



SANDERS-BROWN  
CENTER ON AGING

alzheimer's  
association



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# Non-AD dementias: Dementia with Lewy bodies, Frontotemporal and Vascular dementia, diagnosis, treatment, and research advances

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# Disclosure

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- **Dr. Jicha does not have any relevant financial relationships to disclose and will not discuss the off-label use of a product.**
- **No planners have any relevant financial relationships to disclose.**

# Statement of need

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- Many healthcare providers equate dementia with Alzheimer's disease. Few understand or diagnosis the full spectrum of causes for degenerative dementia (i.e. Dementia with Lewy bodies, frontotemporal dementia, vascular dementia).
- Ideally, a specific diagnosis can lead to improved care and future care planning, as well as heighten surveillance for potential emergent comorbidities associated with specific forms of dementia.

# Practice Gap

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- **Pervasive dogma in the field suggests that such differentiation is not important for healthcare decisions.**
- **Furthermore, the focus of care is focused on the lack of cures for these conditions rather than on identifying treatable symptom complexes that differ widely between types of dementia.**

# Objectives

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**Upon completion of this educational activity, you will be able to:**

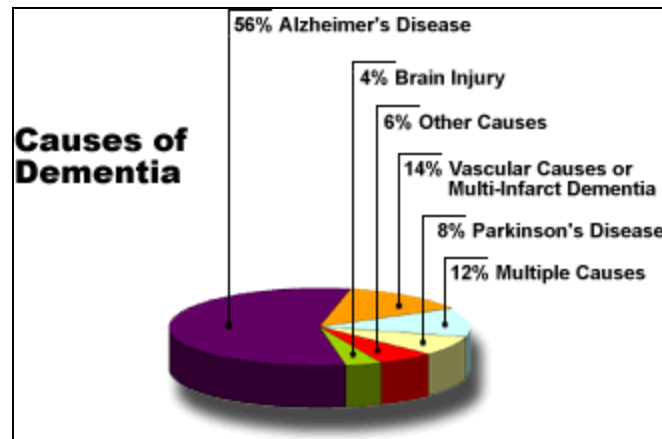
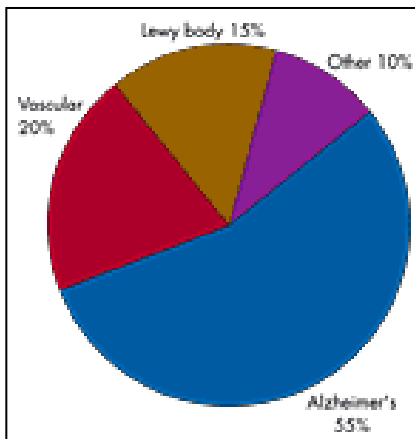
- Describe the differences between treatable symptoms and comorbidities in different forms of dementia**
- Distinguish among the most common types of dementia**

# Expected Outcome

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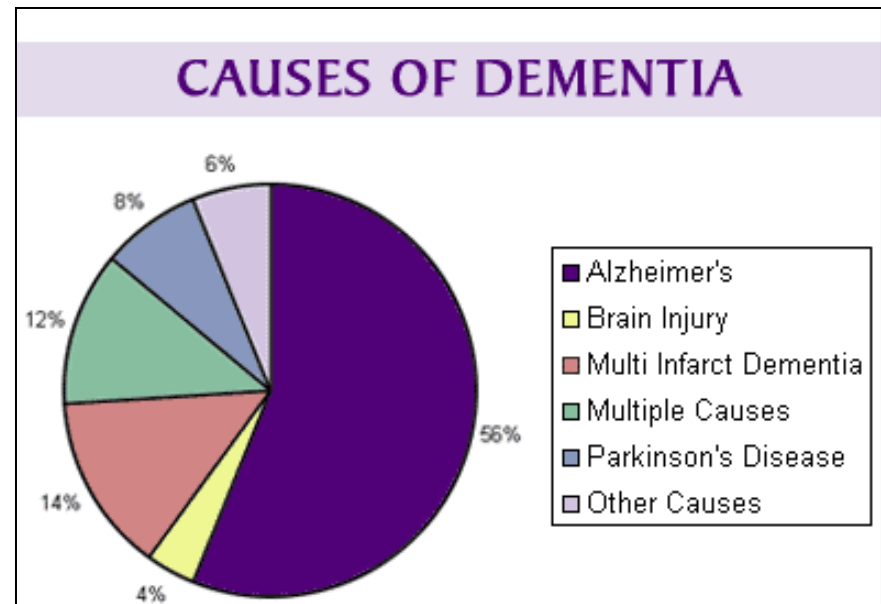
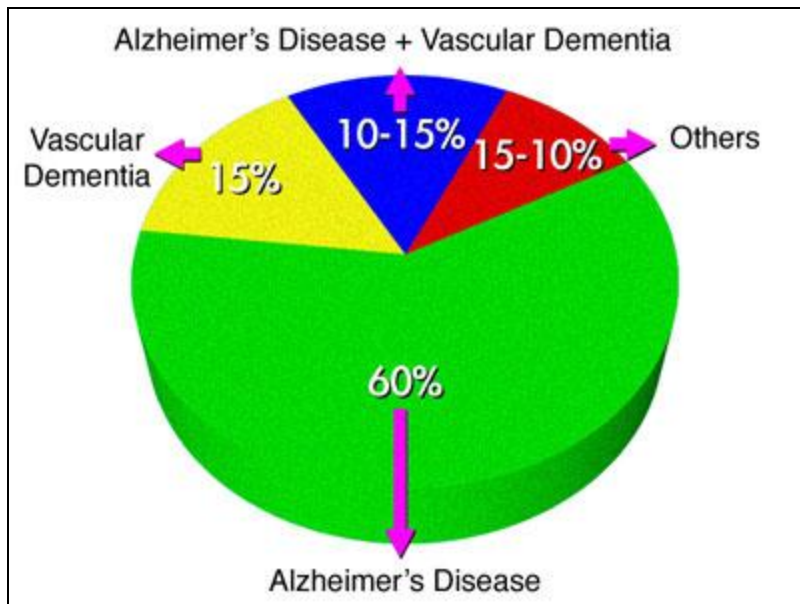
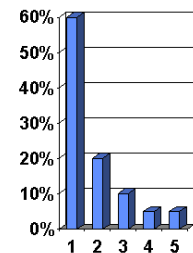
- **Attendees will pass the post-test assessment of knowledge in the differential diagnosis of dementia and therapeutic interventions for symptoms and associated comorbidities in different types of dementia**
- **Improved diagnosis will improve patient care, lessening morbidity for both patient and caregivers**

# It's clear that dementia is a “mixed bag” of disorders



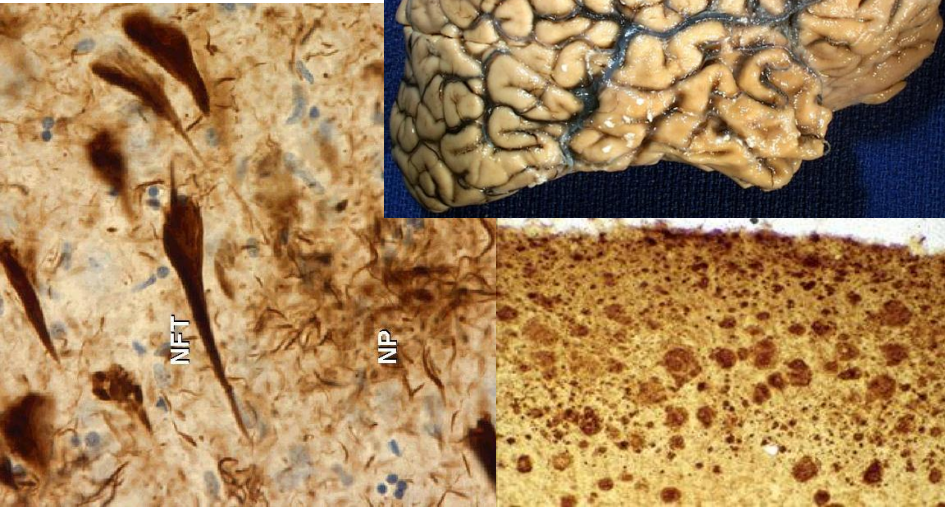
## CAUSES OF DEMENTIA IN THE UNITED STATES

- #1-Dementia of Alzheimer's type.
- #2- Vascular/multi-infarct dementia.
- #3-Lewy Body dementia.
- #4-Mixed dementia (AD/VAS).
- #5-Other.

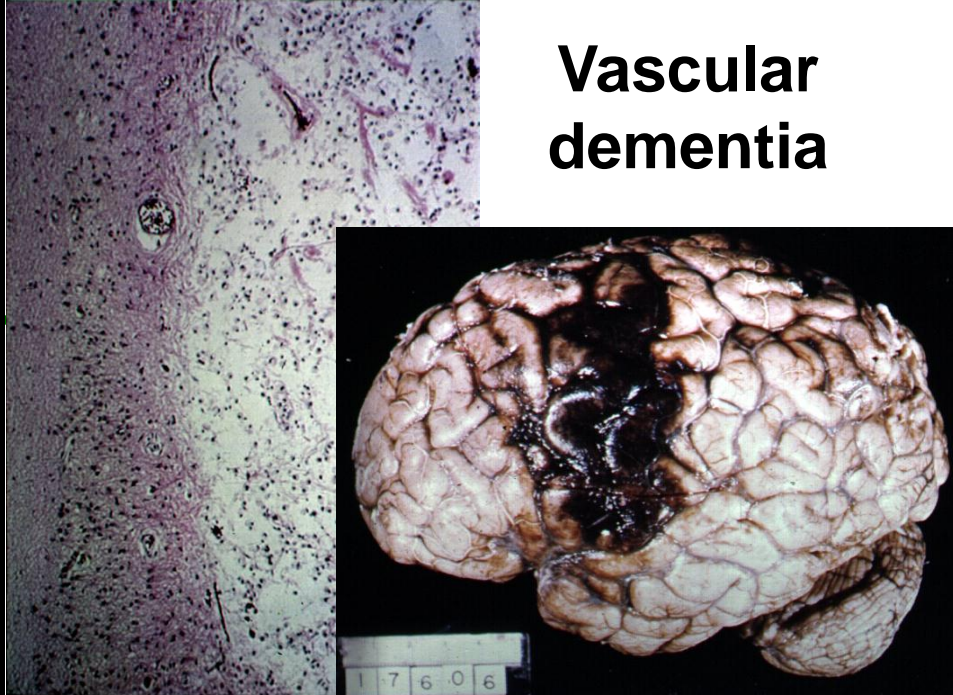




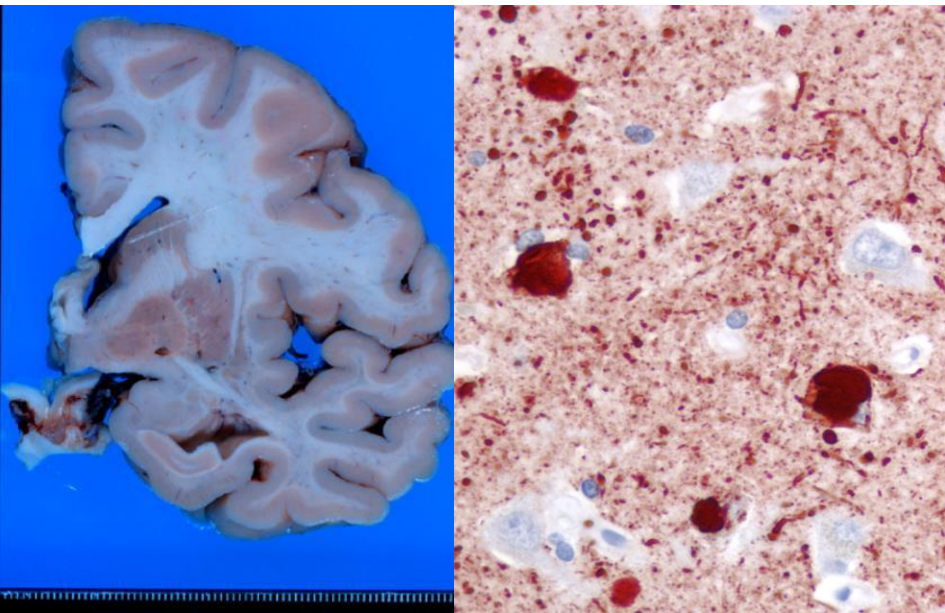
**Alzheimer's  
disease**



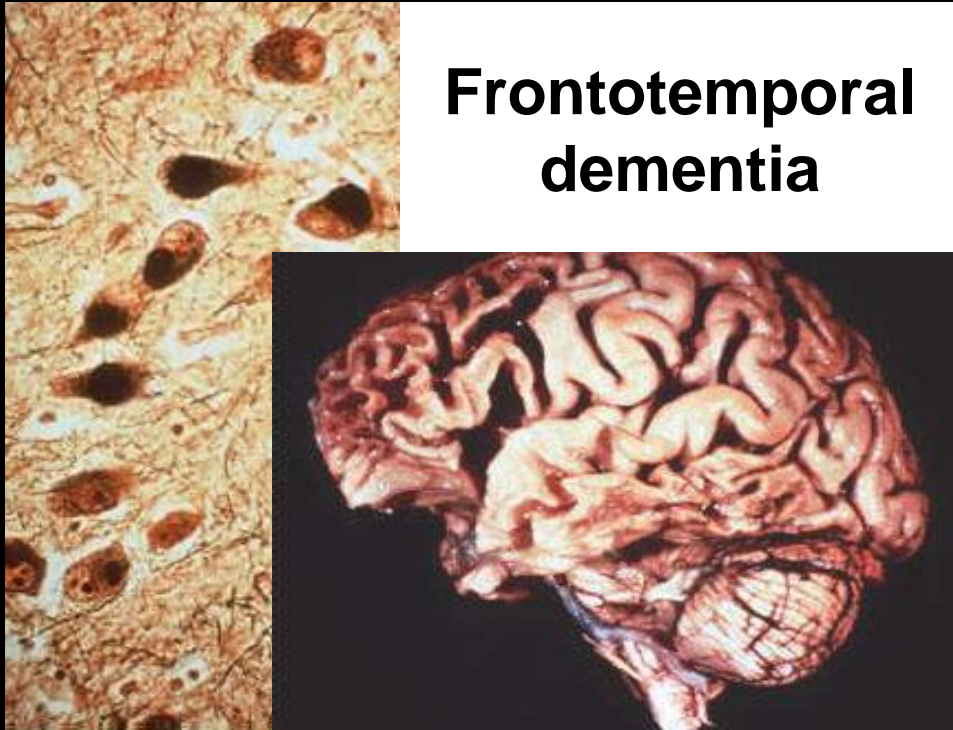
**Vascular  
dementia**



**Dementia with Lewy bodies**



**Frontotemporal  
dementia**

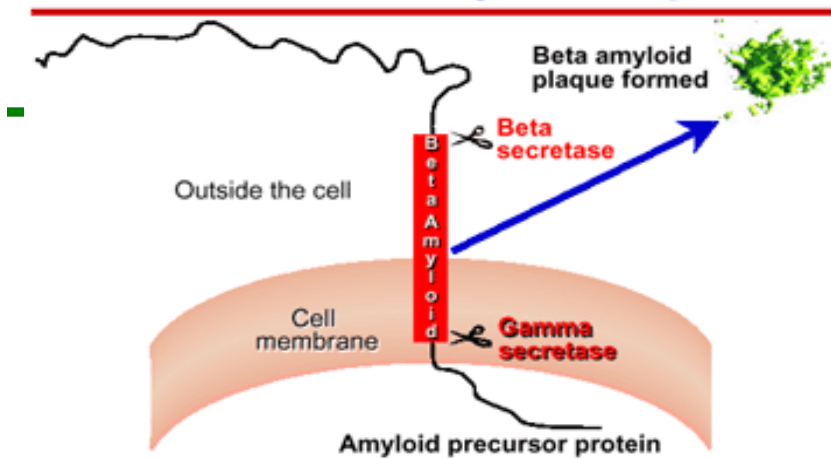




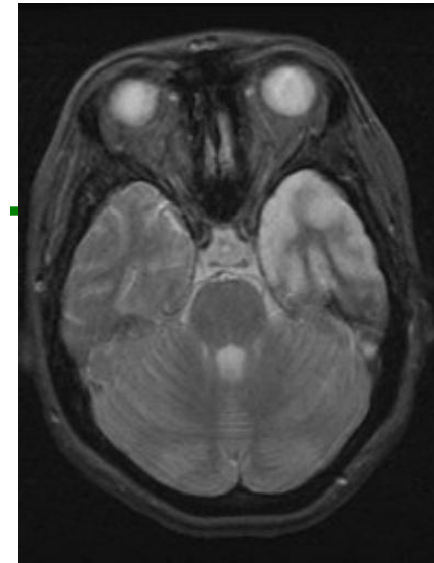
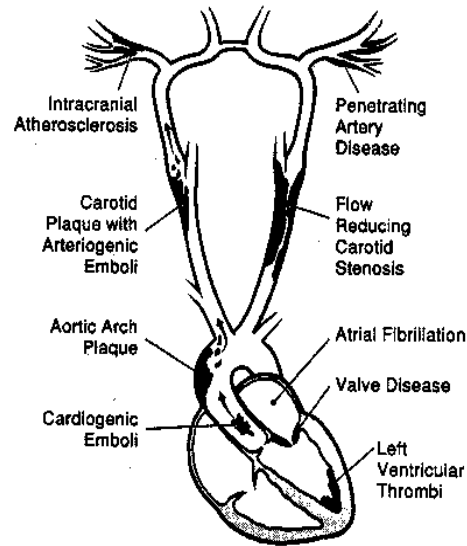
# Alzheimer's disease

## Production of Amyloid Plaques

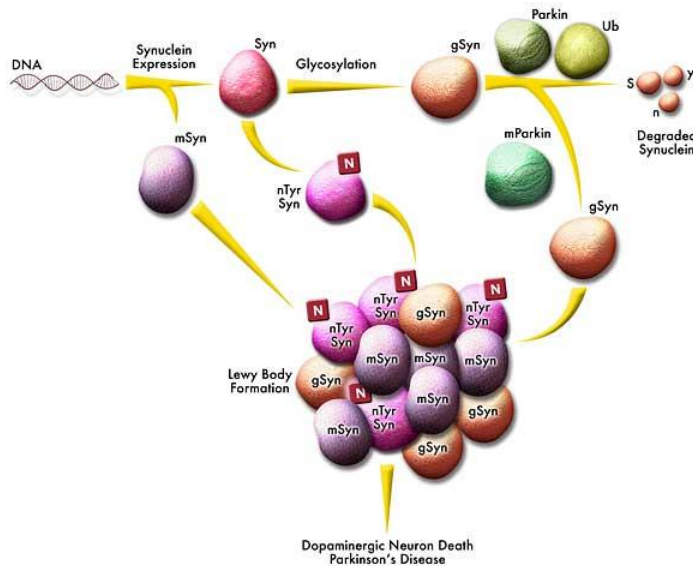
Chart #2



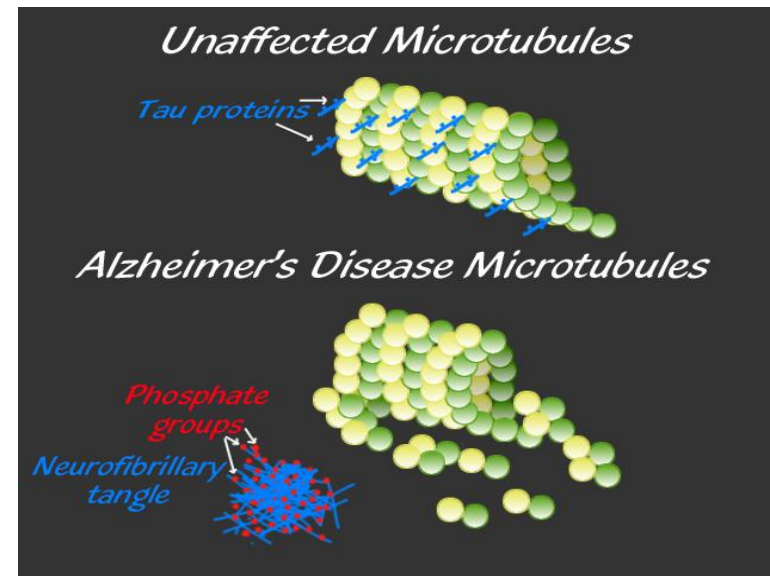
# Vascular dementia



# Dementia with Lewy bodies



# Frontotemporal dementia



**Symptoms vary across time and across the spectrum of disease and need to be considered for...**

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- **Prognosis**
- **Preparedness**
- **Safety issues**
- **Behavioral interventions**
- **Pharmacologic treatments**
- **Quality of life issues for both the person and their caregivers**

## **Alzheimer's disease (NINDS-ADRDA)**

- Dementia by DSM-III-R/V criteria
- Deficits in two or more areas of cognition
- Progressive worsening of memory and cognitive dysfunction
- Onset age 40-90
- Absence of other systemic/brain disorders

## **Vascular dementia (NINDS-AIREN)**

- Dementia by DSM-III-R/V criteria
- Cerebrovascular disease present:
  - a) focal neurologic signs (stroke)
    - history of stroke not necessary
  - b) CT or MRI evidence of stroke
- Onset of dementia within 3 months of stroke, or abrupt deterioration of cognitive function or stepwise course

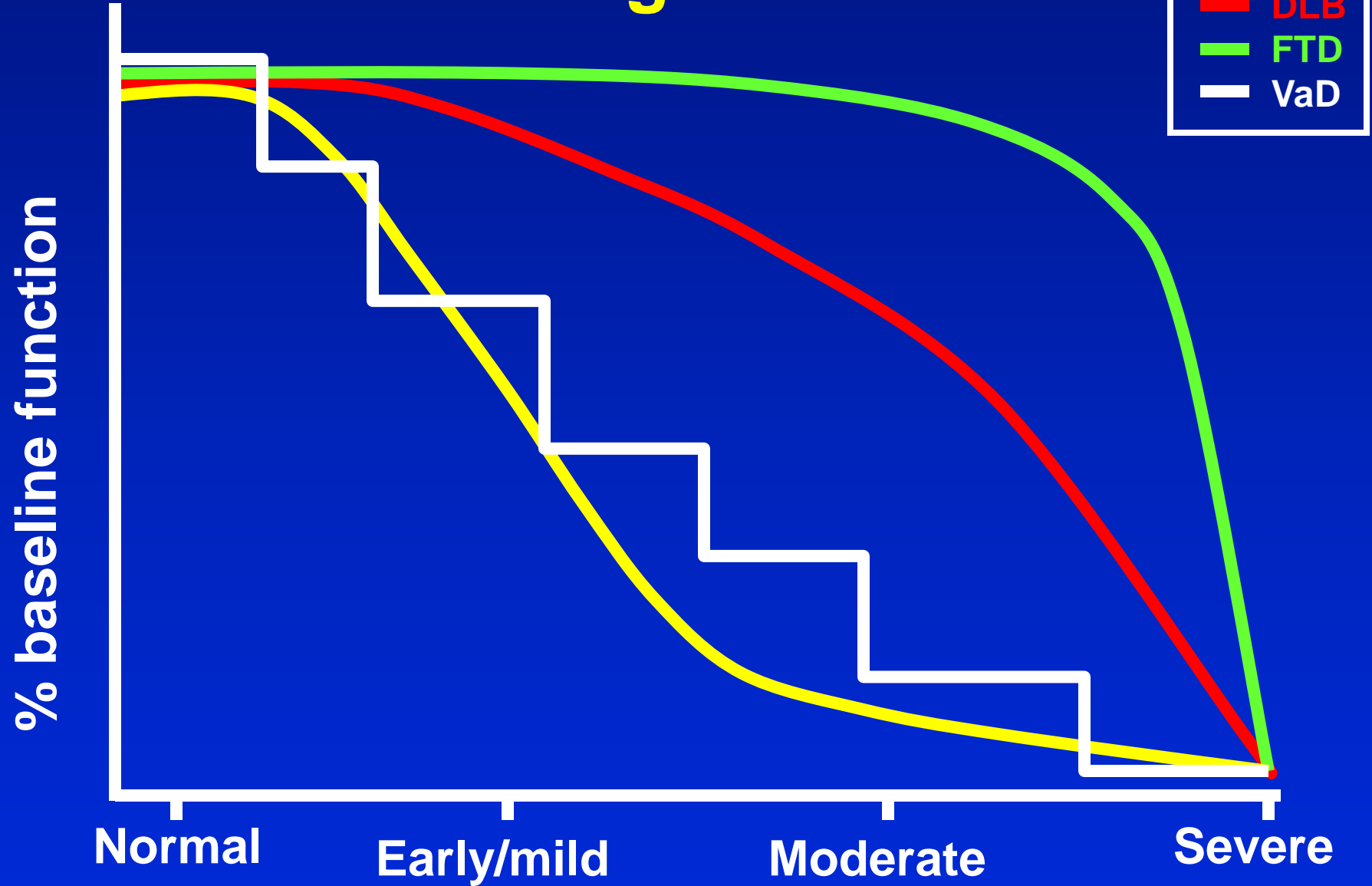
## **Dementia with Lewy bodies (3<sup>rd</sup> Int. Workshop on DLB)**

- Dementia by DSM-III-R/V criteria
- Deficits in cognition may not be memory (usually attention/spatial)
- Parkinsonism
- Early hallucinations
- Fluctuations
- Supportive:
  - Depression
  - REM sleep behavior disorder

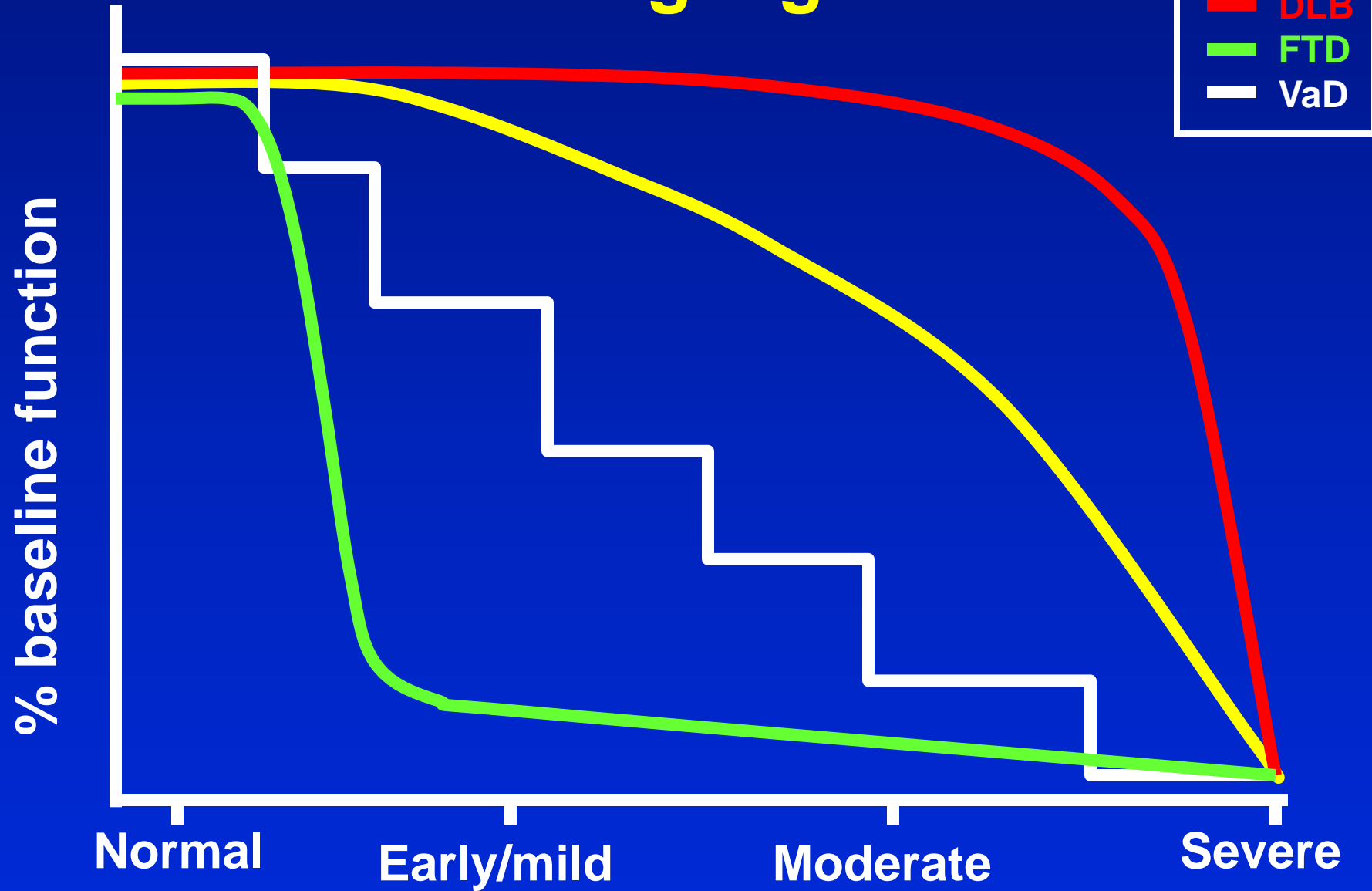
## **Frontotemporal dementia (NIH work group on FTD)**

- Prominent behavioral disorder
  - Loss of interpersonal skills
  - Emotional blunting
  - Perseveration or impersistenceor
- Language involvement
  - Comprehension or fluency
- Cognition typically preserved
- Can be assoc with MND/ALS

# Cognition

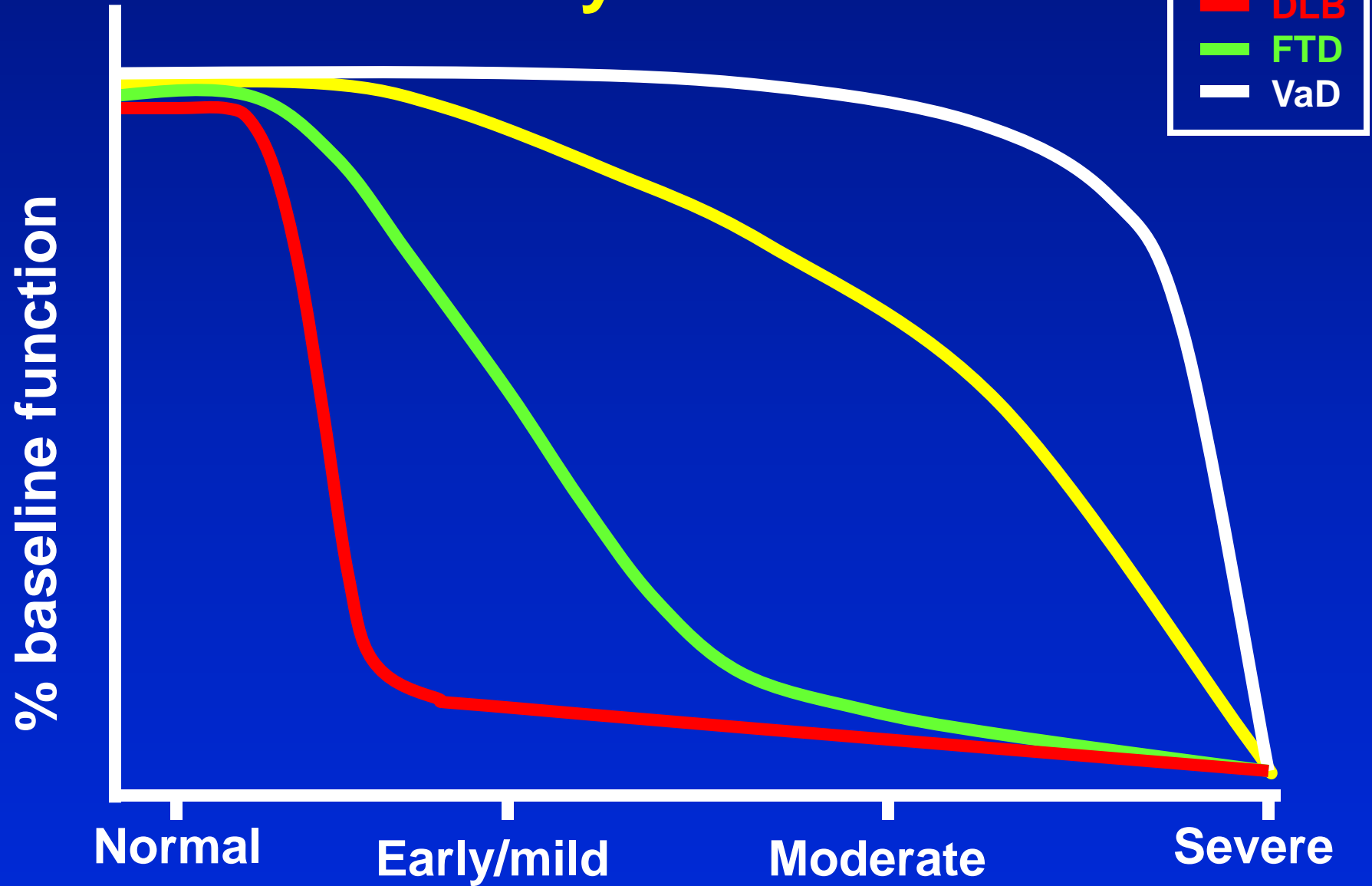


# Language





# Psychiatric



# Psychiatric

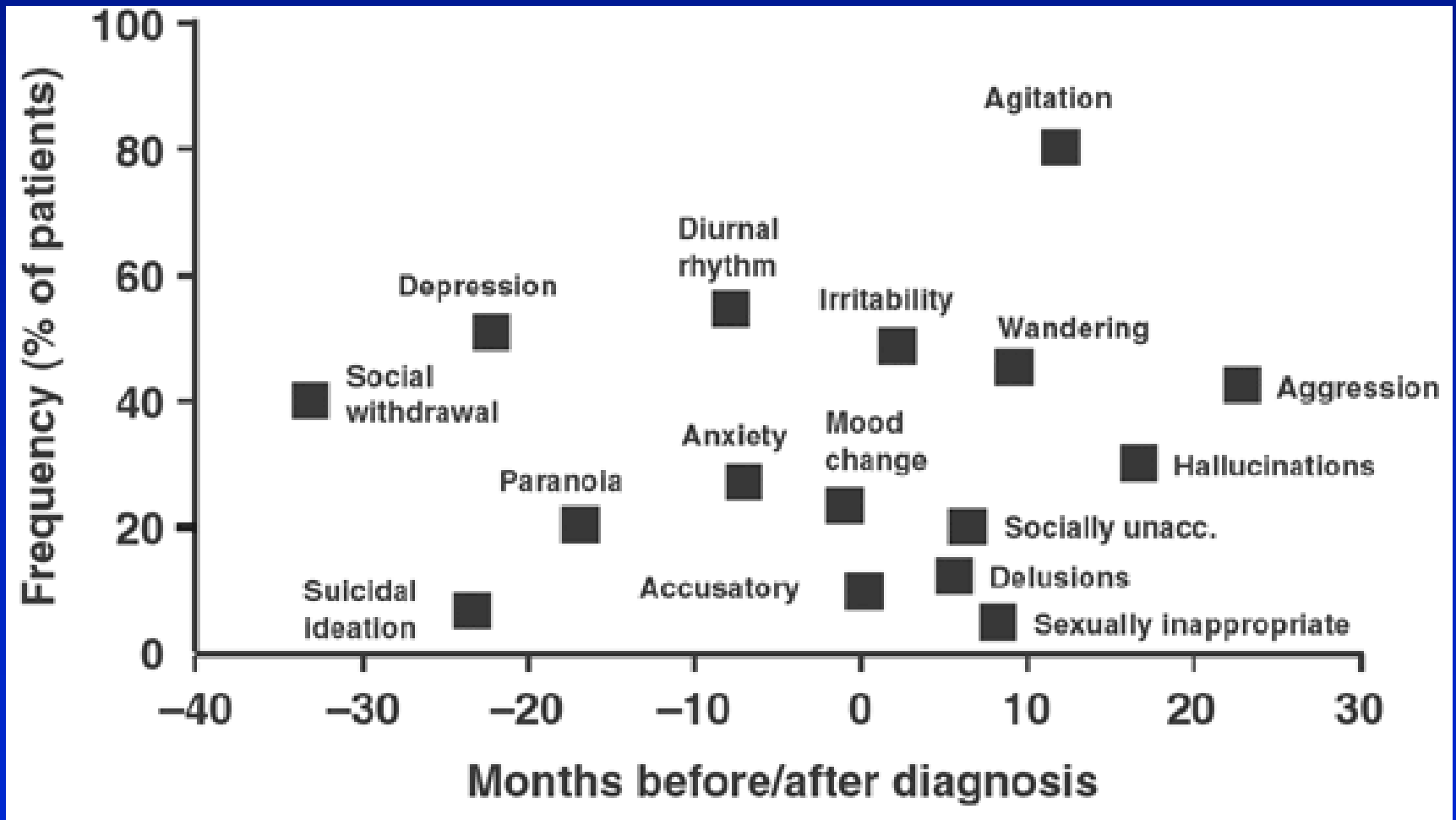
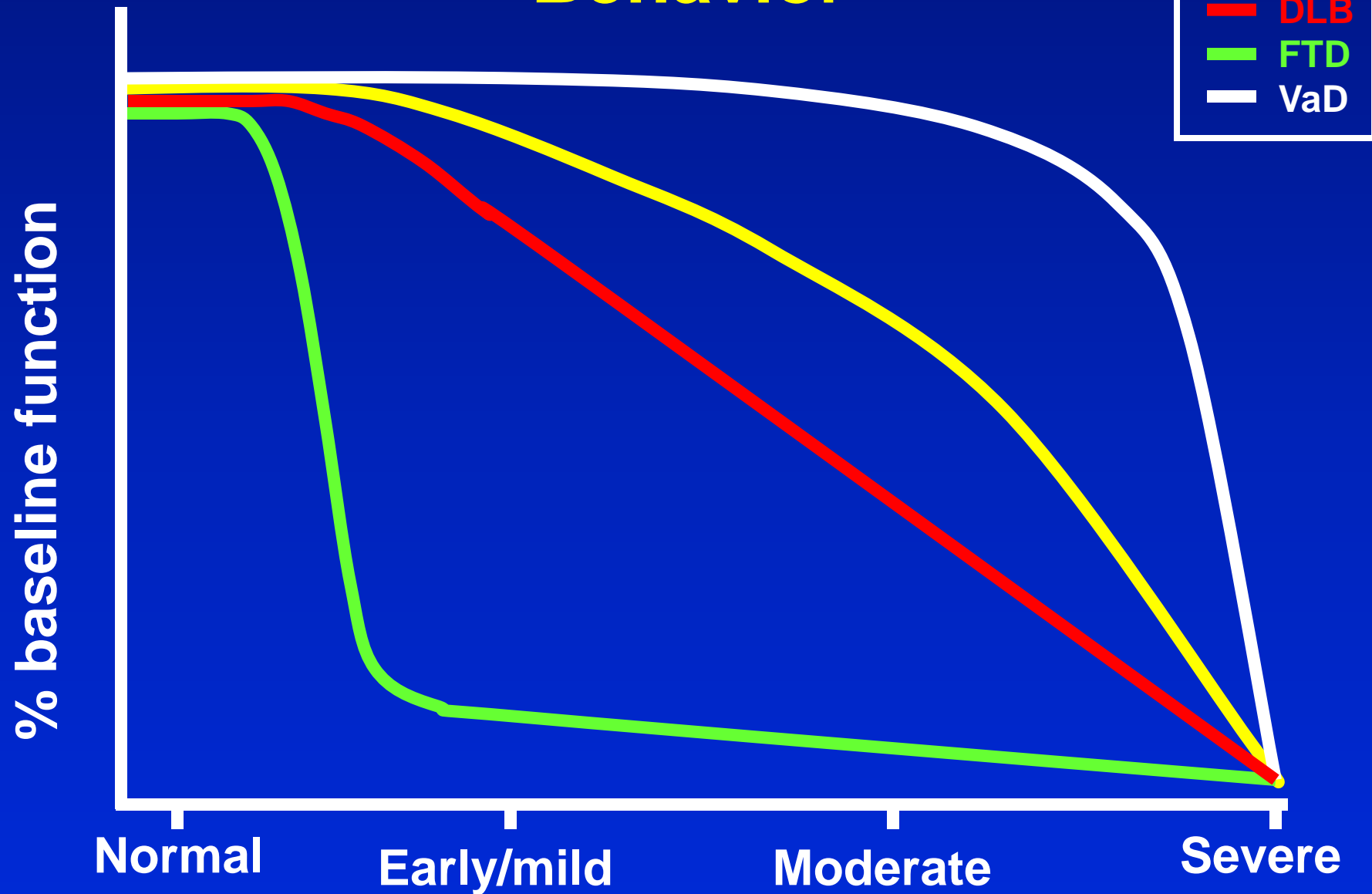
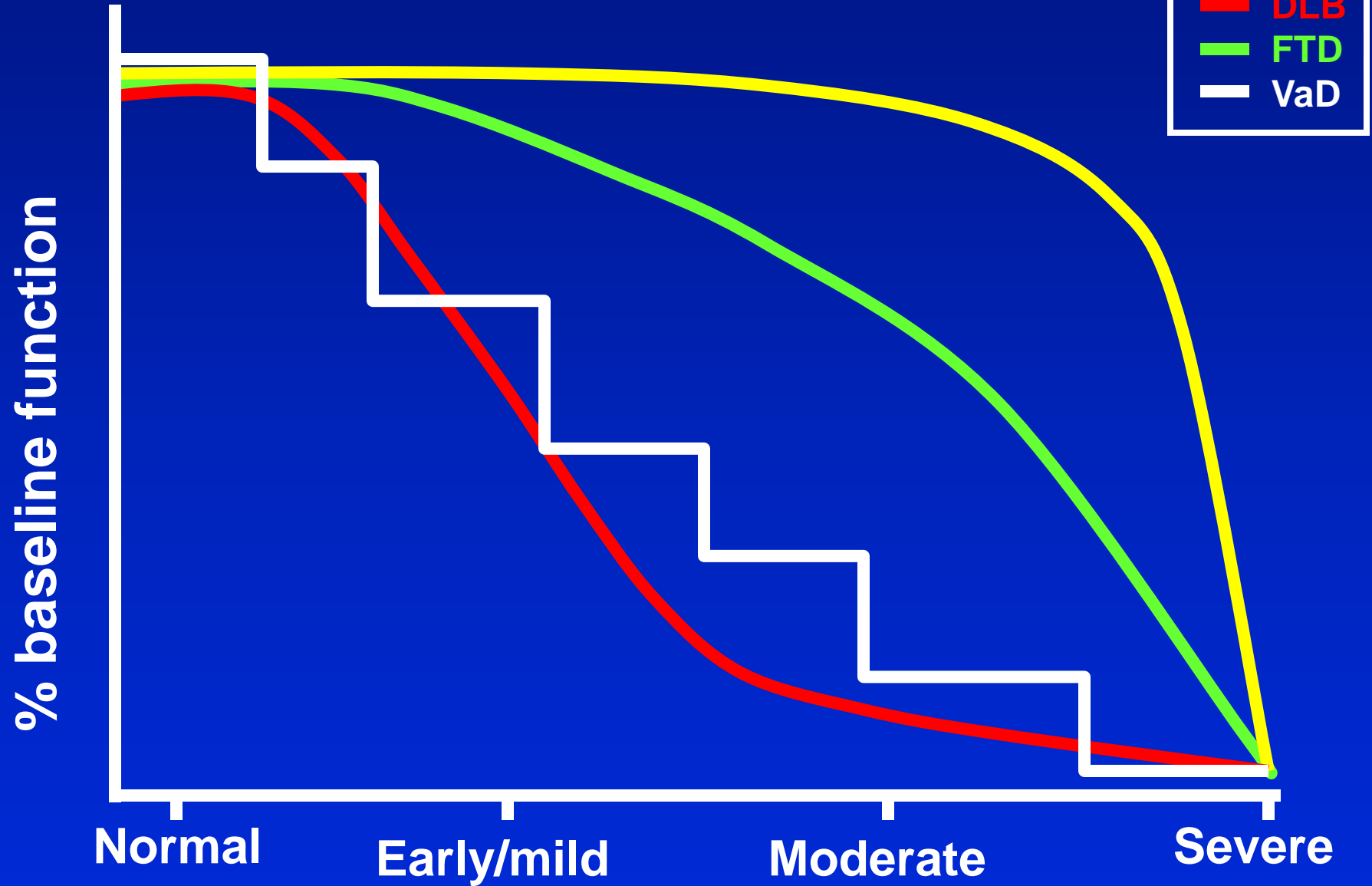


Figure from Medscape.com

# Behavior



# Motor



# Vascular dementia (NINDS-AIREN)

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- **Dementia by DSM-III-R/V criteria**
- **Cerebrovascular disease present:**
  - a) focal neurologic signs (stroke)
    - history of stroke not necessary
  - b) CT or MRI evidence of stroke
- **Onset of dementia within 3 months of stroke, or abrupt deterioration of cognitive function or stepwise course**



# Early/mild VaD

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- **Cognitive deficit: attention/executive**
- **Language: ?aphasia from stroke?**
- **Psychiatric: depression common**
- **Behavior: social withdrawal**
- **Motor: ?focal motor from stroke? Or bradykinesia from subcortical disease**
- **Safety: depend on focality of Sx**
- **Treatment: Control stroke risk factors, consider AChEI +/- SSRI as needed**

# Diagnosing VaD

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- **Cognitive testing**
- **Imaging**
  - MRI is key here
    - FLAIR
    - SWI/ECHO gradient
- **Assessment of Vascular risks**
  - Hachinski Ichemic Scale

# Memory less impaired in VaD

Test variable	Participant group					
	AD			VaD		
	n	mean	SD	n	mean	SD
Faces immediate	294	5.50	2.54	160	6.11	2.78
Faces delayed	287	4.26	2.21	150	5.15	2.69
Words immediate	297	7.47	2.72	162	8.31	2.89
Words delayed	286	5.93	2.48	155	7.25	3.05
Story immediate	299	6.43	7.31	164	11.59	9.31
Story delayed	296	2.21	5.66	162	7.60	9.10
Figure copy	271	70.93	28.85	159	71.48	29.54
Figure immediate	268	16.15	15.79	157	27.10	22.20
Figure delayed	263	9.57	15.02	156	22.80	22.50
Information processing	160	27.94	14.63	99	29.45	15.92
Info pro errors	160	7.66	15.07	99	6.07	10.66
Info pro motor speed	236	31.54	10.91	129	31.88	10.47
NART	293	25.07	10.86	158	24.33	10.41
Verbal fluency	293	22.24	12.83	161	23.78	13.89
BNT	303	8.41	3.08	167	9.88	3.35
Token test	198	33.07	6.92	125	33.31	8.18
HVLT trials	219	9.04	4.80	135	11.61	5.19
HVLT DI	216	6.27	3.31	134	8.04	2.98

The penultimate columns show F ratio and probabilities resulting from ANOVA bet

**Greater variability (SD) in VaD**

# FLAIR sequences visualize “silent” cerebrovascular disease

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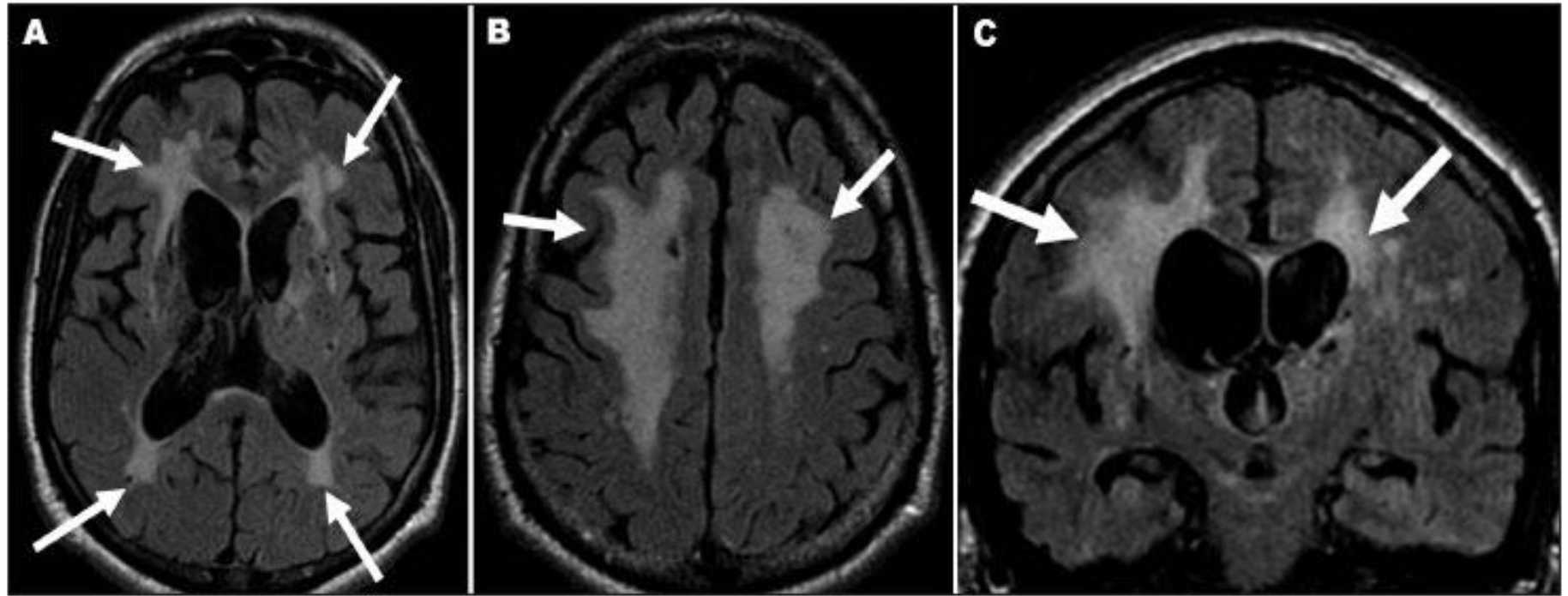


Fig 1. Flair MRI of a patient with higher score in Fazekas scale; white matter lesions (WML) are shown by arrows: [A] periventricular WML affecting anterior and posterior horns, bilaterally (axial section); diffuse ([B] axial section) and deep WML ([C] coronal section). Courtesy of Hospital Pró-Cardiaco, RJ.

# Hachinski Ischemic Scale

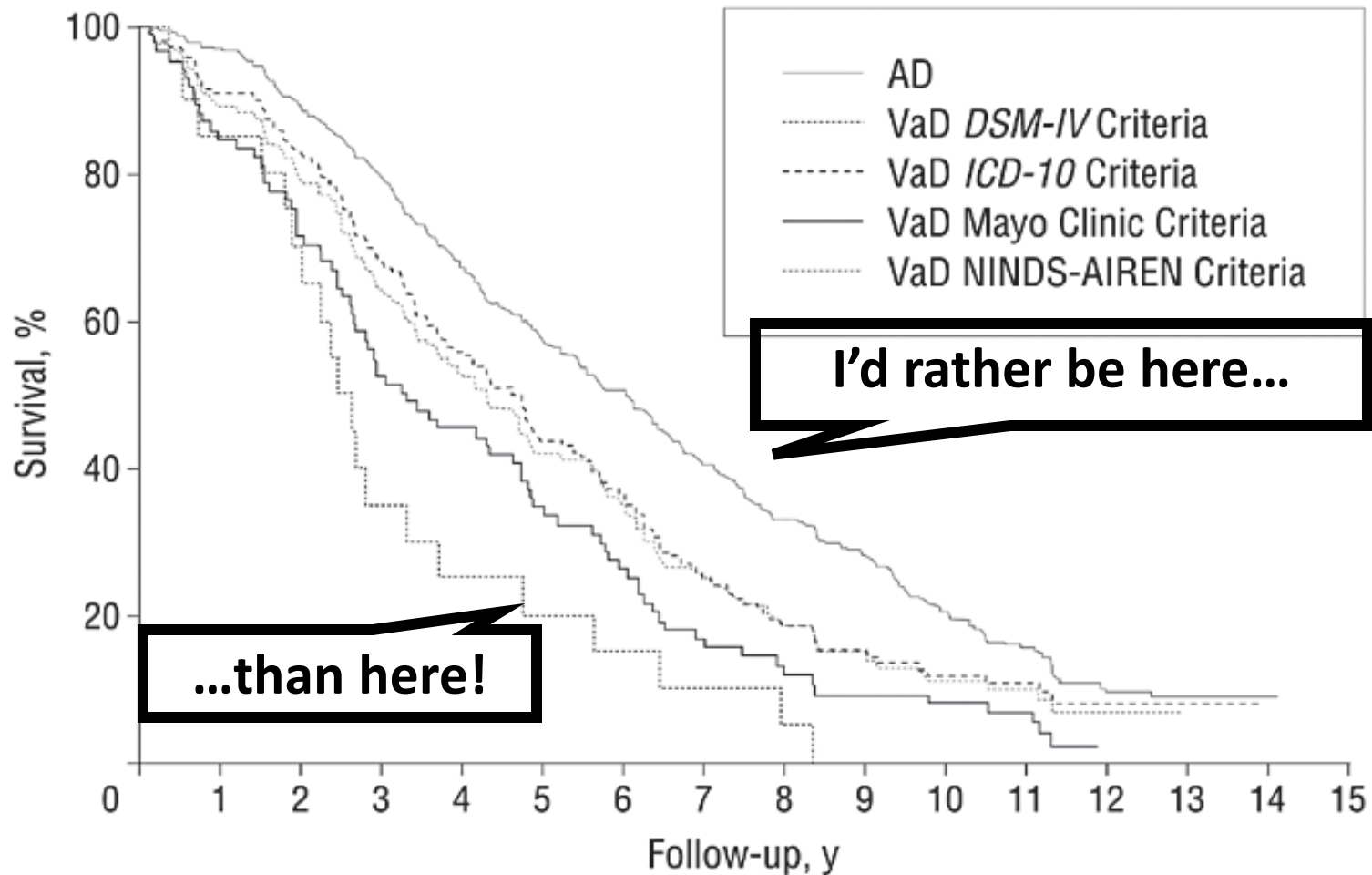
CHARACTERISTIC	SCORE
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic symptoms	1
Emotional incontinence	1
History of hypertension	1
History of stroke	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

- **Scores  $\geq 7$**  indicate VaD
- **Scores between 5-6** indicate mixed dementia
- **Scores  $\leq 4$**  indicate a primary degenerative disease without significant vascular contributions

Hachinski et al. Arch Neurol 1975



# Despite shortcomings, VaD criteria predicts increased mortality



# Cholinergic hypothesis of VaD: White matter changes in cholinergic projection areas

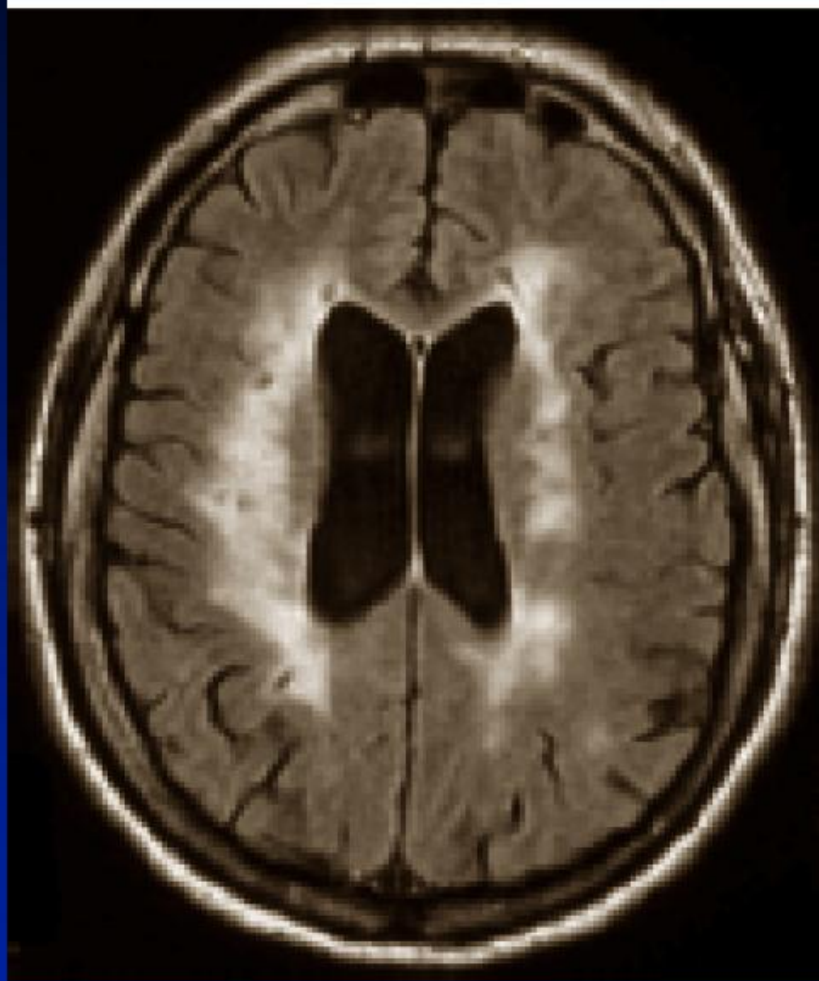
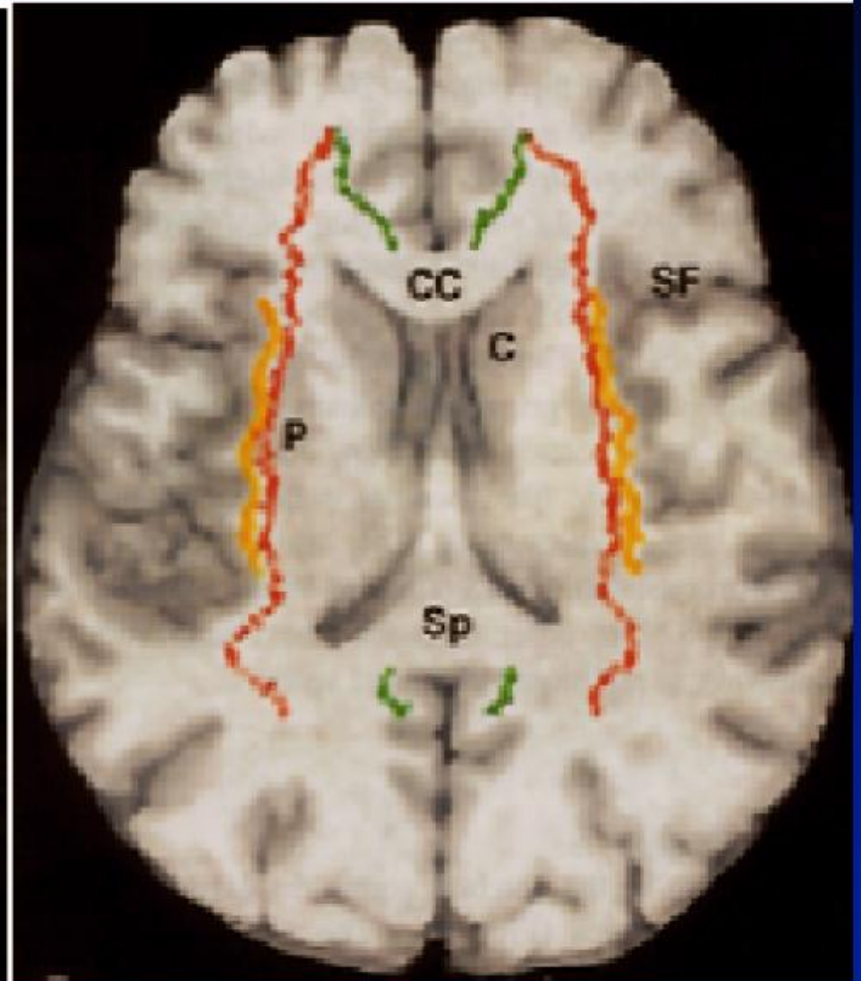
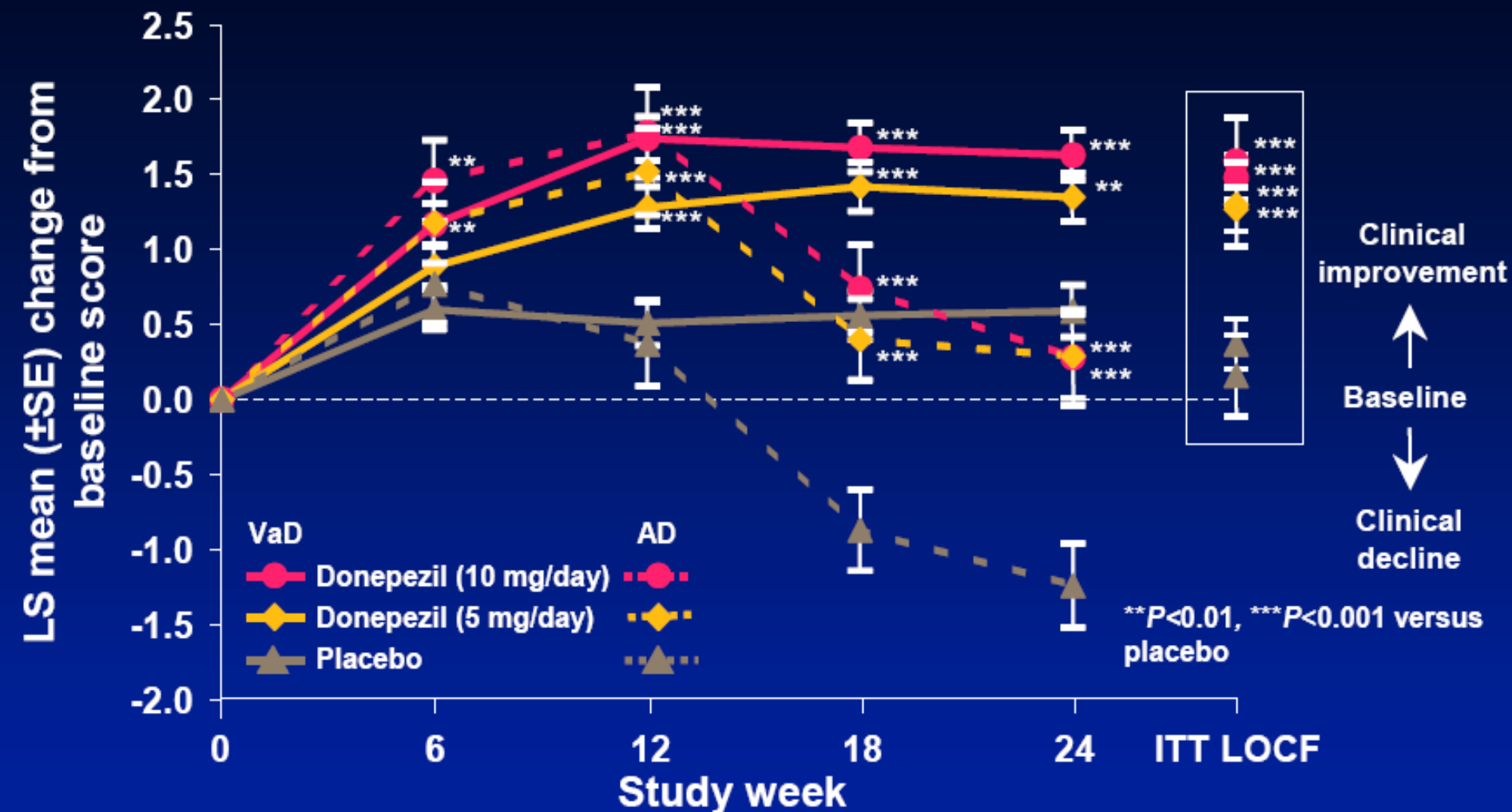


Image reproduced with kind permission  
from Dr S Salloway [TBC]



Selden NR, et al. *Brain*. 1998;121:2249-2257

# VaD and AD cognitive function MMSE



# **Dementia with Lewy bodies (3<sup>rd</sup> Int. Workshop on DLB)**

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- **Dementia by DSM-III-R/V criteria**
  - Deficits in cognition may not be memory (usually attention/spatial)
- **Primary Features (2 of 3 of the following)**
  - **Parkinsonism**
  - **Early hallucinations**
  - **Fluctuations**
- **Supportive:**
  - Depression
  - REM sleep behavior disorder

# Early/mild DLB

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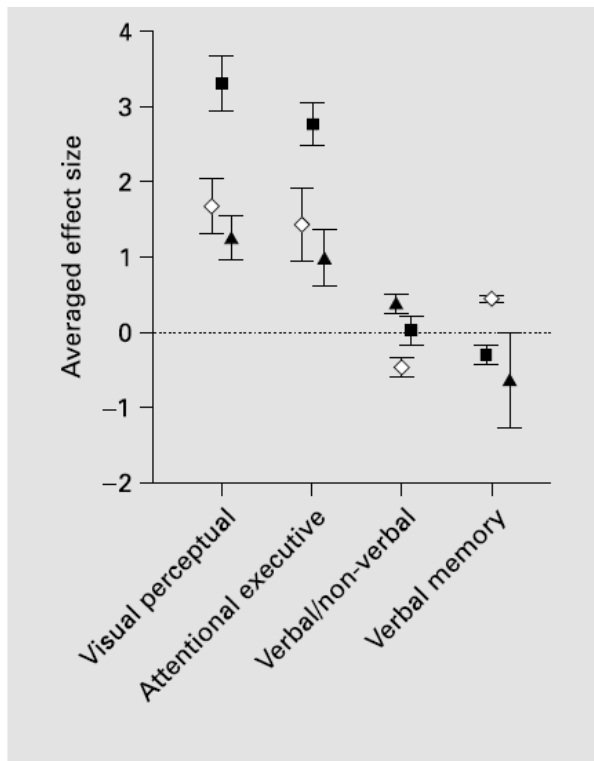
- **Cognitive deficit: attention/visuospatial**
- **Language: rarely impaired**
- **Psychiatric: depression almost universal, early delusions and hallucinations common**
- **Behavior: social withdrawal**
- **Motor: Parkinsonism usually mild**
- **Safety: driving is a biggie here**
- **Treatment: AChEI +/- SSRI +/- atypical antipsychotic as needed**

# Diagnosing DLB

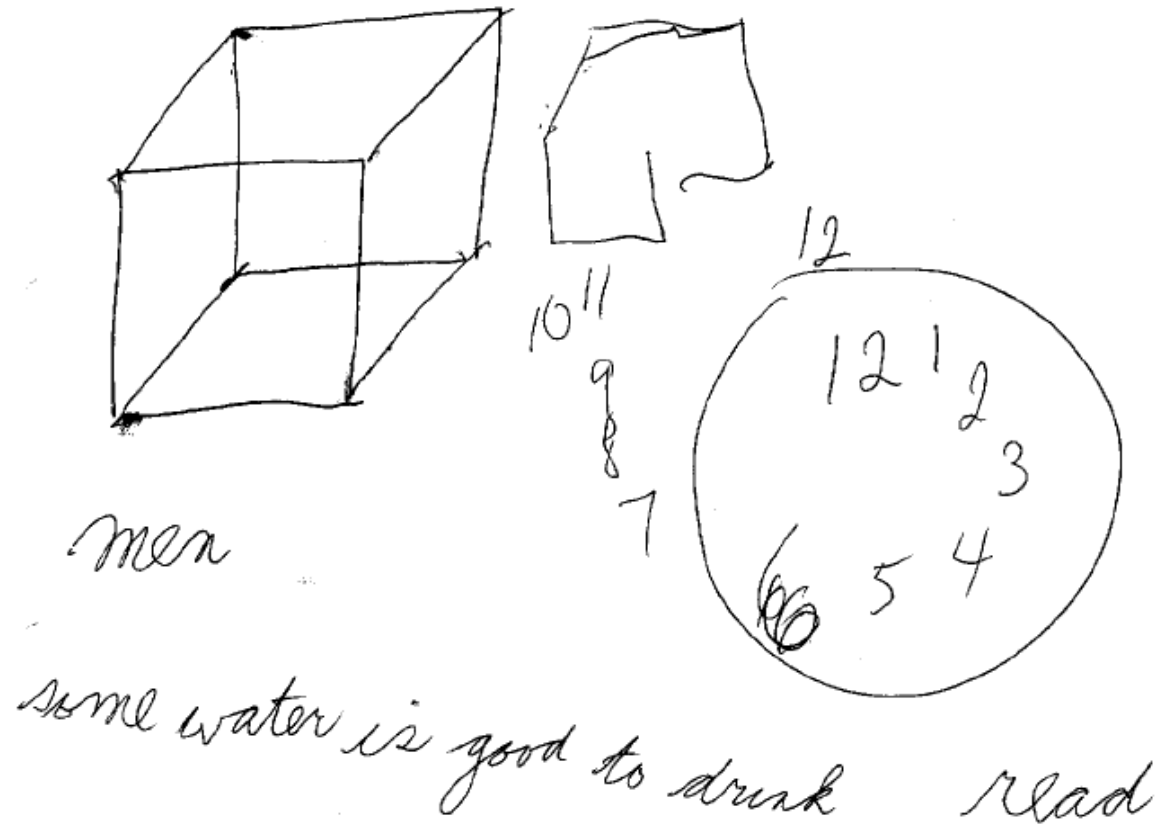
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- **Cognitive testing**
- **Imaging**
  - This is no help here
- **Assessment of risk**
  - Severity of cognitive impairment
  - Gender
- **Sleep disorder**
  - RBD, PLMS

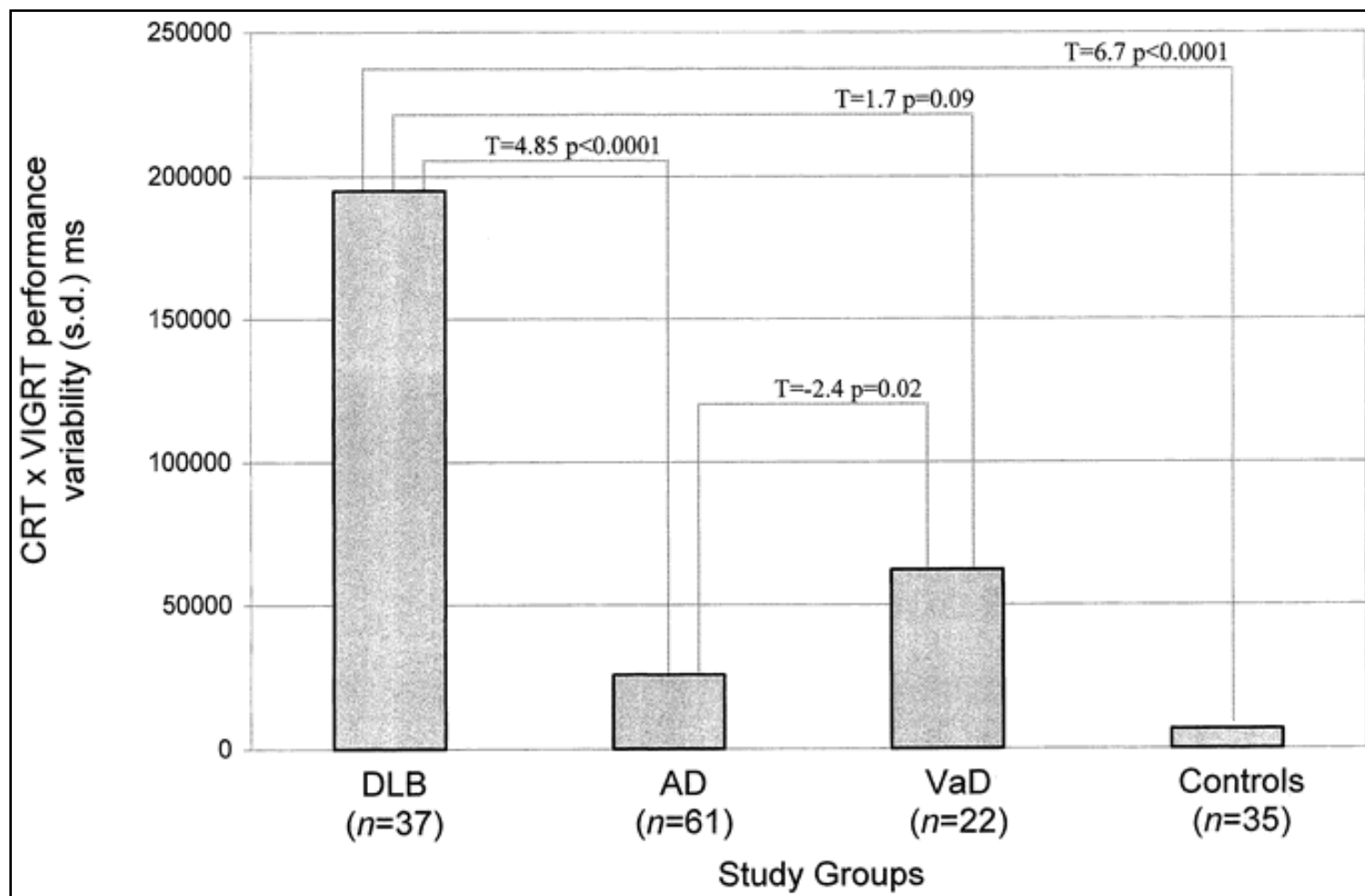
# Attentional/executive & visuospatial dysfunction in DLB



**Fig. 1.** Results of comparisons between DLB and controls, AD, and PD patients on factors. ■ = DLB compared to controls; ◇ = DLB compared to AD; ▲ = DLB compared to PD. Values are mean and 95% CI.



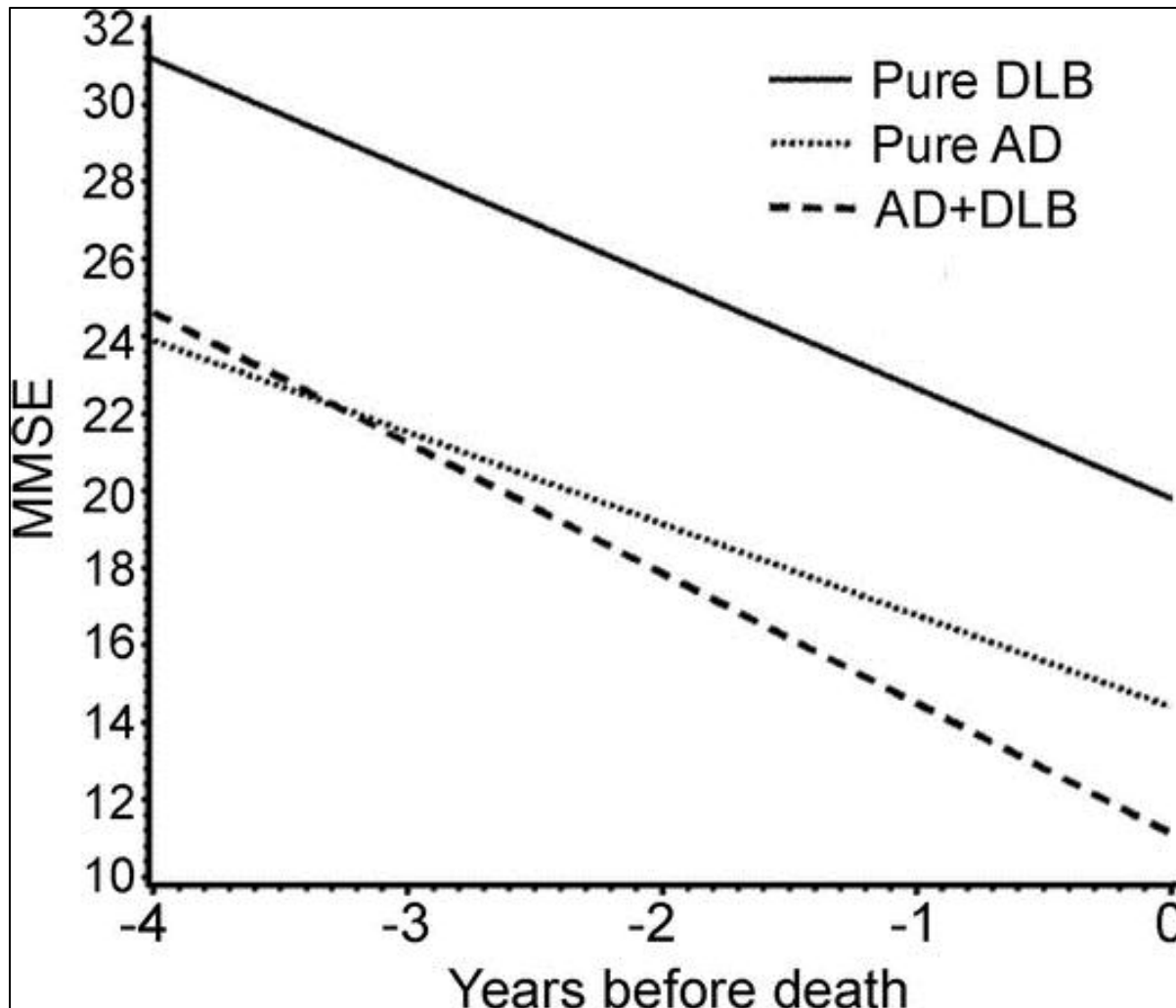
# Fluctuations in DLB



Ballard et al, Arch Neurol 2001;58:977-982



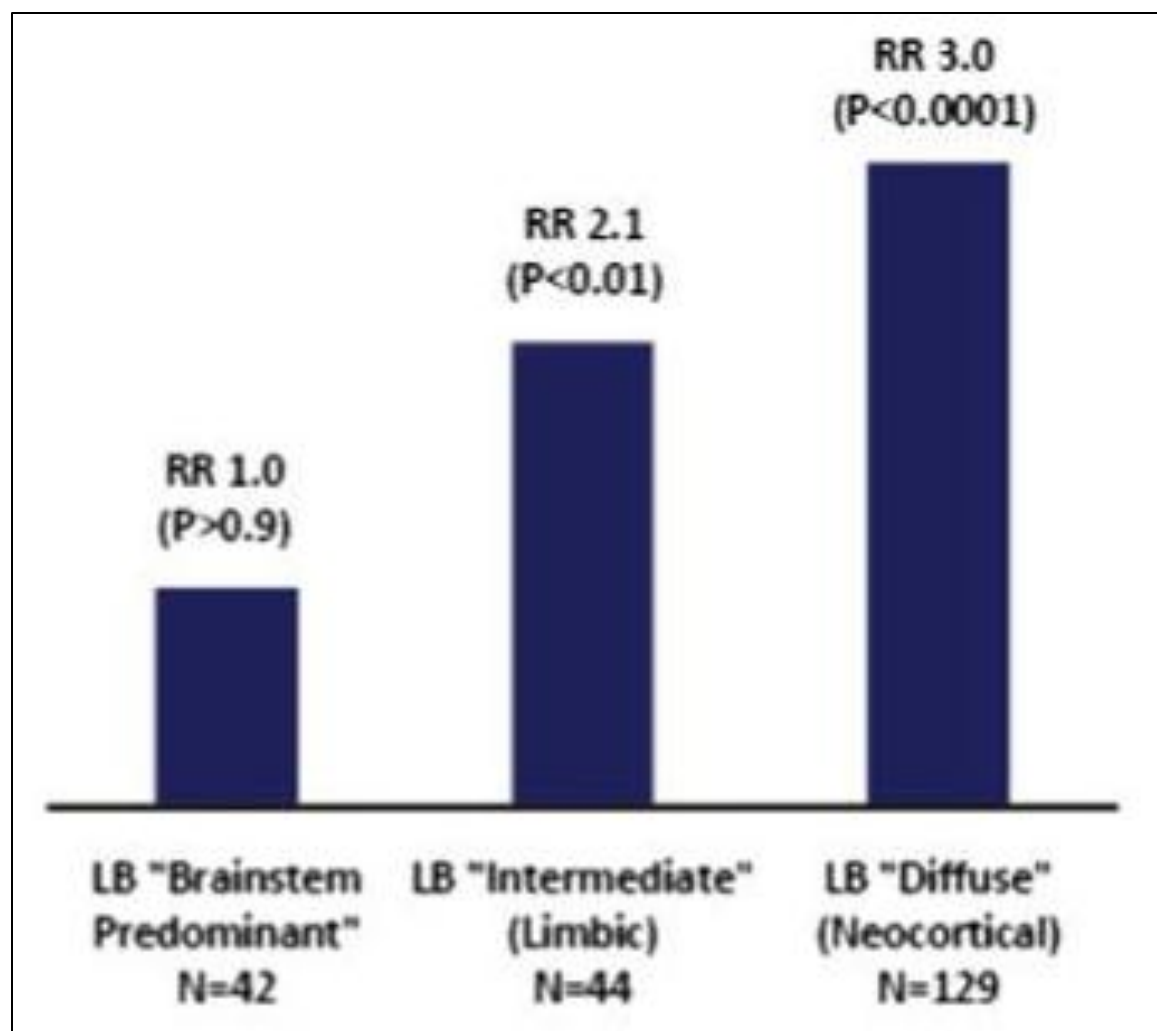
# DLB is associated with a milder cognitive process



- Even at death, average MMSE scores for pure DLB subjects was ~ 21/30
- This contrasts with MMSE 15 in AD subjects

Nelson et al., Neurology. 2009 October 6; 73(14): 1127–1133.

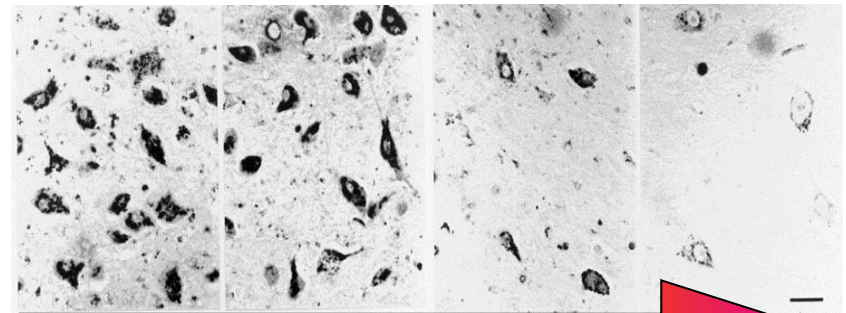
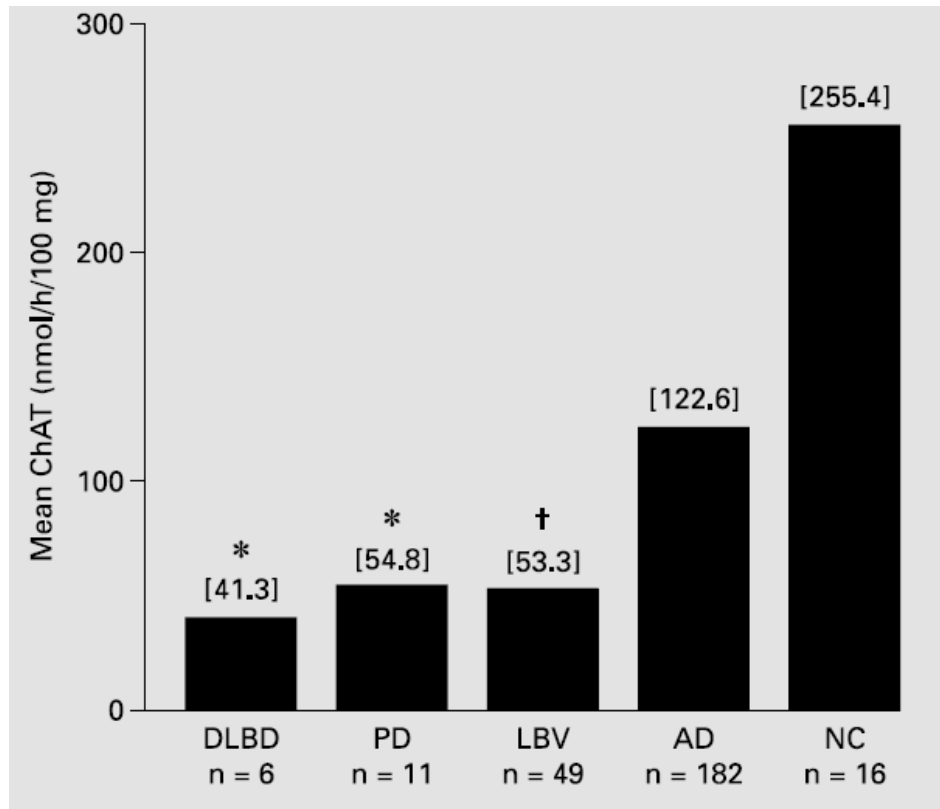
# Male gender is a major risk for DLB



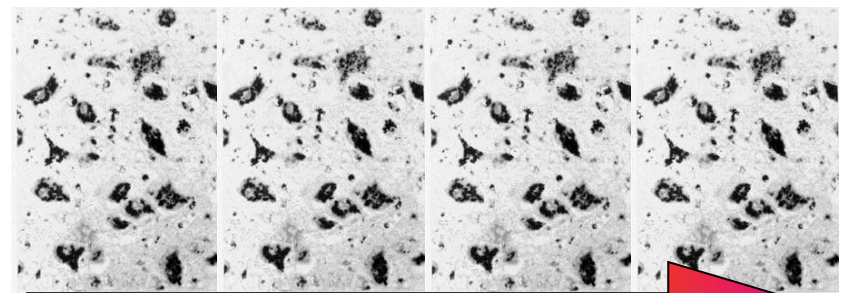
- Males are 3 times more likely to have DLB than women
- This same risk is seen for clinical parkinsonism

Nelson et al., J Neurol. 2010 November; 257(11): 1875–1881.

# ChAT activity dramatically reduced in DLB



Increasing severity of disease  
Alzheimer's disease

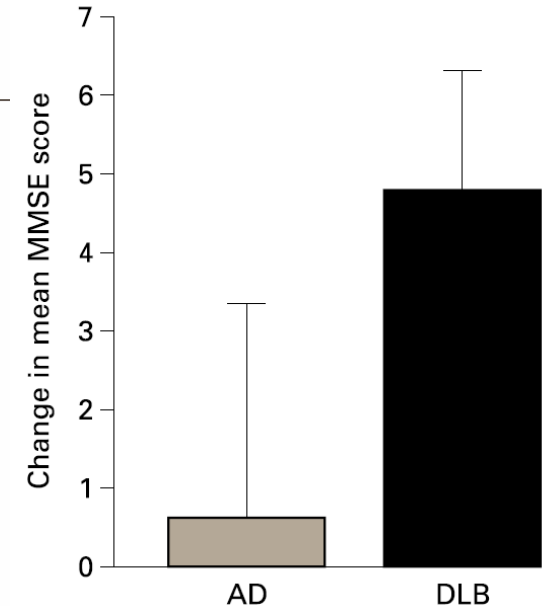


Increasing severity of disease  
Dementia with Lewy bodies

# Cognitive, psychiatric, and motor symptoms, fluctuations, and caregiver distress all improved on donepezil

Test	DLB group ( <i>n</i> = 30)			
	Baseline score	Mean change from baseline		
		4 wk	12 wk	20 wk
MMSE	17.7 (5.3)	3.2	3.3	3.9
NPI total	23.7 (20.8)	−9.5	−13.7	−14.6
UPDRS III total	25.1 (14.3)	−1.4	−1.2	−1.6
Bristol ADL	17.6 (9.2)	−4.4	−2.8	−1.8
NPI carer distress	10.3 (9.1)	−4.1	−5.9	−7.0
FI scale 1 severity score	6.2 (5.2)	−1.6	−4.1	−2.9
FI scale 2 severity score	3.9 (3.7)	−1.5	−2.8	−2.3

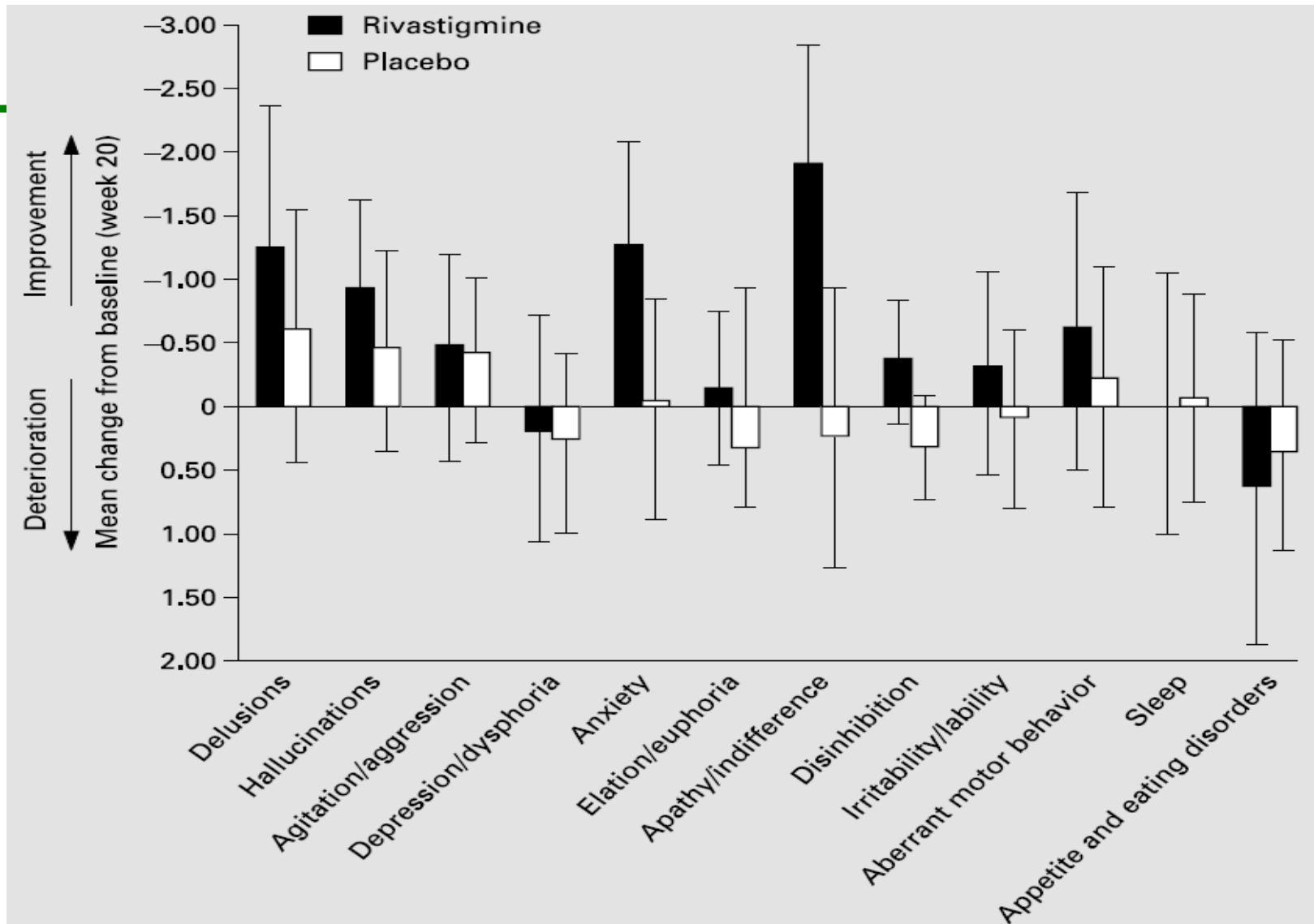
(Mann–Whitney tests were used for NPI and FI comparisons).



**Samuel W, Int J Ger Psych 2000;15:794-802**

**Thomas et al, Int J Ger Psych 2005;20:938-944**

# Psychiatric symptoms improve with AChEI



McKeith et al, Lancet 2000;356-2031-2036

# Frontotemporal dementia (NIH work group on FTD)

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- **Prominent behavioral disorder**
  - Loss of interpersonal skills
  - Emotional blunting
  - Perseveration or impersistence
- **or**
- **Language involvement**
  - Comprehension or fluency
- **Cognition may be preserved**
- **Can be associated with MND/ALS or parkinsonism**

# Early/mild FTD

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- **Cognitive deficit: executive function**
- **Language: Can be primary feature**
- **Psychiatric: OCD-like behavior**
- **Behavior: Prominent loss of social skills, poor hygiene, apathy**
- **Motor: rare to have any Sx unless MND**
- **Safety: across the board 2° to poor judgment**
- **Treatment: SSRI +/- AChEI? Memantine? Atypical antipsychotic?**

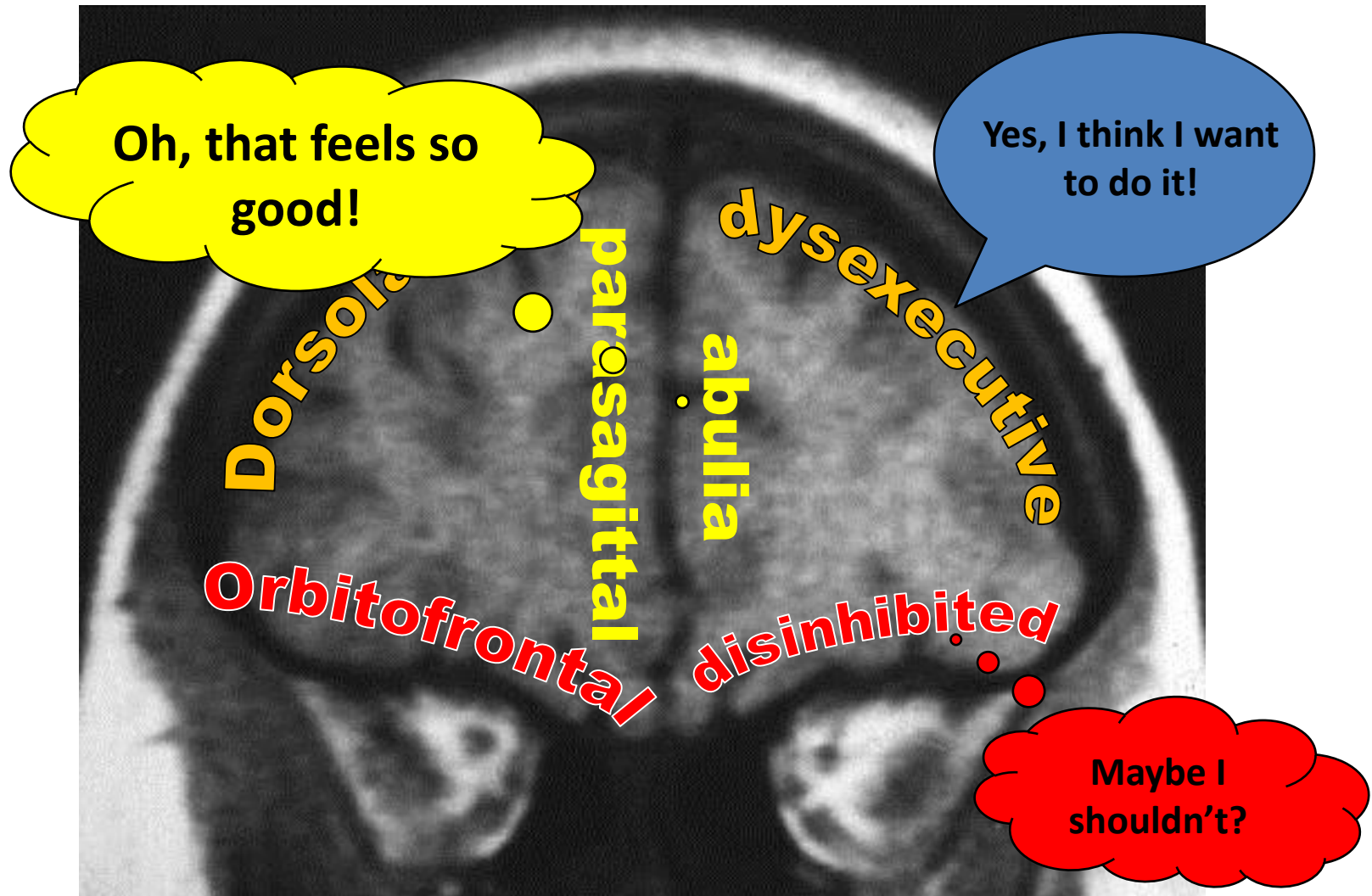
# Diagnosing FTD

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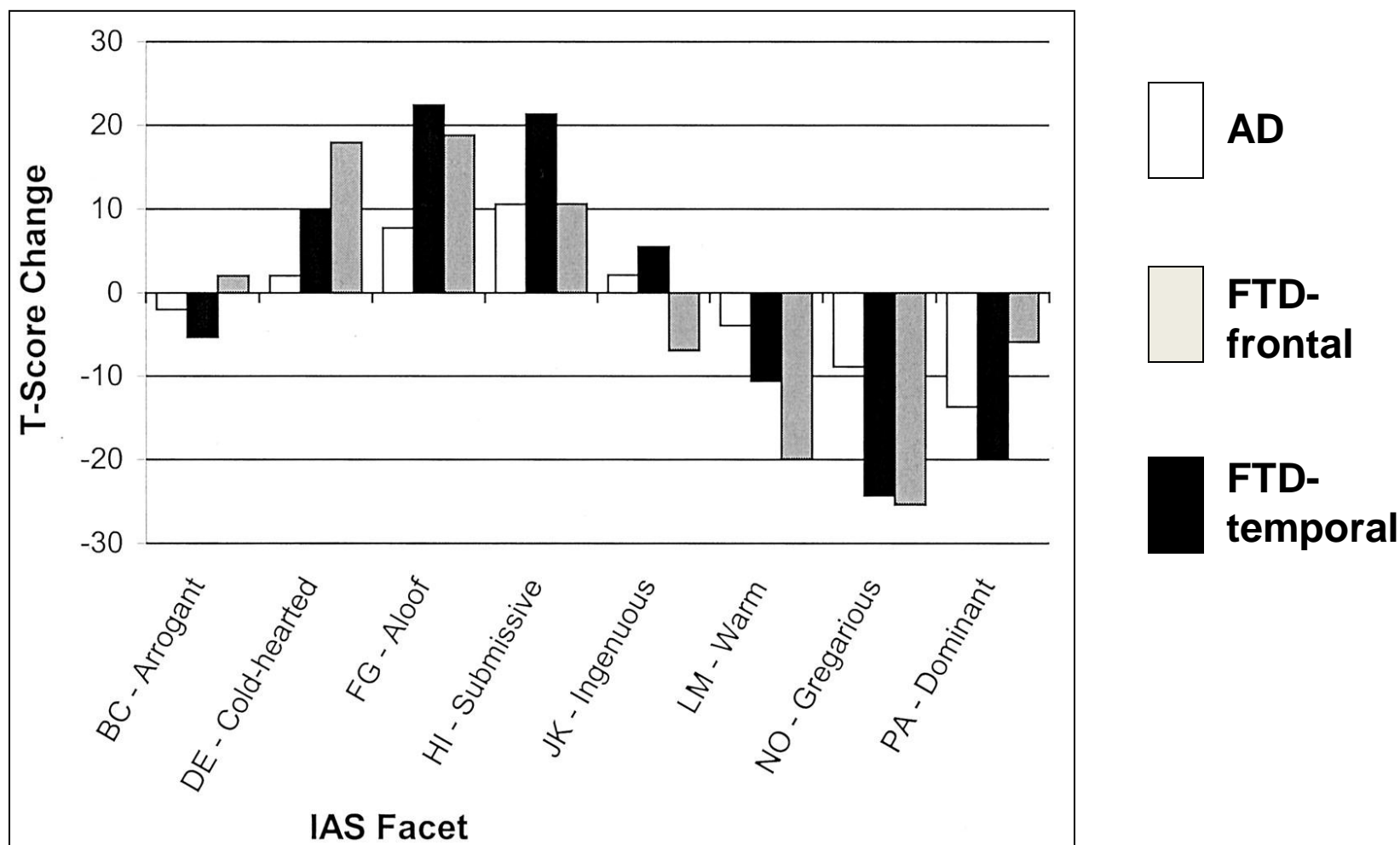
- **Cognitive testing**
  - Behavior
    - Unfortunately there are no good tests
  - Language
- **Imaging**
  - Focal atrophy patterns
- **Assessment of risk**
  - Younger age



# Brief note on “frontal symptoms”

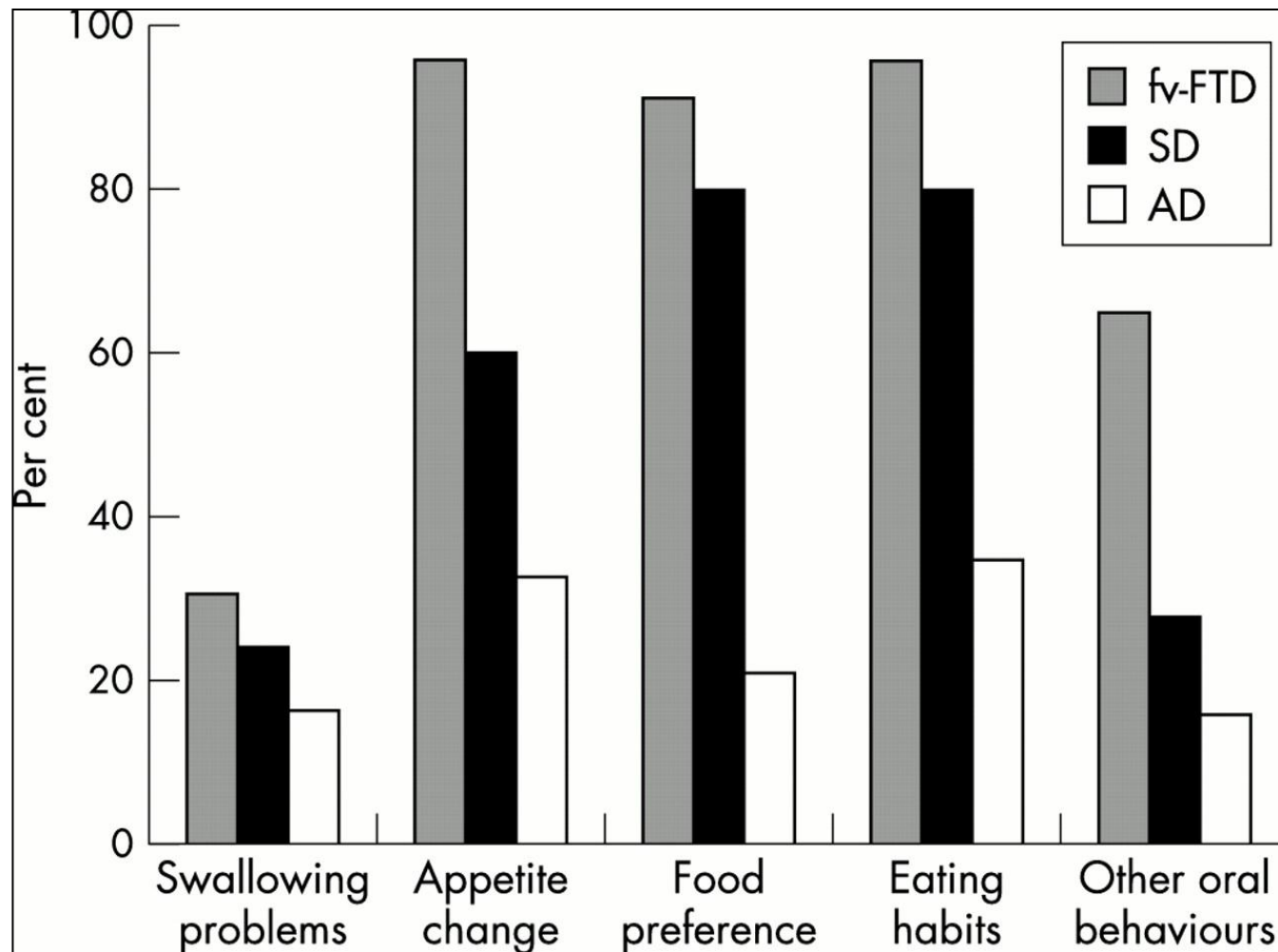


# Personality changes in FTD



Rankin et al, Neurology 2003;60:266-271

# Hyperorality and feeding behavior change is common



**Ikeda et al, JNRP 2002;73:371-376**

# **Frontal Assessment Battery (FAB)**

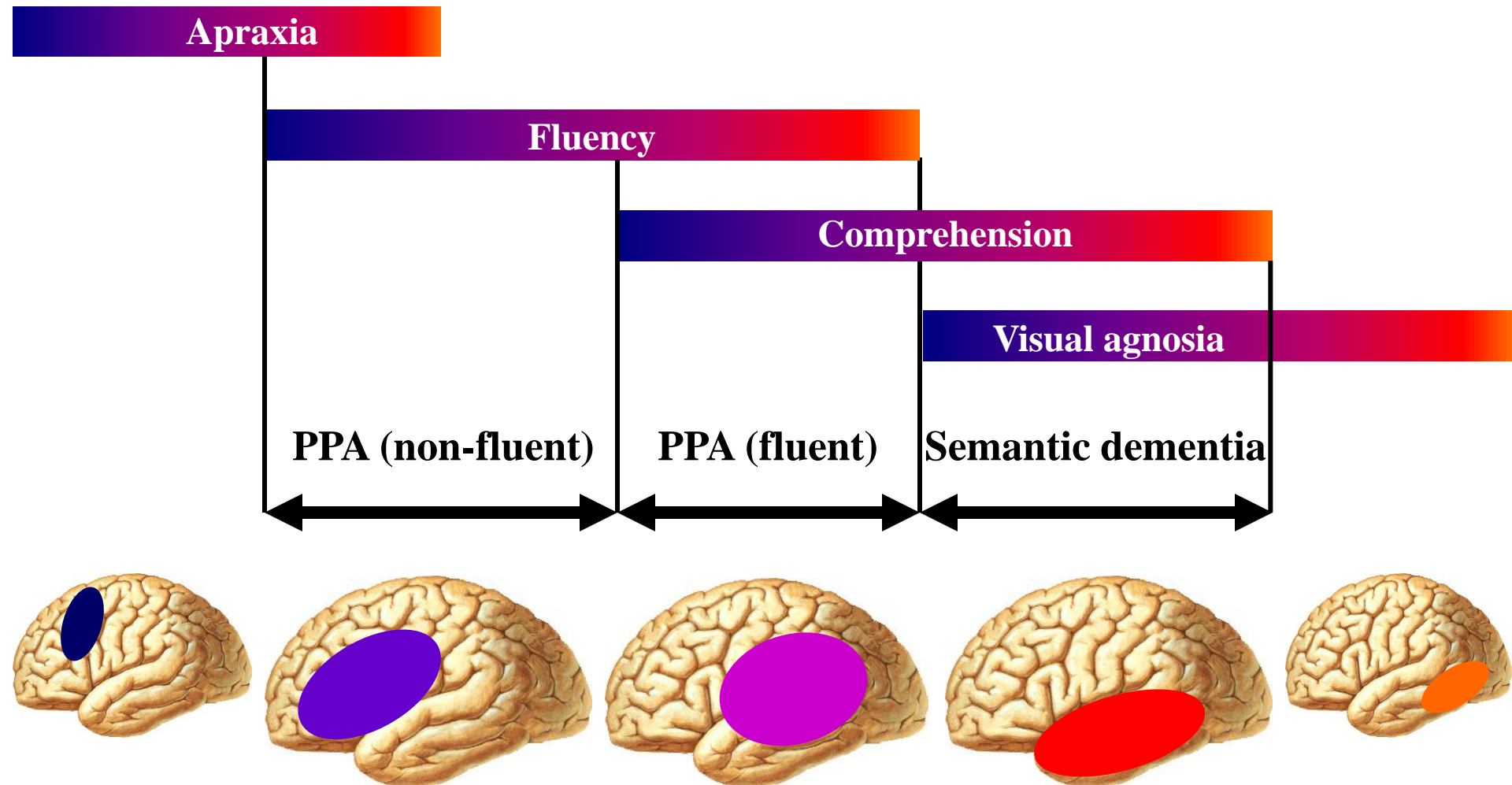
**B Dubois-B Pillon-A Slachevsky-I Litvan**

**Hôpital de la Salpêtrière, 75013 Paris, France**

**Six tests that may be used at bedside with less than 10 minutes total duration**

- 1. Similarities (orange & banana, table & chair, tulip-rose-daisy)**
- 2. Lexical fluency- “s” words in 60 sec**
- 3. Motor programming- Luria 3-step, fist-edge-palm**
- 4. Conflicting instructions- tap 2 when I tap 1...**
- 5. Go-no-go: tap 1 to 1, do not tap to 2 taps**
- 6. Prehension behavior (environmental autonomy)**

# The spectrum of language variants in FTD

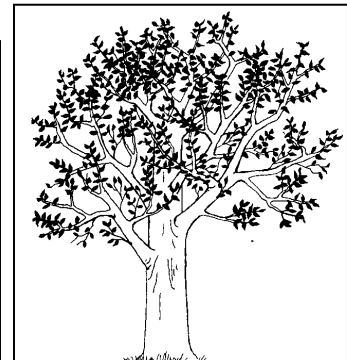
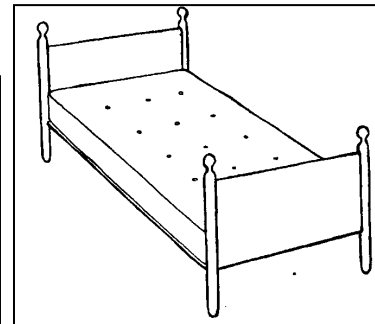
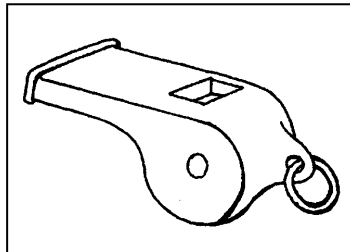
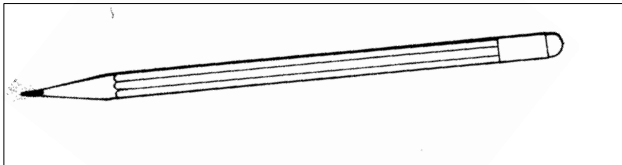


# Tests of language function

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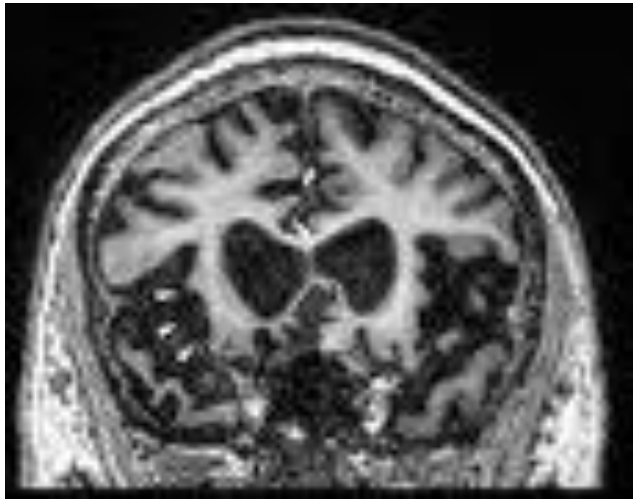
- **Semantic vs. phonemic fluency**
  - Animals vs. words that start with “S”
  - Temporal vs frontal lobe involvement
- **Surface vs. deep dyslexia**
  - Non-phonemic words that require semantics
    - Yacht, colonel, cello, island...
  - Nonsense words requiring pure phonemics
    - Gofagul, modripal, sokumbia...

- **Naming tests**

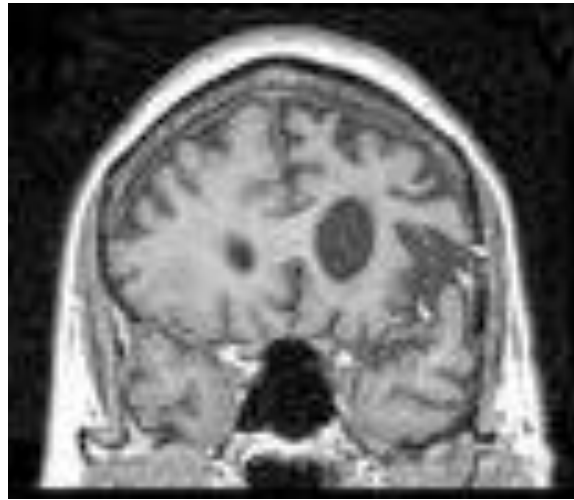


# Imaging in FTD

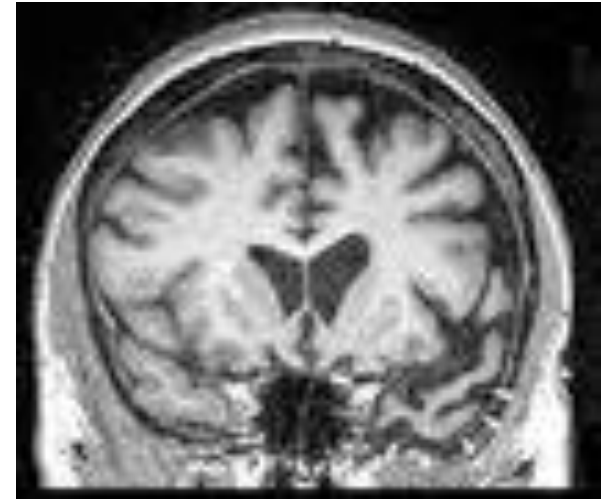
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**Behavioral  
Variant FTD**



**Primary  
Progressive  
Aphasia**

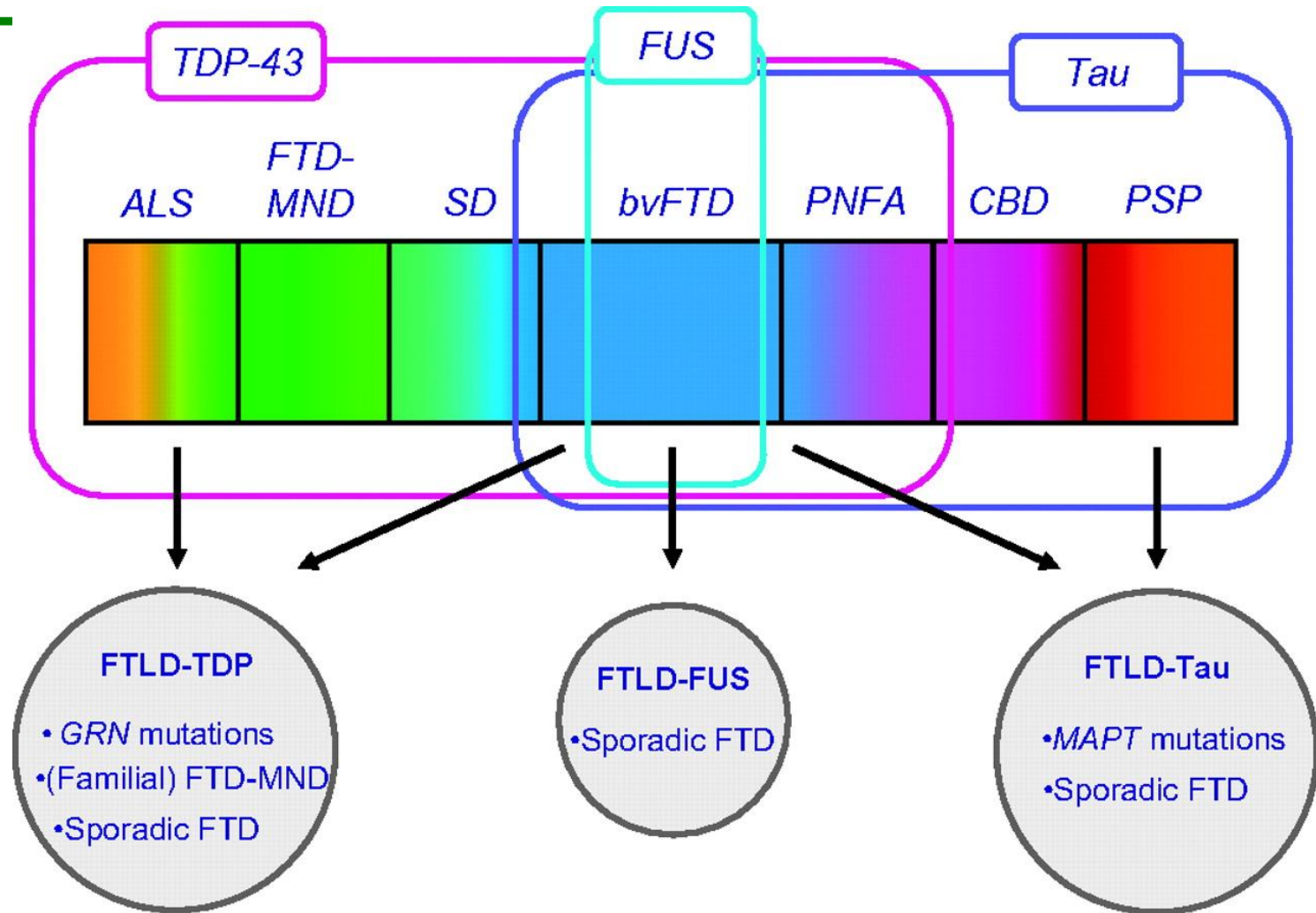


**Semantic  
Dementia**

**\*\*\*Note the distinct patterns of cortical and subcortical atrophy that distinguish subtypes of FTD\*\*\***

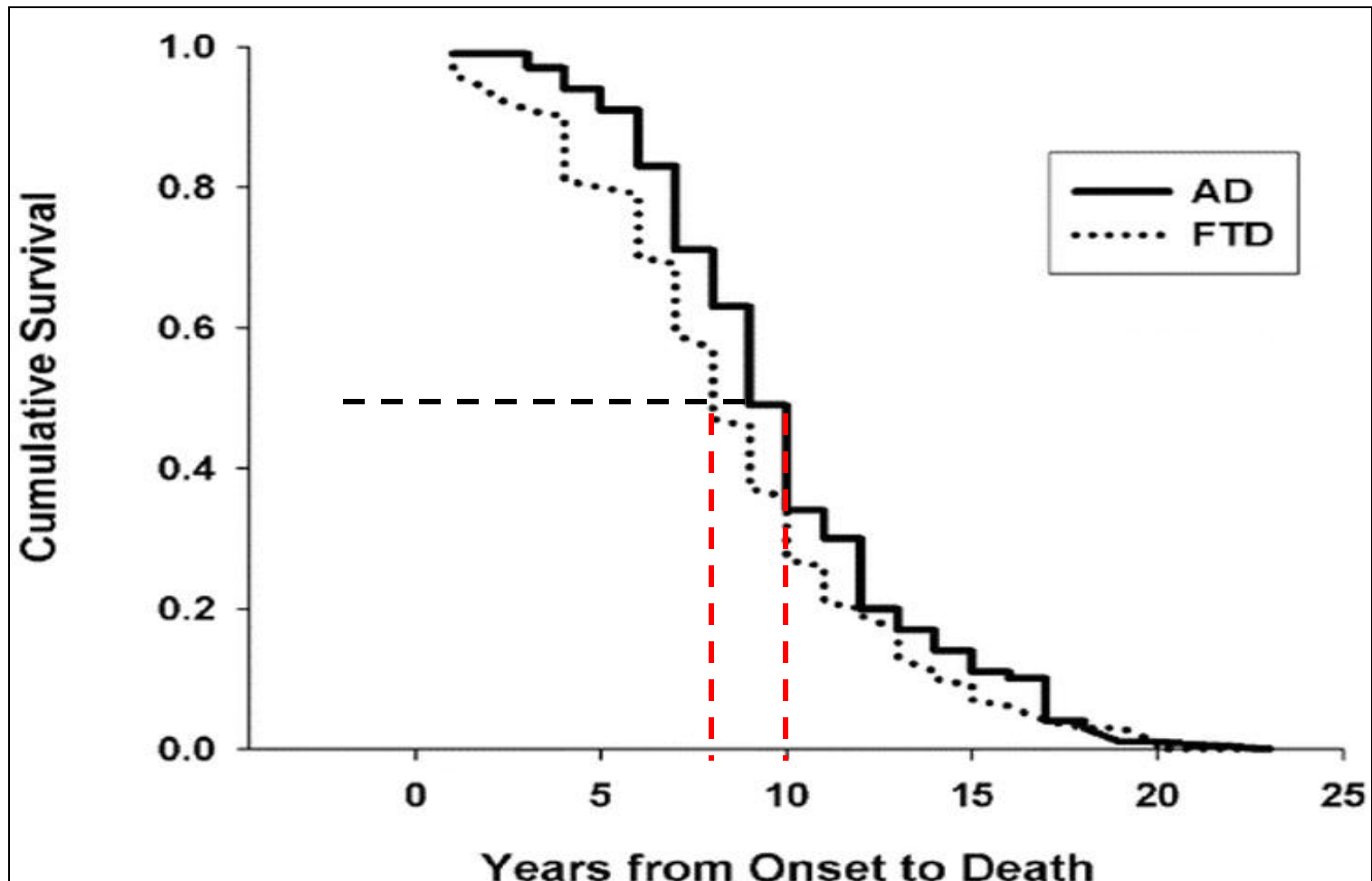


# Clinical, genetic and pathological spectrum of frontotemporal lobar degeneration.



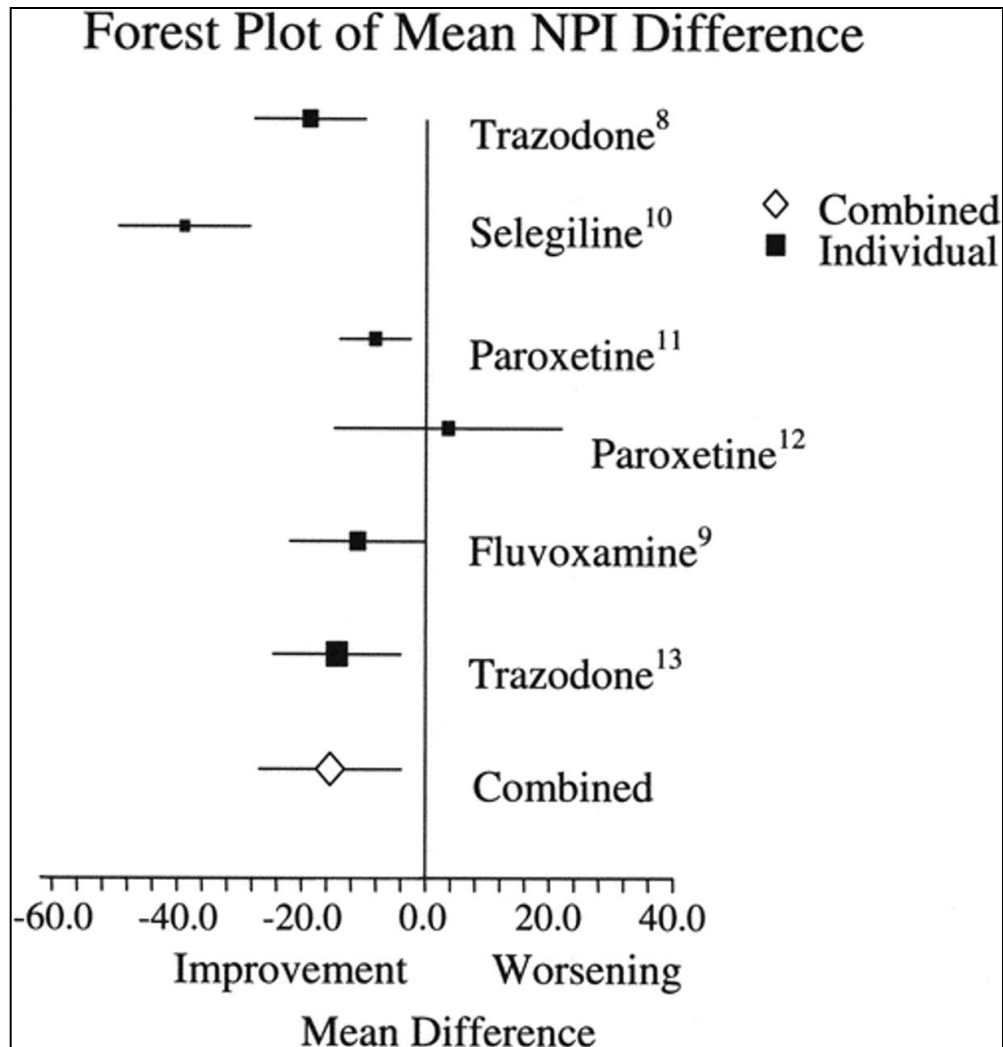


# Survival may be shorter in FTD



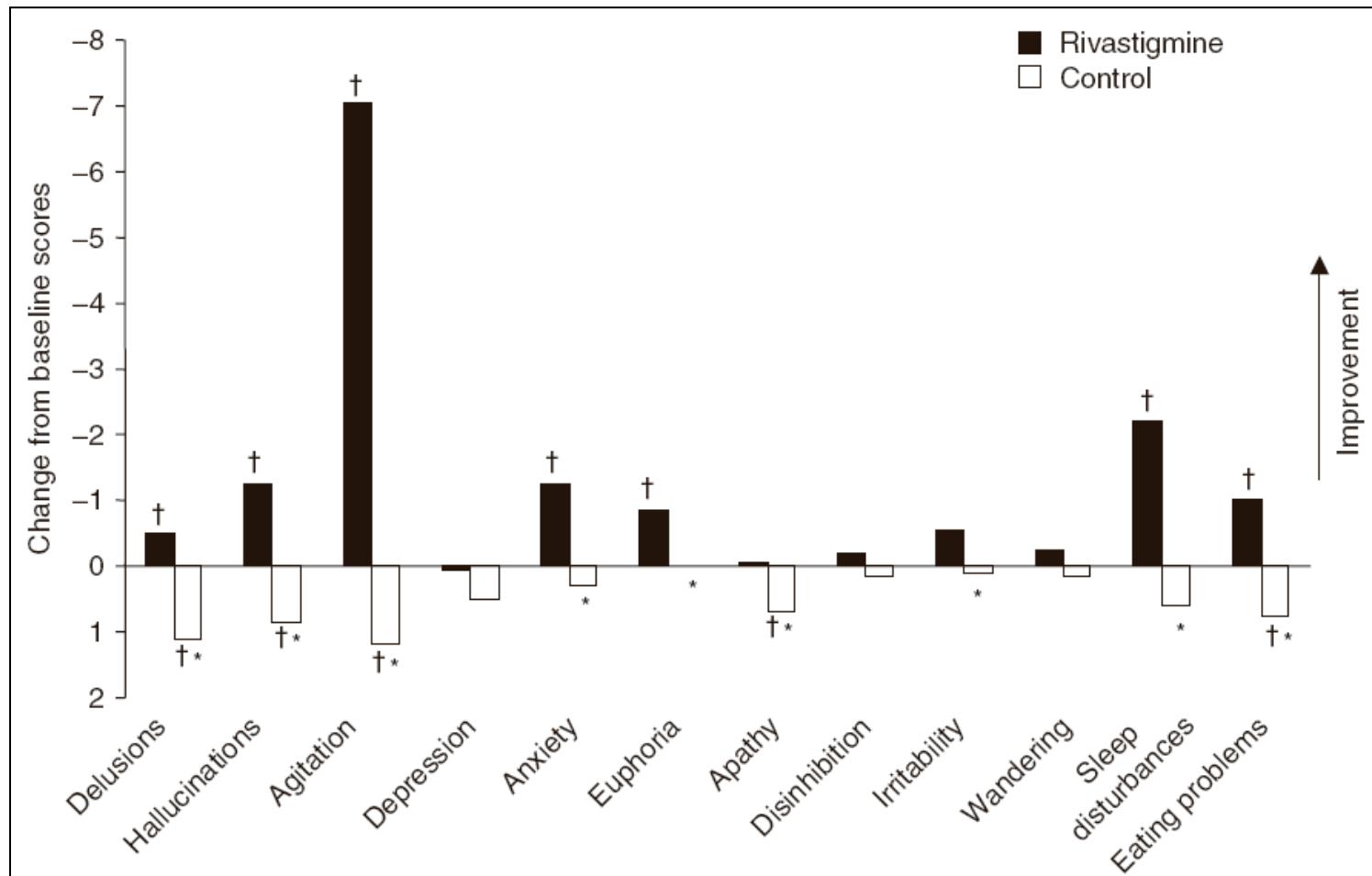
Rascovsky et al, Neurology 2005;65:397-403

# Antidepressants in FTD



Huey et al, Neurology  
2006;66:17-22

# AChEI treat behavioral and psychiatric Sx in FTD



Moretti et al, Drugs Aging 2004;21:931-937

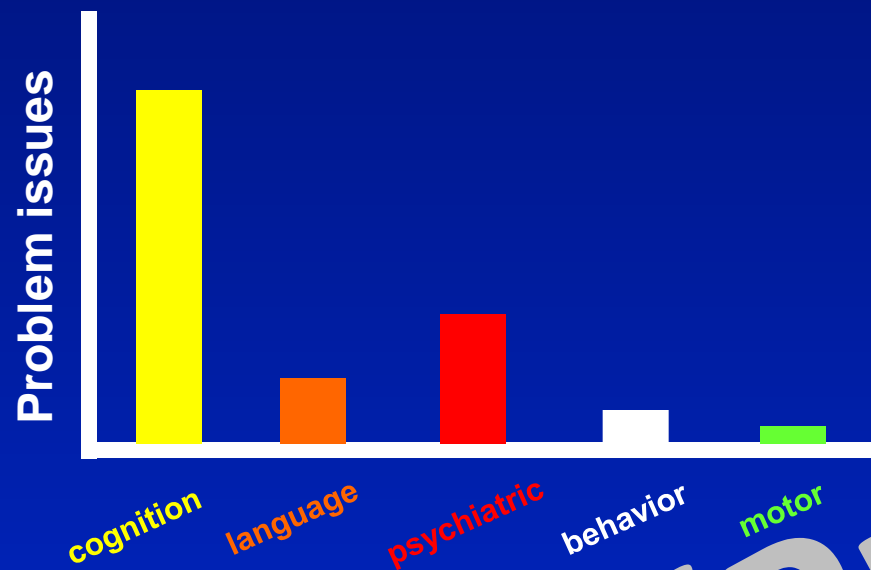
# Watching the Progression disease...

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- **Mild stages can be very discrete**
  - Harder to recognize
  - Easier to classify if recognized
- **Moderate stages begin to blend in terms of signs and symptoms**
- **Severe stages of disease all look exactly alike!**

**\*\*\*Take home point:** Diagnosis early and treat throughout the course of disease appropriately irrespective of etiology\*\*\*

## Alzheimer's disease



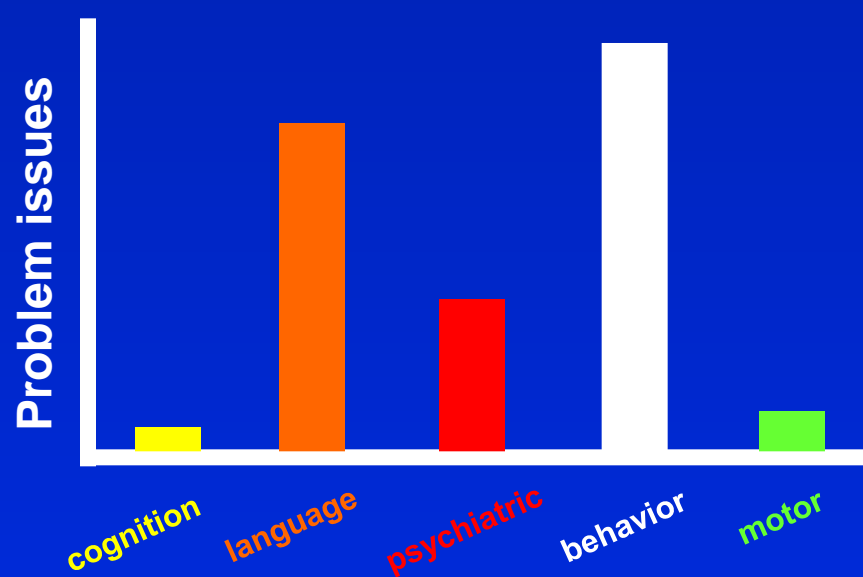
## Vascular dementia



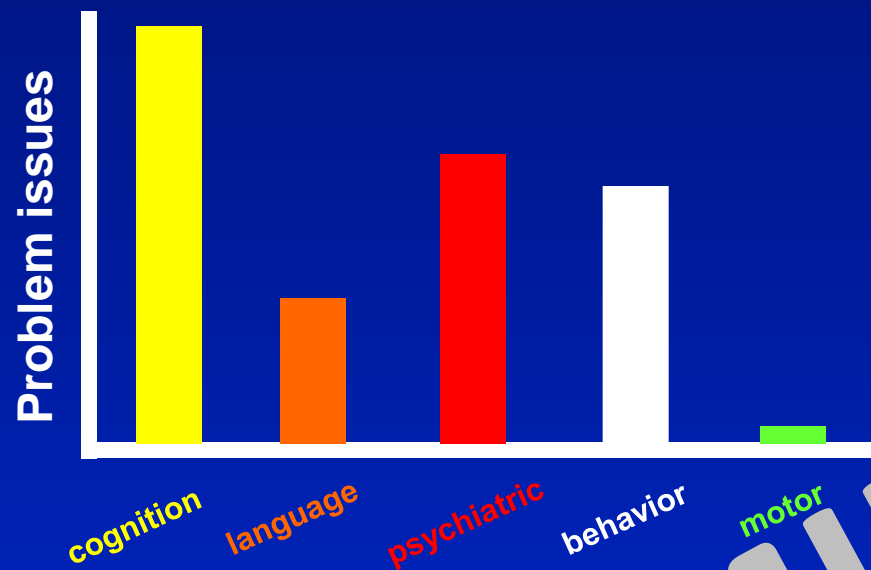
## Dementia with Lewy bodies



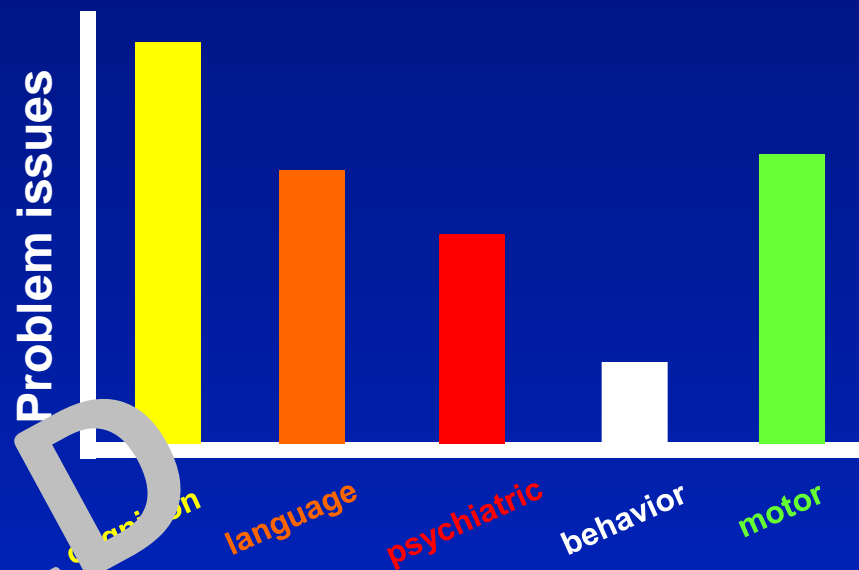
## Frontotemporal dementia



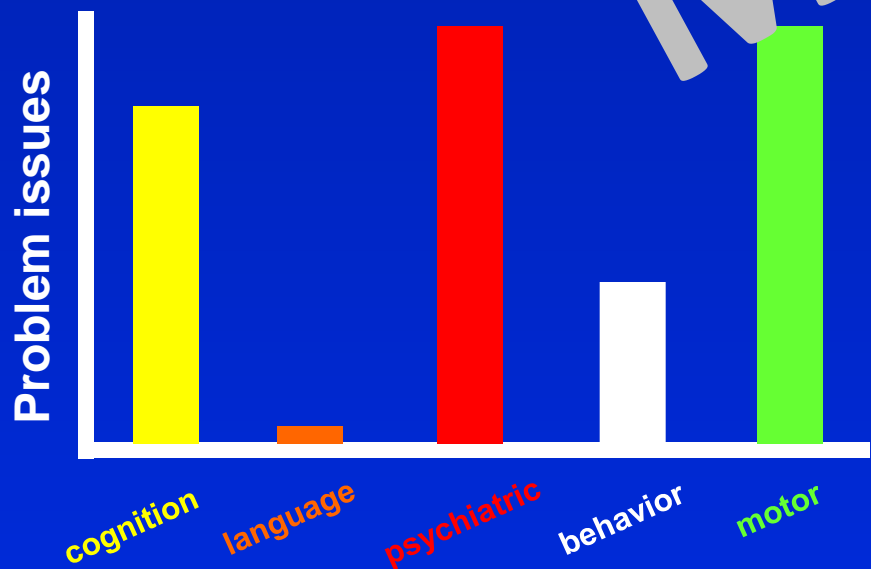
## Alzheimer's disease



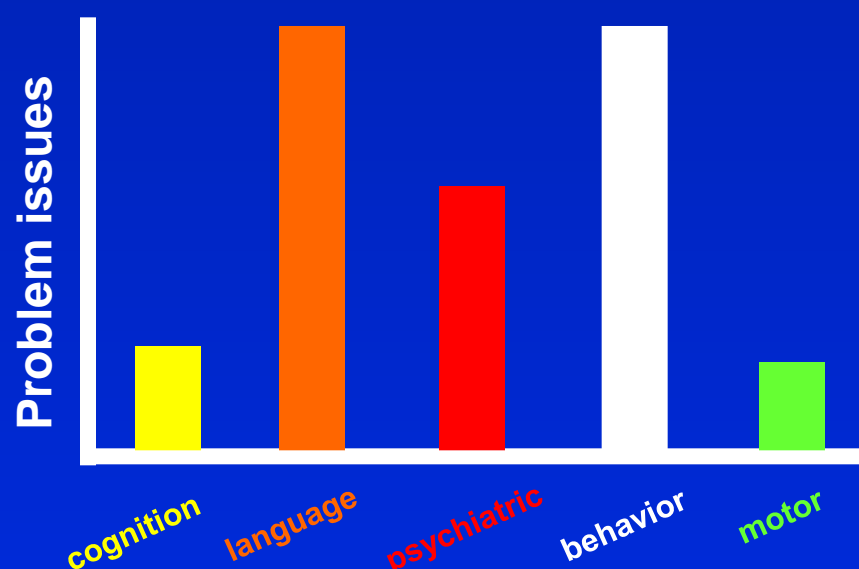
## Vascular dementia



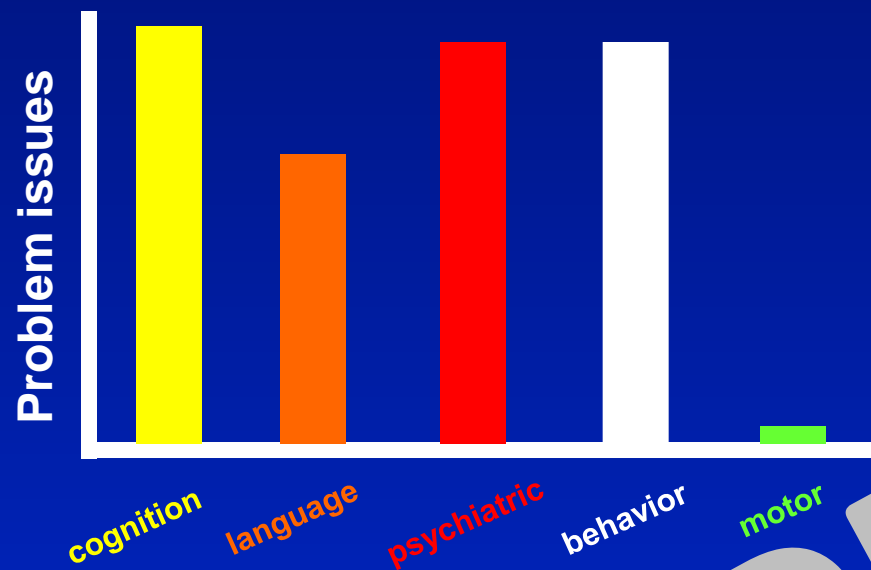
## Dementia with Lewy bodies



## Frontotemporal dementia



## Alzheimer's disease



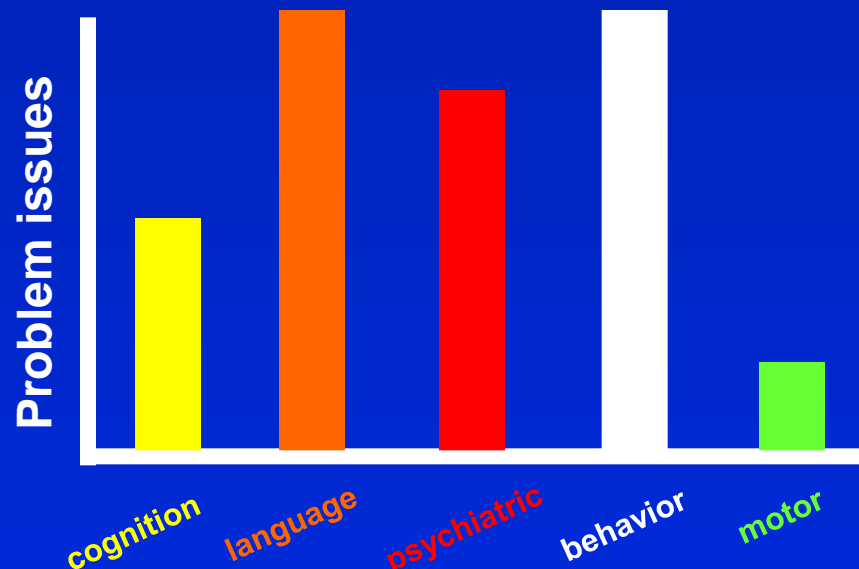
## Vascular dementia



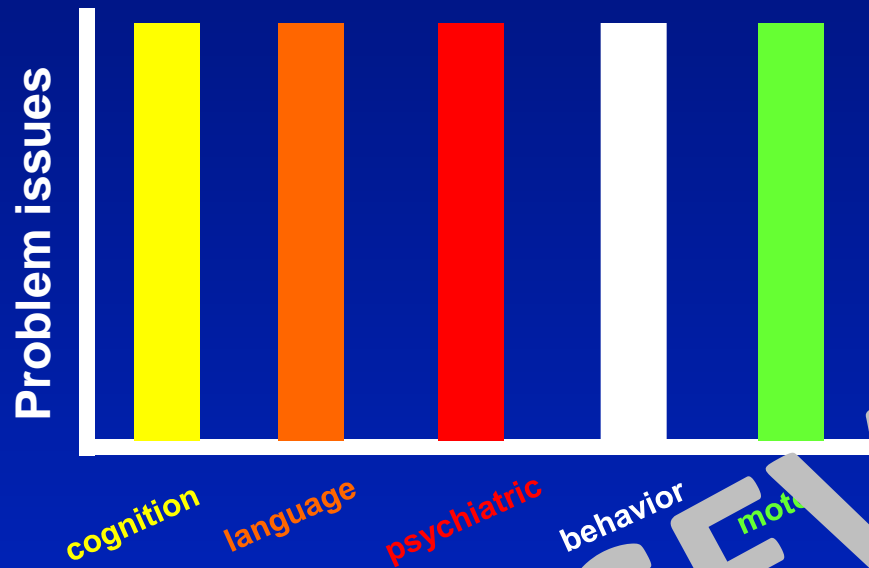
## Dementia with Lewy bodies



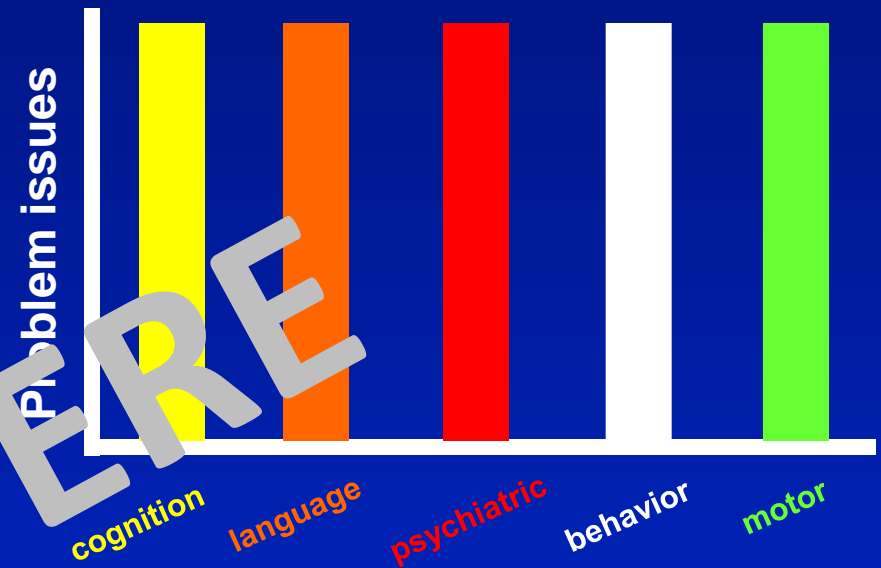
## Frontotemporal dementia



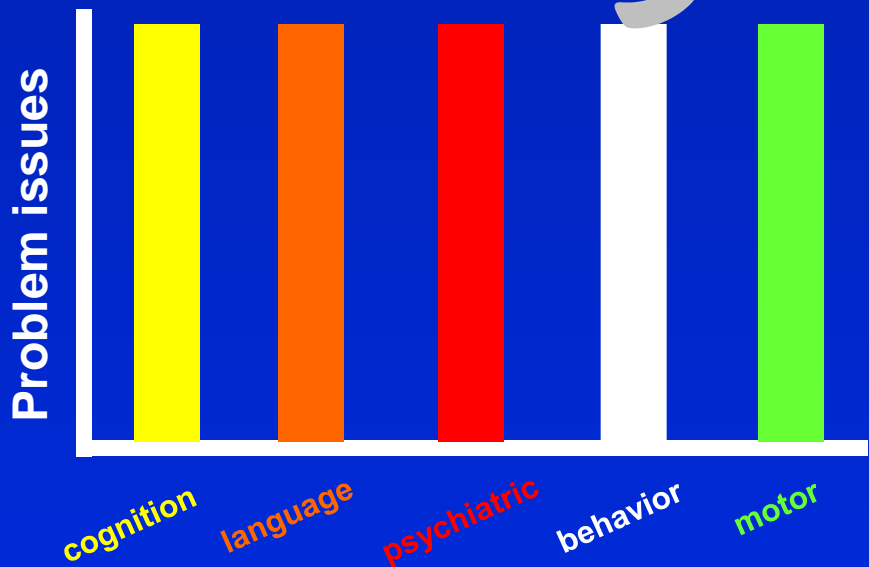
## Alzheimer's disease



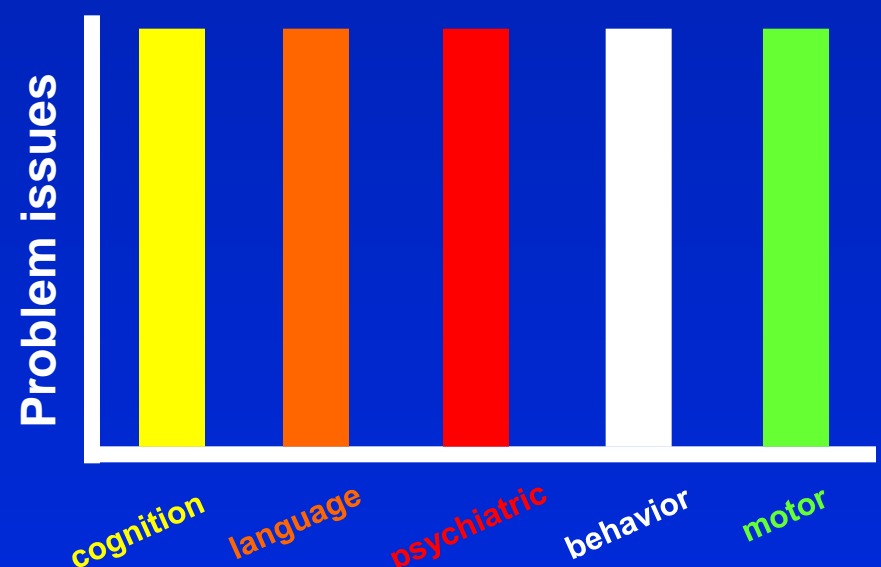
## Vascular dementia



## Dementia with Lewy bodies



## Frontotemporal dementia





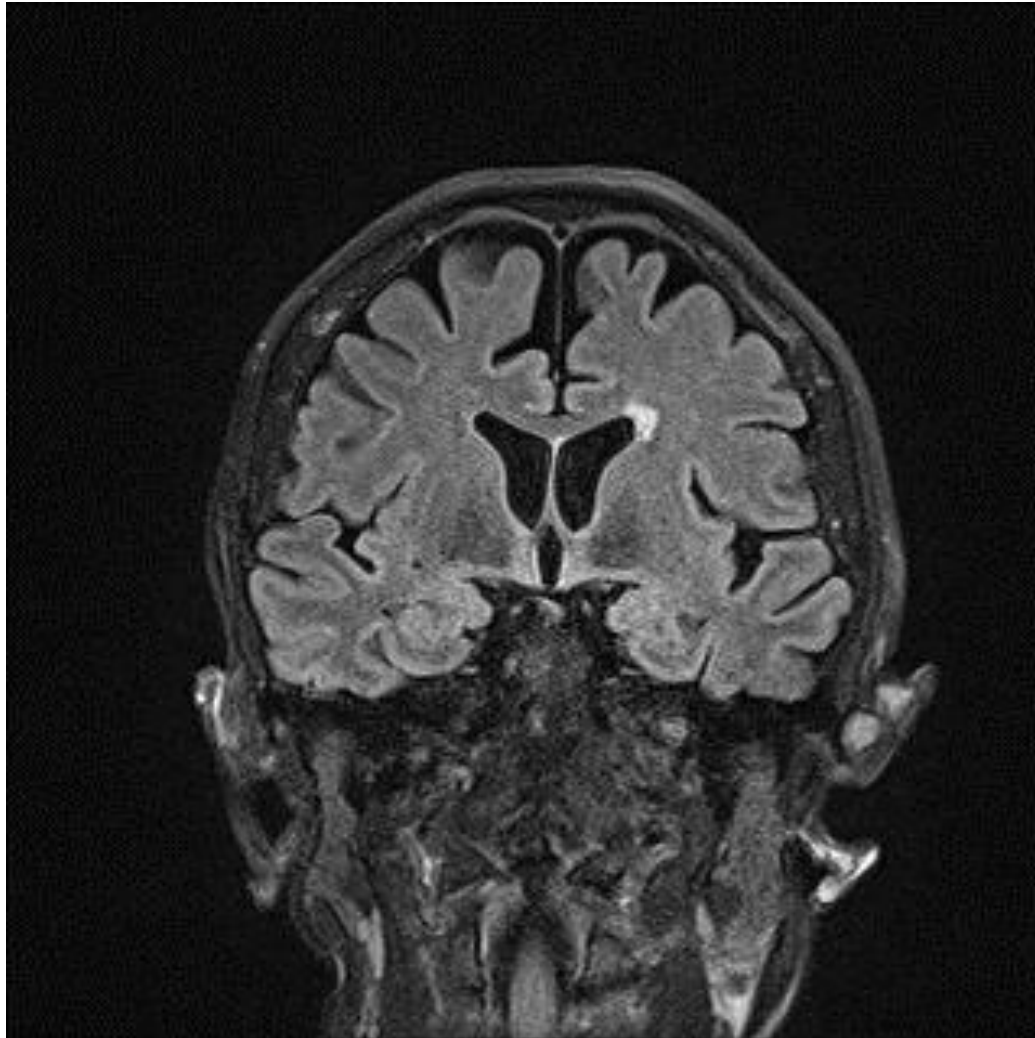
# Case #1: Clinical presentation

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- **74 yo man with two year progressive history of “memory loss”**
- **Symptoms seem to come and go and he has been hospitalized 3 times in the last two years for TIA**
- **He has frequent falls with shuffling gait, but no tremor**
- **Sleep is disrupted by “nightmares”**
- **PMHx: HTN, BPH, HLD**

# Case #1: Imaging

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# Case #1: Discussion

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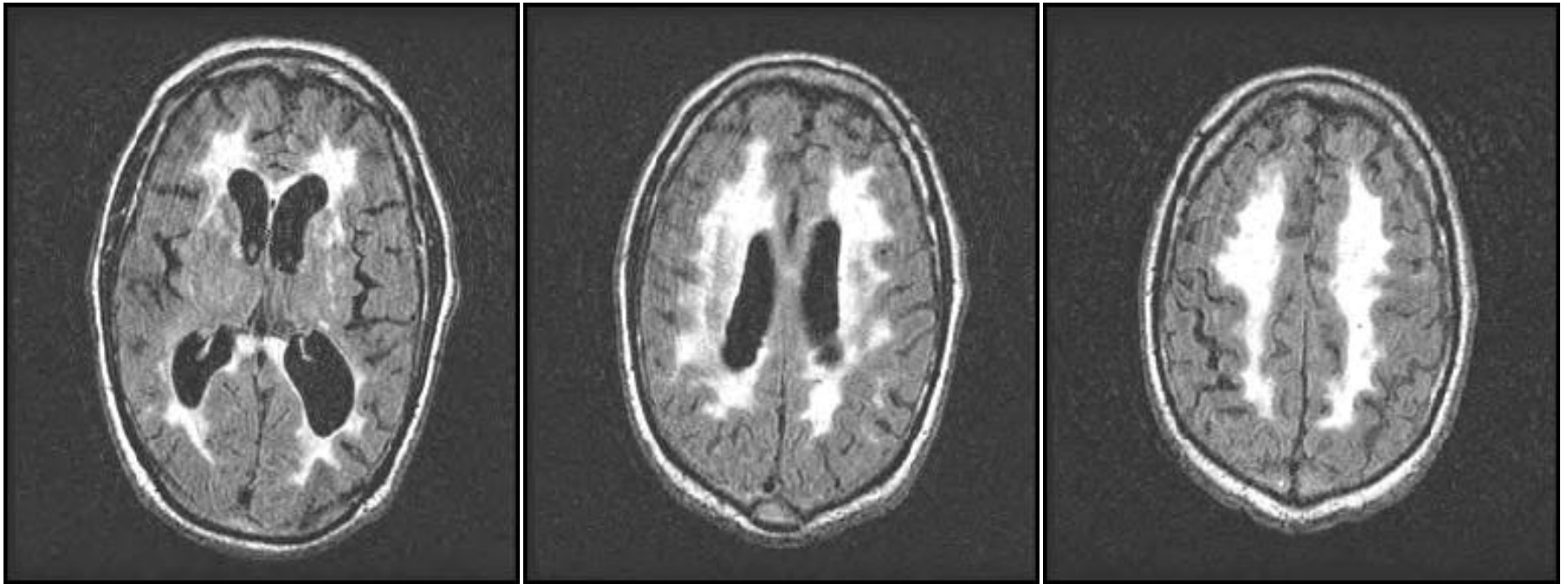
# Case #2: Clinical presentation

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- **87 yo woman with two year progressive history of “memory loss”**
- **Symptoms seem to come and go and she has been hospitalized 3 times in the last two years for TIA**
- **Gait is unsteady, but no tremor**
- **PMHx: HTN, HLD, DM, smoking**
- **Right sided Babinski and mild weakness noted on exam**

# Case #2: Imaging

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# Case #2: Discussion

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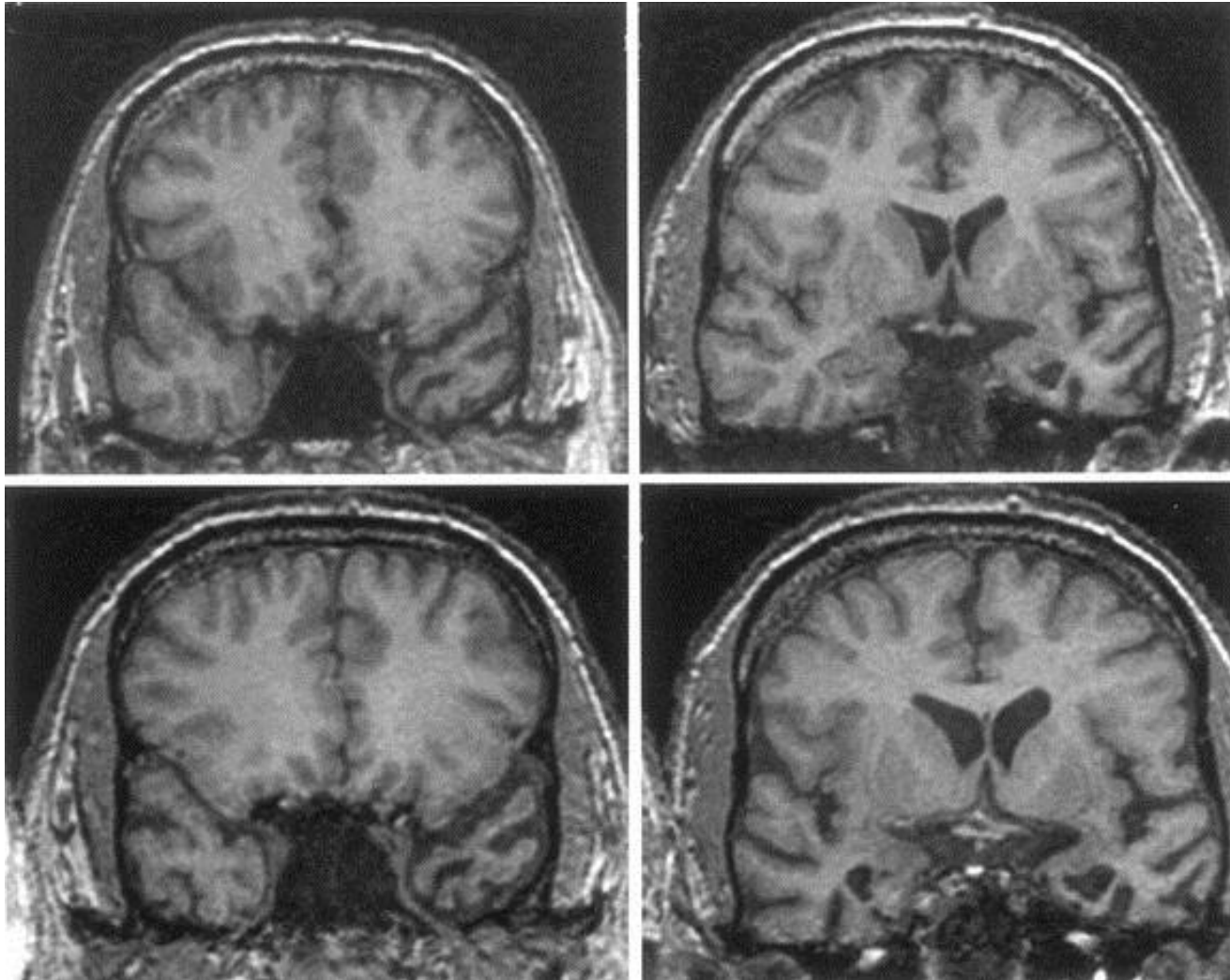
# Case #3: Clinical presentation

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- 57 yo man with two year progressive history of “memory loss”
- At times he seems to not understand what others are saying to him
- Gait is unsteady, and he has lost sig weight, but no tremor
- He is choking on liquids and has a tendency to fill his mouth with food, but forgets to swallow
- PMHx: HTN, BPH, excema
- Does not know what a “chin” is on exam

# Case #3: Imaging

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# Case #3: Discussion

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# More to come...

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