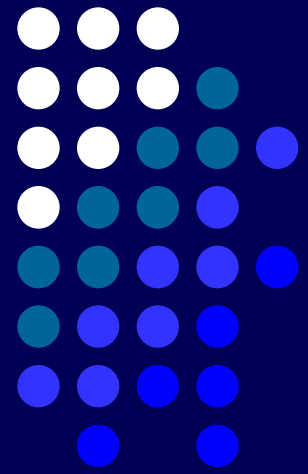
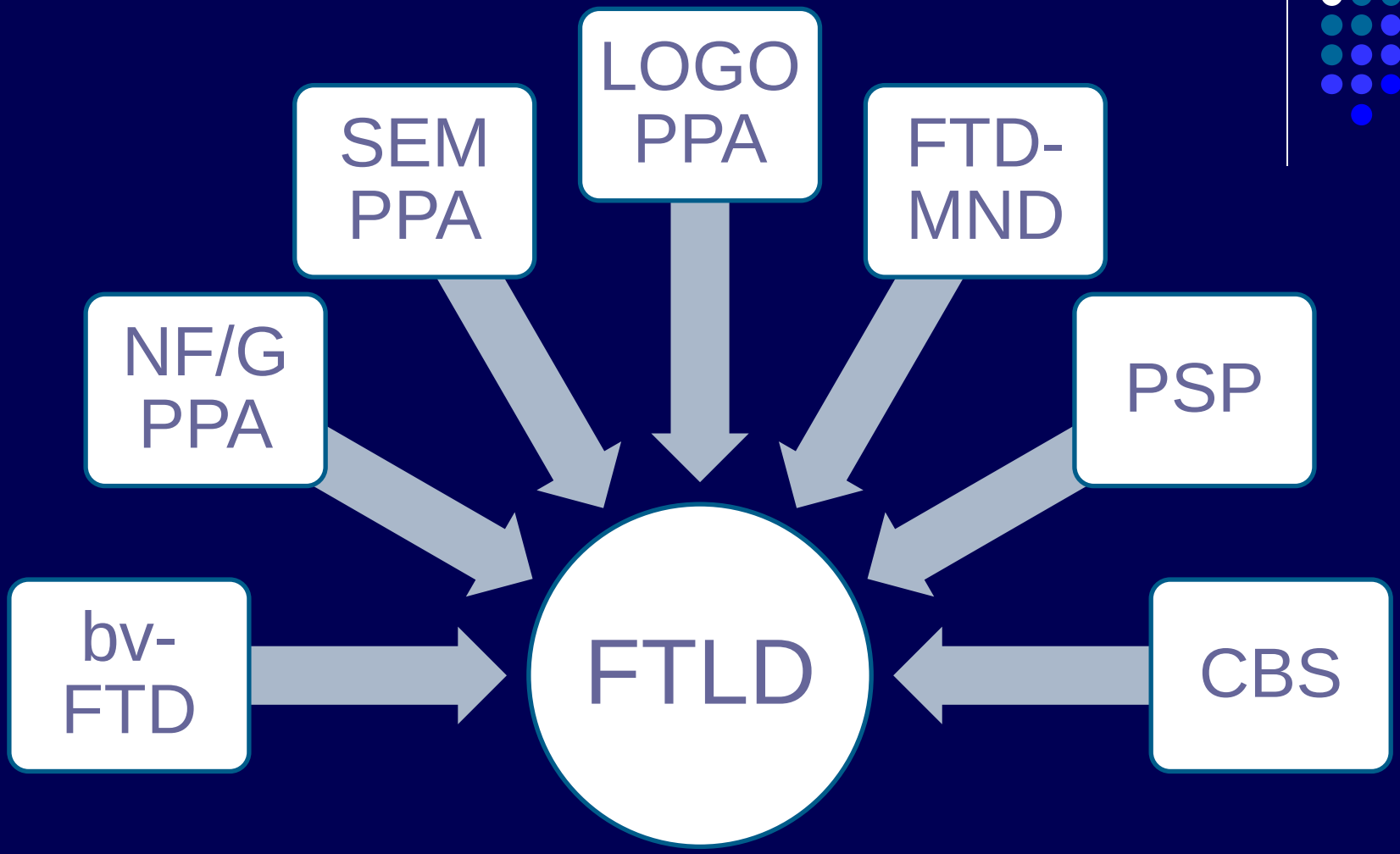
Frontotemporal degeneration (FTD)

Edward (Ted) Huey, M.D.
Herbert Irving Assistant Professor of Psychiatry and Neurology
Taub Institute for Research on Alzheimer's Disease and the Aging Brain
Columbia University



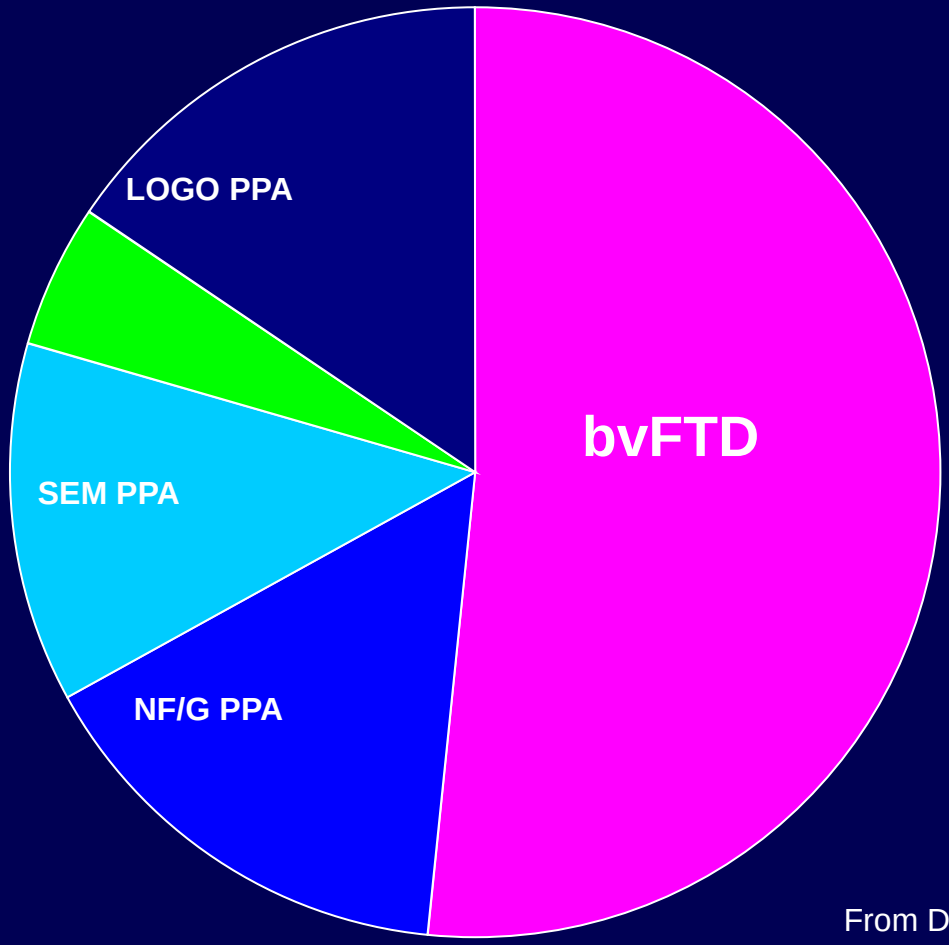
Overview

- Case reports
- Normal function of affected brain areas
- FTD spectrum disorders
- Differential diagnosis
- Treatment
- Future directions


LOGO PPA
SEM PPA
FTD-MND
NF/G PPA
PSP
bv-FTD
FTLD
CBS

Cognitive syndromes of frontotemporal degeneration*

AMNESTIC →



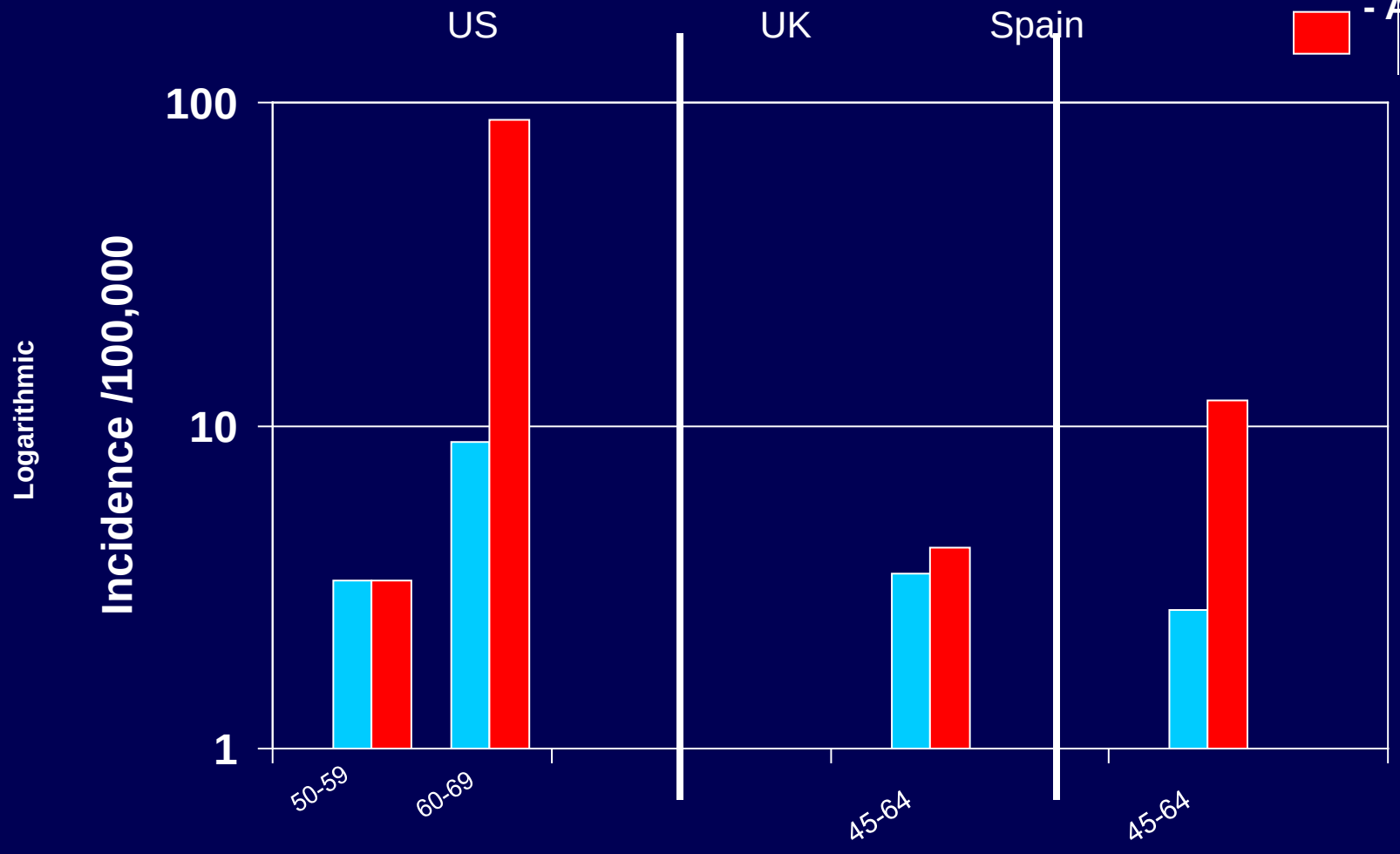
From David Knopman

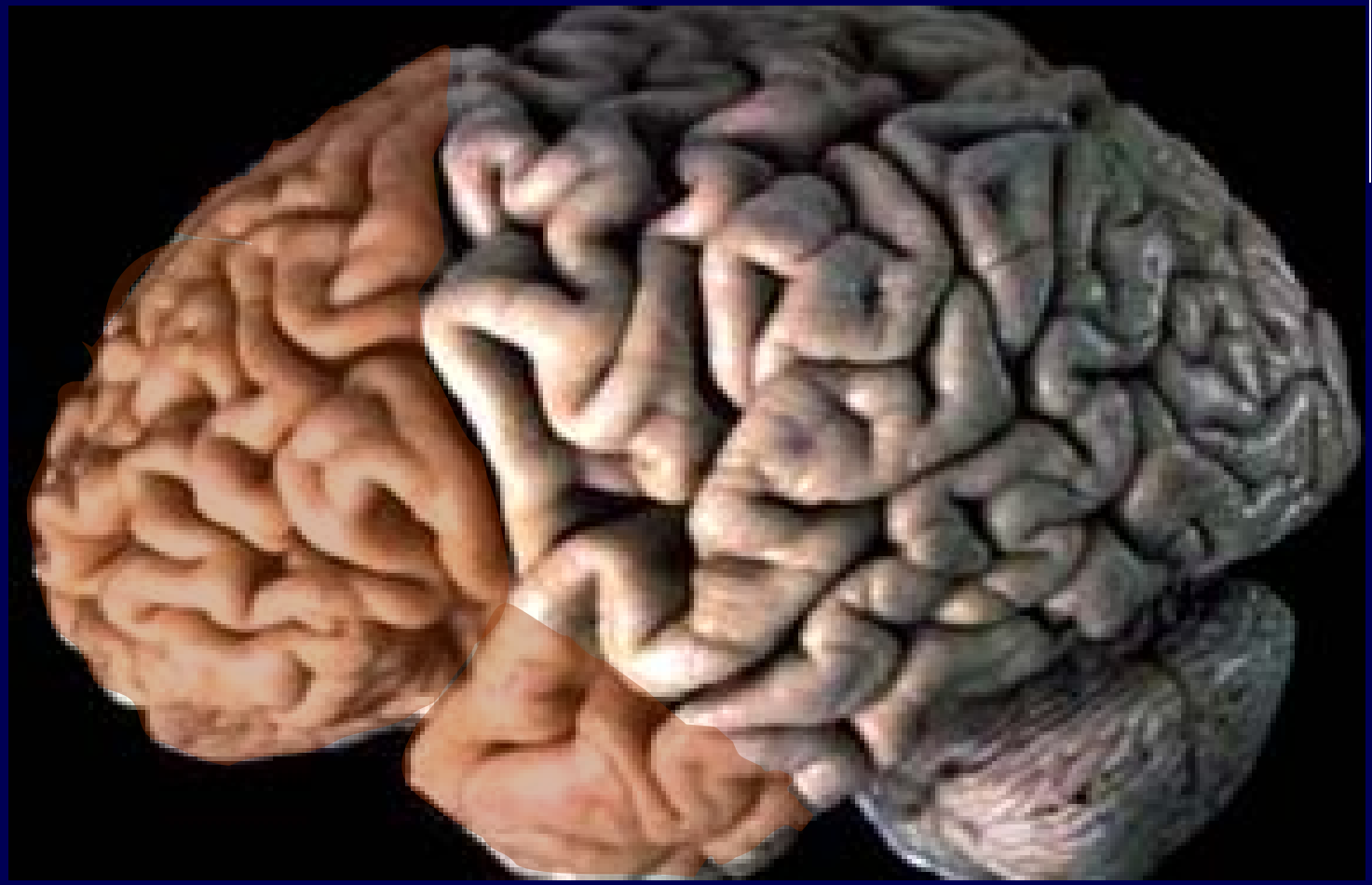
*not including ALS, PSP-like and CBD-like presentations

FTLD background

- 2nd most common cause of dementia in patients < 65 y.o.
- ~ 5-10% of all dementias

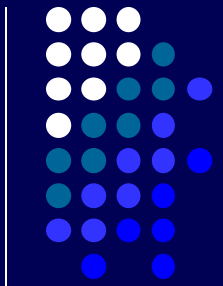
Comparison of FTLD & AD Incidence





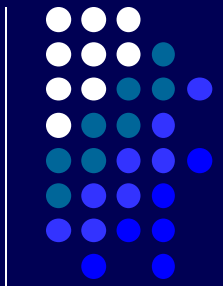
What do these brain areas do normally?

Normal functions of brain areas



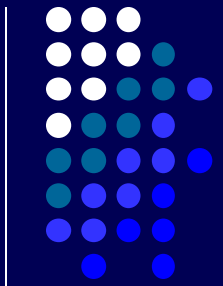
- Frontal lobe
  - Important for personality, higher cognitive functions, language production, how to perform complex activities, attention, motivation, emotional response, empathy, theory of mind
- Temporal lobe
  - Important for language comprehension, storage of knowledge about the attributes and characteristics of things

Symptoms of bv-FTD (Rascovsky et al. Brain 2011)



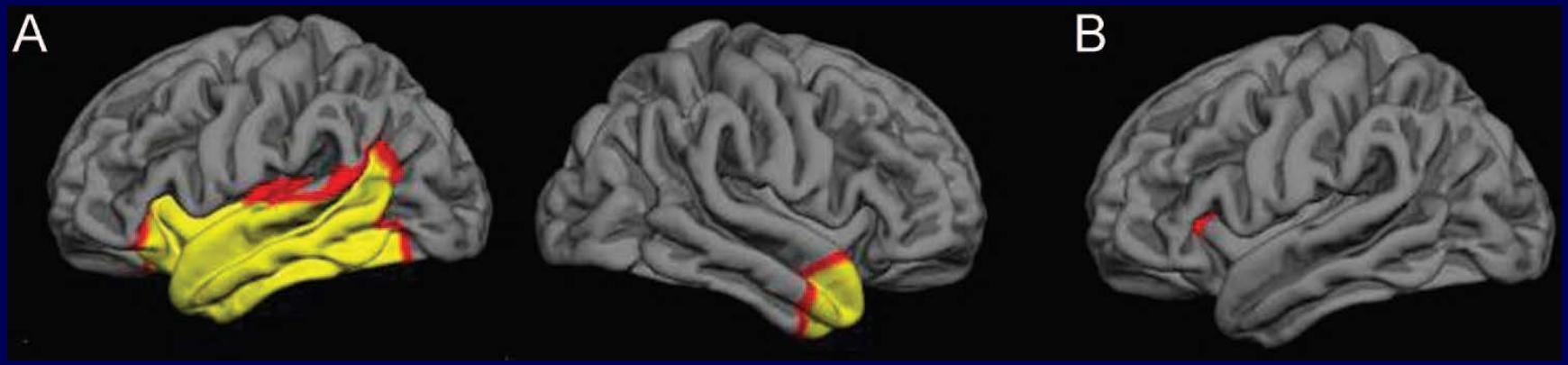
- Progressive deterioration of behavior and cognition
  - Behavioral disinhibition
  - Apathy
  - Loss of empathy
  - Perseverative or compulsive behaviors
  - Hyperorality and dietary changes
  - Neuropsychological profile c/w FTD

Primary Progressive Aphasias (language variant FTD)



- Nonfluent / agrammatic variant PPA
  - Non-fluent (halting, effortful speech), poor grammar, drop-out of words
- Semantic variant PPA
  - Fluent speech, impaired naming and comprehension
- Logopenic PPA
  - Word-finding difficulty, poor repetition, impaired “buffer” system

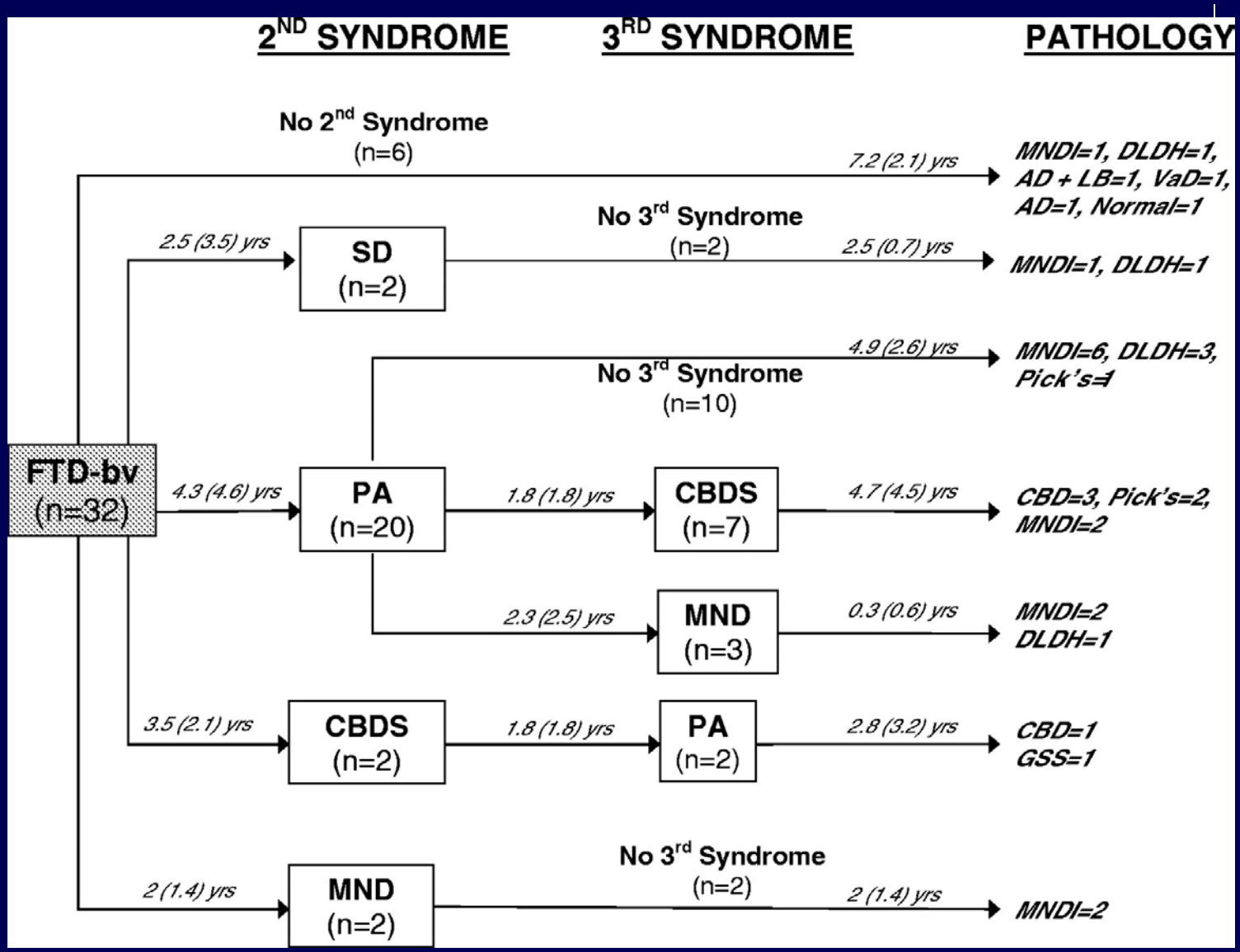
Semantic dementia and PNFA



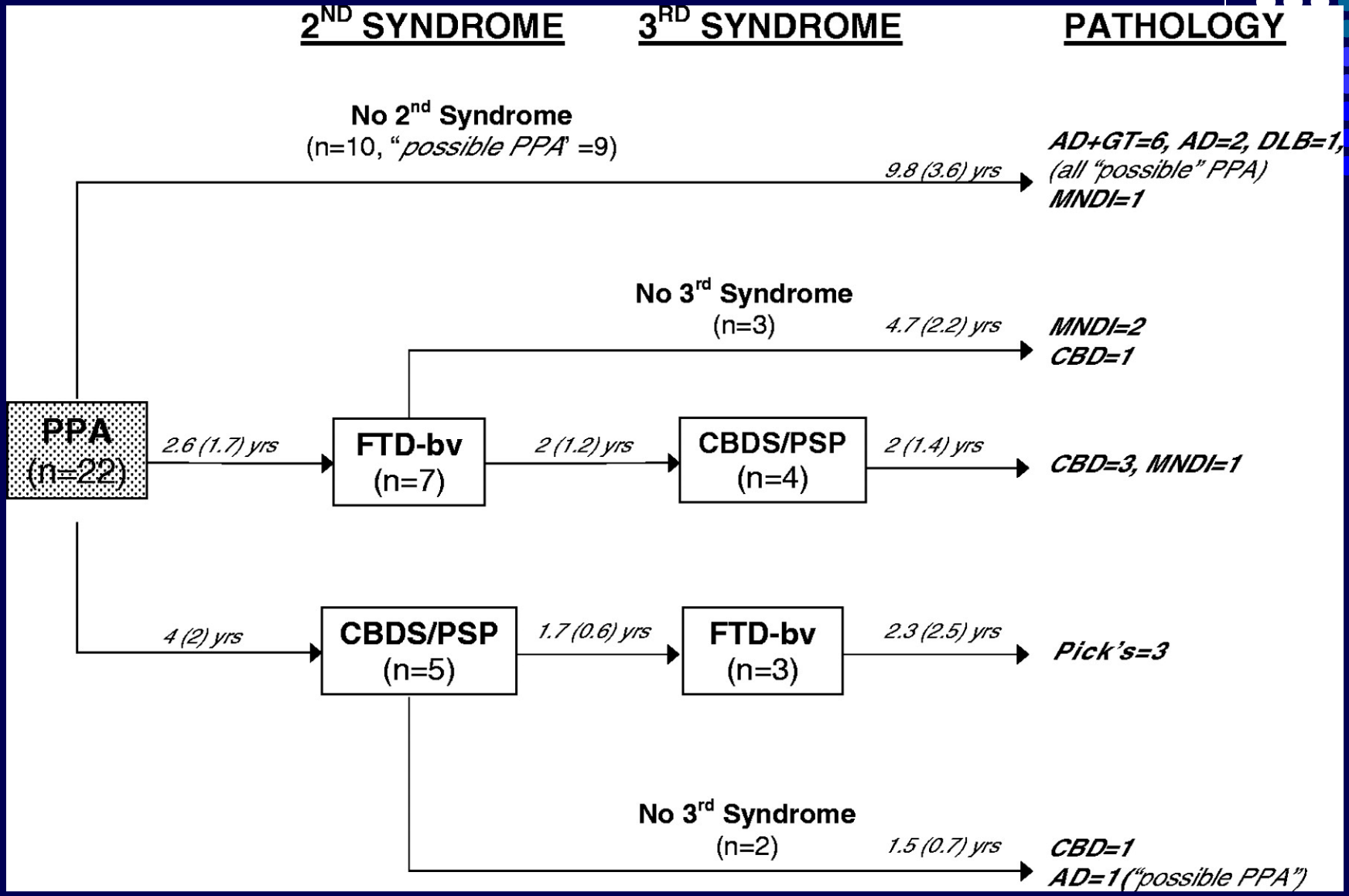
Rohrer et al, *Neurology* 2009

Related syndromes

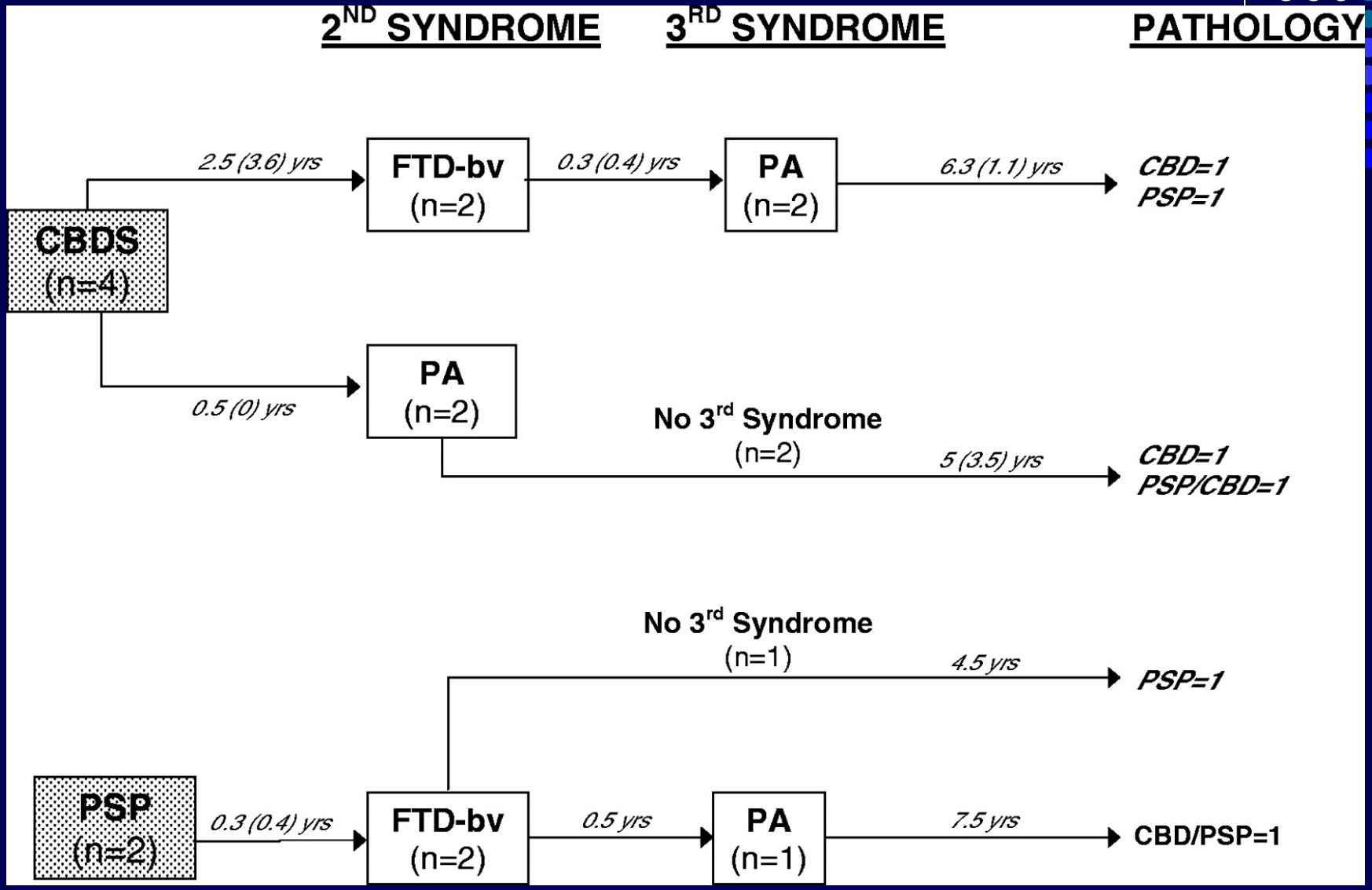
- CBS
  - Cortical:
    - asymmetric apraxia and rigidity
    - alien limb, cortical sensory loss, myoclonus
  - Basal ganglia:
    - bradykinesia
    - increased resistance to passive movement
- PSP
  - vertical gaze palsy, axial dystonia, bradykinesia, rigidity, and falls



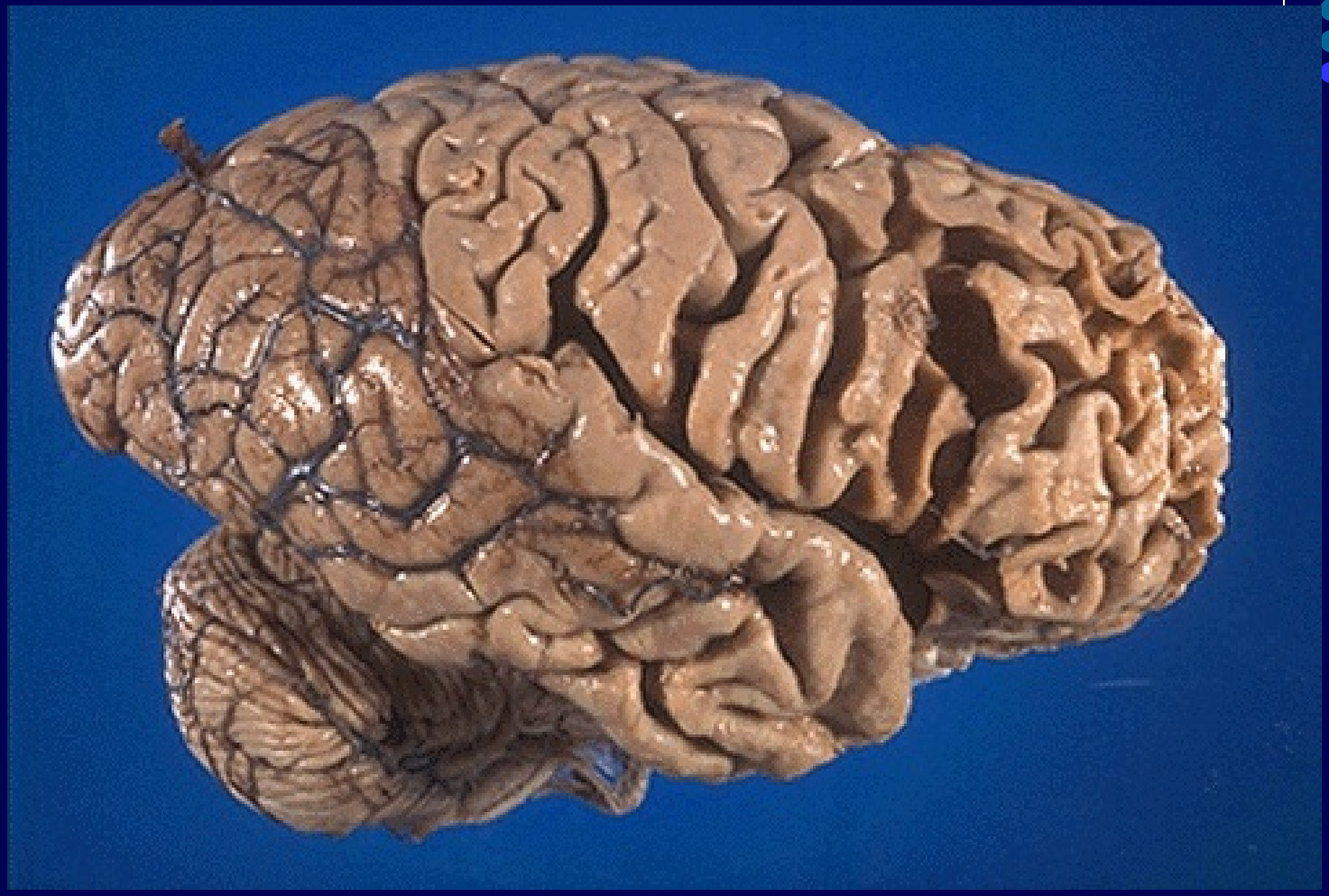
Kertesz et al., *Brain* 2005



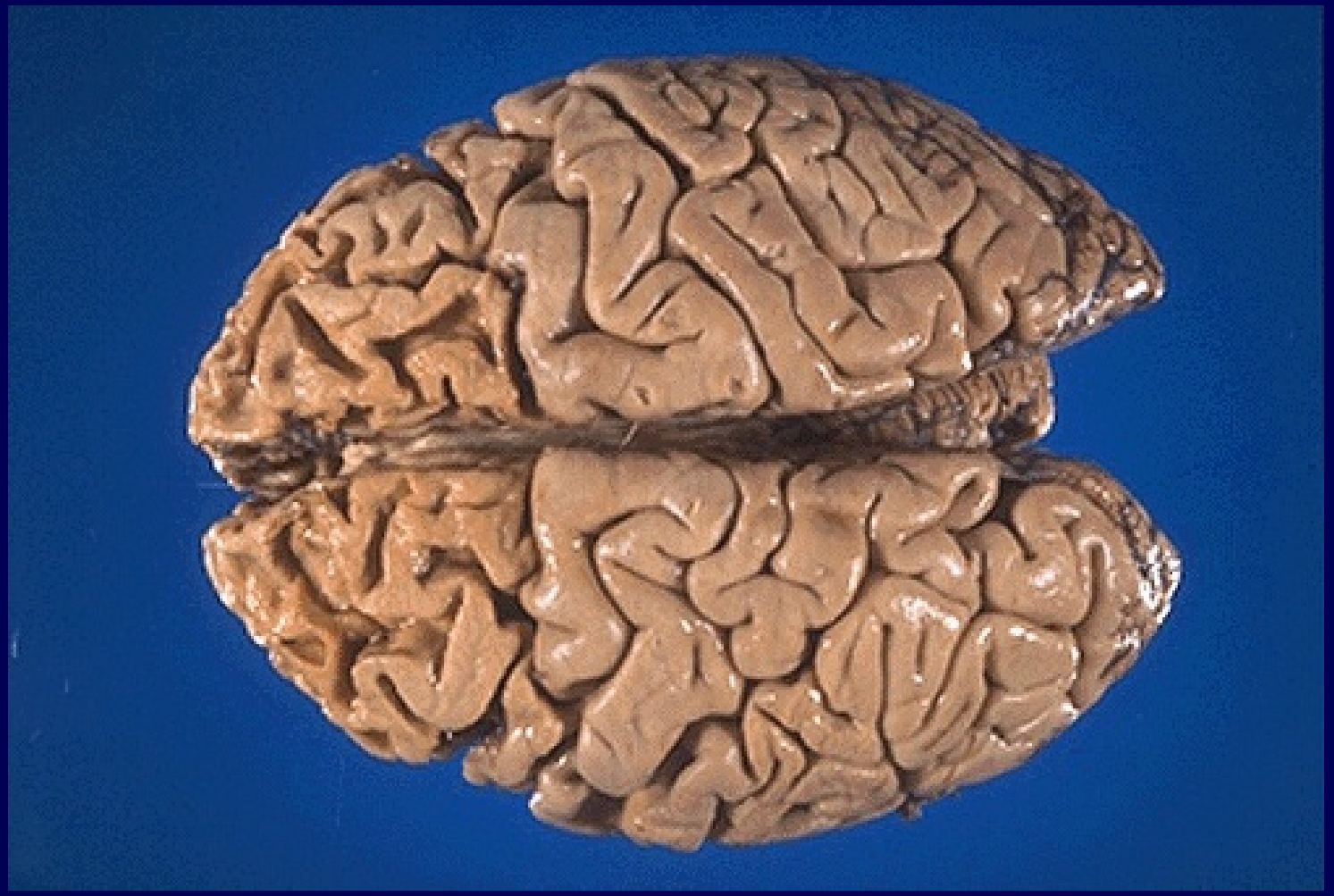
Kertesz et al., *Brain* 2005



Kertesz et al., *Brain* 2005

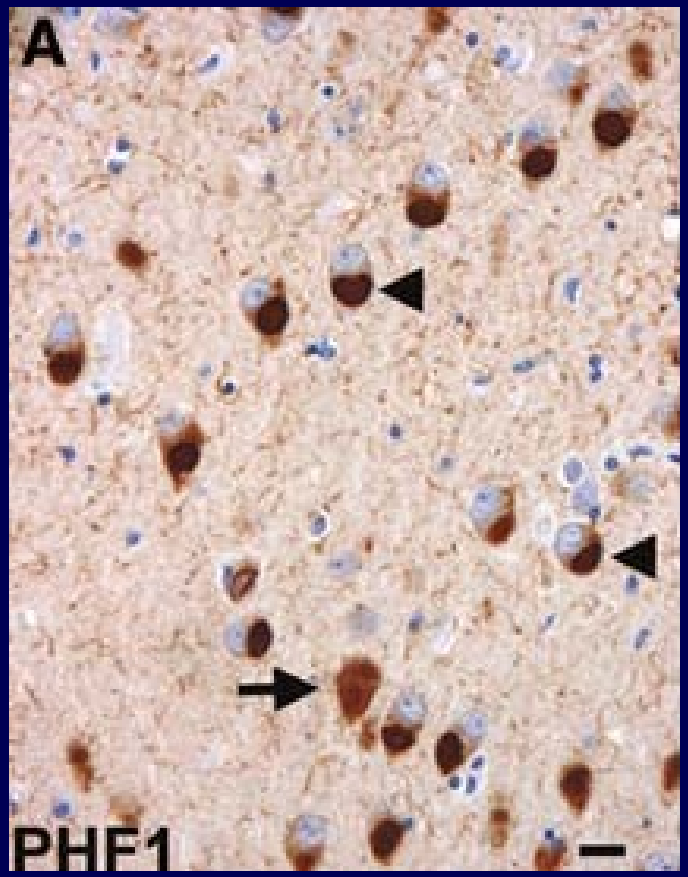


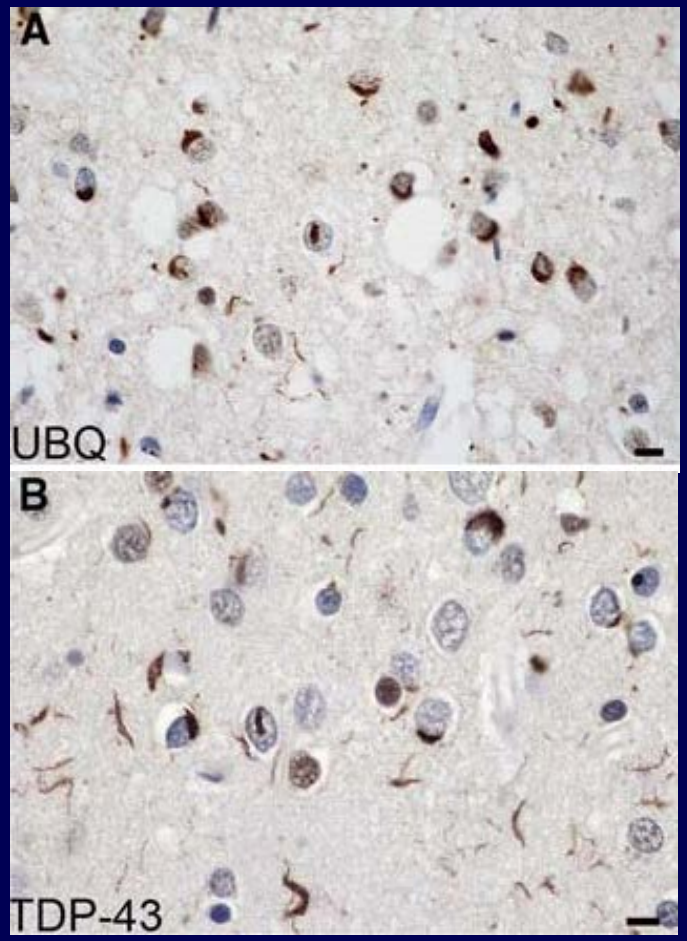
From University of Utah, Dept. of Pathology



From University of Utah, Dept. of Pathology

Three major FTLD neuropathologies

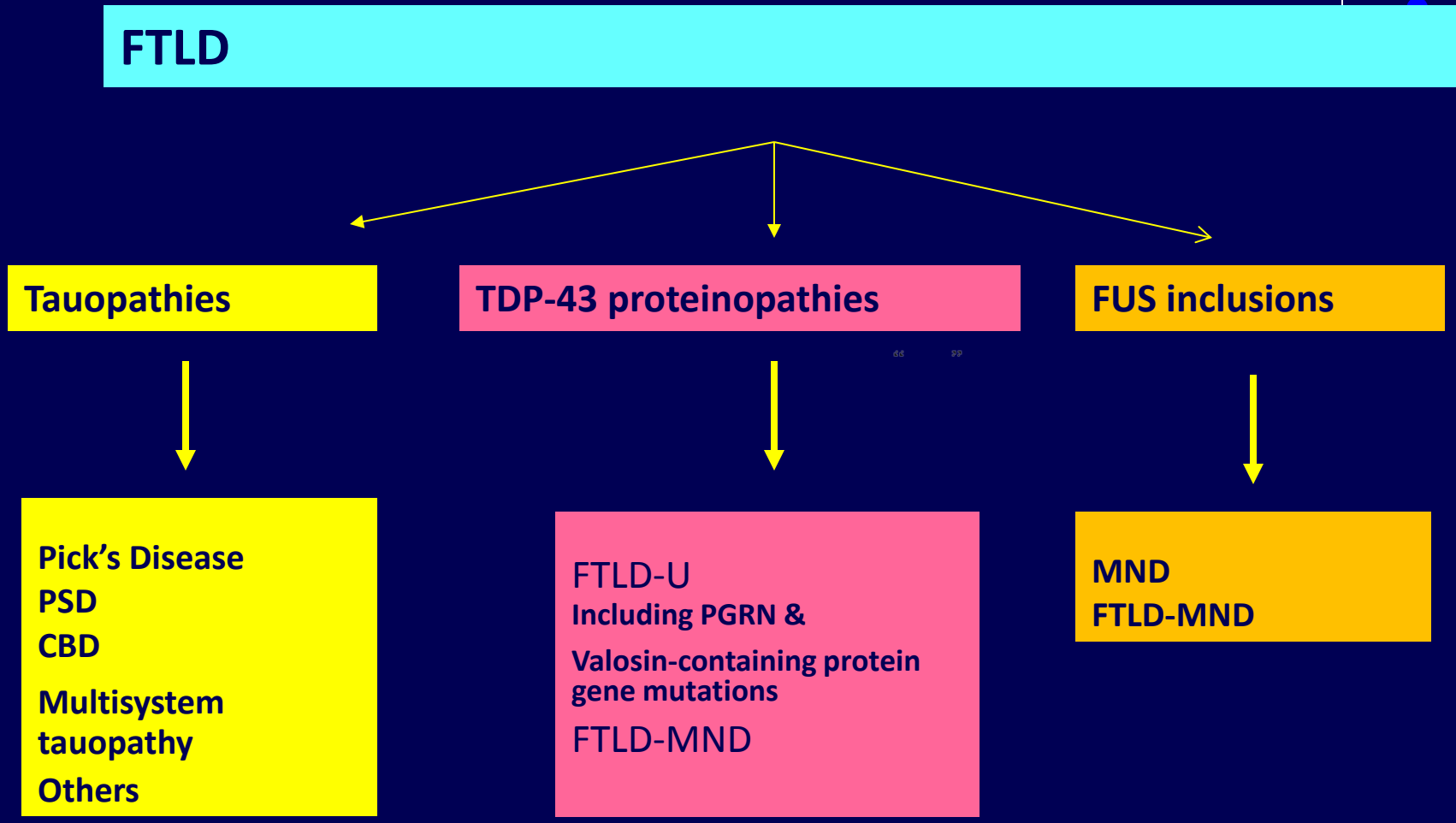




Tau pathology

Ubiquitinated inclusions (FTLD-U)

The Neuropathologic Syndomes



Adapted from: Josephs KA. Ann Neurol. 2008 Jul;64(1):4-14

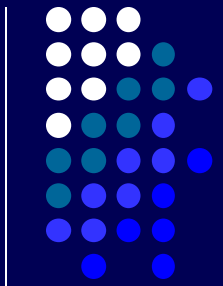
Differential diagnosis

- Patients with FTLD are often initially diagnosed with a different illness
  - Psychiatric disorder
  - Alzheimer’s disease

Distinguishing FTD from AD

- **Bv-FTD**
  - Early changes in personality, behavior, social cognition, and executive function with relatively intact memory and visuospatial ability
  - Motor symptoms
- **Nonfluent/agrammatic variant PPA**
  - Relatively isolated to expressive aphasia
  - Aphasia and not word-finding difficulty
- **Semantic variant primary progressive aphasia**
  - Episodic memory relatively intact
  - Loss of semantic representation and not word-finding difficulty
  - Frontal behavioral syndrome

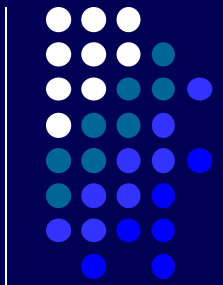
Distinguishing FTLD from a psychiatric disorder



- Cognitive dysfunction, especially executive dysfunction
- Progressive course
- Motor symptoms
- Family history
- New onset of psychiatric disorder
- Distress and deficits in social cognition

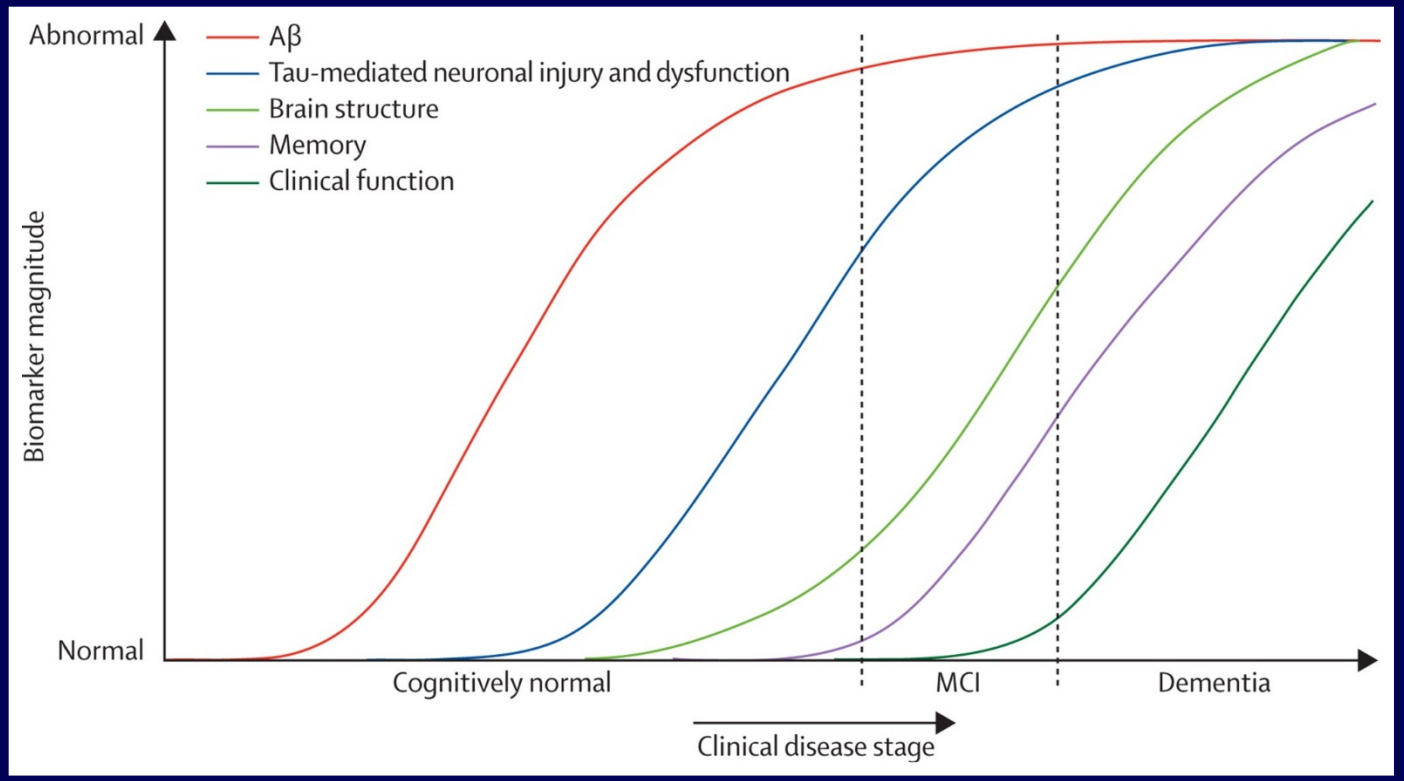
Aspect of multidisciplinary management	Early stage, mild impairment	Middle stage, moderate impairment	Advanced stage, severe impairment
Physician responsibilities	Diagnosis; Discussion of diagnosis and course of disease; Assessment of degree of assistance needed (e.g., home health aides); Assessment of burdensome symptoms and prescribing medications to manage them if necessary; Assessment for genetic testing and referral to a genetic counselor if warranted	Continued assessment of symptoms; Assessment of degree of assistance needed (e.g., possible out-of-home-placement); Discussion of medication efficacy, side effects, and dosing adjustments as needed	Assessment of degree of assistance needed (e.g. possible out-of-home-placement or hospice referral); Discussion of genetic implications of neuropathological findings after autopsy
Programmatic patient support	Consultations with cognitive rehabilitation professionals, physical therapists, speech therapists, and/or occupational therapists to enhance life participation and maintain functional abilities; Caregiver assistance and supervision to complete basic activities of daily living; Day programs for meaningful activity; Home health aides to help with patient self-care tasks and physical and safety needs; Referrals to residential facilities, palliative care and hospice when appropriate		
Caregiver support	Introduction to educational materials and supportive local, national, and online resources; Home health aide or companion to assist caregiver; Day programs to provide caregiver with respite; Meetings with support groups; Emotion-focused coping strategies for grief and loss and bereavement support		
Advance care planning	Identification of health-care proxy; Completion of power-of-attorney; Consultation with social worker regarding benefit eligibility	Consultation with a social worker; Identification of suitable hospice and/or residential care facilities	Discussions to help family and patient plan for a peaceful death; Logistic and financial planning for death

Domain	Symptom	Pharmacologic tx	Non-pharmacologic tx
Language symptoms	Expressive aphasia	None	Speech therapy; caregiver education; compensatory tools such as scripts and AACs
	Naming and comprehension deficits	None	Speech therapy; caregiver education on communication methods
Behavioral and neuropsychiatric symptoms	Apathy and inertia	None	Caregiver education and support; supervision and direction
	Agitation, aggression, and impulsive behaviors	Antidepressants, Atypical antipsychotics	Caregiver education; monitoring and removal of environmental triggers, caregiver oversight of physical and social environment
	Lack of empathy and sympathy	None	Caregiver education; caregiver support groups
	Perseverative and ritualistic behaviors	Antidepressants	Caregiver oversight; toleration of behavior; distraction
	Compulsive eating and dietary abnormalities	Antidepressants	Caregiver oversight of diet; environmental and physical modifications; consultation with dietician
Cognitive symptoms	Executive dysfunction	Evaluation for medications that could impair cognition	Consultation with cognitive rehabilitation therapist; compensatory tools
Motor symptoms	Falls	Evaluation for medications that could contribute to parkinsonism, orthostasis, or balance impairment	Environmental modifications; physical therapy; consultation with occupational therapist; walkers and/or wheelchairs
	Dystonia	Botulinum toxin injections	Splinting; physical therapy
	Parkinsonism	Carbidopa/levodopa trial (in part, for diagnostic purposes)	Caregiver support



Future directions

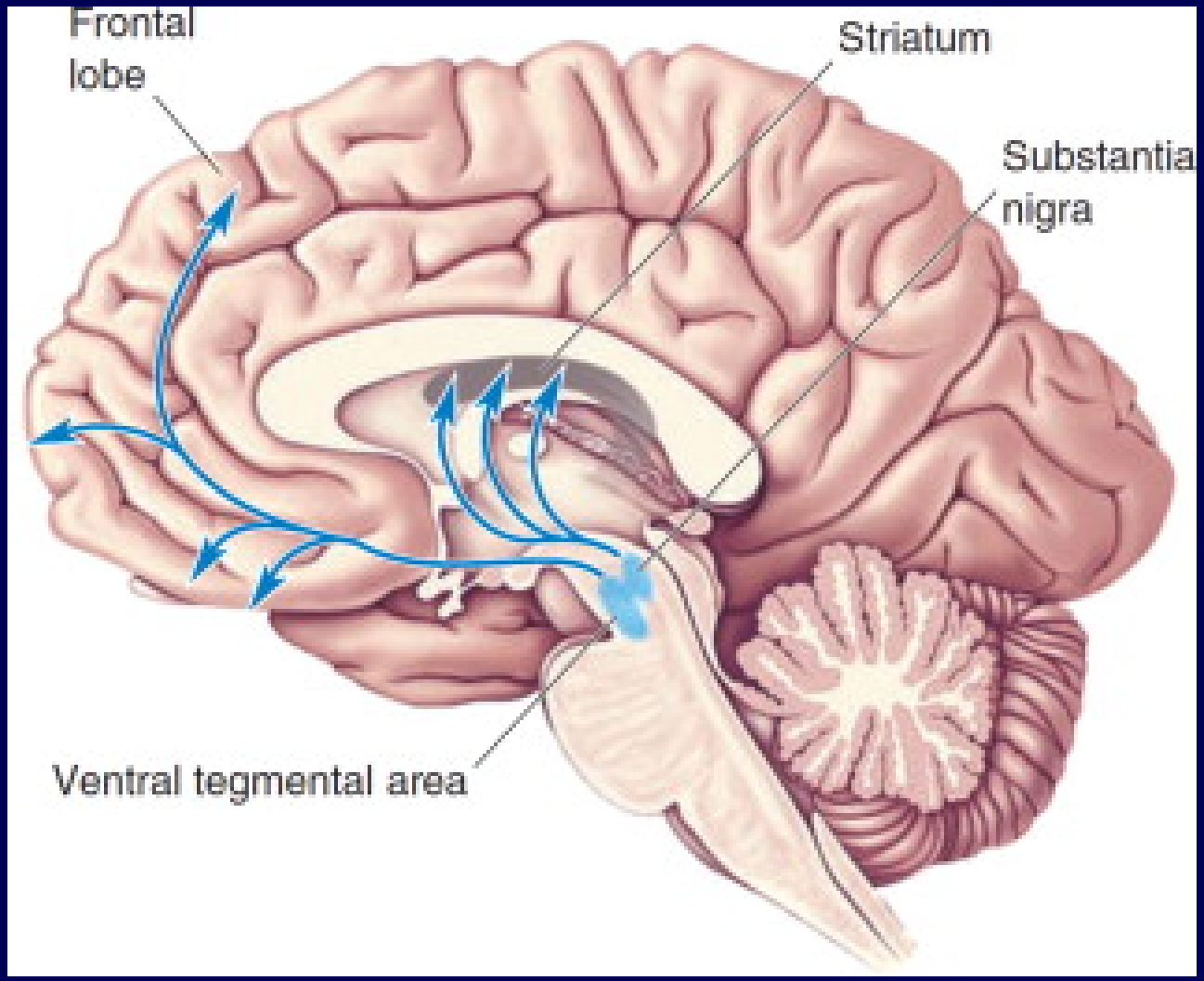
- What is the course of FTD?



Jacks, CR Lancet Neurology 2013

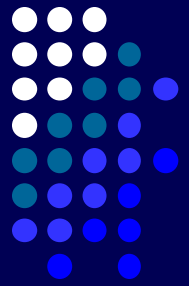
Future directions, cont.

- Treatment development
  - Novel targets
    - Tau (TauRx)
    - Symptom clusters
      - Tolcapone
      - Oxytosin
  - Select groups of FTD patients
    - nimodipine for *PGRN* mutation carriers



From Weng et al, Neural Networks, 2012

Catechol *O*-methyltransferase (COMT)

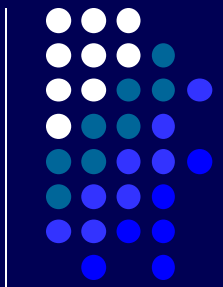


- Inactivates released dopamine through enzymatic conversion to 3-methoxytyramine
- Selectively regulates dopamine in the PFC
  - The cortical dopamine transporter has a 1,000-fold higher affinity for dopamine than does COMT (Lewis et al, *J Comp Neurol* 2001).
  - However, in the PFC, the dopamine transporter is expressed at very low levels and does not appear to affect extracellular dopamine concentrations (Houtari et al, *J Pharm Ex Ther* 2002).

COMT cont.

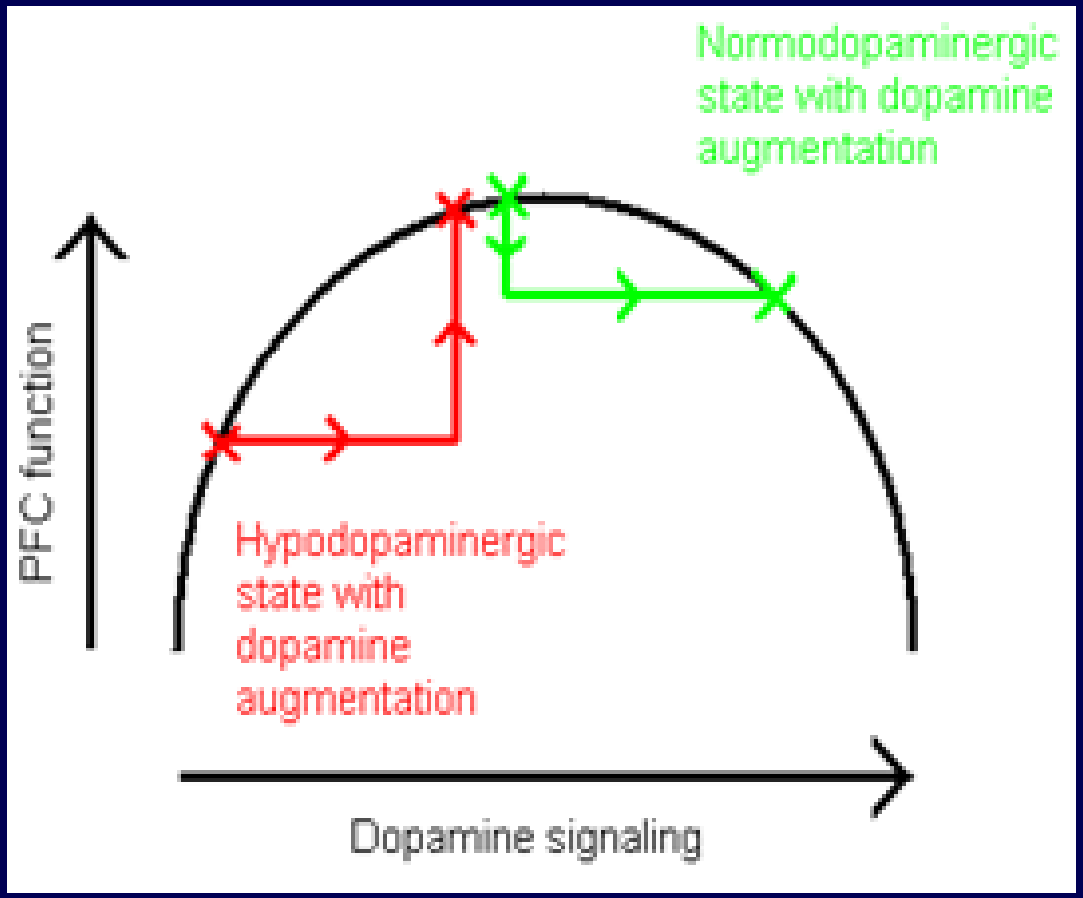
- *COMT* has a has a common polymorphism that affects its function – a methionine (Met) for valine (Val) substitution at codon 158
- The enzyme in individuals with the met/met genotype has 3-4 X lower activity than in individuals with the val/val genotype (Lotta et al, *Biochem* 1995)

Effects of COMT val158met polymorphism in general population (Barnett et al, Biol Psy, 2008)



- Mixed evidence of a small dose-dependent effect (d=0.06) on executive function and WM in healthy control populations
- Larger effect size in patient populations (d=0.3-0.4)
- Findings c/w inverted-U model of frontal dopaminergic function.

inverted-U model of frontal dopaminergic function



Huey et al, submitted

- Examined effect of COMT val158met polymorphism in 110 patients with FTD and 64 patients with CBS.
- Analyzed D-KEFS, MDRS2, WMS-III, NPI, Finger tapping, Grooved pegboard, TOLA, MRI volumetric analysis
- we made a composite score for each of these domains to initially test as follows: the mean of the D-KEFS factor scores (executive), the mean of the WMS-III standardized scores (memory), and the mean of z-scores of the Finger Tapping, Grooved Pegboard, and TOLA scores

COMT Imaging analysis

- VBM analysis in SPM 8
- Images segmented into gray matter, white matter, and CSF. GM images normalized and smoothed. Corrected for TIV.
- Whole brain ANOVA performed in SPM8 on the effects of *COMT* val allele dosage on grey matter volumes. Clusters surviving an uncorrected threshold of $p<0.001$ and a cluster size of 30 voxels were considered significant.

Results

- There was a significant effect of the *COMT* val allele on our composite executive function measure, $F(1, 76)=6.14$, $p=0.015$, but no significant effect of the *COMT* val allele on the memory or motor composite measures.

Imaging results

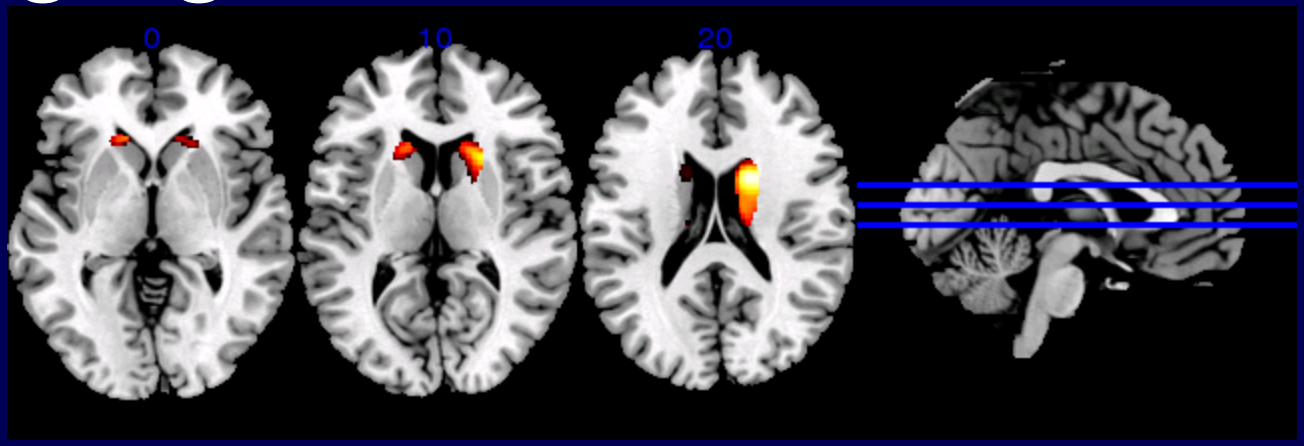


Figure 1. Difference between grey matter volume in patient with two compared to no val alleles at the *COMT* val158met polymorphism. Dark areas show regions of decreased grey matter volume in patients with two val alleles. Areas shown are significant at an uncorrected voxel-level threshold of $p < 0.001$.

Why caudate?

- Included CBS patients
- Caudate receives extensive cortical afferent projections, esp. frontal association areas
- In animal models, head of caudate is especially vulnerable to dopamine depletion (*J Neurol* 2000)

Conclusions

- the *COMT* val158met polymorphism affects executive function and bilateral caudate volume in patients with FTD and CBS
- r = 0.22 between sorting score and *COMT* val dosage. Comparable to other patient populations.

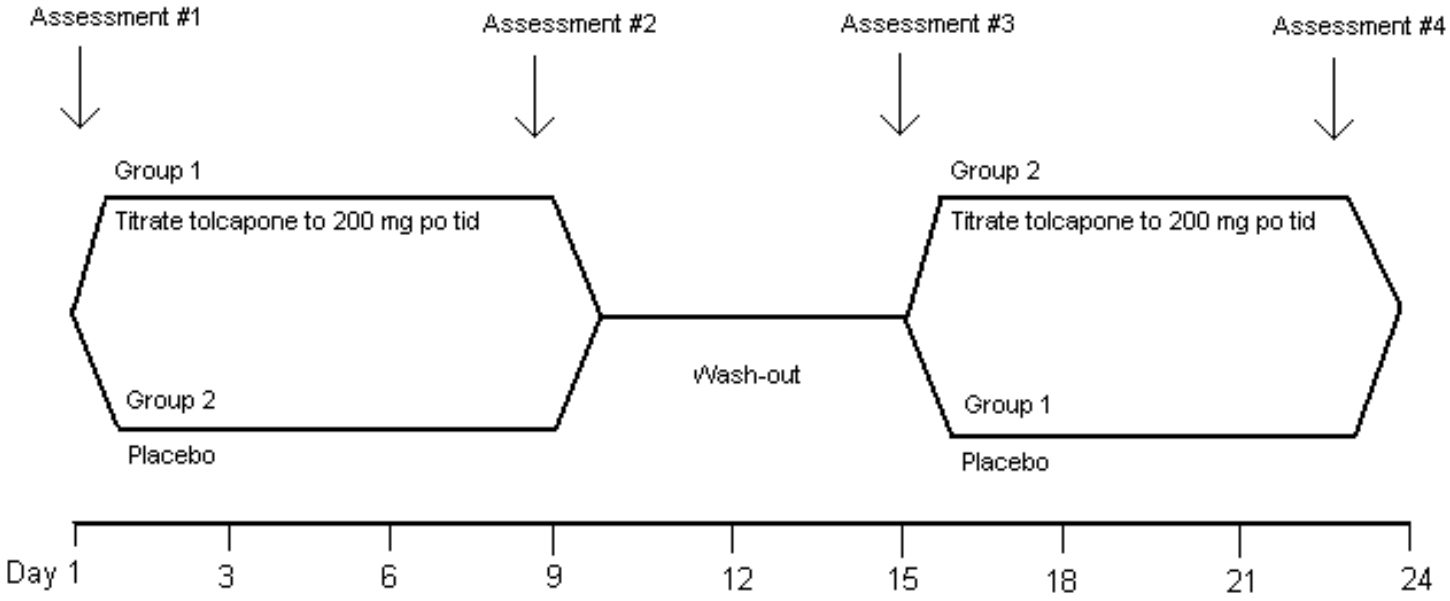


Figure 1. Study design