Frontotemporal dementia:

Where we've been
What's on the horizon

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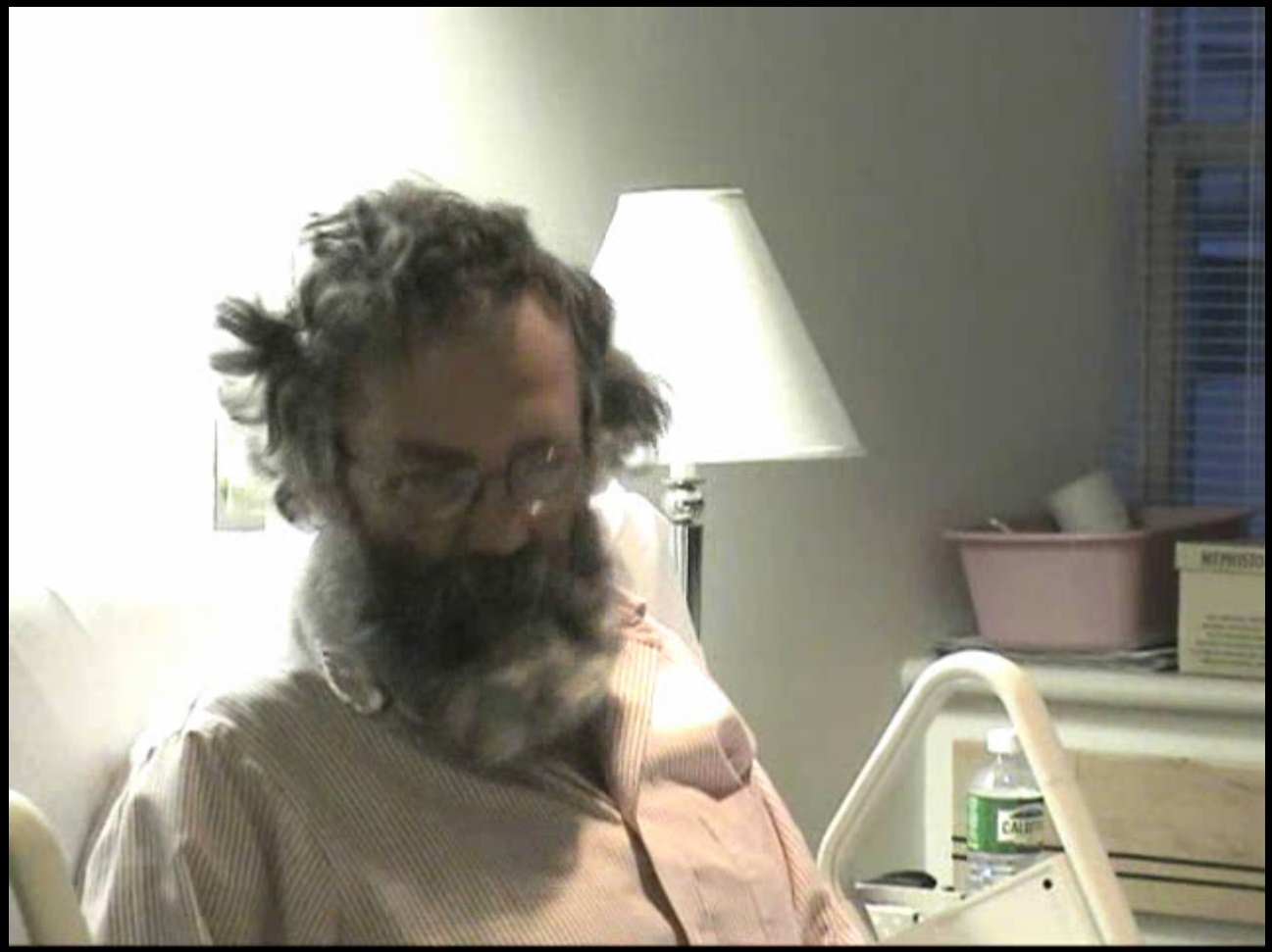
Disclosures

- None

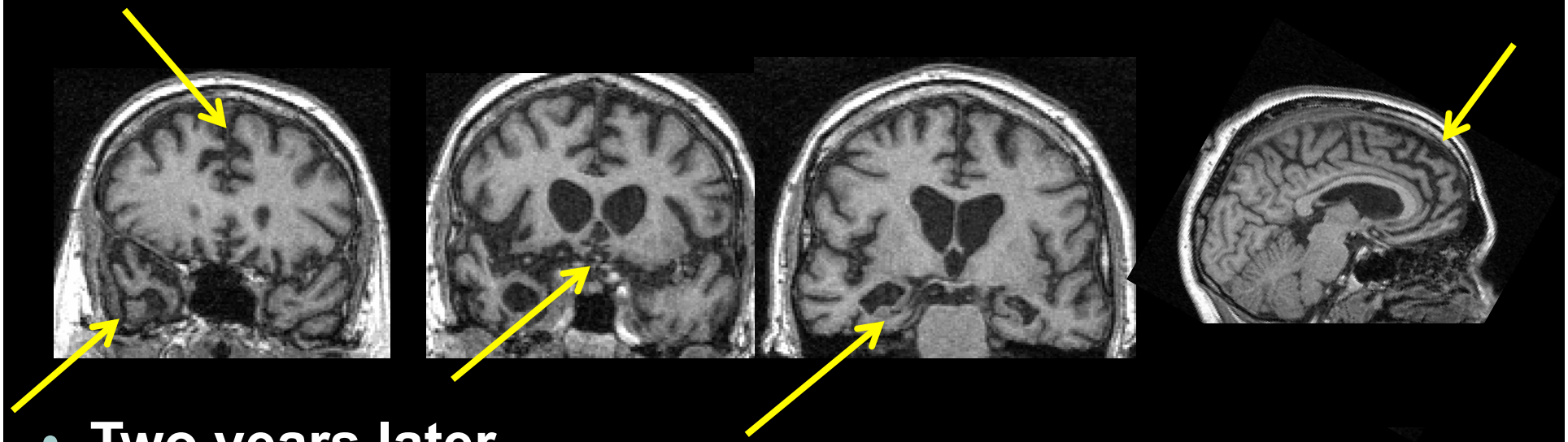
Overview

- **FTD, What is it?**
- **Origins of symptoms**
- **Variants of FTD**
- **Diagnosis/misdiagnosis**
- **Neuropathology of FTD**
  - Links to other disorders
- **Neuroimaging**
- **Current treatments**
- **Future treatment**

51 year old man with four years of personality change



- **MRI at first visit, distinct regions of atrophy**
  - Right >> Left temporal pole
  - Right >> Left medial temporal region, including amygdala
  - Orbitofrontal cortex
  - Anterior cingulate



- **Two years later**
  - Nearly mute
  - Could not complete any cognitive testing

Clinical Features of bvFTD

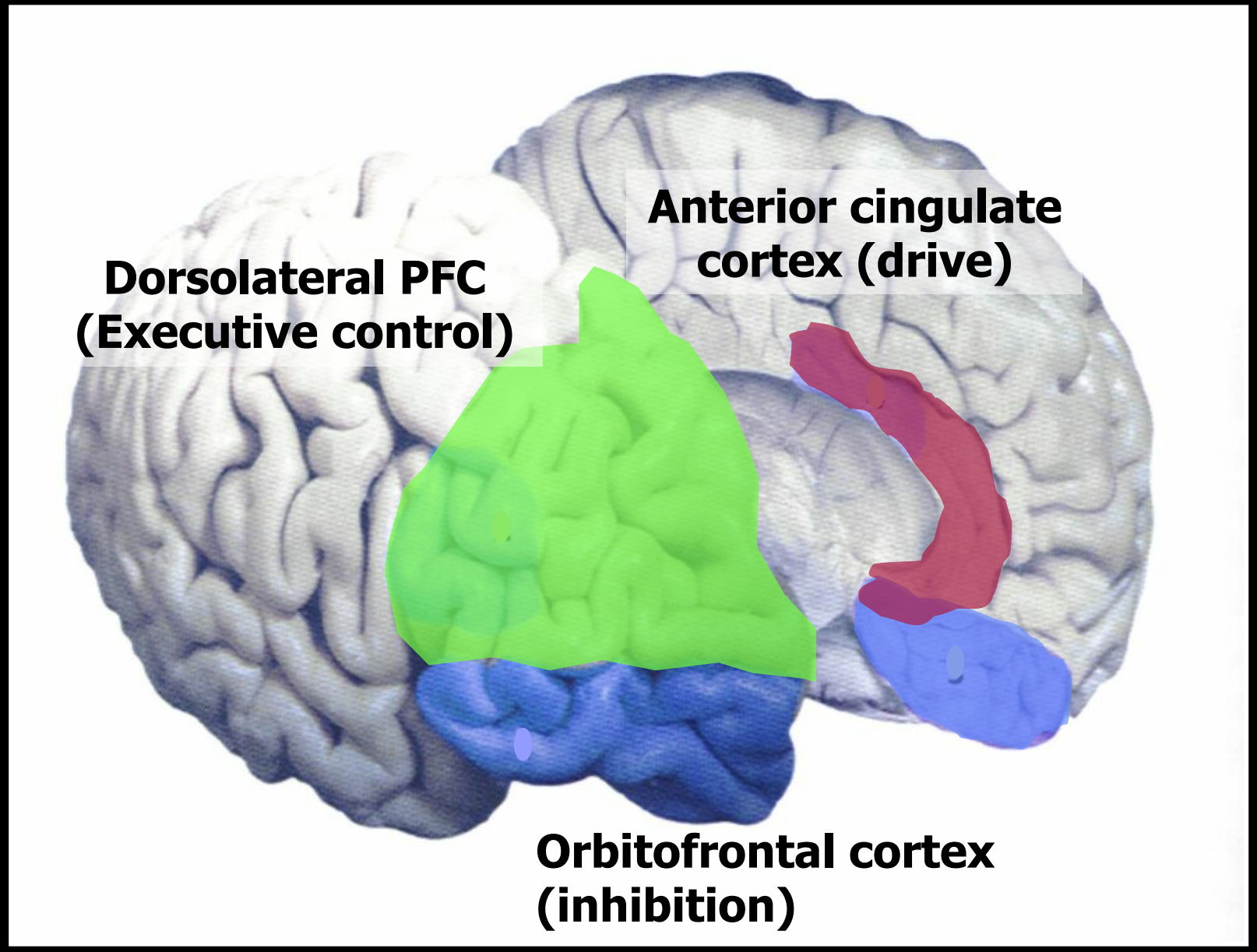
- Disinhibition/antisocial behavior
- Loss of concern for others
- Exceedingly poor judgment
- Overeating
- Compulsive behaviors (collecting)
- Loss of executive control
- Apathy
- Overly friendly
- Loss of disgust

Bob's hobbies

The wife of a man with
FTD explains why they
no longer attend church.

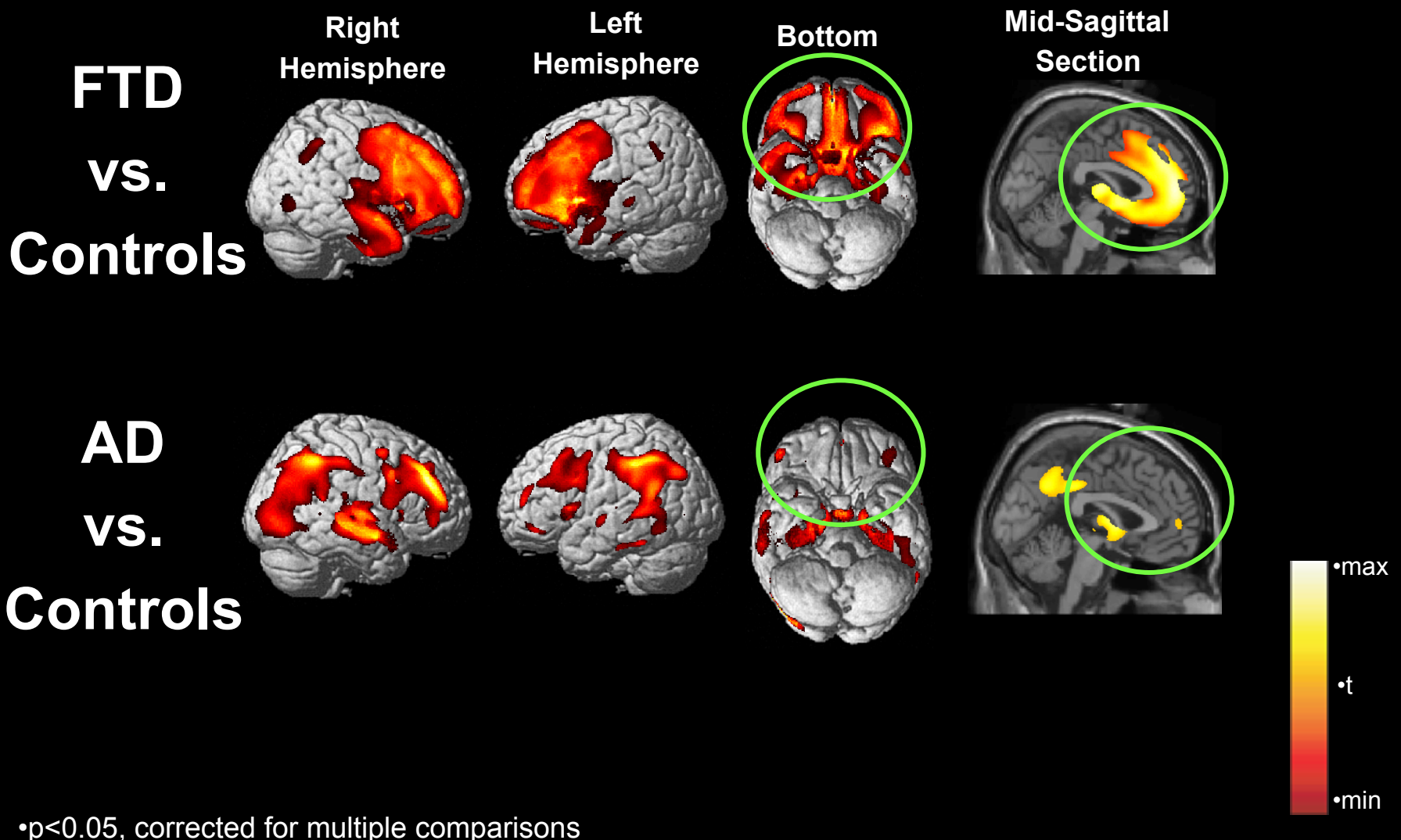
Is FTD Uncommon?

- **Common cause pre-senile dementia**
  - 1:1 with AD 45-64 years (Ratnavalli, Hodges 2002)
  - More common than AD below 60 yrs (Knopman 2004)
- **Rare after 70?**
  - 3% clinical prevalence of FTD 80-90 (2003 Skoog)
  - Include diseases with similar molecules: PSP, CBD, ALS even more common
  - Association TDP-43 & cognition independent of plaque, hippocampal sclerosis (Nelson 2008)
  - Tau and TDP-43 major proteins in “chronic traumatic encephalopathy” NFL football players’ dementia (also found following war trauma)


Anterior cingulate cortex (drive)
Dorsolateral PFC (Executive control)
Orbitofrontal cortex (inhibition)

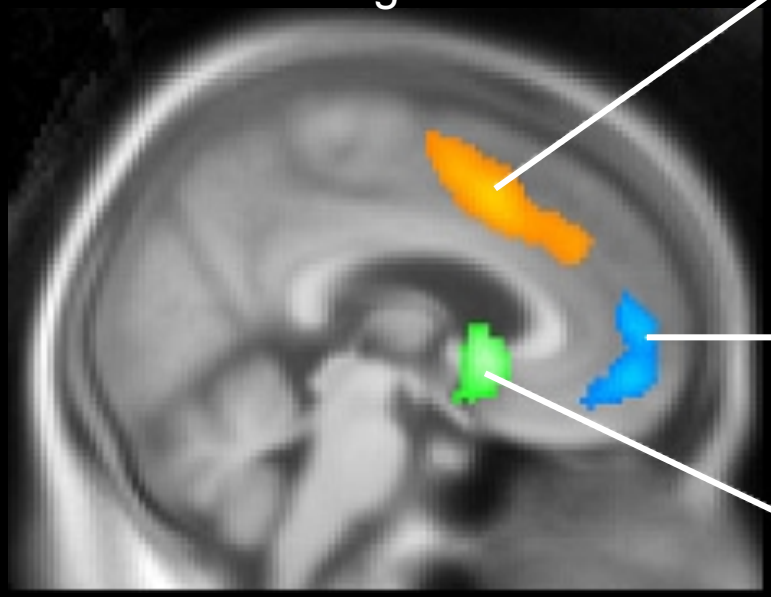
FTD is associated with bizarre socioemotional changes because of its specific neuroanatomy

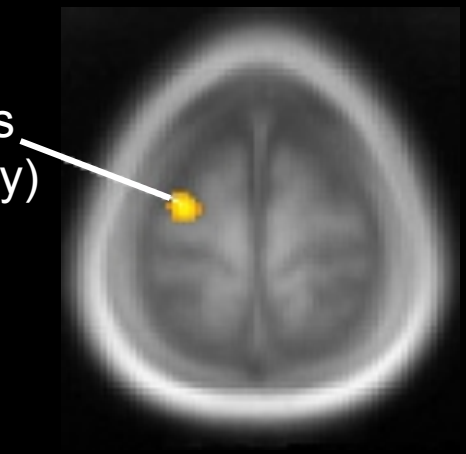
Regions of gray matter atrophy in FTD and AD



•p<0.05, corrected for multiple comparisons

Regions Unique to Individual Behaviors





Dorsal ACC (main effect)

Precentral sulcus (non-FTD/SD only)

Medial SFG (FTD/SD only)

VMFC FTD/SD only

3 T-score 5

Aberrant Motor Behavior (main effect)

3 T-score 5

Apathy (interaction, FTD/SD only)

3 T-score 5

Disinhibition (interaction, FTD/SD only)

n=148

Rosen et al. *Brain, 2005*

Traditional Frontal Neuropsychology: Mostly dorsolateral frontal

- Working memory (BA46) – digit back
- Generation – letters, animals, shapes
- Inhibition – Stroop, antisaccade, flanker task
- Alternate sequence – dorsolateral – Trails B
- Combination – Card sorts
- Abstraction – proverbs

Studies to establish the nature of emotional failure in FTD have discovered changes in self-conscious emotions

Embarrassment

- Emerges after violation of a social convention
- Reparation of disrupted social bonds
- Associated with mPFC

Sturm et al, Cog Affect Nsci, Epub/In press

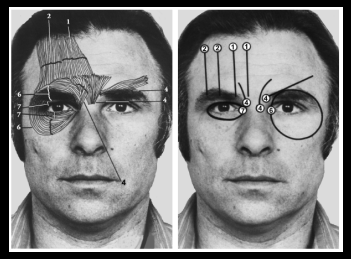
Laboratory Measurement of Emotion

Embarrassment

- Karaoke task
- Subjects watch themselves singing "My Girl"

Physiological Reactivity

Facial Behavior



Self Report

How sad did you feel while watching the film?

1 2 3 4 5

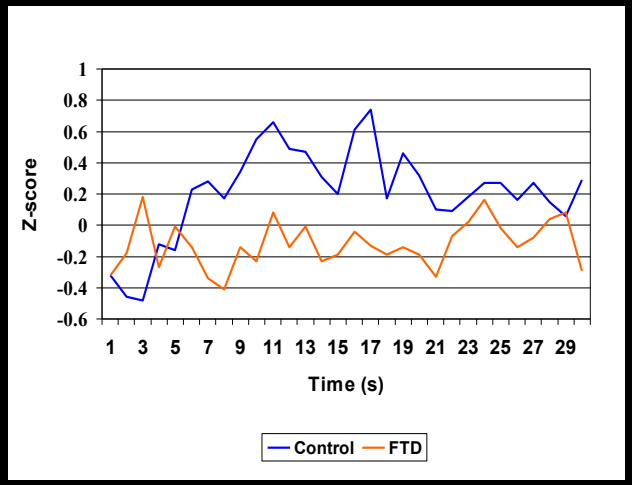
A little A lot

Sturm et al, Cog Affect Nsci, Epub/In press

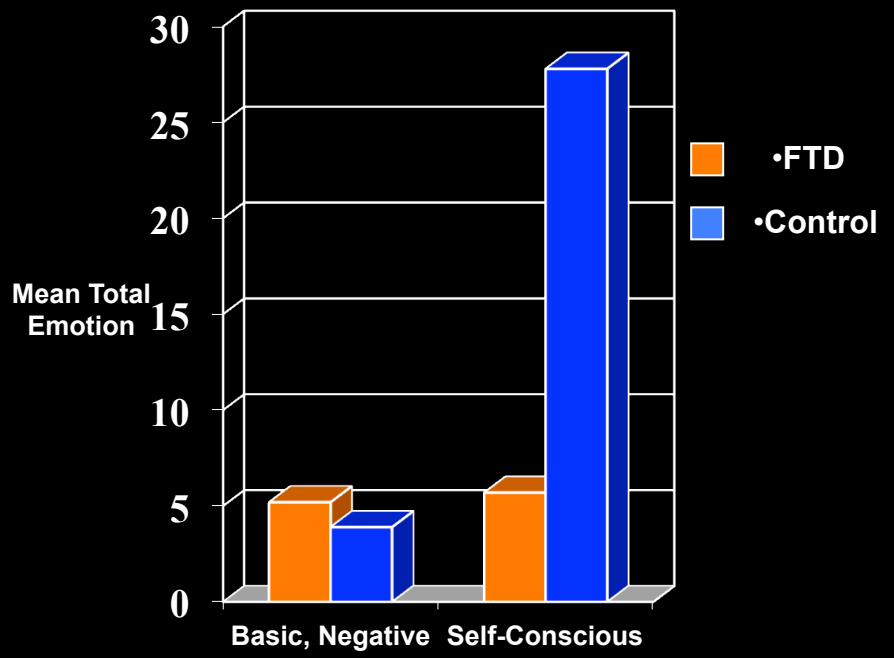
Patients with FTD show no embarrassment (despite showing normal reaction to more basic emotions)

•Physiological Reactivity

- Composite: FTD < Controls
  - Individual channels:
    - FTD < Controls in heart rate, skin conductance, respiration depth



•Emotional Behavior

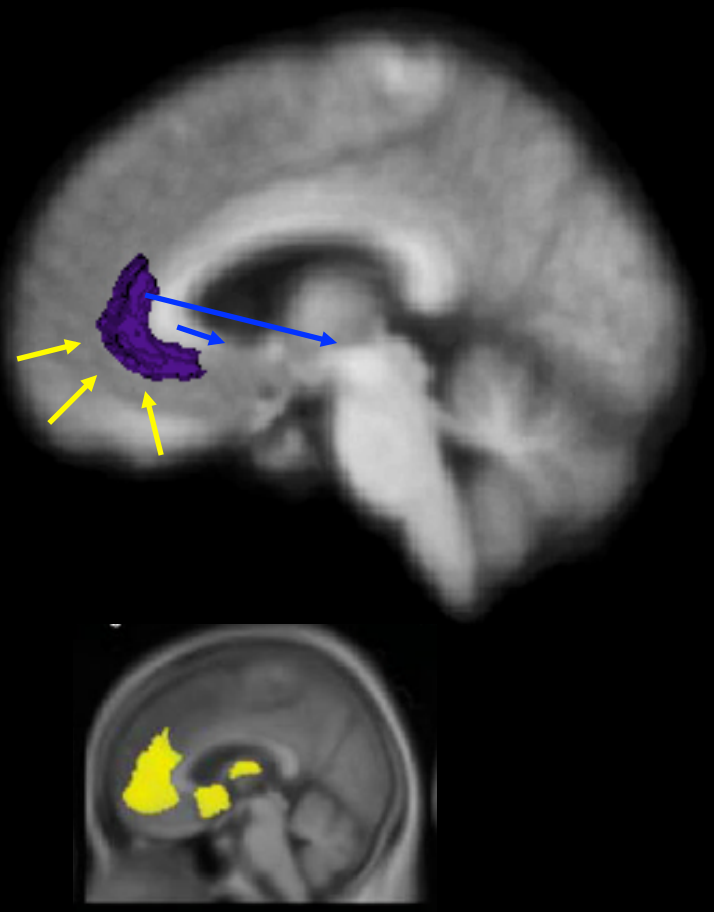


•Self-Report

- Basic emotions: No differences
- Self-conscious emotions: No differences

Sturm et al, Cog Affect Nsci, Epub/In press

Embarrassment: Neural Correlates

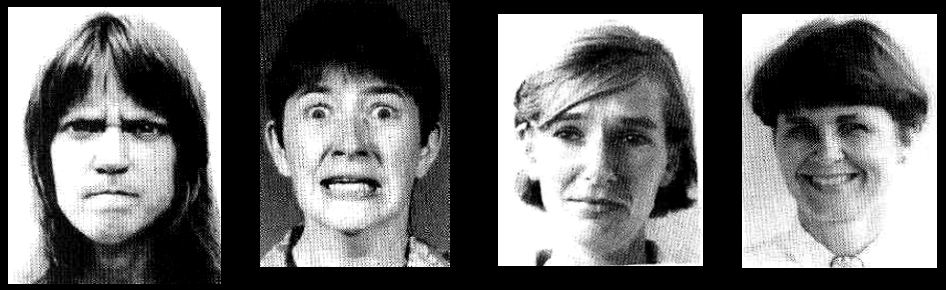


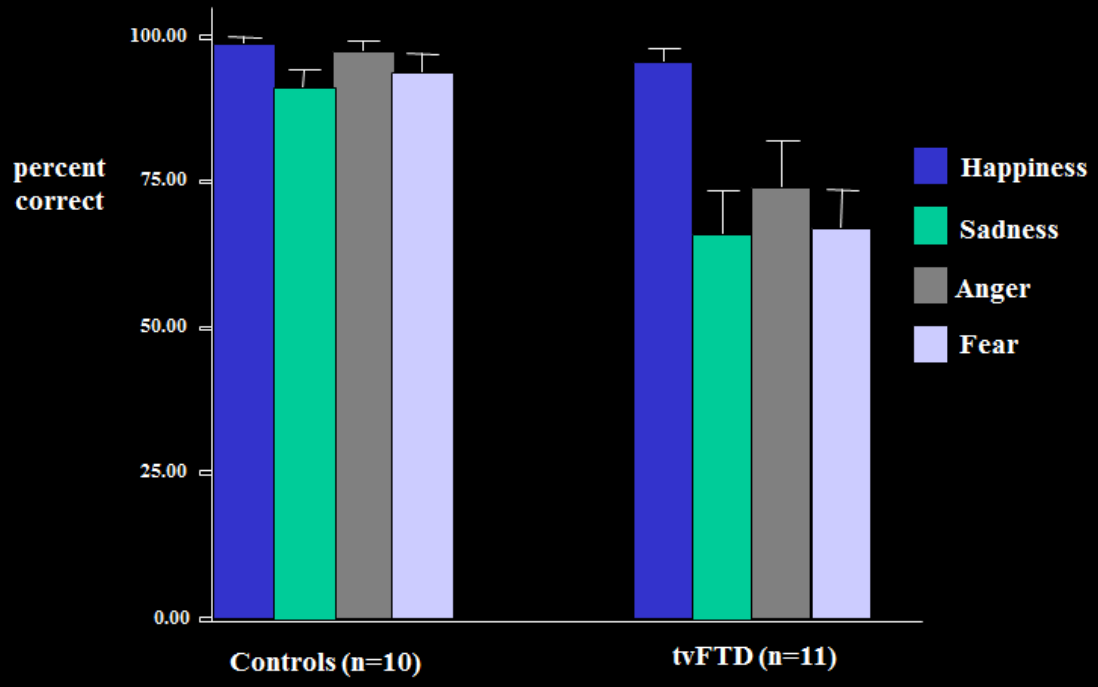
- Smaller right pACC volume is associated with lower physiological and behavioral reactivity during karaoke task
- Early site of atrophy in bvFTD

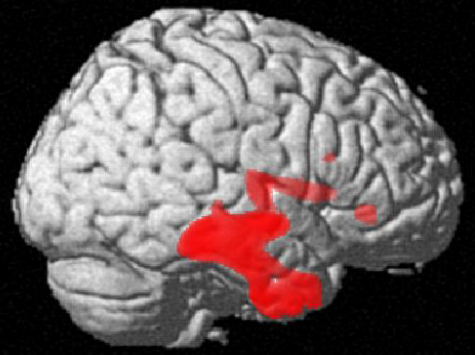
Sturm et al, Brain, 2006

Sturm et al, Cog Affect Nsci, Epub/In press

Emotional processing in FTD is impaired, correlated with right temporal atrophy







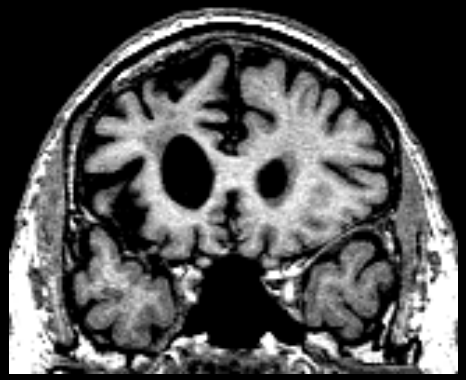
Rosen et al, Brain, 2002

Rosen et al, Dem Ger Cog Disord, 2004

Rosen et al, Neuropsychologia, 2006

3 traditional variants of frontotemporal dementia

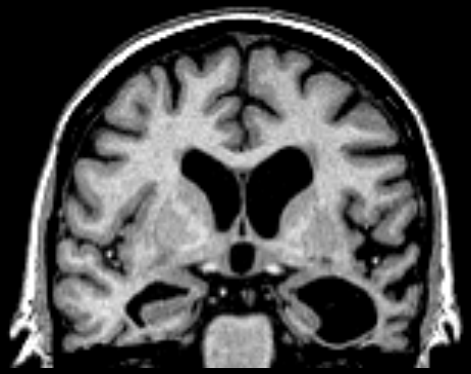
Behavioral variant



R L

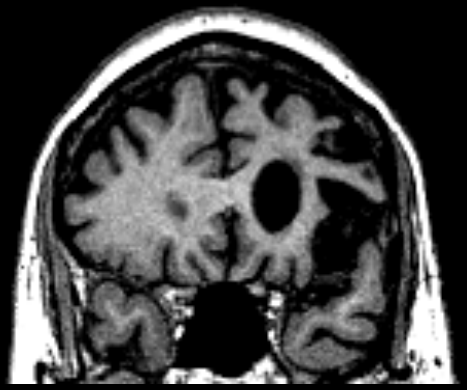
Language variants

Semantic variant



R L

Nonfluent variant



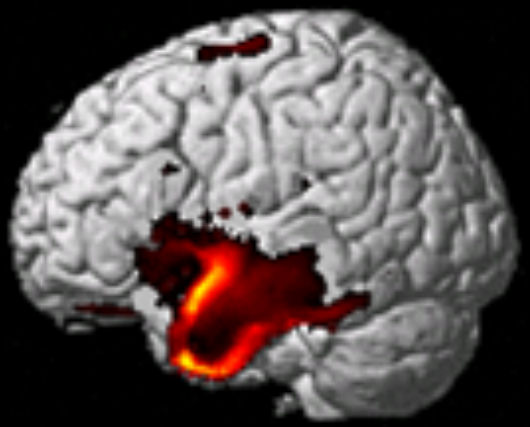
R L

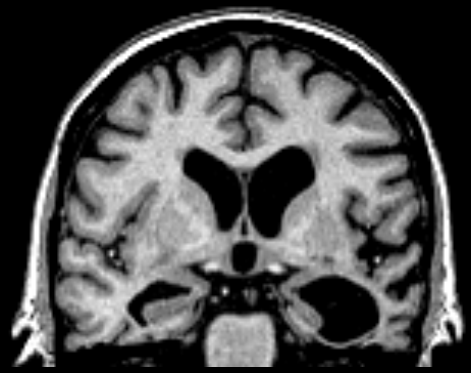
Also:
"Frontal variant" FTD
"FTD"

Semantic variant of Primary Progressive Aphasia (svPPA)

- Profound anomia
- Problems with word comprehension
- Fluent, empty speech
- Trouble with object recognition (agnosia)
- Trouble with recognition of familiar/ famous faces

svPPA

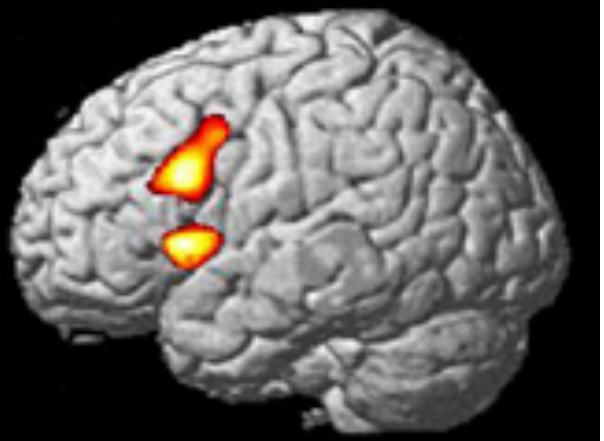


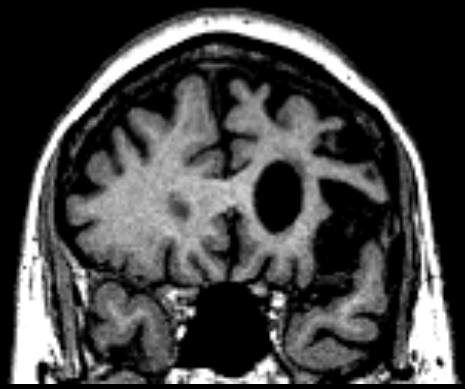


Nonfluent variant of Primary Progressive Aphasia (nfvPPA)

- Hesitant, non-fluent, Broca-like speech
- Agrammatism
  - Decreased use of function words
  - Sometimes “telegraphic” speech
- Articulation difficulties
  - Difficulty with individual words
  - Speech apraxia

nfvPPA

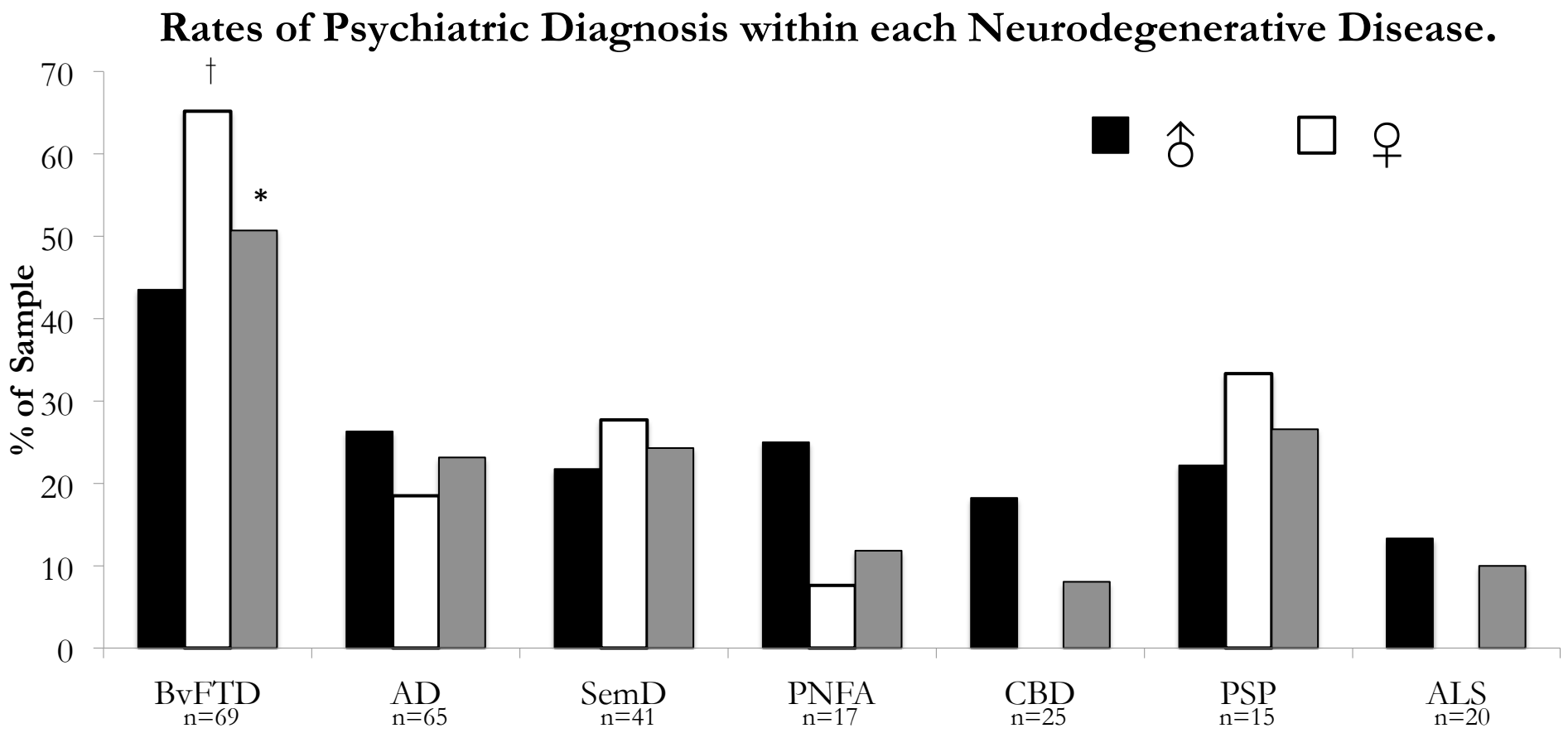




Misdiagnosis of FTD

- Psychiatric syndromes
- Alzheimer's disease
- Logopenic of progressive aphasia

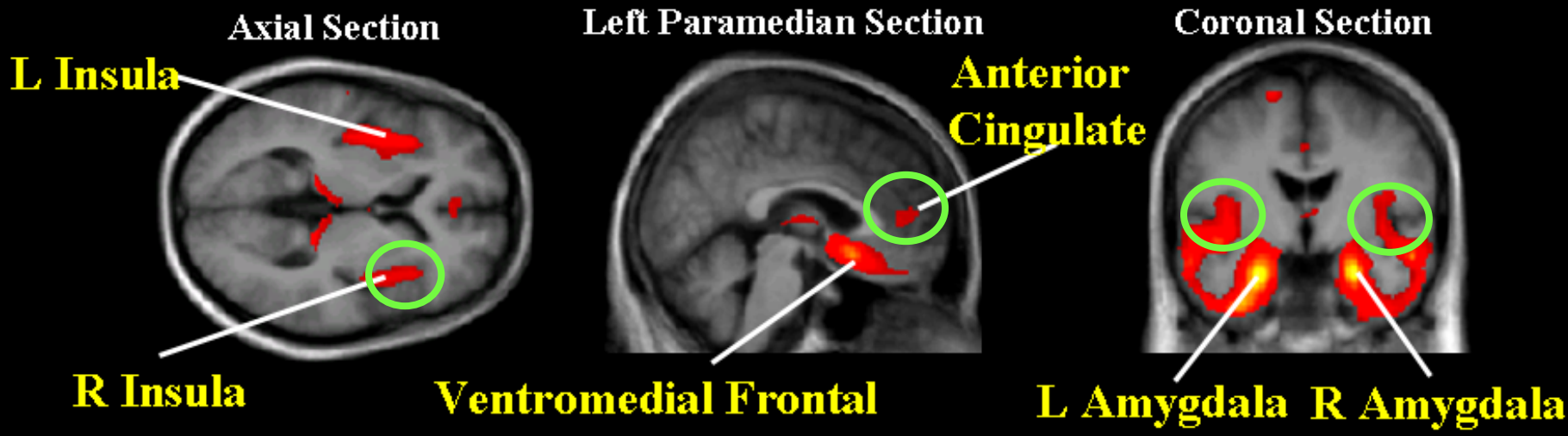
FTD Misdiagnosis



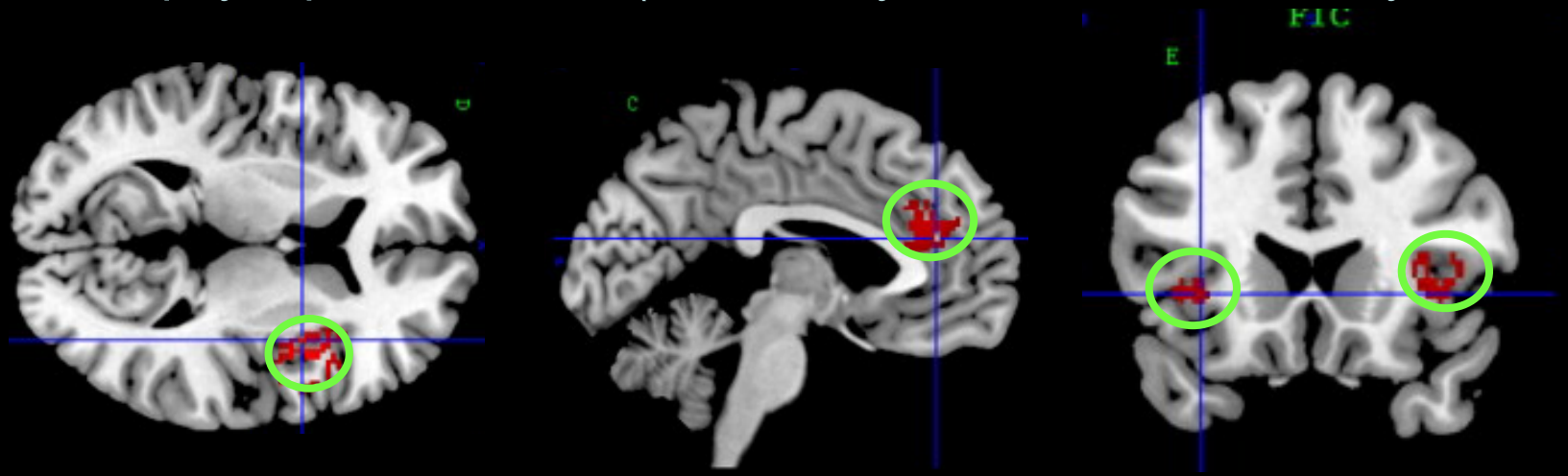
Woolley et al, J. Clin Psychiatry, 2011

Regions of Atrophy in FTD

(Rosen et al, Neurology, 2002)

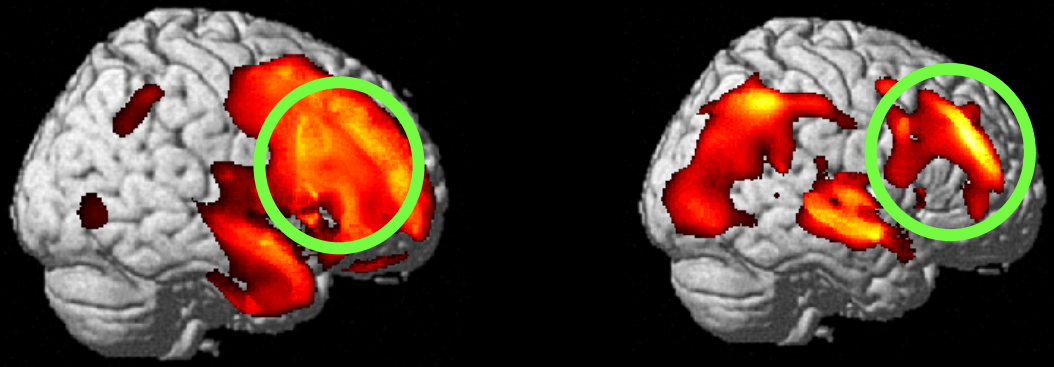


Regions atrophy Bipolar disorder (meta-analysis Bora et al, Biol Psych, 2010)



Alzheimer's disease

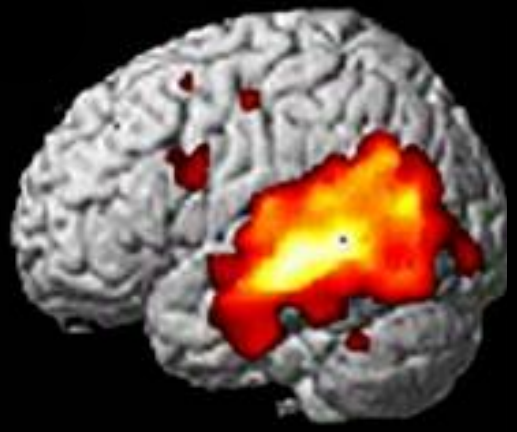
- Sometimes misdiagnosed as FTD
- Mainly because of executive function
  - Disorganization
  - Distraction
  - Poor planning
  - Poor performance on cog testing (executive fxn)

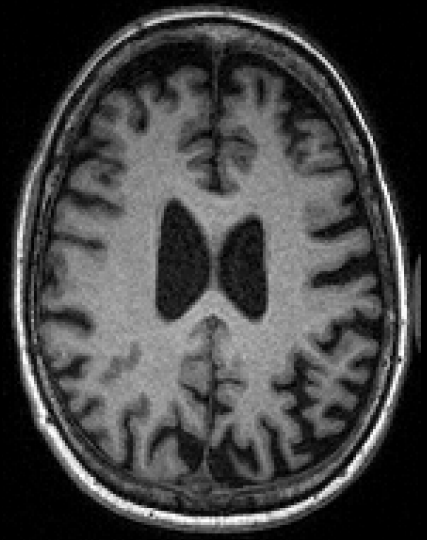


Logopenic variant of primary progressive aphasia (lvPPA)

- Hesitant, nonfluent speech
  - Particularly due to word finding
- Islands of preserved speech/phrases
- Relatively good articulation
- Relatively poor comprehension
- Pathology is usually Alzheimer's disease

lpvPPA





Pathology in FTD

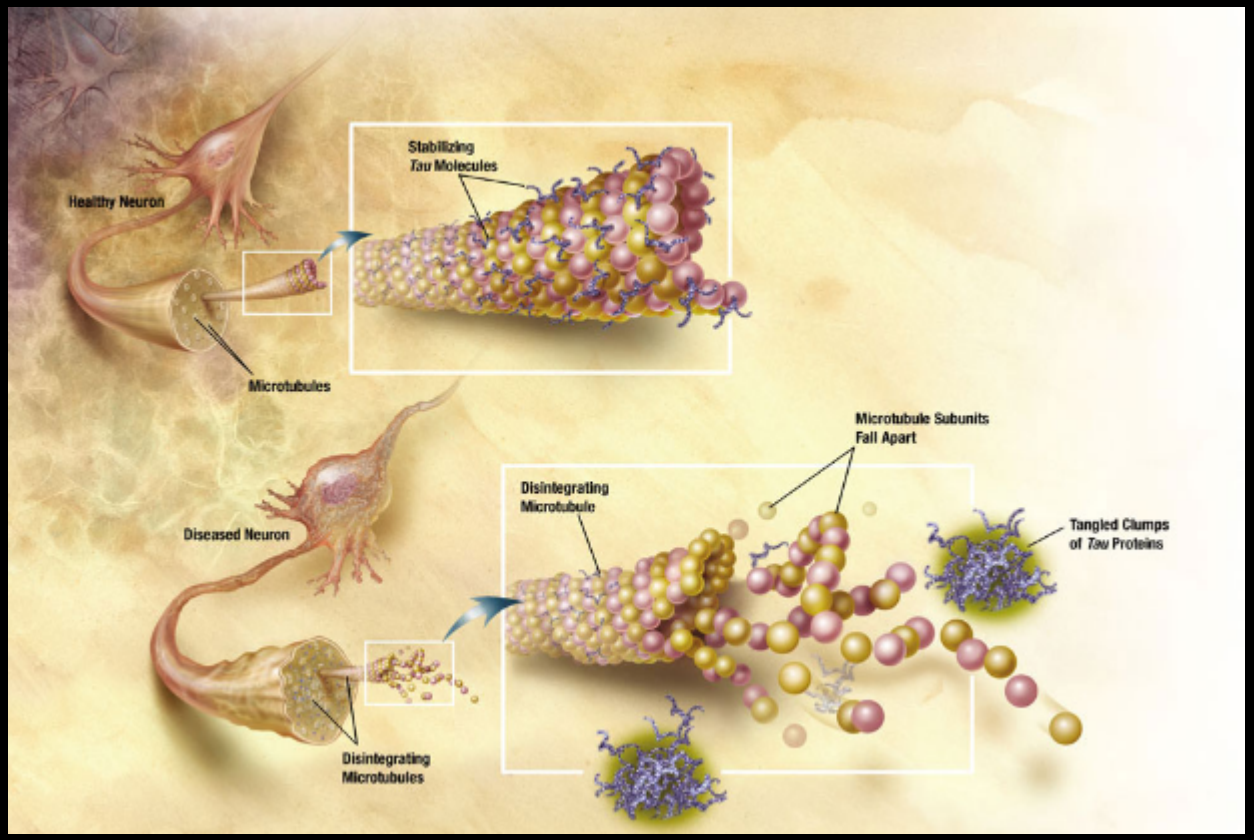
- Nomenclature
  - Frontotemporal lobar degeneration (FTLD)
- Two main pathologies (intracelllular inclusions)
- Partially predicted by clinical
- Overlap with other disorders
  - Tau
    - 50% of bvFTD
    - Large proportion of nfvPPA
    - Progressive Supranuclear Palsy, Corticobasal Degeneration
  - TDP-43
    - 95% of svPPA
    - Amyotrophic Lateral Sclerosis (ALS)
    - bvFTD-ALS (about 15% of bvFTD)
  - bvFTD about 50/50 Tau/TDP-43

Genetics: Three Main Mutations

- At least 30% of all FTD
- 3 main mutations
  - *C9ORF72* (discovered last year)
    - Most common, ~40% of familial FTD, 5% of apparently sporadic FTD
    - Hexanucleotide (GGGGCC) repeat abnormality (like Huntington's, cerebellar ataxias)
    - bvFTD and ALS
    - Most common genetic cause of ALS
  - Progranulin
    - Probably next most common
    - can go posteriorly, present like AD
    - also bvFTD, CBD, PD, AD
  - Tau
    - bvFTD with PSP - like Parkinsonian syndromes

Tau

- Many isoforms
- Stabilizes microtubules
  - Intraneuronal transport infrastructure

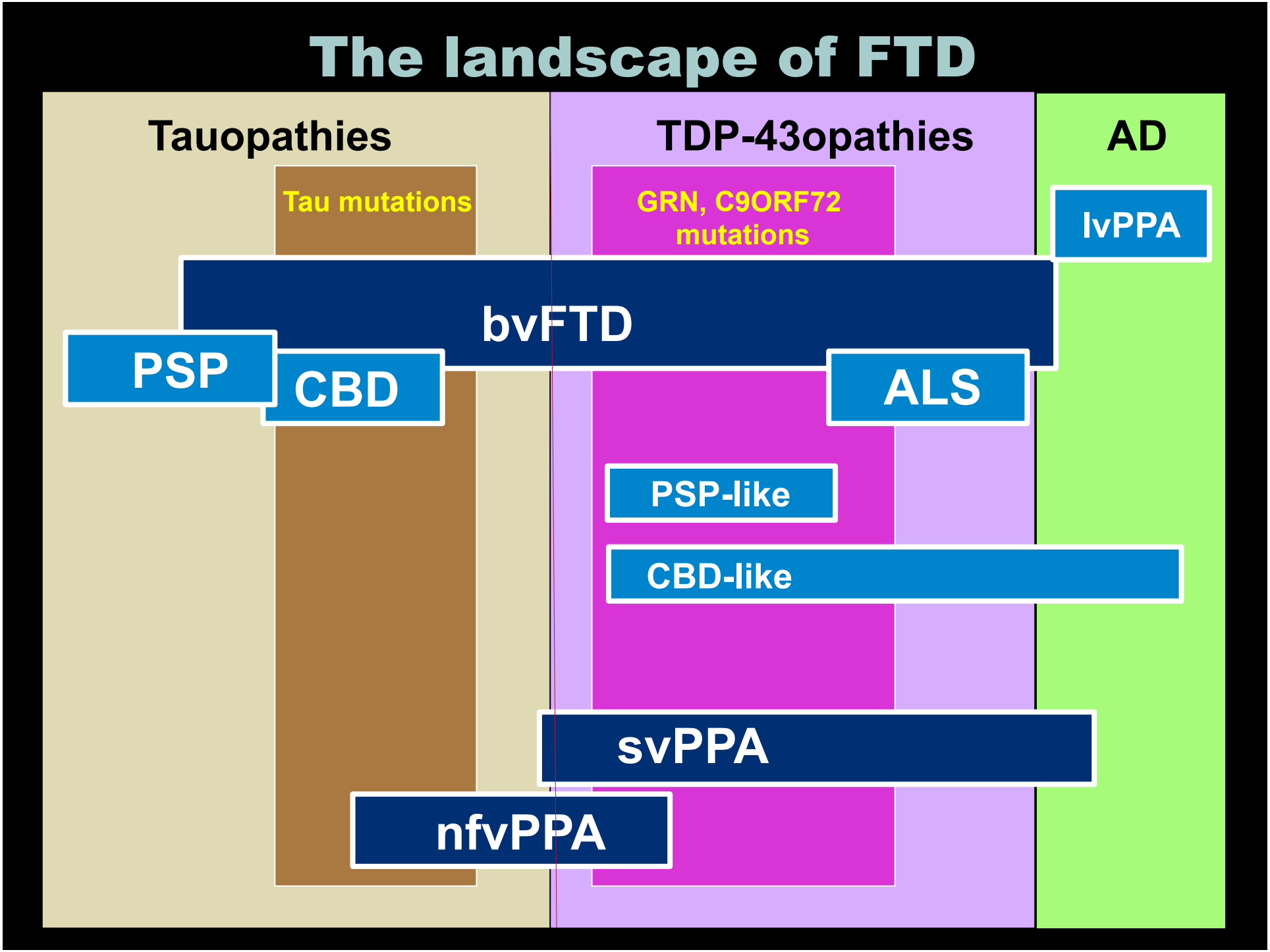


Progranulin

- **Secreted glycoprotein with growth factor-like and immunomodulatory activities**
  - TNF receptor antagonist like activity
- **Contains 7 full and one ½-length granulin domains, which are released following proteolytic cleavage**
- **>60 pathogenic *GRN* mutations have been reported in patients with FTD and all are expected to result in haploinsufficiency**

C9ORF72

- **Functions unknown**
- **No previous disease associations**
- **Current mechanistic hypotheses around toxic accumulation of RNA**
  - Possible interference with transcription of other DNA sequences

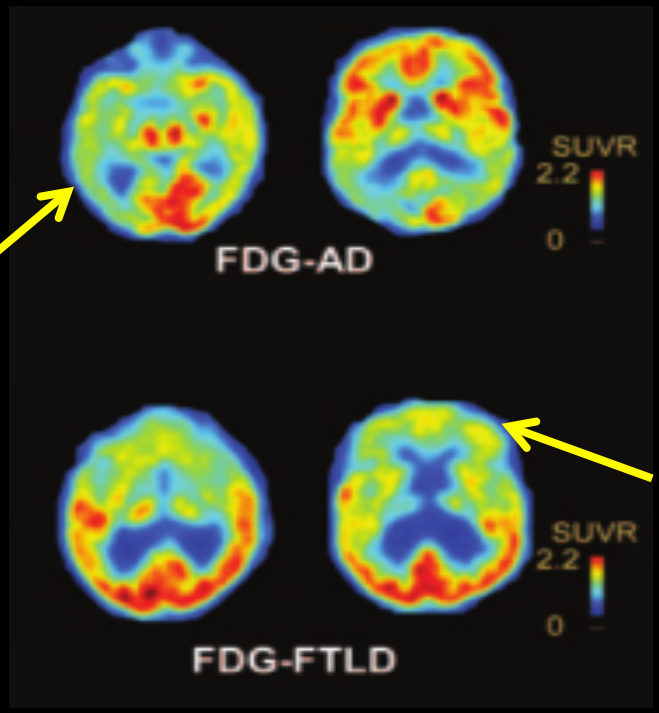

The landscape of FTD
Tauopathies
TDP-43opathies
AD
Tau mutations
GRN, C9ORF72 mutations
lvPPA
bvFTD
PSP
CBD
ALS
PSP-like
CBD-like
svPPA
nfvPPA

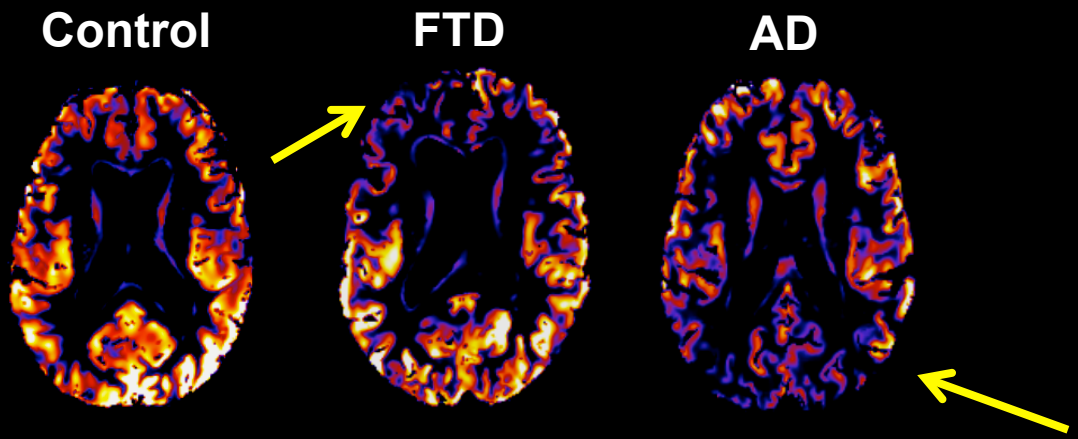
Diagnosis of FTLD

- Clinical features
  - Three main variants
  - Related disorders
  - "Possible" diagnosis
  - Criteria papers
    - Rascovsky et al, Brain, 2011
    - Gorno-Tempini et al, Neurology, 2011
- Imaging
  - MRI
  - PET
  - "Probable" diagnosis
  - Radiologists frequently miss
    - Suarez et al, Neurology, 2009
- Other objective features
  - Genetics
  - Molecular imaging

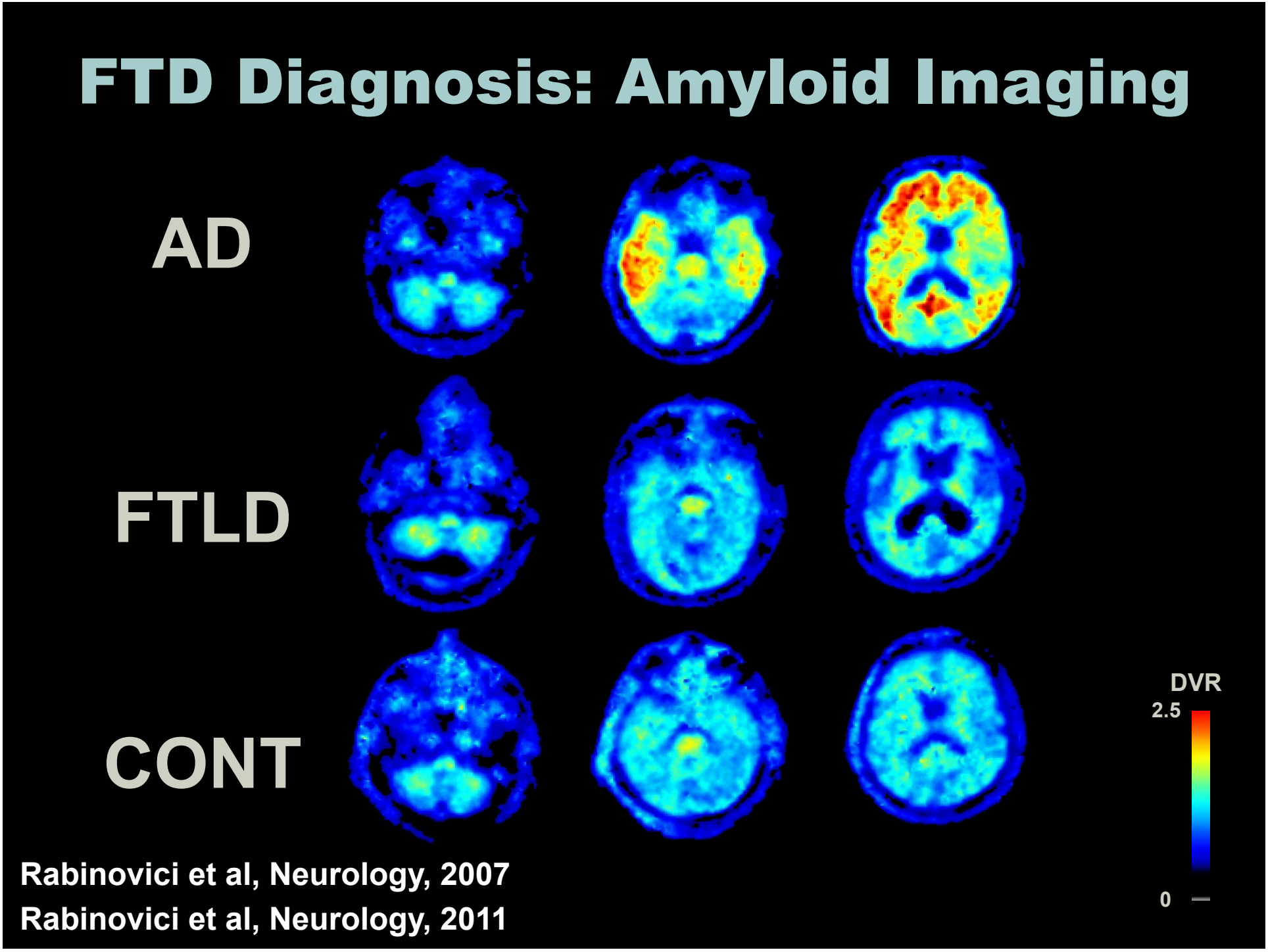
FDG-PET in FTLD

- Increased diagnostic certainty
  - Foster et al, Brain, 2007
  - Rabinovici et al, Neurology, 2011
- Medicare approved use of FDG-PET
  - Only indication for PET in neurodegenerative disease
- Possible role for other metabolic imaging
  - ASL perfusion





FTD Diagnosis: Amyloid Imaging

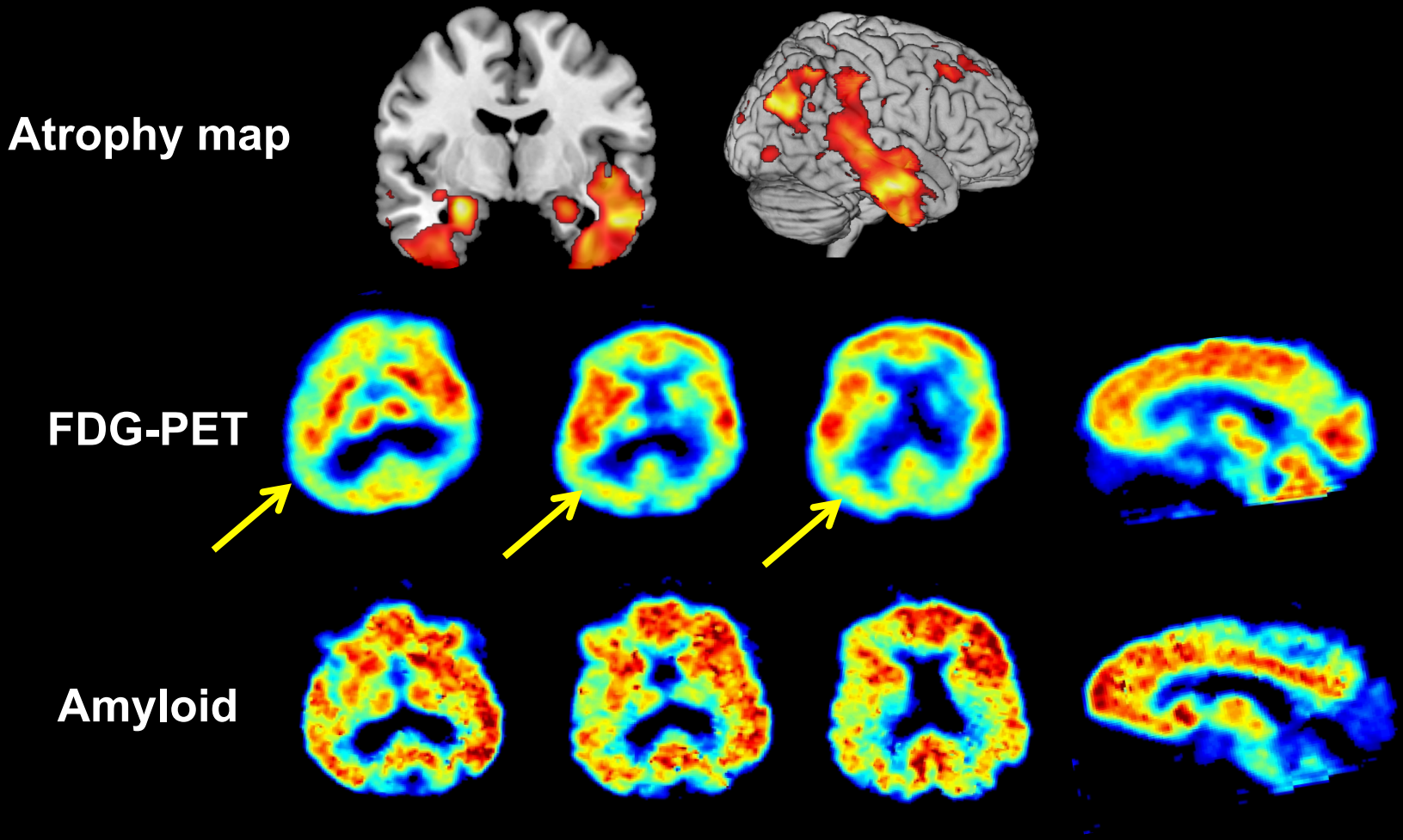


Rabinovici et al, Neurology, 2007

Rabinovici et al, Neurology, 2011

Amyloid Imaging is not 100% diagnostic

65 year old with PRGN mutation, AD like symptoms, Amyloid+



Perry et al, Archives of Neurol, In press

Current treatment of FTD

- Behavioral management
  - Environment
  - Family education
- Symptomatic management
  - SSRIs (e.g. citalopram)
  - Trazadone
  - Atypical antipsychotics
  - AVOID cholinesterase inhibitors in bvFTD
    - May exacerbate symtoms/increase agitation
- Specific treatment
  - Recent trial of memantine failed
- Speech therapy for language disorders
  - Under investigation

Future treatments

- Current/recent work
  - Longitudinal biomarker trials
    - Surrogate endpoints, stratification
  - Divunetide (microtubule stabilizing compound) for PSP
    - Failed
  - Methylene blue for bvFTD
    - Recently failed
  - Tau imaging agents
- Planned work
  - HDAC inhibitor and other drugs for GRN mutations
    - Raise PRGN levels
  - Anti-sense oligonucleotides
  - Tau antibody for PSP and other tau related forms of FTD
  - Beginning to develop “silencing” approaches to the C9ORF72 repeat expansion

Conclusions

- FTD is symptomatically complex
  - Symptoms come from anatomy
- FTD is pathologically, genetically complex
  - Multiple pathologies
  - Overlap with other syndromes (ALS, PSP, CBD)
- Diagnosis multimodal
  - Proper clinical characterization
  - Imaging
- Current treatments limited
- Future treatments will be aimed at specific proteinopathy

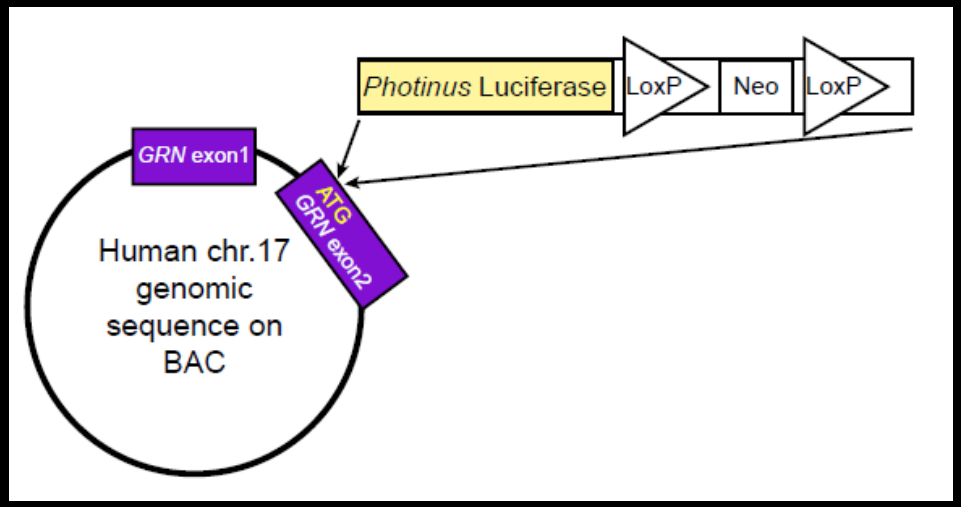
Thank you!

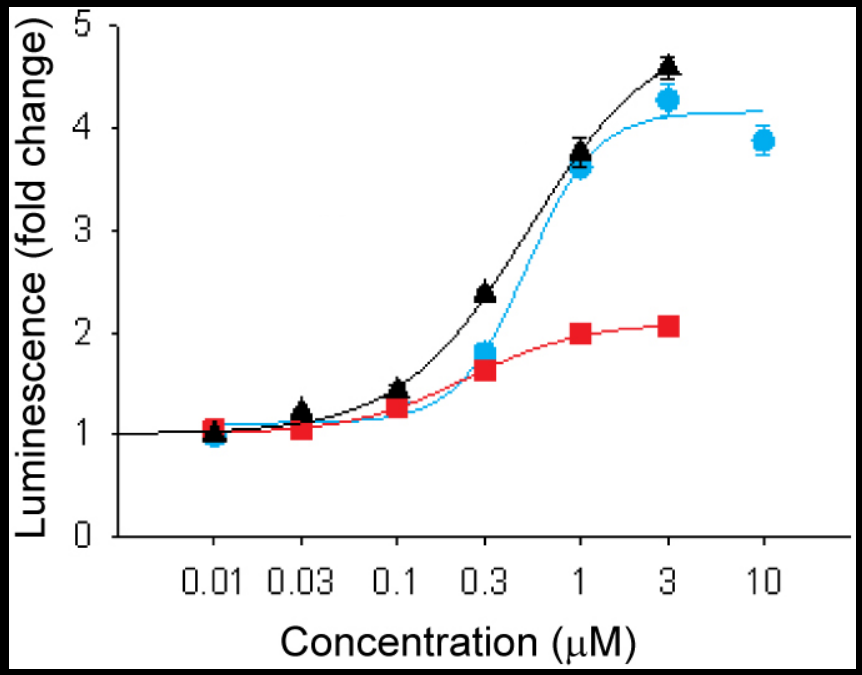
Restoring Progranulin Levels

THERAPEUTIC GOAL: Increase *GRN* transcription from the remaining WT allele

SCREEN: FDA-approved compound library using luciferase-tagged *PGRN* reporter

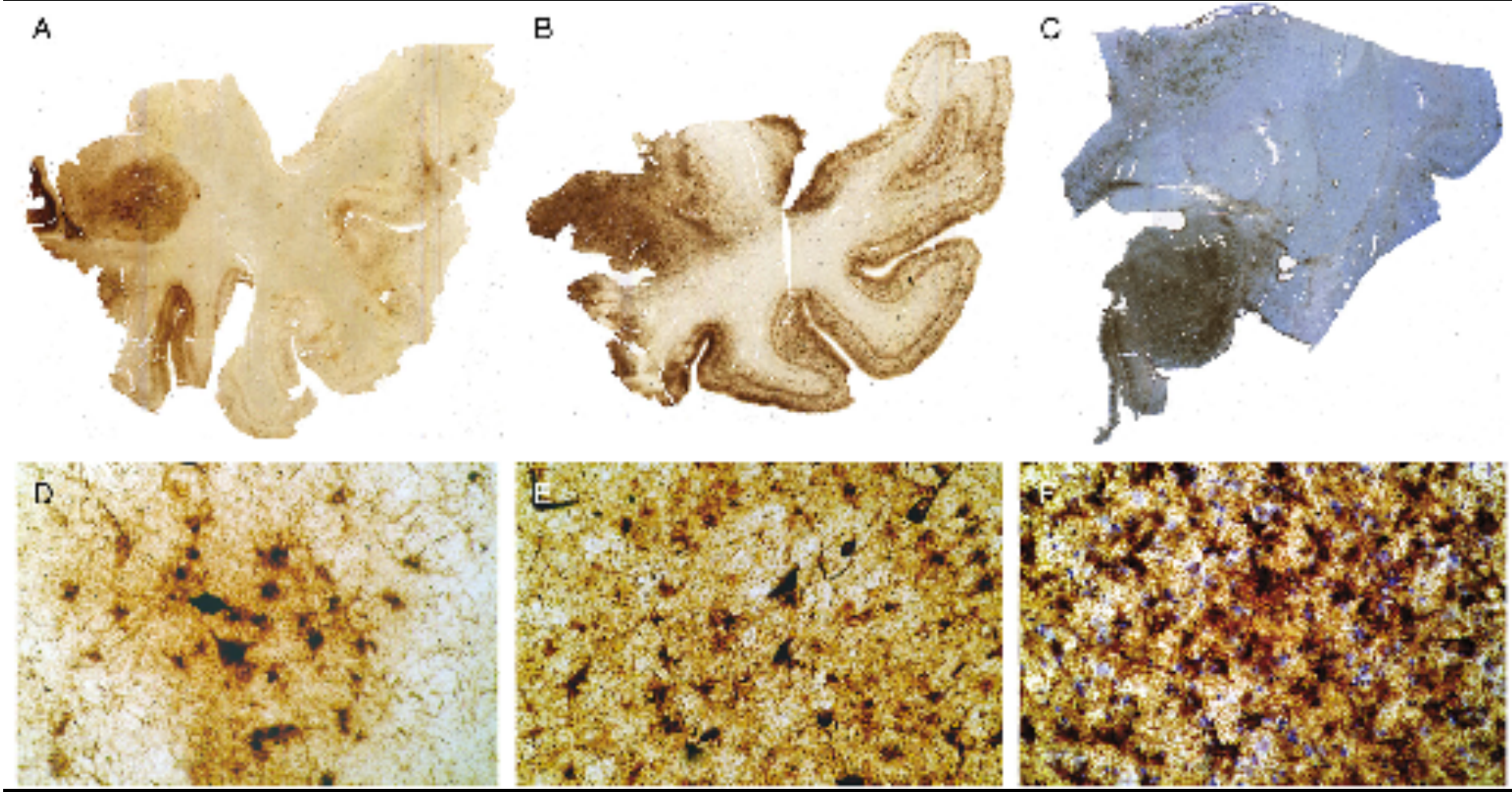
SAHA greatly altered progranulin levels





Joachim Herz & Gang Yu labs, UTSW

CTE: Amygdala/Tau



McKee AC et al. *J Neuropathol Exp Neurol*. 2009;68:709-35.

An illustrative case

- 55 year old man
- Hearing voices beginning early 2010
  - Yelling out window in response to his name
  - Making up stories
  - Voices telling him people died
  - Voices telling him his neighbors want to have sex with him
    - Goes to their houses
- No psychiatric history

An illustrative case

- 55 year old man
- Hearing voices beginning early 2010
  - Yelling out window in response to his name
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- No psychiatric history

Case study (cont'd)

- Neuropsychological testing
  - Mild executive dysfunction
- MRI
  - Non-specific mild-moderate atrophy
- DIAGNOSIS
  - Initially MCI/Lewy body disease
  - Meets criteria for "Late life schizophrenia"

Follow up

- After around 1.5 - 2 years
  - Developed symptoms of FTD
  - Developed motor neuron disease
  - Died a few months ago
- Discovered to have C9ORF72 mutation