Selective white matter connectivity loss (LoCo) identified in the brain-reward system of alcohol dependent individuals

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Introduction: A variety of in vivo magnetic resonance imaging (MRI) techniques have been used to assess the effects of alcohol and substance use disorders on human brain morphology. Widely applied quantitative methods include voxel-based morphometry (VBM), deformation based morphometry (DBM), region of interest (ROI) analyses of cortical volume (for review, see [1]) and, more recently, cortical surface area and thickness [2]. A primary limitation of most of these methods is that they are specific to cortical and subcortical gray matter (GM) and do not permit assessment of the integrity of white matter (WM). Increasing evidence suggests that the development and maintenance of alcohol and other substance use disorders are related to neurobiological abnormalities in corticocortical and corticosubcortical circuits that mediate reward-related processes and behaviors [3]. Therefore, interrogation of the microstructural integrity of WM fiber networks that form the interconnectivity among brain regions involved in reward-related behavior, called the Brain Reward System (BRS), is critical to understanding the mechanisms contributing to the maintenance of these disorders and associated neurocognitive and psychiatric dysfunction.

In this study we exploit the sensitivity of diffusion-based measurements in the WM to inform and estimate concomitant changes occurring in the connectivity of GM regions in abstinent alcohol dependent individuals. WM and/or GM changes in these regions do not necessarily occur at the same time or on the same time scale, nor do the imaging modalities that track their changes have the same sensitivity. Therefore, we postulate that by using whole brain tractography information and the location of alcohol-dependent WM abnormalities, we can estimate the degree of anatomical connectivity disruption for each GM ROI. We implement a recently developed measure of GM integrity called Loss in Connectivity (LoCo) by following the WM fiber tracts passing through regions of significant WM integrity loss (relative to controls) to their terminating GM regions. Specifically, we define LoCo of any GM region as the proportion of fiber tracts out of the total number of tracts terminating in that region which pass through identified damaged WM loci. In addition to the LoCo, the proposed approach provides whole brain connectivity networks and measures how global metrics on these networks change under various conditions associated with WM abnormalities.

Data and Methods: High resolution 55-direction diffusion as well as structural images from 14 healthy young controls ("atlas") were obtained from a joint study with the Brain Trauma Foundation and Weill Cornell Medical College. This set of high-resolution diffusion images were used to create tractograms, as in [4], that were assumed to be a representative sample of the "normal" WM tracts and therefore structural connectivity on a 90-region GM atlas. From a separate study being conducted at the University of California San Francisco, structural and diffusion image data from 35 alcohol dependent individuals (ALC) and 21 age-matched non/light-drinking (LD) controls were obtained. Areas of compromised WM in the ALC population were identified by implementing a voxel-wise t-test (ALC vs. LD) on the FA maps and thresholding the resulting t-maps at a value of $t > 1.96$ (corresponding to a p-value of 0.05), removing clusters of 5 voxels or less to get rid of noise. This WM injury map was then coregistered to each "atlas" tracogram using the FA maps and SPM's coregister function. Then, for each GM region, the LoCo was calculated by recording the percentage of WM tracts connecting to that region that pass through an injured WM area. In addition to the group-wise injury map, we calculated an injury map and corresponding LoCo for each individual by replacing the t-map with a map of the z-scores (ALC vs. LD). GM atrophy for each of the 90 regions was measured for each individual using IBASPM. Each ALC and LD subject's LoCo and GM atrophy were used to classify them into their respective groups using Linear Discriminant Analysis and leave-one-out cross validation.

Connectivity matrices summarizing the amount of connection between each of the 90 ROI's were calculated for the LD and ALC populations by modifying each "atlas" tractogram. The WM fibers going through areas of lower FA than seen in the "atlas" group were completely removed, and the connectivity matrices recalculated. Graph theoretical measures of the ALC and LD connectivity matrices were then compared to assess local and global changes to the modified structural brain network.

Results and Conclusions: Results of the whole brain analyses indicated that the bilateral thalamic structures, bilateral caudate, bilateral pallidum, right putamen and bilateral middle occipital ROIs were among regions with the highest LoCo scores, i.e., greatest relative connectivity loss. Figure 1 visualizes the LoCo by plotting the center of the region with a circle whose size is proportional to its LoCo; the BRS regions are shown in red, the non-BRS regions in blue. The right side (left in the figure) shows higher LoCo values indicating greater connectivity disruption, in particular in frontal cortical regions. The LoCo was shown to be significantly higher ($p = 0.0025$) in the BRS than in non-BRS regions by comparing their values using a t-test. GM volume loss was not found to be significantly higher in the BRS vs. non-BRS regions in this cohort using IBASPM, in contrast to a larger published study [5].

When compared to a more standard metric of brain injury in alcohol dependence (GM atrophy), the LoCo better differentiates between brains of alcohol dependent individuals and non-alcoholic controls (correct classification rates of 82% versus 69%). However, just as volumetric measures, the LoCo was not significantly correlated with drinking severity measures. Various graph theoretic measures were analyzed and only a reduction ($p = 0.035$, uncorrected) in degree density, or number of anatomical connections, was shown to be significantly reduced in alcohol dependence. This reduction in overall degree density is coincident with a significant reduction of degree (p-values FDR corrected) for 12 specific brain regions, 10 of which are components of the BRS. LoCo is a new DTI metric sensitive to brain WM abnormalities which, when applied to alcohol dependence, lends further support to regionally specific changes preferentially localized to the BRS, without relating to more systematic and significant whole-brain network-level disruptions.

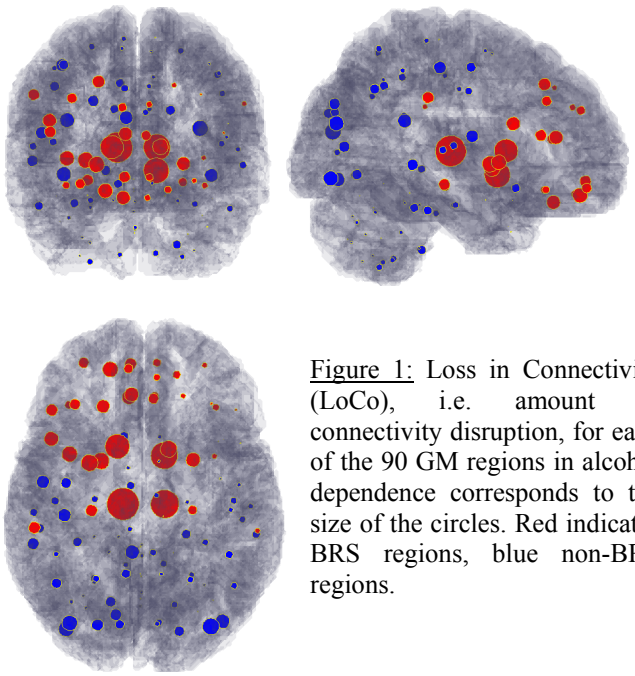

Figure 1: Loss in Connectivity (LoCo), i.e. amount of connectivity disruption, for each of the 90 GM regions in alcohol dependence corresponds to the size of the circles. Red indicates BRS regions, blue non-BRS regions.

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