ADRC Spring Meeting, Clinical Core session

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

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Outline

- I. Late life neuropsychiatric symptoms and mild behavioral impairment

- II. Clinical overlap with primary psychiatric disorders

- III. Neuropsychiatric features of a neurodegenerative disease (emerging, related to underlying degenerative disease) vs. pre-existing or co-morbid psychiatric disorder
  - Principles of Assessment
  - Emerging Biomarkers

- IV. Future Directions

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

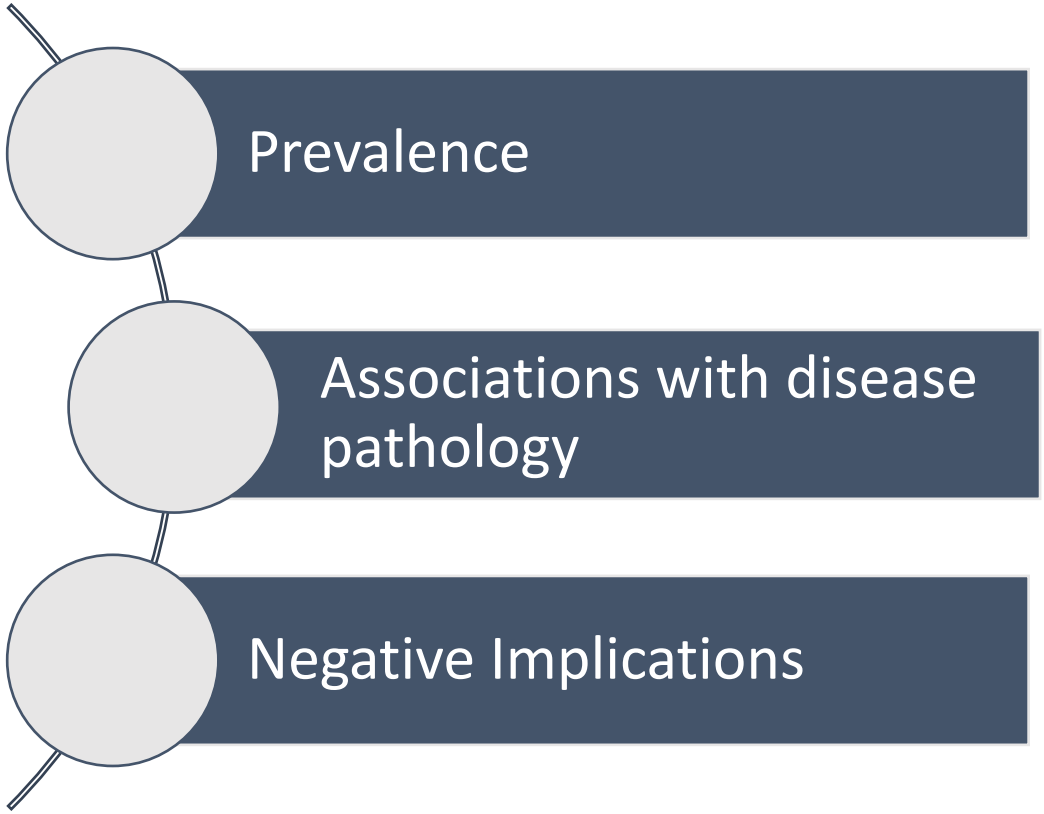
Symptoms	
Delusions	Apathy
Hallucinations	Disinhibition
Agitation	Irritability
Depression	Sleep
Elation	Appetite changes
Anxiety	Aberrant motor behavior
Loss of empathy	Obsessions/compulsions

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

Adapted from ISTAART NPS PIA 2022 Year in Review

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

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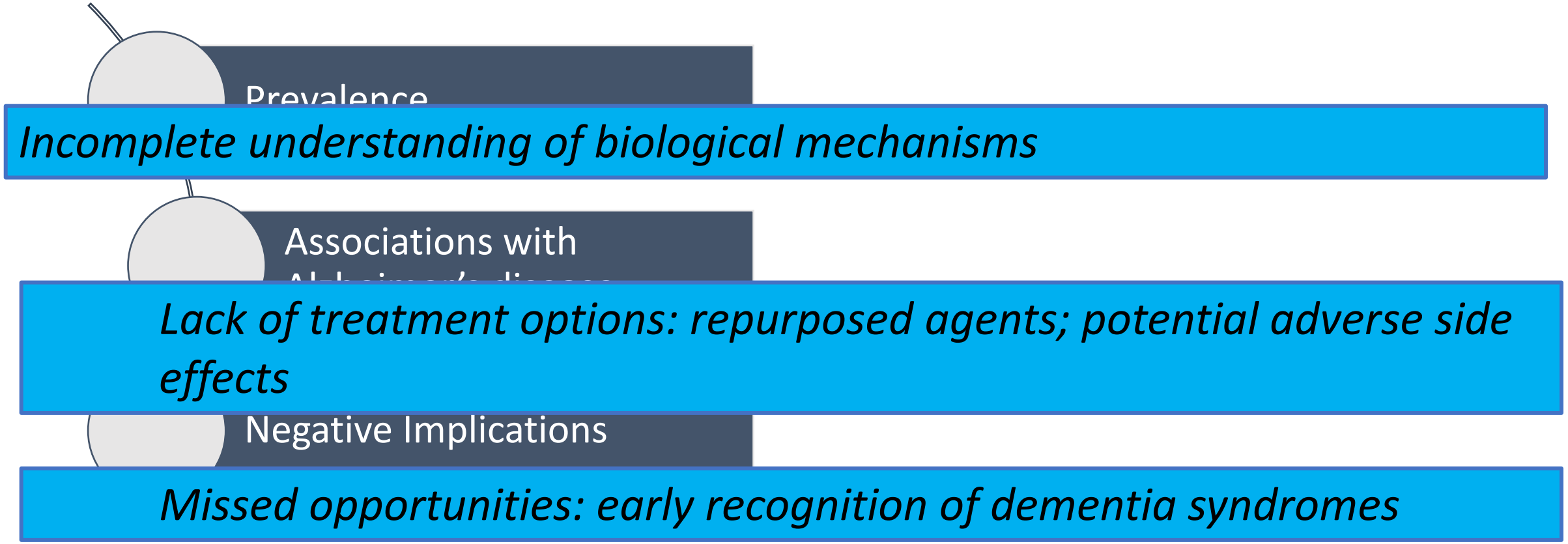

Mild Behavioral Impairment

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

- Decreased motivation
- Emotional dysregulation
- Impulse dyscontrol
- Social inappropriateness
- Psychosis

Scales

- MBI checklist (MBI-C)
- Neuropsychiatric Inventory

Adapted from ISTAART NPS PIA 2022 Year in Review

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 ([^{18}F]RO948 retention 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 multimodal biomarkers of NPS/MBI: Take home points

- 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; Gatchel et al. unpublished data)*

But wait...

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

What's a clinician, or a clinical core, to do?

	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
  - Anhedonia (loss of pleasure)
  - Weight loss (or gain)
  - Insomnia (or hypersomnia)
  - Psychomotor agitation or retardation
  - Fatigue
  - Feeling worthless
  - Problems concentrating, thinking, or making decisions
  - Suicidal ideation

- Symptoms present most of the day, nearly every day, for ≥ 2 weeks
- Symptoms cause functional impairment (change in activities)
- Not better explained by medications, medical illness or bereavement

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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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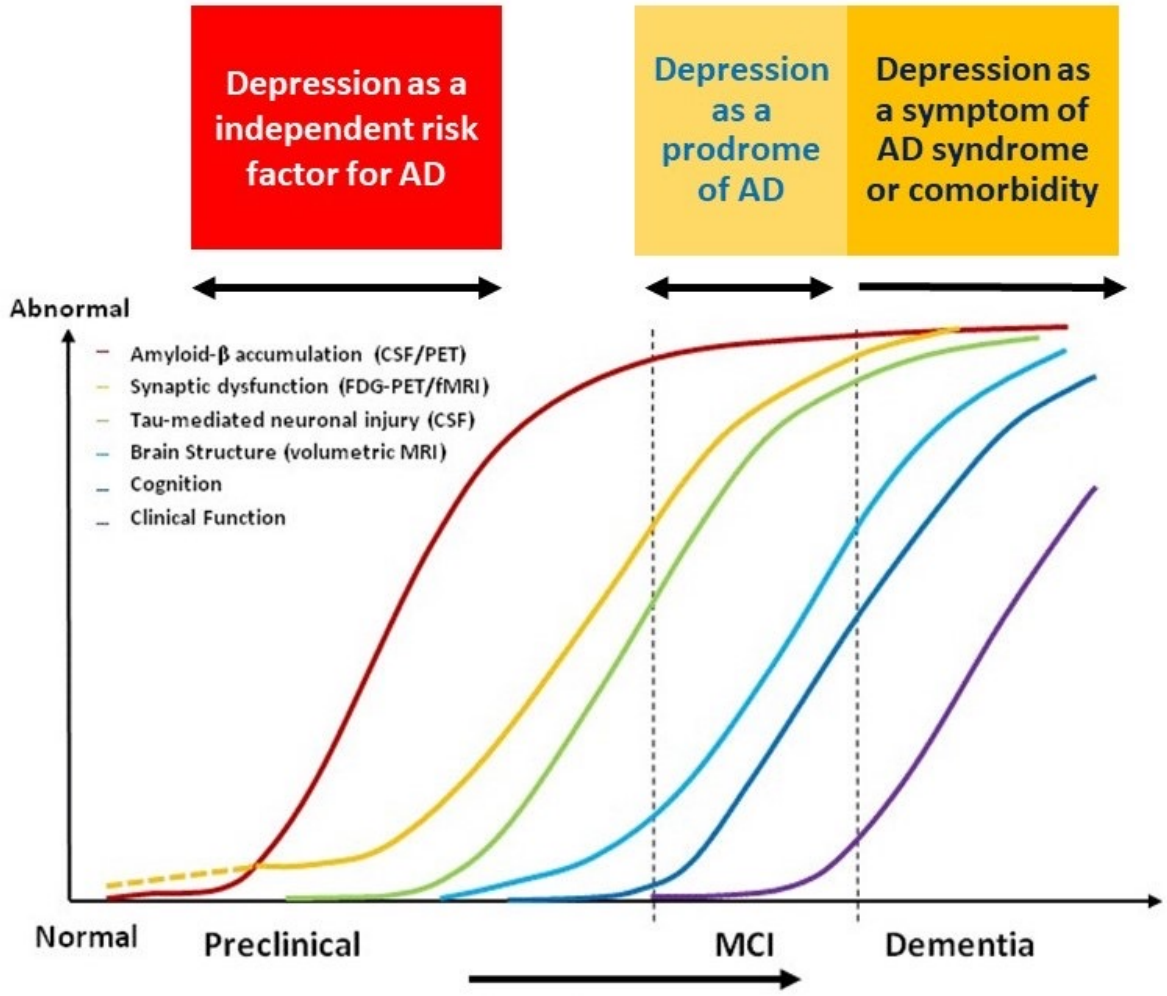
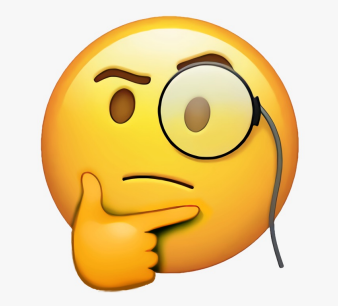
- Frontotemporal dementia (FTD): changes in socioemotional behavior
- bvFTD: clinical symptom overlap with major depressive disorder, bipolar disorder, schizophrenia, obsessive -compulsive disorder, autism spectrum disorders and personality disorders.

- NPS in ADRD may resemble major depressive disorder, generalized anxiety disorder, panic disorder, bipolar disorder, schizophrenia

Important dichotomy?



Adapted from Jack et al. 2011



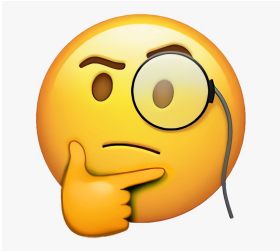
Important dichotomy?

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)



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

Clinical features: atypical presentations

- Obsessions that are non-ego-dystonic (not disturbing to the patient, as is typically observed in OCD); compulsions without obsessions
- Depression with marked apathy or anxious distress; lack of anhedonia

Clinical features: atypical presentations…

- **Newly emergent; change from baseline**
- Late age of onset; (anxiety, mania, OCD, psychosis outside of mood episode)
- loss of empathy; emotional detachment, lack of distress
- Sustained manic state without grandiosity or euphoria; absence of depressive symptoms
- Schizophrenia without complex delusions or hallucinations
- Progressive cognitive dysfunction; progressive impairment
- Lack of treatment response
- Any signs of motor neuron disease or parkinsonism on exam
- Family history of FTD or another dementia; strong family history of psychiatric disease, and/or neurodegenerative disease in a patient whose symptoms develop later in life

False dichotomy…

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

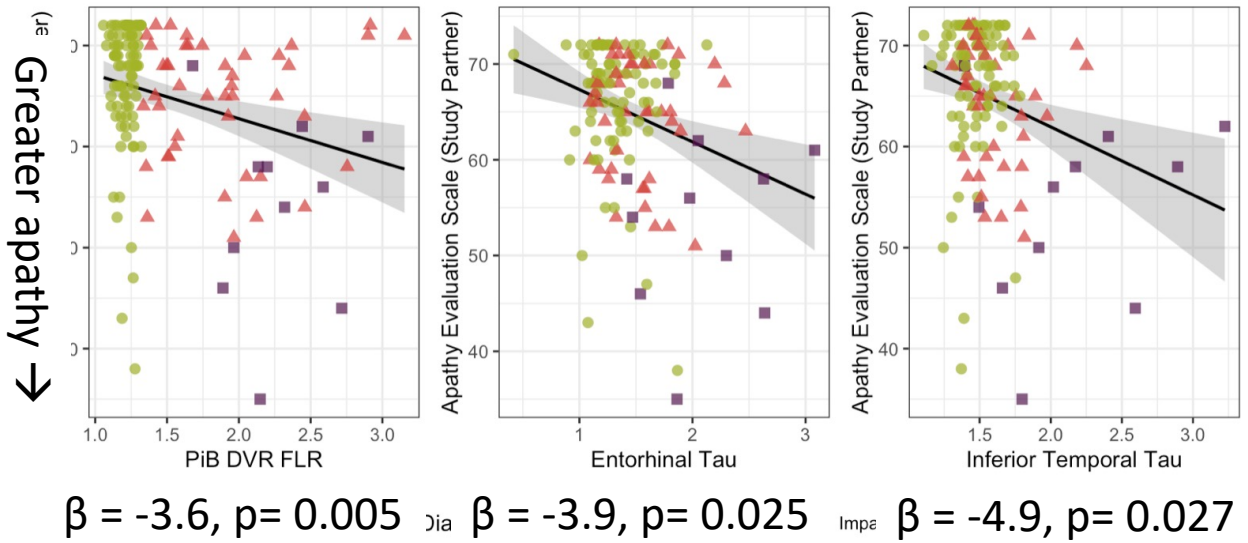
- Patients with neurodegenerative disease will present with syndromes that **do** meet ‘typical’ DSM-5-TR criteria for psychiatric disorders (co-morbidity or prodome); age of onset may be the only outlier
  - *C9orf72* mutations in FTD, most common presentations: bvFTD and ALS, prodromal psychiatric 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 (in FTD--what constitutes a positive family history; Goldman score)
- 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)
  - **Objective assessments** of emotional-behavioral function (emotion recognition paradigms)

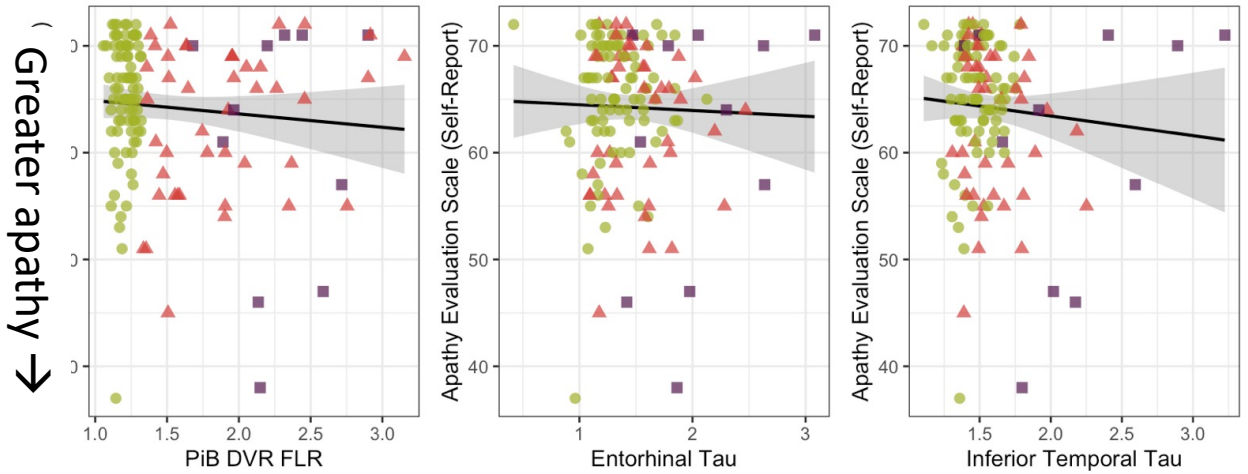
Harvard Aging Brain Study: Elevated Aβ, ER Tau and IT Tau associated with greater study-partner reported apathy

Study-partner-report



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

Self-report



Gatchel et al. unpublished data)

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

Principles of assessment…

- Neuroimaging : standard in neurodegenerative disease assessment, no clear guidelines in psychiatric patients—routine imaging not part of standard work-up
  - Atypical features
  - provide clinical details to the radiologist; neurology +neuroradiological consultation
    - Quantification of structure and function
- Genetic analysis?
  - Screening all psychiatric patients for FTLD-related mutations—not practical
    - Autosomal dominant pattern of inheritance; genetic testing for *C9orf72* if at least one first degree relative with FTD, ALS or other early onset neurodegenerative disease

Consensus recommendations?

The Neuropsychiatric International Consortium for Frontotemporal Dementia: consensus recommendations to distinguish behavioral variant frontotemporal dementia from psychiatric disorders (Ducharme et al. *BRAIN* 2020)

- Clinical assessment: full neuropsychological battery + at least one formal social cognition test
- 3D-T1 brain MRI with standardized review: validated visual atrophy rating scales, volumetric analyses
- 18F-fluorodeoxyglucose PET for the exclusion of bvFTD when normal; “non-specific regional metabolism abnormalities should not be over-interpreted”
- potential role of CSF or plasma neurofilament light chain to differentiate bvFTD
- Screening for *C9orf72* mutation: in all possible/probable bvFTD cases or suspected cases with strong psychiatric features; if at least one first degree relative with FTD, ALS or other early onset neurodegenerative disease

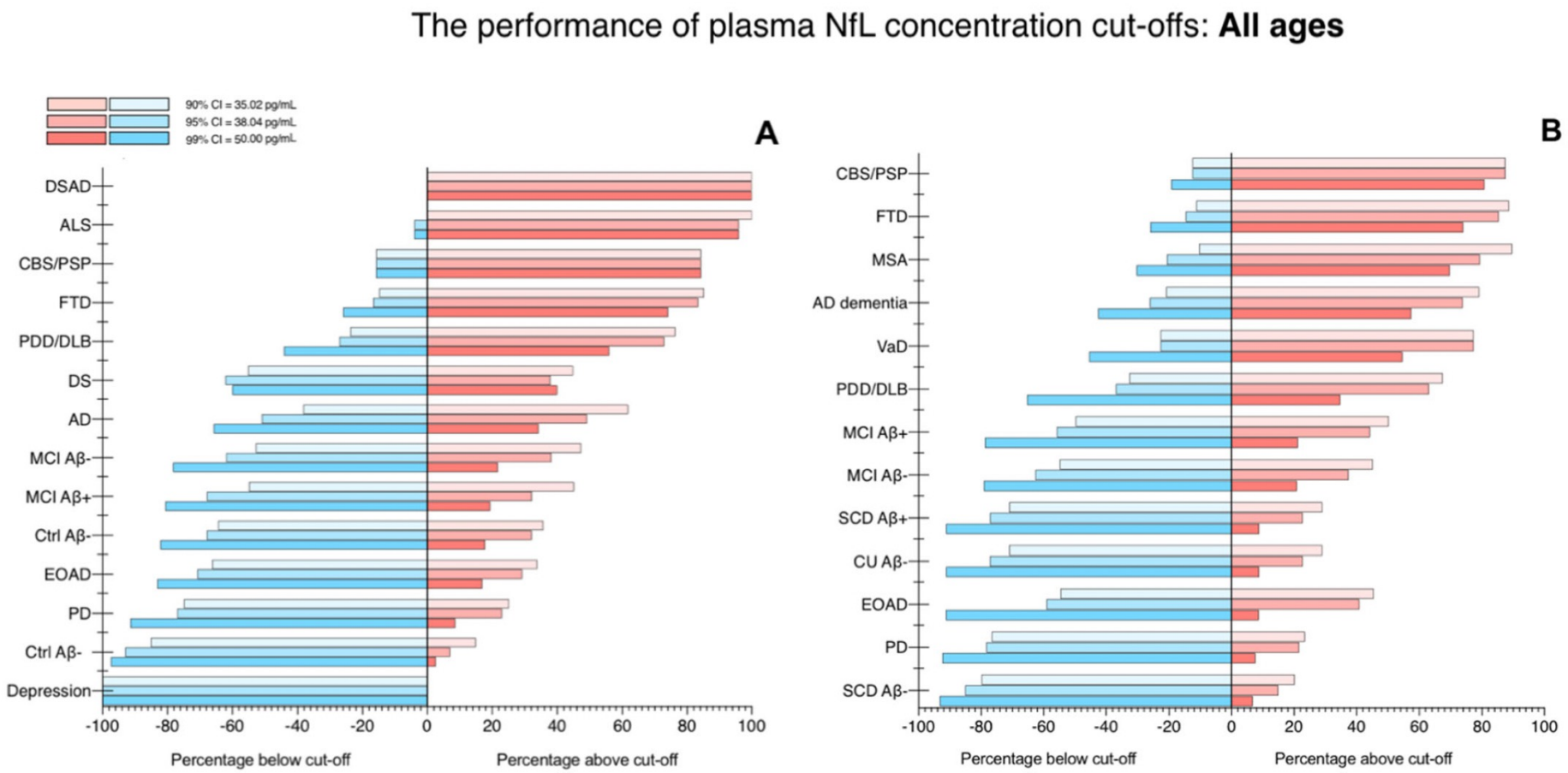
Role of biomarkers

- For AD: CSF amyloid-β (Aβ42), total tau (T-tau), phosphorylated tau (p-tau); amyloid and tau PET imaging
- plasma Aβ42/Aβ40 and p-tau immunoassays: high specificity for AD.

But… no similar biomarkers for other common or rarer neurodegenerative disorders

- CSF analysis: exclude Alzheimer's disease pathology; isolated increase of CSF tau without CSF amyloid-b42: favor a bvFTD diagnosis
- Plasma NfL: high correlation with CSF NfL
- Increasing evidence—serum NfL may differentiate bvFTD from primary psychiatric disorders (Katisko K. et al. *J Neurology* 2020; Al Shweiki et al. *J. Psychiatric Research* 2019).

Role of Biomarkers



Ashton et al. NATURE COMMUNICATIONS (2021)

Conclusions and future investigation of NPS in ADRD

- MBI/NPS: early clinical features of a NDD related to underlying disease pathology
- Common: differential diagnosis: NPS of a neurodegenerative disease vs. a primary psychiatric disorder
  - NPS in dementia: symptom of NDD +/- psychiatric comorbidity + baseline
  - Preclinical or prodromal dementia: consider these etiologies: neurodegenerative disease (NDD); psychiatric or 'NDD + psychiatric'
  - Atypical features, study partner(s) report, objective assessments
  - Role of biomarkers (neuroimaging, genetic, fluid, multimodal)

Conclusions and future investigation of NPS in ADRD…

- Do NPS travel with “core” AD pathology or have distinct neurobiology
  - Measurement properties; subjective + objective assessments
- Formal NPS diagnostic criteria—apathy, psychosis; also needed for other NPS: depression, anxiety, irritability
- Longitudinal study design; well characterized samples; consensus NPS diagnostic criteria + biomarkers + clinical outcomes