Menopause, cognition and dementia – a review

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Abstract

There is increasing evidence that menopausal changes can have an impact on women's cognition and potentially, the future development of dementia. In particular, the role of reduced levels of oestrogen in postmenopausal changes has been linked to an increased risk of developing dementia in observational studies. Not surprisingly, this has led to several clinical trials investigating whether postmenopausal hormone replacement therapy (HRT) can potentially delay/ avoid cognitive changes and subsequently, the onset of dementia. However, the evidence of these trials has been mixed, with some showing positive effects while others show no or even negative effects. In the current review, we investigate this controversy further by reviewing the existing studies and trials in cognition and dementia. Based on the current evidence, we conclude that previous approaches may have used a mixture of women with different genetic risk factors for dementia which might explain these contradicting findings. Therefore, it is recommended that future interventional studies take a more personalised approach towards HRT use in postmenopausal women, by taking into account the women's genetic status for dementia risk.

Keywords: Menopause, oestrogen, cognition, dementia, hormone replacement therapy, 'critical window' hypothesis

Introduction

Dementia is one of the most prevalent diseases for ageing societies worldwide. According to the World Health Organisation report (2015), 47.5 million people worldwide have dementia and there are 7.7 million new cases annually. [1] Historically, dementia has been seen as a disease of old age, with age being the greatest risk factor for dementia. [2,3,4] However, recent evidence suggests that pathophysiological changes leading to dementia can occur up to 20 years before the presentation of clinical symptoms [5,6], which has stimulated an urgent need to investigate how several demographic and life-course factors influence the risk of pathologically-induced cognitive decline. [3] In particular, sex-related differences in neural anatomy is emerging as an important factor for both the development and treatment of dementia. [2,7]

The risk for dementia appears to differ for men and women throughout the ageing process [8], with women showing an increased risk for dementia shortly after menopause. [9] These findings dovetail with women commonly reporting a 'brain fog' descending after menopause, which might be the first indication of increased dementia risk. [7,10] Nonetheless, the relationship of menopause induced cognitive changes and risk of dementia is still under exploration, with previous studies offering conflicting findings to date. The aim of this review is to explore the literature investigating the link between menopause, cognition, and dementia. In this review, we will firstly highlight the current evidence for the relationship between cognition and menopause before exploring the evidence for an association between dementia and menopause. We conclude by outlining potential future directions based on the reviewed evidence.

Cognition and menopause

The occurrence of cognitive changes during menopause is clinically a very common observation, with many subjective reports of 'brain fog' during the menopausal transition, affecting cognitive performance in everyday life. [11] In particular, individuals suffer from impairments to their attention, processing speed and memory, which subsequently manifest as lack of focus, sluggishness and forgetfulness as some of the most common symptoms. [10,12] For example, cross-sectional findings from the Study of Women's Health Across the Nation (SWAN) in a large cohort of women (n=16,065) aged between 40-55 years showed that 31% of premenopausal women reported increased forgetfulness which increased to 41% in postmenopausal women [13,14] although the contribution of other demographic and lifestyle

factors on cognitive performance was not explored. Longitudinal studies have corroborated these cross-sectional changes in cognition, with women reporting worsening cognitive performance from pre- to post-menopause. [12,15,16] Importantly, these subjective reports of altered cognitive performance were further supported by more objective cognitive testing, which have shown that premenopausal women perform better than postmenopausal women on neuropsychological testing, [17] although the sample sizes for such studies are too limited to draw any definite conclusions at this stage.

The reported cognitive changes during menopause have implicated a potential role for hormones (in particular, oestrogen) on cognition. [15,18] Specifically, changes in the levels of oestrogen as well as expression of oestrogen receptor genes (e.g. ESR1, ESR2) have been shown to have an effect on cognition during menopausal transition [10,11] and ageing respectively. [19,20] This should be not surprising as oestrogen is well known to have strong effects on brain function and integrity, in addition to its reproductive function. For example, oestrogen has been shown to have a key role in regulating glucose metabolism in the brain. [21] Glucose metabolism is directly linked to improved cognition, hence a reduction in the provision and potential uptake of glucose in the brain as a result of lower oestrogen levels might partially account for the observed changes in cognitive performance post-menopause. [21,22] Similarly, oestrogen has been shown to have significant neurotrophic factors, [23,24] therefore impacting on neurogenesis and homeostatic brain function, [25] which further highlights the role of this female sex hormone in brain health.

Most importantly, oestrogen also functions in the metabolism of acetylcholine, one of the main neurotransmitters critical for attention and memory processes. [26] Hence the deficits, specifically in attention and memory, post-menopause might potentially be linked to this hormonal-neurotransmitter transaction, although such interactions have to date only been shown in animal models [25] Clearly, future investigations exploring this role of oestrogen towards acetylcholine and cognition, in particular on a longitudinal level, are needed to determine the dynamics of the genotypic and neurotransmitter interactions over long time periods.

On a more mechanistic level, several clinical trials involving hormone replacement therapies (HRT) in postmenopausal women have examined cognitive performance as a secondary outcome measure. [27,28,29] However, the results from these trials have so far been inconsistent,

with some trials showing beneficial effects for cognitive performance, whilst others show no or even deleterious effects on cognitive performance in postmenopausal women. [30,31,32,33]

These findings have led to the emergence of a 'critical window' hypothesis [12], which states that the HRT can have a positive impact on cognition in pre- and perimenopausal women (up until the age of 60 year when dementia risk is small), but might have a negative effect on cognition in postmenopausal women (see also dementia section below). [34] However, it should be noted that null/negative effects of HRT on female cognition are observed particularly among women with a heightened genetic vulnerability to developing dementia. In fact, a recent review suggests [35] that an incomplete understanding of the interactions between drugs and genotype that are not considered for in clinical trials might explain some of the controversial results of HRT trials on cognition. Further, most clinical trials were not specifically designed to measure cognitive performance as a primary outcome measure. [12] Hence it is not clear whether they were statistically powered enough to detect actual cognitive effects. In addition, most studies used clinical cognitive tests which are meant to detect gross effects, hence more subtle effects may have gone undetected. This results in most trials showing so-called 'ceiling effects' (i.e. participants perform close to 100% correct) and thus, subtle differences between groups can be hard to measure. Future trials are clearly needed to investigate a more mechanistic role of hormonal levels and cognitive changes pre- and post-menopause to potentially corroborate the observational findings (or 'critical window' hypothesis).

Dementia and menopause

There is currently a large body of studies and public health data showing that incidences of dementia are higher in women than in men. [36] Until recently, the difference in incidence rates were regarded as a collateral effect of women living on average longer than men. [2] This theory is consistent with age being a major risk factor for dementia and hence, aged women suffer significant cognitive decline and thus a higher incidence rate of dementia. [3,4] However, more recent evidence highlights that even when controlling for survival rates in men and women, the increased risk for women persists. [8] Moreover, from a diagnostic perspective, attentional and mnemonic changes in cognition that are primarily reported in post-menopausal women are also considered key clinical symptomology in the diagnostic work-up of patients presenting at dementia clinics. [12] Clearly, this evidence raises the question as to

whether hormonal changes during the menopause potentially trigger a pathophysiological cascade for Alzheimer's disease (AD). [9]

Already, this notion has recently found strong support by a large meta-analysis of data from over 50,000 women across multiple studies. [37] The study reported that women have a particularly high risk of developing dementia directly in the years following the menopause compared to men (< 70 years), whereas this sex difference in dementia risk dissipates after 70 years of age, by which time the risk between men and women was similar. This non-linear relationship between the sexes nicely dovetails with the 'critical window' hypothesis in females, highlighting that risk for dementia might vary for women even in different postmenopausal stages, a notion that has potential treatment implications.

Still, precisely how hormonal changes might affect the onset of dementia is still being established. Thus, it is necessary to firstly understand how the neuropathology of dementia develops in the brain in order to understand how menopause related hormonal and metabolic fluctuations might influence this process. The pathophysiology of AD (which accounts for two-thirds of all dementia cases) is widely accepted to be caused by the accumulation of two insoluble neurotoxic proteins, amyloid beta plaques and neurofibrillary tau tangles. [12] There is a clear difference in the distribution of amyloid and tau within the brain however, with amyloid being mostly dispersed throughout all the brain, whereas tau specifically appears first in the medial temporal lobes before spreading to other cortical regions.

Currently, research suggests that the confluence of amyloid and tau triggers the cascade for AD, particularly in the medial temporal lobe regions such as the entorhinal cortex and hippocampus. [38] In addition to the amyloid/tau pathophysiology, several other precipitating factors can act as seeds for the AD pathology, including neuroinflammatory processes and vascular related brain changes, which have been shown to increase the risk of dementia considerably. [12]

Several biological mechanisms can potentially be linked to menopausal hormone changes, cognitive impairment, and dementia onset. [13] For example, it has been shown that oestrogen improves synapse formation on dendritic spines in the hippocampus of oophorectomized rat. [21] Thus, reduction in such hormonal induced neuroprotective factors might make the hippocampus – one of the first regions affected by dementia - more vulnerable towards

dementia pathophysiology. Similarly, as mentioned above, oestrogen can improve cerebral blood flow and glucose metabolism, therefore increasing overall perfusion and potentially counteracting the formation of the microvascular lesion events in the brain which can precipitate dementia. Finally, and most importantly, oestrogen has been shown to reduce the deposition of amyloid beta in the brain, [39,40,41] therefore having a more direct impact on the actual pathophysiological processes for dementia.

This then raises the question as to whether HRT, by increasing hormonal neuroprotective factors, might potentially serve as a protective treatment for the onset of AD, [42,43,44] similar to the prescription of statins to reduce cerebral vascular events. [45,46] Indeed, recent work comparing a large cohort of Oophorectomy women to referent women, showed a 20 - 40% reduction in relative risk of AD for women on HRT post-menopause [47,48,49]. The risk discussed is relative as it is expressed as a percentage decrease correlated with undergoing an oophorectomy compared to a group that did not.

However, it must be noted that other studies have reported an increased, rather than a decreased, risk of dementia in women treated by either oestrogen alone or oestrogen plus progestin at age 65 years or later. [50,51] These conflicting findings may be explained by an age-dependent effect of oestrogen on the brain (akin to the 'critical window' hypothesis) for population-level studies which specifies treatment is required before the age of 60 years [12]. Specifically, oestrogen may have a protective effect on the brain if given to women who undergo oophorectomy before reaching natural menopause, or if given in the perimenopausal and early postmenopausal years to women with natural menopause. [18] In contrast, oestrogen may indeed have deleterious effects on the brain if started many years after the onset of natural menopause, consistent with theories for a critical age window for neuroprotection against dementia in women. Clearly, this needs to be confirmed in future studies and trials, as it has potentially major implications for prevention in women at high risk of developing dementia, as well as the overall prevalence of dementia worldwide.

The importance of the hormone especially in young women can also be recognised through a series of pregnancy studies. For example, Paola Gilsanz [49] (retrieved from Fox et al., 2018 [52]) supported the notion that increased oestrogen levels (via reproductive time span and pregnancies) throughout the lifespan, acts as a protective factor. However, the lack of consistent evidence for the effectiveness of HRT in younger vs older individuals suggests the

more carefully controlled HRT trials are needed in future to truly establish if HRT started at an earlier age is a preventative measure for dementia.

Finally, there is sufficient evidence to suggest that the role of genetic information should be considered when looking at the menopause-dementia link, thereby increasing the complexity of this relationship. [35,53] The main recessive genetic risk for dementia is the apolipoprotein epsilon 4 allele (APOE ε4), with heterozygous and homozygous carriers of the APOE ε4 genotype harbouring a 4-fold to 12-fold increase risk of AD, respectively. [27] In particular, several studies have shown that female APOE ε4 carriers in particular have a significantly increased risk for dementia. [5] Interestingly, the APOE genotype [54] is closely linked to oestrogen mechanisms, [36] in particular for the lipid metabolism that both pathways are involved in. Importantly, clinical trials have shown that HRT protective mechanisms towards cognitive decline interacts with APOE genotype. [12,53] More specifically, studies have shown that female APOE ε4 carriers, who are vulnerable to AD, might benefit from HRT to reduce cognitive decline and potentially the onset of dementia. [4,12] However, so far there have been very few menopause studies and trials specifically for APOE genotyped women to explore this relationship, in particular towards the 'critical window' hypothesis. [27]

Summary & outlook

Taken together, there is increasing evidence for not only a correlational, but also, a causal link between menopausal hormone changes and cognition as well as dementia, which has so far been under-explored in the literature. Despite the exciting findings discussed, it emerges that there is complex interaction between menopausal stages, HRT and genetic status (in particular for the APOE genotype) which appears to underlie cognitive deficits and potentially the onset of incipient dementia. In particular, the specific biological mechanisms which link oestrogen to cognitive changes and incipient dementia requires further investigation. In this regard, the impact of genetic risk factors, such as APOE or oestrogen receptors encoded by ESR1/2 genes, seem to be critical to our understanding of the risk profile of women for developing dementia across menopausal stages. Delineating those contributions might help identify women who are at a higher risk for dementia post-menopause, based on their genotype status. This would enable the designing of much more targeted longitudinal and interventional studies for such women, who are potentially at the highest risk of cognitive decline and dementia. In turn, this might also reduce the admixture of women in clinical trials to increase the statistical power for interventions and reduce the

outcome variability. Furthermore, on the cognitive testing side, it is recommended that a more systematic approach be adopted for testing cognitive performance in menopausal women objectively. In particular, more detailed and specific tests to detect potentially incipient dementia processes would be beneficial, as currently most studies and trials use crude cognitive screening tests. Of relevance in this regard might be novel, more dementia pathology specific tests in spatial navigation, which have been shown to be related to entorhinal cortex integrity and underlying amyloid/tau pathology. [38] This would allow the delineation of more general cognitive effects of menopausal hormonal changes from dementia specific ones, again informing future clinical trials. Finally, the identification of such specific menopausal phenotypic and genotypic changes would allow a more personalised approach to identify women 'at-high-risk' of developing dementia, which in turn would allow earlier treatment with a potential to alleviate or even delay the onset of the disease.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

References

1. Prince, M, Wimo, A, Guerchet, M, Ali, GC, Wu, Y. T., and Prina M. World Alzheimer Report 2015 -The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International (ADI); 2015.

2. Kolanowski, Ann M. et al. Gender differences in factors associated with delirium severity in older adults with dementia. Archives of Psychiatric Nursing 2014; 28: 187 - 192.

3. Castellani, R. J., Rolston, R. K., & Smith, M. Alzheimer disease. Dis Mon 2011; 56: 1–60.

4. Maki, P., M. & Henderson, V.W. Hormone therapy, dementia, and cognition: The Women's Health Initiative 10 years on. Climacteric 2012; 15: 256–62.

5. Fleisher AS, Chen K, Quiroz YT et al. Florbetapir PET binding of amyloid-b deposition in the presenilin 1 E289A autosomal dominant Alzheimer's kindred; a cross-sectional study. Lancet Neurol. 2012; 11: 1057–1065.

6. Reiman EM, Quiroz YT, Fleisher AS et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the prensenlin 1 E2804 kindred: a case–control study. Lancet Neurol. 2012; 11: 1048–1056.

7. Maki, P.M., & Henderson, V. W. Cognition and the menopause transition. Menopause 2016; 23: 803-5.

8. Walter, A. et al. Sex and gender differences in the causes of dementia: A narrative review. Maturitas 2014; 79: 196 – 201.

9. Berglund, J. A Time of Forgetting: Menopause May Hold a Key to Understanding the Development of Alzheimer's Disease. IEEE Pulse 2018; 9: 19-21.

10. Woods, N.F., Mitchell, E.S., & Adams, C. Memory functioning among midlife

women: observations from the Seattle Midlife Women's Health Study. Menopause 2000; 7; 257–65.

11. Weber, M.T., Maki, P.M., & McDermott, M.P. Cognition and mood in perimenopause: a systematic review and meta-analysis. J Steroid Biochem Mol Biol 2013; 142: 90–8.

12. Davey, D. A. Alzheimer's disease, Dementia, Mild cognitive impairment and the menopause: A 'Window of Opportunity'? Women's Health 2013; 279–290.

13. Bromberger, J. T., Kravitz, H. M., Chang, Y. F., Cyranowski, J. M., Brown, C., & Matthews, K. A.. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). Psychological medicine, 2011; 41: 1879-1888.

14. 14-Seen in Vega, J. N., Zurkovsky, L., Albert, K., Melo, A., Boyd, B., Dumas, J., … Newhouse, P. A. Altered Brain Connectivity in Early Postmenopausal Women with Subjective Cognitive Impairment. Frontiers in neuroscience, 2016l; 10: 433.

15. Ryan, J., et al. Impact of a premature menopause on cognitive function in later life. BJOG 2014; 201: 1729-1739.

16. Burger, H.G., Hale, G.E., Robertson, D.M., Dennerstein, L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project Hum Reprod Update 2007; 13: 559–565.

17. Huang, J., Bai, F., Yang, X., Chen, C., Bao, X., & Zhang, Y. Identifying brain functional alterations in postmenopausal women with cognitive impairment. Maturitas, 2015; 81: 371-376.

18. Pike, C.J., Carroll, J.C., Rosario, E.R., Barron, A.M. Protective actions of sex steroids. Front. Neuroendocrinol 2009; 30: 239–258.

19. Rettberg, J. R., Yao, J., & Brinton, R. D. Estrogen: a master regulator of bioenergetic systems in the brain and body. Frontiers in neuroendocrinology, 2014; 35: 8–30.

20. Rocca, W. A. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Melton Neurology 2007; 69: 1074-1083.

21. Brinton, R. D. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. Trends in neurosciences, 2008; 31: 529-537.

22. Wang, Y., & Brinton, R. D. Estrogen regulation of mitochondrial respiration is cell type and ER subtype specific. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2017; 13: P665-P666.

23. Spencer, J. L., Waters, E. M., Romeo, R. D., Wood, G. E., Milner, T. A., & McEwen, B. S. Uncovering the mechanisms of estrogen effects on hippocampal function. Frontiers in neuroendocrinology, 2008; 29: 219-237.

24. Brann, D. W., Dhandapani, K., Wakade, C., Mahesh, V. B., & Khan, M. M. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. Steroids, 2007; 72: 381–405.

25. Emmens, C. W., Macintosh, F. C., & Richter, D. Oestrogens and acetylcholine. The Journal of physiology 1943; 101: 460-464.

26. Markowska, A.L, & Savonenko, A.V. Effectiveness of oestrogen replacement in restoration of cognitive function after long-term oestrogen withdrawal in aging rats. J. Neurosci 2002; 22: 10985–95.

27. Depypere, H., Vierin, A., Weyers, S., & Sieben, A. Alzheimer's disease, apolipoprotein E and hormone replacement therapy. Maturitas 2016; 94: 98-105.

28. Hodis, H. N., Mack, W. J., Shoupe, D., Azen, S. P., Stanczyk, F. Z., Hwang-Levine, J., ... & Henderson, V. W. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause (New York, NY) 2015; 22: 391.

29. Woods, N. F., et al. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. The American Journal of Medicine 2005; 118: 14 – 24.

30. Espeland, M.A., et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med 2013; 173: 1429–36.

31. Gleason, C.E., et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS–cognitive and affective study. PLoS Med 2015; 12: 1833.

32. Henderson, V.W., et al. Cognitive effects of estradiol after menopause. Neurology 2016; 87: 699–708.

33. Imtiaz, B., et al. Postmenopausal hormone therapy and Alzheimer disease. Neurology 2017; 88, 1062–8.

34. Ratka, A. Menopausal hot flashes and development of cognitive impairment. Annals of the New York Academy of Sciences 2005; 1052: 11-26.

35. Ferretti, M. T., et al. Sex differences in Alzheimer disease — the gateway to precision medicine. Nature Reviews Neurology 2018; 14: 457–469.

36. Chêne, G., et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2015; 11: 310-320.

37. Neu, S. C. et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. JAMA Neurol. 2017; 74: 1178–1189.

38. Coughlan, G., et al. Spatial navigation deficits — overlooked cognitive marker for preclinical Alzheimer disease? Nature Reviews Neurology 2018; 14: 496–506.

39. Xu, H., Gouras, G. K., Greenfield, J. P., Vincent, B., Naslund, J., Mazzarelli, L., ... & Liao, F. Oestrogen reduces neuronal generation of Alzheimer β-amyloid peptides. Nature medicine 1998; 4: 447.

40. Casadesus, G., Webber, K. M., Atwood, C. S., Pappolla, M. A., Perry, G., Bowen, R. L., & Smith, M. A. Luteinizing hormone modulates cognition and amyloid-β deposition in Alzheimer APP transgenic mice. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 2006; 1762: 447-452.

41. Petanceska, S. S., Nagy, V., Frail, D., & Gandy, S. Ovariectomy and 17β-estradiol modulate the levels of Alzheimer's amyloid β peptides in brain. Neurology 2000; 54: 2212-2217.

42. Takeda, S., & Matsuzawa, T. Age-related brain atrophy: a study with computed tomography. J Gerontol 1985; 40: 159–63.

43. Lethaby, A., Hogervorst, E., Richards, M., Yesufu, A., & Yaffe, K. Hormone replacement therapy for cognitive function in postmenopausal women. Cochrane Database Syst Rev 2008; 23: 3122.

44. Gibbs, R.B., & Gabor, R. Oestrogen and cognition: applying preclinical findings to clinical perspectives. J Neurosci Res 2003; 74: 637–43.

45. Jick, H.Z., Zornberg, G.L., Jick, S.S., Seshadri, S., & Drachman, D.A. Statins and the risk of dementia. The Lancet 2000; 356: 1627-1631.

46. Delanty, N., & Vaughan, C. J. Vascular effects of statins in stroke. Stroke 1997; 28: 2315-2320.

47. Yaffe K, Sawaya G, Lieberburg I, Grady D. Oestrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 1998; 279: 688–695.

48. LeBlanc E S, Janowsky J, Chan B K, Nelson H D. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001; 285: 1489–1499.

49. Hogervorst E.,Williams J.,Budge M., Riedel W., Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in postmenopausal women: a meta-analysis. Neuroscience 2000; 101: 485–512.

50. Anderson, G.L., Limacher, M., Assaf, A.R., Bassford, T., Beresford, S.A., Black, H., et al. Effects of conjugated equine oestrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. Jama 2004; 291: 1701-12.

51. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. Jama 2002; 288: 321-333.

52. Fox M., Berzuini C., Knapp L. A., Glynn L. M. Women's Pregnancy Life History and Alzheimer's Risk: Can Immunoregulation Explain the Link?. Am J Alzheimers Dis Other Demen. 2018; 33: 516-526

53. Buckley, R. F., et al. Sex, amyloid, and APOE ε4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2018; 4: 1193 – 1203

54. Corder, E. H., et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993*;* 261: 921-3.

55. Shanmugan S, Epperson CN. Oestrogen and the prefrontal cortex: Towards a new understanding of oestrogen's effects on executive functions in the menopause transition. *Hum Brain Mapp* 2014; 35: 847–865.

56. Voytko ML, Murray R, Higgs CJ. Executive Function and Attention Are Preserved in Older Surgically Menopausal Monkeys Receiving Oestrogen or Oestrogen Plus Progesterone. *J Neurosci* 2009; 29: 10362–10370.

57. Hara Y, Waters EM, McEwen BS, et al. Oestrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Physiol Rev* 2015; 95: 785–807.

58. Hampson E. Oestrogens, Aging, and Working Memory. *Curr Psychiatry Rep* 2018; 20: 109.

59. Compton J, van Amelsvoort T, Murphy D. HRT and its effect on normal ageing of the brain and dementia. *Br J Clin Pharmacol* 2001; 52: 647–53.

60. Denninger JK, Smith BM, Kirby ED. Novel Object Recognition and Object Location Behavioral Testing in Mice on a Budget. *J Vis Exp*. Epub ahead of print 2018. DOI: 10.3791/58593.

61. Alvarez-De-La-Rosa M, Silva I, Nilsen J, et al. Estradiol prevents neural tau hyperphosphorylation characteristic of Alzheimer's disease. *Ann N Y Acad Sci* 2005; 1052: 210–224.

62. Rosario ER, Chang L, Head EH, et al. Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. *Neurobiol Aging* 2011; 32: 604–613.

63. Shao H, Breitner JCS, Whitmer RA, et al. Hormone therapy and Alzheimer disease dementia: New findings from the Cache County Study. *Neurology* 2012; 79: 1846–1852.

64. Henderson VW. Oestrogens, episodic memory, and alzheimer's disease: A critical update. *Semin Reprod Med* 2009; 27: 283–293.

65. Henderson VW. Cognitive changes after menopause: Influence of oestrogen. *Clin Obstet Gynecol* 2008; 51: 618–626.

66. Poromaa IS, Gingnell. M. Menstrual cycle influence on cognitive function and emotion processing-from a reproductive perspective. *Front Neurosci*. 2014; 8: 380.