Involvement of the cerebellum in structural connectivity enhancement in episodic migraine

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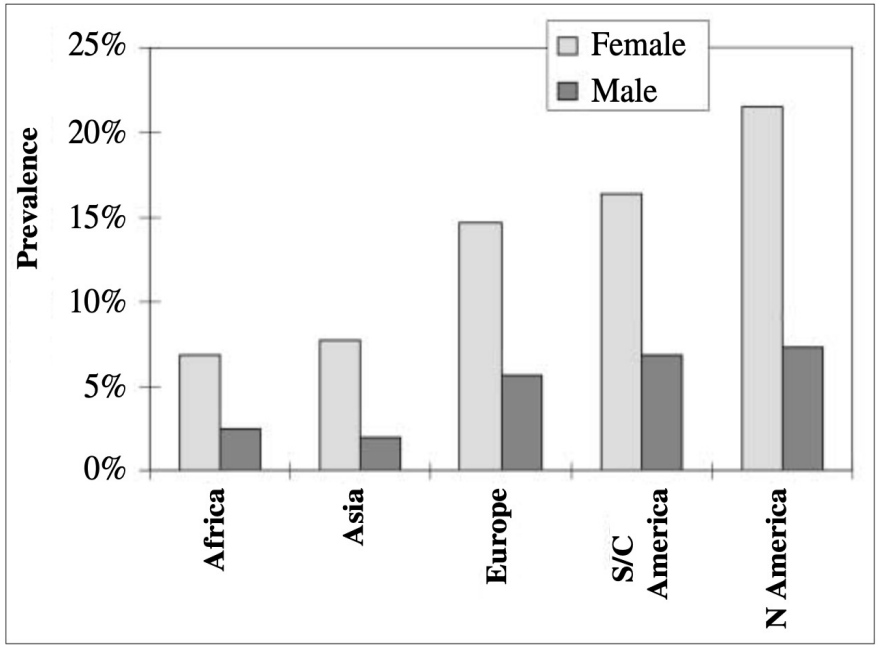
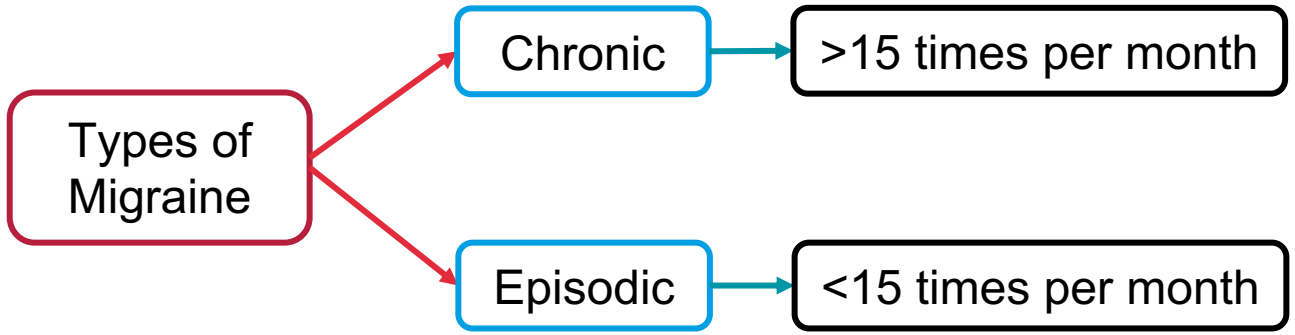
Paper

Introduction – Migraine

- 12% of the population worldwide
- Symptoms:
  - Unilateral pulsating head pain
  - Nausea
  - Vomiting
  - Photophobia
  - Sensitivity to movement





5.6%

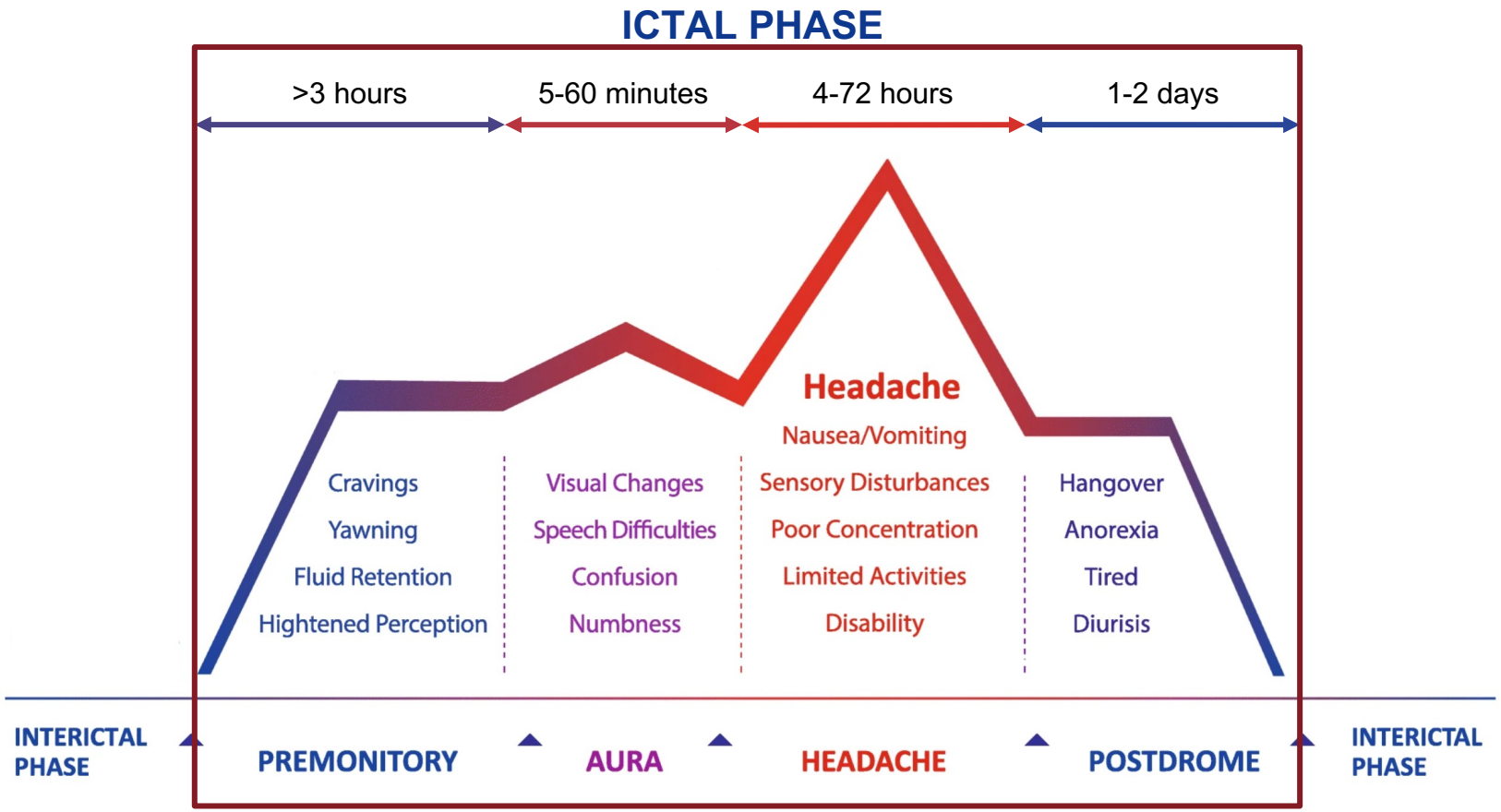
17.1%

Scher, A. I., Stewart, W. F., & Lipton, R. B. (1999). Migraine and headache: a meta-analytic approach. *Epidemiology of pain*, *159*, 170.
Lipton, R. B., Bigal, M. E., Diamond, M., Freitag, F., Reed, M. L., Stewart, W. F., & AMPP Advisory Group. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. Neurology, 17261680.

Introduction – Migraine

Triggers:

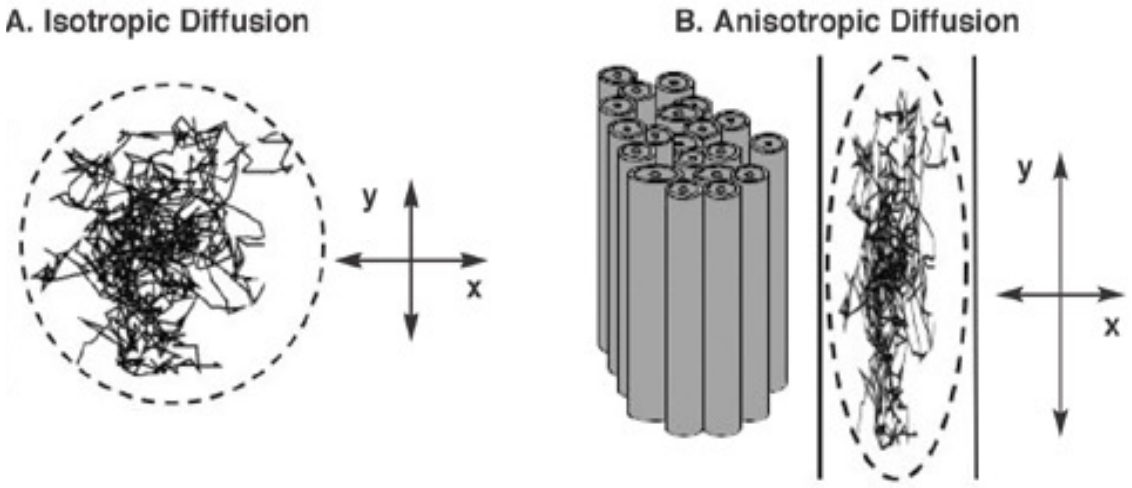
- Sensory
- Dietary (especially fasting)
- Stress
- Hormonal (e.g. menstrual cycle)



Andreou, A. P., & Edvinsson, L. (2019). Mechanisms of migraine as a chronic evolutive condition. J. Headache Pain, 20(1), 1–17. doi: 10.1186/s10194-019-1066-0

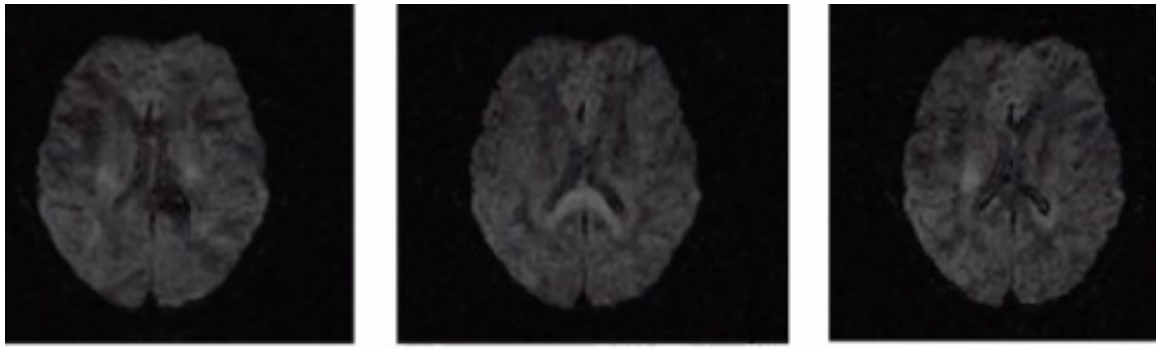
Introduction – Diffusion

- Type of Magnetic Resonance Imaging (MRI)
- Signal measured depends on the anisotropy of diffusion



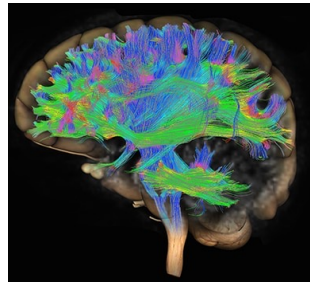
E.g. Necrosis

E.g. Fibrous tissue

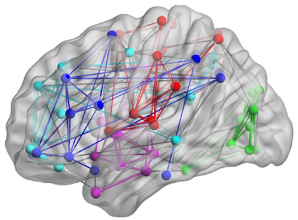


Diffusion weighting along different directions

Determine pathways of white matter fibres



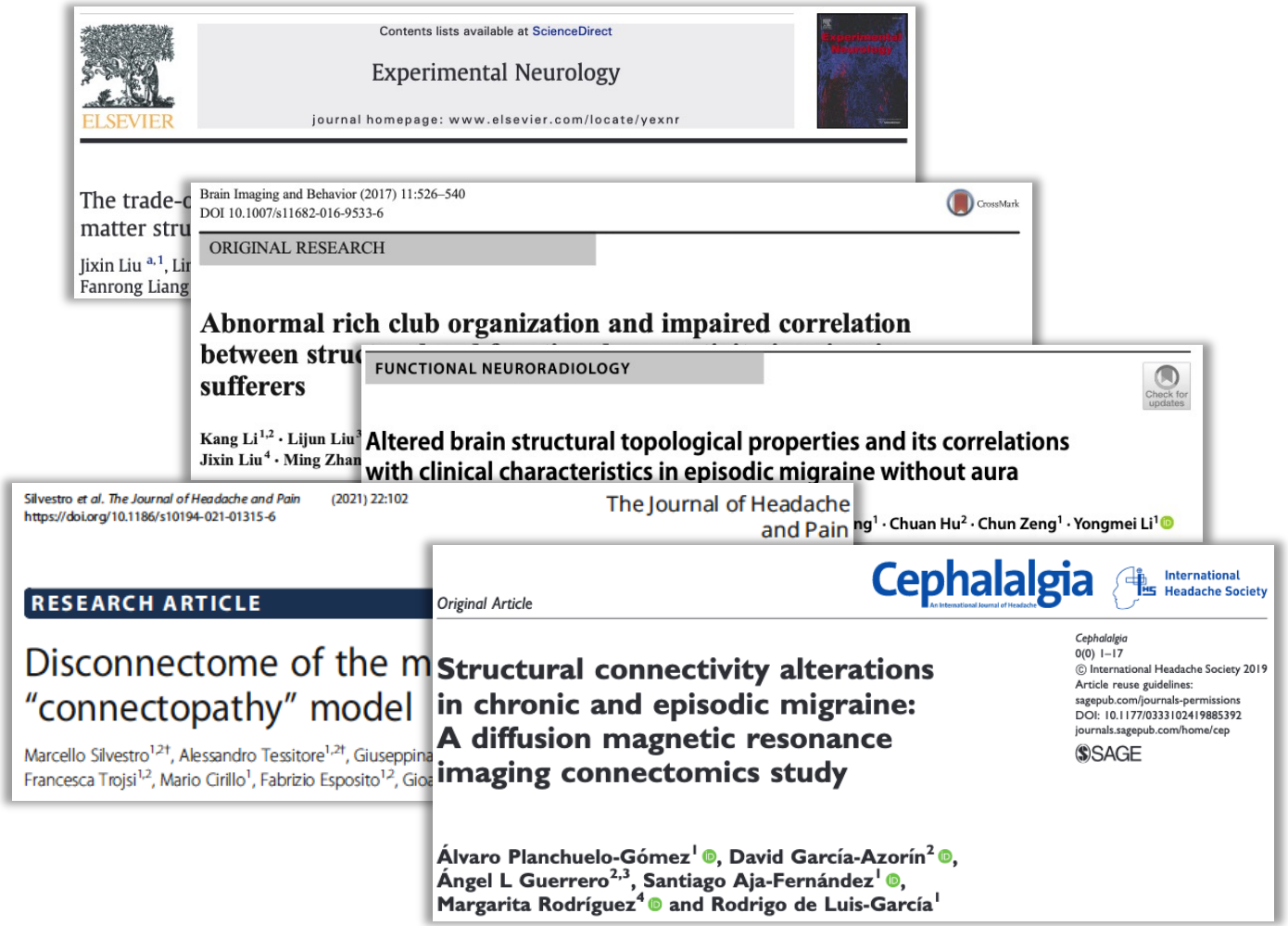
Brain Network (Connectivity Matrix)



Graph theory metrics

State of the art

- Disruptions in brain networks have been found in migraine



Global Efficiency ↑
Small-worldness ↑
Clustering Coefficient ↑
Average Degree ↑

Characteristic Path Length ↓

Limitations:

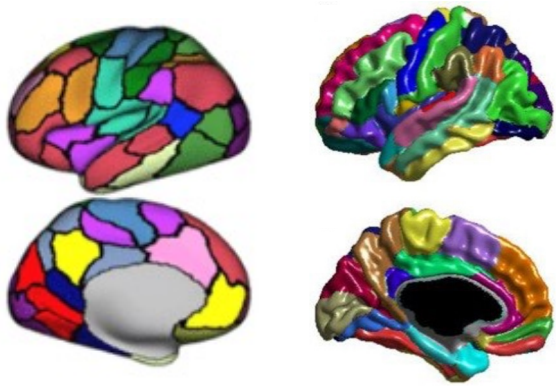
- Heterogenous cohort
- Binary weights
- Simple diffusion models
- Different atlases

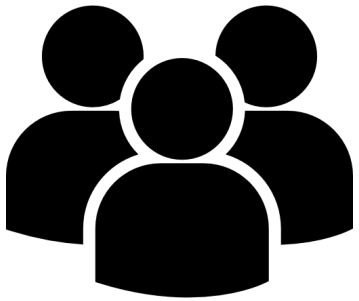
Research Gap

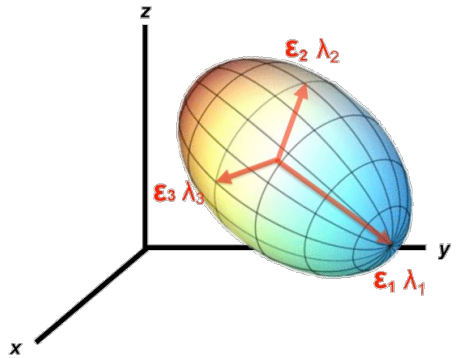
Cortical atlas

Heterogenous cohort

Simple models

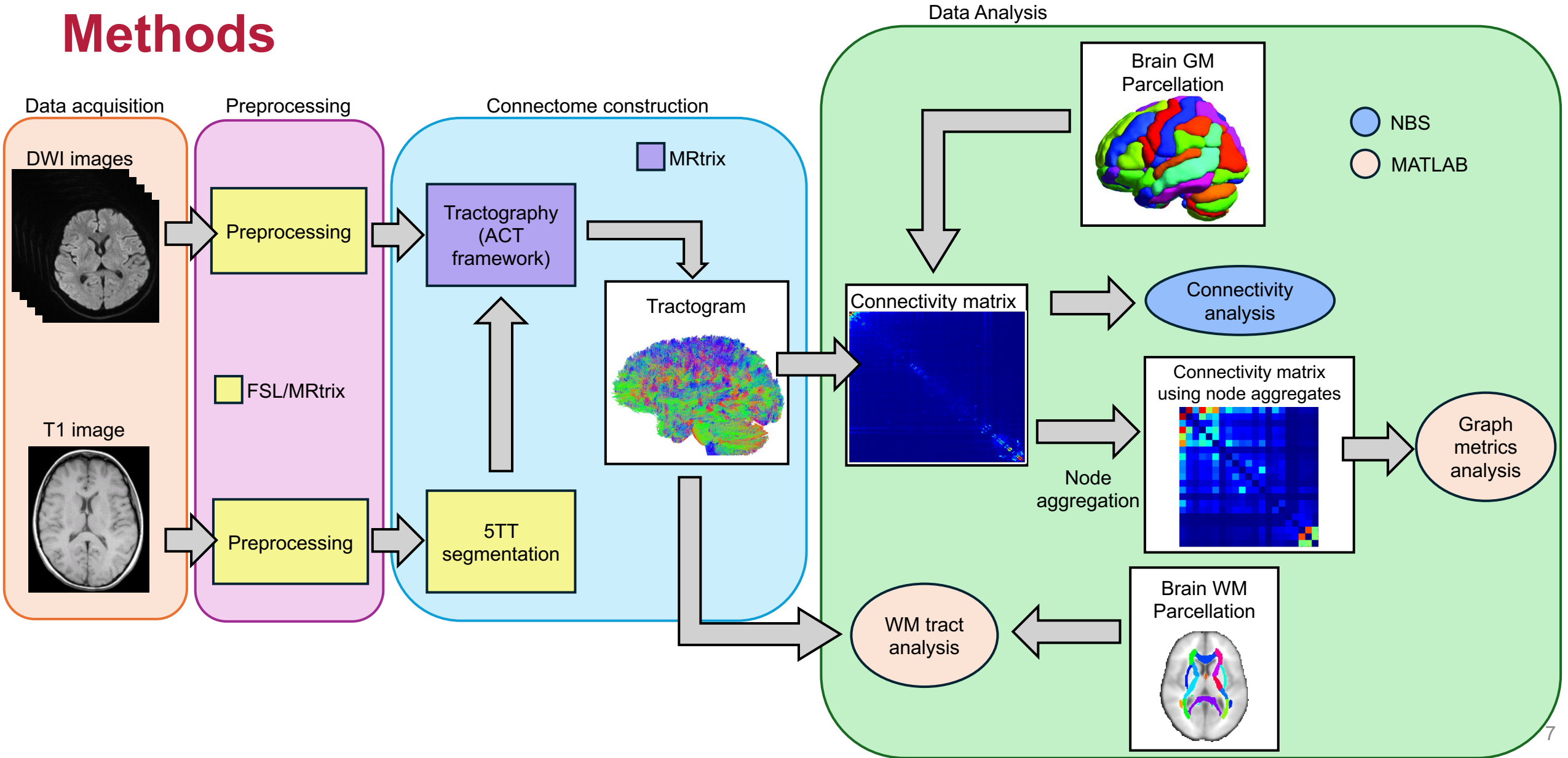






Goal: Investigate the structural connectome changes in migraine patients, in cortical, subcortical and cerebellar regions using advanced diffusion MRI techniques.

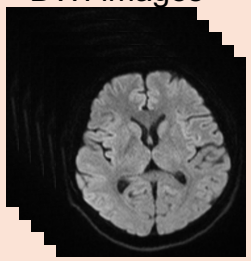
Methods


Data acquisition
Preprocessing
Connectome construction
Data Analysis
DWI images
T1 image
Preprocessing
Preprocessing
FSL/MRtrix
MRtrix
Tractography (ACT framework)
5TT segmentation
Tractogram
Brain GM Parcellation
NBS
MATLAB
Connectivity matrix
Connectivity analysis
Node aggregation
Connectivity matrix using node aggregates
Graph metrics analysis
WM tract analysis
Brain WM Parcellation

Methods

Data acquisition

DWI images



T1 image

Data acquisition

dMRI	T1-weighted
2mm isotropic resolution b=400, 1000, 2000 s/mm^2 along 32, 32, 60 directions 8 b0	1mm isotropic resolution 3D MPRAGE

Siemens Vida 3T

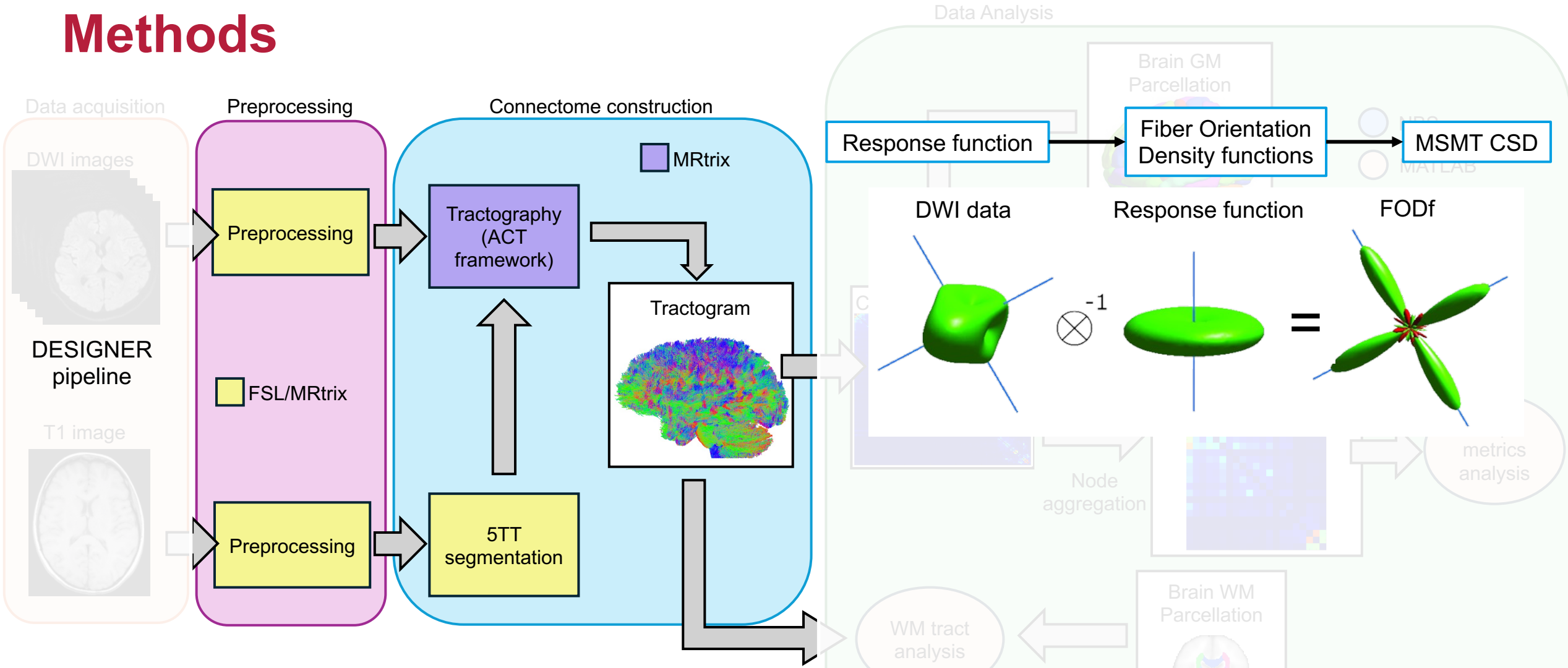
Population

MigN2treat cohort
female menstrual migraineurs

15 Controls

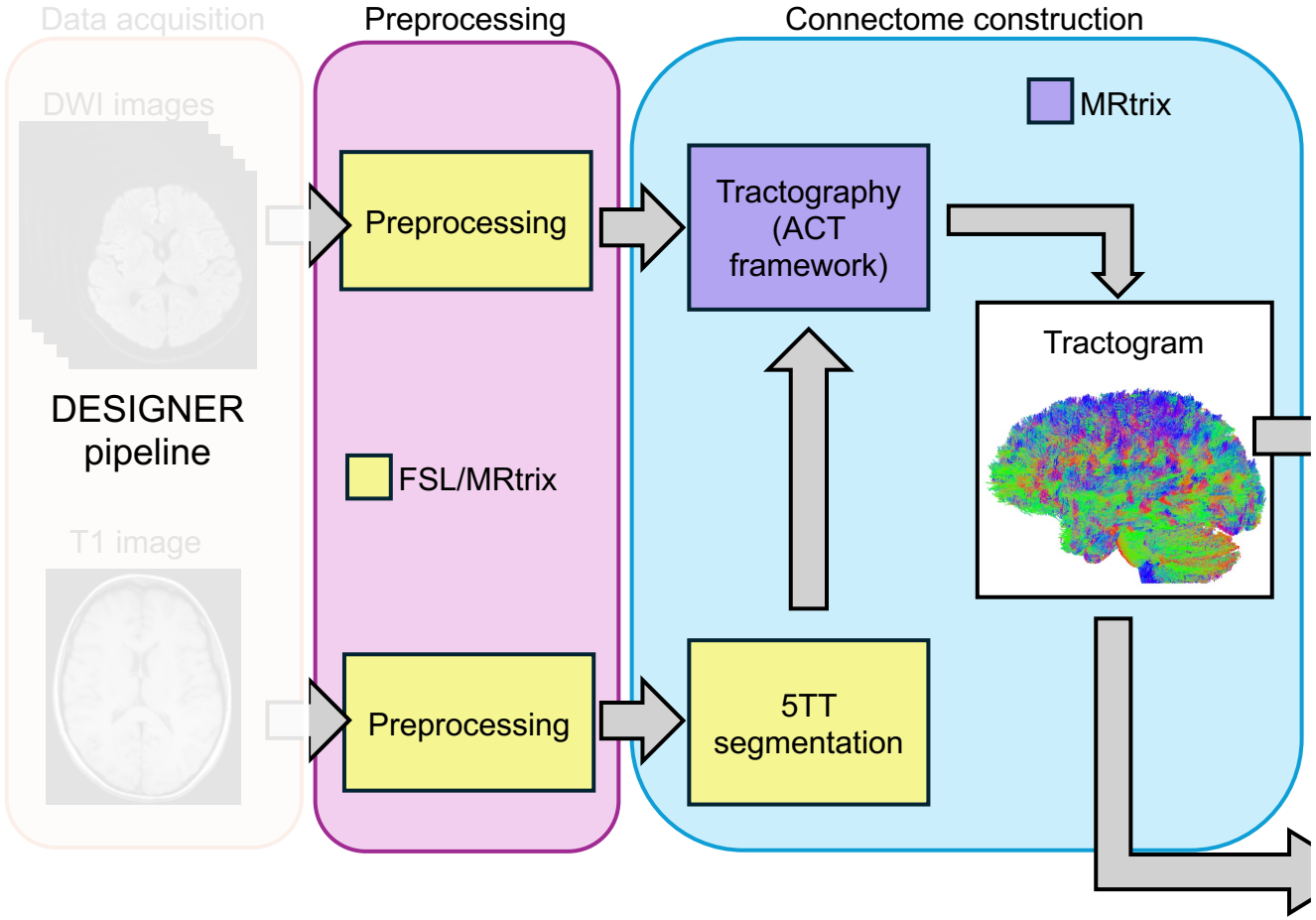
14 Migraine Patients

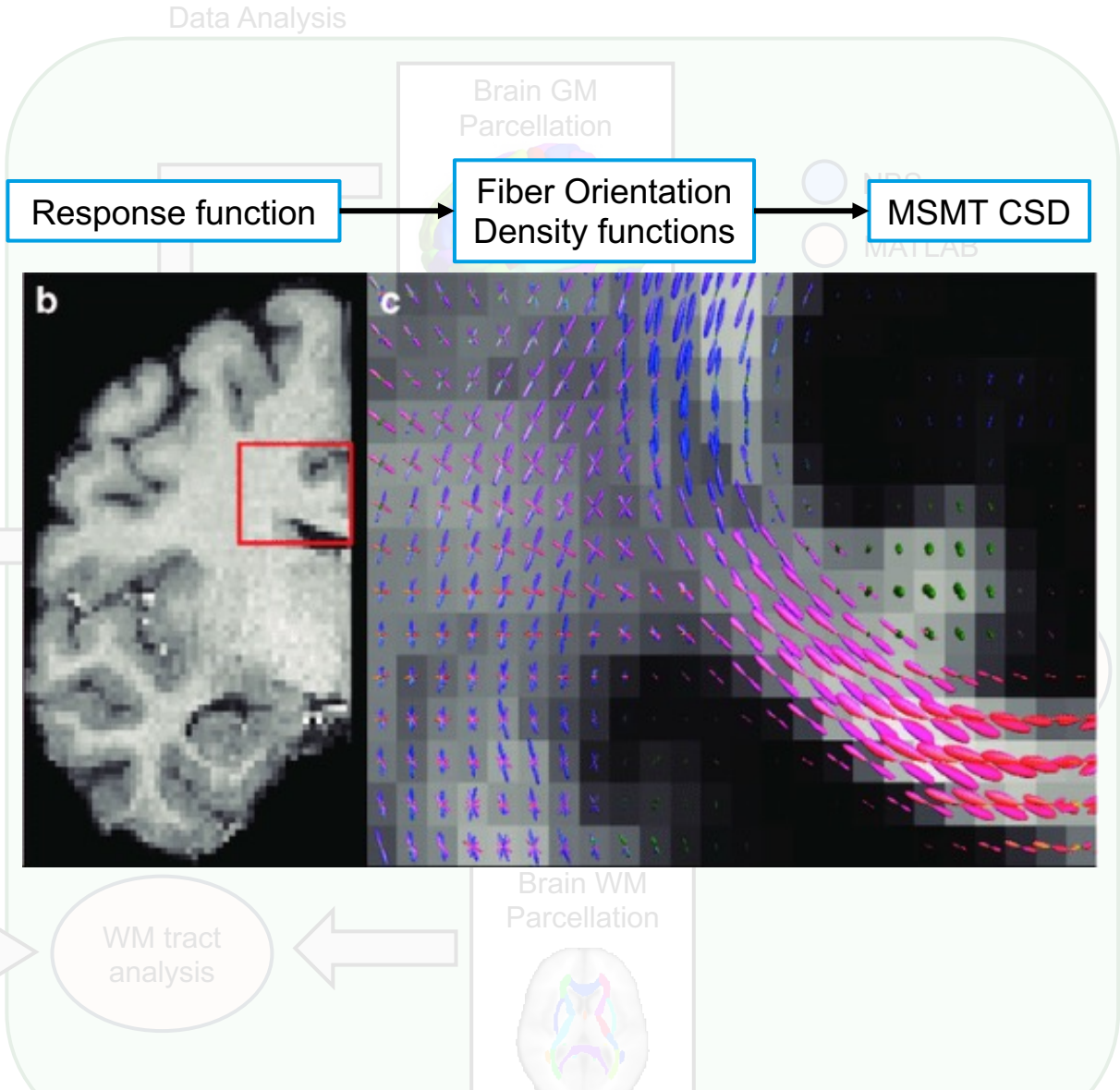
Methods



Ades-Aron B, Veraart J, Kochunov P et al (2018). NeuroImage. https://doi.org/10.1016/j. neuroimage.2018.07.066; Shi, Y & Toga, A. (2017). Molecular Psychiatry. 22. https://doi.org/10.1038/mp.2017.92

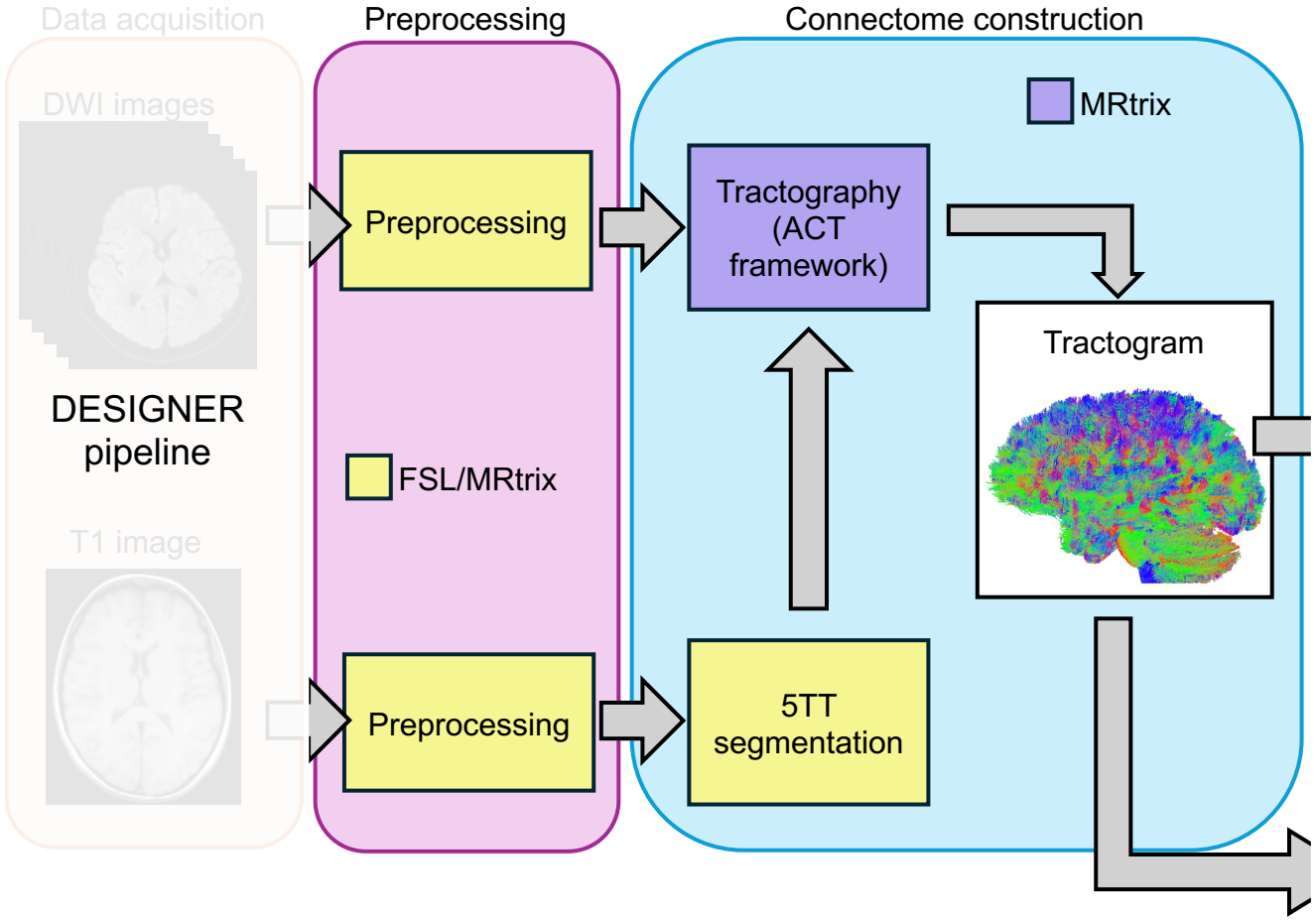
Methods

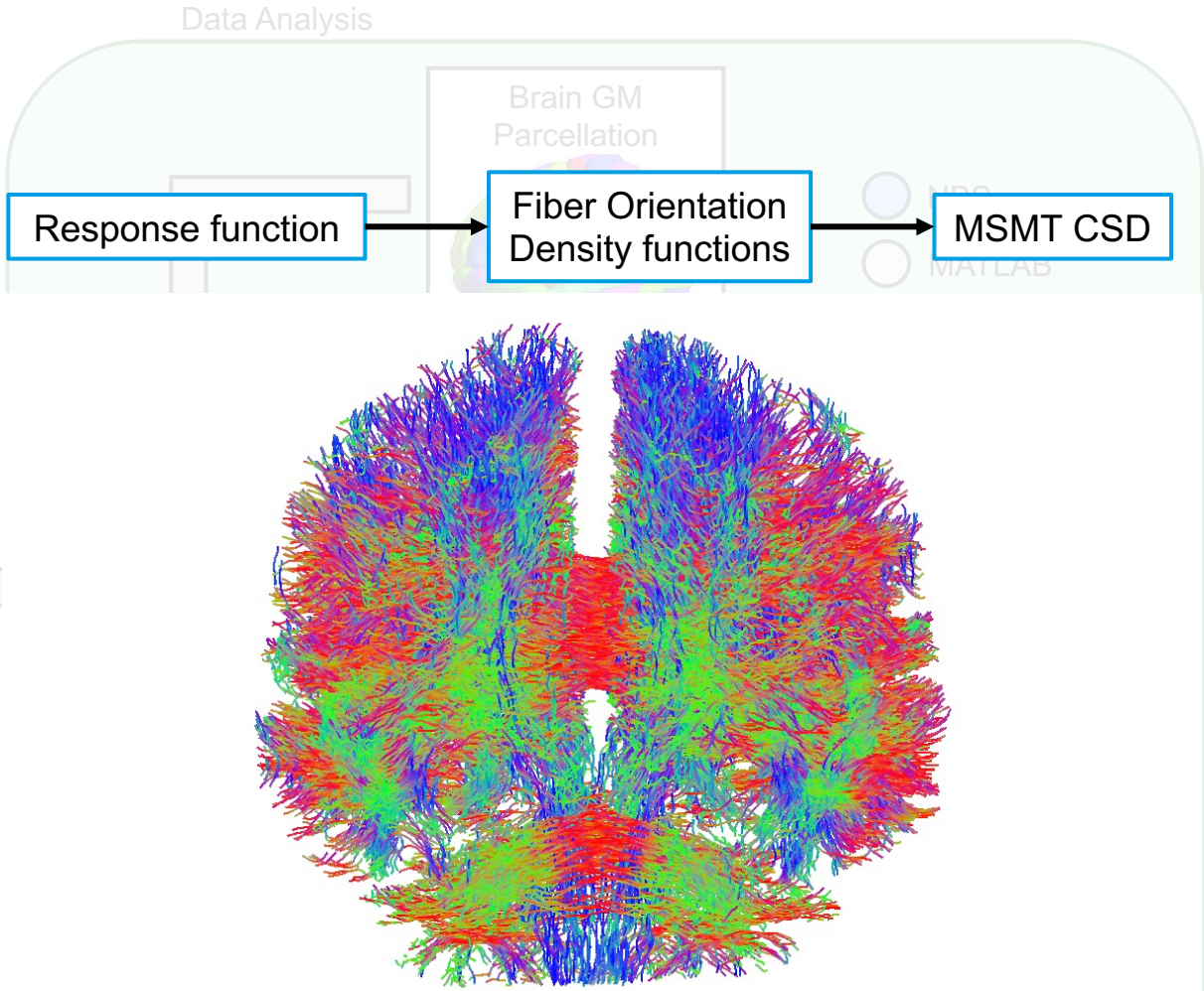




Ades-Aron B, Veraart J, Kochunov P et al (2018). NeuroImage. https://doi.org/10.1016/j. neuroimage.2018.07.066; Shi, Y & Toga, A. (2017). Molecular Psychiatry. 22. https://doi.org/10.1038/mp.2017.92

Methods





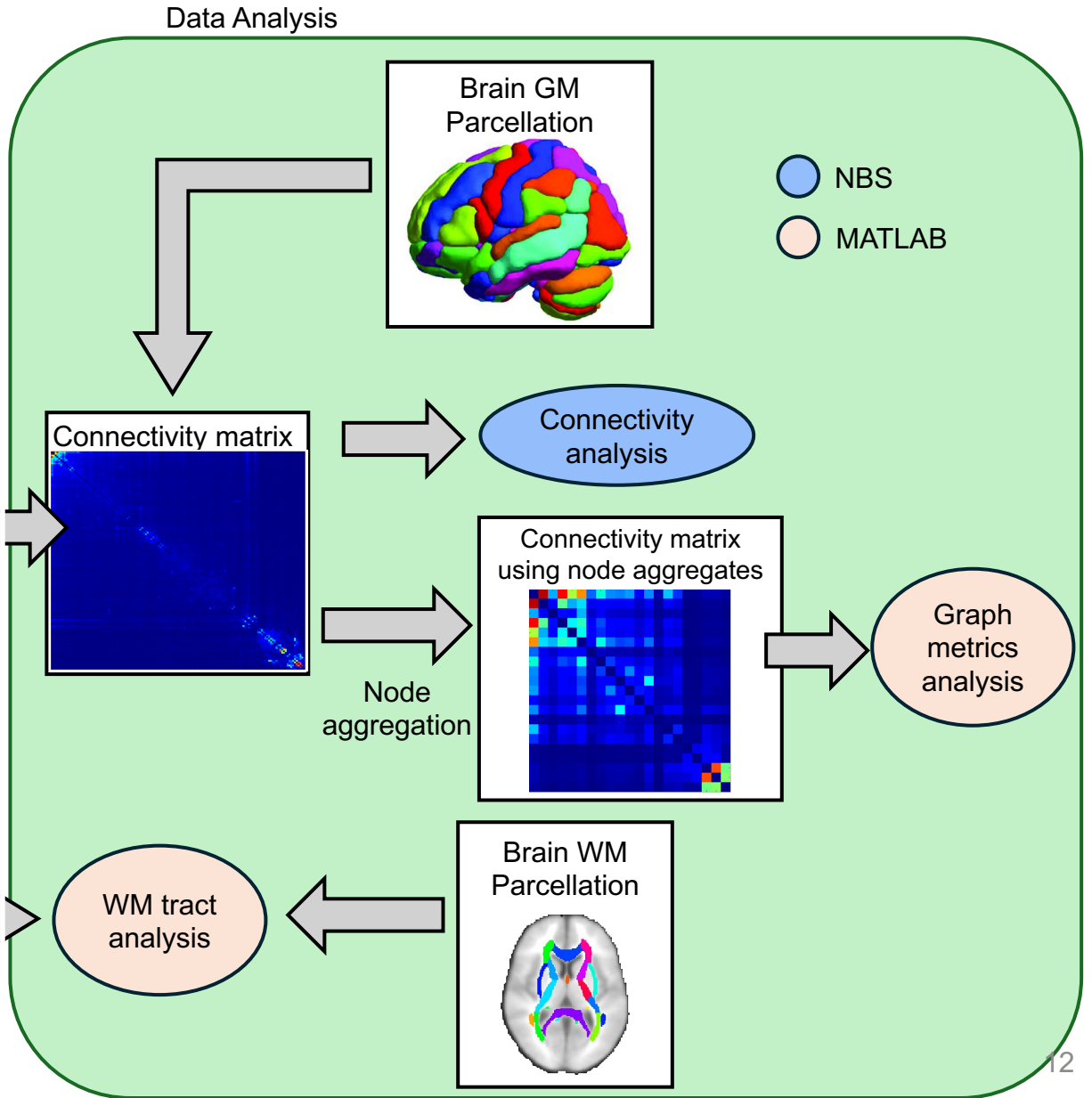
Ades-Aron B, Veraart J, Kochunov P et al (2018). NeuroImage. https://doi.org/10.1016/j. neuroimage.2018.07.066; Shi, Y & Toga, A. (2017). Molecular Psychiatry. 22. https://doi.org/10.1038/mp.2017.92

Methods

- GM Parcellations:
  - AAL116
  - Schaefer100 + SC + CB
- WM Parcellation: ICBM-DTI-81
- Number of streamlines normalized by volume of ROIs
- Self connections not considered

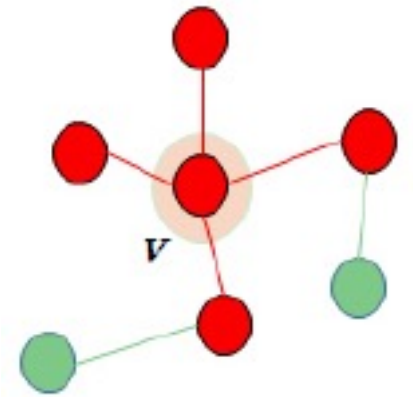
Analysis

- NBS: connectivity analysis between all nodes
- GLM: Graph metrics between node aggregates
- Correlation between graph metrics and clinical data
- GLM: White matter tract differences

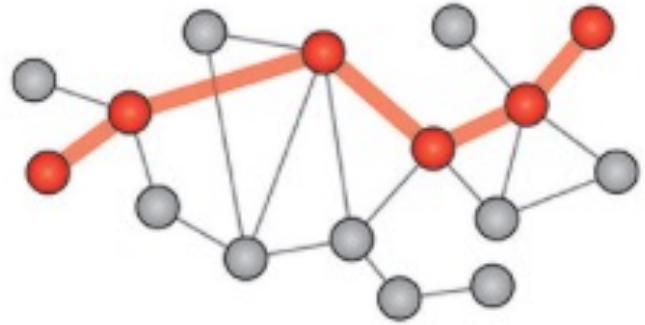


GM=Gray Matter; WM=White Matter; SC=Subcortical; CB=Cerebellum; NBS= Network Based Statistics; GLM=Generalized Linear Model

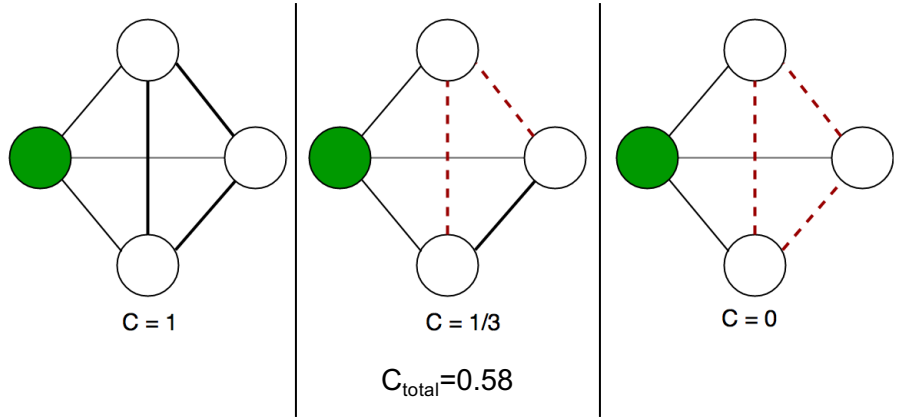
Methods – Graph metrics



Node Degree

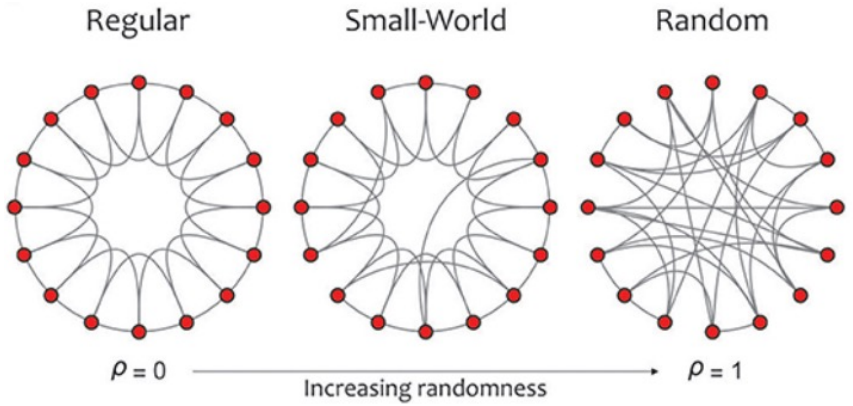


Characteristic Path Length



Clustering Coefficient

Global Efficiency



Small-worldness

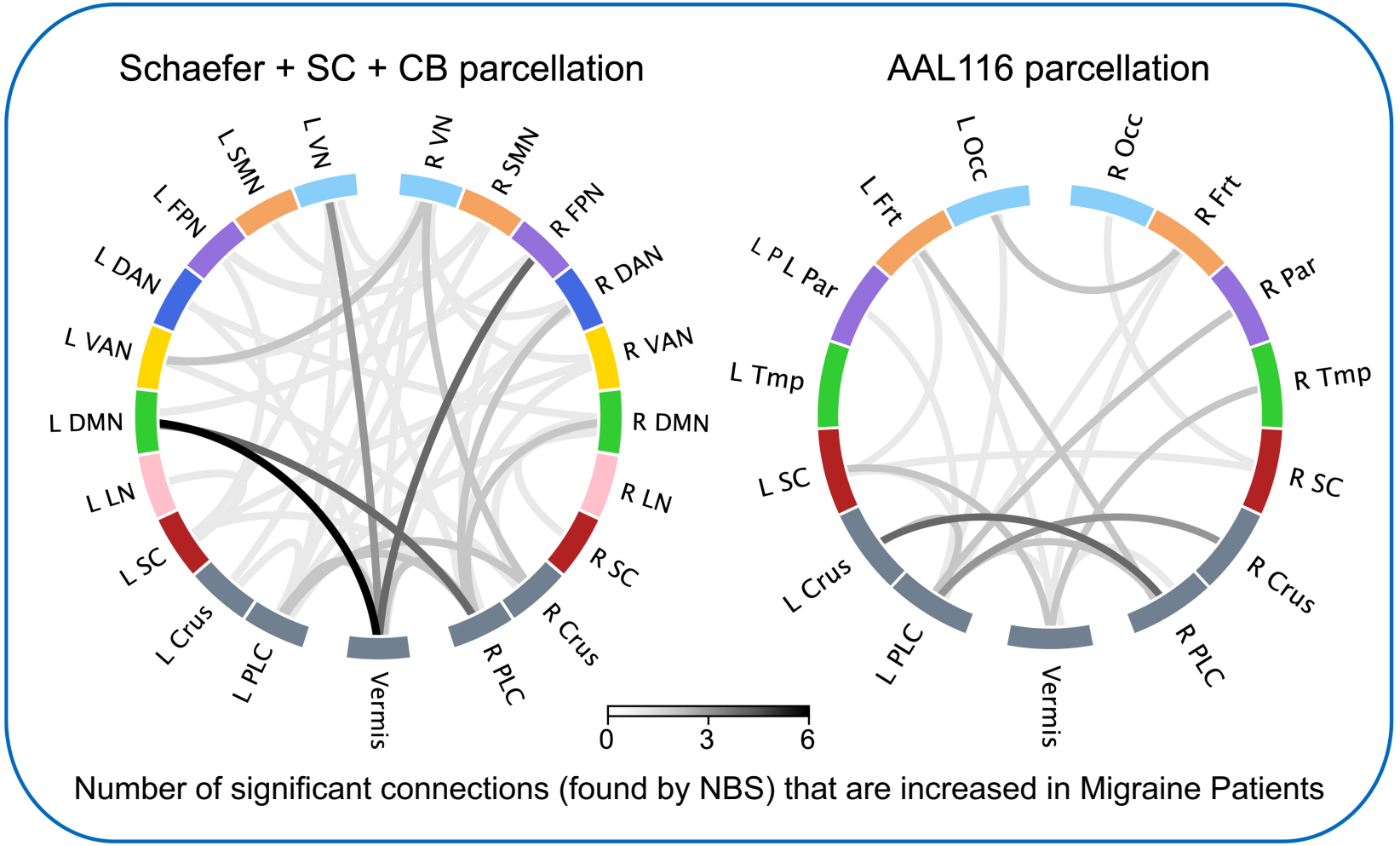
Results - Connectivity

Increased connectivity in patients:

- R Crus – L PLC
- Vermis – Frontal, Parietal
- Cerebellum – Occipital

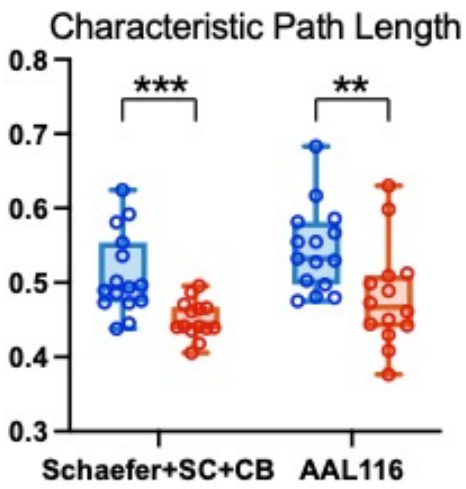
Schaefer Network: p=0.03

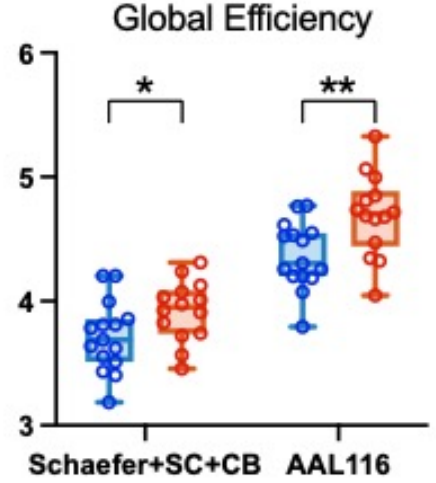
AAL116 Network: p=0.04

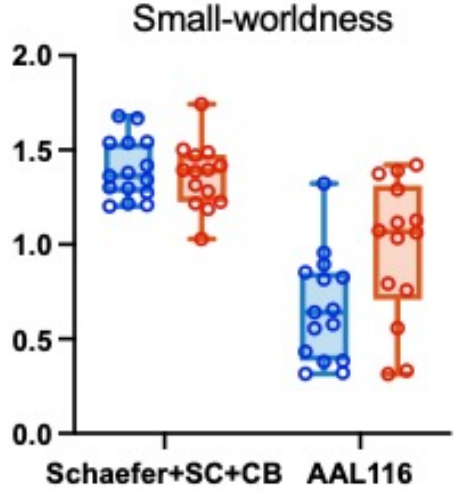


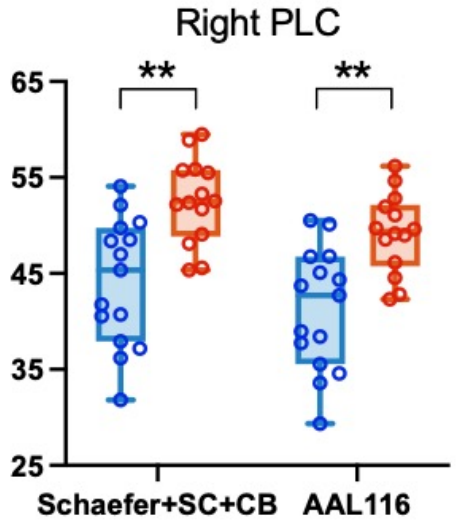
VN=Visual Network, SMN=Somatossensory Network, FPN=Frontal-Parietal Network, DAN=Dorsal Attention Network, VAN= Ventral Attention Network, DMN=Default Mode Network, LN=Limbic Network, SC=Subcortical, PLC=Posterior Lobe of the Cerebellum, Occ = Occipital Lobe, Frt=Frontal Lobe, Par=Parietal Lobe, Tmp=Temporal Lobe

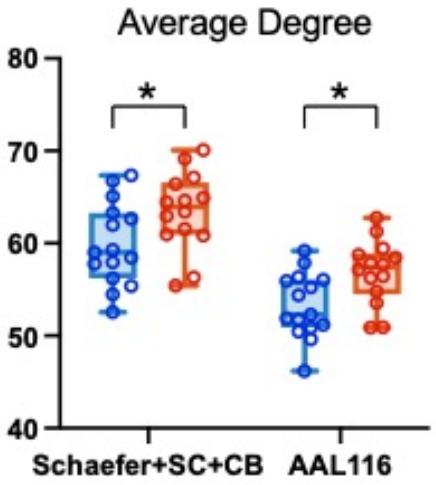
Results – Graph Metrics

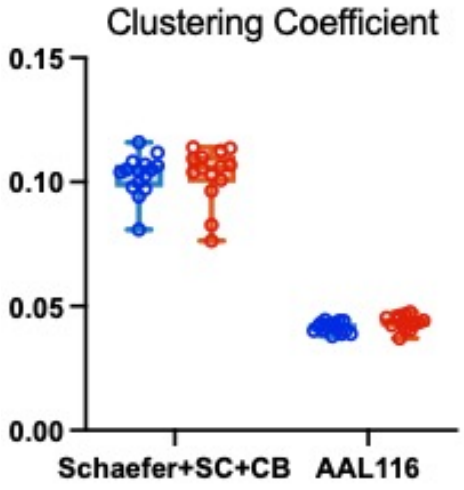


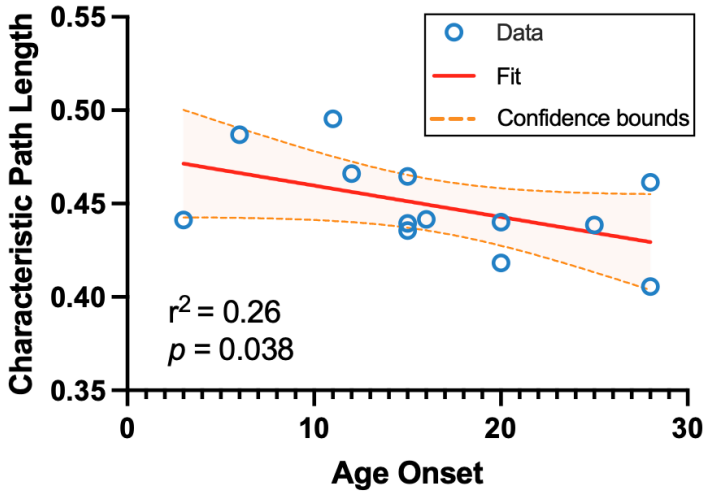


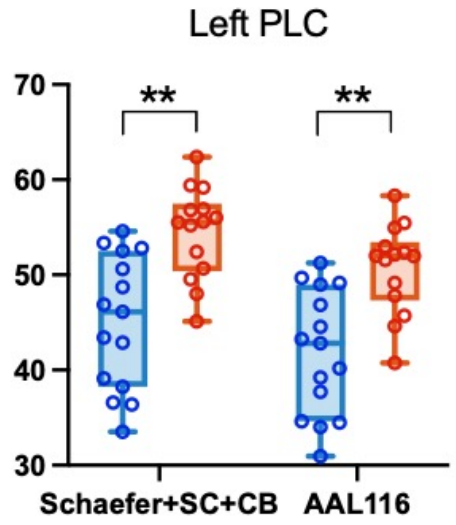




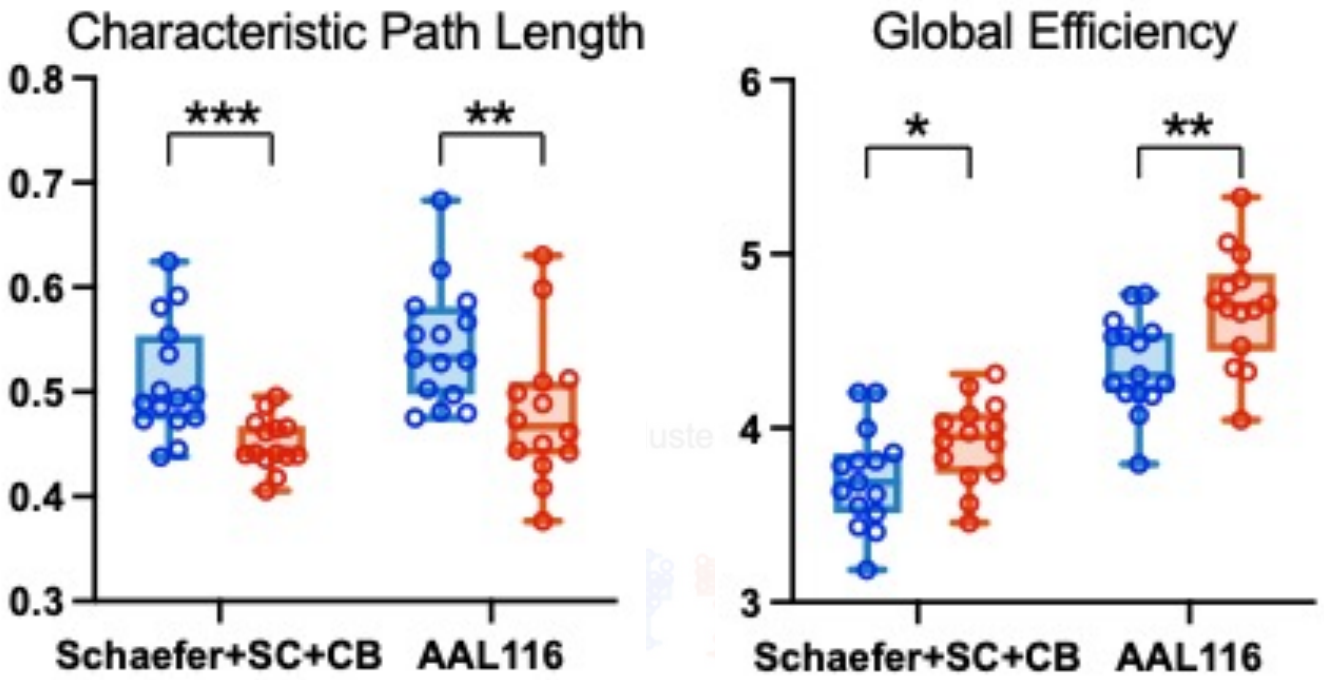








Results – Graph Metrics



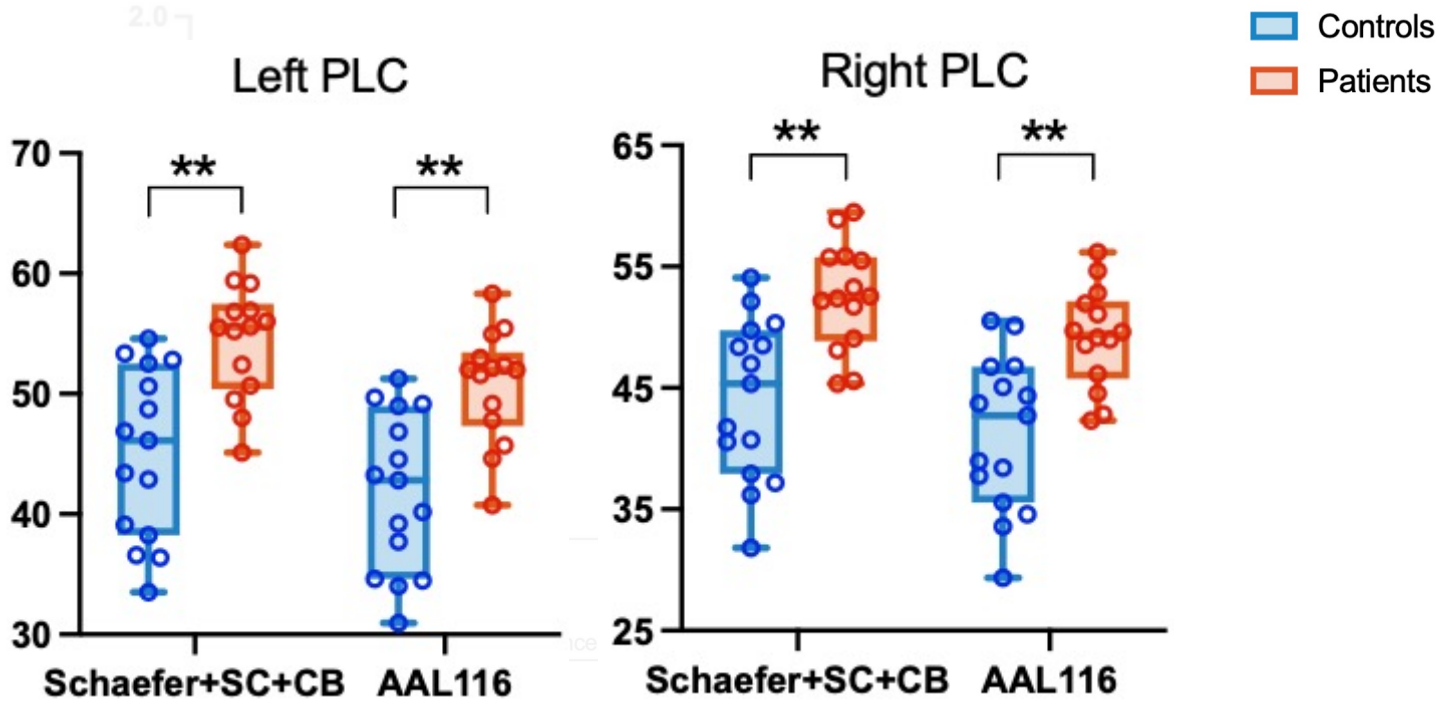
Controls
Patients

In Migraine Patients:

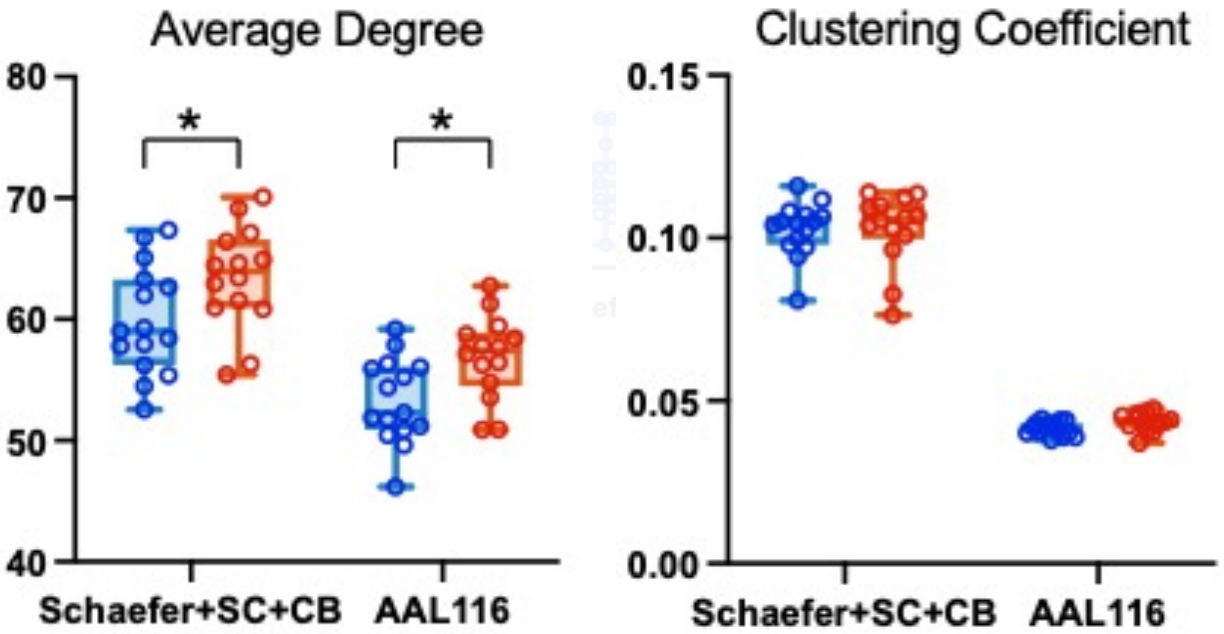
- Increased Global Efficiency
- Decreased Characteristic Path Length

Results – Graph Metrics

- Node degree of bilateral **Posterior Lobe of the Cerebellum** was increased in patients in both parcelations



Results – Graph Metrics

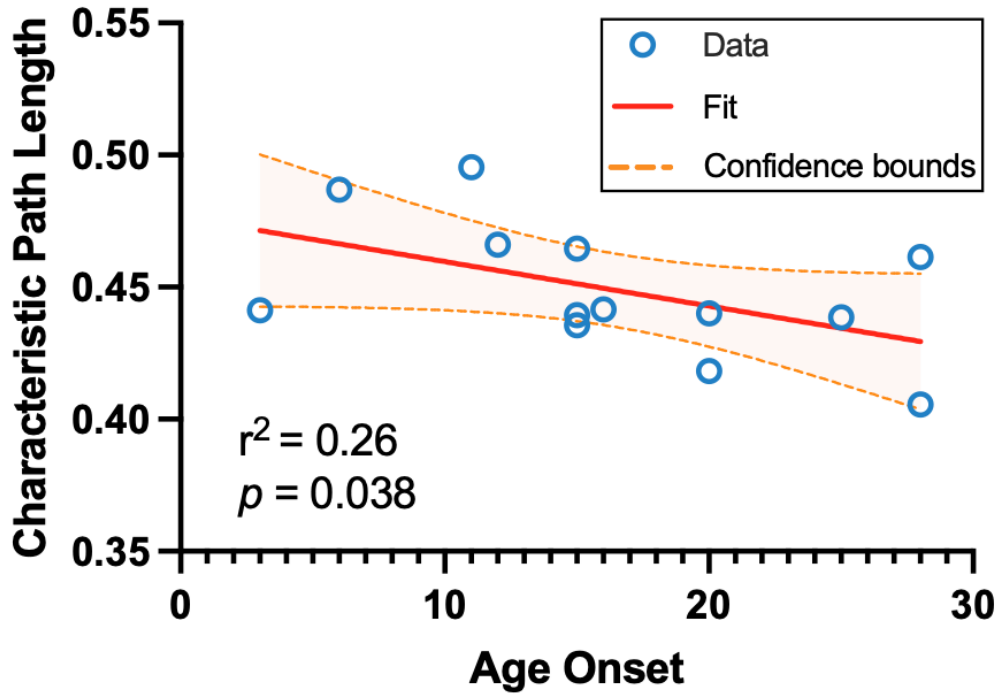


Controls
Patients

Average Degree:

- Slightly increased in patients in both parcellations

Results – Graph Metrics

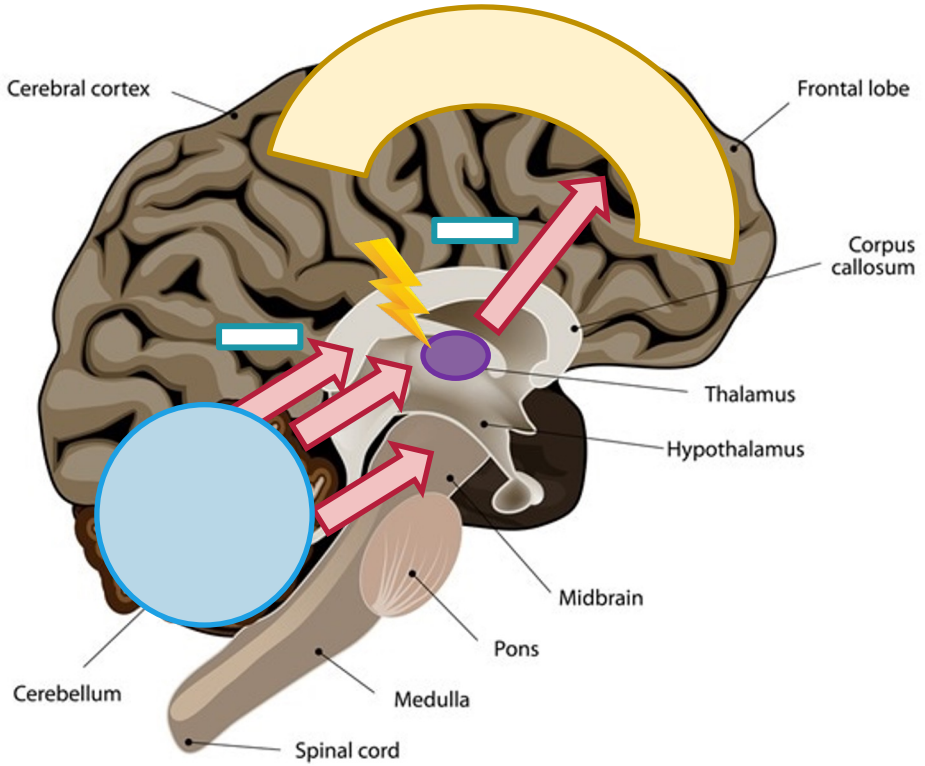


Negative correlation:

- Characteristic Path Length and Age Onset

Discussion

- Structural connectivity disruptions in the cerebellum
  - ↳ Consistent between parcellations
- Cerebellum has inhibitory role in pain processing through thalamus[1,2]
  - ↳ Dysfunctional negative feedback loop[1]
- The crus involved in cognitive and emotional functions[3,4]
  - ↳ Cognitive deficits common in migraine[5,6]



[1] Younis S, et al (2019) Cephalalgia; [2] Middleton FA, et al (2001) J Neurosci [3] Moulton EA et al (2011). J Neurosci;
[4] Stoodley CJ, et al (2010). Cortex. [5] Gil-Gouveia R, et al (2019) Curr Pain Headache; [6] Gu L, et al (2022) J Headache Pain

Discussion

↗ Global Efficiency

↘ Characteristic Path Length

} Increased pain information dissemination[1,2]

↘ Characteristic Path Length

↕

↗ Age Onset

} Plastic Adaptation[3,4]

[1] Silvestro M, et al (2021). J Headache Pain; [2] Dai L, et al (2021. Neuroradiology; [3] Planchuelo-Gómez Á, et al (2020). Cephalalgia; [4] Szabó N, et al (2018). Front Neuroanat

Discussion

Innovative Aspects

- Homogenous Cohort
- Includes Cerebellum and Subcortical Regions
- Tractography using multishell data

Limitations

- Small Sample size
- Interpretation of graph theory metrics
- Validation of tractography model

Conclusion

⇨ **Take-home message 1**: The structural connectome of migraine patients shows to be altered, having an **increased integration** that may be the cause of **heightened pain information dissemination**

⇨ **Take-home message 2**: The **cerebellum** proves to **play an important role** in migraine pathophysiology and should therefore be included in connectome studies

Acknowledgments






Paper

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10.54499/UIDB/50009/2020