Correlating white matter integrity loss and gray matter atrophy in Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is characterized as neuronal death that primarily affects the brain's gray matter (GM); however, there has been a recent increase of evidence showing altered white matter (WM) integrity in early AD [1], as well as in asymptomatic people with genetic predispositions to the disease [2,3,4]. This new evidence seems to be against the classical hypothesis that WM degeneration including loss of axons and myelin occurs secondary to GM pathology, and may provide evidence that white matter degeneration precedes neuronal loss in the associated GM regions. Investigating whether AD first affects GM or WM has immense scientific and clinical implications on diagnosis, prognosis and treatment of the disease. If white matter integrity loss in fact precedes cortical atrophy, focus will shift to quantitative white matter neuroimaging measures like diffusivity, fractional anisotropy, T1 and T2 relaxation rates in disease staging and assessment of AD. Furthermore, baseline WM biomarkers could potentially be used to predict future disease progression and therapeutic interventions could be directed towards myelinopathy. In this study, we propose a computational methodology that utilizes DTI, tractography methods and structural MR images of healthy and AD brains to begin to unravel the connection between WM loss and GM atrophy by analyzing the correlation between WM abnormalities in AD patients and GM regions typically affected in the disease. Our quantitative approach overcomes numerous deficiencies in current methods, which are either restricted to ad hoc structures, or do not consider GM and WM jointly.

Data and Methods: Structural and diffusion image data from 18 Alzheimer's patients and 19 cognitively normal age-matched cohorts were obtained from a study performed by Zhang [5]. The fractional anisotropy, radial diffusivity, and axial diffusivity were calculated to get a measure of white matter integrity in both the AD and control groups. Voxel-wise t-statistics were calculated for the AD versus control groups for all three measures and thresholded so the top 10% most "abnormal" pixels were preserved, resulting in a WM "injury" map. This injury map was coregistered to a single normal subject, for which diffusion data had been processed and white matter tracts constructed that connected 116 different gray matter regions in a standard MNI atlas. The white matter tracts in the normal control that passed through the "injured" voxels were recorded, as were the gray matter regions those tracts connected. The percentage of damaged tracts out of the total number of tracts connected to each of the 116 cortical regions was taken as a measure of cortical involvement, or so-called comparative connectivity loss (CCL); note that scores closer to 1 indicate greater deficit. As validation, 32 AD subjects and 60 normal age-matched cohorts from the ADNI database [6] were used to calculate atrophy levels of the 116 different gray matter regions in the same atlas as in the previous analysis. The atrophy level of each region was taken to be the average z-score of the individual AD subjects' regions versus the normal subjects.

Results and Conclusions: Figure 1 displays the cortical regions with the color of the region indicating the CCL of that region. We inspected this map for agreement with gray matter regions known to be involved in the degenerative process of AD. The most classically associated gray matter region in AD, the hippocampus, was prominent in the list of the most effected. The left hippocampus was the third most affected region, and right hippocampus was in the top 15% most affected. The inferior temporal lobes, both left and right, were second and fifth-most effected. The posterior, middle, and anterior cingular structures were also in the top 15% most effected regions. In addition to the agreement of involved regions with known pathology, cortical structures that are known to be untouched in AD had low CCL. The motor cortex was relatively spared and the cerebellum not at all effected, in accordance with clinical observations of the progression of the disease. In a more quantitative validation study, it was found that there was a significant negative correlation ($p = 0.018$, $R = -0.19$) between the CCL and the z-scores measuring atrophy in the 116 different gray matter regions. We then averaged the CCL for the regions in the different lobes of the brain and recalculated the z-scores for each lobe, and again found a significant negative correlation ($p = 0.024$, $R = -0.88$) between the two measures. The greater correlation with lobe atrophy could be due to problems in coregistration and atlasing inherent in normalization of images to a common atlas. These results represent the first attempt to link white matter integrity loss to connected gray matter regions, and give promising results in that the identified gray matter regions agree with clinical knowledge of the progression of AD. More convincingly, the gray matter regions identified correlate highly with actual observed atrophy in AD patients.

Figure 1: The GM regions and their comparative connectivity loss (CCL) (dark green: high, light yellow: low), i.e. the percent of white matter tracts out of the total connecting to that region in a normal control that pass through a voxel identified in the AD white matter "injury" map as abnormal. The gray matter regions normally associated with AD (hippocampus, temporal lobes, cingulate structures) show high CCL. (Left to Right): lateral views left & right, medial views, left & right.

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