MedicalXpress

Elucidating sex differences in Alzheimer's disease risk

November 9 2016

Women have a two-fold higher risk of developing Alzheimer's disease than men, yet strikingly little is known about how changes in brain function promote this difference—and how early in midlife those changes can be detected. Now, in a population-based study involving more than 200 healthy women and men ages 47 to 55, a team of researchers led by the Brigham and Women's Hospital reveals specific changes in memory function that correspond to sex and menopausal stage, rather than chronological age. The work implicates key areas of the brain that are vulnerable to age-related decline and highlights the importance of ovarian hormones in maintaining memory function.

The new study appears in the Nov. 9 online issue of the journal *Menopause*.

"For years, the dominant thinking in the field was that women were at higher risk of Alzheimer's disease simply because they tend to live longer," said senior author Jill Goldstein, PhD, Director of Research at the Connors Center for Women's Health and Gender Biology at BWH. "But that idea was perpetuated by research that looked late in life—not at middle age, when key hormonal transitions take place and when changes in memory begin to surface."

Age-related cognitive decline impacts both men and women, with people reporting forgetfulness and a lack of mental clarity (so-called "brain fog") as they age. While women in general tend to fare better than men on tests of verbal memory and men have a higher rate of mild cognitive

impairment later in life, women are disproportionately affected by Alzheimer's disease. In the U.S. alone, there are roughly 5.4 million people living with Alzheimer's disease; nearly two-thirds are women.

Goldstein and her colleagues seized an opportunity to examine how and why these sex differences unfold when one of their long-studied community cohorts, known as the New England Family Study, began entering their later-40s and 50s. That allowed the researchers to carefully examine what happens to memory function in healthy, middle-age women over time as menopause unfolds—spanning the pre- , peri-, and post-menopausal periods—and to compare those findings to healthy, age-matched men.

Because the individuals studied showed no signs of dementia or obvious memory loss, standard tests of memory function were not challenging enough to detect changes. So the team turned to a series of neuropsychological tests, refined by Dorene Rentz, PsyD, a lead author on the paper, senior neuropsychologist in the Department of Neurology at BWH, and an expert on Alzheimer's disease. These tests rigorously evaluate different forms of learning and memory, offering a finer-grained view that could identify even early, age-related cognitive deficits.

The researchers found that, when compared to age-matched men, the women scored significantly higher on all categories of memory function assessed by the tests, with one notable exception: Post-menopausal women performed at roughly the same level as their male counterparts (and worse than the other women) on tests of initial learning and retrieval of information. The finding suggested changes in frontal areas of the brain, known for their roles in short-term memory and so-called "executive functions"—advanced cognitive abilities, like organizing, structuring and evaluating information. In addition, hormone measurements revealed that across all women studied, higher estradiol

levels (the form of estrogen that has the greatest effects on the brain) correlated with better memory performance.

When taken together with other recent work, both from Goldstein's group and others, the *Menopause* paper helps paint a picture of the memory circuits in the brain that begin to change with age—in both males and females—and underscores the importance of steroid hormones, especially estradiol for women, in maintaining memory function.

"We need to develop the capability to identify early on who is at highest risk of developing Alzheimer's disease," said Goldstein. "This is critical because the treatments given after disease onset have been unsuccessful. We hope findings from our cohort will ultimately provide clues early in mid-life with regard to who is at highest risk for the disease in later mid-life, and how this may differ for men and women. "

Goldstein and her colleagues are already working toward that goal. Together with collaborator Philip de Jager, MD, PhD, who directs the Program in Translational NeuroPsychiatric Genomics at the Ann Romney Center for Neurologic Diseases at BWH, the researchers are designing a clinical risk tool that can help pinpoint patients who are most vulnerable to Alzheimer's disease. This tool—which is being developed for both men and women—will incorporate genetic risk factors as well as a host of other clinical characteristics known to affect memory decline and the sex differences therein.

"Alzheimer's disease is one of the greatest public health challenges of our time," said Goldstein. "Going forward, it is imperative that we understand how to retain memory function throughout life, and that we incorporate these sex differences into future research and therapeutic discovery strategies."

Provided by Brigham and Women's Hospital