

Supplementary Material: MRI

Supplementary Methods: MRI Acquisition and Processing

MRI Protocols

Scans were acquired on a Siemens Prisma 3T with a 32-channel head coil. The protocol included:

- T1-weighted MPRAGE: TR = 2200 ms, TI = 900 ms, flip angle = 8°, voxel size = 1.0 mm isotropic.
- 3D FLAIR: TR = 5000 ms, TI = 1800 ms, flip angle = 120°, voxel size = 1.0 mm isotropic.
- DCE-MRI: dual flip-angle SPGR T1 mapping (TR = 2.84 ms, flip angles = 2° and 9°) for voxel-wise T1 maps; 3D FLASH (TE = 0.97 ms, TR ≈ 2.88 ms [range 2.88–4.0], flip angle 12.5°–19°, 100 volumes, in-plane resolution 1.375 × 1.375 mm, slice thickness 3 mm). Gadobutrol (0.1 mL/kg, 3 mL/s).
- Diffusion MRI (DTI): single-shot EPI sequence with $b = 1000$ s/mm², 30 diffusion directions acquired twice, and one non-diffusion-weighted (b0) volume. Imaging parameters were: TR = 5600–6200 ms, TE = 54–61 ms, 60 axial slices, voxel size 2.0 × 2.0 × 2.0 mm³.

If a participant had multiple scans within a short interval, we retained the earliest scan that passed QC and had same-session 3D T1 and FLAIR suitable for segmentation/co-registration.

Anatomical Segmentation

FreeSurfer v7.2 was used for cortical and subcortical segmentation [1]. Additional processing details are available elsewhere [2]. The choroid plexus (ChP) was segmented using a deep learning model [3] on FLAIR. ROIs included ChP, putamen, thalamus, caudate, hippocampus, parietal, temporal, frontal, and occipital cortex. White matter and brainstem were extracted but excluded from multiple-comparison correction due to unreliable kinetic modeling. Both regions showed atypical baseline signals and early timepoints inconsistent with physiological uptake curves, suggesting modeling instability. In white matter, this likely reflects low

perfusion and partial volume effects; in the brainstem, motion, susceptibility, and anatomical heterogeneity further degrade signal quality.

All ROI masks were resampled to DCE space using FSL tools, with rigid-body alignment

DCE-MRI Pre-processing

Motion correction and T1 map registration were performed within NordicICE v4 (NordicNeuroLab, Bergen, Norway). The AIF was also extracted using NordicICE's semi-automatic vascular voxel detection algorithm within a user-defined slice positioned near the circle of Willis. The resulting curve was visually inspected and retained if physiologically plausible.

DCE-MRI Analysis

Implementation

Motion-corrected DCE series were exported from NordicICE. Individual arterial voxels as identified in NordicICE (semi-automatic vascular-voxel detection near the circle of Willis), visually quality-controlled, and converted to plasma AIFs using subject-specific hematocrit. To stabilize kinetic fitting in BBB-intact, near-zero-permeability tissue, we then constructed a cohort-derived standardized plasma AIF (cAIF) by time-aligning the subject AIFs to peak and averaging across the cohort (pre-specified in consultation with our MRI physicists). This cAIF preserves cohort-specific bolus shape while minimizing partial-volume/inflow noise from per-subject arterial voxels. All model fits — Patlak and extended Tofts (eTofts) — used the cAIF; Patlak K_{trans}, our guardrail for unidirectional influx, is minimally sensitive to AIF amplitude scaling, and our main inference (no BBB leak) does not depend on AIF choice. Pharmacokinetic modeling and model-free analyses were implemented in Python (v3.6.8) within a virtual environment. Core libraries included NumPy (v1.19.5) for array manipulation, SciPy (v1.5.4) for numerical integration (scipy.integrate.cumtrapz) and curve fitting (scipy.optimize.curve_fit), and Matplotlib (v3.3.4) for visualization. Region-wise time series were extracted using anatomical masks aligned with the DCE series via FSL's fslmeans tool. Both model-free and pharmacokinetic modeling approaches were applied across all predefined ROIs. The eTofts model yielded K_{trans} (plasma-to-EES transfer constant), V_p

(plasma volume fraction), and V_e (EES volume fraction); the Patlak model yielded K_{trans} (also termed K_i in the Patlak formulation) and V_p .

DCE-MRI can capture perfusion and clearance dynamics of the ChP stroma but standard pharmacokinetic models — such as Patlak and Tofts [4,5] — were developed for passive capillary–interstitial exchange of inert small-molecular-weight gadolinium chelates in relatively homogeneous tissues. Unlike brain parenchyma, the ChP has no BBB: its capillaries are fenestrated, permitting passive entry of Gd-chelates into the stroma, whereas the epithelium forms the BCSFB. DCE analyses in the ChP therefore pertain to stromal kinetics. ChP physiology therefore violates key assumptions of the pharmacokinetic models: stromal uptake is not rate-limited by endothelial permeability, and clearance is shaped by bulk fluid movement and active epithelial transport, rather than passive exchange toward plasma equilibrium [6–8]. Accordingly, we utilized a model-free approach — quantifying enhancement and washout directly, without assuming compartmental equilibrium. These model-free metrics capture the physiologically relevant dimensions of ChP function — stromal turnover and epithelial clearance — because they are not constrained by assumptions that require a blood–brain barrier or passive capillary–tissue equilibrium. In the ChP, where fenestrated capillaries and active epithelial transport dominate, model-free washout therefore provides the most valid in-vivo measure of clearance capacity. We treated pharmacokinetic parameters as reference indices of exchange rather than literal permeability, given the lack of a BBB, the fenestrated capillaries and active stromal clearance.

To enable comparison, model-derived parameters were also computed and analyzed across all ROIs. Values for both model-free and model-based features were extracted from anatomical ROIs defined by FreeSurfer and coregistered to the first DCE volume using FSL v6.0.3.

To correct for plasma distribution, subject-specific hematocrit (Hct) values were manually entered; Hct values were obtained from clinical laboratories within six months of imaging. In addition to the ChP, the ROIs described above were included for direct comparison of enhancement curves and to test the specificity of ChP signal dynamics.

Contrast agent (CA) concentrations were estimated using the spoiled gradient echo signal equation, assuming a fixed pre-contrast T1 value for each region of interest. Although voxel-wise T1 maps were available, fixed values were used in all analyses based on physiological plausibility and known limitations of T1 mapping in the choroid plexus, which is highly vascular and structurally heterogeneous. The following fixed T1 values (in milliseconds) were used: CSF / Ventricles: 4000; Choroid Plexus: 2000; Cerebral Cortex: 1350; Deep Gray Matter (putamen, thalamus, caudate, hippocampus): 1250; Cerebellar Gray Matter: 1250; White Matter: 850; Brainstem: 1200. These values were used for signal-to-concentration conversion in both kinetic and model-free DCE-MRI analyses.

Model-Free Curve Analysis

Contrast agent concentration units were extracted from each ChP ROI mask. From each ROI contrast agent concentration curve, we extracted: Area under the curve (AUC), Time to peak, Peak enhancement, Washout slope, Washout ratio (defined as the ratio between the mean of the final 10% of the CA curve and the peak value), Time above half-peak. We adjusted for small differences in repetition times between subjects, and metrics relying on end of scan measurements were taken from last common valid timepoint. These summary metrics were used to characterize signal dynamics across groups, independent of fitting assumptions

Pharmacokinetic Modeling

ROI-level kinetic parameters were computed using both the eTofts (which includes a plasma volume fraction (V_p) term in addition to K_{trans} and V_e from standard Tofts model). Patlak analysis was also performed to estimate V_p and K_{trans} under the assumption of unidirectional tracer uptake. Kinetic parameters were extracted from the same anatomical ROIs used in the model-free analysis. Because models assume synchronous AIF and tissue arrival, we implemented an iterative AIF time-shift strategy to account for vascular delay. For each ROI, a set of $\pm N$ TR shifts were applied to the subject-specific AIF. For each candidate shift, the model was fitted and residual sum of squares (RSS) computed. The final model was selected based on lowest RSS, thereby identifying the optimal time alignment between AIF

and tissue enhancement. This approach mirrors the internal AIF time optimization in NordicICE and was particularly relevant for modeling contrast uptake in the ChP, where delays of 2–4 TRs were common.

Denoising (Exploratory)

PCA-based denoising of ChP voxel time series did not materially change curves or group differences; it was not included in final analyses.

Diffusion Tensor Imaging

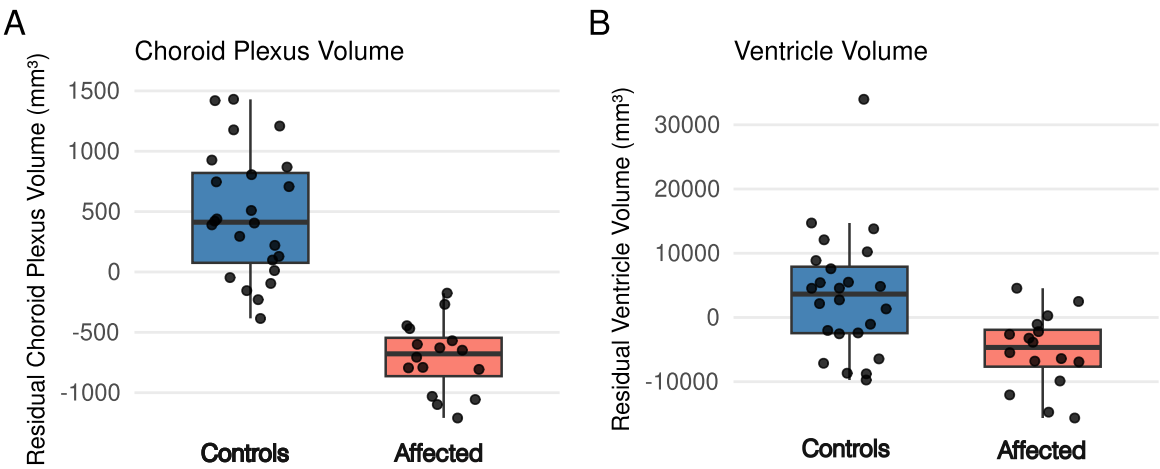
DTI was included to test for indirect evidence of protein stagnation in brain tissue, following findings of reduced parenchymal K_{trans} in dynamic contrast-enhanced (DCE) MRI. These vascular kinetic abnormalities were particularly pronounced in carriers of the suspected mitochondrial disease and suggested a widespread disturbance in CSF-mediated transport. A *priori* DTI analysis, we hypothesized that impaired clearance might lead to protein accumulation and restricted diffusion, reflected as reduced mean diffusivity (MD) in early-stage disease.

DTI data were processed using standard tools in FSL (version 6.0.7.13). Motion and eddy current correction were performed using eddy, with susceptibility-induced distortion correction via topup using a pair of reversed-phase encoding images. FA and MD maps were computed from the corrected diffusion series using dtifit.

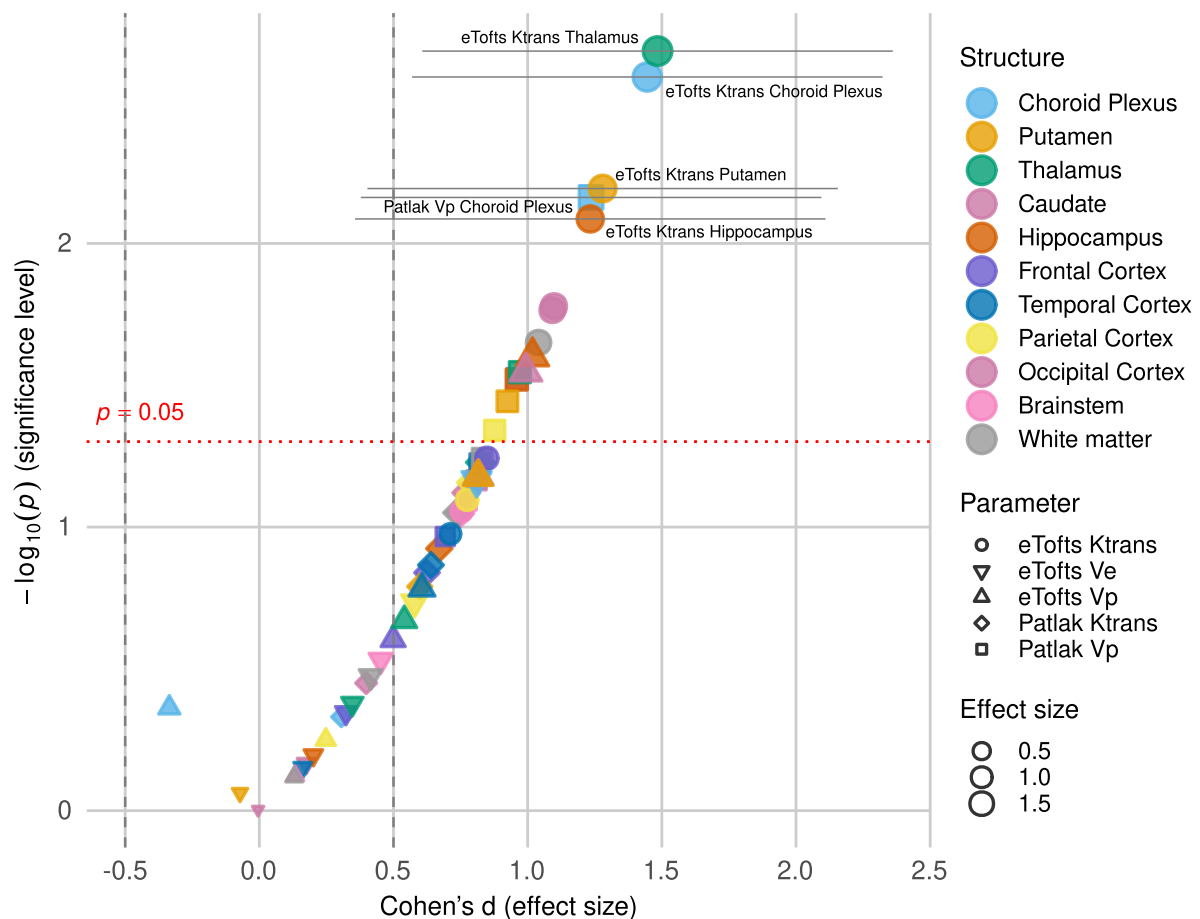
For ROI-level analysis, MD values were extracted in long format across multiple ROIs, including deep gray matter, periventricular and general white matter, and lobar cortical regions. FA was analyzed and included for comparison (non-prespecified). ROIs were derived from subject-specific FreeSurfer segmentations, co-registered to the diffusion space using FSL's flirt with mutual information. Group comparisons were performed using linear models adjusting for age and sex, with false discovery rate (FDR) correction applied to MD results only.

Supplementary Results: MRI

Residual brain volumes in affected individuals vs. controls
Adjusted for age and sex

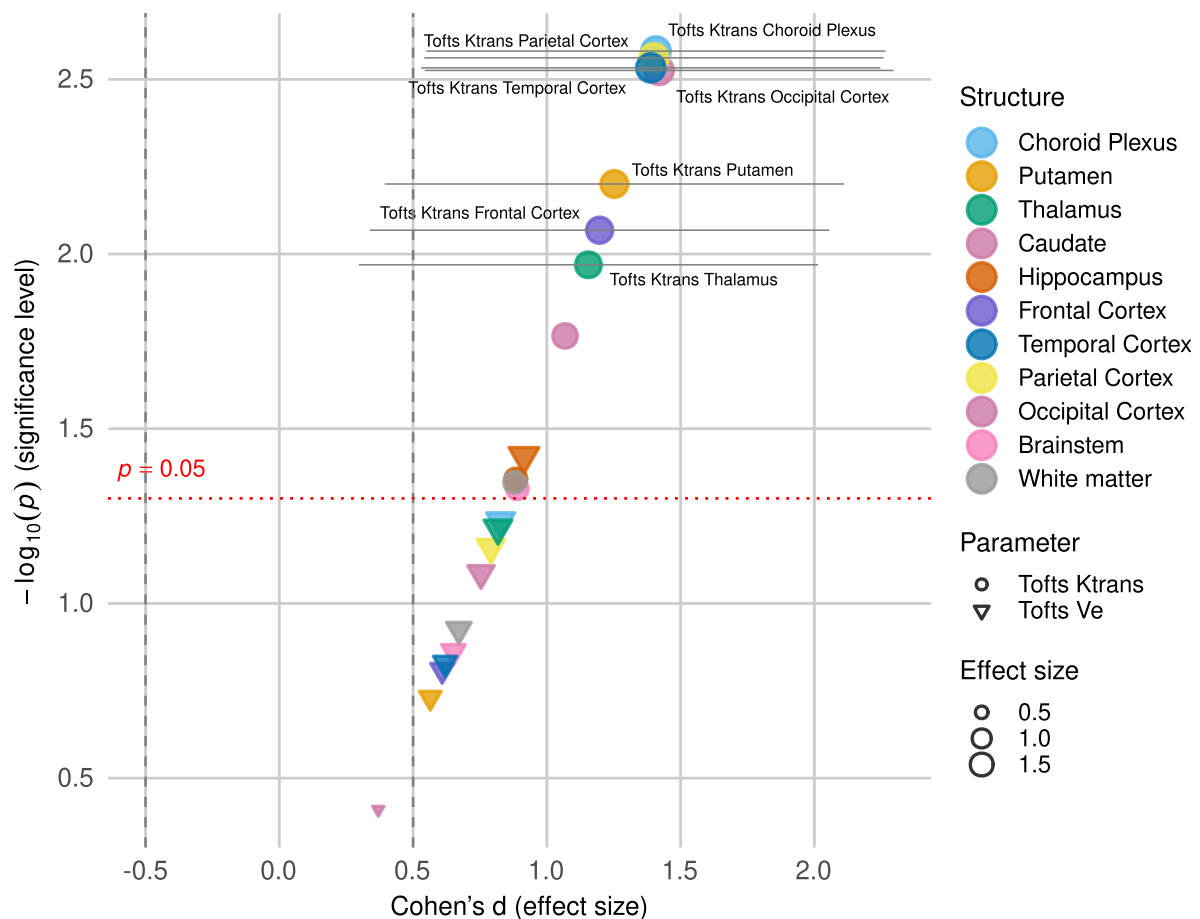


Supplementary Figure S1. Individual participant data for age- and sex-adjusted structural MRI measures. (A) Choroid plexus volume residuals. (B) Lateral ventricle volume residuals. Each point represents one participant. Affected individuals showed substantially lower adjusted choroid plexus and ventricular volumes than controls, consistent with the group-level analyses reported in the main text.



Supplementary Figure 2. DCE kinetic model group differences by brain region and parameter.

Volcano plot of linear-model contrasts (adjusted for age and sex). Each point is a region×parameter; the x-axis shows Cohen's d (positive = higher in non-carriers; negative = higher in carriers) and the y-axis shows $-\log_{10}(p)$. Horizontal bars indicate 95% CIs for d. **No effects survived FDR correction (Benjamini–Hochberg, $q \geq 0.05$); but the nominally most significant are labelled and confidence intervals are shown. Patlak Ktrans showed no group differences in any region (all nominal $p > 0.05$), consistent with no unidirectional plasma-to-tissue influx (no BBB leak).** Several nominal reductions in extended-Tofts Ktrans did not survive FDR; in BBB-intact parenchyma (near-zero, permeability-limited regime) absolute Ktrans is method-sensitive (population-AIF scaling/timing; parameter identifiability) and is used here only as a guardrail confirming no leak, not as a biological read-out. (N carriers = 15; N non-carriers = 10.) Detailed effect sizes, nominal p and q values are provided in Supplementary Table 3.

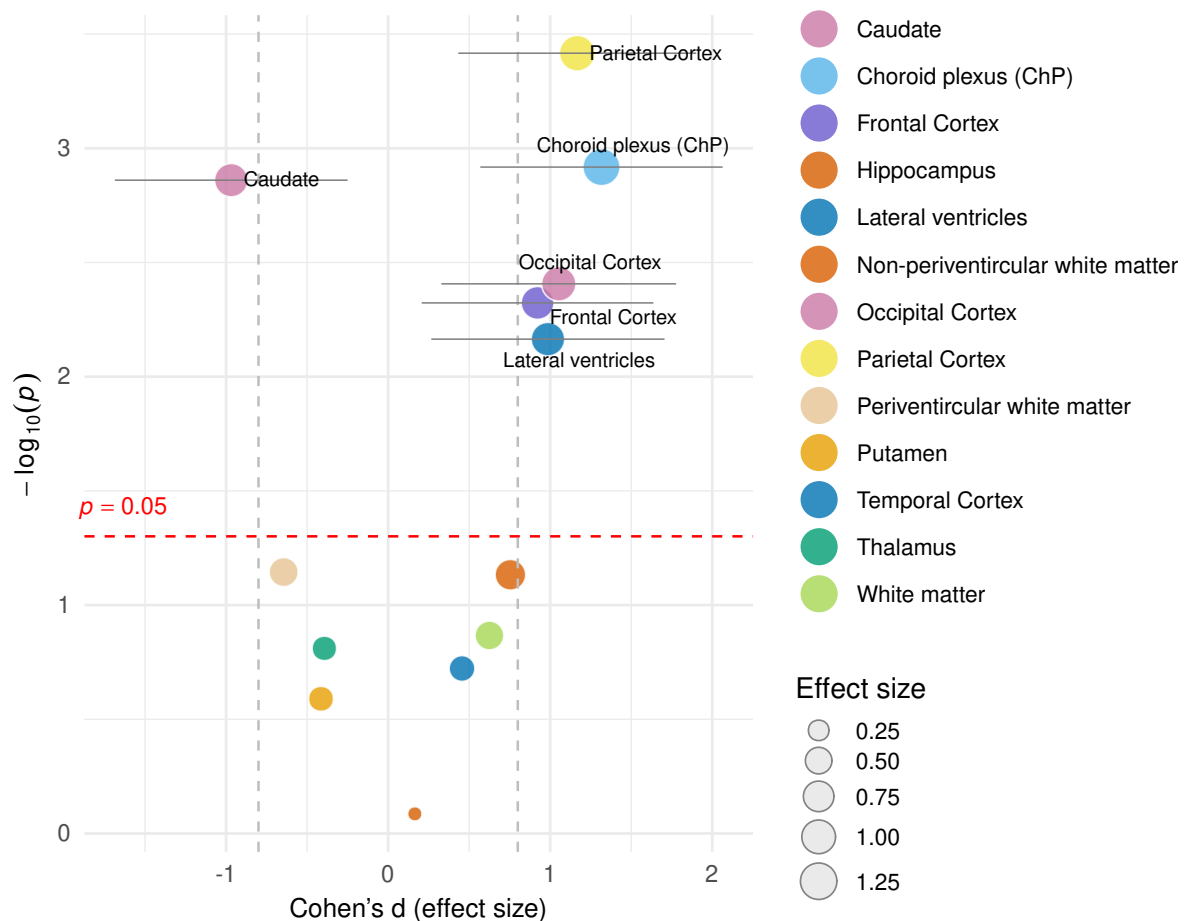


Supplementary Figure S3. Exploratory Tofts-model parameters (Ktrans, Ve) by region.

Volcano plot of age/sex-adjusted group contrasts from the Tofts model (no Vp term). Each point is a region×parameter; the x-axis shows Cohen's d (positive = higher in non-carriers; negative = higher in carriers), and the y-axis shows $-\log_{10}(p)$. Point size scales with $|d|$; horizontal bars indicate 95% CIs. The red dashed line marks nominal $p = 0.05$. Text labels denote effects that pass FDR within this exploratory Tofts set (Benjamini–Hochberg, $q < 0.05$). Symbols: $\circ$ = Tofts Ktrans; ∇ = Tofts Ve. (N carriers = 15; N non-carriers = 10 for DCE.)

Interpretation note. Tofts parameters were not prespecified as primary endpoints and were inspected post hoc for comparison. In BBB-intact parenchyma (near-zero, permeability-limited regime), absolute Ktrans/Ve are method-sensitive (AIF scaling/timing; intravascular conflation in Tofts) and are not interpreted biologically. Main inferences in the manuscript rely on extended-Tofts/Patlak guardrails (no BBB leak: Ktrans unchanged), model-free ChP kinetics, and diffusion MD; the Tofts-only results are presented for completeness/hypothesis generation.

Detailed effect sizes, nominal p and q values are provided in Supplementary Table 5.



Supplementary Figure S4. Exploratory DTI fractional anisotropy (FA) group differences by region; shown descriptively and not interpreted biologically.

Volcano plot of age/sex-adjusted linear-model contrasts. Each point is a region; the x-axis shows Cohen's d (positive = higher FA in carriers/patients, negative = higher in non-carriers/controls) and the y-axis shows $-\log_{10}(p)$. Point size scales with $|d|$; horizontal bars denote 95% CIs. The red dashed line marks nominal $p = 0.05$. Text labels indicate effects that pass FDR within this exploratory FA set (Benjamini-Hochberg, $q < 0.05$).

Interpretation note. FA in gray matter is method-sensitive (free-water/partial-volume, SNR, smoothing) and was not prespecified as a primary endpoint; results were examined post hoc for comparison with MD and are reported for completeness. We do not interpret GM-FA biologically as microstructural reorganization. The cortical FA increases may be compatible with reduced isotropic/free-water contribution under the stagnation model (and with global MD↓), but should be considered supportive and hypothesis-generating only. FA values shown for non-tissue regions (e.g., lateral ventricles) largely reflect boundary/partial-volume effects and are not interpreted.

(N carriers = 16; N non-carriers = 24 for DTI.) Detailed effect sizes, nominal p and q values are provided in Supplementary Table 6.

216 **Supplementary References MRI**

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Supplementary Table 1. Morphometric Group Differences

Region	Metric	Adjusted estimate	Standard error	Cohen's d	95% CI (low)	95% CI (high)	p-value	q-value
Choroid plexus volume (ChP)	Volume (mm ³)	-1177	144	2.64	1.77	3.5	6.57e-10	7.89e-09
ChP volume adjusted for ventricle volume	Volume (mm ³)	-691	125	1.78	1.02	2.52	2.67e-06	1.60e-05
Ventricle volume	Volume (mm ³)	-8704	2696	1.04	0.36	1.71	0.0026	0.0102
Hippocampus volume	Volume (mm ³)	-530	204	0.84	0.17	1.49	0.0132	0.0395
Thalamus volume	Volume (mm ³)	-1084	447	0.78	0.12	1.43	0.0201	0.0483
White matter volume	Volume (mm ³)	-33219	16724	0.64	-0.01	1.29	0.0542	0.1085
Occipital Cortex Thickness	Cortical Thickness (mm)	0.040	0.024	-0.53	-1.18	0.11	0.1057	0.1812
Parietal Cortex Thickness	Cortical Thickness (mm)	0.029	0.022	-0.42	-1.06	0.22	0.1965	0.2947
Temporal Cortex Thickness	Cortical Thickness (mm)	0.017	0.029	-0.18	-0.82	0.45	0.5731	0.7642
Caudate volume	Volume (mm ³)	40	318	-0.04	-0.67	0.59	0.9004	0.9004
Putamen volume	Volume (mm ³)	55	312	-0.06	-0.69	0.58	0.8612	0.9004
Frontal Cortex Thickness	Cortical Thickness (mm)	0.004	0.021	-0.06	-0.69	0.58	0.8627	0.9004

Supplementary Table 1. Group differences in morphometric features between affected individuals and controls.

Cohen’s d effect sizes are shown with 95% confidence intervals and uncorrected p-values from linear models adjusted for age and sex.

The strongest effects were observed for choroid plexus volume, both before and after adjustment for lateral ventricle volume.

Supplementary Table 2. DCE-MRI Model-Free Features

Region	Metric	Adjusted estimate	Standard error	Cohen's d	95% CI (low)	95% CI (high)	p-value	q-value
Choroid Plexus	Time > half peak (s)	448.381	92.132	-4.87	-5.72	-4.01	1.00e-10	7.72e-09
Choroid Plexus	Washout ratio	0.319	0.092	-3.46	-4.32	-2.6	3.90e-08	1.50e-06
Choroid Plexus	Decay slope (mmol/L/s)	0.001	6.30e-04	-2.19	-3.05	-1.33	2.90e-05	7.44e-04
Choroid Plexus	Peak enhancement (s)	-1.000	0.566	1.77	0.91	2.62	3.32e-04	0.006
Putamen	Decay slope (mmol/L/s)	1.56e-04	1.28e-04	-1.22	-2.07	-0.36	0.008	0.099
Putamen	Peak enhancement (s)	-0.184	0.150	1.23	0.37	2.09	0.007	0.099
Thalamus	AUC (mmol-s/L)	-93.147	81.981	1.14	0.28	1.99	0.012	0.131
Caudate	AUC (mmol-s/L)	-91.698	84.490	1.09	0.23	1.94	0.016	0.151
Parietal Cortex	AUC (mmol-s/L)	-83.971	79.452	1.06	0.2	1.92	0.018	0.156
Caudate	Peak enhancement (s)	-0.182	0.184	0.99	0.13	1.84	0.026	0.177
Hippocampus	AUC (mmol-s/L)	-83.811	85.772	0.98	0.12	1.84	0.028	0.177
Parietal Cortex	End concentration (mmol/L)	-0.110	0.111	0.99	0.13	1.85	0.026	0.177
Occipital Cortex	Time > half peak (s)	-15.028	16.791	0.89	0.02	1.77	0.046	0.187
Hippocampus	Decay slope (mmol/L/s)	2.24e-04	2.49e-04	-0.9	-1.76	-0.04	0.041	0.187
Brainstem	AUC (mmol-s/L)	-143.990	161.067	0.89	0.02	1.77	0.046	0.187
Frontal Cortex	AUC (mmol-s/L)	-72.054	80.470	0.9	0.04	1.75	0.042	0.187
Putamen	AUC (mmol-s/L)	-85.553	91.937	0.93	0.07	1.79	0.035	0.187
White matter	AUC (mmol-s/L)	-209.811	227.950	0.92	0.06	1.78	0.037	0.187
Thalamus	End concentration (mmol/L)	-0.113	0.128	0.88	0.02	1.74	0.046	0.187
Hippocampus	Peak enhancement (s)	-0.217	0.254	0.85	0	1.71	0.051	0.197
White matter	Peak enhancement (s)	-0.334	0.401	0.83	-0.03	1.69	0.057	0.208
Temporal Cortex	AUC (mmol-s/L)	-75.320	91.639	0.82	-0.04	1.68	0.060	0.208
White matter	Decay slope (mmol/L/s)	1.20e-04	1.58e-04	-0.76	-1.62	0.1	0.080	0.216
Parietal Cortex	Peak enhancement (s)	-0.153	0.196	0.78	-0.08	1.64	0.073	0.216
Brainstem	End concentration (mmol/L)	-0.184	0.237	0.78	-0.1	1.65	0.079	0.216
Caudate	End concentration (mmol/L)	-0.111	0.139	0.8	-0.06	1.66	0.065	0.216
Frontal Cortex	End concentration (mmol/L)	-0.093	0.122	0.76	-0.1	1.62	0.079	0.216
White matter	End concentration (mmol/L)	-0.261	0.332	0.78	-0.07	1.64	0.071	0.216
Choroid Plexus	Time to peak (s)	68.980	91.340	-0.76	-1.61	0.1	0.081	0.216
Brainstem	Peak enhancement (s)	-0.216	0.282	0.76	-0.11	1.64	0.084	0.217
Frontal Cortex	Peak enhancement (s)	-0.119	0.163	0.73	-0.13	1.59	0.092	0.228
Caudate	Decay slope (mmol/L/s)	1.15e-04	1.66e-04	-0.69	-1.55	0.17	0.109	0.263
Hippocampus	Washout ratio	0.036	0.053	-0.67	-1.53	0.19	0.121	0.266
Choroid Plexus	AUC (mmol-s/L)	-111.559	167.022	0.67	-0.19	1.53	0.120	0.266
Temporal Cortex	End concentration (mmol/L)	-0.090	0.134	0.67	-0.19	1.53	0.119	0.266
Occipital Cortex	AUC (mmol-s/L)	-67.900	104.005	0.65	-0.22	1.53	0.136	0.291
Hippocampus	End concentration (mmol/L)	-0.078	0.129	0.61	-0.25	1.46	0.157	0.327
Thalamus	Peak enhancement (s)	-0.109	0.183	0.6	-0.26	1.45	0.164	0.332
Temporal Cortex	Peak enhancement (s)	-0.115	0.198	0.58	-0.28	1.44	0.175	0.337
Putamen	End concentration (mmol/L)	-0.084	0.144	0.58	-0.28	1.44	0.173	0.337
Thalamus	Washout ratio	-0.024	0.051	0.48	-0.38	1.33	0.261	0.486
Occipital Cortex	End concentration (mmol/L)	-0.074	0.154	0.48	-0.39	1.36	0.265	0.486
Putamen	Washout ratio	0.023	0.052	-0.44	-1.3	0.41	0.293	0.522
Brainstem	Decay slope (mmol/L/s)	5.91e-05	1.32e-04	-0.45	-1.32	0.43	0.300	0.522
Parietal Cortex	Decay slope (mmol/L/s)	7.05e-05	1.63e-04	-0.43	-1.29	0.42	0.305	0.522
Caudate	Time > half peak (s)	-0.812	2.056	0.39	-0.46	1.25	0.349	0.549
Frontal Cortex	Time > half peak (s)	-0.812	2.056	0.39	-0.46	1.25	0.349	0.549
Putamen	Time > half peak (s)	-0.812	2.056	0.39	-0.46	1.25	0.349	0.549
White matter	Time > half peak (s)	-0.812	2.056	0.39	-0.46	1.25	0.349	0.549
Brainstem	Time > half peak (s)	-0.790	2.106	0.38	-0.5	1.25	0.382	0.587
Temporal Cortex	Time > half peak (s)	-4.938	14.057	0.35	-0.51	1.21	0.404	0.587
Brainstem	Washout ratio	-0.013	0.037	0.36	-0.51	1.24	0.399	0.587
Frontal Cortex	Decay slope (mmol/L/s)	4.55e-05	1.27e-04	-0.36	-1.22	0.5	0.395	0.587
Thalamus	Time > half peak (s)	-3.048	8.932	0.34	-0.52	1.2	0.418	0.595
Choroid Plexus	End concentration (mmol/L)	-0.060	0.199	0.3	-0.56	1.16	0.475	0.665
Hippocampus	Time to peak (s)	-1.544	5.324	0.29	-0.57	1.15	0.490	0.674
Occipital Cortex	Washout ratio	-0.019	0.069	0.28	-0.6	1.16	0.511	0.690
Temporal Cortex	Decay slope (mmol/L/s)	4.58e-05	1.75e-04	-0.26	-1.12	0.6	0.532	0.707
Hippocampus	Time > half peak (s)	-18.693	82.455	0.23	-0.63	1.08	0.589	0.768
Occipital Cortex	Peak enhancement (s)	-0.071	0.318	0.22	-0.65	1.1	0.603	0.774
White matter	Washout ratio	0.006	0.030	-0.19	-1.04	0.67	0.657	0.829
Putamen	Time to peak (s)	1.052	5.864	-0.18	-1.04	0.68	0.668	0.830
Parietal Cortex	Time to peak (s)	0.729	4.720	-0.15	-1.01	0.7	0.712	0.870
Temporal Cortex	Washout ratio	-0.007	0.056	0.13	-0.72	0.99	0.750	0.879
Occipital Cortex	Time to peak (s)	0.680	5.082	-0.13	-1.01	0.74	0.754	0.879
Temporal Cortex	Time to peak (s)	-0.774	5.471	0.14	-0.72	1	0.735	0.879
Caudate	Washout ratio	0.006	0.056	-0.11	-0.97	0.74	0.786	0.890
Frontal Cortex	Washout ratio	-0.006	0.051	0.12	-0.74	0.98	0.777	0.890
Parietal Cortex	Washout ratio	-0.004	0.047	0.08	-0.78	0.94	0.849	0.946
Frontal Cortex	Time to peak (s)	-0.407	5.511	0.07	-0.78	0.93	0.860	0.946
Parietal Cortex	Time > half peak (s)	0.438	12.011	-0.04	-0.89	0.82	0.930	0.958
Occipital Cortex	Decay slope (mmol/L/s)	7.28e-06	3.28e-04	-0.02	-0.9	0.85	0.958	0.958
Thalamus	Decay slope (mmol/L/s)	5.37e-06	1.75e-04	-0.03	-0.89	0.83	0.941	0.958
Brainstem	Time to peak (s)	0.117	5.121	-0.02	-0.9	0.85	0.957	0.958
Caudate	Time to peak (s)	0.157	5.168	-0.03	-0.89	0.83	0.942	0.958
Thalamus	Time to peak (s)	-0.201	5.074	0.04	-0.82	0.9	0.924	0.958
White matter	Time to peak (s)	-0.201	5.074	0.04	-0.82	0.9	0.924	0.958
Jackknife leave-one-out statistics								
Metric Region	Beta (mean / SD)			Beta (min)	Beta (max)	P (min)	P (max)	All p < 0.05 & Sign consistent
Time > half peak Choroid Plexus	-4.49E+02 / 1.17E+01			-4.86E+02	-4.31E+02	4.21E-13	6.17E-10	TRUE

Supplementary Table 2. Group differences in dynamic contrast-enhanced MRI (DCE-MRI) model-free features across brain regions.

Metrics reflect signal enhancement and washout characteristics, including time above half-maximum (TAHM), washout slope, and area under the curve (AUC) (mmol-s/L). Time metrics are in seconds (s). Concentration metrics (peak enhancement and end concentration) are in (mmol/L). Decay slope is expressed in mmol/L/s. AUC is expressed in mmol-s/L. Washout ratio is unitless. Cohen’s d values reflect effect sizes from linear models adjusted for age and sex; p-values are uncorrected.

The most pronounced group differences were observed in the choroid plexus, with additional effects in deep grey matter and cortex.

These features do not rely on compartmental assumptions and may better capture dysfunction in tissues with active solute transport.

Jackknife leave-one-out analysis confirmed that group differences in model-free time-above-half-peak in the ChP, were highly robust, with consistent effect signs and p<0.05 in every iteration.

Supplementary Table 3. DCE-MRI Kinetic Model Parameters

Region	Metric	Adjusted estimate	Standard error	Cohen's d	95% CI (low)	95% CI (high)	p-value	q-value
Choroid Plexus	eTofts Ktrans (1/s)	-0.002	5.37e-04	1.45	0.57	2.32	0.0026	0.0712
Thalamus	eTofts Ktrans (1/s)	-5.12e-05	1.45e-05	1.48	0.61	2.36	0.0021	0.0712
Choroid Plexus	Patlak Vp	-0.005	0.002	1.24	0.38	2.09	0.0069	0.0902
Hippocampus	eTofts Ktrans (1/s)	-9.39e-05	3.20e-05	1.23	0.36	2.11	0.0082	0.0902
Putamen	eTofts Ktrans (1/s)	-3.58e-05	1.18e-05	1.28	0.4	2.16	0.0064	0.0902
Caudate	Patlak Vp	-0.003	0.001	0.96	0.1	1.82	0.0301	0.1278
Hippocampus	Patlak Vp	-0.003	0.001	0.96	0.1	1.82	0.0302	0.1278
Thalamus	Patlak Vp	-0.003	0.001	0.97	0.11	1.83	0.0284	0.1278
Caudate	eTofts Ktrans (1/s)	-3.35e-05	1.29e-05	1.09	0.22	1.97	0.0172	0.1278
Occipital Cortex	eTofts Ktrans (1/s)	-3.17e-05	1.21e-05	1.1	0.22	1.97	0.0166	0.1278
White matter	eTofts Ktrans (1/s)	-6.82e-05	2.76e-05	1.04	0.16	1.92	0.0224	0.1278
Hippocampus	eTofts Vp	-0.006	0.002	1.02	0.14	1.89	0.0250	0.1278
Occipital Cortex	eTofts Vp	-0.007	0.003	0.99	0.12	1.87	0.0283	0.1278
Putamen	Patlak Vp	-0.003	0.001	0.92	0.07	1.78	0.0360	0.1415
Parietal Cortex	Patlak Ktrans (1/s)	-1.35e-05	7.07e-06	0.79	-0.07	1.65	0.0697	0.1597
Thalamus	Patlak Ktrans (1/s)	-1.63e-05	8.18e-06	0.82	-0.03	1.68	0.0591	0.1597
Occipital Cortex	Patlak Vp	-0.002	0.001	0.81	-0.07	1.69	0.0684	0.1597
Parietal Cortex	Patlak Vp	-0.002	0.001	0.88	0.02	1.74	0.0456	0.1597
Temporal Cortex	Patlak Vp	-0.002	0.001	0.82	-0.04	1.68	0.0597	0.1597
White matter	Patlak Vp	-0.006	0.003	0.83	-0.03	1.69	0.0572	0.1597
Frontal Cortex	eTofts Ktrans (1/s)	-2.50e-05	1.24e-05	0.85	-0.03	1.72	0.0572	0.1597
Choroid Plexus	eTofts Ve	-0.018	0.009	0.81	-0.07	1.69	0.0683	0.1597
Caudate	eTofts Vp	-0.013	0.007	0.82	-0.06	1.69	0.0663	0.1597
Putamen	eTofts Vp	-0.014	0.007	0.82	-0.06	1.69	0.0666	0.1597
Brainstem	Patlak Ktrans (1/s)	-2.47e-05	1.38e-05	0.75	-0.13	1.63	0.0893	0.1637
Caudate	Patlak Ktrans (1/s)	-1.60e-05	8.57e-06	0.77	-0.09	1.63	0.0757	0.1637
White matter	Patlak Ktrans (1/s)	-3.71e-05	2.08e-05	0.74	-0.12	1.59	0.0890	0.1637
Brainstem	Patlak Vp	-0.004	0.002	0.77	-0.1	1.65	0.0807	0.1637
Brainstem	eTofts Ktrans (1/s)	-4.77e-05	2.66e-05	0.75	-0.12	1.63	0.0879	0.1637
Parietal Cortex	eTofts Ktrans (1/s)	-2.25e-05	1.22e-05	0.77	-0.1	1.65	0.0801	0.1637
Frontal Cortex	Patlak Vp	-0.002	0.001	0.69	-0.17	1.55	0.1080	0.1857
Temporal Cortex	eTofts Ktrans (1/s)	-2.66e-05	1.57e-05	0.71	-0.16	1.59	0.1057	0.1857
Hippocampus	Patlak Ktrans (1/s)	-1.26e-05	7.74e-06	0.67	-0.19	1.53	0.1190	0.1984
Temporal Cortex	Patlak Ktrans (1/s)	-1.23e-05	7.94e-06	0.64	-0.22	1.5	0.1361	0.2202
Frontal Cortex	Patlak Ktrans (1/s)	-1.05e-05	6.96e-06	0.62	-0.23	1.48	0.1449	0.2277
Putamen	Patlak Ktrans (1/s)	-1.36e-05	9.38e-06	0.6	-0.26	1.46	0.1621	0.2449
Temporal Cortex	eTofts Vp	-0.009	0.006	0.61	-0.27	1.48	0.1647	0.2449
Parietal Cortex	eTofts Ve	-0.008	0.006	0.58	-0.3	1.45	0.1842	0.2666
Thalamus	eTofts Vp	-0.007	0.006	0.54	-0.34	1.42	0.2133	0.3008
Frontal Cortex	eTofts Vp	-0.006	0.005	0.5	-0.38	1.38	0.2494	0.3429
Brainstem	eTofts Ve	-0.012	0.011	0.45	-0.42	1.33	0.2945	0.3951
White matter	eTofts Ve	-0.019	0.020	0.41	-0.46	1.29	0.3357	0.4396
Occipital Cortex	Patlak Ktrans (1/s)	-9.31e-06	9.83e-06	0.4	-0.48	1.27	0.3549	0.4539
Thalamus	eTofts Ve	-0.006	0.007	0.35	-0.53	1.22	0.4192	0.5239
Choroid Plexus	eTofts Vp	0.001	0.001	-0.34	-1.21	0.54	0.4340	0.5304
Frontal Cortex	eTofts Ve	-0.005	0.006	0.32	-0.55	1.2	0.4516	0.5400
Choroid Plexus	Patlak Ktrans (1/s)	-8.53e-06	1.15e-05	0.31	-0.55	1.16	0.4673	0.5468
Parietal Cortex	eTofts Vp	-0.002	0.004	0.25	-0.63	1.12	0.5623	0.6443
Hippocampus	eTofts Ve	-0.003	0.006	0.2	-0.68	1.08	0.6372	0.7152
Caudate	eTofts Ve	-0.003	0.007	0.17	-0.7	1.05	0.6823	0.7505
Temporal Cortex	eTofts Ve	-0.002	0.006	0.16	-0.72	1.04	0.7046	0.7599
Brainstem	eTofts Vp	-0.004	0.013	0.13	-0.74	1.01	0.7533	0.7895
White matter	eTofts Vp	-0.003	0.010	0.13	-0.75	1.01	0.7608	0.7895
Putamen	eTofts Ve	0.001	0.008	-0.07	-0.95	0.8	0.8655	0.8816
Occipital Cortex	eTofts Ve	9.04e-05	0.008	0	-0.88	0.87	0.9912	0.9912

Supplementary Table 3. Group differences in Ktrans (1/s)netic model parameters derived from DCE-MRI.

Patlak and extended Tofts models were applied to estimate influx rate (Ktrans (1/s)), plasma volume (Vp), extracellular volume (Ve) and transfer constant (Ktrans (1/s)) across multiple brain regions. Values represent Cohen’s d effect sizes with 95% confidence intervals and uncorrected p-values from age- and sex-adjusted linear models.

No tests survived FDR correction for multiple comparisons.

Supplementary Table 4. DTI indices statistics

DTI index	Region	Adjusted estimate	Standard error	Cohen's D	95% CI (low)	95% CI (high)	p-value	q-value
MD (mm ² /s ×10 ⁻³)	Caudate	-3.08e-05	1.85e-05	0.31	-0.37	1.00	0.105	0.124
MD (mm ² /s ×10 ⁻³)	Frontal Cortex	2.40e-05	1.00e-05	-0.89	-1.61	-0.18	0.022	0.041
MD (mm ² /s ×10 ⁻³)	Occipital Cortex	1.80e-05	9.83e-06	-0.60	-1.29	0.10	0.077	0.111
MD (mm ² /s ×10 ⁻³)	Parietal Cortex	2.44e-05	1.02e-05	-0.85	-1.56	-0.14	0.022	0.041
MD (mm ² /s ×10 ⁻³)	Temporal Cortex	1.23e-05	6.65e-06	-0.72	-1.42	-0.02	0.074	0.111
MD (mm ² /s ×10 ⁻³)	Choroid Plexus	3.95e-04	1.51e-04	-1.01	-1.73	-0.29	0.013	0.034
MD (mm ² /s ×10 ⁻³)	Hippocampus	1.94e-05	1.15e-05	-0.68	-1.38	0.02	0.102	0.124
MD (mm ² /s ×10 ⁻³)	Non-periventrtricular white matter	1.82e-05	6.43e-06	-1.06	-1.78	-0.33	0.008	0.033
MD (mm ² /s ×10 ⁻³)	Putamen	-4.46e-05	1.40e-05	0.81	0.11	1.52	0.003	0.020
MD (mm ² /s ×10 ⁻³)	Periventricular white matter	2.79e-08	1.51e-05	-0.08	-0.76	0.61	0.999	0.999
MD (mm ² /s ×10 ⁻³)	Thalamus	-2.98e-06	9.32e-06	-0.14	-0.83	0.54	0.751	0.813
MD (mm ² /s ×10 ⁻³)	Lateral ventricles	1.18e-04	3.22e-05	-1.32	-2.06	-0.57	0.001	0.011
MD (mm ² /s ×10 ⁻³)	White matter	1.83e-05	6.80e-06	-1.03	-1.75	-0.31	0.011	0.034

Supplementary Table 4. Group differences in diffusion tensor imaging mean diffusivity (MD).

Supplementary Table 5. DCE-MRI Tofts Kinetic Model Parameters

Region	Metric	Cohen's d	95% CI (low)	95% CI (high)	p-value	q-value
Tofts Ktrans (1/s)	Choroid Plexus	1.41	.55	2.27	0.0026	0.0164
Tofts Ktrans (1/s)	Parietal Cortex	1.40	.54	2.26	0.0027	0.0164
Tofts Ktrans (1/s)	Temporal Cortex	1.39	.53	2.25	0.0029	0.0164
Tofts Ktrans (1/s)	Occipital Cortex	1.42	.54	2.30	0.0030	0.0164
Tofts Ktrans (1/s)	Putamen	1.25	.39	2.11	0.0063	0.0277
Tofts Ktrans (1/s)	Frontal Cortex	1.20	.34	2.06	0.0085	0.0313
Tofts Ktrans (1/s)	Thalamus	1.16	.30	2.01	0.0107	0.0337
Tofts Ktrans (1/s)	Caudate	1.07	.21	1.93	0.0171	0.0472
Tofts Ve	Hippocampus	.91	.06	1.77	0.0379	0.0861
Tofts Ktrans (1/s)	Hippocampus	.88	.03	1.74	0.0440	0.0861
Tofts Ktrans (1/s)	White matter	.88	.02	1.74	0.0450	0.0861
Tofts Ktrans (1/s)	Brainstem	.89	.01	1.77	0.0470	0.0861
Tofts Ve	Choroid Plexus	.83	-.03	1.69	0.0581	0.0957
Tofts Ve	Thalamus	.82	-.04	1.68	0.0609	0.0957
Tofts Ve	Parietal Cortex	.79	-.07	1.65	0.0690	0.1013
Tofts Ve	Caudate	.75	-.10	1.61	0.0820	0.1127
Tofts Ve	White matter	.67	-.19	1.53	0.1187	0.1536
Tofts Ve	Brainstem	.65	-.23	1.53	0.1371	0.1676
Tofts Ve	Temporal Cortex	.62	-.24	1.48	0.1480	0.1706
Tofts Ve	Frontal Cortex	.61	-.25	1.47	0.1551	0.1706
Tofts Ve	Putamen	.56	-.29	1.42	0.1860	0.1948
Tofts Ve	Occipital Cortex	.37	-.51	1.25	0.3890	0.3890

Supplementary Table 5. Group differences in Ktrans (1/s)netic model Tofts parameters derived from DCE-MRI.

Supplementary Table 6. DTI FA statistics

DTI index	Region	Adjusted estimate	Standard error	Cohen's d	95% CI (low)	95% CI (high)	p-value	q-value
FA	Parietal Cortex	-0.011463	0.002909	1.17	0.43	1.90	0.000	0.005
FA	Caudate	0.020892	0.005996	-0.97	-1.69	-0.25	0.001	0.006
FA	Choroid Plexus	-0.079528	0.022514	1.32	0.57	2.06	0.001	0.006
FA	Frontal Cortex	-0.008821	0.002919	0.92	0.21	1.64	0.005	0.012
FA	Occipital Cortex	-0.008546	0.002761	1.05	0.33	1.78	0.004	0.012
FA	Lateral ventricles	-0.012706	0.004413	0.99	0.27	1.71	0.007	0.015
FA	Non-periventricular white matter	-0.009549	0.005174	0.75	0.05	1.46	0.074	0.120
FA	Periventricular white matter	0.014506	0.007803	-0.64	-1.34	0.05	0.072	0.120
FA	White matter	-0.007793	0.005101	0.63	-0.07	1.32	0.136	0.196
FA	Thalamus	0.010526	0.007232	-0.39	-1.08	0.29	0.155	0.201
FA	Temporal Cortex	-0.004417	0.003299	0.46	-0.23	1.15	0.189	0.224
FA	Putamen	0.005983	0.005192	-0.41	-1.10	0.27	0.257	0.279
FA	Hippocampus	7.07e-04	0.003087	0.16	-0.52	0.85	0.820	0.820

Supplementary Table 6: Exploratory DTI fractional anisotropy (FA) group differences by region; shown descriptively and not interpreted biologically.