Frontotemporal dementias: an update

Dr James Burrell
Neurologist
Senior Research Officer

NeuRA

What is FTD?

- Rare, but important cause of dementia
- Peak incidence between 50-70 years
- Second most common cause of young-onset dementia
- Prevalence ~ 15-20/100,000

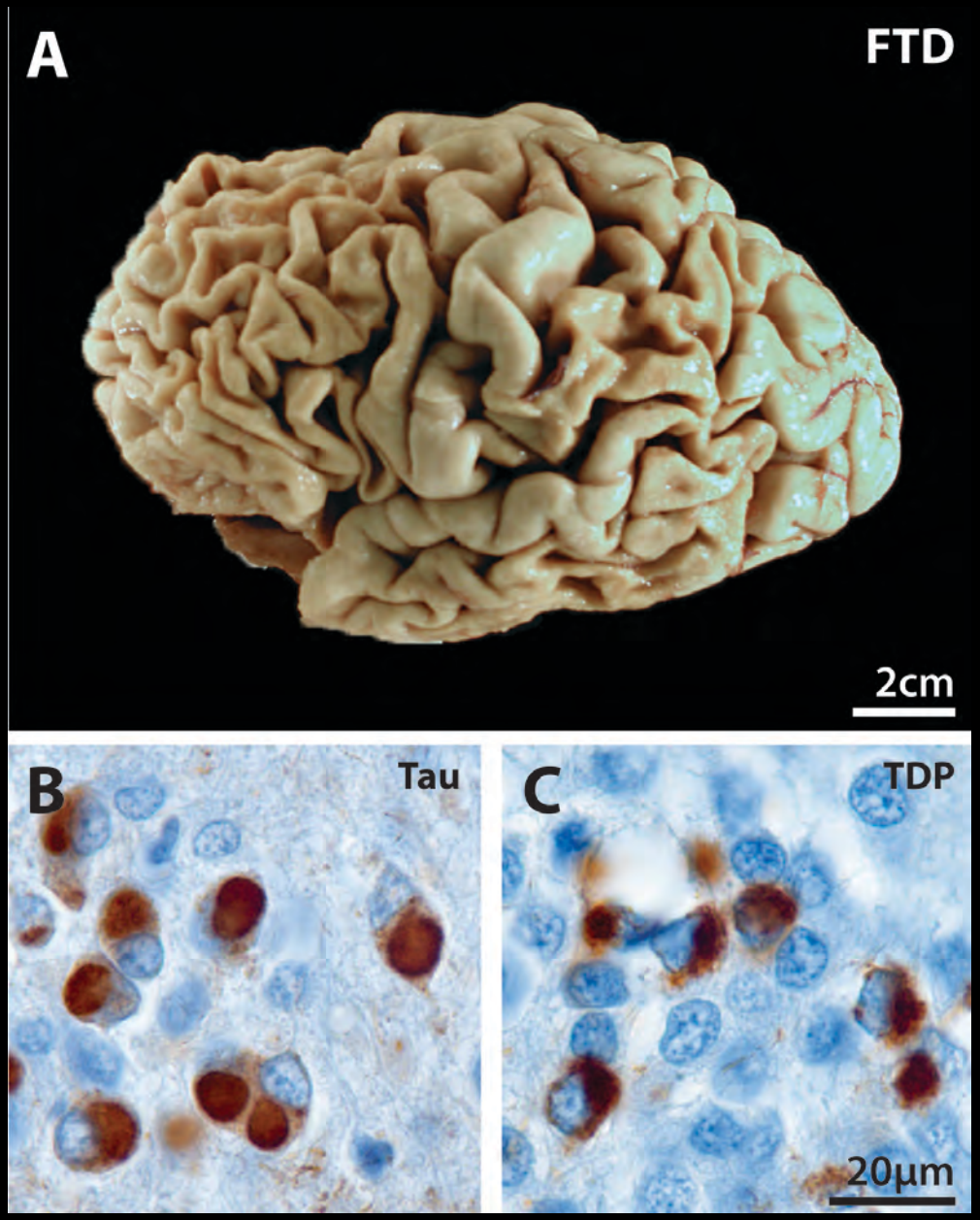
- Presents with changes in **LANGUAGE** or **BEHAVIOUR** (or both)

KNIFE EDGE ATROPHY

Tau

TDP-43

Overlap with other pathologies



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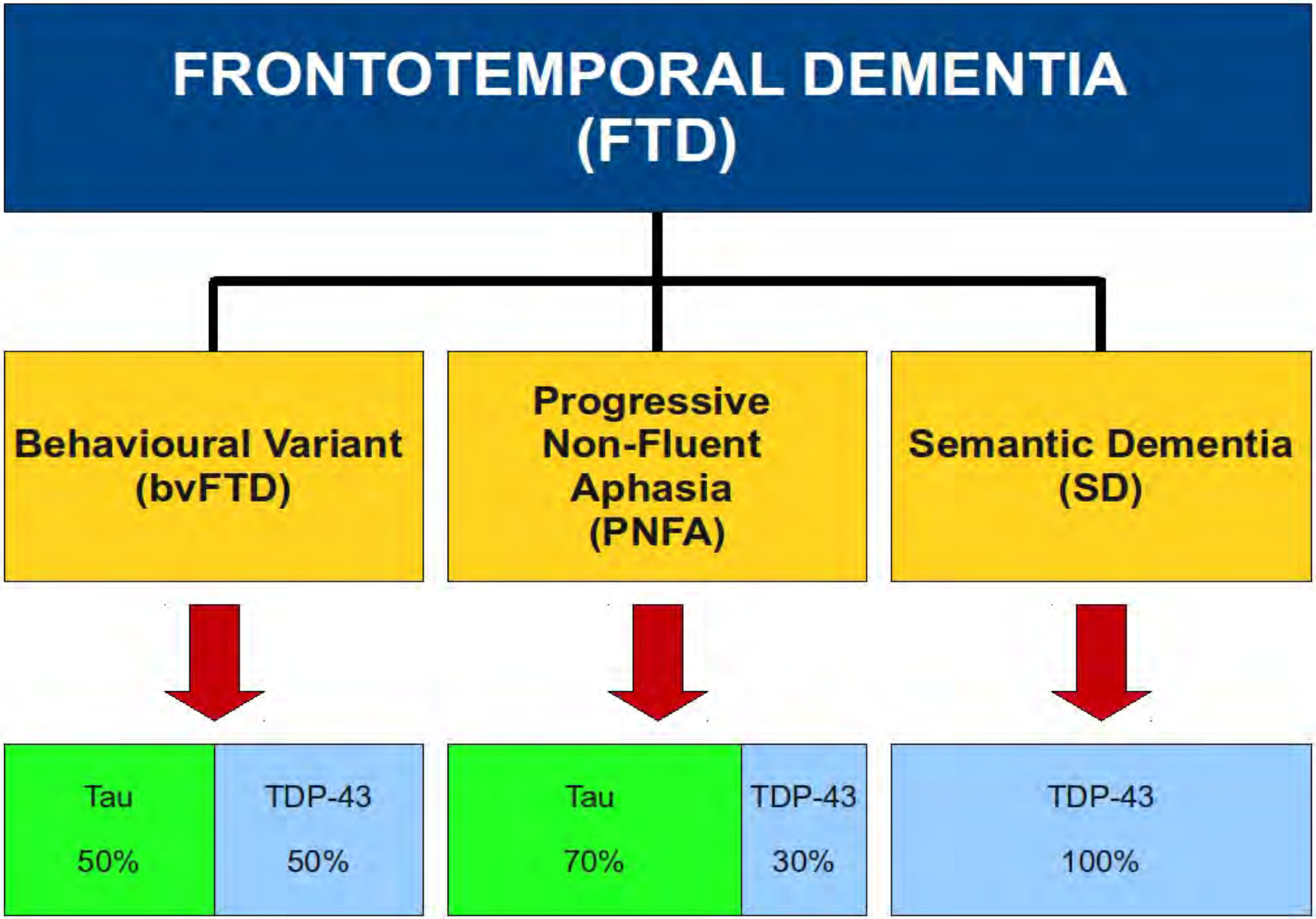
FRONTOTEMPORAL DEMENTIA (FTD)
Behavioural Variant (bvFTD)
Progressive Non-Fluent Aphasia (PNFA)
Semantic Dementia (SD)
Tau 50%
TDP-43 50%
Tau 70%
TDP-43 30%
TDP-43 100%

Case – 1

- 73 year old woman

- 2 year history of progressive language disturbance
  - Word finding difficulty
  - Syntactic errors in speech – pronouns he/she, tense, word ordering (former school principal)

Case – 1

- Effortful, halting speech
- Word-finding difficulties
- Syntactic errors
- Sound distortions (apraxia of speech) and phonemic errors

PROGRESSIVE NON-FLUENT APHASIA (PNFA)

Case – 2

- 57-year-old journalist
- 9 months progressive speech disturbance
  - described by patient as ‘halting’ speech.

Case – 2

- Speech:
  - Reduced content
  - Effortful
  - Syntactic errors
  - Apraxia of speech
  - Generally preserved word/object knowledge

PROGRESSIVE NON-FLUENT APHASIA (PNFA)

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Case – 2

- Speech:
  - Reduced content
  - Effortful
  - Syntactic errors
  - Apraxia of speech
  - Generally preserved word

PROGRESSIVE NON-FLUENT APHASIA (PNFA)

DRAMATIC DECLINE IN ONLY 12 MONTHS

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Case – 3

- 60-year-old woman

- 3 year history of:
  - Word-finding difficulty
  - Comprehension
  - Following thread when reading
  - Writing
  - Poor Concentration

Case – 3

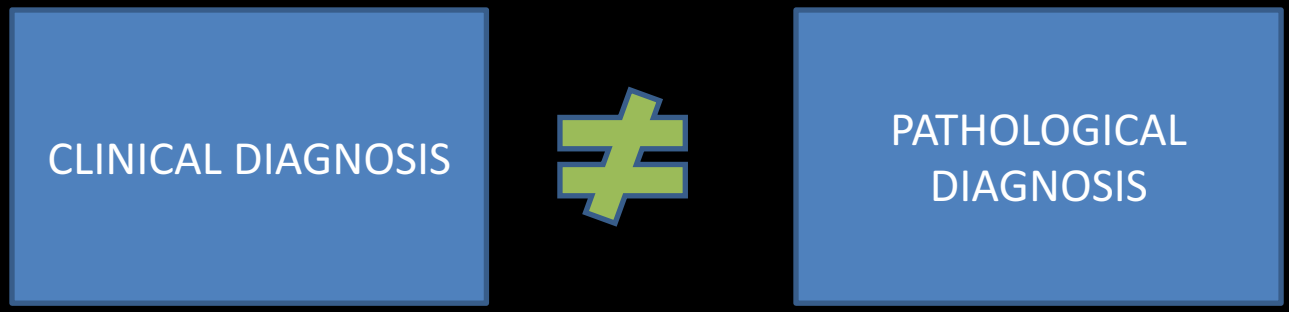
- Severe word finding prob
  - "Umm, umm"
- Phonological errors
  - "Eastwold" rather than "Eastwood"
- Some fluent snippets
- Syntactic errors
  - "That orchard . . . That we[illegible]

NON-FLUENT APHASIA

PROGRESSIVE NON-FLUENT APHASIA?

Overlapping Dementia Syndromes

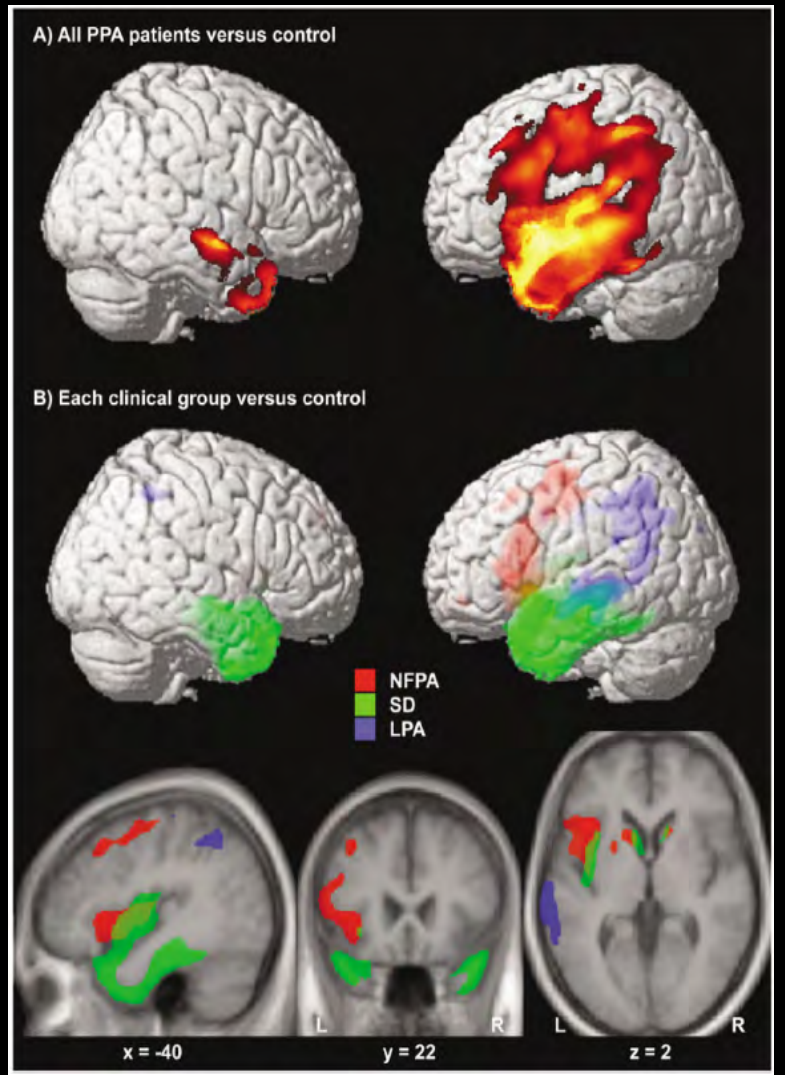
- Symptoms and signs can overlap or evolve
- Diagnosis?
  - **Clinical assessment**, supported by imaging and neuropsychology
  - Biomarkers of **neurodegeneration** (research)



Logopenic Progressive Aphasia

- Atypical Alzheimer's disease
- May be difficult to distinguish from PNFA

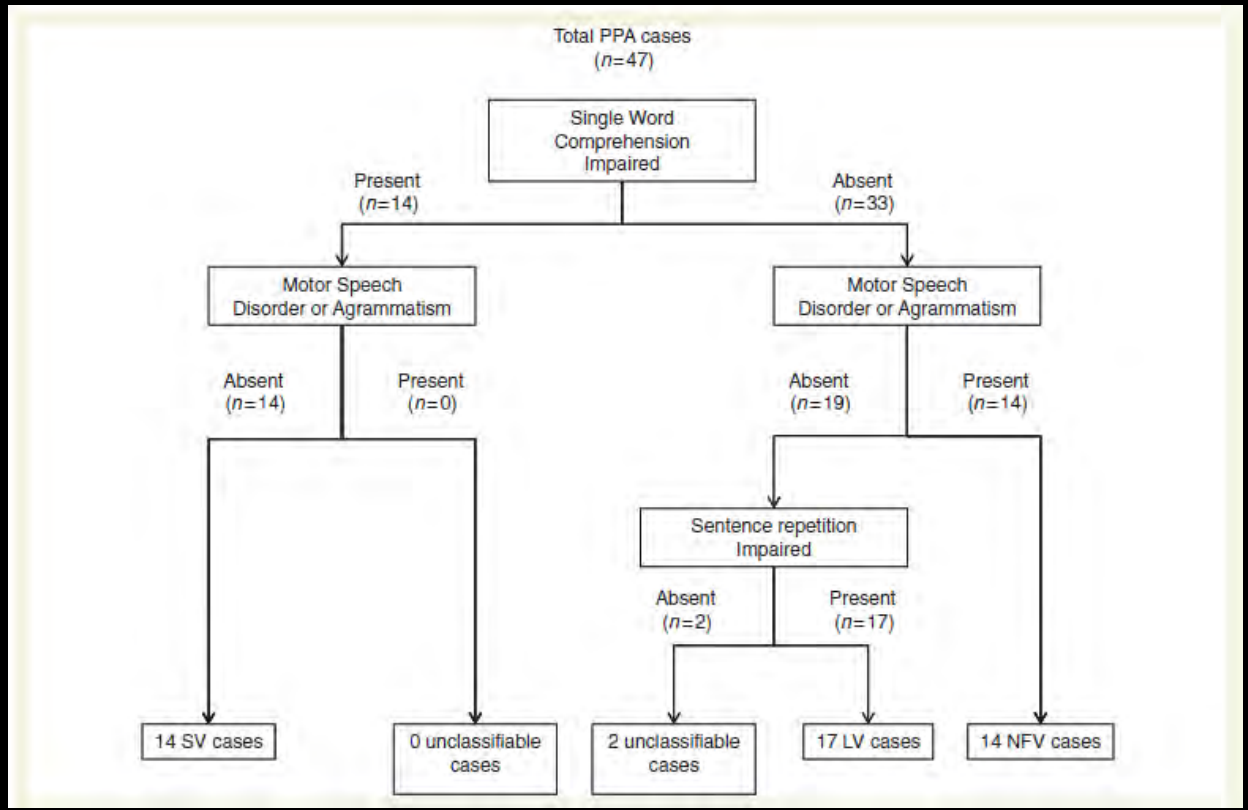
- At a group level, more posterior temporal and parietal atrophy



Ann Neurol. 2004 March ; 55(3): 335–346.

Subtypes of progressive aphasia: application of the international consensus criteria and validation using β-amyloid imaging

Cristian E. Leyton,[1,2] Victor L. Villemagne,[3,4,5] Sharon Savage,[1] Kerryn E. Pike,[3,4,6] Kirrie J. Ballard,[7] Olivier Piguet,[1,2] James R. Burrell,[1,2] Christopher C. Rowe[3,5] and John R. Hodges[1,2]



KEY FEATURES:

ANOMIA

WORD FINDING

IMPAIRED SENTENCE REPETITION

BRAIN
A JOURNAL OF NEUROLOGY

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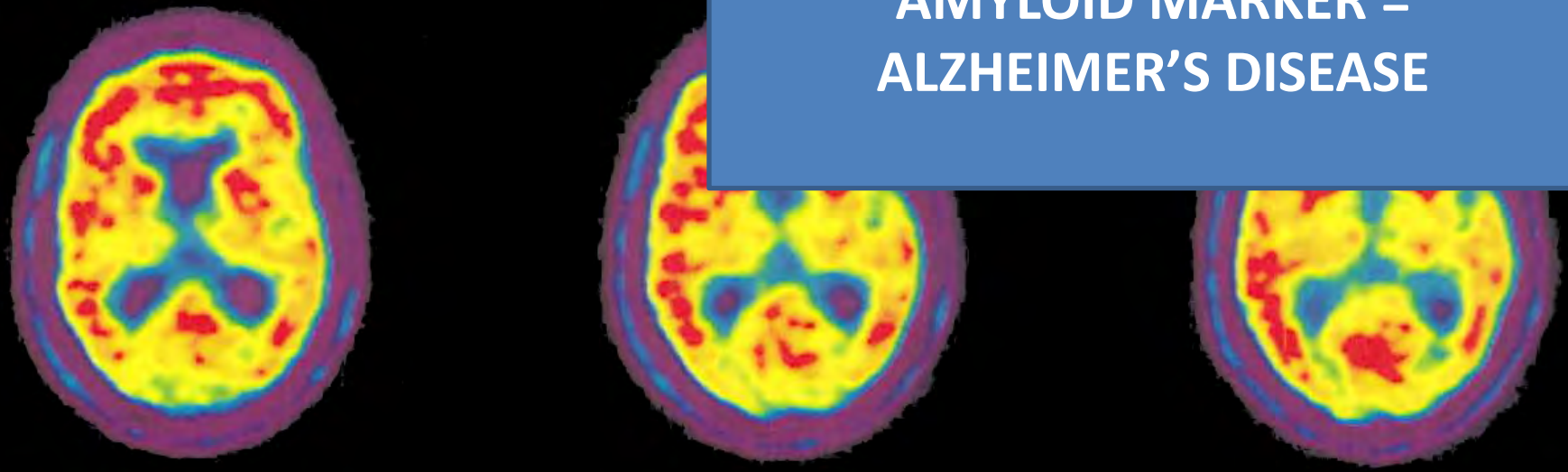
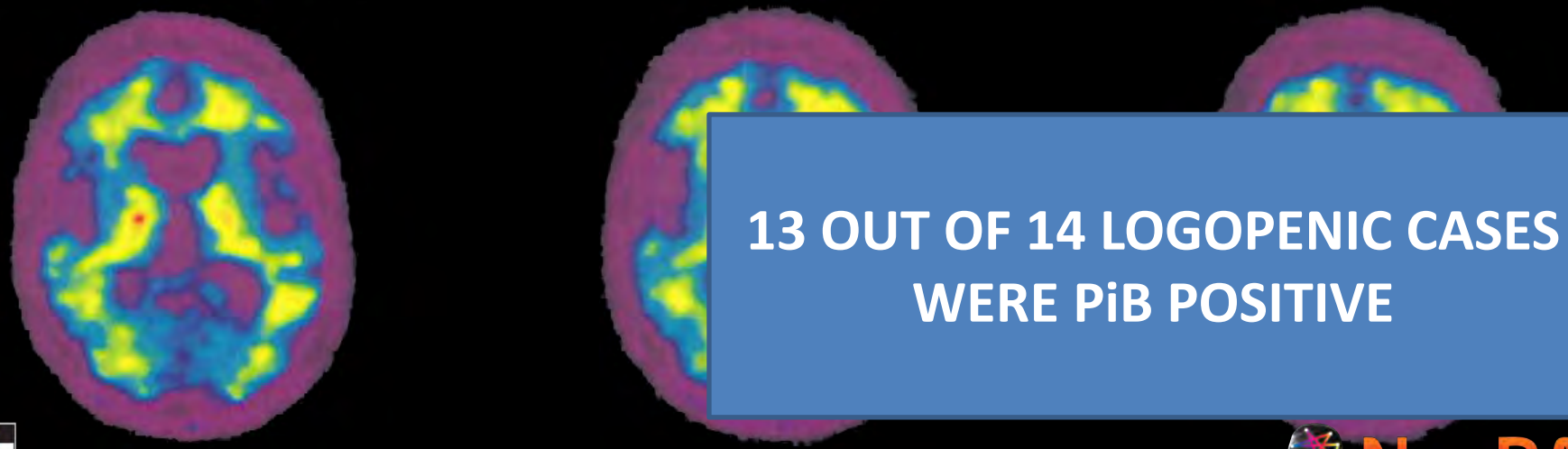
PiB Positive



AMYLOID MARKER =
ALZHEIMER'S DISEASE

PiB Negative



13 OUT OF 14 LOGOPENIC CASES
WERE PiB POSITIVE

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Case – 4

- 48 year old man

- 2-3 history of behavioural changes
  - More withdrawn socially
  - Difficulty following rules (substitutions in soccer)
  - Increased libido (approaching sister-in-law)
  - Much less empathic and affectionate

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Case 4

- Perseverative
- Rigid in routines etc
- Personal hygiene
- Inappropriate comments, behaviour, social conduct
- Language generally preserved (catchphrases)
- Too much fun . . .
- Lack of empathy

Behavioural variant frontotemporal dementia (bvFTD)

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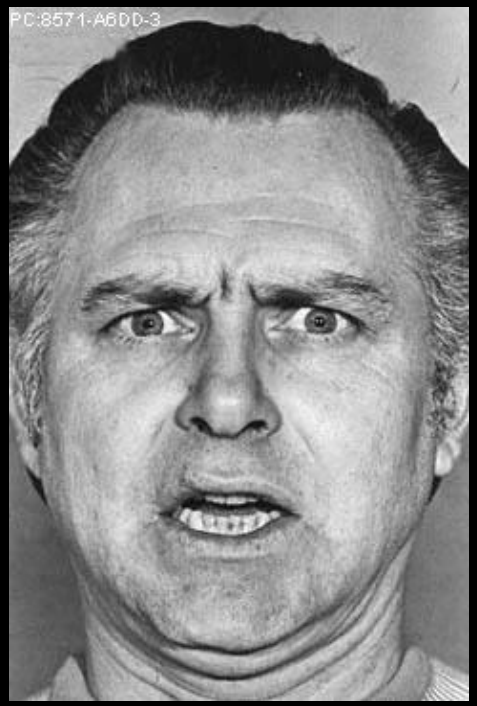
Assessment of Emotion in Frontotemporal Dementia

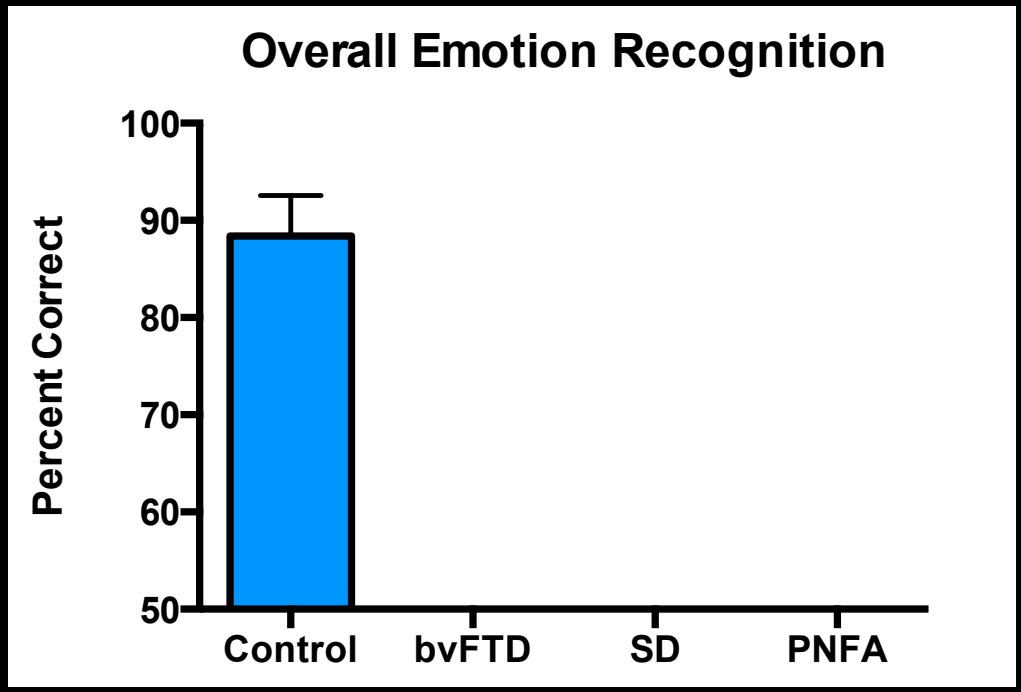
How is this person feeling?



Anger | Disgust | Fear | Sadness | Surprise | Happiness

Emotion recognition ability

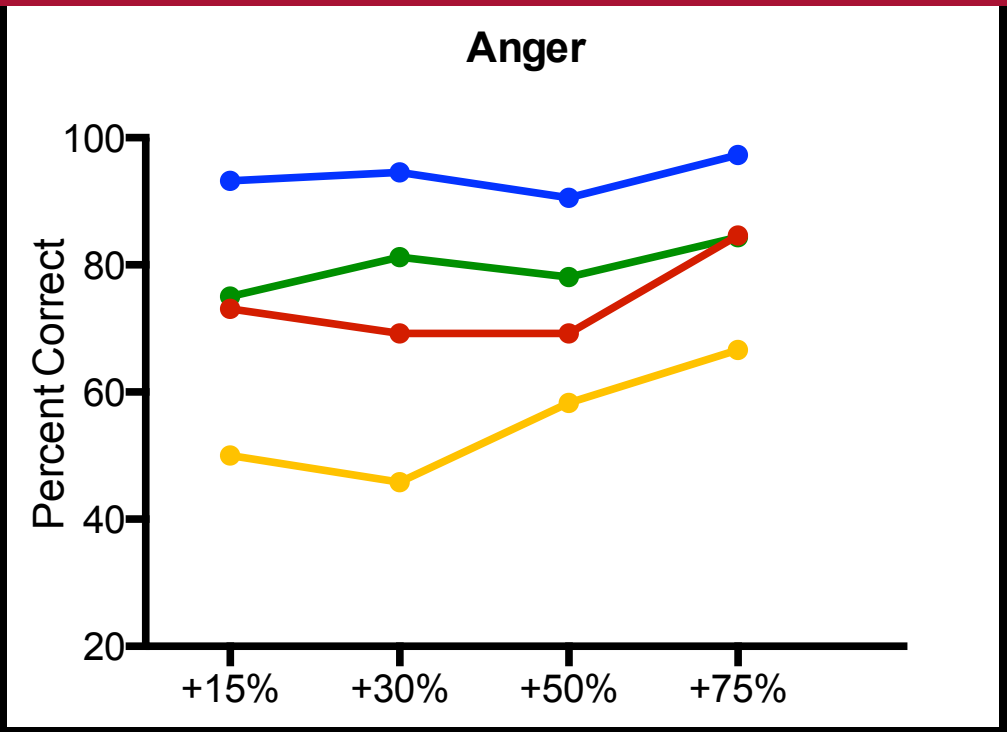
- Ability to recognise emotions from faces is reduced in:
  - behavioural-variant frontotemporal dementia,
  - semantic dementia
  - progressive non-fluent aphasia
- Negative emotions more affected than positive emotions



Kumfor et al (2011) Social Neuroscience

Improving emotion recognition

- Performance improves as the facial expression becomes more exaggerated
- Most effective in behavioural-variant frontotemporal dementia and progressive nonfluent aphasia



healthy controls

behavioural-variant

semantic dementia

progressive nonfluent aphasia

Kumfor et al (2011) Social Neuroscience

Case – 5

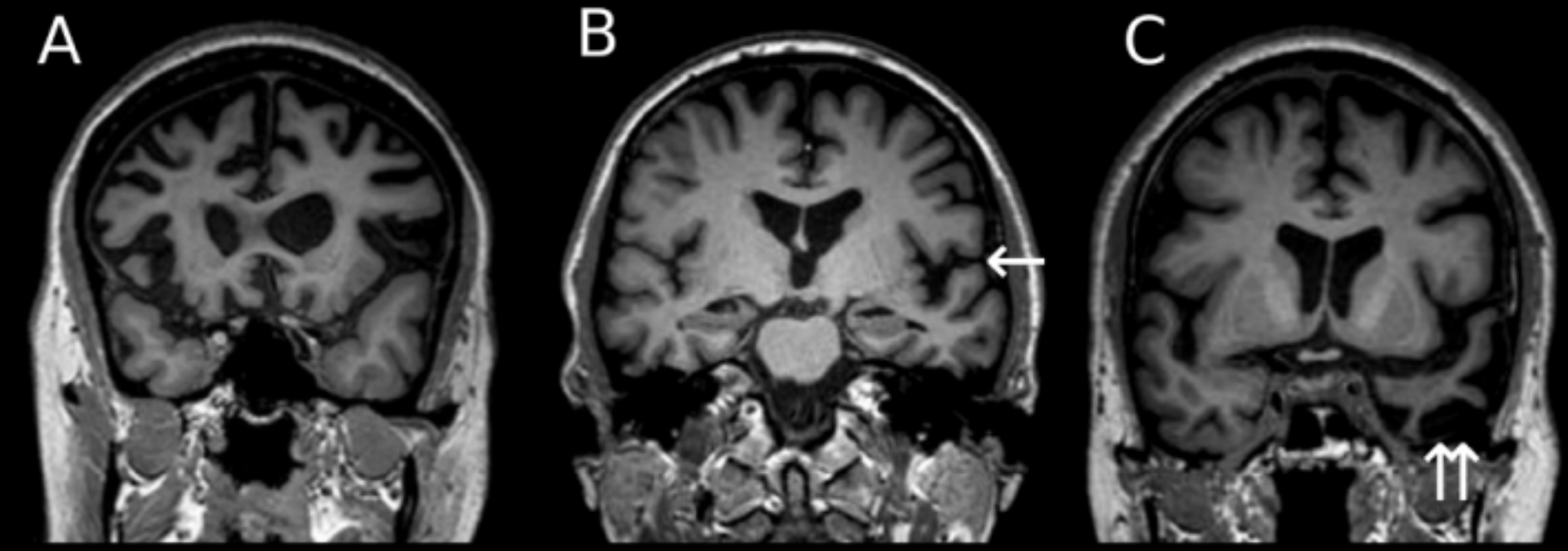
- 55 year old woman

- 3 year history of problems with “memory for words”
  - Names of people/places/objects
  - Word alienation when reading
  - Preserved concentration and general memory performance

Case – 5

- Breakdown in semantic knowledge
  - Naming, word-knowledge
- Preserved fluency, grammar, prosody of speech

Semantic dementia



bvFTD

PNFA

Semantic Dementia

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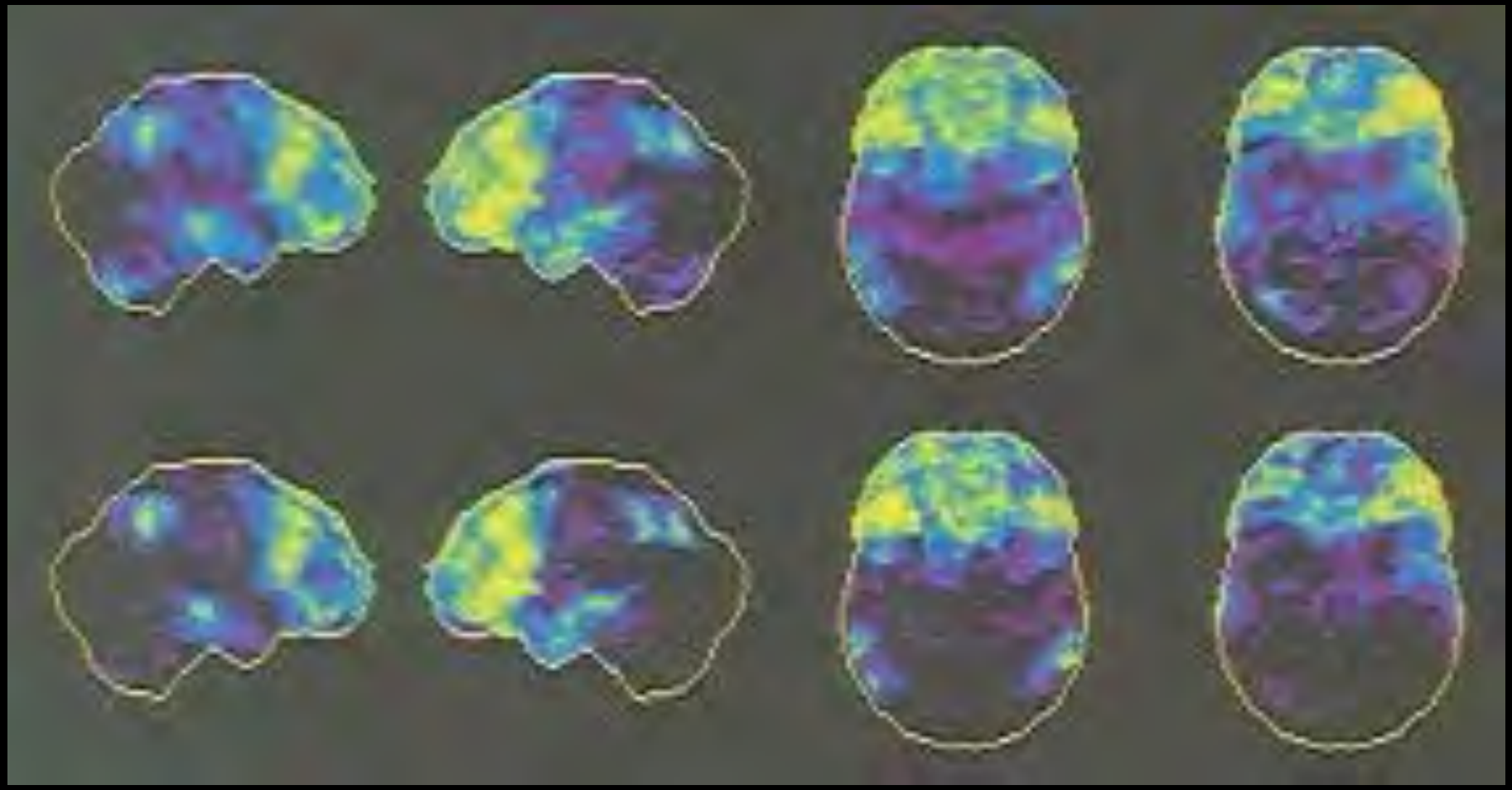

FDG-PET scan
Severe frontal hypometabolism
Temporal hypometabolism

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Case – 6

- 60 year old male

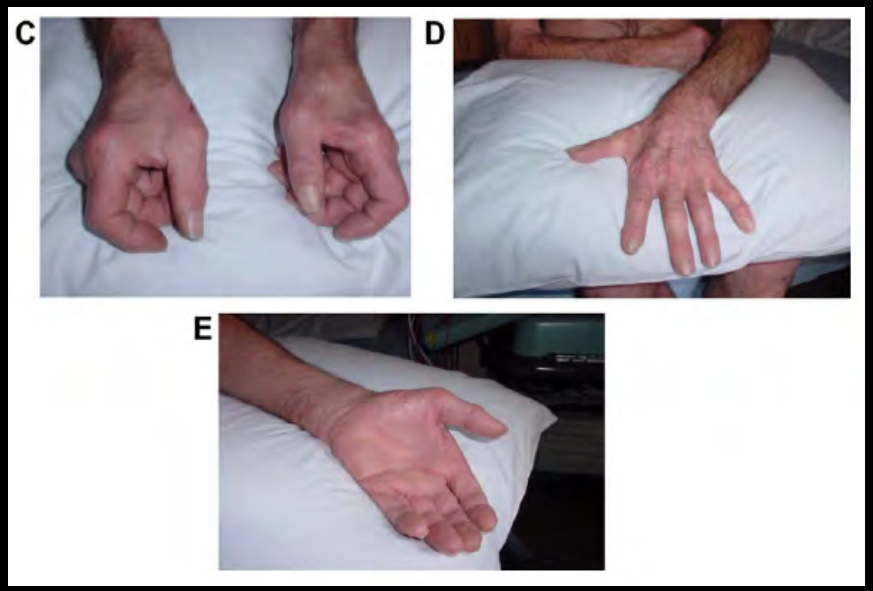
- 12/12 history of speech problems
  - Dysarthria
  - Dysphagia
  - Weight loss
  - No limb wasting/weakness
  - Behavioural changes (apathy)

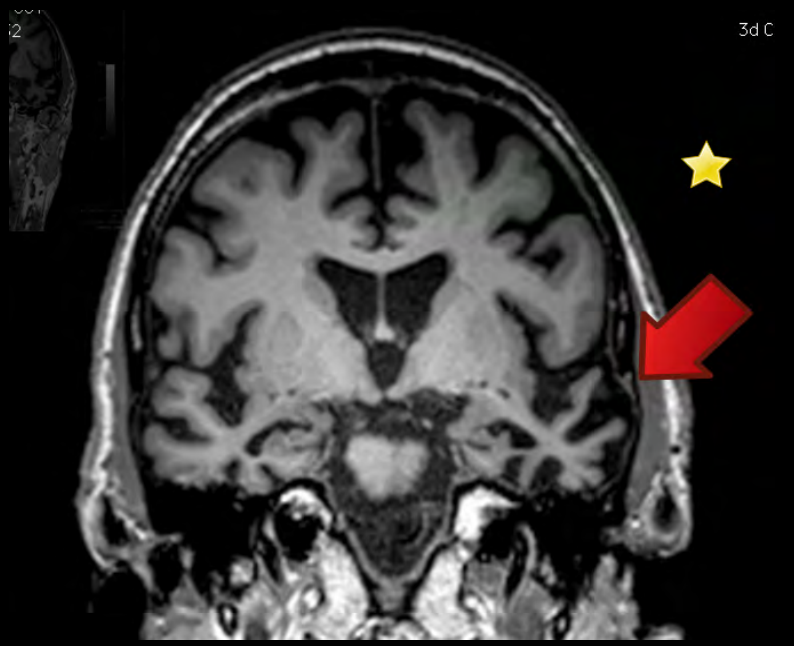
Case – 6

- 60 year old male
- 12/12 history of speech pr
  - Dysarthria
  - Dysphagia
  - Weight loss
  - No limb wasting/weakness
  - Behavioural changes (apathy)

Frontotemporal dementia
AND
Motor neuron disease

MND — **MND + Cognitive symptoms** — **FTD + Motor Symptoms** — **FTD**



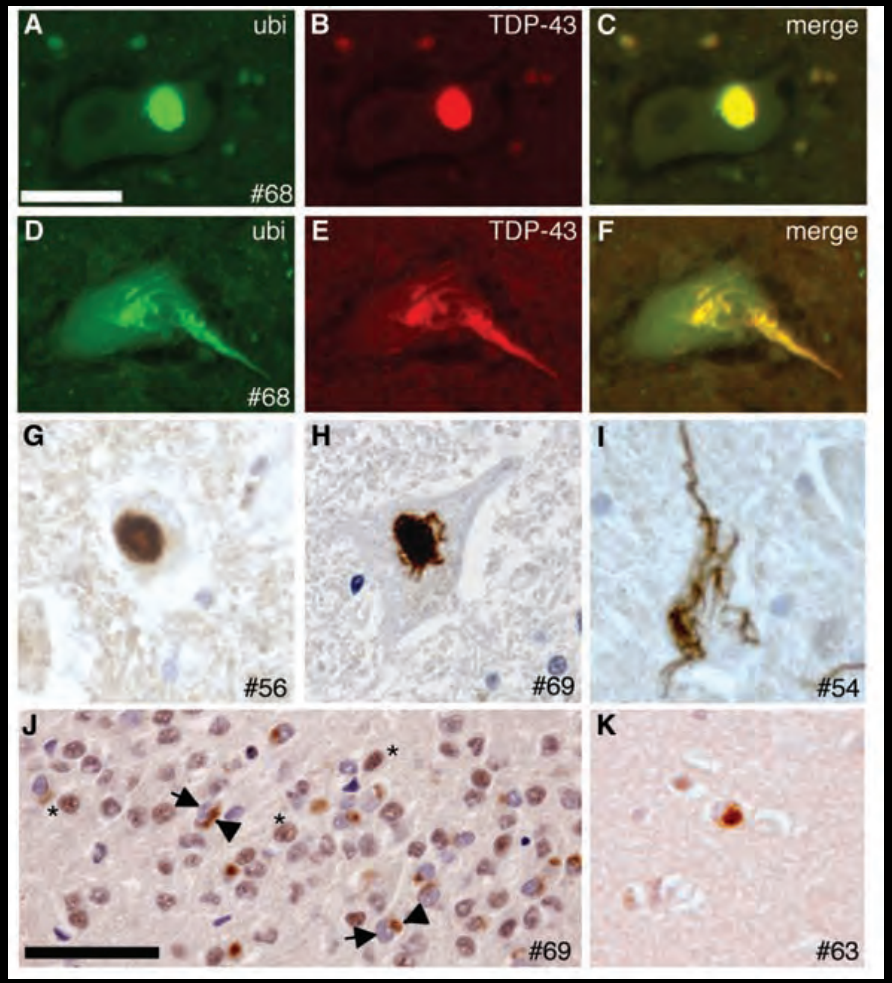


Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,[1,11]* Deepak M. Sampathu,[1]* Linda K. Kwong,[1]* Adam C. Truax,[1] Matthew C. Micsenyi,[1] Thomas T. Chou,[2] Jennifer Bruce,[1] Theresa Schuck,[1] Murray Grossman,[3,4] Christopher M. Clark,[3,4] Leo F. McCluskey,[3] Bruce L. Miller,[6] Eliezer Masliah,[7] Ian R. Mackenzie,[8] Howard Feldman,[9] Wolfgang Feiden,[10] Hans A. Kretzschmar,[11] John Q. Trojanowski,[1,4,5] Virginia M.-Y. Lee[1,4,5]†

Science. 2006 Oct 6;314(5796):130-3.

TDP-43 > 90% of MND



TDP-43 > 50% of FTD

Rest = Tau

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Motor Neuron dysfunction in frontotemporal dementia

James R. Burrell,[1,2,3] Matthew C. Kiernan,[1,2,3] Steve Vucic[1,4] and John R. Hodges[1,3]

- 40 consecutive FTD patients
- 42 age and gender matched MND
- 26 controls

- **5 (12.5%) FTD patients developed MND**
  - 3 presented with bvFTD
  - 2 presented with PNFA

Subclinical Motor Dysfunction –

Up to 30% of FTD patients

Brain. 2011 Sep;134(Pt 9):2582-94.

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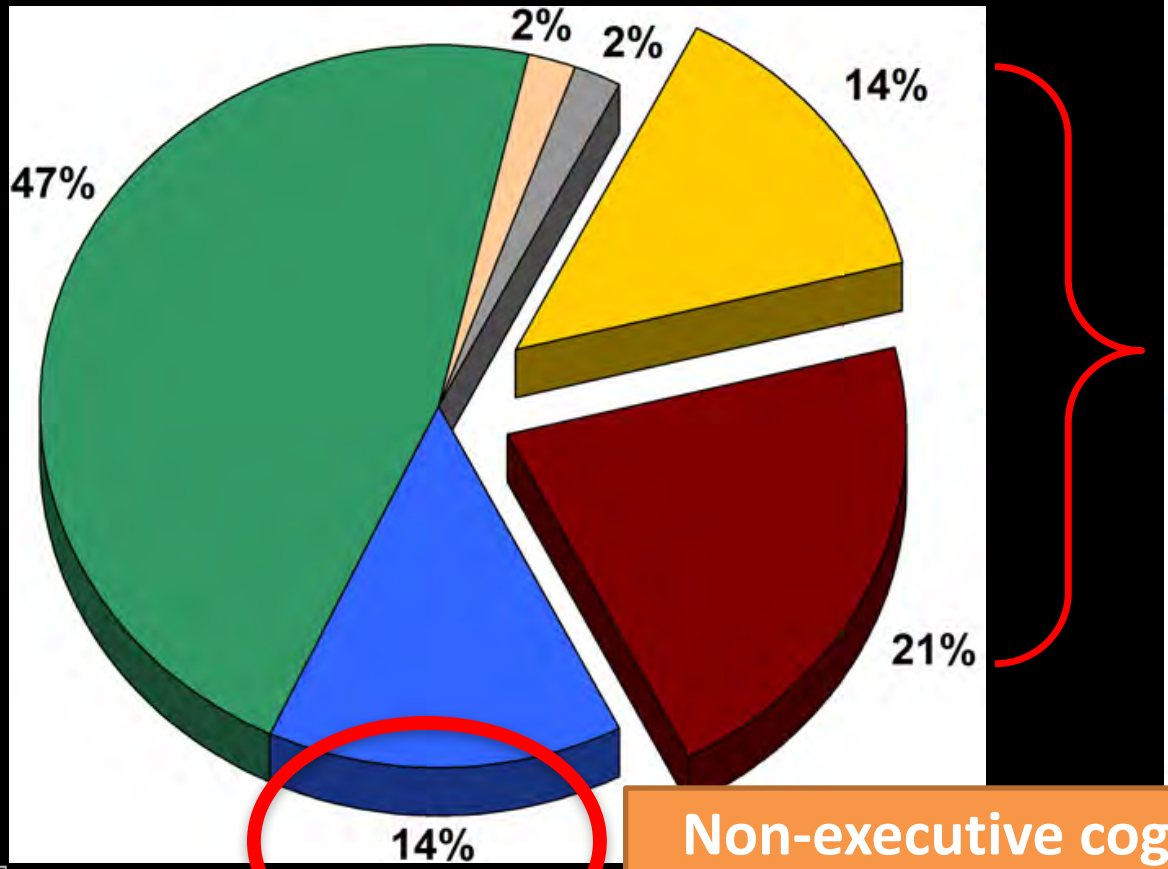
The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study

Julie Phukan,[1] Marwa Elamin,[1] Peter Bede,[1] Norah Jordan,[2] Laura Gallagher,[2] Susan Byrne,[1] Catherine Lynch,[1] Niall Pender,[2] Orla Hardiman[1,3]



J Neurol Neurosurg P

Non-executive cognitive impairment

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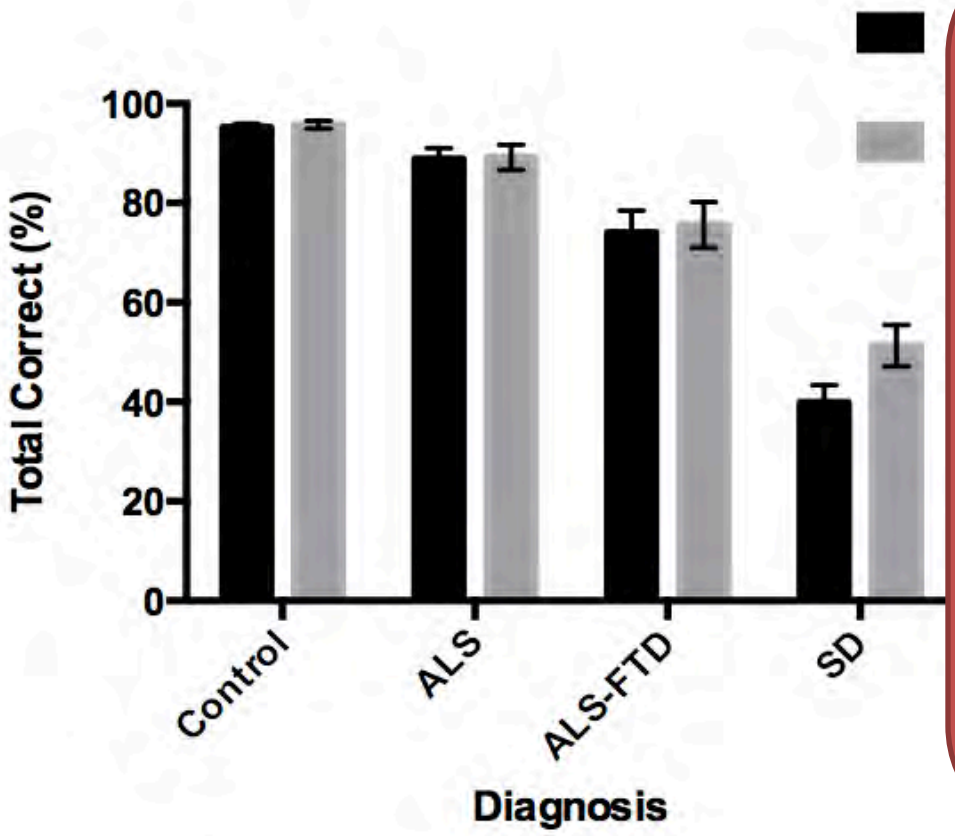
Results



% Impaired:

SD – 100%

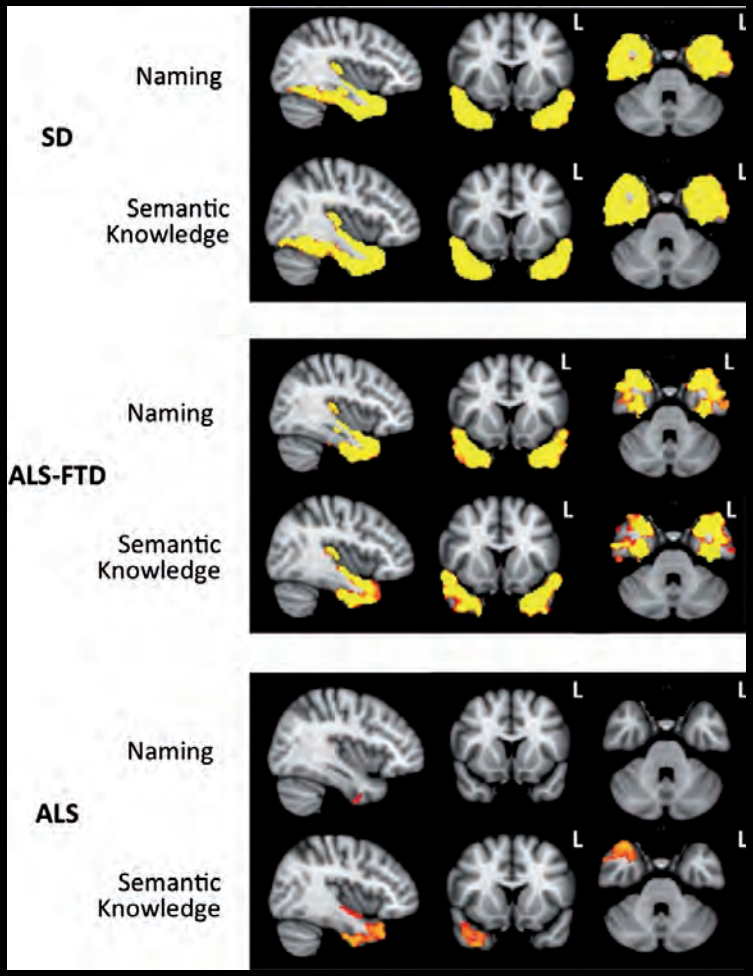
FTD-MND – 80%

ALS – 58.3%

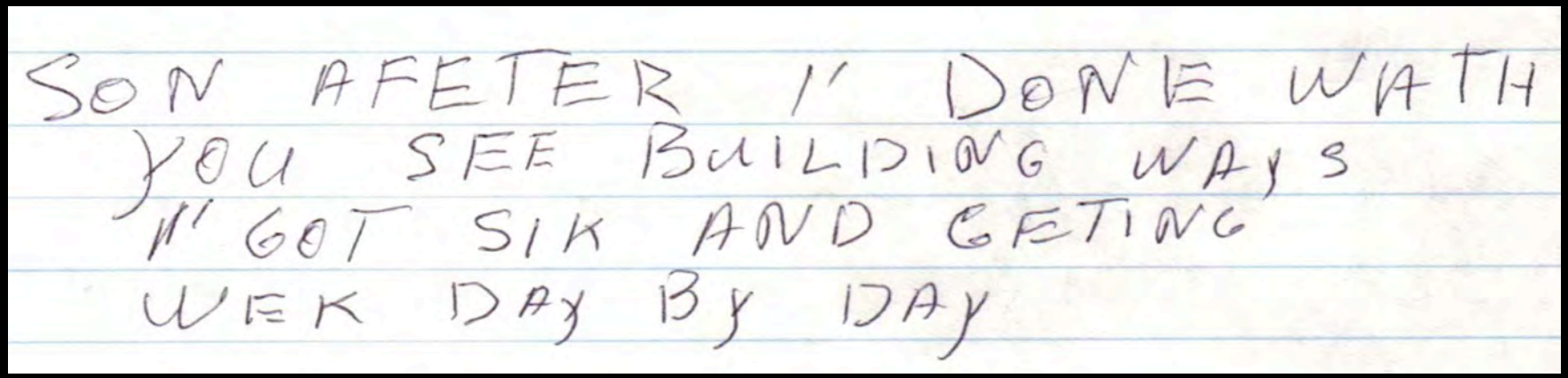
Semantic deficits in amyotrophic lateral sclerosis

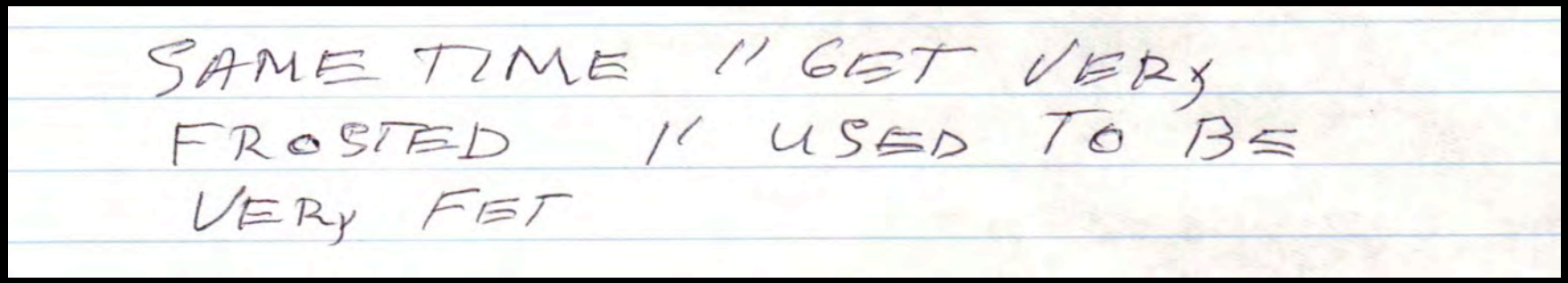
FELICITY V. C. LESLIE[1,2,3,4], SHARPLEY HSIEH[1,3,4], JASHELLE CAGA[4], SHARON A. SAVAGE[1], ENEIDA MIOSHI[5], MICHAEL HORNBERGER[6], MATTHEW C. KIERNAN[1,4], JOHN R. HODGES[1,2,3] & JAMES R. BURRELL[1,2,3]

[1]*Neuroscience Research Australia, Sydney,* [2]*School of Medical Science, University of New South Wales, Sydney,* [3]*ARC Centre of Excellence in Cognition and its Disorders, University of New South Wales, Sydney,* [4]*Brain and Mind Research Institute, The University of Sydney, Sydney, Australia, and Departments of* [5]*Psychiatry and* [6]*Department of Clinical Neuroscience, Cambridge University, Cambridge, UK*



FTD-MND - Syntax





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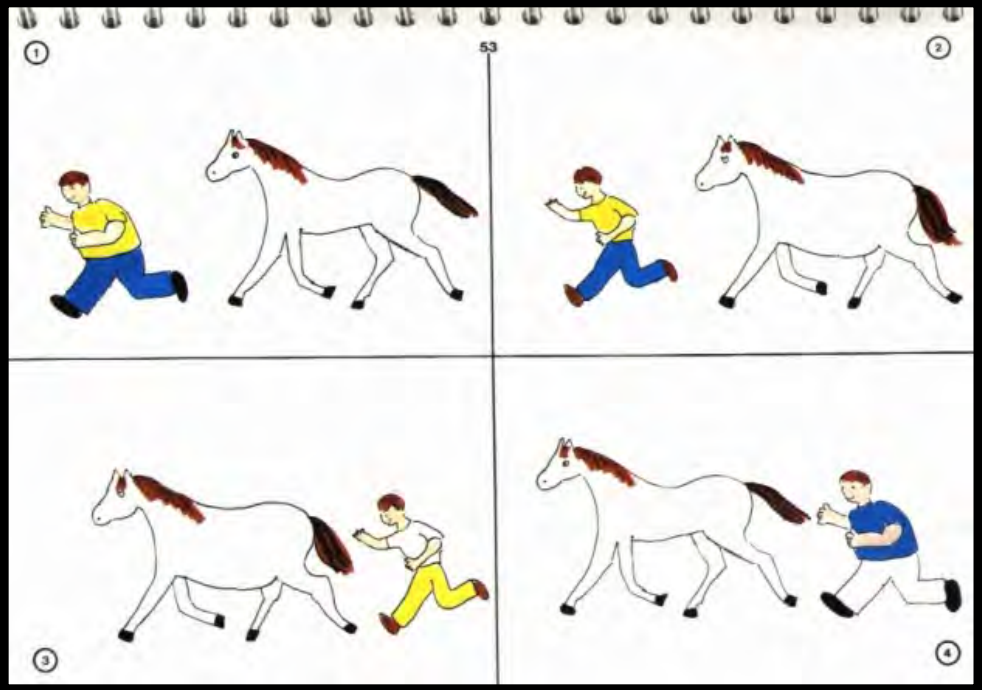
Test of Reception of Grammar (TROG)



Point to:

"The boy chasing the horse is fat"

20 blocks
Normal = 4 items per block (80 total)
Modified = 2 items per block (40 total)

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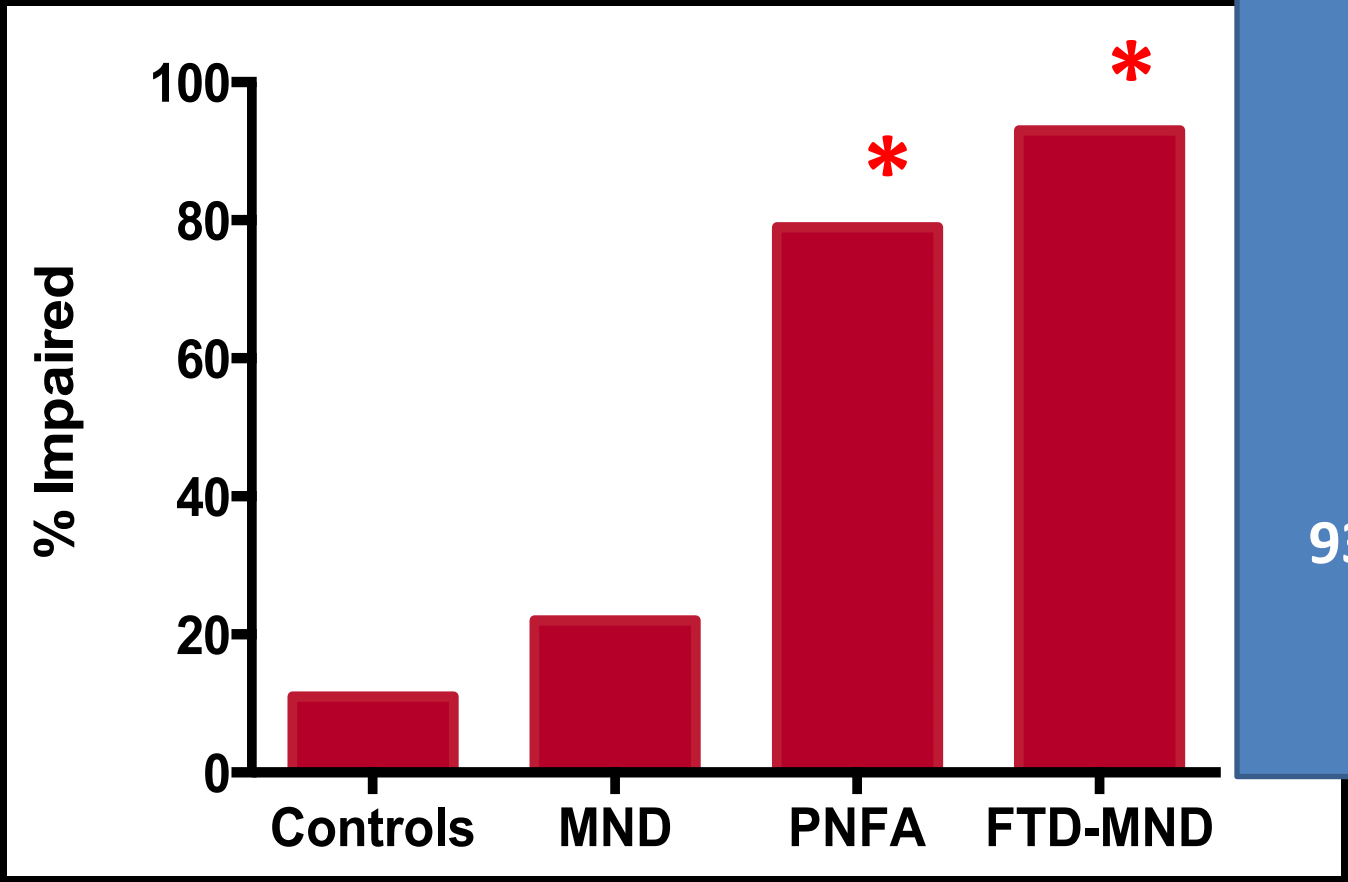
Results



22.2% of MND
(NS)

78.6% of PNFA
(P < 0.001)

93.3% of FTD-MND
(P < 0.001)

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P < 0.001 v controls (*) and MND (*)

Case – 5

- 5 years earlier . . .

- Complaints about “legs pulling”
- Obsessed with bowel movements
- Convinced he was about to die
- Paranoia
- Catatonia nihilistic delusions
- Marked apathy

Case 5 – Summary

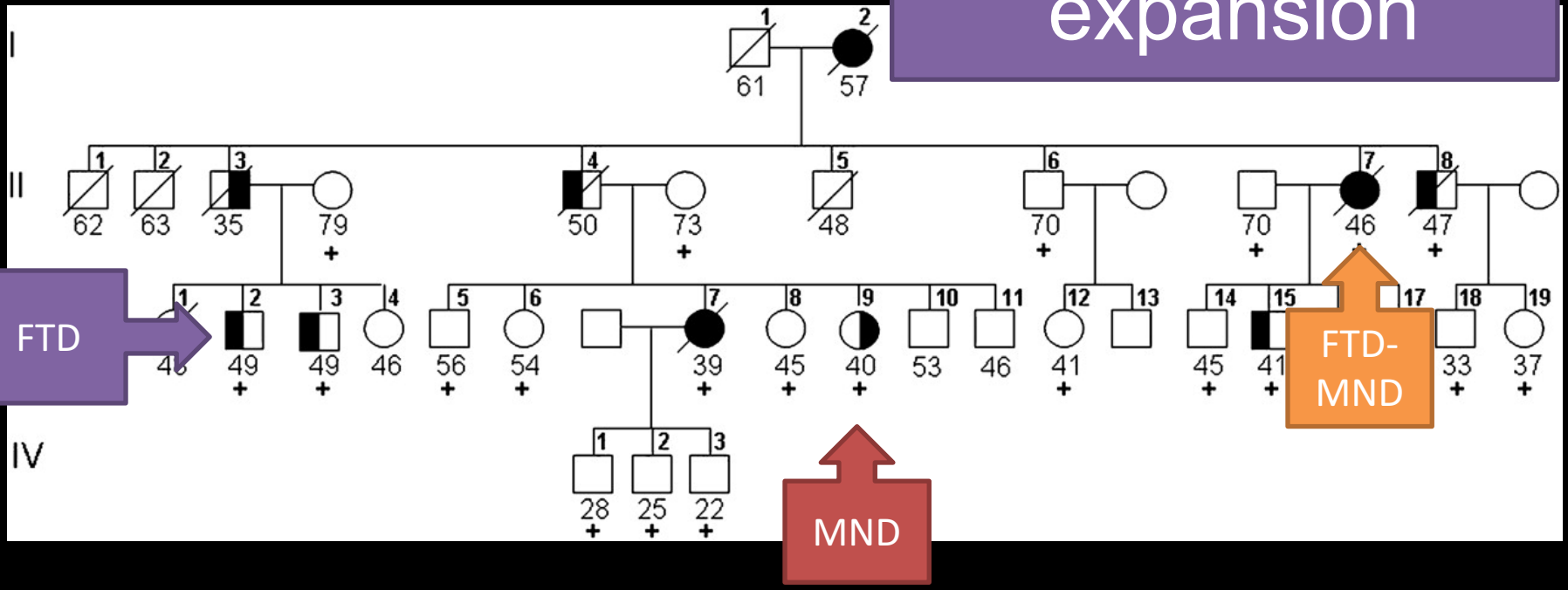
BROTHER DIED of MND @ 59 years

Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family

Adam L Boxer,[1] Ian R Mackenzie,[2] Bradley F Boeve,[3] Matthew Baker,[4] William W Seeley,[1] Richard Crook,[4] Howard Feldman,[5] Ging-Yuek R Hsiung, Nicola Rutherford,[4] Victor Laluz,[1] Jennifer Whitwell,[6] Dean Foti,[5] Eric McDa Jennifer Molano,[3] Anna Karydas,[1] Aleksandra Wojtas,[4,7] Jill Goldman,[8] Jacob Mirsky,[1] Pheth Sengdy,[5] Stephen DeArmond,[9] Bruce L Miller,[1] Rosa Rademakers[4]

JNNP ONLINE

C9ORF72 repeat expansion



Boxer A L et al. J Neurol Neurosurg Psychiatry doi:10.1136/jnnp.2009.204081

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NEW CAUSE FOR FTD-MND IDENTIFIED IN 2011

C9orf72 REPEAT EXPANSION

FAMILY CLUSTERS

FAMILIAL AND SPORADIC DISEASE

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Distinct clinical and pathological characteristics of frontotemporal dementia associated with *C9ORF72* mutations

Brain 2012: 135; 693–708

Julie S. Snowden,[1,2] Sara Rollinson,[2] Jennifer C. Thompson,[1,2] Jennifer M. Harris,[1,2] Cheryl L. Stopford,[1,2] Anna M. T. Richardson,[1,2] Matthew Jones,[1,2] Alex Gerhard,[1,2] Yvonne S. Davidson,[2] Andrew Robinson,[2] Linda Gibbons,[2] Quan Hu,[2] Daniel DuPlessis,[3] David Neary,[1,2] David M. A. Mann[2] and Stuart M. Pickering-Brown[2]

- 12/32 of C9ORF72 patients = **37.5%** presented with psychosis or mixture of **behavioural** and **psychotic features**
  - Psychosis on presentation = OR 15.4, 95% CI 5.9–40.0 of having C9ORF72

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C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts

NEURA COHORT

- Psychotic symptoms:
  - 56% of C9ORF72 positive cases
  - 14% of C9ORF72 negative cases
- Clinical presentation
  - bvFTD
  - FTD-MND

Neurology. 2012 Sep 4;79(10):995-1001

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Clinical heterogeneity of the *C9orf72* genetic mutation in frontotemporal dementia

E. Devenney[a,b,c]*, D. Foxe[a], C. Dobson-Stone[a,d], J.B. Kwok[a,d], M.C. Kiernan[a,c] and J.R. Hodges[a,d]

[a]*Neuroscience Research Australia, Sydney, NSW, Australia;* [b]*Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia;* [c]*Brain and Mind Research Institute, University of Sydney, Sydney, NSW, Australia;* [d]*School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia*

(*Received 14 January 2014; accepted 29 July 2014*)

- Two cases
  - First was very **SLOWLY** progressive
    - ?FTD
  - Second was very **RAPIDLY** progressive
- Often more widespread cognitive deficits (memory, visuospatial)
- Marked clinical heterogeneity

SHOULD CONSIDER TESTING

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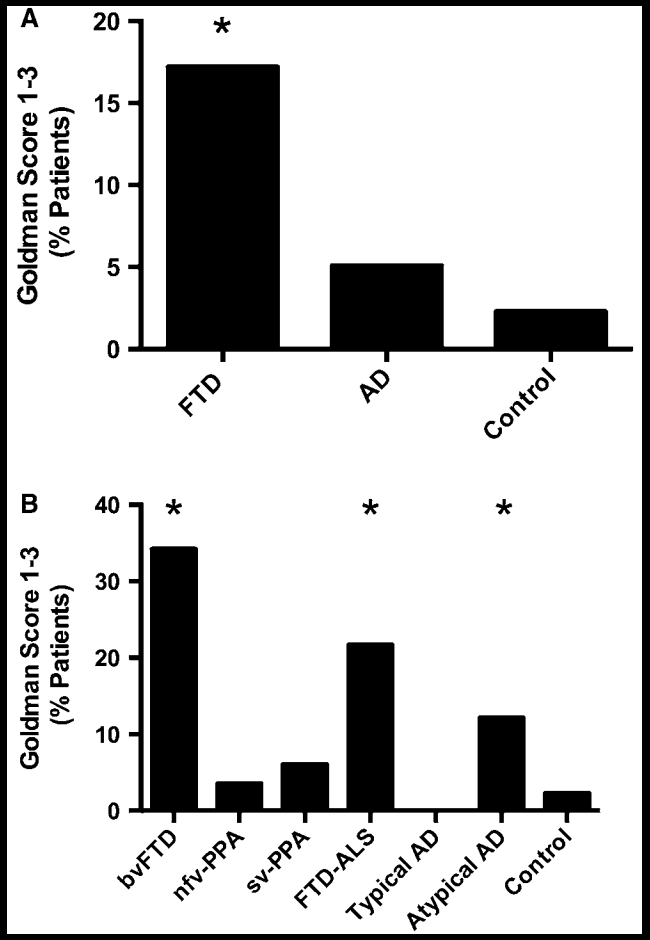
Heritability in frontotemporal dementia: more missing pieces?

Kieren Po · Felicity V. C. Leslie · Natalie Gracia · Lauren Bartley · John B. J. Kwok · Glenda M. Halliday · John R. Hodges · James R. Burrell



- FTD more heritable than Alzheimer's Disease
  - bvFTD, FTD-MND especially

Less than half of patients with strong family history had a documented genetic lesion

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Management of FTD

- Few treatment options
- Education, carer support
- Management of behavioural symptoms
  - Non-pharmacological
  - Pharmacological
    - Atypical antipsychotics
    - Anti-depressants
- Respite or placement issues

Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis

- Families with autosomal dominant history
- At risk, pre-sympt
- Double-blind to g
- Carriers and cont
- Detailed neurops
- Structural imaging (MRI)

Neuropsychological changes 5 years prior to expected onset

Neuroanatomical changes 10+ years prior to expected disease onset

Rohrer et al, Lancet Neurol 2015; 14: 253–62

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Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis

- Neuropsychological abnormalities detected at ~ 5 years prior to expected disease onset
- Subtle cortical atrophy detectable 10 years prior to expected disease onset
- Some differences by genetic cause
  - C9orf72 changes as early as 20 years prior
  - GRN mutations asymmetry (L > R)

Rohrer et al, Lancet Neurol 2015; 14: 253–62

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Summary

- FTD rare, important cause of dementia
- Heterogeneous pathology
  - TDP-43, tau, overlap with Alzheimer's pathology
- Presents with changes in **behaviour** (bvFTD) or **language** (PNFA, SD) or **both**
- Clinical overlaps:
  - Alzheimer's disease – Logopenic progressive aphasia
  - Motor neuron disease
- C9orf72 repeat expansion
  - Late onset psychosis
  - Depression, other psychiatric illnesses

Thanks to:
- Prof John Hodges
- Prof Matthew Kiernan
- A/Prof Olivier Piguet
- Frontier group

- Patient and families

FRONTIER
Frontotemporal Dementia Research Group

Funding:
- NHMRC of Australia
- ARC
- MNDRIA
- RACP Foundation

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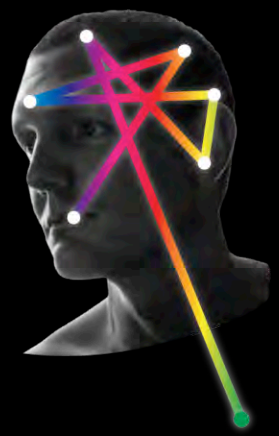
SCIENTIA
MANU ET MENTE



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