World Congress of Neurology, Santiago de Chile
Teaching Course 29 on MND/ALS, 4 November 2015

Thomas H. Bak

What wires together, dies together: MND/ALS as a multisystem disorder

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Nothing to disclose

Learning objectives

- To understand the reasons for the long neglect of cognitive & behavioural symptoms in MND/ALS
- To become familiar with the most common cognitive and behavioural symptoms in MND/ALS
- To appreciate the differences as well as similarities between ALS/MND and FTD
- To develop a view of MND/ALS that integrates cognition
- To learn how cognitive and behavioural symptoms can be assessed through a brief clinical screening

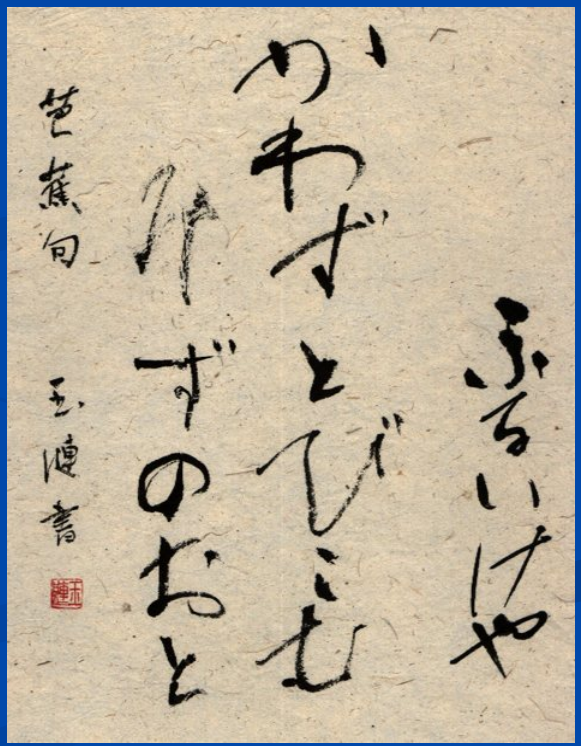
The history gets longer every time we look at it…

- The knowledge that MND/ALS can be associated with cognitive & behavioural symptoms…
- … is not new
- This has been already recognised in late 19th Century
- … but less so in the Anglo-saxon world
- Why?

Watanabe 1893

Journal of the Medical Society of Okayama

- Became available in English only recently
  (Ichikawa et al, European Neurology 2011)
- First aphasia description in Japan
- Aphasia in the context of MND
- Predominant impairment in kana
- (rather than kanji)



The other story: cognitive & behavioural symptoms; reports from early 20th Century (before 1939)

Dornblüth 1889

Marie 1892

Raymond & Cestan 1905

Fragnito 1907

Westphal 1909

Gerbert & Naville 1921

Büscher 1922

van Bogaert 1925

Meyer 1929

Ziegler 1930

von Braunmühl 1932

Wechsler & Davison 1932

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Teichmann 1935

* Publications in English

Cognitive & behavioural symptoms in ALS
Early reports

Single case reports of overt Dementia

Dornblüth 1889

Meyer 1929

von Braunmühl 1932

Teichmann 1935

Subtle cognitive changes in non-demented patients

Marie 1892

Raymond & Cestan 1905

Van Bogaert 1925

Ziegler 1930

Cognitive & behavioural changes in ALS: frequency

- Marie (1892)
  - "psychic disturbances are fairly common"
- Raymond & Cestan (1905)
  - Half of 18 pathologically confirmed cases described as "psychologically feeble"
- Van Bogaert (1925)
  - "psychic alterations" in 13 out of 31 patients

Dementia associated with ALS: Clinical features

- Characteristic time course:
  - Cognitive/behavioural symptoms followed by classical ALS
  - => dementia not explained by non-specific physical impairments
- ALS with prominent bulbar features (dysarthria, dysphagia)
- Faster deterioration than in ALS without dementia
- Pathology, when available:
  - Typical ALS pathology (particular involvement of hypoglossus nucleus)
  - Frontal or frontotemporal cortical atrophy & neuronal loss

Cognitive changes in ALS

- Intellectual impairment:
  - "impoverishment of the usual intellectual processes"
  - Memory: impairment of "Merkfähigkeit" rather than "Gedächtnis"
  - Preserved visuo-spatial functions
- Language:
  - "Speechlessness", "inability to speak"
  - Perseverations, echolalia, stereotypic expressions
  - Spelling errors
  - Semantic paraphasias
  - Comprehension deficits

ALS and FTD coming nearer and nearer…

- Hudson 1981 *(Brain)*: Review of 155 articles, 30 ALS/Dementia
- Neary et al 1990 (*JNNP*): The concept of MND/FTD
- Gunnarson et al 1991 (*Acta Neur Scand*): ALS & FTD in 13 members of the same family
- Lomen-Hoerth 2003 (*Neurology*): Are ALS patients cognitively intact?
- De Jesus Hernandez 2011 (*Neuron*): C9ORF72, *Brain March 2012*
- Towards a consensus: 10-20% FTD, 35-50% subtle cognitive changes, 30-50% preserved cognition (*Rakowicz, Lomen-Hoerth, Ringholz, Elamin)*

Why has the evidence for cognitive & behavioural symptoms in ALS been neglected for so long?

- Different traditions:
  - The close relation between neurology & psychiatry in Europe
  - The separation between the two in the Anglosaxon world
- Development of specialisation & specialist clinics
- Nomen est omen - MOTOR neuron disease
- Perceived relative irrelevance of cognitive symptoms in the context of a fast and terminal illness
- An effort to "protect the patients", assuring them that the mental functions will remain unimpaired

How common are cognitive & behavioural symptoms in ALS?

MND-motor 50%

SPECTRUM

MND-cognitive/behaviour change 35%

Frontotemporal dementia (FTD) 15%

Abrahams et al. (1996; 1997)
Rackowicz and Hodges (1998) 38%
Lomen-Hoerth et al (2003) 33%
Ringholz et al. (2005) 37%
Elamin et al (2010) 35%

The progression of ALS

Classical motor form

(Ravits et al 2007, 2009)

- Focal onset (limb or bulbar)
- Contiguous spread to connected areas
- Predominant caudal direction
- "An orderly process"

Dementing-aphasic form

(Bak 2010, Bak & Chandran 2011)

- Dementia & aphasia occur early, often initial presentation (similar as PSP & MS)
- Pattern of progression:
  - Dementia, then bulbar symptoms
  - Reverse pattern less frequent
  - Lower limbs least involved

Cognitive & behavioural symptoms in ALS

- Personality change, apathy, inappropriate behaviour, social cognition
- Psychotic features most common in C9ORF72 patients
- Frontal executive deficits, e.g. verbal fluency
- Language: mutism, comprehension deficits, spelling errors
- Visuospatial & memory deficits less common

Behavioural changes in ALS

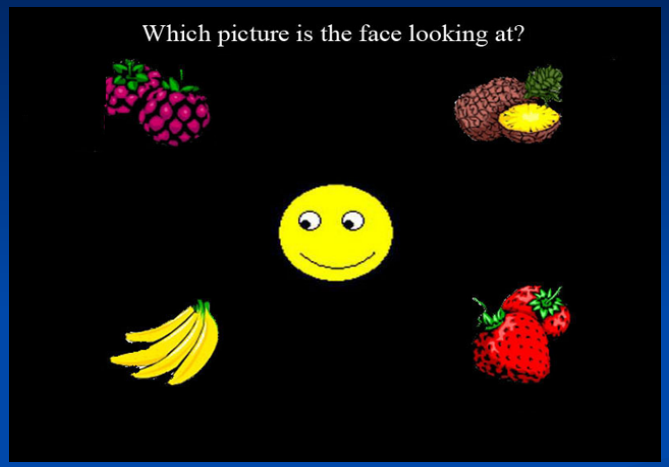
- Emotional changes:
  - Depression & manic-depressive illness
  - Emotional lability, irritability
  - Apathy
- Changes in personality:
  - Suspiciousness, stubborness & obstinacy
  - Pathological greed
  - Obsessive tendency to hoard things, particularly food
- Psychotic symptoms:
  - Delusions & paranoid ideation
  - Bizarre behaviours
  - ? Hallucinations

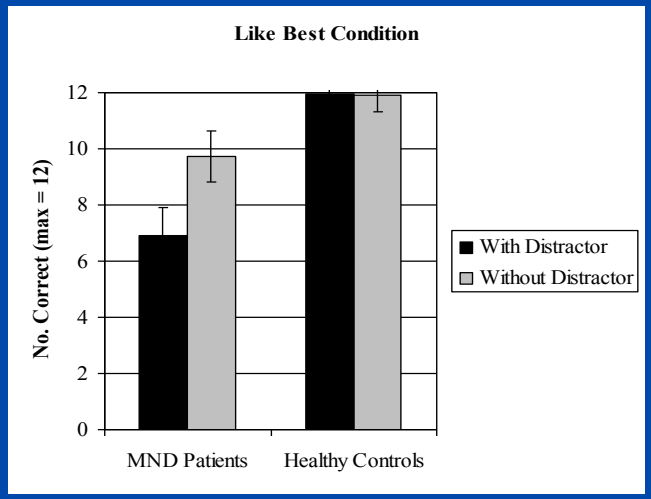
Neuropsychology
2011, Vol. 25, No. 1, 53–65

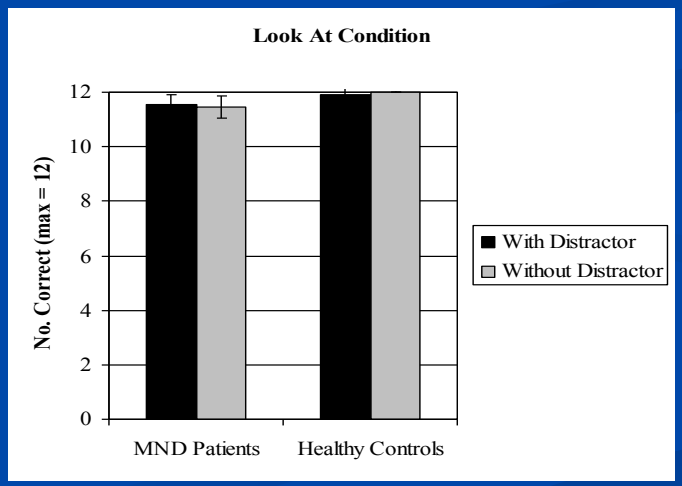
0894-4105/10/$12.00 DOI: 10.1

Deficits in Emotional and Social Cognition in Amyotrophic Lateral Sclerosis

Alessandra Girardi, Sarah E. MacPherson, and Sharon Abrahams
University of Edinburgh







36% of MND impaired in simple theory of mind test (Judgement of Preference)
Increased egocentric responses in MND.

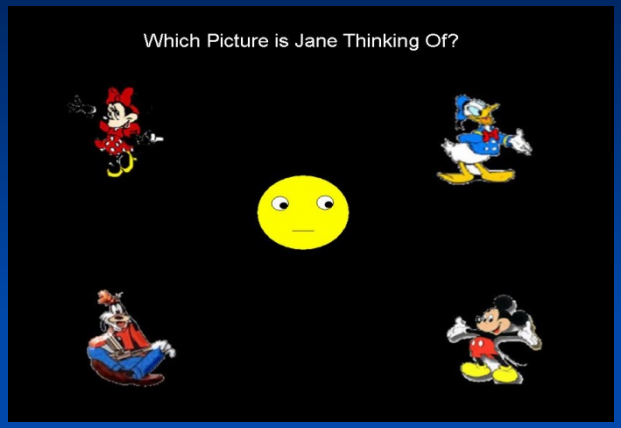
Sharon Abrahams Inaugural Lecture
28th October 2015

JNNP Online First, published on December 4, 2014 as 10.1136/jnnp-2014-309290
Movement disorders

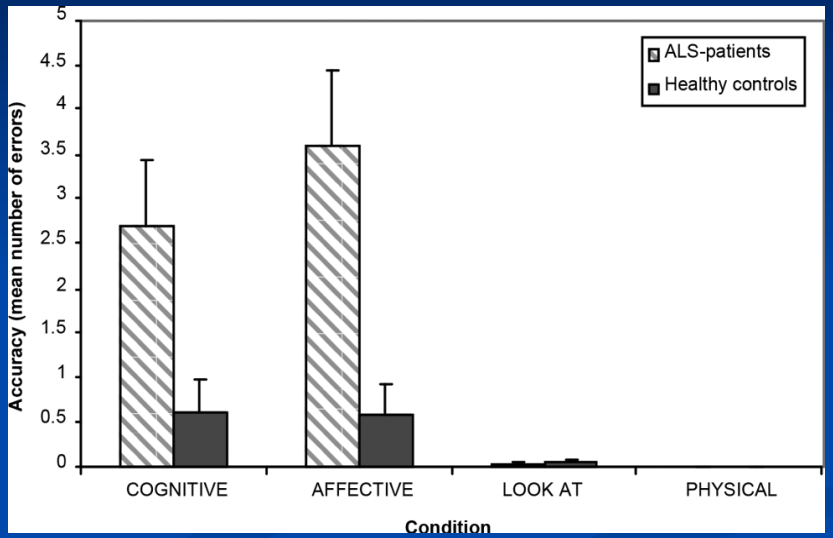
RESEARCH PAPER

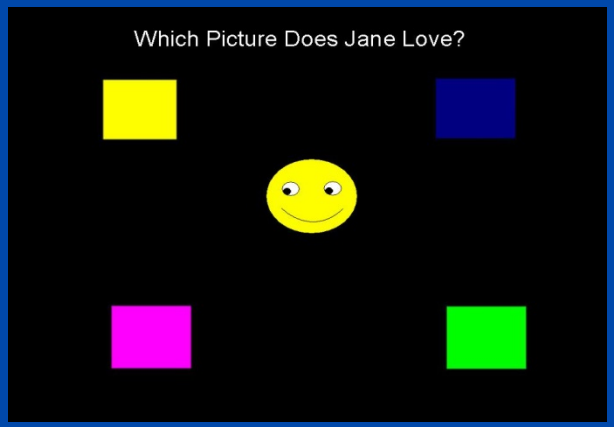
Impaired affective and cognitive theory of mind and behavioural change in amyotrophic lateral sclerosis

Egberdina-Józefa van der Hulst,[1] Thomas H Bak,[1,2,3,4] Sharon Abrahams[1,2,3,4]



Cognitive





Affective

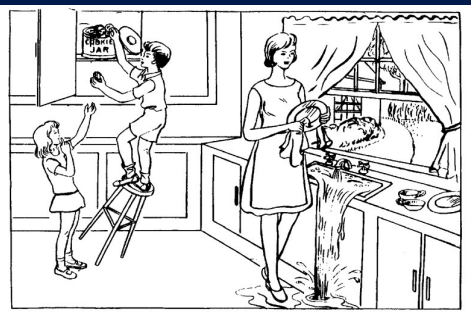
36% of MND patients showed affective while 27% showed a cognitive theory of mind deficit

Sharon Abrahams Inaugural Lecture
28th October 2015

Language in ALS/FTD

- **Typical presentation:**
  - Cognitive/behavioural symptoms followed by classical MND
- **Language:**
  - Most common symptom: progressive reduction in verbal output (+/- dysarthria) leading to mutism
  - Some patients still able to write after the onset of mutism
  - In some patients "progressive aphasia" as the initial diagnosis
  - All patients show abnormalities on formal language testing

Language in ALS (*Bak et al 2001, 2004)*

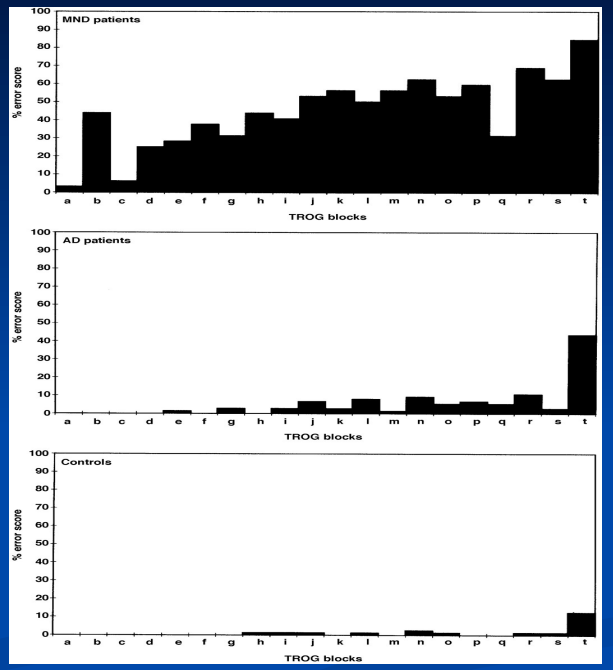


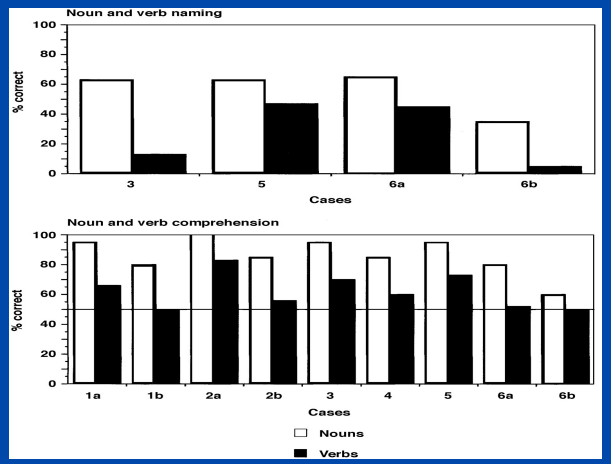
Drawn Water will goes.
Dawn, with well well going to push within down, cookie jar to go with thong they water wast.
with we they was will down down the will angola the preated.

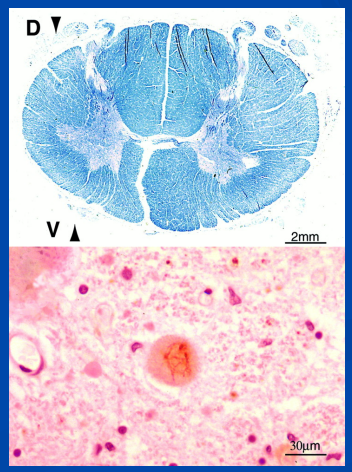
Case 1

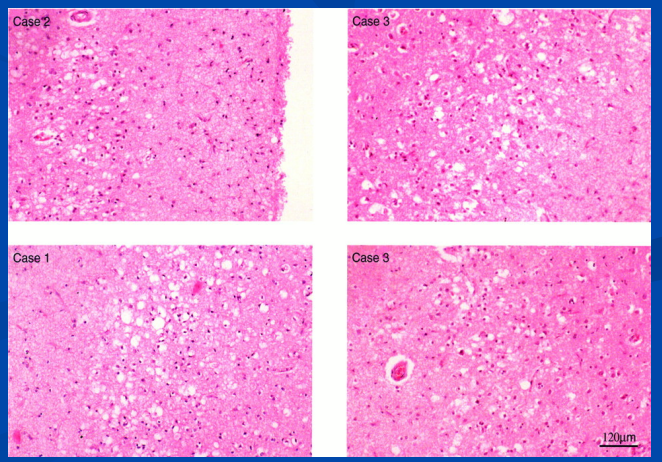
WASHING UP
COOKIE JAR
SINK FLOW
LITTLE GIRL HAD A BISCUIT
STOOL FALLING OVER
CURTAINS DRAWED
WINDOW FAST GROWING

Case 2



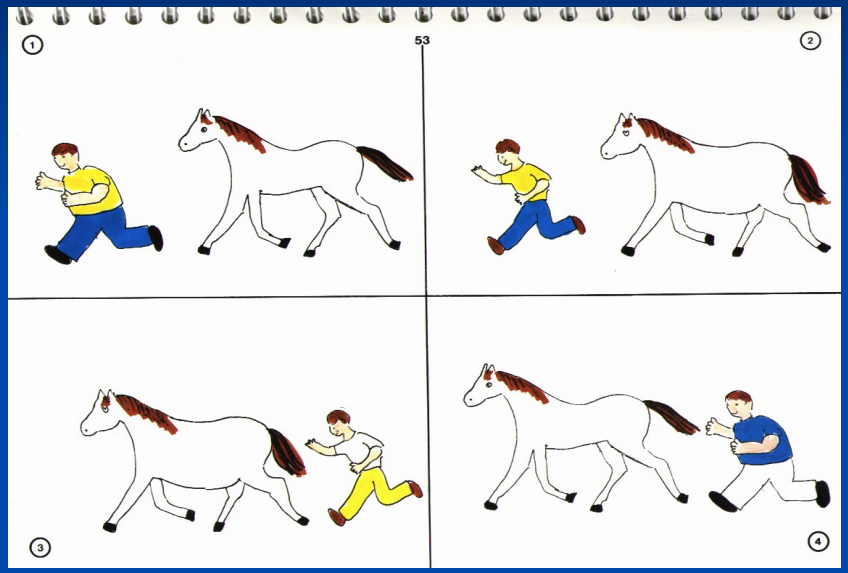


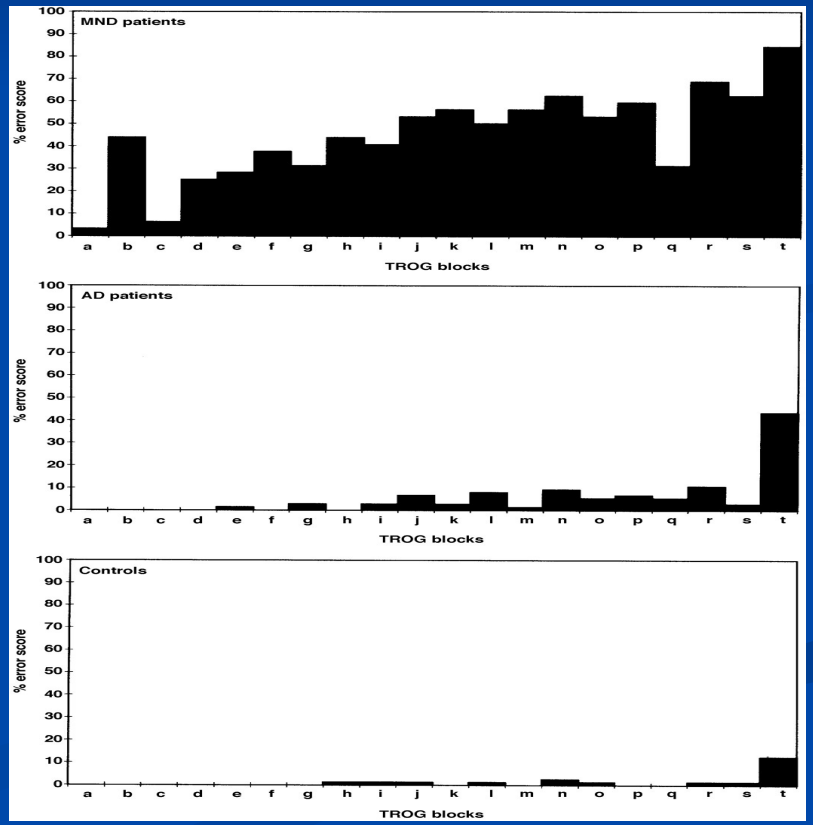




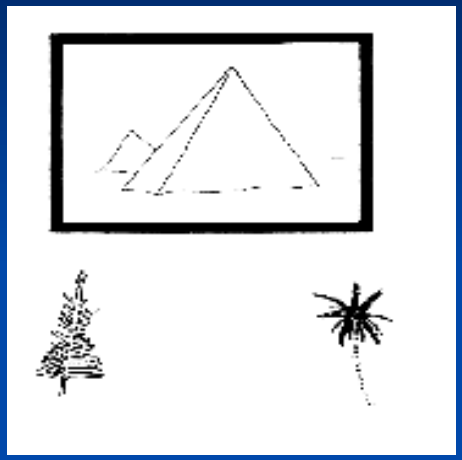
Language Comprehension in MND/Dementia

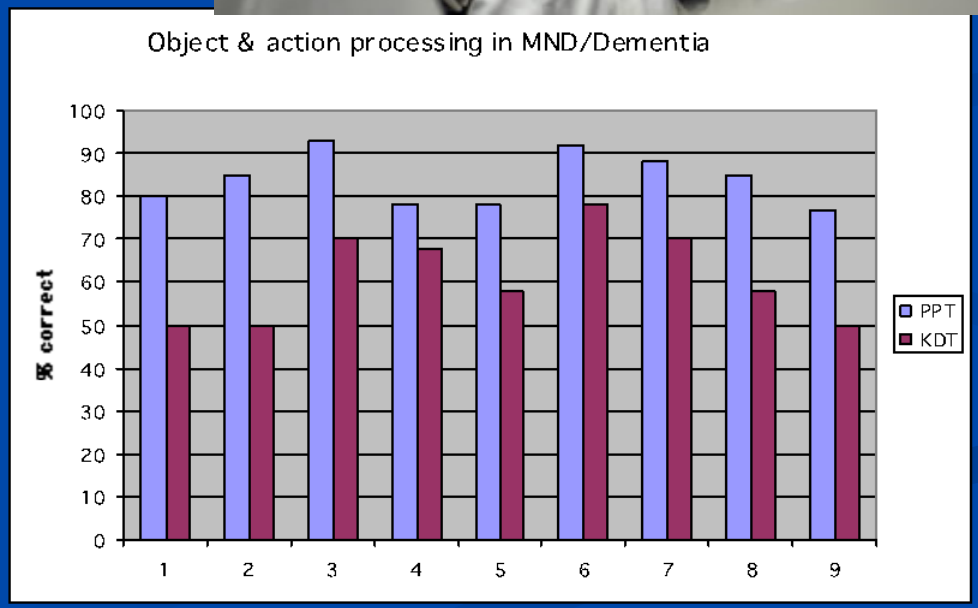
Bak et al 2001, Brain



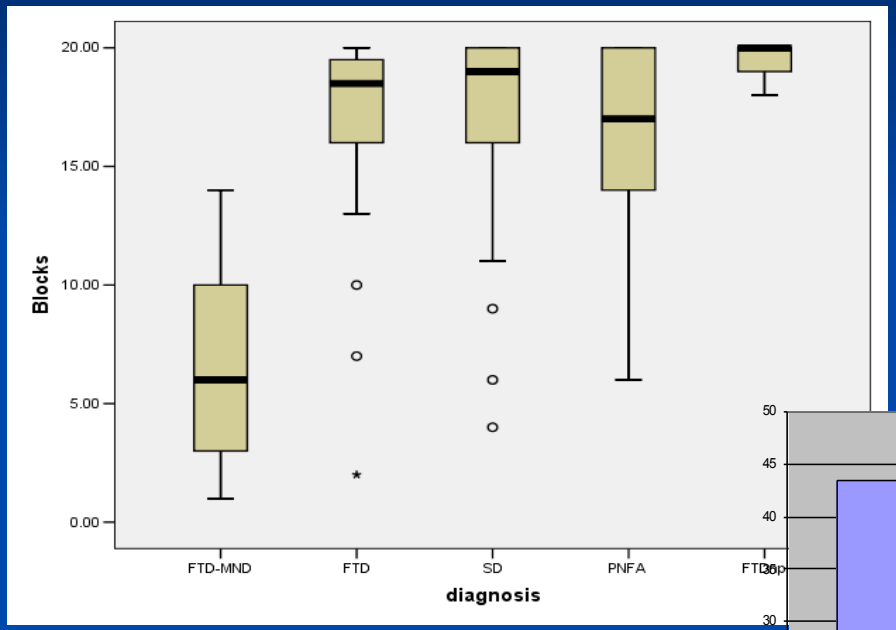


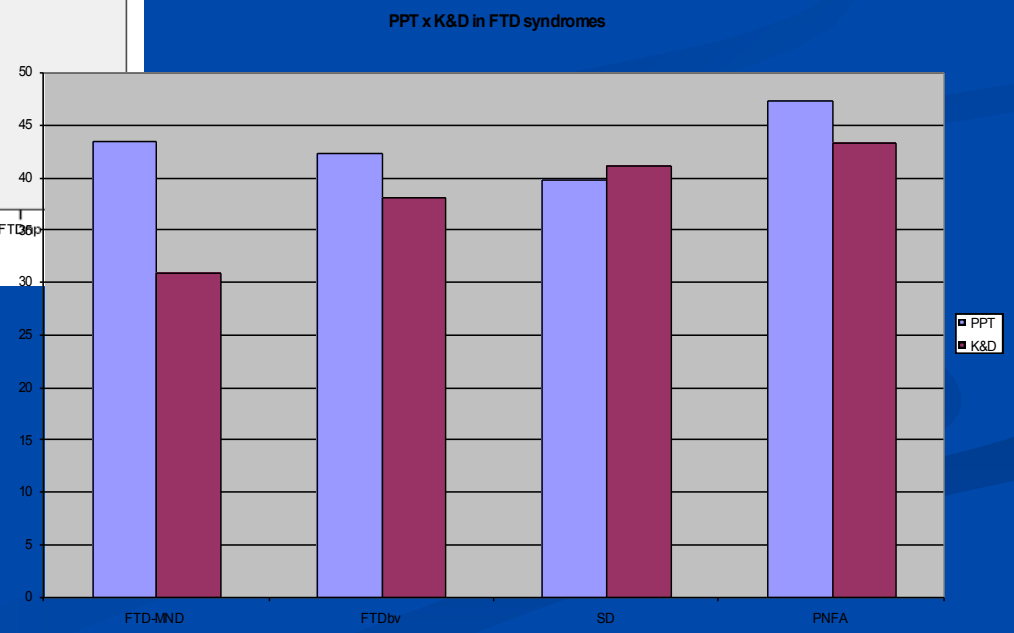
Kissing & Dancing Test (*Bak & Hodges 2003*)





FTD/MND versus bvFTD, SD & NFPA





FTD & MND: one, two of three diseases

(Bak 2010, Annals of Indian Academy of Neurology)

- 2001 - ALS and FTD:
  - Coincidence
  - Co-occurance
  - Continuum
- 2010 -Specific features of ALS/FTD:
  - Psychotic features (*Bak, Lillo, Snowden*: particularly in C9ORF72)
  - Comprehension deficits (*Caselli, Rakowicz, Bak, Goldstein*)
  - Spelling errors (*Watanabe, Kawamura, Silani, Abrahams & Bak*)
  - Does not map neatly into bvFTD, NFPA and SD
- => Interaction rather than addition

ALS/FTD versus FTD: the differences

- Natural history:
  - Order of presentation: FTD, bulbar ALS, limb ALS
  - FTD/ALS much faster than classical FTD
- FTD/ALS does not map simply into the three subtypes of FTD
- More severe language involvement:
  - Comprehension deficits (*Caselli, Rakowicz, Bak, Taylor)*
  - Spelling errors (*Watanabe, Kawamura, Silani, Abrahams & Bak)*
- Psychotic symptoms (*Bak, Lillo, Snowden*, particularly in C9ORF72)
- MND & FTD: one, two or three diseases? (*Bak 2010 versus Bak 2001*)

Language, cognition & behaviour in MND

- Observed deficits:
  - Planning of actions
  - Decision making, including social cognition & inhibition
  - Knowledge of actions
- => Deficits in "Motor cognition" (*Marc Jeannerod 2006*)
- Distinct from (opposite to) the deficits seen in SD
- Extension of Hebb's Rule (*Bak & Chandran 2011*):
  - **What fires together wires together**
  - **What wires together dies together**

The relevance of cognitive symptoms

- Theoretical importance for the models of neurodegeneration
- Prognosis
- Quality of life
- Costs of care
- Carer burden

Comment from ALS Patient's wife

"My own GP has told me that MND just affects the limbs and NOT the brain functions. I have to disagree as in one year of my late husbands life I saw the change of a caring conscientious family man change into an uncaring, unsympathetic, aggressive person that none of his family or friends recognised. A professional man that did the most bizarre things that were totally out of character.

Even colleagues had noticed that he had gone from a very efficient team leader to a 'couldn't care less attitude' even before he was diagnosed. … He became unrecognisable like a stranger even though we had been married 22 years. The Professionals he saw did not in their appointments see the man he had become"

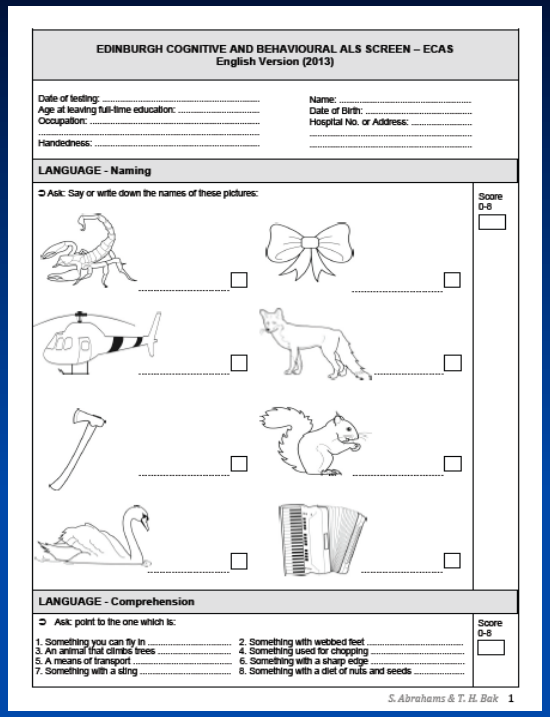
Edinburgh Cognitive Assessment (ECAS) Rationale

- All major cognitive tests designed for patients with normal motor functions (MMSE, MoCA, DRS, ACE)
- => the necessity of a test adapted to patients with motor dysfunction
- Current screening tools in MND are unidimensional
- => the necessity of a multidimensional screening tool

Edinburgh Cognitive Assessment (ECAS) Structure

- Frontal-executive (including social cognition)
- Language (naming, comprehension, spelling)
- Verbal Fluency (index)
- Memory (encoding, recall & retrieval)
- Visuospatial functions (dots, cubes)

ALS Specific



EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS
English Version (2013)

Date of testing: ..... Name: .....
Age at leaving full-time education: ..... Date of Birth: .....
Occupation: ..... Hospital No. or Address: .....
....
Handedness: ....

LANGUAGE - Naming

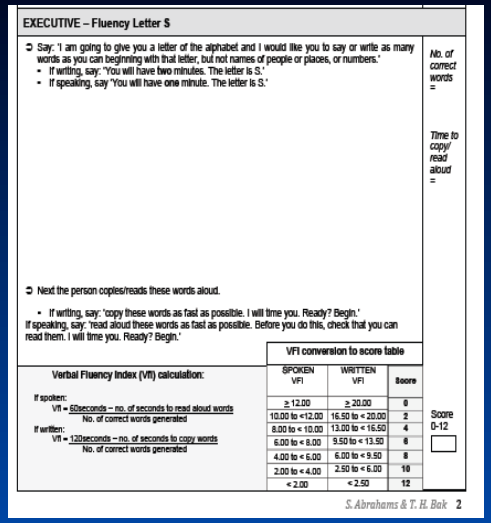
➲ Ask: Say or write down the names of these pictures: Score 0-8

LANGUAGE - Comprehension

➲ Ask: point to the one which is: Score 0-8

1. Something you can fly in ..... 2. Something with webbed feet .....
3. An animal that climbs trees ..... 4. Something used for chopping .....
5. A means of transport ..... 6. Something with a sharp edge .....
7. Something with a sting ..... 8. Something with a diet of nuts and seeds .....

S. Abrahams & T. H. Bak 1



EXECUTIVE – Fluency Letter S

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many 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.'

No. of correct words =

Time to copy/ read aloud =

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Score 0-12

Verbal Fluency Index (VFI) calculation:

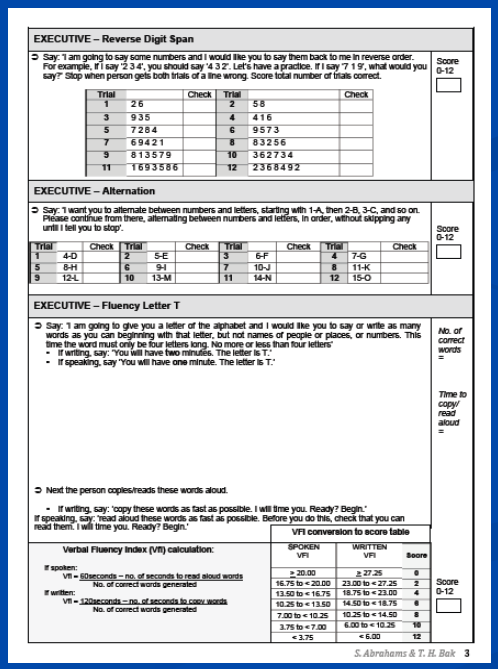
If spoken: VFI = 60seconds – no. of seconds to read aloud words / No. of correct words generated

If written: VFI = 120seconds – no. of seconds to copy words / No. of correct words generated

VFI conversion to score table

SPOKEN VFI	WRITTEN VFI	Score
≥ 12.00	≥ 20.00	0
10.00 to <12.00	16.50 to < 20.00	2
8.00 to < 10.00	13.00 to < 16.50	4
6.00 to < 8.00	9.50 to < 13.50	6
4.00 to < 6.00	6.00 to < 9.50	8
2.00 to < 4.00	2.50 to < 6.00	10
< 2.00	< 2.50	12

S. Abrahams & T. H. Bak 2



EXECUTIVE – Reverse Digit Span

➲ Say: 'I am going to say some numbers and I would like you to say them back to me in reverse order. For example, if I say '2 3 4', you should say '4 3 2'. Let's have a practice. If I say '7 1 9', what would you say?' Stop when person gets both trials of a line wrong. Score total number of trials correct. Score 0-12

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	

EXECUTIVE – Alternation

➲ Say: 'I want you to alternate between numbers and letters, starting with 1-A, then 2-B, 3-C, and so on. Please continue from there, alternating between numbers and letters, in order, without skipping any until I tell you to stop'. Score 0-12

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	

EXECUTIVE – 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 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.'

No. of correct words =

Time to copy/ read aloud =

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Score 0-12

Verbal Fluency Index (VFI) calculation:

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If written: VFI = 120seconds – no. of seconds to copy words / No. of correct words generated

VFI conversion to score table

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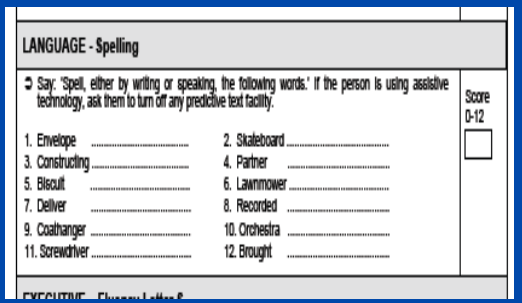
10.25 to < 13.50	14.50 to < 18.75	6
7.00 to < 10.25	10.25 to < 14.50	8
3.75 to < 7.00	6.00 to < 10.25	10
< 3.75	< 6.00	12

S. Abrahams & T. H. Bak 3

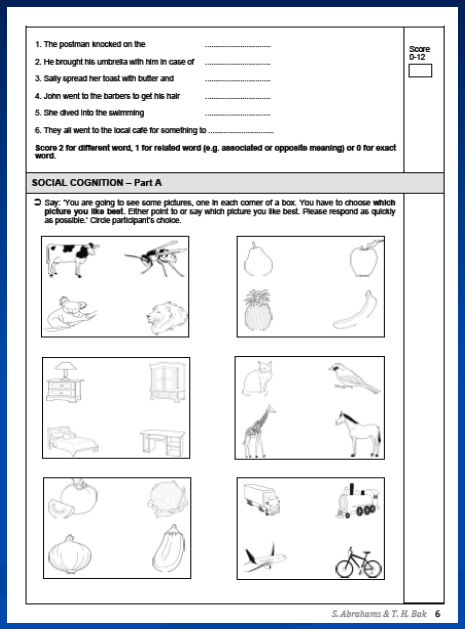


LANGUAGE - Spelling

➲ Say: 'Spell, either by writing or speaking, the following words.' If the person is using assistive technology, ask them to turn off any predictive text facility. Score 0-12

1. Envelope ..... 2. Skateboard .....
3. Constructing ..... 4. Partner .....
5. Biscuit ..... 6. Lawnmower .....
7. Deliver ..... 8. Recorded .....
9. Coathanger ..... 10. Orchestra .....
11. Screwdriver ..... 12. Brought .....

EXECUTIVE – Fluency Letter P



1. The postman knocked on the .....
2. He brought his umbrella with him in case of .....
3. Sally spread her toast with butter and .....
4. John went to the barbers to get his hair .....
5. She dived into the swimming .....
6. They all went to the local café for something to .....

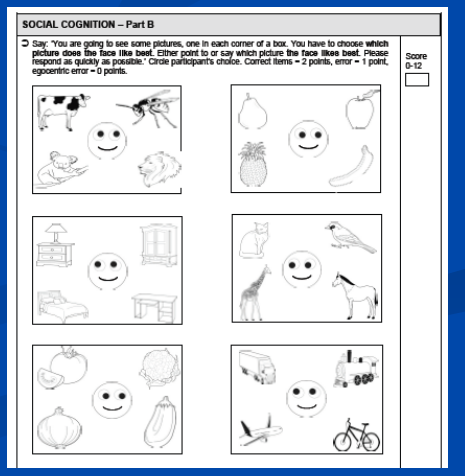
Score 0-12

Score 2 for different word, 1 for related word (e.g. associated or opposite meaning) or 0 for exact word.

SOCIAL COGNITION – Part A

➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose which picture you like best. Either point to or say which picture you like best. Please respond as quickly as possible.' Circle participant's choice.

S. Abrahams & T. H. Bak 6



SOCIAL COGNITION – Part B

➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose which picture does the face like best. Either point to or say which picture the face likes best. Please respond as quickly as possible.' Circle participant's choice. Correct items = 2 points, error = 1 point, egocentric error = 0 points. Score 0-12

ALS Non-specific

MEMORY – Immediate recall

Score 0-10

➲ Say: 'I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember'. Score 1 point for each (either entire or part of) underlined section recalled.

Last Sunday, the annual litter collection took place in Primrose Woods. Forty two people joined in to remove old bicycles and shopping trolleys. Mr Douglas Watt from the woodland project told local reporters that he was very impressed and especially proud of the 17 children who came along.

Also use this score to calculate % retention later

MEMORY – Delayed Recognition

If all items recalled, skip and score 4. Otherwise ask questions below.

Say: 'Lets see if you can remember anything more about that story. I will ask you some questions, please tell me if they are true or false'.

Circle responses (true or false) and score 1 point for each item recognised in this section. Use table below to calculate score.

Score 0-4

Was the story about an event that occurred last Saturday?	T	F	1
Was the event the annual litter collection?	T	F	1
Did this take place in Primrose Woods?	T	F	1
Did they remove old drink cans and sweet wrappers?	T	F	1
Was the man in the story called Mr Watt?	T	F	1
Was his first name 'Thomas'?	T	F	1
Was he from the local council?	T	F	1
Was he especially proud of the children for coming along?	T	F	1

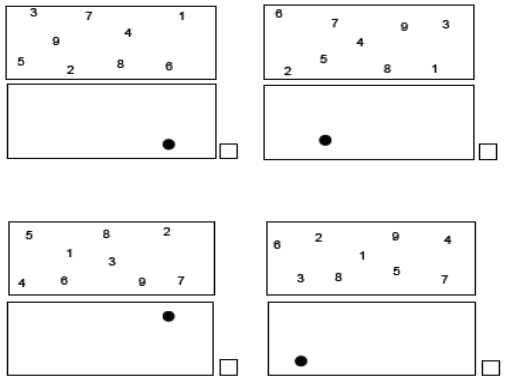
Recognition to recognition score table

Number of correct answers	Converted Score
0-4	0
5	1
6	2
7	3
8	4

VISUOSPATIAL – Number Location

➲ Say: 'Which number corresponds to the position of the dot?'

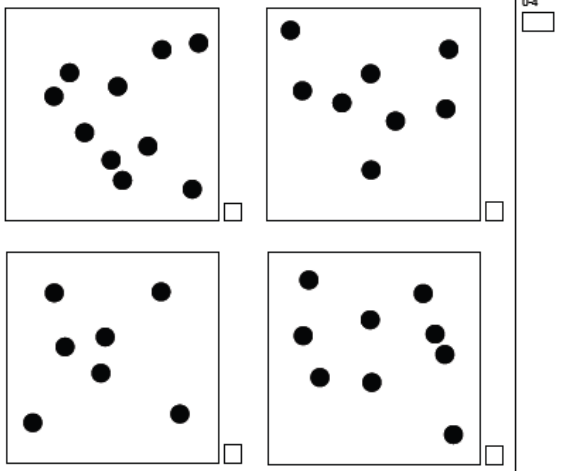
Score 0-4



VISUOSPATIAL – Dot Counting

➲ Say: 'I would like you to count how many dots are in each box, but without pointing to them.'

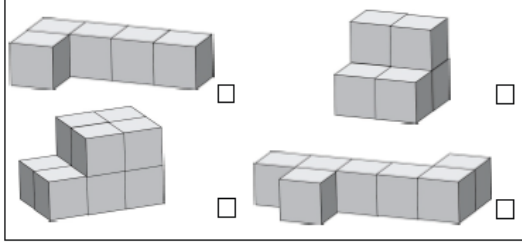
Score 0-4



VISUOSPATIAL – Cube Counting

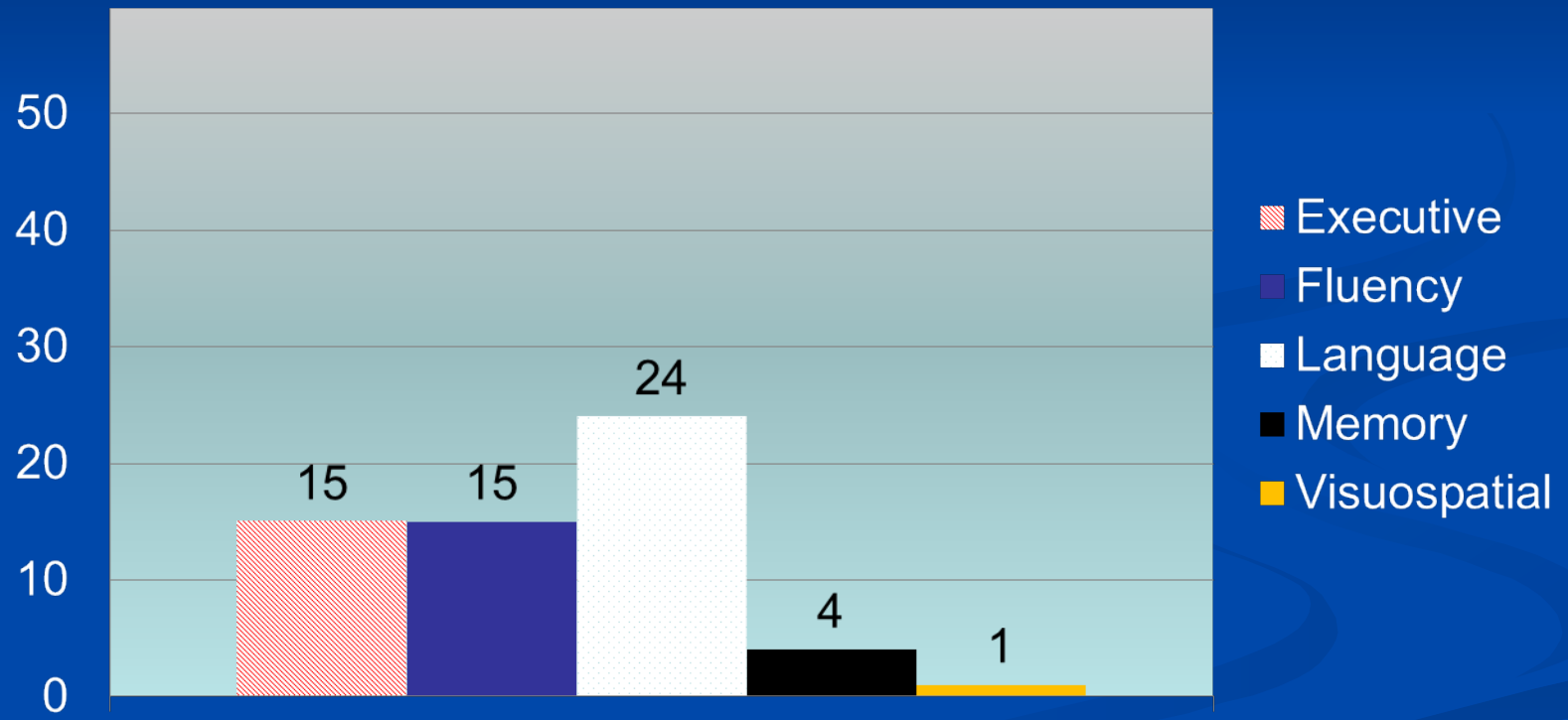
➲ Say: 'How many cubes are in each structure, including the ones you may not be able to see?'

Score 0-4



ECAS Subdomains:
Frequency of Abnormal Performance

59 Patients



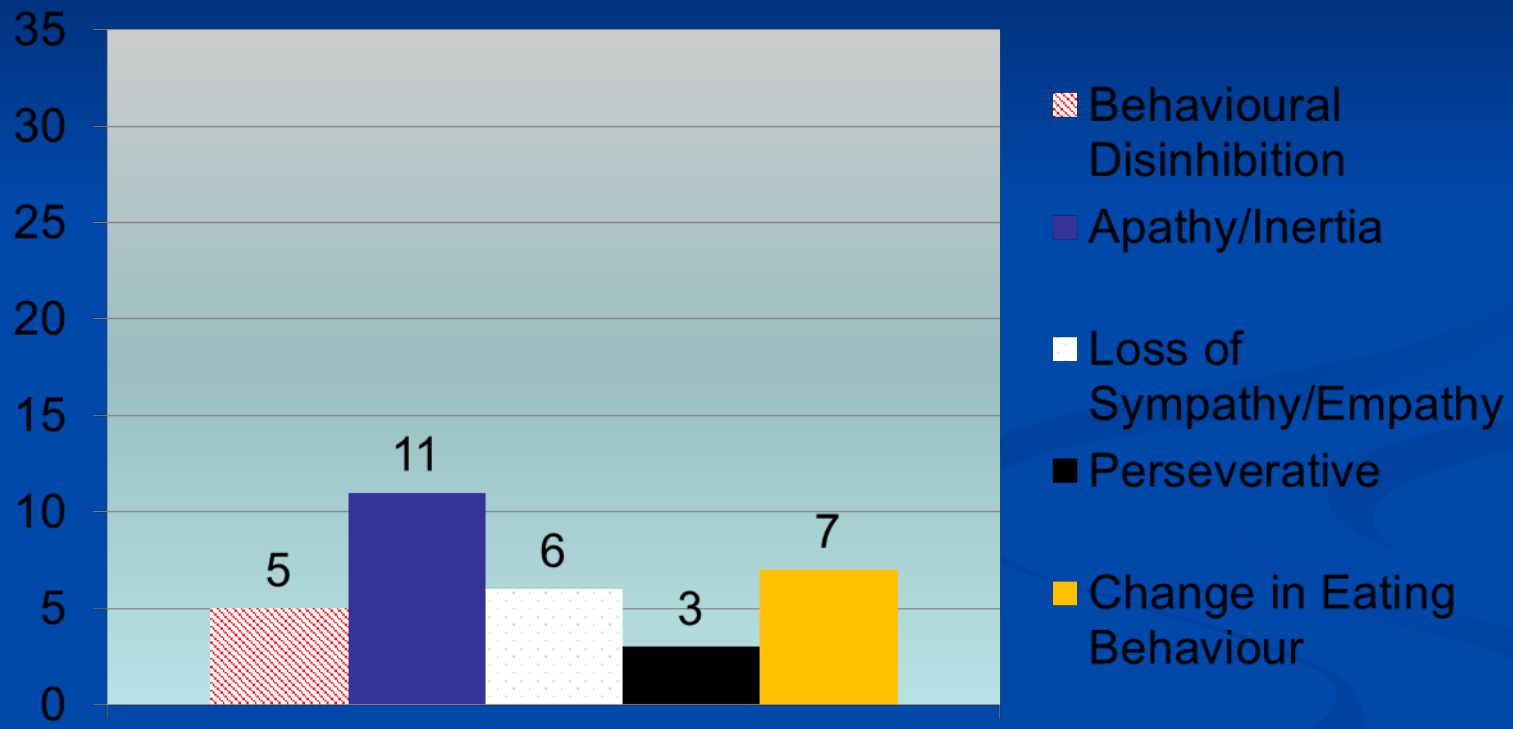
Validation: 24 ALS & 24 Healthy Controls

Executive deficit: z>2 in 2/5 subdomains

Language deficit: z>2 in 2/3 subdomains

	Executive Deficit	Language Deficit	ALS cognitive impaired	ECAS Specific	ECAS Total	ECAS Impaired
1	X		YES	X		YES
2						
3						
4	X		YES	X	X	YES
5						
6						
7	X		YES	X	X	YES
8						
9						
10						
11						
12	X		YES	X		YES
13						
14		X	YES	X	X	YES
15						
16		X	YES	X		YES
17	X		YES			
18						
19	X	X	YES		X	YES
20		X	YES	X	X	YES
21						
22						
23						
24		X	YES	X	X	YES

ECAS behaviour screen based on diagnosis of bvFTD



35 carer interviews, 51% of patients with behaviour change (1 or more domain)

Comment from Prof Al-Chalabi after first using the ECAS

"I have to say it was really good being able to do the cognitive tests myself in clinic. Being able to quantify the cognitive problems in the patient directly was incredibly useful and empowering for the clinical review.

She really did not seem cognitively impaired during the consultation and I can easily see why FTD was missed as a feature of ALS for so long. Seeing her responses was very surprising.

Of course the same information was available before, but only after a delay for neuropsychometry to be performed, and even then it was a list of statements from someone else - not the same as doing it yourself"

ECAS Translations

German/ Swiss German

Italian

Spanish

Portuguese

Dutch

French

Polish

Norwegian

Greek

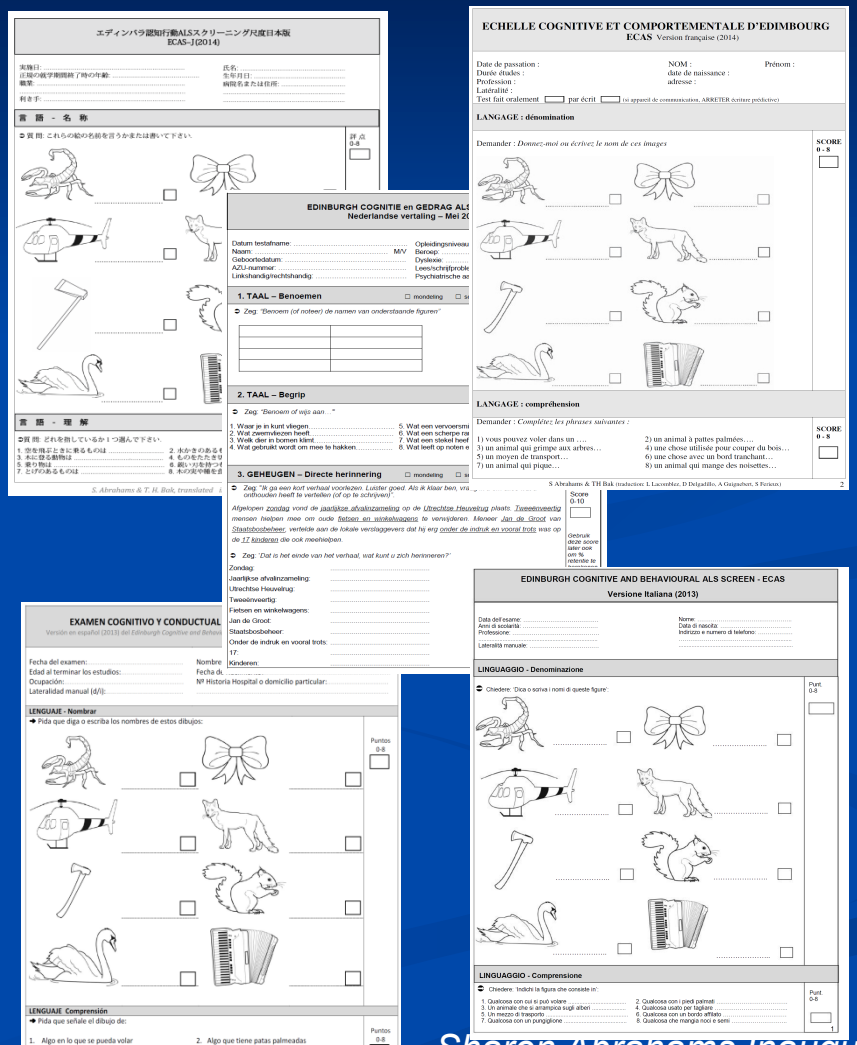
Slovak

Hebrew

Japanese

Chinese

North American English



Key messages

- Cognitive symptoms in ALS are common, *but not universal:*
  - Ca. 15% dementia, 35% subtle cognitive changes, 50% normal
- Many (*but not all*) cognitive domains are affected:
  - Change of personality, inappropriate behaviour, apathy, social cognition
  - Frontal-executive symptoms, e.g. verbal fluency deficits
  - Language dysfunction: mutism, spelling errors, comprehension deficits
  - *Visuospatial functions and memory tend to be relatively preserved*
- Cognitive changes in ALS and FTD are similar, *but are not identical*
- Traditional cognitive tests assume normal motor function; ECAS has been developed specifically to assess patients with motor deficits