Introduction to functional MRI
& applications to neurological diseases

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Disclosures

Dr Spinelli has nothing to disclose

Outline of the presentation / Intro to fMRI

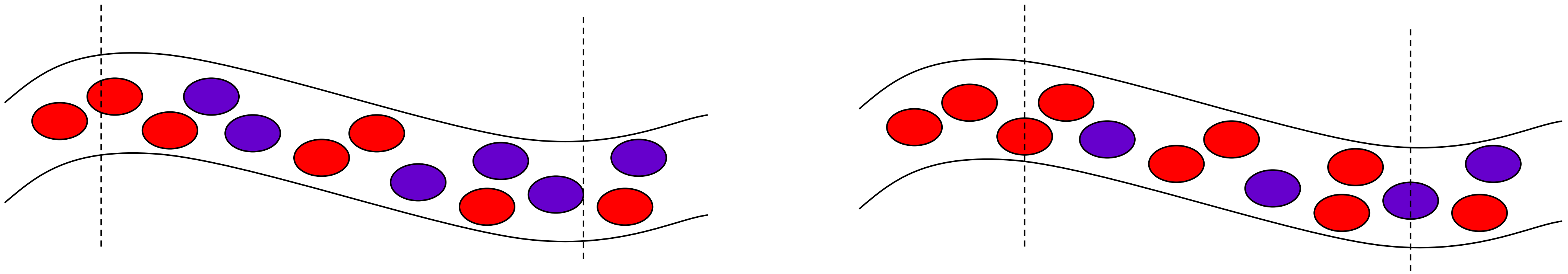
- Basic principles of functional MRI
- fMRI acquisition
- Basic pre-processing steps of fMRI data
- Analysis of task-based fMRI scans
- Analysis of resting state fMRI scans

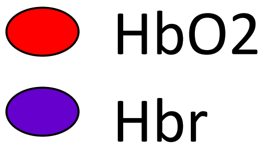
The BOLD effect

BOLD=Blood Oxygenation Level Dependent

Basal state

Activated state





- normal flow
- basal level [Hbr]
- basal CBV
- normal MRI signal

- increased flow
- decreased [Hbr]
- increased CBV
- **increased MRI signal**

Ogawa et al, PNAS 1990

The BOLD effect at resting state

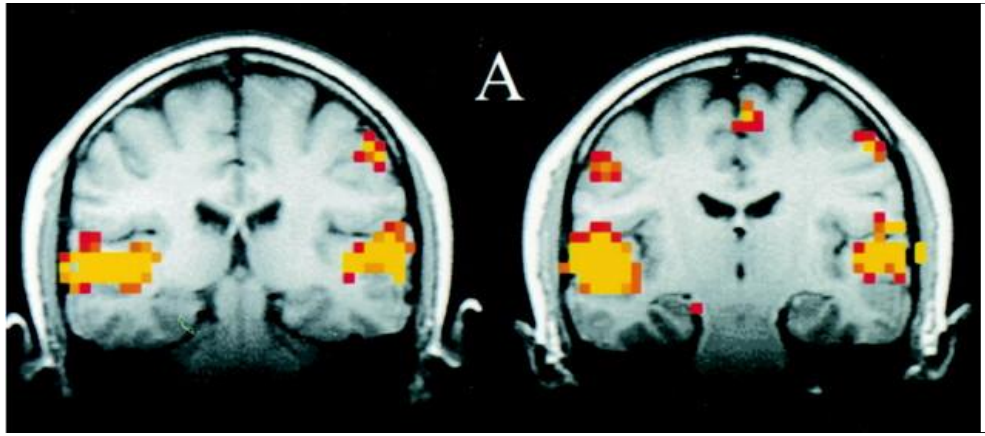
- **Several studies showed in fMRI data acquired at rest (i.e., in absence of external stimulation) the presence of spontaneous low-frequency (0.01-0.1 Hz) fluctuations with high temporal coherence between spatially distinct, functionally-related brain regions**

- **It has been hypothesized that these low-frequency fluctuations reflect an intrinsic property of brain functional organization**

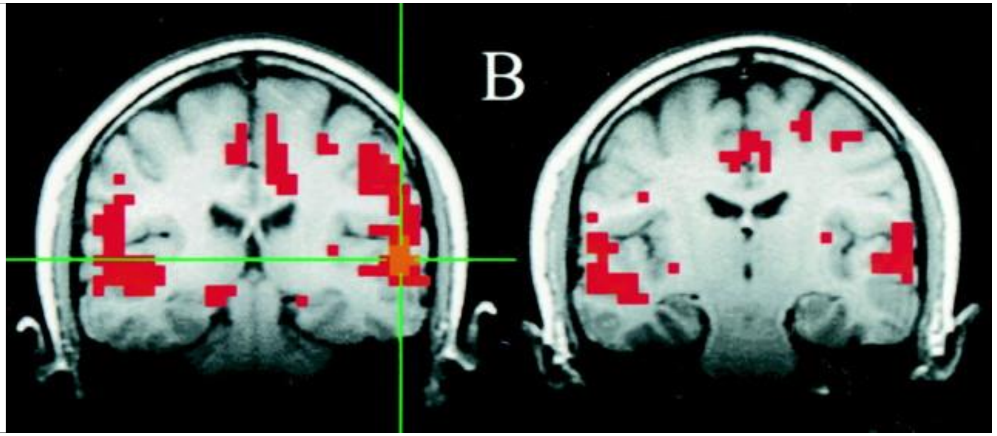
Cordes et al, AJNR 2000; Biswal et al, MRM 1995; Lowe et al, Radiology 2002

The BOLD effect at resting state

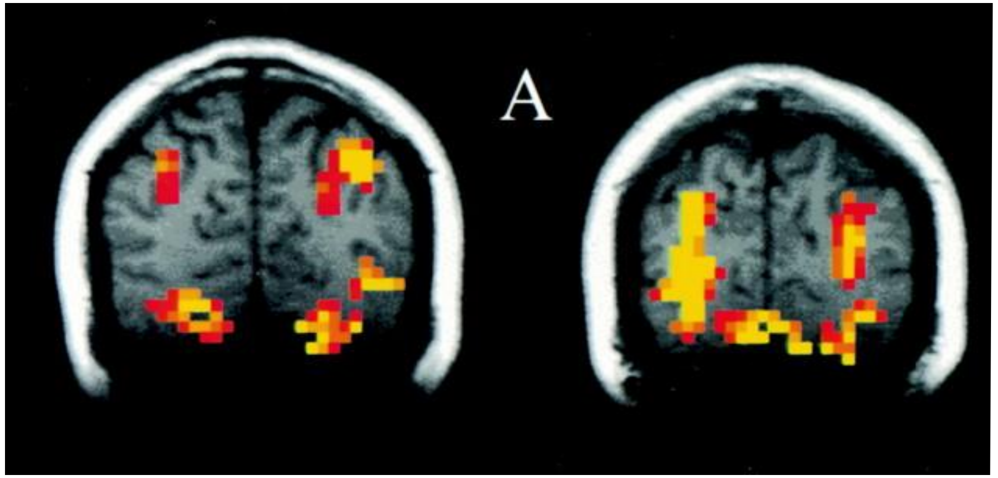
Active fMRI auditory task



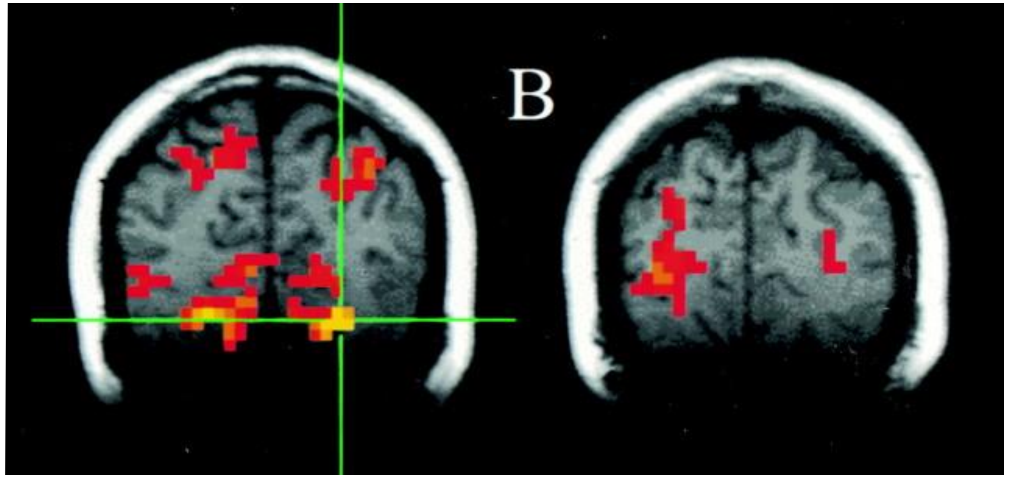
Auditory fMRI network at resting state



Active fMRI visual task



Visual fMRI network at resting state



Cordes et al, AJNR 2000

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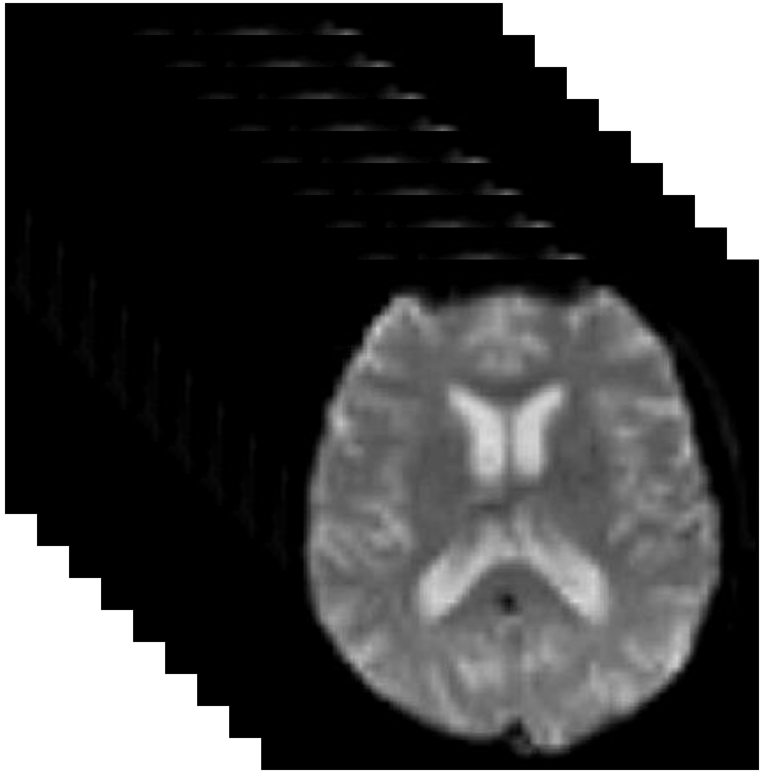
fMRI acquisition

Typical fMRI sequence: T2*-weighted EPI sequence



- Gradient echo
- Several volumes required ⇒ fast acquisition of each volume

(typical TR=2/3 sec)

Voxel Resolution=3x3x3 mm

Whole-brain coverage

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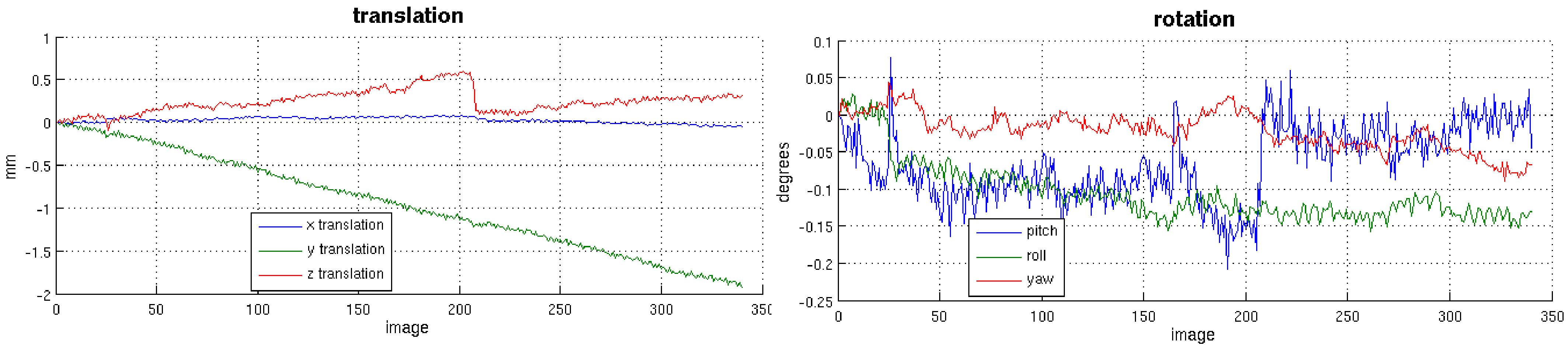
Basic pre-processing of fMRI data

Motion correction (realignment):

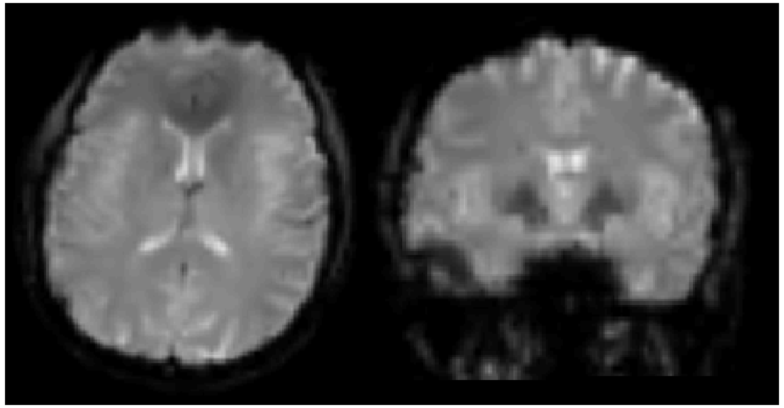
- **Subjects move a little over the course of the session**
- **This can introduce artefacts and a bias in fMRI activity estimation**



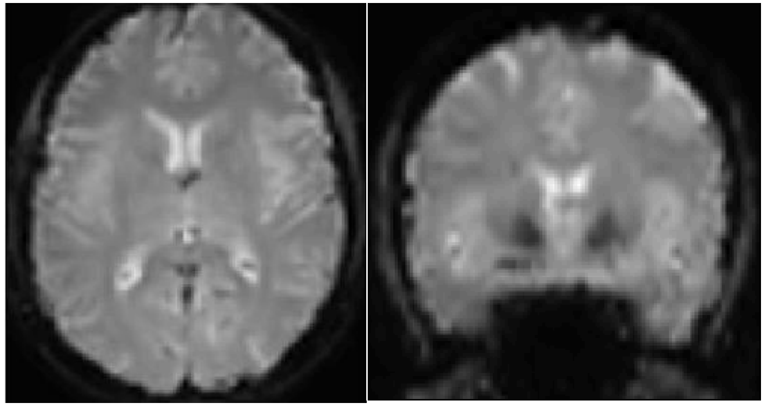
Basic pre-processing of fMRI data

Normalization to standard space:

- **Heads have different shapes and sizes**
- **fMRI activity is usually calculated in a space that allows group statistics and between-group comparisons**
- **Non linear warping to Montreal Neurological Institute space**



Original image

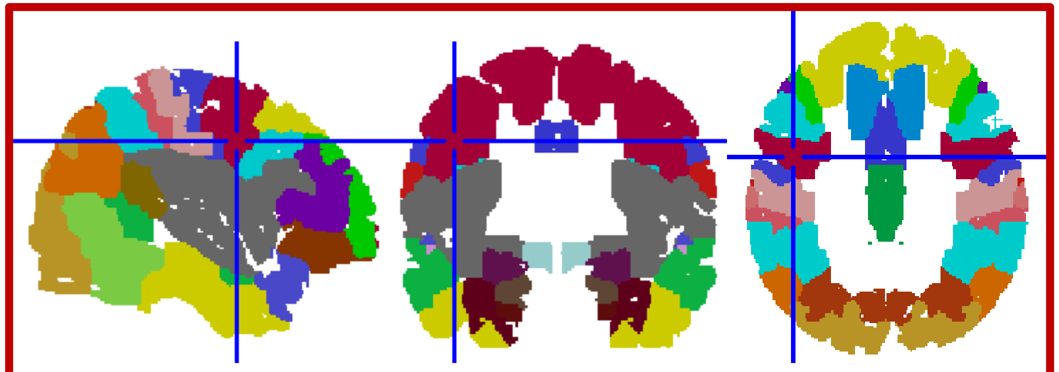


Normalized image

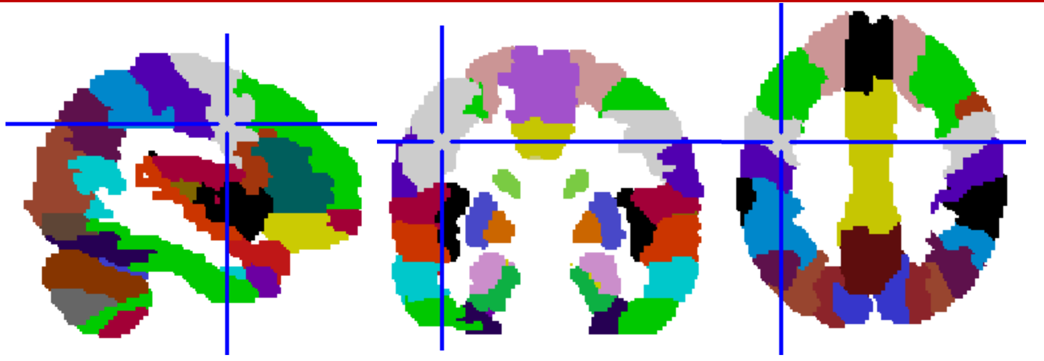
Basic pre-processing of fMRI data

- **Normalization to standard space also allows precise localization of fMRI activity on standard atlases, designed on MNI space coordinates:**

E.g. MNI space coordinates (x y z): -43 0 39:



Brodmann area atlas: BA6



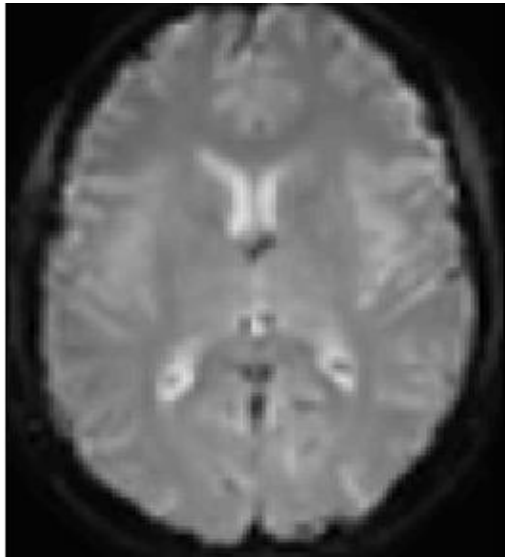
Automatic anatomical labeling (AAL) atlas: Left precentral gyrus

Tzourio-Mazoyer et al., Neuroimage 2002

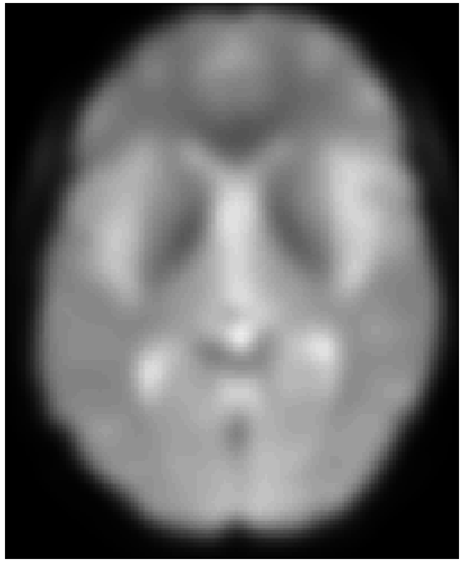
Basic pre-processing of fMRI data

Smoothing:

- **Makes data more normal across space and time**
- **Increases signal to noise for spatial scale of interest**



Before smoothing



After smoothing

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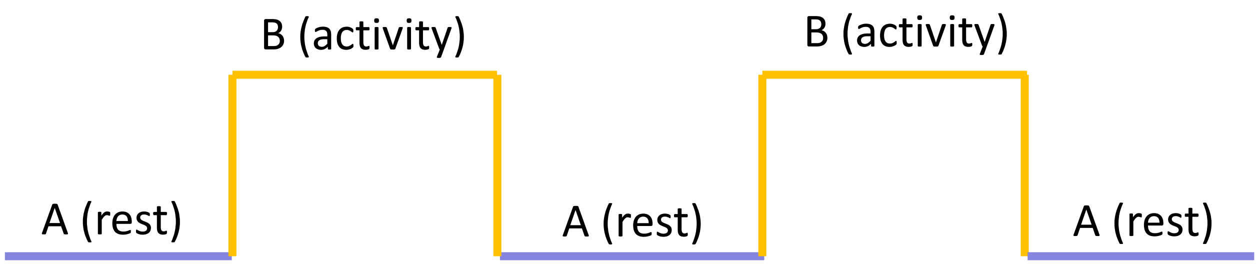
Task-based fMRI acquisition

Block designs:

• well suited to localize functional areas and to study steady state processes

• powerful in terms of fMRI activity detection

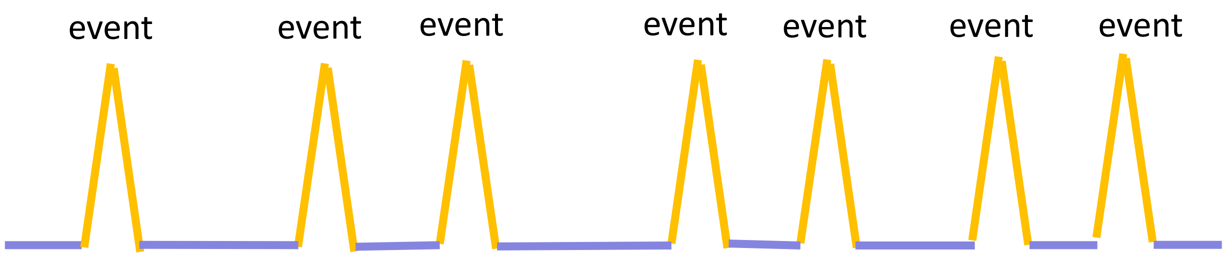


Event-related designs:

• events separated in time by a certain inter-stimulus interval

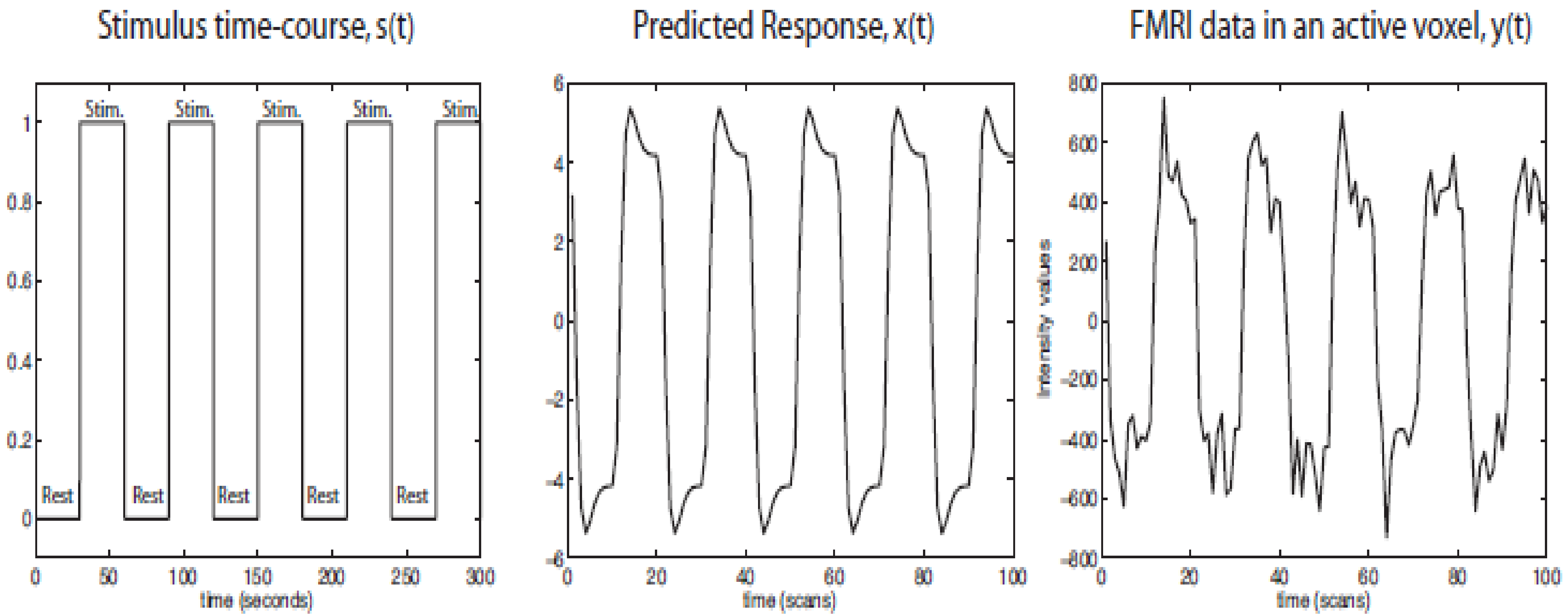
• able to measure transient changes in brain activity

• more flexible, but less powerful than block designs



First-level analysis of task-based fMRI scans

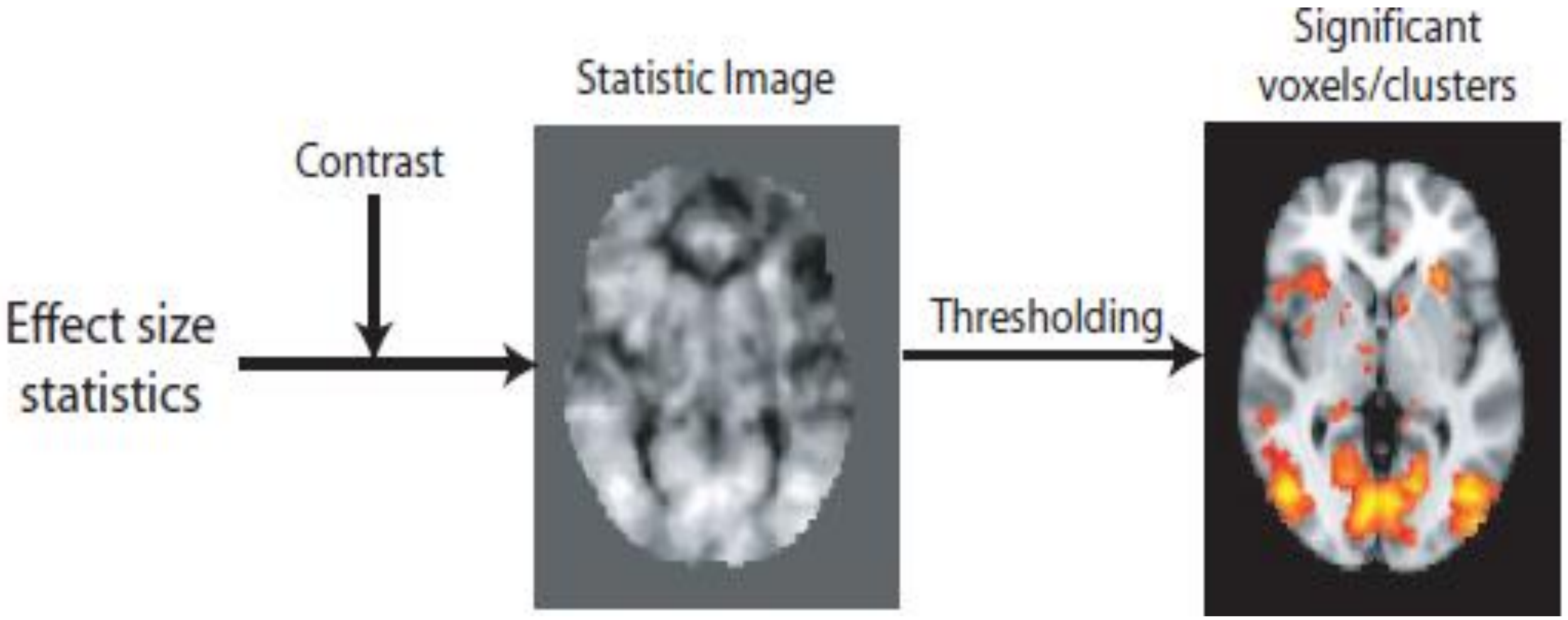
The General Linear Model



For each voxel of the brain, linear regression models assess partial correlation between stimulus time-course and fMRI time course

First-level analysis of task-based fMRI scans

The General Linear Model ⇒ Statistical Parametric Mapping



Statistical maps reflect how much each voxel of the brain is likely to be activated by the stimulus task

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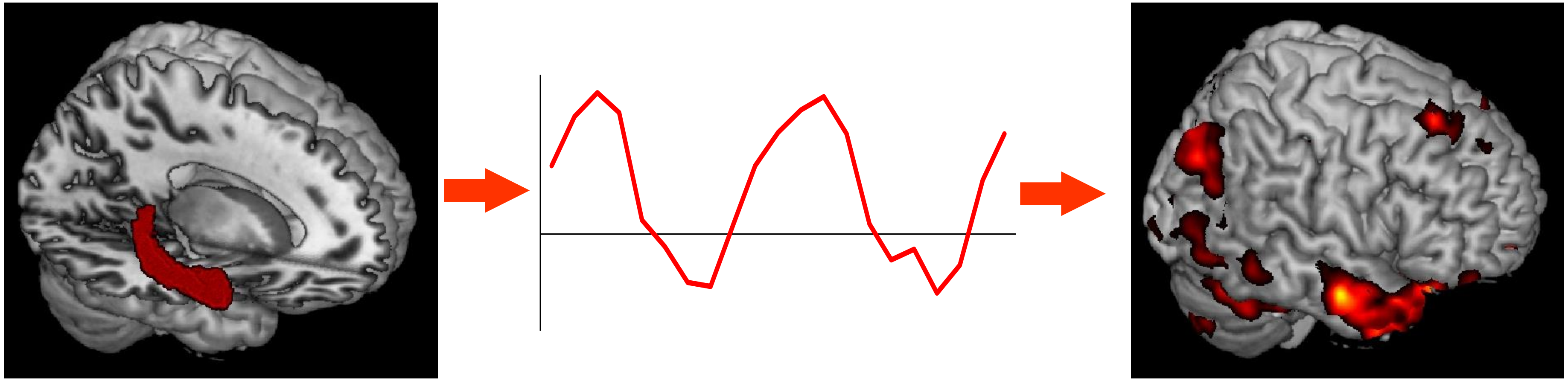
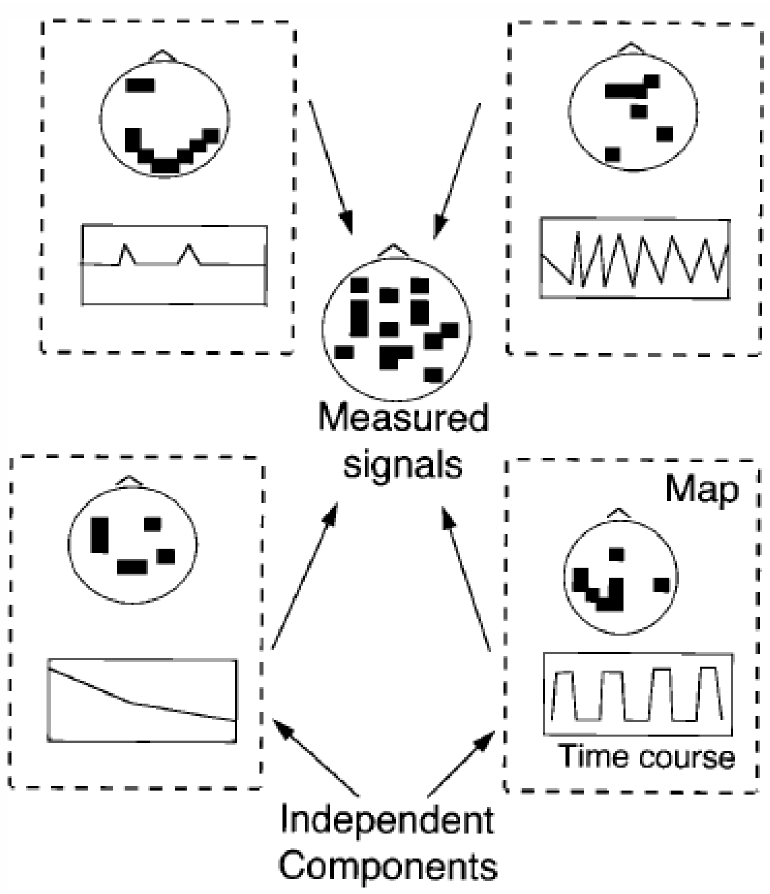
Seed-based resting state functional connectivity

- Choice of the region of interest (ROI)
- Assessment of the correlation between the time series of the seed region and any other time series of the brain: cross-correlation map



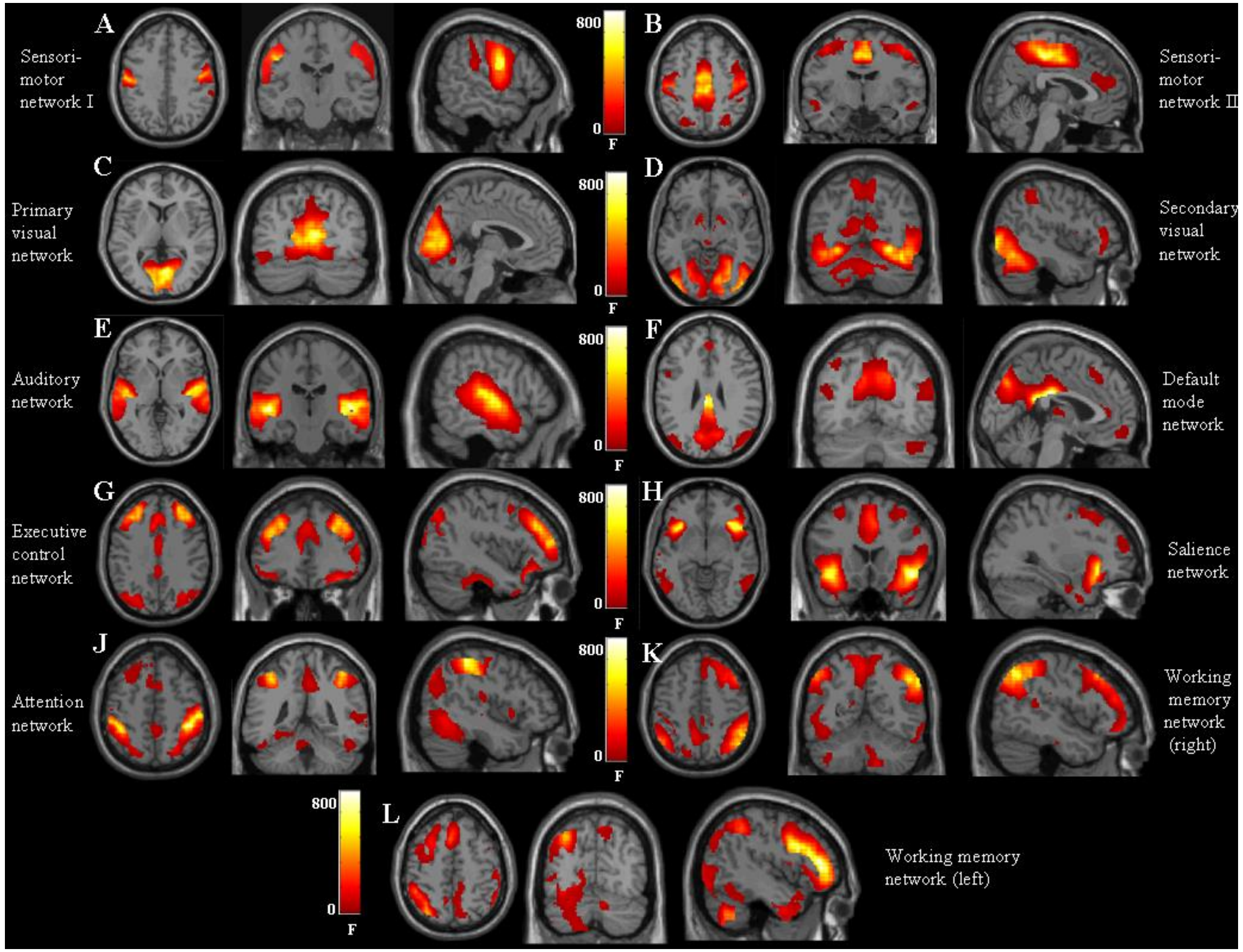
Biswal et al., MRM 1995

Independent component analysis



McKeown et al., Hum Brain Mapp 1998

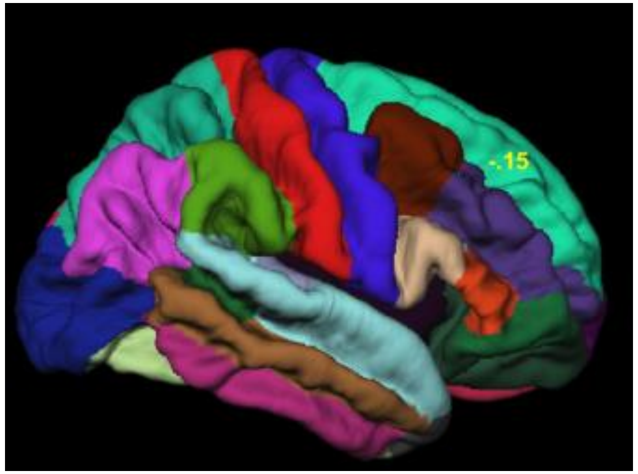
Main ICA-derived functional brain networks



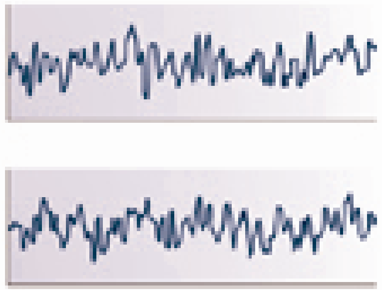
Filippi et al., Hum Brain Mapp 2013

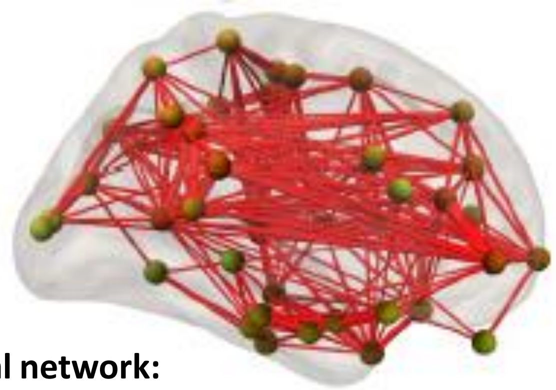
Graph analysis

Brain parcellation

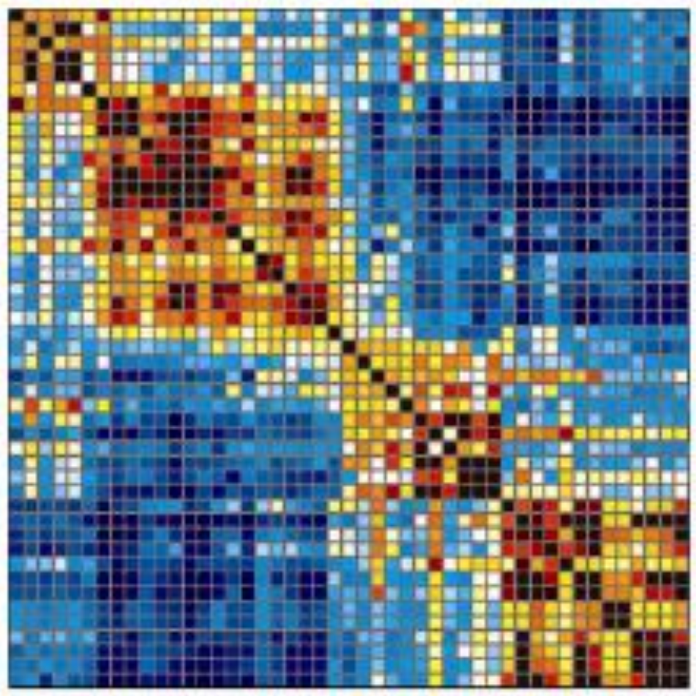


fMRI time series extraction





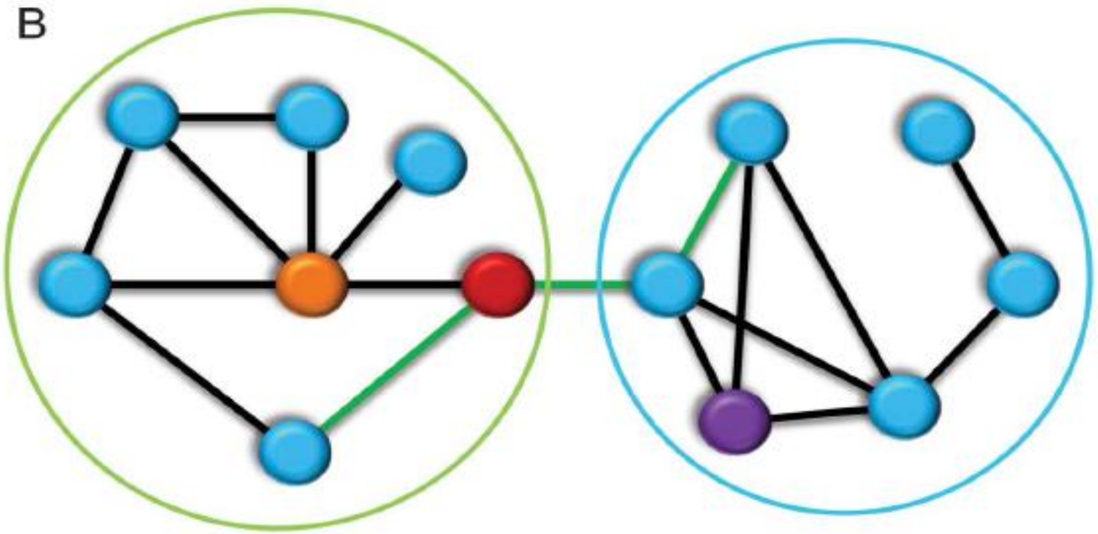
Functional network:
Pearson’s correlations between time series



Calculation of general network properties on functional connectivity matrix

Bullmore et al., Nat Rev Neurosci 2009 Rubinov et al., Neuroimage 2009

Graph analysis



Shortest path lenght

Highest degree

Connector hub

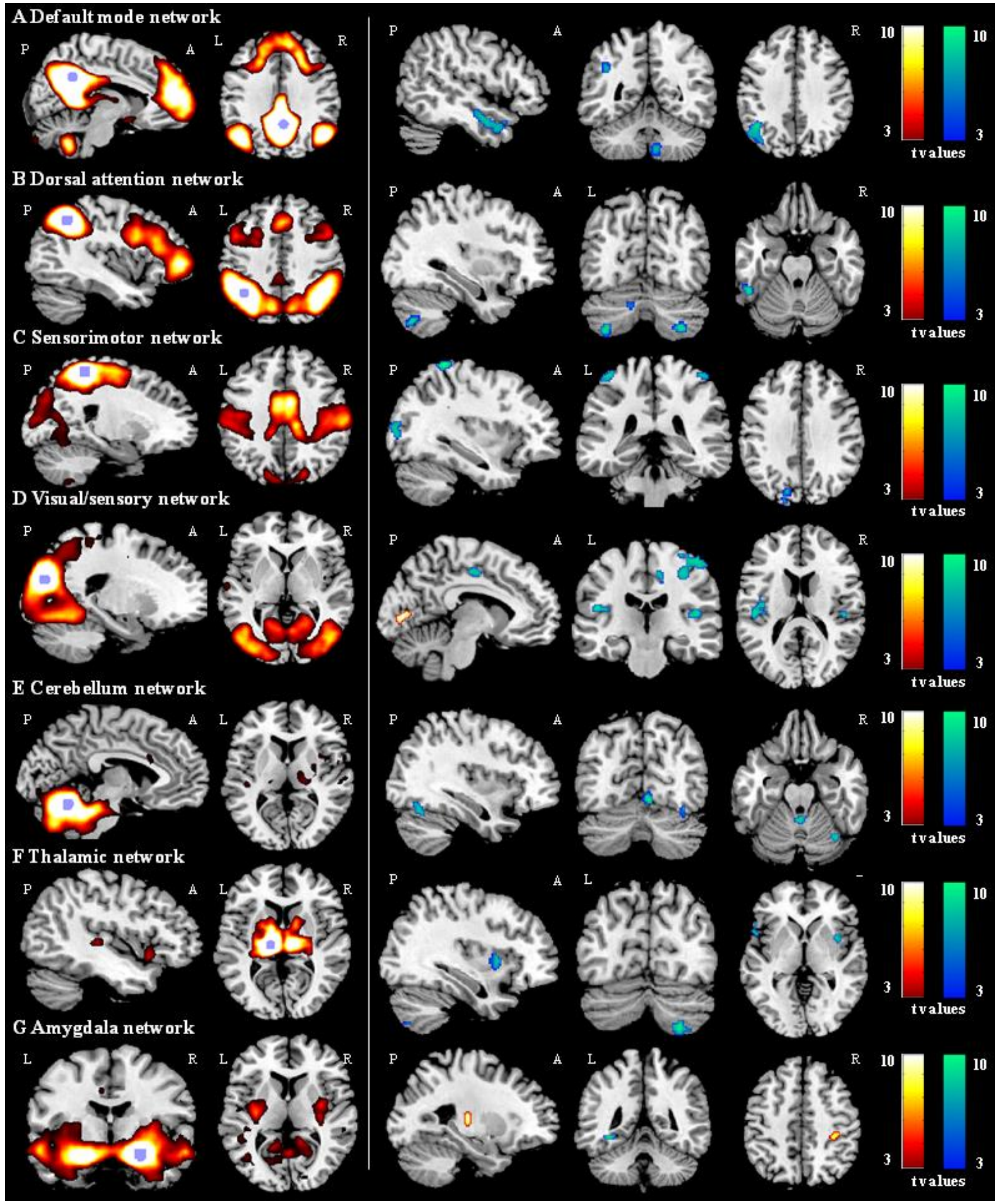
Highest clustering coefficient (its neighbors are all neighbors of each other)

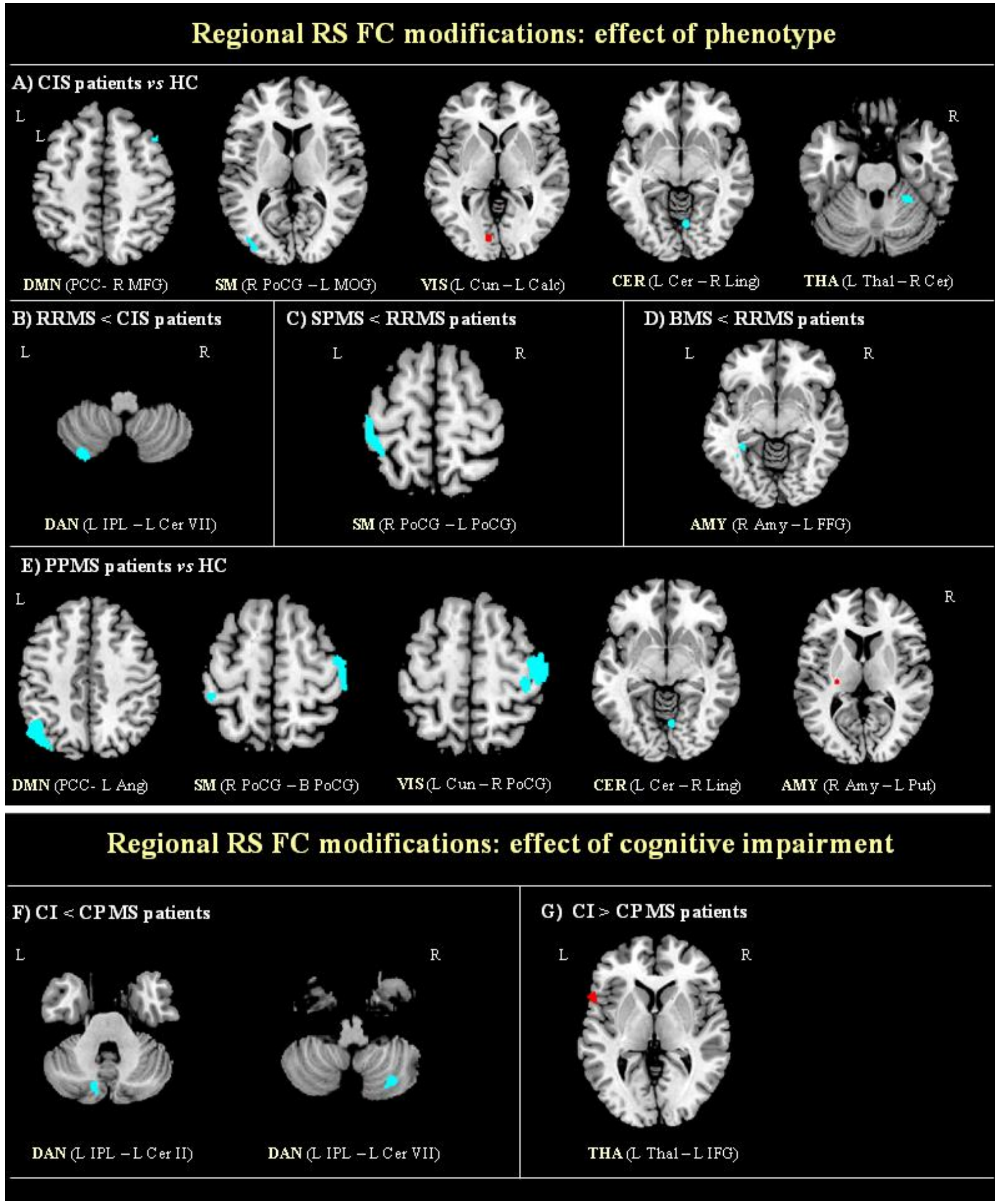
Filippi et al., Lancet Neurol 2013

Outline of the presentation / Applications

- Diagnosis & phenotyping
- Tracking & predicting progression
- Network spreading modelling

Multiple Sclerosis / Diagnosis & phenotyping



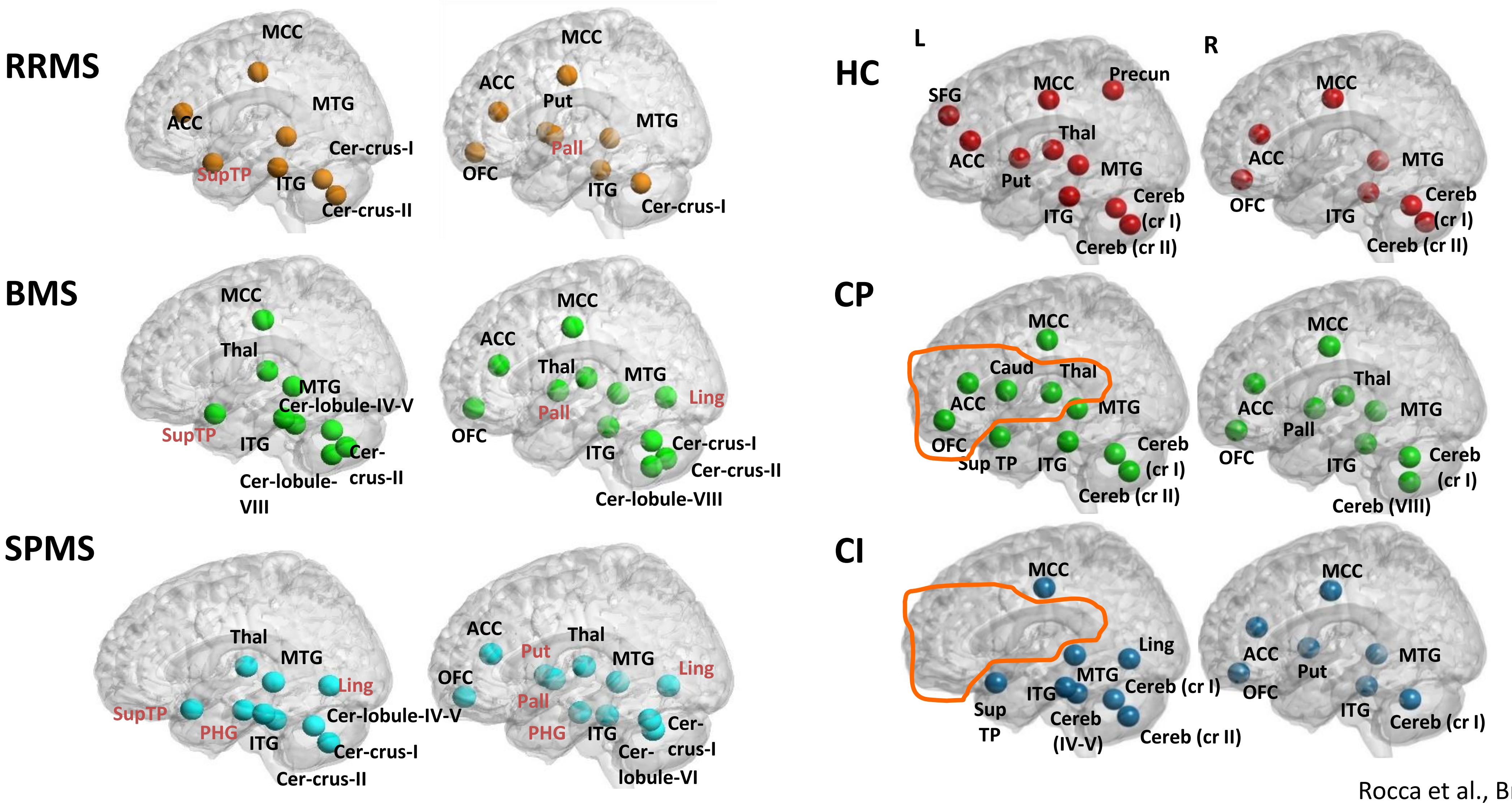


Rocca et al., MSJ 2018

Multiple Sclerosis / Diagnosis & phenotyping

Effect of phenotype

Effect of cognitive impairment

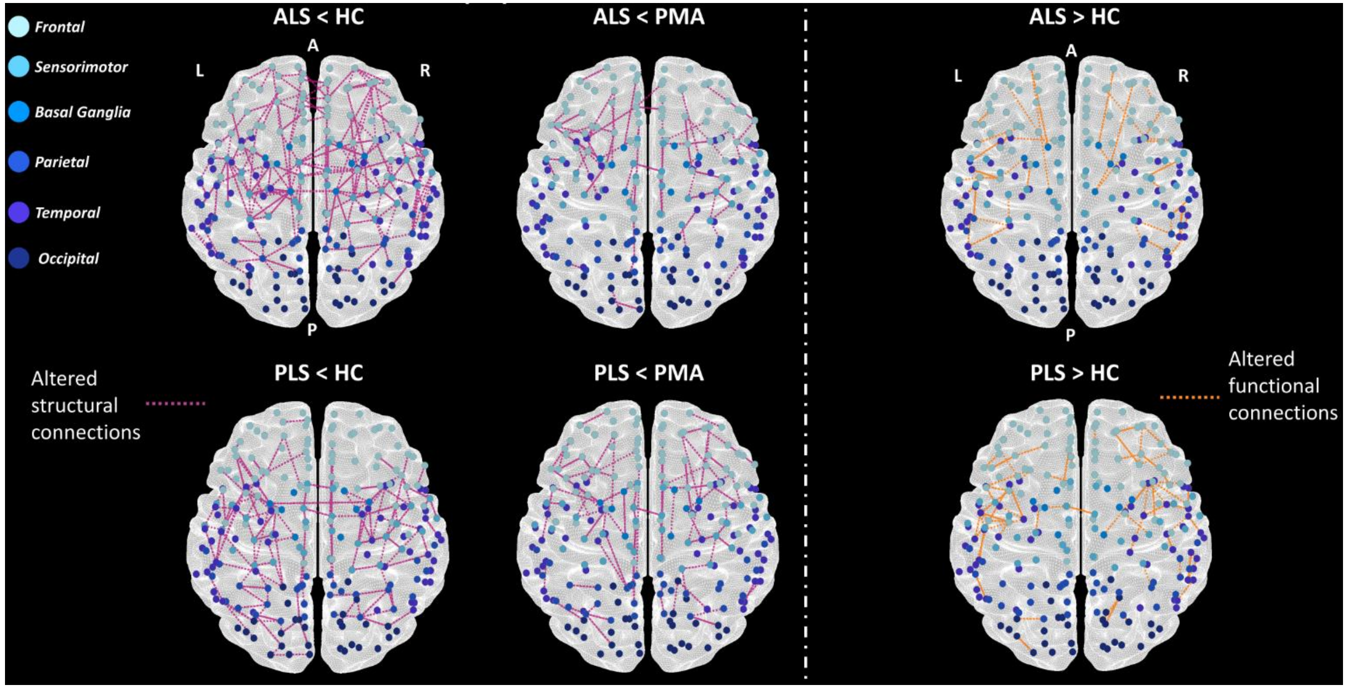


Rocca et al., Brain Struct & Funct 2016

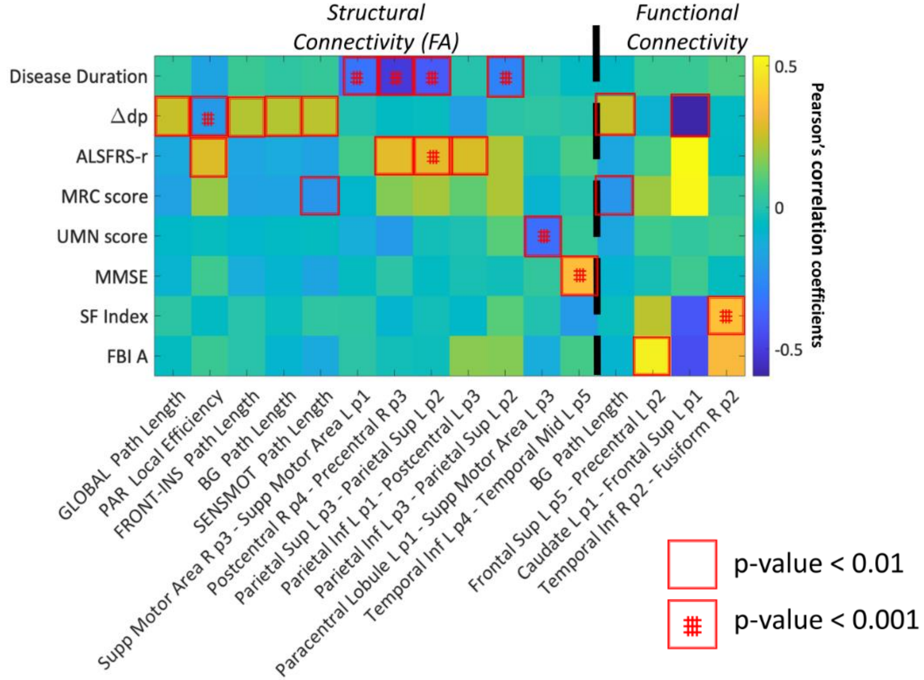
ALS / Diagnosis & phenotyping

173 ALS, 38 PLS, 28 PMA patients and 79 healthy controls

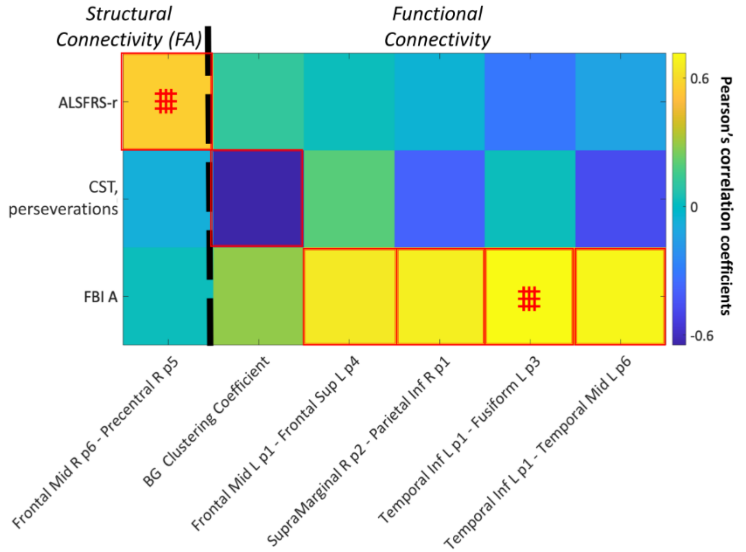
STRUCTURAL CONNECTIVITY (FA) **FUNCTIONAL CONNECTIVITY**



ALS

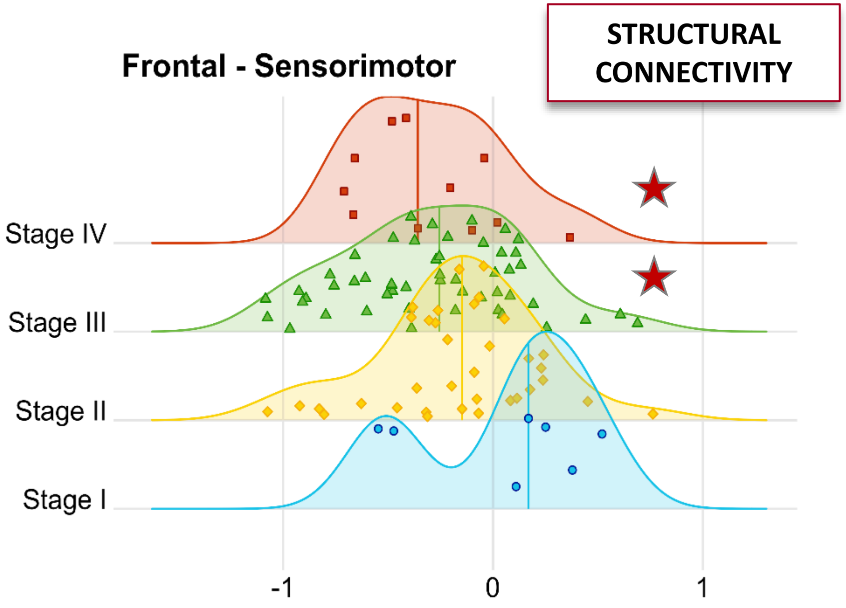


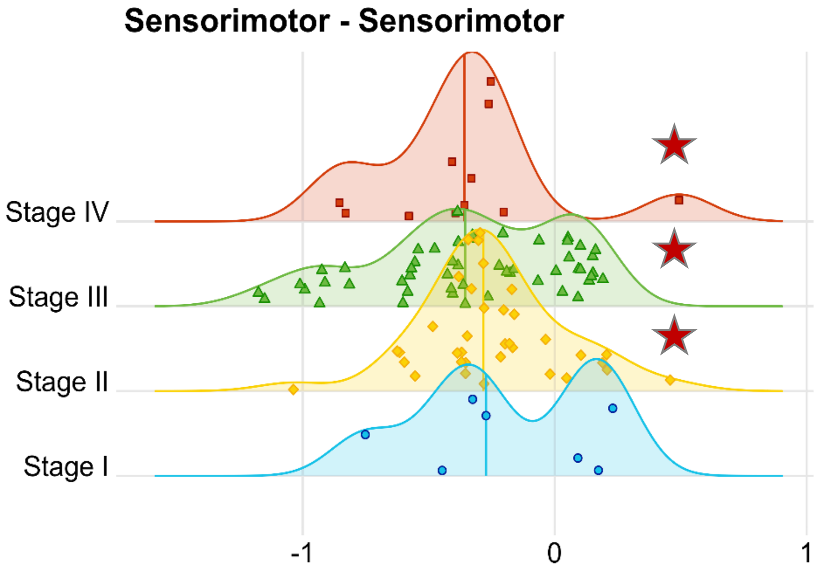
PLS

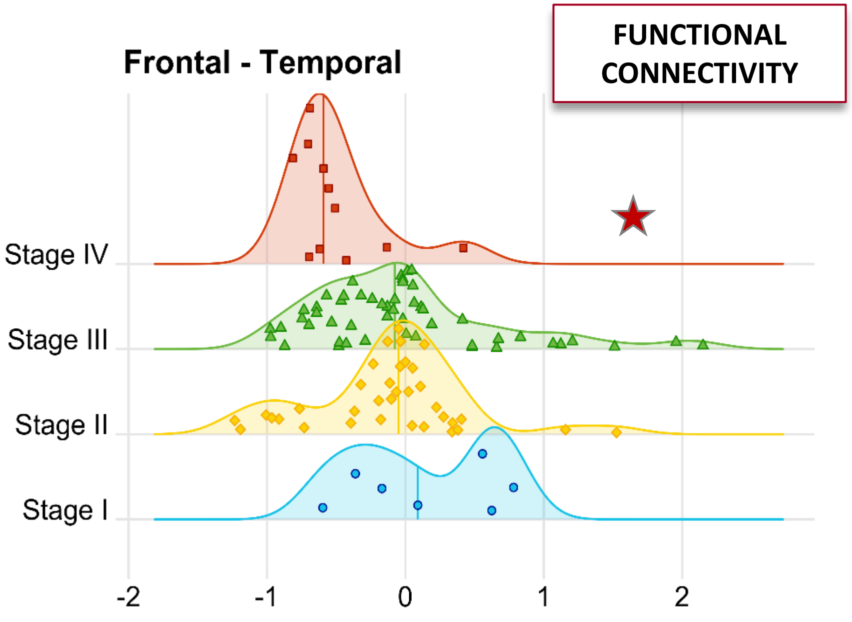


Basaia et al., Neurology 2020

ALS / Diagnosis & phenotyping







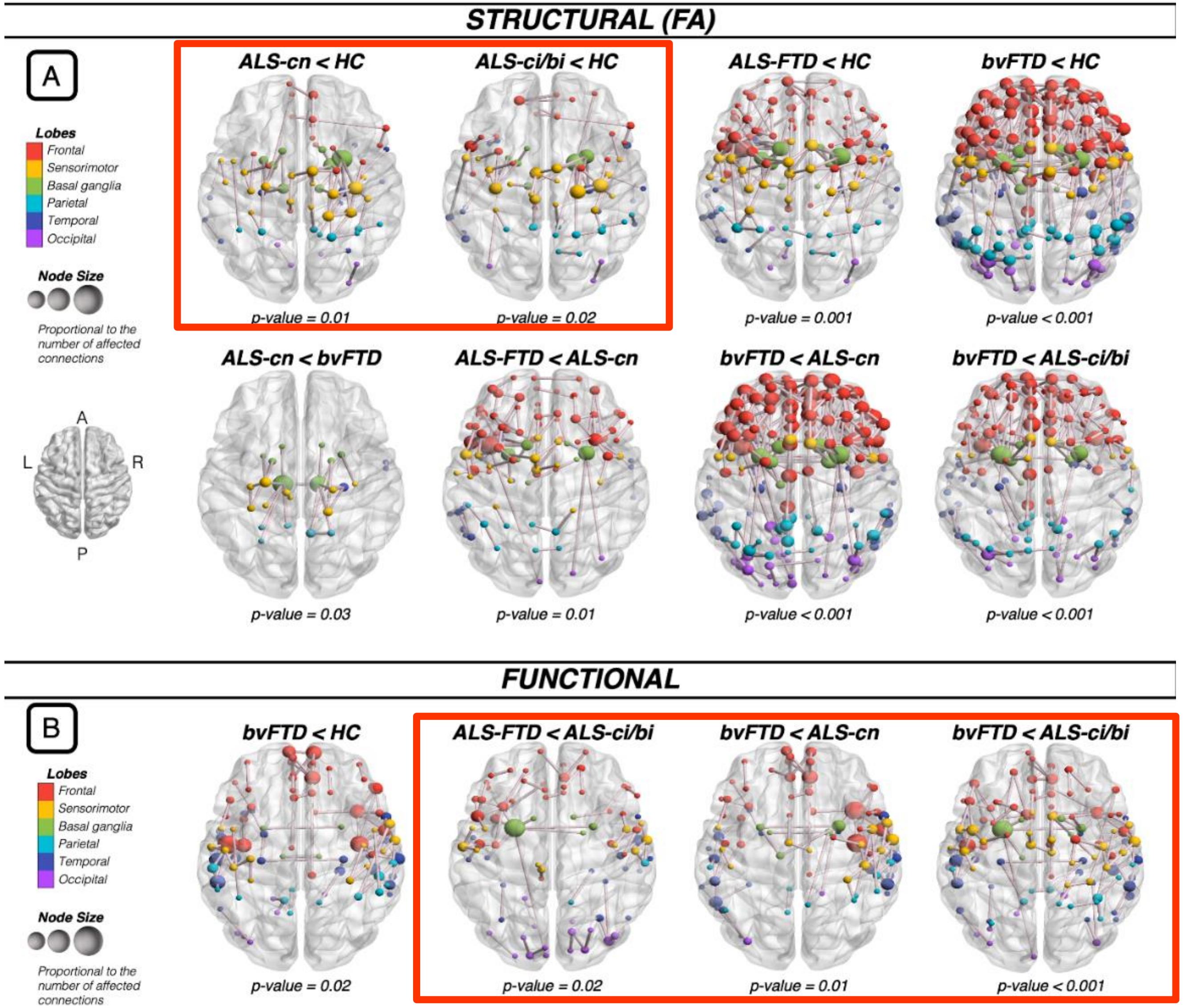
KING'S STAGE

- Stage I
- Stage II
- Stage III
- Stage IV

★ **Significant compared with HC**

Spinelli et al., in preparation

ALS / Diagnosis & phenotyping



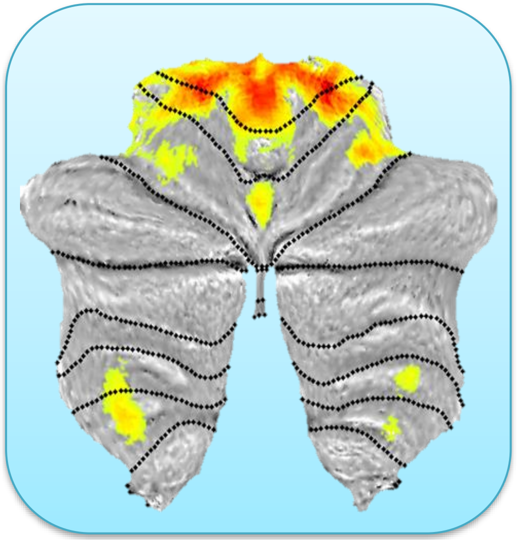
Cividini et al., Neurology 2021

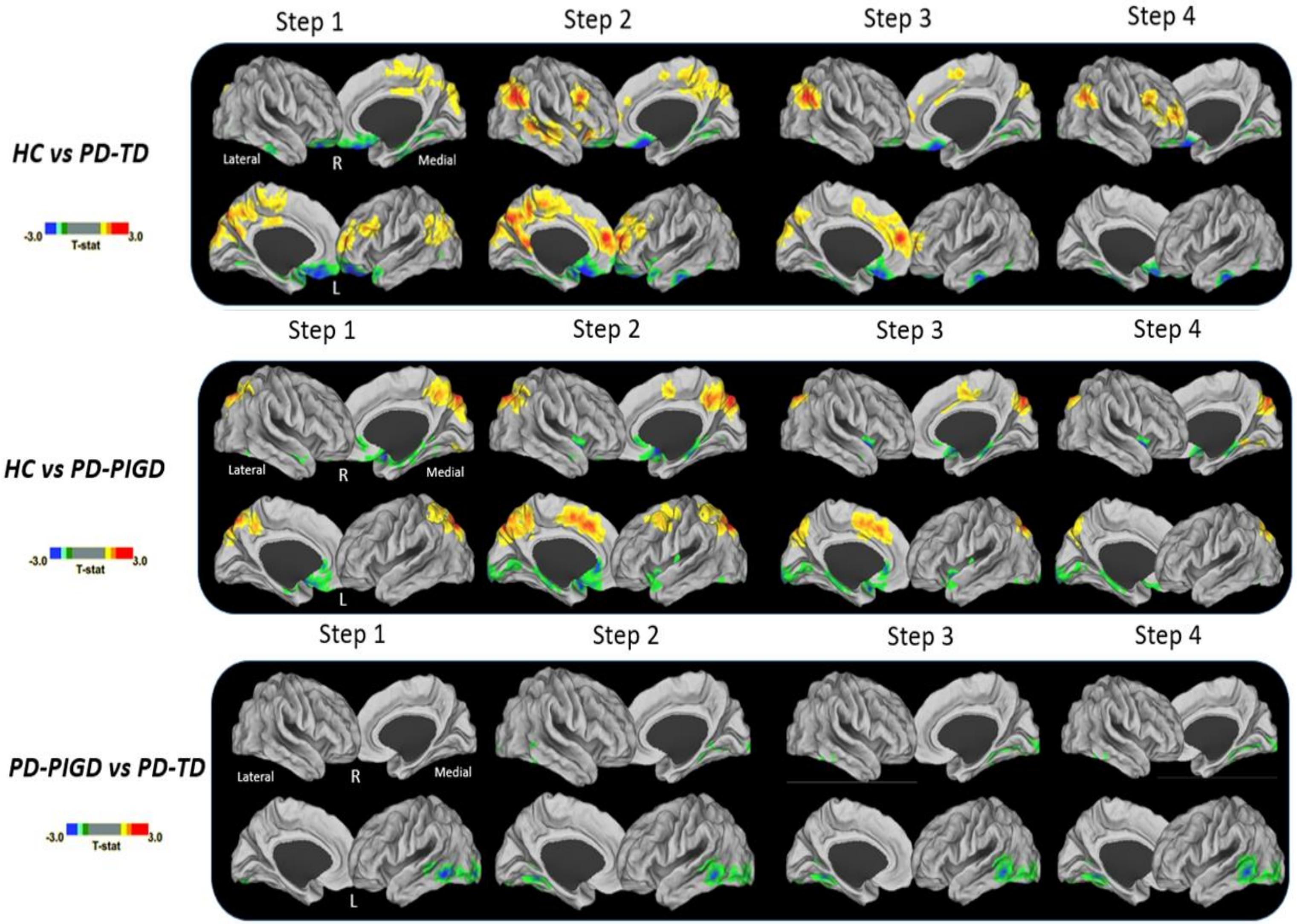
Parkinson's disease / Diagnosis & phenotyping

Tremor dominant *vs* PIGD PD

Motor cerebro-cerebellar networks

Seed region - Cerebellar motor activation map





Basaia et al., NPJ Parkinsons Dis 2022

Outline of the presentation / Applications

- Diagnosis & phenotyping
- **Tracking & predicting progression**
- Network spreading modelling

Multiple Sclerosis / Predicting progression

Prediction of clinical worsening at 6.4-year follow-up

105/233 MS patients (45%) clinically worsened
26/157 (16%) RRMS patients evolved to SPMS

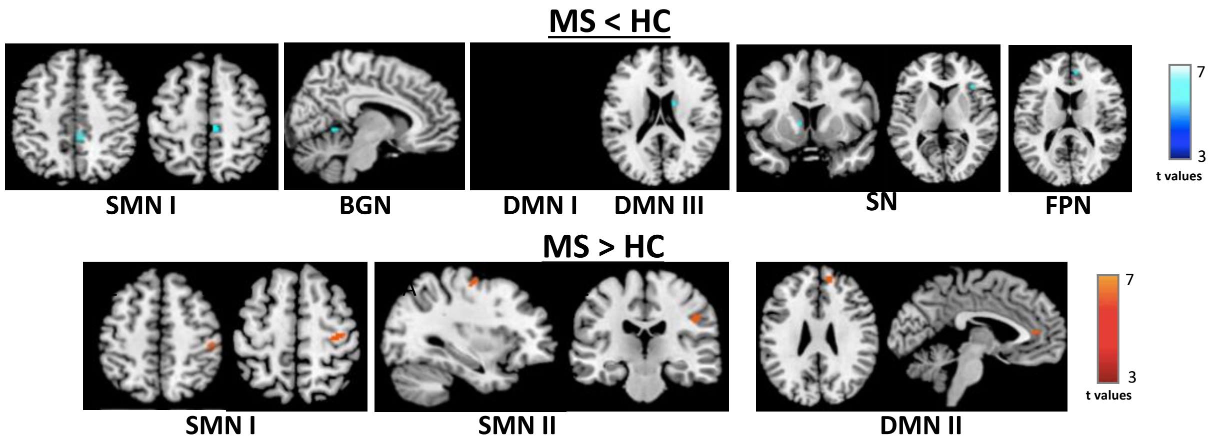
Predictors of disability worsening

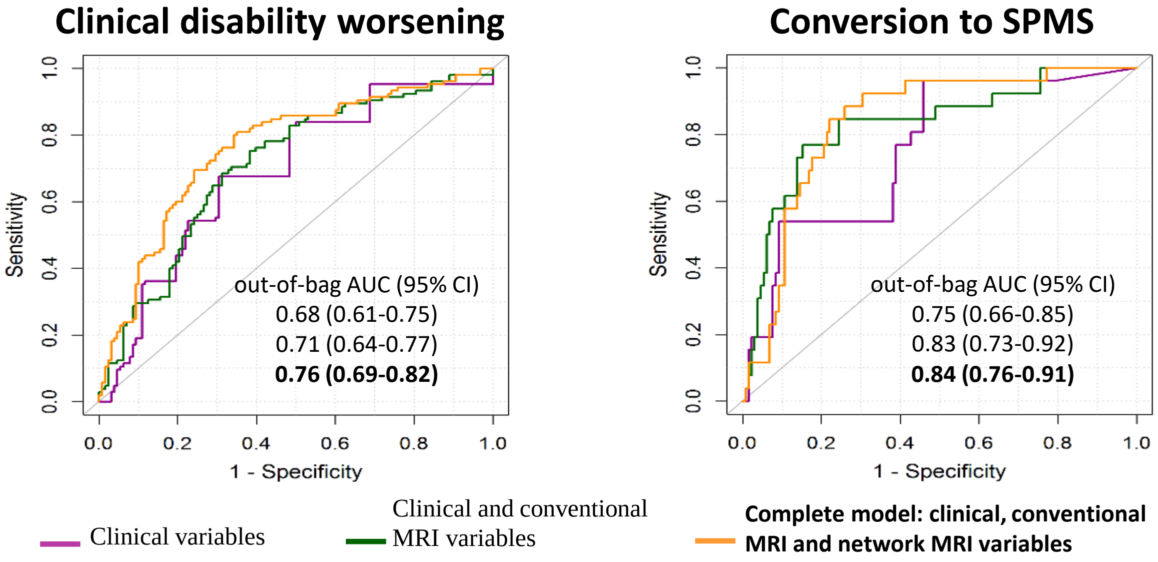
	Relative importance	p	OOB AUC (95% CI)	p
Baseline EDSS	100.0	0.001	0.76 (0.69-0.82)	0.009*
NGMV	73.5	0.001		
NBV	35.7	0.005		
FNC DMN II-DMN III	23.9	0.03		
RS FC SMN II - L precentral gyrus	18.9	0.03		
GM FPN	18.2	0.03		
GM SMN II	16.8	0.04		
GM SN	15.4	0.04		
DMT change	7.9	0.01		

Predictors of SPMS conversion

	Relative importance	p	OOB AUC (95% CI)	p
Baseline EDSS	100.0	<0.001	0.84 (0.76-0.91)	0.02*
NGMV	99.4	0.001		
GM SMN I	47.7	0.03		
DMT change	14.8	0.002		

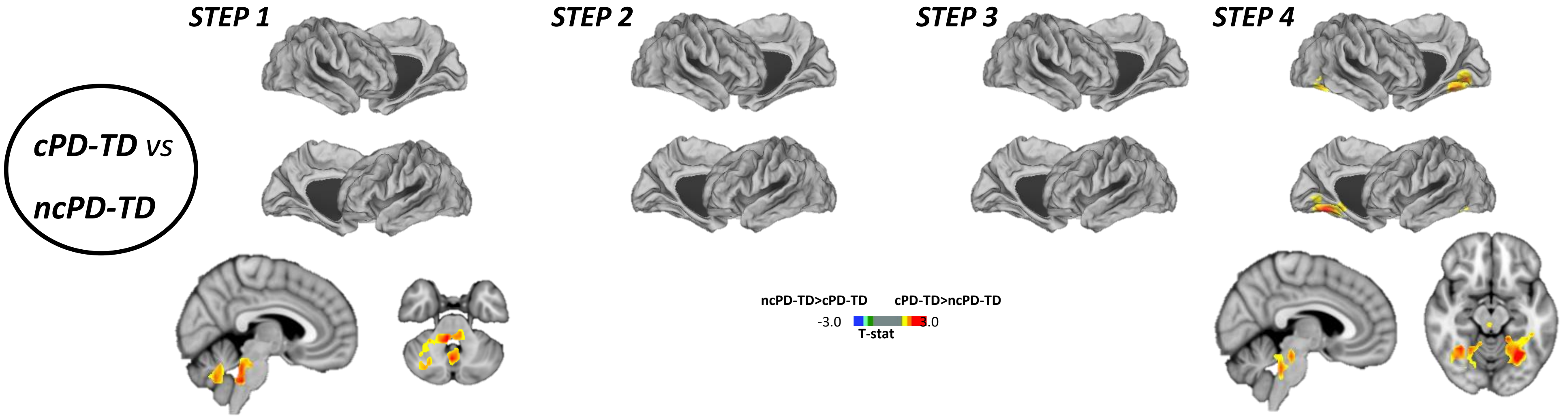
*compared to the model including confounding covariates and clinical variables

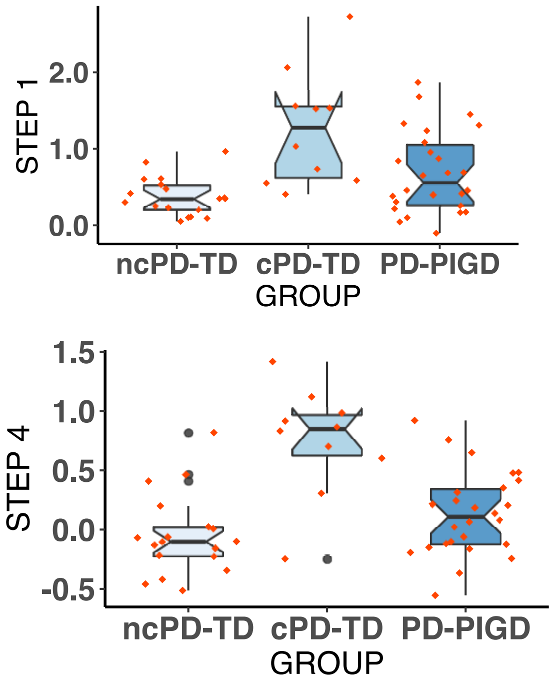


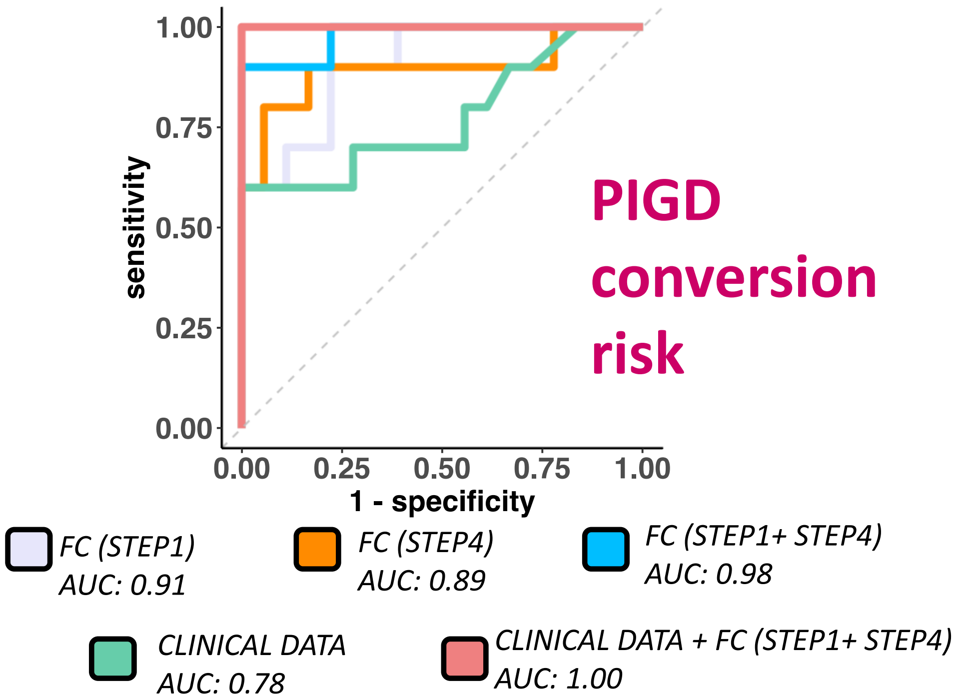


Rocca et al., Neurol Neuroimmunol Neuroinflamm 2021

Parkinson's disease / Predicting progression



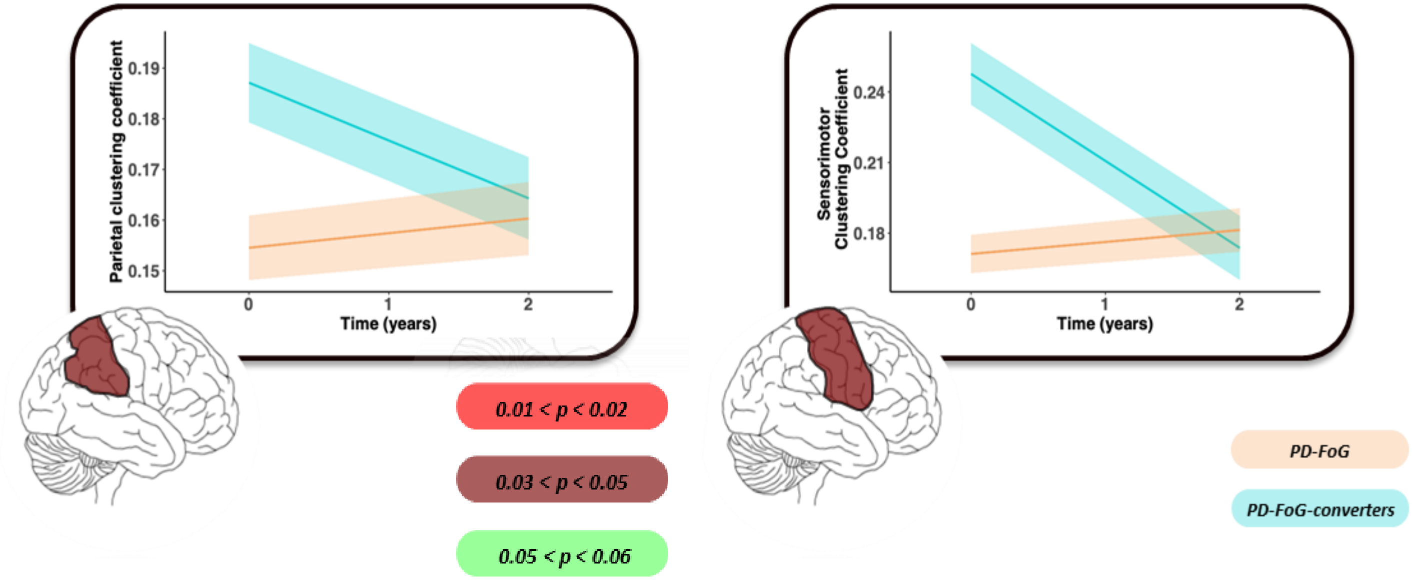


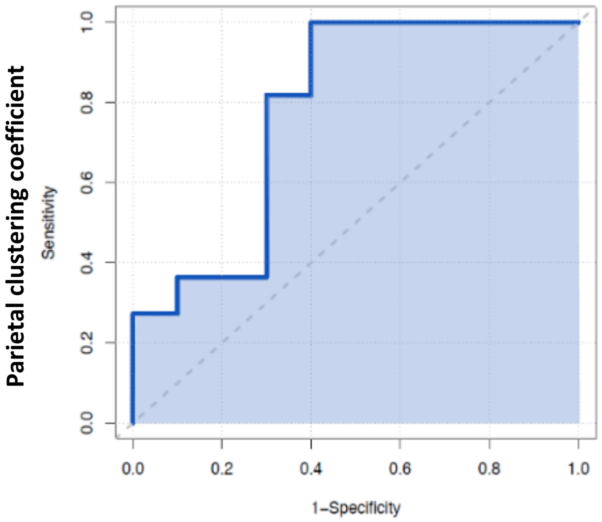


Basaia et al., NPJ Parkinsons Dis 2022

Parkinson's disease / Predicting progression

Freezing of gait





FOG conversion risk

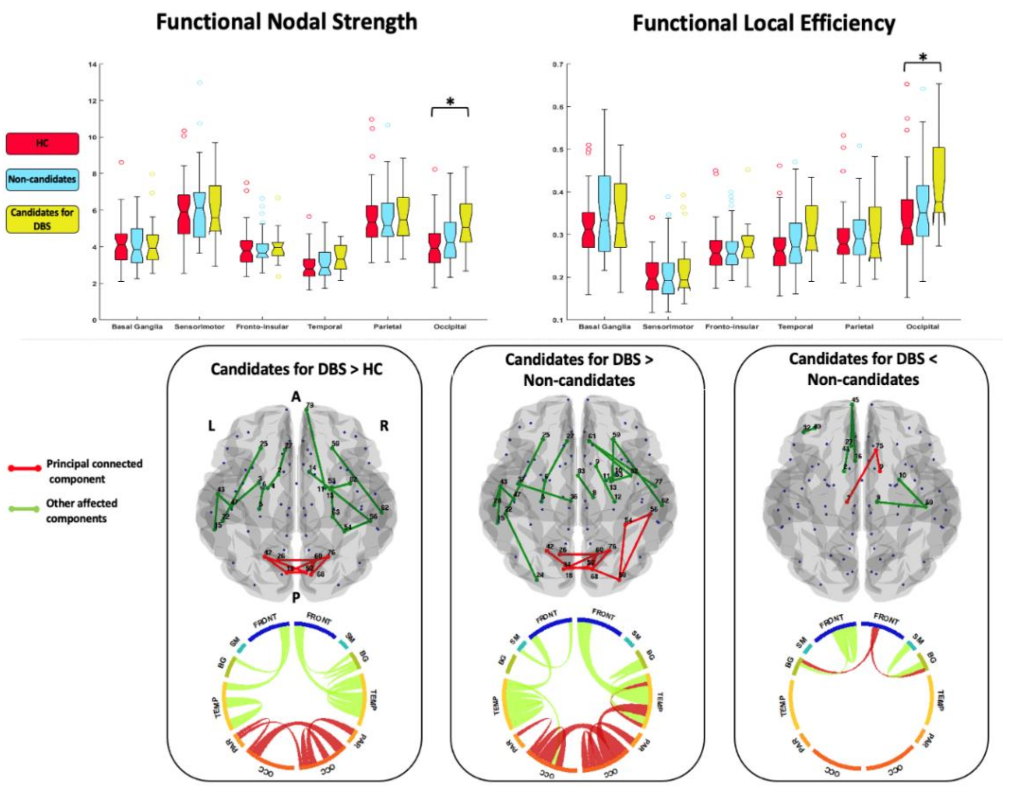
ROC curve area	0.78
Standard error	0.11
Sign.	0.03
95% CI inf	0.57
95% CI sup	0.99

Sarasso et al., NPJ Parkinsons Dis 2022

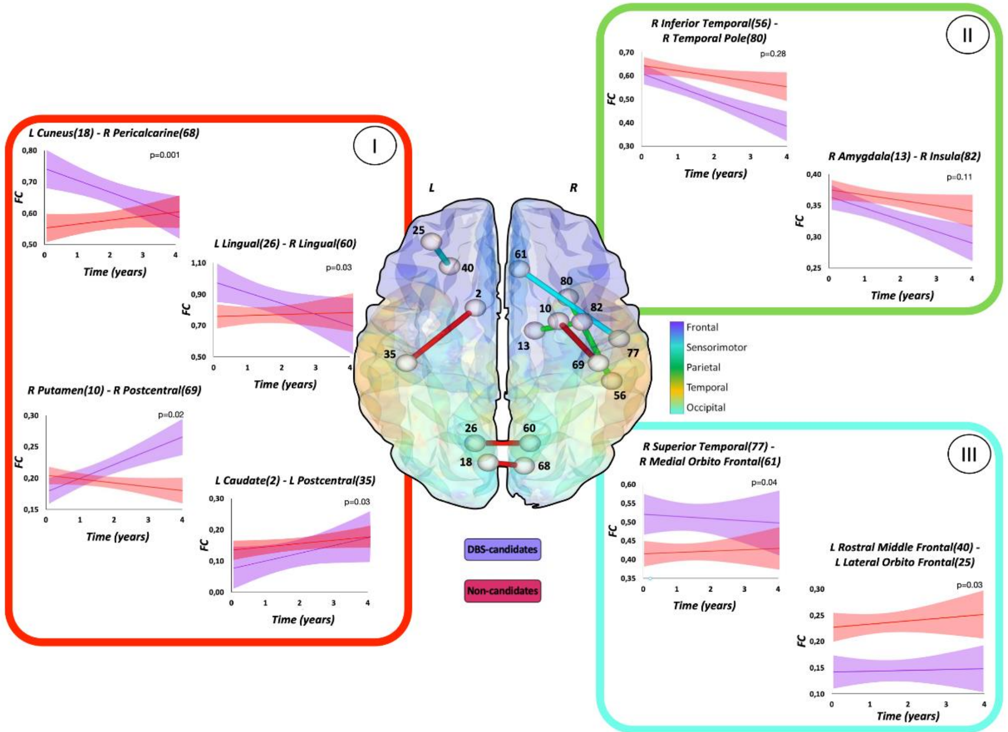
Parkinson's disease / Predicting DBS indications

Functional connectivity in PD candidates for Deep Brain Stimulation

Baseline



Longitudinal



Albano et al., NPJ Parkinsons Dis 2022

Could **functional connectivity predict** clinical indications of DBS for PD?

- ✓ Occipital hyperconnectivity and/or basal ganglia-sensorimotor/frontal hypoconnectivity
- ✓ Progressive increased connectivity between basal ganglia and sensorimotor/frontal areas and decreased connectivity in the posterior regions

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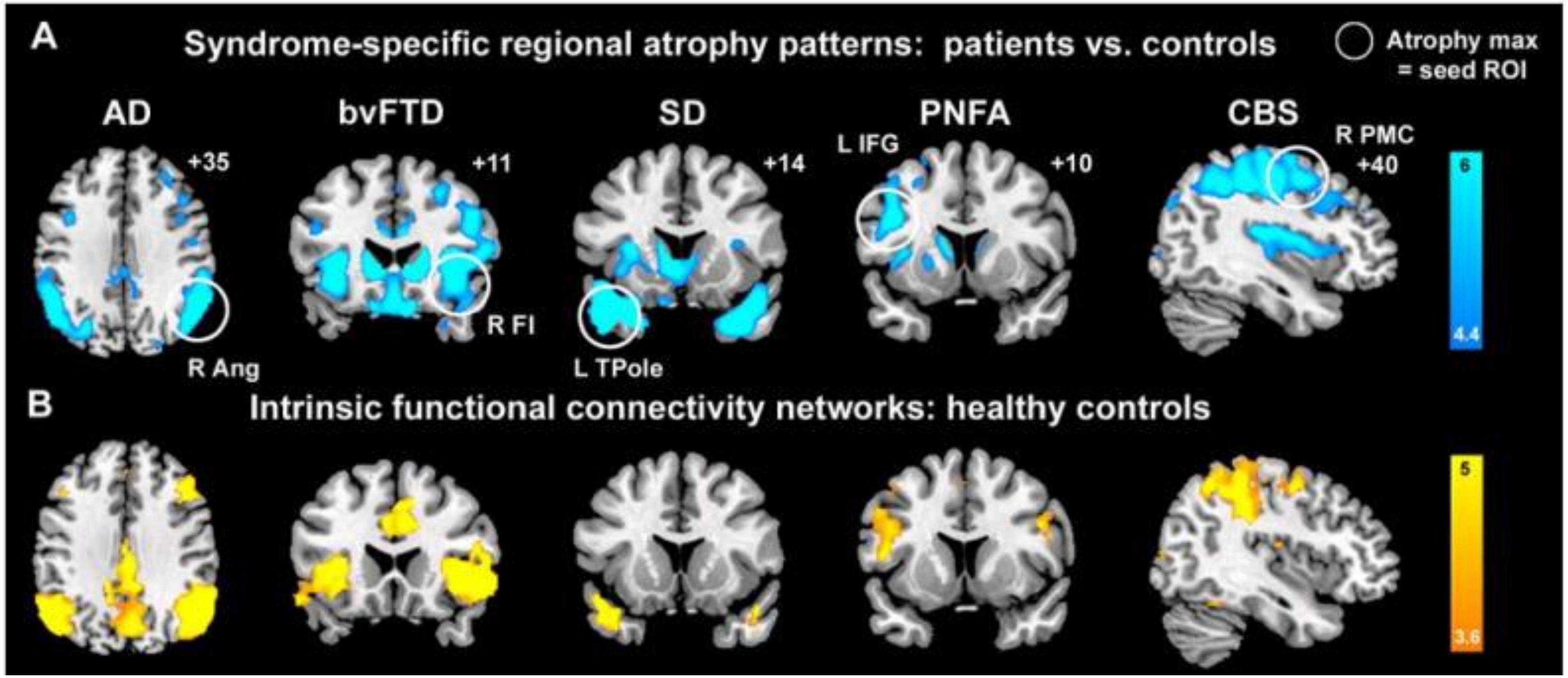
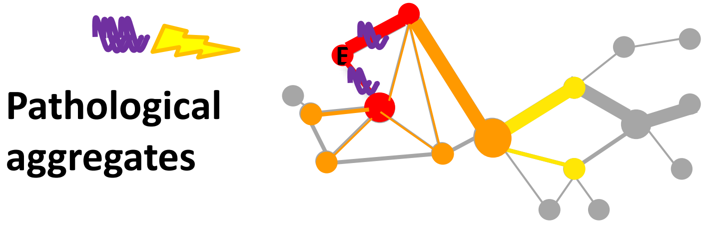
- Tracking & predicting progression
- Network spreading modelling

Background / The «network-based degeneration» hypothesis



Seeley et al., Neuron 2009



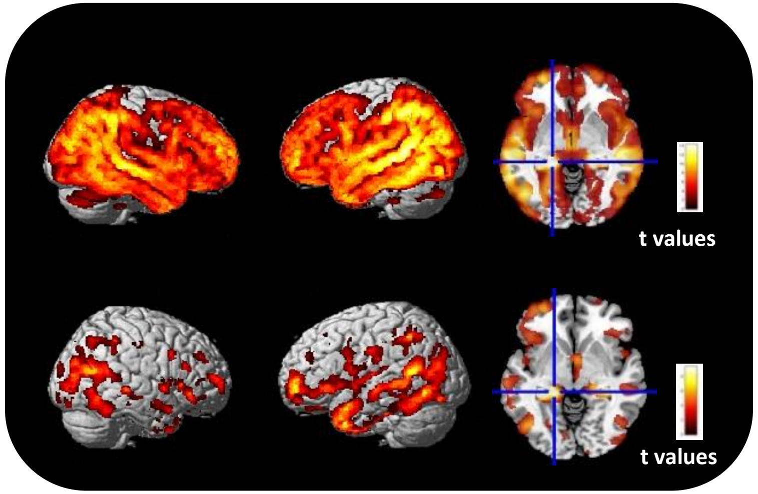
Epicenter

«Target» network

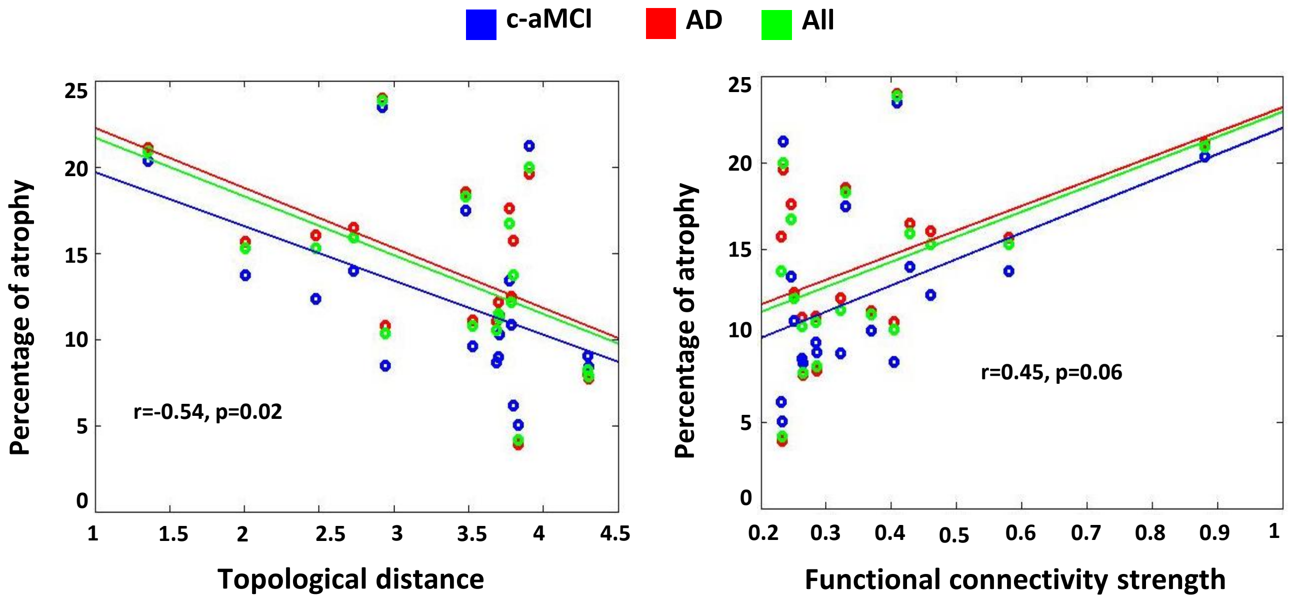
«Off-target» network

Alzheimer's disease / Network spreading modelling

Atrophy *vs* healthy brain connectome in AD

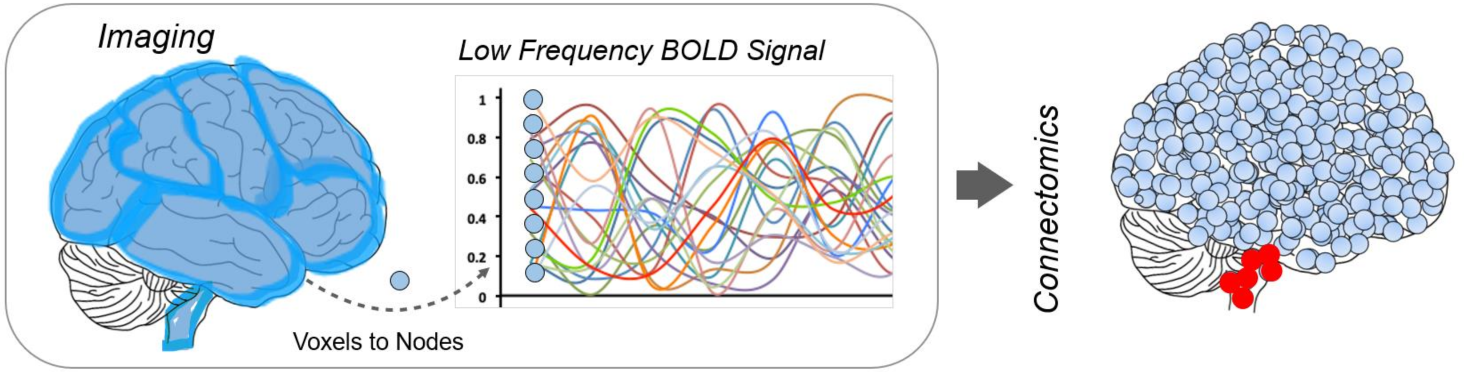


EPICENTER: Left hippocampus



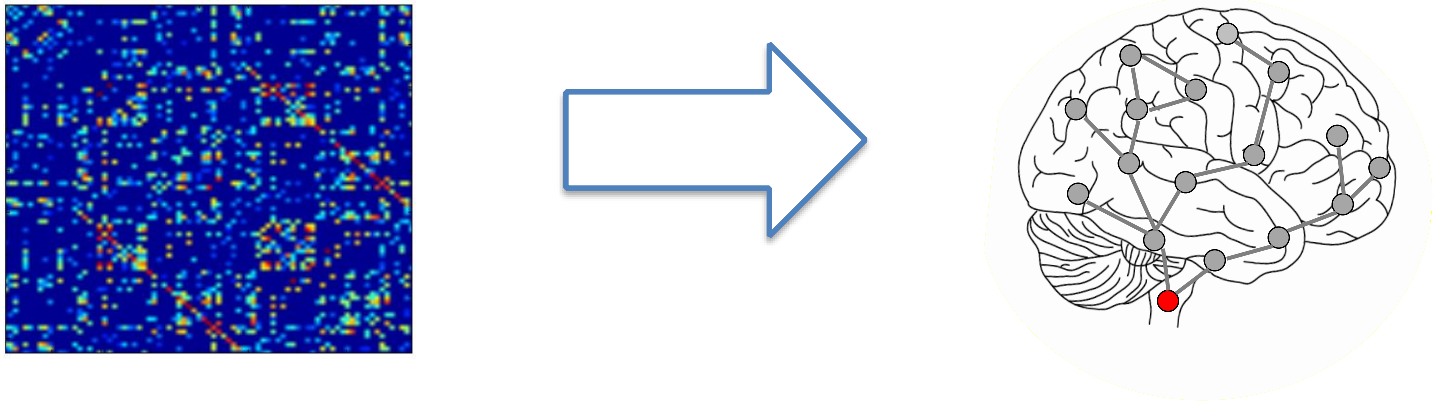
Filippi et al., Mol Psychiatry 2020

Background / Stepwise functional connectivity



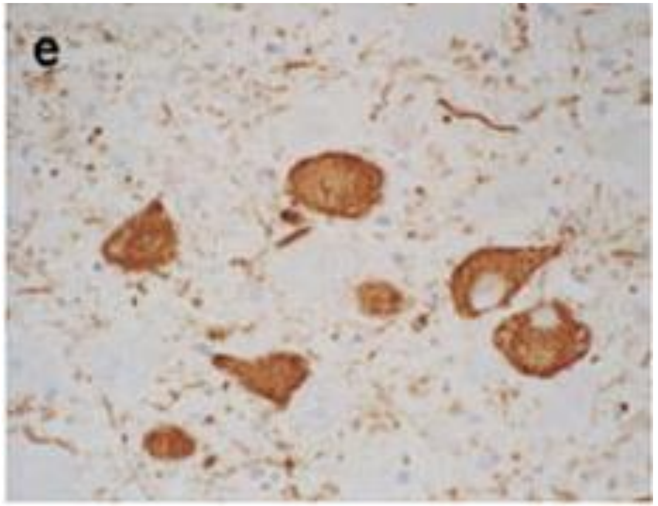
"Classic" functional connectivity matrix

Stepwise functional connectivity (SFC)

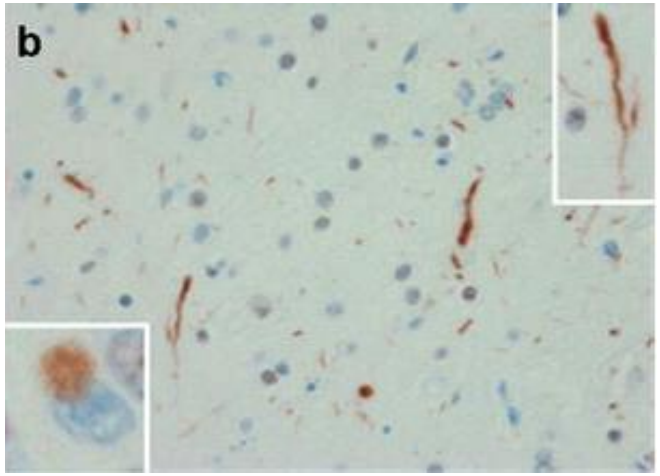


Frontotemporal dementia / Network spreading modelling

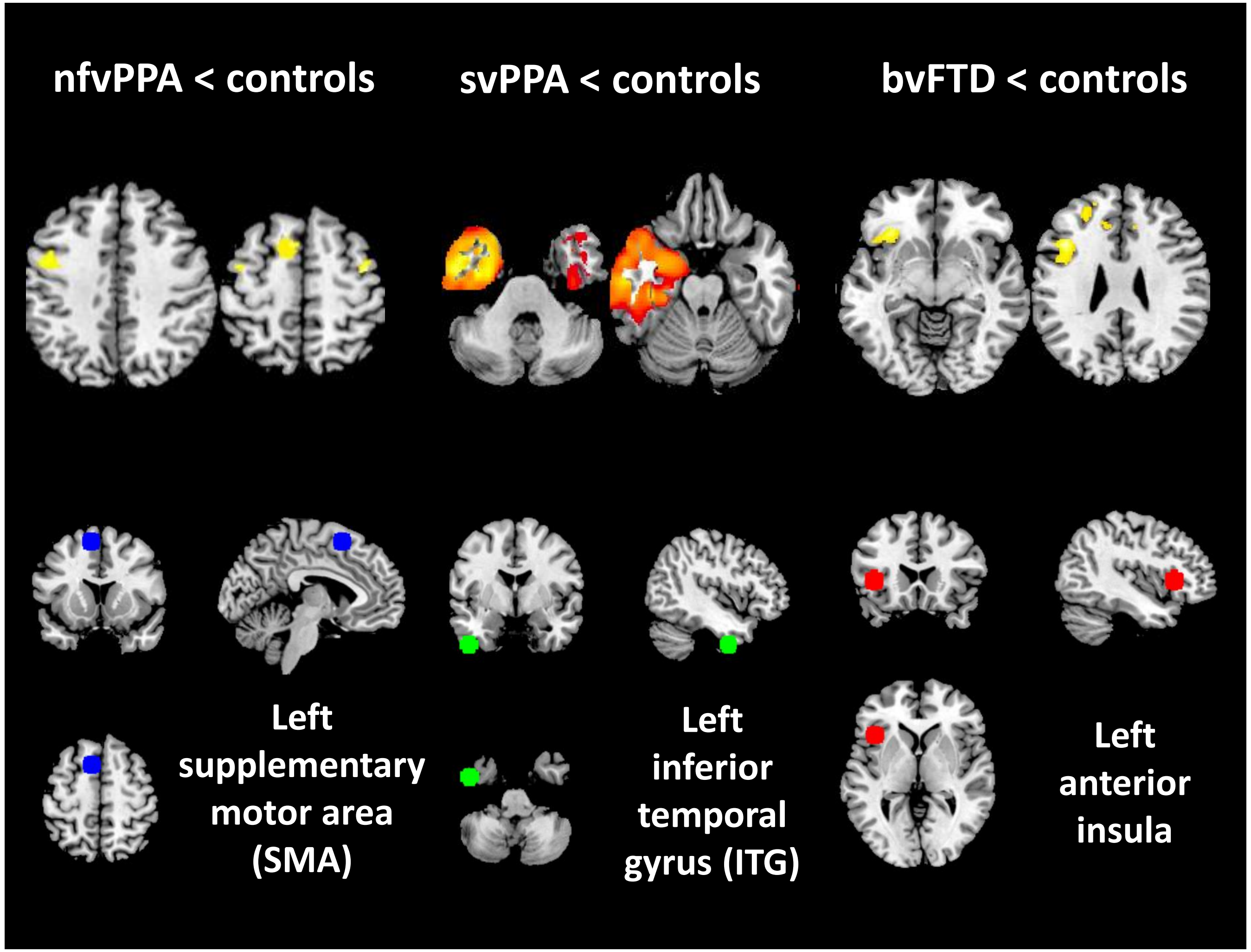
Patterns of atrophy in an independent cohort of path-proven FTD (Mayo Clinic)



FTLD-tau



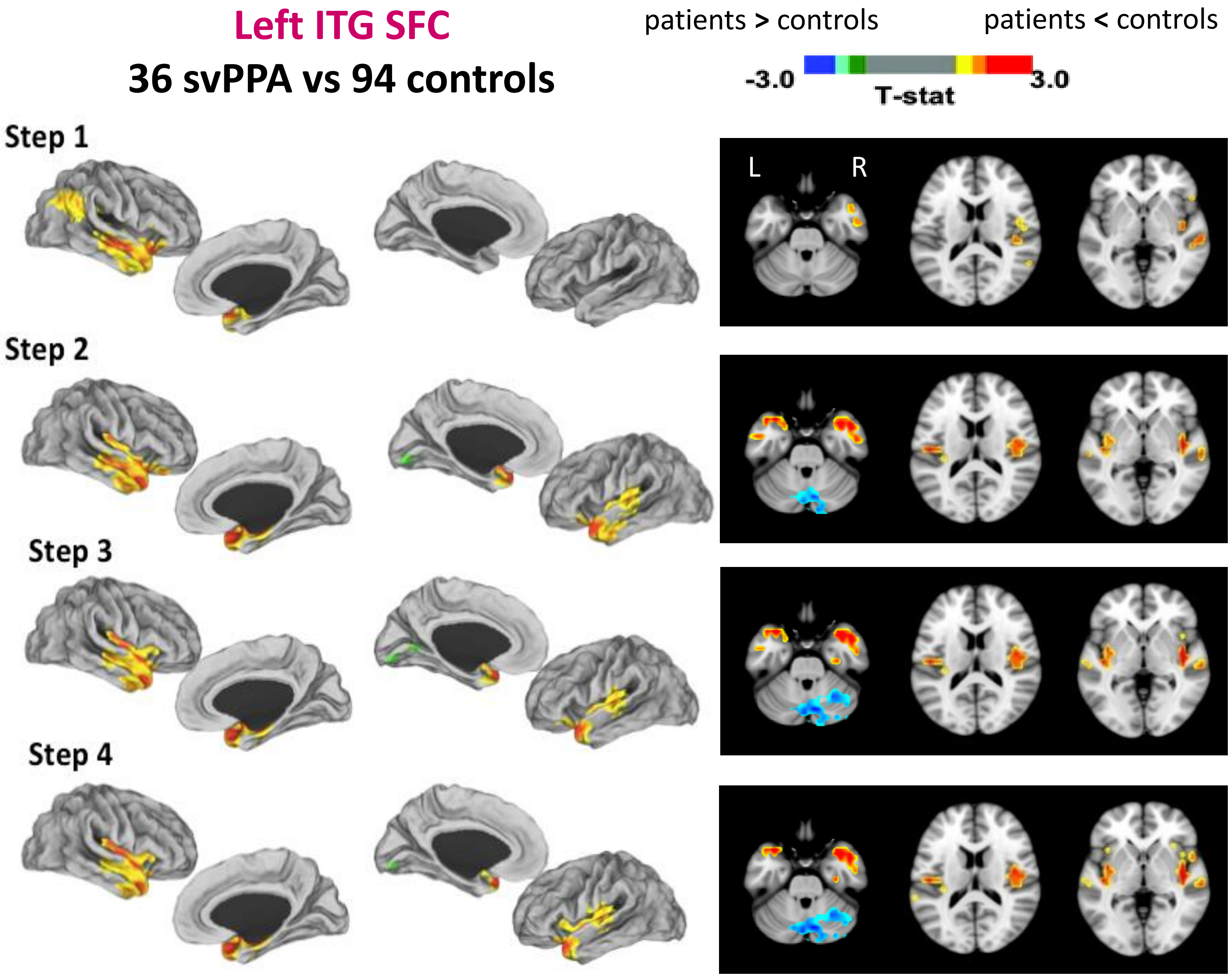
FTLD-TDP

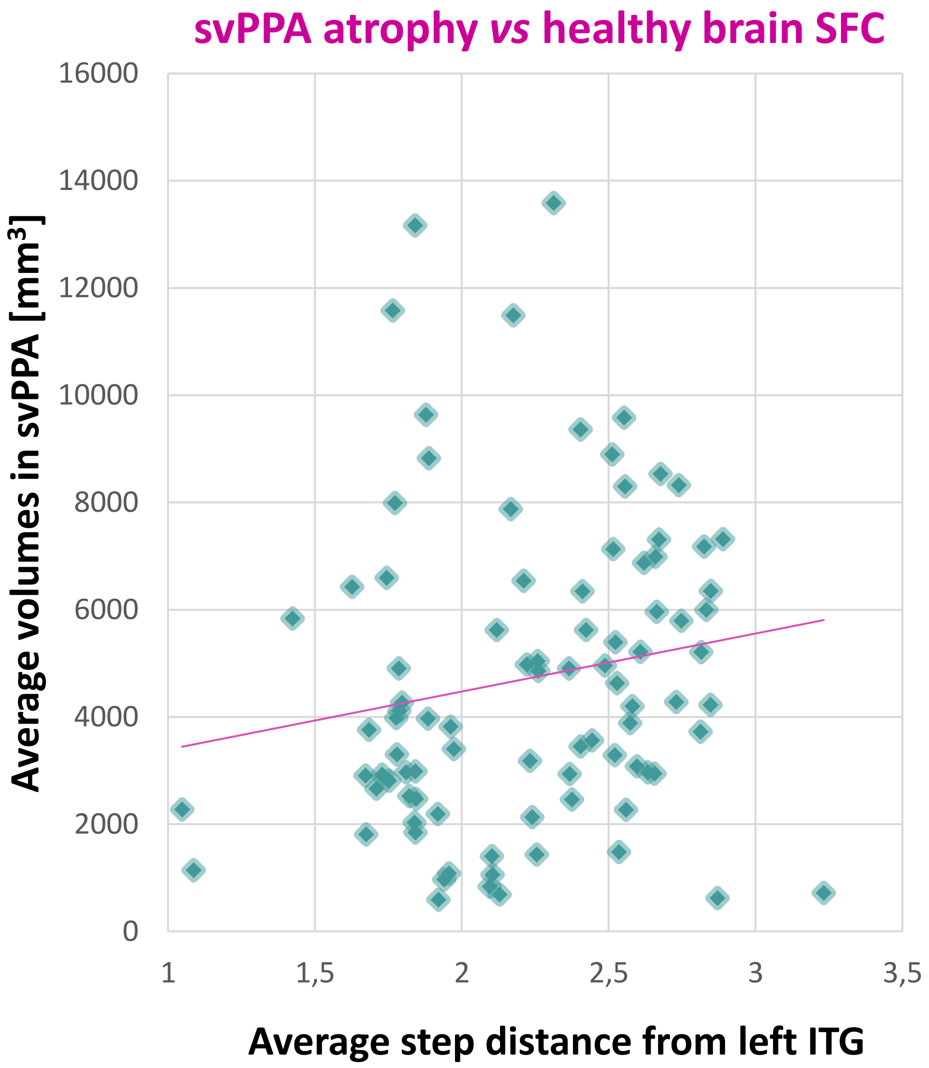


Josephs et al., Acta Neuropathol 2011

Agosta et al., Neurology 2023 (in press)

Frontotemporal dementia / Network spreading modelling





Agosta et al., Neurology 2023 (in press)

Conclusions

- **Although fMRI requires extensive image post-acquisition processing, it is a state-of-the-art technique sensitive to alterations in brain activation in task-based and resting-state settings, both in normal and pathological conditions**
- **Network analysis provides a powerful method to quantitatively describe the topological organization of brain connectivity**
- **Disrupted functional connectivities have been associated with several neurodegenerative disorders, including MS, dementia, Parkinson's disease and amyotrophic lateral sclerosis**
- **These assessments are of special interest for their potential to characterize the signature of each neurodegenerative condition and aid both the diagnostic process and the monitoring of disease progression**

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