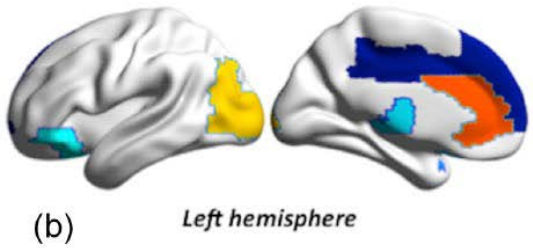
Amsterdam UMC
University Medical Centers

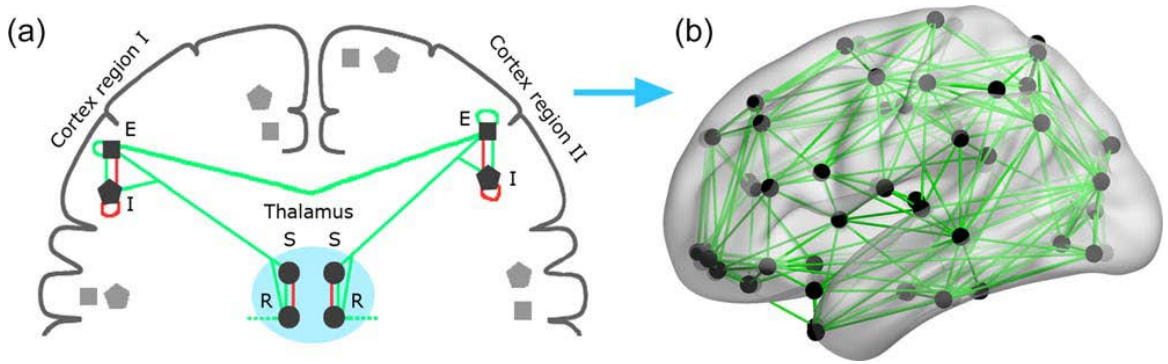
MS Center Amsterdam

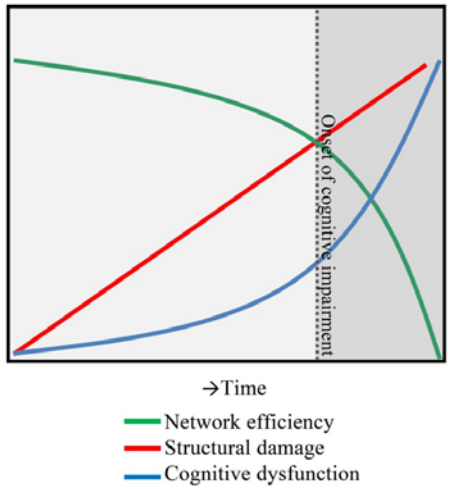
MAGNIMS teaching session 26

Menno M. Schoonheim, PhD

Structural connectivity







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Disclosures

M.M. Schoonheim

- Serves as an editorial board member of Frontiers in Neurology
- Received research support from the Dutch MS Research Foundation
- Received consulting or speaking fees from ExceMed, Sanofi-Genzyme, Novartis, and Biogen.

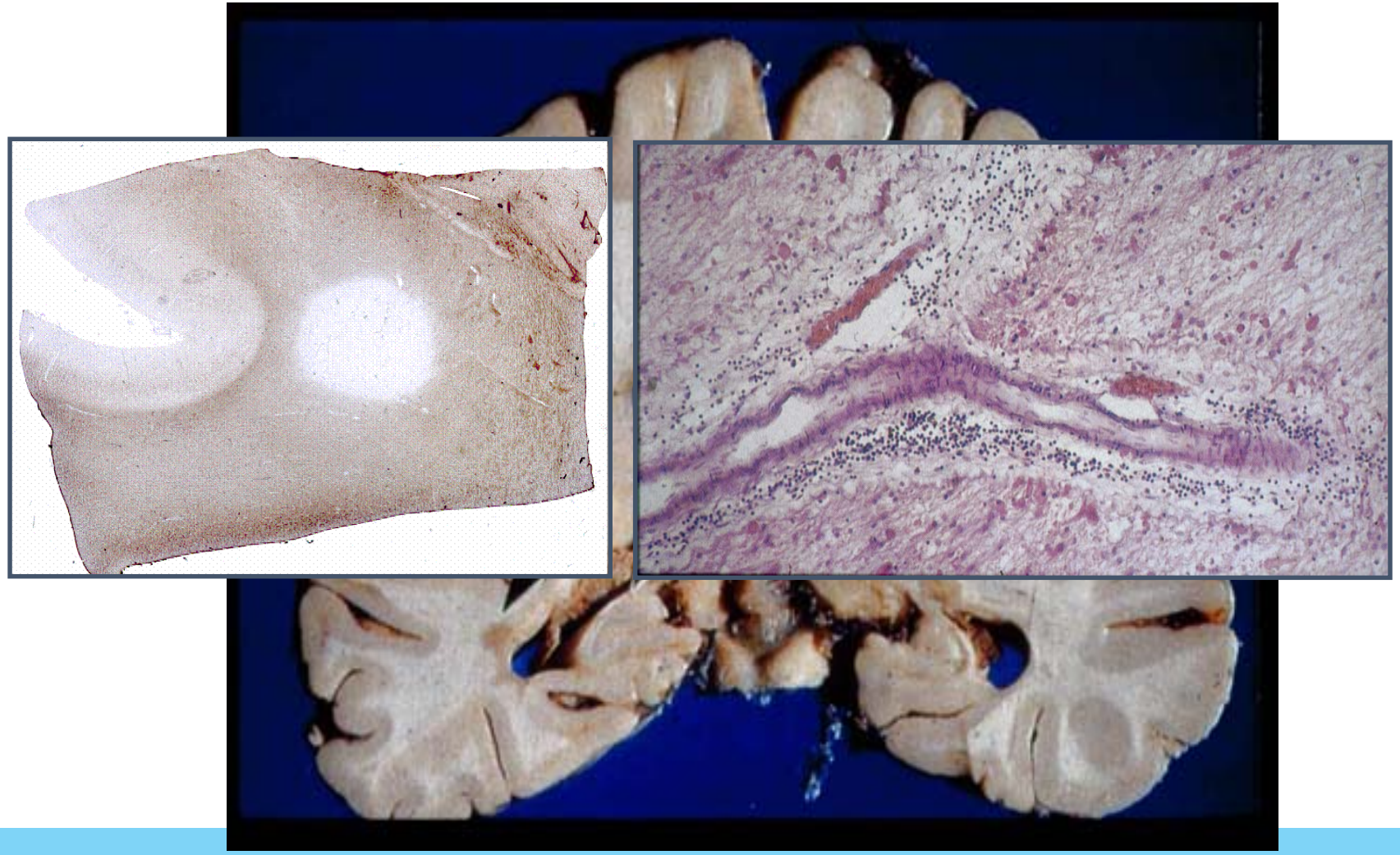
What are we going to discuss?

1. Why did we begin to study structural connectivity?

2. How can we study structural networks in MS?

3. Currently available data
   a) Corticospinal tract and disability
   b) Relations with cortical damage
   c) Structure versus function
   d) Advanced network analyses
      - Cognition!

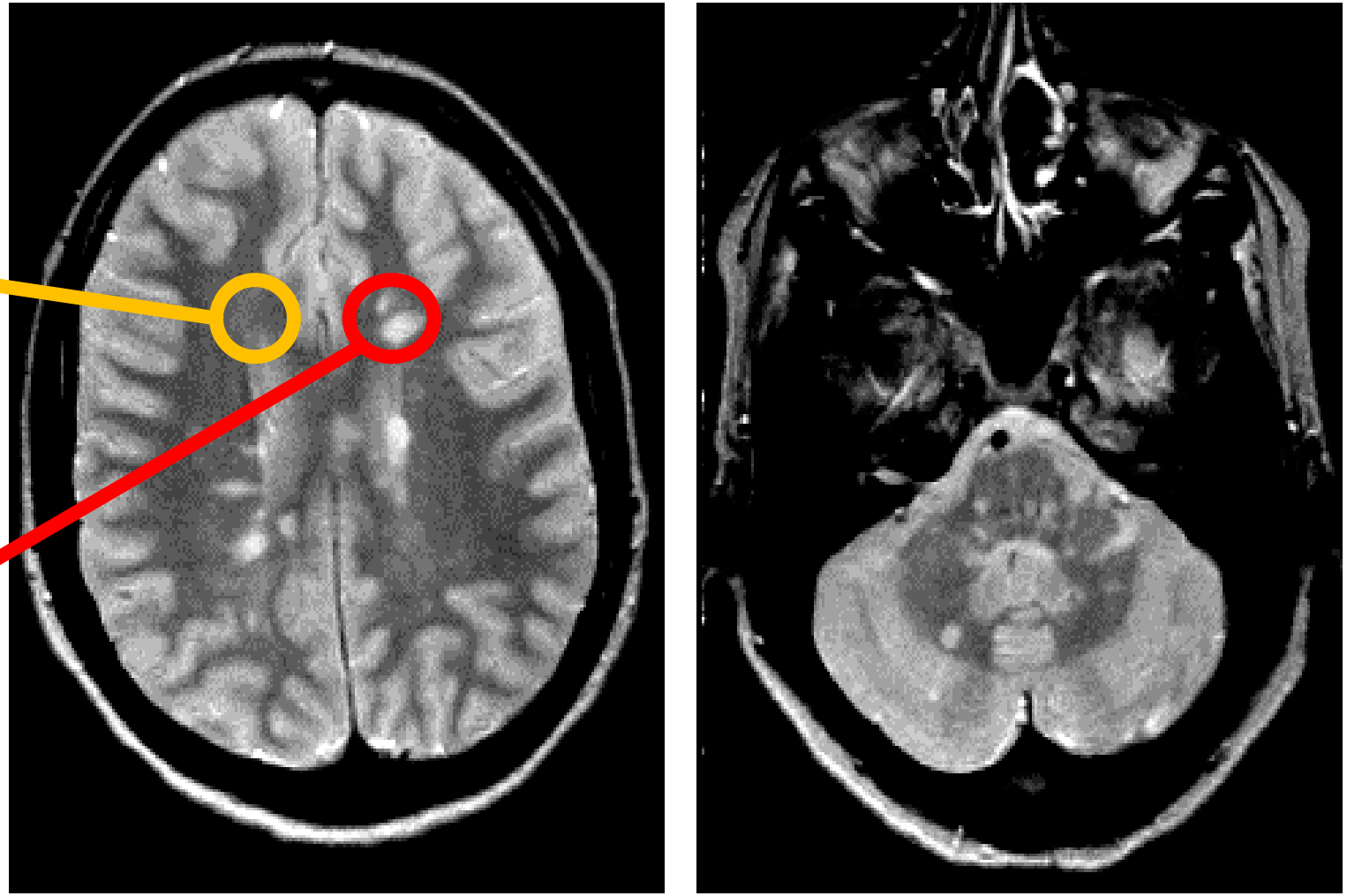
Perivenous inflammation



T2-weighted magnetic resonance imaging (MRI)

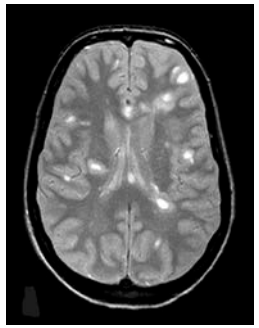
NAWM:
Underestimation
of damage!

Lesions:
Overestimation
of damage!

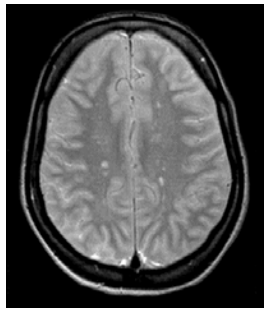


Clinico-radiological paradox

Patients with many lesions do not have to be severely impaired



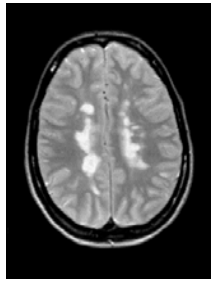
The reverse is also true; patients with few lesions can be severely impaired



Clinico-radiological paradox

- Clinico-cognitive dysfunction is difficult to predict in MS

- Conventional MRI measures insufficient
  - Poor relation with clinic
    - Poor estimate of “real” damage

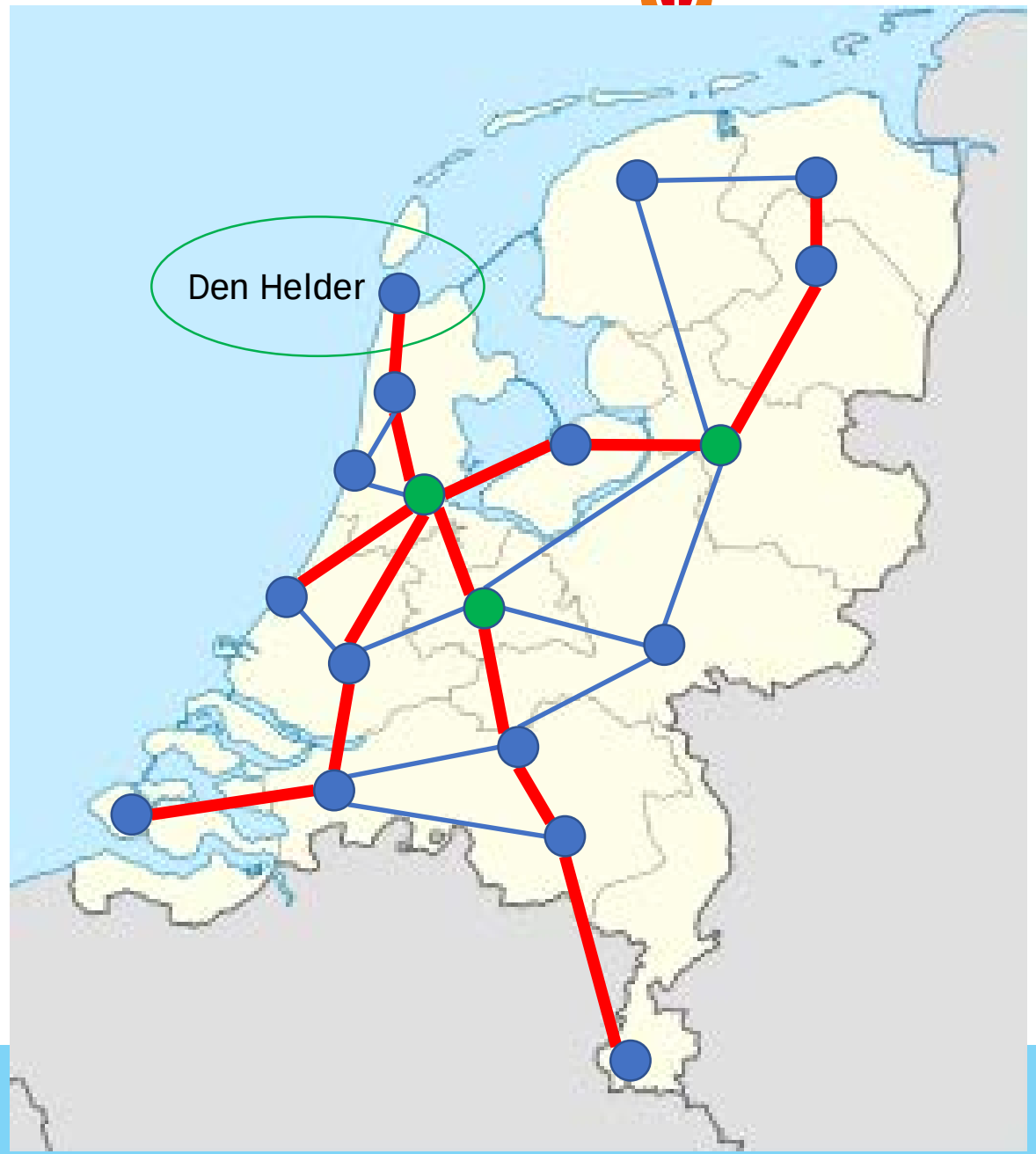


- How can we understand the mechanism?
  - Advanced techniques
    - Structure and function!
    - And: The brain is a network!

Eijlers et al, Neurology 2017


Leeuwarden
Groningen
Assen
Den Helder
Alkmaar
Lelystad
Zwolle
Haarlem
Amsterdam
Den Haag
Utrecht
Arnhem
Rotterdam
Den Bosch
Breda
Eindhoven
Middelburg
Maastricht

The functional network

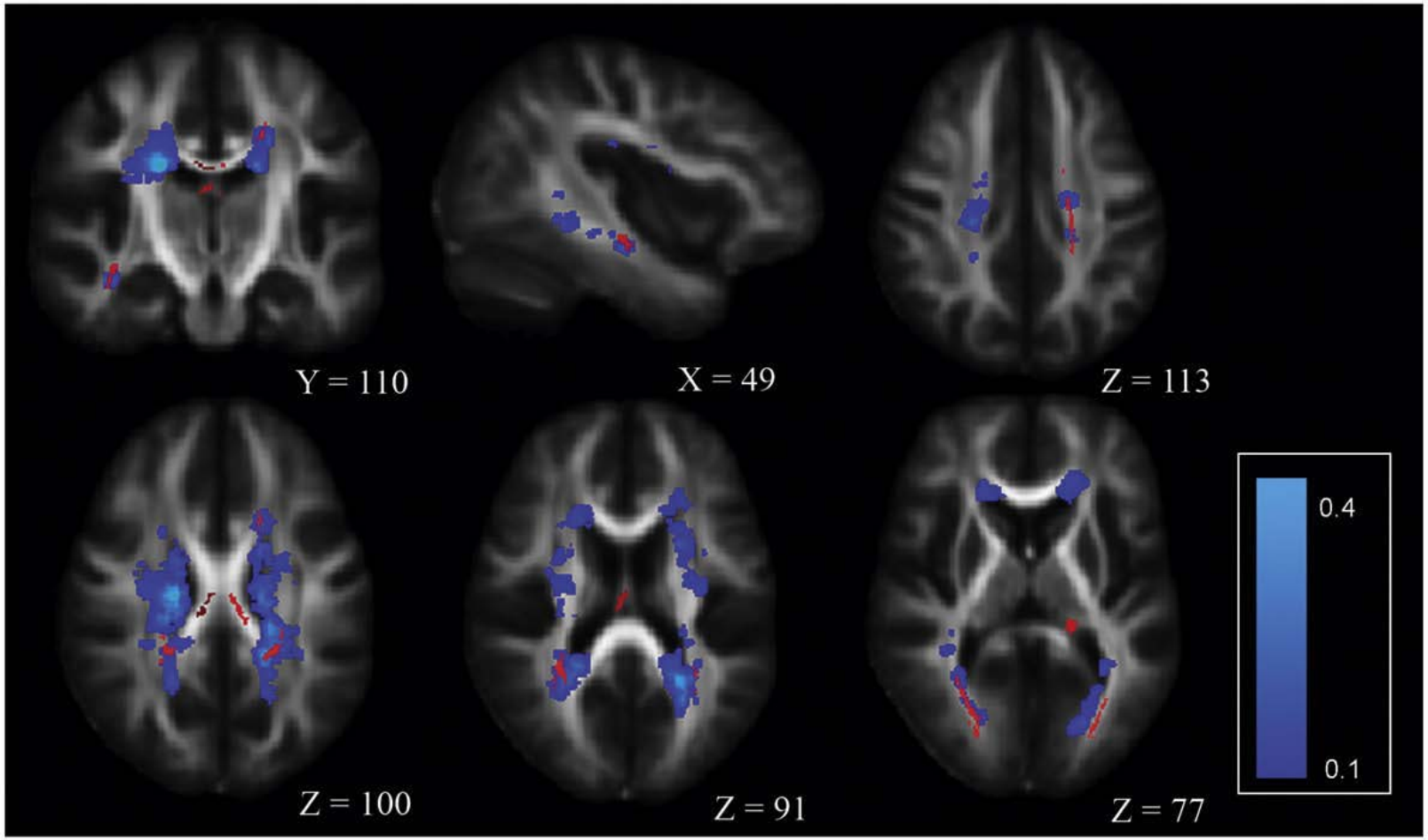


Hubs!

MS effect

White matter tracts

- Basic analy
- Tract-based
  - Not rea
    - Ma



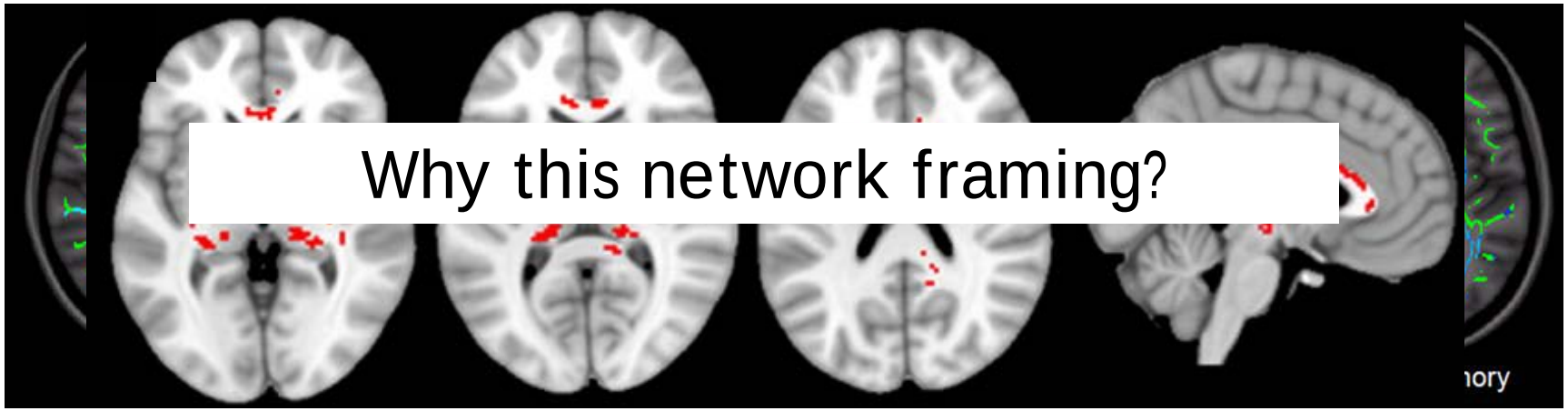
/ynimg

NeuroImage

r [b], J.A. Castelijns [a],

TBSS

- Main message: MS is a disconnection syndrome (Enzinger et al, 2015)

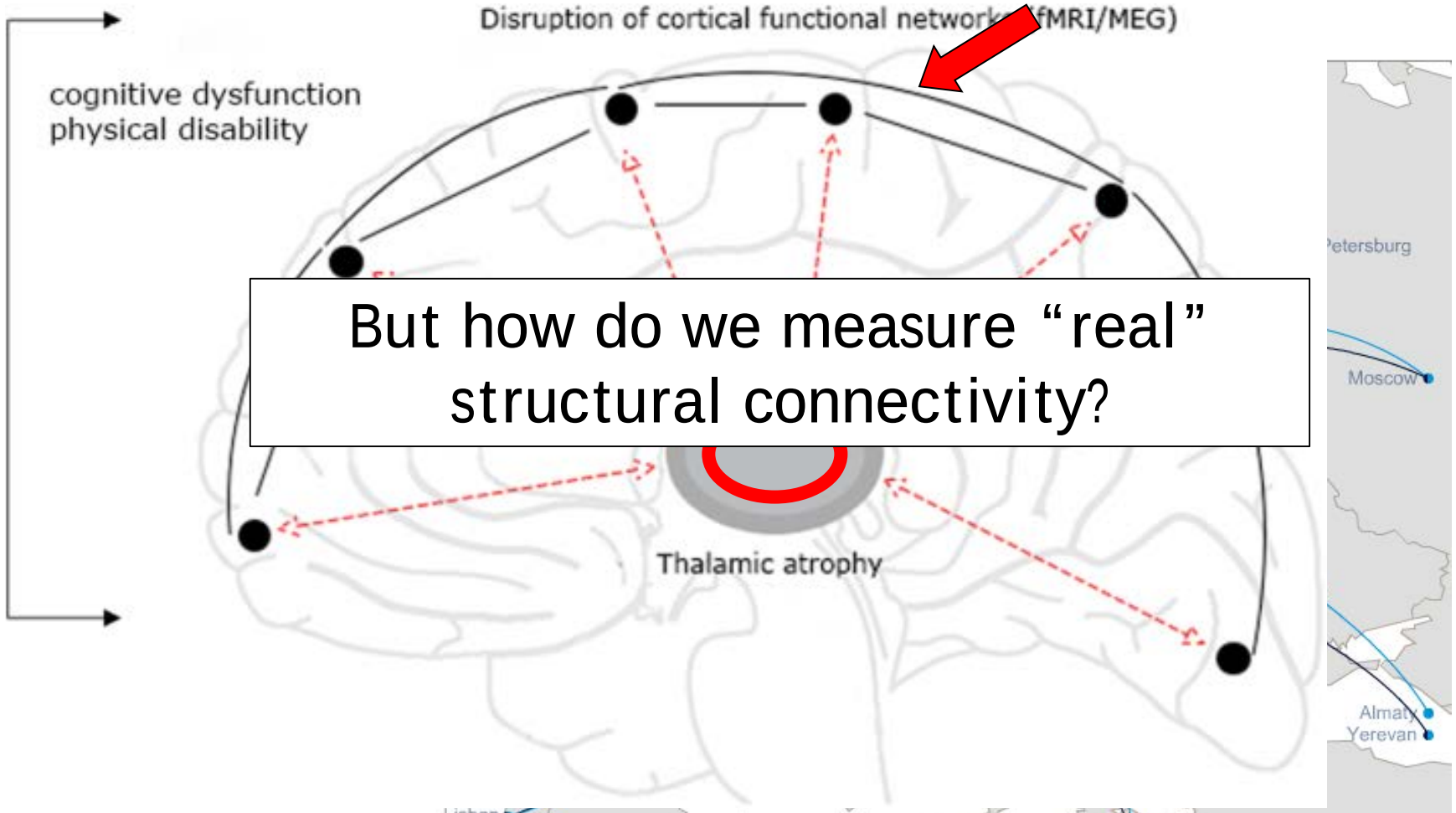


- Thalamus!
- Some (hub-) connections are more important
- Meta-analysis: Decreased FA related to cognition
- But: TBSS is too simple

Welton et al, 2015 Schoonheim et al, 2014 Hulst et al, 2013

Why this network framing?

Schiphol vs Trondheim



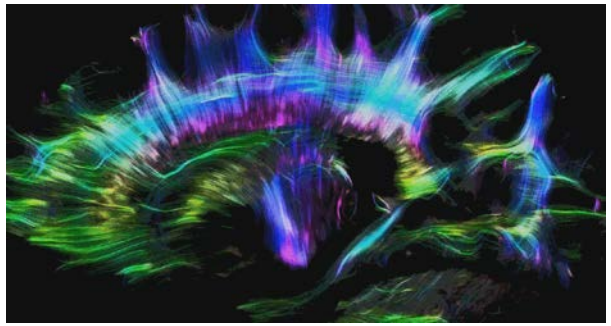
http://www.klm.nl

Tewarie et al., 2014

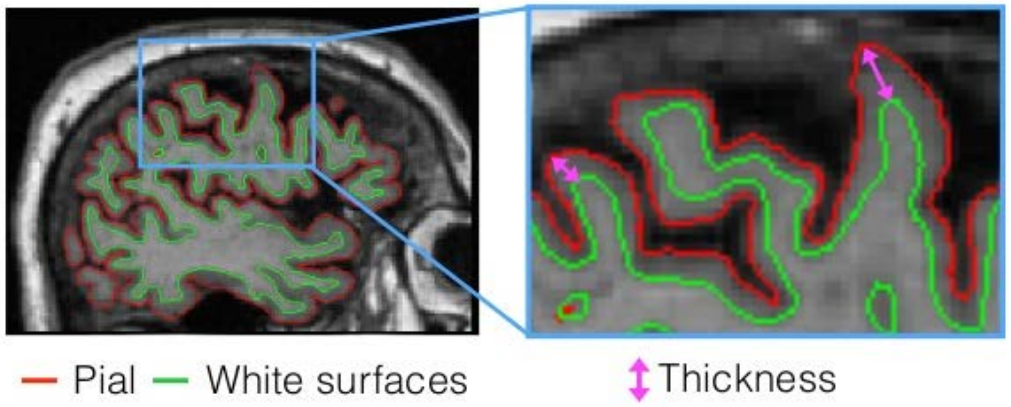
How to measure structural connectivity?

- Two main approaches of measuring structural connectivity:

1. Delineate tracts in the white matter (WM)
    1. Deterministic tractography
    2. Probabilistic tractography

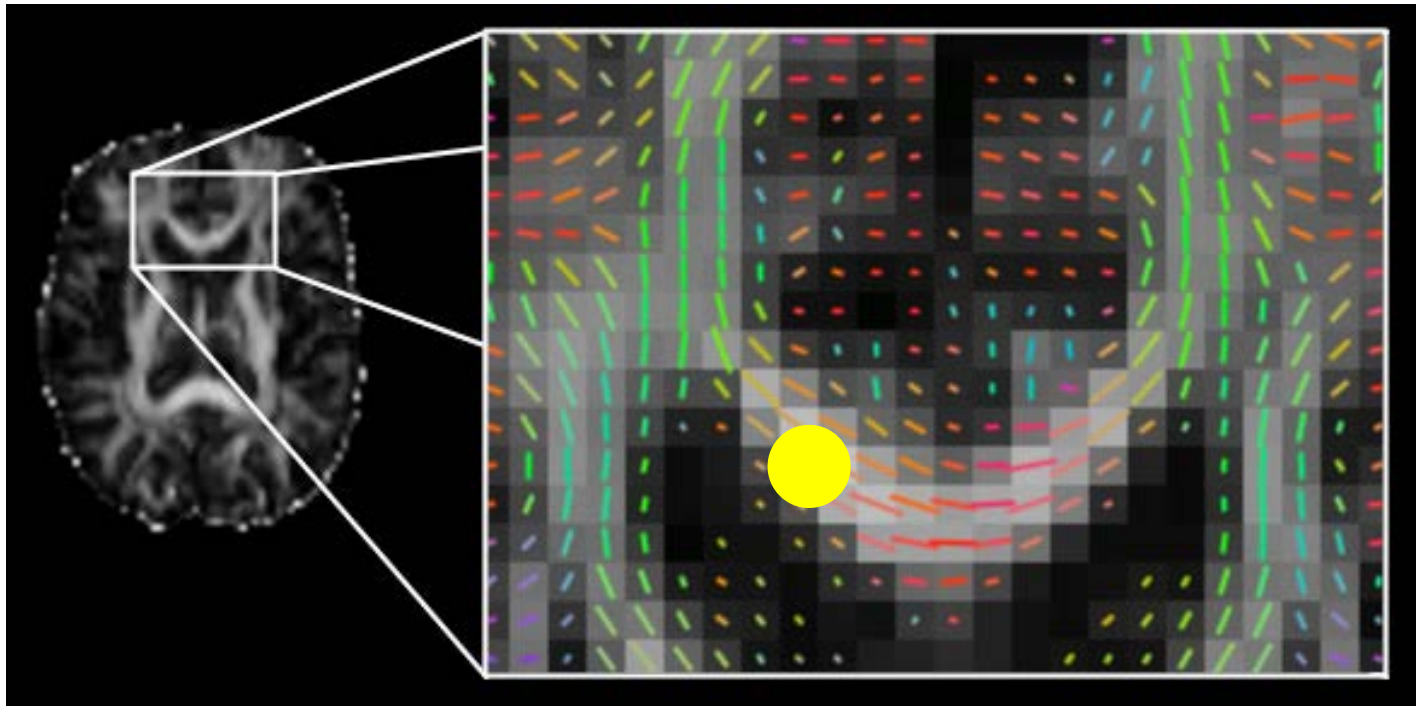


2. Co-variance of patterns in the grey matter (GM)
    1. Cortical thickness correlations
    2. Grey matter intensity correlations

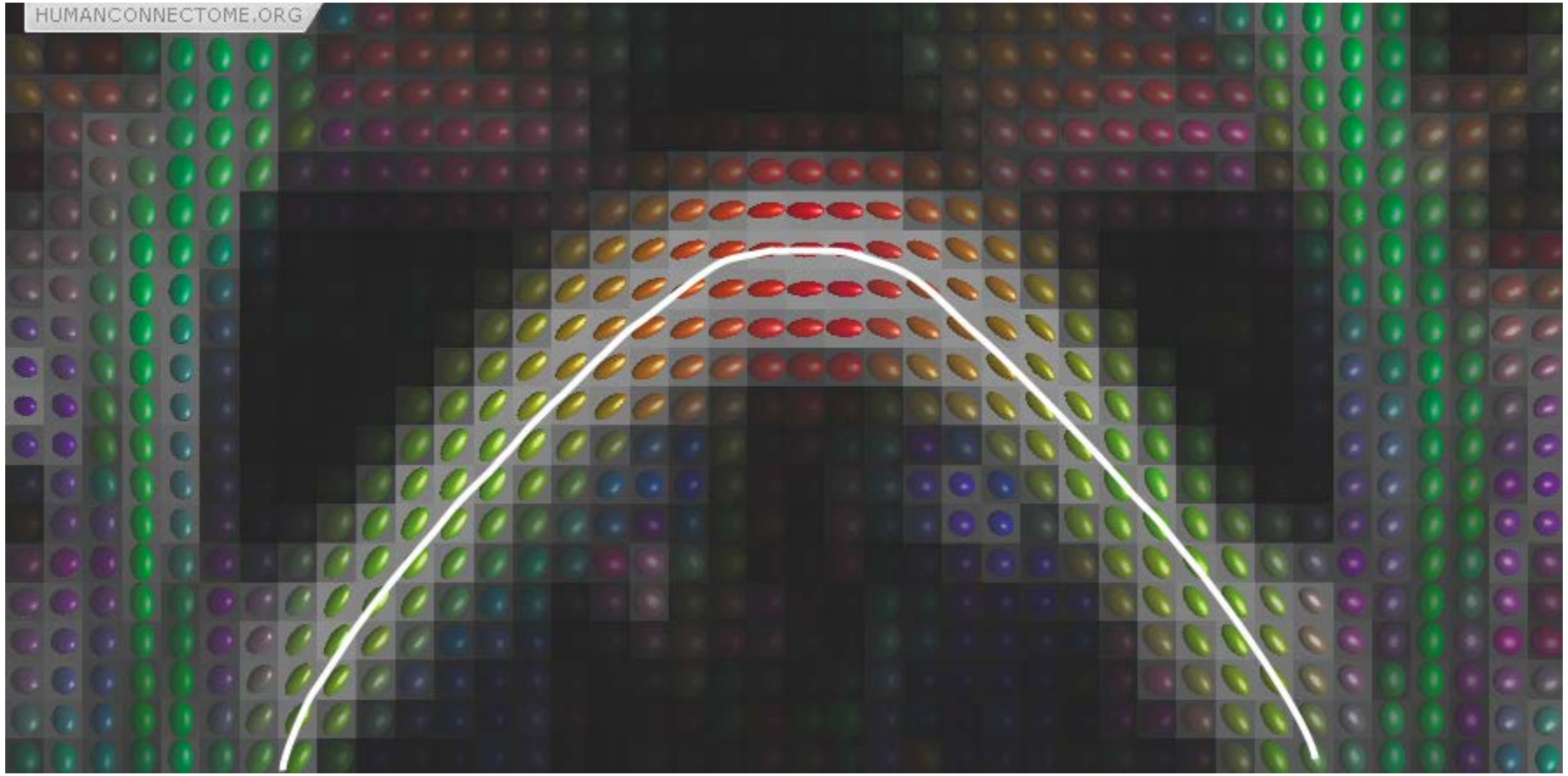


WM tractography

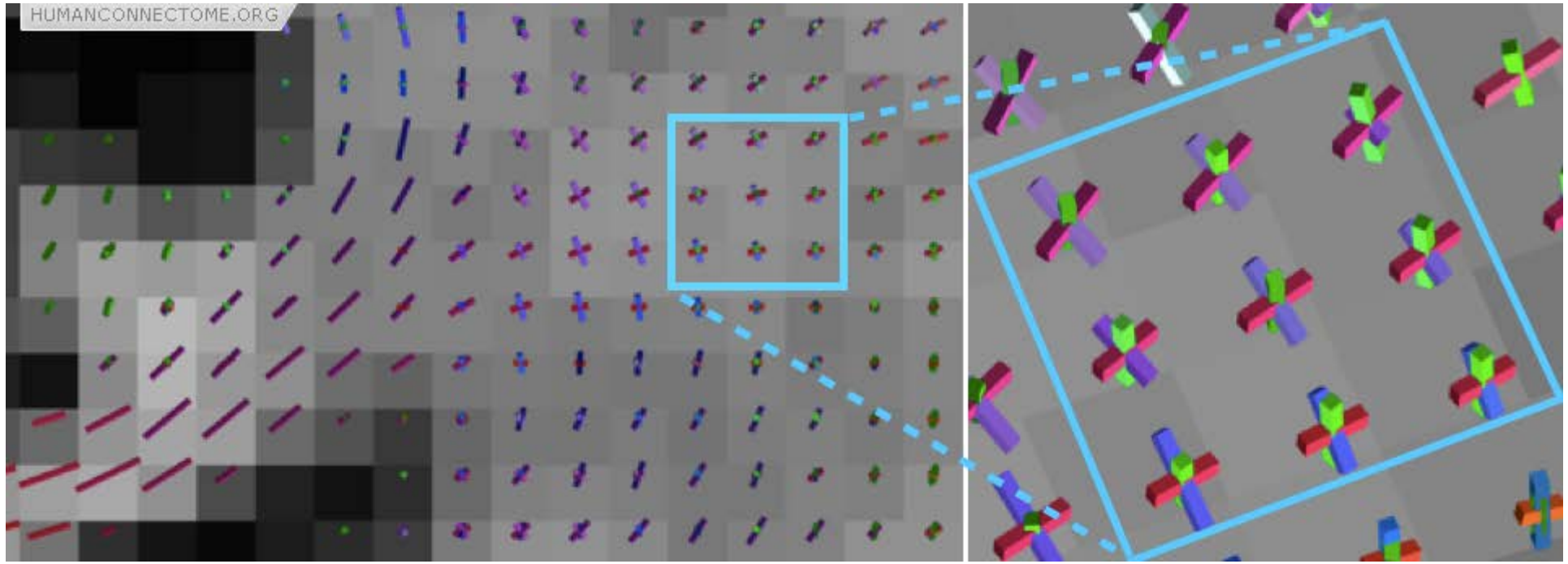
- Aim: Visualize structural connections in vivo
  - MS: Investigate the effects of damage on connectivity



Deterministic tractography



Deterministic tractography

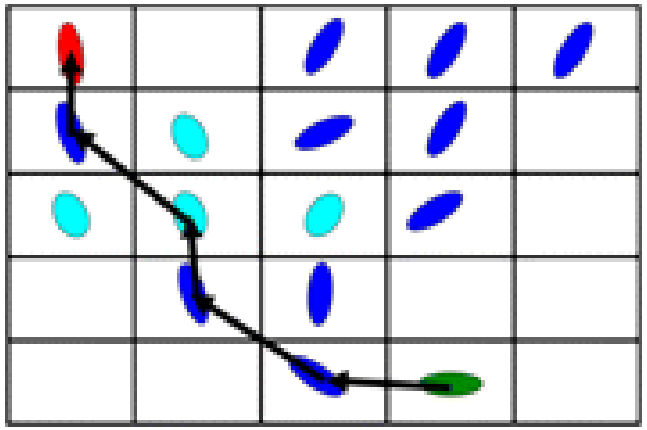


- Deterministic tractography is limited

Probabilistic tractography

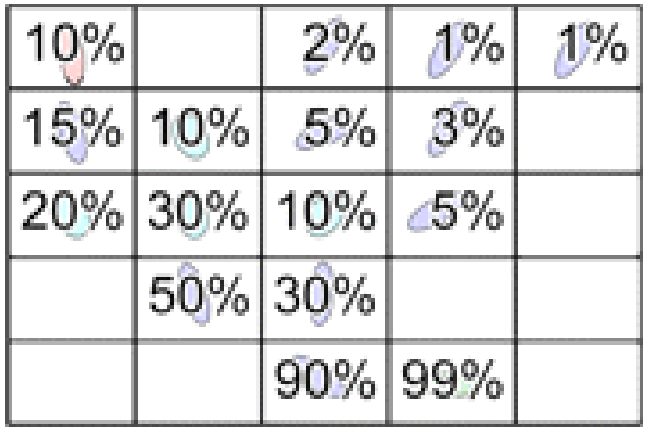
- Performed in FSL, MRTrix, FreeSurfer,..

Deterministic



1 “strongest” pathway

Probabilistic



Many possibilities

The data so far

- So what has been published?

- Main topics:
  1. Corticospinal tract / disability
  2. Relations with cortical damage
  3. Structure/function relationships
  4. Advanced techniques: Graph analysis
     - Cognition!

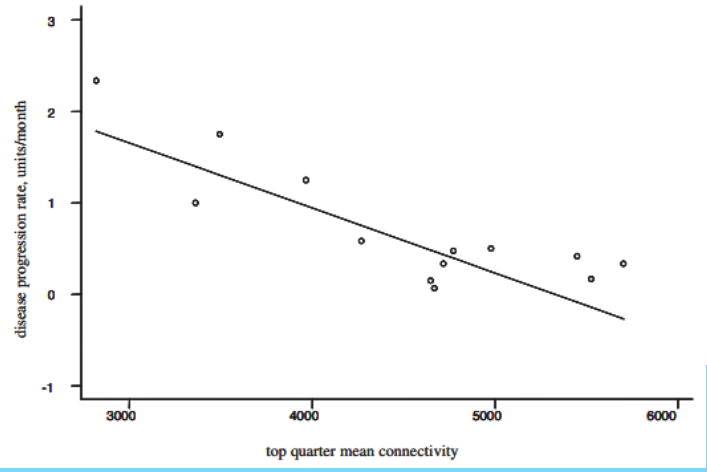
Corticospinal tract 2006

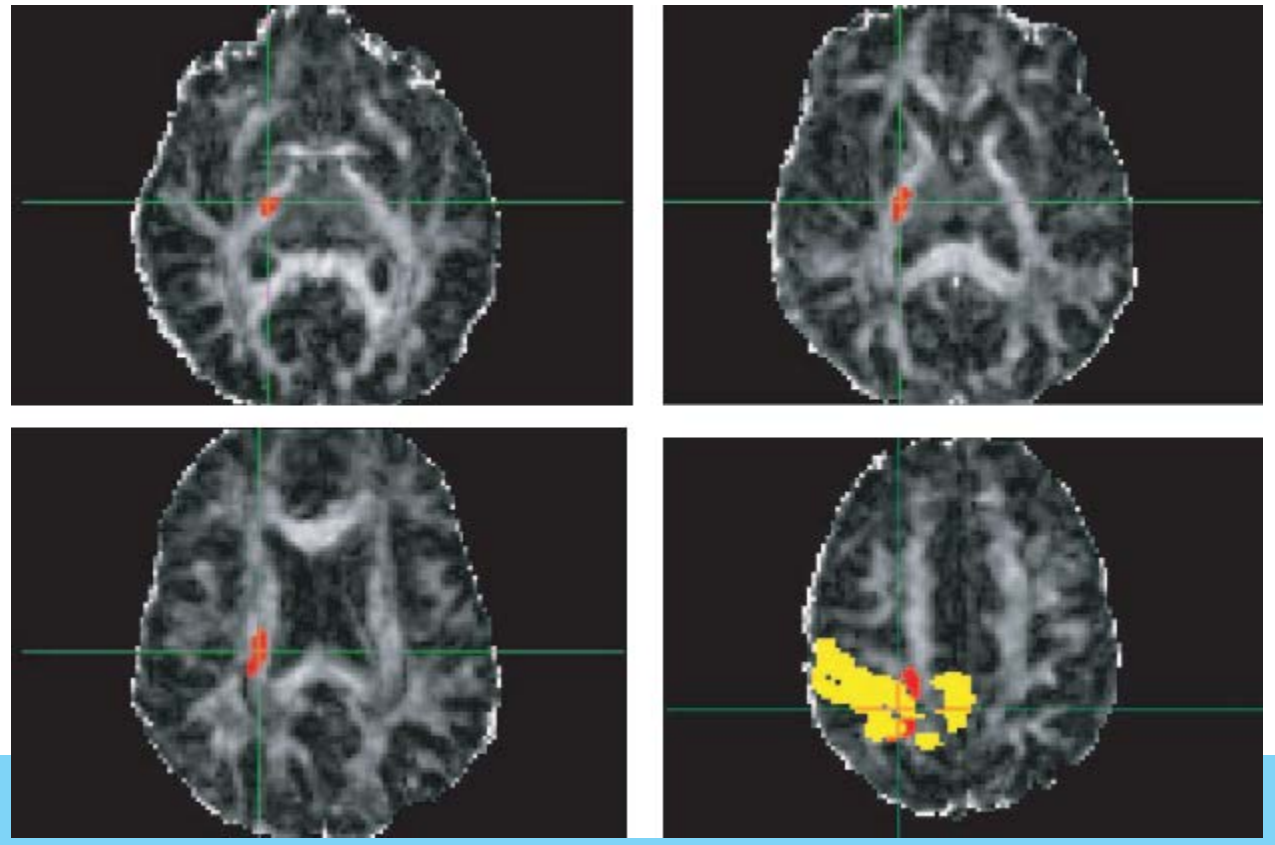
- Ciccarelli et al. – Brain
- Probabilistic tractography in ALS
- CST FA related to progression

doi:10.1093/brain/awl100 Brain (2006), 129, 1859–1871

Probabilistic diffusion tractography: a potential tool to assess the rate of disease progression in amyotrophic lateral sclerosis

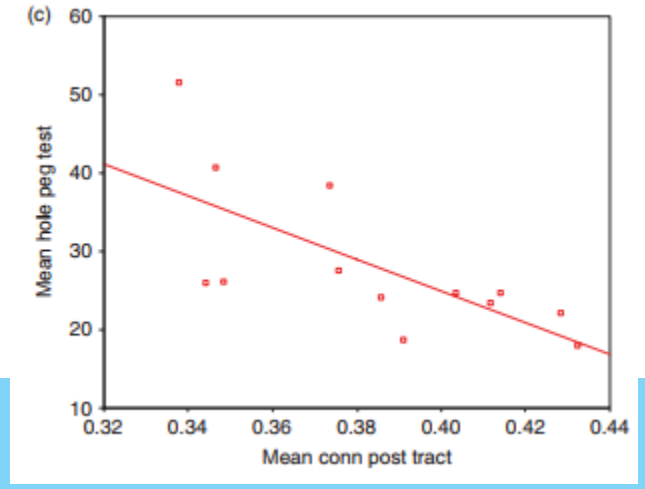
O. Ciccarelli,[1,5] T. E. Behrens,[5] D. R. Altmann,[2,6] R. W. Orrell,[3,4] R. S. Howard,[4] H. Johansen-Berg,[5] D. H. Miller,[2] P. M. Matthews[5] and A. J. Thompson[1]





Corticospinal tract 2007 - 2010

- Ciccarelli et al. – Brain
- Cervical cord: Spectroscopy + tractography
- Lower NAA and connectivity vs <u>disability</u>
  - In specific compartments of the cord!



Research Paper

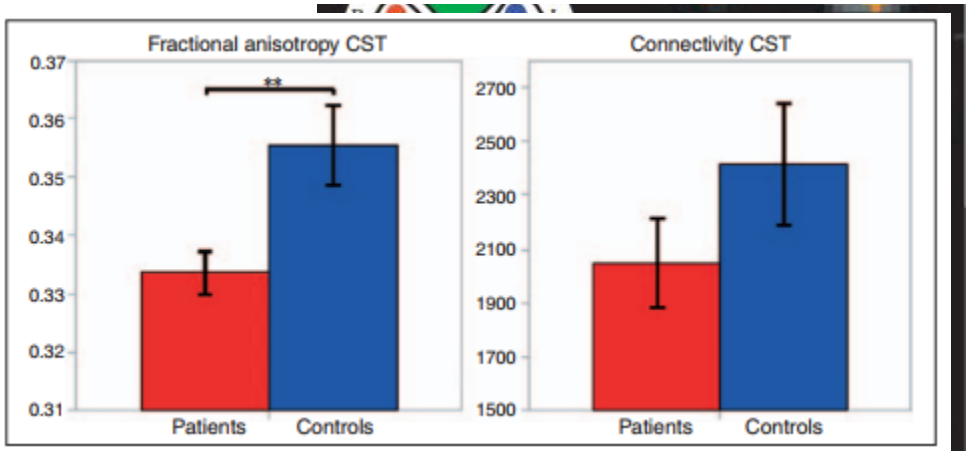
Multiple Sclerosis

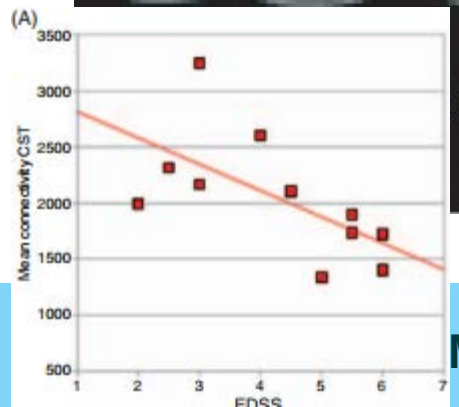
Multiple Sclerosis
16(5) 555–565

DOI: 10.1177/1352458510362440
msj.sagepub.com
SAGE

Combining tractography and cortical measures to test system-specific hypotheses in multiple sclerosis

Nikos Gorgoraptis[1], Claudia AM Wheeler-Kingshott[1], Thomas M Jenkins[1], Daniel R Altmann[1,2,3], David H Miller[2], Alan J Thompson[1] and Olga Ciccarelli[1]



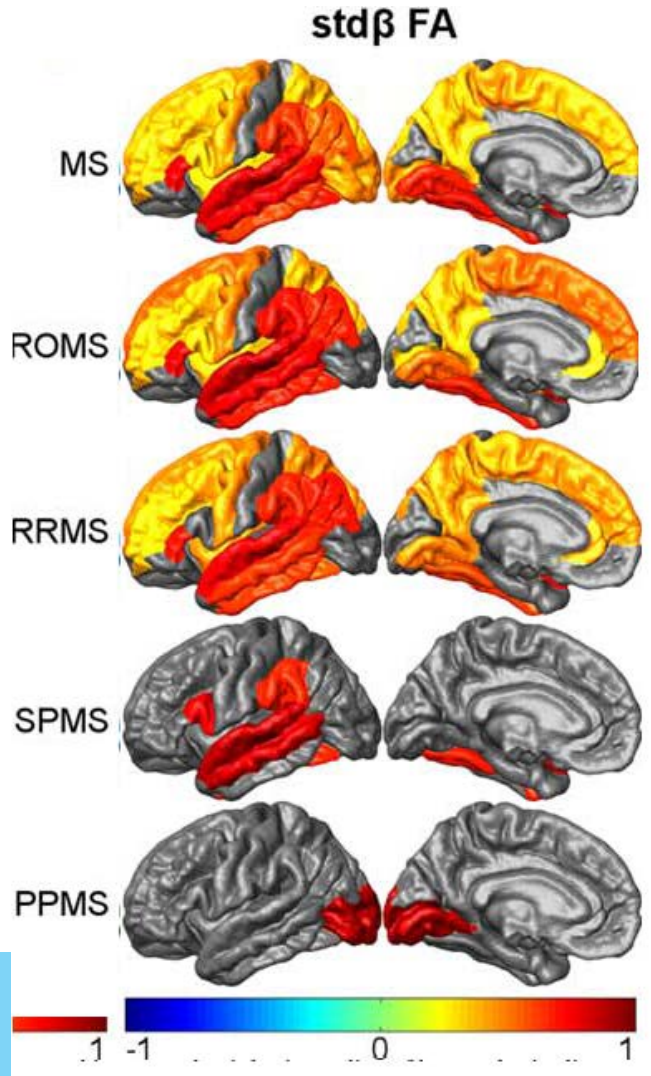


Cortical damage 2015

- Steenwijk et al. – HBM & Radiology
- DGM atrophy related to WM disconnection
- Cortical atrophy only related in RRMS
  - Progressive MS different mechanism?

◆ Human Brain Mapping 36:1796–1807 (2015) ◆

Unraveling the Relationship Between Regional Gray Matter Atrophy and Pathology in Connected White Matter Tracts in Long-Standing Multiple Sclerosis

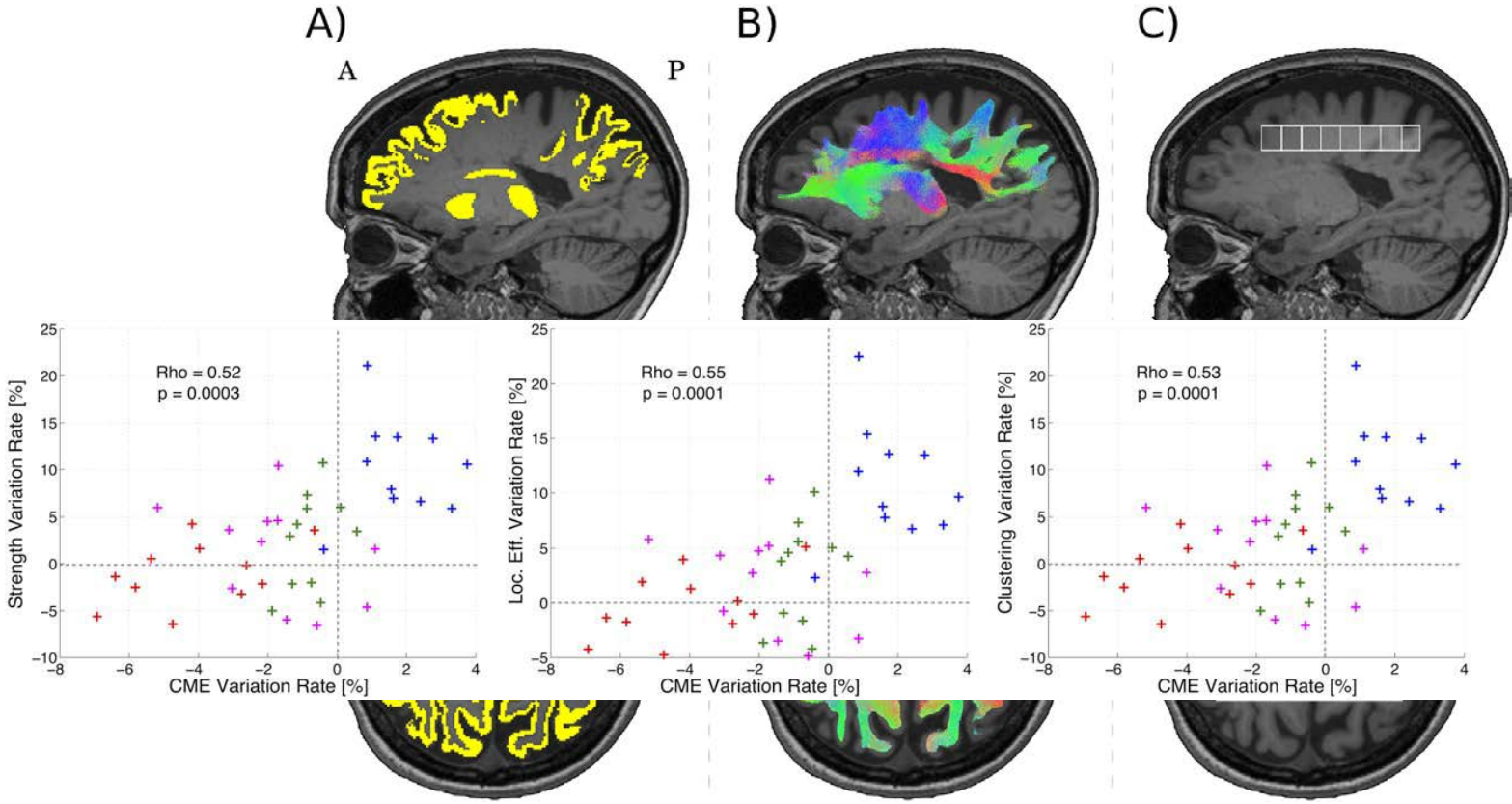


Cortical damage 2018

- Solana et al. – Neuroimage Clinical
  - Structural disconnection related to
    - GM NAA (integrity)
    - GM myo-inositol (gliosis)
    - Demyelination
- Mangeat et al. – HBM
  - Structural disconnection
    - Related to cortical myelin

Changes in structural network are associated with cortical demyelination in early multiple sclerosis

Gabriel Mangeat[1,2] | Atef Badji[1,3] | Russell Ouellette[2,4] | Constantina A. Treaba[2,5] | Elena Herranz[2,5] | Tobias Granberg[2,4,5] | Céline Louapre[2,5,6] | Nikola Stikov[1,7] | Jacob A. Sloane[5,8] | Pierre Bellec[3,9] | Caterina Mainero[2,5*] | Julien Cohen-Adad[1,3*]
Irene Pulido-Valdeolivas[a], Irati Zubizarreta[a], Albert Saiz[a], Sara Llufriu[a,*]



Structure/Function 2007

- Rocca et al. -
- All studied tr
- Some tracts

M.A. Rocca, MD
E. Pagani, PhD
M. Absinta, MD
P. Valsasina, PhD
A. Falini, MD
G. Scotti, MD
G. Comi, MD
M. Filippi, MD

Altered functional and structural connectivities in patients with MS

A 3-T study

Radiology

Maria A. Rocca, MD
Martina Absinta, MD
Lucia Moiola, MD
Angelo Ghezzi, MD
Bruno Colombo, MD
Vittorio Martinelli, MD
Giancarlo Comi, MD
Massimo Filippi, MD

Functional and Structural Connectivity of the Motor Network in Pediatric and Adult-Onset Relapsing-Remitting Multiple Sclerosis[1]

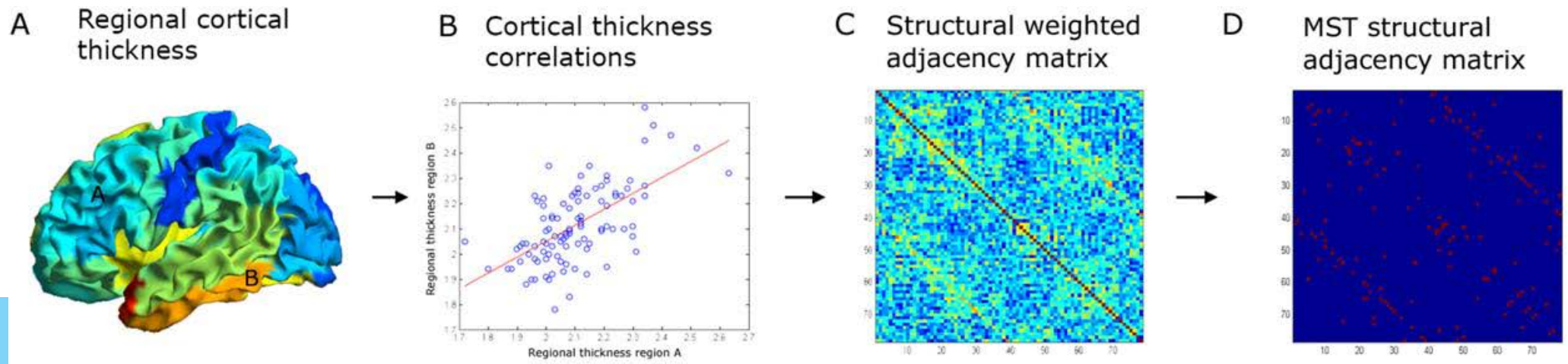
◆ Human Brain Mapping 35:5946–5961 (2014) ◆

Disruption of Structural and Functional Networks in Long-Standing Multiple Sclerosis

Prejaas Tewarie,[1]* Martijn D. Steenwijk,[2] Betty M. Tijms,[3] Marita Daams,[2,4] Lisanne J. Balk,[1] Cornelis J. Stam,[5] Bernard M.J. Uitdehaag,[1] Chris H. Polman,[1] Jeroen J.G. Geurts,[3] Frederik Barkhof,[2] Petra J.W. Pouwels,[6] Hugo Vrenken,[2,6] and Arjan Hillebrand[5]

Structure vs function 2014

- Tewarie et al. – HBM
- Changes in functional connectivity (MEG)
  - NOT related to <u>local</u> cortical thickness
    - But: Correlated to cortical thickness <u>network topology</u>!



Structure vs function 2018

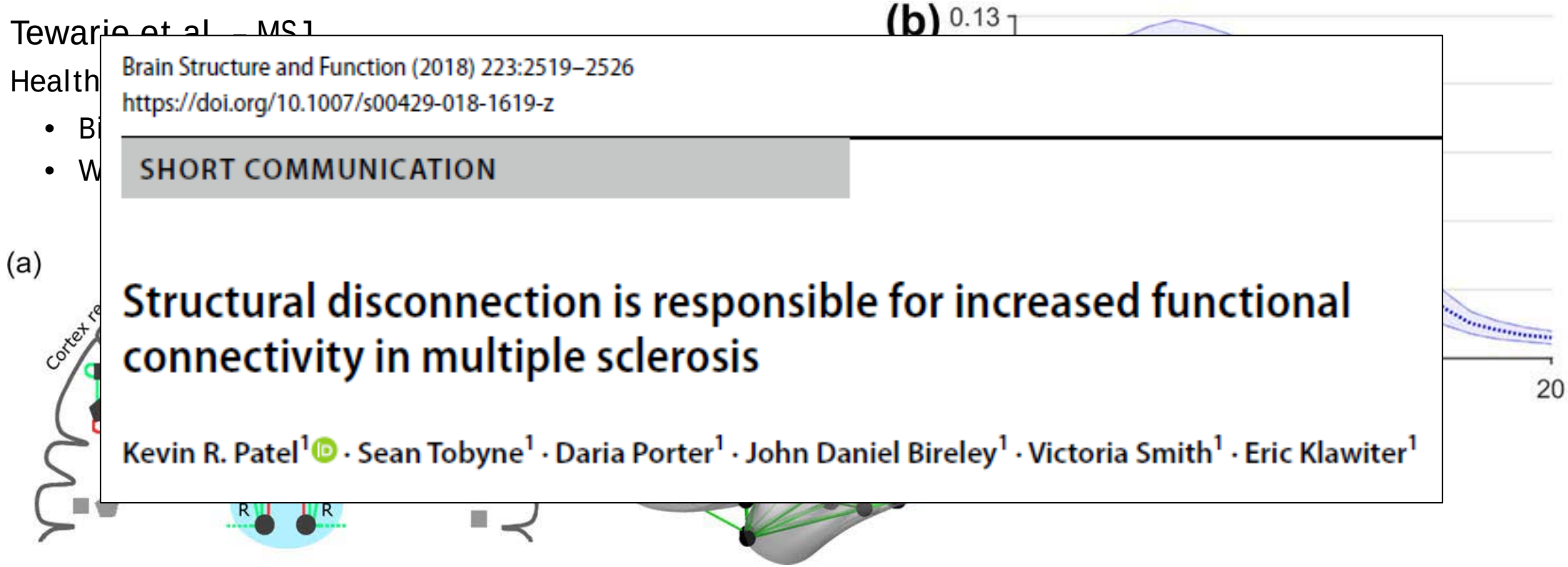
- Tewarie et al., MS 1
- Health
  - Bi
  - W

RESEARCH ARTICLE

WILEY

Explaining the heterogeneity of functional connectivity findings in multiple sclerosis: An empirically informed modeling study

Prejaas Tewarie[1] | Martijn D. Steenwijk[2,3] | Matthew J. Brookes[1] | Bernard M. J. Uitdehaag[2] | Jeroen J. G. Geurts[3] | Cornelis J. Stam[4] | Menno M. Schoonheim[3]



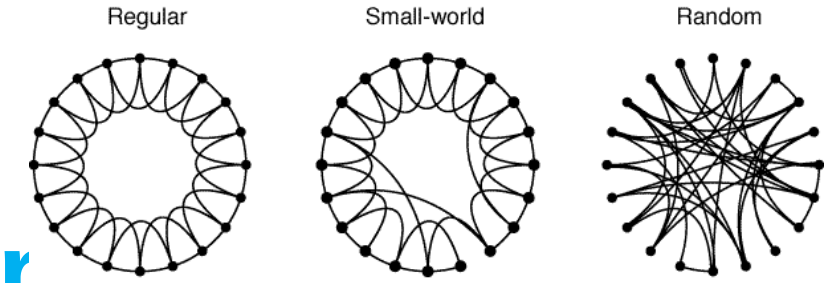
Brain Structure and Function (2018) 223:2519–2526
https://doi.org/10.1007/s00429-018-1619-z

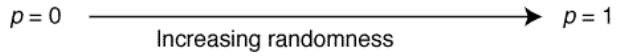
SHORT COMMUNICATION

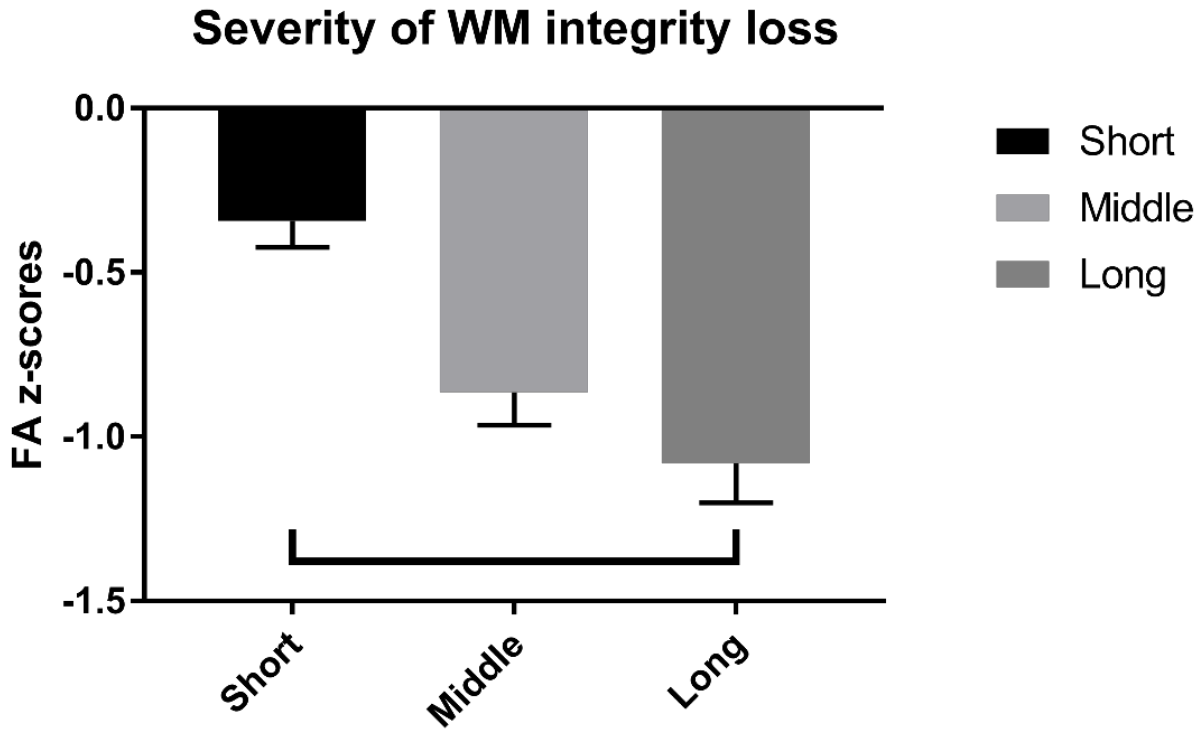
Structural disconnection is responsible for increased functional connectivity in multiple sclerosis

Kevin R. Patel[1] · Sean Tobyne[1] · Daria Porter[1] · John Daniel Bireley[1] · Victoria Smith[1] · Eric Klawiter[1]

Structure vs fur
2018





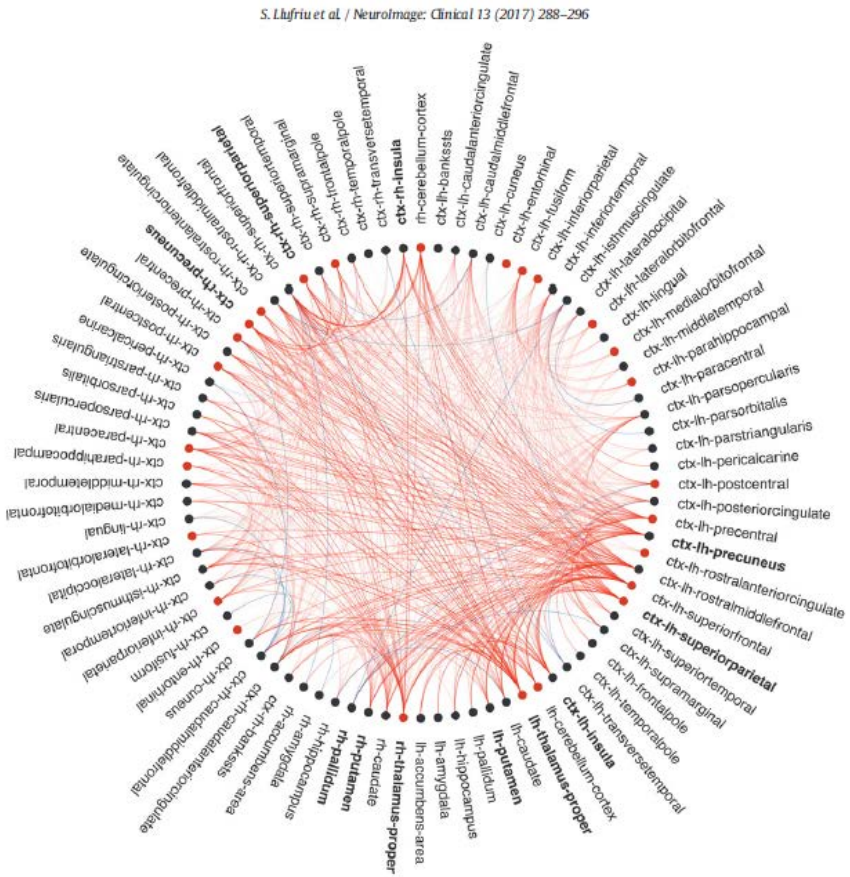


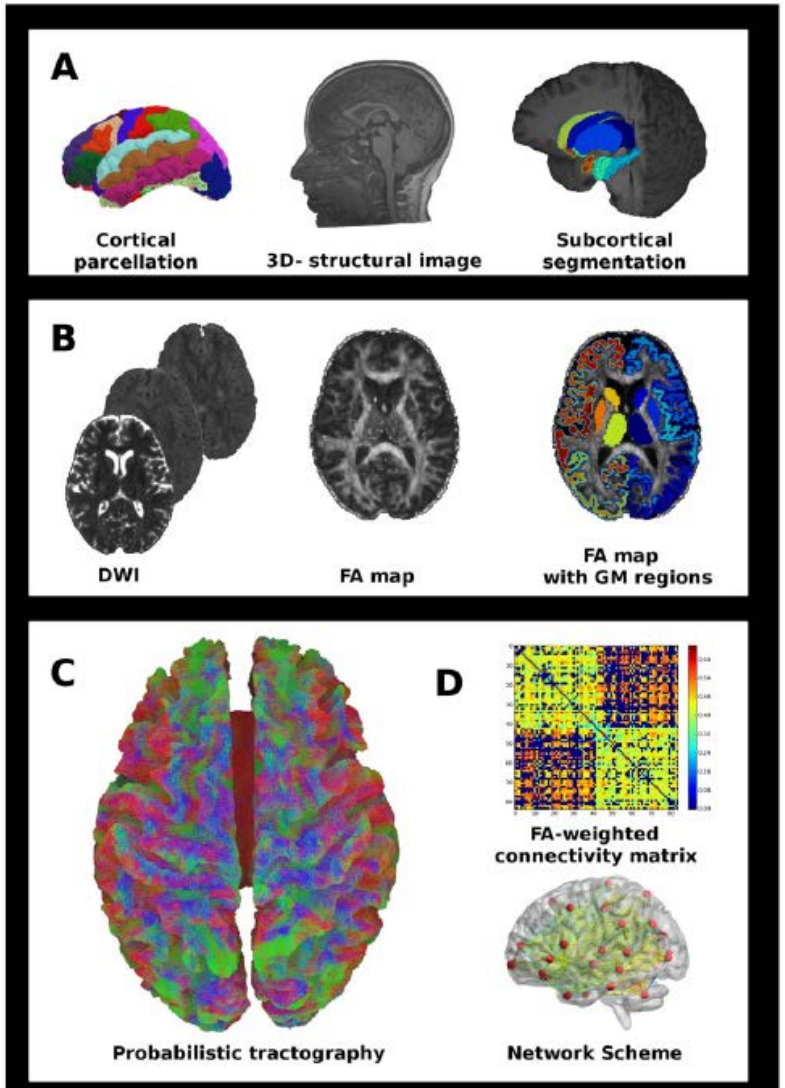
Kim Meijer, ECTRIMS 2018 (wednesday)

<u>Long versus short distance structural connections</u>:
More damage and a larger impact on brain function (and cognition!)

Watts & Strogatz (1999)

Advanced network analysis





Clustering coefficient

Path length: red vs green

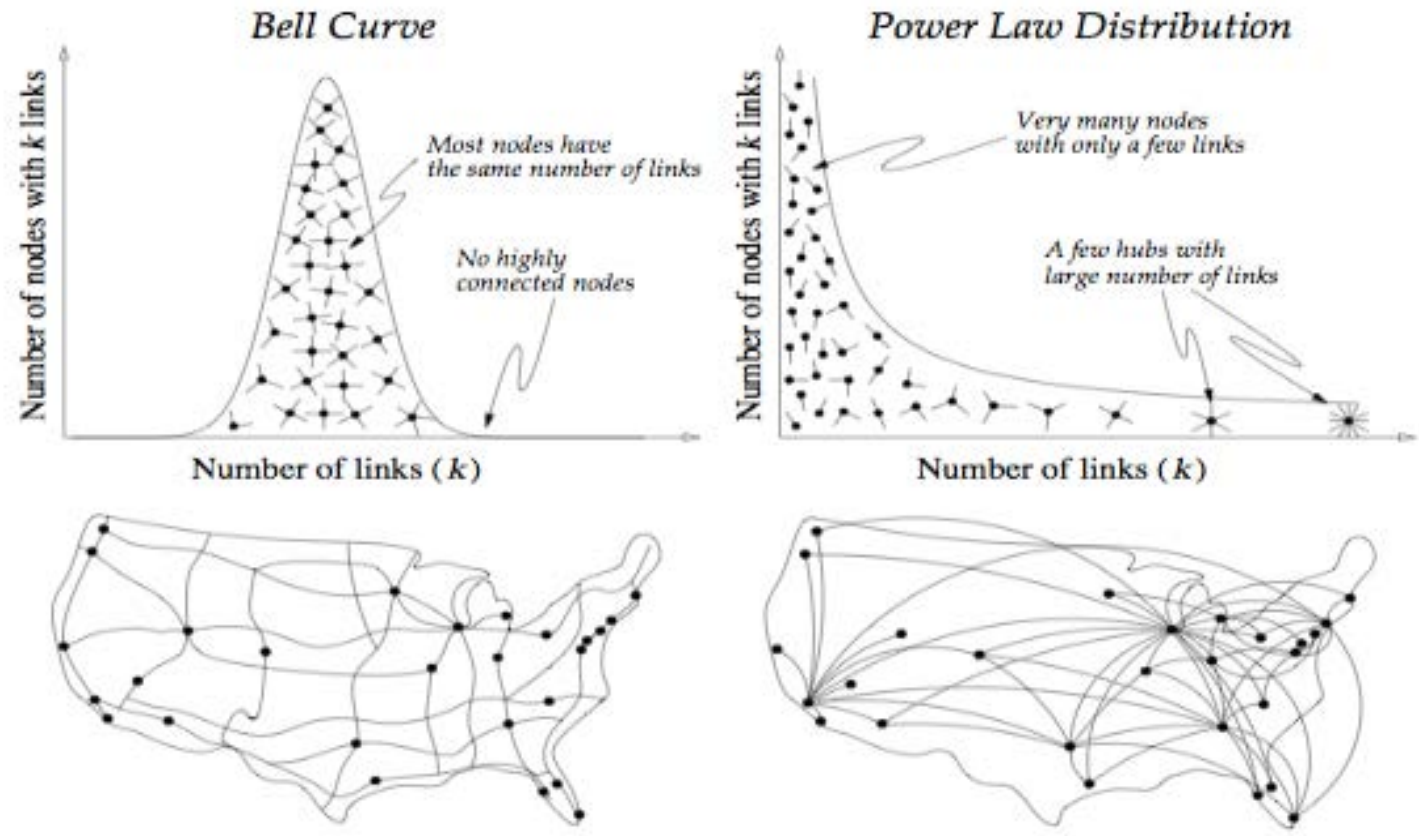
Degree: purple >4 connections

Hubs

Llufriu et al. 2017

MS Center Amsterdam

Network efficiency: Hubs!



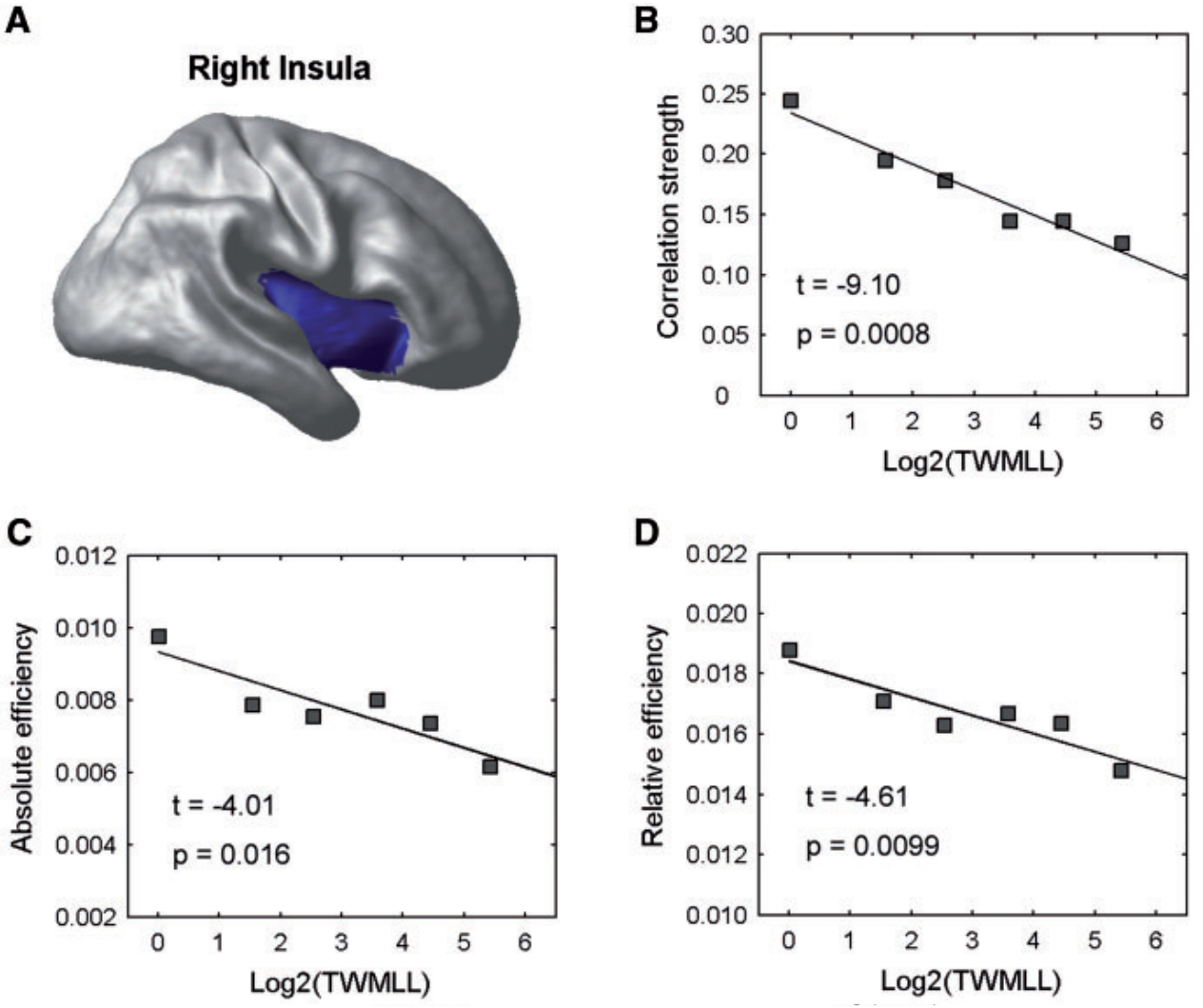
R. Albert, H. Jeong, A-L Barabasi, *Nature*, 401 130 (1999).

FIGURE (6.1)

doi:10.1093/brain/awp089 Brain 2009: 132; 3366–3379 | 3366
BRAIN
A JOURNAL OF NEUROLOGY

Efficiency: Lesion load 2009

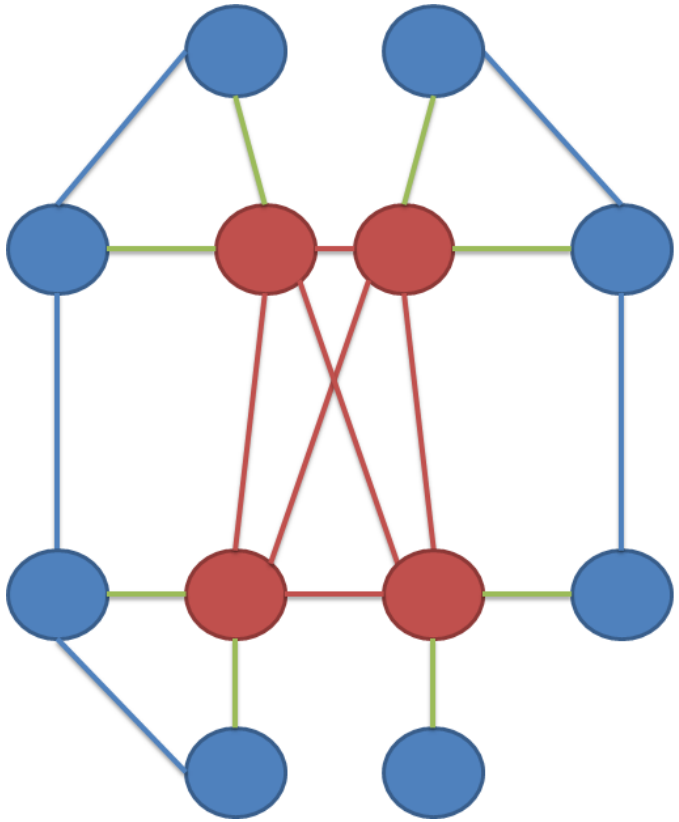
- He et al – Brain
  - Groups of MS based on lesion load
  - GM cortical thickness correlations
  - Changes in network topology related to lesion load
    - Higher lesion load:
      - Lower global efficiency
      - Lower local efficiency
        - Strong effects for insula



Behavioral/Systems/Cognitive The Journal of Neuroscience, November 2, 2011 • 31(44):15775–15786 • 15775

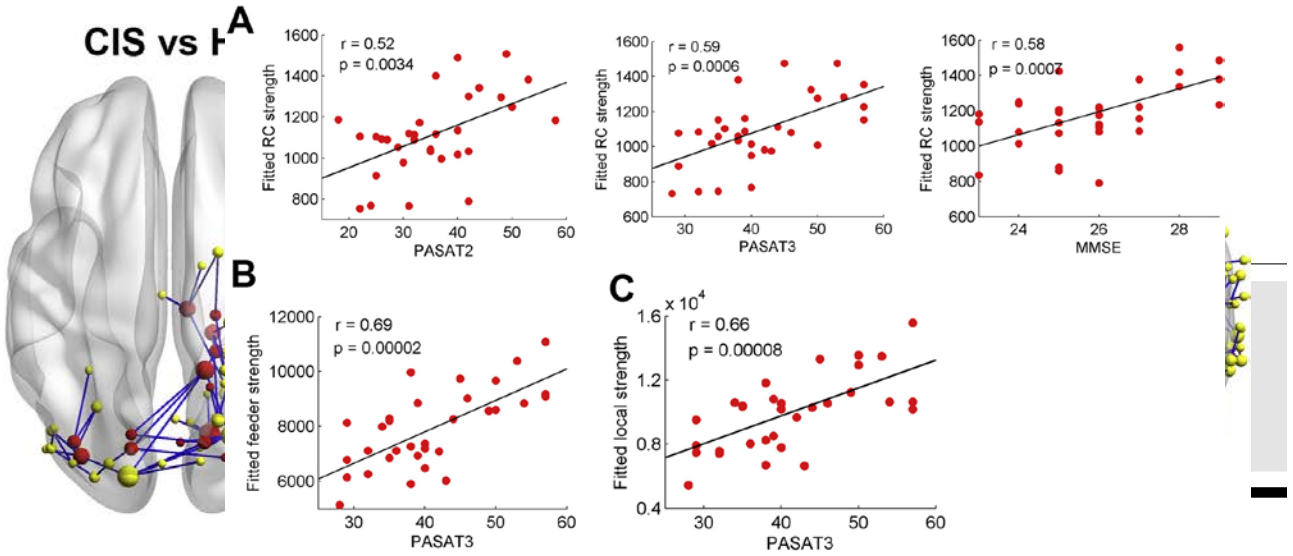
Rich-Club Organization of the Human Connectome

Martijn P. van den Heuvel[1] and Olaf Sporns[2]
[1]Department of Psychiatry, University Medical Center Utrecht, Rudolf Magnus Institute of Neuroscience, 3508 GA Utrecht, The Netherlands, and
[2]Department of Psychological and Brain Sciences and Program in Cognitive Science, Indiana University, Bloomington, Indiana 47405



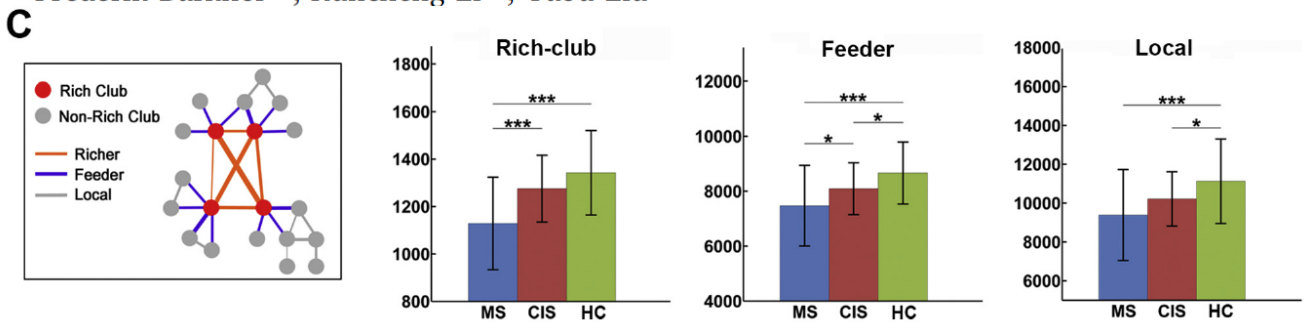
- Rich club node
- Non-rich club node

/ Rich club connection
/ Feeder connection
/ Local connection



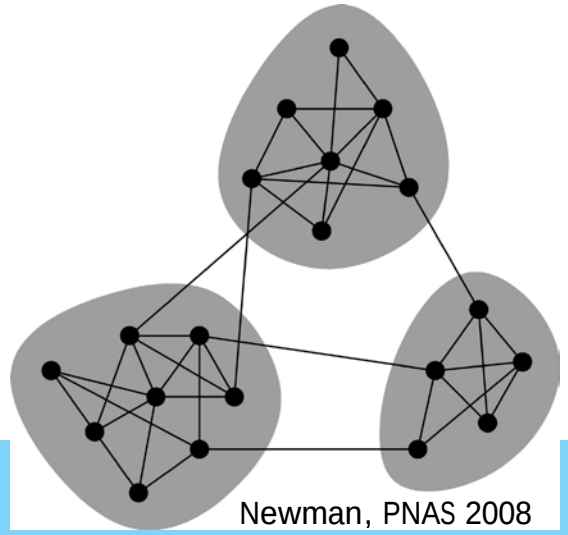
Progressive brain rich-club network disruption from clinically isolated syndrome towards multiple sclerosis

Ni Shu[a,b,c], Yunyun Duan[d,e,f], Jing Huang[f], Zhuoqiong Ren[f], Zheng Liu[g], Huiqing Dong[g], Frederik Barkhof[h,i], Kuncheng Li[f,*], Yaou Liu[d,e,f,h,*]



Modularity: CDMS 2017 - 2018

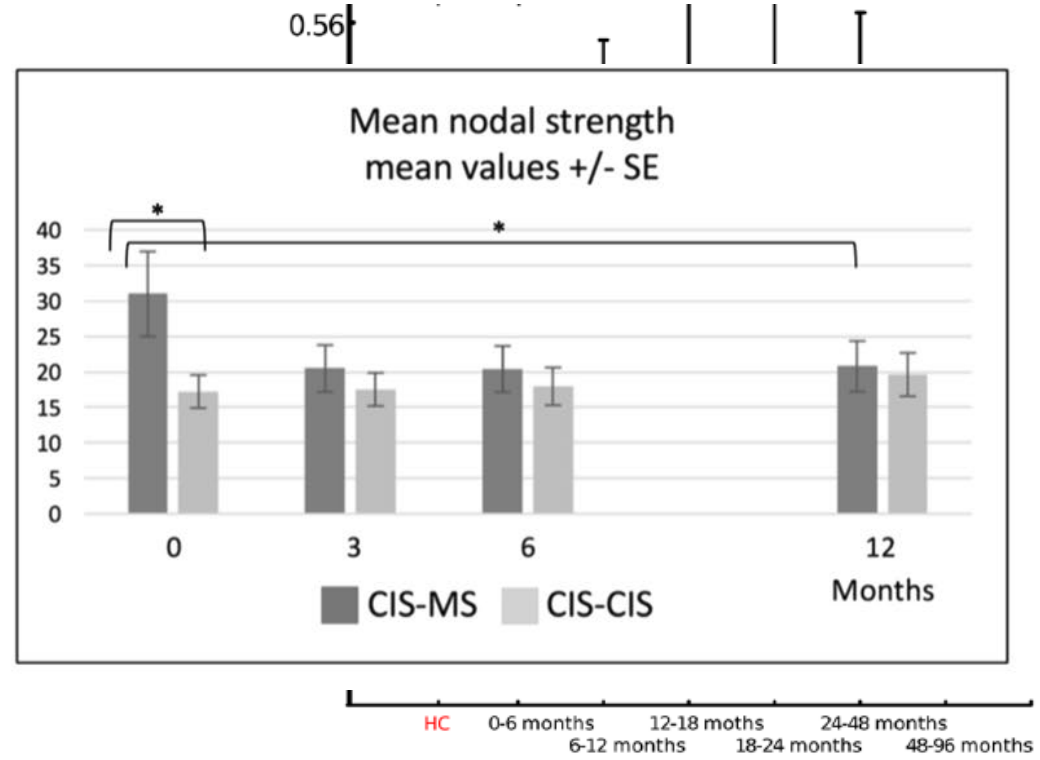
- Tur et al – MSJ
  - Grouping based on disease duration
  - No effect for modularity
- Fleischer et al – MSJ
  - Within- / between module connectivity
  - Balance with ...
  - Modularity:
    - But: Overall baseline difference
      - Converting higher connectivity vs non-converting CIS



Newman, PNAS 2008

Structural cortical network reorganization associated with early conversion to multiple sclerosis

C. Tur[1], A. Eshaghi[1,2], D. R. Altmann[1,3], T. M. Jenkins[1], F. Prados[1,4], F. Grussu[1,2], T. Charalambous[1], A. Schmidt[5], S. Ourselin[4], J. D. Clayden[6], C. A. M. G. Wheeler-Kingshott[1,7,8], A. J. Thompson[1,9], O. Ciccarelli[1,9] & A. T. Toosy[1]

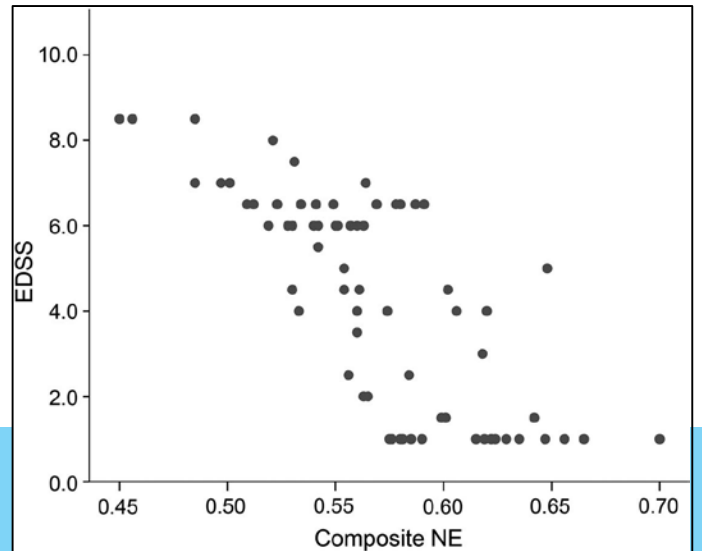


Motor impairment 2015: Efficiency

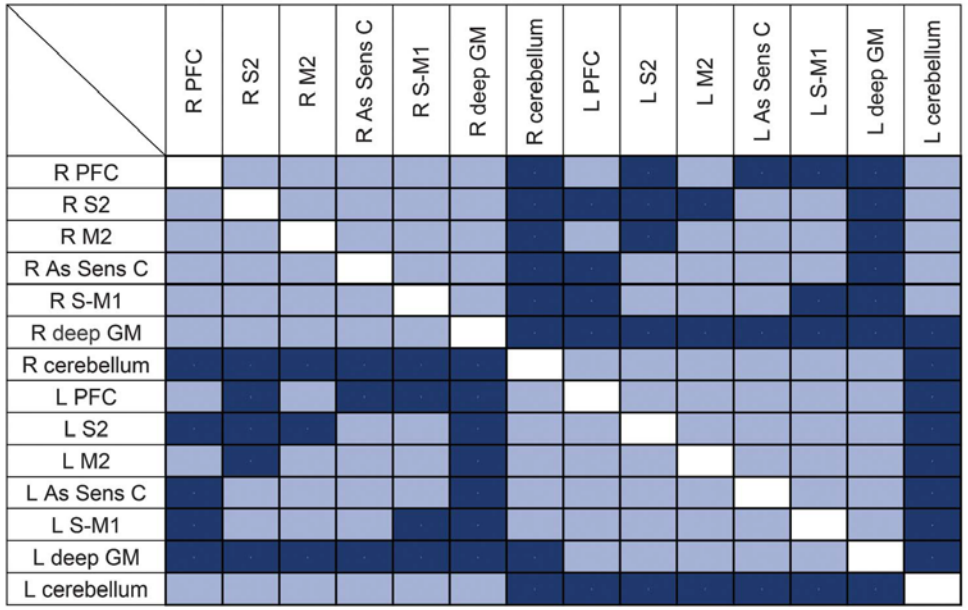
- Pardini et al – Neurology
  - Structural connectivity within the motor network
  - Efficiency loss explained 58% of disability
    - More than any other MR measure
      - Note: Motor system FA 28% !

Matteo Pardini, MD
Özgür Yaldizli, MD
Varun Sethi, MD, PhD
Nils Muhlert, PhD
Zheng Liu, MD
Rebecca S. Samson, PhD
Daniel R. Altmann, PhD
Maria A. Ron, PhD, FRCPsych
Claudia A.M. Wheeler-Kingshott, PhD
David H. Miller, MD, FMedSci
Declan T. Chard, PhD, FRCP

Motor network efficiency and disability in multiple sclerosis



B



Cognitive relevance 2017 – 2018: Hubs

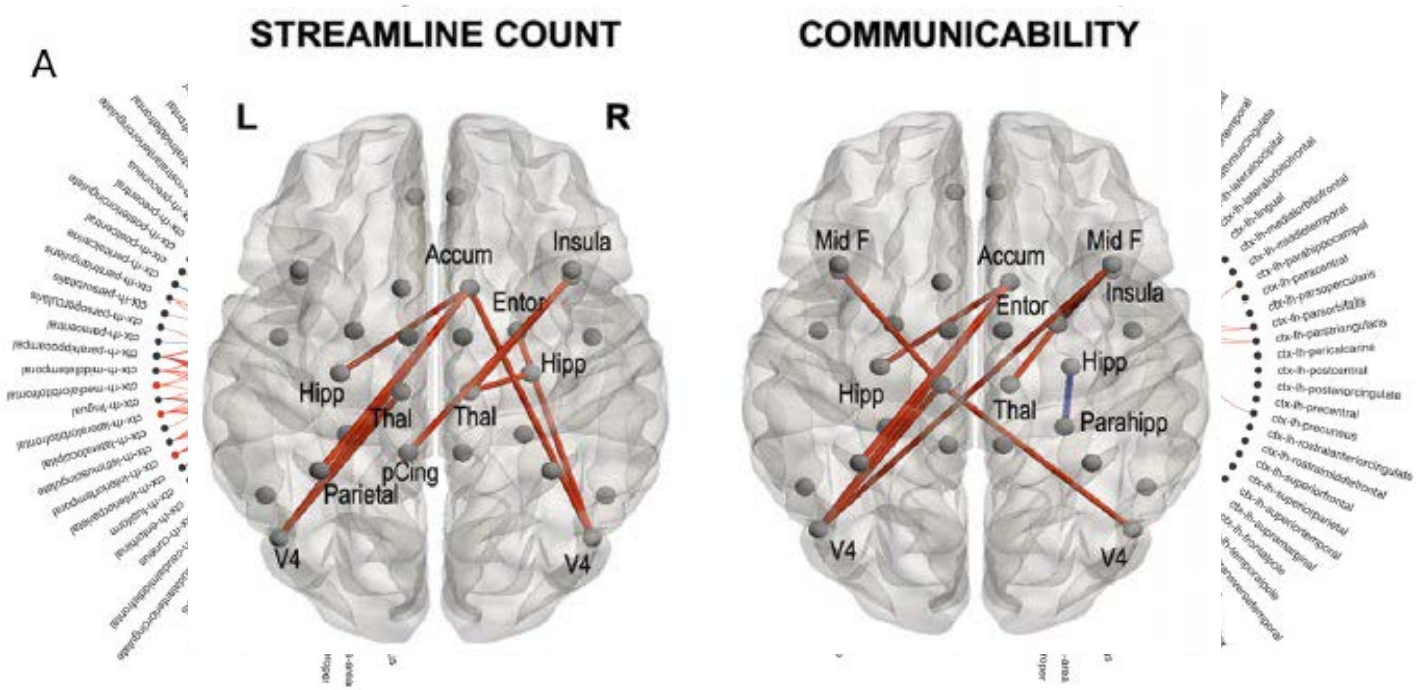
- Llufriu et al – MSJ (2x)
  - Hub disconnection related to cognition
  - Memory network disconnection

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Hippocampal-related memory network in multiple sclerosis: A structural connectivity analysis

Sara Llufriu, Maria A Rocca, Elisabetta Pagani, Gianna C Riccitelli, Elisabeth Solana, Bruno Colombo, Mariaemma Rodegher, Andrea Falini, Giancarlo Comi and Massimo Filippi



RESEARCH ARTICLE

WILEY

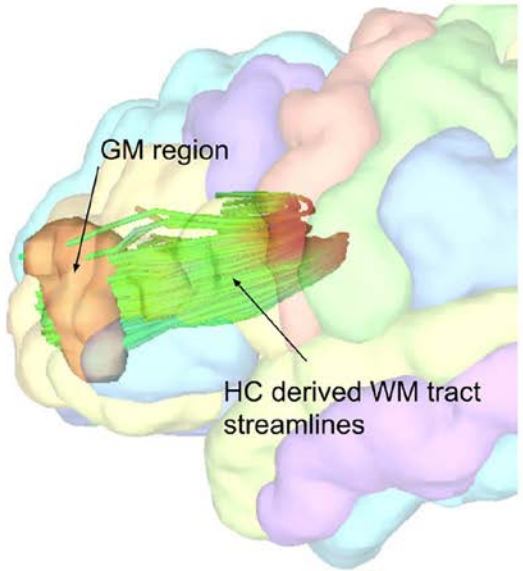
DOI: 10.1002/hbm.24203

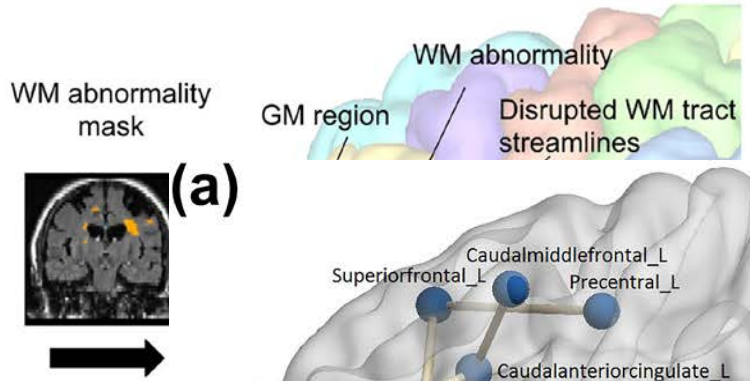
White matter tract network disruption explains reduced conscientiousness in multiple sclerosis

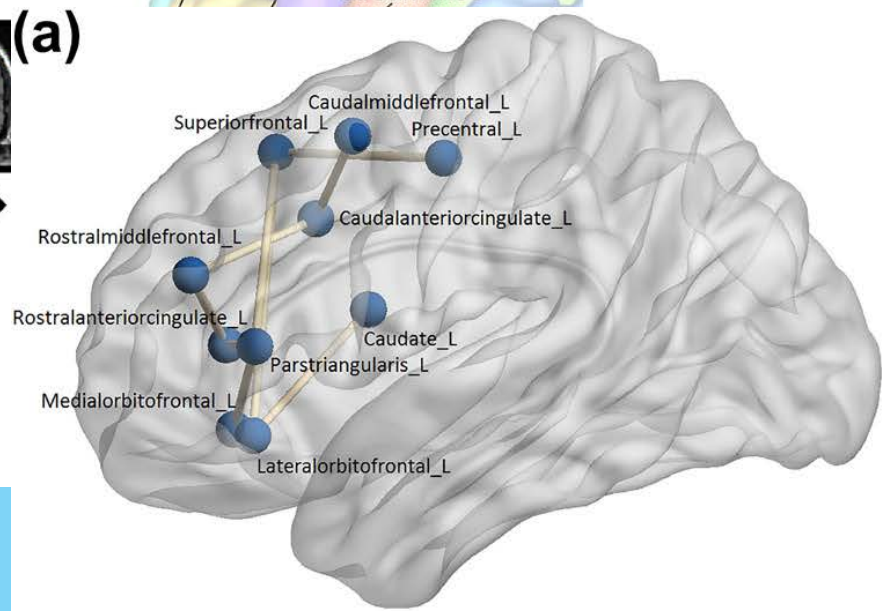
Tom A. Fuchs[1,2] | Michael G. Dwyer[1,2] | Amy Kuceyeski[4] | Sanjeevani Choudhery[1,2] | Keith Carolus[1,2] | Xian Li[1,2] | Matthew Mallory[1,2] | Bianca Weinstock-Guttman[1] | Dejan Jakimovski[1,2] | Deepa Ramasamy[1,2,3] | Robert Zivadinov[1,2,3] | Ralph H.B. Benedict[1]

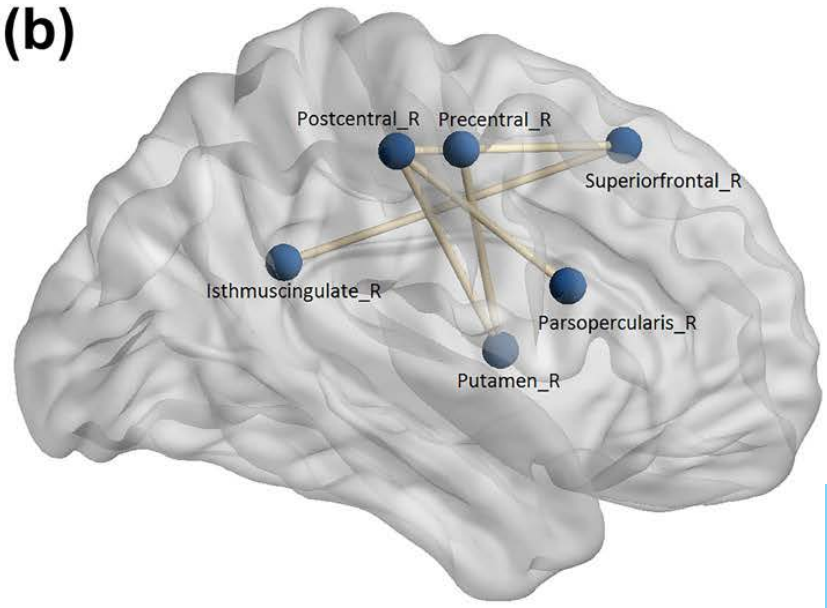
Cognitive relevance 2018: 3DT1

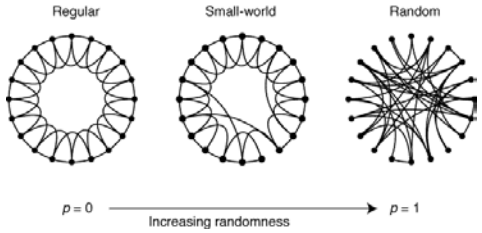
- Fuchs et al. – HBM
- WM disconnection based on 3DT1 data with lesion maps











Cognitive relevance 2018: Small world

- Rimkus et al. – MSJ
- GM networks
  - Based on individual subjects!
    - Disrupted small-world parameters
    - Related to cognitive impairment

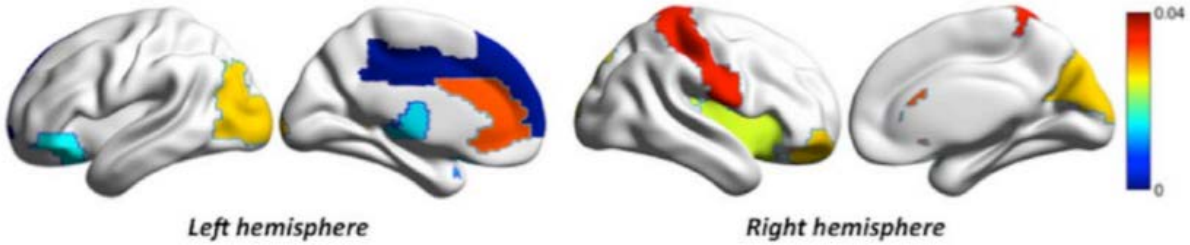
- Executive function (see figure)
- Information processing speed
- Working memory
- Attention

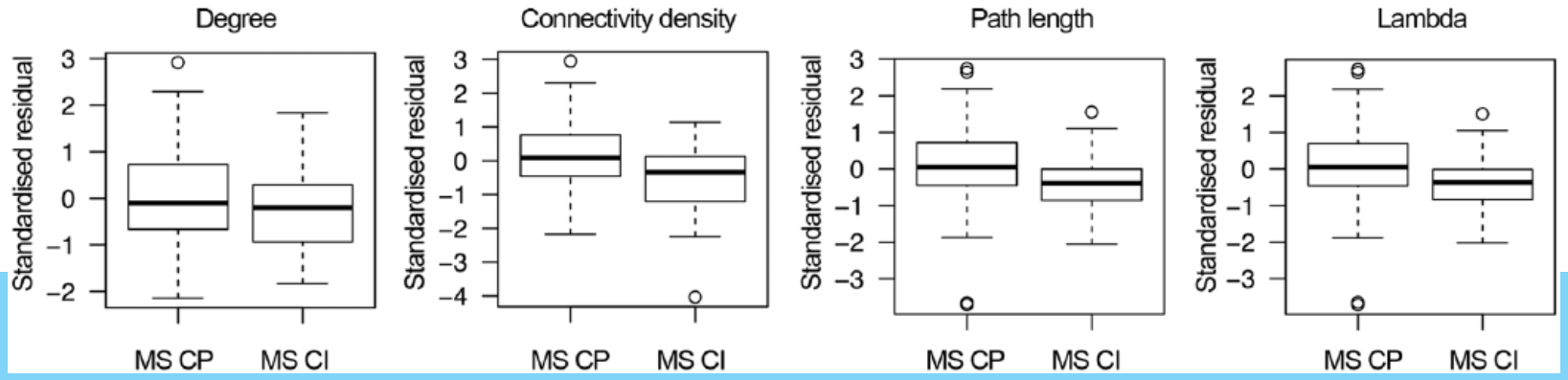
MULTIPLE SCLEROSIS JOURNAL | MSJ

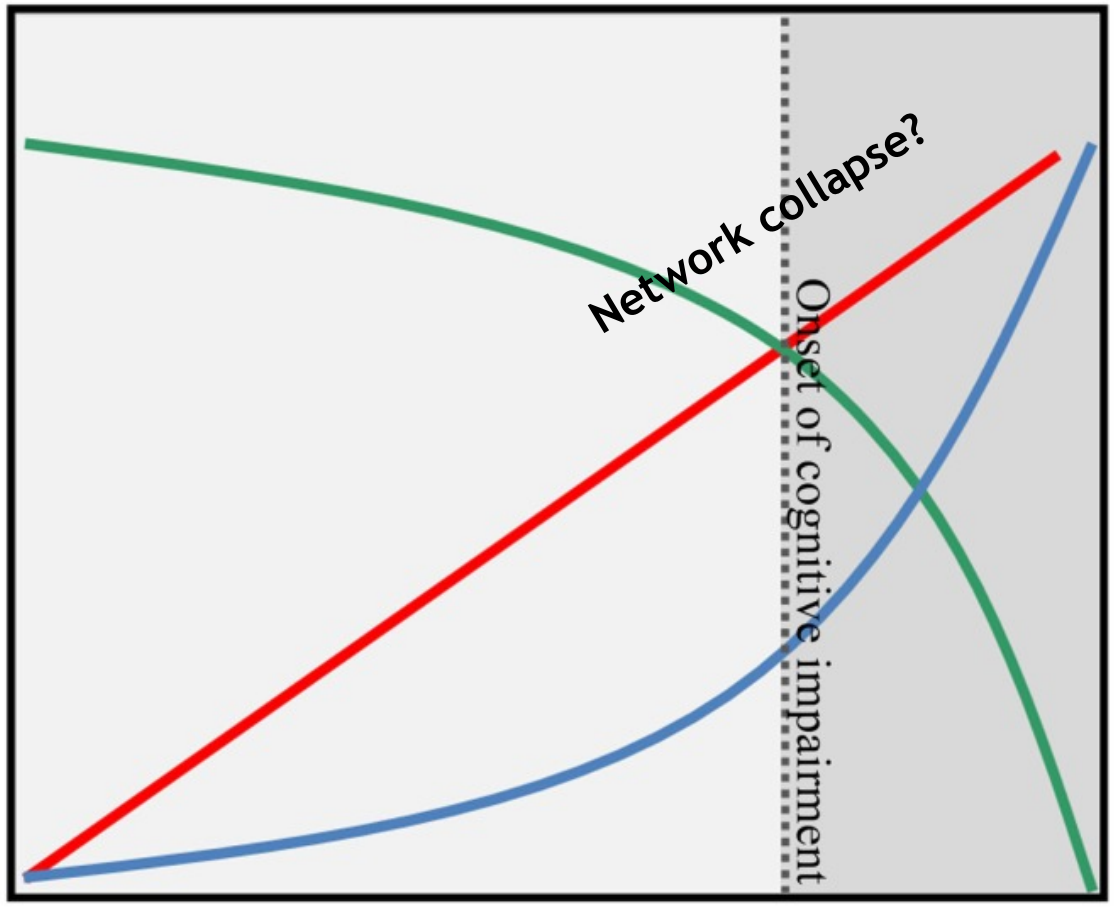
Original Research Paper

Gray matter networks and cognitive impairment in multiple sclerosis

Carolina M Rimkus, Menno M Schoonheim, Martijn D Steenwijk, Hugo Vrenken, Anand JC Eijlers, Joep Killestein, Mike P Wattjes, Claudia C Leite, Frederik Barkhof and Betty M Tijms

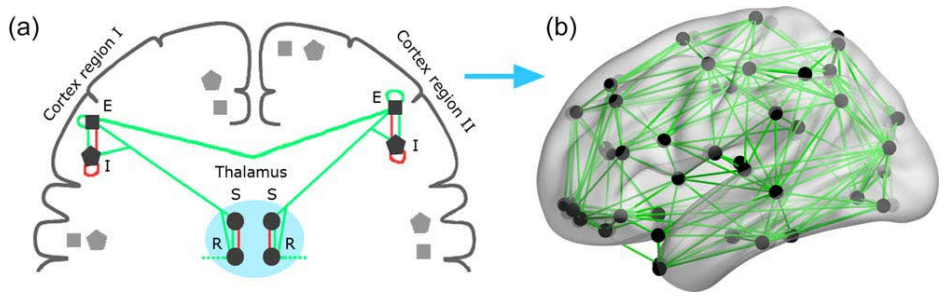






Schoonheim et al, Front Neurol, 2015

Summary



So what have we learnt so far?

- Early days!
  - New methods like MRTrix could possibly track through lesions
- Loss of structural network efficiency is related to disability and cognition
  - As well as increased functional connectivity
- Network topology analyses can provide unique information
  - Graph analysis to analyze the entire brain network at once
- The future: Longitudinal studies, computational models and relations with histopathology

Amsterdam UMC
University Medical Centers

MS Center Amsterdam

Thank you!

Clinical Neuroscience

anatomy & neurosciences

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