Toward Quantitation of Whole-Brain Tractography Group Comparisons with Application to Alzheimer Disease

M. Singh[1], W. Sungkarat[1], A. Shetty[1], A. Rajagopalan[1], D. Hwang[1], C. W. Wong[1], H. Chui[2], N. Schuff[3], and M. Weiner[3]

[1]Radiology/Biomedical Engineering, University of Southern California, Los Angeles, California, United States, [2]Neurology, University of Southern California, Los Angeles, California, United States, [3]Center for Imaging of Neurodegenerative Disease, VA Medical Center, San Francisco, CA, United States

Introduction

Though there are numerous publications on voxel based whole-brain FA group comparisons, there are very few reports of similar comparisons using whole-brain tractography. Tractography comparisons are usually based on sorting ROI-constrained tracts in subject space, which are then voxelated and mapped to a normalized space for group studies. This requires *a priori* hypotheses to identify tracts and may miss key differences. Another approach is based on averaging tensors in normalized space [1] but does not fully account for inherent primary eigenvector variations in individuals. Voxel based normalization procedures which incorporate tensor correction [2] generally impart smoothing and frequently divide known tracts into non-contiguous segments. A recent method of tract segmentation by choosing anatomically equivalent seed points in subject space in conjunction with similarity measures [3] would work under certain conditions but is not applicable to general whole-brain tractography where no particular tracts are specified. We have developed a method to perform whole-brain tractography group comparisons where the same number of seed points is used in each subject at anatomically equivalent positions throughout the entire brain. All tracts contained within each voxel per subject are mapped into a normalized space while retaining each tract's continuity. Tractography for each subject is then voxelated in normalized space using a "weighted count" (WC) of tracts per voxel to impart a quantitative measure of connectivity to voxel intensities, thereby providing a framework for group comparisons. As all tracts reside in normalized space, it becomes possible to show directly tracts/pathways affected by regions that are delineated in group comparisons. Details of the approach and its application to detect pathways affected in Alzheimer Disease (AD) are reported here. Also whole-brain tractography differences are compared to whole-brain FA differences to illustrate consistency and complementarities of the two approaches.

Method

FLAIR diffusion weighted images (DWI) were acquired in 5 mm thick slices on a 1.5 T Siemens scanner from 10 age-matched Normal Controls (NC) and 15 probable AD subjects using six encoding gradient directions at b-values of 0, 160, 360, 640, and 1000 sec/mm^2. A customized FA template was created from the 10 NC subjects through a two-step normalization procedure where segmented white matter voxels, co-registered to the b_0 images, were first normalized to the MNI white-matter template using a 12 parameter affine/non-linear transformation. This minimized ventricular variations among subjects. The resulting parameters were refined by a whole-brain EPI to EPI normalization, and applied to individual FA maps to create the FA template. This FA template was used to map the center points of all voxels (seed points) from normalized space to each subject's space (point to point mapping), creating the same number and anatomically equivalent distribution of seed-points in each subject. All tracts from each subject (streamline tractography, 0.2mm step size, FA<0.15, deflection<45°) were similarly mapped back to normalized space on a point-to-point basis from all seeds contained within a common mask for the entire population (AD + NC). When interpolation is used, all voxels connected to a seed voxel generally send tracts back into the same seed voxel. Thus the number of tracts intersecting a voxel is a reflection of how many voxels are connected to it, which provides a convenient metric to quantify "connectivity". We refine this measure by weighting the count of tracts per voxel by the length of the intercept of each tract, and call this the "weighted count" metric, which then becomes the voxel intensity for group comparisons.

Results and Discussion

The global NC>AD SPM2 group comparisons (p<0.005), projected upon sagittal and axial views of the SPM "glass brain", are shown in **Fig. 1(left)** for FA and **Fig. 1(right)** for tractography. In addition to corpus callosum (cc) tracts, several regions are highlighted in the tractography comparison. As an example of pathways (other than cc) disrupted in AD, tracts were generated from ROIs labeled **a-f** in **Fig. 1(bottom right)** from all NC subjects, voxelated and averaged. Due to significant inter-subject variations, a threshold was set to include only those voxels where at least 50% of the subjects overlap. The resulting tracts corresponding to ROIs **a-f** are shown in **Fig. 2 (a-f).** These tracts suggest involvement of the following pathways**: (a)** left parahippocampal cingulum; **(b)** left occipitotemporal; **(c)** ILF and IFO (**b** and **c** partially overlap in the ILF); **(d)** right parahippocampal cingulum; **(e)** right occipitotemporal; **(f)** parietotemporal. These tracts are consistent with pathways likely to be affected in AD.

The FA and tractography differences are highly correlated. In general, because of FA thresholding, the tractography differences would be a subset of the FA differences. However, because the voxel intensity in tractography reflects connectivity along a string of voxels, as defined above, tractography differences are expected to be more sensitive and may delineate the entire pathway (if the differences are near the middle of a tract) or portions of a tract (if the differences are near an end), thereby providing information complementary to FA voxel based comparisons.

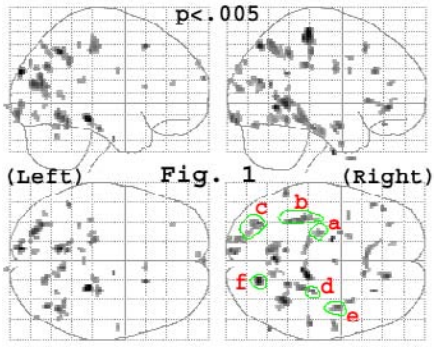

Fig. 1: Whole-brain NC>AD (p<0.005) group differences. (left) FA; (right) tractography.

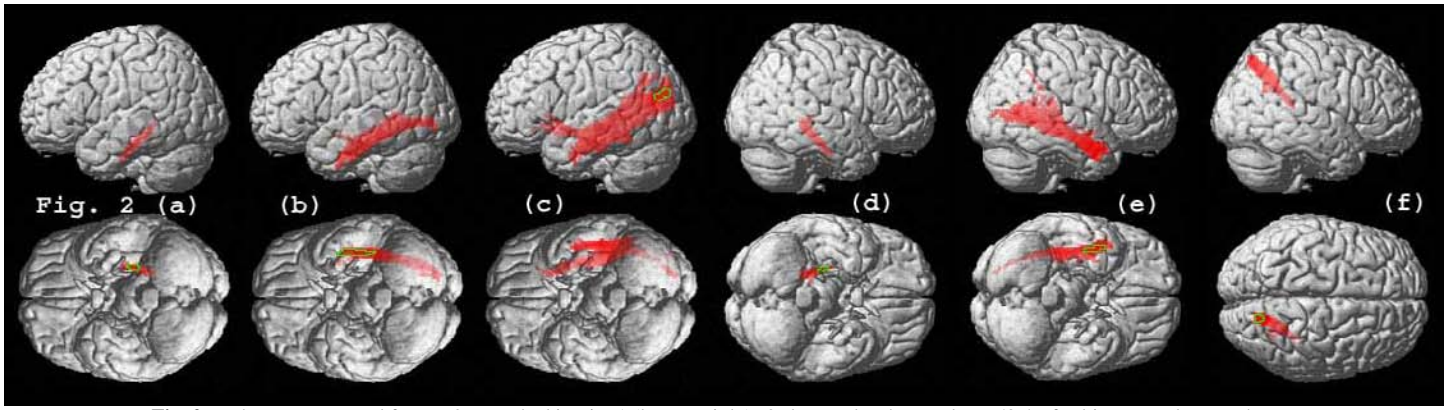

Fig. 2: Pathways generated from ROIs marked in Fig. 1 (bottom right). Only voxels where at least 50% of subjects overlap are shown.

[1] Jones et al., NeuroImage 17:592-617(2002); [2] Alexander et al., IEEE Trans Med Imaging 20:1131- 1139 (2001); [3] Clayden et al., NeuroImage (in Press) 2006.