



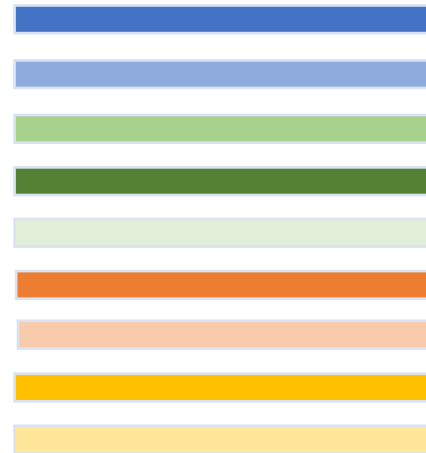
Disease-specific Neuropsychiatric Prodromes in Neurodegeneration

What do we know?

Howie Rosen
**Dorothy Kirsten French Endowed Professor for Parkinsonism
and Other Neurodegenerative Disorders**
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UCSF Department of Neurology

Different neurodegenerative disorders have different profiles of neuropsychiatric changes

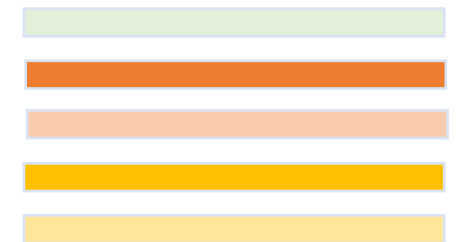
"All possible" neuropsychiatric symptoms



Disease A



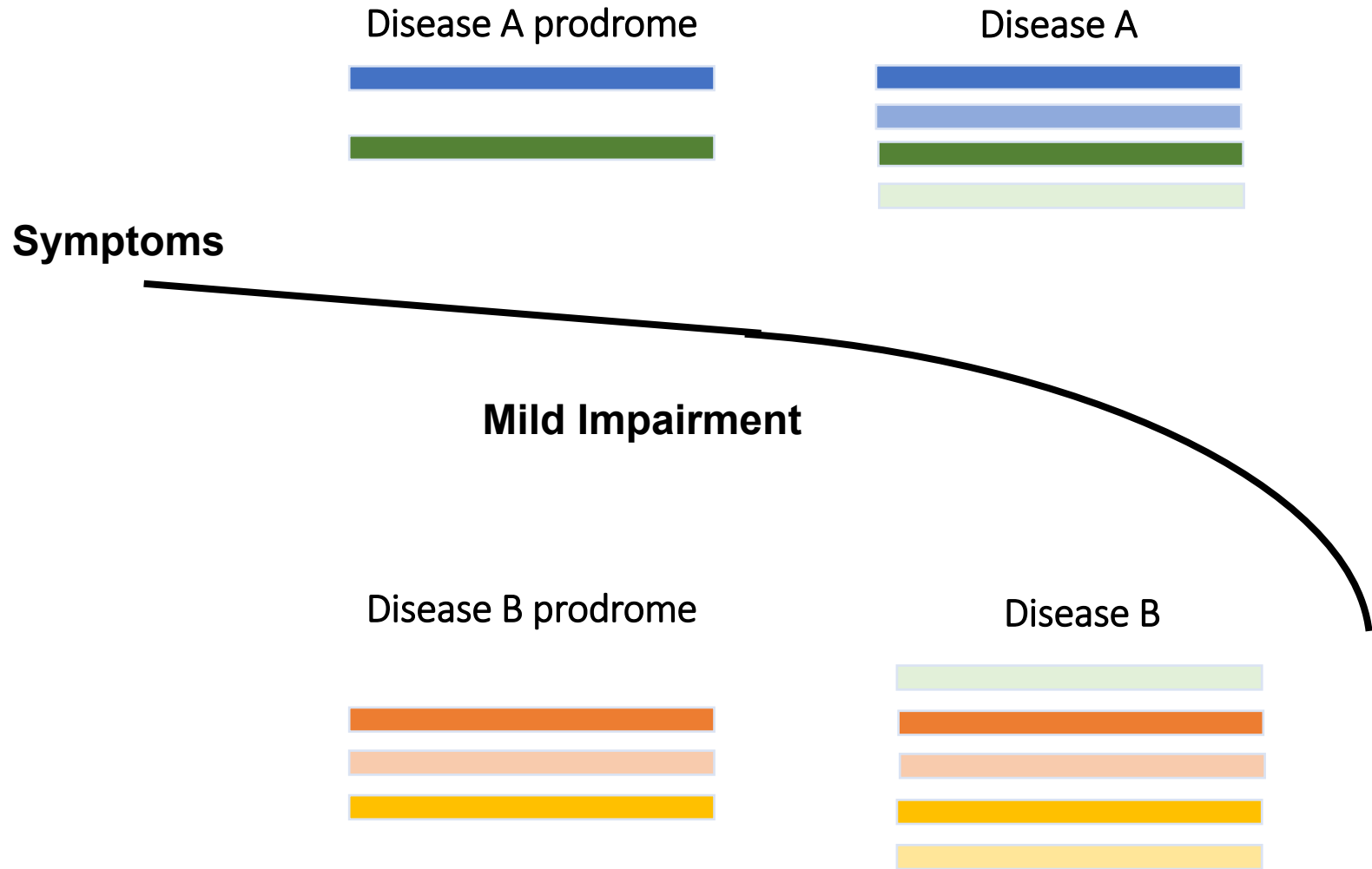
Disease B



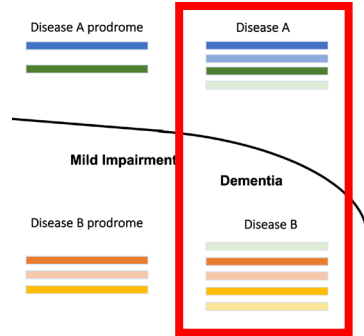
Symptoms of dementia represent the end stage of a long process

- Goals

- Examine current knowledge
 - Disease specificity overall
 - Disease specificity in prodromal states
- Highlight developments in assessment
- Focus on FTLD and Synuclein
 - AD by comparison



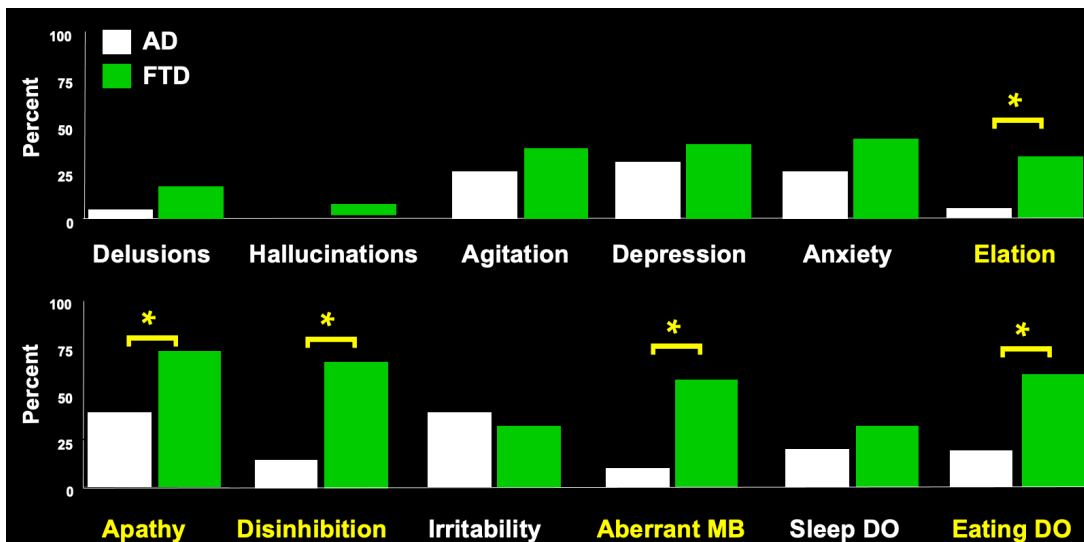
Studies of pathology confirmed cases support disease specificity for frontotemporal dementia (FTD) vs Alzheimer's disease (AD)



CME

Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD

H.J. Rosen, MD; K.M. Hartikainen, MD, PhD; W. Jagust, MD; J.H. Kramer, PsyD; B.R. Reed, PhD; J.L. Cummings, MD; K. Boone, PhD; W. Ellis, MD; C. Miller, MD; and B.L. Miller, MD



Liu et al, Neurology, 2004

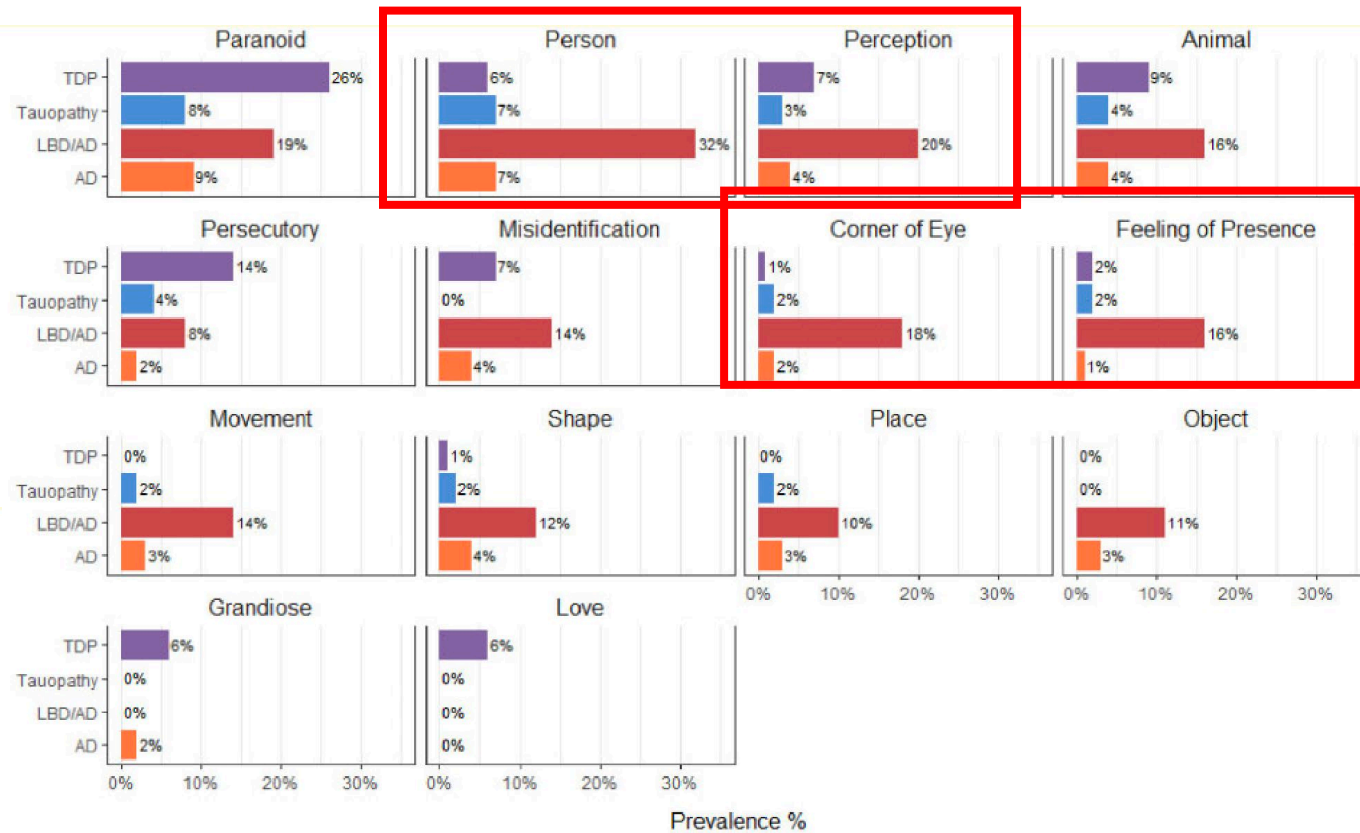
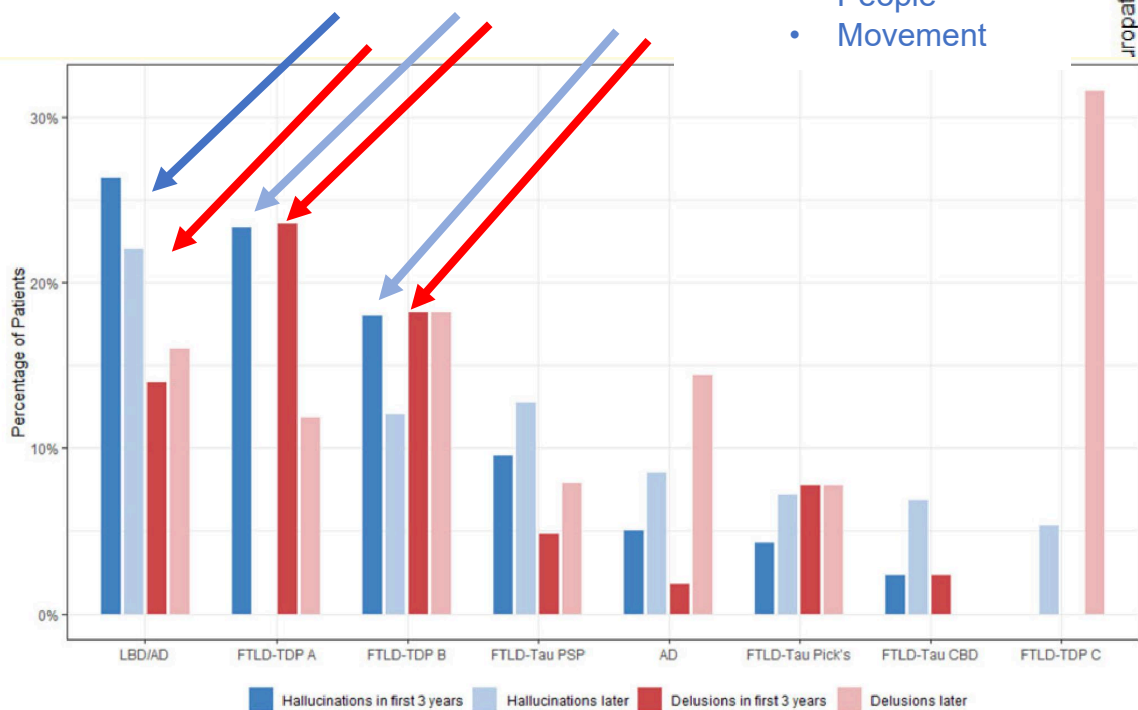
	FTLD (n=30)	AD (n=30)	Sample Sx
Social Conduct	80	0	Disinhibition Aggressiveness
Personal Conduct	86	31	Apathy Restlessness
Emotional Blunting	72	13	
Dietary Changes	56	0	Overeating Chewing gum Smoking

Rosen et al, Neurology, 2002

Dementia with Lewy bodies (DLB) also differs from AD but overlap with some forms of FTD

- 111 cases with pathologically verified diagnoses and psychosis
 - AD/DLB, FTLD, AD
- Hallucinations
 - Sensory modality
 - Content
- Delusions
 - Content

- DLB Hallucinations
 - Shapes, colors
 - Shapeless
 - People
 - Movement



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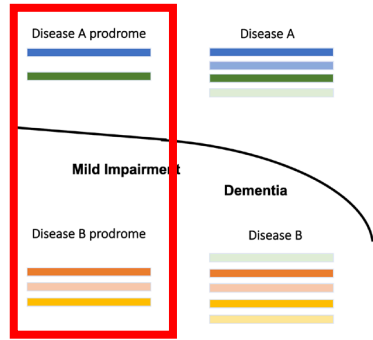
RESEARCH ARTICLE

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Neuropathological correlates of neuropsychiatric symptoms in dementia

Lucy L. Gibson¹ | Lea T. Grinberg^{2,3} | Dominic ffytche¹ | Renata E. P. Leite³ | Roberta D. Rodriguez³ | Renata E. L. Ferretti-Rebustini⁴ | Carlos A. Pasqualucci³ | Ricardo Nitrini³ | Wilson Jacob-Filho³ | Dag Aarsland^{4,5} | Claudia K. Suemoto³

Growing array of studies are prospectively examining the prodrome of neurodegenerative disease



- Prospectively follow participants with high risk for neurodegeneration
- FTLD
 - Autosomal dominant mutations
- DLB
 - Genetic Mutations
 - Genetic Risk variants
 - Clinical syndromes (e.g. RBD)



ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration study (ALLFTD)
www.allftd.org



North American Prodromal Synucleinopathy Cohort (NAPS)



Parkinson's Progressive Markers Initiative

Parkinson's Progressive Markers Initiative (PPMI)

Prodromal bvFTD often looks like bvFTD



- Core features
 - Apathy without dysphoria
 - Disinhibition
 - Irritability/agitation
 - Reduced sympathy/empathy
 - Repetitive behaviors
 - Joviality/gregariousness
 - Appetite changes/hyperorality
- Supportive features
 - Executive dysfunction on neuropsych
 - Reduced insight
 - Poor social cognition
- Good sensitivity vs. AD and Controls

BRAIN
ORIGINAL ARTICLE



Proposed research criteria for prodromal behavioural variant frontotemporal dementia

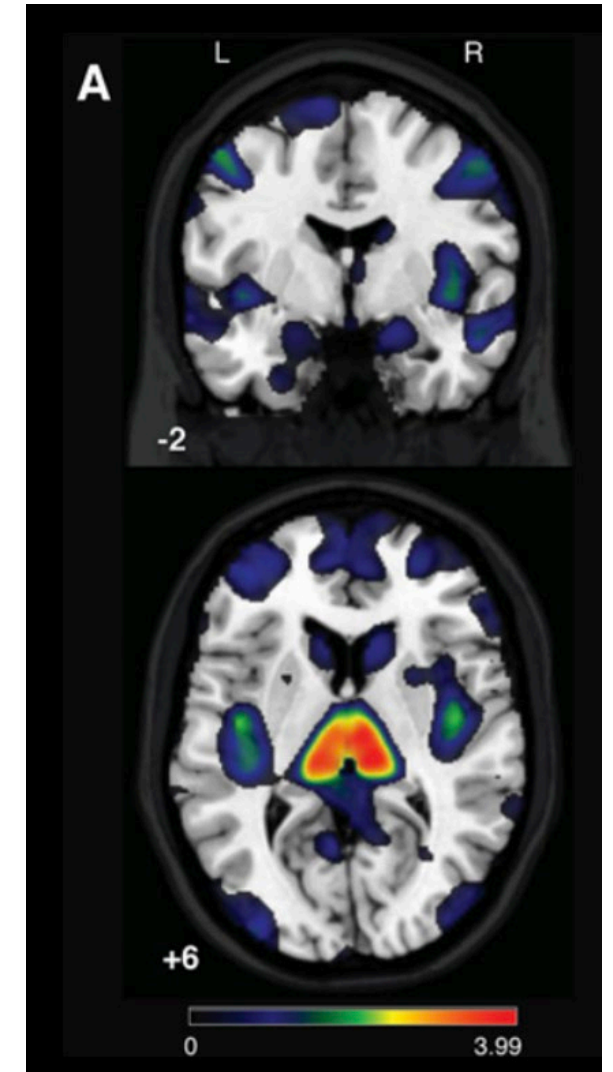
© Megan S. Barker,¹ Reena T. Gottesman,² Masood Manoochehri,¹ Silvia Chapman,¹ Brian S. Appleby,³ Danielle Brushaber,⁴ © Katrina L. Devick,⁴ Bradford C. Dickerson,⁵ Kimiko Domoto-Reilly,⁶ Julie A. Fields,⁷ Leah K. Forsberg,⁸ Douglas R. Galasko,⁹ Nupur Ghoshal,¹⁰ Jill Goldman,^{1,2} Neill R. Graff-Radford,¹¹ Murray Grossman,¹² Hilary W. Heuer,¹³ Ging-Yuek Hsiung,¹⁴ David S. Knopman,⁸ John Kornak,¹⁵ Irene Litvan,⁹ Ian R. Mackenzie,¹⁶ © Joseph C. Masdeu,¹⁷ Mario F. Mendez,^{18,19} © Belen Pascual,¹⁷ Adam M. Staffaroni,¹³ Maria Carmela Tartaglia,²⁰ © Bradley F. Boeve,⁸ Adam L. Boxer,¹³ Howard J. Rosen,¹³ Katherine P. Rankin,¹³ Stephanie Cosentino,^{1,2,21} Katya Rascovsky¹² and Edward D. Huey^{1,2,22} on behalf of the ALLFTD Consortium

But, earliest symptoms may not be very specific

- 66 yo male, family history of FTD due to *MAPT* mutation
 - Age 53 – 56
 - irritability, easy to anger, bickering with his wife, lost a couple of jobs b/o losing temper
 - By age 56
 - habit of making annoying sounds when eating, clanging fork
 - Eating peanuts every day, insists on having them in the house
 - Got fooled by internet scam
 - By age 60
 - Saying socially inappropriate things in public (not that bad)
 - Loss of social warmth, empathy
 - Distracted while driving, not always completing tasks at home
 - By age 62
 - Could no longer keep a job because of temper
 - Approaching strangers in street, doesn't notice they're not interested in talking to him
 - Diagnosis of bvFTD

Very early FTLD may not look like FTD, may not be “mild”

- Late 50s
 - Delusions typical of schizophrenia
 - Home is bugged
 - Glasses have cameras in them
 - Neurologist killed and replaced (Capgras)
 - Sex god
 - Hallucinations (hearing voices)
 - Mild exec dysfunction
 - Imaging without prominent atrophy
 - DSM-V criteria for late life delusional disorder
- Genetic testing showed *C9orf72* mutation (couple of years later)
- Developed more symptoms over 3 years
 - Overeating
 - Apathy/social withdrawal
 - motor neuron disease



NPS in DLB prodrome may not look like fully developed DLB

UDS Clinical Assessment with DLB module

Hallucinations prominent in dementia stage, as expected

Variable	Symptoms present (%)				Post hoc AD versus DLB
	Controls (n = 53)	AD (n = 78)	DLB (n = 110)	Overall P	
Delusions	2.3	16.7	28.2	.002	.17
Hallucinations	0.0	4.8	35.2	<.001	<.001
Agitation	18.2	42.9	56.3	<.001	.17
Depression	22.7	53.7	69.0	<.001	.10
Anxiety	9.1	45.2	42.3	<.001	.76

MCI-DLB characterized by depressive and anxiety symptoms

Variable	MCI-AD n = 79	MCI-DLB n = 22	P
Age, years	73.5 (8.8)	75.3 (5.3)	.37
Sex, %M	51.9	68.7	.17
Education, years	15.9 (2.6)	17.0 (2.0)	.09
Hachinski	0.7 (0.8)	0.7 (0.9)	.74
FAQ	2.6 (3.6)	3.4 (4.8)	.42
NPI	4.3 (3.9)	6.3 (5.9)	.06
Depression, %	28.8	64.3	.01
Depression, total	0.4 (0.7)	1.1 (0.9)	.004
Anxiety, %	18.6	46.7	.02
Anxiety, total	0.2 (0.5)	0.7 (0.8)	.005
Apathy, %	27.1	46.7	.14
Apathy, total	0.4 (0.7)	0.8 (1.0)	.09

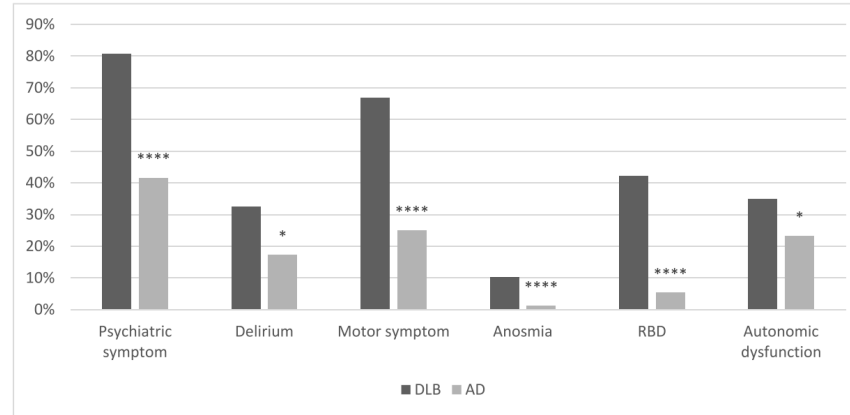
NPS in DLB prodrome may not look like fully developed DLB

...although more typical symptoms may develop as prodrome progresses



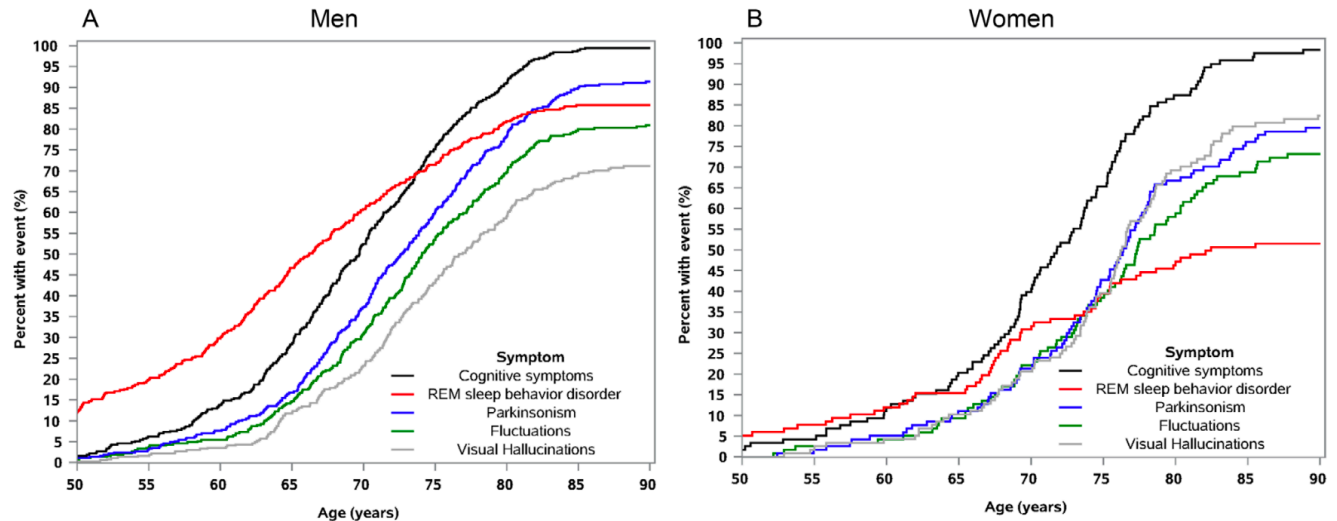
Mental health

BAI, score	8.1 ± 8.8
Anxiety, self-report	142 (39%)
PHQ-9, score	5.2 ± 5.4
Depression, <2 years self-report	112 (31%)
PCL-5, score	12.3 ± 15.6
PTSD, self-report	48 (13%)
Obsessive-compulsive disorder	21 (6%)
Developmental disorder	33 (9%)
Neuropsychiatric inventory	
Delusions	17 (4%)
Hallucinations	20 (6%)
Anxiety	80 (22%)
Apathy/indifference	72 (20%)



Hallucinations in ~70% of prodromal patients eventually

Mellergard et al, Park & Rel Dis, 2023



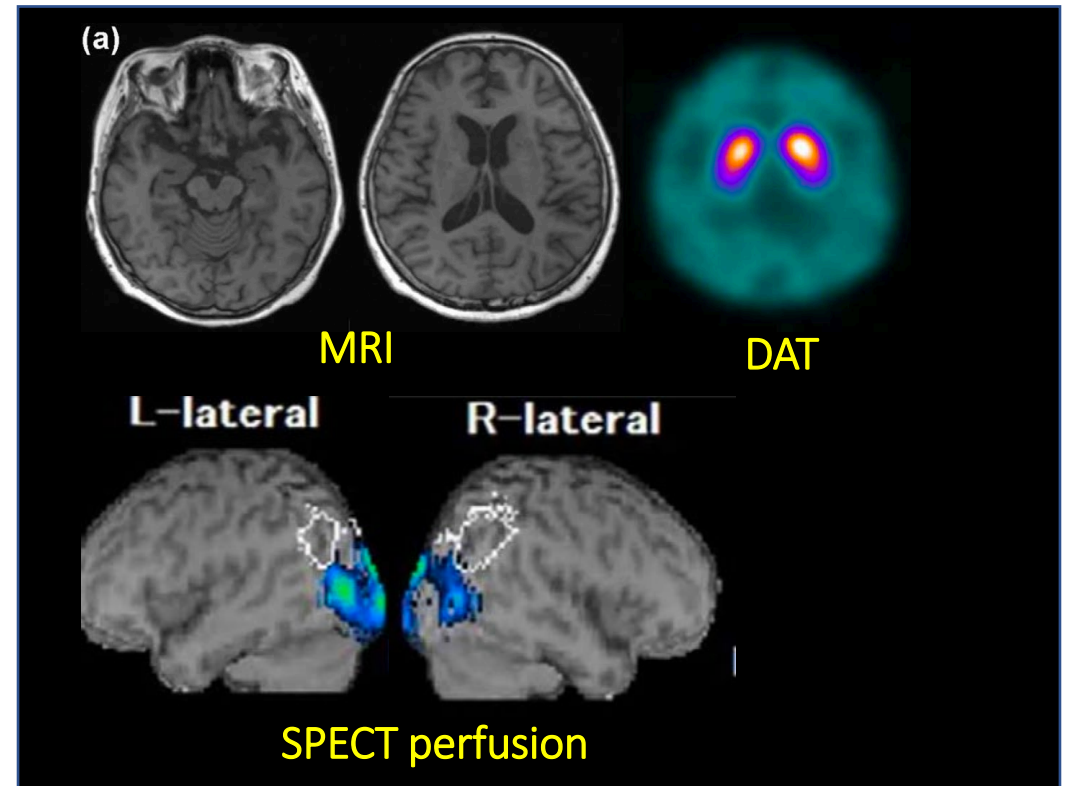
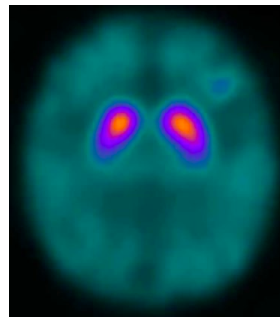
Choudhury et al, Alz & Dem, 2020

Elliot et al, Ann Clin Trans Neurol, 2023

Early syndromes may not be “mild” in DLB either

Prodromes can be long (> 10 years)

- Woman first symptoms of depression age 62
 - Could not do daily chores
 - Recovered after 6 weeks with treatment
- Second episode of depression with suicidality age 69
 - Parkinsonism
 - Sweating at night, constipation
- Depression improved with treatment
 - Parkinsonism improved with changing meds
- Third episode depression age 75
 - No parkinsonism
 - Confusion and hallucinations with aripiprazole
 - Improved with med adjustments



- Age 76
 - Developed dementia
 - Overt parkinsonism, DOPA-responsive
 - Diagnosed with DLB

Fujishiro et al, Psychogeriatrics, 2023

McKeith et al, Neurology, 2020

Possible model for evolution of NPS over course of illness

Earliest Prodrome

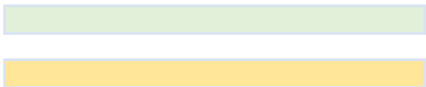


Later Prodrome

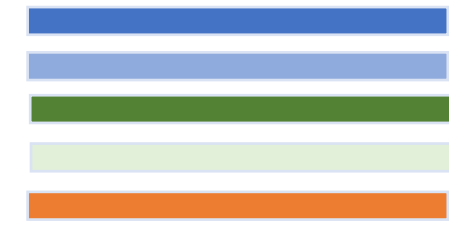
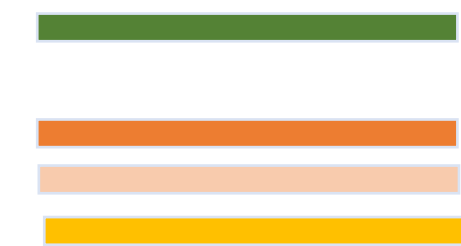


Dementia

Mild Behavioral Impairment

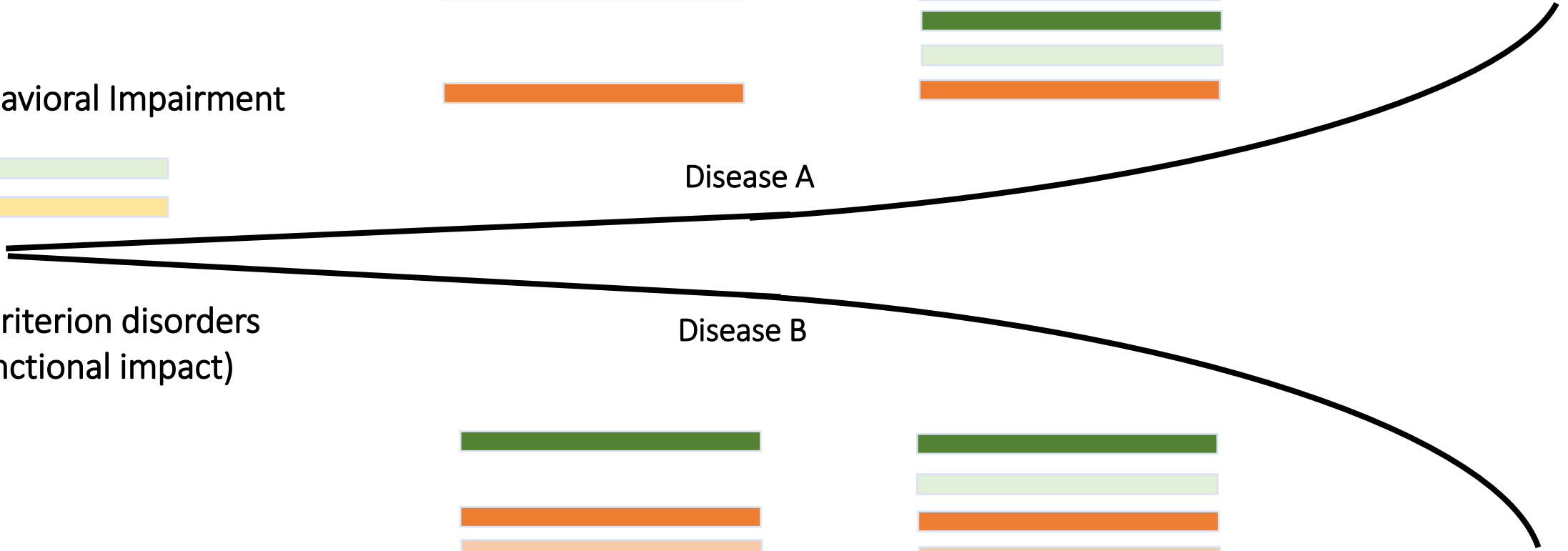


DSM-V criterion disorders
(with functional impact)



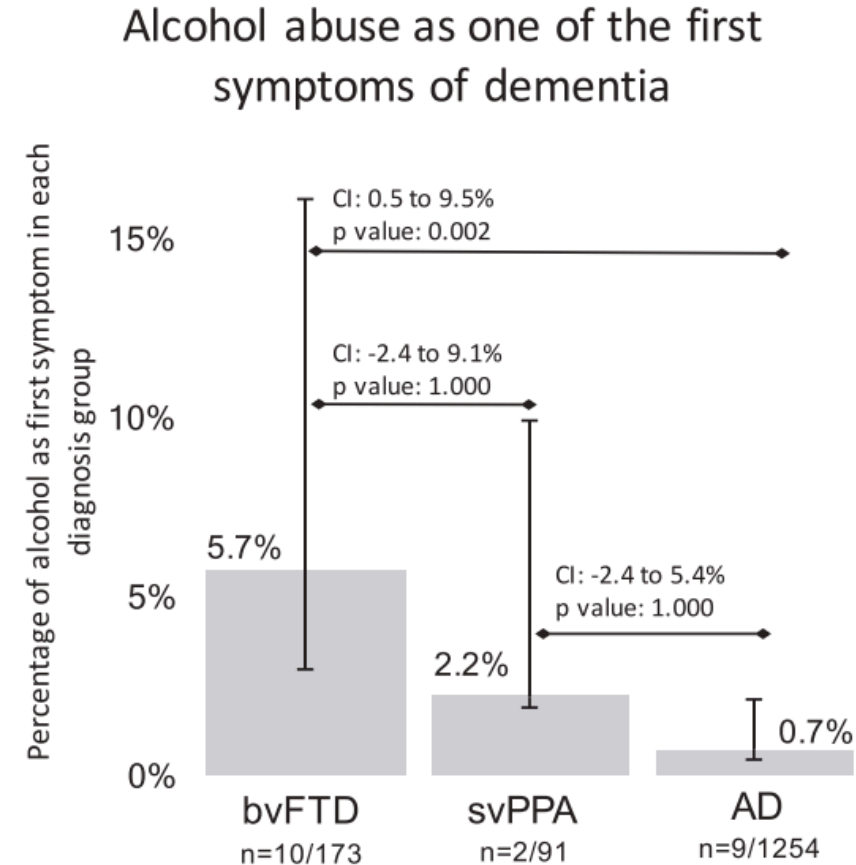
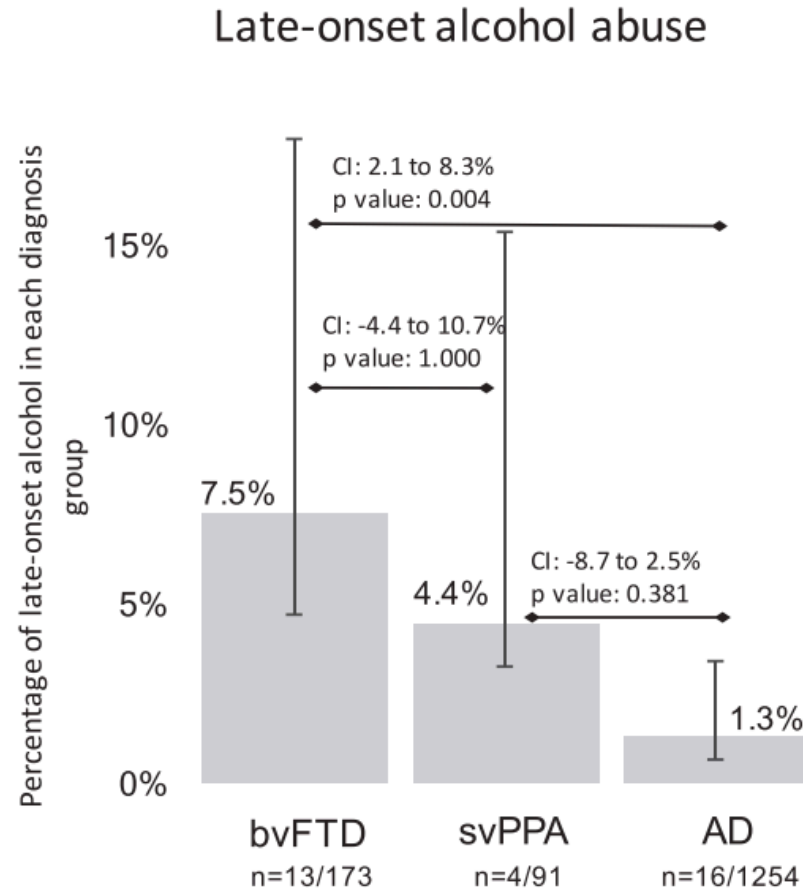
Disease A

Disease B

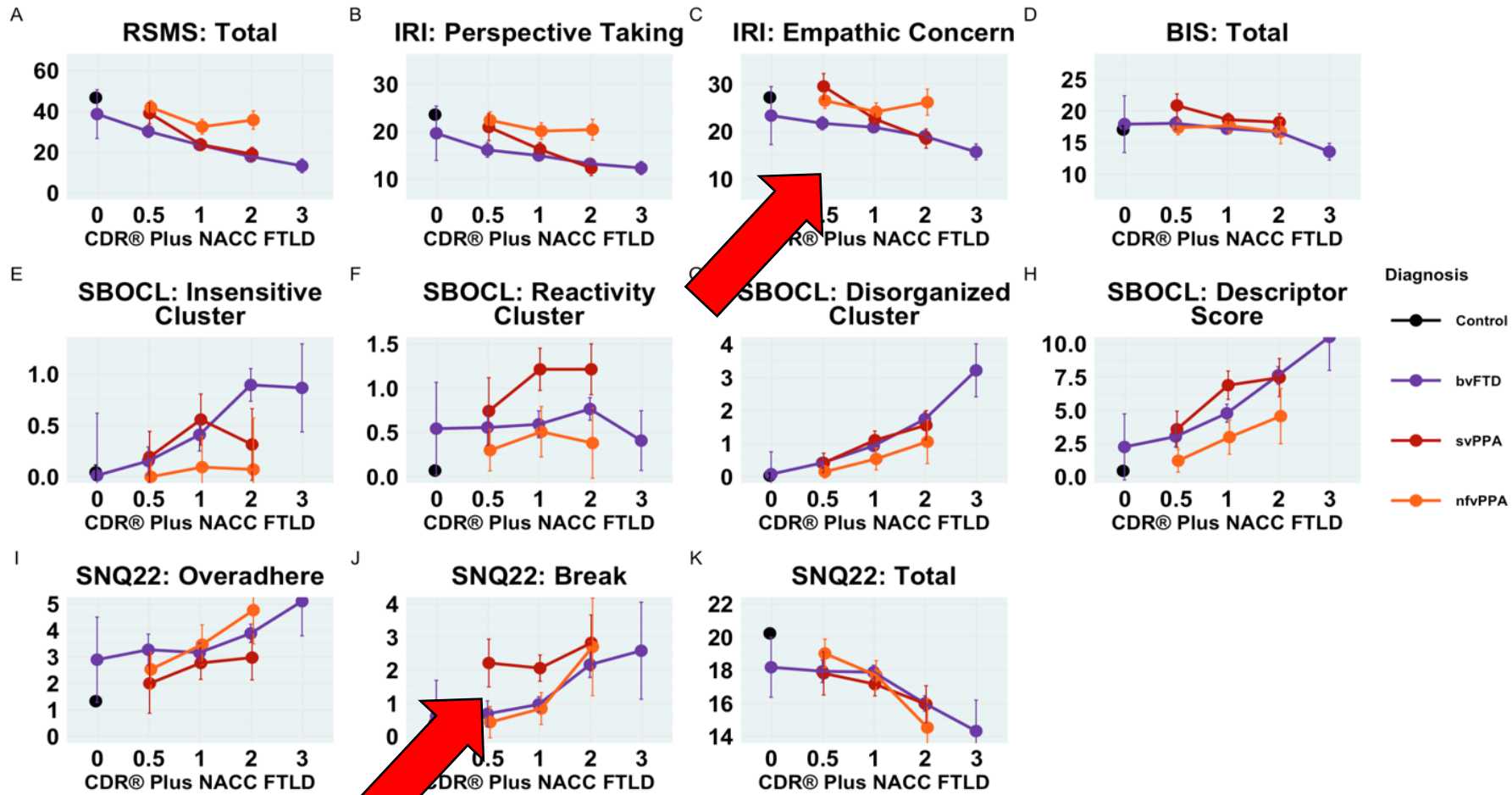


We need to be alert to changes that are not part of standard syndromes in dementia

Frequency and specificity in the prodrome remain to be determined



Emerging approaches are trying to standardize assessment of prodromal symptoms

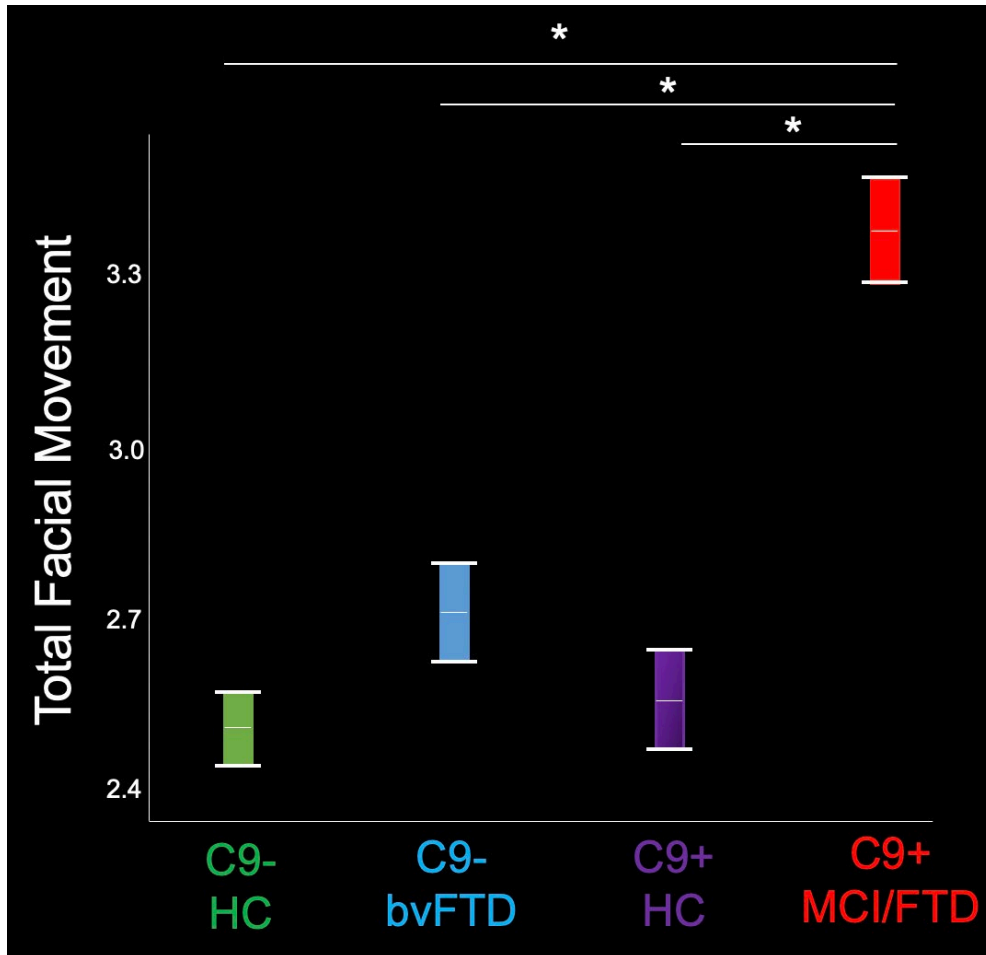


EARLY DETECTION

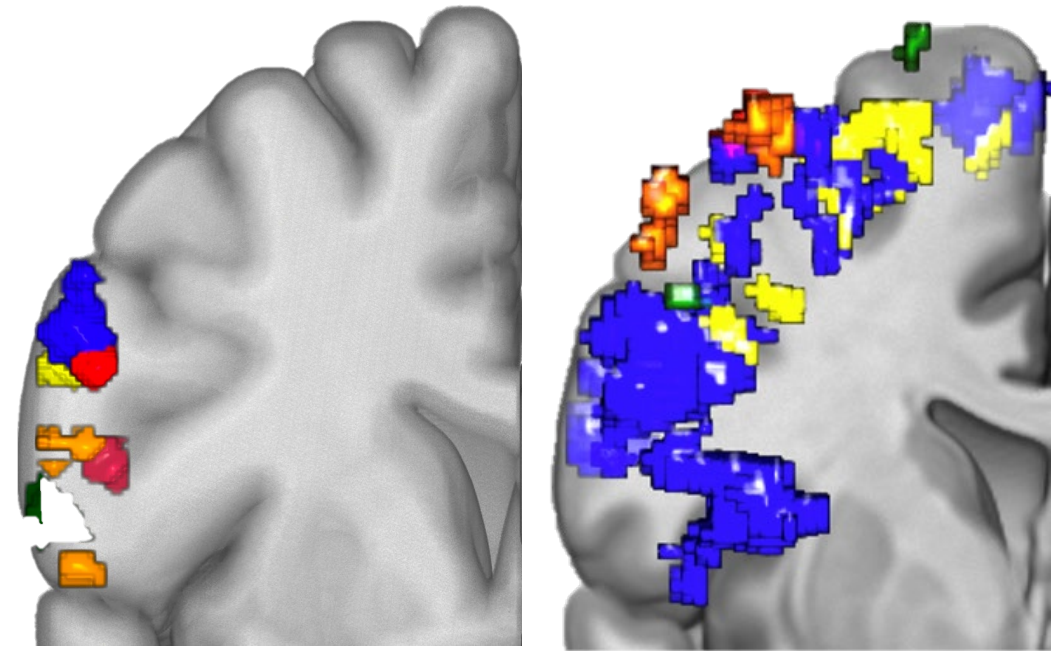
- At CDR=0.5, bvFTDs performed significantly worse than NCs on all measures, svPPA < NC on all but IRI
- Early deficits < NC in one group only:
 - IRI-EC – bvFTD only
 - SNQ22 Break – svPPA

Objective measures of emotional reactivity show promise

Elevated facial reactivity to emotional stimuli in prodromal C9orf72 mutation carriers



Abnormal representation of facial musculature in motor cortex



Healthy Controls

C9+ Symptomatic

Conclusions

- Specific pathological etiologies are associated with specific NPS's
 - Substantial overlap
 - Some differences are in the details of the individual patient's NPS
- Very early prodrome
 - May not be very specific (depression, anxiety, irritability)
 - May include “full blown” psychiatric disorder with functional impact meeting DSM criteria
 - May evolve into more specific pattern as prodrome progresses
 - Continuing prospective study is needed
- Future opportunities
 - More standardized informant/self report measures
 - Objective measurements of socioemotional function/processing

A narrative illustration of loss of empathy

- Bruce Miller, MD
 - A.W. and Mary Margaret Clausen Distinguished Professor in Neurology
 - Director, UCSF Memory and Aging Center
- Pioneer in elucidating the behavioral manifestations of frontal and temporal lobe degeneration
 - Defined modern concept of FTD
- Virginia Sturm, PhD
 - John Douglas French Alzheimer's Foundation Endowed Professor at UCSF in Neurology
 - Director, UCSF Clinical Affective Neuroscience (CAN) lab
- Studies emotional functioning and behavioral and physiological changes in emotional systems in brain disease

