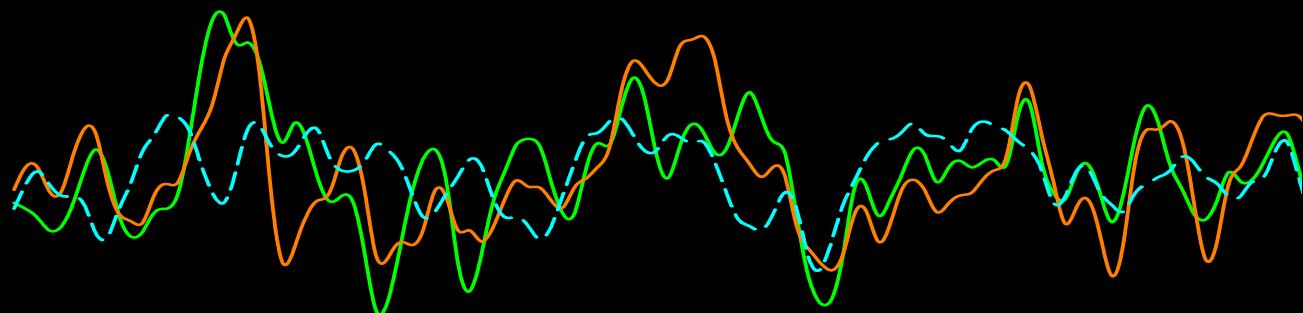


# Selective Vulnerability of von Economo Neurons in Frontotemporal Dementia

William W. Seeley, MD  
Assistant Professor of Neurology  
UCSF

August 3, 2007



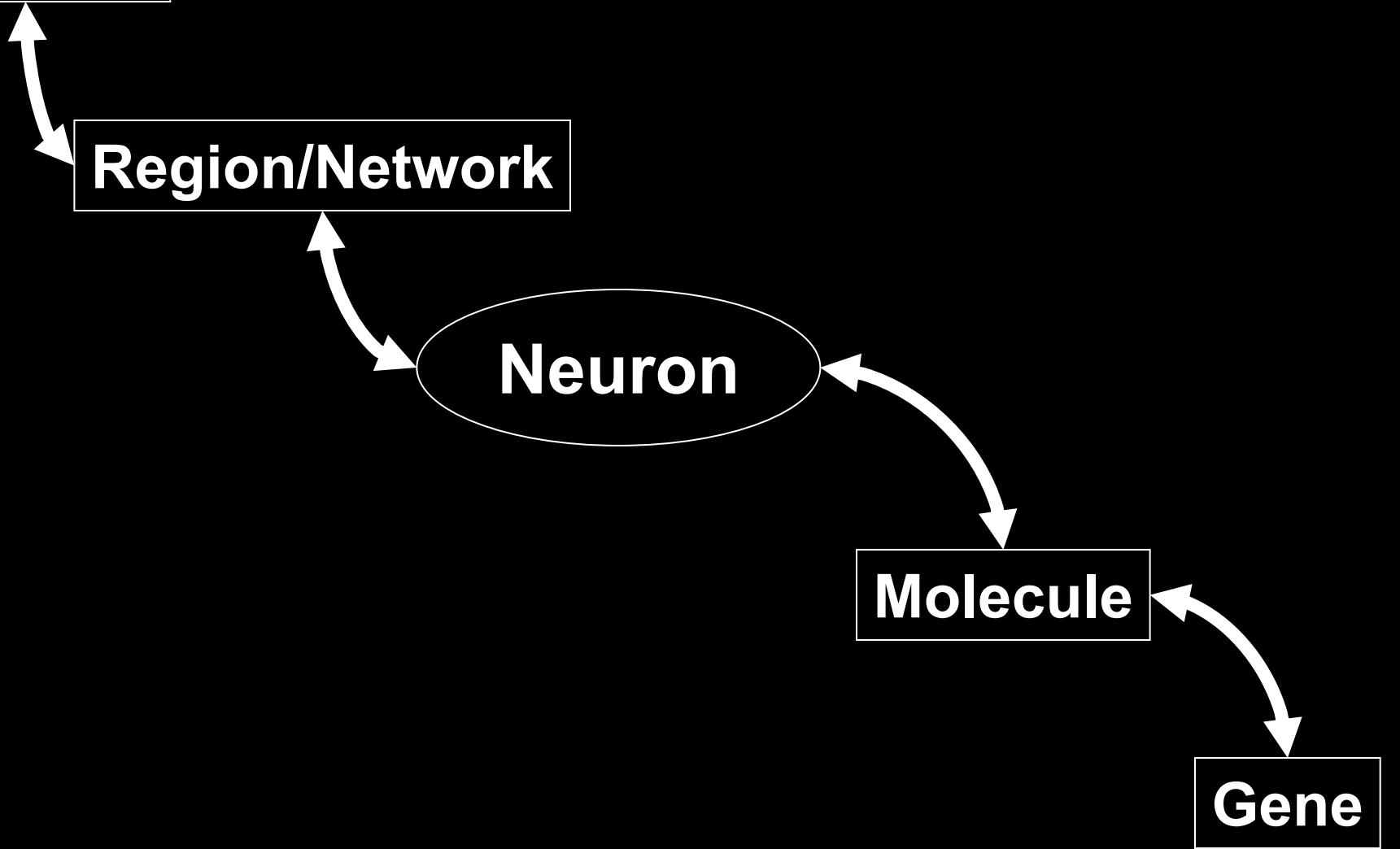
**Function**

**Region/Network**

**Neuron**

**Molecule**

**Gene**



# Why study selective vulnerability?

## Dementia diagnosis and treatment

- Dx: Selective vulnerability dictates early, disease-specific symptoms & signs
- Rx: Global targeting of aberrant proteins may not be enough
  - Need to stop disease early, while confined to most vulnerable cells and circuits...may prevent downstream degeneration
  - Vulnerable neurons may express susceptibility or response genes that relate to pathogenesis and impact treatment
  - Invulnerable neurons may employ cell-protective mechanisms that could be used to rescue vulnerable cells
  - Disease-related proteins have normal functions. Systemic treatments may confer toxicity.

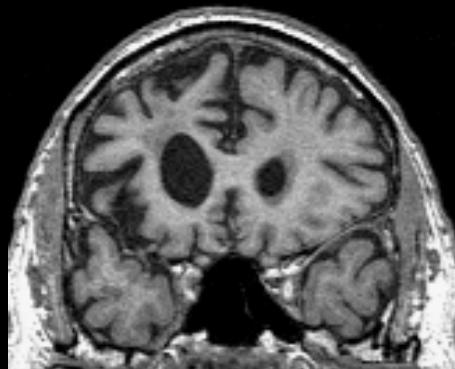
# Why study selective vulnerability?

Neuroscience

- Selective vulnerability provides an opportunity to study the function of specific cells and circuits targeted by disease
- Selective vulnerability provides a window into human brain systems that cannot be modeled in laboratory animals

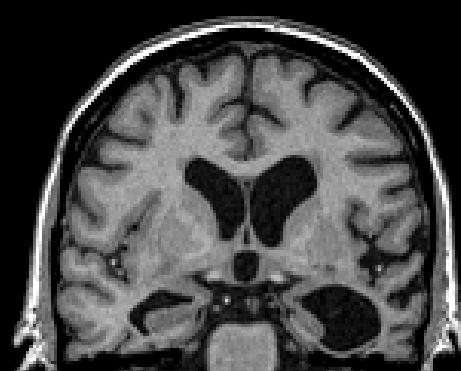
## Frontotemporal dementia

Behavioral variant



Language variants

Semantic  
Dementia

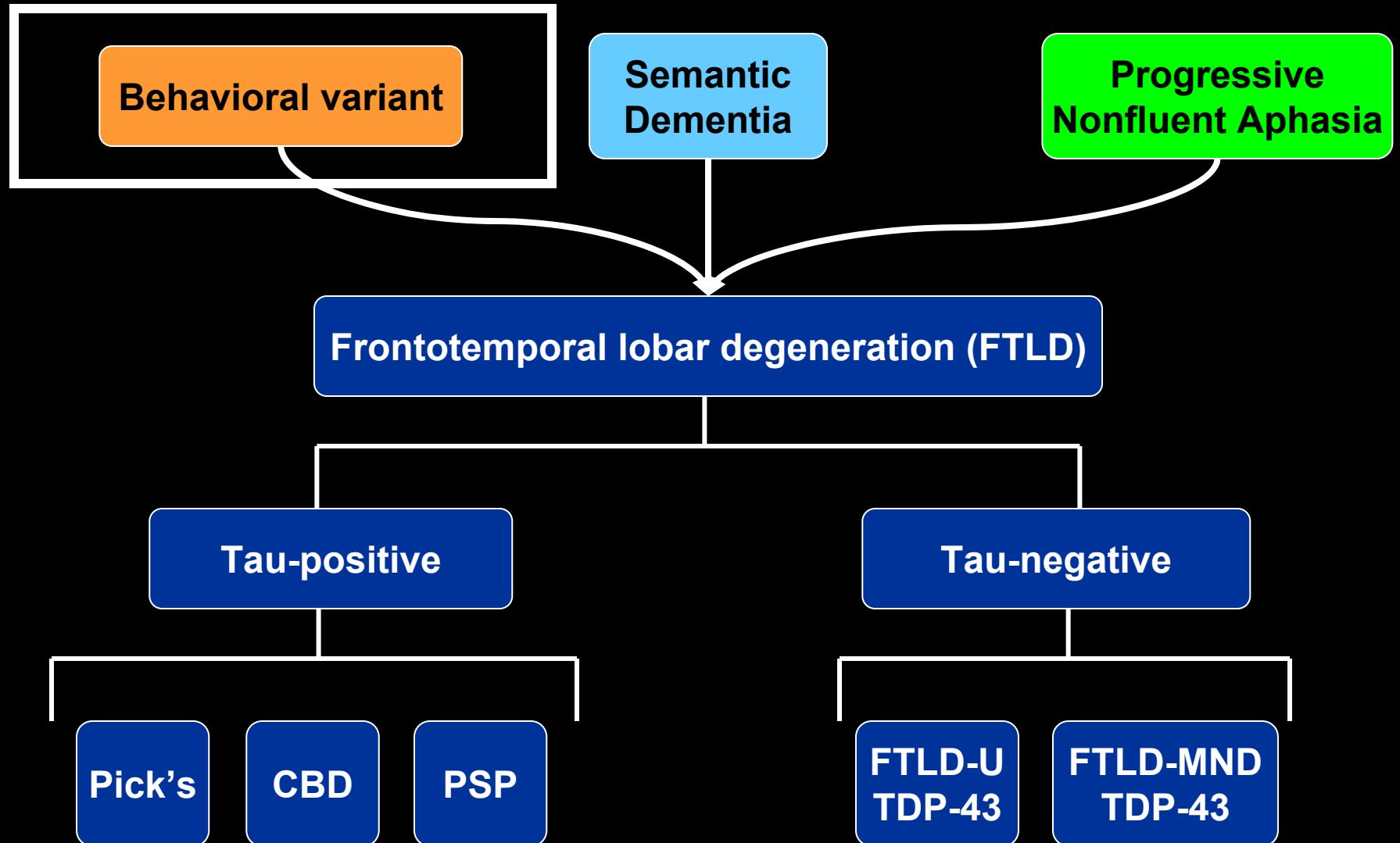


Progressive  
Nonfluent Aphasia



Also:

“Frontal variant” FTD  
“FTD”



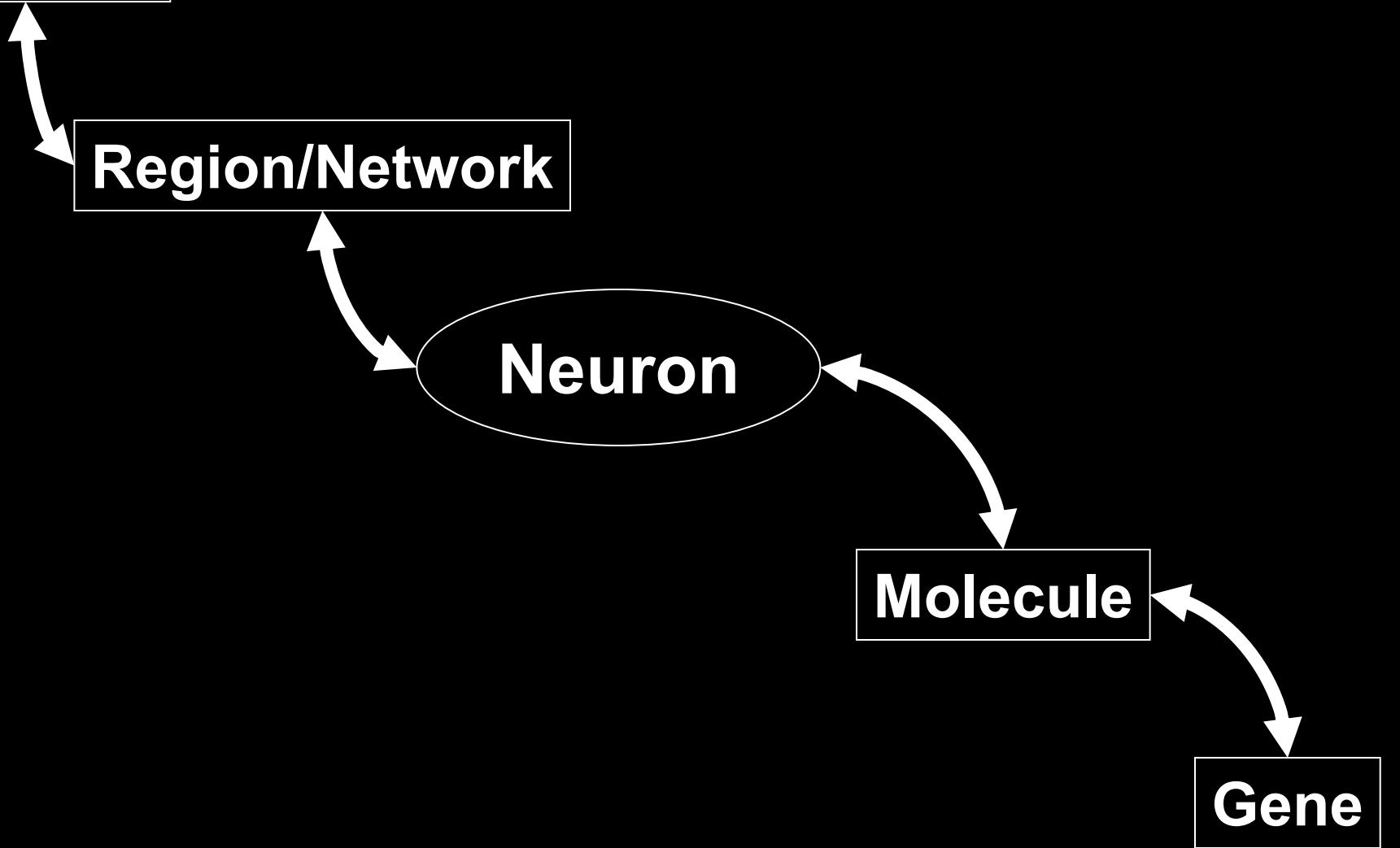
**Function**

**Region/Network**

**Neuron**

**Molecule**

**Gene**



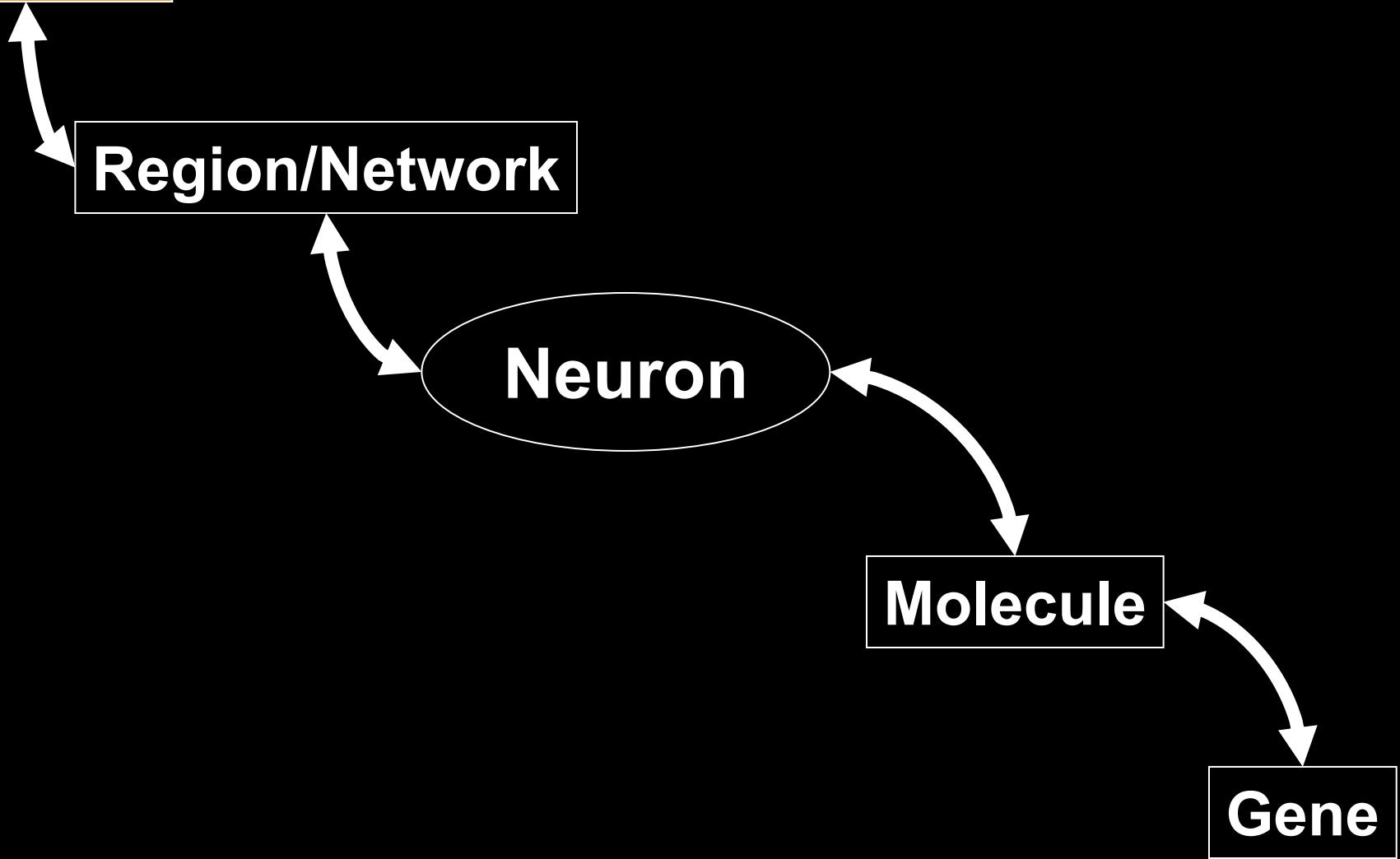
**Function**

**Region/Network**

**Neuron**

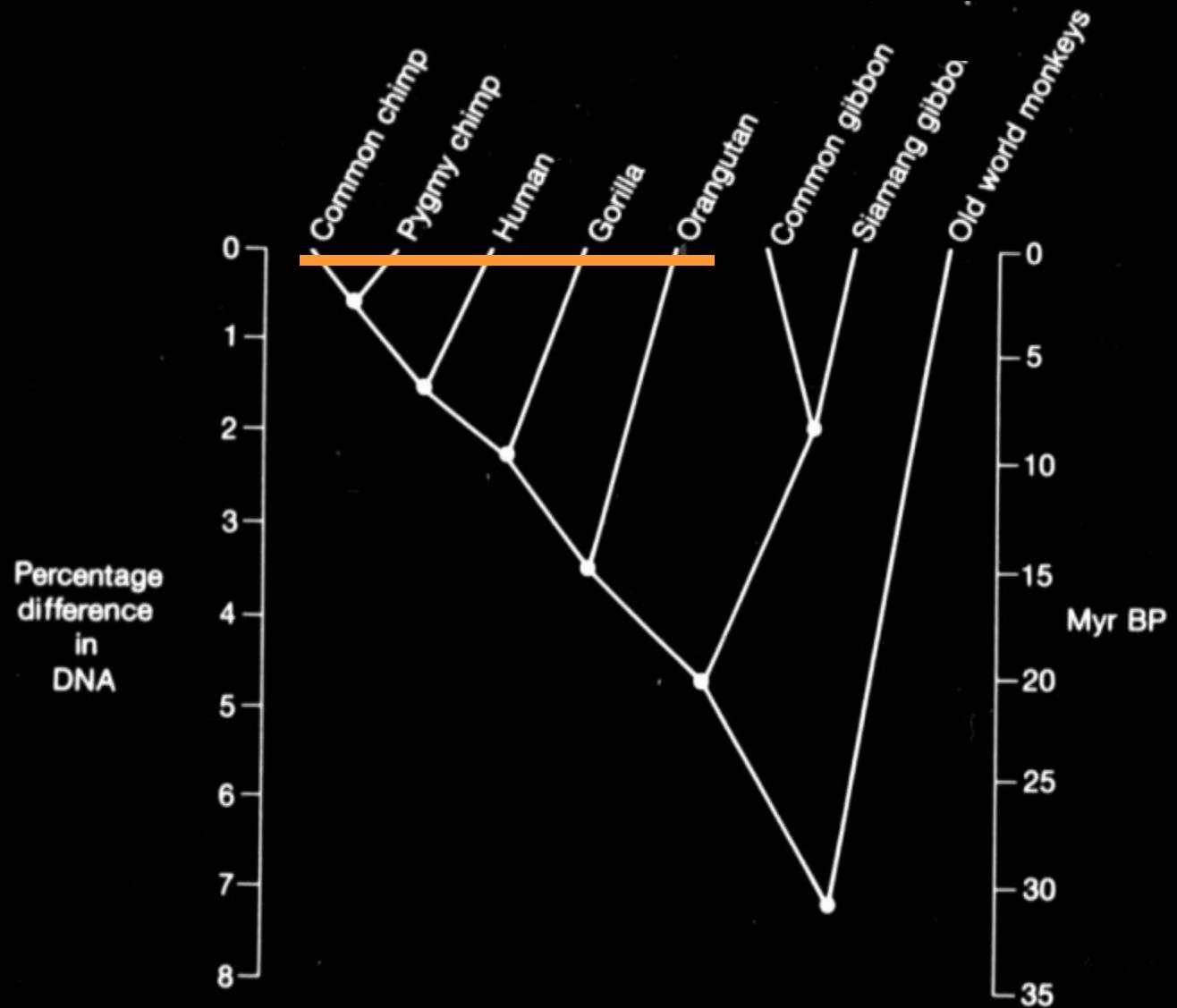
**Molecule**

**Gene**



# BvFTD social cognitive deficits: Representations of self and others

- Self-concept Miller 2001
- Self-conscious emotion Sturm 2006
- Empathy \*\*Rankin 2005, 2006
- Social self-monitoring \*\*Rankin unpublished
- Theory of Mind \*\*Gregory 2002  
Snowden 2003  
Lough 2006
- Metacognitive judgment \*\*Eslinger 2005
- Moral reasoning \*\*Mendez 2005  
Lough 2006



Ridley 1993

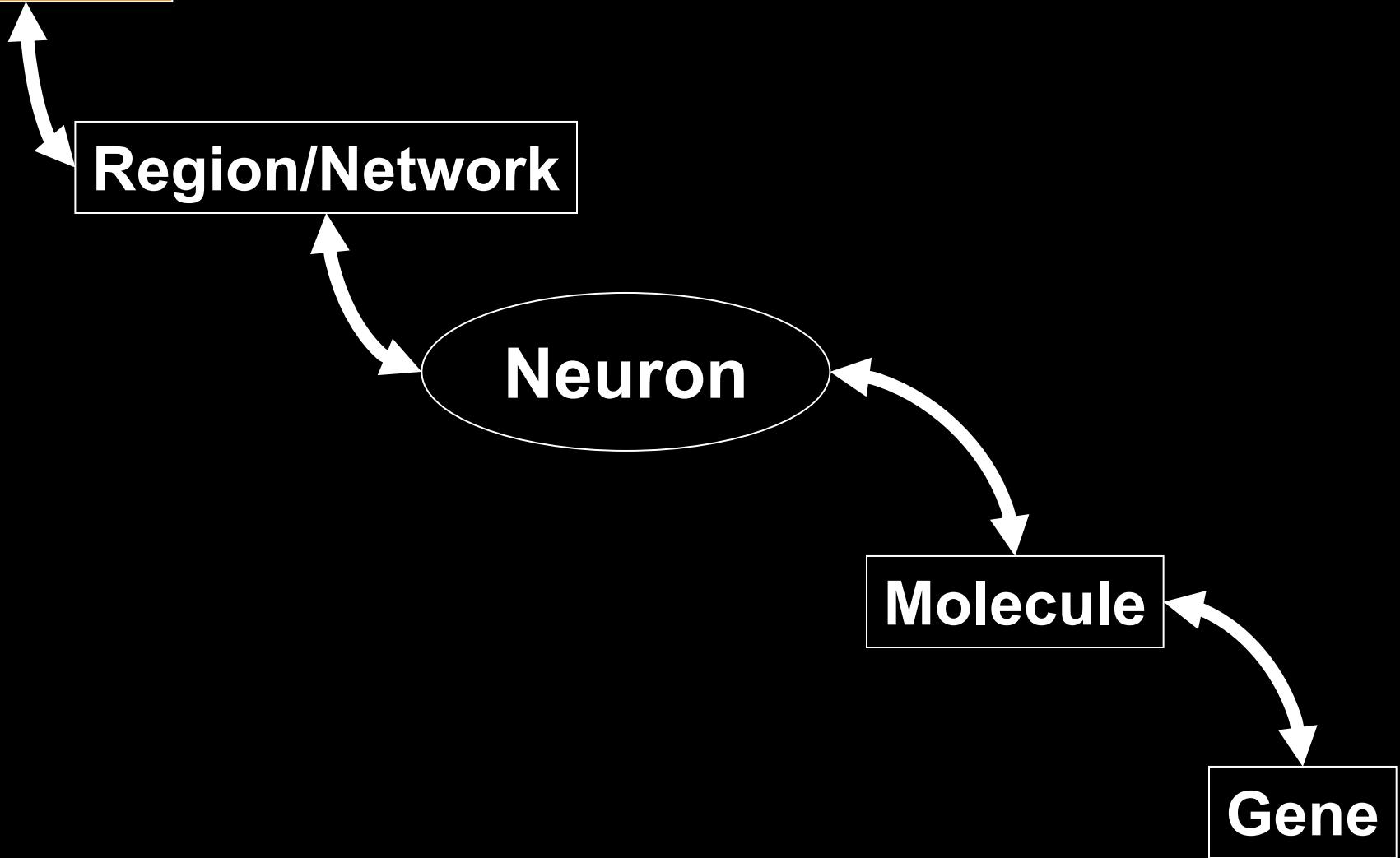
**Function**

**Region/Network**

**Neuron**

**Molecule**

**Gene**



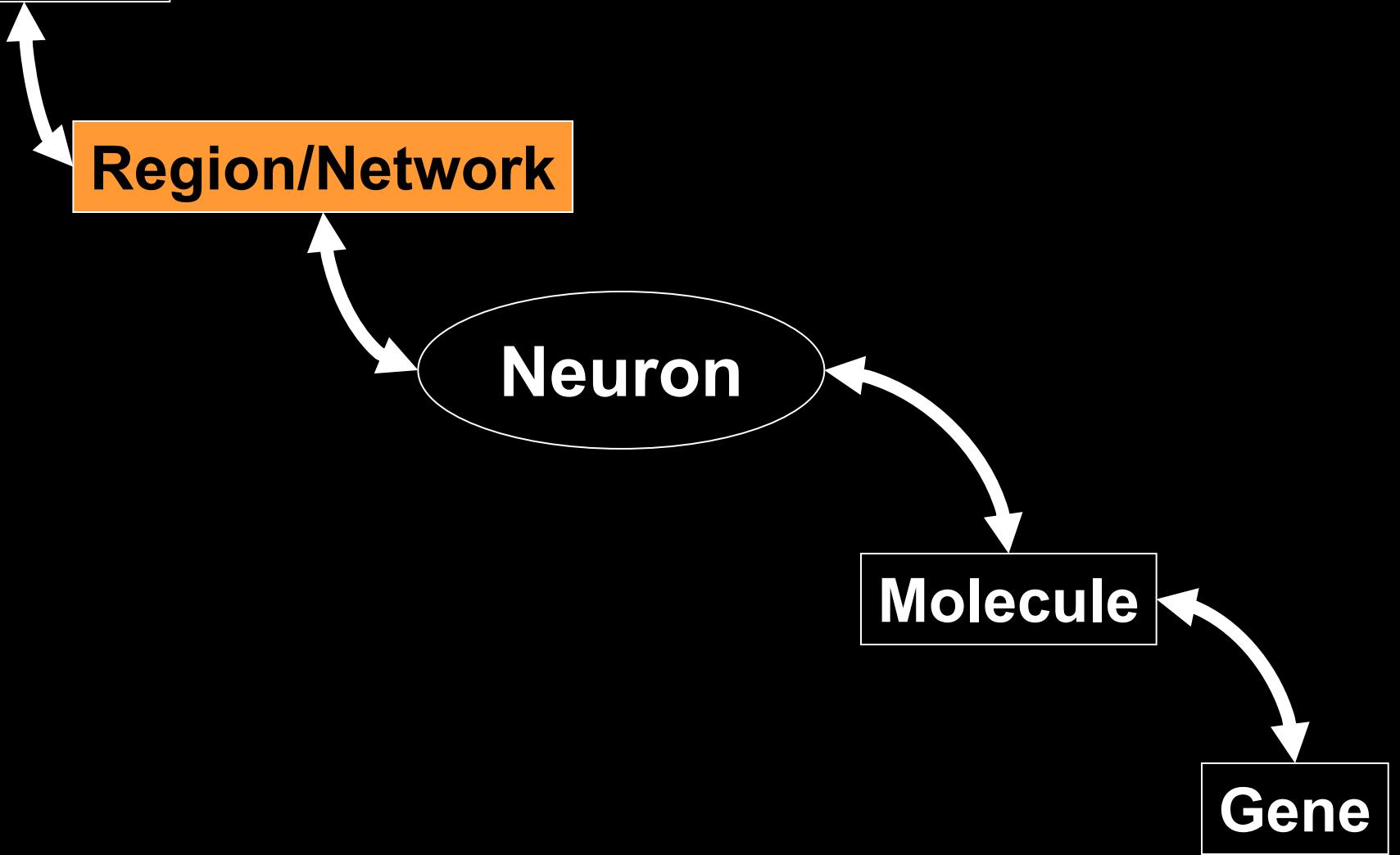
**Function**

**Region/Network**

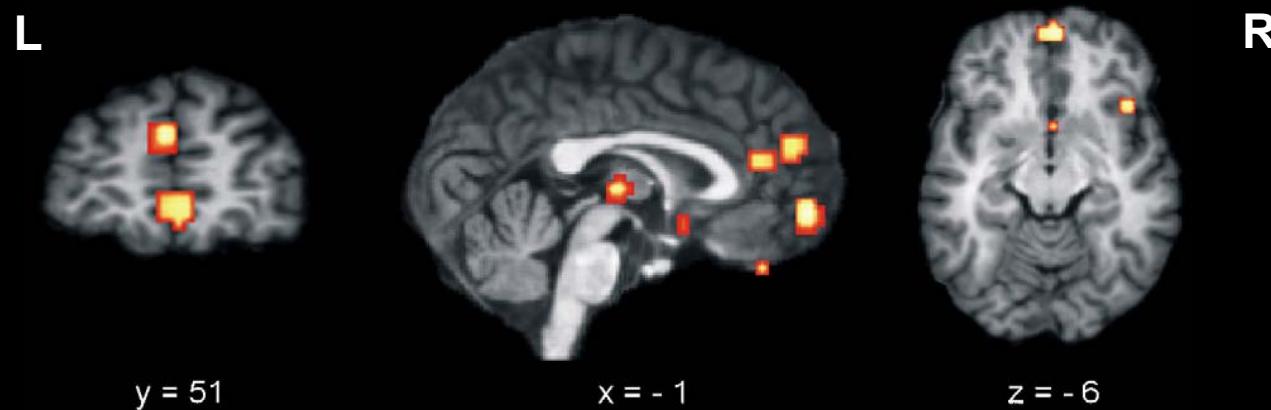
**Neuron**

**Molecule**

**Gene**

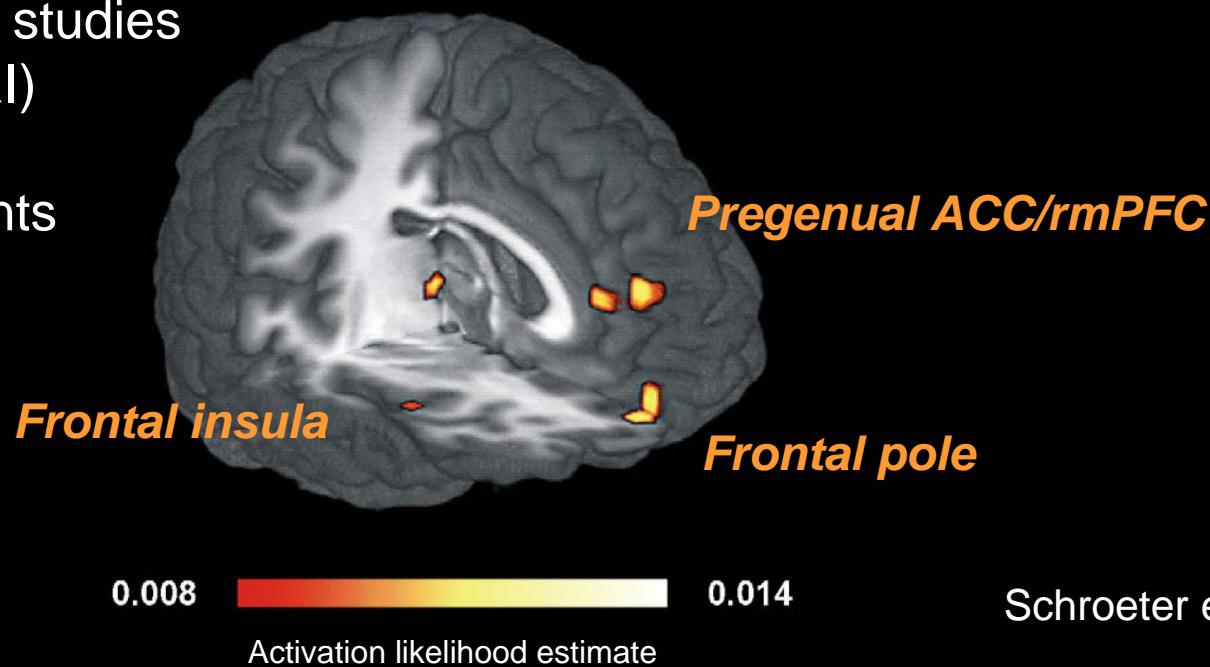


# Early bvFTD network: Very mild dementia (CDR 0.5)



9 bvFTD imaging studies  
(PET/SPECT/MRI)

132 bvFTD patients  
166 controls



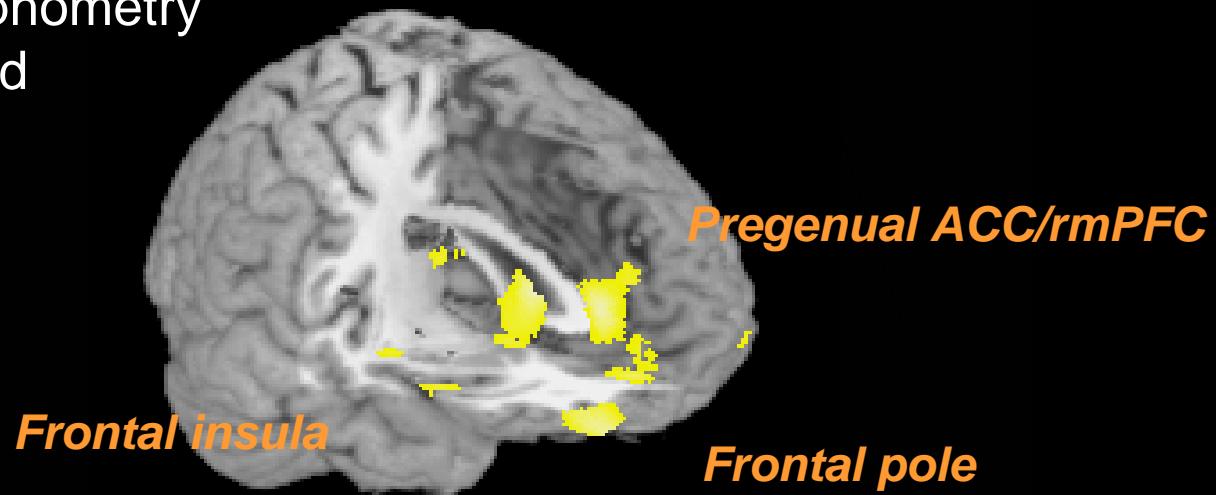
Schroeter et al 2006

# Early bvFTD network: very mild dementia (CDR 0.5)



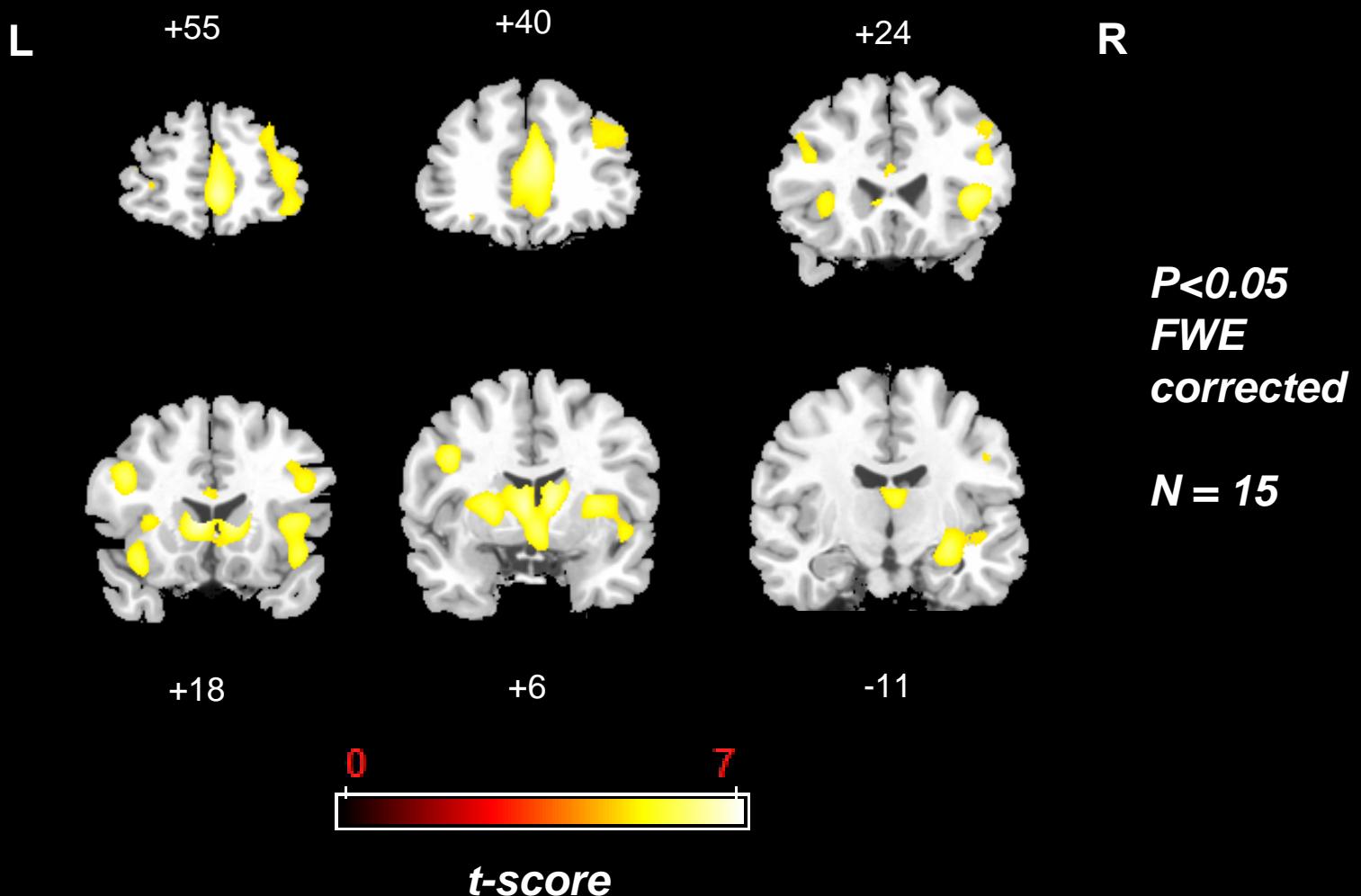
# Voxel-based morphometry $P < 0.05$ , corrected

N = 15



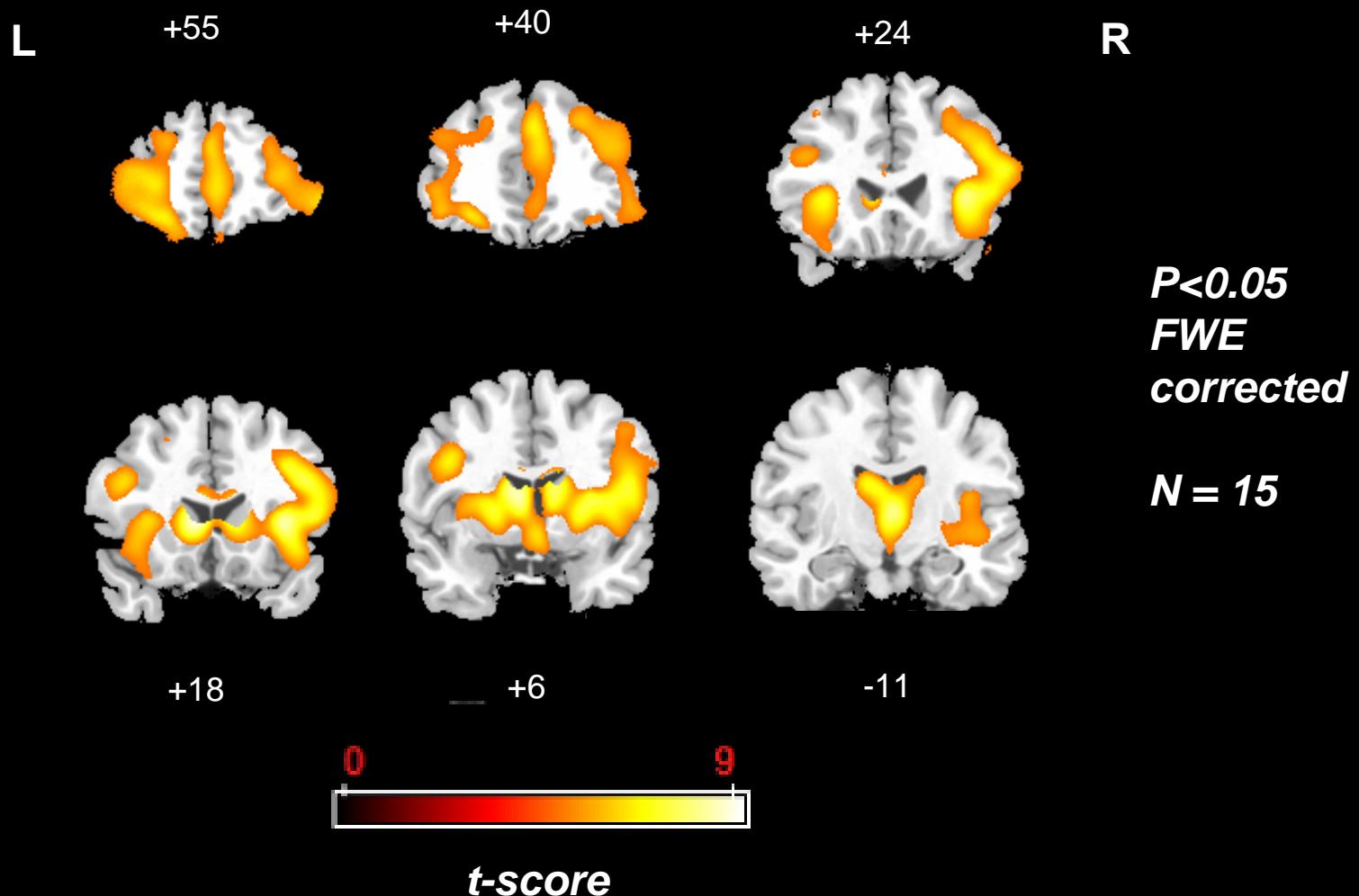
Very mild bvFTD:

CDR = 0.5



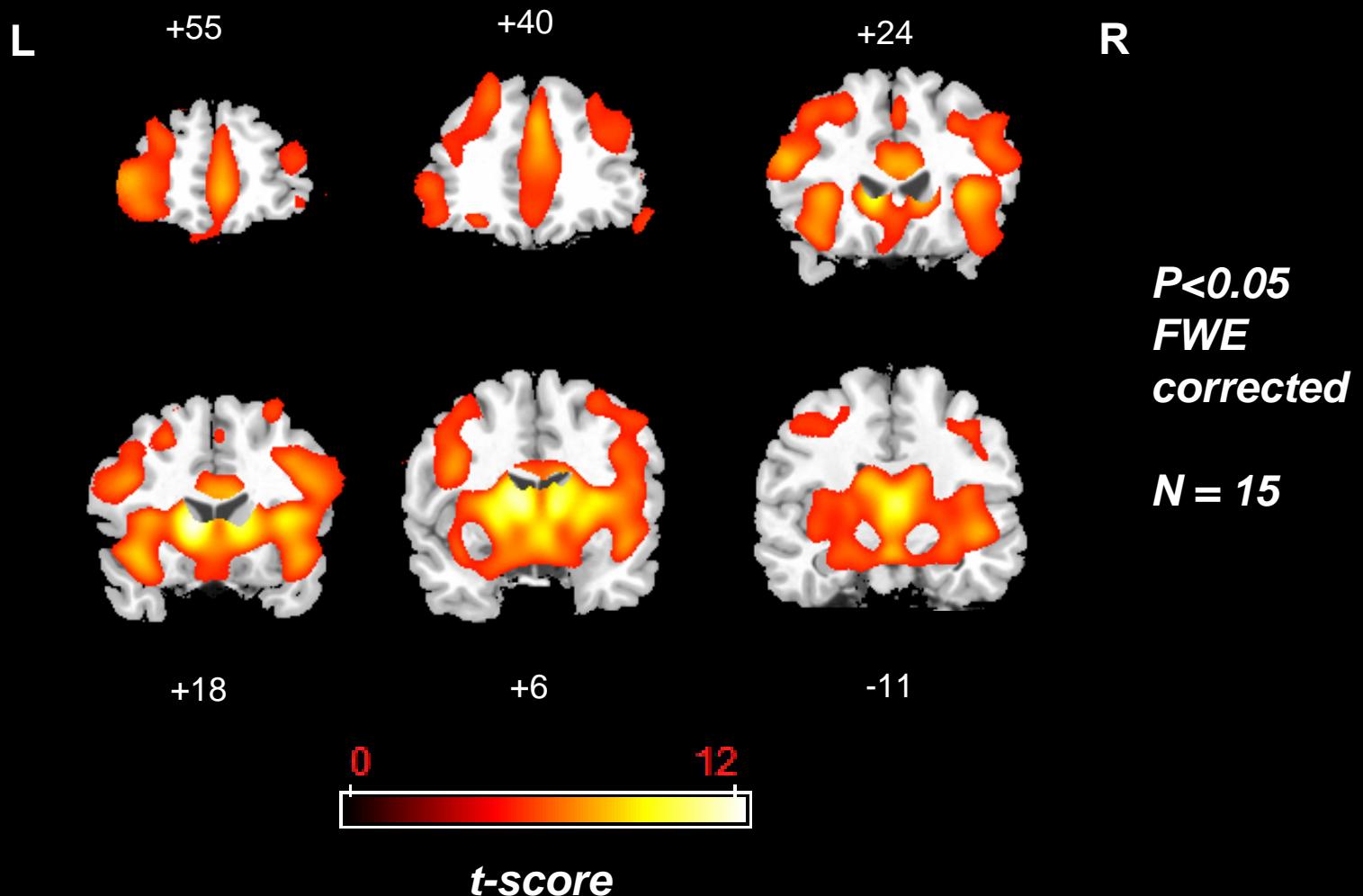
# Mild bvFTD:

CDR = 1



# Moderate-to-severe bvFTD:

CDR = 2-3



# An ACC-FI network in healthy humans?

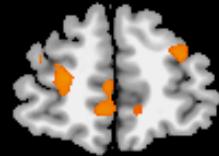
In healthy subjects,  
baseline low frequency  
fMRI BOLD signal  
fluctuations in R FI are  
correlated with...



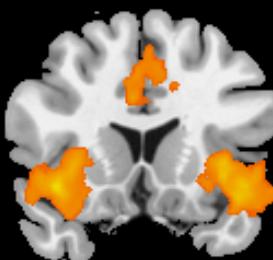
Right FI  
seed  
ROI

Left

DLPFC



Frontal pole

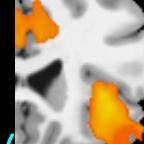


FI

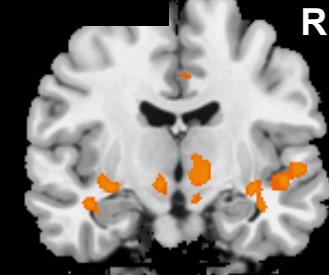
FI

SLEA VSP

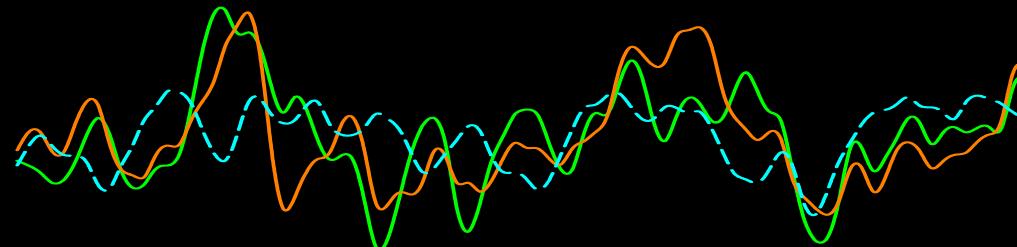
Right



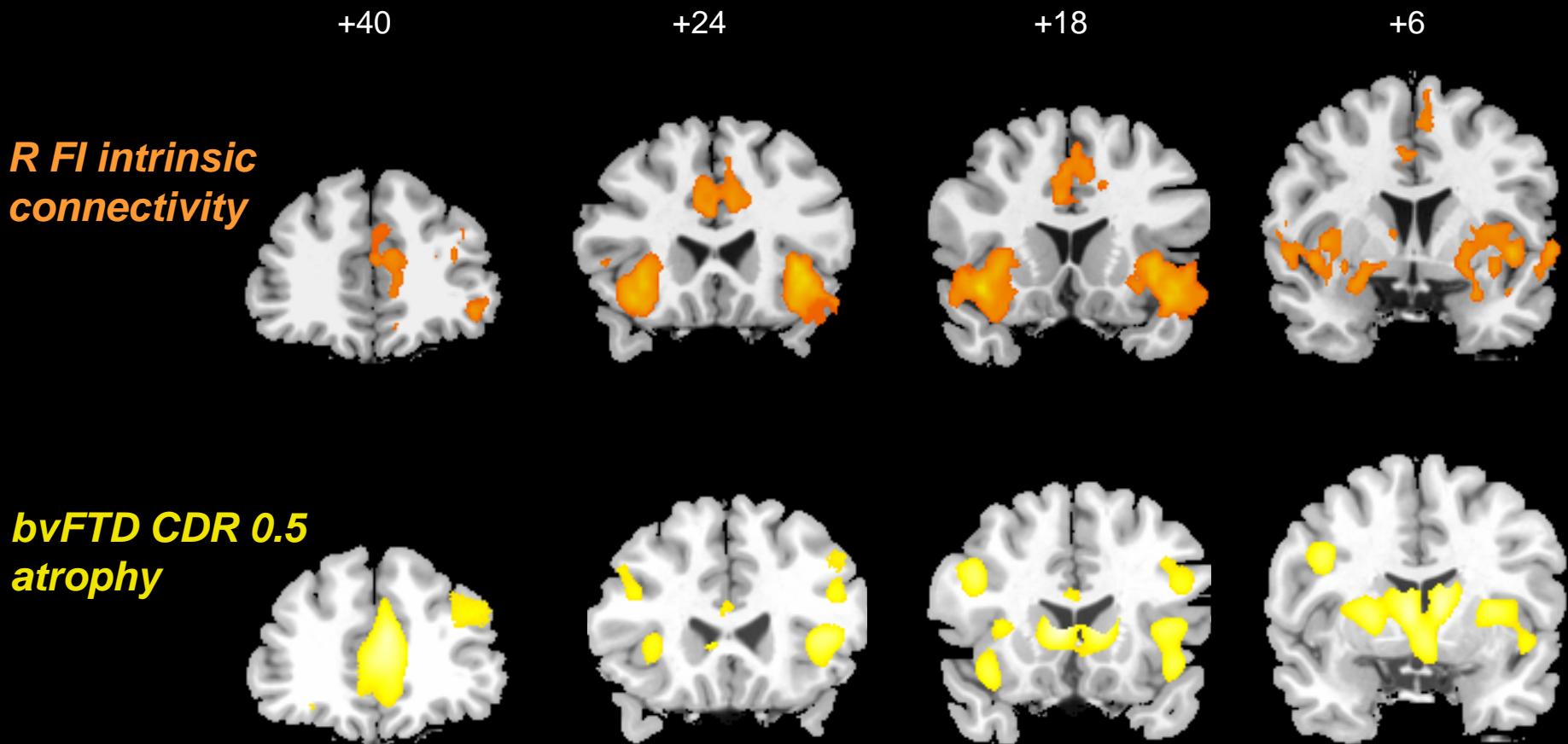
Lat OFC



Hypothalamus



# Early bvFTD targets an ACC-FI paralimbic network



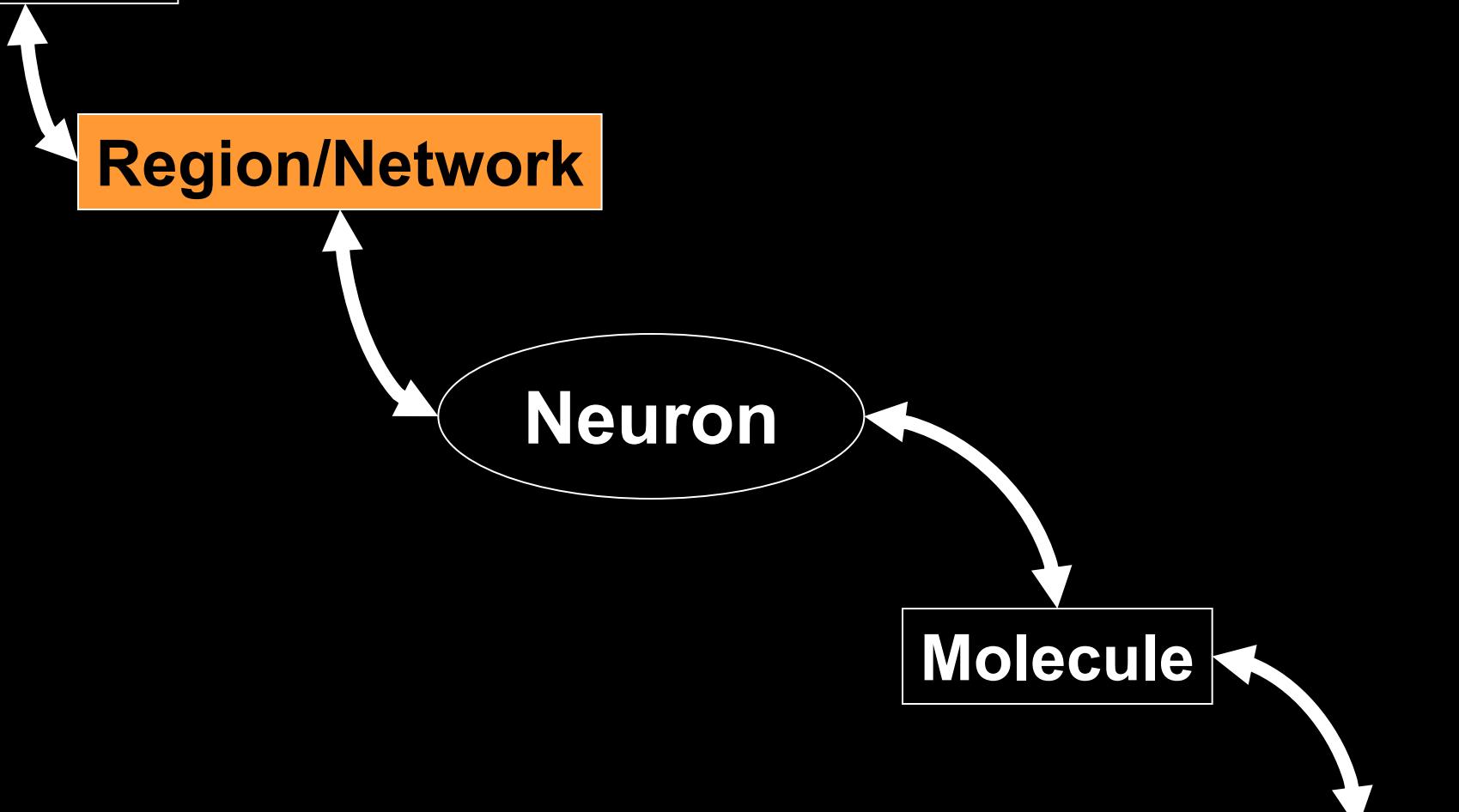
**Function**

**Region/Network**

**Neuron**

**Molecule**

**Gene**



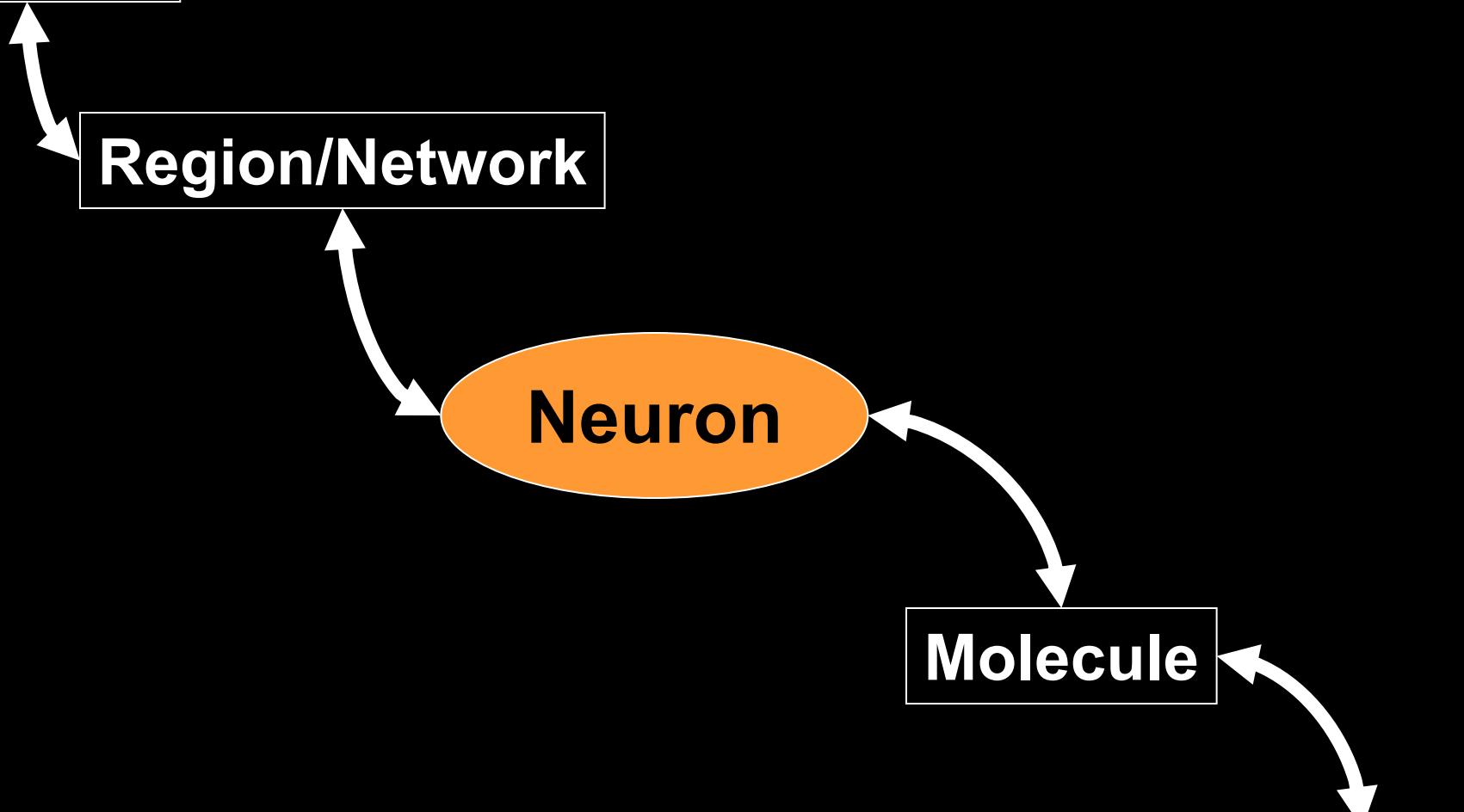
**Function**

**Region/Network**

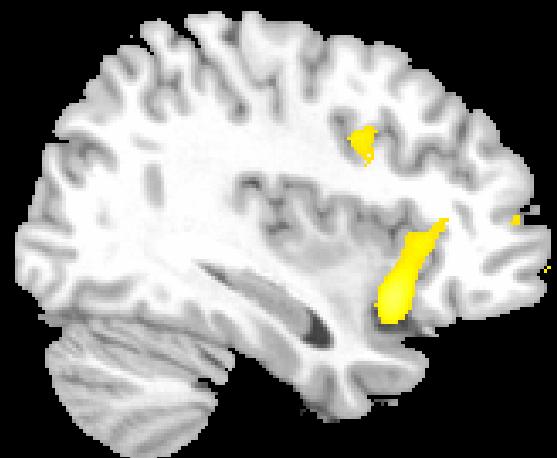
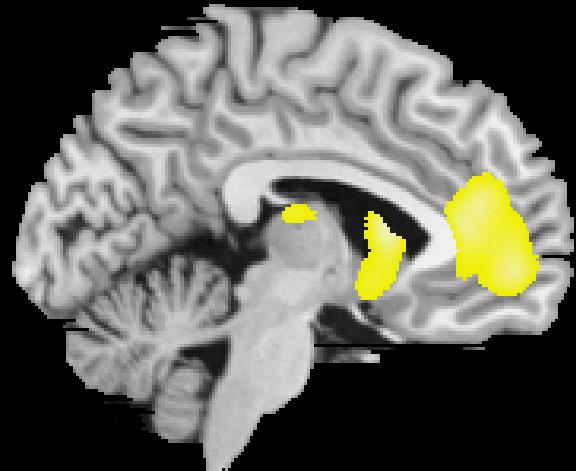
**Neuron**

**Molecule**

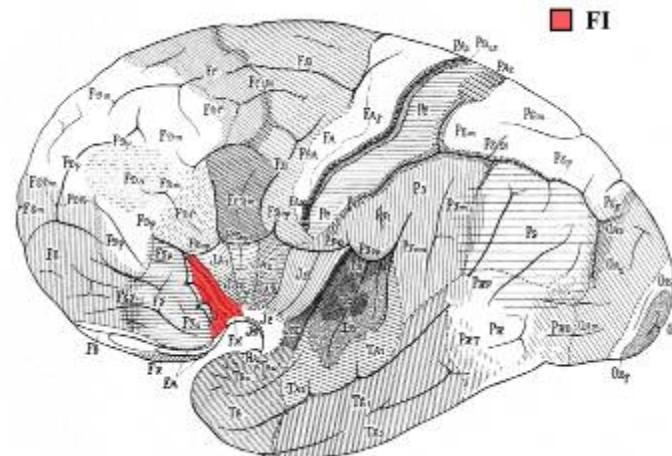
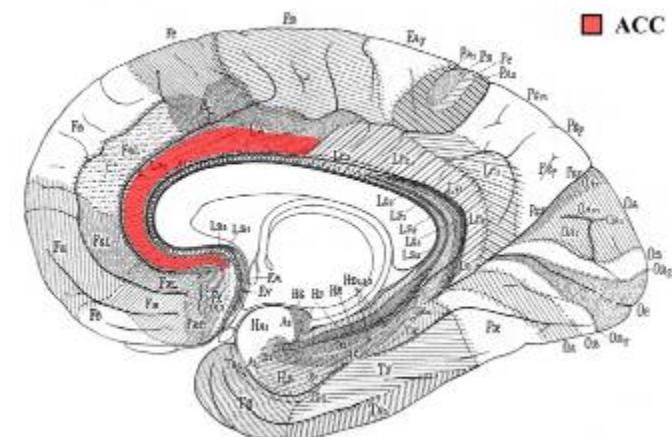
**Gene**



**Very mild FTD**  
**CDR 0.5**



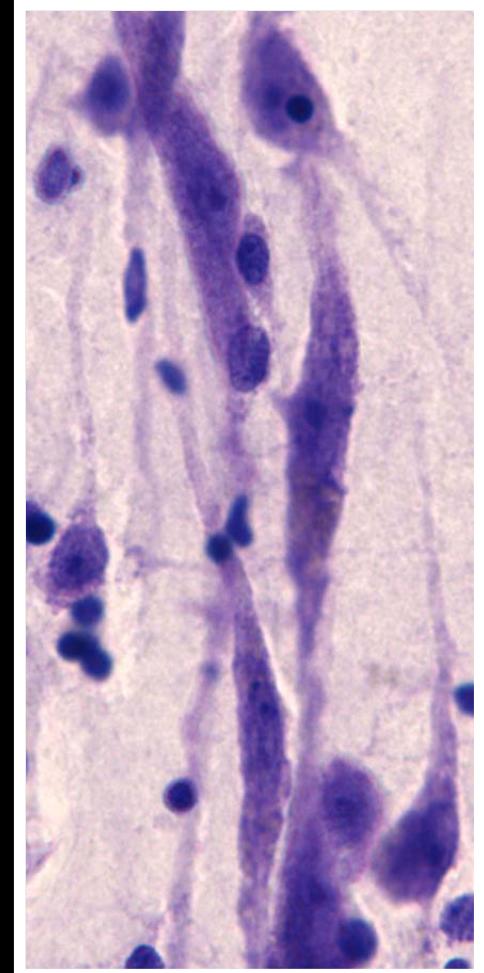
**Cytoarchitecture**



von Economo and Koskinas, 1925

# von Economo Neurons

- 1881 Betz
- 1899 Cajal
- 1925 von Economo
- 1927 Rose
- 1979 H. Braak
- 1995 Nimchinsky & Hof



# Von Economo neurons: Phylogeny

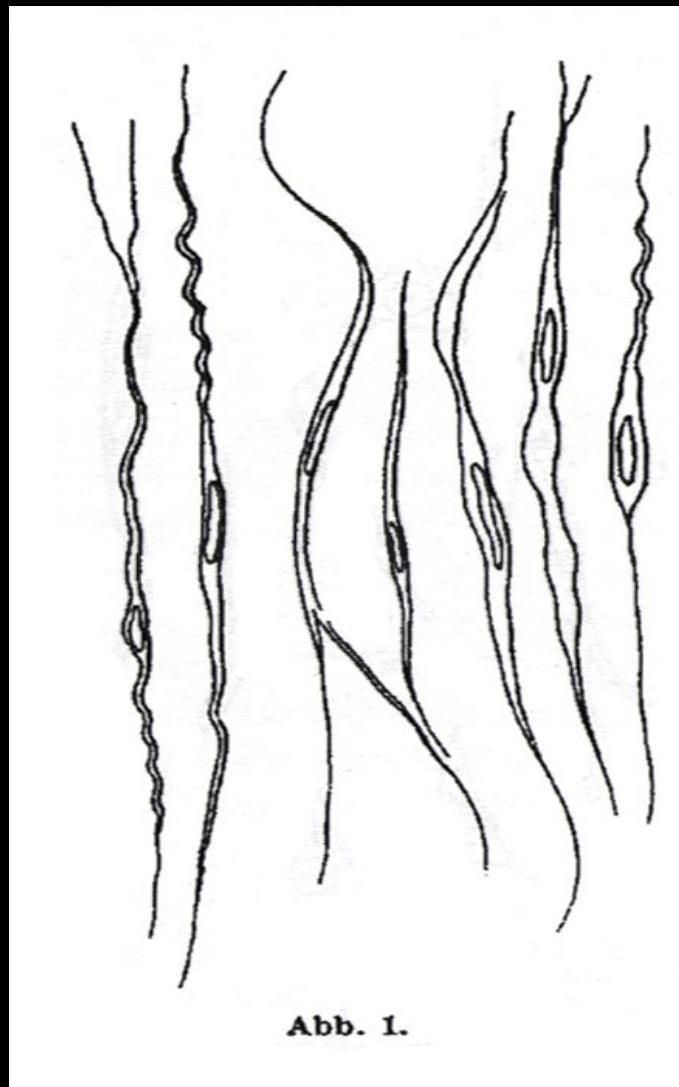


Abb. 1.

von Economo 1925

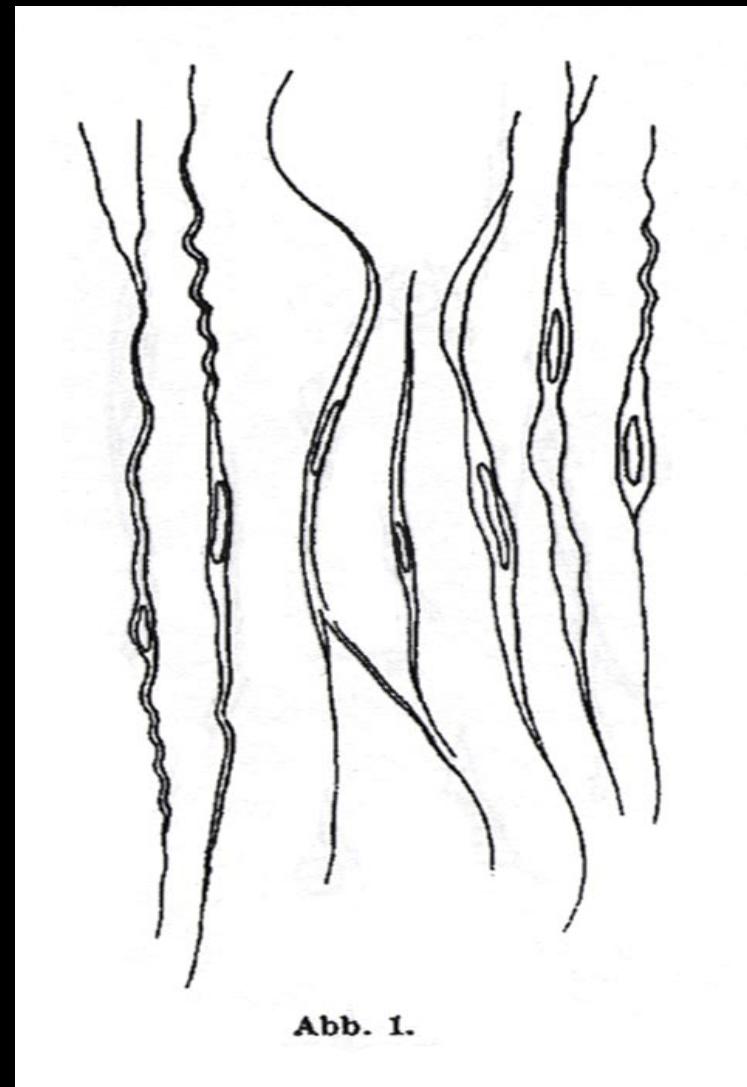
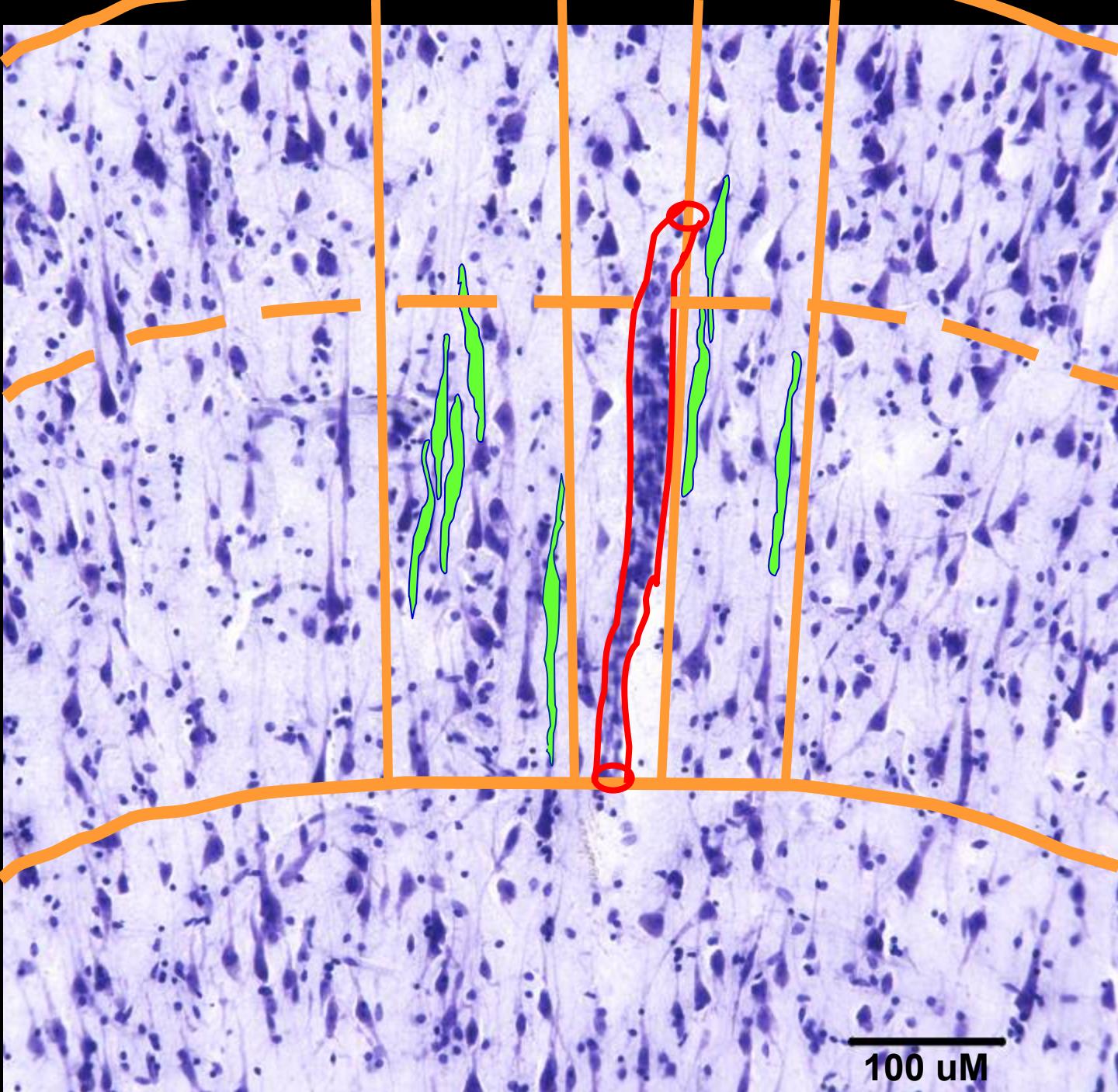


Abb. 1.

Nimchinsky PNAS 1999

**Layer Va**



**Layer VI**

**100 uM**

I

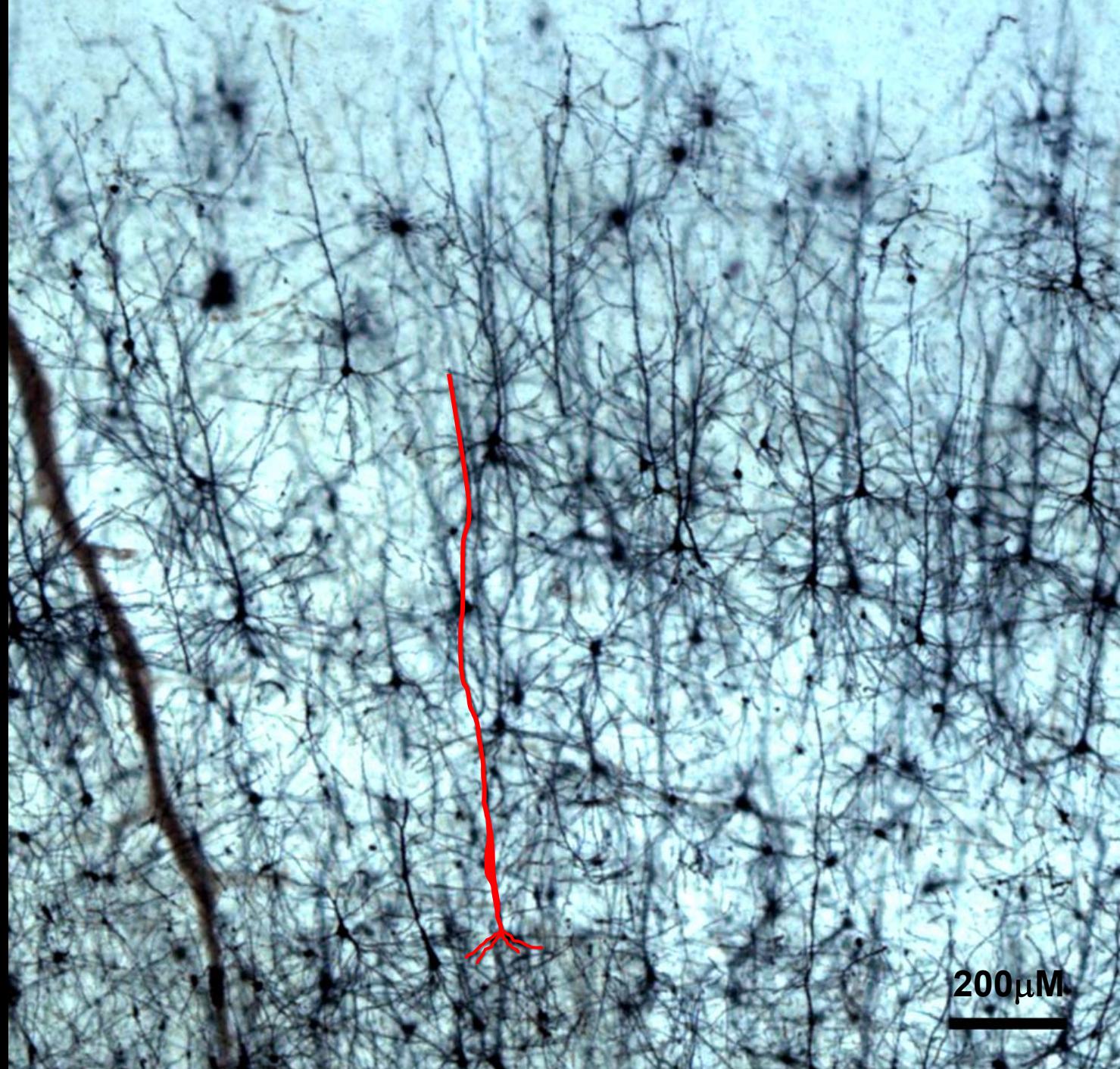
II

III

Va

Vb

VI



$200\mu M$

# VE<sup>N</sup>s

## Structure

- Simplified architecture
- Layer Vb, Fl>>ACC
- Columnar clusters parallel to small arterioles
- Project axons into WM, targets unknown
- R/L hemisphere = 1.3

## Neurochemistry

- Somata & prox dendrites express receptors:  
D3  
5HT1b/2b  
Vasopressin 1a

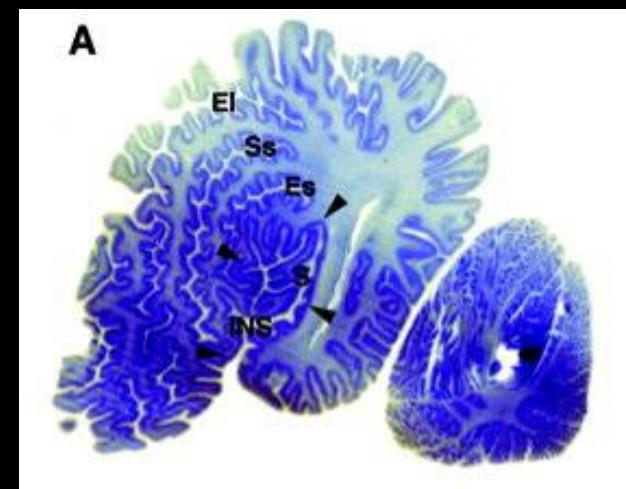
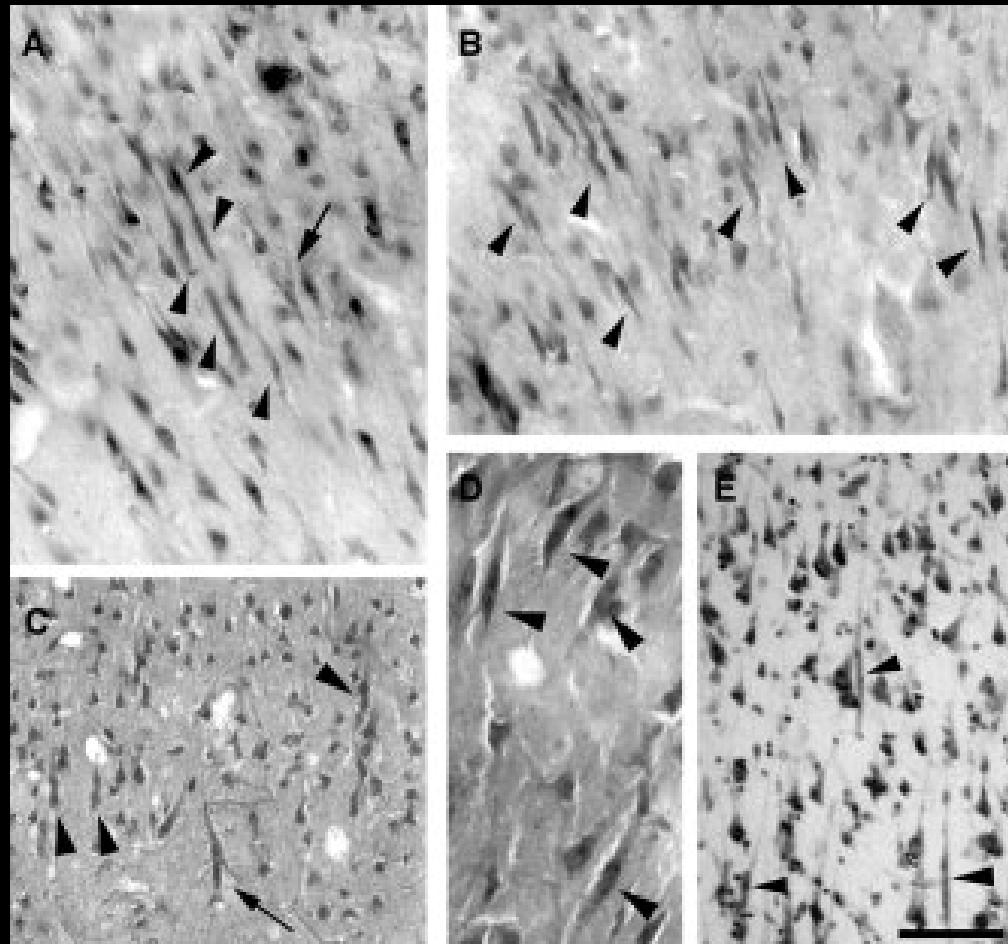
## Ontogeny

- Emerge late in gestation (34-38 wks)
- Peak total # = 8 mo-4 yrs
- Pruned to adult prevalence by 8-10 yrs

## Phylogeny

- Absent in monkeys and lesser apes
- Orangutan<Gorilla<Chimps
- Great apes<<<Human
- Whales

# What drove VEN specialization in primates?



# VENs: The key vulnerable neuron in bvFTD?

## bvFTD

Self-awareness  
Social cognition

Early ACC-FI injury

Asymmetric right-sided  
degeneration

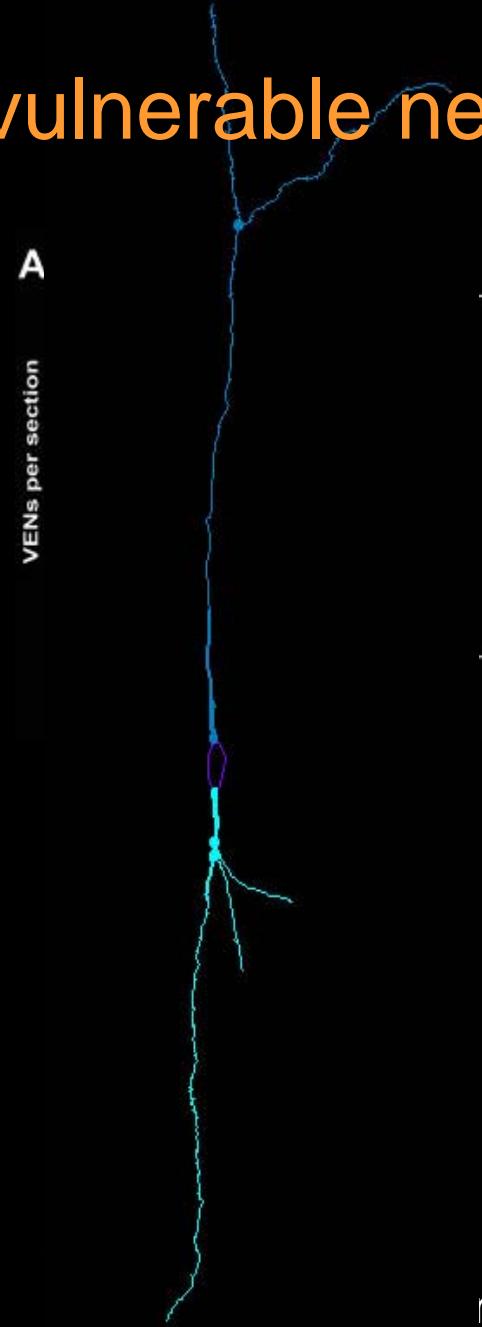
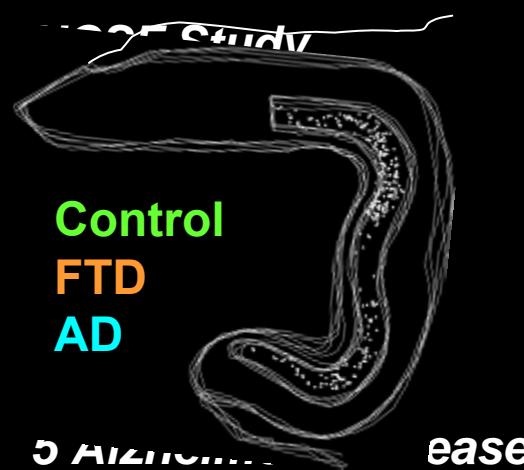
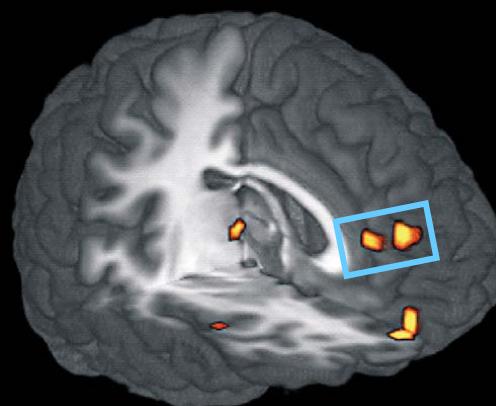
## VENs

Late-evolving  
Late-developing

Restricted to ACC and FI

30% more abundant on  
right

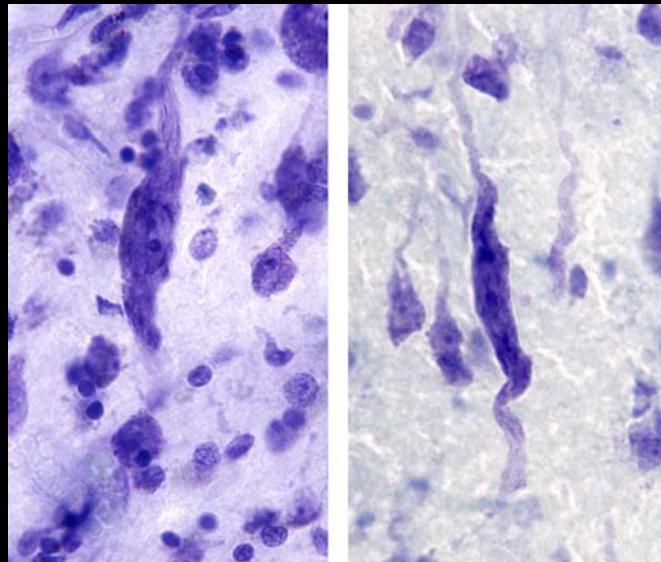
# VENs: The key vulnerable neuron in bvFTD?



n et al, Ann Neurol, 2006

# FTLD

Tau immunohistochemistry

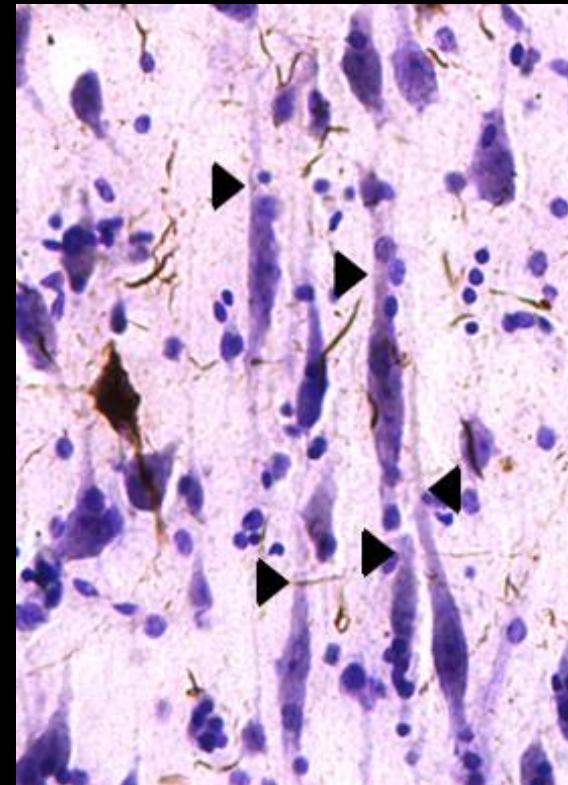


Pick's

FTLD-U

0.4% (0.1-0.7%)

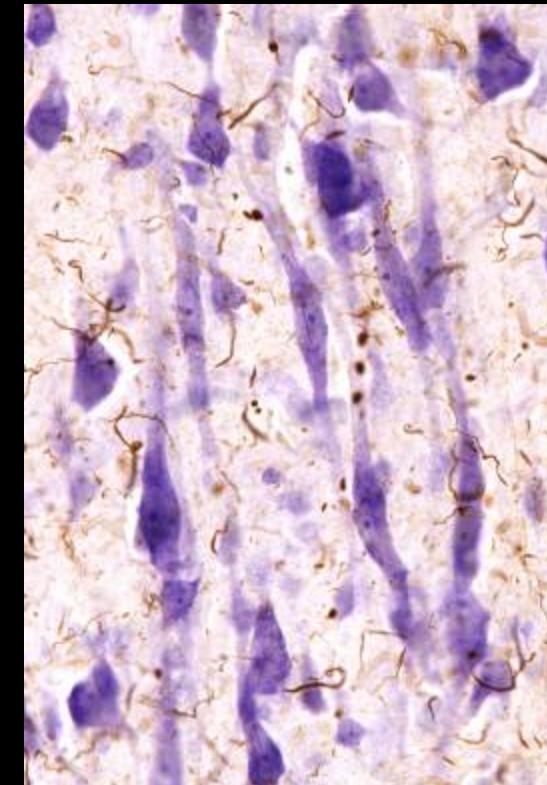
*N* = 7



AD

1.5% (0.7-2.2%)

*N* = 5

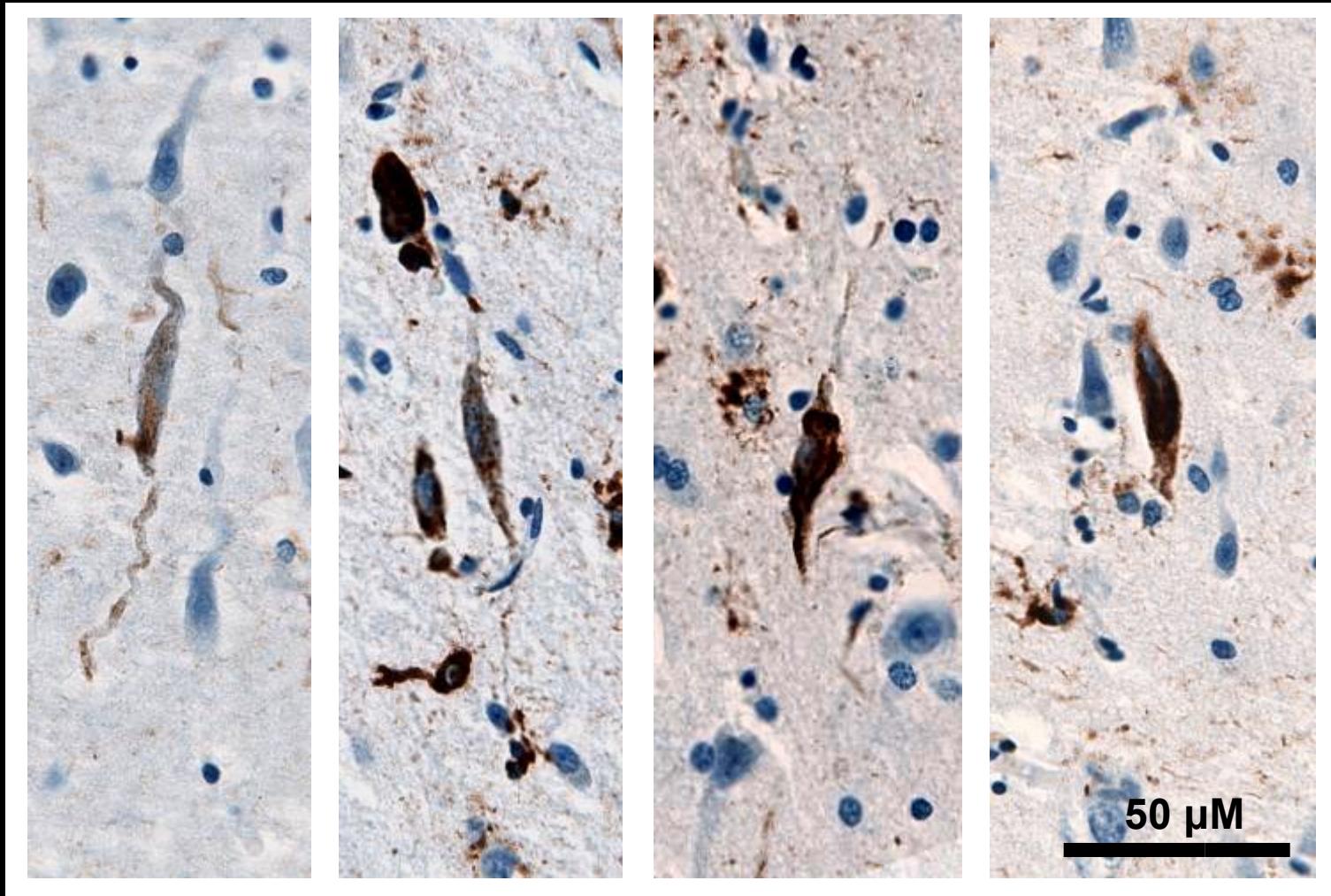


CBD

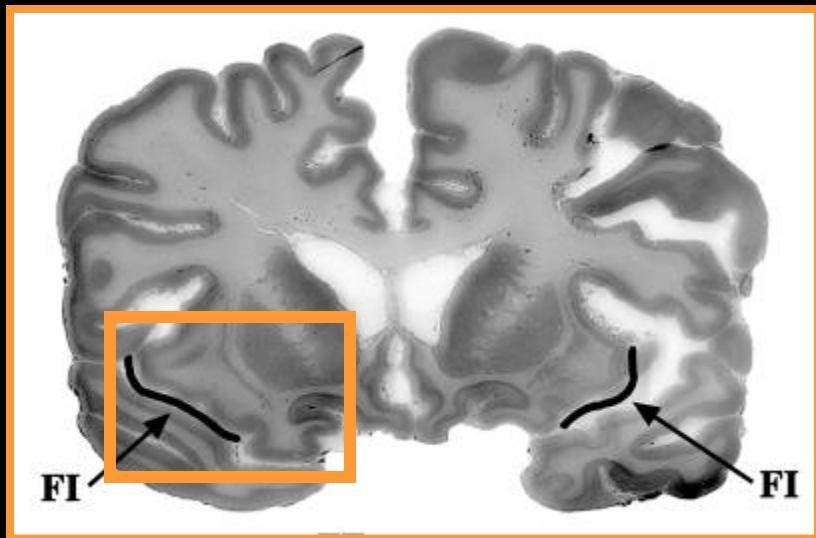
1.4%

*N* = 1

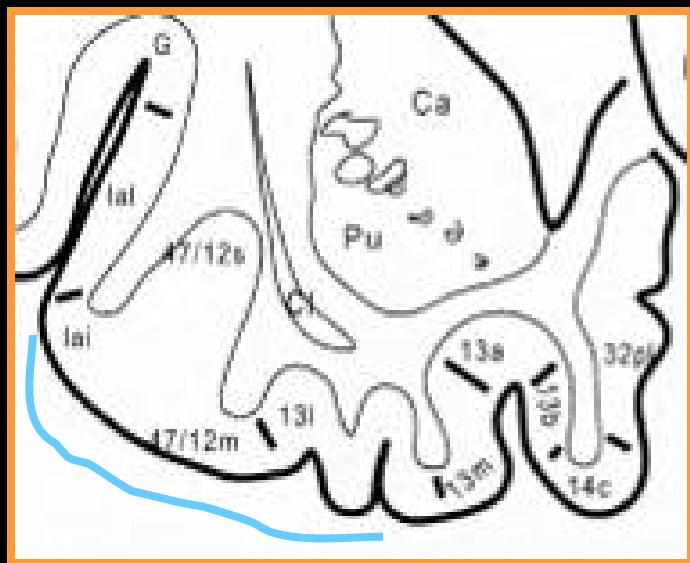
# VEN tauopathy: Pick's disease



Tau immunohistochemistry (CP-13 antibody)



## Healthy human VENs in FI



Ongur & Price, JCN 2003

# VEN Hypothesis: Summary

1. In bvFTD, VENs show early selective vulnerability, akin to the early loss of ERC Layer 2 projection neurons in AD
2. Early VEN injury incites a degenerative cascade throughout an anterior paralimbic network rooted in the ACC and FI
3. VENs may provide the ACC-FI network with new information processing capacities in humans that are lost in early FTD

# Next steps

- VEN neurochemistry
- VEN connectivity
- Early VEN pathogenesis in FTD
- VEN physiology
- VEN gene and protein expression profiles

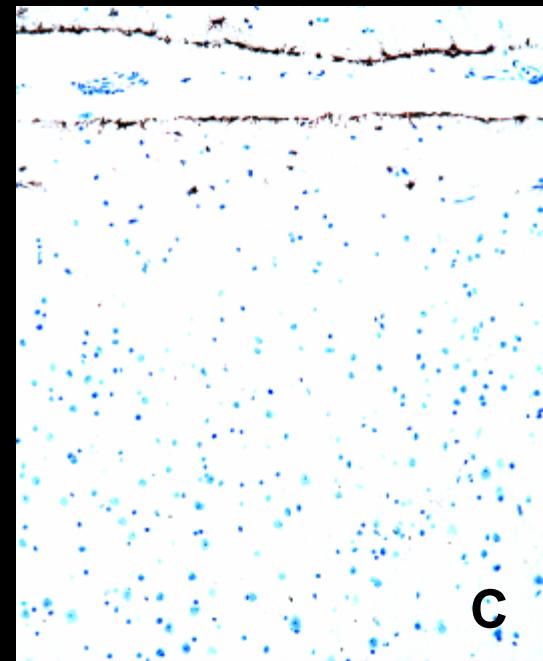
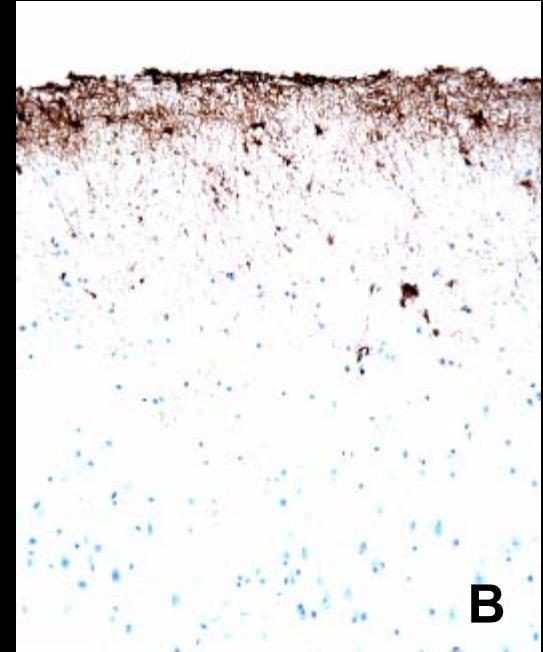
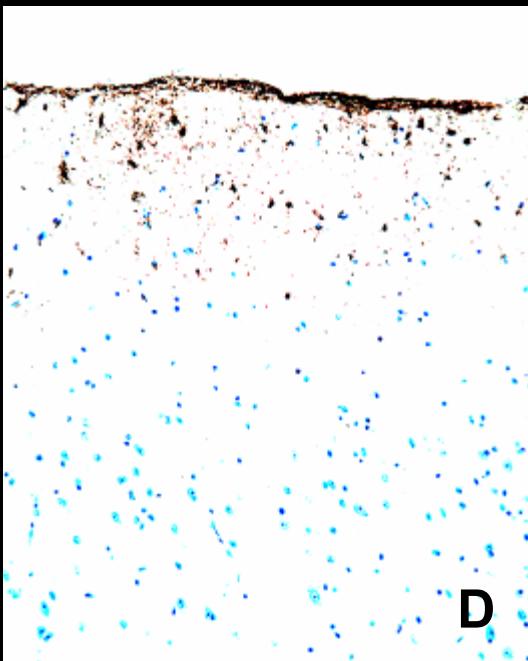
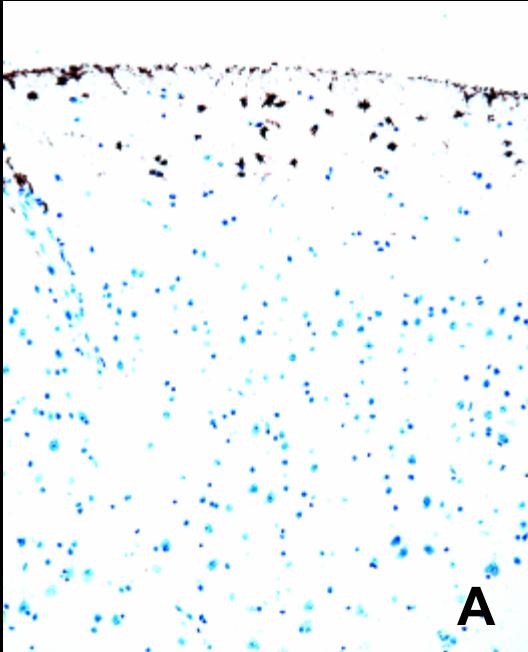
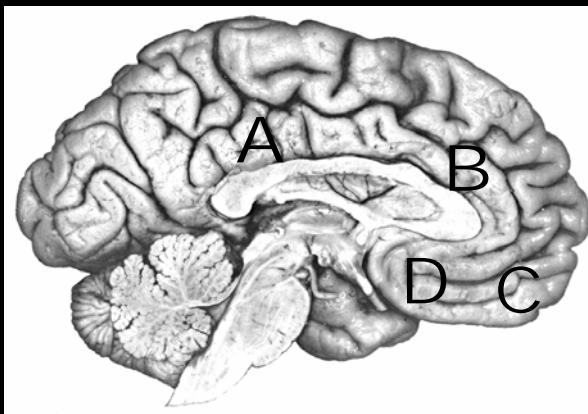
# Next steps

- ✓ VEN neurochemistry
- ✓ VEN connectivity
- ✓ Early VEN pathogenesis in bvFTD

---
- VEN physiology
- ✓ VEN gene and protein expression profiles

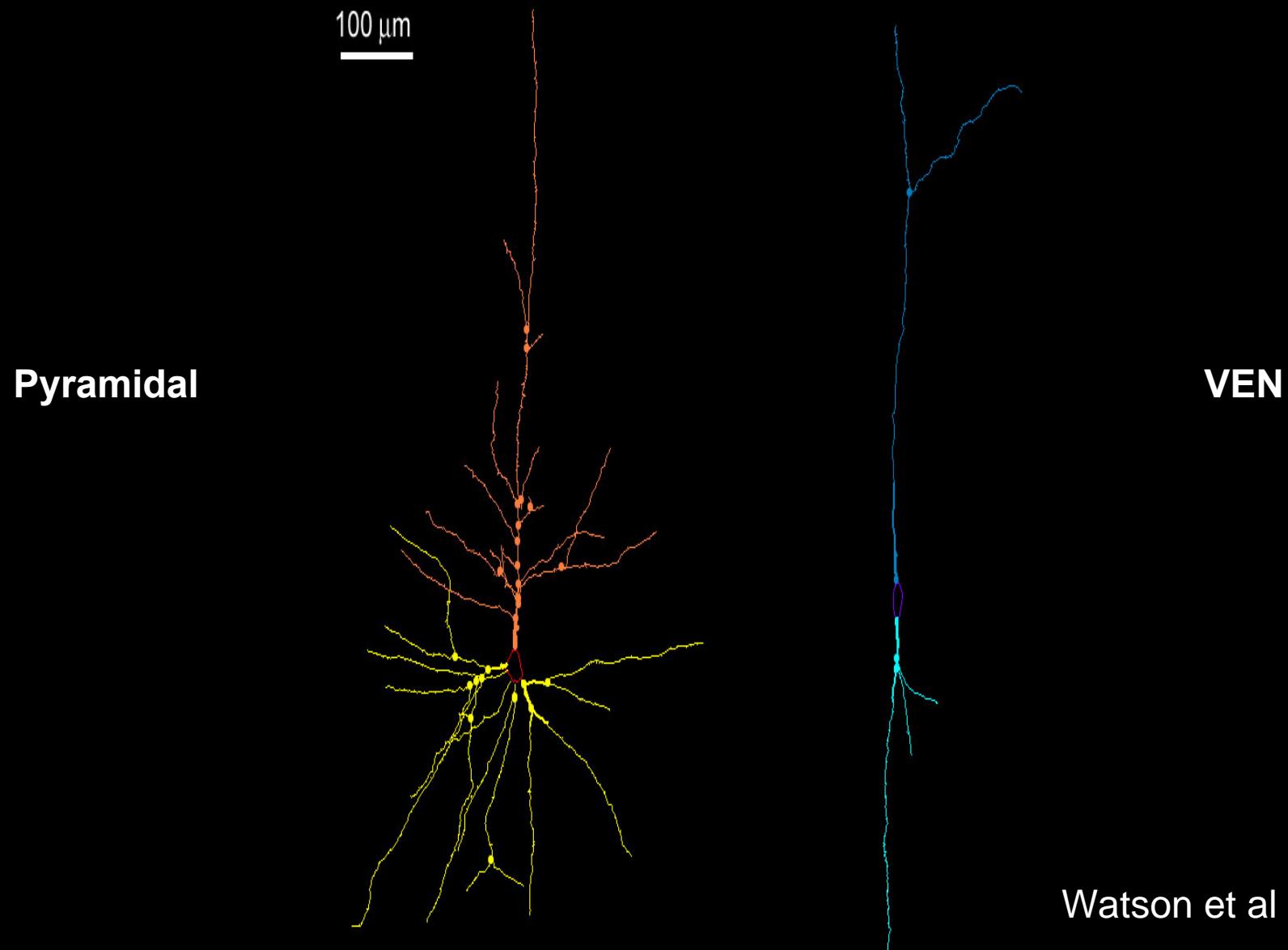
48 y.o. man w/  
familial FTD-MND

CDR = 0



GFAP

# Normal ACC/FI neuronal morphology

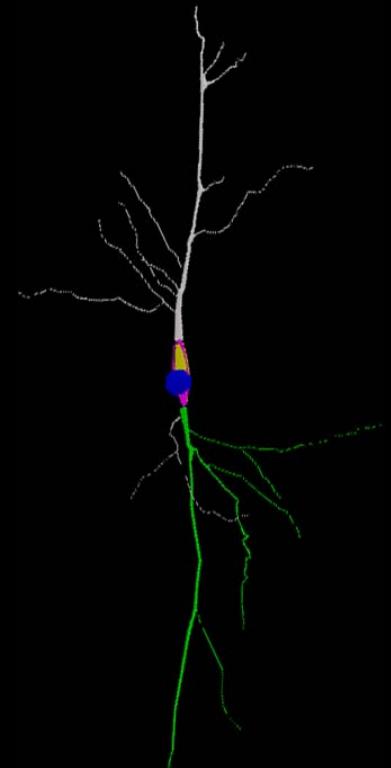


# Early VEN pathogenesis?

Normal

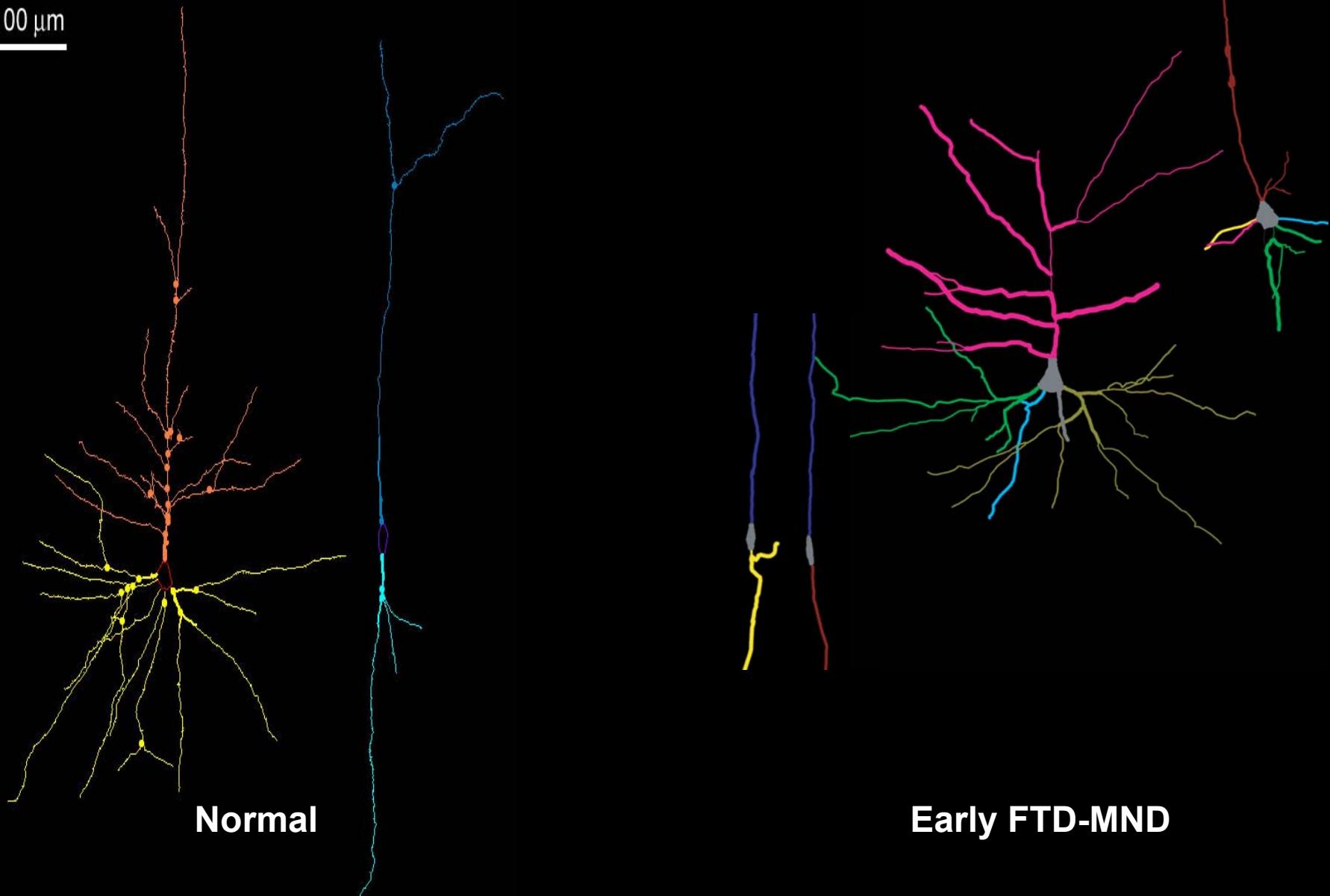


Early FTD-MND



# Early VEN pathogenesis?

100  $\mu$ m



# Alzheimer's disease

Episodic  
Memory

■ Known  
■ Hypothesized

ERC-DG-CA3-  
CA1-subic-FF-PCC

?

?

ERC Layer II  
pyramidal

?

A $\beta$ 42, tau

?

RX

Presenilins  
ApoE, APP

# FTD

■ Known  
■ Hypothesized

Behavior?

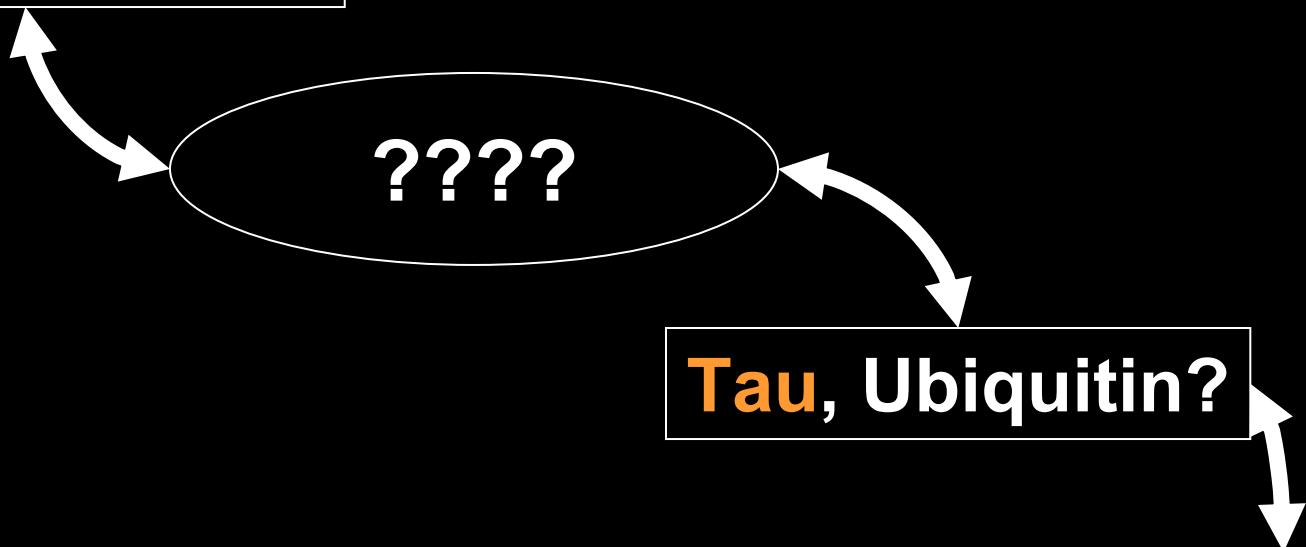
Frontotemporal?

????

Tau, Ubiquitin?

**MAPT**  
??????

1999



FTD

Social cognition  
Self-representation  
Response inhibition

■ Known  
■ Hypothesized

ACC-FI network

????

Tau, Ubiquitin?

**MAPT**  
?????

1999 → 2002

FTD

Social cognition  
Self-representation  
Response inhibition

Known  
Hypothesized

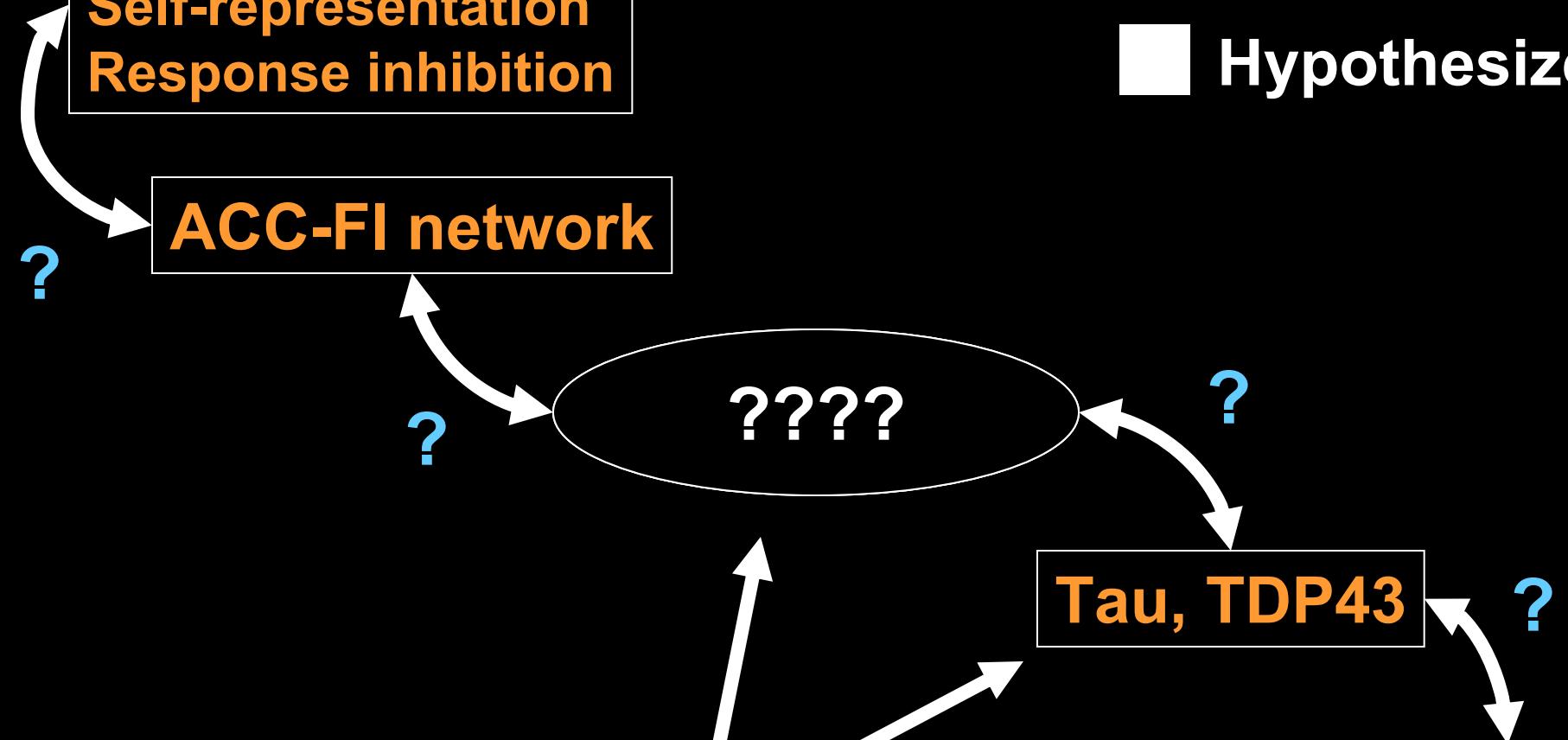
ACC-FI network

????

Tau, TDP43

*MAPT*  
*PGRN*

1999 → 2002 → 2006



# Acknowledgments

## Seeley Lab

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Carolina Court  
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Eric Huang  
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Mamta Sattavat  
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**NIH Loan Repayment Program**  
**UCSF patients and families**