Single-subject cortical networks' analysis in clinically isolated syndrome

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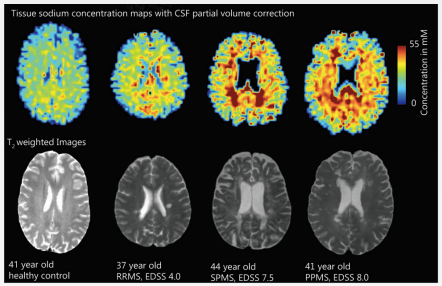
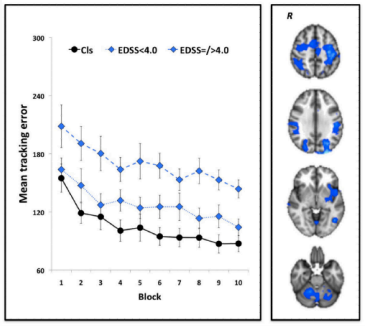
Background

- **Clinical-radiological paradox:**
  - In multiple sclerosis (MS), the T2 lesion load poorly correlated with disability (Nijeholt et al., Brain 1998)
  - In clinically isolated syndrome (CIS), 20% of patients with T2 lesions may not convert to MS after decades (Fisniku et al.,Brain 2008)



Pailing et al., Brain 2013

Damage in the non-lesional tissue (Enzinger et al., Nat Rev Neurol. 2015)



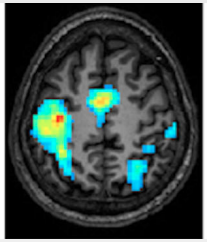
Disconnection (Filippi et al., J Neurol 2013)

Neuroplasticity (Tomassini et al., Nat Rev Neurology 2012)

Tomassini et al., Nat Rev Neurology 2012

Background

Brain connectivity analysis



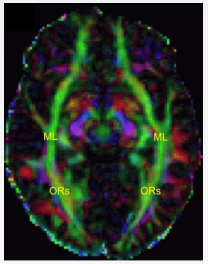
Alahmadi et al.,Brain Struct Funct 2016

Functional Connectivity:

Connection between areas = synchronic activation

Task fMRI

Resting state fMRI

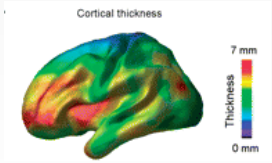


Tur et al., Brain 2016

Structural Connectivity:

Connection between areas = presence of a tract

Diffusion related parameters



He et al., Brain 2009

Cortical Connectivity:

Connection between areas = covariance of cortical thickness/volume

Anatomical acquisition (3D T1)

Background

- Cortical networks' analysis in MS:
  - Decrease in local network efficiency as WM lesion load increases (He et al., Brain 2009)
  - More random topology vs. healthy controls (HCs) (Tewarie et al., Hum. Brain Mapp. 2014)
  - More random topology associated with cognitive impairment (*Rimkus et al., MSJ 2018*)

Group level analysis
No clinical parameters

Individual level analysis
Clinical parameters

- Cortical networks' analysis in CIS:
  - CIS patients showed lower clustering coefficient vs MS patients and higher clustering coefficient vs HCs (*Muthuraman et al., Front. Neurosci. 2016*)

Group level analysis
No clinical parameters

Objectives

1. to compare cortical network parameters determined at the individual level between CIS patients and HCs

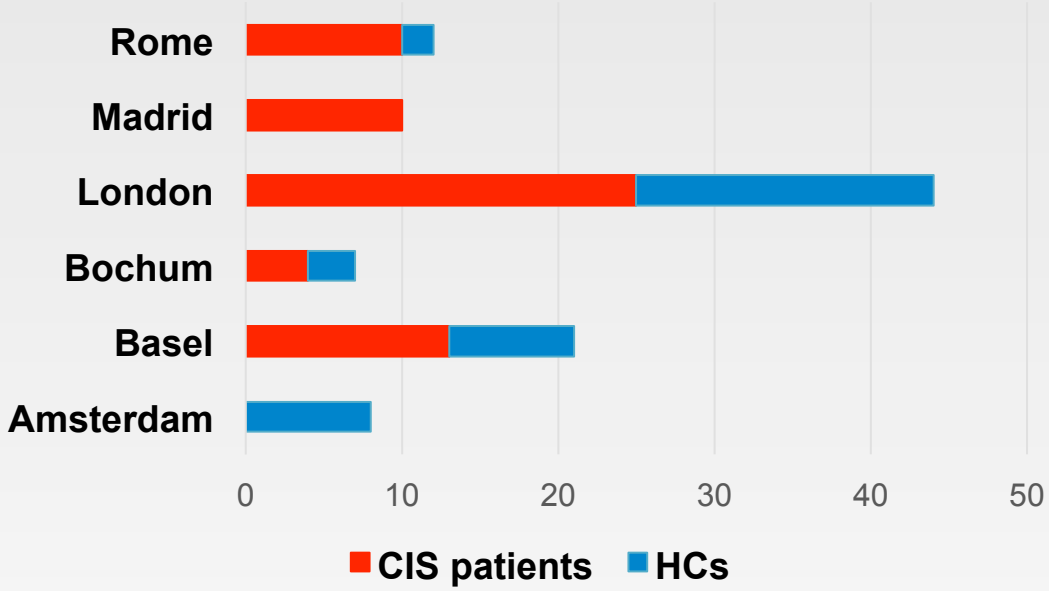
2. to determine the association of cortical network metrics with clinical and radiological parameters

Methods

STUDY POPULATION

3T-CIS MAGNIMS Trial cohort:

- 62 CIS patients
- 40 HCs



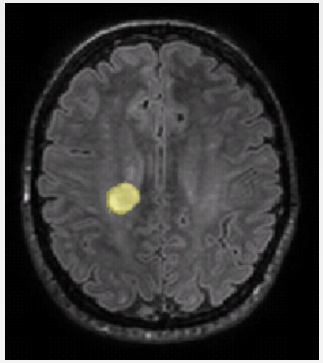
MRI PROTOCOL AND CLINICAL SCALES

3T MRI
Brain 3D FLAIR
Brain 3D T1
Spine PD/T2
Brain and spine 2D T1 post gadolinium (patients only)

CLINICAL SCALES
EDSS
Symbol digit modality test (SDMT) (46 patients only)

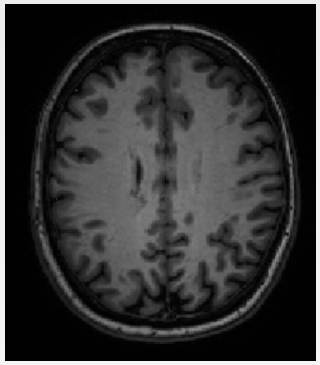
Methods

MRI PROCESSING



Semi-automatic, multi-modal, lesion segmentation using 3D FLAIR, 3D T1 and PDT2

(Sudre et al., IEEE Trans Med Imaging. 2015)



Lesion filling of 3D T1 for the baseline scans in the native space

(Prados et al., Neuroimage 2016)

Cortical volume extraction with Geodesical Information Flows (GIF)

(Cardoso et al., IEEE Trans Med Imaging. 2015)

XNAT

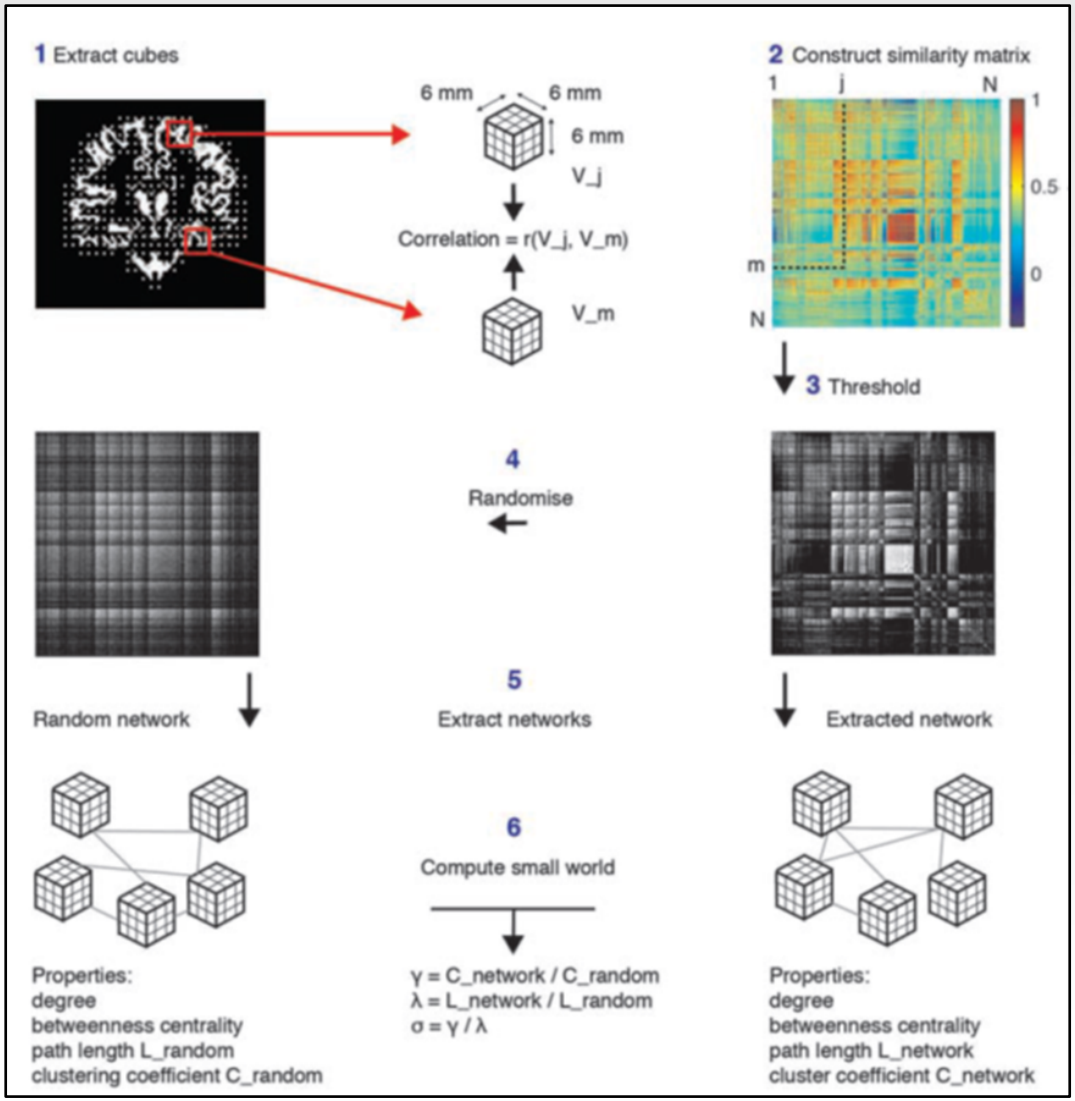
An integrated imaging informatics software platform for image processing and data management

(Kanber et al., ECTRIMS 2016)

Methods

SINGLE-SUBJECT CORTICAL NETWORK CONSTRUCTION

Tijms et al.,
Cerebral Cortex 2012



Methods

GRAPH PROPERTIES

CORTICAL NETWORKS' DEFINING PROPERTIES	CORTICAL NETWORKS' METRICS
Size	Betweenness Centrality
Connectivity Density (CD)	Eigenvector Centrality
Average Degree	Clustering Coefficient
	Path Length
	Normalized Clustering Coefficient γ
	Normalized Path Length λ
	Small world coefficient (γ/λ)

STATISTICAL ANALYSIS

Linear regression model for comparison between groups in terms of cortical network metrics adjusting for:

- Age
- Gender
- Cortical grey matter (CGM) volume

Results

3 HCs and **3 CIS patients** excluded during the quality check → **37 HCs; 59 CIS pt**.

DEMOGRAPHICS

	CIS Patients	HCs
Age mean ± SD	34 ± 7.8	34 ± 8.3
Gender n° F (%)	39 F (66%)	22 F (60%)

CLINICAL AND RADIOLOGICAL METRICS

	CIS Patients
WM lesion vol. ml *median (range)*	0.84 (0-19.4)
WM lesion n° * *median (range)*	10 (0-109)
MS according to McDonald criteria 2010* *n° patients (%)*	5 (8.5 %)
EDSS *median (range)*	1.5 (0-3)
SDMT (46 patients) *mean ± SD*	55 ± 14.6

*scans analysed in Amsterdam by expert raters for lesion count and 2010 McDonald criteria fulfilment

Results

CORTICAL NETWORKS DEFINING PROPERTIES

	CIS Patients	HCs	p
CGM Vol. (ml) *mean ± SD*	510.45 ± 52.6	523.73 ± 47.5	p>0.05
Size *mean ± SD*	**6979**	**7096**	**p<0.05**
CD (%) *mean ± SD*	25 ± 1.3 %	25 ± 1.3%	p>0.05
Av. Degree (norm. 0-1) *mean ± SD*	0.42 ± 0.2	0.48 ± 0.2	p>0.05

INTER-CENTER VARIABILITY

Scanning center effects were seen for connectivity density (Beta= -0.26) and average degree (Beta= -0.28) (p<0.001),

→ size, CD and av. degree were added as covariates to the model for comparisons of cortical network metrics

Results

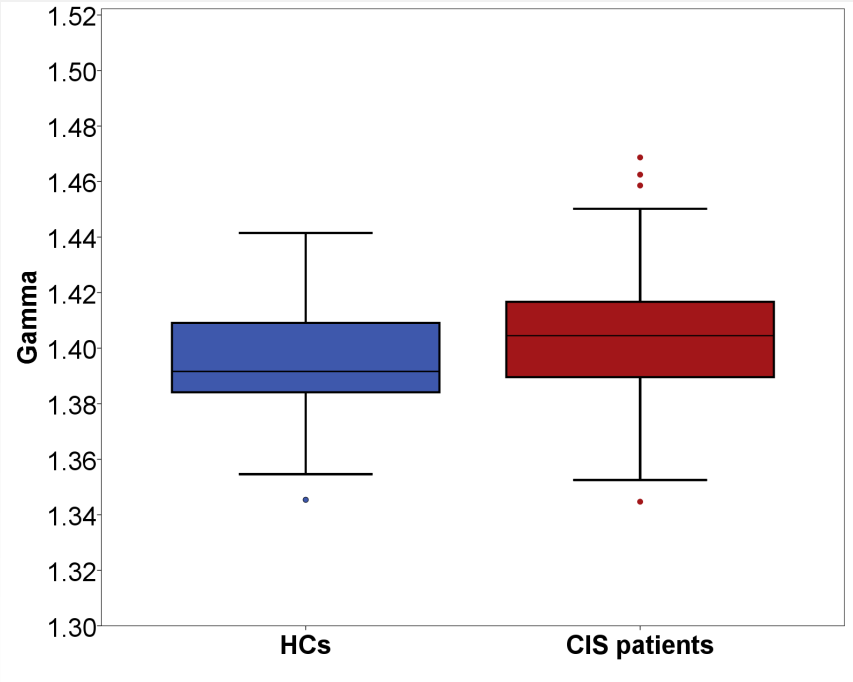
CORTICAL NETWORKS METRICS

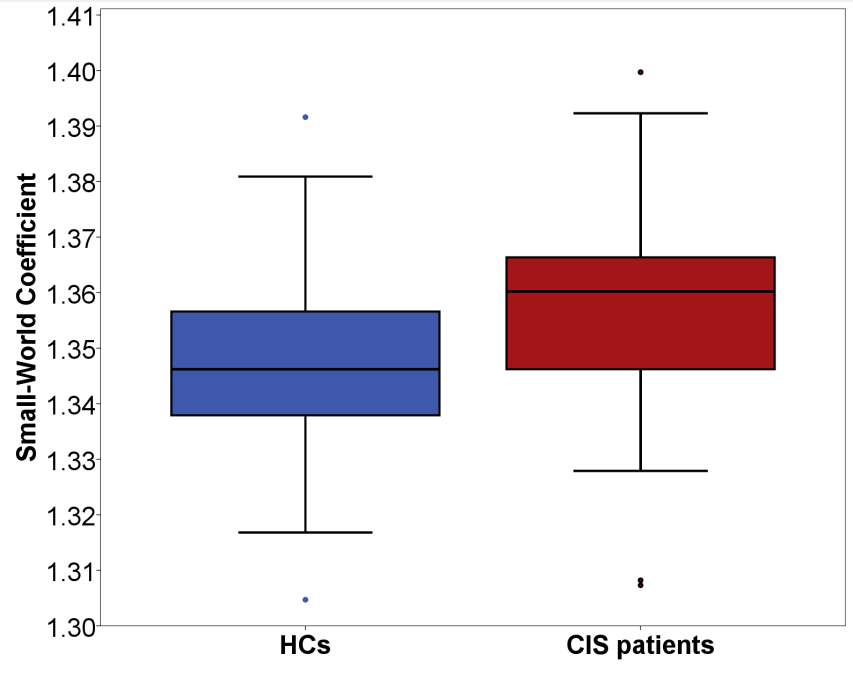
	CIS patients	HCs	p value
Betweenness Centrality (norm. 0-1) *mean ± SD*	0.58 ± 0.18	0.64 ± 0.18	p>0.05
Eigenvector Centrality (norm. 0-1) *mean ± SD*	0.39 ± 0.2	0.30 ± 0.2	p>0.05
Clustering Coefficient *mean ± SD*	0.55 ± 0.02	0.55 ± 0.01	p>0.05
Average Path Length *mean ± SD*	1.8 ± 0.02	1.8 ± 0.02	p>0.05

Results

CORTICAL NETWORKS METRICS

	CIS patients	HCs	Beta	p
ɣ *mean ± SD*	**1.41 ± 0.02**	**1.39 ± 0.02**	**0.2**	**p<0.05**
ƛ *mean ± SD*	1.04 ± 0.006	1.04 ± 0.003	0.08	p>0.05
s-w coefficient *mean ± SD*	**1.36 ± 0.02**	**1.35 ± 0.02**	**0.2**	**p<0.05**

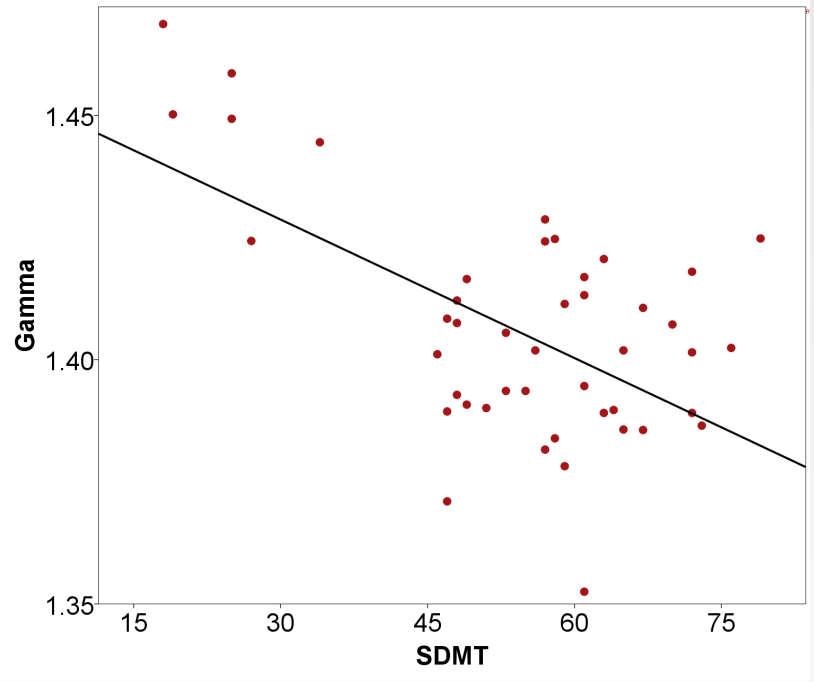




Results

CORTICAL NETWORKS METRICS

- Among CIS patients, s-w coefficient was:
  - **positively correlated** to :
    - WM Lesion volume (Beta = 0.3; p<0.05)
    - Juxta-cortical lesions (Beta = 0.3; p<0.05)
  - **negatively correlated** to:
    - SDMT (Beta = -0.4; p<0.05)
- Among CIS patients, γ was:
  - **negatively correlated** to:
    - SDMT (Beta = -0.6; p<0.001)



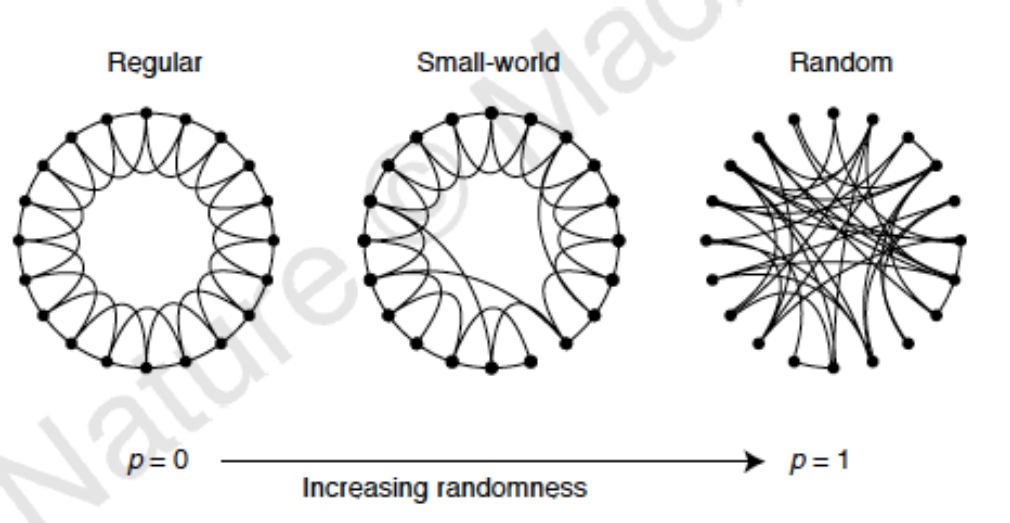
	CIS patients	MS patients*	Beta	p
γ *mean ± SD*	**1.41 ± 0.02**	**1.43 ± 0.03**	**0.4**	**p<0.05**
s-w coefficient *mean ± SD*	**1.36 ± 0.02**	**1.38 ± 0.02**	**0.4**	**p<0.05**

*2010 McDonald criteria fulfilment

Conclusion

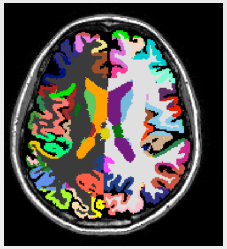
- **Size smaller in CIS patients than in HCs:**
  - possible partial volume effect

- **Gamma and s-w coefficient higher in CIS patients than in HCs:**
  - Increased clustering coefficient shown in previous studies in CIS and RRMS patients (Muthuraman et al., Front. Neurosci. 2016, Tewarie et al., Hum. Brain Mapp. 2014)
  - Possible expression of network alteration:
    - negatively related to SDMT and positively related to WM lesion load
      → possible maladaptive response



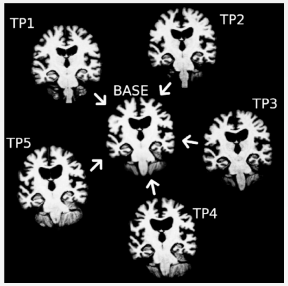
Watts and Strogatz, Nature 1998

Next Steps:



http://cmictig.cs.ucl.ac.uk/niftyweb/

Computation of the spatial distribution of graph parameters:
Anatomical mask derived from GIF parcellation of cortical grey matter



Reuter et al., Neuroimage 2012

Longitudinal analysis:
Using a 4D lesion filling on the 3D T1 registered in a within-subject template

Thank you for your attention!

Acknowledgments:

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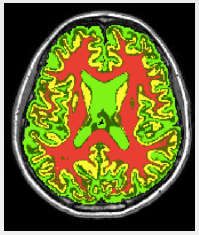

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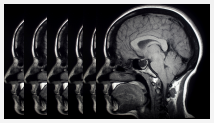

Dr C Tur