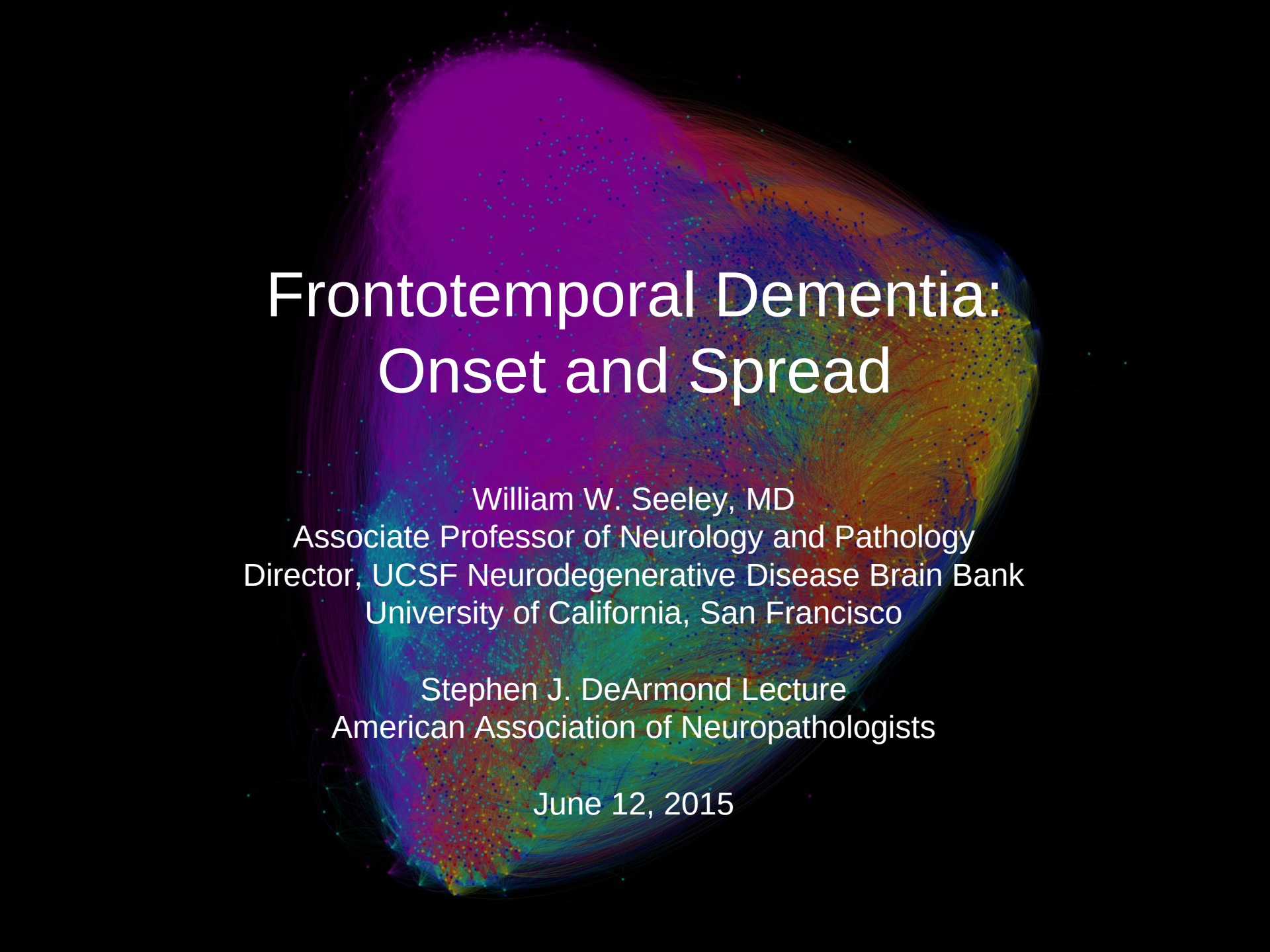
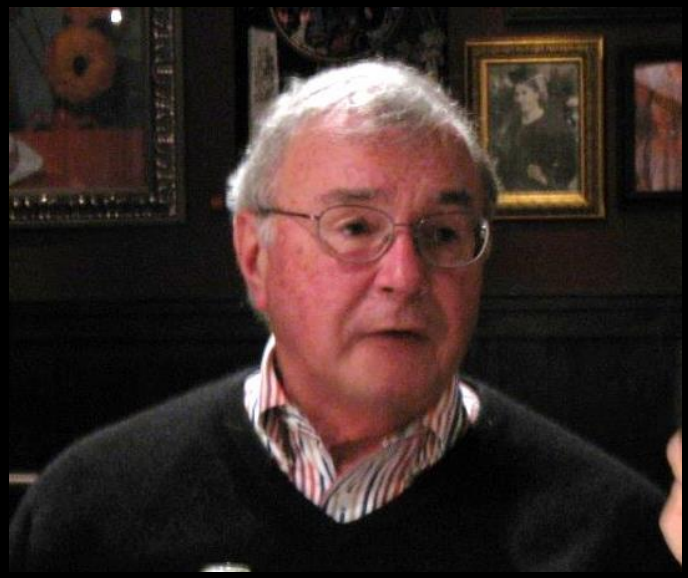


Frontotemporal Dementia: Onset and Spread

William W. Seeley, MD
Associate Professor of Neurology and Pathology
Director, UCSF Neurodegenerative Disease Brain Bank
University of California, San Francisco

Stephen J. DeArmond Lecture
American Association of Neuropathologists

June 12, 2015

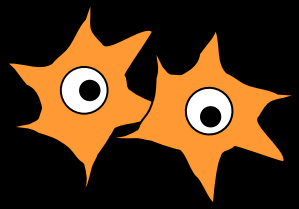


Overview

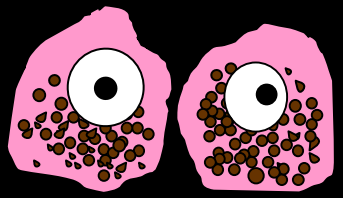
- Conceptual framework: onset and spread
- FTD terminology and background
- bvFTD onset: nodes, network, and neurons
  - Brief review of published studies
  - Unpublished data: earliest stage bvFTD neuropathological findings available to date
- C9ORF72
  - Relationship to sporadic bvFTD
  - Unpublished data on presymptomatic phase and timing/impact of expansion-specific pathology
- Translation/future

Selective Vulnerability in Neurodegenerative Diseases

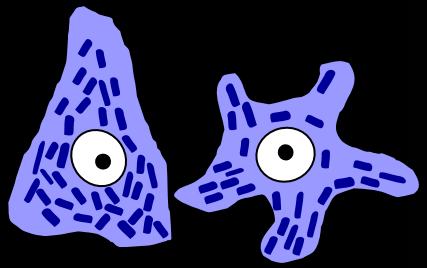
Alzheimer's Disease



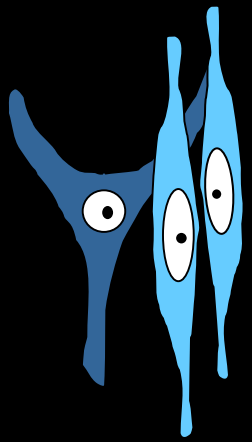
Parkinson's Disease

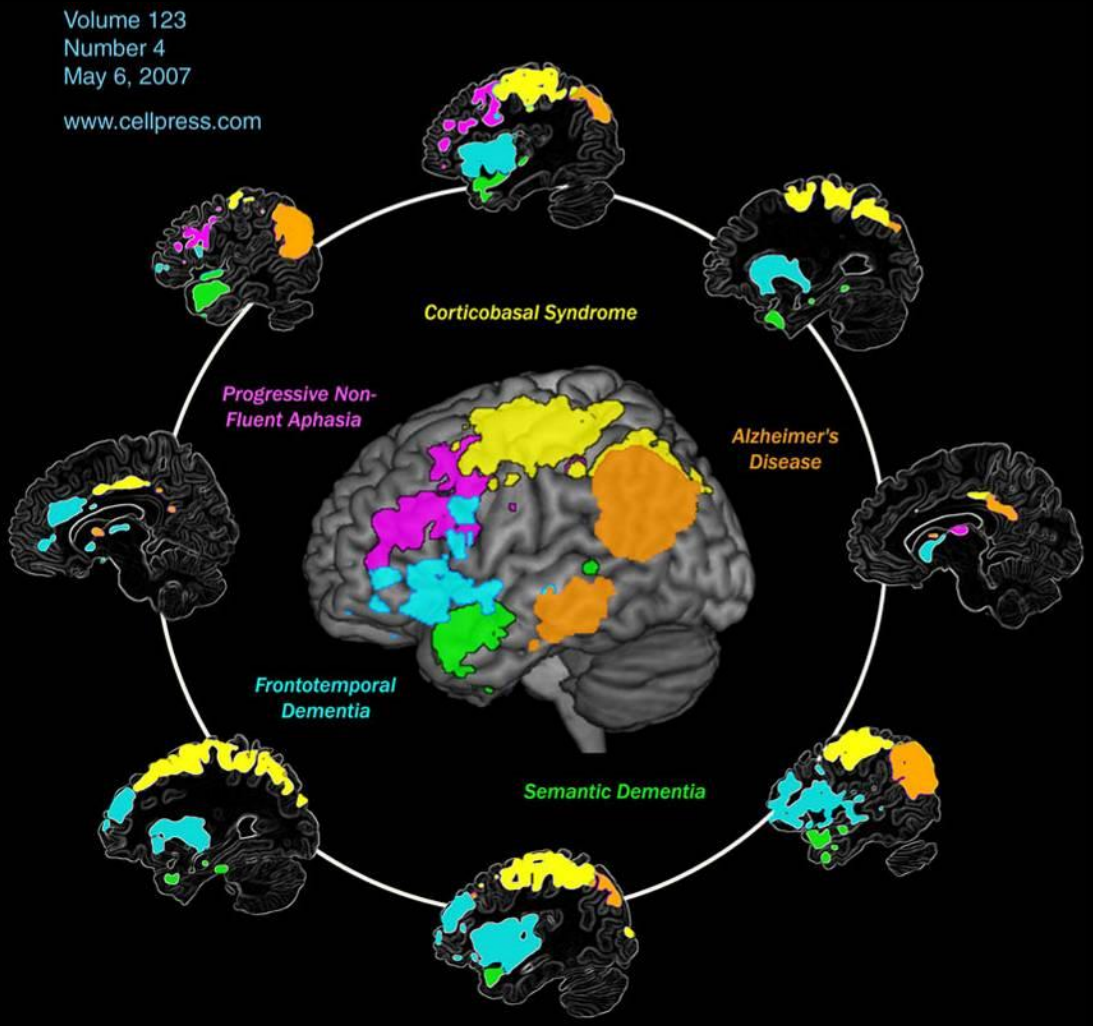


Amyotrophic Lateral Sclerosis



Behavioral Variant Frontotemporal Dementia





Neurodegeneration Targets Intrinsic Brain Networks

Connectomic prediction of regional vulnerability

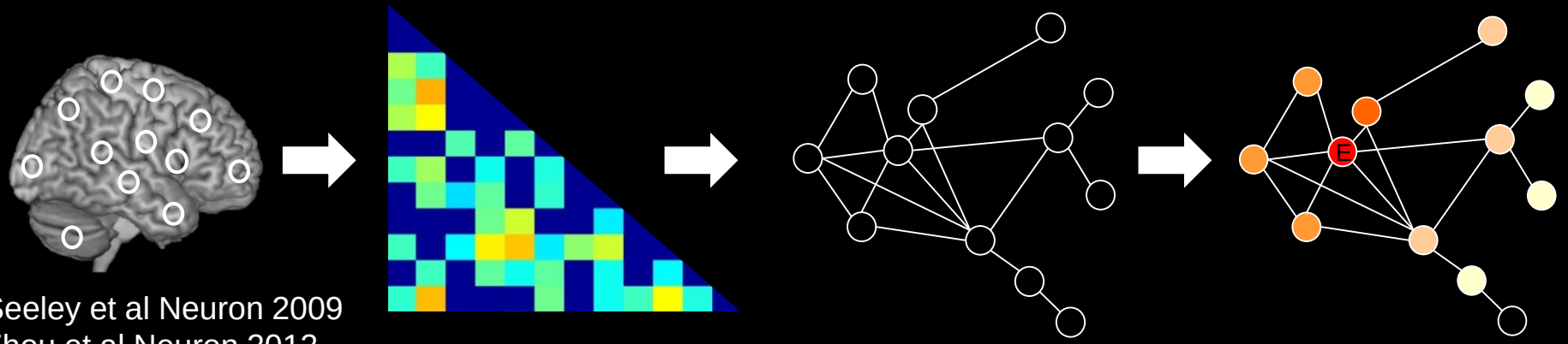
Intrinsic functional connectivity

Brain regions of interest

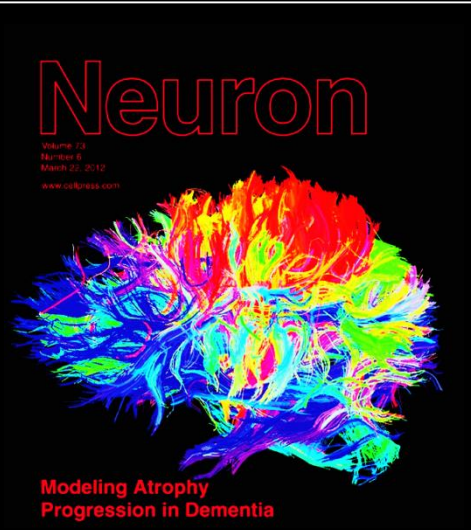
Healthy correlation matrix

Healthy network graph

Spatial patterning of disease

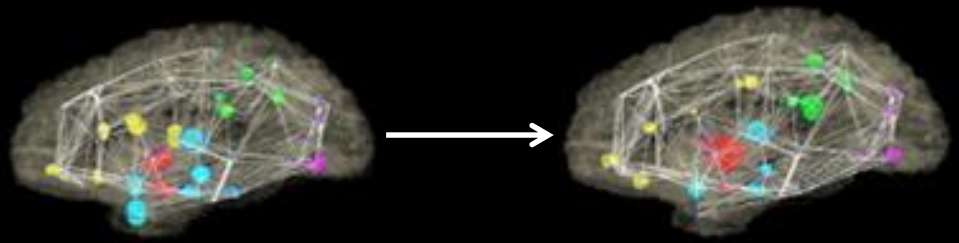


Seeley et al Neuron 2009
Zhou et al Neuron 2012



Structural connectivity

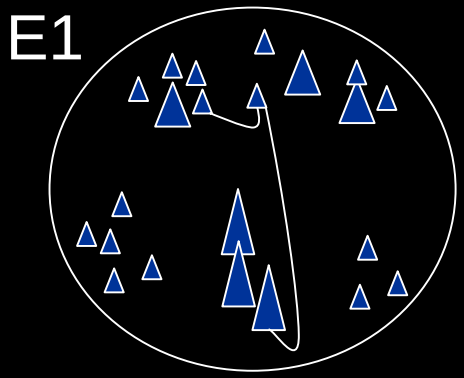
Raj et al Neuron 2012

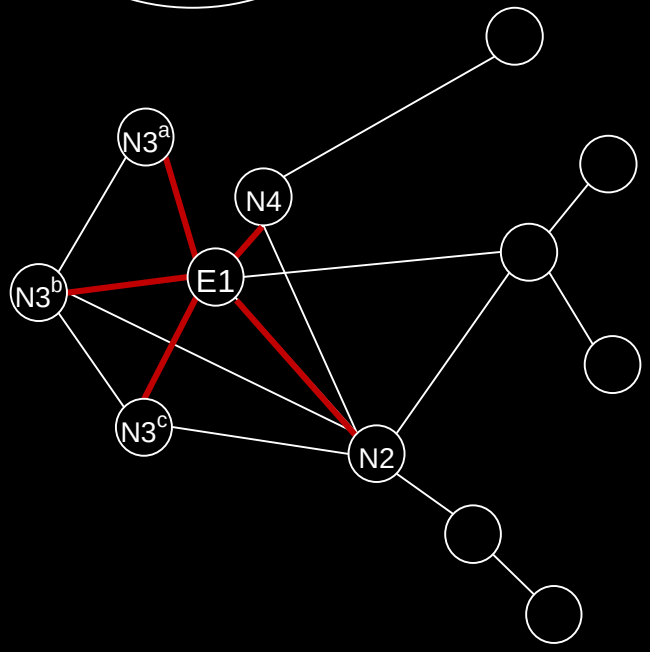


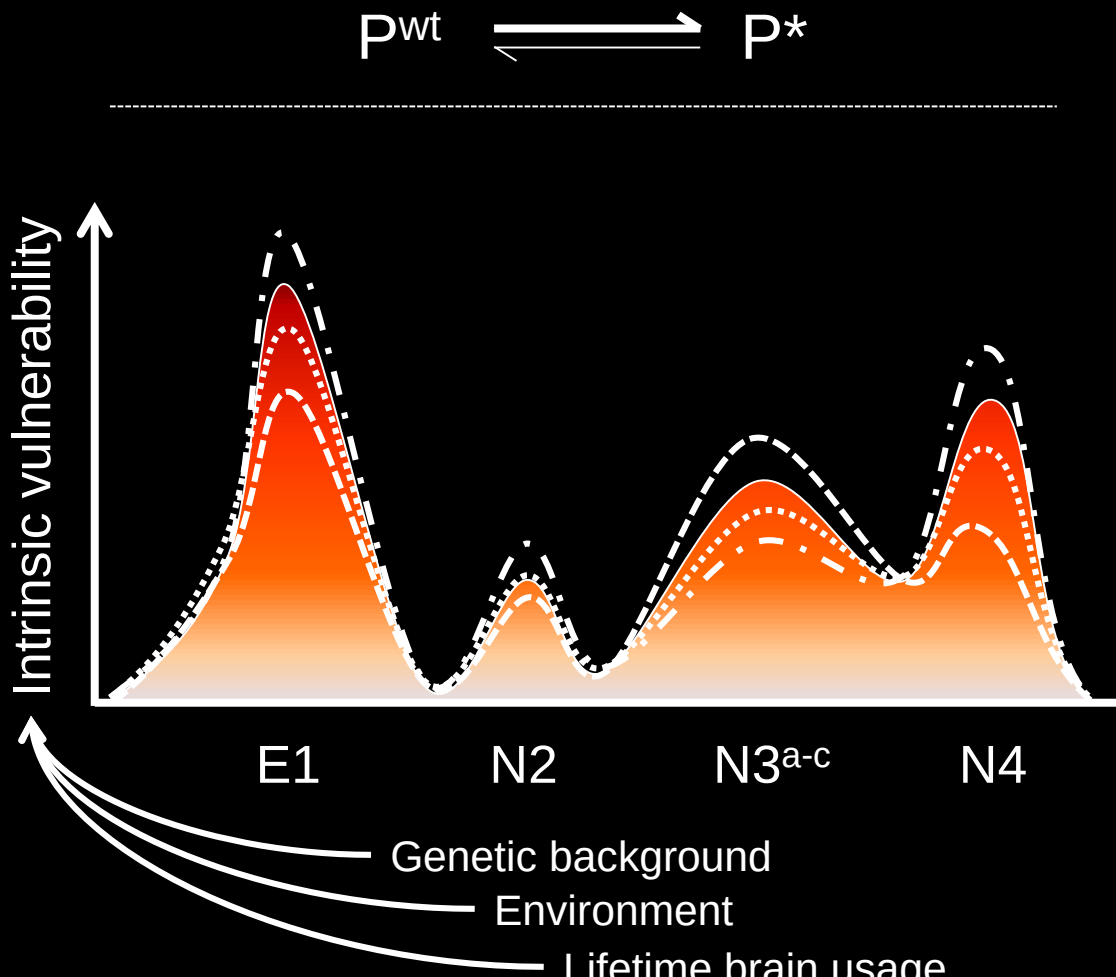
Health

Disease

Generic working model: onset and spread







FTD Background

Frontotemporal dementia

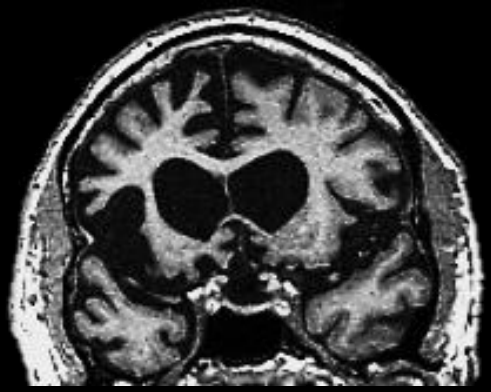
Behavioral variant (bvFTD)

Primary Progressive Aphasia (PPA)

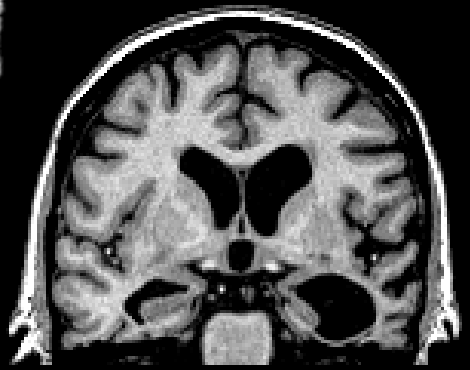
FTD-MND

Semantic variant (svPPA)

Nonfluent/agrammatic variant (nfvPPA)

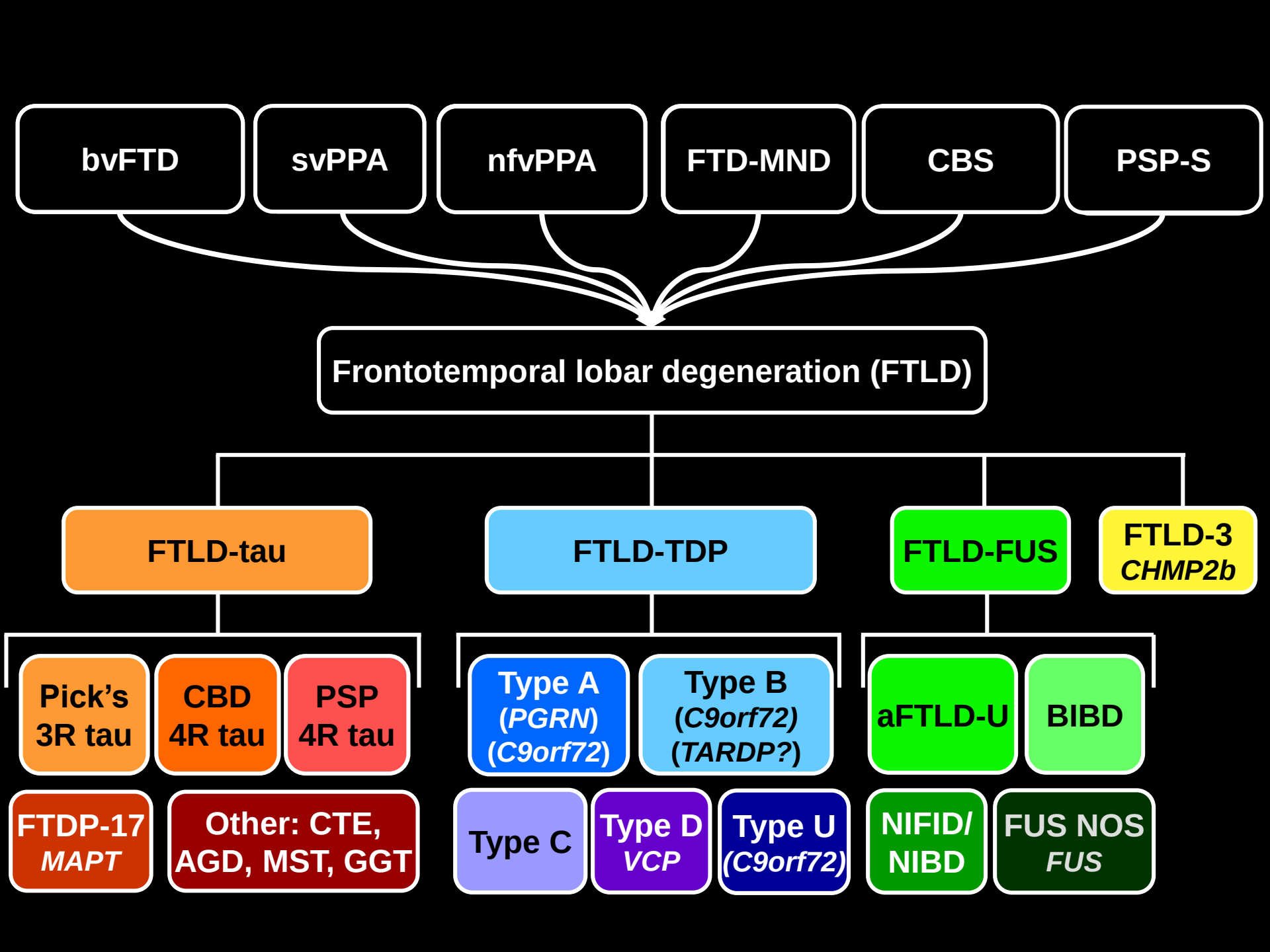


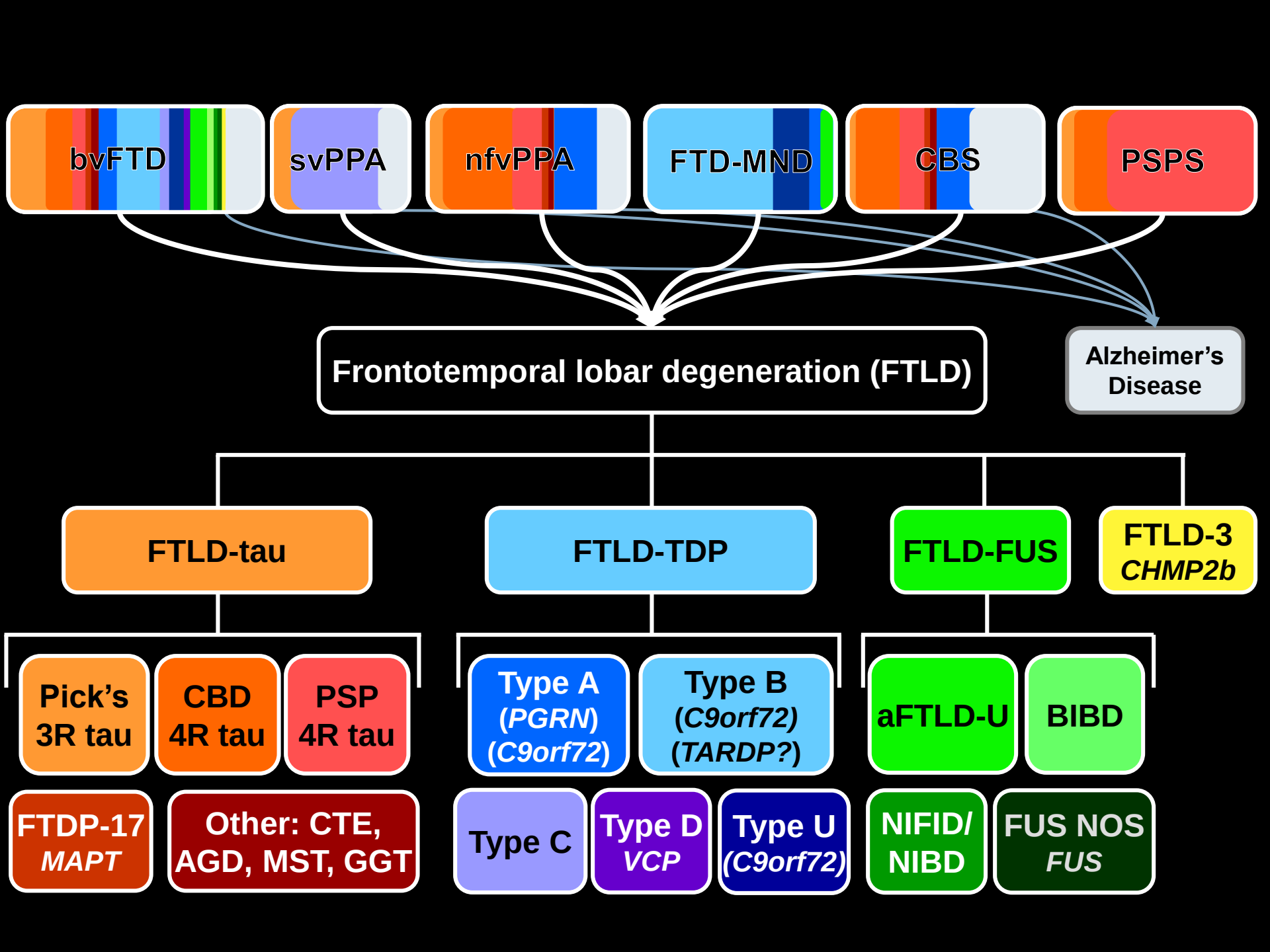
R L

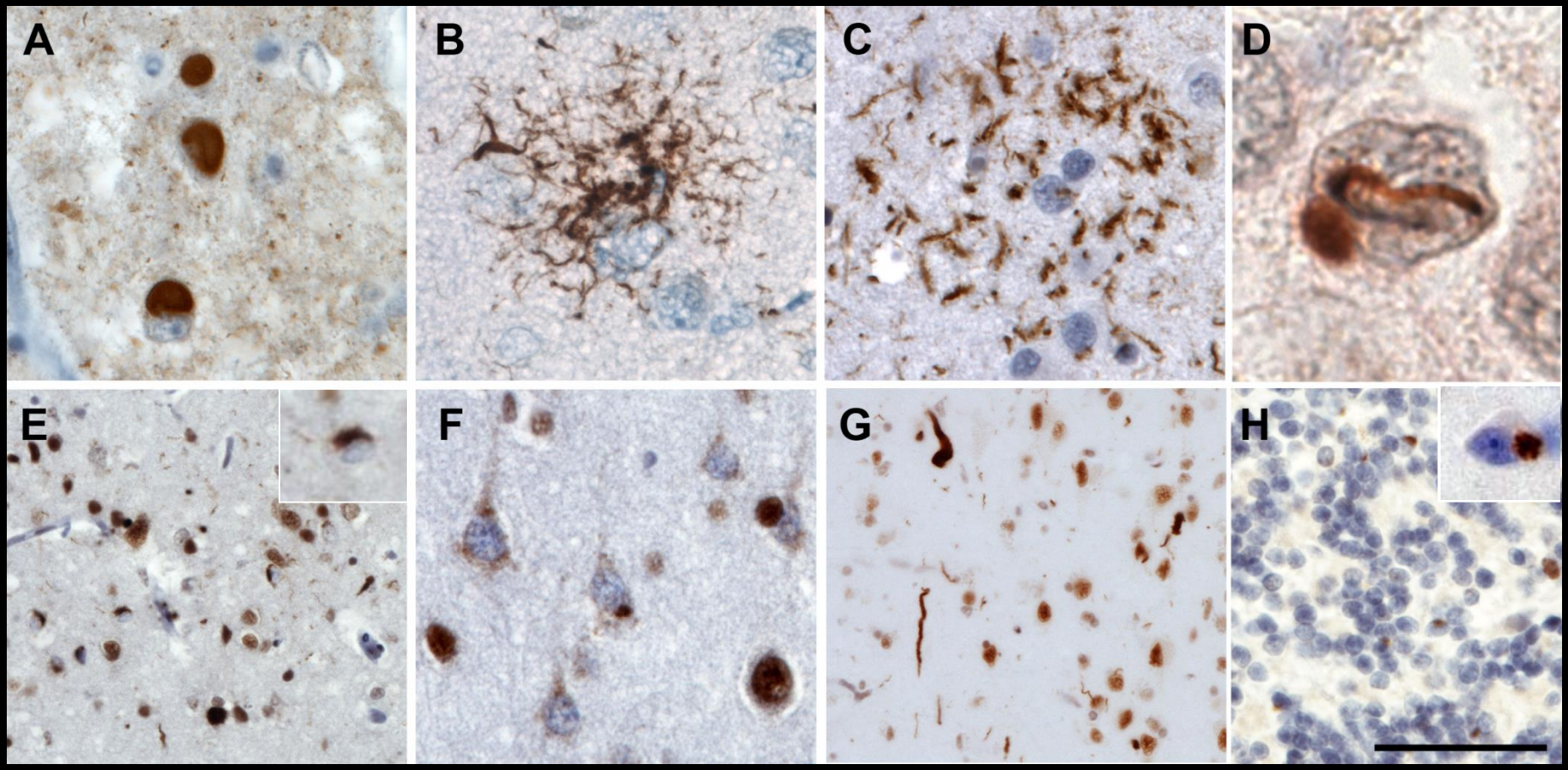


R L

R L


bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSP-S
Frontotemporal lobar degeneration (FTLD)
FTLD-tau
FTLD-TDP
FTLD-FUS
FTLD-3
CHMP2b
Pick's
3R tau
CBD
4R tau
PSP
4R tau
Type A
(PGRN)
(C9orf72)
Type B
(C9orf72)
(TARDP?)
aFTLD-U
BIBD
FTDP-17
MAPT
Other: CTE,
AGD, MST, GGT
Type C
Type D
VCP
Type U
(C9orf72)
NIFID/
NIBD
FUS NOS
FUS


bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSPS
Frontotemporal lobar degeneration (FTLD)
Alzheimer's Disease
FTLD-tau
FTLD-TDP
FTLD-FUS
FTLD-3 CHMP2b
Pick's 3R tau
CBD 4R tau
PSP 4R tau
Type A (PGRN) (C9orf72)
Type B (C9orf72) (TARDP?)
aFTLD-U
BIBD
FTDP-17 MAPT
Other: CTE, AGD, MST, GGT
Type C
Type D VCP
Type U (C9orf72)
NIFID/ NIBD
FUS NOS FUS


FTLD-tau
FTLD-FUS
Pick's
PSP
CBD
aFTLD-U
A
B
C
D
E
F
G
H
TDP-A
TDP-B
TDP-C
DPR
(C9ORF72)
FTLD-TDP

What is bvFTD?

bvFTD: a syndrome, not a disease

International consensus clinical research criteria for bvFTD

Rascovsky et al Brain 2012

II. Possible bvFTD

Three of the following:

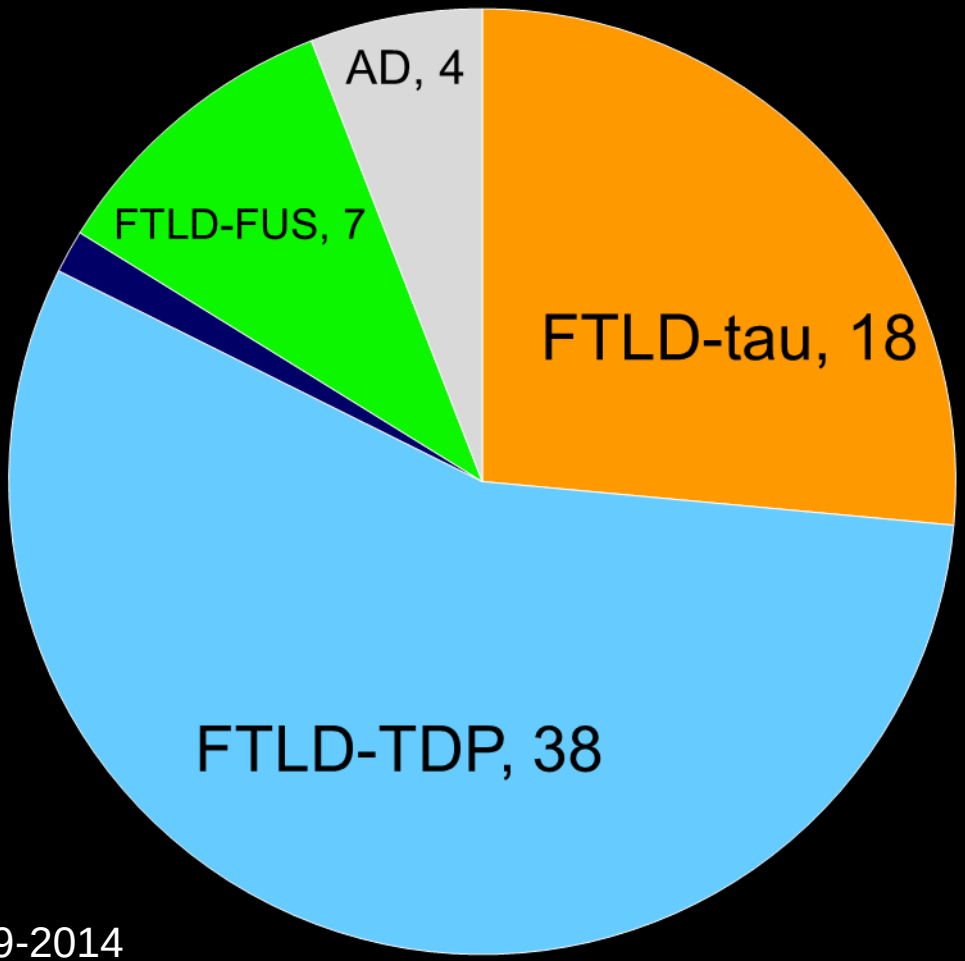
A. Early behavioral disinhibition
B. Early apathy or inertia
C. Early loss of sympathy or empathy
D. Early perseverative, stereotyped or compulsive/ritualistic behavior
E. Hyperorality and dietary changes
F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions

III. Probable bvFTD

All of the following symptoms:

A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report, CDR or FAQ)
C. Imaging results consistent with bvFTD:
    C.1. Frontal and/or anterior temporal atrophy on MRI or CT or
    C.2. Frontal and/or anterior temporal deficits on PET or SPECT

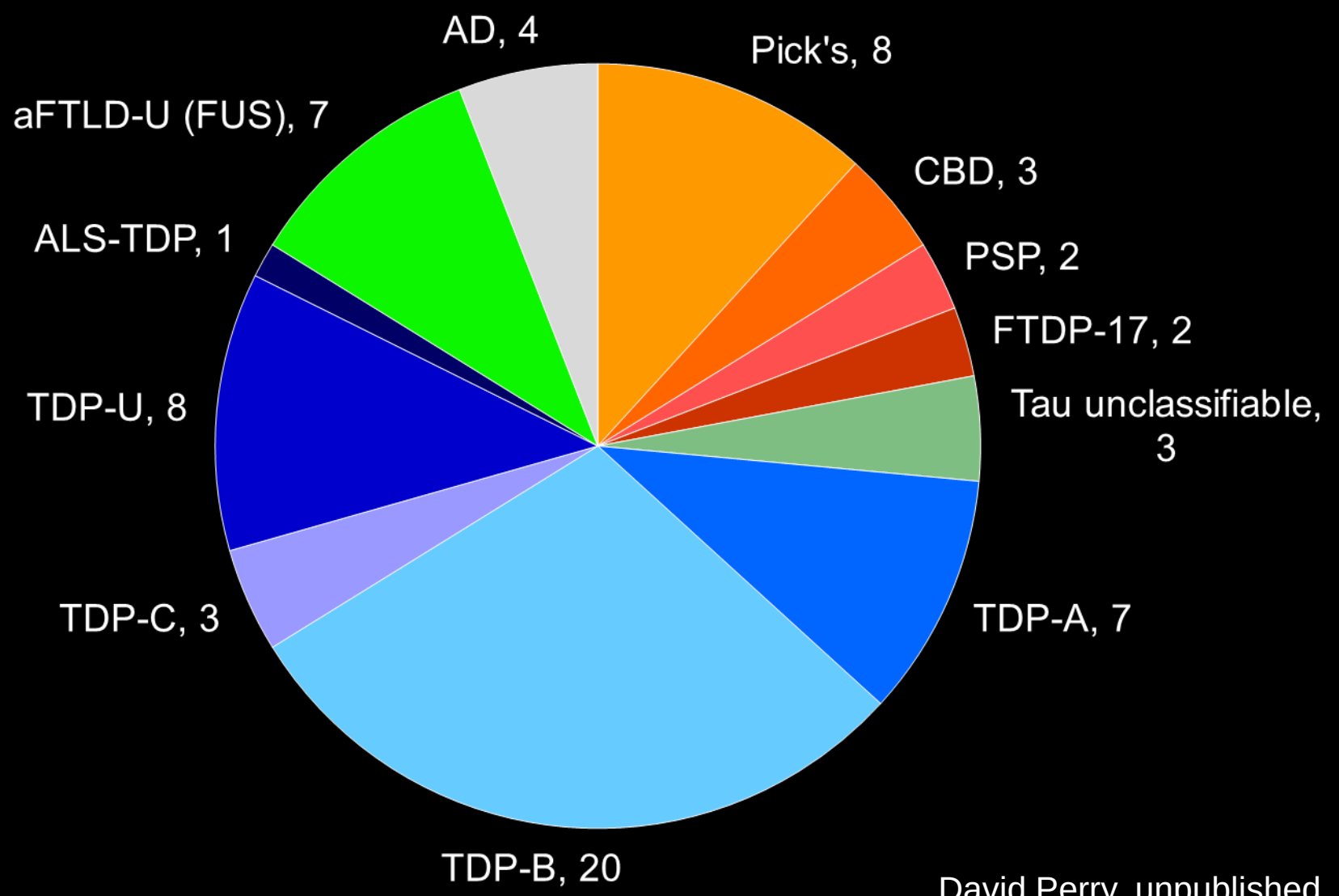
bvFTD, high confidence, n = 68



Consecutive series, 1999-2014
All clinically assessed at the UCSF MAC
Autopsies performed at UCSF, PENN or other sites

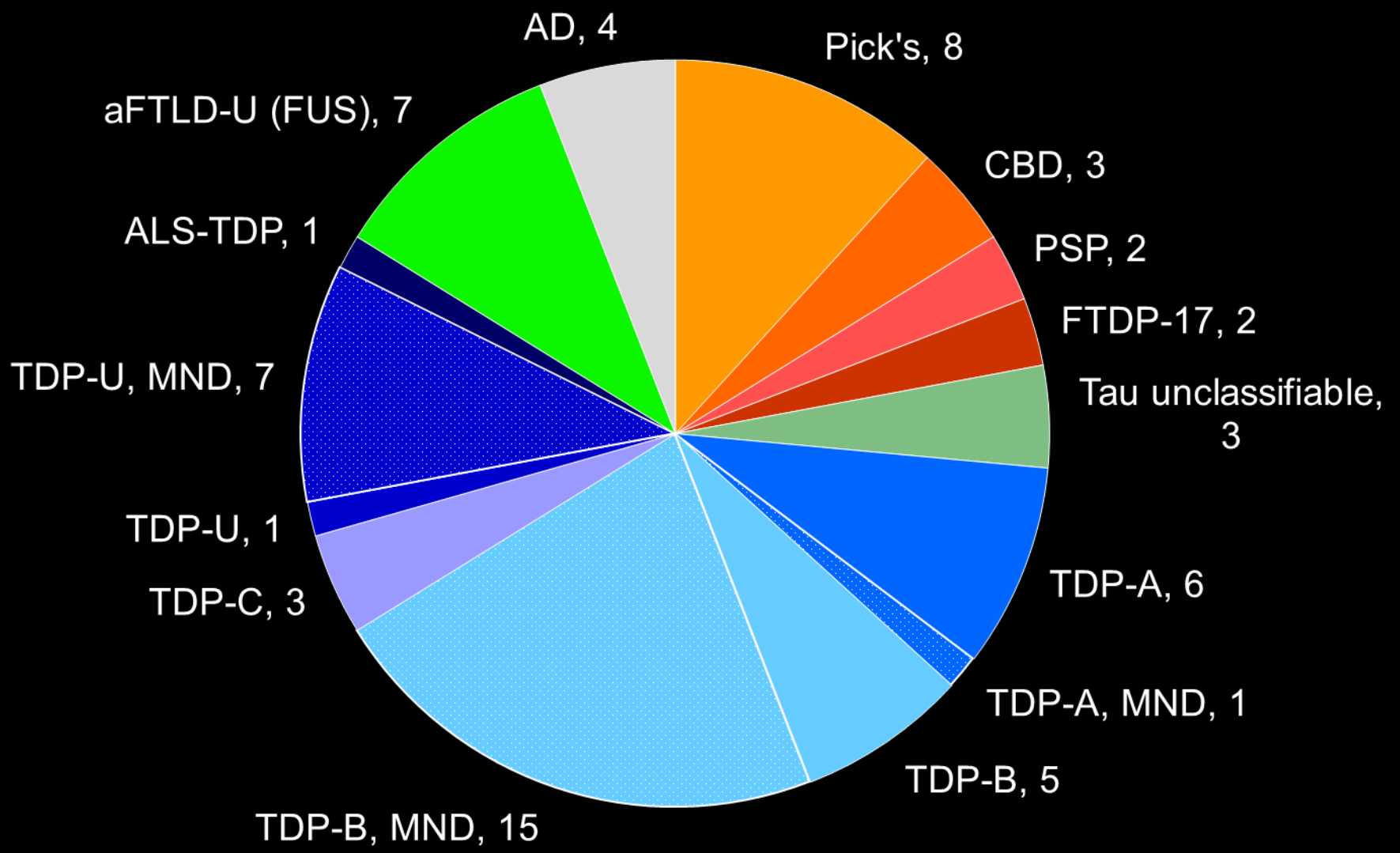
David Perry, unpublished

bvFTD, high confidence, n = 68



David Perry, unpublished

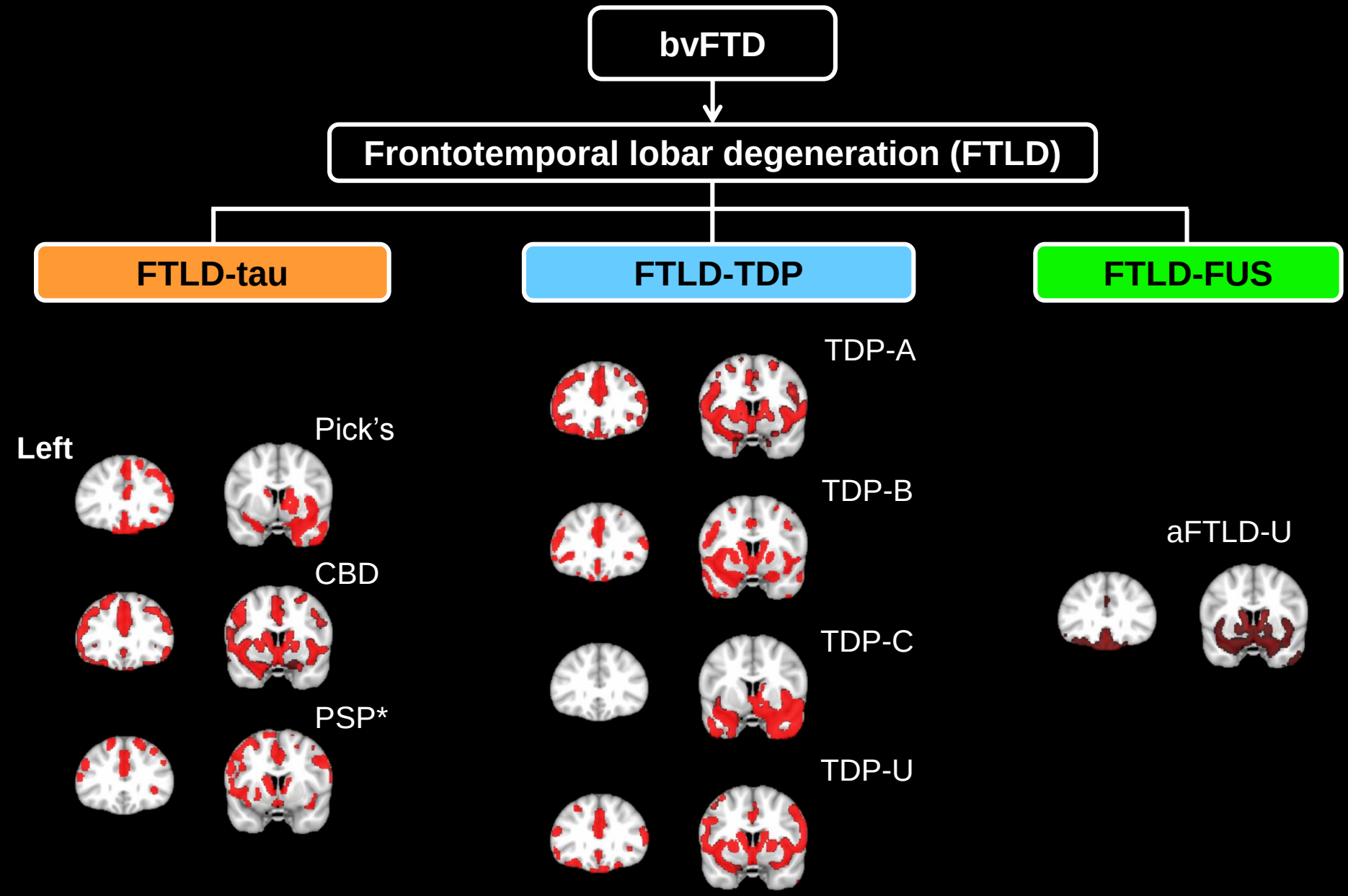
bvFTD, high confidence, n = 68



David Perry, unpublished

Syndromic differential diagnosis

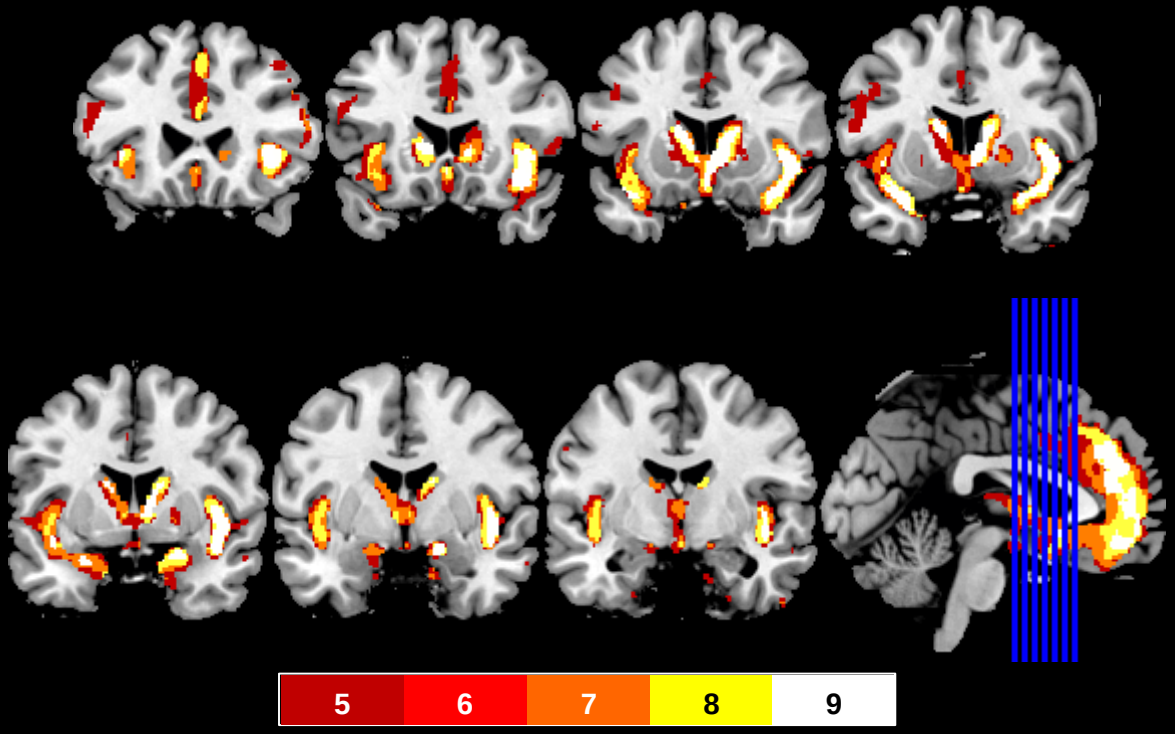
bvFTD	anemia
TDP-B	iron deficiency
Pick's	chronic disease
TDP-A	Marrow aplasia
CBD	hemolysis
TDP-U	B12 deficiency
aFTLD-U	lead poisoning
PSP	sickle cell
TDP-C	thalassemia
AD	acanthocytosis


bvFTD
Frontotemporal lobar degeneration (FTLD)
FTLD-tau
FTLD-TDP
FTLD-FUS
Left
Pick's
CBD
PSP*
TDP-A
TDP-B
TDP-C
TDP-U
aFTLD-U
VBM, $p_{FWE} < 0.05$
David Perry, unpublished

bvFTD

Frontotemporal lobar degeneration (FTLD)

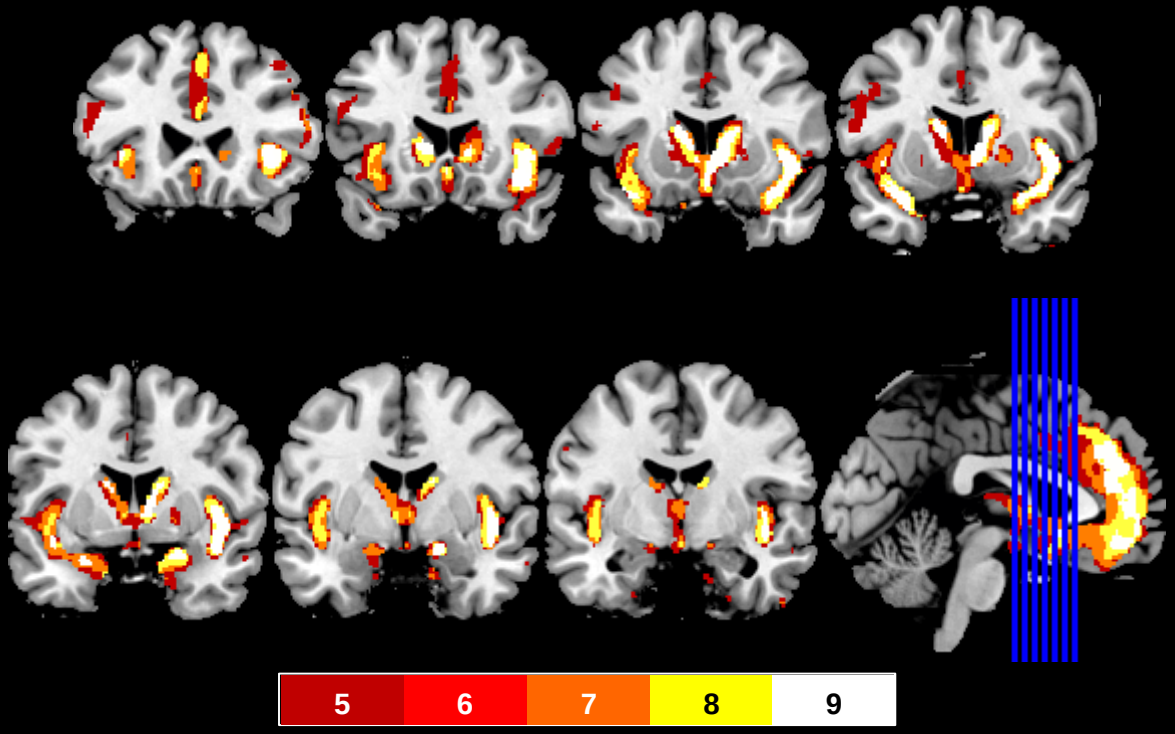
FTLD-tau | FTLD-TDP | FTLD-FUS



Overlap: # subtypes

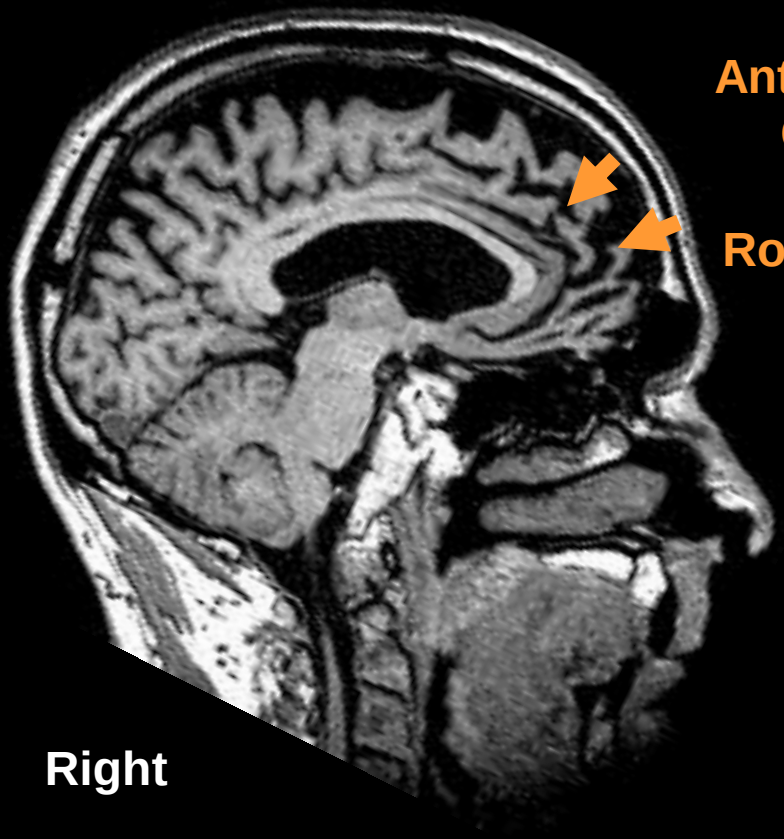
David Perry, unpublished

“behavioral variant cinguloinsular dementia”



Overlap: # subtypes

David Perry, unpublished



Right

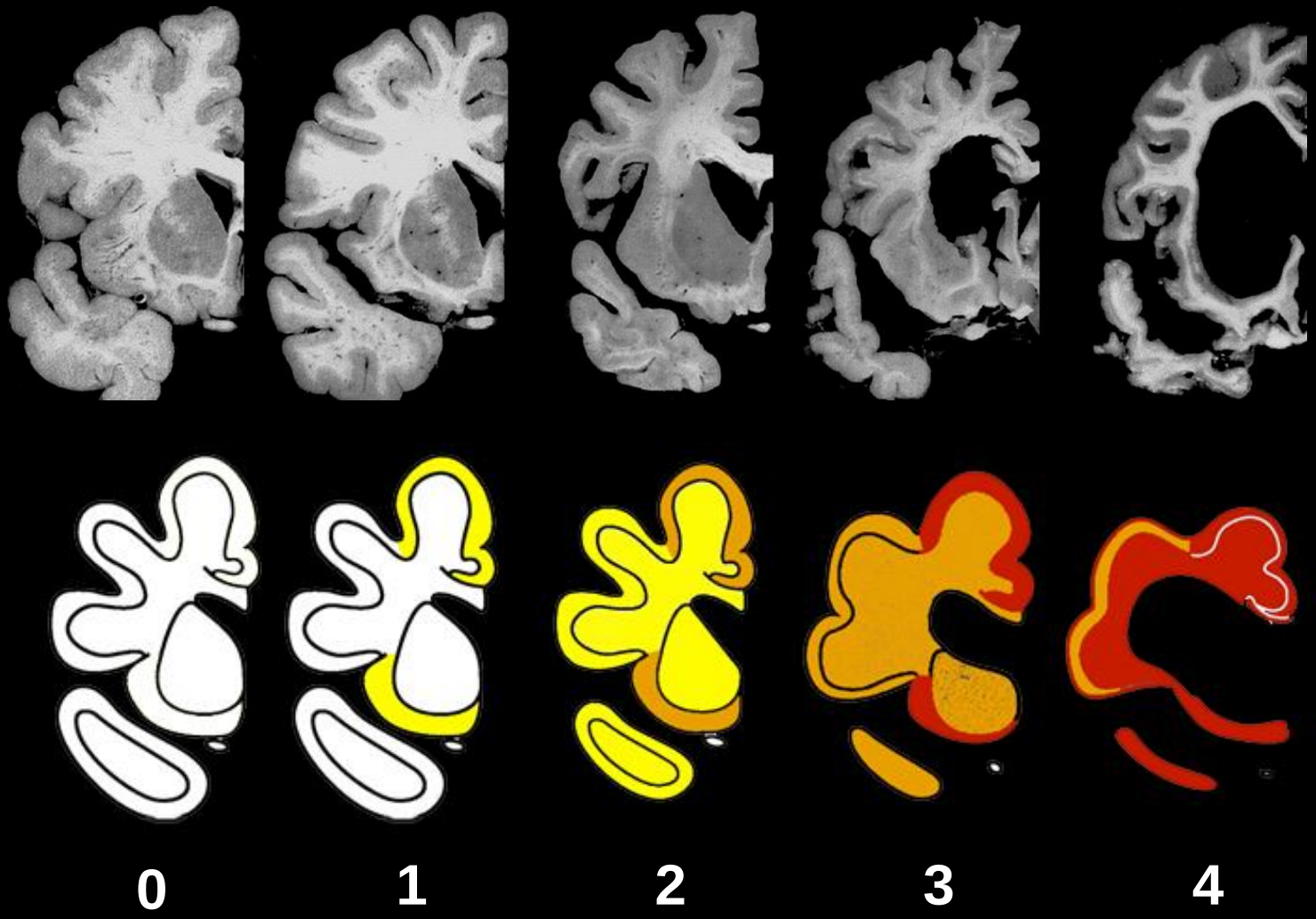
Anterior Cingulate
Cortex (ACC)
and
Rostromedial PFC

Frontal
Insula
(FI)

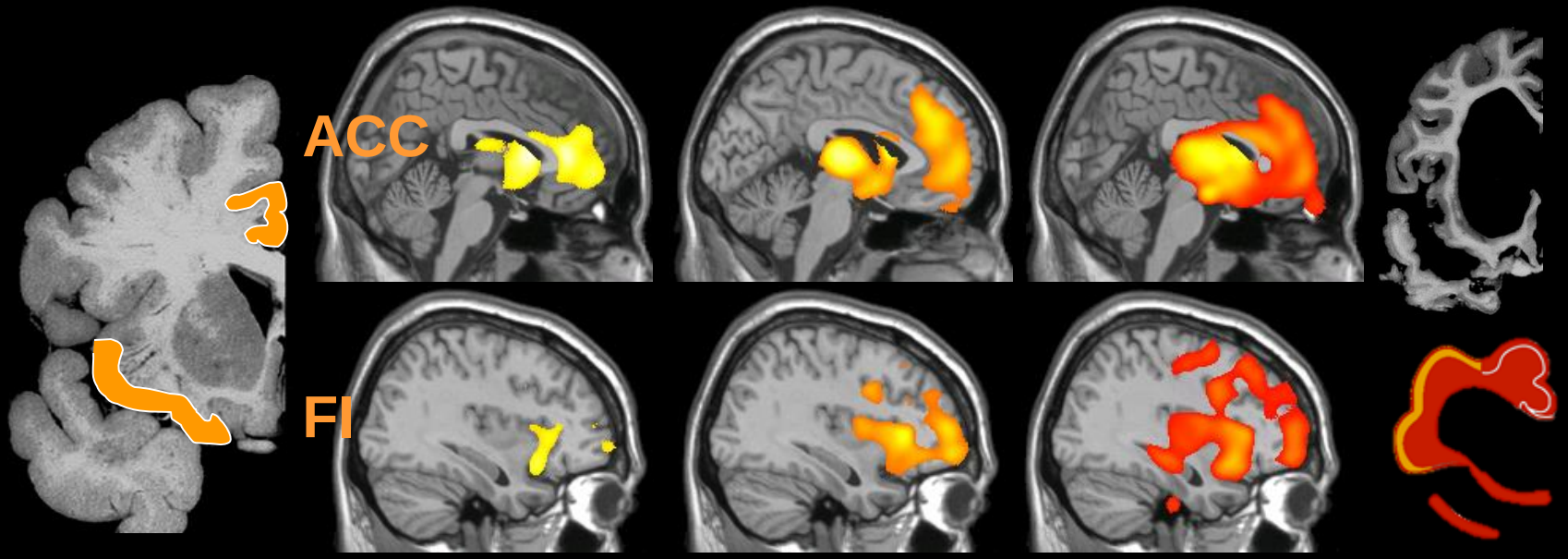
R L

bvFTD gross pathological staging: post-mortem

Broe et al Neurology 2003



bvFTD MR atrophy staging: ante-mortem



Normal
CDR = 0

CDR 0.5 → CDR 1 → CDR 2-3

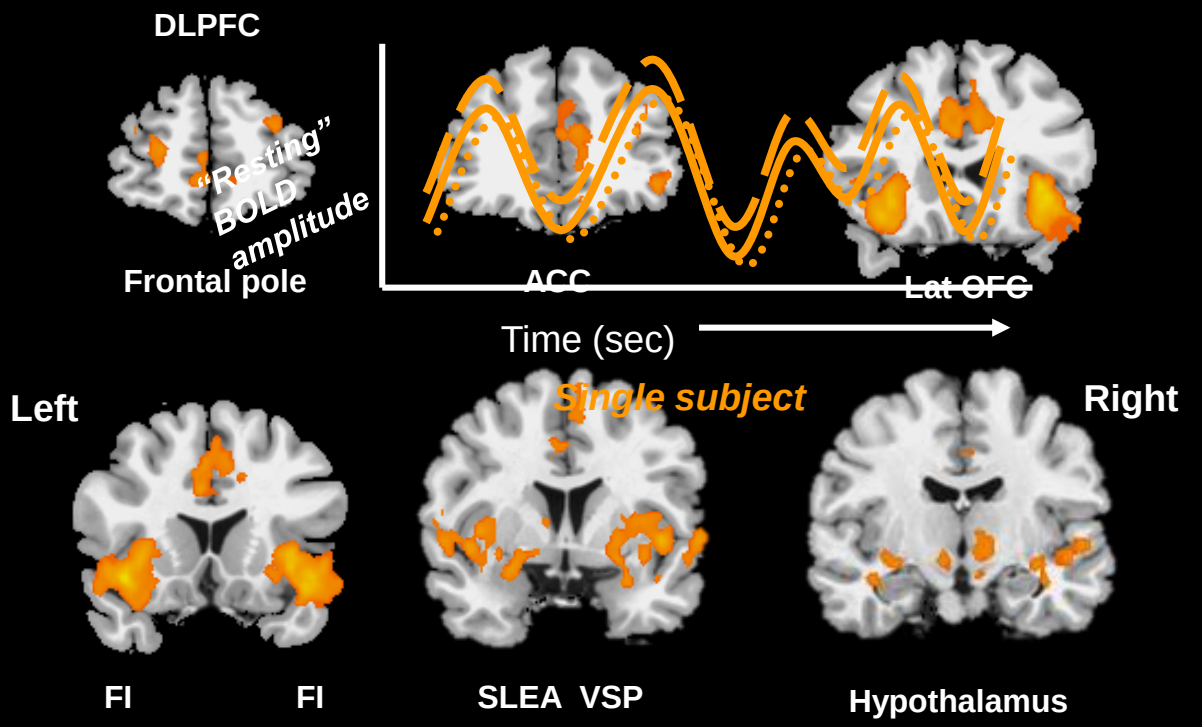
End-Stage
CDR 2-4

Groups of 15 bvFTD vs. 45 healthy controls

Seeley et al Arch Neurol 2008

Intrinsic connectivity measured with task-free MRI

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



Right FI seed ROI

3T fcMRI
19 healthy controls

"Salience Network" (Intrinsic connectivity network)

Seeley et al J Neurosci 2007

Intrinsic connectivity measured with task-free MRI

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

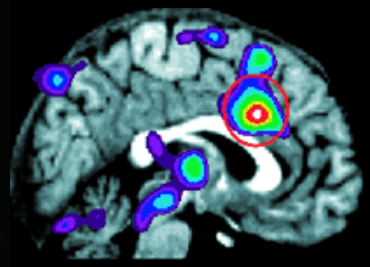
Right FI seed ROI

3T fcMRI
19 healthy controls

THIRST

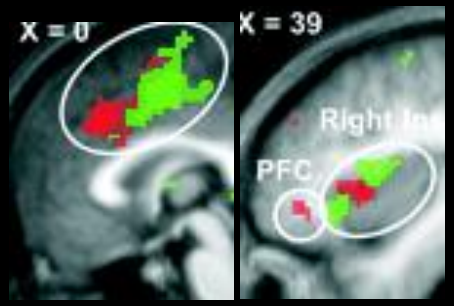
DeAruojo 2003

PAIN



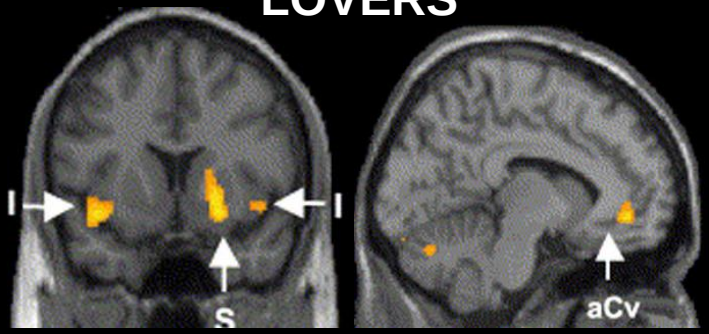
Rainville 1997

SPOUSE'S PAIN



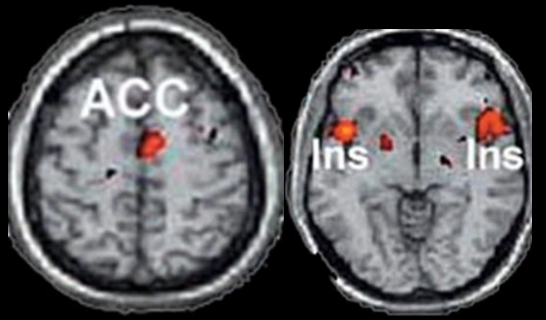
Singer 2004

LOVERS



Bartels and Zeki, 2004

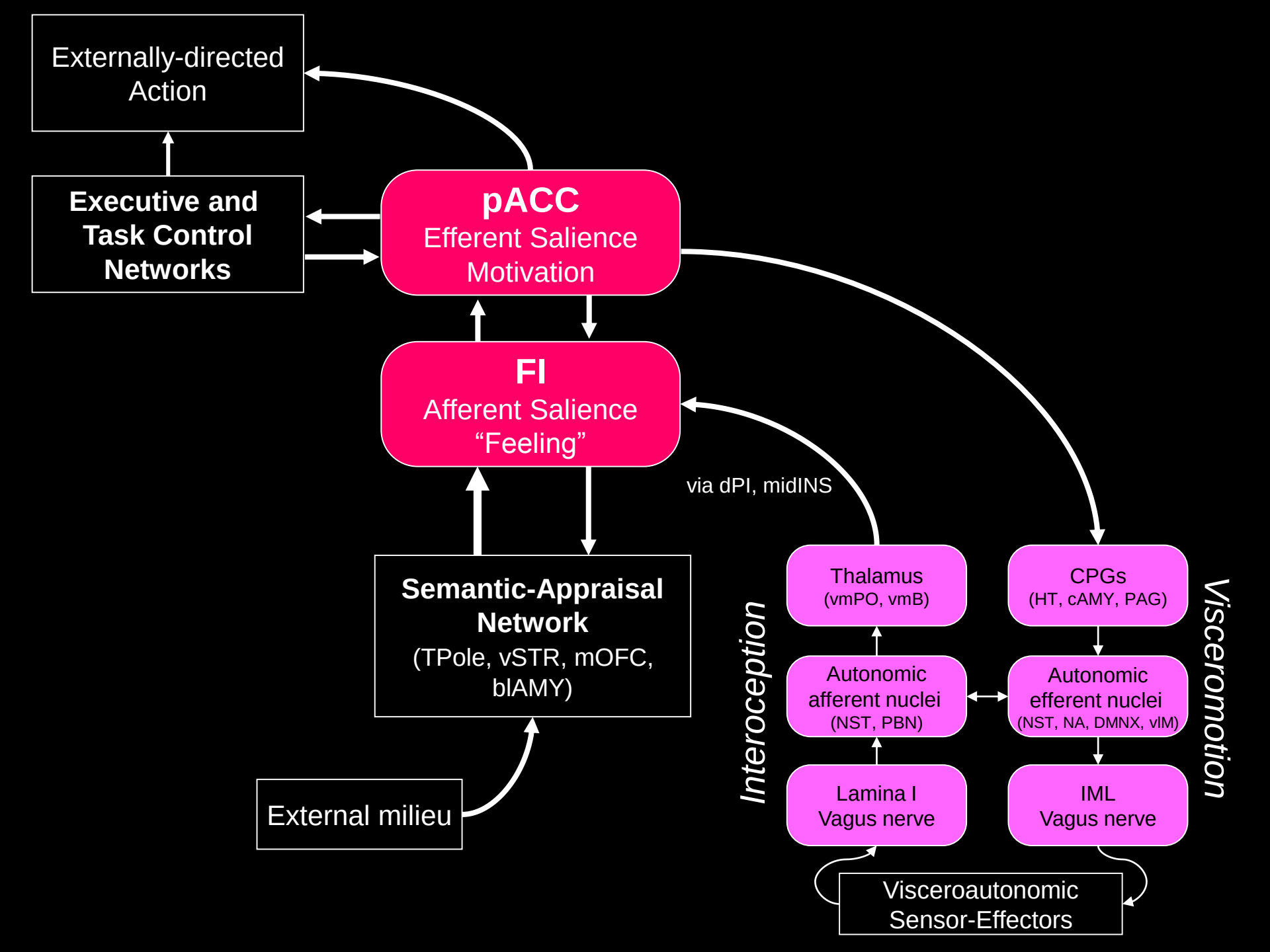
HR DETECTION



Critchley 2004

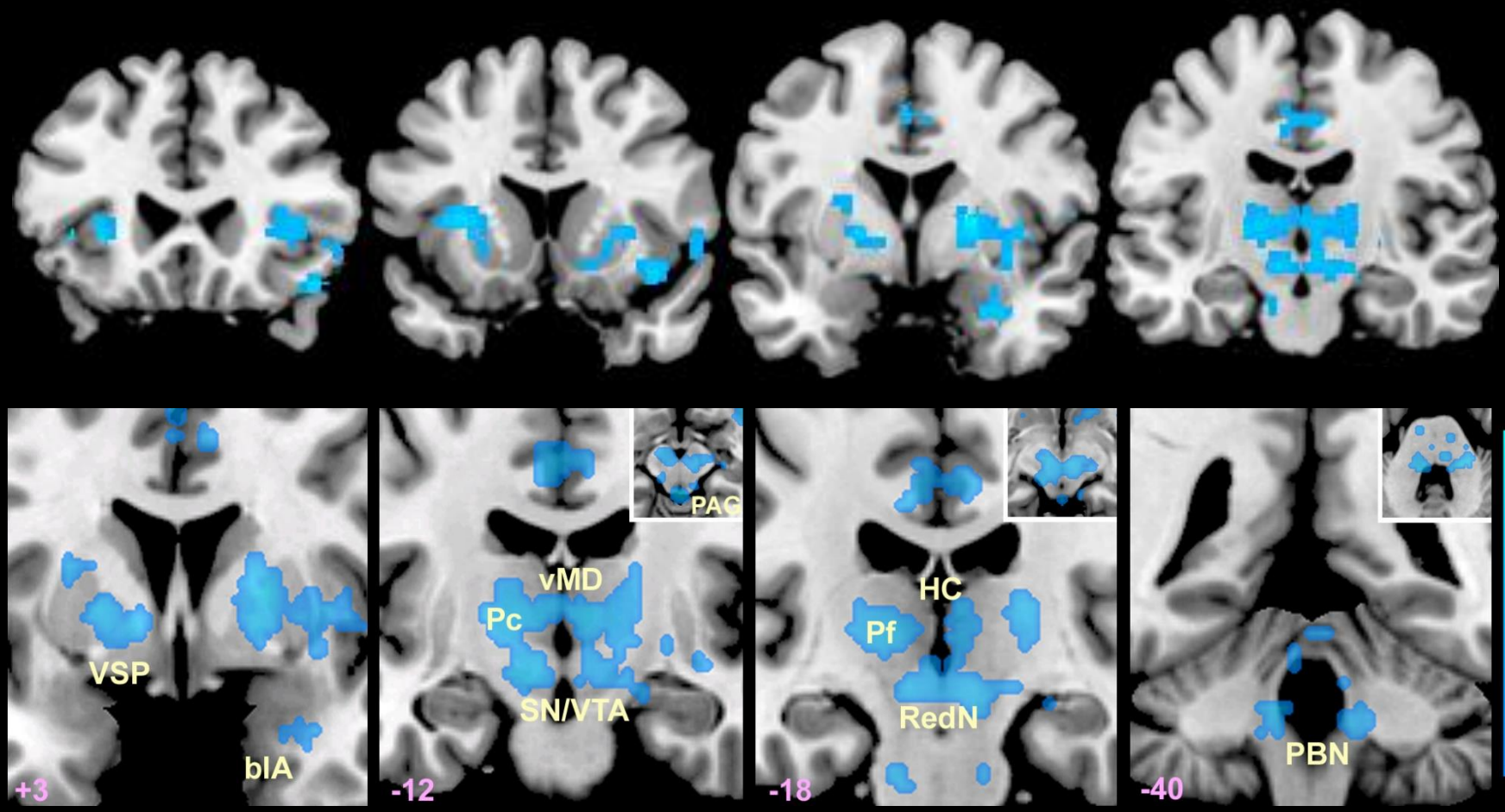
"Salience Network"
(Intrinsic connectivity network)

Seeley et al J Neurosci 2007


Externally-directed Action
Executive and Task Control Networks
pACC
Efferent Salience
Motivation
FI
Afferent Salience
“Feeling”
via dPI, midINS
Semantic-Appraisal Network
(TPole, vSTR, mOFC, blAMY)
External milieu
Thalamus
(vmPO, vmB)
CPGs
(HT, cAMY, PAG)
Interoception
Visceromotion
Autonomic afferent nuclei
(NST, PBN)
Autonomic efferent nuclei
(NST, NA, DMNX, vlM)
Lamina I
Vagus nerve
IML
Vagus nerve
Visceroautonomic Sensor-Effectors

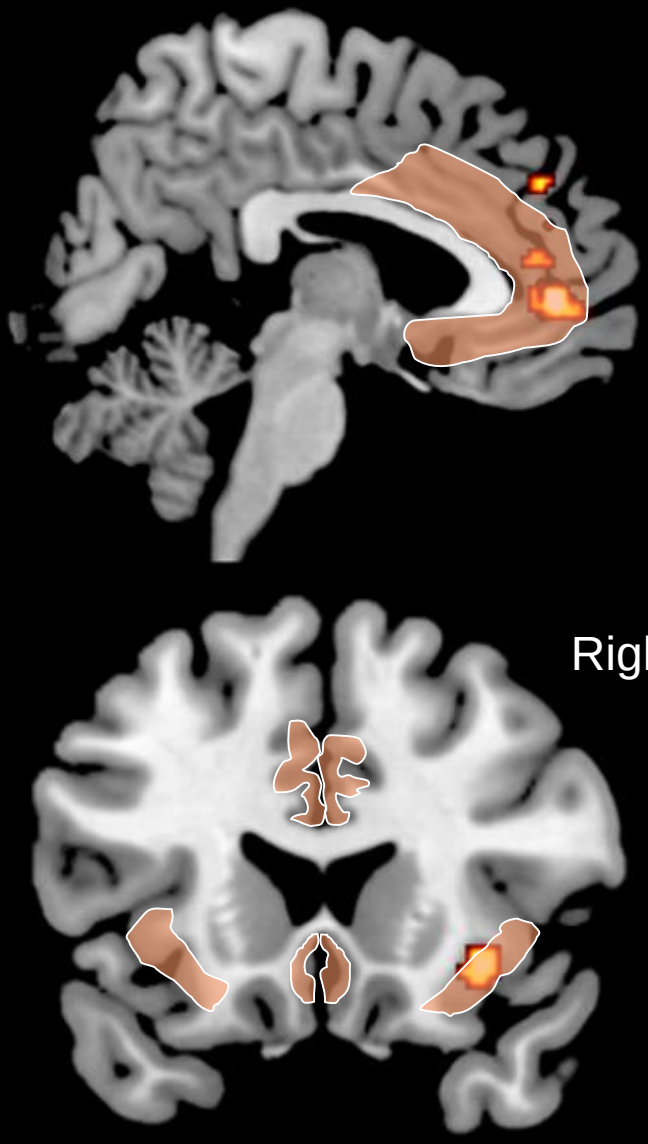
bvFTD involves distributed salience network connectivity disruptions

bvFTD < HC



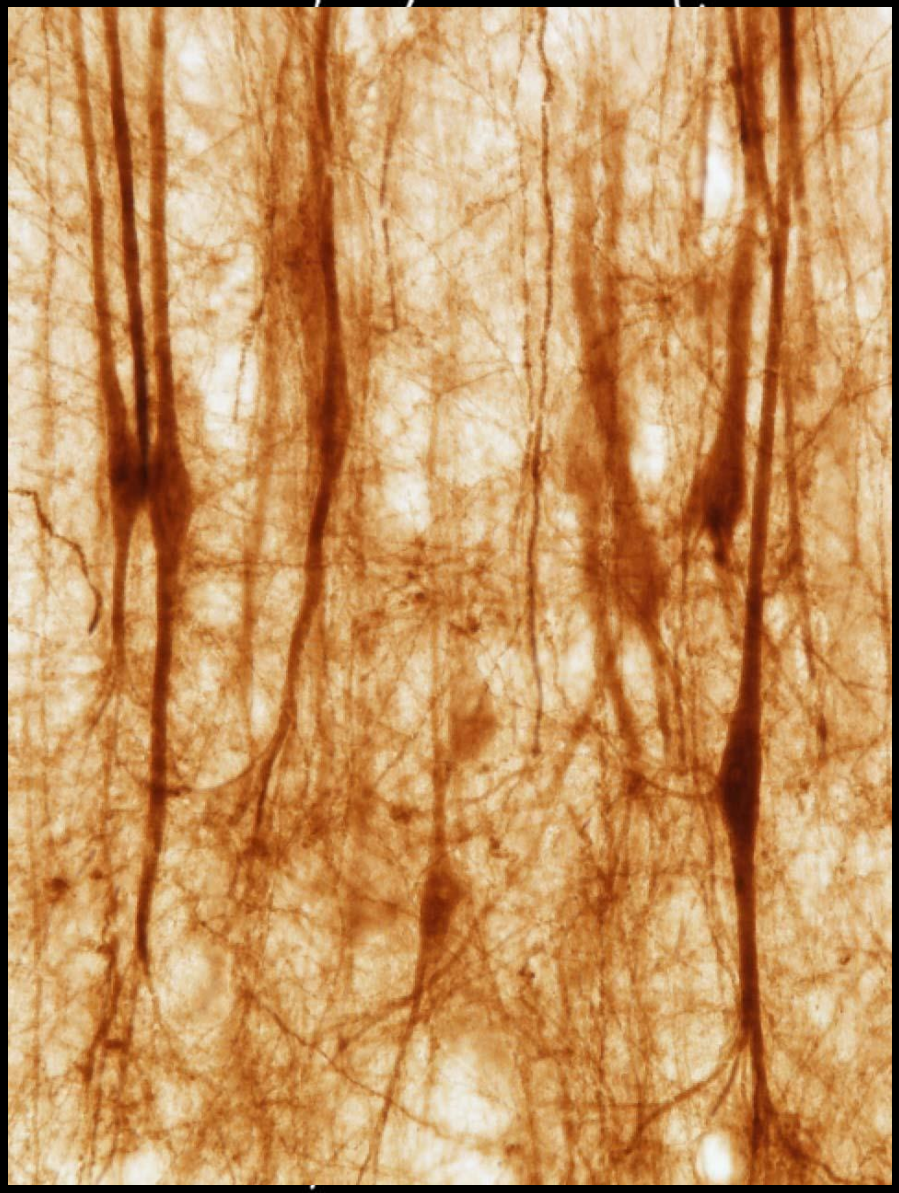
Zhou et al Brain 2010

Where within the bvFTD salience network epicenters does disease begin?



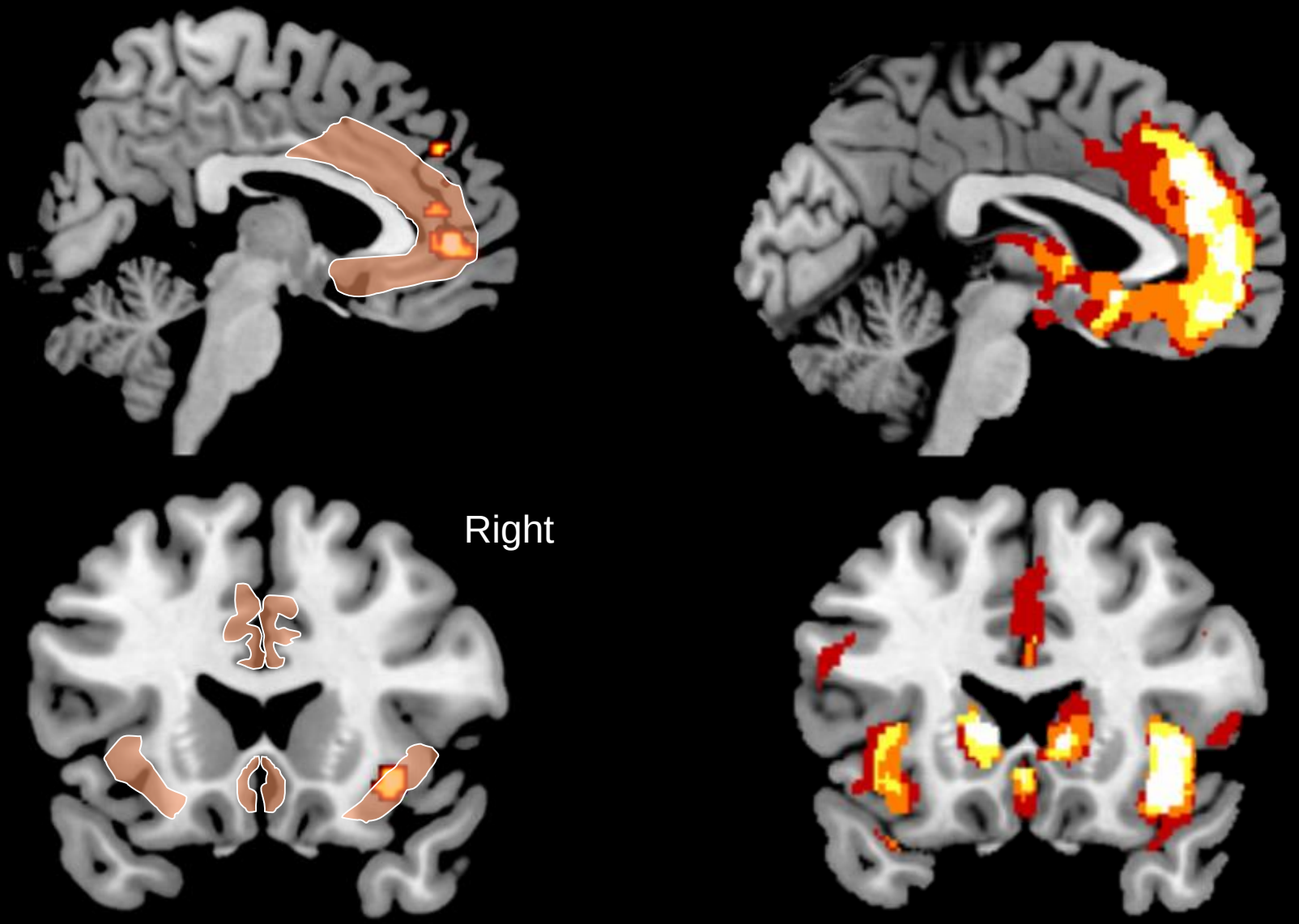
Right

VEN-containing regions



MAP2

von Economo 1926


Right
5
6
7
8
9
VEN-containing regions
bvFTD overlap

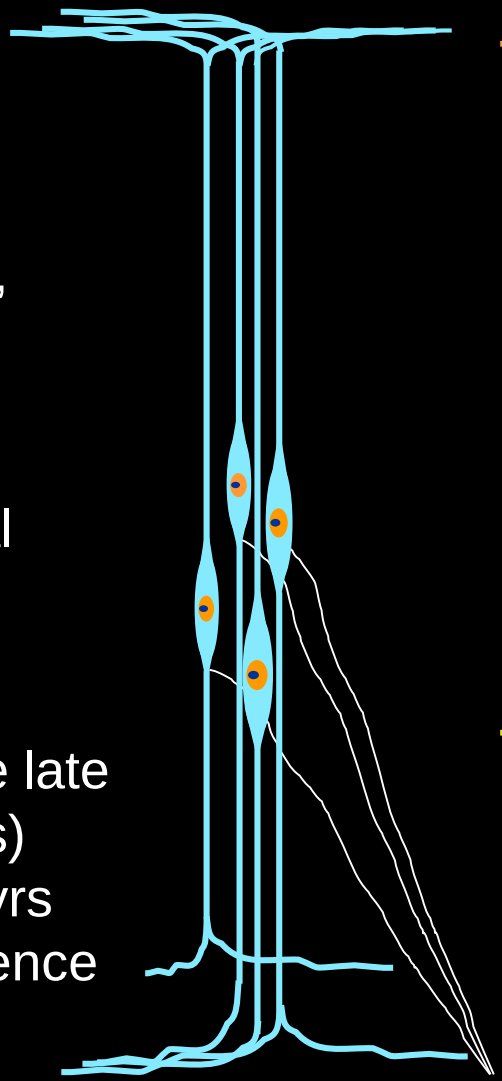
VENs

Structure

- Simplified architecture
- Layer Vb, FI>>ACC
- Columnar clusters
- Project axons into WM, targets unknown*
- R/L hemisphere ~ 1.3
- Express CTIP2 and FEZF2 c/w subcerebral projections

Ontogeny

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



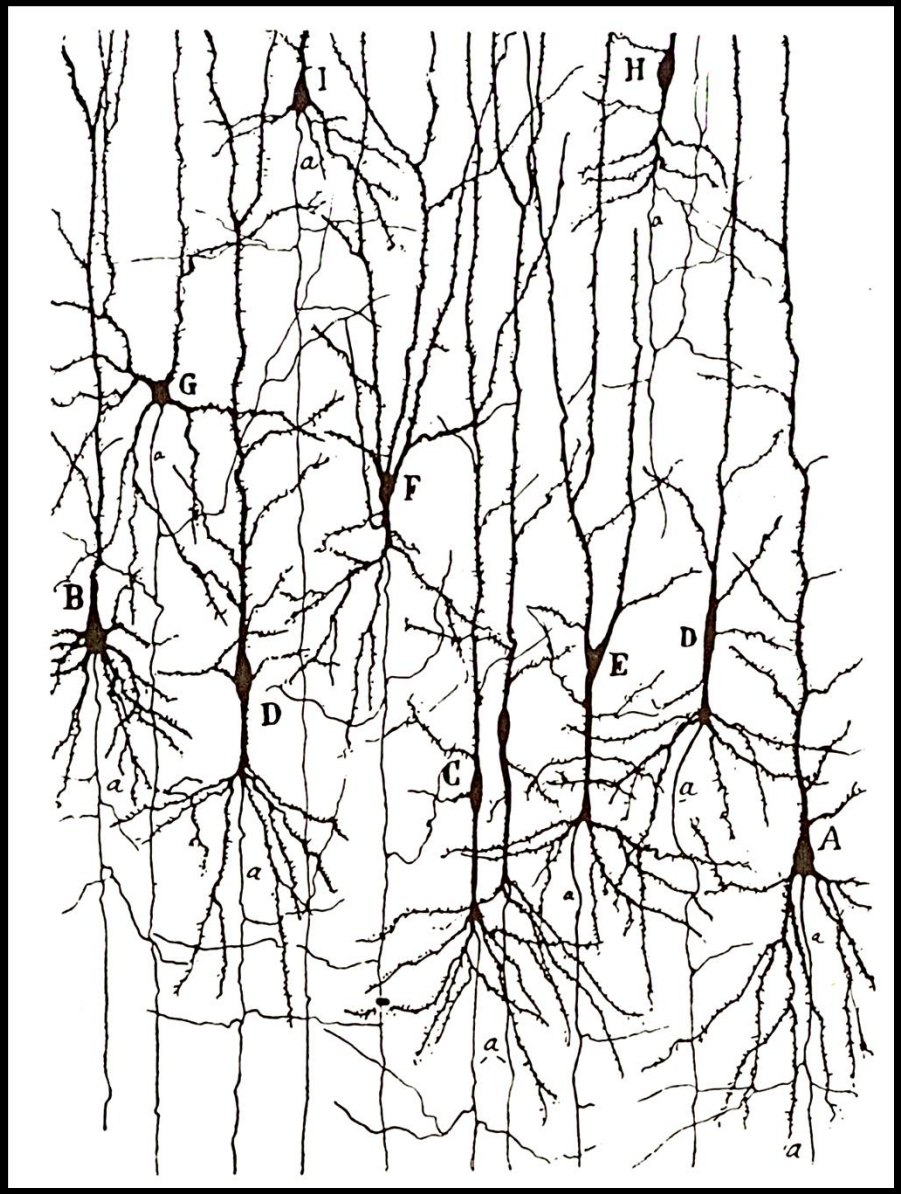
Chemistry/proteome

- Glutamatergic
- Rich in nonphosphorylated neurofilaments (SMI-32)
- Express various receptors for DA, NE, 5HT
- Also express NMB, ILR4α, ATF3, DISC1
- More specific markers coming soon

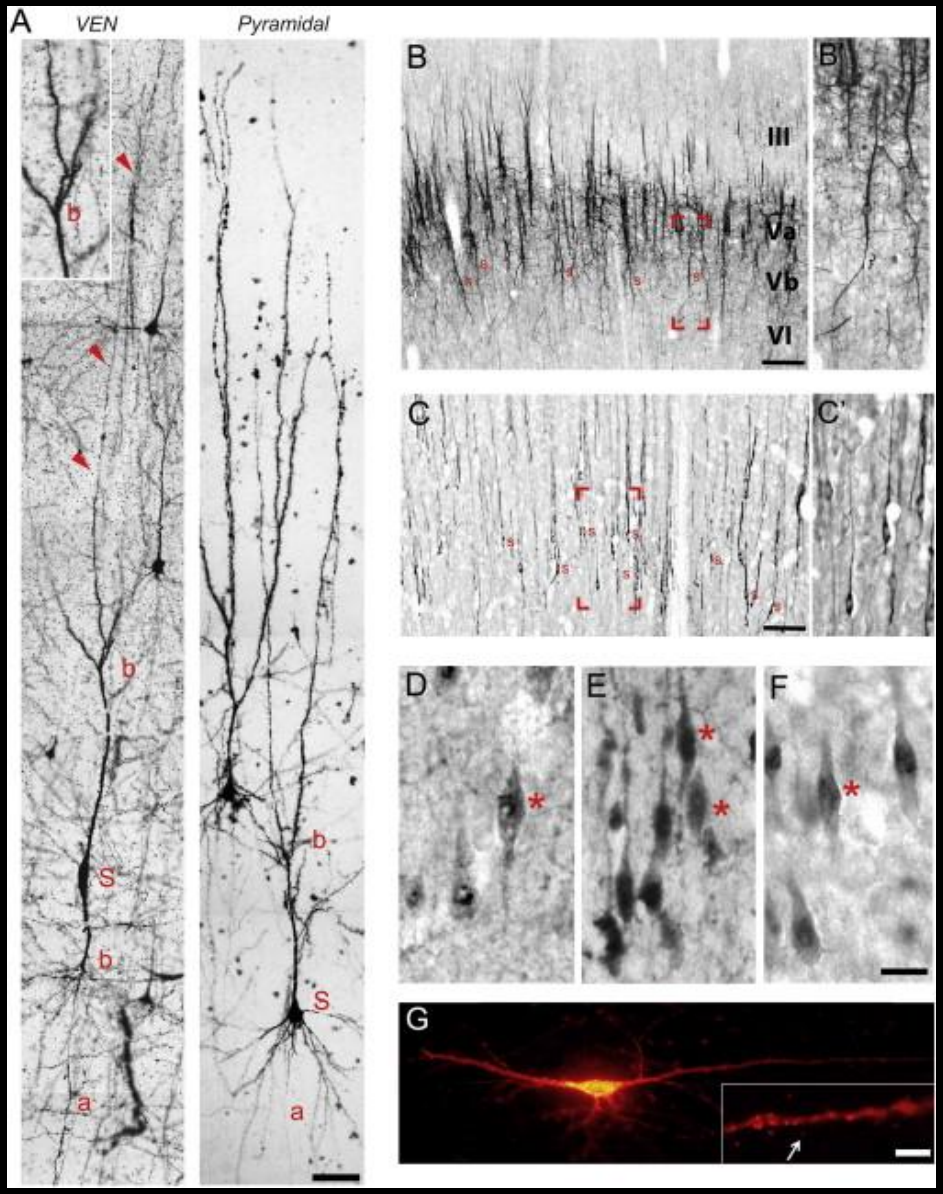
Phylogeny

- Great apes<<<Human
- Orangutan<Gorilla<Chimps
- Monkeys!
- Cetaceans
- Elephants
- Assorted others

(See work of J. Allman, P. Hof, and C. Sherwood labs)



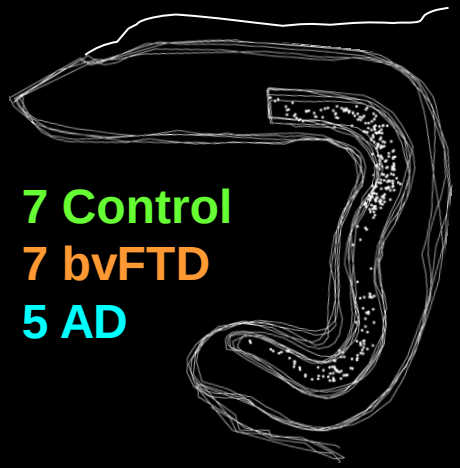
Ramon y Cajal, 1900
Human FI



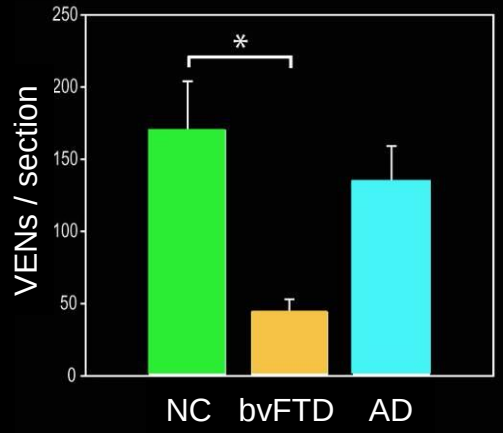
Evrard et al, Neuron 2012
Macaque AAI

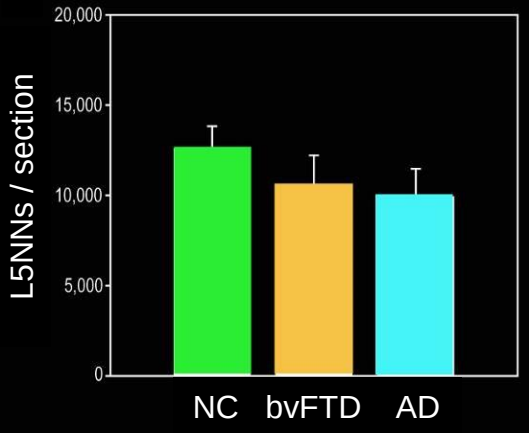
VENs: the early vulnerable neuron in bvFTD? Evidence from ACC

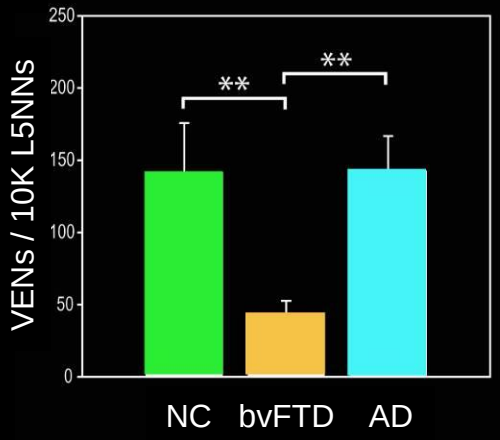
Left ACC



Seeley et al, 2006





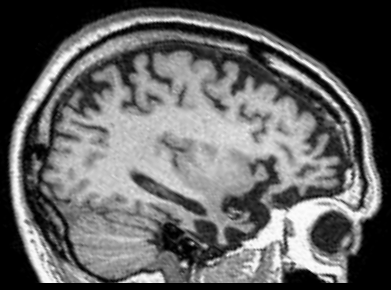


See also Santillo et al 2013

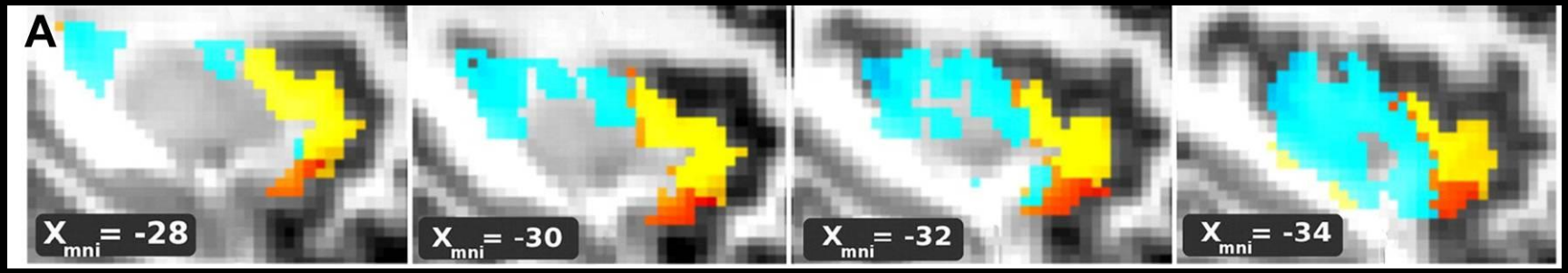
Adapted from Santillo et al 2014

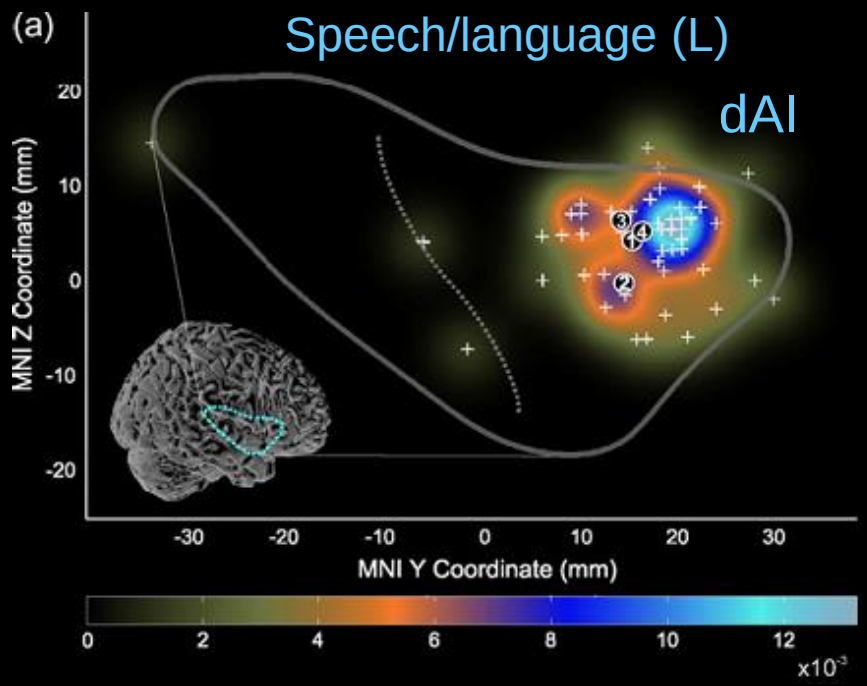

bvFTD, Broe Stage 4, due to Pick’s

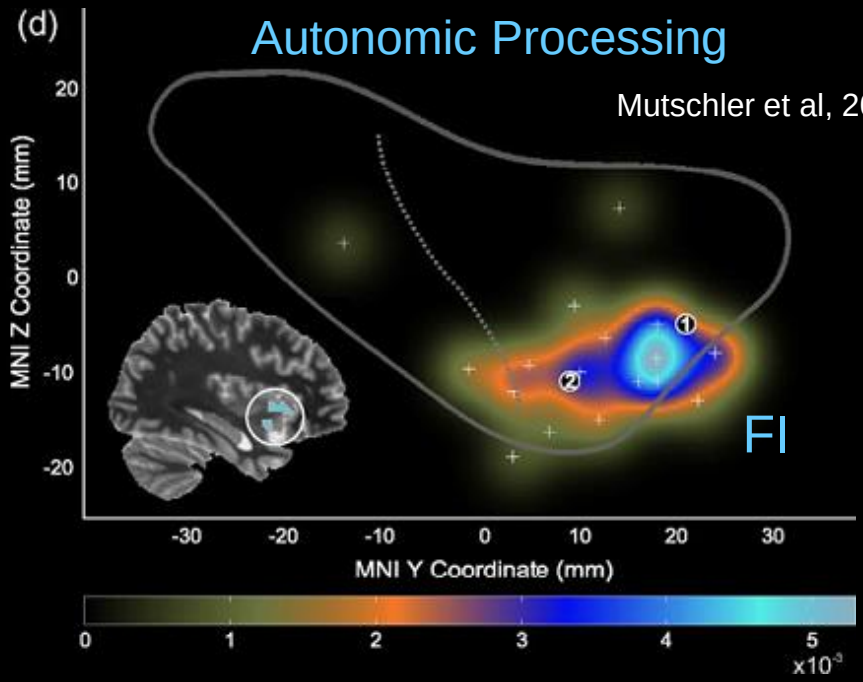
Area FI



Nanetti et al, 2009



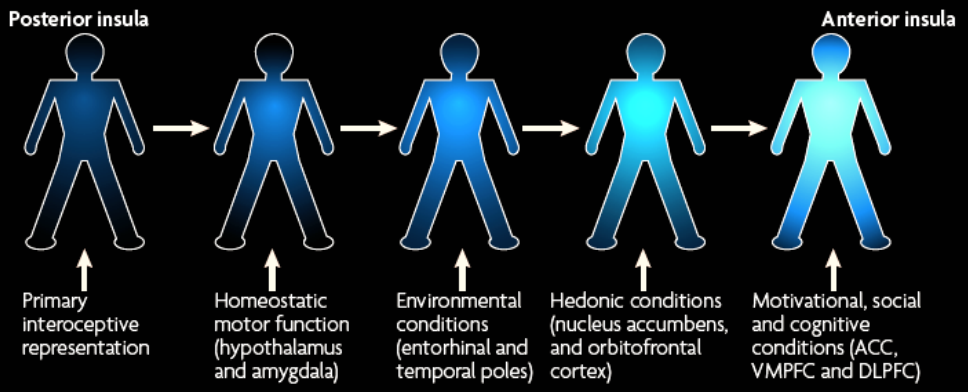




Area FI

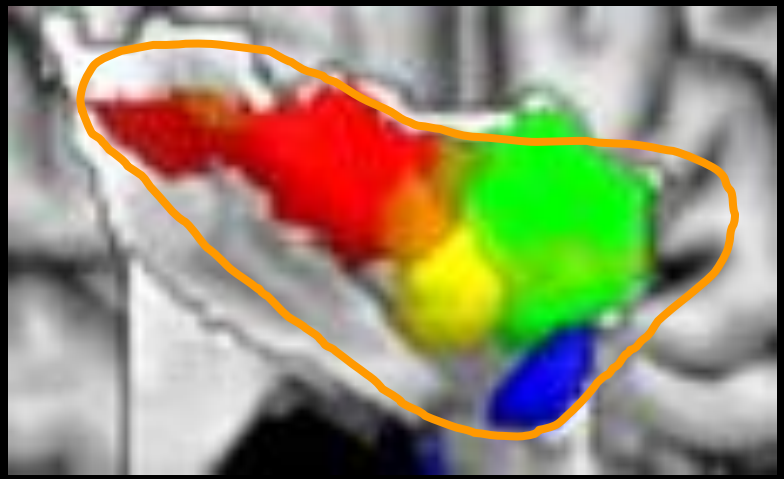
bvFTD

A.D. Craig, *NRN* 2009



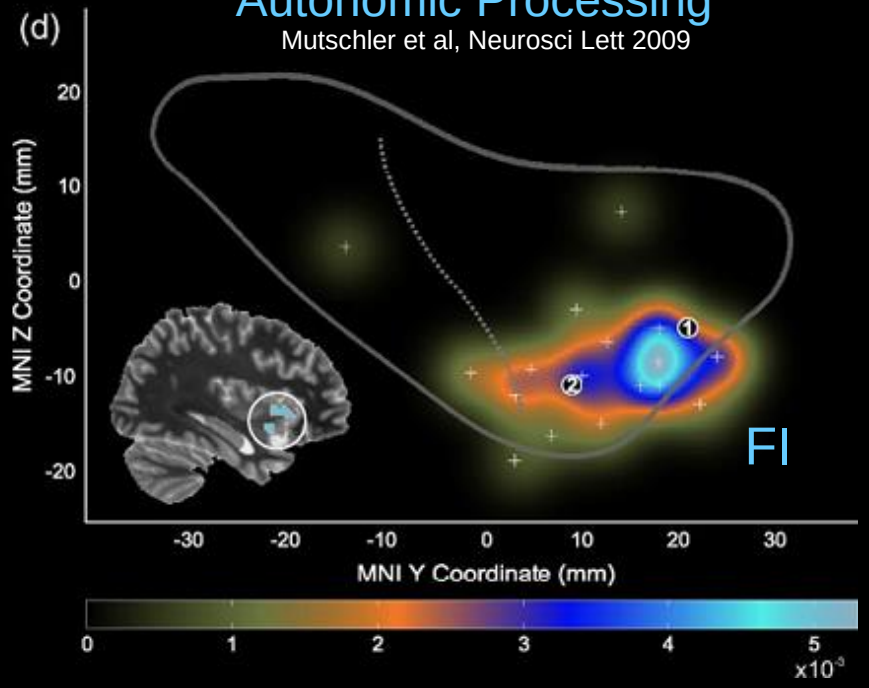
Social-emotional function

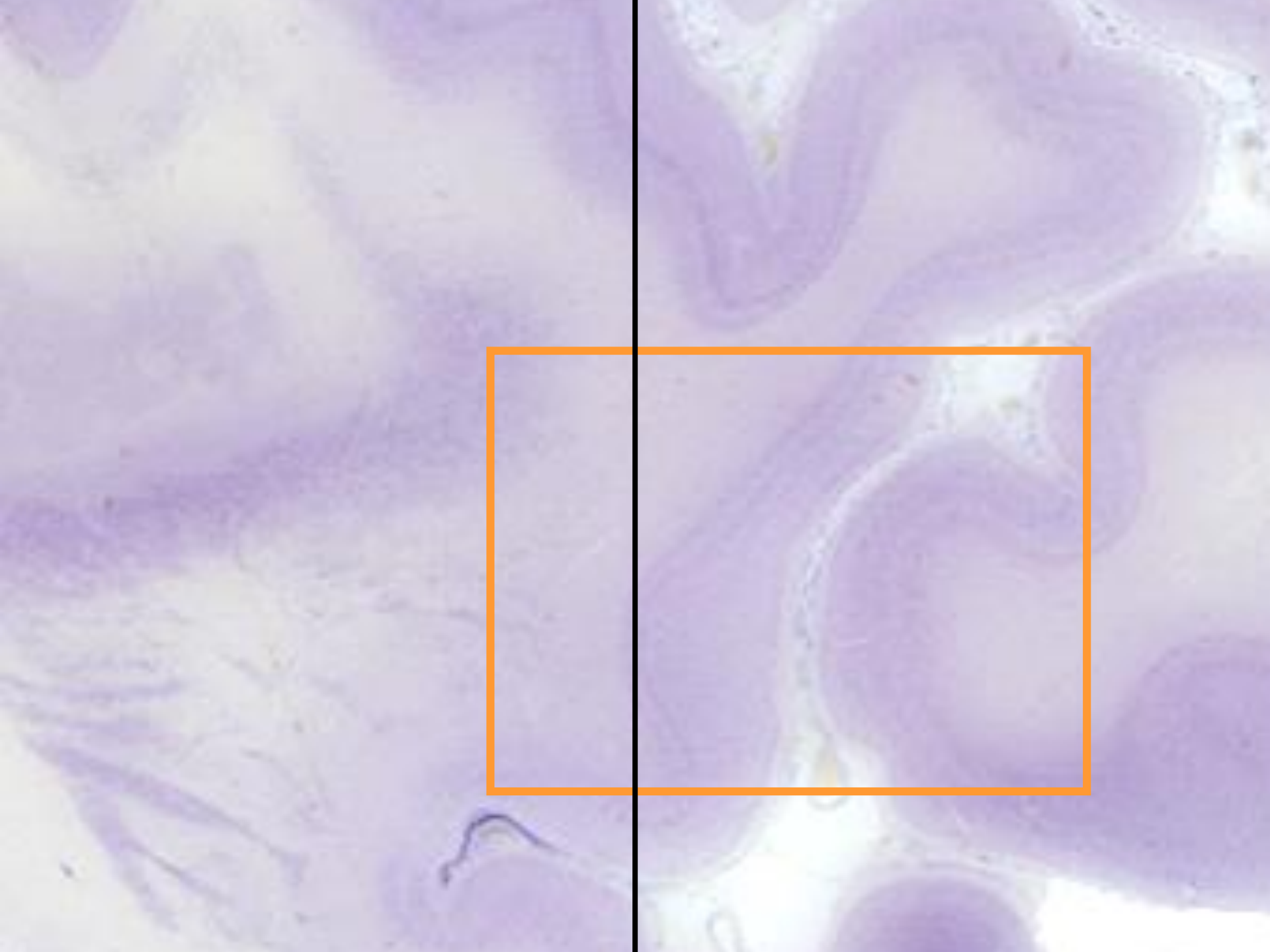
Kurth et al, Brain Structure and Function 2010

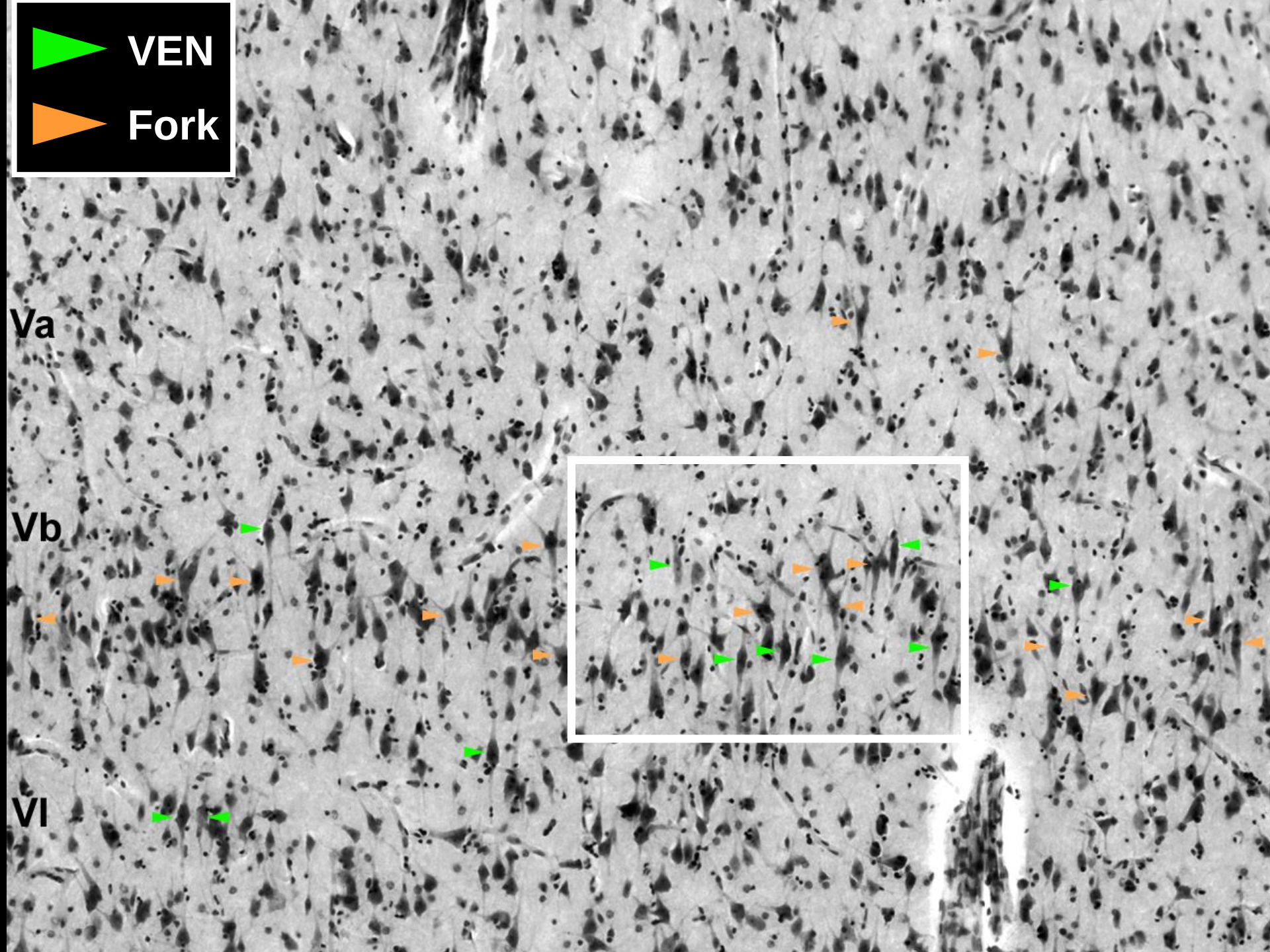


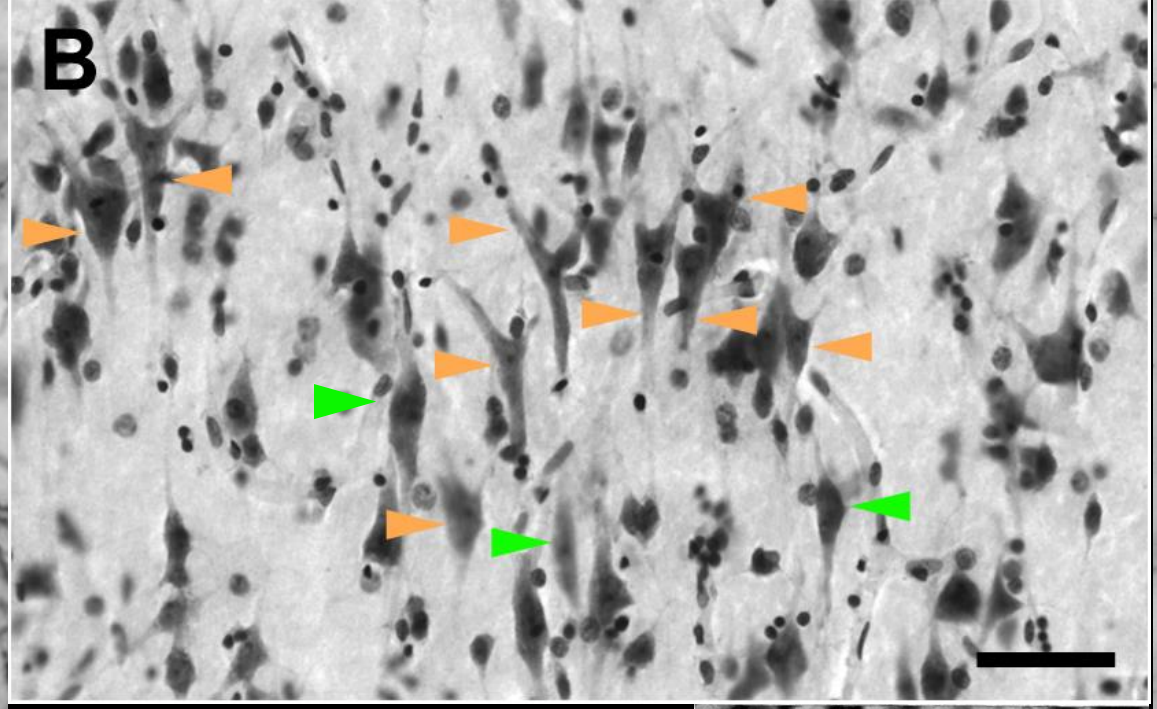
Autonomic Processing

Mutschler et al, Neurosci Lett 2009






VEN
Fork
Va
Vb
VI

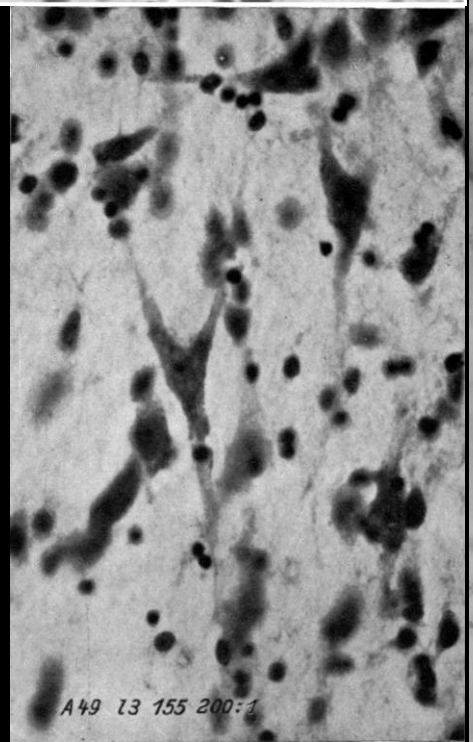


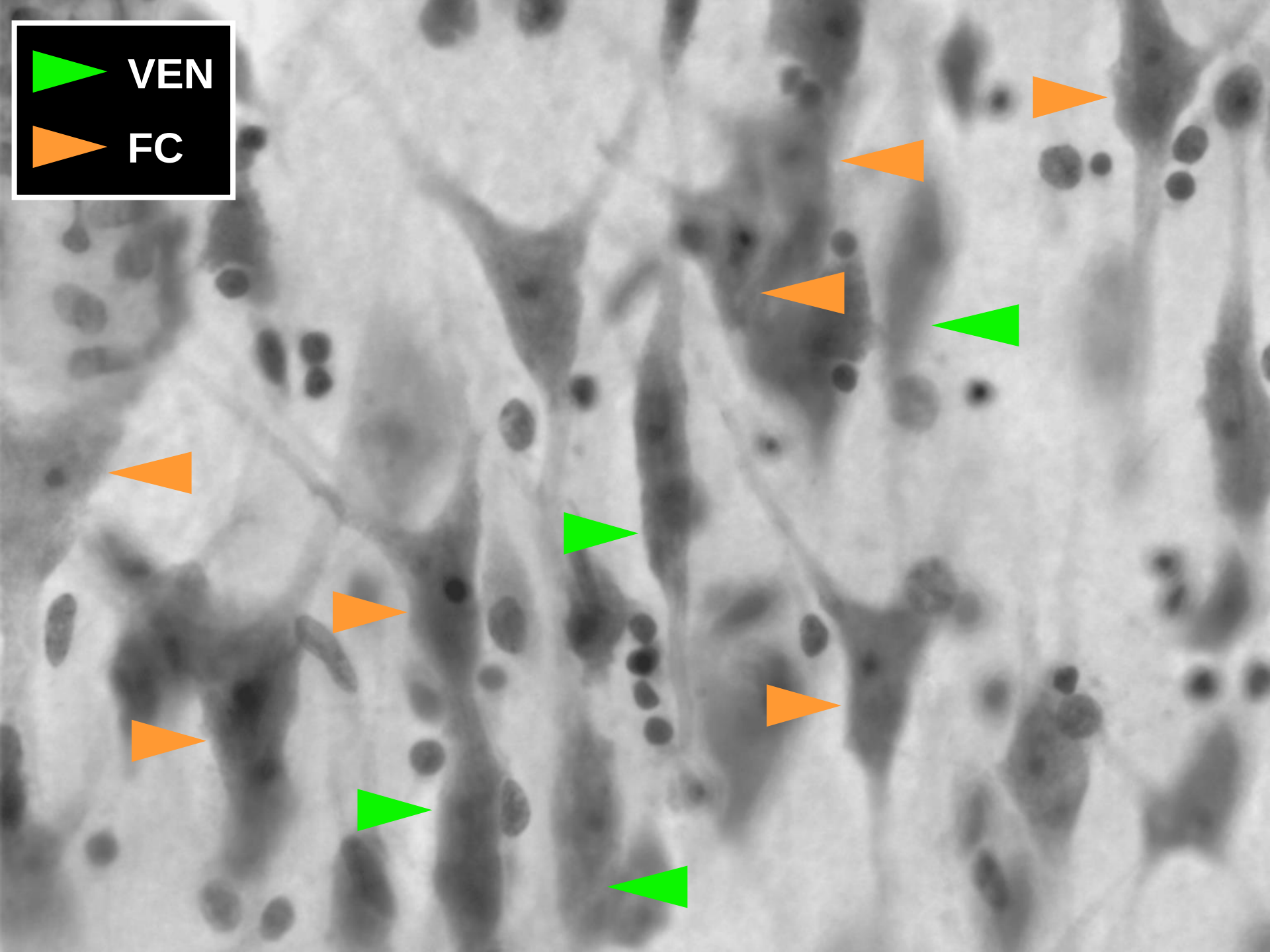
Ngowyang 1932

Gabelzellen =

“Fork cells”

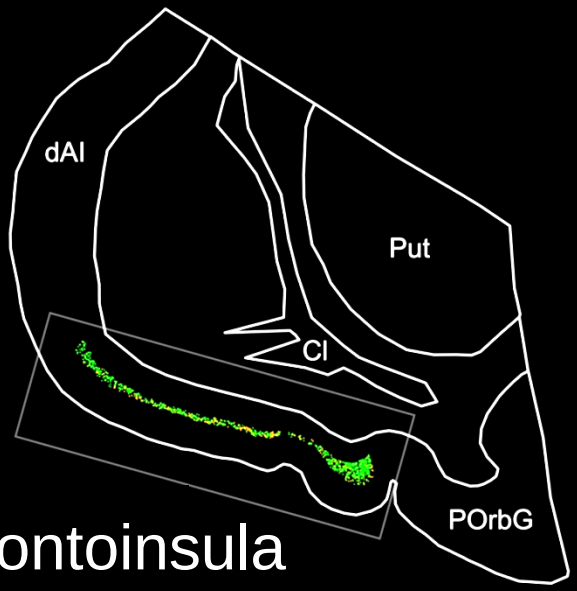
(See Seeley et al 2011 for commentary and translation)



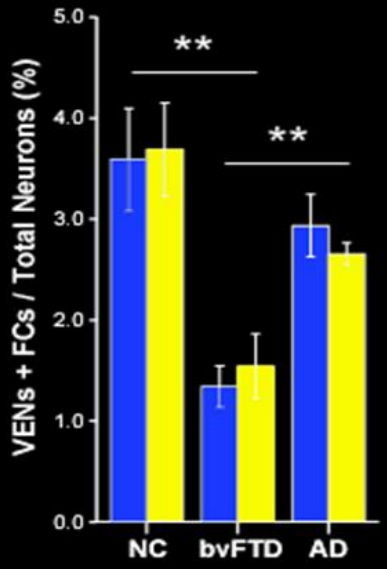

VEN
FC

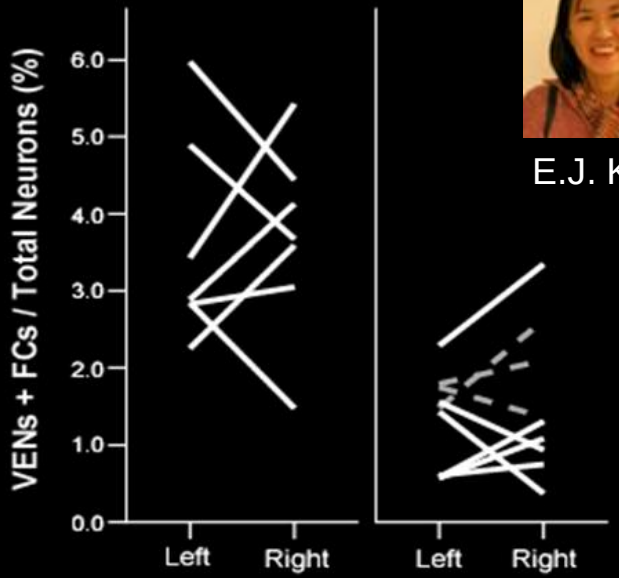

EVOLUTION ONE
SAFEGRIP
GOLGI Fixative

Kim et al, Cerebral Cortex 2011



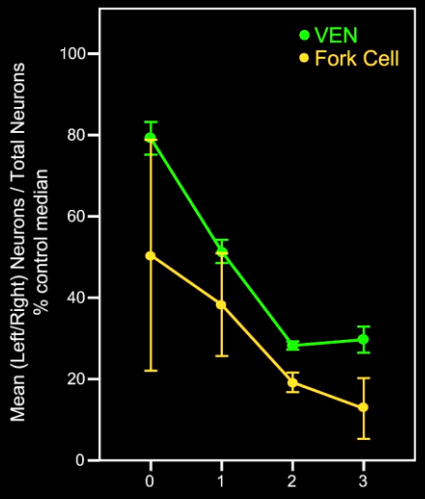
Frontoinsula





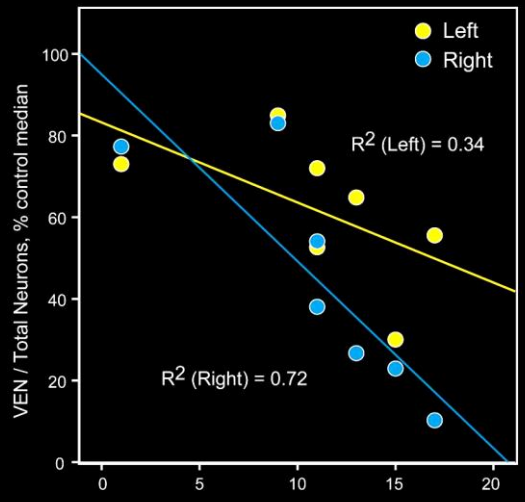
E.J. Kim

Atrophy severity



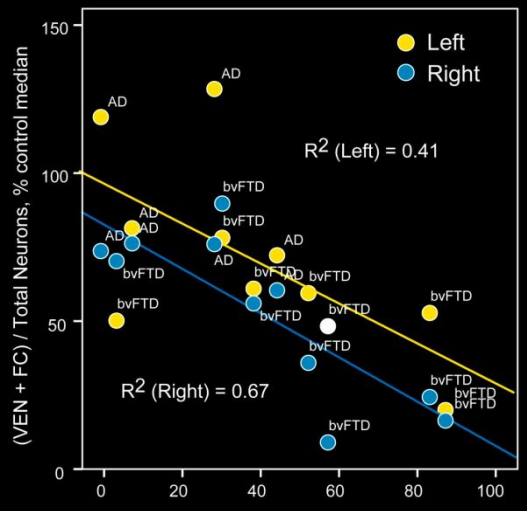
Broe Stage

Clinical severity



CDR, sum of boxes

Behavioral severity



NPI Total

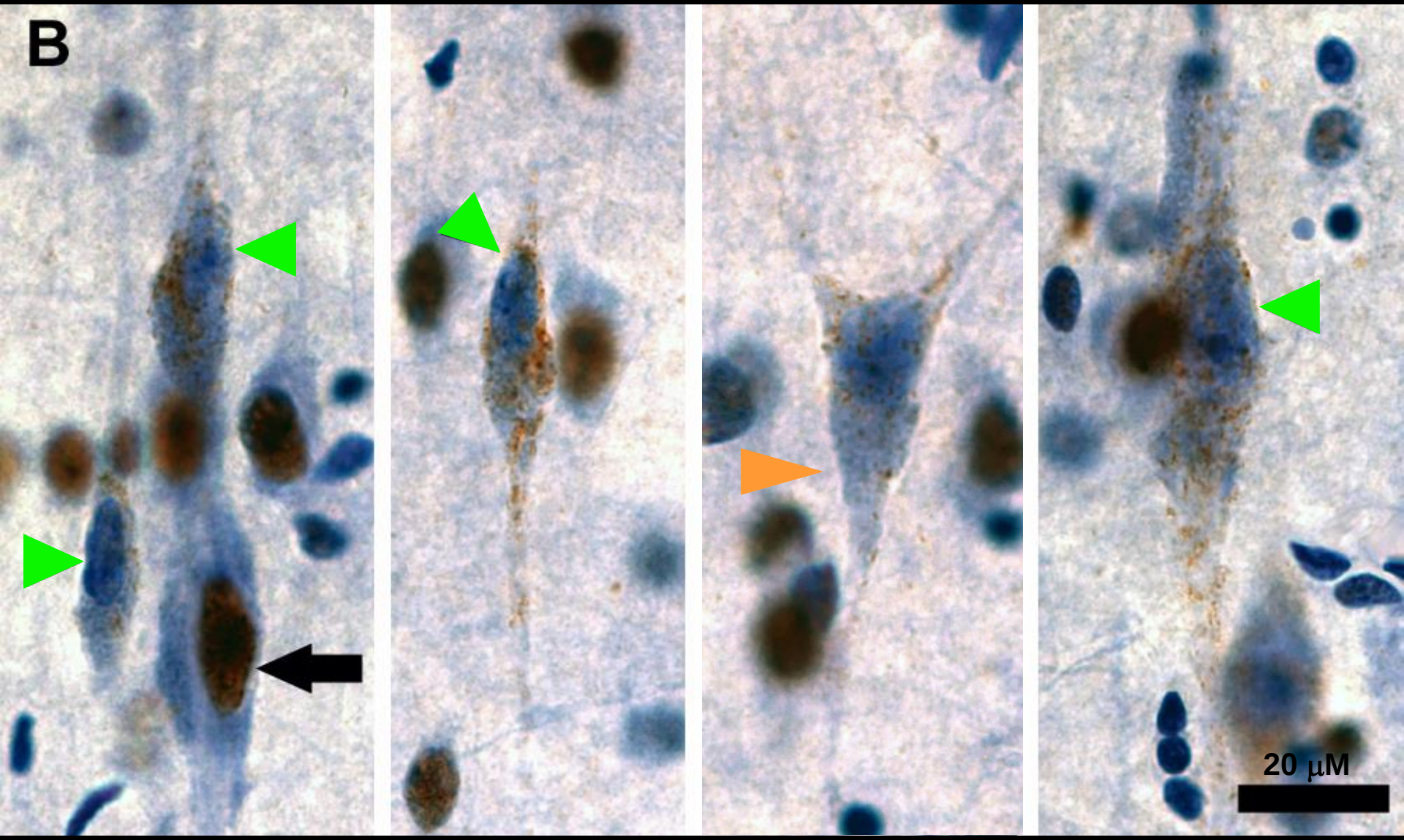
How early can selective VEN and fork cell vulnerability be detected?

How does the selectivity manifest before neuronal dropout?

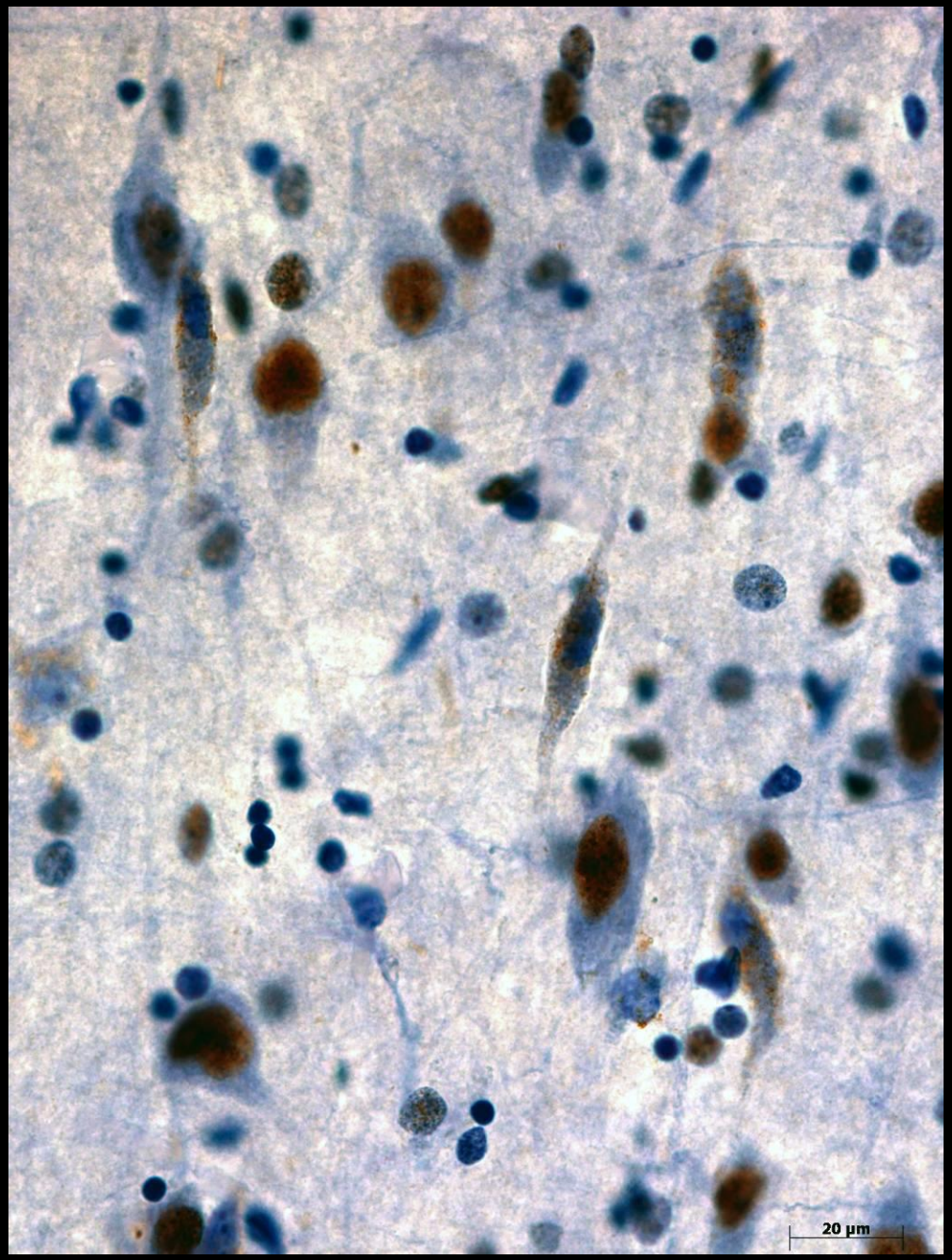
	ALS	bvFTD
Onset neuron	UMNs and LMNs	VENs and fork cells
Onset sites / “epicenters”	Primary motor cortex, bulbar motor nuclei, AHC	Anterior cingulate and frontoinsula
Network spread	Pyramidal motor network	Salience network
1st symptom	Voluntary motor	Social-emotional

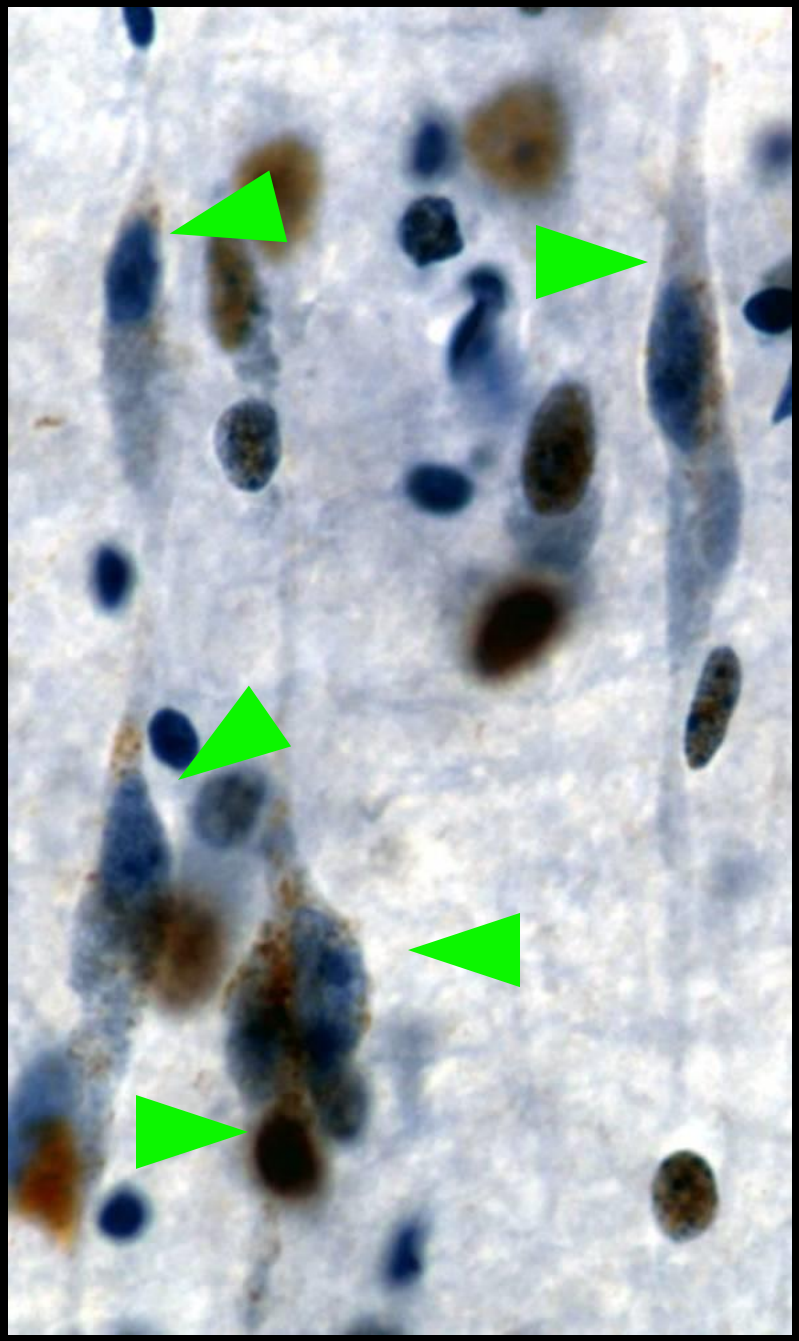
ALS bvMCI-MND bvFTD-MND bvFTD

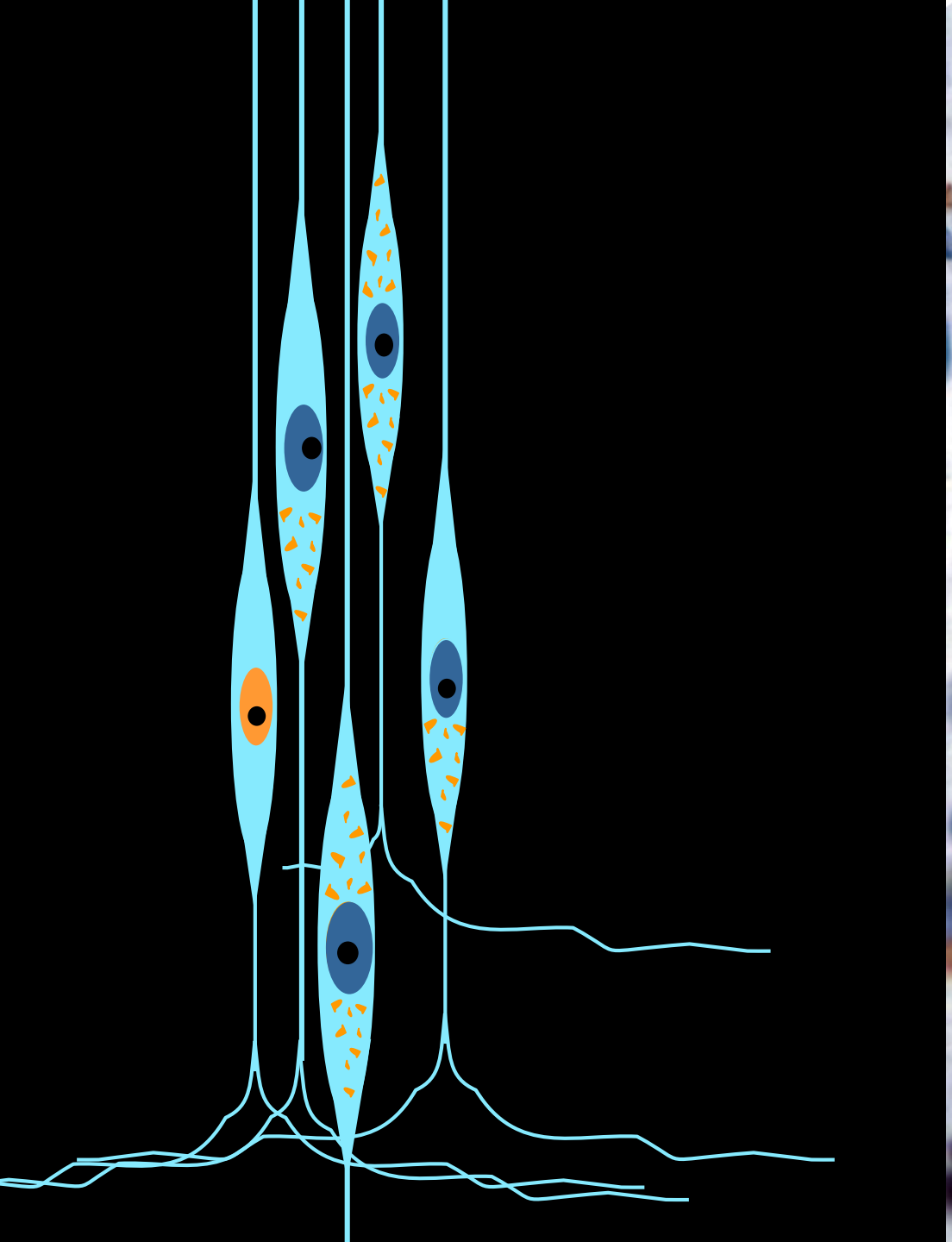
	ALS	bvFTD
Onset neuron	UMNs and LMNs	VENs and fork cells
Onset sites / “epicenters”	Primary motor cortex, bulbar motor nuclei, AHC	Anterior cingulate and frontoinsula
Network spread	Pyramidal motor network	Salience network
1st symptom	Voluntary motor	Social-emotional
Later syndrome	bvFTD, Dysexecutive	Dysexecutive, ALS
Most common protein	TDP-43	TDP-43
Other inclusion proteins	FUS, SOD1, Ubiquilin2	Tau, FUS
Most common gene	*C9ORF72*	*C9ORF72*
Other genes	*SOD1, FUS, TARDBP, Ubiquilin2, VCP*	*MAPT, GRN, FUS, TARDBP, VCP*

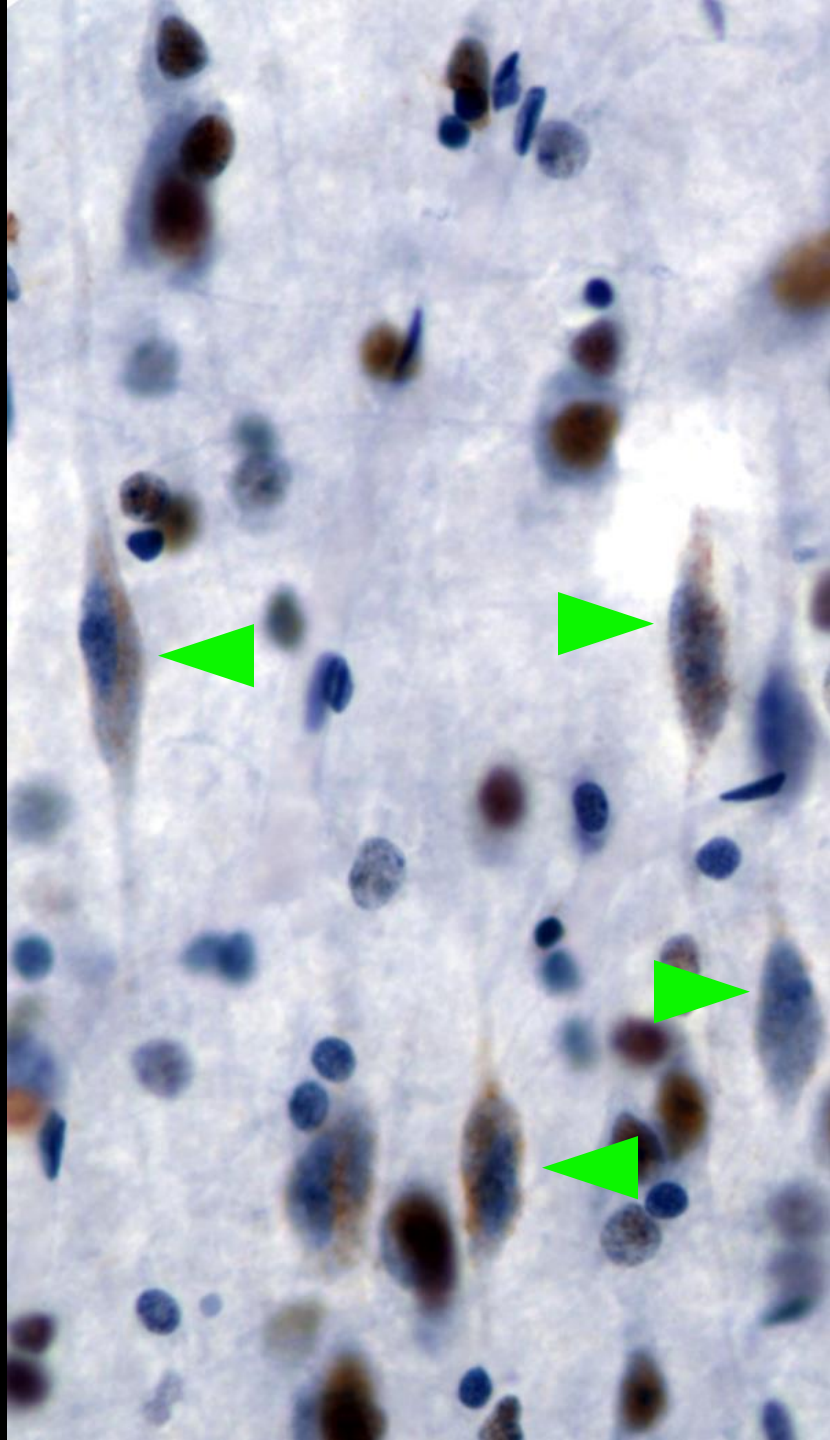


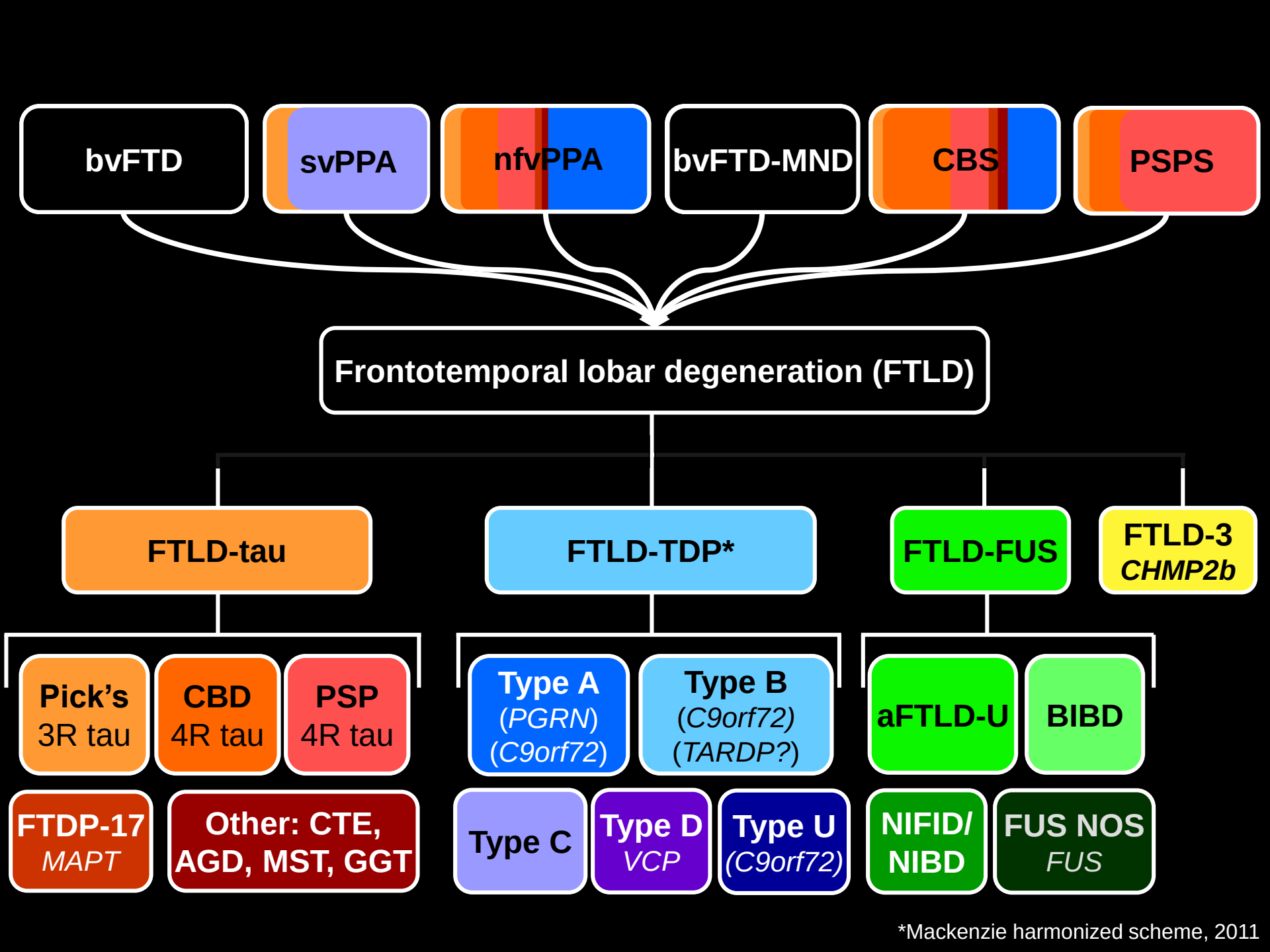
bvFTD-MND, Stage 1, Right FI, TDP-43 immunohistochemistry


20 µm





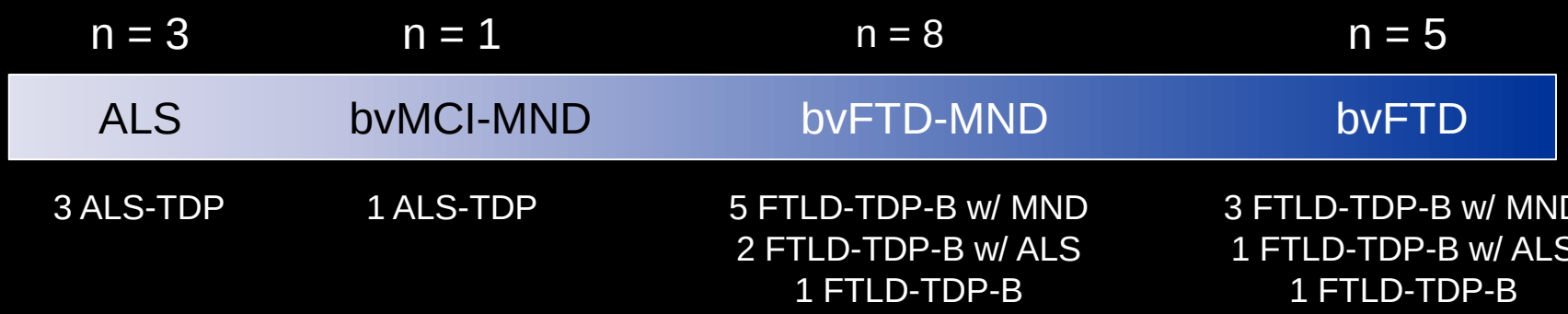




*Mackenzie harmonized scheme, 2011

Subject characteristics

	Control	bvFTD-ALS spectrum
N	10	17
Gender (M:F)	6:4	10:7
Age at death (yrs)	63.6	61.8
Hemisphere (bilateral/R only/L only)	10/0/0	10/6/1
PMI (h)	24.5	13.0
Brain weight (g)	1383	1284
Symptom duration in years	--	4.0
CDR total	--	1.8
CDR Sum of boxes	--	8.9
NPI total	--	41.9



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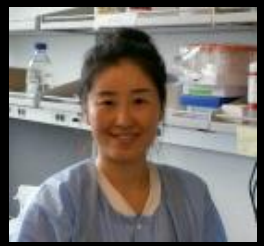
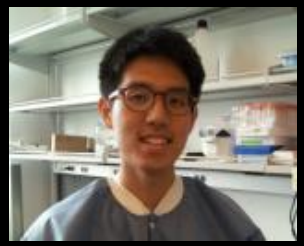
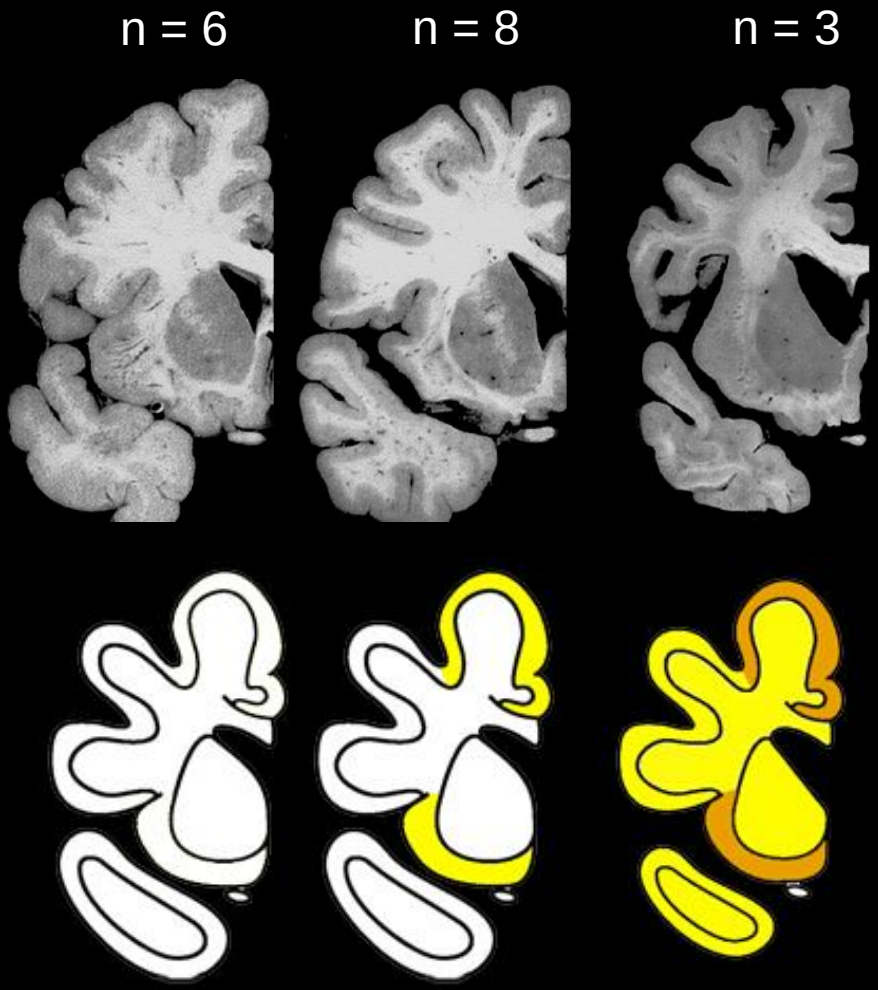
A. Nana Li **S. Gaus** **M. Sidhu** **J-H. Hwang** **Y. Park** **L. Li**




Sample represents earliest bvFTD disease stage that can be studied post-mortem



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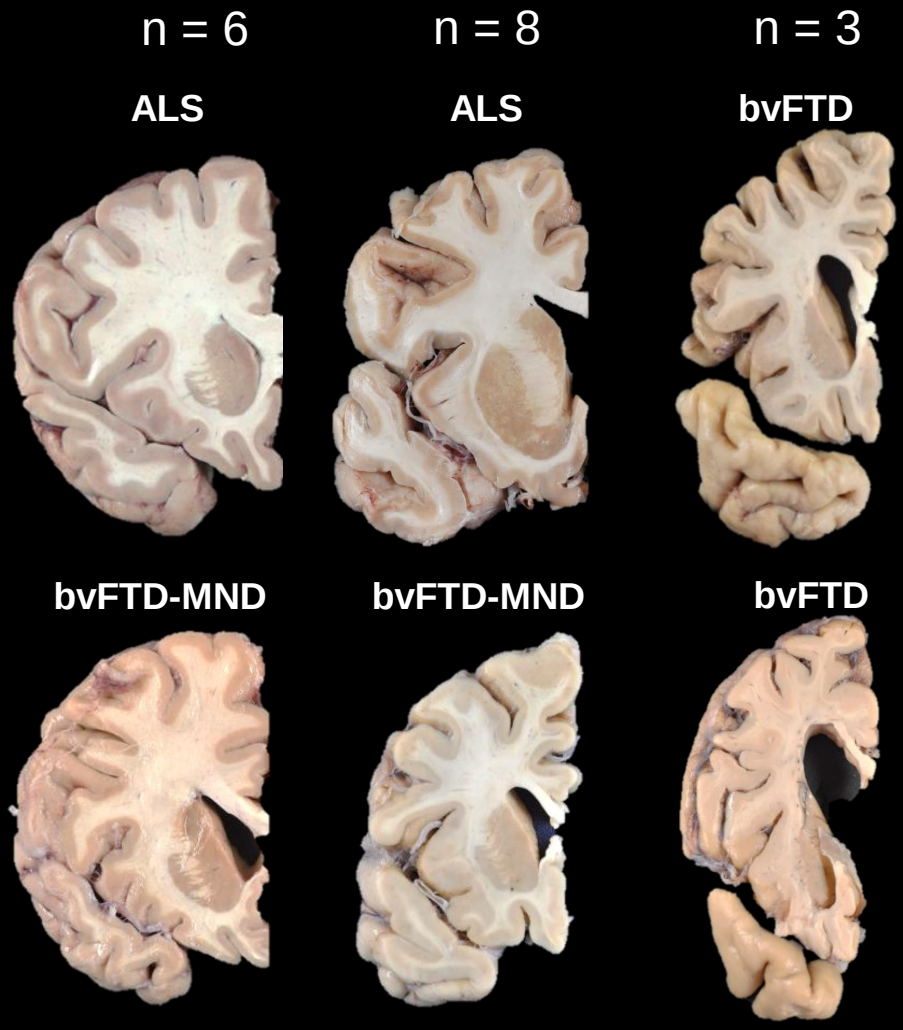
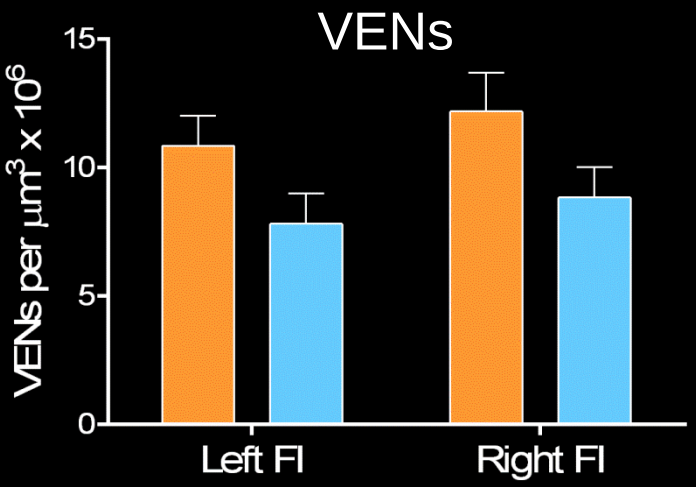
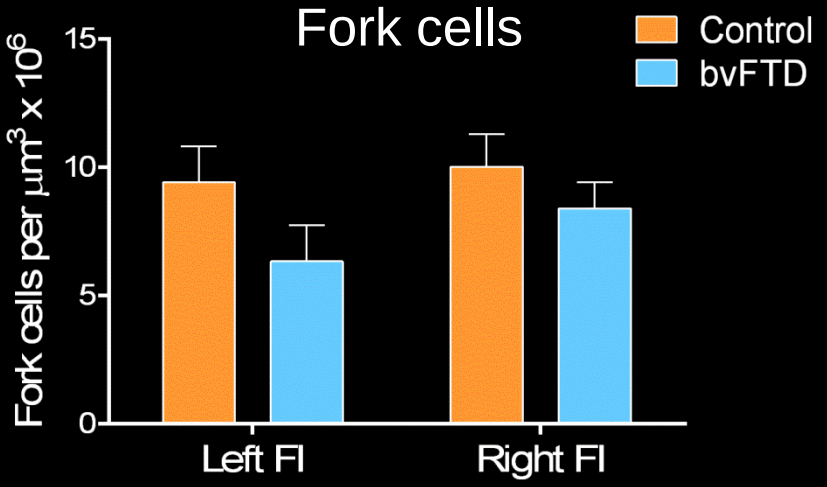
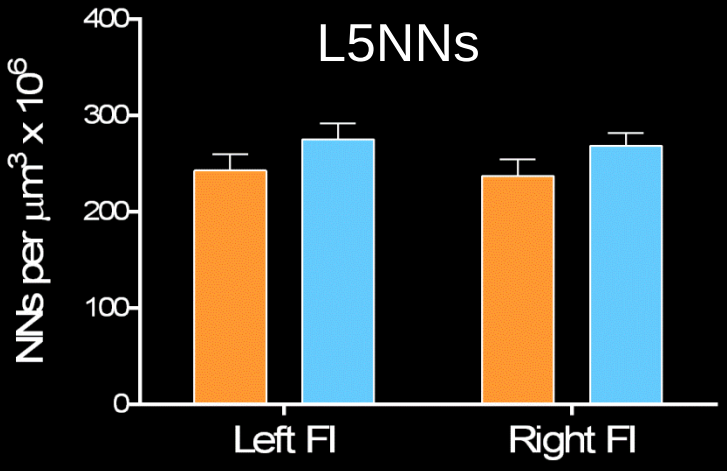


Early stage disease: before neuronal loss



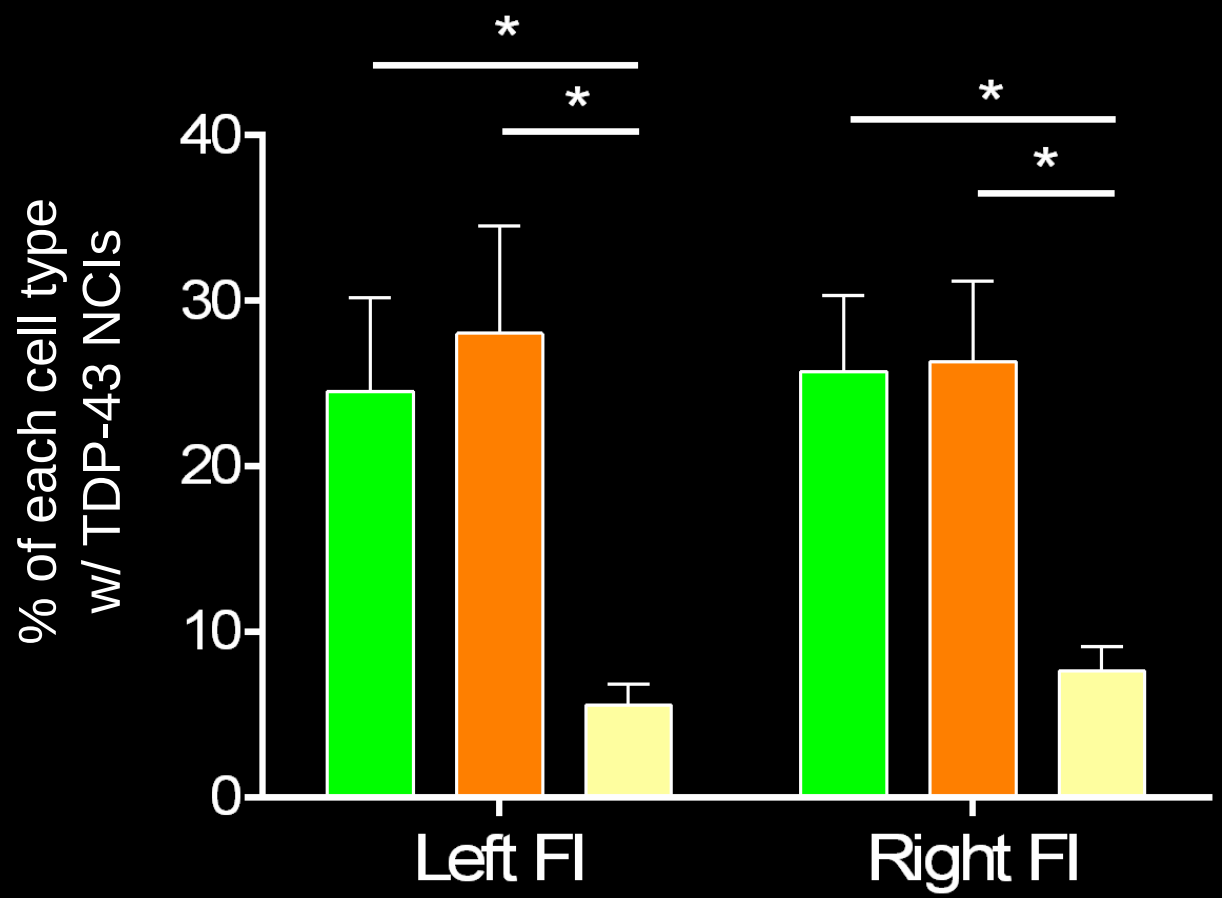




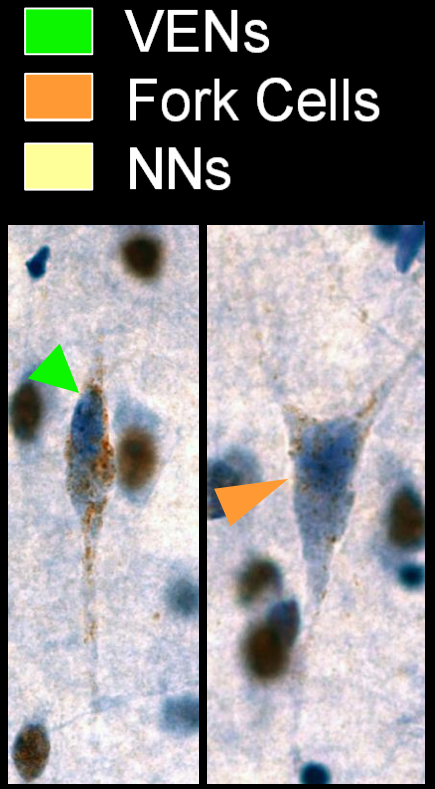
A. Nana Li

Estimated marginal means with rater ± SEM

TDP-43 NCIs target VENs and fork cells in early bvFTD

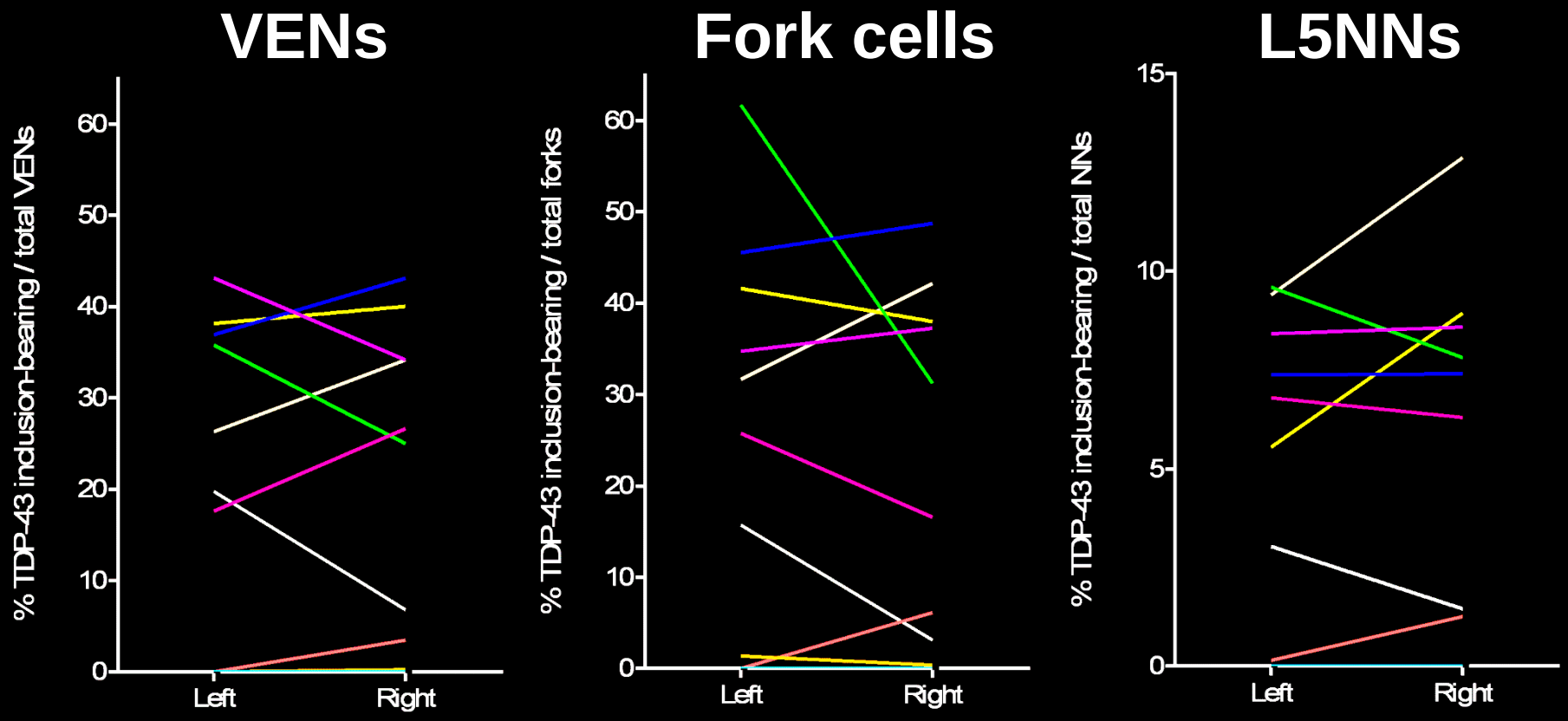


Mean ± SEM, * p<0.001



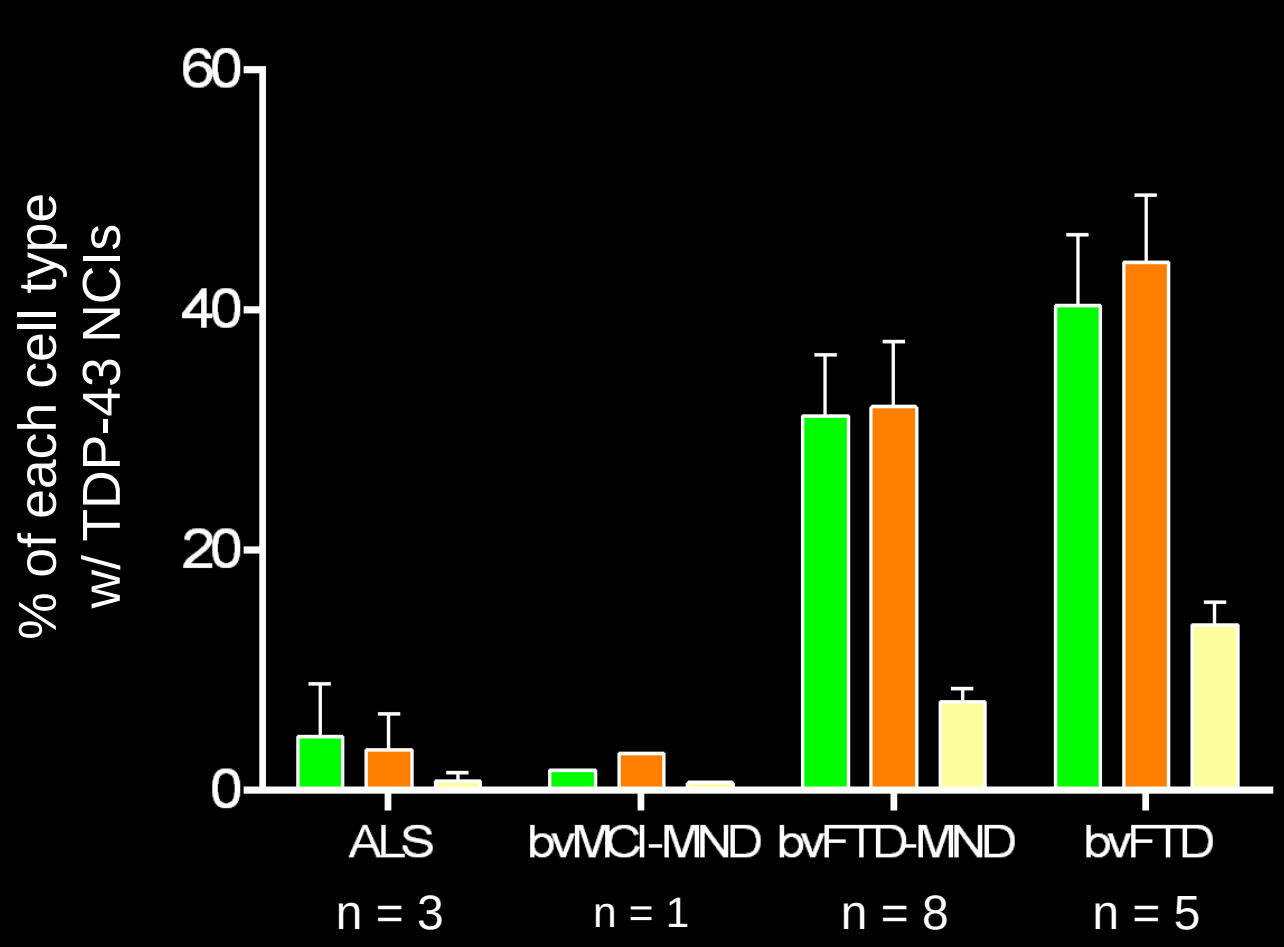
Nana Li et al, unpublished

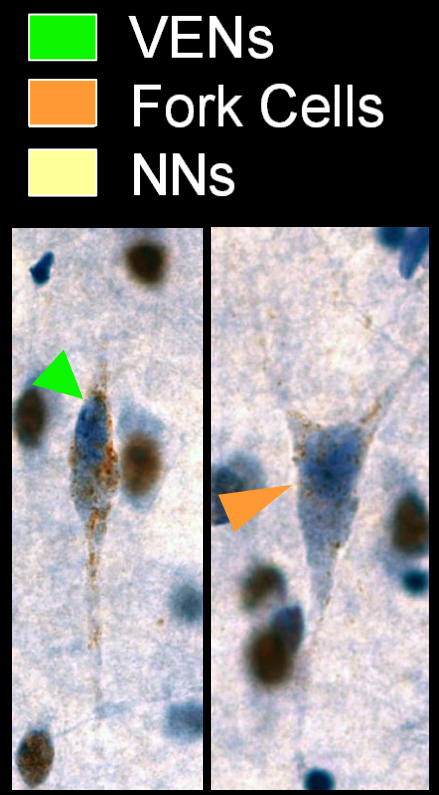
Lateralization of frontoinsular TDP-43 NCIs



Each color represents a single subject. Only subjects with bilateral data are shown.

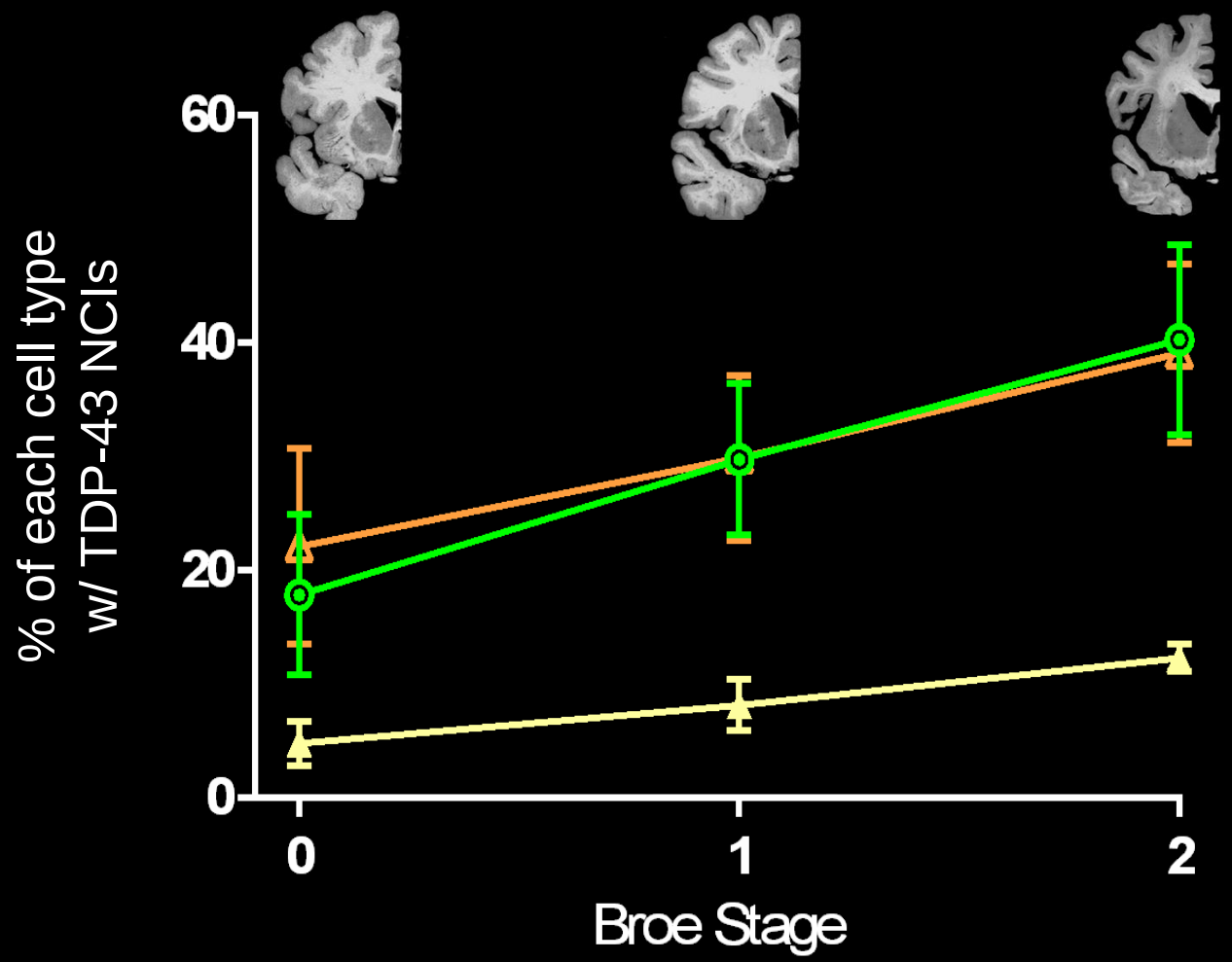
VEN and fork cell TDP-43 inclusions in absence of bvFTD symptoms

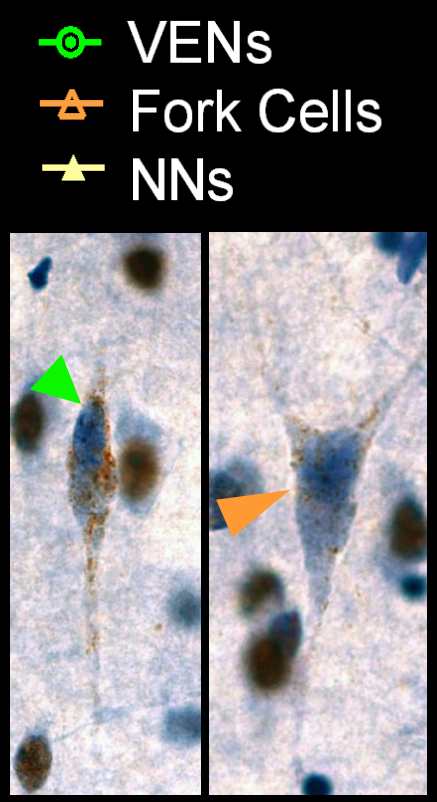




Nana Li et al, unpublished

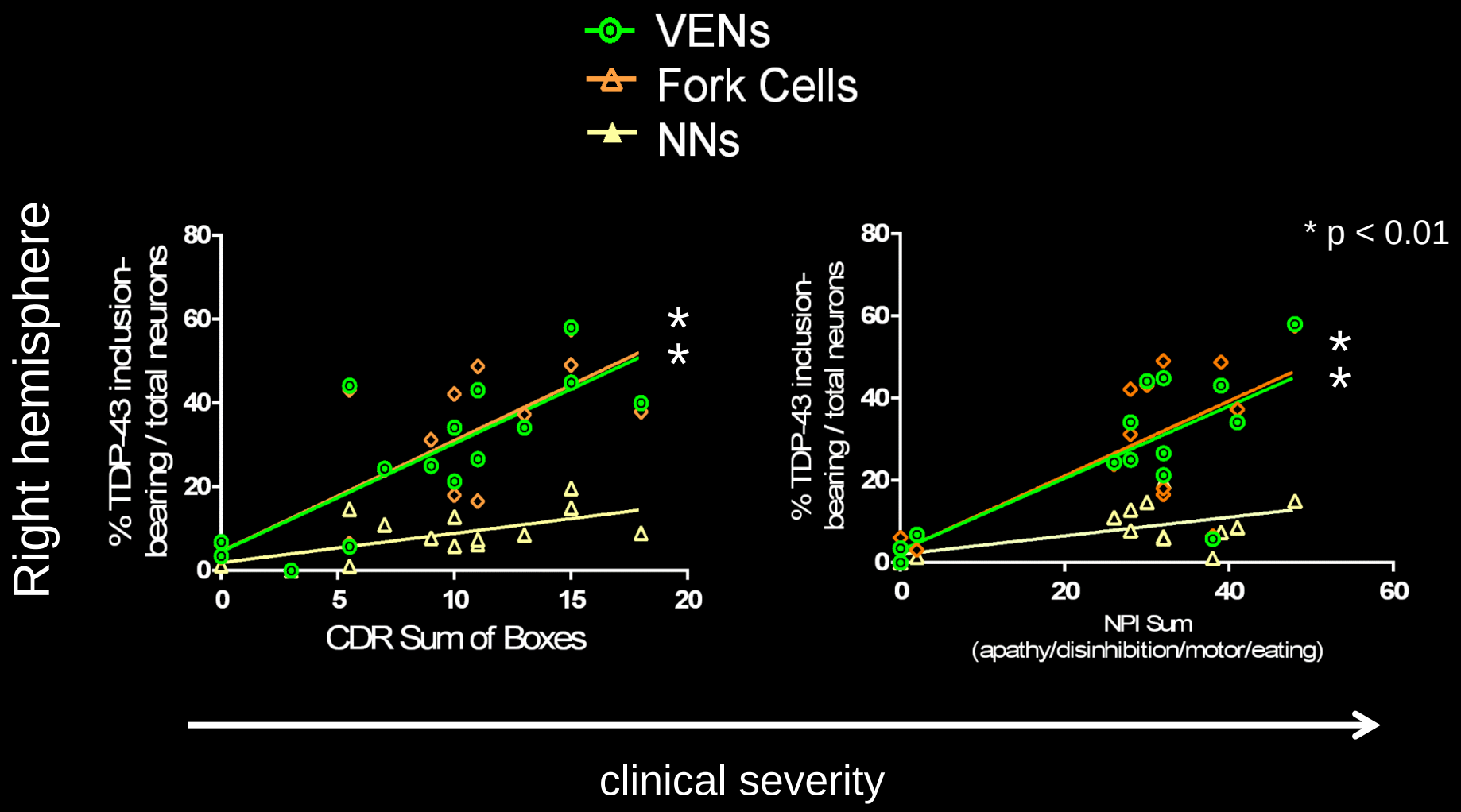
VEN and fork cell TDP-43 inclusions in absence of gross atrophy



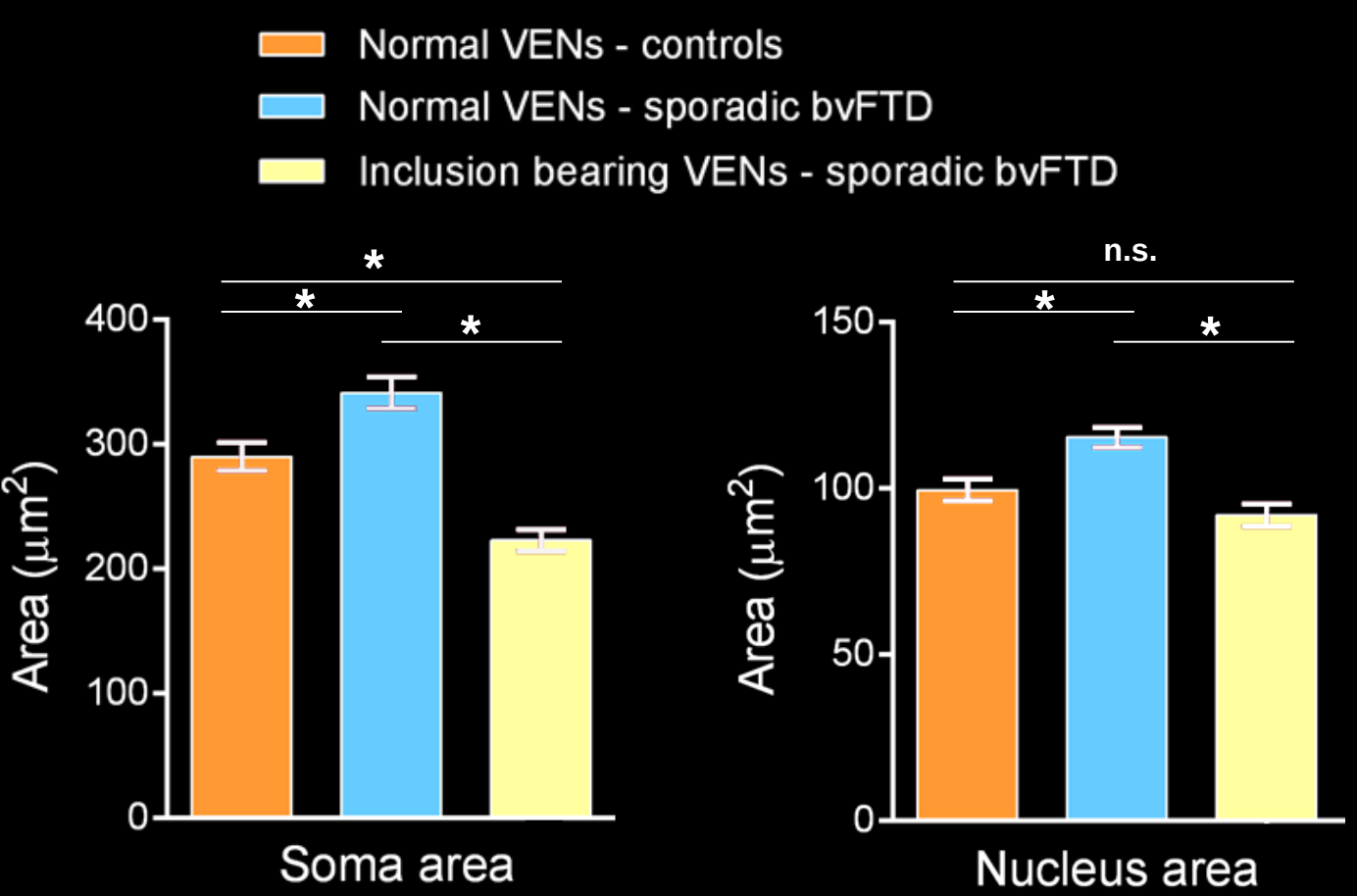


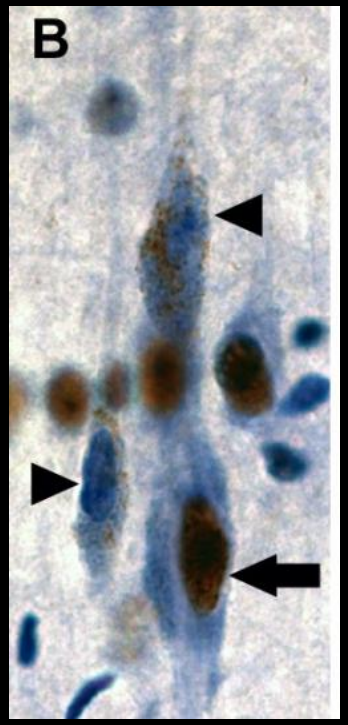
Nana Li et al, unpublished

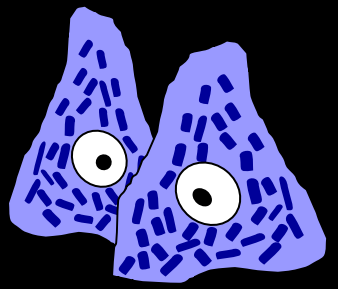
VEN and fork cell TDP-43 inclusions correlate with clinical severity



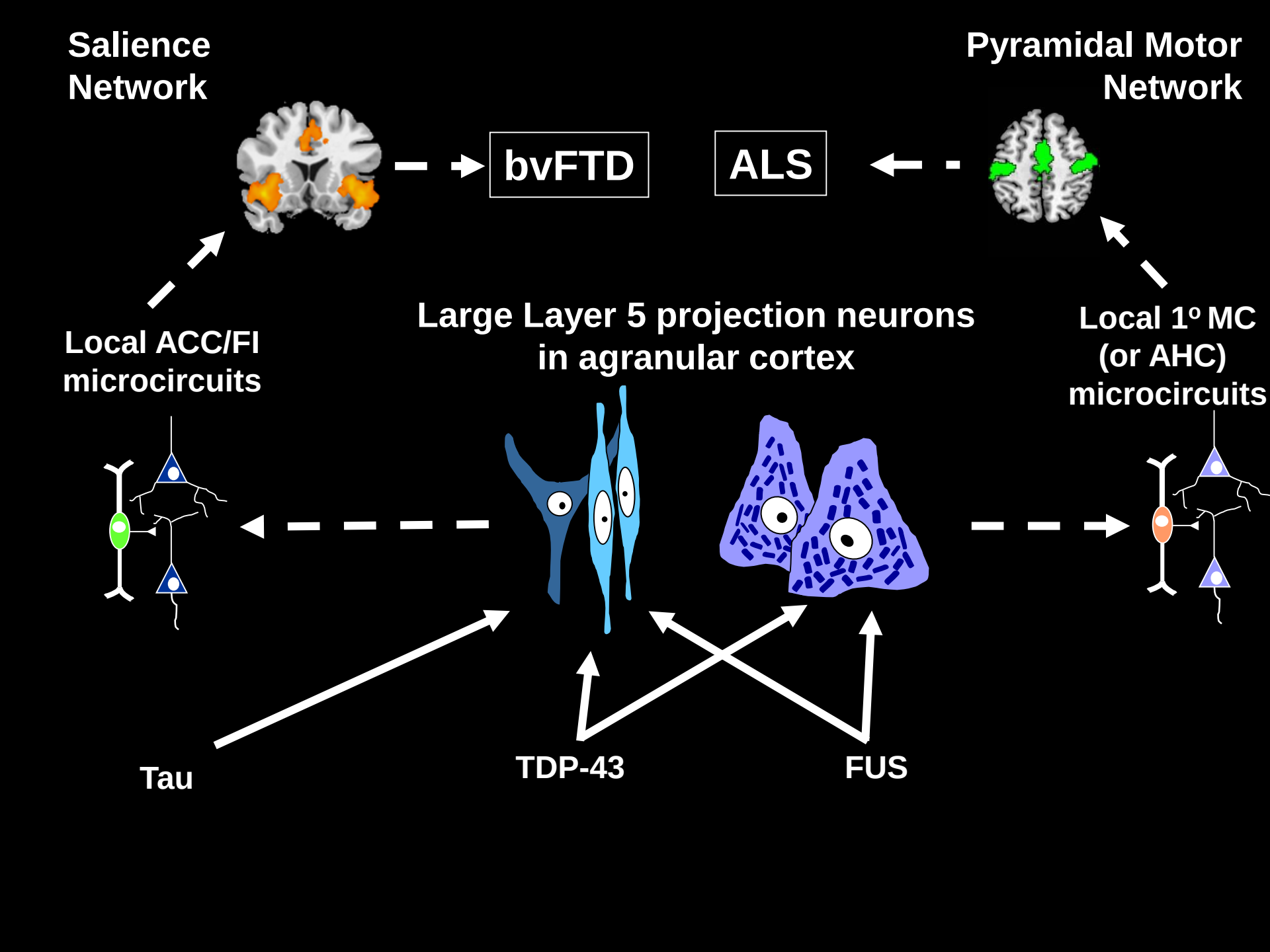
VEN and fork cell TDP-43 inclusions are associated with neuronal atrophy

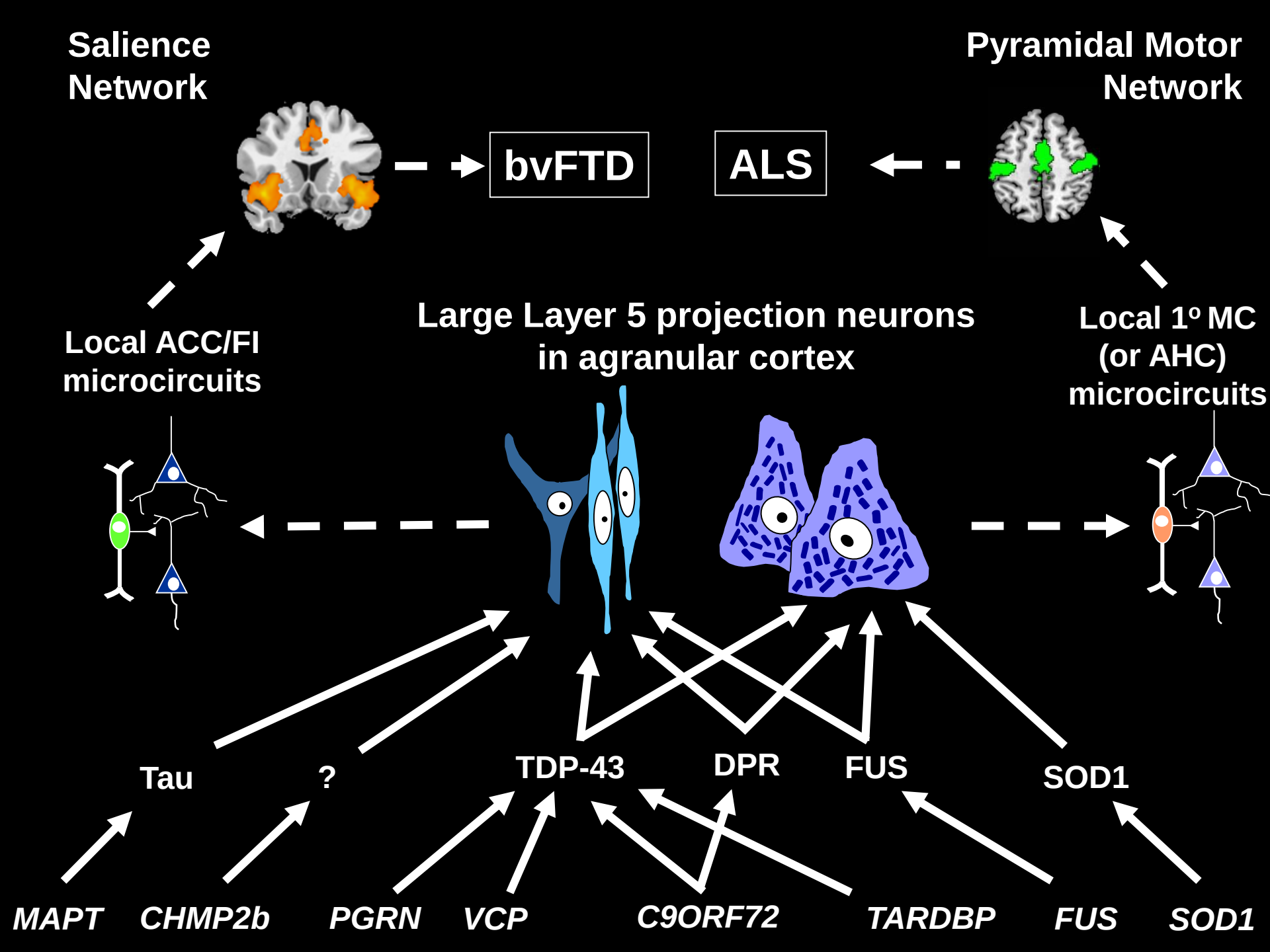






	VEN	CSMN
1st described by	Betz	Betz
Named for	Von Economo	Betz
Morphology	Large bipolar, columnar clusters	Large pyramidal, columnar clusters
Laminar position	5b	5b
Brain-wide localization	ACC/FI	Primary motor cortex
Total number, CNS-wide	~400,000	~200,000
Transcription factor	CTIP2/FEZF2	CTIP2/FEZF2
Neurotransmitter	Glutamate/others?	Glutamate
Projection target	Subcerebral?	AHCs (and other regions)


Salience Network
Pyramidal Motor Network
bvFTD
ALS
Local ACC/FI microcircuits
Large Layer 5 projection neurons in agranular cortex
Local 1º MC (or AHC) microcircuits
Tau
TDP-43
FUS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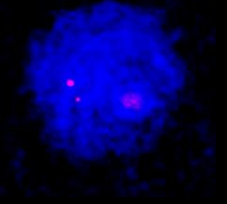
Tau
?
TDP-43
DPR
FUS
SOD1
MAPT
CHMP2b
PGRN
VCP
C9ORF72
TARDBP
FUS
SOD1

bvFTD onset: the special case of C9ORF72

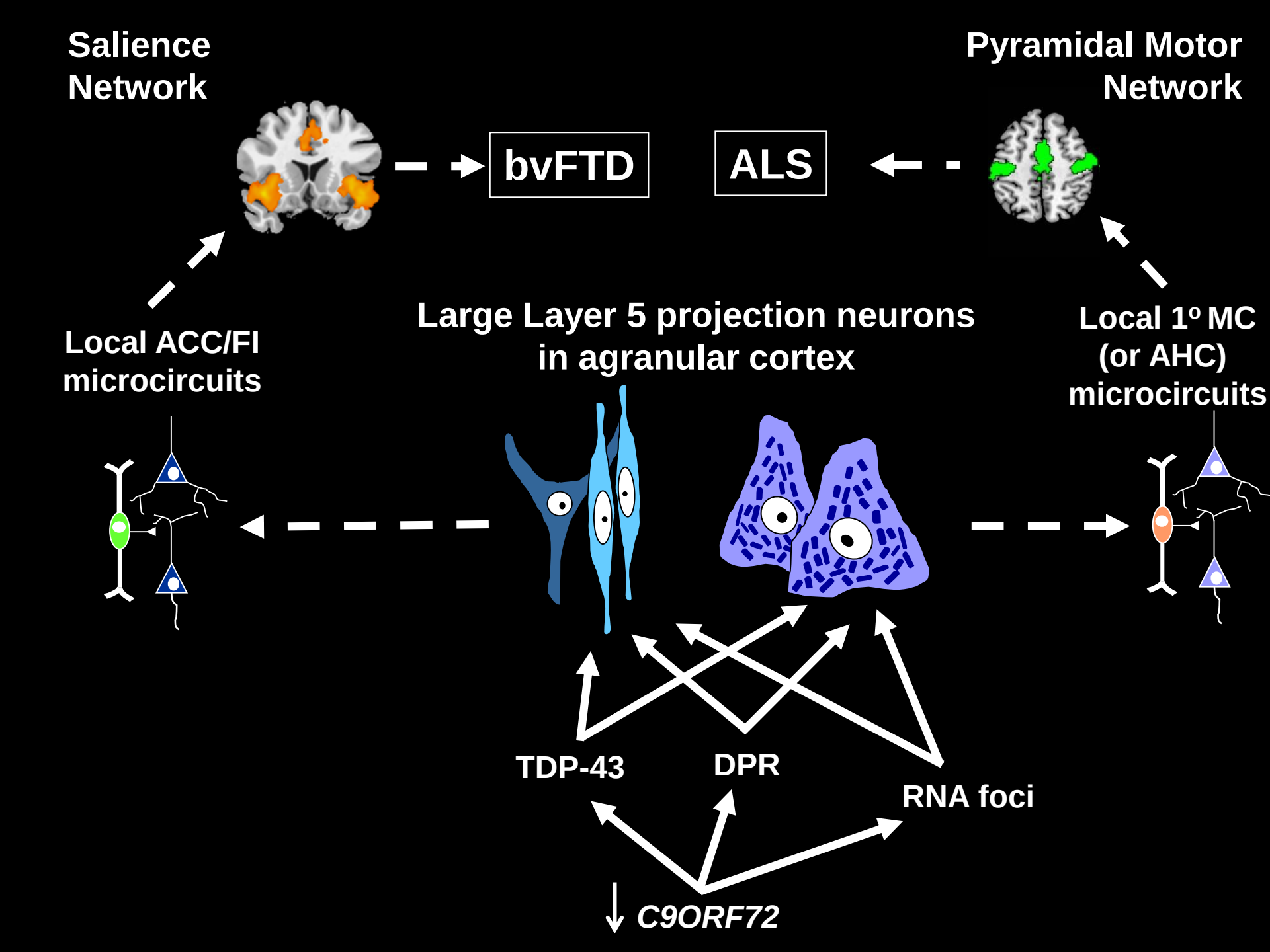
C9ORF72

- Major syndromes are bvFTD, ALS, and bvFTD-ALS but heterogeneity even among family members
- MRI in C9ORF72-bvFTD shows typical atrophy in some but can be mild, atypical, or absent.
- Neuropathology = FTLD-TDP, Types B>U>A
- C9-specific neuropathology:
  - RNA foci (sense and antisense)
  - Dipeptide repeat proteins (GA, GP, GR, PA, PR)
  - Reduced C9ORF72 expression (histone trimethylation)

RNA foci
FISH



DPR, p62 IHC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Pyramidal Motor Network
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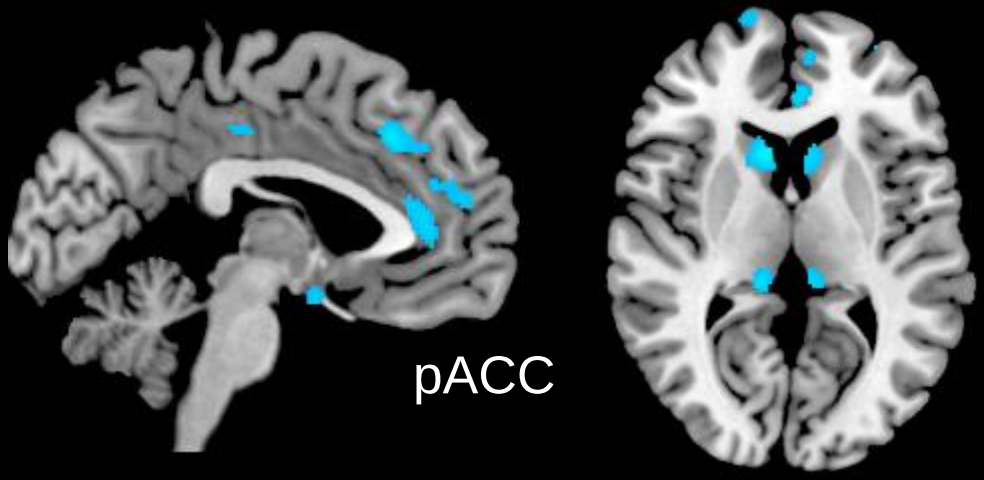
ALS
Local ACC/FI microcircuits
Large Layer 5 projection neurons in agranular cortex
Local 1º MC (or AHC) microcircuits
TDP-43
DPR
RNA foci
C9ORF72

C9ORF72 carriers show gray matter volume deficits by the 3rd decade

Suzee Lee

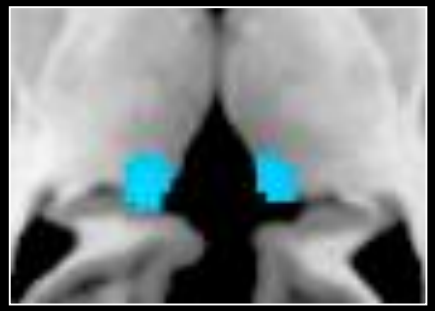
Voxel-based morphometry
13 asymptomatic carriers < 13 matched HC



pACC

R FI

vmSTR

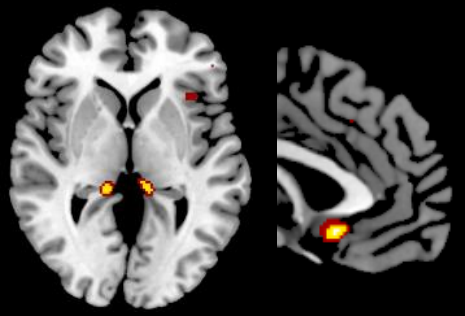


mPULV

Single case illustrations provide key insights into *C9ORF72* pathogenesis

S. Vatsavayai

Case 1: C9+ bvFTD w/ sparse TDP-43

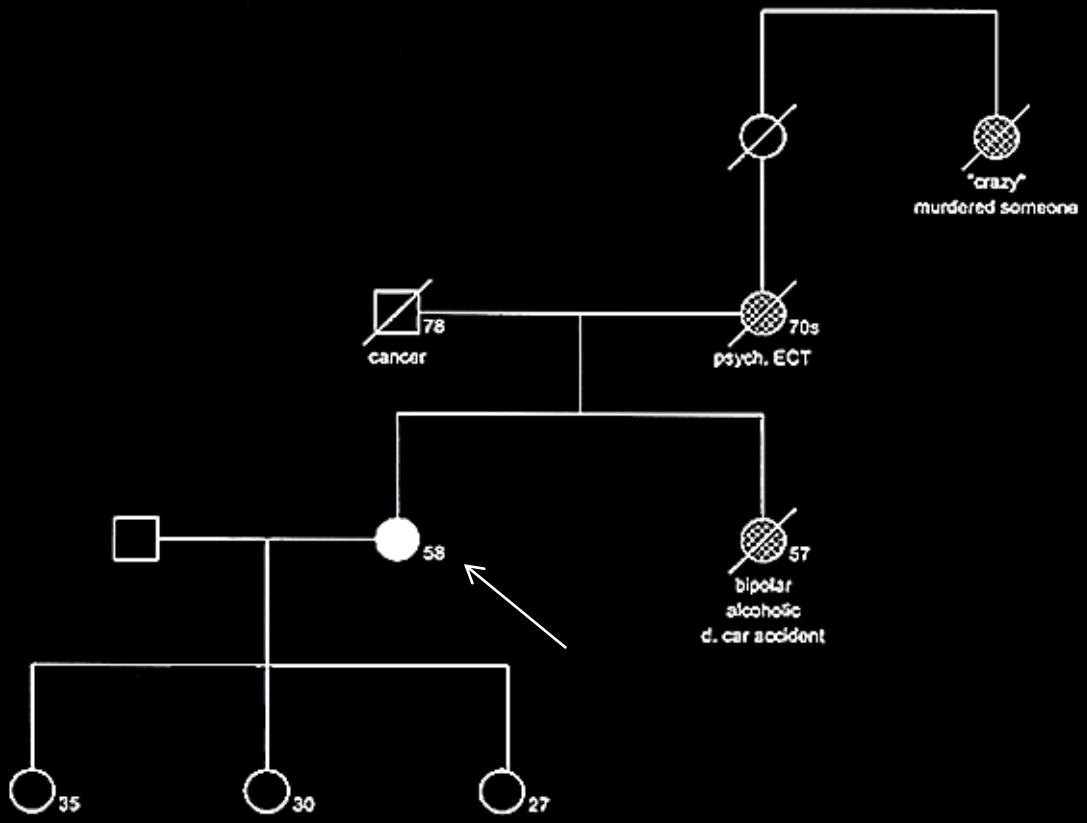


Case 2: C9+ bvFTD with pre-symptomatic histopathological assessment

Case 1:
Focal C9-bvFTD with sparse TDP-43 pathology

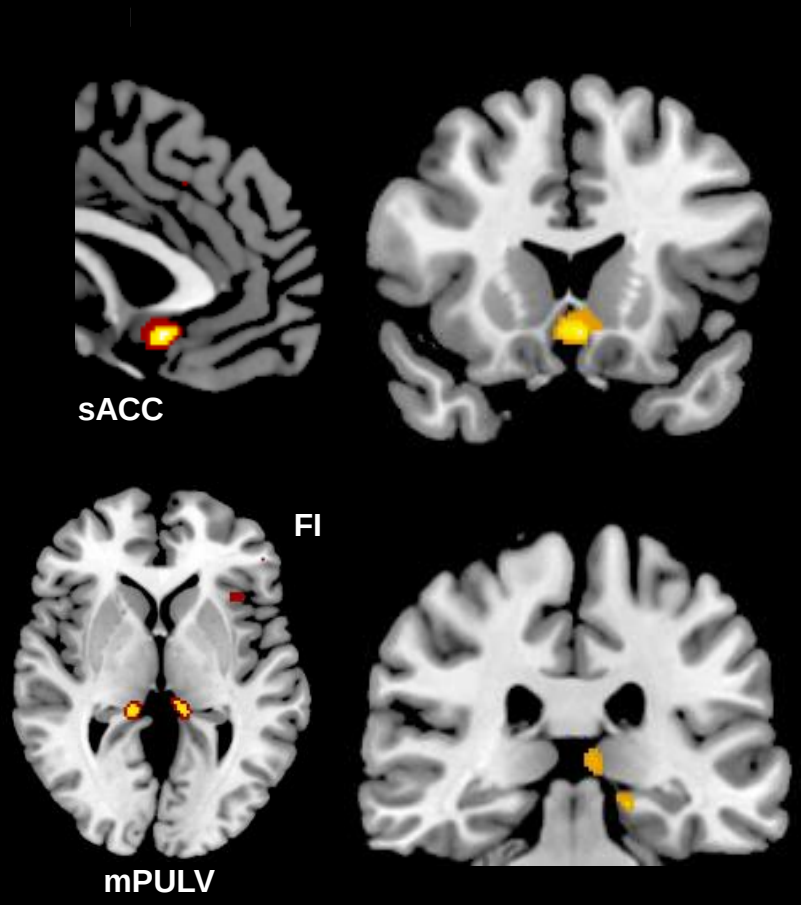
- Age 55: New binge EtOH, “verbal tantrums”, spells of prolonged pacing and mumbling or driving around block, followed by full-blown bvFTD syndrome before death at 65 in setting of a recent hip fracture. Family history = psychiatric disease in 3 generations

- Primary neuropath Dx – FTLD-TDP-U, too sparse to classify



Focal C9-bvFTD with sparse TDP-43 pathology

Brain region	Vacuolation	Astrogliosis
pACC	-	-
sACC	**++**	**++**
preCG	-	-
postCG	-	-
Inf temp gyrus	-	-
Calcarine ctx	-	-
Entorhinal ctx	-	-
Hip – DG		-
Hip - CA3-4		-
Hip - CA2		-
Hip - CA1/Subiculum		-
Amygdala		**++**
Thalamus (mPULV)		**+++**
vSTR		-
Cerebellar cortex		-
Cerebellar DentNuc		-
Inferior olive		-
Spinal cord AHC		-

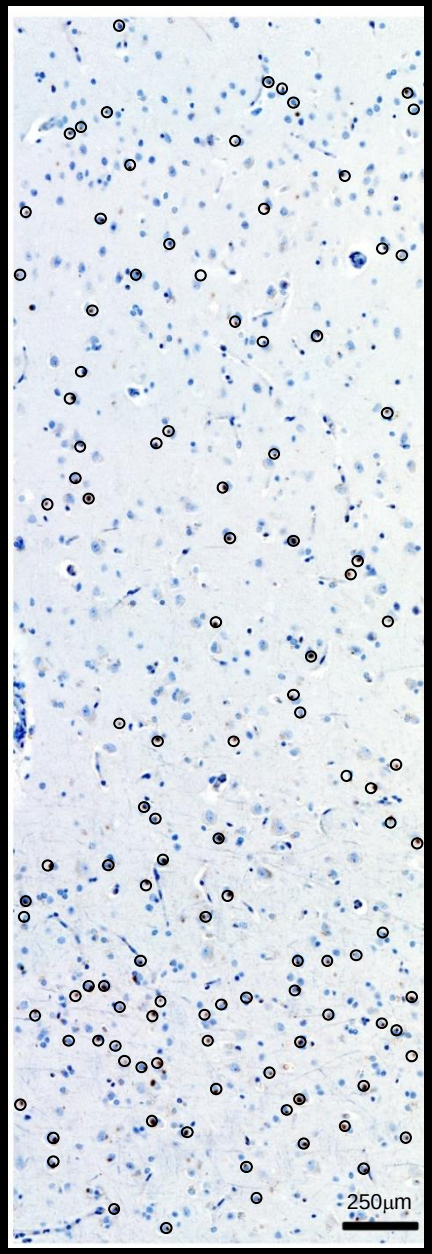


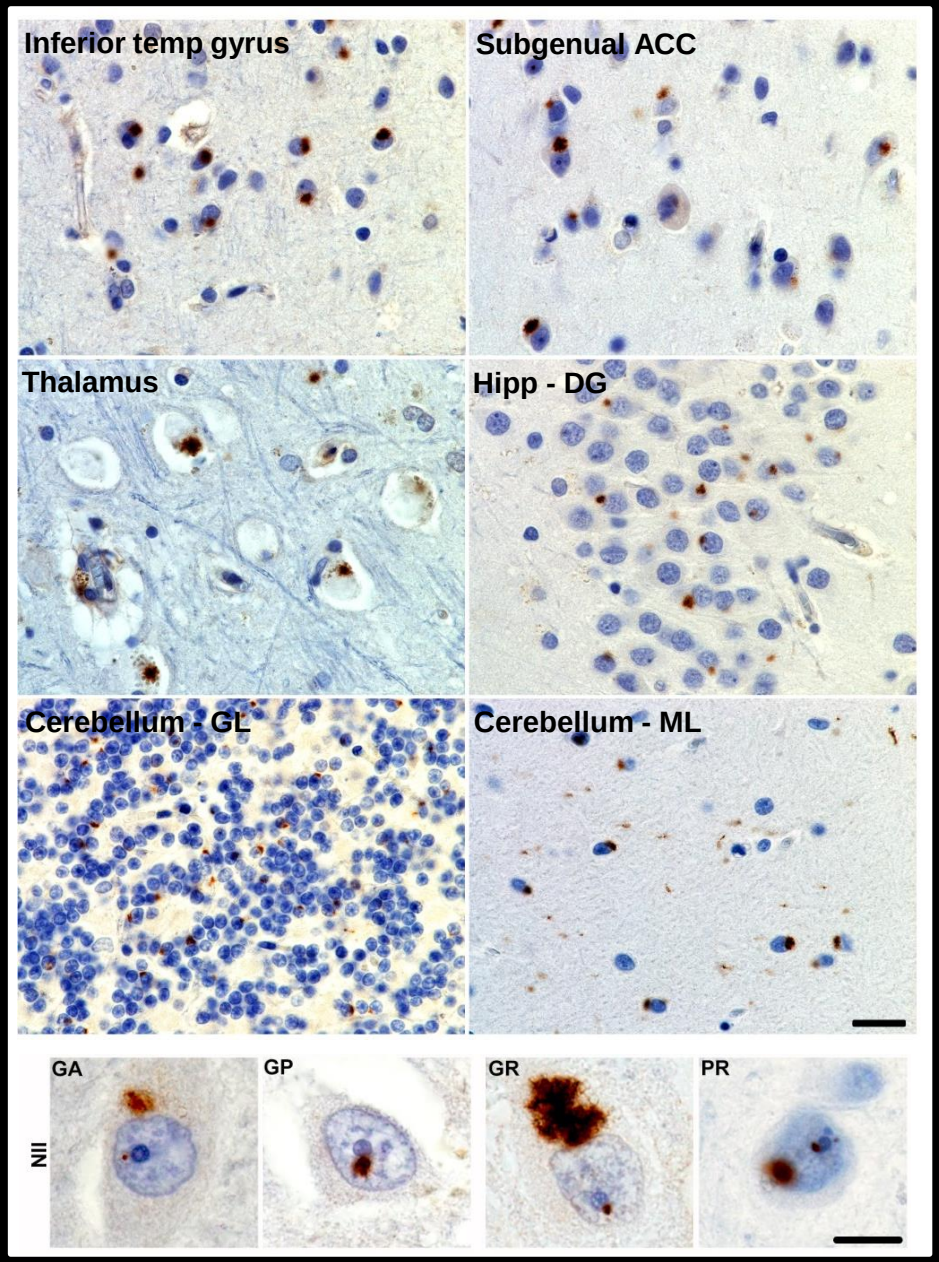
VBM, pt < 30 controls

- absent, (+) scarce, + rare, ++ mild, +++ moderate, ++++ abundant

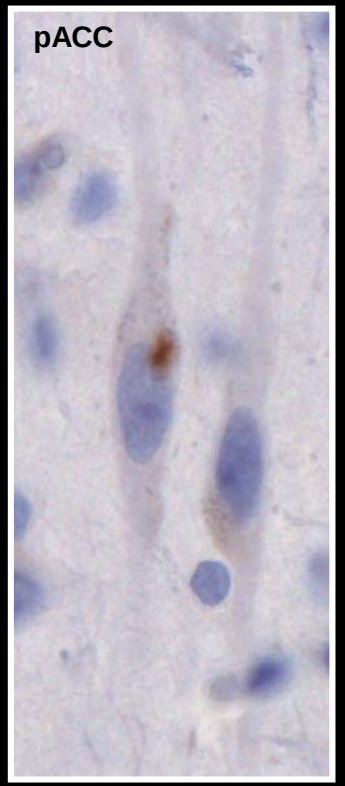
DPR antibodies kindly provided by Len Petrucelli and Tania Gendron

Case 1: GA dipeptide inclusion pathology

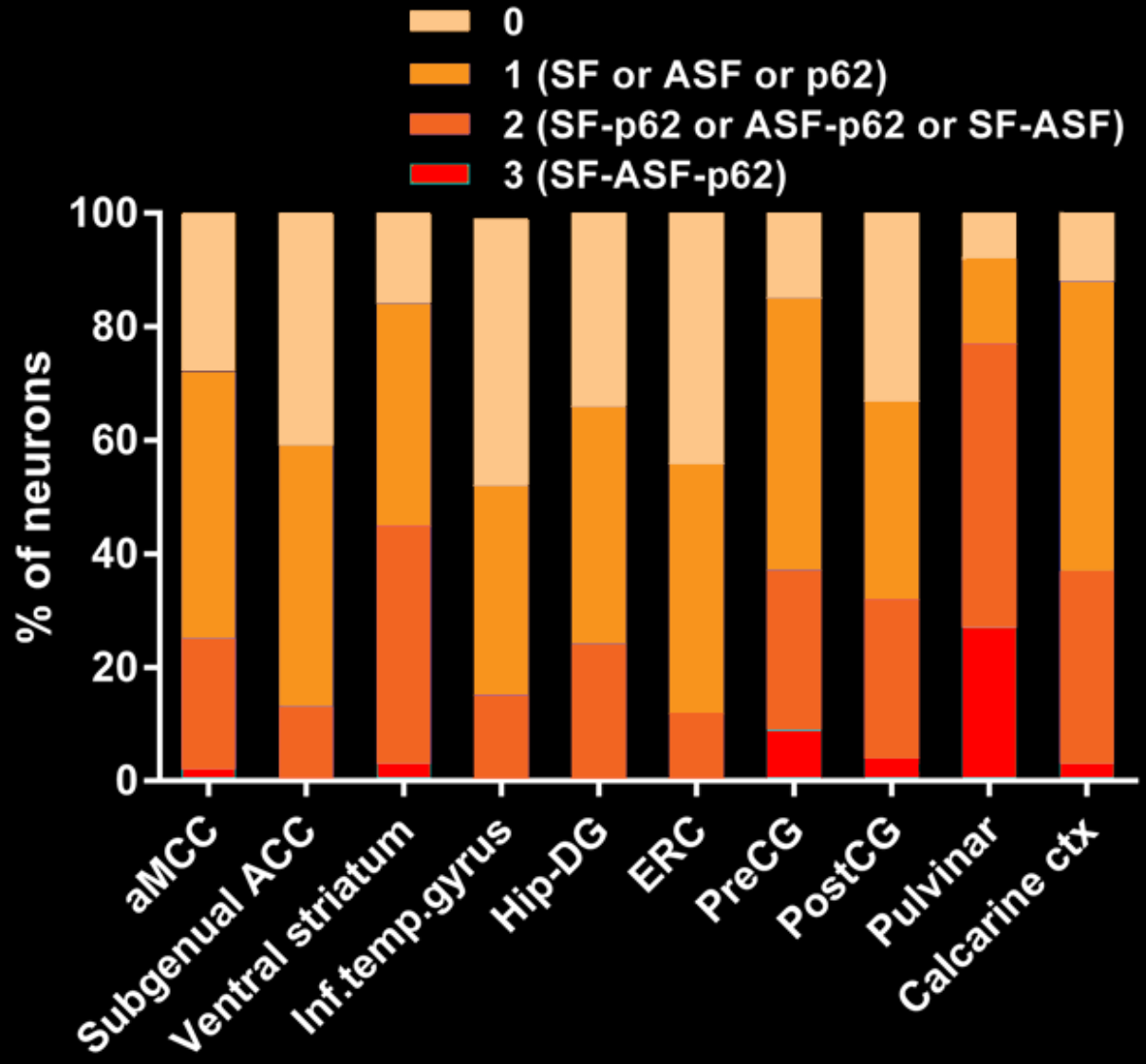


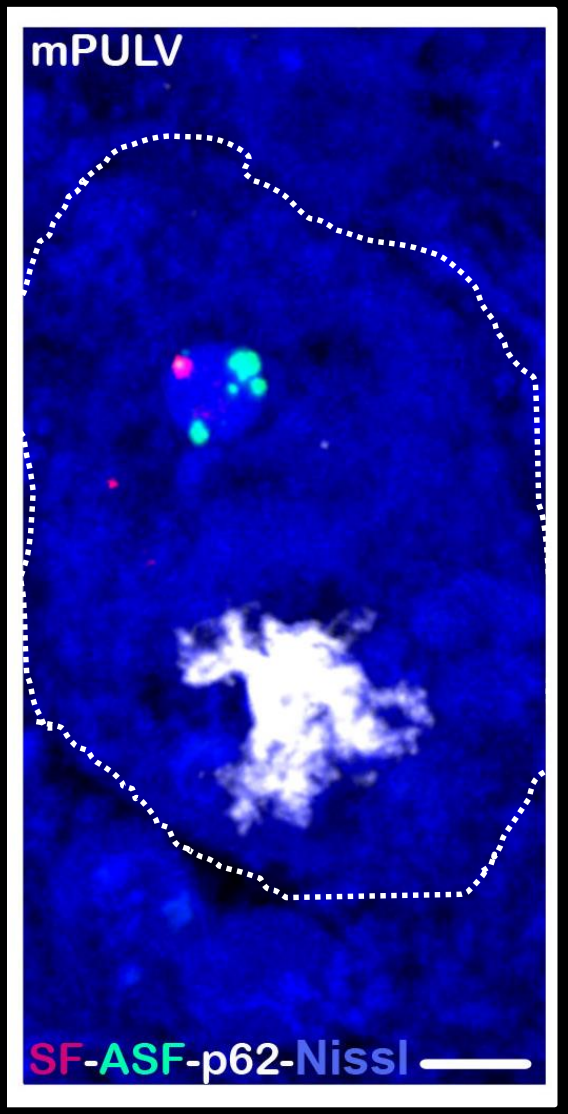


S. Vatsavayai



Case 1: Does the multiplicity of C9-related pathological findings predict neurodeneration?





Case 2:
Surgical epilepsy followed by atypical FTD

74 y.o. woman suffered a severe childhood head trauma. Developed epilepsy in her 30's, refractory in her 50's.

Age 61: Surgical resection of anterior and mesial temporal-limbic structures, seizure free on fewer meds. Mild post-operative aphasia resolved within days.

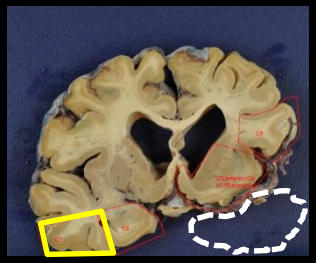
Age 66 : New non-epileptic spells of confusion, coldness, and urinary urges (10-30 sec). Progressive mixed dementia with anomia and amnesia but also prominent behavioral and visuospatial deficits, progressing to mutism.

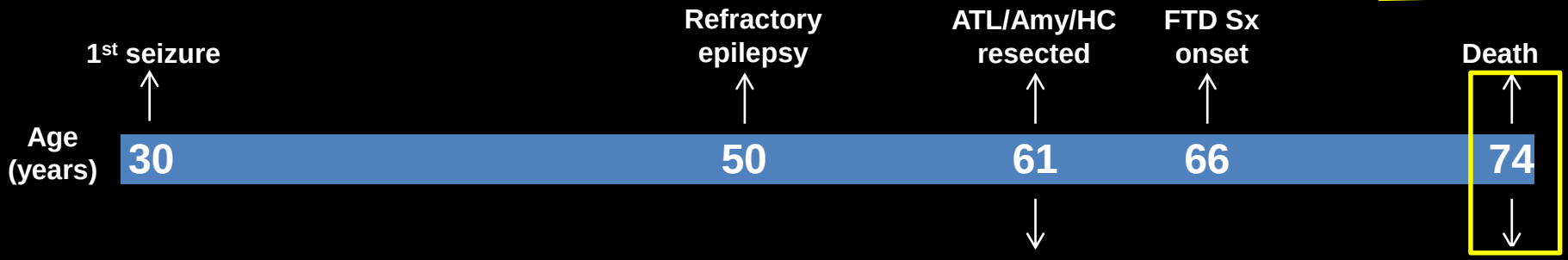
Primary neuropathological Dx: FTLD-TDP, Type B

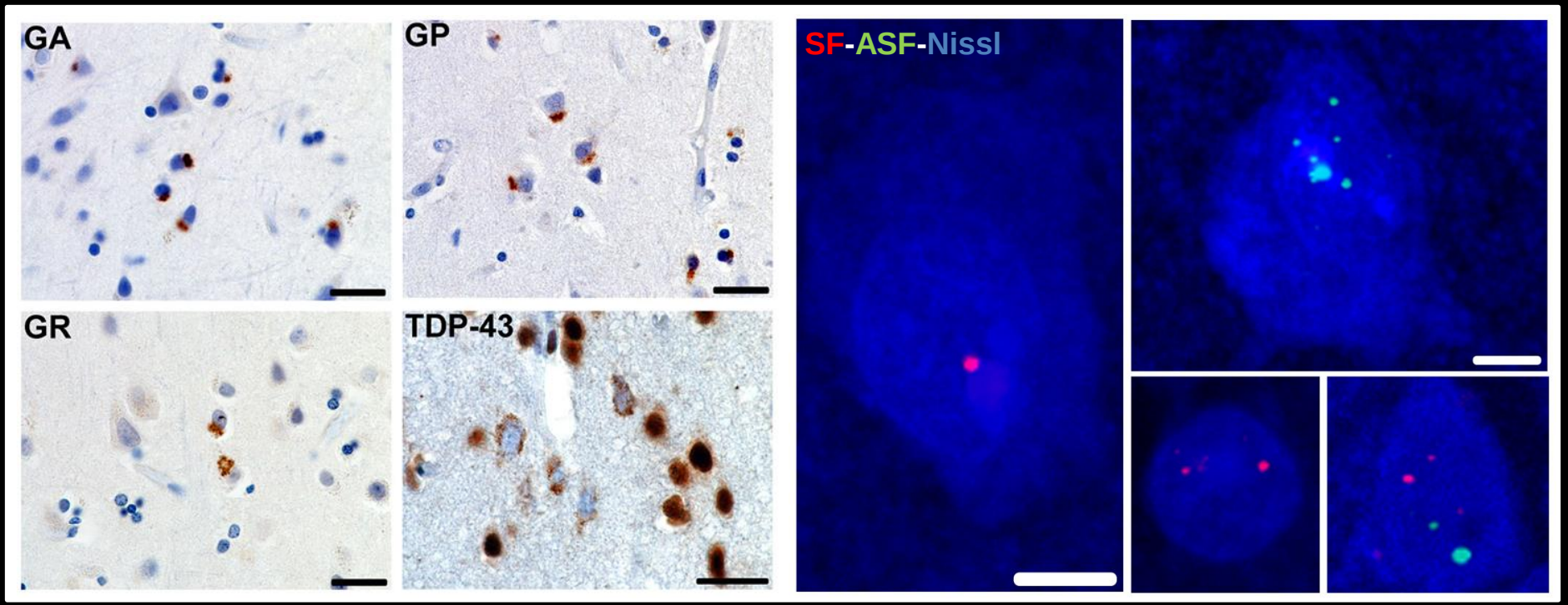
Age (years)

Refractory epilepsy	1st UCSF EMU visit	ATL/Amy/HC resected	FTD Sx onset	1st UCSF MAC visit	Death
50	51	61	66	69	74

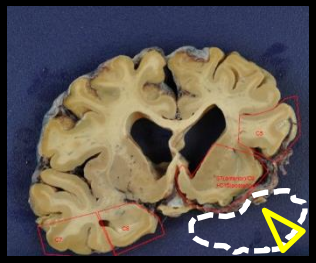
Case 2: Post-mortem findings

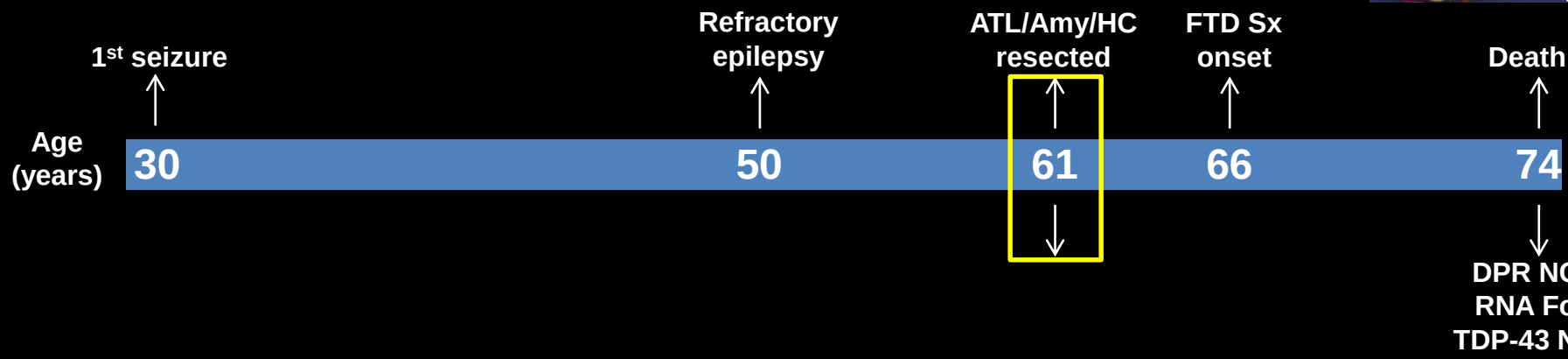


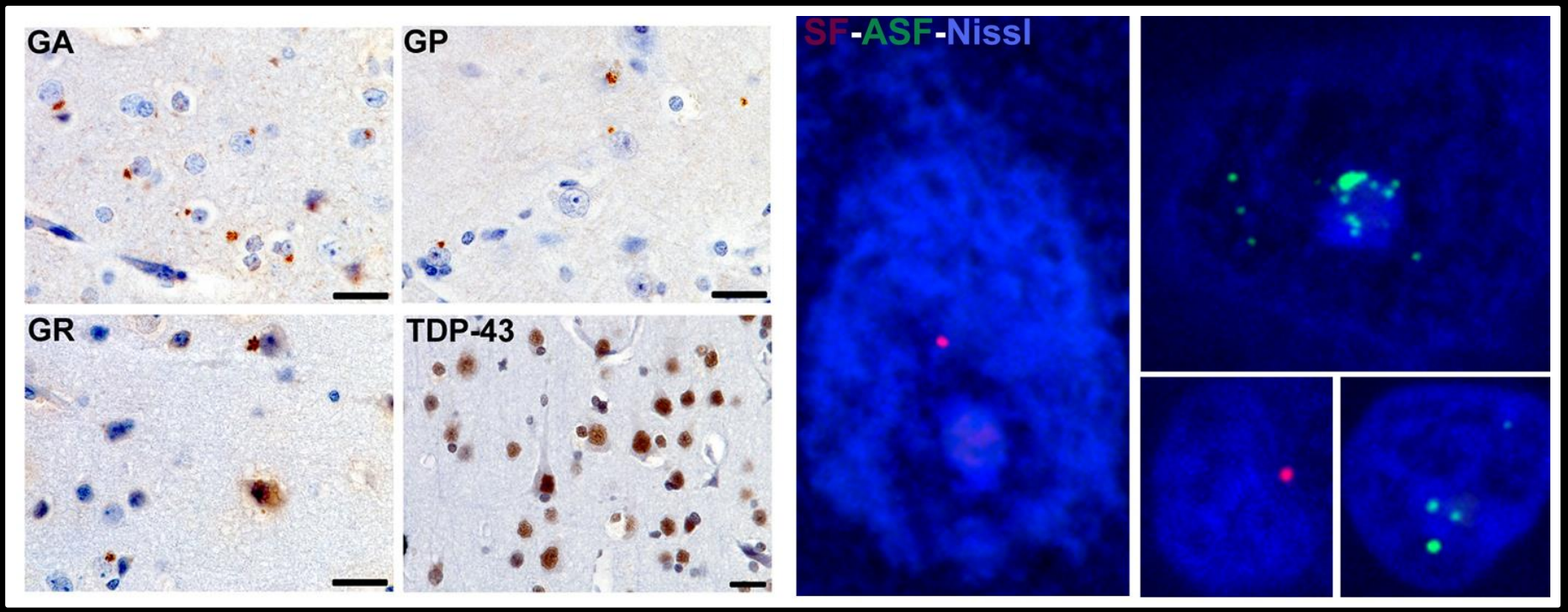


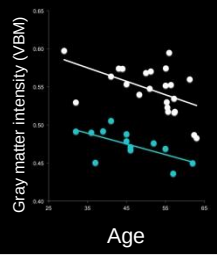


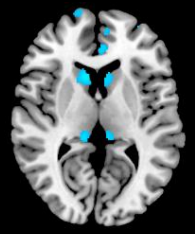
Case 2: Resected ATL
5 yrs prior to 1st Sx, 13 yrs prior to death

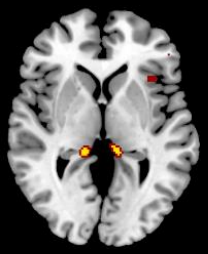


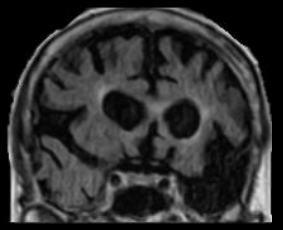


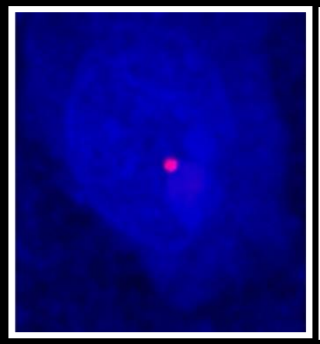


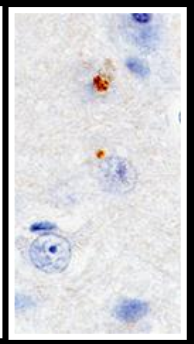

Gray matter intensity (VBM)
Age

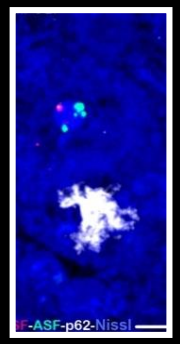


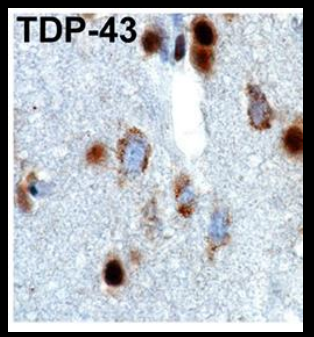


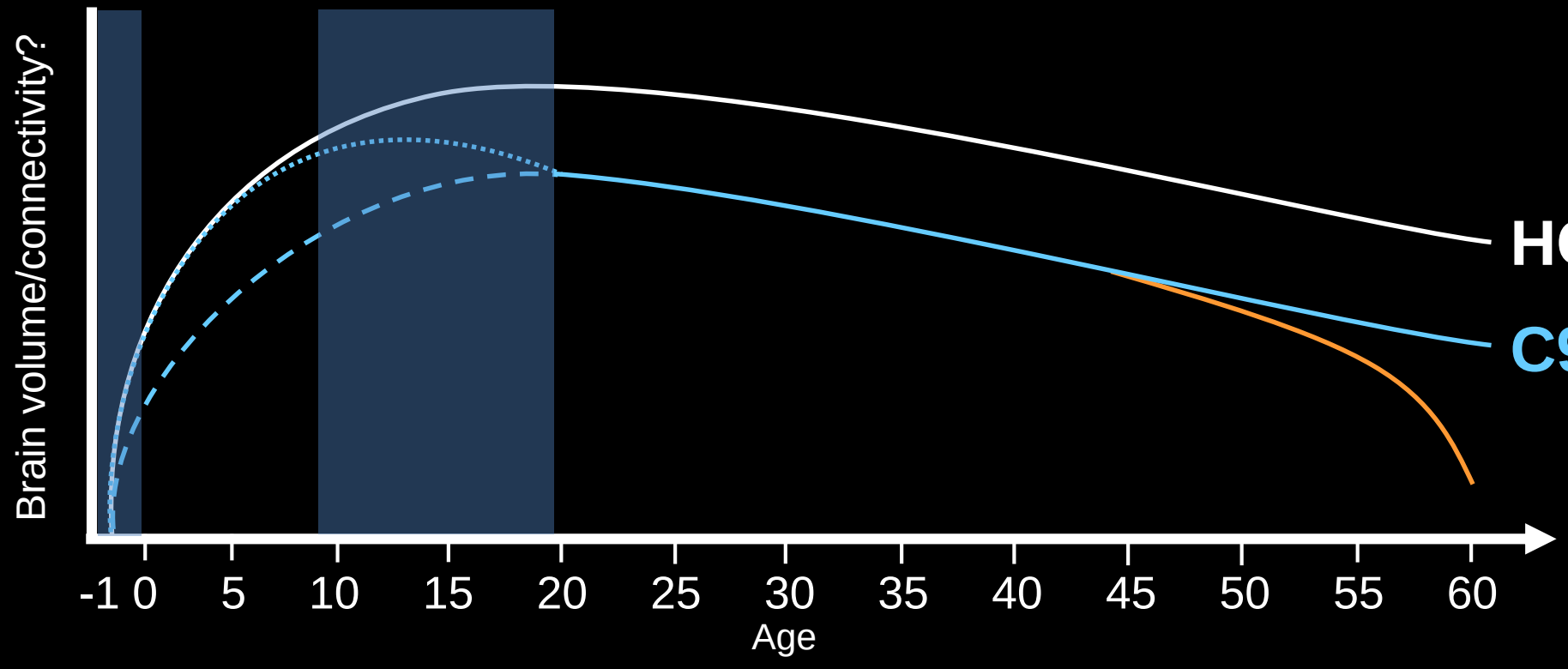






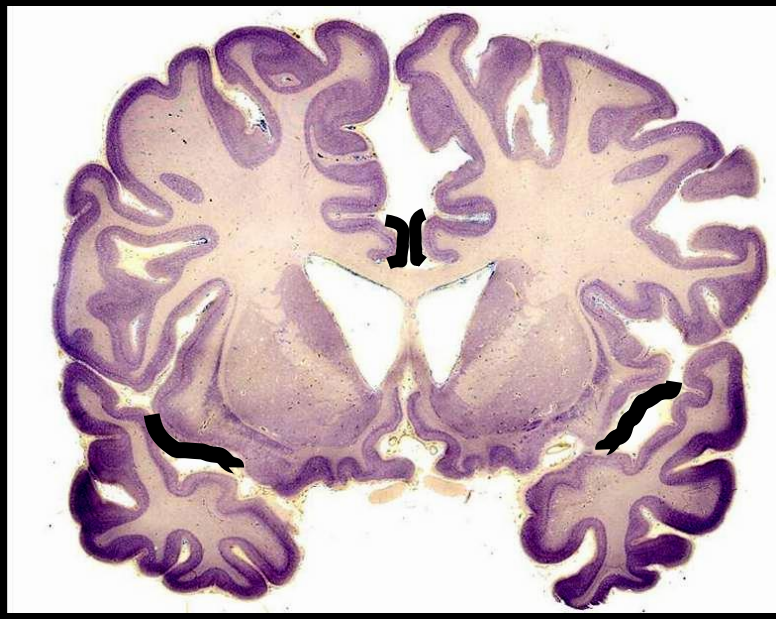

F-ASF-p62-Nissl


TDP-43

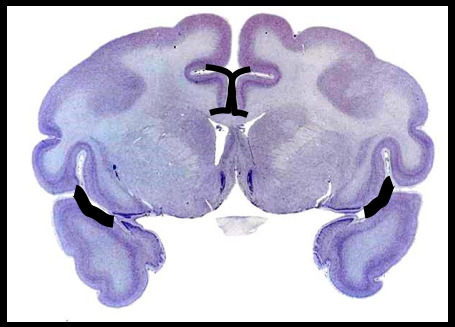

Brain volume/connectivity?
HC
C9
-1 0 5 10 15 20 25 30 35 40 45 50 55 60
Age

Translation/Future

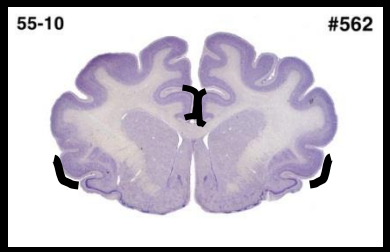
Allocortex ↔ Paralimbic Transition Zones ↔ Neocortex



HUMAN



MONKEY



CAT

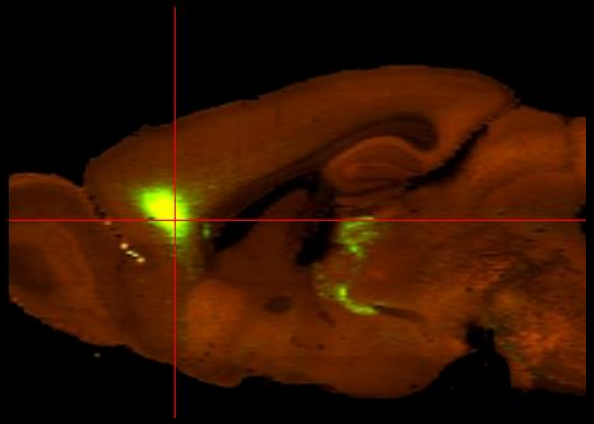
MOUSE

(not drawn to scale)

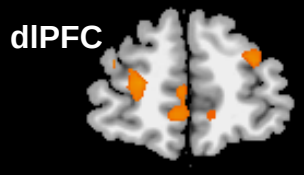
Salience network homolog in the mouse brain

Right FI seed ROI

3T fcMRI
19 healthy controls



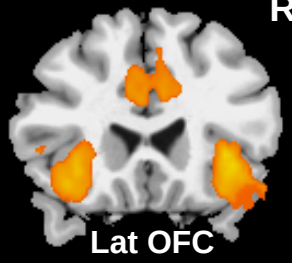
Mouse AAV injection, PL
Allen Brain Institute



dlPFC

Frontal pole

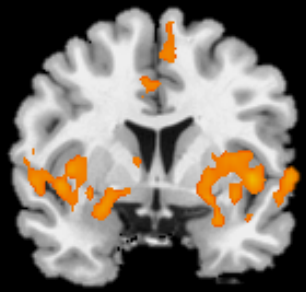
ACC



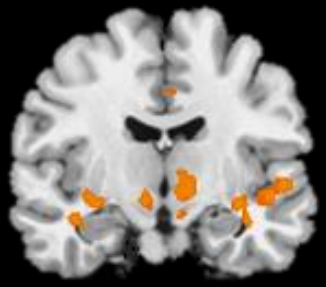
Right

Lat OFC

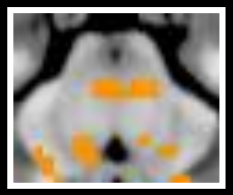
FI FI

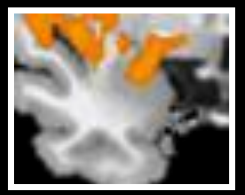


cAMY VSP

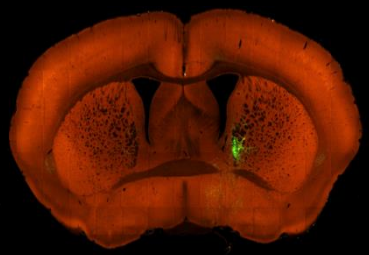


Hypothalamus

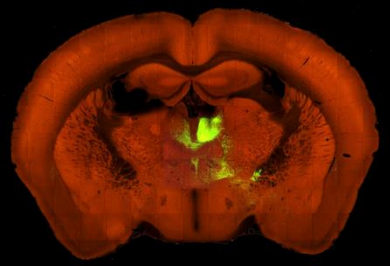




AIv AIv

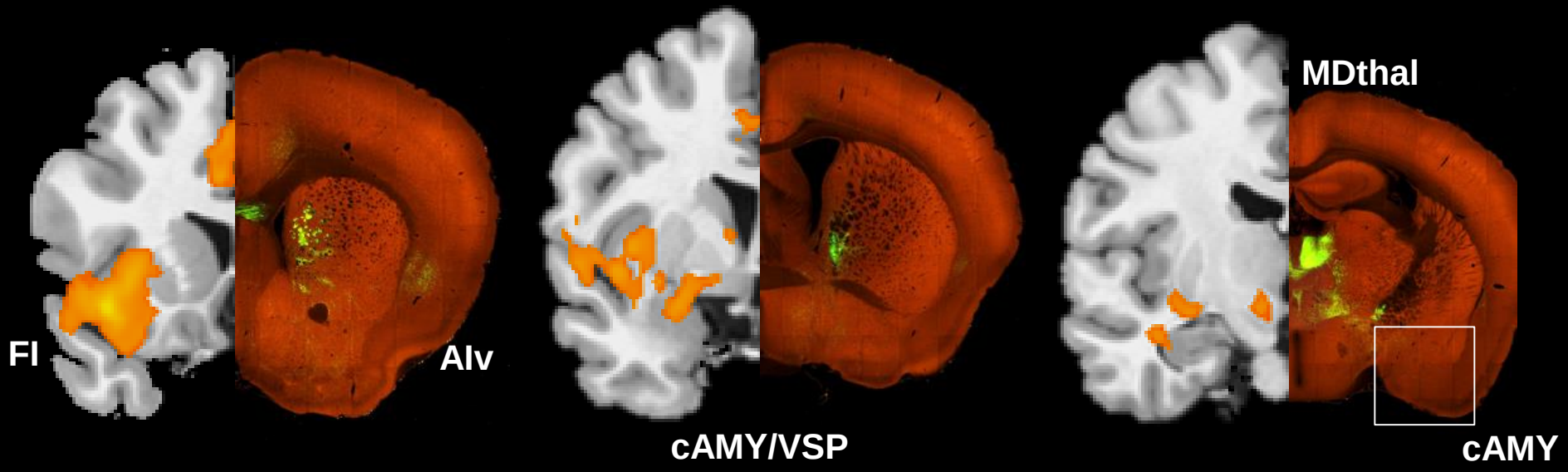


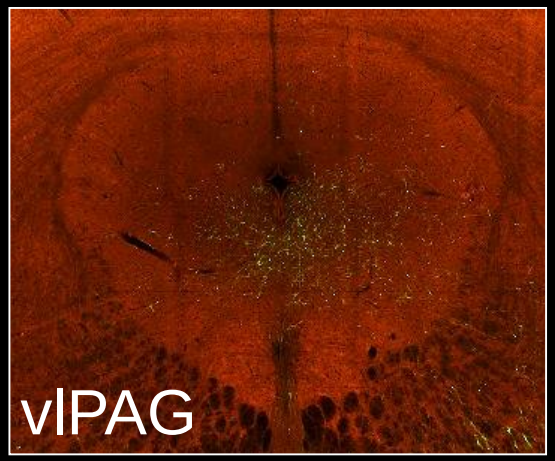
VSP



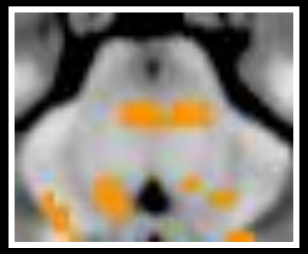
Hypothalamus

Salience network homolog in the mouse brain





vlPAG



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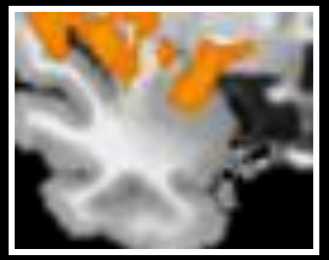
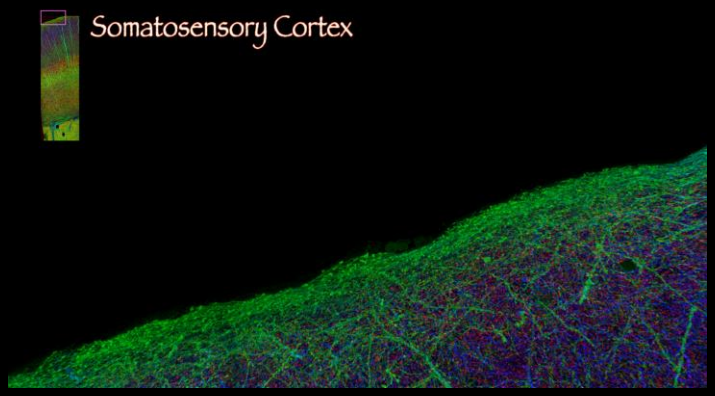
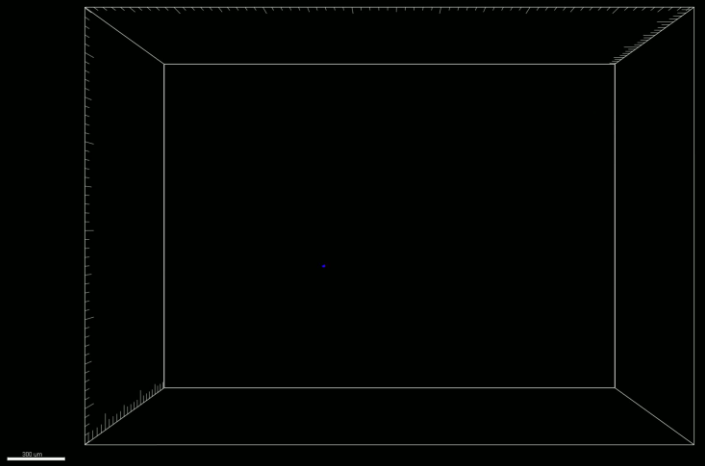


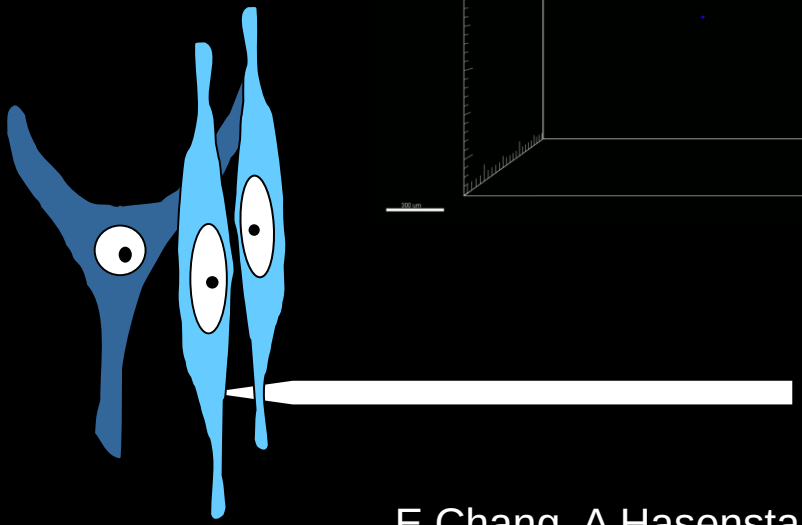
Ongoing projects: VEN identity and vulnerability

Courtesy S. Smith Lab, Stanford/AIBS

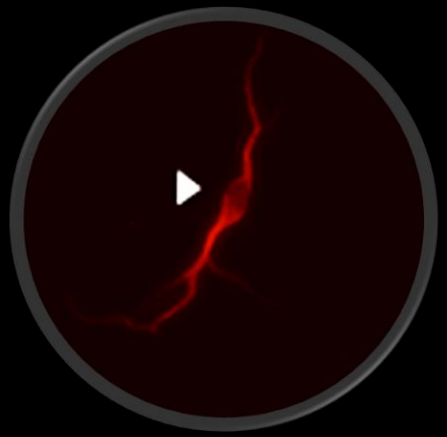


Courtesy K. Deisseroth Lab, Stanford

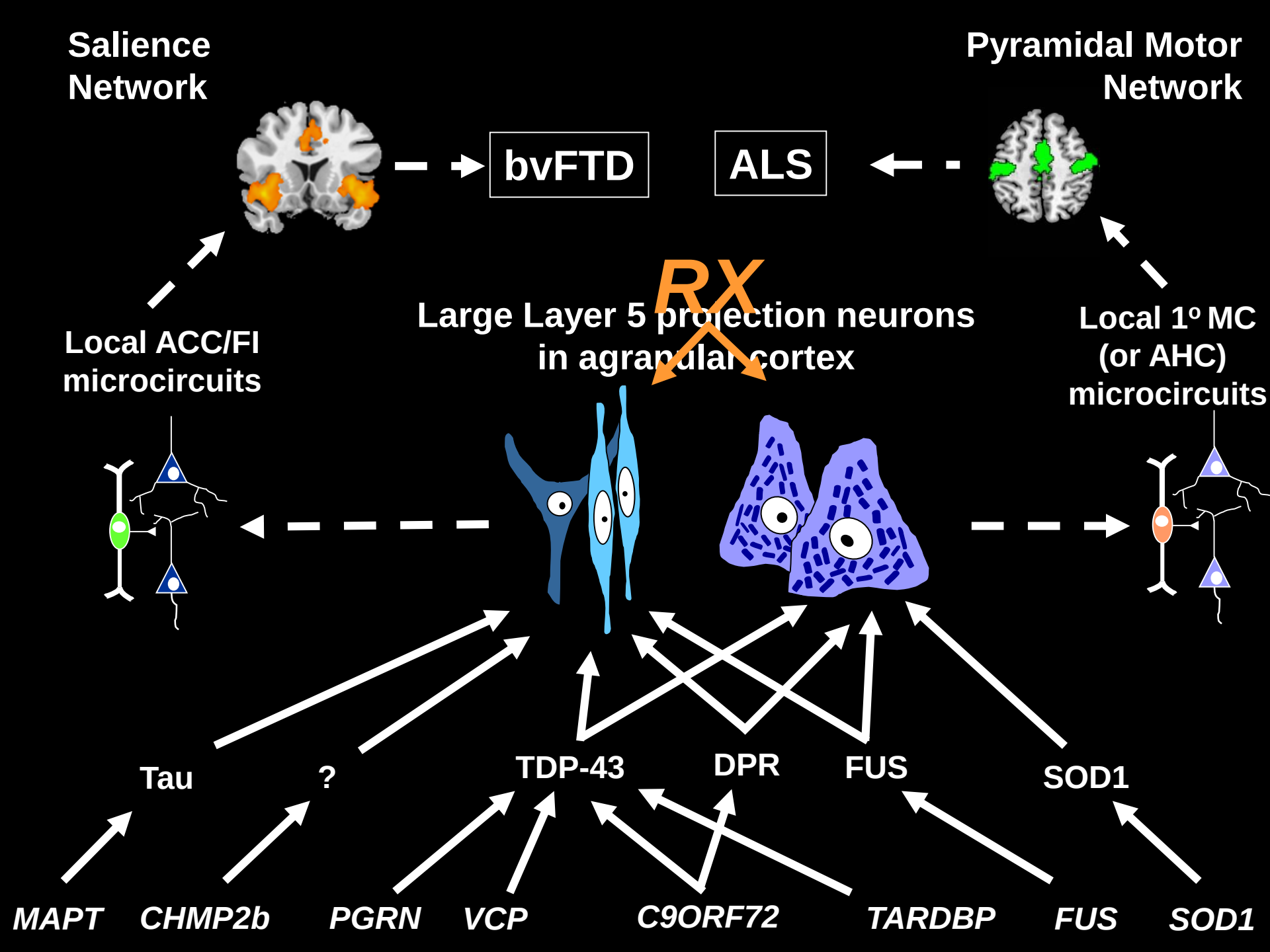




E Chang, A Hasenstaub, K Bender



Finkbeiner Lab (K. Haston), UCSF


Salience Network
Pyramidal Motor Network
bvFTD
ALS
RX
Large Layer 5 projection neurons in agranular cortex
Local ACC/FI microcircuits
Local 1º MC (or AHC) microcircuits
Tau
?
TDP-43
DPR
FUS
SOD1
MAPT
CHMP2b
PGRN
VCP
C9ORF72
TARDBP
FUS
SOD1

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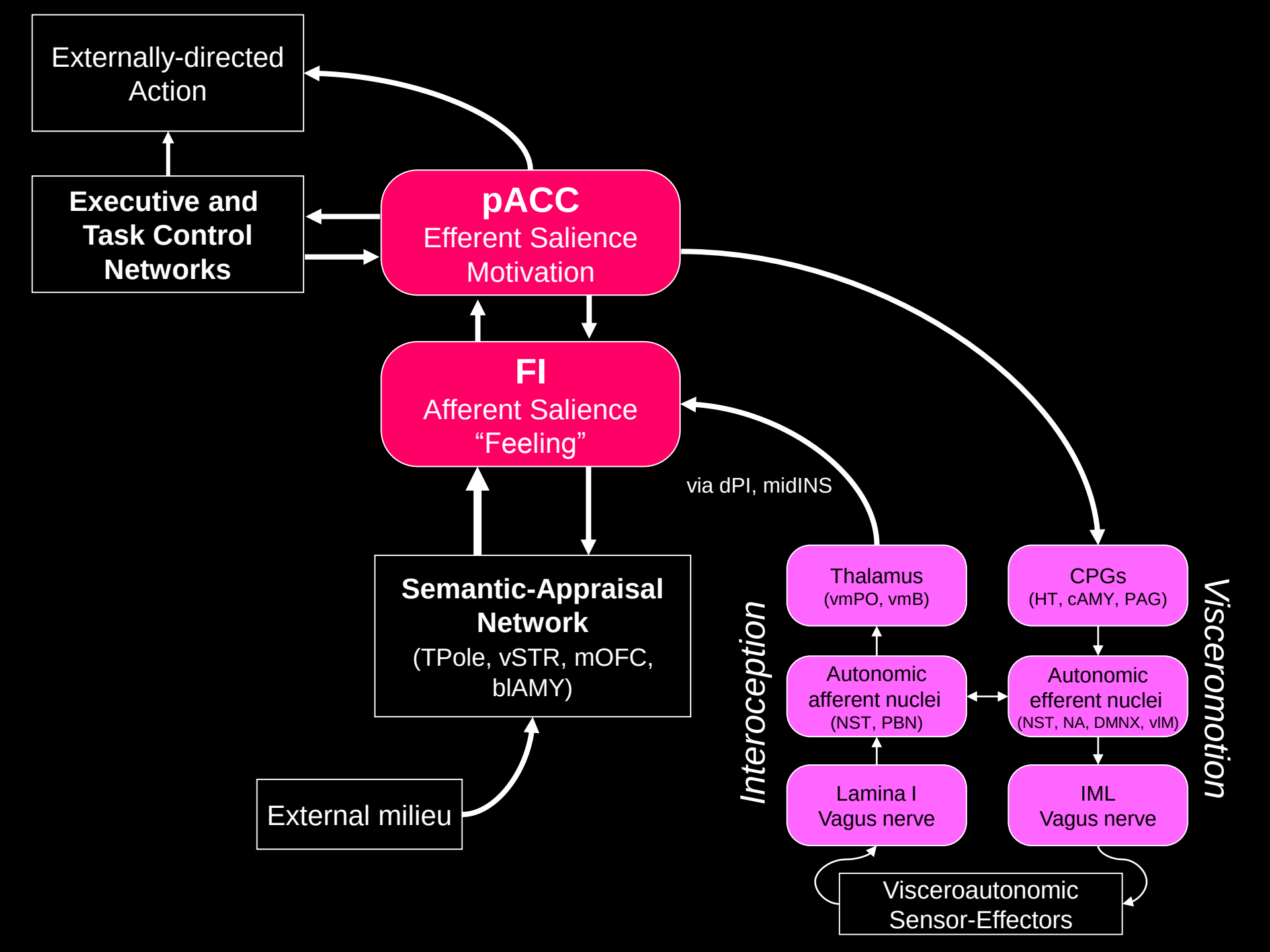
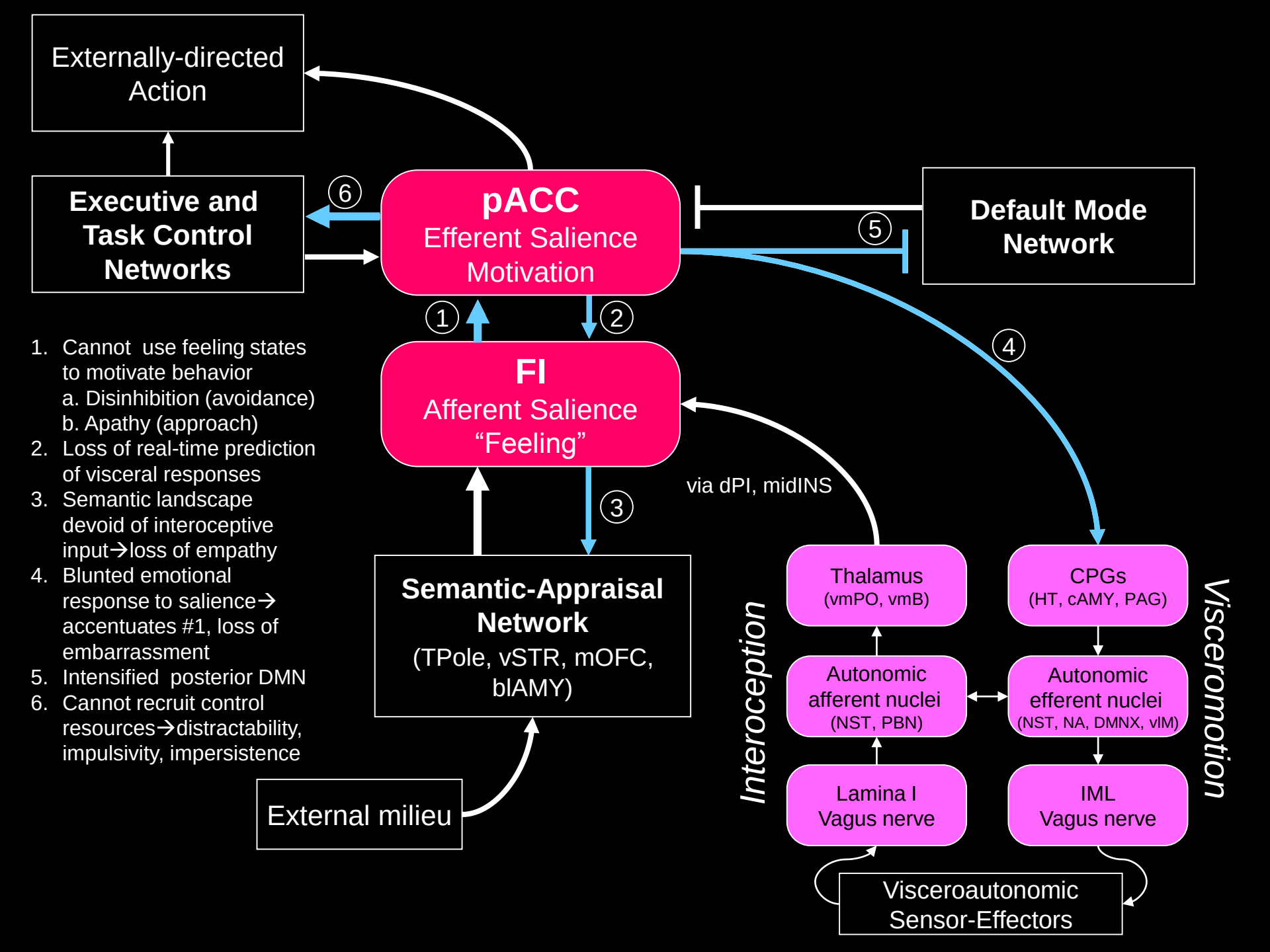
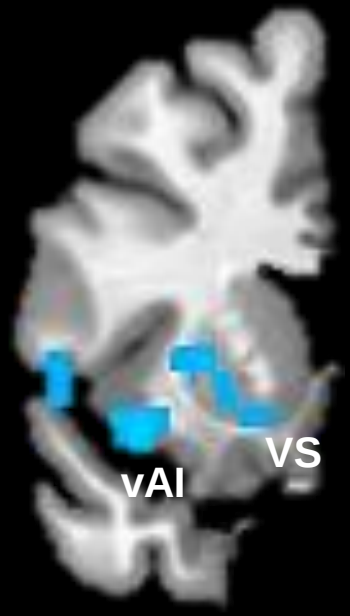
Consortium for FTD Research
Tau Consortium
Hellman Family Foundation
John D. and Catherine T. MacArthur Foundation

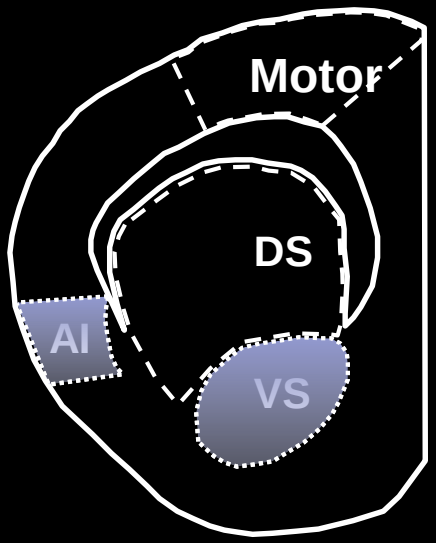

Externally-directed Action
Executive and Task Control Networks
pACC
Efferent Salience
Motivation
FI
Afferent Salience
“Feeling”
via dPI, midINS
Semantic-Appraisal Network
(TPole, vSTR, mOFC, blAMY)
External milieu
Thalamus
(vmPO, vmB)
CPGs
(HT, cAMY, PAG)
Interoception
Visceromotion
Autonomic afferent nuclei
(NST, PBN)
Autonomic efferent nuclei
(NST, NA, DMNX, vlM)
Lamina I
Vagus nerve
IML
Vagus nerve
Visceroautonomic Sensor-Effectors


Externally-directed Action
Executive and Task Control Networks
6
pACC
Efferent Salience
Motivation
5
Default Mode Network
1
2
4
FI
Afferent Salience
"Feeling"
3
via dPI, midINS
1. Cannot use feeling states to motivate behavior
a. Disinhibition (avoidance)
b. Apathy (approach)
2. Loss of real-time prediction of visceral responses
3. Semantic landscape devoid of interoceptive input→loss of empathy
4. Blunted emotional response to salience→ accentuates #1, loss of embarrassment
5. Intensified posterior DMN
6. Cannot recruit control resources→distractability, impulsivity, impersistence
Semantic-Appraisal Network
(TPole, vSTR, mOFC, blAMY)
External milieu
Interoception
Thalamus
(vmPO, vmB)
CPGs
(HT, cAMY, PAG)
Visceromotion
Autonomic afferent nuclei
(NST, PBN)
Autonomic efferent nuclei
(NST, NA, DMNX, vlM)
Lamina I
Vagus nerve
IML
Vagus nerve
Visceroautonomic Sensor-Effectors

V337M *MAPT* transgenic mice show age-dependent synapse loss in insulo-striatal regions

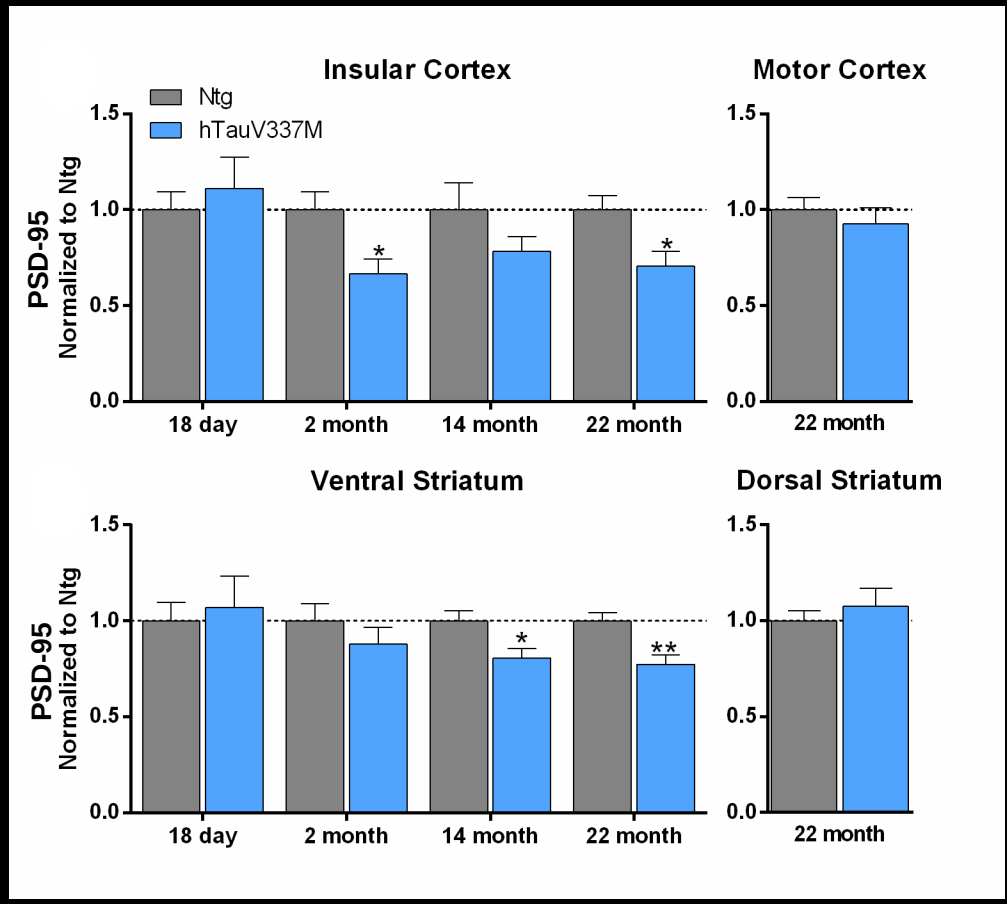
hTau V337M transgenic mice: “disinhibition”, reduced nesting, and repetitive/compulsive grooming despite normal spatial learning/memory and motor function





bvFTD < HC
Zhou Brain 2010

Courtesy
E. Roberson



Implications for FTLD neuropathological research

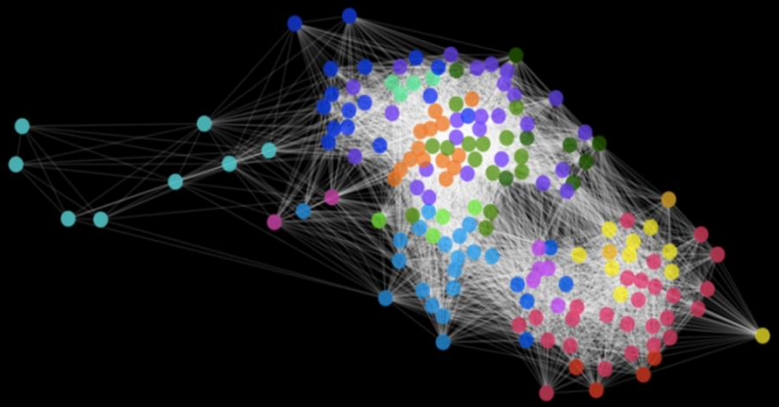
- Deeper insights may emerge from reconceptualizing FTLD as a “cinguloinsular” degeneration. Studying generic “frontal cortex” is likely to prove less powerful.

- Routine FFPE sections are not sufficient to answer every important human neuropathological question.

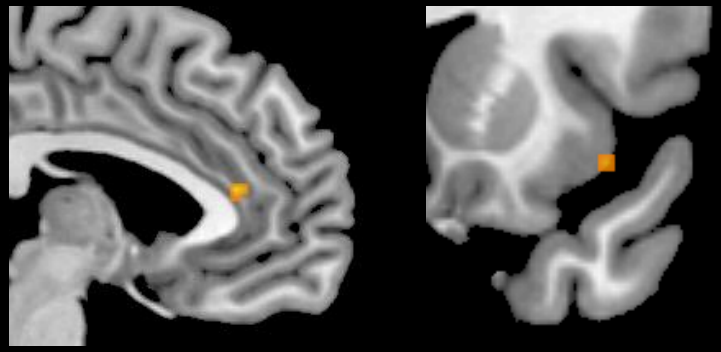
- Mouse-human homology in ACC and anterior insula is in most ways stronger than for “frontal cortex”. FTLD model mouse insights may require that we not study hippocampus or “frontal cortex” just because they are familiar or convenient.

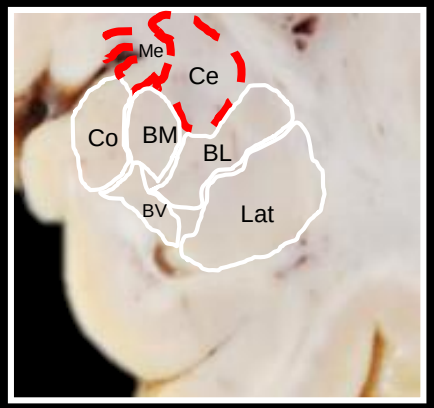
Ongoing projects: network degeneration

Jesse Brown: longitudinal biomarkers

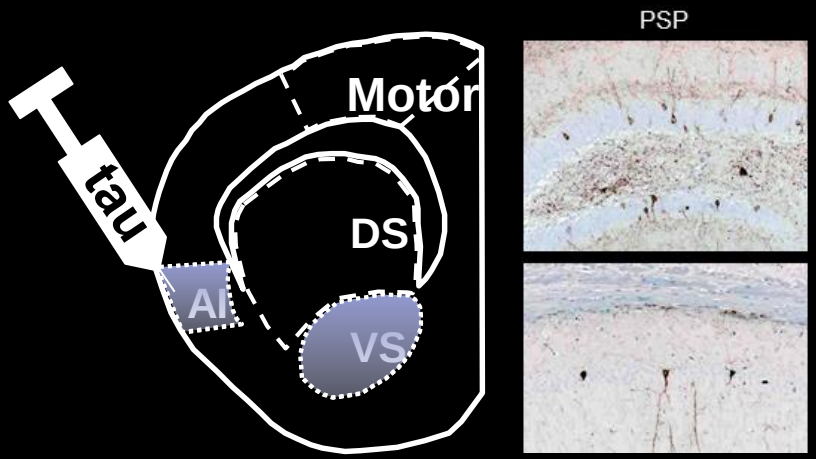


Suzee Lee: connectivity reductions in presymptomatic mutation carriers



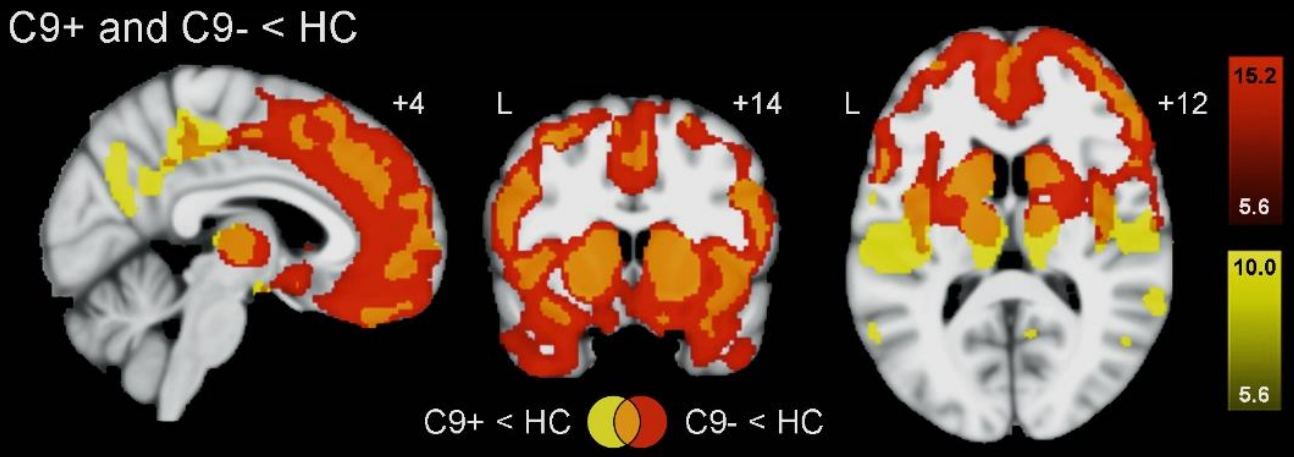


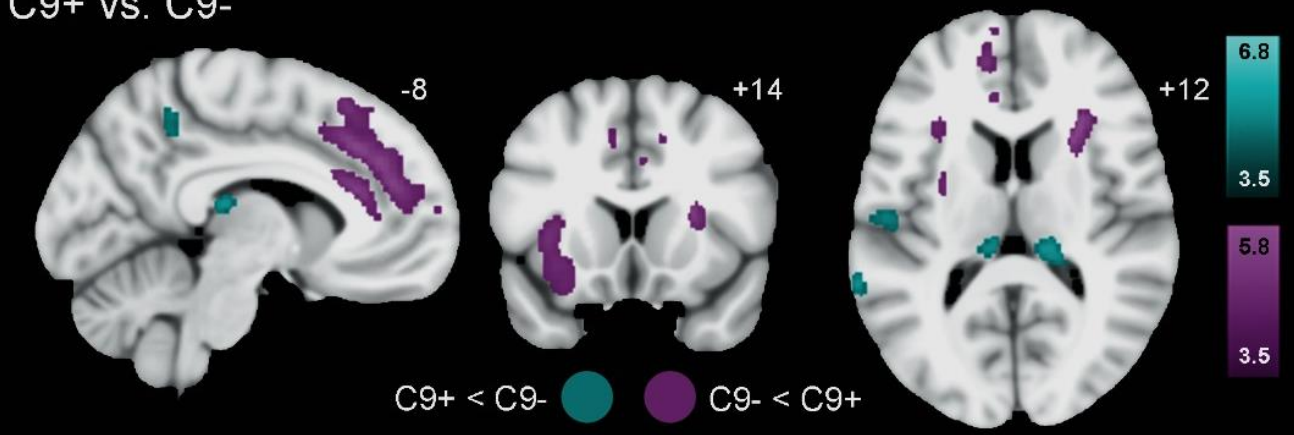
Salvo Spina: imaging-pathology correlation



K. Giles, S. Prusiner: tau seeding

Overlapping but distinct atrophy patterns in bvFTD +/- *C9ORF72*

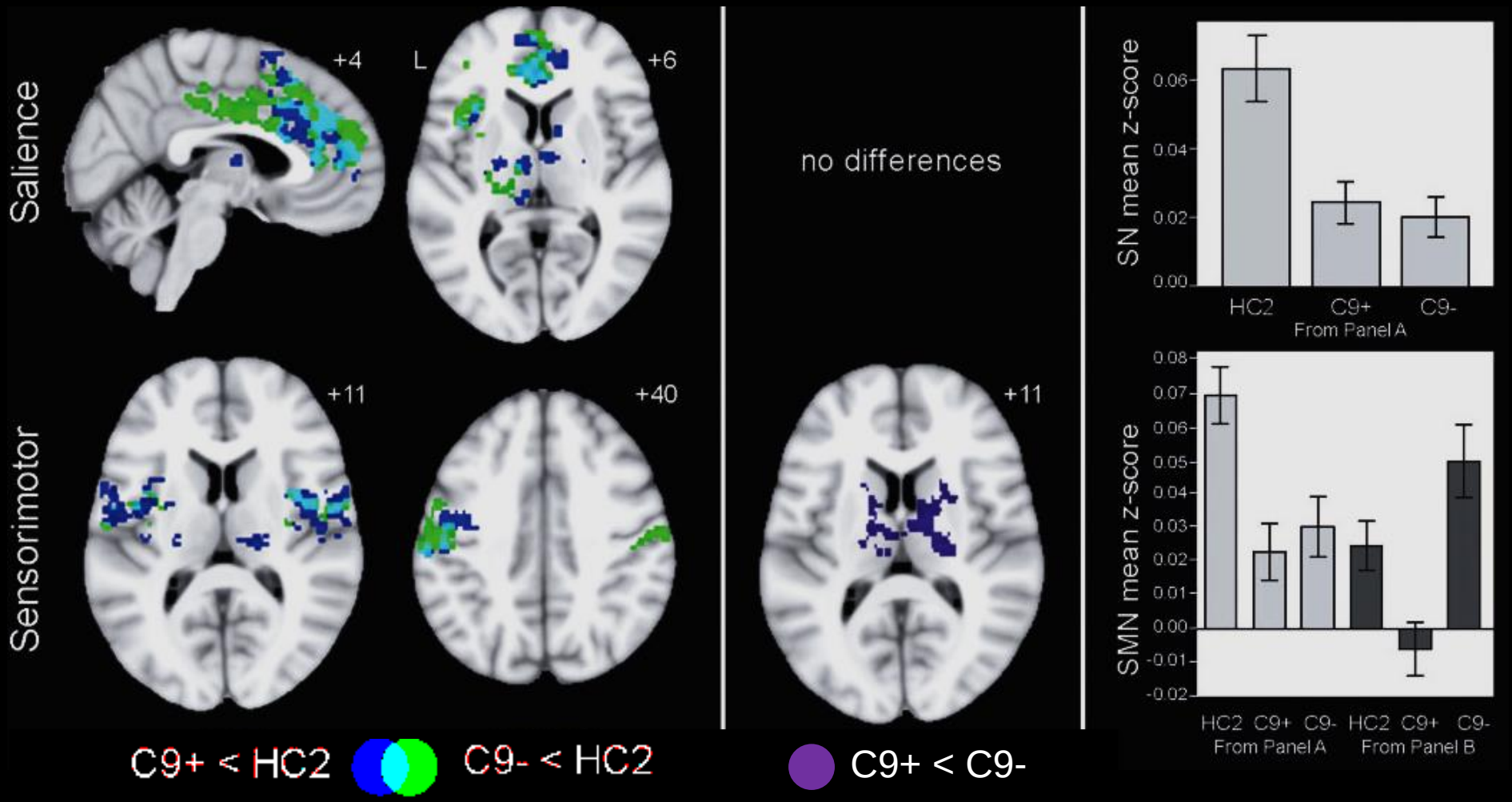




14 C9+ bvFTD (5 w/ MND)
14 C9- bvFTD (5 w/ MND)
28 Healthy controls

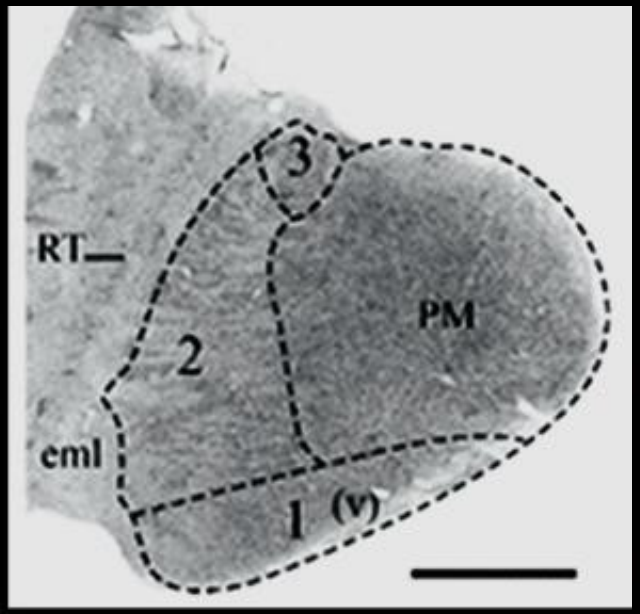
Lee et al Brain 2014

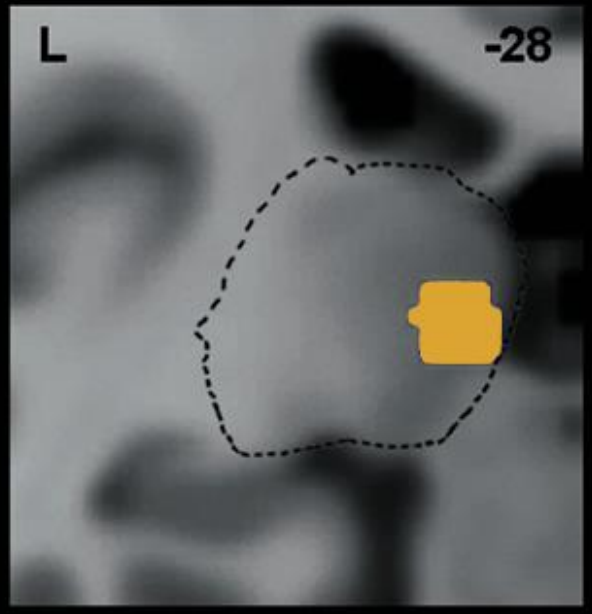
C9+ and C9- bvFTD: similar salience and sensorimotor network disruption despite contrasting atrophy

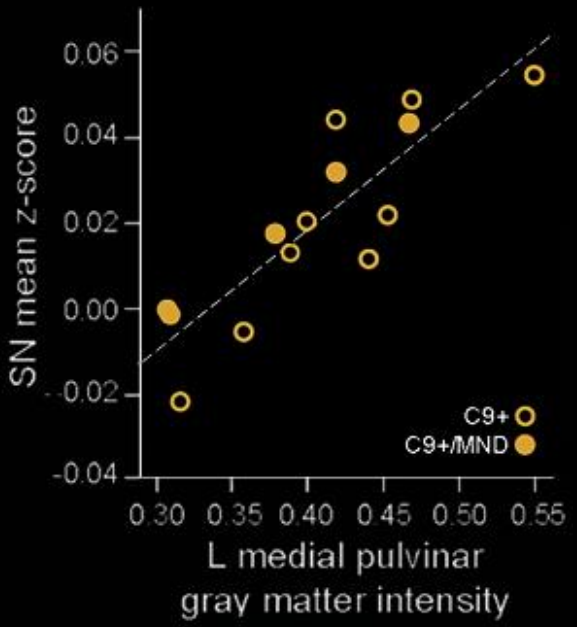


Lee et al Brain 2014

Medial pulvinar thalamic atrophy correlates with reduced SN connectivity





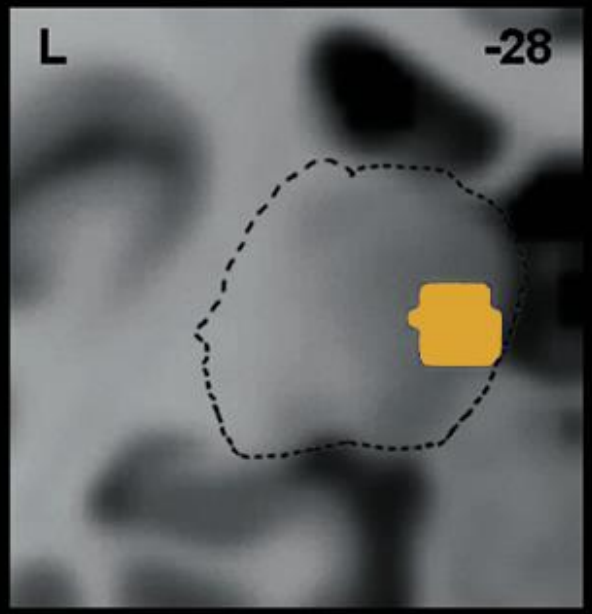


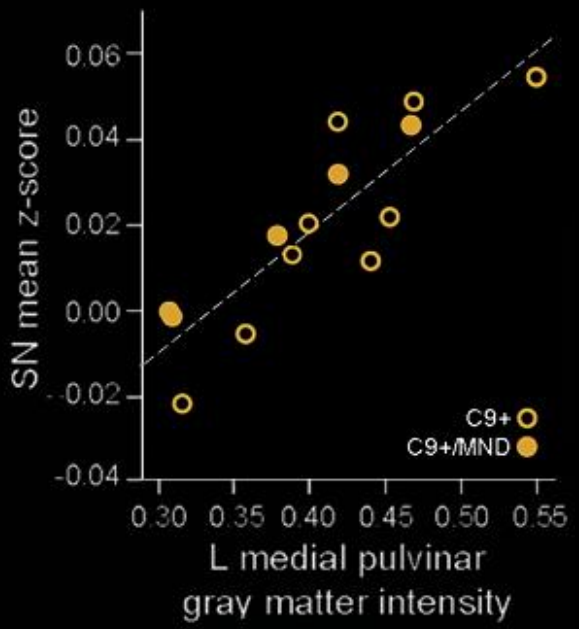
Searched thalamus for GM voxels where greater atrophy predicted reduced mean salience network connectivity

Lee et al Brain 2014

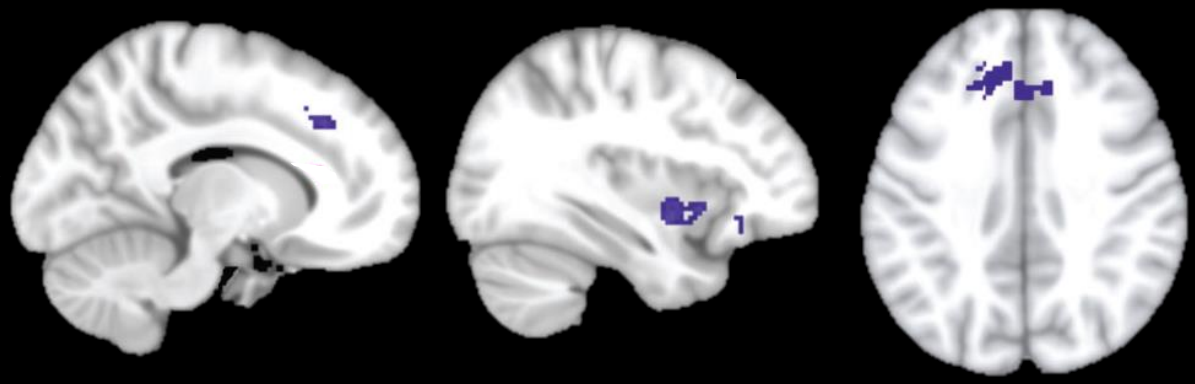
Medial pulvinar connectivity to salience network hubs is reduced in C9+ vs. C9- bvFTD

mPULV as seed in differential intrinsic connectivity analysis





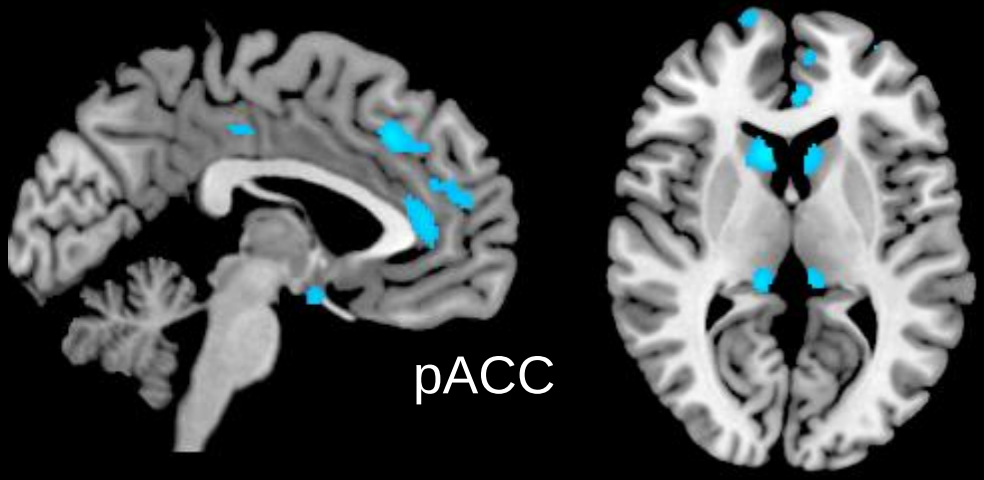
Regions showing reduced connectivity to mPULV in C9+ vs. C9- bvFTD



C9ORF72 carriers show gray matter volume deficits by the 3rd decade

Suzee Lee

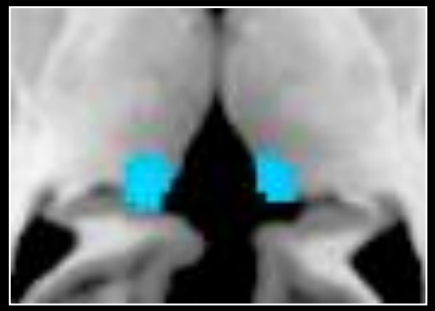
Voxel-based morphometry
13 asymptomatic carriers < 13 matched HC



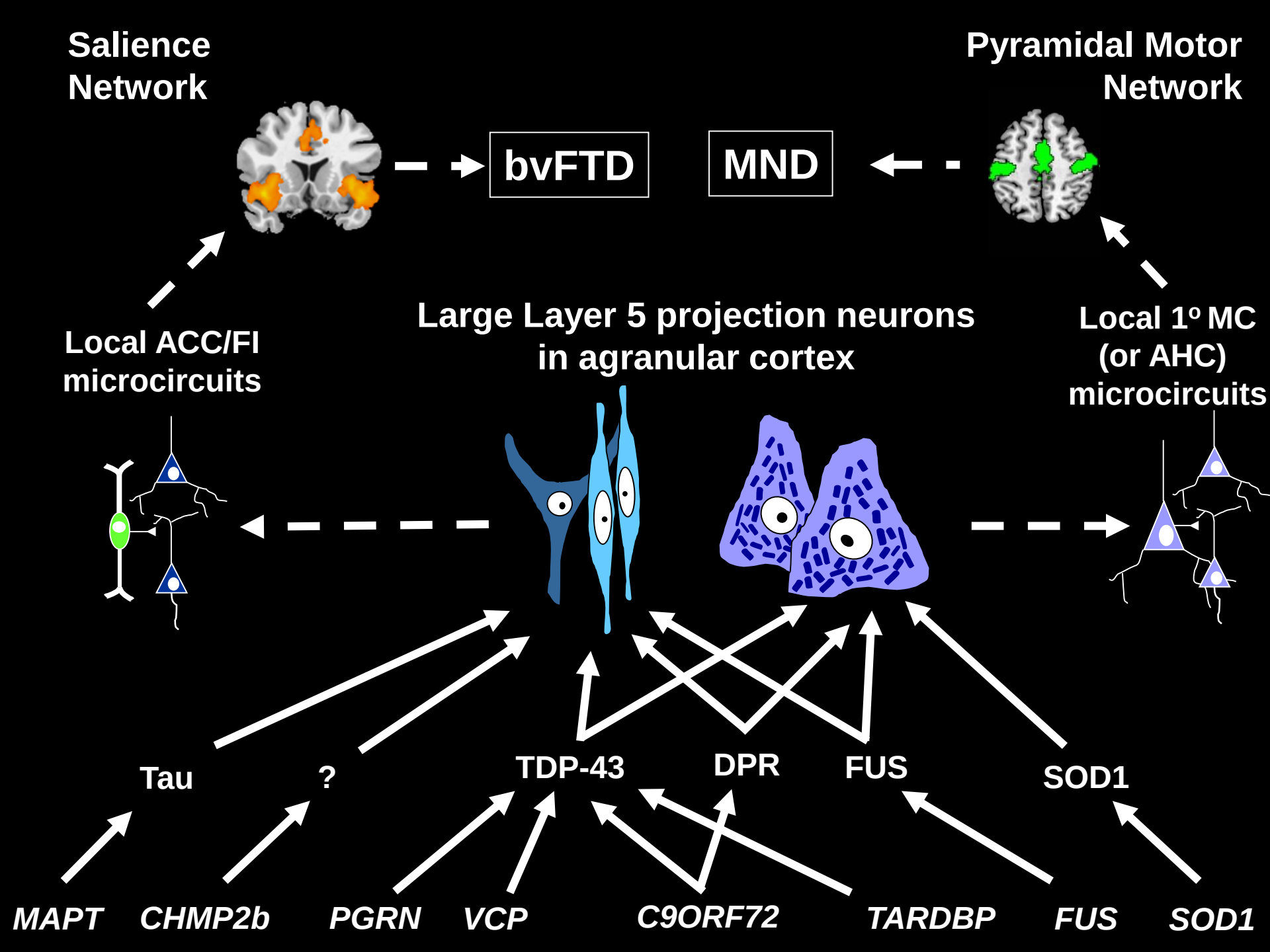
pACC

R FI

vmSTR

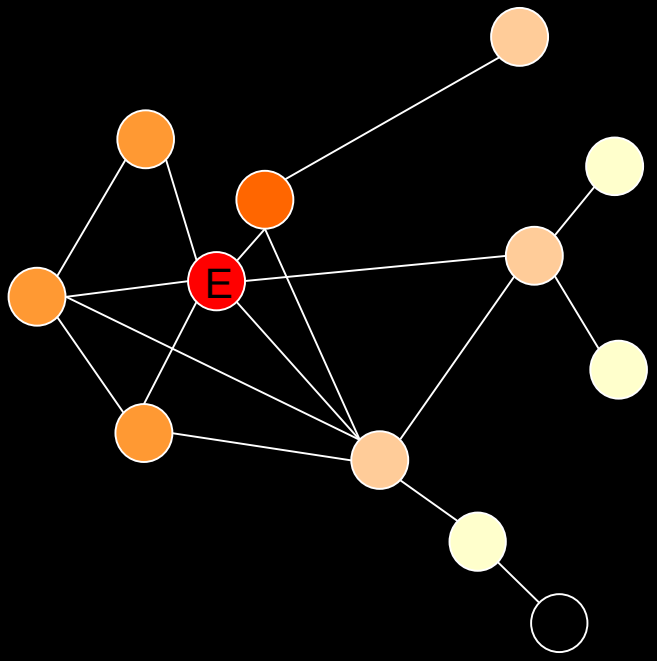


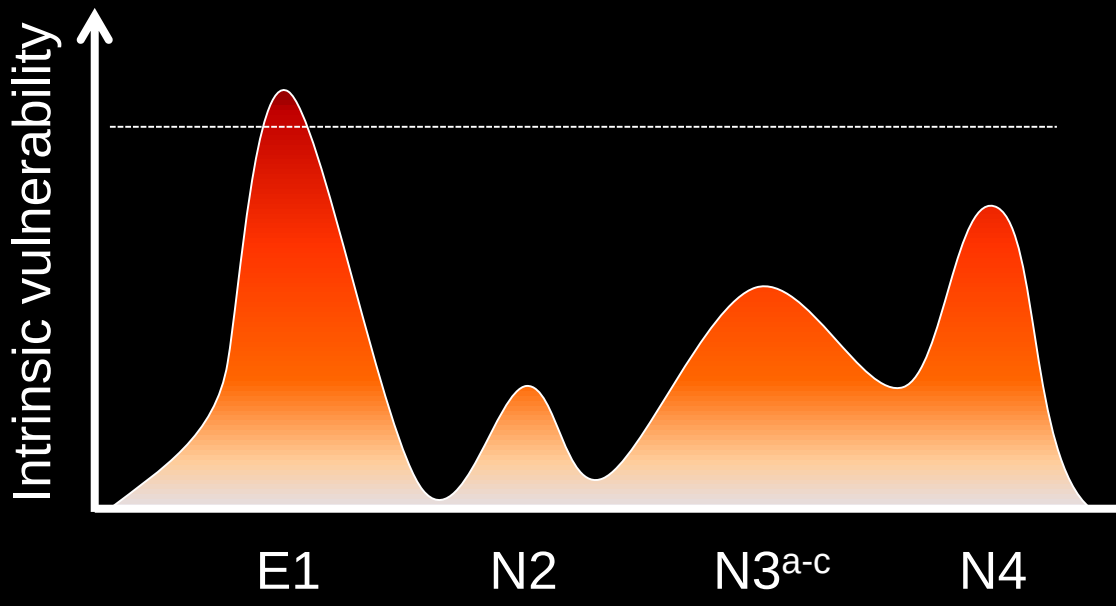
mPULV


Salience Network
Pyramidal Motor Network
bvFTD
MND
Local ACC/FI microcircuits
Large Layer 5 projection neurons in agranular cortex
Local 1º MC (or AHC) microcircuits
Tau
?
TDP-43
DPR
FUS
SOD1
MAPT
CHMP2b
PGRN
VCP
C9ORF72
TARDBP
FUS
SOD1

Working model of disease progression:

Transneuronal spread or staggered multifocal onset?

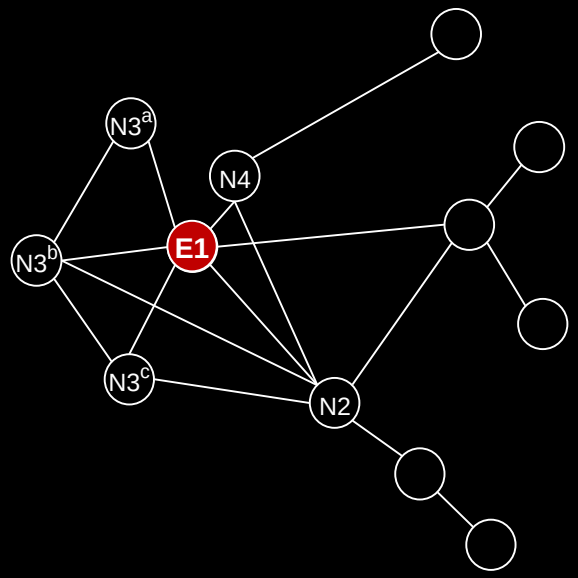


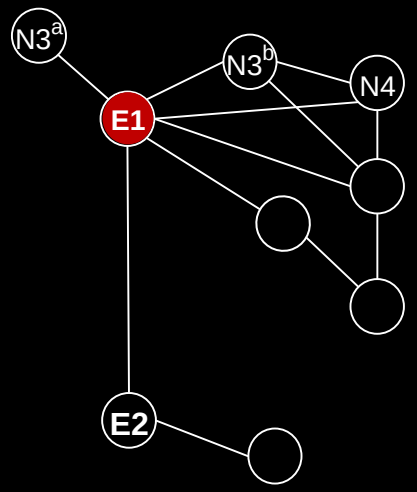


Working model: syndromic heterogeneity

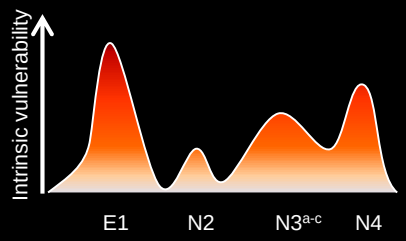
Multifocal onset, 2 networks: C9orf72

bvFTD-MND

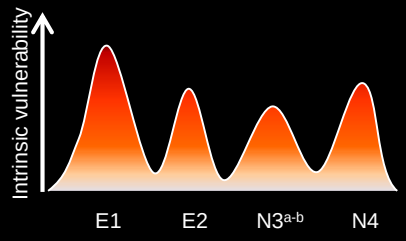




Salience network (bvFTD)



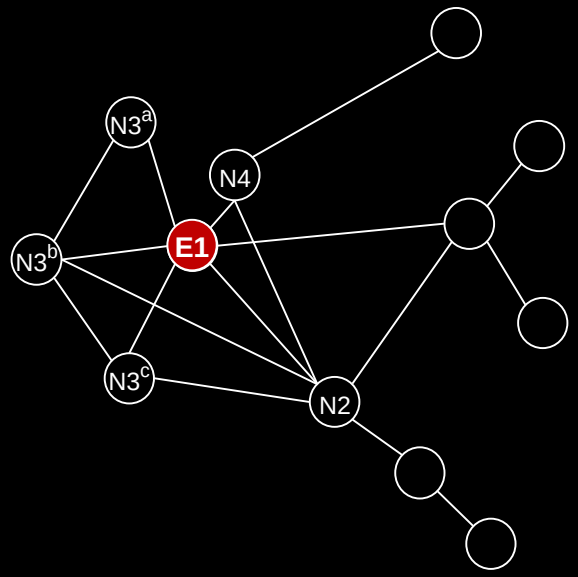
1° motor network (MND)

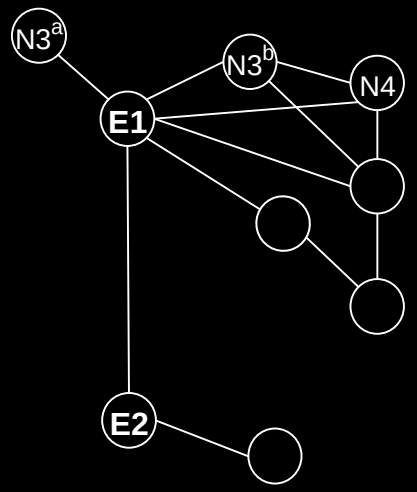


Working model: syndromic heterogeneity

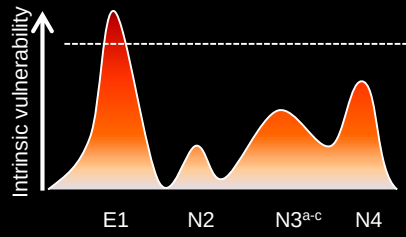
Multifocal onset, 2 networks: C9orf72

bvFTD

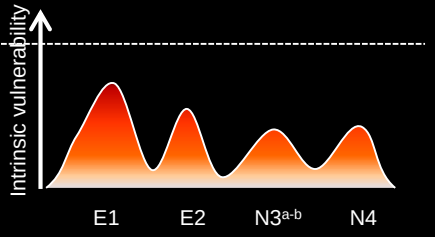




Salience network (bvFTD)



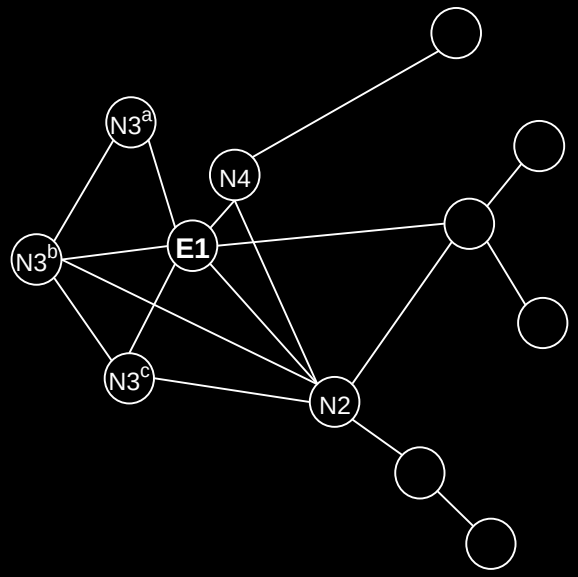
1° motor network (MND)

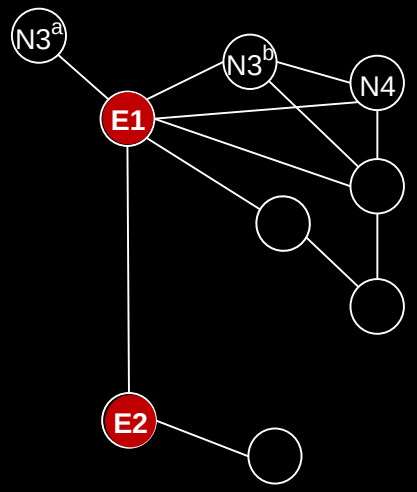


Working model: syndromic heterogeneity

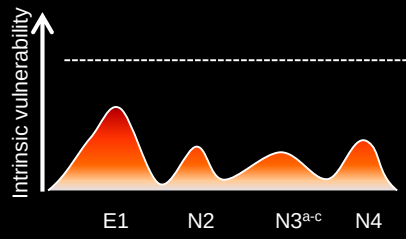
Multifocal onset, 2 networks: C9orf72

ALS

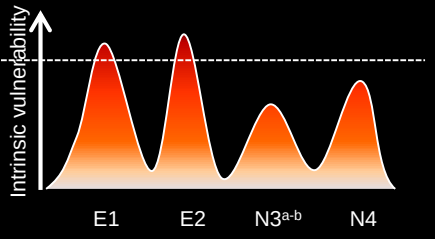




Salience network (bvFTD)

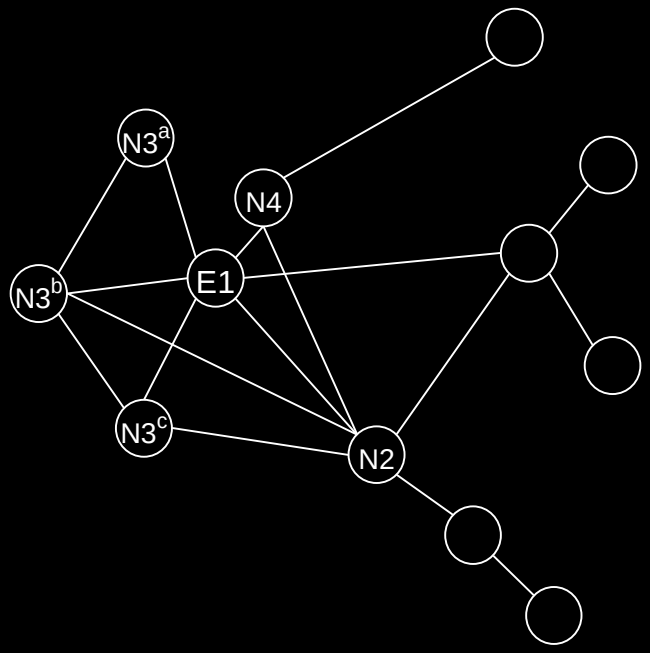


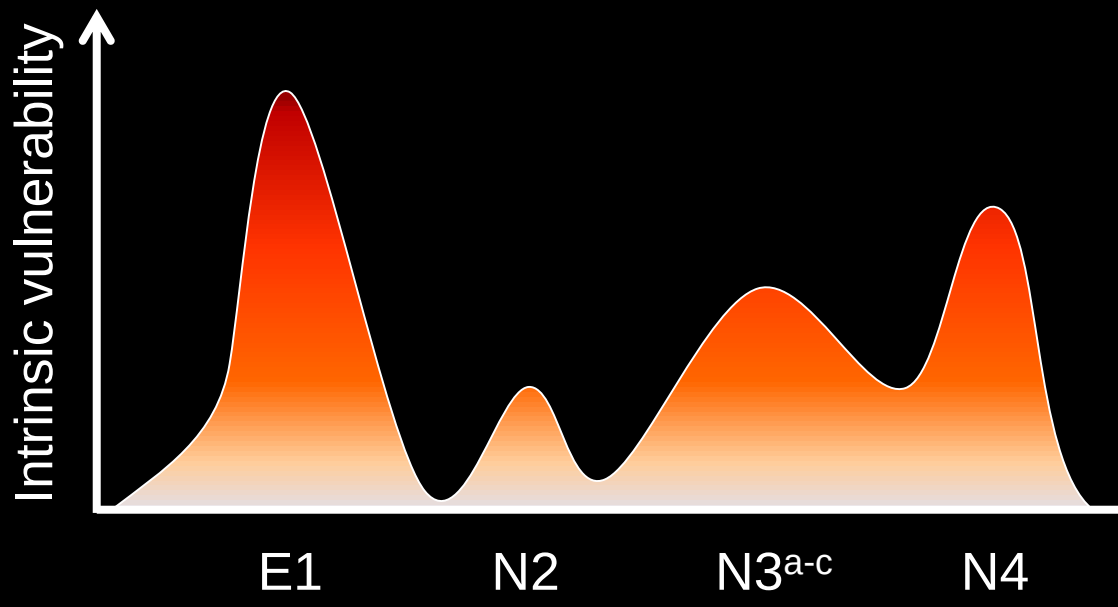
1° motor network (MND)

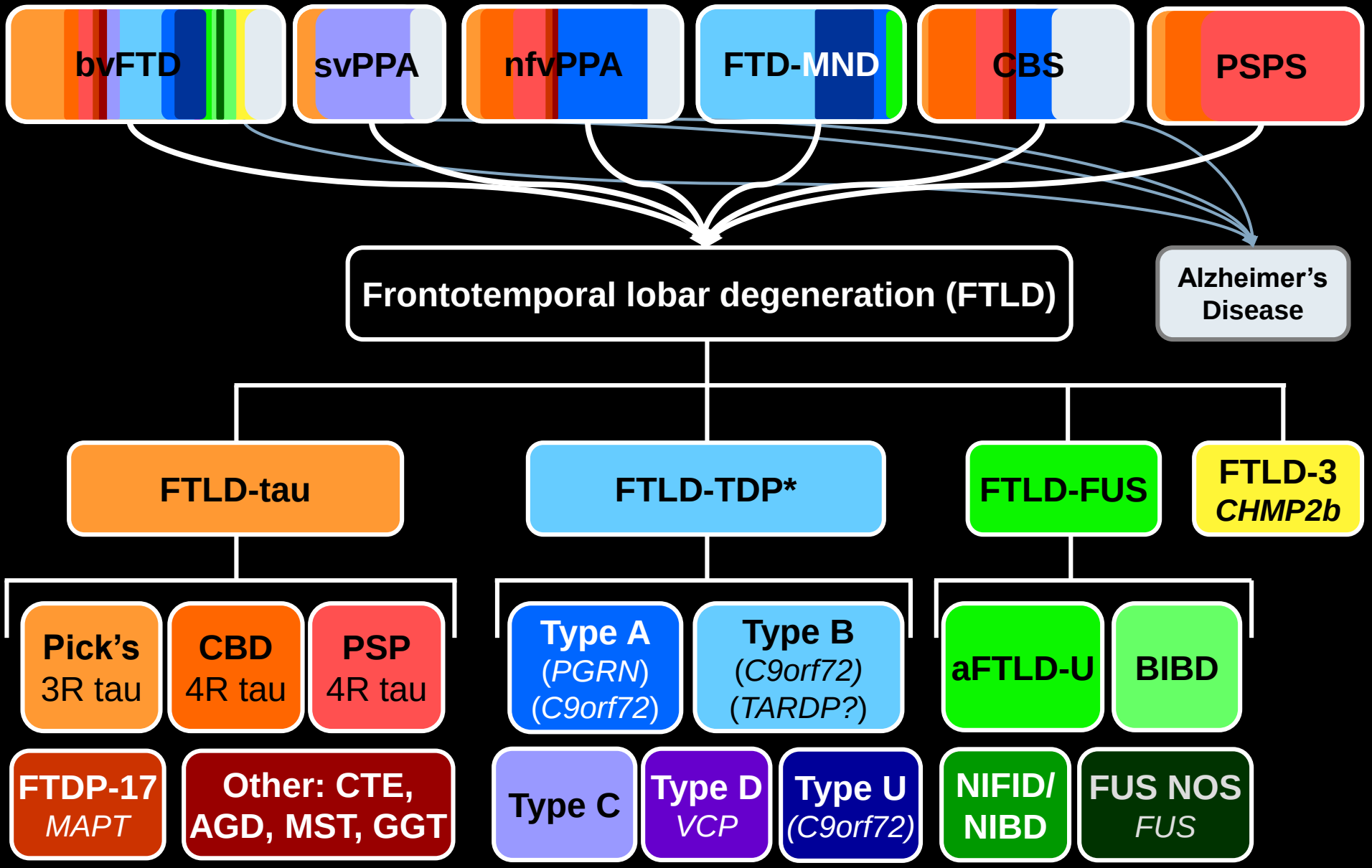


Disease progression model:

Transneuronal spread or staggered multifocal onset?

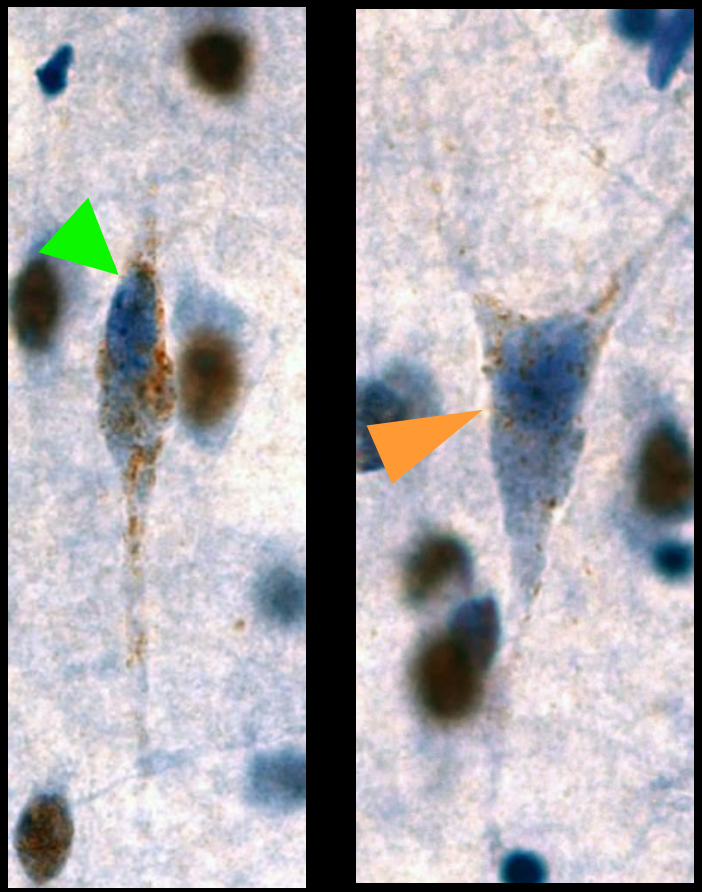


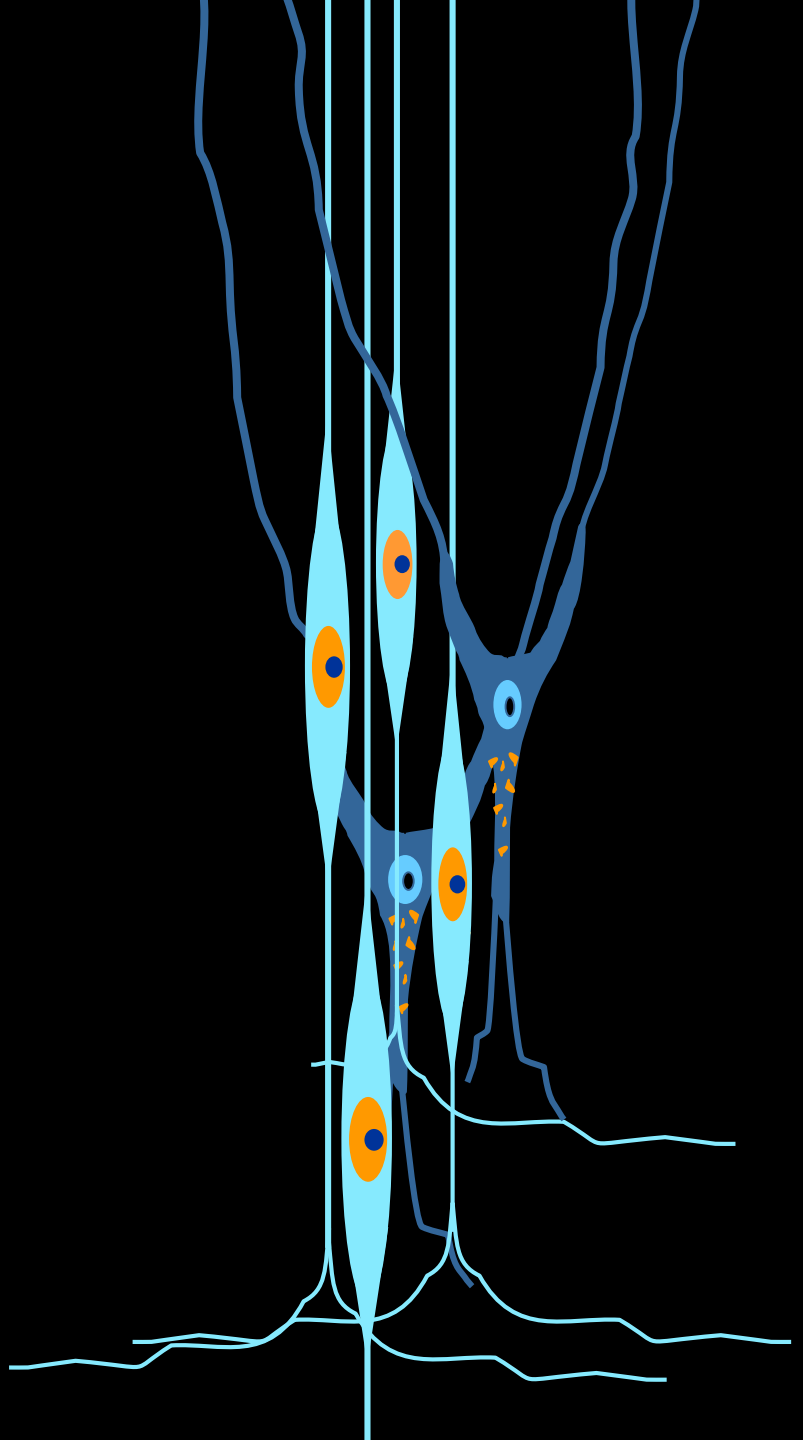


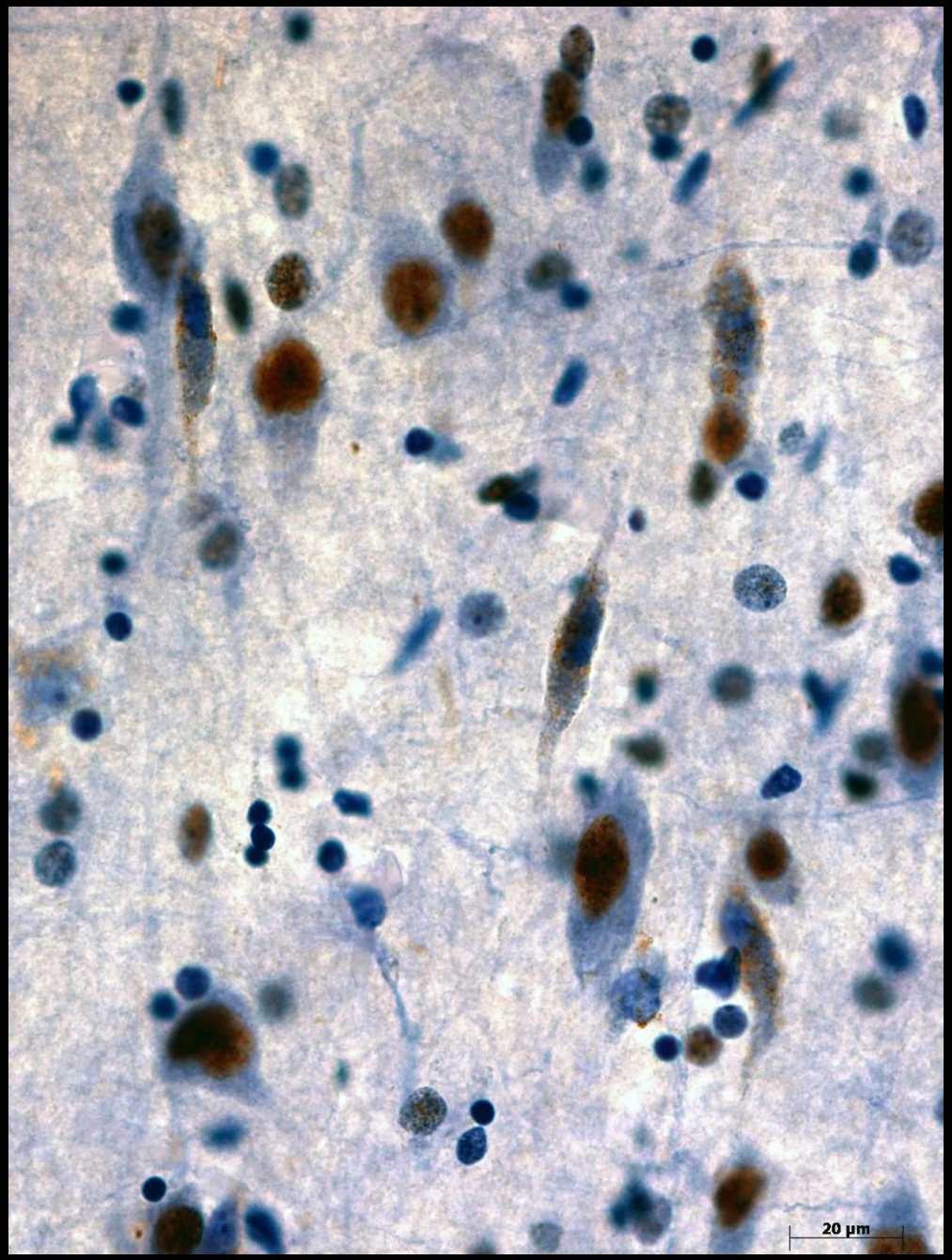


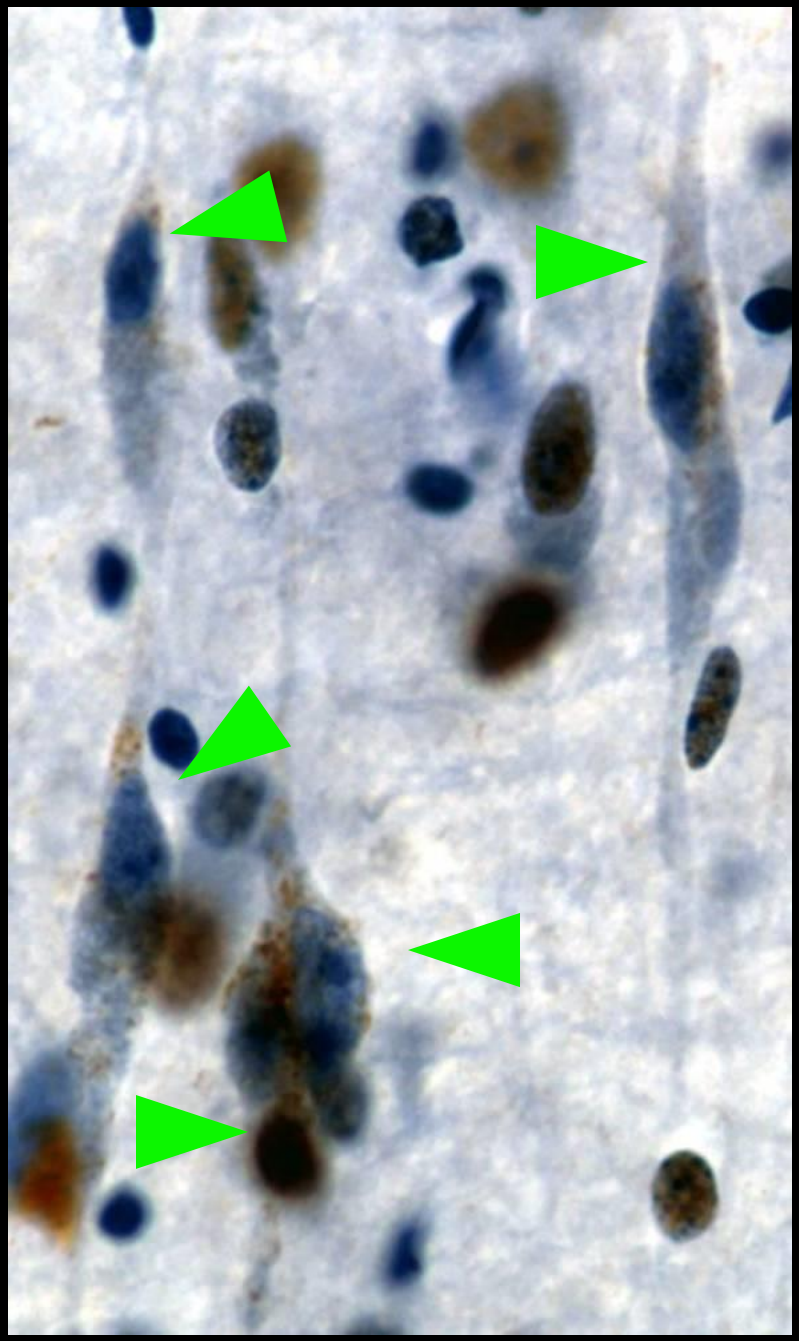
*Mackenzie harmonized scheme, 2011

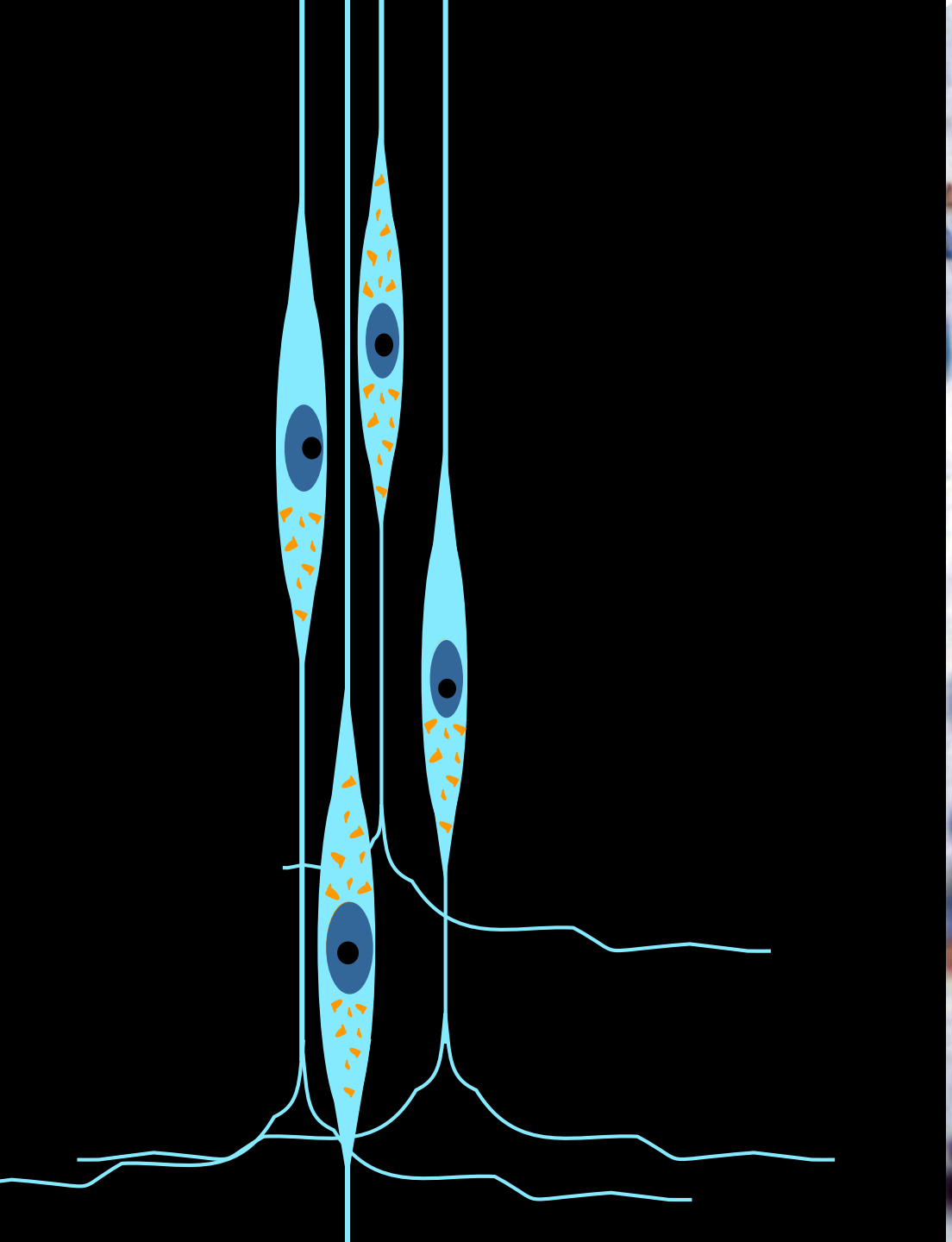
VEN/FC minicolumnopathy?

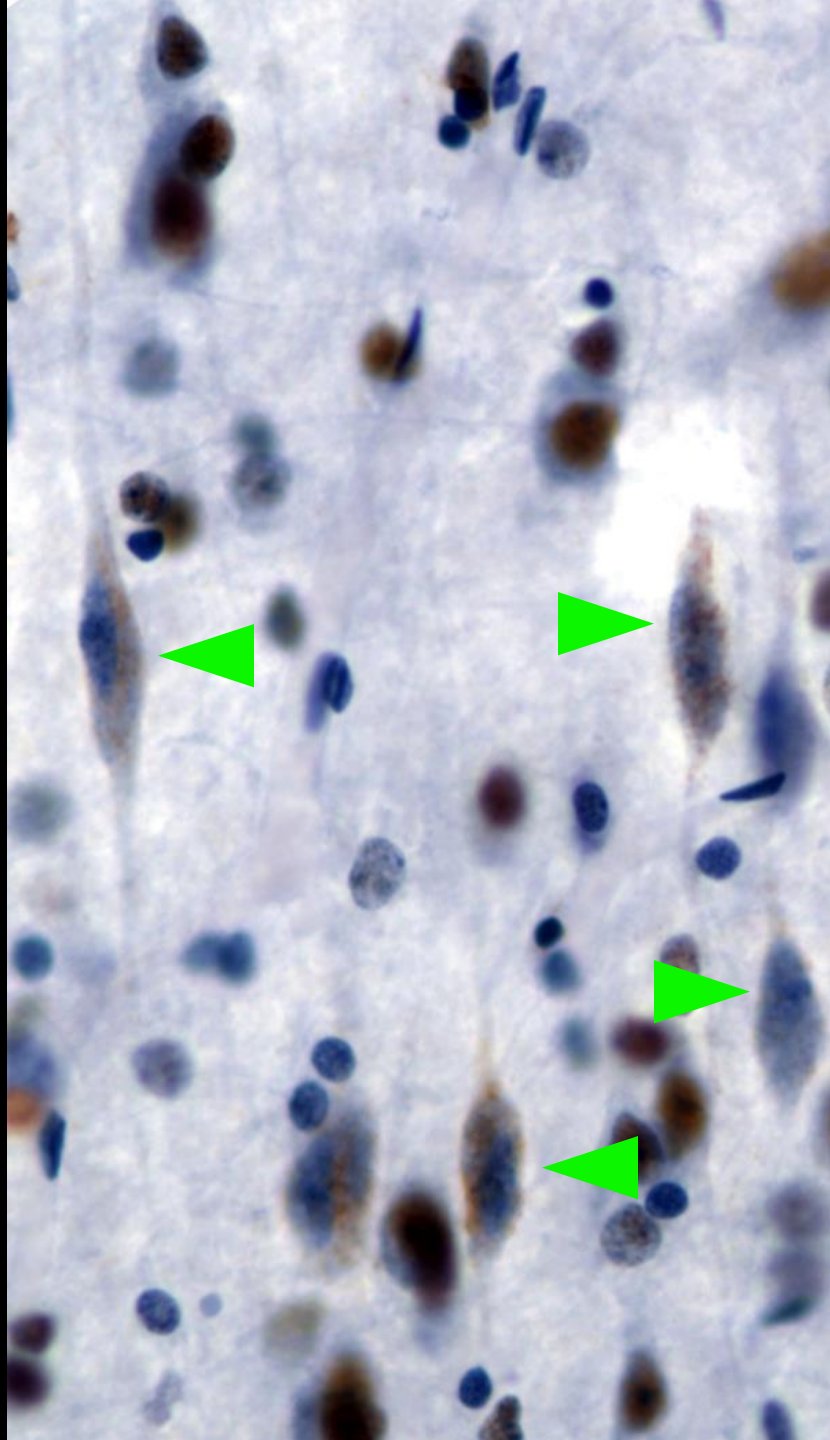




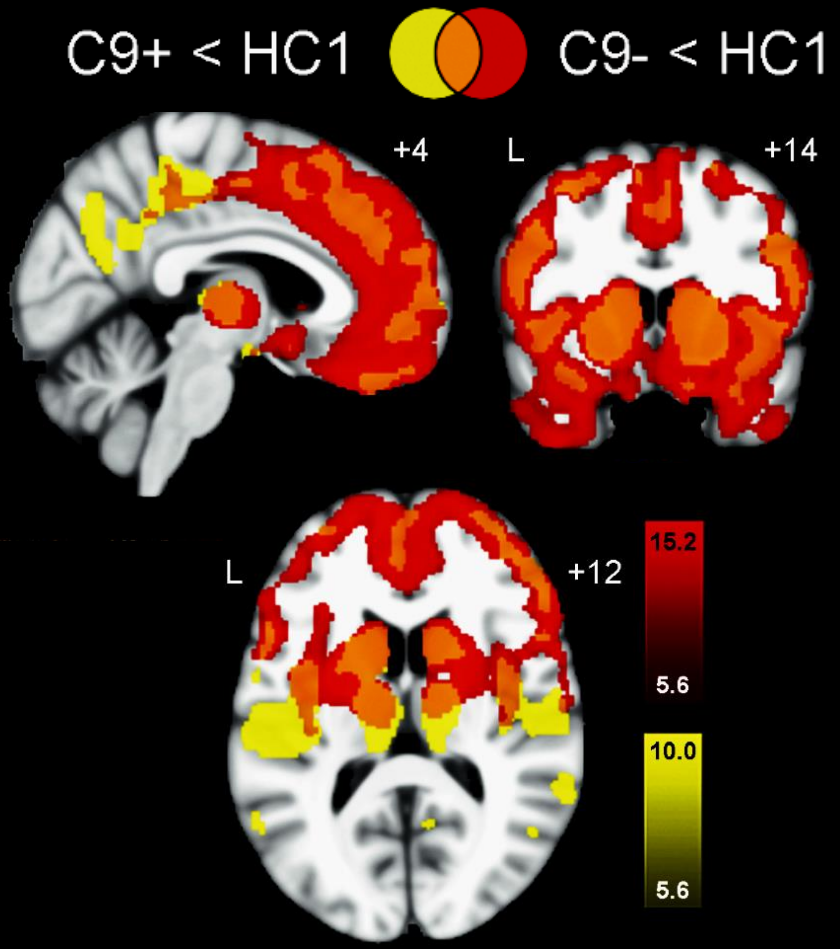

20 µm

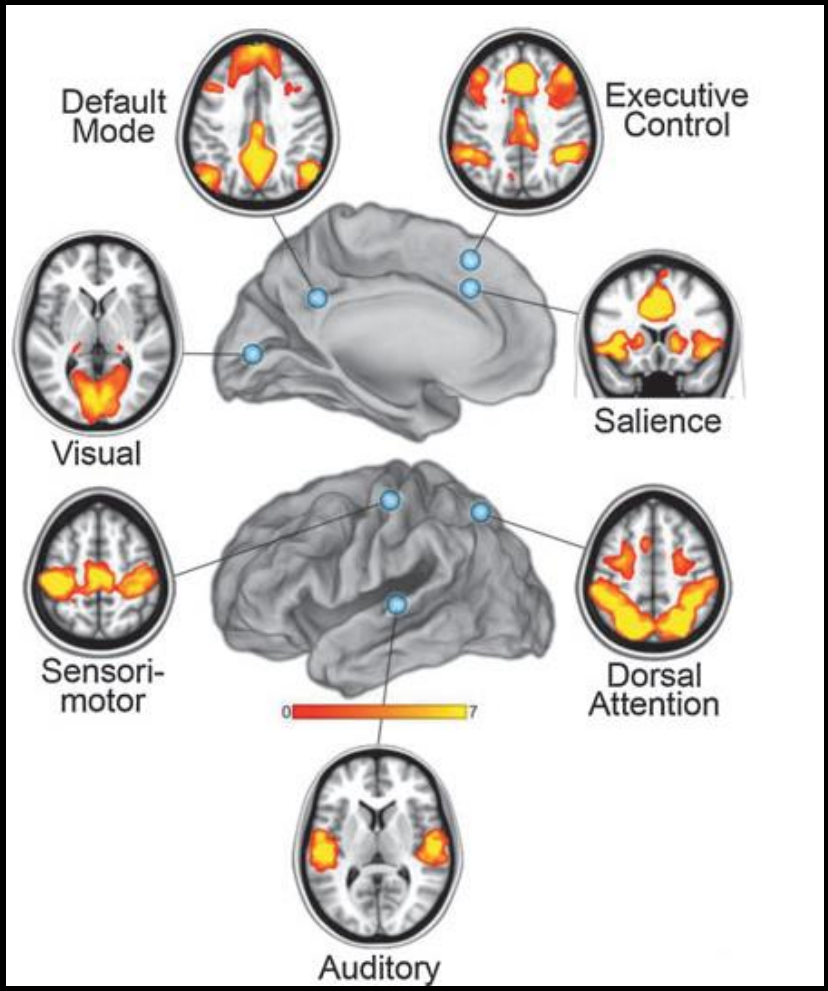




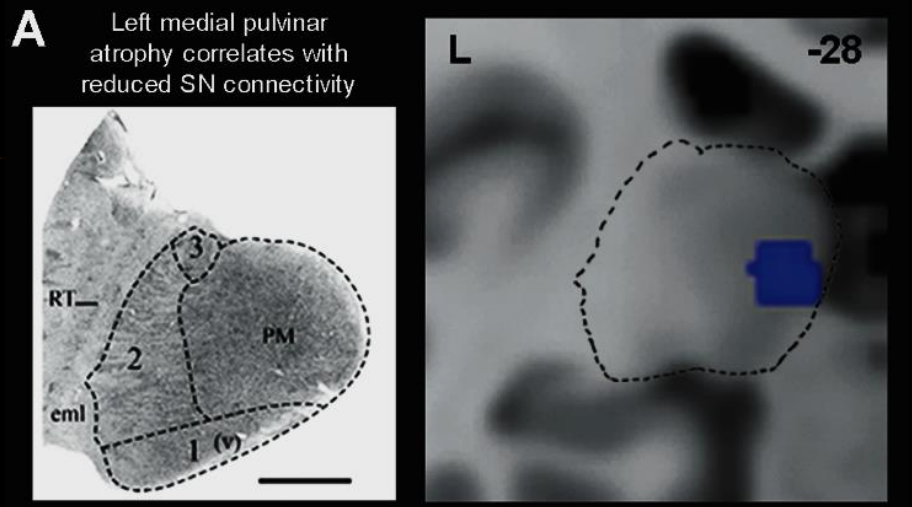


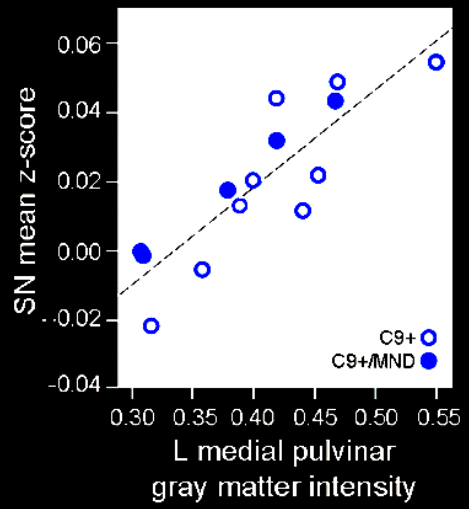
C9ORF72 bvFTD shows comparable network disruption despite milder atrophy

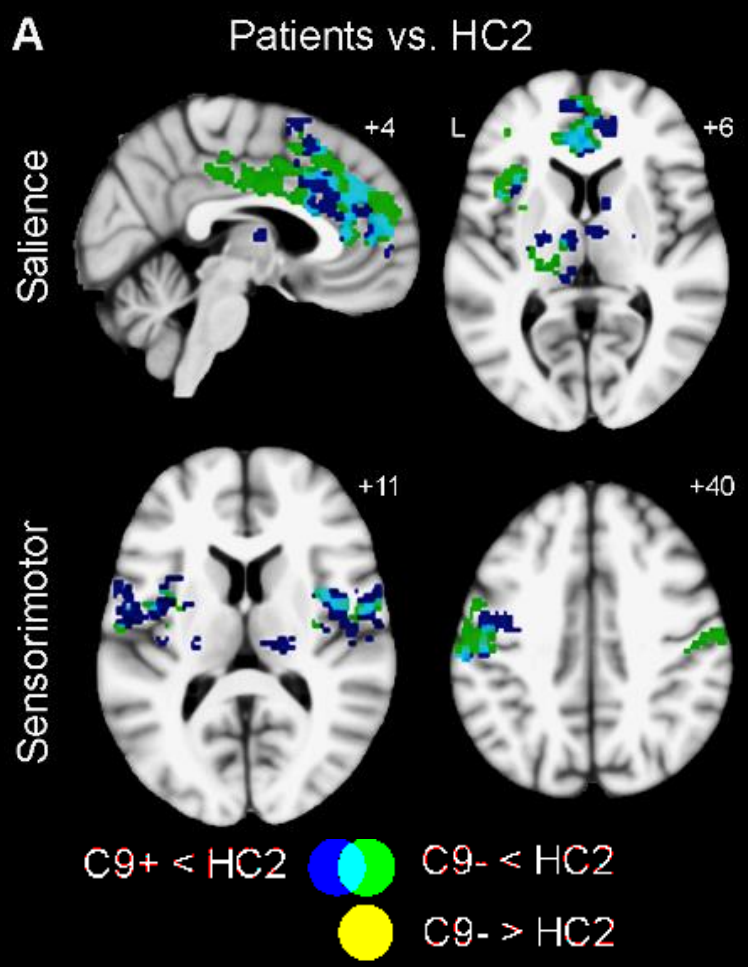




C9ORF72 bvFTD shows comparable network disruption despite milder atrophy

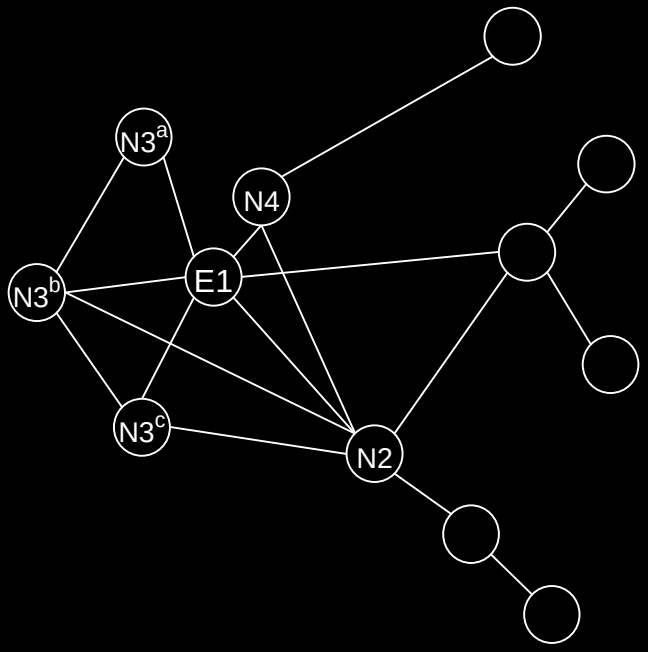


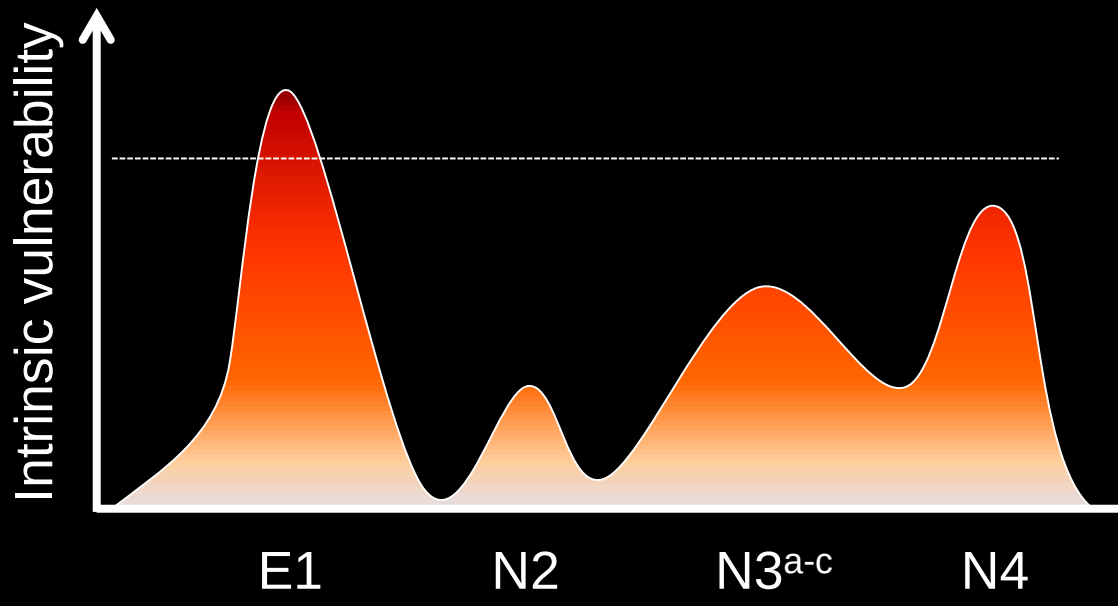




Disease progression model:

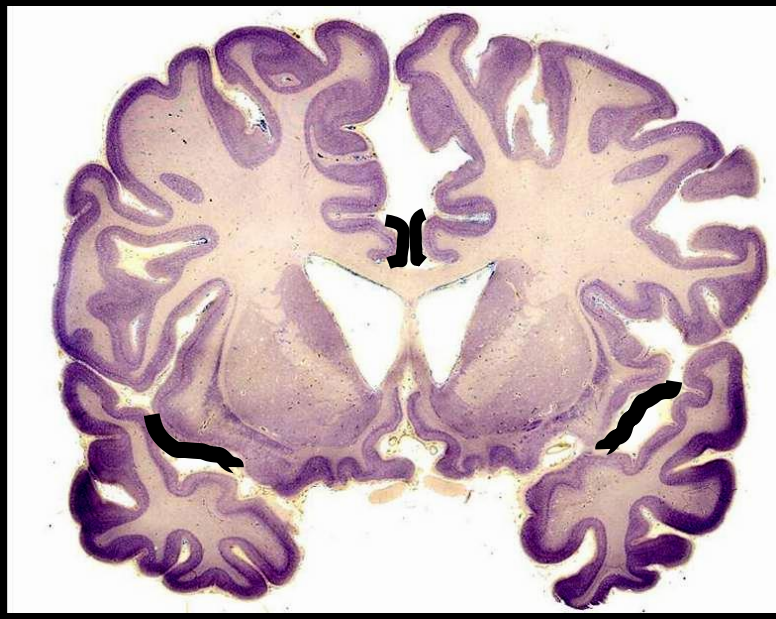
Transneuronal spread or staggered multifocal onset?



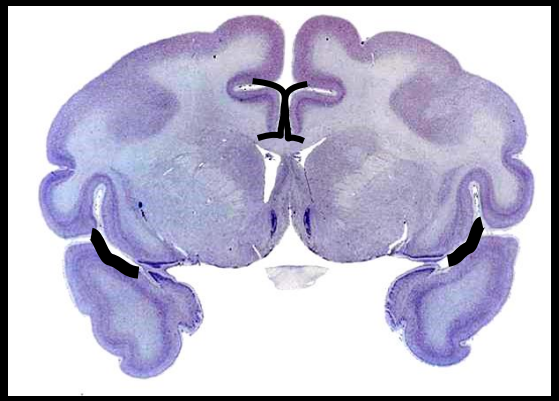


Onset Progression Translation Future

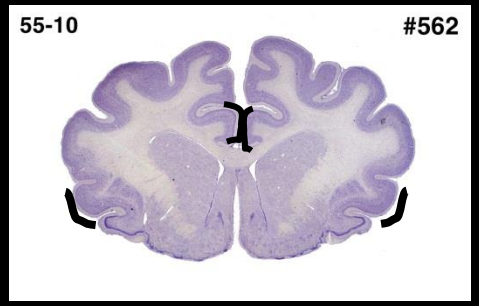
Allocortex ↔ Paralimbic Transition Zones ↔ Neocortex



HUMAN



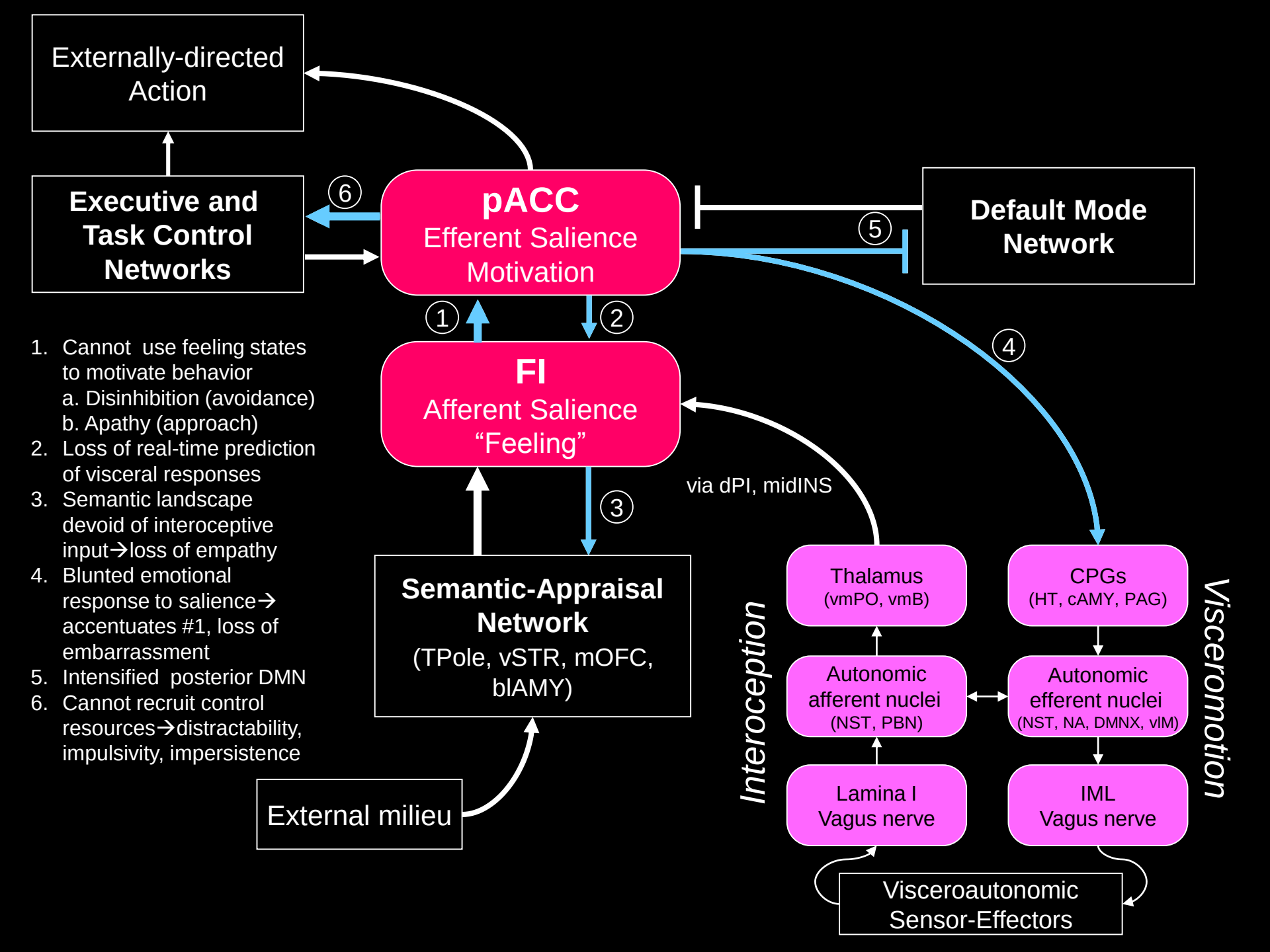
MONKEY



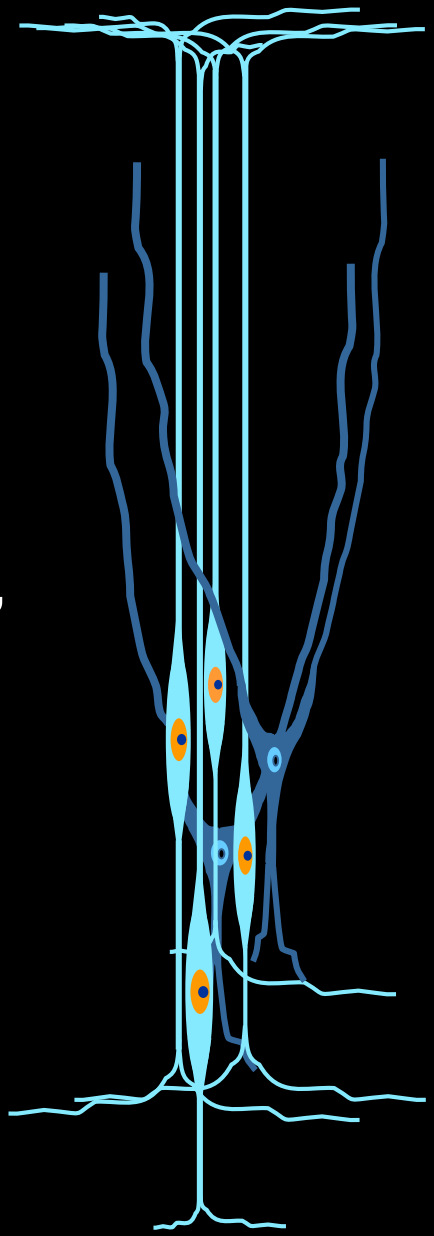
CAT

MOUSE

(not drawn to scale)


Externally-directed Action
Executive and Task Control Networks
6
pACC
Efferent Salience
Motivation
5
Default Mode Network
1
2
4
FI
Afferent Salience
"Feeling"
3
via dPI, midINS
1. Cannot use feeling states to motivate behavior
a. Disinhibition (avoidance)
b. Apathy (approach)
2. Loss of real-time prediction of visceral responses
3. Semantic landscape devoid of interoceptive input→loss of empathy
4. Blunted emotional response to salience→ accentuates #1, loss of embarrassment
5. Intensified posterior DMN
6. Cannot recruit control resources→distractability, impulsivity, impersistence
Semantic-Appraisal Network
(TPole, vSTR, mOFC, blAMY)
External milieu
Interoception
Thalamus
(vmPO, vmB)
CPGs
(HT, cAMY, PAG)
Visceromotion
Autonomic afferent nuclei
(NST, PBN)
Autonomic efferent nuclei
(NST, NA, DMNX, vlM)
Lamina I
Vagus nerve
IML
Vagus nerve
Visceroautonomic Sensor-Effectors

VENs + Fork Cells



Physiology

- The “language” of the VENS and FCs: coincidence detectors or input integrators (A. Hasenstaub, E. Chang)?
- Differentiate VENs/FCs from iPS cells (K. Haston, S. Finkbeiner)

Structure

- Local microcircuitry
  - Selective cell filling
  - DiOlistic labeling
  - Array Tomography
  - CLARITY
- Ultrastructure
- Connectivity (H. Barbas)

Chemistry/Proteome

- More detailed neurochemical/receptor profiling
- Validate leads from genomic analyses

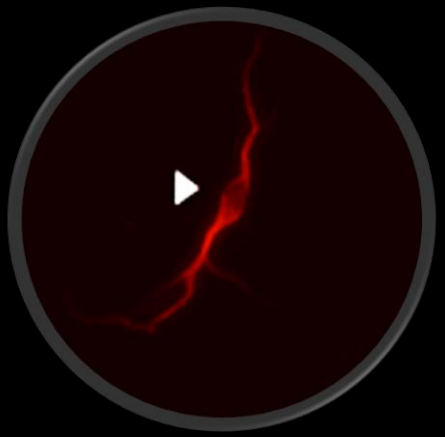
Gene expression

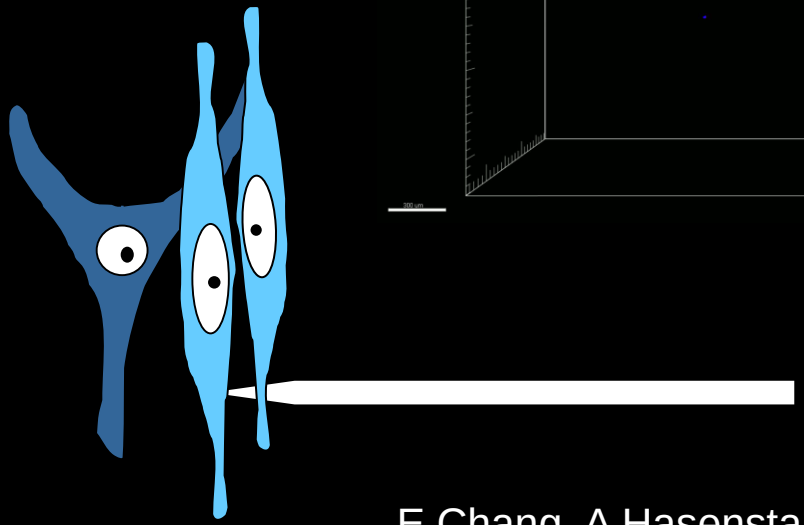
- ACC/FI gene co-expression analysis (M. Oldham)
- Single cell genomic profiling (laser capture)
- Seek rodent homologs

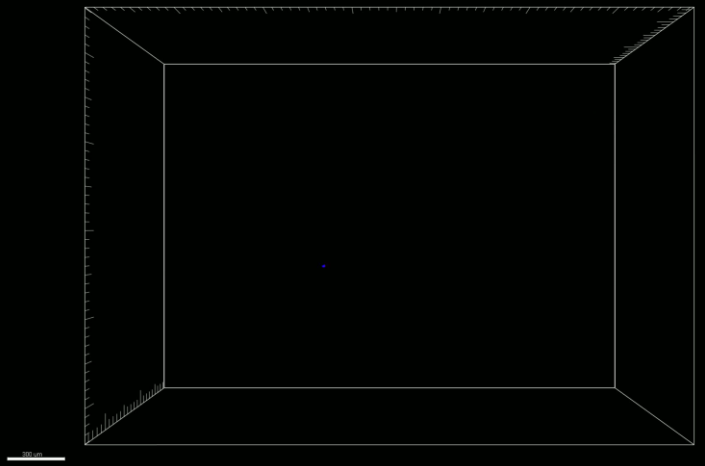
Future projects: VEN identity and vulnerability

Courtesy S. Smith Lab, Stanford

Courtesy K. Deisseroth Lab, Stanford



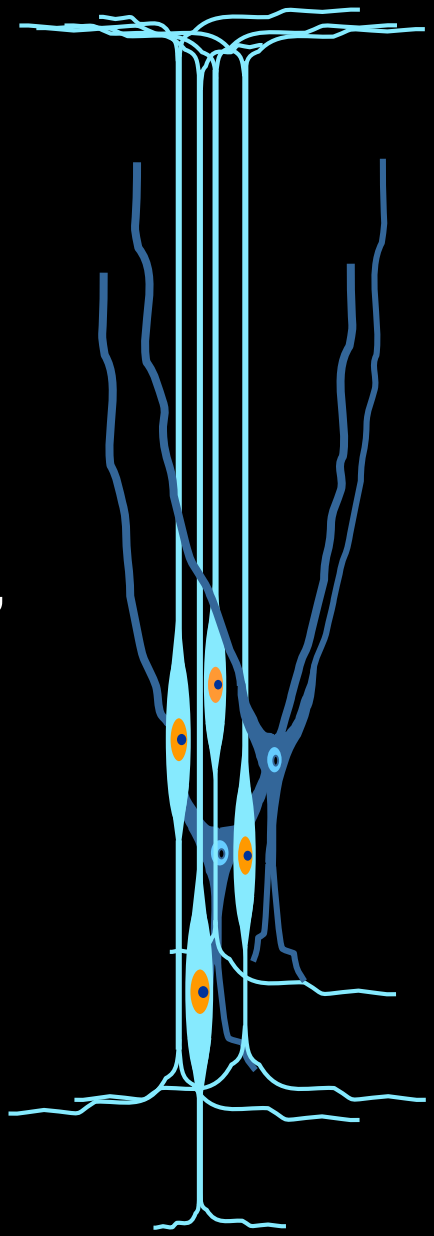




E Chang, A Hasenstaub, K Bender

Finkbeiner Lab (K. Haston), UCSF

VENs + Fork Cells: health



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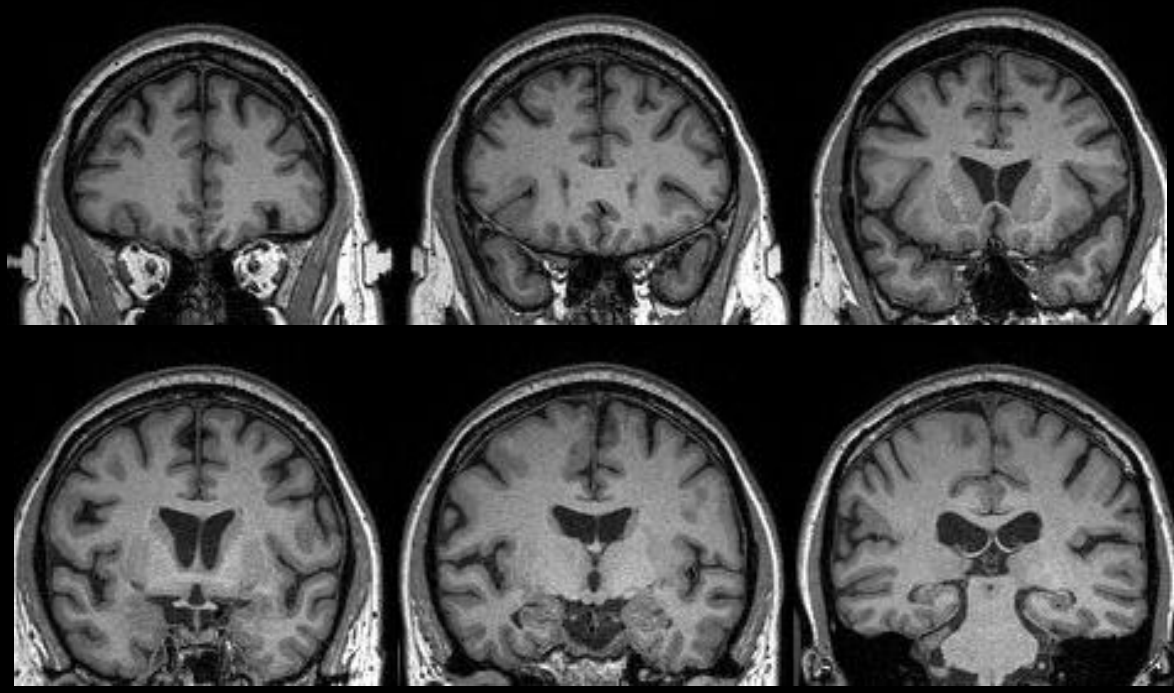
55 y.o. woman followed for 8 years of non-progressive behavioral change:

Lifelong lack of disgust
Bizarre delusions
Dissociative episodes
Panic attacks
Food fads
Self-injurious, suicidal
Diagnosed “bipolar”

Family history:
Father progressive behavioral and motor disorder with autopsy showing “progressive subcortical gliosis”

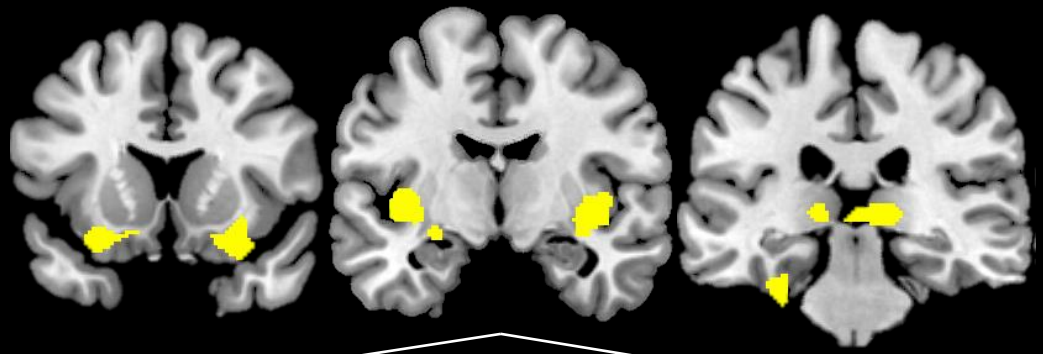
bvFTD “phenocopy”



Khan et al, JNNP 2012

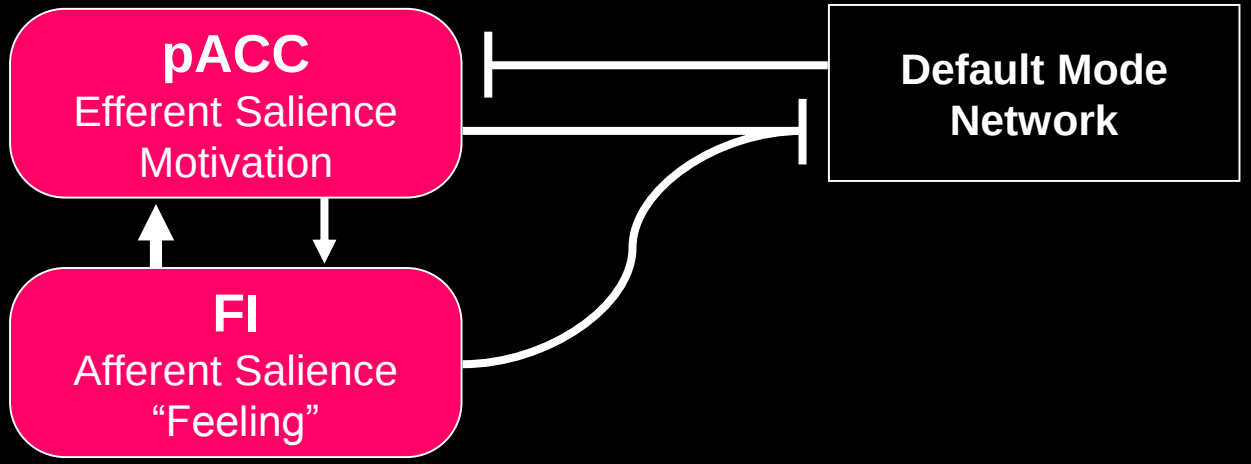
55F w/ 8 years non-progressive behavioral change compared with 30 age-matched healthy women

Gray matter atrophy



Salience network

Default mode network



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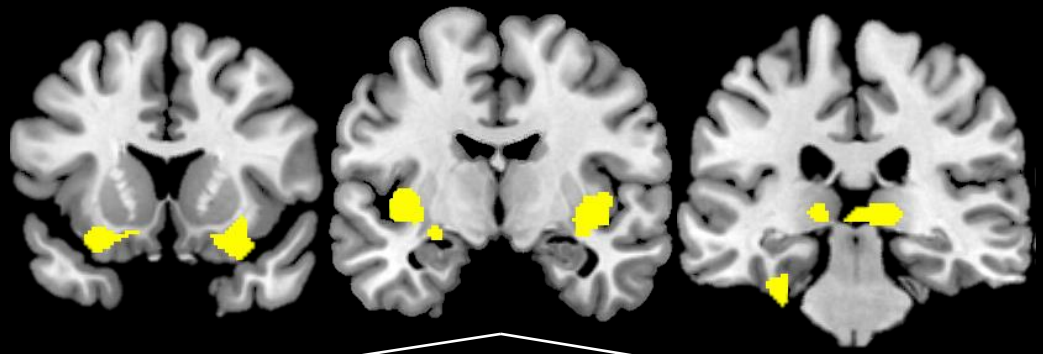
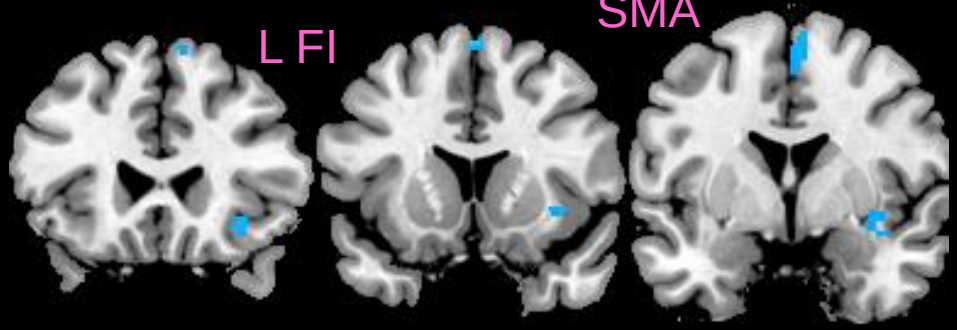
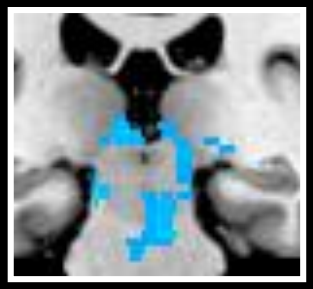


Disrupted R FI connectivity

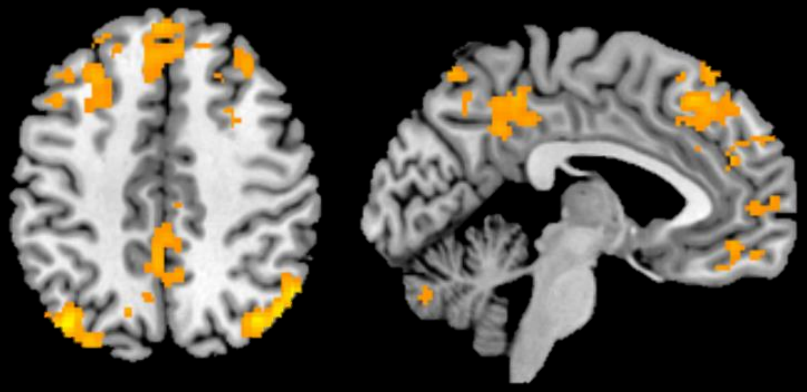


mPULV

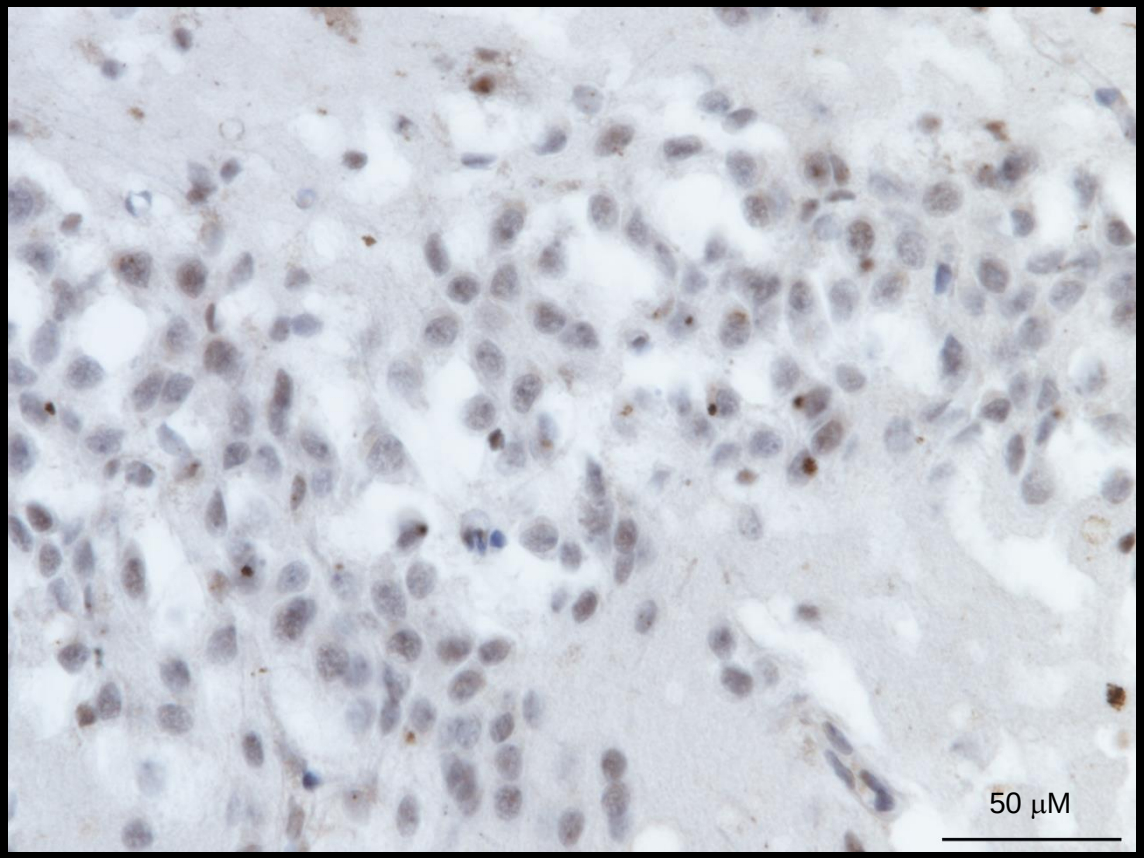


Enhanced R ANG connectivity

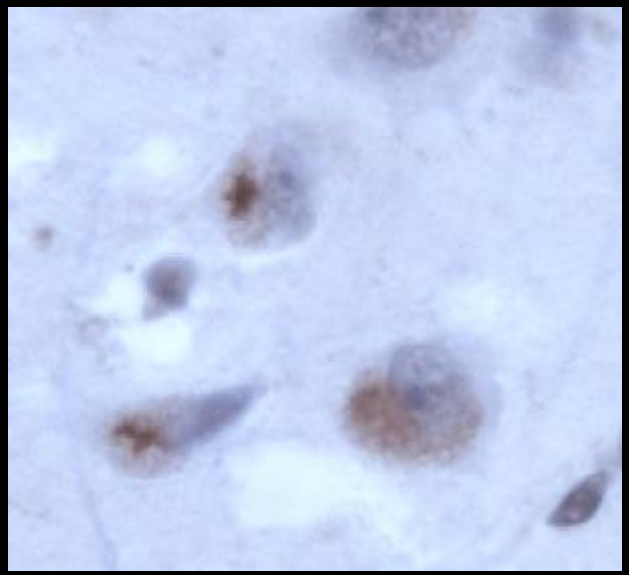
Default mode network



Father’s postmortem: Ubiquitin IHC



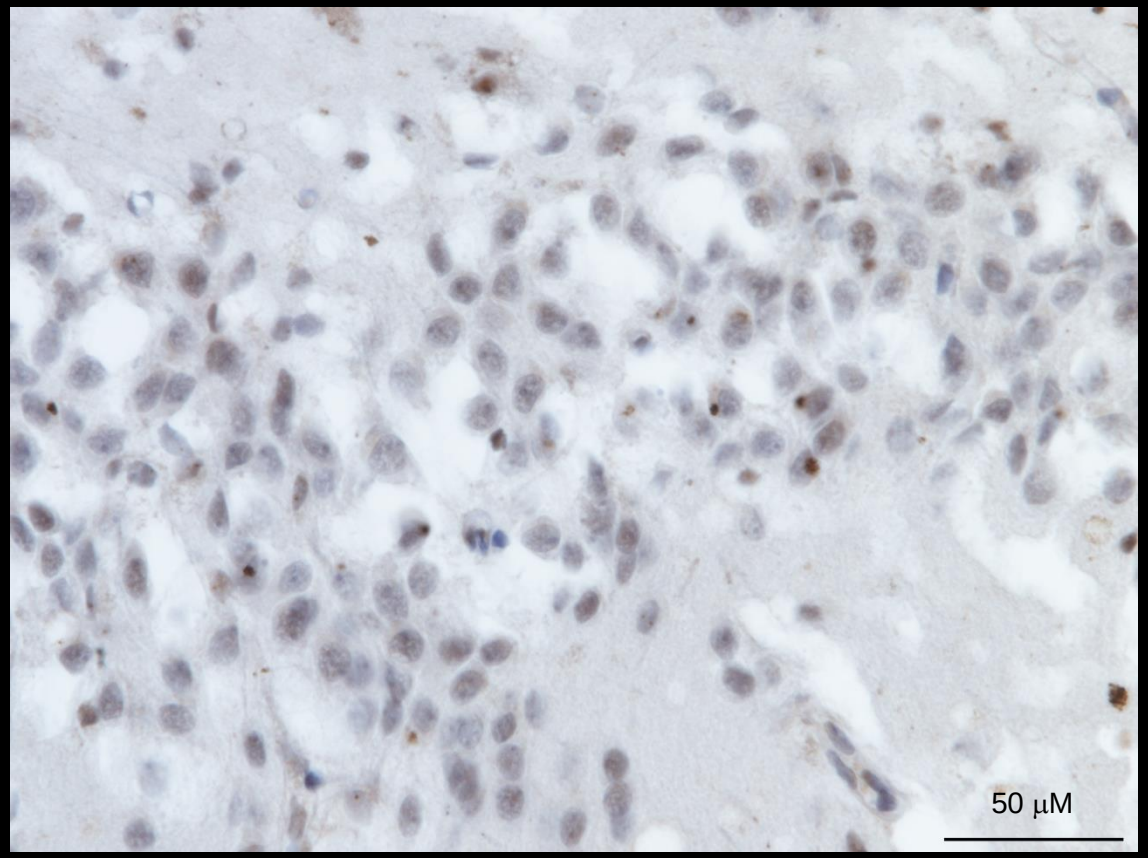
Dentate gyrus



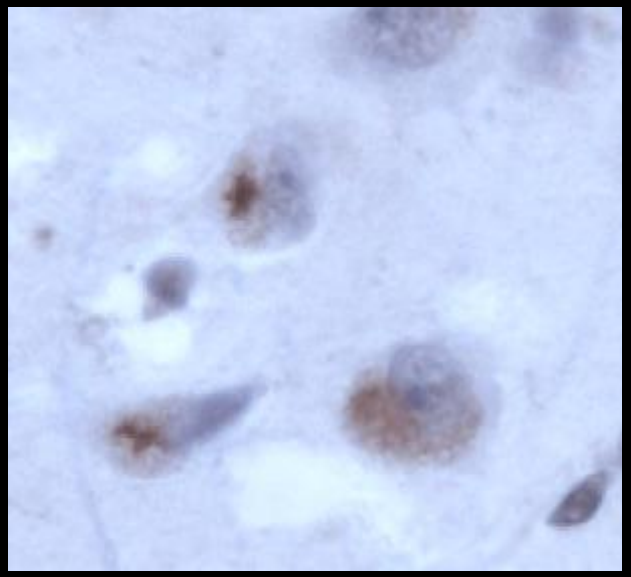
CA4

Frequent ubiquitin-positive, TDP-negative NCIs in dentate granule cells, as well as small round or stellate NCIs in CA3/4, CA2, CA1/subiculum

Father’s postmortem: Ubiquitin IHC

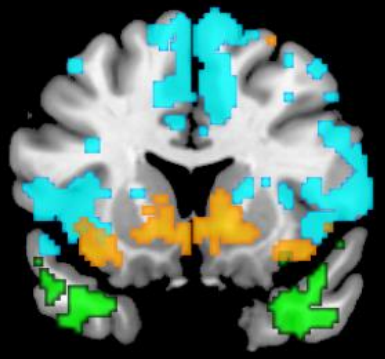


Dentate gyrus



CA4

Ubiquitin IHC NP diagnosis:
C9orf72-related FTLD
(now, FTLD-DPR)



Dorsal Salience
PNFA (L)
bvFTD (R)
CBS (L or R)
PGRN
MAPT

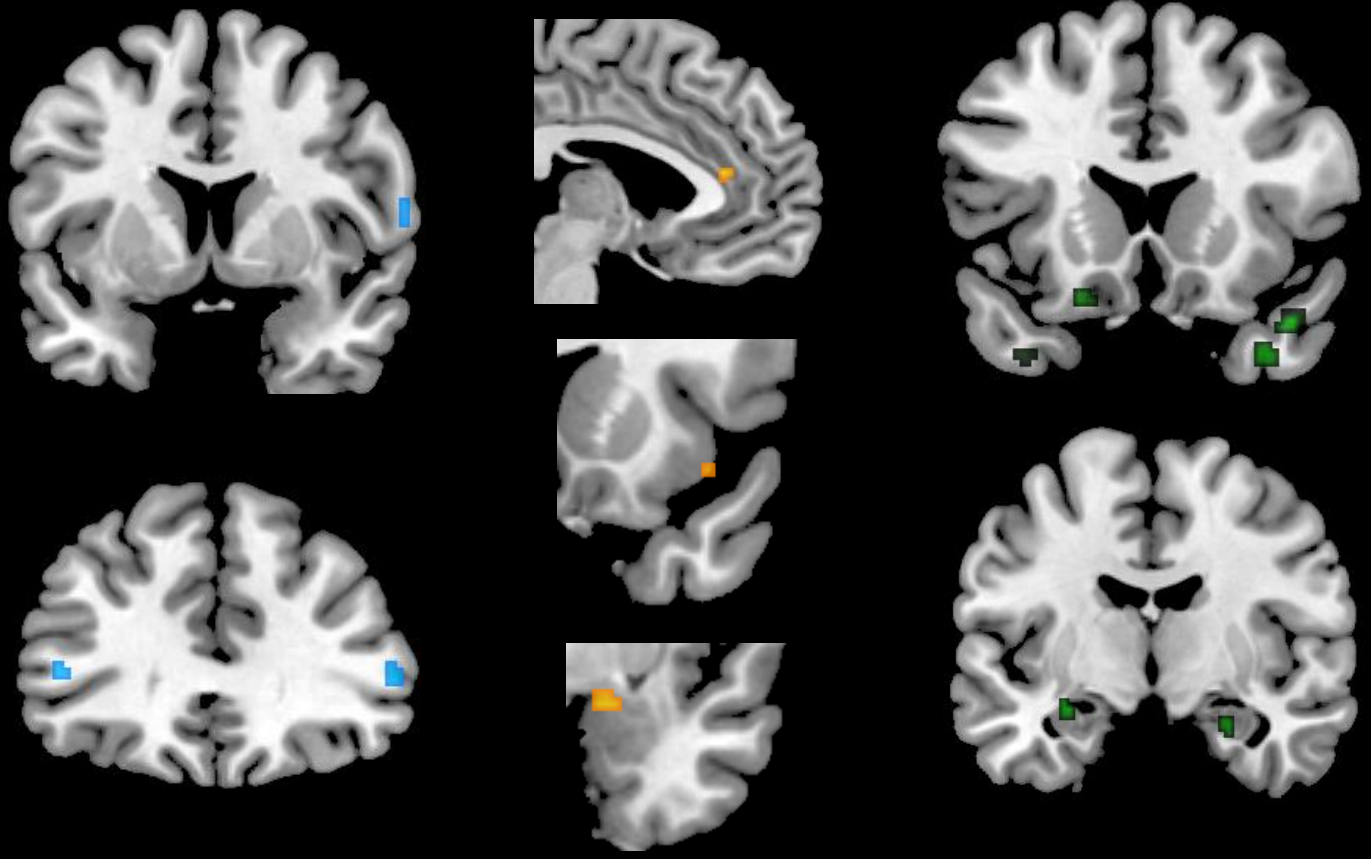
Ventral Salience
bvFTD (R>>L)
PGRN
CHR9
MAPT

Semantic/TPN
SD (L>>R)
MAPT

12 Gene Carriers
3 MAPT
6 PGRN
3 CHR9

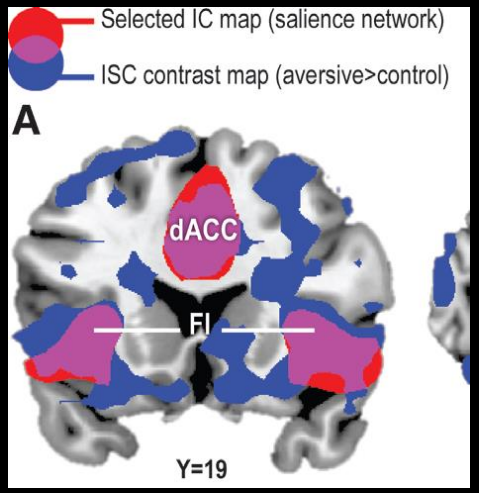
<

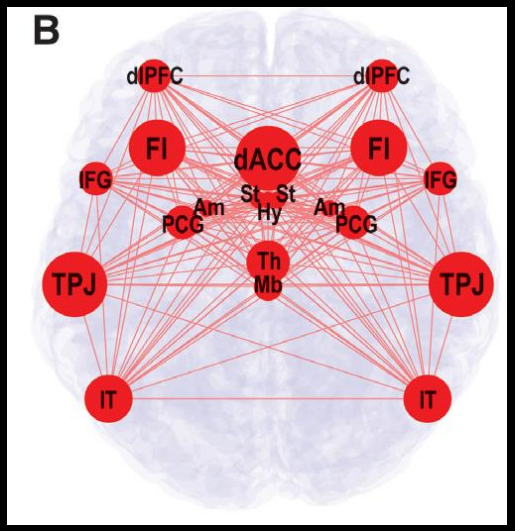
9 Non-carrier family members

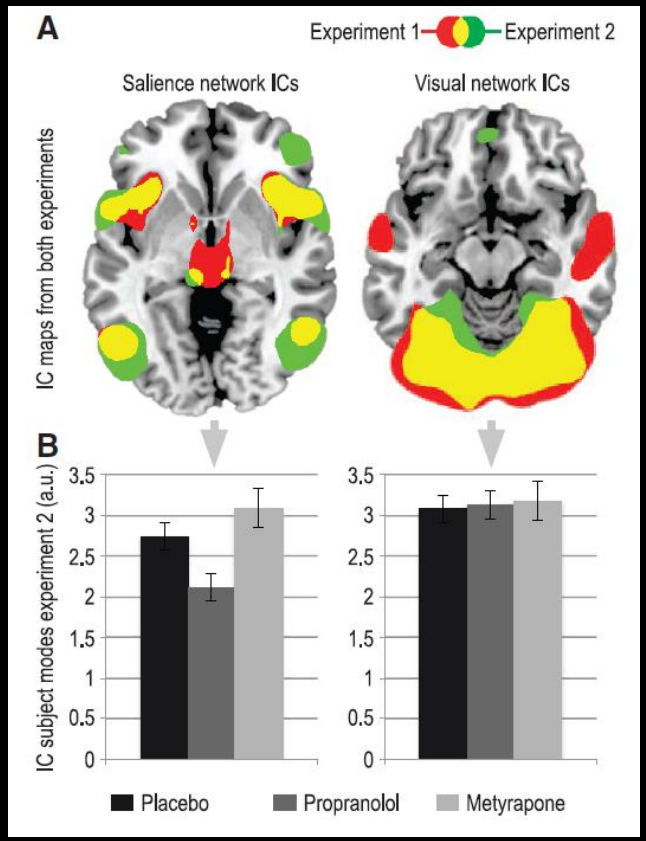


P<0.01 (uncorrected)

Salience network connectivity is modulated by noradrenergic tone







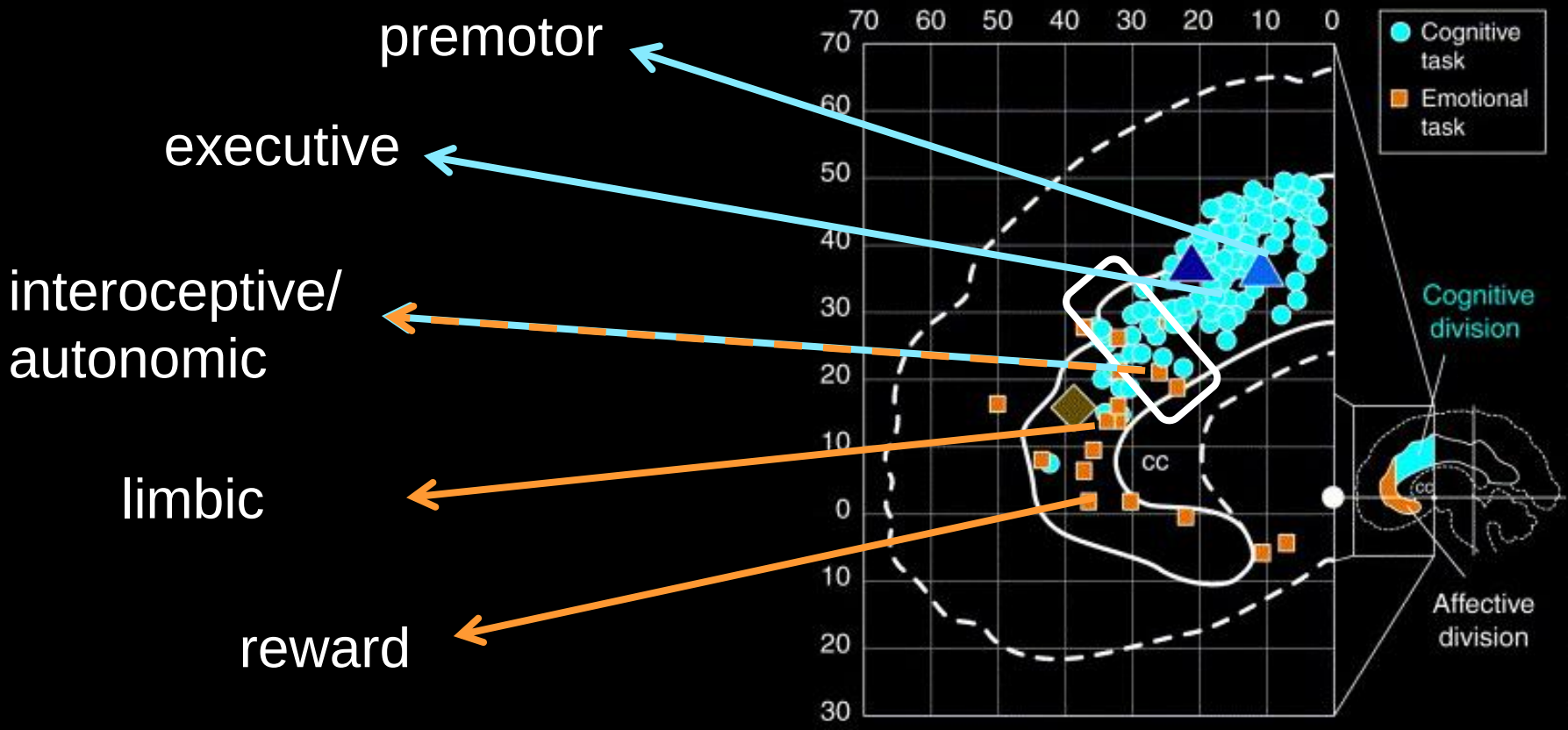
Hernans et al Science 2011

Table 1. Regional Correlates of Core bvFTD Social-Emotional Deficits

Deficit	Imaging	Patients Included	Regional Correlates	Reference
Emotional empathy (empathic concern)	MRI	bvFTD, svPPA, nfvPPA, CBS, PSP, AD	Right ATL, FI, sACC, pACC, striatum	Rankin and others (2006)
	MRI	bvFTD, svPPA, nfvPPA	dmPFC, pACC	Eslinger and others (2011)
Cognitive empathy (perspective taking)	MRI	bvFTD, svPPA, nfvPPA, CBS, PSP, AD	Right ATL, fusiform gyrus, dmPFC, sACC, striatum	Rankin and others (2006)
	MRI	bvFTD, svPPA, nfvPPA	FP, dmPFC, dlPFC, ATL, lateral parietal	Eslinger and others (2011)
Interpersonal warmth	MRI	bvFTD, svPPA, nfvPPA, CBS, AD	Right FI, mOFC > ATL	Sollberger and others (2009)
Emotion recognition: faces (negative emotion)	MRI	bvFTD, svPPA, nfvPPA, PSP, MCI, AD, HC	Right ITG, lat OFC	Rosen and others (2006)
	MRI	bvFTD, svPPA	Bilateral AI, lat OFC	Omar and others (2011)
Emotion recognition: music	MRI	bvFTD, svPPA	Bilateral pACC, sACC, AI, OFC, dmPFC, ATL, amygdala, striatum	Omar and others (2011)
Emotional moral judgment	SPECT	bvFTD, AD, HC	Right frontotemporal[a]	Mendez and Shapira (2009)
Prosocial sentiments (guilt, pity, embarrassment)	PET	bvFTD	Right FP, septum	Moll and others (2011)
Other critical sentiments (anger, disgust)	PET	bvFTD	dmPFC, right amygdala	Moll and others (2011)
Embarrassment	NA	bvFTD, svPPA, nfvPPA, HC	Not studied	Sturm and others (2006)
Autonomic response to embarrassment	MRI	bvFTD, svPPA, nfvPPA, HC	pACC	Sturm and others (2008), Sturm and others (2011)
Mutual gaze during dyadic interaction	NA	bvFTD, svPPA, AD, HC	Not studied	Sturm and others (2010)

*Seeley Brain Structure and Function, 2011

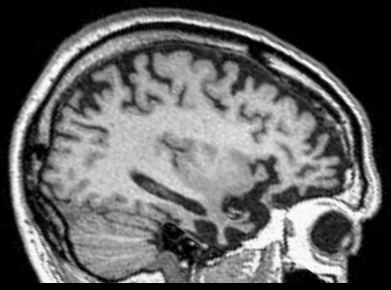
ACC drives autonomic efference and provides the will to act



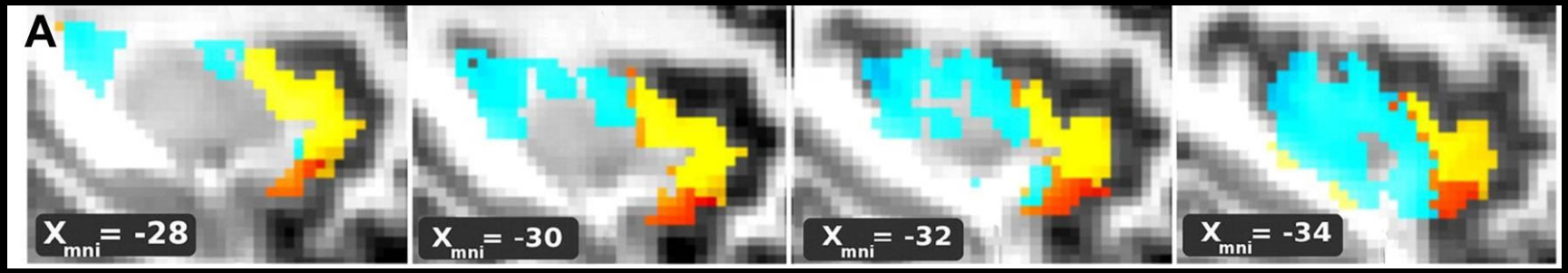
- Lesions produce apathy-abulia-akinetic mutism
- Task-based fMRI activation scales with effort

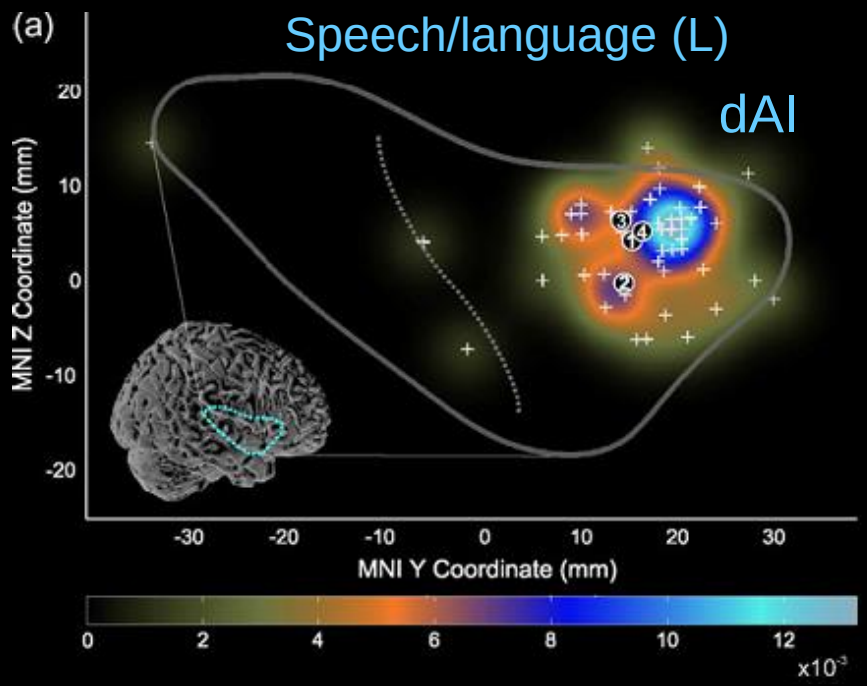

bvFTD, Stage 4, due to Pick’s

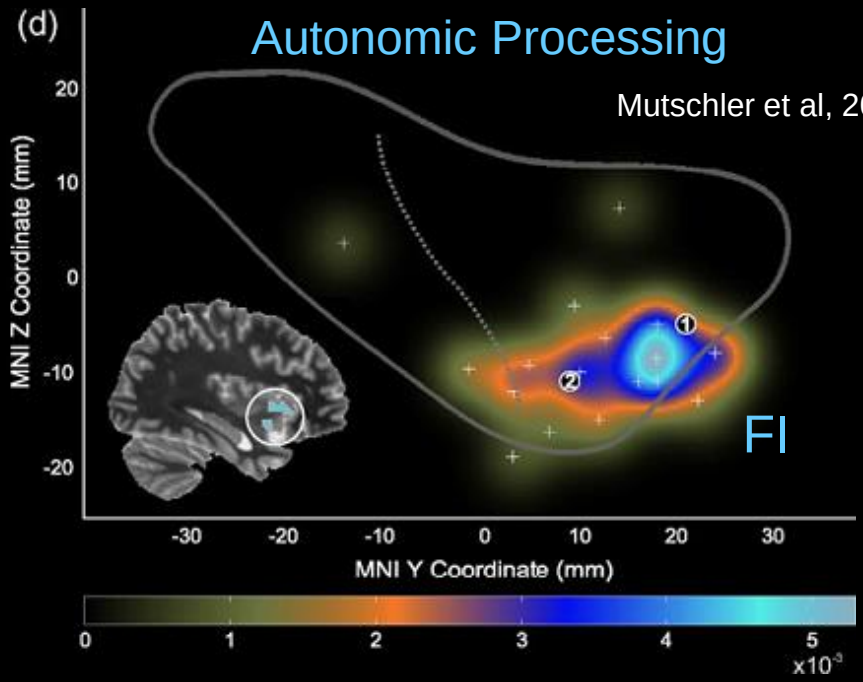
Area FI



Nanetti et al, 2009



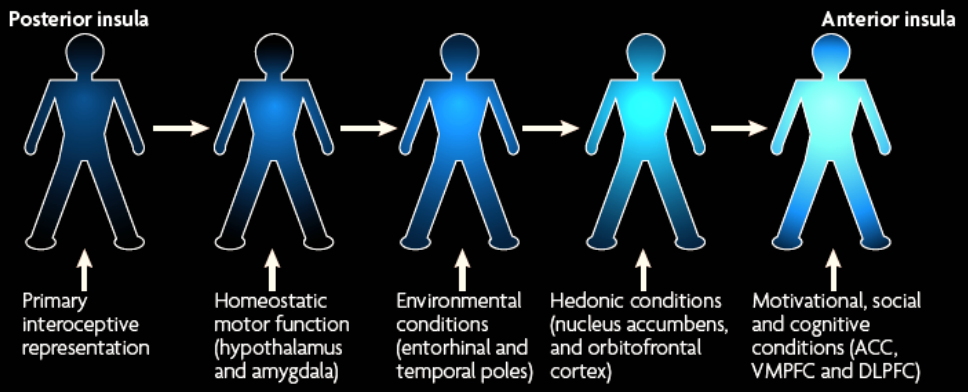




Area FI

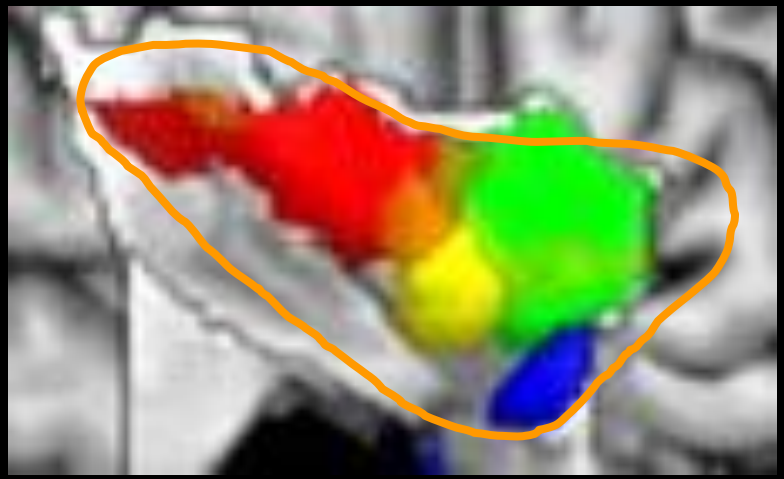
bvFTD

A.D. Craig, *NRN* 2009



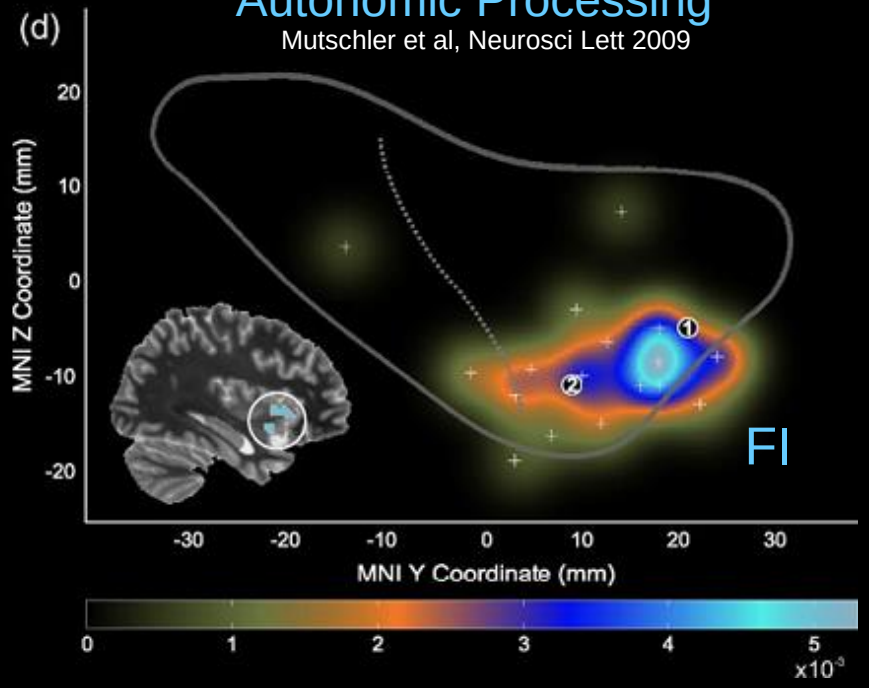
Social-emotional function

Kurth et al, Brain Structure and Function 2010



Autonomic Processing

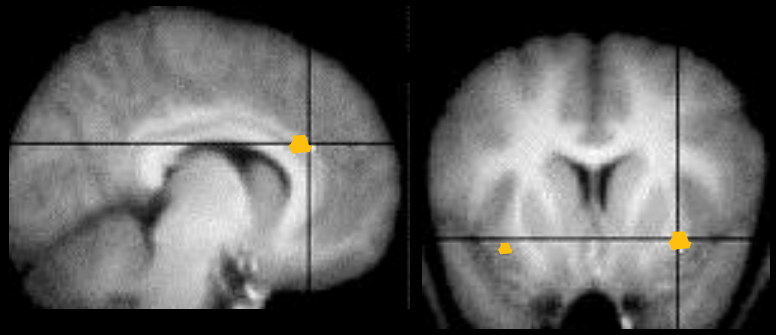
Mutschler et al, Neurosci Lett 2009



Area FI

bvFTD

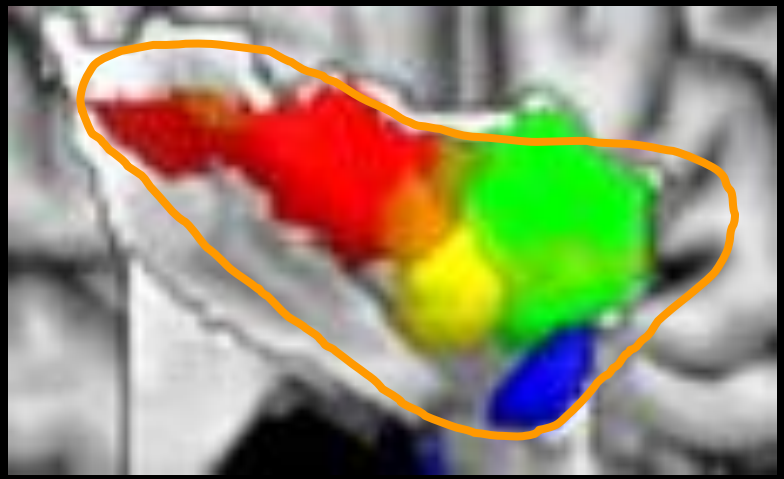
Self-recognition



Devue 2007

Social-emotional function

Kurth et al, Brain Structure and Function 2010



Sensory/ motor

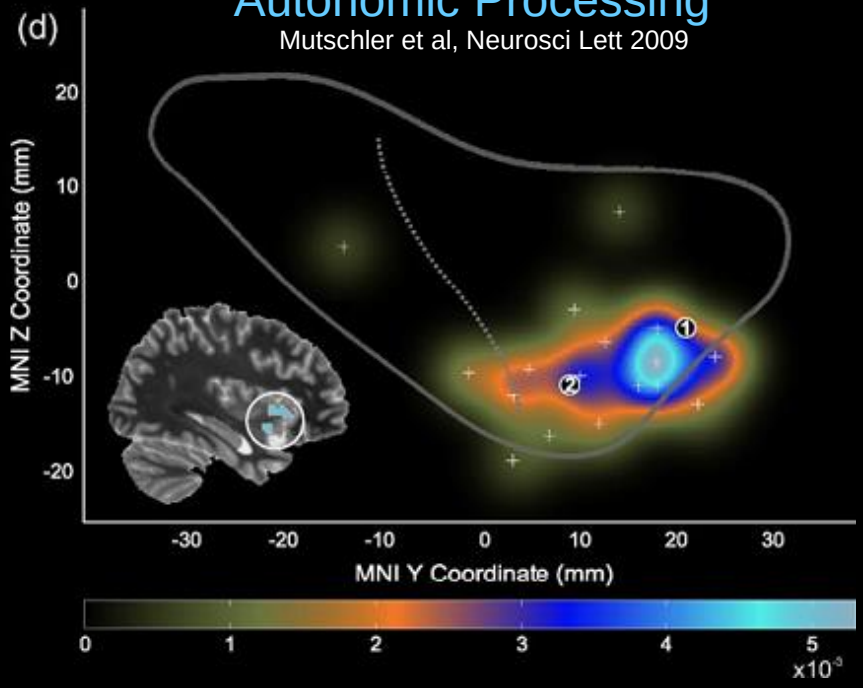
Taste/ Smell

Cognitive

Social/ Emotional

Autonomic Processing

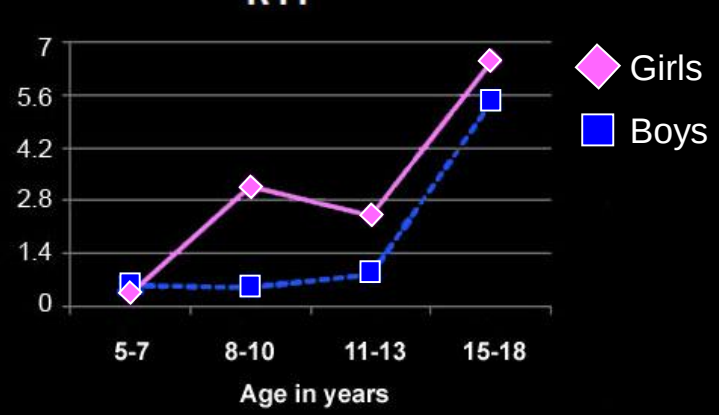
Mutschler et al, Neurosci Lett 2009



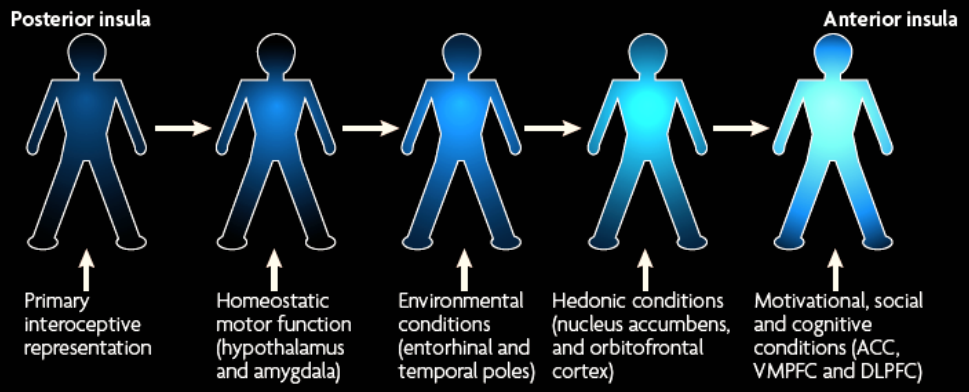
Area FI

Developmental trajectory

Zielinski et al, PNAS 2010

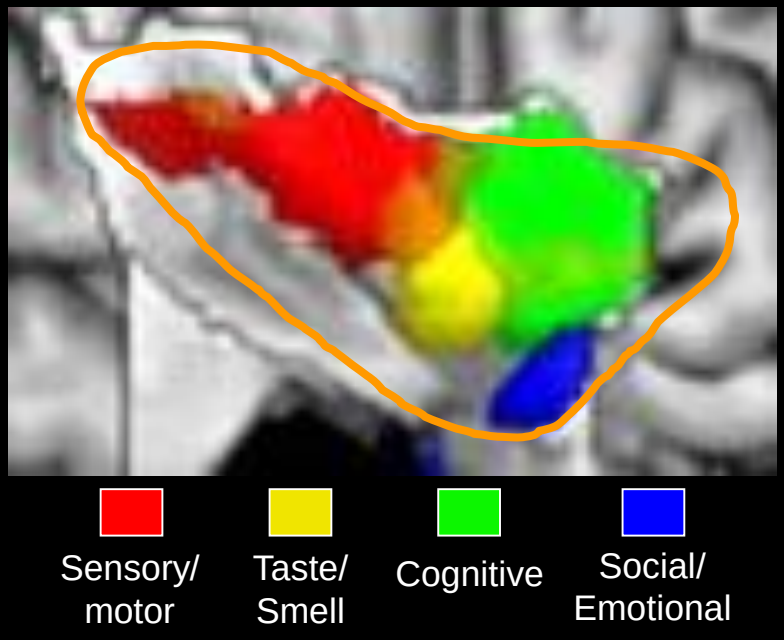


A.D. Craig, *NRN* 2009



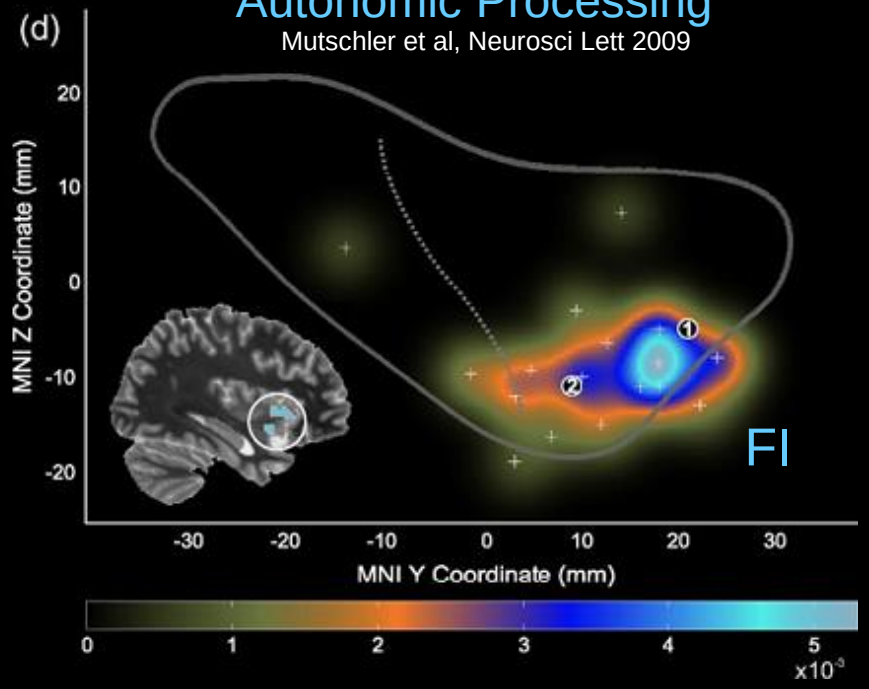
Social-emotional function

Kurth et al, Brain Structure and Function 2010



Autonomic Processing

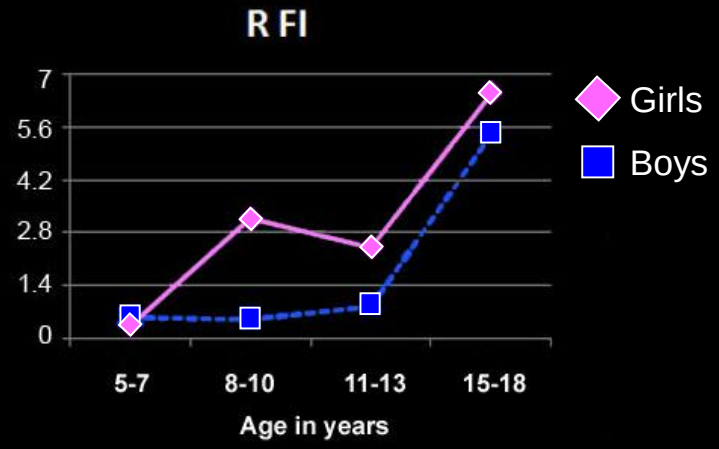
Mutschler et al, Neurosci Lett 2009



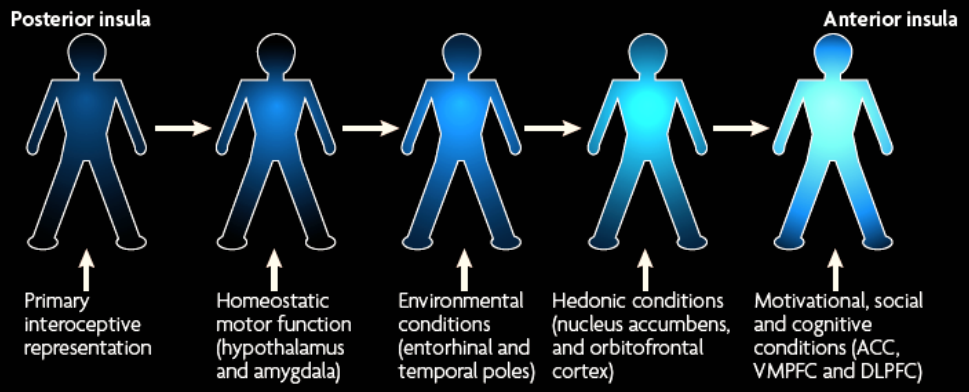
Area FI

Developmental trajectory

Zielinski, Gennatas et al, PNAS 2010

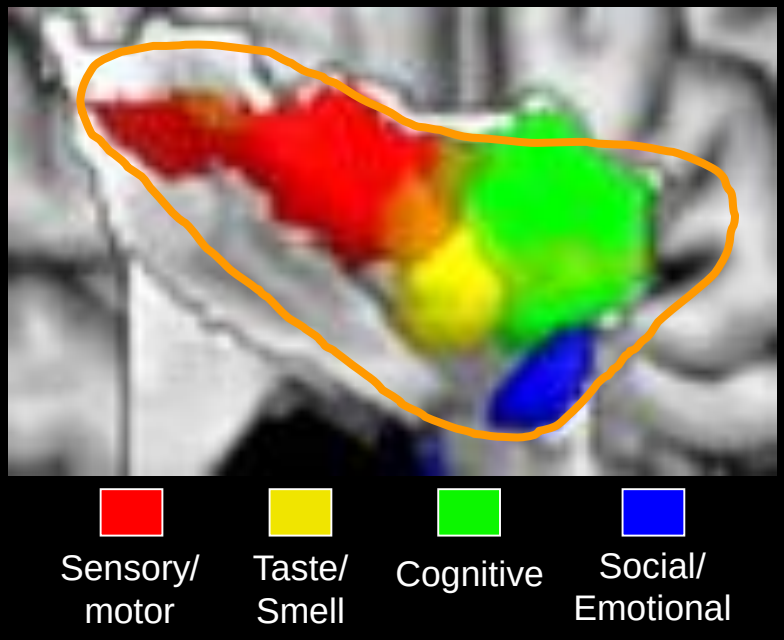


A.D. Craig, *NRN* 2009



Social-emotional function

Kurth et al, Brain Structure and Function 2010



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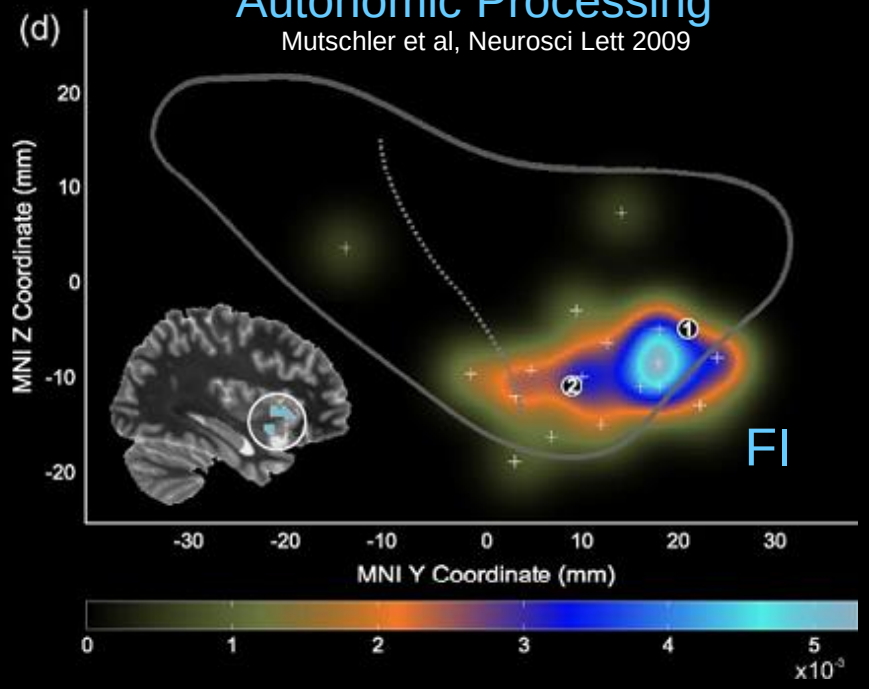
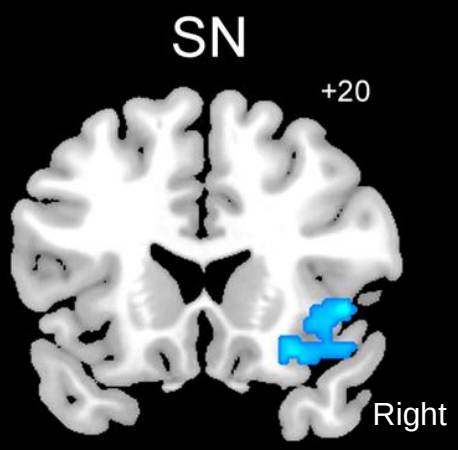
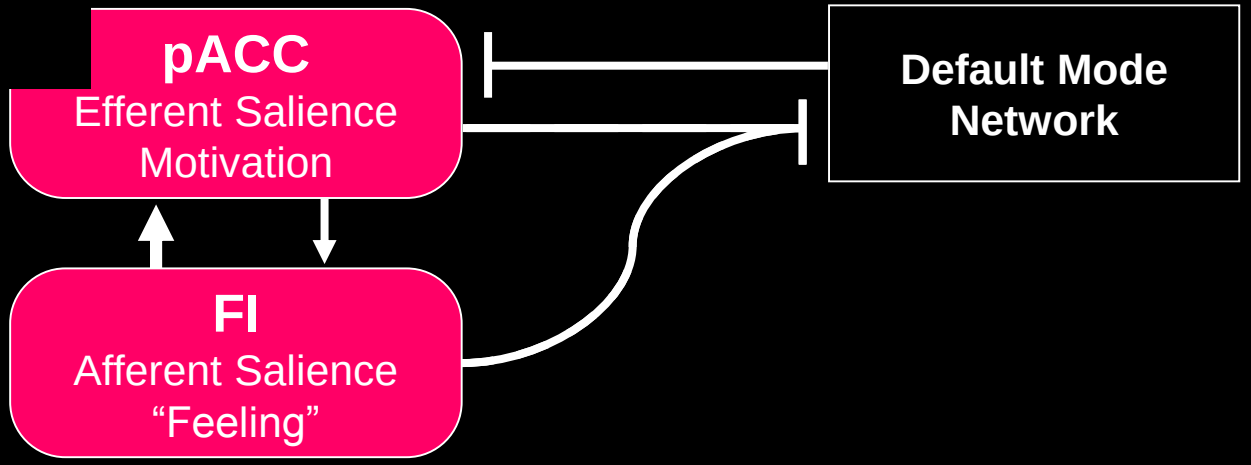
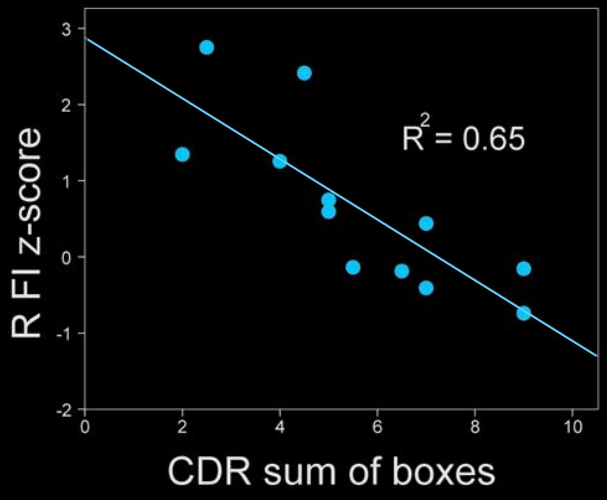
Mutschler et al, Neurosci Lett 2009

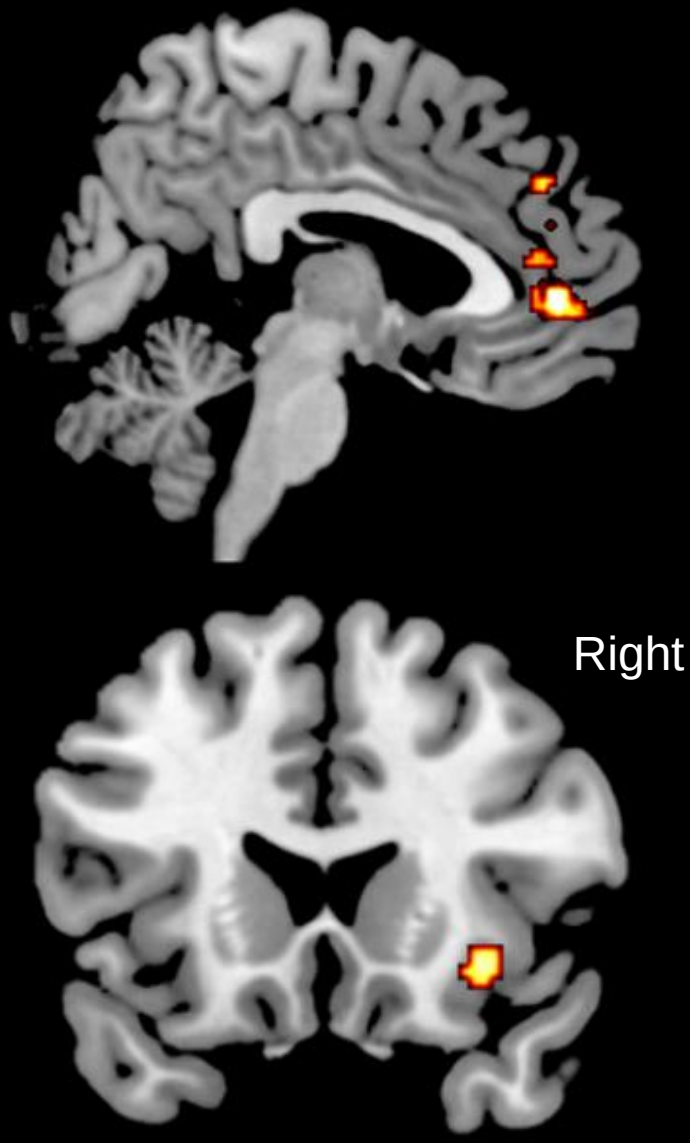


Salience Network breakdown and DMN enhancement track bvFTD severity









bvFTD epicenters

Where does bvFTD begin?

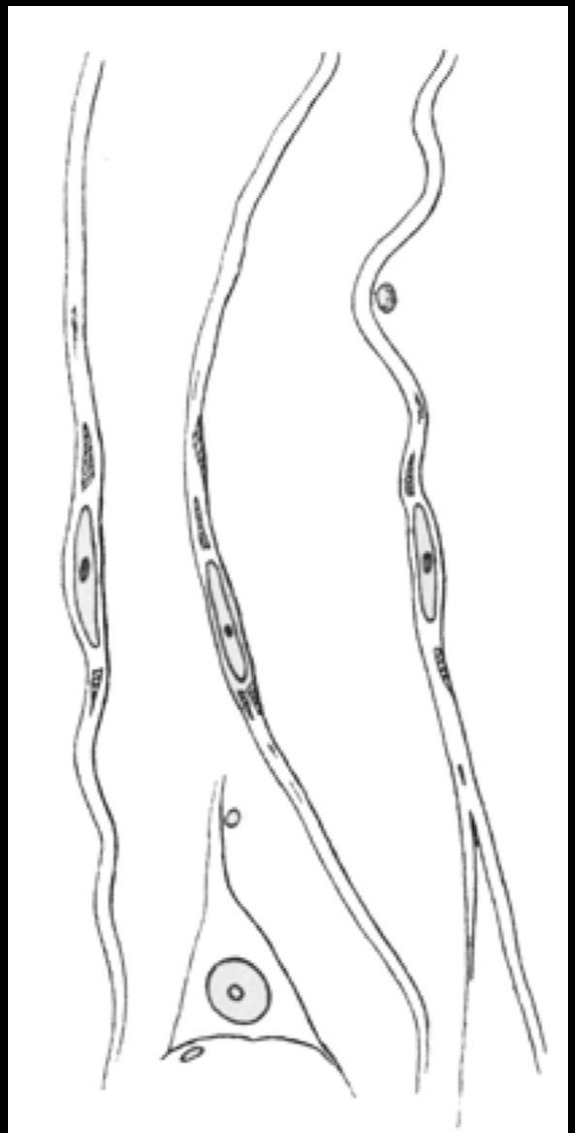
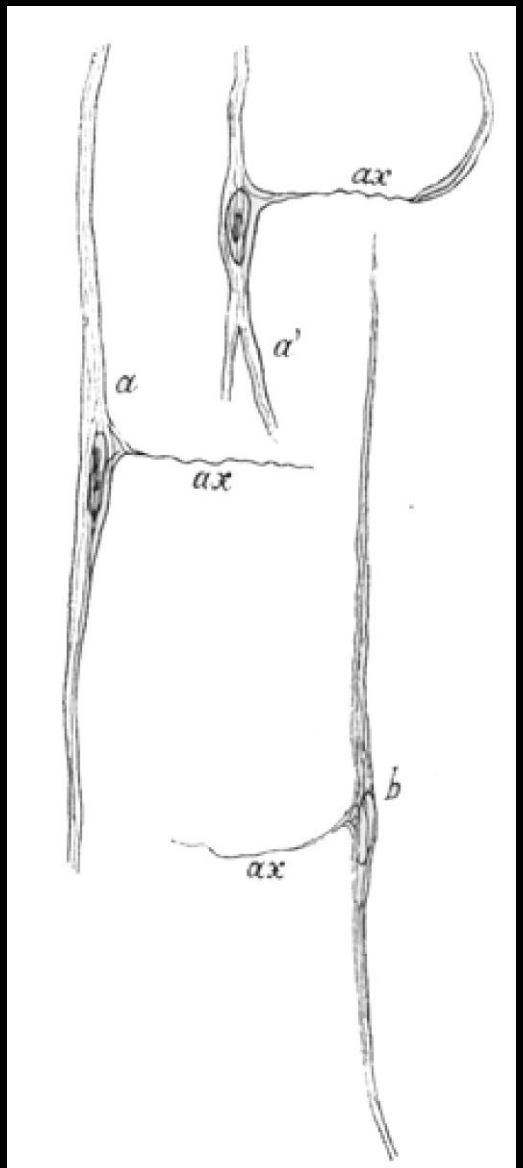


Abb. 4.



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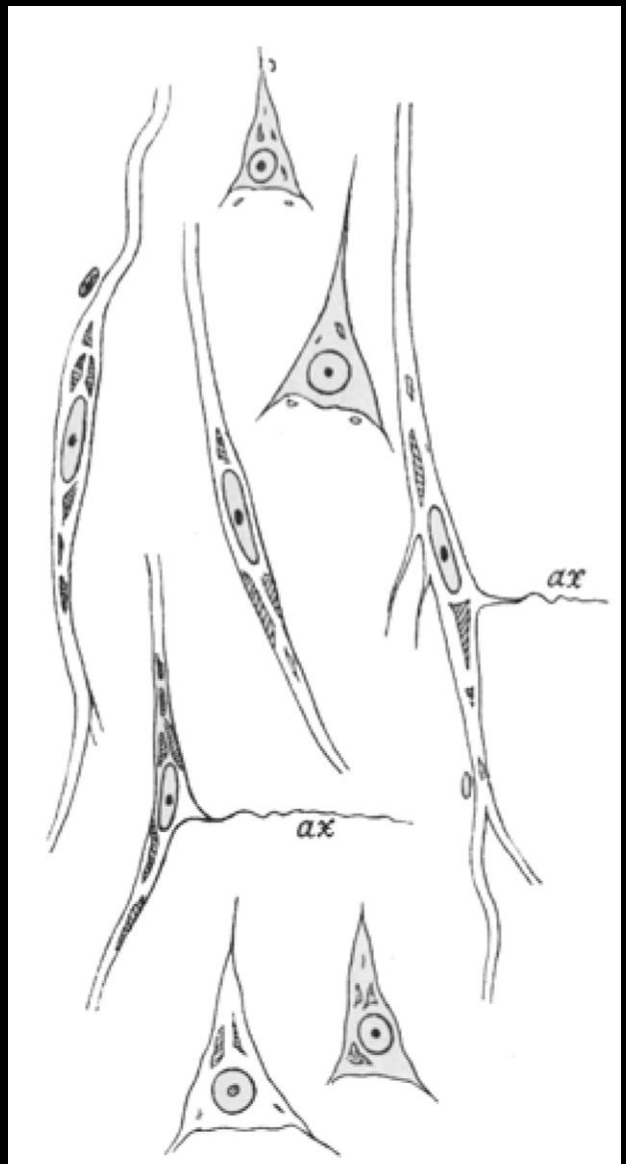


Abb. 3.

(See Seeley et al Cerebral Cortex 2011 for translation and commentary)

von Economo 1926

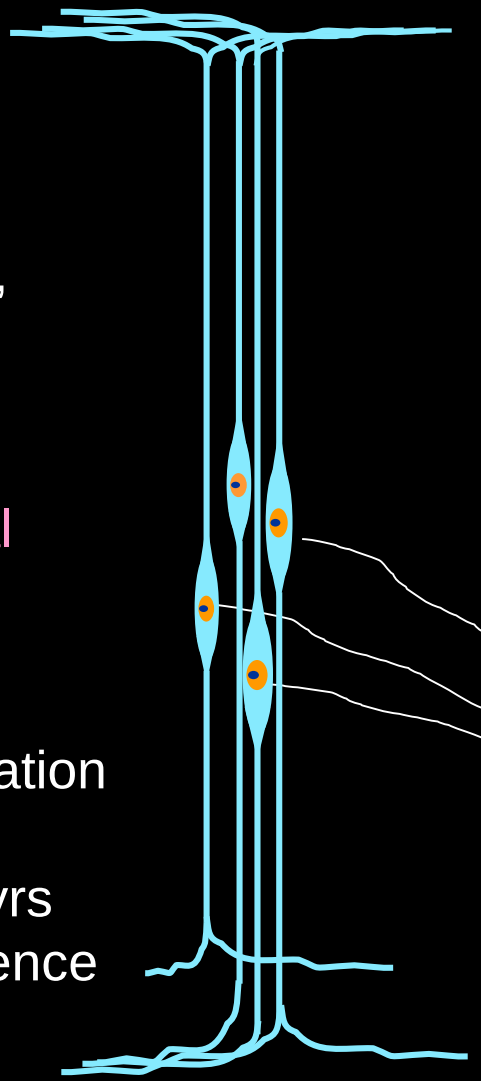
VENs

Structure

- Simplified architecture
- Layer Vb, FI>>ACC
- Columnar clusters
- Project axons into WM, targets unknown
- R/L hemisphere ~ 1.3
- Express CTIP2 and FEZF2 c/w subcerebral projections (I. Cobos)

Ontogeny

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



Chemistry/proteome

- Glutamatergic
- Rich in nonphosphorylated neurofilaments (SMI-32)
- Somata & prox dendrites express receptors:
  - D3
  - 5HT1b/2b
  - Vasopressin 1a
- NMB, ILR4α, ATF3, DISC1

Phylogeny

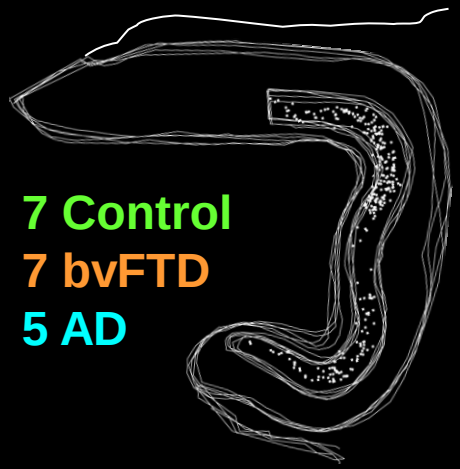
- Great apes<<<Human
- Orangutan<Gorilla<Chimps
- Cetaceans
- Elephants
- Monkeys!

(See work of J. Allman, P. Hof, and C. Sherwood labs)

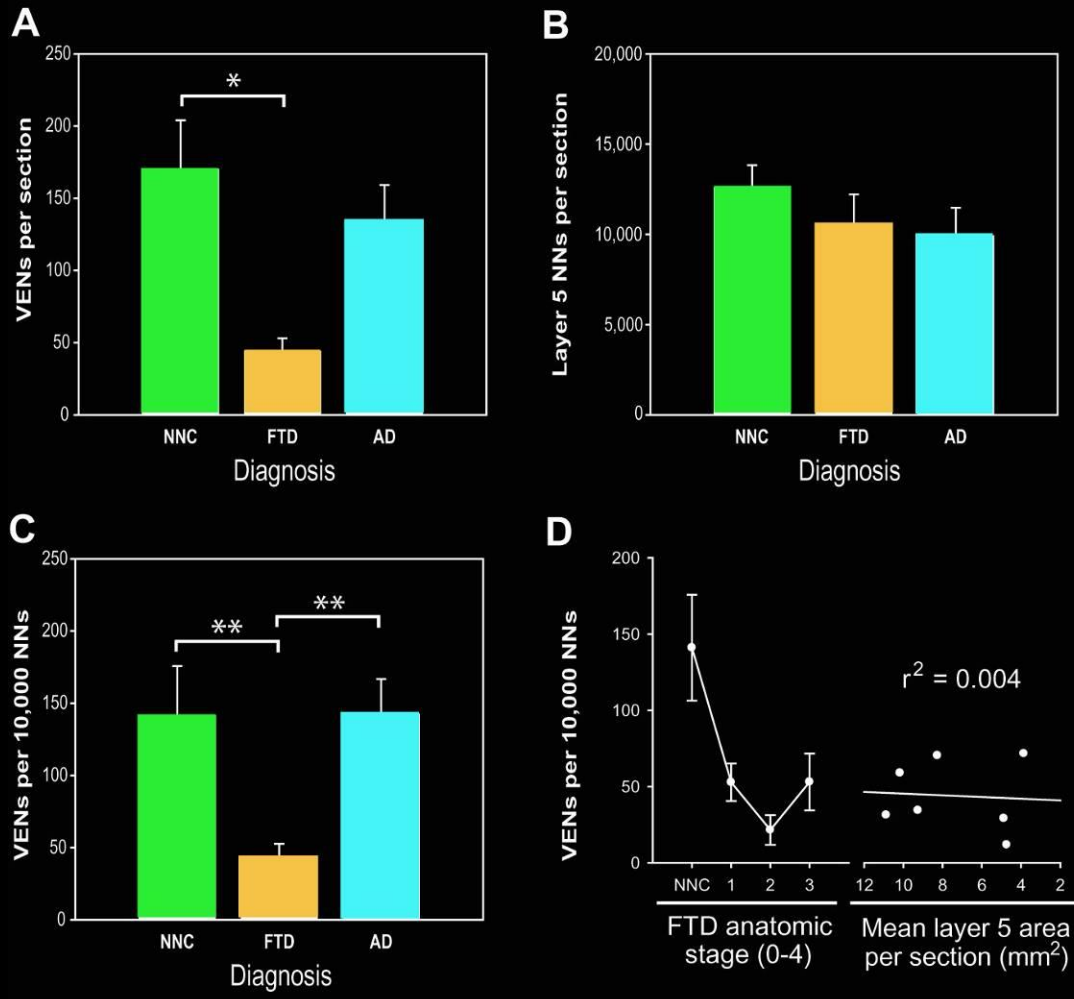
VENs: The early vulnerable neuron in bvFTD?

Schroeter et al 2006
bvFTD meta-analysis

Left ACC



7 Control
7 bvFTD
5 AD



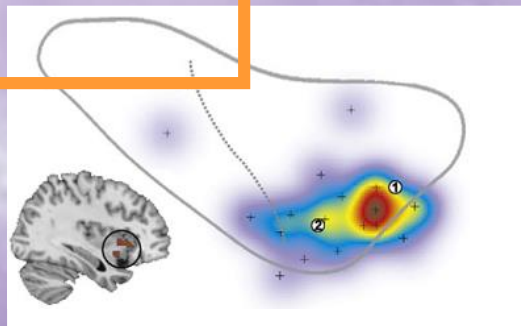
Seeley, Carlin et al, Ann Neurol, 2006

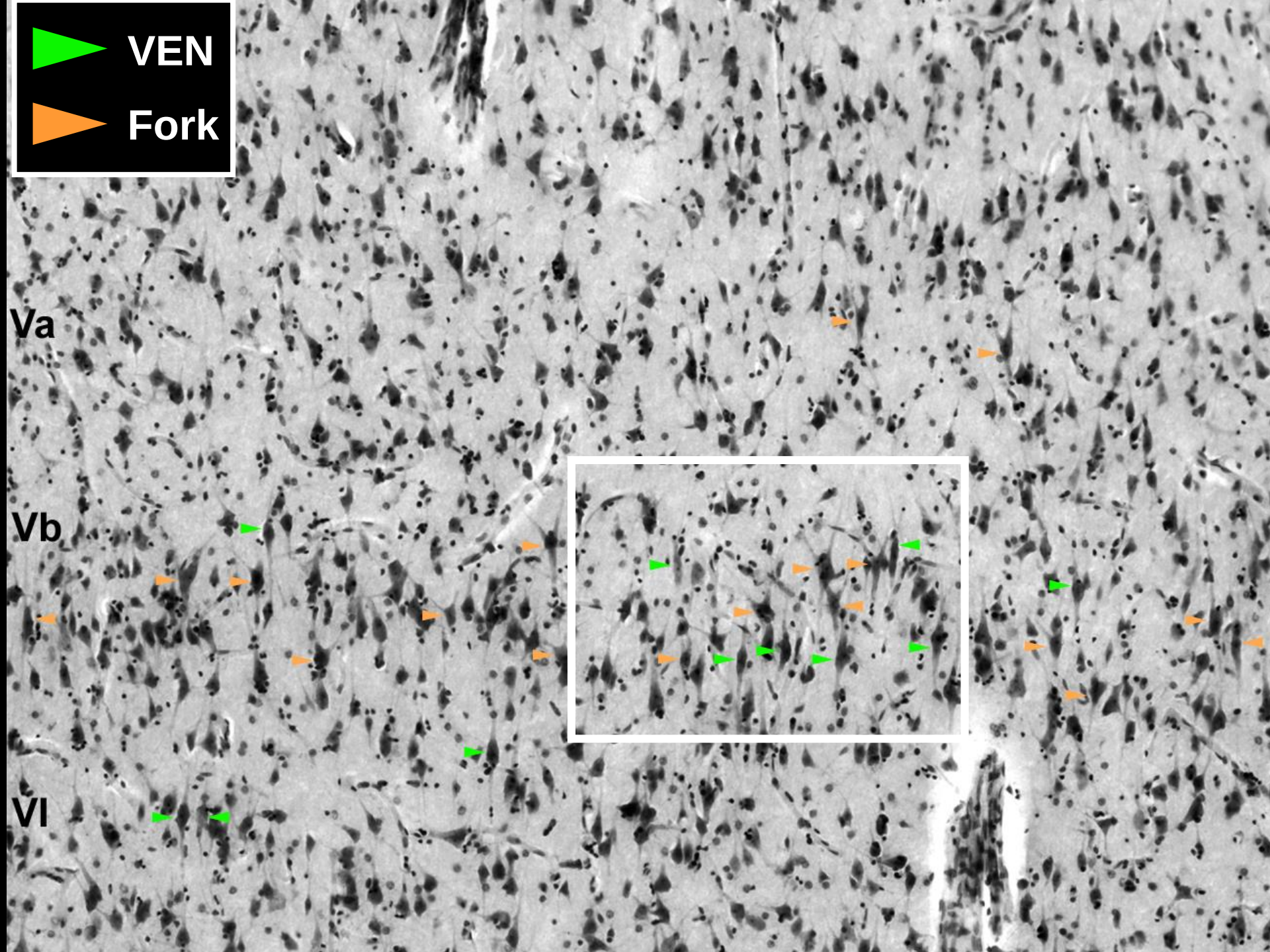
Onset

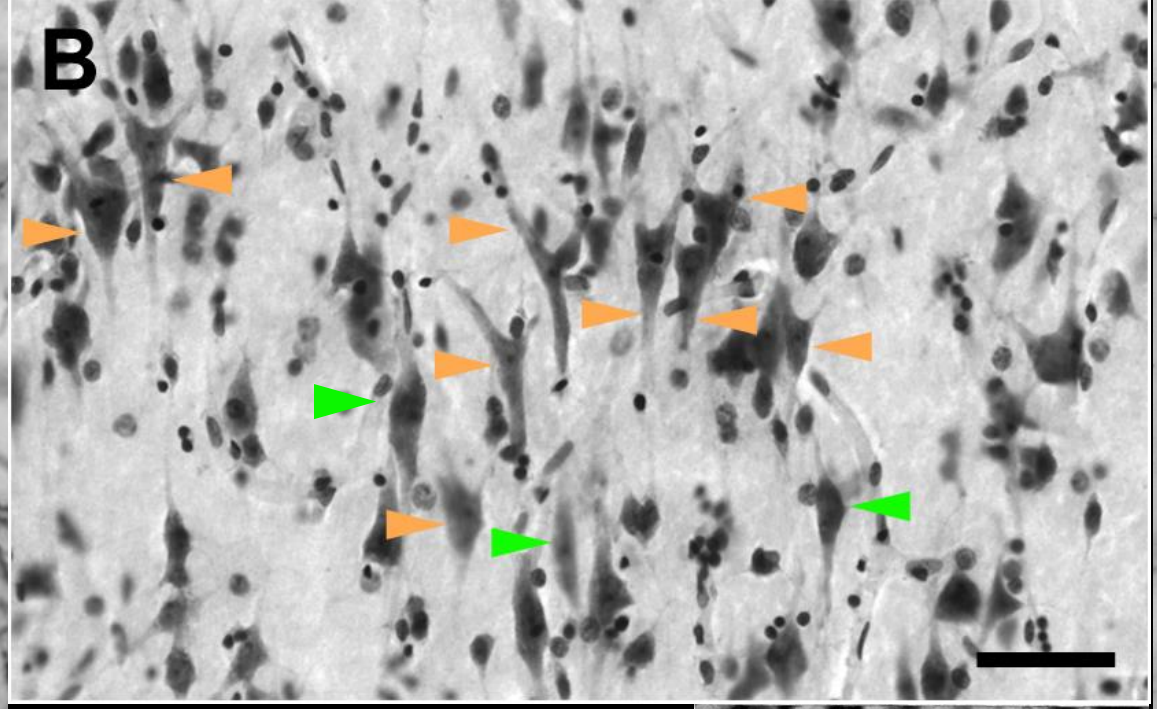
Progression

Translation

Future




VEN
Fork
Va
Vb
VI

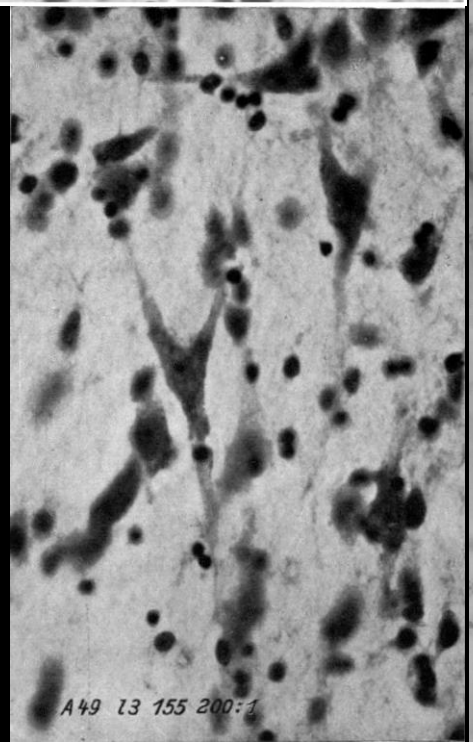


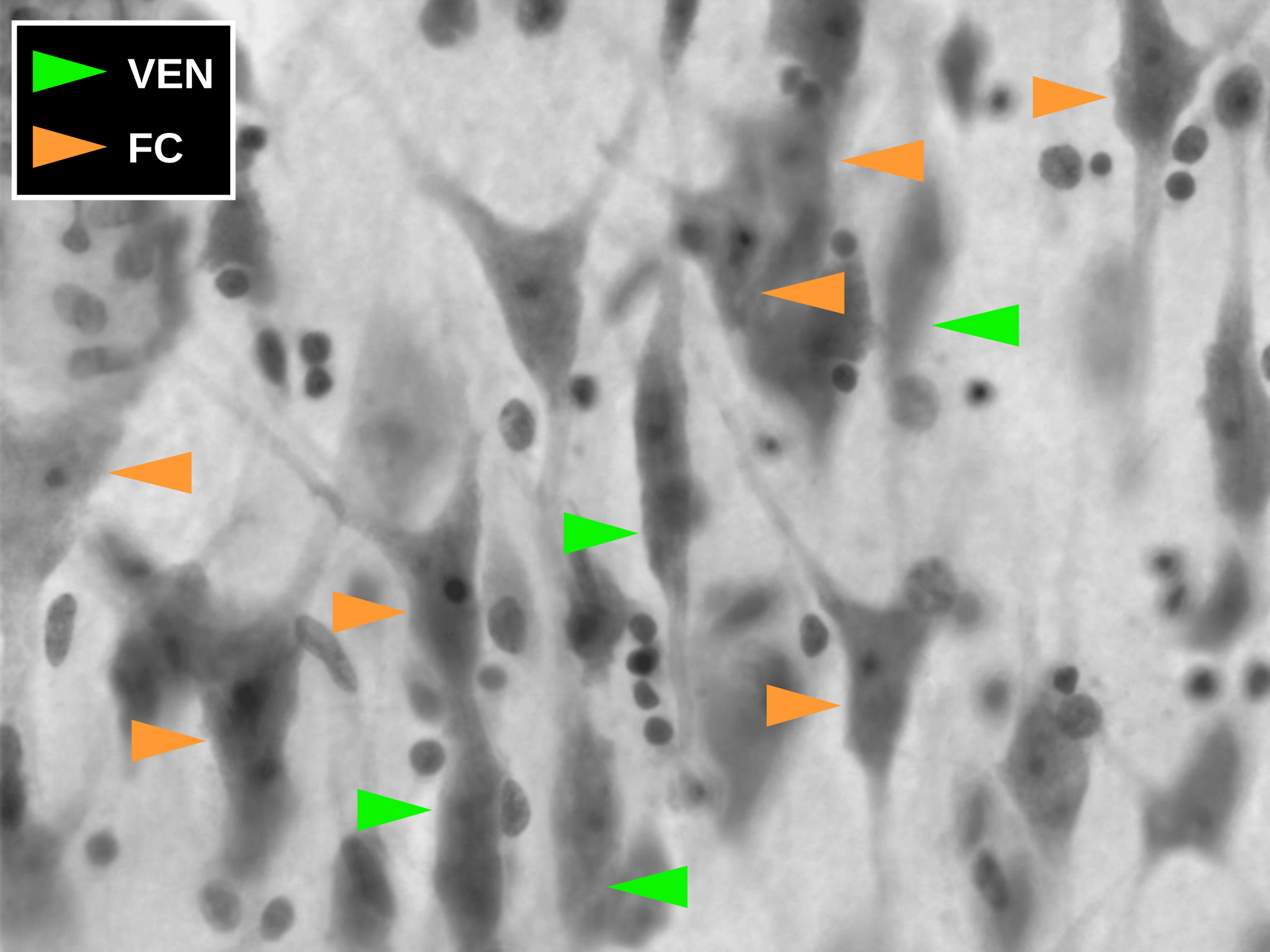
Ngowyang 1932

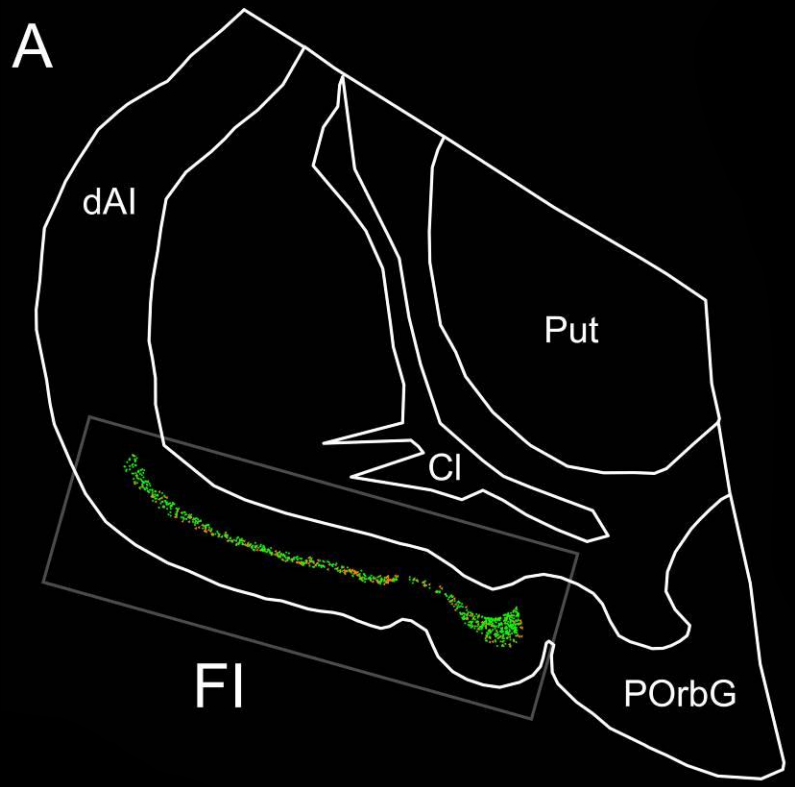
Gabelzellen =

“Fork cells”

(See Seeley et al 2011 for commentary and translation)




VEN
FC


A
dAI
Put
Cl
FI
POrbG

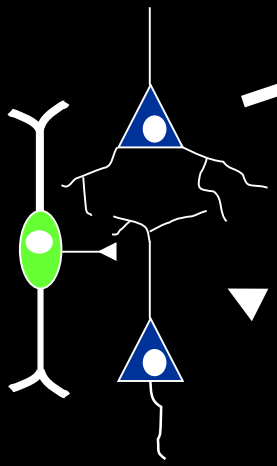
Work-in-progress to fill in the landscape and timing of VEN degeneration in bvFTD

NP Dx Category	Age	M:F	Clinical Dx	Path Dx
FTLD-tau	60.8	6:1	bvFTD	2 Pick's, 2 CBD, 2 FTDP-17, 1 PSP
FTLD-TDP without MND	64.5	5:8	bvFTD	11 TDP-B, 2 TDP-A
FTLD-TDP with MND	54.7	15:4	bvFTD-MND	TDP-B, MND

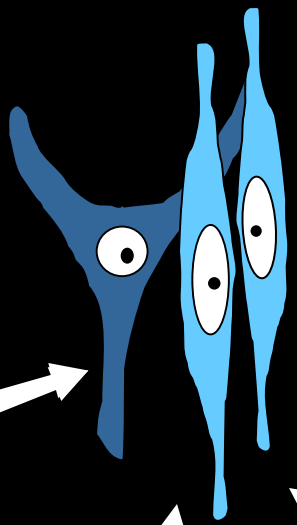
Onset Progression Translation Future

Salience Network

Local microcircuits



Social-Emotional Salience Processing



RX

C9ORF72

DPR

TDP-43

PGRN

TARDBP

VCP

FUS

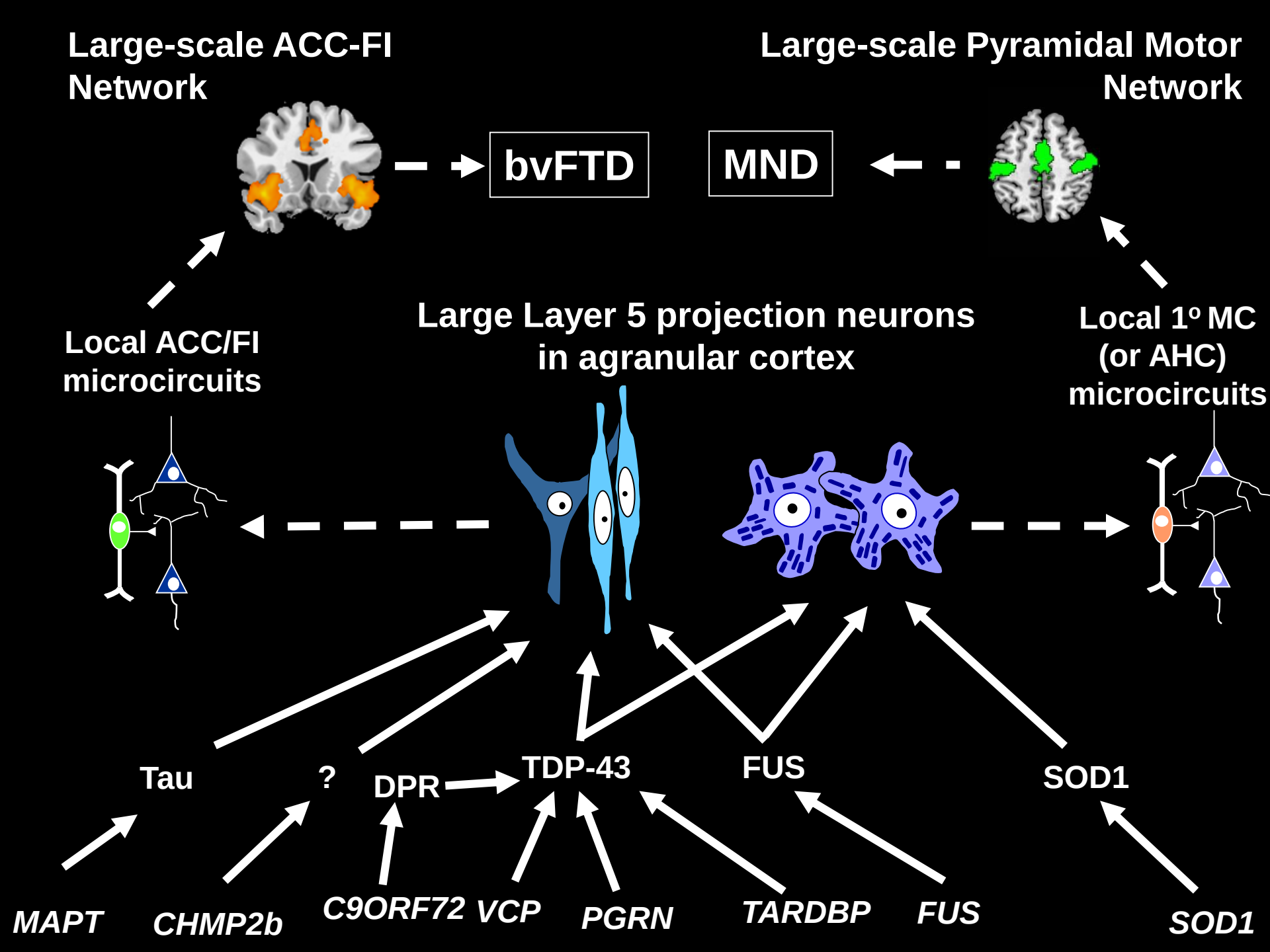
FUS

?

CHMP2b

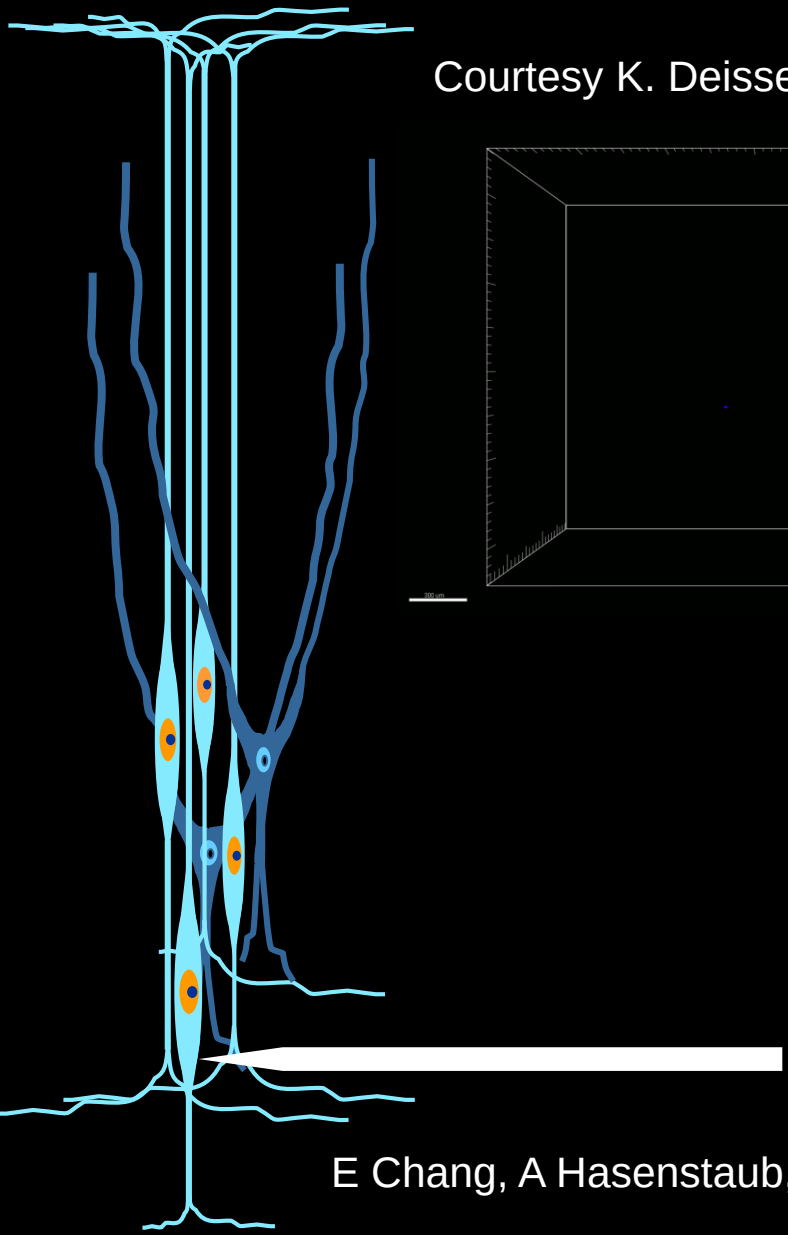
Tau

MAPT

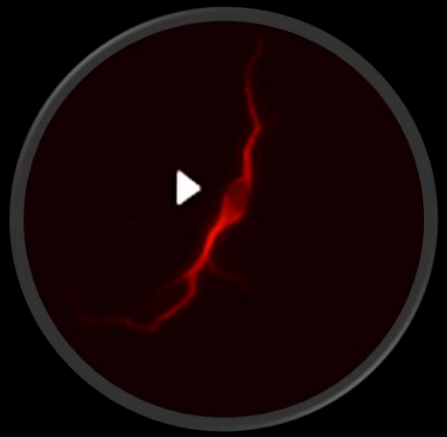

Large-scale ACC-FI Network
Large-scale Pyramidal Motor Network
bvFTD
MND
Local ACC/FI microcircuits
Large Layer 5 projection neurons in agranular cortex
Local 1º MC (or AHC) microcircuits
Tau
?
DPR
TDP-43
FUS
SOD1
MAPT
CHMP2b
C9ORF72
VCP
PGRN
TARDBP
FUS
SOD1

Future projects: VEN identity and vulnerability

Courtesy S. Smith Lab, Stanford



Courtesy K. Deisseroth Lab, Stanford



Finkbeiner Lab (K. Haston), UCSF

E Chang, A Hasenstaub, K Bender

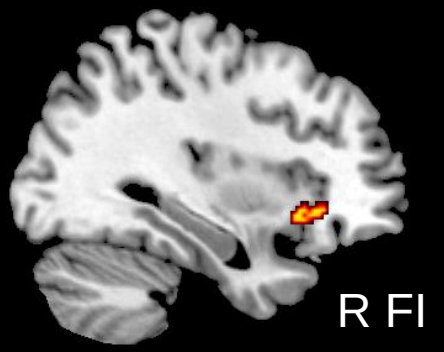
Behavioral variant FTD

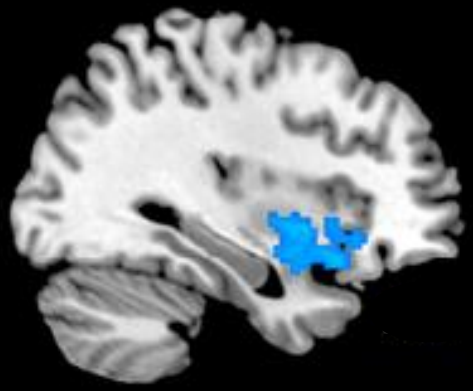
bvFTD “epicenters”

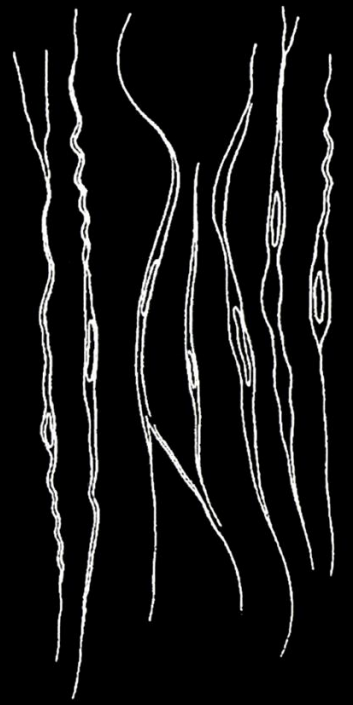
bvFTD atrophy
CDR 0.5

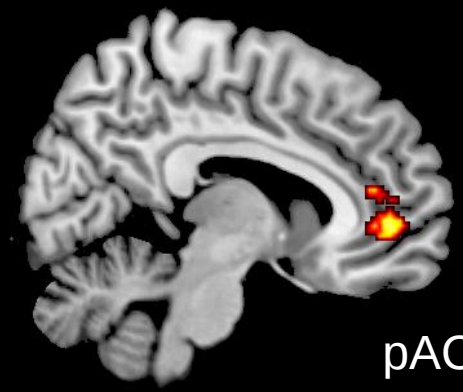
bvFTD severity
(CDR-SB)

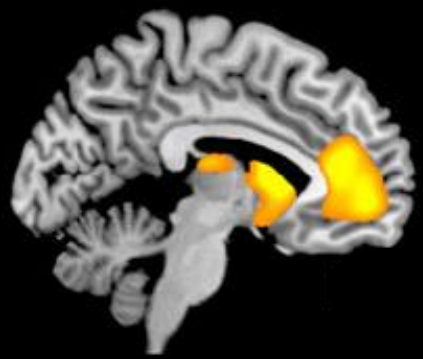
von Economo
Neurons (VENs)

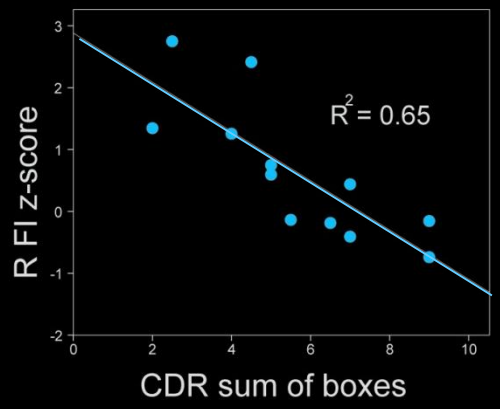












Zhou et al, 2012

Seeley et al, 2008

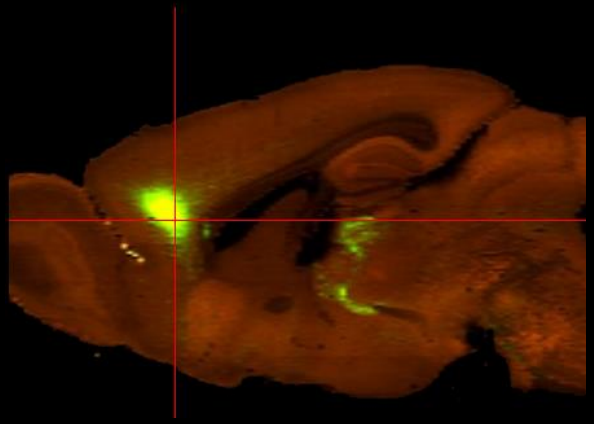
Zhou et al, 2010

Seeley et al, 2006
Kim et al, 2011

Intrinsic connectivity measured with task-free MRI

Right FI seed ROI

3T fcMRI
19 healthy controls

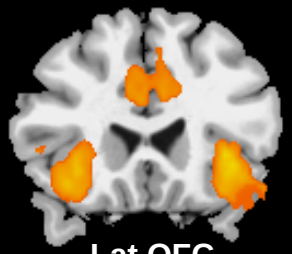


Mouse AAV injection, PL
Allen Brain Institute

DLPFC

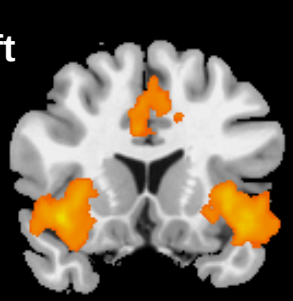
Frontal pole

ACC

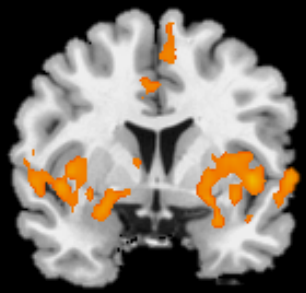


Lat OFC

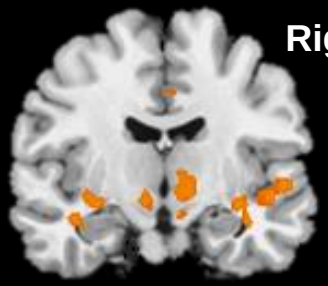
Left **Right**



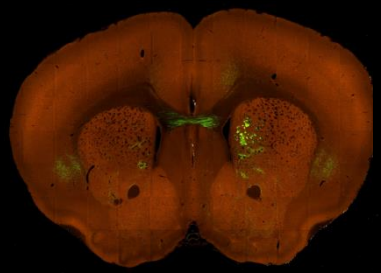
FI **FI**



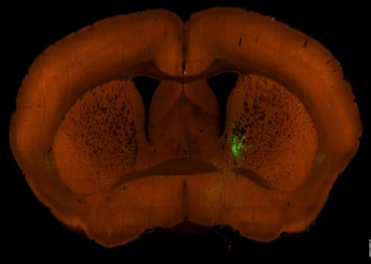
SLEA **VSP**



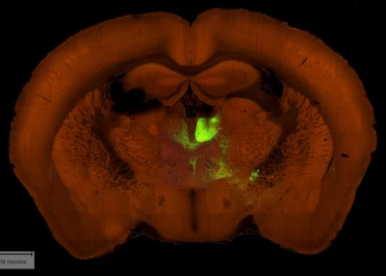
Hypothalamus



AIv **AIv**



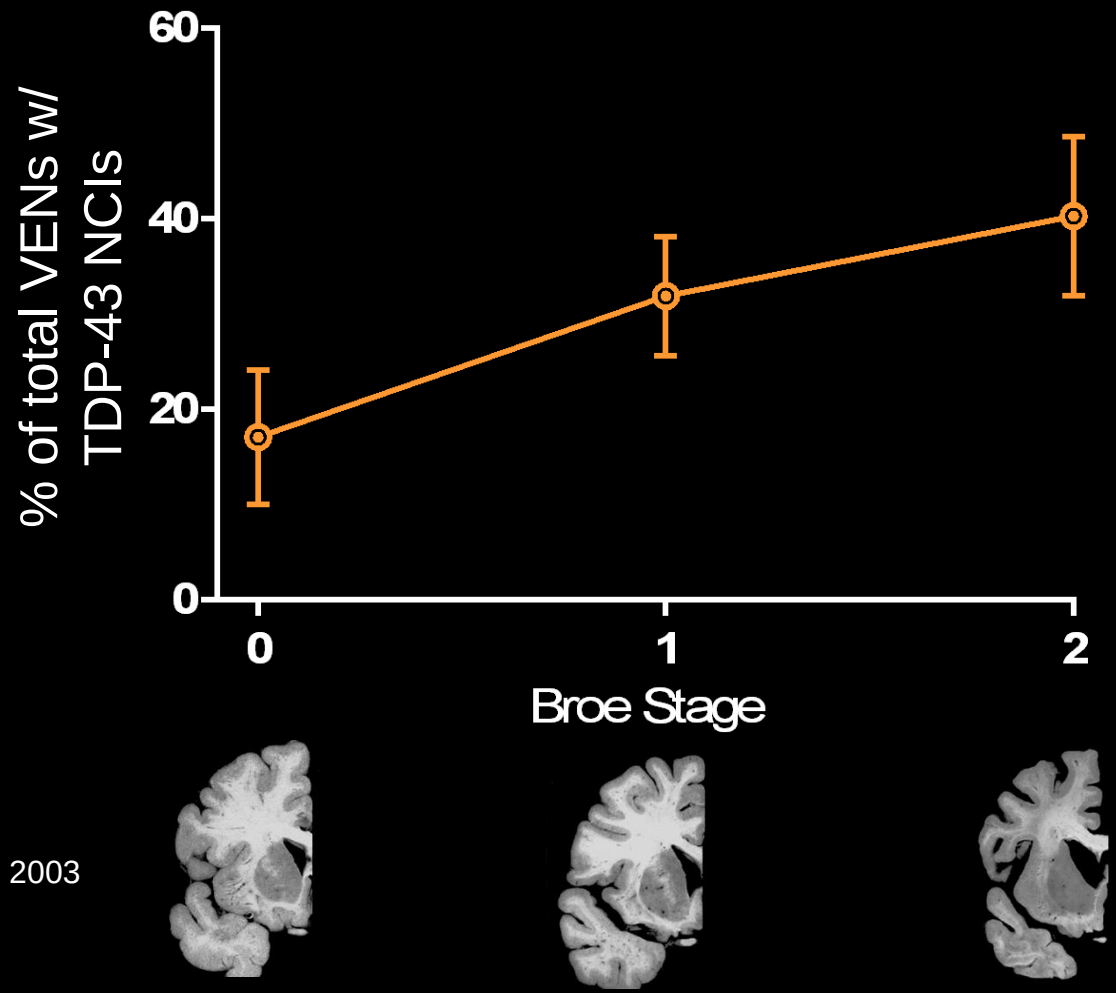
VSP



Hypothalamus

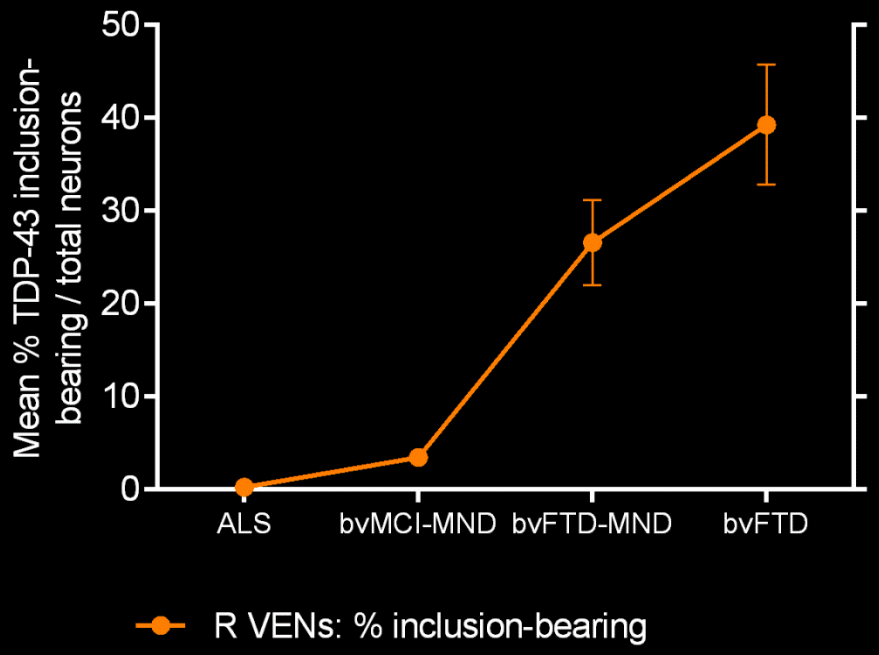
Also labeled: cAMY, medial pyramid

Does increased TDP-43 aggregation in FI VENs and fork cells occur in early stage disease?



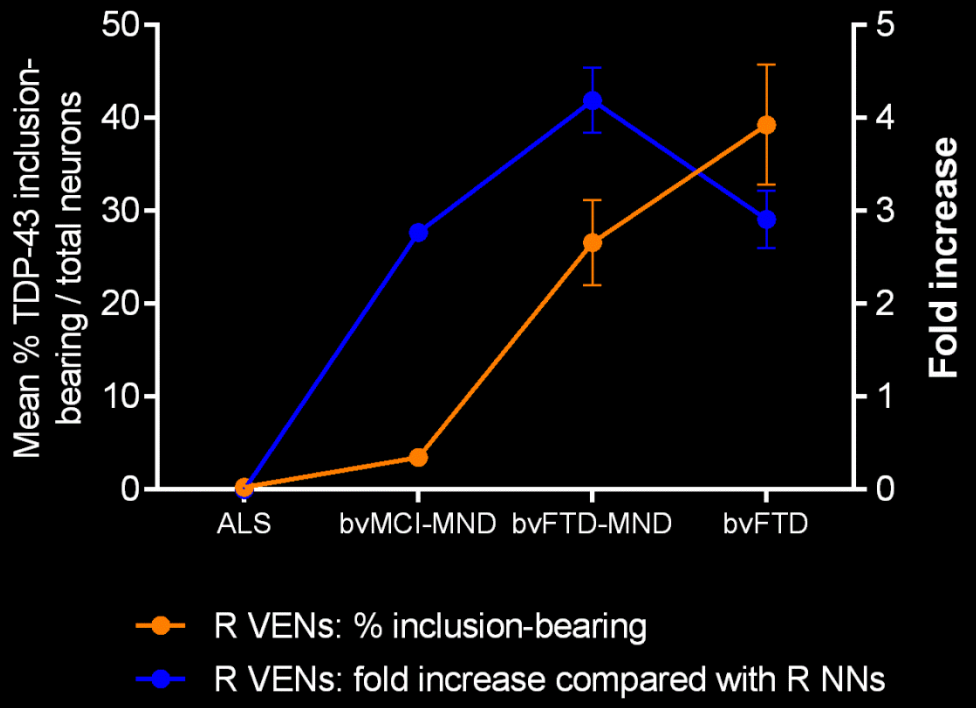
Broe et al. Neurology, 2003

VENs are 3- to 4- fold more prone to inclusion formation in behavioral symptom progression



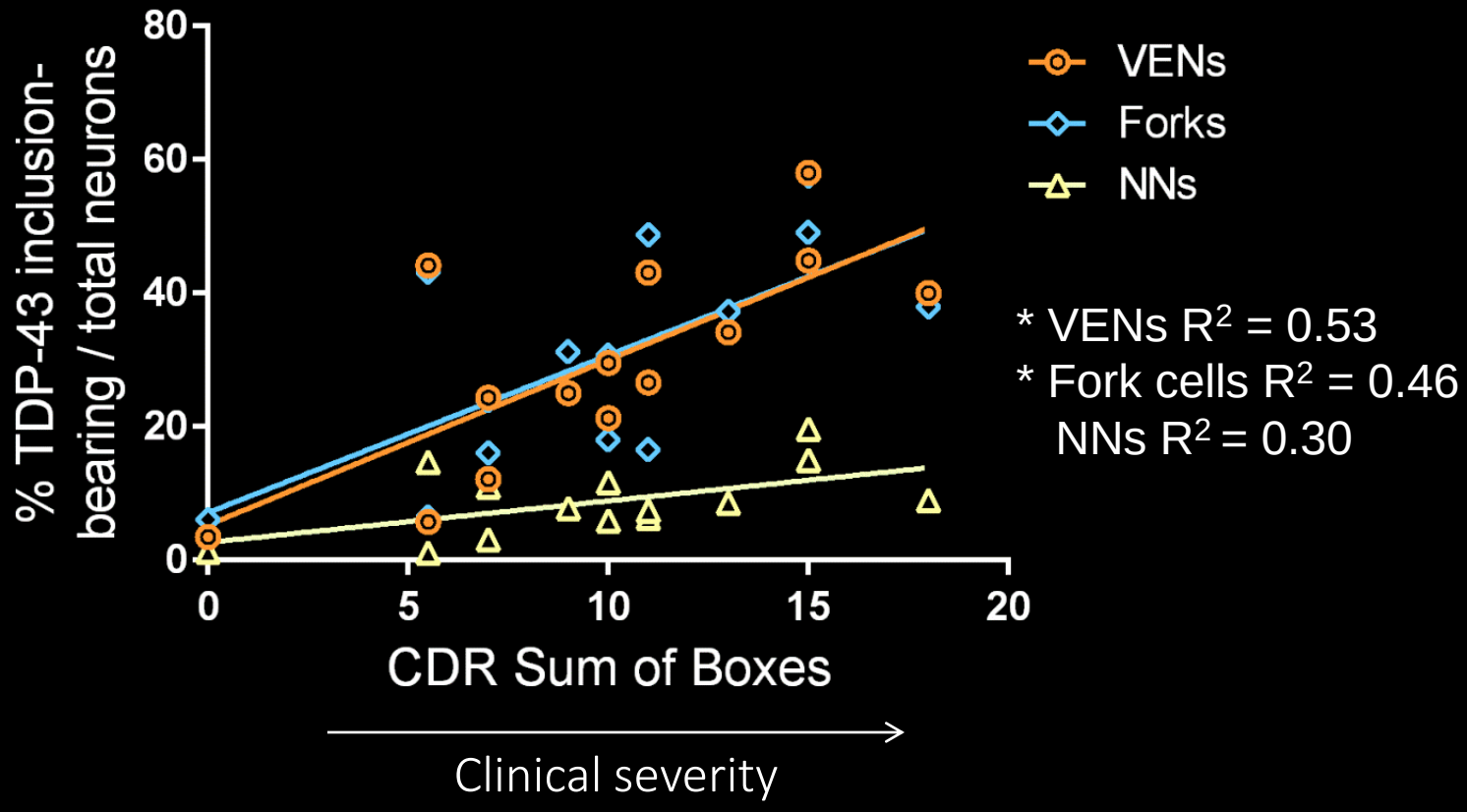
ALS bvMCI-MND bvFTD-MND bvFTD

VENs are 3- to 4- fold more prone to inclusion formation in behavioral symptom progression



ALS bvMCI-MND bvFTD-MND bvFTD

Proportion of VEN and forks with TDP-43 inclusions correlate with clinical measures of disease severity



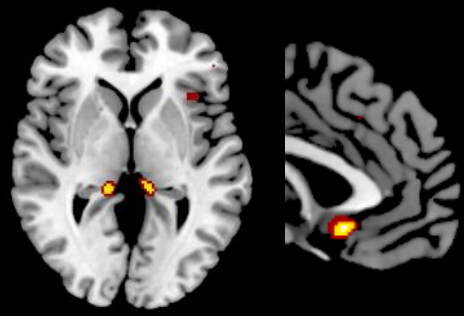
Right FI
n=14

* $p<0.01$

Single case illustrations provide key insights into *C9ORF72* pathogenesis

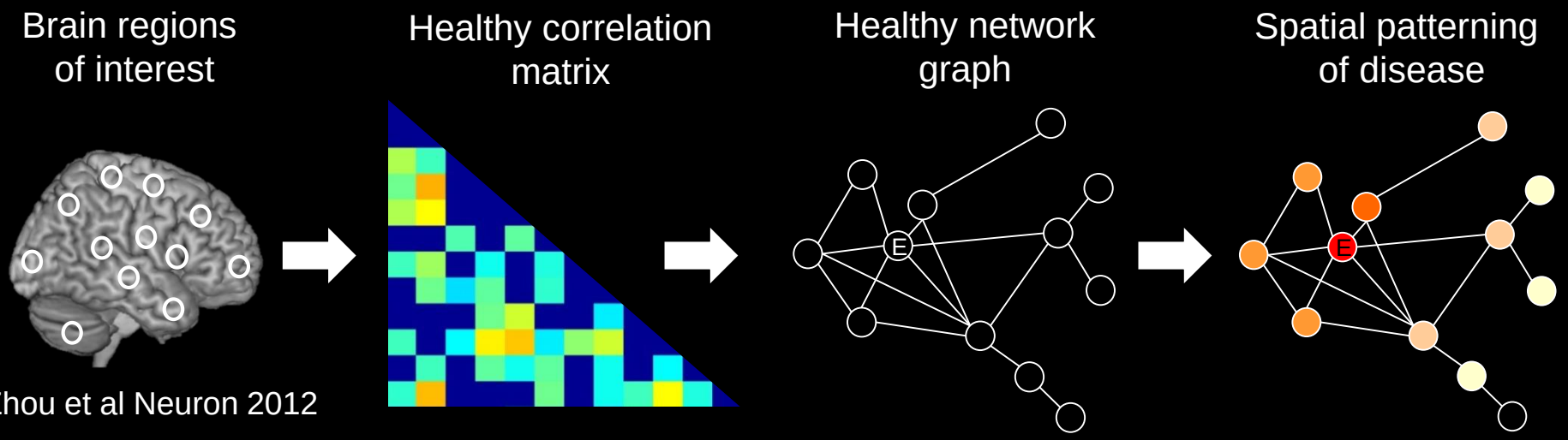
S. Vatsavayai

Case 1: A 65 y.o. woman with C9-bvFTD, minimal and focal degeneration, and sparse TDP-43 pathology

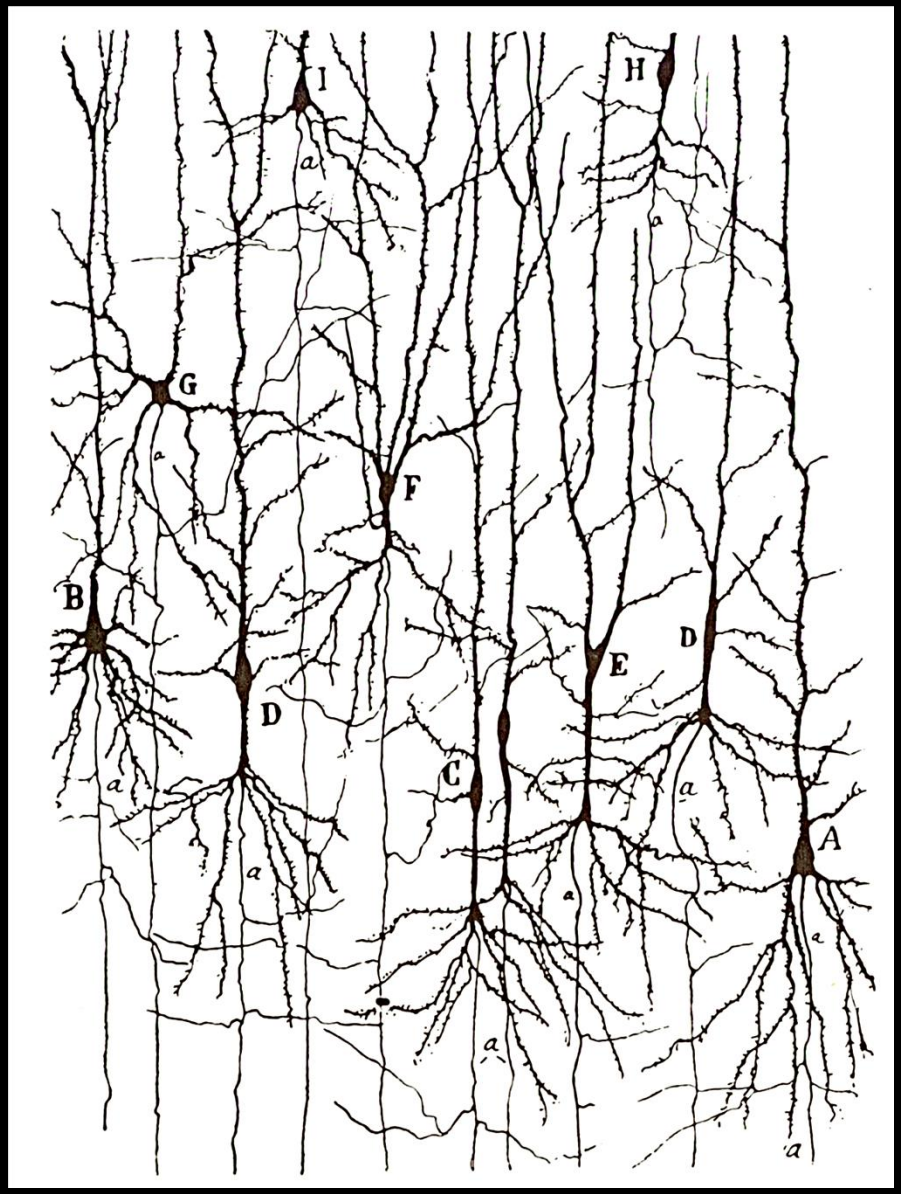


Case 2: A 74 y.o. woman with C9-FTD and two neuropathological assessments 13 years apart

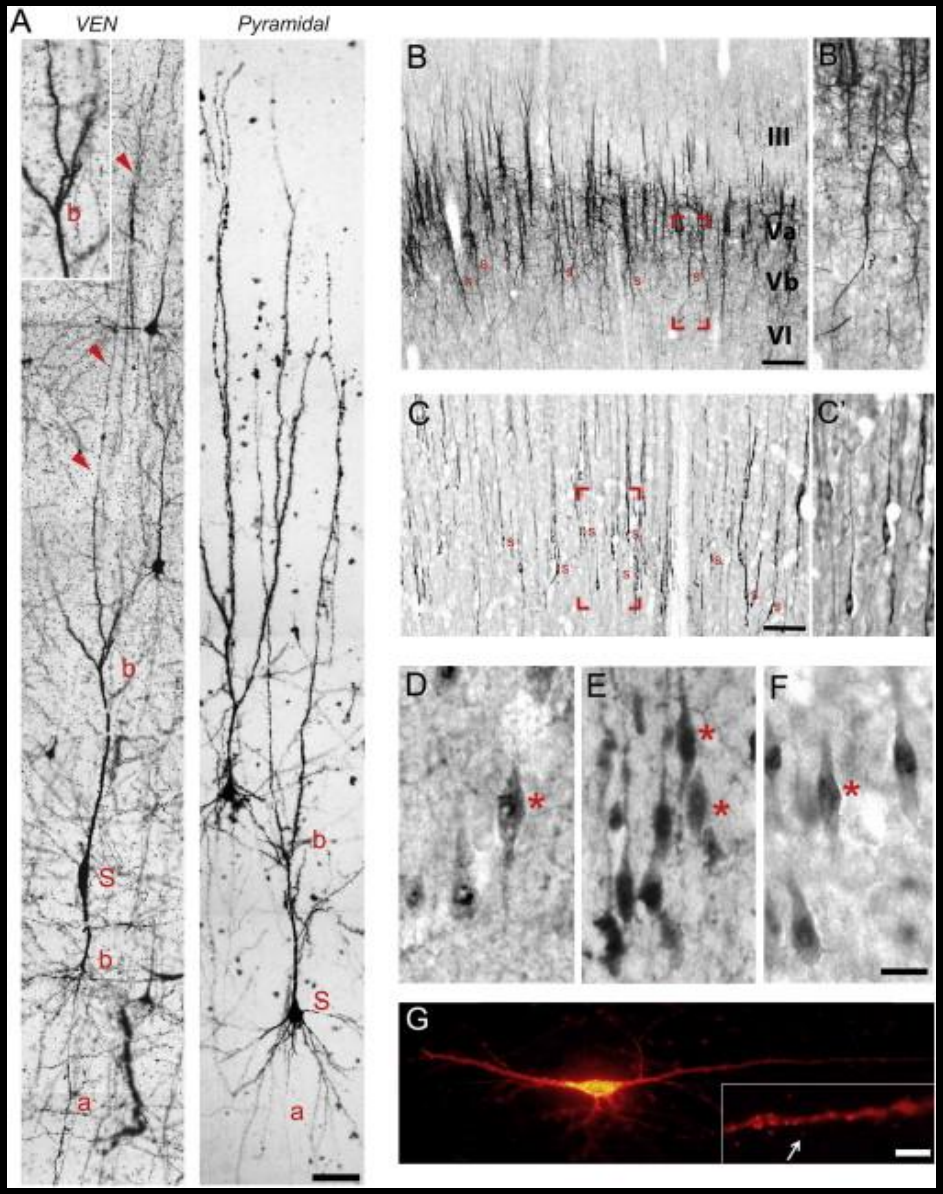
Mapping connectivity within disease-vulnerable brain systems



Zhou et al Neuron 2012

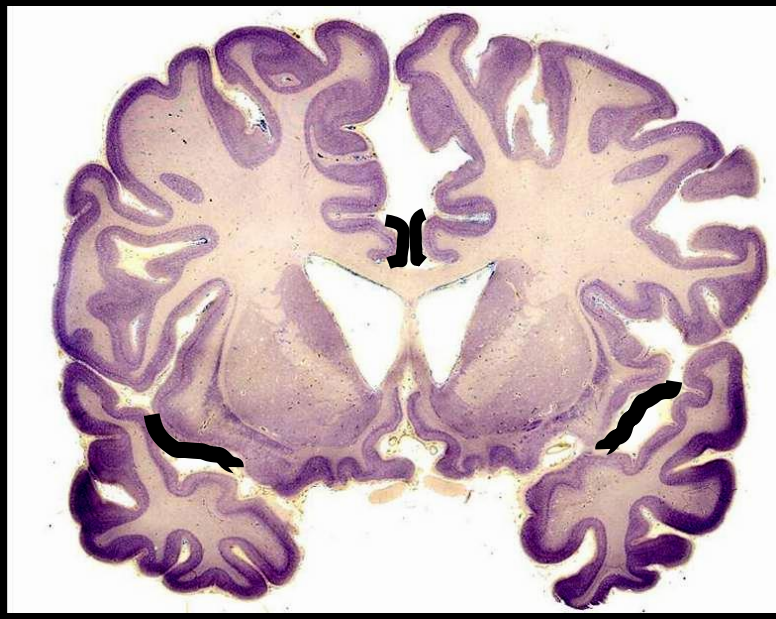


Ramon y Cajal, 1900
Human FI

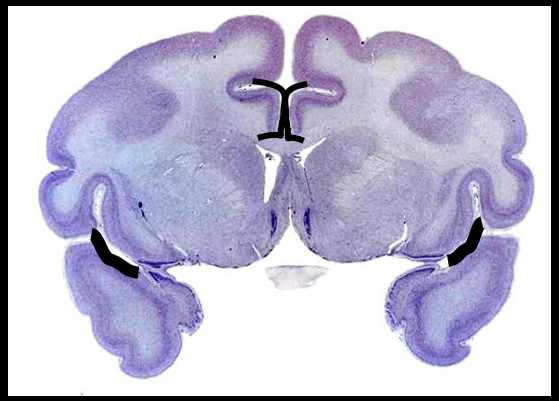


Evrard et al, Neuron 2012
Macaque AAI

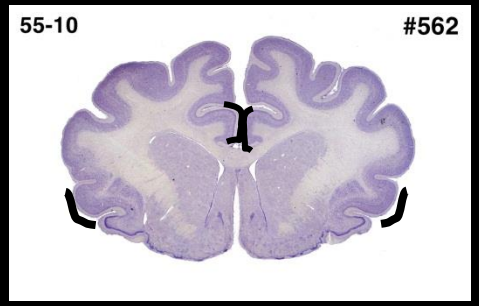
Allocortex ↔ Paralimbic Transition Zones ↔ Neocortex



HUMAN



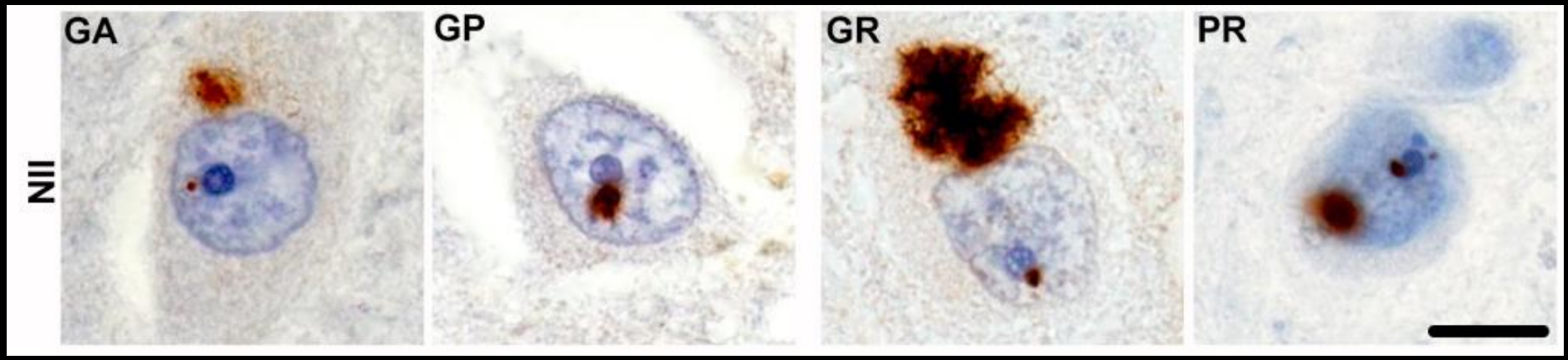
MONKEY



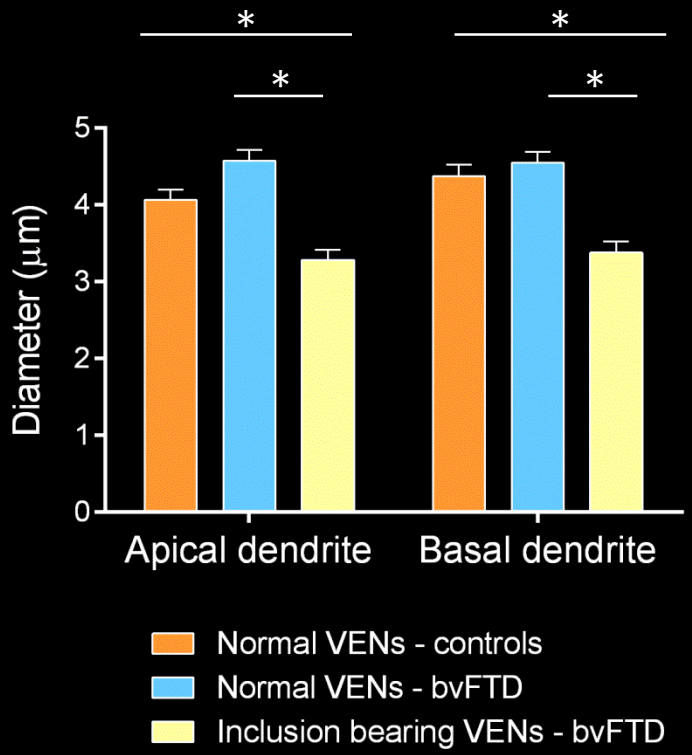
CAT

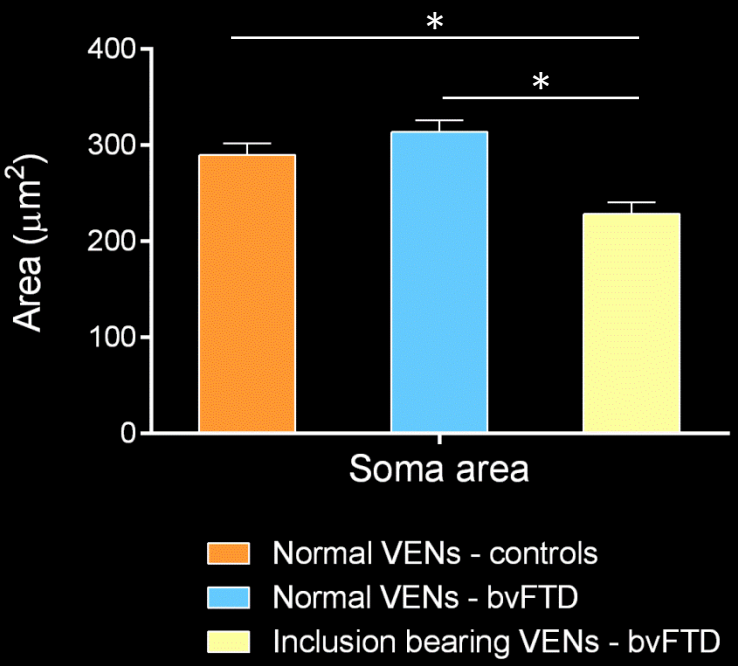
MOUSE

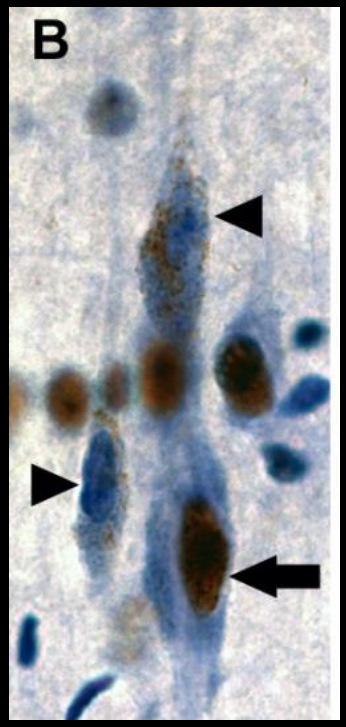
(not drawn to scale)


GA
GP
GR
PR
NII

TDP-43 inclusion-bearing VENs show somatodendritic atrophy

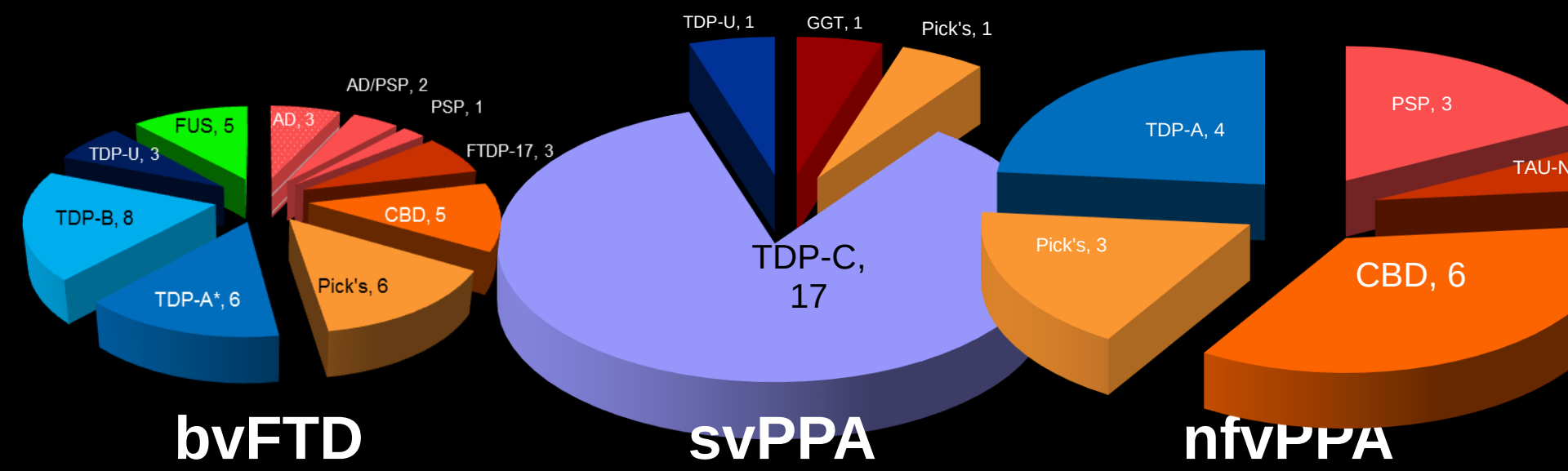




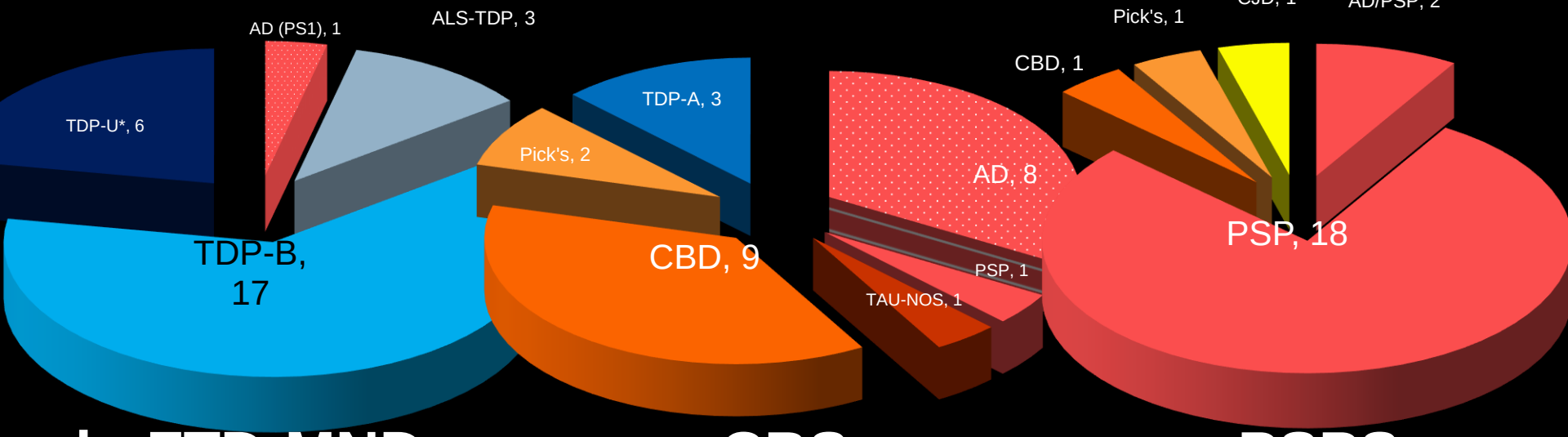


* p < 0.004, Bonferroni corrected

UCSF Neurodegenerative Disease Brain Bank

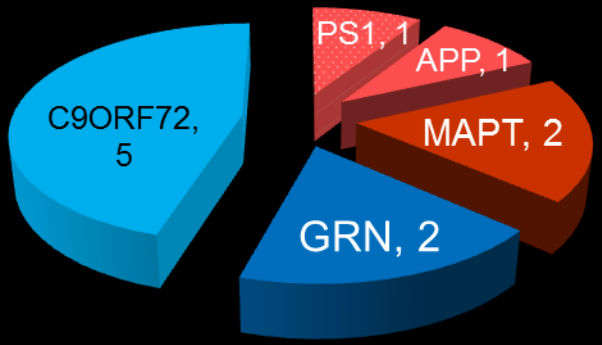


bvFTD **svPPA** **nfvPPA**



bvFTD-MND **CBS** **PSPS**

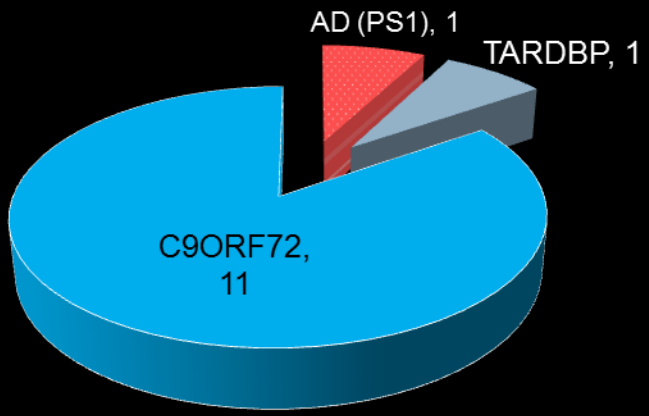
UCSF Neurodegenerative Disease Brain Bank
Patients with known mutations (n = 25)



bvFTD

svPPA

nfvPPA



bvFTD-MND

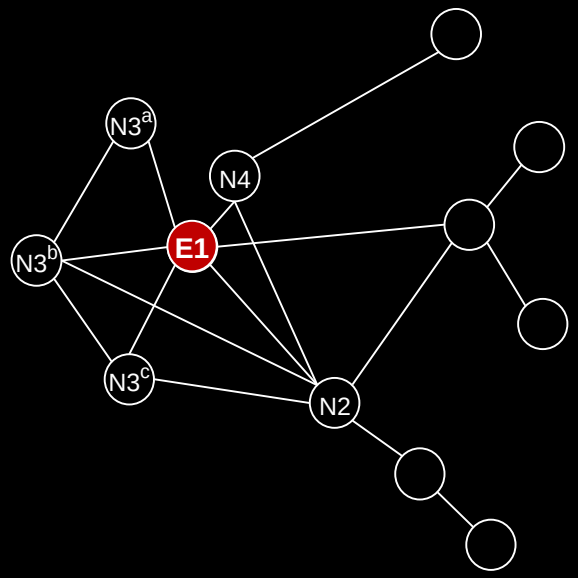
CBS

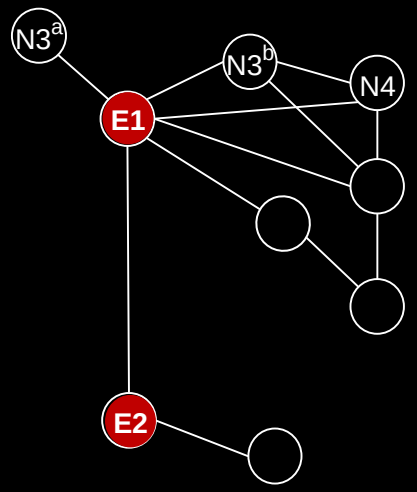
PSPS

Working model: syndromic heterogeneity

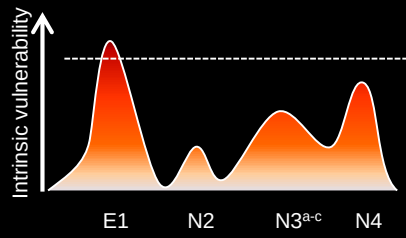
Multifocal onset, 2 networks: C9orf72

bvFTD-ALS

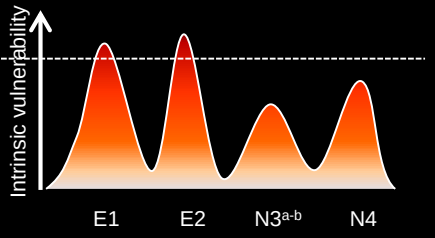




Salience network (bvFTD)



1° motor network (MND)



C9ORF72 studies: Summary

1. C9ORF72 expansion carriers show early life gray matter deficits in regions destined for neurodegeneration. Suggests abnormal brain development that sets stage for later degeneration.

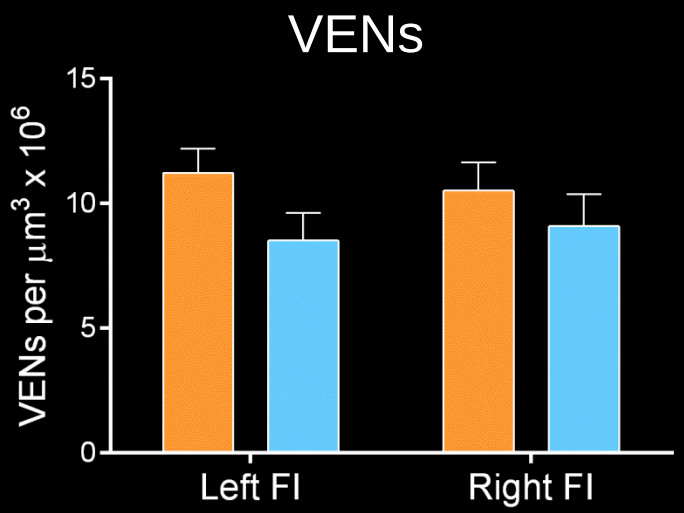
2. Widespread distribution of DPR pathology, including degenerate and spared regions (Cases 1-2), suggests DPR aggregates (esp. GA/GP/GR) may be necessary but not sufficient to produce neurodegeneration.

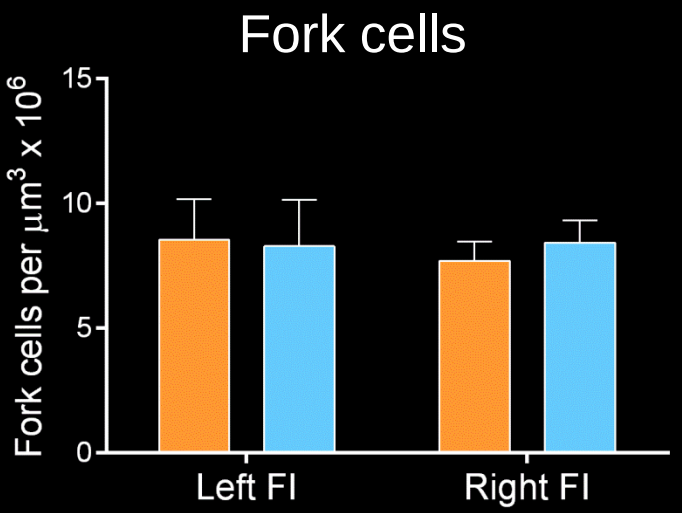
3. Absence of TDP-43 inclusions in severely degenerate areas (Case 1). suggests that TDP-43 inclusions not necessary for neurodegeneration

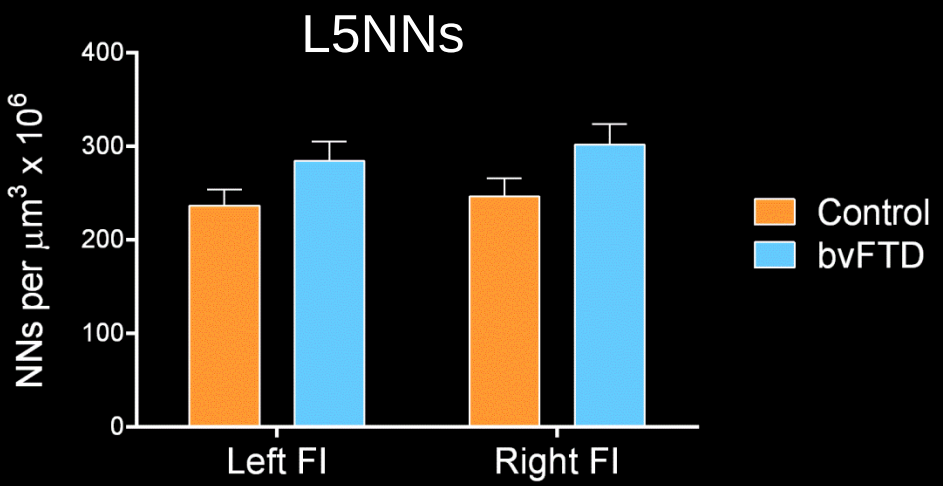
4. Multiplicity of C9ORF72-related pathological findings may predict neurodegeneration (Case 1). Region-specific repeat instability?

5. DPR pathology (esp. GA/GR/GP) **precedes** TDP-43 (Case 2). Correlate of early life psychiatric phenomena?

Early stage disease: before neuronal loss

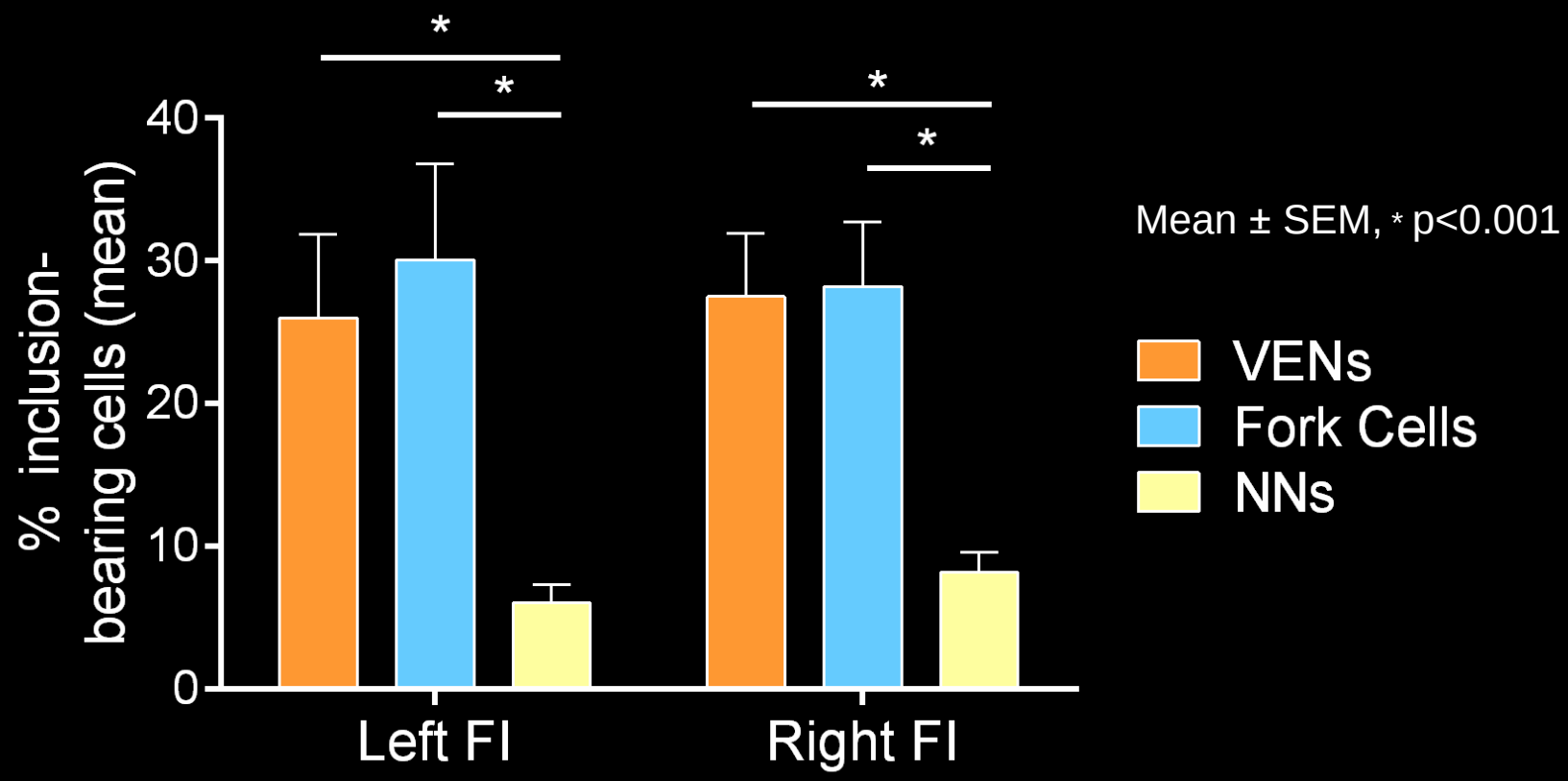






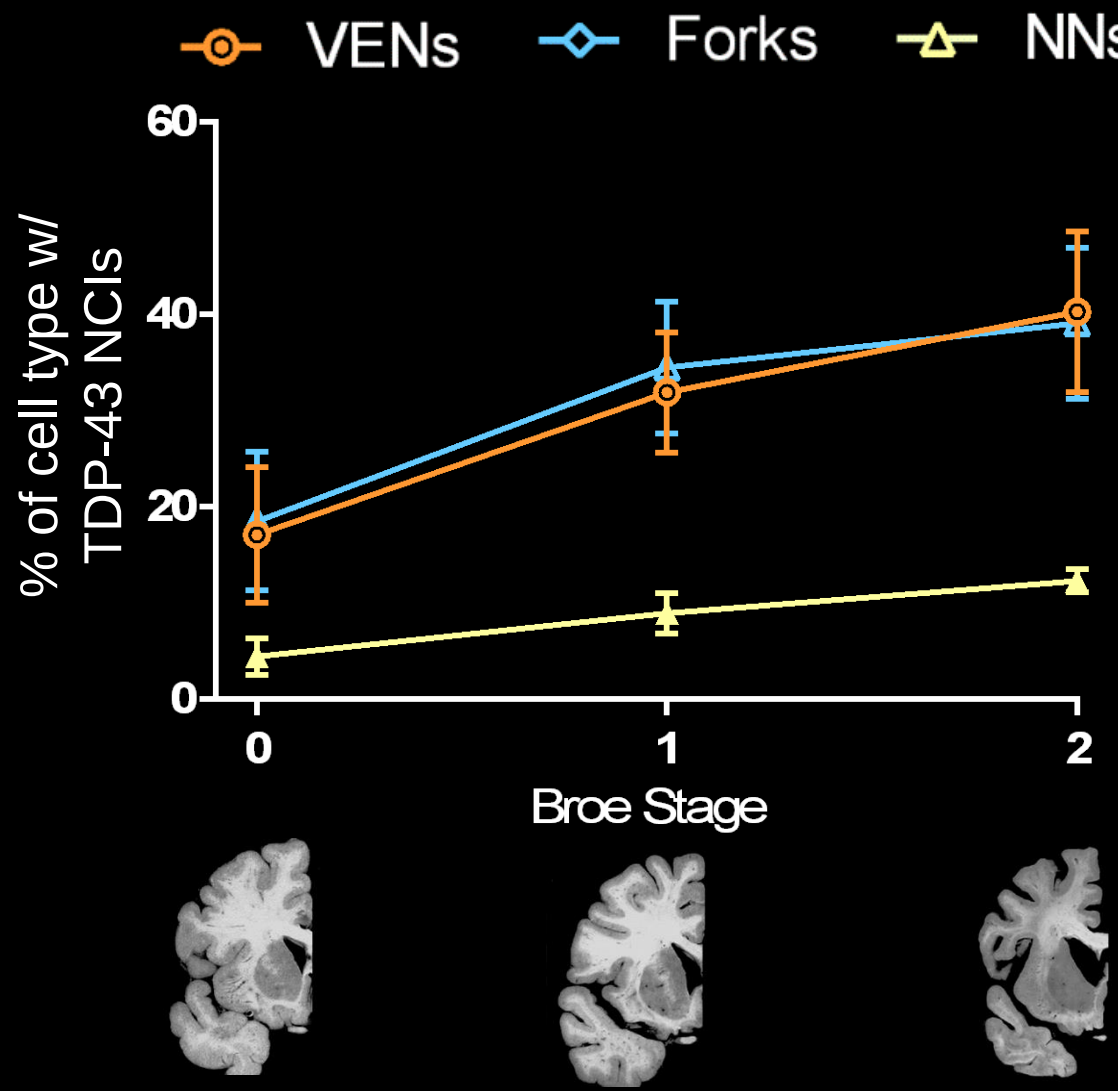
Estimated marginal means with rater ± SEM

TDP-43 NCIs target VENs and fork cells in early bvFTD

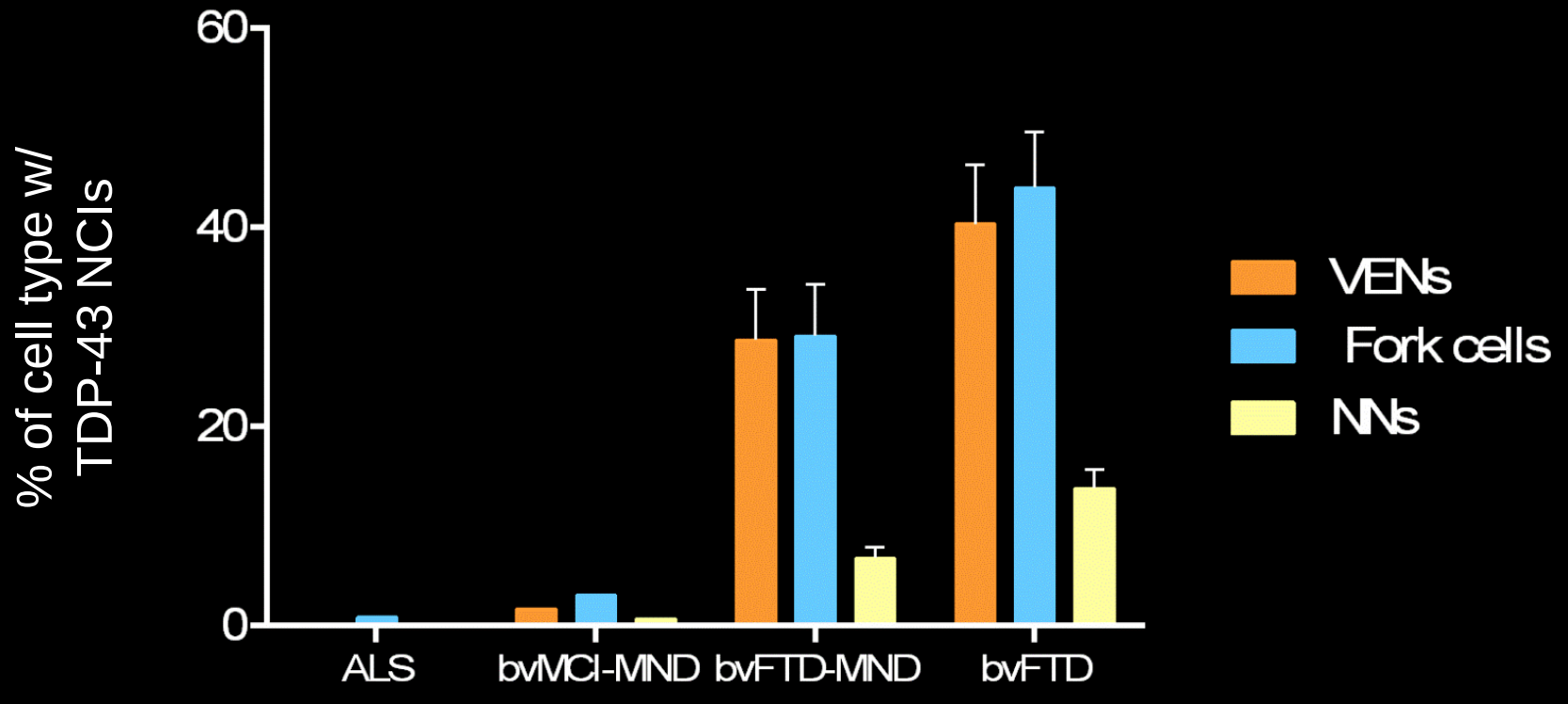


Nana Li et al, unpublished

Does increased TDP-43 aggregation in FI VENs and fork cells occur in early stage disease?

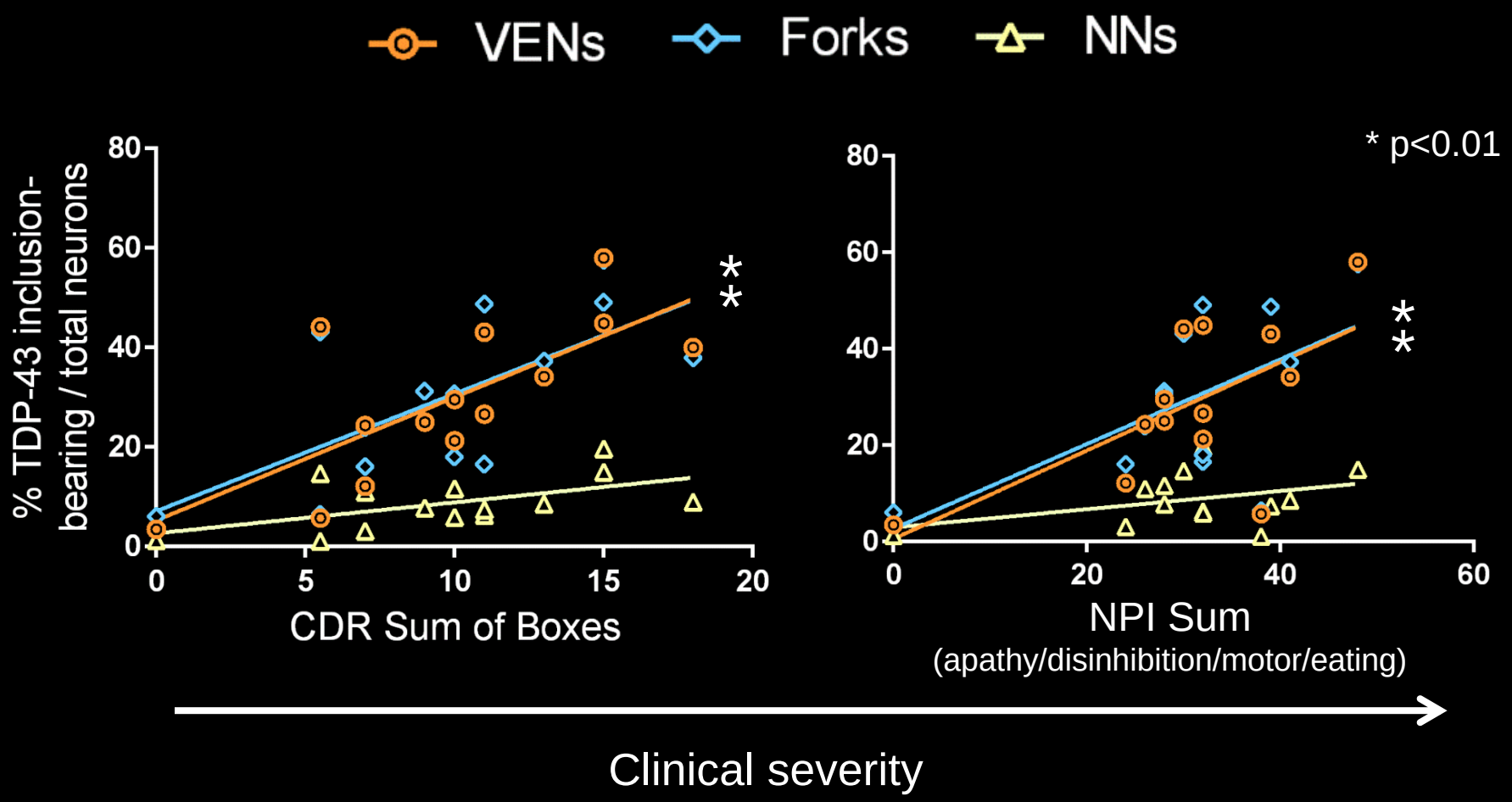


Does increased TDP-43 aggregation in FI VENs and fork cells occur in early clinical disease?

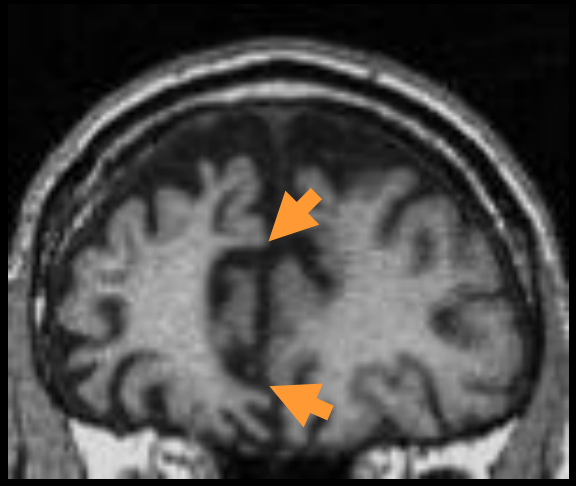


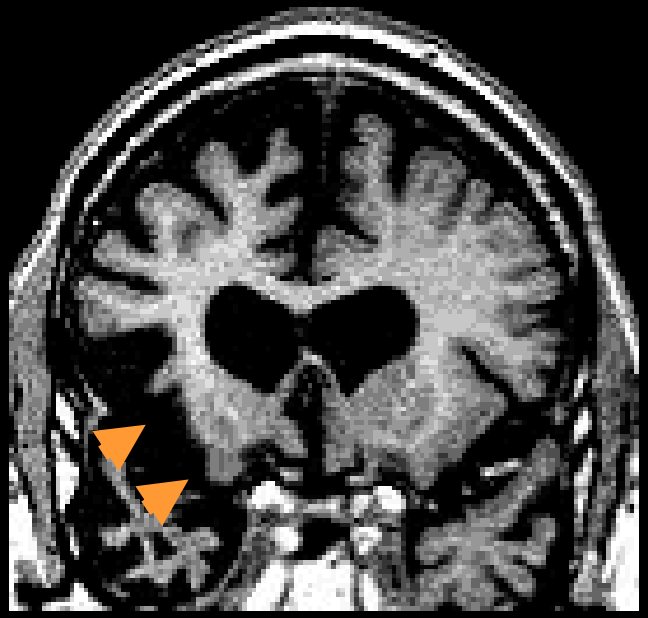
ALS bvMCI-MND bvFTD-MND bvFTD

Proportion of VEN and forks with TDP-43 inclusions correlate with clinical measures of disease severity



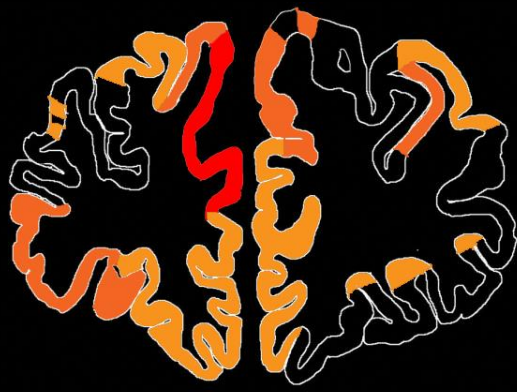
58 y.o. man with bvFTD due to Pick's disease

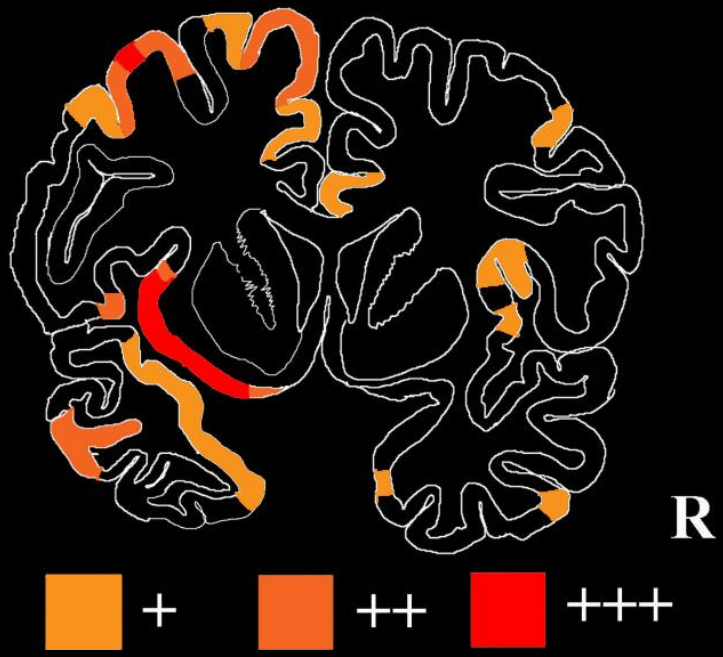




R L

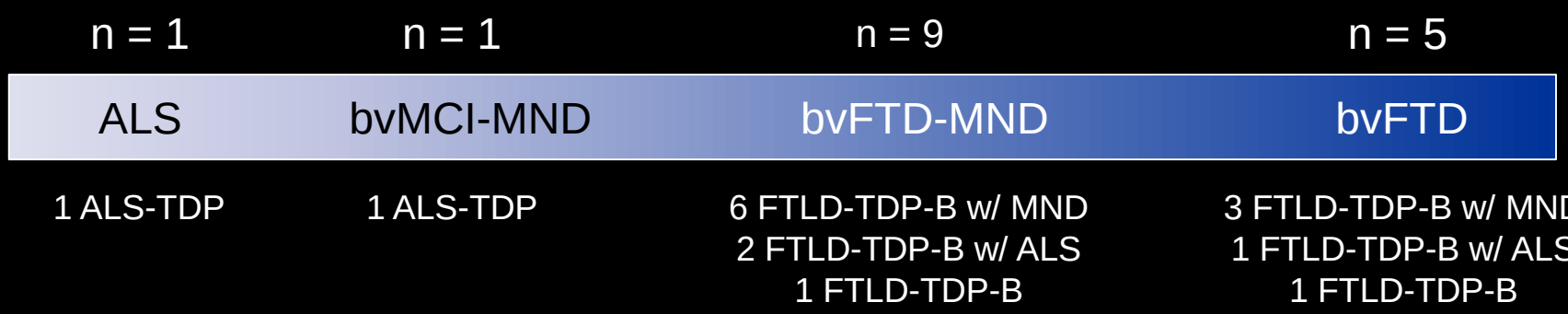
62 y.o. man with incidental Pick's disease (Miki et al 2014)





Subject characteristics

	Control	bvFTD-ALS spectrum
N	10	16
Gender (M:F)	6:4	10:6
Age at death (yrs)	63.6	62.5
PMI (h)	24.5	14.3
Brain weight (g)	1383	1297
Symptom duration in years	--	5.1
CDR total	--	1.9
CDR Sum of boxes	--	9.7
NPI total	--	42.9



	bvFTD	ALS
Onset neuron	??	UMNs and LMNs
Onset sites / “epicenters”	Anterior cingulate and frontoinsula	Primary motor cortex, bulbar motor nuclei, AHC
Network spread	Salience network	Pyramidal motor network
1st symptom	Social-emotional	Motor

bvFTD bvFTD-MND bvFTD-ALS bvMCI-ALS ALS

	bvFTD	ALS
Onset neuron	??	UMNs and LMNs
Onset sites	Anterior cingulate and frontoinsula	Motor cortex, bulbar motor nuclei, AHC
Network spread	Salience network	Pyramidal motor network
1st symptom	Social-emotional	Motor
Later syndrome	Dysexecutive, ALS	bvFTD, Dysexecutive
Most common protein	TDP-43	TDP-43
Other inclusion proteins	Tau, FUS	FUS, SOD1, Ubiquilin2
Most common gene	*C9ORF72*	*C9ORF72*
Other genes	*MAPT, GRN, FUS, TARDBP, VCP*	*SOD1, FUS, TARDBP, Ubiquilin2, VCP*

bvFTD bvFTD-MND bvFTD-ALS bvMCI-ALS ALS

	bvFTD	ALS
Onset neuron	VENs and fork cells	UMNs and LMNs
Onset sites / “epicenters”	Anterior cingulate and frontoinsula	Primary motor cortex, bulbar motor nuclei, AHC
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Most common gene	*C9ORF72*	*C9ORF72*
Other genes	*MAPT, GRN, FUS, TARDBP, VCP*	*SOD1, FUS, TARDBP, Ubiquilin2, VCP*

Subject characteristics

	Control	bvFTD-ALS spectrum
N	10	17
Gender (M:F)	6:4	10:7
Age at death (yrs)	63.6	61.8
PMI (h)	24.5	13.0
Brain weight (g)	1383	1284
Symptom duration in years	--	4.0
CDR total	--	1.8
CDR Sum of boxes	--	8.9
NPI total	--	41.9

3 FTLD-TDP-B w/ MND
1 FTLD-TDP-B w/ ALS
1 FTLD-TDP-B

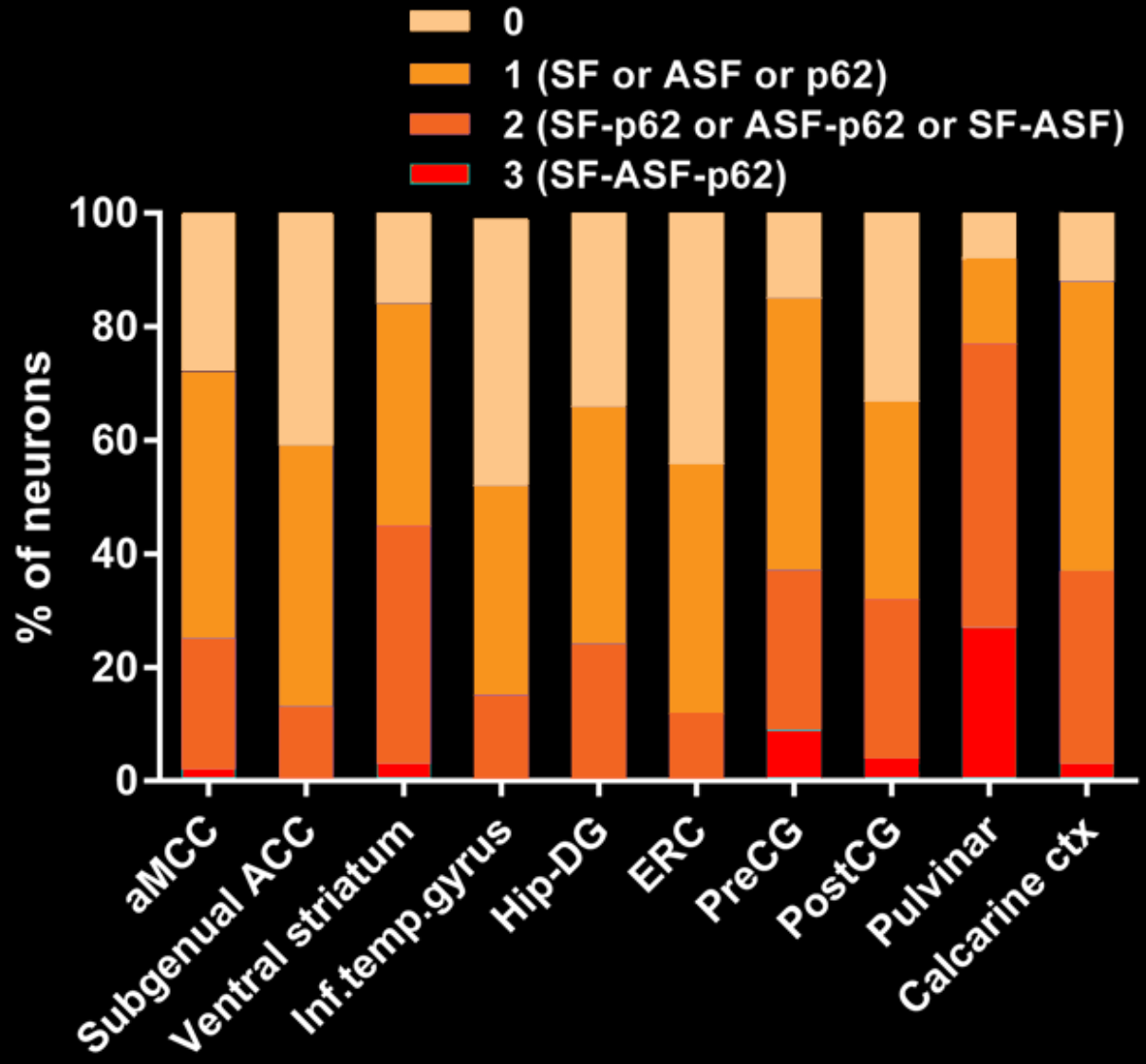
5 FTLD-TDP-B w/ MND
2 FTLD-TDP-B w/ ALS
1 FTLD-TDP-B

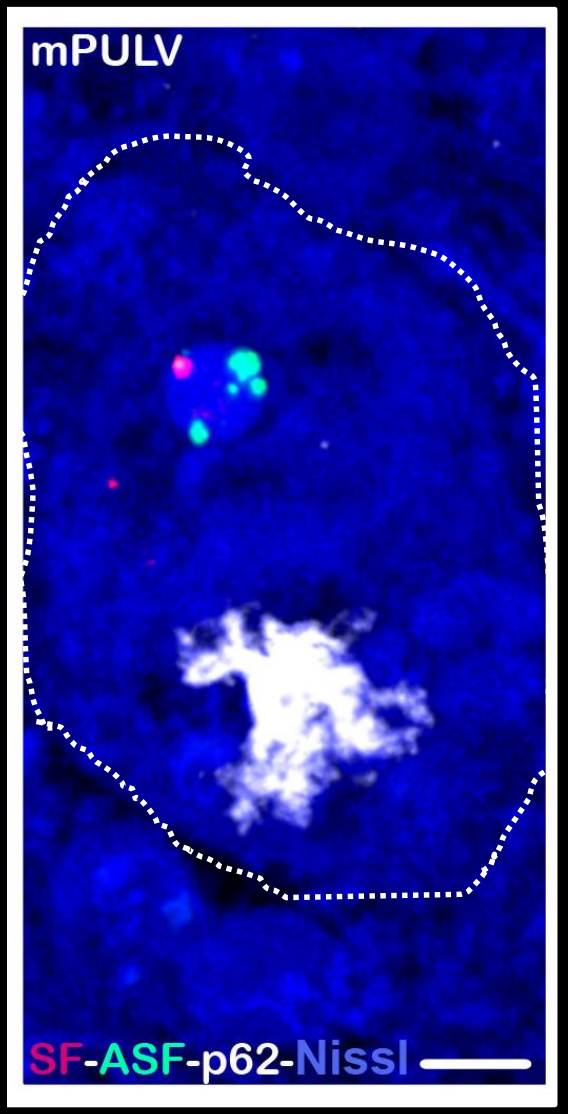
1 ALS-TDP

3 ALS-TDP

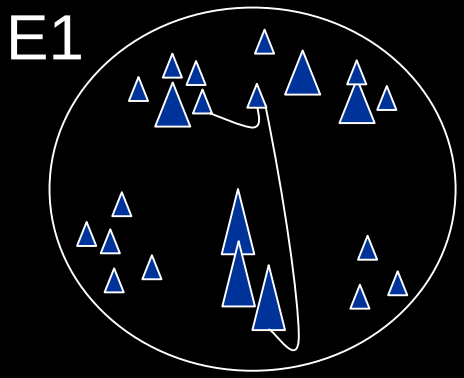
bvFTD, Stage 2, due to FTDP-17, *MAPT* mutation

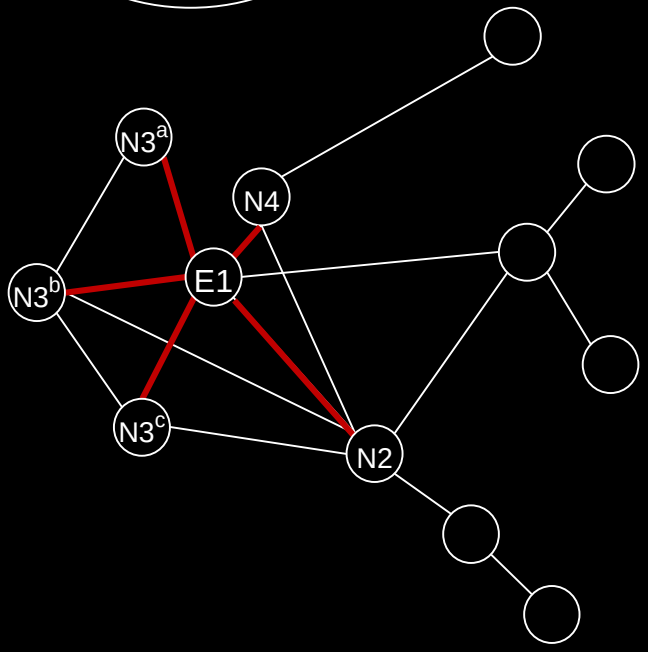
Case 1: Does the multiplicity of C9-related pathological findings predict neurodeneration?

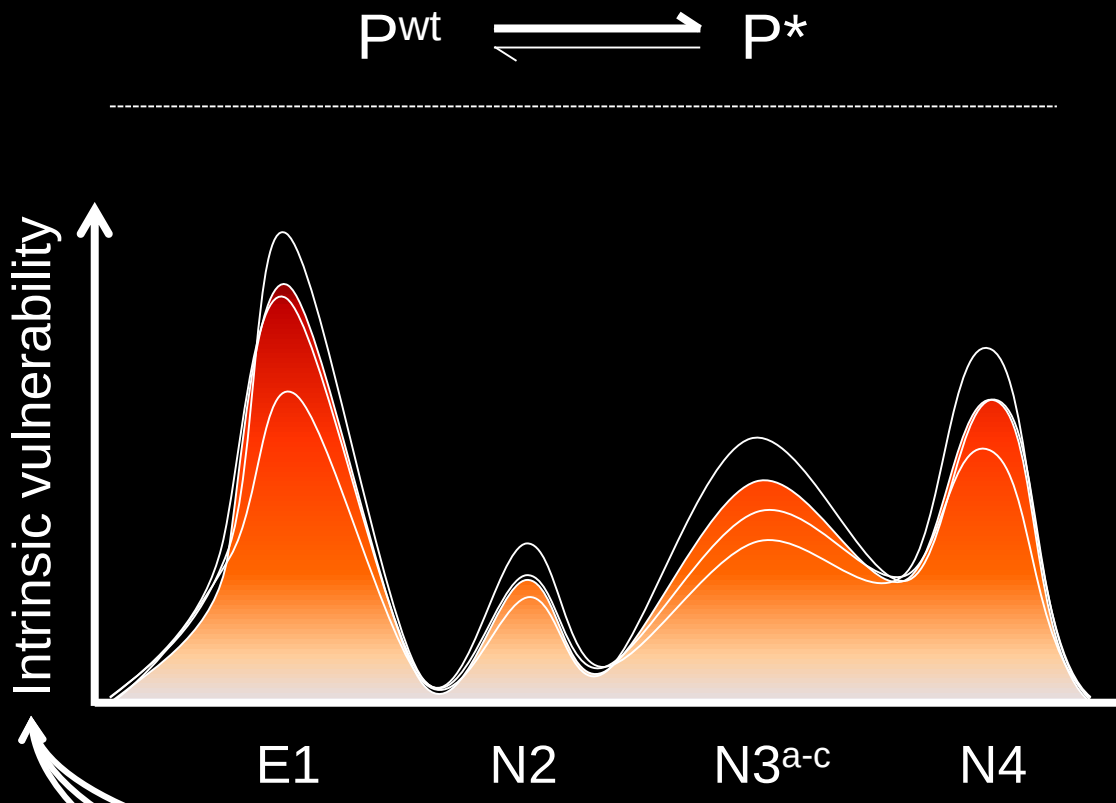


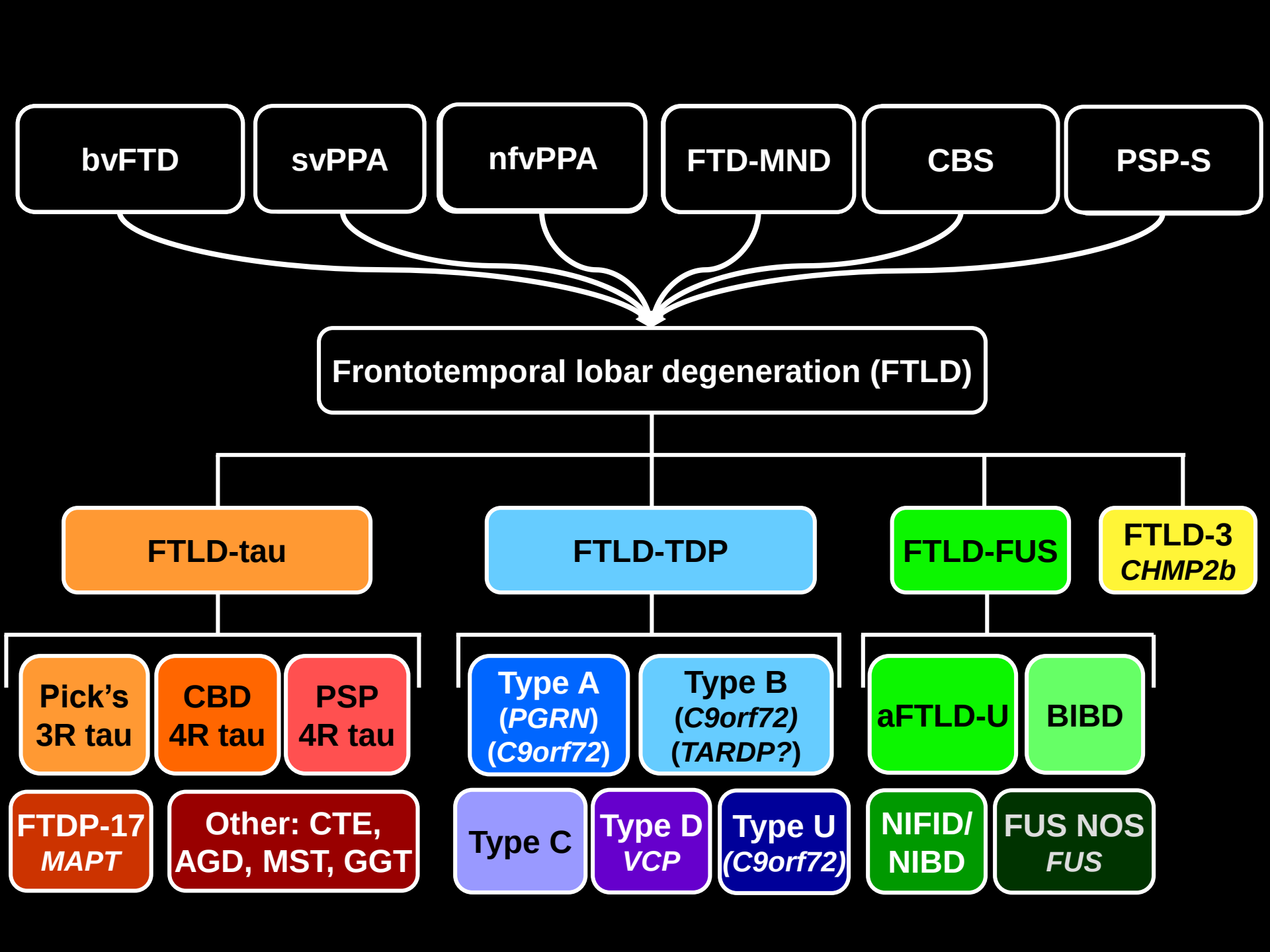


Generic working model: onset and spread



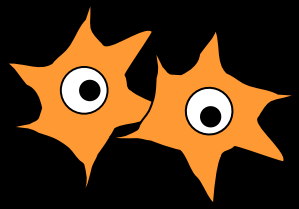





bvFTD
svPPA
nfvPPA
FTD-MND
CBS
PSP-S
Frontotemporal lobar degeneration (FTLD)
FTLD-tau
FTLD-TDP
FTLD-FUS
FTLD-3
CHMP2b
Pick's
3R tau
CBD
4R tau
PSP
4R tau
Type A
(PGRN)
(C9orf72)
Type B
(C9orf72)
(TARDP?)
aFTLD-U
BIBD
FTDP-17
MAPT
Other: CTE,
AGD, MST, GGT
Type C
Type D
VCP
Type U
(C9orf72)
NIFID/
NIBD
FUS NOS
FUS

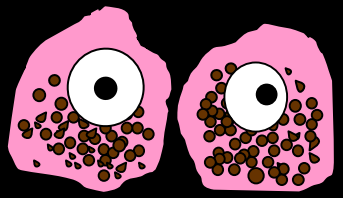
Why Onset matters…imagine:

Alzheimer's Disease



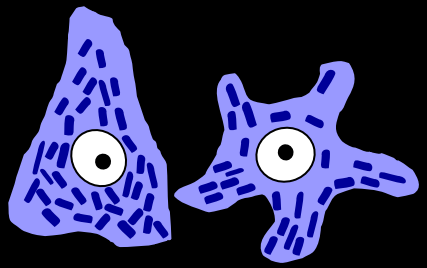
- AD translational research without the Morris water maze

Parkinson's Disease



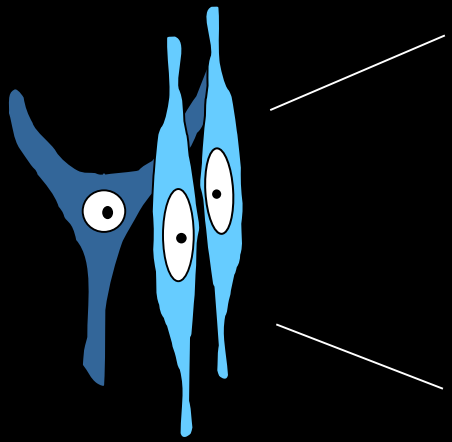
- Parkinson's disease treatment without levodopa/carbidopa

Amyotrophic Lateral Sclerosis



- ALS diagnosis without EMG

Behavioral Variant Frontotemporal Dementia



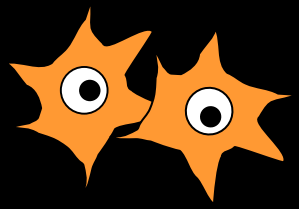
- Difficulty making and interpreting mouse models
- No disease-modifying or effective symptomatic treatments
- No direct physiological readout of early-affected neurons

Topics not covered

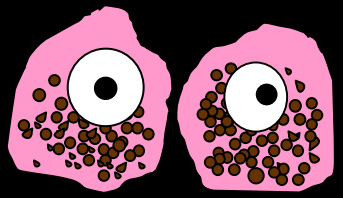
- Network-based neurodegeneration*
- Longitudinal FTD imaging biomarkers
- Autonomic dysfunction in bvFTD
- FTD syndromes other than bvFTD
- FTD genes other than *C9ORF72*

Why Onset matters…imagine:

Alzheimer's Disease



Parkinson's Disease



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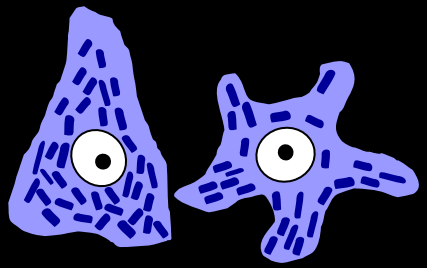
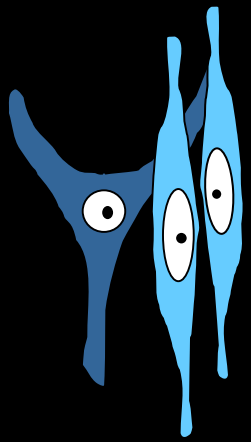


Behavioral Variant Frontotemporal Dementia

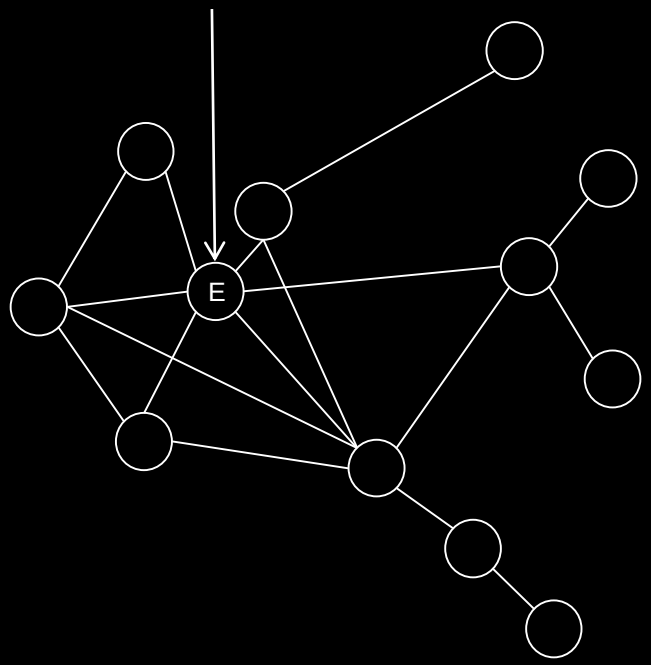


- AD translational research without the Morris water maze
- Parkinson's disease treatment without levodopa/carbidopa
- ALS diagnosis without EMG

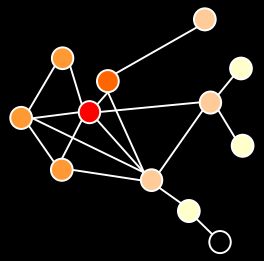
Working model: anatomical convergence

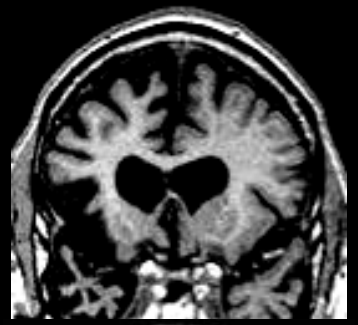
Different diseases, same onset epicenter, same spread

Tau, TDP-43, or FUS

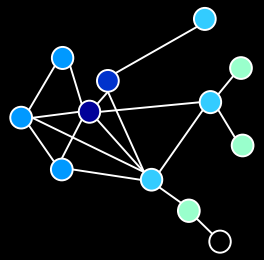


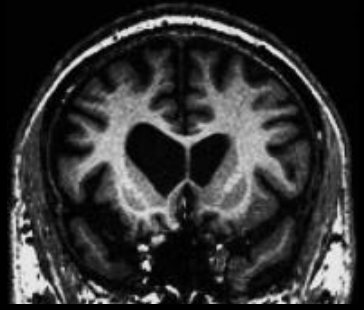
bvFTD



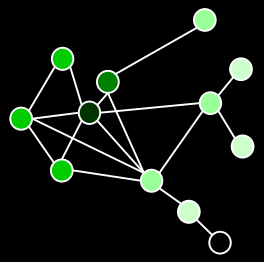


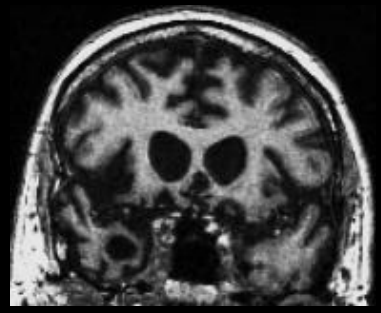
Pick's (Tau)





TDP-43 Type B



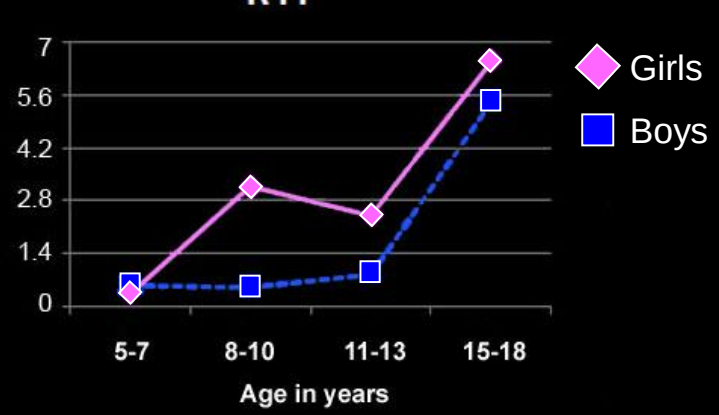


aFTLD-U (FUS)

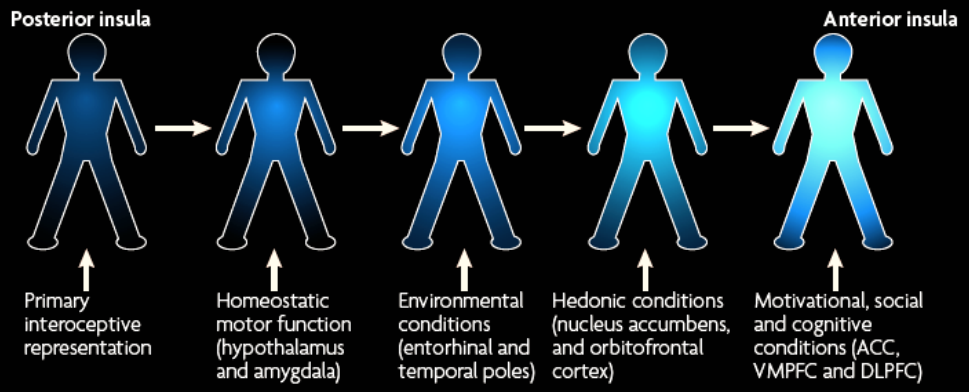
Area FI

Developmental trajectory

Zielinski et al, PNAS 2010

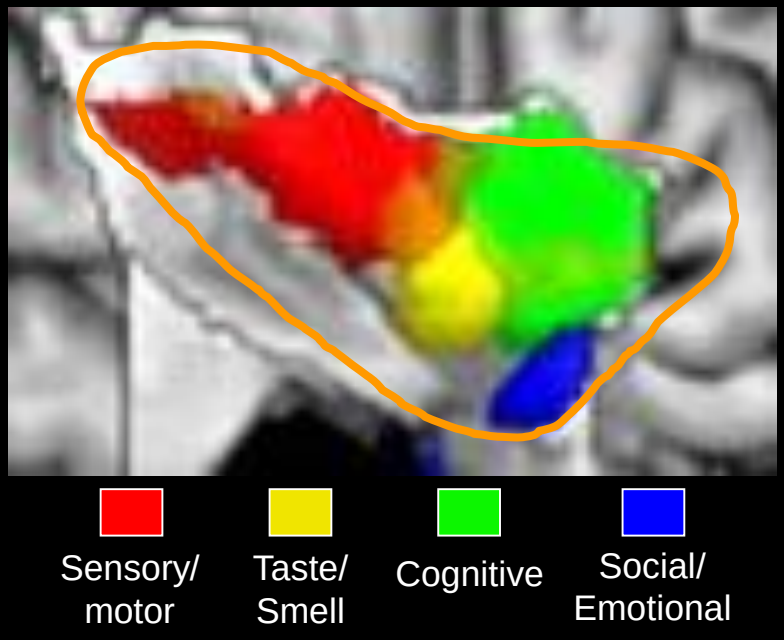


A.D. Craig, *NRN* 2009



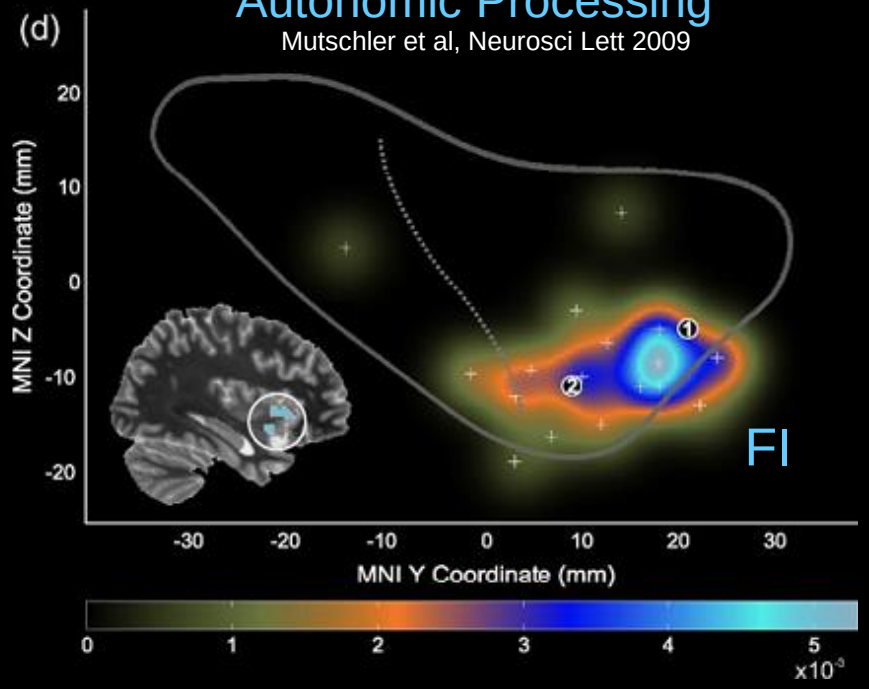
Social-emotional function

Kurth et al, Brain Structure and Function 2010



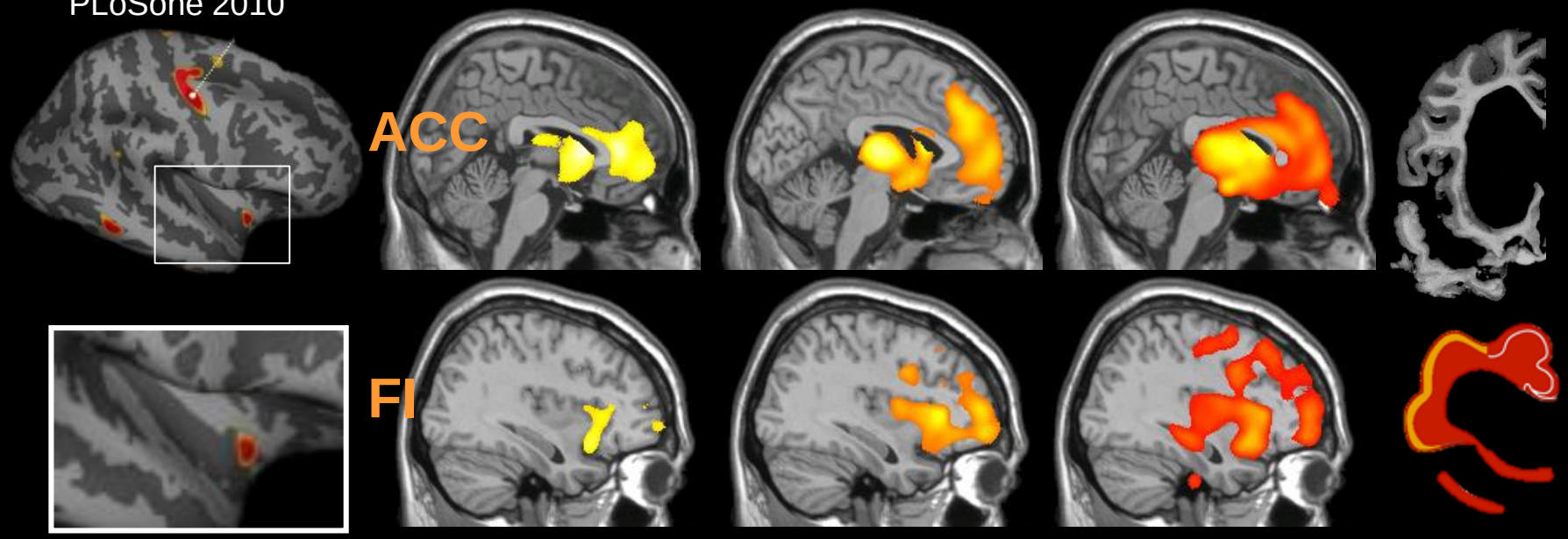
Autonomic Processing

Mutschler et al, Neurosci Lett 2009



bvFTD MR atrophy staging: ante-mortem

Verstraete et al
PLoSone 2010



ALS, pre-bvFTD? → CDR 0.5 → CDR 1 → CDR 2-3 → End-Stage CDR 2-4

Groups of 15 bvFTD vs. 45 healthy controls

Seeley et al Arch Neurol 2008

	ALS	bvFTD
Onset neuron	UMNs and LMNs	??
Onset sites / “epicenters”	Primary motor cortex, bulbar motor nuclei, AHC	Anterior cingulate and frontoinsula
Network spread	Pyramidal motor network	Salience network
1st symptom	Motor	Social-emotional
Later syndrome	bvFTD, Dysexecutive	Dysexecutive, ALS
Most common protein	TDP-43	TDP-43
Other inclusion proteins	FUS, SOD1, Ubiquilin2	Tau, FUS
Most common gene	*C9ORF72*	*C9ORF72*
Other genes	*SOD1, FUS, TARDBP, Ubiquilin2, VCP*	*MAPT, GRN, FUS, TARDBP, VCP*

ALS bvMCI-MND bvFTD-MND bvFTD

	ALS	bvFTD
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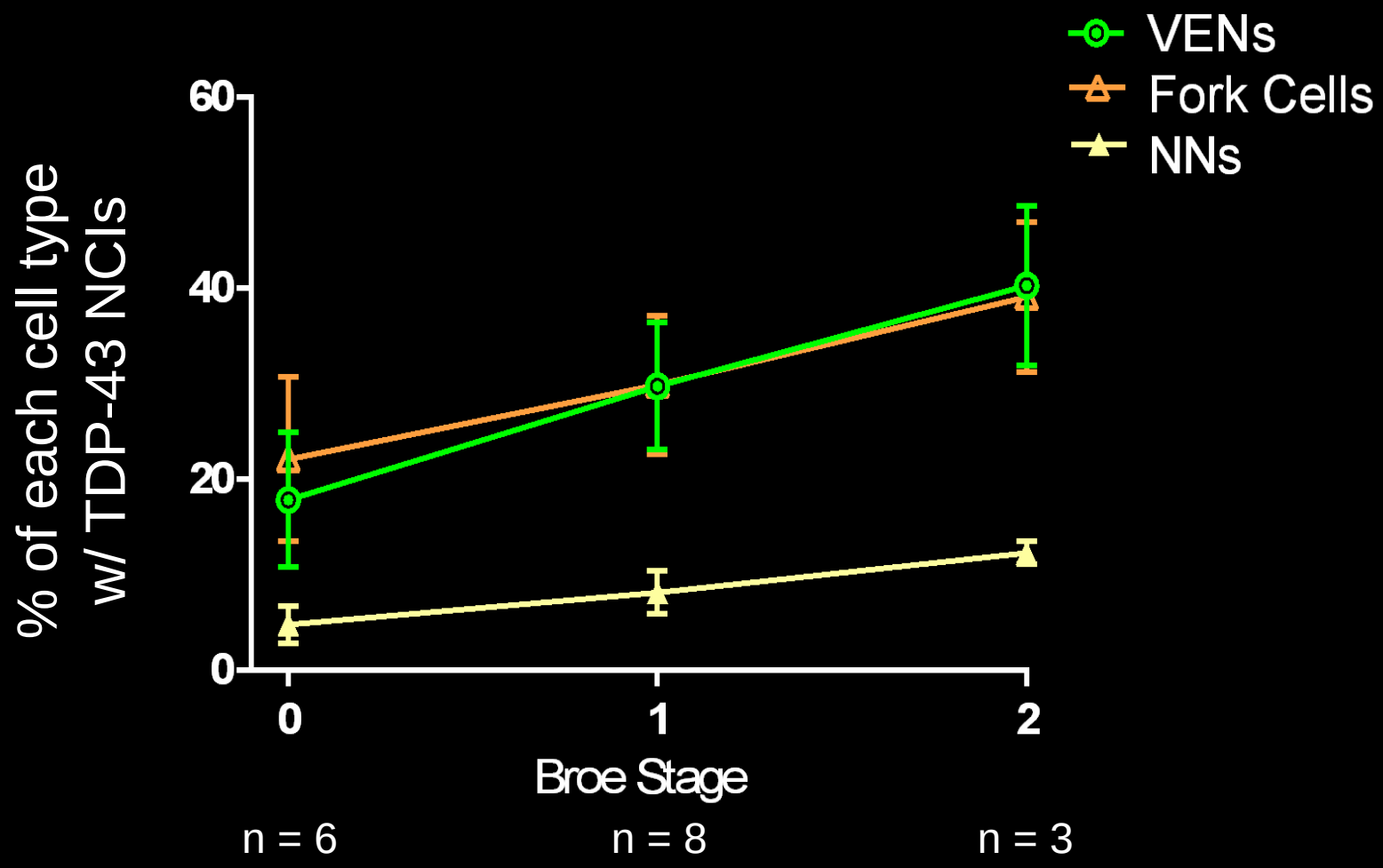
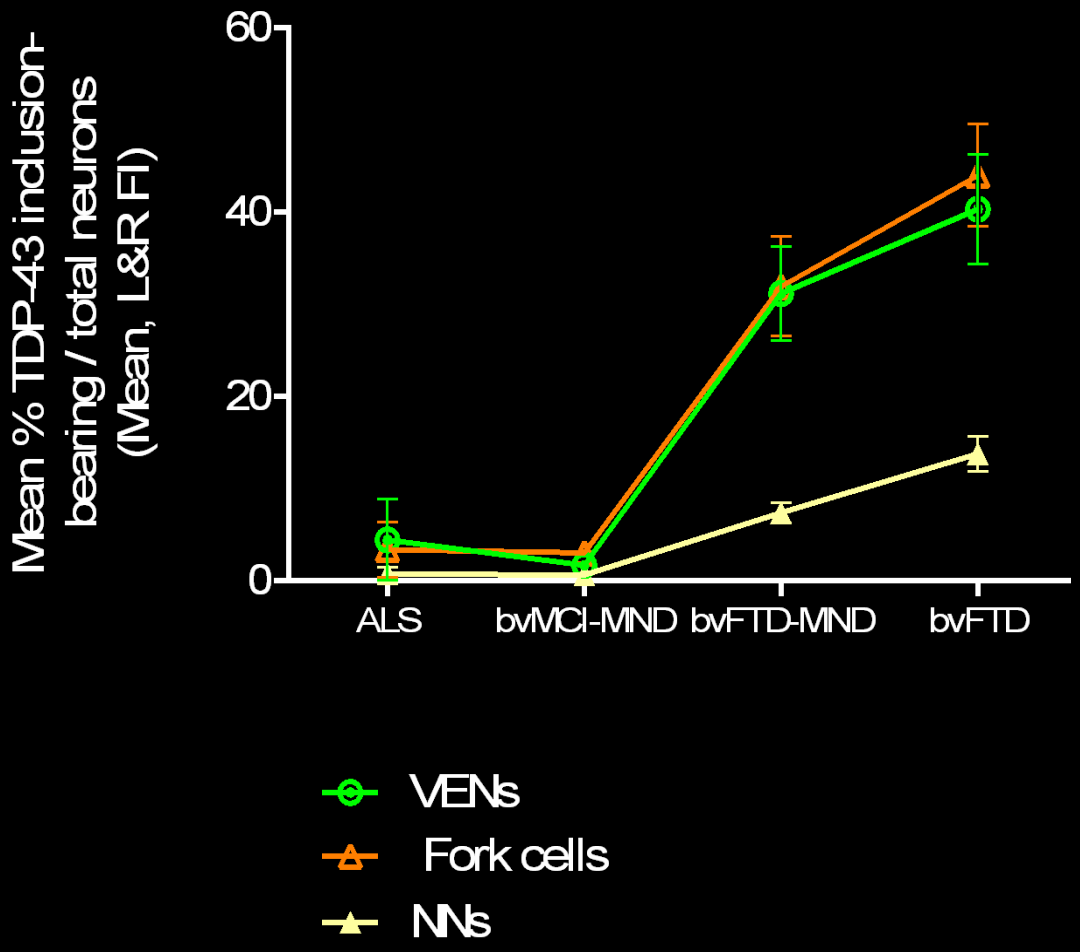
VEN and fork cell TDP-43 inclusions in absence of gross atrophy




Mean % TDP-43 inclusion-bearing / total neurons (Mean, L&R FI)
60
40
20
0
ALS
bvMCI-MND
bvFTD-MND
bvFTD
VENs
Fork cells
NNs

Astrogliosis accompanies TDP-43 NCI formation