White matter disruption in early- and late-onset depression: a tract-based spatial statistical analysis

K. Choi[1], R. C. Craddock[2], P. E. Holtzheimer[1], X. P. Hu[3], and H. S. Mayberg[1]

[1]Department of Psychiatry, Emory University School of Medicine, Atlanta, Georgia, United States, [2]Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, Georgia, United States, [3]Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, Georgia, United States

Introduction

White matter (WM) fractional anisotropy (FA) is thought to be related to WM integrity. The ability to detect differences in anisotropy may be useful in the study of brain diseases associated with white matter disruption.[1,2] However, comparing FA across groups can be confounded by imprecise alignment of white matter, especially when comparing populations with altered brain development or significant atrophy. Tract-based spatial statistics (TBSS) may have utility in such situations. In this study we used TBSS to assess differences in white matter FA associated with early- or late-onset major depressive disorder (MDD).

Methods

A. Subjects: Twenty-three subjects participated in accordance with Institutional Review Board policies. Subjects were classified into four groups: (1) six younger (<50 years old) patients with early-onset depression (EOD; 0 F, mean age 29.75 +/- 4.2); (2) four older (>50) patients with late-onset depression (LOD; 1 F, mean age 71.25 +/- 9.8); (3) seven younger controls (YC; 2 F, mean age 29.7 +/- 4.7); and (4) six older controls (OC; 3 F, mean age 65.5 +/- 5.5). Controls had no history of depression or any major psychiatric illness.

B. Image Acquisition: Data were acquired on a 3T Siemens Trio scanner using a TX/RX birdcage head coil. DTI data were collected using a diffusion weighted single-shot spin-echo planer imaging sequence with the following parameters: b =1000 sec/mm2; voxel resolution = 1.72*1.72*2.5mm; number of slices = 34; matrix=128*128, 12 directions with 6 averages for each direction; TR/TE=6500/90ms.

C. Track-Based Spatial Statistics: FSL's TBSS toolbox was used for group analysis of FA [3]. Diffusion data underwent brain extraction, eddy current correction, and local DTI fitting to generate FA images. The image with the minimum mean distance to all other images was selected from the subject data, and all other FA images were aligned to this reference. The FA images were then transformed into MNI152 space and then averaged. The mean FA image was thinned to produce a skeleton that represents tracts common to all subjects. Subject FA data were then projected onto this skeleton resulting in an aligned and normalized FA map for each subject. FSL's randomize tool was used to implement two sample unpaired t-tests for group comparisons. Statistical significance of results was assessed at a family wise error corrected $p < 0.05$ (cluster size permutation test).

Results & Discussion

Figure 1 illustrates the mean FA skeleton derived from the TBSS process. Comparing younger controls to EOD patients, a significant reduction in FA was found in the anterior limb of the right internal capsule extending into the genu and posterior limb of the internal capsule (Figure 2A). Interestingly, this region is spatially proximate to a target proposed for deep brain stimulation for treatment resistant depression.[4] There are several areas of reduced FA along the right corpus callosum in LOD compared to EOD patients, one of which is in white matter adjacent to the subgenual cingulate, another target for DBS in depression[5] (Figure 2B). As expected, there are several regions of significantly lower FA in old controls compared to young controls (Figure 2C). These are found in the fornix, bilateral internal capsule, cingulum bundle, and right uncinate fasciculus. No significant differences in white matter FA values were found between older controls and LOD (not shown). This is interesting since white matter disruption has been proposed as an etiologic factor for LOD; however, the negative findings of this comparison may be due to a large variance in FA resulting from brain atrophy – variance that was not overcome with the TBSS approach. These results suggest that TBSS may be useful for comparing white matter integrity between clinically relevant populations (such as younger patients with depression versus age-matched controls) but it is not yet clear whether this approach will improve the ability to compare older subjects (with varying degrees of cerebral atrophy) to other clinically relevant populations.

References: [1] Olga Ciccarelli et al., *J Neurol*, 2003, 250:287-292. [2] B. Benedetti et al., *Neurology,* 2006, 67:161-163. [3] Stephen M. Smith, et al., *NeuroImage* 2006, 52:1487-1505. [4] Nuttin Bart J., et al., *Neurosurgery* 2003, 52:1263-1272. [5] H. S. Mayberg et al. *Neuron*. 2005, 45(5):651.

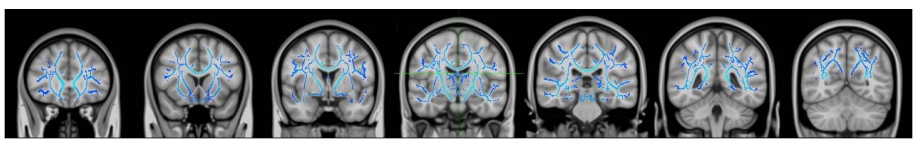
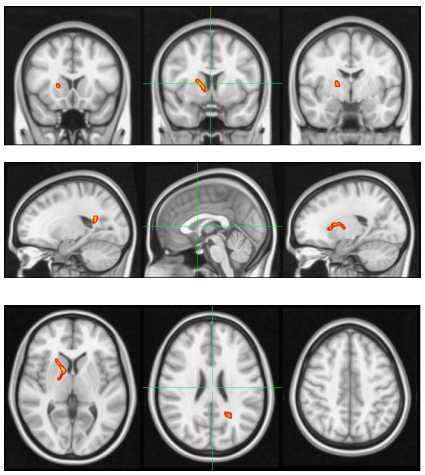
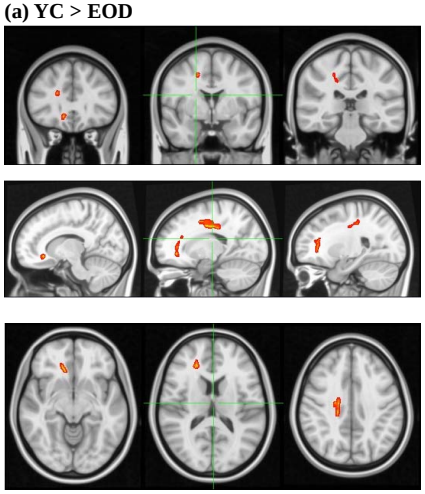


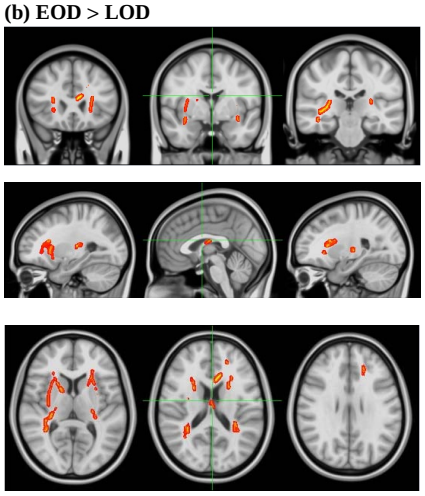
Figure 1. Mean FA skeleton derived from TBSS processing.



(a) YC > EOD



(b) EOD > LOD



(c) YC > OC

Figure 2. TBSS results