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EDITORIAL

Scientific insights into brain fog during the menopausal transition

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Clinicians and researchers engaged in the field of menopausal health understand that there are myriad physiological and psychological effects associated with the menopausal transition, including changes in cognitive function [1]. Longitudinal cohort studies suggest a 'window of vulnerability' for cognitive difficulties [2,3], particularly memory, beginning in the early menopause transition and apparently ending, at least for most women, in the postmenopause. Changes in sex steroid hormones, particularly 17β-estradiol, which exerts potent effects on the brain, play a key role in memory performance at midlife [4] as do vasomotor symptoms, sleep disturbance, and mood/anxiety [5]. Some studies suggest that longer lifetime exposure to endogenous 17β-estradiol may be related to better cognitive processes in older women [6].

There are critical gaps in the knowledge of the neurobiological mechanisms contributing to those declines, the persistence of those declines, the extent to which hormonal changes and menopause symptoms contribute to cognitive declines, potential interventions that might be effective in ameliorating cognitive difficulties, and the long-term clinical significance of midlife cognitive changes. This themed edition of *Climacteric* focuses on menopause and cognition from a clinical translational perspective and addresses some of these gaps by drawing on both clinical and basic science.

Four of the articles in this special edition address clinical presentation and protective/risk factors. Menopause practitioners can draw on a systematic review of 19 studies by Reuben and colleagues [7] to normalize and validate cognitive complaints in their patients. The authors found that cognitive complaints not only increased across the menopause transition, but were also associated with poorer performance on tests of attention, verbal and working memory. Focusing on cognitive test performance, Weber and colleagues [8] analyzed data from the Rochester Investigation of Cognition and Memory (RICAM) to examine the heterogeneity in cognitive changes in the perimenopause. They identified four distinct cognitive profiles, each characterized by different patterns of relative strengths and weaknesses in cognition over the perimenopause. Among 85 women evaluated over 400 bi-annual visits, about 20% of observations fit into a cognitively vulnerable profile characterized by weaknesses in verbal learning and memory. The factors associated with that profile were sleep disturbances and, interestingly, *less* hormonal variability. The good news for patients is that the remaining 80% of observations were in the other three cognitive profiles, which were distinct in terms of strengths and weaknesses but which fell under the normal range of cognitive performance. Lastly, among Thai women with a history of surgical menopause, Orprayoona and colleagues [9] demonstrate a high prevalence of frontal lobe dysfunction, while Chaikittisilpa and colleagues [10] reported a risk of mild cognitive impairment (MCI). These articles contribute to a better understanding of the types of cognitive changes experienced by women.

Two papers consider mechanisms of action of estrogens in the brain. Baumgartner and Daniels [11] make a compelling case for the importance of estrogen receptor alpha (ERα) in female brain aging, even in the absence of endogenous or exogenous hormones. Prakapenka and Korol [12] present evidence that estrogens do not uniformly benefit cognition, but rather enhance or impair cognition in a task-dependent manner depending on the metabolic status of the brain areas subserving those tasks. For example, estrogens can enhance hippocampal-dependent memory by increasing glucose in the hippocampus but impair cognitive tasks dependent on the striatum by decreasing levels of lactate and ketones.

Effects of menopausal hormone therapy (MHT) on cognition and brain function are complex, with guidelines from the International Menopause Society [13] noting that there is insufficient evidence to recommend its use for the treatment or prevention of cognitive dysfunction. A review by Kim and Brinton [14] makes the case for a personalized treatment approach that focuses on symptomatic women, and considers the duration and type of MHT, as well as genetic risk factors. Li and Dreher [15] review clinical neuroimaging studies showing beneficial effects of MHT on the structure and function of the prefrontal cortex in postmenopausal women. Hugenschmidt and colleagues [16] review evidence, including data from the Women's Health Initiative, suggesting that type 2 diabetes mellitus modifies the effects of MHT on brain function in older women, conferring reliable negative effects and suggesting a need for a personalized medicine approach that limits use of MHT in women with that condition. Drawing from both clinical and basic science studies, they make a compelling case that the combination of hormone

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therapy, older age, and metabolic dysregulation poses a unique, harmful risk to the brain. These reviews provide insights into the factors that determine whether MHT has a positive or negative influence on cognition and brain health, and how these insights might guide clinical practice.

Lastly, two articles help to direct future research efforts. The first is a primer for studies of cognitive changes across the menopause transition. In an evidence-based manner, Maki and Weber [17] draw on the existing data to address such key issues as objective versus subjective cognitive measures; cognitive domains and tests; implementation of criteria to stage menopause; key issues of study design; and hormonal and non-hormonal mediators of cognitive effects. The replicability and reproducibility of findings in human studies have been difficult to demonstrate, in large part due to differences in these key issues. With a focus on clinical translational research, Biamonte-Nelson and colleagues [18] make a strong argument for embracing the complexity of women's experience of menopause and different types of MHT regimens. Drawing on their own clinical translational studies, they show how basic science advances the understanding of the female brain through studies of different estrogenic formulations, different progestins, variations in timing of intervention in relation to age, and the role not only of the ovaries but also the uterus.

Given the scope and clinical relevance of this problem, the articles in the themed edition address some of the gaps in knowledge about cognition and the menopause transition. The studies herein can guide menopause practitioners in normalizing cognitive complaints in the perimenopause, provide a deeper understanding of the multiple mechanisms underlying cognitive changes, and help guide decision-making regarding the use of MHT on cognition. For researchers, the studies in this special edition can help to identify key gaps in understanding, offer new frameworks and insight into the complex and sometimes contradictory findings in the literature, and help to direct future basic, clinical and translational research.

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References

[1] Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. J Steroid Biochem Mol Biol. 2014;142:90–98.

[2] Epperson C, Sammel MD, Freeman EW. Menopause effects on verbal memory: findings from a longitudinal community cohort. J Clin Endocrinol Metab. 2013;98:3829–3838.

[3] Greendale, GA, Derby CA, Maki PM. Perimenopause and cognition. Obstet Gynecol Clin North Am. 2011;3:519–535.

[4] Rettberg JR, Yao J, Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol. 2014;35:8–30.

[5] Maki PM, Weber MT. Do menopausal symptoms account for the declines in cognitive function during the menopausal transition? In: Brinton RD, Genazzani AR, Simoncini T, Stevenson JC. (eds) Sex Steroids' Effects on Brain, Heart and Vessels. ISGE Series. Springer International Publishing, 2019.

[6] Matyi JM, Rattinger GB, Schwartz S, Buhusi M, Tschanz JT. Lifetime estrogen exposure and cognition in late life: the Cache County Study. Menopause. 2019;26:1366–1374.

[7] Reuben R, Karkaby L, NcNamee C, Phillips NA, Einstein G. Menopause and cognitive complaints: are ovarian hormones linked with subjective cognitive decline? Climacteric. 2021;24:321–332.

[8] Weber MT, Rubin LH, Schroeder R, Steffenella T, Maki PM. Cognitive profiles in perimenopause: hormonal and menopausal symptom correlates. Climacteric. 2021;24:401–409.

[9] Orprayoona N, Santibenchakul S, Hemrungrojn S, et al. Effect of surgical menopause and frontal lobe cognitive function. Climacteric. 2021;24:389–393.

[10] Chaikittisilpa S, Orprayoona N, Santibenchakul S, et al. Prevalence of mild cognitive impairment in surgical menopause: subtypes and associated factors. Climacteric. 2021;24:394–400.

[11] Baumgartner NE, Daniels JM. Estrogen receptor ∝: a critical role in successful female cognitive aging. Climacteric. 2021;24:333–339.

[12] Prakapenka AV, Korol DL. Estradiol selectively regulates metabolic substrates across memory systems in models of menopause. Climacteric. 2021;24:366–372.

[13] Baber RJ, Panay N, Fenton A, the IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19:109–150.

[14] Kim YJ, Brinton RD. Precision hormone therapy: identification of positive responders. Climacteric. 2021;24:350–358.

[15] Li Y, Dreher J-C. A review of the impact of hormone therapy on prefrontal structure and function at menopause. Climacteric. 2021;24:340–349.

[16] Hugenschmidt CE, Duran T, Espeland MA. Interactions between estradiol, diabetes, and brain aging and the risk for cognitive impairment. Climacteric. 2021;24:359–365.

[17] Maki PM, Weber MT. A research primer for studies of cognitive changes across the menopause transition. Climacteric. 2021;24:382–388.

[18] Biamonte-Nelson HA, Bernaud VE, Koebele SV. Menopause hormone therapy and cognition: maximizing translation from preclinical research. Climacteric. 2021;24:373–381.