (left lateral PFC, bilateral AMY-HPC complex, vmPFC, right caudate, and left ventral putamen); E2+P4 vs. placebo: overall increased response of reward-related areas (striatum, vMPFC) in parallel with shorter RTs to reward anticipation
Wei et al. (2021)	N=63 females; n=43 healthy (X_{age}=33.9 y.); n=20 PMDD diagnosis (X_{age}=37.6 y.); within-subjects counter- balanced protocol; t0: baseline (week 0); t1: PET in week 10-12 after 3 months GnRHa injections alone; t2: PET in week 14-16 after GnRHa injections plus E2 or P4 add-back; t3: PET in week 21-23 after GnRHa injection, plus opposite add-back	What are the neural substrates associated with behavioral and cellular response to sex steroid hormones in PMDD? Whole-brain	[^{15}O]H_2O-PET for resting rCBF; RNA sequencing; pair-wise analyses of between-hormone effects; intervention: GnRHa (for hormone suppression; "Lupron", 3.75 mg; weeks 0, 4, 8, 12, 16, 12), two add-back periods (weeks 12-17 and 19-24) with E2 (transdermal, 0.1 mg/day), and P4 (vaginal, 200 mg twice/day), counter-balanced (weeks 17-19 wash-out)	plasma E2 per visit, LC-MS/MS (*no manufacturer/ sensitivity information*)	no basal difference in resting rCBF between groups; PMDD: decreased resting rCBF in the subgenual CC in E2 and P4 add-back, absent in controls; OFC, medial PFC, subgenual CC and inferior and superior temporal gyri with greater resting rCBF during E2 add-back compared to P4 add-back; ESC/E(Z) gene expression negatively correlated with change in resting rCBF between GnRHa and P4

					add-back, absent in controls
Wen et al. (2021)	N=90 females (age range: 18-30 y.); n=57 monophasic COC users: n=35 E2, n=22 placebo; n=33 NC (early FP): n=18 E2, n=15 placebo; 3 subsequent days: t1: fear conditioning; t2: E2 vs. placebo, and fMRI (learning); t3: fMRI (retention)	How does acute E2 administration impact neural activation and connectivity during and after fear extinction learning? Fear circuit: vmPFC, HPC, AMY	task-based fMRI (extinction learning at t2, extinction retention at t3; 3T) and rs-fMRI (post-extinction at t2, pre-retention at t3; 3T); PPI and mediation analyses; skin conductance response; intervention: placebo vs. E2 pill (2 mg, for n=16 COC users and n=10 NC; or 4 mg, for n=19 COC users, and n=8 NC)	serum E2 per visit (*no type of assay/ manufacturer/ sensitivity information*)	E2 levels positively associated with precuneus and vmPFC activation in early early and late extinction learning; early extinction learning: E2 negatively associated with task-based FC within DMN and SMN, and positively associated with dACC activation (in COC and NC); COC: stronger positive associations of E2 with rs-FC post-extinction (day 2); stronger negative associations with task-based FC after extinction retention (day 3); FC in early extinction partially mediated effects of E2 on post-extinction rsFC

Note. Retrieved and included studies on exogenous estrogen effects, sorted by study design. *ACC* anterior cingulate cortex, *AG* angular gyrus, *AMY* amygdala, *BSO* bilateral salpingo-oophorectomy, *CA* cornu ammonis, *CC* cingulate cortex, *CG* cingulum, *CLIA* chemiluminescence assay, *CM* cisgender men, *CMRglc* regional cerebral glucose consumption, *COC* combined oral contraceptive, *CT* cortical thickness, *CW* cisgender women, *DASB* [11C]3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile, *DMN* default mode network, *DWI* diffusion weighted imaging, *E1* estrone, *E2* estradiol, *eBP* estimated binding potential, *ECLIA* electrochemiluminescence immunoassay, *ECN* executive control network, *ELISA* enzyme-linked immunosorbent assay, *ERC* entorhinal cortex, *ERT* estrogen replacement therapy, *FA* fractional anisotropy, *FC* functional connectivity, *FDG* fluorodeoxyglucose, *FFG* fusiform gyrus, *fMRI* functional magnetic resonance imaging, *FP* follicular phase, *FSH* follicle stimulating hormone, *GAHT* gender affirming hormone therapy, *GAS* gender affirming surgery, *GM(V)* gray matter (volume), *GnRHa* gondadotropin-releasing hormone agonist, *HPC* hippocampus, *ICA* independent component analysis, *INS* insula/ insular cortex, *LC-MS/MS* liquid chromatography-mass spectrometry, *LD* longitudinal diffusivity, *LH* luteinizing hormone, *LME* linear mixed-

effects model, *LP* luteal phase, *med.* median, *MD* mean diffusivity, *MFG* middle frontal gyrus, *MHT* menopausal hormone therapy, *MP* menopause, *MPRAGE* magnetization prepared rapid gradient echo, *MTC* middle temporal cortex, *MTG* middle temporal gyrus, *MVPA* multi-voxel pattern analysis, *NAcc* nucleus accumbens, *NC* naturally cycling, *OC* oral contraceptive, *OFC* orbitofrontal cortex, *OP* ovulatory phase, *OXT* oxytocin, *P4* progesterone, *PCC* posterior cingulate cortex, *PCG* posterior cingulate gyrus, *PET* positron emission tomopgraphy, *PFC* prefrontal cortex, *PHC* parahippocampal cortex, *PRC* perirhinal cortex, *rCBF* regional cerebral blood flow, *RIA* radioimmunoassay, *ROI* region of interest, *rs(-fMRI/-FC)* resting state-fMRI/-FC, *RSN* resting state network, *RT* response time, *Sen* (assay) sensitivity), *SFG* superior frontal gyrus, *SMC* sensorimotor cortex, *SMG* supramarginal gyrus, *SMN* sensorimotor network, *SN* salience network, *SPECT* single photon emission computed tomography, *SPL* superior parietal lobe, *STC* superior temporal cortex, *TM* transgender men, *TW* transgender women, *VBM* voxel-based morphometry, *vmPFC* ventro-medial prefrontal cortex, *VTA* ventral tegmental area, *WM(V)* white matter (volume)

Highlights

- Neuroendocrine and neurocognitive research on estrogen has increased substantially in the last 15 years.
- Across all studies, a profound heterogeneity in study designs, as well as in imaging and analysis methods was observed.
- E2 levels relate to changes in human brain network functional and structural architecture, across the lifespan.
- Dense-sampling precision neuroimaging and preregistered RCTs are needed to address the gap in women's brain health.
- Future research should include distinguished measures of endogenous and exogenous estrogen levels.