

Perspectives on Frontotemporal Dementia and Primary Progressive Aphasia

COGNITIVE NEUROLOGY AND
ALZHEIMER'S DISEASE CENTER

.....
**FRONTOTEMPORAL DEMENTIA AND
PRIMARY PROGRESSIVE APHASIA**

**CAREGIVER
EDUCATION *and* SUPPORT
CONFERENCE**
.....

Cosponsored by the Association for Frontotemporal
Dementias and the National Aphasia Association

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Rochester, Minnesota**

**Alzheimer's Disease Research Center
Mayo Foundation**



Disclosures

Financial/Other

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- Honoraria from the American Academy of Neurology
- Research support from the NIA, NINDS, and the Alzheimer's Association

Off-label and/or Investigational Use

- I will discuss use of some medications not FDA-approved for the indications to be reviewed

Perspectives on FTD and PPA

Outline

- **Symptoms**
- **Brain-Behavior Correlations**
- **Genetics**
- **Pathophysiology and Future Perspectives**
- **Resources/Websites**

Symptoms

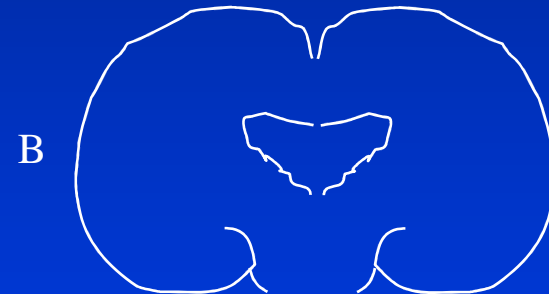
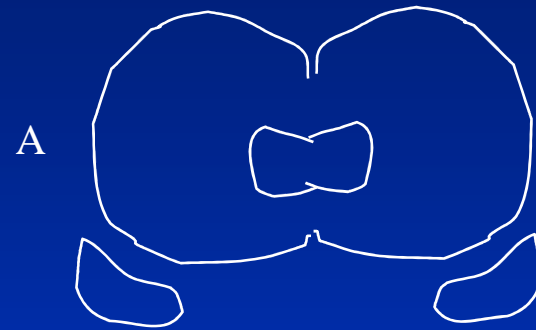
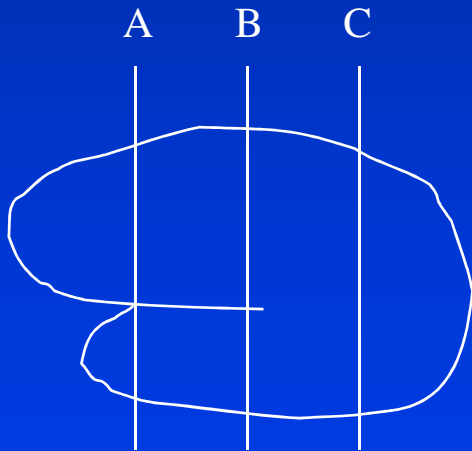
Patient Examples

Brain-Behavior Correlations

FTD and PPA

Brain-Behavior Correlations

Templates



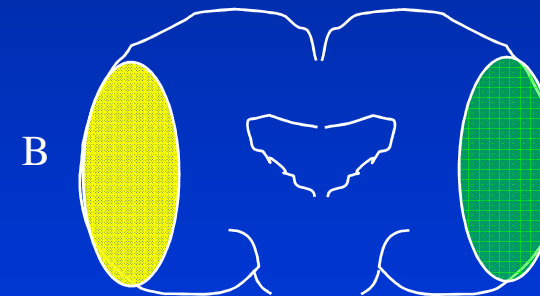
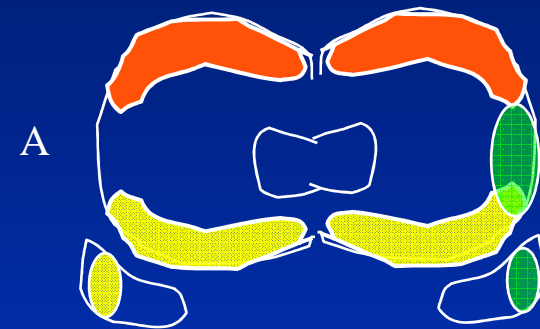
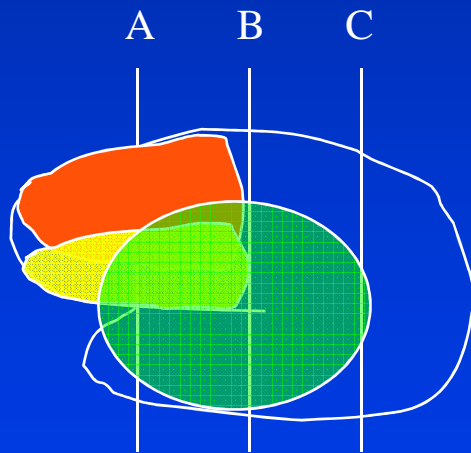
FTD and PPA

Brain-Behavior Correlations

● Thinking/Cognitive

● Behavior

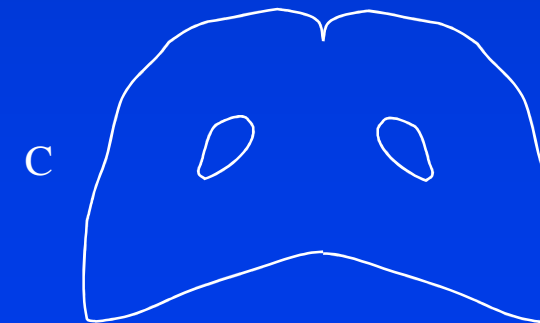
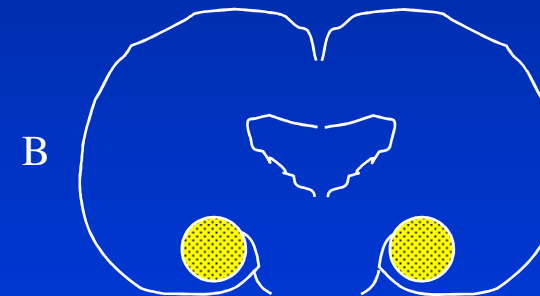
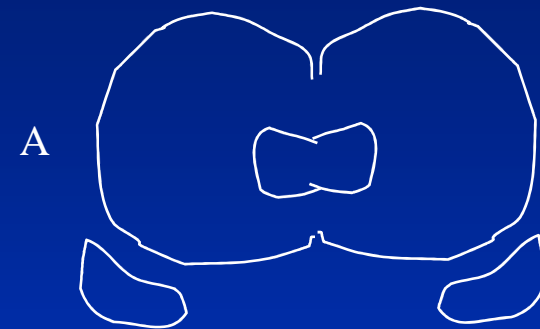
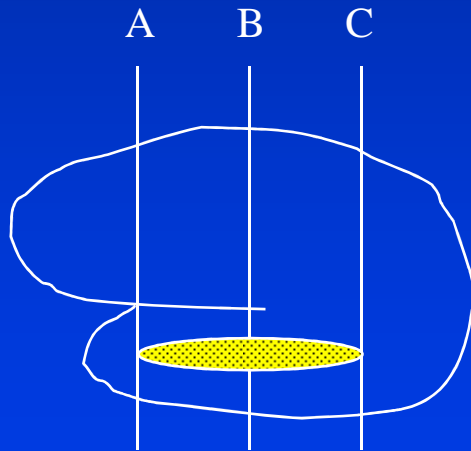
● Language



FTD and PPA

Brain-Behavior Correlations

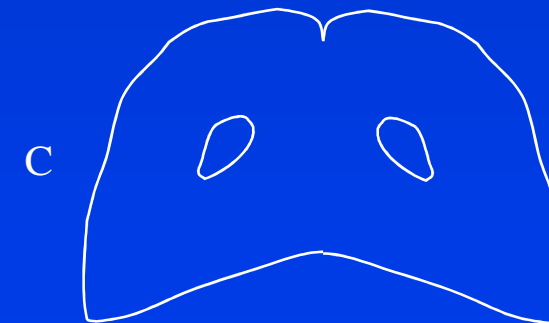
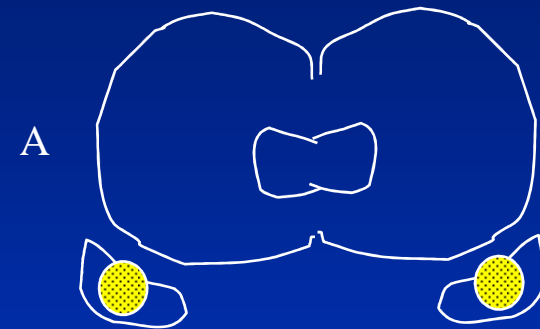
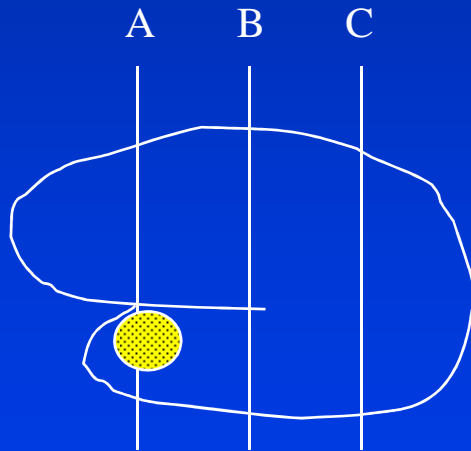
● Memory - hippocampi



FTD and PPA

Brain-Behavior Correlations

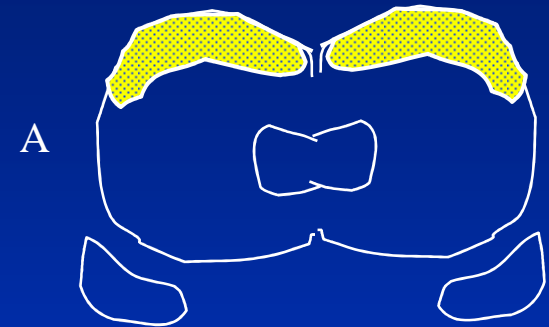
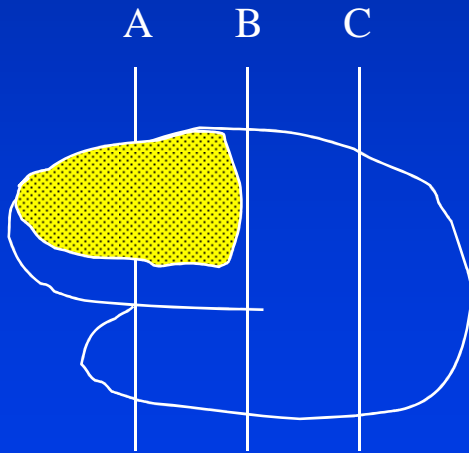
● “Emotional valence”
- amygdala



FTD and PPA

Brain-Behavior Correlations

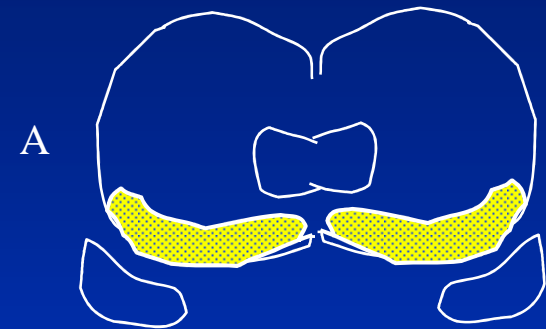
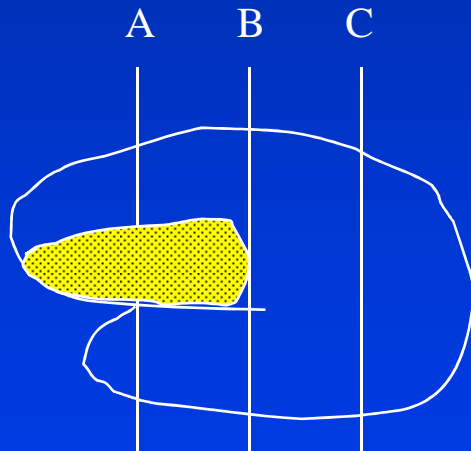
- Problem-solving, reasoning, complex decision-making - dorsolateral frontal regions



FTD and PPA

Brain-Behavior Correlations

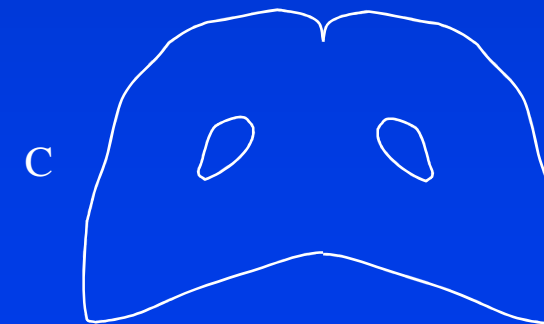
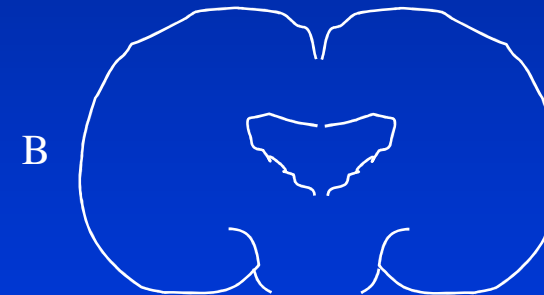
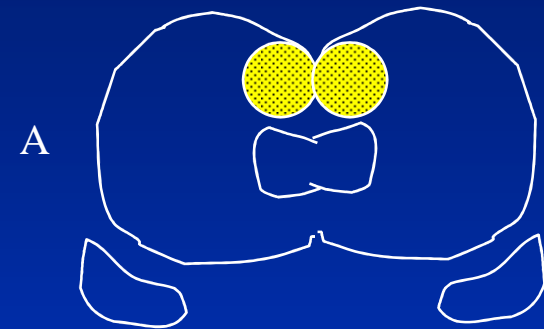
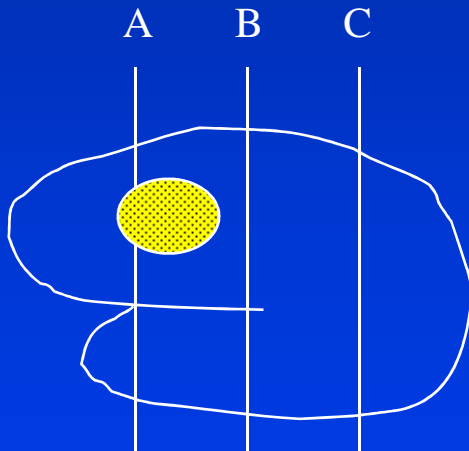
- Socially appropriate behavior, “theory of mind” - ventromedial frontal regions



FTD and PPA

Brain-Behavior Correlations

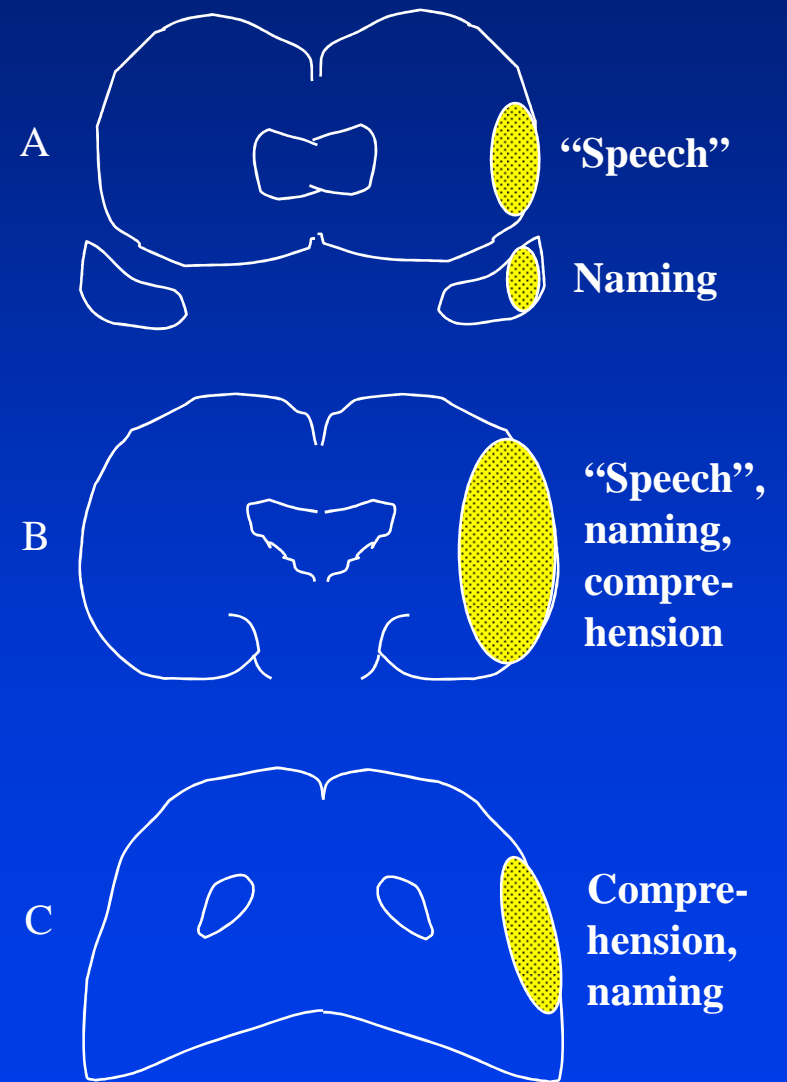
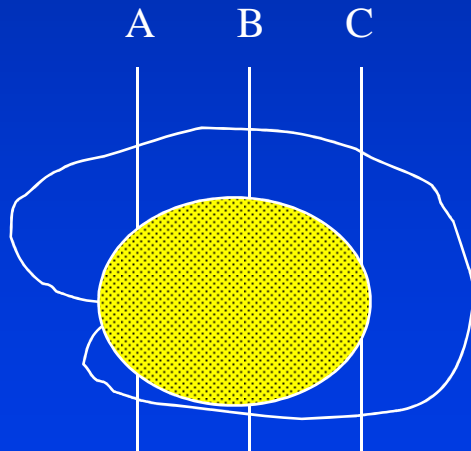
- **Motivation, spontaneous actions** - anterior cingulate region



FTD and PPA

Brain-Behavior Correlations

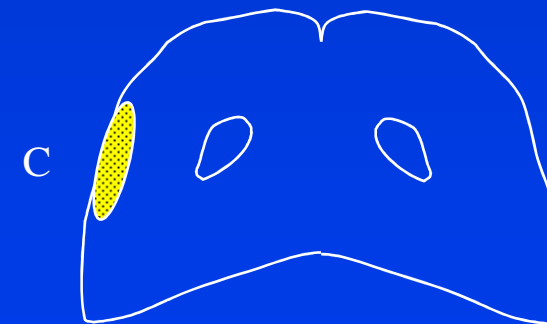
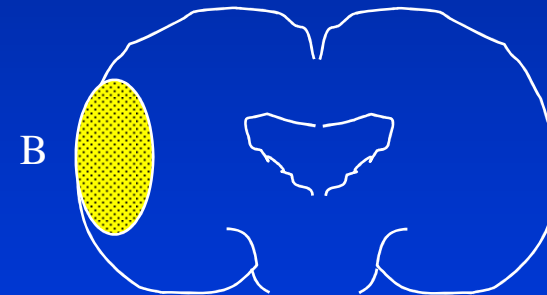
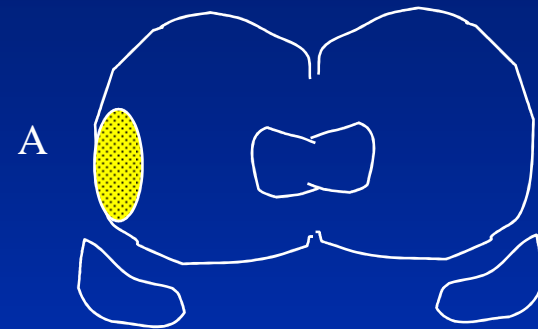
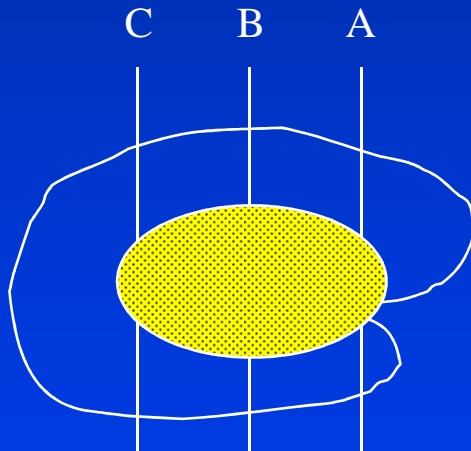
- **Language** - left frontal, temporal, parietal regions



FTD and PPA

Brain-Behavior Correlations

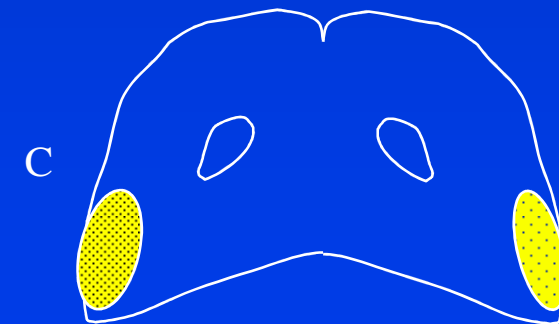
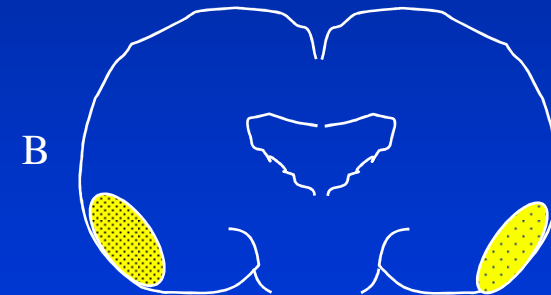
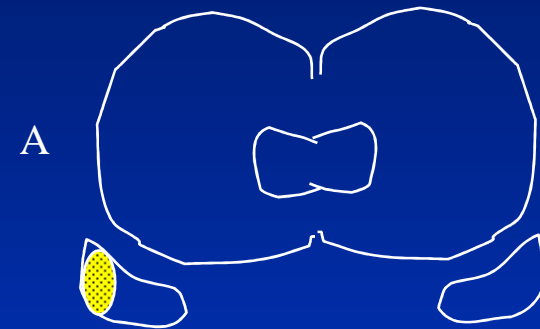
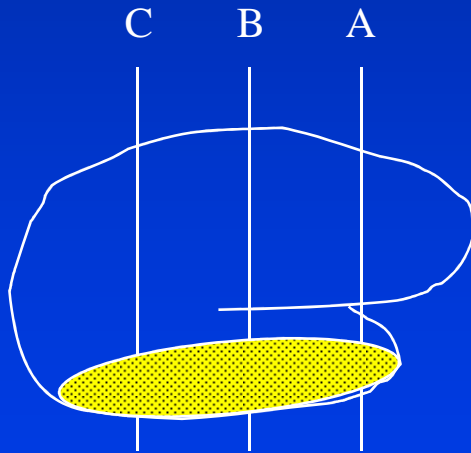
- **Prosody** - right frontal, temporal, parietal regions



FTD and PPA

Brain-Behavior Correlations

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



FTD and PPA

Brain-Behavior Correlations

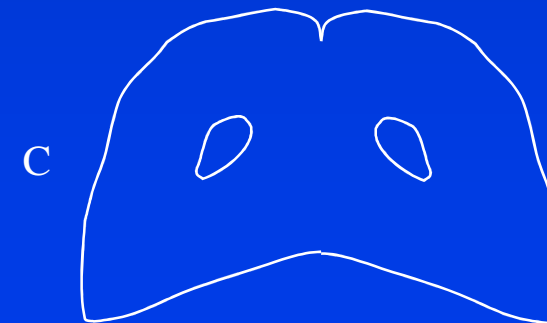
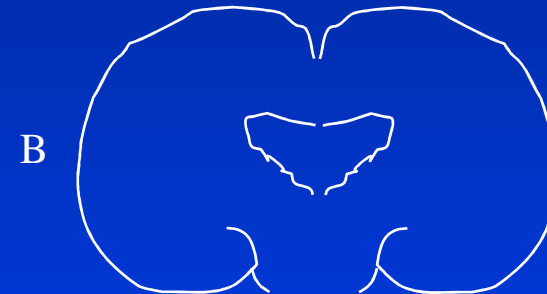
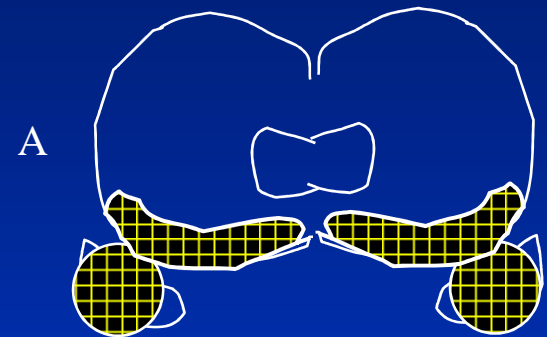
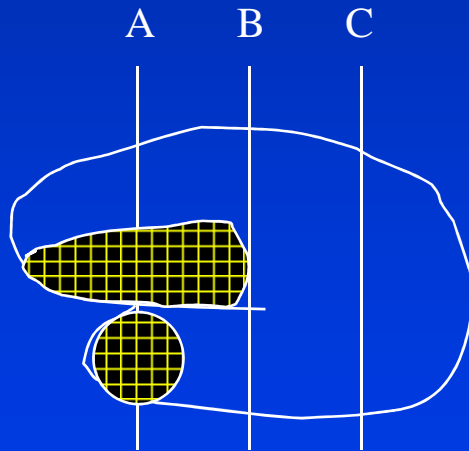


Social disinhibition

Loss of empathy and insight

Ritualistic behavior

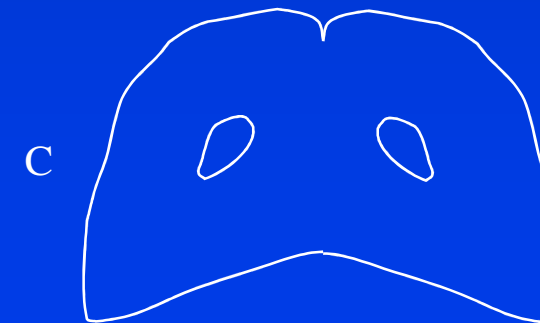
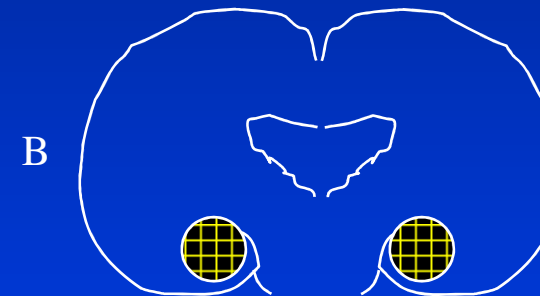
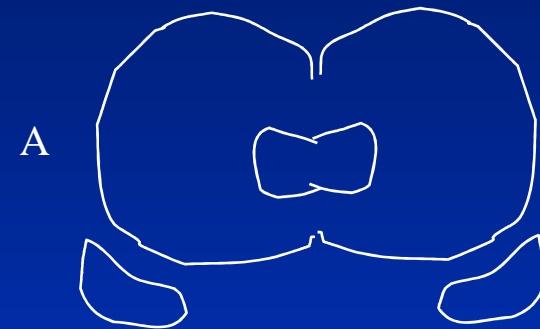
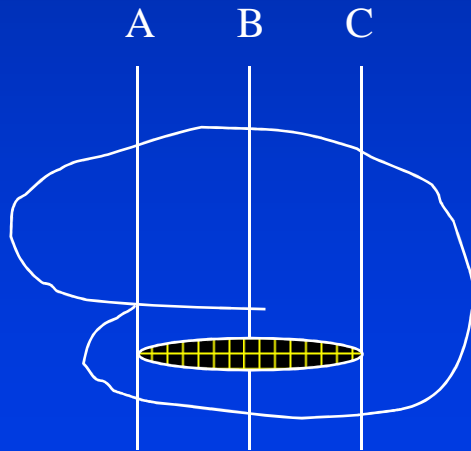
Change in eating behavior



FTD and PPA

Brain-Behavior Correlations

 **Memory loss**



FTD and PPA

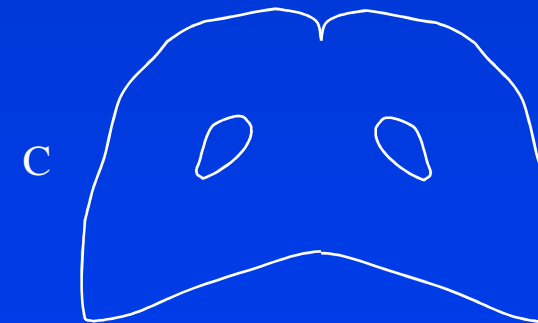
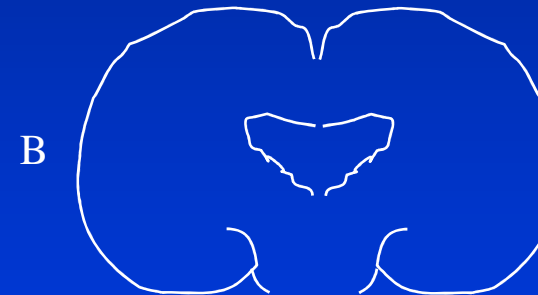
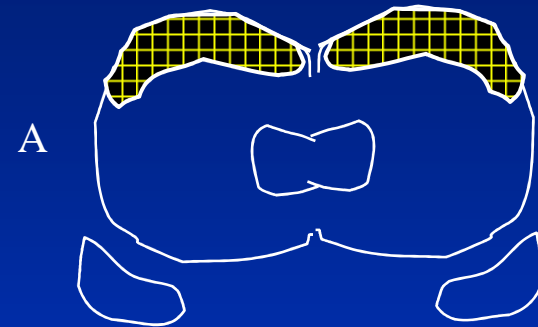
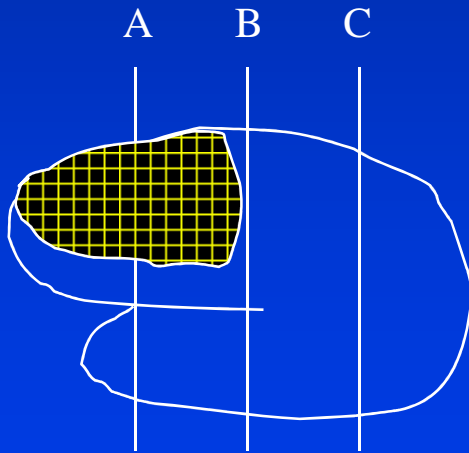
Brain-Behavior Correlations



Executive dysfunction

Poor planning and judgement

Inability to multitask

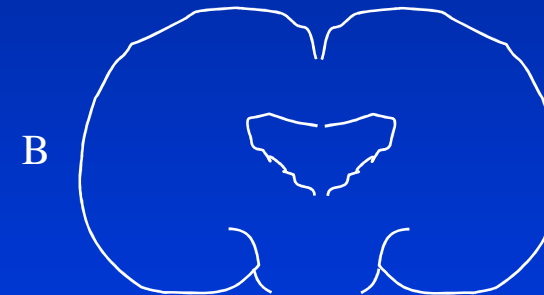
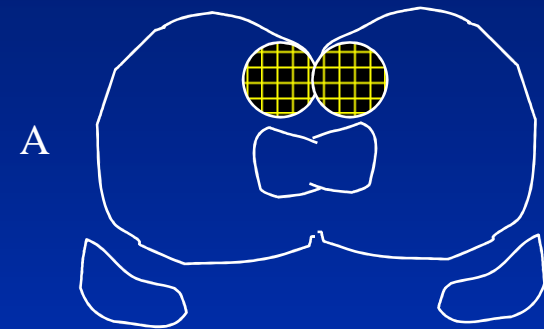
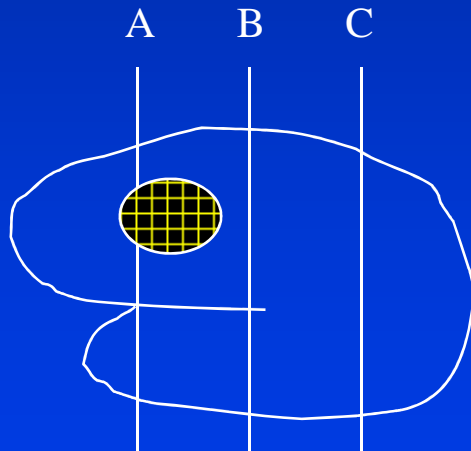


FTD and PPA

Brain-Behavior Correlations

● Loss of motivation

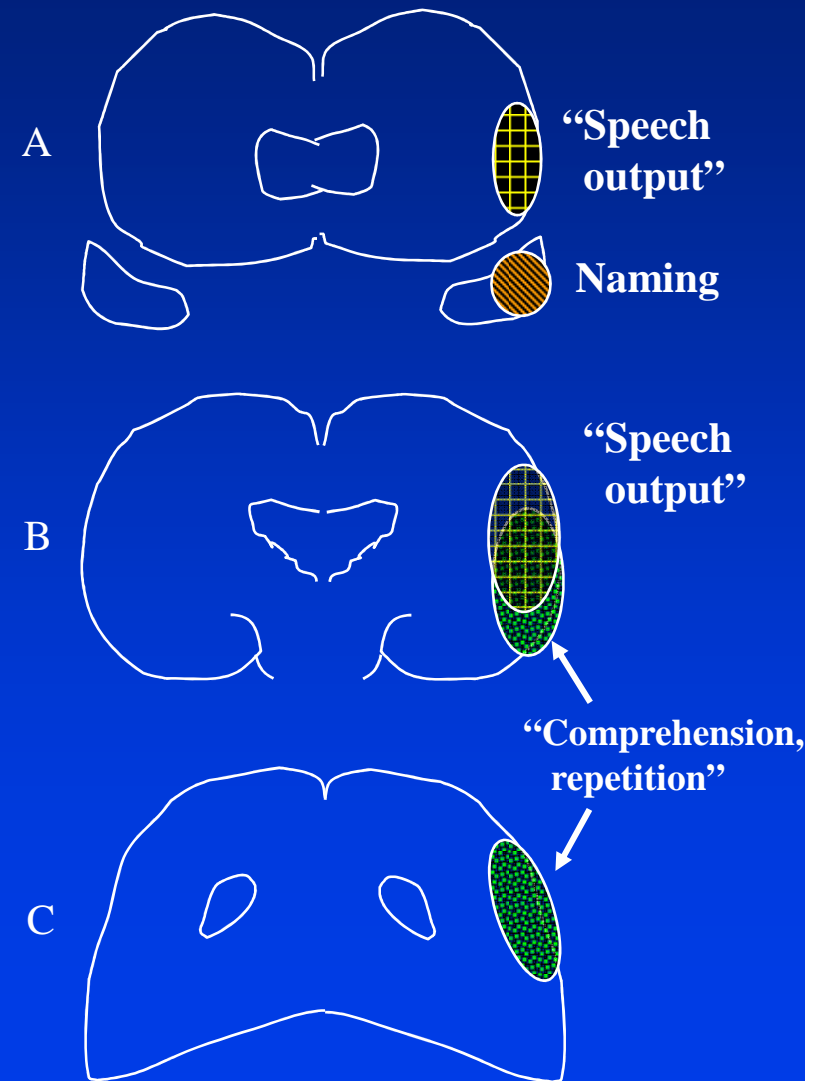
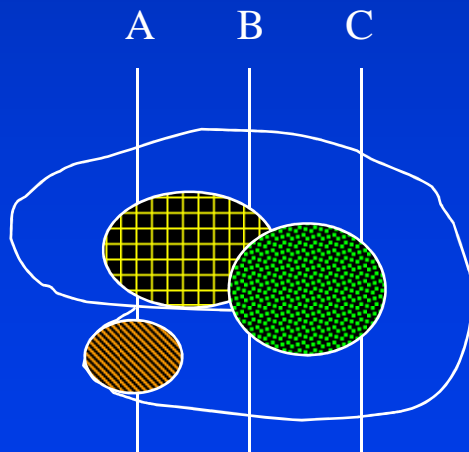
Tendency to sit, not initiative
conversations or actions



FTD and PPA

Brain-Behavior Correlations

- Poor verbal expression
- Poor naming of objects and people
- Poor comprehension and repetition



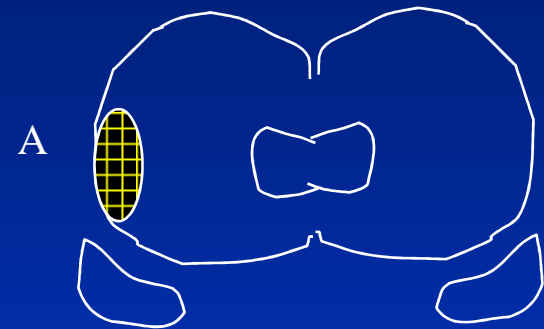
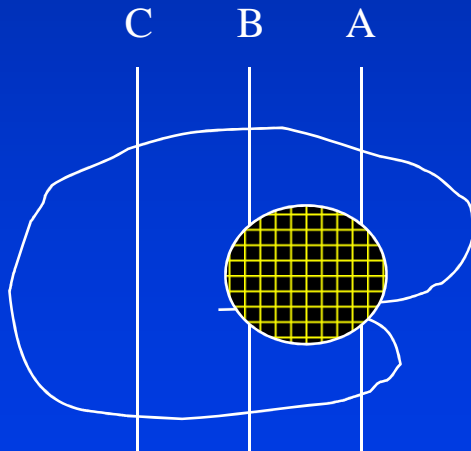
FTD and PPA

Brain-Behavior Correlations

Aprosodia

Monotone voice

Unable to interpret inflections in
voice another person's voice



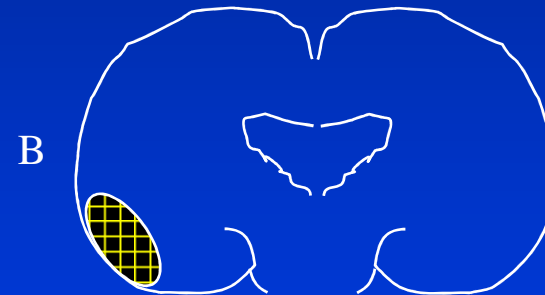
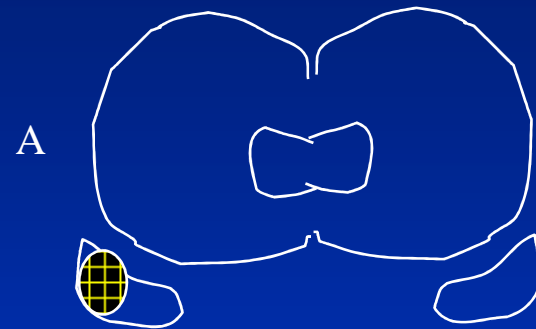
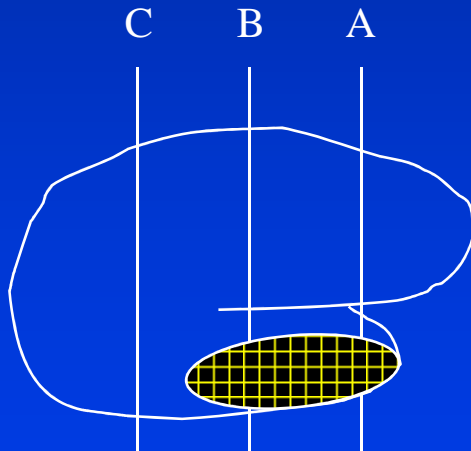
FTD and PPA

Brain-Behavior Correlations



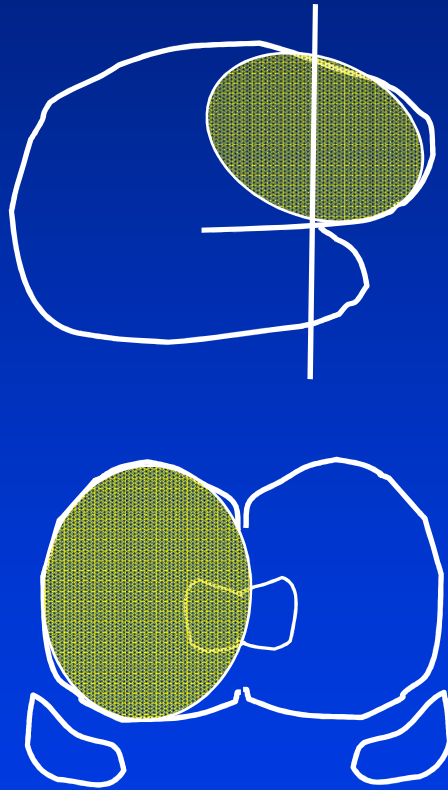
Visual agnosia

Unable to recognize objects and people



FTD and PPA

Brain-Behavior Correlations



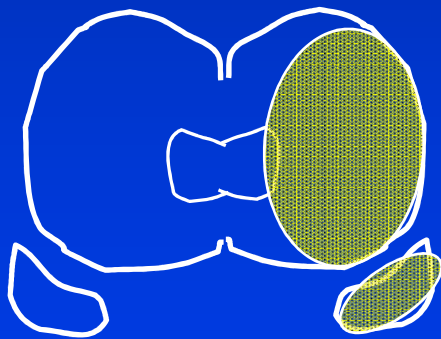
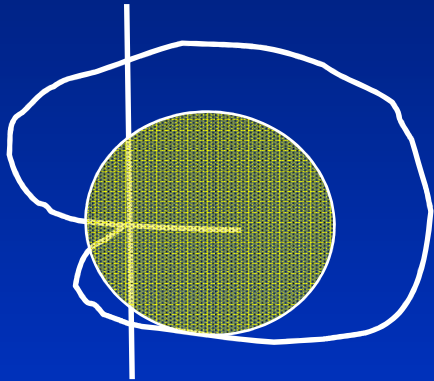
FTD

Core features

- Behavioral disinhibition
 - Socially inappropriate behavior
 - Loss of manners or decorum
 - Impulsive, rash or careless actions
- Apathy or inertia
- Loss of sympathy or empathy
- Perseverative, stereotyped or compulsive/ritualistic behavior
- Hyperorality and dietary changes
 - Altered food preferences
 - Binge eating
 - Oral exploration or consumption of inedible objects

FTD and PPA

Brain-Behavior Correlations



PPA

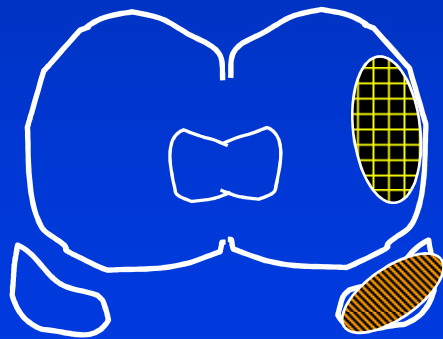
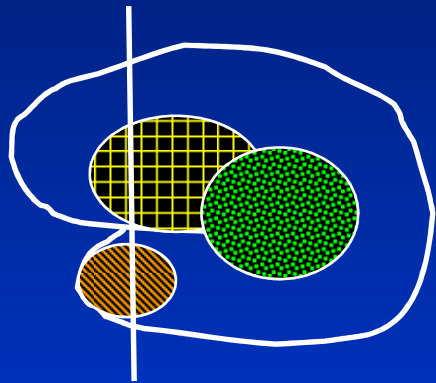
Core features

- Most prominent clinical feature is difficulty with language
- These deficits are the principal cause of impaired daily living activities
- Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease

Mesulam MM. Ann Neurol 2001
Gorno-Tempini et al, Neurology 2011

FTD and PPA

Brain-Behavior Correlations



PPA

Core features

- Most prominent clinical feature is difficulty with language
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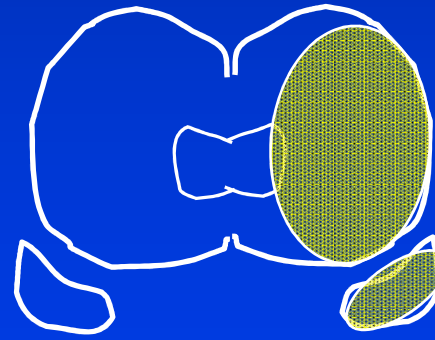
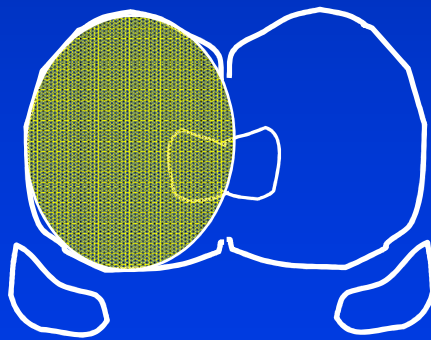
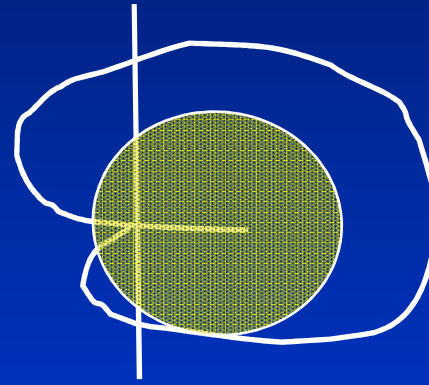
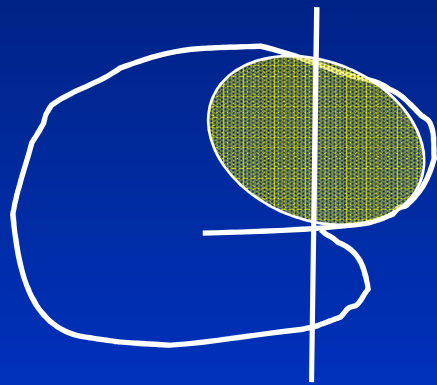
Variants

- **Nonfluent/agrammatic**
- **Semantic**
- **Logopenic**

Mesulam MM. Ann Neurol 2001
Gorno-Tempini et al, Neurology 2011

FTD and PPA

Brain-Behavior Correlations



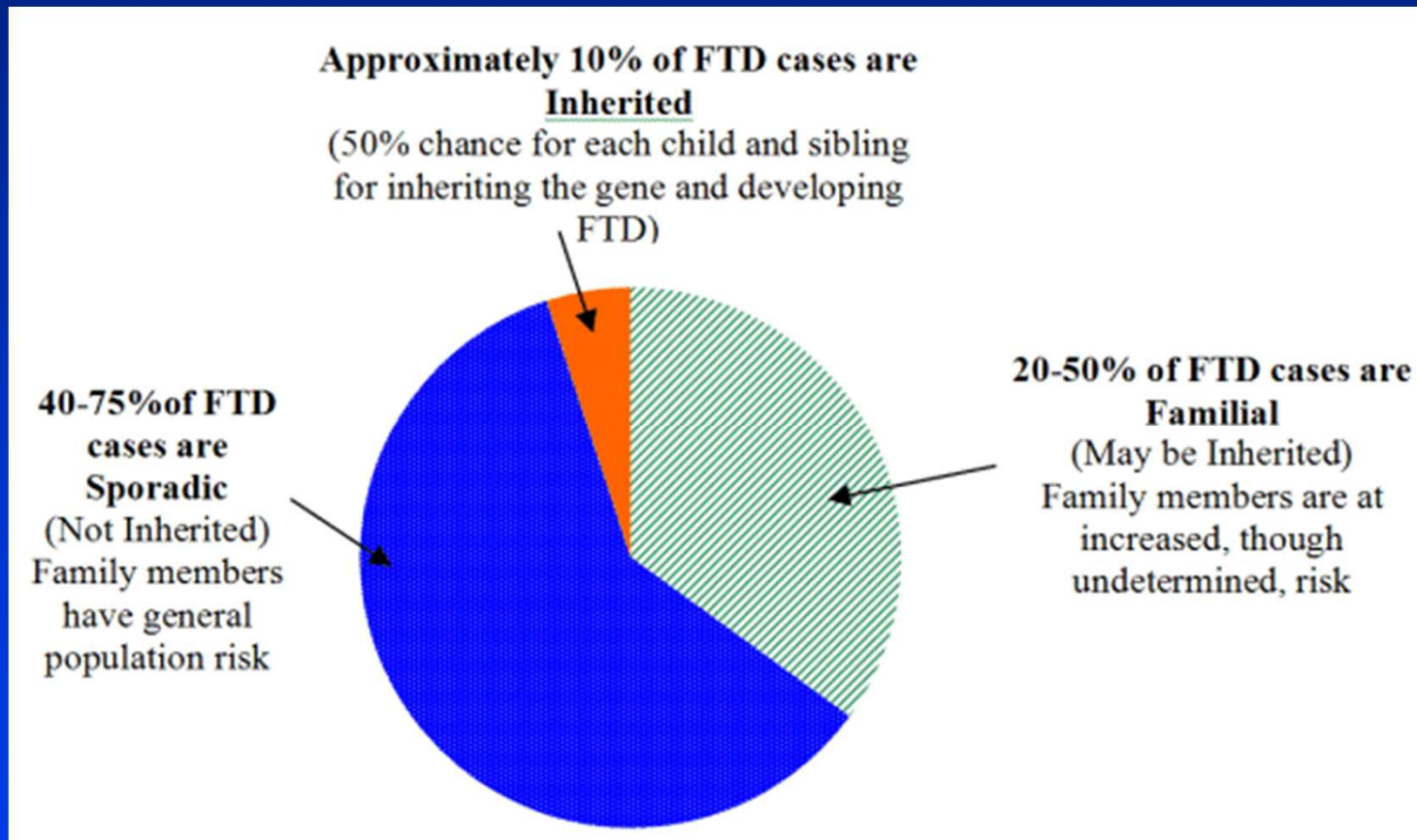
FTD

PPA

Genetics

FTD and PPA

Genetics



FTD and PPA

Genetics

- ? Inherited form – if you have 1 or more 1st degree relatives with dementia and/or parkinsonism and/or ALS
- Genetic considerations:
 - Microtubule associated protein **tau** (clinical testing available)
 - **Progranulin** (clinical testing available)
 - Valosin-containing protein (**VCP**) (clinical testing not yet available)
 - **CHMP2B** (clinical testing not yet available)
 - **TDP-43**
 - **FUS**
 - Chromosome 9 gene not yet found

Pathophysiology and Implications for Future Therapies

FTD and PPA

Underlying Disorders

FTLD - the pathologies

- Pick's disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Multisystem tauopathy
- Frontotemporal dementia with Parkinsonism associated with mutations in microtubule associated protein tau on chromosome 17 (FTDP-17*MAPT*)
- 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*)
- Dementia lacking distinctive histopathology (DLDH)

Alzheimer's Disease

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*)

tau

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*)

TDP-43

FTD and PPA

Pathophysiology and Implications for Future Therapies

Tauopathies

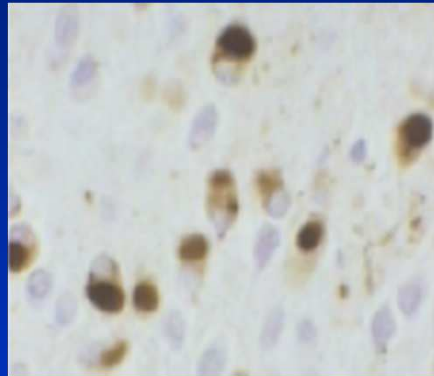
Pick's disease

CBD

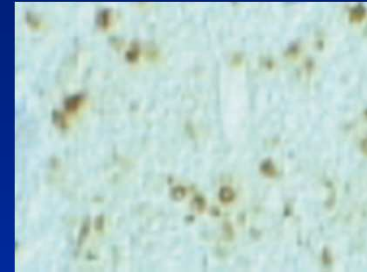
PSP

AGD

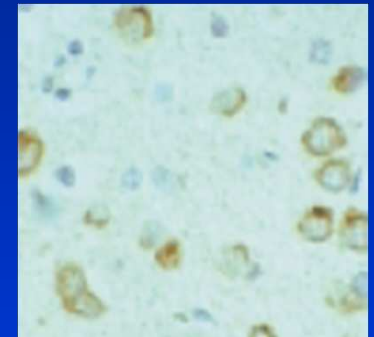
FTDP-17-*MAPT*



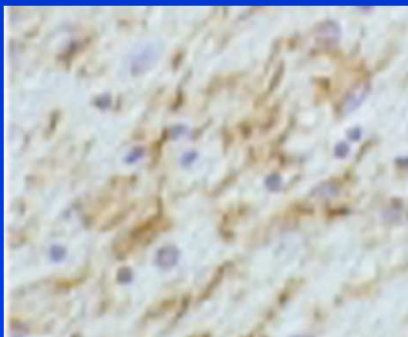
Pick



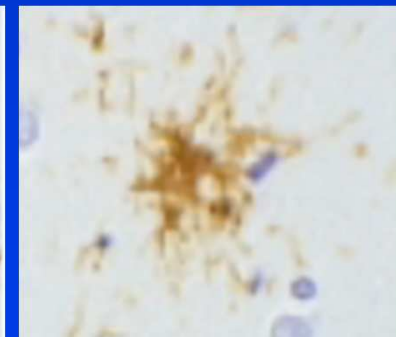
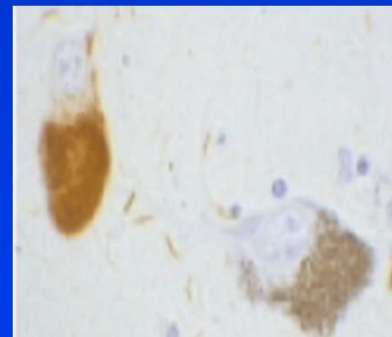
AGD



FTDP-17
MAPT



CBD



PSP

FTD and PPA

Pathophysiology and Implications for Future Therapies

TDP-43opathies

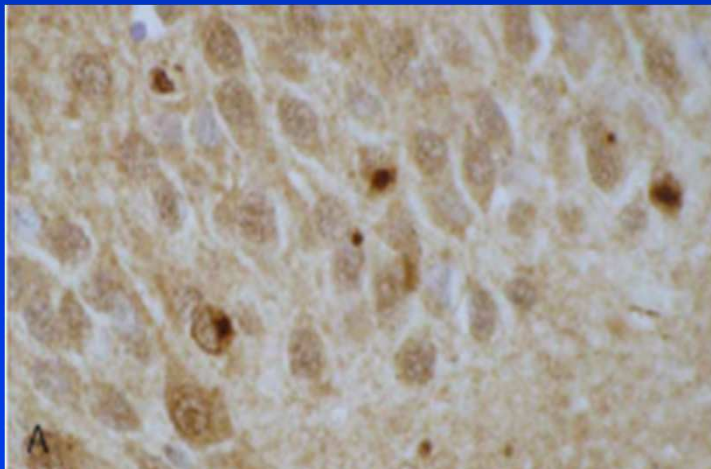
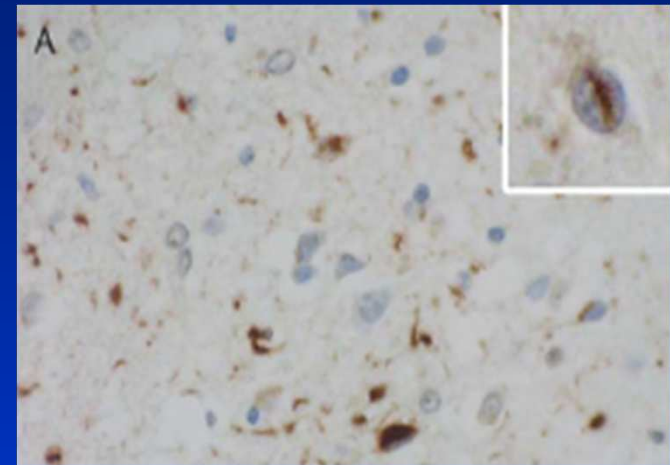
FTLD-U/TDP-43

FTLD-MND

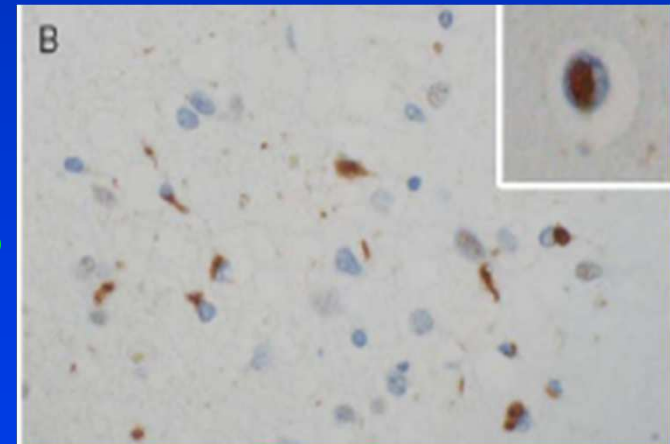
FTDP-17-*PGRN*

ALS

ubiquitin



TDP-43



FTD and PPA

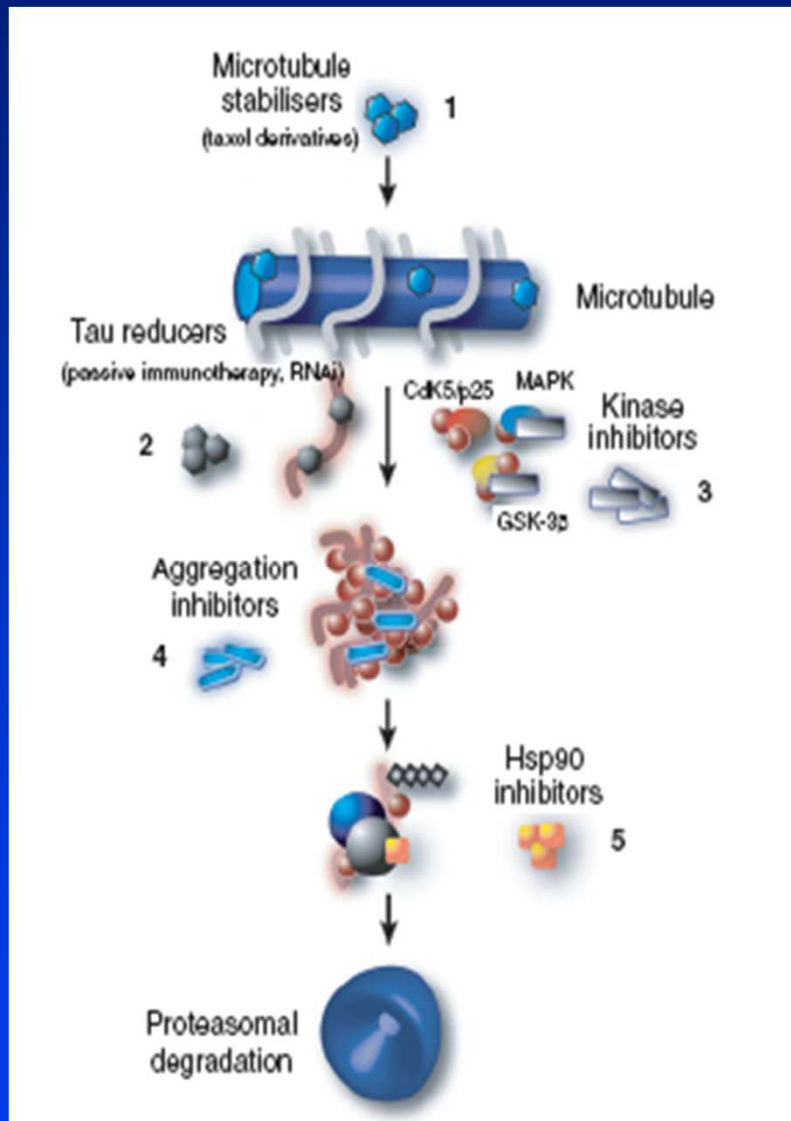
Pathophysiology and Implications for Future Therapies

Tauopathies

TDP-43opathies

FTD and PPA

Pathophysiology and Implications for Future Therapies



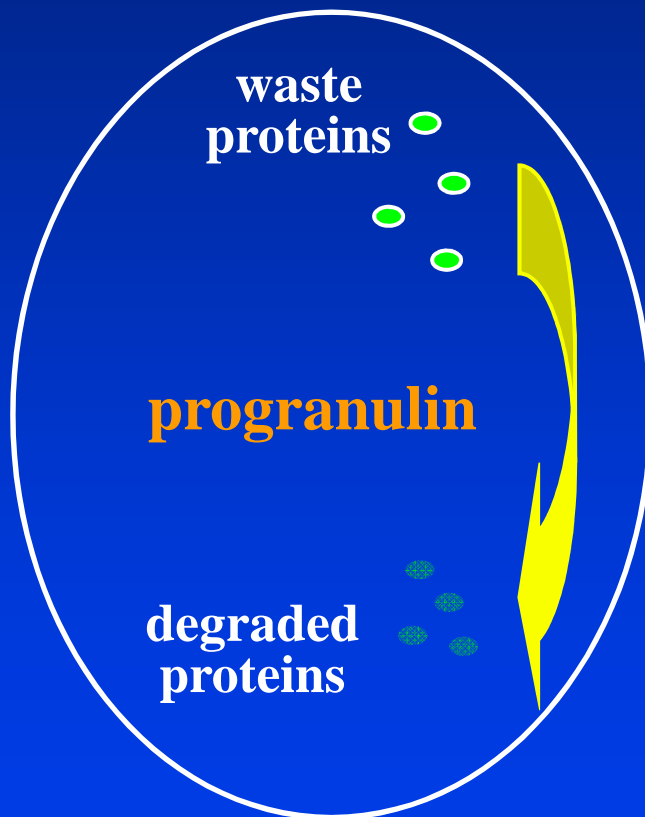
? Tauopathy therapies

- Microtubule stabilizers
- Tau reducers (vaccine)
- Tau kinase inhibitors
- tau aggregation inhibitors
- Hsp90 inhibitors

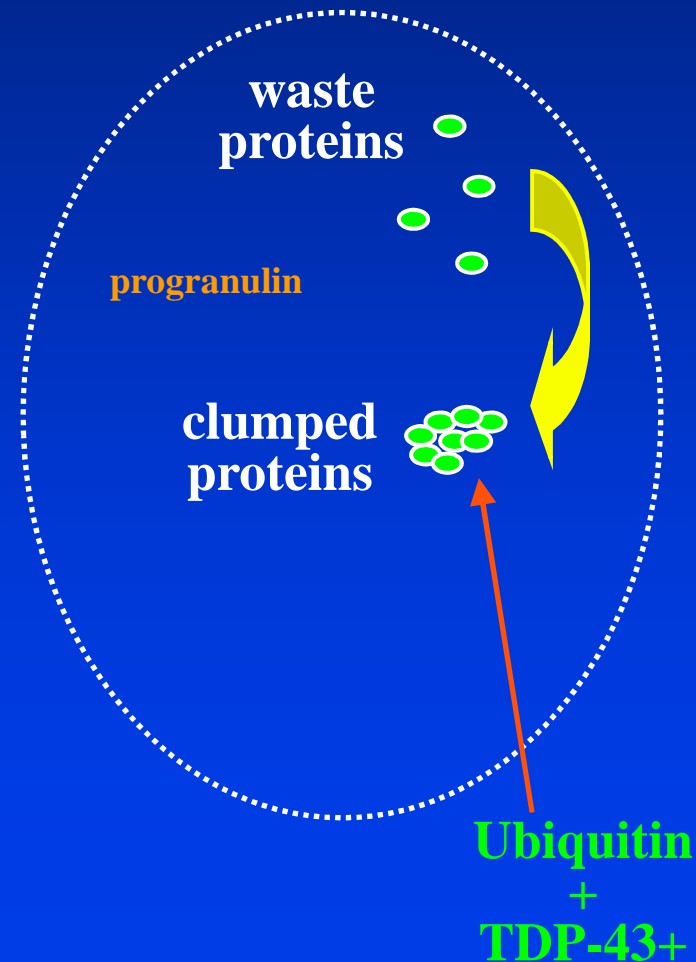
FTD and PPA

Pathophysiology and Implications for Future Therapies

Normal neuron



Abnormal neuron

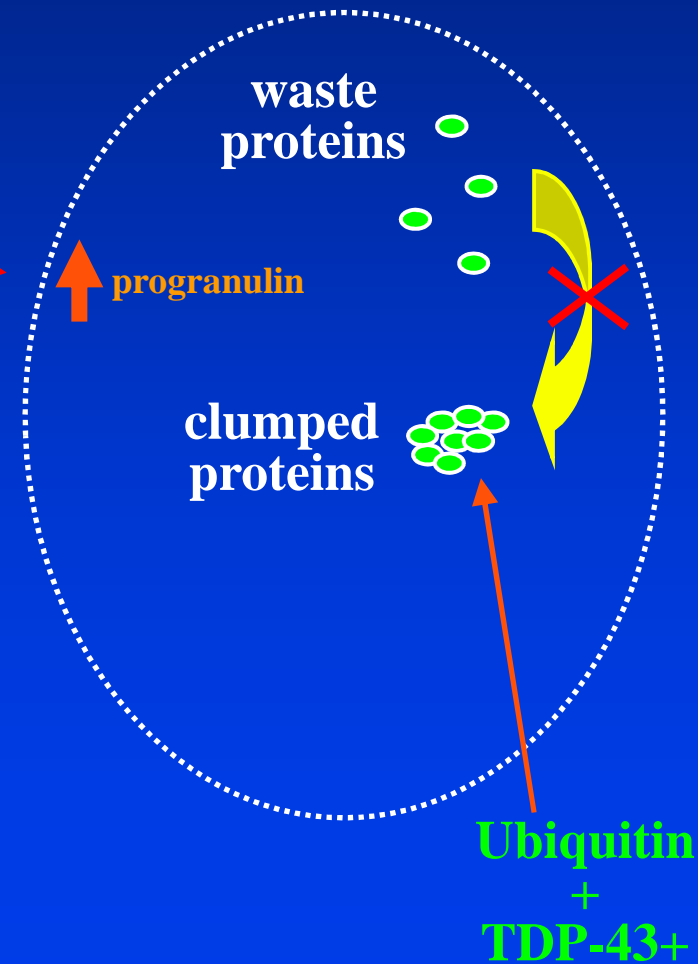


FTD and PPA

Pathophysiology and Implications for Future Therapies

Abnormal neuron

Use drugs that increase
production or secretion of
progranulin

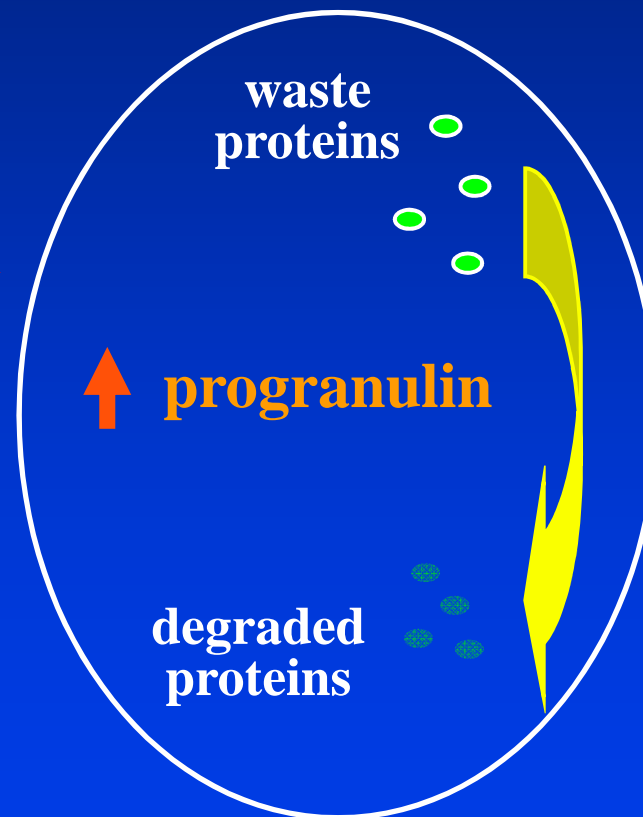


FTD and PPA

Pathophysiology and Implications for Future Therapies

Normal neuron

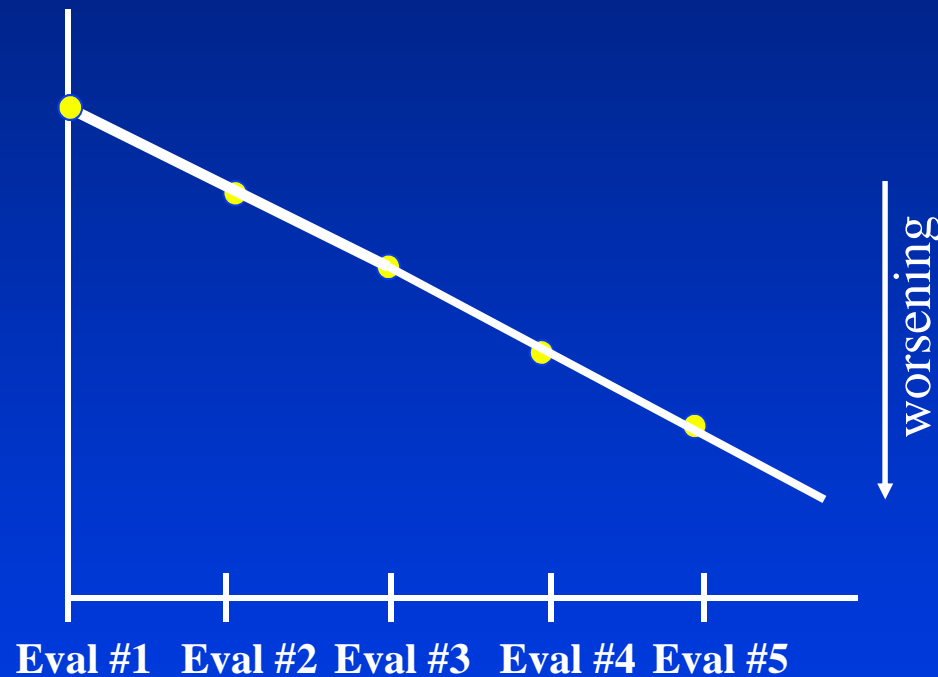
Use drugs that increase
production or secretion of
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FTD and PPA

Pathophysiology and Implications for Future Therapies

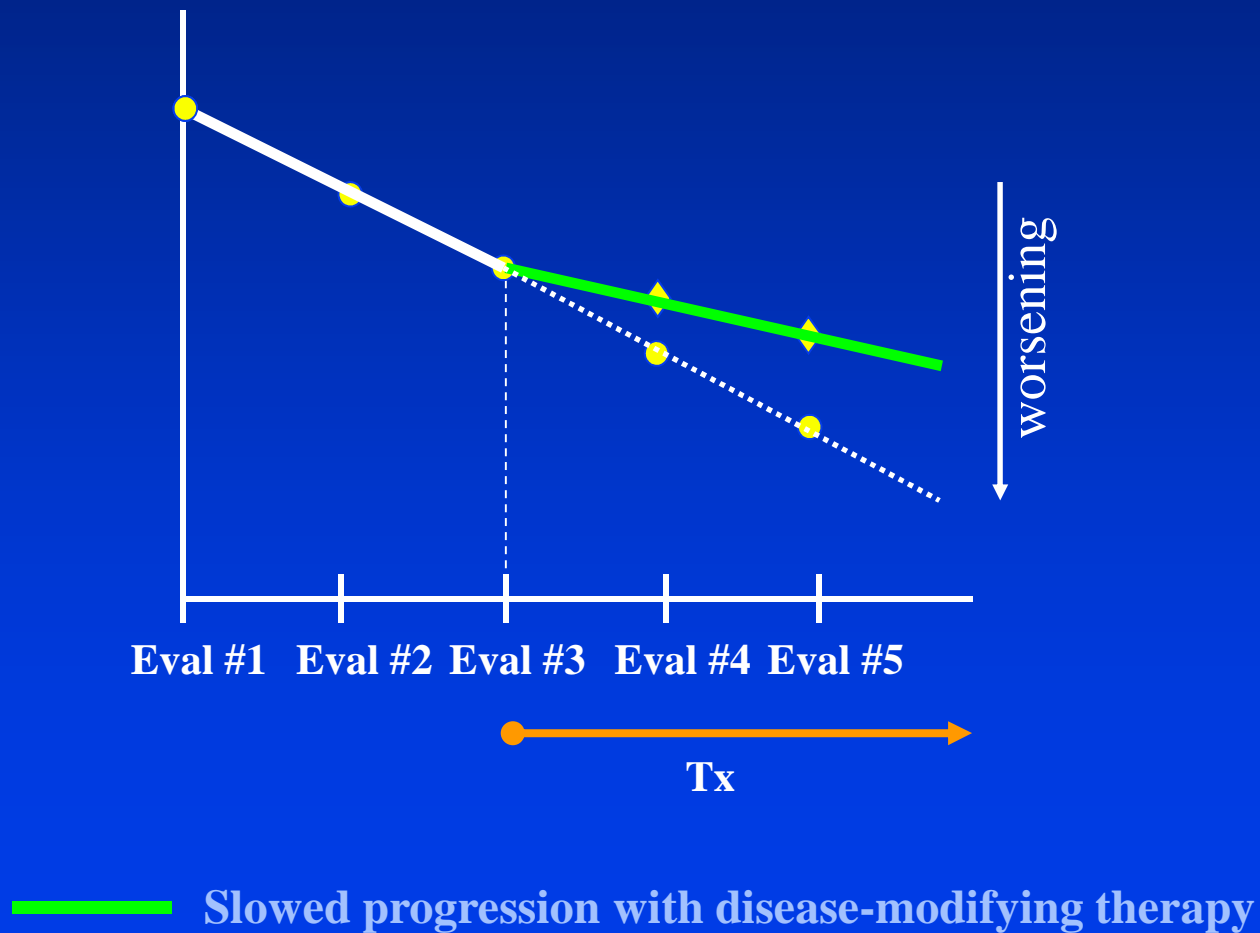
Theoretical considerations for future experimental drug trials



FTD and PPA

Pathophysiology and Implications for Future Therapies

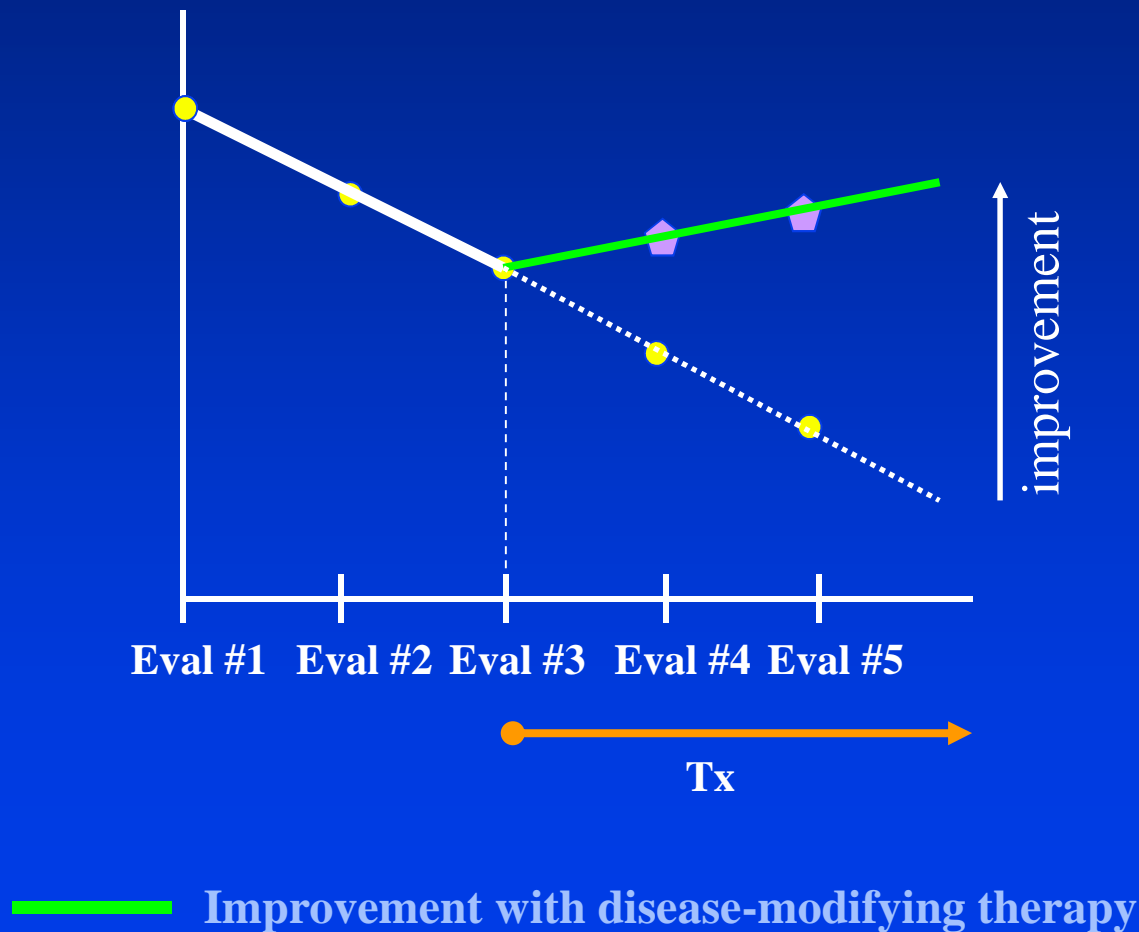
Theoretical considerations for future experimental drug trials



FTD and PPA

Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials



FTD and PPA

Pathophysiology and Implications for Future Therapies

Without knowledge about the natural history of patients with FTD and PPA, we will not know where to start when promising medications are identified/developed

This is one of many reasons involvement in research studies are so critical

FTD and PPA

Pathophysiology and Implications for Future Therapies

If you participate in research - thank you!!

*If you are interested in participating in research –
please contact any of the staff at this conference*

FTD and PPA

Resources - Websites



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



<http://www.theaftd.org>

FTD and PPA

Resources - Websites



FTD/PPA Genetics

<http://www.theaftd.org/frontotemporal-dementias/genetics>



The Frontal Lobes

Scientific American Frontiers
Make Up Your Mind

<http://www.pbs.org/saf/1302/>