Psychiatric disorders vs. early neuropsychiatric symptoms of a neurodegenerative disease: What's a clinician to do?

University of Washington Medicine Project ECHO (**E**xtension for **C**ommunity **H**ealthcare **O**utcomes) Dementia

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- Salary support from NIH/NIA; Mass General Hospital, Rappaport Foundation
- Consultant for Eisai

Learning objectives:

1. To review the spectrum of neuropsychiatric symptoms in neurocognitive disorders.

2. To learn the definition of mild behavioral impairment (MBI) in neurocognitive disorders.

3. To evaluate the relationship of neuropsychiatric symptoms to multimodal biomarkers of Alzheimer's disease and related dementias

4. To understand how neuropsychiatric symptoms and MBI relate to updated Alzheimer's Disease Staging Criteria

5. To review challenges and approaches to recognition of early neurobehavioral syndromes

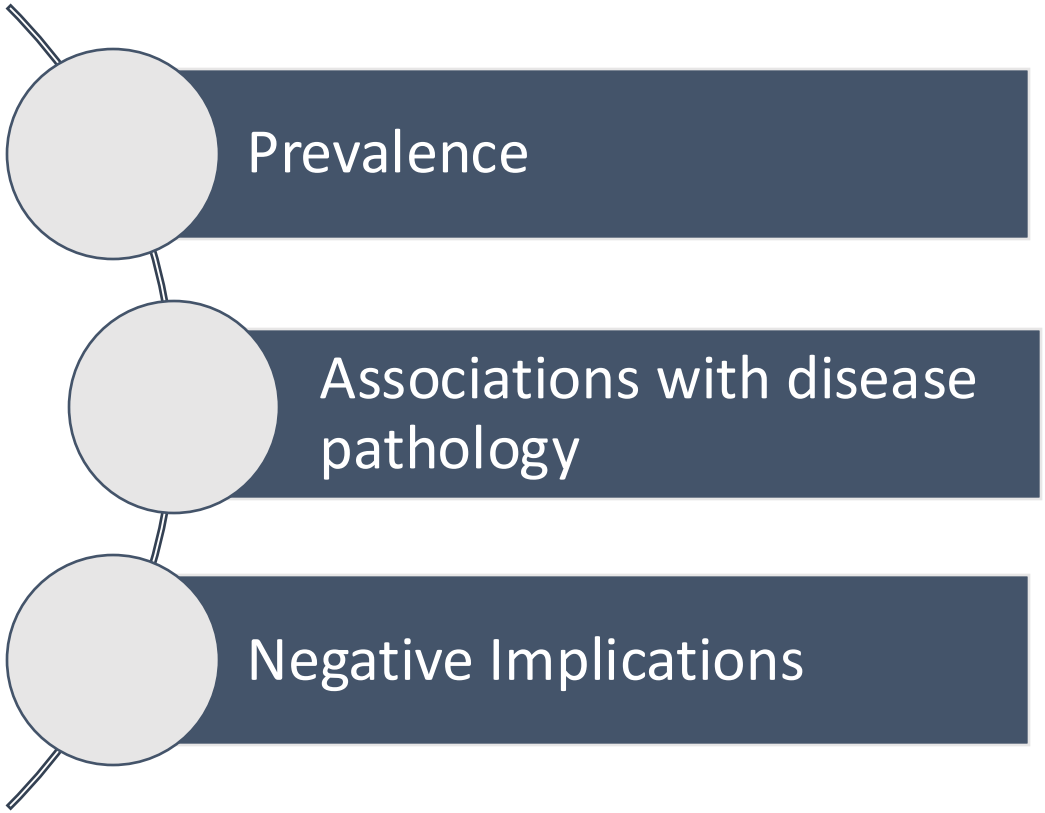
Neuropsychiatric Symptoms: multi-dimensional, ranging from mild to severe, across the dementia clinical spectrum

Symptoms	
Delusions	Apathy
Hallucinations	Disinhibition
Agitation	Irritability
Depression	Sleep
Elation	Appetite changes
Anxiety	Aberrant motor behavior
Loss of empathy	Obsessions/compulsions

Scales

- Geriatric Depression Scale
- Apathy Evaluation Scale
- Hospital Depression and Anxiety Scale
- Cohen Mansfield Agitation Inventory
- Beck's Depression Inventory
- Beck's Anxiety Inventory
- Neuropsychiatric Inventory

Neuropsychiatric Symptoms have Widespread Impact



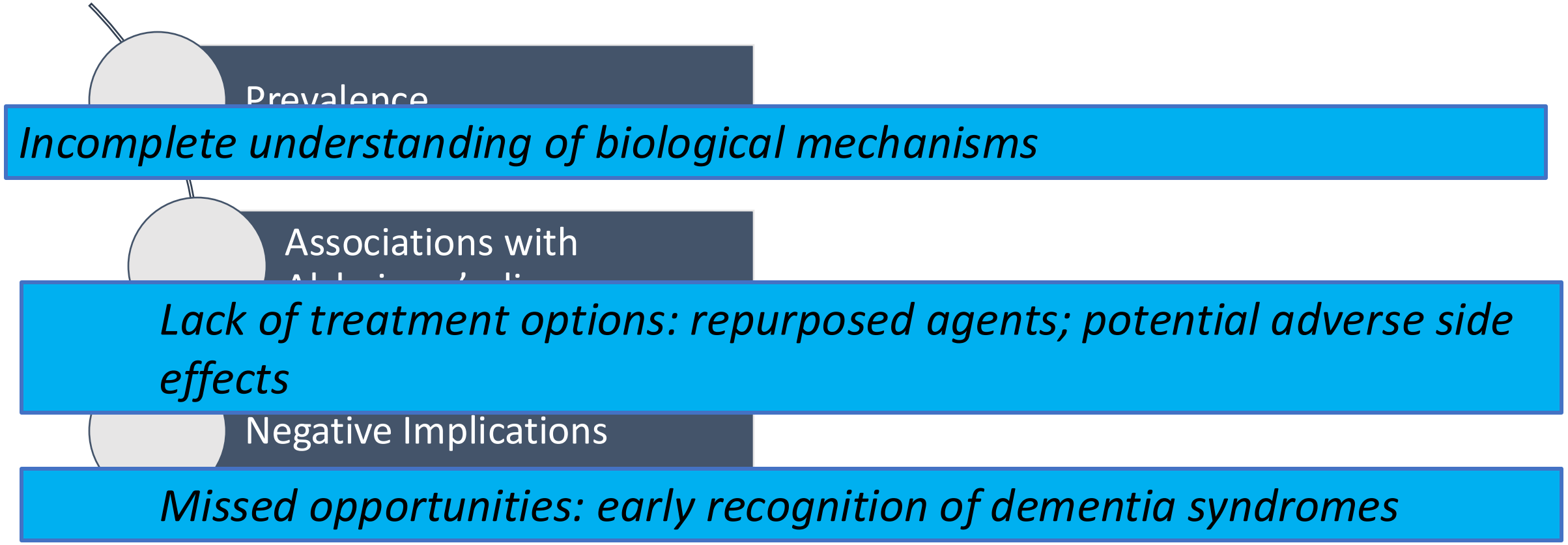
Cognitively normal
Mild Cognitive Impairment
Dementia

AB, tau, phospho-tau, NfL, other disease markers

↓ decline in IADL/ADL
↓ quality of life
↑ disease progression; mortality
↑ care partner burden
↑ institutionalization
↑ burden on healthcare system

Adapted from ISTAART NPS PIA 2022 Year in Review

Neuropsychiatric Symptoms have Widespread Impact



Mild Behavioral Impairment

Emergence of NPS in late life (age 50 or later); persistence for 6 months or longer
(normal cognition, subjective cognitive impairment, mild cognitive impairment)

MBI domains	Scales
• Decreased motivation • Emotional dysregulation • Impulse dyscontrol • Social inappropriateness • Psychosis	• MBI checklist (MBI-C) • Neuropsychiatric Inventory

Ismail Z,et al. J Alzheimers Dis. 2017

MBI: early clinical manifestation related to disease pathology

- Johansson et al. 2022, *Biol Psychiatry*
- Johansson et al. 2021, *Translational Psychiatry*
- Johansson et al., 2020, *Neurobiology of Aging*

Sample: N=50 cognitively unimpaired Aβ+ from BioFINDER2

Biomarkers tau-PET in entorhinal cortex/hippocampus and cerebrospinal fluid (CSF) P-tau_{181}

- higher tau-PET signal + CSF P-tau_{181} levels: higher MBI-C scores
- MBI ~ tau association: independent of memory deficits

MBI may be an important early clinical manifestation related to tau pathology in preclinical AD

Study of NPS in relation to biomarkers: summary

- Preclinical and prodromal populations: NPS/MBI associated with:
  - Abeta 42, t-tau/Abeta 42 and p-tau (**CSF**)
  - p-tau-181, markers of AD, neurofilament light (NfL) (**plasma**)
- **Neuroimaging** markers (amyloid PET, regional tau-PET, atrophy)

- Depressive symptoms, apathy, anxiety: associated with AD pathology (Aβ + tau) + accelerated cognitive decline *(Gatchel et al. 2019; Johansson et al., 2020; Johansson et al. 2021; Donovan et al. 2018; Burling..Gatchel. 2024; Munro..Gatchel 2024)*

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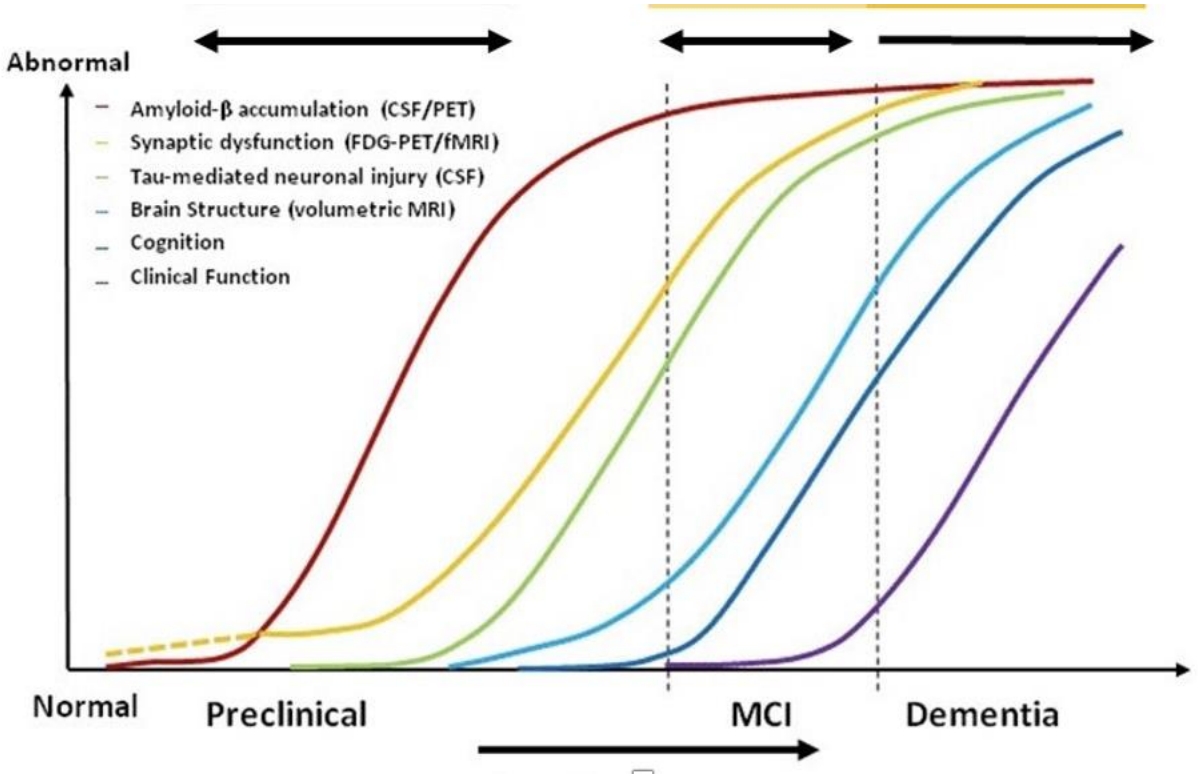
Revised Criteria for Diagnosis and Staging of Alzheimer's Disease

- 2011: The National Institute on Aging (NIA) and the Alzheimer's Association convened workgroups who published diagnostic guidelines in 2011 across the disease continuum (preclinical due to AD, mild cognitive impairment due to AD, dementia due to AD)



Sperling et al. 2011; Jack et al. 2018

Several core principles:

a. Alzheimer's disease (AD) is a continuum: appearance of brain pathology in asymptomatic individuals => increasing pathologic burden => progression of clinical symptoms.

b. Disease is diagnosed *in vivo* by abnormalities on core biomarkers.

AA AD Diagnostic Criteria Work Group, Oct 2023 draft version

2022 Revision and Workgroup:

- In early 2022, the Alzheimer's Association convened a steering committee (Dr. Clifford Jack): translation of 2011 diagnostic guidelines and 2018 research framework into the newly proposed diagnostic criteria.

- Work presented at Associations International Conference (AAIC) 2023; *"These new criteria do not constitute clinical practice guideline recommendations"*

AA AD Diagnostic Criteria Work Group, Oct 2023 draft version

Biological staging: Core 1 and Core 2 biomarkers

- Core I biomarker: required for diagnosis of AD
  - amyloid PET, CSF Ab42/40; CSF or plasma analytes: ptau181, 217, 231, CSF t-tau/Ab42; 'accurate' plasma assays

- Core 2 biomarker: not stand-alone tests for AD diagnosis; can be combined with Core I biomarkers to stage biological disease severity, likely risk of progression in asymptomatic individuals; inform on rate of progression in symptomatic individuals
  - tau PET, MBTR-423, pT205, non-phospho-tau

AA AD Diagnostic Criteria Work Group, 2023; 2024

ATN IVS

Table 1. Categorization of fluid analyte and imaging biomarkers

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau 217, p-tau 181, p-tau 231	
Core 2		
T_2 (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragments	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR or CT, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH
S α-synuclein	αSyn-SAA*	

Integrated with Clinical Staging:

- Stage 0: Asymptomatic, deterministic gene
- Stage 1: Asymptomatic, biomarker evidence only
- Stage 2: Transitional Cognitive Decline: Mild detectable change; but minimal impact on daily function
- Stage 3: Cognitive impairment with early functional impact
- Stage 4-6: Dementia with mild, moderate and severe functional impairment

Clinical Staging

- Stage 0: Asymptomatic, deterministic gene
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- Stage 2: Transitional Cognitive Decline: Mild detectable change; but minimal impact on daily function
  - Normal functioning on objective tests
  - **Decline from previous cognitive or neurobehavioral functioning; persistent change from baseline**
  - **Subjective cognitive decline**
  - **Recent change in mood, anxiety, motivation**
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Neuropsychiatric symptoms (NPS)

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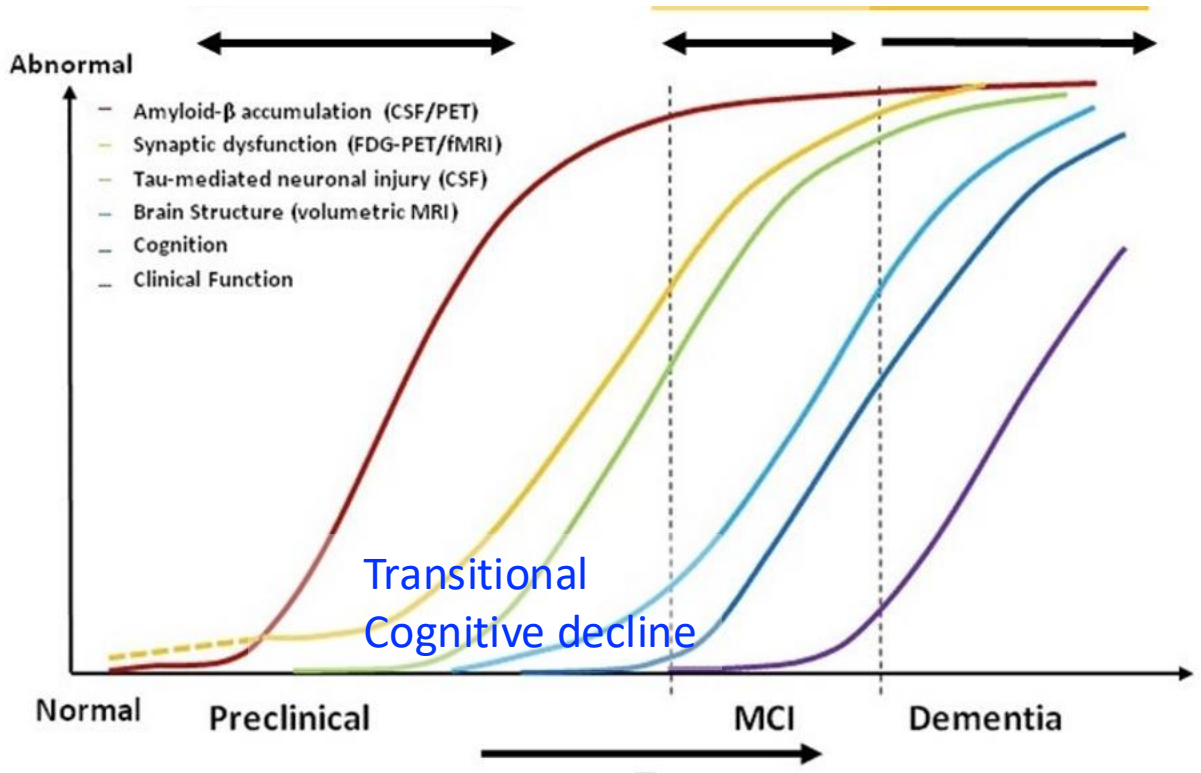

Stages 0-1 Stage 2 Stage 3 Stages 4-6

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But wait…

MBI/NPS, map onto symptoms that may be related to primary psychiatric disorders.

Mild behavioral impairment (MBI) checklist

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost the motivation to act on their obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3

Ismail et al.
J Alzheimers Dis 2017

Major depressive disorder (MDE) Diagnostic criteria (summarized from DSM-5-TR)

- 5 of 9 criteria
  - Depressed mood
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  - Weight loss (or gain)
  - Insomnia (or hypersomnia)
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  - Fatigue
  - Feeling worthless
  - Problems concentrating, thinking, or making decisions
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Bipolar depression in Older Adults:

- Disturbances in sleep, appetite and activity level
- Cognitive impairment
- Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy

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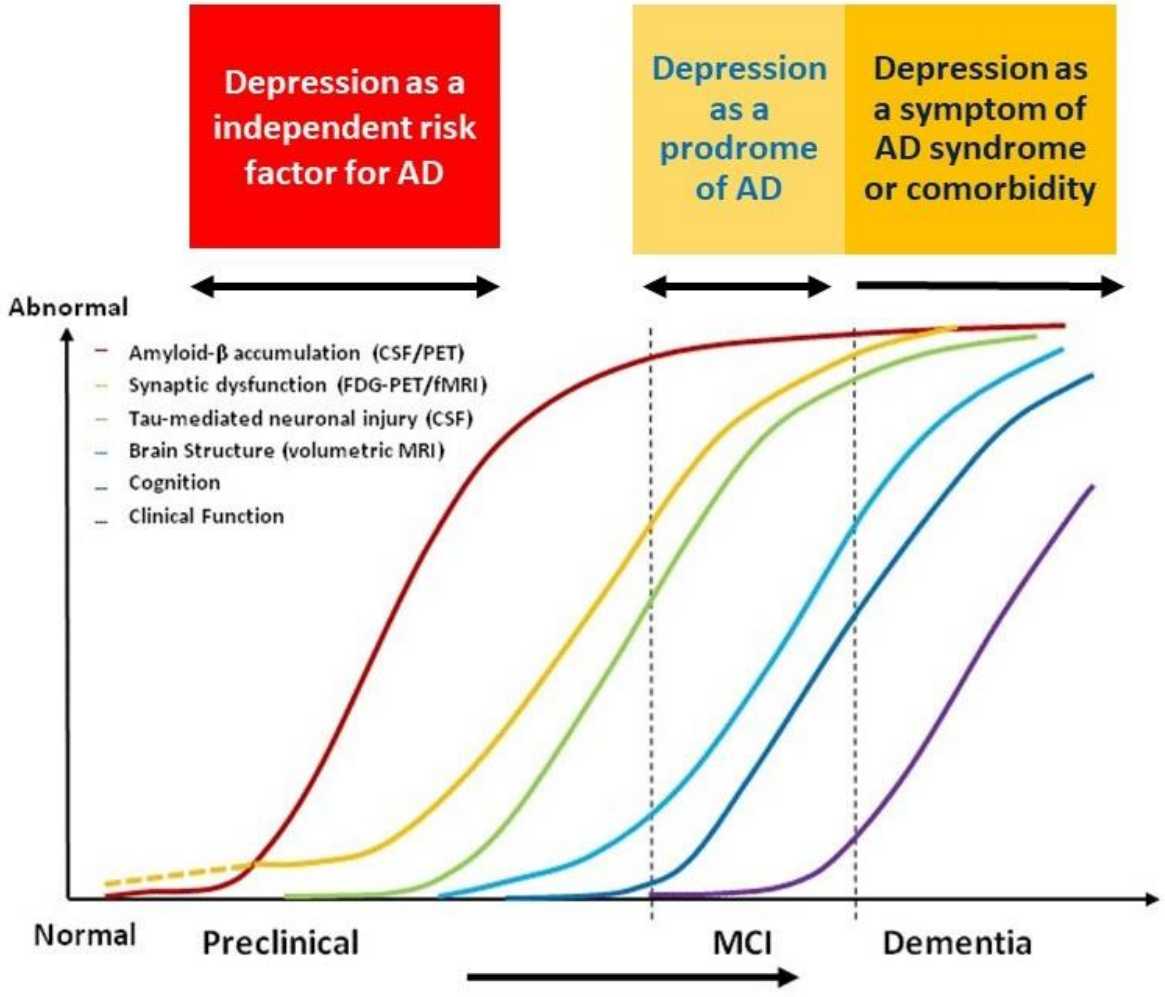
Important dichotomy?

Mood and Memory in Aging Study

Harvard Aging Brain Study

ADNI, NACC



Adapted from Jack et al. 2011

Clinical features: atypical presentations…

- **Newly emergent; <u>change from baseline</u>**
- Late age of onset; (anxiety, mania, OCD, psychosis outside of mood episode)
- Depression with marked apathy or anxious distress > tearfulness, anhedonia; cognitive concerns
- Obsessions that are non-ego-dystonic (not disturbing to the patient, as is typically observed in OCD); compulsions without obsessions
- Loss of empathy; emotional detachment, lack of distress
- Sustained manic state without grandiosity or euphoria
- Progressive cognitive dysfunction; progressive impairment
- Lack of treatment response; atypical response
- Any signs of motor neuron disease or parkinsonism on exam
- Family history of FTD or another dementia

False dichotomy…

- In some cases, psychiatric symptoms are more “typical”

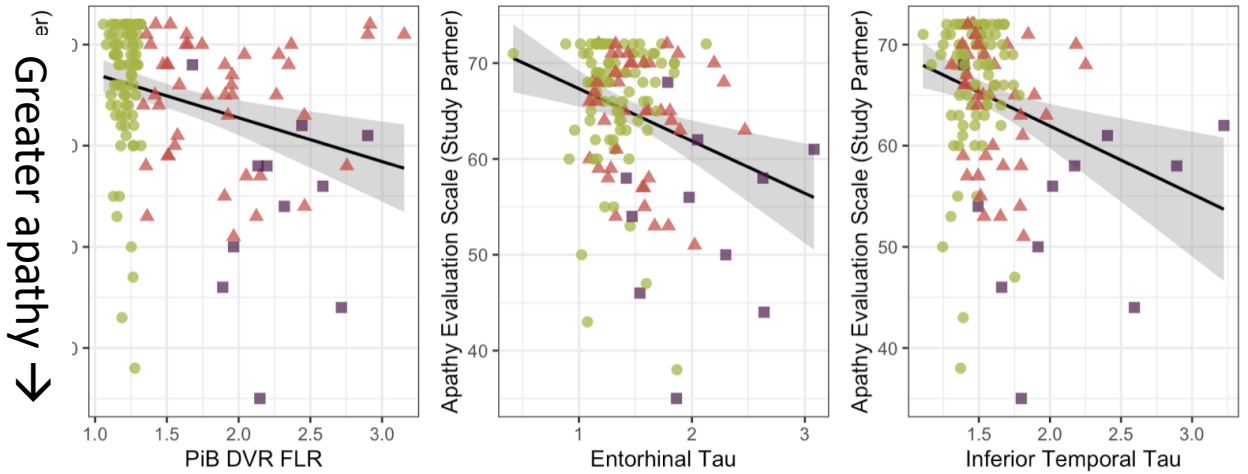
- Patients with neurodegenerative disease will present with syndromes that **do** meet ‘typical’ DSM-5-TR criteria for psychiatric disorders (co-morbidity or prodome); age of onset may be the only outlier
  - *C9orf72* mutations in FTD, most common presentations: bvFTD and ALS, prodromal psychiatric syndromes

Principles of Assessment

- History: medical and neuropsychiatric (informant(s)) report; onset and persistence
- Current medications, overt and covert substance use, vascular risk factors.
- Family history
- Physical and Neurological exam
- Clinical assessment: all sections of the standard medical and neuropsychiatric assessment; mental status exam
- Consideration of impaired insight (almost always present in bvFTD, but also in other dementia syndromes in preclinical/prodromal stages):
  - **a care-partner-based history is essential** +/- independent relative or friend (given potential bias in care-partner or relational tensions in the dyad)
  - **Cultural context**
  - **Objective assessments** of emotional-behavioral function (emotion recognition paradigms)

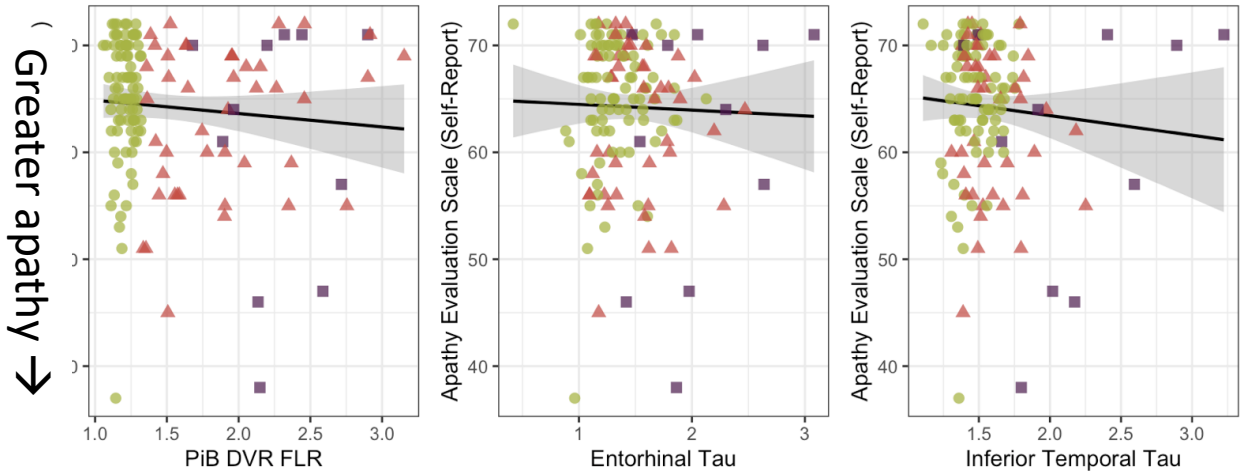
Harvard Aging Brain Study: Elevated Aβ, ER Tau and IT Tau associated with greater study-partner reported apathy

Study-partner-report



β = -3.6, p= 0.005 β = -3.9, p= 0.025 β = -4.9, p= 0.027

Self-report



Burling, Gatchel, AJGP 2024)

Characterizing Mild Behavioral Impairment and Its Relationship to Cognition in Community-dwelling older Latinos from the Boston Latino Aging Study (BLAST)

Jorge Alcina, PsyD[1], Diana Munera, BS[1], Alex L. Badillo Cabrera, BA[1], Nikole A. Bonillas Félix, BA[1], Lusiana Martinez, BA[1], Averi Giudicessi, MA[1], Elizabeth Kaplan, BS[1], Jairo E. Martinez, MA[1], Clara Vila-Castelar, PhD[1], Nadine Schwab, PhD[1], Liliana A. Ramirez-Gomez, MD[1], Marta Gonzalez Catalan, PhD[1], Daniel G. Saldana PhD[1], **Jennifer R. Gatchel, MD PhD**[1,2], **Yakeel T. Quiroz, PhD**[1]

[1] Multicultural Alzheimer's Prevention Program, Massachusetts General Hospital, Harvard Medical School
[2] McLean Hospital, Harvard Medical School

Important dichotomy?

NPS in late life: preclinical or prodromal stages of a dementia syndrome?

- manifestation of a neurodegenerative disease (NDD) (mechanisms may be shared or distinct from those underlying cognitive decline +/- psychological reaction superimposed on character traits) NDD

- primary psychiatric disorder (variable underlying neurobiology, predominantly non-neurodegenerative; risk for subsequent dementia syndrome ↓ "*neuropsychiatric reserve*") psychiatric

- Both phenomena (manifestation of NDD + primary psychiatric disorder comorbidity or prodrome)

  NDD + psychiatric

⇒ Implications for early detection, accurate diagnosis, management and prognosis (i.e. bvFTD vs. bipolar disorder or MDD); patient and care partner counselling; quality of life

Conclusions and avenues of future investigation in ADRD

- NPS: early clinical features of a NDD related to underlying disease pathology
  - Stages 0-6; transitional cognitive decline (clinical stage 2)
- Common differential diagnosis of MBI/NPS of a neurodegenerative disease vs. a primary psychiatric disorder
  - consider NDD, psychiatric or 'NDD + psychiatric' etiologies
- Atypical features, study partner(s) report, cultural context, objective assessments, NP measures
- Role of biomarkers (neuroimaging, genetic, fluid, multimodal)
- Do NPS travel with "core" AD pathology or have distinct neurobiology?
- **Formal NPS diagnostic criteria—apathy, psychosis; also needed for affective NPS**
- Longitudinal study design; well characterized samples; consensus NPS diagnostic criteria + biomarkers + clinical outcomes
- Treatment of NPS to prevent dementia or cognitive decline?

MOMENT, HABS, MAPP participants, study partners, and colleagues, —THANK YOU!

15 years ISTAART ALZHEIMER'S ASSOCIATION 2008-2023 Neurpsychiatric Syndromes PIA

alzheimer's association

NIH

NIH National Institute on Aging

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MGH Rappaport Fellowship (PI: Gatchel)
NIH/NIA R01 AG067021 (PI: Marshall)

NIMH SRI (CIMA)
NIMH ARI
Jovier Evans PhD
Laura Rowland PhD

Clinical Staging

Biological staging

Table 6. Integrated biological and clinical staging

	Stage 0	clinical Stage 1	clinical Stage 2	clinical Stage 3	clinical Stages 4-6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

AA AD Diagnostic Criteria Work Group, Oct 2023 draft version

Stage 2: Transitional cognitive decline

- Normal functioning on objective tests
- Decline from previous cognitive or neurobehavioral functioning; persistent change from baseline
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- MBI/NPS: early clinical features of a NDD related to underlying disease pathology
- Common: differential diagnosis of MBI/NPS of a neurodegenerative disease vs. a primary psychiatric disorder
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Important dichotomy?

NPS: symptom of dementia syndrome or comorbidity

- Manifestation of neurodegenerative disease (NDD) (mechanisms may be shared or distinct from those underlying cognitive decline); +/- comorbid psychiatric illness, superimposed on character traits => distinct symptom constellation

    - Clinical case: patient with probable AD dementia, no past psychiatric illness, develops apathy, anxiety, and paranoia: manifestations of neurodegenerative disease (NDD) superimposed on character traits (dependent + avoidant personality traits)

- Implications for management: response to conventional psychotropics or DMT (future directions: develop more targeted treatments for NPS in dementia syndrome)

- “Recommend biomarker tests only be performed under supervision of a clinician”
- **Clinically symptomatic individuals**: population in which biomarker testing would be medically actionable
- In absence of current treatments **for asymptomatic individuals**, do not advocate biomarker testing in this population at the current time
- “We do not advocate initiating treatments targeting core AD pathology in all symptomatic individuals with biomarker confirmed AD without regard to clinical context.”
- Treatment in symptomatic individuals: based on clinical assessment of risk/benefit ratio and made on an individual patient level

AA AD Diagnostic Criteria Work Group, Oct 2023 draft version

Why change, why now?

- In 2018: no disease targeted therapies had received regulatory approval

⇒"Progression of framework for research to criteria for diagnosis and staging that are intended for clinical use as well as research."

- Validated biomarkers in 2018 were based on either CSF assays or imaging

⇒Incorporation of plasma biomarkers into updated criteria

⇒Updated biomarker classification criteria to accommodate nonequivalence between fluid and imaging biomarkers

AA AD Diagnostic Criteria Work Group, 2024

But wait…

MBI/NPS, map onto symptoms that may be related to primary psychiatric disorders.

What's a clinician, to do?

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- Cognitive impairment
- Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Does the person lost the motivation to act on their obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3

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Consider underlying somatic illness or medication (example: late onset mania)

- Neurologic
  - Dementia
  - Traumatic Head injury
  - CNS tumor
  - Multiple sclerosis
  - CVA
  - Epilepsy
  - Huntington's; Wilson's disease
- Sleep apnea
- Vitamin B12/niacin deficiency
- Endocrine
  - Hypo- or hyperthyroidism
  - Hypercortisolemia
- Infectious
  - HIV encephalopathy
  - Neurosyphilis
  - Lyme disease
  - Viral encephalitis
- Toxic
  - Substances
  - Medications

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- Consider neuropsychological testing
- Laboratory evaluation:
  - CMP, Creatinine, GFR, CBC
  - TSH; free T3/T4 if TSH abnormal; liver function tests
  - Urinalysis and Urine drug screen
  - B12, folic acid
  - Serum blood levels of current medications
  - Infectious serologies if indicated
- MRI or CT consider functional imaging or EEG