

## Additional File 1

**Additional File 1: Figure S1. Probability of tract reaching brain regions.** Reach probability of tract connecting to 82 ROIs are visualized in **A)** heatmap and **B)** barplots for AD-associated tracts that have been replicated in two independent cohorts in the current study.

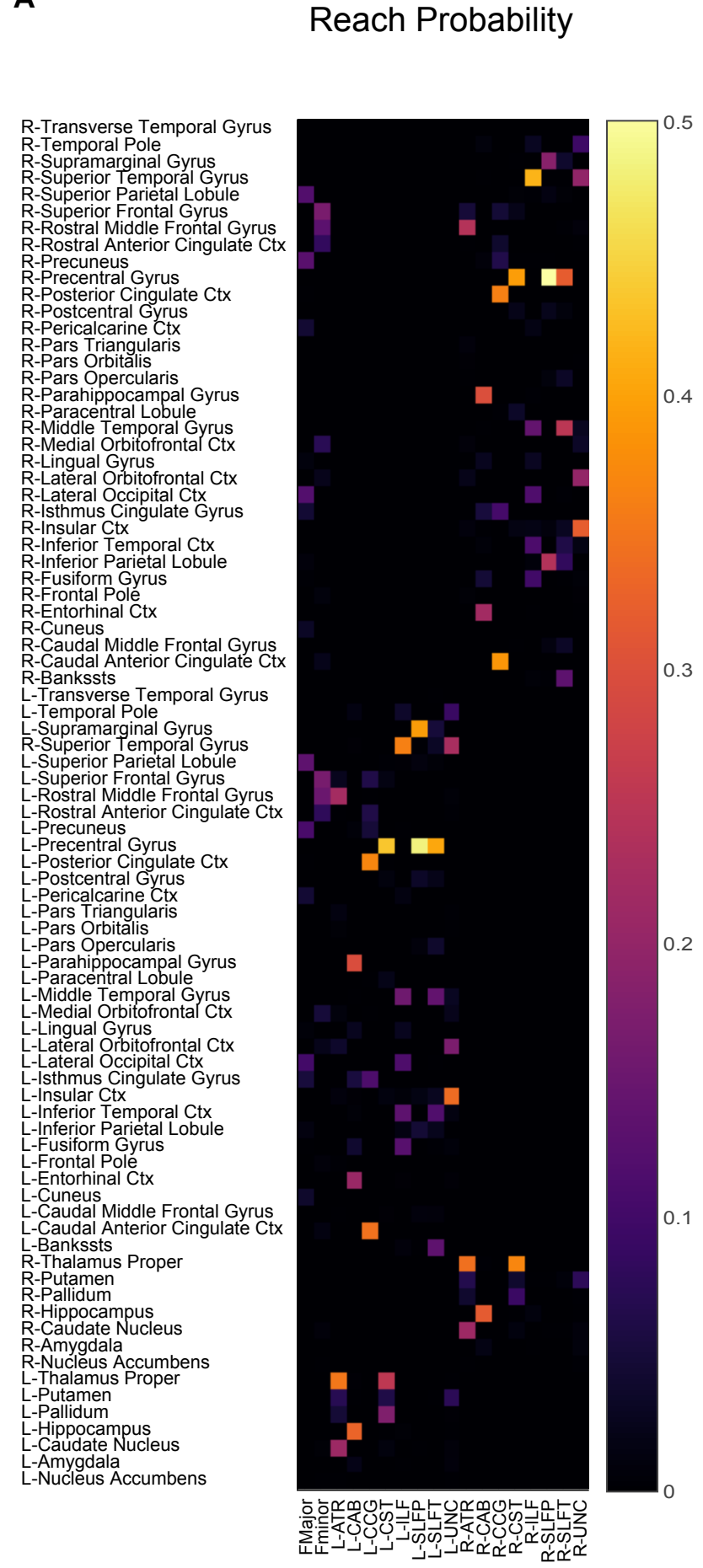
**Additional File 1: Figure S2. Reach probability distribution.** The distribution of reach probability is extremely heavy tailed and large proportion of reach probability measures are low. **A)** Histogram demonstrates this extreme value distribution. The orange dashed vertical line is reach probability of 0.002 and it cuts the distribution. This threshold is a reflection point based on Empirical Cumulative Distribution Function of reach probabilities. **B)** Empirical Cumulative Distribution Function of reaching probability below 5% is plotted. The orange dashed vertical line is reach probability of 0.002 and is an approximal reflection point.

**Additional File 1: Figure S3. Pathway interaction analysis and results.** Interaction between TTC genes by brain ROIs at the molecular pathways were examined. **A)** For a pair of ROIs, pathways significantly over-represented by TTC genes were binarized for each ROIs. The two binarized vectors for a ROI pair was transformed to adjacency matrix and this defines pathway interaction between a ROI pair. This was repeated for all 136 ROI pairs. **B)** The 136 adjacency matrices were grouped by white matter connection definition where not-tract-bound (72 ROI pairs), tract-bound (64 ROI pairs), and AD-tract-bound (34 ROI pairs). The heatmaps display proportion of pathway interactions normalized by number of ROI pairs in each group for not-tract-bound (left), tract-bound (middle), and AD-tract-bound (right). **C)** Significant difference in the proportion of pathway interaction between not-tract-bound and tract-bound was assessed using Chi-square test. The P-values were  $-\log_{10}$  transformed and are hierarchically clustered. Strongly interacting pathways are highlighted in dashed rectangles. Pathway labels at two levels (Pathway Types and Signaling Types) are also added on the heatmap. **D)** Significant difference in the proportion of pathway interaction between not-tract-bound and AD-tract-bound was assessed using Chi-square test. Same heatmap display options as C) is applied here.

**Additional File 1: Figure S4. Correlation between tract-specific measures in ADNI3.** The correlation between Volume, average tract length (Length), Axial Diffusivity (AxD), Radial Diffusivity (RD), Mean Diffusivity (MD), and Fractional Anisotropy (FA) were examined for each tract.

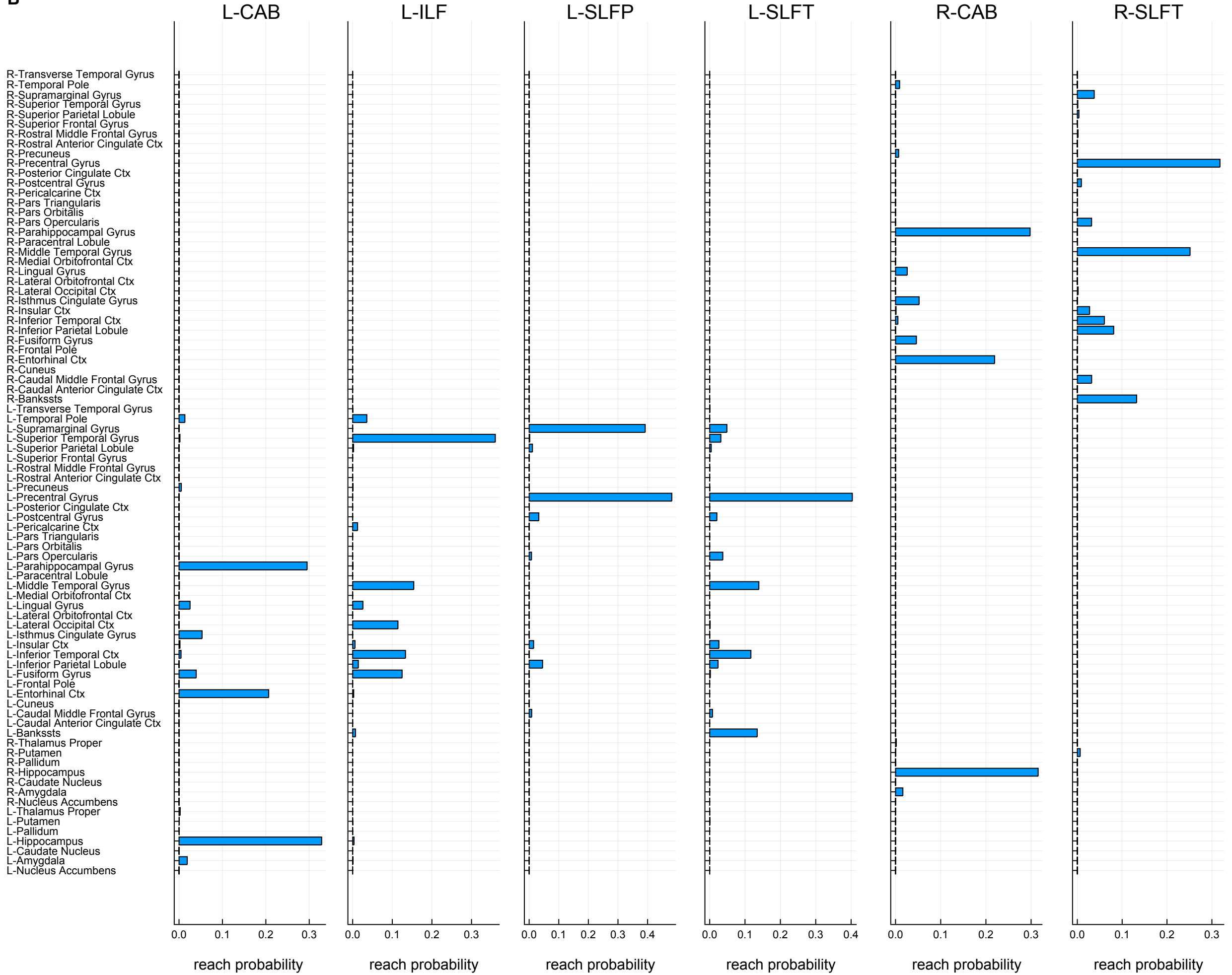
**Figure S1**

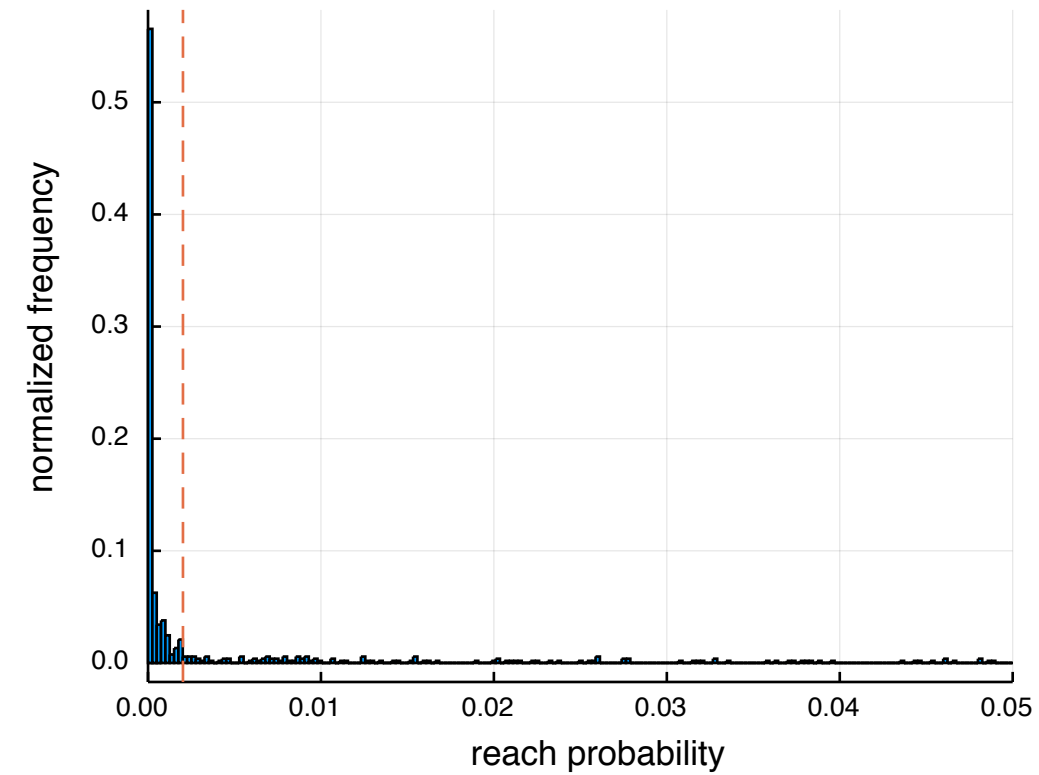
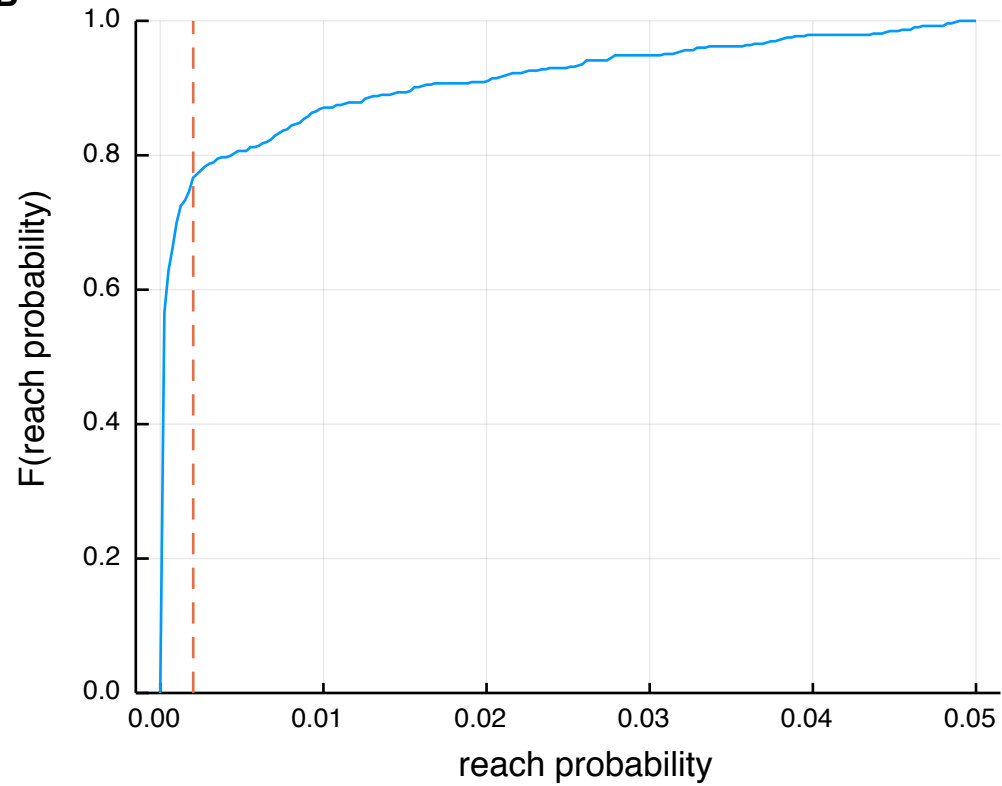
**A**



Bankssts: Banks of Superior Temporal Sulcus

**B**



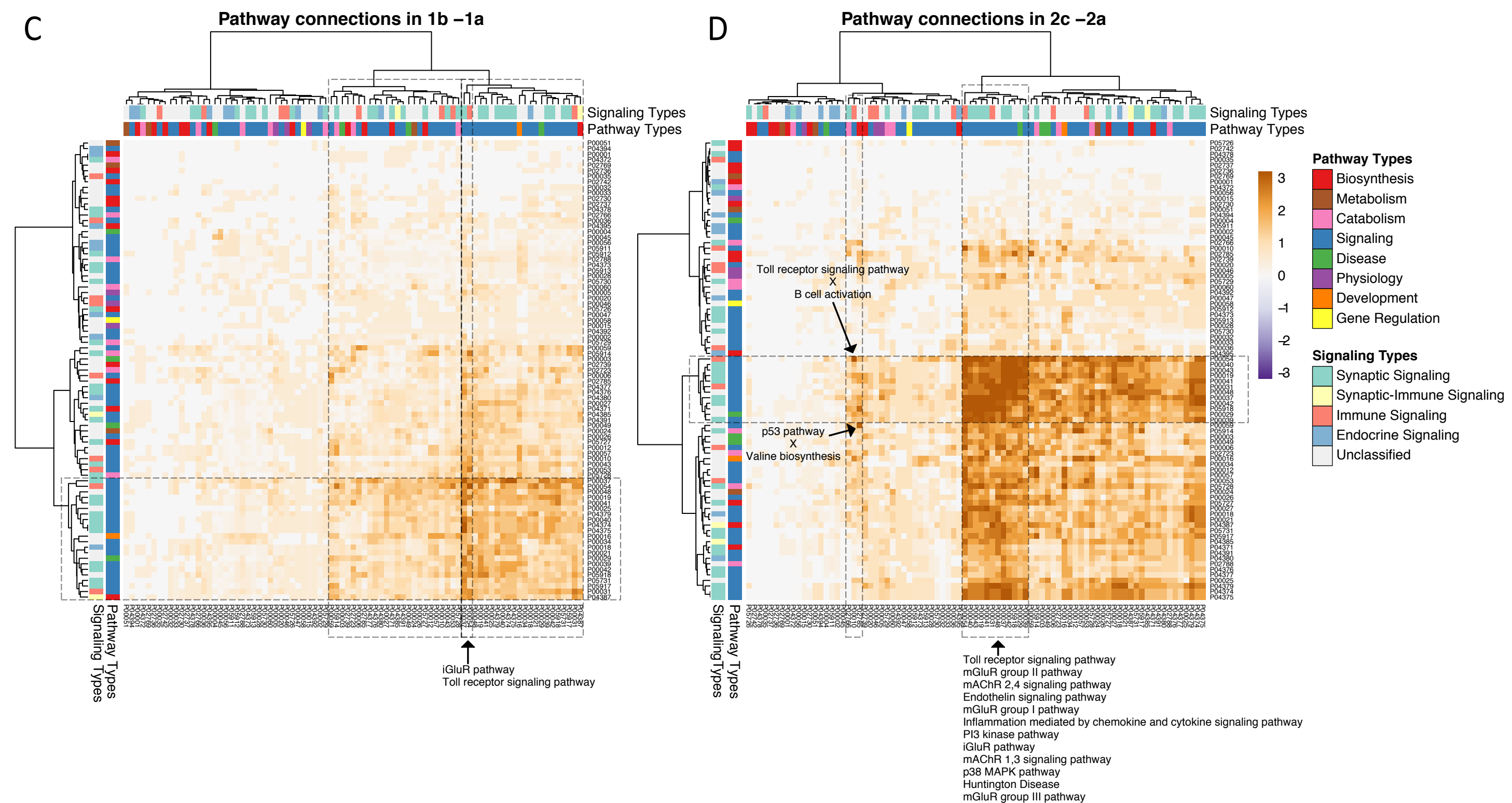
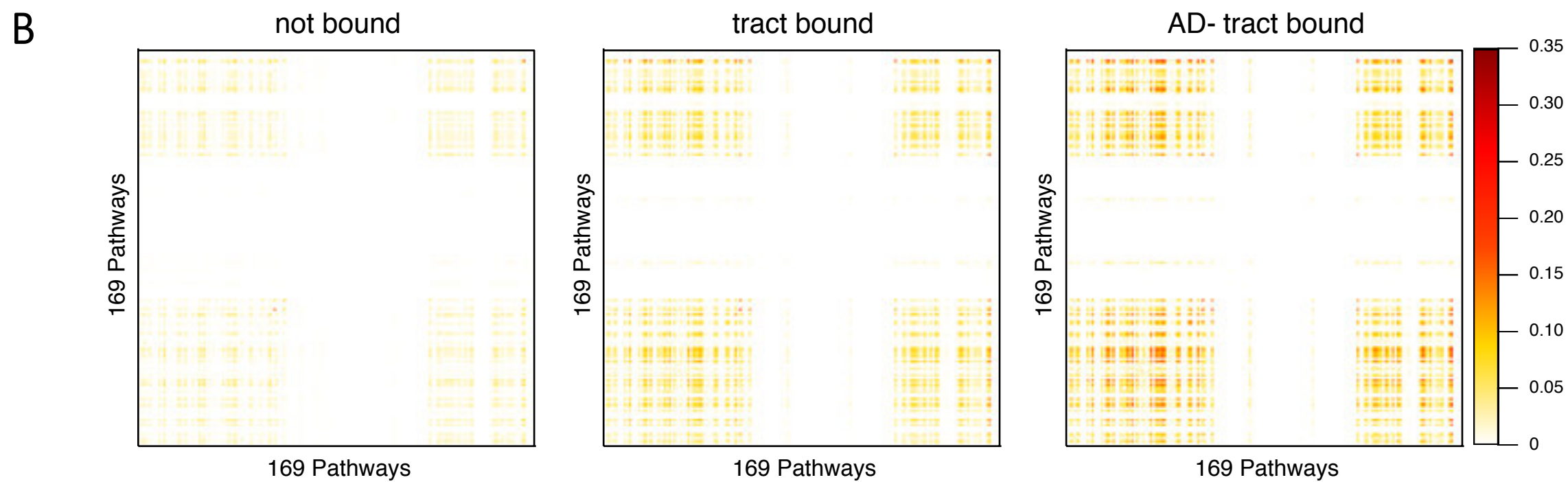
**Figure S2****A****B**

# Figure S3

**A**

Pathway	ROI1	ROI2		p1	p2	p3	
p1	0	1		p1	0	0	0
p2	1	1		p2	1	1	1
p3	1	1		p3	1	1	1

$A_i$  = Adjacency matrix  
(Pathway interaction b/w ROIpairs)



**Figure S4**

**Correlation between diffusion variables**

