# The Atypical Dementias

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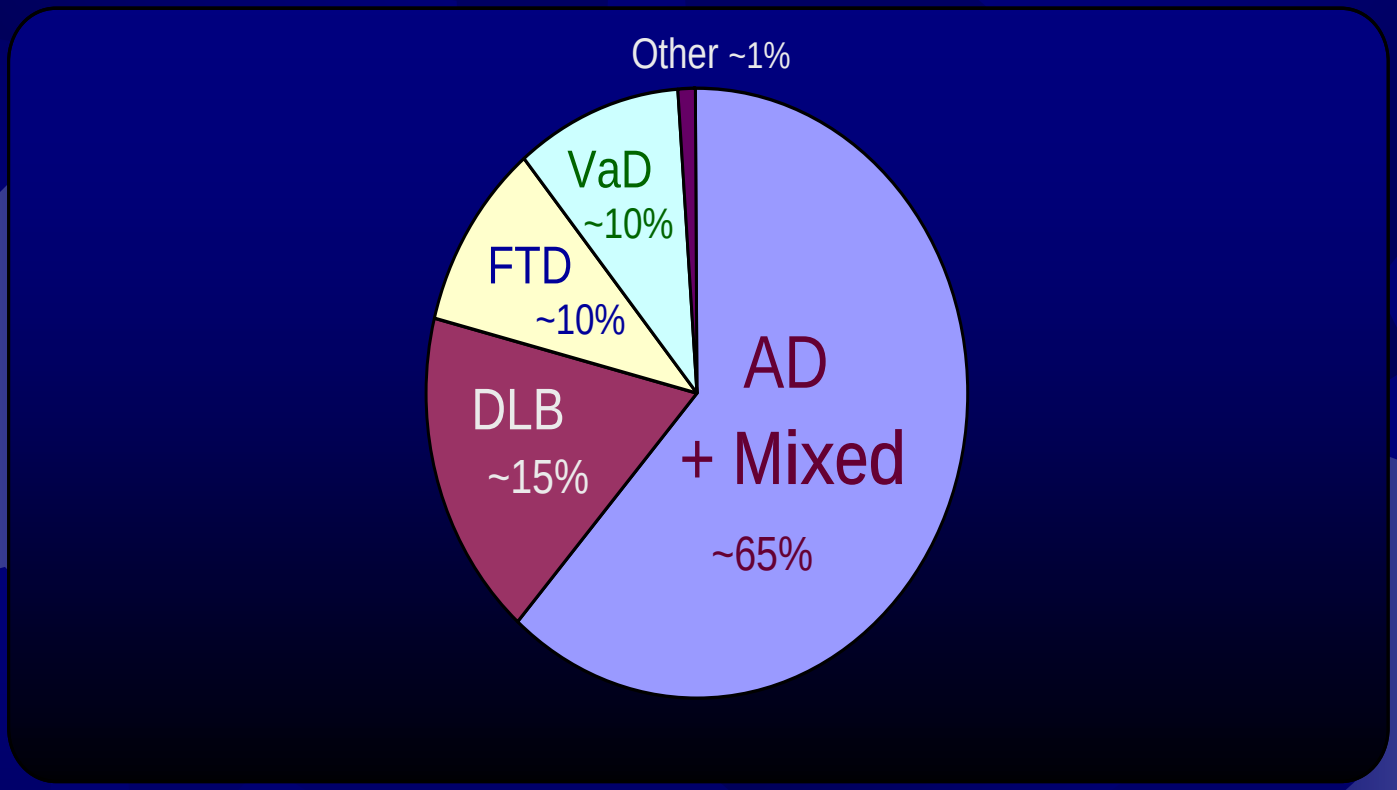
# Disclosure

- Speaker Honorarium
  - Merck Pharmaceuticals

# Prevalence of Dementia Types




McKeith IG et al. Neurology. 1996;47:1113-1124.
Bird T Knopman D et al. Ann Neurol 2003;54:S29-S31.
Hulette C Neurology. 1995 Nov;45(11):1991-5.
Jellinger KA J Neural Transm. 2002 May;109(5-6):813-36.
Klatka LA et al. Arch Neurol. 1996 Jan;53(1):35-42.
Barker WW et al. Alzheimer Dis Assoc Disord. 2002 Oct-Dec;16(4):203-12.

# Frontotemporal Dementia (FTD)

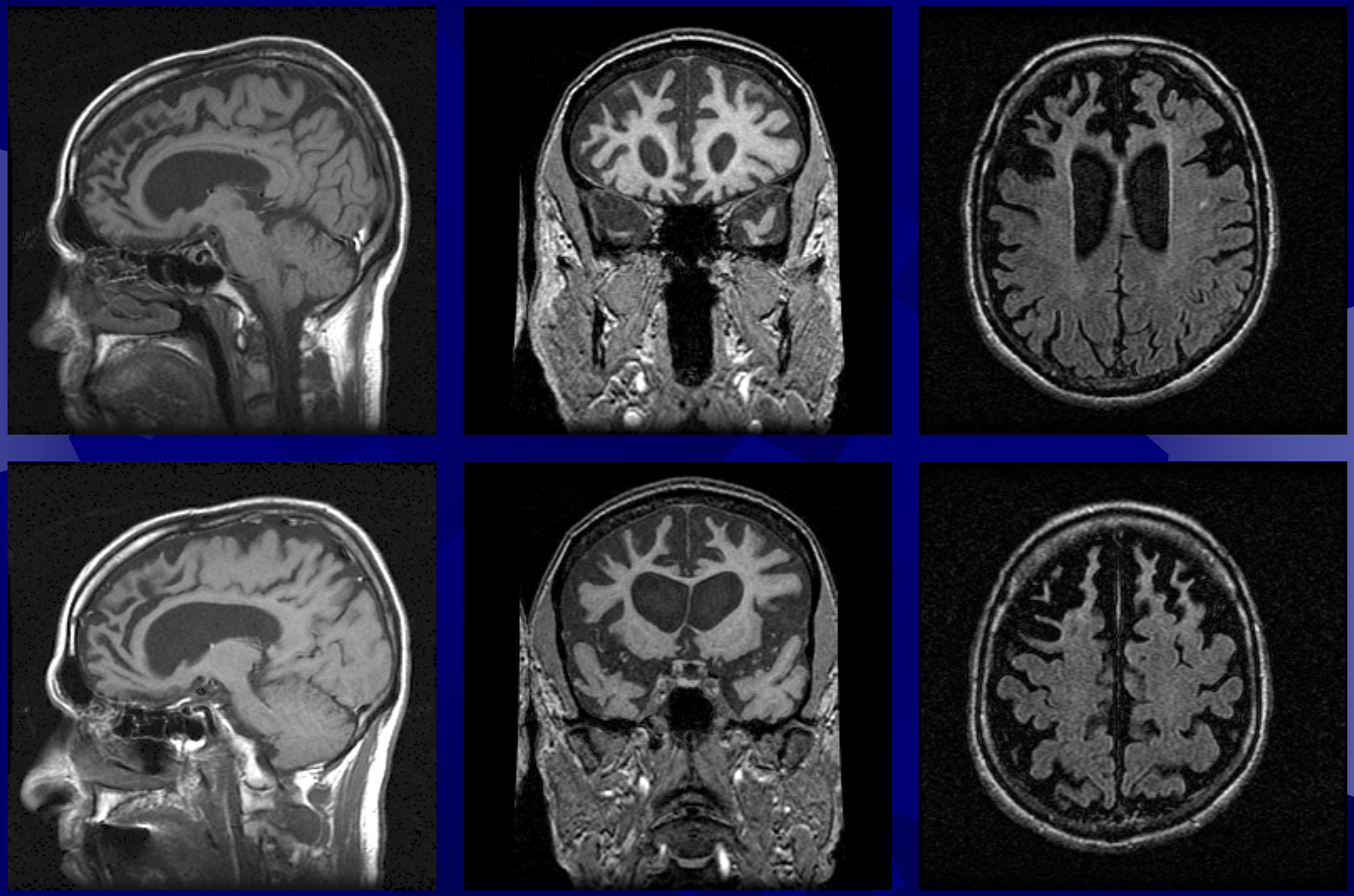
# Frontotemporal Dementia (FTD) Syndromes (Neary et al. 1998)

- Behavioral/Dysexecutive (or Frontal variant)
- Progressive Non-Fluent Aphasia
- Progressive Fluent Aphasia or Semantic Dementia
- Prosopagnosia

# Frontotemporal Dementia Syndromes (Neary et al. 1998)

- **Frontal Variant**
  - Dysregulation and Decline in social interpersonal conduct
  - Loss of Insight
  - Emotional Blunting
  - Decline in personal hygiene/comportment
  - Hyperorality, increased oral intake
  - Mental rigidity
  - Obsessive/compulsivity, Stereotyped behaviour
  - Utilization behaviour

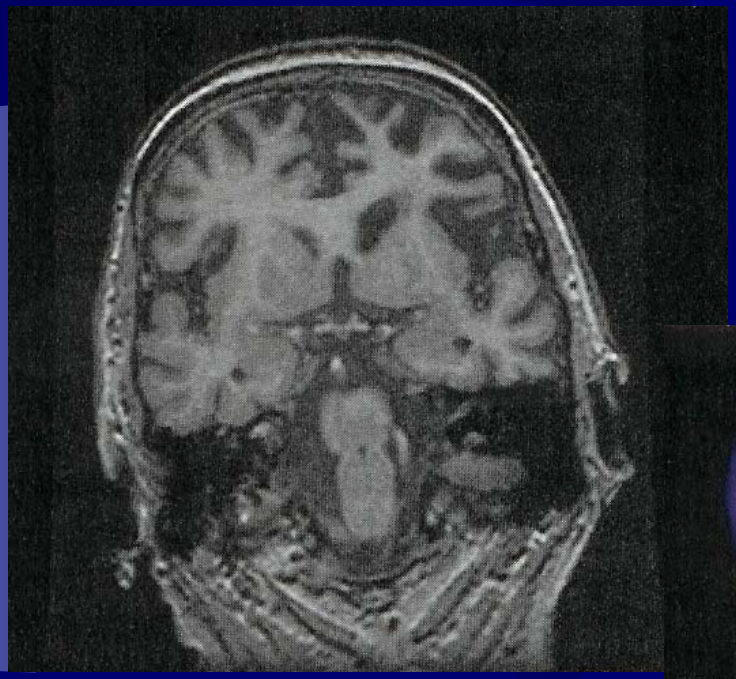
# Frontal Variant FTD

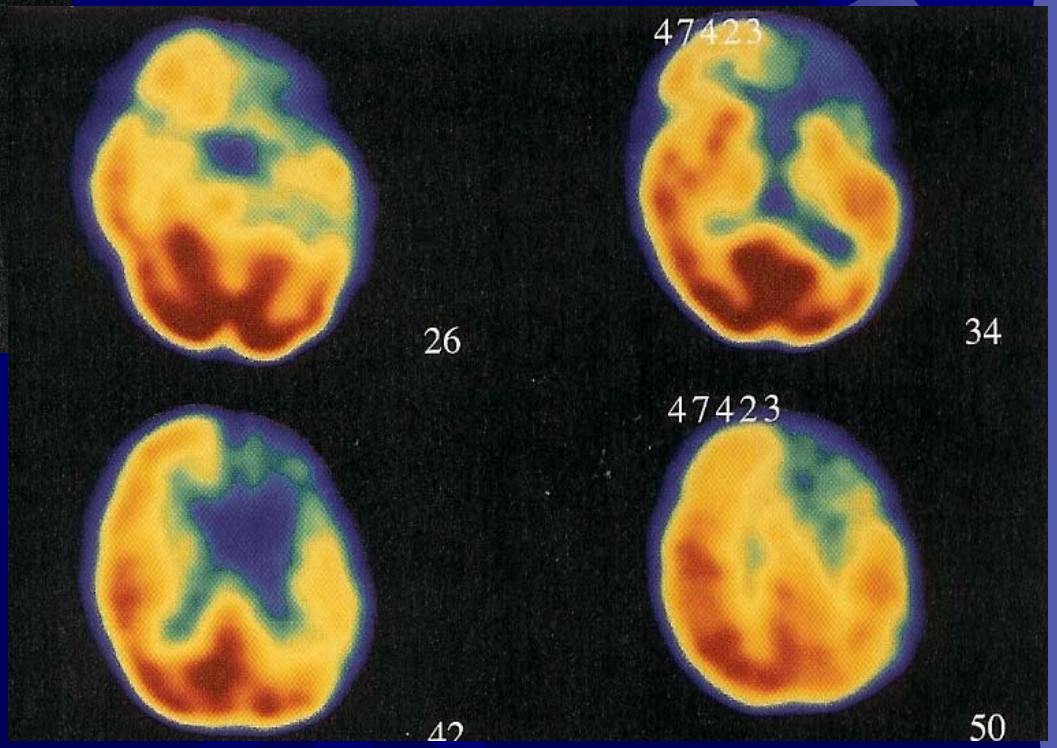


# Frontotemporal Dementia Syndromes (Neary et al. 1998)

- **Progressive Nonfluent Aphasia (PNFA)**
  - Nonfluent spontaneous speech
  - Anomia
  - Agrammatism
  - Phonemic paraphasias
  - Oral apraxia
  - Impaired repetition
  - Alexia
  - Agraphia

# Progressive Nonfluent Aphasia (PNFA)





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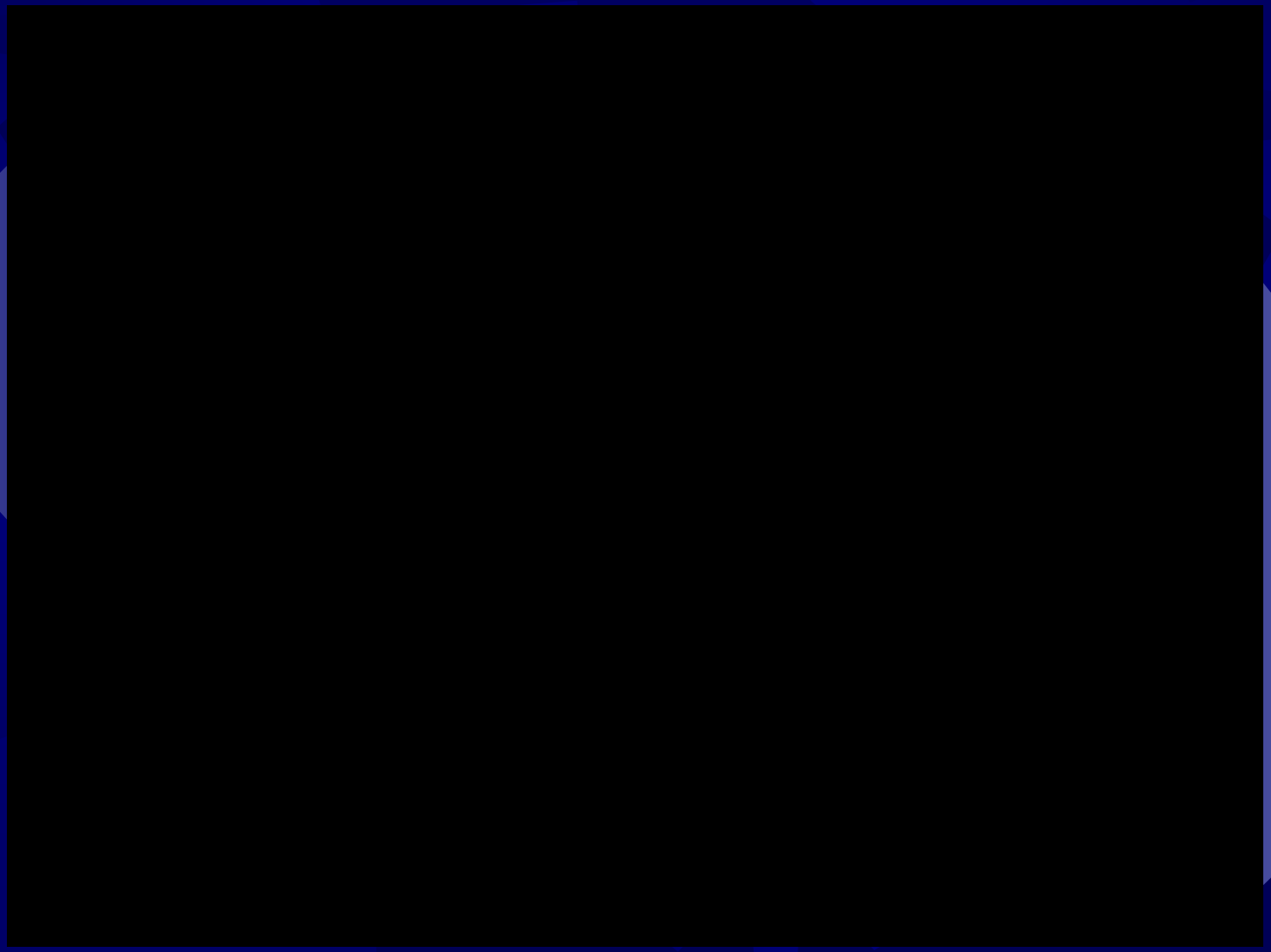
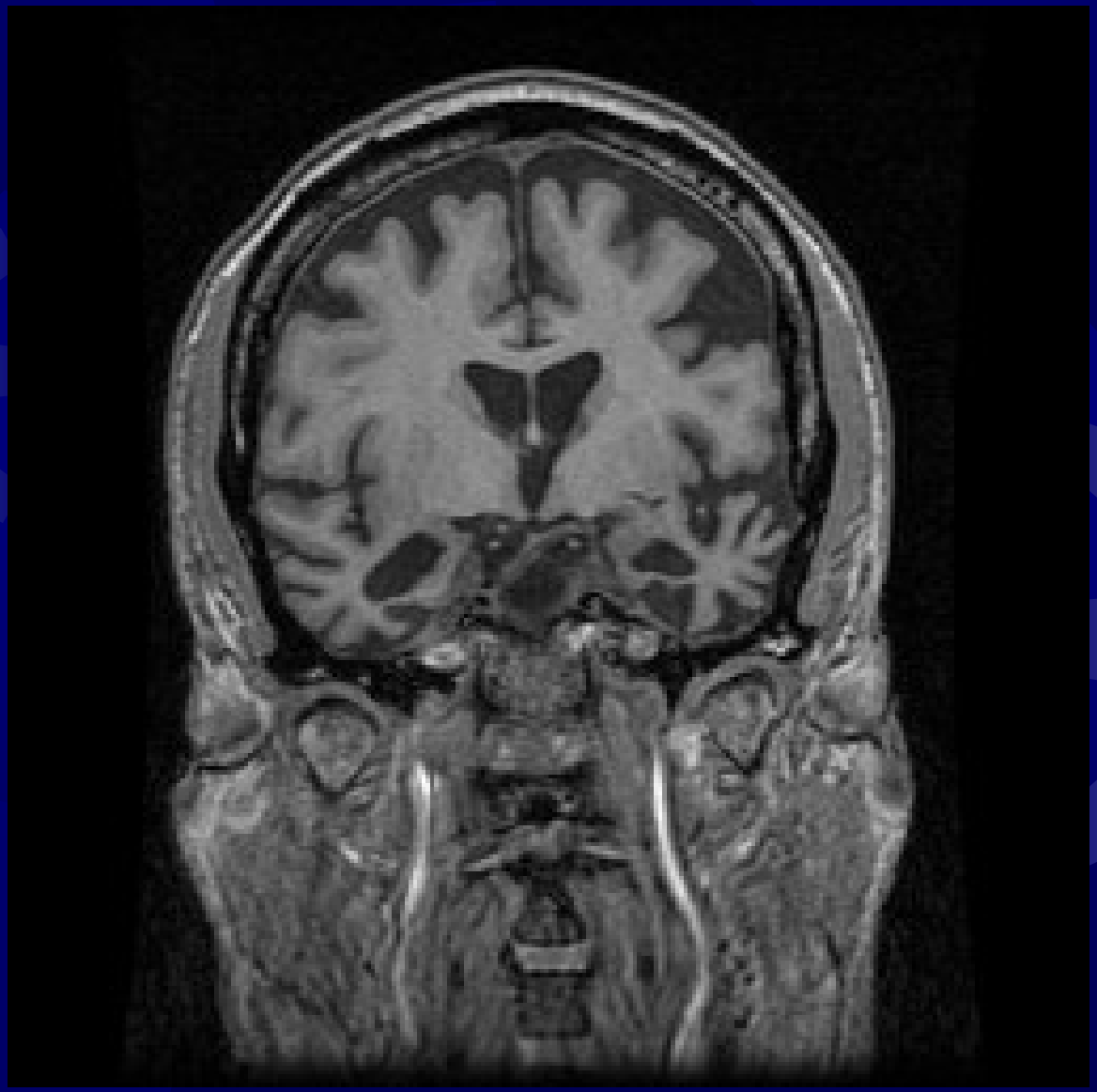


# Frontotemporal Dementia Syndromes (Neary et al. 1998)

- **Progressive Fluent Aphasia (Semantic Dementia - SD)**
  - Fluent, though empty spontaneous speech
  - Decreased comprehension
  - Anomia with Loss of word meaning
  - Semantic Paraphasias

  - Surface dyslexia/dysgraphia
    - (i.e. literal reading of YACHT or COLONEL)

# Progressive Fluent Aphasia (Semantic Dementia - SD)



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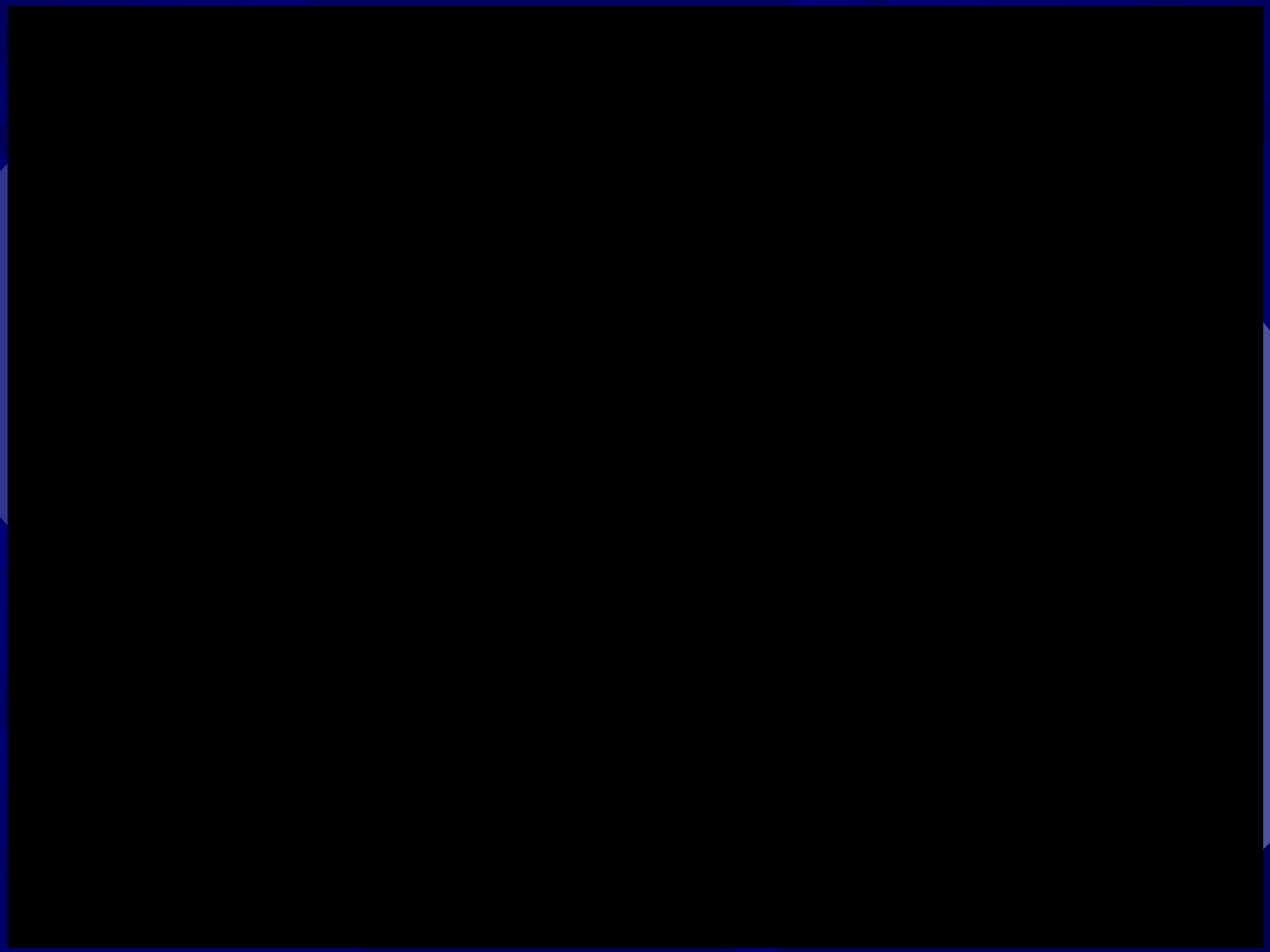
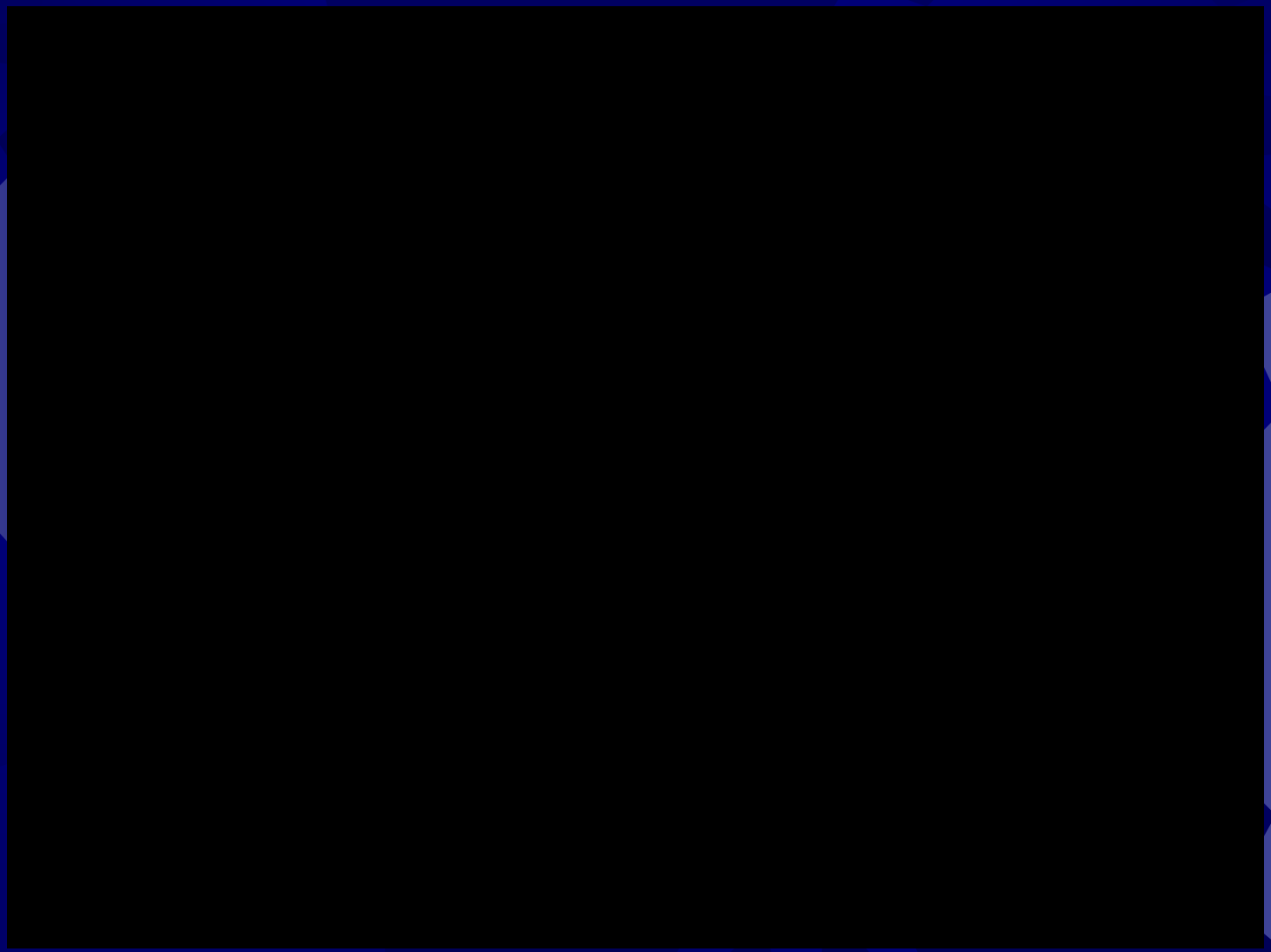


# Progressive Fluent Aphasia (Semantic Dementia - SD)

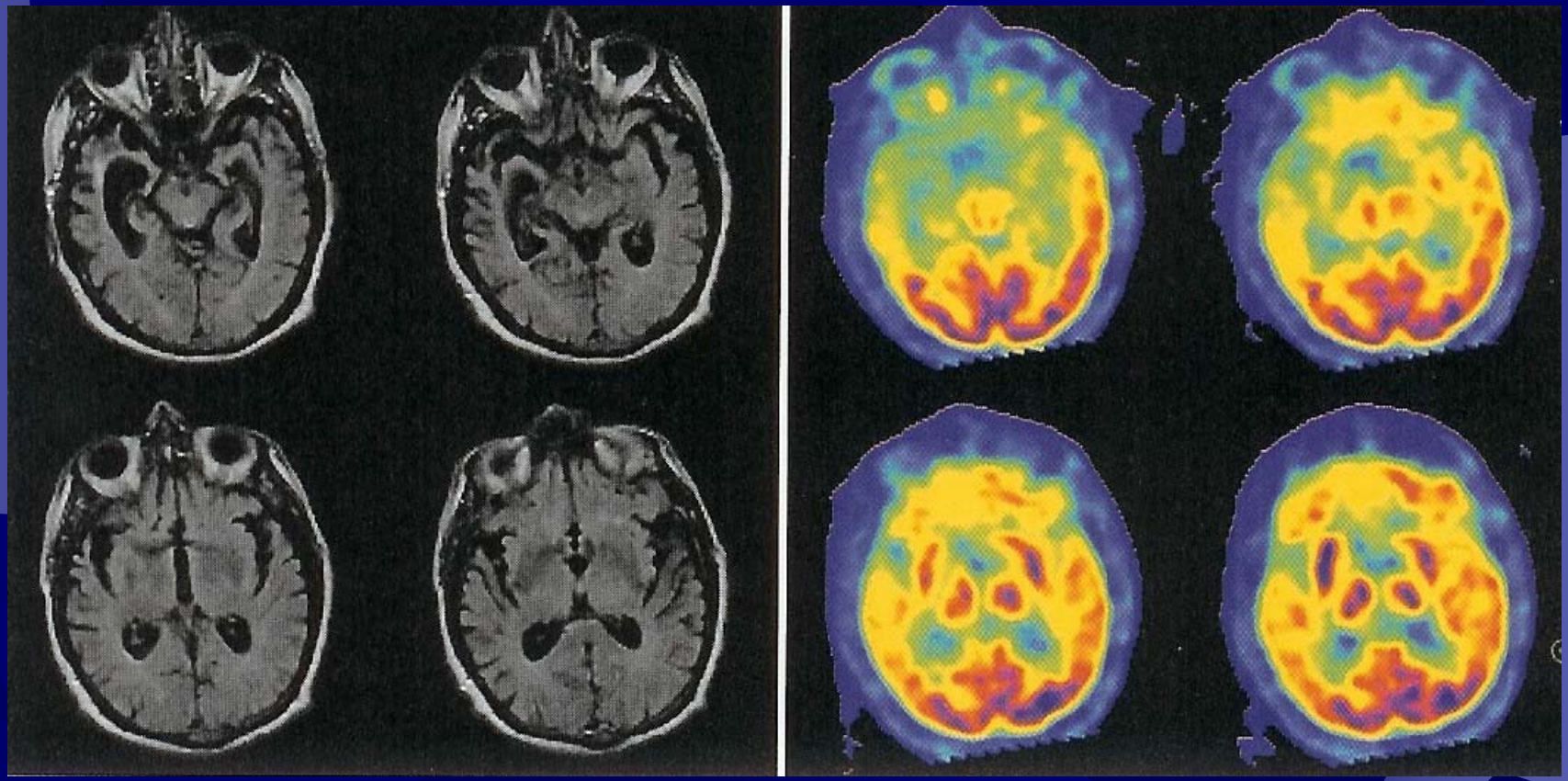


Surface Dyslexia: YACHT COLONEL

# Frontotemporal Dementia Syndromes (Neary et al. 1998)

- **Prosopagnosia**
  - Impaired recognition of familiar faces
  - Impaired identification of specific members in a group
  - May also have prominent neuropsychiatric disturbance

# Prosopagnosia



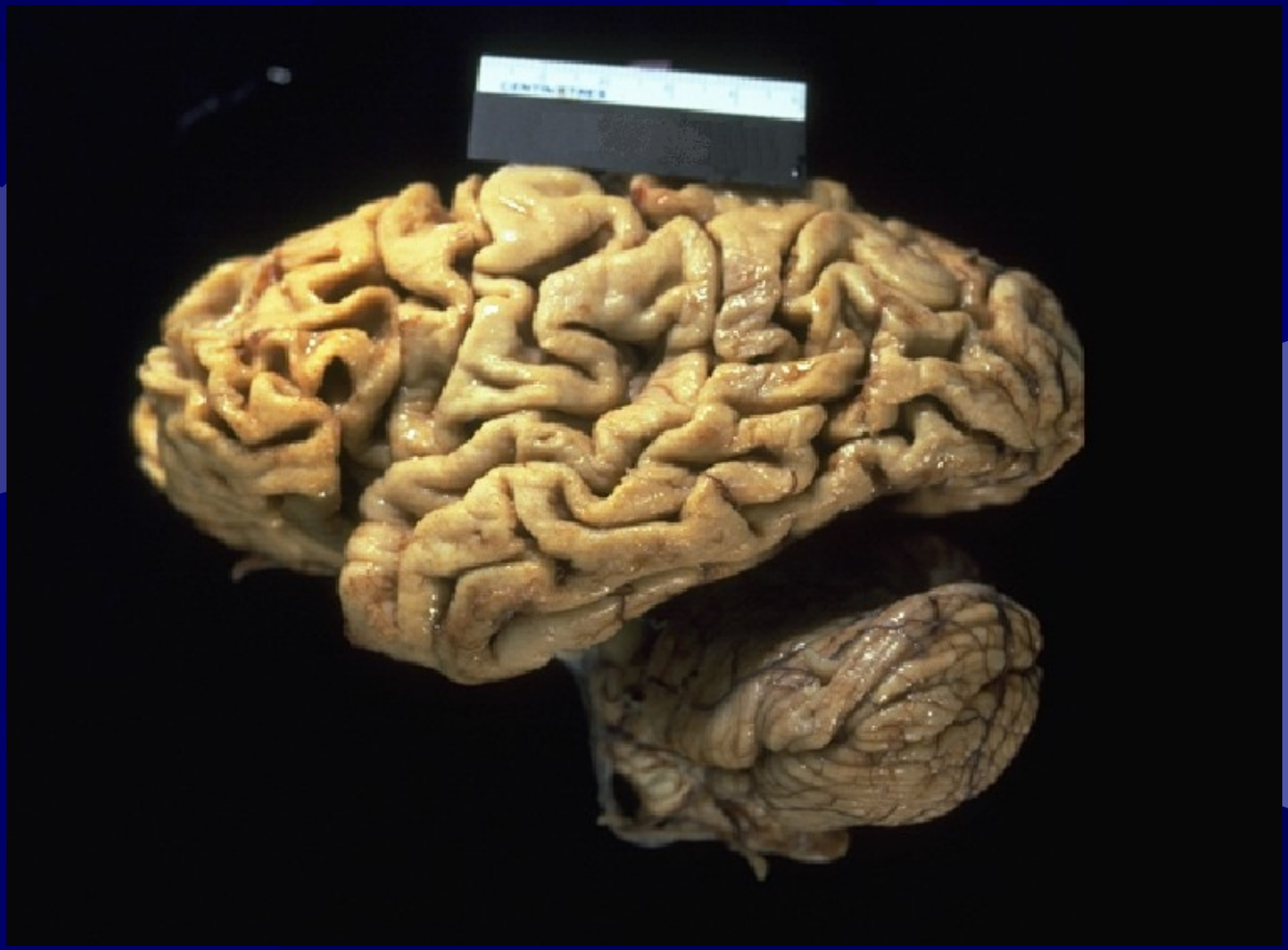
# Frontotemporal Dementia Associated Features

- Onset often prior to age 65
- Slight male predominance
- Family history of similar disorder

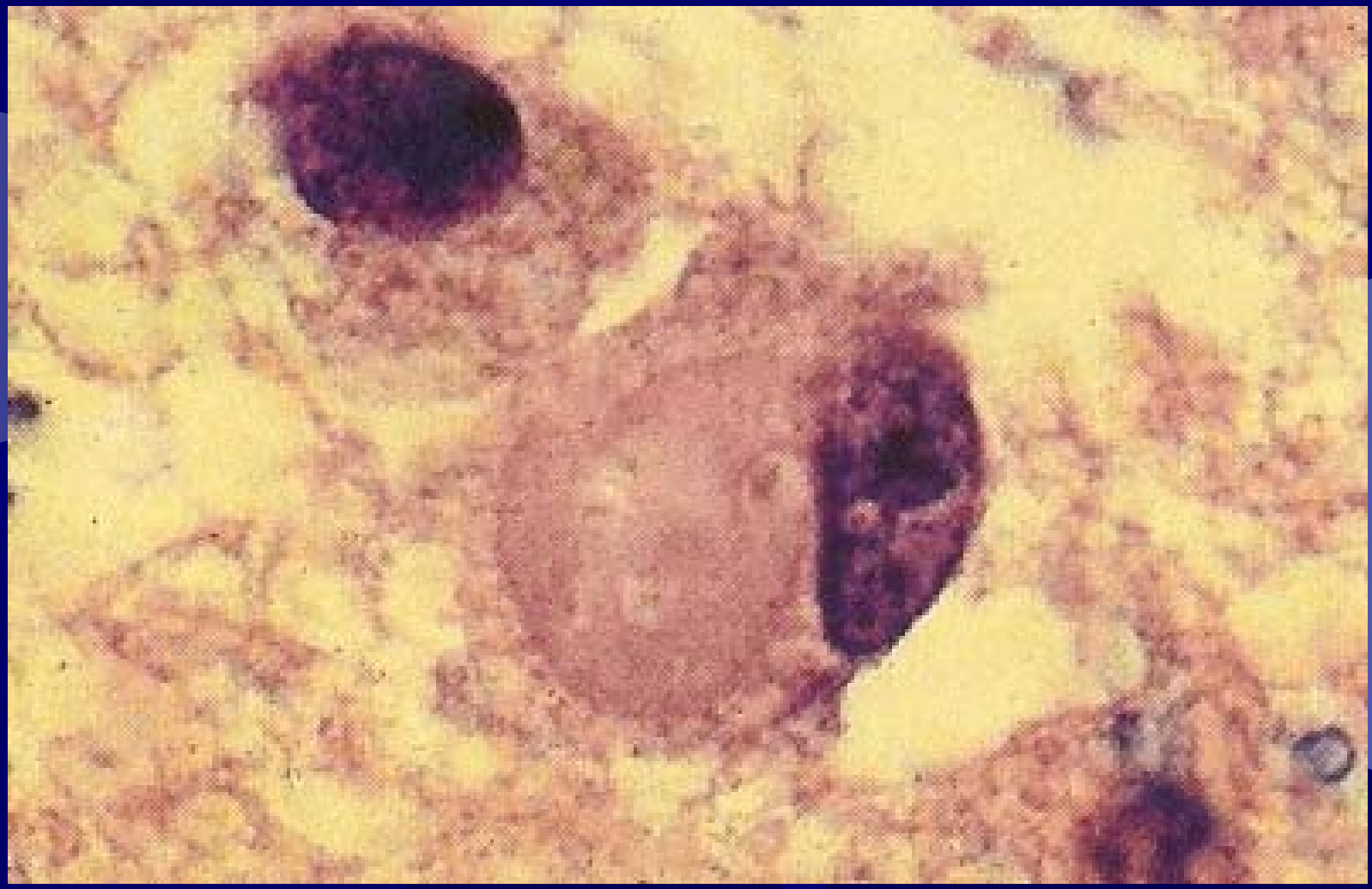
- Parkinsonism

- Motor Neuron Disease
  - Fasciculations
  - Muscle atrophy
  - Weakness

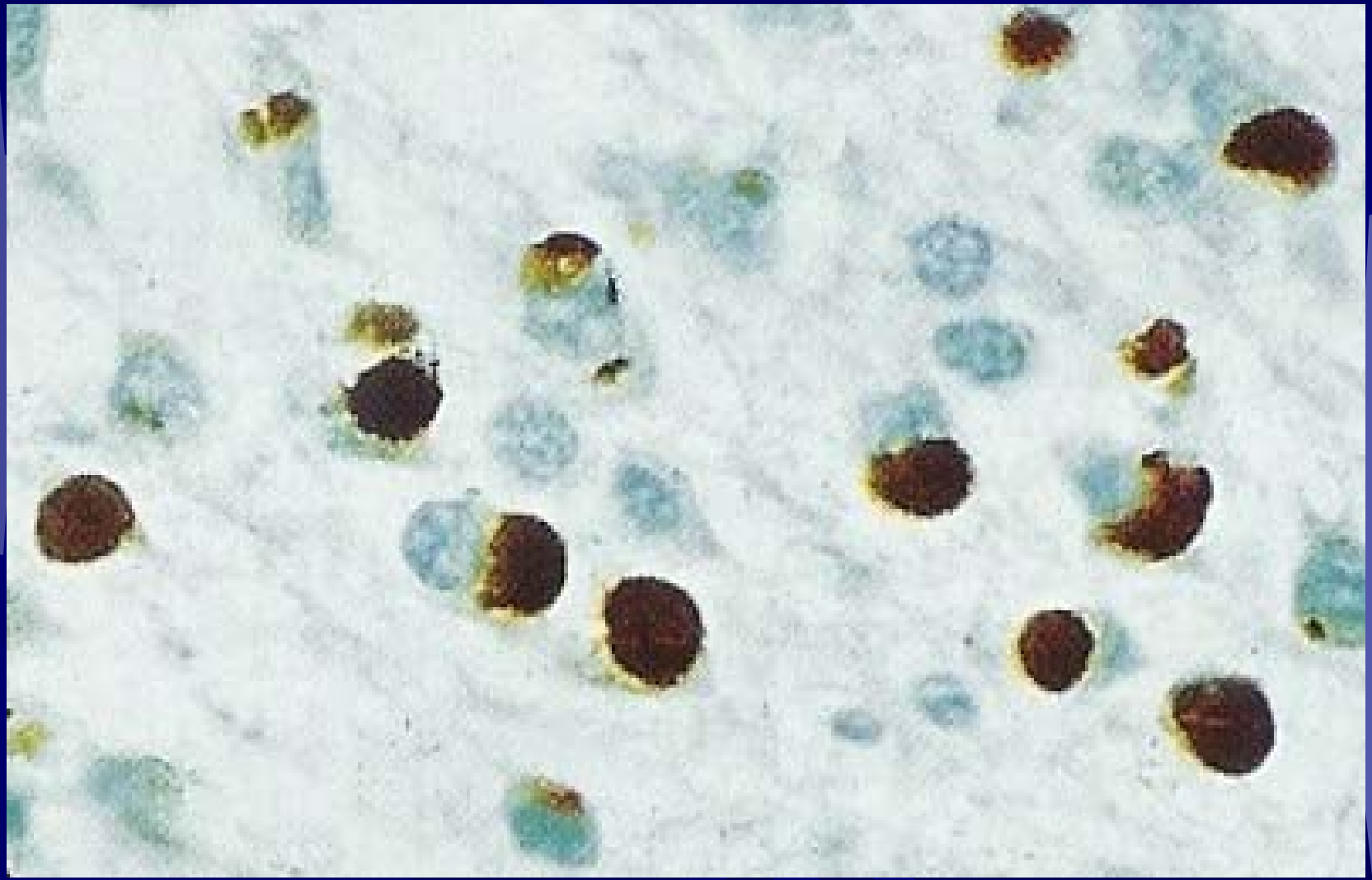
# Gross Pathology - FTD



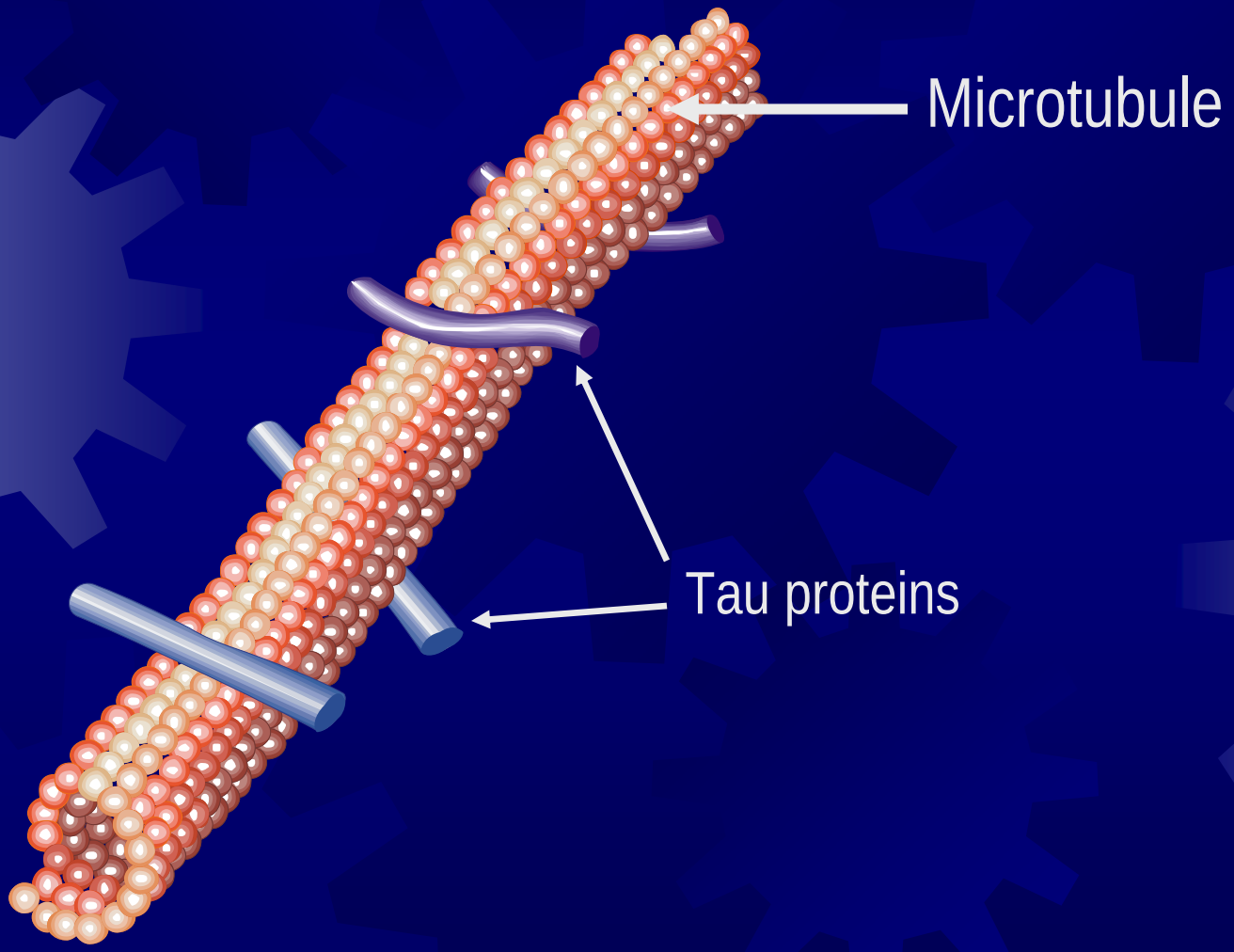
# Histopathology - Pick's Disease (H+E)



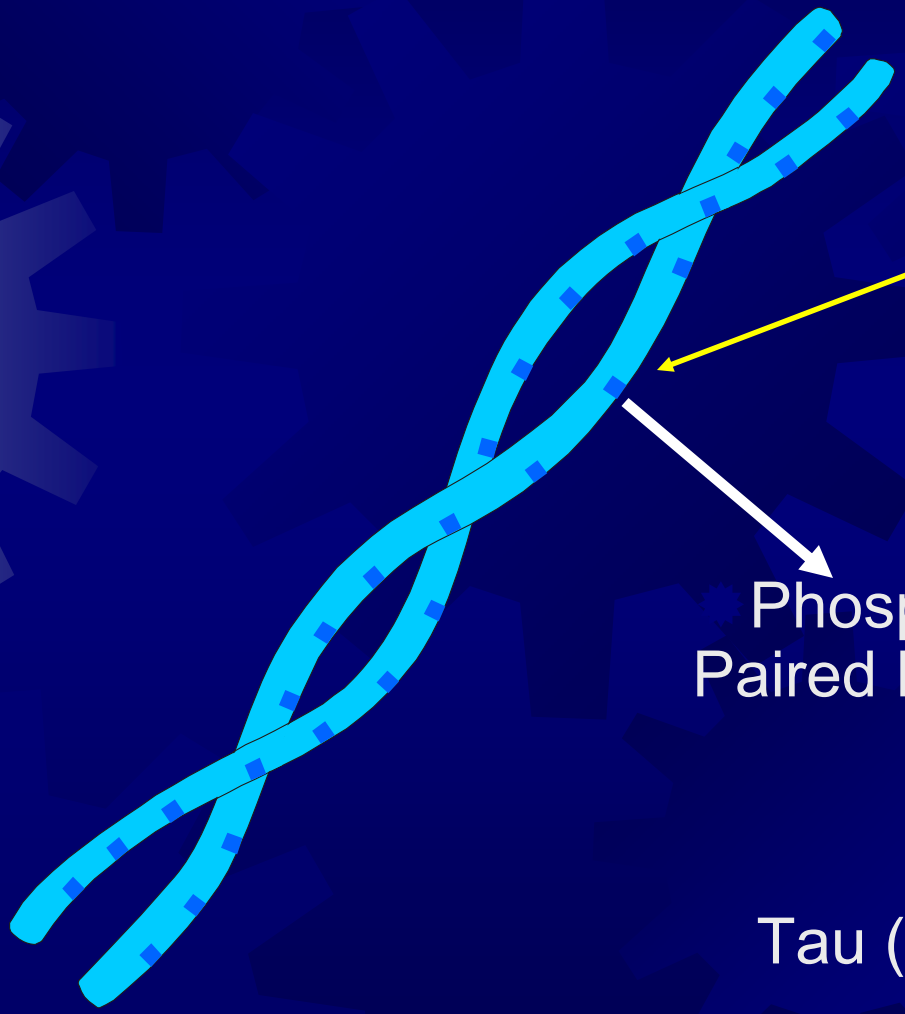
# Tau Immunohistochemistry - FTD



# Tau



# Tau Hyperphosphorylation



glycogen synthase kinase-3β (GSK-3β)

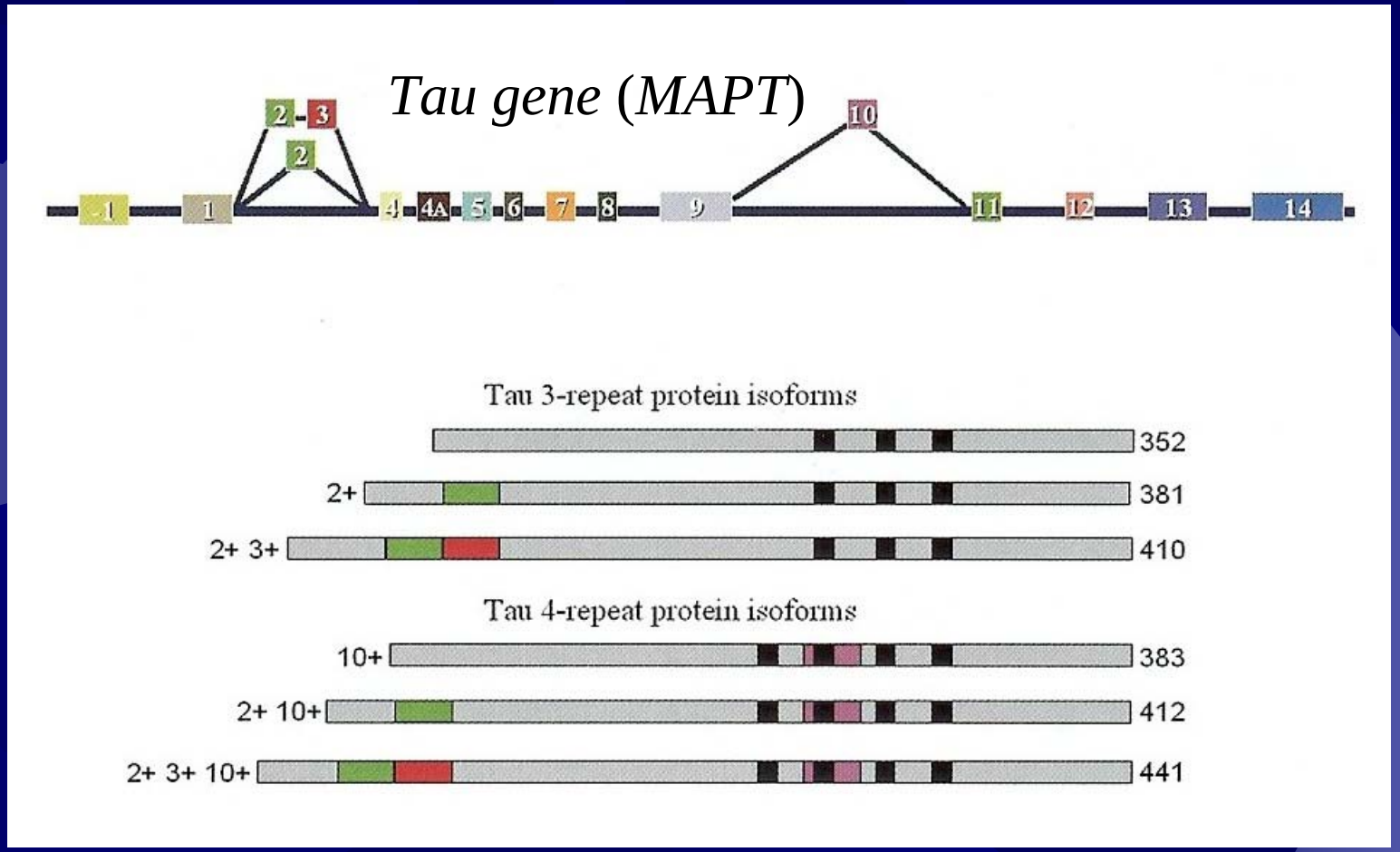
Phosphotau forming Paired Helical Filament

Tau (+) Inclusions

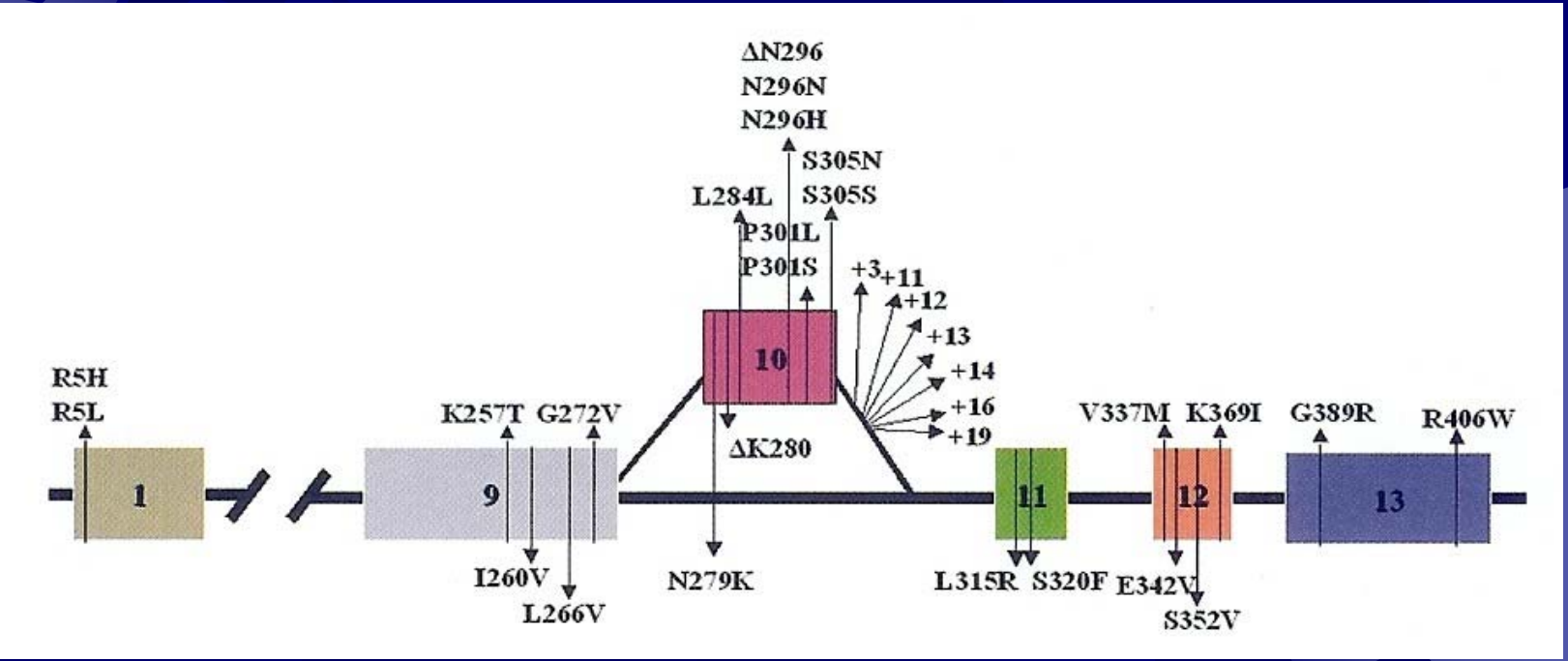
# The Central Question of Neurodegeneration

Are the changes noted on pathology causative of the disease, or simply an "innocent" marker of disease progress?

# *Tau* Gene on Chromosome 17



# Tau Mutations Causing FTD



# FTD with Ubiquitin Pathology

- FTD cases clinically
- Neuropathologically, NO tau inclusions
- Ubiquitin inclusions present
  - Likely represents majority of FTD cases neuropathologically
- Ubiquitinated inclusions also found to stain for TDP-43
  - TAR DNA binding Protein-43
  - mRNA splicing mediator

# FTD with TDP-43/Ubiquitin

- Causative gene determined to be **Progranulin (GRN)**
  - Autosomal Dominant
  - Nerve growth factor
  - Present in 5-10% of all cases of FTD
- Unknown how Progranulin mutation leads to ubiquitinated TDP-43 inclusions pathologically

# FTD with TDP-43/Ubiquitin

- Other known genetic loci
  - TARDBP (TDP-43)
  - C9ORF72
    - Causative of familial FTD+ALS
  - VCP
  - CHMP2B

# Treatment of FTD

- No FDA approved treatment
- Cholinesterase Inhibitors
  - Rivastigmine (Exelon)
    - Open Label RCT (n=20) for 12 months showed significant improvement on Neuropsychiatric Inventory and Caregiver Relative Stress Scale ($p<0.001$) (Drugs Aging. 2004;21(14):931-7)
- SSRIs
  - Theorized to be efficacious due to prominent serotonergic pathways in frontal lobe function
  - Paroxetine (Paxil)
    - Open Label RCT (n=16) of Paroxetine 20 mg daily for 14 months showed significant improvements in behavioral symptoms, reflected by a reduction of caregiver stress (Moretti R et al. Eur Neurol. 2003;49(1):13-9)
    - Double-blinded RCT (n=10) of Paroxetine 40 mg daily showed no benefit on Neuropsychiatric Inventory and some detriment on certain cognitive measures (Deakin JB et al. Psychopharmacology (Berl). 2004 Apr;172(4):400-8)
  - Fluvoxamine (Luvox)
    - Open trial (n=16) of Fluvoxamine 50 to 150 mg daily for 12 weeks showed improvement on Neuropsychiatric Inventory (Ikeda et al. Dement Geriatr Cogn Disord. 2004;17(3):117-21)
  - Sertraline (Zoloft), Citalopram (Celexa)

# Treatment of FTD

- Trazodone
  - Double-blinded RCT (n=26) of Trazodone 300 mg daily showed significant (p=0.028) effect on Neuropsychiatric Inventory (irritability, agitation, depressive symptoms and eating disorders)
    (Dement Geriatr Cogn Disord. 2004;17(4):355-9)
  - Adverse reactions:  drowsiness, hypotension, syncope
- Atypical antipsychotics
  - Quetiapine (Seroquel)
  - Risperidone (Risperdal)
  - Olanzapine (Zyprexa)
- Stimulants
  - Methylphenidate (Ritalin)
    - Administration of methylphenidate (n=1) partially normalized bifrontal EEG slowing and SPECT hypoperfusion
      (Goforth HW et al. Clin EEG Neurosci. 2004 Apr;35(2):108-11)
- Ebixa/memantine
  - No benefit in FTD (Lancet Neurol. 2013 Feb;12(2):149-56. doi: 10.1016/S1474-4422(12)70320-4.)

# Investigational Agents

- Anti-tau aggregation
  - Rember
  - TauRx
- Glycogen Synthase Kinase-3β (GSK-3β) Inhibitors
  - Lithium
  - AR-A014418
  - Cysteamine
- Cyclin Dependent Kinase Inhibitors
- Microtubule Stabilizing Drugs
  - Paclitaxel

# Logopenic Progressive Aphasia (LPA)

- Intermediate findings between PNFA and SD
- Slowed word-finding and slowed comprehension

- Atrophy in the left posterior temporal cortex and inferior parietal lobule
- Underlying pathology usually Alzheimer's disease (i.e. amyloid + tau)

# Dementia with Lewy bodies (DLB)

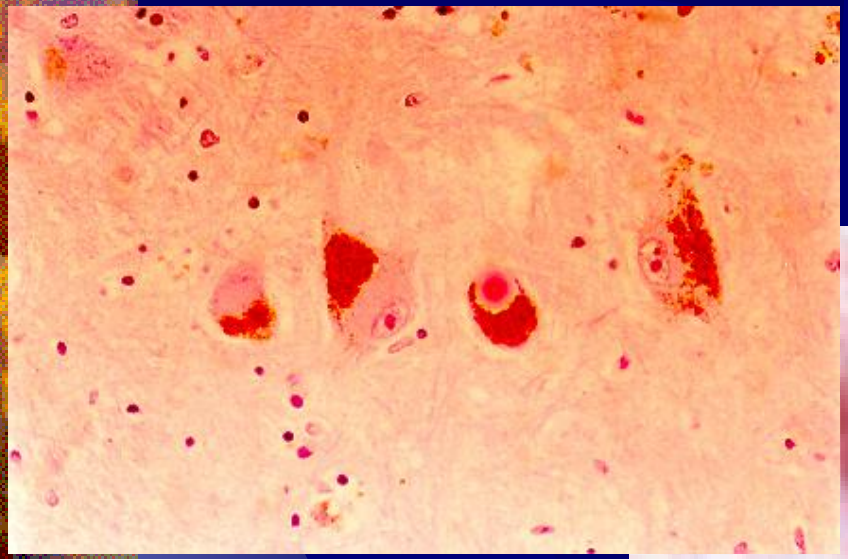
# Dementia with Lewy bodies (DLB) (McKeith et al. 1996)

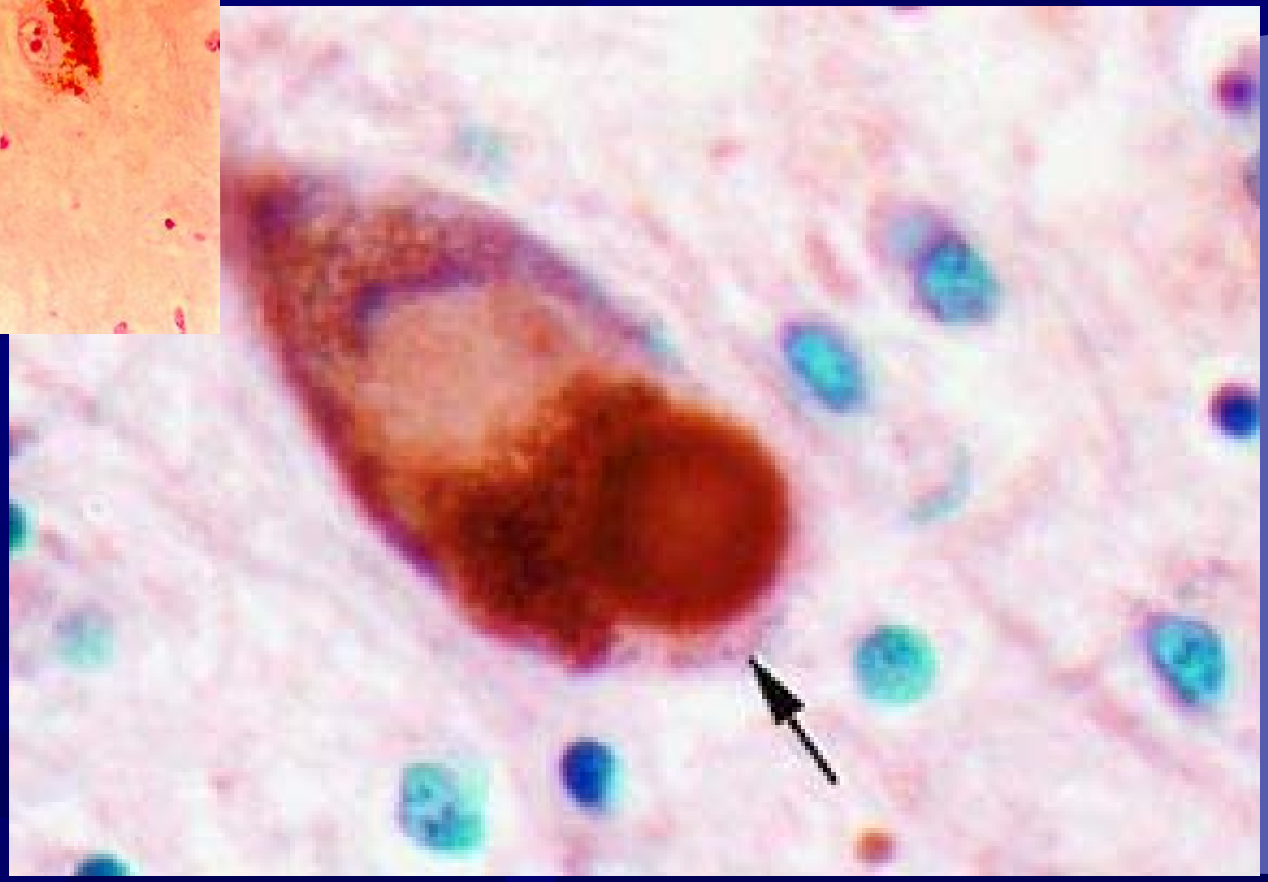
- Dementia
  - Visuospatial and/or Attentional/Executive dysfunction may be more prominent
- Two of the following for probable DLB, One of the following for possible DLB
  - Visual hallucinations
    - Well formed (e.g. people or small animals)
  - Fluctuation in cognition over hours, or from day-to-day
  - Spontaneous motor features of parkinsonism

# Dementia with Lewy bodies (DLB) (McKeith et al. 1996)

- Supportive features
  - REM Behavioural Sleep Disorder
    - Physical “acting-out” of dream content (e.g. limb flailing)
  - Neuroleptic sensitivity
  - Delusional thinking

# Neuropathology of DLB





# Treatment of DLB

- Cholinesterase Inhibitors
  - Striking cholinergic deficit in DLB may make it even more responsive to cholinesterase inhibitors than AD
  - Most robust evidence with Exelon (rivastigmine)
- Levodopa/Carbidopa
  - For disabling parkinsonian symptoms (i.e. rigidity and gait)

# Treatment of DLB

- Benzodiazepine
  - e.g. clonazepam
  - For REM Behavioural Sleep Disorder
- Atypical Antipsychotics
  - e.g. Seroquel (quetiapine)
  - Use with caution given neuroleptic sensitivity and known increased mortality with this class of medication in dementia

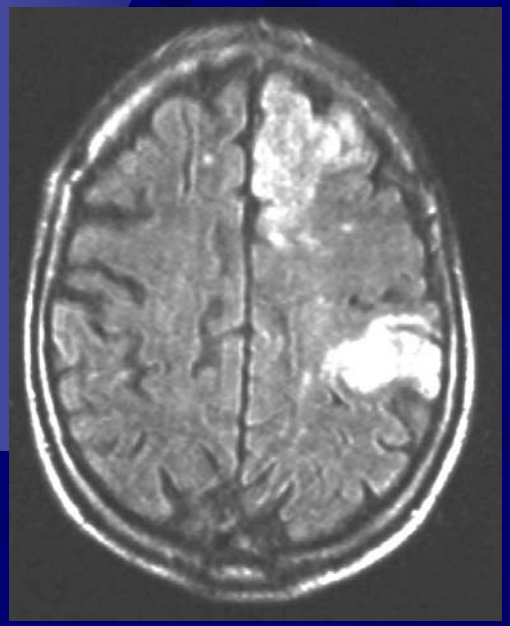
# Vascular Dementia (VaD)

# NINDS-AIREN Criteria for Vascular Dementia (VaD)

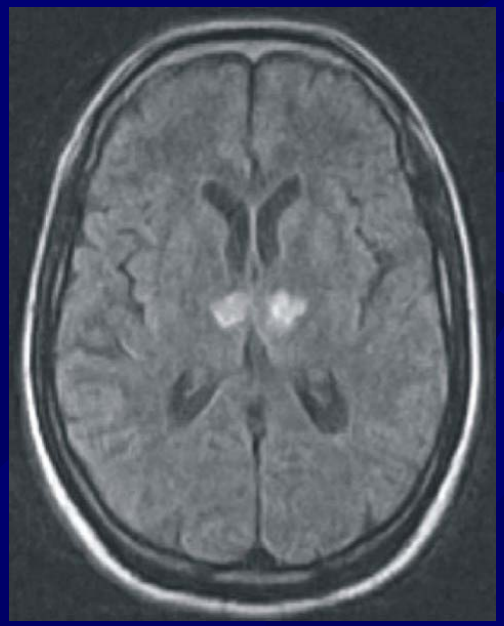
- Dementia
- Cerebrovascular disease
  - On Neurological examination
  - On Neuroimaging (CT or MRI)
    - Multiple Large Territory Infarctions (“Multi-infarct”)
    - Single Small “Strategic” Infarctions
      - Thalamus, angular gyrus, basal forebrain, hippocampus,or PCA or ACA territories
    - Multiple basal ganglia or white matter lacunar infarcts
    - Extensive periventricular white matter ischemic change

Roman GC et al. Neurology 1993 Feb;43(2):250-60.

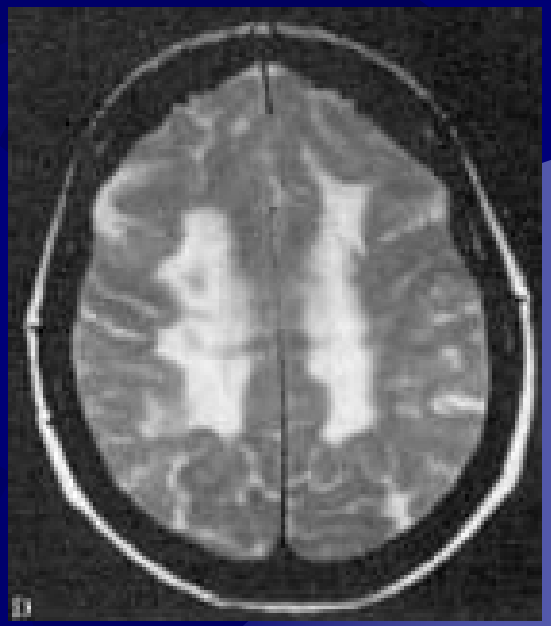
# MRI in Vascular Dementia (VaD)



Multi-infarct



Strategic Infarcts



Periventricular

# NINDS-AIREN Criteria for Vascular Dementia (VaD)

- Relationship between Dementia and Cerebrovascular disease
  - Onset of dementia within **3 months** of stroke
  - Sudden, fluctuating, or stepwise onset of dementia
  - Condition may remain stable if no further strokes occur

Roman GC et al. Neurology 1993 Feb;43(2):250-60.

# Hypertension and VaD

- SYST-EUR (Lancet 1998 Oct 24;352(9137):1347-51)
  - Double-blind, placebo-controlled
  - Hypertensive patients over 60 without known cognitive disease (n=2418)
  - Nitrendipine +/- enalapril +/- hydrochlorthiazide vs. placebo
  - Target SBP < 150
  - Followed for a median of 2.0 years

  - Treatment reduced incidence of dementia by 50% (p=0.05)
  - Treatment prevented 19 cases of dementia in 1000 patients over 5 years

# Hypertension and VaD

- PROGRESS (Arch Intern Med. 2003 May 12;163(9):1069-75)
  - Double-blind, placebo-controlled
  - Patients with prior stroke or TIA (n=6105)
  - Perindopril +/- indapamide vs. placebo
  - Followed for a mean of 3.9 years
  - Treatment reduced cognitive decline (drop of 3 points on MMSE) by 19% (p=0.01)
  - Effect driven by patients in both groups who suffered recurrent stroke during the study (i.e. No clear effect on cognition in patients without recurrent stroke)

# Treatment of VaD

- Control of vascular risk factors recommended
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Obesity
  - Smoking

  - Atrial Fibrillation
  - Coronary Artery Disease
  - Congestive Heart Failure
  - Peripheral Artery Disease

  - Cerebrovascular Disease / Stroke

- Cholinesterase Inhibitors

# “Mixed” AD/Vascular Dementia

- Dementia sharing a mixture of qualities of Alzheimer’s disease and Vascular disease

- Prominent short-term memory decline
- Also prominent occurrence of cerebrovascular events, clinically or neuroradiologically, which appear to have influenced the clinical course

- More common than pure Vascular Dementia, it is likely the **most common** cause of dementia

- Treatment:  Cholinesterase Inhibitors and Management of Vascular Risk Factors

# Conclusions

- Frontotemporal dementia (FTD) is a relatively early-onset, aggressive neurodegeneration initially affecting personality and/or language
- Dementia with Lewy bodies (DLB) is a later-onset, sometimes aggressive neurodegeneration with parkinsonism, visual hallucinations, and REM Behavioural disorder
- Vascular dementia (VaD) is temporally associated with stroke, and may remain quite stable over time