Fractional anisotropy is affected by white matter lesions in a TBSS study of Alzheimer's disease

P. Raniga[1], D. Raffelt[1], A. Connelly[2,3], P. Desmond[4], and O. Salvado[1]

[1]CSIRO Preventative Health National Research Flagship ICTC, The Australian e-Health Research Centre, Brisbane, Queensland, Australia, [2]Brain Research Institute, Florey Neuroscience Institutes (Austin), Melbourne, Victoria, Australia, [3]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia, [4]Department of Radiology, University of Melbourne, Melbourne, Victoria, Australia

Introduction: Diffusion MRI provides an unparalleled ability to investigate white matter micro-structure. The diffusion tensor imaging (DTI) model and its related indices such as fractional anisotropy (FA) and mean diffusivity have been widely used to study white matter characteristics in Alzheimer's disease [1], [2]. The short-comings of and alternatives to the diffusion tensor model are the focus of current research [3] [4]. Considerably less attention has been placed on the impact of co-morbid pathologies in such studies. Concomitant cerebro-vascular disease and cerebral amyloid angiopathy (CAA) may result in damage to white matter [5], [6] and may have an impact on quantitative analysis of diffusion indices. The current study investigates the impact of concomitant CAA and white matter hyperintensities (WMH) on DTI analysis of Alzheimer's disease.

Method: Scans from a subset of 28 AD and 31 normal control (NC) subjects from the Australian Imaging Biomarkers and Lifestyle (AIBL) study were included. Fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI) and high angular resolution diffusion imaging (HARDI) (60 directions and 8 b=0 images, b-value = 3000 s/mm^2) were available for each subject. WMH were manually segmented using FLAIR. SWI images were read for the presence of micro-bleeds and superficial siderosis. AD subjects were classified as having probable (n=7) or possible (n=7) CAA based on the modified Boston criteria for CAA [7], and the rest (n=14) as non-CAA (NCAA).

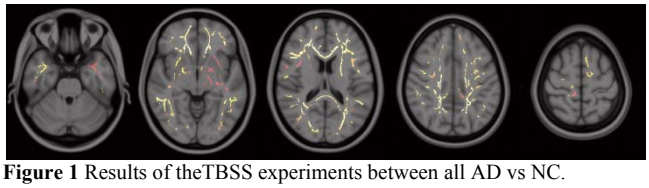

Figure 1 Results of theTBSS experiments between all AD vs NC.

HARDI scans were corrected for motion by linearly aligning each of the diffusion weighted images to the first b=0 image. Diffusion tensor and FA maps were generated using MRtrix software [8]. The tract based spatial statistics (TBSS) [9] tool from FSL was used to align and analyse the FA maps. A study specific FA template was chosen using TBSS and all remaining FA maps were co-registered to it. Three AD scans with probable (n=1) and possible (n=2) CAA were excluded from analysis due to registration errors.

The first TBSS experiment compared all AD (n=25, mean global white matter hyperintensity volume (μWMHV) =16.3±19.0 ml) to all NC (n=31, μWMHV=3.8±2.2 ml) subjects. Next two sets of TBSS analysis were conducted: (1) AD CAA (n=11, μWMHV=24.2±26.4 ml) v NC; and (2) AD NCAA (n=14, μWMHV=10.1±6.3 ml) v NC. A leave three out method was employed for each of these experiments whereby all possible combinations of n-3 subjects from the AD groups were compared to the entire NC group. This was done to avoid outlier scans from biasing the results, and resulted in 165 and 364 individual TBSS experiments for (1) and (2) respectively. A fourth experiment was conducted between AD CAA and AD NCAA. A fifth TBSS analysis was performed by stratifying the AD subjects into those having high global WMH volume (> 10ml, n=13) (AD HWMHV, μWMHV=27.1±21.2 ml) and low global WMH volume (<10ml, n=12) (AD LWMHV, μWMHV=4.6±3.2 ml) All results were corrected for multiple comparisons using the threshold free cluster environment (TFCE). Significance was assumed for p-values < 0.05. All other parameters used were defaults as proposed in the TBSS reference (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html).

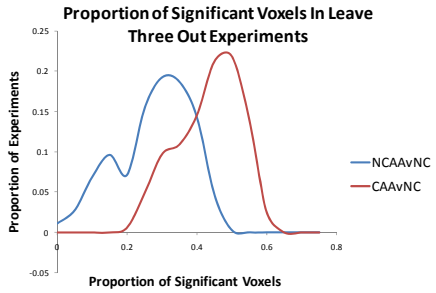

Figure 2. Distribution of significant voxels in the leave three out experiments between AD CAA and NC and AD NCAA and NC.

Results: The results of the TBSS analyses are presented in Figures 1-4. Figure 1 shows example results of the TBSS comparison between all AD and NC. Figure 2 shows the distribution of the proportion of significant p-values of the leave three out experiments between AD CAA versus NC, and NCAA versus NC. The distribution for AD CAA was significantly different from that for AD NCAA (p-value < 0.001 using Mann-Whitney U test and Kolmogorov-Smirnov test). On average, over 45% of the voxels were significant when comparing AD CAA subjects to NC (Figure 3A). On the other hand, on average only 30% of voxels were significant when comparing AD NCAA subjects to NC (Figure 3B). There was however were no significant differences between AD CAA and AD NCAA (Figure 4A). Ten percent of voxels were significantly different when the AD HWMHV were compared to AD LWMHV (Figure 4B).

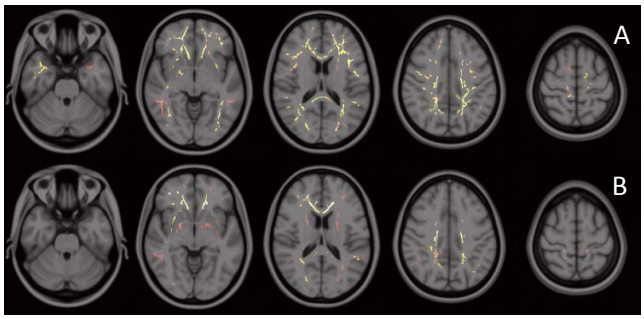

Figure 3. Average results of the TBSS experiments between AD CAA and NC (A; top row) and AD NCAA and NC (B; bottom row).

Discussion and Conclusion: We investigated the impact of WMH on the analysis of DTI measure of FA using TBSS. Although our data was acquired at b-value of 3000 s/mm^2, which is not ideal for DTI analysis, our results do indicate that including subjects with large amount of WMH can alter the analysis. In particular, AD subjects with evidence of concomitant CAA had more significant differences than AD subjects without evidence of CAA when compared to NC subjects using TBSS. There were however no significant differences on direct comparison of CAA and NCAA subjects. This may be due to the smaller number of subjects in each of these groups (11 vs 14, as opposed to 31 in NC group) as well as greater variability in the μWMHV (24.2±26.4 ml, 10.1±6.3 ml, 3.8±2.2 ml respectively). However, when AD subjects were explicitly split based on global WMH volumes, those with high global WMH volumes had significantly lower FA in ~10% of voxels than those with low WMH volumes. These results suggest that although differences in FA in AD groups compared to controls may not entirely be due to WMH, they can have a considerable impact on analysis of FA using the TBSS method as has been previously suggested [10]. Moreover care should be taken when reporting results in clinical studies of Alzheimer's disease where WMH due to concomitant cerebro-vascular disease and CAA can have an impact.

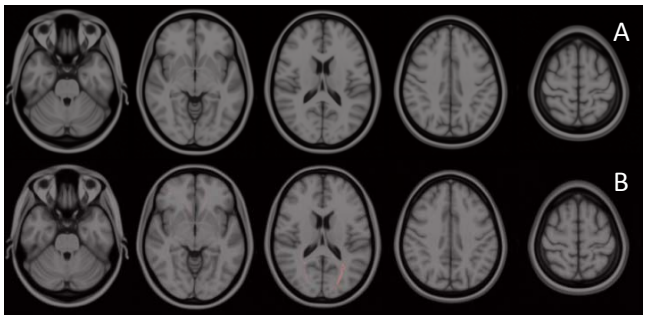

Figure 4. Results of the TBSS experiments between AD CAA and AD NCAA (A; top row) and AD HWMHV and AD LWMHV (B; bottom row).

References: **[1]** M. Bozzali et al., *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 72, no. 6, pp. 742 -746, 2002. **[2]** S. E. Rose et al., *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 69, no. 4, pp. 528 -530, 2000. **[3]** D. K. Jones et al., *NeuroImage*, vol. 26, no. 2, pp. 546-554, 2005. **[4]** J. Tournier et al., *NeuroImage*, vol. 35, no. 4, pp. 1459-1472, 2007. **[5]** M. M. Esiri et al., *The Lancet*, vol. 354, no. 9182, pp. 919-920, 1999. **[6]** K. A. Jellinger and J. Attems, *Journal of the Neurological Sciences*, vol. 229, pp. 37-41, 2005. **[7]** J. Linn et al., *Neurology*, vol. 74, no. 17, pp. 1346-1350, 2010. **[8]** MRtrix. *http://www.brain.org.au/software/* **[9]** S. M. Smith et al., *NeuroImage*, vol. 31, no. 4, pp. 1487-1505, 2006. **[10]** D. K. Jones and M. Cercignani, *NMR in Biomedicine*, vol. 23, no. 7, pp. 803-820, 2010.