Altered White Matter Microstructure for Cognitive Impairment Associated with First-episode Drug-naïve Late-onset Depression: A 6-month Follow-up Study with Diffusion Tensor Imaging

Daniel Han-en Chang[1], Huali Wang[2,3], Na Zhang[2,3], Huishu Yuan[4], Xin Yu[2,3], L. Tugan Muftuler[5], and Min-Ying Su[1]

[1]Tu & Yuen Center for Functional Onco-Imaging, Department of Radiological Sciences, University of California, Irvine, CA, United States, [2]Dementia Care and Research Center, Peking University Institute of Mental Health, Beijing, China, People's Republic of, [3]Key Laboratory for Mental Health, Ministry of Health (Peking University), Beijing, China, People's Republic of, [4]Department of Radiology, Peking University Third Hospital, Beijing, China, People's Republic of, [5]Department of Neurosurgery and Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States

Purpose:

Major depressive disorder affects a large subset of the elderly population. Although it can be caused by heredity and psychosocial adversity factors, it is also commonly associated with aging and neurological diseases. In recent years, it has been found that the white matter microstructure integrity was compromised in the neural networks and structures involved in regulating emotion, particularly the frontostriatal pathways, and that has led to a better understanding about the etiology of the disease. The frontostriatal pathways mainly link the anterior and posterior cingulate, orbitofrontal cortex, and dorsolateral prefrontal cortex, as well as amygdala and hippocampus. A significant portion of elderly patients with late-onset depression (LOD) are cognitively impaired; however, there are also patients who do not have sustained impairment after the depression symptoms are improved. It may be possible that neuroimaging can differentiate between these patients through evaluation of the underlying alterations in the integrity of white matter microstructure in the brain regions that are involved in cognitive processes. Therefore, the purpose of this work is to use diffusion tensor imaging (DTI) to examine the neural pathway integrity in LOD patients compared to age-matched controls, and further to compare the LOD patients with cognitive impairment and those without cognitive deficit after the depressive symptoms were improved. The fractional anisotropy (FA) which measures of the degree of anisotropic diffusion, and the mean diffusivity (MD) which measures the mean diffusion in all directions, were analyzed. In order to assess which tracts are affected in the whole brain, a robust tract-based-spatial-statistics (TBSS) method was applied first for comparing the FA and MD maps in the whole-brain. Then based on the TBSS results, the group differences in several involved tracts were further analyzed.

Materials & Methods:

A total of 45 subjects, including 22 late-onset depression patients and 23 age-matched normal controls (NC), were studied. The LOD patients were treated, and they were followed closely during the next 6 months. Based on the cognitive test results obtained at 6 months, they were separated into 2 groups, patients with sustained cognitive impairment (ciLOD), and those with normal cognitive function (nLOD) when depressive symptoms were improved. Diffusion tensor imaging was performed on a Siemens 3T MRI scanner, by using a spin-echo single-shot EPI sequence and 64 encoding directions. The three groups were matched in age. The NC subjects (n=23; 12 male, 11 female) had a mean age of 70.9+/-7.6; the normal LOD subjects (n=12; 6 male, 6 female) had a mean age of 68.8+/-6.0, and the cognitively impaired LOD subjects (n=10; 6 male, 4 female) had a mean age of 72.4+/-7.5. The processing of DTI images and statistical analysis was conducted with the Oxford Analysis Group's FSL software package [1]. The FA maps from 44 brains were analyzed with TBSS, with nonlinear registration of individual FA maps to the most representative FA map within the cohort. The MD maps from the 44 subjects were also analyzed using the same nonlinear registration and projection vectors as the FA maps. Once the skeletonized FA and MD maps were generated, FA and MD values were then compared in a voxelwise fashion among the NC, normal LOD, and cognitive impaired LOD groups using a permutation test with threshold-free cluster enhancement. Significance was taken to be at $p<0.05$ after being fully corrected for multiple comparisons across space.

Result

The voxel-wise group comparisons were performed to find the differences among three groups using paired analyses: nLOD vs. NC, ciLOD vs. NC, and ciLOD vs. nLOD. The ciLOD subjects, when compared to both NC and nLOD subjects, were found to have significantly decreased FA values in all major white matter tracts, including the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, the anterior and posterior cingulate gyrus, and the uncinate fasciculus. These tracts were involved in various neural pathways and structures within the limbic and prefrontal cortical regions of the brain. The MD analysis also revealed similar findings. Compared to NC and nLOD subjects, the ciLOD subjects also had markedly increased MD values corresponding to the very same neural pathways exhibiting the FA differences. **Figure 1** illustrates the comparison between ciLOD and nLOD subjects. The voxel-wise comparison of FA and MD values between ciLOD and NC subjects were remarkably similar to the results depicted in figure 1. When comparing the nLOD subjects with NC subjects, there were no significant differences in either FA or MD maps.

Discussion:

In this study, we have demonstrated LOD patients with sustained cognitive impairment exhibit significant white matter differences in neural pathways that link the distributed brain networks supporting high-level cognitive functions, which closely parallels the regions reported in the literature concerning non-depressed cognitively impaired subjects. Interestingly, for the LOD patients who were not cognitively impaired 6 months later, their baseline white matter integrity was not significantly different from those of healthy controls in all examined major tracts. This finding may indicate that the underlying physiological changes, such as changes in white matter microstructure, may be the substrates that can be used to predict the neurocognitive outcome of late-onset depression.

Reference: [1] S.M. Smith, et.al. NeuroImage, 23(S1):208-219, 2004.

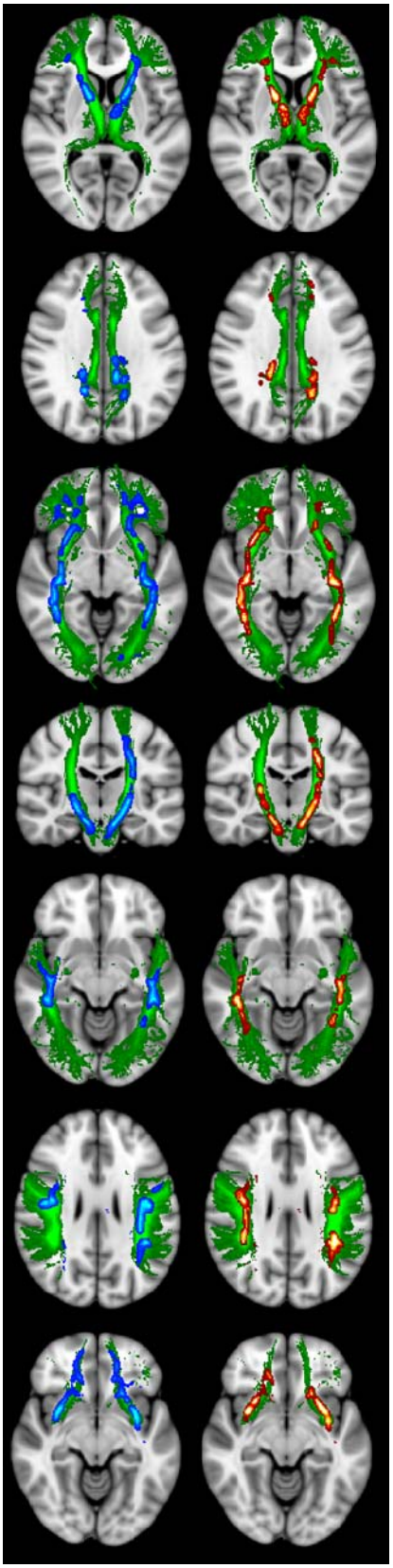

Figure 1. Major fiber tracts where ciLOD subjects had significantly decreased FA (blue overlay, left column) and significantly increased MD (red overlay, right column) compared to nLOD subjects. From top to bottom: thalamic projection, cingulate gyrus, inferior fronto-occipital fasciculus, corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus.