Sex differences in AD biomarker progression: Sensitive measures of cognition

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- Director of Neuropsychology, UCSD Center for Brain Health and Memory Disorders
Why care about sex* differences in cognition?

1) They impact who gets diagnosed early
2) They impact who gets into clinical trials, and the results
3) If addressed, we will understand Alzheimer’s better for everyone

*I will use “sex” as a very oversimplified, binary term which sometimes involves gender.
Considerations for how we measure cognition in AD

- Lifelong sex differences in cognition
- The verbal memory advantage
- What about visual memory?
- Subtle preclinical changes and sex differences
- Relationships with biomarkers
Cognitive development is lifelong, and women and men show lifelong cognitive differences (on average)
Women have a verbal advantage
Men have a visuospatial advantage

LIFELONG SEX DIFFS

Pauls et al 2013
What do we use to test memory in AD?

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Total Learning: _/80_
These tests are used to identify cognitive impairment which declines with progression of the disease.

Forlenza et al., 2010
VERBAL MEMORY, WOMEN’s ADVANTAGE?

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Does the female advantage in verbal memory contribute to underestimating AD pathology in women versus men?

Erin E. Sundermann, PhD; Anat Blegon, PhD; Leah H. Rubin, PhD, MPH; Richard B. Lipton, MD; Susan Landau, PhD; Pauline M. Maki, PhD; Alzheimer’s Disease Neuroimaging Initiative

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LIFELONG SEX DIFFS VERBAL MEM ADV

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Presentation title
Women accumulate more tau pathology, especially during MCI phase.
Women can bear a bigger burden: ante- and post-mortem evidence for reserve in the face of tau

Leonardino A. Digma, John R. Madsen, Robert A. Rissman, Diane M. Jacobs, James B. Brewer and Sarah J. Banks, for the Alzheimer's Disease Neuroimaging Initiative*
Why is the verbal memory advantage a problem?

- Sex differences influence who gets diagnosed when
- Late diagnosis may lead to lack of intervention

- And who participates in clinical trials:
  - E.g. for lecanemab which used a cut off on Logical Memory (as verbal memory task) for inclusion:
    - Women may have been further along
    - And did not show same benefits when analyzed separately

- And how their outcomes are measured

Stern, 2012
Why is the verbal memory advantage a problem?
What about visual memory in women?

- Recruiting women with MCI and elevated genetic risk
- Battery designed to compare with ADNI
- Also focus on nonverbal memory
- Brief-Visuospatial Memory Test-R
- Does not show sex differences like verbal memory

Faux BVMT stimuli, Langdon et al 2011
Visual memory and tau

- WITS data shows stronger associations with tau for visual than verbal memory
- Perhaps using visual memory measures would be more accurate?
SEX DIFFERENCE IN COGNITION CAN IMPACT TRIAL DESIGN: Composite outcomes

LIFELONG SEX DIFFS  VERBAL MEM ADV  VISUAL MEM
A4 study, uses various tasks to detect subtle changes in cognition in preclinical AD.

Papp et al., 2021
SEX Differences in COGNITION IN preclinical phase

Study on A4 by Xin Wang
Cognitive test results in preclinical AD show sex diffs in relation to tau PET
Understanding AD risk in Black Women

- Black Women: Inflammation and Tau Study leverages progress in blood based biomarkers and community based participatory research to learn more about risk factors in Black women, who are at a particularly high risk of AD yet rarely studied.
- Same cognitive test battery as WITS but all biomarkers accessed from blood, and all data collection completed in the community.
- Watch this space!
Sex differences in cognition are important for AD research

1) They impact who gets diagnosed early

2) They impact who gets into clinical trials, and the results

3) If addressed, we will understand Alzheimer’s better for everyone
Thank you

• Participants

• WITS and BWITS teams
  • Erin Sundermann
  • Marc Norman
  • April Thames
  • Nadine Heyworth
  • Alyx Shepherd
  • Melanie Dratva

• Human Memory Lab
  • Emilie Reas
  • Charlotte Rivera
  • Xin Wang
  • Qian Shen

• ADNI and A4 Study Teams

• Funders
  • NIA
  • CDPH
  • Alzheimer’s Association
  • Women’s Alzheimer’s Movement
SEX DIFFERENCES IN PTAU 181 in PLASMA

Sex differences in plasma p-tau181 associations with Alzheimer’s disease biomarkers, cognitive decline, and clinical progression