dr. Van Langenhove T.
Ghent University Hospital, Belgium

Frontotemporal dementia vs. primary psychiatric disorders

23rd May 2023

UZ GENT
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European Reference Network
Neurological Diseases (ERN-RND)
Neuropsychiatric International Consortium Frontotemporal Dementia
GENFI GENETIC FTD INITIATIVE

Disclosures

- PI for clinical trials in dementia
  - Biogen, Roche, Novartis, Janssen, Eli Lilly, Novo Nordisk, AB Science

Learning objectives

- By the end of this webinar you will be able to:
  - Known about the multiple possible causes of late-onset behavioral changes
  - Choose the most appropriate strategy for differential diagnosis of bvFTD vs PPD

Webinar outline

- Introduction
- Differential diagnosis
- Assessment
- Conclusions

Question 1

- What is your professional background?
  1. Neurologist
  2. Neurology resident
  3. Psychiatrist
  4. Psychiatry resident
  5. Nurse
  6. Physiotherapist
  7. Geneticist
  8. Psychologist
  9. Patient or patient representative
  10. Other

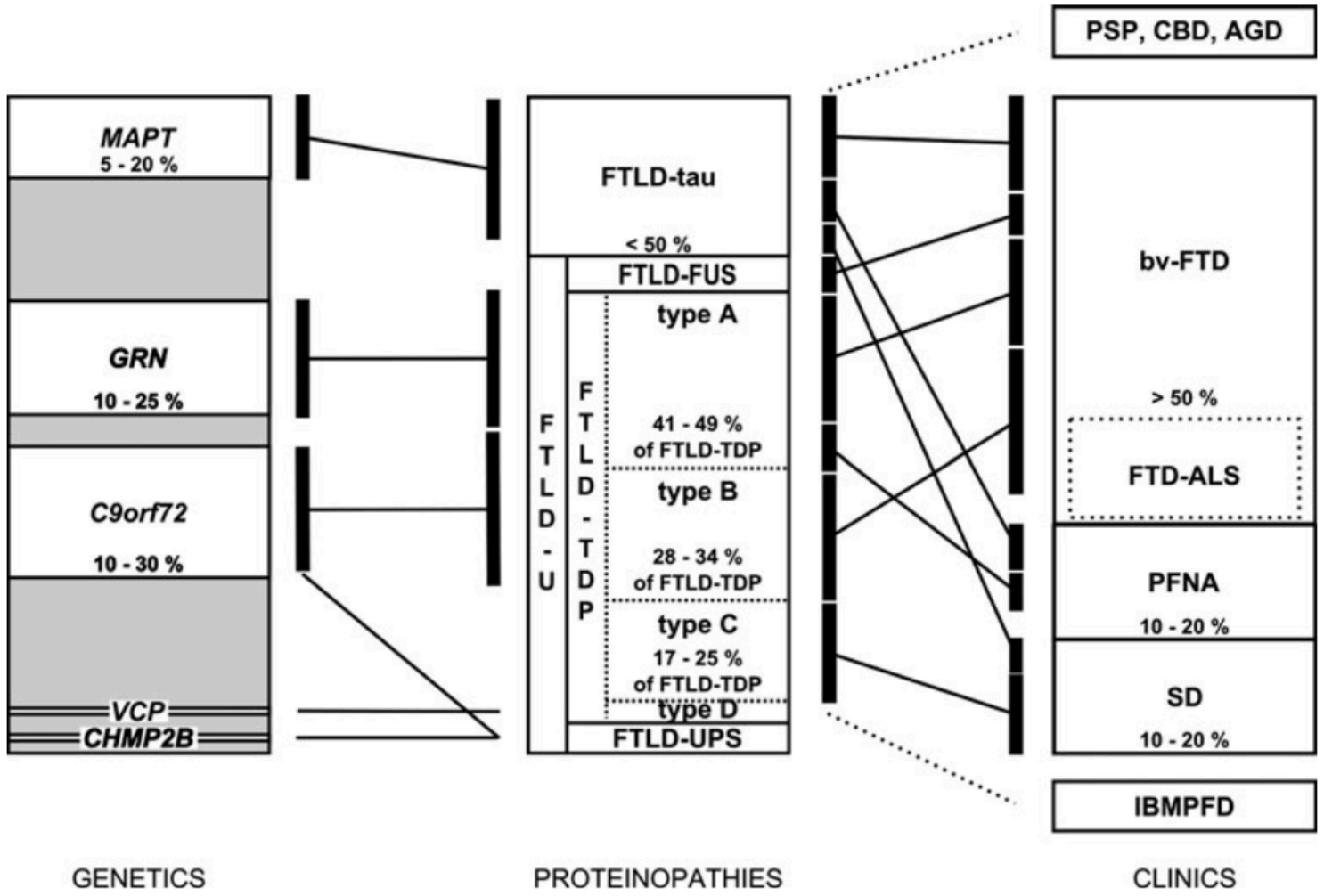
Question 2

- How many patients do you follow with ongoing diagnostic confusion between bvFTD and PPD?
  1. None
  2. <5
  3. 5-10
  4. >10

Frontotemporal dementia

- Neuropathological entity characterized by progressive neurodegeneration predominantly affecting the frontal and temporal lobes
- Prevalence: 10-20/100.000
- Age of symptom onset: usually 45-65 years
- Heterogenous disorder
  - Different phenotypes: bvFTD, nfv-PPA, sv-PPA (+ALS, CBS, PSP)
  - Different types of pathology: TDP-43, Tau, FUS/FET
  - Different causal genes: *C9orf72, GRN, MAPT, TKB-1, VCP, CHMP2B*

Fig. 1 Diagram illustrating the clinical, genetic and neuropathological correlations in FTLD. The *gray background* of the genetics box represents the genetically unexplained fraction in FTLD cases overall (as compared to familial cases in Table 2)



Sieben A, Van Langenhove T et al. Acta Neuropathol 2012

Table 3 International consensus criteria for behavioural variant FTD (FTDC)

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

- A. Meets criteria for possible bvFTD
- B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
- C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
  - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
  - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

- A. Meets criteria for possible or probable bvFTD
- B. Histopathological evidence of FTLD on biopsy or at post-mortem
- C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

- A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
- B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
- C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Rascovsky K et al., Brain 2011

bvFTD differential diagnosis

- Alzheimer’s disease
- Primary psychiatric disease
- bvFTD phenocopy syndrome
- Lewy body dementia
- Cerebrovascular disease
- Traumatic brain injury
- Brain tumors
- Infectious and inflammatory diseases
- Frontotemporal brain sagging syndrome
- Others

Table 2
Overlapping and differentiating clinical features of bvFTD and primary psychiatric disorders

Primary Psychiatric Disorders	Overlapping Features with bvFTD	Main Differentiating Features with bvFTD
Major depressive disorder	Lack of interest, decreased motivation, low energy, poor concentration, social and occupational withdrawal	Sustained dysphoria, guilt, and suicidal thoughts in major depression only
Bipolar disorder	Disinhibition, irritability, socially inappropriate behaviors	Euphoria and grandiosity in mania, cyclical nature
Schizophrenia	Low motivation, decreased initiative, social withdrawal, cognitive deficits (executive, working memory)	Psychotic symptoms rare in FTD, different epidemiology (earlier onset in schizophrenia)
Obsessive-compulsive disorder	Identical compulsive behaviors	Lack of obsessions and anxiety in FTD
Hoarding disorder	Pathologic accumulation	Primary hoarding motivated by anxiety and rational for future use as opposed to cognitive disorganization in FTD
Catatonia	Perseveration, stereotypies, mutism, echophenomenon	Fluctuating course, marked acute improvement with benzodiazepines/ECT in catatonia
Autism spectrum disorder	Social cognition impairment	Symptoms present since early childhood without major deterioration over time
ADHD	Distractibility, disorganization, restlessness, impulsive decisions	Symptoms present before 12 years of age, better response to psychostimulants in ADHD
Personality disorders (PD)	Lack of empathy of narcissistic and antisocial PD, impulsivity of borderline PD	Longitudinal maladaptive pattern in PD; problematic behaviors are a break from longitudinal personality in bvFTD

Ducharme & Dickerson
Psychiatr Clin N Am 2015

Complex differential diagnosis between bvFTD and PPD

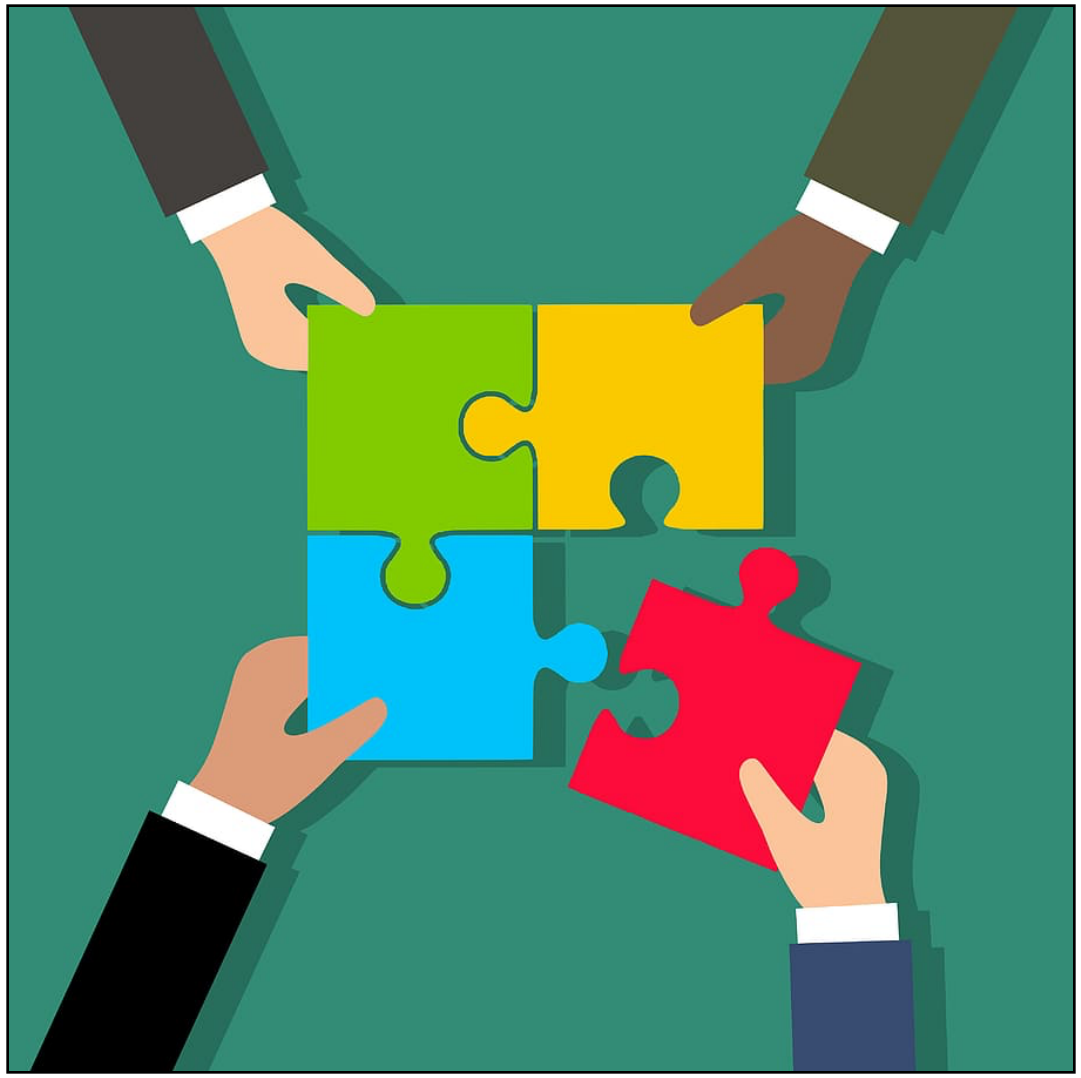
- Many patients with bvFTD are first seen by a psychiatrist
- 50% of bvFTD were initially diagnosed with a PPD
  - 30% MDD, 11% BPD, 3% schizophrenia, 1% anxiety disorder
- 31.5% of bvFTD were reclassified with a psychiatric diagnosis after two years of multidisciplinary neuropsychiatric follow-up
- A cause of referral and diagnostic delay in bvFTD
  - 3-4 years or more

Woolley J et al., J Clin Psychiatry 2011; Krudop W et al., J Alzheimers Dis 2017

Misdiagnosis or comorbidity?

	Probable or definite bvFTD (n=23)	Other neurodeg. disorder (n=25)	Psychiatric diagnosis (n=40)
Current psychiatric disorder (DSM-IV)	21.7%	12.0%	57.5%
Past psychiatric disorder (DSM-IV)	8.7%	16.0%	62.5%

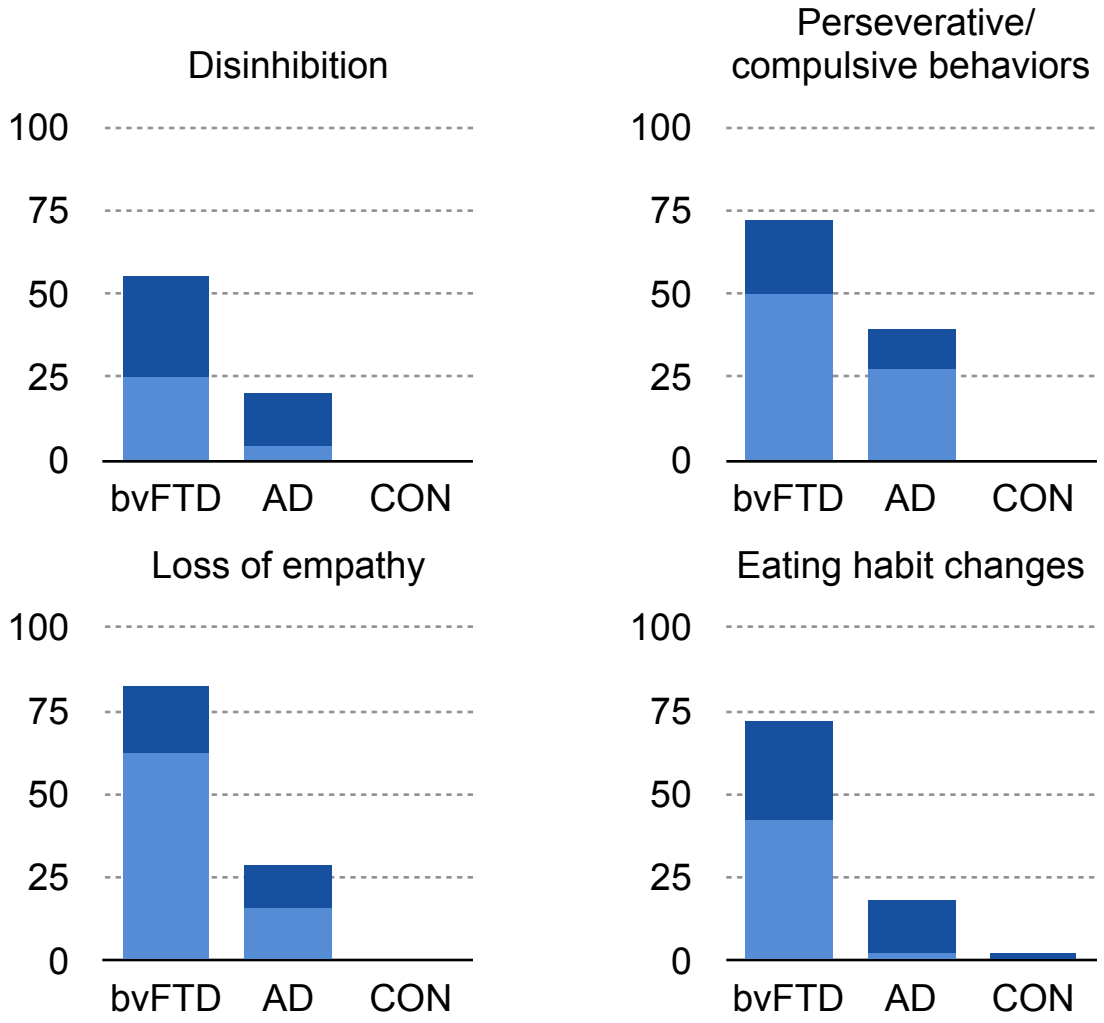
Gossink F et al., JAD 2016



Distribution and severity of frontal behavioral symptoms in probable bvFTD

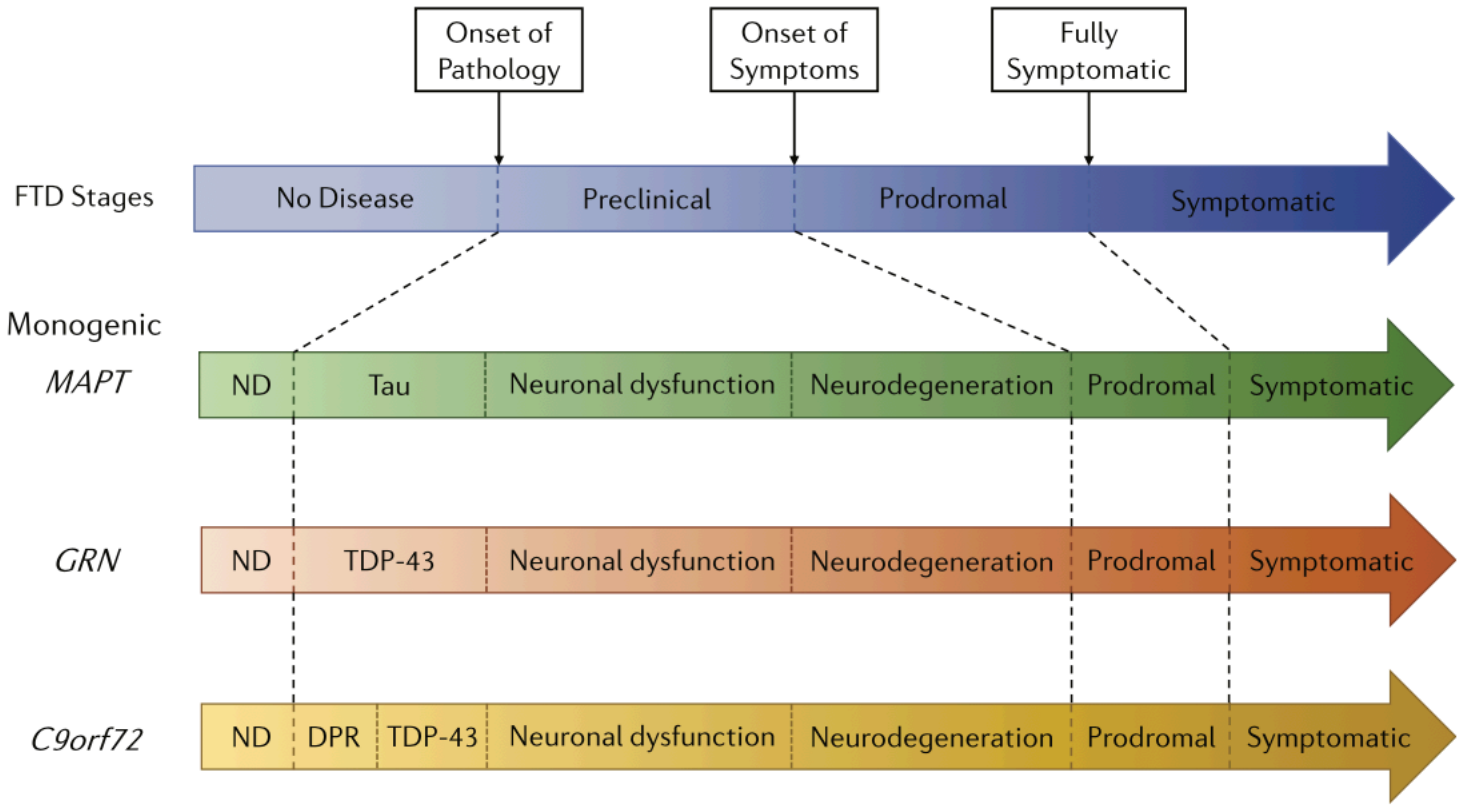
Based on the baseline CBI-R score

Mild Moderate to severe



Adapted from Van Langenhove T. et al. JAD 2016

Mild behavioural and/or cognitive impairment in bvFTD



Benussi A et al. Alzheimers Dement 2022

Definition of MBCI-FTD

A clinical syndrome defined by the presence of persistent and progressive decline in behaviour and/or cognition for more than six months based on observation or history provided by knowledgeable informant.

1. Must be present to diagnose MBCI-FTD

A. Concern regarding behavioural and/or cognitive change from previous functioning, per informant, clinician, or patient
B. Preserved instrumental activities of daily living (unless due to physical impairment, e.g. motor neuron disease or parkinsonism)
C. >18 years old

2. Possible MBCI-FTD

At least three of the following core features (A–G) are sufficient, and must represent a change from previous behaviour, to diagnose possible MBCI-FTD

A. Apathy without moderate-severe dysphoria
B. Behavioural disinhibition
C. Irritability or agitation
D. Loss of empathy or sympathy
E. Repetitive behaviours (either E1 or E2)
   E1. Simple: Aberrant motor behaviour, or restlessness (e.g. pacing, fidgeting, tapping)
   E2. Complex: Perseverative, compulsive or ritualistic behaviour (e.g. rigidity, rituals, hoarding)
F. Joviality or gregariousness
G. Appetite changes/hyperorality

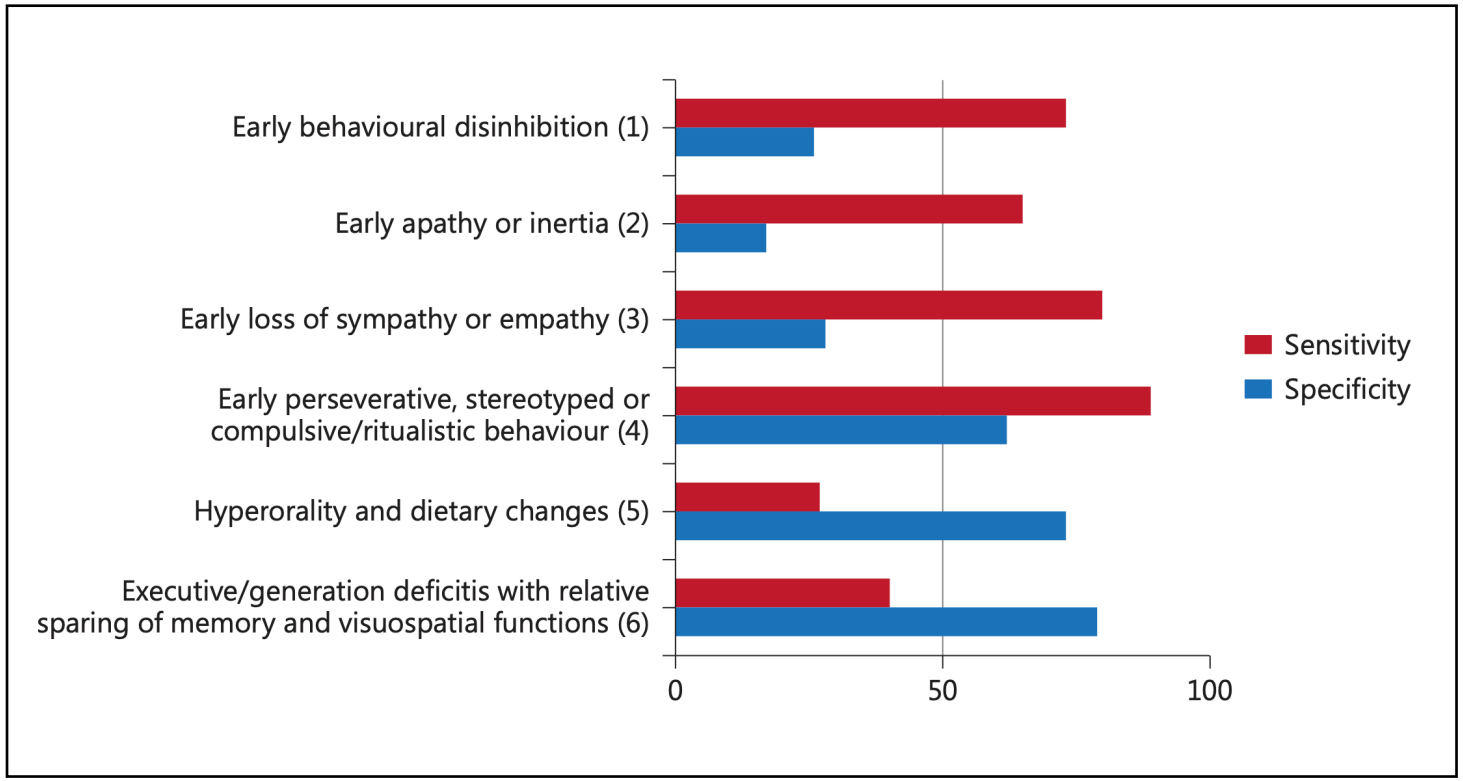
If only two of the above core features (A–G) are present, then at least one of the following (H or I or J) must also be present to diagnose Possible MBCI-FTD:

H. Neuropsychological deficits in context of intact or relatively preserved time/place orientation and visuospatial skills (one of H1–H2 must be present)
   H1. Clinical impairment or clinically significant decline on executive tasks (e.g. verbal generation, set-shifting, etc.)
   H2. Clinical impairment or clinically significant decline on naming tests
I. Reduced insight for at least one aspect of behavioural or cognitive change
J. Impairments on standardized measures of social cognition (one of J1-J2 must be present)
   J1. Reduced understanding or awareness of social expectations
   J2. Low socioemotional sensitivity

Barker M et al. Brain 2022

Diagnostic accuracy of the FTDC in late-onset frontal behavioural changes

	Possible bvFTD	Probable bvFTD
Sensitivity	85%	85%
Specificity	27%	82%



Vijverberg E et al. Dement Geriatr Cogn Disord 2016

Questionnaires to measure behavioural changes

- Cambridge Behavioural Inventory Revised (CBI-R)
- Frontal Behavioural Inventory (FBI)
- Neuropsychiatric Inventory (NPI), with FTD Module
- FTD Rating Scale (FRS)
- DAPHNE
- Others

Question 3

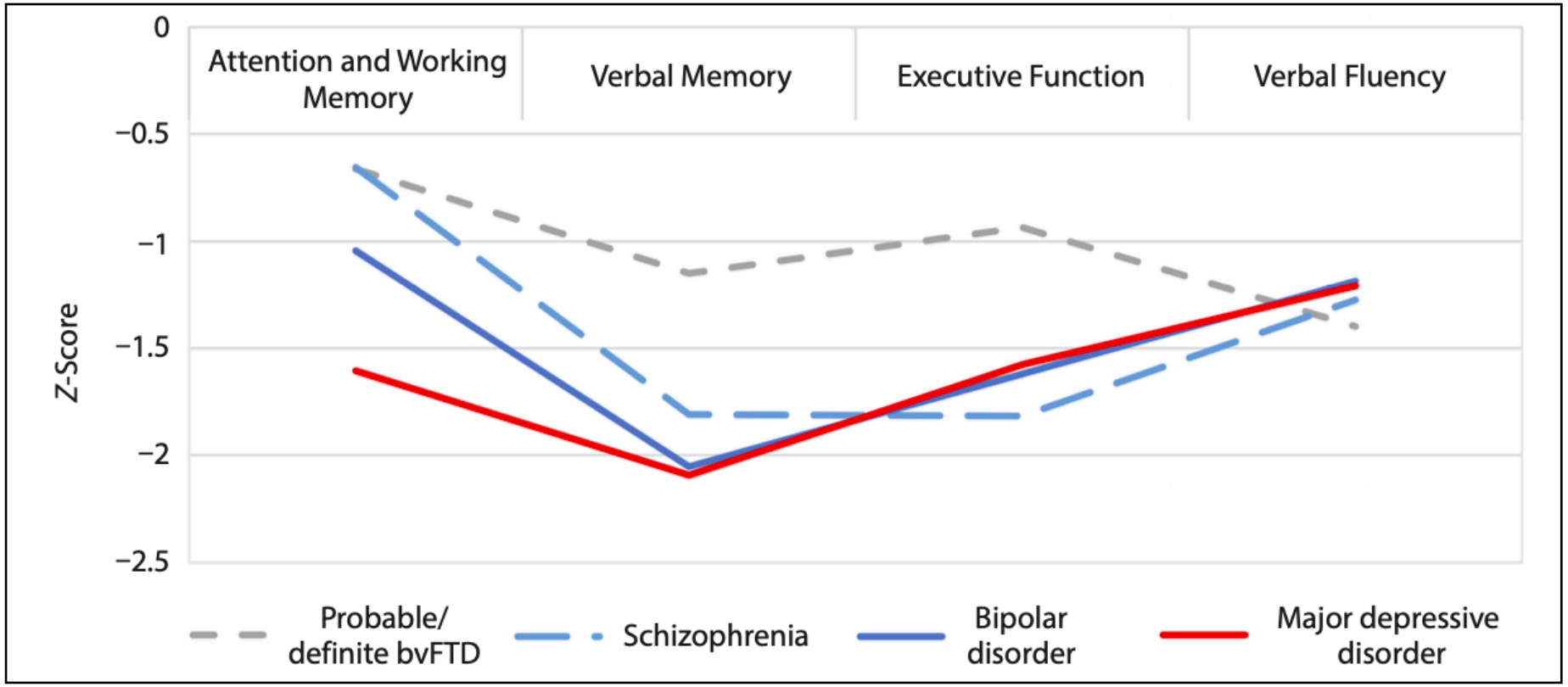
- Which statement on the neuropsychological profile of bvFTD is the most correct?
  1. Encoding memory deficits do not occur in bvFTD
  2. Social cognition deficits are common in bvFTD
  3. Executive function deficits are typical for bvFTD
  4. Executive function deficits are always the most prominent deficit in bvFTD

Patterns of cognitive impairment across dementia syndromes

	bvFTD	AD	DLB	VCI
Attention and concentration	-	+ to ++	+ to ++	+ to ++
Memory	Variable	+++	+ to ++	+
Naming	-	+	-	-
Visuospatial	-	++	++ to +++	+
Executive	++ to +++	+ to ++	+	+ to +++
Social cognition	++ to +++	+	-	-

Burrell J et al, JNNP 2015

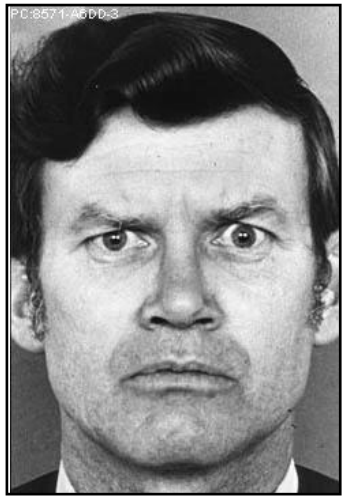
Similar neuropsychological profile of poor attention and working memory, and executive dysfunction in bvFTD and PPD



Vijverberg et al., J Clin Psychiatry 2017

Elements of social cognition

- Face processing
- Emotion recognition/perception
- Empathy
- Mentalizing and theory of mind



Selected tests for social cognition

- Emotion recognition/perception
  - Ekman 60 Faces Test (FEEST)
- ToM
  - Faux pas
  - Reading the Mind in the Eyes (RME)
- Empathy
  - Interpersonal Reactivity Index (IRI)
- Composite tests
  - Social Cognition and Emotional Assessment (SEA)
  - The Awareness of Social Inference Test (TASIT)

Social cognition tests to dd bvFTD from HC

	Study groups			Social Cognition Task				Accuracy Measures			
Paper	BvFTD (n; age; MMSE)	HC (n;age; MMSE)	Biomarker for bvFTD diagnosis	Social Task	Social cognition skill	Stimuli	Index test	Sens	Spec	AUC	Accuracy
Diehl-Schmid et al., 2007	25; 63.2 ± 10.6; 25.3 ± 3.1	33; 60.9 ± 10.8; 29 ± 1.2	FDG-PET	Ek60F	Emotion Recognition	Photos	Ek60F	94%	100%	0.97	–
Glechgerrcht et al., 2010	35; 68.5 ± 7.2 26.9 ± 2.9	14; 65.5 ± 6.5; 29.2 ± 1	CLINICAL DIAGNOSIS (2 experts K:0.91) + MRI-SPECT (frontal damage)	IGT + MIE + FAUX	Affective decision making Affective ToM Cognitive ToM	Photos Stories	IGT + MIE + FAUX IGT + MIE IGT + FAUX MIE + FAUX	–	–	0.971 0.957 0.960 0.930	–
Downey et al., 2013	20; 64 ± 9.3; -	20; 65 ± 8.5; -	MRI (frontal atrophy)	Mentalizing Music Tasks	Affective ToM	Music Listen-ing	Mentalizing Music Tasks	–	–	0.88	85%
Bertoux et al., 2013	20; 69.1 ± 10.59; 23.5 ± 4.5	30; 67.2 ± 8.6; 28.9 ± 0.8	MRI + FDG-PET + FOLLOW-UP (18 months)	Mini-SEA	Emotion Recognition Cognitive ToM	Photos Stories	Mini-SEA	–	–	–	88%
Schroeter et al., 2018	86; 63.9 ± 9.6 -	43; 66.1 ± 10.1; -	UNCLEAR	RME	Affective ToM	Photos	RME	–	–	0.895	–
Baez et al., 2019	16; 65.8 ± 7 25.8 ± 4.1	22; 62.5 ± 7.1; 29.2 ± 2.7	MRI (frontal atrophy)	RME	Affective ToM	Photos	Composite	–	–	–	97.4% ∫

Dodich A et al., Neuropsychol Rev 2021

Social cognition tests to dd bvFTD from PPD

	Study groups			Social Cognition Task				Accuracy Measures			
Paper	bvFTD (n; age; MMSE)	Psych (n; age; MMSE)	Biomarker for bvFTD diagnosis	Task/Battery	Social cognition skill	Stimuli	Index test	Sens	Spec	AUC	Accuracy
Bertoux et al., 2012	37 (17 E-bvFTD, 20 M-bvFTD) 63.1 ± 9.1 (E-bvFTD) 66.7 ± 8.3 (M-bvFTD) 27.1 ± 2.3 (E-bvFTD) 23.3 ± 3.9 (M-bvFTD)	19 MDD 63.3 ± 8.4 26.7 ± 2.2	IMAGING BIOMARKERS	SEA	Emotion Recognition Cognitive ToM	Photos Stories	Composite	91.9% All bvFTD 94.1% E-bvFTD 90% M-bvFTD	89.5% All bvFTD 89.5% E-bvFTD 89.5% M-bvFTD	0.97 All bvFTD	–
				Mini-SEA	Emotion Recognition Cognitive ToM	Photos Stories	Composite	89.2% All bvFTD 94.1% E-bvFTD 85% M-bvFTD	100% All bvFTD E-bvFTD M-bvFTD	0.98 All bvFTD	–
Chiu et al., 2018	25 66.08 ± 9.06 24.80 ± 3.40	20 MDD 61.95 ± 12.79 28.40 ± 1.67	FOLLOW-UP (1 year)	FEE	Emotion Recognition	Photos	FEE	–	–	0.93–0.99	–
Gossink et al., 2018	22; 62.8 ± 6.7 26.1 ± 2.8	24; 64.7 ± 6.7 25.4 ± 2.5	MRI + FDG-PET+ FOLLOWUP (24 months)	EK60F & FAUX	Emotion Recognition Cognitive ToM	Photos/Stories	EK60F FAUX	66.7% n.s.	68.2% n.s.	0.73 n.s.	- n.s.
Baez et al., 2019	16 65.8 ± 7 25.8 ± 4.1	13 BD 61.9 ± 9.1 29.4 ± 0.5	MRI (frontal atrophy)	RME	Affective ToM	Photos	Composite	–	–	–	89% ∫

Dodich A et al., Neuropsychol Rev 2021

Question 4

- A 59-year-old man is referred to a neurologist because of inappropriate behavior, decreased self-care, and increased hoarding, that had developed after a conflict at work. His adult children report that he could also make inappropriate comments when they were young. He has no family history of dementia or ALS. On the NPE, he has mild attention, mild executive function, and severe social cognition deficits. MRI of the brain shows no obvious abnormalities. FDG-PET of the brain is reported as normal. What would you recommend?

  1. Referral to a psychiatrist, including a request for review for possible ASD
  2. To repeat the neuropsychological examination after one year
  3. To repeat the FDG-PET scan after one year
  4. To perform testing for the *C9orf72* repeat expansion

Social cognition disturbances in psychiatric disorders

- Autism spectrum disorder
- Depression
- Bipolar disorder
- Schizophrenia

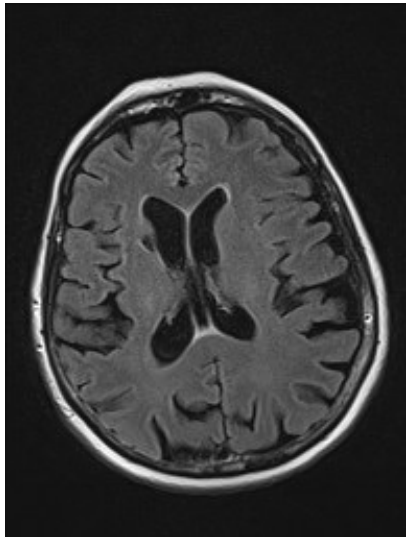
Facial emotion recognition

Test result	bvFTD	MDD/BD
Normal	0	2
Borderline	2	9
Abnormal	27	2

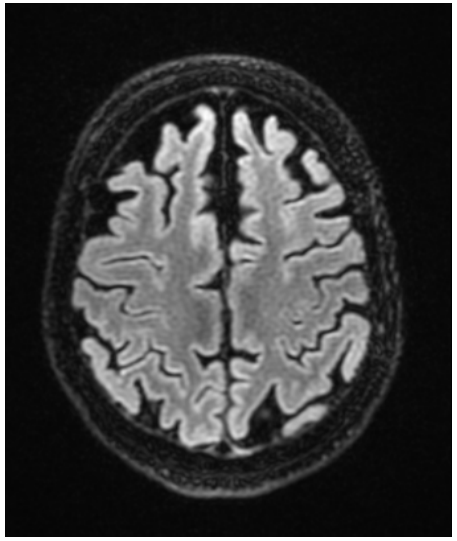
Vantyghem et al., unpublished results

Structural neuroimaging: moderate sensitivity and high specificity

- Autopsy confirmed FTD cases
  - 50% with clear frontotemporal atrophy at presentation
- Late-onset frontal lobe study
  - Sensitivity of 70% (95% CI 52–85%)
  - Specificity of 93% (95% CI 86–97%)



75yo bvFTD, C9orf72+



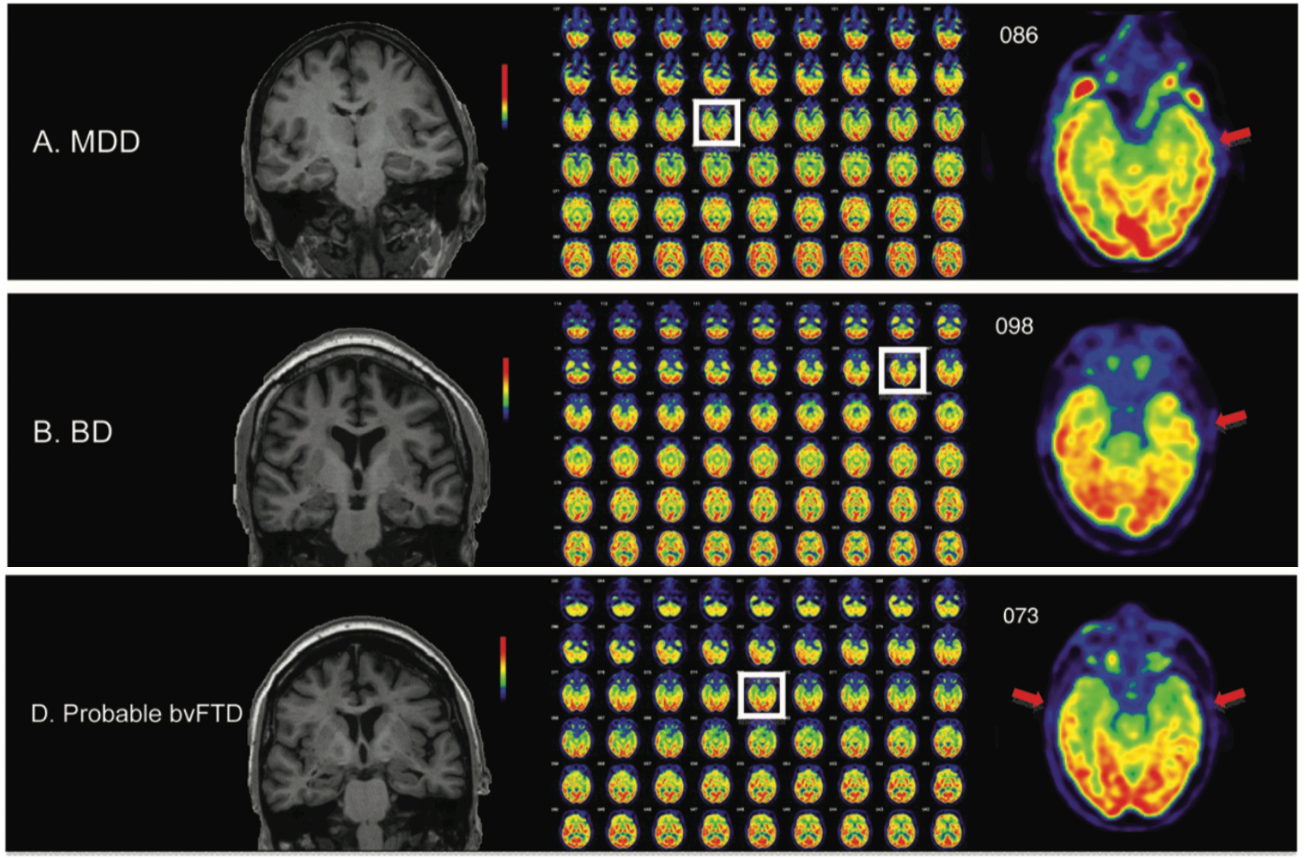
49yo bvFTD

Knopman D et al., Ann Neurol, 2005 ; Vijverberg E et al., JAD 2016

Functional neuroimaging: high sensitivity and moderate specificity

- Late-onset frontal lobe study
  - Sensitivity of 90%
  - Specificity of 68%

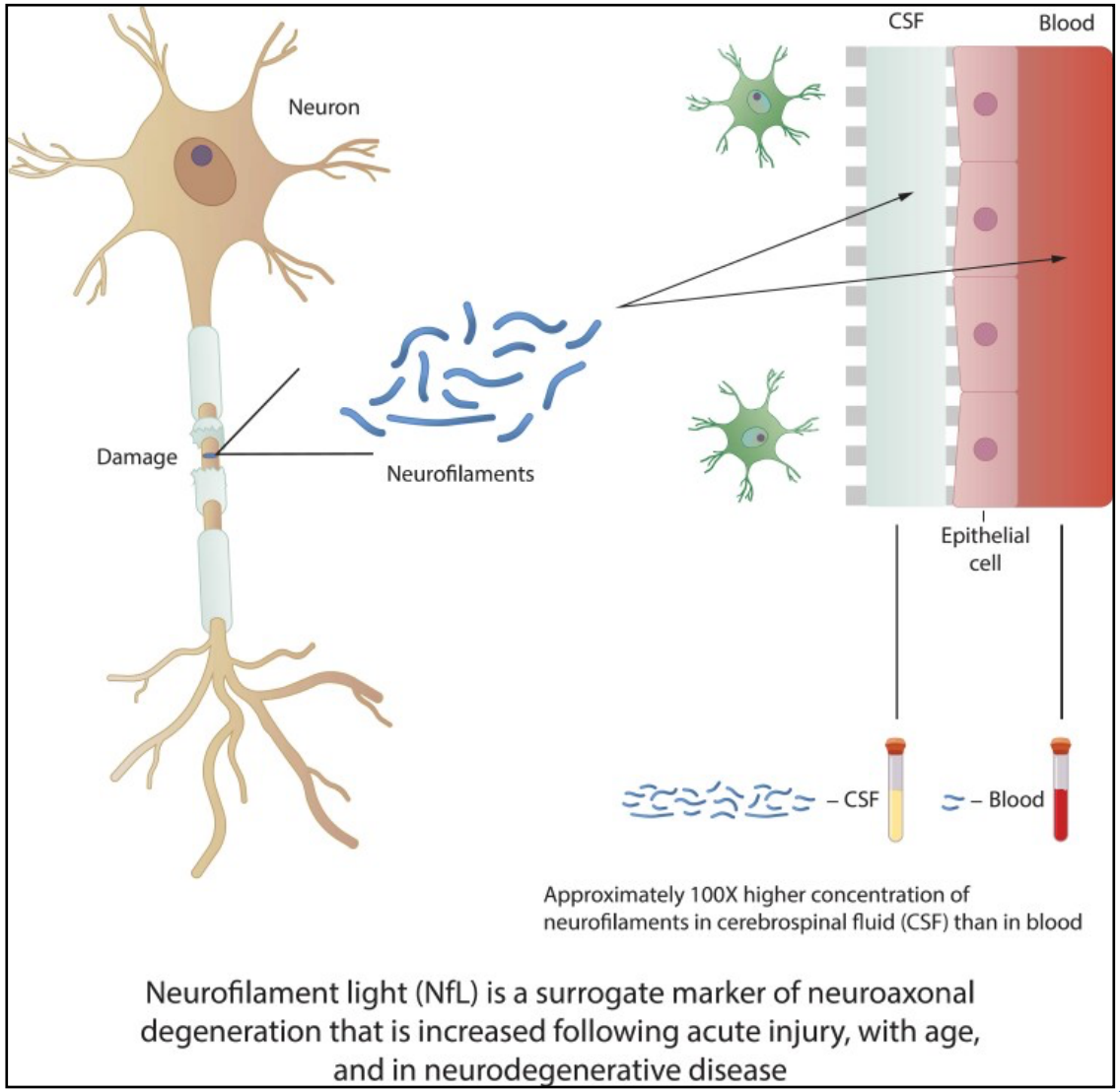
	bvFTD	Psychiatric
PET +	10	12
PET -	1	24



Vijverberg E et al., *JAD* 2016

Neurofilament light (NfL)

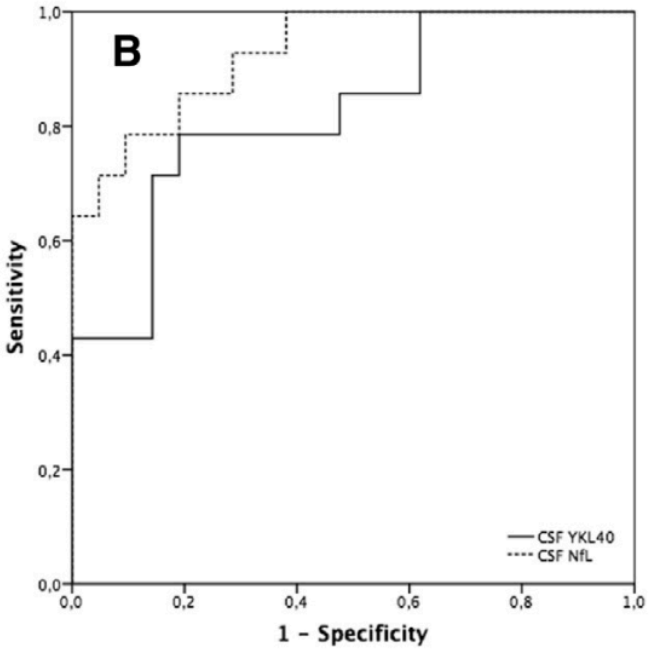
- Structural protein located in the neuronal cytoplasm
- Nonspecific marker for CNS axonal damage
- Strong correlation between CSF NfL and blood NfL

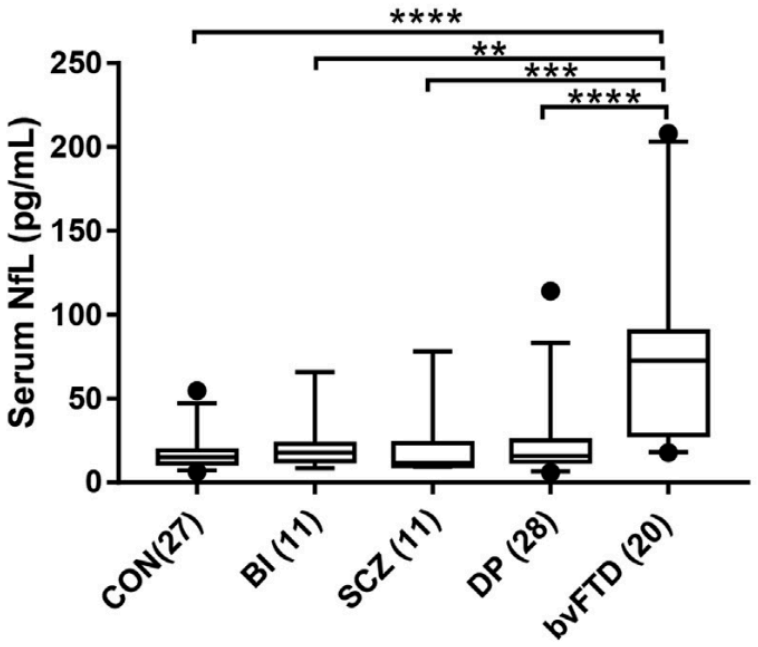


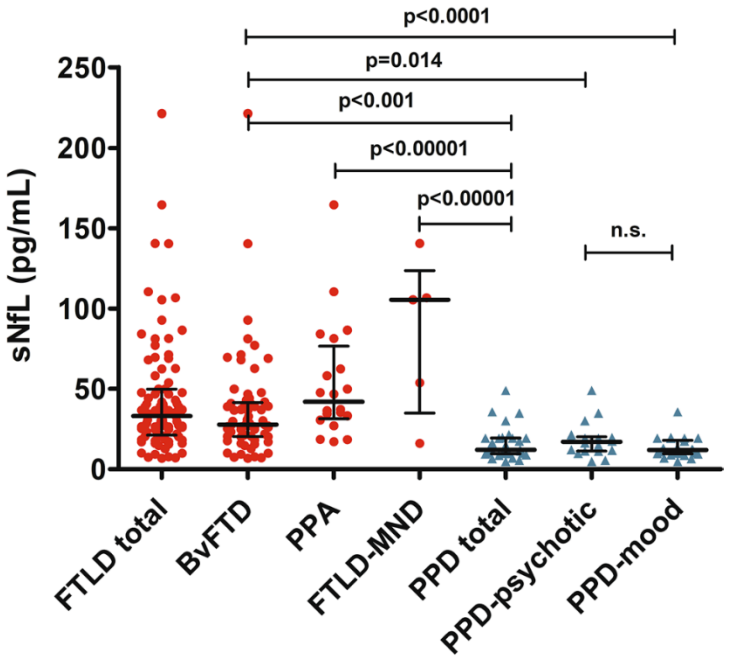
Neurofilament light (NfL) is a surrogate marker of neuroaxonal degeneration that is increased following acute injury, with age, and in neurodegenerative disease

Zetterberg H et al., Brain Commun 2023

CSF and blood NfL to differentiate bvFTD from PPD







Vijverberg E et al., Alzheimer & Dementia 2017; Al Shweiki R et al., J Psychiatr Res 2019; Katisko K et al., Journal of Neurology 2020

NfL levels increase with age

Table 2 Plasma neurofilament light chain levels in each of the age classes in controls

Age class (years)	N	5th P	25th P	Median (50th percentile)	75th P	95th P
<30	8	3.69	4.40	5.01	6.73	7.22
30.0–39.9	25	4.00	6.02	7.26	7.99	11.47
40.0–49.9	24	4.61	6.96	8.25	9.62	11.60
50.0–54.4	19	5.42	7.10	8.73	10.29	14.26
55.0–59.9	20	7.20	8.11	9.84	11.86	16.80
60.0–64.9	21	7.38	9.09	12.03	14.36	23.41
65.0–69.9	23	9.82	12.55	15.14	19.05	27.27
≥70	25	11.70	14.57	17.52	22.83	31.60

Values are indicated in pg/mL.

Saracino D et al., JNNP 2021

Monogenetic forms of neurodegenerative diseases

Disease	% familial	Main genes implicated	Mutation %		
			Fam, <65y	Fam	All
AD	~25%	*PSEN1, APP, PSEN2*	15%	<1%	<1%
FTD	30-40%	*C9orf72, GRN, MAPT*	50%	40%	**15%**
LBD	5-10%	*SNCA1, LRRK1*	?	<1%	<1%
CJD	10-15%	*PRNP*	100%	100%	10-15%
VCI	?	*NOTCH3*	<1%	<1%	<1%

Psychiatric presentations of *C9orf72* mutations

- Psychiatric symptoms can precede by several years the typical bvFTD features
  - Psychotic symptoms are the most common
- Progression of symptoms can be (very) slow over many years
- Neuroimaging can be normal in the initial phase of the disease
- Subjects may not have a positive family history (either no cases or only cases of apparent primary psychiatric disorders)

Ducharme S et al., J Neuropsychiatry Clin Neurosci 2017

Progression of bvFTD

- A longitudinal cohort study in specialist tertiary FTD research clinic
- 8/11 progressors carried the *C9orf72* repeat expansion

	Prob bvFTD	**Pos bvFTD**
Baseline	38	20
Follow-up	36	11

Devenney E et al., JAMA Neurology 2015

Table 2 Percentage frequency of individual neuropsychiatric symptoms in controls and mutation carriers

		All mutation carriers			*C9orf72*			*GRN*			*MAPT*		
	Controls	CDR 0	CDR 0.5	CDR ≥1	CDR 0	CDR 0.5	CDR ≥1	CDR 0	CDR 0.5	CDR ≥1	CDR 0	CDR 0.5	CDR ≥1
Visual hallucinations	0.3	0.3	**6.1**	**15.4**	0.9	**5.4**	**23.6**	0.0	**6.5**	**7.7**	0.0	**7.1**	**8.0**
Auditory hallucinations	1.3	0.3	0.0	**13.4**	0.9	0.0	**22.2**	0.0	0.0	**7.7**	0.0	0.0	0.0
Tactile hallucinations	0.0	0.3	2.4	**5.4**	0.9	5.4	**9.7**	0.0	0.0	0.0	0.0	0.0	4.0
Delusions	1.0	0.7	1.2	**25.5**	0.9	0.0	**36.1**	0.0	0.0	**17.3**	2.0	7.1	**12.0**
Depression	12.9	8.9	**32.9**	**40.3**	8.9	21.6	**40.3**	7.7	**41.9**	**42.3**	12.2	**42.9**	**36.0**
Anxiety	15.5	*10.0*	**40.2**	**49.7**	8.9	**35.1**	**51.4**	10.8	**41.9**	**48.1**	10.2	**50.0**	**48.0**
Irritability/lability	11.9	*4.8*	**26.8**	**51.7**	5.4	**32.4**	**56.9**	*3.8*	22.6	**42.3**	6.1	21.4	**56.0**
Agitation/aggression	2.6	1.4	**11.0**	**33.6**	1.8	**10.8**	**37.5**	0.8	**16.1**	**25.0**	2.0	*0.0*	**40.0**
Euphoria/elation	0.3	1.0	**6.1**	**29.5**	**2.7**	**5.4**	**34.7**	0.0	3.2	**21.2**	0.0	**14.3**	**32.0**
Aberrant motor behaviour	1.3	0.3	**6.1**	**24.2**	*0.0*	5.4	**40.3**	*0.0*	**9.7**	**32.7**	2.0	0.0	**40.0**
Hypersexuality	0.3	0.0	**3.7**	**14.8**	0.0	**8.1**	**16.7**	0.0	0.0	**11.5**	0.0	0.0	**16.0**
Hyperreligiosity	0.0	0.3	2.4	**10.7**	0.0	0.0	**12.5**	0.8	6.5	5.8	0.0	0.0	**16.0**
Impaired sleep	13.2	*7.2*	**26.8**	**44.3**	*3.6*	**27.0**	**48.6**	9.2	**29.0**	**40.4**	10.2	21.4	**40.0**
Altered sense of humour	0.6	0.3	**4.9**	**46.3**	0.0	**8.1**	**40.3**	0.8	3.2	**42.3**	0.0	0.0	**72.0**

Number of cases is as per table 1. Bold items are significantly more frequent than controls and italicised items are significantly less frequent than controls ($p<0.05$). Other differences are shown as *significantly more frequent compared with *GRN*, †significantly more frequent compared with *MAPT* and ‡significantly more frequent compared with *C9orf72* ($p<0.05$). See online supplemental file 1 for similar analysis of severity.

Phenocopy syndrome of bvFTD

- Meet criteria for possible bvFTD but minimal progression over time
- Mostly male
- Less impaired in executive functions and ADL/IADL
- No supportive features on imaging
- Normal lifespan
- Most patients at autopsy do not have FTLD
- The etiology of phenocopy bvFTD remains unknown

Valente E et al., Alzheimers Res Ther 2019

Pathology of behavioural and psychiatric symptoms in FTD

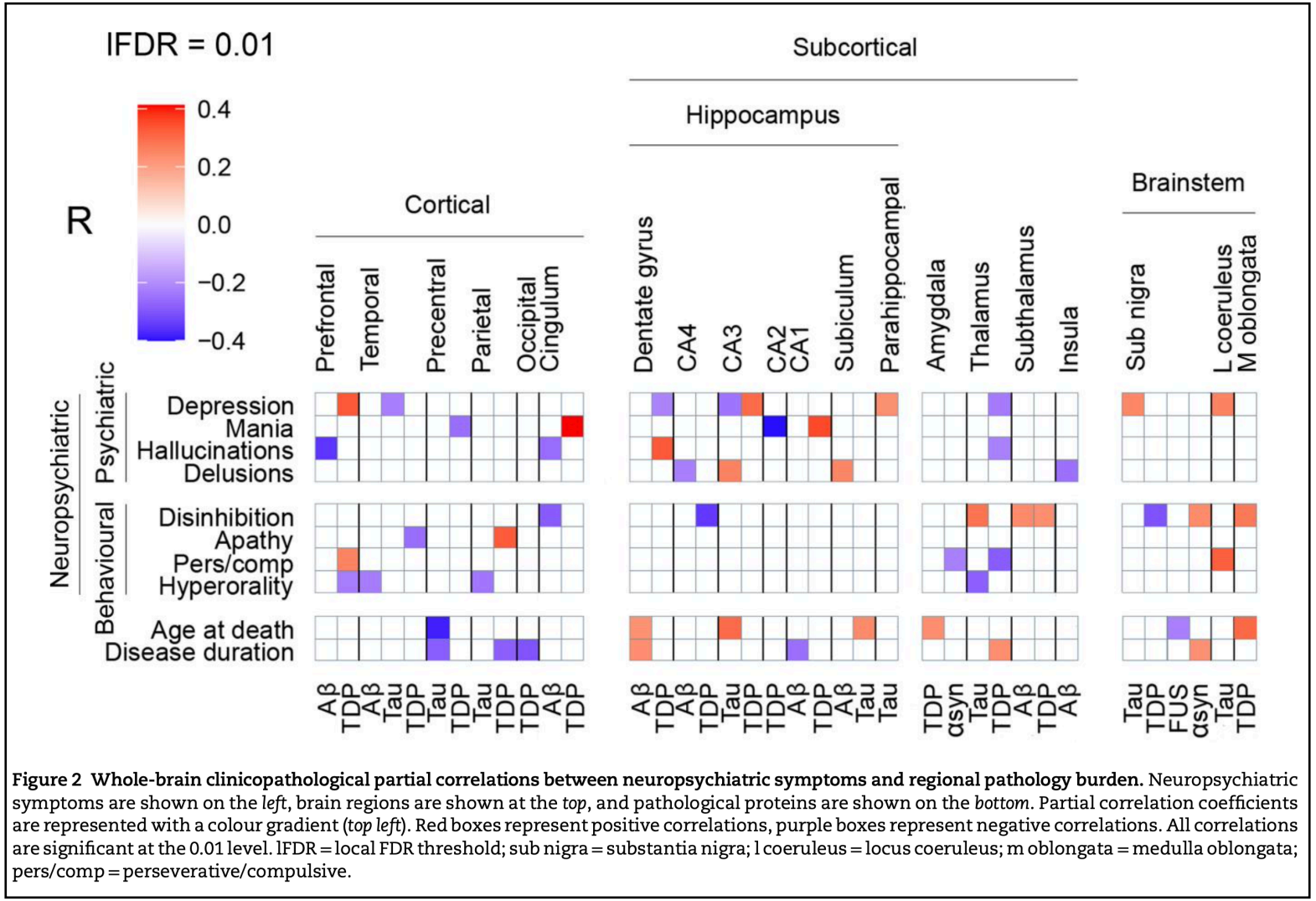
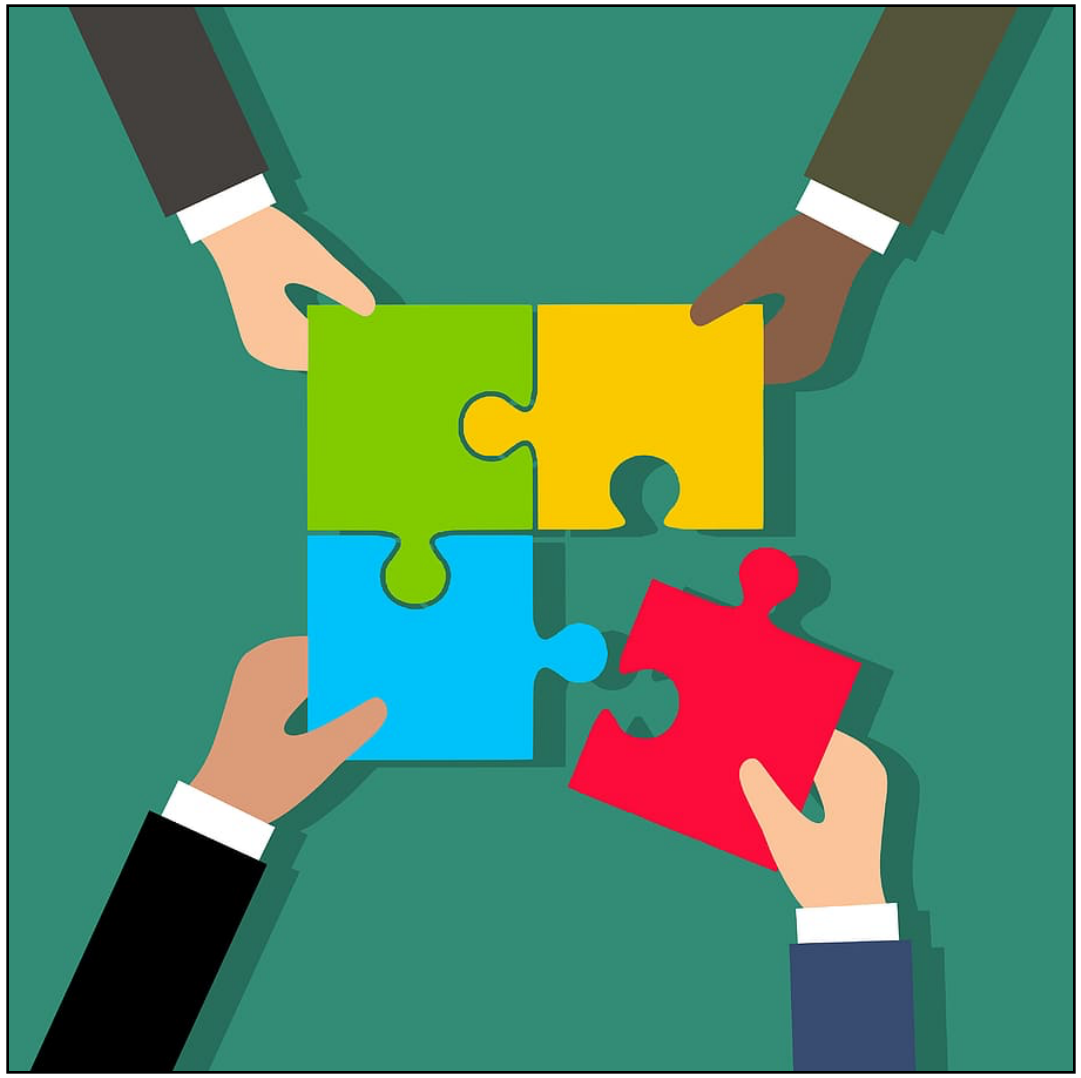


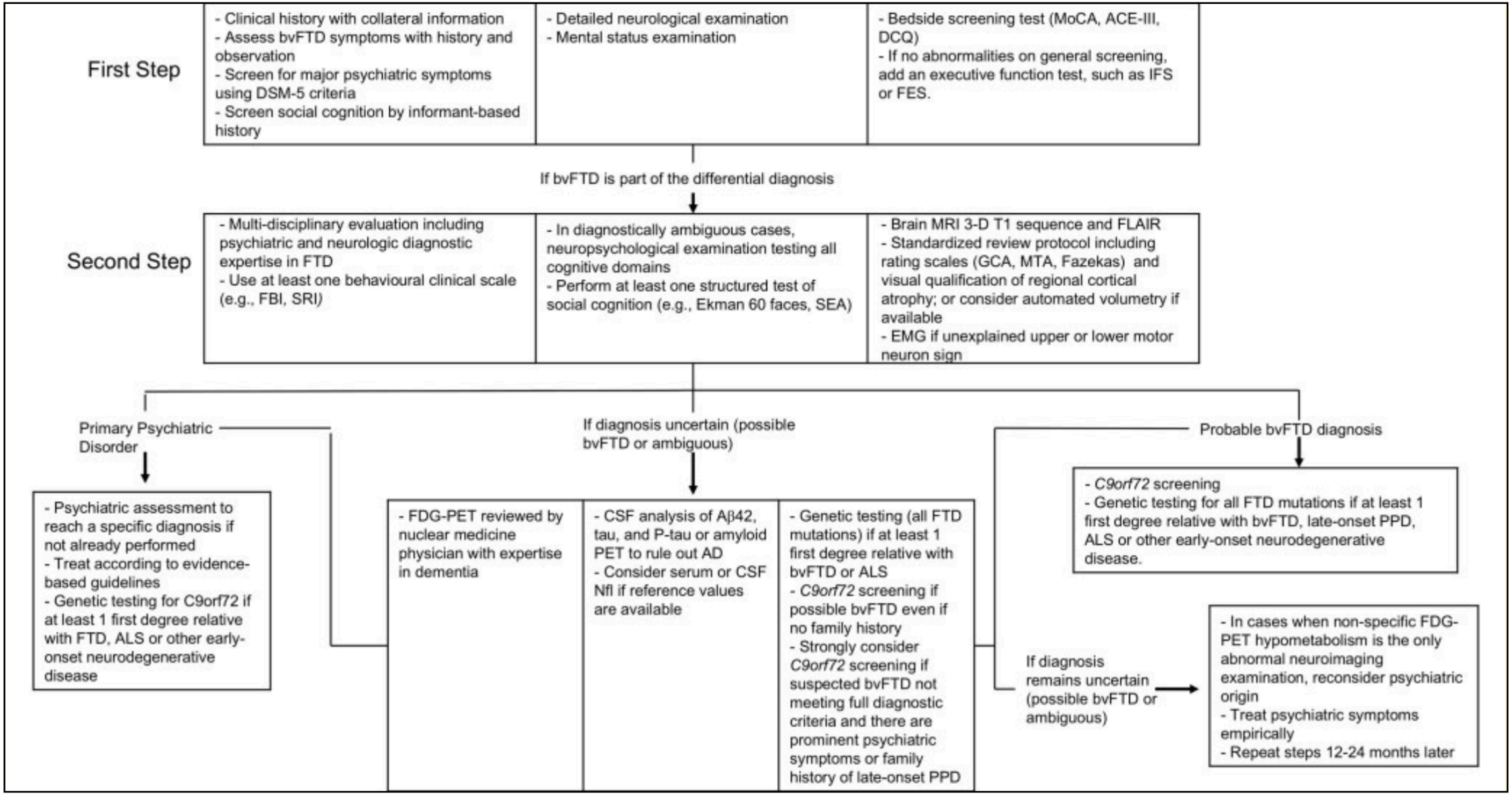
Figure 2 Whole-brain clinicopathological partial correlations between neuropsychiatric symptoms and regional pathology burden. Neuropsychiatric symptoms are shown on the *left*, brain regions are shown at the *top*, and pathological proteins are shown on the *bottom*. Partial correlation coefficients are represented with a colour gradient (*top left*). Red boxes represent positive correlations, purple boxes represent negative correlations. All correlations are significant at the 0.01 level. lFDR = local FDR threshold; sub nigra = substantia nigra; l coeruleus = locus coeruleus; m oblongata = medulla oblongata; pers/comp = perseverative/compulsive.

Scarioni M et al., Brain 2022

Question 5

- What would you consider as a red flag for FTD in a psychiatric syndrome (multiple answers possible):
  1. Behavioral disinhibition
  2. Family history of late-onset dementia
  3. Changes in food preferences
  4. Cognitive decline
  5. Mid or late-life onset
  6. Clear word-finding difficulties
  7. Occurrence of falls





Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. Ducharme S et al., Brain 2020

Key recommendations

- Use a interdisciplinary approach
- Use standardized tests and questionnaires
- Use tests for social cognition
- In patients with only FDG-PET imaging abnormalities reconsider psychiatric origin
- Use NfL in clinical practice
- In cases with possible bvFTD and familial history of dementia, ALS or psychiatric diseases consider *C9orf72* testing
- If diagnosis remains uncertain repeat steps after 1-2 years

Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. Ducharme S et al., Brain 2020

FTD vs PPD checklist

- In patients with late-onset frontal behavioural changes
  - AUC: 0.895
  - A score of ≥11 had a PPV of 89.2% for bvFTD
  - A score of ≤8 had a PPV of 92.7% for a PPD

Part A

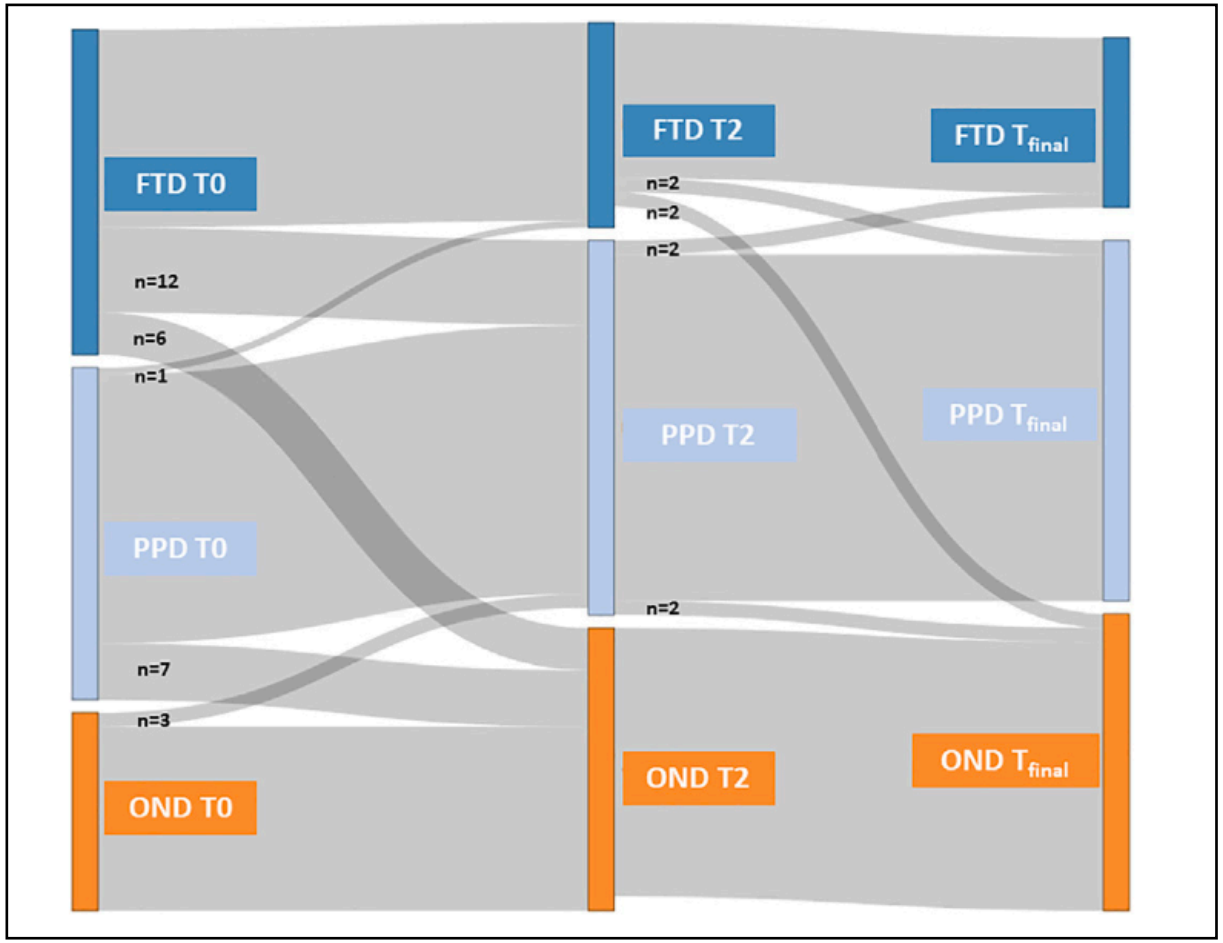
1. Was the patient self-referred?
2. Is there a past history of mood, anxiety, psychotic or personality disorder?
3. Is the patient emotionally distressed (dysphoria, anxiety) by the current situation?
4. Is the patient expressing guilt, self-blame, or suicidal thoughts?
5. Is the main complaint of the family that the patient has anger problems?
6. Is the patient aware of or concerned about cognitive or behavioral changes?
7. Is the duration of neuropsychiatric symptoms longer than 5 years?
8. Are the cognitive or behavioral symptoms fluctuating?
9. Is the patient showing interest in learning about FTD?
10. Does the patient understand what FTD is?
11. Is the patient reporting more severe disability than expected based on clinical and cognitive examination?
12. Is there a legal or compensation issue associated with the case?
13. Are the patient and/or relatives upset or doubtful if told they might not have FTD (as opposed to expressing relief, joy, etc.)?

Part B

14. Is there a 1st degree family history of FTD or ALS?
15. Are there language related complaints?
16. Are there stereotypical or simple repetitive behaviors?
17. Are there changes in food preferences?
18. Are there abnormalities on elemental neurological examinations (including eye movement, parkinsonism)?

Ducharme S et al., J. Alzheimers Dis 2019

Diagnostic instability over time in late-onset frontal behavioural changes



FTD T2 = after 2 years
FTD Tfinal = after 5-8 years

de Boer S et al., Brain 2020

The importance of an accurate diagnosis

- Different prognosis
- Diagnostic uncertainty affects patients and family members
- Access to day programs or respite residential programs
- Evidence-based pharmacological or psychotherapeutic treatment
- Therapeutic persistence
- Genetic testing and counseling

Key conclusions

- bvFTD is a complex neurodegenerative disease that may present with neuropsychiatric symptoms overlapping with mood disorders, bipolar disorders, catatonia, obsessive-compulsive disorder, autism spectrum disorders, personality disorders, and ADHD
- An interdisciplinary approach, and improvements in clinical, neuropsychological, imaging, fluid and genetic assessment of late-onset behavioural changes may lead to an improved differential diagnosis of bvFTD from PPD in the early stages
- Further research on this topic is necessary

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Cognitive Center of UZ Gent

UZ GENT

UNIVERSITEIT GENT

European Reference Network

Neurological Diseases (ERN-RND)

Neuropsychiatric International Consortium Frontotemporal Dementia

GENFI GENETIC FTD INITIATIVE

tim.vanlangenhove@uzgent.be **@tvlangen**

UZ GENT

UNIVERSITEIT GENT

European Reference Network

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GENFI GENETIC FTD INITIATIVE