Tracking ALS progression using neuroimaging

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OSPEDALE SAN RAFFAELE

Tracking ALS progression

- **Do we have MRI biomarkers for ALS?**
- **Can we track ALS progression using MRI?**
- **Foreseeing before disease onset**
- **Network analysis: a new approach to track ALS**

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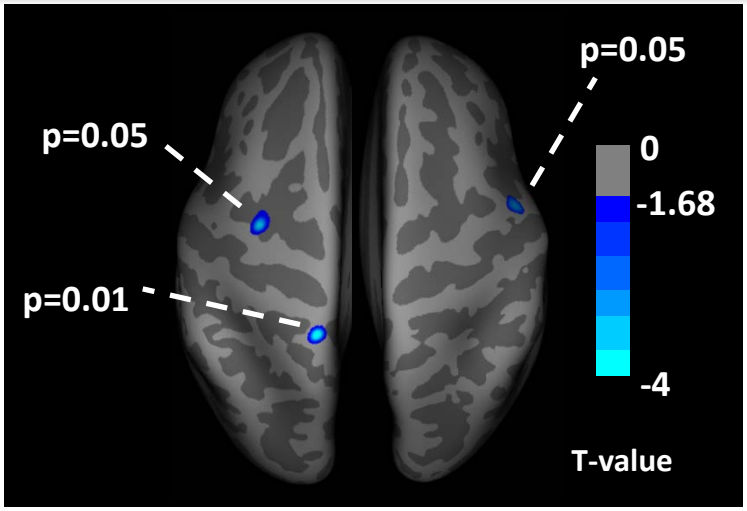
MRI biomarkers in ALS

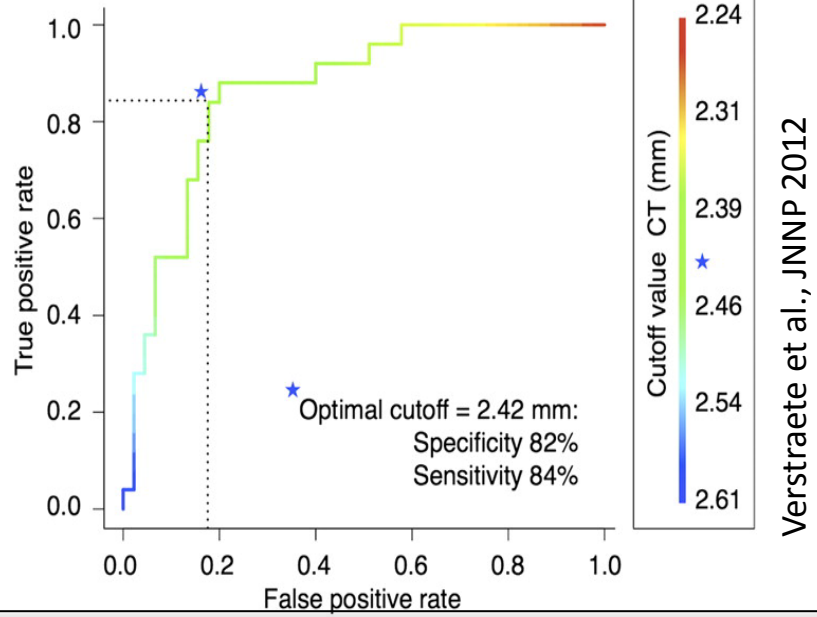
MRI biomarkers in ALS

ALS *vs* HC



Agosta et al., PlosONE 2012

C-Index ALS *vs* controls: 0.75



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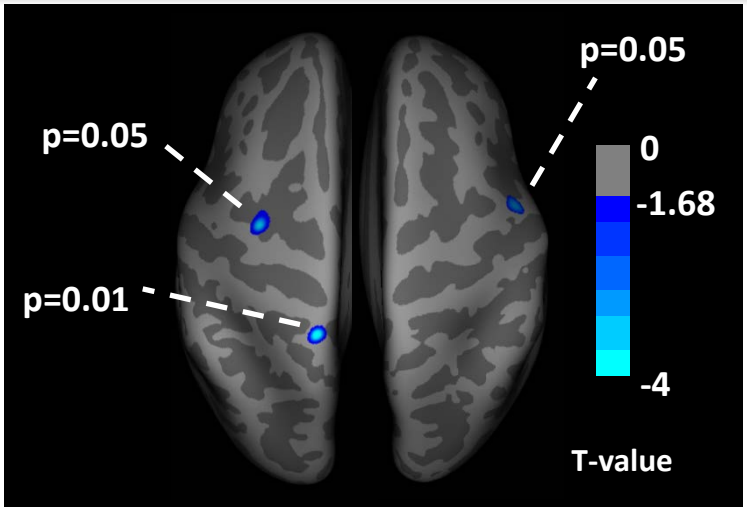

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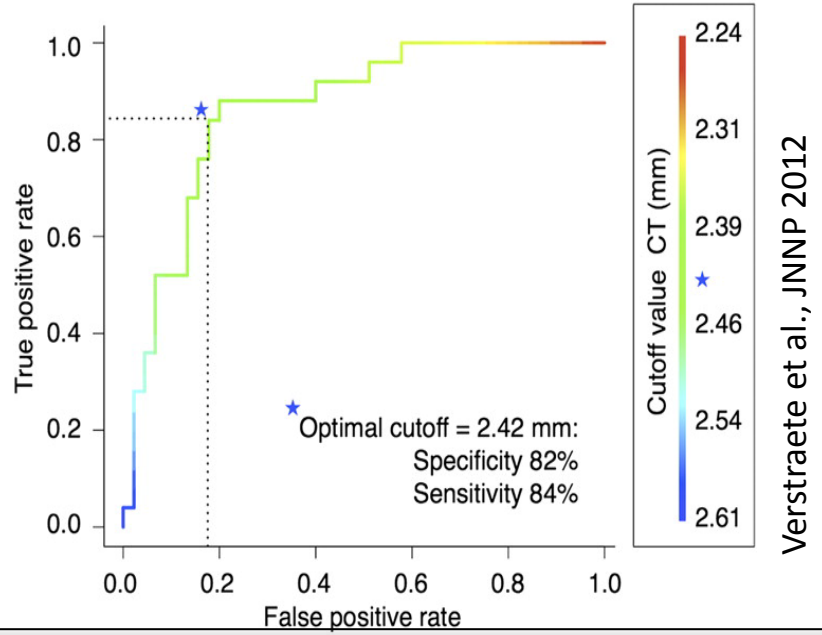

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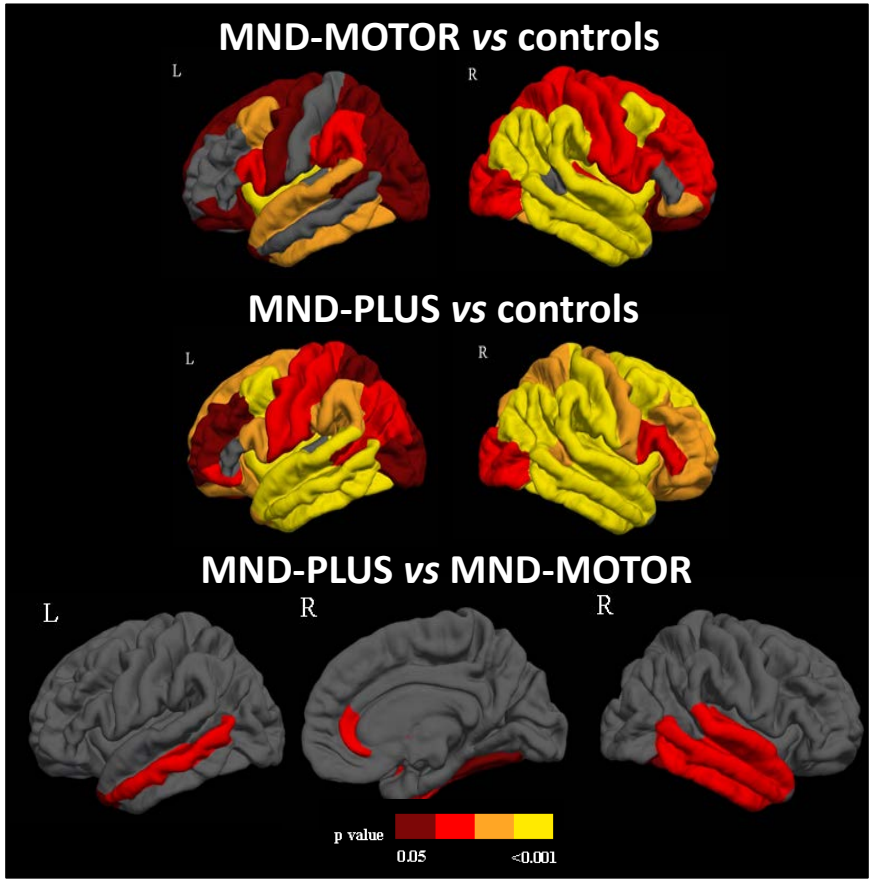

Agosta et al., Hum Brain Mapp 2016

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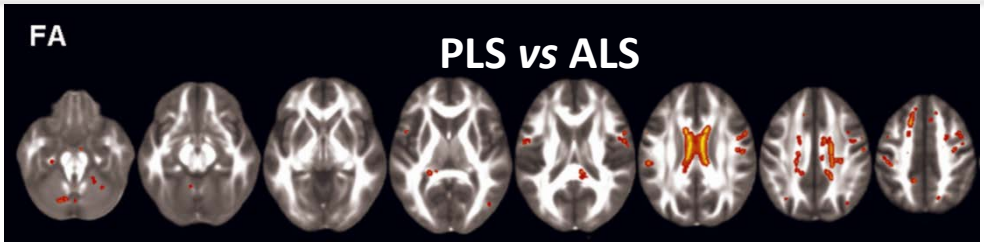

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CST FA	0.66	0.72	0.69	0.58
CC-PMC FA	0.68	0.91	0.79	0.74
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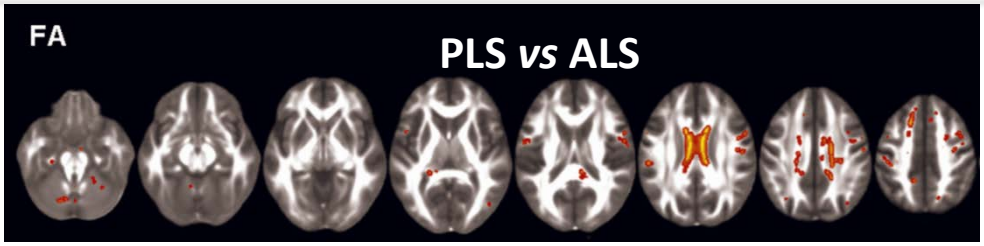

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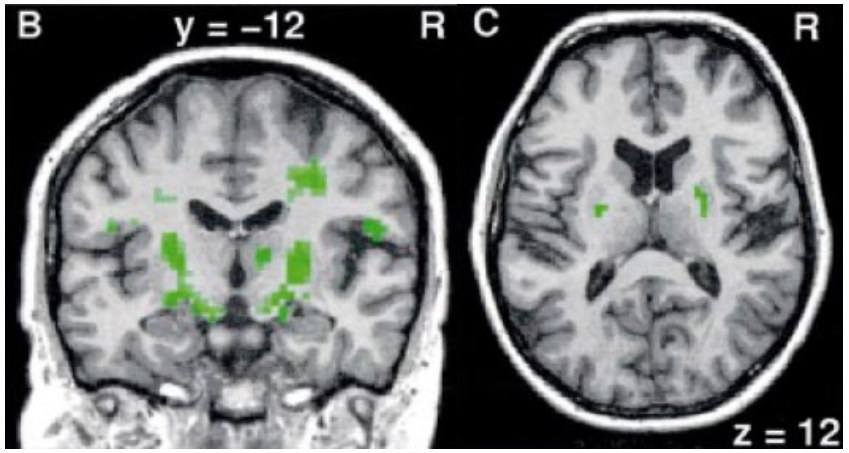
CST FA decrease in patients without UMN signs at the time of MRI



Sach et al., Brain 2004

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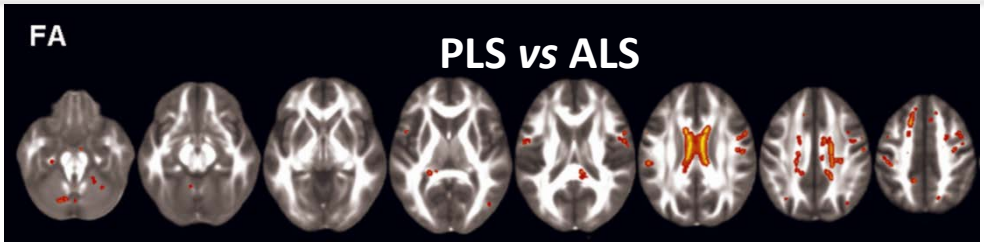

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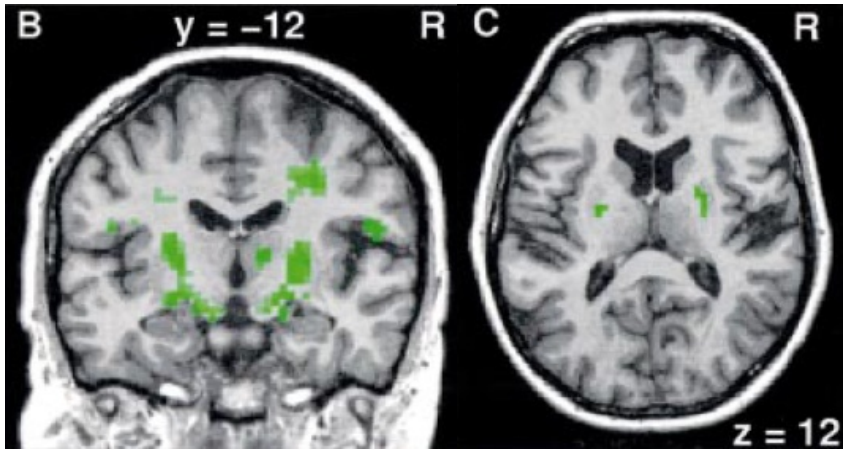
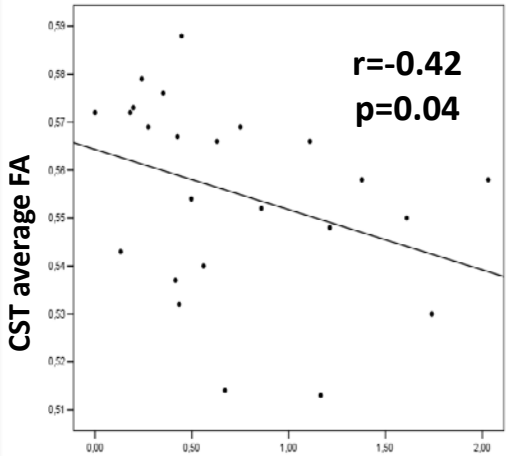
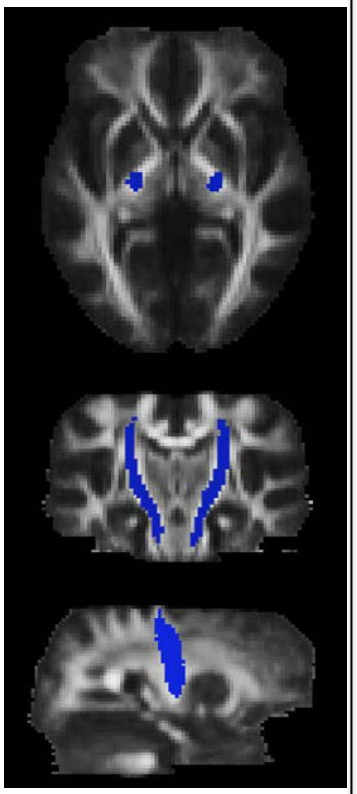


Sach et al., Brain 2004

CST damage *vs* progression rate and survival



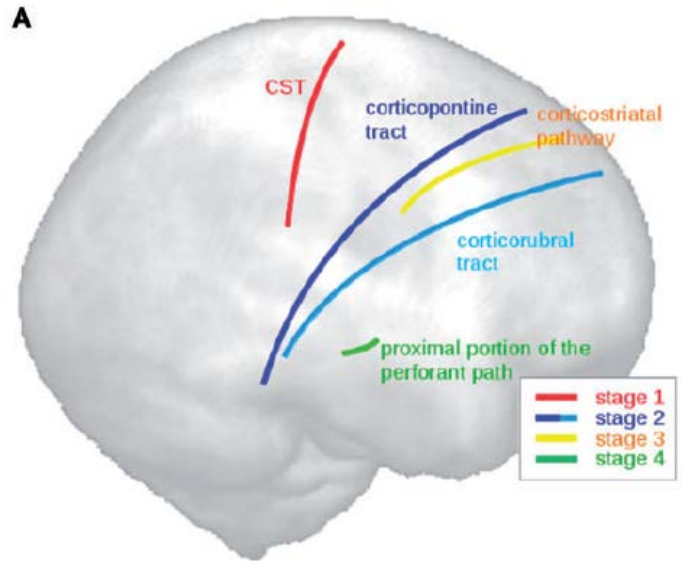


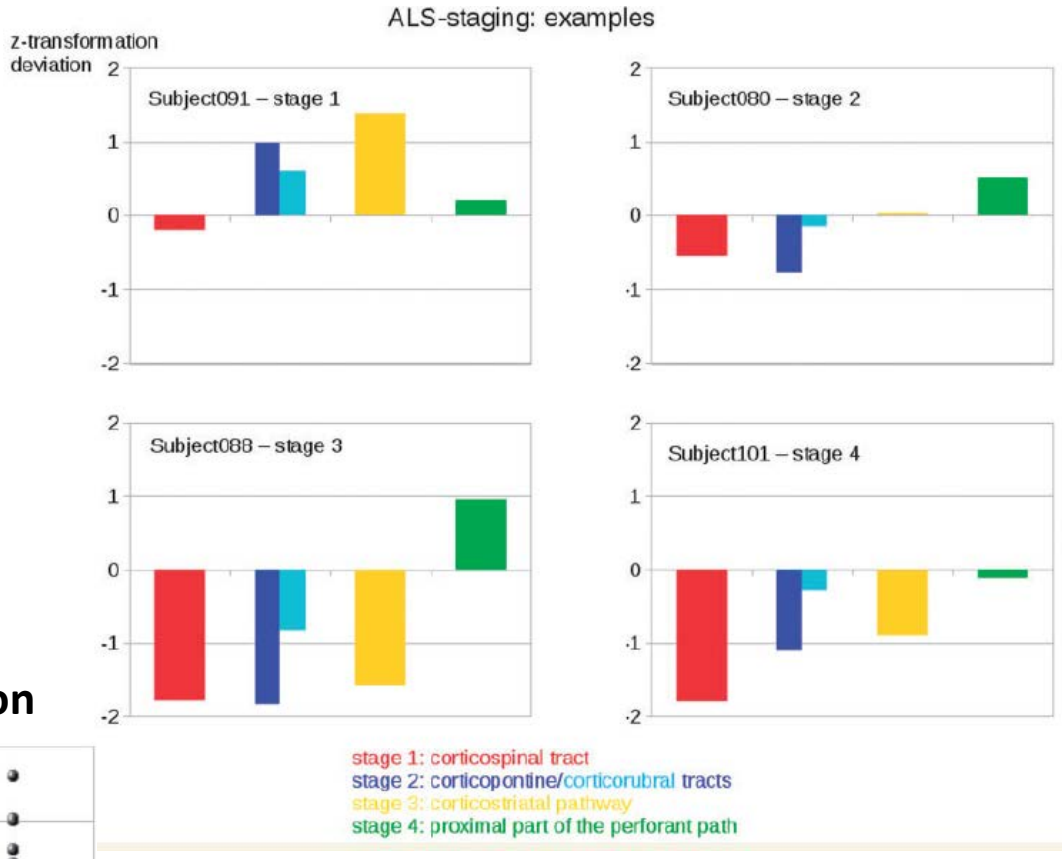
Independent predictors of survival:
ALSFRS deterioration rate
(p=0.01, HR=2.2, 95% CI=1.2-3.9)
CST FA
(p=0.06, HR=0.94, 95% CI=0.89-1.00)

Agosta et al., Eur J Neurosci 2010

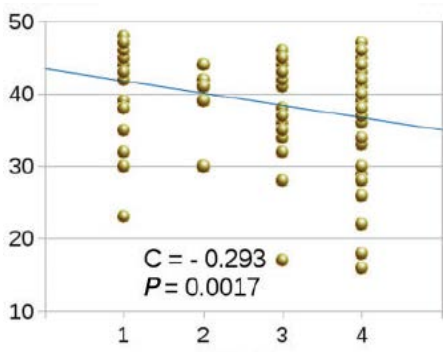
MRI biomarkers in ALS

MRI biomarkers in ALS

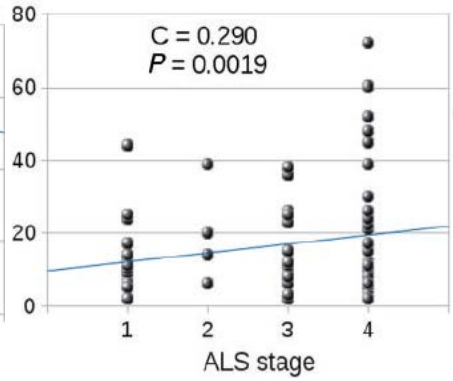




ALSFRS-R



Disease duration



Kassubek et al., Brain 2014

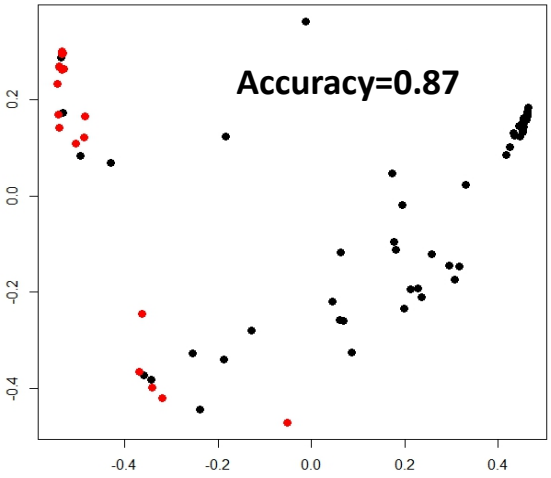
MRI biomarkers in ALS

MRI biomarkers in ALS

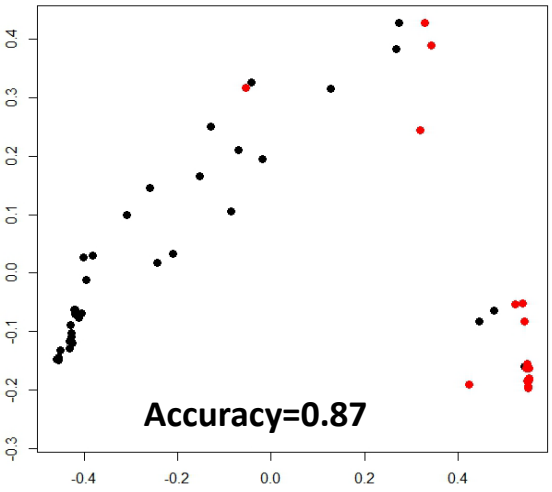
Diagnostic accuracy

ALS *vs* ALS mimic dorders

DT MRI values



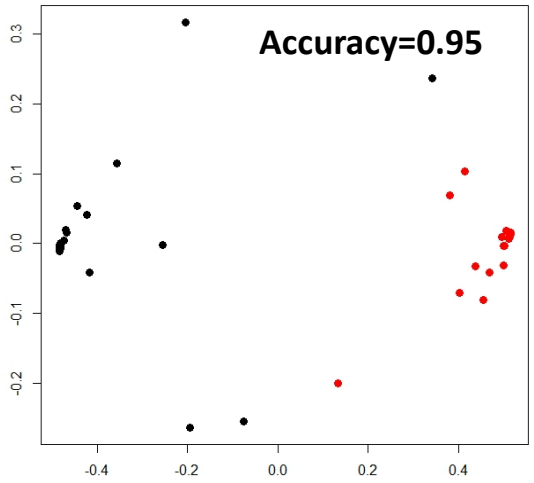
Combined MRI metrics



● ALS
● MIMIC

PUMN *vs* ALS mimic disorders

DT MRI values



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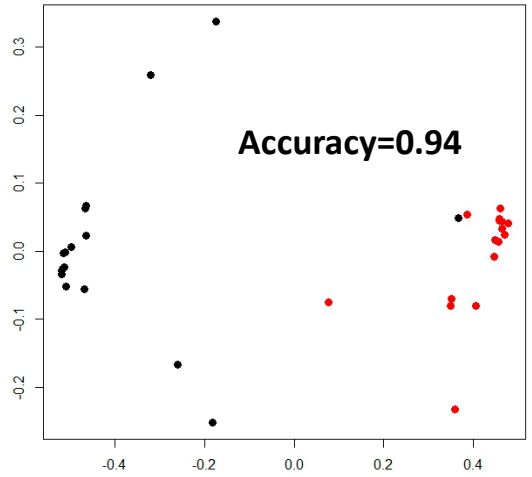


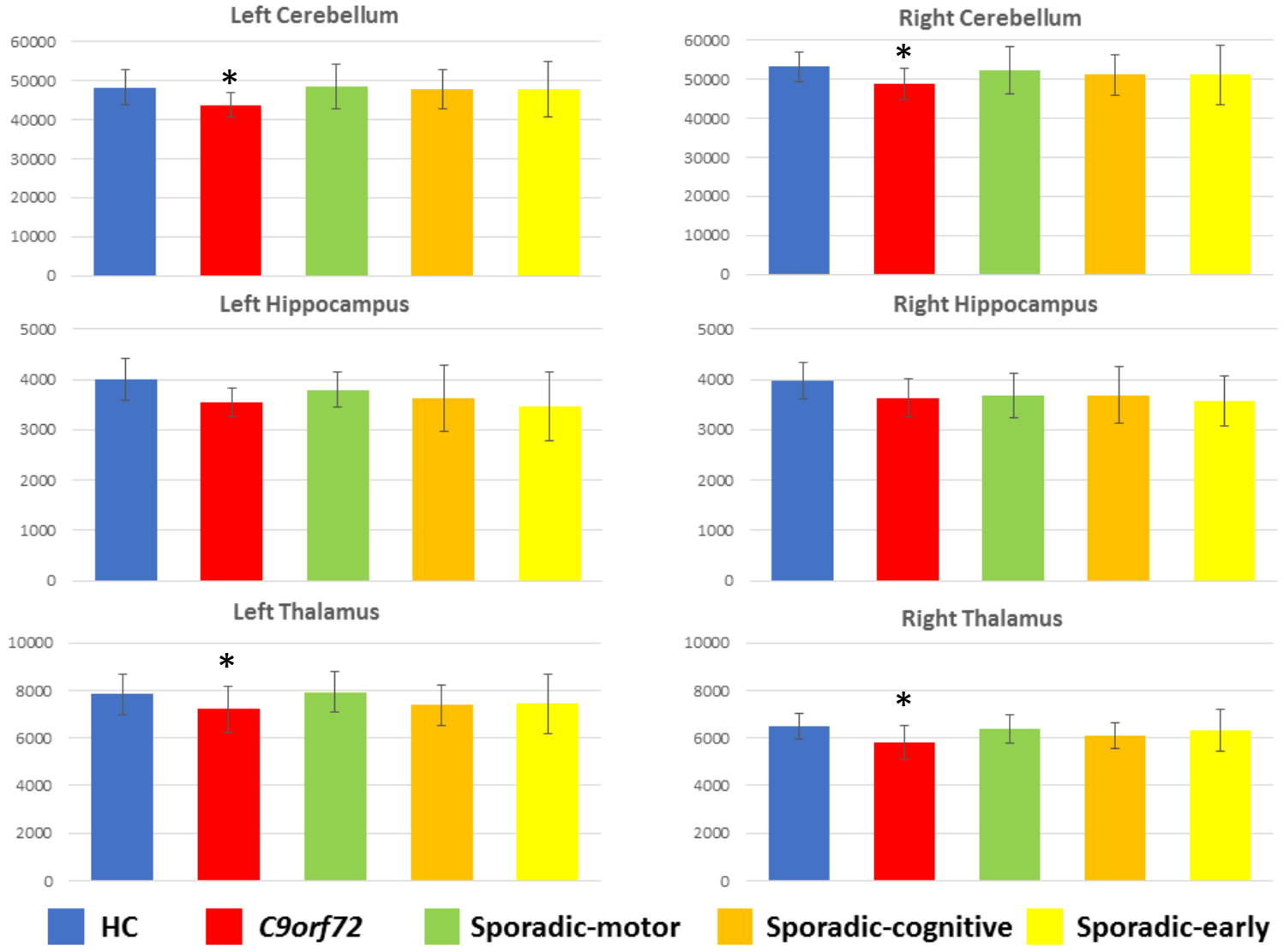
● PUMN
● MIMIC

Agosta et al., AAN 2017

MRI biomarkers in ALS

MRI biomarkers in ALS

C9orf72 *vs* sporadic ALS

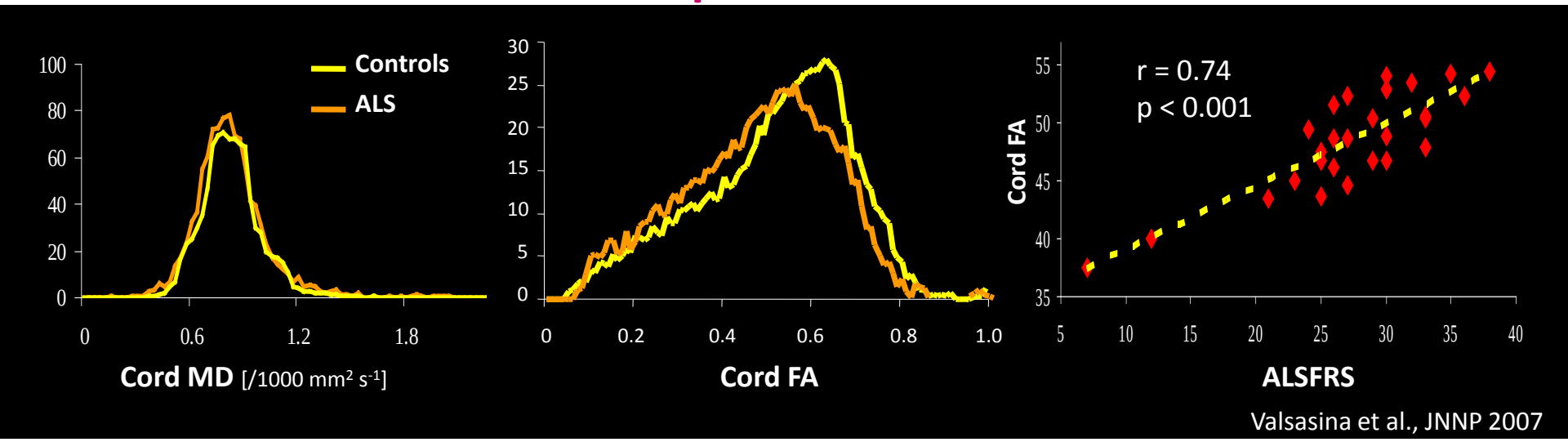


Agosta et al., Neurobiol Aging Under review

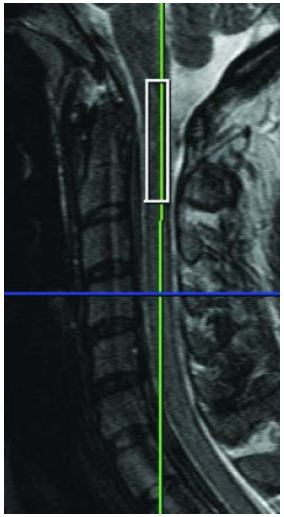
MRI biomarkers in ALS

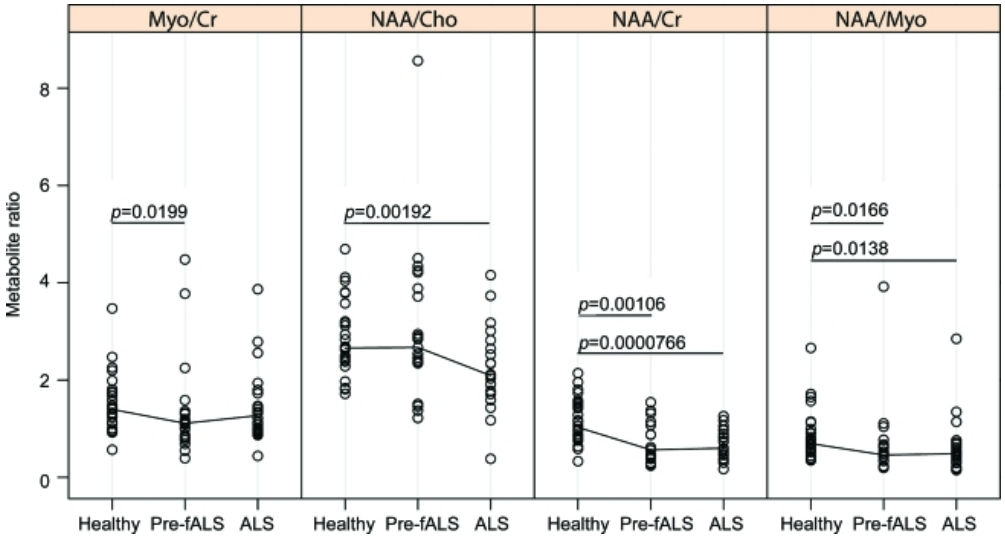
MRI biomarkers in ALS

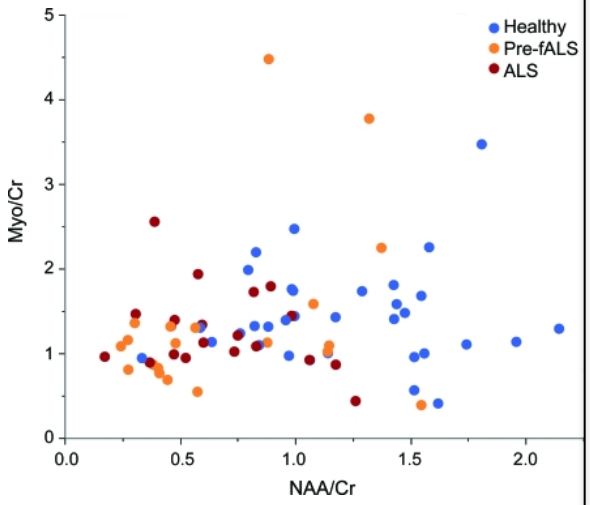
Spinal cord



Valsasina et al., JNNP 2007







Carew et al., Neurology 2012

MRI biomarkers in ALS

MRI biomarkers in ALS

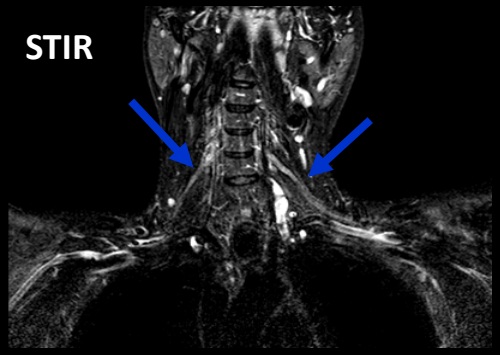
Peripheral nervous system

Healthy control

STIR

Nerve root increased signal

STIR



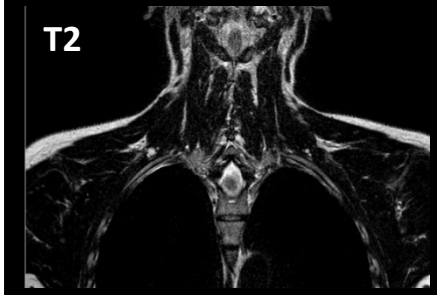
3D T2 VISTA

Nerve root T2 signal *vs* disease progression: r = 0.40

Supraspinatus muscle edema

Healthy control

T2



T2

STIR

T1

Adipose tissue deposition between trapezius and supraspinatus muscle

Gerevini et al., Radiology 2016

Tracking ALS progression

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Tracking ALS progression

Field strength	n*	Method	Interval between scans	ALSFRS-R baseline–follow-up	Main results
1.5 T	11	DTI FA and MD in CST ROIs	~6 months	40–35	No significant changes
1.5 T	17	CSA/FA/MD in cervical cord, average FA and MD in CST	9 months	27–21	All metrics in the spinal cord, but not in the CST, changed significantly
3 T	14	Spinal cord CSA, FA, L1, RD, MD, and MTR in cervical region of lateral CST	11 months	40–31	Significant CSA and MTR changes
3 T	16	DTI tractography of CST, VBM using whole-brain FA maps	6 months	42 - 38	FA decreases in CST and CC
3 T	17	ROI analysis based on DTI tractography of CST, VBM of whole-brain FA and MD maps	8 months	35–29	FA decreases in right superior CST, MD stable
1.5 T	15	VBM using FA and ADC maps	6 months	35–33	FA decreases in CST, frontal areas, and cerebellum
3 T	19	TBSS of FA, MD, L1, RD	6 months	34–30	L1 increases in posterior limb of left internal capsule
1.5 T	16	TBM analysis of gray matter	9 months	27–21	Progression of atrophy in left premotor cortex and right putamen and caudate
3 T	20	Surface-based CT analysis	3–10 months	42–37	No significant changes
3 T	51	Surface-based CT analysis	7.8 months	39–33	No significant changes
3 T	39	Volumetry of subcortical gray matter and ventricles	5.5 months	41–36	Shrinkage of right CA 2/3, and CA 4/dentate gyrus; enlargement of both lateral ventricles and right third and fourth ventricle
3 T	17	VBM of gray matter structure and FA and MD	6 months	37–32	Widespread gray matter decreases, FA and MD changes in right cerebral peduncles
3 T	9	Gray matter CT, regional brain volumes, FA and CSA of CST and CC	1.3 years	40–34	CT and volume decreases of precentral gyri. FA stable, but CST CSA declined
3 T	27	VBM and TBSS of FA, MD, L1, and RD	>6 months	35–28	Widespread gray matter volume decreases, minor L1 and MD increases in CC, minor L1 increases in left CST
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1.5 T	9	^{1}H MRS: NAA, Cre, and Cho in motor and nonmotor regions	1 months, 3 months	–	NAA/Cre and NAA/(Cre + Cho) decreases in motor cortex after 1 month; absolute NAA, Cre, and Cho decreases after 3 months
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Menke et al., Neurotherapeutics 2017

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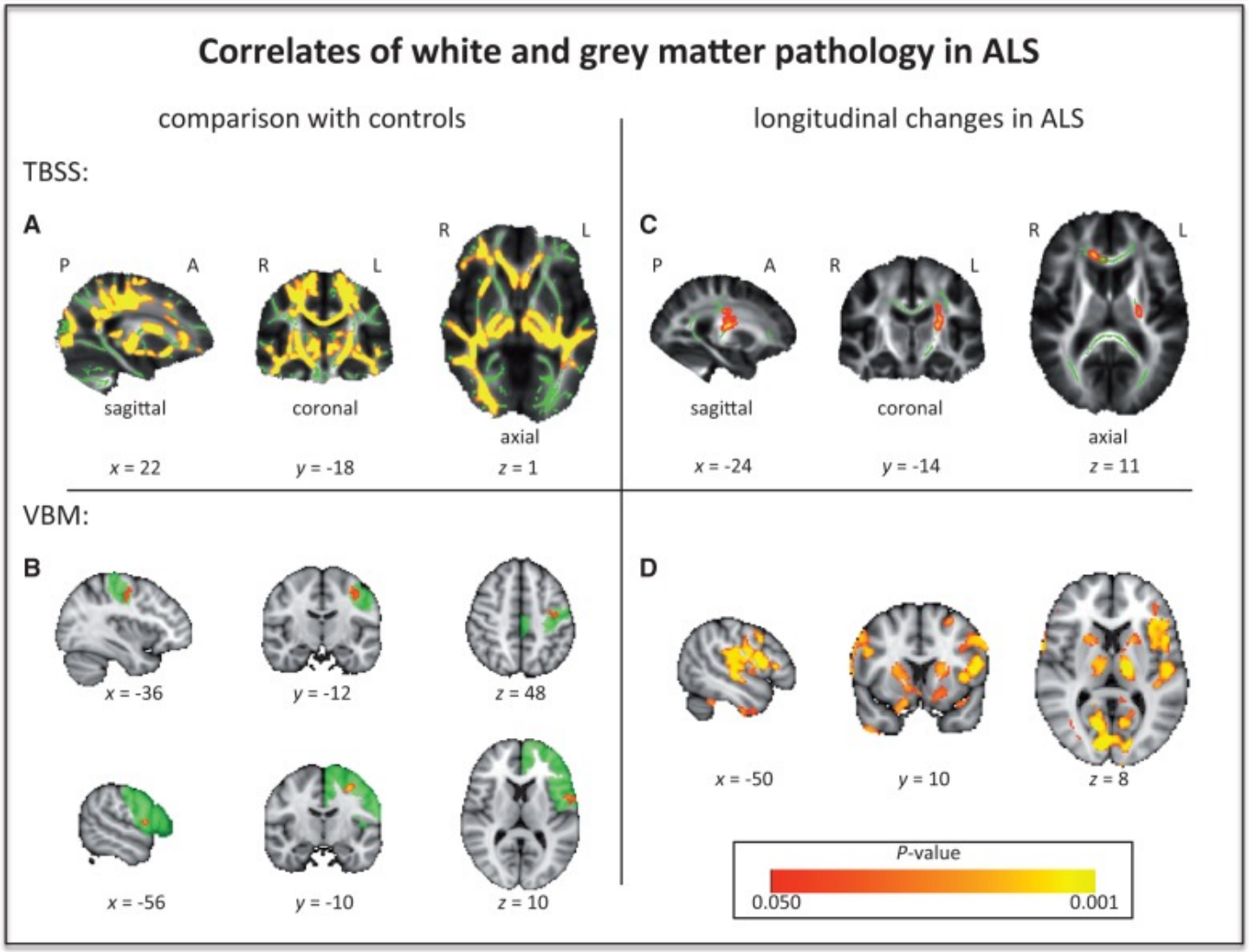
Menke et al., Neurotherapeutics 2017

Tracking ALS progression

Tracking ALS progression

Longitudinal WM damage *vs* GM atrophy in ALS



Menke et al., Brain 2014

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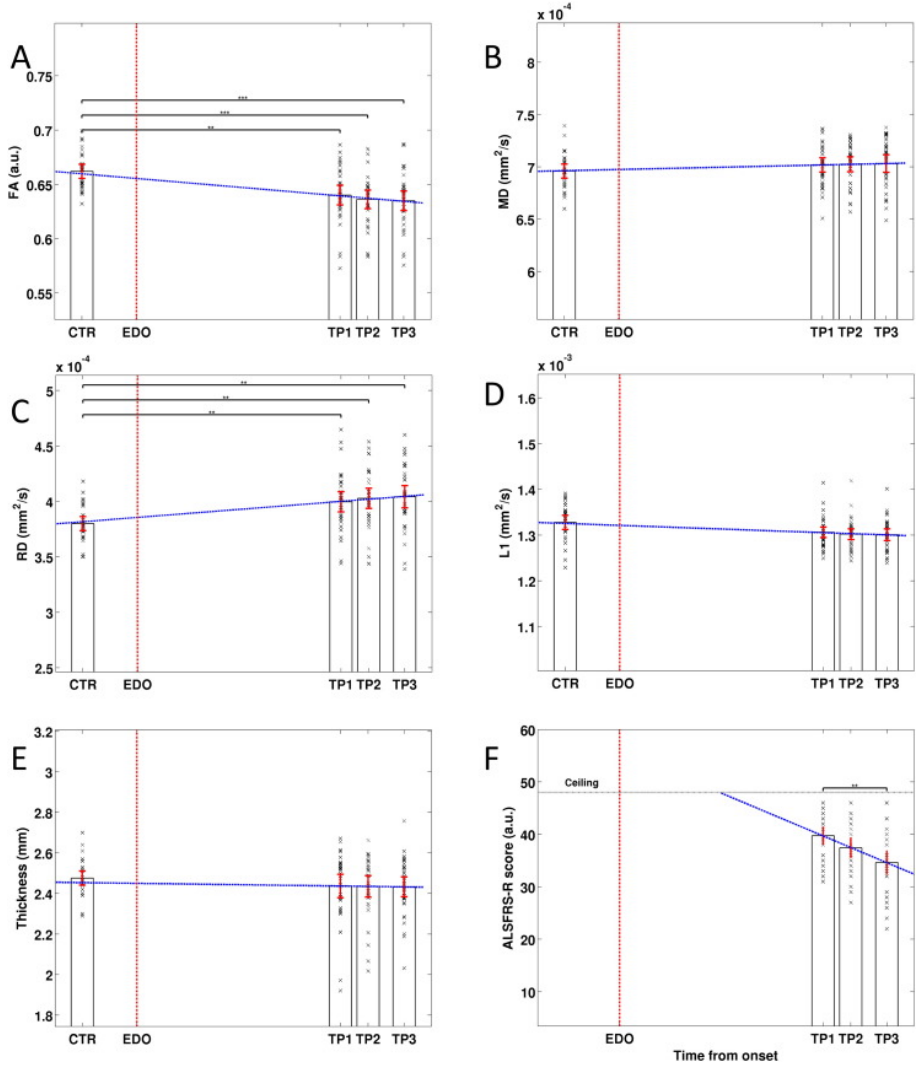

Measure		AROC	SE	t-stat	DF	*P*-value
ALSFRS-R score (/48)		−7.3	0.73	−7.87	100	<0.000[a]
Diffusion: cortico-spinal tract	FA (a. u.)	−0.0066	0.002	−2.65	100	0.009[a]
	MD (mm^2/s)	1.7×10^{-6}	2.8×10^{-6}	0.59	100	0.55
	L1 (mm^2/s)	-7.5×10^{-6}	4.1×10^{-6}	−1.82	100	0.07
	RD (mm^2/s)	6.1×10^{-6}	2.0×10^{-6}	2.09	100	0.038[a]
Precentral gyrus thickness (mm)		−0.02	0.03	−0.62	100	0.54
Volumetry (mm^3)	Amygdala	−25.6	69.4	−0.41	100	0.68
	Caudate	182.5	109.5	1.69	100	0.09
	Hippocampus	11.0	98.6	0.12	100	0.90
	Pallidum	11.0	51.1	0.28	100	0.78
	Putamen	120.5	102.2	1.15	100	0.25
	Thalamus	142.7	84.0	−1.67	100	0.09

[a] Significant changes.

No longitudinal GM changes

Cardenas-Blanco et al., NeuroImage: Clinical 2016

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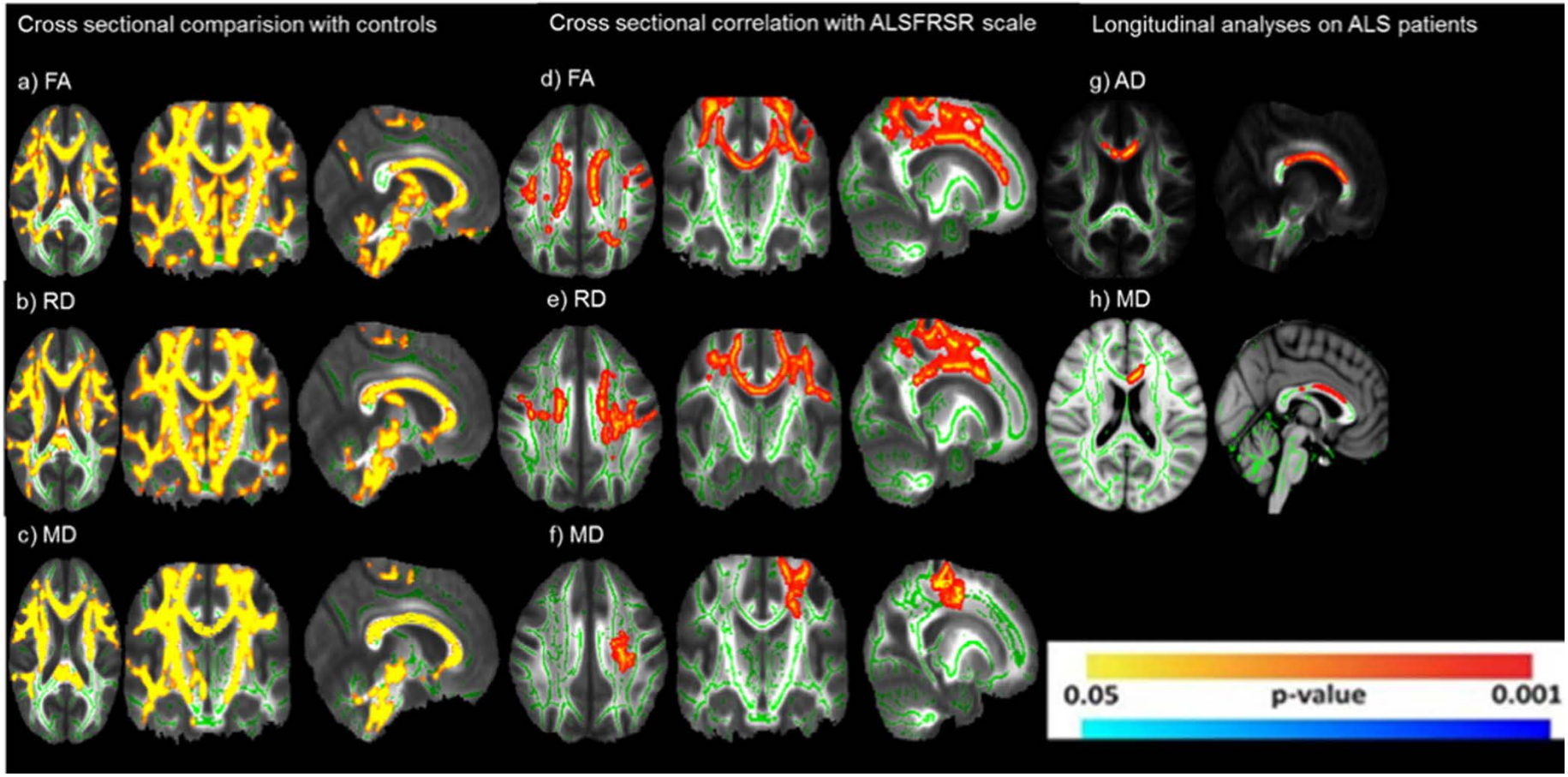
Tracking ALS progression

Longitudinal WM damage *vs* GM atrophy in ALS



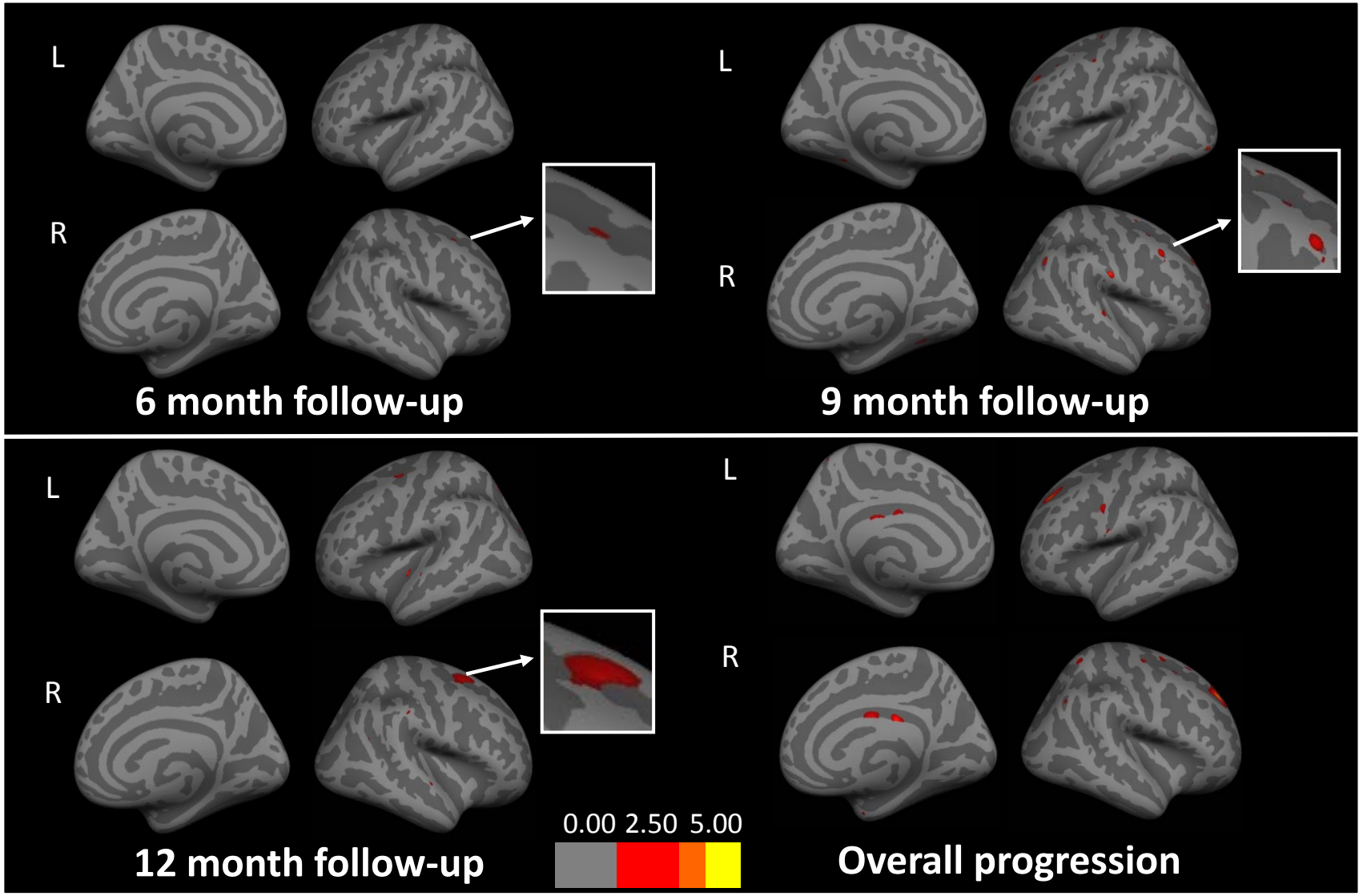
No longitudinal GM changes

de Albuquerque et al., NeuroImage: Clinical 2017

Tracking ALS progression

Tracking ALS progression

Longitudinal WM damage *vs* GM atrophy in ALS

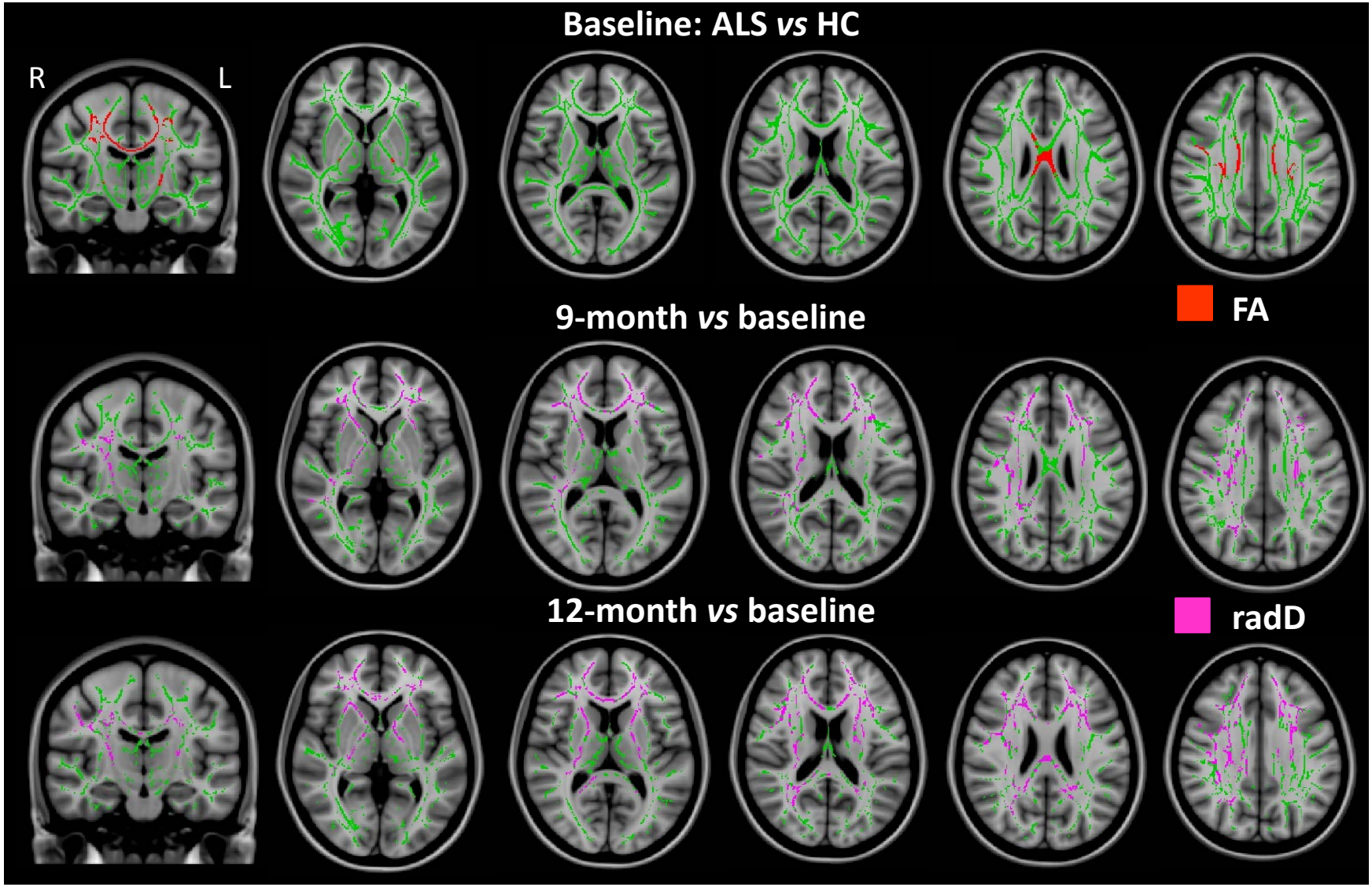


Ferraro et al., AAN 2017

Tracking ALS progression

Tracking ALS progression

Longitudinal WM damage *vs* GM atrophy in ALS

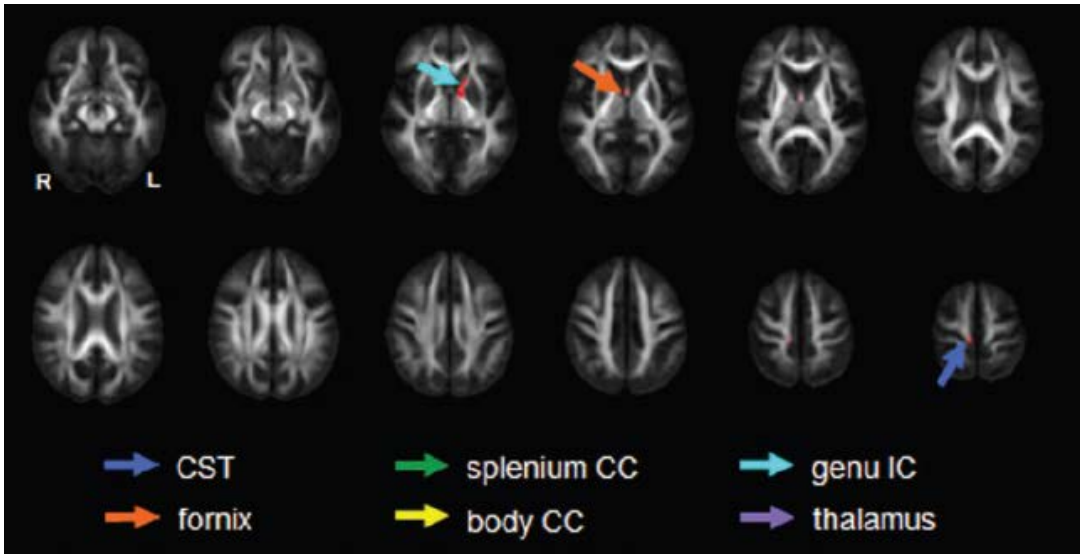


Ferraro et al., AAN 2017

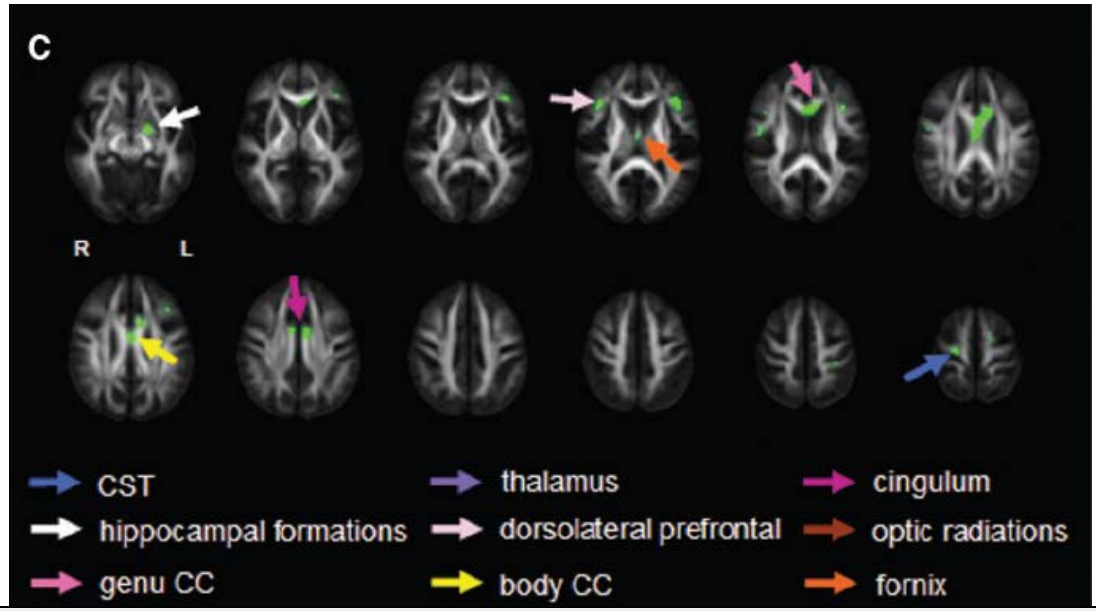
Tracking ALS progression

Tracking ALS progression

PMA *vs* controls



PMA – 6 month follow up



Van der Graaff e tal., Brain 2011

Tracking ALS progression

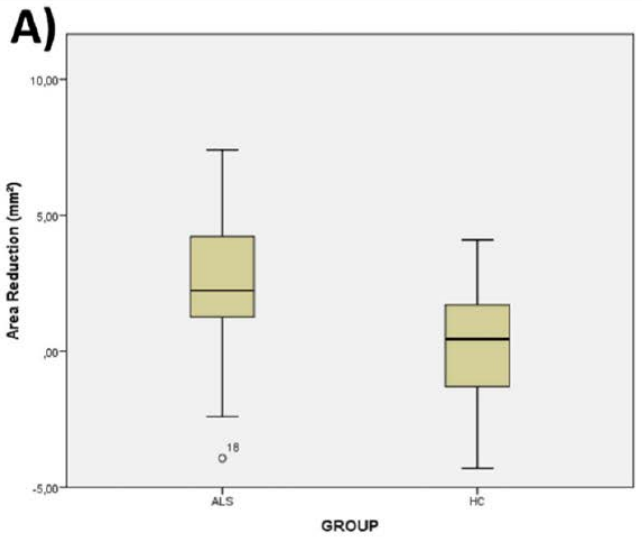
Tracking ALS progression

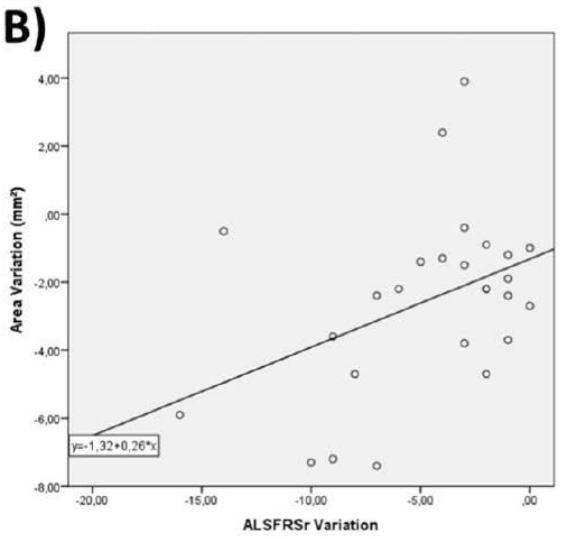
Spinal cord MRI

		Baseline	Follow-up	p Value*
Cord cross-sectional area (mm^3)	Mean (SD)	71.1 (6.2)	69.4 (5.6)	0.003
	Range	59.3 to 83.4	57.8 to 78.6	
Cord average MD ($\times 10^{-3}$ mm^2 s^{-1})	Mean (SD)	0.89 (0.06)	0.95 (0.08)	0.01
	Range	0.78 to 0.99	0.81 to 1.07	
Cord average FA	Mean (SD)	0.48 (0.03)	0.45 (0.04)	0.01
	Range	0.42 to 0.53	0.39 to 0.54	
Brain CST average MD ($\times 10^{-3}$ mm^2 s^{-1})	Mean (SD)	0.80 (0.03)	0.79 (0.03)	NS
	Range	0.74 to 0.87	0.73 to 0.84	
Brain CST FA	Mean (SD)	0.56 (0.03)	0.56 (0.02)	NS
	Range	0.50 to 0.60	0.52 to 0.60	

*Adjusted for follow-up duration. See the text for further details.
CST, corticospinal tract; FA, fractional anisotropy; MD, mean diffusivity; NS, not significant.

Agosta et al., JNNP 2009



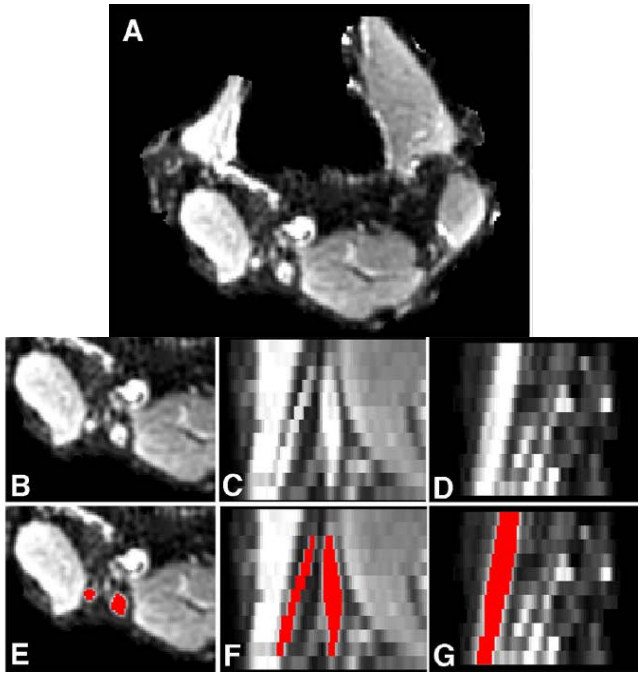


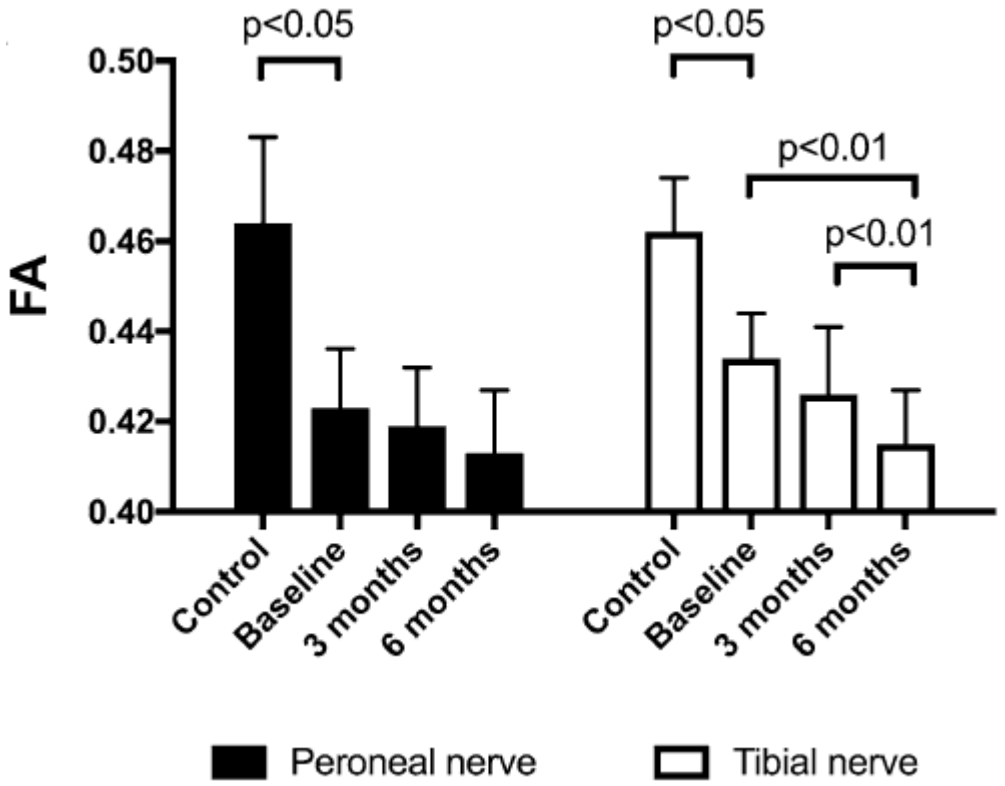
de Albuquerque et al., NeuroImage: Clinical 2017

Tracking ALS progression

Tracking ALS progression

Peroneal and tibial nerve DTI





	ΔALSFRS-R	ΔMRCSS-LL	ΔCMAP	ΔMUNE
ΔFA peroneal	−0.11 (0.53)	−0.06 (0.75)	−0.01 (0.94)	0.01 (0.97)
ΔFA tibial	0.05 (0.77)	−0.40 (0.02)	−0.13 (0.94)	0.13 (0.45)
ΔAD peroneal	0.22 (0.21)	0.21 (0.22)	0.05 (0.76)	0.20 (0.26)
ΔAD tibial	0.38 (0.03)	−0.23 (0.20)	0.02 (0.91)	0.18 (0.32)

Simons et al J Neurol 2017

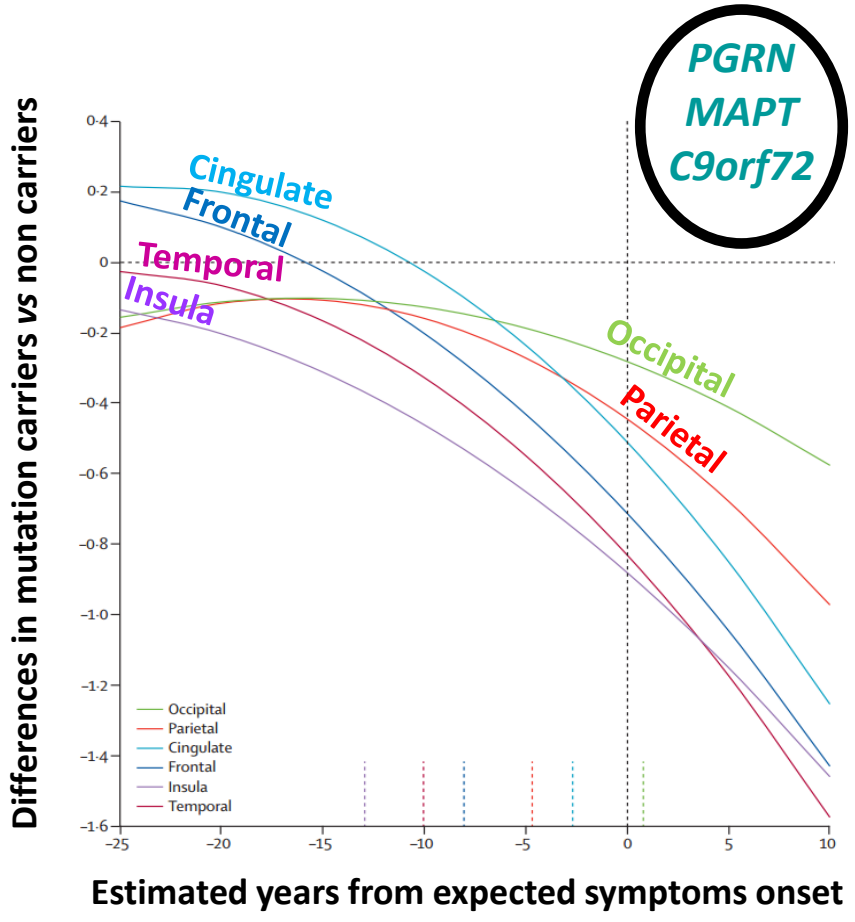
Tracking ALS progression

- Do we have MRI biomarkers for ALS?
- Can we track ALS progression using MRI?
- **Foreseeing before disease onset**
- Network analysis: a new approach to track ALS

Foreseeing before disease onset

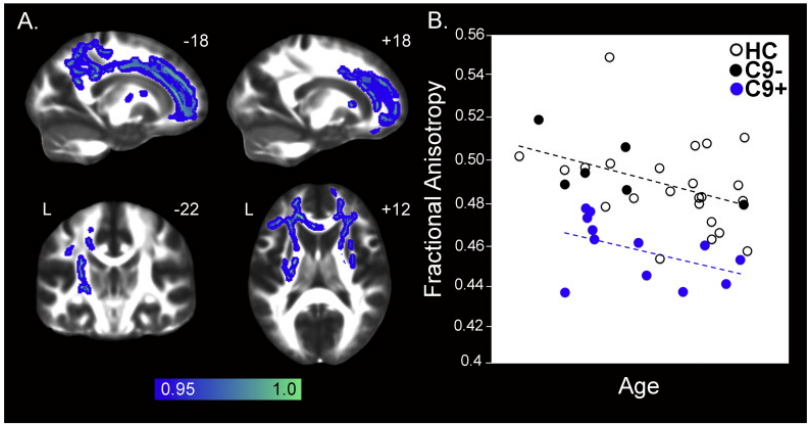
Foreseeing before disease onset

GM atrophy



Rohrer et al., Lancet Neurol 2015

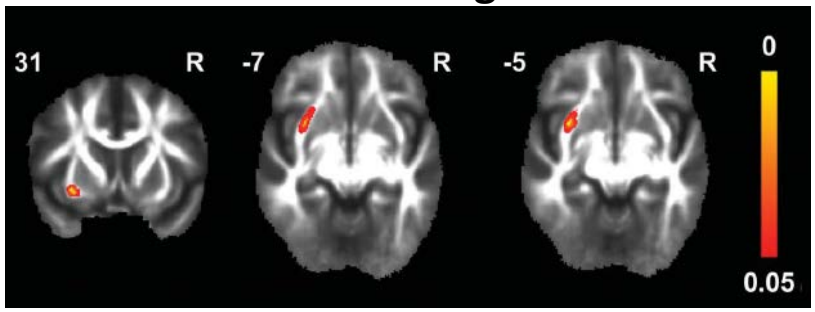
WM damage



15 presymptomatic carriers (*C9orf72*)

Lee et al., NeuroImage: Clinical 2017

WM damage



39 presymptomatic carriers (28 *PGRN*, 11 *MAPT*)

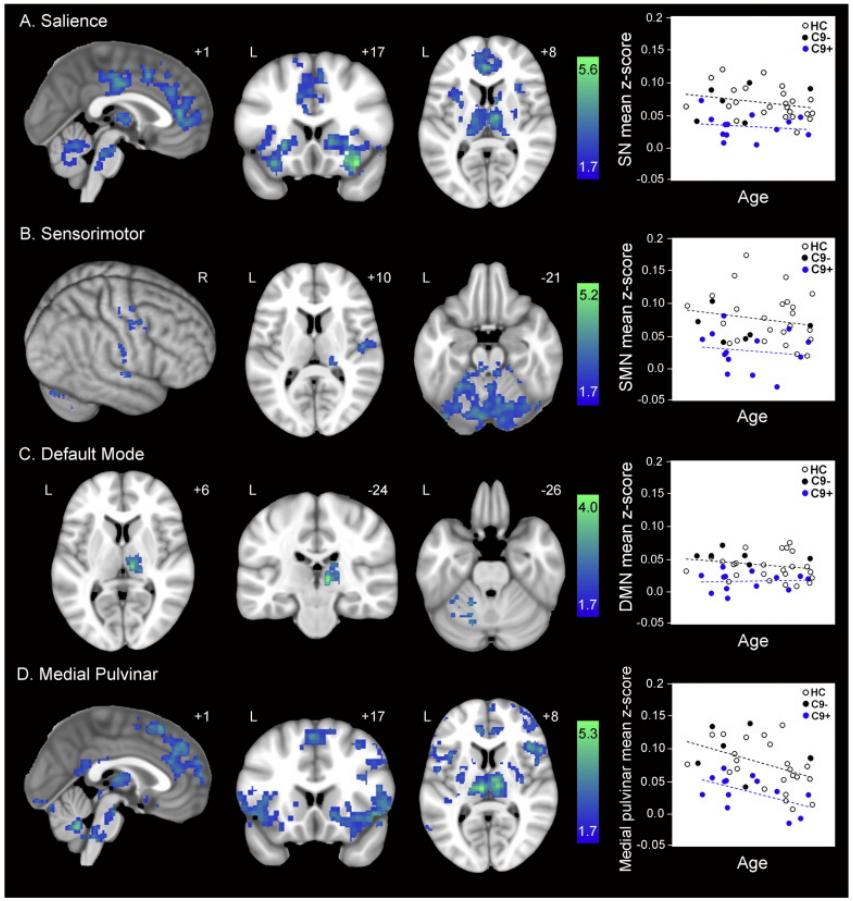
Dopper et al., Neurology 2014

Foreseeing before disease onset

Foreseeing before disease onset

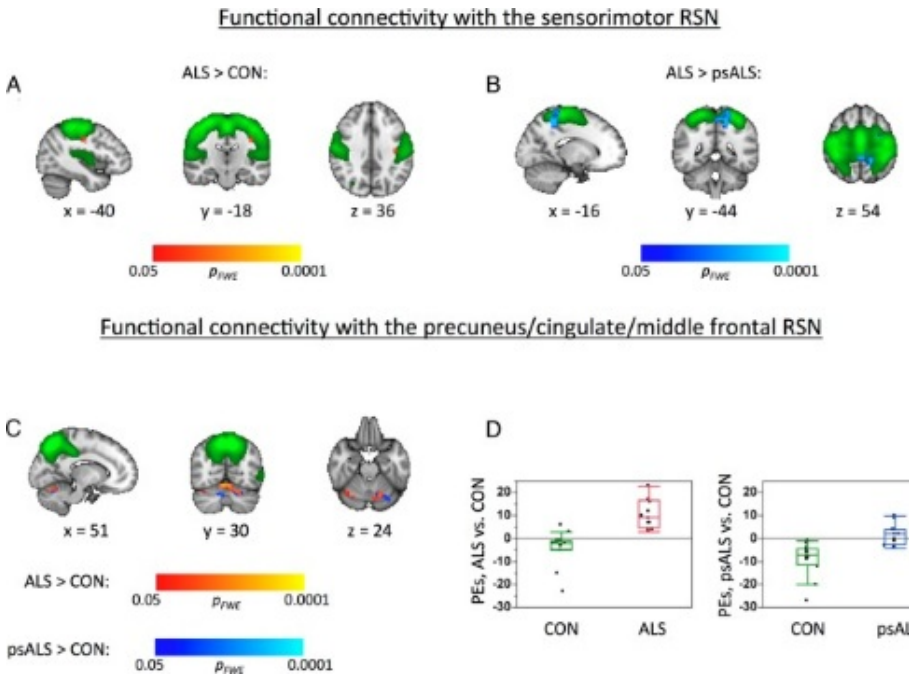
Altered functional connectivity

15 presymptomatic carriers (*C9orf72*)



Lee et al., NeuroImage: Clinical 2017

12 presymptomatic carriers (SOD1, *C9orf72*)



Menke et al., JNNP 2016

Tracking ALS progression

- Do we have MRI biomarkers for ALS?
- Can we track ALS progression using MRI?
- Foreseeing before disease onset
- **Network analysis: a new approach to track ALS**

The Network-based Degeneration Hypothesis

Alzheimer disease: Tau

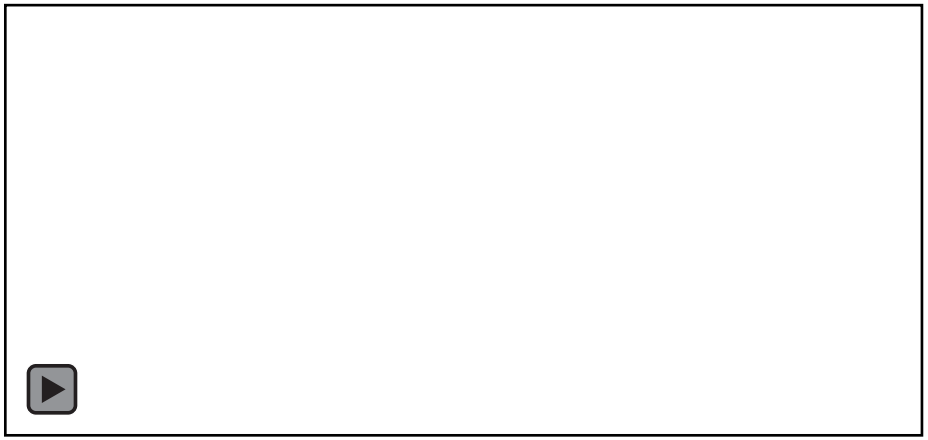
Parkinson disease: α-synuclein

Amyotrophic lateral sclerosis: TDP-43

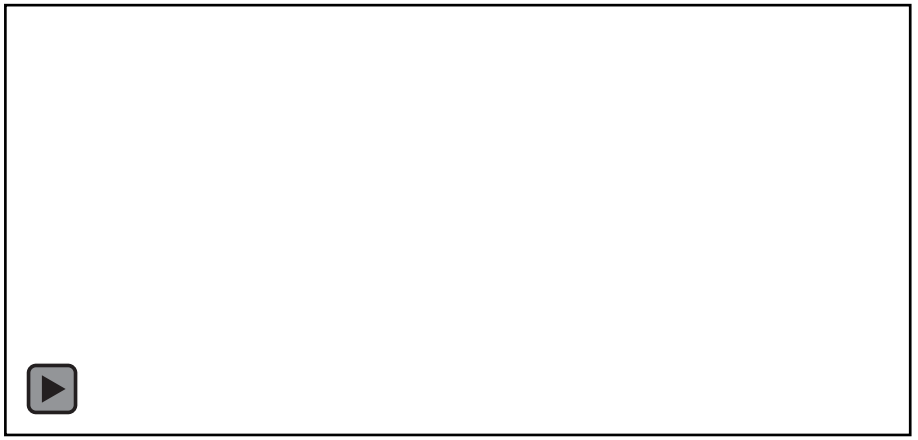
Frontotemporal dementia: TDP-43

The Network-based Degeneration Hypothesis

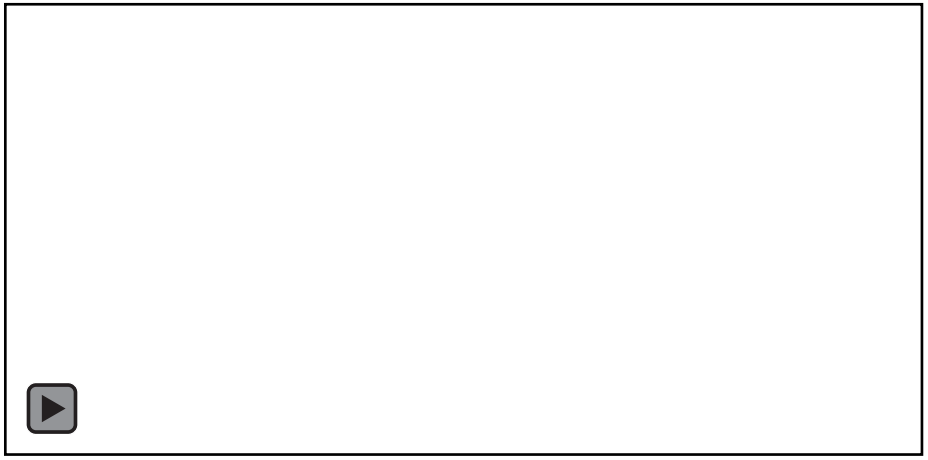
Alzheimer disease: Tau



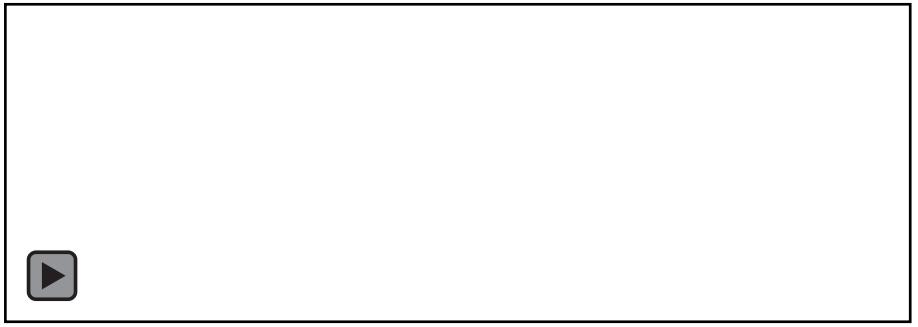
Parkinson disease: α-synuclein



Amyotrophic lateral sclerosis: TDP-43



Frontotemporal dementia: TDP-43



The Network-based Degeneration Hypothesis

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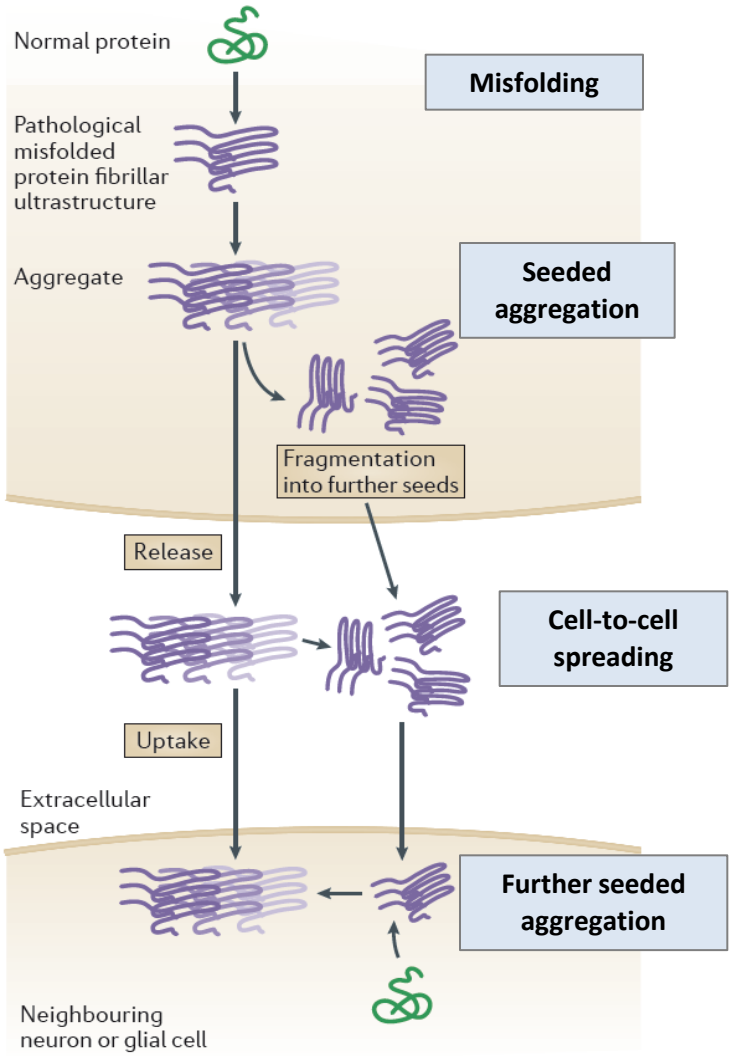
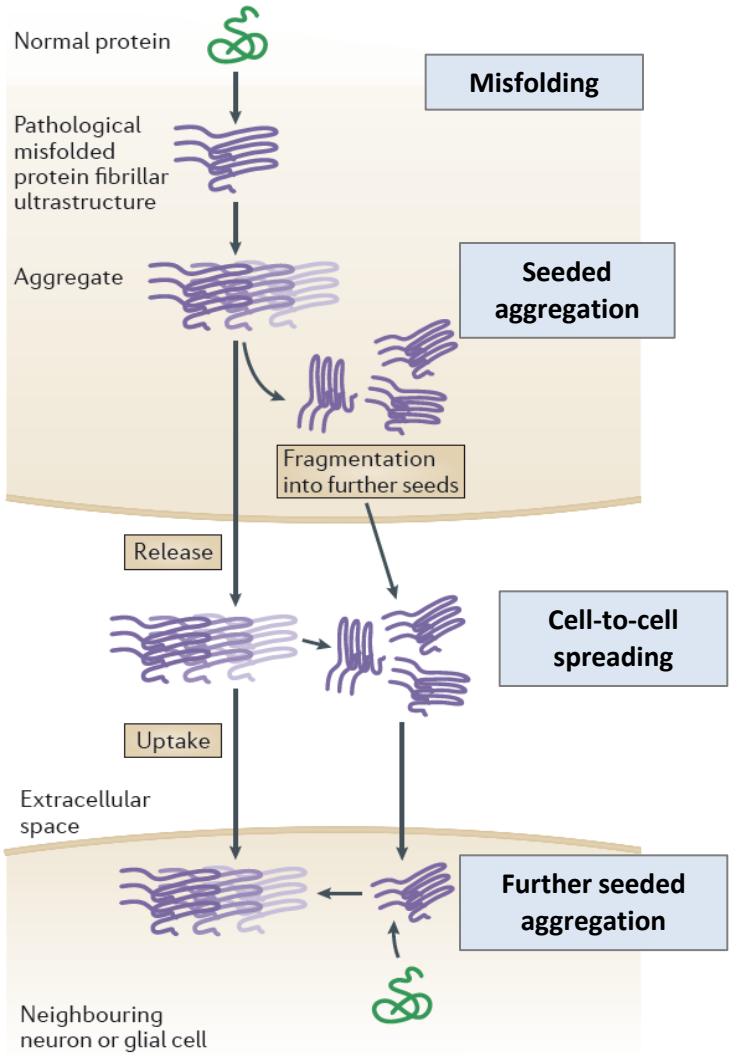
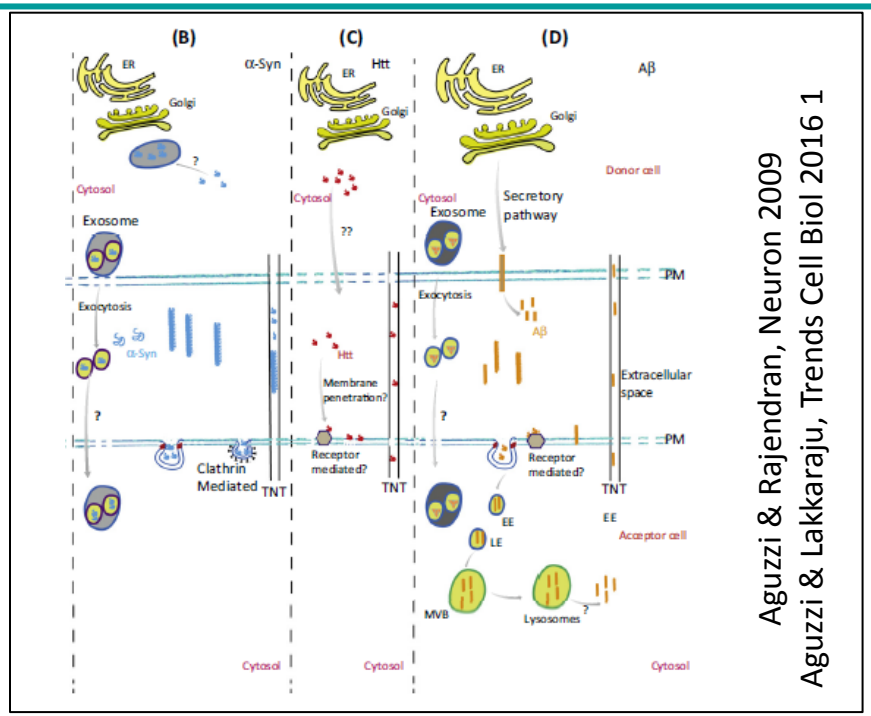


Brettschneider et al., Nature Reviews 2015

The Network-based Degeneration Hypothesis



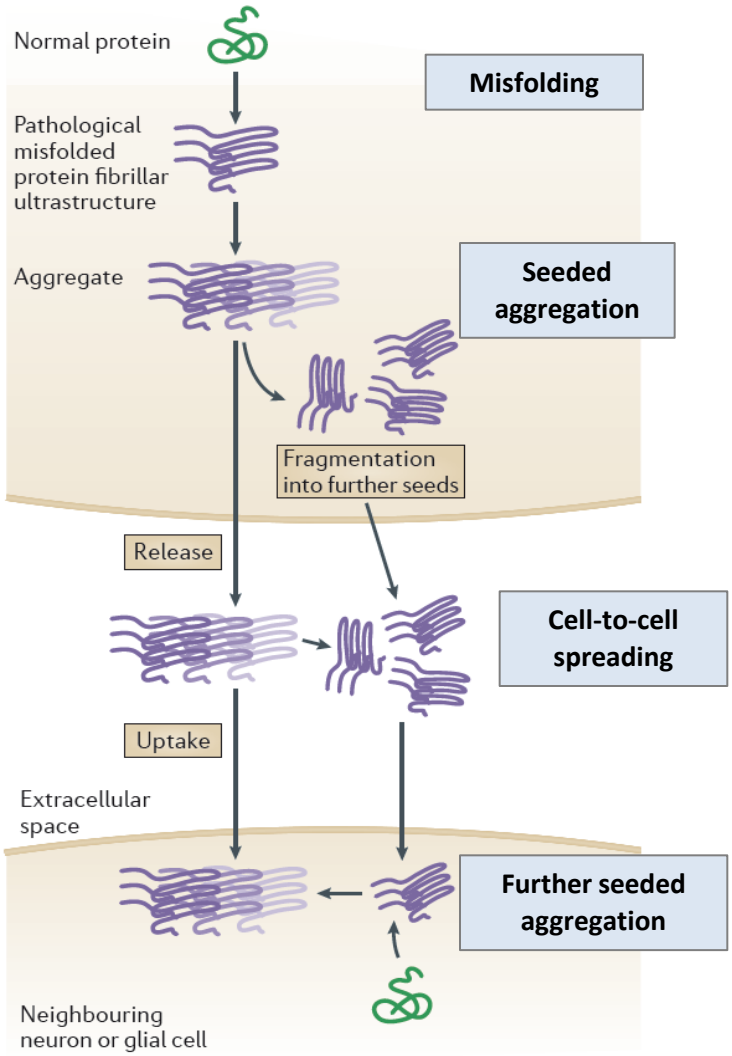
Brettschneider et al., Nature Reviews 2015



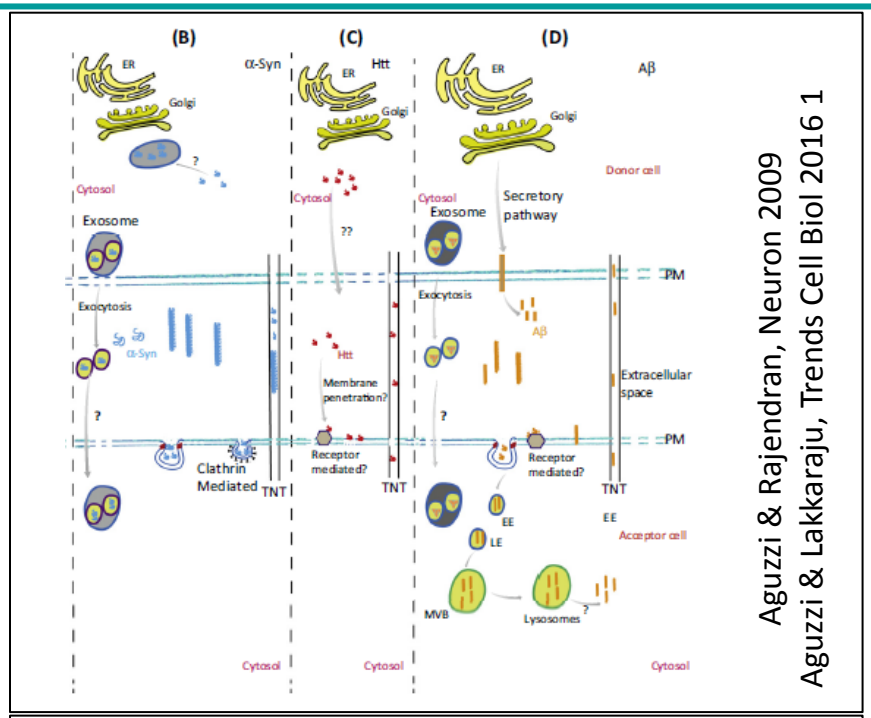
Aguzzi & Rajendran, Neuron 2009
Aguzzi & Lakkaraju, Trends Cell Biol 2016 1

The Network-based Degeneration Hypothesis

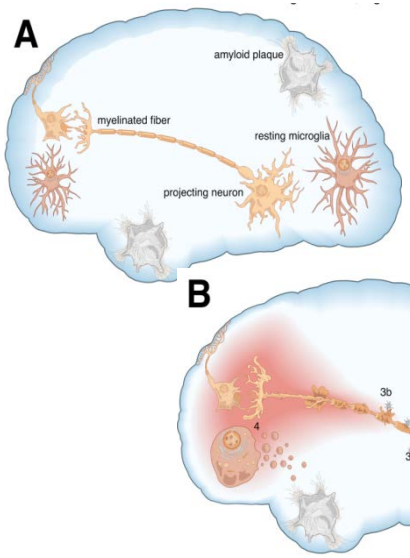
Neuron-to-neuron spreading



Brettschneider et al., Nature Reviews 2015



Aguzzi & Rajendran, Neuron 2009
Aguzzi & Lakkaraju, Trends Cell Biol 2016 1

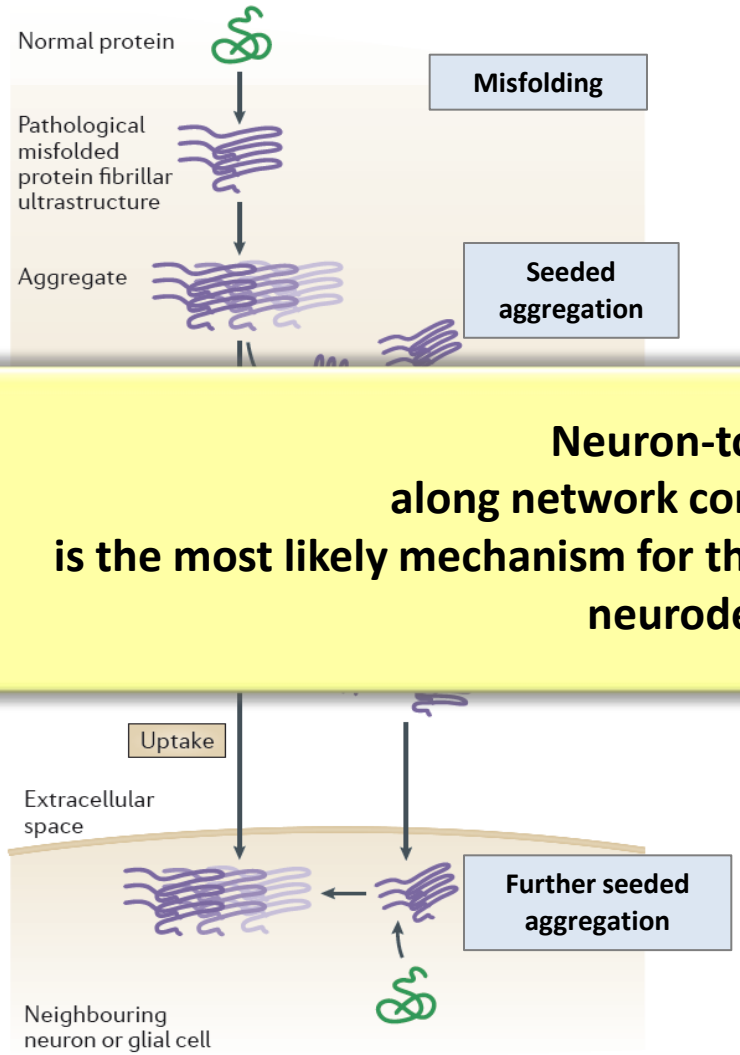


Agosta et al., Ann Neurol 2014

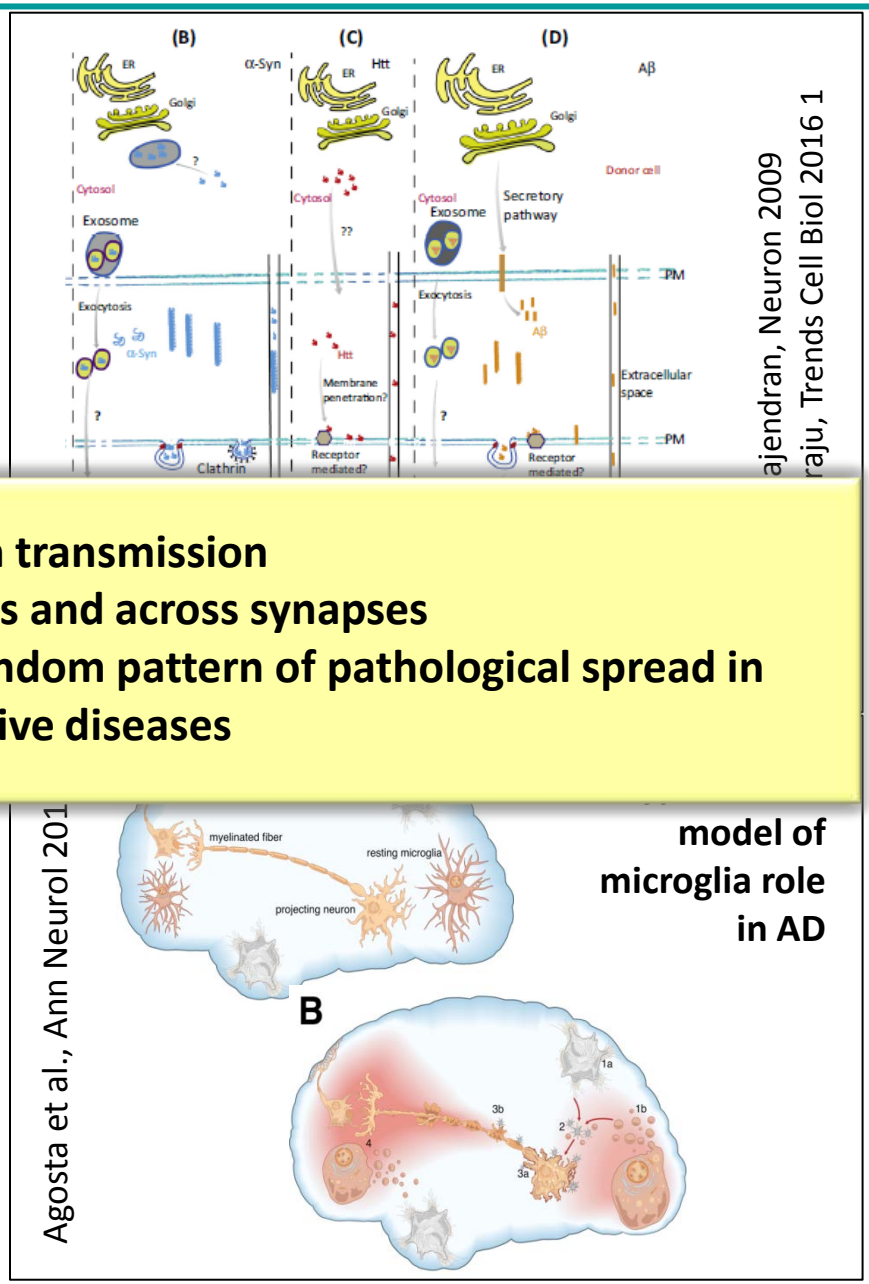
Hypothetical model of microglia role in AD

The Network-based Degeneration Hypothesis

Neuron-to-neuron spreading



Brettschneider et al., Nature Reviews 2015



ajendran, Neuron 2009
raju, Trends Cell Biol 2016 1

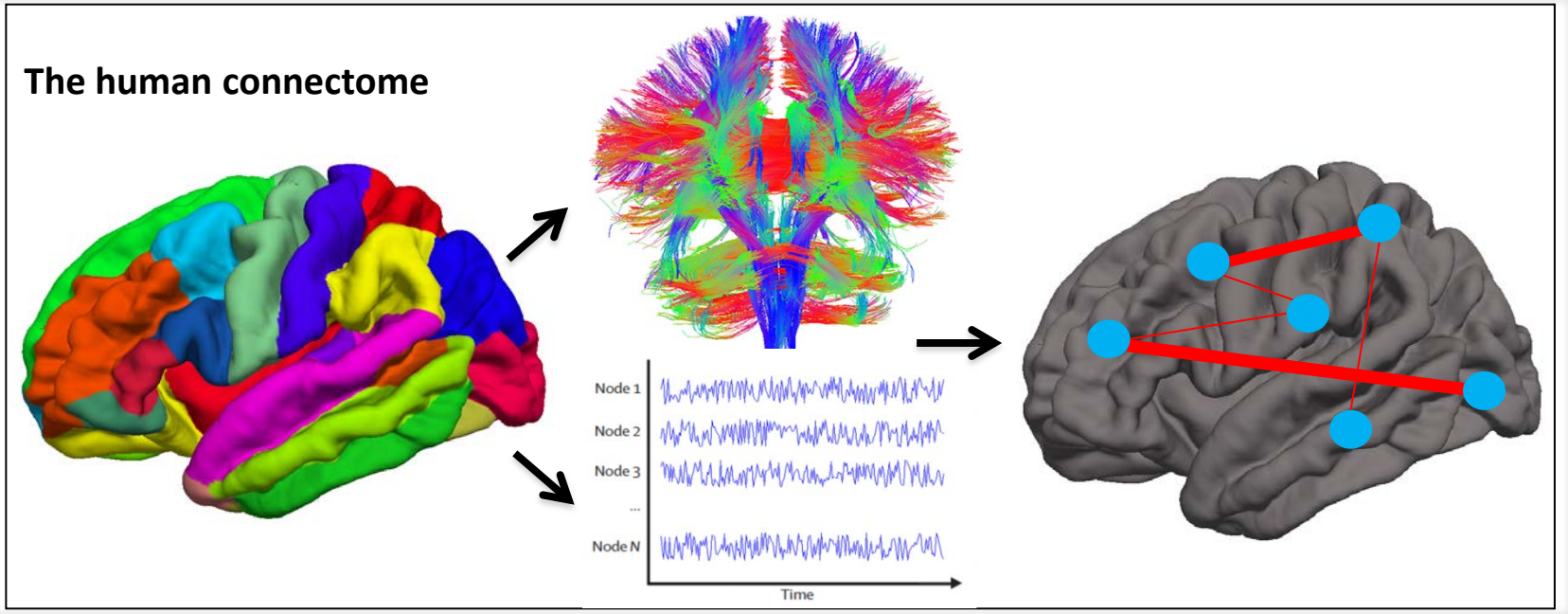
Neuron-to-neuron transmission
along network connections and across synapses
is the most likely mechanism for the nonrandom pattern of pathological spread in neurodegenerative diseases

Agosta et al., Ann Neurol 201

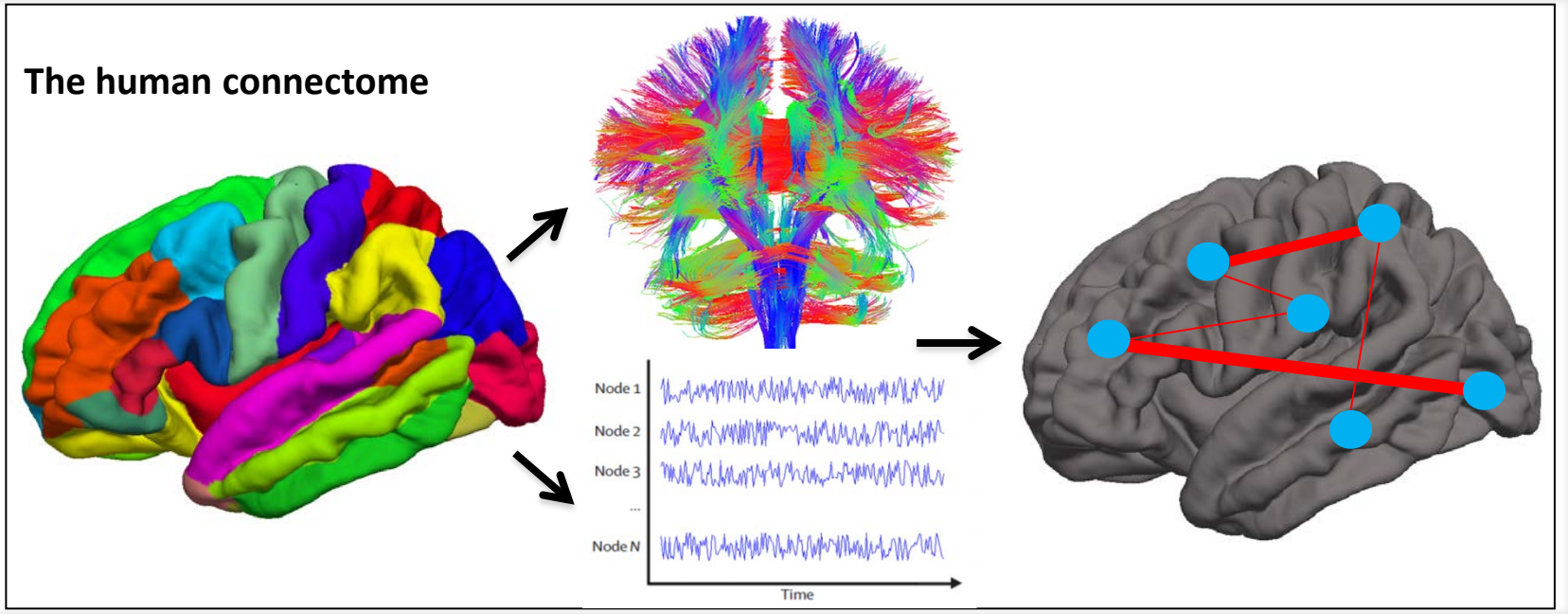
model of microglia role in AD

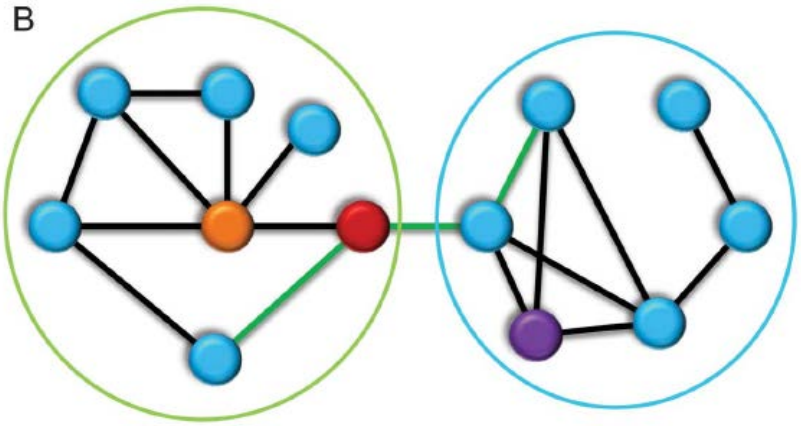
The Human Connectome: An innovative paradigm

The Human Connectome: An innovative paradigm



The Human Connectome: An innovative paradigm





Shortest path lenght

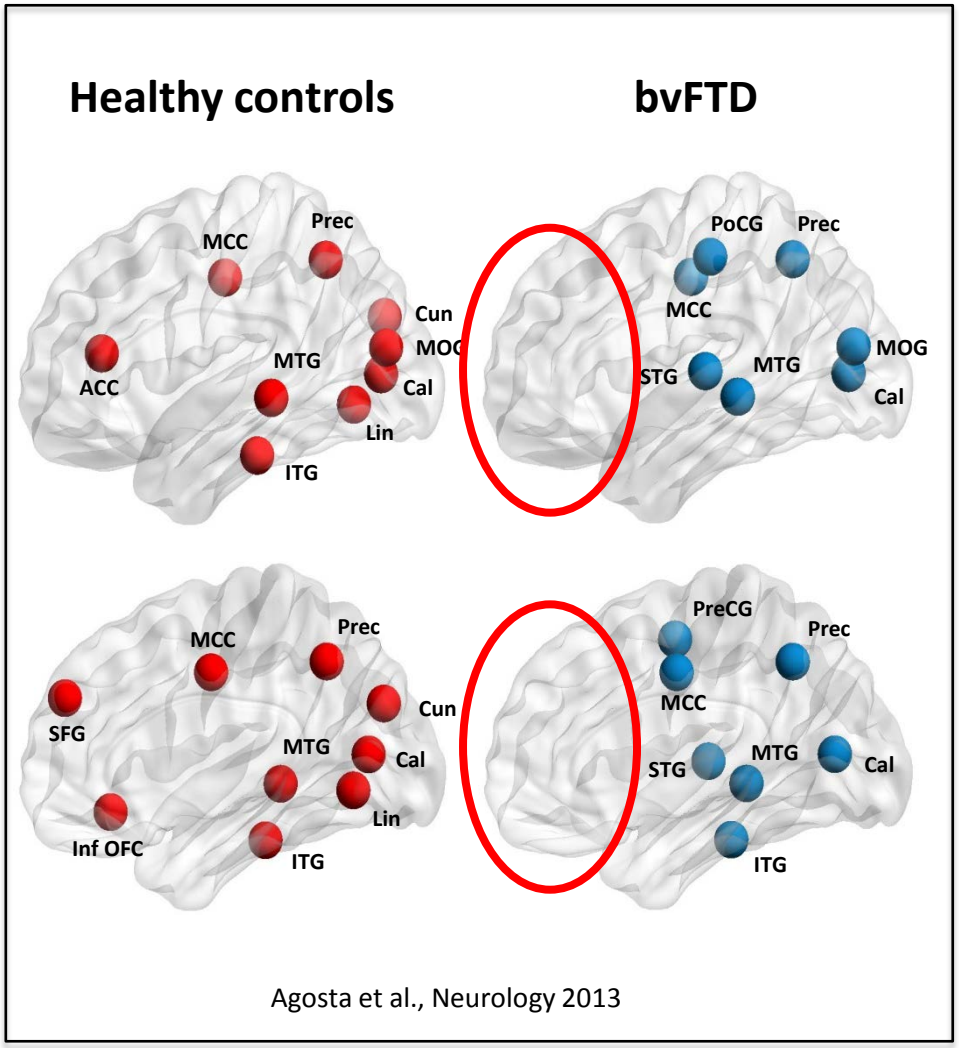
Highest degree

Connector hub

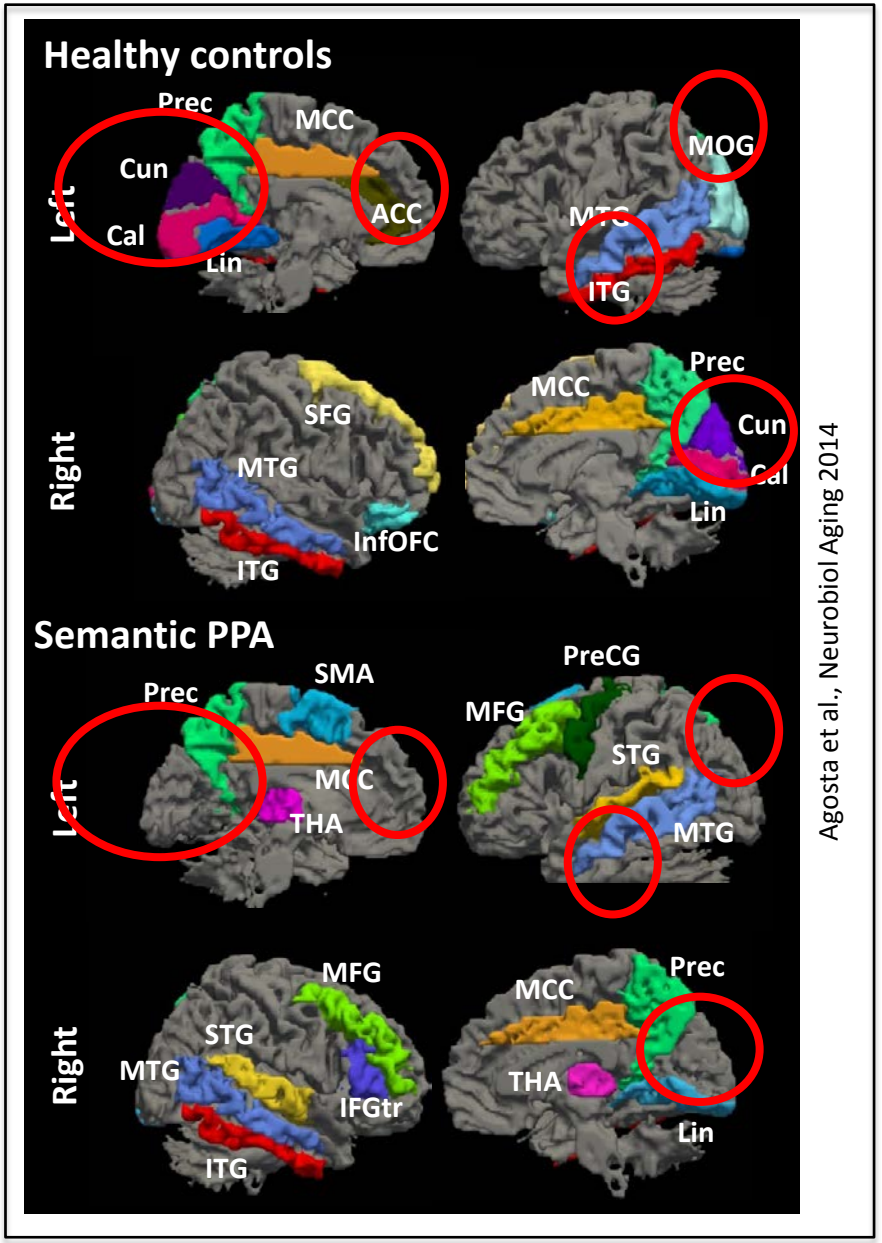
Highest clustering coefficient (its neighbors are all neighbors of each other)

The Human Connectome in FTD & ALS

The Human Connectome in FTD & ALS



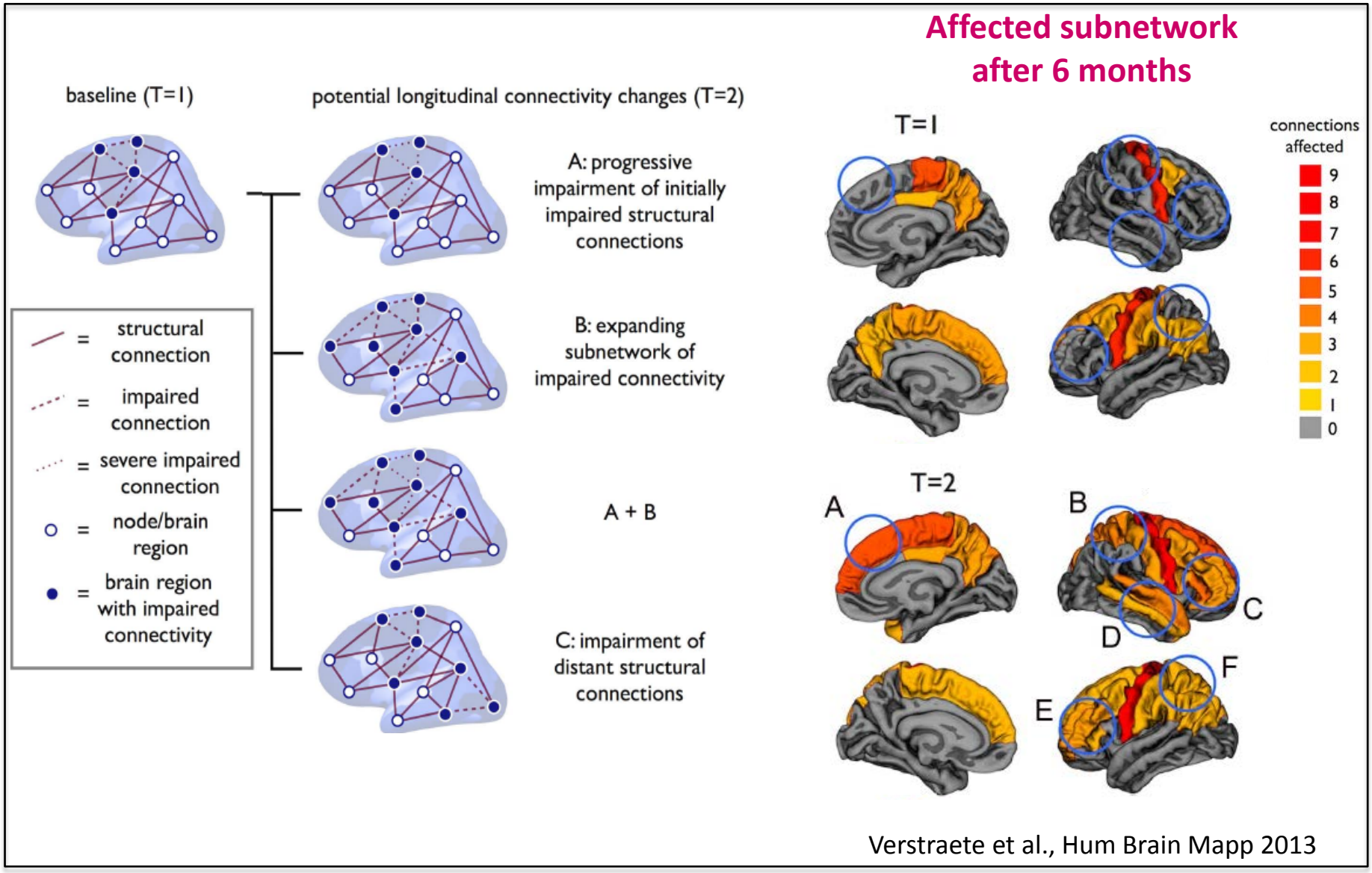
Agosta et al., Neurology 2013



Agosta et al., Neurobiol Aging 2014

The Human Connectome in FTD & ALS

The Human Connectome in FTD & ALS

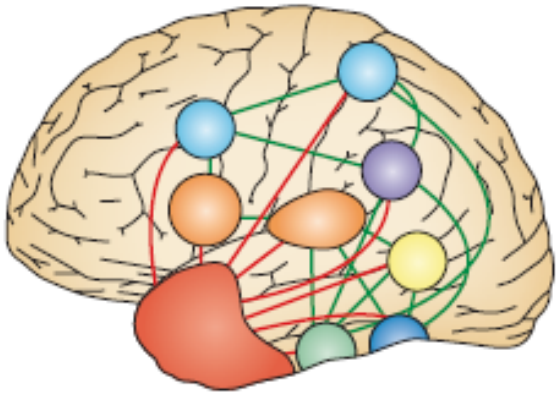


Verstraete et al., Hum Brain Mapp 2013

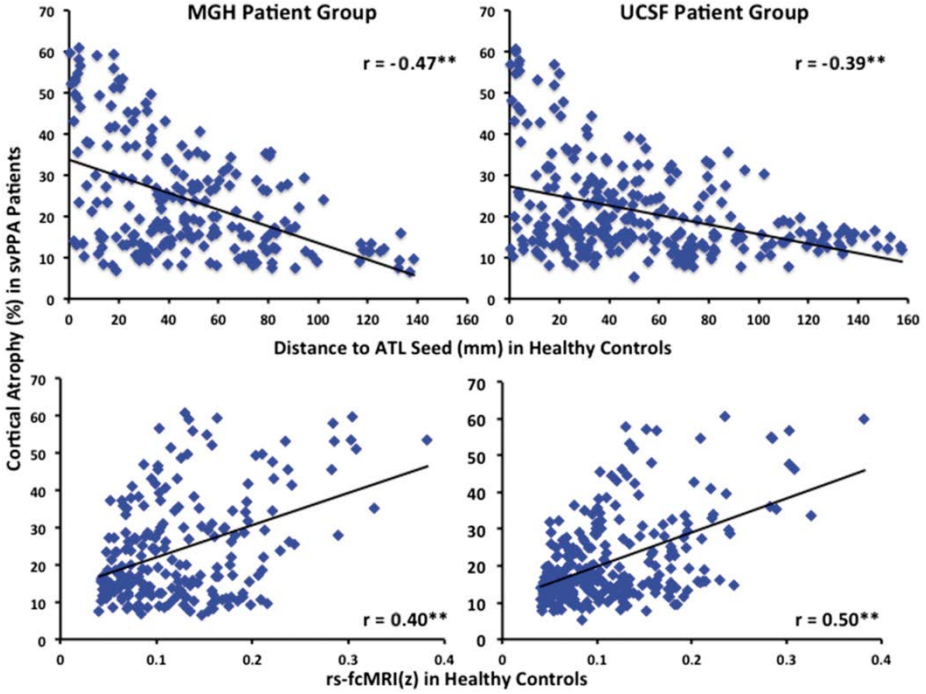
The Human Connectome in FTD & ALS

The Human Connectome in FTD & ALS

Semantic PPA



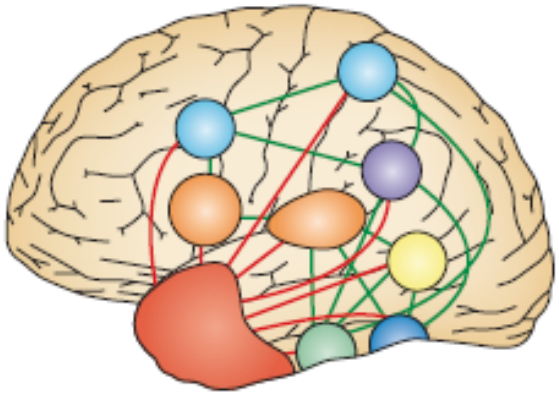
Patterson et al.
Nat Rev Neurosci 2007



Collins et al., Brain 2017

The Human Connectome in FTD & ALS

Semantic PPA



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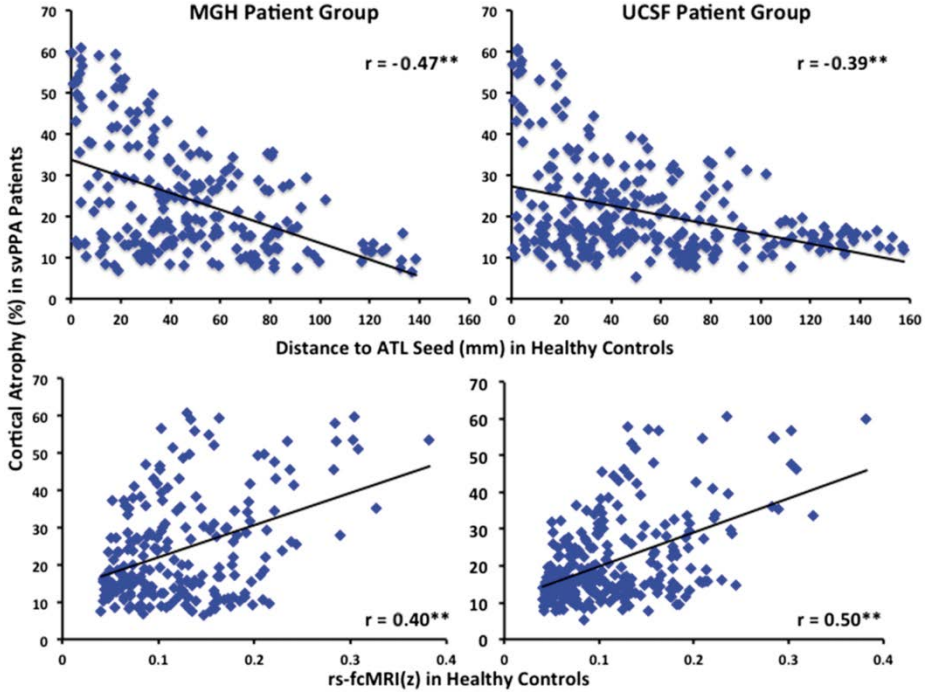
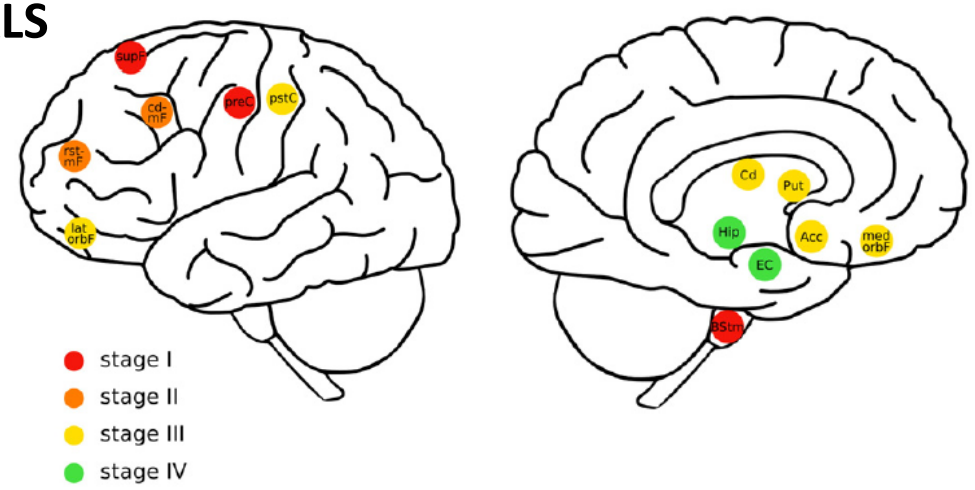
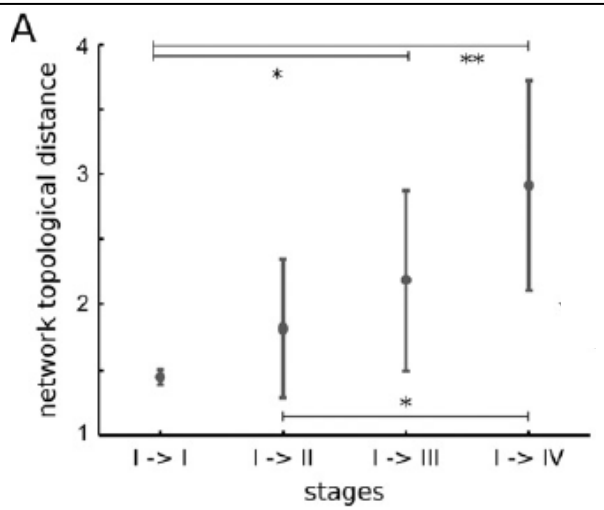


Collins et al., Brain 2017

ALS





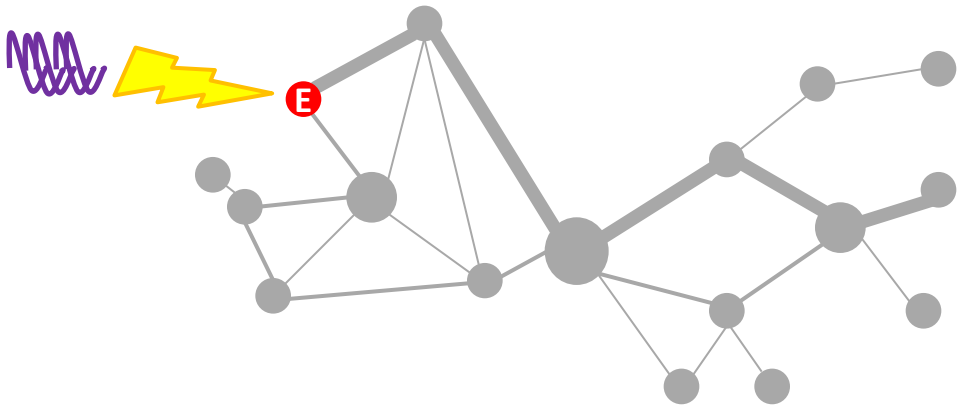
Schmidt et al., NeuroImage 2016

Tracking longitudinal changes (NeuroTRACK)

European Research Council

Tracking longitudinal changes (NeuroTRACK)

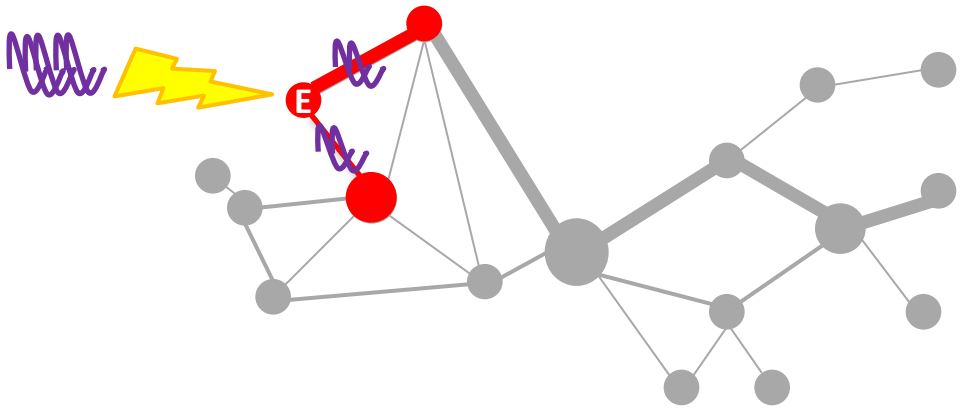
Pathological aggregates



Shortest path

Tracking longitudinal changes (NeuroTRACK)

Pathological aggregates



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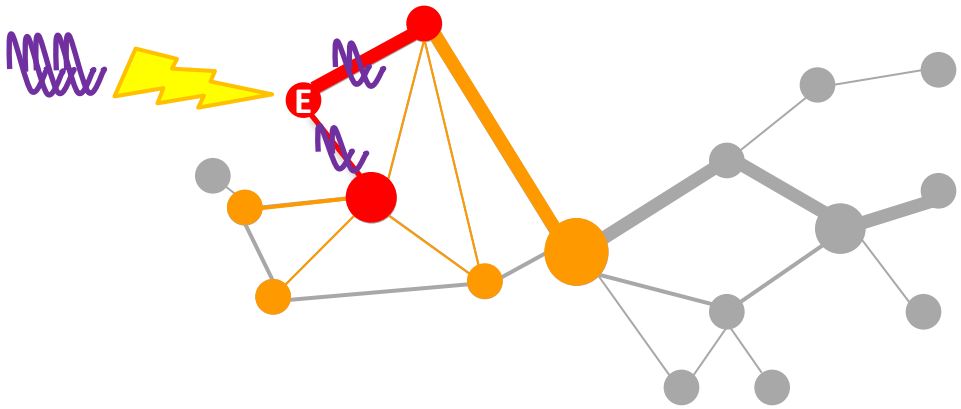
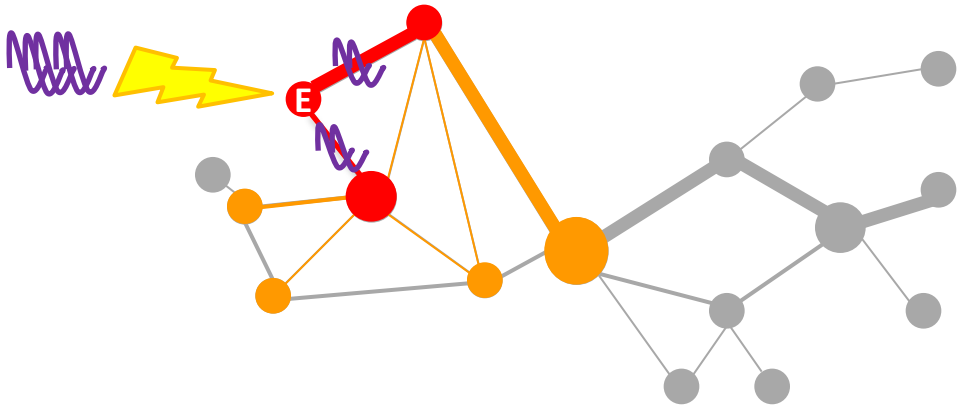


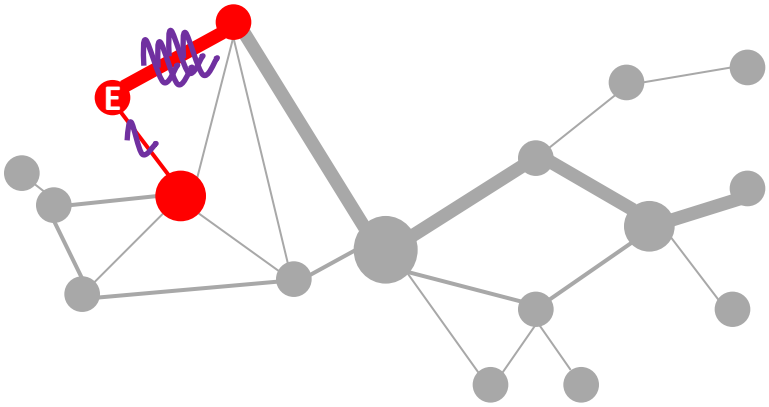
Shortest path

Tracking longitudinal changes (NeuroTRACK)

Pathological aggregates



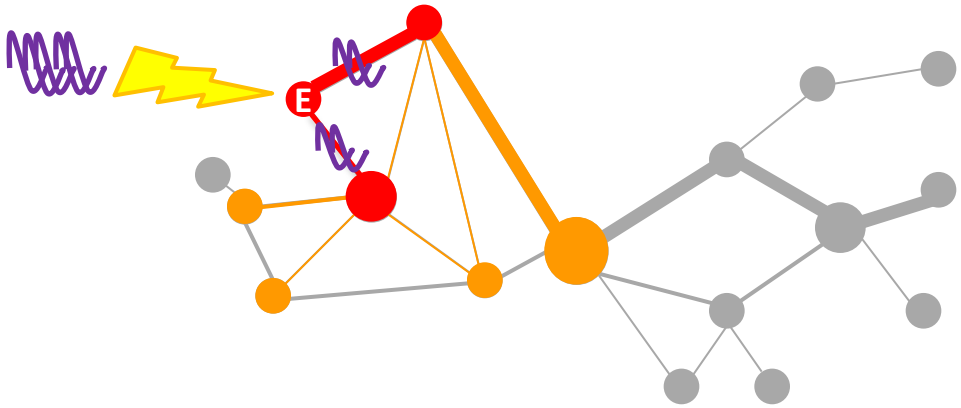
Shortest path



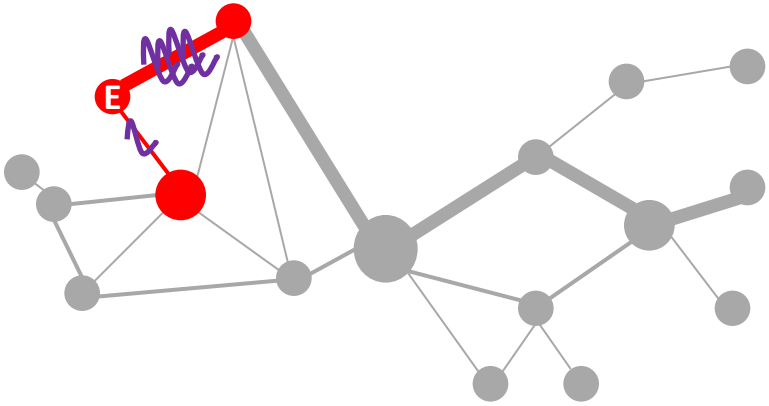
Connection strength

Tracking longitudinal changes (NeuroTRACK)

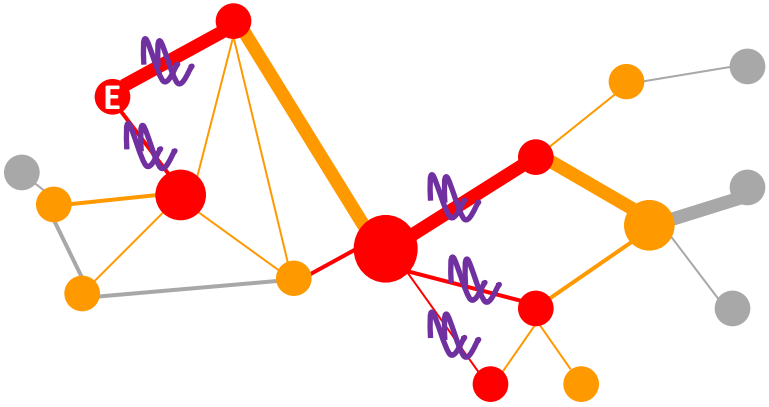
Pathological aggregates



Shortest path



Connection strength

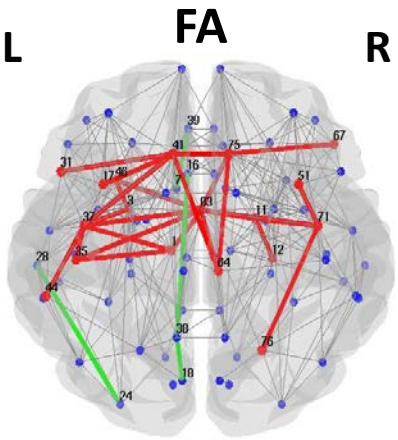


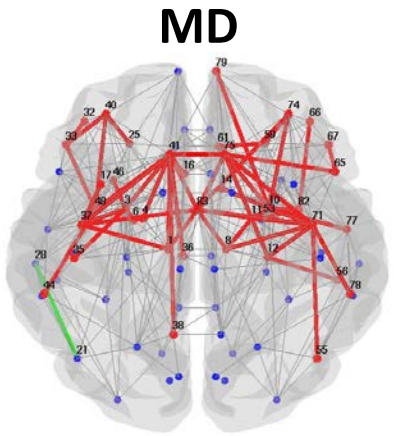
Connector hub

The Human Connectome in FTD & ALS

The Human Connectome in FTD & ALS

ALS *vs* HC



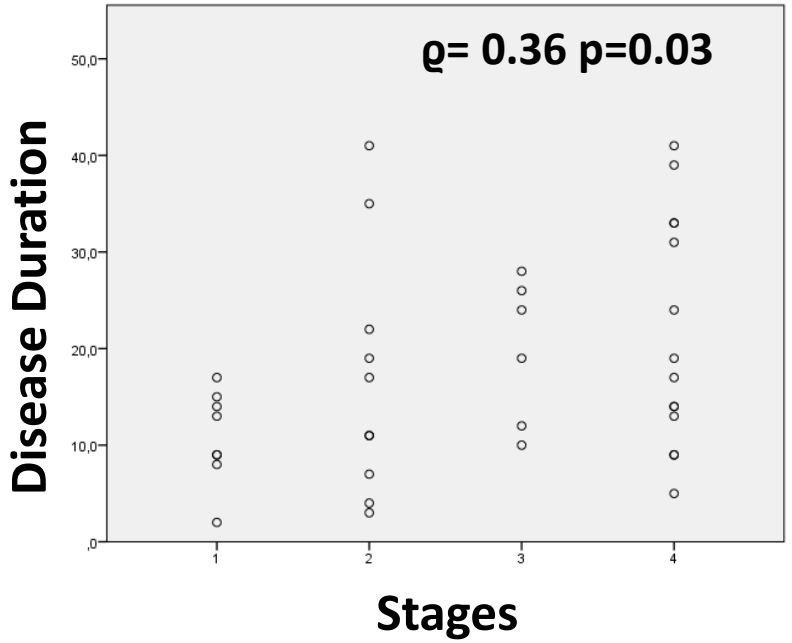


Principal connected component

Other affected components

$p<0.01_{\text{permuted t test}}$

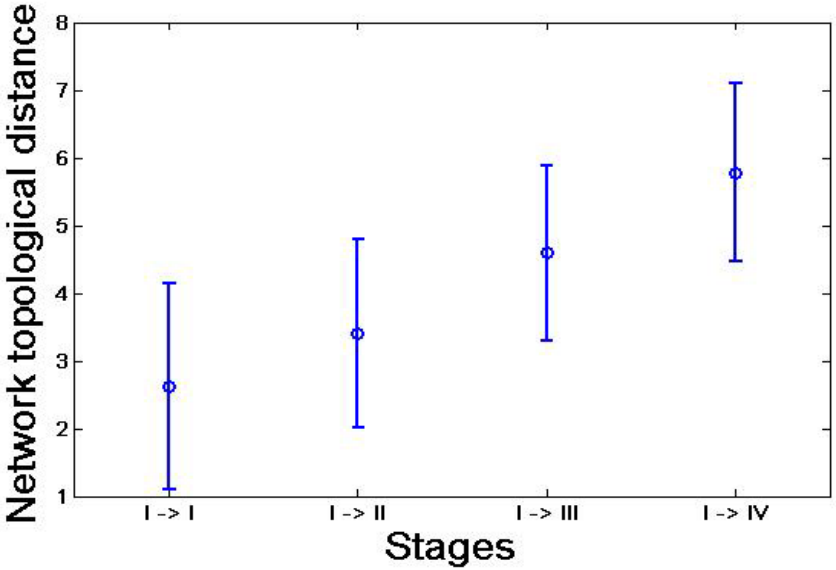
	Number of subjects
ALS stage 1	8
ALS stage 2	10
ALS stage 3	6
ALS stage 4	14
Σ	38



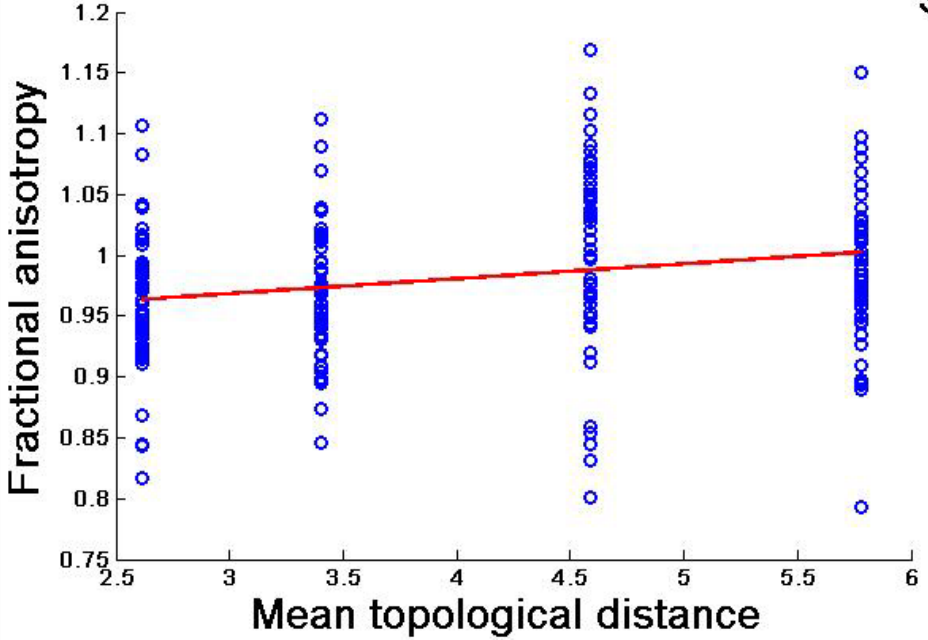
Basaia et al., AAN 2017

The Human Connectome in FTD & ALS

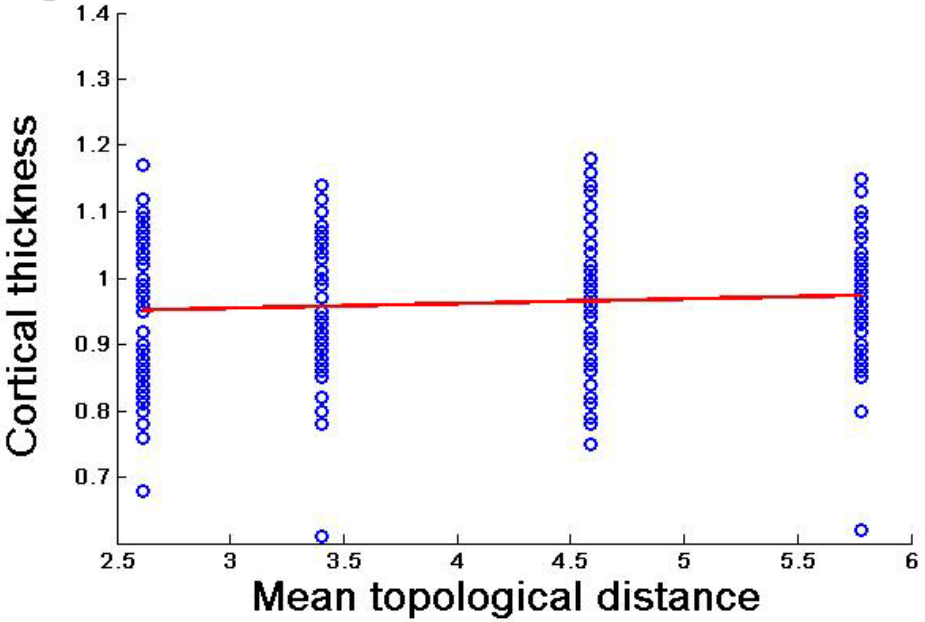
The Human Connectome in FTD & ALS



Basaia et al., AAN 2017



ρ= 0.23 p<0.001



ρ= 0.08 p=0.22

Conclusions

FROM A DISEASE *BURDEN…*

- ***"Young"*** onset (40-65 years)
- ***Treatments in development***
- ***Lack of reliable outcome measures***
- High healthcare ***costs***

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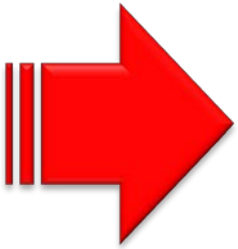

…TO A HIGH *GAIN*

- Novel, ***reliable markers*** for neurodegeneration prediction and monitoring
- ***(Preclinical)*** protein-based network degeneration patterns
- ***Personalized therapies***
- Investigations into ***other proteinopathies*** (Alzheimer's and Parkinson's Diseases)

OSPEDALE SAN RAFFAELE

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INSTITUTE OF EXPERIMENTAL NEUROLOGY

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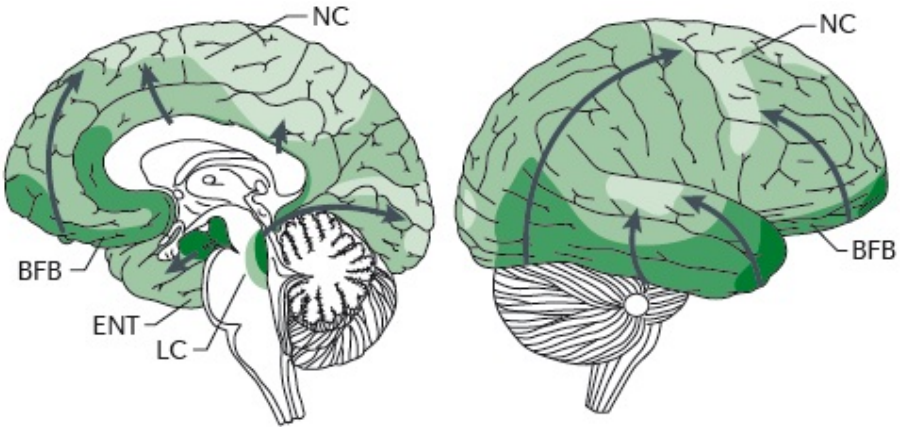
Alzheimer's Drug Discovery Foundation

AriSLA

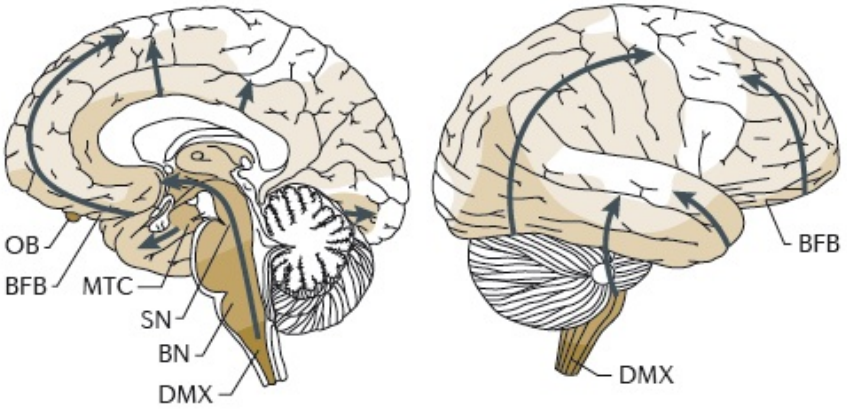
The network-based degeneration hypothesis

The network-based degeneration hypothesis

Alzheimer disease: Tau



Parkinson disease: α-synuclein



Amyotrophic lateral sclerosis: TDP-43