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Estrogen and Memory during the Perimenopause Period: A Critical Review

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ABSTRACT

Menopause is an encompassing neuroendocrine aging process, marked by declining sex hormones, particularly estradiol, with significant consequences for cognitive brain function that will affect every woman who lives long enough to enter the phase. This critical review examines recent neuroimaging studies investigating the underlying biological mechanisms of cognitive changes during menopause, focusing on estrogen receptor density in the brain. Advanced neuroimaging techniques, such as ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET), have provided novel insights into the distribution and density of estrogen receptors across different menopausal stages. Key findings reveal that estrogen receptor (ER) density in the brain increases progressively over the menopause transition, independent of age and plasma estradiol levels. Notably, higher ER density is associated with poorer memory performance and predicts mood and cognitive symptoms in postmenopausal women. These results suggest a potential compensatory mechanism in response to declining estrogen levels, offering a neurobiological explanation for cognitive changes observed during menopause.

KEYWORDS: menopause, estrogen receptor density, neuroimaging, cognitive function, ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET)

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ESTROGEN AND MEMORY DURING THE PERIMENOPAUSE PERIOD

A longitudinal study identified distinct cognitive profiles during perimenopause (Weber et al., 2021). This research involved 85 perimenopausal women who underwent bi-annual cognitive assessments and hormonal measurements over 400 visits. The study employed a comprehensive neuropsychological battery to assess various cognitive domains, including attention, working memory, verbal fluency, fine motor speed, visuospatial skills, and learning and memory. Specific tests included the Digit Span subtest, D2 Test of Attention, Letter-Number Sequencing subtest, Controlled Oral Word Association Test, Grooved Pegboard Test, Hooper Visual Organization Test, and Rey Auditory Verbal Learning Test.

Using multilevel latent profile analysis (MLPA), the researchers identified four distinct cognitive profiles: cognitively normal, weaknesses in verbal learning and memory, strengths in verbal learning and memory, and strengths in attention and executive function. Profile 2, characterized by weaknesses in verbal learning and memory, showed less hormonal variability and more sleep disturbances. Profile 3 had higher FSH levels and fewer depressive and vasomotor symptoms, while Profile 4 showed a trend towards fewer sleep symptoms.

This study highlighted the significant heterogeneity in cognitive function during perimenopause and suggested that a minority of women may experience cognitive vulnerabilities similar to amnestic mild cognitive impairment. The authors emphasized the need for further research to determine if these weaknesses persist post-menopause. By establishing these cognitive profiles and their hormonal correlates, (Weber et al., 2021) laid the foundation for more focused neuroimaging investigations into the underlying biological mechanisms of cognitive changes during menopause.

ESTROGEN RECEPTOR DENSITY CHANGES

Building on the cognitive profile findings, a cross-sectional study used advanced ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET)
imaging to assess brain estrogen receptor (ER) density across menopausal stages (Mosconi et al., 2024). The study involved 54 midlife women aged 40-65, divided into three groups based on menopausal stage. Participants were carefully screened, excluding those with significant neurological or

psychiatric diseases, evidence of brain infarction or demyelination, history of drug or alcohol dependence, use of psychoactive medications, contraindications to MRI or PET imaging, history of oophorectomy or hysterectomy, use of hormonal therapy, or active pregnancy.

These authors measured plasma estradiol and SHBG levels, and cognitive measures included logical memory, animal naming, and object naming. Statistical analysis involved multivariate linear regression models to assess the effect of menopausal status on estrogen receptor density across different brain regions. Cohen's d effect size was calculated to examine the separation of menopause status based on ROI DVRs, and voxel-based analysis was conducted using factorial models with post-hoc t-contrast in SPM12.

Key findings revealed that ER density in the brain increases progressively over the menopause transition, independent of age, plasma estradiol, and sex hormone-binding globulin (SHBG) levels. Significantly, higher ER density was associated with poorer memory performance and predicted mood and cognitive symptoms in postmenopausal women. These results suggest estrogen receptor regulation in crucial brain regions is critical to postmenopausal cognitive decline.

This study provided a neurobiological basis for the cognitive changes observed in previous research, suggesting that increased ER density might be a compensatory mechanism in response to declining estrogen levels (Weber et al., 2021). These authors proposed that this compensatory response could explain the cognitive vulnerabilities observed in some perimenopausal women.

SPONTANEOUS BRAIN ACTIVITY CHANGES

Complementing the ER density findings, a study explored the association between spontaneous brain activity changes, serum estradiol levels, and global cognition using resting-state fMRI (He et al., 2021). The study included 32 premenopausal and 25 perimenopausal women. Resting-state fMRI scans were conducted, and Regional Homogeneity (ReHo) was used to evaluate spontaneous brain activity (He et al., 2021).

Results showed increased ReHo value in the right lingual gyrus (LG) and decreased ReHo value in the right superior frontal gyrus (SFG) in perimenopausal women compared to premenopausal women. In perimenopausal women, ReHo of the right LG showed a negative correlation with estradiol levels, while ReHo of the right SFG showed a positive correlation with both estradiol levels and Mini-Mental State Examination (MMSE) scores (He et al., 2021).

The findings indicate alterations in spontaneous brain activity and functional compensation in perimenopausal women, suggesting that the decline in estradiol during menopause is linked to reduced brain activity in regions critical for cognition. The study provided further evidence of the brain's functional adaptation to changing estrogen levels, supporting the compensatory mechanism hypothesis suggested by previous research (Mosconi et al., 2024).

STRUCTURAL BRAIN CHANGES AND HORMONE THERAPY

The Kronos Early Estrogen Prevention Study (KEEPS) investigated the effects of hormone therapy on cognitive function and brain structure (Miller et al., 2019). This randomized, double-blinded, placebo-controlled trial involved 727 recently postmenopausal women aged 42-58, with 693 women enrolled in the KEEPS Cognitive sub-study. Participants were randomized to receive either oral conjugated equine estrogens (o-CEE), transdermal 17β-estradiol (t-E2), or placebo.

The primary measure used in the KEEPS study was carotid artery intima-media thickness (CIMT) to assess the progression of atherosclerosis. For cognitive effects, 19 cognitive tests were administered to assess various domains of cognitive function, and the Modified Mini-Mental State examination was used to measure global cognition.

An ancillary brain MRI study on a subset of KEEPS participants found that rates of ventricular volume increases were greater in women who received o-CEE compared to those receiving a placebo. However, these structural changes were not accompanied by significant differences in global cognition within or between groups.

This research group expanded on the previous findings by examining how exogenous hormone therapy might influence brain structure and function, providing a link between the observed ER density changes and potential intervention strategies. The results suggest that while hormone therapy may affect brain structure, its impact on cognitive function may be more complex and require further investigation (Miller et al., 2019).

GENETIC FACTORS AND BRAIN AGING

Integrating genetic considerations, a study analyzed structural brain imaging data from 16,854 middle-aged women in the UK Biobank, focusing on brain aging in relation to hormone exposure and genetic factors (de Lange et al., 2020). The researchers used brain age prediction models and regression analysis to explore interactions between cumulative hormone exposure, APOE genotype, and brain aging.

The study measured brain aging, brain age gap, Index of Cumulative Estrogen Exposure (ICEE), and exogenous hormone exposure through HRT and OC use. Results showed that women with the APOE4 genotype and high cumulative estrogen exposure exhibited accelerated brain aging. Early initiation of hormone replacement therapy was linked to less brain aging, but only in APOE4 carriers.

These findings suggest that genetic predisposition and the timing of hormone therapy play crucial roles in cognitive outcomes in menopausal women. The study built upon the

previous research by introducing genetic factors as modulators of the relationship between hormone exposure and brain aging, suggesting a more complex relationship between genetics, hormones, and cognitive function during menopause.

CRITICAL REVIEW

Research Design

The studies had a broad range of research designs that contributed unique findings into the complex relationship between menopause, brain structure, and cognitive function. Utilizing a cross-sectional design, Mosconi et al. (2024) investigated estrogen receptor (ER) density across different perimenopausal stages by comparing 54 midlife women, who were divided into three groups: premenopausal (n=16), perimenopausal (n=20), and postmenopausal (n=18). Although the design provided valuable data on group differences, it also limited the ability to establish causal relationships or track individual changes over time. The study employed advanced ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET) imaging to assess brain ER density. A key methodological refinement was the use of a custom-built cerebellar gray matter region as a reference for deriving ^{18}F-FES distribution volume ratios (DVRs), based on evidence that this area minimally expresses ERα. The research design incorporated both region of interest (ROI) and voxel-based analyses, revealing regional specificity in ER density changes and laterality effects. The study design also included the collection and analysis of biomarkers and genetic factors.

The He et al. (2021) study also used a cross-sectional design to compare brain activity between premenopausal and perimenopausal women. The study included 32 premenopausal and 25 perimenopausal women and focused on spontaneous brain activity changes rather than ER density. Contrastingly, a more robust longitudinal design followed 85 perimenopausal women over 400 bi-annual visits (Weber et al., 2021). The approach used by Weber et al. (2021) observed cognitive and hormonal changes in women, which accounted for the variability in menopausal progression, which strengthened drawing causal inferences and tracking the trajectory of changes over time.

The Kronos Early Estrogen Prevention Study (KEEPS) implemented a randomized, double-blind, placebo-controlled trial with 727 recently postmenopausal women (Miller et al., 2019). This gold-standard design enabled direct comparison between hormone therapy interventions and placebo, minimizing potential biases and providing robust evidence for the effects of hormone therapy on brain structure and function.

A large-scale cohort study design leveraging the power of big data utilized 16,854 women from the UK Biobank (de Lange et al., 2020). The implemented strategy offered robust statistical power and the ability to detect subtle effects and complex interactions between variables, including genetic factors and hormone exposure. The many research designs used across the studies provided a comprehensive view of brain changes during menopause. While the cross-sectional studies offer essential insights into group differences, the longitudinal and interventional designs provide more substantial evidence for causal relationships and changes over time. The large-scale cohort study complements these approaches by allowing for the investigation of rare variants and complex interactions.

DATA COLLECTION METHODS

Neuroimaging Techniques

The studies employed various advanced neuroimaging techniques to investigate brain changes during menopause. Mosconi et al. (2024) utilized ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET) imaging to assess brain estrogen receptor density. This novel approach provides direct visualization of ER distribution but involves radiation exposure and is relatively costly. The (^{18}F-FES) tracer was injected intravenously, and imaging was performed using a high-resolution PET scanner. Data acquisition typically lasted 60-90 minutes post-injection, allowing for adequate tracer uptake and distribution. The study revealed regional specificity in ER density changes, with the pituitary gland showing the strongest tracer uptake across menopausal stages.

Resting-state functional Magnetic Resonance Imaging (fMRI) was used to investigate spontaneous brain activity (He et al., 2021). This non-invasive technique offers good spatial and temporal resolution but may be sensitive to motion artifacts. Participants underwent a 6-minute resting-state fMRI scan, which provided insights into functional brain changes during the menopausal transition.

A study by de Lange et al. (2020) used structural MRI data to estimate brain age which provided detailed anatomical information but may not have captured functional changes in the brain. The structural MRI scans were acquired using standardized protocols across multiple UK Biobank sites, ensuring consistency in data collection.

The KEEPS study included an ancillary brain MRI component that examined structural brain changes in response to hormone therapy (Miller et al., 2019). This approach offers insights into how exogenous hormones might influence brain structure during menopause. These diverse neuroimaging techniques provide complementary information about brain structure and function during menopause. The (^{18}F-FES PET) imaging is unique and provides new insights into ER density. fMRI and structural MRI continue to provide information about functional and structural brain changes, respectively.

Hormone Measurements

Hormone measurement techniques varied across studies, reflecting the challenge of capturing the dynamic hormonal environment of menopause. The Mosconi et al. (2024) study

measured plasma estradiol and sex hormone-binding globulin (SHBG) levels. Participants were instructed to fast overnight to minimize diurnal hormone level variations and blood samples were collected in the morning. Estradiol levels were then measured using liquid chromatography-tandem mass spectrometry because the technique provides higher sensitivity and specificity than traditional immunoassays. The advanced method is significant in neuroimaging studies of estrogen receptor density because it is more accurate and reliable at measuring circulating estradiol levels. Precision was crucial in examining the relationship between peripheral hormone levels and brain estrogen receptor density because it minimizes the risk of measurement error, which could confound the observed associations. The researchers were more confident with the correlated serum estradiol levels with the neuroimaging findings on estrogen receptor density in the brain, which enhanced the overall reliability and interpretability of the study's results. The study found that ER density in the brain increases progressively over the menopause transition, independent of age, plasma estradiol, and (SHBG) levels.

Serum levels of estradiol, free testosterone, progesterone, prolactin, follicle-stimulating hormone, and luteinizing hormone were assessed (He et al., 2021). These measurements provide a more comprehensive hormonal profile but were taken at a single time point, which may not fully represent the fluctuating nature of hormones during menopause.

Bi-annual hormone measurements of 17β-estradiol and follicle-stimulating hormone were conducted (Weber et al., 2021). This longitudinal approach to hormone measurement allows for a more comprehensive understanding of hormonal fluctuations over time. However, even this frequency may miss short-term fluctuations characteristic of perimenopause.

An Index of Cumulative Estrogen Exposure (ICEE) was developed to account for lifetime estrogen exposure through factors such as age at menarche, number of pregnancies, and the use of hormonal contraception (de Lange et al., 2020). While this approach provided a more comprehensive picture of estrogen exposure, it relied on retrospective self-reporting, which may have introduced recall bias.

The variability in hormone measurement techniques across studies highlights the complexity of capturing hormonal changes during menopause. Each approach offers unique insights but has limitations in fully representing the dynamic hormonal environment.

Hormone Measurements in Relation to Neuroimaging Studies of Estrogen Receptor Density

The hormone measurement technique used in the studies added context to the neuroimaging findings on estrogen receptor density, making it easier to interpret the observed brain changes. The Mosconi et al. (2024) study used ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET) imaging to assess brain estrogen receptor density, measured plasma estradiol, and sex hormone-binding globulin (SHBG) levels. This approach allowed for a direct correlation between circulating hormone levels and ER density in the brain, enhancing our understanding of how peripheral hormone levels relate to central ER expression.

Using liquid chromatography-tandem mass spectrometry for estradiol measurement offered higher sensitivity and specificity than traditional immunoassays (Mosconi et al., 2024). Higher sensitivity was essential for examining the relationship between circulating estradiol levels and brain ER density so that the risk of measurement error was minimized, which could confound the observed associations.

While ER density was not directly measured, the hormone measurement approaches used in these studies provide valuable insights into the hormonal milieu during menopause (He et al., 2021; Weber et al., 2021). Comprehensive hormonal profile, including estradiol, free testosterone, progesterone, prolactin, follicle-stimulating hormone, and luteinizing hormone, offers a broader view of the endocrine changes occurring during menopause (He et al., 2021). This comprehensive nature of hormonal changes over time and the longitudinal data could be particularly valuable in future studies examining how fluctuations in hormone levels over the menopausal transition relate to changes in ER density.

The de Lange et al. (2020) study used the Index of Cumulative Estrogen Exposure (ICEE), which provided a unique perspective on lifetime estrogen exposure. While this approach does not directly measure current hormone levels or ER density, it offers insights into how cumulative exposure might influence brain structure and function, which could be particularly relevant for understanding the long-term effects of estrogen exposure on ER expression and distribution in the brain.

The variability in hormone measurement techniques across these studies highlights the complexity of capturing the hormonal environment during menopause. When considered alongside neuroimaging studies of ER density, these diverse approaches to hormone measurement provide a more comprehensive picture of the relationship between peripheral hormone levels, cumulative hormone exposure, and central ER expression. Future studies should consider combining detailed hormone profiling with advanced neuroimaging techniques like ^{18}F-FES PET because of the potential to define the multifaceted interactions between circulating hormones and brain ER density during perimenopause.

Cognitive Assessments

The studies employed various cognitive assessment tools, varying in comprehensiveness and sensitivity. A comprehensive neuropsychological battery was used, including tests such as the Digit Span subtest, D2 Test of Attention, Letter-Number Sequencing subtest, Controlled

Oral Word Association Test, Grooved Pegboard Test, Hooper Visual Organization Test, and Rey Auditory Verbal Learning Test (Weber et al., 2021). This extensive battery provides a detailed assessment of multiple cognitive domains.

The KEEPS study employed a set of 19 cognitive tests to assess various domains of cognitive function, along with the Modified Mini-Mental State Examination for global cognition (Miller et al., 2019). These comprehensive approaches offer nuanced insights into cognitive changes but can be time-consuming and may lead to participant fatigue.

In contrast, He et al. (2021) relied on the Mini-Mental State Examination (MMSE), which is quick to administer but may lack sensitivity to subtle cognitive changes in relatively healthy middle-aged women.

The variation in cognitive assessment tools across studies makes direct comparisons challenging. However, it also provides a range of perspectives on cognitive function during menopause, from global measures to detailed domain-specific assessments.

Cognitive Assessments in Relation to Neuroimaging Studies of Estrogen Receptor Density

The cognitive assessment approaches employed in these studies complement neuroimaging investigations of estrogen receptor (ER) density by providing crucial behavioral correlates to the observed brain changes (Mosconi et al., 2024). These authors in their study using ^{18}F-fluoroestradiol (^{18}F-FES) Positron Emission Tomography (PET) imaging to assess brain ER density found that higher ER density was associated with poorer memory performance and predicted mood and cognitive symptoms in postmenopausal women. This finding underscores the importance of comprehensive cognitive assessments in understanding the functional implications of ER density changes. The study specifically found that ER density in regions with established cognitive functions, such as the hippocampus, amygdala, posterior cingulate cortex, and frontal cortex, were associated with lower scores on logical memory delayed recall (Mosconi et al., 2024).

The use of an extensive neuropsychological battery test in the study, including assessments of attention, working memory, verbal fluency, fine motor speed, visuospatial skills, and learning and memory, provided a detailed evaluation of multiple cognitive domains in perimenopausal women (Weber et al., 2021). The comprehensive approach allowed for a nuanced analysis of cognitive function during perimenopause. Researchers used this battery of approach could help elucidate how various hormones might influence ER expression and distribution in the brain.

The Weber et al. (2021) study had a Longitudinal approach, with bi-annual hormone measurements, complements ER density studies by capturing the dynamic tests to identify distinct cognitive profiles and how they would associate with hormones, allowing for the possible detection of cognitive function that may be sensitive to hormonal fluctuations during perimenopause. While the study did not directly measure ER density, the findings contribute to understanding how hormonal changes during menopause might relate to cognitive performance. The approach establishes the foundation for future research where comprehensive cognitive assessments would be integrated with the direct measurement of ER density to further elucidate the relationship between hormonal changes, brain function, and cognition during menopause.

The KEEPS study offers a similarly comprehensive assessment with its set of 19 cognitive tests and global cognition measures (Miller et al., 2019). While this study focused on the effects of hormone therapy rather than directly measuring ER density, its findings can inform our understanding of how modulating estrogen levels might influence ER expression and cognitive function.

In contrast, the use of the Mini-Mental State Examination (MMSE) provides a more global measure of cognitive function (He et al., 2021). While less sensitive to subtle cognitive changes, this approach can help identify broader cognitive patterns associated with ER density alterations. While the variation in cognitive assessment tools across these studies makes direct comparisons challenging, it offers a range of perspectives on cognitive function during menopause. When considered alongside neuroimaging data on ER density, these diverse cognitive measures can help elucidate the complex relationships between ER expression, brain structure and function, and cognitive performance.

Future studies combining detailed cognitive assessments with advanced neuroimaging techniques like ^{18}F-FES PET could provide even more comprehensive insights into how changes in ER density relate to specific cognitive functions. Integrated approaches, including ^{18}F-FES PET, have the potential to allow researchers to map the functional consequences of ER density changes more accurately, which could lead to targeted interventions supporting cognitive health during perimenopause.

Sampling Techniques

Sample sizes varied considerably across studies, which impacted their statistical power and generalizability. Mosconi et al. (2024), Weber et al. (2021), and He et al. (2021) had relatively small samples (54, 85, and 57 participants, respectively). These small sample sizes may limit the generalizability of findings and reduce statistical power for detecting subtle effects.

The KEEPS study included a larger sample of 727 women, providing better statistical power (Miller et al., 2019). de Lange et al. (2020) Utilized data from 16,854 women in the UK Biobank, offering substantial statistical power and the ability to detect small effect sizes. A standard limitation across all studies is the lack of diversity in study populations, with participants predominantly being well-educated and white, which may affect the generalizability to more diverse populations and could mask significant ethnic or

socioeconomic differences in menopausal experiences and brain changes.

DATA ANALYSIS PROCEDURES

The studies employed sophisticated statistical techniques to analyze their complex datasets. Mosconi et al. (2024) used multivariate linear regression models and voxel-based analysis, allowing for whole-brain analysis and identification of regions where ER density differs significantly between menopausal stages. The study also calculated Cohen's d effect size to evaluate the statistical effect of the group analysis and used Gaussian random field correction to control for false positives in the voxel-based analysis.

Weber et al. (2021) employed Multilevel Latent Profile Analysis (MLPA) to identify distinct cognitive profiles, enabling the identification of subgroups based on patterns of cognitive performance and hormonal fluctuations.

He et al. (2021) used correlation analyses and general linear models for ReHo map comparisons, examining relationships between brain activity patterns, hormone levels, and cognitive performance.

de Lange et al. (2020) utilized brain age prediction models and regression analyses, exploring interactions between hormone exposure, APOE genotype, and brain aging. Using machine learning algorithms in these models offers new insights but may be sensitive to the specific training data used. KEEPS used linear mixed-effects regressions to plot the determinants of cognition and mood over time and controlled for both within-subject and between-subject variability in longitudinal data.

These advanced statistical approaches allow for exploring complex relationships between variables but may be sensitive to violations of underlying assumptions and can be challenging to interpret.

Potential Biases and Limitations

Several potential biases were present across all of the studies. Selection bias may have been a limitation, particularly in the studies with smaller sample sizes and specific inclusion criteria. In addition, using volunteer participants may result in samples not representative of the general population. Recall bias is a concern in studies that rely on self-reported data, particularly for measures of lifetime hormone exposure and menopausal symptoms. The cross-sectional nature of some studies introduces the potential for cohort effects, where observed differences may be due to generational factors rather than menopausal status. Observer bias may exist in studies involving cognitive assessments or neuroimaging analysis, although many studies employed blinding procedures to mitigate this risk.

Common limitations included the lack of diversity in study populations, which limits generalizability. The cross-sectional design of some studies limits causal inferences, while even longitudinal studies may not capture the entire trajectory of menopausal changes. The reliance on self-reported data for some measures introduces potential inaccuracies, and the variability in assessment tools across studies makes direct comparisons challenging.

Appropriateness and Reliability of Methods

The neuroimaging used, especially the ^{18}F-FES PET imaging in Mosconi et al. (2024), is among the most advanced in the science of menopausal brain-change analysis. These nonbiased techniques for assessing brain structure and function make measurements more reliable. The comprehensive cognitive assessments used in some of the studies offered a nuanced understanding of cognitive changes but may be subject to practice effects in longitudinal designs.

The variability in hormone measurement techniques across studies highlights the challenge of accurately capturing the dynamic hormonal environment of menopause. The complex nature of the data required careful interpretation, and the statistical approaches were sophisticated. Using machine learning algorithms to predict brain age offered new insights but may also be sensitive to the specific training data used. The use of a custom-built cerebellar gray matter region as a reference for deriving ^{18}F-FES distribution volume ratios (DVRs) enhanced the accuracy of ER density measurements. However, the authors acknowledged the need for longitudinal studies to characterize temporal trajectories of ER changes and to differentiate between induced and spontaneous menopause.

CONCLUSION

Although the precise mechanisms underlying the relationship between estrogen receptor (ER) density and cognitive function during menopause are not fully clarified, recognizing the neurobiological changes associated with perimenopause will lead to substantial advances in understanding cognitive aging in women. The finding that ER density in the brain increases progressively over the menopause transition, independent of age, plasma estradiol, and sex hormone-binding globulin (SHBG) levels, challenges previous assumptions about estrogen signaling in the aging female brain. The paradoxical finding that increased ER density is associated with poorer cognitive outcomes accentuates the complexity of neuroendocrine influences on brain function during perimenopause. Specifically, higher ER density in regions with established cognitive functions, such as the hippocampus, amygdala, posterior cingulate cortex, and frontal cortex, was associated with lower scores on logical memory delayed recall.

This understanding can inform scientist in creating new treatment plans to preserve cognitive health throughout a woman’s lifespan. In addition, further research is required to define the role of ER density as a potential biomarker for cognitive vulnerability during perimenopause. Past research has had considerable limitations in measuring and interpreting ER density changes, primarily due to the historical focus on circulating hormone levels rather than receptor expression in the brain because of a lack of advanced neuroimaging techniques like ^{18}F-fluoroestradiol (^{18}F-FES)

Positron Emission Tomography (PET) is a significant invention, that for the first time allows for direct visualization and quantification of ERs in the human brain. Because of this invention scientist are now able to provide a measurable signal of estrogen signaling in the brain. This is unprecedented and offers new possibilities for understanding the complex interaction between hormones and cognition.

Moreover, genetic studies highlight how variation in the effect of hormones on brain aging across individuals should be put in context with genetic risk factors such as APOE genotype. The identification of genetic variants within innate immunity pathways that may contribute to vascular changes during menopause helps to explain the importance of considering genetic factors in hormone-brain interactions. By implementing personalized approaches, that consider genetic predisposition, combined with standardized measures of estrogen receptor density and cognitive function, has the potential to preserve cognitive health throughout and following the menopausal transition.

In summary, much progress has been made in delineating sex steroid and ER-related neurobiological changes during and after menopause, including changes in the density of ER and brain function. The observation of regional specificity in ER density changes, with the pituitary gland showing the strongest tracer uptake across menopausal stages, provides new insights into the neuroanatomical basis of menopausal symptoms. Future works should help to investigate the mechanisms leading to the observed increase in ER density, how such changes relate to cognitive outcomes, and whether specific interventions may help support cognitive health in menopausal women. Longitudinal studies are particularly needed to characterize temporal trajectories of ER changes and to differentiate between induced and spontaneous menopause. Future studies should consider a more integrative approach by combining advanced neuroimaging techniques, detailed cognitive assessments, and genetic profiling to women's cognitive health during this critical life stage.

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