Women’s Brain Project
An international non-profit organization advocating for women’s brain and mental health

womensbrainproject.com
Sex and gender differences in Alzheimer’s disease. An update from the Women’s Brain Project

Maria Teresa Ferretti, PhD
Co-founder and Chief Scientific Officer, Women’s Brain Project
www.womensbrainproject.com
Women, on average, have more:

- Neuroticism (higher anxiety, lower stress tolerance). This may contribute to the higher levels of anxiety women report on Googlegeist and to the lower number of women in high stress jobs.
Dementia
Some brain tumors
Migraine
Depression
NMDA encephalitis
...

Parkinson disease
ALS
Schizophrenia
Autism
Midlife stroke
...

Sex differences in pathology - neurological and neuropsychiatric disorders

McCarthy, Phil. Trans. Royal Society 2016
Account for sex in brain research for precision medicine

Maria Teresa Ferretti, Antonella Santuccione-Chadha & Harald Hampel

In her review of Gina Rippon's book The Gendered Brain, Lise Eliot uses the term "neurosexism" to describe the "myth" of brain differences in men and women (Nature 566, 453–454; 2019). Although the field is indeed rife with misinterpretation and methodological flaws, that is no justification for dismissing sex differences in neuroscience (see also R. Voskuhl and S. Klein Nature 568, 171; 2019).
1. Sex differences and mechanistic insights
2. Sex differences and disease presentation
Dementia
Neuropathological AD signature (ATN)

- **A**: Amyloid plaques
- **N**: Neurodegeneration
- **T**: Tau neurofibrillary tangles
Current diagnostic pathway of AD

- CSF, cerebrospinal fluid; CT, computerised tomography; FDG, fluorodeoxyglucose; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PET, positron-emission tomography

Occasionally conducted for differential diagnosis with frontotemporal or Lewy body dementia (~10–15% of patients with suspected AD)
Phenotypic heterogeneity
Dementia disproportionately affects women

Sex differences in Alzheimer disease — the gateway to precision medicine

Maria Teresa Ferretti, Maria Florencia Iulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Miscoh, Ezio Giacobini, Herman Depypere, Harald Hampel & for the Women's Brain Project and the Alzheimer Precision Medicine Initiative

Sex and gender differences in Alzheimer’s disease
Prevention of AD – the role of sex and gender

35% of Alzheimer risk is **modifiable**

Higher risk of AD in women is debated by the experts, but

**Sex and gender affect modifiable risk factors**

- **Early life**
  - 8% low education

- **Midlife**
  - 9% hearing loss
  - 2% hypertension
  - 1% obesity

- **Late life**
  - 5% smoking
  - 4% depression
  - 3% physical inactivity
  - 2% social isolation
  - 1% diabetes

*Apol. apolipoprotein E; DMT, disease-modifying therapy*  
Potential female-specific risk factors:

- Early menopause
- Hypertensive complications during pregnancy
- Pregnancies
- Migraine
Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy

**ABSTRACT**

**Objective** To examine sex differences in the relationship between clinical symptoms related to Alzheimer disease (AD) (verbal memory deficits) and neurodegeneration (hippocampal volume/intracranial volume ratio [HpVR]) across AD stages. **Methods** The sample included 379 healthy participants, 604 participants with amnestic mild cognitive impairment (aMCI), and 252 participants with AD and dementia from the Alzheimer’s Disease Neuroimaging Initiative who completed the Rey Auditory Verbal Learning Test (RAVLT). Cross-sectional analyses were conducted using linear regression to examine the interaction between sex and HpVR on RAVLT across and within diagnostic groups adjusting for age, education, and APOE e4 status. **Results** Across groups, there were significant sex × HpVR interactions for immediate and delayed free recall. **Conclusions** Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI.

**Sundermann et al., Neurology 2016**
Faster disease progression in women

2x faster cognitive decline

Faster brain shrinkage (darker blue)

Lin et al., 2015, A&D  Hua et al, Neurobiol of aging 2010
Women displayed greater tau-mediated metabolic dysfunction than men (Ramanan et al., JAMA Neurology 2019)
Sex-specific differential response to AD pathology

Single-cell transcriptomic analysis of Alzheimer’s disease

Hansruedi Mathys, Jose Davila-Velderrain, Zhuyu Peng, Fan Gao, Shahin Mohammadi, Jennie Z. Young, Madhi Menon, Liang He, Fatema Abdurrob, Xueqiao Jiang, Anthony J. Martorell, Richard M. Ransohoff, Brian P. Haffner, David A. Bennett, Manolis Kellis & Li-Huei Tsai

Nature (2019) | Download Citation
Call to action

Moving from ‘one size fits all’ medicine....

...to Precision Medicine

- Preventative campaigns
- Early diagnosis
- Treatment
- In Clinical trial design
- In preclinical research

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Meet the WBP Team!

III Women’s Brain Forum, Zurich, September 18th-19th 2020