Prof Tim Anderson

Neurologist

University of Otago

Christchurch

Insidious Cognitive Loss - Main Session

Friday, 16 August 2013 Start 8:30am Duration: 25mins Plenary

Tim Anderson Christchurch

Insidious cognitive loss

"From subjective memory complaints (SMC) to dementia"

Case 1. AR. 64 yrs Male

GP referral

"Thank you for seeing A who use to be my neighbor. He was pushed by family to see me for failing memory.

Case 1. AR. 64 yrs Male

GP referral

"Thank you for seeing A who use to be my neighbor. He was pushed by family to see me for failing memory. This however appears to be a nominal dysphasia only and no memory impairment but he is very slow in conversation due to difficulty finding words. His MSQ was fine but needed some prompting with names that were on the tip of his tongue…….Other than his trouble finding words he is just as when we were next door 7-8 years ago. He is an amazing mathematician and musician and it seems these areas are intact but he cannot name a piece of music however he can play it."

Patient 1. AR

- 64 yrs ♂ computer software programmer
- 18 months progressive history

- "problems with naming people and objects"
  - ***initially*** "could remember the name of something that he wanted to say but just couldn't say it"
  - ***now*** *"cant even remember the names of things as well"*

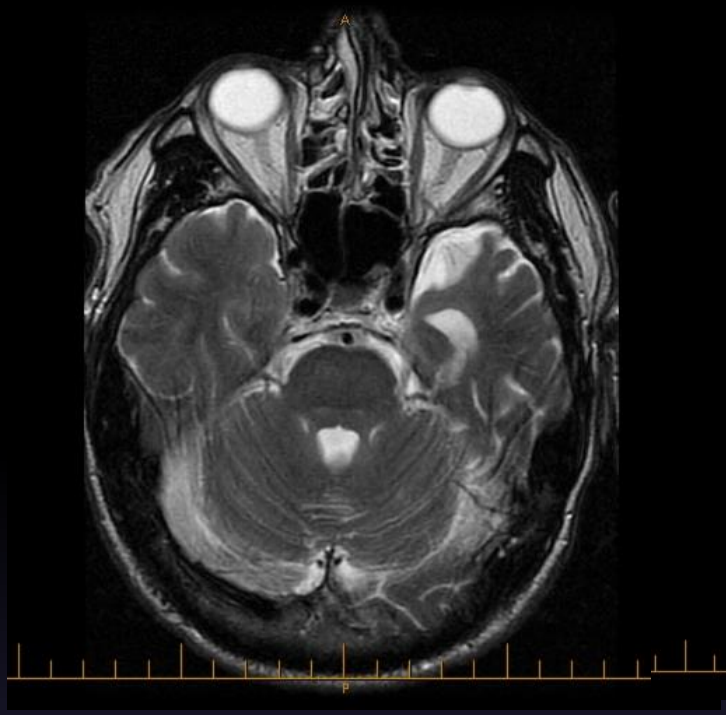
- *No change in personality, motivation, temperament, calculation, dressing or visuospatial function*

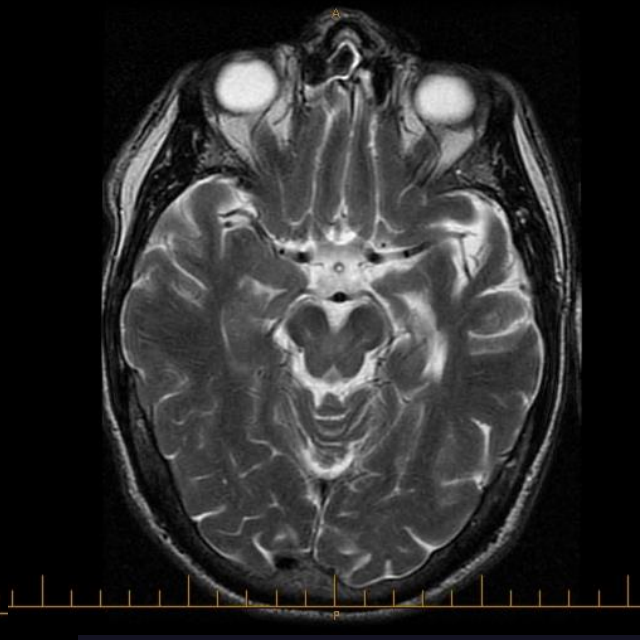
- *No difficulty understanding speech of others*

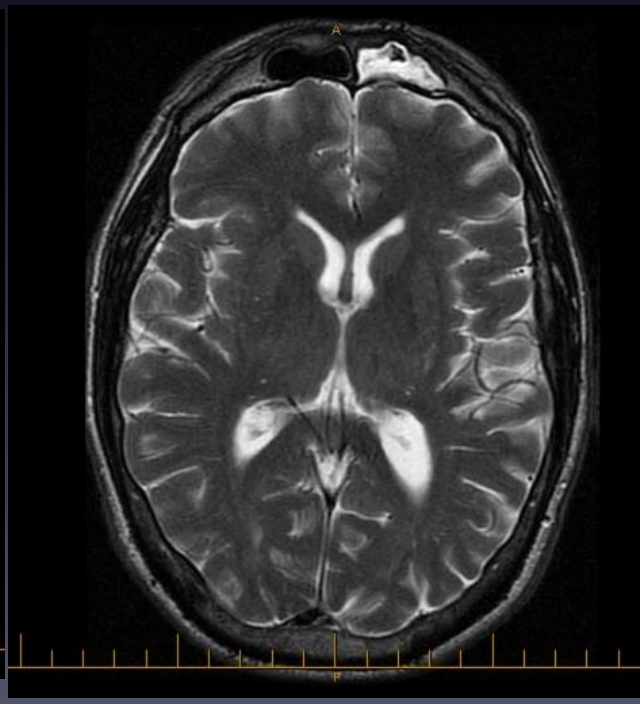
Patient 1. AR

- Examination
  - memory/attention
    - digit span normal
    - normal registration, ↓retrieval (1/4 but 3 from list)
  - language
    - mild ↓ spelling (couldn't spell "neighbour" or "aunt")
    - normal repetition
    - marked anomia (couldn't name any animals)
    - some hesitancy of speech and word finding difficulty
  - other domains normal

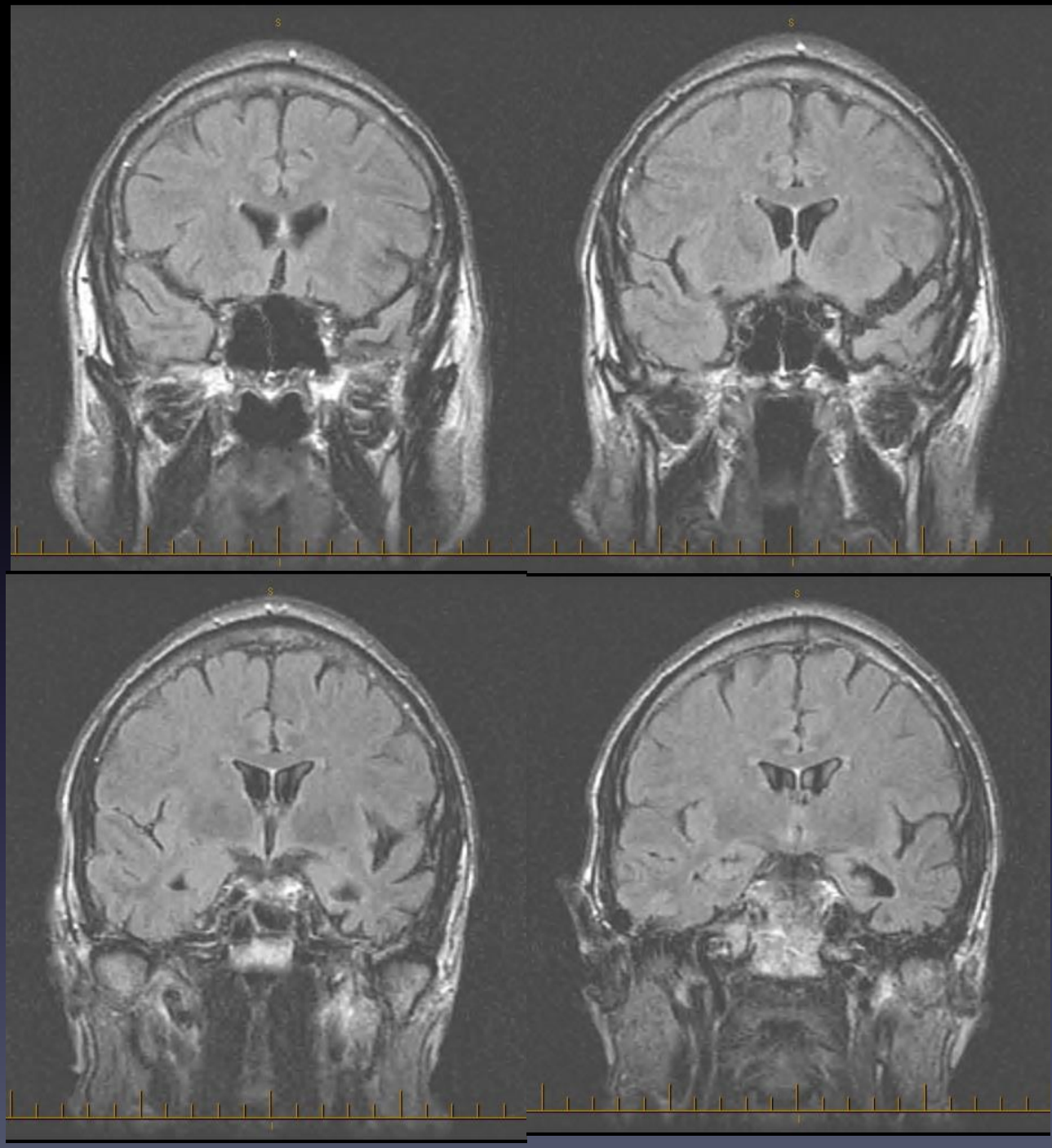
Patient 1. AR



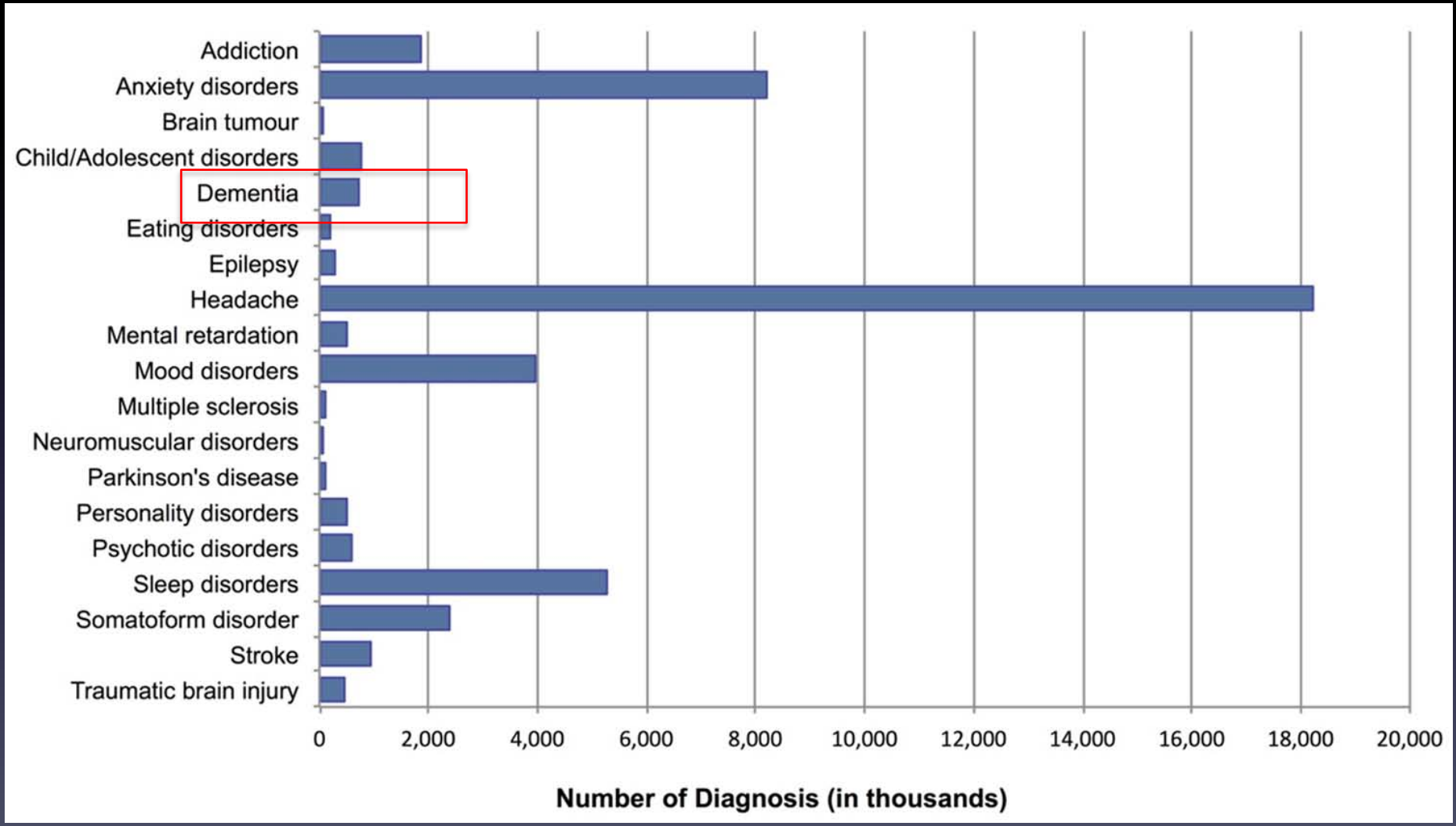




Patient 1. AR

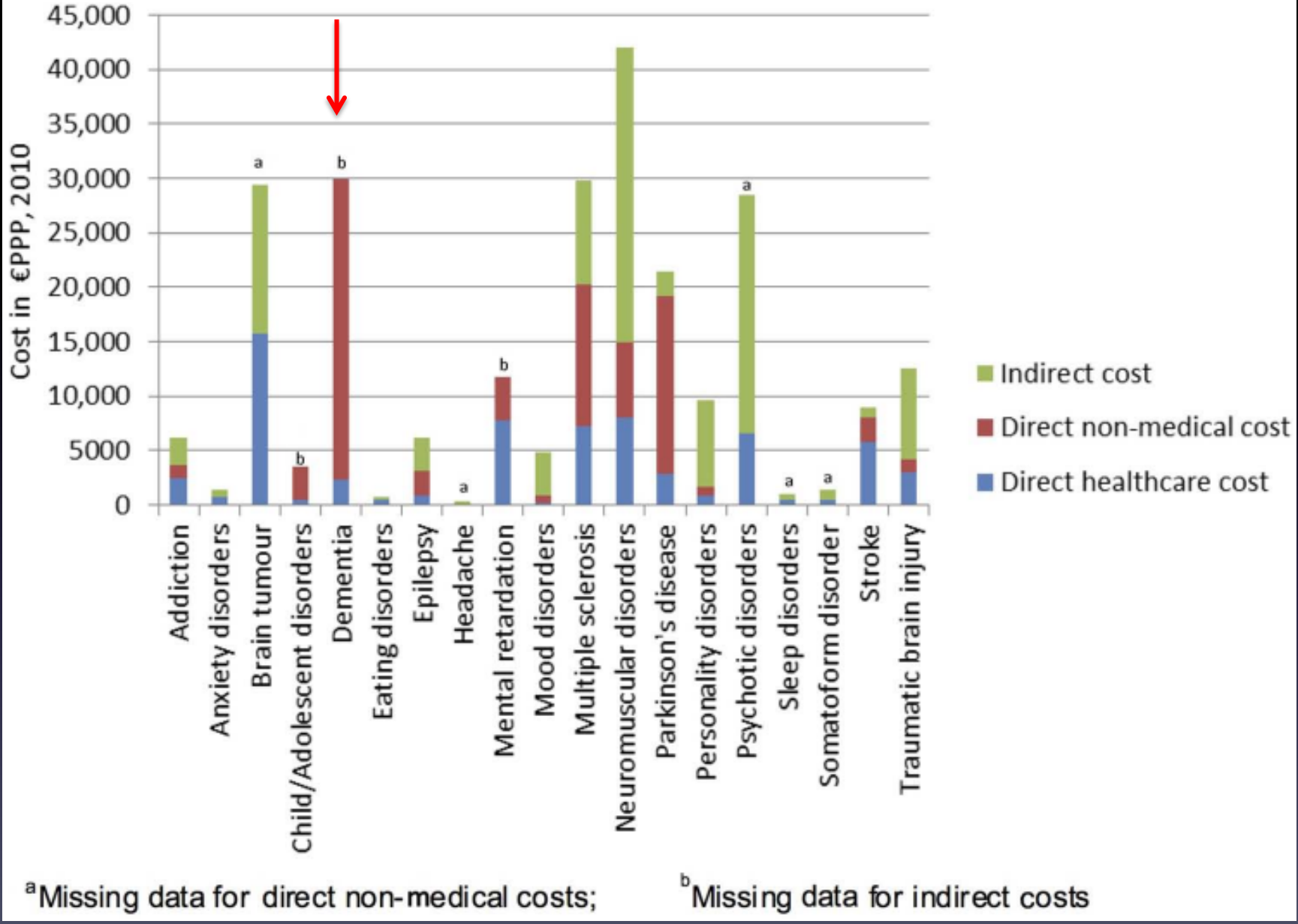


Estimated 12-month UK prevalence of disorders of the brain



Fineberg , *J Psychopharmacol* published online 24 July 2013

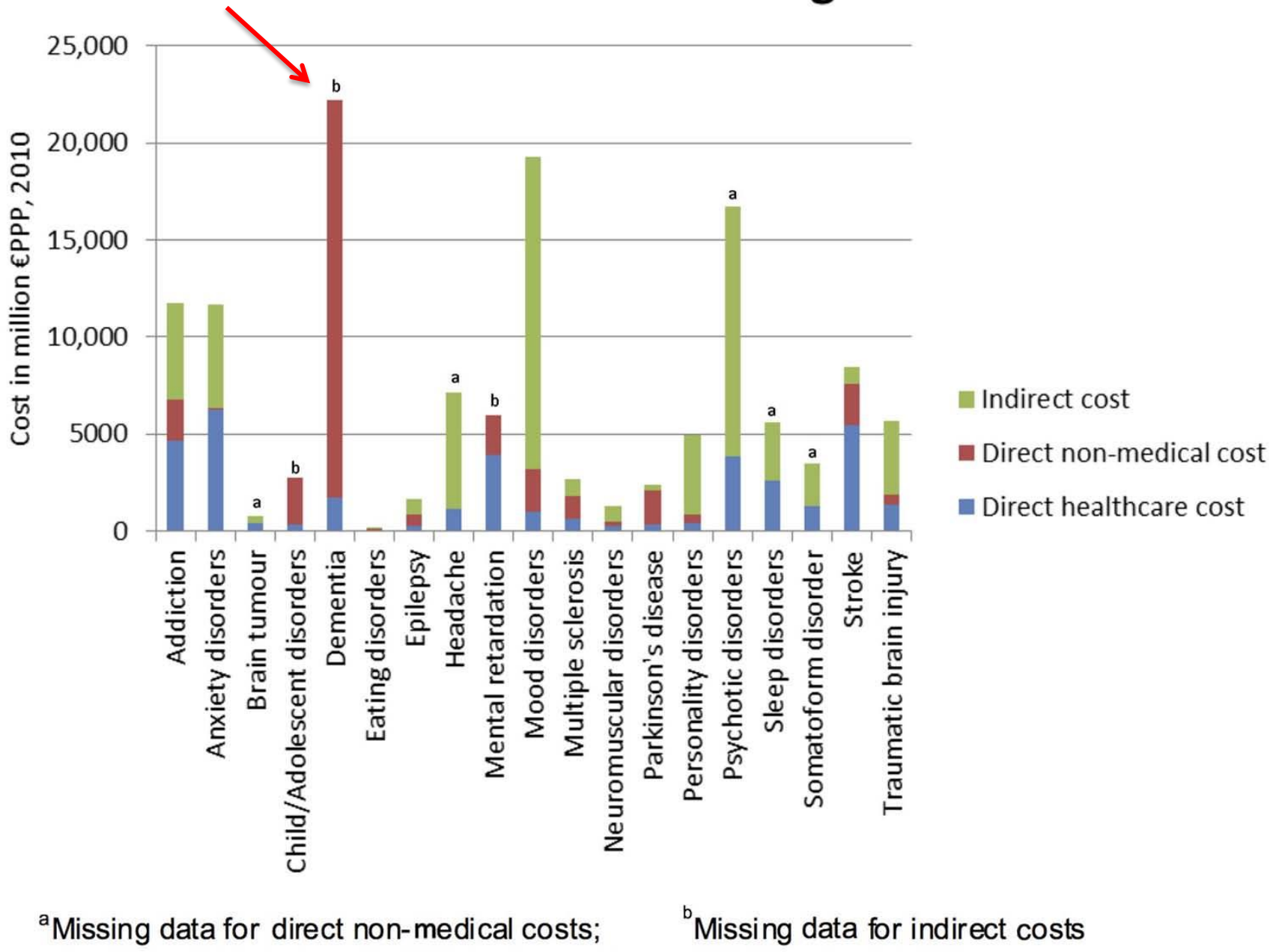
Cost per subject - United Kingdom



[a]Missing data for direct non-medical costs; [b]Missing data for indirect costs

Fineberg , *J Psychopharmacol* published online 24 July 2013

Total Cost - United Kingdom



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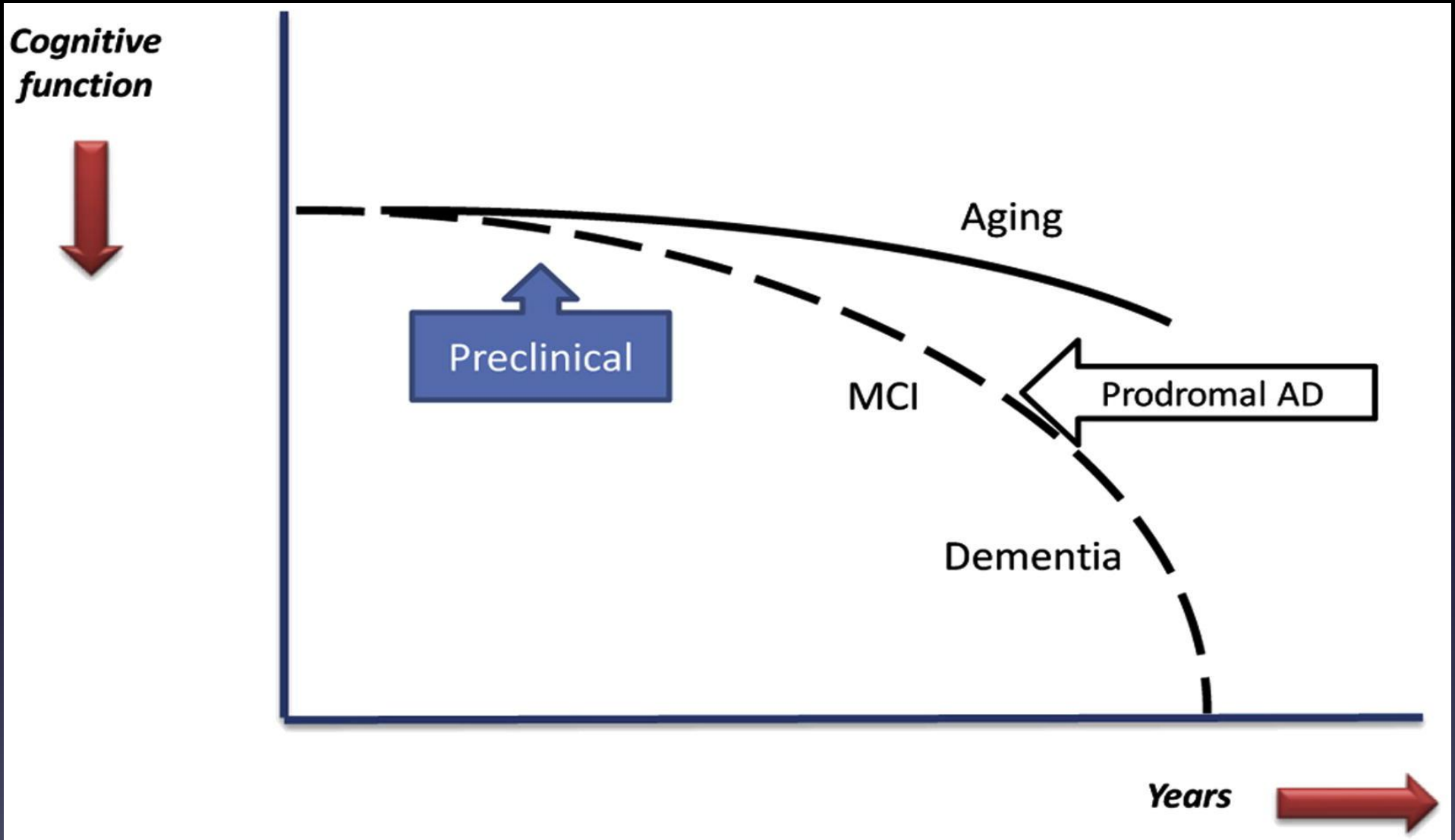

Cognitive function
Aging
Preclinical
MCI
Prodromal AD
Dementia
Years

Prevalence of Dementia

M. Prince et al. / Alzheimer's & Dementia 9 (2013) 63–75

Age range	60-64	65-69	70-74	75-79	80-84	85-89	90+
%	2	3	4.5	7.5	13	20	38

5-7% >60 yrs

(10-15% MCI)

Criteria for dementia: Core clinical criteria

Cognitive or behavioural (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment

G.M. McKhann et al. Alzheimer's & Dementia 7 (2011) 263–269

5. The cognitive or behavioural impairment involves a minimum of two of the following domains:

1. Memory

   (repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route)

2. Impaired reasoning and handling of complex tasks

   (poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities)

3. Visuospatial

   (recognise faces or common objects, find objects)

4. Impaired language functions

5. Changes in personality, behaviour, or comportment

   (agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, de- creased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors)

G.M. McKhann et al. Alzheimer's & Dementia 7 (2011) 263–269

Probable AD dementia: Core clinical criteria

A. Insidious onset

B. Clear-cut history of worsening of cognition; and

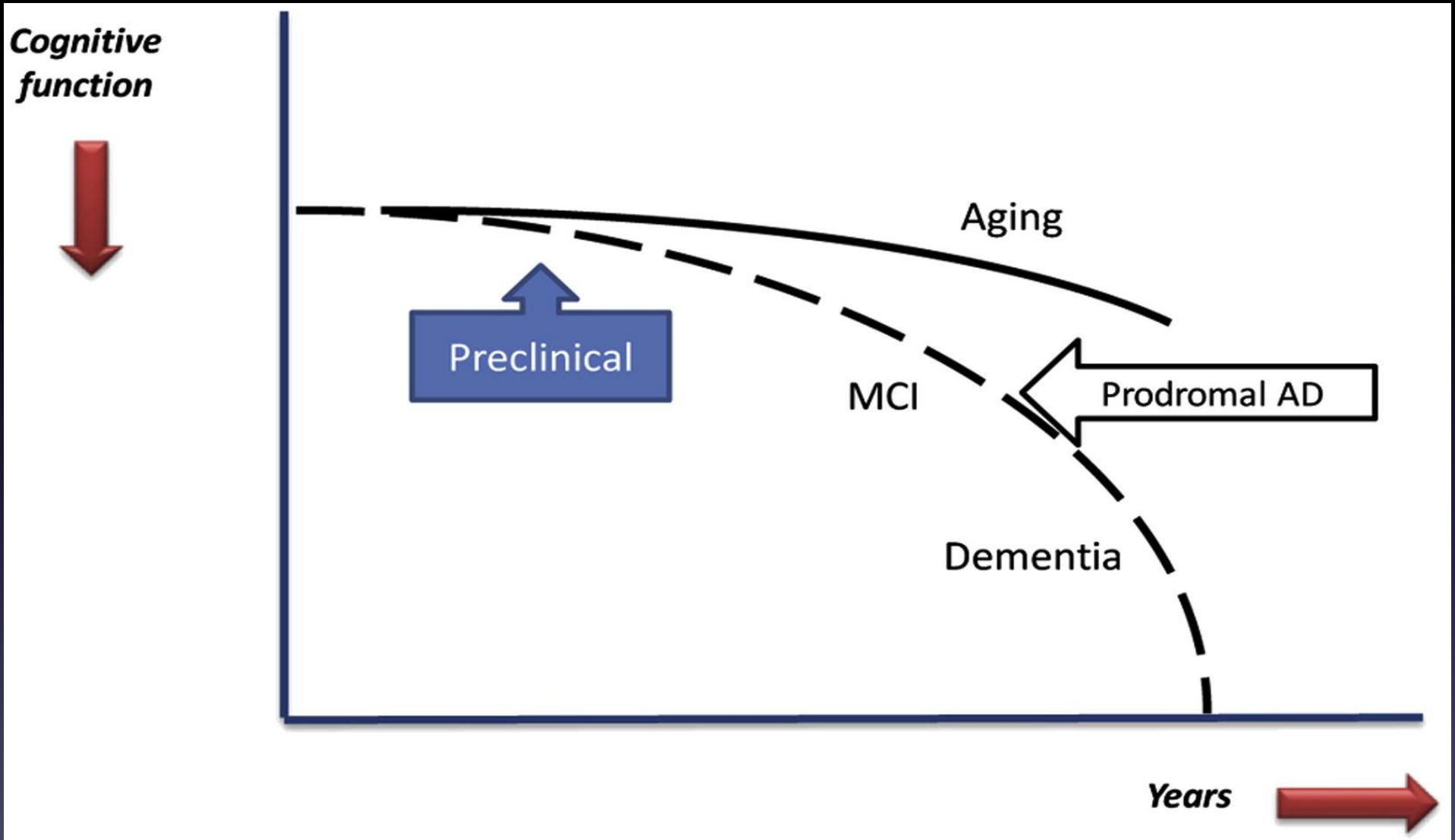
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
   - **Amnestic presentation** (the most common). Plus one other domain deficit.
   - **Nonamnestic presentations** (plus one other domain deficit):
     - Language presentation: The most prominent deficits are in word-finding.
     - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia.
     - Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving

G.M. McKhann et al. Alzheimer's & Dementia 7 (2011) 263–269

Probable AD dementia: Core clinical criteria

No evidence of:

- Significant cerebrovascular disease
- Dementia with Lewy Bodies (DLB)
- Frontotemporal Dementia (FTD)


Cognitive function
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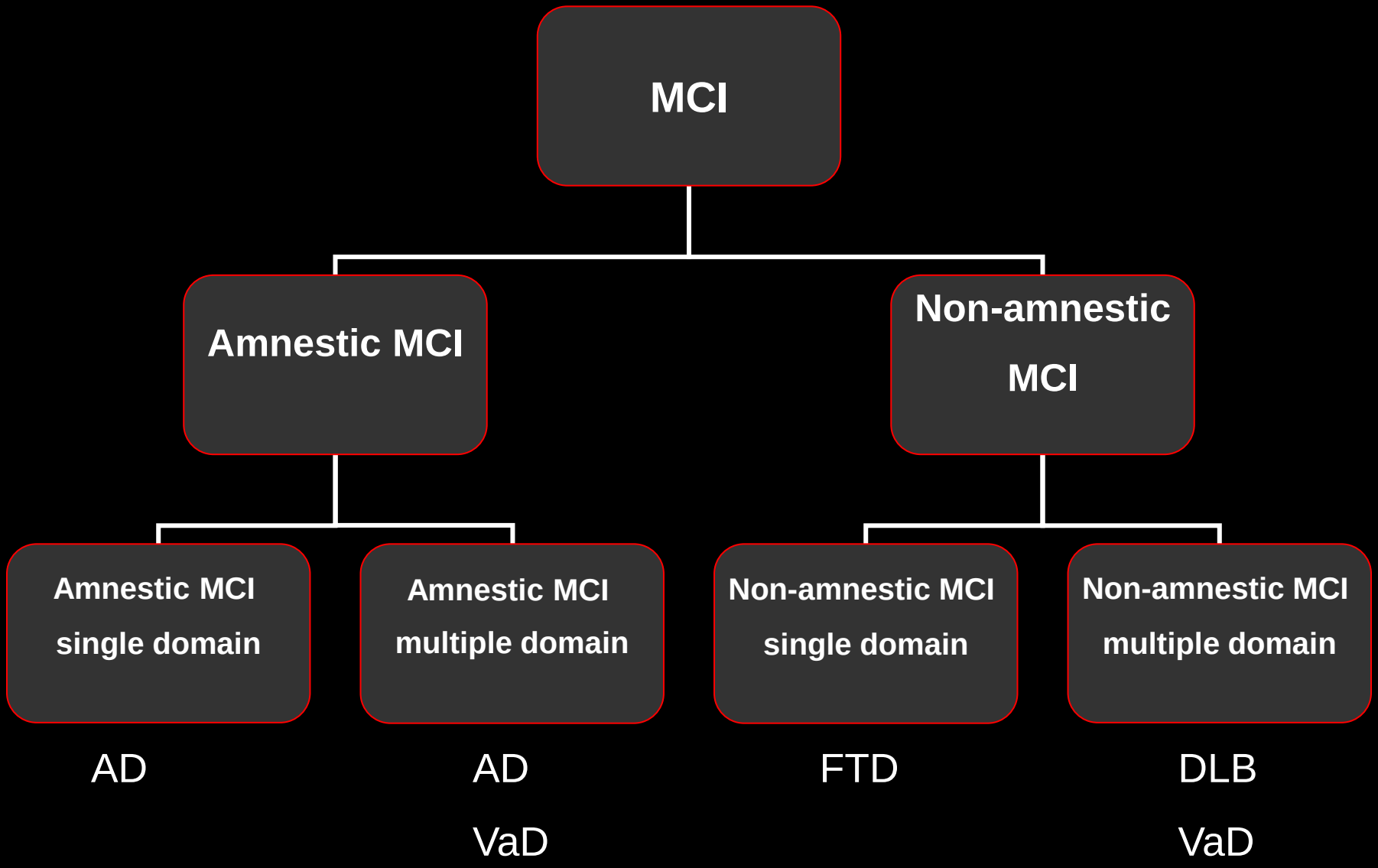
Dementia
Years

MCI due to AD

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician
- Objective evidence of Impairment in **one or more** cognitive domains, typically including memory
  - Scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean
- Preservation of independence in functional abilities
- Not demented

M.S. Albert et al. / Alzheimer's & Dementia 7 (2011) 270–279

MCI and the Dementias: Heterogeneity



Detection of cognitive loss: the GP

Mild cognitive impairment (MCI)

- Low annual rates of conversion from MCI to dementia
  - 10 -15% in people aged 85
  - as low as 0.7% in 65- to 69-year-olds
- MCI may not progress to dementia
  - 50%
- MCI may revert to normal (7 - 60%)

ELSEVIER

Archives of Medical Research 43 (2012) 609e614

Archives of Medical Research

REVIEW ARTICLE

Mild Cognitive Impairment—The Continuing Challenge of its ''Real-world'' Detection and Diagnosis

Robert Stewart

King's College London (Institute of Psychiatry), London, UK

"If an intervention were proven to be effective for preventing transition from MCI to dementia in the near future, there would be a serious lack of knowledge about how MCI can be identified in routine clinical practice."

Detection of cognitive loss: the GP

Subjective memory complaints (SMC)

- SMC common in older community samples
  - 50% for any reported memory complaint
  - 10-20% for a memory deficit that is noticed frequently, or causing concern.
- SMC low positive prediction for eventual dementia (but association).

Detection of cognitive loss: the GP

Subjective memory complaints (SMC)

- Few older people with SMC seek help
  - 20–25%
- Survey of 388 older general practice attenders
  - 40% admitted to SMC when asked
  - (18% classified as MCI)
  - none spontaneously self-reported the symptom
- GP sample of 126 older people
  - SMC in 65% by questioning
  - only one person had mentioned to GP

SCREENING AND DETECTION OF COGNITIVE LOSS

Screening: the AD8

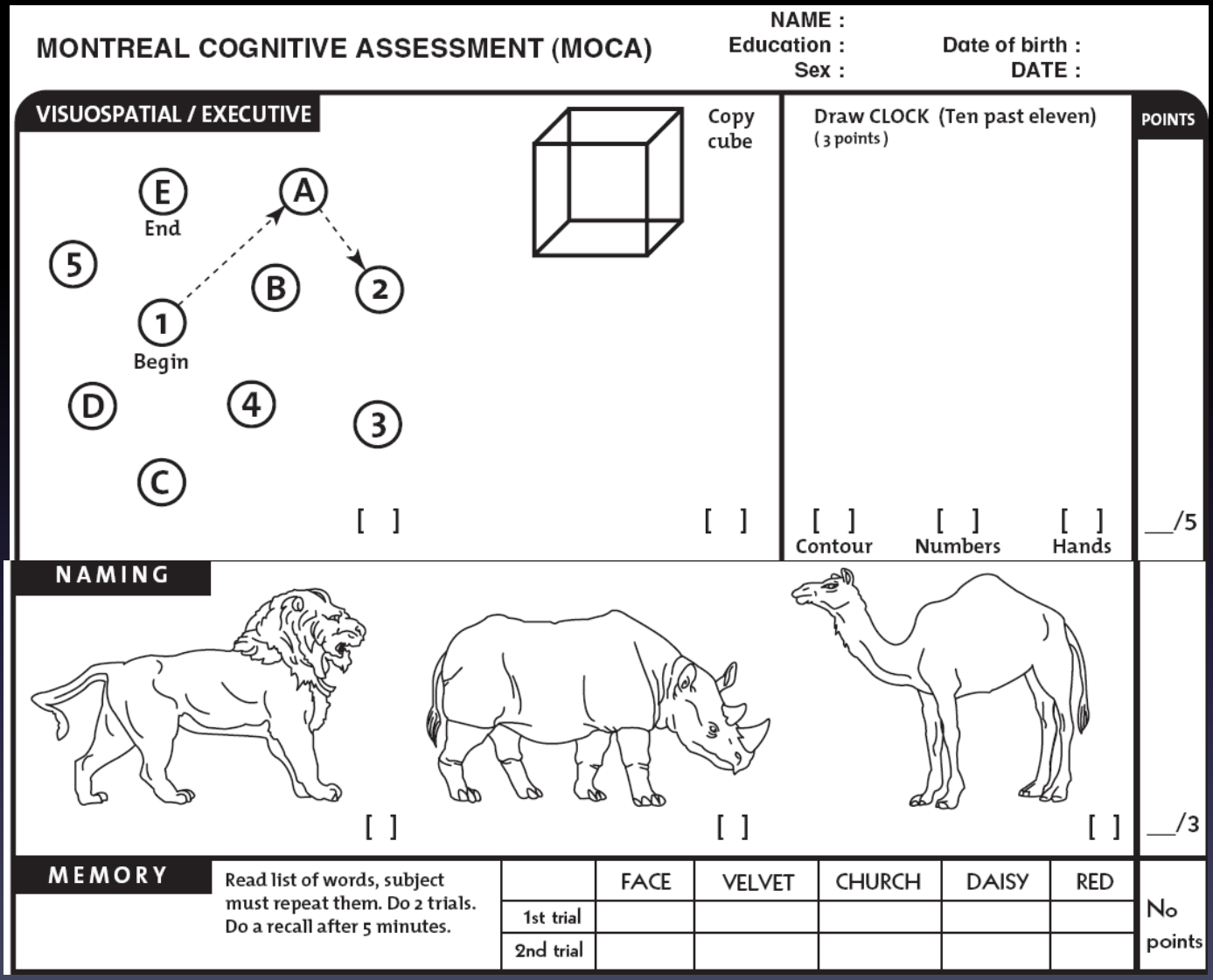
sensitivity 74%, and specificity 86% for mild dementia

Remember, "Yes, a change" indicates that you think there has been a change in the last several years cause by cognitive (thinking and memory) problems	**YES**, A change	**NO**, No change	**N/A**, Don't know
Problems with judgment (e.g. falls for scams, bad financial decisions, buys gifts inappropriate for recipients)			
Reduced interest in hobbies/activities			
Repeats questions, stories or statements			
Trouble learning how to use a tool, appliance or gadget (e.g. VCR, computer, microwave, remote control)			
Forgets correct month or year			
Difficulty handling complicated financial affairs (e.g. balancing checkbook, income taxes, paying bills)			
Difficulty remembering appointments			
Consistent problems with thinking and/or memory			
TOTAL AD8 SCORE			

Score >2/8 is abnormal

Galvin et al., *Neurology, 65 4 559-564 2005*

Detection/Measurement: the MoCA



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

POINTS

E End
A
5
B
2
1 Begin
D
4
3
C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

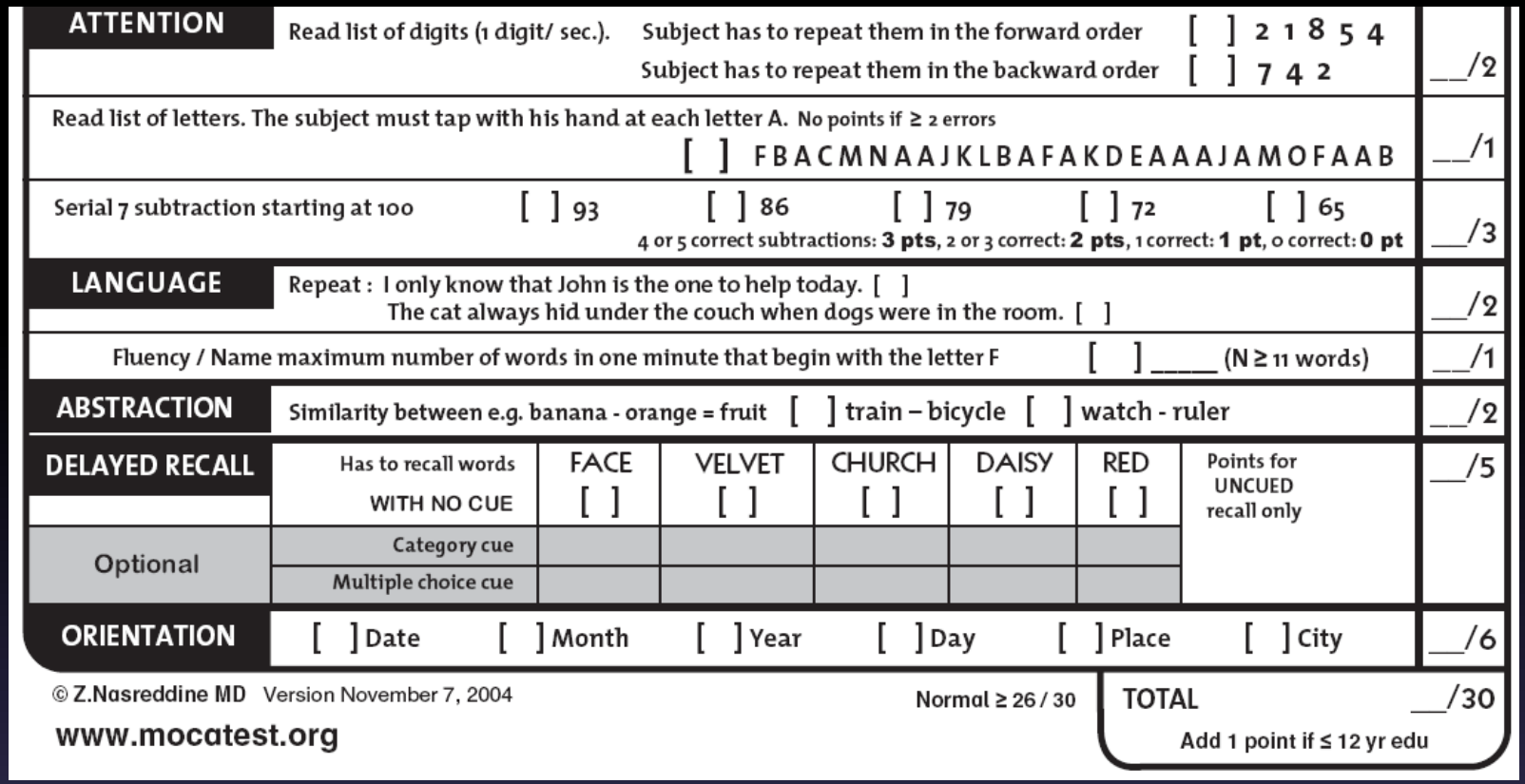
MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

The Montreal Cognitive Assessment Nasreddine et al., 2005)



ATTENTION	Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4 Subject has to repeat them in the backward order [ ] 7 4 2	__/2
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B	__/1
	Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**	__/3
LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]	__/2
	Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)	__/1
ABSTRACTION	Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler	__/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	__/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City	__/6

© Z.Nasreddine MD Version November 7, 2004
www.mocatest.org

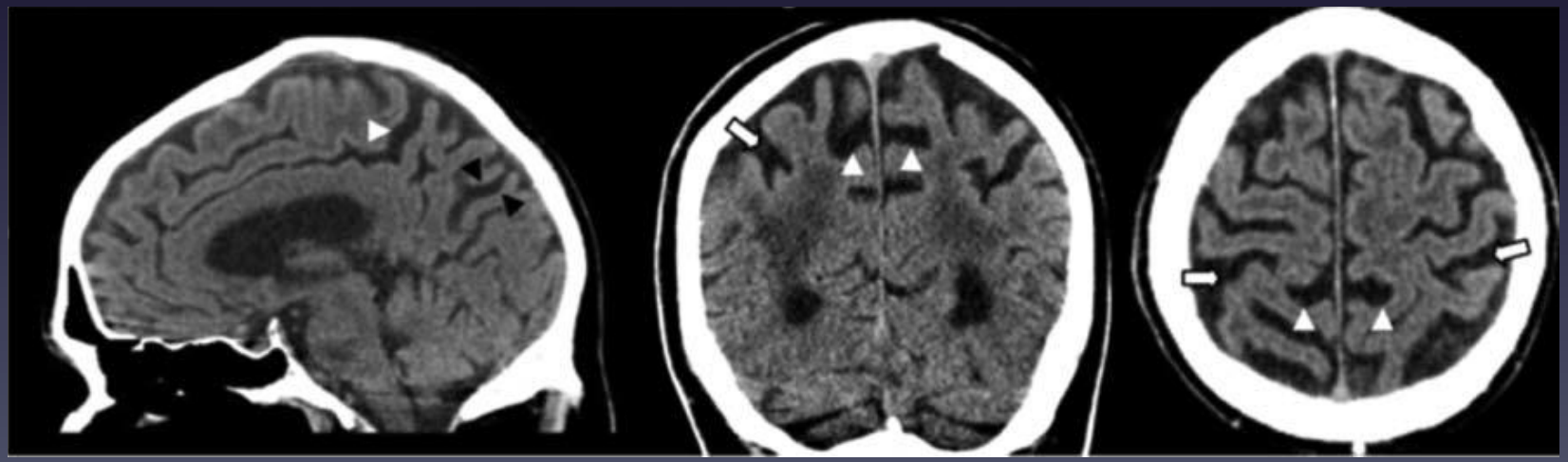
Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

MCI (and AD) : Cut-off score <26

http://www.mocatest.org

AD: medial temporal and parietal atrophy



Treatment of MCI and AD

- AD
  - evidence for modest efficacy with cholinesterase inhibitors and memantine
- MCI
  - no evidence for efficacy

Adverse Effects of AChEs

- GI upset and salivation
- If PR <50 bpm or arrhythmia get ECG

Patient 1. AR

- Review 6 months later
  - Wife: more “dogmatic” and “compulsive” in relation to “small things”
- 18 months later
  - spelling problems
  - ↓recognition of objects/persons
  - normal piano/violin and reading music
  - normal memory
- 6 yrs later
  - food foraging/hoarding
  - mute, little understanding of speech
  - just resigned from orchestra

OTHER CAUSES OF COGNITIVE LOSS AND DEMENTIA

FTD – Frontotemporal Dementia
(FTLD – frontotemporal lobar degeneration)

3 Major Clinical Syndromes

I.	Frontal/Behavioral Variant (Dementia of Frontal Type)	40%
I.	Semantic Dementia (SD)	40%
II.	Progressive Nonfluent Aphasia (PNFA)	10%

± CBD, PSP and MND

FTD - epidemiology

- FTD = 5-20% of dementias
- In 45-64 yrs epoch, FTD = AD prevalence
- most 55-65yrs at onset
- 5-10% familial (i.e. > one 1st degree relative)
- M = F
- A minority testable gene mutations

FTD

I. Frontal/Behavioral Variant (bvFTD)

Changes in social behaviour and personality

- **orbitofrontal:** disinhibition, poor impulse control, ritualised behaviour (e.g. insistent on eating food at same time of day), often a "sweet-tooth", ↓insight
- **fronto-medial**: apathy
- **dorsolateral prefrontal:** dysexecutive syndrome e.g. impaired planning

Neuropysch

- risk taking/decision making tasks (inferences)
- ↓remote memory
- normal visuospatial function

Neuroimaging

- normal early
- frontal and anterior temporal atrophy late

FTD

II. Progressive Nonfluent Aphasia (PNFA)

speech dysfluency and word finding problems

comprehension preserved initially

later global cognitive decline

behavioural changes rare

Neuropysch

- minimal anomia
- poor repetition
- **letter (phonemic) worse than semantic verbal fluency**
- normal visuospatial function

Neuroimaging

- may be normal early
- widening of Sylvian fissure
- anterior insula and Broca's area atrophy

up to 50% may have AD pathology at postmortem

FTD

III. Semantic Dementia

- loss of memory for words
  - memory for recent day to day events spared
- deterioration in receptive vocabulary
  - initially for less common words
- spontaneous speech characterised by anomia (grammar OK)
  - specific terms replaced by commoner, more general terms (e.g. "thing" instead of "briefcase")

Semantic Dementia

(deficit in category knowledge or meaning of words)

Examination

- generally fluent
- **semantic (category) verbal fluency worse than phonemic (first letter) verbal fluency**
- poor at naming pictures of objects (anomia)
- worse if asked to put a name to a description (e.g. “what do you call a bird that lives on water and quacks”), or to write rather than speak the object
- **repetition preserved** (e.g. repeat “chrysanthemum” and then describe)

Semantic Dementia

Neuroimaging

1. Early: bilateral asymmetric anterior temporal atrophy
2. Late: posterior temporal and posterior/inferior frontal
3. Left>>Right

Hodges 2006

Dementia with Lewy Bodies (DLB)

- Clinical features[1]
  - Progressive cognitive decline
  - Deficits on tests of:
    - attention
    - frontal-subcortical skills
    - visuospatial ability

- Core features *(require at least two for "probable")*

  (a) Fluctuating cognition with pronounced variations in attention and alertness

  (b) Recurrent visual hallucinations, typically well formed and detailed

  (c) parkinsonism

- Suggestive features

  REM sleep behavior disorder

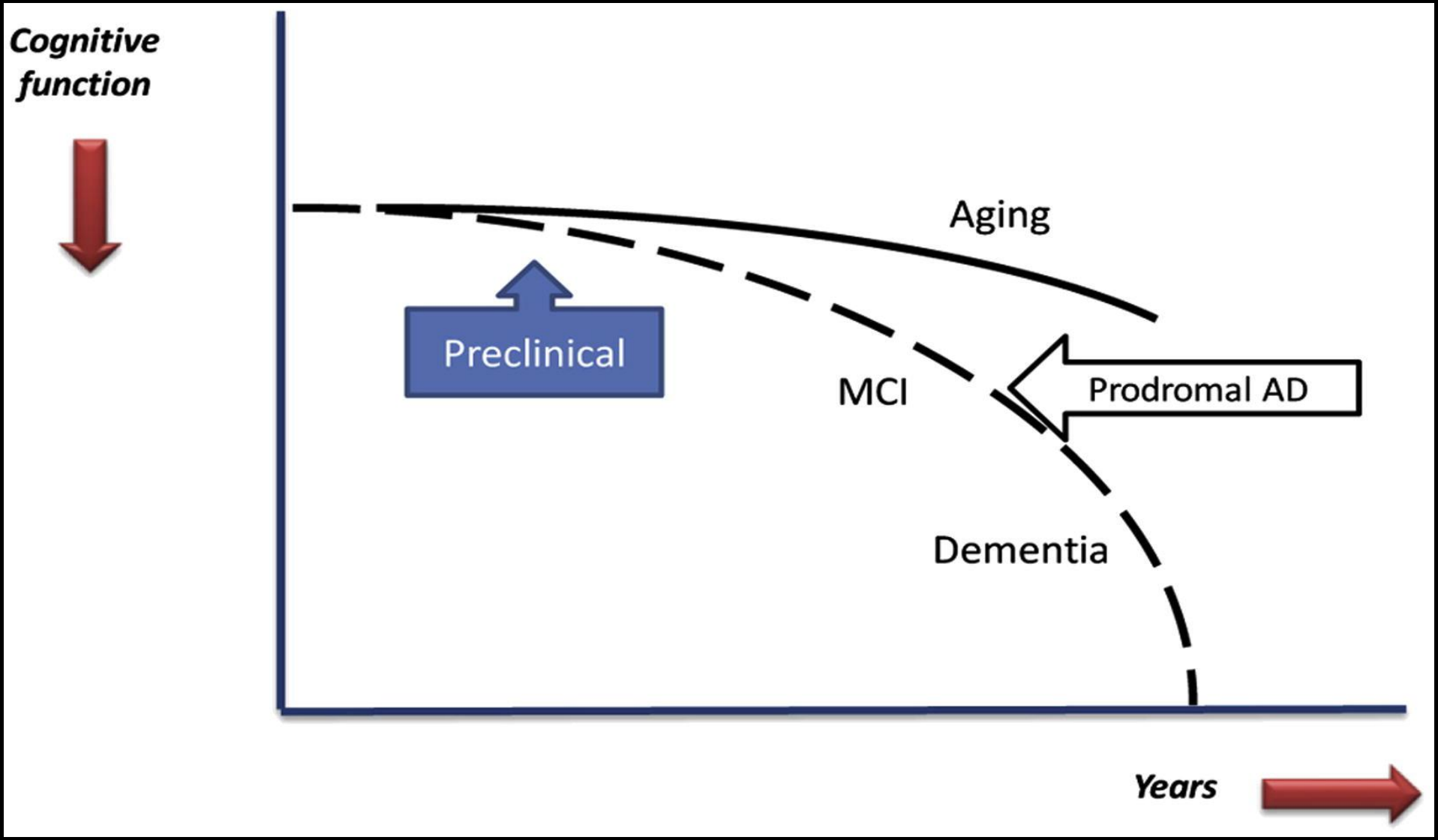
  Severe neuroleptic sensitivity

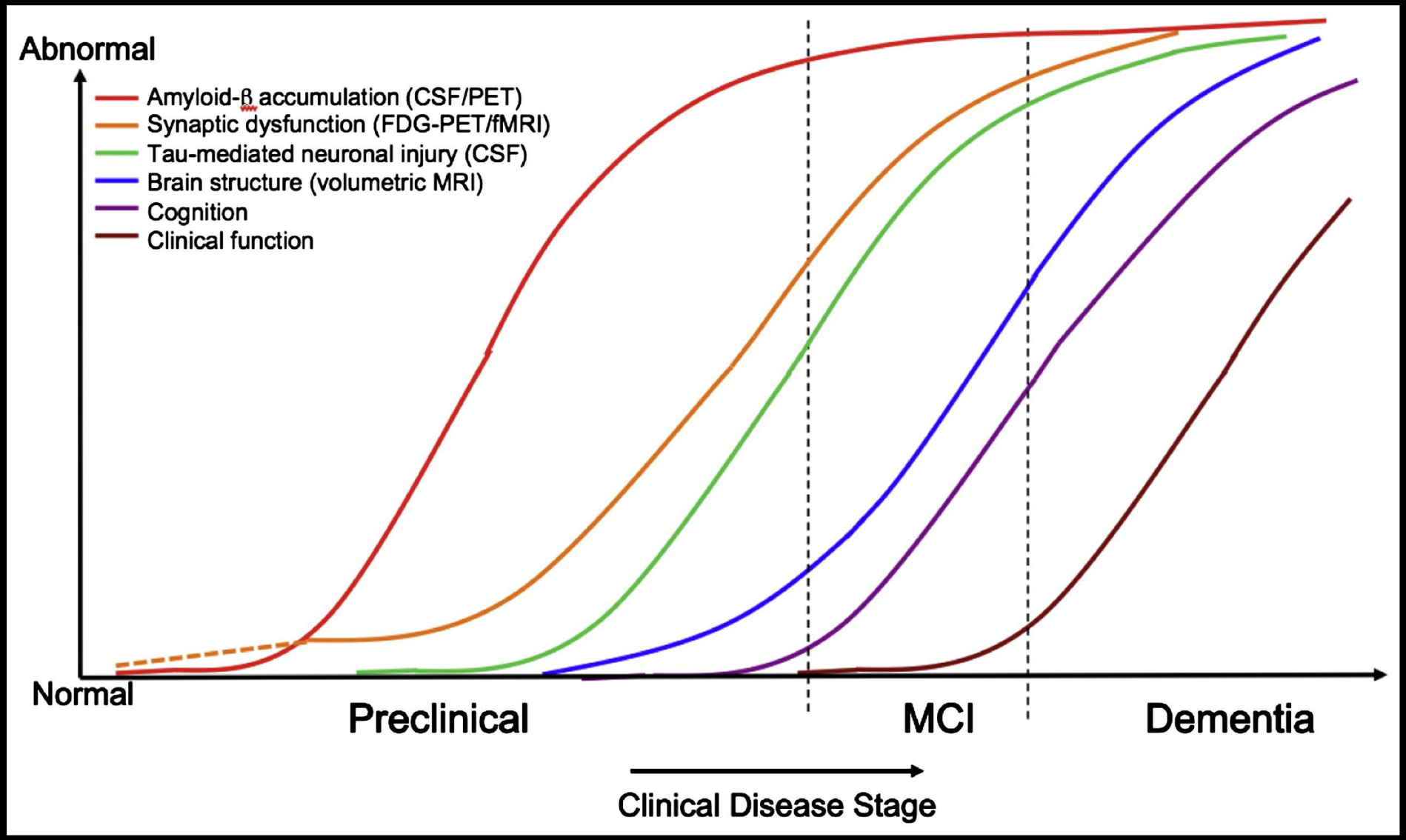
[1] McKeith IGConsensus , et al. guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 2005.

DLB treatment

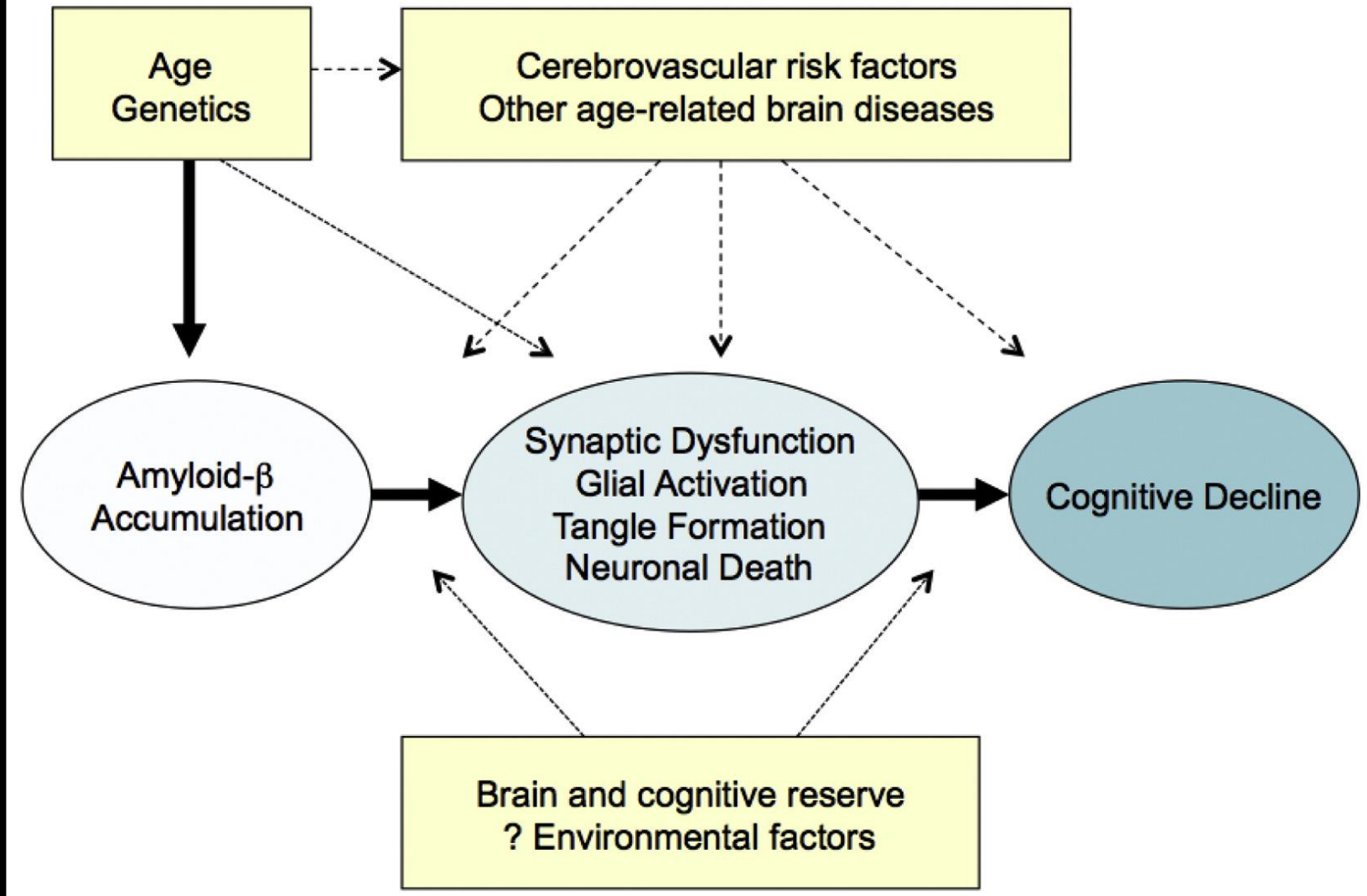
- Cholinesterase inhibitors
  - similar efficacy as in AD
  - but sometimes spectacular
- Levodopa
  - low dose for parkinsonism if necessary

Applause Sign




Abnormal
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function
Normal
Preclinical
MCI
Dementia
Clinical Disease Stage

Hypothetical model of AD pathophysiological cascade



Patient 2. SM

- 58 yrs ♀ school matron
- 5 yrs progressive language disorder
  - especially naming objects, people and places
  - some problems with reading and spelling
  - relative preservation of memory
  - no visuospatial problems
  - ? some personality change

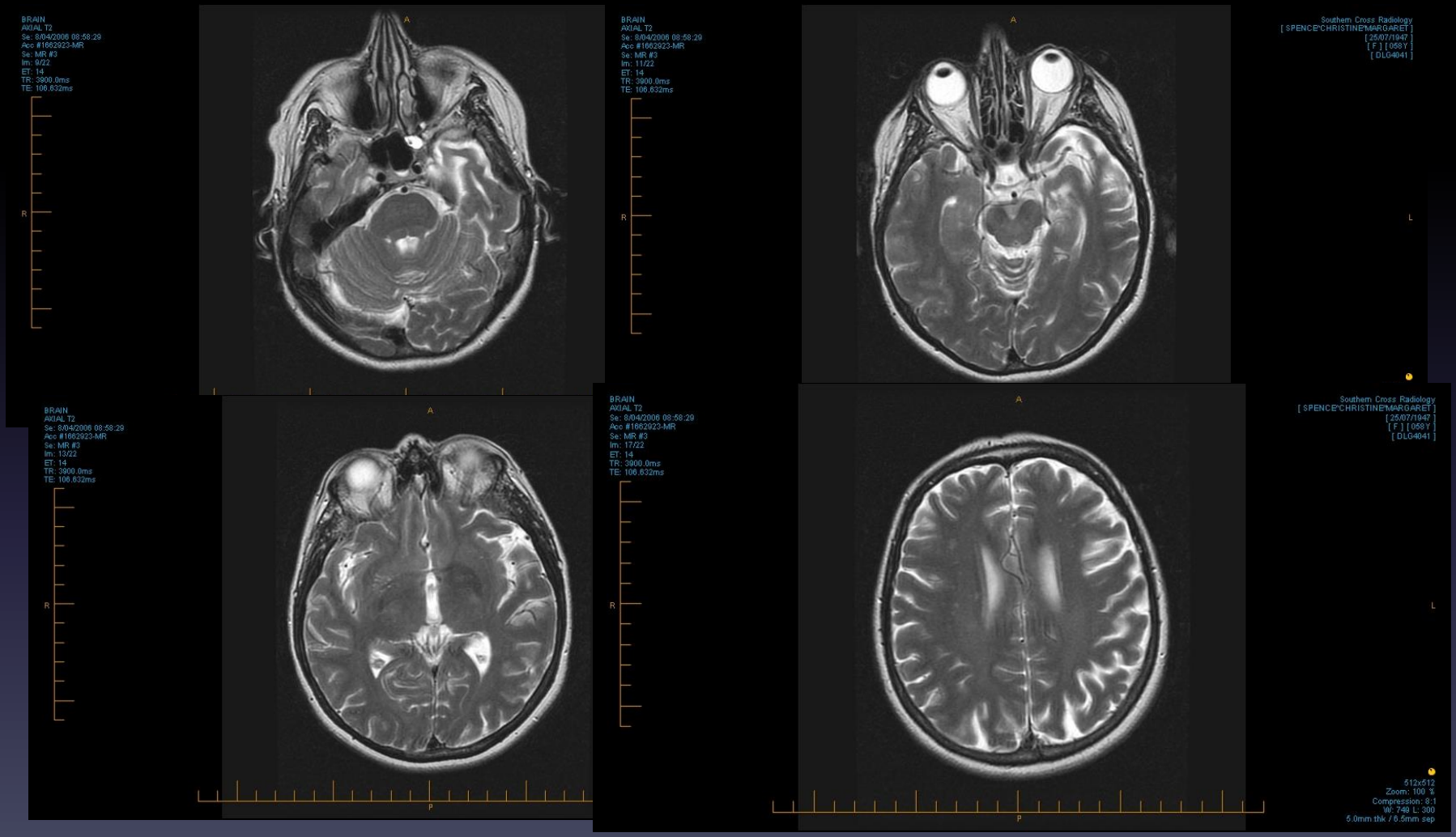
Patient 2. SM

- Examination
  - ?mild disinhibition
  - ↓↓ verbal fluency 3/10 four legged animals on 3MS
  - fluent speech but with word finding difficulties
  - all else, including memory, normal

Patient 2. SM

- 6 months later
  - progressive memory impairment
    - "forgets conversations from one day to next"
    - loses things
  - ↑↑ anomia, peoples names "love"
  - couldn't complete tax return
  - driving OK, no personality change
- Examination
  - fluent "aphasia" worse
  - no other change

Patient 2. SM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TE: 106.832ms
Southern Cross Radiology
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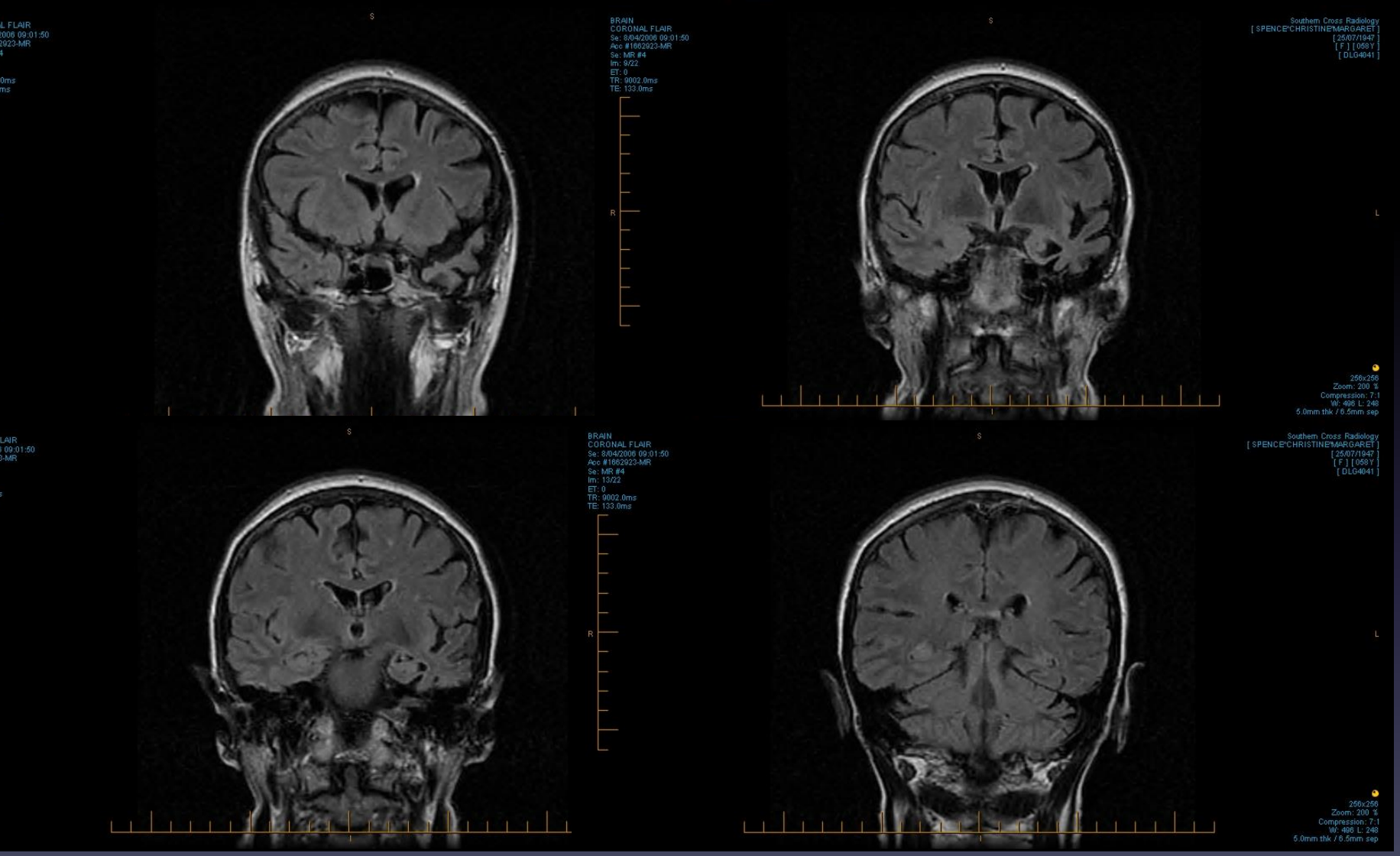
Patient 2. SM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