

Cognitive and behavioural impairment in Motor Neuron Disease

Dr Christine Albertyn

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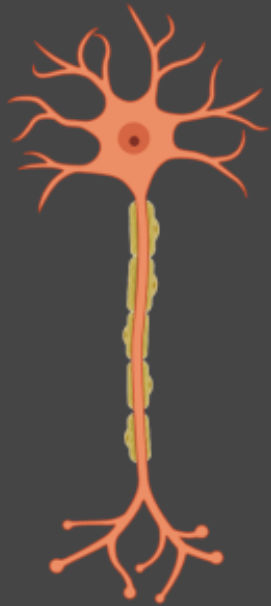
ALS-FTD continuum

Motoneurons:

- muscle weakness
- muscle atrophy
- fasciculations
- dysarthria and dysphagia

Frontotemporal cortices:

- behavior disorders
- language impairment
- executive deficits
- emotional lability

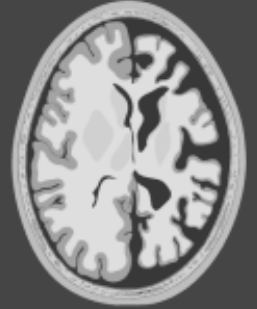


MOTOR

MOTOR

COGNITION

COGNITION



ALS

ALS-FTD

FTD

SOD1

ANG

NEK1

ALS2

SETX

VAPB

FUS

TARDBP

C9ORF72

TBK1

VCP

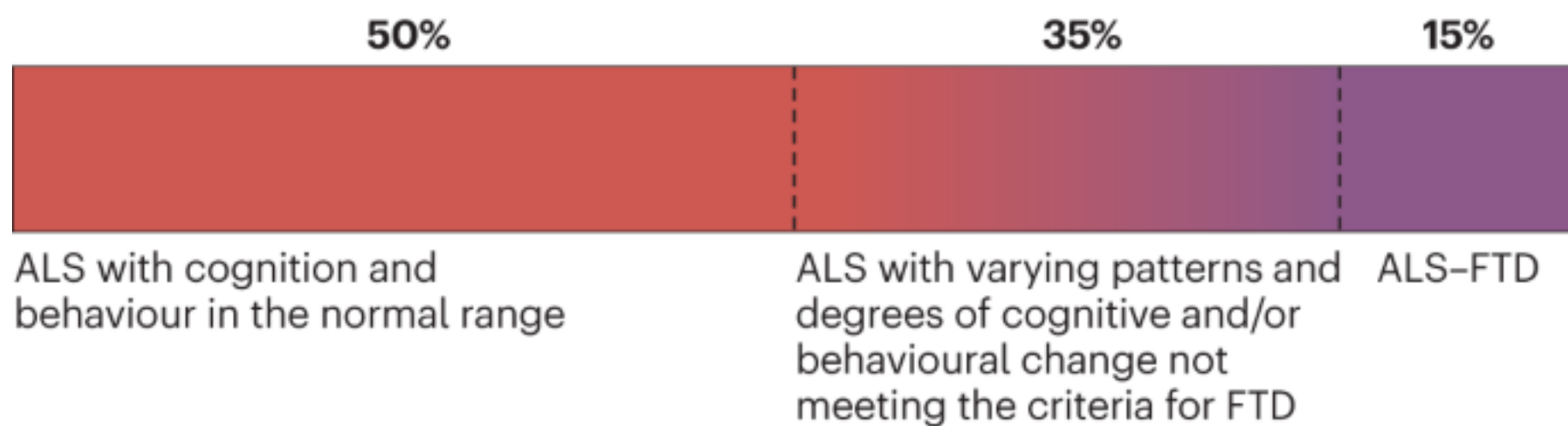
SQSTM-1

OPTN

CHCHD10

GNR

MAPT



ALS-frontotemporal spectrum of disease

Axis I – defining the motor neuron disease variant;

Axis II – defining the cognitive and behavioral dysfunction; and

Axis III – additional non-motor disease manifestations.

Cognitive and behavioral dysfunction

- ALS with cognitive impairment (ALSci)
 - either executive dysfunction (including social cognition) or language dysfunction or a combination of the two.
- ALS with behavioral impairment (ALSbi)
 - informant questionnaires which demonstrate apathy with or without other behavior change OR the presence of two or more listed behavioral symptoms.
- ALS with combined cognitive and behavioral impairment (ALS-cbi)
 - Both present
- ALS-FTD
 - behavioral/cognitive changes in keeping with behavioral variant FTD (bvFTD), or present with language impairment in keeping with progressive non-fluent aphasia (PNFA) or semantic dementia (SD)

About half of patients will have milder cognitive impairment:

- executive dysfunction
- impaired fluency
- poor working memory

Even mild impairment can have significant impact on functioning:

generate thought and think flexibly

to update and manipulate information mentally

to inhibit what is irrelevant to current goals

to self-monitor

to plan and adjust behavior as appropriate to the present context

Recognising cognitive-behavioral impairment

- Associated with worse prognosis
- Contributes to carer burden
- Impacts adversely on compliance with symptomatic interventions such as non-invasive ventilation and percutaneous endoscopic gastrostomy
- Curatorships
- Bulbar onset of symptoms and lower educational attainment have been associated with cognitive involvement

Behavioral manifestations

Pathology in:

- dorsolateral
- prefrontal
- orbitofrontal
- medial prefrontal lobes

Behavioural signs

- Disinhibition
- Stereotypy
- Lack of empathy
- Change in personality
- Aggression
- Agitation
- Change in appetite

Most pervasive symptom: apathy (70% of patients)

Presence of psychotic symptoms: strong association with C9orf72 mutations

Social cognition, theory of mind, and emotional processing

Social cognition

- Judging facial emotional expression
- Assessing approachability of others based on non-verbal cues
- Gauging mental states through eye expressions
- Interpretation of conversations based on prosody of speech

Theory of mind

- the ability to infer mental states in others (i.e. by putting oneself in someone else's shoes).

Social cognition, theory of mind, and emotional processing

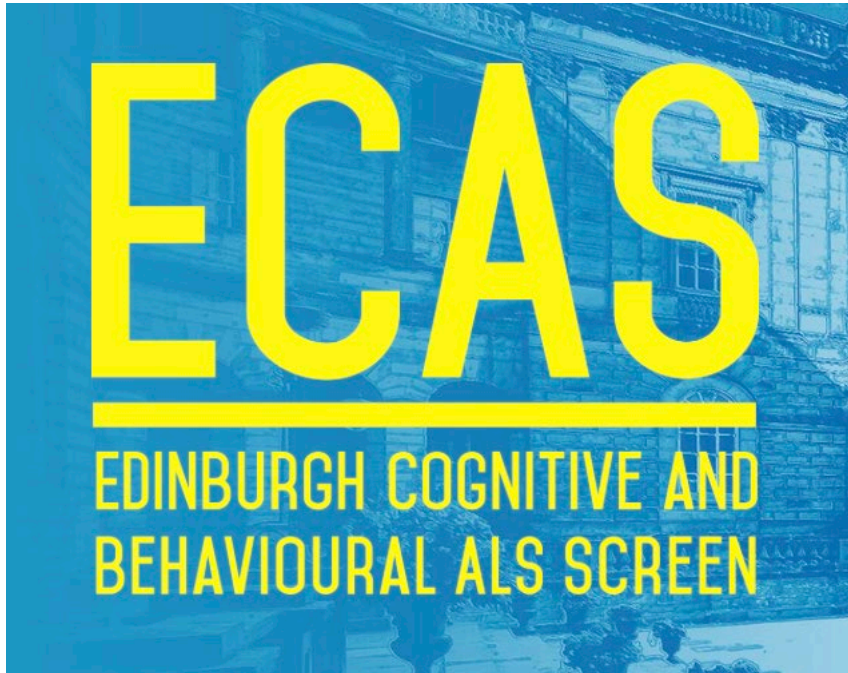
Testing

- grasping the humor of specific cartoons
- story comprehension tests
- judgments of whether faux pas have been committed
- understanding social contexts

A challenge remains to improve the ecological validity: the extent to which an impaired test performance translates to difficulty in real-life settings

Special considerations of neuropsychological testing in the ALS population

Behavioral and neuropsychological testing



poral Degeneration, 2022; 0: 1–10



Language

- 1) Bafikile
- 2) Ukwakha (the verb)
- 3) Siyatshata
- 4) Bamenyiwe
- 5) Umhlala-phantsi
- 6) Imvelaphi

- 7) Intshona
- 8) Umphathi
- 9) Ubuhle
- 10) Isitiya
- 11) Uthuli
- 12) Umhlakulo

1. Envelope
3. Constructing
5. Biscuit
7. Deliver
9. Coathanger
11. Screwdriver

2. Skateboard
4. Partner.....
6. Lawnmower
8. Recorded
10. Orchestra
12. Brought

LANGUAGE – Spelling

Sê: "Spel die volgende woorde óf deur te praat óf neer te skryf". As die persoon hulptechnologie gebruik, vra hulle om enige voorspellende teks af te skakel.

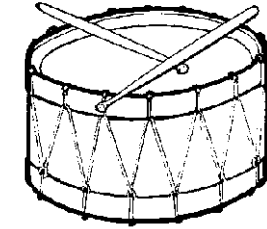
1. Hotel
3. Swembad
5. Geslaap
7. Braaivleis
9. Lê
11. Beskryf

2. Grassnyer
4. Fiets
6. Olifant
8. Verstaan
10. Poskantoor
12. Rekenaar

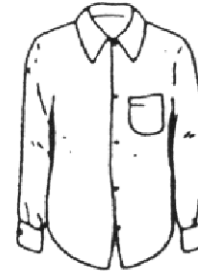
Score
0-12



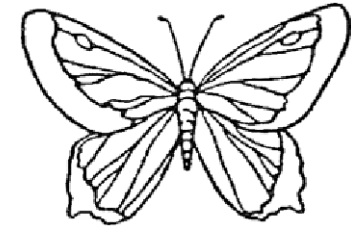
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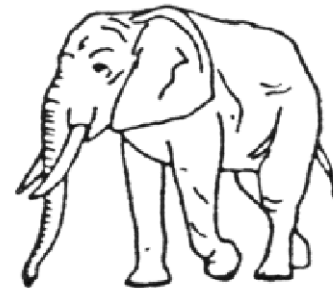
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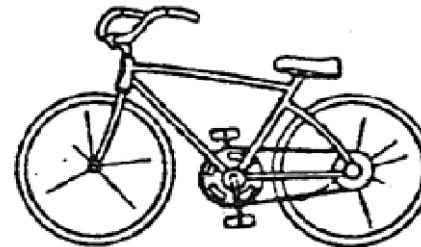
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Memory

Verlede Sondag het 'n vuur uitgebreek in 'n dorpie 120km buite Kaapstad. Die vlamme het na baie huise versprei en Willem Adonis se kar is ook beskadig. Drie mense is dood en 40 mense is beseer terwyl hulle probeer het om hulle besittings te red.

Last Sunday a fire broke out in a township 120km outside Cape Town. The flames spread to many houses and Robert Wilson's car was also damaged. Three people died and many people were injured while they were trying to save their possessions.

Kule Cawa iphelileyo kuye kwaqhambuka umlilo kwilokishi ekwiikhilomitha ezili-120 ngaphandle kwaseKapa. Amadangatye aye anwenwela kwizindlu ezininzi yaye kuchaphazeleke nemoto kaVuyo Dlamini. Kusweleke abantu abathathu kwaza kwenzakala abantu abangama-40 ngelixa bebezama ukusindisa izinto zabo.

Fluency

FLUENCY - letter S

Verbal

☐

Written

☐

Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers.'

If writing, say: 'You will have **two** minutes. The letter is S.'

If speaking, say 'You will have **one** minute. The letter is S.'

FLUENCY – Letter T

Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers. This time the word must only be four letters long. No more or less than four letters'

- ☐ If writing, say: 'You will have **two minutes**. The letter is T.'
- ☐ If speaking, say 'You will have **one minute**. The letter is T.'

Executive function

EXECUTIVE - Reverse digit span

Sê: “Ek gaan ’n paar getalle noem en ek wil hê dat jy hulle vir my in die omgekeerde volgorde moet terugse. As ek byvoorbeeld sê “2 3 4”, moet jy sê “4 3 2”. Kom ons oefen. As ek sê “7 1 9”, wat sal jy sê?” Stop wanneer die persoon albei probeerslae van ’n reël verkeerd kry. Merk die totale getal probeerslae wat korrek is.

Trial		Check	Trial		Check
1	2 6		2	5 8	
3	9 3 5		4	4 1 6	
5	7 2 8 4		6	9 5 7 3	
7	6 9 4 2 1		8	8 3 2 5 6	
9	8 1 3 5 7 9		10	3 6 2 7 3 4	
11	1 6 9 3 5 8 6		12	2 3 6 8 4 9 2	

Score
0-12

Executive function

EXECUTIVE - Alternation

Sê: “Ek wil hê dat jy tussen getalle en letters moet wissel, beginnende by 1A, dan 2B, dan 3C en so aan. Gaan so aan, wissel tussen nommers en letters, in volgorde, sonder om enige oor te slaan, tot ek sê stop. Kom ons begin saam. 1A, 2B, 3C....”

Trial		Check	Trial		Check	Trial		Check	Trial		Check
1	4-D		2	5-E		3	6-F		4	7-G	
5	8-H		6	9-I		7	10-J		8	11-K	
9	12-L		10	13-M		11	14-N		12	15-O	

Score
0-12

Executive function

EXECUTIVE – Sentence completion

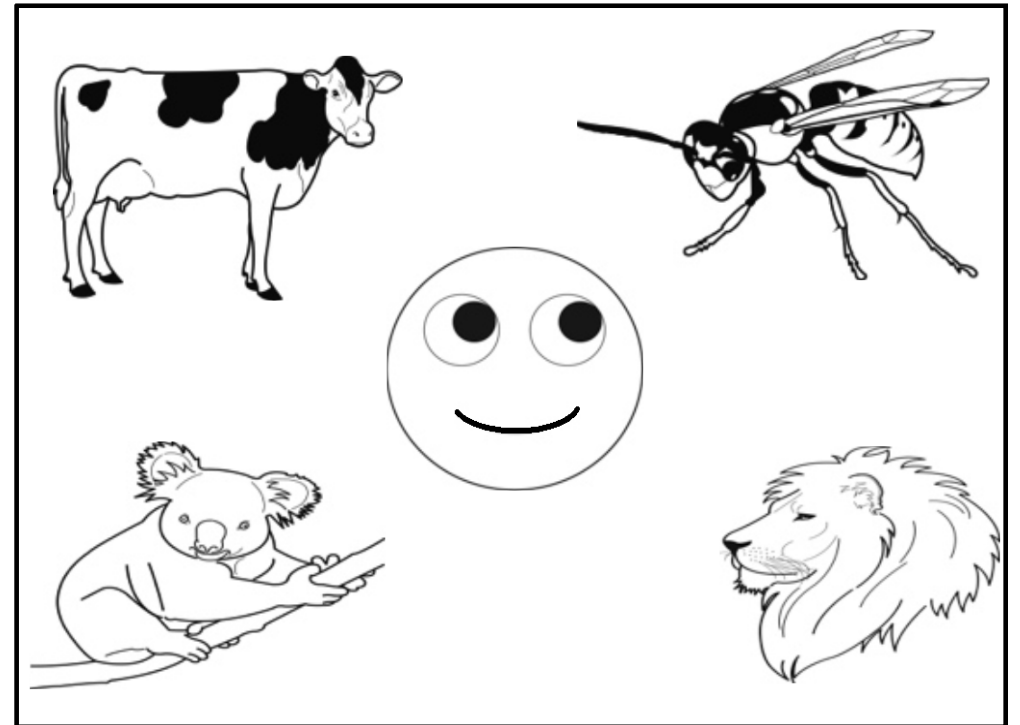
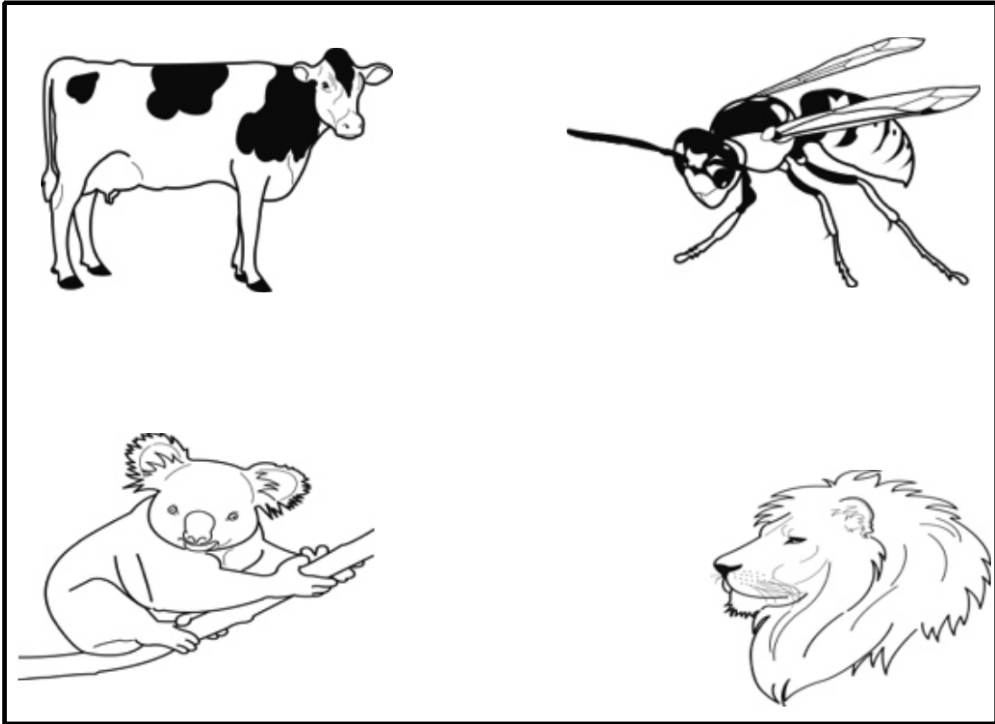
Say: 'Listen carefully to these sentences and as soon as I have finished reading them, please tell me, or write, a word that finishes the sentence as quickly as possible. For example, 'She was so tired that she went straight to...bed'. Do not score:

1. He phoned up the restaurant to reserve a
2. When she got up in the morning, the sun was.....

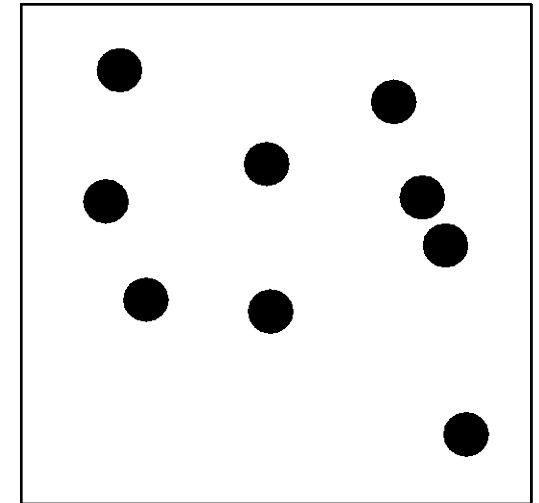
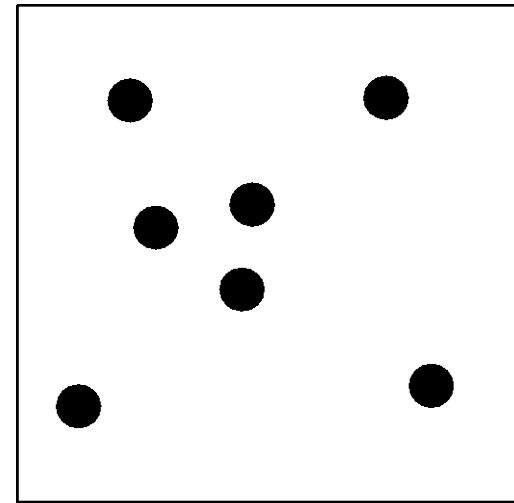
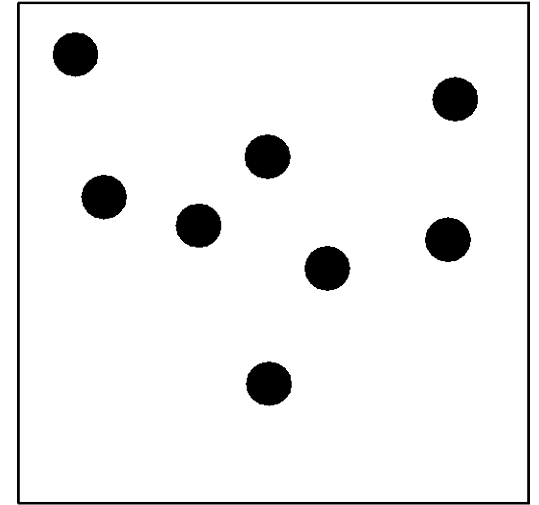
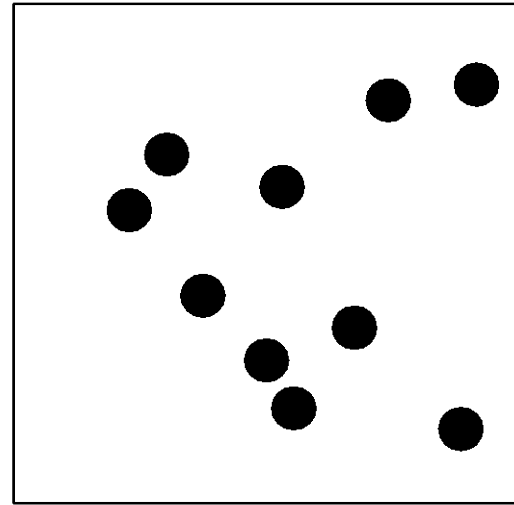
Say: 'Now I'd like you to do that again, but this time the word you give should not make sense whatsoever in the context of the sentence. It must not be related to the word that actually completes the sentence. For example, 'John cut his hand with the sharp...orange'. If the person does not respond within 20 seconds, move onto the next question.

1. The postman knocked on the
2. He brought his umbrella with him in case of
3. Sally spread her toast with butter and

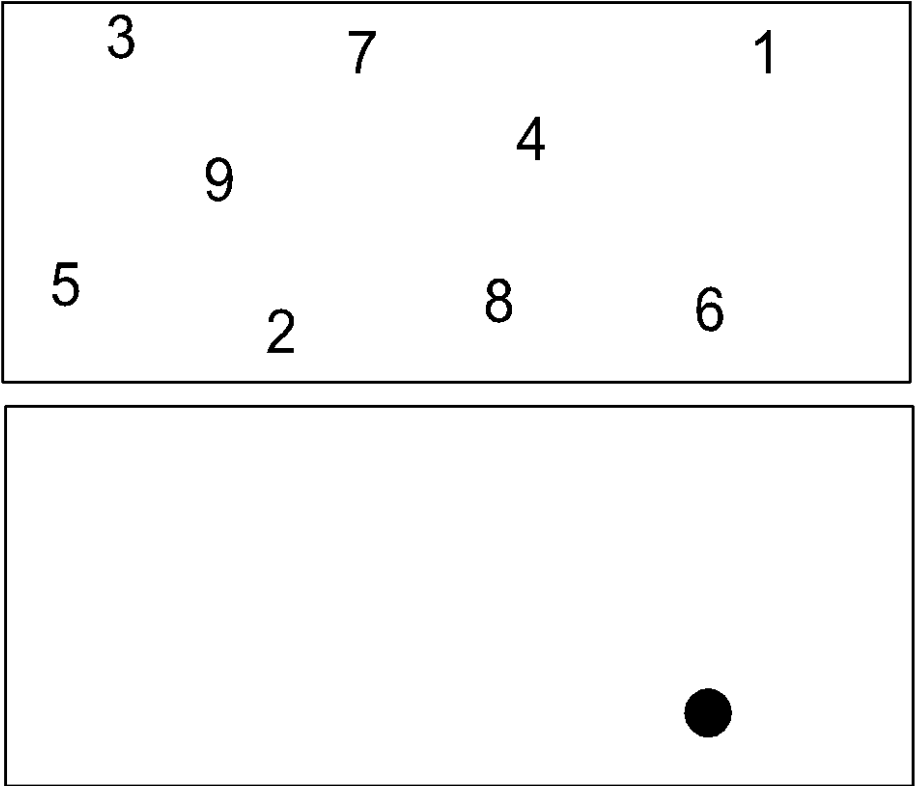
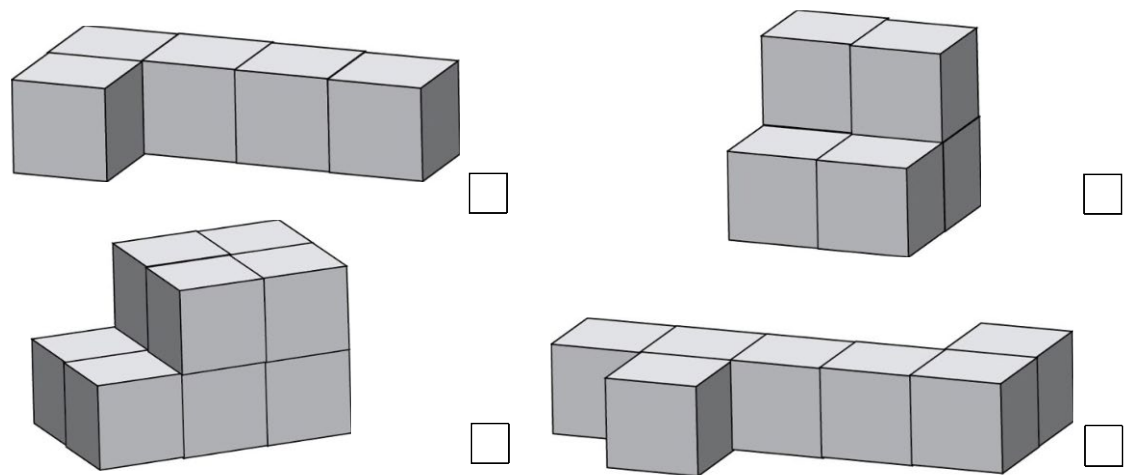
Executive function



Visuospatial



Visuospatial



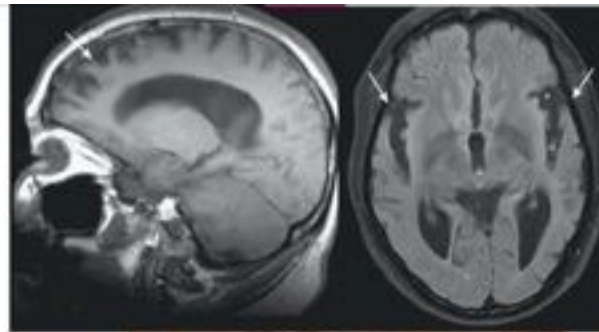
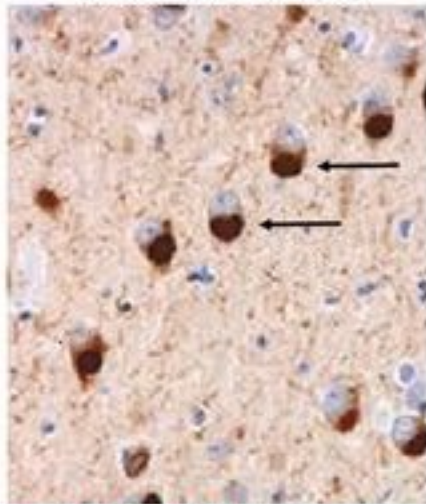
SCORES

Language	Naming, Comprehension, Spelling	/28
Verbal Fluency	Fluency Letter S, Fluency Letter T	/24
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48
ALS-SPECIFIC:		/100
Memory	Immediate recall, Delayed recall score, Delayed recognition	/24
Visuospatial	Dot Counting, Cube Counting, Number Location	/12
ALS NON-SPECIFIC:		/36
ECAS TOTAL SCORE:		/136

Behavioural questionnaire

A	Behavioural disinhibition
1	Socially inappropriate behaviour, e.g. <i>inappropriate behaviour with strangers</i> <i>criminal behaviour</i>
2	Loss of manners or decorum, e.g. <i>crude or sexually explicit remarks, jokes or opinions that</i> <i>may be offensive to others</i> <i>lack of response to social cues</i>
3	Impulsive, rash or careless actions, e.g. <i>new onset gambling, or buying or selling property without regard for consequences</i> <i>giving out personal information inappropriately, e.g. credit card numbers</i>

Pick Bodies
(labeled anti-tau antibodies)



Atrophy of frontal and/or temporal areas

Decreased concern and empathy for others



ubiquitinated TDP-43 inclusions seen on histology

Amyotrophic lateral sclerosis (ALS)

Clinical features of frontal lobe variant

Decrease in speech

Loss of awareness of personal appearance and hygiene



Oral fixation: increased eating causes weight gain



FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) is a heterogeneous spectrum of disorders marked by degeneration in the frontal and anterior temporal lobes, resulting in various symptoms of disturbed personality, behavior, and language. FTD is the third most common form of neurodegenerative dementia, ranking after Alzheimer disease and dementia with Lewy bodies, accounting for perhaps 5% of all dementia cases. FTD generally presents at a

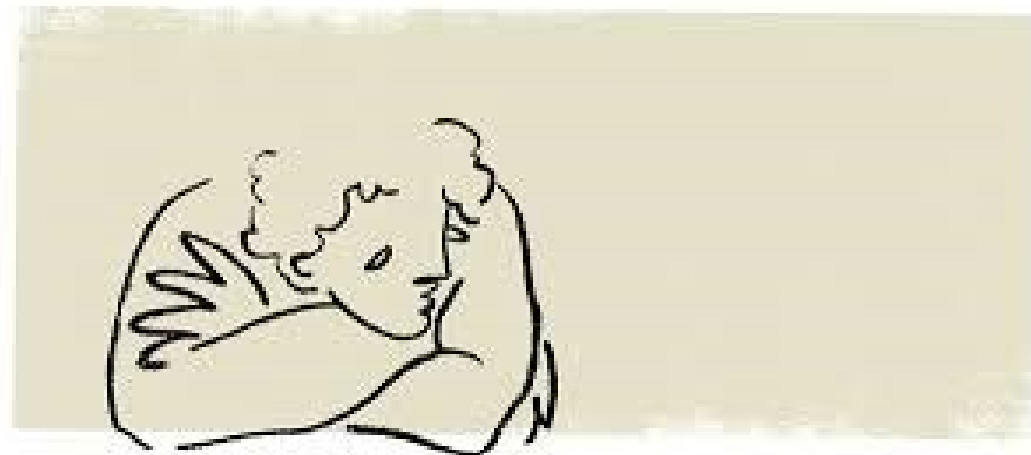


MR. RUDE

Roger Hargreaves



B	Apathy or inertia
4	Loss of interest, drive or motivation, e.g. <i>passivity and lack of spontaneity</i> <i>needs prompting to initiate or continue routine activities</i>



C	Loss of sympathy or empathy
5	Diminished response to other people's needs and feelings <i>Positive rating on this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings, e.g</i> <i>hurtful comments</i> <i>disregard for others' pain or distress</i>
6	Diminished social interest, interrelatedness, personal warmth or general closeness in social engagement, e.g. <i>coldness</i> <i>lack of eye contact</i>



CX903185



"Your back is killing me!"

D	Perseverative, stereotyped, compulsive or ritualistic behaviour
7	Simple repetitive movements, e.g. <i>tapping, clapping</i> <i>scratching, picking skin or clothing</i> <i>repeating words</i>
8	Complex, compulsive or ritualistic behaviours, e.g. <i>counting, cleaning rituals, checking</i> <i>collecting, hoarding</i>



E	Hyperorality and altered food preferences
9	Altered food preferences, e.g. <i>food fads</i> <i>carbohydrate craving (particularly sweets)</i>
10	Binge eating or hyperorality, e.g., <i>cramming or continuing to eat despite satiety</i> <i>oral exploration or consumption of inedible objects</i>



ALS Psychosis Screen

➡ Please ask the carer about the following possible symptoms. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 3).

1	Has strange and/or bizarre beliefs and behaviours	Y	N	DK
2	Hears or sees things that are not there, and/or feels the presence of someone who is not there	Y	N	DK
3	Is overly suspicious, and/or feels persecuted	Y	N	DK
SCORE				
TOTAL			/3	



- Recognise symptoms and signs
- Screen
- Offer support to patient and family
- Genetic testing where appropriate