Mini Review
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The neuropsychological aftermath of reproductive senescence: hormonal transitions, cognitive reserve and affective disorders in aging populations

Abstract

Reproductive senescence is a pivotal biological transition that exerts profound and lasting effects on brain health, cognitive reserve, and affective well-being in older adults. The decline of gonadal hormones – oestradiol in women and testosterone in men – triggers neurobiological changes that increase vulnerability to Alzheimer's disease, mild cognitive impairment, and late-life depression. Beyond immediate hormonal shifts, reproductive history parameters (parity, age at menarche and menopause, reproductive span) modulate cognitive trajectories through both biological and psychosocial pathways. However, the physiological kinetics of hormonal decline differ drastically between sexes, complicating direct comparisons. This opinion article argues for the routine integration of reproductive health history into neuropsychological assessments and advocates for sex-sensitive public health strategies that address the unique neuropsychological vulnerabilities emerging from reproductive senescence. We propose a novel *Reproductive Senescence Neuropsychological Framework (RSNF)* to guide future clinical risk stratification.

Keywords: reproductive senescence, cognitive reserve, affective disorders, hormonal transitions, neuropsychology, aging

Volume 11 Issue 2 - 2026

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Received: June 28, 2026 | **Published:** July 13, 2026

Introduction

The global ageing population has intensified the need to understand the biological and psychological determinants of healthy cognitive and emotional ageing. Reproductive senescence – the gradual decline and eventual cessation of reproductive function – represents a critical life transition with far-reaching neuropsychological implications. In women, menopause entails a precipitous drop in oestradiol; in men, testosterone declines more gradually, yet both hormonal shifts exert extensive modulatory effects on brain structure, synaptic plasticity, neurotransmitter systems, and neuroinflammatory pathways.[1–3] Women, who comprise two-thirds of all Alzheimer's disease cases, face elevated risks of cognitive decline and mood disorders during and after the menopausal transition.[4] In men, age-related hypotestosteronaemia is increasingly linked to depressive symptomatology and specific cognitive deficits.[5]

This opinion article critically examines the neuropsychological aftermath of reproductive senescence through three interconnected lenses: (1) neuroendocrine mechanisms linking hormonal transitions to cognitive and affective outcomes; (2) the role of reproductive history as a modulator of cognitive reserve, including rigorous appraisal of confounding variables; and (3) the clinical and policy implications of these findings, culminating in a distinctive clinical framework for geriatric neuropsychology and public health.

Neuroendocrine mechanisms: hormonal transitions and brain health

A critical nuance often overlooked in the literature is that female menopause and male age-related testosterone decline are not direct biological equivalents. In women, the perimenopausal transition involves a relatively acute and profound collapse of ovarian function over a span of 5–10 years, resulting in a precipitous 80–90% reduction in circulating oestradiol. In contrast, male reproductive aging is characterized by a gradual, linear decline in total and bioavailable testosterone beginning in the third decade, often accompanied by a concurrent rise in sex hormone-binding globulin (SHBG). While both states result in hypogonadism, the magnitude, tempo and systemic impact of hormonal withdrawal differ substantially, meaning that neuropsychological outcomes in women and men cannot be mapped onto a single etiological pathway. Explicitly recognizing this distinction is essential to avoid oversimplification in clinical reasoning.

Oestrogens exert pleiotropic neuroprotective effects through both genomic (classical nuclear ERα and ERβ receptors regulating gene transcription) and non-genomic (membrane-associated GPER1 and rapid signaling cascades) pathways.[1] Specifically, oestradiol enhances cholinergic, dopaminergic and serotonergic signalling, promotes hippocampal synaptogenesis and neurogenesis, and critically, upregulates Brain-Derived Neurotrophic Factor (BDNF) – a key trophic factor for synaptic plasticity.[2] Furthermore, oestradiol preserves cerebral glucose metabolism by enhancing insulin sensitivity in the brain and supports mitochondrial function, reducing oxidative stress. Its anti-amyloidogenic properties involve promoting non-amyloidogenic processing of the amyloid precursor protein (APP) and enhancing microglial clearance of amyloid-β aggregates.[2,4] The menopausal loss of oestradiol therefore precipitates a constellation of adverse neural changes – impaired spatial memory, altered neurotransmitter balance, upregulated neuroinflammation, and reduced synaptic plasticity – that collectively heighten vulnerability to mild cognitive impairment and Alzheimer's disease.[2,4] Notably, the perimenopausal period, characterised by profound hormonal fluctuations, represents a particularly vulnerable window during which structural and functional brain alterations accelerate.[3]

In men, while total testosterone declines progressively, it is crucial to note that testosterone is aromatized to oestradiol in the brain; thus, some of testosterone's cognitive effects are mediated via oestrogen receptors. Robust inverse correlations exist between testosterone and depressive symptoms, and low testosterone has been linked to faster cognitive decline in older men, possibly through synergistic effects with neurodegeneration markers.[5,6] These findings underscore that hormonal transitions in both sexes are critical determinants of brain ageing, albeit via divergent kinetics.

Reproductive history as a modulator of cognitive reserve: beyond the biological narrative

Beyond acute hormonal changes, an individual's reproductive history – including age at menarche, parity, age at first and last childbirth, and timing of menopause – exerts lasting influences on late-life cognitive trajectories.[7–9] Late menarche and early menopause have been consistently associated with poorer cognitive function and increased dementia risk.[7] A longer reproductive span and older age at first birth appear to confer protective effects, possibly through prolonged exposure to endogenous oestrogens.[8] Moreover, a Mendelian randomisation study provided genetic evidence that age at menarche, age at first birth, and menopause are independently associated with Alzheimer's disease risk.[9]

However, the interpretation of parity findings demands cautious editing. While parity modulates cognitive health, nulliparity and childlessness are heavily intertwined with major socioeconomic, marital, lifestyle, and social isolation variables. Lower educational attainment, reduced lifetime earnings, lack of spousal support and higher rates of sedentary behavior or smoking are all associated with both childlessness and poorer cognitive outcomes. Therefore, to attribute these differences solely to a "hormonal exposure" or "caregiving" pathway risks oversimplification. While we acknowledge the psychosocial benefits of social engagement through parenting, future studies must rigorously adjust for these deep-seated confounders to delineate the true biological contribution of parity to cognitive reserve.

Furthermore, the disposable soma theory, initially proposed by Kirkwood and Holliday, posits that organisms face an evolutionary trade-off in energy allocation: investment in reproductive effort (e.g., gestation, lactation) diverts resources away from somatic maintenance and repair, theoretically accelerating senescence. However, emerging evidence challenges the universal applicability of this theory to the brain. The "reproductive experience" paradox – wherein reproductive investment appears to positively adjust the trajectory of senescence in animal models – suggests alternative mechanisms. We propose two reconciliatory pathways: (a) Hormesis: The significant oxidative and inflammatory stress associated with pregnancy and lactation acts as a mild "stressor" that upregulates endogenous antioxidant and neuroprotective pathways (e.g., Nrf2 activation), rendering the brain more resilient to subsequent insults; (b) Behavioral Enrichment: The cognitive, motor, and social demands of nurturing offspring provide profound environmental enrichment, enhancing hippocampal neurogenesis and dendritic arborization.[10,11] This reframing allows for the coexistence of somatic energy costs with enhanced cognitive resilience.

Affective disorders and the neuropsychology of reproductive aging

The neuropsychological consequences of reproductive senescence extend beyond cognition to encompass affective disorders and require deeper mechanistic description.

Hormonal variations throughout the female reproductive cycle significantly impact mental health, with the perimenopausal transition associated with heightened vulnerability to depression, anxiety, and sleep disturbances.[3,6] Beyond simple neurotransmitter depletion, the decline of oestradiol affects mood through several specific mechanisms:

1. Serotonin Transporter (SERT) Regulation: Oestradiol modulates SERT density and promoter activity, affecting synaptic serotonin availability and tryptophan metabolism.
2. Allopregnanolone Fluctuations: This neuroactive metabolite of progesterone acts as a positive allosteric modulator of GABA-A receptors. The erratic fluctuations of its precursors during perimenopause lead to GABA-ergic instability, directly causing emotional lability, heightened anxiety and stress sensitivity.
3. HPA Axis Dysregulation: Oestrogen and testosterone both modulate cortisol reactivity. Withdrawal of these hormones is associated with hyperactive hypothalamic-pituitary-adrenal (HPA) axis responses to psychosocial stressors, leading to chronic glucocorticoid exposure, which exacerbates hippocampal atrophy and glutamatergic excitotoxicity.

In males, testosterone decline correlates with increased depressive symptoms, partly due to reduced amygdala-prefrontal connectivity, impairing top-down emotional regulation[5]. Accelerated reproductive ageing has been linked to heightened stress sensitivity and psychological maladjustment across the life course, with brain dynamics revealing divergent patterns of ageing linked to reproductive maturation versus senescence.[12] These findings highlight the need to consider reproductive ageing not as an isolated biological event but as a critical determinant of neuropsychological vulnerability that shapes the risk for both cognitive and affective disorders in later life.

Clinical and policy implications: the reproductive senescence neuropsychological framework (RSNF)

The evidence reviewed carries clear implications for clinical practice and public health.**To move beyond summarizing association studies and toward a distinctive conceptual model, we propose the Reproductive Senescence Neuropsychological Framework (RSNF). The RSNF categorizes patient risk along a quadrant-based model determined by two axes:

Axis A: Hormonal Trajectory (Tempo and timing of hormonal decline – e.g., early vs. late menopause, rapid vs. gradual decline in testosterone).

Axis B: Psychosocial Reserve (Combined score of social engagement, marital status, educational attainment, and economic stability).

This model allows clinicians to stratify patients into high- or low-risk groups for targeted intervention. Specifically, we recommend the following actionable clinical strategies:

Citation: Oyovwi MO, Adegor EC, Oja-alumehe EF, et al. The neuropsychological aftermath of reproductive senescence: hormonal transitions, cognitive reserve and affective disorders in aging populations. *MOJ Gerontol Ger.* 2026;11(2):39–41. DOI: 10.15406/mojgg.2026.11.00357

1. **Routine Reproductive Health Screening**: Reproductive health history – including menstrual history, parity, age at menarche and menopause, history of hormone replacement therapy, and reproductive complications – should be integrated as a "vital sign" into neuropsychological assessments for older adults.
2. **Enhanced Surveillance**: Women with early menopause (<45 years), late menarche (>15 years), or nulliparity, particularly when combined with low psychosocial reserve, may benefit from enhanced cognitive screening **(e.g., annual Montreal Cognitive Assessment [MoCA])** and targeted lifestyle interventions aimed at preserving cognitive reserve.
3. **Timing Hypothesis and Clinical Judgement**: The timing hypothesis of hormone therapy – suggesting oestrogen replacement is most beneficial when initiated during the perimenopausal window – merits careful consideration on a case-by-case basis, balancing neuroprotective potential against thromboembolic and oncological risks.[2,4]
4. **Non-Hormonal Interventions**: Clinicians should prioritize lifestyle modifications, including aerobic exercise (which independently elevates BDNF), cognitive stimulation, and phytoestrogen-rich diets.
5. **Sex-Sensitive Public Health Strategies**: The disproportionate burden of dementia among women and the emerging sex-specific risk factors underscore the need for dementia prevention frameworks that specifically incorporate reproductive health metrics.

Conclusion

Reproductive senescence constitutes a critical neurobiological transition with profound and lasting consequences for cognitive and affective health in ageing populations. However, the physiological trajectories of this transition differ markedly between sexes, necessitating nuanced, non-equivalent conceptualizations of hormonal withdrawal in men and women. By moving beyond simplistic biological determinism and acknowledging the intricate interplay of hormonal shifts, psychosocial confounders (such as socioeconomic status and isolation), and neurochemical cascades (including BDNF and allopregnanolone pathways), we can better understand the mechanisms of cognitive reserve.

We advocate for moving reproductive senescence from a "biological footnote" to a "central pillar" of geriatric neuropsychology. The proposed Reproductive Senescence Neuropsychological Framework (RSNF) offers a foundational model for future longitudinal and interventional studies. Integrating reproductive health into geriatric neuropsychology offers opportunities for enhanced risk stratification, personalised intervention and more effective public health planning. Future research must prioritize longitudinal, multimodal studies that integrate high-resolution neuroimaging, dynamic hormonal assays, and comprehensive psychosocial interviews to elucidate causal pathways and evaluate the efficacy of hormone-based and behavioural interventions tailored to sex-specific vulnerabilities.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. El-Bana MA, Hussein J, El-Daly SM, et al. Exploring the diverse signaling mechanisms of 17β-estradiol deficiency and replacement: Impacts on cognitive dysfunction in a post-menopausal experimental model. *Prostaglandins & Other Lipid Mediators*. 2025: 107024.
2. Hynd M. The brain in transition: Perimenopause through a translational lens. *Neuroscience & Biobehavioral Reviews*. 2026; 25:106773.
3. Silva GB, Pascucci JA, Karim H, et al. Influence of the onset of menopause on the risk of developing alzheimer's disease. *Cureus*. 2024: 16(9).
4. Song Y, Rosano C, Cvejkus RK, et al. Reproductive health history and later life cognition in African Caribbean women. *Alzheimer's & Dementia*. 2025; 21(8): e70547.
5. Caetano CC, Liberman S, Ie JM, et al. The influence of sex steroids on cognition in elderly men. *Clinics*. 2026; 81:100892.
6. Neitzke EV, Dos Santos FG, Zanini BM, et al. The influence of ovarian activity and menopause on mental health: evidence from animal models and women. *Physiology & Behavior*. 2025; 294: 114886.
7. Wolfova K, Strand BH, Weiss J, et al. Reproductive history and cognitive health among older Norwegian females and males: the population-based HUNT Study. *Journal of Psychiatric Research*. 2026: 3.
8. You W. Age at first childbirth and dementia risk: a cross□sectional ecological analysis of female prevalence, sex disparities, and public health implications. *Health Science Reports*. 2025; 8(8): e71145.
9. Wang Y, Zhao D, Kong T, et al. Associations between reproductive milestones and Alzheimer's disease risk: a Mendelian randomization study. *Brain Research*. 2025: 149972.
10. Retained as general reference context for HUNT4 70+.
11. Kinsley CH, Franssen RA, Meyer EA. Reproductive experience may positively adjust the trajectory of senescence. *Behavioral Neurobiology of Aging*. 2011: 317–345.
12. Petrican R, Chopra S, Segal A, et al. Functional brain network dynamics mediate the relationship between female reproductive aging and interpersonal adversity. *Nature Mental Health*. 2025; 3(1): 104–123.