Functional Connectivity Based Clustering of White Matter

Clare Kelly[1], Greg J. Siegle[2], and Michael P. Milham[3,4]

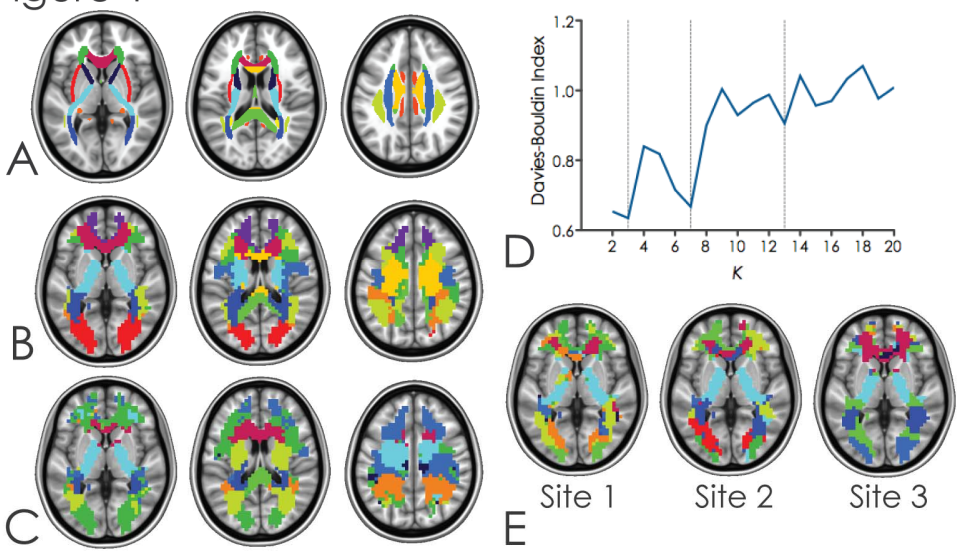
[1]NYU Child Study Center, New York, NY, United States, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [3]Nathan S. Kline Institute for Psychiatric Research, NY, United States, [4]Child Mind Institute, New York, NY, United States

Objectives: Data-driven clustering methods applied to intrinsic (resting state) functional connectivity (iFC) measures can be used to partition the brain into its functional "building blocks," based on the insight that patterns of iFC differ qualitatively among functionally distinct regions. These approaches have been highly successful at detecting known functional, anatomical, architectonic and neurochemical subdivisions in the brain. To date however, with the exception of one study (Mezer et al., 2008), these efforts have avoided white matter (WM), likely due to continued skepticism regarding the fidelity of WM BOLD signal. Here, in light of mounting evidence supporting the neurophysiological veracity of WM BOLD (e.g., Yarkoni et al., 2009), and the potential utility of iFC approaches in WM disorders such as multiple sclerosis and traumatic brain injury, we performed a data-driven parcellation of WM on the basis of iFC, using a multi-site large-*n* dataset (http://fcon_1000.projects.nitrc.org). We also explored the similarity between the resultant parcellations and those obtained by clustering T1 structural covariance maps.

Methods: MRI data were selected from the 1093 healthy adult datasets available at http://fcon_1000.projects.nitrc.org. A sample of 18 participants was selected (where possible) from each of 19 sites for whom resting state EPI and T1 images with full-brain coverage were available (340 participants; 167 females; age 29.3±8.5). Scan parameters are available from the website. Resting state data were processed using a standard processing pipeline (http://www.nitrc.org/frs/?group_id=296) that included spatial smoothing (6mm FWHM), temporal filtering (0.009-0.1Hz) and nuisance signal regression (CSF, WM and global signal). WM volume images were created using FSL's VBM pipeline applied to segmented T1 WM images (smoothing = 6mm FWHM).

For each voxel within a mask comprising 7017 WM voxels (MNI152 tissue prior; 50% tissue type probability; 4mm^3 voxels), we computed voxel-wise maps of (1) Pearson correlation-based intrinsic functional connectivity and (2) using the same subjects, whole-brain WM inter-subject structural covariance. Next, separately for each data type, we used eta^2 to quantify the pair-wise similarity between the maps associated with each of the 7017 voxels. We then used spectral clustering (Miela and Shi, 2001; http://www.stat.washington.edu/spectral/) to identify clustering solutions for *K*=2:20. Finally, we performed consensus clustering (e.g., Bellec et al., 2010) to produce a final set of solutions, based on the stability with which pairs of voxels were placed in the same cluster *across sites*. We computed the Davies-Bouldin (DB) index to identify "optimal" solutions.

Figure 1



Results: The DB index (Fig. 1D) indicated that solutions 3, 7 and 13 were optimal. The 13-cluster solution is shown. Clustering of WM on the basis of iFC (Fig. 1B) revealed a symmetrical topography consistent with WM atlases constructed on the basis of DTI tractography, such as the ICBM DTI-81 Atlas (Fig 1A; http://www.loni.ucla.edu/). In particular, the 3 sections of the corpus callosum (genu, body, splenium), the internal capsule, and the superior longitudinal fasciculus were easily identifiable. This organization was consistent across multiple sites, as illustrated with 3 examples (Fig. 1E). Although less precisely organized and exhibiting somewhat poor consistency with the iFC-based clusters (<50% agreement), the clustering solutions derived on the basis of T1 WM structural covariance (Fig. 1C) do show some similarities with the DTI-based atlas, separating the internal capsule, for example. Further analyses will restrict the spatial extent of the WM mask and reduce the voxel resolution used (to address potential partial voluming issues), and will investigate the impact of nuisance signal regression on the results obtained. In addition, we will examine the factors influencing clustering across sites, for both resting state (EPI) and T1 data.

Conclusions: In line with previous findings (Mezer et al., 2008), our results suggest that synchronous BOLD signal in WM exhibits an organization that follows known structure. Additional work is required to investigate the extent to which the similarity between iFC clusters and DTI-based WM tracts is engendered by anatomical connectivity, rather than extraneous physiological phenomena or registration artifact. Nonetheless, we suggest that these findings support the use of IFC measures to investigate WM organization, which may have utility for the investigation of clinical disorders characterized by WM alterations.

References: Bellec P, Rosa-Neto P, Lyttelton OC, Benali H, Evans AC, 2010. Multi-level bootstrap analysis of stable clusters in resting-state fMRI. *NeuroImage,* 51, 1126-1139; Miela M, Shi J, 2001. A random walks view of spectral segmentation. *8th International Workshop on Artificial Intelligence and Statistics (AISTATS*), Key West, Florida; Mezer A, Yovel Y, Pasternk O, Gorfine T, Assaf Y, 2008. Cluster analysis of resting-state fMRI time series. *NeuroImage* 45, 1117-1125; Yarkoni T, Barch DM, Gray JR, Conturo TE, Braver TS, 2009. BOLD Correlates of Trial-by-Trial Reaction Time Variability in Gray and White Matter: A Multi-Study fMRI Analysis. *PLoS ONE*,4, e4257