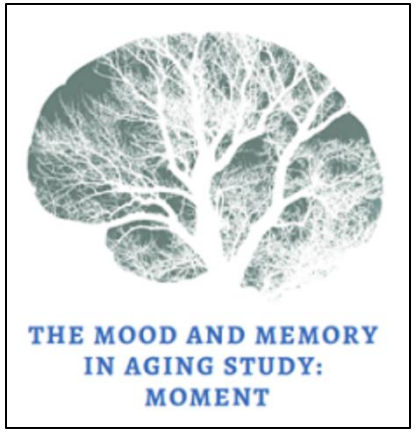

Psychiatric Symptoms and Dementia Risk

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Chair ISTAART Neuropsychiatric Symptoms PIA

UCI MIND 36th Annual Southern California Alzheimer's Disease (AD) Research Conference

Nature, Nurture, and Neurodegeneration

Jennifer R. Gatchel, MD PhD

Disclosure of Interest

Research Support

1. NIH/NIA
2. Massachusetts General Hospital Rappaport Fellowship
3. Alzheimer's Association Clinical Fellowship
4. BrightFocus Foundation Alzheimer's Disease Research Fellowship

Speakers Bureau

- Massachusetts Alzheimer's Disease Research Center Speaker's Bureau

Clinical Trials

N/A

Consultant

Eisai

Huron Life Sciences

I own no stocks or equity in any pharmaceutical company

Objectives:

- o Describe the available literature assessing associations between major psychiatric conditions and dementia, focusing on depression
- o Analyze the bidirectional relationships and possible mechanisms linking psychiatric disorders to dementia
- o Assess the potential impact of psychiatric treatments in dementia risk, progression and prevention

Nana Rose and Me

Austin, TX

Late Life Depressive Symptoms and Neurodegenerative Disease

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Are new or worsening depressive and behavioral symptoms in late life related to Alzheimer's Disease (ADRD) pathology?

Late Life Depressive Symptoms and Neurodegenerative Disease

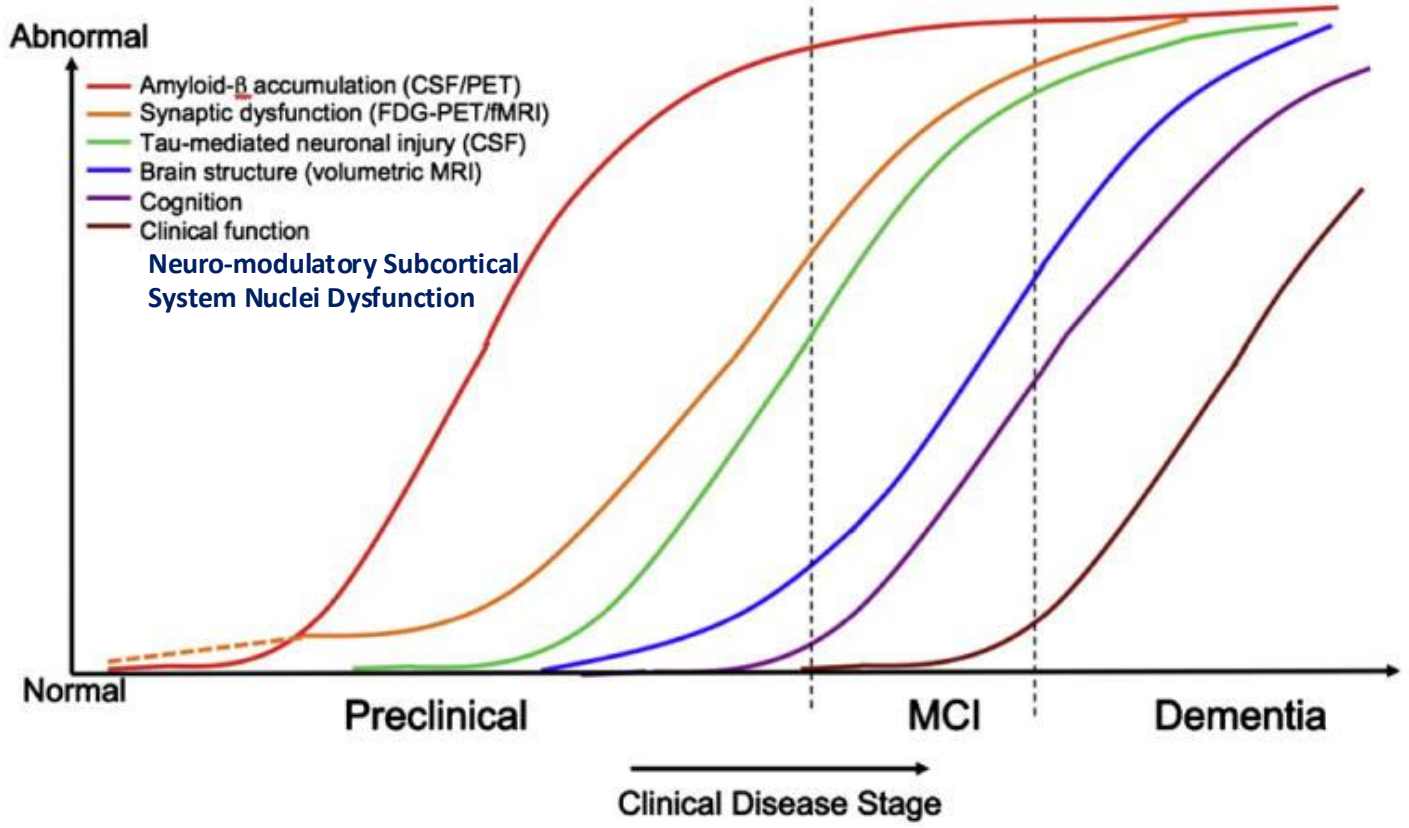
Are new or worsening depressive and behavioral symptoms in late life related to Alzheimer's Disease (ADRD) pathology?

Depressive and behavioral symptoms: early clinical indicators of ADRD?

Late Life Depressive Symptoms and Dementia

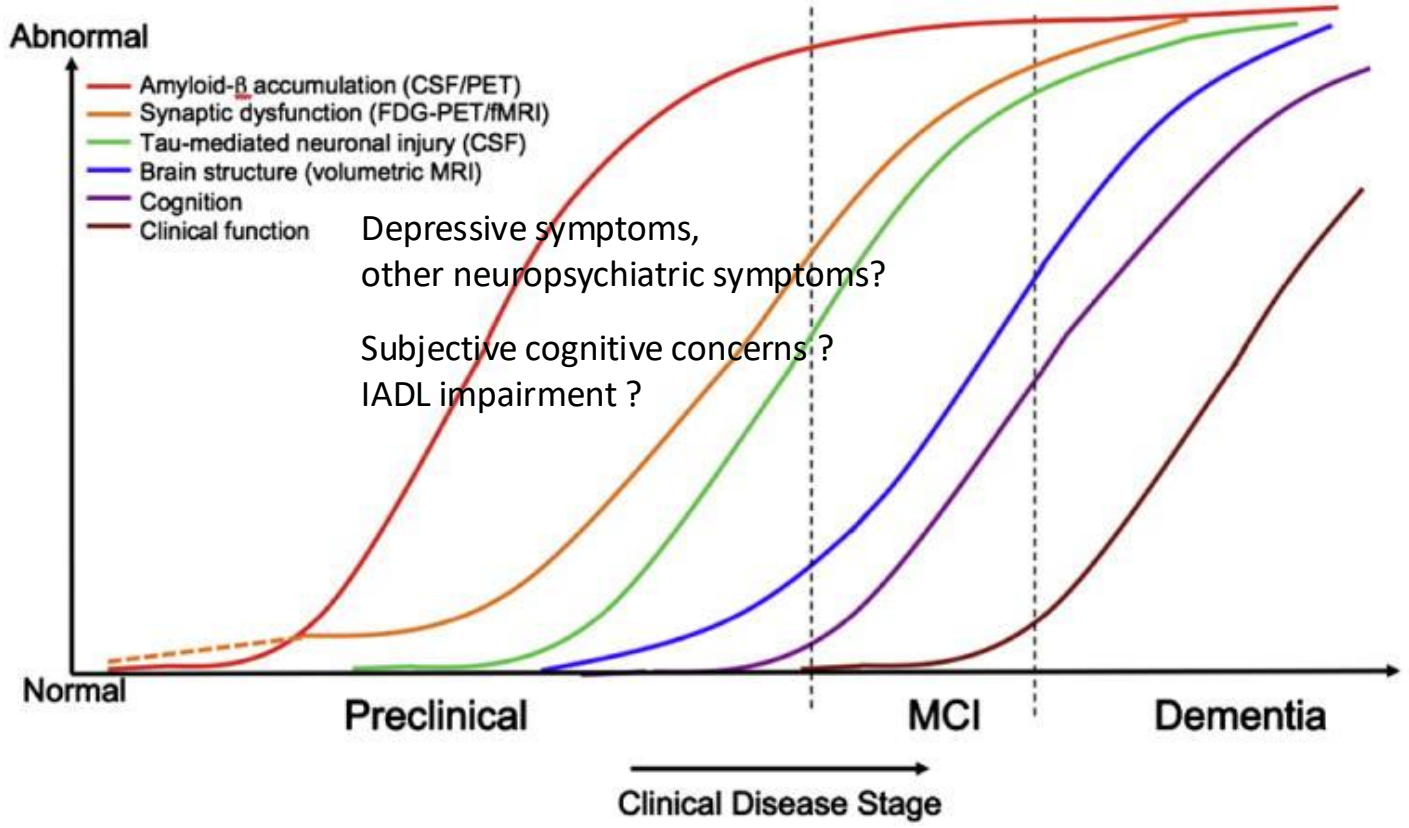
Does Alzheimer's Disease (AD) pathology underlie new or worsening depressive and behavioral symptoms in late life?

How do neuropsychiatric symptoms relate to AD biomarkers and opportunities for prevention?



Adapted from Sperling et al. Alz Dementia 2011; 2. Jack et al. Alz Dementia, 2018

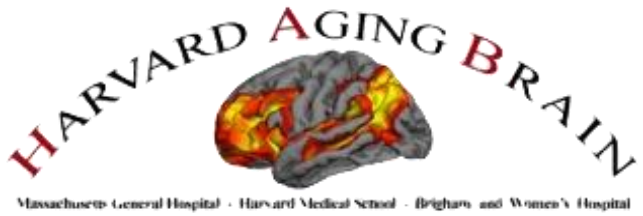
How do depressive symptoms relate to AD biomarkers and opportunities for prevention?



Adapted from Sperling et al. Alz Dementia 2011; 2. Jack et al. Alz Dementia, 2018

Are emergent, worsening depressive symptoms related to underlying AD pathology and cognition?

P01 AG036694 (Sperling and Johnson)



- Prospective longitudinal observational cohort study of cognitive aging, entering year 15, n=350-400 participants
- Community dwelling English-speaking older adults, ages 55-90 at entry; cognitively unimpaired
- Exclusion Criteria at entry:

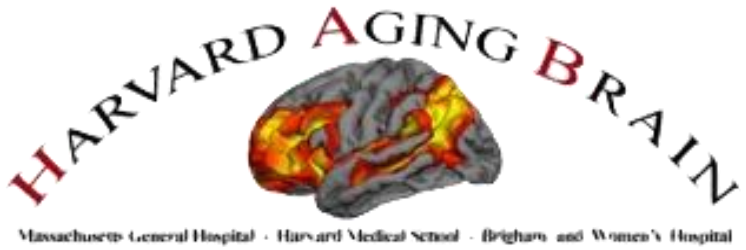
  Unstable medical illness; neurological disease or stroke

  History of serious mental illness (schizoaffective disorder, bipolar disorder); substance use disorder, moderate to severe depression; Score of >=11 on the 30 item Geriatric Depression Scale (GDS)

  Not excluded: history of mild depression or anxiety; treatment with stable dose of an antidepressant (SSRI/SNRI/buproprion, nortriptyline)

- Exclusion criteria at entry, but not at subsequent follow-ups

P01 AG036694 (Sperling and Johnson)



- Annual clinical assessments: cognitive batteries, Preclinical Alzheimer Cognitive Composite (PACC); Geriatric Depression Scale

  (GDS)-30 item (self-report, yes/no)

- Serial multimodal neuroimaging: MRI, ^{11}C-PiB-PET Amyloid Imaging, ^{18}F-Flortaucipir (FTP) Tau-PET Imaging; at baseline and every 3 years;

- Serial plasma collection: ATN^{+} fluid biomarkers

P01 AG036694 (Sperling and Johnson)

Does AD pathology underlie emergent or worsening depressive symptoms: focus on regional tau

Sample: n= 252 older adults; average follow up= 5.87 annual visits, cognitively unimpaired, without clinically significant depression at study entry (average Geriatric Depression Scale-30 item (GDS) score =3.3 ± 3.1).

Age (mean ± SD years)	73.1 ±9.0
Sex (% male)	39.5
Race (% White)	92
Education (mean ± SD years)	16.1±2.9
Mini Mental State Examination (MMSE) Score	29.0 ± 1.2
Depression history (%) None/Recent/Remote	80.9/13.5/5.6

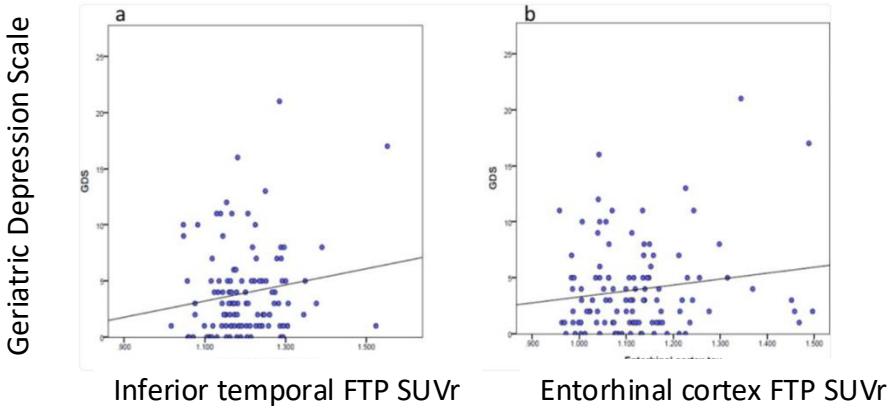
Mixed effects model: GDS (each annual study visit) ~ random slope and intercept for each participant + tau (**EC or IT**, at study year 3 or 4) + cortical amyloid + time (of tau PET) + age + sex

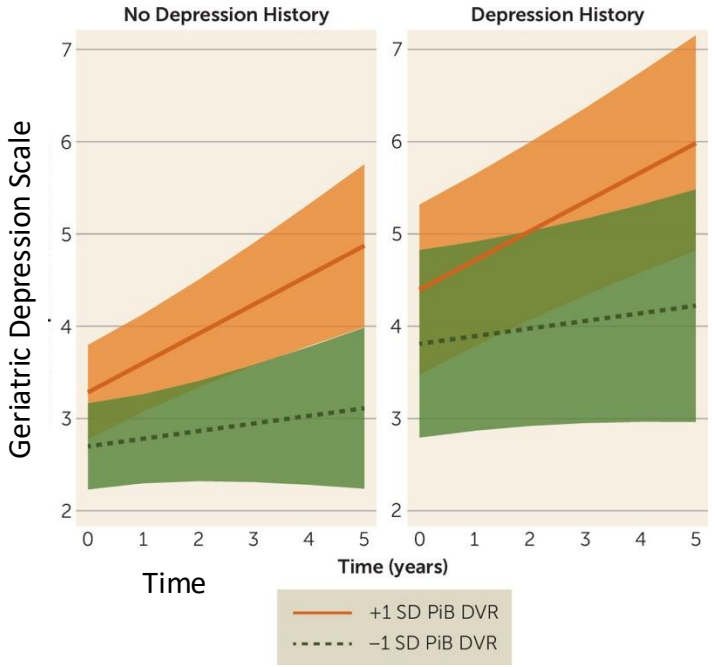
Gatchel et al. in preparation, 2023

Are emergent, worsening depressive symptoms related to underlying AD pathology and cognition?

- *Donovan et al. JAD 2015*
  - cross-sectional, baseline GDS ~ baseline cortical amyloid (PiB PET)
- *Gatchel et al. JAD 2017*
  - cross-sectional, baseline GDS ~ baseline regional tau (FTP PET)

- *Donovan et al. AJP 2018*
  - longitudinal GDS ~ baseline cortical amyloid PiB PET)

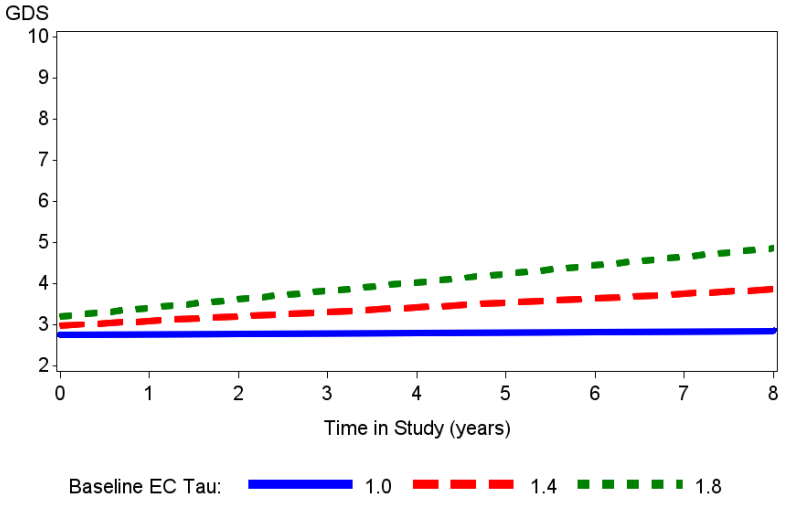




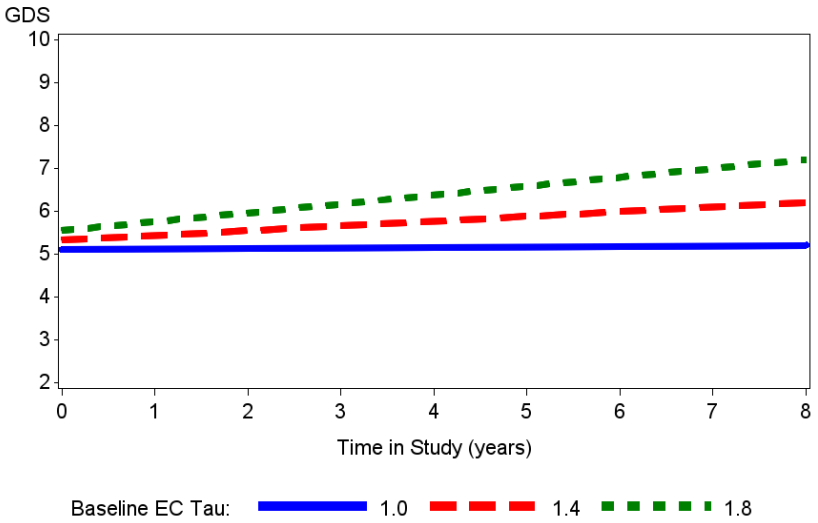
NIH/NIA K23 AG058805, PI Gatchel

Significant longitudinal association between tau (FTP PET) and GDS

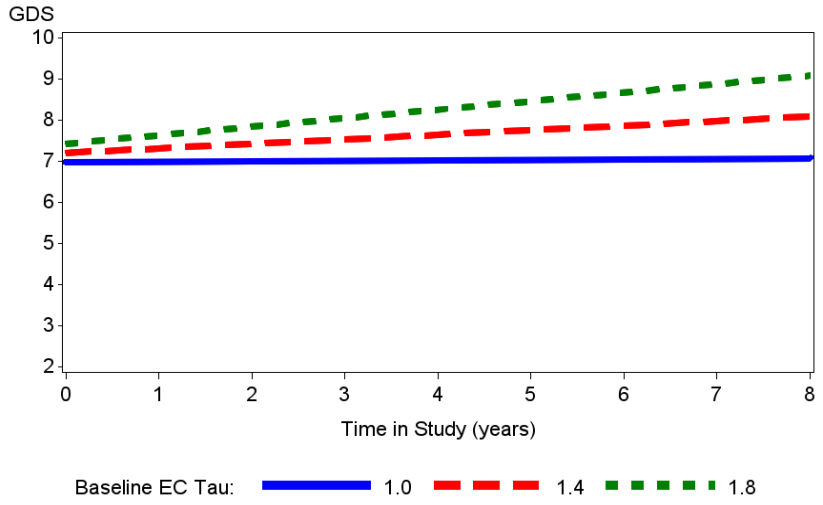
Depression History: none



Depression History: recent



Depression History: remote



Sensitivity analyses: adjusting for antidepressant use, objective cognition, repeating analyses with a GDS value removing items targeting subjective cognitive concern ➔ did not alter the direction or magnitude of results

NIH/NIA K23 AG058805, PI: Gatchel

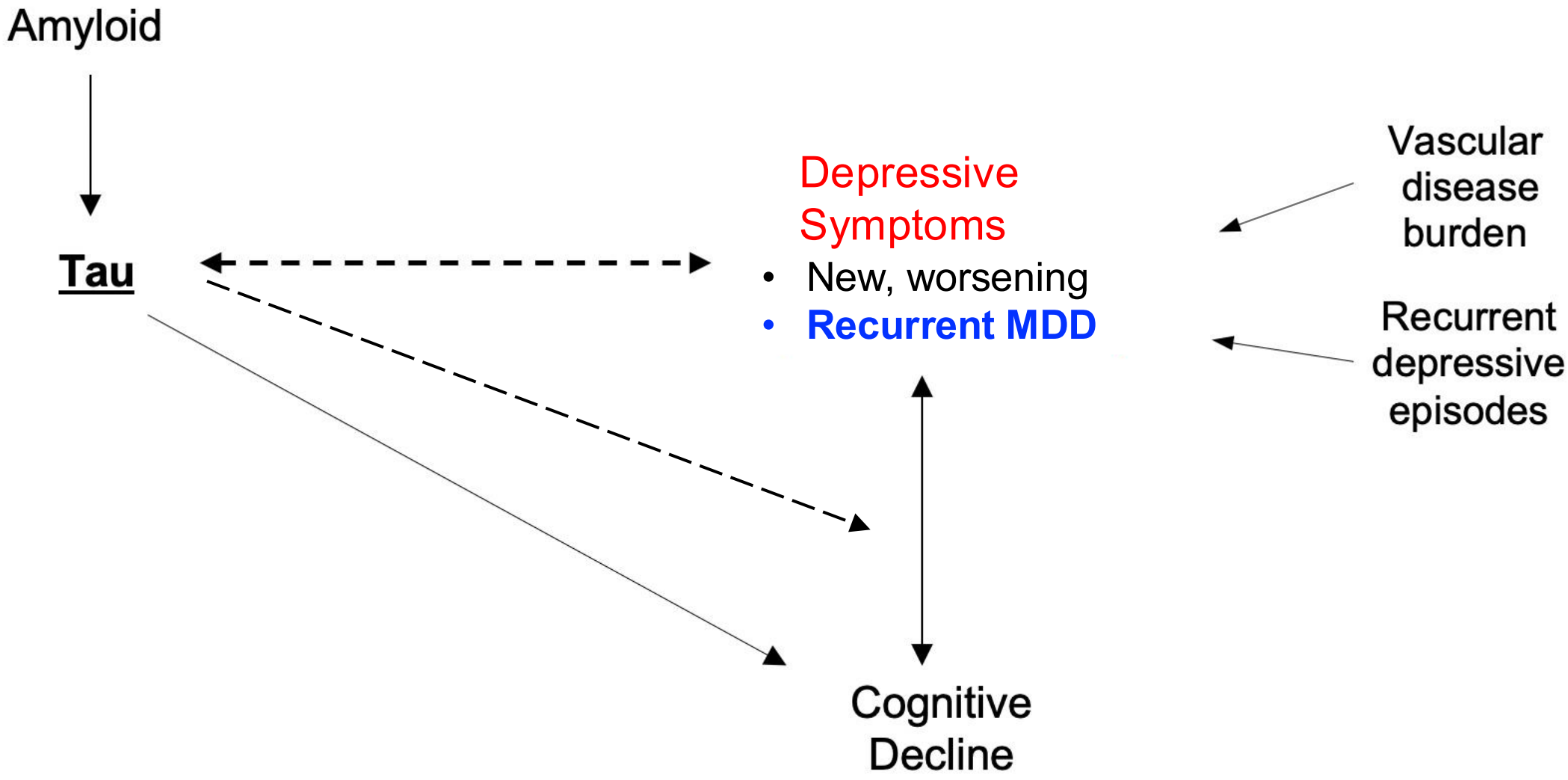
Gatchel *et al.* in preparation

AD pathology and emergent depressive symptoms:

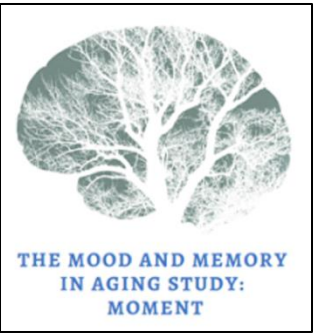
- Regional tau, early amyloid accumulation: associated with increasing depressive symptoms over time in older adults (cognitively normal, low/no depression at baseline)
- Depressive symptoms synergize with AD pathology to potentiate cognitive changes in the preclinical stage
  - Highly educated sample, predominantly white, low vascular burden

- Related and ongoing work:
  - Probe distinct affective phenotypes
    - Apathy (Premnath..Gatchel, *Alz Dement*, 2024), (Burling..Gatchel, *AJGP*, 2024); (Scher..Gatchel, AAIC 2025)
  - Investigate mechanism(s)
  - Impact on cognition and function
  - Examine in **diverse cohorts with greater symptom burden**
    - (Alcina…Gatchel, *Alzheimer's Dementia*, 2024)
  - Interventions (behavioral, neuromodulation, pharamacological)

Late life depressive symptoms:



Mood and Memory in Aging Study (MOMENT)



In parallel to the Harvard Aging Brain Study; identical infrastructure

Inclusion criteria: age 65 and above DSM-5 Major depressive disorder or persistent depressive disorder; currently depressed (GDS>12); do not meet criteria for dementia at enrollment

- *First study (along with ADNI-depression) of amyloid + tau PET + MRI + plasma ATN+ markers in older adults with MDD/persistent depressive disorder (diagnostic interview + life course history) and current moderate to severe symptoms.*

NIH/NIA K23 AG058805 (PI: Gatchel)
NIH/NIA R01 AGR01AG078191 (PI: Gatchel)

Methods:

- **Participants:** 75 older adults with MDD/PDD (DSM5), recruited from the community and MGB psychiatry clinics, not meeting criteria for MCI *(predominantly early-onset (prior to age 50), recurrent illness*); 100 CN non-depressed older adults (no depression history or current symptoms) in related studies at our stie
- **Clinical Measures:** MINI International Neuropsychiatric Interview; Geriatric Depression Scale (GDS), QIDS-SR, Mild Behavioral Impairment Checklist:, apathy anhedonia, anxiety
- **Neuroimaging:** [^{11}C] PiB-PET (amyloid), [^{18}F] FTP-PET (tau), MRI (atrophy)
- **Plasma ATN assays**
- **Actigraphy, digital cognitive assessments**
- **Statistical Analyses:** Pearson correlations; linear regressions adjusted for age + sex

NIH/NIA R01 AGR01AG078191 (PI: Gatchel)
NIH/NIA K23 AG058805 (PI: Gatchel)

Characteristic	Non-Depressed N = 167[1]	Depressed N = 82[1]	p-value[2]
Baseline Age	74 (70, 79)	74 (71, 80)	0.4
Sex			0.7
F	98 (59%)	50 (61%)	
M	69 (41%)	32 (39%)	
Geriatric Depression Scale (GDS) total	2.0 (1.0, 4.0)	10.0 (7.0, 14.0)	<0.001
Fusiform tau (bh)	-0.01 (-0.05, 0.04)	-0.03 (-0.06, 0.01)	0.058
Middle temporal tau (bh)	-0.01 (-0.06, 0.03)	-0.02 (-0.06, 0.04)	0.8
Inferior temporal tau (bh)	-0.01 (-0.06, 0.04)	-0.02 (-0.06, 0.04)	0.6
Entorhinal tau (bh)	-0.03 (-0.09, 0.04)	-0.03 (-0.08, 0.08)	0.6
Amygdala tau (bh)	-0.01 (-0.07, 0.06)	-0.02 (-0.11, 0.05)	0.2
Rhinal tau (bh)	-0.01 (-0.10, 0.06)	-0.04 (-0.11, 0.07)	0.7
Unknown	24	16	
PiB FLR	-0.08 (-0.13, 0.05)	-0.07 (-0.12, 0.08)	0.8
PIB_HRC_FS_DVR_Group			0.6
PIB-	121 (72%)	57 (70%)	
PIB+	46 (28%)	25 (30%)	

[1] Median (Q1, Q3); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test

NIH/NIA R01 AGR01AG078191 (PI: Gatchel)
NIH/NIA K23 AG058805 (PI: Gatchel)

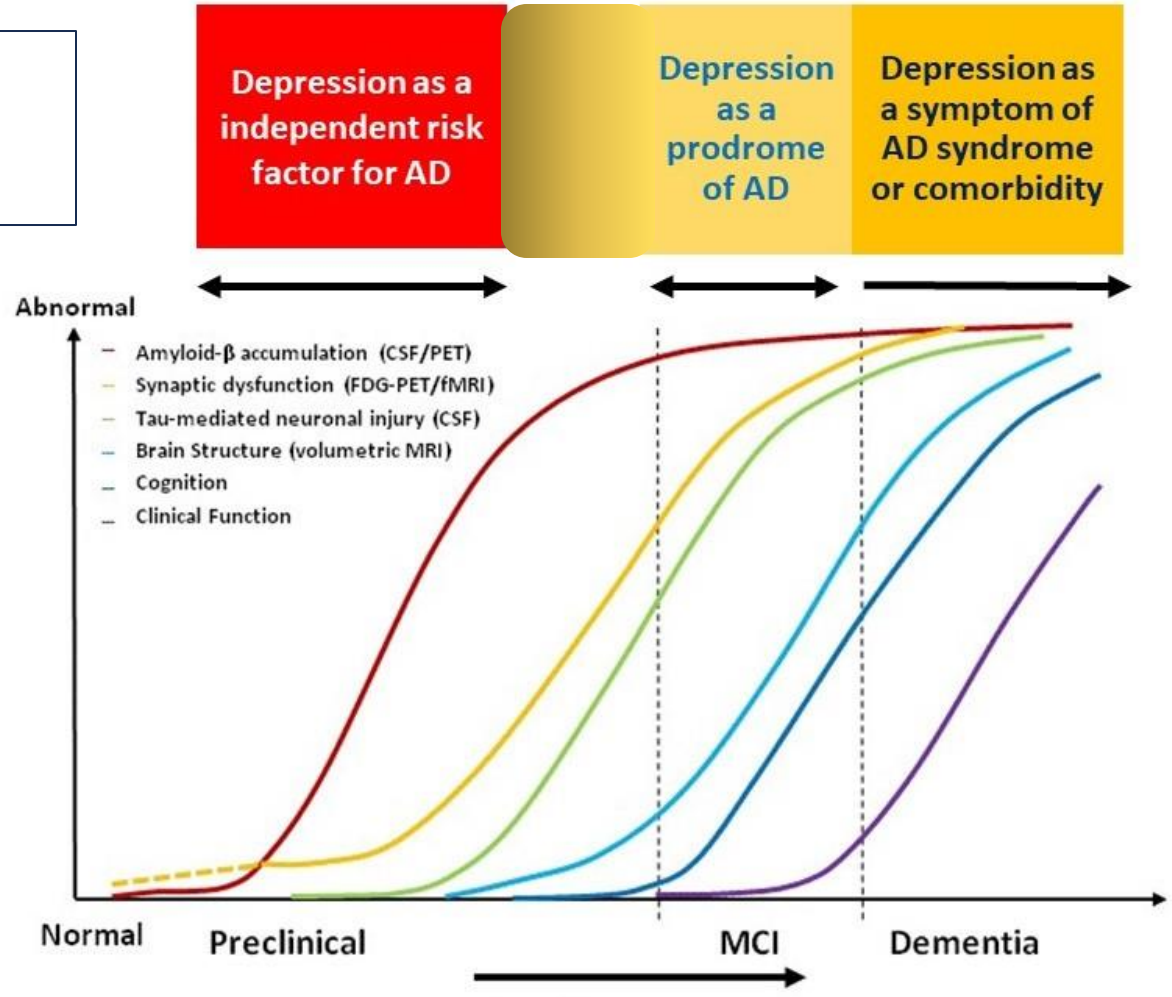
Depression and dementia vulnerability

Does depression confer *decreased resistance and resilience* to AD pathology ?

Decreased resistance: Greater pathology accumulation

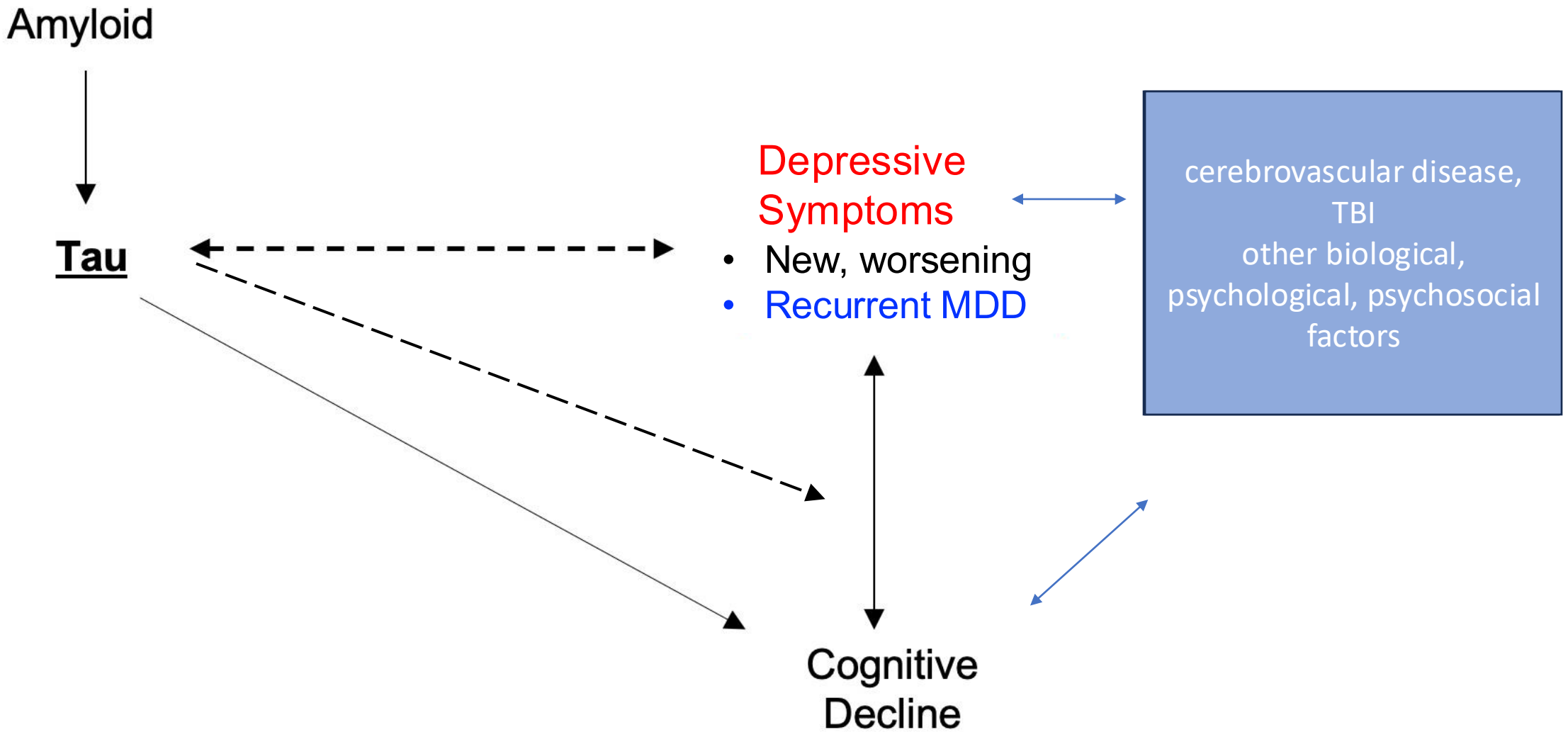
Decreased resilience: Greater cognitive decline and behavioral manifestations for a given amount of pathology

Different biomarker thresholds for diagnosis and progression?

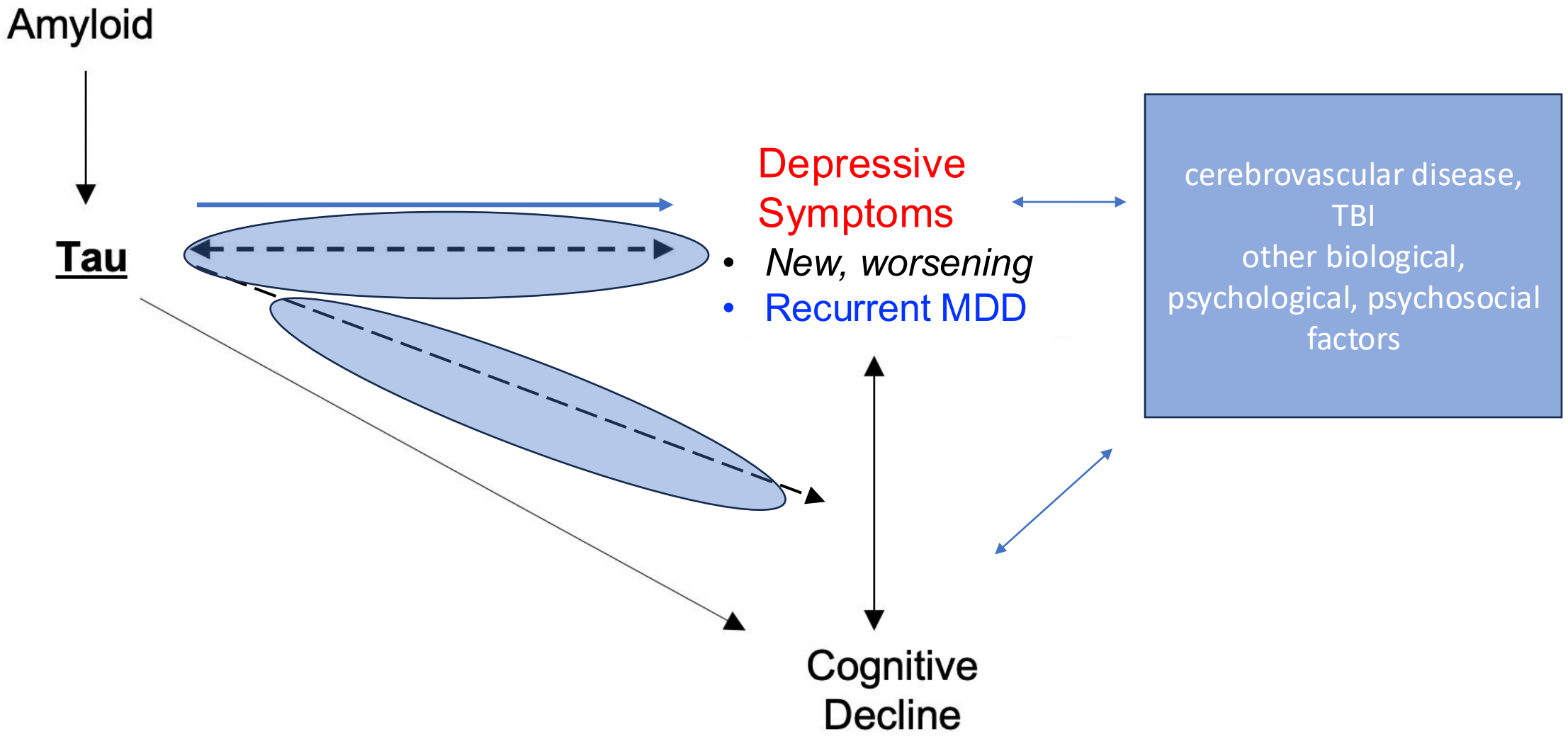


Adapted from Jack et al. 2011

Late life depressive symptoms:



Late life depressive symptoms:



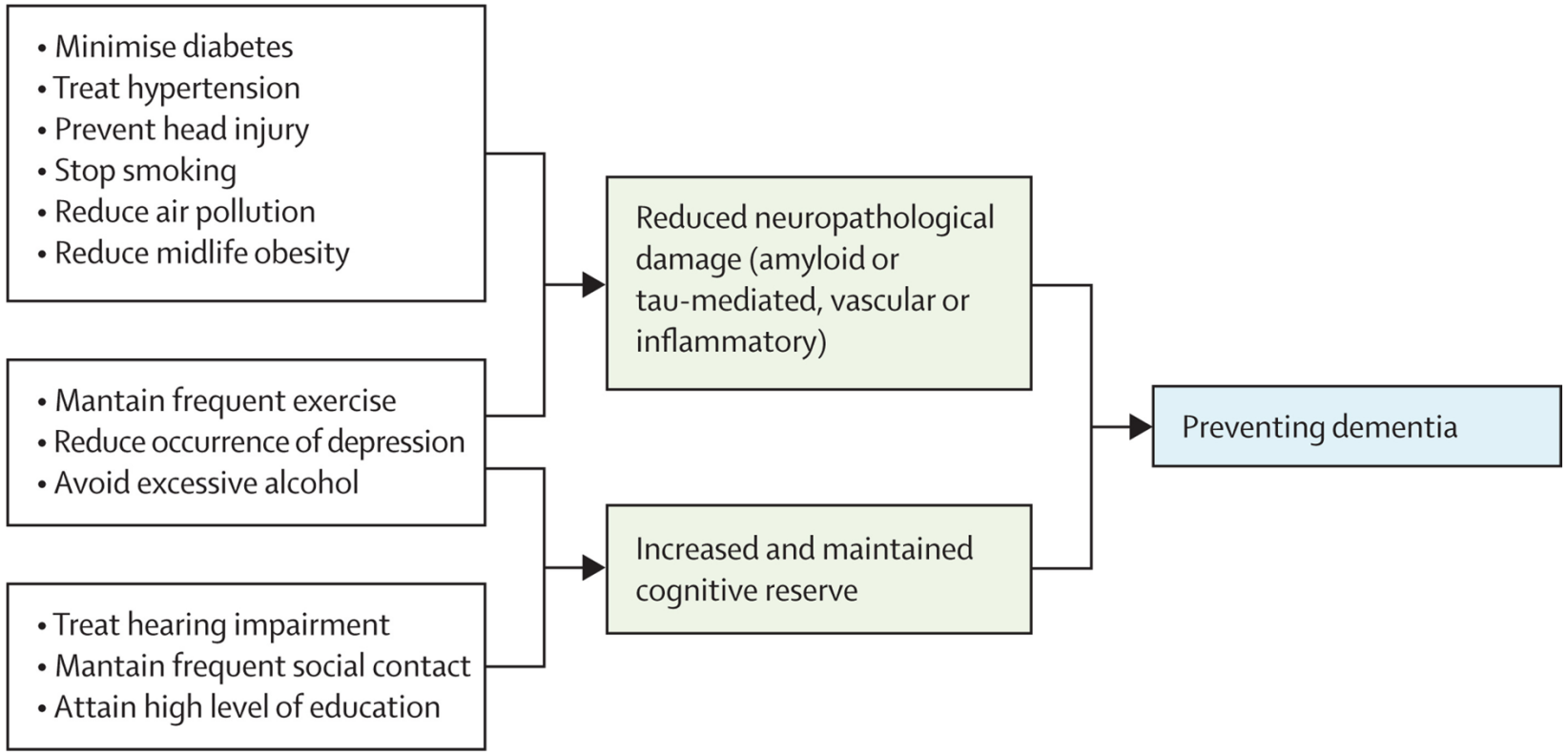
Potential Clinical implications..

- Older adults presenting with depression, even in mild range: monitor cognitive changes over time; AD biomarker profiles + clinical symptoms profile may provide some predictive information; collateral report *

- Do not overlook this population (including those with recurrent MDD) when considering AD disease modifying therapies

- Manage/prevent depression to decrease this modifiable risk; biomarker profiles may eventually guide management plans

Lancet Commission on dementia prevention, intervention and care, 2020

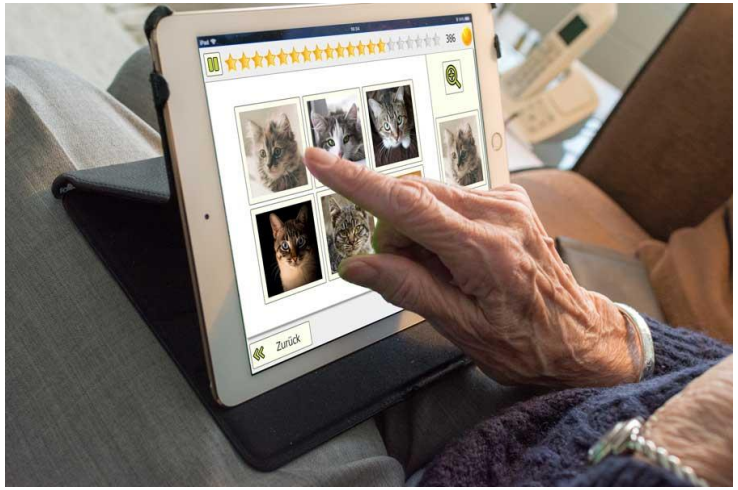


Emerging therapies

Patient undergoes infusion of drug Donanemab

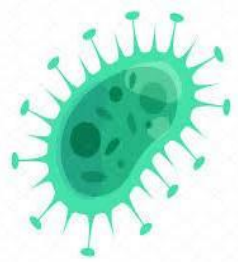
Patient undergoing Transcranial Direct nt Stimulation S) treatment

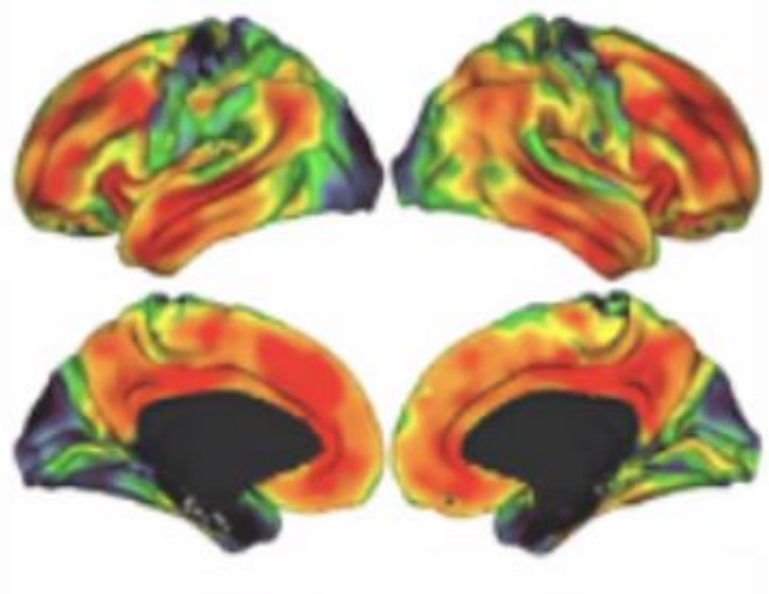
Patient undergoing Transcranial Magnetic Stimulation (TMS) treatment

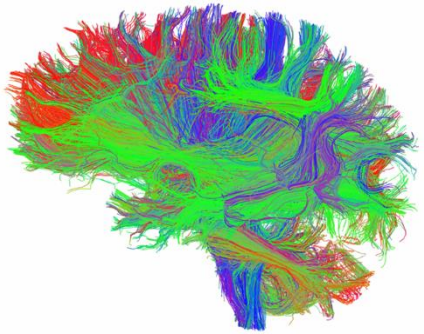


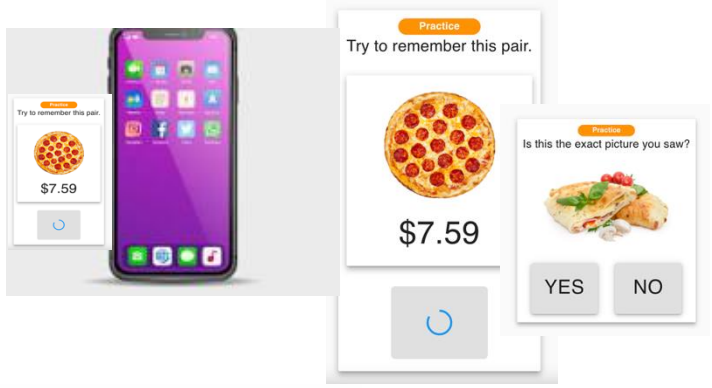
Digital cognitive performance exercises

Personalized risk profiles for vulnerable individuals (patients + care partners) to *prevent dementia*









Centralized Brain Health Treatment for Patients and Care Partners

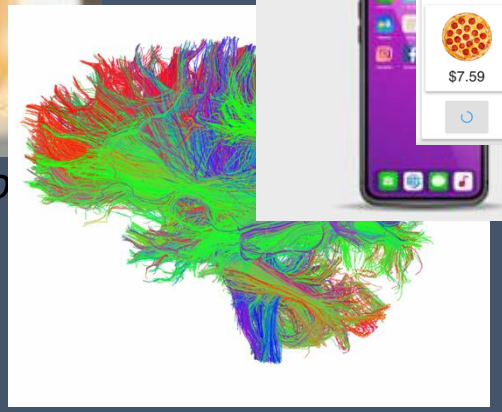
Brain Biology

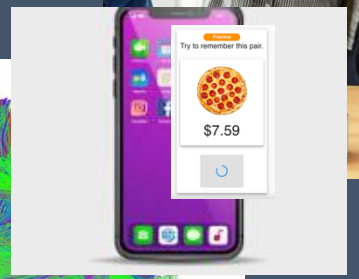
Patient

Anxiety, depressio

Environment

Care-partner, family





Neuropsychiatric Symptoms (NPS) in late life and ADRD

Career Objectives

Neurobiological mechanisms

Targeted interventions

Clinical care (neuromodulation (TMS), pharmacological and non-pharmacological approaches)

Support of patients, care partners

Training geriatric mental health clinicians and scientists

Faculty career development;

Resiliency and wellness

Can we prevent dementia?

Patient, Care-partner, Family Challenges:

- Psychological
- Physical
- Financial