The LoCo (Loss in Connectivity) tool: a new way to investigate changes to the structural brain network in various types of disease or injury

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Introduction: There are many tools to assess pathologic brain changes in structural or diffusion MRI such as voxel-based morphometry, deformation based morphometry, Tract-Based Spatial Statistics (TBSS) and MR volumetrics [1,2,3]. To our knowledge, the LoCo (Loss in Connection) Tool is the first that associates localized white matter (WM) lesions with disruptions in gray matter connectivity as a step toward understanding the lesions' functional implications. This tool uses tractograms (set of white matter fibers) from a large set of normal healthy individuals that have been coregistered to a common space (MNI) to assess structural network disruption related to a WM lesion mask. This method leverages the relative sensitivity of diffusion MRI (compared to standard structural MRI) to investigate changes in connectivity due to various brain diseases.

The LoCo tool is an easy way for researchers and clinicians to investigate changes to the structural brain network without having to perform tractography on their own normal data or on diseased/injured brains where the results are known to be unpredictable and may not represent the underlying physiology. In addition to reporting connectivity changes for an individual GM region in a standard atlas, the LoCo GUI also reports changes to overall brain network metrics like efficiency, path length, average clustering coefficient, etc. Because the LoCo scores are a result of analyses on many different normal tractograms, we can also analyze their variation per GM region.

We previously applied a similar methodology to neurodegenerative diseases such as Alzheimer's disease and Fronto-temporal dementia [5], where it was shown that the projected connection loss correlated positively with GM atrophy. It was also shown that this metric better differentiated between the AD, FTD, and normal age-matched controls than GM atrophy alone. This methodology also showed that the brain reward-system is preferentially disrupted in alcohol dependent individuals [6], and is better at differentiated them from non/light drinking controls than compared to GM atrophy. In this work, we have streamlined and automated the original time-consuming and computationally intensive method by transforming all of the WM tracts from each individual to a common space. This eliminated the need to individually coregister to each tractogram, thus improving the speed of the required computation to allow completion in less than 15 minutes on a desktop computer. The improved algorithm was applied to the study of Normal Pressure Hydrocephalus (NPH), a neurologic disorder characterized by pathologic increases in ventricular size and transependymal fluid movement into peri-ventricular WM.

Data and Methods: *Creation of the tractogram database* Structural and diffusion image data from 14 young healthy normal subjects were processed and WM tractograms constructed that connect 116 different GM regions in the standard AAL atlas. SPM was used to find the 12-parameter non-affine transform that coregistered each subject's T1 image to the MNI T1 atlas. The coefficients of the deformation field that correspond to this transform were defined for each voxel center. These coefficients must be interpolated to be applied to points not at the center of a voxel. The interpolated coefficients are applied on a point-by-point basis to each 3-valued (x,y,z) triplet in a fiber tract, providing the corresponding fiber tract in MNI space. We found no significant differences between the tract connectivity derived from this methodology compared to that in our earlier analysis, suggesting that the two methods are essentially equivalent.

Implementation of the LoCo Tool Within the tool, the user uploads an "injury" mask. This mask can be narrowly or broadly defined by parameters such as diffusion summary statistics, fractional anisotropy, radial, axial and mean diffusivity, or other structural abnormalities like WM hyperintensities. The WM tracts in the normal controls that pass through the "injured" voxels are identified. The percentage of damaged tracts out of the total number of tracts connecting to each of the 116 cortical regions is taken as the measure of Loss in Connectivity (LoCo). Scores closer to 1 indicate greater connectivity disruption.

The user-friendly toolkit can display the results of the LoCo analysis in various ways. Figure 1 shows the GUI with one possible mode of display - called the "glass brain" that conveys the LoCo scores by the size of the nodes, each of which is centered at one of the 116 GM regions. The colors correspond to the lobe to which that GM region belongs. Alternatively, the user can display the LoCo scores as the color on the surface of the GM region (as in Figure 2). To investigate the variation of the LoCo scores across the normal tractograms, one can generate a boxplot with the scores per GM region (Figure 3). In addition, the LoCo GUI will output global connectivity changes, such as loss in efficiency, increases in characteristic path length, and changes to clustering coefficients.

Application to NPH Subjects meeting criteria for Probable NPH [7] underwent structural and diffusion imaging on a 3-Tesla GE scanner. For analysis of the NPH WM lesion connectivity, we calculated the WM injury map by taking the WM voxels of clusters of 5 or more that were greater than 2.5 standard deviations above the mean T2-FLAIR signal in the WM.

Results and Conclusions: The LoCo results for a Normal Pressure Hydrocephalus (NPH) subject are displayed in Figures 1-3. A high amount of connection disruption was found in the orbital-frontal region as well as the anterior cingulate. Connectivity changes were also seen in GM loci within the parietal and occipital lobes. This analysis confined the mask to the peri-ventricular WM hyperintensities which is only one component of the WM abnormalities seen in NPH. Future studies will use other metrics to find WM abnormalities, such as changes in FA, MD, axial and radial diffusivity, and free water to further explore structure-dysfunction relationships in NPH and other disorders.

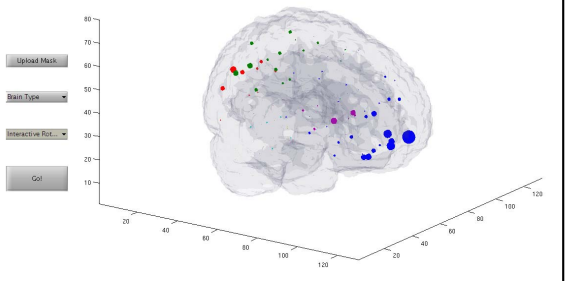

Figure 1: The LoCo GUI, with the results from an NPH patient.

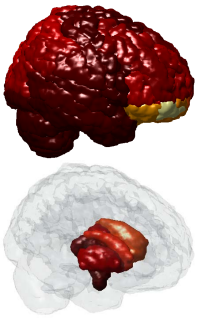

Figure 2: The LoCo scores for each GM region for an NPH subj.

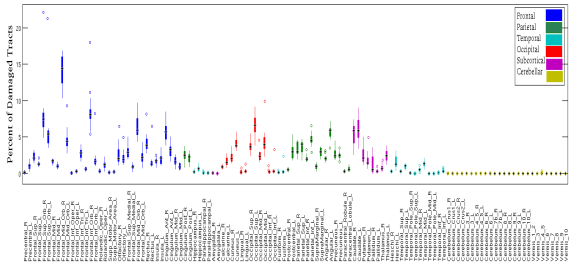

Figure 3: Variation analysis of the LoCo scores for an NPH subject per GM region across the population of normal tractograms.

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