# Supplementary S1 – Extended methods

## Regions of interest

The regions of interest (ROIs) included known regions relevant to neuropathological progression in neurodegenerative diseases, such as Braak staging for tau pathology and Aβ staging based on its progression.1–3 The ROIs also included commonly used Temporal meta-ROI which is based on Braak I-IV and Global (i.e., whole-brain) ROI. See Table S1.1 for detailed overview of the ROIs and the regions involved.

**Table S1.1**. Regions of interest.

|  |  |  |
| --- | --- | --- |
| **ROI name** |  | **Regions involved** |
| **Global** | | *whole brain* (i.e., all Desikan-Killiany regions) |
| **Temporal** | | entorhinal cortex, parahippocampal cortex, fusiform cortex, amygdala, inferior temporal cortex, middle temporal cortex |
| **Braak I-II** | | entorhinal cortex |
| **Braak III-IV** | | parahippocampal cortex, fusiform cortex, amygdala, inferior temporal cortex, middle temporal cortex |
| **Braak V-VI** | | caudal anterior cingulate cortex, caudal middle frontal cortex, cuneus, inferior parietal cortex, isthmus cingulate cortex, lateral occipital cortex, lateral orbitofrontal cortex, lingual cortex, medial orbitofrontal cortex, paracentral cortex, pars opercularis, pars triangularis, pars orbitalis, pericalcarine cortex, postcentral cortex, posterior cingulate cortex, precentral cortex, precuneus, rostral anterior cingulate cortex, rostral middle frontal cortex, superior frontal cortex, superior parietal cortex, superior temporal cortex, supramarginal cortex, frontal pole, temporal pole, transverse temporal cortex, insula |
| **Early-Aβ** | | precuneus, posterior cingulate cortex, isthmus cingulate cortex, insula, medial orbitofrontal cortex, lateral orbitofrontal cortex |
| **Intermediate-Aβ** | | banks of superior temporal sulcus, caudal middle frontal cortex, cuneus, frontal pole, fusiform cortex, inferior parietal cortex, inferior temporal cortex, lateral occipital cortex, middle temporal cortex, parahippocampal cortex, pars opercularis, pars orbitalis, pars triangularis, putamen, rostral anterior cingulate cortex, rostral middle frontal cortex, superior frontal cortex, superior parietal cortex, superior temporal cortex, supramarginal cortex |
| **Late-Aβ** | | lingual cortex, pericalcarine cortex, paracentral cortex, precentral cortex, postcentral cortex |

## MRI protocol

The MRI imaging was conducted using a MAGNETOM Prisma 3T MRI scanner (Siemens Healthcare) with a 64-channel head coil. For capturing spontaneous blood oxygen level-dependent (BOLD) oscillations, gradient-echo planar sequence was acquired (eyes closed; in-plane resolution = 3×3mm2; slice thickness = 3.6mm; repetition time = 1020ms; echo time = 30ms; flip-angle = 63°; 462 dynamic scans over a period of 7.85min). 104 diffusion-weighted imaging volumes were acquired using a single-shot echo-planar imaging sequence (repetition time = 3500ms; echo time = 73ms; resolution = 2×2×2mm3; field of view = 220×220×124mm3; b-values range = 0, 100, 1000 and 2500s/mm2 distributed over 2, 6, 32 and 64 directions; 2-fold parallel acceleration and partial Fourier factor = 7/8). T1-weighted structural images were acquired using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence (inversion time = 1100ms; flip-angle = 9°; echo time = 2.54ms; echo spacing = 7.3ms; repetition time = 1900ms; receiver bandwidth = 220 Hz/pixel; voxel size = 1×1×1mm3). Generalized autocalibrating partially parallel acquisitions (GRAPPA) was applied with an acceleration factor of 2 and 24 reference lines.

## Structural and functional connectivity

Structural connectivity (SC) and its associated measures were calculated using Mrtrix3,4 FSL5 and FreeSurfer6 software packages. Functional connectivity (FC) was estimated using Nilearn software.7 For developing complete Python-based pipelines for the integration of these software packages, NiPype software was utilised.8

Firstly, a single set of response functions for white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) were estimated by "dhollander" algorithm9,10 using pre-processed DWI data from 60 CU A-T- and 40 CU A+T- participants of the BioFinder2 (BF2) cohort. These were then utilised to estimate fiber orientation distributions (FOD) based on multi-shell multi-tissue Constrained Spherical Deconvolution (CSD)11 using "msmt\_csd" algorithm,12 which enables to calculate three separate FODs for three tissue types (i.e., WM, GM, CSF) based on multi-shell DWI data.

Secondly, a five-tissue-type (5TT) segmented tissue image was generated based on Hybrid Surface and Volume Segmentation (HSVS) using "hsvs" algorithm13 which uses FreeSurfer and FSL to create segmentations of different tissue types (i.e, cortical GM, sub-cortical GM, WM, CSF, and optionally pathological tissue). 5TT image is important for employing anatomical constraints for later fiber tracking i.e. it increases biological plausibility of the tractogram. After that, the 5TT and T1-weighted images are co-registered to the DWI data using FSL's "flirt"14,15 with the average of the not gradient weighted b0 DWI data.

Thirdly, Anatomically-Constrained Tractography (ACT) was performed using a probabilistic "iFOD2" tracking algorithm16,17 by estimating 10 million streamlines with applying the 5TT image and dynamic determination of seed points.18 Following that, to reduce the bias in overestimation of streamlines compared to biological WM fibres, Spherical-deconvolution Informed Filtering of Tractograms 2 (SIFT2) method18 was utilised to calculate weights for all streamlines. After that, structural connectivity (SC) matrix based on Desikan-Killiany atlas19 (i.e., 84 regions from FreeSurfer’s "aparcaseg") was generated from the sum of SIFT2-weighted streamlines.20

Fourthly, a diffusion tensor image (DTI) image was estimated using weighted least-squares method21 and removing the b2500 volumes from DWI data beforehand (i.e., using only b0, b100, b1000 shells). Then, maps of fractional anisotropy (FA) and mean diffusivity (MD) were calculated using the DTI.22 White matter tract segmentation was performed using TractSeg, a convolutional neural network-based approach that directly segments tracts from fiber orientation distribution function peaks.23 The algorithm generated bundle segmentations of the main inter-hemispheric white matter tracts (corpus callosum, forceps major, forceps minor), from which mean FA and MD values were extracted for each tract.

Functional connectivity (FC) matrices were constructed from the subject-space pre-processed resting state fMRI data by extracting time series data24 from the same Desikan-Killiany regions as previously done for SC. After that, Pearson correlation with Fisher’s z-transformation25 was applied between all brain regions for calculating FC.

# References

1. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol (Berl)*. 1991;82(4):239-259. doi:10.1007/BF00308809

2. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol (Berl)*. 2006;112(4):389-404. doi:10.1007/s00401-006-0127-z

3. Mattsson N, Palmqvist S, Stomrud E, Vogel J, Hansson O. Staging β-Amyloid Pathology With Amyloid Positron Emission Tomography. *JAMA Neurol*. 2019;76(11):1319-1329. doi:10.1001/jamaneurol.2019.2214

4. Tournier JD, Smith R, Raffelt D, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *NeuroImage*. 2019;202:116137. doi:10.1016/j.neuroimage.2019.116137

5. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *NeuroImage*. 2012;62(2):782-790. doi:10.1016/j.neuroimage.2011.09.015

6. Fischl B. FreeSurfer. *NeuroImage*. 2012;62(2):774-781. doi:10.1016/j.neuroimage.2012.01.021

7. Abraham A, Pedregosa F, Eickenberg M, et al. Machine learning for neuroimaging with scikit-learn. *Front Neuroinformatics*. 2014;8. doi:10.3389/fninf.2014.00014

8. Esteban O, Markiewicz CJ, Burns C, et al. nipy/nipype: 1.8.3. Published online July 14, 2022. doi:10.5281/zenodo.6834519

9. Dhollander T, Raffelt D, Connelly A. Unsupervised 3-tissue response function estimation from single-shell or multi-shell diffusion MR data without a co-registered T1 image. In: *ISMRM Workshop on Breaking the Barriers of Diffusion MRI, 2016, 5*. ; 2016.

10. Dhollander T, Mito R, Raffelt D, Connelly A. Improved white matter response function estimation for 3-tissue constrained spherical deconvolution. In: *Proc Intl Soc Mag Reson Med, 2019, 555*. ; 2019.

11. Tournier JD, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage*. 2004;23(3):1176-1185. doi:10.1016/j.neuroimage.2004.07.037

12. Jeurissen B, Tournier JD, Dhollander T, Connelly A, Sijbers J. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *NeuroImage*. 2014;103:411-426. doi:10.1016/j.neuroimage.2014.07.061

13. Smith R, Skoch A, Bajada C, Caspers S, Connelly A. Hybrid Surface-Volume Segmentation for improved Anatomically-Constrained Tractography. In: *Proceedings of the Oganisation for Human Brain Mapping*. ; 2020.

14. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5(2):143-156. doi:10.1016/s1361-8415(01)00036-6

15. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*. 2002;17(2):825-841. doi:10.1016/s1053-8119(02)91132-8

16. Tournier JD, Calamante F, Connelly A. Improved probabilistic streamlines tractography by 2nd order integration over fibre orientation distributions. In: *Proceedings of the International Society for Magnetic Resonance in Medicine, 2010, 1670*. ; 2010.

17. Smith RE, Tournier JD, Calamante F, Connelly A. Anatomically-constrained tractography: Improved diffusion MRI streamlines tractography through effective use of anatomical information. *NeuroImage*. 2012;62(3):1924-1938. doi:10.1016/j.neuroimage.2012.06.005

18. Smith RE, Tournier JD, Calamante F, Connelly A. SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. *NeuroImage*. 2015;119:338-351. doi:10.1016/j.neuroimage.2015.06.092

19. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006;31(3):968-980. doi:10.1016/j.neuroimage.2006.01.021

20. Smith RE, Tournier JD, Calamante F, Connelly A. The effects of SIFT on the reproducibility and biological accuracy of the structural connectome. *NeuroImage*. 2015;104:253-265. doi:10.1016/j.neuroimage.2014.10.004

21. Basser PJ, Mattiello J, Lebihan D. Estimation of the Effective Self-Diffusion *Tensor* from the NMR Spin Echo. *J Magn Reson B*. 1994;103(3):247-254. doi:10.1006/jmrb.1994.1037

22. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J*. 1994;66(1):259-267. doi:10.1016/S0006-3495(94)80775-1

23. Wasserthal J, Neher P, Maier-Hein KH. TractSeg - Fast and accurate white matter tract segmentation. *NeuroImage*. 2018;183:239-253. doi:10.1016/j.neuroimage.2018.07.070

24. Friston KJ. Functional and effective connectivity: a review. *Brain Connect*. 2011;1(1):13-36. doi:10.1089/brain.2011.0008

25. Fisher RA. On the" probable error" of a coefficient of correlation deduced from a small sample. Published online 1921.