

# **Cognitive and Behavioral Issues in PSP, CBD, FTD, and PPA**

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**Mayo Foundation**



# **Cognitive and Behavioral Issues in PSP, CBD, FTD, and PPA Outline**

- **History**
- **Brain-Behavior Correlations**
- **The Syndromes/Disorders**
- **Management**
- **Resources**
- **Questions**

# History

# **PSP, CBD, FTD, and PPA**

## **History**

- PSP – initially characterized in the 1960s
- CBD – initially characterized in the late 1960s
- PPA – initially characterized in 1982
  - nonfluent variant
  - semantic variant
- FTD – initially characterized in 1994

# **PSP, CBD, FTD, and PPA**

## **History**

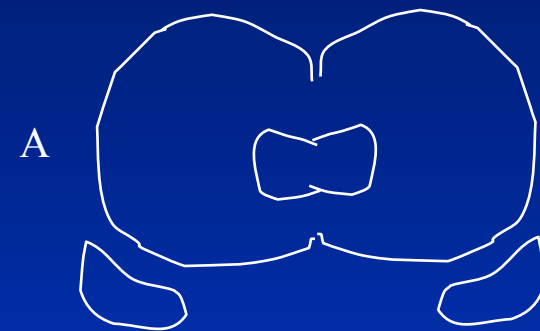
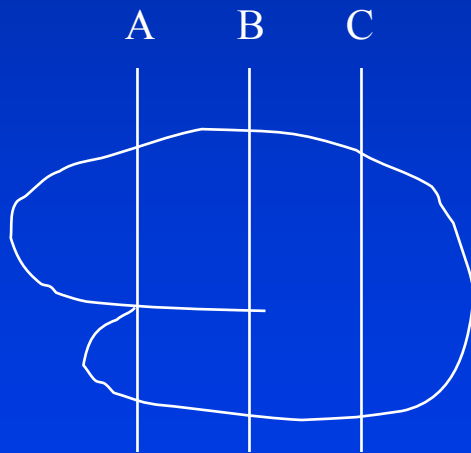
- The 4 different disorders have been classically considered to be distinct and separate
- Growing evidence that these are strikingly similar, with one of the primary distinctions being what parts of the brain are maximally affected

# **Brain-Behavior Correlations**

# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

*Templates*



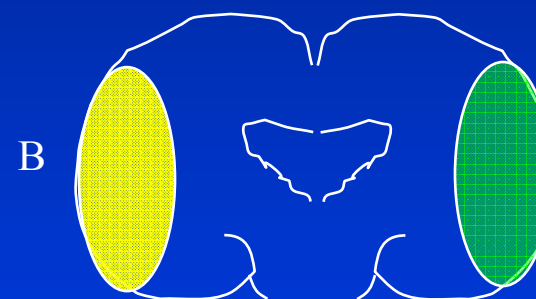
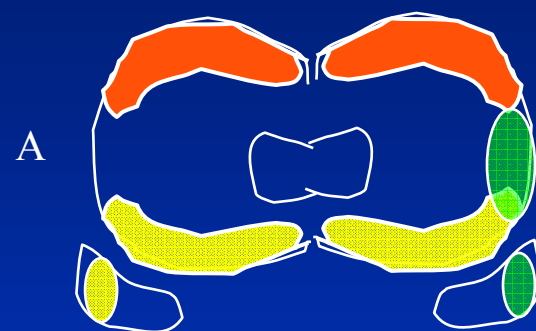
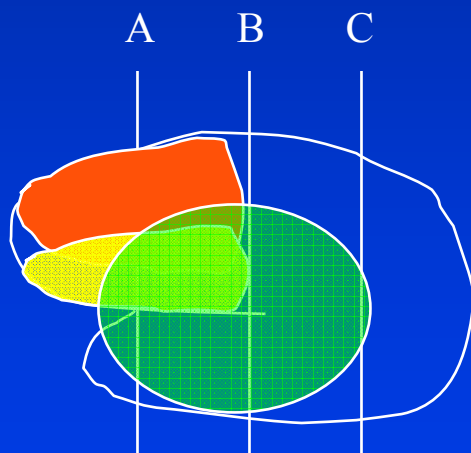
# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

● Thinking/Cognitive

● Behavior

● Language

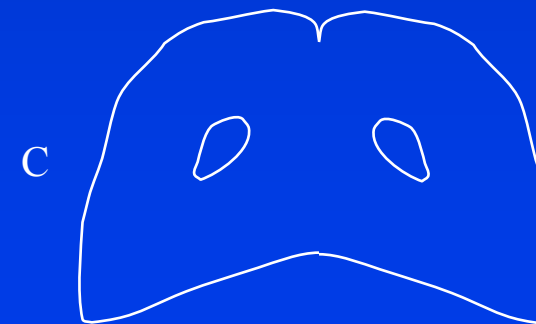
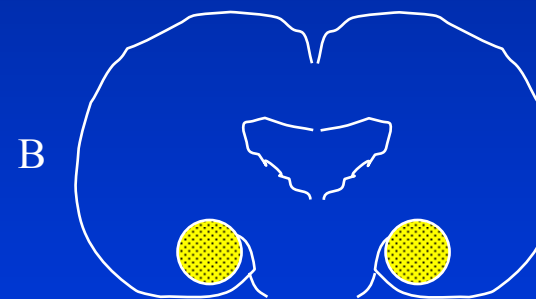
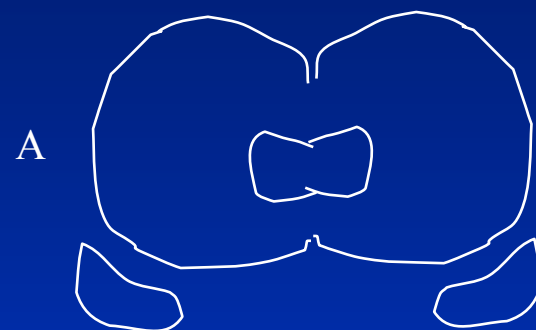
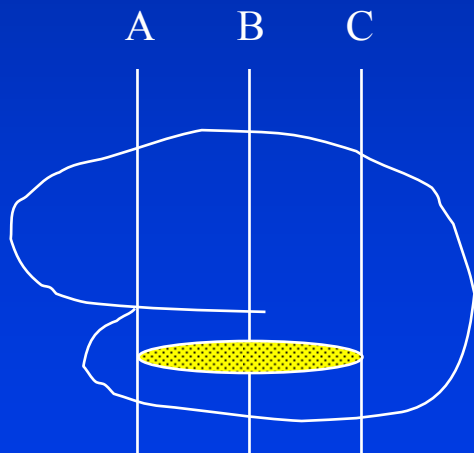




# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

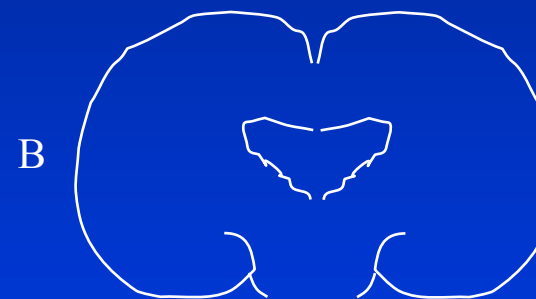
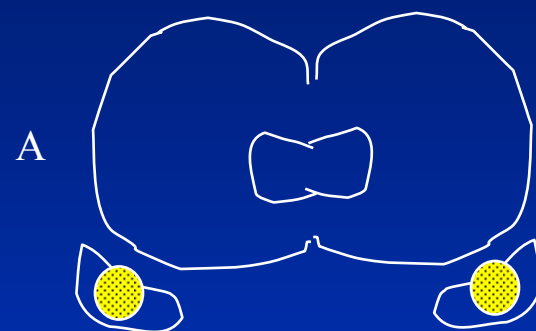
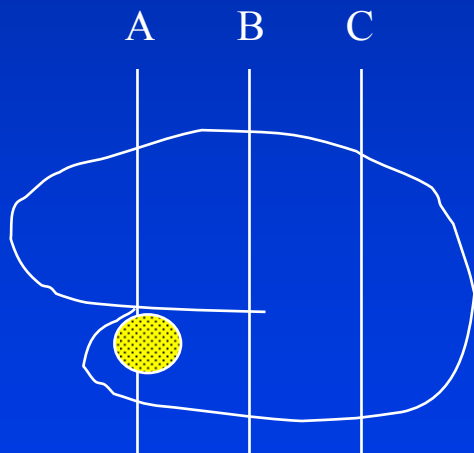
● Memory - hippocampi



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

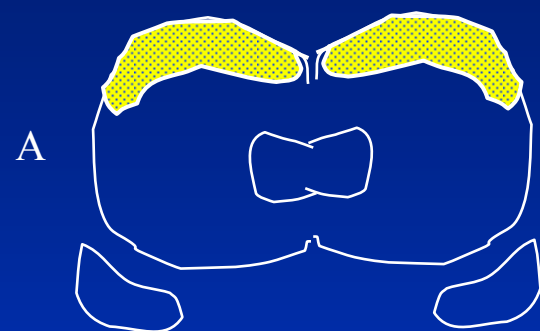
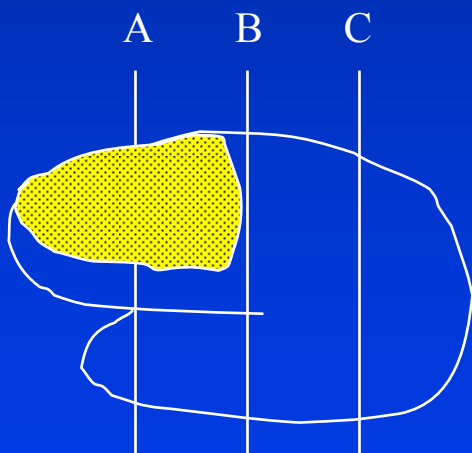
● “Emotional valence”  
- amygdala



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

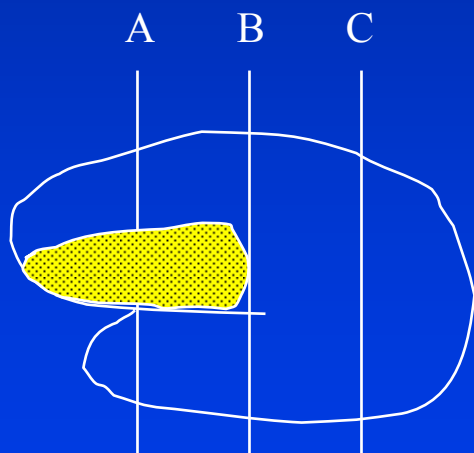
- Problem-solving, reasoning, complex decision-making - dorsolateral frontal regions



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

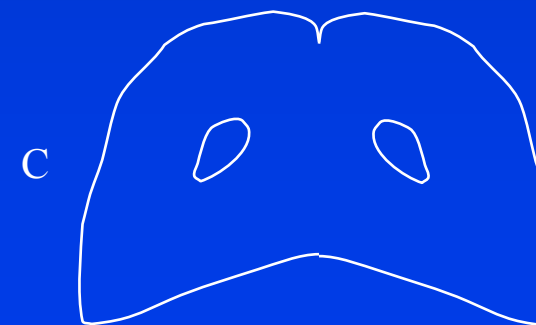
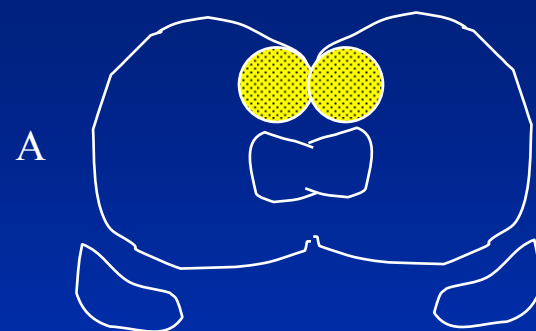
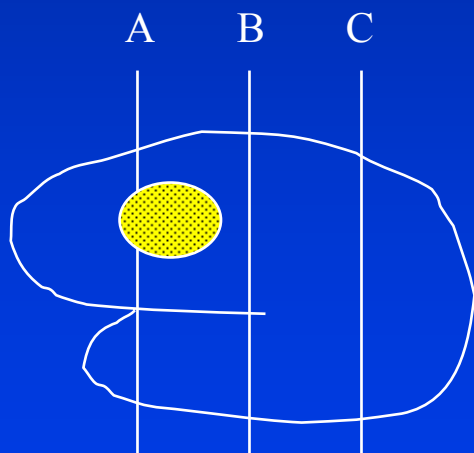
- Socially appropriate behavior, “theory of mind” - ventromedial frontal regions



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

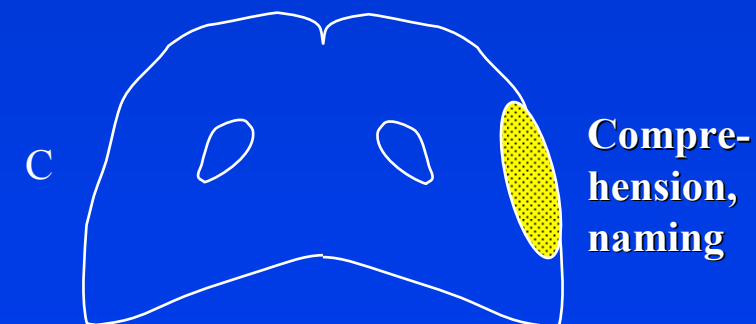
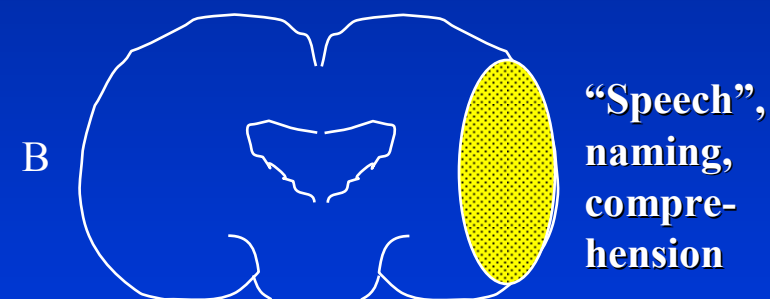
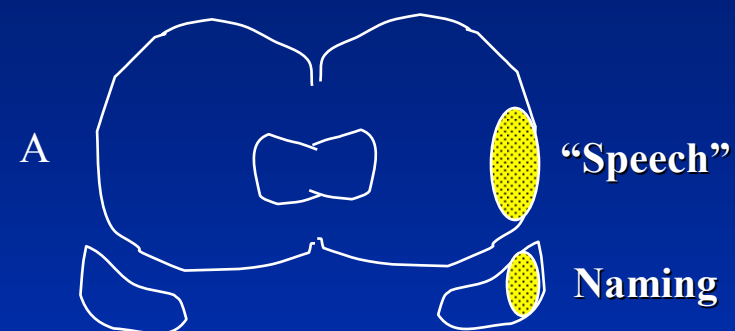
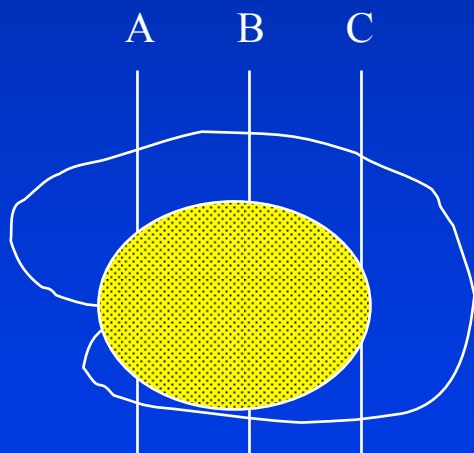
- Motivation, spontaneous actions - anterior cingulate region



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

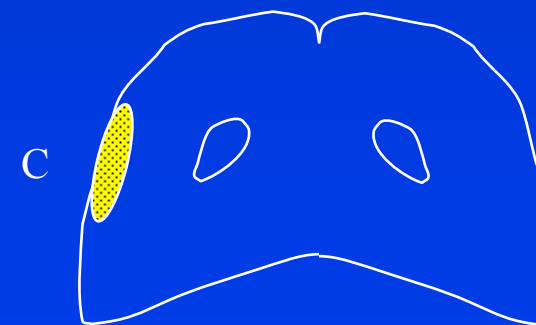
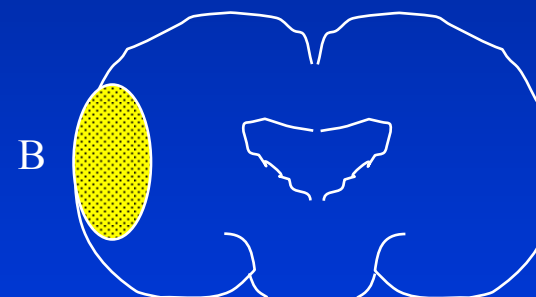
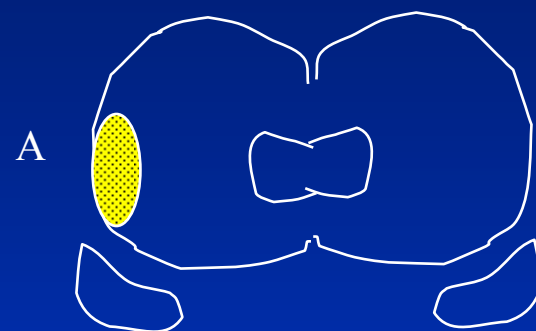
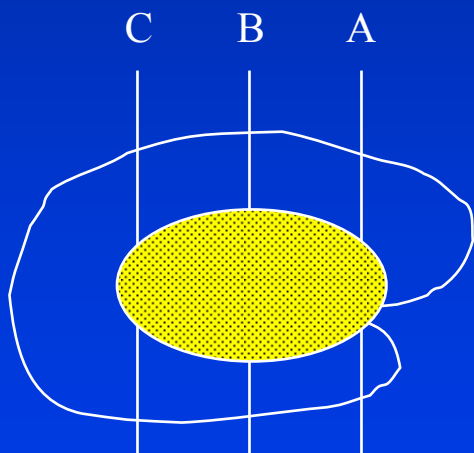
- Language - left frontal, temporal, parietal regions



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

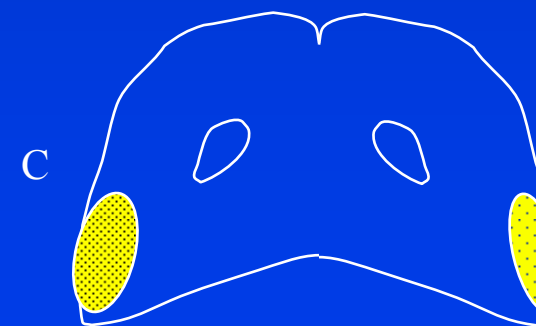
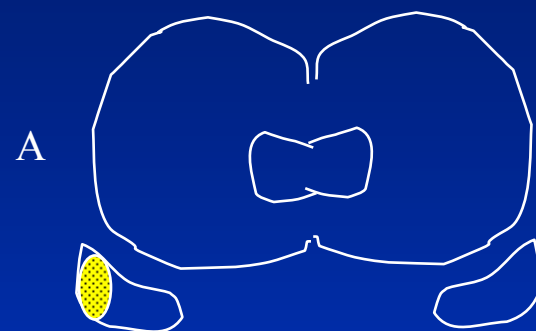
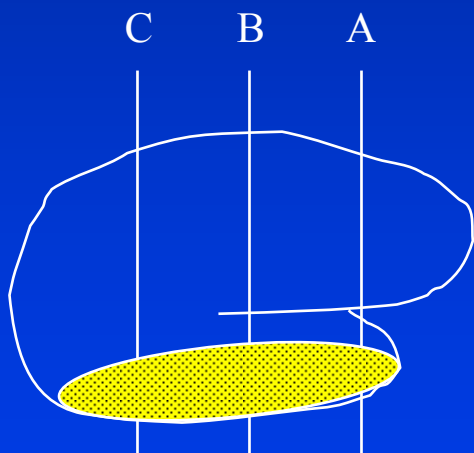
- **Prosody** - right frontal, temporal, parietal regions



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

- **Visual recognition** - right > left temporal and occipital regions





# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations



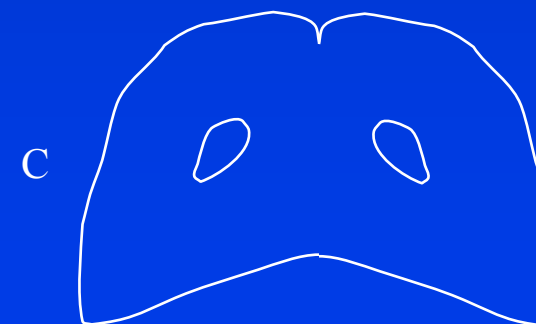
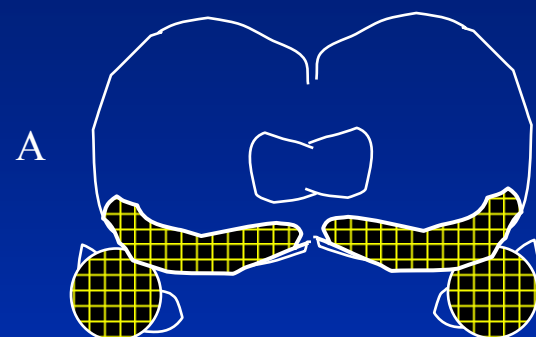
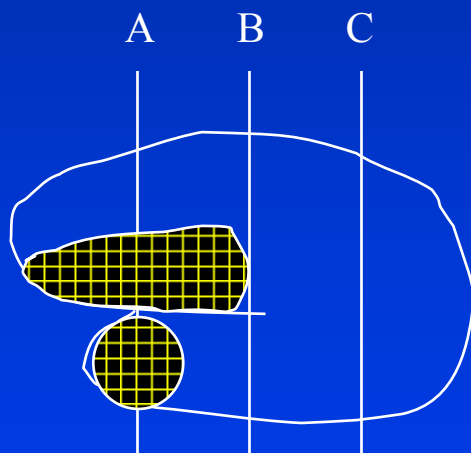
### Social disinhibition

Loss of empathy and insight

Change in food preferences

Hoarding of food

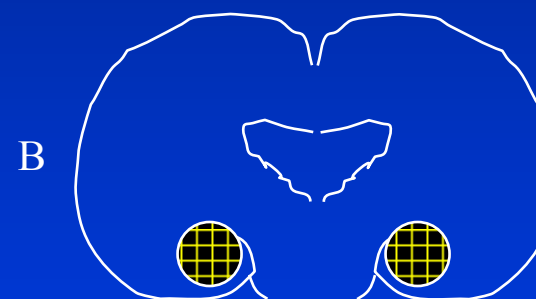
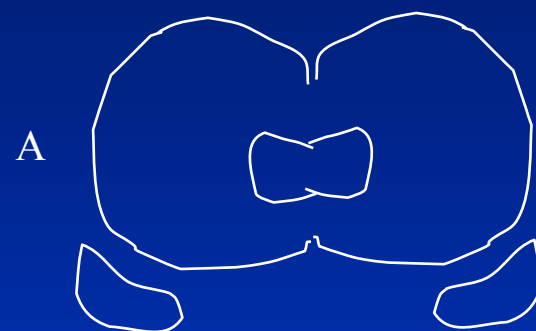
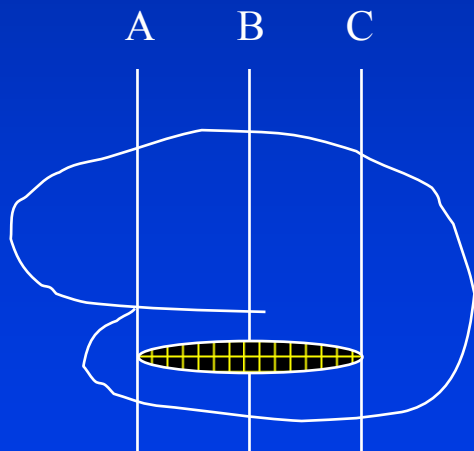
Utilization behavior



# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

 **Memory loss**



# PSP, CBD, FTD, and PPA

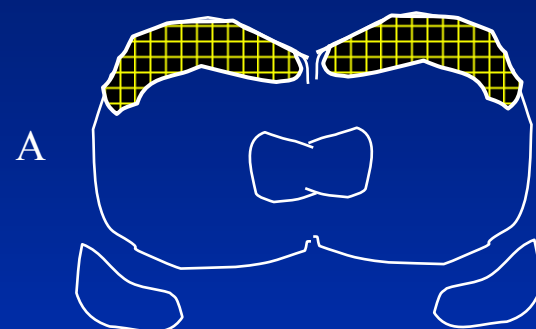
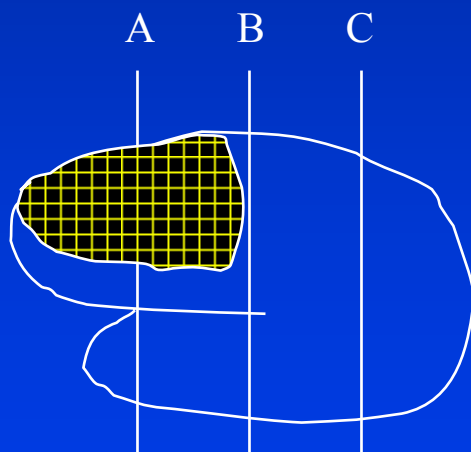
## Brain-Behavior Correlations



### Executive dysfunction

Poor planning and judgement

Inability to multitask

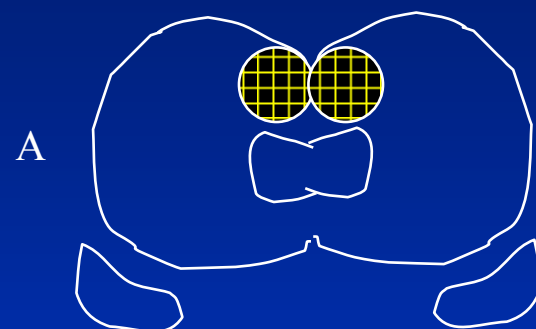
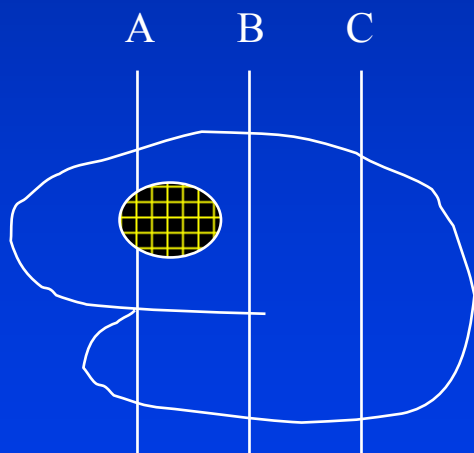


# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

### ● Loss of motivation

Tendency to sit, not initiative  
conversations or actions

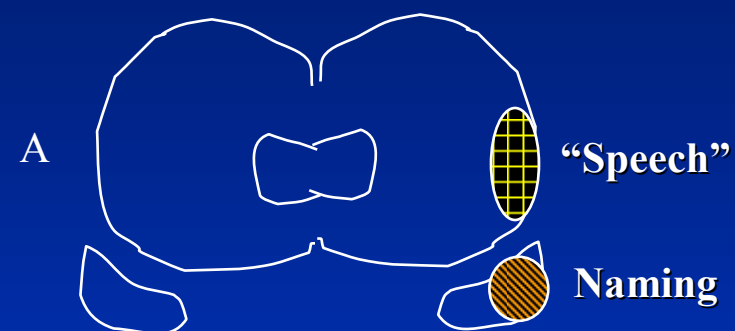
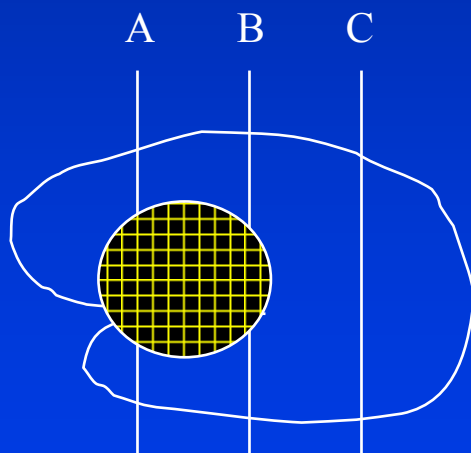


# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

● Poor verbal expression

● Poor naming of objects and people



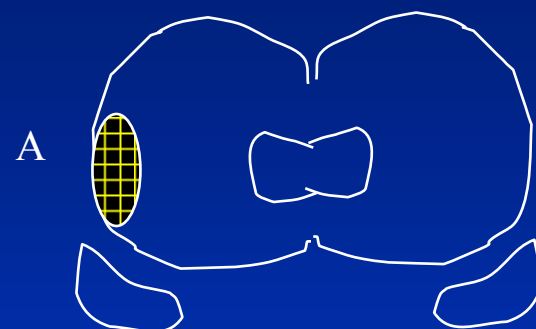
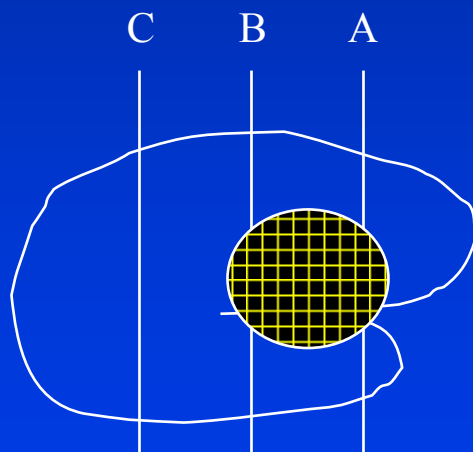
# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

### **Aprosodia**

Monotone voice

Unable to interpret inflections in  
voice another person's voice

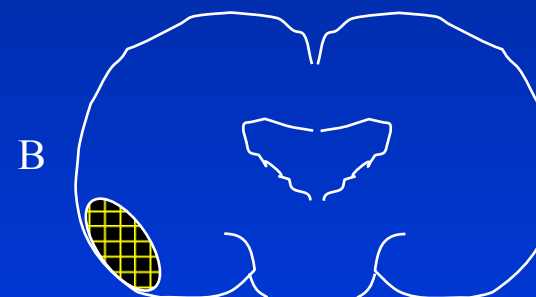
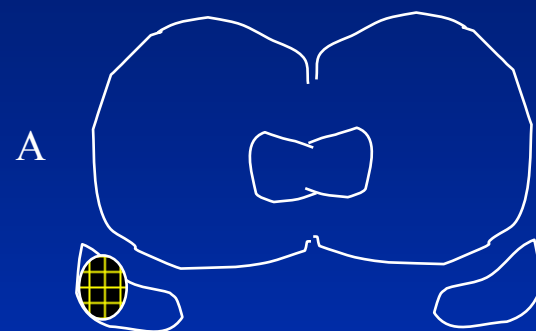
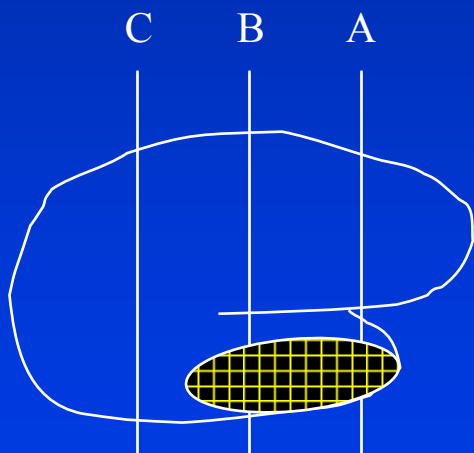


# PSP, CBD, FTD, and PPA

## Brain-Behavior Correlations

### Visual agnosia

Unable to recognize objects and people



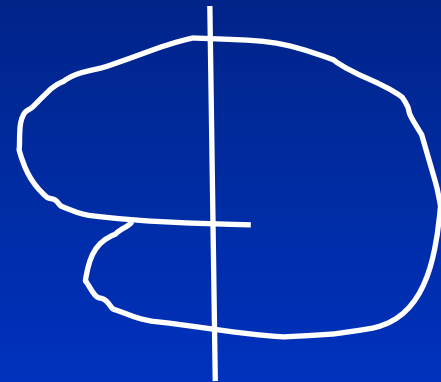
# **The Syndromes/Disorders**



# Progressive Supranuclear Palsy

## Clinical Features

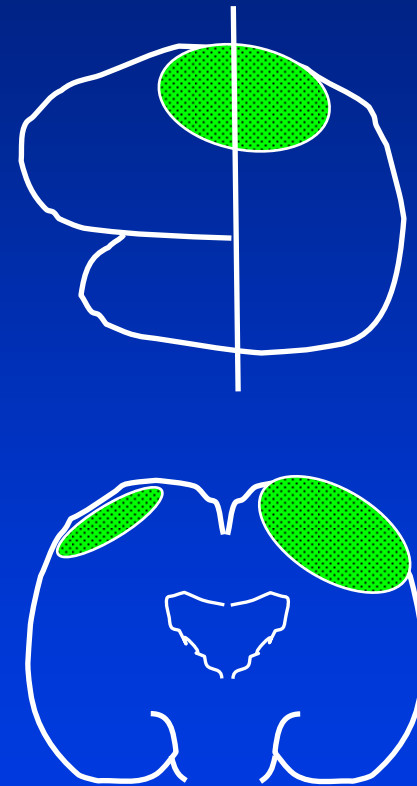
- symmetric rigidity and bradykinesia
  - axial > appendicular
  - levodopa unresponsive
- postural/gait instability
  - frequent falls
- extraocular movement dysfunction
  - saccadic pursuits
  - delayed, slowed saccades
  - supranuclear gaze palsy, particularly downgaze
- apathy, bradyphrenia



# Corticobasal Syndrome/Corticobasal Degeneration

## Clinical Features

- Progressive course
- Asymmetric findings
- Limb rigidity
- Limb apraxia

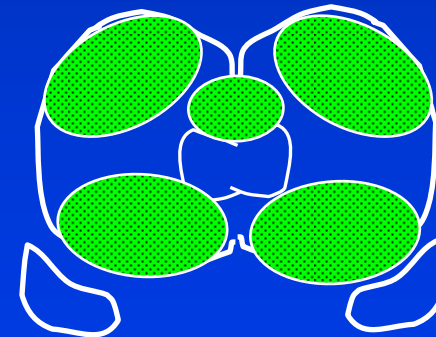
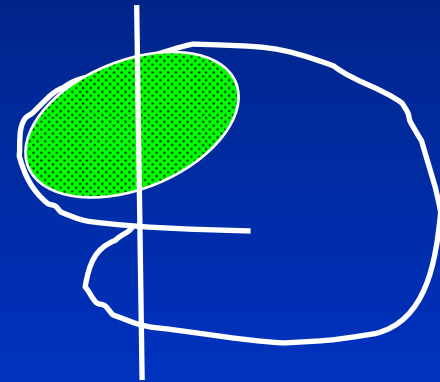


*Progressive asymmetric rigidity and apraxia*

# Behavioral Variant Frontotemporal Dementia

## Clinical Features

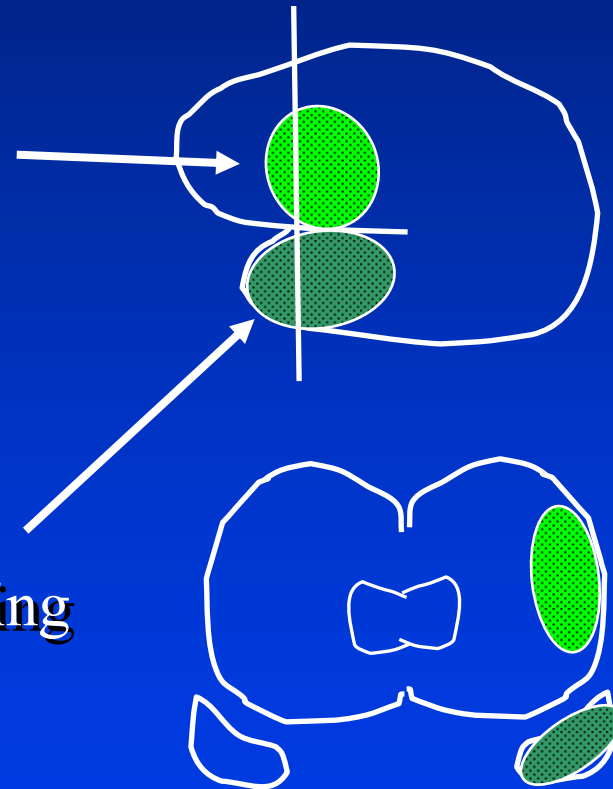
- personality/behavioral changes
- loss of empathy/sympathy
- loss of insight
- apathy
- social disinhibition
- change in food preferences
- poor judgement and planning



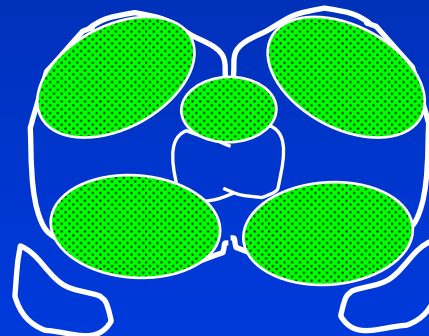
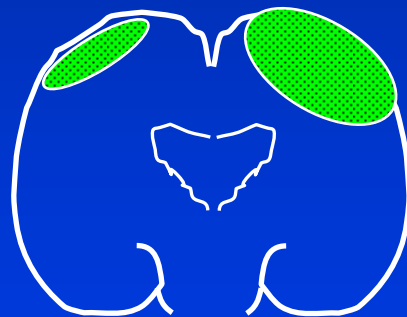
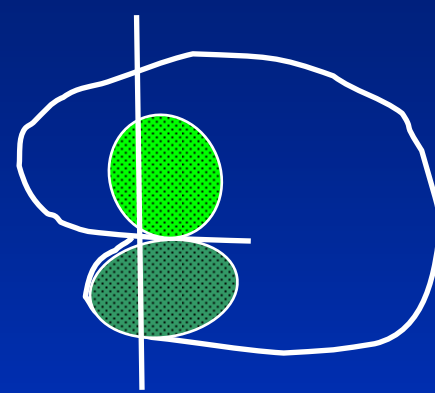
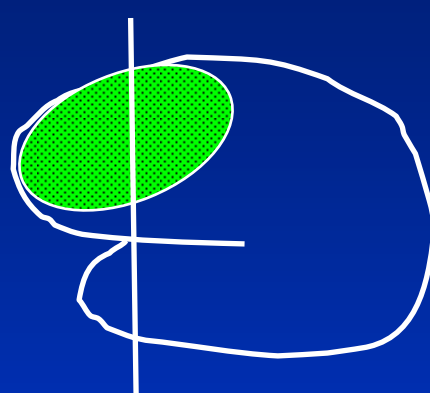
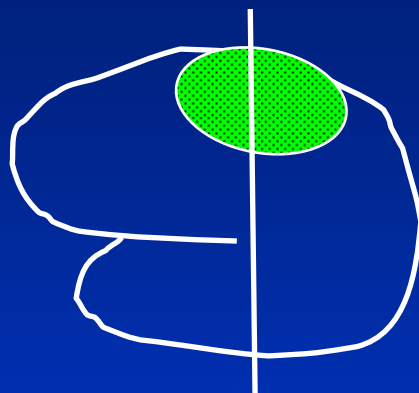
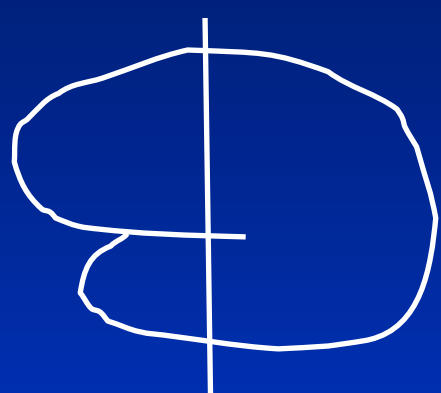
# Primary Progressive Aphasia

## Clinical Features

- Nonfluent
  - changes in speech/language production
- Semantic
  - loss of nouns and word meaning



# Frontotemporal Lobar Degenerations



**PSP**

**CBD**

**FTD**

**PPA**

# **Management**

# **PSP, CBD, FTD, and PPA**

## **Management**

### **Pharmacotherapy**

Improve symptoms

Manage behaviors

Decrease injury risk

### **Non-Pharmacotherapy**

Improve symptoms

Manage behaviors

Decrease injury risk

Improve caregiving strategies

*Improve QOL for all involved*

# PSP, CBD, FTD, and PPA

## Management

- Approach – ask patients and caregivers to list and then rank which symptoms/problems are most bothersome, which allows the clinicians to tailor the management plan
- Problem list:
  - Cognitive
  - Neuropsychiatric
  - Motor
  - Speech/swallowing
  - Sleep



# **PSP, CBD, FTD, and PPA**

## **Management**

- There are no FTD-approved medications specifically developed to impact PPA, CBD, FTD, and PPA
- There are few well-designed studies that have shown that any medication improves symptoms in any of these disorders
- There is considerable debate among clinicians whether any medications are worth using in patients with any of these disorders
- Almost all medications to be discussed are expensive and are associated with mild to severe side-effects

# **PSP, CBD, FTD, and PPA**

## **Management**

### **Cognitive**

Education/Counseling/Behavioral Management:

Stay physically, mentally, and socially active

Establish and maintain a daily routine

Religious use of a daily planner

# PSP, CBD, FTD, and PPA

## Management

### Cognitive (cont.)

Executive dysfunction, memory impairment:

? Carbidopa/levodopa, dopamine agonists

Sinemet®, Mirapex®, Requip®

? Cholinesterase inhibitors

Aricept®, Exelon®, Razadyne®

? Psychostimulants

Provigil®, Nuvigil®, Ritalin®, Adderall®, Desoxyn®

? NMDA antagonists

Namenda®

# **PSP, CBD, FTD, and PPA**

## **Management**

### **Neuropsychiatric**

Education/Counseling/Behavioral Management:

Develop tolerance and choose your battles!

Acknowledge and redirect; refrain from arguing

“Employ therapeutic fibs”

Support group involvement

Work with local psychologists and psychiatrists

# PSP, CBD, FTD, and PPA

## Management

### Neuropsychiatric (cont.)

Disinhibition, socially inappropriate behavior, delusions:

? Selective serotonin reuptake inhibitors

Celexa®, Lexapro®, Paxil®, Prozac®, Remeron®, Zoloft®

? Atypical neuroleptics

Seroquel®, Risperdal®, Zyprexa®

? Anticonvulsants

Depakote®, Neurontin®, Tegretol®

? Beta-blockers

Inderal®

# PSP, CBD, FTD, and PPA

## Management

### Neuropsychiatric (cont)

Apathy:

? Selective serotonin reuptake inhibitors

Celexa®, Lexapro®, Paxil®, Prozac®, Zoloft®

? Psychostimulants

Provigil®, Nuvigil®, Ritalin®, Adderall®, Desoxyn®

? Carbidopa/levodopa, dopamine agonists

Sinemet®, Mirapex®, Requip®

? Cholinesterase inhibitors

Aricept®, Exelon®, Razadyne®

# PSP, CBD, FTD, and PPA

## Management

### Motor

Parkinsonism:

? Carbidopa/levodopa, dopamine agonists  
Sinemet®, Mirapex®, Requip®

Deep brain stimulation (experimental)

Gait impairment/falls:

Gait assistance devices and PT

Power operated vehicle (POV)

# PSP, CBD, FTD, and PPA

## Management

### Speech/Swallowing

Dysarthria/nonfluent aphasia/apraxia of speech:

Speech therapy

? Carbidopa/levodopa, dopamine agonists

Sinemet®, Mirapex®, Requip®

Dysphagia:

Swallowing study

Thick-It, pureed food, PEG tube



# **PSP, CBD, FTD, and PPA**

## **Management**

### **Sleep Disorders**

Insomnia

Daytime hypersomnia

Obstructive sleep apnea

Central sleep apnea

Restless legs syndrome

Periodic limb movements during sleep

\* Discuss with primary MD, and in select cases, consider a formal sleep medicine evaluation and sleep study

# **Pathophysiology and Implications for Future Therapies**

# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies

### Tauopathies

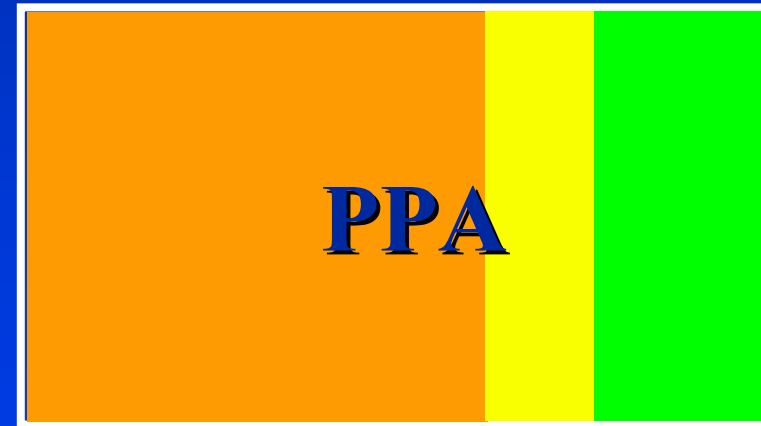
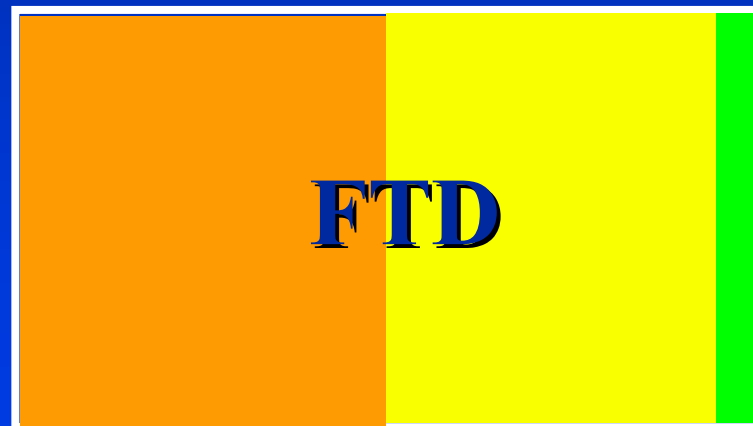
- Pick's disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Argyrophilic grain disease
- Frontotemporal dementia with Parkinsonism associated with mutations in microtubule associated protein tau on chromosome 17 (FTDP-17*MAPT*)

### TDP-43opathies

- Frontotemporal lobar degeneration (FTLD) with motor neuron disease (MND)
- Frontotemporal lobar degeneration (FTLD) with ubiquitin/TDP-43-positive inclusions
- Frontotemporal dementia with Parkinsonism associated with mutations in progranulin on chromosome 17 (FTDP-17*PGRN*)

# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies



tau



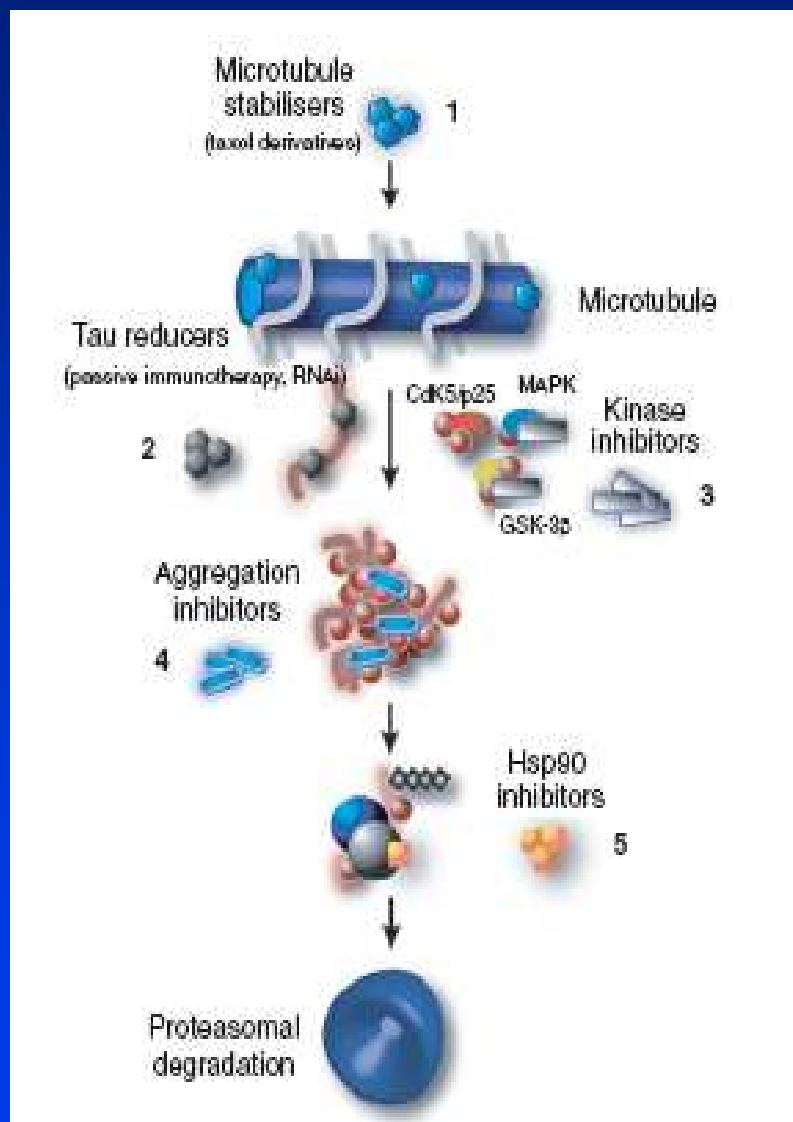
TDP-43



amyloid

# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies



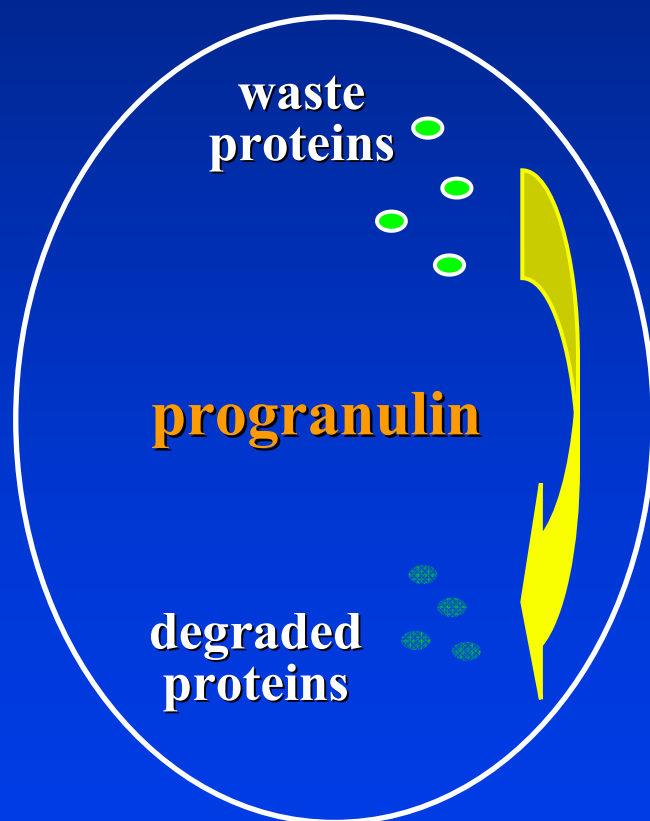
### ? Tauopathy therapies

- Microtubule stabilizers
- tau kinase inhibitors
- Hsp90 inhibitors
- tau aggregation inhibitors
  - davunetide
  - rember

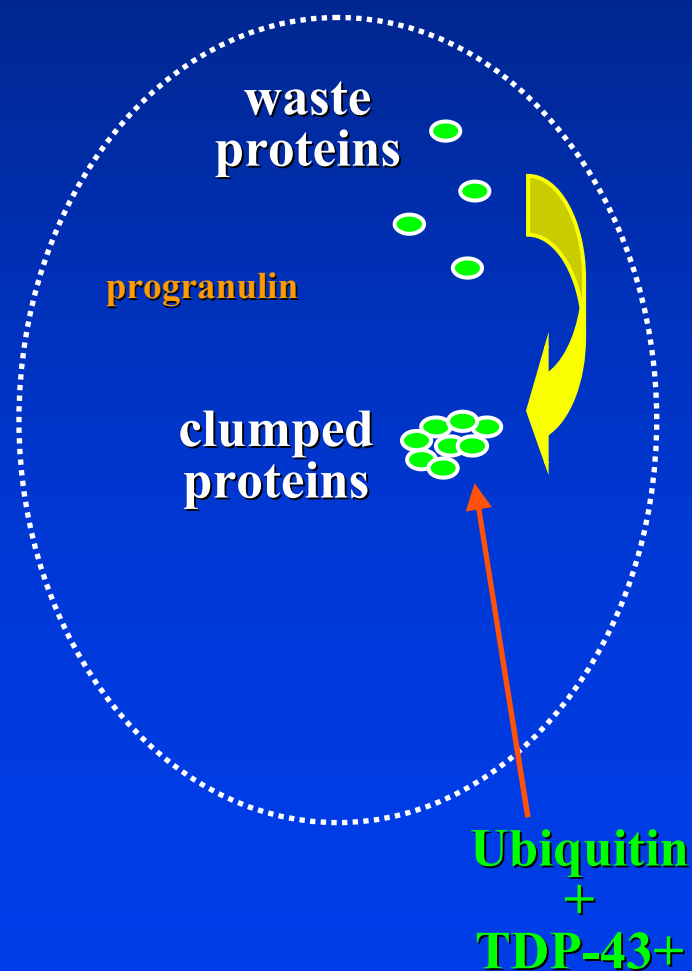
# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies

Normal neuron



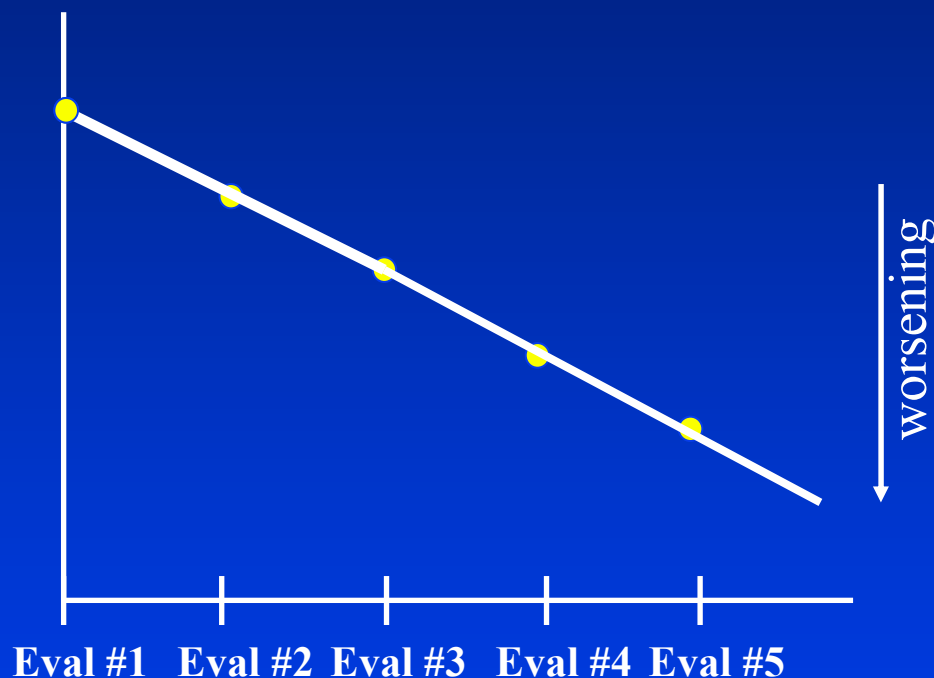
Abnormal neuron



# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies

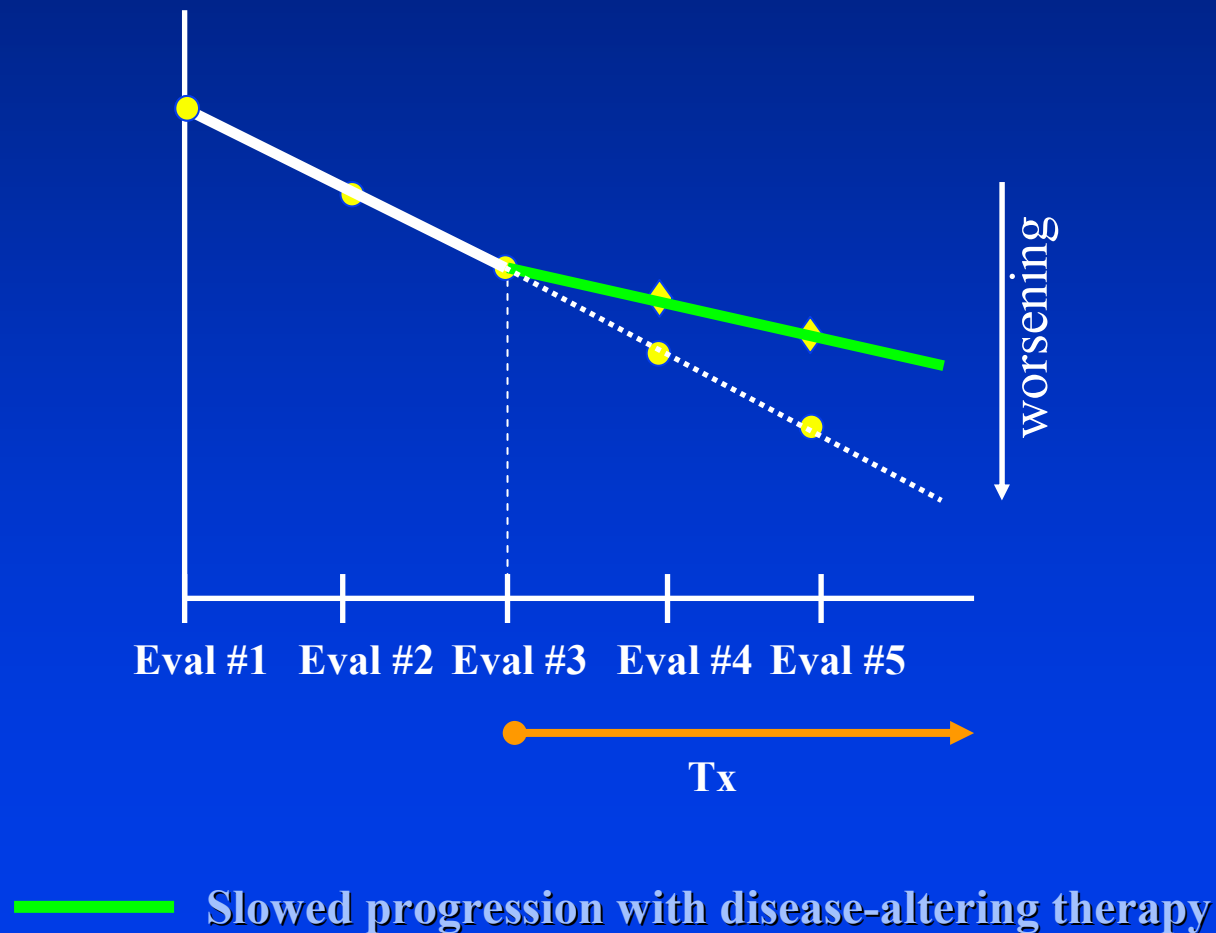
Theoretical considerations for future experimental drug trials



# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials

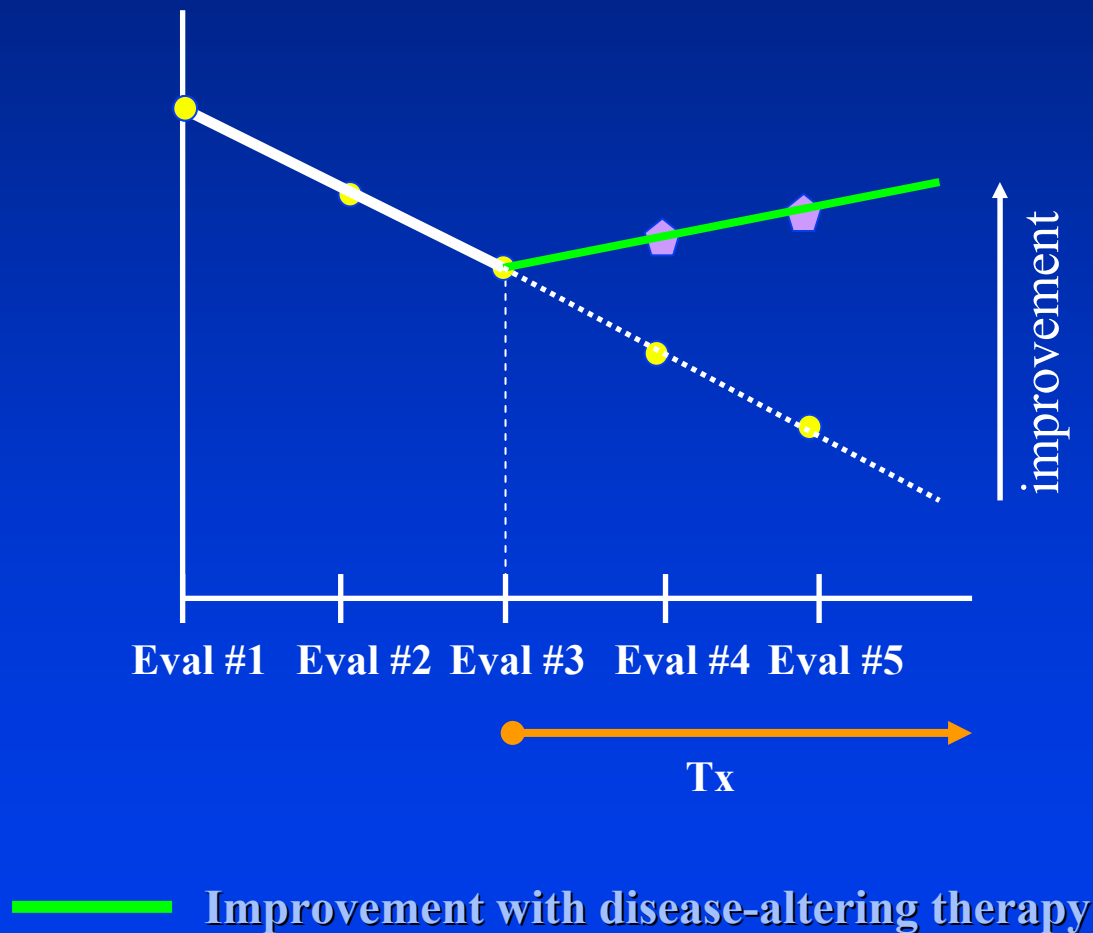




# PSP, CBD, FTD, and PPA

## Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials



# PSP, CBD, FTD, and PPA

## Research Protocol Participation

*Consider participating in research studies!!*

*Thank you!!*

# **PSP, CBD, FTD, and PPA**

## **Future Directions**

- Increase awareness among the public and health care professions that PSP, CBD, FTD, and PPA exist, are recognizable disorders, and can be diagnosed and managed
- Develop networks of patients, families, friends, and health care professionals to improve managing the day-to-day aspects of the disorders
- Increase federal and private funding for research, education, and counseling

**This is where you can help!**

# PSP, CBD, FTD, and PPA

## Future Directions

- Refine the clinical, genetic, neuropsychological, radiologic, and pathologic characterization of the disorders that cause these disorders
- Improve our understanding of tau and TDP-43 protein physiology and pathophysiology so promising therapies can be developed and tested
- Identify and develop clinical, laboratory, neuropsychological, and radiologic measures for future therapeutic drug trials

***Ultimately prevent, delay the onset, and slow the progression of the disorders that cause PSP, CBD, FTD, and PPA***

# **Resources**

**(some of many excellent resources)**

# FTD and PPA

## Resources - Websites



The Association for  
Frontotemporal Dementias  
*Opening the gateway to help and a cure*

<http://www.ftd-picks.org>



NORTHWESTERN  
UNIVERSITY

Feinberg School of Medicine

CNADC > PPA & Frontotemporal Dementia

PPA Newsletter  
Diagnosis

Primary Progressive Aphasia

<http://www.brain.northwestern.edu/ppa/index.html>

# PSP and CBD

## Resources - Websites



<http://curepsp.org>



<http://www.ftd-picks.org>

**Questions?**