The Effect of Estradiol on Delayed Memory Performance in Women

Alzheimer's Disease (AD) is the most common form of dementia, making up about 60% of all dementia cases. It occurs in 1 in every 9 people over the age of 65 and causes severe memory, thinking, and behavioral problems. With over 6 million cases of AD in the United States, about two-thirds of these cases are women with reasons still unknown as to why they are more vulnerable. It is the overall fifth leading cause of death in women, while it is only the eighth leading cause of death in men.

Women have double the lifetime risk of developing AD at age 45 compared to men. This increased risk can be partially attributed to the longer life expectancy of women, given that age is one of the biggest risk factors for AD. However, the longer life expectancy doesn't fully explain the higher risk of developing AD in women. Although these reasons for women's enhanced risk are not fully understood, researchers hypothesize that risk factors such as cardiometabolic risk factors may have a stronger effect in one sex than the other.

The hallmark characteristics of AD that cause such memory deficits are the formation of neurofibrillary tangles, made of the tau protein, and amyloid-beta plaques, made of aggregated amyloid-beta peptides. While this pathology has been well-documented, the causes behind the disease still remain unclear. Many therapeutic approaches have been developed, such as antibodies targeting one or more of the aforementioned proteins, but these approaches haven't specifically taken into account the sex differences that make women more susceptible.

In many of the other risk factors associated with Alzheimer's Disease, such as depression and sleep disruption, sex differences are significantly apparent. Depression in midlife is thought to increase the risk of AD by as much as 70%, and women have twice the risk of depression compared to men. Similarly, disturbances in the sleep cycle have been linked to an increase in the AD pathology and women tend to have more disruptions in their sleep cycle during their midlife. A major life event during midlife for women that has no parallel in men and may be highly significant for AD risk is menopause, as previous studies have found that a decrease in verbal memory occurs during the menopausal transition.

Menopause is defined as the period during a woman's life when the menstruation cycle ceases (typically during the ages of 45-50). It is characterized by hot flashes, insomnia, anxiety, and irritability as well as hormonal changes. During premenopause, a woman typically shows no symptoms of menopause at all, still having periods and is considered to be in her reproductive years. Right before menopause, women undergo the perimenopausal phase, which is marked by a drop in estrogen levels as symptoms begin to appear. After the menopausal transition, the postmenopausal phase occurs in which a woman's hormone levels will be at a constant low level, they will cease to have periods, and will have no more menopause symptoms.

Given the overall higher prevalence of Alzheimer's Disease (AD) in women and so many factors still unknown as to why they are more vulnerable, this study aims to examine further the relationship between changes during menopause and cognitive ability. Specifically, we will investigate the relationship between the estradiol levels in women ages 36 to 100 and their scores on the Montreal Cognitive Test (MoCA), Picture Sequence Memory Test (PSM), and the Rey Auditory Verbal Learning Test (RAVLT).

The Montreal Cognitive Test (MoCA) is a test used to screen for mild cognitive impairment and scores subjects across eight cognitive domains: visuospatial abilities, short-term memory, executive function, attention, concentration, working memory, language, and orientation. In this study, we will analyze delayed recall performance, graded on a 5 point scale. Poor delayed recall performance in the past has been shown to be able to predict Alzhimer's Disease pathology in the future and thus, we will try to determine if estradiol facilitates or hinders the development of such pathology.

The Picture Sequence Memory Test (PSM) is an assessment of episodic memory involving recalling a series of illustrations presented in a particular order. Credit is awarded to participants who correctly place pairs of pictures in order and those with more credit are considered to have stronger episodic memory. Episodic memory impairment has been long thought to be a hallmark of the early stages of Alzheimer's Disease and this study will look to confirm if there is a relationship between estradiol levels and episodic memory impairment.

The Rey Auditory Verbal Learning Test (RAVLT) is a measure of verbal learning ability that involves reading out an unrelated word list (List A) and an interference list (List B). In the first five trials, subjects will recall as many words as possible when prompted and then on the sixth trial, they will listen to the interference list and recall words from that list. In the final trial, they will repeat words from List A again without having listened to it again. This test is highly regarded as a pure measure of verbal memory and episodic memory and poorer scores would be found in subjects with Alzheimer's Disease.

For this study, we will examine the subjects' performance on these tests (adjusted for age and sex) and look for either a positive or negative correlation between estradiol levels and their scores during the pre-menopause, perimenopause, and postmenopause phase. A significant correlation would indicate that the estradiol changes during menopause in women possibly makes them more vulnerable to cognitive impairment.