ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Educational Session 26:
From structural and functional connectivity to clinical impairment in multiple sclerosis (MAGNIMS)

FUNCTIONAL CONNECTIVITY IN MS

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Disclosures

Dr. Maria A. Rocca

Received speakers honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis, Teva, Merck Serono, and Roche and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla

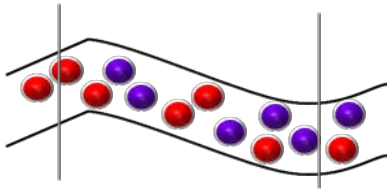
Outline of the presentation

- Methodological considerations (a few)
- Active fMRI paradigms: what have we learned?
- RS fMRI: is that the solution?
- What else?
- Conclusions

Methodological considerations

BOLD

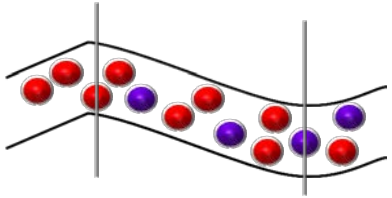
Basal state



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

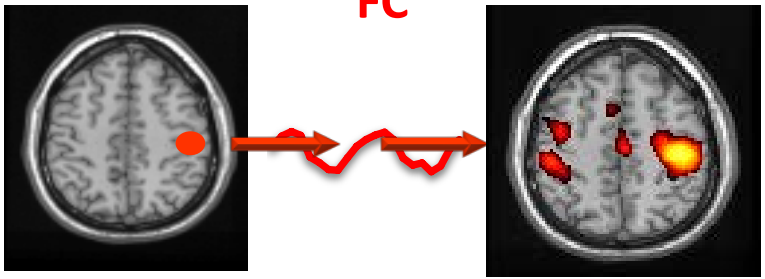
HbO_2
Hbr

Activated state

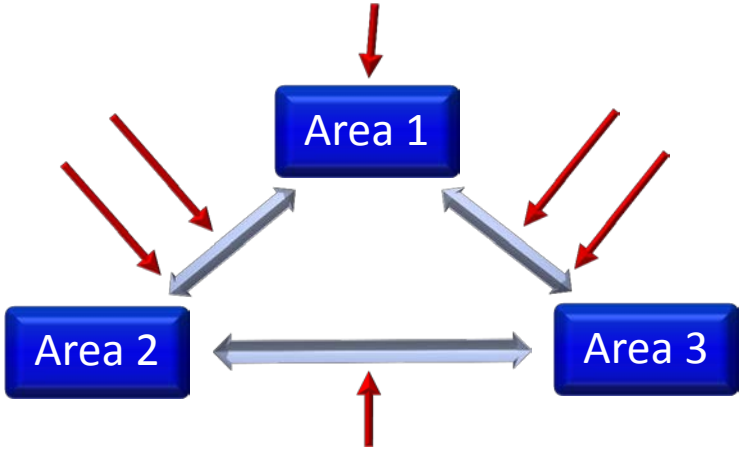


- increased flow
- decreased [Hbr]
- increased CBV
- increased MRI signal

FC

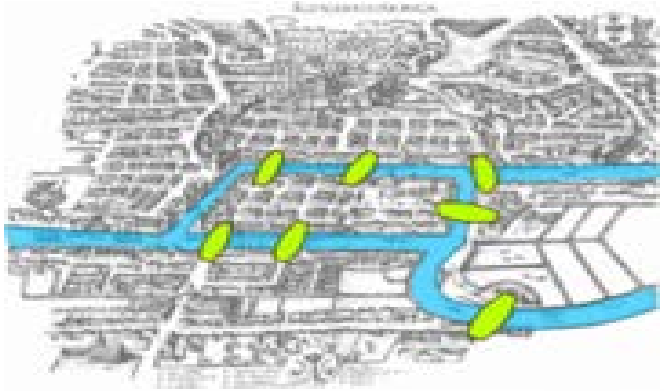


Effective connectivity

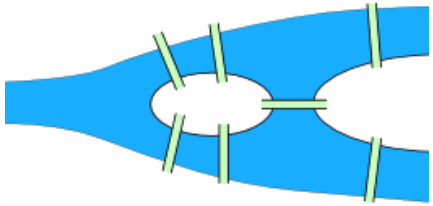


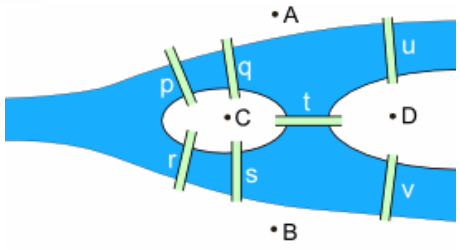
Methodological considerations

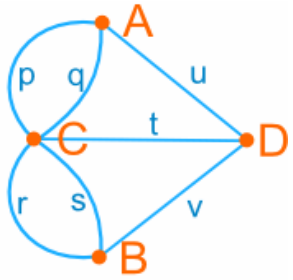
The Seven Bridges of Königsberg



Can you take a walk through the town, visiting each part of the town and crossing each bridge only once?

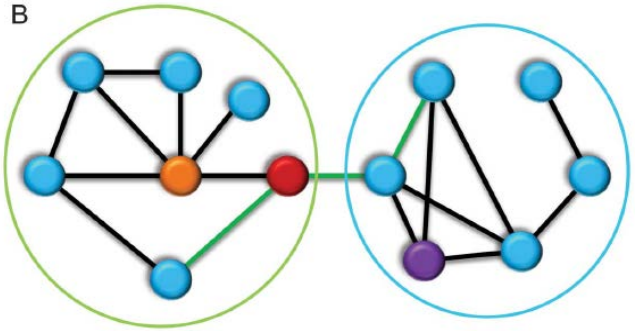






Euler, 1741

Methodological considerations / Graph theory

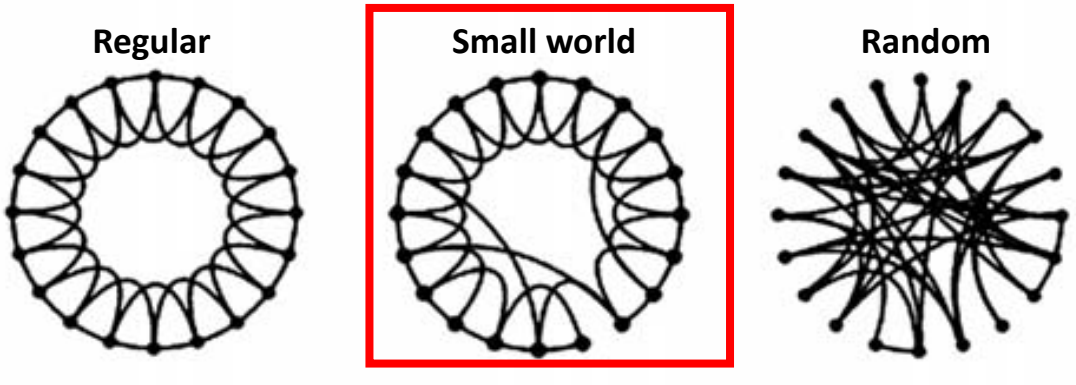


Shortest path lenght

Highest degree

Connecter hub

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



Small world network: high clustering coefficient, short characteristic path length

Outline of the presentation

- Methodological considerations (a few)
- Active fMRI paradigms: what have we learned?
- RS fMRI: is that the solution?
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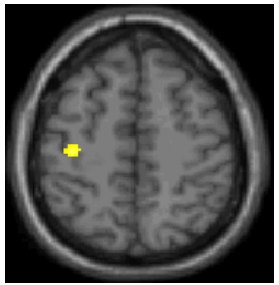
Active fMRI / Motor system

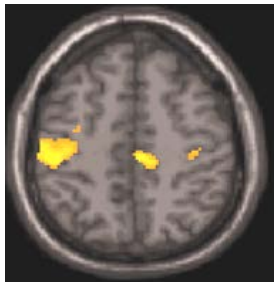
CIS *vs* non-disabled RRMS

SMC

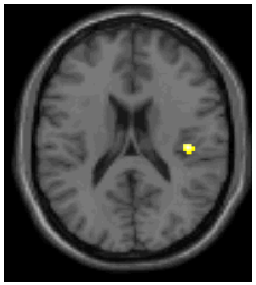


Non-disabled *vs* mildly disabled

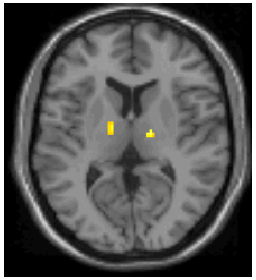
SMC, SMA



Mildly disabled RRMS *vs* SPMS



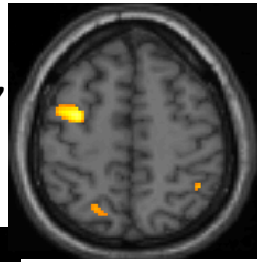
SII

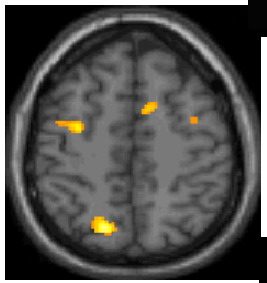


Thalamus

SPMS *vs* mildly disabled RRMS

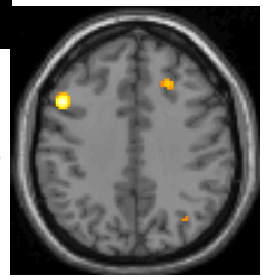
Precuneus, IPL, MFG





Precuneus, CMA, MFG

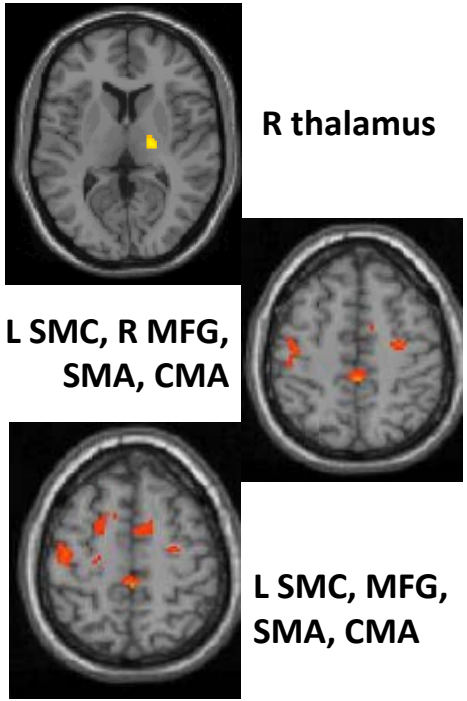
MFG, IPL



Rocca et al., Lancet Neurol 2005

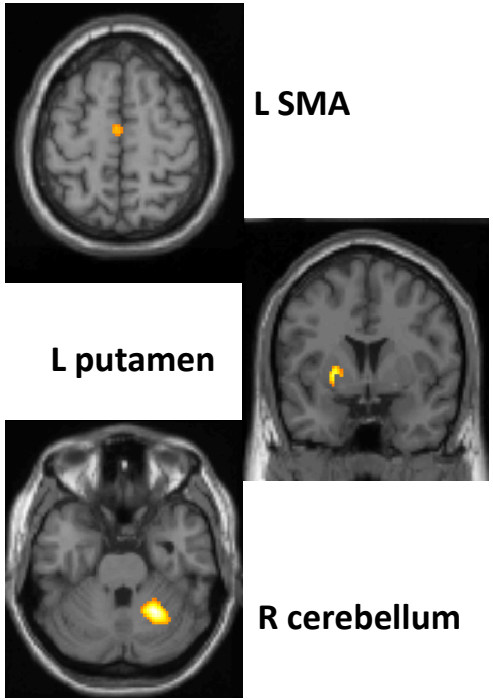
Active fMRI / Motor system

F MS day 1 *vs* baseline + day 4



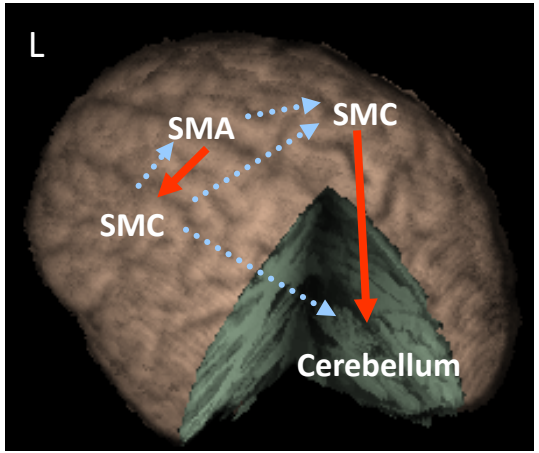
Rocca et al., Hum Brain Mapp 2007

SPMS (reduced activations)



Rocca et al., Neurology 2010

Active fMRI / Correlation with structural damage



Rocca et al. Neurology 2007

Increased connectivity in patients

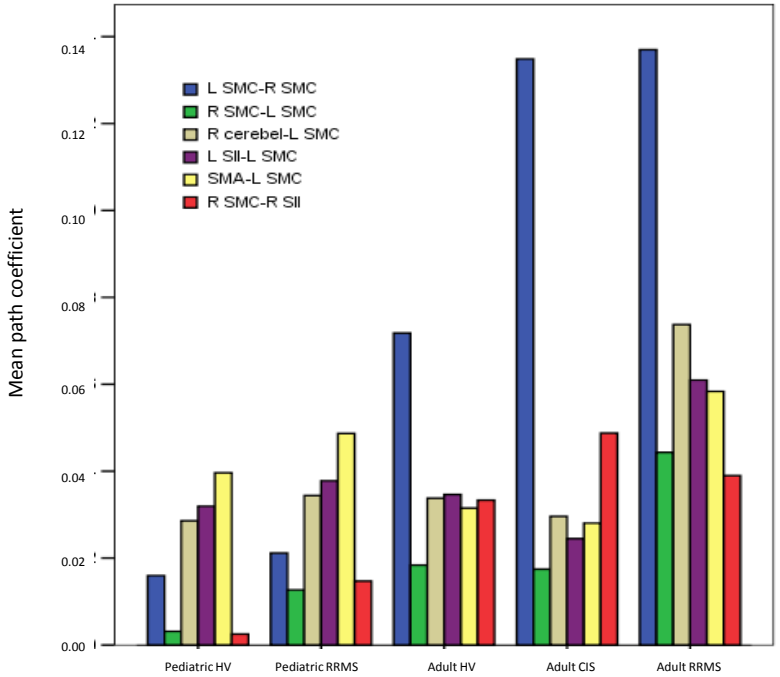
Similar connectivity in patients and controls

SMA to L primary SMC:

- CST LL (r = 0.64, p = 0.04)

R SMC to cerebellum:

- DRT-FA (r = -0.73, p = 0.02)
- DRT-MD (r = 0.85, p = 0.004)

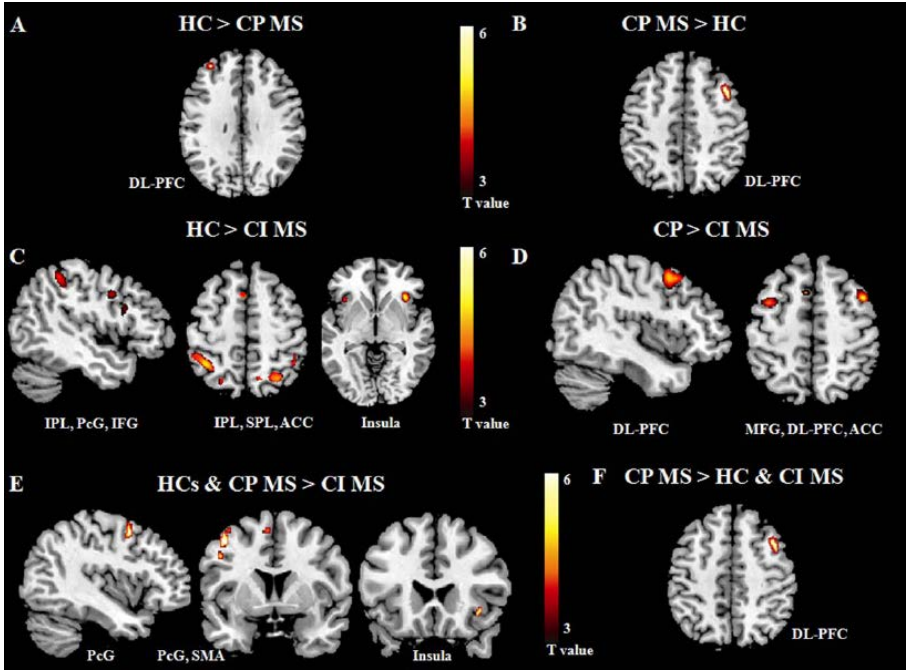


Rocca et al., Radiology 2010

Connectivity coefficients *vs* CC and CST damage (r = -0.34 to 0.40)

Active fMRI / Cognition

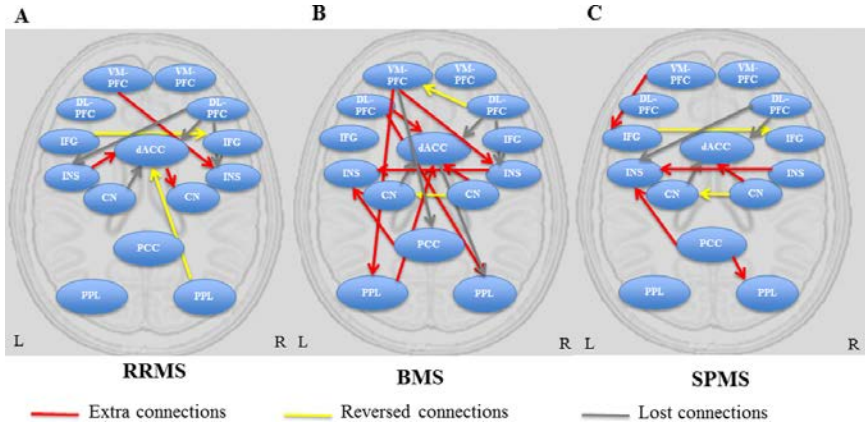
N-back task



Rocca et al., Hum Brain Mapp 2014

Stroop task

- 84 MS patients (33 RRMS, 33 SPMS and 18 BMS)
- 37 age- and gender-matched HCs



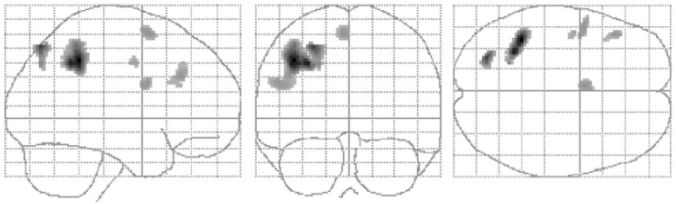
Dobryakova et al., HBM 2016

Depending on the phenotype, patients with MS use different strategies when cognitive control demands are high and rely on different network connections

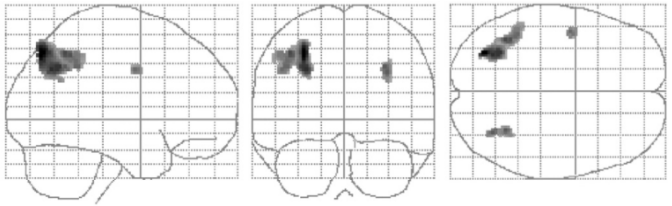
Active fMRI / Correlation with structural damage

PASAT and SLF damage

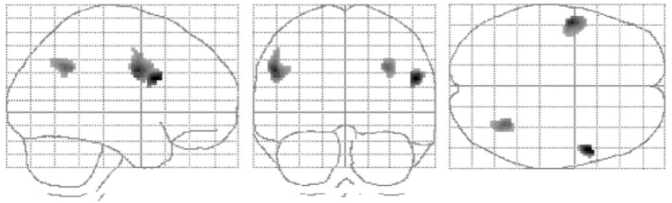
Healthy controls



MS patients with high SLF FA

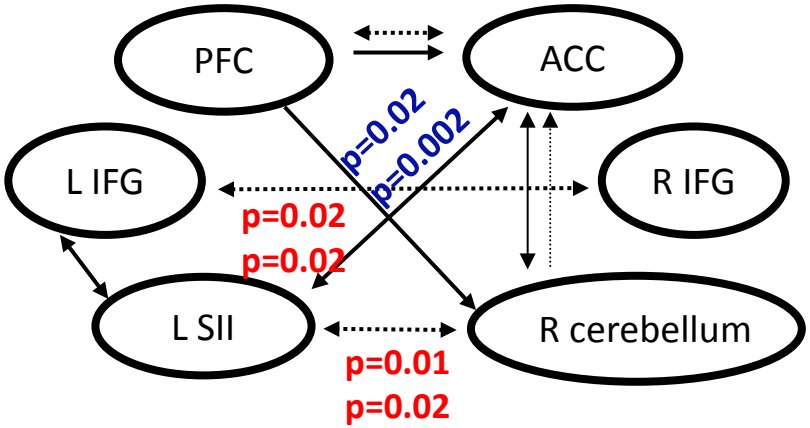


MS patients with low SLF FA



Bonzano et al., NeuroImage 2009

Stroop test/BMS



Increased connectivity in patients
Reduced connectivity in patients

Rocca et al., HBM 2009

FC *vs* WM microstructural damage

Significant correlation with SFOF, uncinate, CC and fornix damage: (r values between -0.66 and 0.60)

Outline of the presentation

- Methodological considerations (a few)
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- RS fMRI: is that the solution?
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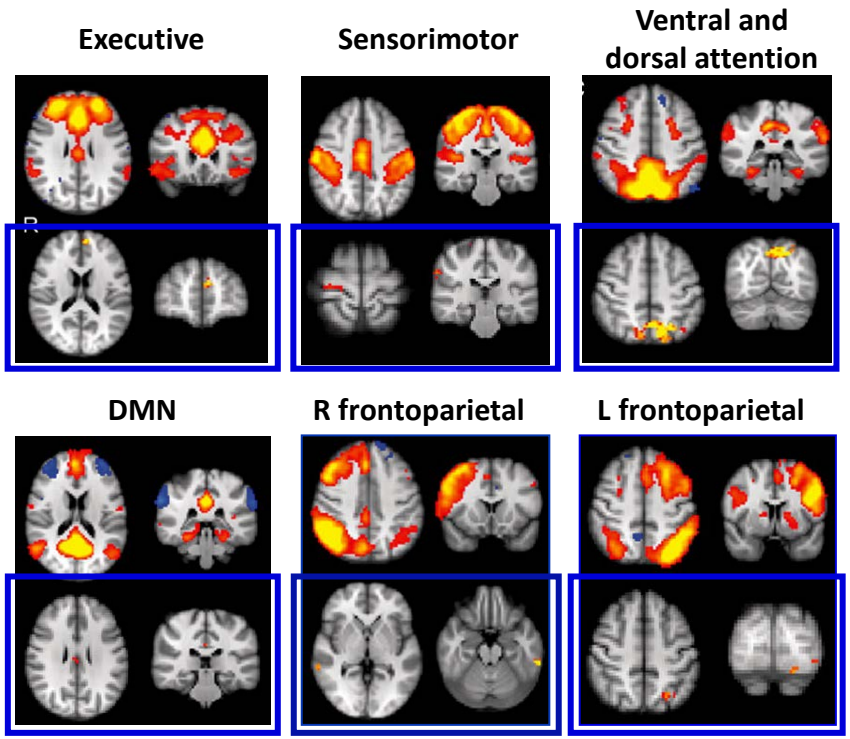
RS fMRI / Intra-network abnormalities

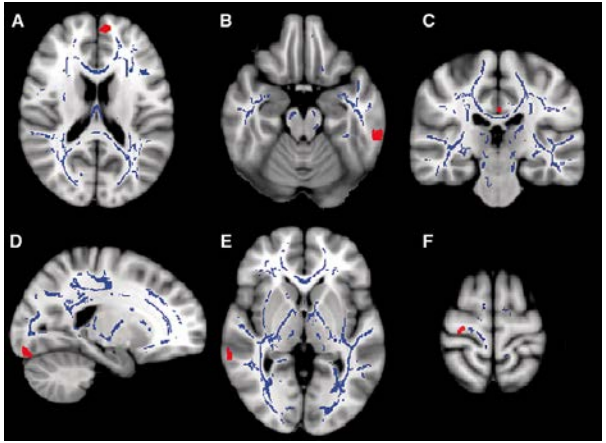
CIS



Roosendaal et al., Brain 2010

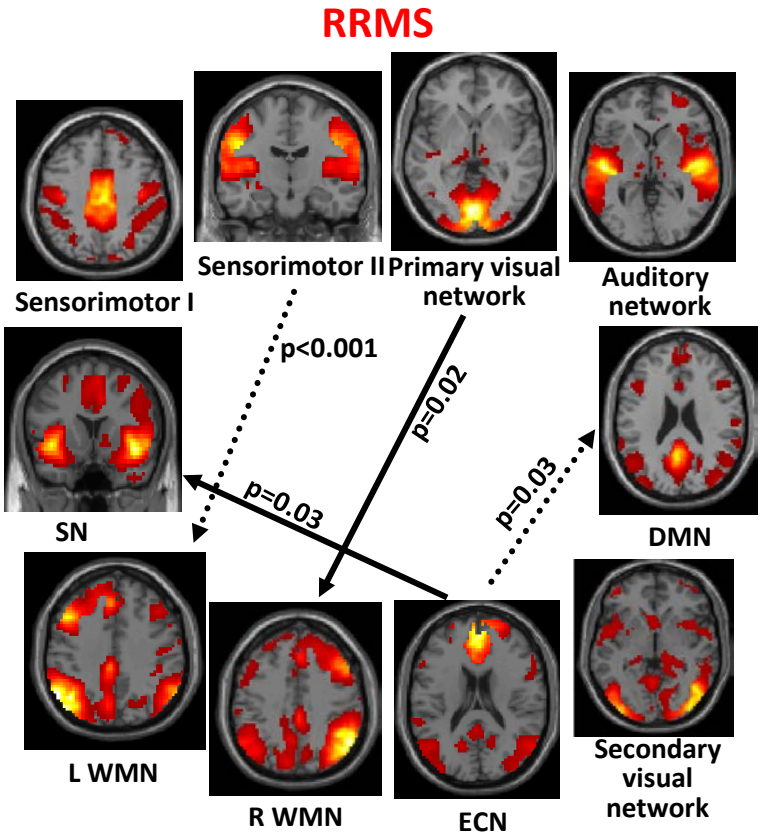
Table 2 Synchronization values (Z-scores) extracted from areas of significantly increased synchronization in patients with clinically isolated syndrome for each network

	Controls	CIS	RR
	median	median	median
Executive function (Fig. 1A)	20.8	32.7	21.9
Sensorimotor function (Fig. 1B)	26.0	37.0	25.4
Attention system (Fig. 1C)	43.2	49.0	43.0
Default mode network (Fig. 1D)	30.0	40.8	24.7
Frontoparietal right (Fig. 1E)	11.1	23.1	6.0
Frontoparietal left (Fig. 1F)	5.9	14.9	4.8



Increased synchronization CIS
Decreased FA RRMS

RS fMRI / Inter-network abnormalities

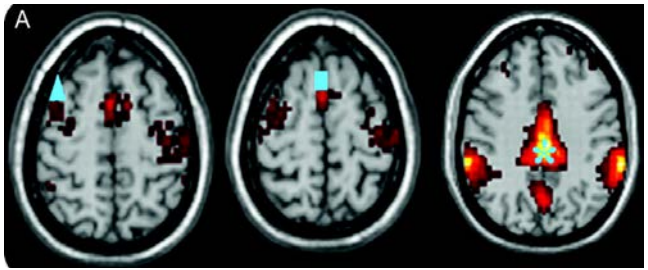


Rocca et al., Neurology 2012

	RS netv	Regions	R (p)
T2 LV	ECN	R angular gyrus	−0.26 (0.01)
		L IFG	−0.26 (0.02)
	DMN	R IFG	−0.28 (0.01)
	SN	R insula	−0.27 (0.01)
	R WMN	L cerebellum	−0.45 (<0.001)
	L WMN	R cerebellum	−0.32 (0.003)
EDSS	ECN	R angular gyrus	−0.35 (0.001)
	DMN	R IFG	−0.24 (0.03)
	R WMN	L cerebellum	−0.28 (0.01)
	L WMN	R cerebellum	−0.33 (0.002)

RS fMRI / Cognitive impairment

↓ DMN in progressive MS patients



Correlations between ↓ DMN RS FC and:

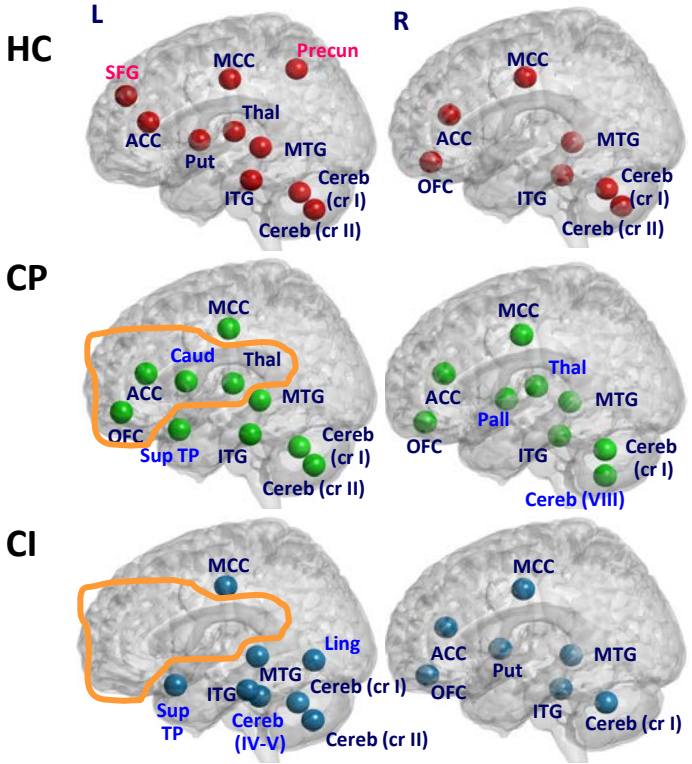
PASAT (r=0.42, p<0.001)

CC FA and atrophy (r from 0.54 to 0.87, p<0.001)

Cingulum FA (r=0.83, p<0.001)

Rocca et al., Neurology 2010

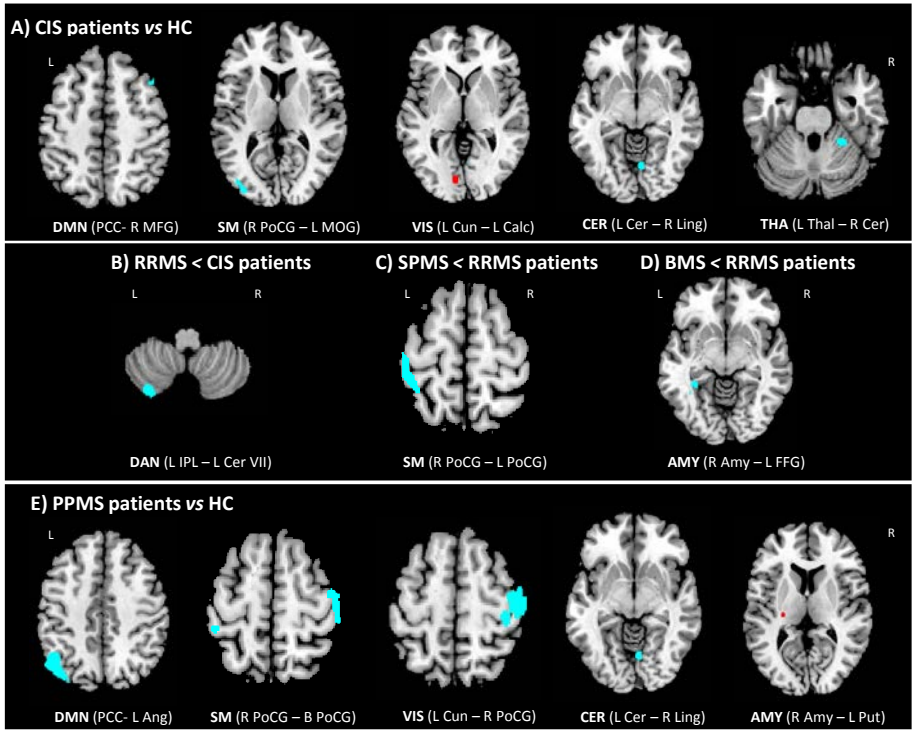
MS connectome



Rocca et al., Brain Struct Funct 2015

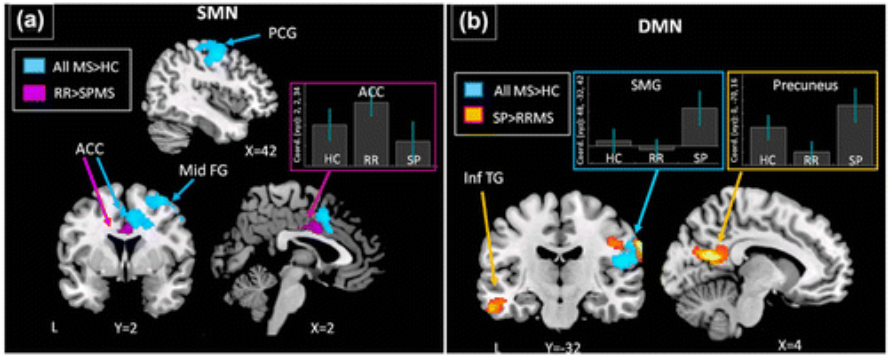
RS fMRI / MS clinical phenotypes

MS clinical phenotypes



Rocca et al., MSJ 2018

RRMS & SPMS

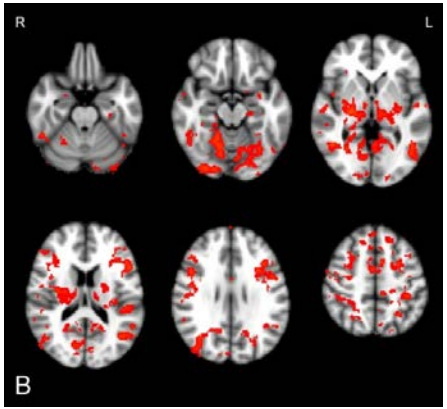


Basile et al., MSJ 2013

RS FC abnormalities seem to parallel patients' clinical state and capability of compensating for the severity of clinical/cognitive disabilities

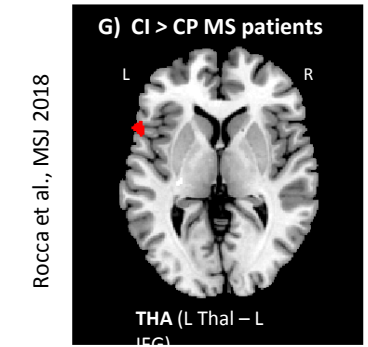
RS fMRI / The thalamus and cognitive impairment

↑ RS FC *vs* worse PASAT



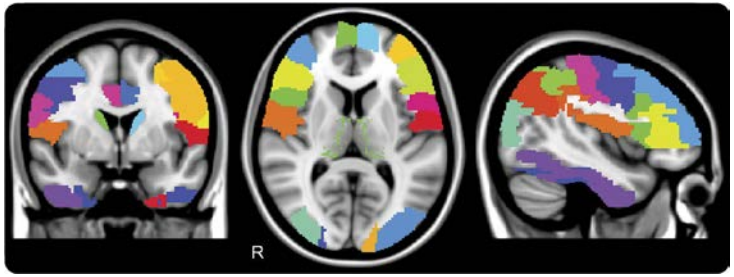
Tona et al., Radiology 2014

↑ thalamic RS FC in CI



Rocca et al., MSJ 2018

↑ thalamic RS FC in CI MS

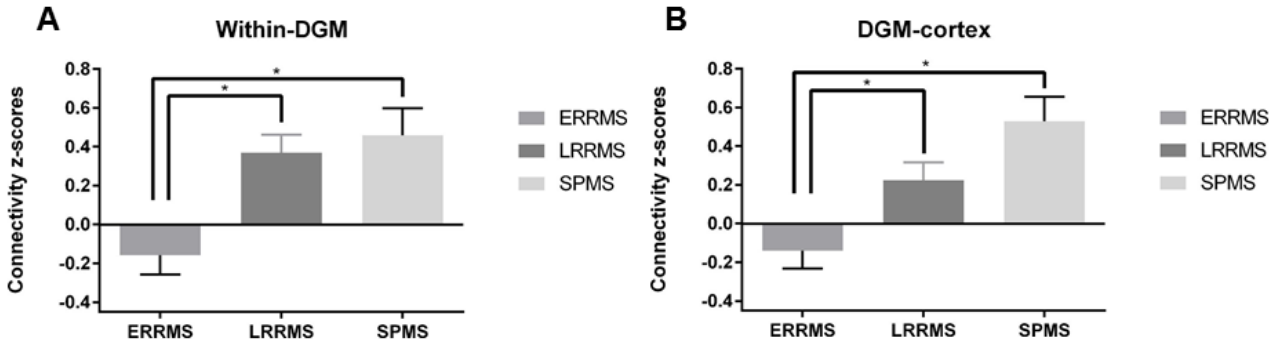


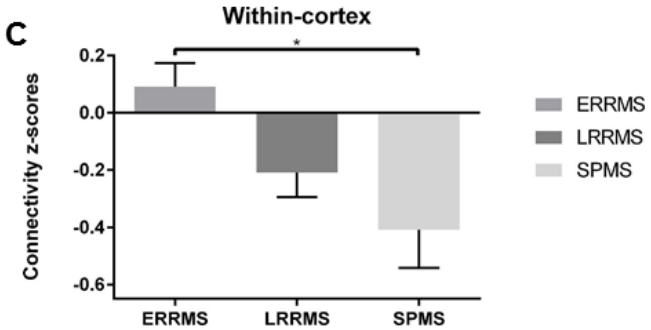
Schoonheim et al., Neurology 2015

Predictors of cognition

		β	p-value	95% CI Lower	95% CI Upper
Block 1	*Adjusted R^2 0.203*				
	Education 2	0.620	0.001	0.340	0.868
	Sex	-0.243	0.031	-0.467	-0.027
	Education 1	0.239	0.110	-0.061	0.519
	Age	-0.009	0.187	-0.023	0.004
Block 2	*Adjusted R^2 0.447*				
	Thalamic SL (1/x)	0.073	0.004	0.021	0.121
	Thalamic volume ($*10^{-4}$)	1.179	0.007	0.335	1.963
	Thalamic MD ($*10^{-3}$)	-1.636	0.211	-4.046	1.263
	Thalamic FA	1.372	0.542	-2.948	6.260
Block 3	*Adjusted R^2 0.462*				
	EDSS	-0.180	0.117	-0.402	0.050
	MS Phenotype	-0.225	0.138	-0.547	0.071
	T2 lesion volume	-0.205	0.265	-0.591	0.218
	T1 lesion volume	0.130	0.333	-0.163	0.411
	NBV ($*10^{-6}$)	-0.272	0.822	-2.597	2.190

RS fMRI / Deep GM and MS phenotypes





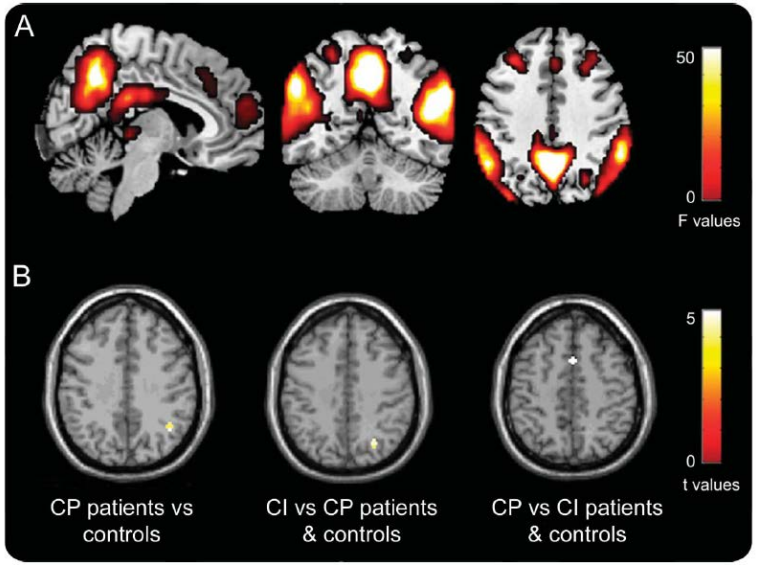
Meijer et al., JNNP 2018

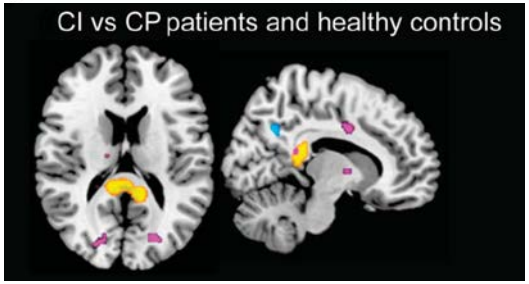
- 295 MS patients (121 early RRMS patients, 122 late RRMS and 52 SPMS)
- 96 HCs

- Increased connectivity of the deep GM became apparent in late RRMS and further increased in SPMS
- The additive effect of cortical network degeneration, which was only seen in SPMS, may explain the sudden clinical deterioration characteristic to this phase of the disease

RS fMRI / Pediatric MS

Intra-network abnormalities

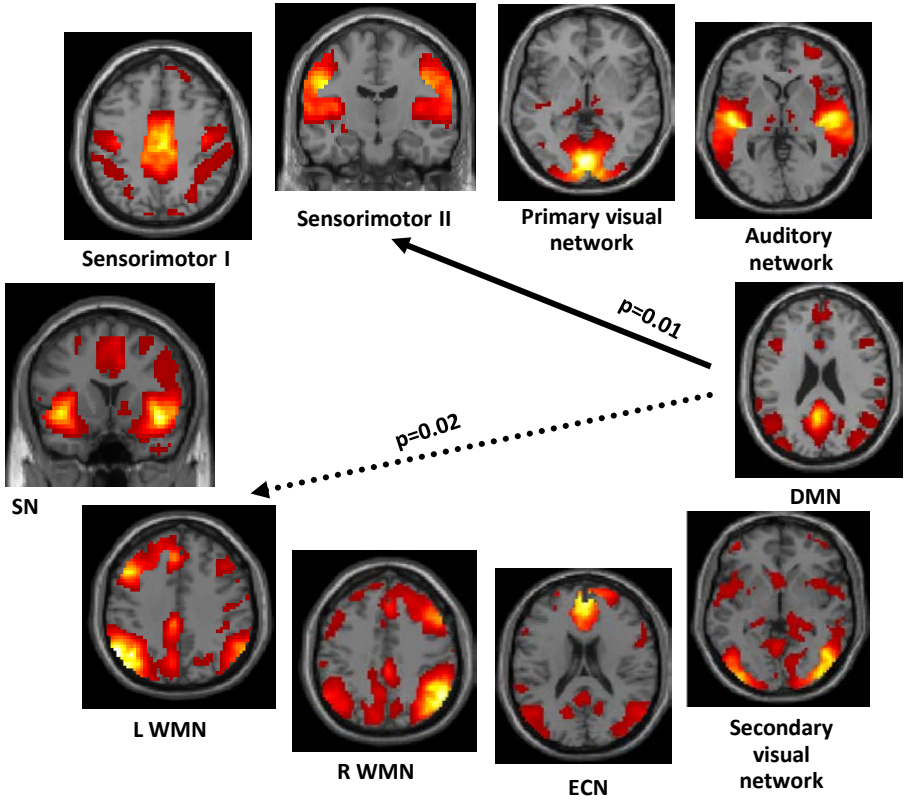




CI explained by:
cingulum FA
CC MD
R precuneus RS
C-index=0.99

Rocca et al., Neurology 2014

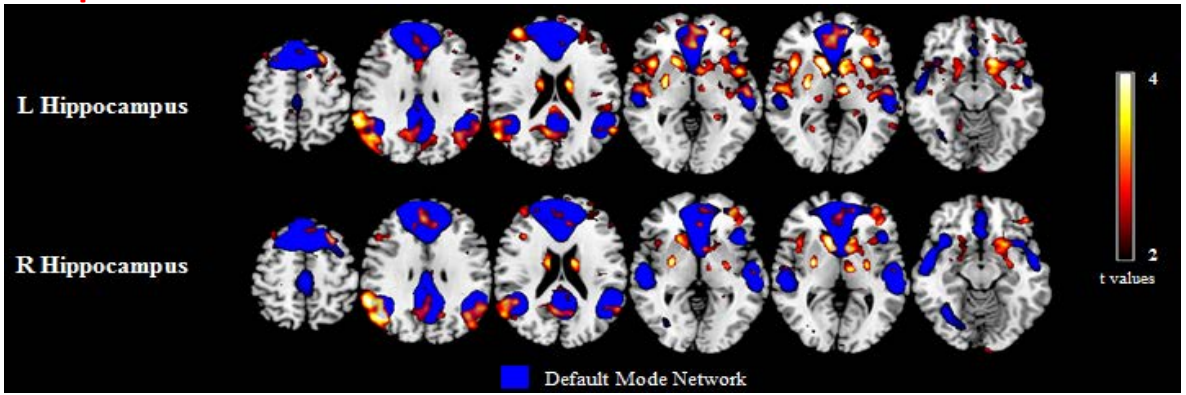
Inter-network abnormalities



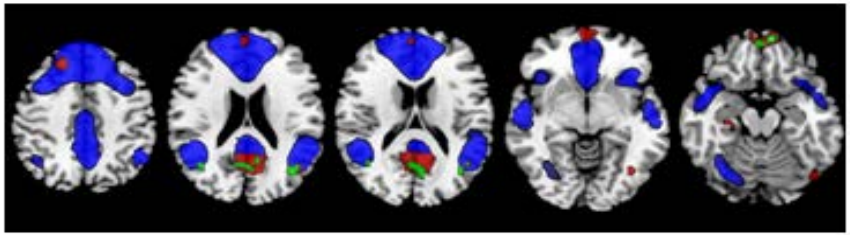
Rocca et al., Human Brain Mapp 2014

RS fMRI / Correlation with T2 lesions

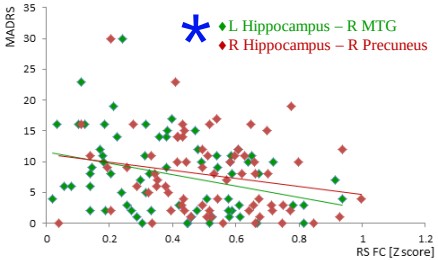
MS patients vs HC

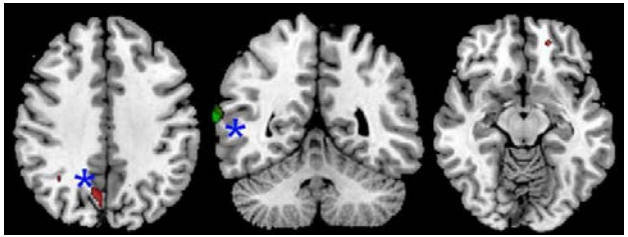


T2 lesion volume



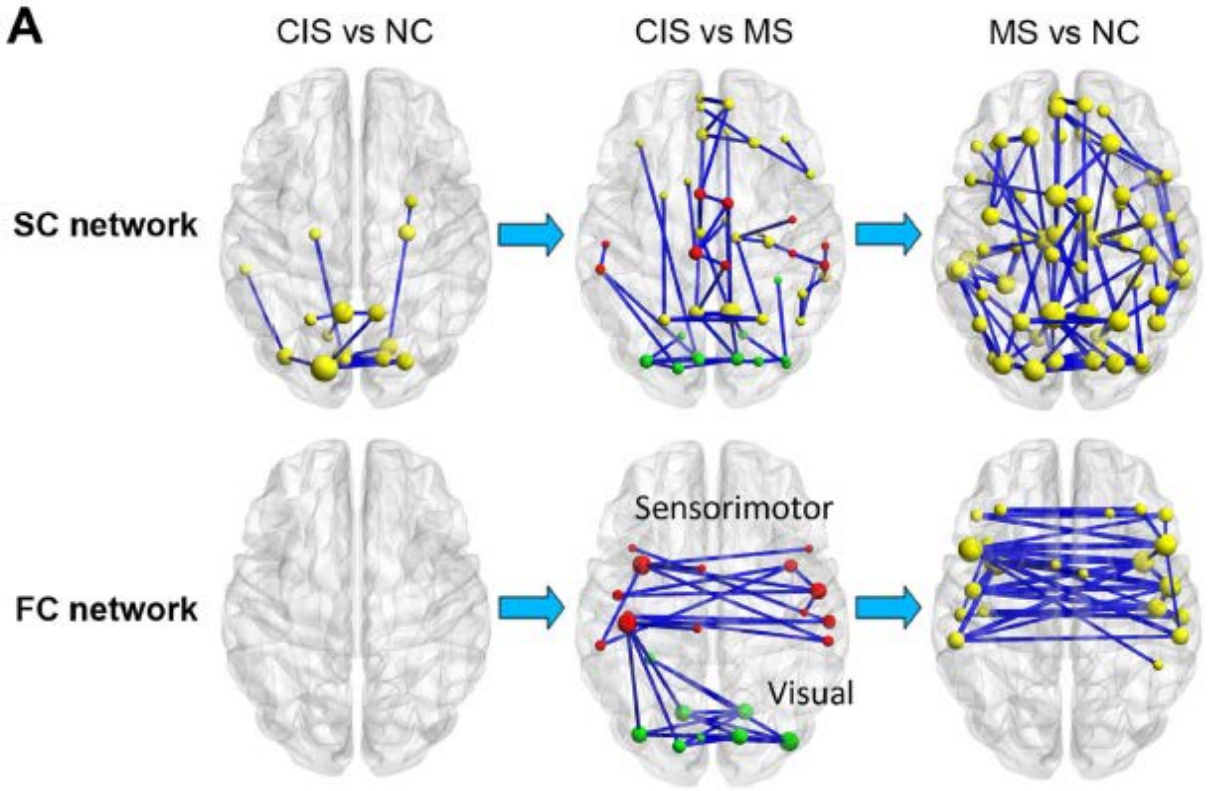
MADRS





Rocca et al., Hum Brain Mapp 2015

RS fMRI / Correlation with structural damage



Shu et al., Scie Rep 2016

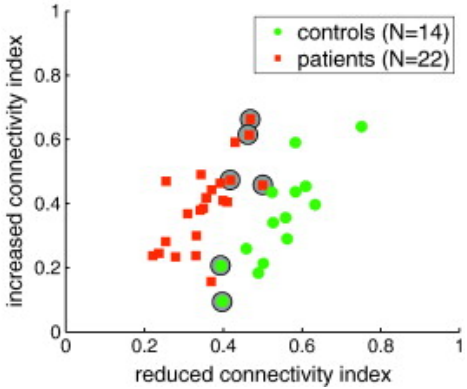
Significant correlations between SC abnormalities and clinical variables

Outline of the presentation

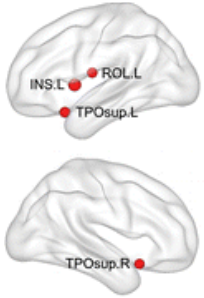
- Methodological consi
- Active fMRI paradigm
- RS fMRI: is that the sc
- What else?
- Conclusions

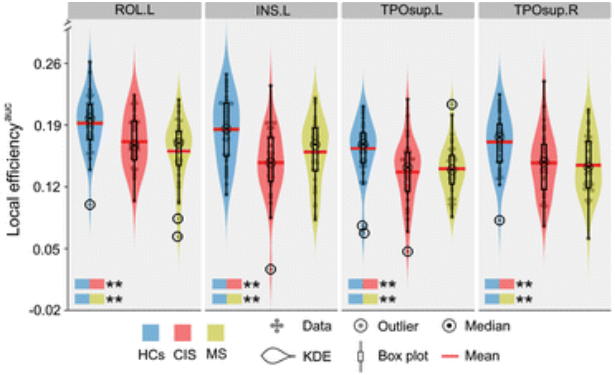
- Diagnosis
- Longitudinal changes
- Treatment monitoring
- Dynamic functional connectivity

What else? / Diagnosis

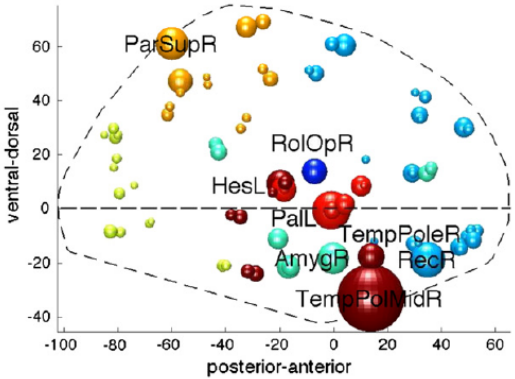


Pattern recognition technique
4% of total connections (161/4005) are discriminative
Connections on average stronger in controls
Correct classification:
18/22 MS patients
12/14 HC
Sensitiviy 82%
Specificity 86%





- **Subcortical and fronto-parieto-temporal regions**
- **No role of occipital regions**
- **Important hubs in the temporal lobe and subcortical GM**



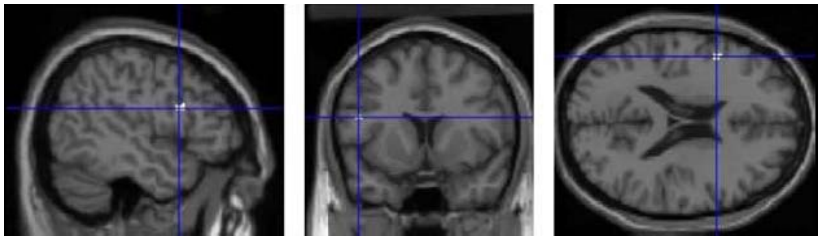
Richiardi et al., NeuroImage 2012

- Connectivity strength exhibited the highest power in distinguishing MS and CIS patients from HC, with **sensitivity of 88.2%** and **61.8%** and **specificity of 66.7%** and **91.7%**, respectively
- **Accuracy of 77.1%** for the classification of MS patients vs HC and of **77.1%** for the classification of CIS patients vs HC

Liu et al., Radiology 2016

What else? / Longitudinal changes

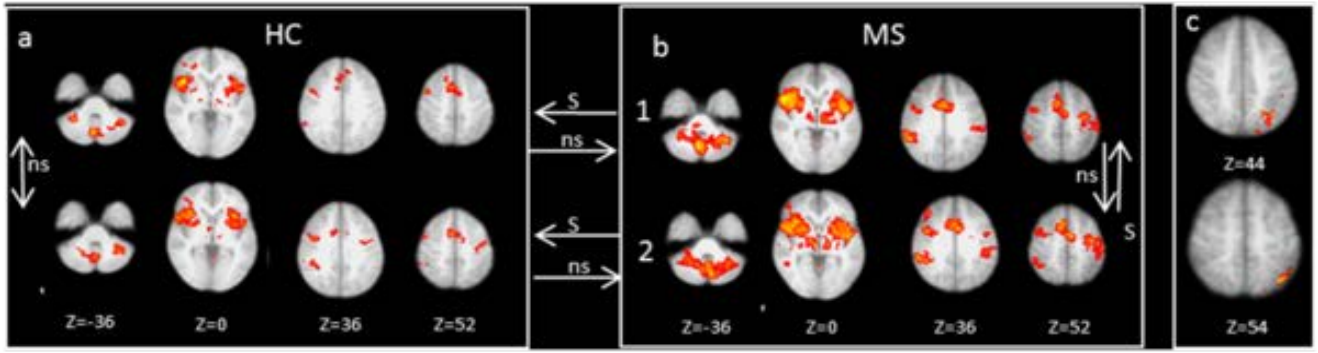
CIS/R DLPFC 1 year activation change



Cognitively improved *vs* stable patients

Audoin et al., Mult Scler 2008

Early RRMS /L IPL 1 year activation change

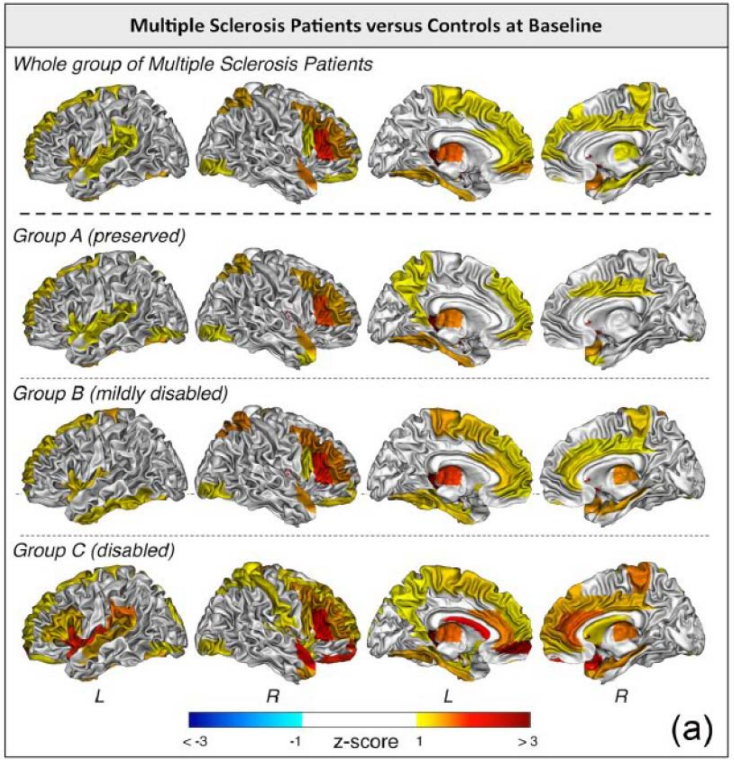


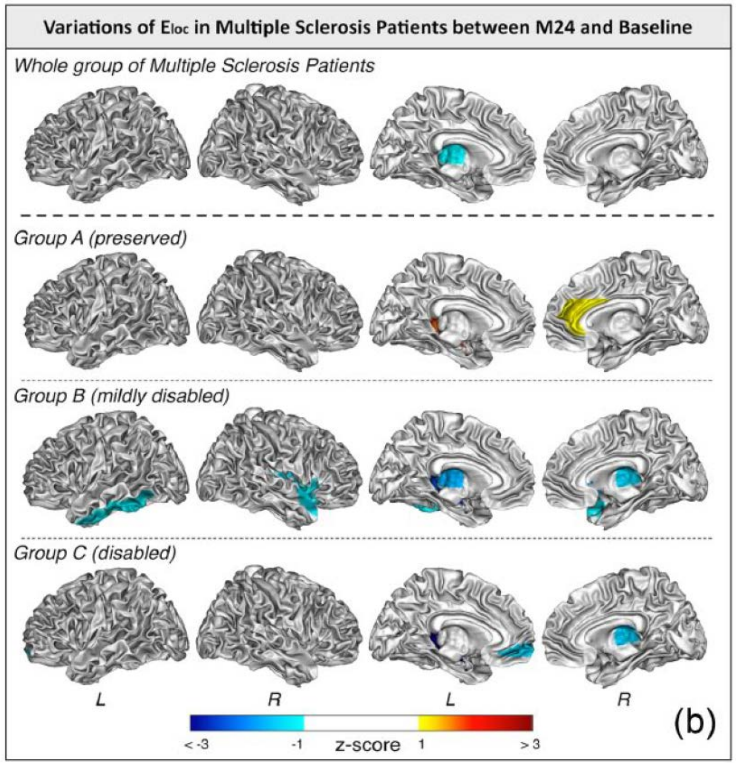
L IPL *vs* worse SDMT performanc e

Loitfelder et al., PlosOne 2014

What else? / Longitudinal changes

Early RRMS /2 year connectivity changes

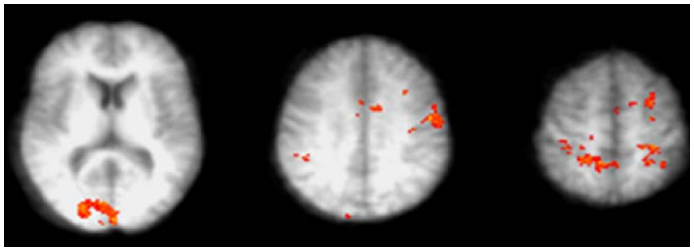




Faivre et al., MSJ 2016

What else? / Treatment monitoring

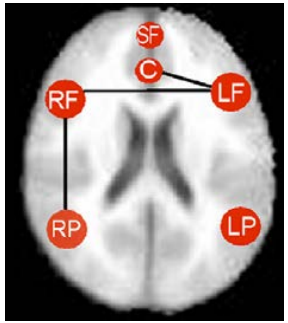
N-back task *vs* rivastigmine (4.5 mg bid)



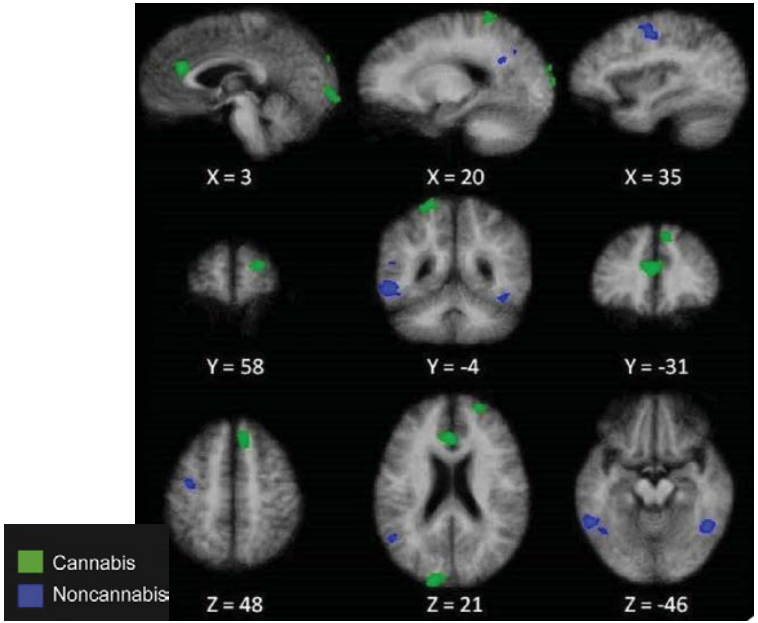
ON- *vs* OFF-rivastigmine: increased activation with increasing task difficulty

Cader et al., J Psychopharmacol 2009

Increased FC in ON-rivastigmine



Cannabis & poor cognitive performance

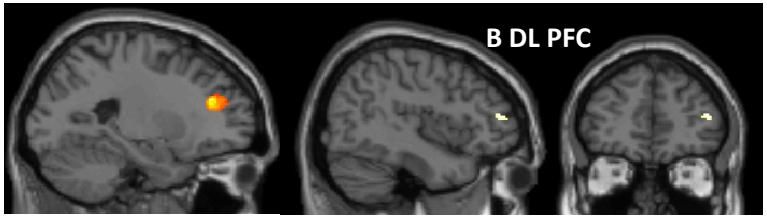


Pavisian et al., Neurology 2014

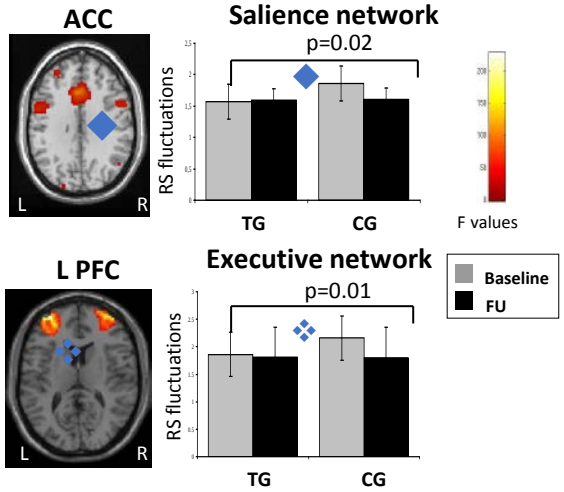
What else? / Treatment monitoring

Stroop task

Stroop interference condition: TG *vs* CG

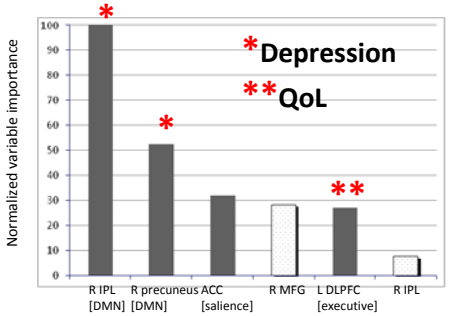


RS fMRI



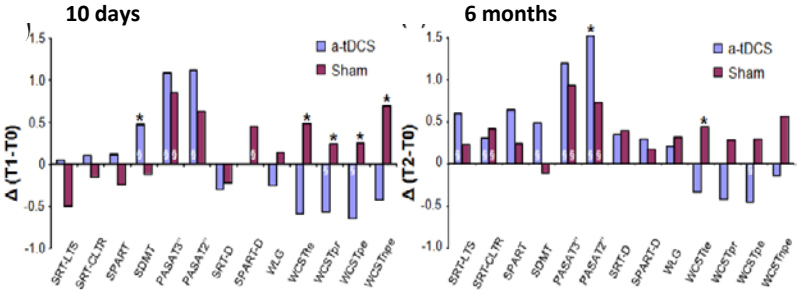
Filippi et al., Radiology 2012

6 month follow-up



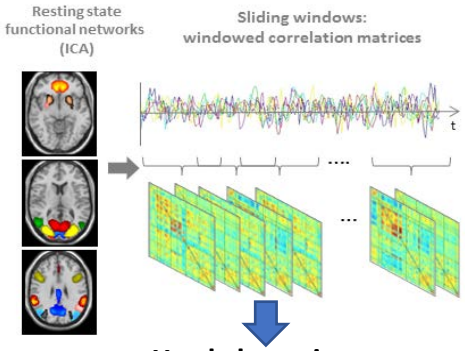
Parisi et al., MSJ 2014

L DLPFC anodal tDCS stimulation



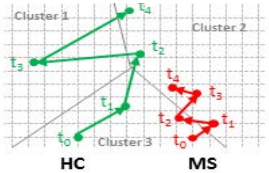
Mattioli et al., MSJ 2015

What else? / Dynamic functional connectivity



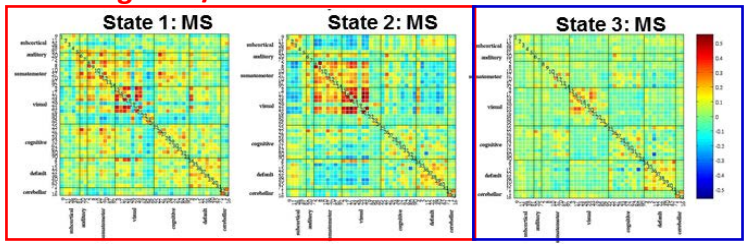
Hard clustering

Fuzzy meta-states

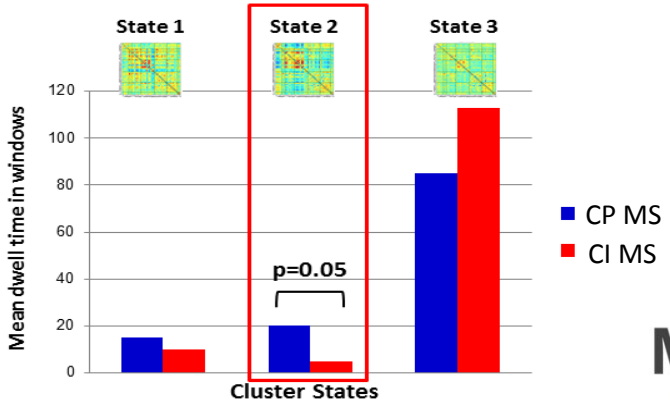


Connectivity

strong intra/inter-network **weak inter-network**



Shorter dwell time in State 2 in cognitively impaired MS



Magnims

Magnetic Resonance Imaging in Multiple Sclerosi

Conclusions

- **The assessment of intra-network and inter-network RS FC abnormalities contributes to characterize MS clinical phenotypes and patients' heterogeneity in terms of disability and cognitive impairment**
- **The evaluation of network alterations at a system level improves and complements the results obtained from regional approaches**
- **Functional network abnormalities are influenced by CNS structural damage**
- **Future studies should ascertain the role of integration of functional connectivity analysis for diagnosis, prognosis and treatment monitoring**
- **Improved understanding of recovery mechanisms may guide the development of new recovery-oriented strategies in MS**

OSPEDALE SAN RAFFAELE

DIVISION OF NEUROSCIENCE

BRAINMAP
Human BRAin IN-vivo MAPping with neuroimaging

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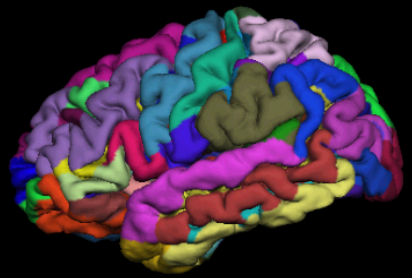
2019 ECTRIMS-MAGNIMS Research Fellowship



Applications are now open

Deadline for applications will close on 01 / February / 2019

MAGNIMS (Magnetic Resonance Imaging in MS) is a European network of academics that share a common interest in the study of multiple sclerosis using magnetic resonance imaging techniques.

We are MAGNIMS

Such a group has collaborated since 1990 and has collectively made a major contribution to defining the role of MRI in diagnosis and monitoring treatments in MS.

The MAGNIMS network is independent of any other organization and is run by a Steering Committee whose members are:

2019 ECTRIMS-MAGNIMS Research Fellowship Programme

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2019 ECTRIMS-MAGNIMS Research Fellowship Programme

ECTRIMS and MAGNIMS are pleased to announce its Research Fellowship program for the coming year.

Aim:

This fellowship wants to foster the development of young researchers in the field of MS by supporting their work on scientific projects at renowned host institutions within the **MAGNIMS** network in Europe. The program shall achieve transfer and broadening of knowledge regarding the application of magnetic resonance to MS research and will promote the researcher's integration into the international scientific community.

Duration and funding:

ECTRIMS will support two fellowships annually, each with duration of 1 year, with an annual stipend of up to €55,000.

Eligibility:

Applicants should be under 40 years and affiliated to an academic department, which can guarantee a continuation of his or her research.

Selection:

The Adjudication Committee will be made by three external reviewers (non-MAGNIMS members) and members of the MAGNIMS steering committee (unless they have any conflict of interest with the applicants). The Committee decision will be based on the following criteria:

- Applicant's curriculum vitae
- Applicants potential for scientific development including the capacity to carry out proposed research project
- Quality of research project and its potential to serve the aims of the MAGNIMS network
- Appropriateness of home and host institutions

A final decision, including reviewer's comments will be notified to all applicants.

Application: