Sex differences in cognition

Does the "fairer sex" need a fairer test?

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Understanding the underlying biology of cognitive loss and dementia is an important first step to developing approaches to preventing or reversing these conditions. In this issue of *Neurology*®, Sundermann et al.[1] describe a secondary analysis of data from an Alzheimer's Disease Neuroimaging Initiative (ADNI) study that examines differences in verbal memory between men and women as a function of hippocampal volume ratio (HpVR). The association is described within 3 diagnostic groups: cognitively healthy, those with amnestic mild cognitive impairment (aMCI), and those with mild Alzheimer disease (AD). This cross-sectional analysis demonstrates that women with aMCI have better verbal memory than men despite similar levels of hippocampal atrophy as measured by the HpVR. The authors interpret this sex-related difference in performance vs atrophy as a reflection of cognitive reserve. The report has many strengths and considerations for the clinician evaluating complaints of cognitive loss. However, it is worth noting that the study also illustrates several pitfalls of secondary data analyses and limitations of use of historical data. This is especially notable because such issues can perpetuate sex biases in scientific observation.

A strength of this article is the thoughtful analysis about sex differences in cognitive aging, including a reiteration of the well-established observation that women show better cognitive performance across the entire age span, including into older ages. This is exemplified in a table that shows better memory performance in women despite less education and greater diversity, both of which are variables that have been associated with lower performance.

Selection of diagnostic groups in ADNI was based on cut scores on a verbal memory test that was not adjusted for sex; therefore, perhaps it is unsurprising that fewer women fall into disease groups. However, there are sufficient numbers of women to identify some of the consequences of this sample selection. Given that women perform better than men, particularly on verbal memory, and because few cognitive tests used to detect incipient dementia are adjusted for sex, it is highly likely that cut scores useful for detecting early impairment in men will detect women at later stages of impairment. The obvious consequence may be that this methodology will fail to detect the earliest changes in cognitive function in women, including aMCI. There is supporting evidence for this insensitivity to early changes in women when the rich ADNI dataset is considered. One example can be found when comparing scores in the Clinical Dementia Rating (CDR) sum of boxes parameter, a noncognitive measure of function. In this report, within the AD group there is poorer performance (higher scores) on the CDR in women than in men despite better verbal memory performance in women.

The insensitivity of cognitive measures to detect the earliest dysfunction in women (and, by implication, the earliest underpinning neurodegeneration in this group) provides a real challenge to care delivery. Several reports have suggested that subjective impairment may be an early predictor of both cognitive and brain deterioration,[2] though such assessments and clinical complaints, especially when not corroborated by a family member or other informant, do not carry the same weight of evidence in clinical practice.

A particularly striking finding is that HpVR is greater in women across all disease states, though the difference is smaller in the AD group in this study. This finding is consistent with the work of Jack et al.,[3] who identified female advantage for both brain volume and cognitive performance in a population-based, age-stratified sample. That analysis, by decade of age and sex, demonstrates deterioration in both women and men in brain volume and cognitive performance, highlighting the importance of selecting the right unbiased comparison group from which to measure deterioration. The ADNI cohort does not have the advantage of population selection, primarily because it was designed to understand neurodegenerative disease pathogenesis rather than demography and epidemiology. A measure of deterioration or change from an appropriate norm may reduce this bias, and the longitudinal data available in ADNI may eventually help identify sensitive unbiased measures of change.

The concept of cognitive reserve has been invoked as a source of the female advantage in the MCI

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cohort. Cognitive reserve has had many definitions, with subtle but critically different interpretations. Here the lifelong female over male advantage in cognition is described as cognitive reserve, with the further postulation that, at the point of detection that is apparently sensitive enough for men but is too crude for women, women appear to have accelerated cognitive decline. This is a convenient interpretation overly focused on cross-sectional findings that do not fully appreciate the degenerative nature of the disease. Accumulated evidence does not support the notion that individuals undergo accelerated loss at some tipping point. Longitudinal studies suggest a more slowly progressive change with the performance and structural brain changes of women with aging and disease state being similar to those parameters in men. Of note, in the same ADNI dataset, the presence of an *APOE* ε4 allele has been interpreted as conferring a greater risk of AD for women than for men.[4] This comparison is based on a sex-specific comparison in which female *APOE ε4* noncarriers have a lower risk of dementia than male noncarriers. Thus the women's cognitive reserve has the appearance of increasing the risk conferred by the *APOE ε4* allele when, in fact, the female comparison group shows less cognitive decline than the male comparison group.

Should not change of similar magnitude have the same diagnostic value in both sexes? This decrement should be worthy of attention and intervention regardless of sex. Here the concept of cognitive reserve may inadvertently lead to underdetection and undertreatment of clinically important neurodegeneration in women. If we consider the earliest change in brain and cognitive performance to be the best timing for therapeutic interventions, then this concept of cognitive reserve may inadvertently place women at a systematic disadvantage.

Regardless of interpretation, this study clearly illustrates the need for better methods to detect early, meaningful change in cognition and brain function for women. This need may be addressed by emphasizing recommendations for baseline cognitive assessments, by developing sensitive but accurate subjective measures, and by developing more granular tests of memory and other cognitive domains. At a policy level, the potential health care cost that will be encumbered by underdetection or delayed diagnosis of women with prodromal or overt dementia (including AD) is staggering and should motivate increased research attention and funding in this focused area. It is ironic that women are disadvantaged by their superior brain volume and cognitive function, which apparently lead to delay in disease detection.

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