

Supplementary Methods

MRI data acquisition

MRI images were acquired on a 3T Siemens MAGNETOM Tim Trio MRI machine (Siemens, Erlangen) equipped with a 32-channel head coil at the Berlin Center of Advanced Neuroimaging (BCAN). The imaging protocol included a 3D 1mm-isotropic T1 weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE/TI=1900/2.55/900 ms, matrix 240×240[PCC51.1]), a 3D 1mm-isotropic fluid-attenuated inversion recovery sequence (3D FLAIR) (TR/TE/TI=6000/388/2100 ms, matrix=256×256), a single-shot echo planar imaging diffusion-weighted imaging (DWI) sequence (TR/TE=7500/86 ms, matrix 96×96, 61 slices no gap, slice thickness 2.3 mm, 64 non-colinear directions, b-value=1000 s/mm²), as well as a 2D-sagittal T2-weighted SC sequence (slice thickness=2 mm, TR=3500 ms, TE=101 ms, in-plane resolution=0.91 mm×0.91 mm) at the cervical, thoracic, and lumbar level of the spinal cord. Follow-up assessments were conducted using an identical imaging protocol and test battery across all time points. Comorbidities were recorded based on Samadzadeh et al..¹

Brain T2-weighted lesion segmentation

The eight categories were: 1) corpus callosum (>50% coverage in length), 2) lateral ventricle, 3) brainstem including fourth ventricle, 4) cerebellum, 5) juxtacortical, 6) diencephalic including third ventricle, 7) corticospinal tract extending into the pons, and 8) non-specific white matter lesions.² Brain total T2-hyperintense lesions were counted and volumes extracted in mL using FSL cluster (<https://fsl.fmrib.ox.ac.uk/fsl/docs/statistics/cluster.html?h=cluster>).

Longitudinal fibre-bundle regional damage calculation

For calculating the number of slices per bundle region, the median coordinates of streamline endpoints in start and end regions defined in the tractogram *TractSeg* output were calculated for each bundle in R. Tractograms for the bundles of interest were then resampled to equidistant slices in a straight line between the median bundle starting and endpoints using MRtrix3 *tckresample*. The number of slices per bundle was selected by dividing the distances between starting and endpoints per tractogram by the largest dimension of the DWI voxel-size (2.5cm) and rounding to the closest multiple of 10. This was chosen, as the constraints of MRI resolution should be taken into consideration when creating slices to measure from in a tractogram. This total number of slices sampled were further subdivided into two to three regions depending on the tract of interest. For example, the CST (left and right) had 50 sampled slices, which is not a multiple of three. Thus, to achieve three regions, it was decided to select the first 15 slices as the cortical projecting region, the next 20 slices as the mid-region, and the last 15 slices as the brainstem projecting region. When the total number of slices were

a multiple of two or three, all regions contained equal number of slices. In the case of the corpus callosum, the total number of slices were only subdivided into left and right hemispheres (five slices per hemisphere). The other WM tracts of interest analysed were: IFOF with three regions (anterior = 15 slices, mid = 10 slices, posterior = 15 slices); cingulum with three regions (anterior = 15 slices, posterior = 15 slices); optic radiation with three regions (cortical = 10 slices, mid = 10 slices, thalamic = 10 slices); TPOL with three regions (anterior = 10 slices, mid = 10 slices, posterior = 10 slices); and TPFC with three regions (anterior = 10 slices, mid = 10 slices, posterior = 10 slices).

Supplementary Results

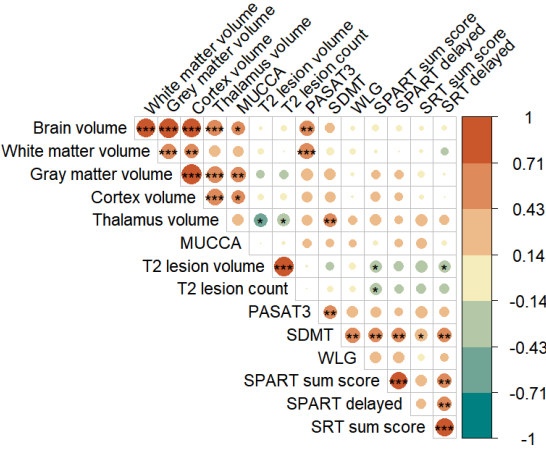
Whole cohort white matter regions with increasing FA

Meanwhile, moderate to large effect sizes were found for increasing mean FA longitudinally in the following regions with some fluctuations: the 1) left brainstem region of the CST, 2) left mid region of the CST, 3) right mid region of the IFOF, 4) right posterior region of the IFOF, and the 5) right posterior region of the TPFC. Over time, greater FA increases in the CST were significantly associated with better attention (PASAT 3s: $\beta=0.002$, $SE=0.0002$, $P_{FDR}=0.017$) and spatial memory outcomes at last visit (SPART delayed recall: $\beta=0.011$, $SE=0.001$, $P_{FDR}=0.017$, Supplementary Fig. 2). Similarly, higher FA gains in the right mid IFOF predicted better functional outcomes (MSFC: $\rho_s=0.68$, $P_{FDR}=0.026$) and better self-rated visual function at last follow-up (VFQ25: $\rho_s=0.64$, $P_{FDR}=0.011$). All regions showed the largest increase in FA in the comparison between the last follow-up and the first clinical visit MRI, again with the possibility that the data is skewed towards patients with more visits ($n=4$). However, the left brainstem and left mid-regions of the CST and the right mid and right posterior regions of the IFOF showed consistent increasing mean FA over all sessions. Meanwhile, the right posterior TPFC showed an interesting decrease in mean FA between the third MRI visit and first available clinical visit ($n=27$), then showed increased mean FAs compared to the first DWI scans (Table 4, Supplementary Fig. 4D-H).

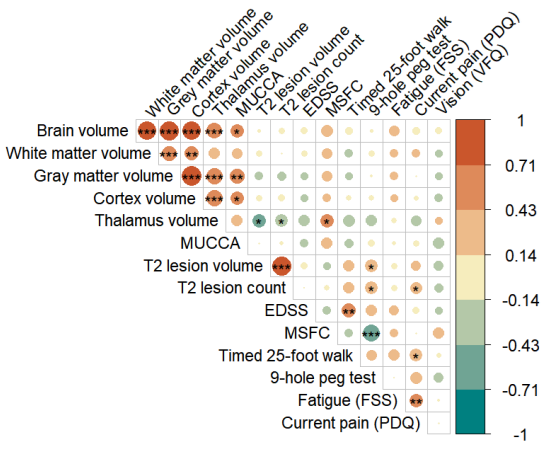
References

1. Samadzadeh S, Oertel FC, Salih H, et al. Comorbidities Are Associated With Unfavorable Outcome in Aquaporin-4 Antibody Positive Neuromyelitis Optica Spectrum Disorders and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease: Exploratory Study From the CROCTINO Cohort. *European Journal of Neurology*. 2025;32(6):e70214. doi:10.1111/ene.70214
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189. doi:10.1212/WNL.0000000000001729

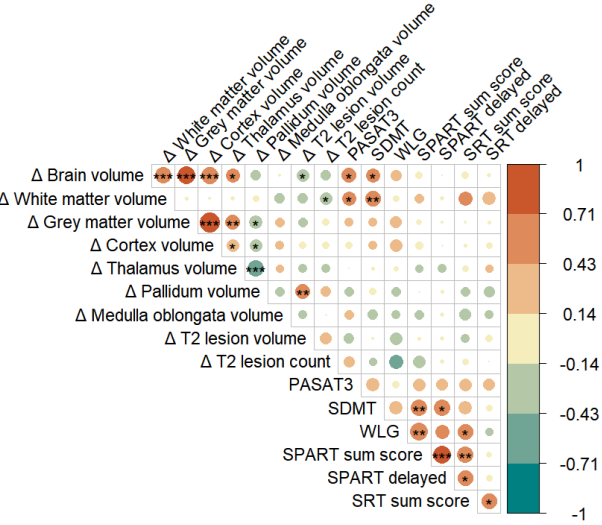
A Cross-sectional volumes and cognitive outcomes



B Cross-sectional volumes and functional outcomes



C Change scores and cognitive outcomes



D Change scores and functional outcomes

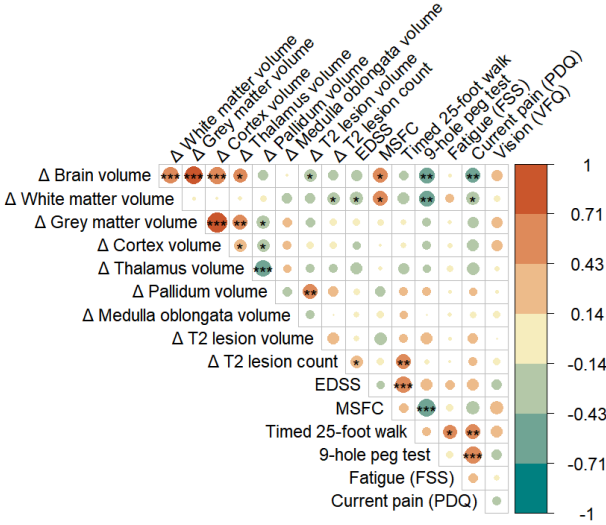
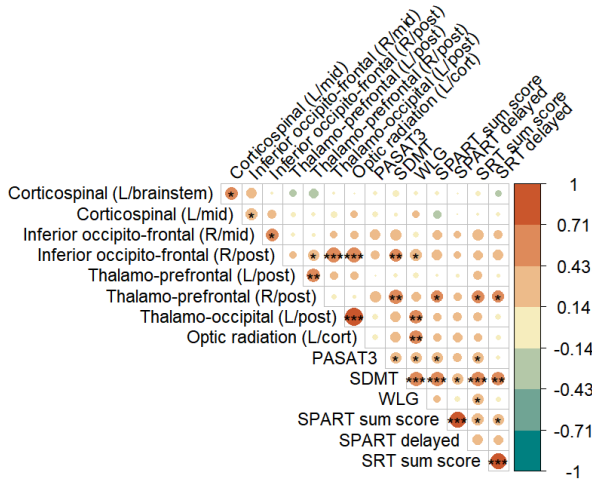
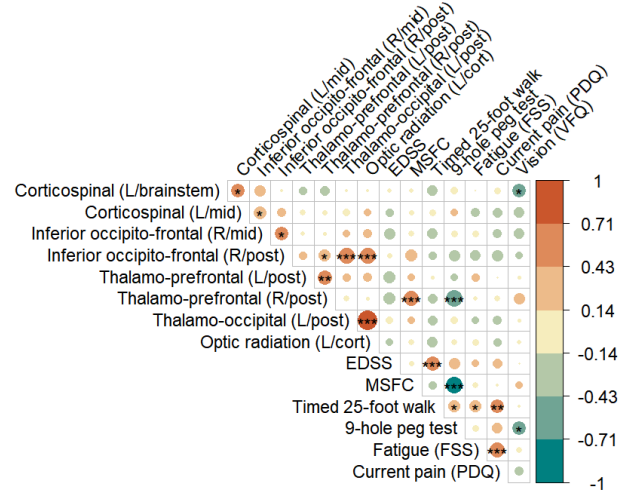


Fig. S1. Visualization of Spearman correlation plots showing initial associations at first stable visit (A-B), and between longitudinal change and outcomes at last visit (C-D). Abbreviations: EDSS – Expanded Disability Status Scale, FSS – Fatigue Severity Scale, MSFC – Multiple Sclerosis Functional Composite, MUCCA – Mean Upper Cervical Cord Area, PASAT – Paced Auditory Serial Addition Test, PDQ – PainDETECT Questionnaire, SDMT – Symbol Digit Modalities Test, SPART – Spatial Recall Test, SRT – Selective Reminding Test, VFQ – Visual Function Questionnaire 25, WLG – Word List Generation. (* $P_{\text{unadj}} < 0.05$, ** $P_{\text{unadj}} < 0.01$, *** $P_{\text{unadj}} < 0.001$)

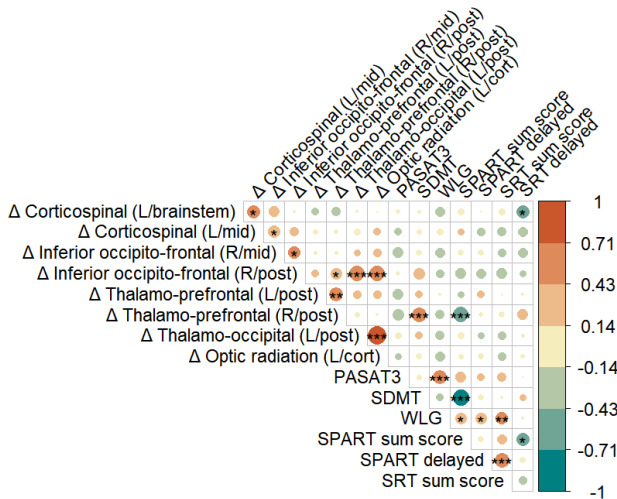
A Cross-sectional mean FA and cognitive outcomes



B Cross-sectional mean FA and functional outcomes



C Change scores and cognitive outcomes



D Change scores and functional outcomes

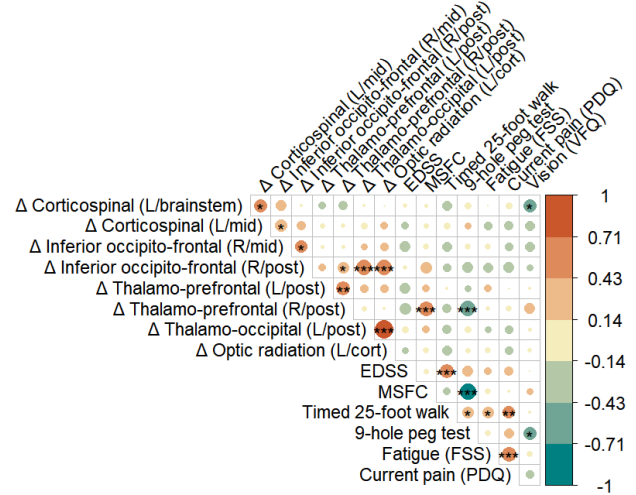


Fig. S2. Visualization of Spearman correlation plots showing initial associations at first stable visit (A-B), and between longitudinal change and outcomes at last visit (C-D). Abbreviations: cort – cortical, EDSS – Expanded Disability Status Scale, FA – Fractional Anisotropy, FSS – Fatigue Severity Scale, L – left, MSFC – Multiple Sclerosis Functional Composite, MUCCA – Mean Upper Cervical Cord Area, PASAT – Paced Auditory Serial Addition Test, PDQ – PainDETECT Questionnaire, post – posterior, R – right, SDMT – Symbol Digit Modalities Test, SPART – Spatial Recall Test, SRT – Selective Reminding Test, VFQ – Visual Function Questionnaire 25, WLG – Word List Generation. (* $P_{\text{unadj}} < 0.05$, ** $P_{\text{unadj}} < 0.01$, *** $P_{\text{unadj}} < 0.001$)

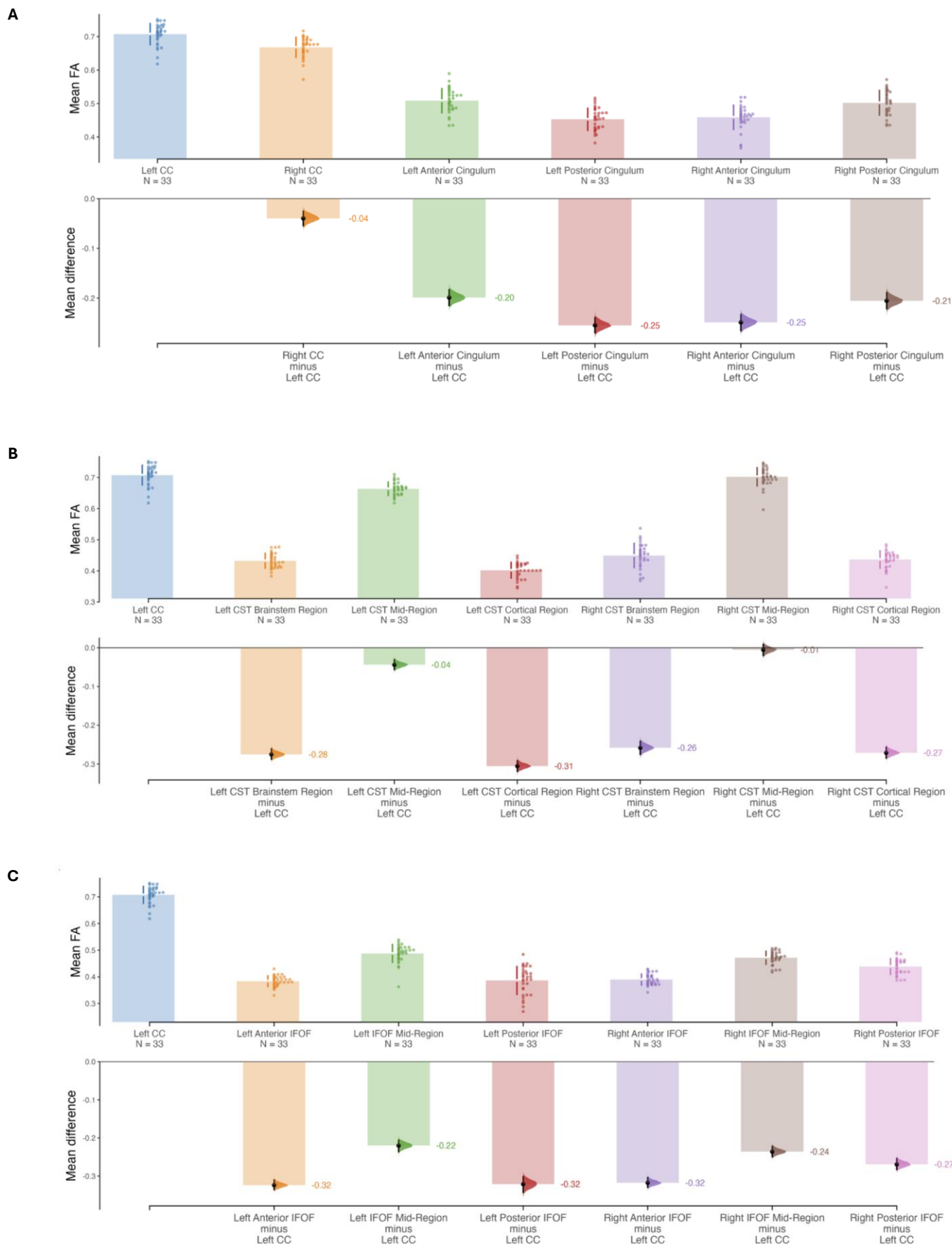


Fig. S3. Mean differences in regional mean FA measures between the left CC and the rest of the WM fibre bundle regions. Between the **(A)** left CC, right CC, and cingulum regions; **(B)** left CC and CST regions; **(C)** left CC and IFOF regions; **(D)** left CC and OR regions; **(E)** left CC and TPFC regions; and **(F)** left CC and TPOL regions. Abbreviations: CC – corpus callosum, CST – corticospinal tract, FA – fractional anisotropy, IFOF – inferior fronto-occipital fasciculus, OR – optic radiation, TPFC – thalamic projection to the prefrontal cortex, TPOL – thalamic projection to the occipital lobe, WM – white matter.

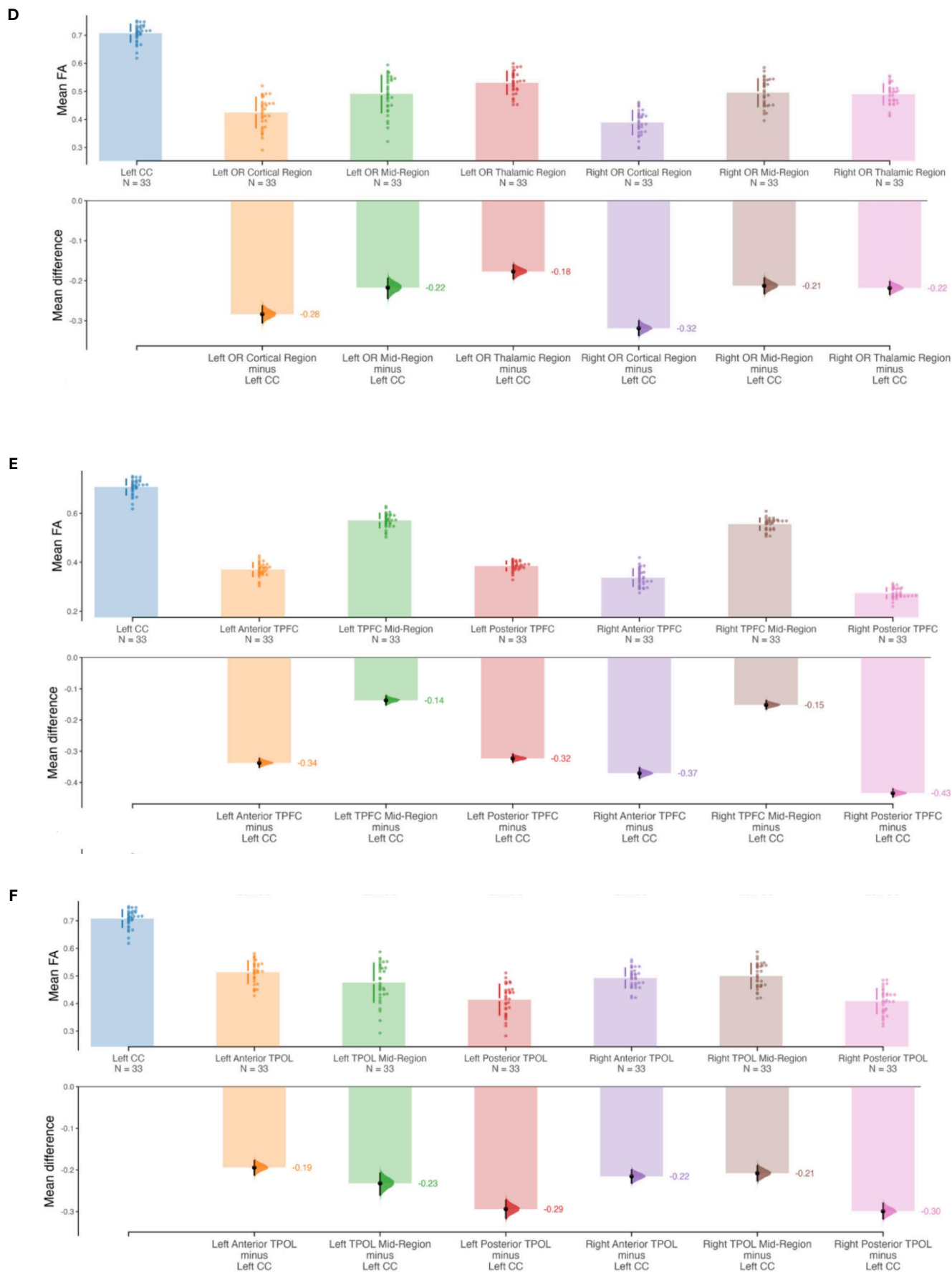


Fig. S3. Mean differences in regional mean FA measures between the left CC and the rest of the WM fibre bundle regions. Between the (A) left CC, right CC, and cingulum regions; (B) left CC and CST regions; (C) left CC and IFOF regions; (D) left CC and OR regions; (E) left CC and TPFC regions; and (F) left CC and TPOL regions. Abbreviations: CC – corpus callosum, CST – corticospinal tract, FA – fractional anisotropy, IFOF – inferior fronto-occipital fasciculus, OR – optic radiation, TPFC – thalamic projection to the prefrontal cortex, TPOL – thalamic projection to the occipital lobe, WM – white matter.

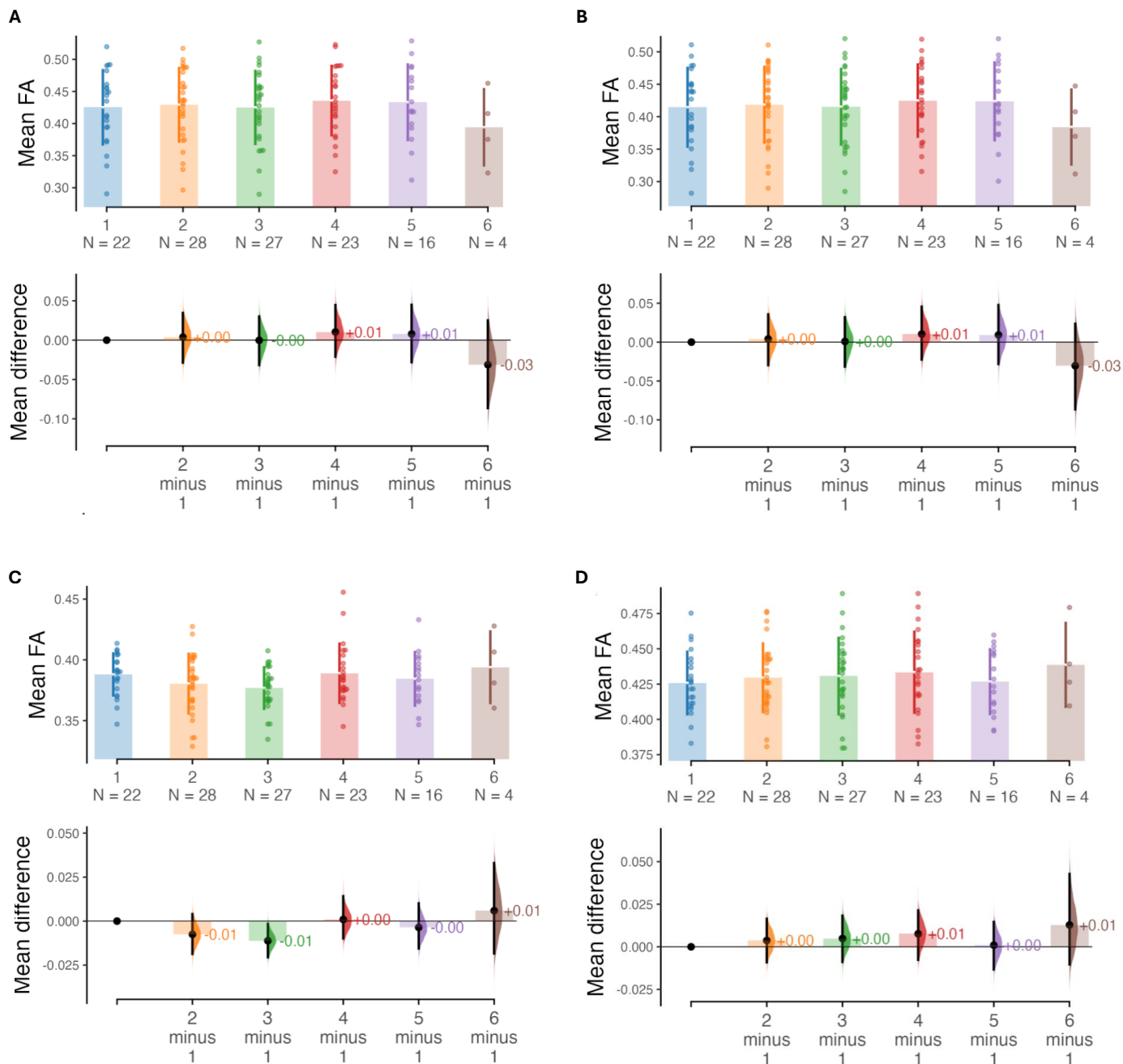


Fig. S4. Whole cohort mean differences between mean FA values calculated at each available DWI timepoint in regions showing decreased and increased FA. Mean differences were calculated between each follow-up timepoint and the first available scan showing decreasing FAs in the: **(A)** left cortical region of the OR; **(B)** left posterior region of the TPOL; and **(C)** left posterior region of the TPFC. Meanwhile, mean differences calculated between each follow-up timepoint and the first available scan showed increasing FAs in the: **(D)** left brainstem region of the CST; **(E)** left mid-region of the CST; **(F)** right mid-region of the IFOF; **(G)** right posterior region of the IFOF; and **(H)** right posterior region of the TPFC. Abbreviations: CST – corticospinal tract, DWI – diffusion weighted imaging, FA – fractional anisotropy, IFOF – inferior fronto-occipital fasciculus, OR – optic radiation, TPFC – thalamic projection to the prefrontal cortex, TPOL – thalamic projection to the occipital lobe.

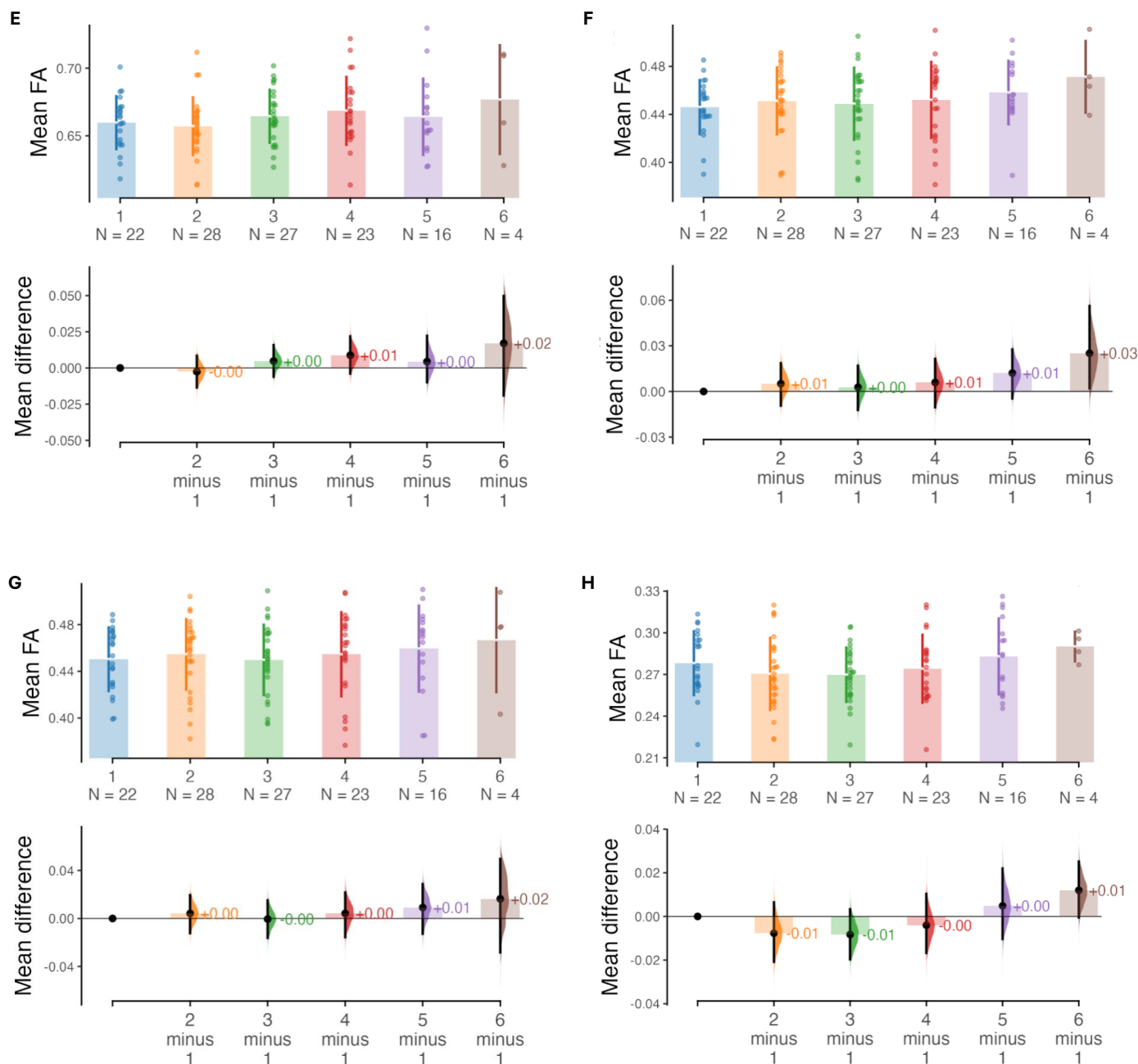


Fig. S4. Whole cohort mean differences between mean FA values calculated at each available DWI timepoint in regions showing decreased and increased FA. Mean differences were calculated between each follow-up timepoint and the first available scan showing decreasing FAs in the: **(A)** left cortical region of the OR; **(B)** left posterior region of the TPOL; and **(C)** left posterior region of the TPFC. Meanwhile, mean differences calculated between each follow-up timepoint and the first available scan showed increasing FAs in the: **(D)** left brainstem region of the CST; **(E)** left mid-region of the CST; **(F)** right mid-region of the IFOF; **(G)** right posterior region of the IFOF; and **(H)** right posterior region of the TPFC. Abbreviations: CST – corticospinal tract, DWI – diffusion weighted imaging, FA – fractional anisotropy, IFOF – inferior fronto-occipital fasciculus, OR – optic radiation, , TPFC – thalamic projection to the prefrontal cortex, TPOL – thalamic projection to the occipital lobe.

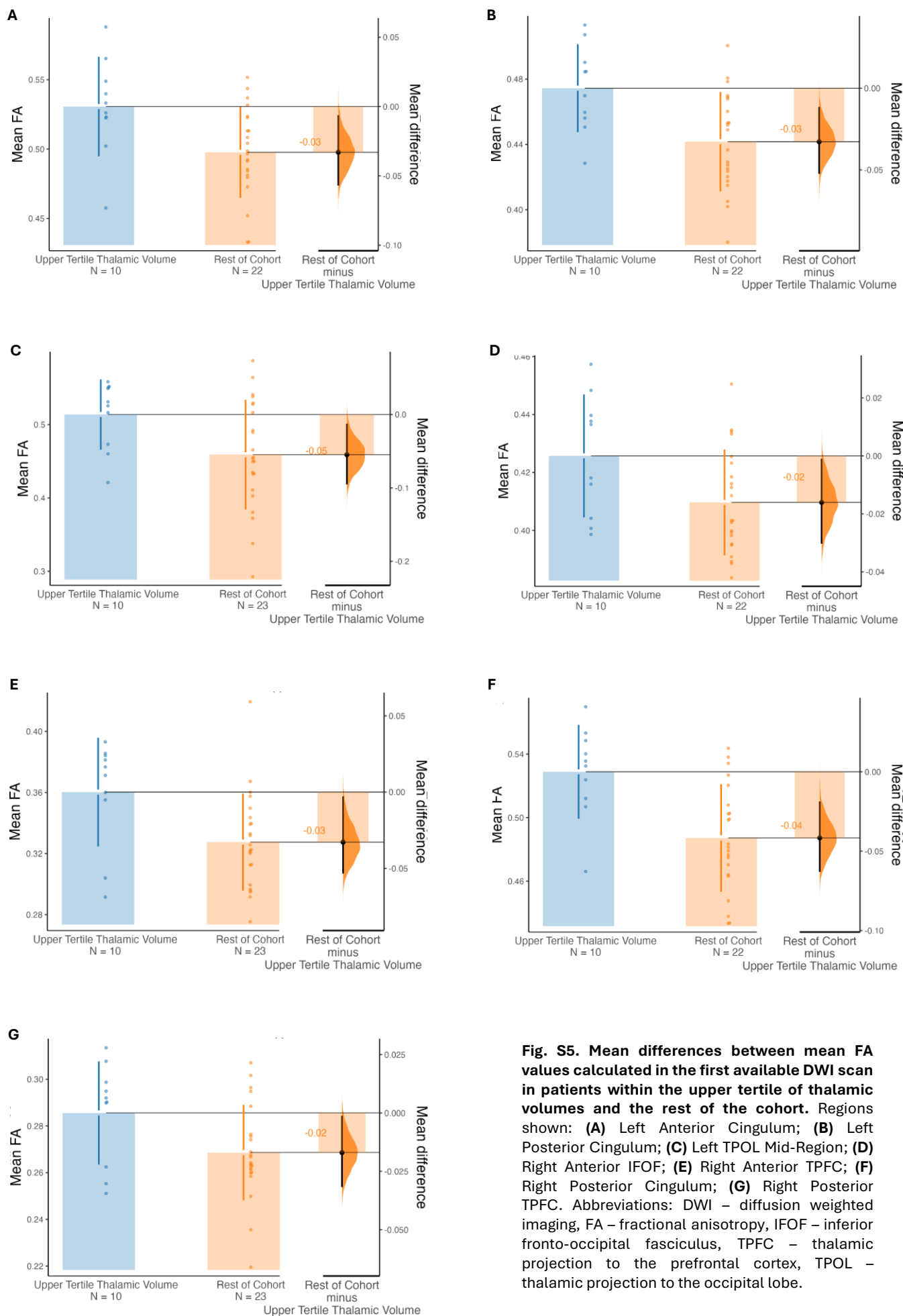


Fig. S5. Mean differences between mean FA values calculated in the first available DWI scan in patients within the upper tertile of thalamic volumes and the rest of the cohort. Regions shown: **(A)** Left Anterior Cingulum; **(B)** Left Posterior Cingulum; **(C)** Left TPOL Mid-Region; **(D)** Right Anterior IFOF; **(E)** Right Anterior TPFC; **(F)** Right Posterior Cingulum; **(G)** Right Posterior TPFC. Abbreviations: DWI – diffusion weighted imaging, FA – fractional anisotropy, IFOF – inferior fronto-occipital fasciculus, TPFC – thalamic projection to the prefrontal cortex, TPOL – thalamic projection to the occipital lobe.

Supplementary Table 1 | Treatments, comorbidities, and study exclusion

	N (%)	Comment
Comorbidities		
Patients with any comorbidity	18/33 (55%)	
Autoimmune (any)	17/33 (52%)	
Endocrine (any)	8/33 (24%)	
Rheumatologic (any)	7/33 (21%)	
Thyroid disorder	6/33 (18%)	
Systemic lupus erythematosus (SLE)	3/33 (9%)	
Myasthenia gravis	2/33 (6%)	
Cerebral venous sinus thrombosis	1/33 (3%)	Five years prior to first included MRI
Transient ischaemic attack	1/33 (3%)	Seven years prior to first included MRI
Pituitary adenoma	1/33 (3%)	Treatment 11 years prior to first included MRI
Treatment during stable phase		
Attack-preventing treatment	30/33 (91%)	
Rituximab	20/33 (61%)	
Azathioprine	7/33 (21%)	
Prednisolone	5/33 (15%)	
Mycophenolic acid	4/33 (12%)	
Tocilizumab	1/33 (3%)	
Glatiramer acetate	1/33 (3%)	
Pain medication	13/33 (39%)	
Gabapentin	5/33 (15%)	
Oxycodone	1/33 (3%)	
Metamizole	1/33 (3%)	
Tilidine	1/33 (3%)	
Ibuprofen	1/33 (3%)	
Other	4/33 (12%)	
Treatment for spasticity	6/33 (18%)	
Baclofen	3/33 (9%)	
Pramipexole	2/33 (6%)	
Tizanidine	1/33 (3%)	
Hyoscine butyl bromide	1/33 (3%)	
Anxiolytic/antidepressant medication	7/33 (21%)	
Pregabalin	5/33 (15%)	
Mirtazapine	2/33 (6%)	
Amitriptyline	2/33 (6%)	
Treatment for hypertension	10/33 (30%)	
Reasons for study exclusion		
MOG-IgG-seropositive	20	
Double-seropositive (AQP4-IgG/MOG-IgG)	1	
AQP4-IgG-seronegative	3	
Recent relapses (< 1 year before MRI)	3	
Significant CNS comorbidity	2	Ischaemic stroke, suspected secondary MS
Unable to confirm stable disease course	12	
Unable to confirm AQP4-IgG serostatus	5	

Supplementary Table 2 | Brain Lesion Subsegmentation Values at Patient Baseline MRI

Brain Lesion Location	Median Lesion Count [range]	Proportion of Patients with Lesions		Lesion Volume (mL)	
		<i>n/N [decimal fraction]</i>	<i>95% CI</i>	<i>Mean</i>	<i>SD</i>
Non-specific WM	4 [0 - 48]	27/33 [0.82]	0.69 - 0.95	0.469	0.768
Juxtacortical	1 [0 - 13]	18/33 [54.5]	0.38 - 0.72	0.127	0.245
Lateral Ventricle	3 [0 - 21]	29/33 [87.9]	0.51 - 0.83	1.244	2.094
Diencephalic including 3rd Ventricle	0 [0 - 3]	6/33 [18.2]	0.05 - 0.31	0.013	0.035
Corpus Callosum	0 [0 - 0]	0/33 [0.0]	NA	0.000	0.000
Brainstem including 4th Ventricle	0 [0 - 5]	6/33 [18.2]	0.05 - 0.31	0.024	0.087
Cerebellum	0 [0 - 1]	1/33 [0.03]	-0.03 - 0.09	0.002	0.009
CST Extensive	0 [0 - 1]	1/33 [0.03]	-0.03 - 0.09	0.002	0.009

Supplementary Table 3 | Mean damage of cohort white matter tract regions extracted from longitudinal DWI in each individual patient

White Matter Tract Region	Mean Damage (%) [$\pm$ SD, range]	Thresholded Mean Damage (%) [$\pm$ SD, range]
Left CC	6.8 [$\pm$ 4.9, 0.0 – 16.3]	0.0 [$\pm$ 0.0, 0.0 – 0.0]
Right CC	7.9 [$\pm$ 4.9, 0.0 – 21.7]	0.0 [$\pm$ 0.0, 0.0 – 0.0]
Left Anterior Cingulum	7.9 [$\pm$ 4.2, 0.0 – 23.5]	0.3 [$\pm$ 2.0, 0.0 – 18.6]
Left Posterior Cingulum	7.8 [$\pm$ 4.4, 0.9 – 18.9]	0.4 [$\pm$ 1.3, 0.0 – 8.0]
Right Anterior Cingulum	8.1 [$\pm$ 4.0, 0.2 – 19.9]	0.2 [$\pm$ 1.2, 0.0 – 9.7]
Right Posterior Cingulum	8.4 [$\pm$ 4.4, 1.6 – 19.5]	0.1 [$\pm$ 0.8, 0 – 6.1]
Left CST Brainstem Region	14.1 [$\pm$6.9, 0.0 – 37.5]	6.9 [$\pm$6.9, 0.0 – 36.6]
Left CST Cortical Region	9.6 [$\pm$ 5.3, 0.1 – 28.1]	1.8 [$\pm$ 3.4, 0.0 – 14.2]
Left CST Mid-Region	11.7 [$\pm$8.7, 0.0 – 62.0]	5.5 [$\pm$8.1, 0.0 – 58.7]
Right CST Brainstem Region	9.7 [$\pm$ 4.9, 0.2 – 25.3]	1.8 [$\pm$ 3.7, 0.0 – 20.0]
Right CST Cortical Region	8.6 [$\pm$ 5.3, 0.9 – 29.9]	1.7 [$\pm$ 3.8, 0.0 – 20.8]
Right CST Mid-Region	13.0 [$\pm$10.6, 0.6 – 51.3]	7.2 [$\pm$10.0, 0.0 – 47.2]
Left Anterior IFOF	7.4 [$\pm$ 3.0, 0.7 – 14.9]	0.1 [$\pm$ 0.5, 0.0 – 3.6]
Left IFOF Mid-Region	7.2 [$\pm$ 4.7, 0.0 – 21.1]	0.5 [$\pm$ 1.5, 0.0 – 8.2]
Left Posterior IFOF	7.7 [$\pm$ 3.6, 0.8 – 15.0]	0.0 [$\pm$ 0.0, 0.0 – 0.0]
Right Anterior IFOF	7.7 [$\pm$ 3.4, 1.9 – 22.4]	0.3 [$\pm$ 1.2, 0.0 – 8.3]
Right IFOF Mid-Region	7.3 [$\pm$ 5.1, 0.0 – 25.6]	0.5 [$\pm$ 1.8, 0.0 – 11.3]
Right Posterior IFOF	7.3 [$\pm$ 4.5, 0.1 – 24.3]	0.2 [$\pm$ 1.0, 0.0 – 6.1]
Left OR Cortical Region	7.7 [$\pm$ 4.6, 0.2 – 25.2]	0.6 [$\pm$ 2.3, 0.0 – 18.3]
Left OR Mid-Region	8.3 [$\pm$ 6.1, 0.0 – 26.5]	1.6 [$\pm$ 2.7, 0.0 – 11.0]
Left OR Thalamic Region	6.9 [$\pm$ 6.4, 0.0 – 25.7]	1.1 [$\pm$ 2.6, 0.0 – 11.2]
Right OR Cortical Region	7.7 [$\pm$ 4.4, 0.4 – 18.2]	0.3 [$\pm$ 1.3, 0.0 – 7.4]
Right OR Mid-Region	8.6 [$\pm$7.0, 0.0 – 30.9]	2.2 [$\pm$4.4, 0.0 – 22.6]
Right OR Thalamic Region	6.6 [$\pm$ 4.6, 0.0 – 18.2]	0.3 [$\pm$ 1.2, 0.0 – 8.0]
Left Anterior TPOL	7.7 [$\pm$ 5.8, 0.0 – 22.8]	0.5 [$\pm$ 1.7, 0.0 – 8.4]
Left TPOL Mid-Region	8.5 [$\pm$ 5.3, 0.0 – 21.3]	0.8 [$\pm$ 2.1, 0.0 – 10.6]
Left Posterior TPOL	7.6 [$\pm$ 4.1, 0.2 – 27.2]	0.3 [$\pm$ 2.1, 0.0 – 19.0]
Right Anterior TPOL	6.5 [$\pm$ 4.4, 0.0 – 18.4]	0.1 [$\pm$ 0.6, 0.0 – 4.2]
Right TPOL Mid-Region	7.9 [$\pm$ 6.6, 0.0 – 25.3]	1.5 [$\pm$ 3.0, 0.0 – 14.3]
Right Posterior TPOL	7.7 [$\pm$ 4.3, 0.9 – 19.1]	0.4 [$\pm$ 1.2, 0.0 – 5.5]
Left Anterior TPFC	7.8 [$\pm$ 3.4, 1.1 – 15.6]	0.0 [$\pm$ 0.4, 0.0 – 3.8]
Left TPFC Mid-Region	7.3 [$\pm$ 4.9, 0.0 – 24.7]	0.2 [$\pm$ 1.5, 0.0 – 13.4]
Left Posterior TPFC	10.6 [$\pm$9.4, 0.0 – 57.2]	3.4 [$\pm$7.6, 0.0 – 52.7]
Right Anterior TPFC	9.2 [$\pm$ 4.7, 0.2 – 20.8]	0.1 [$\pm$ 0.8, 0.0 – 4.3]
Right TPFC Mid-Region	8.3 [$\pm$ 5.2, 0.5 – 25.6]	0.5 [$\pm$ 1.6, 0.0 – 7.7]
Right Posterior TPFC	15.2 [$\pm$11.2, 0.0 – 59.4]	8.9 [$\pm$11.0, 0.0 – 56.0]

Supplementary Table 4 | Cross-sectional analysis of first available DWI regional mean FA values in patients with the upper tertile of thalamic volumes versus the rest of the cohort

WM Fibre Bundle Region	Group 1	Group 2	Effect Size (Cohen's d)	Effect Size 95% CI		Effect Size Magnitude
Left Anterior Cingulum	upper tertile	rest of cohort	0.98	0.21	2	large
Left Anterior IFOF	upper tertile	rest of cohort	0.45	-0.27	1.46	small
Left Anterior TPFC	upper tertile	rest of cohort	0.58	-0.2	1.59	moderate
Left Anterior TPOL	upper tertile	rest of cohort	0.13	-0.64	0.97	negligible
Left CC	upper tertile	rest of cohort	0.37	-0.45	1.09	small
Left CST Brainstem Region	upper tertile	rest of cohort	-0.03	-1.05	0.81	negligible
Left CST Cortical Region	upper tertile	rest of cohort	0.32	-0.47	1.74	small
Left CST Mid-Region	upper tertile	rest of cohort	0.09	-0.68	0.83	negligible
Left IFOF Mid-Region	upper tertile	rest of cohort	0.58	-0.05	1.38	moderate
Left OR Cortical Region	upper tertile	rest of cohort	0.59	-0.11	1.47	moderate
Left OR Mid-Region	upper tertile	rest of cohort	0.68	-0.01	1.66	moderate
Left OR Thalamic Region	upper tertile	rest of cohort	0.18	-0.61	1.14	negligible
Left Posterior Cingulum	upper tertile	rest of cohort	1.16	0.4	2.16	large
Left Posterior IFOF	upper tertile	rest of cohort	0.75	0.08	1.49	moderate
Left Posterior TPFC	upper tertile	rest of cohort	0.27	-0.42	1.05	small
Left Posterior TPOL	upper tertile	rest of cohort	0.65	-0.08	1.58	moderate
Left TPFC Mid-Region	upper tertile	rest of cohort	0.19	-0.64	0.99	negligible
Left TPOL Mid-Region	upper tertile	rest of cohort	0.83	0.09	1.72	large
Right Anterior Cingulum	upper tertile	rest of cohort	0.58	-0.16	1.7	moderate
Right Anterior IFOF	upper tertile	rest of cohort	0.82	0.06	1.85	large
Right Anterior TPFC	upper tertile	rest of cohort	0.95	0.14	2.61	large

Right Anterior TPOL	upper tertile	rest of cohort	0.18	-0.59	1.1	negligible
Right CC	upper tertile	rest of cohort	0.62	-0.12	1.32	moderate
Right CST Brainstem Region	upper tertile	rest of cohort	0.58	-0.08	1.34	moderate
Right CST Cortical Region	upper tertile	rest of cohort	0.55	-0.25	1.57	moderate
Right CST Mid-Region	upper tertile	rest of cohort	-0.04	-0.82	0.59	negligible
Right IFOF Mid-Region	upper tertile	rest of cohort	0.07	-0.73	0.76	negligible
Right OR Cortical Region	upper tertile	rest of cohort	0.37	-0.32	1.16	small
Right OR Mid-Region	upper tertile	rest of cohort	0.68	-7.9e-4	1.52	moderate
Right OR Thalamic Region	upper tertile	rest of cohort	0.21	-0.56	1.12	small
Right Posterior Cingulum	upper tertile	rest of cohort	1.33	0.54	2.52	large
Right Posterior IFOF	upper tertile	rest of cohort	0.68	-0.07	1.96	moderate
Right Posterior TPFC	upper tertile	rest of cohort	0.88	0.08	2.02	large
Right Posterior TPOL	upper tertile	rest of cohort	0.39	-0.29	1.32	small
Right TPFC Mid-Region	upper tertile	rest of cohort	0.16	-0.59	1	negligible
Right TPOL Mid-Region	upper tertile	rest of cohort	0.63	-0.08	1.53	moderate

Supplementary Table 5 | Representative patients with highest thalamic volumes and the longitudinal change in their white matter fibre-bundle regions

Subject	Session	White Matter Tract Region	Mean FA	Delta Mean FA (Visit 2 – Visit 1)	Percent Change in FA from Visit 1
1	1	Left CC	0.73	NA	NA
1	1	Right CC	0.69	NA	NA
1	1	Left Anterior Cingulum	0.57	NA	NA
1	1	Left Posterior Cingulum	0.51	NA	NA
1	1	Right Anterior Cingulum	0.52	NA	NA
1	1	Right Posterior Cingulum	0.55	NA	NA
1	1	Left CST Brainstem Region	0.4	NA	NA
1	1	Left CST Cortical Region	0.43	NA	NA
1	1	Left CST Mid-Region	0.66	NA	NA
1	1	Right CST Brainstem Region	0.45	NA	NA
1	1	Right CST Cortical Region	0.45	NA	NA
1	1	Right CST Mid-Region	0.72	NA	NA
1	1	Left Anterior IFOF	0.41	NA	NA
1	1	Left IFOF Mid-Region	0.46	NA	NA
1	1	Left Posterior IFOF	0.46	NA	NA
1	1	Right Anterior IFOF	0.42	NA	NA
1	1	Right IFOF Mid-Region	0.47	NA	NA
1	1	Right Posterior IFOF	0.49	NA	NA
1	1	Left OR Cortical Region	0.49	NA	NA
1	1	Left OR Mid-Region	0.55	NA	NA
1	1	Left OR Thalamic Region	0.54	NA	NA
1	1	Right OR Cortical Region	0.41	NA	NA
1	1	Right OR Mid-Region	0.53	NA	NA
1	1	Right OR Thalamic Region	0.5	NA	NA
1	1	Left Anterior TPOL	0.53	NA	NA
1	1	Left TPOL Mid-Region	0.55	NA	NA
1	1	Left Posterior TPOL	0.48	NA	NA
1	1	Right Anterior TPOL	0.5	NA	NA
1	1	Right TPOL Mid-Region	0.53	NA	NA
1	1	Right Posterior TPOL	0.43	NA	NA
1	1	Left Anterior TPFC	0.39	NA	NA
1	1	Left TPFC Mid-Region	0.6	NA	NA
1	1	Left Posterior TPFC	0.41	NA	NA
1	1	Right Anterior TPFC	0.38	NA	NA
1	1	Right TPFC Mid-Region	0.56	NA	NA

1	1	Right Posterior TPFC	0.3	NA	NA
1	2	Left CC	0.71	-0.02	-2.74
1	2	Right CC	0.68	-0.01	-1.44
1	2	Left Anterior Cingulum	0.52	-0.04	-7.08
1	2	Left Posterior Cingulum	0.47	-0.04	-7.8
1	2	Right Anterior Cingulum	0.47	-0.05	-9.65
1	2	Right Posterior Cingulum	0.49	-0.05	-9.12
1	2	Left CST Brainstem Region	0.41	0.01	2.47
1	2	Left CST Cortical Region	0.41	-0.02	-4.64
1	2	Left CST Mid-Region	0.64	-0.02	-3.03
1	2	Right CST Brainstem Region	0.43	-0.02	-4.41
1	2	Right CST Cortical Region	0.43	-0.02	-4.43
1	2	Right CST Mid-Region	0.68	-0.04	-5.59
1	2	Left Anterior IFOF	0.41	0	0
1	2	Left IFOF Mid-Region	0.48	0.01	2.15
1	2	Left Posterior IFOF	0.46	0	0
1	2	Right Anterior IFOF	0.42	0	0
1	2	Right IFOF Mid-Region	0.48	0.01	2.13
1	2	Right Posterior IFOF	0.47	-0.02	-4.09
1	2	Left OR Cortical Region	0.49	0	0
1	2	Left OR Mid-Region	0.57	0.01	1.81
1	2	Left OR Thalamic Region	0.54	0	0
1	2	Right OR Cortical Region	0.4	-0.01	-2.46
1	2	Right OR Mid-Region	0.52	-0.01	-1.88
1	2	Right OR Thalamic Region	0.51	0.01	1.99
1	2	Left Anterior TPOL	0.52	0	0
1	2	Left TPOL Mid-Region	0.57	0.01	1.81
1	2	Left Posterior TPOL	0.48	0	0
1	2	Right Anterior TPOL	0.51	0.01	1.98
1	2	Right TPOL Mid-Region	0.52	-0.01	-1.87
1	2	Right Posterior TPOL	0.43	-0.01	-2.3
1	2	Left Anterior TPFC	0.38	-0.01	-2.57
1	2	Left TPFC Mid-Region	0.6	0	0
1	2	Left Posterior TPFC	0.34	-0.08	-19.35
1	2	Right Anterior TPFC	0.35	-0.03	-7.87
1	2	Right TPFC Mid-Region	0.55	-0.01	-1.79
1	2	Right Posterior TPFC	0.22	-0.07	-23.43
2	1	Left CC	0.71	NA	NA
2	1	Right CC	0.67	NA	NA
2	1	Left Anterior Cingulum	0.59	NA	NA

2	1	Left Posterior Cingulum	0.51	NA	NA
2	1	Right Anterior Cingulum	0.52	NA	NA
2	1	Right Posterior Cingulum	0.57	NA	NA
2	1	Left CST Brainstem Region	0.42	NA	NA
2	1	Left CST Cortical Region	0.37	NA	NA
2	1	Left CST Mid-Region	0.67	NA	NA
2	1	Right CST Brainstem Region	0.45	NA	NA
2	1	Right CST Cortical Region	0.45	NA	NA
2	1	Right CST Mid-Region	0.69	NA	NA
2	1	Left Anterior IFOF	0.45	NA	NA
2	1	Left IFOF Mid-Region	0.51	NA	NA
2	1	Left Posterior IFOF	0.41	NA	NA
2	1	Right Anterior IFOF	0.45	NA	NA
2	1	Right IFOF Mid-Region	0.47	NA	NA
2	1	Right Posterior IFOF	0.45	NA	NA
2	1	Left OR Cortical Region	0.45	NA	NA
2	1	Left OR Mid-Region	0.52	NA	NA
2	1	Left OR Thalamic Region	0.54	NA	NA
2	1	Right OR Cortical Region	0.41	NA	NA
2	1	Right OR Mid-Region	0.54	NA	NA
2	1	Right OR Thalamic Region	0.51	NA	NA
2	1	Left Anterior TPOL	0.52	NA	NA
2	1	Left TPOL Mid-Region	0.52	NA	NA
2	1	Left Posterior TPOL	0.44	NA	NA
2	1	Right Anterior TPOL	0.51	NA	NA
2	1	Right TPOL Mid-Region	0.54	NA	NA
2	1	Right Posterior TPOL	0.43	NA	NA
2	1	Left Anterior TPFC	0.39	NA	NA
2	1	Left TPFC Mid-Region	0.58	NA	NA
2	1	Left Posterior TPFC	0.4	NA	NA
2	1	Right Anterior TPFC	0.36	NA	NA
2	1	Right TPFC Mid-Region	0.57	NA	NA
2	1	Right Posterior TPFC	0.29	NA	NA
2	2	Left CC	0.7	0	0
2	2	Right CC	0.69	0.01	1.48
2	2	Left Anterior Cingulum	0.57	-0.02	-3.4
2	2	Left Posterior Cingulum	0.51	0	0
2	2	Right Anterior Cingulum	0.52	0.01	1.93
2	2	Right Posterior Cingulum	0.58	0.01	1.76
2	2	Left CST Brainstem Region	0.41	0	0

2	2	Left CST Cortical Region	0.37	0	0
2	2	Left CST Mid-Region	0.66	-0.01	-1.49
2	2	Right CST Brainstem Region	0.44	-0.01	-2.21
2	2	Right CST Cortical Region	0.46	0.01	2.23
2	2	Right CST Mid-Region	0.7	0.01	1.45
2	2	Left Anterior IFOF	0.43	-0.01	-2.24
2	2	Left IFOF Mid-Region	0.5	-0.01	-1.96
2	2	Left Posterior IFOF	0.4	-0.01	-2.42
2	2	Right Anterior IFOF	0.44	0	0
2	2	Right IFOF Mid-Region	0.49	0.02	4.27
2	2	Right Posterior IFOF	0.45	0.01	2.24
2	2	Left OR Cortical Region	0.43	-0.02	-4.45
2	2	Left OR Mid-Region	0.5	-0.01	-1.93
2	2	Left OR Thalamic Region	0.53	-0.01	-1.86
2	2	Right OR Cortical Region	0.41	0	0
2	2	Right OR Mid-Region	0.54	-0.01	-1.84
2	2	Right OR Thalamic Region	0.52	0.01	1.96
2	2	Left Anterior TPOL	0.51	-0.01	-1.94
2	2	Left TPOL Mid-Region	0.5	-0.02	-3.87
2	2	Left Posterior TPOL	0.42	-0.02	-4.56
2	2	Right Anterior TPOL	0.52	0.01	1.97
2	2	Right TPOL Mid-Region	0.53	-0.01	-1.86
2	2	Right Posterior TPOL	0.43	0	0
2	2	Left Anterior TPFC	0.39	-0.01	-2.54
2	2	Left TPFC Mid-Region	0.58	-0.01	-1.71
2	2	Left Posterior TPFC	0.38	-0.01	-2.51
2	2	Right Anterior TPFC	0.35	0	0
2	2	Right TPFC Mid-Region	0.57	0	0
2	2	Right Posterior TPFC	0.29	0	0