

## MRI Acquisition

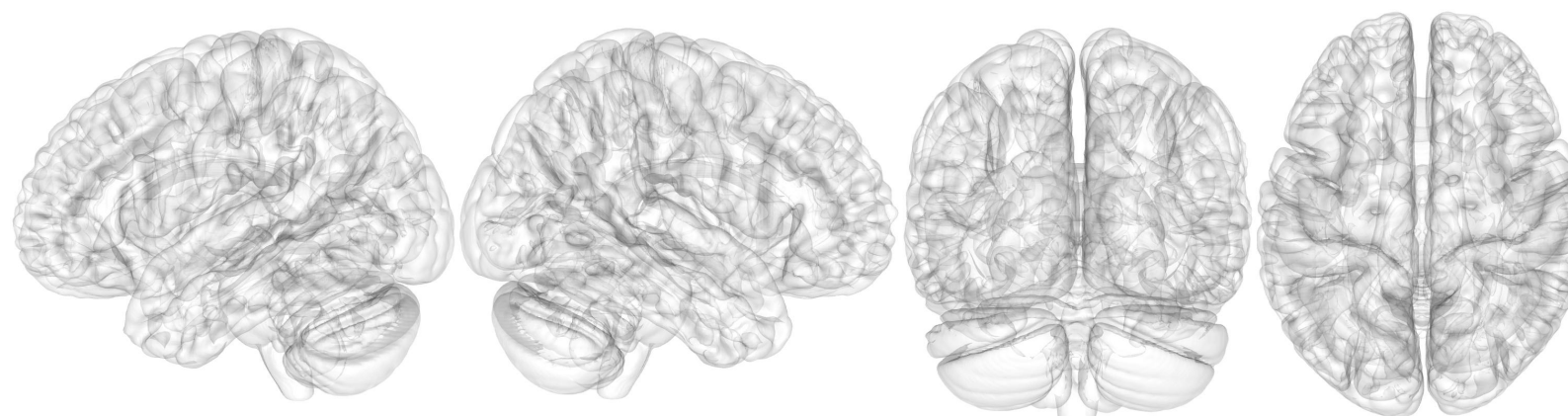
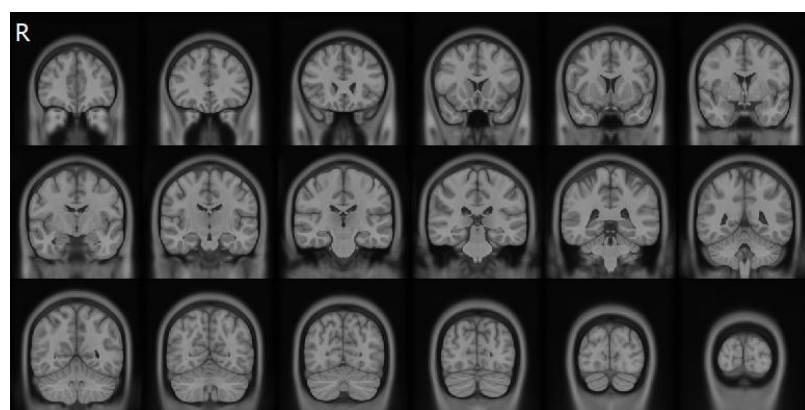
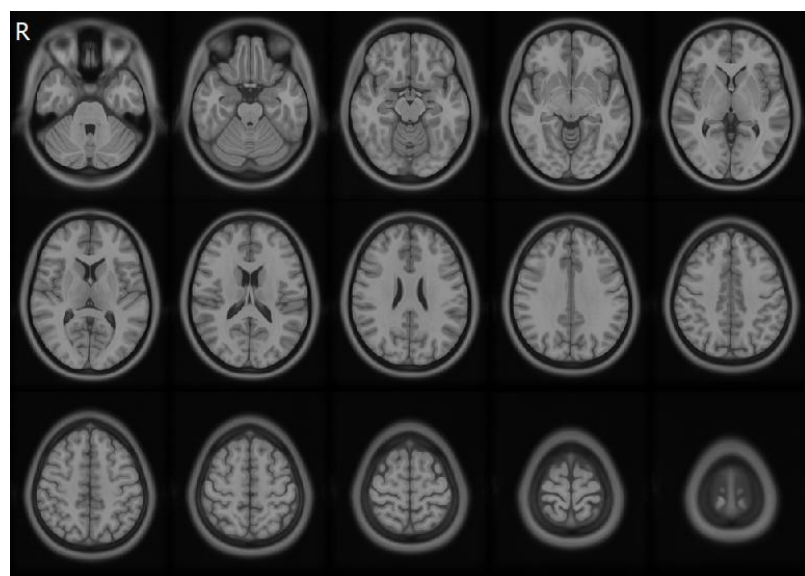
A total of 389 diffusion MRI scans were included in the connectometry database. A DTI diffusion scheme was used, and a total of 30 diffusion sampling directions were acquired. The b-value was 900 s/mm<sup>2</sup>. The in-plane resolution was 2.5 mm. The slice thickness was 2.5 mm. The accuracy of b-table orientation was examined by comparing fiber orientations with those of a population-averaged template (Yeh et al. Neuroimage, 2018). The diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction (Yeh et al., Neuroimage, 58(1):91-9, 2011) to obtain the spin distribution function (Yeh et al., IEEE TMI, ;29(9):1626-35, 2010). A diffusion sampling length ratio of 1.25 was used. The output resolution in diffeomorphic reconstruction was 2 mm isotropic. The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., MRM, 77:603-612 (2017)). The tensor metrics were calculated. The dti\_fa values were used in the connectometry analysis.

## Connectometry analysis

Diffusion MRI connectometry (Yeh et al. NeuroImage 125 (2016): 162-171) was used to derive the correlational tractography that has dti\_fa correlated with WMH. A nonparametric Spearman partial correlation was used to derive the correlation, and the effect of age, sex, and education was removed using a multiple regression model. A total of 389 subjects were included in the analysis. A T-score threshold of 2 was assigned and tracked using a deterministic fiber tracking algorithm (Yeh et al. PLoS ONE 8(11): e80713, 2013) to obtain correlational tractography. A seeding region was placed at whole brain. The tracks were filtered by topology-informed pruning (Yeh et al. Neurotherapeutics, 16(1), 52-58, 2019) with 4 iteration(s). An FDR threshold of 0.05 was used to select tracks. To estimate the false discovery rate, a total of 4000 randomized permutations were applied to the group label to obtain the null distribution of the track length.

## Results

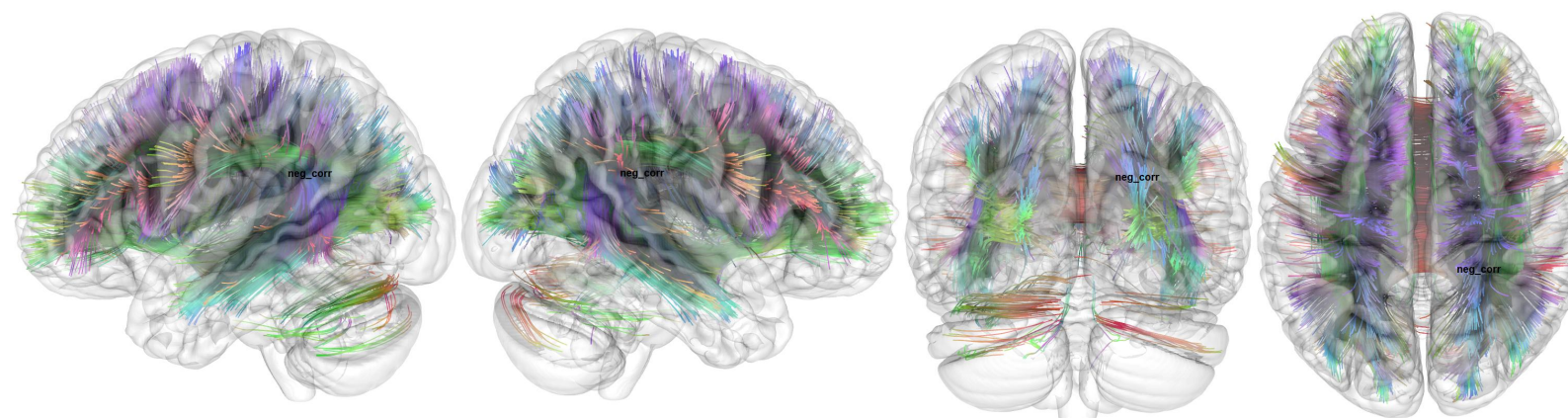
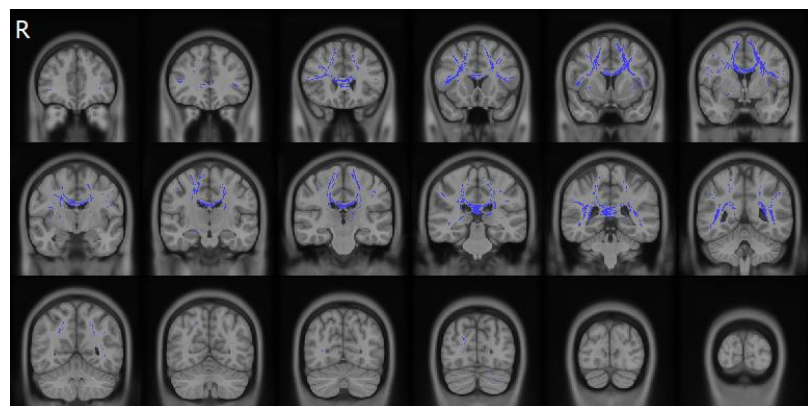
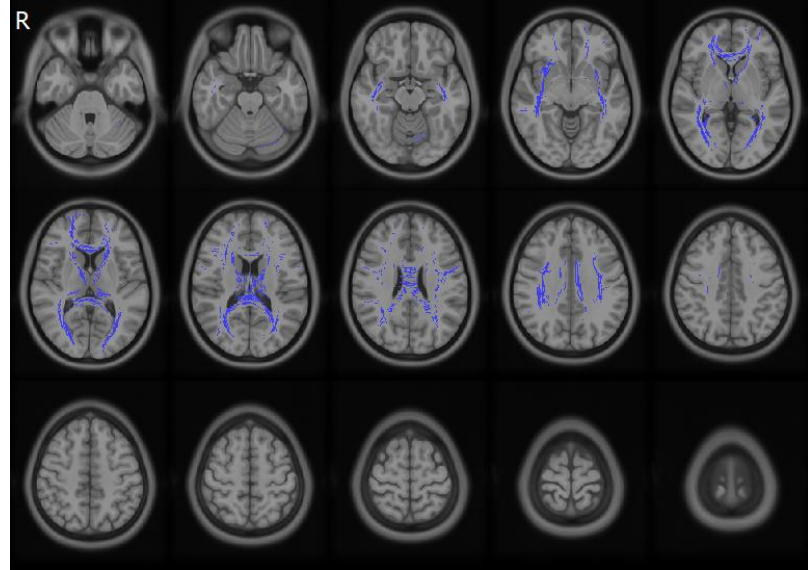
### Tracks with DTI\_FA positively correlated with WMH



**Fig.** Tracks with DTI\_FA positively correlated with WMH (FDR  $\leq$  0.050000)

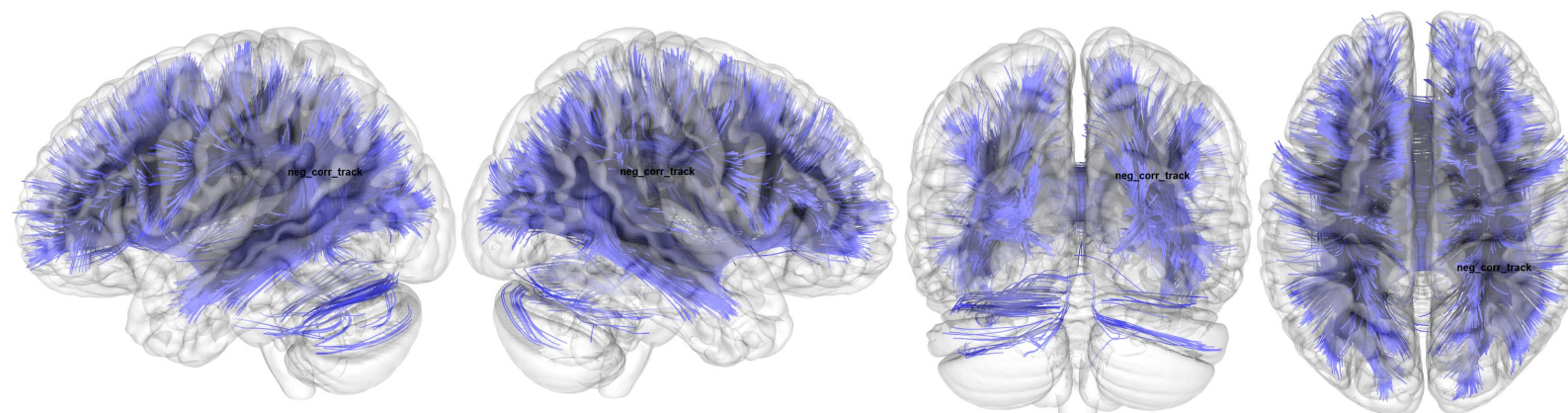
The connectometry analysis found no significant result in tracks with DTI\_FA positively correlated with WMH (FDR  $\leq$  0.050000).

### Tracks with DTI\_FA negatively correlated with WMH



**Fig.** Tracks with DTI\_FA negatively correlated with WMH ( $FDR \leq 0.050000$ )

The connectometry analysis found Corpus\_Callosum\_Body, Inferior\_Fronto\_Occipital\_Fasciculus\_R, Corpus\_Callosum\_Tapetum, Corpus\_Callosum\_Forceps\_Major, Corpus\_Callosum\_Forceps\_Minor, Inferior\_Longitudinal\_Fasciculus\_R, Arcuate\_Fasciculus\_L, Superior\_Longitudinal\_Fasciculus2\_R, Frontal\_Aslant\_Tract\_L, Inferior\_Longitudinal\_Fasciculus\_L, Inferior\_Fronto\_Occipital\_Fasciculus\_L, Arcuate\_Fasciculus\_R, Frontal\_Aslant\_Tract\_R, Cingulum\_Frontal\_Parahippocampal\_L, Thalamic\_Radiation\_Anterior\_L, Thalamic\_Radiation\_Posterior\_L, Thalamic\_Radiation\_Anterior\_R, Superior\_Longitudinal\_Fasciculus2\_L, Anterior\_Commissure, Corticostriatal\_Tract\_Posterior\_L, Superior\_Longitudinal\_Fasciculus3\_R, Corticostriatal\_Tract\_Posterior\_R, Fornix\_L, Thalamic\_Radiation\_Posterior\_R, Thalamic\_Radiation\_Superior\_L, Cingulum\_Frontal\_Parietal\_L showing DTI\_FA negatively correlated with WMH ( $FDR \leq 0.050000$ ).

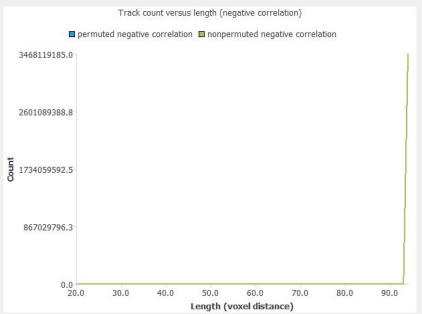


**Fig.** Correlational tractography with positive correlation (red)( $FDR \leq 0.050000$ ) and negative correlation (blue)( $FDR \leq 0.050000$ ).

### False discovery rate analysis

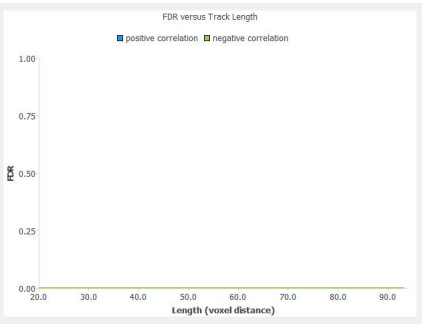


**Fig.** Permutation test showing the histograms of track counts with DTI\_FA positively correlated with WMH.



**Fig.** Permutation test showing the histograms of track counts with DTI\_FA negatively correlated with WMH.

The permutation was applied to subject labels to test results against permuted condition. The histogram under permuted condition represents the result under the null hypothesis. This null result is then used to test the histogram under nonpermuted condition to compute the FDR. A smaller difference between histograms suggests that the study finding is similar to null finding and having a lower significance, whereas a larger difference suggests greater significance of the study finding.



**Fig.** The False discovery rate (FDR) at different track length