

Conserved Thalamic Astrocytic Pathology in Mice and Patients

Links TBI to Epilepsy

Federico Moro^{1†}, Ilaria Lisi^{1†}, Edward Needham², Elaine O'Loughlin³, Rossella Di Sapia¹, Karthik Chary⁴, Stefano Fabrizio Columbro⁵, Anastasia Lubarsky², Luther Loose¹, Edoardo Mazzone¹, Sam Husarik⁶, Karinn Sytsma⁶, Firas Kobeissy⁷, Edoardo Micotti⁵, Annamaria Vezzani¹, Virginia F.J. Newcombe⁴, Emmanuel A. Stamatakis⁴, Valentina Bonetto⁵, Teresa Ravizza¹, Laura Lubbers³, Kevin K. W. Wang⁷, William E. Haskins⁸, the CENTER-TBI Participants and Investigators, Amber L. Nolan^{6*}, David K. Menon^{4*}, Elisa R. Zanier^{1*}

[†] **Equal contribution first-author**

*** Co-last authors**

Author affiliations:

¹ Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.

² Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

³ CURE Epilepsy, Chicago, IL, USA.

⁴ Perioperative, Acute, Critical Care and Emergency Medicine (PACE) Section, Department of Medicine, University of Cambridge, Cambridge, UK.

⁵ Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.

⁶ Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA.

⁷ Center for Neurotrauma, MultiOmics and Biomarkers, Morehouse School of Medicine, Atlanta, GA, USA.

⁸ Gryphon Bio, South San Francisco, CA, USA & Owl Therapeutics, Cambridge, MA, USA.

Correspondence to: Elisa R. Zanier

Address: Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.

Email: elisa.zanier@marionegri.it

Supplementary materials

MRI acquisition and analysis in mice

MRI was performed under isoflurane anesthesia as previously describe using a 7T small-bore animal scanner (BioSpec®; Bruker, Ettlingen, Germany) running ParaVision 6.01 with a quadrature 1H CryoProbe™ (Bruker, Ettlingen, Germany) surface coil. For ¹H-MRS two actively decoupled radio frequency (RF) coils were used: a volume coil of 7.2 cm diameter used as the transmitter and a surface coil as the receiver

DTI acquisition: echo-planar imaging sequences were acquired (TR/TE = 7000/32msec, resolution 125×125μm²; FOV 1.5×1.5cm²; acquisition matrix 120×120, slice thickness 0.3mm). Diffusion encoding b factors of 800 mm²/s were applied along 19 isotropic directions and two B0 unweighted images for each repetition. Analysis: the diffusion tensor was computed using FSL software. A group mean full tensor template was first created with a population-based DTI atlas construction algorithm that uses a tensor-based registration procedure embedded in the DTI-TK software as previously described¹. The mean value of each DTI metric for each mouse was calculated through a region of interest (ROI) analysis. ROIs were initially drawn on a template and subsequently inspected at the single-subject level by a trained operator to ensure accuracy.

Anatomical images. Anatomical images were acquired using 3D fast low-angle shot magnetic resonance imaging (FLASH) sequence (TR/TE 250/3ms; Flip angle 15°; image resolution 100×100×100μm³; FOV 3×0.8×1.1cm²; acquisition matrix 300×80×110). After the creation of an in-house set of mouse brain atlases as previously described¹, a multi-atlas segmentation approach was adopted, using the antsJointLabelFusion.sh script embedded in the ANTs software library.

¹H-MRS. A short echo times was performed using a Point Resolved Spectroscopy Sequence as previously described (repetition time TR/TE = 2500/10ms, 512 scans, spectral width 20ppm, 8192 points). Each measurement was carried out in a single voxel of 2.2×1.5×2mm positioned in the ipsilateral thalamus. Water suppression was performed with VAPOR and first and second order shims were adjusted using FASTMAP (Fast, Automatic Shimming technique by Mapping Along Projections). ¹H-MRS spectra were quantified using TARQUIN 4.2.1. The amplitudes of the metabolites signals obtained by the fit that had a Cramer-Raolower bound higher than 35% were excluded from the results. Relative metabolites levels were then derived by scaling the fitted amplitudes by the amplitude of the total Creatine (tCr: Cr +phospho Cr). ¹H-MRS spectra were quantified using TARQUIN 4.2.1 for the estimation of metabolites levels². Each spectrum was pre-processed by applying automated zero-order phasing and referencing, and by performing residual water line removal with the HSVD method. The processed signal was fit to a linear combination of selected metabolites. The reliability and quality of the fitting procedure was assessed both by visual inspection and by checking the quality parameter Q retrieved by TARQUIN. The mean value of Q was included between 1.15 and 1.3, indicating a very high fit quality (Q=1 corresponds to a perfect fit).

Histology acquisition and quantification in mice

Two FFPE brain sagittal sections were analyzed per marker and animal at 20x with an Olympus BX-61-VS microscope (Olympus, Tokyo, Japan) with 10% overlap for stitching, z-axis 5μm (step size 1μm) or 60x with Nikon A1 confocal scan unit managed by the NIS elements software with 10% overlap for stitching, z-axis 8μm (step size 0.6μm).

Pixel thresholder was set to a downsampling rate of 2.00, smoothing sigma 0, and threshold ranging from 0.25-0.35. Minimum object size was set to 40μm to eliminate background noise. Following an automated phase, objects were manually pruned to include only cells with an identifiable soma. The cell count

obtained through this process was then expressed as number of cells per $100'000\mu\text{m}^2$ to normalize for variations in ROI size.

MRI structural and functional preprocessing in patients

Skull stripping of structural T1w data was performed using the ANTs (v2.5.3)³ antsBrainExtraction workflow with OASIS30ANTs as the target template. Brain tissue segmentation into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) was performed on the skull-stripped T1w reference using FSL FAST⁴. T1w images were non-linearly registered to the MNI152NLin2009cAsym standard template (ICBM 152 Nonlinear Asymmetrical version 2009c) using TemplateFlow v24.2.0⁵ at 2 mm isotropic resolution using antsRegistration. Susceptibility distortion correction (SDC) was performed using fMRIPrep's fieldmap-less approach for all subjects. A deformation field was estimated by co-registering the EPI reference to the same-subject T1w with inverted intensity contrast^{6,7}, using ANTs SyN registration constrained to the phase-encoding direction and modulated with an average fieldmap template⁸.

One non-steady-state volume was identified in the fMRI data and discarded prior to further processing. Slice timing correction was applied to account for the sequential acquisition of slices across each TR. Head motion parameters (six rotation and translation parameters) were estimated using FSL MCFLIRT⁹ before any spatiotemporal filtering. The BOLD reference was co-registered to the T1w reference using mri_coreg (FreeSurfer) followed by FSL FLIRT(8) with boundary-based registration (six degrees of freedom)¹⁰. WM and CSF nuisance signals were estimated from MNI-space template probability masks (MNI152NLin2009cAsym, 2 mm; TemplateFlow)⁵ to provide a consistent mask definition across subjects and acquisition sites. The MNI WM mask was thresholded at a probability of ≥ 0.90 and eroded by two iterations to reduce partial-volume contamination from adjacent GM, while the CSF mask was thresholded at ≥ 0.90 and eroded by one iteration. In TBI patients, voxels within the eroded WM mask were additionally excluded if the corresponding fMRIPrep CSF probability map exceeded 0.50, thereby removing lesion cavities that were classified as WM in template space but identified as non-WM tissue in the subject-specific segmentation. This lesion-aware WM mask was used to minimise contamination of the WM nuisance regressor by signal arising from lesioned tissue. In healthy controls, this step removed zero voxels by design.

Motion-contaminated volumes were identified using a scrubbing approach¹². Volumes exceeding a framewise displacement (FD) threshold of 0.5 mm or a standardised DVARS threshold of 1.5 were flagged for censoring. Flagged volumes were then physically removed from the BOLD timeseries before functional connectivity extraction, and nuisance regressors, including motion parameters, were aligned to the retained volumes to preserve temporal alignment. The discrete cosine transform high-pass basis was recomputed for each subject's censored timeseries length. Subjects with fewer than 96 clean volumes remaining after censoring (approximately four minutes at the study TR) were excluded from all analyses¹³. BOLD images were resampled to MNI152NLin2009cAsym 2 mm space using a single interpolation step composing all transforms (motion correction, SDC, and co-registration to anatomical and output spaces), implemented with cubic B-spline interpolation via nitransforms. fMRIPrep outputs included per-volume framewise displacement (FD) and standardised DVARS timeseries, which were used for subsequent motion quality control. Mean FD was retained as a covariate in all group-level statistical models to account for residual between-subject variation in head motion.

Image Quality Control. For each subject, the following metrics were computed: T1w-to-MNI cross-correlation (ANTs MeasureImageSimilarity); BOLDref-to-T1w and BOLDref-to-MNI mutual information; and edge-correlation metrics between T1w, BOLDref, and MNI template edge images. In severe TBI, focal lesions and haemorrhage produce legitimate deviations from the MNI template that

would cause spurious failures on edge-correlation and segmentation entropy metrics when evaluated against healthy brain priors. These metrics were therefore treated as informational, and active exclusion decisions were based on registration similarity metrics (T1w→MNI cross-correlation; BOLDref→T1w and BOLDref→MNI mutual information) and WM nuisance mask adequacy. Outliers were identified using robust z-scores ($z = [x - \text{median}] / [1.4826 \times \text{MAD}]$, threshold $|z| > 3.5$), computed pooled across all subjects, within diagnostic group (patients vs controls), and within scanner vendor (GE/Philips/Siemens) separately; a subject was flagged if any layer exceeded the threshold. Additionally, subjects for whom fewer than 200 WM voxels remained after erosion and lesion exclusion were flagged, as the WM nuisance regressor would otherwise be estimated from an insufficient sample.

Thalamus-specific registration quality was additionally assessed by computing, within the projected thalamic atlas mask in MNI space: edge correlation between the subject's MNI-normalised T1w and the MNI template; Dice overlap between the binarised T1w image and the atlas mask; voxel count within the mask; and mean T1w signal intensity within the mask. The same three-layer robust z-score outlier detection procedure was applied. This thalamus-focused QC step directly validated registration quality in the primary region, i.e., thalamic nuclei for all downstream connectivity analyses.

Motion quality control and sample derivation. Head motion differed significantly across groups (one-way ANOVA: $F=10.18$, $p<0.001$). Mean FD was numerically higher in TBI (0.208 ± 0.144 mm) and PTE+ (0.462 ± 0.570 mm) relative to HC (0.151 ± 0.077 mm), though pairwise comparisons did not reach significance (TBI vs HC: $p=0.100$; PTE+ vs HC: $p=0.087$; Mann-Whitney U). Subjects were not excluded based on motion alone to avoid systematic sampling bias toward less severely injured patients; mean FD was instead included as a nuisance covariate in all subsequent analyses. Importantly, no significant correlation was observed between any motion metric and mean thalamocortical FC following denoising in any of the 16 thalamic seeds (all FDR $q>0.13$, max $r=0.26$), indicating that group differences in FC were not attributable to group differences in motion.

Multi-site harmonisation validation. To validate NeuroCombat harmonisation, Kruskal-Wallis tests were conducted on each thalamocortical FC feature (1600 features; 16 seeds $\times$ 100 parcels) and within-thalamus FC connection pair (120 pairs) before and after harmonisation, across 12 acquisition sites (one site with $n=1$ excluded). FDR correction was applied using the Benjamini-Hochberg procedure¹⁴ across features within each FC type. Before harmonisation, significant site differences were observed in 36/120 within-thalamus connection pairs (FDR $q<0.05$) and 255/1600 thalamocortical features (FDR $q<0.05$), confirming the need for site correction in this multi-centre dataset. Following NeuroCombat harmonisation, site differences were eliminated in both FC types (0/120 within-thalamus and 0/1600 thalamocortical), demonstrating effective removal of site-related variance without requiring exclusion of any acquisition site. Full validation results are provided in **Suppl. Table 4**.

Supplementary Tables

Suppl. Table 1. Demographic and clinical characteristics of human MRI cohort

	PTE(-)	PTE(+)
Demographics		
Number	124	10
Age (range)	44 (29-56)	39 (24-55)
% Male	60	69
TBI data		
Days from injury to MRI (range)	184 (177-195)	200 (185-212)
GCS Motor Score (Range)	6 (1-6)	4 (1-6)
Marshall Score		
1	52 (42)	3 (30)
2	48 (39)	2 (20)
3	2 (2)	0 (0)
4	0 (0)	0 (0)
5	0 (0)	0 (0)
6	17 (14)	4 (40)
Missing	5 (4)	1 (10)
Pupil reactivity		
Both reactive	118 (95)	10 (100)
One reactive	2 (2)	0 (0)
Both unreactive	4 (3)	0 (0)

MRI: magnetic resonance imaging; TBI: traumatic brain injury; TBI; PTE: post traumatic epilepsy.

Suppl. Table 2. Participant Demographics (Full Cohort pre-QC)

	Ctrl (n=75)	PTE(-) (n=32)	PTE(+) (n=14)	p-value
Age (mean ± SD)	41.7 ± 11.7	42.5 ± 18.1	43.4 ± 17.1	0.902 a
Sex (M/F)	44M / 31F	25M / 7F	11M / 3F	0.087 b
Days since injury, median (IQR)	N/A	174.0 (19.8–201.5)	204.0 (185.2–218.8)	0.013 c
GCS at baseline, median (IQR)	N/A	4.0 (3.0–7.0)	9.0 (4.2–13.5)	0.006 c

Ctrl: Healthy Controls; TBI: traumatic brain injury; PTE: post-traumatic epilepsy; IQR: interquartile range; GCS: Glasgow Coma Scale.

a One-way ANOVA (all three groups); b Chi-squared test (all three groups); c Mann-Whitney U test (PTE vs TBI only).

Suppl. Table 3. Participant Demographics (Days since injury-Matched Sample post-QC)

	Ctrl (n=65)	TBI, PTE- (n=14)	TBI, PTE+ (n=7)	p-value
Age (mean ± SD)	41.5 ± 11.5	37.9 ± 14.0	48.3 ± 17.3	0.198 a
Sex (M/F)	37M / 28F	10M / 4F	6M / 1F	0.235 b
Days since injury, median (IQR)	N/A	196.0 (184.8–214.5)	210.0 (193.5–236.0)	0.455 c
GCS at baseline, median (IQR)	N/A	5.0 (3.0–7.0)	9.0 (4.5–13.5)	0.080 c

Ctrl: Healthy Controls; TBI: traumatic brain injury; PTE: post traumatic epilepsy; IQR: interquartile range; GCS: Glasgow Coma Scale.

a One-way ANOVA; b Chi-squared test; c Mann-Whitney U test (PTE vs TBI only).

Suppl. Table 4. ComBat Harmonisation Validation

Kruskal-Wallis H statistics across 12 acquisition sites before and after NeuroCombat harmonisation. H is the Kruskal-Wallis test statistic (larger values indicate greater between-site variation). FDR correction by Benjamini-Hochberg. Bold values indicate FDR-significant effects ($q < 0.05$). ~ = nominally significant ($p < 0.05$, not FDR-corrected); ✓ = FDR-significant ($q < 0.05$). One site ($n=1$) was excluded from Kruskal-Wallis (requires ≥ 2 observations per site).

ROI / Connection Pair	Pre-ComBat				Post-ComBat			
	H	P	q	Sig.	H	P	q	Sig.
Part A: Thalamocortical FC (16 ROIs) 5/16 nominally significant pre-ComBat ($p < 0.05$); 0/16 FDR-significant. Post-ComBat: 0/16 significant.								
R-Pulvinar	27.05	0.005	0.072	~	2.764	0.994	>0.999	
R-mDorsal	23.38	0.016	0.086	~	3.011	0.991	>0.999	
L-Anterior	23.28	0.016	0.086	~	2.068	0.998	>0.999	
R-Thalamus	20.82	0.035	0.135	~	1.224	>0.999	>0.999	
L-mDorsal	19.72	0.049	0.135	~	1.090	>0.999	>0.999	
R-Anterior	19.22	0.057	0.135		1.625	0.999	>0.999	
L-Central	19.11	0.059	0.135		2.193	0.998	>0.999	
L-Pulvinar	16.82	0.113	0.207		1.868	0.999	>0.999	
L-Thalamus	16.72	0.116	0.207		0.620	>0.999	>0.999	
R-vAnterior	15.59	0.157	0.252		5.160	0.923	>0.999	
R-vlVentral	13.49	0.262	0.382		2.608	0.995	>0.999	
R-Central	12.41	0.333	0.411		3.004	0.991	>0.999	
L-vlVentral	12.40	0.334	0.411		2.134	0.998	>0.999	
L-vlDorsal	11.91	0.371	0.423		1.322	>0.999	>0.999	

R-vlDorsal	8.32	0.684	0.730		4.581	0.950	>0.999	
L-vAnterior	5.76	0.889	0.889		2.018	0.998	>0.999	
Part B: Within-Thalamus FC (120 pairs) 36/120 FDR-significant pre-ComBat. Post-ComBat: 0/120 significant.								
FDR-significant pairs (36/120), sorted by q:								
R-Pulvinar ↔ R-vlVentral	36.89	<0.001	0.013	✓	—	>0.05	>0.05	
R-Anterior ↔ R-vlVentral	34.50	<0.001	0.013	✓	—	>0.05	>0.05	
L-vlVentral ↔ R-Pulvinar	34.06	<0.001	0.013	✓	—	>0.05	>0.05	
L-mDorsal ↔ R-vlDorsal	33.61	<0.001	0.013	✓	—	>0.05	>0.05	
L-Anterior ↔ R-vlVentral	31.70	0.001	0.016	✓	—	>0.05	>0.05	
R-Anterior ↔ R-vlDorsal	31.44	0.001	0.016	✓	—	>0.05	>0.05	
R-Anterior ↔ L-Thalamus	31.95	0.001	0.016	✓	—	>0.05	>0.05	
L-Anterior ↔ L-vlDorsal	30.76	0.001	0.018	✓	—	>0.05	>0.05	
L-Anterior ↔ R-Thalamus	30.32	0.001	0.019	✓	—	>0.05	>0.05	
R-Anterior ↔ R-vAnterior	29.62	0.002	0.020	✓	—	>0.05	>0.05	
L-Pulvinar ↔ R-Anterior	29.86	0.002	0.020	✓	—	>0.05	>0.05	

L-vlDorsal ↔ R-Anterior	29.02	0.002	0.021	✓	—	>0.05	>0.05	
L-Anterior ↔ R-Pulvinar	28.69	0.003	0.021	✓	—	>0.05	>0.05	
R-Anterior ↔ R-Thalamus	28.64	0.003	0.021	✓	—	>0.05	>0.05	
R-mDorsal ↔ R-vlDorsal	29.16	0.002	0.021	✓	—	>0.05	>0.05	
L-vAnterior ↔ R-Anterior	28.27	0.003	0.022	✓	—	>0.05	>0.05	
R-Central ↔ R-vlVentral	28.06	0.003	0.022	✓	—	>0.05	>0.05	
L-Anterior ↔ L-mDorsal	27.87	0.003	0.022	✓	—	>0.05	>0.05	
L-Anterior ↔ L-Thalamus	27.76	0.004	0.022	✓	—	>0.05	>0.05	
L-Anterior ↔ L-Central	27.58	0.004	0.023	✓	—	>0.05	>0.05	
L-Central ↔ R-vlDorsal	27.02	0.005	0.024	✓	—	>0.05	>0.05	
L-mDorsal ↔ L-vlDorsal	27.10	0.004	0.024	✓	—	>0.05	>0.05	
L-vlDorsal ↔ L-Thalamus	26.99	0.005	0.024	✓	—	>0.05	>0.05	
L-Anterior ↔ L-vAnterior	26.62	0.005	0.026	✓	—	>0.05	>0.05	
R-vlDorsal ↔ L-Thalamus	26.10	0.006	0.030	✓	—	>0.05	>0.05	
L-Central ↔ R-Anterior	25.90	0.007	0.031	✓	—	>0.05	>0.05	

L-Anterior ↔ R-vlDorsal	25.81	0.007	0.031	✓	—	>0.05	>0.05	
L-vlVentral ↔ R-Anterior	25.32	0.008	0.035	✓	—	>0.05	>0.05	
L-mDorsal ↔ R-Anterior	25.20	0.009	0.035	✓	—	>0.05	>0.05	
R-vlVentral ↔ R-Thalamus	24.87	0.010	0.038	✓	—	>0.05	>0.05	
L-vlVentral ↔ R-Central	24.49	0.011	0.042	✓	—	>0.05	>0.05	
R-Pulvinar ↔ R-vlDorsal	24.08	0.012	0.045	✓	—	>0.05	>0.05	
L-Anterior ↔ R-Central	24.07	0.012	0.045	✓	—	>0.05	>0.05	
L-mDorsal ↔ L-vAnterior	23.74	0.014	0.049	✓	—	>0.05	>0.05	
R-vlDorsal ↔ R-Thalamus	23.65	0.014	0.049	✓	—	>0.05	>0.05	
L-vlDorsal ↔ R-mDorsal	23.54	0.015	0.049	✓	—	>0.05	>0.05	

Non-significant pairs (84/120): all $p>0.05$, $q>0.05$ before and after ComBat - not shown for brevity.

Suppl. Table 5. Demographic and clinical characteristics of human brain donors

	Ctrl	PTE(-)	PTE(+)
Demographics			
Number	13	12	11
Age (SD)	51.0 (8.6)	48.2 (9.5)	48.7 (12.8)
% Male	77	92	82
TBI data			
Years post injury	--	10 (10)	22 (14)
Histopathology			
% Contusion	0%	17%	55%
% + CTE	0%	33%	27%
% $\geq$ ADRC intermediate	0%	0%	0%
% + LBD	0%	17%	0%
% + TDP-43	0%	0%	18%

Ctrl: Healthy Controls; PTE: post traumatic epilepsy; CTE: chronic traumatic encephalopathy; LBD: Lewy Body Deposition; PTE: post traumatic epilepsy; SD: standard deviation; TBI: traumatic brain injury; TDP-43: TAR DNA-binding protein 43

Suppl. Table 6. Within-thalamus functional connectivity: full results

Fisher-z-transformed Pearson correlations modelled using linear mixed models ($FC \sim \text{group} \times \text{hemisphere} + \text{age} + \text{sex} + \text{mean FD} + \text{GCS}_{\text{baseline}} + (1|\text{subject})$). Cohen's d computed from per-hemisphere pairwise contrasts (positive = higher FC in TBI(all)/PTE(+) group). FDR correction by Benjamini-Hochberg. q = FDR-corrected p -value for main group effect. Bold values indicate FDR-significant effects ($q < 0.05$). Group $\times$ Hemisphere interaction q -values are reported inline where applicable. ns = not significant; — = not applicable (interhemispheric pairs have a single d value).

Connection pair	Ctrl vs TBI(all)			PTE(-) vs PTE(+)		
	d Left	d Right	q	d Left	d Right	q
<i>Pulvinar: hypothesis-driven (restricted FDR, 3 pairs)</i>						
Pulvinar↔Anterior	-0.484	-0.591	0.003	0.039	-0.122	0.177
Pulvinar↔mDorsal	-0.473	-0.644	0.020	-0.266	-0.009	0.031
Pulvinar↔Central	-0.070	0.059	0.118	-0.755	-0.599	0.023

<i>Pulvinar: exploratory (separate FDR, 5 pairs + interhemispheric)</i>						
Pulvinar↔Anterior	-0.484	-0.591	0.008	0.039	-0.122	0.177
Pulvinar↔mDorsal	-0.473	-0.644	0.030	-0.266	-0.009	0.029
Pulvinar↔Central	-0.070	0.059	0.138	-0.755	-0.599	0.020
Pulvinar↔vlDorsal	-0.006	-0.148	0.087	-0.542	0.152	0.023
Pulvinar↔vlVentral	-0.139	-0.429	0.023	-0.147	-0.024	0.120
Pulvinar↔vAnterior	0.211	-0.494	0.442	-1.010	0.166	0.020
Group $\times$ Hemisphere	$q=0.014$	-	-	-		
Pulvinar↔Pulvinar (interhemispheric)	-0.315		0.138	-1.020		0.005

<i>Other nuclei: hypothesis-driven (restricted FDR, 3 pairs)</i>						
mDorsal↔Anterior	-0.461	-0.516	0.359	-0.049	-0.961	0.753

mDorsal↔Central	-0.241	-0.203	0.450	-0.358	-0.282	0.502
Anterior↔Central	0.115	0.074	0.450	0.091	-0.239	0.753

<i>Other nuclei: exploratory (separate FDR, 15 pairs)</i>						
mDorsal↔Anterior	-0.461	-0.516	0.313	-0.049	-0.961	0.753
mDorsal↔Central	-0.241	-0.203	0.514	-0.358	-0.282	0.314
Anterior↔Central	0.115	0.074	0.563	0.091	-0.239	0.753
mDorsal↔vlDorsal	-0.414	-0.691	0.313	-1.254	0.238	0.032
mDorsal↔vlVentral	-0.183	-0.369	0.313	0.169	0.123	0.753
mDorsal↔vAnterior	-0.266	-0.757	0.570	-1.071	-0.452	0.212
Anterior↔vlDorsal	-0.412	-0.383	0.313	0.146	0.417	0.753
Anterior↔vlVentral	0.066	0.126	0.520	0.210	-0.387	0.753
Anterior↔vAnterior	-0.355	-0.298	0.313	0.154	-0.399	0.753
Central↔vlDorsal	0.053	0.226	0.313	-0.748	0.093	0.032
Central↔vlVentral	0.058	0.353	0.313	-0.568	-0.173	0.212
Central↔vAnterior	0.231	0.297	0.832	-0.963	-0.226	0.212
vlDorsal↔vlVentral	0.035	-0.076	0.313	0.044	0.167	0.398
vlDorsal↔vAnterior	-0.087	-0.046	0.514	-0.970	-0.402	0.051
vlVentral↔vAnterior	0.172	-0.002	0.677	-0.629	-0.406	0.241

Suppl. Table 7. Thalamocortical functional connectivity - full results

Fisher-z-transformed Pearson correlations modelled using linear mixed models ($FC \sim \text{group} \times \text{hemisphere} + \text{age} + \text{sex} + \text{mean FD} + \text{GCS}_{\text{baseline}} + (1|\text{subject})$). Cohen's d computed from per-hemisphere pairwise contrasts (positive = higher FC in TBI(all)/PTE(+) group). FDR correction by Benjamini–Hochberg (restricted FDR within each seed set for hypothesis-driven analyses; separate FDR across all parcels for exploratory analyses). q = FDR-corrected p -value for main group effect. Bold values indicate FDR-significant effects ($q < 0.05$). — = not tested in this contrast. CC: anterior cingulate cortex; MTL: medial temporal lobe; PostParietal: posterior parietal cortex; Vis = Visual network; Default = Default Mode Network; Temp: temporal cortex network; pCunPCC: precuneus/posterior cingulate cortex network.

Seed	ROI	HC vs TBI(all)			PTE(-) vs PTE(+)		
		d Left	d Right	q	d Left	d Right	q
<i>Pulvinar seeds × hypothesis-driven ROIs (restricted FDR, 6 pairs)</i>							
L-Pulvinar	MTL	-0.035	-0.241	0.187	-0.631	0.221	0.398
L-Pulvinar	ACC	-0.335	-0.405	0.175	0.077	0.792	0.740
L-Pulvinar	PostParietal	-0.345	-0.326	0.120	-0.236	0.243	0.645
R-Pulvinar	MTL	-0.446	-0.370	0.120	0.042	-0.022	0.795
R-Pulvinar	ACC	-0.487	-0.574	0.120	0.512	0.663	0.645
R-Pulvinar	PostParietal	-0.748	-0.560	0.068	0.598	0.183	0.645

<i>Other nuclei × hypothesis-driven ROIs (restricted FDR, 18 pairs)</i>							
L-mDorsal	MTL	-0.124	-0.114	0.914	0.063	-0.068	0.780
L-mDorsal	ACC	-0.268	-0.402	0.914	0.363	0.729	0.510
L-mDorsal	PostParietal	-0.365	-0.273	0.914	0.341	0.138	0.693
R-mDorsal	MTL	-0.613	-0.711	0.914	-0.034	0.008	0.780
R-mDorsal	ACC	-0.700	-0.750	0.914	0.679	-0.054	0.510
R-mDorsal	PostParietal	-0.626	-0.697	0.914	0.226	-0.047	0.693
L-Anterior	MTL	0.073	-0.080	0.940	0.317	0.195	0.693

L-Anterior	ACC	-0.211	-0.346	0.940	0.464	0.511	0.510
L-Anterior	PostParietal	-0.085	0.023	0.914	0.459	0.515	0.693
R-Anterior	MTL	0.029	-0.161	0.940	0.088	-0.001	0.693
R-Anterior	ACC	-0.240	-0.319	0.914	0.216	0.044	0.693
R-Anterior	PostParietal	-0.124	-0.061	0.914	0.232	0.274	0.693
L-Central	MTL	0.135	0.204	0.940	-0.507	0.100	0.693
L-Central	ACC	-0.012	-0.186	0.940	0.394	0.826	0.510
L-Central	PostParietal	-0.129	-0.062	0.914	0.121	0.457	0.693
R-Central	MTL	0.350	0.140	0.940	0.009	0.090	0.693
R-Central	ACC	0.181	-0.023	0.940	0.243	0.378	0.693
R-Central	PostParietal	-0.012	0.001	0.914	0.188	0.256	0.693

<i>L-Pulvinar × all cortical parcels: PTE(−) vs PTE(+): FDR-significant parcels (HC vs TBI(all): all null)</i>							
L-Pulvinar	Vis_1	—	—	—	-1.103	-1.481	0.027
L-Pulvinar	Vis_2	—	—	—	-0.808	-0.981	0.045
L-Pulvinar	Vis_3	—	—	—	-1.487	-1.307	0.007
L-Pulvinar	Vis_4	—	—	—	-1.341	-1.210	0.018
L-Pulvinar	Vis_5	—	—	—	-1.018	-1.140	0.007
L-Pulvinar	Vis_7	—	—	—	-1.284	-1.435	0.006
L-Pulvinar	Vis_8	—	—	—	-1.226	-0.252	0.045
L-Pulvinar	Default_Temp_2	—	—	—	-0.803	-0.109	0.045
L-Pulvinar	Default_pCunPCC_1	—	—	—	-1.617	-0.904	0.006

All other seeds × all cortical parcels: exploratory (all null)

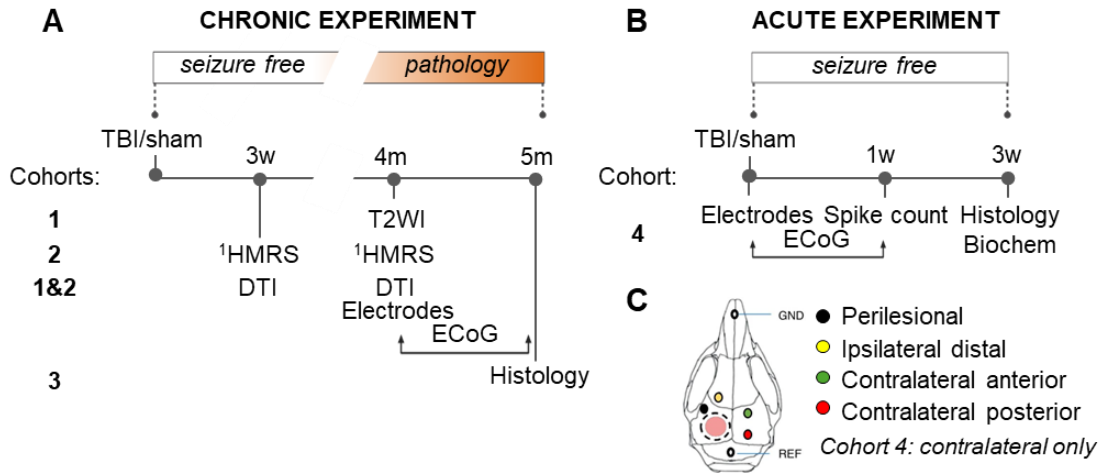
L/R-Pulvinar (Ctrl vs TBI(all)), L/R-mDorsal, L/R-Anterior, L/R-Central, R-Pulvinar PTE(-) vs PTE(+): no parcels survived FDR correction in any contrast. R-Central HC vs TBI(all): parcels with $p < 0.10$ shown in supplementary figure but none FDR-significant (q all > 0.50).

Suppl. Table 8. Corticocortical functional connectivity: full results

Fisher-z-transformed Pearson correlations modelled using linear mixed models ($FC \sim \text{group} \times \text{hemisphere} + \text{age} + \text{sex} + \text{mean_FD} + \text{GCS_baseline} + (1|\text{subject})$). Three composite ROI pairs tested. Cohen's d computed from per-hemisphere pairwise contrasts (positive = higher FC in TBI(all)/PTE+ group). FDR correction by Benjamini–Hochberg. q = FDR-corrected p -value for main group effect; q (inter.) = FDR-corrected p -value for Group×Hemisphere interaction. No pairs survived FDR correction in either contrast.

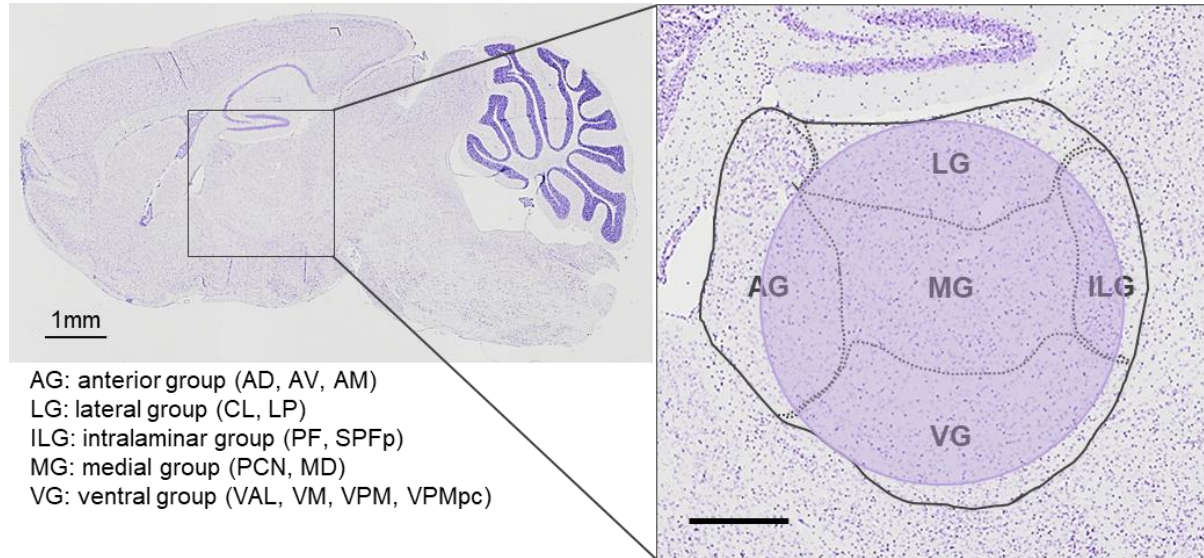
ROI pair	HC vs TBI(all)				TBI, PTE- vs TBI, PTE+			
	d Left	d Right	q	q (inter.)	d Left	d Right	q	q (inter.)
MTL↔ACC	0.185	-0.174	0.907	0.369	-0.015	0.320	0.816	0.847
MTL↔PostParietal	-0.395	0.155	0.498	0.093	-0.063	-0.063	0.816	0.987
ACC↔PostParietal	-0.187	0.042	0.907	0.377	-0.069	0.197	0.816	0.847

Supplementary Figures



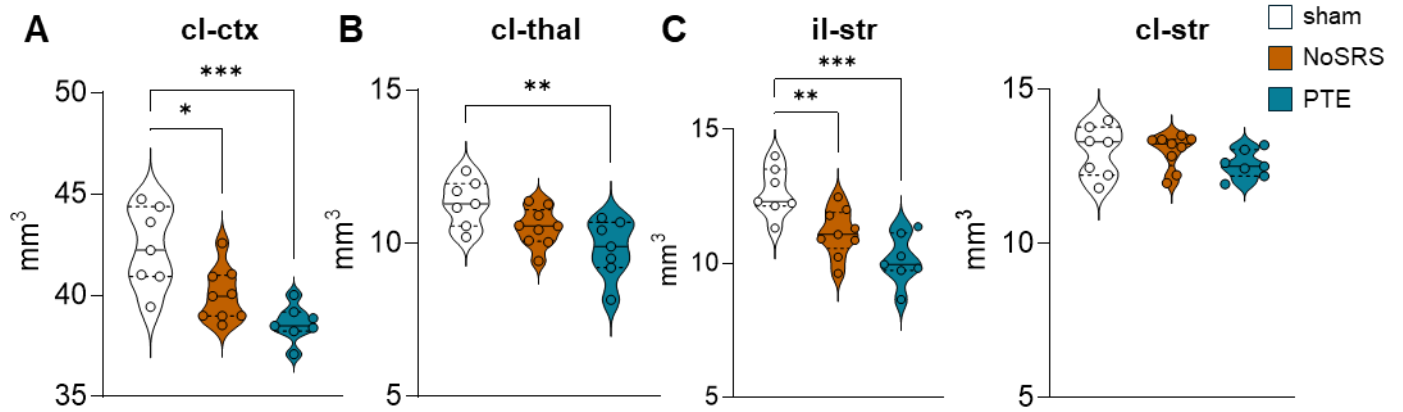
Suppl. Fig 1. Experimental design. (A) Schematic representation of the study design for the chronic experiment; (B) Schematic representation of the study design for the acute experiment. TBI was induced by CCI on the left parieto-temporal cortex in anesthetized CD1 mice. (C) Schematic representation of electrode placement in respect to injury site (large pink dot and dotted line).

¹HMRS: one-proton magnetic resonance spectroscopy; Biochem: biochemistry; DTI: diffusion tensor imaging; ECoG: Electrocorticography; GND: ground; REF: reference; T2WI: T2 weighted imaging; TBI: traumatic brain injury; w: week; m: month.



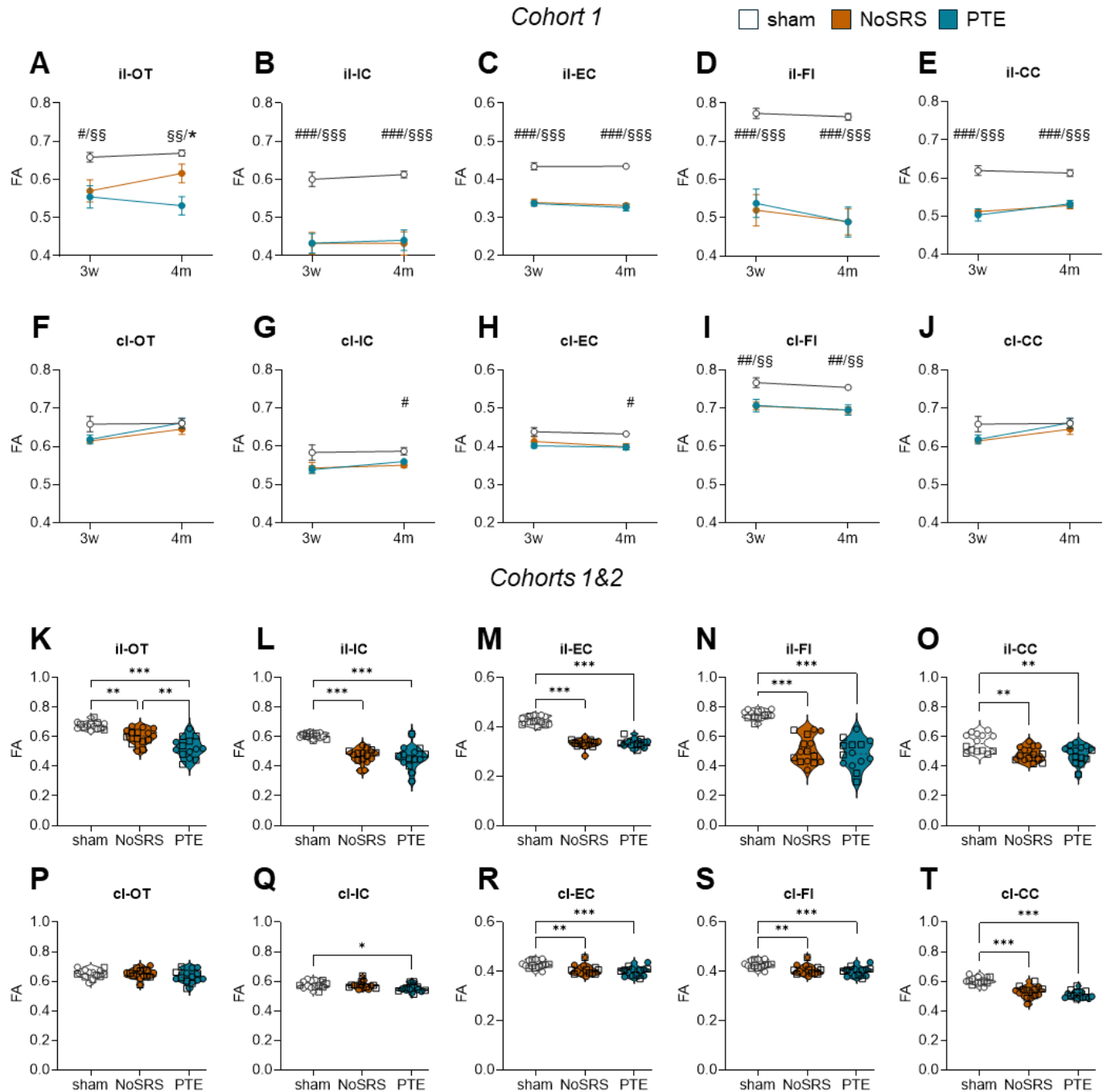
Suppl. Fig. 2. Definition of thalamic nuclei. Overview panel illustrates the mediolaterality analyzed. The inset (20× magnification) highlights the thalamic regions examined, with major thalamic groups outlined, and region of interest quantified coloured in purple. All thalamic groups indicated were included in the immunohistochemical analyses.

AG: anterior group, AD: anterior dorsal nucleus, AM: anterior medial nucleus, AV: anterior ventral nucleus, CL: central lateral nucleus, ILG: intralaminar group, LG: lateral group, LP: lateral posterior nucleus, MD: mediodorsal nucleus, MG: medial group, PCN: paracentral nucleus, PF: parafascicular nucleus, SPFp: suprafascicular nucleus - parvicellular part, VAL: ventral anterior lateral complex, VG: ventral group, VM: ventromedial nucleus, VPM: ventroposterior medial nucleus, VPMpc: ventroposterior medial nucleus - parvicellular part.



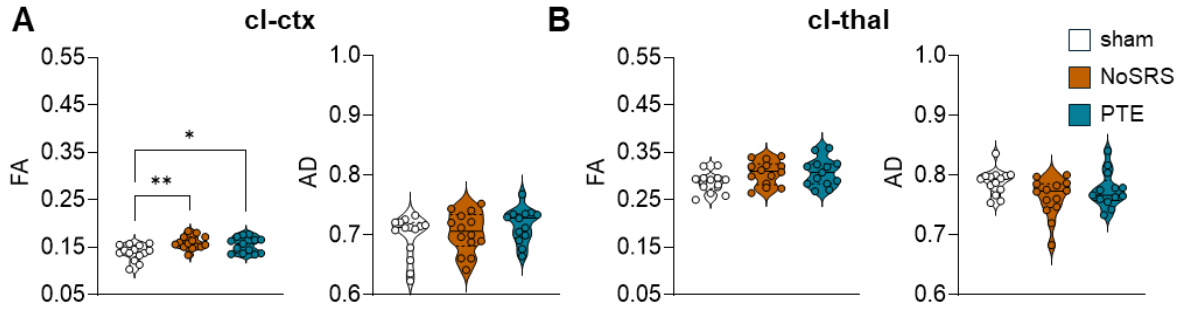
Suppl. Fig. 3. Structural MRI. (A-C) Volumetric analyses of the **(A)** cl-ctx, **(B)** cl-thal, **(C)** il-str and cl-str 4 months after TBI. Data are mean $\pm$ SEM. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ One-way ANOVA, Tukey post-hoc test.

cl: contralateral; ctx: cortex; il: ipsilateral; NoSRS: no spontaneous recurrent seizures; PTE: post-traumatic epilepsy; str: striatum; TBI: traumatic brain injury; thal: thalamus.



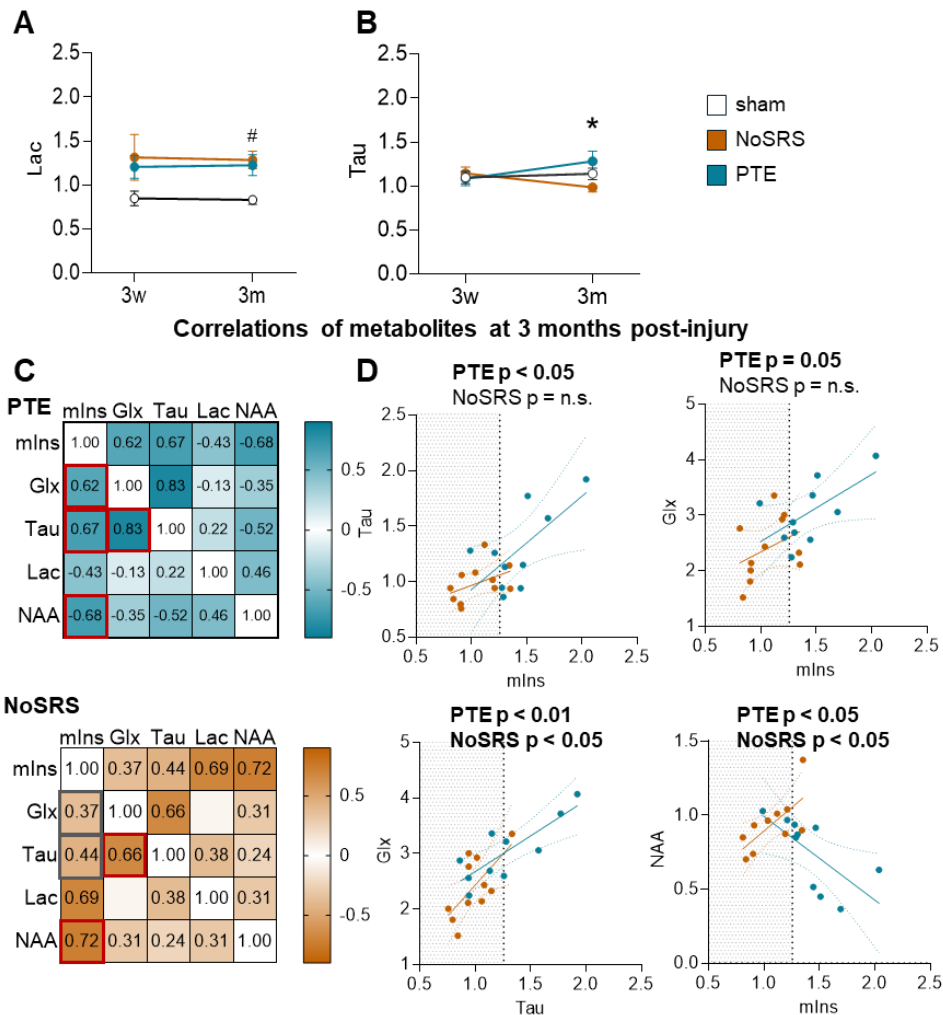
Suppl. Fig 4. PTE mice display widespread white matter damage at 4m but not 3w post TBI. (A-J) Longitudinal evaluation of white matter FA at 3w and 4m in Cohort 1. Data are mean $\pm$ SEM. #PTE vs sham, §NoSRS vs sham, *PTE vs NoSRS. Mixed Effects Model, Tukey post-hoc test. **(K-T)** Assessment of white matter FA at 4m in Cohort 1 (dots) and 2 (squares) indicating more widespread white matter damage in PTE vs sham mice. Data are mean $\pm$ SEM. ***p<0.001, **p<0.01, *p<0.05 One-way ANOVA, Tukey post-hoc test.

cl: contralateral; CC: corpus callosum; EC: external capsule; FA: fractional anisotropy; FI: fimbria; IC: internal capsule; il: ipsilateral; NoSRS: no spontaneous recurrent seizures; OT: optic tract; PTE: post-traumatic epilepsy.



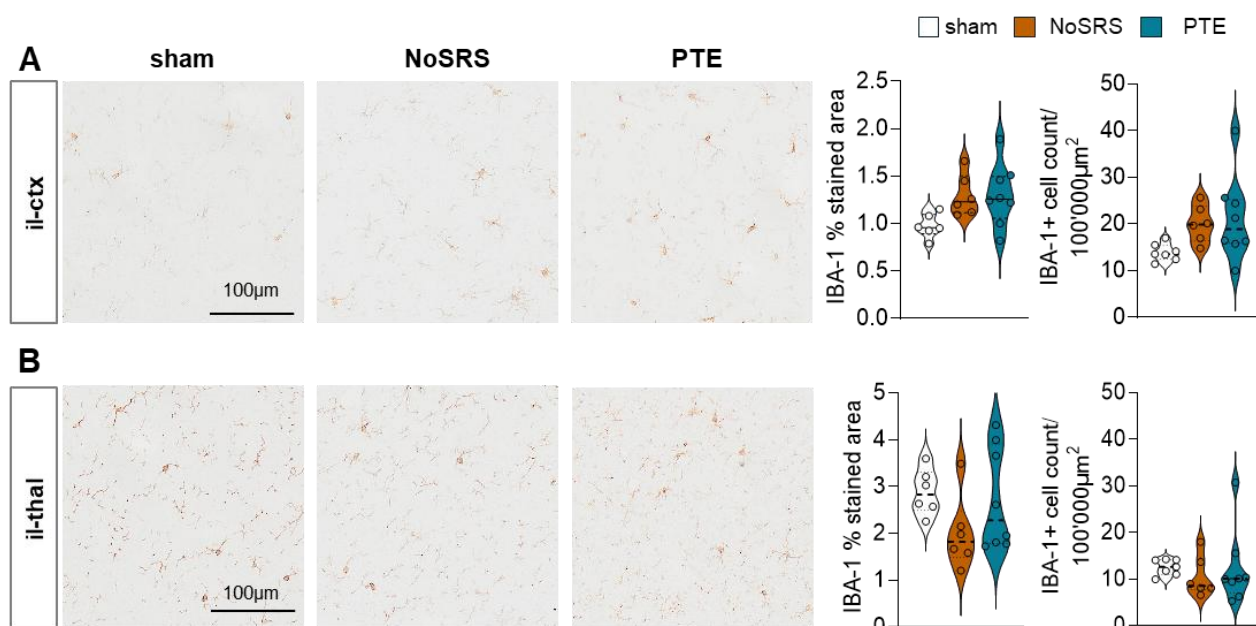
Suppl. Fig 5. PTE mice display changes in gray matter microstructure compatible with ongoing gliosis. **(A-B)** FA and AD measures in the **(A)** cl-ctx and **(B)** cl-thal 4m after TBI. Data are mean $\pm$ SEM. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ One-way ANOVA, Tukey post-hoc test.

AD: axial diffusivity; cl: contralateral; ctx: cortex; FA: fractional anisotropy; NoSRS: no spontaneous recurrent seizures; PTE: post-traumatic epilepsy; TBI: traumatic brain injury; thal: thalamus.

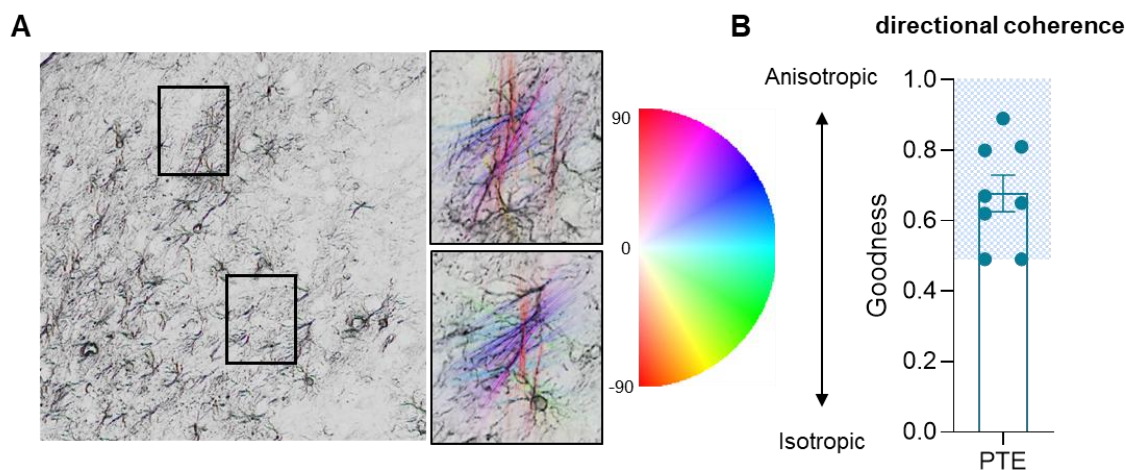


Suppl. Fig 6. ^1H MRS reveals alterations in thalamic neuron-astrocyte integrity in PTE mice. Quantification of **(A)** Lac and **(B)** Tau levels by in vivo ^1H MRS at 3w and 3m post injury. **(C)** Correlation matrices of metabolites in PTE (above) and NoSRS (below) mice and **(D)** scatterplots of significant correlations identified in each group. Data are mean $\pm$ SEM. # $p < 0.05$ NoSRS vs sham, * $p < 0.05$ PTE vs NoSRS; Mixed model effect, Tukey post-hoc test.

^1H MRS: one-proton magnetic resonance spectroscopy; AUC: area under the curve; Cr: creatinine; Glx: glutamate+glutamine; il: ipsilateral; m: months; mIns: myo-Inositol; mm: millimeters; NAA: N-acetyl aspartate; NoSRS: no spontaneous recurrent seizures; PTE: post-traumatic epilepsy; TBI: traumatic brain injury; thal: thalamus; w: weeks.

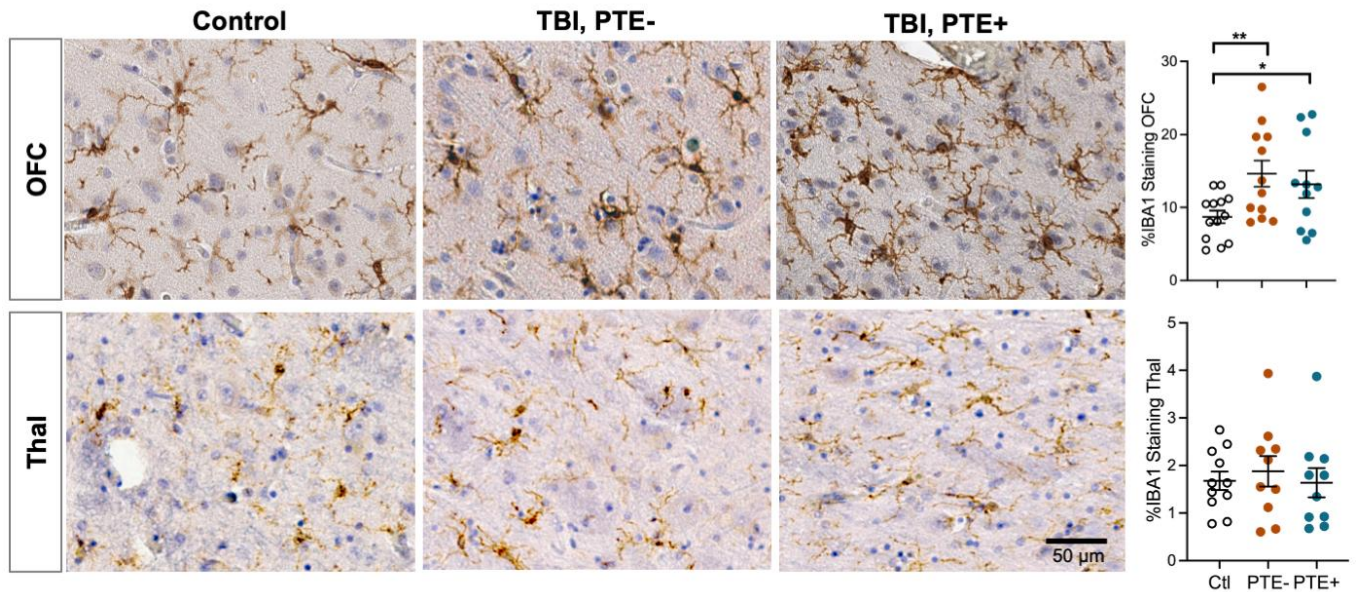


Suppl. Fig. 7. Microglial reactivity in the cortex and thalamus of PTE mice. (A-B) Representative images and quantification of IBA-1 stained area and IBA-1+ cell count in the il-ctx and il-thal 5m post-injury. Data are mean $\pm$ SEM. One-way ANOVA. ctx: cortex; il: ipsilateral; NoSRS: no spontaneous recurrent seizures; PTE: post-traumatic epilepsy; TBI: traumatic brain injury; thal: thalamus.

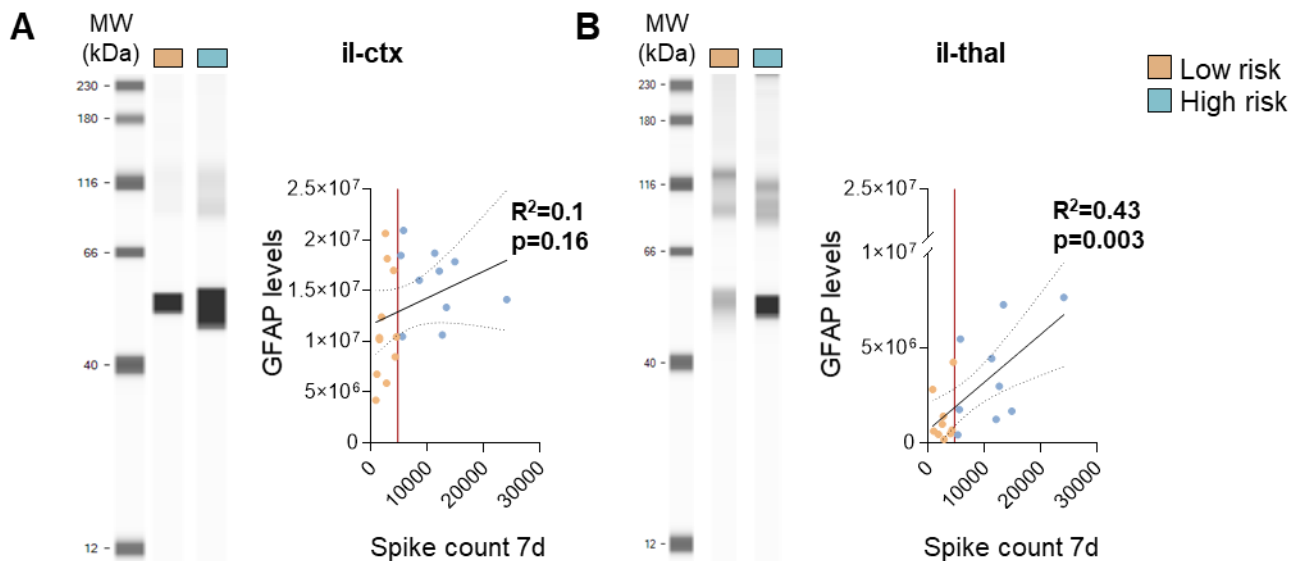


Suppl. Fig. 8. Directional coherence of GFAP positive astrocytes. (A) representative image of GFAP staining astrocyte in the il-thal. (B) Quantification of the goodness of orientation of GFAP positive cell. Blue mesh represents values with good coherence, indicating higher directional coherence of astrocytes resulting in anisotropic tissue properties. Data are mean $\pm$ SEM.

il: ipsilateral; PTE: post-traumatic epilepsy; TBI: traumatic brain injury; thal: thalamus.



Suppl. Fig. 9. *Changes in human microglial staining are not associated with post-traumatic epilepsy.* Representative images for IBA-1 immunostains across control, traumatic brain injury without epilepsy (PTE-) and traumatic brain injury with post-traumatic epilepsy (PTE+) conditions in both the OFC and Thal along with quantification of the percent area of staining (for OFC: $p = 0.0239$, one-way ANOVA and $*p=0.0496$ and $**p=0.0091$, post hoc test controlling for the false discovery rate; for Thal: $p = 0.8076$, one-way ANOVA). OFC: orbitofrontal cortex; PTE: post-traumatic epilepsy; TBI: traumatic brain injury; thal: thalamus.



Suppl. Fig. 10. *Insoluble GFAP levels.* (A) Representative image of JESS lane stained with anti-GFAP Ab and in the il-ctx of high and low risk mice and correlation with spike count at 7d post TBI. (B) Representative image of JESS lane stained with anti-GFAP Ab in the il-thal of high and low risk mice and correlation with spike count at 7d post TBI.

References

1. Moro F, Lisi I, Tolomeo D, et al. Acute Blood Levels of Neurofilament Light Indicate One-Year White Matter Pathology and Functional Impairment in Repetitive Mild Traumatic Brain Injured Mice. *J Neurotrauma*. 2023;40(11-12):1144-1163. doi:10.1089/neu.2022.0252
2. Pascente R, Frigerio F, Rizzi M, et al. Cognitive deficits and brain myo-Inositol are early biomarkers of epileptogenesis in a rat model of epilepsy. *Neurobiol Dis*. 2016;93:146-155. doi:10.1016/j.nbd.2016.05.001
3. Avants BB, Epstein CL, Grossman M, et al. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008;12(1):26-41.
4. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001;20(1):45-57.
5. Ciric R, Thompson WH, Lorenz R, et al. TemplateFlow: FAIR-sharing of multi-scale, multi-species brain models. *Nat Methods*. 2022;19(12):1568-1571.
6. Wang S, Peterson DJ, Gatenby JC, et al. Evaluation of Field Map and Nonlinear Registration Methods for Correction of Susceptibility Artifacts in Diffusion MRI. *Front Neuroinform*. 2017;11:17.
7. Huntenburg, Julia M. Evaluating Nonlinear Coregistration of BOLD EPI and T1w Images. Master's Thesis, Berlin: Freie Universität. 2014.
8. Treiber JM, White NS, Steed TC, et al. Characterization and Correction of Geometric Distortions in 814 Diffusion Weighted Images. *PLoS One*. 2016;11(3):e0152472.
9. Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825-841.
10. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5(2):143-156.
11. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*. 2009;48(1):63-72.
12. Power JD, Mitra A, Laumann TO, et al. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage*. 2014;84:320-341.
13. Birn RM, Molloy EK, Patriat R, et al. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage*. 2013;83:550-558.
14. Benjamini, Y. and Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*. 1995;57:289-300.

Appendix 1

The CENTER-TBI Participants and Investigators:

Cecilia Åkerlund¹, Krisztina Amrein², Nada Andelic³, Lasse Andreassen⁴, Audny Anke⁵, Anna Antoni⁶, Gérard Audibert⁷, Philippe Azouvi⁸, Maria Luisa Azzolini⁹, Ronald Bartels¹⁰, Pál Barzó¹¹, Romuald Beauvais¹², Ronny Beer¹³, Bo-Michael Bellander¹⁴, Antonio Belli¹⁵, Habib Benali¹⁶, Maurizio Berardino¹⁷, Luigi Beretta⁹, Morten Blaabjerg¹⁸, Peter Bragge¹⁹, Alexandra Brazinova²⁰, Vibeke Brinck²¹, Joanne Brooker²², Camilla Brorsson²³, Andras Buki²⁴, Monika Bullinger²⁵, Manuel Cabeleira²⁶, Alessio Caccioppola²⁷, Emiliana Calappi²⁷, Maria Rosa Calvi⁹, Peter Cameron²⁸, Guillermo Carbayo Lozano²⁹, Marco Carbonara²⁷, Simona Cavallo¹⁷, Giorgio Chevallard³⁰, Arturo Chierigato³⁰, Giuseppe Citerio^{31, 32}, Hans Clusmann³³, Mark Coburn³⁴, Jonathan Coles³⁵, Jamie D. Cooper³⁶, Marta Correia³⁷, Amra Čović³⁸, Nicola Curry³⁹, Endre Czeiter⁴⁰, Marek Czosnyka²⁶, Claire Dahyot-Fizelier⁴¹, Paul Dark⁴², Helen Dawes⁴³, Véronique De Keyser⁴⁴, Vincent Degos¹⁶, Francesco Della Corte⁴⁵, Hugo den Boogert¹⁰, Bart Depreitere⁴⁶, Đula Đilvesi⁴⁷, Abhishek Dixit⁴⁸, Emma Donoghue²², Jens Dreier⁴⁹, Guy-Loup Dulière⁵⁰, Ari Ercole⁴⁸, Patrick Esser⁴³, Erzsébet Ezer⁵¹, Martin Fabricius⁵², Valery L. Feigin⁵³, Kelly Foks⁵⁴, Shirin Frisvold⁵⁵, Alex Furmanov⁵⁶, Pablo Gagliardo⁵⁷, Damien Galanaud¹⁶, Dashiell Gantner²⁸, Guoyi Gao⁵⁸, Pradeep George⁵⁹, Alexandre Ghuysen⁶⁰, Lelde Giga⁶¹, Ben Glocker⁶², Jagoš Golubovic⁴⁷, Pedro A. Gomez⁶³, Johannes Gratz⁶⁴, Benjamin Gravesteijn⁶⁵, Francesca Grossi⁴⁵, Russell L. Gruen⁶⁶, Deepak Gupta⁶⁷, Juanita A. Haagsma⁶⁵, Iain Haitsma⁶⁸, Raimund Helbok^{69,70}, Eirik Helseth⁷¹, Lindsay Horton⁷², Jilske Huijben⁶⁵, Peter J. Hutchinson⁷³, Bram Jacobs⁷⁴, Stefan Jankowski⁷⁵, Mike Jarrett²¹, Ji-yao Jiang⁵⁹, Faye Johnson⁷⁶, Kelly Jones⁵³, Mladen Karan⁴⁷, Angelos G. Kolias⁷³, Erwin Kompanje⁷⁷, Daniel Kondziella⁵², Evgenios Kornaropoulos⁴⁸, Lars-Owe Koskinen⁷⁸, Noémi Kovács⁷⁹, Ana Kowark⁸⁰, Alfonso Lagares⁶³, Linda Lanyon⁵⁹, Steven Laureys⁸¹, Fiona Lecky^{82, 83}, Didier Ledoux⁸¹, Rolf Lefering⁸⁴, Valerie Legrand⁸⁵, Aurelie Lejeune⁸⁶, Leon Levi⁸⁷, Roger Lightfoot⁸⁸, Hester Lingsma⁶⁵, Andrew I.R. Maas^{44,89}, Ana M. Castaño-León⁶³, Marc Maegle⁹⁰, Marek Majdan²⁰, Alex Manara⁹¹, Geoffrey Manley⁹², Costanza Martino⁹³, Hugues Maréchal⁵⁰, Julia Mattern⁹⁴, Catherine McMahon⁹⁵, Béla Meleg⁹⁶, David Menon⁴⁸, Tomas Menovsky^{44,89}, Ana Mikolic⁶⁵, Benoit Misset⁸¹, Visakh Muraleedharan⁵⁹, Lynnette Murray²⁸, Ancuta Negru⁹⁷, David Nelson¹, Virginia Newcombe⁴⁸, Daan Nieboer⁶⁵, József Nyirádi², Otesile Olubukola⁸², Matej Oresic⁹⁸, Fabrizio Ortolano²⁷, Aarno Palotie^{99, 100, 101}, Paul M. Parizel¹⁰², Jean-François Payen¹⁰³, Natascha Perera¹², Vincent Perlberg¹⁶, Paolo Persona¹⁰⁴, Wilco Peul¹⁰⁵, Anna Piippo-Karjalainen¹⁰⁶, Matti Pirinen⁹⁹, Dana Pisica⁶⁵, Horia Ples⁹⁷, Suzanne Polinder⁶⁵, Inigo Pomposo²⁹, Jussi P. Posti¹⁰⁷, Louis Puybasset¹⁰⁸, Andreea Radoi¹⁰⁹, Arminas Ragauskas¹¹⁰, Rahul Raj¹⁰⁶, Malinka Rambadagalla¹¹¹, Isabel Retel Helmrich⁶⁵, Jonathan Rhodes¹¹², Sylvia Richardson¹¹³, Sophie Richter⁴⁸, Samuli Ripatti⁹⁹, Saulius Rocka¹¹⁰, Cecilie Roe¹¹⁴, Olav Roise^{115,116}, Jonathan Rosand¹¹⁷, Jeffrey V. Rosenfeld¹¹⁸, Christina Rosenlund¹¹⁹, Guy Rosenthal⁵⁶, Rolf Rossaint⁸⁰, Sandra Rossi¹⁰⁴, Daniel Rueckert⁶², Martin Rusnák¹²⁰, Juan Sahuquillo¹⁰⁹, Oliver Sakowitz^{94, 121}, Renan Sanchez-Porras¹²¹, Janos Sandor¹²², Nadine Schäfer⁸⁴, Silke Schmidt¹²³, Herbert Schoechl¹²⁴, Guus Schoonman¹²⁵, Rico Frederik Schou¹²⁶, Elisabeth Schwendenwein⁶, Charlie Sewalt⁶⁵, Ranjit D. Singh¹⁰⁵, Toril Skandsen^{127, 128}, Peter Smielewski²⁶, Abayomi Sorinola¹²⁹, Emmanuel Stamatakis⁴⁸, Simon Stanworth³⁹, Robert Stevens¹³⁰, William Stewart¹³¹, Ewout W. Steyerberg^{65, 132, 133}, Nino Stocchetti¹³⁴, Nina Sundström¹³⁵, Riikka Takala¹³⁶, Viktória Tamás¹²⁹, Tomas Tamosiutis¹³⁷, Mark Steven Taylor²⁰, Aurore Thibaut⁸¹, Braden Te Ao⁵³, Olli Tenovuo¹⁰⁷, Alice Theadom⁵³, Matt Thomas⁹¹, Dick Tibboel¹³⁸, Marjolein Timmers⁷⁷, Christos Tolia¹³⁹, Tony Trapani²⁸, Cristina Maria Tudora⁹⁷, Andreas Unterberg⁹⁴, Peter Vajkoczy¹⁴⁰, Shirley Vallance²⁸, Egils Valeinis⁶¹, Zoltán Vámos⁵¹, Mathieu van der Jagt¹⁴¹, Gregory

Van der Steen⁴⁴, Joukje van der Naalt⁷⁴, Jeroen T.J.M. van Dijk¹⁰⁵, Inge A. M. van Erp¹⁰⁵, Thomas A. van Essen¹⁰⁵, Wim Van Hecke¹⁴², Caroline van Heugten¹⁴³, Ernest van Veen⁶⁵, Thijs Vande Vyvere¹⁴⁴, Roel P. J. van Wijk¹⁰⁵, Alessia Vargiolu³², Emmanuel Vega⁸⁶, Kimberley Velt⁶⁵, Jan Verheyden¹⁴², Paul M. Vespa¹⁴⁵, Anne Vik^{127, 146}, Rimantas Vilcinis¹³⁷, Victor Volovici⁶⁸, Nicole von Steinbüchel³⁸, Daphne Voormolen⁶⁵, Petar Vulekovic⁴⁷, Kevin K.W. Wang¹⁴⁷, Daniel Whitehouse⁴⁸, Eveline Wiegers⁶⁵, Guy Williams⁴⁸, Lindsay Wilson⁷², Stefan Winzeck⁴⁸, Stefan Wolf¹⁴⁸, Zhihui Yang¹¹⁷, Peter Ylén¹⁴⁹, Alexander Younsi⁹⁴, Marina Zeldovich¹⁵⁰, Frederick A. Zeiler^{48,151}, Veronika Zelinkova²⁰, Agate Ziverte⁶¹, Tommaso Zoerle²⁷

¹ Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden

² János Szentágothai Research Centre, University of Pécs, Pécs, Hungary

³ Division of Clinical Neuroscience, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway

⁴ Department of Neurosurgery, University Hospital Northern Norway, Tromsø, Norway

⁵ Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromsø, Norway

⁶ Trauma Surgery, Medical University Vienna, Vienna, Austria

⁷ Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France

⁸ Raymond Poincaré hospital, Assistance Publique – Hôpitaux de Paris, Paris, France

⁹ Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy

¹⁰ Department of Neurosurgery, Radboud University Medical Center, Nijmegen, The Netherlands

¹¹ Department of Neurosurgery, University of Szeged, Szeged, Hungary

¹² International Projects Management, ARTTIC, München, Germany

¹³ Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria

¹⁴ Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska University Hospital, Stockholm, Sweden

¹⁵ NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK

¹⁶ Anesthésie-Réanimation, Assistance Publique – Hôpitaux de Paris, Paris, France

¹⁷ Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino - Orthopedic and Trauma Center, Torino, Italy

¹⁸ Department of Neurology, Odense University Hospital, Odense, Denmark

¹⁹ BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia

²⁰ Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia

²¹ Quesgen Systems Inc., Burlingame, California, USA

²² Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

²³ Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden

²⁴ Department of Neurosurgery, Örebro University and University Hospital, Örebro, Sweden

- ²⁵ Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
- ²⁶ Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
- ²⁷ Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
- ²⁸ ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia
- ²⁹ Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain
- ³⁰ NeuroIntensive Care, Niguarda Hospital, Milan, Italy
- ³¹ School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy
- ³² NeuroIntensive Care Unit, Department Neuroscience, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy
- ³³ Department of Neurosurgery, Medical Faculty RWTH Aachen University, Aachen, Germany
- ³⁴ Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany
- ³⁵ Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK
- ³⁶ School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia
- ³⁷ Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, UK
- ³⁸ Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany
- ³⁹ Oxford University Hospitals NHS Trust, Oxford, UK
- ⁴⁰ Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Hungary
- ⁴¹ Intensive Care Unit, CHU Poitiers, Poitiers, France
- ⁴² University of Manchester NIHR Biomedical Research Centre, Critical Care Directorate, Salford Royal Hospital NHS Foundation Trust, Salford, UK
- ⁴³ Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
- ⁴⁴ Department of Neurosurgery, Antwerp University Hospital, Edegem, Belgium
- ⁴⁵ Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy
- ⁴⁶ Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium
- ⁴⁷ Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
- ⁴⁸ Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
- ⁴⁹ Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
- ⁵⁰ Intensive Care Unit, CHR Citadelle, Liège, Belgium
- ⁵¹ Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary
- ⁵² Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Rigshospitalet, Copenhagen, Denmark
- ⁵³ National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand
- ⁵⁴ Department of Neurology, Erasmus MC, Rotterdam, the Netherlands
- ⁵⁵ Department of Anesthesiology and Intensive care, University Hospital Northern Norway, Tromsø, Norway
- ⁵⁶ Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel
- ⁵⁷ Fundación Instituto Valenciano de Neurorrehabilitación (FIVAN), Valencia, Spain

- ⁵⁸ Department of Neurosurgery, Shanghai Renji hospital, Shanghai Jiaotong University/school of medicine, Shanghai, China
- ⁵⁹ Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden
- ⁶⁰ Emergency Department, CHU, Liège, Belgium
- ⁶¹ Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia
- ⁶² Department of Computing, Imperial College London, London, UK
- ⁶³ Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain
- ⁶⁴ Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Austria
- ⁶⁵ Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, The Netherlands
- ⁶⁶ College of Health and Medicine, Australian National University, Canberra, Australia
- ⁶⁷ Department of Neurosurgery, Neurosciences Centre & JPN Apex trauma centre, All India Institute of Medical Sciences, New Delhi-110029, India
- ⁶⁸ Department of Neurosurgery, Erasmus MC, Rotterdam, the Netherlands
- ⁶⁹ Department of Neurology, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria.
- ⁷⁰ Clinical Research Institute for Neuroscience, Johannes Kepler University Linz, Linz, Austria
- ⁷¹ Department of Neurosurgery, Oslo University Hospital, Oslo, Norway
- ⁷² Division of Psychology, University of Stirling, Stirling, UK
- ⁷³ Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, Cambridge, UK
- ⁷⁴ Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
- ⁷⁵ Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
- ⁷⁶ Salford Royal Hospital NHS Foundation Trust Acute Research Delivery Team, Salford, UK
- ⁷⁷ Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
- ⁷⁸ Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden
- ⁷⁹ Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/8, University of Pécs, Pécs, Hungary
- ⁸⁰ Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany
- ⁸¹ Cyclotron Research Center, University of Liège, Liège, Belgium
- ⁸² Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK
- ⁸³ Emergency Department, Salford Royal Hospital, Salford UK
- ⁸⁴ Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany
- ⁸⁵ VP Global Project Management CNS, ICON, Paris, France
- ⁸⁶ Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France
- ⁸⁷ Department of Neurosurgery, Rambam Medical Center, Haifa, Israel
- ⁸⁸ Department of Anesthesiology & Intensive Care, University Hospitals Southampton NHS Trust, Southampton, UK
- ⁸⁹ Department of Translational Neuroscience, Faculty of Medicine and Health Science, University of Antwerp, Antwerp, Belgium
- ⁹⁰ Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany
- ⁹¹ Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK

- ⁹² Department of Neurological Surgery, University of California, San Francisco, California, USA
- ⁹³ Department of Anesthesia & Intensive Care, M. Bufalini Hospital, Cesena, Italy
- ⁹⁴ Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany
- ⁹⁵ Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK
- ⁹⁶ Department of Medical Genetics, University of Pécs, Pécs, Hungary
- ⁹⁷ Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania
- ⁹⁸ School of Medical Sciences, Örebro University, Örebro, Sweden
- ⁹⁹ Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
- ¹⁰⁰ Analytic and Translational Genetics Unit, Department of Medicine; Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
- ¹⁰¹ Program in Medical and Population Genetics; The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA
- ¹⁰² Department of Radiology, University of Antwerp, Edegem, Belgium
- ¹⁰³ Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France
- ¹⁰⁴ Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy
- ¹⁰⁵ Dept. of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands and Dept. of Neurosurgery, Medical Center Haaglanden, The Hague, The Netherlands
- ¹⁰⁶ Department of Neurosurgery, Helsinki University Central Hospital
- ¹⁰⁷ Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland
- ¹⁰⁸ Department of Anesthesiology and Critical Care, Pitié -Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France
- ¹⁰⁹ Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d'Hebron Research Institute, Barcelona, Spain
- ¹¹⁰ Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania
- ¹¹¹ Department of Neurosurgery, Rezekne Hospital, Latvia
- ¹¹² Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburgh, Edinburgh, UK
- ¹¹³ Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK
- ¹¹⁴ Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway
- ¹¹⁵ Division of Orthopedics, Oslo University Hospital, Oslo, Norway
- ¹¹⁶ Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
- ¹¹⁷ Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston MA, USA
- ¹¹⁸ National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
- ¹¹⁹ Department of Neurosurgery, Odense University Hospital, Odense, Denmark
- ¹²⁰ International Neurotrauma Research Organisation, Vienna, Austria
- ¹²¹ Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany
- ¹²² Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary
- ¹²³ Department Health and Prevention, University Greifswald, Greifswald, Germany
- ¹²⁴ Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Salzburg, Austria
- ¹²⁵ Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands

- ¹²⁶ Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark
- ¹²⁷ Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
- ¹²⁸ Department of Physical Medicine and Rehabilitation, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
- ¹²⁹ Department of Neurosurgery, University of Pécs, Pécs, Hungary
- ¹³⁰ Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA
- ¹³¹ Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK
- ¹³² Dept. of Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands
- ¹³³ Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
- ¹³⁴ Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
- ¹³⁵ Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden
- ¹³⁶ Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland
- ¹³⁷ Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania
- ¹³⁸ Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
- ¹³⁹ Department of Neurosurgery, Kings college London, London, UK
- ¹⁴⁰ Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany
- ¹⁴¹ Department of Intensive Care Adults, Erasmus MC– University Medical Center Rotterdam, Rotterdam, the Netherlands
- ¹⁴² icoMetrix NV, Leuven, Belgium
- ¹⁴³ Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
- ¹⁴⁴ Radiology Department, Antwerp University Hospital and University of Antwerp, Edegem, Belgium
- ¹⁴⁵ Director of Neurocritical Care, University of California, Los Angeles, USA
- ¹⁴⁶ Department of Neurosurgery, St.Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
- ¹⁴⁷ Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA
- ¹⁴⁸ Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
- ¹⁴⁹ VTT Technical Research Centre, Tampere, Finland
- ¹⁵⁰ Sigmund Freud University, Faculty of Psychotherapy Science, Vienna, Austria
- ¹⁵¹ Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada