Women and Brain Aging

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Disclosures
- Consultant: Pfizer, Noven
- Speaking Honorarium: Abbott
- Research: NIH

Objectives
1. Describe sex/gender differences in Alzheimer’s Disease (AD)
2. Describe sex/gender differences in risk factors for AD
3. Elucidate the role of reproductive aging on cognition and brain aging in women

Objectives
1. Describe sex/gender differences in Alzheimer’s Disease

Alois Alzheimer
Prevalence of Alzheimer’s Disease (AD)

- More women than men have AD
- Of 5 million with AD in US
  - 3.2 million are women
  - 1.8 million are men
- ~2/3rds of AD patients in US are women

Source: Heron, M. CDC National Vital Statistics Report; Vol 62, No 6, 2013

Women and AD

- At age 65, women without Alzheimer’s have more than a 1 in 6 chance of developing AD during the remainder of their lives, compared with a 1 in 11 chance for men.
- Women in their 60s are about twice as likely to develop AD over the rest of their lives as they are to develop breast cancer.


Why is the Prevalence of AD Higher in Women Than Men?

- Major contributing factor to higher prevalence of AD in women is that women live longer than men
- Age is the major risk factor for AD


Greater cognitive deterioration in women than men with Alzheimer’s: A meta analysis

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Male Advantage</th>
<th>Female Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic</td>
<td></td>
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<tr>
<td>Nonsemantic</td>
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<tr>
<td>Verbal</td>
<td></td>
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<tr>
<td>Visuospatial</td>
<td></td>
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<tr>
<td>Memory</td>
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</tbody>
</table>

Effect Size (95% CI)

Prevalence of AD Will Triple By 2050

Cost of AD from 2010-2050 will exceed $20 trillion

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AD Can Be Prevented/Delayed


Lewin Group for the Alzheimer’s Association: www.alz.org/trajectory

Prevalence of Risk Factors for AD: Differences Between Men and Women

Compared to men, women have:

- Higher BMI
- Lower rates of exercise
- Higher cholesterol levels
- Higher rates of hypertension in older adulthood
- Higher rates of depression
- Higher rates of television viewing in adulthood
- Greater risk due to the predominant genetic risk factor (ApoE4)

Body Mass Index (BMI) > 30 doubles risk of AD 21 years later


APOE4 Status Matters More in Healthy Older Women Than in Men

A single APOE4 allele increases the risk of clinical decline in healthy older women, but not men.


Female Advantage in Verbal Memory

- Women show a lifelong advantage in verbal memory
- Thought to be largely due to organizational effects of sex steroid hormones on brain systems underlying memory


Importance of Verbal Memory

• Declines in verbal memory are the earliest signs of Alzheimer’s disease (AD) and central to its diagnosis
• New findings suggest that women maintain verbal memory early in the course of AD and then rapidly decline


Women Show an Advantage In Verbal Memory Despite Similar Levels of Hippocampal Atrophy

<table>
<thead>
<tr>
<th>Total Words Recalled</th>
<th>Immediate Recall</th>
<th>Delayed Recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women perform better than men</td>
<td>Once atrophy reaches a threshold, women rapidly decline</td>
</tr>
<tr>
<td></td>
<td>$p = .001$</td>
<td>$p = .001$</td>
</tr>
</tbody>
</table>

Hippocampal Volume

RAVLT Total Words Recalled

Females: $\beta$, $p = .001$
Males: $\beta$, $p = .001$

Women perform better than men

Once atrophy reaches a threshold, women rapidly decline

$P = .001$ $P = .001$

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Memory Performance Depends on Menopausal Status: Worsens during Transition

Penn Ovarian Aging Study

$n = 465$ followed for 10 years

Memory and Other Cognitive Functions Vary with Menopausal Stage


Relationship between Cognitive Changes and Menopausal Symptoms

Megamonalis.com

Measuring Physiologic VMS Objectively with Ambulatory Monitors

- Biolog Skin Conductance Monitor
  - Objective hot flash defined as a 2 mmho increase in skin conductance across a 30 second period
  - Button press used for subjective recognition of hot flash

Women under-report VMS

Placebo effect is not evident when VMS are measured objectively


Placebo Red Clover Black Cohosh Prempro

Baseline 1-year

Subjective

Objective

Objective VMS are associated with worse verbal memory


Delayed Paragraph Recall (score adjusted for other significant predictors)

Total Number of Objective Hot Flashes during Sleeping Hours

29 midlife women (mean age = 53 y) with moderate to severe hot flashes

Number of hours of sleep independently predicted worse memory

Decreases in objective VMS relate to improvements in verbal memory


Physiologic VMS are associated with adverse brain outcomes

More white matter hyperintensities

Hyperconnectivity in brain at rest, especially in hippocampus


Early use of HT and AD Risk

- Three prospective studies have examined timing of initiation of HT in relation to risk of AD
- Each of the three provides support for the timing hypothesis
- Unfortunately, a randomized clinical trial to test that hypothesis is not feasible


Early use of HT has neutral effect on cognitive functions

- Keeps (Kronos Early Estrogen Prevention Study) 1
  - 5-yr cyclic micro P (200 mg, 12 d/month) + transdermal E2 (50 μg/wk) or CEE (0.45 mg) in 720 women (42-58 yrs) ≤ 36 m of FMP
  - Neutral cognitive effects after 48 m; some mood benefit with CEE on depression and anxiety

WHIMS (WHI Memory Study of Younger Women) 2
  - CEE alone or with MPA in women (50 to 54 y) upon enrollment; n =1326
  - Published: neutral cognitive effects when tested on average 7.2 years after the trials ended
  - “CEE-based therapies produced no overall sustained benefit or risk to cognitive function when administered to postmenopausal women aged 50–55 years”

ELITE (Early Versus Late Intervention Trial with Estradiol)
  - Oral E2 1 mg/d + vaginal P gel for 10 days per month in 643 younger (< 6 y since FMP) and older (> 10 y since FMP)
  - Neutral effects


Take-home Messages

- Women have a higher prevalence of AD and of many risk factors for AD
- Modifying risk factors such as obesity can lower the public health burden of AD
- Verbal memory is key to diagnosing AD, and women might "mask" AD in the early stages because they have an advantage in verbal memory
- Verbal memory declines during the menopause; might rebound
- New evidence suggests that VMS are linked to memory declines and structural and functional brain abnormalities
- Early use of HT might lower risk of AD; use of HT early in women has neutral cognitive effects; effects in symptomatic women are not known