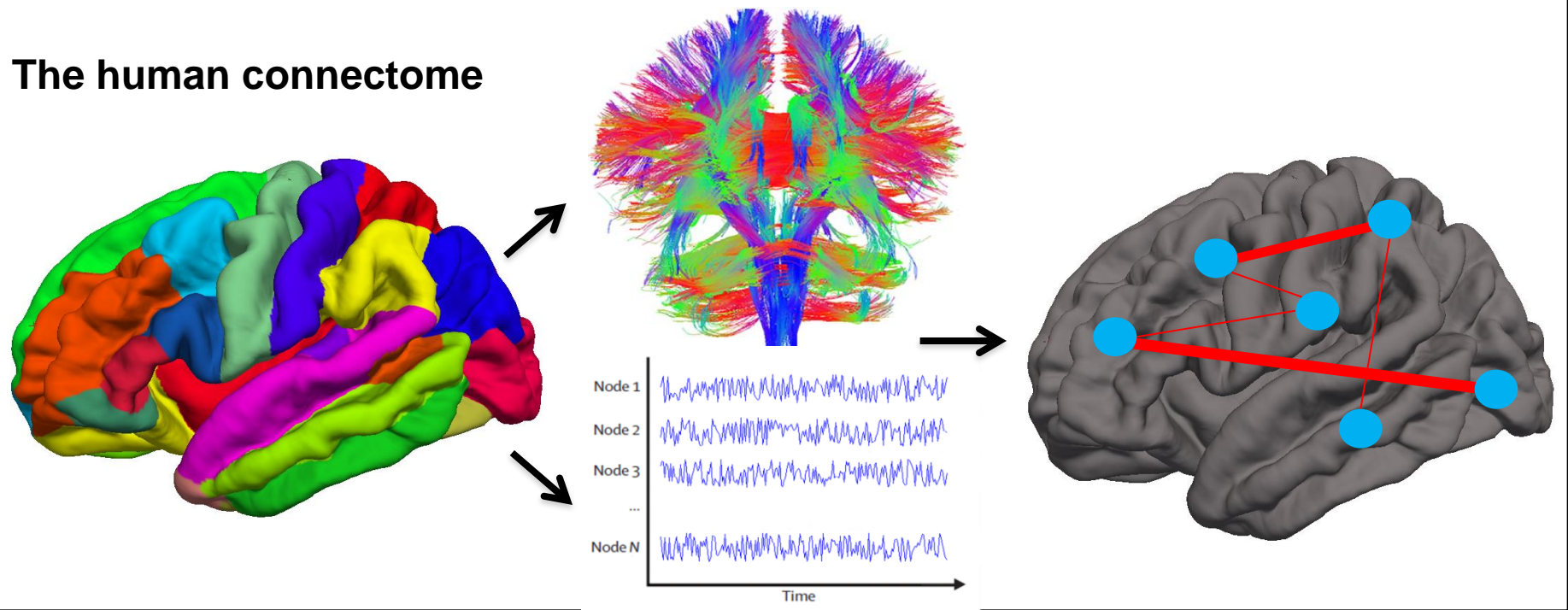# STRUCTURAL CONNECTIVITY

Federica Agosta

Neuroimaging Research Unit,
Institute of Experimental Neurology, Division of Neuroscience,
San Raffaele Scientific Institute, Vita-Salute San Raffaele University,
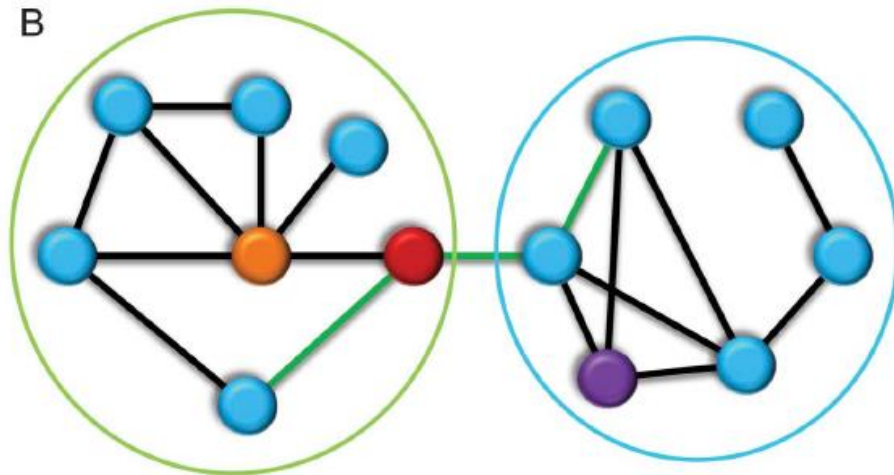Milan, Italy

STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome: An innovative paradigm

The human connectome

Node 1
Node 2
Node 3
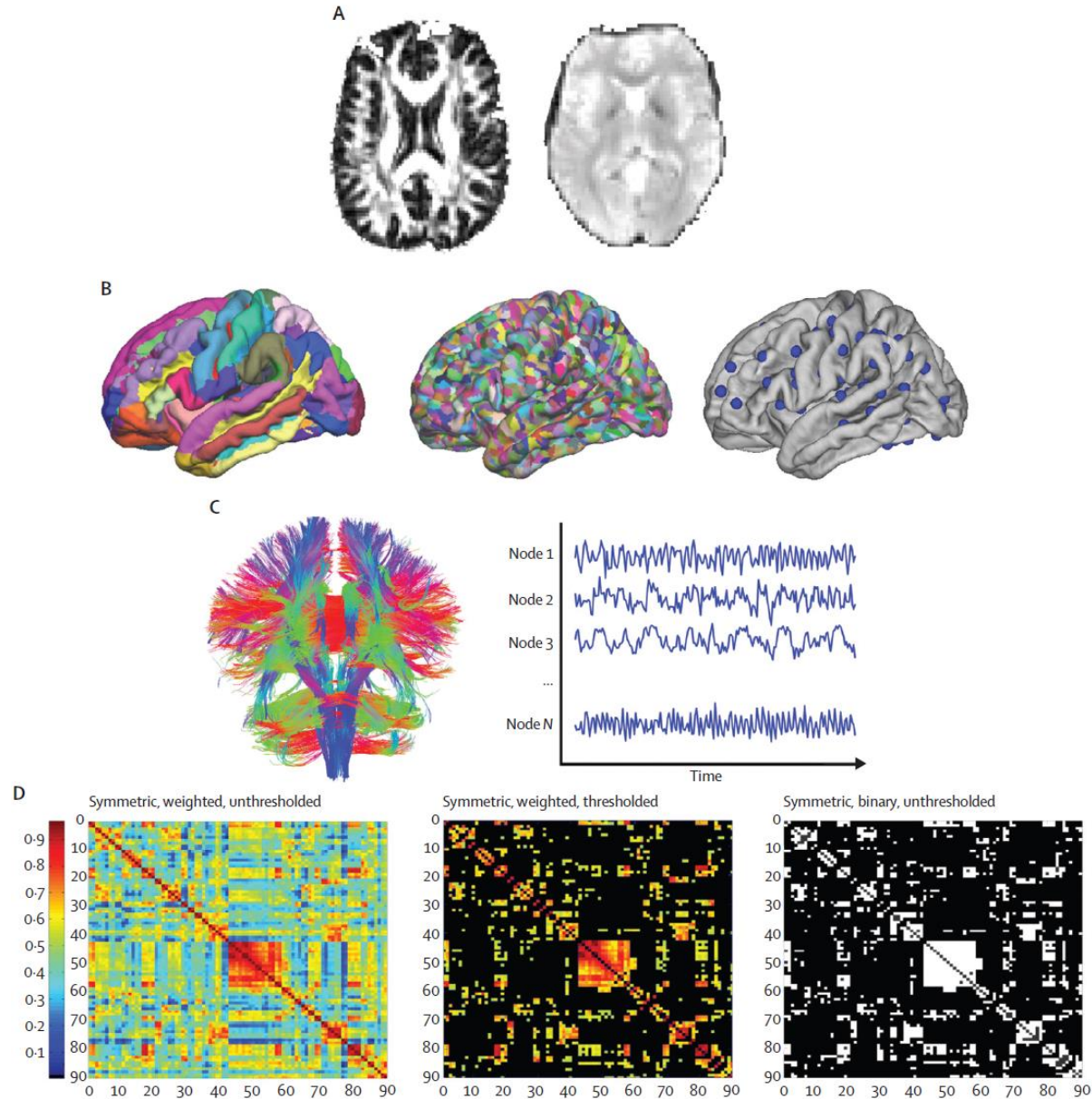...
Node N

Time

B

— Shortest path lenght

● Highest degree

● Connector hub

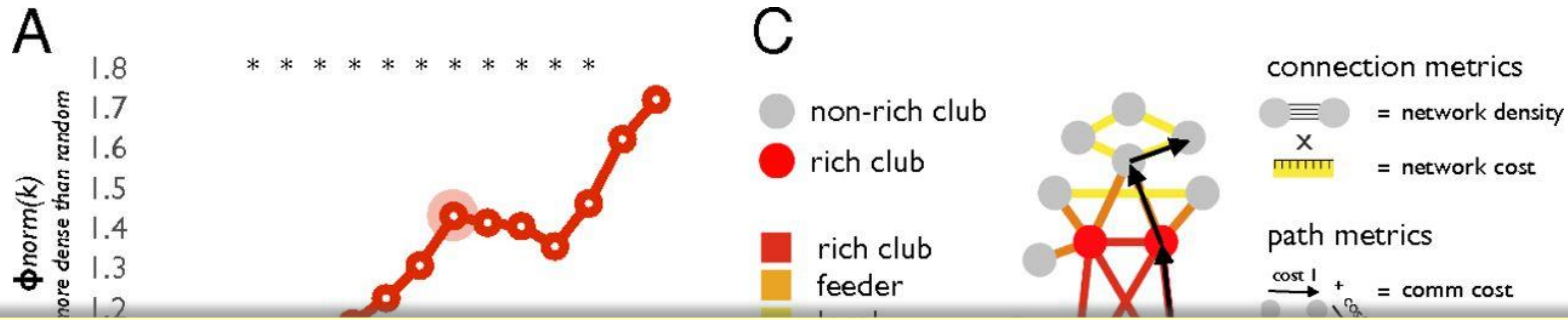● Highest clustering coefficient (its neighbors are all neighbors of each other)

STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome: An innovative paradigm

STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome: An innovative paradigm

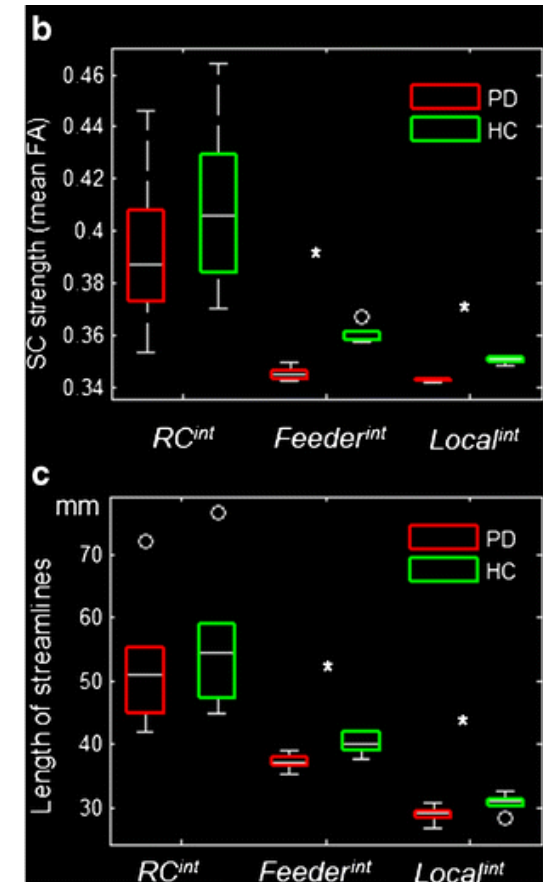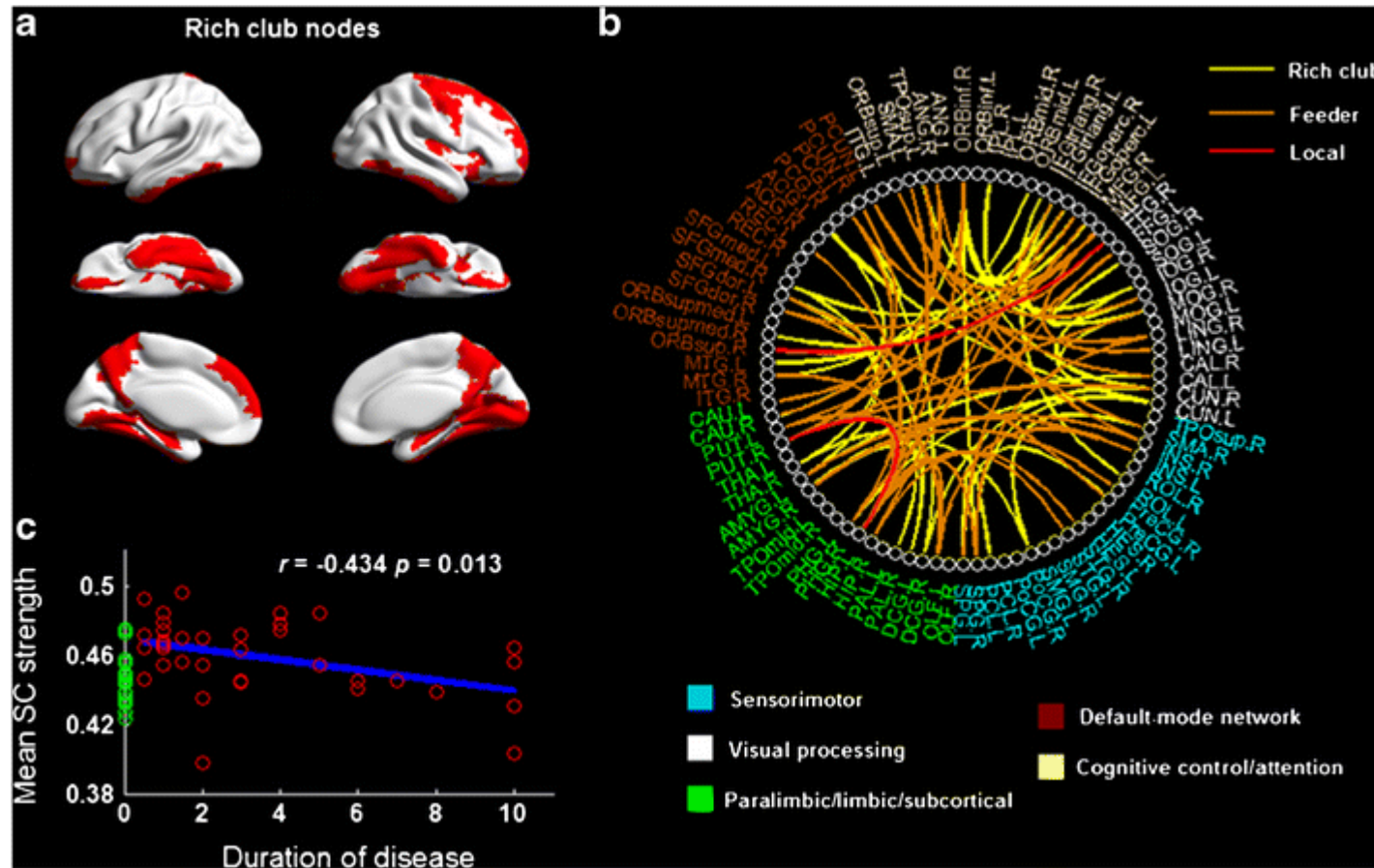**Human Connectome Project,
NIH Director Francis Collins, 2013:**
"Five years ago, this might have seemed out of reach. Five years from now, it will seem like we waited too late to take advantage of the opportunity."

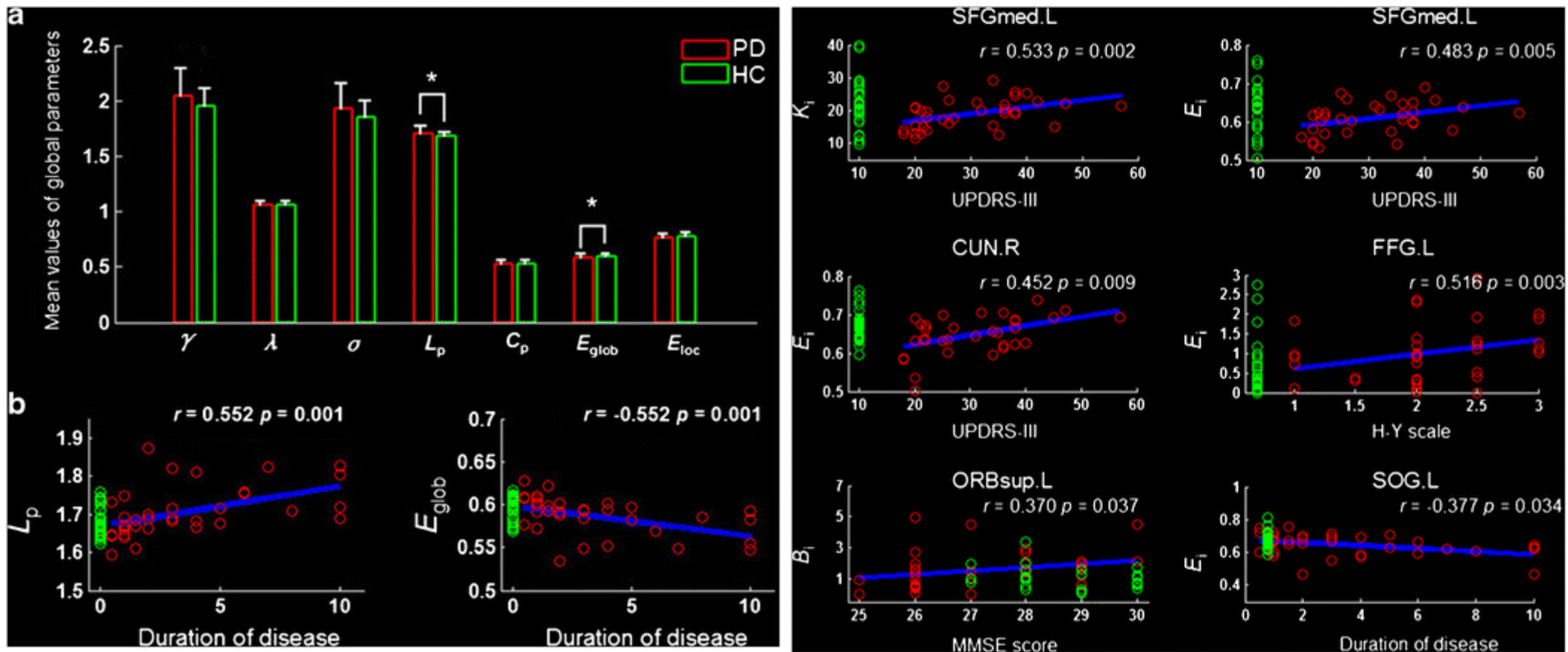# STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome in PD

Disrupted edge architecture

Li et al., Brain Imaging Behav 2016

STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome in PD

Altered network parameters

Li et al., Brain Imaging Behav 2016

STRUCTURAL CONNECTIVITY in PARKINSONISMS
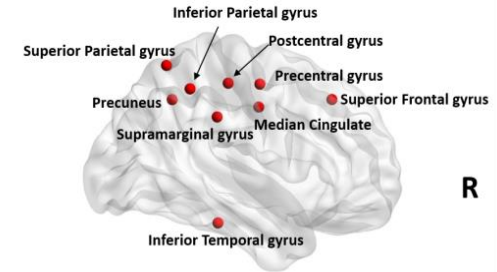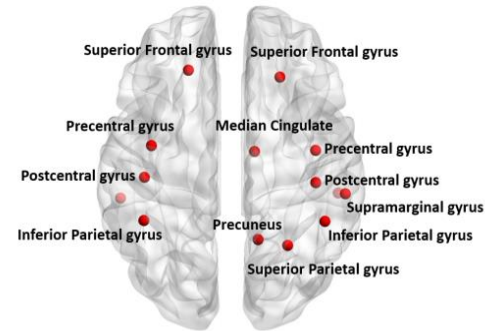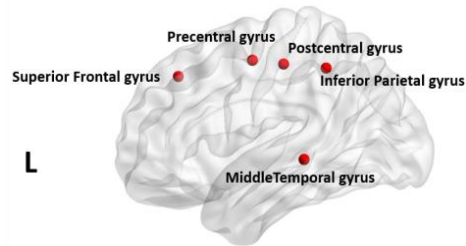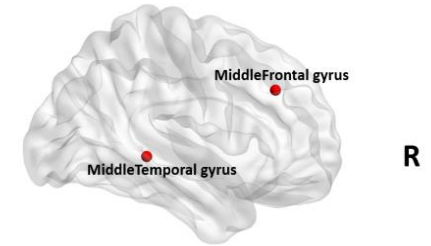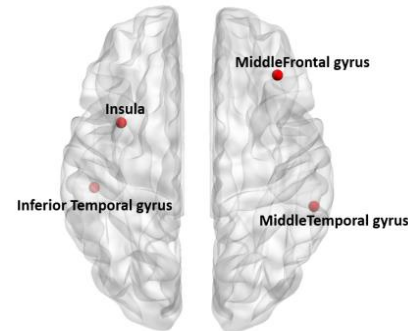## The Human Connectome in de novo PD

Brain hubs

Nigro et al., Hum Brain Mapp 2016
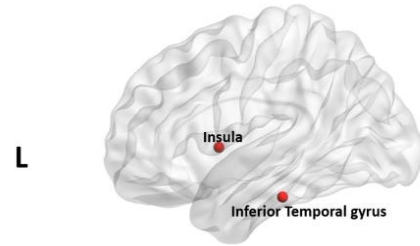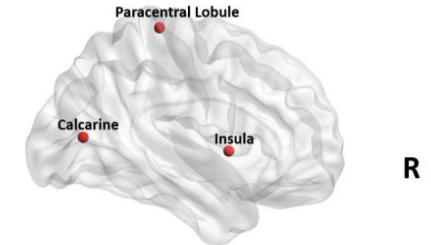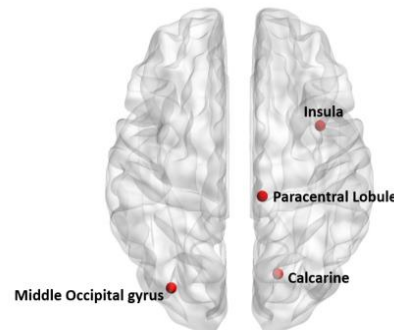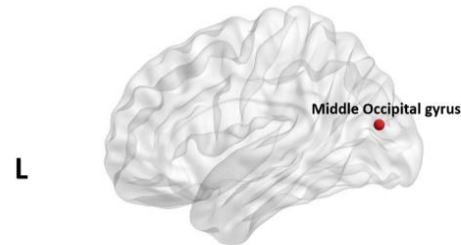
STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome in de novo PD

TABLE II. Main effect of group in the global network metrics

	HC	De novo PD	t value	P value (FDR-corrected)	Cohen's d
Global clustering	0.04 (0.005)	0.03 (0.004)	$t_{(49)} = 2.96$	0.023	0.84
Global efficiency	0.06 (0.01)	0.05 (0.01)	$t_{(49)} = 2.55$	0.026	0.73
global strength	1.13 (0.15)	1.03 (0.12)	$t_{(49)} = 2.51$	0.026	0.72
Characteristic path length	24.49 (4.27)	26.87 (3.77)	$t_{(49)} = -2.05$	0.09	0.59
Density	0.14 (0.01)	0.14 (0.01)	$t_{(49)} = 1.75$	0.10	0.5

De novo PD patients displayed a reduced global clustering, global efficiency and global strength in comparison to healthy controls. Data are expressed as mean (SD). No main effect of group was found in the characteristic path length and density. HC, Healthy controls; de novo PD, De novo PD patients; SD, standard deviation.

↓ **Strength**   ↓ **Clustering**   ↓ **Efficiency**   ↓ **Eigenvector centrality**
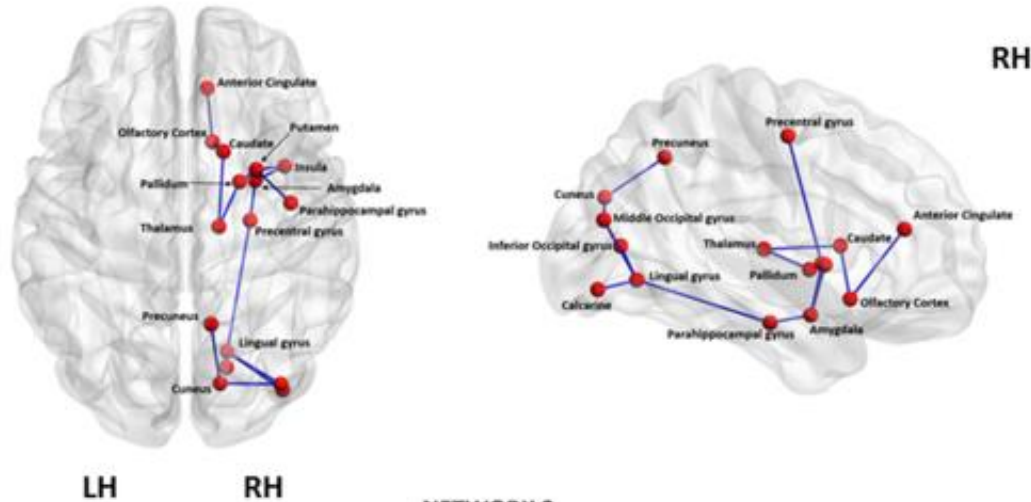
Nigro et al., Hum Brain Mapp 2016
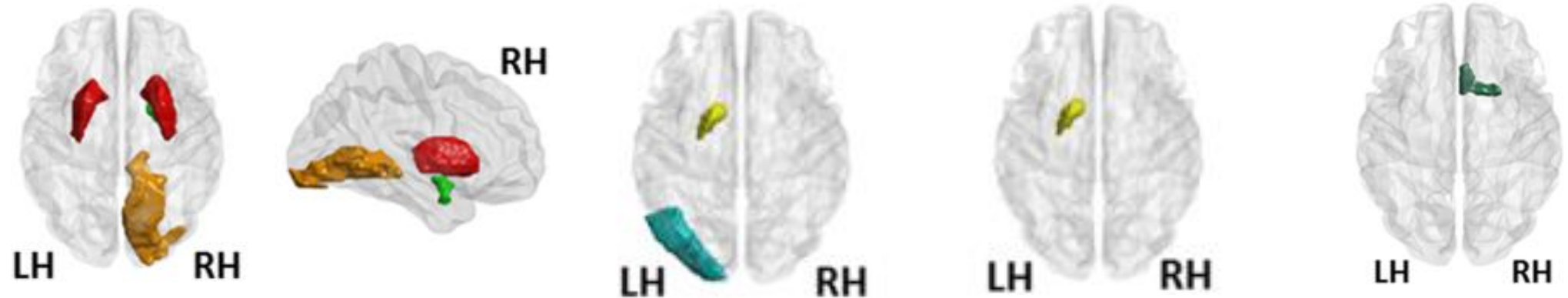
STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome in de novo PD

Reduced FA

Limbic system, basal ganglia and sensorimotor areas
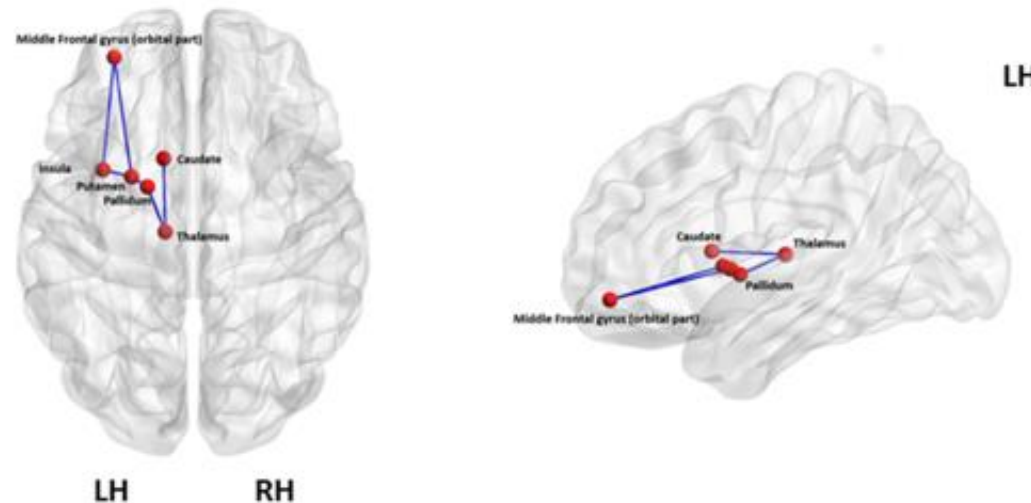
Basal ganglia, insula, orbital frontal areas

Nigro et al., Hum Brain Mapp 2016

STRUCTURAL CONNECTIVITY in PARKINSONISMS
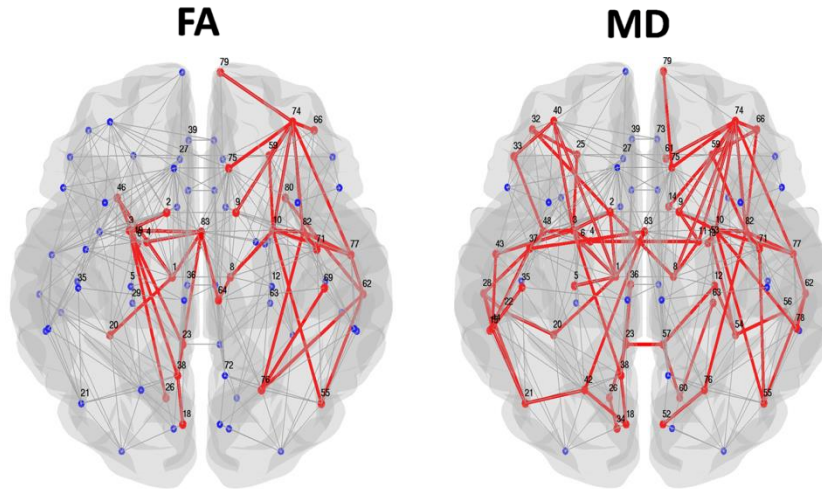## The Human Connectome in PD with cognitive impairment

Connectivity Matrix Type	Control Subjects	Patients with PD with MCI	Patients with PD without MCI	P Value for Patients with PD and MCI vs Control Subjects	P Values for Matched Patients with PD without MCI vs Control Subjects	P Values for Patients with PD and MCI vs Matched Patients with PD without MCI
Betweenness centrality						
FA	145.88 ± 6.34	149.68 ± 7.88	148.64 ± 7.37	.03	.05	.62
MD	138.82 ± 4.82	142.02 ± 5.61	140.48 ± 5.68	.01	.11	.11
Degree	9.65 ± 0.37	9.44 ± 0.38	9.54 ± 0.37	.02	.16	.16
Clustering coefficient						
FA	0.25 ± 0.01	0.24 ± 0.01	0.25 ± 0.01	.02	.60	.05
MD	$7.11 \times 10^{-4} \pm 3.02 \times 10^{-5}$	$7.37 \times 10^{-4} \pm 4.33 \times 10^{-5}$	$7.18 \times 10^{-4} \pm 3.86 \times 10^{-5}$	.002	.52	.02
Assortativity						
FA	0.13 ± 0.04	0.15 ± 0.05	0.13 ± 0.05	.02	.61	.005
MD	0.06 ± 0.04	0.07 ± 0.04	0.05 ± 0.04	.06	.03	.03
Density	0.1298 ± 0.004	0.1273 ± 0.004	0.1286 ± 0.005	.02	.16	.16
Global efficiency						
FA	0.1642 ± 0.006	0.1578 ± 0.010	0.1616 ± 0.008	<.001	.35	.01
MD	$4.17 \times 10^{-4} \pm 1.91 \times 10^{-5}$	$4.25 \times 10^{-4} \pm 2.44 \times 10^{-5}$	$4.16 \times 10^{-4} \pm 1.68 \times 10^{-5}$	.12	.67	.08
Path length	2.66 ± 0.06	2.69 ± 0.07	2.68 ± 0.07	.01	.14	.16
Small worldness						
FA	5.05 ± 0.78	5.17 ± 0.65	5.06 ± 0.57	.21	.67	.48
MD	5.13 ± 0.54	5.33 ± 0.60	5.29 ± 0.66	.08	.22	.35

STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome in PD with cognitive impairment
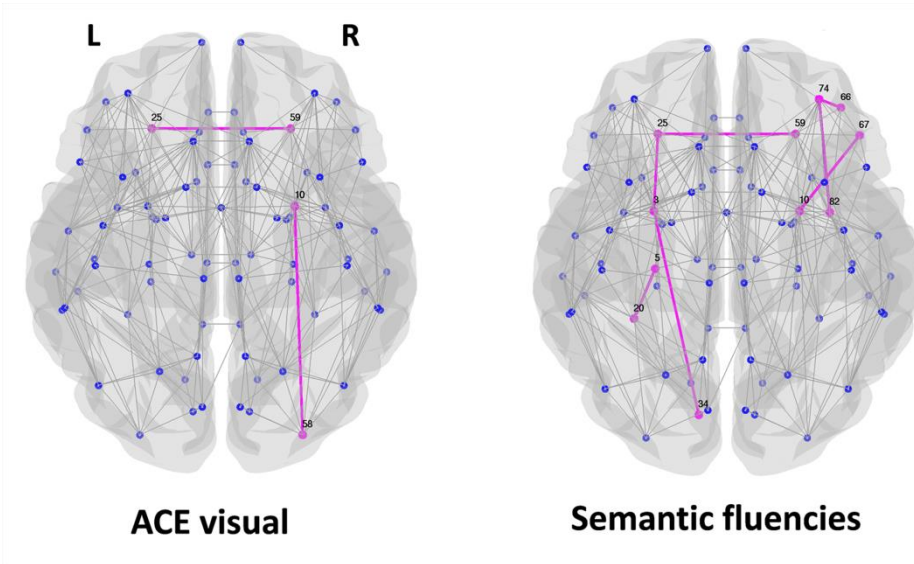
Altered structural connections
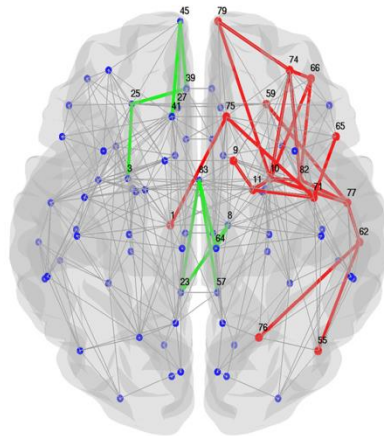
Decreased FA *vs* cognitive deficits

PD-MCI *vs* controls

FA

MD

L

R

ACE visual

Semantic fluencies

PD-MCI *vs* PD-noMCI

●—● Principal connected component
●—● Other affected components

Adjusting for UPDRS III

FA

L

R

Galantucci et al., Radiology 2017
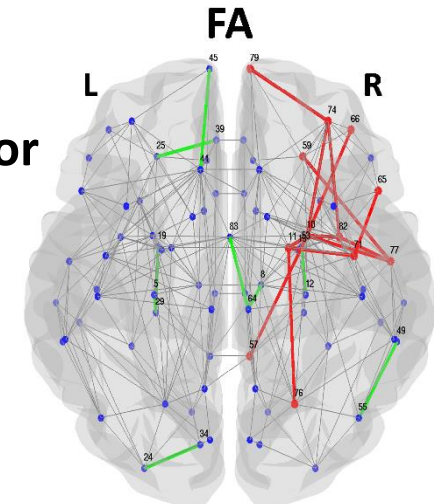
STRUCTURAL CONNECTIVITY in PARKINSONISMS
Genetic dystonia

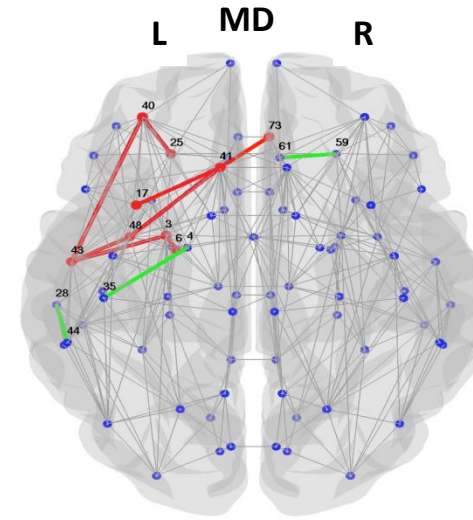### Altered cerebellothalamocortical connectivity

Argyelan et al., J Neurosci 2009
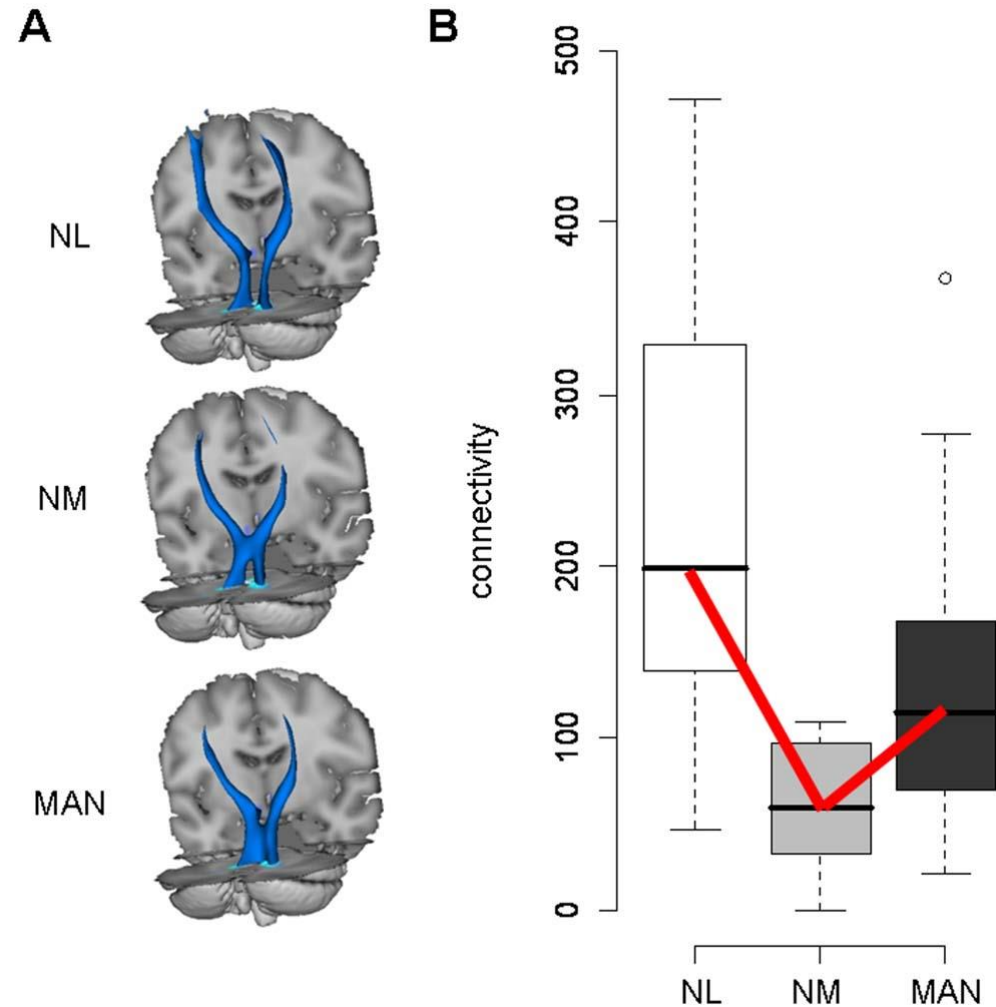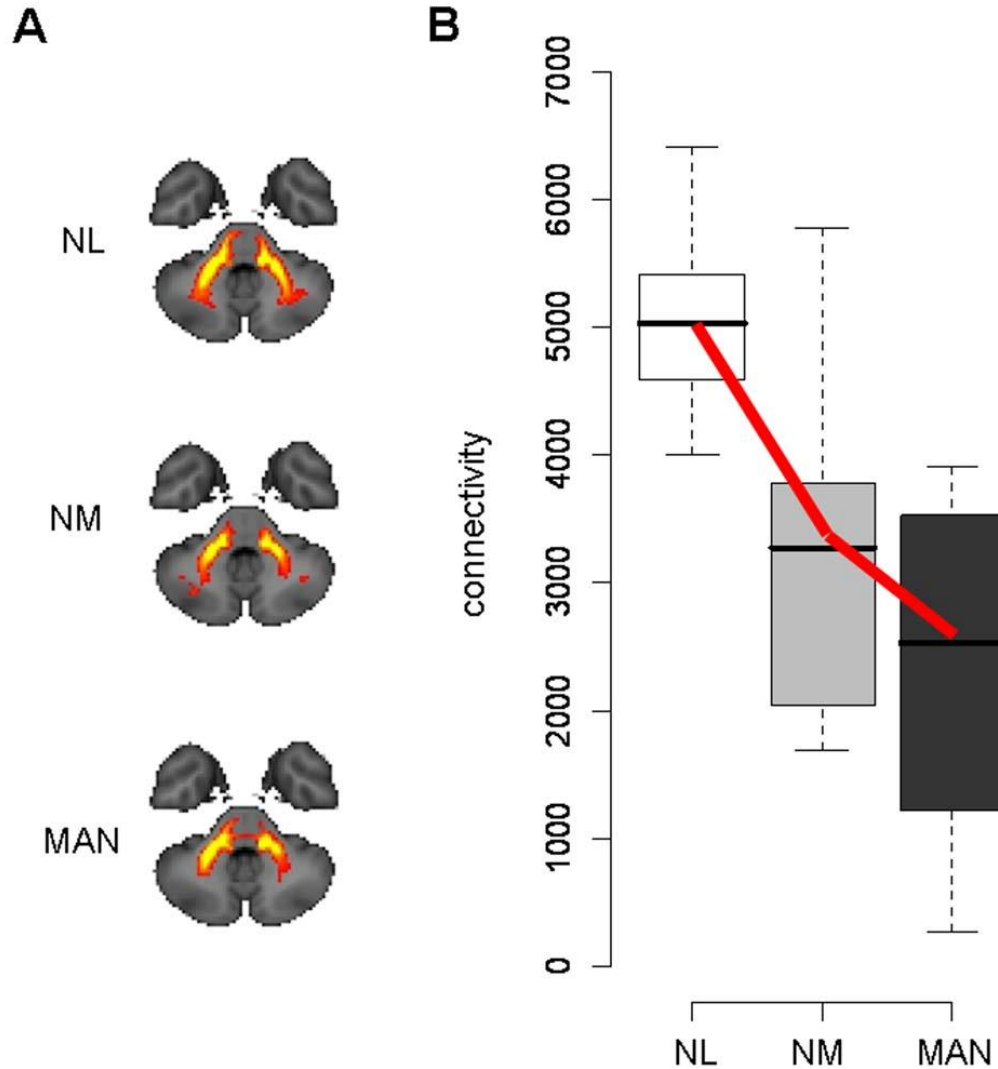
STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome in genetic dystonia

Symptomatic DYT carriers *vs* controls

Asymptomatic DYT carriers *vs* controls

— Principal connected component
— Other affected components

M. Filippi et al., unpublished data
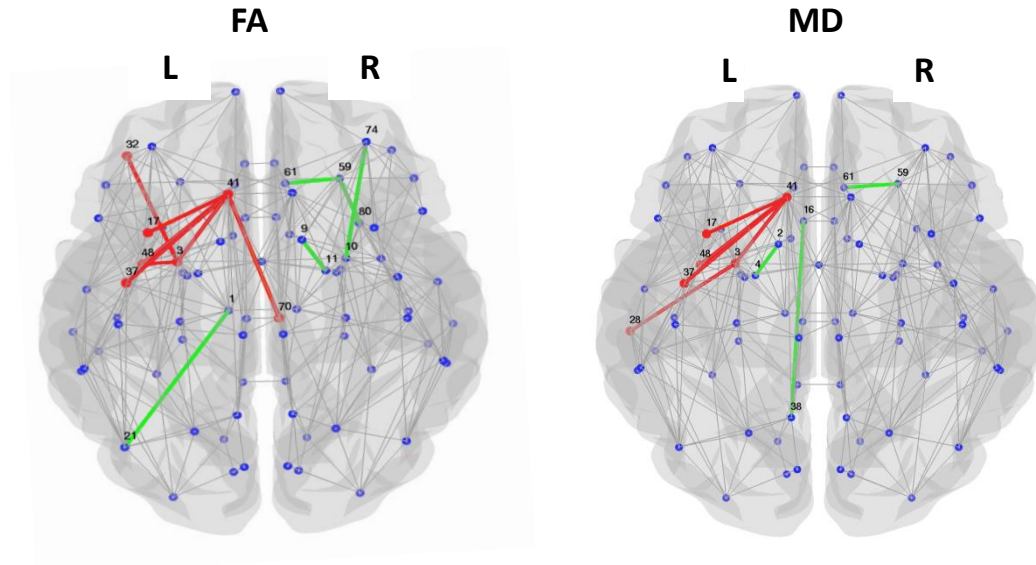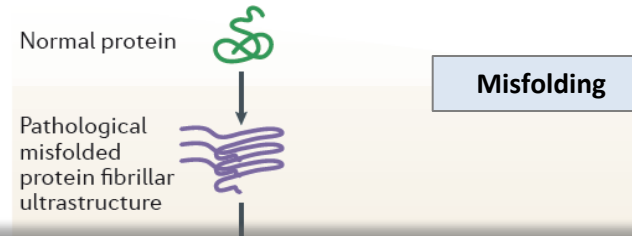
STRUCTURAL CONNECTIVITY in PARKINSONISMS
Disease-vulnerable brain networks

Alzheimer's disease: tau
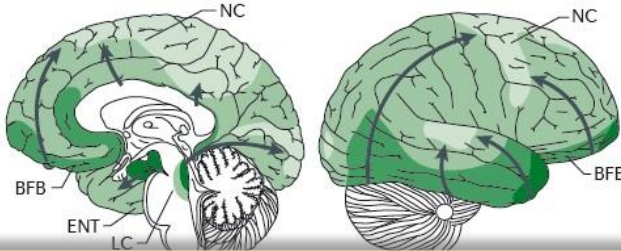
Neuron-to-neuron spreading

Normal protein

Misfolding

Pathological
misfolded
protein fibrillar
ultrastructure

NC

NC

BFB

BFB

ENT

LC

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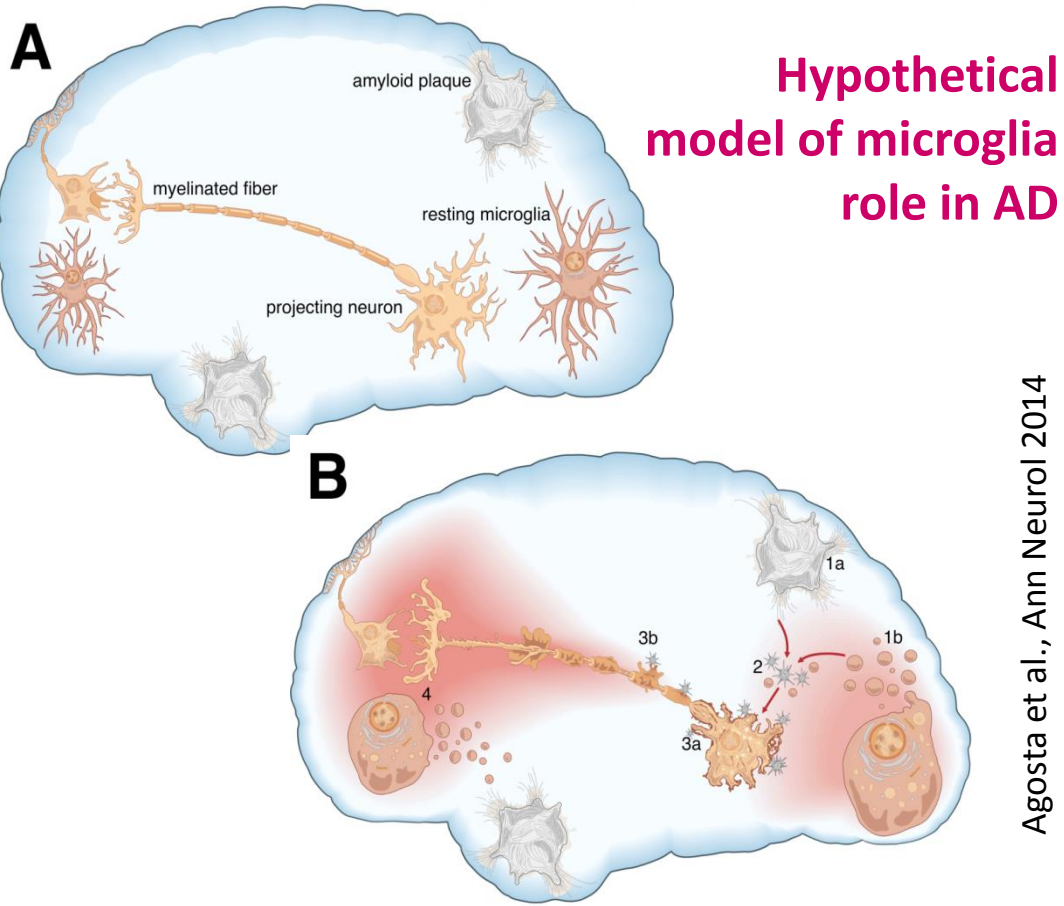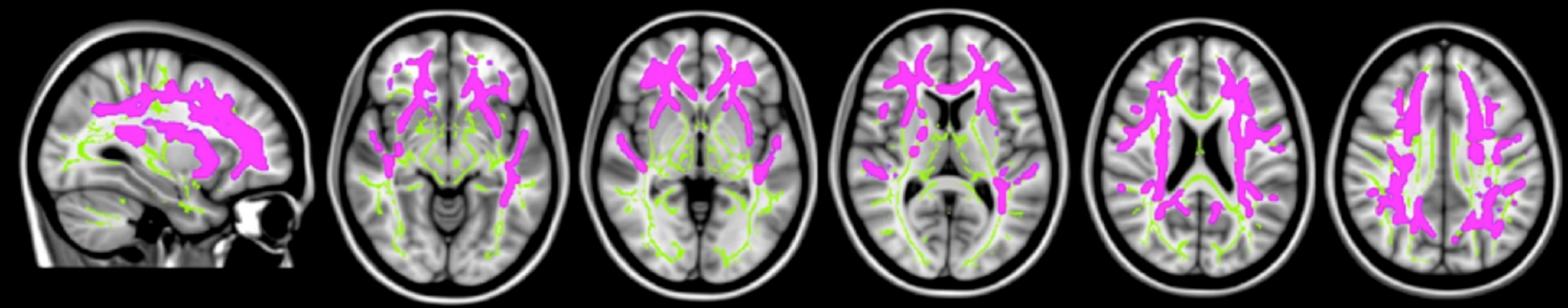diseases**

space

**Further seeded
aggregation**

TH

BSM

BSM

SC9

SC9

Neighbouring
neuron or glial cell
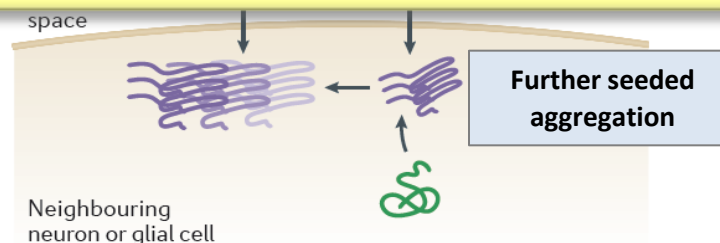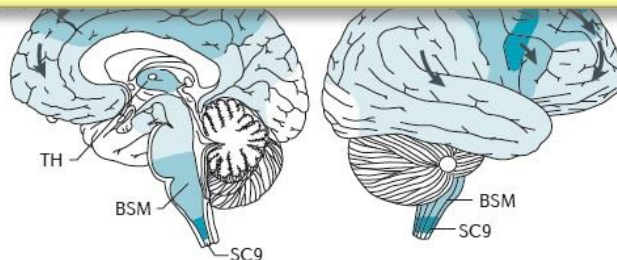
STRUCTURAL CONNECTIVITY in PARKINSONISMS Disease-vulnerable brain networks
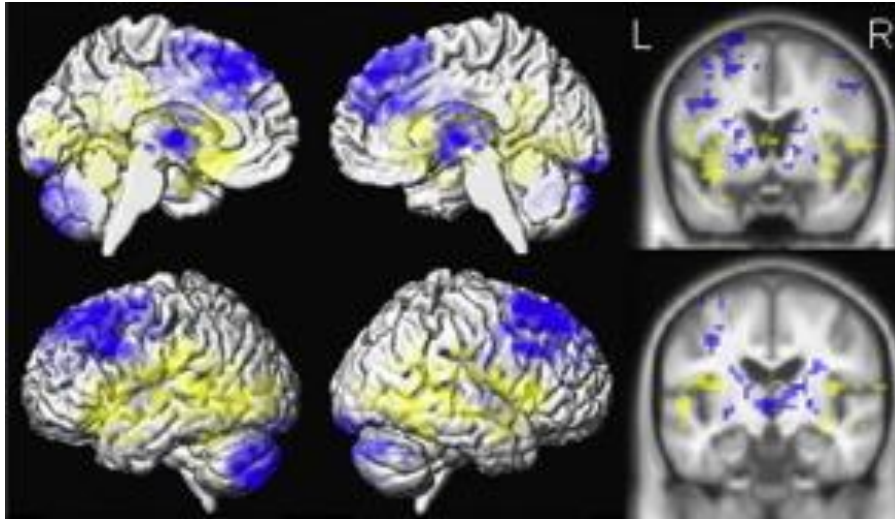
Increased CSF MVs in AD and MCI

Hypothetical model of microglia role in AD

Agosta et al., Ann Neurol 2014
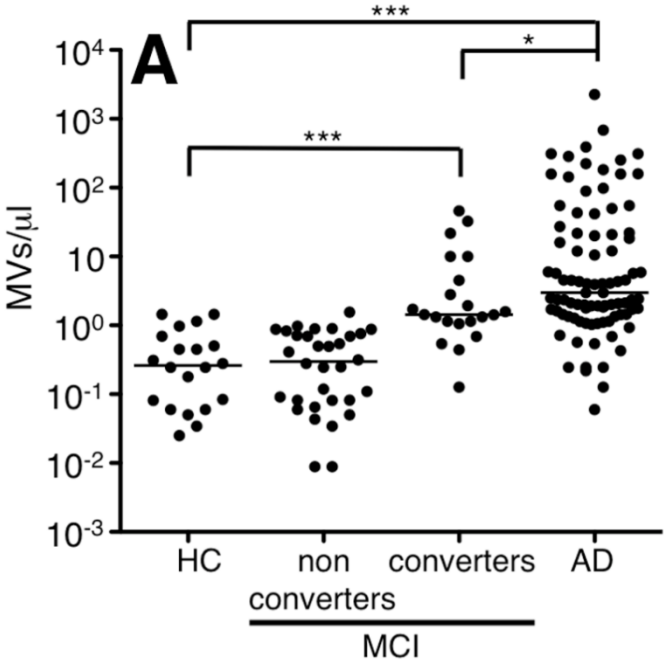
MVs *vs* WM damage in MCI

STRUCTURAL CONNECTIVITY in PARKINSONISMS
PSP

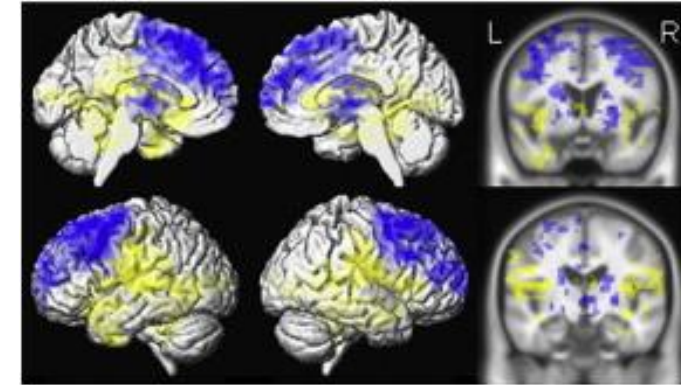### Seed-analysis thalamus

■ (yellow) Increased connectivity
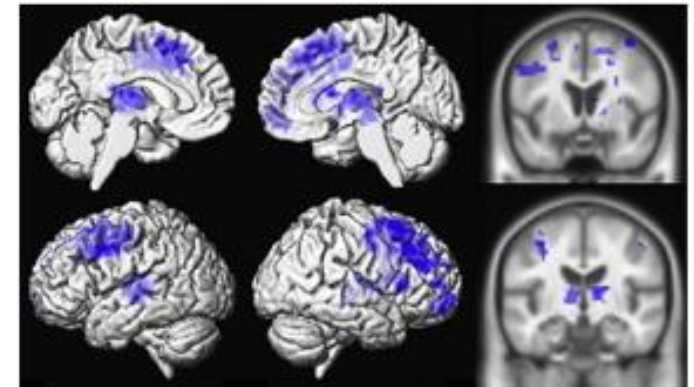
■ (blue) Decreased connectivity

Mean FA of the SCP was correlated with functional connectivity changes in the thalamus
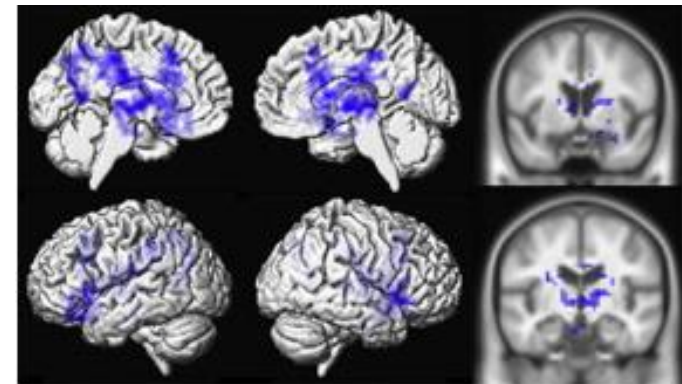
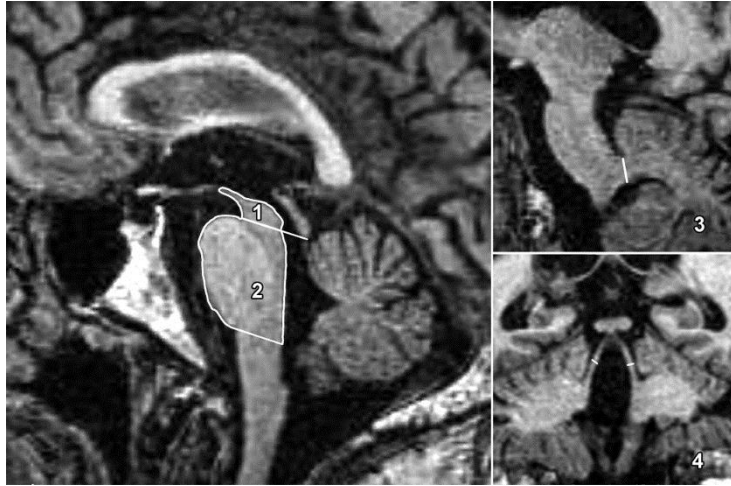Whitwell et al., Parkinsonism & Relat Disord 2011
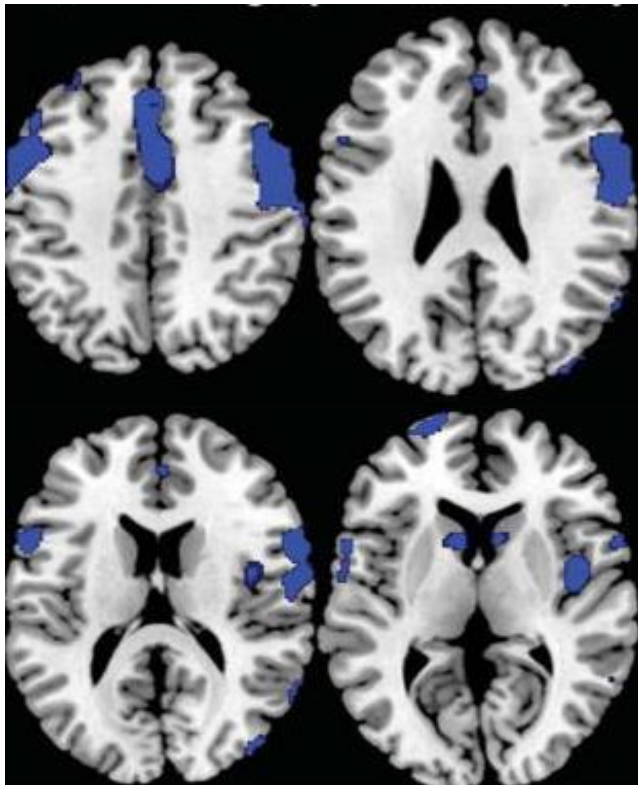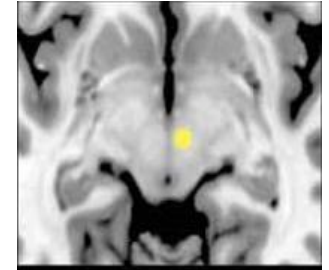
Basal ganglia network

DMN

Salience network

STRUCTURAL CONNECTIVITY in PARKINSONISMS
PSP

Atrophy in PSP

Quattrone et al., Radiology 2008

Gardner et al., Ann Neurol 2013

Dorsal midbrain tegmentum-associated network

PSP *vs* controls

PSP < HC3

preSMA — FEF — SFS — dCN — pACC — dAI/IFGoper — Thal — IPL
FI/LatOFC — PutGPe — SC — vermis — dMT — DentN

43   21   14   3
-5   -13   -31
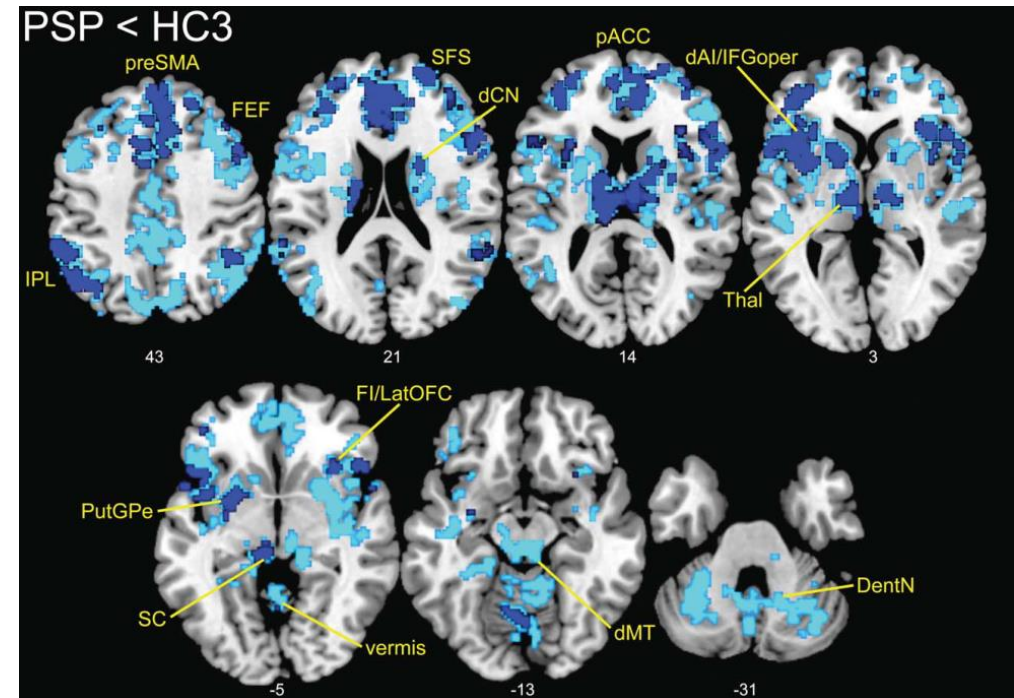
Gardner et al., Ann Neurol 2013

STRUCTURAL CONNECTIVITY in PARKINSONISMS
PSP
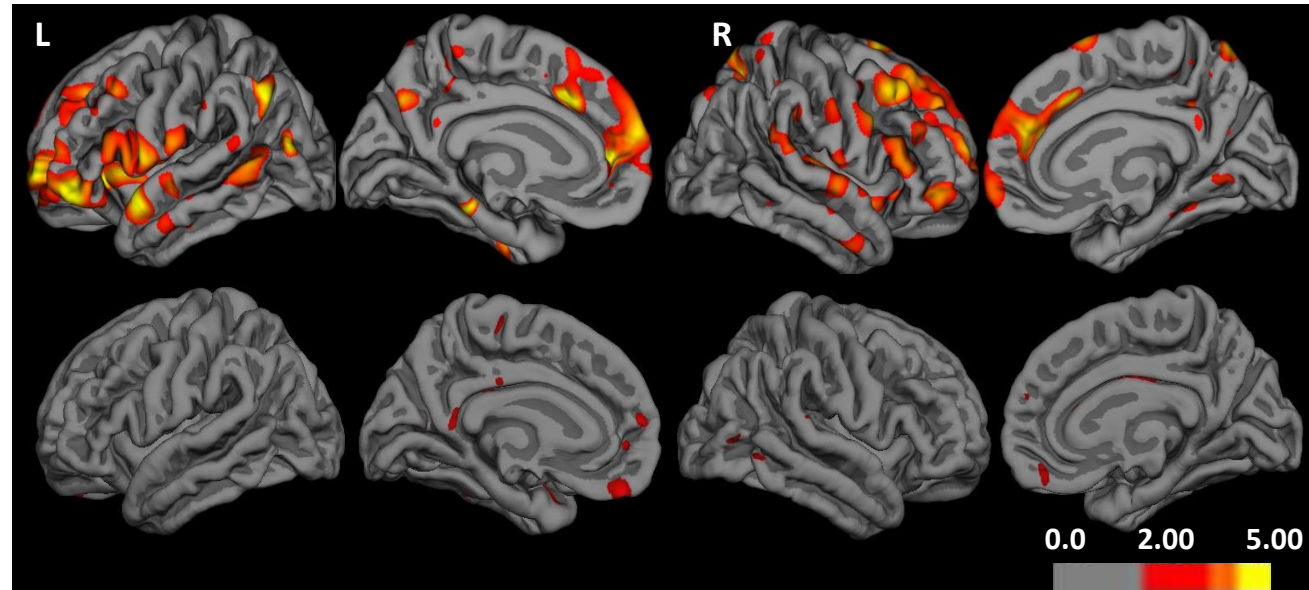
M. Filippi et al., unpublished data
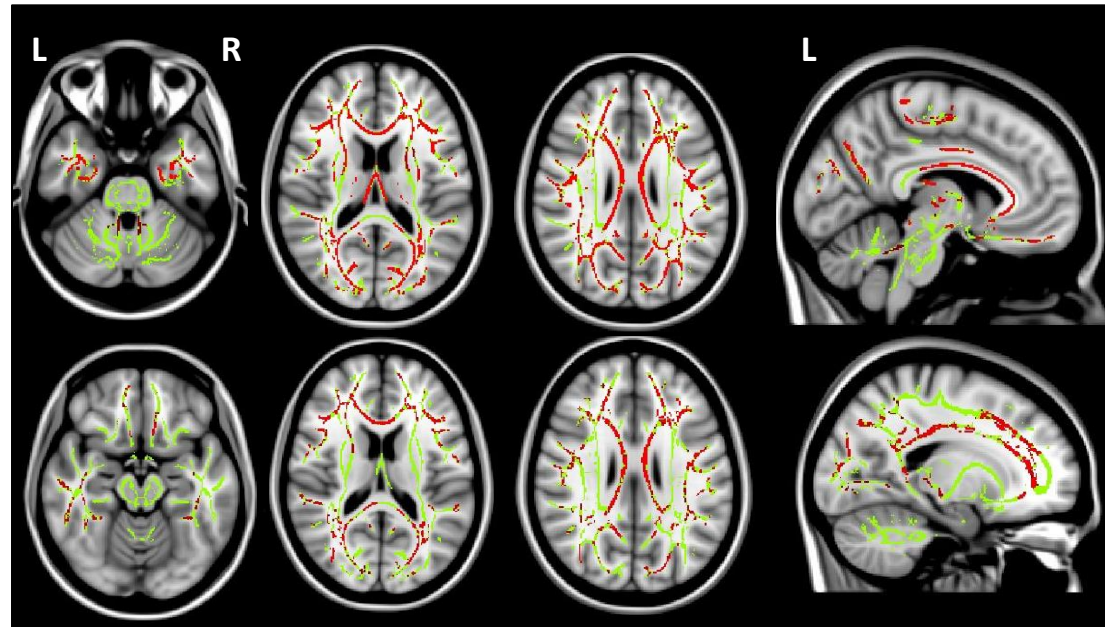
Pathological aggregates
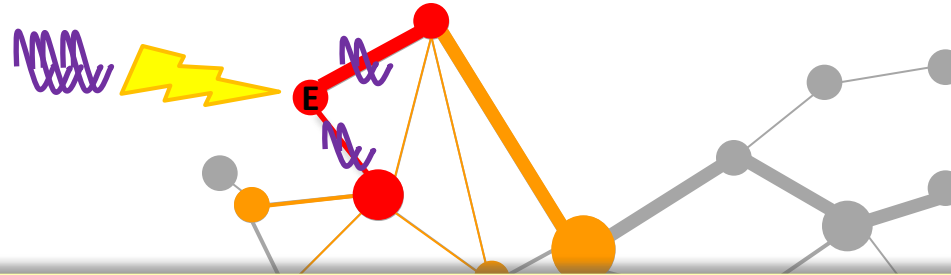
Longitudinal maps of network degeneration
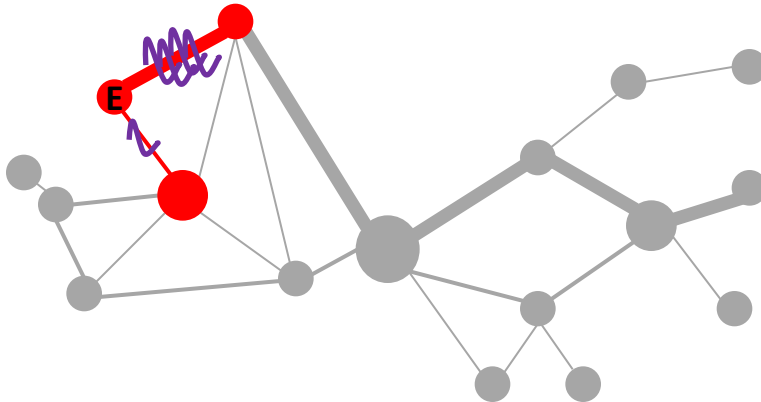
Connection strength
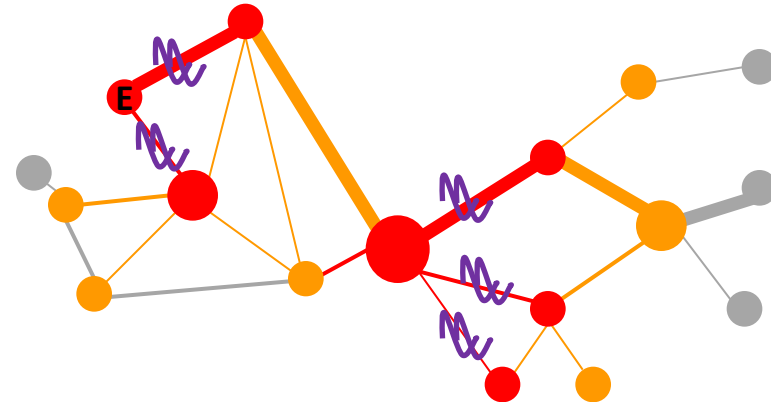
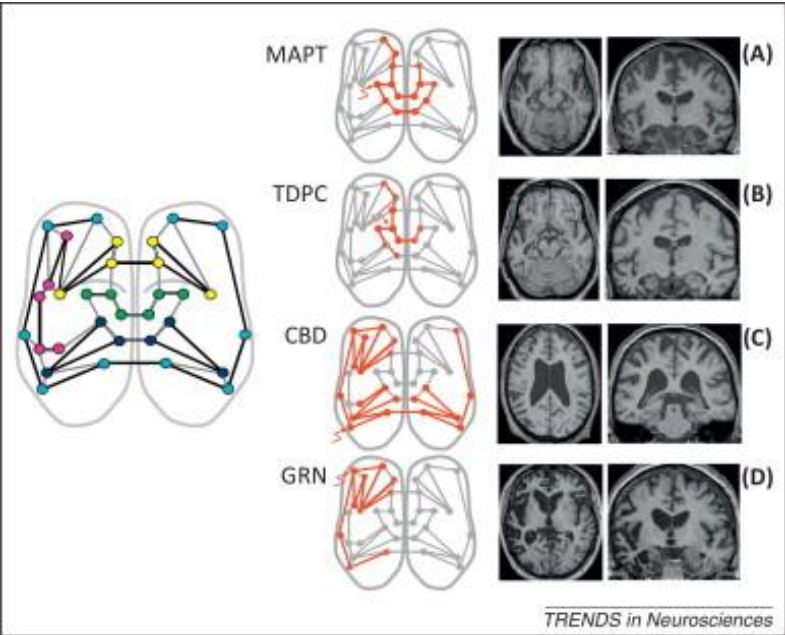**Connector hub**

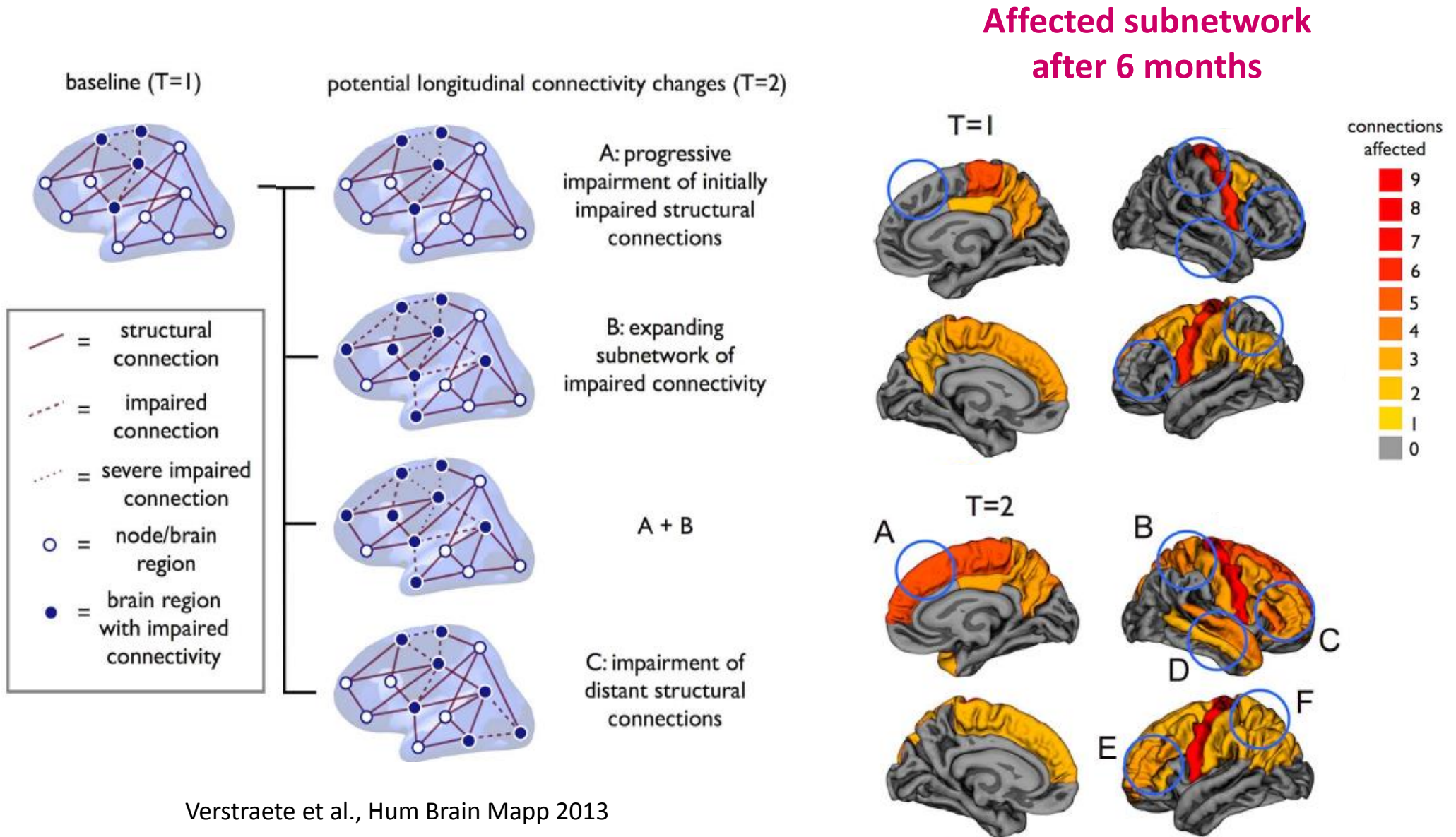# STRUCTURAL CONNECTIVITY in PARKINSONISMS

The Human Connectome: NeuroTRACK

Atrophy *vs* pathology

Rohrer et al., Brain 2011
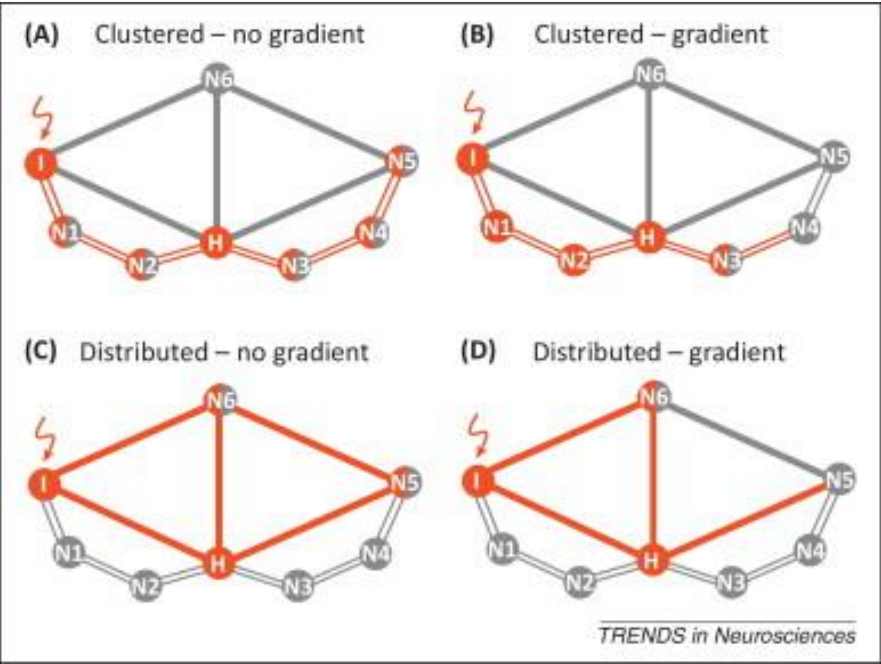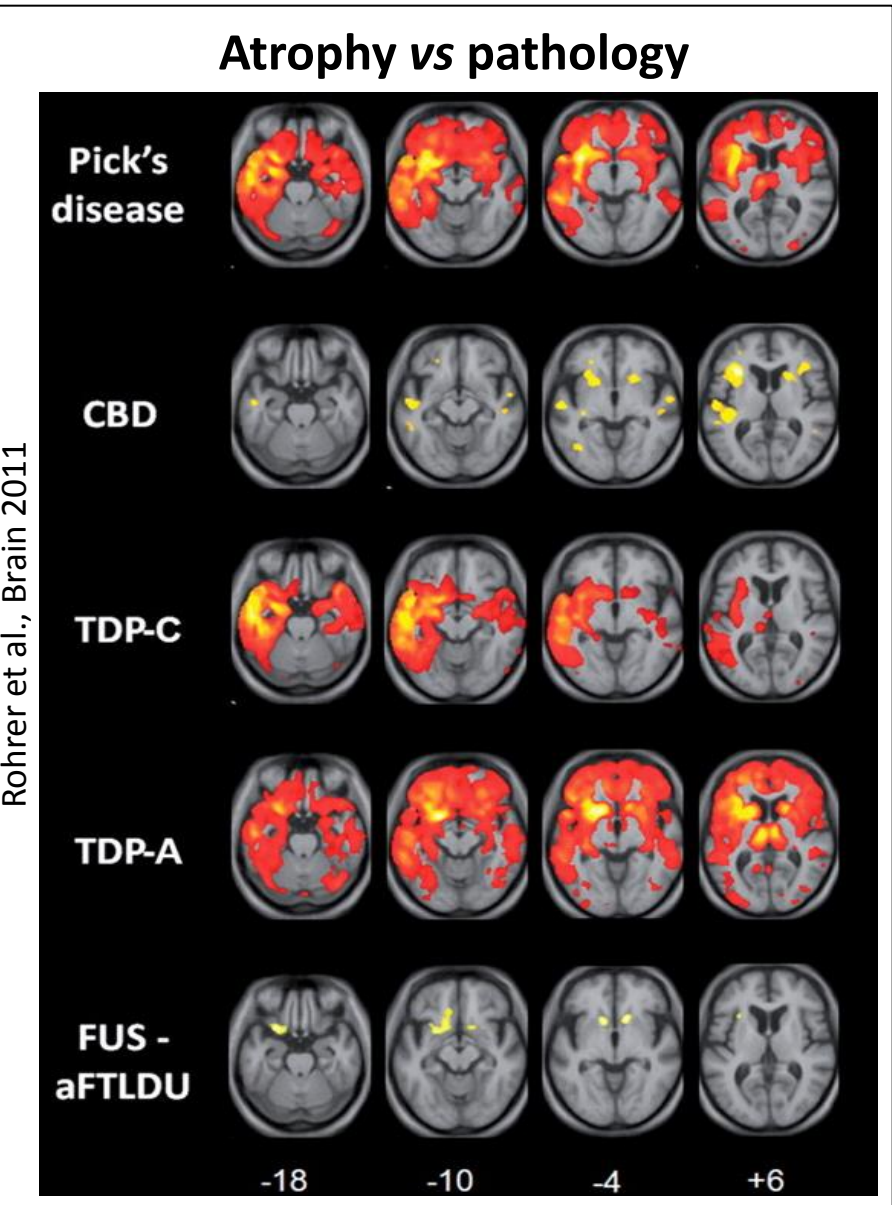
Warren al., Trends Neurosci. 2013

STRUCTURAL CONNECTIVITY in PARKINSONISMS
The Human Connectome

Affected subnetwork after 6 months

Verstraete et al., Hum Brain Mapp 2013

STRUCTURAL CONNECTIVITY in PARKINSONISMS

The Human Connectome: NeuroTRACK

erc
European Research Council

Symptomatic genetic FTLD

Presymptomatic genetic FTLD

t0 m6 m12 m18 m24

Neurological/Neuropsychological assessment

3T MRI

MAPT TAU

GRN TDP43

C9orf72 TDP43

MAPT TAU

GRN TDP43

C9orf72 TDP43

Tracking preclinical network degeneration

Tracking network degeneration

E

(Preclinical) protein-specific models of network degeneration

Structural and functional network changes vs expected time of onset

T0 m12 m24

Clinical prediction

Preclinical stage

Clinical onset

Clinical stage

Time

Neuroimaging Research Unit & Neurodegenerative Diseases Group

Director: M. Filippi
Scientific coordinator: F. Agosta

S. Basaia	P.M. Ferraro
E. Canu	S. Galantucci
F. Caso	F. Imperiale
M. Copetti	E. Sarasso
	E. G. Spinelli

STRUCTURAL CONNECTIVITY in PARKINSONISMS
Genetic dystonia