Recommendations to Distinguish Behavioural Variant Frontotemporal Dementia from Psychiatric Disorders

Simon Ducharme, MD MSc FRCP(C)

Douglas Mental Health University Institute Montreal
Neurological Institute McConnell Brain Imaging Centre

Associate Professor of Psychiatry, McGill University

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A research centre affiliated with:

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Centre intégré universitaire de santé et de services sociaux de l'Ouest-de-l'île-de-Montréal
Québec

Disclosure

- PI for clinical trials in dementia
  - Biogen
  - Ionis Pharmaceuticals
  - AZTherapies Inc.
  - Wave Life Sciences
  - Janssen
- Consultant
  - Innodem Neurosciences
  - Eisai
  - QuRALIS
- Honorarium for presentations and advisory board
  - Sunovion
  - Eisai
  - Biogen
- Co-founder of AFX Medical (artificial intelligence solutions for neuroradiology)

OUTLINE

- bvFTD Diagnosis
- bvFTD versus Primary Psychiatric Disorders
- Neurpsychiatric International Consortium for FTD (NIC-FTD) Recommendations
- Updates on Neuroimaging Research

TROUBLE PSYCHIATRIQUE PRIMAIRE OU MALADIE NEURODÉGÉNÉRATIVE?

- H42, Hassidic Jewish, married, several children
- 32: Unspecified encephalitis (likely viral)
- 35: New schizo-affective bipolar disorder subtype – excellent response to olanzapine 7.5mg daily
- 40: Marked functional and cognitive decline
  - Behavioral changes: faster speech, verbal stereotypies, perseveration, loss of interpersonal boundaries
  - Dependent for ADLs
  - Neglects hygiene, incontinence

CLINICAL QUESTIONS

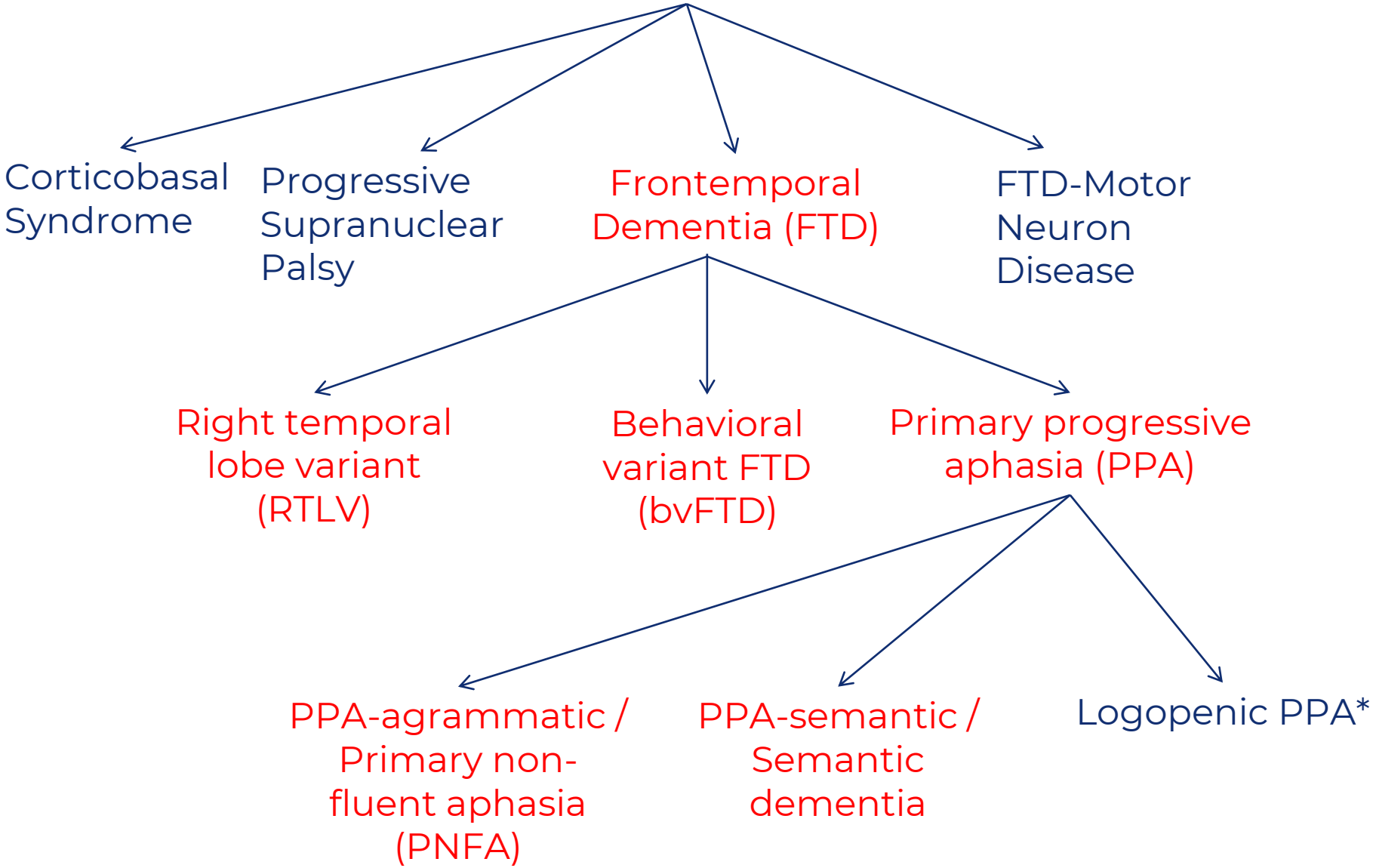
IS THIS A PRIMARY PSYCHIATRIC DISORDER OR NEURODEGENRATIVE

- MoCA 5/30 – Multidomain deficits
- Neuro exam WNL except hypermotoric behavior
- Brain MRI: mild diffuse atrophy involving the cerebellum
- Mother died from dementia at age 48

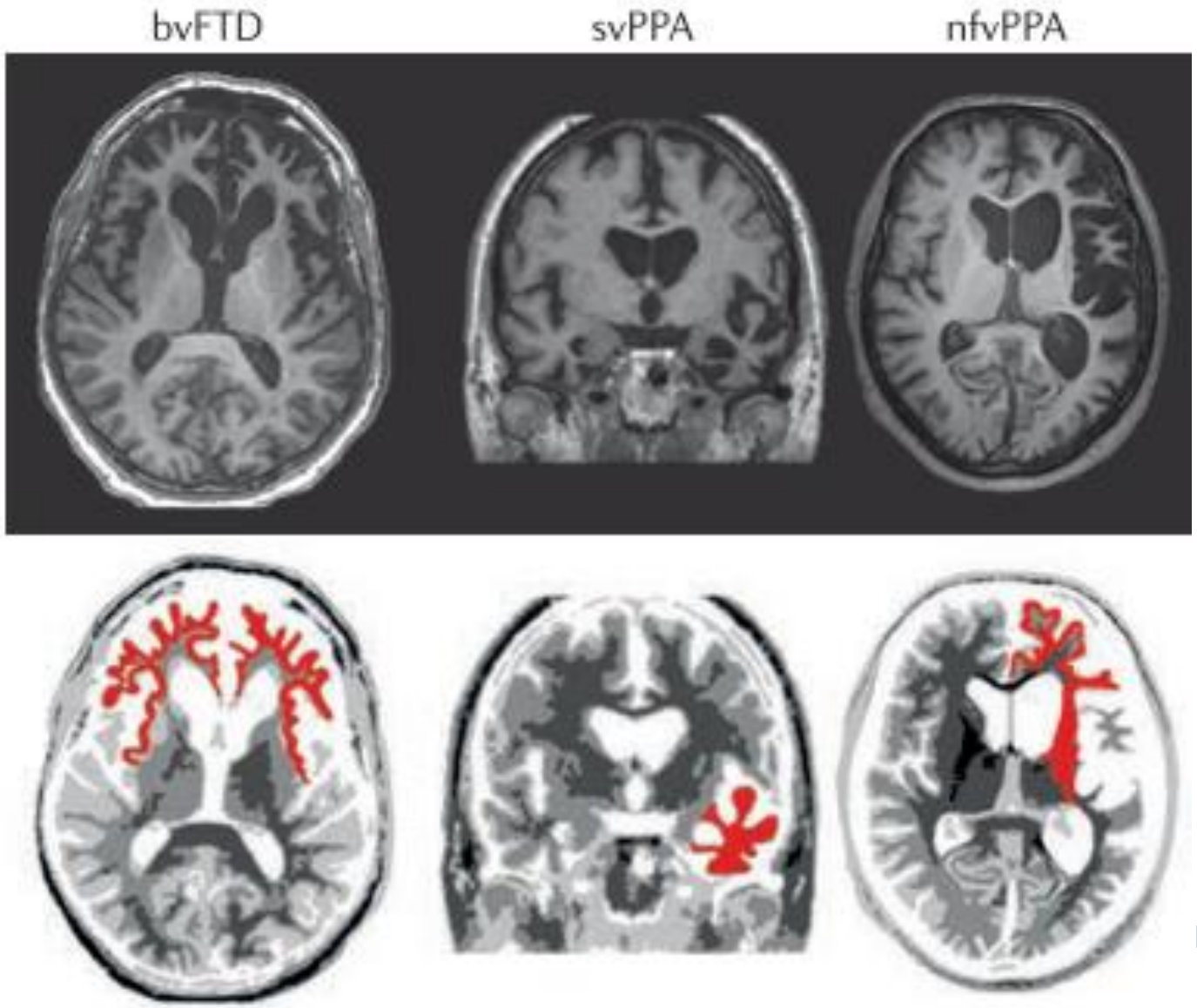
IS SCHIZO-AFFECTIVE DISORDER ETIOLOGY LINKED TO DEMENTIA OR A COMORBIDITY?

- Shared origin: encéphalitis?
- Medication related adverse effects?
- Is SCZA the initial manifestation of neurodegeneration

Frontotemporal Lobar Degeneration Spectrum (FTLD)



Predominant Atrophy Patterns



Meeter et al., Nat Rev Neurol, 2016

DSM-5 Behavioral Variant FTD

- A. Criteria met for mild/major neurocognitive disorder
- B. Insidious onset and gradual progression
- C1a. 3 or more of the following
  - Behavioral disinhibition
  - Apathy or inertia
  - Loss of sympathy or empathy
  - Perseverative, stereotyped or compulsive/ritualistic behavior
  - hyperorality and dietary changes
- C1b. Prominent decline in social cognition and/or executive abilities
- D. Relative sparing of learning and memory and perceptual-motor function
- E. Not better explained by another neurodegenerative disease, effects of a substance, or another mental, neurological, or systemic disorder

Rascovsky et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain,* 2011; 134:2456–2477.

DSM-5 Behavioral Variant FTD - Biomarkers

- Possible bvFTD if only clinical criteria are met
- Probable bvFTD if:
  - Evidence of disproportionate frontal and/or anterior temporal lobe involvement from neuroimaging
  - Evidence of a causative genetic mutation from family history or genetic testing (bvFTD with definite FTLD pathology)
- Sensitivity and Specificity
  - Possible bvFTD: 95% sensitivity / 82% specificity
  - Probable bvFTD: 85% sensitivity / 95% specificity

Harris et al. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. *Neurology, 2013;80*(20), 1881-1887.

Right Temporal Variant

- Less frequent than semantic PPA (1:2)
- Predominantly behavioral syndrome
- Emotional distance
- Inability to read and understand other's emotions
- Irritability
- Prosopagnosia
- Disruption of physiological drives
  - Sleep, appetite, libido
- Repetitive and stereotypical behaviors
  - Preoccupied with words, numbers, games

Seeley et al. The natural history of temporal variant frontotemporal dementia. *Neurology* 2005;64:1384-1390

Epidemiology

- Who might be suffering from FTD?
  - Average age of onset between 35-70 (peak 45-65)
    - ≈5% of all dementia cases
    - As common, if not more common than AD before age 60
    - No direct increase in prevalence with aging
    - 25% cases are late-onset
    - Slight male predominance for bvFTD
- How common is FTD?
  - Point prevalence ≈20/100,000
  - Annual incidence ≈4/100,000 – over 300 new cases per year in Québec
- What are the risk factors?
  - ≈20% with family history
  - No replicated environment risk factor

Onyike & Diel-Schmid. The epidemiology of frontotemporal dementia. *International Review of Psychiatry,* April 2013; 25(2): 130–137.

Prognosis

- bvFTD (≈55-60% cases)
  - Survival 4-20 years
  - 15% develop amyotrophic lateral sclerosis (ALS) – mean survival 2-3 years
- PPA-semantic (≈20% cases)
  - Older age of onset (mean 59)
  - Mean survival 12 years
- PPA-agrammatic (≈25% cases)
  - Mean survival 9 years
  - Association with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP)

Miller BL and Boeve BF. The Behavioral Neurology of Dementia. Cambridge University Press 2009.

Pathology Distribution

- bvFTD
  - Equal proportion of Tau and TDP-43 (association with motor neuron disease)
  - Rarely AD (5-10%)
  - 5-10% FTLD-FUS
- PPA-agrammatic
  - Mostly Tau (association with PSP and CBD)
  - ≈20% AD
- PPA-semantic
  - Mostly TDP-43
  - ≈20% AD
- Logopenic PPA
  - Mostly AD (≈60%)
  - ≈40% FTLD pathology

Genetics

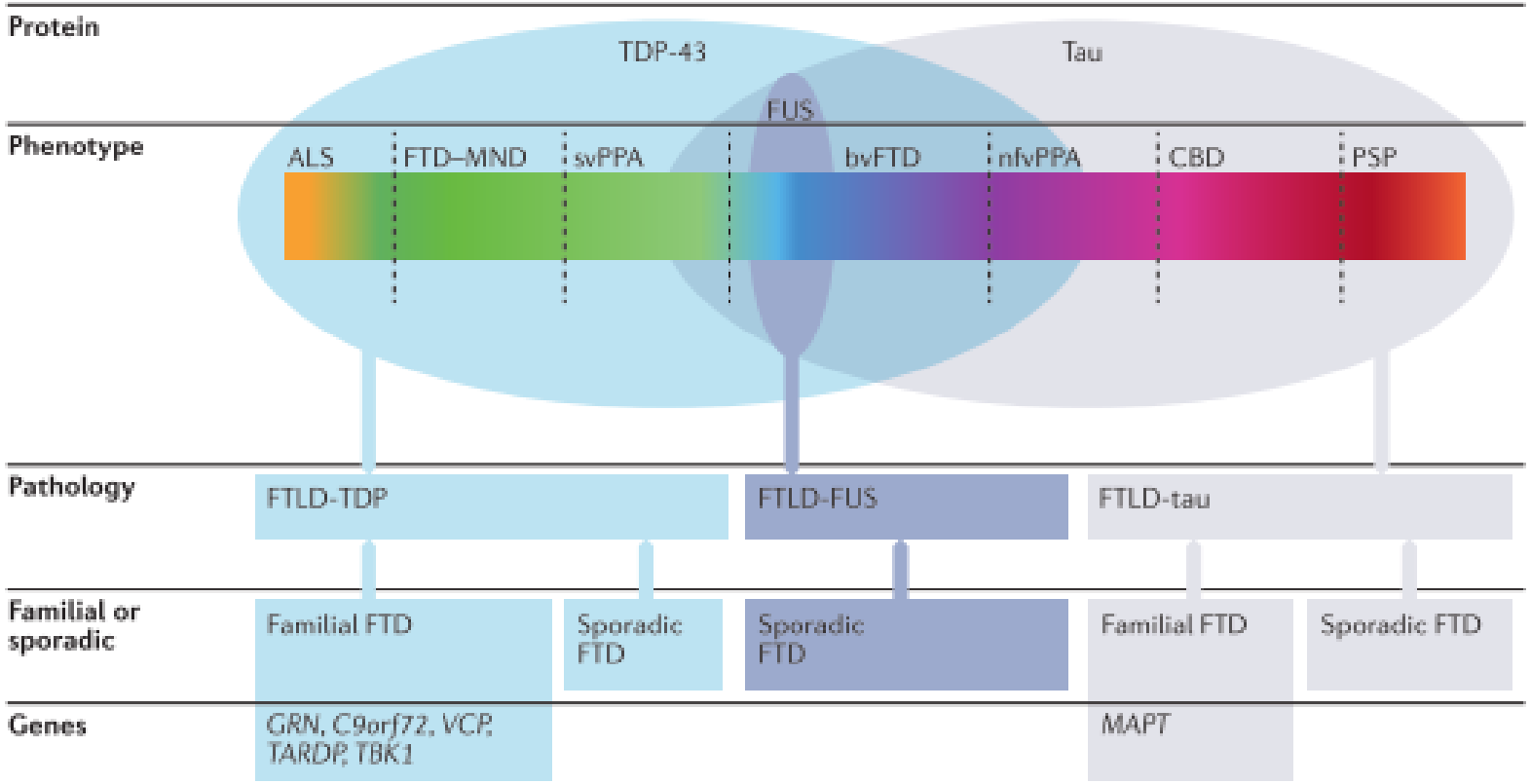
- ≈20% have positive family history
- Chromosome 17
  - *Progranulin (PGRN)* – associated with TDP-43 pathology
    - Autosomal dominant with 90% penetrance
  - *MAPT mutations* – Tau gene 17q21
    - Autosomal dominant with full penetrance
    - Link with familial Parkinson's
- Chromosome 9 - *C9ORF72* hexanucleotid repeat
  - Most common cause of FTD-ALS complex (2011)
  - Probably the most common causative mutation of bvFTD

CLINICAL – GENETICS - PATHOLOGY

Clinical syndromes
- bvFTD
- PPAs
- CBD/PSP

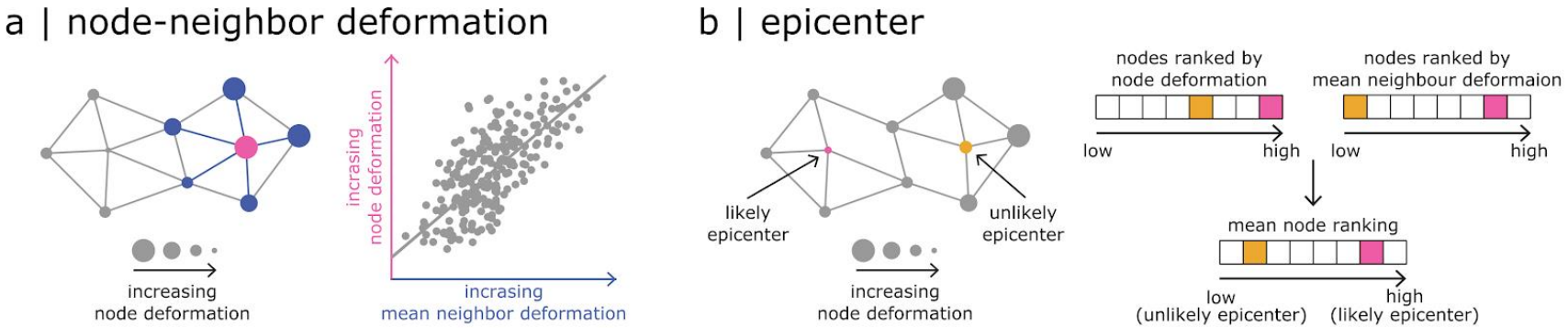
Genetics
- C9orf72
- GRN
- MAPT

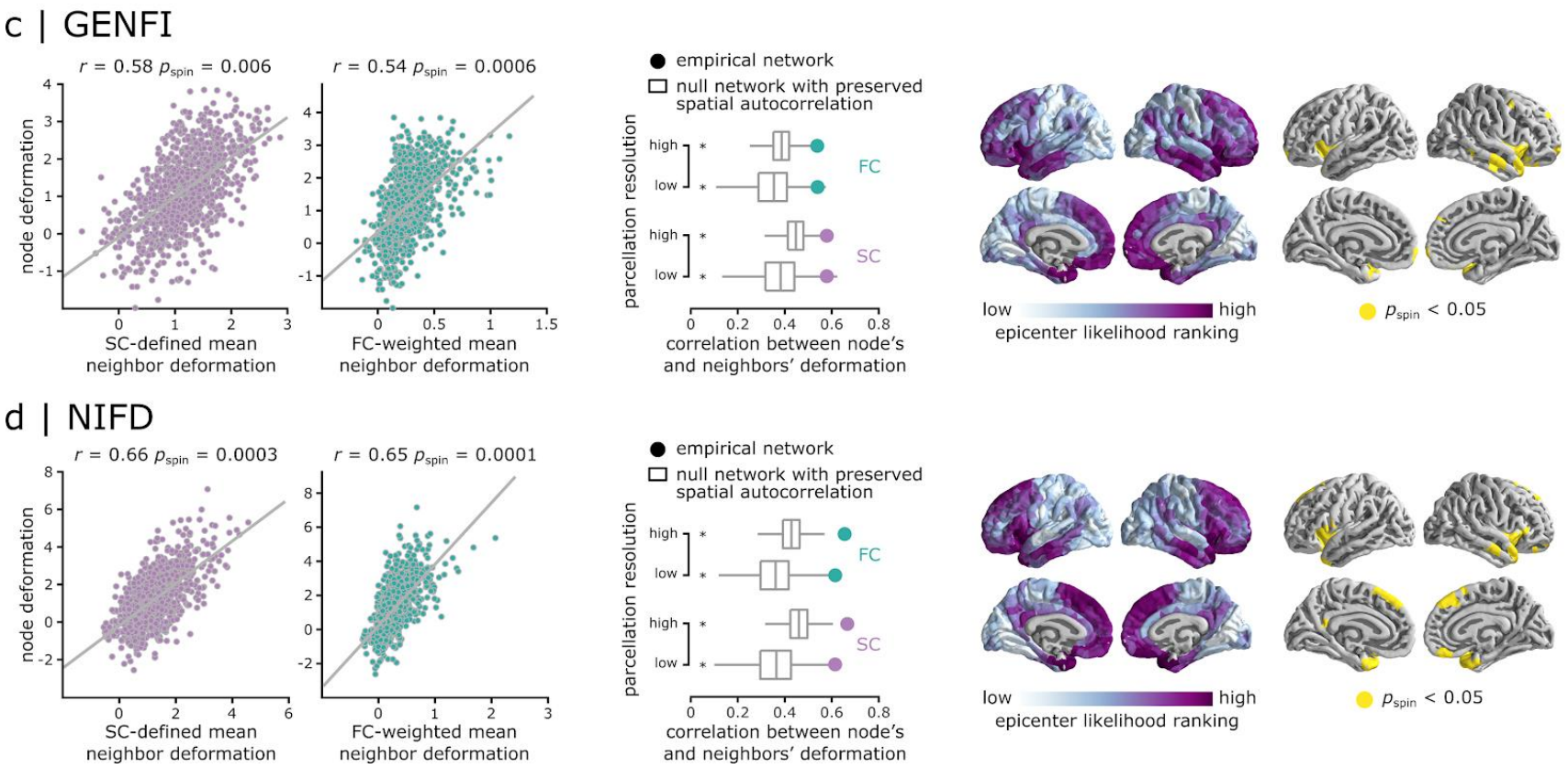
Pathologies
- Tau
- TDP-43
- FUS



Meeter et al., 2016

NETWORK PROPAGATION OF FTD





Shafiei et al. Brain, 2022

Non-Progressive bvFTD

- Meet criteria for possible bvFTD but minimal progression over time – 'bvFTD phenocopy' Mostly male
- Less impaired in executive functions and ADL/IADL
- No supportive features on imaging
- Normal lifespan
- Most subjects at autopsy do not have FTLD changes
- Probably not bvFTD, but what else?
  - Autism spectrum?
  - Low-grade mood or psychotic disorders?
  - Residual symptoms of catatonia?

Shafiei et al. Brain, 2022

bvFTD versus Primary Psychiatric Disorders

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bvFTD in Psychiatry: A Complex Challenge

- Most patients with bvFTD are first evaluated in general psychiatric settings
- 50% are initially diagnosed with a primary psychiatric disorder (Woolley 2011)
  - Missed diagnosis
  - Prodromal psychiatric disorders
- Most cases are sporadic – without family history

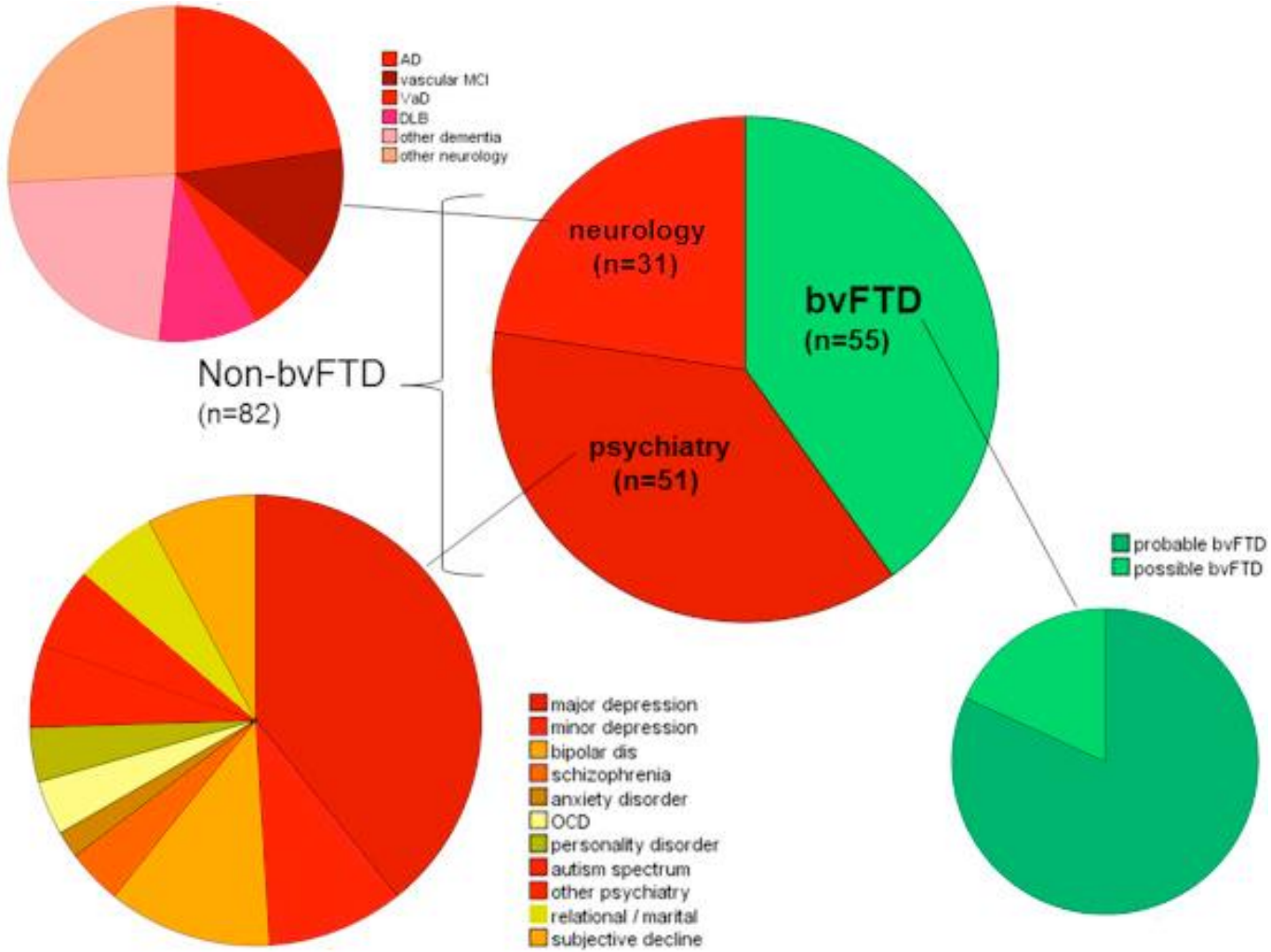
- Diagnostic challenges of bvFTD:
  - Onset is in an age range in which the probability of dementia is low
  - Symptoms overlap with primary psychiatric disorders
  - Early symptoms combine features traditionally in the realm of psychiatry and neurology
  - Psychiatric prodrome can last 4-5 years prior to the onset of clear bvFTD features

Normal or Abnormal Behavior?

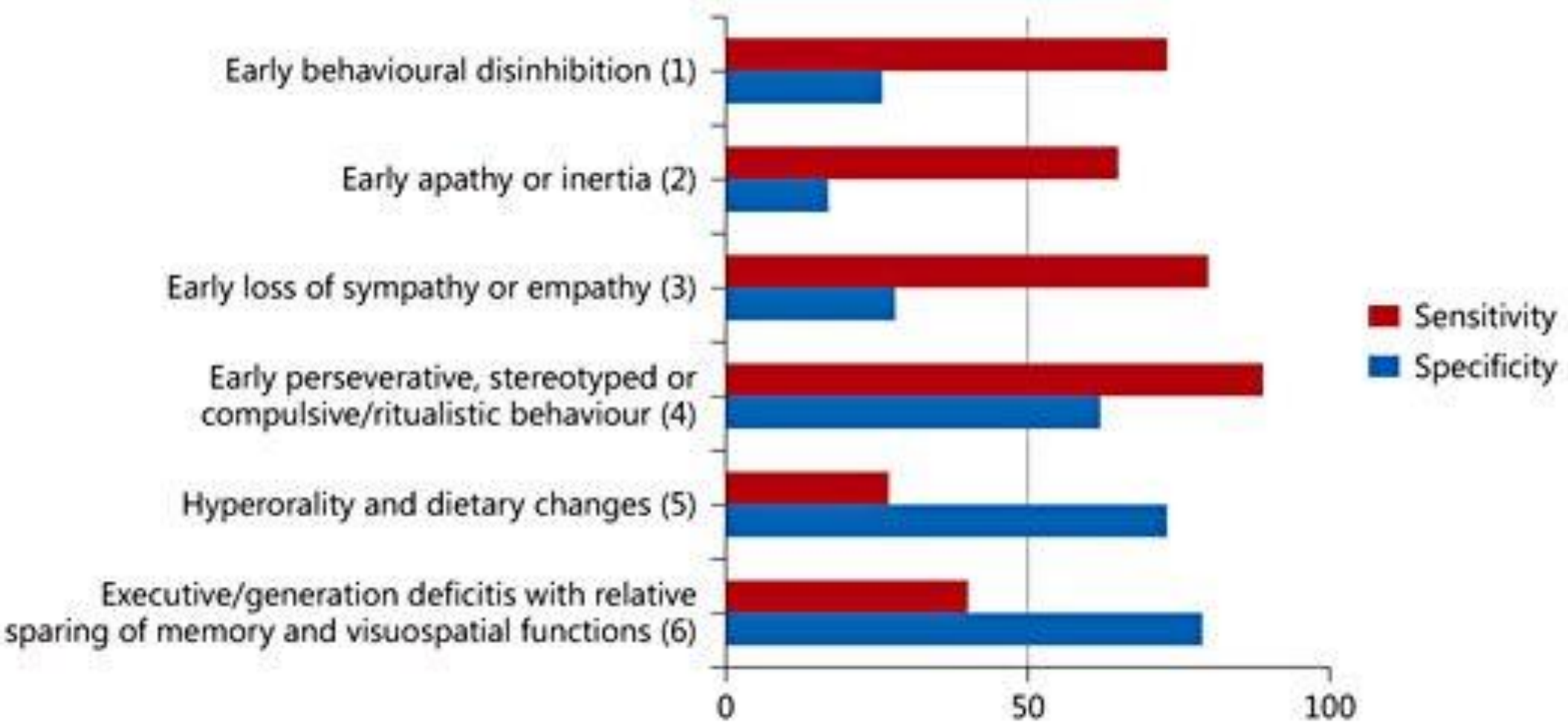
- Early symptoms include subtle changes in personality, values, and beliefs
- The initial phase is interpreted as a psychosocial crisis leading to major life changes and legal repercussions
- Patients rationalize their behavior and blame the environment for overreacting
- With public awareness, families can erroneously interpret interpersonal conflicts as Sx of bvFTD…
- Behaviors have to be interpreted in light of premorbid personality

Late Onset Frontal Lobe Study

- Naturalistic cohort study (Netherlands) – PI Y. Pijnenburg
- 137 consecutive patient with late onset (45-75) with predominant behavioral complaints (rated on FBI, SRI)
- Final diagnosis established at 2-year follow-up



ARE BVFTD INDIVIDUAL CRITERIA ACCURATE?



Vijberberg et al. Diagnostic Accuracy of the Frontotemporal Dementia Consensus Criteria in the Late-Onset Frontal Lobe Syndrome, Dement Geriat Cogn Disord, 2016

Is neuroimaging accurate?

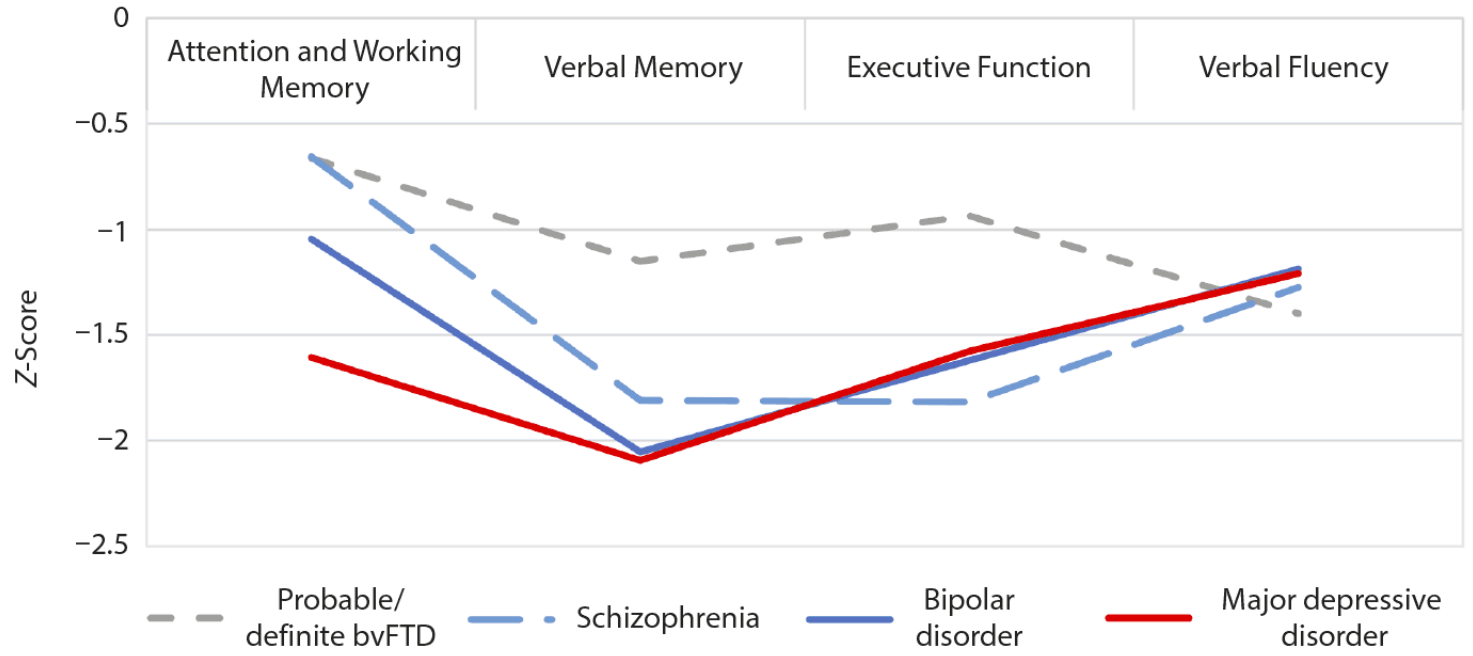
- Accuracy of brain MRI?
  - MRI sensitivity 70% and specificity 93%
  - 66% of genetic FTD without atrophy at baseline
- Accuracy of FDG-PET?
  - FDG-PET sensitivity 90% and specificity 68%
  - 40% of patients with primary psychiatric disorders had abnormal PET findings
- Combined MRI and FDG-PET
  - PPV 53% - NPV 98%

Vijberberg et al. Diagnostic Accuracy of the Frontotemporal Dementia Consensus Criteria in the Late-Onset Frontal Lobe Syndrome, Dement Geriat Cogn Disord, 2016

Is neuropsychology better?

- Executive function worse in all PPD vs bvFTD
- Attention and working memory worse in MDD and BD compared to bvFTD
- Better verbal memory in bvFTD
- Lower verbal fluency score in bvFTD vs BD, but not other disorders

Figure 1. *Z*-Scores of the Individual Cognitive Domains



Vijverberg et al. Cognitive Deficits in Patients With Neuropsychiatric Symptoms: A Comparative Study Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders, J Clin Psychiatry, 2017


To-Do-List
1. make
2. things
3. better

NEUROPSYCHIATRIC INTERNATIONAL CONSORTIUM FOR FTD (NIC-FTD)

Recommendations

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Neuropsychiatric International Consortium for FTD (NIC-FTD)

- Created in 2017
- International group of clinicians & researchers
- Structure:
  - Leader: Yolande Pijnenburg (Amsterdam, Netherlands)
  - Co-leader: Simon Ducharme (Montreal, Canada)
  - 45 participants from 15 countries
- Aims:
  - Establish clinical assessment guidelines to differentiate bvFTD from bvFTD
  - Establish a research database

Neuropsychiatric International Consortium
Frontotemporal Dementia

Methods

- Systematic literature search in two databases (Pubmed & Embase) with keyword approach divided by diagnostic components
- Team of 2-3 experts assigned to review manuscripts of each section
- Recommendations divided in 3 levels: ‘Minimal requirements’, ‘Clinical recommendation’ and ‘Tools that require further research’
- In-person meeting to determine a first set of recommendations
- Online survey with multiple rounds to determine final expert consensus (> 85%)

doi:10.1093/brain/awaa018 BRAIN 2020: 0; 1–19 | 1

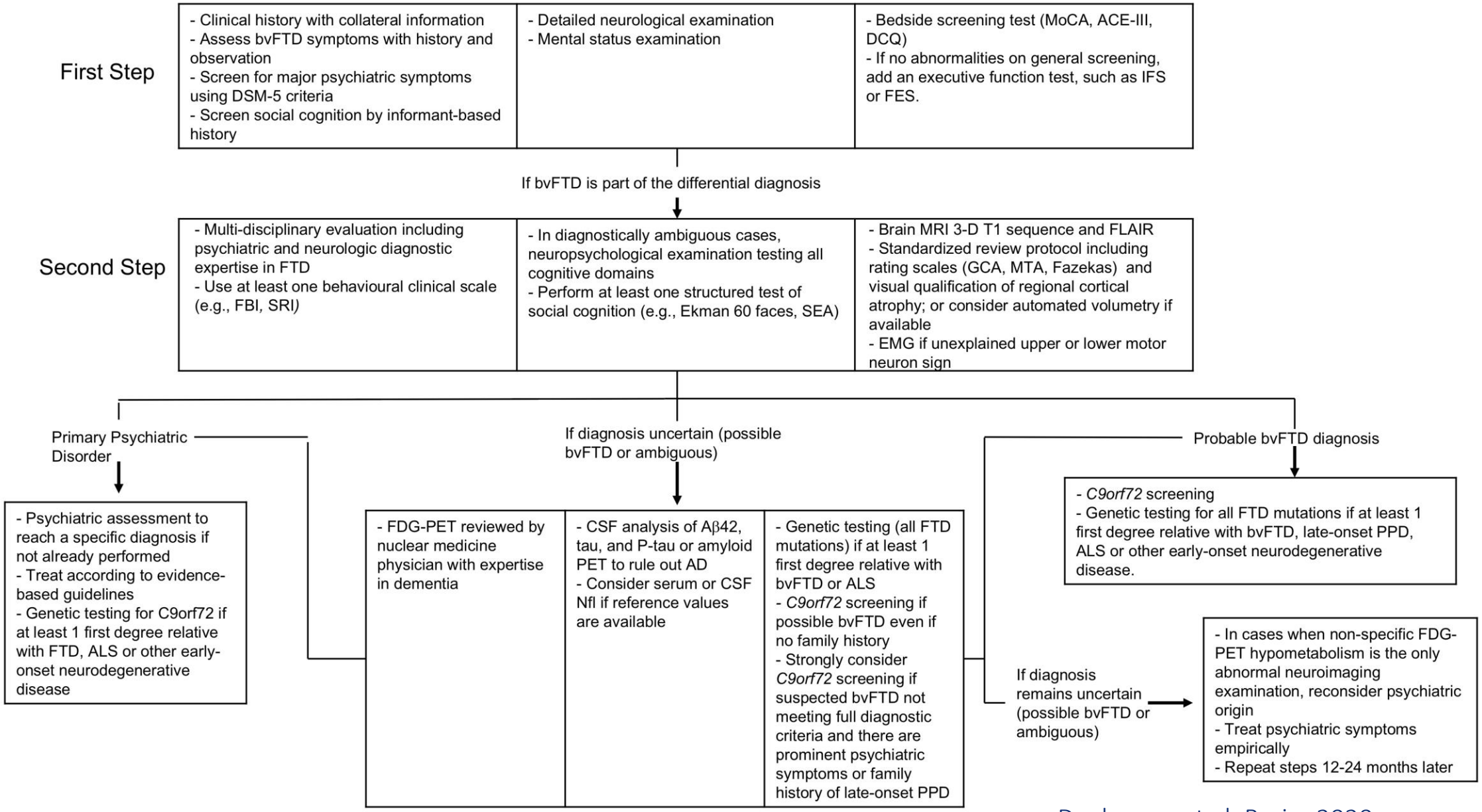
BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders

Simon Ducharme,[1,2] Annemiek Dols,[3] Robert Laforce,[4] Emma Devenney,[5] Fiona Kumfor,[5] Jan van den Stock,[6] Caroline Dallaire-Théroux,[7] Harro Seelaar,[8] Flora Gossink,[3] Everard Vijverberg,[9] Edward Huey,[10] Mathieu Vandenbulcke,[11] Mario Masellis,[12] Calvin Trieu,[3] Chiadi Onyike,[13] Paulo Caramelli,[14] Leonardo Cruz de Souza,[14] Alexander Santillo,[15] Maria Landqvist Waldö,[16] Ramon Landin-Romero,[5] Olivier Piguet,[16] Wendy Kelso,[17] Dhamidhu Eratne,[17] Dennis Velakoulis,[17] Manabu Ikeda,[18] David Perry,[19] Peter Pressman,[20] Bradley Boeve,[21] Rik Vandenberghe,[22] Mario Mendez,[23] Carole Azuar,[24] Richard Levy,[24] Isabelle Le Ber,[24] Sandra Baez,[25] Alan Lerner,[26] Ratnavalli Ellayosyula,[27] Florence Pasquier,[28] Daniela Galimberti,[29,30] Elio Scarpini,[29,30] John van Swieten,[8] Michael Hornberger,[31] Howard Rosen,[32] John Hodges,[5] Janine Diehl-Schmid[33] and Yolande Pijnenburg[9]

RECOMMENDATIONS TO DISTINGUISH BVFTD FROM PPD



Ducharme et al. Brain, 2020

Key Points

Neuropsychiatric International Consortium
Frontotemporal Dementia

- Mutli-disciplinary assessment is recommended
- Include one social cognition test in neuropsychological testing (face recognition task)
- Brain MRI should include high resolution T1 and FLAIR with a standardized review protocol including semi-structured visual rating scales or volumetry
- If the only supportive finding is a mildly abnormal FDG-PET, a primary psychiatric disorder should be reconsidered
- Consider serum of CSF neurofilament light chain if locally available

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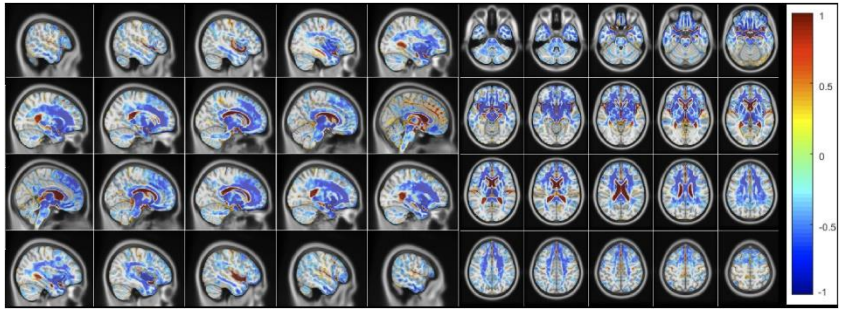
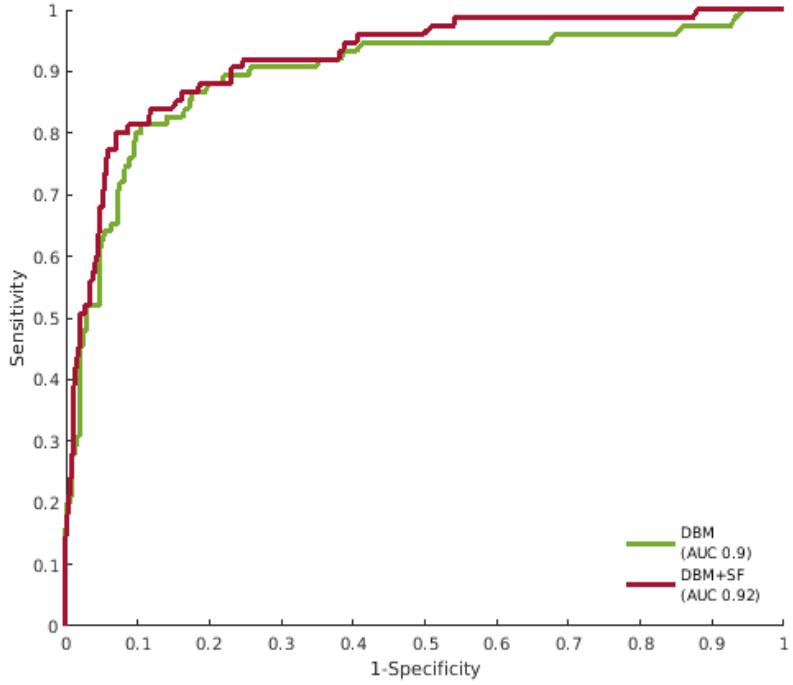
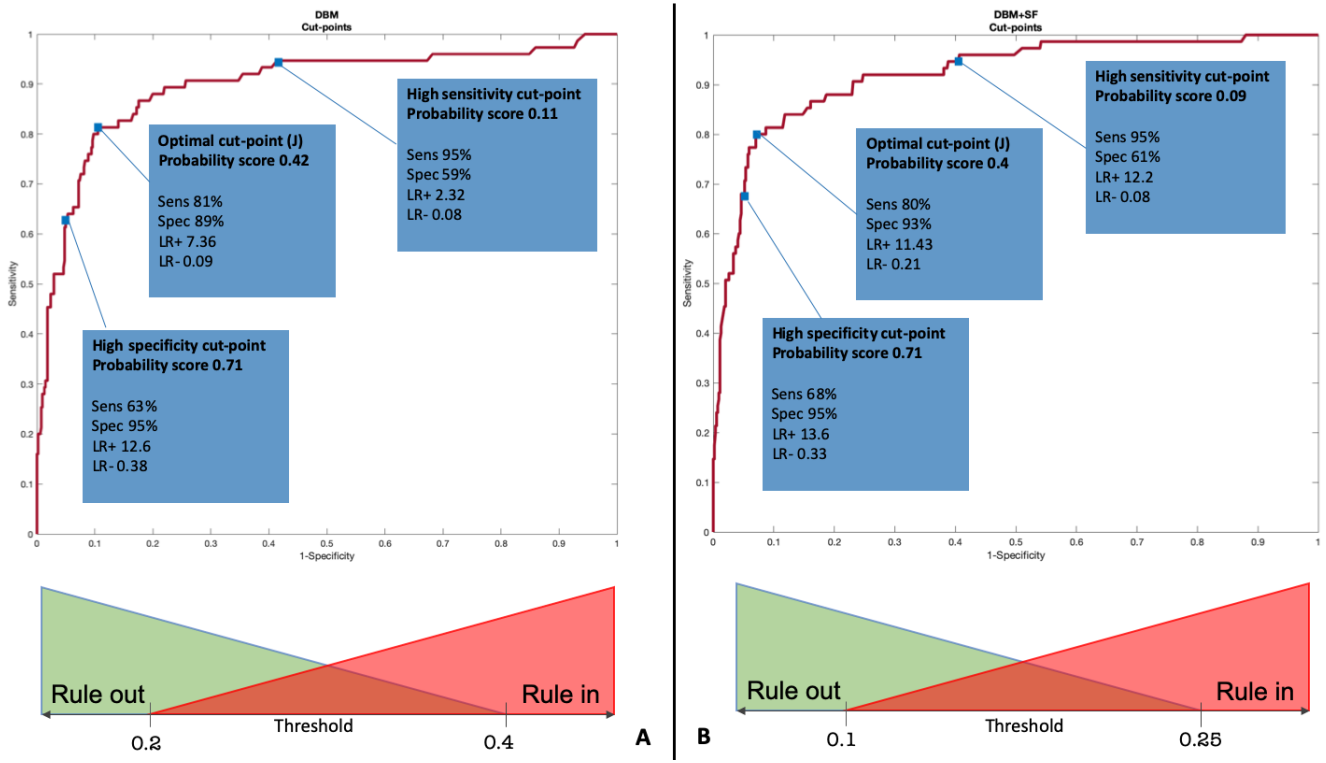
CAN WE EXTRACT MORE INFORMATION FROM MRI WITH ML?







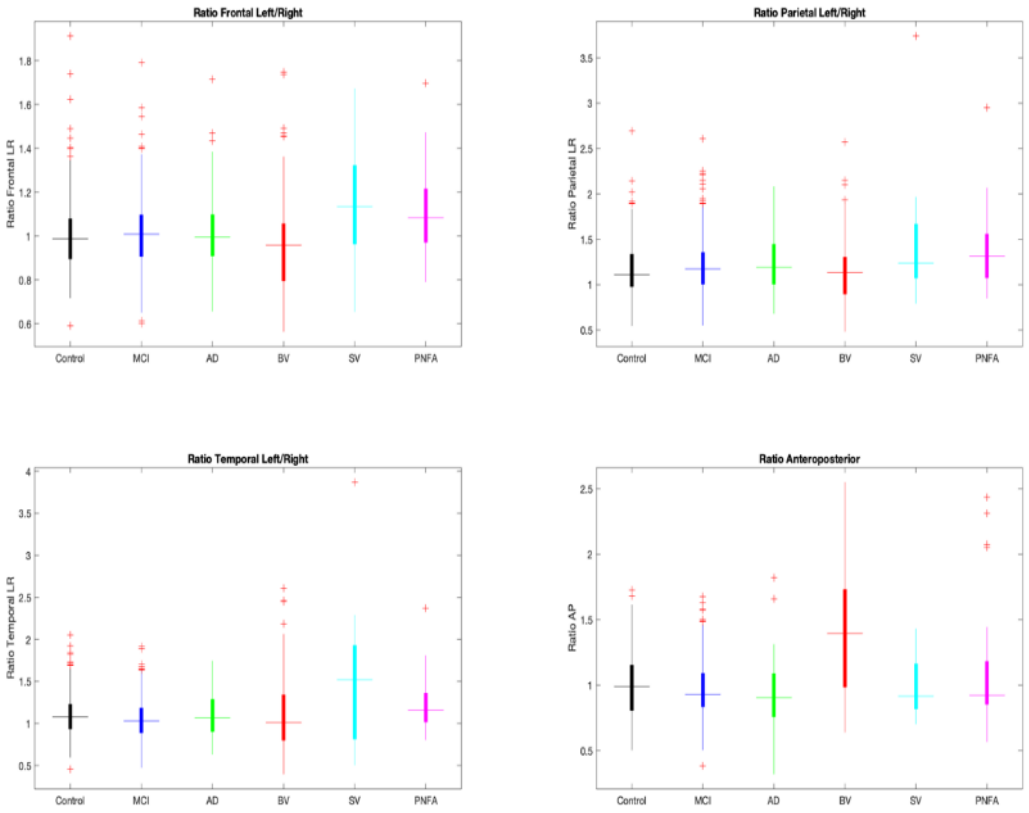
Manera et al. J Neurol Neurosurg Psychiatry, 2021

ANTERO-POSTERIOR VENTRICULAR RATIO AS A DIAGNOSTIC MARKER

- The antero-posterior ratio was the only feature found to be significantly different i bvFTD compared to all other cohorts (Controls: MCI-AD, AD, SV, PNFA).

- bvFTD patients show a faster increase in the ventricular antero-posterior ratio compared to other cohorts

- Differentiates bvFTD from primary psychiatric disorders with 84% accuracy



Manera et al. NeuroImage: Clin., 2022

Psychiatric Presentations of *C9orf72* Mutation: What Are the Diagnostic Implications for Clinicians?

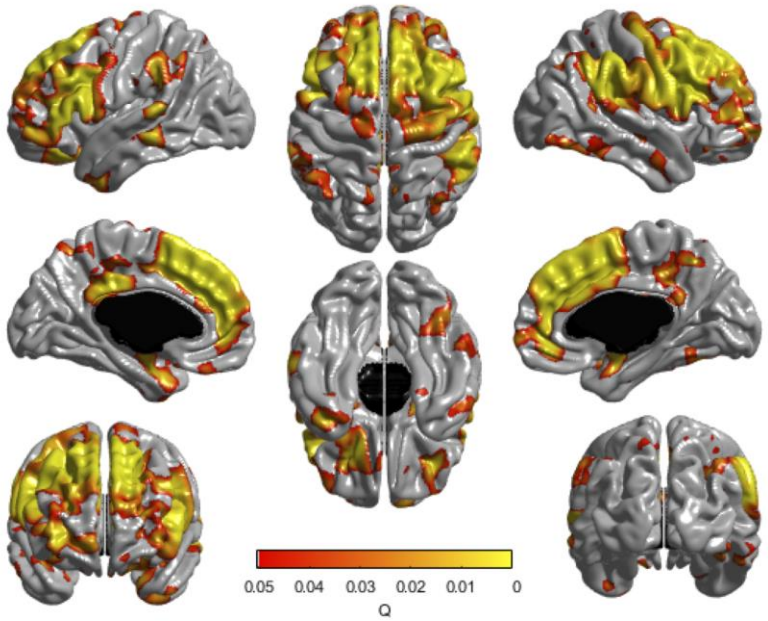
Simon Ducharme, M.D., M.Sc., F.R.C.P.(C), Sepideh Bajestan, M.D., Ph.D., Bradford C. Dickerson, M.D., Valerie Voon, M.D., Ph.D.

The *C9orf72* mutation was identified as the most frequent genetic cause of frontotemporal dementia (FTD). In light of multiple reports of predominant psychiatric presentations of FTD secondary to *C9orf72* mutation, the American Neuropsychiatric Association Committee on Research reviewed all studies on psychiatric aspects of this mutation to identify clinically relevant features for diagnosis. The most common psychiatric presentation is psychosis (21%–56%), with delusions, and/or multimodal hallucinations. Other presentations include late-onset mania and depression with cognitive impairment or catatonia. However, the frequency of *C9orf72* mutations is low in typical schizophrenia or bipolar disorders (<0.1%). The authors provide clinical guidance on diagnosis and genetic testing.

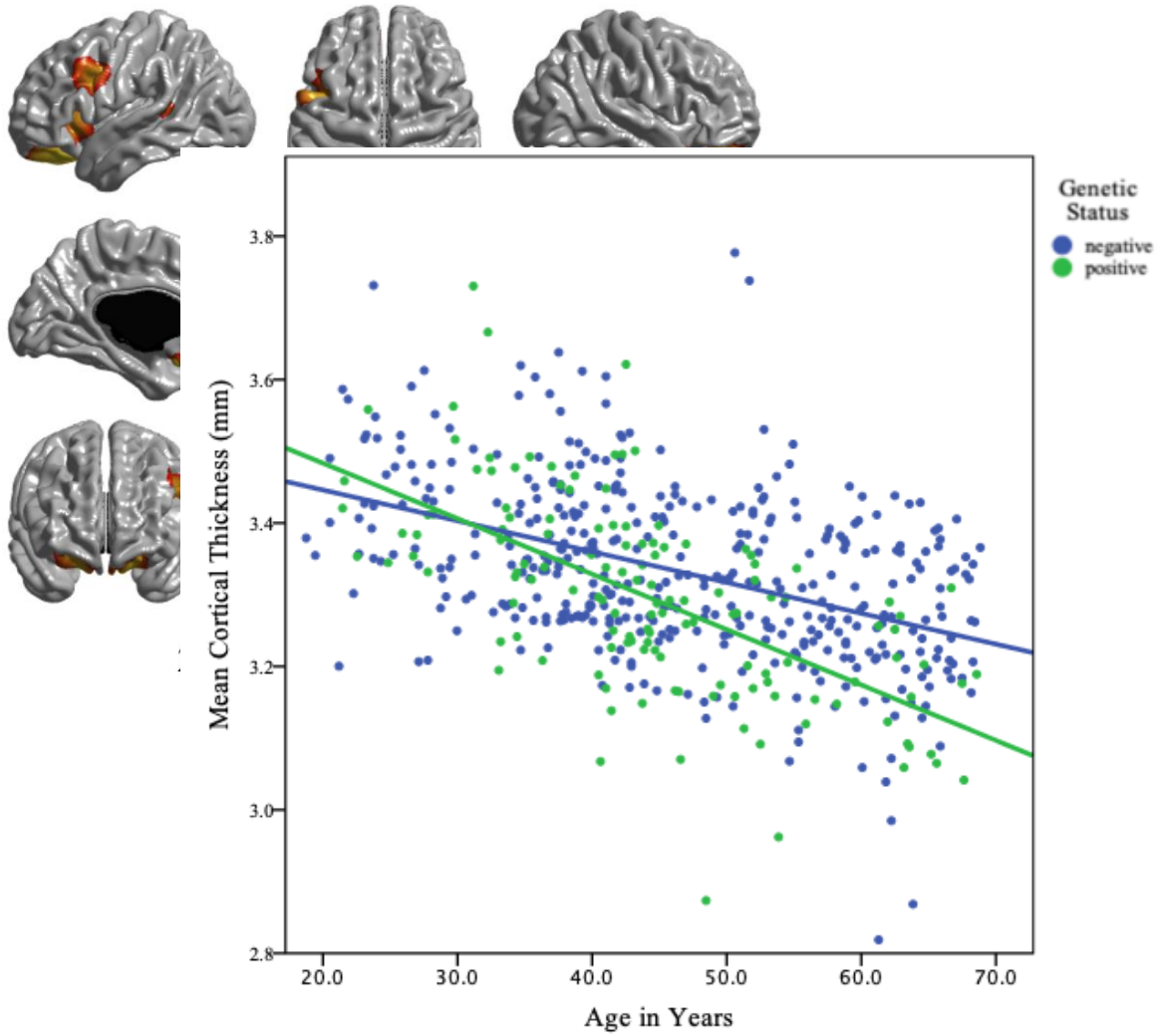
JNCN in Advance (doi: 10.1176/appi.neuropsych.16090168)

J Neuropsychiatry Clin Neurosci, 2017

Cortical Aging trajectories in c9orf72 carriers



2A. Cortical Thickness



Le Blanc et al. Annals Neurol, 2020

Recommendations - Genetics

Box 7

Assessment recommendations for genetic testing

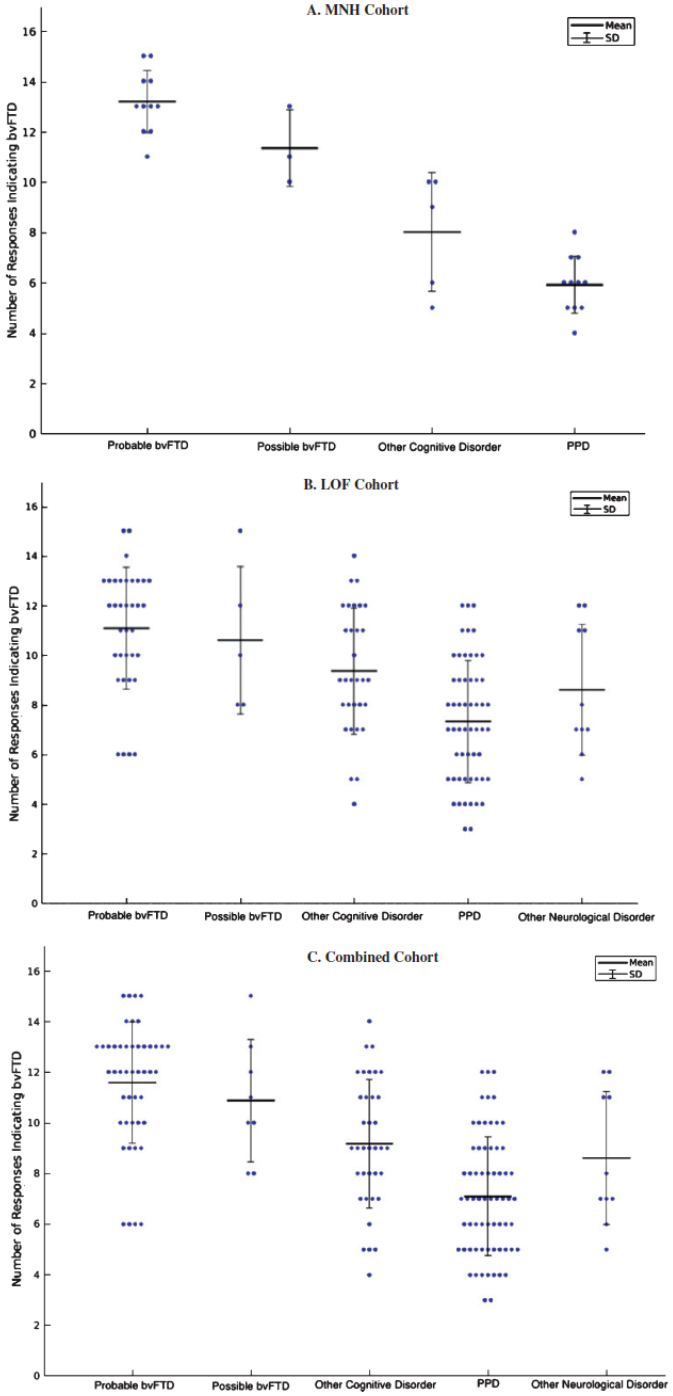
Genetic testing		
Minimal requirements	**Clinical recommendation**	**Requires further research**
• Access to clinical care provider and laboratory that can perform FTD genetic testing.	• Genetic testing (all FTD mutations) in probable bvFTD with at least one first-degree relative with bvFTD, late-onset PPD, ALS or other early onset neurodegenerative disease. • *C9orf72* screening in all cases with possible or probable bvFTD, regardless of family history. • *C9orf72* screening in late-onset PPD with at least one first-degree relative with FTD or ALS. • Strongly consider *C9orf72* screening in all cases of suspected bvFTD not meeting full diagnostic criteria if there is prominent psychiatric symptoms or family history of late-onset PPD.	• Whole exome or genome sequencing in multiple (>2) family members with unknown genetic deficit.

Journal of Alzheimer's Disease 67 (2019) 113–124
DOI 10.3233/JAD-180839
IOS Press

The Frontotemporal Dementia versus Primary Psychiatric Disorder (FTD versus PPD) Checklist: A Bedside Clinical Tool to Identify Behavioral Variant FTD in Patients with Late-Onset Behavioral Changes

Simon Ducharme[a,b,*], Leora Pearl-Dowler[a], Flora Gossink[c,d], Jillian McCarthy[b], Jimmy Lai[b], Bradford C. Dickerson[e], Howard Chertkow[f], Lucile Rapin[b], Everard Vijverberg[c,d], Welmoed Krudop[c,d], Annemieke Dols[c,d] and Yolande Pijnenburg[d]

[a]*Department of Psychiatry, McGill University Health Centre, Montreal, QC, Canada*
[b]*McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, Canada*
[c]*Department of Old Age Psychiatry, GGZinGeest/Amsterdam University Medical Centre, Amsterdam, The Netherlands*
[d]*Department of Neurology, Alzheimer Center Amsterdam, Amsterdam Neuroscience Campus, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands*
[e]*Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[f]*Department of Neurology, Jewish General Hospital, McGill University, Montreal, QC, Canada*



- Score ≥11 strongly indicative of bvFTD (specificity 93.9%, PPV 88.2 %)
- Scores ≤8 strongly indicative of a PPD (specificity 91.3%, PPV 92.7%)

Current behavioral treatments

Future developments

FTD Symptomatic Treatments

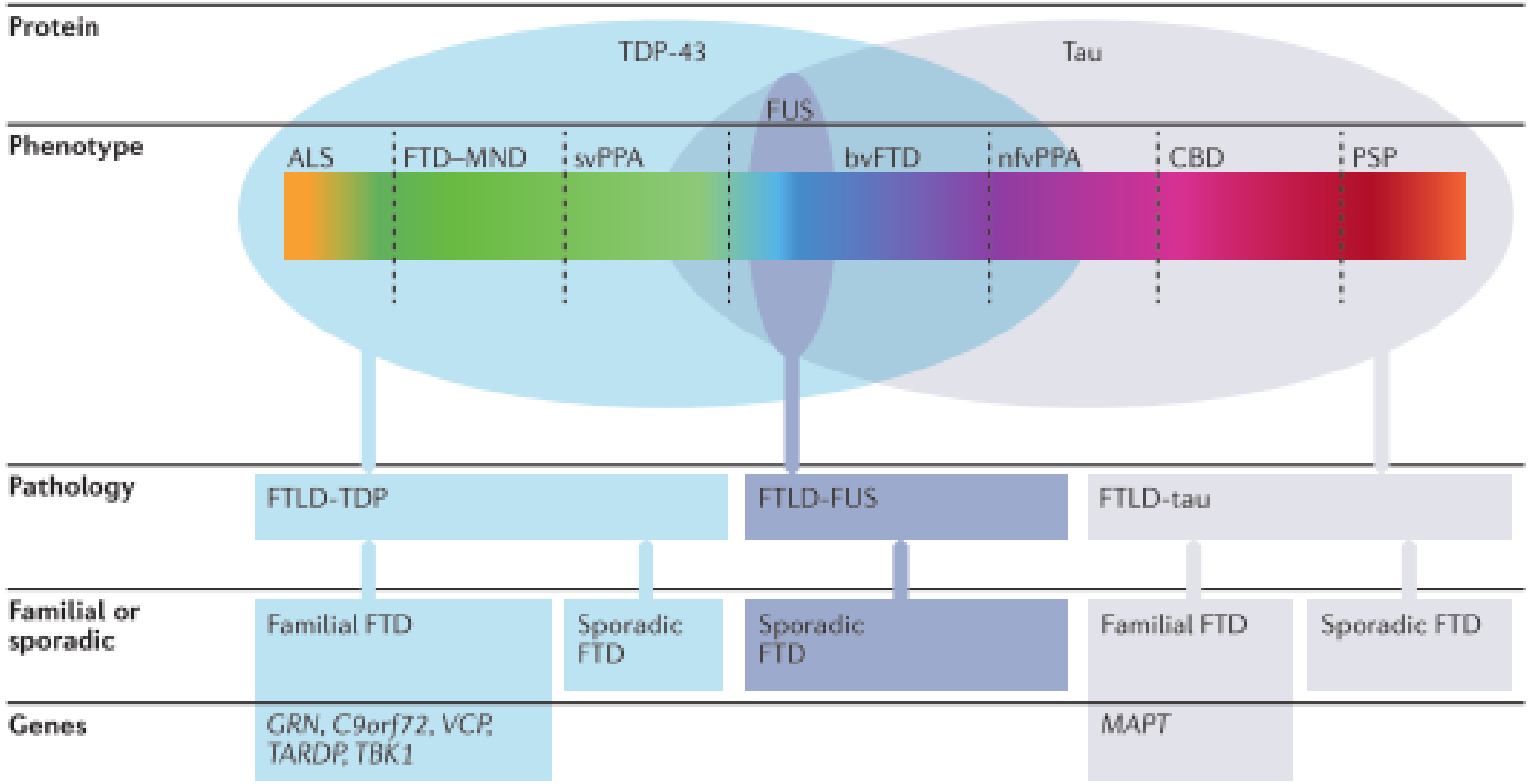
- No disease modifying treatment
- Cholinesterase inhibitors can increase agitation, but can be tried if there is a possibility of AD
- Memantine not useful
- Trazodone – 1 positive RCT for agitation
- SSRI – Decrease repetitive and compulsive behavior
- Mood stabilizers and antipsychotics for agitation (limited data)
- Psychostimulants for apathy?
- Speech therapy for PPA?
- 1 positive small RCT on oxytocin
- TauRx (methylen blue derivative) - ineffective

CLINICAL – GENETICS - PATHOLOGY

Clinical syndromes
- bvFTD
- PPAs
- CBD/PSP

Genetics
- C9orf72
- GRN
- MAPT

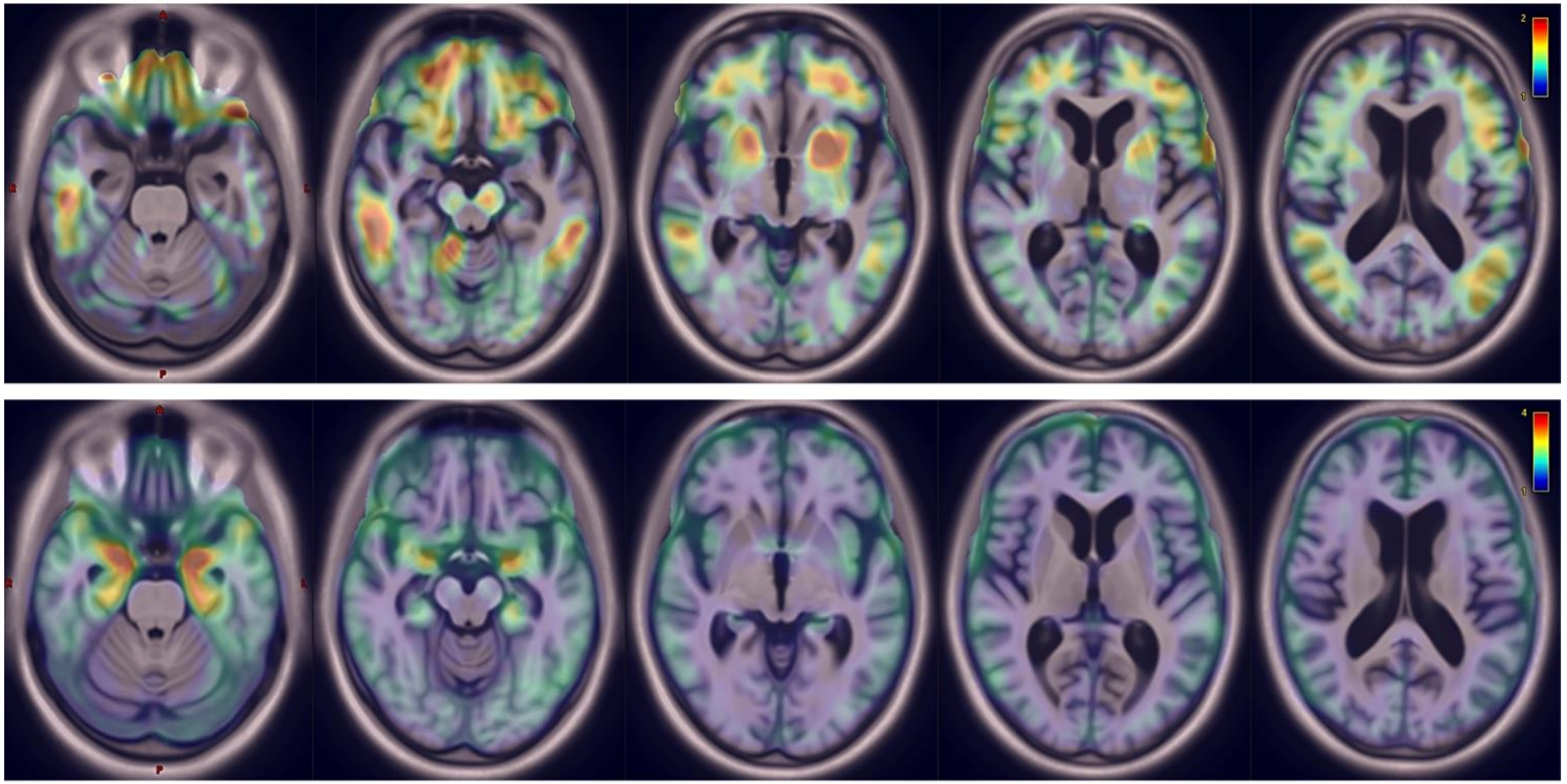
Pathologies
- Tau
- TDP-43
- FUS



Meeter et al., 2016

MK-6240 TAU TRACER IN GENETIC FTD

#1 – 71 male, bvFTD due to P301L MAPT mutation, CDR-FTLD 2, MoCA 6/30



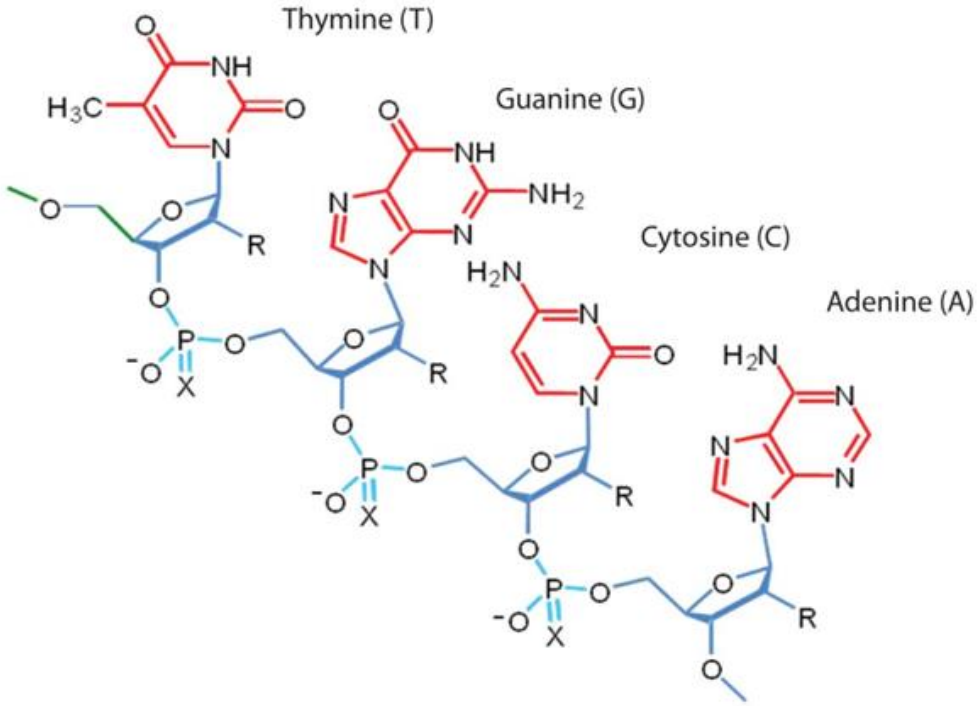
#2 – 60 female, bvFTD due to R406W MAPT mutation, CDR-FTLD 0.5, MoCA 29/30

Levy et al. Brain 2021

ANTISENSE OLIGONUCLEOTIDES (ASO)

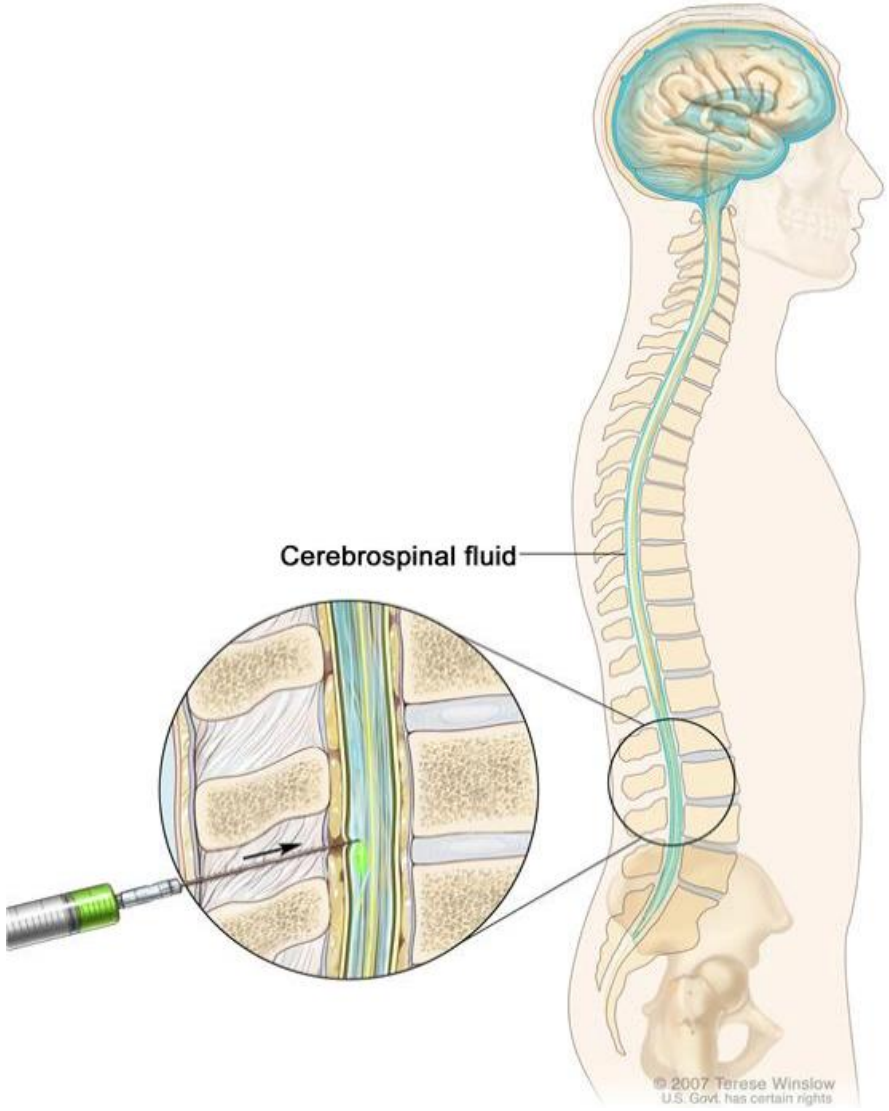
Clinical Research Unit – Dr. Ducharme

- Nucleic acid chains that block the transcription of a specific protein RNA



INTRETHECAL BOLUS ADMINISTRATION

Clinical Research Unit – Dr. Ducharme



- Distribution through the CNS
- Possible administration q3 months of more

Image adapted from www.cancer.gov

ASO for Genetic FTD

- Two molecules under investigation for C9orf72 (ALS and FTD-ALS)
- One molecule for MAPT currently tested in AD (Phase 1 completing, phase 2 planned)
- Development of disease progression models using biomarkers from longitudinal progression cohorts (GENFI-ARTFL)

NEUROIMAGING FOR FTD TRIALS

- CHANGE IN LATERAL VENTRICLES VOLUME MOST SENSITIVE SURROGATE BIOMARKER OF TREATMENT RESPONSE

Region	Controls N=107 (ΔDBM Jacobian)	bvFTD N=53 (ΔDBM Jacobian)	p-Value	Sample Size 12 months	Sample Size 24 months
Lateral Ventricles	0.06±0.06	0.34±0.32	<0.001	194	50
Posterior Cingulate-L	0±0.01	-0.02±0.03	<0.001	251	65
Ventral Diencephalon	0±0.01	-0.02±0.02	<0.001	257	66
Third Ventricle	0.03±0.03	0.12±0.13	<0.001	264	68
Putamen-L	0±0.01	-0.03±0.03	<0.001	282	73
Putamen-R	0±0.01	-0.03±0.03	<0.001	286	73
Isthmus Cingulate-L	0±0.03	-0.02±0.03	0.001	306	79
Inferior Lateral Ventricle-L	0.01	0.1±0.14	<0.001	344	89
Middle Temporal-R	0±0.02	-0.02±0.03	<0.001	433	110
Thalamus-L	0±0.01	-0.02±0.02	<0.001	460	118
Middle Temporal-L	0±0.02	-0.02±0.03	0.001	468	119
Superior Temporal-L	0±0.01	-0.02±0.03	<0.001	475	121
Superior Parietal-R	0.01±0.06	-0.02±0.04	0.019	493	126
Inferior Lateral Ventricle-R	0.01	0.1±0.18	<0.001	542	138
Precuneus-L	0±0.02	-0.01±0.03	0.001	570	145
Caudate-L	0-0.02	0.04±0.;09	<0.001	586	149
Amygdala-L	-0.01±0.02	-0.04±0.07	<0.001	593	150
Thalamus-R	0±0.01	-0.01±0.02	<0.001	605	154
Pallidum-R	0±0.02	-0.02±0.05	<0.001	605	154
Basal Forebrain	0±0.02	-0.02±0.04	0.001	620	157
Brain Stem	0±0.01	-0.01±0.02	<0.001	635	161

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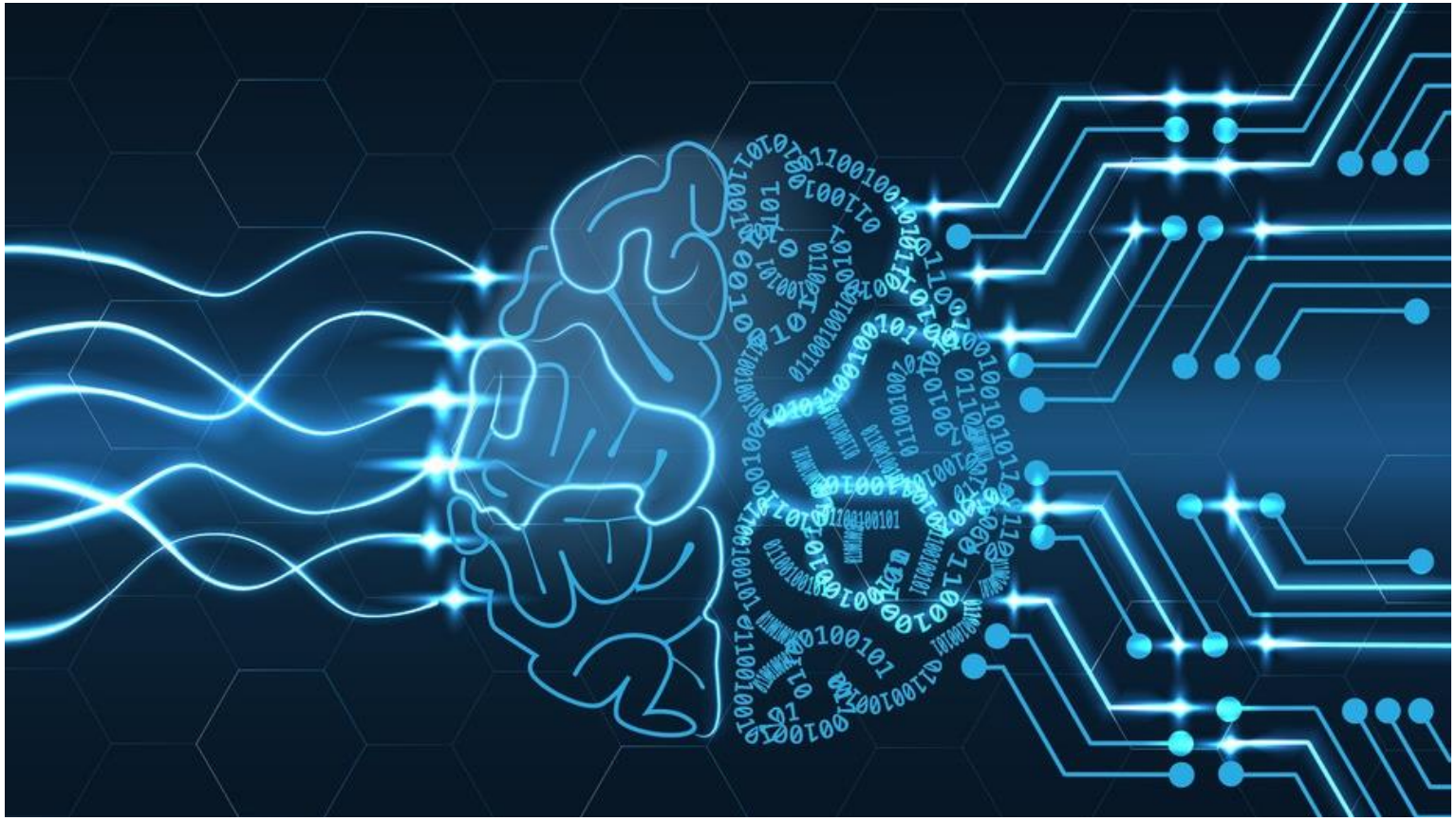
THANK YOU!

Douglas
CENTRE DE RECHERCHE
RESEARCH CENTRE

QUESTIONS



Contact simon.ducharme@mcgill.ca

Douglas
CENTRE DE RECHERCHE
RESEARCH CENTRE