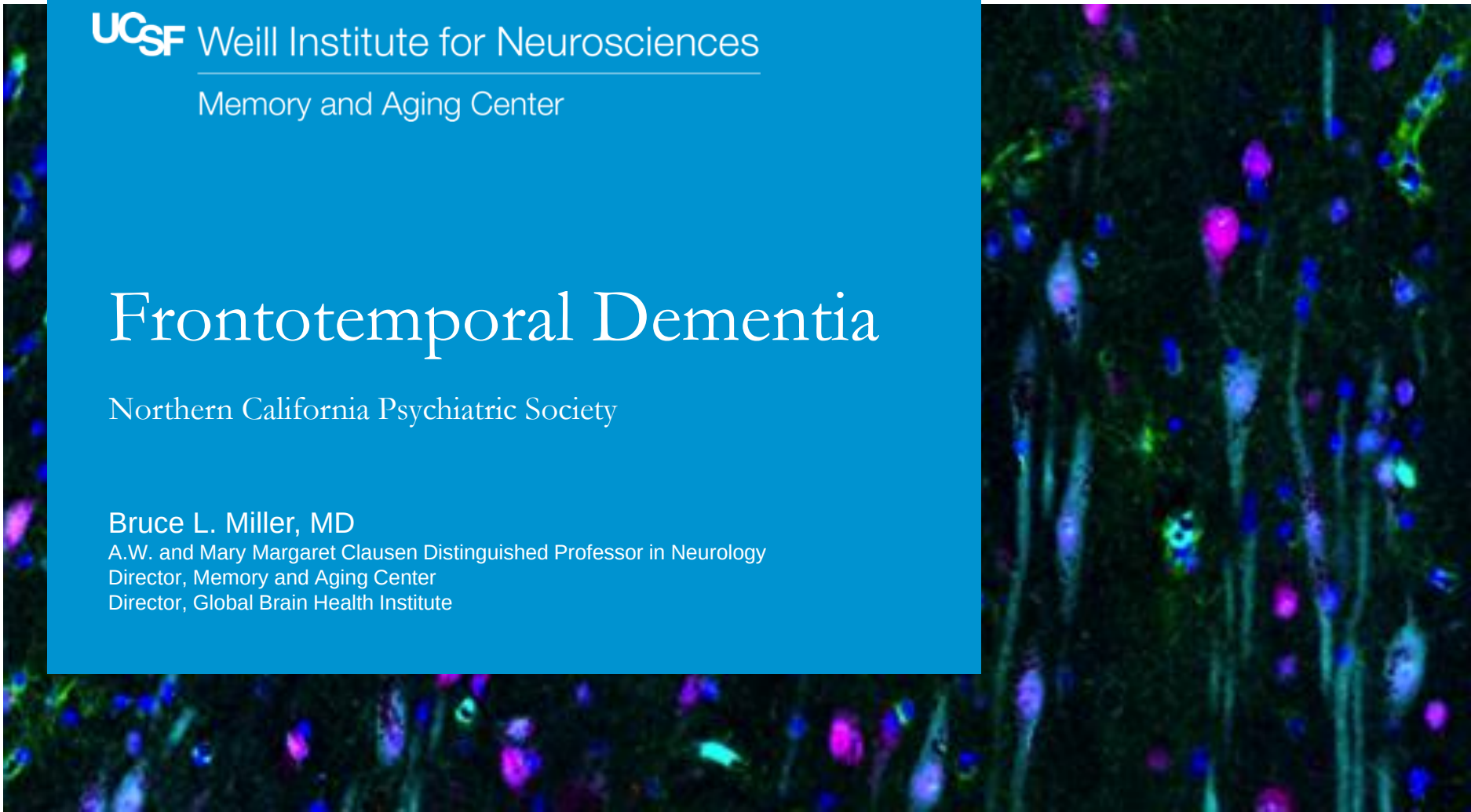

UCSF Weill Institute for Neurosciences

Memory and Aging Center

Frontotemporal Dementia

Northern California Psychiatric Society

Bruce L. Miller, MD
A.W. and Mary Margaret Clausen Distinguished Professor in Neurology
Director, Memory and Aging Center
Director, Global Brain Health Institute

UCSF Memory and Aging Center 2016

UCSF Mission Bay Campus, Sculpture by Mark di Suvero

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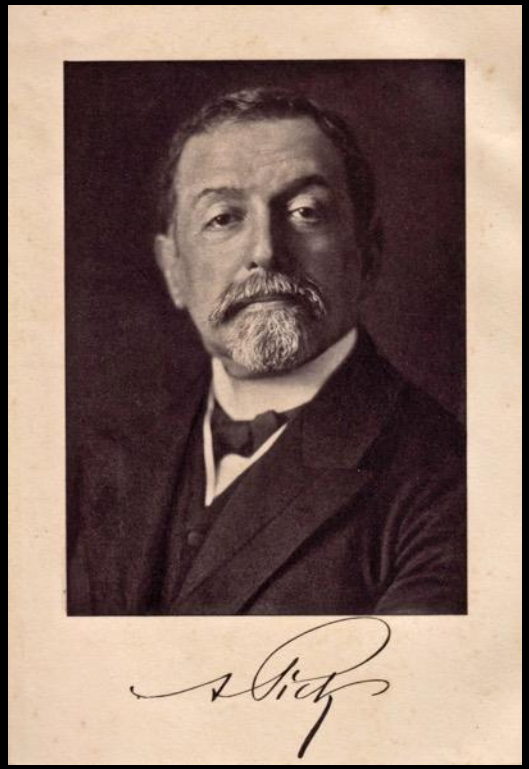
Overview

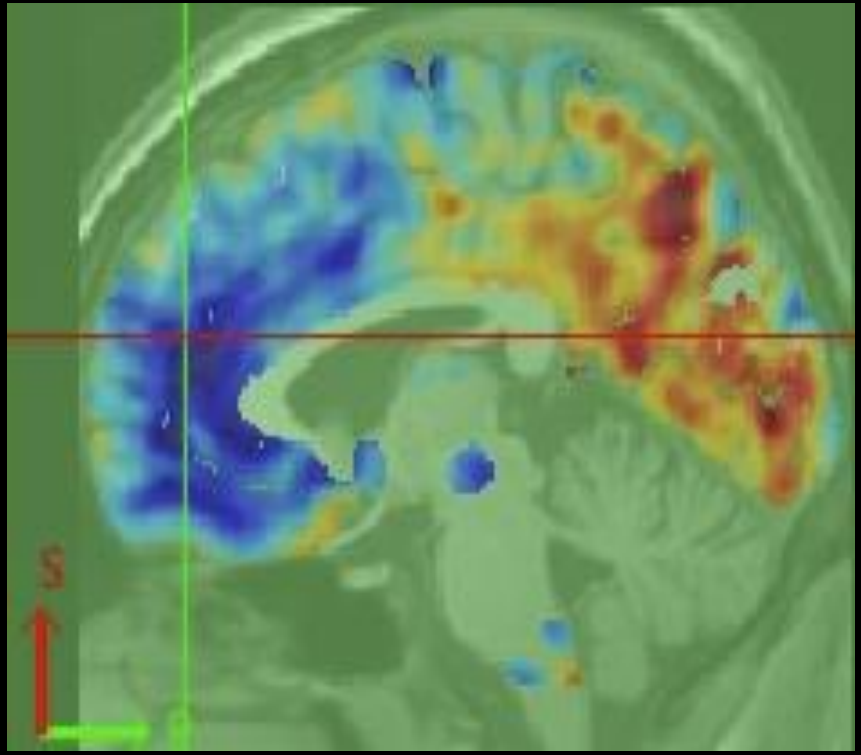
- Introduction to FTD (it's important)
- Brief neuropathology/genetics
- Clinical – bvFTD
  - Reward
  - Emotion
- Tau imaging
- Tau therapeutics

Frontotemporal Dementia (FTD)



- 1892, Arnold Pick describes a focal neurodegenerative condition
- Pick's disease preferentially affects the frontal and temporal lobes
- Pick body
  (Alzheimer 2011)

VBM of FTD & AD vs Controls



Concept from Delay, Brion Escourolle 1950s,
Thibodeau MP, Miller BL. Neurocase. 2013

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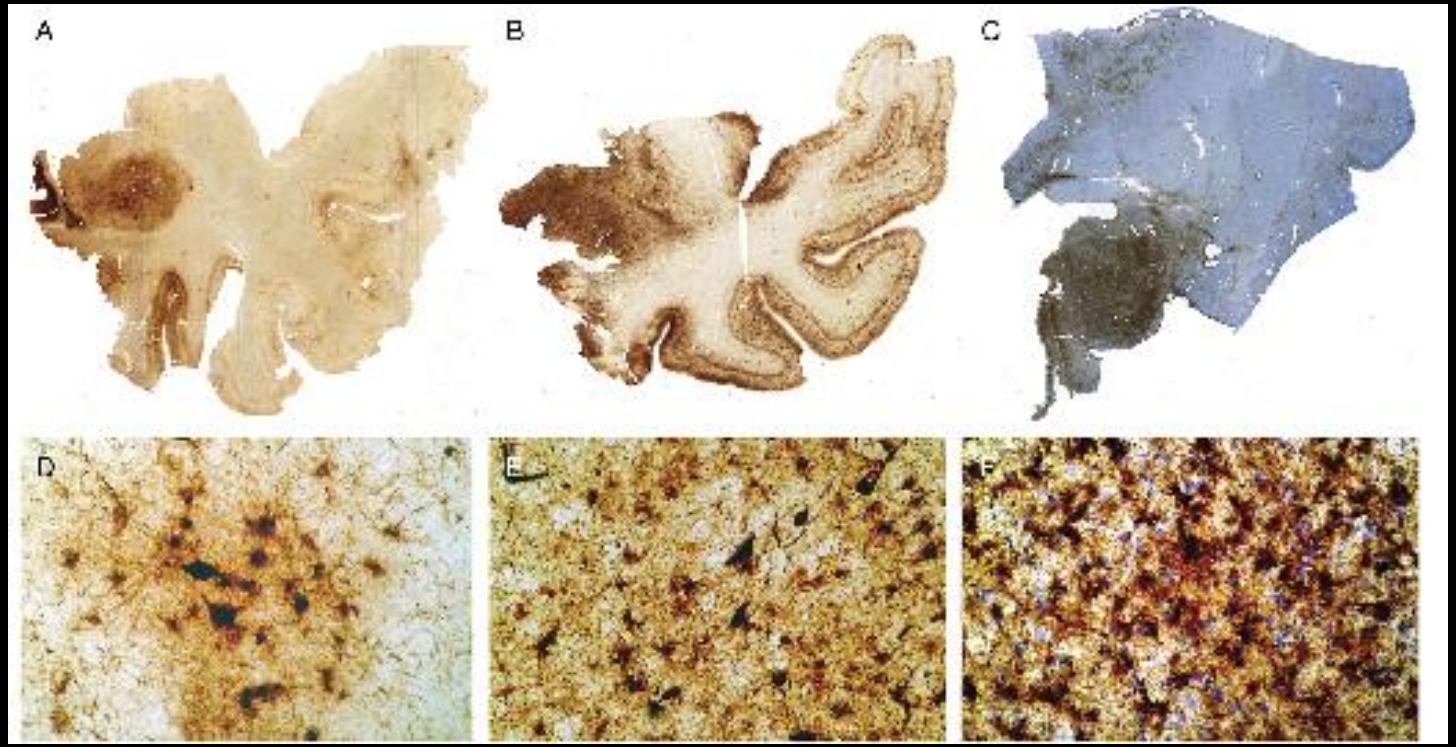
Frontotemporal Dementia (FTD)

- Common cause pre-senile dementia
  - 1:1 with AD 45–64 years (Hodges 2002), most common dementia <60
  - 40% familial, 10% dominant (Chow, 1999)
- Rare after 70?
  - Strong links with ALS, PSP, CBD
  - TDP-43 & hippocampal sclerosis common dementia over 80 (Nelson 2007, 2013, Nag 2015)

Chronic Traumatic Encephalopathy/Tau



McKee AC et al. *J Neuropathol Exp Neurol*. 2009

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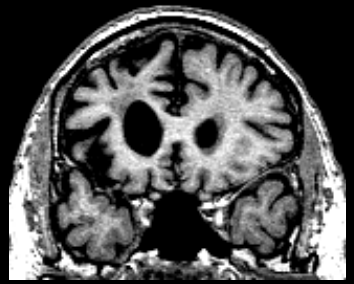
3 Types Frontotemporal Dementia

Behavioral Variant

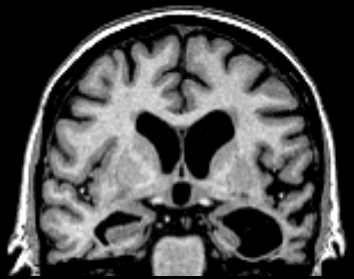


R L

Often genetic
Tau, TDP, FUS
2/3 TDP

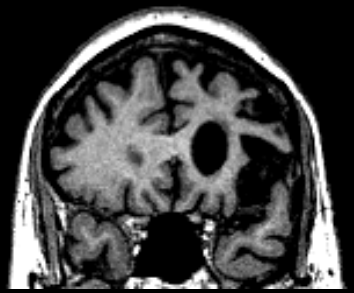
Language Variants

Semantic Variant



Rarely genetic
83% TDP-C

Nonfluent Variant



Some genetic
85% Tau, TDP-A

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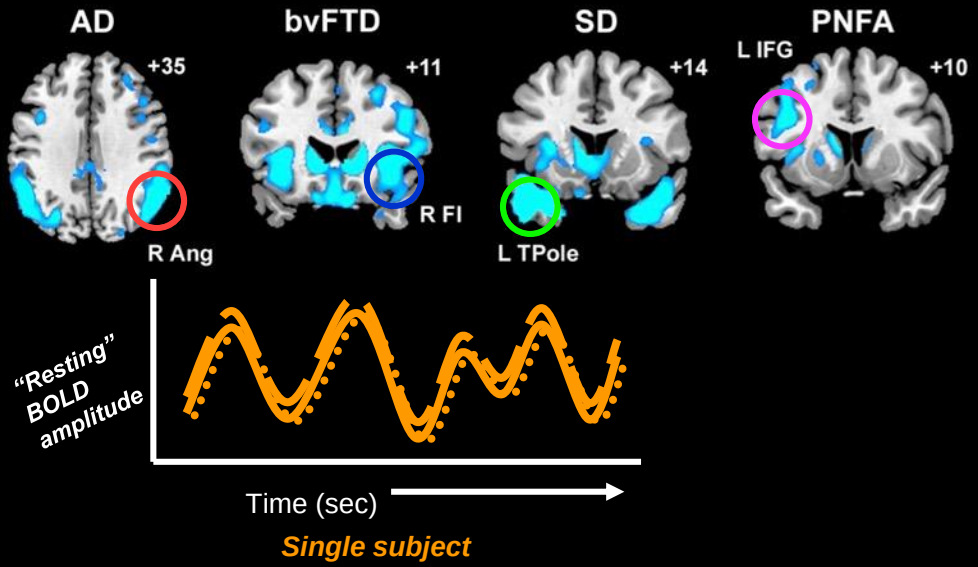
Network-based Neurodegeneration

Syndrome-specific regional atrophy patterns: patients vs. controls



Seeley et al Neuron 2009

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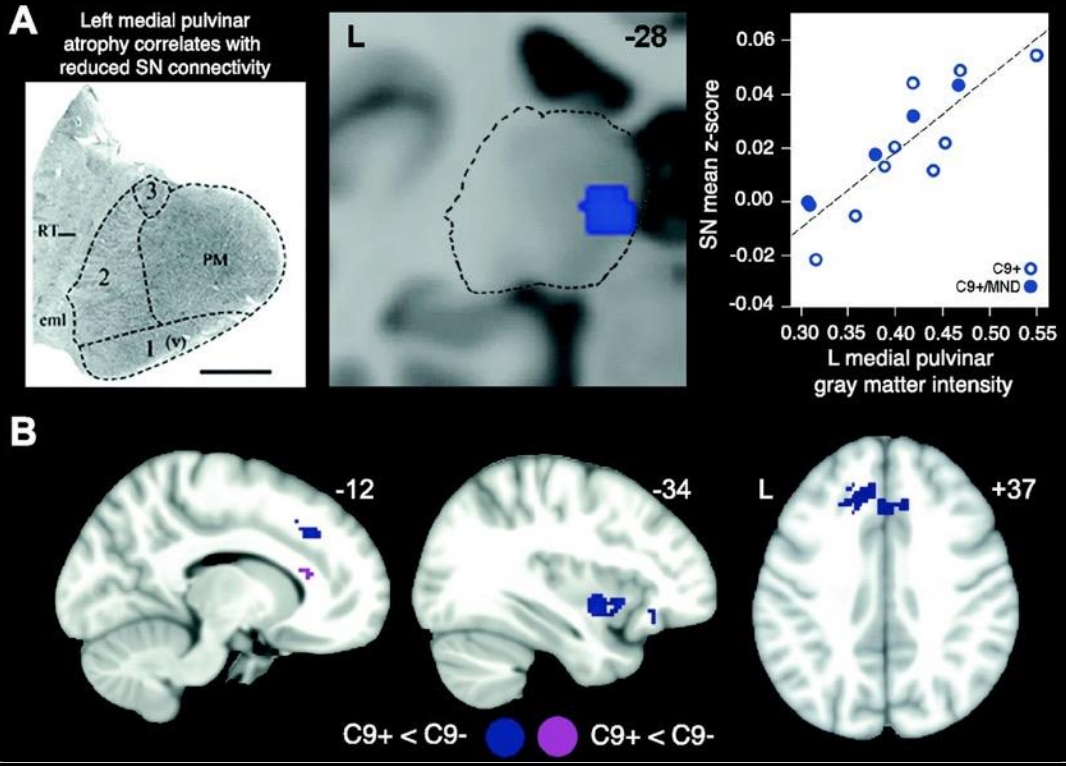
C9ORF72 Small Medial Pulvinar

Salience Network Disruption



Lee SE et al. Brain 2014

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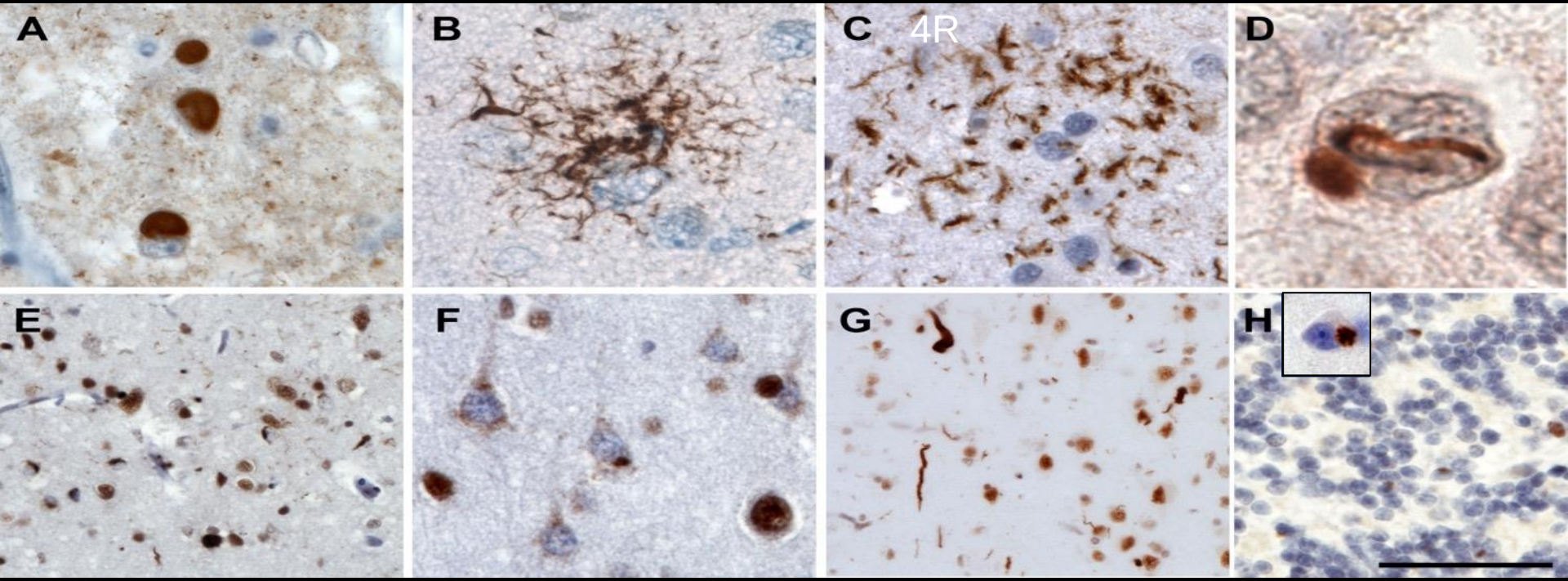
FTLD-tau

Pick 3R | PSP 4R | CBD | FTLD-FUS



TDP-A | TDP-B | TDP-C | Dipeptides (C9ORF72)

FTLD-TDP

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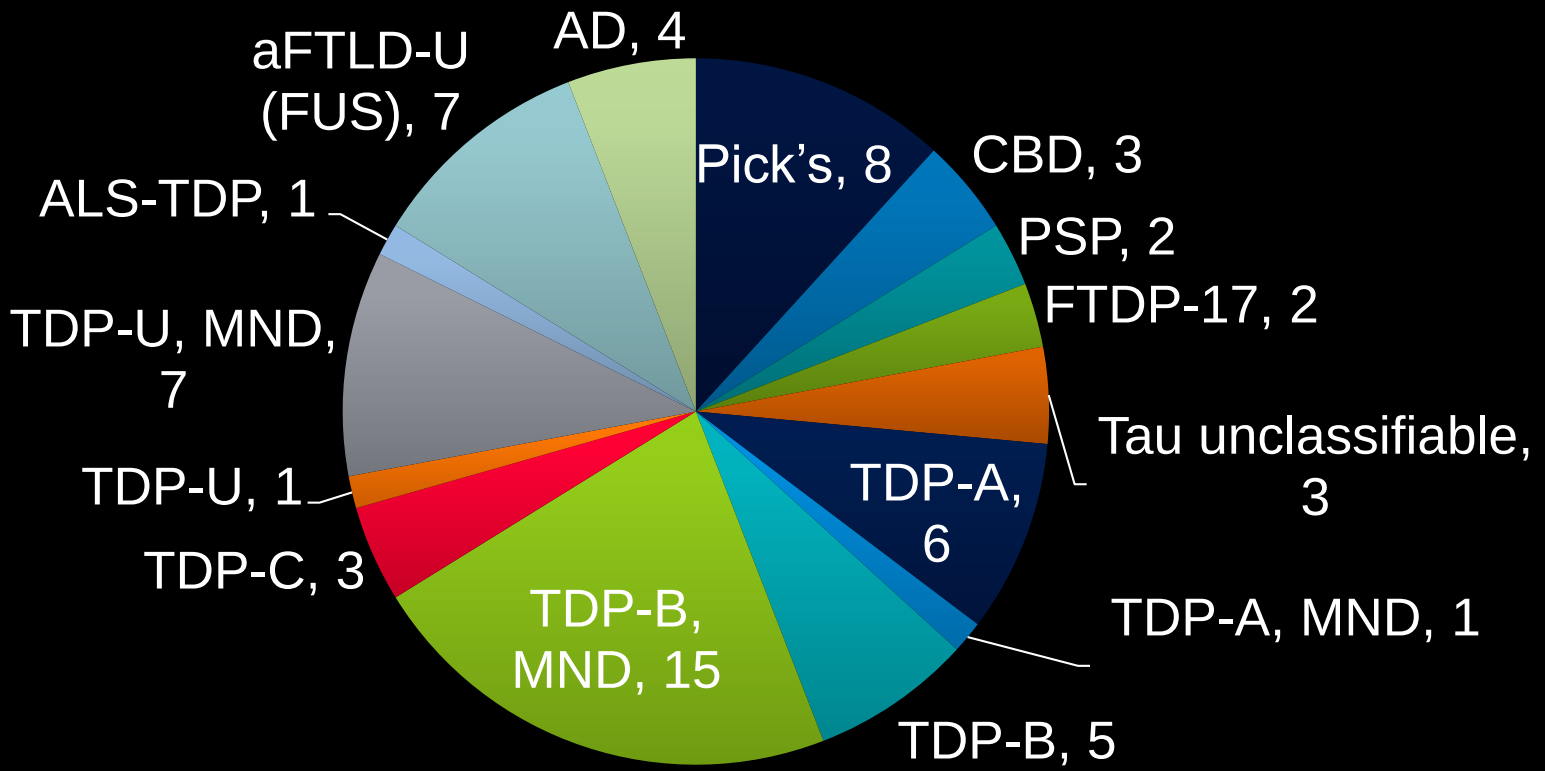
bvFTD, high confidence, n = 68



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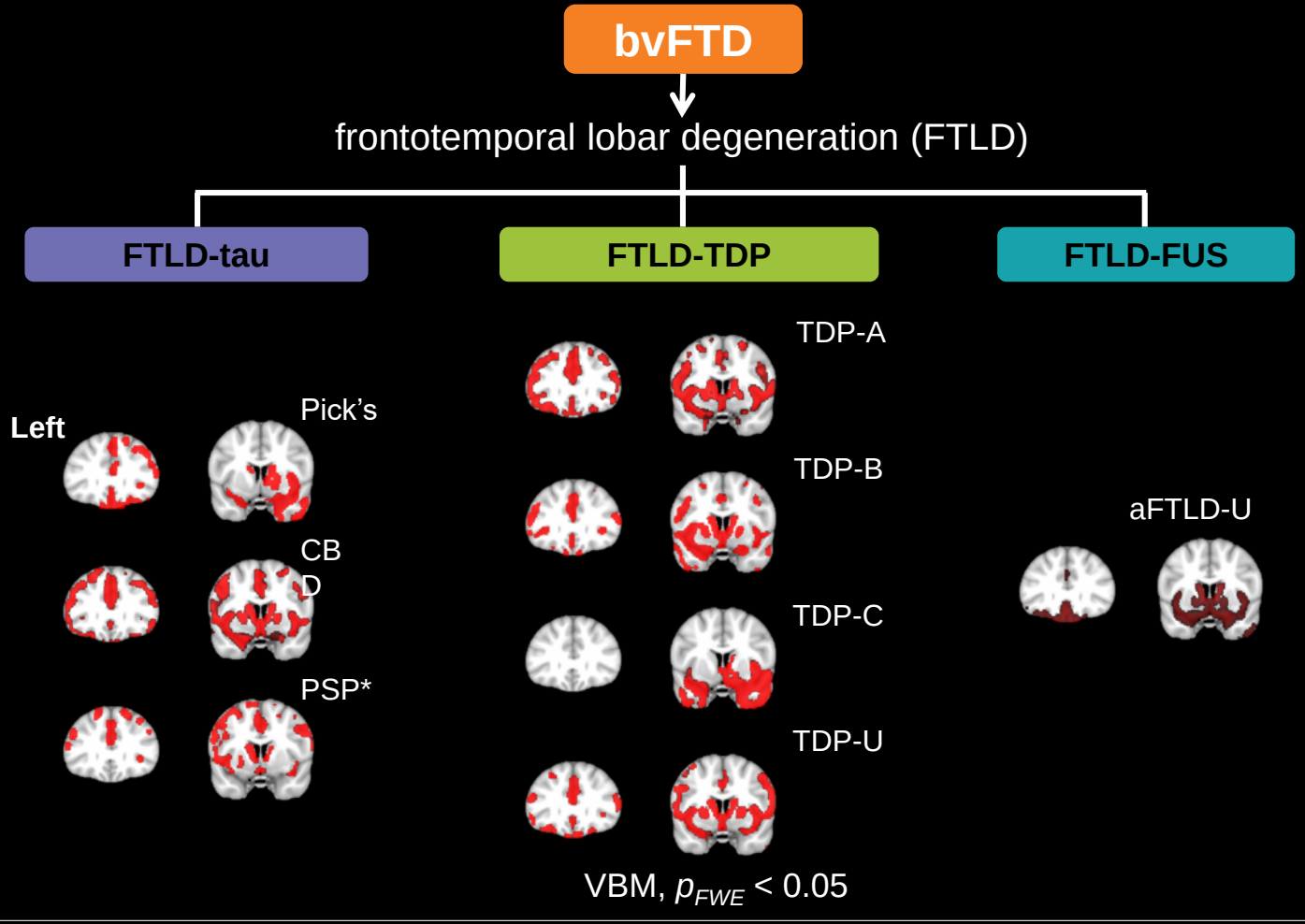
bvFTD
frontotemporal lobar degeneration (FTLD)
FTLD-tau
FTLD-TDP
FTLD-FUS
Left
Pick's
CB
D
PSP*
TDP-A
TDP-B
TDP-C
TDP-U
aFTLD-U
VBM, $p_{FWE} < 0.05$

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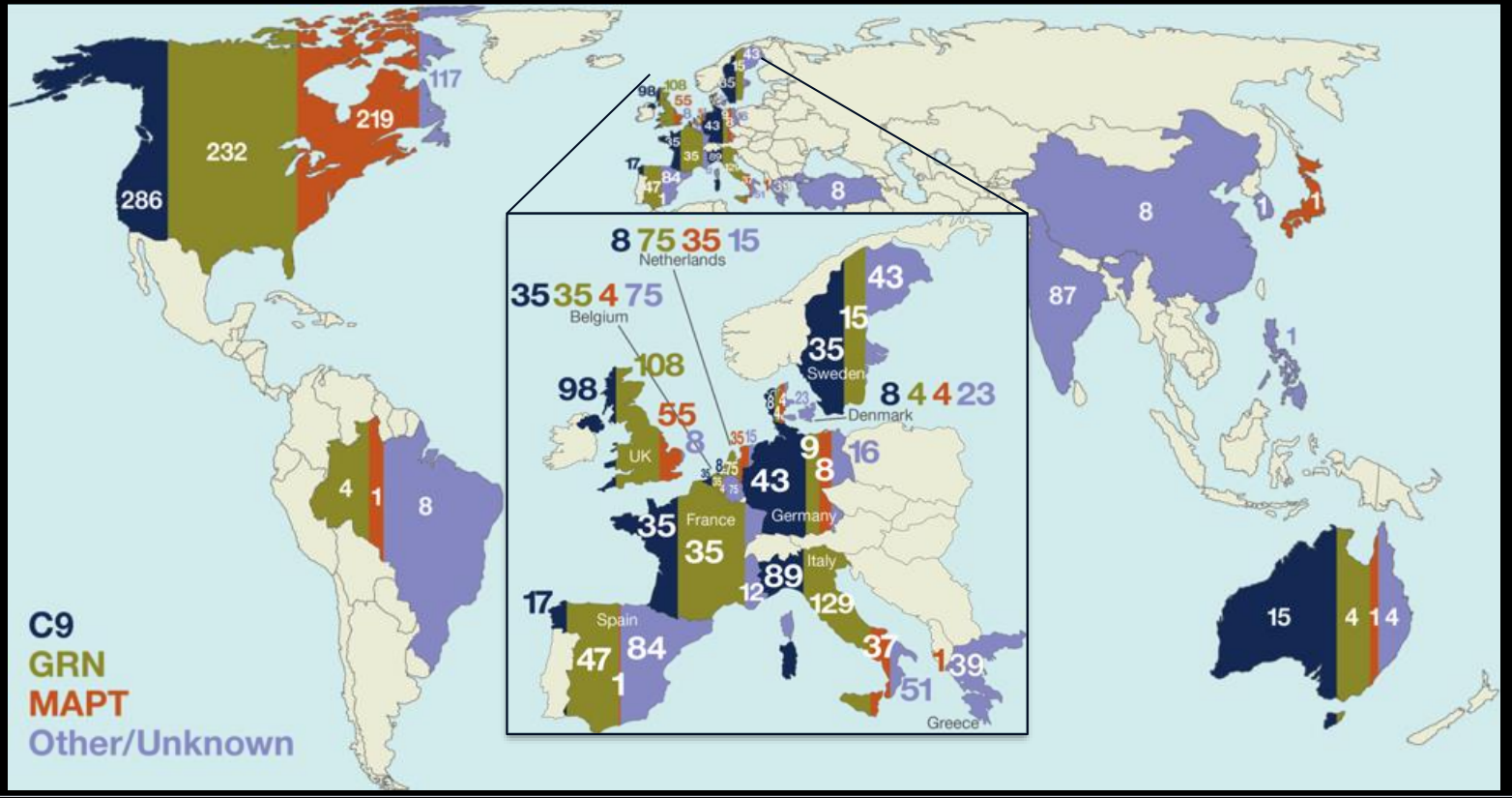
Three Main Genetic Mutations

- *MAPT:* 52 years, MRI symmetrical, bvFTD with parkinsonian syndromes, 1998
- *GRN:* 62 years, MRI asymmetric, bvFTD, progressive aphasia, PD, AD, 2006
- *C9ORF72:* 56 years, MRI symmetric, cerebellar involvement (subtler frontal involvement), bvFTD and ALS, 2011

*Adeline Ng Neurology 2015

How Many Familial FTD Do You Follow?



MAC Genetic Cohort

Gene	Number of Families	Mutation Negative	Presymp Mutation carrier	Affected mutation Carrier	Unknown Status/ at risk
C9ORF72	53	29	22	71	16
GRN	25	35	19	34	5
MAPT	10	13	6	14	3
TARDBP	5	1	1	5/2 (AV90)	
PSEN1	7	0	1	6	
APP	2	3	2	4	
A152T variant	13	1	3	12	1

Rare Variants FTD-ALS Syndromes

Gene	Variant	Phenotype	Publication
TARDBP	P112H	FTD	Moreno et al 2015
FUS	Q140H	tauopathy	Ferrer et al 2015
LRRK2	C2154F	tauopathy	Chen-Plotkin et al 2008
TBK-1	Nonsense variant	FTD-ALS	Le Ber et al 2015
PRNP	Q160X	dementia	Fong et al 2016
OPTN	deletion, nonsense & missense mutation	ALS	Maruyama et al 2010
UBQLN2	PXX	ALS	Deng et al 2011

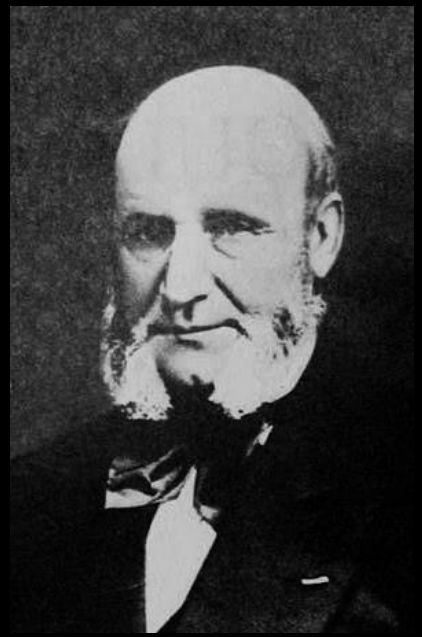
Giovanni Coppola personal communication

bvFTD Early Changes

- Selfishness
- Passivity
- Addictive behaviors
- Odd affiliations (changes in self)
- Disinhibition
- Criminal behaviors
- Loss of empathy for others

Leaders of the Neuroscience of Emotion

Guillaume-Benjamin-Amand Duchenne de Boulogne

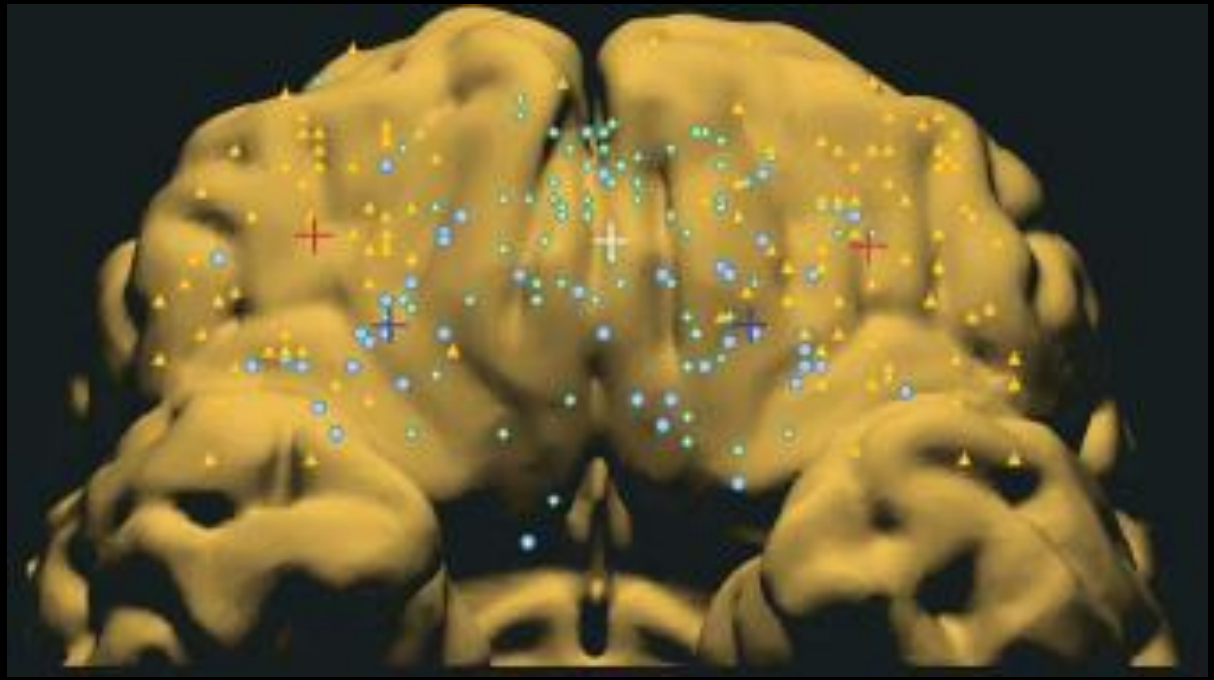


Paul Ekman

Robert Levenson

UCSF

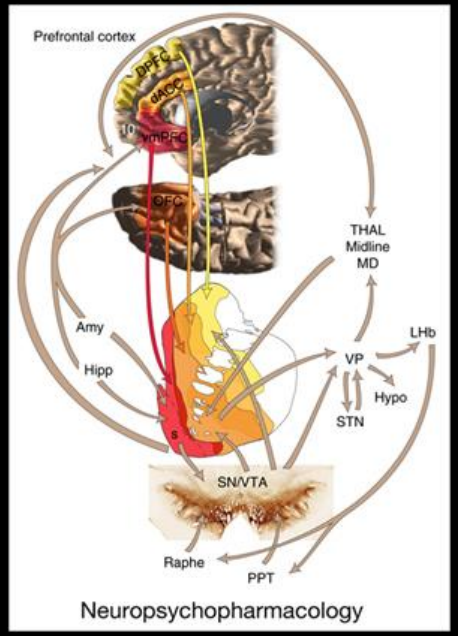
Medial Versus Lateral Orbital Cortex



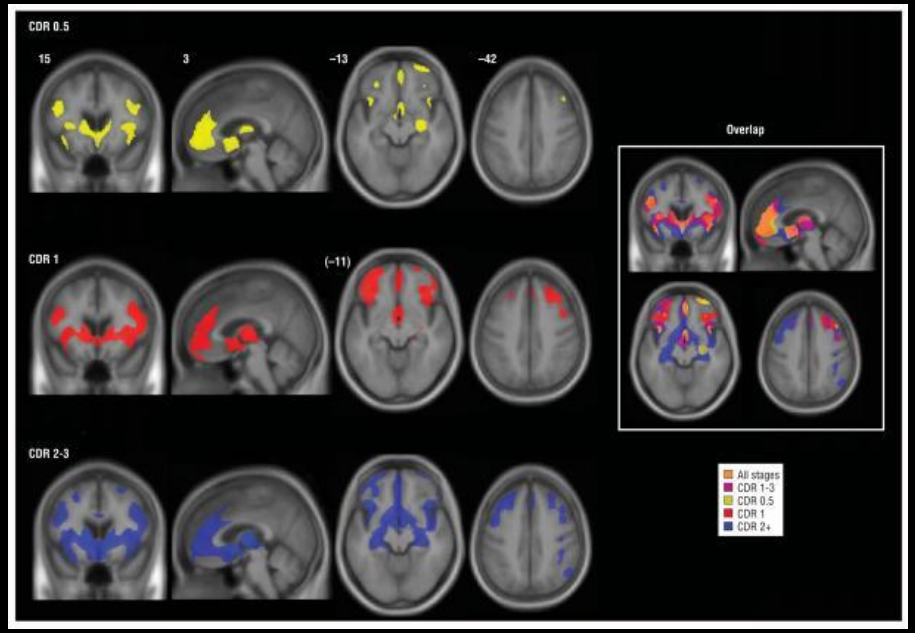
+ monitoring reward value
+ punishers leading to change in behavior

Kringelbach & Rolls 2004

Overlapping Anatomy of Reward Processing and bvFTD

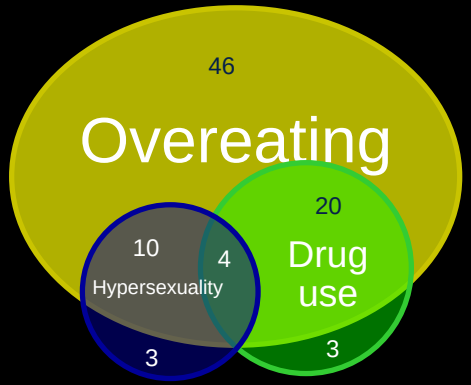


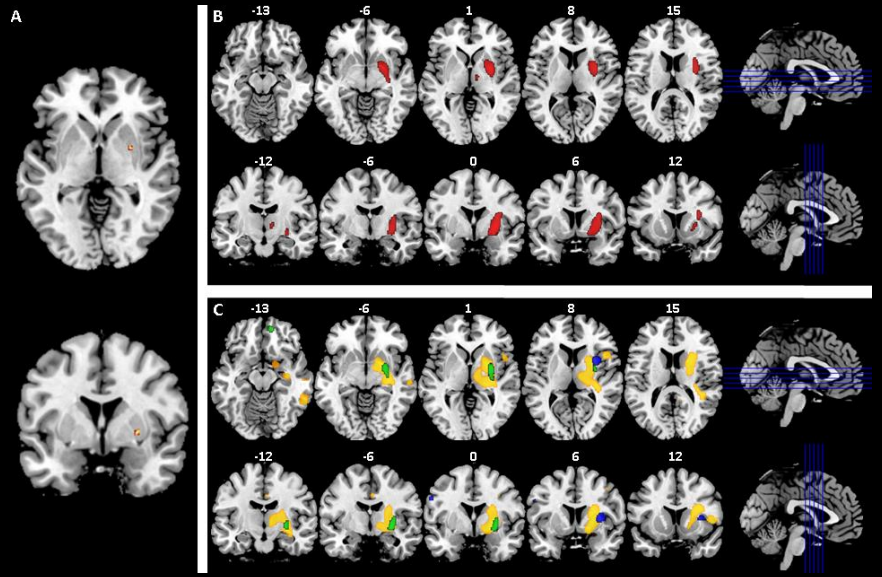
Haber and Knutson, *Neuropsychopharmacology, 2010*



Seeley et al, *Archives of Neurology, 2008*

Reward Seeking in bvFTD



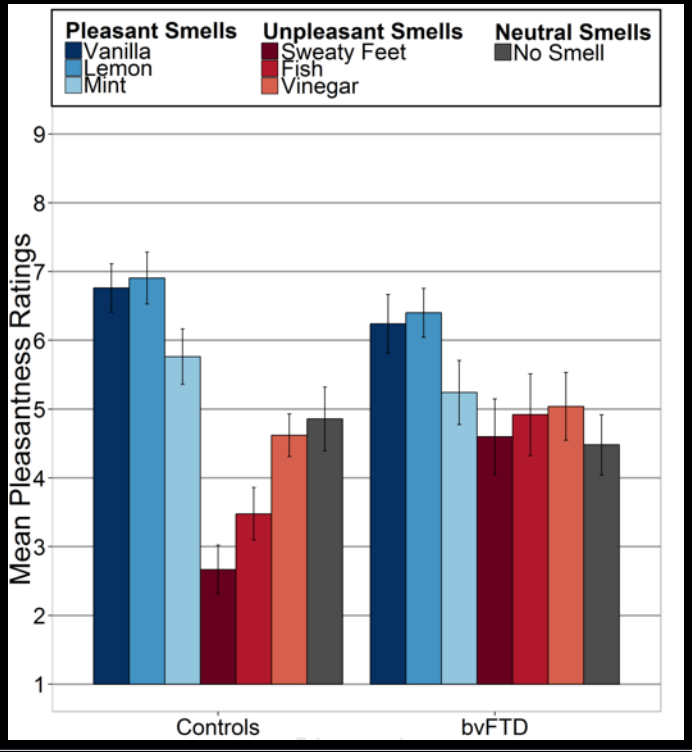


Perry, *Brain*, 2014

UCSF

Olfactory Reward Tasks

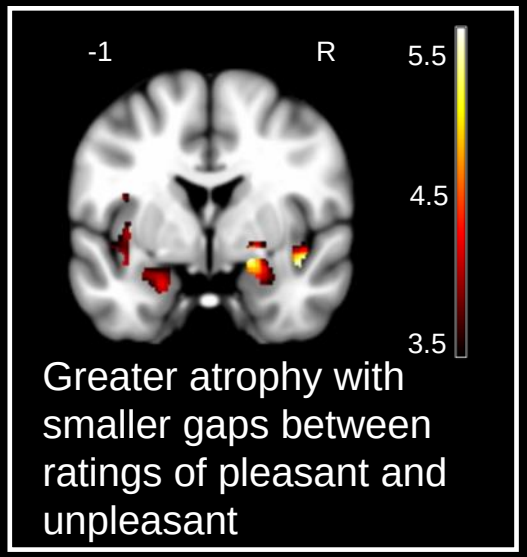
Less aversion to unpleasant smells in bvFTD



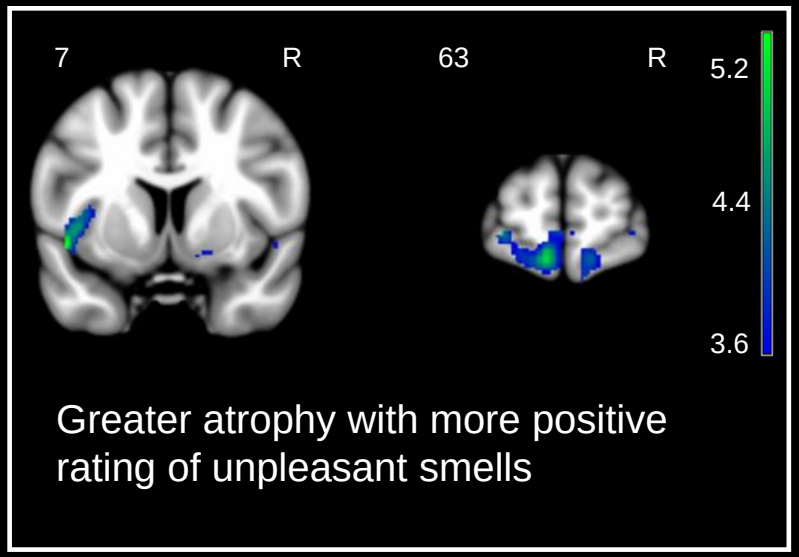
Perry et al, unpublished

UCSF

Reward Changes in FTD Relate to Atrophy in Reward Processing Structures



Greater atrophy with smaller gaps between ratings of pleasant and unpleasant



Greater atrophy with more positive rating of unpleasant smells

Displayed at p<.001 within regions known to be involved in reward

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Crime with Dementia

Dx	Number	Percentage
AD	545	7.7%
bvFTD	171	37.4%
svPPA	89	27%
HD	30	20%
MCI	243	3.3%

Liljegren & Naasan et al JAMA Neurol 2015

Crime: bvFTD, svPPA & AD

	bvFTD	svPPA	AD
Frequency	37.40%	27%	7.70%
Onset	Early	Early	Late
Types	Sexual advance, theft, public urination, violence	Theft, traffic violation	Traffic violation, trespass/wander
Cause	Disinhibition, impulsivity, reward/punish	Compulsive attracted to visual stimuli	Cognitive dysfunction
Anatomy	Anterior insular, orbitofrontal, ventral striatum	Ant. temporal orbitofrontal, ventral striatum	Hippocampus, parietal lobe

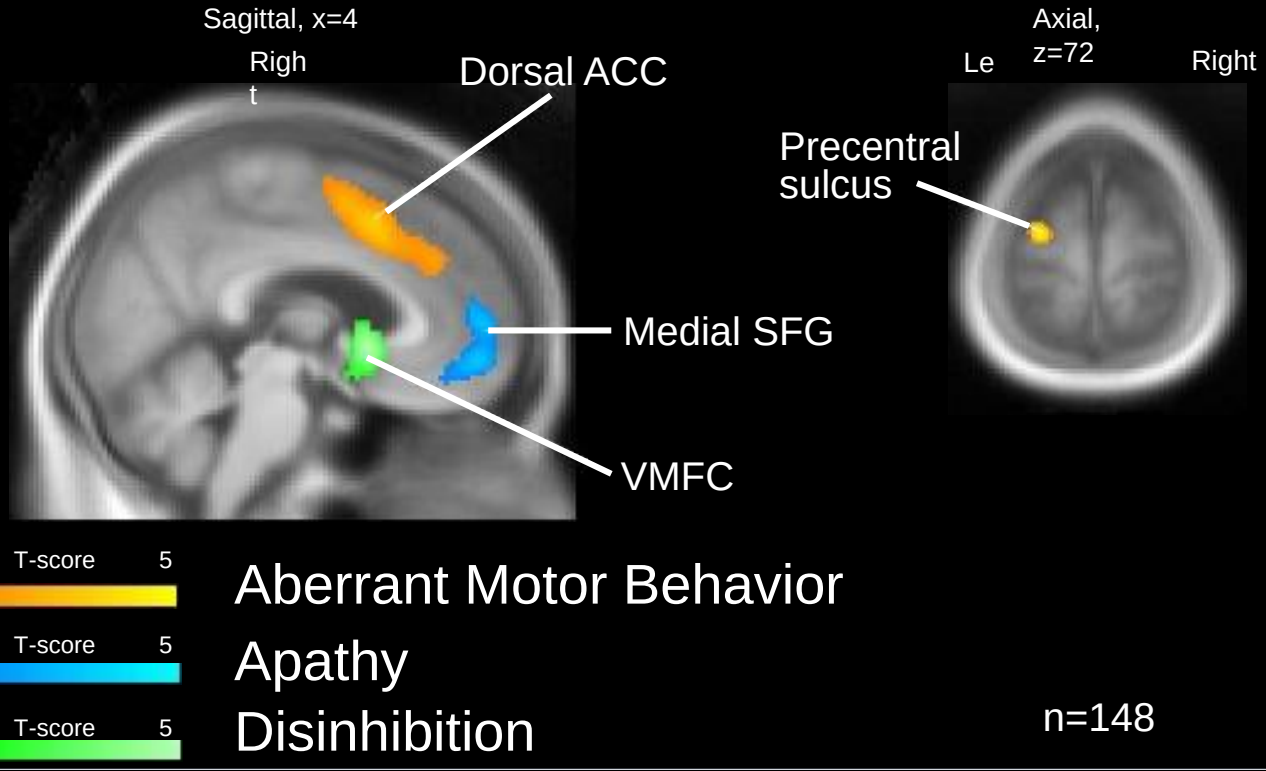
Liljegren & Naasan et al JAMA Neurol 2015

International Research Criteria for Behavioral Variant FTD

1. Early (2–3 yrs) behavioral disinhibition
2. Early (2–3 yrs) apathy or inertia
3. Early (2–3 yrs) loss of emotional reactivity, sympathy and empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile
7. Frontal or anterior temporal atrophy on MRI
8. Presence of known mutation

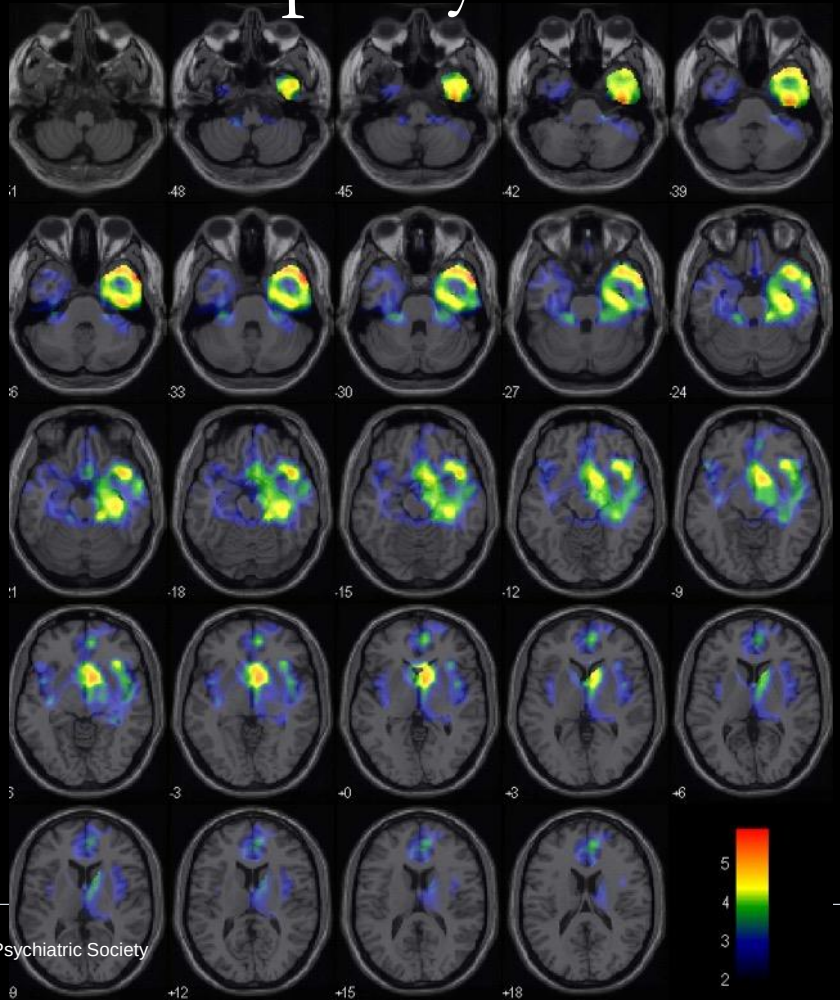
International Consortium, Brain, 2011

Abnormal Behavior Driven by Right Hemisphere Dysfunction



Rosen et al. *Brain, 2005*

Loss of Empathy



- R temporal pole
- R medial OFC
- R caudate
- R medial frontal

Only right hemisphere mediates these empathy changes

Rankin et al. Brain 2006

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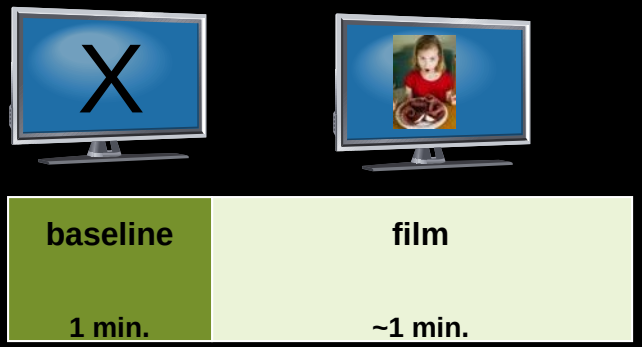
Disgust: Levenson Lab Methods

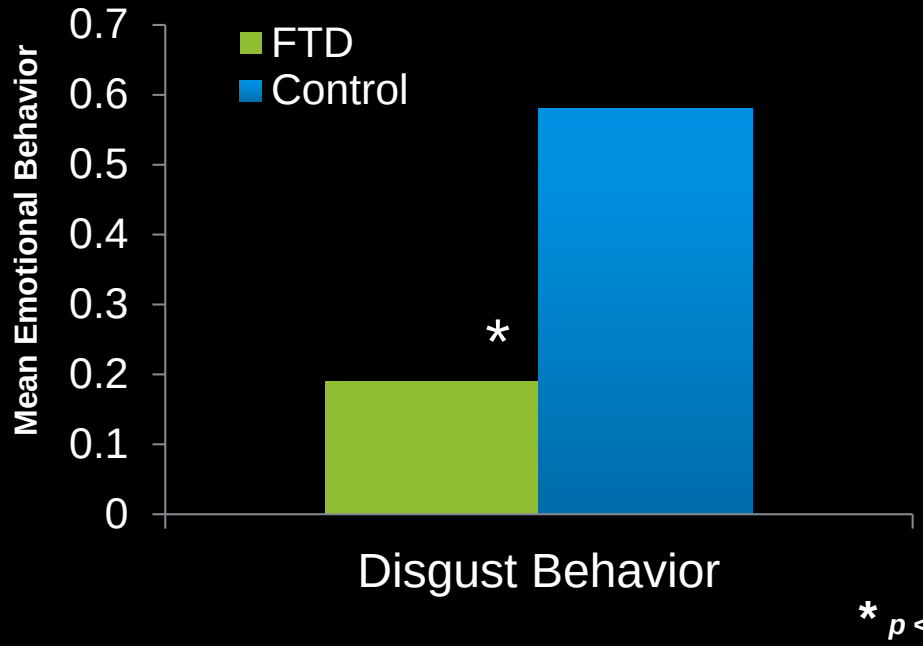


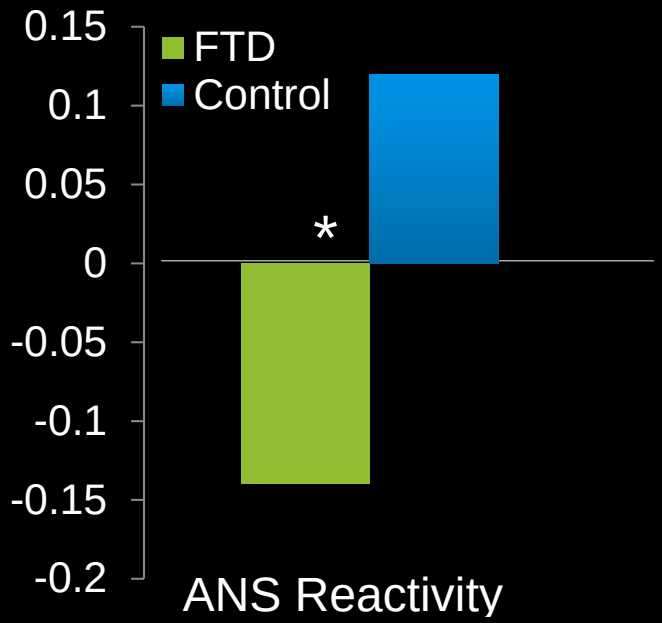
Behavior
Physiological reactivity
Self-report

Eckart et al., 2012

Loss of Disgust in FTD

Self-Reported Experience: FTD < controls





Eckart et al., 2012

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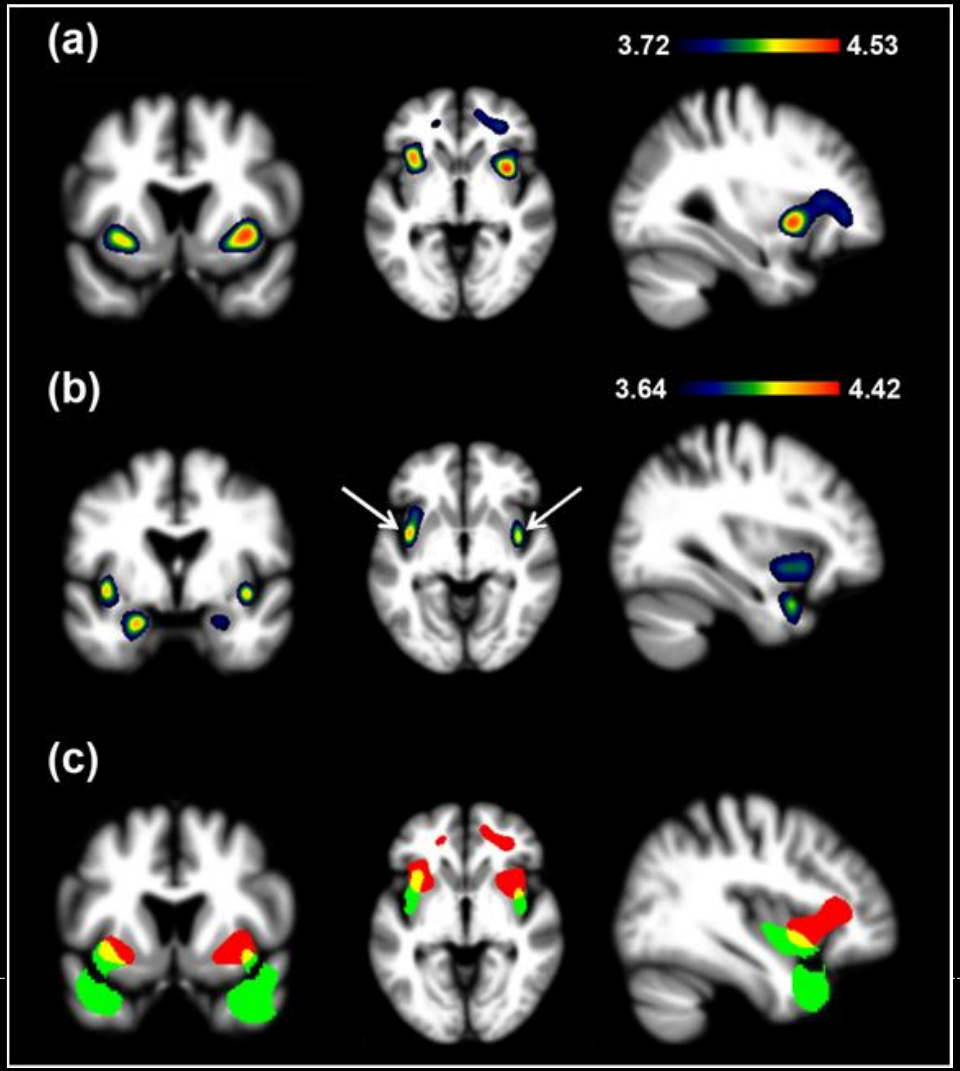
Disgust Behaviors

Disgust Recognition

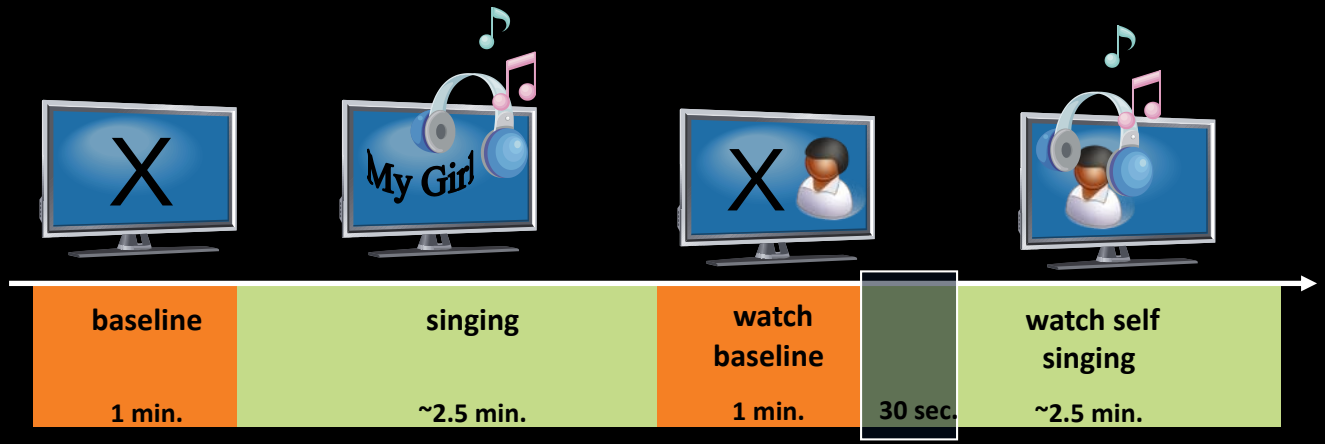
Overlap



Woolley et al. 2015

UCSF

Laboratory Assessment: Karaoke Task



Facial Behavior

- Anger, sadness, disgust, fear, surprise, confusion, contempt, happiness, embarrassment
- Intensity: 0-3

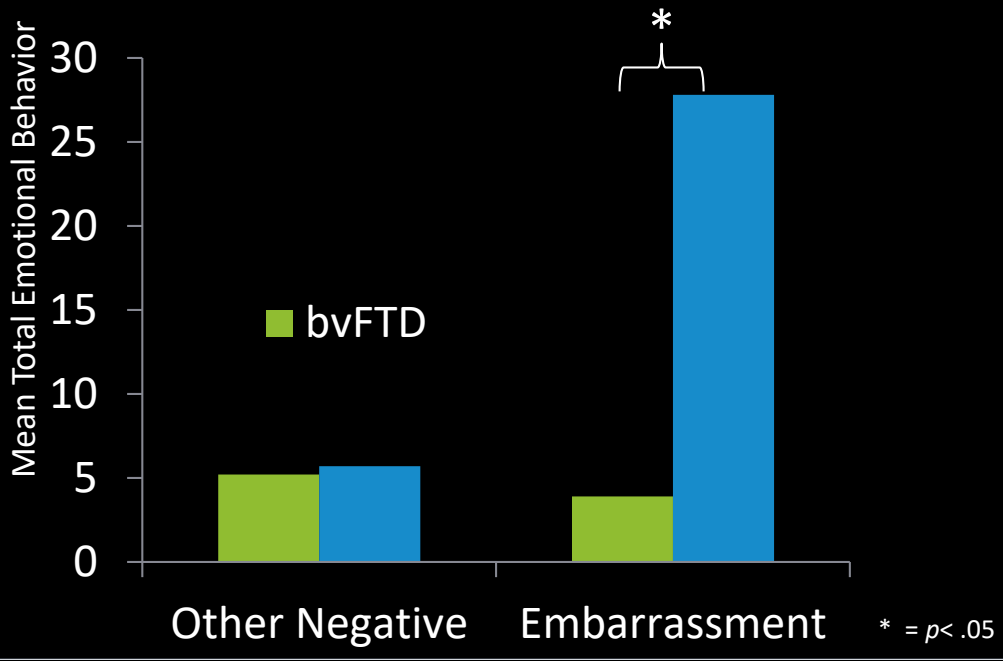
Autonomic Reactivity

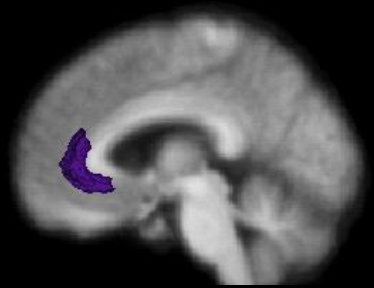
- Heart rate
- Respiration
- Skin conductance level

Sturm et al., *Emotion*, 2008

Diminished Self-Conscious Emotional Reactivity in Patients with bvFTD

- bvFTD < controls embarrassment behavior and ANS reactivity
- Smaller right pregenual cingulate lower ANS & behavioral response

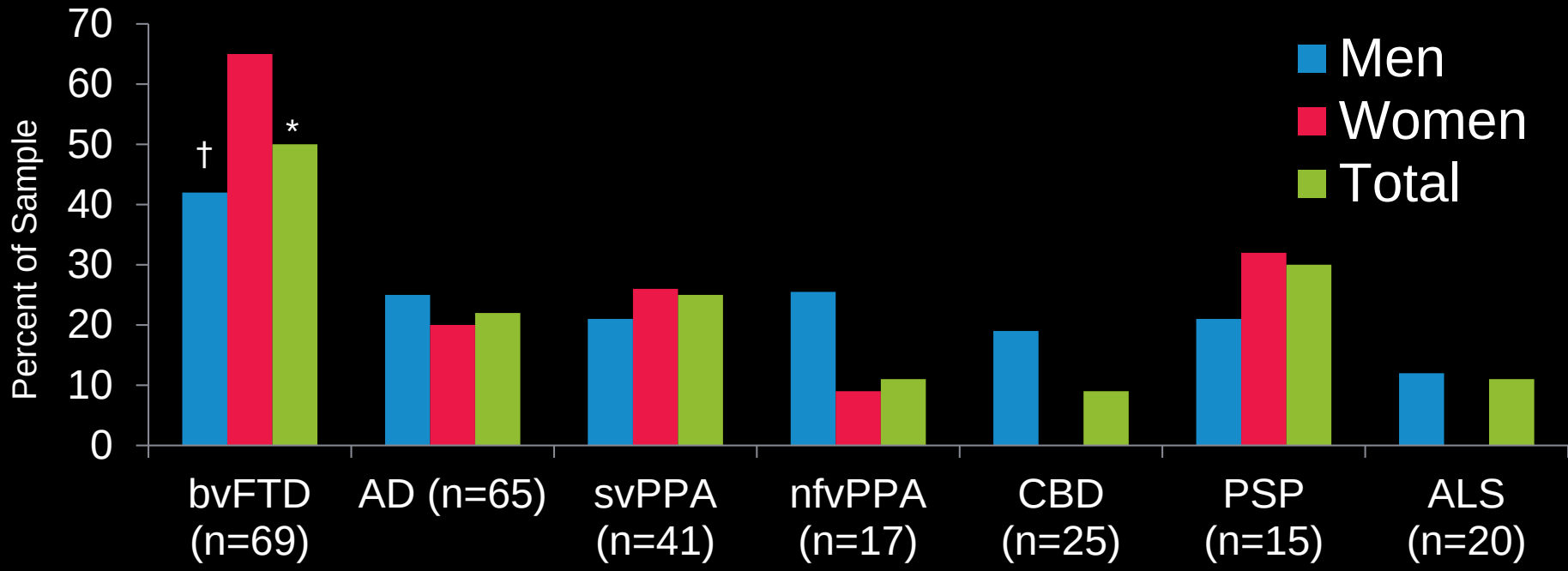




Sturm et al., *Emotion*, 2008; Sturm et al., *SCAN*, 2012

Psychiatric Misdiagnosis

Rates Psychiatric Diagnosis within each Neurodegenerative Disease



Woolley et al. J Clin Psychiatry 2011

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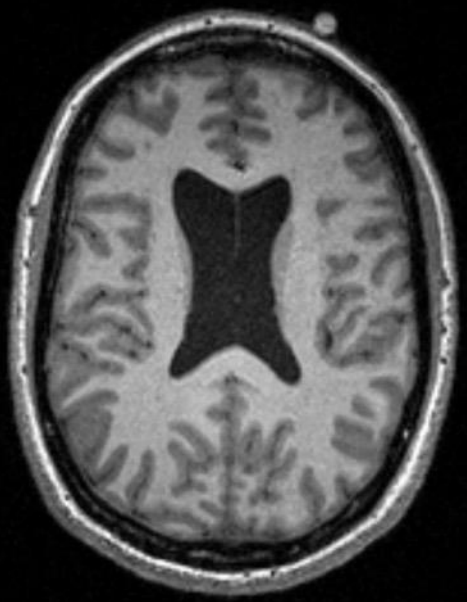
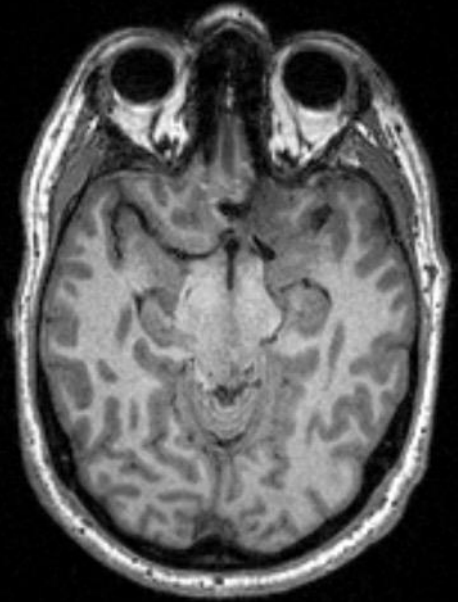
Treatable Disorders Missed

NPH



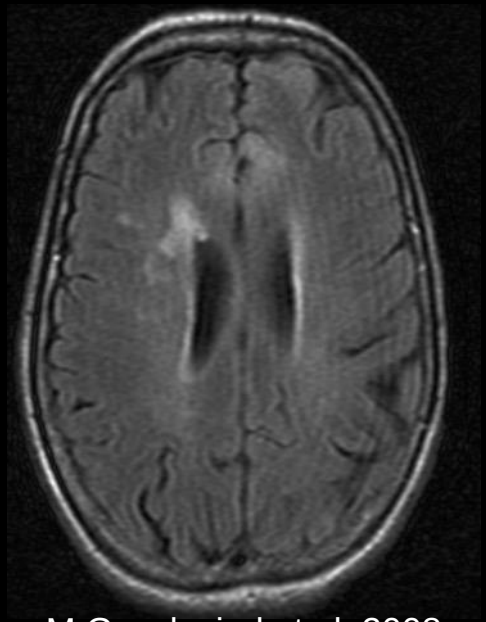
Klassen & Ahlskog 2011

Sagging Brain



M Hong et al. 2002

K channel ab



M Geschwind et al. 2008

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Therapies

- bvFTD
  - Environment, social, legal
  - Consider antidepressant
  - Avoid other meds
  - Clinical trials beginning

AD vs FTD Amyloid PET > FDG-PET

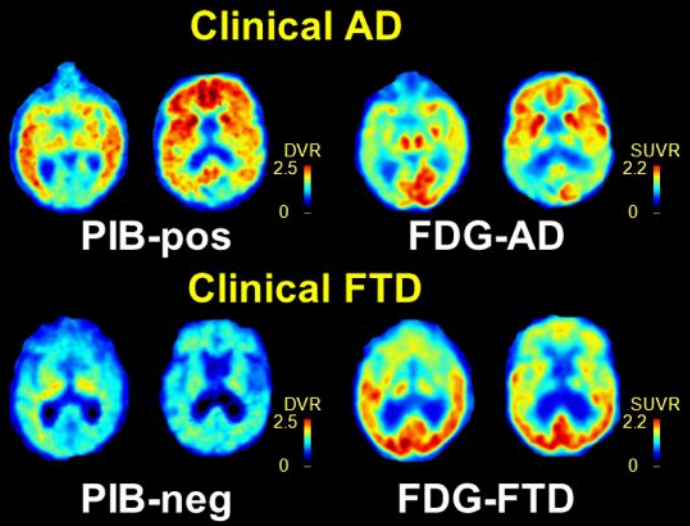
47 autopsy-proven cases

Amyloid (PIB) PET visual reads

- 100% sensitivity
- 90% specificity

FDG-PET visual reads

- 87% sensitivity
- 79% specificity



Rabinovici et al. Neurology 2011

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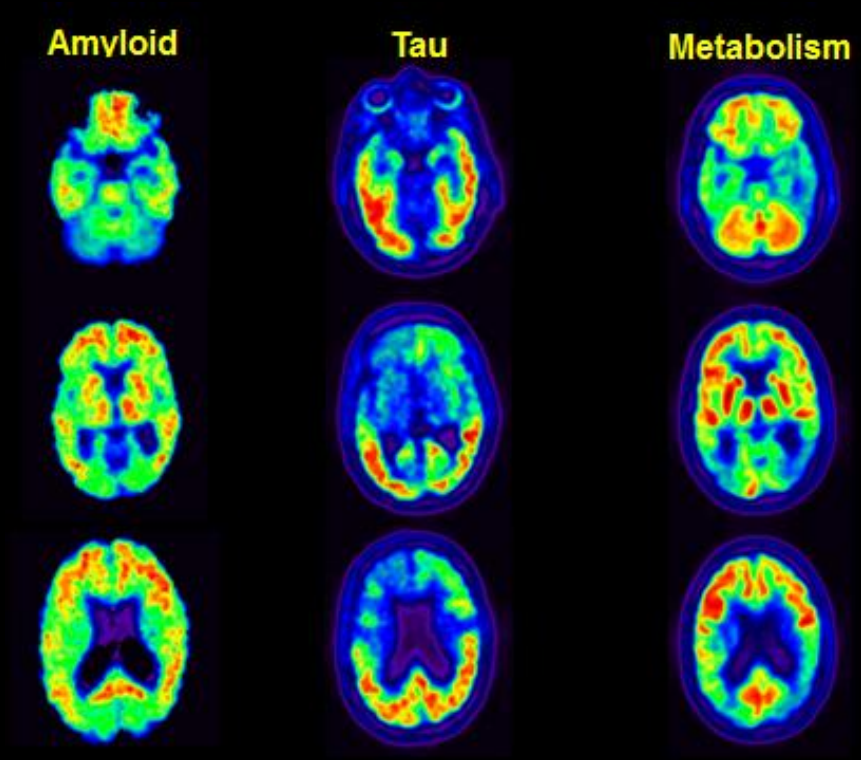
Tau PET: The New Frontier

Amyloid, tau &
brain metabolism
57 year-old AD

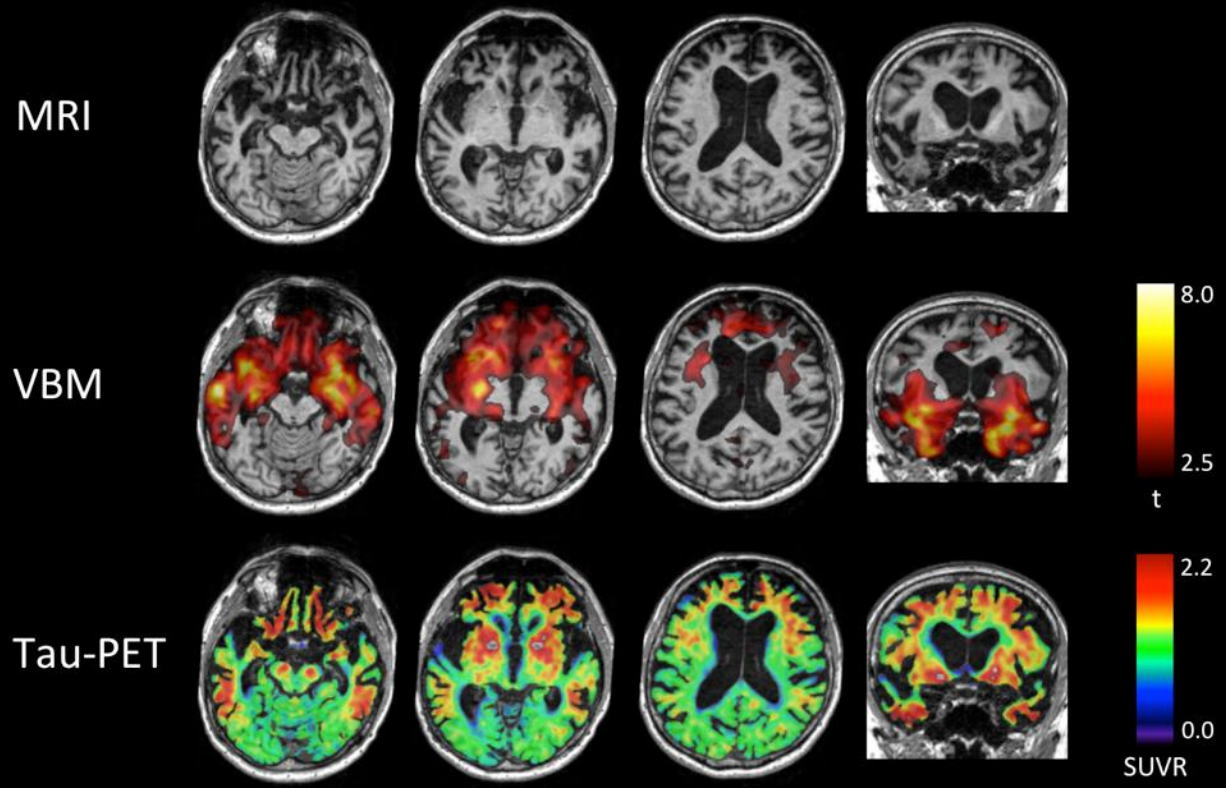
Brain dysfunction
correlates with
tau but not
amyloid



Ossenkoppele R et al. Brain 2016

UCSF

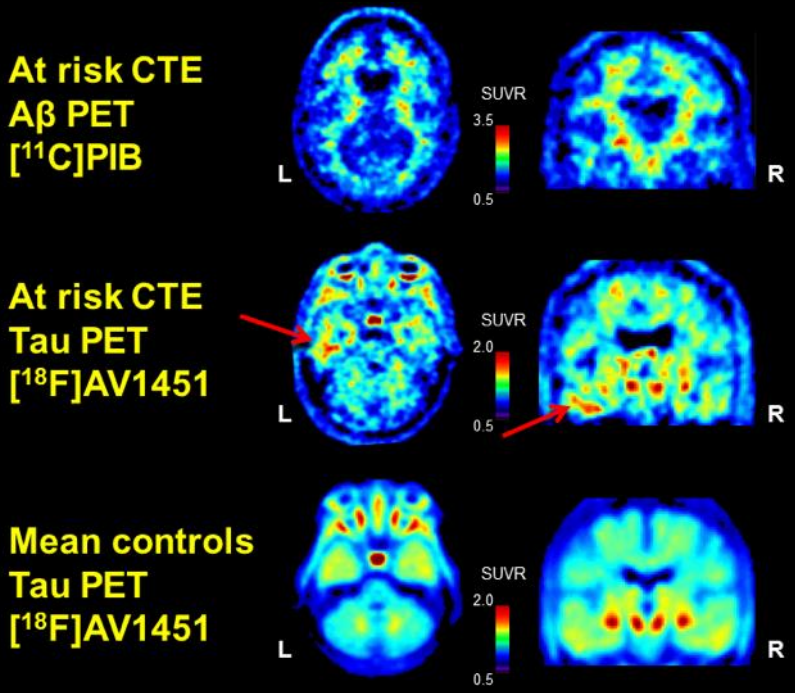
bvFTD V337M MAPT Mutation



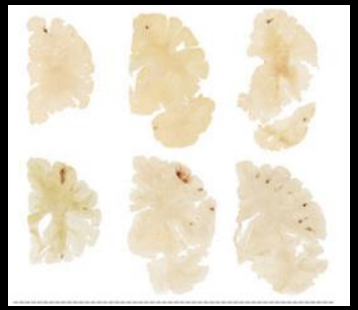
Salvo Spina et al, Neurology, 2017

UCSF

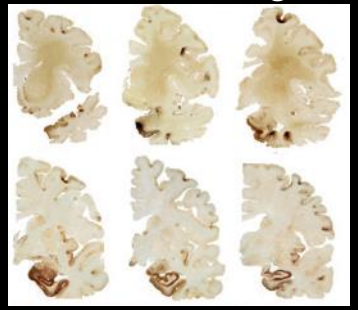
68 Retired NFL Slow Neurologic Decline



McKee CTE Stage II



McKee CTE Stage III



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Tau Consortium

Synthesis
(Bateman, Disney, Gan, Holtzman, Kao, T Miller)

Clearance
(Cuervo, Gestwicki, Haggarty, Rubinsztein)

Propagation
(Diamond, Duff, Goate, Han, Prusiner)

Models
(Mucke, Rubinsztein)

Stem cells
(Crary, Goate, Haggarty, Ichida, Kampmann, Kao, Karch, Temple)

Genomics
(Coppola, Geschwind, Goate, Lee, Yokoyama)

Biomarkers
(Geschwind, Grinberg, Jagust, Kramer, Mathis, B Miller, Neylan, Rabinovici, Rankin, Seeley, Steen, Nasdev, Walsh)

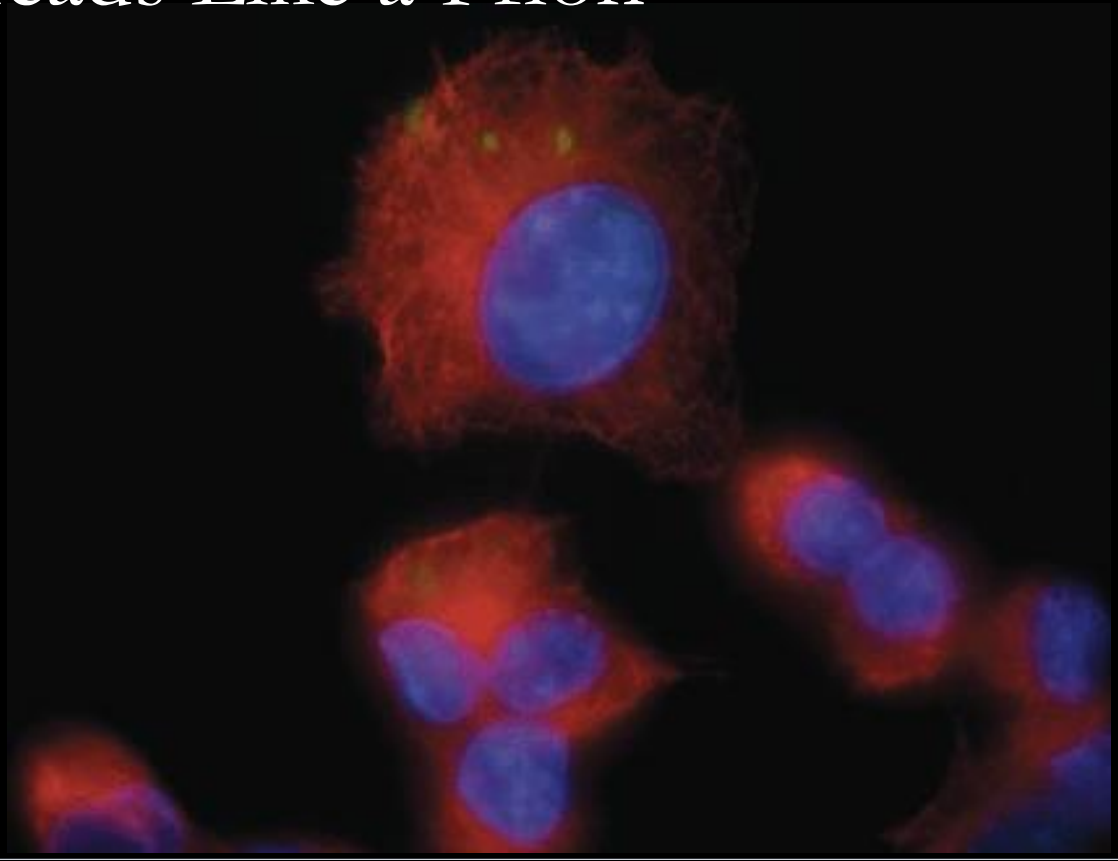
Treatments
(Arkin, Boxer, Cuervo, Diamond, Disney, Gan, Gestwicki, Haggarty, Kosik, Krichevsky, T Miller, Prusiner, Rubinsztein)

Pure Tauopathies vs. Mixed Tauopathy

- Mutations – bvFTD, nfvPPA, PSP, CBD
- Pick – bvFTD, nfvPPA
- CBD – bvFTD, nfvPPA, executive/motor
- PSP – falls, gaze, axial PD, dementia

- AD*
- CTE*
- Guam-PD-Dementia
- Postencephalitic Parkinson's
- Niemann-Pick disease

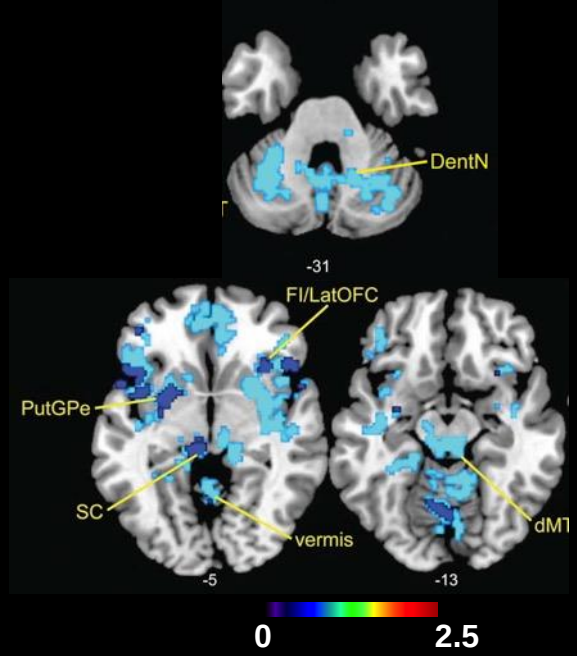
Tau Spreads Like a Prion



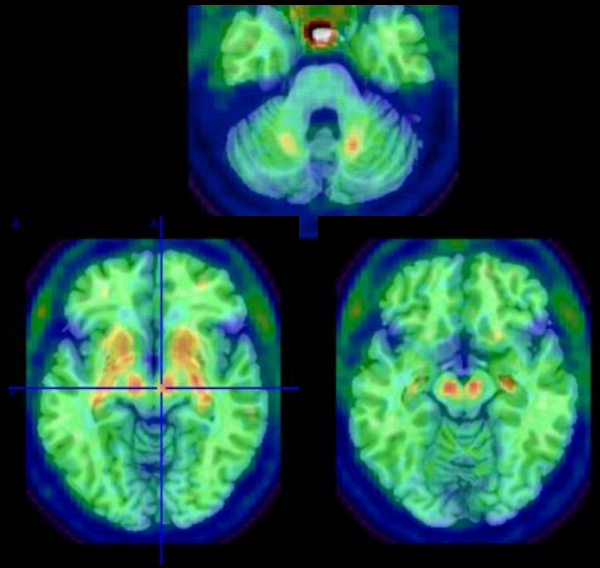
Courtesy of Marc Diamond

Functional Connectivity Dorsal Midbrain Tegmental Network & Tau PET in PSP

Functional Connectivity



Tau PET



Gardner et al. Ann Neurol 2013, Rabinovici 2015

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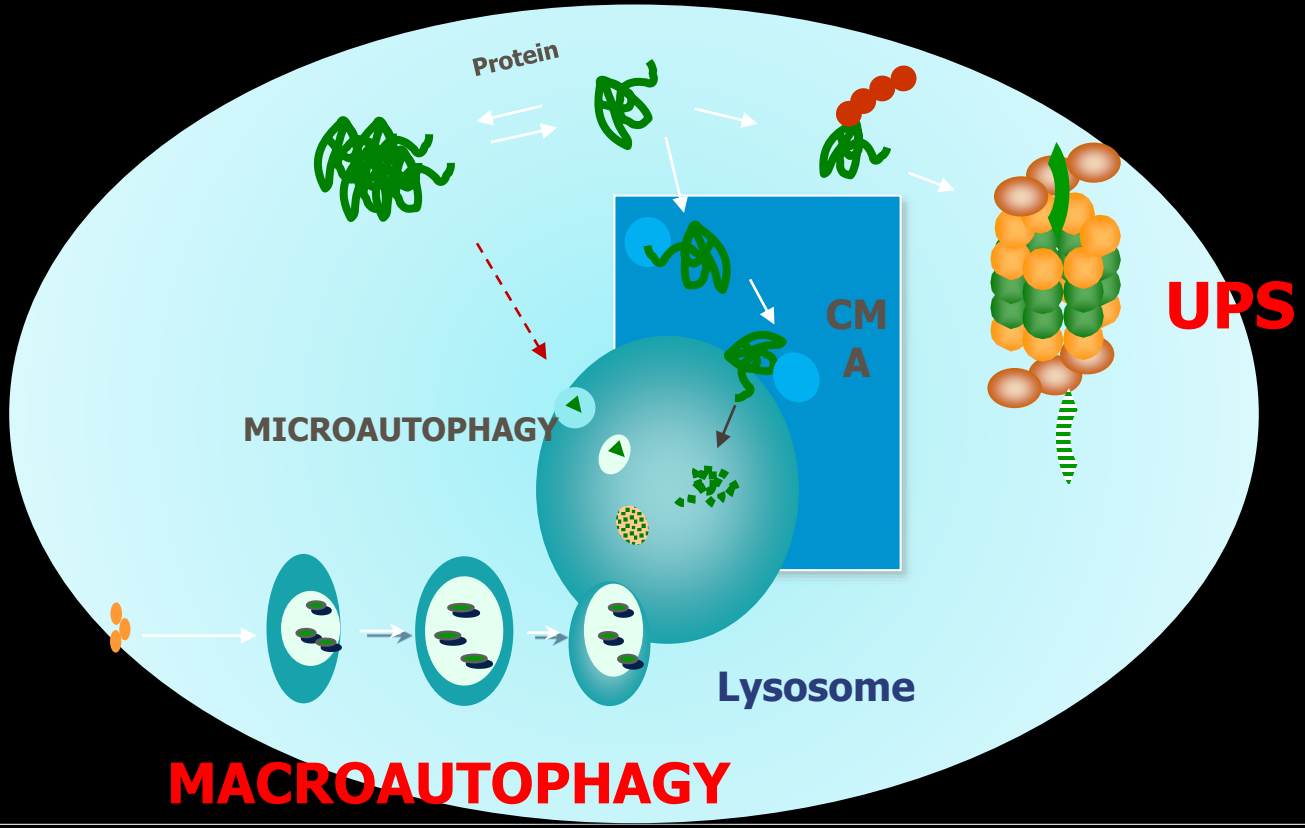
Tau Clearance



Courtesy Ana Maria Cuervo

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Coming Next

- Better diagnosis of tau-related FTD
- New causal and risk genes
- U grants (Boxer Orphan Disease, Boeve & Rosen FTD Genetics, Rohrer GENFI)
- Tau-lowering trials with antibodies
- For TDP-43 subtypes
  - Anti-inflammatory compounds for svPPA
  - Progranulin-elevating therapies
  - Genetic therapies silence gene in C9ORF72

Bluefield Research Consortium (progranulin)

Progranulin knockout and knock-in mice
(Farese, Harvard)

Behavior
(Roberson, UAB; Gan, UCSF)

Progranulin & granulin pathways
(Gan, UCSF)

High throughput screen
(Herz & Gang, UTSW; Gan, UCSF; Haggarty, Harvard)

Clinical/pathology/ gene carrier
(Seeley, Lee, Rosen, B Miller, UCSF; Van Swieten, Erasmus)

Skin/iPS/neuron
(Farese; Ward NIH, Kao UCSF)

PGRN genetics
(Rademakers, Mayo; Yokoyama, UCSF)

Lysosome
(Ferguson, Yale; Farese & Walther, Harvard; Huang, UCSF)

Treatment trials
(Boxer, Tsai, Z Miller, Ljubenkov, Rojas, UCSF)

Prosocial Actions Are Inherently Rewarding

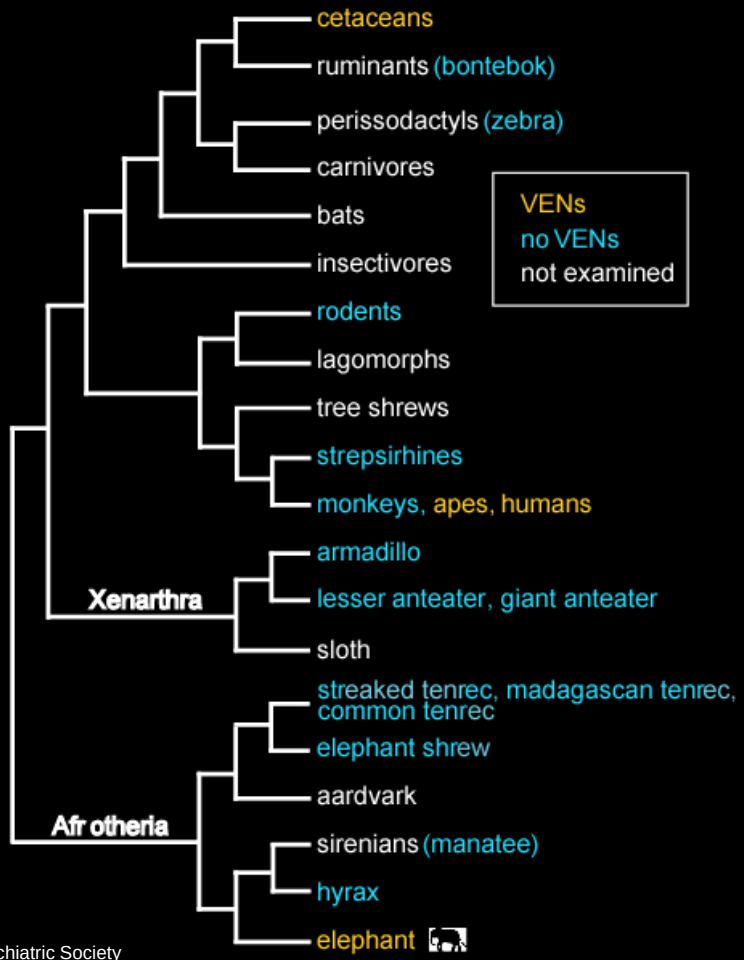
- Prosocial behaviors prioritize the needs of others over one's own
- Other-focused affiliative actions
  - Consolation, helping, cooperation, giving
- Empathy and vicarious positive emotional experience make giving to others inherently rewarding despite no material gains for self
- Prosocial behaviors activate reward systems affected in bvFTD

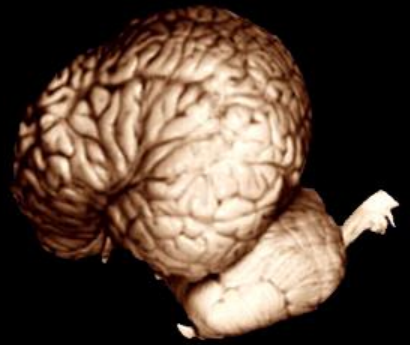
Giving Game Task: Assess Prosocial Giving

Computer-task based on animal token task assess prosocial giving

Patients choose A or B. Play with experimenter to win money

Prosocial giving is giving money to experimenter when it costs one nothing to do so





Hof Anat Rec 2006

Nimchinsky PNAS 1999

Hakeem Anat Rec (in press)

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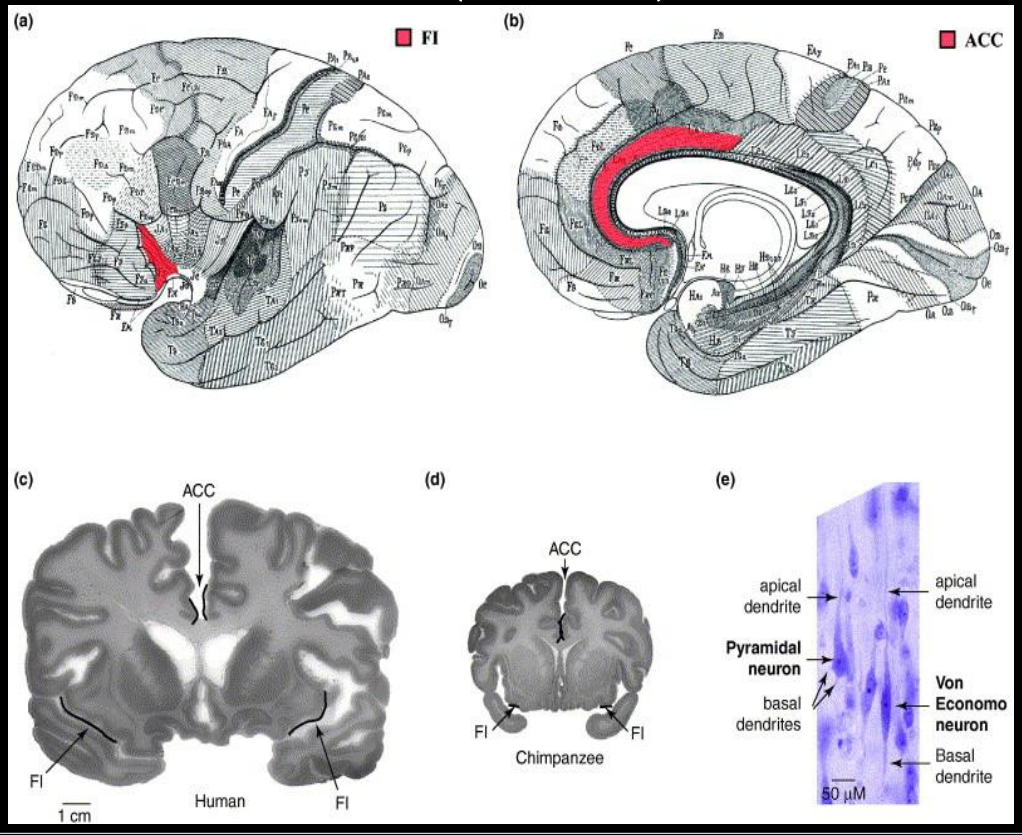
Von Economo Neurons (VENs)



Allman et al, 2006

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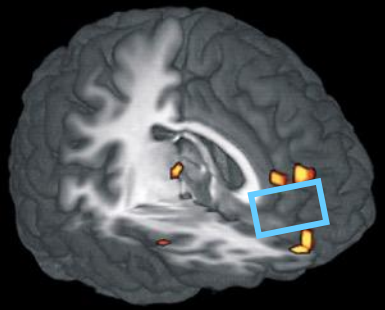
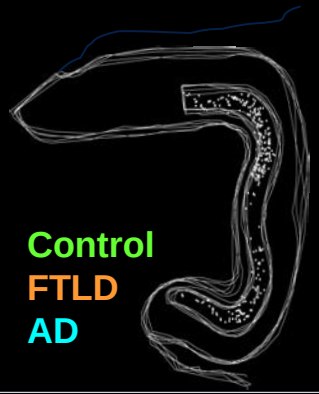
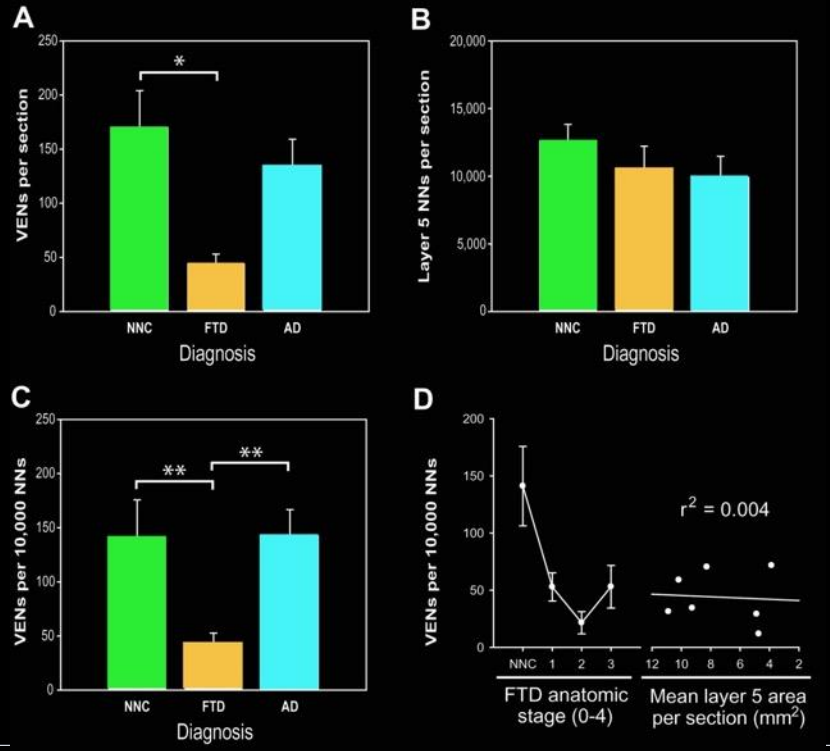
VENs: Vulnerable Neuron FTD?







Seeley, et al, *Ann Neurol*, 2006

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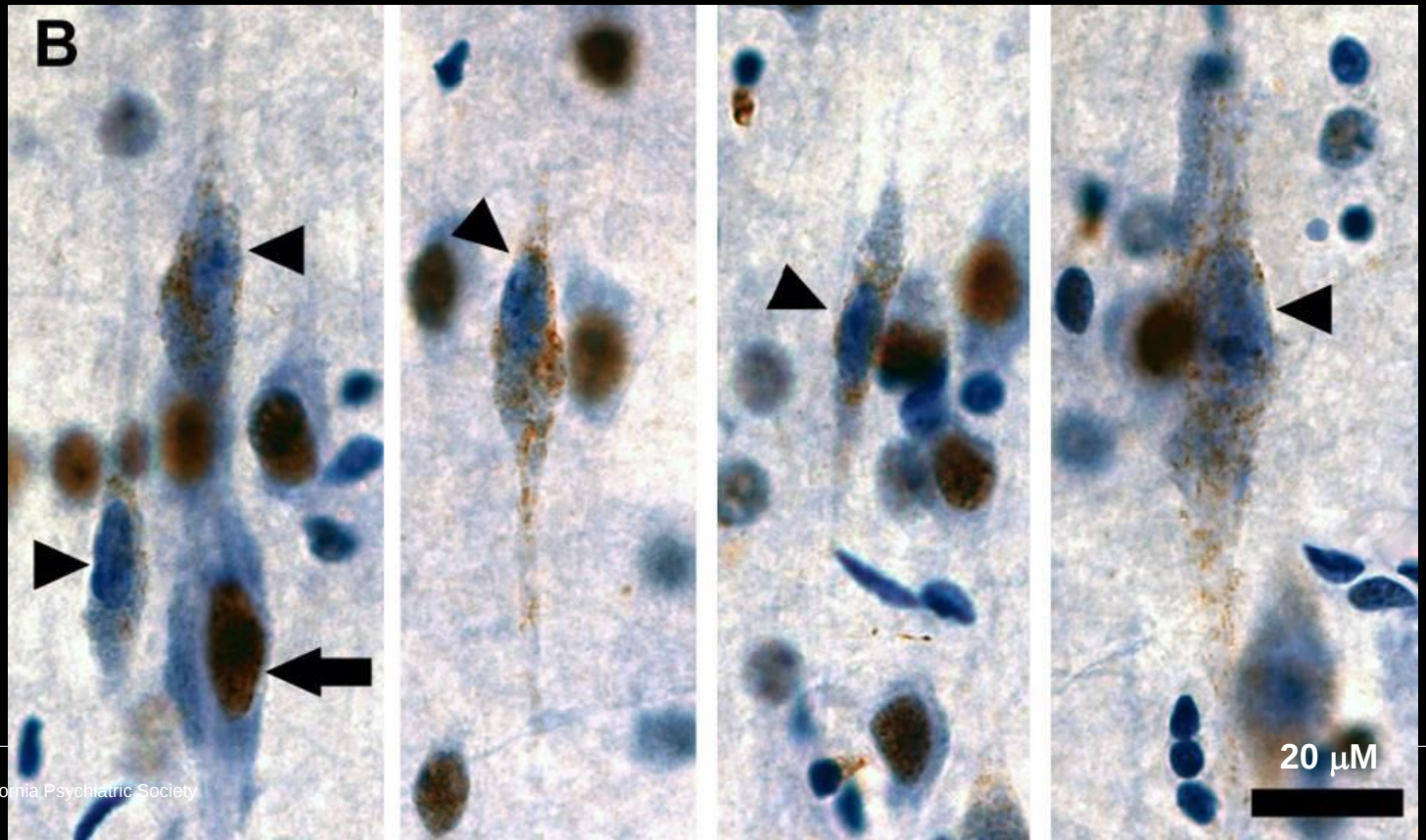
Early FTD: Speckled TDP-43 Inclusions

Right FI, FTLD-MND, Broe Stage 1



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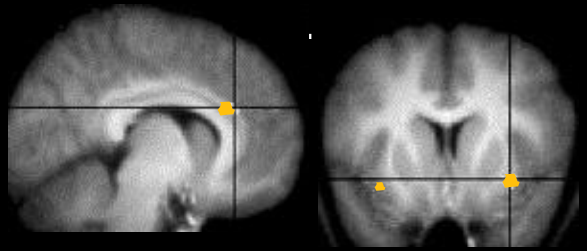
Traditional Frontal Neuropsychology

- Working memory (BA46) – digit back
- Generation – letters, animals, shapes
- Inhibition – antisaccade, flanker task
- Reward/punishment – gambling, eating (orbital?)
- Alternate sequence – dorsolateral – Trails B
- Abstraction – proverbs

Area FI

bvFTD

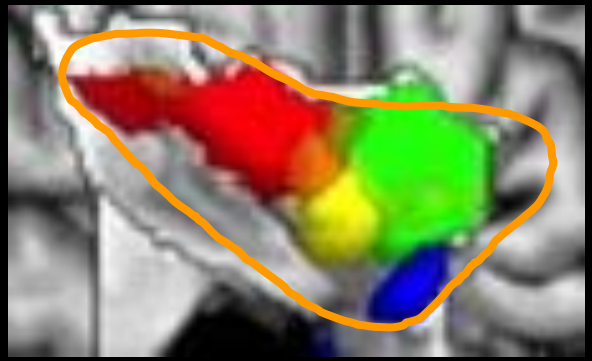
Self-recognition



Devue 2007

Social-emotional function

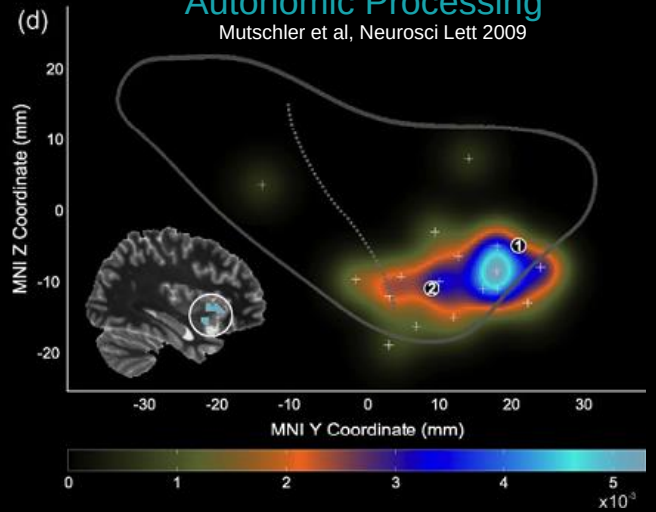
Kurth et al, Brain Structure and Function 2010



Sensory/ motor | Taste/ Smell | Cognitive | Social/ Emotional

Autonomic Processing

Mutschler et al, Neurosci Lett 2009



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Post-Evaluation Behavior Rating

- Agitation
- Stimulus-bound
- Perseverative
- Decreased initiation
- Motor stereotypies
- Distractibility
- Lack of social/emotional engagement
- Impulsivity
- Socially inappropriate

Battery Development

Conceptual Model

- Updating (working memory)
- Inhibition
- Set shifting
- Fluency (generativity)
- Planning
- Social cognition
- Behavior
- Insight

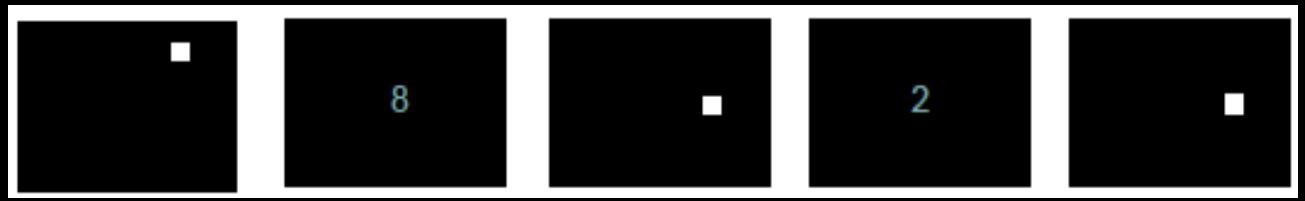
NIH EXAMINER Scales

Working memory
Inhibition
Set-Shifting
Fluency
Planning
Social cognition
Behavior
Insight

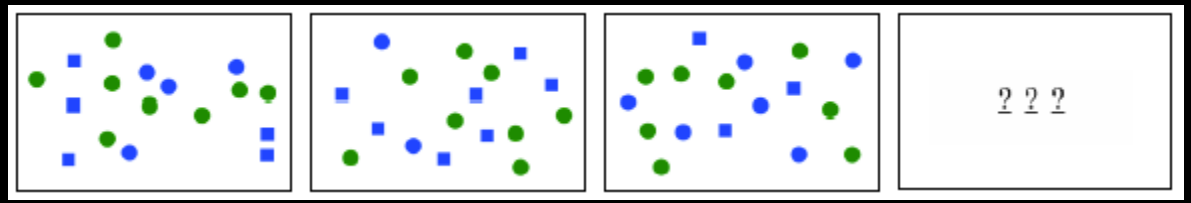
} Executive Composite

Working Memory Score

1-Back and 2-Back: spatial working memory

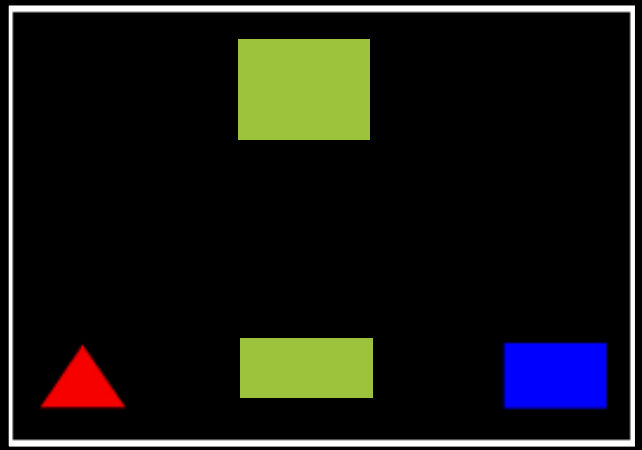


Dot Counting Test: verbal working memory

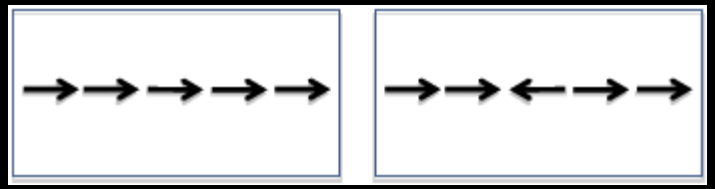


Cognitive Control Score

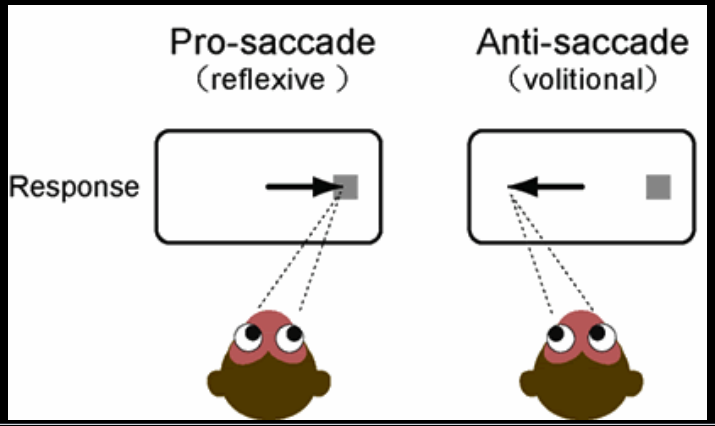
Set-Shifting



Flanker: inhibition



Antisaccade: inhibition



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Fluency Score

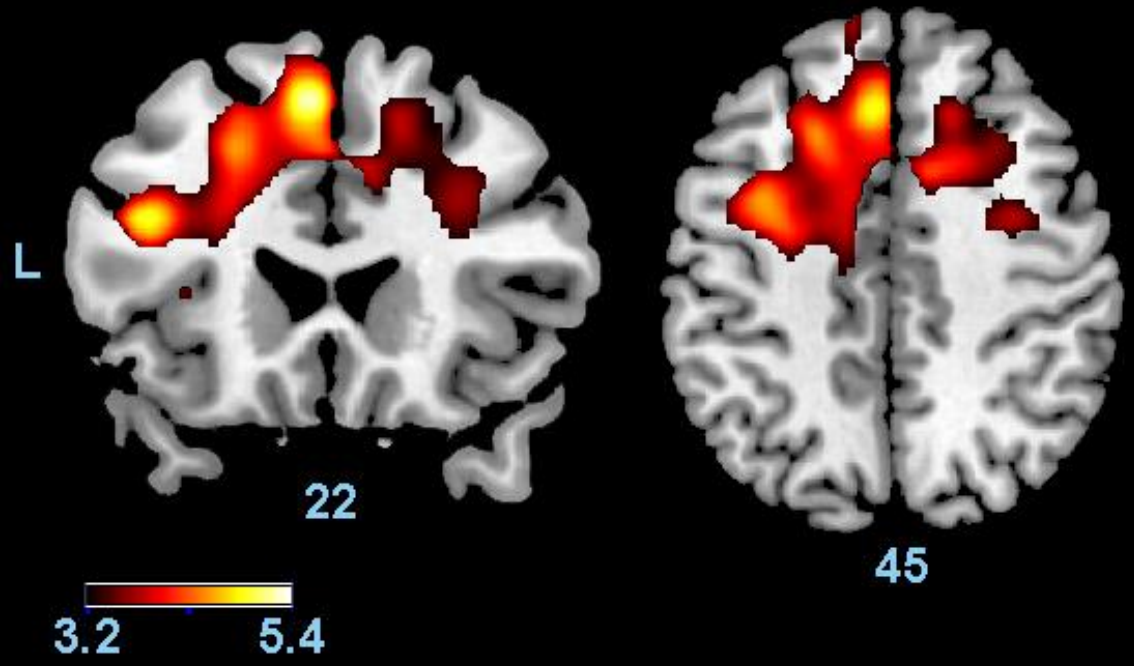
Letter Fluency: “F” and “L”

Category Fluency: animals and vegetables

Executive Composite Score

- Alternate form reliability = .94
- Correlation with an informant rating of day-to-day executive functioning = .57 in adults, .21 in children
- Sensitive to decline in dementia patients and to development in normal children

The Executive Composite correlates with lateral and medial PFC volume



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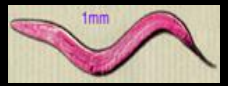
Neuropathology & Chemistry of Inclusions

- CJD: prions (1982)
- AD: plaque (Aβ-42, 1984),
  tangle (tau, 1986)
- PD/DLB: Lewy body (α-synuclein, 1998)
- FTLD: Pick body (tau, 1990), ubiquitin positive tau negative inclusions (TDP43, 2006), (FUS, 2009), dipeptides from C9 mutations (2013)

The Prusiner Model

All degenerative dementias have:

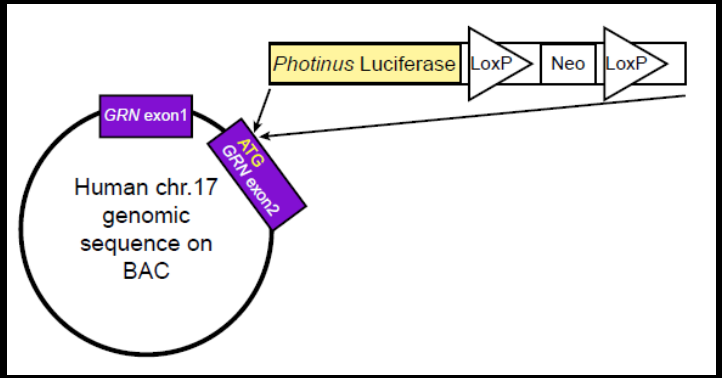
- Genetic and sporadic form
- Cell culture and animal model

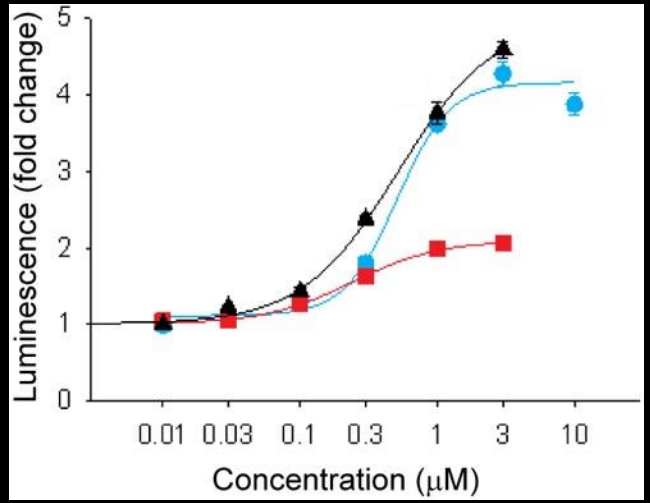



- Preclinical, early symptomatic and symptomatic phase
- Abnormal protein aggregation
- Proteins spread from cell to cell

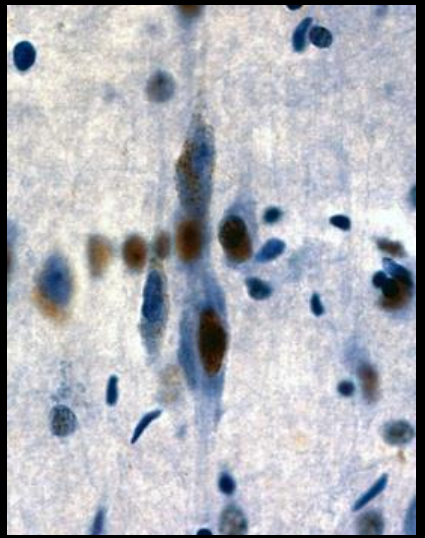
Restoring Progranulin Levels

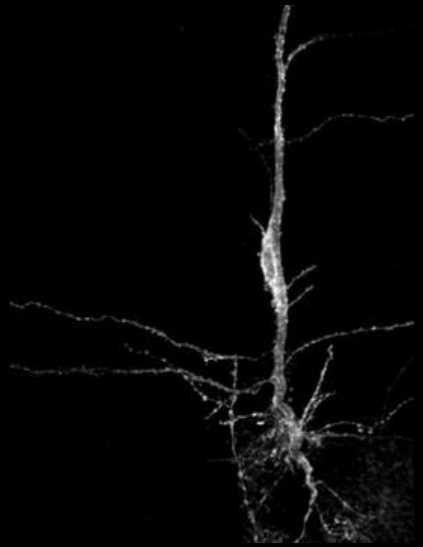
THERAPEUTIC GOAL: Increase *GRN* transcription from the remaining WT allele
SCREEN: FDA-approved compound library using luciferase-tagged *PGRN* reporter
SAHA greatly altered progranulin levels





Joachim Herz & Gang Yu labs, UTSW





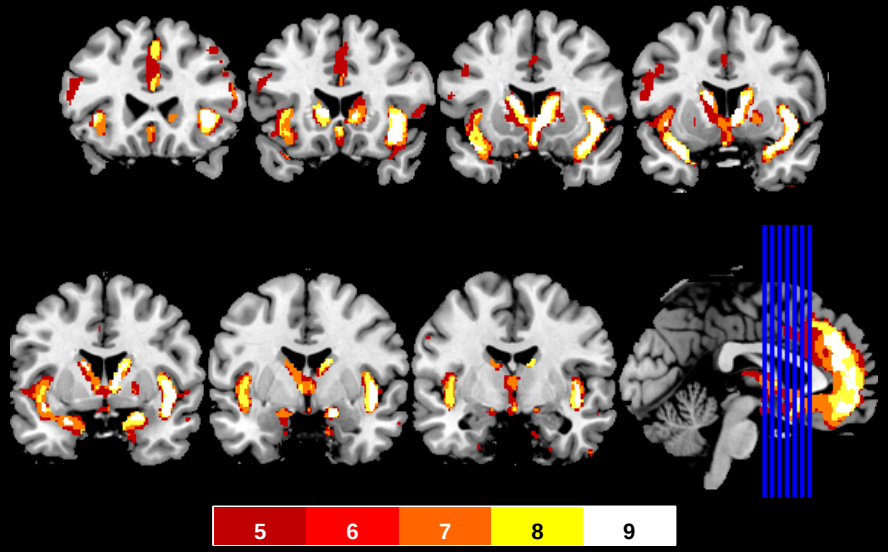
Emily Dickinson on Decay

Crumbling is not an instant's Act
A fundamental pause
Dilapidation's processes
Are organized Decays.

'Tis first a Cobweb on the Soul
A Cuticle of Dust
A Borer in the Axis
An Elemental Rust—

Ruin is formal—Devil's work
Consecutive and slow—
Fail in an instant, no man did
Slipping—is Crash's law

“behavioral variant cinguloinsular dementia”



Overlap: # subtypes

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Emotional Contagion Promotes Prosocial Behavior in Highly Social Species

consolation

Plotnik & deWaal, 2014

deWaal & Suchak, 2010

helping

Douglas et al., 2006

deWaal, 2007

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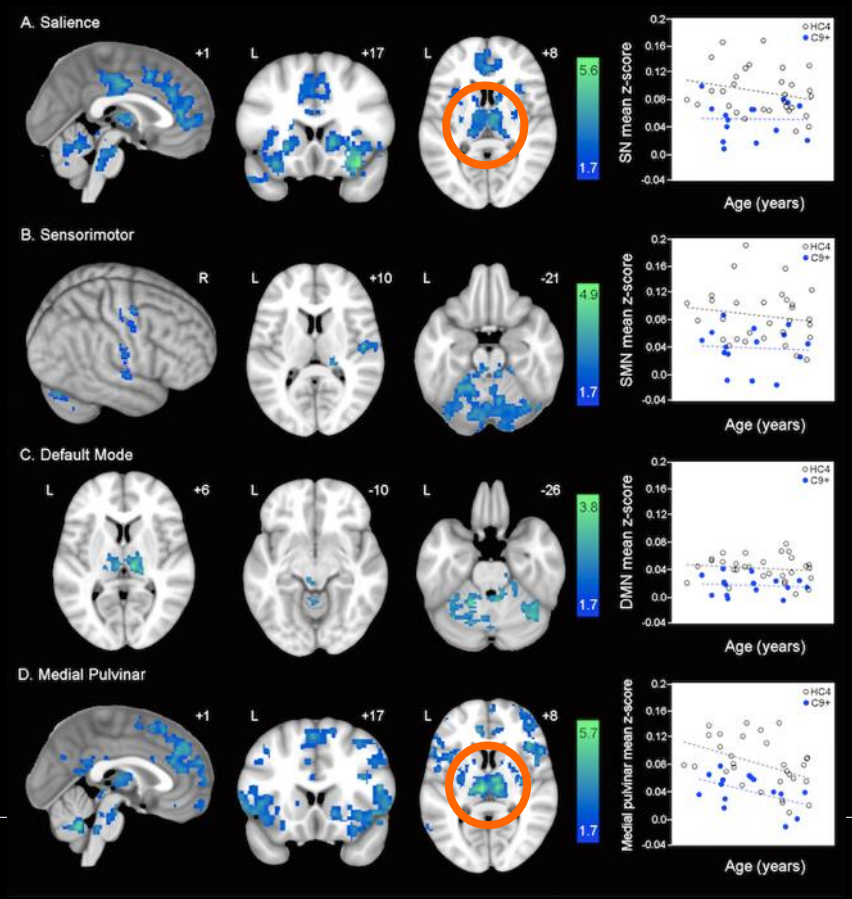
PreSx C9ORF72 Connectivity Reduced Thalamus

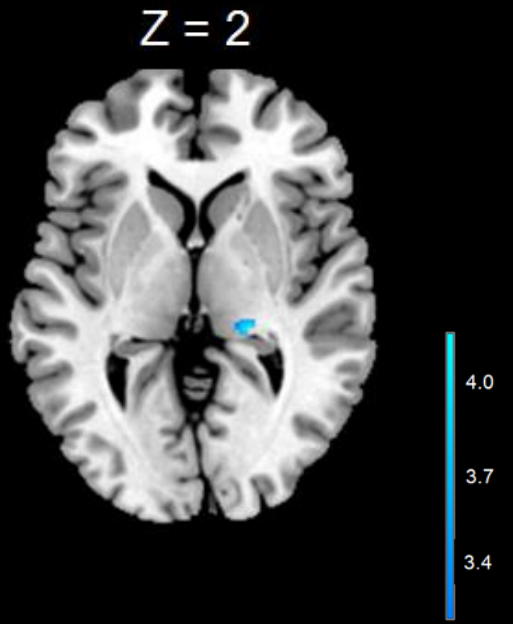


Suzee Lee
Submitted

UCSF

Prosocial Giving Impaired bvFTD

- bvFTD give less to experimenter than controls although it costs them nothing to give
- Lower prosocial giving, atrophy right pulvinar nucleus thalamus



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