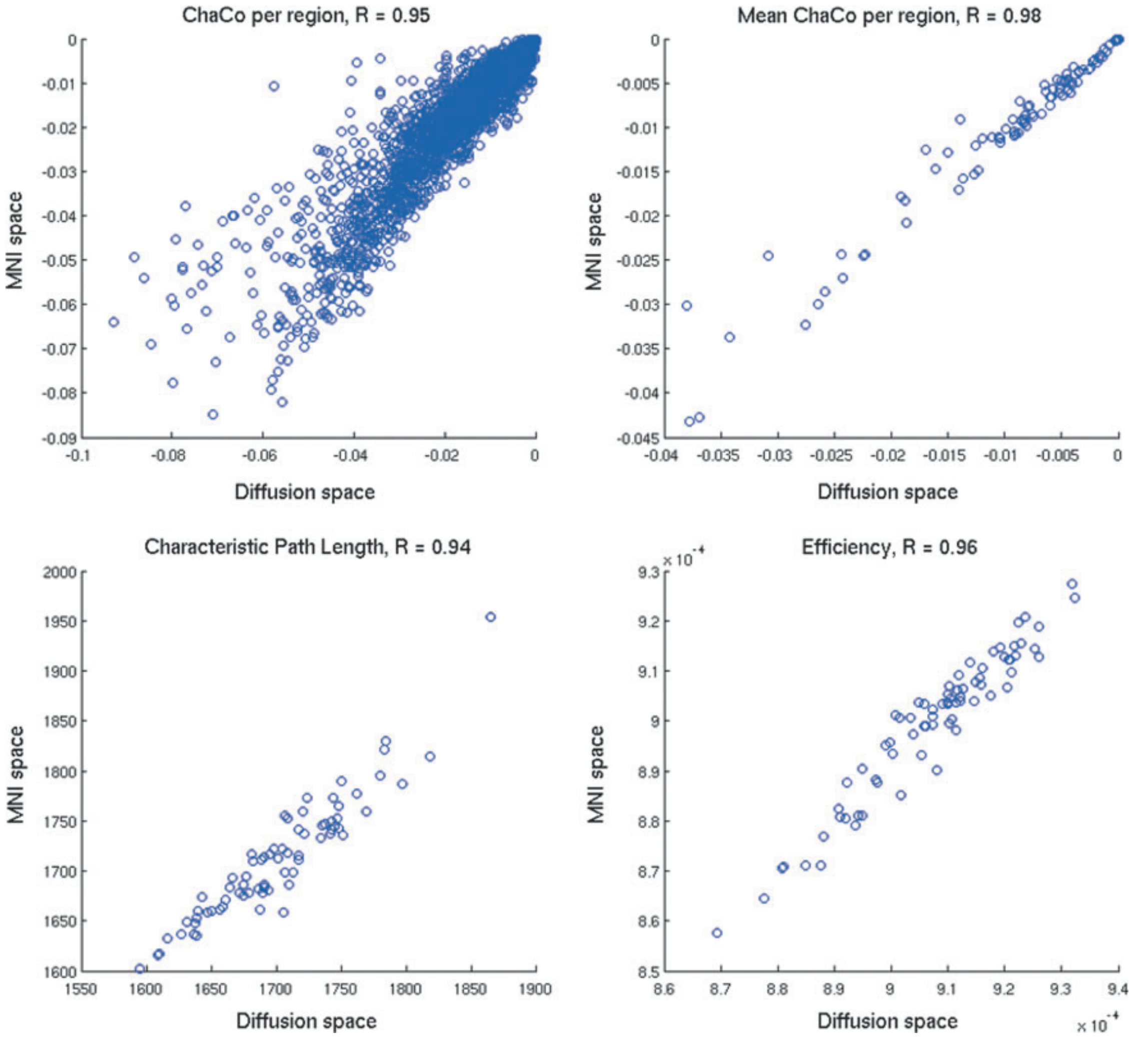
Supplementary Data

Supplementary Data S1: Validation of the Tractogram Normalization to Montreal Neurological Institute Space

We validate the transformation of the streamlines from an individual's diffusion image space to common Montreal Neurological Institute (MNI) space in three ways. First, the level of agreement in the terminal regions of interest (ROIs) for each streamline before and after normalization is measured. The two ends of each streamline are within cortical or subcortical regions by the design of the tractography algorithm. The cortical parcellation is normalized from diffusion to MNI space using the same non-linear transformation as the streamlines and nearest-neighbor interpolation. Finally, the percentage of agreement in the ROIs of the start and end voxels are counted before and after normalization. As a second verification, the two sets of connectivity matrices are compared by first identifying the non-zero entries in the two sets of matrices using Student's *t*-test. For each significantly non-zero entry ($p < 0.05$, Bonferroni corrected), testing is performed for significant ($p < 0.05$, Bonferroni corrected) differences using a paired *t*-test. In addition, overall network metrics are tested for differences using a *t*-test. As a third validation, the Change in Connectivity (ChaCo) metric, an output of the NeMo Tool, is calculated in MNI space for a lesion mask, which is then transformed into the diffusion space of each subject by applying the inverse



SUPPLEMENTARY FIG. S1.

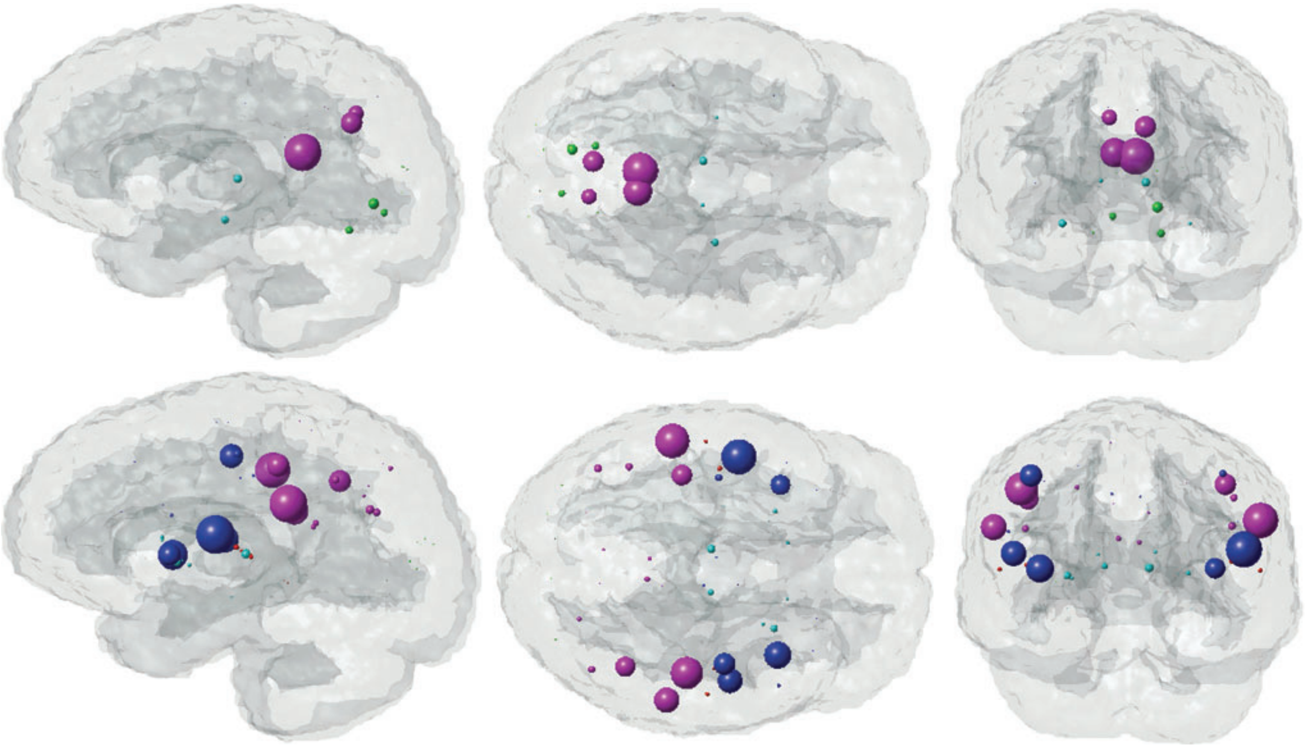
of the non-linear transformation used in the MNI normalization (with nearest-neighbor interpolation). After transformation into diffusion space, the ChaCo is calculated for each subject and averaged. The mean diffusion space ChaCo and MNI space ChaCo are compared using Pearson's correlation, as are the graph network metrics for the connectivity matrices.

The MNI transformation of the tracts was validated using the 116 region atlas. The terminal gray matter (GM) regions for each streamline were compared before and after normalization for each of the 73 normal individuals in the Tractogram Reference Set (TRS), and 91.5±4.1% were in agreement. At a higher-level validation, the connectivity matrices derived from the tractograms before and after normalization were compared. Out of the 6670 total possible pairwise connections (as measured by total streamline count between GM region pairs), 1157 were significantly non-zero and none of these were significantly different. In addition, no graph network metrics (characteristic path length and efficiency) in the two sets of matrices were significantly different.

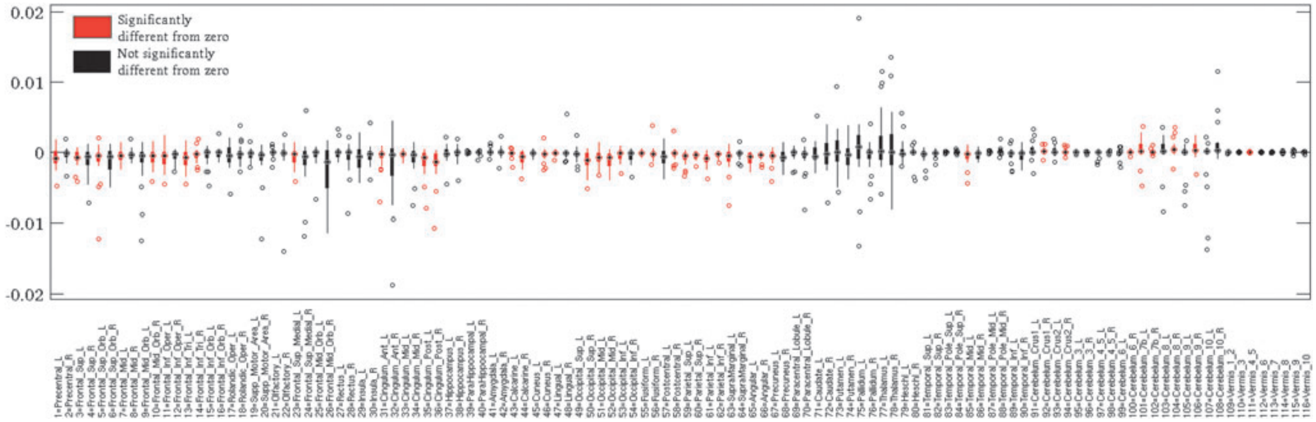
Finally, we validated the transformation into MNI space by producing the Network Modification (NeMo) results in both MNI and diffusion space for a hand-drawn white matter (WM) alteration mask similar to the one used in the normal pressure hydrocephalus (NPH) study. As shown in the upper left panel of Supplementary Figure S1, the correlation of the ChaCo scores over the 73 subjects in the TRS and 116 regions was high ($R = 0.95$). The average regional ChaCo over the 73 subjects (upper right panel of Supplementary Fig. S1) was also highly correlated ($R = 0.98$), as were the graph network metrics of characteristic path length ($R = 0.94$) and efficiency ($R = 0.96$) (bottom panels of Supplementary Fig. S1).

Supplementary Data S2: Removal of Whole WM Structures

To provide initial validation that the correct GM regions are identified given a WM lesion, we made two binary WM alteration masks that removed (1) the splenium of the corpus callosum and (2) the superior longitudinal fasciculus, as defined in the JHU-MNI "Eve" atlas (Oishi et al., 2009). The ChaCo results for the hand-drawn masks are given in Supplementary Figure S2. Bilateral parietal and occipital areas are identified as disconnected from the splenium removal (top row). The removal of the superior longitudinal fasciculus disrupts mostly frontal and parietal regions, along with some temporal and subcortical regions, which is, again, unsurprising (bottom row). These results are encouraging, as the regions we expected to be involved were identified by our tool. Some regions further from the WM were less emphasized, a fact that sheds light on of the limitations of our tool which stems from its dependence on probabilistic tractography (see section "Limitations" in the main text). Regions that are closer to the WM lesions will



SUPPLEMENTARY FIG. S2.



SUPPLEMENTARY FIG. S3.

tend to have relatively more disconnection than those further from the lesion.

Supplementary Data S3: Results for Normals Using the WM Alteration Masks as Defined in the Traumatic Brain Injury Study

Due to the way in which the value assignment for WM alteration masks is defined, it is expected that 1% of voxels in the mask of a normal subject have non-zero entries. A boxplot of the ChaCo results for the 20 randomly selected normal controls is given in Supplementary Figure S3. The effects of these phenomena on the NeMo outputs were relatively small; only 41 of the 116 regions had ChaCo significantly different from zero, all the mean values were less than 0.3%, and all regions had extreme values less than 2%. These results show that when using the method in Section ChaCo values of less than 1–2% should be interpreted as noise.

Supplementary S4: ChaCo Results for Alzheimer's Disease, Frontotemporal Dementia, NPH, and Traumatic Brain Injury

Tables that give the amount of disconnection per region for the various datasets used in the article are depicted next. The tables are colored by regional membership using the same color-coding scheme as the boxplots and glassbrain visualizations (frontal = blue, parietal = pink, occipital = green, temporal = red, subcortical = cyan, and cerebellar = yellow). For each set of results, the table has been arranged from most decreased connection to most increased connection.