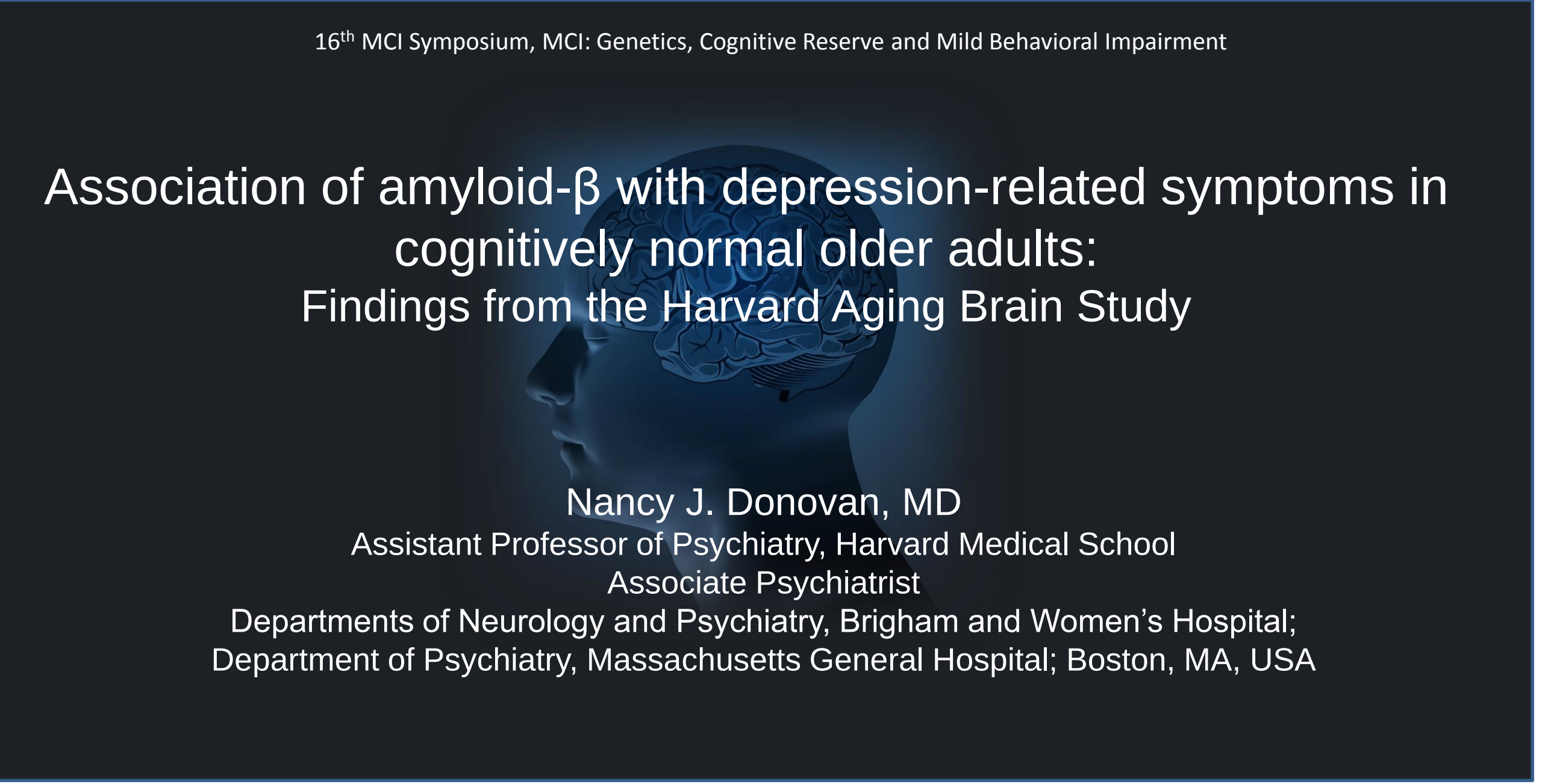

Association of amyloid-β with depression-related symptoms in cognitively normal older adults:
Findings from the Harvard Aging Brain Study

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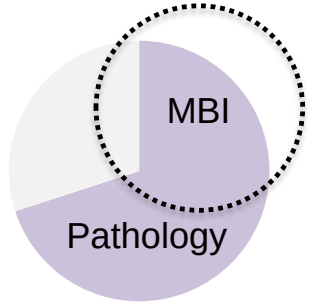
DISCLOSURES

- Funding: NIA R03 AG045080 (Donovan), R21 AG054953 (Donovan), the Harvard Aging Brain Study ((NIA P01 AG036694, Co-PI: Sperling, Johnson), R01 AG037497 (Sperling)), the Massachusetts Alzheimer's Disease Research Center (P50 AG005134).

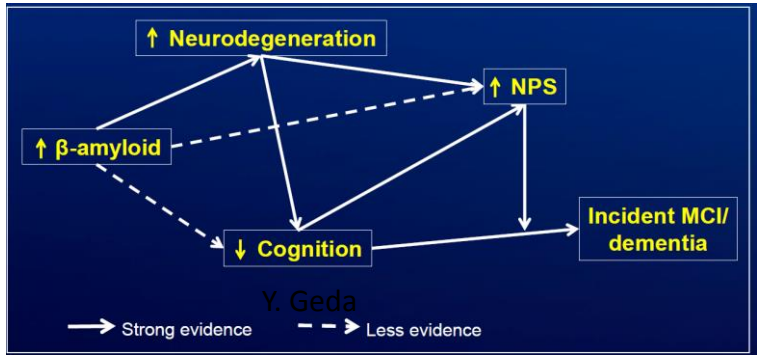
- I have received salary support from Eisai Inc. and Eli Lilly and Company. I have served as a paid consultant to Avanir Pharmaceuticals, Inc. My spouse is employed at Alkermes, PLC.

- **None of these relationships are related to the presented findings.**

Overview



- Alzheimer's disease (AD) as a possible etiology of NPS/MBI at the preclinical stage.
- Does amyloid- β (Aβ) predict worsening depressive symptoms in older individuals without cognitive impairment?



Geda, Knopman

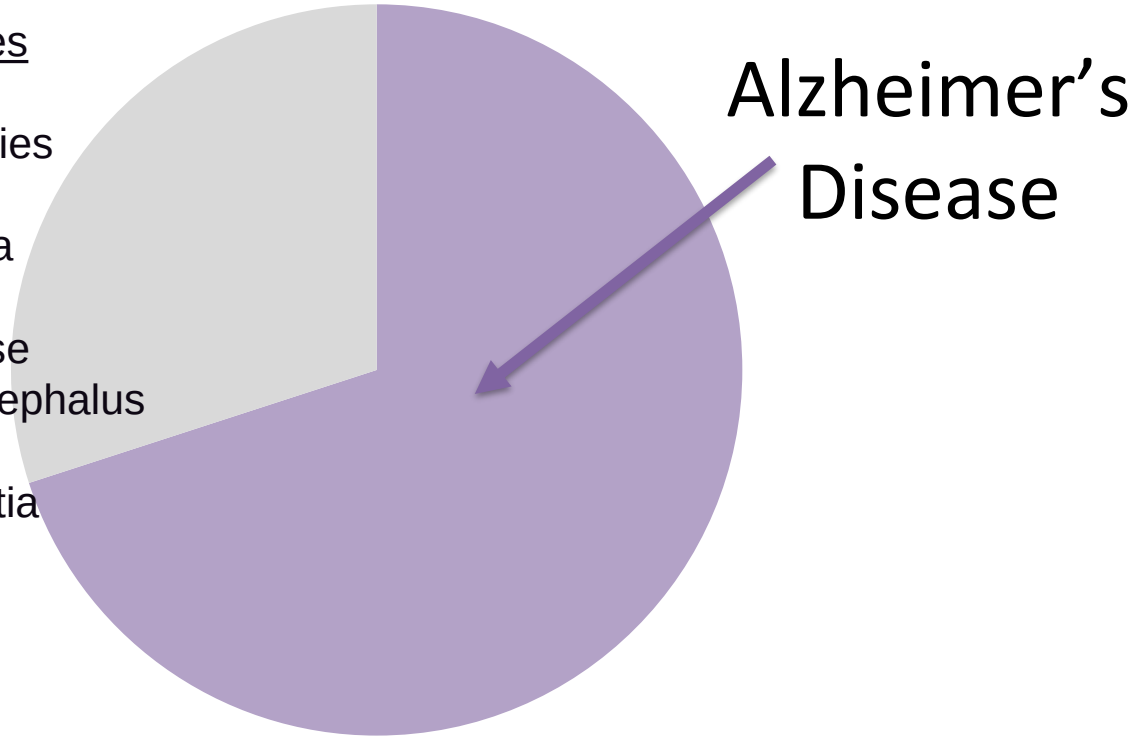
- If so,
  - Are these clinically meaningful relationships/effects?
  - Do these findings have clinical applications?

NPS= Neuropsychiatric symptoms
MBI= Mild Behavioral Impairment

Alzheimer's Disease

- AD is the most common neurodegenerative disorder and cause of dementia (60-80% of 1^{o} or mixed dementia cases).

<u>Other Dementia Etiologies</u>
Vascular Dementia
Dementia with Lewy Bodies
Parkinson's Disease
Frontotemporal Dementia
Huntington's Disease
Creutzfeldt-Jakob Disease
Normal Pressure Hydrocephalus
Traumatic Brain Injury
Down Syndrome Dementia
Korsakoff Syndrome

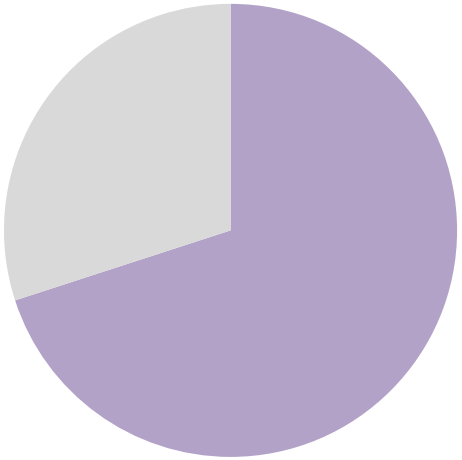


Alzheimer's Association Facts and Figures 2017

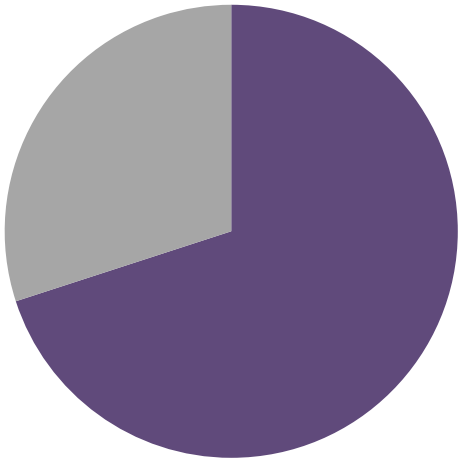
AD is a pathophysiological process

- Encompasses preclinical, mild cognitive impairment (MCI) and dementia stages
  - defined by accumulating pathologies and clinical impairment

Normal Cognition/Preclinical Stage



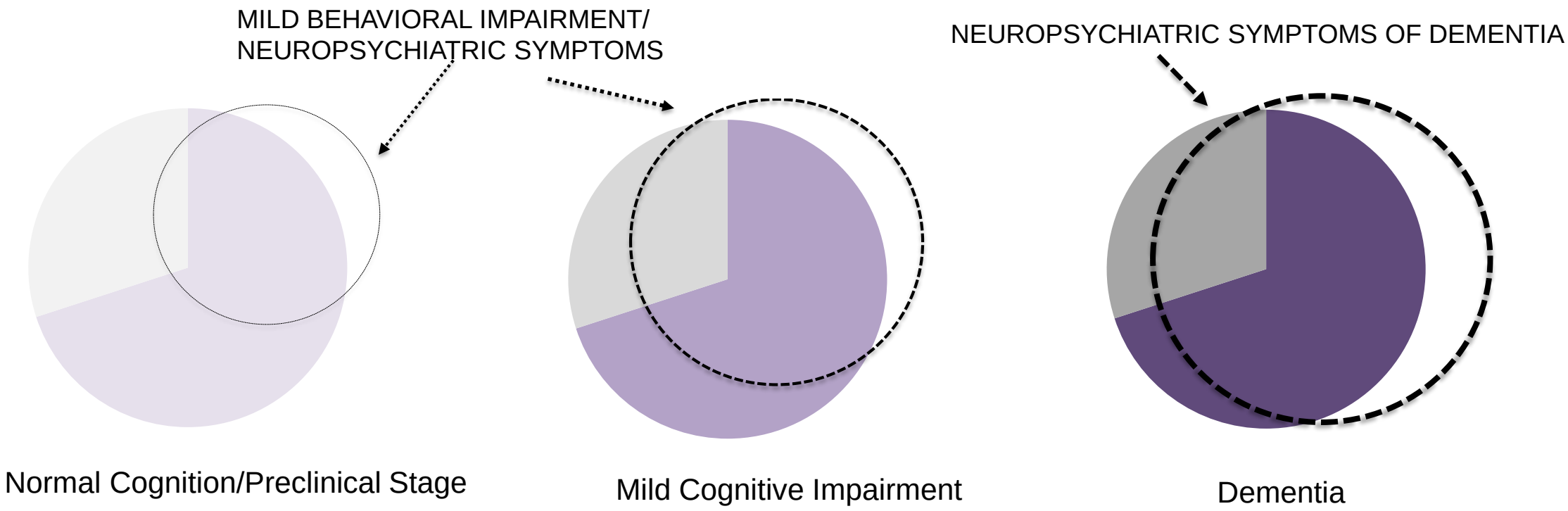
Mild Cognitive Impairment



Dementia

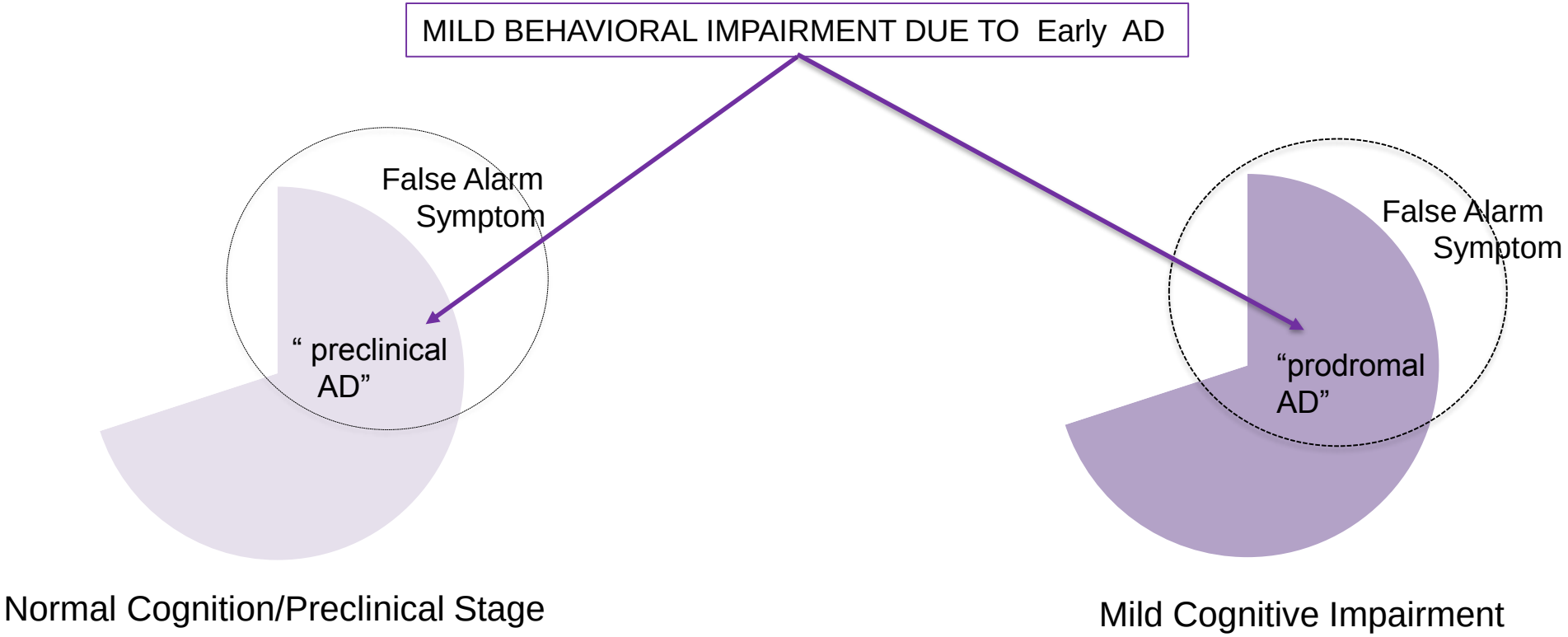
Mild Behavioral Impairment (MBI) and AD

- Neuropsychiatric morbidity also increases across these stages



NPS/MBI and Early AD

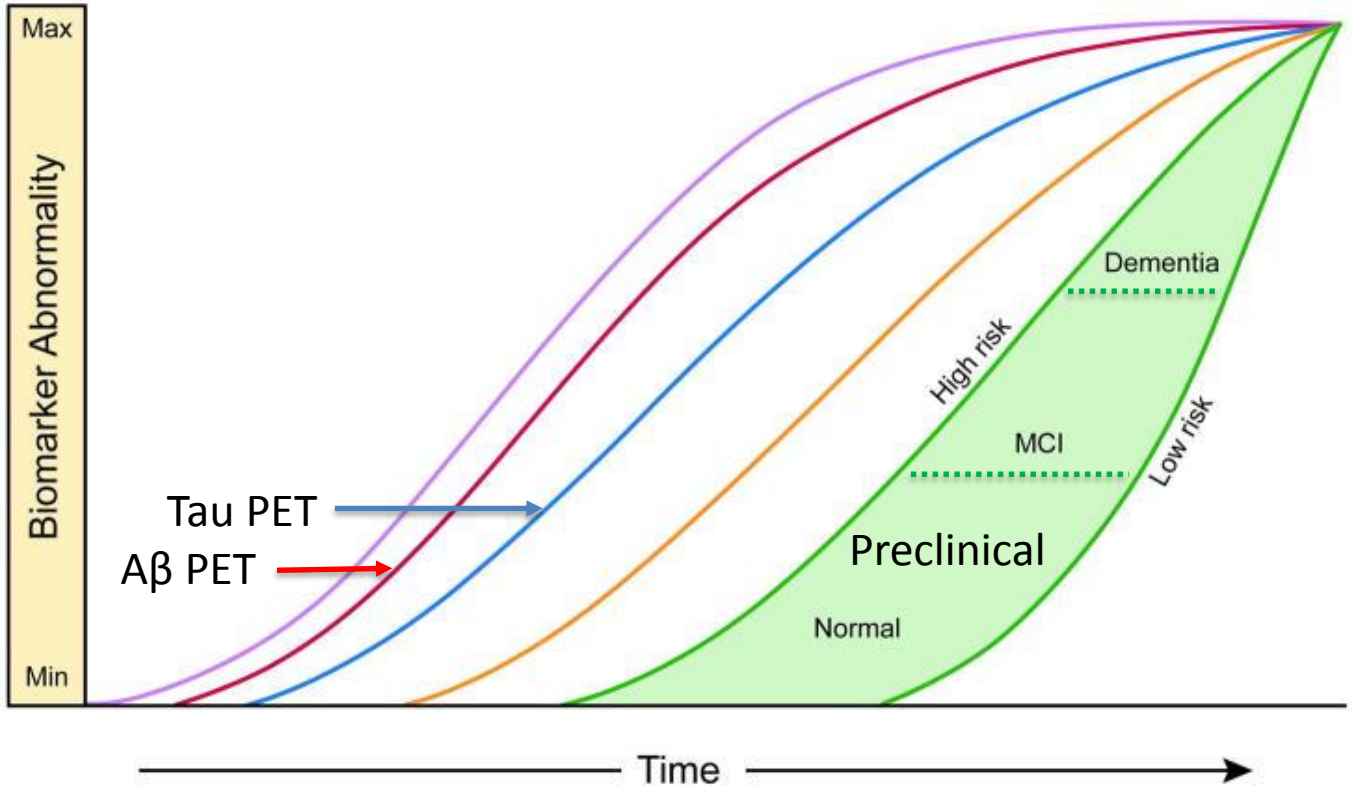
- Clinical challenge: how to differentiate NPS due to preclinical or prodromal AD from other pathologies, primary psychiatric “symptoms” or “false alarms” ?



- A first step in this process is to define associations of specific neuropsychiatric symptoms with AD biomarkers to reveal “phenotypic” changes across AD stages.

Preclinical Alzheimer's Disease

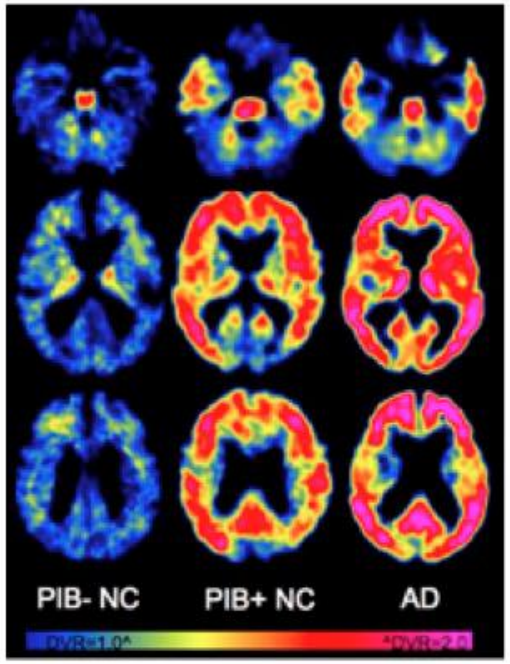
- Is a disease stage that transpires for more than a decade before the onset of mild cognitive impairment
  - initially defined by the accumulation of brain amyloid-β (Aβ)

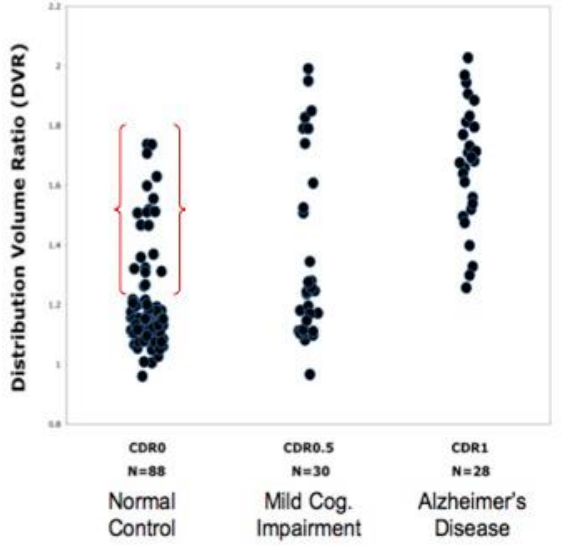


adapted from Jack 2013 Lancet Neurology 12(2): 207–216

Preclinical Alzheimer's Disease

- We use Pittsburgh Compound-B (PiB) PET ligand to measure Aβ
  - this provides a continuous measure of PiB/Aβ burden
  - we can also classify older adults as PiB+ or PiB-/ high or low Aβ burden





Sperling R, Johnson K *NeuroMolecular Medicine* 2010

Depression-related symptoms as possible phenotypic markers of preclinical AD

- Recent studies have begun to investigate the association of depressive symptoms with CSF and neuroimaging biomarkers of AD in non-impaired samples.
- In our own prior work, we found no cross-sectional association of Aβ measured by PiB-PET and subclinical depressive symptoms in CN elderly. (Donovan 2015)
- We have found weak cross-sectional associations of these depressive symptoms with neurodegeneration markers in this sample. (Donovan 2015, Gatchel 2017)

Other cross-sectional studies of depressive symptoms and Aβ in cognitively normal older people

- From AIBL and Washington University ADRC: no cross-sectional associations of high Aβ (PET) and greater depressive symptoms (Geriatric Depression Scale) in cognitively normal older samples. (Harrington 2016; Babulal 2016)
- However, greater depression scores (Hamilton Depression Rating) were associated with abnormal [CSF Aβ 1-42], as observed in AD, in other cross-sectional analyses (Pomara 2012)
- Certain specific neuropsychiatric symptoms such as anxiety (Hospital Anxiety and Depression Scale) and loneliness (UCLA loneliness scale) have been associated with higher Aβ (PET), especially in APOEε4 carriers (Holmes 2016, Donovan 2016)

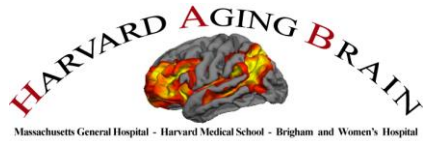
Objective

Aim 1: To examine the relationship of baseline Aβ with longitudinal depression, measured by the Geriatric Depression Scale, 30-item (GDS), in the Harvard Aging Brain Study cohort.

Aim 2: To examine the relationship of Aβ to 3 clusters of GDS items corresponding to symptoms of

- Apathy-Anhedonia
- Dysphoria
- Anxiety-Concentration Disturbance

Methods



- **Sample:** 270 CN older adults followed for up to 5 years (mean 3.8)
  - CDR global score 0, normal MMSE and Logical Memory performance.
- At screening, individuals with major psychiatric diagnoses were excluded except those with a history of remitted mild depression and anxiety were allowed .
  - All scored below GDS cut-off for mild depression at screening.
- **Cortical Aβ** was assessed using PiB-PET.
  - a **continuous aggregate measure of PIB DVR** was used in these analyses.

Depression outcome measures

- **Depression:** 30-item **Geriatric Depression Scale (GDS)** total score measured annually.
- **GDS Cluster Scores: Apathy-Anhedonia Cluster, Dysphoria Cluster, Anxiety-Concentration Disturbance Cluster**
  - we calculated a mean score for items pertaining to each of these 3 clusters.
  - Assignment of GDS items to one of these three clusters was based on principal component analyses of baseline HABS data as previously published (Donovan, 2015)

Statistical Analyses

In these mixed effects models with backward elimination

The pool of predictors included:

PiB

clinical: age, sex, Hollingshead, AMNART

APOEε4

depression history

the interaction of each variable with time (years in study).

Depression (GDS)
or
Depression Clusters

- the retention threshold was $p<0.05$

Baseline demographic and clinical data

Donovan et al., American Journal of Psychiatry, in press

Unadjusted Tests of Association

Donovan et al., American Journal of Psychiatry, in press

Higher PiB predicted steeper rates of increase in GDS total scores

Donovan et al., American Journal of Psychiatry, in press

Higher PiB predicted steeper rates of increase in Anxiety-Concentration Disturbance Scores but not other cluster scores

Donovan et al., American Journal of Psychiatry, in press

In a post-hoc model estimating Anxiety cluster scores without concentration disturbance items the PiB-time relationship remained significant

.

Donovan et al., American Journal of Psychiatry, in press

Conclusions

- In preclinical AD, Aβ may be more closely associated with anxiety than other depressive symptoms (as captured by the GDS).
- Depression history was associated with higher PiB at baseline but not with worsening depressive symptoms.
- Aβ as measured by PiB-PET, accounted for a small percent of the variance for anxious-depressive scores over time.

Questions:

- Was this association diminished by antidepressant medication use?
- Are other unmeasured variables, such as tau accumulation more directly and strongly associated with rising neuropsychiatric symptoms in early AD?

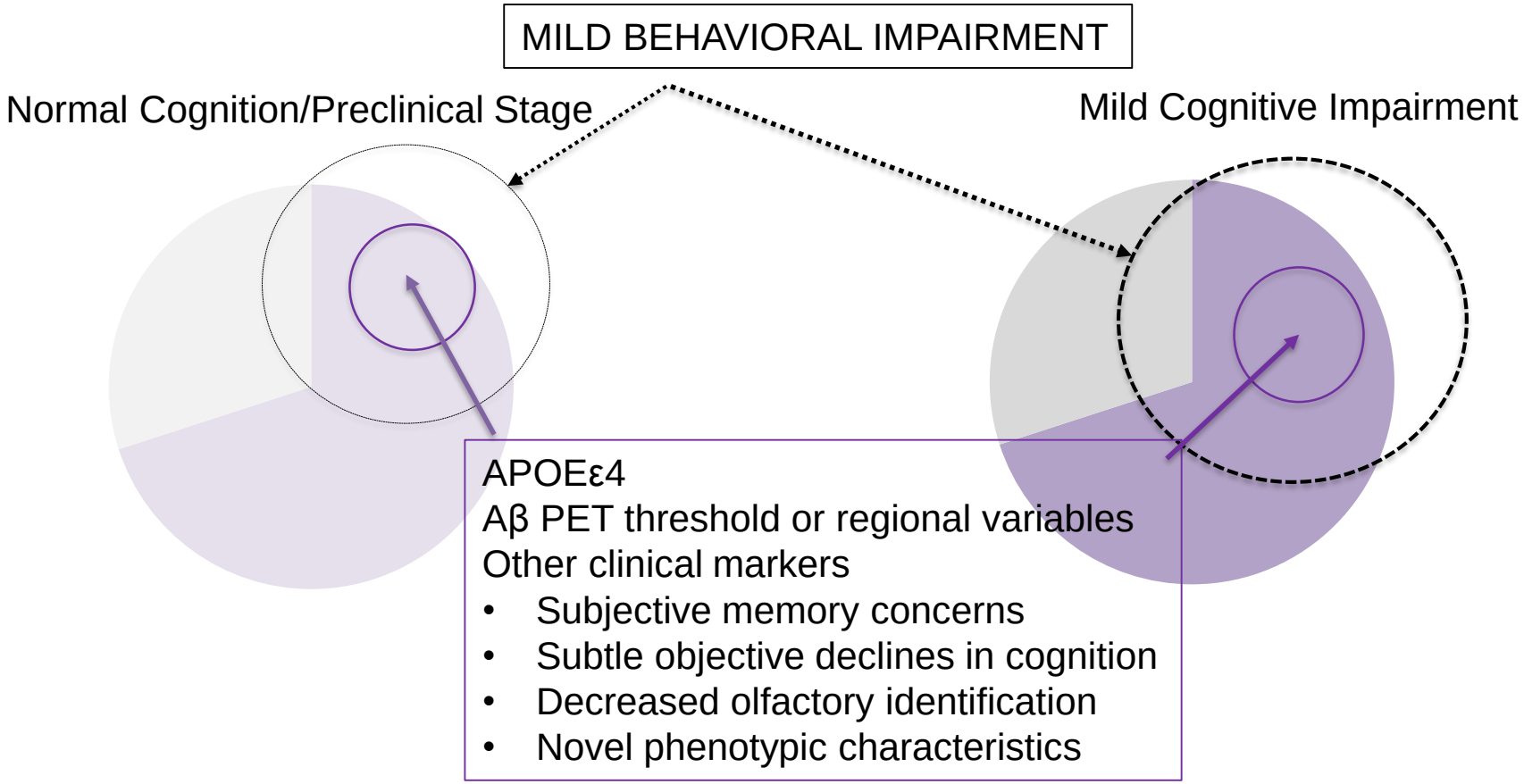
Clinical implications

- Formal anxiety disorders are present in 15% of older adults but 32% of non-depressed, community-dwelling older adults report anxiety symptoms (Braam 2014)
- Burke and colleagues (2016) studied >12,000 cognitively normal older adults for a mean follow-up of 4 years
  - **Anxiety** – **2X** more likely to progress **to MCI**; **3X to AD dementia**
  - **Anxiety** in **APOEε4** carriers - **2.7X to MCI** and **8.5X to AD dementia**
  - **Among APOEε4** carriers with anxiety, use of anxiolytic medications appeared to reduce or neutralize the risk of progression to MCI and AD dementia (more favorable effect- Venlafaxine, unfavorable effect- Clonazepam)

- If anxiety symptoms are related to early AD progression
  - It may be important to recognize and treat these symptoms with AD-directed therapies and/or with selective anxiety-specific treatments.

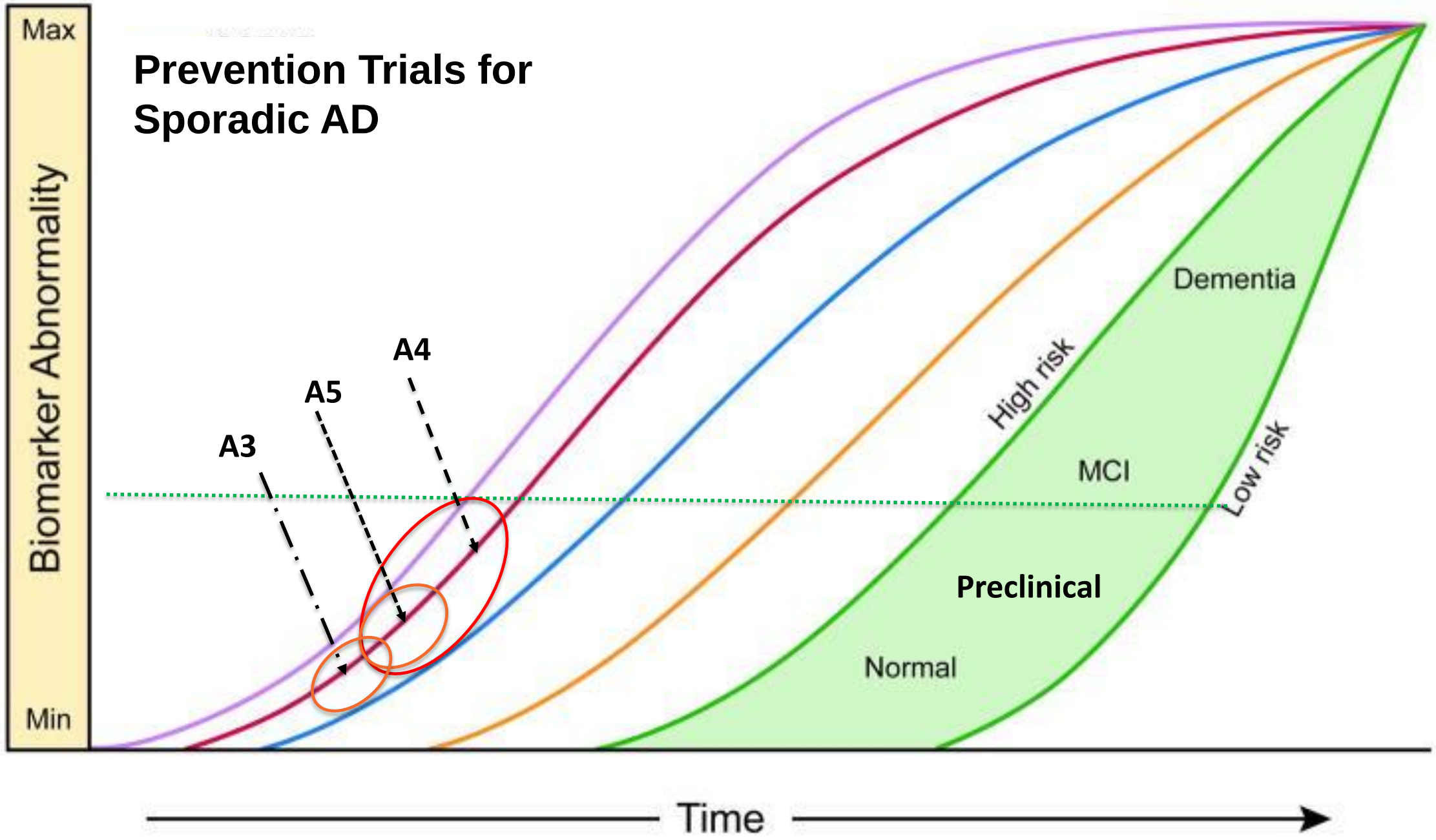
Early Detection of AD in cognitively normal individuals

- NPS, such as anxiety, may be most useful as prognostic markers in individuals with other biological risk factors or sentinels of decline



AD Secondary Prevention Trials

- Dominantly Inherited Alzheimer Network (DIAN)
  - PS-1, PS-2, APP – Solanezumab, Gantanerumab, BACEi
- Alzheimer Prevention Initiative (API)
  - PS-1 Colombian kindred – Crenezumab
  - APOE 4/4 – Active Vaccine, BACEi
- TOMMorrow Trial – TOMM40- Pioglitazone
- Anti-Amyloid Treatment in Asymptomatic AD (A4)
  - A4 – Ab+ normal 65-85yo– Solanezumab
  - EARLY (“A5”) Ab+ normal 60-85yo–BACE inhibitor
  - A3 – Getting closer to primary prevention - >Age 50


Prevention Trials for Sporadic AD
Max
Biomarker Abnormality
Min
A3
A5
A4
High risk
Low risk
Dementia
MCI
Preclinical
Normal
Time

CONCLUSIONS

- Recognition of phenotypic neuropsychiatric changes may enhance the identification of CN older individuals at high risk of progression to MCI and AD dementia.
- NPS are most likely to be important “preclinical” or “prodromal markers” in subgroups, such as APOEε4 carriers, or individuals with other stigmata of early decline.
- Treatment of NPS at the preclinical stage could have disease modifying effects.

Acknowledgements

Co-Investigators

Reisa A. Sperling, MD
Keith Johnson, MD
Dorene M. Rentz, PsyD
Gad Marshall, MD
Rebecca Amariglio, PhD
Kathryn Papp, PhD
Bernard Hanseeuw, MD
Jennifer Gatchel, MD, PhD
Patrizia Vannini, PhD
Heidi Jacobs, PhD
Trey Hedden, PhD
Jasmeer Chhatwal, MD
Jonathan Jackson, PhD
Elizabeth Mormino, PhD
Yakeel Quiroz, PhD
John Alex Becker, PhD
Jennifer Rabin, PhD
Rodrigo Perea, PhD
Aaron P. Schultz, PhD
Jorge Sepulcre, PhD

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- Emily Kilpatrick
- Molly Lapoint
- Kathryn Paige Sparks
- Irina Orlovsky
- Molly LaPoint
- Martha Muniz
- Olivia Hampton
- Lyssa Manning

HARVARD AGING BRAIN
Massachusetts General Hospital - Harvard Medical School - Brigham and Women's Hospital

Thank you to the participants in the Harvard Aging Brain Study, and their families.