ALZHEIMER'S DISEASE: SEX DIFFERENCES IN RISK AND EXPRESSION

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Associate Professor, Dept of Neurosciences
UC San Diego

QUESTIONS FOR TODAY

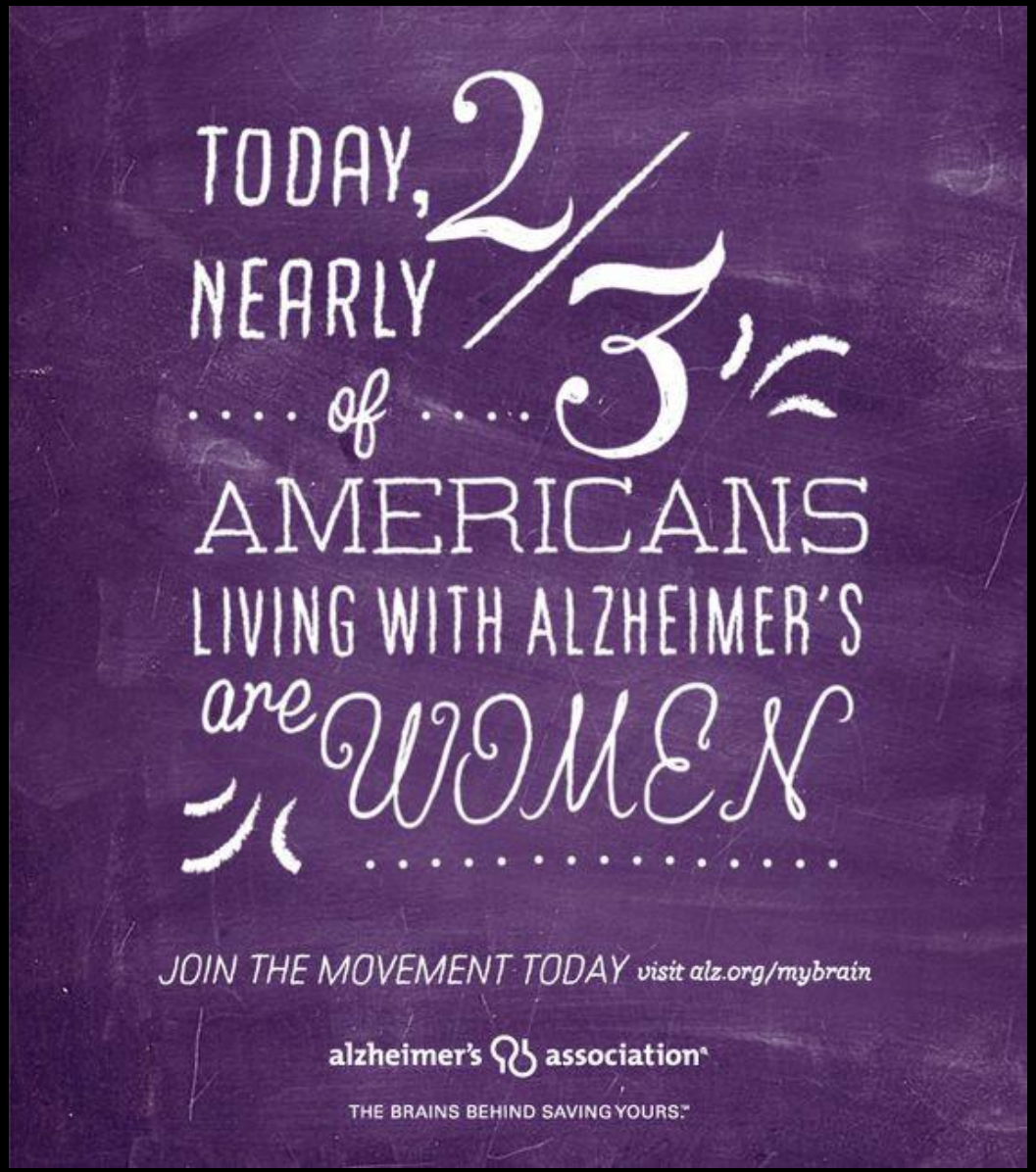
- What is Alzheimer's Disease (AD)?
- How can sex* differences help us answer important questions about AD?
- What factors promote AD in women?
- How can we help individuals to reduce their risk of cognitive decline?

* biological sex dichotomized, but sometimes incorporating gender factors. Its complicated and I'm oversimplifying

WHAT IS AD?

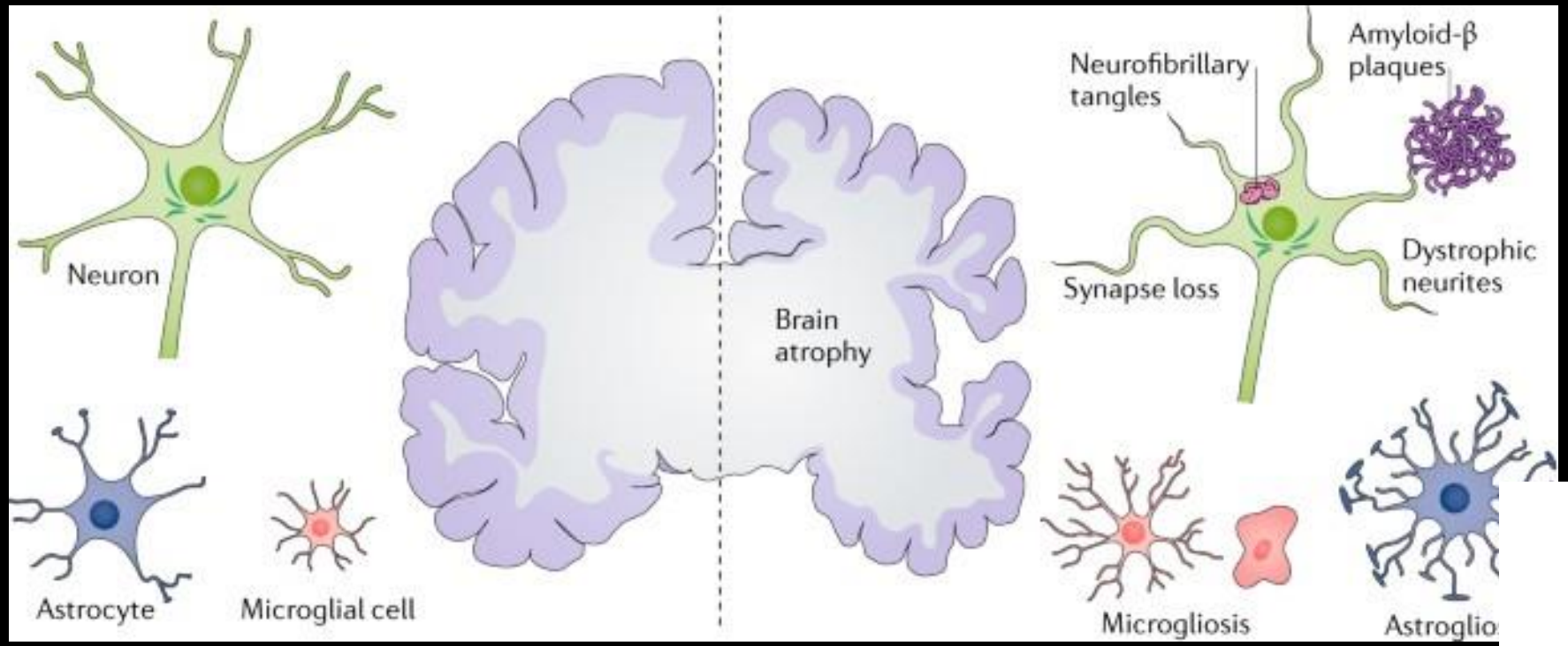
- Brain disease which is the most common cause of dementia
- Dementia is the progressive loss of cognitive abilities and independence due to brain disease

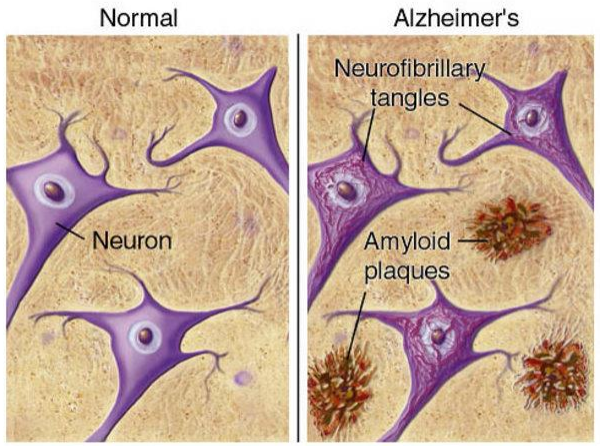

1 in 3
seniors dies with Alzheimer's or another dementia
More than
6 million
Americans are living with Alzheimer's


TODAY, NEARLY 2/3 of
AMERICANS
LIVING WITH ALZHEIMER'S
are WOMEN
JOIN THE MOVEMENT TODAY visit alz.org/mybrain
alzheimer's association
THE BRAINS BEHIND SAVING YOURS.

WHAT IS AD?

WHAT DOES AD DO TO THE BRAIN?

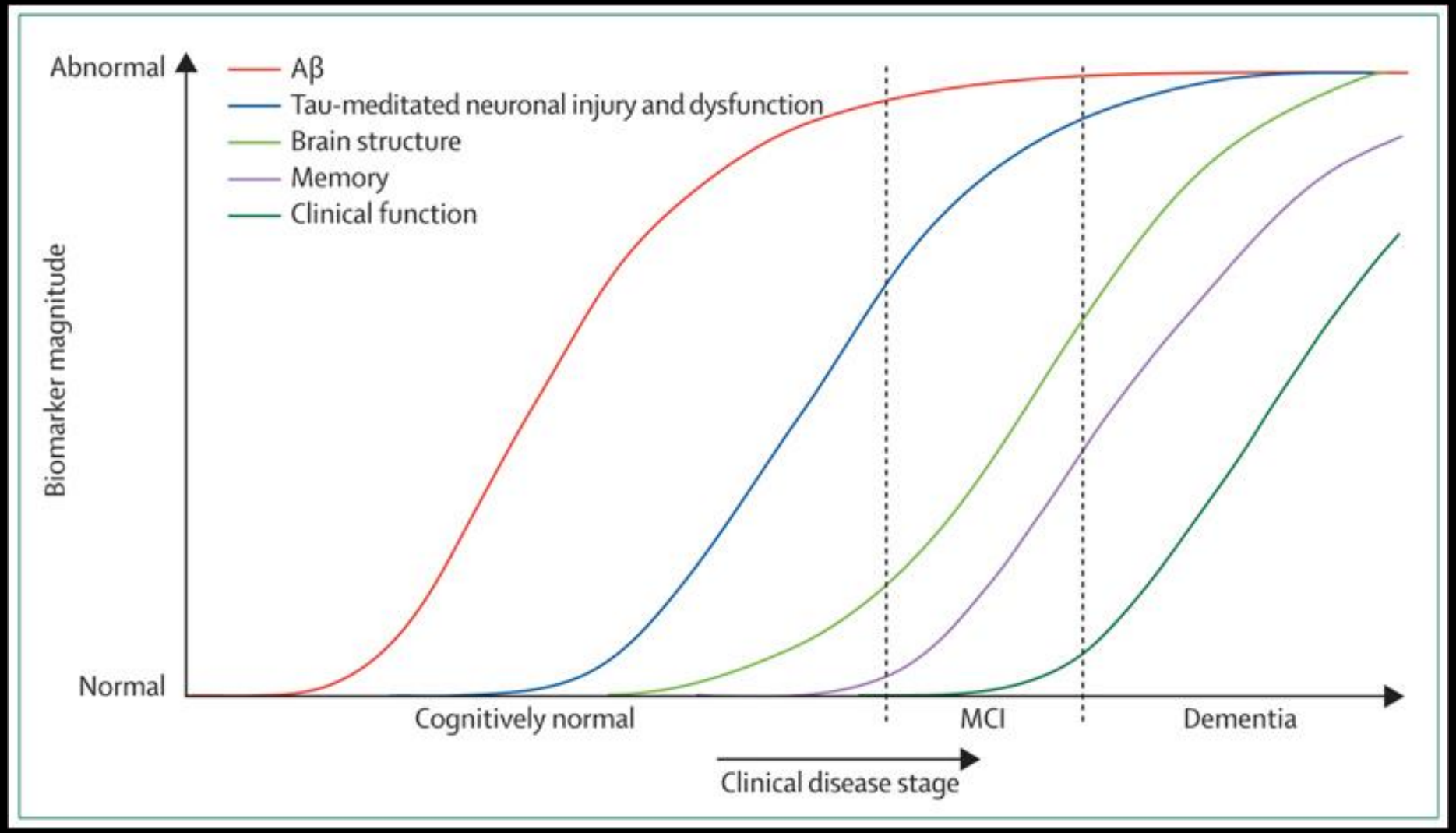




BrightFocus® Foundation
Cure in Mind. Cure in Sight.

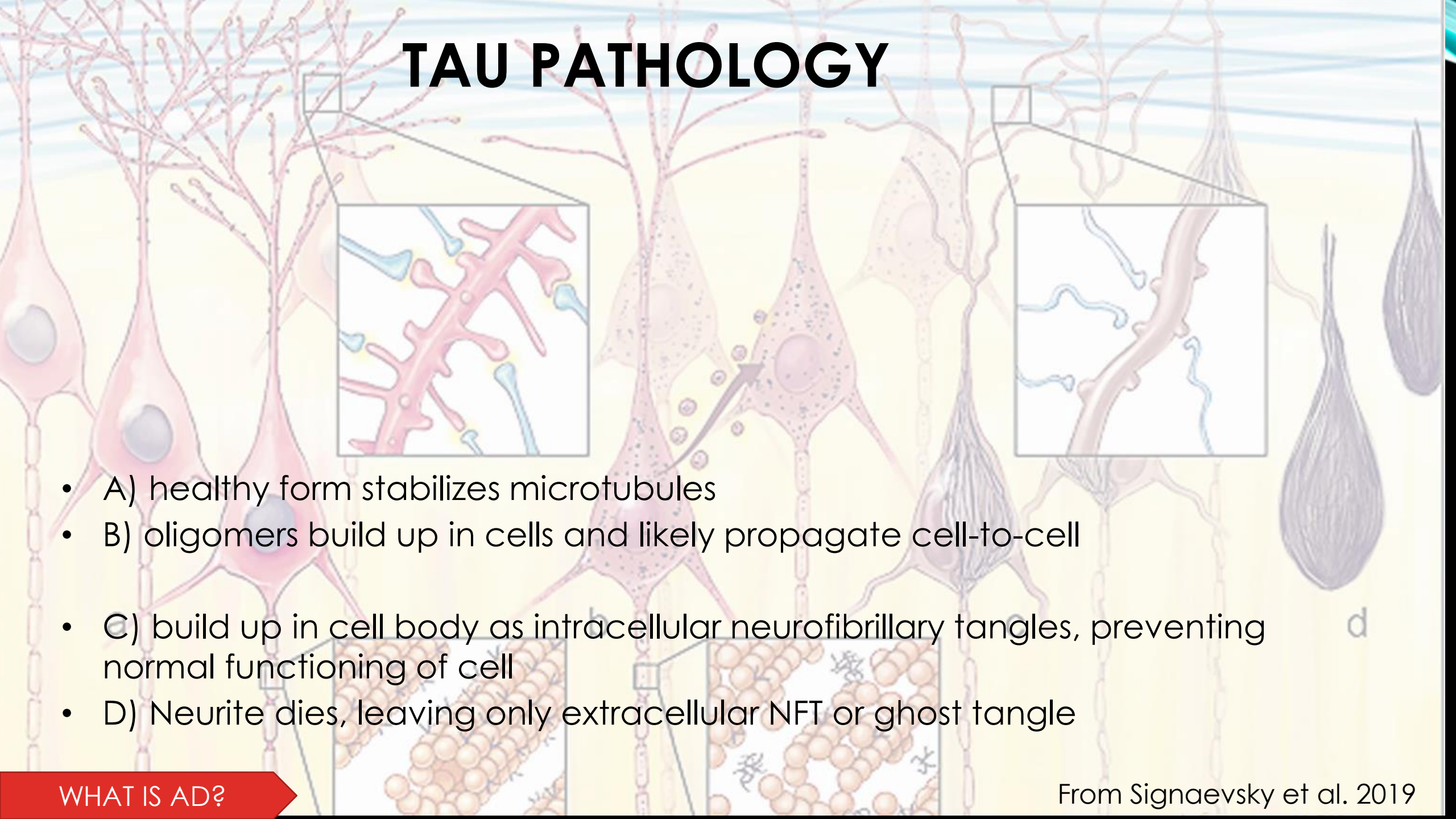
WHAT IS AD?

TIMING OF CHANGES?



- Jack 2010

TAU PATHOLOGY

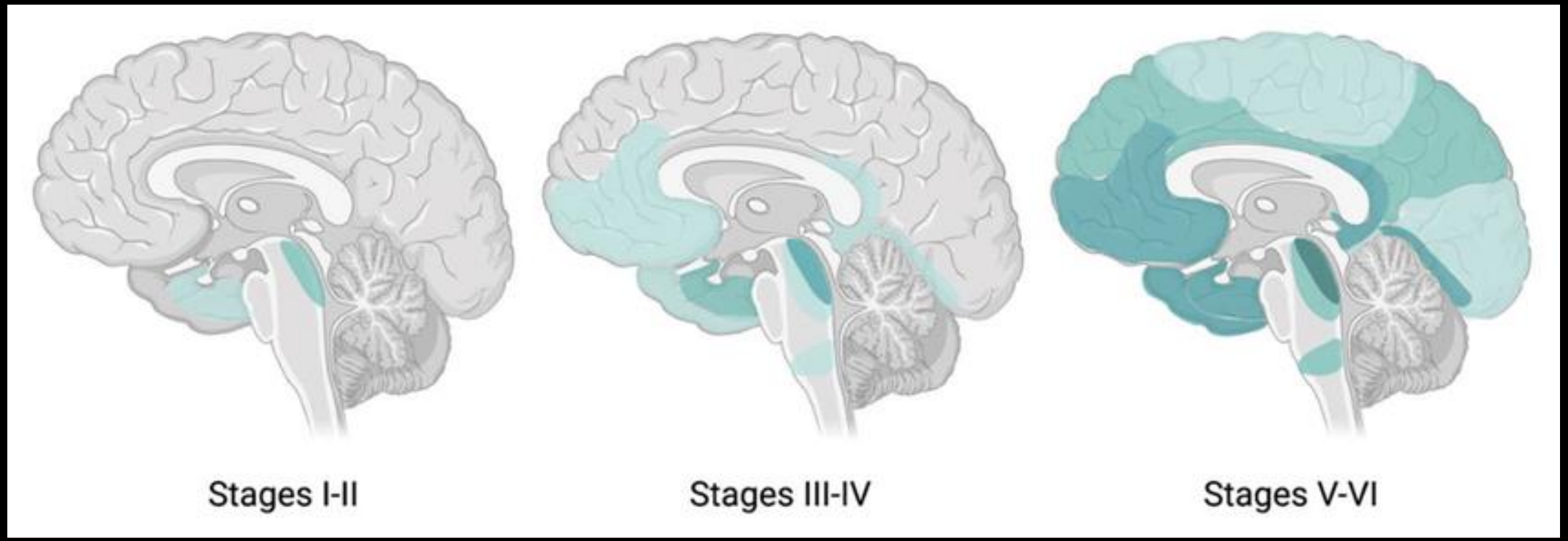


- A) healthy form stabilizes microtubules
- B) oligomers build up in cells and likely propagate cell-to-cell

- C) build up in cell body as intracellular neurofibrillary tangles, preventing normal functioning of cell
- D) Neurite dies, leaving only extracellular NFT or ghost tangle

From Signaevsky et al. 2019

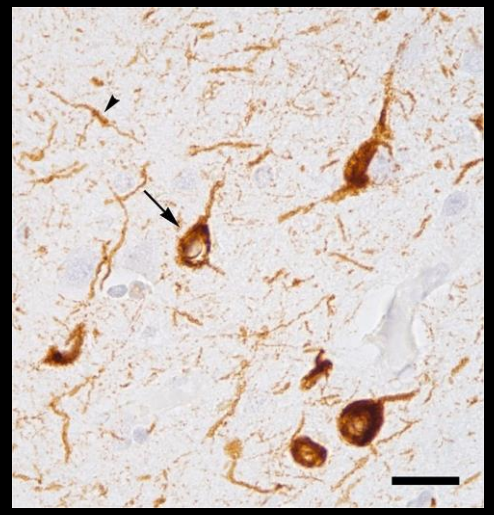
TAU SPREAD IN THE BRAIN: BRAAK STAGES

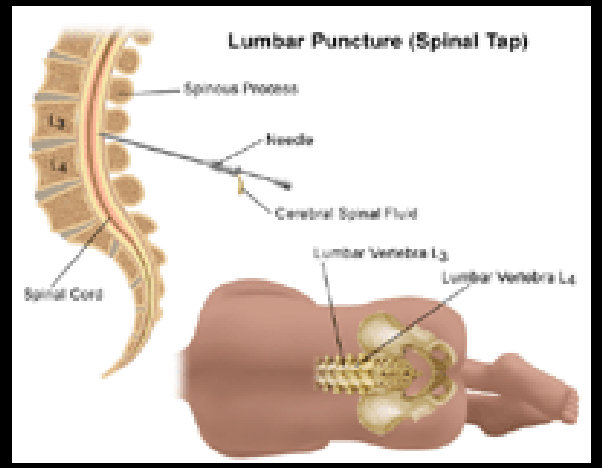


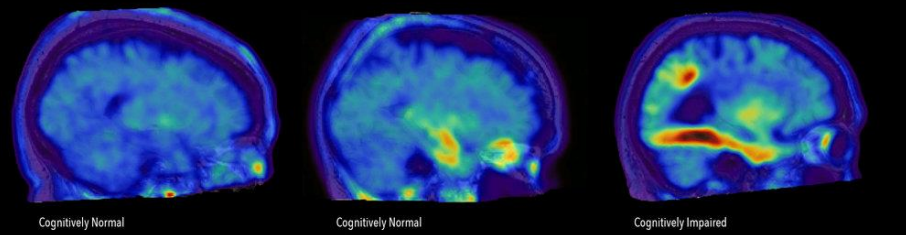
Van Oostveen et al 2021

HOW DO WE MEASURE TAU?

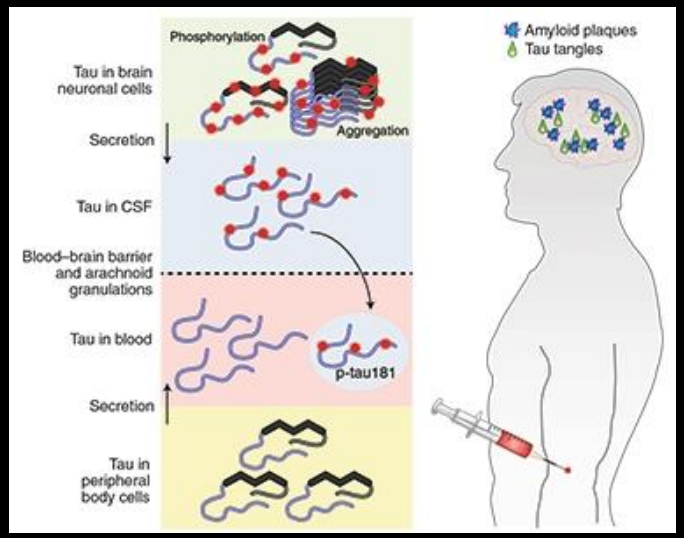
- Autopsy
- Cerebrospinal fluid
- PET
- … and now plasma







Tau PET Imaging



Images: Wikepedia, Johns Hopkins, Jagust Lab, Bateman Lab

WHAT ABOUT NEUROINFLAMMATION?

Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

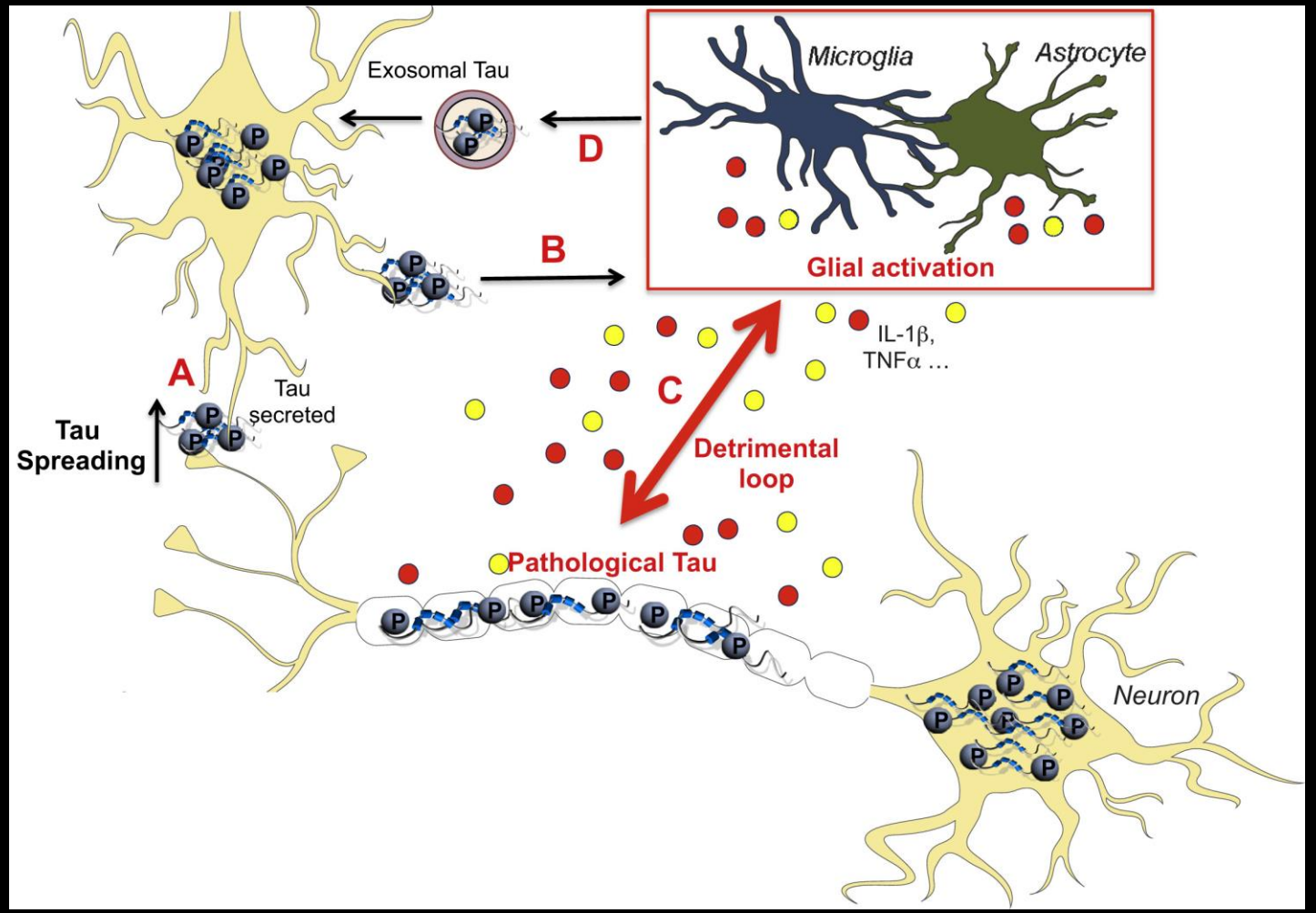
journal homepage: www.elsevier.com/locate/bj

Review Article

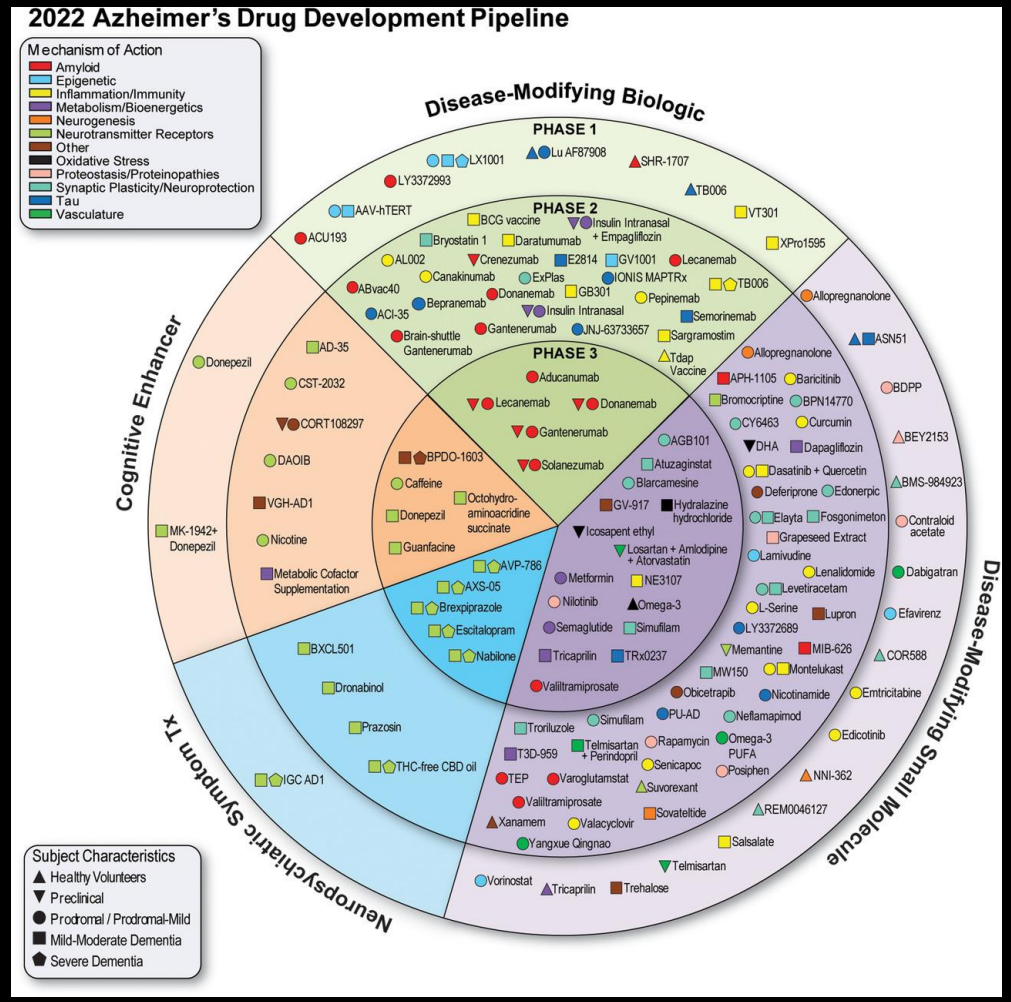
Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies?

Cyril Laurent [a,b,c], *Luc Buée* [a,b,c], *David Blum* [a,b,c,*]

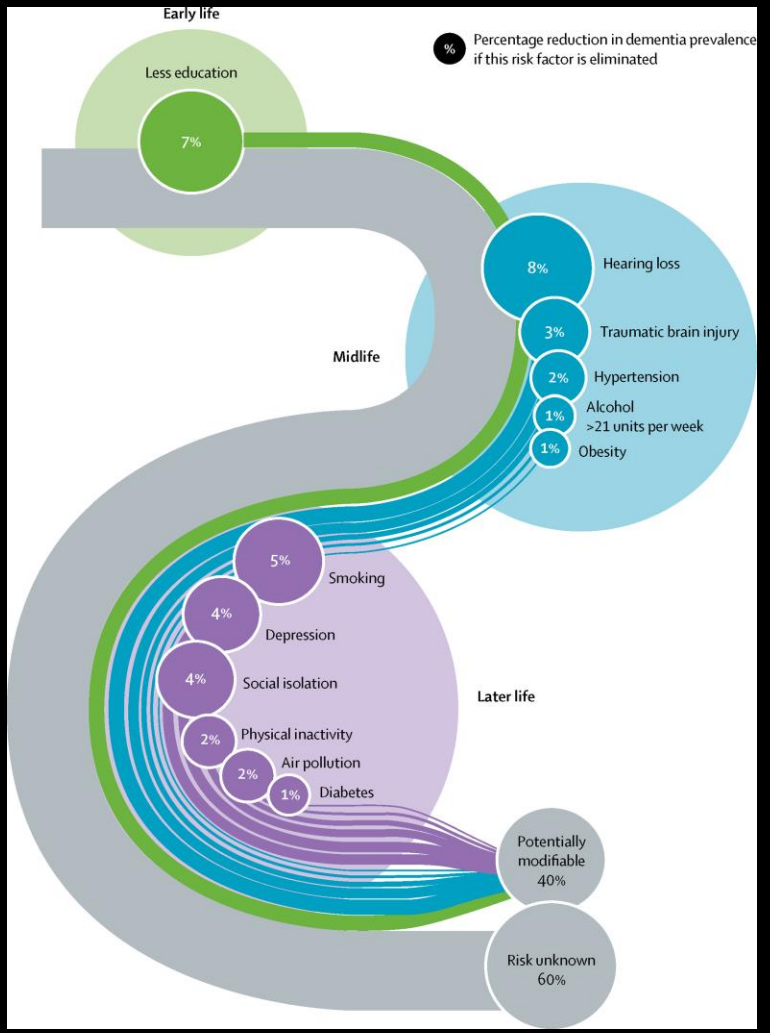
[a] University of Lille, Lille, France
[b] Inserm UMR-S 1172, "Alzheimer & Tauopathies", Lille, France
[c] Labex DISTALZ, Lille, France



TREAMENTS HAVENT WORKED YET



- >99% failure rate
- Trials cost billions and take years
- But …hope with new breakthroughs and understanding of modifiable risk
- Could sex stratification help us to find effective treatments?



WHAT IS AD?

Cummings et al., 2022; Lancet Commission, 2020

3 RESEARCH QUESTIONS

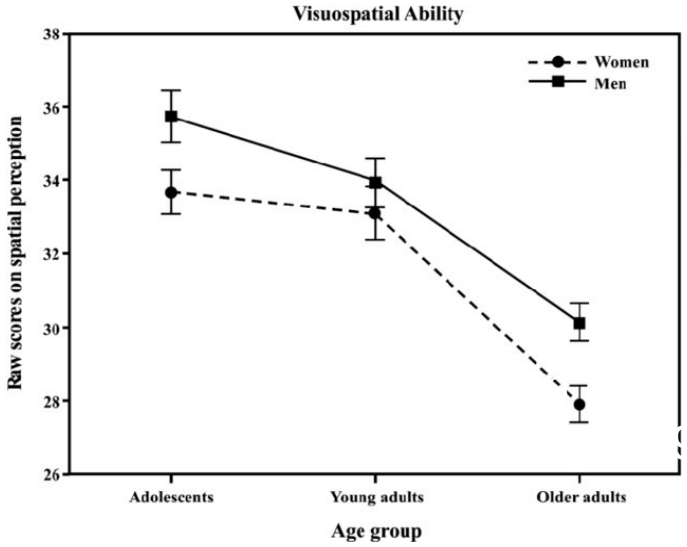
SEX DIFFERENCES IN RISK & EXPRESSION OF AD

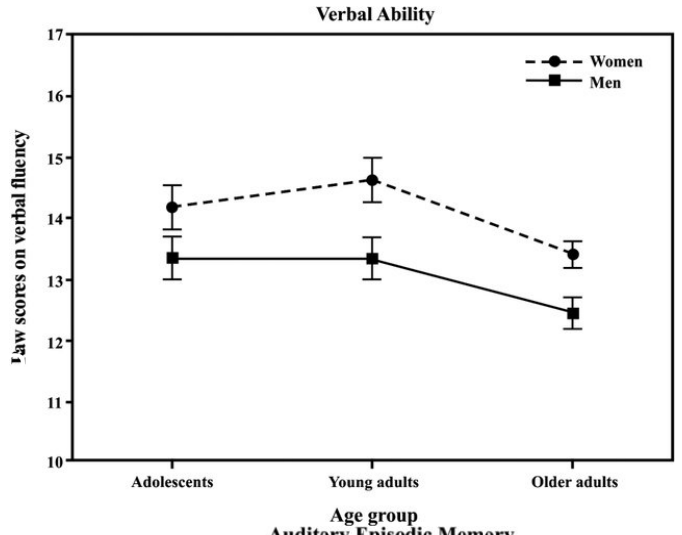
WHAT FACTORS PROMOTE AD IN WOMEN?

HOW DO WE HELP INDIVIDUALS REDUCE THEIR RISK?

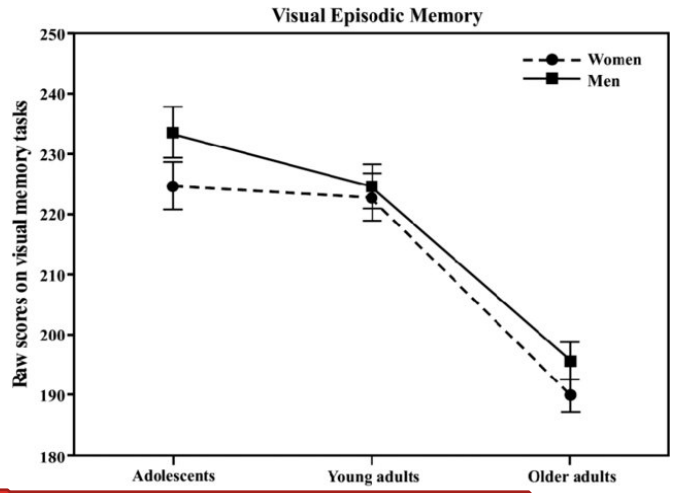
SEX DIFFERENCES IN LIFESPAN COGNITIVE EXPRESSION

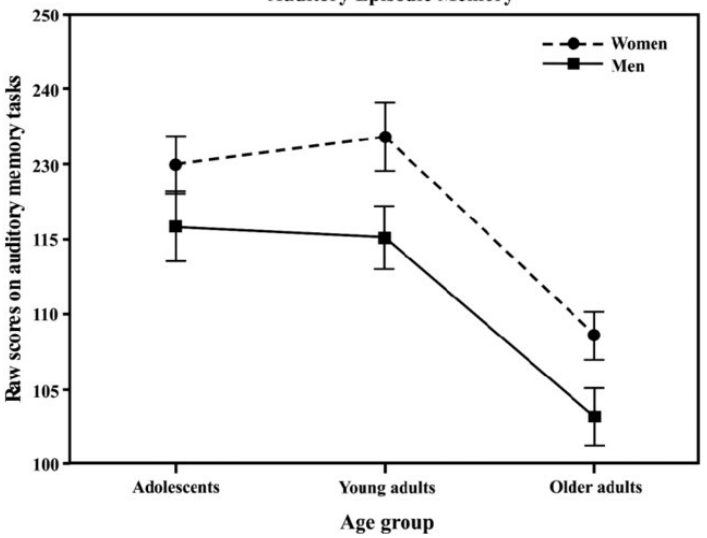
Men have a visuospatial advantage





Women have a verbal advantage





PAULS ET AL 2013

WHAT DO WE USE TO TEST MEMORY IN AD?

	Trial 1 Recall	Trial 2 Recall	Trial 3 Recall	Trial 4 Recall	Trial 5 Recall
football					
notebook					
island					
billiards					
paper					
river					
tennis					
cake					
folder					
boxing					
mountain					
pie					
candy					
envelope					
valley					
ice cream					
	__/16	__/16	__/16	__/16	__/16

Total Learning ___/80]

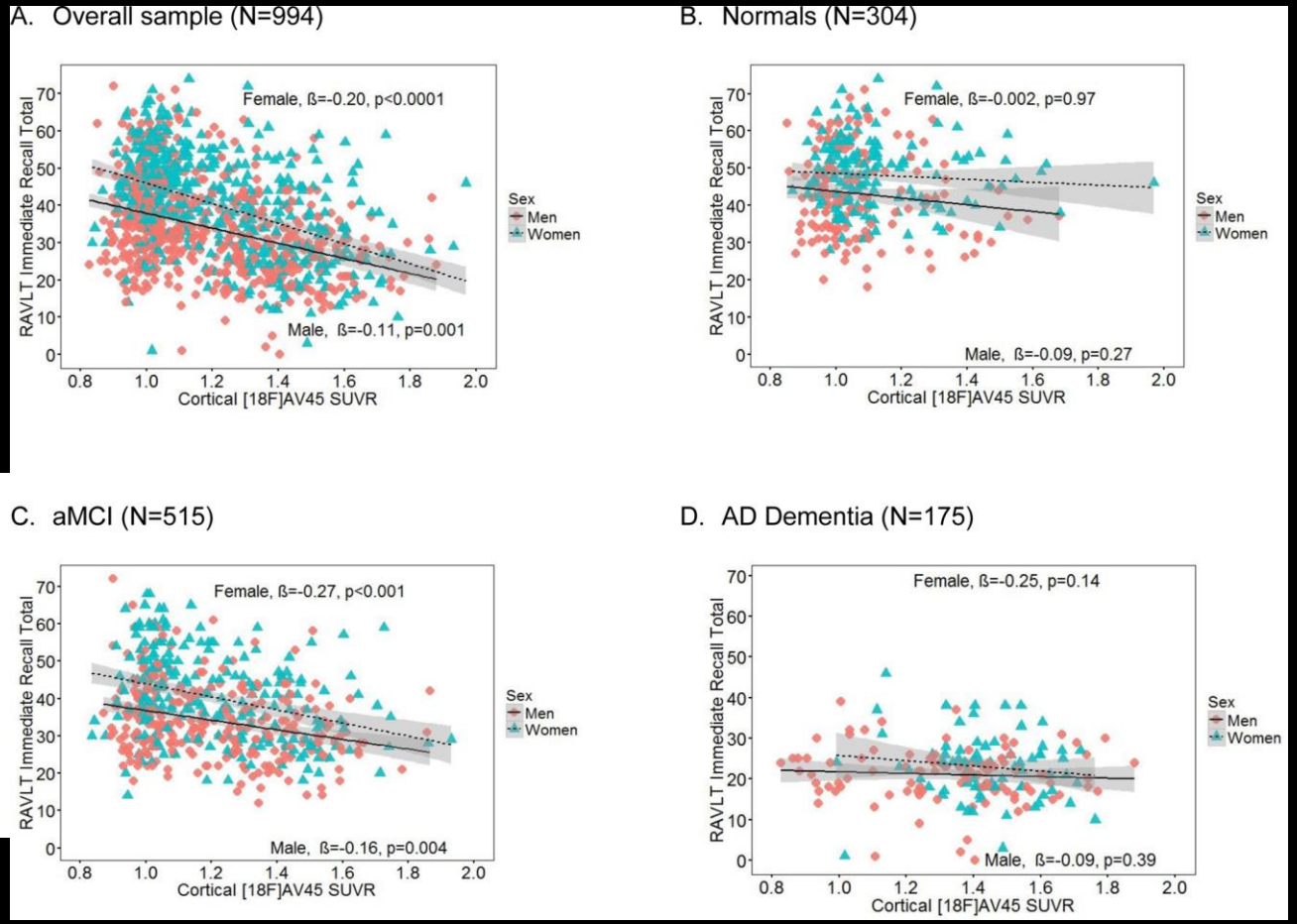
Benedict et al, 2012 (faux CVLT stimuli)

VERBAL MEMORY, WOMEN'S ADVANTAGE?

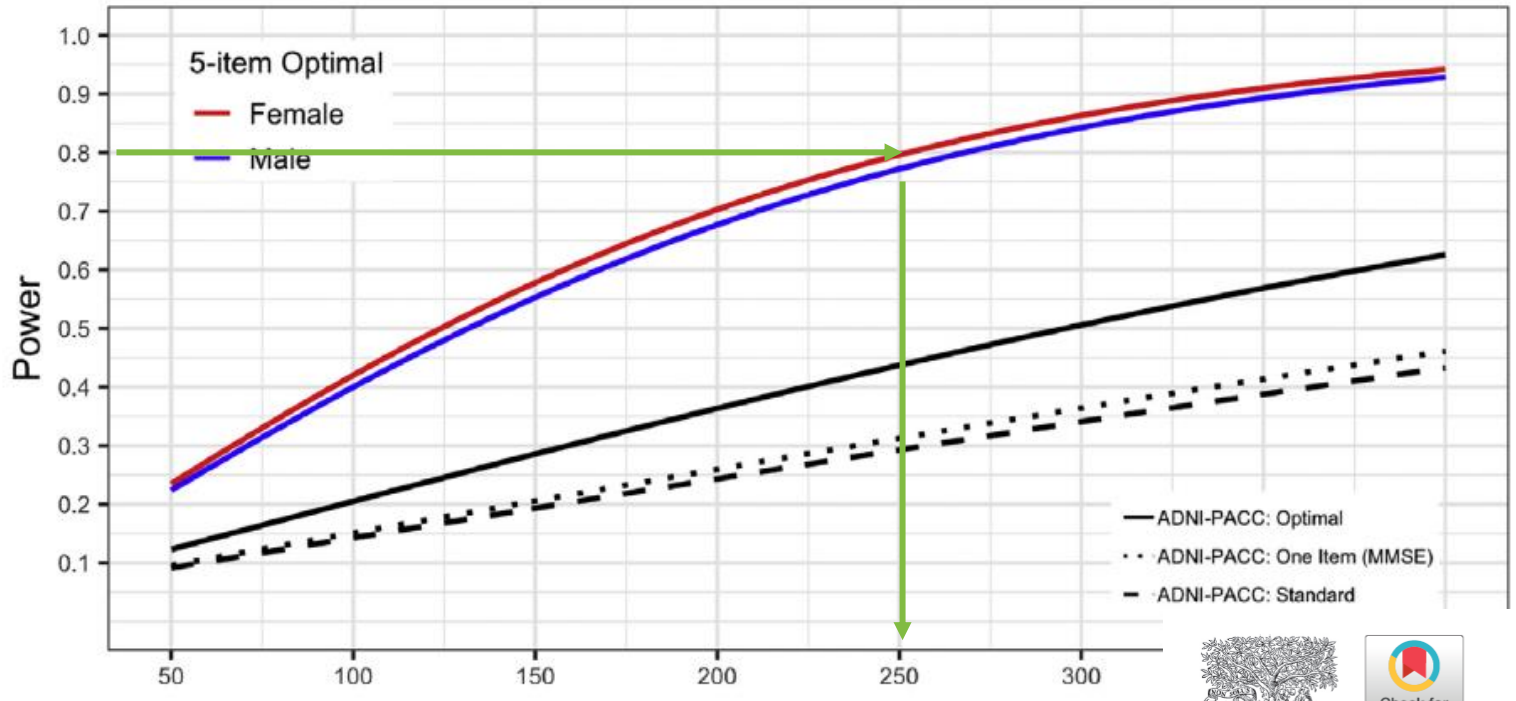
Published in final edited form as:
J Alzheimers Dis. 2017 ; 56(3): 947–957. doi:10.3233/JAD-160716.

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

Erin E. Sundermann, PhD[a], Anat Biegon, PhD[b], Leah H. Rubin, PhD, MPH[c], Richard B. Lipton, MD[a], Susan Landau, PhD[d], Pauline M. Maki, PhD[c], Alzheimer's Disease Neuroimaging Initiative¥



SEX DIFFERENCE IN COGNITION CAN IMPACT TRIAL DESIGN



ELSEVIER

Check for updates

Alzheimer's & Dementia

Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019) 508-514

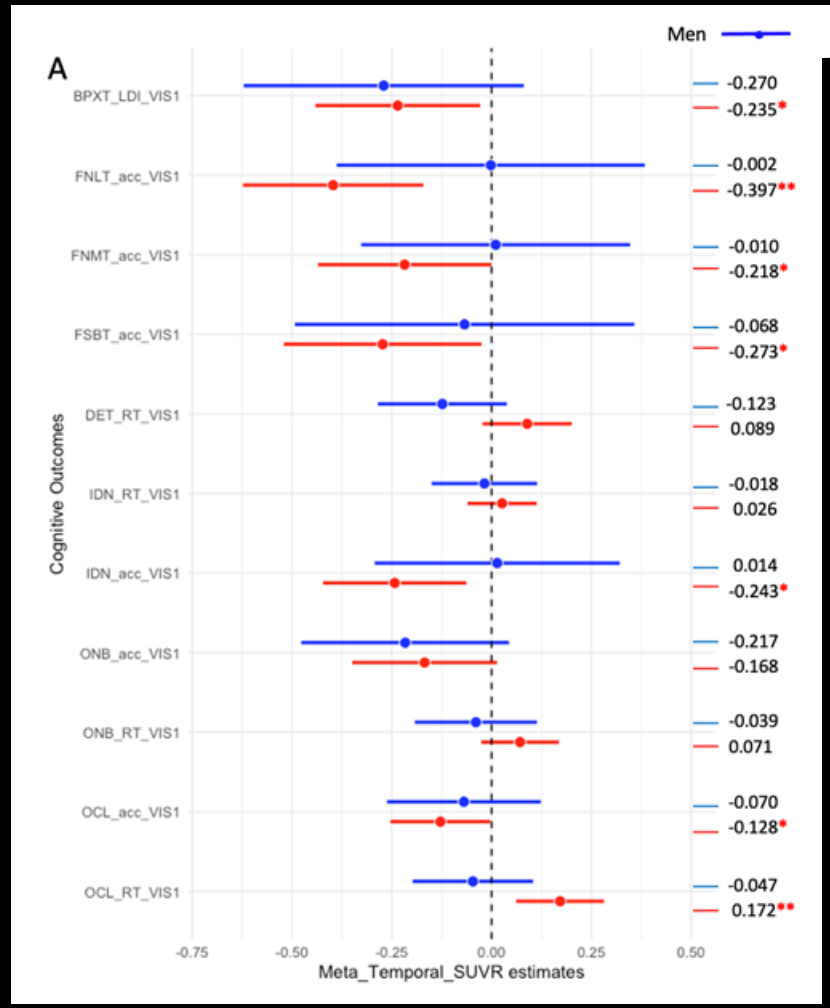
Featured Article

Sex-specific composite scales for longitudinal studies of incipient Alzheimer's disease

Sarah J. Banks[a,*], Benjamin Shifflett[b], Jody-Lynn Berg[a], Erin Sundermann[c], Guerry Peavy[a], Mark W. Bondi[c,d], Steven D. Edland[b], for the Alzheimer's Disease Neuroimaging Initiative[1]

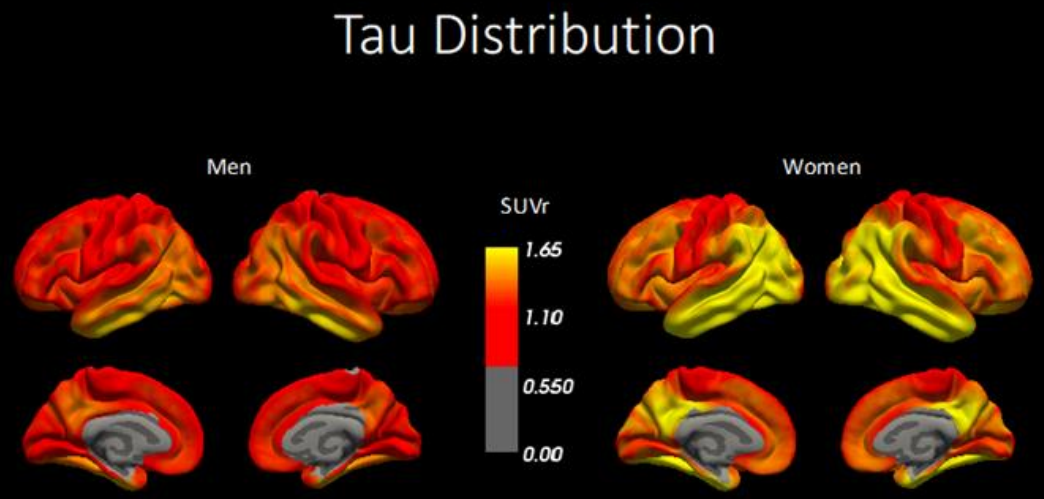
WHAT IS AD? RISK & EXPRESSION

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

WOMEN ACCUMULATE MORE TAU



Neurobiology of Aging 107 (2021) 70–77

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Sex differences in Alzheimer's disease: do differences in tau explain the verbal memory gap?

Sarah J. Banks[a,b,*], Murray J. Andrews[a], Leonardino Digma[a], John Madsen[a], Emilie T. Reas[a], Jessica Z.K. Caldwell[b], Linda K. McEvoy[d], Chun Chieh Fan[c], Anders M. Dale[a,d,e,f], e Alzheimer's Disease Neuroimaging Initiative[#]

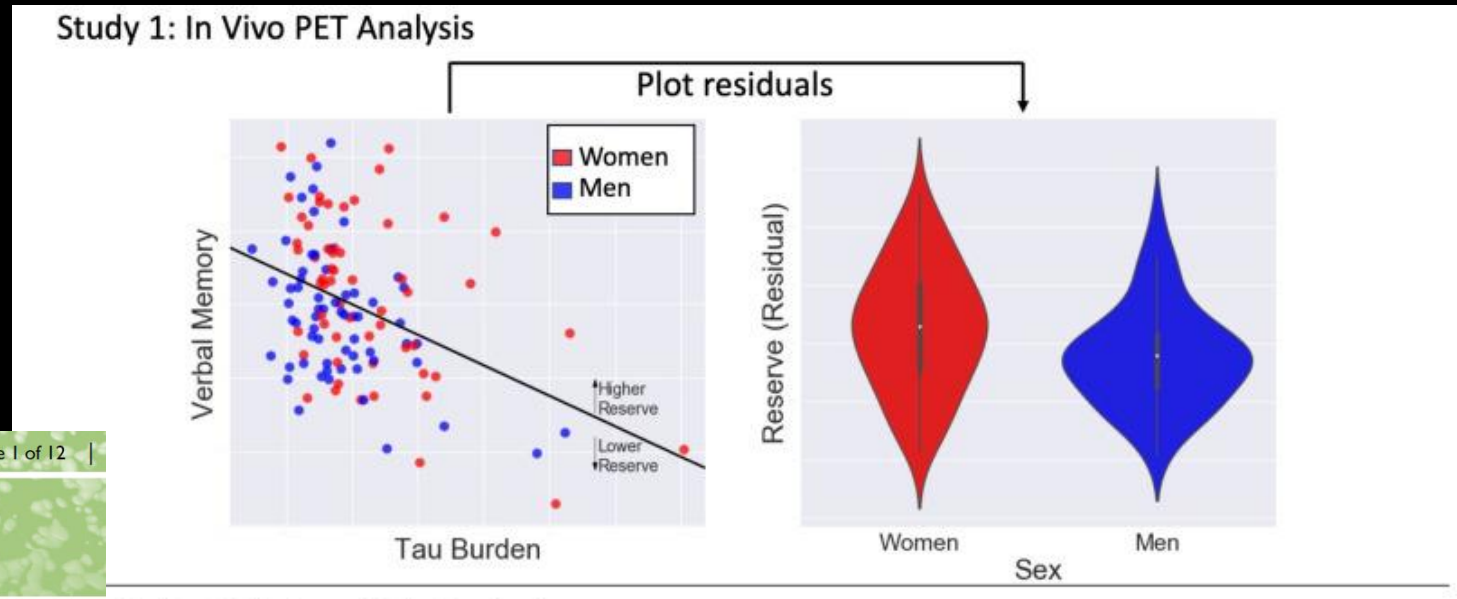
WOMEN CAN BEAR A BIGGER BURDEN (OF TAU)

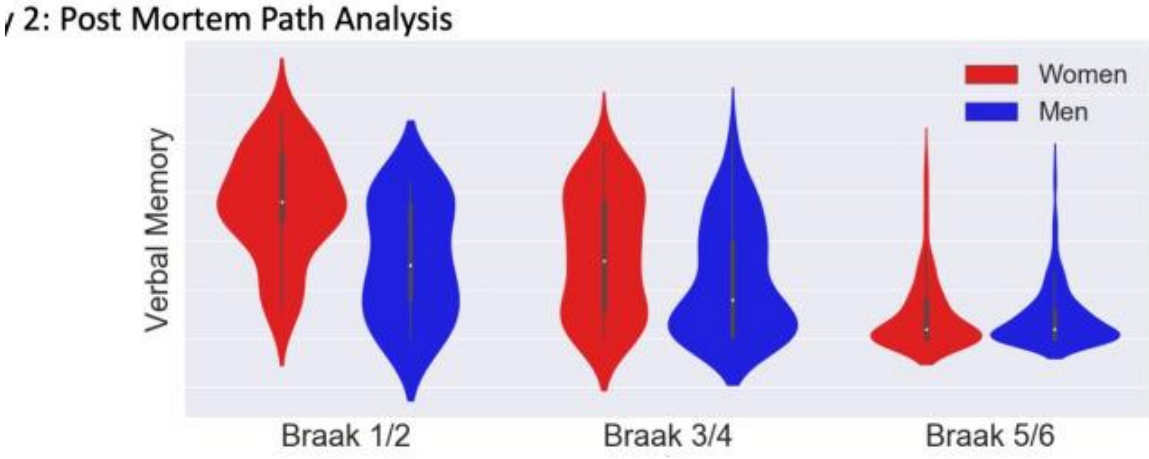
doi:10.1093/braincomms/fcaa025 BRAIN COMMUNICATIONS 2020: Page 1 of 12 |

BRAIN COMMUNICATIONS

Women can bear a bigger burden: ante- and post-mortem evidence for reserve in the face of tau

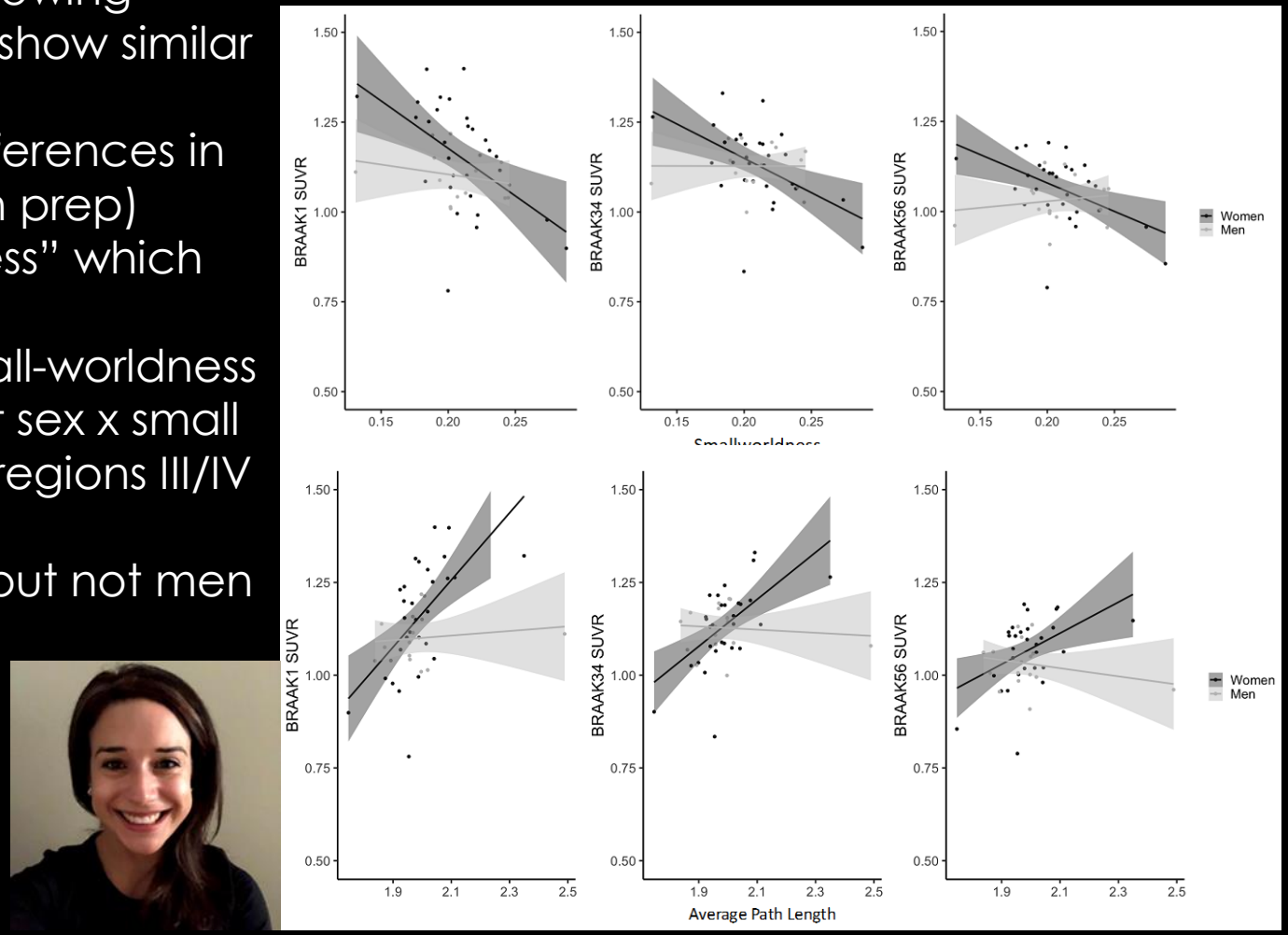
Leonardino A. Digma,[1] John R. Madsen,[1] Robert A. Rissman,[1,2] Diane M. Jacobs,[1] James B. Brewer[1,3] and Sarah J. Banks[1,4], for the Alzheimer's Disease Neuroimaging Initiative*



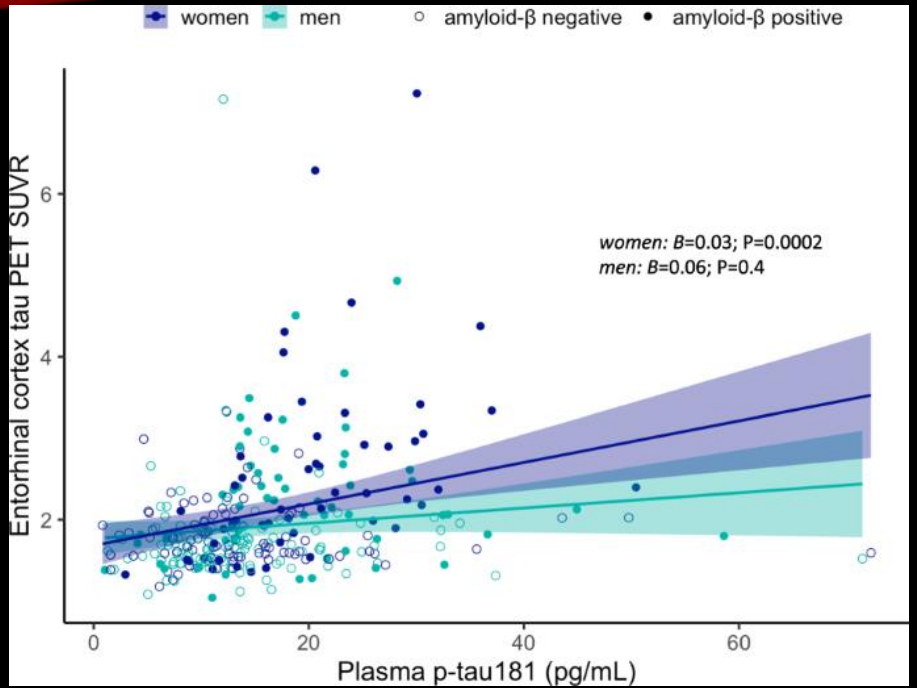


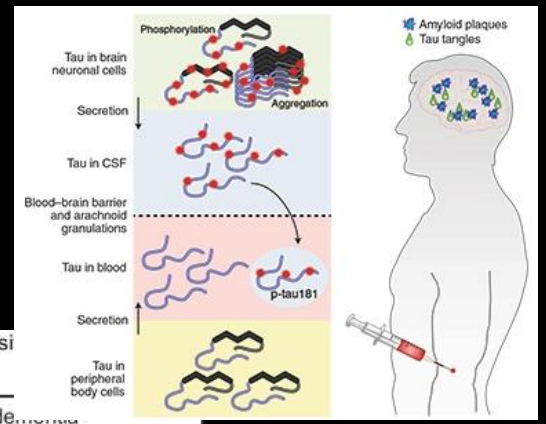
RELATIONSHIP BETWEEN RSFMRI AND TAU

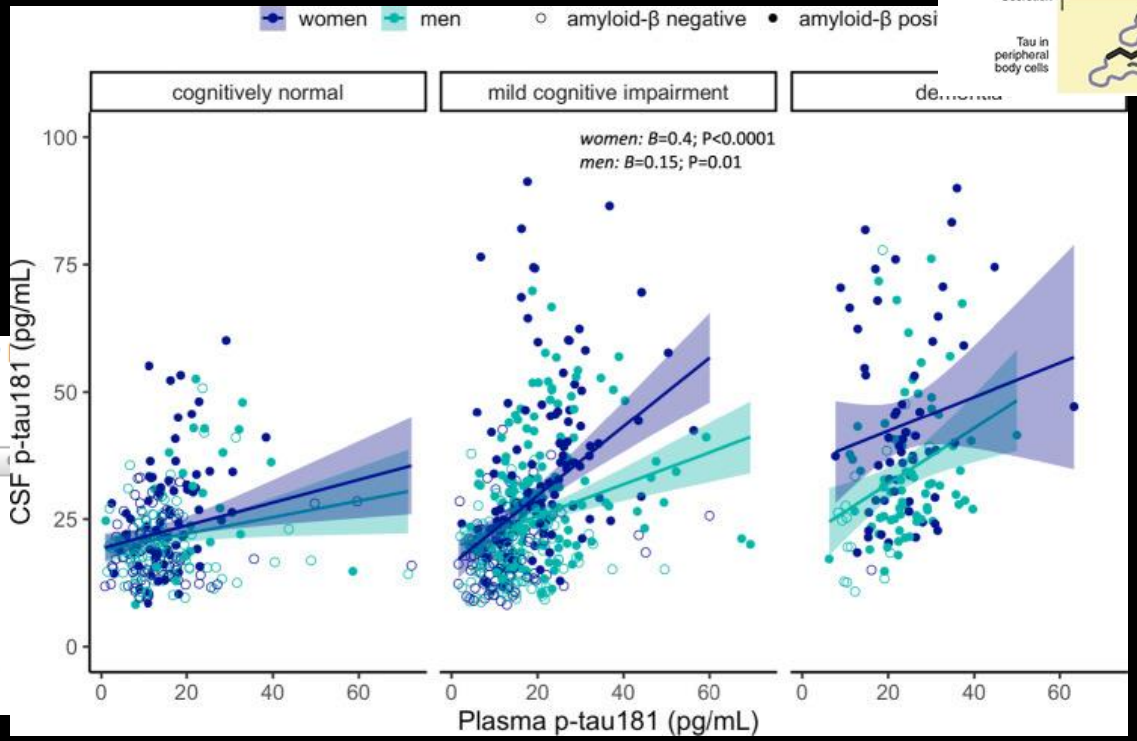
- Building on Franzmeier's (2020) work showing functionally highly-connected regions show similar tau PET increase
- Postdoc Rachel Bernier studied sex differences in cognitively normal adults from ADNI (in prep)
- Focused on the idea of "small-worldness" which can be seen as network efficiency
- No overall sex differences in mean small-worldness or average path length, but significant sex x small worldness interactions on tau in Braak regions III/IV and V/VI
  - Relationships are seen in women, but not men



SEX DIFFERENCES IN PTAU 181 IN PLASMA







www.nature.com/mp Molecular

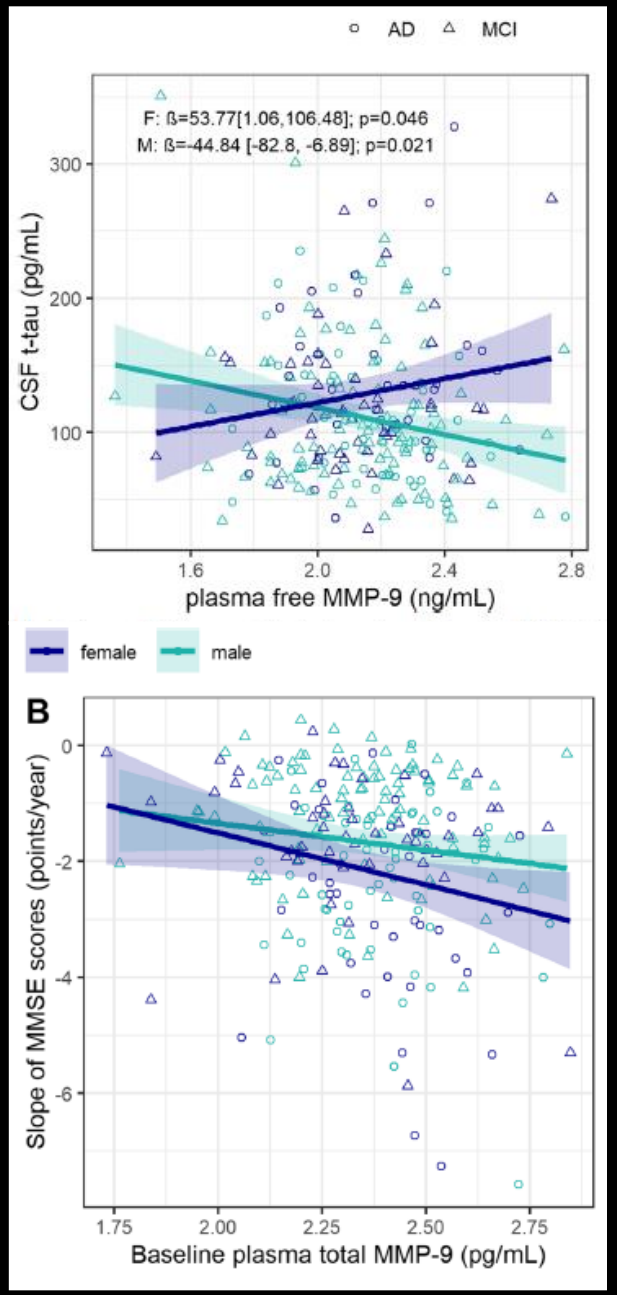
ARTICLE OPEN

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

Amaryllis A. Tsiknia[1], Steven D. Edland[1,2], Erin E. Sundermann[3,4], Emilie T. Reas[1], James B. Brewer[1], Douglas Galasko[1], Sarah J. Banks[1,3✉] and for the Alzheimer's Disease Neuroimaging Initiative*

MMP9: A POTENTIAL MECHANISM?

- Endopeptidase which has wide ranging roles in healthy conditions but in disease can be dysregulated causing BBB breakdown and neuroinflammation
- Measures in blood are higher in MCI and AD than healthy cognition
- Estrogen regulates MMP9 pathways
- Potentially a sex and genotype specific intervention?



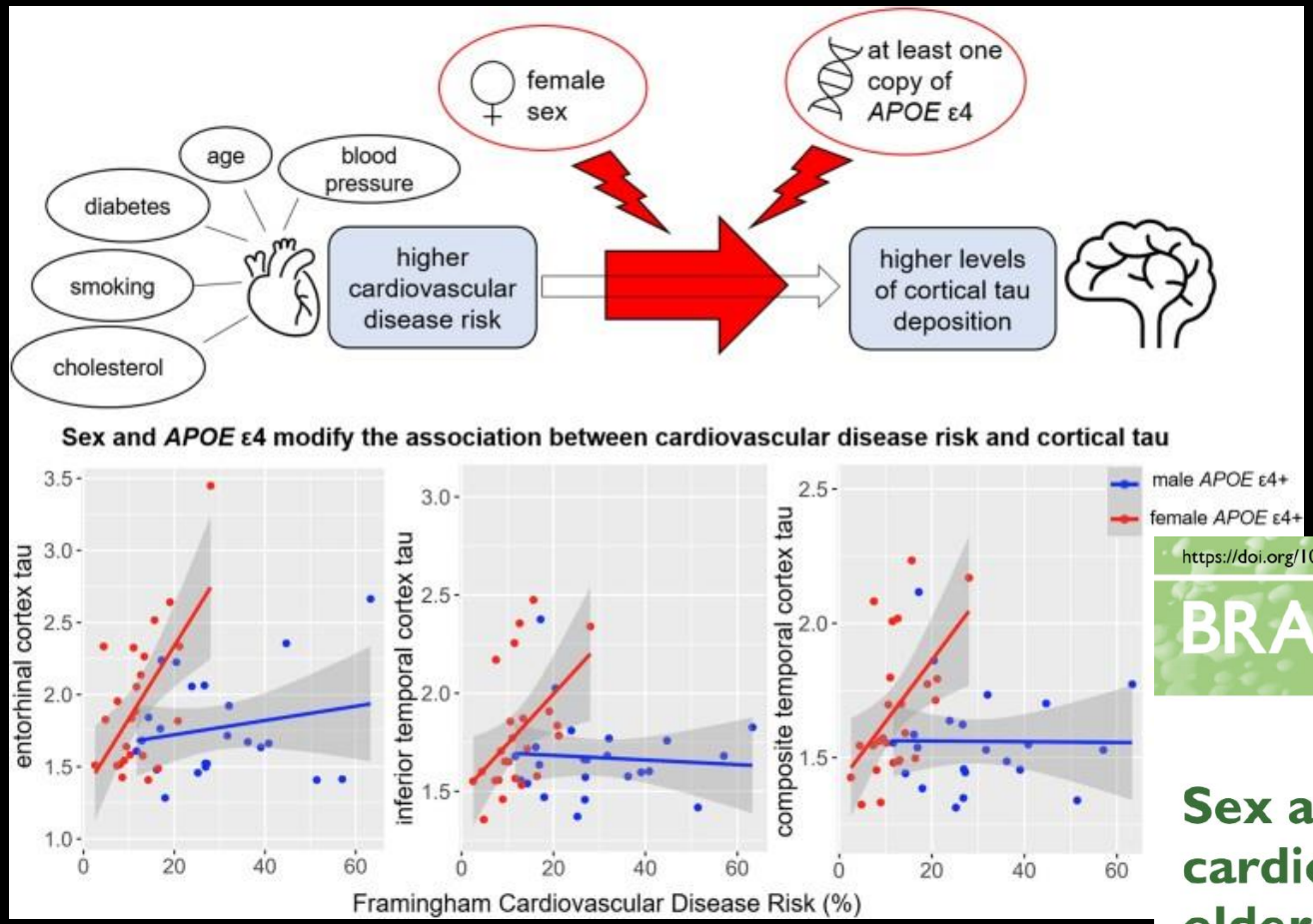

Tsiknia et al. Alzheimer's Research & Therapy (2022) 14:160
https://doi.org/10.1186/s13195-022-01106-4
Alzheimer's Research & Therapy
RESEARCH
Open Access

Sex differences in Alzheimer's disease: plasma MMP-9 and markers of disease severity

Amaryllis A. Tsiknia[1], Erin E. Sundermann[2,3], Emilie T. Reas[1], Steven D. Edland[1,4], James B. Brewer[1], Douglas Galasko[1], Sarah J. Banks[1*] and for the Alzheimer's Disease Neuroimaging Initiative

WHAT ABOUT GENETICS?

VASCULAR RISK ASSOCIATED WITH *APOE* ε4 & TAU IN WOMEN, NOT MEN



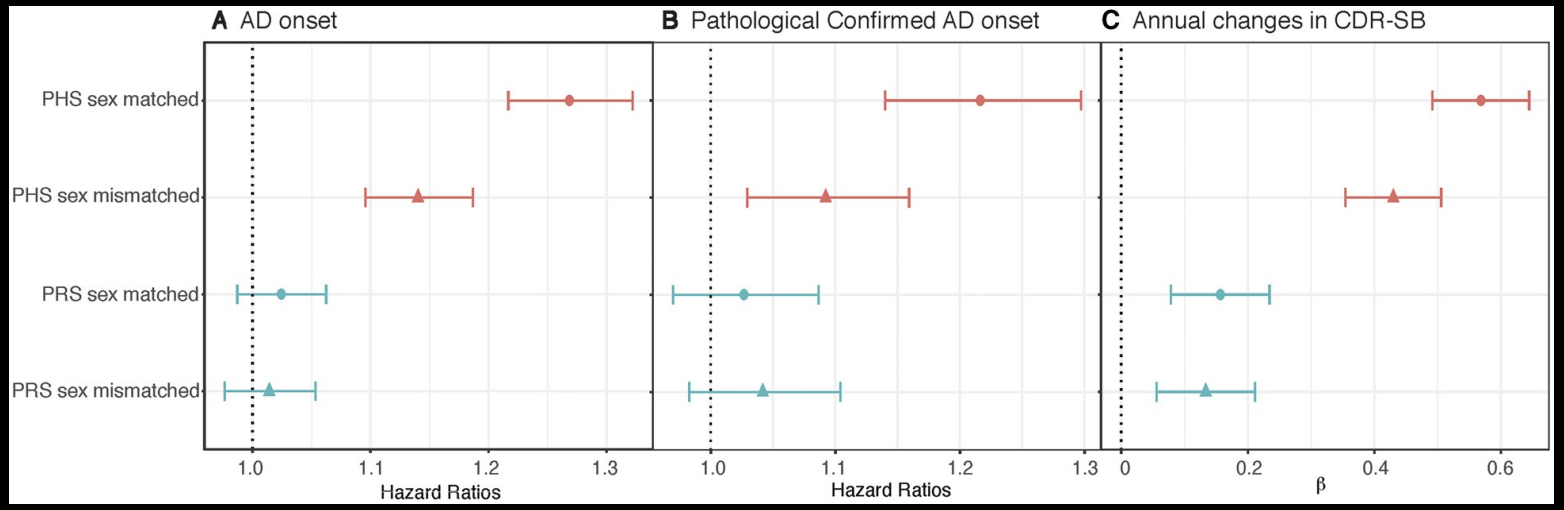
https://doi.org/10.1093/braincomms/fcac035

BRAIN COMMUNICATIONS

Sex and *APOE* ε4 modify the effect of cardiovascular risk on tau in cognitively normal older adults

Amaryllis A. Tsiknia,[1] Emilie Reas,[1] Katherine J. Bangen,[2,3] Erin E. Sundermann,[3] Linda McEvoy,[4,5] James B. Brewer,[1,4] Steven D. Edland,[5] Sarah J. Banks[1,3] and for the Alzheimer's Disease Neuroimaging Initiative*

WOMEN AND MEN DIFFER IN GENETIC RISK FACTORS



doi:10.1093/brain/awaa164 BRAIN 2020: 143; 2272–2280 | 2272

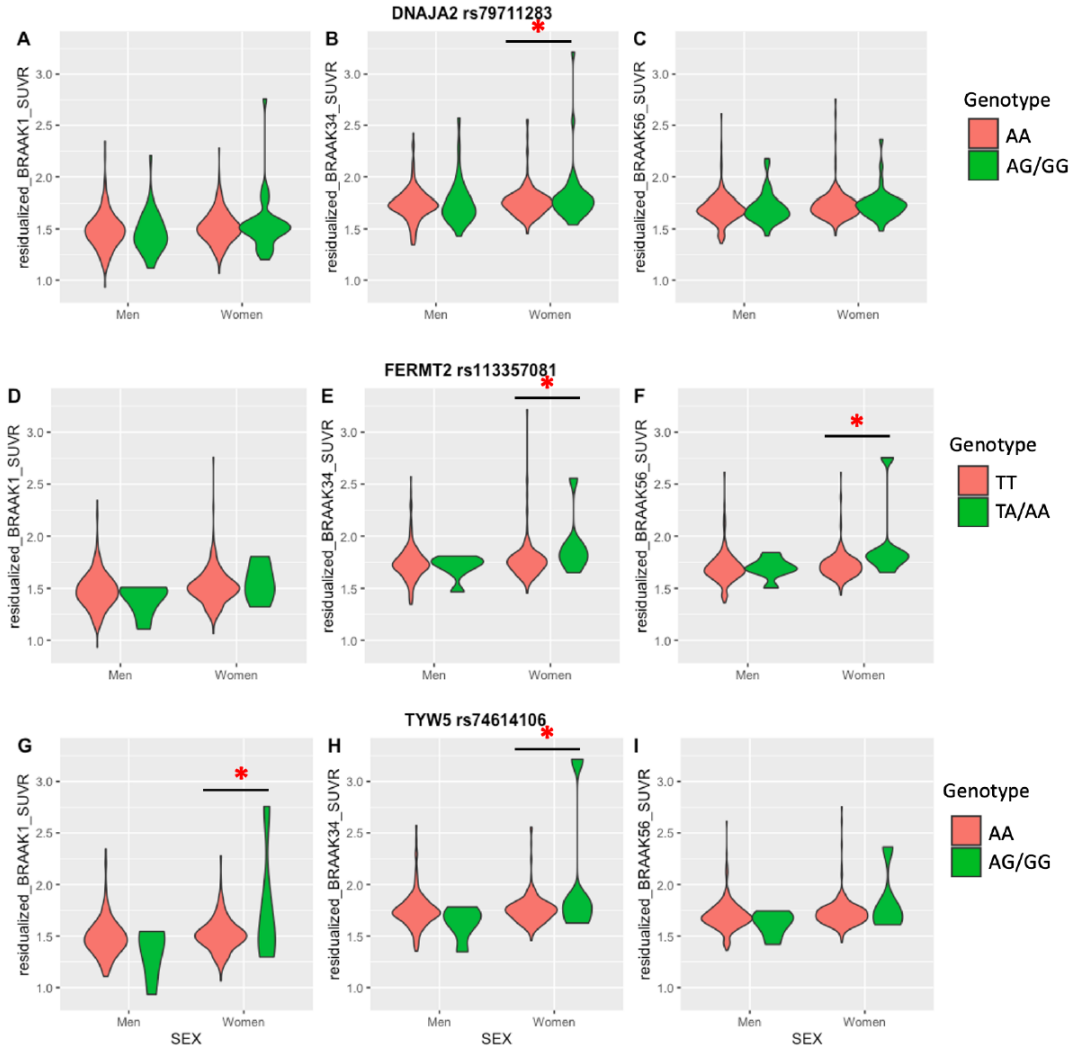
BRAIN
A JOURNAL OF NEUROLOGY

Sex-dependent autosomal effects on clinical progression of Alzheimer's disease

Chun Chieh Fan,[1,*] Sarah J. Banks,[2,*] Wesley K. Thompson,[3] Chi-Hua Chen,[4] Linda K. McEvoy,[3,4] Chin Hong Tan,[5] Walter Kukull,[6] David A. Bennett,[7] Lindsay A. Farrer,[8] Richard Mayeux,[9] Gerard D. Schellenberg,[10] Ole A. Andreassen,[11] Rahul Desikan[12,#] and Anders M. Dale[4,13]

SEX SPECIFIC GENETIC PREDICTORS OF TAU PET

Figure 1 Comparison of tau PET in each ROI by women-specific SNPs



Violin plots showing comparison of residualized tau SUVR in each ROI by women-specific SNPs. $p < 0.05$: *.

RESEARCH ARTICLE OPEN ACCESS

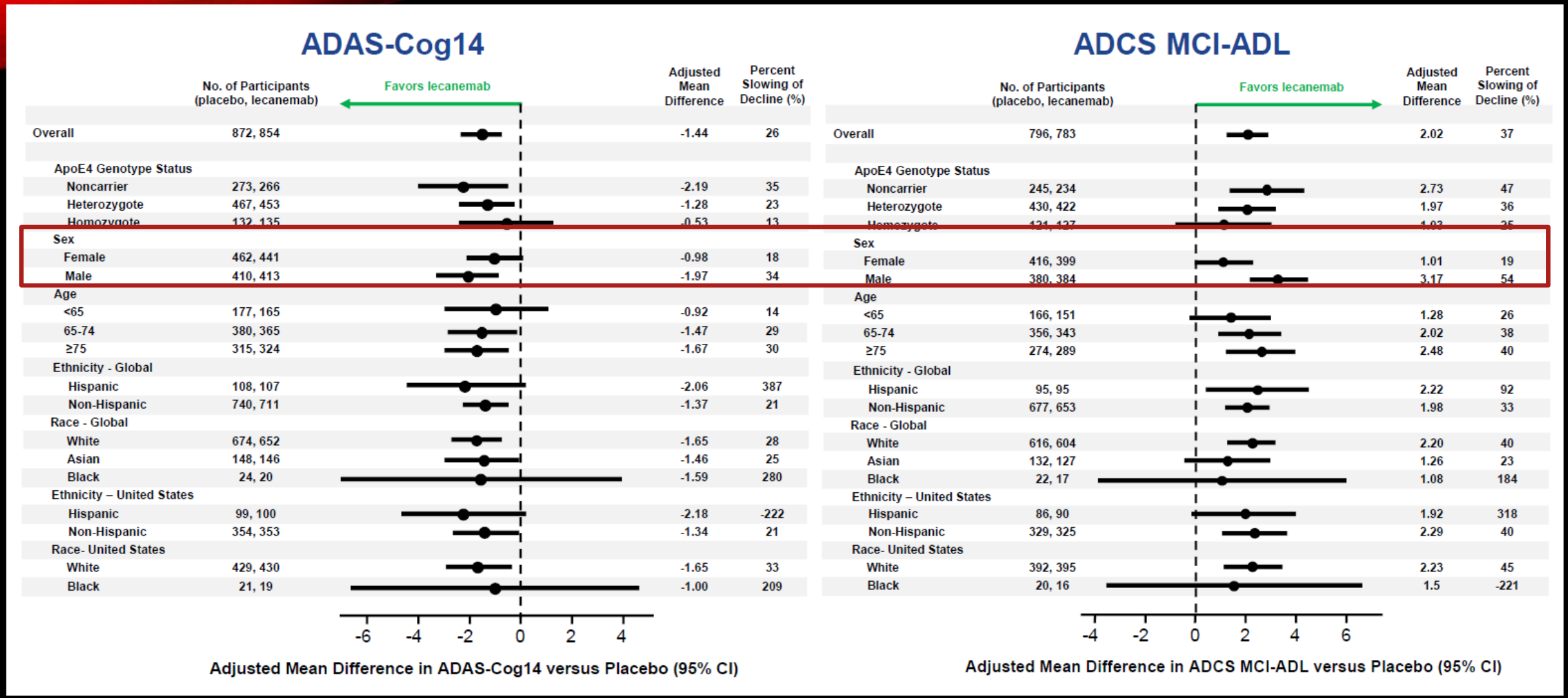
Identification of Sex-Specific Genetic Variants Associated With Tau PET

Xin Wang, MS, Iris Broce, PhD, Kacie D. Deters, PhD, Chun Chieh Fan, MD, PhD, Sarah Jane Banks, PhD, for the Alzheimer's Disease Neuroimaging Initiative*

Correspondence
Dr. Banks

Neurol Genet 2022;8:e200043. doi:10.1212/NXG.0000000000200043

WHY DO SEX DIFFERENCES MATTER?



3 RESEARCH QUESTIONS

SEX DIFFERENCES IN RISK & EXPRESSION OF AD

WHAT FACTORS PROMOTE AD IN WOMEN?

HOW DO WE HELP INDIVIDUALS REDUCE THEIR RISK?

WITS

Women: Inflammation and Tau Study

- Co-lead with Dr. Erin Sundermann, original funding from CDPH
- Does inflammation promote tau in women?
- Do modifiable risk factors (sleep apnea, sedentary behavior, diet) promote inflammation in women?

STUDY PROTOCOL

Participants

- 110 women aged 65+ with elevated risk of AD based on:
  - Upper 50th percentile of AD polygenic hazard score
  - Mild cognitive impairments demonstrated on MoCA (17-26)

Recruitment

- ADRC
- Clinic
- Postcards
- Community resources
- Via collaboration

Remote Screening Visit

- Zoom MoCA
- Shipment of saliva kit for DNA testing through Diagnomics

Longitudinal Study Design

- 4 study visits (2 at baseline and 2 a year later) involving remote cognitive battery, MRI and PET scans, blood draw, LP, and 1-week of wearing watch-sized devices to measure sleep and physical activity.

Remote Screening

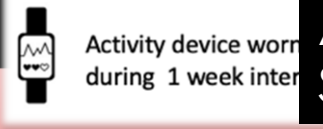
Brief thinking test, questionnaires, saliva sample

1 Month

Visit 1

Blood draw, lumbar puncture, thinking tests, MRI brain scan

1 Week



AT HOME SLEEP STUDY

Visit 2

PET brain scan

24 Months

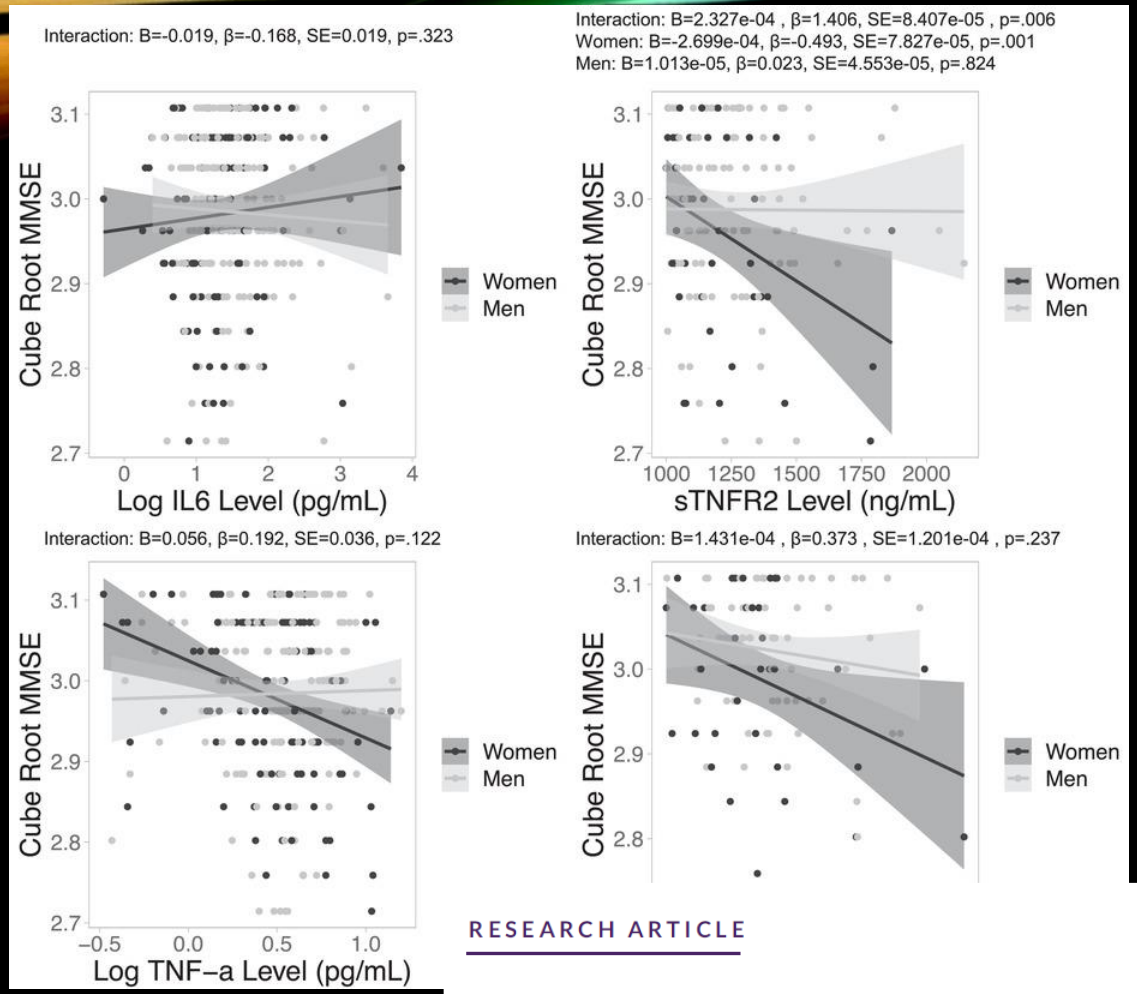
Visit 3

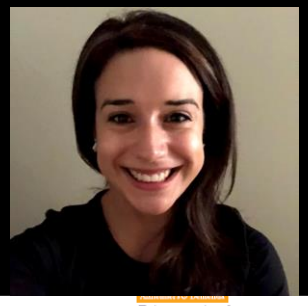
MRI brain scan and thinking tests

1 Week

Visit 4

PET brain can





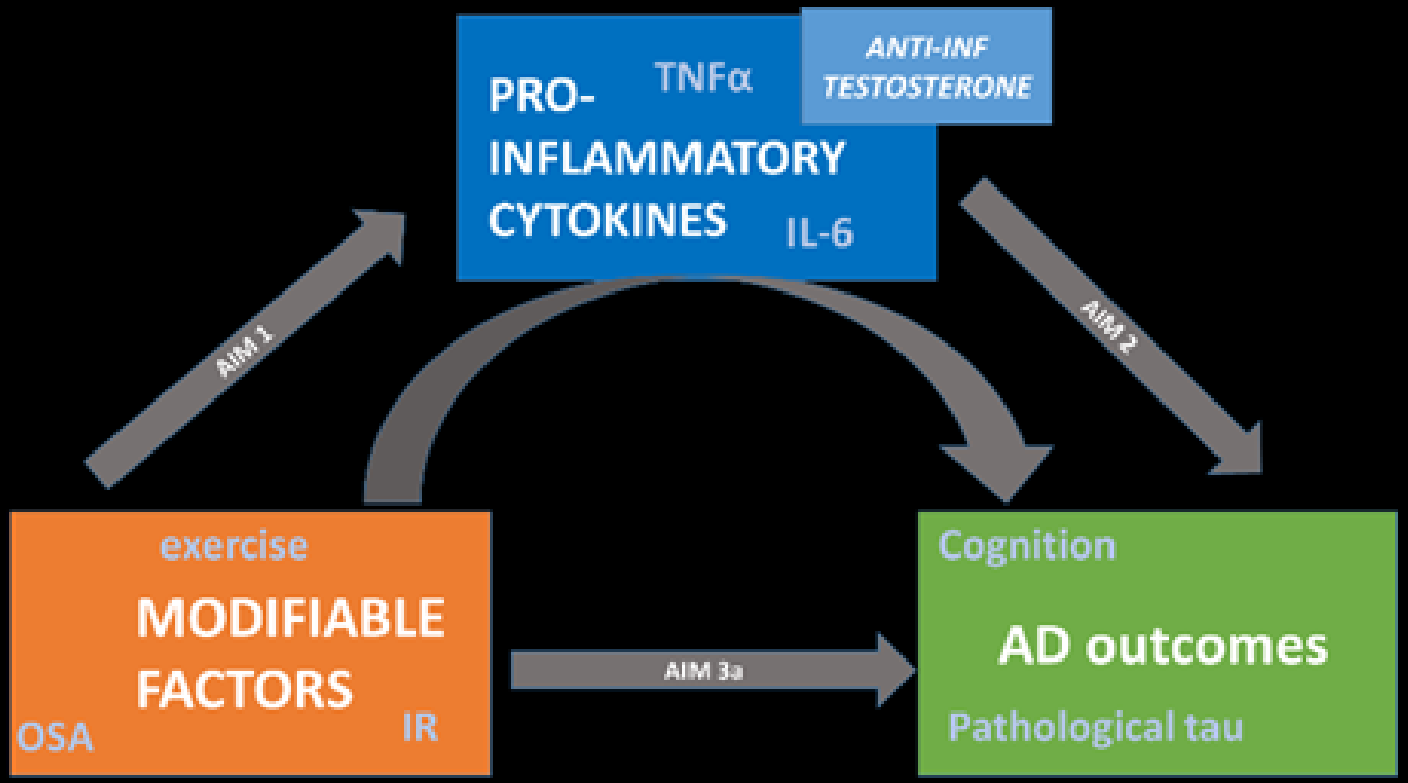
sTNFR2 association with cognition is mediated by CSF ptau 181

Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

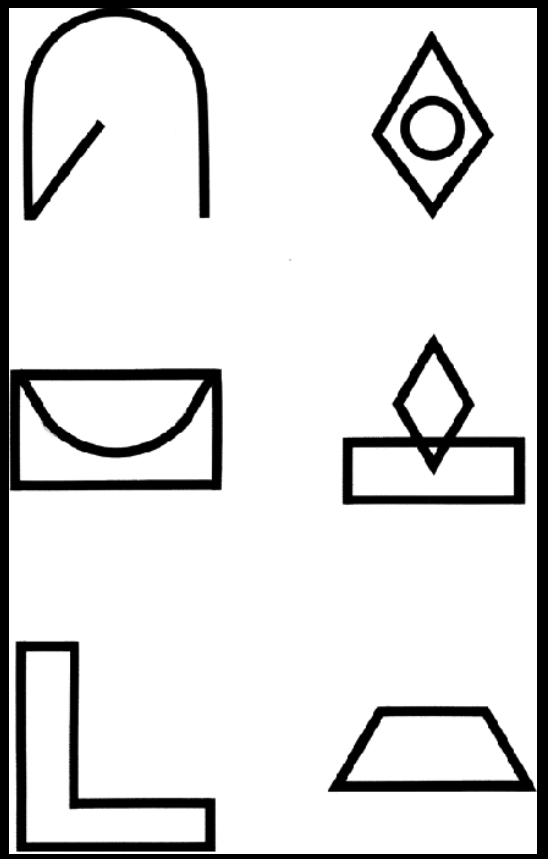
The neuroinflammatory marker sTNFR2 relates to worse cognition and tau in women across the Alzheimer's disease spectrum

Rachel A. Bernier[1] | Sarah J. Banks[1] | Matthew S. Panizzon[2,3] | Murray J. Andrews[1] | Emily G. Jacobs[4] | Douglas R. Galasko[1] | Alyx L. Shepherd[1] | Katerina Akassoglou[5,6,7] | for the Alzheimer's Disease Neuroimaging Initiative[1,†]


PRO-
INFLAMMATORY
CYTOKINES
TNFα
IL-6
ANTI-INF
TESTOSTERONE
AIM 1
AIM 2
exercise
MODIFIABLE
FACTORS
OSA
IR
AIM 3a
Cognition
AD outcomes
Pathological tau

COGNITIVE TESTING IN WITS

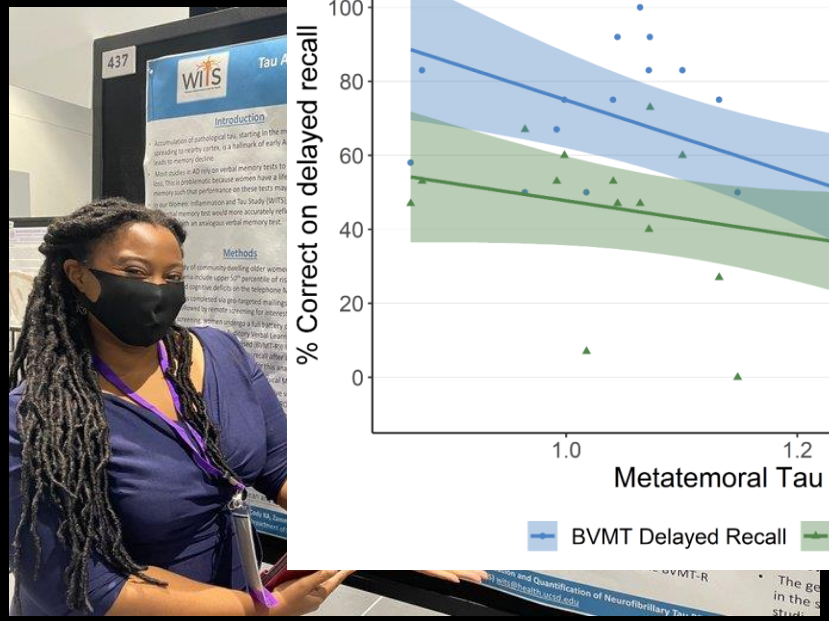
- Battery designed to compare with ADNI
- Also focus on nonverbal memory
- Brief-Visuospatial Memory Test-R
- Does not show sex differences like verbal memory

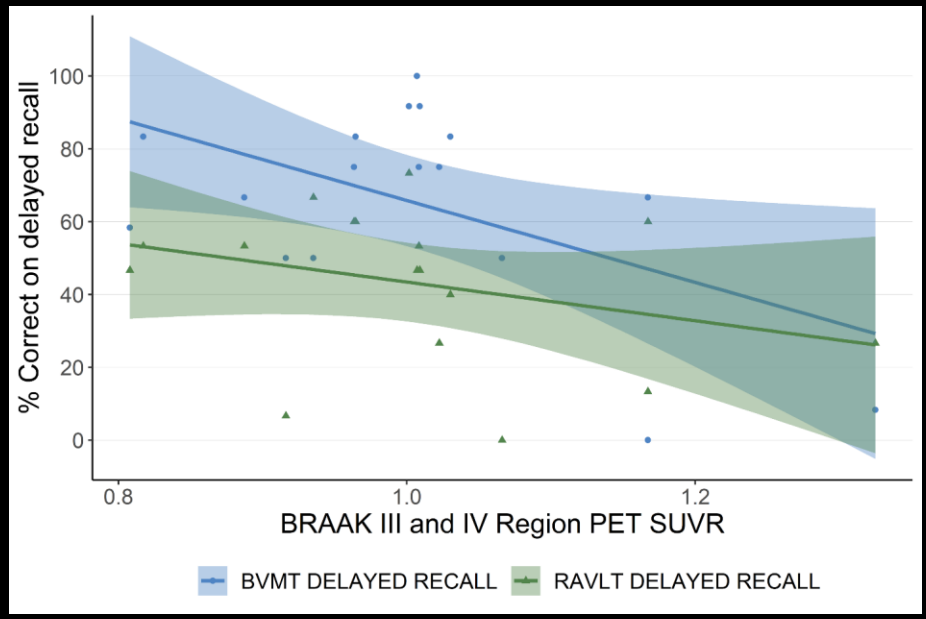


Faux BVMT stimuli, Langdon et al 2011

ASSOCIATIONS BETWEEN TAU PET AND VISUAL VS VERBAL MEMORY

- Presented by Alyx Shepherd at AAIC 2022



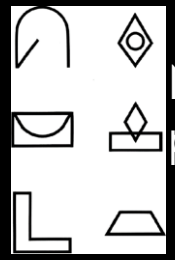


WITS
Women: Inflammation and Tau Study

Work by grad student Kitty Lui

- Strong relationships between OSA and tau

- But, even strong relationships between self reported sleep and tau



Nonverbal memory also closely related to both tau and poor sleep

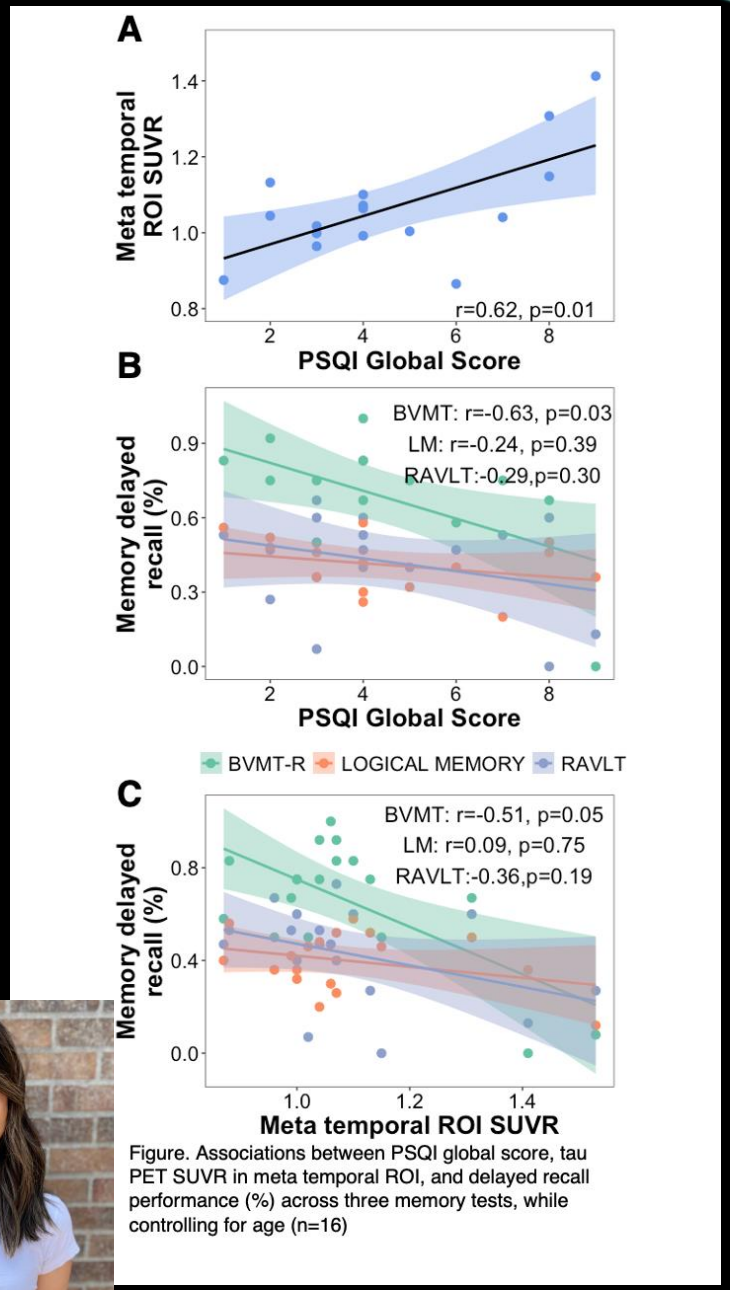
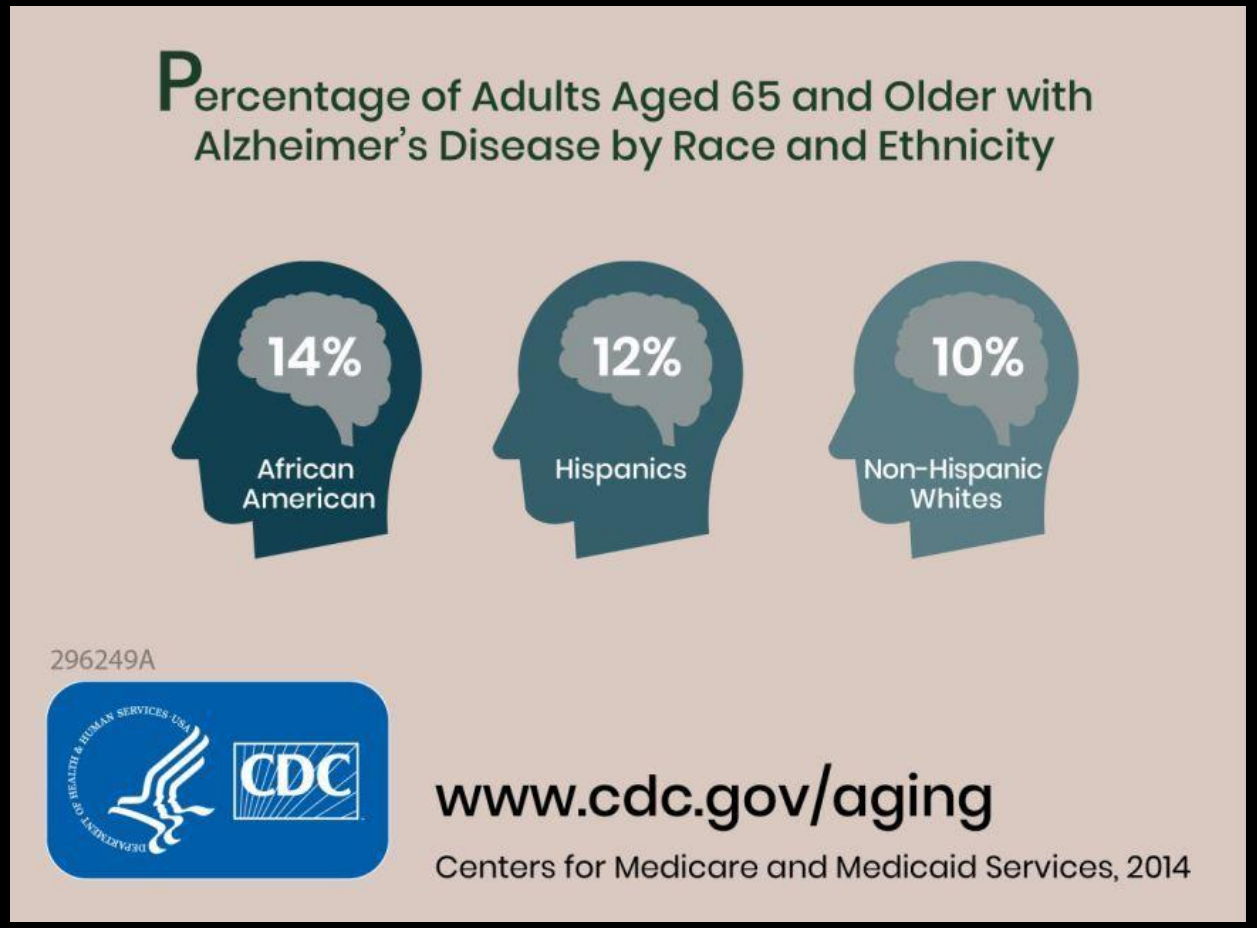
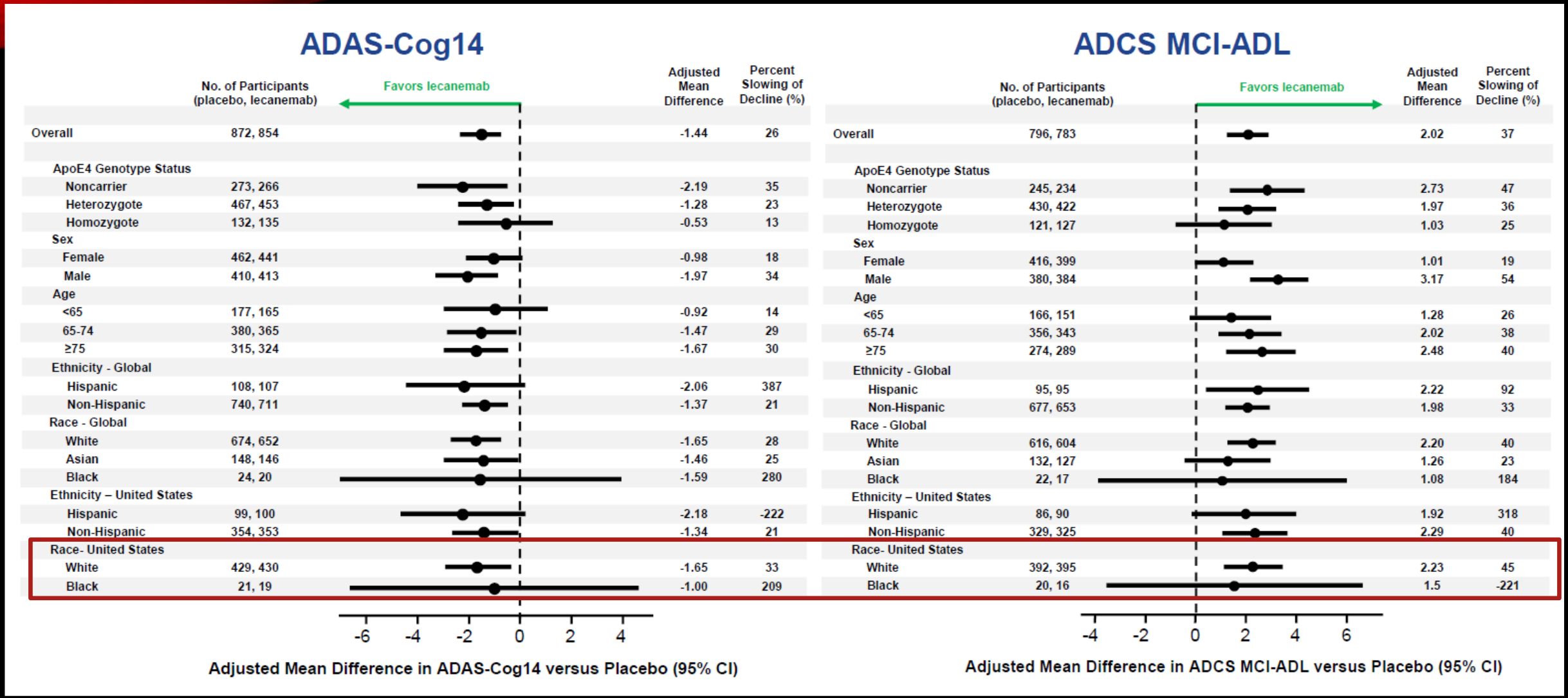


Figure. Associations between PSQI global score, tau PET SUVR in meta temporal ROI, and delayed recall performance (%) across three memory tests, while controlling for age (n=16)

MAKING WITS MORE INCLUSIVE



WHY DOES RACE MATTER IN AD STUDIES?



BWITS

- Newly funded R01
- Will allow us to leverage plasma markers to bring WITS to the community
- Will recruit using Community Based Participatory Research practices
- 50 women in Los Angeles (with Dr. April Thames)
- 50 women in San Diego (with Dr. Marc Norman)
- No imaging or lumbar puncture, but otherwise reflects WITS protocol

STUDY OF LATINOS: INVESTIGATION OF NEUROCOGNITIVE AGING

- Recent A&D publication on reproductive history and cognitive outcomes with Hector Gonzalez and Ariana Stickel: oral contraceptive use associated with less cognitive decline
- Plasma tau markers grant just funded

3 RESEARCH QUESTIONS

SEX DIFFERENCES IN RISK & EXPRESSION OF AD

WHAT FACTORS PROMOTE AD IN WOMEN?

HOW DO WE HELP INDIVIDUALS REDUCE THEIR RISK?

HOW CAN WE HELP REDUCE RISK?

With Howard Feldman and Sara Moukarzel

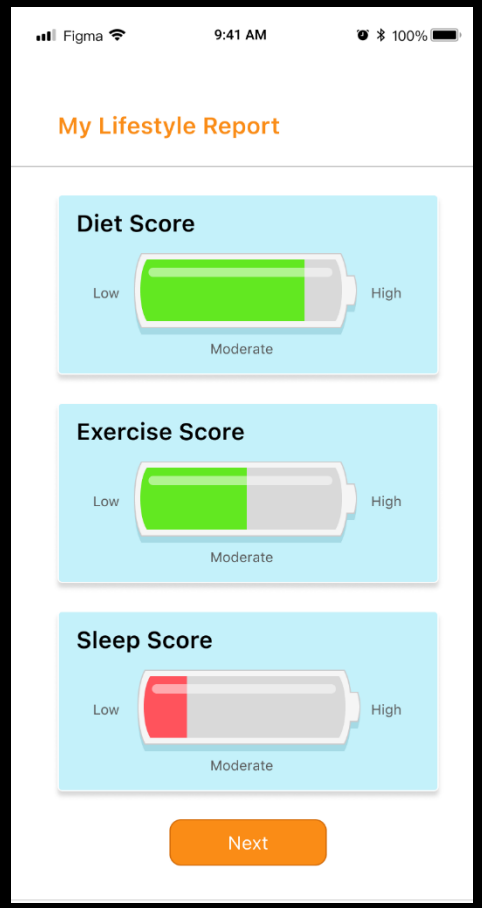
- Increasing recognition of modifiable risk factors
- Including sleep disruption, poor diet and low exercise assessed in WITS
- How do we educate and empower older adults to make lifestyle changes?

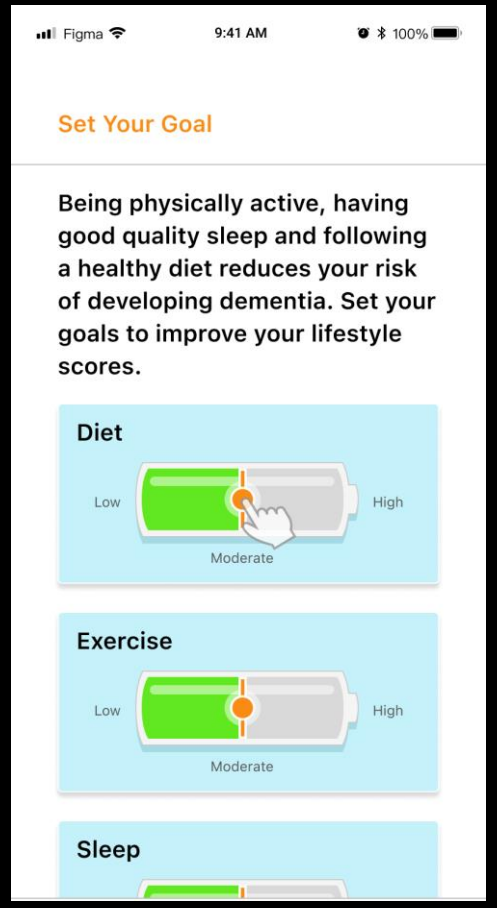
HALT-AD

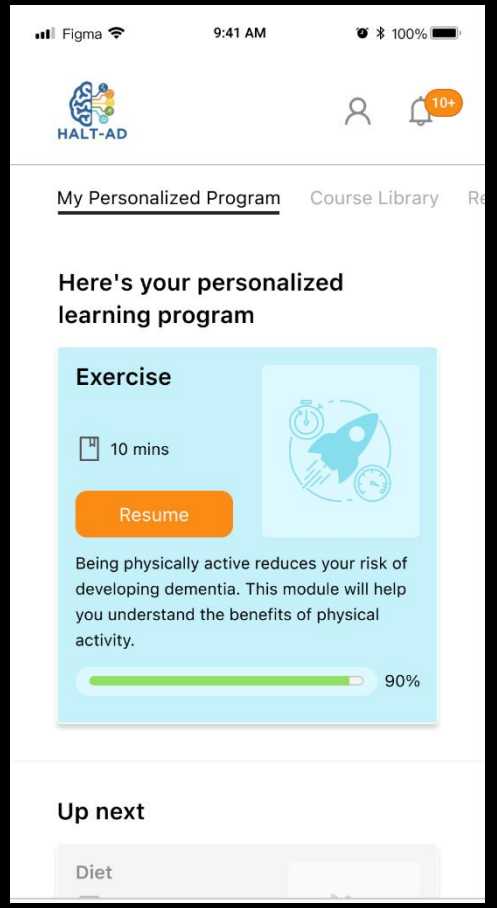
- Healthy Activities and Lifestyles to Avoid Dementia, or Hispanos y el ALTo a la Demencia

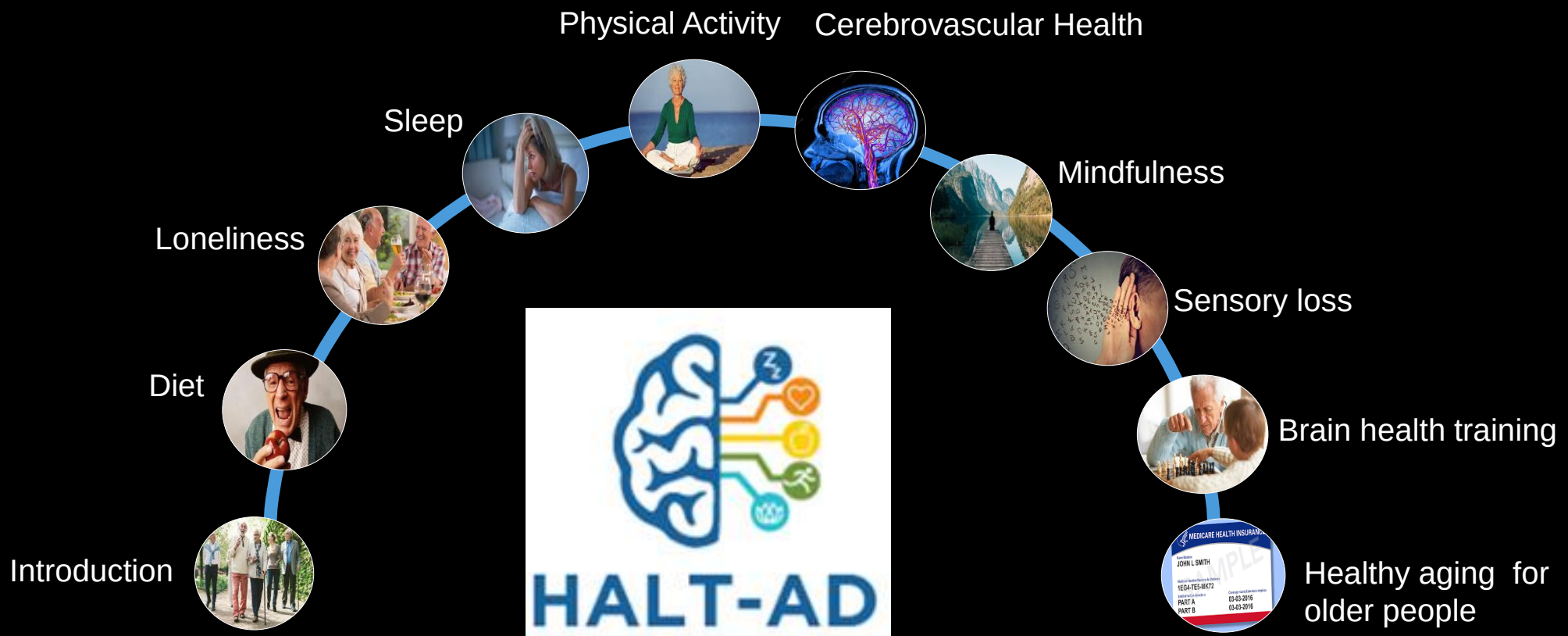
- Educational program, delivered online to provide quality information about modifiable risk factors
- Accompanied by psychosocial support groups via Zoom

HALT-AD: A PERSONALIZED AND INTERACTIVE USER EXPERIENCE








Physical Activity
Cerebrovascular Health
Sleep
Mindfulness
Loneliness
Sensory loss
Diet
Brain health training
Introduction
Healthy aging for older people
HALT-AD

THANK YOU

Participants

ADNI

Funding sources including National Institute on Aging

Human Memory Lab
WITS Lab
HALT AD Group

THANK YOU!

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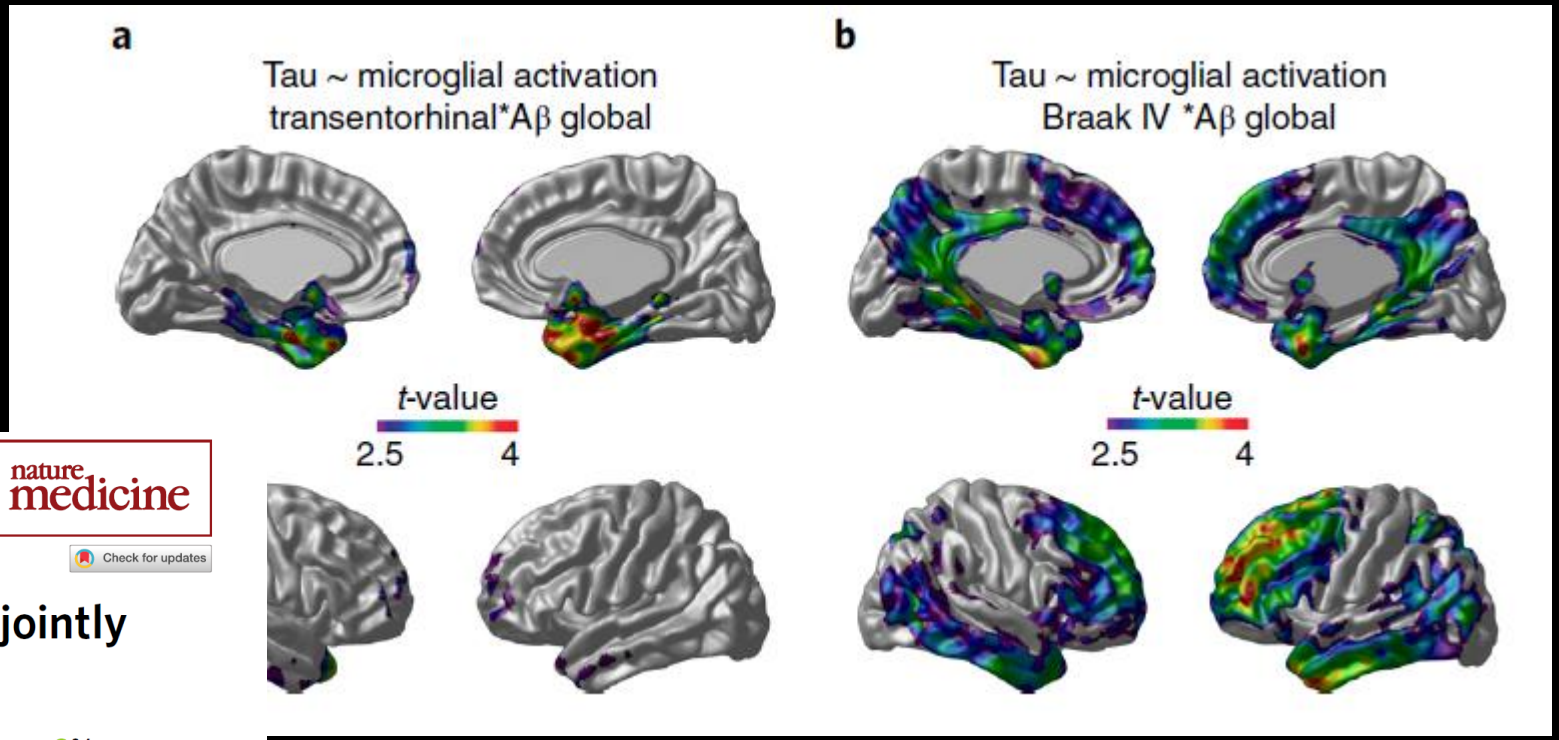
MICROGLIAL ACTIVATION PROMOTES SPREAD OF TAU ON AD TRAJECTORY

Longitudinal tau propagation pathways depends on baseline microglia network



ARTICLES
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nature medicine
Check for updates

Microglial activation and tau propagate jointly across Braak stages

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MY BACKGROUND

- Grew up in London
- Undergrad in psychology at University of Edinburgh
- Worked as a RA at the Oxford Infirmary (neurosurgical hospital, epilepsy and movement disorders)
- PhD at Notherwestern in Chicago (PPA, FTD, AD)
  –course on MRI at Martinos/MGH
- Internship at University of Chicago (first imaging lab)
- Postdoc at the Montreal Neurological Institute (epilepsy, MRI)
- First faculty/clinical position at the Cleveland Clinic Lou Ruvo Center in Vegas
  - Director Jeff Cummings introduced me to Bill Jagust as mentor on P20 COBRE grant
- UCSD, Associate Professor in Neuroscience/clinical
  - First independent federal and state funding