

Supplementary Data

Post-acute blood biomarkers and disease progression in traumatic brain injury

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MRI Sequence Details:

Turku University Hospital Cohort

MR imaging was performed with a 3T MRI scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany). Diffusion MRI (dMRI) was performed using a spin-echo echo-planar imaging sequence with a repetition time of 11.7 s, echo time 106ms, $2 \times 2 \times 2$ mm voxel size resulting in 77 axial slices and a field of view of 192×192 mm. Sixty-four encoding directions uniformly distributed on a unit sphere with diffusion gradients of $b = 1000$ s/mm² were used. The T1 weighted sequence was a Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) sequence was acquired with parameters: TR 2300 ms, TE 2.98 ms, TI 900 ms, flip angle 9°, matrix size 256 x 249 x 176 and an isotropic voxel size of 1.0 x 1.0 x 1.0 mm, sagittal slices, using Prescan Normalizer 2D distortion correction. Additional acquired MRI sequences included Proton Density Weighted T2 (PD-T2), susceptibility weighted imaging (repetition time of 28ms, echo time 20ms and $0.6 \times 0.5 \times 1.2$ mm voxel size) and fluid attenuated inversion recovery (FLAIR).

Cambridge University Cohort

For the >5 year time point and associated controls MR imaging was performed with a 3T MRI scanner (Siemens Magnetom Prisma Fit Siemens Healthcare, Erlangen, Germany). The diffusion weighted sequence was a multi-band, multi-shell acquisition protocol with the following parameters: TR = 2433 ms, TE = 75 ms, flip angle = 80 degrees, voxel size = 1.75mm isotropic, 98 directions, with 3 diffusion shells at $b = 300$ s/mm² (8 directions), 1000 s/mm² (30 directions) and 2000 s/mm² (60 directions). The sequence included 5 $b = 0$ s/mm² interspersed throughout. Both the posterior to anterior and the anterior to posterior phase encoding directions were collected to correct for phase-encoding direction-induced distortions. The T1 weighted sequence was a Magnetization-Prepared Rapid Gradient-Echo

(MPRAGE) sequence was acquired with parameters: TR 2300 ms, TE 2.98 ms, TI 900 ms, flip angle 9°, matrix size 256 x 249 x 176 and an isotropic voxel size of 1.0 x 1.0 x 1.0 mm, sagittal slices, using Prescan Normalizer 2D distortion correction. Additional acquired MRI sequences included susceptibility weighted imaging (repetition time of 29ms, echo time 20ms and 0.5 × 0.5 × 2.0 mm voxel size), 3D T2 (voxel size 0.7 x 0.7 x 4.0 mm) and 3D fluid attenuated inversion recovery (FLAIR, voxel size 0.7 x 0.7 x 2.0 mm).

For the 12 patients and 15 controls who had longitudinal imaging the initial scanning was performed on a 3T MRI scanner (Siemens Magnetom Verio, Siemens Healthcare, Erlangen, Germany). The T1 weighted sequence was a Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) sequence was acquired with parameters: TR 2300 ms, TE 2.98 ms, TI 900 ms, flip angle 9°, matrix size 256 x 249 x 176 and an isotropic voxel size of 1.0 x 1.0 x 1.0 mm, sagittal slices, using Prescan Normalizer 2D distortion correction.

Machine Learning Model for Brain Age Regression

We employed three-dimensional, deep convolutional neural networks (CNNs) for brain age regression. The networks consist of two convolutional and three fully-connected layers. The outputs of the two convolutional layers and the first two fully-connected layers were passed through rectified linear unit activation functions. The convolutional layers used a kernel size of 5x5x5, stride of one, and no padding. Max pooling with a kernel size of 2 x 2 x 2 on the outputs of the convolutional layers was used to reduce the spatial dimensionality of the output feature maps. The number of feature maps for the two convolutional layers were 6 and 16, respectively. The number of output features for the three fully-connected layers were 120, 84, and 1, where the last output corresponds to the age prediction.

Age regression was performed on SPM12-derived whole brain grey matter (WBGM) and white matter (WBWM) probability maps, spatially normalized to MNI space. The WBGM and WBWM maps were extracted from the anatomical, T1-weighted brain MRI. As pre-processing step, we resample the input GM and WM probability maps to 96 x 96 x 96 with an isotropic voxel size of 2 x 2 x 2 mm. Two separate CNNs, one for WBGM and one for WBWM-based age regression were trained. We utilized the Cam-CAN dataset with 652 healthy controls for method development, where we used a random split of 600 subjects for model training, and 52 subjects for internal validation and parameter tuning. The CNNs were each trained for 100 epochs with a batch size of 16, resulting in about 3,700 iterations. We used the Adam optimizer with a learning rate of 0.001. The internal validation on the 52 subjects shows a mean absolute error of 5.03 and 6.20 years and an R^2 of 0.90 and 0.85 for the WBGM and WBWM models, respectively. The software implementations were done in Python (v3.8) using the deep learning framework PyTorch (v1.8.1) and machine learning library scikit-learn (v0.24.1). The software code for brain age regression will be available on GitHub (<https://github.com/biomediamira/brain-age-cnn>).

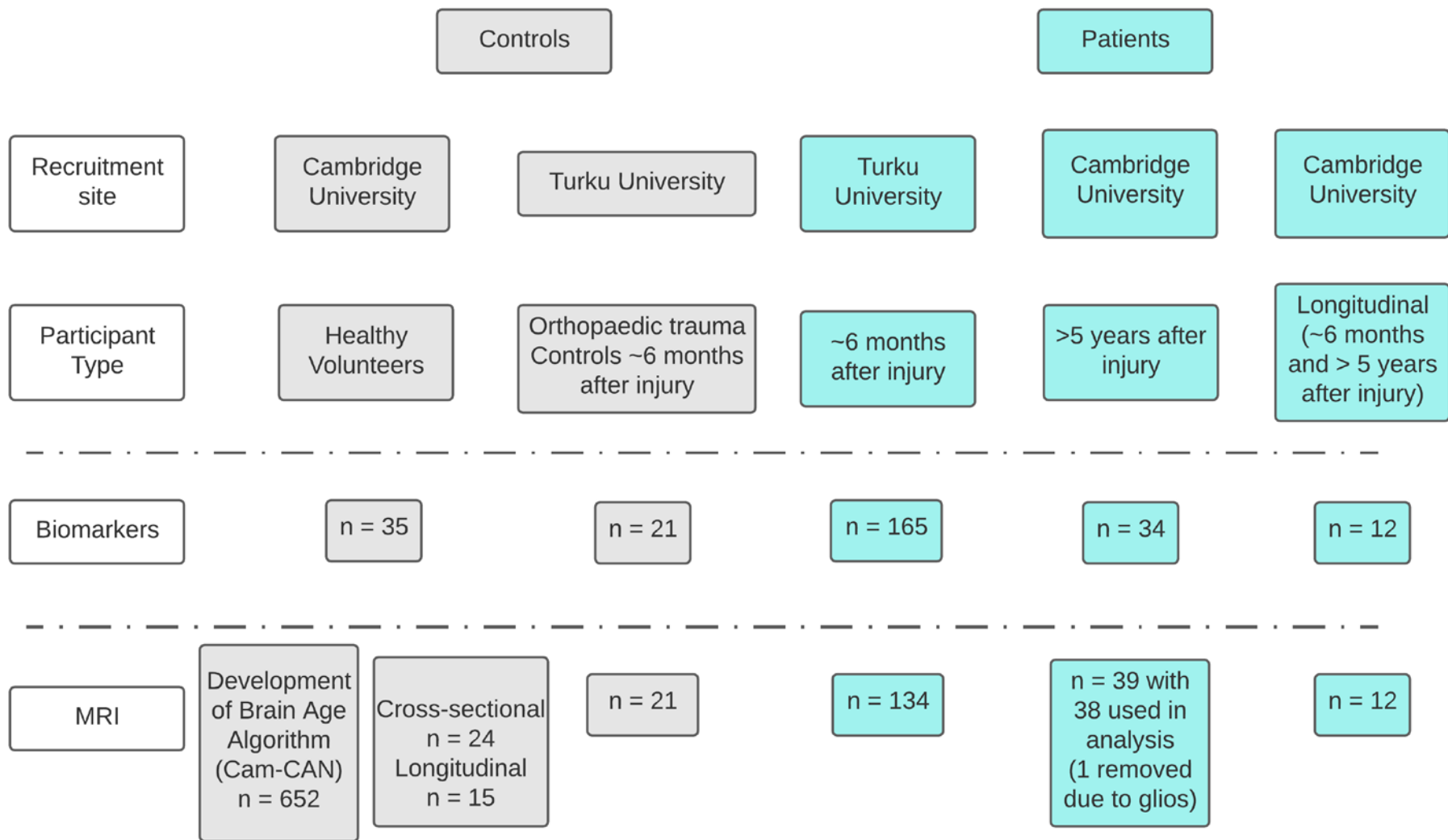


Figure S1: Diagram of study participants.

Imaging controls (Healthy volunteers or orthopaedic trauma controls) were used specific to each recruitment site.

Table S1: Control and patient cohorts

| | Healthy Volunteers | Healthy Volunteers | Healthy Volunteers | Trauma Controls | TBI ~8 months after injury | TBI >5 years after injury | Longitudinal scans | |
|-----------------------------------|--------------------|--------------------|--------------------|--------------------------|----------------------------|---------------------------|--------------------------|------------------------|
| Biomarkers | 35 | | | 21 | 165 | 34 | | |
| MRI | | 24 | 15 | 21 | 134 | 38 | | 12 |
| Age (years, mean (SD)) | 46 (± 13) | 46.8(± 19) | | 45.8(± 16) | 46 (± 19) | 49 (± 18) | | 12 42.4(± 17) |
| Sex | | | | | | | | |
| Male | 23 (66 %) | 16 (66.6%) | 10 (66.6%) | 11 | 124 (75 %) | 29 (76 %) | | 10 |
| Female | 12 (34 %) | 8 (33.3%) | 5 (33.3%) | 10 | 41 (25 %) | 9 (24 %) | | 2(17%) 7 (3 to 11) |
| GCS (median (range)) | | | | | 14 (3 - 15) | 7 (3 - 15) | | |
| Marshall CT Score | | | | | | | | |
| I | | | | | 59 (36 %) | 2 (5 %) | | 1 (8%) |
| II | | | | | 33 (20 %) | 18 (47 %) | | 5 (42%) |
| III | | | | | 1 (1 %) | 1 (3 %) | | 0 (0%) |
| IV | | | | | 1 (1 %) | 0 (0 %) | | 0 (0%) |
| V | | | | | 36 (22 %) | 9 (24 %) | | 3 (25%) |
| VI | | | | | 35 (21 %) | 8 (21 %) | | 3 (25%) |
| Time to biomarker sampling | | | | | | | Scan 1 | Scan 2 |
| mean(SD) | | | | 8.1(±2.2) months | 8.2 (± 2.4) months | 8.3 (± 2.1) years | 7.3 (± 2.1) months | 6.1(± 0.8) years |
| median (range) | | | | 7.8 (5.7 to 15.6) months | 6.4 (5.6 to 16.3) months | 7.5(3.6 to 13.7) years | 6.2 (5.5 to 12.6) months | 6.3 (3.6 to 7.1) years |
| Time to MRI | | | | | | | | |
| mean(SD) | | | | 8.1(±2.2) months | 8.3 (± 2.7) months | 8.4 (± 2.3) years | 7.3 (± 2.1) months | 6.1(± 0.8) years |
| median (range) | | | | 7.8 (5.7 to 15.6) months | 6.8 (5.6 to 16.3) months | 7.6(3.6 to 13.7) years | 6.2 (5.5 to 12.6) months | 6.3 (3.6 to 7.1) years |
| Mechanism of Injury | | | | | | | | |
| RTC | | | | | 59 (36%) | 22 (65%) | | 7 (6%) |
| Assault | | | | | 14 (8%) | 1 (3%) | | 1 (8%) |
| Fall | | | | | 85 (52%) | 7 (21%) | | 4 (33%) |
| Impact to head | | | | | 0 (0%) | 4 (12%) | | 0 (0%) |
| Other | | | | | 7 (4%) | 0 (0%) | | 0 (0%) |
| GOSE (median (range)) | | | | | 7 (3 - 8) | 6 (3 - 8) | | 6 (5 to 8) |

GCS = Glasgow Coma Score upon admission or initial injury assessment, CT = Computed Tomography, MRI = magnetic resonance imaging, RTC = road traffic collision, GOSE = Glasgow Outcome Score Extended.

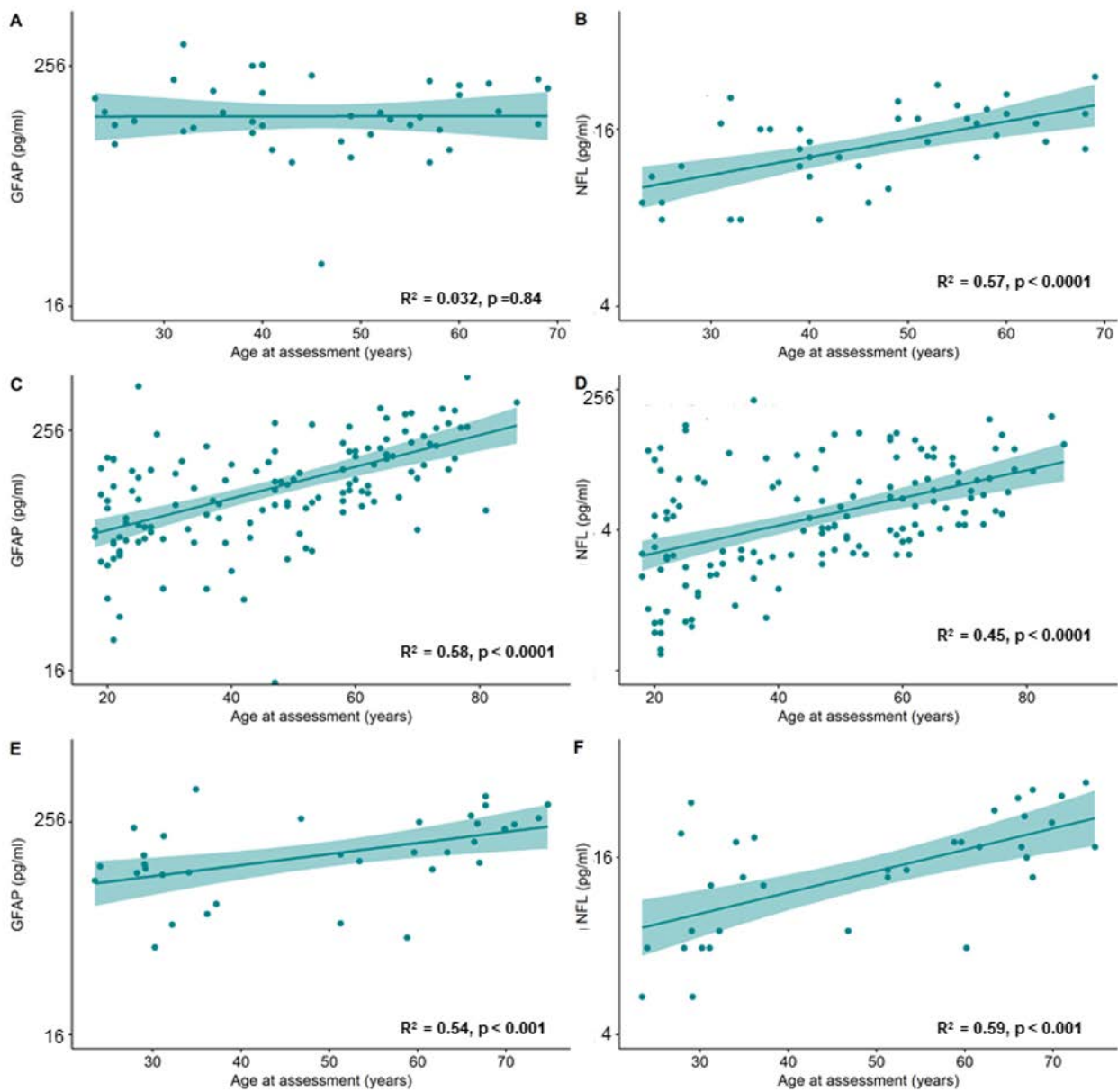


Figure S2: Relationship of age and levels of NFL and GFP. A and B are healthy volunteers, C and D patients ~8 months after TBI, E and D patients > 5 years after TBI. . Biomarker levels are shown on a log2 scale, but with original measured biomarker concentrations in pg/ml to facilitate clinical interpretation. Unadjusted R values shown.

Supplementary Table S2: Fractional anisotropy and mean diffusivity for the projection fibre tracts, commissural fibre tracts and thalamic radiations for patients ~6 months after TBI compared to trauma controls. All data reported as median (IQR). Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| | Fractional Anisotropy | | | | Mean Diffusivity ($\times 10^{-3}$ mm ² /s) | | | |
|--|-----------------------|---------------------|---------|------------------|---|---------------------|---------|------------------|
| | Controls | Patients | P-value | Adjusted P-Value | Controls | Patients | P-value | Adjusted P-Value |
| Projection Fibres | | | | | | | | |
| <i>Corticospinal tract Right</i> | 0.49 (\pm 0.034) | 0.50 (\pm 0.020) | 0.319 | 0.333 | 0.69 (\pm 0.050) | 0.68 (\pm 0.029) | 0.083 | 0.087 |
| <i>Corticospinal tract Left</i> | 0.50 (\pm 0.031) | 0.50 (\pm 0.034) | 0.290 | 0.316 | 0.69 (\pm 0.045) | 0.67 (\pm 0.039) | 0.031 | 0.038 |
| Commissural Fibres | | | | | | | | |
| <i>CC Genu</i> | 0.37 (\pm 0.051) | 0.38 (\pm 0.021) | 0.0096 | 0.041* | 0.79 (\pm 0.097) | 0.76 (\pm 0.033) | 0.011 | 0.022* |
| <i>CC Body</i> | 0.44 (\pm 0.038) | 0.46 (\pm 0.032) | 0.002 | 0.041* | 0.77 (\pm 0.068) | 0.74 (\pm 0.025) | 0.002 | 0.017* |
| <i>Splenium</i> | 0.39 (\pm 0.040) | 0.41 (\pm 0.021) | 0.005 | 0.041* | 0.81 (\pm 0.078) | 0.77 (\pm 0.026) | 0.005 | 0.017* |
| <i>Commissure Anterior</i> | 0.35 (\pm 0.044) | 0.37 (\pm 0.049) | 0.012 | 0.041* | 0.83 (\pm 0.090) | 0.80 (\pm 0.058) | 0.005 | 0.017* |
| <i>Fornix Right</i> | 0.33 (\pm 0.083) | 0.39 (\pm 0.053) | <0.001 | 0.041* | 1.6 (\pm 0.27) | 1.4 (\pm 0.18) | <0.0001 | 0.005* |
| <i>Fornix Left</i> | 0.34 (\pm 0.12) | 0.40 (\pm 0.061) | 0.006 | 0.041* | 1.6 (\pm 0.45) | 1.5 (\pm 0.24) | 0.021 | 0.030* |
| Thalamic Radiations | | | | | | | | |
| <i>Thalamo-prefrontal Right</i> | 0.36 (\pm 0.040) | 0.38 (\pm 0.027) | 0.027 | 0.051 | 0.76 (\pm 0.087) | 0.73 (\pm 0.034) | 0.014 | 0.025* |
| <i>Thalamo-prefrontal Left</i> | 0.38 (\pm 0.037) | 0.39 (\pm 0.032) | 0.022 | 0.048* | 0.75 (\pm 0.094) | 0.72 (\pm 0.033) | 0.012 | 0.022* |
| <i>Thalamo-premotor Right</i> | 0.41 (\pm 0.032) | 0.42 (\pm 0.030) | 0.0433 | 0.067 | 0.71 (\pm 0.082) | 0.69 (\pm 0.045) | 0.021 | 0.030* |
| <i>Thalamo-premotor Left</i> | 0.40 (\pm 0.037) | 0.41 (\pm 0.028) | 0.045 | 0.067 | 0.72 (\pm 0.098) | 0.69 (\pm 0.047) | 0.010 | 0.022* |
| <i>Thalamo-precentral Right</i> | 0.43 (\pm 0.033) | 0.44 (\pm 0.018) | 0.090 | 0.118 | 0.70 (\pm 0.059) | 0.69 (\pm 0.027) | 0.022 | 0.030* |
| <i>Thalamo-precentral Left</i> | 0.44 (\pm 0.035) | 0.44 (\pm 0.028) | 0.322 | 0.332 | 0.69 (\pm 0.062) | 0.68 (\pm 0.038) | 0.019 | 0.030* |
| <i>Thalamo-postcentral Right</i> | 0.44 (\pm 0.028) | 0.45 (\pm 0.028) | 0.149 | 0.174 | 0.71 (\pm 0.052) | 0.70 (\pm 0.028) | 0.002 | 0.017* |
| <i>Thalamo-postcentral Left</i> | 0.43 (\pm 0.033) | 0.43 (\pm 0.026) | 0.434 | 0.434 | 0.71 (\pm 0.050) | 0.69 (\pm 0.028) | 0.003 | 0.017* |
| <i>Thalamo-parietal Right</i> | 0.40 (\pm 0.034) | 0.41 (\pm 0.027) | 0.010 | 0.041* | 0.79 (\pm 0.079) | 0.75 (\pm 0.028) | 0.005 | 0.017* |
| <i>Thalamo-parietal Left</i> | 0.40 (\pm 0.033) | 0.42 (\pm 0.026) | 0.021 | 0.048* | 0.76 (\pm 0.075) | 0.74 (\pm 0.020) | 0.006 | 0.017* |
| <i>Thalamo-occipital Right</i> | 0.38 (\pm 0.038) | 0.39 (\pm 0.028) | 0.003 | 0.041* | 0.84 (\pm 0.11) | 0.80 (\pm 0.043) | 0.003 | 0.017* |
| <i>Thalamo-occipital Left</i> | 0.37 (\pm 0.034) | 0.38 (\pm 0.038) | 0.086 | 0.115 | 0.82 (\pm 0.10) | 0.80 (\pm 0.040) | 0.004 | 0.017* |
| <i>Superior Thalamic Radiation Right</i> | 0.45 (\pm 0.036) | 0.47 (\pm 0.025) | 0.078 | 0.106 | 0.69 (\pm 0.064) | 0.67 (\pm 0.027) | 0.003 | 0.017* |
| <i>Superior Thalamic Radiation Left</i> | 0.46 (\pm 0.042) | 0.47 (\pm 0.049) | 0.292 | 0.316 | 0.69 (\pm 0.057) | 0.67 (\pm 0.039) | 0.003 | 0.017* |
| <i>Anterior Thalamic Radiation Right</i> | 0.35 (\pm 0.042) | 0.36 (\pm 0.030) | 0.027 | 0.051 | 0.77 (\pm 0.11) | 0.74 (\pm 0.043) | 0.010 | 0.022* |
| <i>Anterior Thalamic Radiation Left</i> | 0.36 (\pm 0.040) | 0.37 (\pm 0.024) | 0.028 | 0.051 | 0.77 (\pm 0.11) | 0.74 (\pm 0.038) | 0.009 | 0.022* |

Supplementary Table S3: Fractional anisotropy and mean diffusivity for the striatal fibre tracts and brainstem tracts for patients ~6 months after TBI compared to trauma controls.

All data reported as median (IQR). Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| | Fractional Anisotropy | | | | Mean Diffusivity ($\times 10^{-3}$ mm ² /s) | | | |
|---|-----------------------|---------------------|---------|------------------|---|---------------------|---------|------------------|
| | Controls | Patients | P-value | Adjusted P-Value | Controls | Patients | P-value | Adjusted P-Value |
| Striatal Fibres | | | | | | | | |
| <i>Striato-fronto-orbital Right</i> | 0.35 (\pm 0.051) | 0.37 (\pm 0.031) | 0.010 | 0.041* | 0.78 (\pm 0.079) | 0.76 (\pm 0.028) | 0.002 | 0.017* |
| <i>Striato-fronto-orbital Left</i> | 0.36 (\pm 0.051) | 0.38 (\pm 0.026) | 0.011 | 0.041* | 0.79 (\pm 0.091) | 0.75 (\pm 0.043) | 0.003 | 0.017* |
| <i>Striato-prefrontal Right</i> | 0.36 (\pm 0.041) | 0.37 (\pm 0.024) | 0.025 | 0.051 | 0.76 (\pm 0.079) | 0.74 (\pm 0.030) | 0.019 | 0.030* |
| <i>Striato-prefrontal Left</i> | 0.36 (\pm 0.040) | 0.38 (\pm 0.026) | 0.018 | 0.046* | 0.77 (\pm 0.098) | 0.74 (\pm 0.025) | 0.013 | 0.024* |
| <i>Striato-premotor Right</i> | 0.40 (\pm 0.038) | 0.41 (\pm 0.037) | 0.098 | 0.124 | 0.72 (\pm 0.085) | 0.70 (\pm 0.039) | 0.073 | 0.077 |
| <i>Striato-premotor Left</i> | 0.39 (\pm 0.037) | 0.40 (\pm 0.031) | 0.044 | 0.067 | 0.74 (\pm 0.092) | 0.71 (\pm 0.033) | 0.011 | 0.022* |
| <i>Striato-precentral Right</i> | 0.42 (\pm 0.038) | 0.43 (\pm 0.019) | 0.108 | 0.134 | 0.71 (\pm 0.066) | 0.69 (\pm 0.026) | 0.022 | 0.030* |
| <i>Striato-precentral Left</i> | 0.42 (\pm 0.032) | 0.43 (\pm 0.025) | 0.141 | 0.169 | 0.72 (\pm 0.071) | 0.70 (\pm 0.033) | 0.009 | 0.022* |
| <i>Striato-postcentral Right</i> | 0.42 (\pm 0.027) | 0.43 (\pm 0.026) | 0.031 | 0.054 | 0.72 (\pm 0.064) | 0.70 (\pm 0.033) | 0.005 | 0.017* |
| <i>Striato-postcentral Left</i> | 0.42 (\pm 0.028) | 0.43 (\pm 0.024) | 0.180 | 0.201 | 0.71 (\pm 0.058) | 0.69 (\pm 0.027) | 0.003 | 0.017* |
| <i>Striato-parietal Right</i> | 0.40 (\pm 0.037) | 0.41 (\pm 0.027) | 0.009 | 0.041* | 0.78 (\pm 0.077) | 0.74 (\pm 0.021) | 0.008 | 0.022* |
| <i>Striato-parietal Left</i> | 0.40 (\pm 0.031) | 0.41 (\pm 0.030) | 0.011 | 0.041* | 0.76 (\pm 0.062) | 0.73 (\pm 0.022) | 0.008 | 0.022* |
| <i>Striato-occipital Right</i> | 0.37 (\pm 0.038) | 0.38 (\pm 0.025) | 0.005 | 0.041* | 0.83 (\pm 0.111) | 0.80 (\pm 0.033) | 0.004 | 0.017* |
| <i>Striato-occipital Left</i> | 0.37 (\pm 0.035) | 0.39 (\pm 0.037) | 0.051 | 0.072 | 0.82 (\pm 0.089) | 0.79 (\pm 0.028) | 0.005 | 0.017* |
| Brainstem | | | | | | | | |
| <i>Parieto Occipital pontine Right</i> | 0.45 (\pm 0.030) | 0.46 (\pm 0.026) | 0.012 | 0.041* | 0.76 (\pm 0.060) | 0.73 (\pm 0.029) | 0.006 | 0.017* |
| <i>Parieto Occipital pontine Left</i> | 0.45 (\pm 0.028) | 0.47 (\pm 0.021) | 0.028 | 0.051 | 0.74 (\pm 0.051) | 0.71 (\pm 0.026) | 0.003 | 0.017* |
| <i>Fronto-pontine tract Right</i> | 0.44 (\pm 0.034) | 0.45 (\pm 0.030) | 0.024 | 0.051 | 0.73 (\pm 0.070) | 0.71 (\pm 0.025) | 0.016 | 0.027* |
| <i>Fronto-pontine tract Left</i> | 0.45 (\pm 0.030) | 0.45 (\pm 0.043) | 0.045 | 0.067 | 0.73 (\pm 0.063) | 0.71 (\pm 0.041) | 0.013 | 0.024* |
| <i>Superior cerebellar peduncle Right</i> | 0.42 (\pm 0.032) | 0.43 (\pm 0.020) | 0.076 | 0.106 | 0.70 (\pm 0.057) | 0.69 (\pm 0.042) | 0.038 | 0.043* |
| <i>Superior cerebellar peduncle Left</i> | 0.44 (\pm 0.030) | 0.44 (\pm 0.020) | 0.419 | 0.426 | 0.70 (\pm 0.051) | 0.68 (\pm 0.024) | 0.064 | 0.070 |
| <i>Inferior cerebellar peduncle Right</i> | 0.38 (\pm 0.038) | 0.38 (\pm 0.031) | 0.140 | 0.169 | 0.69 (\pm 0.054) | 0.68 (\pm 0.036) | 0.269 | 0.269 |
| <i>Inferior cerebellar peduncle Left</i> | 0.41 (\pm 0.031) | 0.41 (\pm 0.023) | 0.307 | 0.326 | 0.68 (\pm 0.046) | 0.67 (\pm 0.026) | 0.116 | 0.120 |
| <i>Middle cerebellar peduncle</i> | 0.42 (\pm 0.026) | 0.43 (\pm 0.020) | 0.180 | 0.201 | 0.68 (\pm 0.050) | 0.67 (\pm 0.019) | 0.122 | 0.124 |

Supplementary Table S4: Fractional anisotropy and mean diffusivity for the association tracts for patients ~6 months after TBI compared to trauma controls. All data reported as median (IQR). Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| | Fractional Anisotropy | | | Adjusted P-Value | Mean Diffusivity ($\times 10^{-3}$ mm ² /s) | | | Adjusted P-Value |
|---|-----------------------|---------------------|---------|------------------|---|---------------------|---------|------------------|
| | Controls | Patients | P-value | | Controls | Patients | P-value | |
| Association Fibres | | | | | | | | |
| <i>Superior longitudinal fascicle I Right</i> | 0.41 (\pm 0.041) | 0.43 (\pm 0.025) | 0.016 | 0.046* | 0.73 (\pm 0.065) | 0.71 (\pm 0.039) | 0.039 | 0.044* |
| <i>Superior longitudinal fascicle I Left</i> | 0.42 (\pm 0.043) | 0.43 (\pm 0.034) | 0.017 | 0.046* | 0.71 (\pm 0.059) | 0.69 (\pm 0.047) | 0.030 | 0.038* |
| <i>Superior longitudinal fascicle II Right</i> | 0.38 (\pm 0.049) | 0.39 (\pm 0.018) | 0.047 | 0.068 | 0.73 (\pm 0.069) | 0.71 (\pm 0.033) | 0.031 | 0.038* |
| <i>Superior longitudinal fascicle II Left</i> | 0.39 (\pm 0.039) | 0.40 (\pm 0.019) | 0.007 | 0.041* | 0.72 (\pm 0.059) | 0.71 (\pm 0.041) | 0.020 | 0.030* |
| <i>Superior longitudinal fascicle III Right</i> | 0.37 (\pm 0.054) | 0.39 (\pm 0.024) | 0.041 | 0.067 | 0.73 (\pm 0.079) | 0.71 (\pm 0.031) | 0.031 | 0.038* |
| <i>Superior longitudinal fascicle III Left</i> | 0.40 (\pm 0.046) | 0.41 (\pm 0.034) | 0.010 | 0.041* | 0.71 (\pm 0.066) | 0.70 (\pm 0.046) | 0.019 | 0.030* |
| <i>Inferior longitudinal fascicle Right</i> | 0.36 (\pm 0.048) | 0.38 (\pm 0.034) | 0.020 | 0.047* | 0.79 (\pm 0.097) | 0.76 (\pm 0.046) | 0.029 | 0.038* |
| <i>Inferior longitudinal fascicle Left</i> | 0.36 (\pm 0.043) | 0.38 (\pm 0.032) | 0.017 | 0.046* | 0.79 (\pm 0.086) | 0.77 (\pm 0.039) | 0.011 | 0.022* |
| <i>Uncinate fascicle Right</i> | 0.32 (\pm 0.043) | 0.33 (\pm 0.031) | 0.041 | 0.067 | 0.79 (\pm 0.067) | 0.78 (\pm 0.034) | 0.037 | 0.043* |
| <i>Uncinate fascicle Left</i> | 0.35 (\pm 0.045) | 0.36 (\pm 0.043) | 0.156 | 0.180 | 0.78 (\pm 0.084) | 0.76 (\pm 0.038) | 0.070 | 0.076 |
| <i>Arcuate fascicle Right</i> | 0.37 (\pm 0.049) | 0.38 (\pm 0.027) | 0.040 | 0.067 | 0.74 (\pm 0.074) | 0.71 (\pm 0.034) | 0.021 | 0.030* |
| <i>Arcuate fascicle Left</i> | 0.36 (\pm 0.043) | 0.38 (\pm 0.024) | 0.015 | 0.046* | 0.73 (\pm 0.066) | 0.72 (\pm 0.047) | 0.020 | 0.030* |
| <i>Cingulum Right</i> | 0.37 (\pm 0.041) | 0.38 (\pm 0.021) | 0.021 | 0.048* | 0.75 (\pm 0.061) | 0.73 (\pm 0.030) | 0.037 | 0.043* |
| <i>Cingulum Left</i> | 0.38 (\pm 0.044) | 0.40 (\pm 0.024) | 0.006 | 0.041* | 0.74 (\pm 0.058) | 0.73 (\pm 0.028) | 0.023 | 0.030* |
| <i>Middle longitudinal fascicle Right</i> | 0.36 (\pm 0.045) | 0.38 (\pm 0.030) | 0.015 | 0.046* | 0.78 (\pm 0.077) | 0.75 (\pm 0.027) | 0.012 | 0.022* |
| <i>Middle longitudinal fascicle Left</i> | 0.36 (\pm 0.039) | 0.38 (\pm 0.023) | 0.010 | 0.041* | 0.76 (\pm 0.067) | 0.74 (\pm 0.040) | 0.009 | 0.022* |
| <i>Inferior occipito-frontal fascicle Right</i> | 0.33 (\pm 0.038) | 0.35 (\pm 0.021) | 0.011 | 0.041* | 0.84 (\pm 0.11) | 0.80 (\pm 0.033) | 0.004 | 0.017* |
| <i>Inferior occipito-frontal fascicle Left</i> | 0.35 (\pm 0.037) | 0.36 (\pm 0.023) | 0.019 | 0.047* | 0.82 (\pm 0.10) | 0.78 (\pm 0.032) | 0.012 | 0.022* |
| <i>Optic Radiation Right</i> | 0.39 (\pm 0.039) | 0.41 (\pm 0.030) | 0.004 | 0.041* | 0.83 (\pm 0.11) | 0.79 (\pm 0.037) | 0.003 | 0.017* |
| <i>Optic Radiation Left</i> | 0.37 (\pm 0.036) | 0.38 (\pm 0.035) | 0.097 | 0.124 | 0.82 (\pm 0.097) | 0.79 (\pm 0.041) | 0.004 | 0.017* |

Supplementary Table S5: Fractional anisotropy and mean diffusivity for the projection fibre tracts, commissural fibre tracts and thalamic radiations for patients >5 years after TBI.

All data reported as median (IQR). Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| | Fractional Anisotropy | | | | Mean Diffusivity ($\times 10^{-3}$ mm ² /s) | | | |
|--|-----------------------|---------------------|---------|------------------|---|---------------------|---------|------------------|
| | Controls | Patients | P-value | Adjusted P-Value | Controls | Patients | P-value | Adjusted P-Value |
| Projection Fibres | | | | | | | | |
| <i>Corticospinal tract Right</i> | 0.45 (\pm 0.034) | 0.46 (\pm 0.029) | 0.546 | 0.581 | 0.57 (\pm 0.017) | 0.58 (\pm 0.022) | 0.021 | 0.026* |
| <i>Corticospinal tract Left</i> | 0.45 (\pm 0.030) | 0.46 (\pm 0.031) | 0.608 | 0.636 | 0.57 (\pm 0.017) | 0.57 (\pm 0.029) | 0.209 | 0.230 |
| Commissural Fibres | | | | | | | | |
| <i>CC Genu</i> | 0.37 (\pm 0.013) | 0.35 (\pm 0.038) | <0.001 | 0.011* | 0.62 (\pm 0.017) | 0.65 (\pm 0.036) | <0.001 | <0.001* |
| <i>CC Body</i> | 0.41 (\pm 0.018) | 0.40 (\pm 0.031) | 0.003 | 0.014* | 0.61 (\pm 0.014) | 0.62 (\pm 0.034) | 0.001 | 0.004* |
| <i>Splenium</i> | 0.38 (\pm 0.012) | 0.36 (\pm 0.029) | 0.004 | 0.018* | 0.63 (\pm 0.0090) | 0.64 (\pm 0.028) | <0.001 | 0.001* |
| <i>Commissure Anterior</i> | 0.33 (\pm 0.022) | 0.31 (\pm 0.037) | 0.006 | 0.019* | 0.64 (\pm 0.020) | 0.65 (\pm 0.049) | 0.090 | 0.102 |
| <i>Fornix Right</i> | 0.52 (\pm 0.042) | 0.49 (\pm 0.079) | 0.037 | 0.057 | 0.78 (\pm 0.038) | 0.80 (\pm 0.083) | 0.109 | 0.121 |
| <i>Fornix Left</i> | 0.51 (\pm 0.043) | 0.48 (\pm 0.093) | <0.001 | 0.011* | 0.80 (\pm 0.042) | 0.87 (\pm 0.096) | <0.001 | 0.001* |
| Thalamic Radiations | | | | | | | | |
| <i>Thalamo-prefrontal Right</i> | 0.37 (\pm 0.017) | 0.36 (\pm 0.028) | 0.007 | 0.019* | 0.61 (\pm 0.020) | 0.63 (\pm 0.030) | 0.000 | <0.001* |
| <i>Thalamo-prefrontal Left</i> | 0.38 (\pm 0.017) | 0.36 (\pm 0.029) | 0.005 | 0.019* | 0.60 (\pm 0.018) | 0.61 (\pm 0.030) | 0.002 | 0.004* |
| <i>Thalamo-premotor Right</i> | 0.41 (\pm 0.021) | 0.40 (\pm 0.029) | 0.075 | 0.107 | 0.59 (\pm 0.021) | 0.60 (\pm 0.029) | <0.001 | 0.002* |
| <i>Thalamo-premotor Left</i> | 0.40 (\pm 0.022) | 0.39 (\pm 0.023) | 0.013 | 0.026* | 0.59 (\pm 0.017) | 0.60 (\pm 0.027) | 0.002 | 0.005* |
| <i>Thalamo-precentral Right</i> | 0.41 (\pm 0.029) | 0.41 (\pm 0.031) | 0.182 | 0.222 | 0.58 (\pm 0.018) | 0.59 (\pm 0.027) | 0.013 | 0.017* |
| <i>Thalamo-precentral Left</i> | 0.42 (\pm 0.031) | 0.41 (\pm 0.030) | 0.080 | 0.112 | 0.58 (\pm 0.012) | 0.59 (\pm 0.032) | 0.022 | 0.026* |
| <i>Thalamo-postcentral Right</i> | 0.41 (\pm 0.037) | 0.41 (\pm 0.034) | 0.389 | 0.427 | 0.58 (\pm 0.016) | 0.59 (\pm 0.030) | 0.037 | 0.044* |
| <i>Thalamo-postcentral Left</i> | 0.40 (\pm 0.034) | 0.40 (\pm 0.027) | 0.297 | 0.343 | 0.59 (\pm 0.021) | 0.60 (\pm 0.033) | 0.074 | 0.085 |
| <i>Thalamo-parietal Right</i> | 0.40 (\pm 0.026) | 0.39 (\pm 0.026) | 0.008 | 0.019* | 0.61 (\pm 0.0095) | 0.63 (\pm 0.029) | <0.001 | 0.001* |
| <i>Thalamo-parietal Left</i> | 0.40 (\pm 0.026) | 0.38 (\pm 0.028) | 0.028 | 0.045* | 0.62 (\pm 0.011) | 0.63 (\pm 0.029) | 0.001 | 0.003* |
| <i>Thalamo-occipital Right</i> | 0.38 (\pm 0.023) | 0.36 (\pm 0.030) | <0.001 | 0.011* | 0.63 (\pm 0.014) | 0.64 (\pm 0.028) | 0.001 | 0.003* |
| <i>Thalamo-occipital Left</i> | 0.37 (\pm 0.015) | 0.36 (\pm 0.024) | 0.012 | 0.026* | 0.63 (\pm 0.017) | 0.64 (\pm 0.038) | 0.014 | 0.018* |
| <i>Superior Thalamic Radiation Right</i> | 0.43 (\pm 0.036) | 0.42 (\pm 0.037) | 0.154 | 0.195 | 0.58 (\pm 0.017) | 0.59 (\pm 0.026) | 0.005 | 0.009* |
| <i>Superior Thalamic Radiation Left</i> | 0.44 (\pm 0.036) | 0.43 (\pm 0.039) | 0.198 | 0.237 | 0.57 (\pm 0.012) | 0.58 (\pm 0.030) | 0.008 | 0.012* |
| <i>Anterior Thalamic Radiation Right</i> | 0.35 (\pm 0.019) | 0.34 (\pm 0.031) | 0.061 | 0.089 | 0.61 (\pm 0.016) | 0.62 (\pm 0.030) | <0.001 | 0.001* |
| <i>Anterior Thalamic Radiation Left</i> | 0.35 (\pm 0.011) | 0.34 (\pm 0.028) | 0.018 | 0.033* | 0.61 (\pm 0.017) | 0.62 (\pm 0.025) | 0.008 | 0.012* |

Supplementary Table S6: Fractional anisotropy and mean diffusivity for the striatal fibre tracts and brainstem tracts. All data reported as median (IQR) radiations for patients >5 years after TBI. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| | Fractional Anisotropy | | | | Mean Diffusivity ($\times 10^{-3}$ mm ² /s) | | | |
|---|-----------------------|---------------------|---------|------------------|---|---------------------|---------|------------------|
| | Controls | Patients | P-value | Adjusted P-Value | Controls | Patients | P-value | Adjusted P-Value |
| Striatal Fibres | | | | | | | | |
| <i>Striato-fronto-orbital Right</i> | 0.35 (\pm 0.026) | 0.34 (\pm 0.048) | 0.008 | 0.019* | 0.61 (\pm 0.022) | 0.63 (\pm 0.040) | 0.005 | 0.009* |
| <i>Striato-fronto-orbital Left</i> | 0.35 (\pm 0.020) | 0.33 (\pm 0.042) | 0.056 | 0.084 | 0.61 (\pm 0.019) | 0.62 (\pm 0.049) | 0.263 | 0.284 |
| <i>Striato-prefrontal Right</i> | 0.36 (\pm 0.017) | 0.35 (\pm 0.029) | 0.006 | 0.019* | 0.61 (\pm 0.020) | 0.63 (\pm 0.035) | <0.001 | <0.001* |
| <i>Striato-prefrontal Left</i> | 0.36 (\pm 0.017) | 0.34 (\pm 0.034) | 0.025 | 0.042* | 0.61 (\pm 0.016) | 0.62 (\pm 0.029) | 0.003 | 0.006* |
| <i>Striato-premotor Right</i> | 0.41 (\pm 0.025) | 0.40 (\pm 0.030) | 0.112 | 0.150 | 0.58 (\pm 0.026) | 0.60 (\pm 0.024) | <0.001 | 0.001* |
| <i>Striato-premotor Left</i> | 0.40 (\pm 0.022) | 0.38 (\pm 0.029) | 0.007 | 0.019* | 0.59 (\pm 0.018) | 0.60 (\pm 0.028) | 0.002 | 0.005* |
| <i>Striato-precentral Right</i> | 0.41 (\pm 0.026) | 0.40 (\pm 0.025) | 0.173 | 0.214 | 0.58 (\pm 0.022) | 0.59 (\pm 0.026) | 0.007 | 0.011* |
| <i>Striato-precentral Left</i> | 0.41 (\pm 0.027) | 0.39 (\pm 0.030) | 0.025 | 0.042* | 0.58 (\pm 0.012) | 0.59 (\pm 0.034) | 0.018 | 0.023* |
| <i>Striato-postcentral Right</i> | 0.41 (\pm 0.032) | 0.40 (\pm 0.029) | 0.304 | 0.345 | 0.58 (\pm 0.018) | 0.60 (\pm 0.030) | 0.010 | 0.015* |
| <i>Striato-postcentral Left</i> | 0.40 (\pm 0.032) | 0.39 (\pm 0.027) | 0.133 | 0.175 | 0.59 (\pm 0.018) | 0.60 (\pm 0.033) | 0.065 | 0.076 |
| <i>Striato-parietal Right</i> | 0.40 (\pm 0.028) | 0.39 (\pm 0.027) | 0.008 | 0.019* | 0.61 (\pm 0.013) | 0.63 (\pm 0.029) | <0.001 | < 0.001* |
| <i>Striato-parietal Left</i> | 0.39 (\pm 0.024) | 0.38 (\pm 0.028) | 0.012 | 0.026* | 0.62 (\pm 0.012) | 0.63 (\pm 0.029) | 0.002 | 0.004* |
| <i>Striato-occipital Right</i> | 0.37 (\pm 0.022) | 0.35 (\pm 0.026) | 0.000 | 0.007* | 0.63 (\pm 0.016) | 0.64 (\pm 0.028) | 0.002 | 0.005* |
| <i>Striato-occipital Left</i> | 0.38 (\pm 0.018) | 0.36 (\pm 0.026) | 0.001 | 0.011* | 0.63 (\pm 0.018) | 0.64 (\pm 0.034) | 0.017 | 0.021* |
| Brainstem | | | | | | | | |
| <i>Parieto Occipital pontine Right</i> | 0.43 (\pm 0.032) | 0.43 (\pm 0.029) | 0.037 | 0.057 | 0.60 (\pm 0.011) | 0.62 (\pm 0.031) | <0.001 | 0.002* |
| <i>Parieto Occipital pontine Left</i> | 0.43 (\pm 0.029) | 0.42 (\pm 0.027) | 0.145 | 0.187 | 0.60 (\pm 0.012) | 0.61 (\pm 0.027) | 0.012 | 0.017* |
| <i>Fronto-pontine tract Right</i> | 0.42 (\pm 0.026) | 0.41 (\pm 0.032) | 0.043 | 0.065 | 0.59 (\pm 0.016) | 0.61 (\pm 0.027) | <0.001 | 0.001* |
| <i>Fronto-pontine tract Left</i> | 0.43 (\pm 0.028) | 0.42 (\pm 0.032) | 0.107 | 0.147 | 0.59 (\pm 0.015) | 0.60 (\pm 0.032) | 0.007 | 0.011* |
| <i>Superior cerebellar peduncle Right</i> | 0.38 (\pm 0.022) | 0.38 (\pm 0.029) | 0.729 | 0.751 | 0.57 (\pm 0.027) | 0.57 (\pm 0.017) | 0.994 | 0.994 |
| <i>Superior cerebellar peduncle Left</i> | 0.39 (\pm 0.020) | 0.39 (\pm 0.023) | 0.833 | 0.833 | 0.57 (\pm 0.025) | 0.57 (\pm 0.018) | 0.654 | 0.695 |
| <i>Inferior cerebellar peduncle Right</i> | 0.34 (\pm 0.019) | 0.34 (\pm 0.028) | 0.364 | 0.407 | 0.56 (\pm 0.026) | 0.57 (\pm 0.019) | 0.687 | 0.719 |
| <i>Inferior cerebellar peduncle Left</i> | 0.37 (\pm 0.021) | 0.37 (\pm 0.021) | 0.774 | 0.786 | 0.56 (\pm 0.022) | 0.57 (\pm 0.015) | 0.879 | 0.892 |
| <i>Middle cerebellar peduncle</i> | 0.36 (\pm 0.024) | 0.36 (\pm 0.024) | 0.450 | 0.486 | 0.56 (\pm 0.023) | 0.56 (\pm 0.017) | 0.843 | 0.869 |

Supplementary Table S7: Fractional anisotropy and mean diffusivity for the association tracts radiations for patients >5 years after TBI. All data reported as median (IQR). Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| | Fractional Anisotropy | | | Adjusted P-Value | Mean Diffusivity ($\times 10^{-3}$ mm ² /s) | | | Adjusted P-Value |
|---|-----------------------|---------------------|---------|------------------|---|---------------------|---------|-------------------|
| | Controls | Patients | P-value | | Controls | Patients | P-value | |
| Association Fibres | | | | | | | | |
| <i>Superior longitudinal fascicle I Right</i> | 0.42 (\pm 0.015) | 0.40 (\pm 0.030) | 0.003 | 0.016* | 0.60 (\pm 0.021) | 0.62 (\pm 0.031) | <0.001 | 0.001* |
| <i>Superior longitudinal fascicle I Left</i> | 0.41 (\pm 0.016) | 0.40 (\pm 0.031) | 0.022 | 0.039* | 0.60 (\pm 0.015) | 0.61 (\pm 0.035) | 0.002 | 0.004* |
| <i>Superior longitudinal fascicle II Right</i> | 0.40 (\pm 0.016) | 0.38 (\pm 0.030) | 0.001 | 0.011* | 0.60 (\pm 0.017) | 0.62 (\pm 0.032) | <0.001 | 0.001* |
| <i>Superior longitudinal fascicle II Left</i> | 0.40 (\pm 0.018) | 0.39 (\pm 0.025) | 0.005 | 0.019* | 0.59 (\pm 0.012) | 0.61 (\pm 0.030) | 0.001 | 0.003* |
| <i>Superior longitudinal fascicle III Right</i> | 0.37 (\pm 0.022) | 0.36 (\pm 0.027) | 0.002 | 0.011* | 0.59 (\pm 0.018) | 0.62 (\pm 0.033) | <0.001 | 0.001* |
| <i>Superior longitudinal fascicle III Left</i> | 0.38 (\pm 0.022) | 0.37 (\pm 0.030) | 0.005 | 0.019* | 0.59 (\pm 0.019) | 0.60 (\pm 0.032) | 0.008 | 0.012* |
| <i>Inferior longitudinal fascicle Right</i> | 0.36 (\pm 0.024) | 0.34 (\pm 0.032) | 0.006 | 0.019* | 0.63 (\pm 0.018) | 0.64 (\pm 0.032) | 0.004 | 0.008* |
| <i>Inferior longitudinal fascicle Left</i> | 0.36 (\pm 0.018) | 0.35 (\pm 0.029) | 0.013 | 0.026* | 0.62 (\pm 0.017) | 0.64 (\pm 0.029) | 0.005 | 0.009* |
| <i>Uncinate fascicle Right</i> | 0.31 (\pm 0.019) | 0.29 (\pm 0.041) | 0.002 | 0.011* | 0.64 (\pm 0.016) | 0.67 (\pm 0.044) | <0.001 | <0.001* |
| <i>Uncinate fascicle Left</i> | 0.33 (\pm 0.018) | 0.32 (\pm 0.049) | 0.290 | 0.340 | 0.64 (\pm 0.018) | 0.65 (\pm 0.047) | 0.006 | 0.010* |
| <i>Arcuate fascicle Right</i> | 0.36 (\pm 0.017) | 0.35 (\pm 0.027) | 0.007 | 0.019* | 0.61 (\pm 0.016) | 0.62 (\pm 0.030) | <0.001 | <0.001* |
| <i>Arcuate fascicle Left</i> | 0.61 (\pm 0.014) | 0.62 (\pm 0.030) | 0.005 | 0.019* | 0.61 (\pm 0.014) | 0.62 (\pm 0.030) | 0.005 | 0.009* |
| <i>Cingulum Right</i> | 0.62 (\pm 0.019) | 0.64 (\pm 0.029) | <0.001 | 0.007* | 0.62 (\pm 0.019) | 0.64 (\pm 0.029) | <0.001 | 0.001* |
| <i>Cingulum Left</i> | 0.37 (\pm 0.015) | 0.35 (\pm 0.033) | 0.001 | 0.011* | 0.62 (\pm 0.013) | 0.64 (\pm 0.035) | <0.001 | 0.010* |
| <i>Middle longitudinal fascicle Right</i> | 0.37 (\pm 0.011) | 0.35 (\pm 0.023) | 0.009 | 0.019* | 0.63 (\pm 0.012) | 0.64 (\pm 0.022) | <0.001 | 0.001* |
| <i>Middle longitudinal fascicle Left</i> | 0.36 (\pm 0.011) | 0.34 (\pm 0.028) | 0.006 | 0.019* | 0.62 (\pm 0.011) | 0.64 (\pm 0.026) | <0.001 | 0.001* |
| <i>Inferior occipito-frontal fascicle Right</i> | 0.33 (\pm 0.013) | 0.31 (\pm 0.028) | <0.001 | 0.007* | 0.64 (\pm 0.014) | 0.65 (\pm 0.033) | <0.001 | 0.002* |
| <i>Inferior occipito-frontal fascicle Left</i> | 0.34 (\pm 0.014) | 0.33 (\pm 0.029) | 0.027 | 0.045* | 0.63 (\pm 0.016) | 0.64 (\pm 0.037) | 0.003 | 0.006* |
| <i>Optic Radiation Right</i> | 0.39 (\pm 0.025) | 0.37 (\pm 0.031) | 0.002 | 0.011* | 0.62 (\pm 0.014) | 0.64 (\pm 0.033) | 0.001 | 0.004* |
| <i>Optic Radiation Left</i> | 0.37 (\pm 0.014) | 0.36 (\pm 0.024) | 0.017 | 0.032* | 0.63 (\pm 0.018) | 0.64 (\pm 0.036) | 0.012 | 0.017* |

Supplementary Table S8: Correlations of GFAP with fractional anisotropy and mean diffusivity for projection fibres, commissural fibres and thalamic radiations.

The R² are shown adjusted for age, time since injury and sex. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| Projection Fibres | Trauma Controls ~6months after injury | | | | | | Patients after TBI ~6months after injury | | | | | | Patients after TBI >5 years after injury | | | | | |
|--|---------------------------------------|---------|--------------|---------------------|---------|---------------|--|---------|-------------------|---------------------|----------|-------------------|--|---------|--------------|---------------------|---------|--------------|
| | FA | | | MD | | | FA | | | MD | | | FA | | | MD | | |
| | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value |
| <i>Corticospinal tract Right</i> | -0.09 | 0.671 | 0.886 | -0.18 | 0.961 | 0.985 | 0.08 | 0.006 | 0.007* | 0.34 | 0.000 | <0.001* | -0.05 | 0.626 | 0.891 | 0.16 | 0.071 | 0.748 |
| <i>Corticospinal tract Left</i> | -0.16 | 0.924 | 0.983 | -0.03 | 0.506 | 0.750 | 0.06 | 0.020 | 0.021* | 0.25 | 0.000 | <0.001* | -0.05 | 0.626 | 0.891 | 0.11 | 0.135 | 0.748 |
| Commissural Fibres | | | | | | | | | | | | <0.001* | | | | | | |
| <i>CC Genu</i> | -0.16 | 0.906 | 0.983 | 0.19 | 0.111 | 0.295 | 0.11 | 0.001 | 0.001* | 0.39 | 0.000 | <0.001* | 0.07 | 0.204 | 0.748 | 0.26 | 0.018 | 0.748 |
| <i>CC Body</i> | -0.14 | 0.842 | 0.945 | 0.35 | 0.022 | 0.104 | 0.20 | 0.000 | <0.001* | 0.50 | <2.2e-16 | <0.001* | 0.11 | 0.142 | 0.748 | 0.22 | 0.032 | 0.748 |
| <i>Splenium</i> | -0.13 | 0.816 | 0.945 | 0.36 | 0.022 | 0.104 | 0.11 | 0.001 | 0.001* | 0.40 | 0.000 | <0.001* | 0.12 | 0.126 | 0.748 | 0.19 | 0.051 | 0.748 |
| <i>Commissure Anterior</i> | 0.13 | 0.170 | 0.389 | 0.14 | 0.164 | 0.388 | 0.18 | 0.000 | <0.001* | 0.28 | 0.000 | <0.001* | -0.02 | 0.495 | 0.851 | 0.07 | 0.208 | 0.748 |
| <i>Fornix Right</i> | 0.47 | 0.006 | 0.077 | 0.36 | 0.022 | 0.104 | 0.27 | 0.000 | <0.001* | 0.16 | 0.000 | <0.001* | -0.04 | 0.584 | 0.886 | 0.02 | 0.344 | 0.755 |
| <i>Fornix Left</i> | 0.45 | 0.007 | 0.077 | 0.45 | 0.007 | 0.077 | 0.32 | 0.000 | <0.001* | 0.34 | 0.000 | <0.001* | -0.04 | 0.584 | 0.886 | -0.05 | 0.626 | 0.891 |
| Thalamic Radiations | | | | | | | | | | | | | | | | | | |
| <i>Thalamo-prefrontal Right</i> | -0.01 | 0.451 | 0.710 | 0.32 | 0.031 | 0.127 | 0.38 | 0.000 | <0.001* | 0.33 | 0.000 | <0.001* | 0.18 | 0.331 | 0.755 | 0.20 | 0.293 | 0.748 |
| <i>Thalamo-prefrontal Left</i> | 0.08 | 0.249 | 0.468 | 0.50 | 0.004 | 0.070 | 0.31 | 0.000 | <0.001* | 0.44 | 0.000 | <0.001* | 0.11 | 0.570 | 0.886 | 0.11 | 0.571 | 0.886 |
| <i>Thalamo-premotor Right</i> | -0.11 | 0.742 | 0.927 | 0.41 | 0.011 | 0.077 | 0.24 | 0.000 | <0.001* | 0.44 | 0.000 | <0.001* | 0.19 | 0.300 | 0.748 | 0.06 | 0.757 | 0.916 |
| <i>Thalamo-premotor Left</i> | 0.00 | 0.429 | 0.694 | 0.57 | 0.001 | 0.066 | 0.22 | 0.000 | <0.001* | 0.40 | 0.000 | <0.001* | 0.01 | 0.955 | 0.974 | 0.21 | 0.253 | 0.748 |
| <i>Thalamo-precentral Right</i> | -0.12 | 0.790 | 0.945 | 0.13 | 0.179 | 0.396 | 0.21 | 0.000 | <0.001* | 0.44 | 0.000 | <0.001* | 0.18 | 0.340 | 0.755 | -0.05 | 0.779 | 0.916 |
| <i>Thalamo-precentral Left</i> | -0.11 | 0.767 | 0.938 | 0.41 | 0.012 | 0.080 | 0.11 | 0.001 | 0.001 | 0.35 | 0.000 | <0.001* | 0.24 | 0.189 | 0.748 | -0.05 | 0.793 | 0.916 |
| <i>Thalamo-postcentral Right</i> | -0.05 | 0.555 | 0.800 | -0.11 | 0.752 | 0.929 | 0.00 | 0.378 | 0.379 | 0.34 | 0.000 | <0.001* | 0.22 | 0.239 | 0.748 | -0.24 | 0.185 | 0.748 |
| <i>Thalamo-postcentral Left</i> | -0.18 | 0.959 | 0.985 | 0.18 | 0.122 | 0.310 | 0.04 | 0.059 | 0.060 | 0.30 | 0.000 | <0.001* | 0.26 | 0.160 | 0.748 | -0.12 | 0.533 | 0.882 |
| <i>Thalamo-parietal Right</i> | -0.07 | 0.624 | 0.862 | 0.42 | 0.010 | 0.077 | 0.17 | 0.000 | <0.001* | 0.45 | 0.000 | <0.001* | -0.04 | 0.833 | 0.920 | 0.17 | 0.355 | 0.755 |
| <i>Thalamo-parietal Left</i> | -0.17 | 0.932 | 0.983 | 0.37 | 0.018 | 0.104 | 0.14 | 0.000 | <0.001* | 0.44 | 0.000 | <0.001* | 0.08 | 0.653 | 0.891 | 0.05 | 0.781 | 0.916 |
| <i>Thalamo-occipital Right</i> | 0.13 | 0.180 | 0.396 | 0.52 | 0.003 | 0.066 | 0.16 | 0.000 | <0.001* | 0.47 | 0.000 | <0.001* | -0.22 | 0.236 | 0.748 | 0.32 | 0.079 | 0.748 |
| <i>Thalamo-occipital Left</i> | -0.02 | 0.460 | 0.712 | 0.38 | 0.017 | 0.104 | 0.17 | 0.000 | <0.001* | 0.34 | 0.000 | <0.001* | -0.17 | 0.371 | 0.761 | 0.17 | 0.365 | 0.760 |
| <i>Superior Thalamic Radiation Right</i> | -0.08 | 0.643 | 0.869 | 0.29 | 0.044 | 0.157 | 0.11 | 0.001 | 0.001 | 0.40 | 0.000 | <0.001* | 0.15 | 0.436 | 0.821 | -0.09 | 0.618 | 0.891 |
| <i>Superior Thalamic Radiation Left</i> | 0.04 | 0.323 | 0.562 | 0.52 | 0.003 | 0.066 | 0.06 | 0.021 | 0.021 | 0.39 | 0.000 | <0.001* | 0.19 | 0.307 | 0.748 | -0.04 | 0.849 | 0.920 |
| <i>Anterior Thalamic Radiation Right</i> | 0.07 | 0.263 | 0.486 | 0.41 | 0.012 | 0.077 | 0.41 | 0.000 | <0.001* | 0.21 | 0.000 | <0.001* | 0.11 | 0.557 | 0.886 | 0.26 | 0.161 | 0.748 |
| <i>Anterior Thalamic Radiation Left</i> | 0.19 | 0.106 | 0.288 | 0.61 | 0.001 | 0.044* | 0.34 | 0.000 | <0.001* | 0.46 | 0.000 | <0.001* | 0.08 | 0.669 | 0.891 | 0.23 | 0.214 | 0.748 |

Supplementary Table S9: Correlations of GFAP with fractional anisotropy and mean diffusivity for striatal and brainstem tracts. The R² are shown adjusted for age, time since injury and sex. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| Projection Fibres | Trauma Controls ~6months after injury | | | | | | Patients after TBI ~6months after injury | | | | | | Patients after TBI >5 years after injury | | | | | |
|---|---------------------------------------|---------|---------------|---------------------|---------|--------------|--|---------|-------------------|---------------------|-----------|-------------------|--|---------|--------------|---------------------|---------|--------------|
| | FA | | | MD | | | FA | | | MD | | | FA | | | MD | | |
| | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value |
| Striatal Fibres | | | | | | | | | | | | | | | | | | |
| <i>Striato-fronto-orbital Right</i> | 0.61 | 0.001 | 0.044* | 0.42 | 0.010 | 0.077 | 0.21 | 0.000 | <0.001* | 0.27 | 0.000 | <0.001* | 0.14 | 0.457 | 0.837 | 0.05 | 0.457 | 0.837 |
| <i>Striato-fronto-orbital Left</i> | 0.61 | 0.001 | 0.044* | 0.42 | 0.010 | 0.077 | 0.21 | 0.000 | <0.001* | 0.34 | 0.000 | <0.001* | 0.20 | 0.289 | 0.748 | -0.14 | 0.289 | 0.748 |
| <i>Striato-prefrontal Right</i> | -0.08 | 0.638 | 0.869 | 0.21 | 0.209 | 0.429 | 0.37 | 0.000 | <0.001* | 0.26 | 0.000 | <0.001* | 0.21 | 0.267 | 0.748 | 0.16 | 0.267 | 0.748 |
| <i>Striato-prefrontal Left</i> | 0.02 | 0.365 | 0.621 | 0.46 | 0.007 | 0.077 | 0.31 | 0.000 | <0.001* | 0.43 | 0.000 | <0.001* | 0.20 | 0.272 | 0.748 | 0.08 | 0.272 | 0.748 |
| <i>Striato-premotor Right</i> | -0.13 | 0.808 | 0.945 | 0.30 | 0.038 | 0.143 | 0.27 | 0.000 | <0.001* | 0.42 | 0.000 | <0.001* | 0.25 | 0.181 | 0.748 | 0.01 | 0.181 | 0.748 |
| <i>Striato-premotor Left</i> | -0.07 | 0.616 | 0.855 | 0.51 | 0.003 | 0.066 | 0.22 | 0.000 | <0.001* | 0.38 | 0.000 | <0.001* | 0.02 | 0.897 | 0.939 | 0.22 | 0.897 | 0.939 |
| <i>Striato-precentral Right</i> | -0.14 | 0.862 | 0.955 | 0.04 | 0.317 | 0.555 | 0.22 | 0.000 | <0.001* | 0.41 | 0.000 | <0.001* | 0.20 | 0.280 | 0.748 | -0.04 | 0.280 | 0.748 |
| <i>Striato-precentral Left</i> | -0.11 | 0.743 | 0.927 | 0.36 | 0.021 | 0.104 | 0.14 | 0.000 | <0.001* | 0.35 | 0.000 | <0.001* | 0.24 | 0.193 | 0.748 | -0.02 | 0.193 | 0.748 |
| <i>Striato-postcentral Right</i> | -0.19 | 0.982 | 0.985 | -0.08 | 0.644 | 0.869 | 0.08 | 0.006 | 0.007* | 0.37 | 0.000 | <0.001* | 0.24 | 0.194 | 0.748 | -0.17 | 0.194 | 0.748 |
| <i>Striato-postcentral Left</i> | -0.16 | 0.914 | 0.983 | 0.09 | 0.229 | 0.444 | 0.06 | 0.019 | 0.019* | 0.29 | 0.000 | <0.001* | 0.18 | 0.344 | 0.755 | -0.07 | 0.344 | 0.755 |
| <i>Striato-parietal Right</i> | -0.13 | 0.812 | 0.945 | 0.32 | 0.033 | 0.129 | 0.21 | 0.000 | <0.001* | 0.46 | 0.000 | <0.001* | 0.03 | 0.860 | 0.922 | 0.17 | 0.860 | 0.922 |
| <i>Striato-parietal Left</i> | -0.13 | 0.828 | 0.945 | 0.30 | 0.040 | 0.145 | 0.17 | 0.000 | <0.001* | 0.37 | 0.000 | <0.001* | 0.04 | 0.819 | 0.916 | 0.02 | 0.819 | 0.916 |
| <i>Striato-occipital Right</i> | 0.10 | 0.209 | 0.429 | 0.44 | 0.008 | 0.077 | 0.22 | 0.000 | <0.001* | 0.49 | < 2.2e-16 | <0.001* | -0.25 | 0.167 | 0.748 | 0.27 | 0.167 | 0.748 |
| <i>Striato-occipital Left</i> | 0.03 | 0.355 | 0.610 | 0.35 | 0.022 | 0.104 | 0.21 | 0.000 | <0.001* | 0.32 | 0.000 | <0.001* | -0.19 | 0.305 | 0.748 | 0.15 | 0.305 | 0.748 |
| Brainstem | | | | | | | | | | | | <0.001* | | | | | | |
| <i>Parieto Occipital pontine Right</i> | 0.33 | 0.031 | 0.127 | 0.11 | 0.199 | 0.426 | 0.01 | 0.237 | 0.239 | 0.40 | 0.000 | <0.001* | -0.04 | 0.820 | 0.916 | 0.13 | 0.820 | 0.916 |
| <i>Parieto Occipital pontine Left</i> | -0.12 | 0.788 | 0.945 | 0.08 | 0.242 | 0.461 | 0.07 | 0.011 | 0.011* | 0.35 | 0.000 | <0.001* | 0.13 | 0.476 | 0.851 | -0.06 | 0.476 | 0.851 |
| <i>Fronto-pontine tract Right</i> | -0.08 | 0.648 | 0.869 | 0.06 | 0.296 | 0.528 | 0.25 | 0.000 | <0.001* | 0.39 | 0.000 | <0.001* | 0.28 | 0.128 | 0.748 | -0.04 | 0.128 | 0.748 |
| <i>Fronto-pontine tract Left</i> | -0.03 | 0.496 | 0.743 | 0.10 | 0.216 | 0.429 | 0.23 | 0.000 | <0.001* | 0.35 | 0.000 | <0.001* | 0.19 | 0.305 | 0.748 | -0.04 | 0.305 | 0.748 |
| <i>Superior cerebellar peduncle Right</i> | 0.21 | 0.090 | 0.263 | -0.15 | 0.870 | 0.956 | 0.03 | 0.082 | 0.084 | 0.19 | 0.000 | <0.001* | 0.38 | 0.033 | 0.748 | -0.18 | 0.033 | 0.748 |
| <i>Superior cerebellar peduncle Left</i> | 0.06 | 0.294 | 0.528 | -0.14 | 0.843 | 0.945 | 0.02 | 0.173 | 0.175 | 0.11 | 0.001 | 0.001* | 0.23 | 0.220 | 0.748 | -0.15 | 0.220 | 0.748 |
| <i>Inferior cerebellar peduncle Right</i> | 0.26 | 0.058 | 0.193 | 0.00 | 0.421 | 0.693 | 0.15 | 0.000 | <0.001* | 0.10 | 0.002 | 0.002* | 0.33 | 0.066 | 0.748 | -0.28 | 0.066 | 0.748 |
| <i>Inferior cerebellar peduncle Left</i> | 0.38 | 0.017 | 0.104 | 0.16 | 0.133 | 0.330 | 0.06 | 0.019 | 0.019* | 0.05 | 0.044 | 0.045* | 0.38 | 0.038 | 0.748 | -0.12 | 0.038 | 0.748 |
| <i>Middle cerebellar peduncle</i> | 0.18 | 0.116 | 0.301 | -0.10 | 0.7027 | 0.89252891 | 0.01 | 0.237 | 0.239 | 0.14 | 0.000 | <0.001* | 0.31 | 0.093 | 0.748 | -0.35 | 0.093 | 0.748 |

Supplementary Table S10: Correlations of GFAP with fractional anisotropy and mean diffusivity for Association fibres. The R² are shown adjusted for age, time since injury and sex. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| Projection Fibres | Trauma Controls ~6months after injury | | | | | | Patients after TBI ~6months after injury | | | | | | Patients after TBI >5 years after injury | | | | | | |
|---|---------------------------------------|---------|--------------|---------------------|---------|--------------|--|--------------|---------------------|---------|---------|-------------------|--|---------------------|---------|--------------|---------|--------------|---------------------|
| | FA | | MD | | P-value | Adj. P-Value | FA | | MD | | P-value | Adj. P-Value | FA | | MD | | P-value | Adj. P-Value | |
| | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | | | P-value | Adj. P-Value | Adj. R ² | P-value | | | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | | | Adj. R ² |
| Association Fibres | | | | | | | | | | | | | | | | | | | |
| <i>Superior longitudinal fascicle I Right</i> | -0.16 | 0.922 | 0.983 | 0.13 | 0.169 | 0.389 | 0.34 | <0.001 | <0.001* | 0.40 | <0.001 | <0.001* | -0.12 | 0.529 | 0.882 | 0.08 | 0.675 | 0.891 | |
| <i>Superior longitudinal fascicle I Left</i> | -0.18 | 0.963 | 0.985 | 0.08 | 0.077 | 0.236 | 0.24 | <0.001 | <0.001* | 0.32 | <0.001 | <0.001* | 0.06 | 0.737 | 0.916 | -0.10 | 0.591 | 0.886 | |
| <i>Superior longitudinal fascicle II Right</i> | -0.12 | 0.795 | 0.945 | 0.18 | 0.120 | 0.310 | 0.38 | <0.001 | <0.001* | 0.44 | <0.001 | <0.001* | -0.08 | 0.666 | 0.891 | 0.18 | 0.331 | 0.755 | |
| <i>Superior longitudinal fascicle II Left</i> | -0.12 | 0.796 | 0.945 | 0.14 | 0.163 | 0.388 | 0.31 | <0.001 | <0.001* | 0.39 | <0.001 | <0.001* | 0.02 | 0.896 | 0.939 | -0.01 | 0.967 | 0.974 | |
| <i>Superior longitudinal fascicle III Right</i> | 0.10 | 0.215 | 0.429 | 0.42 | 0.010 | 0.077 | 0.49 | <0.001 | <0.001* | 0.54 | <0.001 | <0.001* | 0.09 | 0.629 | 0.891 | 0.12 | 0.521 | 0.882 | |
| <i>Superior longitudinal fascicle III Left</i> | -0.08 | 0.660 | 0.876 | 0.32 | 0.031 | 0.127 | 0.40 | 0.001 | 0.001* | 0.44 | 0.001 | 0.001* | -0.05 | 0.794 | 0.916 | 0.11 | 0.560 | 0.886 | |
| <i>Inferior longitudinal fascicle Right</i> | 0.21 | 0.092 | 0.263 | 0.24 | 0.071 | 0.224 | 0.25 | <0.001 | <0.001* | 0.40 | <0.001 | <0.001* | -0.08 | 0.681 | 0.891 | 0.08 | 0.683 | 0.891 | |
| <i>Inferior longitudinal fascicle Left</i> | 0.10 | 0.211 | 0.429 | 0.42 | 0.010 | 0.077 | 0.27 | <0.001 | <0.001* | 0.25 | <0.001 | <0.001* | 0.11 | 0.565 | 0.886 | 0.05 | 0.807 | 0.916 | |
| <i>Uncinate fascicle Right</i> | -0.14 | 0.836 | 0.945 | -0.09 | 0.699 | 0.893 | 0.24 | <0.001 | <0.001* | 0.28 | <0.001 | <0.001* | 0.05 | 0.796 | 0.916 | 0.21 | 0.246 | 0.748 | |
| <i>Uncinate fascicle Left</i> | -0.02 | 0.473 | 0.720 | -0.09 | 0.685 | 0.891 | 0.22 | <0.001 | <0.001* | 0.27 | <0.001 | <0.001* | 0.20 | 0.282 | 0.748 | 0.01 | 0.949 | 0.974 | |
| <i>Arcuate fascicle Right</i> | 0.09 | 0.238 | 0.455 | 0.11 | 0.204 | 0.429 | 0.39 | <0.001 | <0.001* | 0.49 | <0.001 | <0.001* | 0.17 | 0.372 | 0.761 | 0.12 | 0.532 | 0.882 | |
| <i>Arcuate fascicle Left</i> | -0.02 | 0.468 | 0.717 | 0.24 | 0.067 | 0.216 | 0.31 | <0.001 | <0.001* | 0.37 | <0.001 | 0.001* | 0.17 | 0.351 | 0.755 | -0.08 | 0.674 | 0.891 | |
| <i>Cingulum Right</i> | 0.00 | 0.431 | 0.694 | -0.10 | 0.734 | 0.923 | 0.23 | <0.001 | <0.001* | 0.39 | <0.001 | <0.001* | -0.08 | 0.686 | 0.891 | 0.07 | 0.697 | 0.898 | |
| <i>Cingulum Left</i> | -0.01 | 0.433 | 0.694 | -0.09 | 0.688 | 0.891 | 0.30 | <0.001 | <0.001* | 0.34 | <0.001 | <0.001* | -0.04 | 0.851 | 0.920 | -0.07 | 0.711 | 0.899 | |
| <i>Middle longitudinal fascicle Right</i> | 0.00 | 0.416 | 0.693 | 0.16 | 0.138 | 0.340 | 0.28 | <0.001 | <0.001* | 0.46 | <0.001 | <0.001* | 0.08 | 0.677 | 0.891 | 0.16 | 0.403 | 0.806 | |
| <i>Middle longitudinal fascicle Left</i> | -0.07 | 0.608 | 0.854 | 0.26 | 0.058 | 0.193 | 0.27 | <0.001 | <0.001* | 0.27 | <0.001 | <0.001* | 0.31 | 0.088 | 0.748 | 0.04 | 0.819 | 0.916 | |
| <i>Inferior occipito-frontal fascicle Right</i> | 0.13 | 0.175 | 0.390 | 0.52 | 0.003 | 0.066 | 0.28 | <0.001 | <0.001* | 0.53 | <0.001 | <0.001* | -0.19 | 0.304 | 0.748 | 0.33 | 0.072 | 0.748 | |
| <i>Inferior occipito-frontal fascicle Left</i> | 0.10 | 0.213 | 0.429 | 0.48 | 0.005 | 0.076 | 0.28 | <0.001 | <0.001* | 0.49 | <0.001 | 0.001* | 0.01 | 0.970 | 0.974 | 0.23 | 0.208 | 0.748 | |
| <i>Optic Radiation Right</i> | 0.08 | 0.250 | 0.468 | 0.51 | 0.003 | 0.069 | 0.18 | <0.001 | <0.001* | 0.47 | <0.001 | <0.001* | -0.21 | 0.267 | 0.748 | 0.34 | 0.063 | 0.748 | |
| <i>Optic Radiation Left</i> | -0.05 | 0.553 | 0.800 | 0.37 | 0.018 | 0.104 | 0.17 | <0.001 | <0.001* | 0.32 | <0.001 | <0.001* | -0.14 | 0.437 | 0.821 | 0.17 | 0.365 | 0.760 | |

Supplementary Table S11: Correlations of NFL with fractional anisotropy and mean diffusivity for projection fibres, commissural fibres and thalamic radiations. The R² are shown adjusted for age, time since injury and sex. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

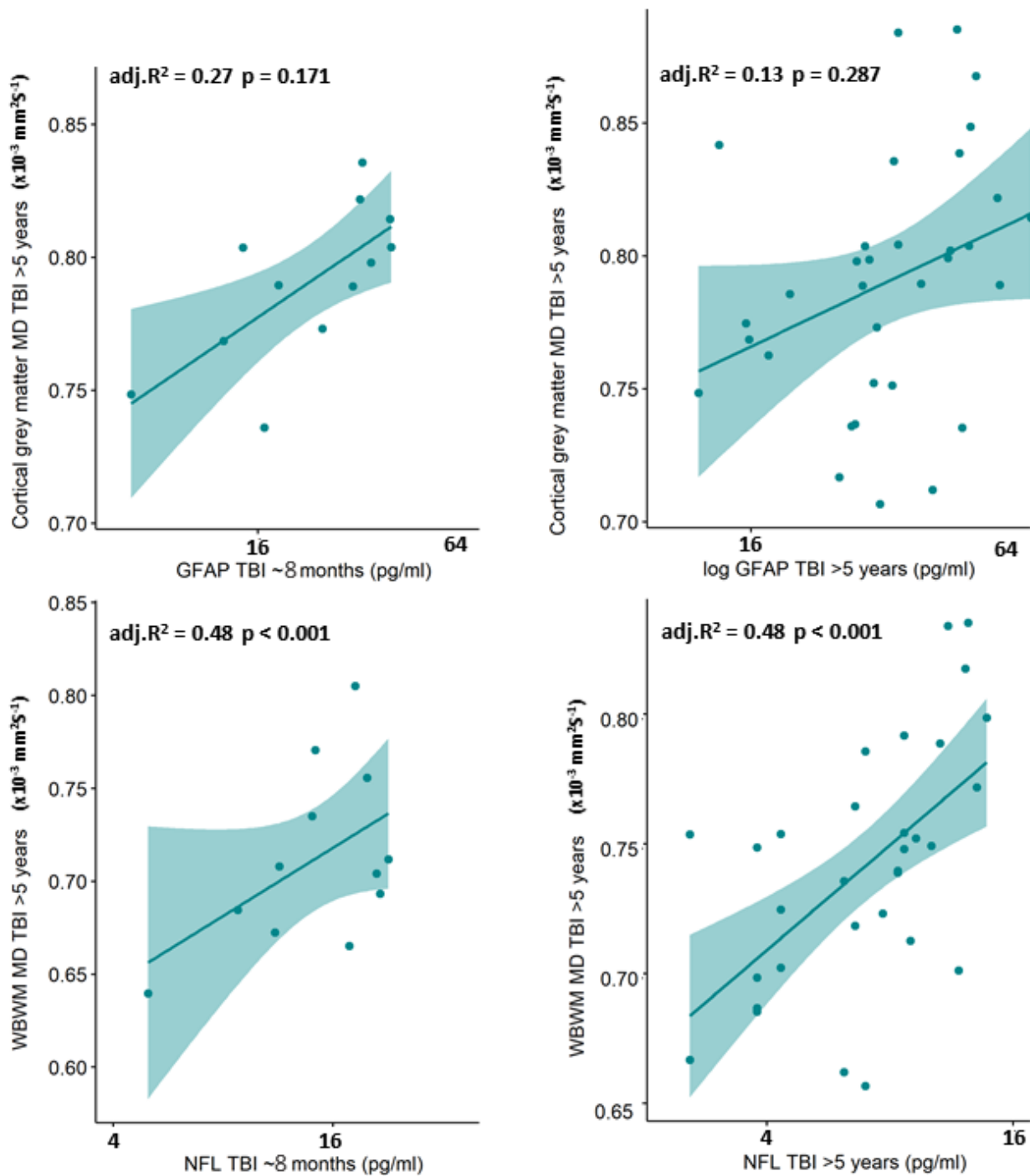
| NFL Projection Fibres | Trauma Controls ~6months after injury | | | | | | Patients after TBI ~6months after injury | | | | | | Patients after TBI >5 years after injury | | | | | |
|--|---------------------------------------|---------|--------------|---------------------|-----------|---------------|--|---------|-------------------|---------------------|---------|-------------------|--|---------|--------------|---------------------|---------|--------------|
| | FA | | | MD | | | FA | | | MD | | | FA | | | MD | | |
| | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value |
| <i>Corticospinal tract Right</i> | -0.16 | 0.923 | 0.983 | -0.14 | 0.838 | 0.945 | 0.21 | <0.001 | <0.001* | 0.38 | <0.001 | <0.001* | 0.18 | 0.054 | 0.748 | -0.06 | 0.763 | 0.916 |
| <i>Corticospinal tract Left</i> | -0.13 | 0.832 | 0.945 | -0.04 | 0.537 | 0.782 | 0.14 | <0.001 | <0.001* | 0.28 | <0.001 | <0.001* | 0.24 | 0.024 | 0.748 | -0.12 | 0.513 | 0.876 |
| Commissural Fibres | | | | | | | | <0.001 | 0.001* | | <0.001 | 0.001* | | | | | | |
| <i>CC Genu</i> | -0.05 | 0.568 | 0.814 | 0.22 | 0.086 | 0.260 | 0.27 | <0.001 | <0.001* | 0.43 | <0.001 | <0.001* | 0.08 | 0.189 | 0.748 | 0.22 | 0.234 | 0.748 |
| <i>CC Body</i> | -0.17 | 0.929 | 0.983 | 0.35 | 0.023 | 0.104 | 0.33 | <0.001 | <0.001* | 0.51 | <0.001 | <0.001* | 0.11 | 0.142 | 0.748 | 0.22 | 0.235 | 0.748 |
| <i>Splenium</i> | -0.02 | 0.466 | 0.717 | 0.31 | 0.035 | 0.136 | 0.22 | 0.001 | <0.001* | 0.40 | 0.001 | <0.001* | 0.13 | 0.107 | 0.748 | 0.13 | 0.478 | 0.851 |
| <i>Commissure Anterior</i> | 0.22 | 0.082 | 0.250 | 0.17 | 0.128 | 0.322 | 0.22 | <0.001 | <0.001* | 0.27 | <0.001 | <0.001* | 0.08 | 0.189 | 0.748 | -0.14 | 0.459 | 0.837 |
| <i>Fornix Right</i> | 0.10 | 0.214 | 0.429 | 0.18 | 0.115 | 0.301 | 0.30 | <0.001 | <0.001* | 0.18 | <0.001 | <0.001* | 0.25 | 0.020 | 0.748 | -0.29 | 0.108 | 0.748 |
| <i>Fornix Left</i> | 0.42 | 0.010 | 0.077 | 0.44 | 0.009 | 0.077 | 0.35 | <0.001 | <0.001* | 0.35 | <0.001 | <0.001* | 0.23 | 0.029 | 0.748 | -0.09 | 0.622 | 0.891 |
| Thalamic Radiations | | | | | | | | <0.001 | <0.001* | | <0.001 | <0.001* | | | | | | |
| <i>Thalamo-prefrontal Right</i> | -0.03 | 0.496 | 0.743 | 0.33 | 0.031 | 0.127 | 0.45 | <0.001 | <0.001* | 0.34 | <0.001 | <0.001* | 0.05 | 0.770 | 0.916 | 0.24 | 0.185 | 0.748 |
| <i>Thalamo-prefrontal Left</i> | -0.01 | 0.447 | 0.709 | 0.49 | 0.004 | 0.071 | 0.37 | <0.001 | <0.001* | 0.46 | <0.001 | <0.001* | 0.05 | 0.777 | 0.916 | 0.22 | 0.229 | 0.748 |
| <i>Thalamo-premotor Right</i> | -0.14 | 0.858 | 0.954 | 0.41 | 0.011 | 0.077 | 0.30 | <0.001 | <0.001* | 0.46 | <0.001 | <0.001* | 0.07 | 0.705 | 0.898 | 0.28 | 0.124 | 0.748 |
| <i>Thalamo-premotor Left</i> | -0.12 | 0.770 | 0.938 | 0.55 | 0.002 | 0.066 | 0.25 | <0.001 | 0.001* | 0.41 | <0.001 | 0.001* | 0.00 | 0.983 | 0.983 | 0.20 | 0.276 | 0.748 |
| <i>Thalamo-precentral Right</i> | -0.18 | 0.955 | 0.985 | 0.16 | 0.142 | 0.345 | 0.31 | <0.001 | <0.001* | 0.47 | <0.001 | <0.001* | 0.10 | 0.582 | 0.886 | 0.14 | 0.441 | 0.821 |
| <i>Thalamo-precentral Left</i> | -0.18 | 0.955 | 0.985 | 0.41 | 0.012 | 0.077 | 0.17 | <0.001 | <0.001* | 0.35 | <0.001 | <0.001* | 0.15 | 0.411 | 0.810 | 0.10 | 0.606 | 0.891 |
| <i>Thalamo-postcentral Right</i> | -0.08 | 0.657 | 0.876 | -0.11 | 0.753 | 0.929 | 0.10 | 0.002 | 0.002* | 0.42 | <0.001 | <0.001* | 0.15 | 0.425 | 0.821 | -0.06 | 0.766 | 0.916 |
| <i>Thalamo-postcentral Left</i> | -0.13 | 0.830 | 0.945 | 0.19 | 0.104 | 0.287 | 0.13 | <0.001 | 0.001* | 0.32 | <0.001 | <0.001* | 0.14 | 0.439 | 0.821 | 0.07 | 0.704 | 0.898 |
| <i>Thalamo-parietal Right</i> | -0.16 | 0.919 | 0.983 | 0.43 | 0.009 | 0.077 | 0.31 | <0.001 | <0.001* | 0.50 | <0.001 | <0.001* | 0.04 | 0.820 | 0.916 | 0.09 | 0.648 | 0.891 |
| <i>Thalamo-parietal Left</i> | -0.18 | 0.971 | 0.985 | 0.36 | 0.020 | 0.104 | 0.23 | <0.001 | <0.001* | 0.44 | <0.001 | <0.001* | 0.13 | 0.490 | 0.851 | 0.17 | 0.355 | 0.755 |
| <i>Thalamo-occipital Right</i> | 0.05 | 0.045 | 0.159 | 0.50 | 0.004 | 0.070 | 0.30 | <0.001 | 0.001* | 0.52 | <0.001 | <0.001* | 0.06 | 0.764 | 0.916 | 0.22 | 0.242 | 0.748 |
| <i>Thalamo-occipital Left</i> | -0.03 | 0.496 | 0.743 | 0.34 | 0.026 | 0.120 | 0.19 | <0.001 | <0.001* | 0.30 | <0.001 | <0.001* | -0.01 | 0.969 | 0.974 | 0.26 | 0.150 | 0.748 |
| <i>Superior Thalamic Radiation Right</i> | -0.11 | 0.761 | 0.935 | 0.30 | 0.038 | 0.143 | 0.21 | 0.001 | <0.001* | 0.44 | <0.001 | <0.001* | 0.08 | 0.669 | 0.891 | 0.04 | 0.819 | 0.916 |
| <i>Superior Thalamic Radiation Left</i> | -0.01 | 0.453 | 0.710 | 0.52 | 0.003 | 0.066 | 0.11 | 0.001 | 0.002* | 0.38 | <0.001 | <0.001* | 0.10 | 0.595 | 0.886 | 0.04 | 0.850 | 0.920 |
| <i>Anterior Thalamic Radiation Right</i> | 0.05 | 0.299 | 0.530 | 0.41 | 0.011 | 0.077 | 0.49 | <0.001 | <0.001* | 0.21 | <0.001 | 0.001* | -0.08 | 0.665 | 0.891 | 0.26 | 0.158 | 0.748 |
| <i>Anterior Thalamic Radiation Left</i> | 0.11 | 0.208 | 0.429 | 0.61 | 0.0006529 | 0.044* | 0.42 | <0.001 | <0.001* | 0.50 | 0.001 | <0.001* | -0.02 | 0.933 | 0.965 | 0.24 | 0.197 | 0.748 |

Supplementary Table S12: Correlations of NFL with fractional anisotropy and mean diffusivity for striatal and brainstem tracts. The R² are shown adjusted for age, time since injury and sex. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

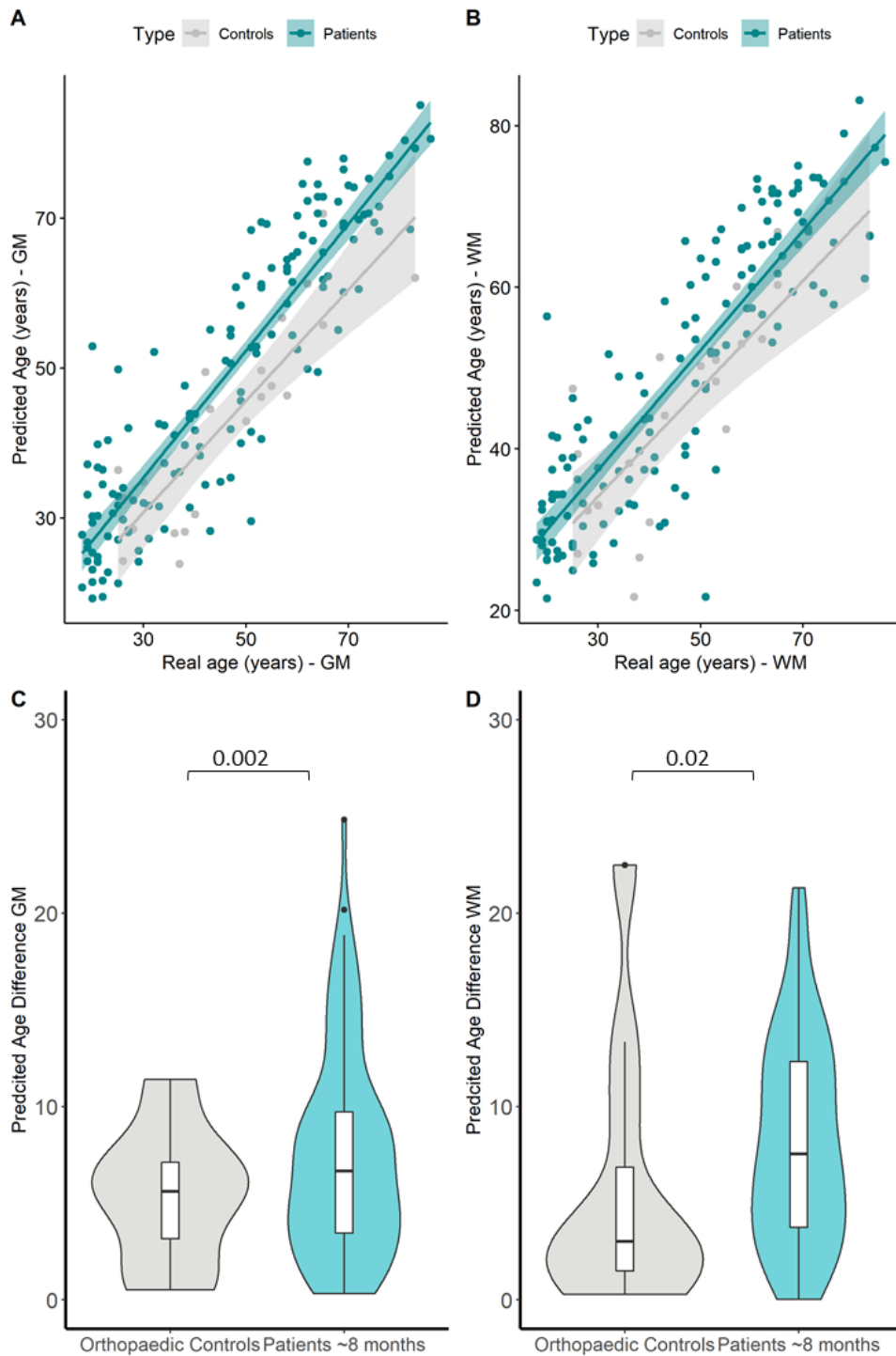
| Projection Fibres | Trauma Controls ~6months after injury | | | | | | Patients after TBI ~6months after injury | | | | | | Patients after TBI >5 years after injury | | | | | |
|---|---------------------------------------|---------|--------------|---------------------|---------|--------------|--|---------|-------------------|---------------------|---------|-------------------|--|---------|--------------|---------------------|---------|--------------|
| | FA | | MD | | | | FA | | MD | | | | FA | | MD | | | |
| | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value |
| Striatal Fibres | | | | | | | | | | | | | | | | | | |
| <i>Striato-fronto-orbital Right</i> | 0.35 | 0.022 | 0.104 | -0.04 | 0.529 | 0.774 | 0.32 | <0.001 | <0.001* | 0.42 | <0.001 | <0.001* | 0.13 | 0.491 | 0.851 | 0.17 | 0.376 | 0.763 |
| <i>Striato-fronto-orbital Left</i> | 0.35 | 0.022 | 0.104 | 0.28 | 0.050 | 0.171 | 0.32 | <0.001 | <0.001* | 0.42 | <0.001 | <0.001* | 0.08 | 0.688 | 0.891 | -0.03 | 0.885 | 0.939 |
| <i>Striato-prefrontal Right</i> | 0.08 | 0.648 | 0.869 | 0.21 | 0.092 | 0.263 | 0.44 | <0.001 | 0.001* | 0.27 | <0.001 | 0.001* | 0.10 | 0.611 | 0.891 | 0.18 | 0.342 | 0.755 |
| <i>Striato-prefrontal Left</i> | -0.07 | 0.612 | 0.854 | 0.43 | 0.009 | 0.077 | 0.39 | <0.001 | <0.001* | 0.46 | <0.001 | <0.001* | 0.10 | 0.588 | 0.886 | 0.20 | 0.287 | 0.748 |
| <i>Striato-premotor Right</i> | -0.12 | 0.793 | 0.945 | 0.31 | 0.036 | 0.136 | 0.30 | <0.001 | <0.001* | 0.43 | <0.001 | <0.001* | 0.01 | 0.963 | 0.974 | 0.20 | 0.299 | 0.748 |
| <i>Striato-premotor Left</i> | -0.17 | 0.939 | 0.985 | 0.45 | 0.007 | 0.077 | 0.25 | 0.001 | <0.001* | 0.39 | 0.001 | <0.001* | 0.08 | 0.675 | 0.891 | 0.19 | 0.300 | 0.748 |
| <i>Striato-precentral Right</i> | -0.17 | 0.928 | 0.983 | 0.06 | 0.292 | 0.528 | 0.30 | <0.001 | <0.001* | 0.44 | <0.001 | <0.001* | -0.10 | 0.594 | 0.886 | 0.16 | 0.393 | 0.792 |
| <i>Striato-precentral Left</i> | -0.19 | 0.981 | 0.985 | 0.35 | 0.023 | 0.104 | 0.19 | <0.001 | <0.001* | 0.34 | <0.001 | <0.001* | 0.18 | 0.320 | 0.755 | 0.11 | 0.567 | 0.886 |
| <i>Striato-postcentral Right</i> | -0.18 | 0.967 | 0.985 | -0.08 | 0.643 | 0.869 | 0.21 | <0.001 | <0.001* | 0.44 | <0.001 | <0.001* | 0.03 | 0.888 | 0.939 | 0.04 | 0.675 | 0.891 |
| <i>Striato-postcentral Left</i> | -0.16 | 0.904 | 0.983 | 0.11 | 0.207 | 0.429 | 0.15 | <0.001 | <0.001* | 0.31 | <0.001 | <0.001* | 0.14 | 0.439 | 0.821 | 0.08 | 0.675 | 0.891 |
| <i>Striato-parietal Right</i> | -0.18 | 0.974 | 0.985 | 0.33 | 0.029 | 0.125 | 0.36 | <0.001 | <0.001* | 0.50 | <0.001 | <0.001* | 0.04 | 0.841 | 0.920 | 0.09 | 0.642 | 0.891 |
| <i>Striato-parietal Left</i> | -0.17 | 0.941 | 0.985 | 0.30 | 0.040 | 0.145 | 0.26 | <0.001 | <0.001* | 0.36 | <0.001 | <0.001* | 0.09 | 0.625 | 0.891 | 0.19 | 0.299 | 0.748 |
| <i>Striato-occipital Right</i> | 0.06 | 0.294 | 0.528 | 0.43 | 0.010 | 0.077 | 0.37 | <0.001 | <0.001* | 0.52 | <0.001 | <0.001* | -0.05 | 0.775 | 0.916 | 0.18 | 0.333 | 0.755 |
| <i>Striato-occipital Left</i> | 0.01 | 0.395 | 0.666 | 0.33 | 0.031 | 0.127 | 0.22 | <0.001 | 0.001* | 0.27 | <0.001 | 0.001* | -0.06 | 0.746 | 0.916 | 0.26 | 0.157 | 0.748 |
| Brainstem | | | | | | | | | | | | | | | | | | |
| <i>Parieto Occipital pontine Right</i> | -0.20 | 0.997 | 0.997 | 0.12 | 0.186 | 0.401 | 0.29 | <0.001 | <0.001* | 0.46 | <0.001 | <0.001* | 0.12 | 0.537 | 0.883 | 0.07 | 0.720 | 0.906 |
| <i>Parieto Occipital pontine Left</i> | 0.18 | 0.960 | 0.985 | 0.08 | 0.255 | 0.474 | 0.17 | <0.001 | 0.002* | 0.36 | <0.001 | 0.002* | 0.11 | 0.572 | 0.886 | 0.13 | 0.482 | 0.851 |
| <i>Fronto-pontine tract Right</i> | -0.13 | 0.807 | 0.945 | 0.05 | 0.305 | 0.538 | 0.33 | <0.001 | 0.001* | 0.42 | <0.001 | 0.001* | 0.22 | 0.233 | 0.748 | 0.13 | 0.487 | 0.851 |
| <i>Fronto-pontine tract Left</i> | -0.13 | 0.808 | 0.945 | 0.09 | 0.228 | 0.444 | 0.30 | <0.001 | <0.001* | 0.37 | <0.001 | <0.001* | 0.20 | 0.288 | 0.748 | 0.11 | 0.566 | 0.886 |
| <i>Superior cerebellar peduncle Right</i> | 0.26 | 0.058 | 0.193 | 0.17 | 0.130 | 0.326 | 0.08 | 0.008 | 0.009* | 0.20 | <0.001 | <0.001* | 0.36 | 0.047 | 0.748 | -0.20 | 0.286 | 0.748 |
| <i>Superior cerebellar peduncle Left</i> | 0.15 | 0.154 | 0.371 | -0.13 | 0.834 | 0.945 | 0.08 | 0.007 | 0.007* | 0.17 | <0.001 | 0.001* | 0.18 | 0.328 | 0.755 | -0.21 | 0.258 | 0.748 |
| <i>Inferior cerebellar peduncle Right</i> | 0.21 | 0.090 | 0.263 | 0.32 | 0.032 | 0.129 | 0.17 | <0.001 | 0.001* | 0.11 | 0.001 | <0.001* | 0.30 | 0.100 | 0.748 | -0.21 | 0.254 | 0.748 |
| <i>Inferior cerebellar peduncle Left</i> | 0.24 | 0.071 | 0.224 | 0.28 | 0.048 | 0.168 | 0.11 | 0.001 | 0.002* | 0.13 | <0.001 | <0.001* | 0.30 | 0.106 | 0.748 | -0.20 | 0.292 | 0.748 |
| <i>Middle cerebellar peduncle</i> | 0.19 | 0.108 | 0.290 | -0.07 | 0.610 | 0.854 | 0.06 | 0.020 | 0.020* | 0.20 | <0.001 | <0.001* | 0.41 | 0.021 | 0.748 | -0.34 | 0.058 | 0.748 |

Supplementary Table S13: Correlations of GFAP with fractional anisotropy and mean diffusivity for Association fibres. The R² are shown adjusted for age, time since injury and sex. Adjusted p-values (Benjamini & Hochberg Correction) are significant if <0.05. Significant values are shown in bold with *

| Projection Fibres | Trauma Controls ~6months after injury | | | | | | Patients after TBI ~6months after injury | | | | | | Patients after TBI >5 years after injury | | | | | |
|---|---------------------------------------|---------|--------------|---------------------|---------|--------------|--|---------|-------------------|---------------------|---------|-------------------|--|---------|--------------|---------------------|---------|--------------|
| | FA | | MD | | P-value | | FA | | MD | | P-value | | FA | | MD | | P-value | |
| | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value | Adj. R ² | P-value | Adj. P-Value |
| Association Fibres | | | | | | | | | | | | | | | | | | |
| <i>Superior longitudinal fascicle I Right</i> | -0.12 | 0.800 | 0.945 | 0.13 | 0.167 | 0.389 | 0.44 | <0.001 | <0.001* | 0.45 | <0.001 | <0.001* | -0.09 | 0.639 | 0.891 | 0.04 | 0.817 | 0.916 |
| <i>Superior longitudinal fascicle I Left</i> | -0.09 | 0.695 | 0.893 | 0.06 | 0.278 | 0.510 | 0.33 | <0.001 | <0.001* | 0.34 | <0.001 | <0.001* | 0.18 | 0.323 | 0.755 | 0.06 | 0.764 | 0.916 |
| <i>Superior longitudinal fascicle II Right</i> | -0.09 | 0.682 | 0.891 | 0.21 | 0.091 | 0.263 | 0.47 | <0.001 | 0.001* | 0.48 | <0.001 | 0.001* | -0.15 | 0.432 | 0.821 | 0.11 | 0.563 | 0.886 |
| <i>Superior longitudinal fascicle II Left</i> | 0.14 | 0.853 | 0.952 | 0.13 | 0.174 | 0.390 | 0.38 | <0.001 | <0.001* | 0.41 | <0.001 | <0.001* | -0.02 | 0.907 | 0.942 | 0.19 | 0.305 | 0.748 |
| <i>Superior longitudinal fascicle III Right</i> | 0.12 | 0.182 | 0.397 | 0.41 | 0.012 | 0.077 | 0.56 | <0.001 | <0.001* | 0.56 | <0.001 | <0.001* | -0.23 | 0.227 | 0.748 | 0.30 | 0.106 | 0.748 |
| <i>Superior longitudinal fascicle III Left</i> | 0.02 | 0.366 | 0.621 | 0.36 | 0.020 | 0.104 | 0.47 | <0.001 | <0.001* | 0.44 | <0.001 | <0.001* | 0.02 | 0.895 | 0.939 | 0.21 | 0.255 | 0.748 |
| <i>Inferior longitudinal fascicle Right</i> | 0.20 | 0.096 | 0.271 | 0.19 | 0.107 | 0.288 | 0.41 | 0.001 | <0.001* | 0.44 | 0.001 | <0.001* | 0.15 | 0.411 | 0.810 | 0.04 | 0.813 | 0.916 |
| <i>Inferior longitudinal fascicle Left</i> | 0.13 | 0.171 | 0.389 | 0.36 | 0.021 | 0.104 | 0.30 | <0.001 | <0.001* | 0.22 | <0.001 | <0.001* | 0.19 | 0.295 | 0.748 | 0.15 | 0.434 | 0.821 |
| <i>Uncinate fascicle Right</i> | -0.09 | 0.700 | 0.893 | -0.14 | 0.866 | 0.955 | 0.37 | <0.001 | <0.001* | 0.30 | <0.001 | <0.001* | 0.10 | 0.585 | 0.886 | 0.22 | 0.232 | 0.748 |
| <i>Uncinate fascicle Left</i> | 0.01 | 0.407 | 0.681 | -0.01 | 0.456 | 0.711 | 0.30 | <0.001 | <0.001* | 0.30 | <0.001 | <0.001* | 0.25 | 0.168 | 0.748 | -0.04 | 0.830 | 0.920 |
| <i>Arcuate fascicle Right</i> | 0.09 | 0.232 | 0.447 | 0.13 | 0.171 | 0.389 | 0.50 | <0.001 | <0.001* | 0.53 | <0.001 | <0.001* | 0.12 | 0.525 | 0.882 | 0.18 | 0.341 | 0.755 |
| <i>Arcuate fascicle Left</i> | -0.01 | 0.444 | 0.709 | 0.24 | 0.073 | 0.227 | 0.38 | <0.001 | <0.001* | 0.36 | <0.001 | <0.001* | 0.23 | 0.210 | 0.748 | 0.17 | 0.366 | 0.760 |
| <i>Cingulum Right</i> | -0.04 | 0.523 | 0.769 | -0.10 | 0.722 | 0.912 | 0.34 | <0.001 | <0.001* | 0.42 | <0.001 | <0.001* | 0.04 | 0.842 | 0.920 | 0.02 | 0.903 | 0.942 |
| <i>Cingulum Left</i> | -0.03 | 0.499 | 0.743 | -0.09 | 0.686 | 0.891 | 0.40 | <0.001 | 0.001* | 0.38 | <0.001 | 0.001* | 0.01 | 0.945 | 0.974 | 0.06 | 0.729 | 0.913 |
| <i>Middle longitudinal fascicle Right</i> | 0.00 | 0.421 | 0.693 | 0.20 | 0.101 | 0.283 | 0.41 | <0.001 | <0.001* | 0.51 | <0.001 | <0.001* | 0.13 | 0.495 | 0.851 | 0.04 | 0.849 | 0.920 |
| <i>Middle longitudinal fascicle Left</i> | -0.06 | 0.581 | 0.828 | 0.25 | 0.063 | 0.204 | 0.32 | <0.001 | <0.001* | 0.25 | <0.001 | <0.001* | 0.27 | 0.150 | 0.748 | 0.23 | 0.215 | 0.748 |
| <i>Inferior occipito-frontal fascicle Right</i> | 0.10 | 0.221 | 0.436 | 0.51 | 0.003 | 0.066 | 0.42 | <0.001 | 0.001* | 0.54 | <0.001 | 0.001* | -0.06 | 0.742 | 0.916 | 0.31 | 0.094 | 0.748 |
| <i>Inferior occipito-frontal fascicle Left</i> | 0.04 | 0.329 | 0.568 | 0.46 | 0.006 | 0.077 | 0.34 | 0.001 | <0.001* | 0.47 | 0.001 | <0.001* | 0.17 | 0.351 | 0.755 | 0.31 | 0.085 | 0.748 |
| <i>Optic Radiation Right</i> | 0.00 | 0.429 | 0.694 | 0.48 | 0.005 | 0.075 | 0.31 | <0.001 | <0.001* | 0.51 | <0.001 | <0.001* | 0.07 | 0.707 | 0.898 | 0.22 | 0.230 | 0.748 |
| <i>Optic Radiation Left</i> | -0.06 | 0.589 | 0.836 | 0.33 | 0.028 | 0.124 | 0.19 | <0.001 | <0.001* | 0.28 | <0.001 | <0.001* | 0.01 | 0.960 | 0.974 | 0.28 | 0.122 | 0.748 |

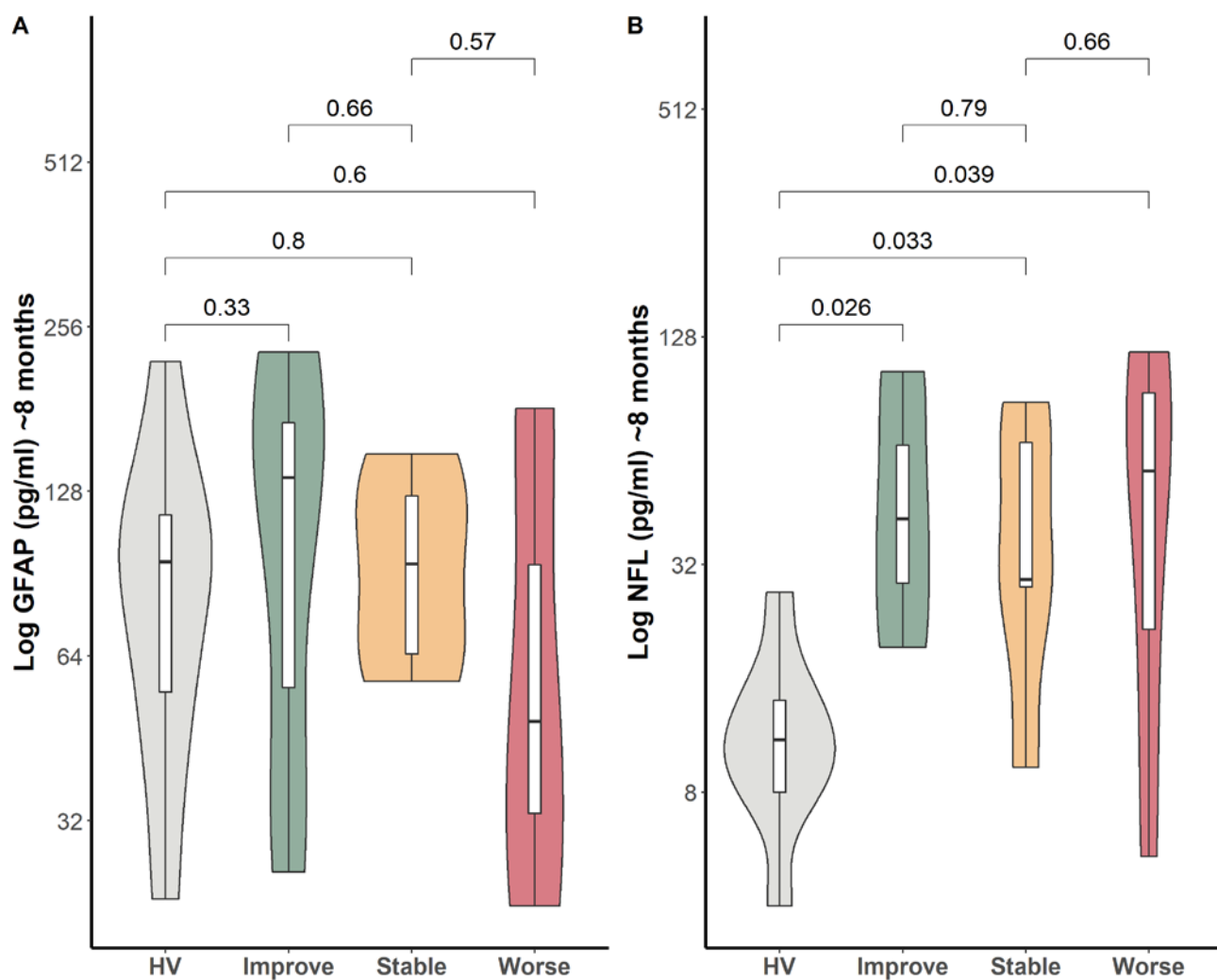


Supplementary Figure S3. GFAP at ~8 months is associated with WBGM MD levels >5 years after injury (Panel A). NFL levels >5 years after injury significantly correlate with MD in WBWM (Panel D). The correlations of panels A and C become non-significant when corrected for age and sex (A: adjusted R^2 0.27 $p = 0.171$, C: adjusted R^2 -0.02 $p = 0.471$).



Supplementary Figure S4. Predicted brain age and predicted brain age difference for patients imaged ~8 months after injury compared to orthopaedic trauma controls.

Predicted brain age versus actual for grey matter (WBGM) (Panel A: Orthopaedic trauma controls $R = 0.86$ $P < 0.0001$, Patients $R = 0.79$, $P < 0.0001$) and white matter (WBWM) (Panel B: Orthopaedic trauma controls $R = 0.90$, $P < 0.0001$, Patients $R = 0.88$, $P < 0.0001$). Comparison of predicted brain age difference and mean Jacobian Determinants for WBGM and WBWM between orthopaedic trauma controls and patients ~8 months after injury (Mann-Whitney U, Uncorrected p-values; WBGM $p = 0.002$, WBWM $p = 0.02$) (Panels C and D).

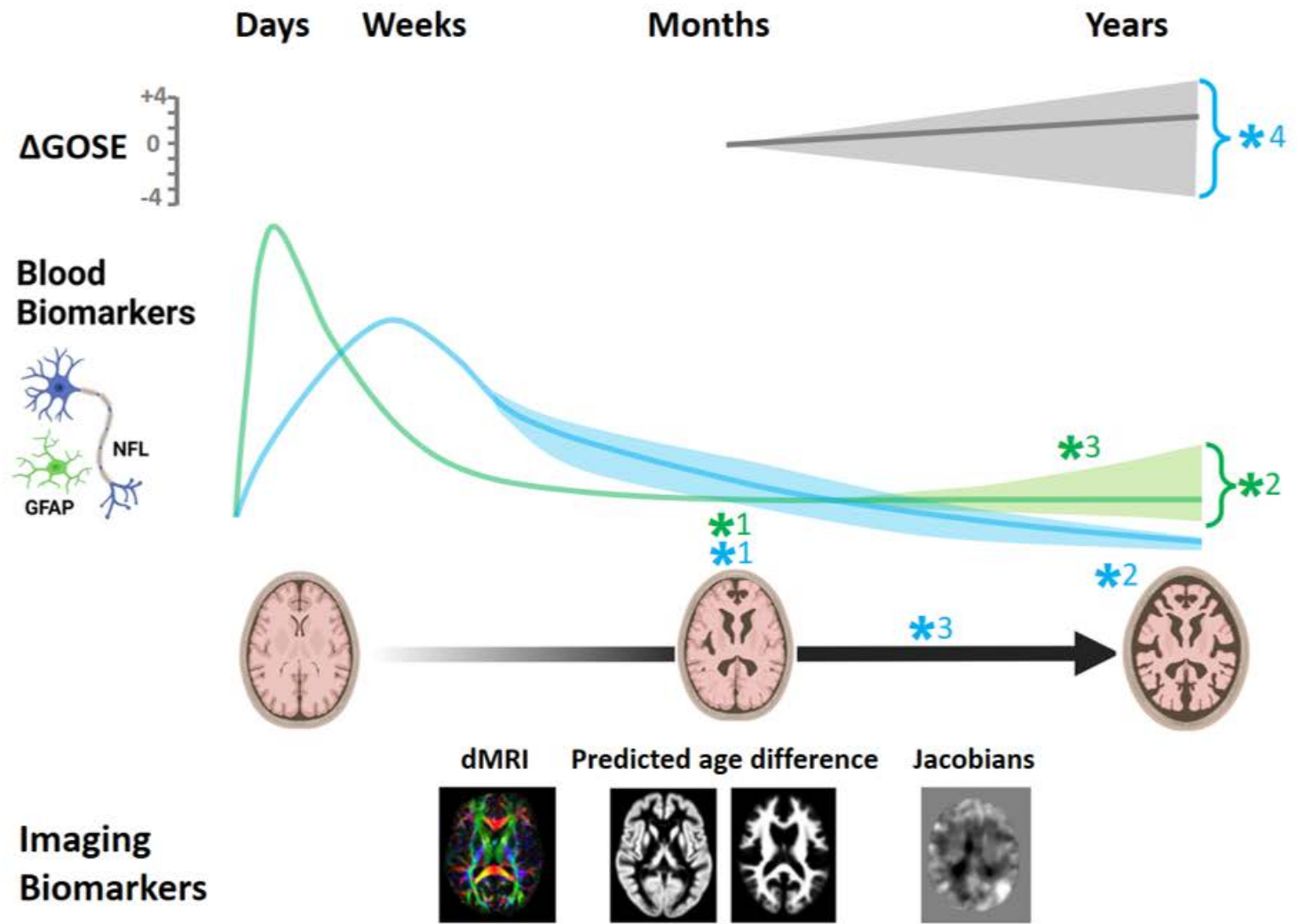


Supplementary Figure S5. Levels of GFAP and NFL taken at ~8 months after injury (panels A and B) in subgroups of patients who showed improving (Improve; increase in GOSE \geq 1 point), Stable (no change in GOSE), or worsening (Worse; reduction in GOSE \geq 1 point) between ~8 months and >5 years post-injury.

HV = healthy volunteers. Figures above box plots show unadjusted p values for comparisons (Mann-Whitney 'U').

Key findings

- *1: NFL at ~8 m correlates with imaging at ~8 months
- *1: GFAP at ~8 months correlates with imaging at ~8 months
- *2: NFL at > 5 years correlates with imaging at >5 years
- *2: Variable secondary elevation of GFAP at >5 years
- *3: NFL at ~8 months predicts change in imaging (~8m → >5y)
- *3: GFAP at ~8 months predicts GFAP at >5 years
- *4: NFL at 5 years differs depending on GOSE trajectory



Supplementary Figure S6. Schematic diagram summarising the key results.