



UCSF Weill Institute for Neurosciences

Memory and Aging Center

# Recent Advancements & the Hope Ahead

Bruce L. Miller, MD

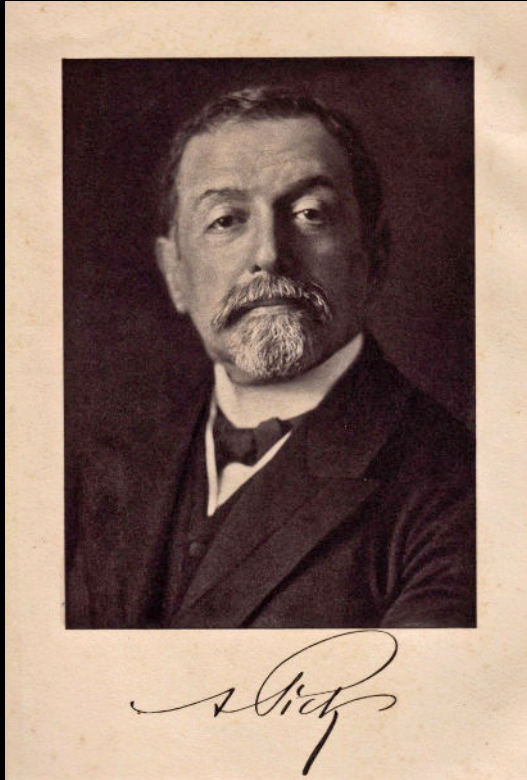
A.W. and Mary Margaret Clausen Distinguished Professor in Neurology

Director, Memory and Aging Center

Founding Director, Global Brain Health Institute at UCSF

Joint Appointment in Psychiatry

# Frontotemporal Dementia (FTD)



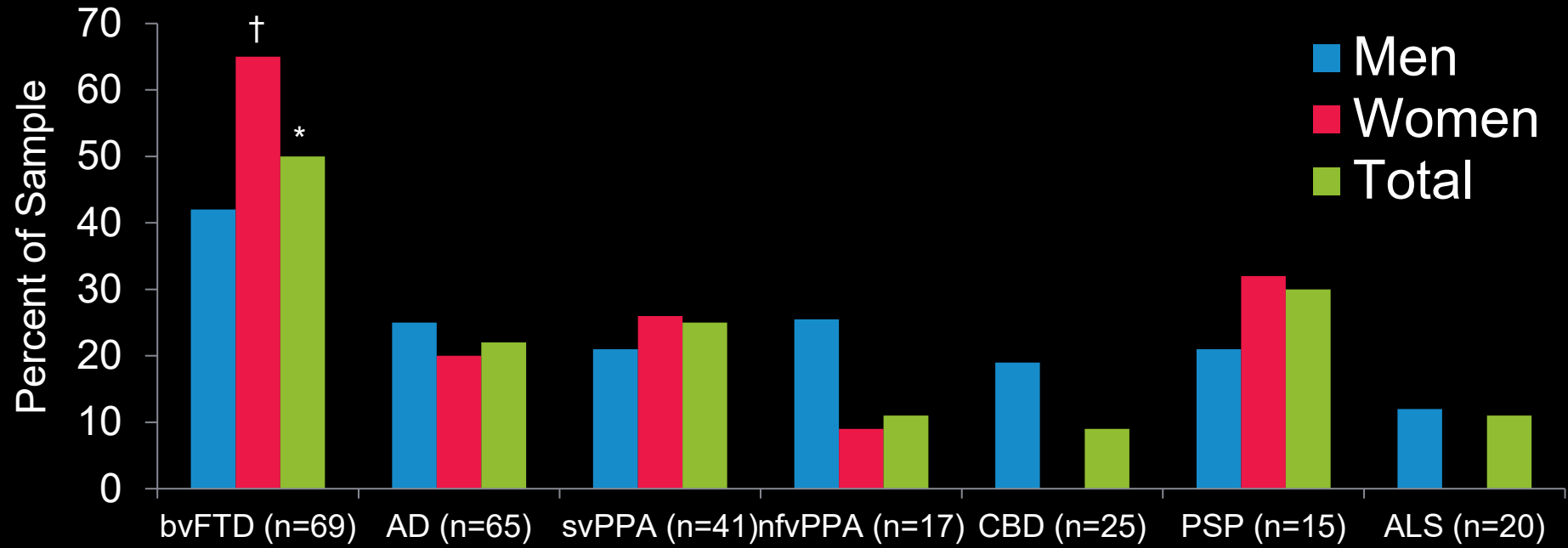
- 1892, Arnold Pick describes a focal neurodegenerative condition
- Pick's disease preferentially affects the frontal and temporal lobes
- Pick body (Alzheimer 1911)

# Frontotemporal Dementia (FTD)

- **Common** cause pre-senile dementia
  - 1:1 with AD 45–64 years (Ratnavalli, Hodges 2002), most common dementia <60 (Knopman 2004)
  - More common if ALS, PSP & CBD, CTE considered
- **Also occurs after 70**
  - 25% FTD over 65, late onset tau more common (SW Seo 2018)
  - TDP-43 & hippocampal sclerosis common in AD-dementia over 80 (Nelson 2007, 2013, Nag 2015)

# Psychiatric Misdiagnosis

*Rates of Psychiatric Diagnosis within each Neurodegenerative Disease*



# Psychiatric Syndromes in FTD

- Bipolar
- Antisocial personality
- Schizophrenia
- Borderline personality
- Schizoaffective disorder
- Borderline
- Conversion
- Addiction
- Body dysmorphic disorder
- Schizotypal
- Schizoid
- OCD
- Unipolar depression

# International Research Criteria for bvFTD

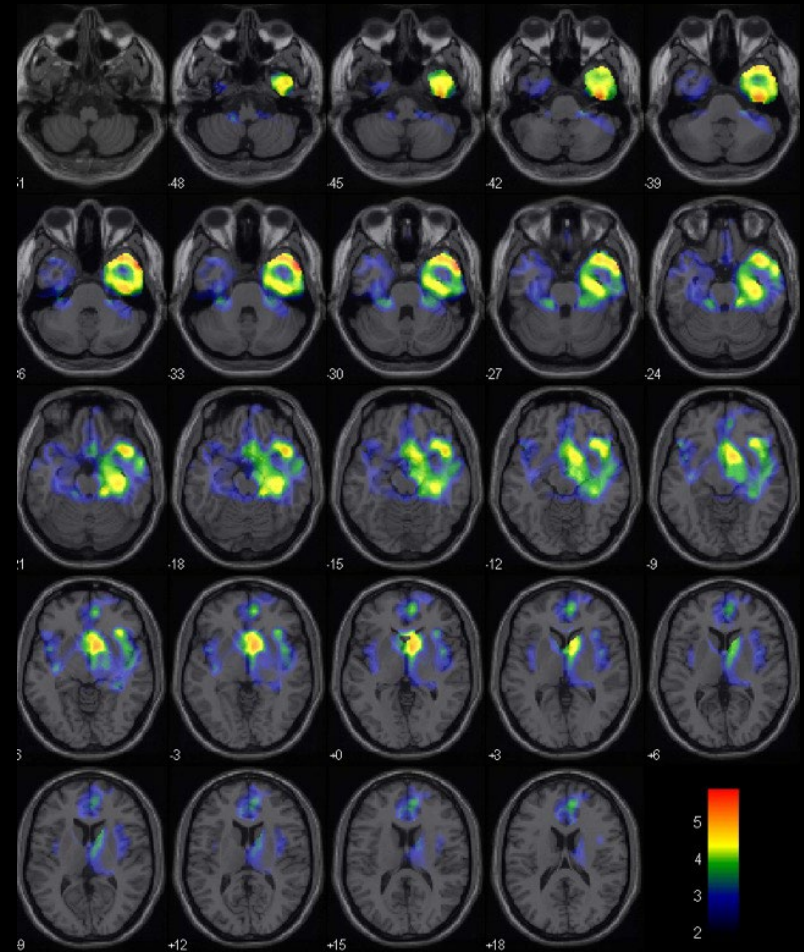
1. Early (2–3 yrs) behavioral disinhibition
2. Early (2–3 yrs) apathy or inertia
3. Early (2–3 yrs) loss of emotional reactivity, sympathy & empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile
7. Frontal or anterior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

# Crime with Dementia

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

# Loss of Empathy

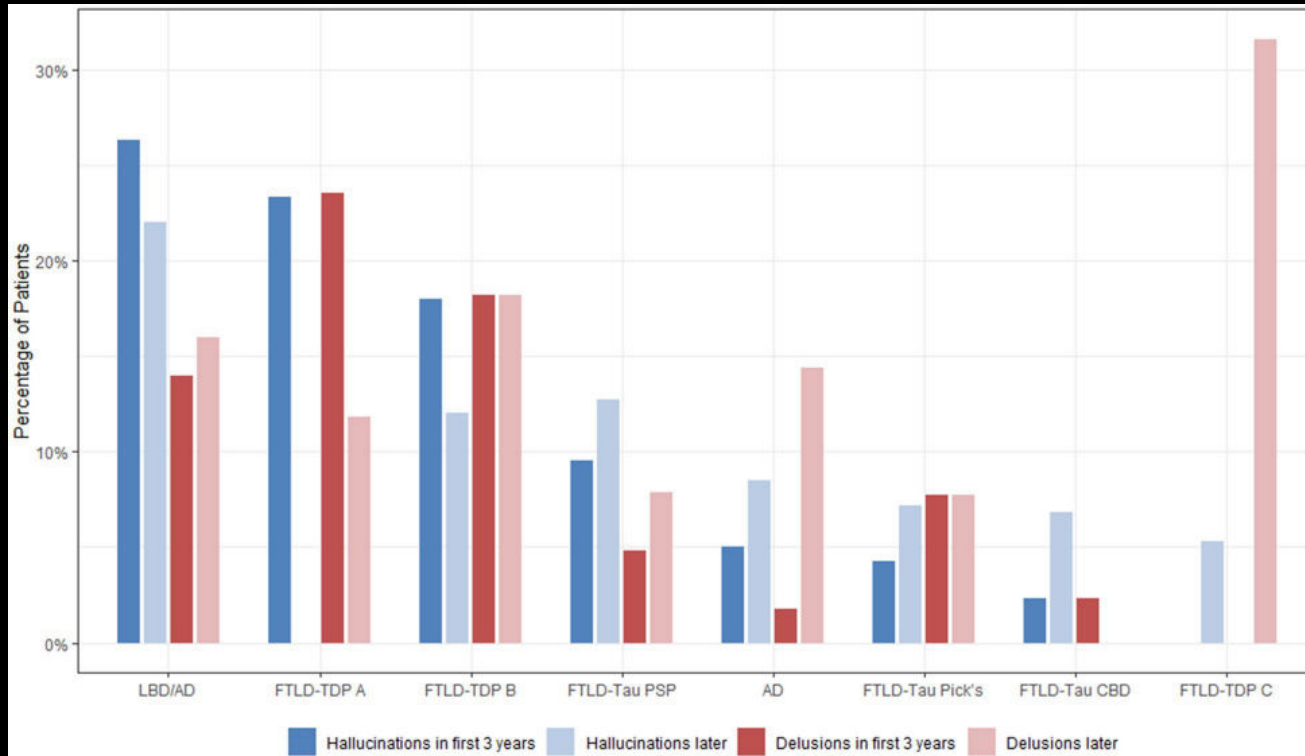
- R temporal pole
- R medial OFC
- R caudate
- R medial frontal
- Only right hemisphere mediates these empathy changes





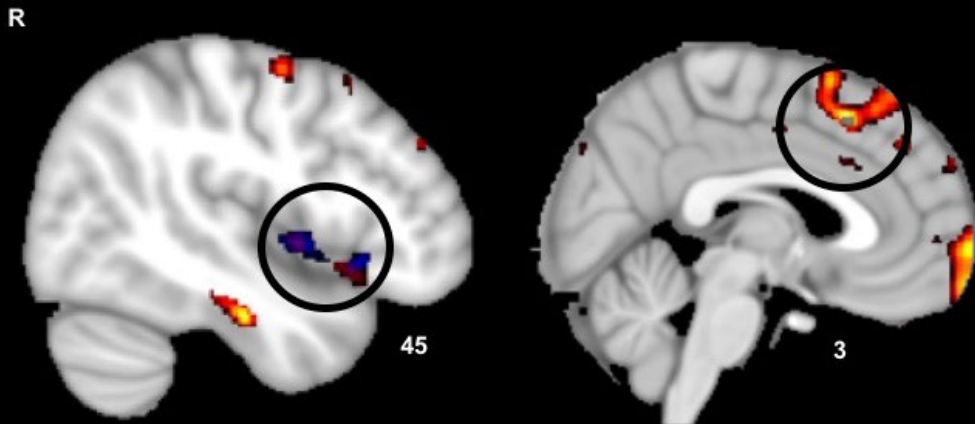
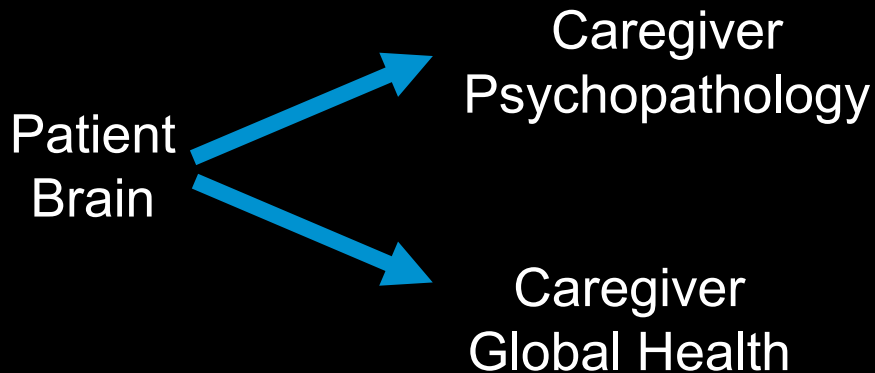
# Frequency of Psychotic Symptoms

Across Neuropathological Cohorts



Naasan et al., Brain 2021

# Brain Atrophy Caregiver Health



## Covariates:

- caregiver age and sex
- patient diagnosis, disease severity, cognitive functioning, head size
- MRI scanner field strength



# Consequences of Behavioral Symptoms in Dementia

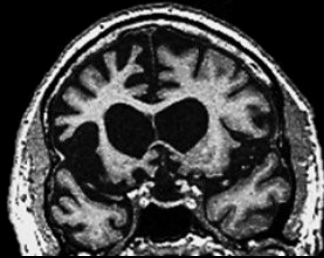
- Significant caregiver stress (professional & non-professional)
- May endanger the individual/caregiver
- Reduced quality of care/life
- Accelerated functional decline and higher risk of placement in more restrictive setting
- High risk chemical restraint with concomitant side effects

# Treatment of Behavior

- Identify problem
- Should it be treated?
- Consider protection of caregiver and family
- Try environmental intervention (Care Ecosystem)
- Is the deficit due to a serotonergic deficit?
- Antidepressants may be helpful

# 3 Types Frontotemporal Dementia

Behavioral Variant

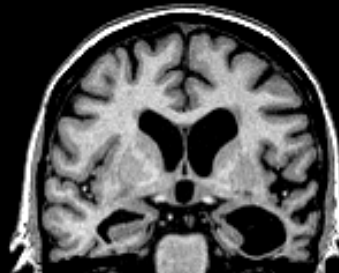


R L

Often genetic  
Tau, TDP, FUS  
50% TDP

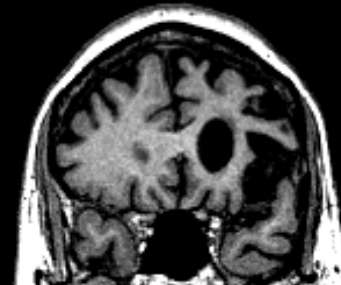
Language Variants

Semantic  
Variant



Rarely genetic  
83% TDP-C

Nonfluent  
Variant



Some genetic  
85% Tau, TDP-A

# Three Main Genetic Mutations

1

## ***MAPT***

52 years, symmetrical MRI, bvFTD with parkinsonian syndromes, 1998 (tau aggregation)

**Therapy:** turn off or degrade tau

2

## ***GRN***

62 years, asymmetric MRI, bvFTD, PPA, PD, AD, 2006 (TDP A), haploinsufficient

**Therapy:** replace PGRN

3

## ***C9orf72***

56 years, symmetric MRI, cerebellar involvement (subtler frontal involvement), bvFTD and ALS, 2011 (TDP B, dipeptides) (hexanucleotide repeat)

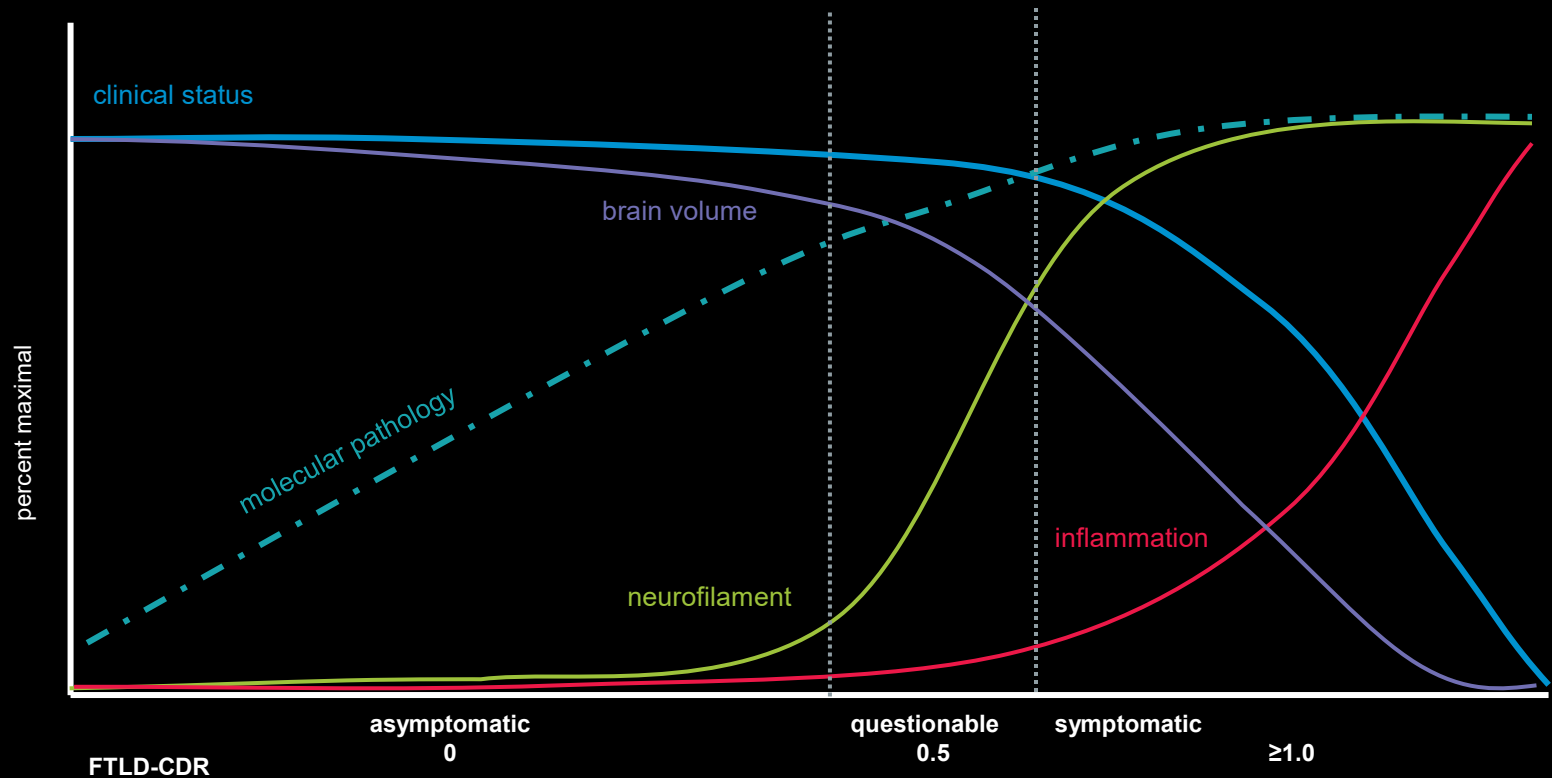
**Therapy:** turn off gene

# ARTFL / LEFFTDS Longitudinal FTLD

(ALLFTD)

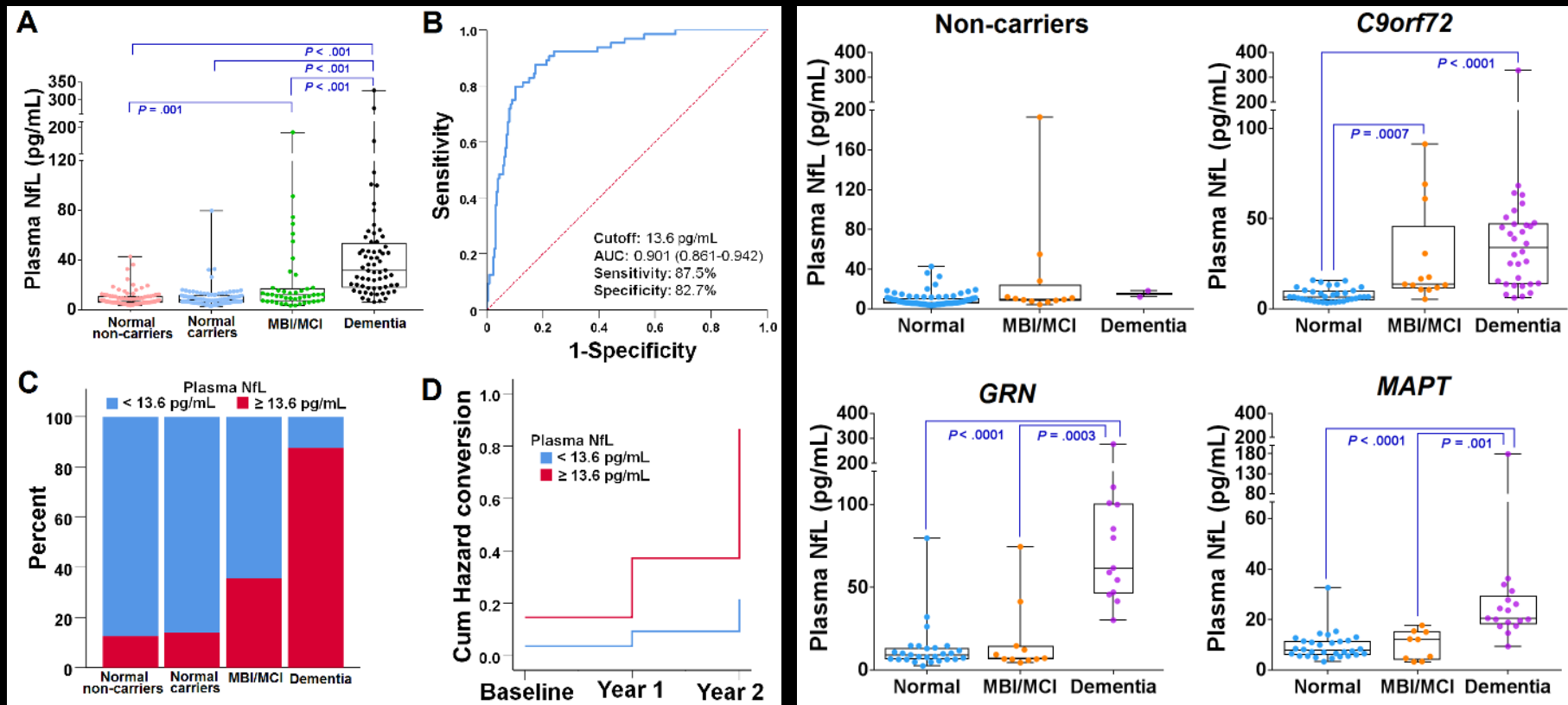


# Disease Progression in FTLD



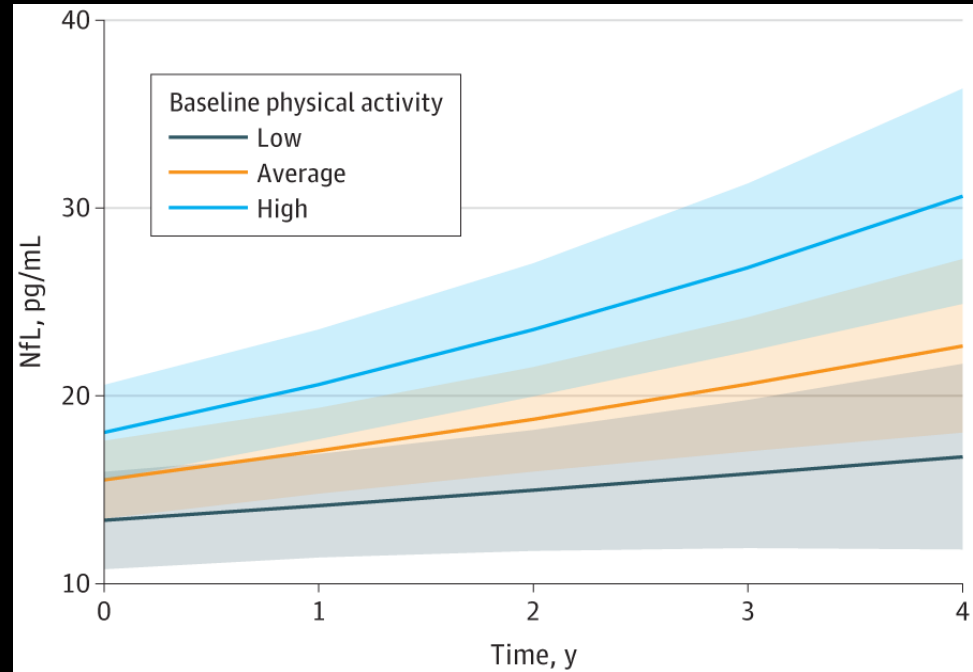


# Neurofilament Predicts State/D Decline



# Baseline Activity Levels and Rate of Plasma NfL Progression in FTL D Variant Carriers

- Higher physical activity is associated with slowed cognitive and functional declines over time
- Even in autosomal dominant variants of frontotemporal lobar degeneration (FTLD)



# Treatment of FTD

- MAPT
  - Antibody delivery
  - CRISPR
- C9orf72
  - Antisense oligonucleotides
  - CRISPR
  - Small molecules
- GRN
  - Antibody delivery via transferrin receptor
  - AAV delivery
  - Anti-sortilin antibody

# Creativity

# Cave Painting Lascaux 15,000 BCE



# Creativity Networks in the Brain

The whole is more  
than the sum of its parts.

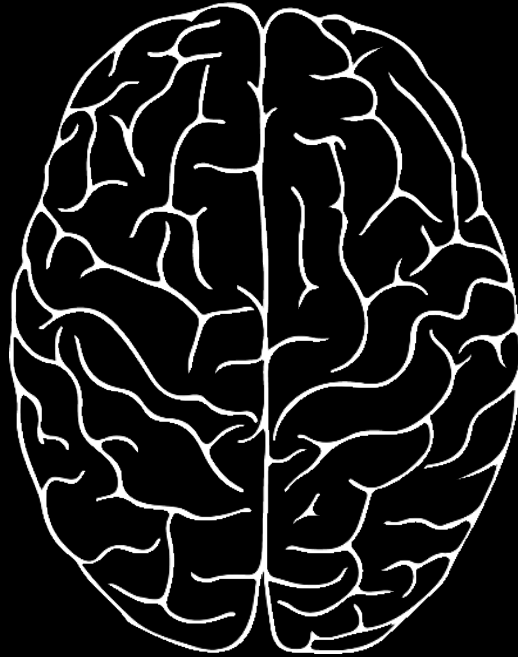
LEFT

*Lorem ipsum  
dolor sit amet*



$$ax^2 + bx + c = 0$$

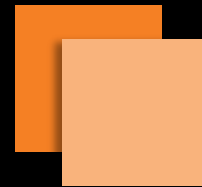
FRONT



BACK

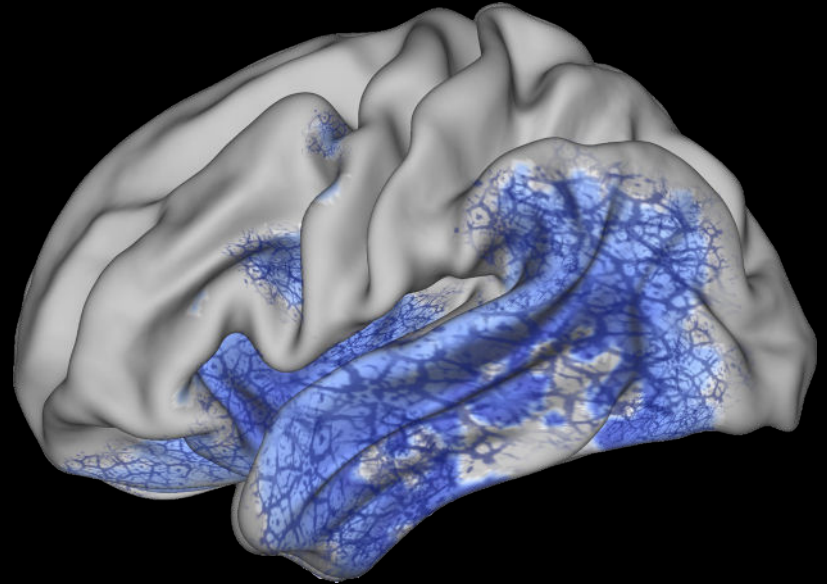


RIGHT



# Clinical Diagnosis of svPPA

- **Both** core features must be present:
  - Impaired **confrontation naming**
  - Impaired **single-word comprehension**
- **≥3** of the following must be present:
  - Impaired **object knowledge**, particularly for low-frequency or low-familiarity items
  - **Surface dyslexia** or **dysgraphia**
  - **Spared repetition**
  - **Spared speech production** (grammar and motor speech)



# Creativity in FTD Not Rare

## Anatomy is Evident



Patients with FTD can develop new artistic skills after disease onset\*



Visual creativity more common when anterior temporal lobes or left frontal lobe show focal degeneration



12 patients showing emergence of musical or visual ability, all with FTD\*



Art in FTD is not a coincidence!



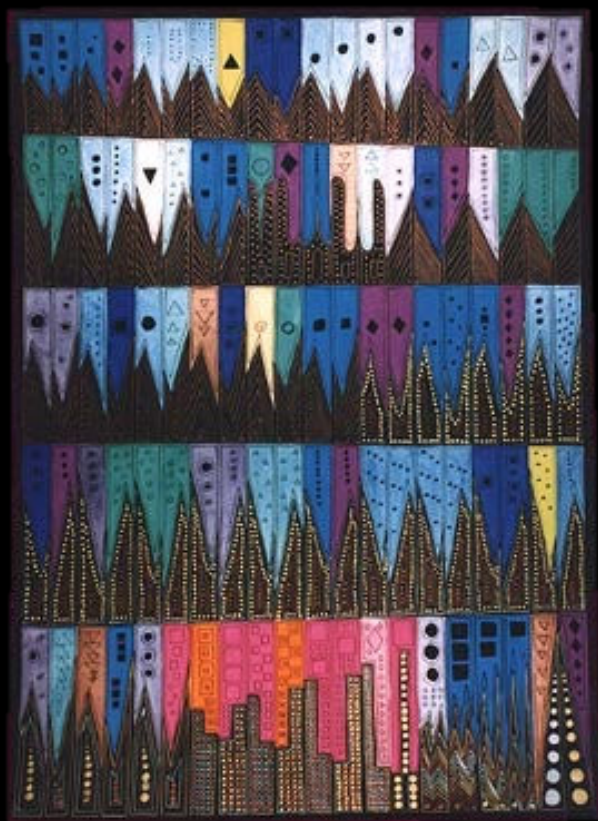
Associated with language variants

\*Miller BL et al. *Neurology*. 1998





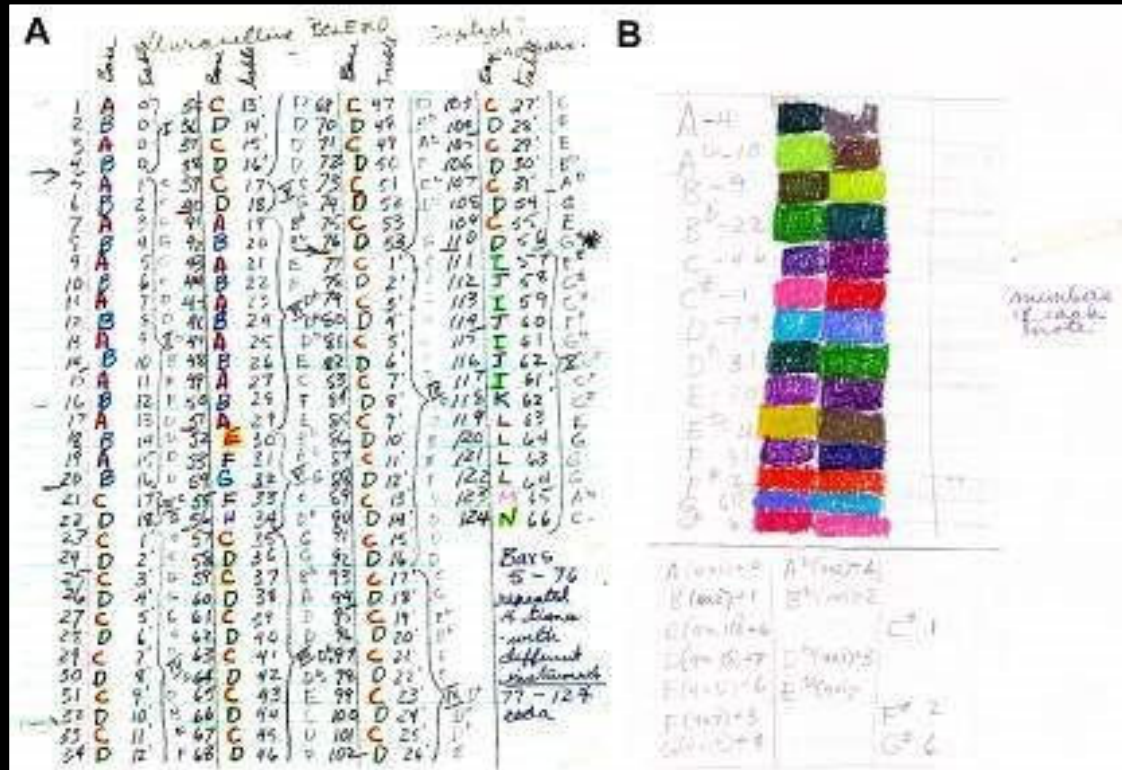




1994



# Each Bar Favorite Note Has a Color



# Meter 321 Change of Key

A

"The colored, treble parts are embellished with geometric shapes in black and also engraved into the paper to represent the quality of tone of each note. When the modulation finally does occur I use gaudy fluorescent colors to make the few #'s in the piece. The music soon collapses and dies in the final two bars.

I find Bolero an exciting experiment in sound, one which Ravel didn't really consider true 'music'."

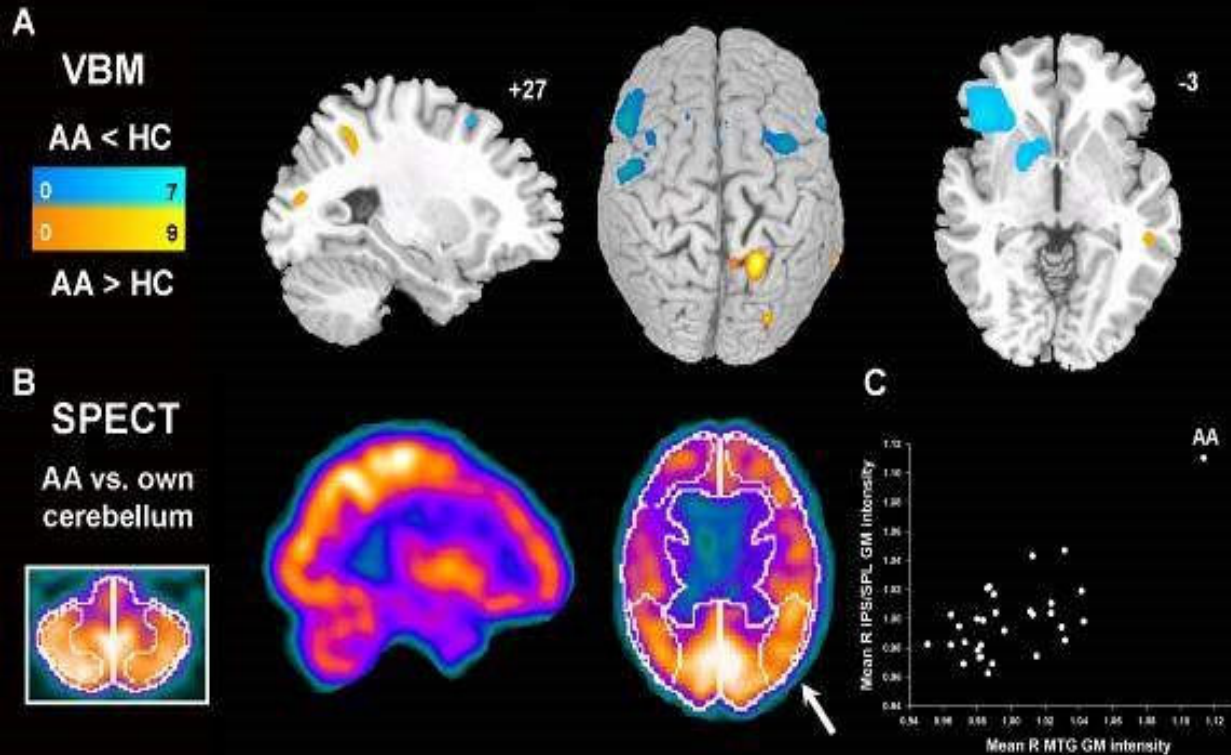
B



C



# Right Posterior Cortex is Hypermetabolic and Thicker than Matched Controls







# Complementary Network Strengths

Focal left frontal injury accompanied  
by right posterior enhancements

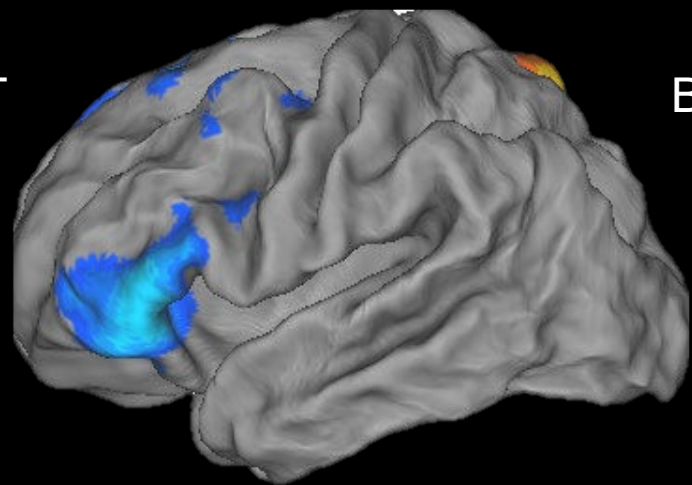
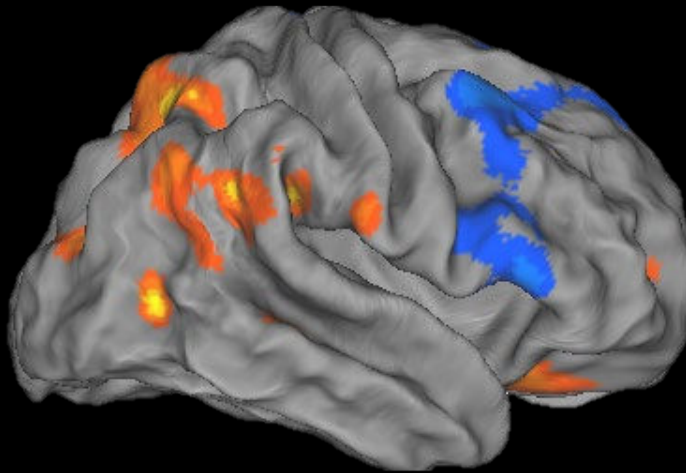
RIGHT

LEFT

BACK

FRONT

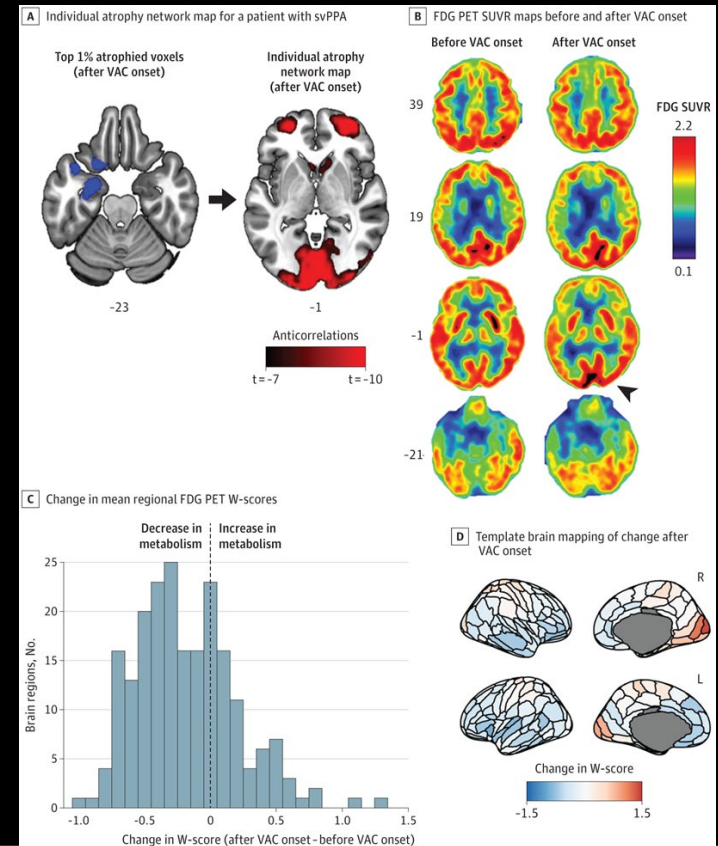
BACK





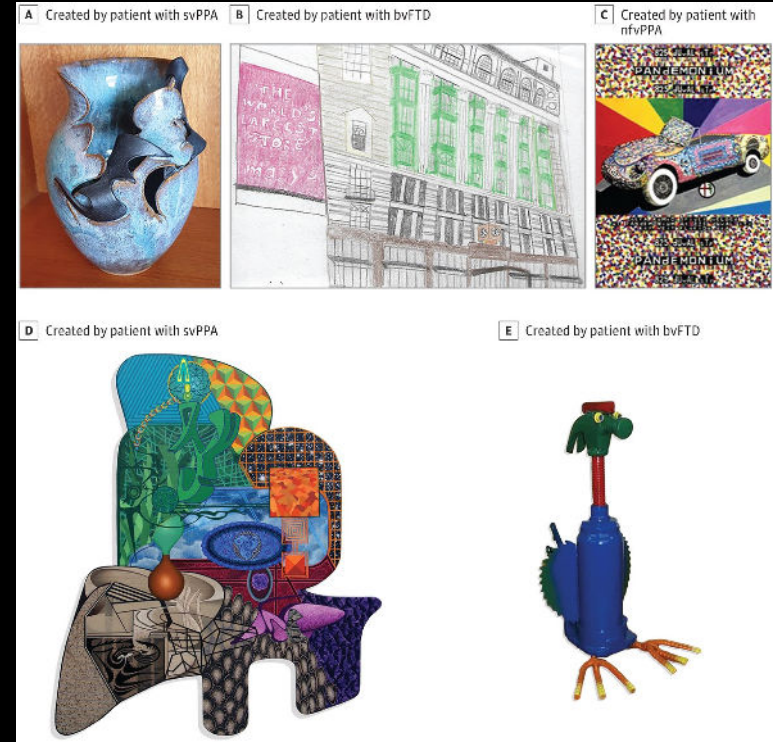
# Review of 17 Artists with Dementia

- Of 689 FTD-spectrum patients, 17 artists (2.5%)
  - 8 of 17 artists had temporal variant of FTD (6.7%)
  - 8 de novo, 7 some interest, 2 artists who changed
  - Most severe atrophy anterior temp, amygdala striatum insula (left >right), amygdalae, striatum, and left insula
- Same region correlated with left motor strip (hand), no correlation in FTD or healthy controls
- Visual artistic creativity occurred early in FTD
- Disproportionately temporal lobe degeneration
- Damaged brain regions normally suppress dorsomedial greater occipital cortex function



# Prevalence, Timing, and Network Localization of Emergent Visual Creativity in FTD

- Bright colors common, art rarely focused on human faces
- 2 svPPA patients generated animal sculptures lacking features of species
- When present, facial expressions bizarre and did not convey natural emotions

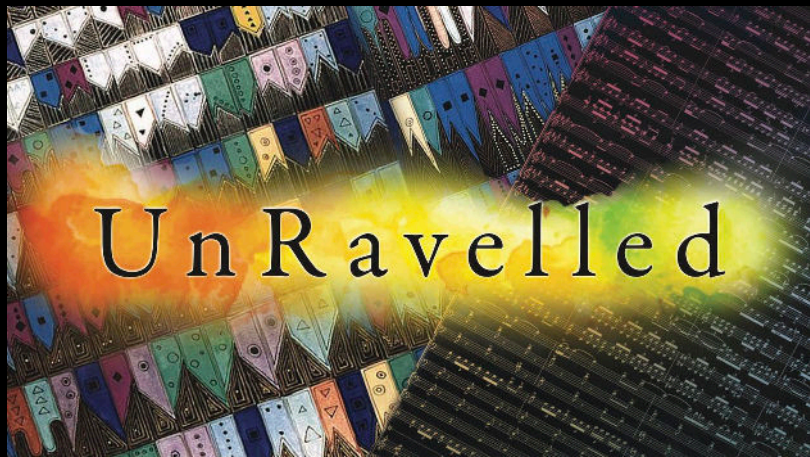


# Conclusions

- Art uses both hemispheres
  - Double consciousness?
- Artistic creativity may emerge in association with left hemisphere dysfunction
  - Rewiring of posterior brain?
- Insights into the degenerative process: strengths important in diagnosis & care
- Insights into our humanity: brain asymmetry is at core of our strengths and weaknesses

# Join Us for UnRavelled

a play by Jake Broder



- Award-winning cast, with projection, sound design and a finale of Ravel's Bolero performed by musicians from the San Francisco Conservatory of Music.
- [July 21, 2023](#), at the San Francisco Conservatory of Music
- In association with the Global Brain Health Institute, The Association for Frontotemporal Degeneration and San Francisco Conservatory of Music, Jake Broder, James Bonas and Cath Brittan

Best Scientific  
Play

This Week in New York  
Pandemic Award

Streaming  
Design

Los Angeles Drama  
Critics Circle Award

Writing, Production  
Ensemble & Lead  
Performance

Los Angeles Drama  
Critics Circle Nominations



University of California  
San Francisco