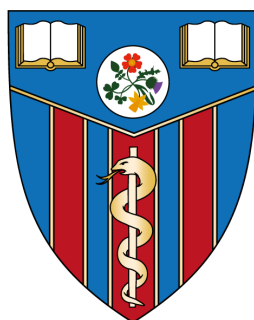


Regional progression of grey matter atrophy in multiple sclerosis

Arman Eshaghi*, Razvan V. Marinescu, Alexandra Young², Nicholas Firth, Ferran Prados, M Jorge Cardoso, Carmen Tur, Floriana De Angelis, Niamh Cawley, Wallace Brownlee, Nicola De Stefano, M. Laura Stromillo, Marco Battaglini, Serena Ruggieri, Claudio Gasperini, Massimo Filippi, Maria A. Rocca, Alex Rovira, Jaume Sastre-Garriga, Jeroen Geurts, Hugo Vrenken, Viktor Wottschel, Cyra E Leurs, Bernard Uitdehaag, Lukas Pirpamer, Christian Enzinger, Sebastien Ourselin, Claudia A.G. Wheeler-Kingshott, Declan Chard, Alan J. Thompson, Frederik Barkhof, Daniel C. Alexander, Olga Ciccarelli,
on behalf of the MAGNIMS study group



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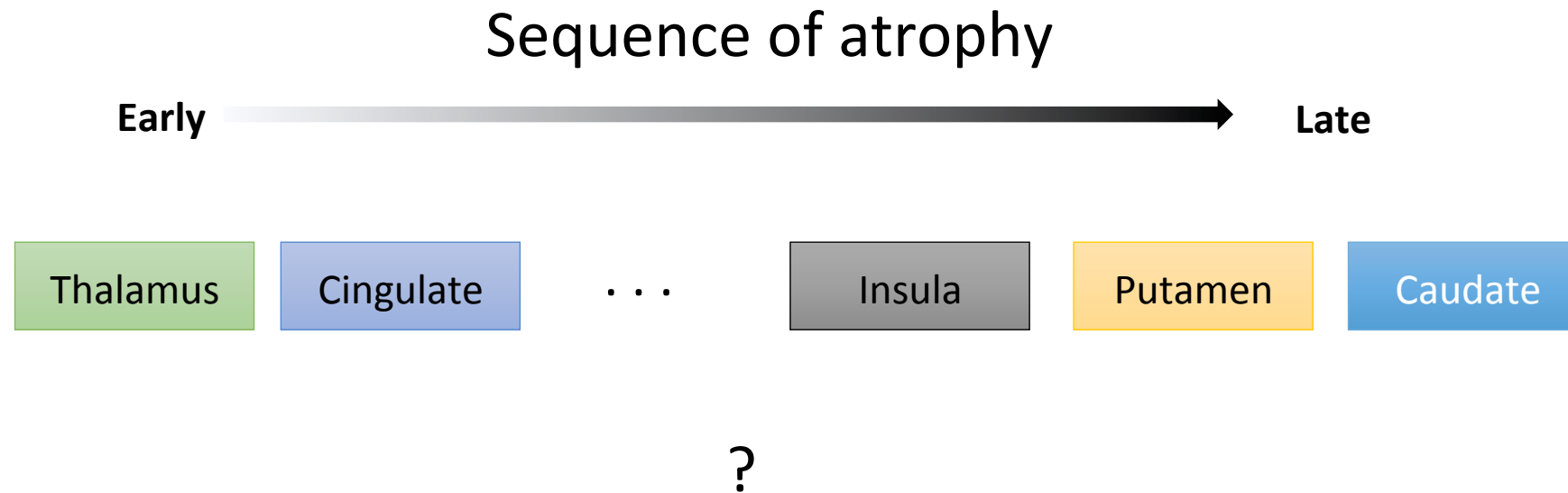


Introduction

- Whole brain atrophy is mainly driven by grey matter (Fisher et al, 2008)
- Some brain regions are preferentially affected (Preziosa et al 2017)
- The temporal order at which atrophy progresses to affect more regions remains unclear

Aim 1:

To establish the **order** or **sequence** at which atrophy occurs in brain regions



Aim 2:

To **stage** individual patients according to the number of atrophic regions

Participants

- **1,417** subjects
- **3,604** T1-weighted scans
- **203** healthy controls
- **1,214** people with MS

Eligibility criteria

- At least two MRI scans acquired on a single scanner with a minimum interval of 6-months
- High resolution T1-weighted

Length of Follow-up

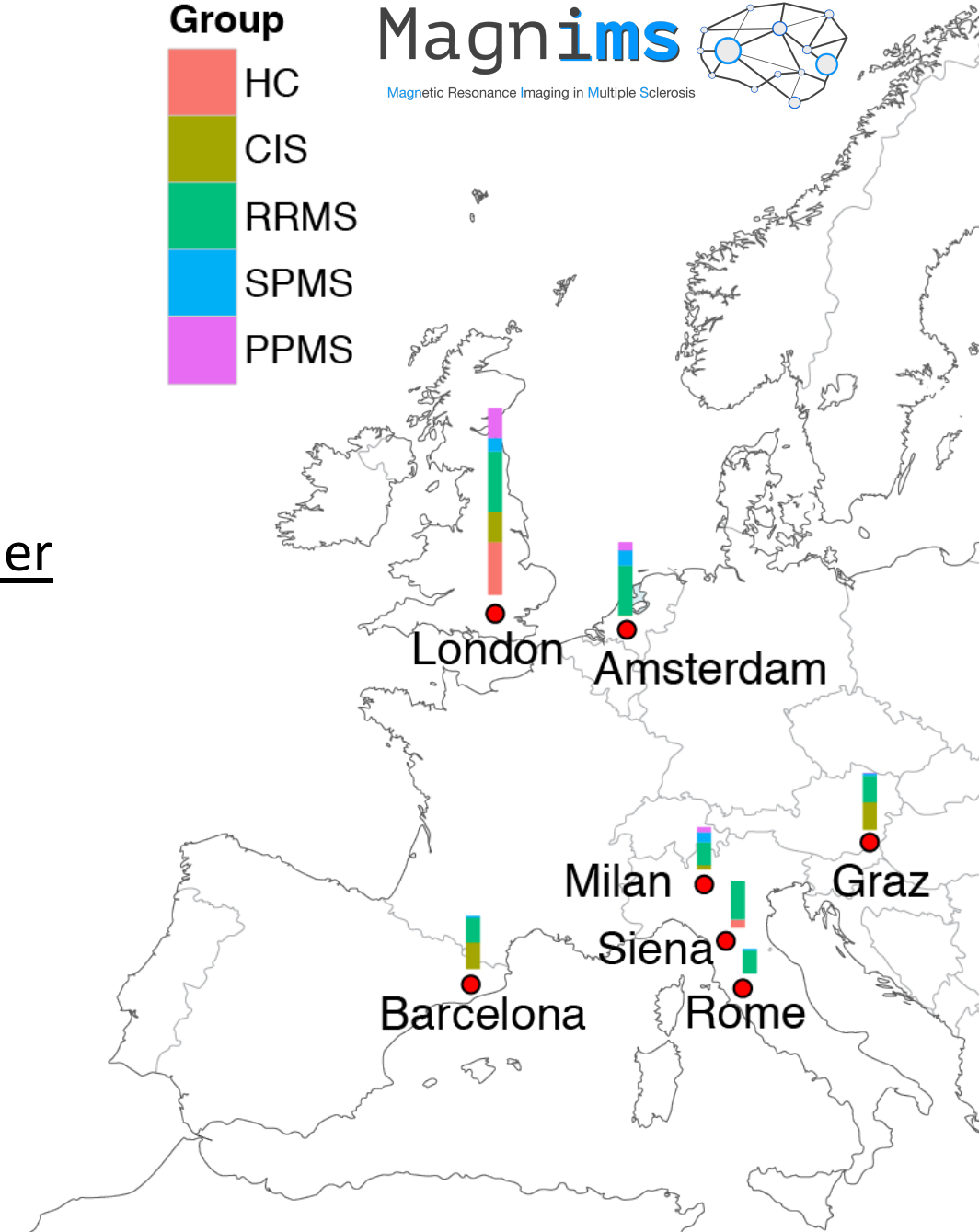
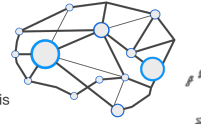
- Patients: 2.4 years \pm 1.9
- HCs: 1.8 year \pm 1.77

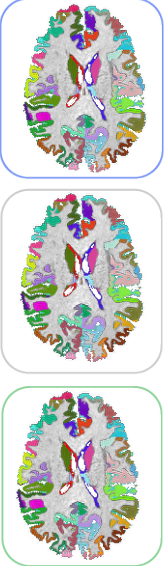
Group



Magnims

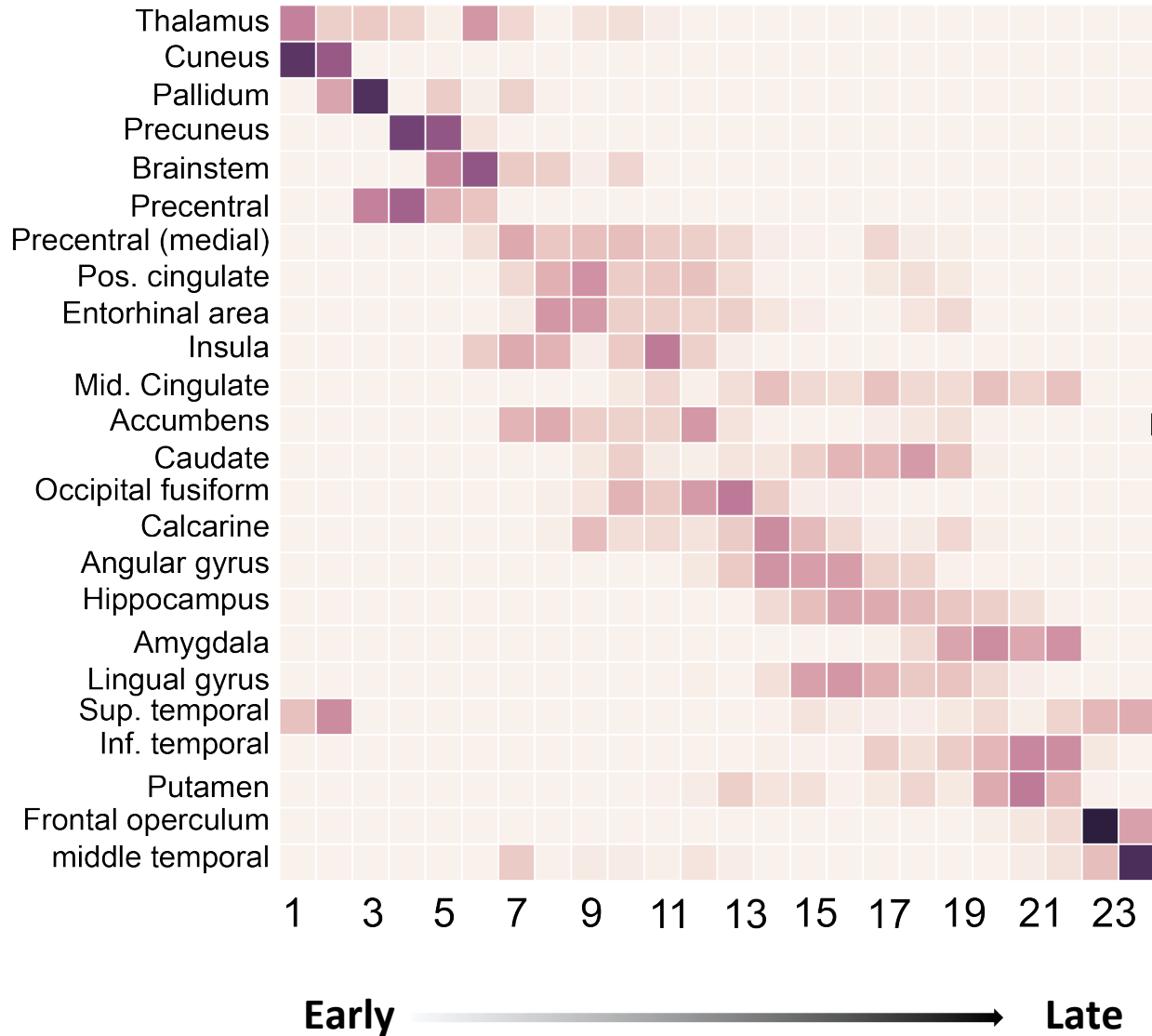
Magnetic Resonance Imaging in Multiple Sclerosis



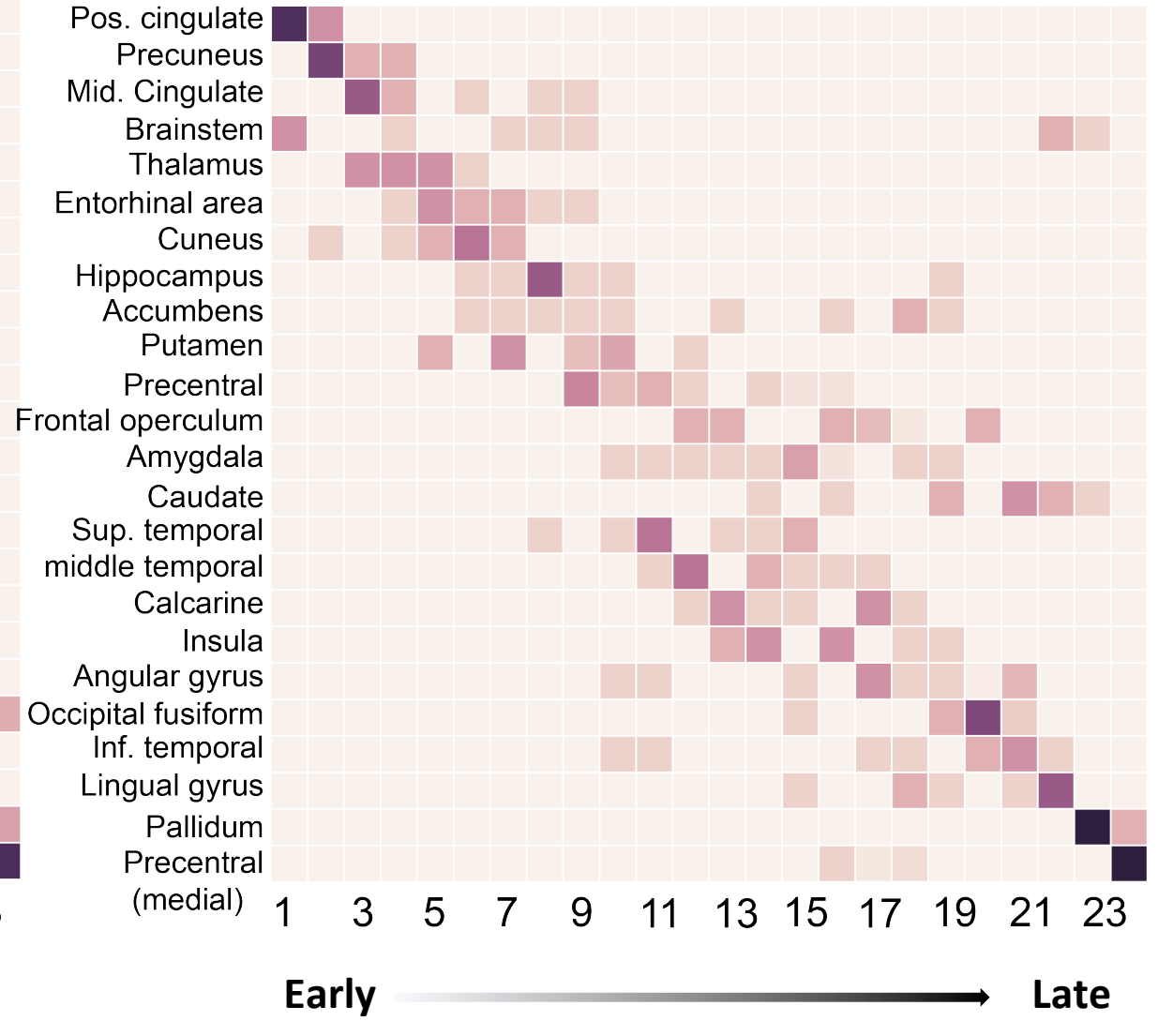
Raw data	1- N4 bias-field correction	2- Creating symmetric within-subject template	3- Symmetric transformation of time-points to the template	4- Longitudinal lesion segmentation (BaMoS)	5- Manual editing of white-matter lesion masks
<p>Baseline T1</p> <p>Baseline T2</p> <p>Baseline PD</p> <p>Year-1 T1</p> <p>Year-1 T2</p> <p>Year-1 PD</p> <p>Year-2 T1</p> <p>Year-2 T2</p> <p>Year-2 PD</p>	<p>Baseline T1</p> <p>Year-1 T1</p> <p>Year-2 T1</p>	<p>T1 Template</p>	<p>Baseline T1</p> <p>Baseline T2</p> <p>Baseline PD</p> <p>Year-1 T1</p> <p>Year-1 T2</p> <p>Year-1 PD</p> <p>Year-2 T1</p> <p>Year-2 T2</p> <p>Year-2 PD</p>	<p>Baseline T1</p> <p>Baseline T2</p> <p>Baseline PD</p> <p>Year-1 T1</p> <p>Year-1 T2</p> <p>Year-1 PD</p> <p>Year-2 T1</p> <p>Year-2 T2</p> <p>Year-2 PD</p>	<p>Baseline lesion mask</p> <p>Year-1 lesion mask</p> <p>Year-2 lesion mask</p>
6- Normal-appearing white matter segmentation	7- Multi-time point lesion filling	8- Segmentation and parcellation	9- SIENA with GIF segmentations in the symmetric-space	10- Mixed-effects modelling of regional and whole-brain measures	
<p>T1</p> <p>White-matter mask</p> <p>Lesion mask</p> <p>T1</p> <p>White-matter mask</p> <p>Lesion mask</p> <p>T1</p> <p>White-matter mask</p> <p>Lesion mask</p>	<p>lesion-filled T1</p> <p>lesion-filled T1</p> <p>lesion-filled T1</p>		<p>T1 ↔^{PBVC} T1</p> <p>T1 ↔^{PBVC} T1</p> <p>T1 ↔^{PBVC} T1</p>	<p>Whole brain</p> <p>Outcome variable: SIENA PBVC</p> <p>Time variable: Interval between scans</p> <hr/> <p>Regional</p> <p>Outcome variable: volume</p> <p>Time variable: Interval from study entry</p>	

Group	Healthy controls	CIS	RRMS	SPMS	PPMS
Total number (women)	203 (112)	253 (171)	708 (473)	128 (75)	125 (55)
Average age (\pm SD)	38.7 \pm 10.5	33 \pm 8	38.2 \pm 9.8	48.2 \pm 9.8	48.5 \pm 10.1
Average disease duration (\pm SD)	—	0.4 \pm 1.4	6.7 \pm 7.3	15.6 \pm 9.9	6.8 \pm 5.9
Median EDSS (range)	—	1 (0-4.5)	2 (0-7)	6 (2.5-9)	5 (2-8)
% (number) of patients on DMTs	—	20% (52)	49% (345)	41% (52)	6% (8)

PPMS



Relapse onset MS



Primary-progressive MS

Probability of atrophy

Relapse-onset MS



Stage number

Early

Late

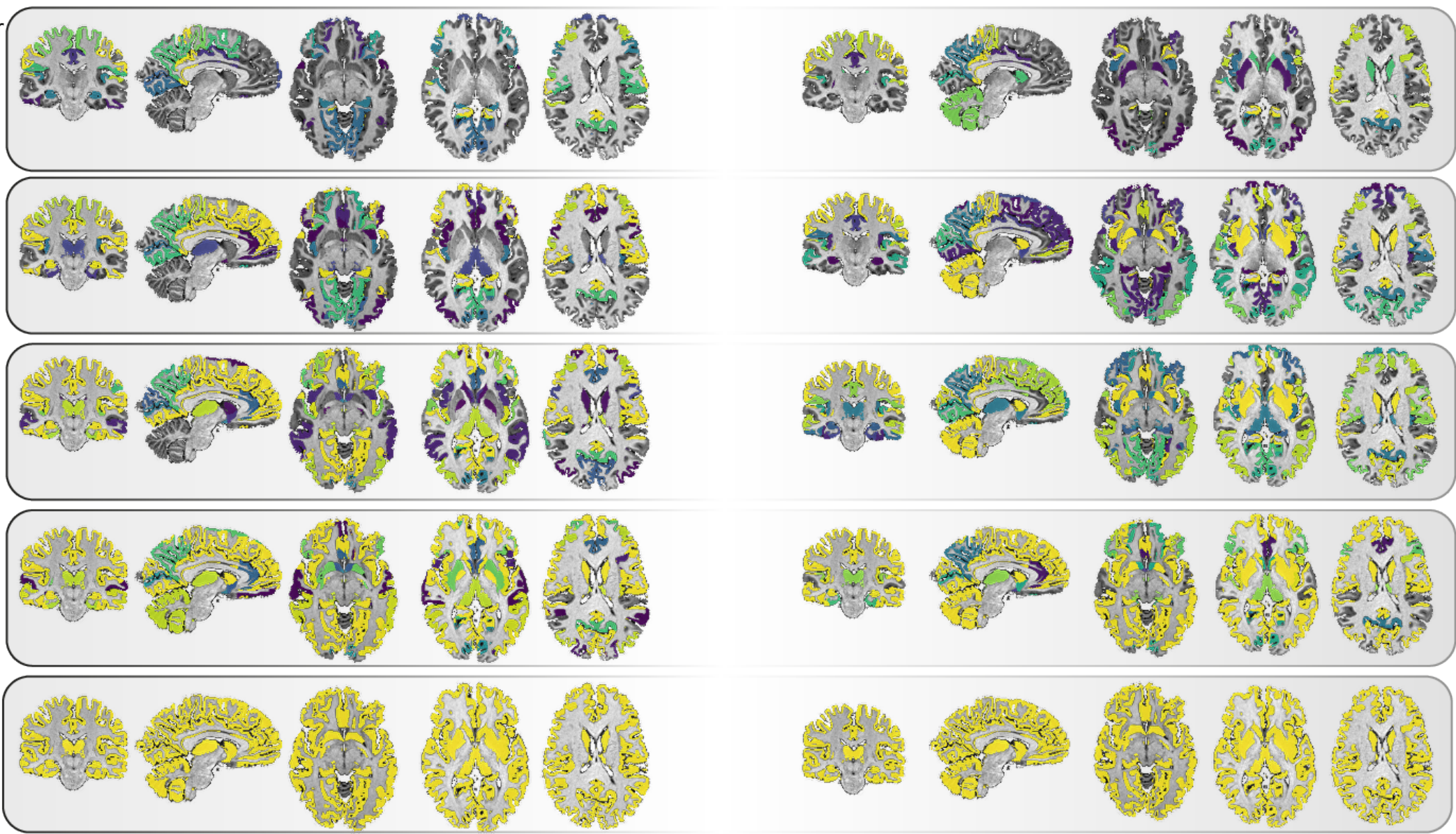
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24

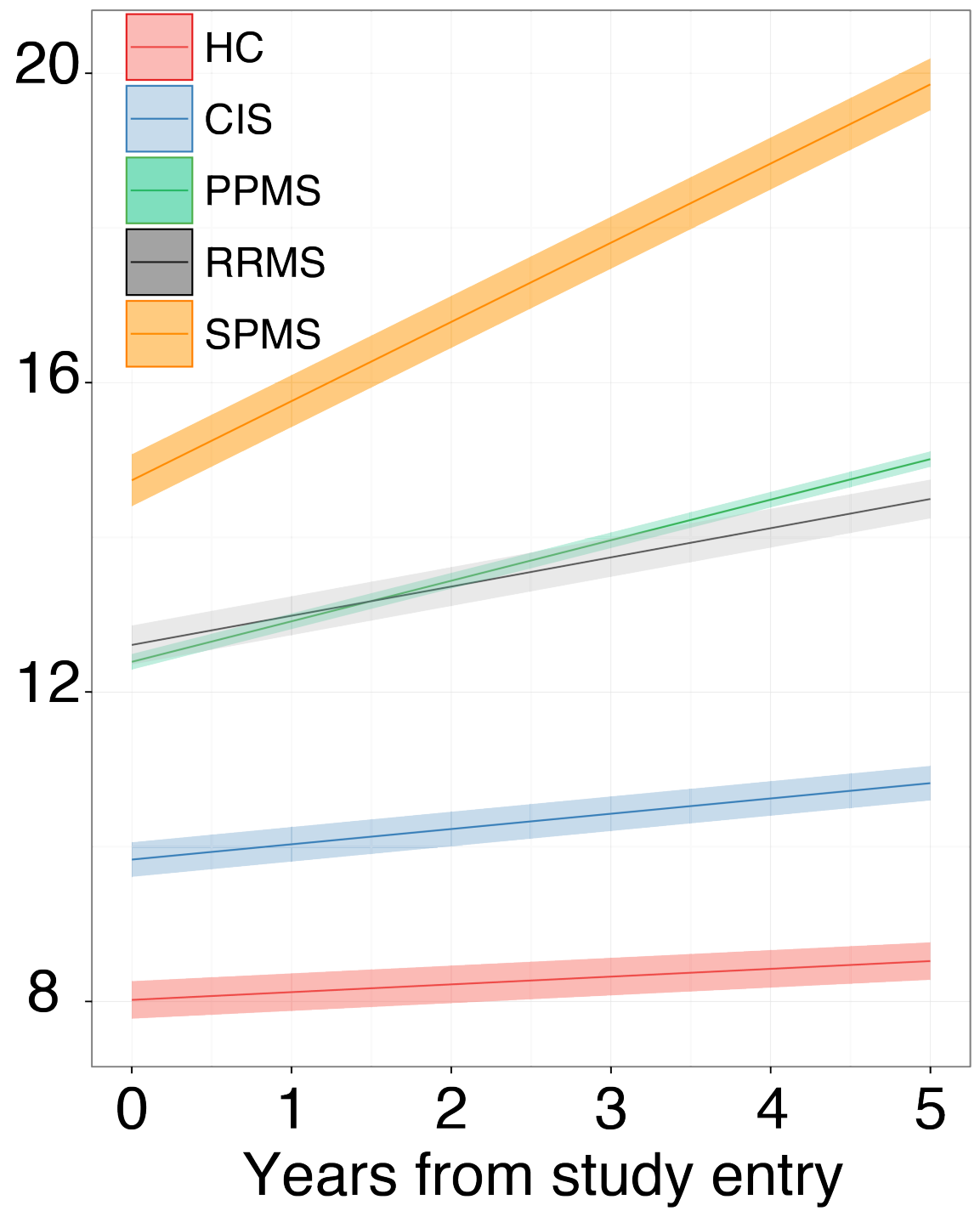
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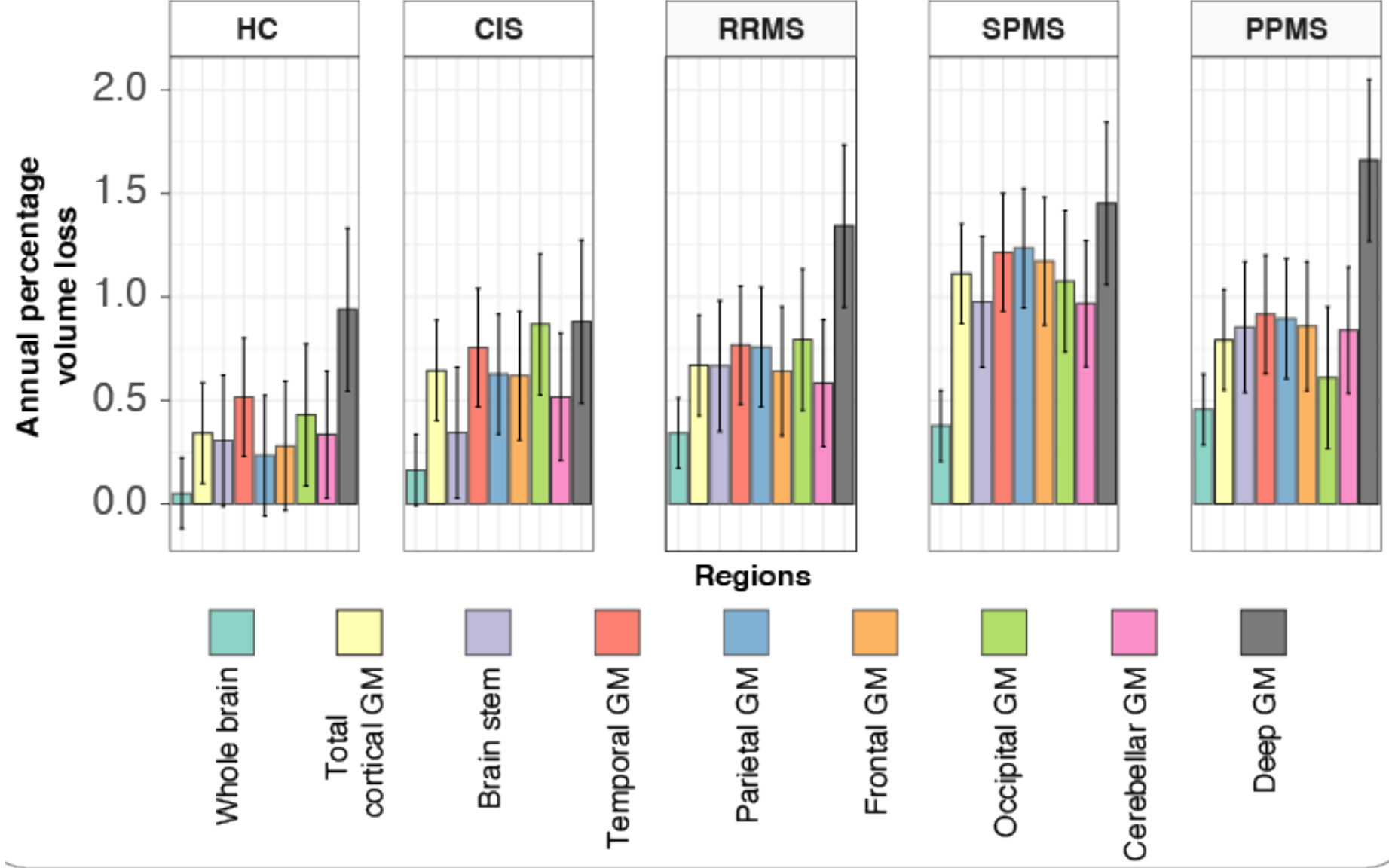
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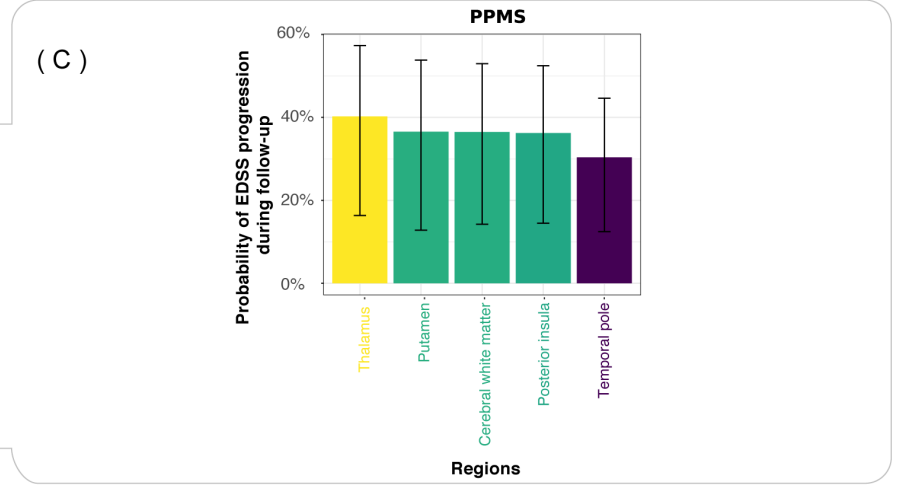
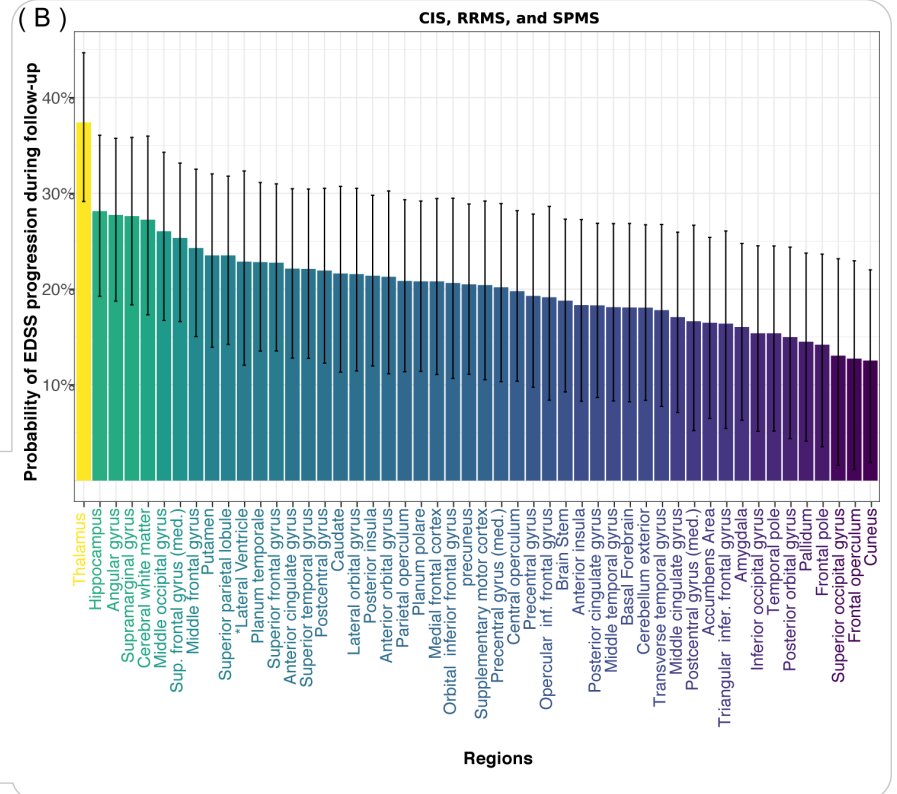
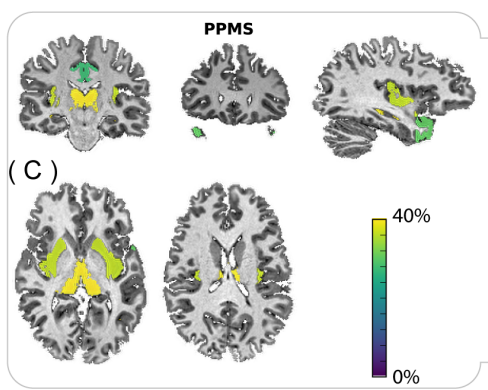
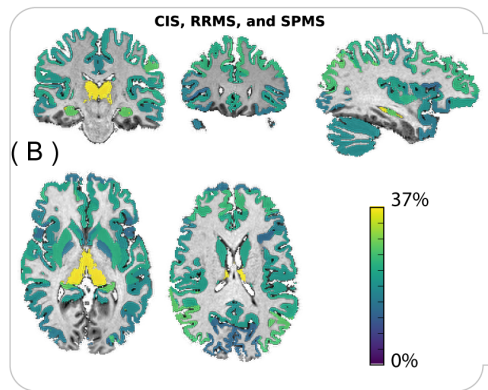
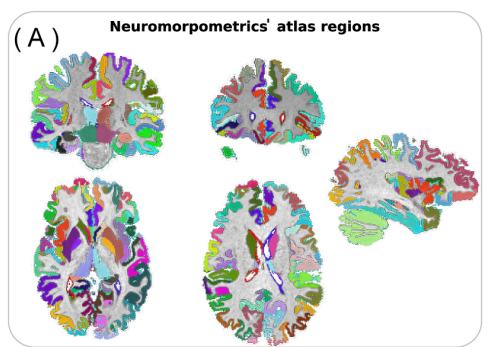
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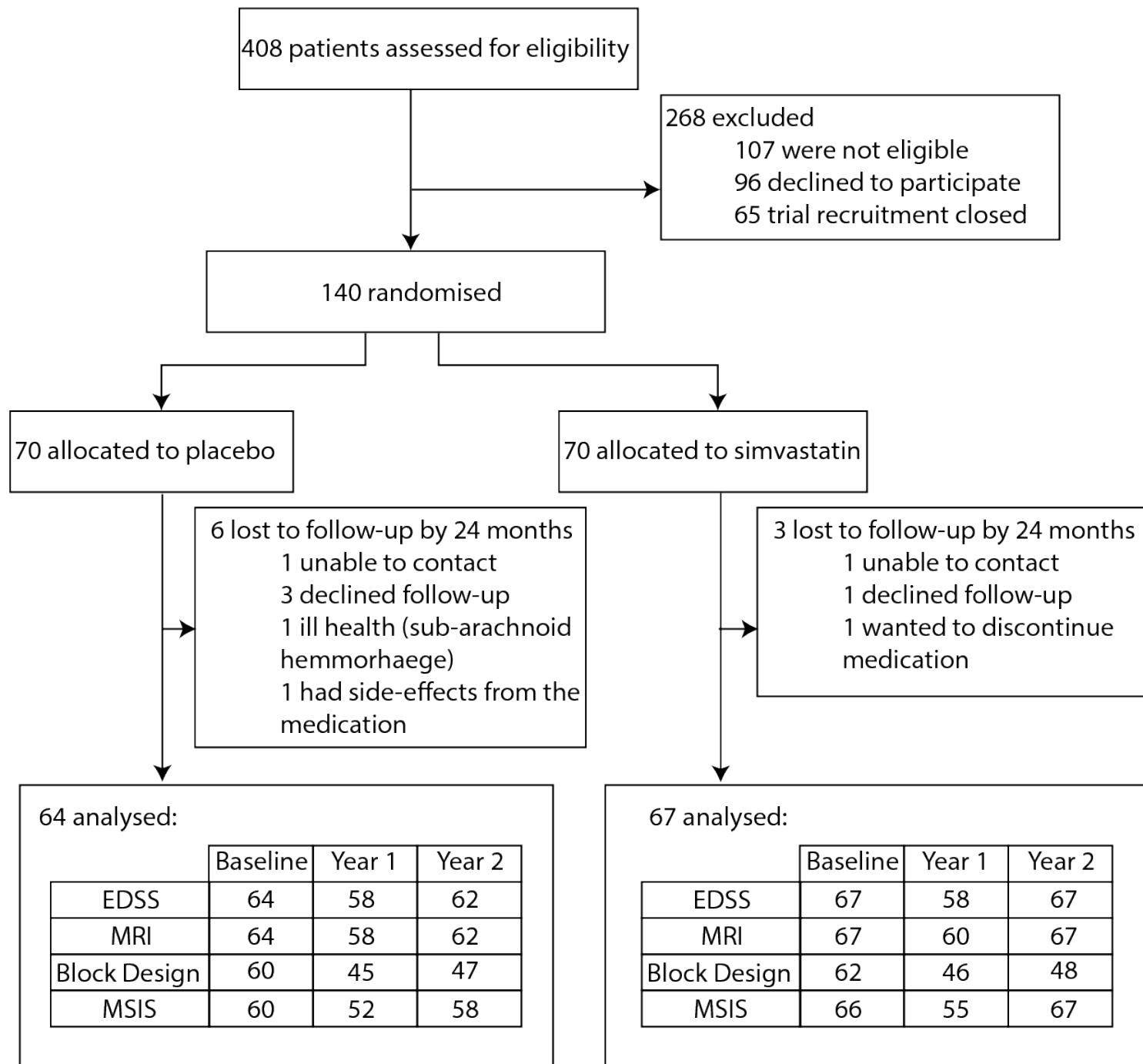
EBM Stage
(number of atrophic regions)

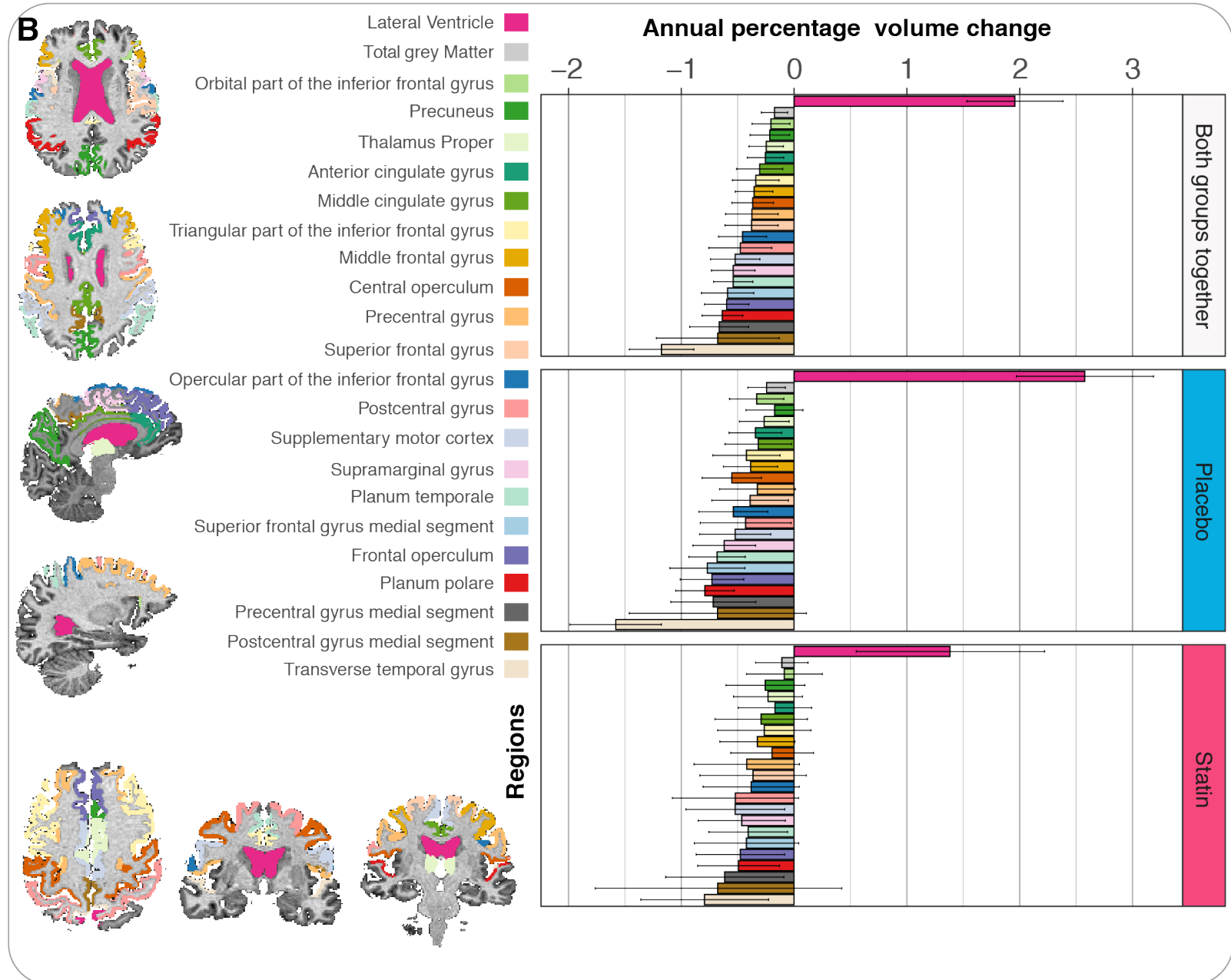
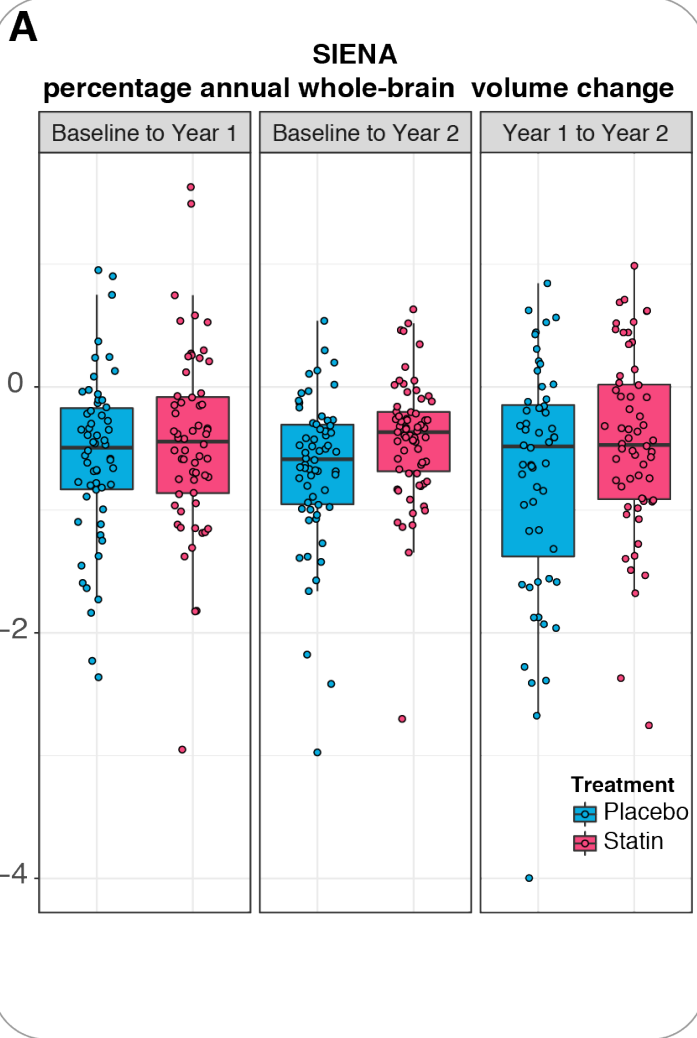


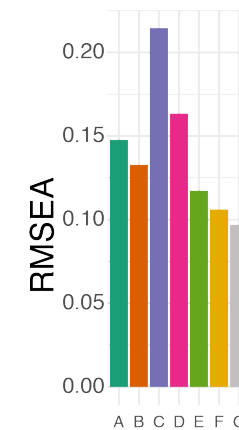
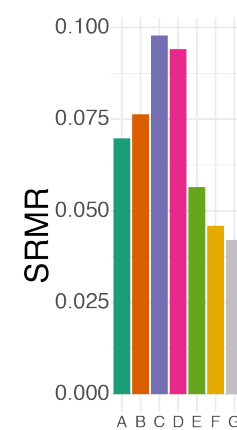
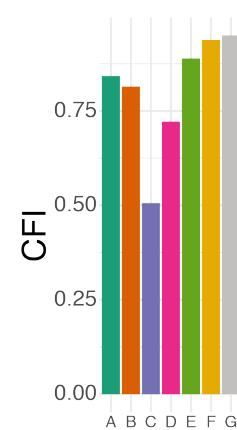
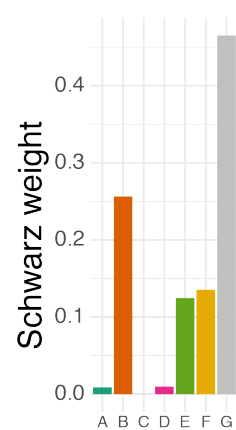
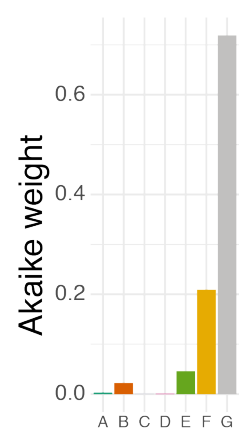
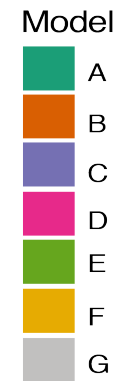
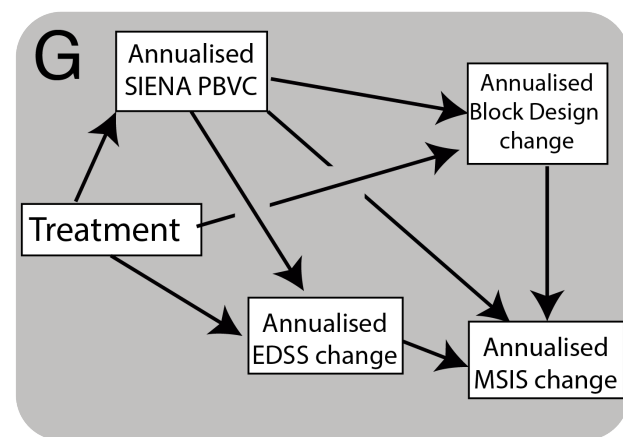
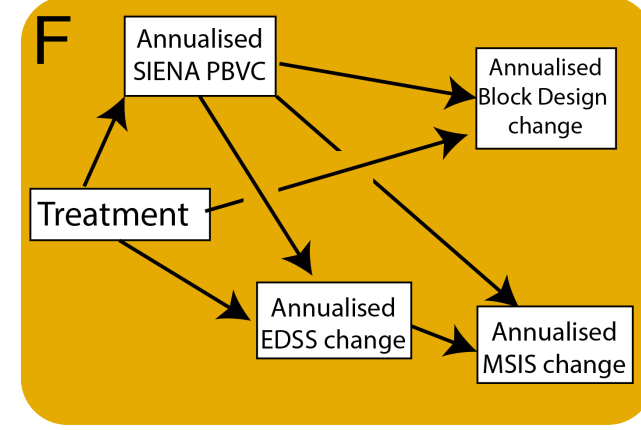
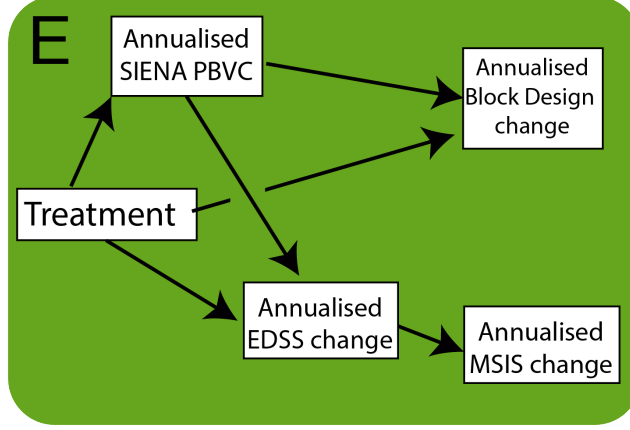
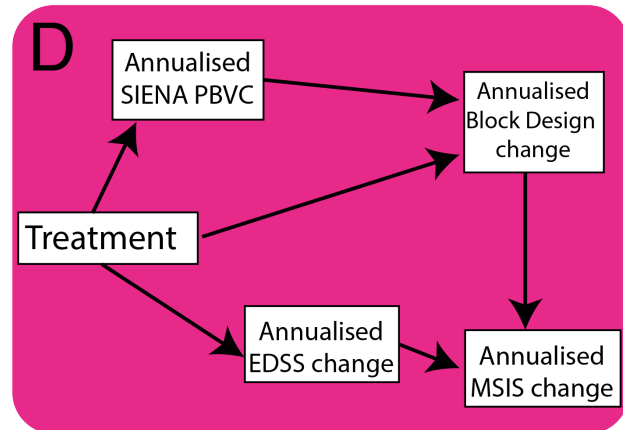
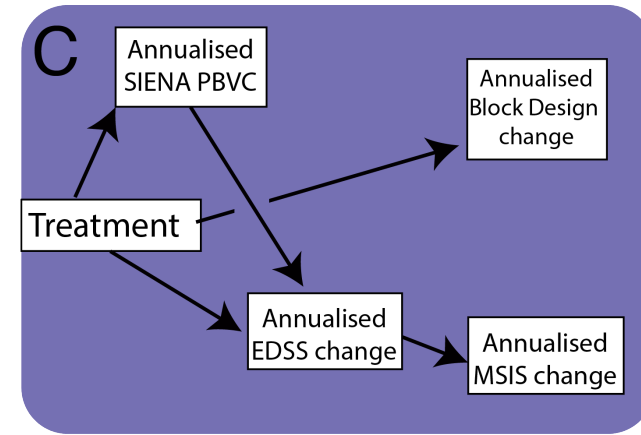
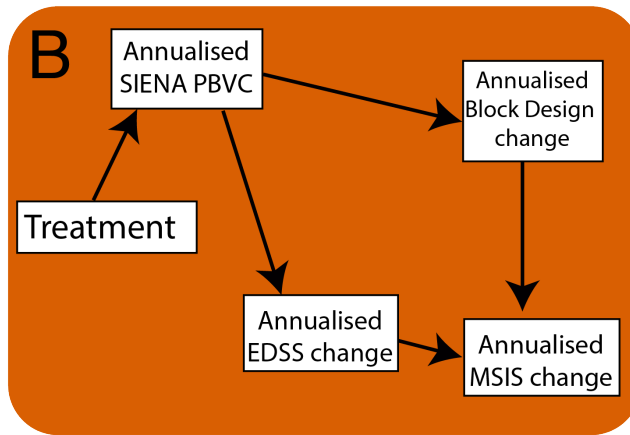
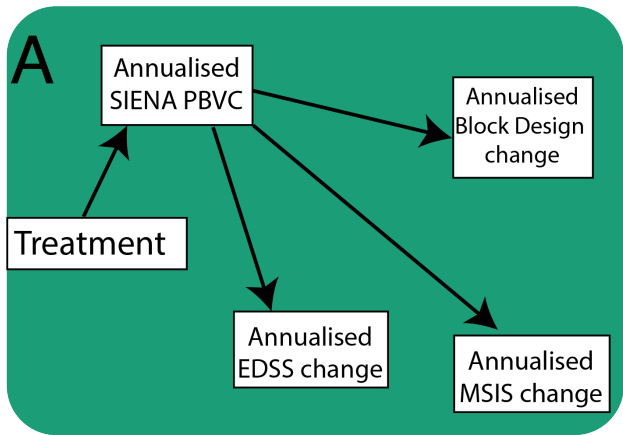


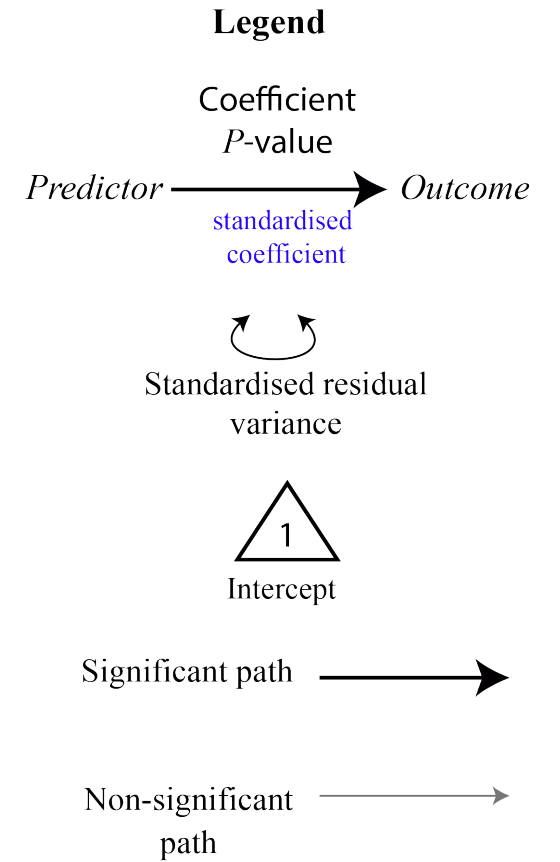
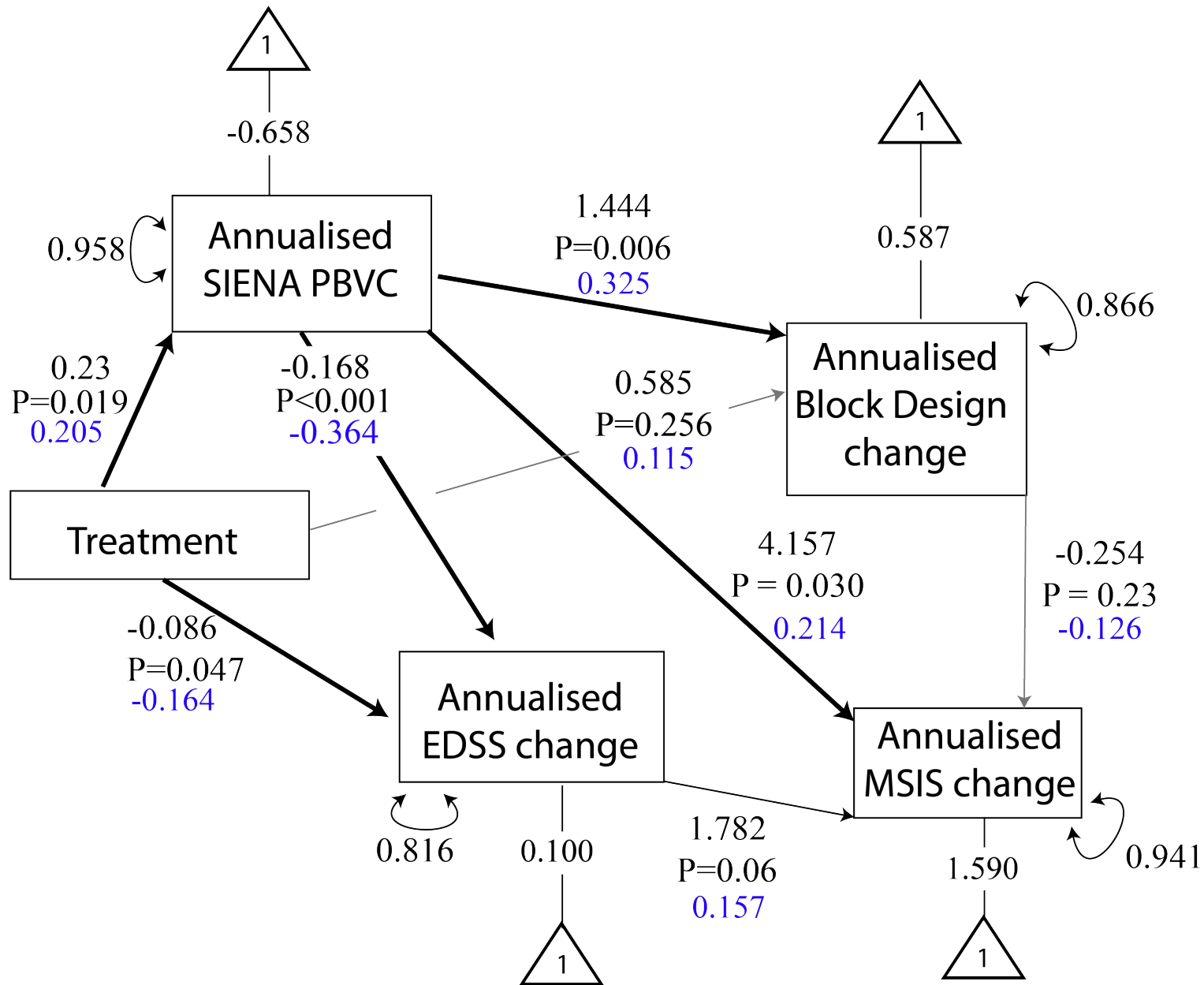


Applications in clinical trials









CONCLUSIONS

A.

B.

C.



Acknowledgments

Supervisors

- Olga Ciccarelli
- Daniel C Alexander
- Frederik Barkhof
- Alan J Thompson
- Jeremy Chataway

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