The LoCo: a measure of gray matter structural connectivity loss and its application to neurodegenerative disorders

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Introduction: Alzheimer's disease (AD) and fronto-temporal dementia (FTD) have been classically characterized as neuronal death primarily affecting the cerebral gray matter (GM) [1,2]. Although these dementias are seen as GM-mediated diseases, it is now well known that the progression involves white matter (WM) fiber pathways via secondary Wallerian degeneration, disconnection, loss of myelinated axons, loss of signaling, axonal reaction, post-synaptic dendrite retraction, and possibly the propagation of misfolded proteins (in AD) across synapses. Studies of measures of WM integrity such as fractional anisotropy (FA) measured from diffusion MRI data have shown significant findings that are sensitive to early changes, sometimes earlier than gross cortical atrophy is measurable [3,4]. It is therefore clear that both GM and WM disruptions play a role in the disease process in dementias; however, there has been a relative lack of studies investigating the changes of the two tissue types together, see [5, 6].

In this work, we propose a computational methodology that integrates diffusion MRI, tractography and structural MRI of a cohort of young healthy controls, FTD and AD patients as well as age-matched normal controls. This fully quantitative and spatially unbiased approach overcomes numerous deficiencies in current methods, which are either restricted to *ad hoc* structures, do not consider GM and WM jointly, or do not consider the topology of structural WM fiber connections in the healthy brain. Our approach exploits the enhanced sensitivity of WM-specific measurements like DTI in order to obtain a spatially distributed GM-specific measure which is expected to be much more sensitive and specific than gross measurements of cortical atrophy. The so-called Comparative Connectivity Loss (LoCo) measures GM regions' connectivity disruption via WM integrity losses in their connecting fibers, without having to perform tractography in abnormal cohorts. Using this technique we demonstrate unbiased and statistical correlations between whole brain WM and GM measurements. We also show that LoCo is a better and more sensitive measure of dementia-related changes than cortical atrophy, and similar to diffusion MRI summary statistics.

Data and Methods: Structural and diffusion image data from 18 AD, 18 FTD and 19 cognitively normal (NC) age-matched cohorts were obtained from a study performed by Zhang, et al. [4]. The fractional anisotropy (FA), radial diffusivity (RD), and longitudinal diffusivity (LD) were calculated to assess WM integrity. Voxel-wise t-statistics were calculated for the AD and FTD versus control groups for all three measures and the resulting t-maps thresholded at a significance level of p <0.05 after FDR correction, resulting in a WM "injury" map for each disease. Lastly, each individual was assigned an "injury" map by using the same procedure above, but replacing the group-wise t-maps with an individual's map of z-scores (using the NC group as the control). All of the injury maps were then coregistered to each of 14 young normal subjects, for which diffusion data had been processed and WM tractograms constructed that connect 116 different GM regions in the standard AAL atlas. The WM tracts in the normal control that passed through the "injured" voxels were recorded, as were the GM regions those tracts connected. The percentage of damaged tracts out of the total number of tracts connecting to each of the 116 cortical regions was taken as a measure of cortical involvement, or so-called Loss in Connectivity (LoCo); note that scores closer to 1 indicate greater deficit. In addition, the measurements of structural volume for the 116 regions (normalized by intracranial volume) from the IBASPM output for the same subjects were used to calculate atrophy, taken to be the t-score of the group of AD and FTD subjects' regions versus NC subjects' regions.

Results and Conclusions: The GM regions most classically associated with AD, the hippocampi, were in the top 15% most affected. The bilateral posterior cingulate structures, thalami, and many temporal (inferior and middle) structures were also in the top 20%. Many structures normally associated with the default mode network were affected, i.e. the cuneus, precuneus, and occipital regions. In addition to the general agreement of involved regions with known pathology, cortical structures that are known to be uninvolved in AD had low LoCo, i.e. the motor cortex and cerebellum. The pattern of LoCo in the FTD cohort also agrees generally with what is known about the pattern of the disease areas with the highest 20% LoCo scores were in the subcortical and medial frontal cortices. It should be noted that the LoCo scores in the FTD population are around 10 times greater than that of the AD population, in agreement with previous studies that demonstrate larger volumes of tissue with significant WM integrity loss in FTD when compared to AD. In a more quantitative validation study, it was found that there was a highly significant correlation (Spearman's, after Bonferroni correction) between the group-wise LoCo and the group-wise t-scores measuring atrophy in the 116 different GM regions for both the AD group ($R = 0.51$, $p = 2.2 \times 10^{-9}$) and FTD group ($R = 0.49$, $p = 2.5 \times 10^{-8}$). The cross-disease correlations (of AD's LoCo and FTD's GM atrophy and vice versa) were either non-significant or had a lower values than the paired groups' correlations, demonstrating the specificity of the LoCo metric.

Classification of each patient into one of the three groups (AD/FTD/CN) was performed using Linear Discriminant Analysis and leave-one-out cross-validation. Various metrics were used as classifiers, namely the LoCo, GM atrophy, Mini-mental State Exam scores, and average z-scores of WM integrity measures (FA, RD, and LD) over each region in a standard WM atlas with 106 regions. Dimensionality reduction was performed by projecting the data onto the first N eigenvalues, where N is the number that gave the highest correct classification rate. The LoCo, RD and LD had approximately equal classification rates at 87%, 89%, and 85%, respectively, however the LoCo did so by using only about a half and a quarter of the dimensions of the other WM integrity measures (4 for LoCo versus 15 RD and 7 for LD). The MMSE, FA and GM atrophy measures had correct classification rates of 58%, 76% and 76%, much lower than both LoCo, RD and LD.

These results represent the first attempt to link WM integrity loss and their connected GM regions, and give promising results in that the identified gray matter regions agree with clinical knowledge of the pathology of AD and FTD. More convincingly, the GM regions identified as travelling through injured WM tracts correlate highly with observed GM atrophy in patients, and LoCo outperformed GM atrophy in differentiating between the three groups. While the current analysis does not answer the question of a causal or temporal relationship between GM/WM damage, it represents one step in a future longitudinal study using this methodology that may be able to discern such details. Knowing the progression of tissue degeneration in the brain may lead to more accurate early detection as well as an increased precision in tracking of the disease. It may provide useful information to physicians for better prognosis, treatment and assessment of these two debilitating dementias.

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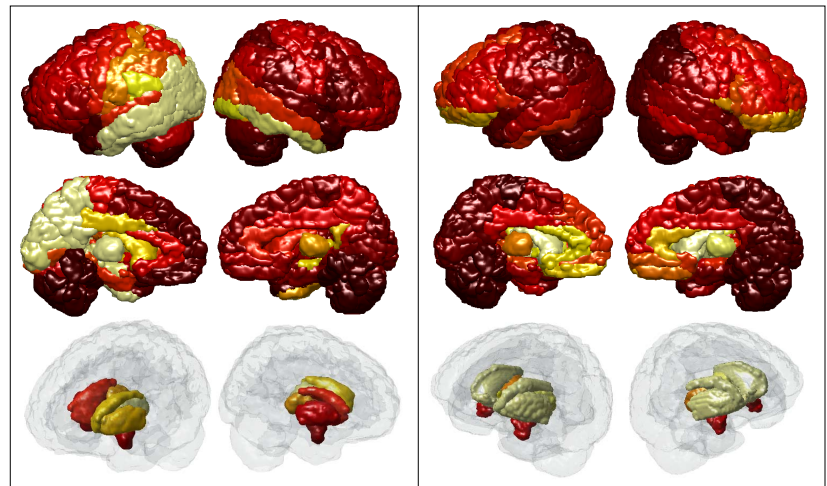
Figure 1: The LoCo scores for each GM region for AD (left) and FTD (right), including subcortical displays (bottom). Dark red (lowest), light yellow (highest).