On the Stability of Skeleton-Based Analyses of Diffusion Tensor MRI-based Measures

Sonya Bells[1], Luke Dustan[1], David J McGonigle[1,2], C John Evans[1], and Derek K Jones[1]
[1]*School of Psychology, CUBRIC, Cardiff, Wales, United Kingdom,* [2]*School of Biosciences, Cardiff University, Cardiff, Wales, United Kingdom*

INTRODUCTION: Diffusion tensor MRI is the only non-invasive tool capable of quantifying differences in tissue microstructure and, given that the white matter mediates brain connections[1], it has been rapidly adopted by the neuroscientific community. The literature is awash with studies of differences in diffusion anisotropy (most typically characterized by fractional anisotropy (FA)) between groups, studies of hemispheric asymmetry, or studies correlating individual differences in performance on a cognitive / behavioural task with individual differences in white matter microstructure[2,3]. An increasingly popular approach to conducting these studies is to perform a global search for differences /asymmetries/ correlations on a voxel-by-voxel basis, the most widely used method being 'Tract Based Spatial Statistics' (TBSS[4]) – which combines a normalization-skeleton-projection step to maximize chances of comparing 'like with like', followed by statistical inference using threshold free cluster enhancement (TFCE[5]). This work reports on the stability of results obtained with this approach when looking for correlations between DTI metrics and behaviour (i.e. performance-microstructure measures), and when looking at hemispheric assymetries. In particular, we focus on the sensitivity of the method with respect to the sample of 'normal healthy' participants recruited to the study.

METHODS: Healthy right-handed participant (*N*=24, age=31.1±6.7y) were recruited to the study. **MR Data Acquisition**: Cardiac-gated diffusion-weighted (DW) data were acquired using a 3T GE HDx MRI scanner, with the following parameters: b-value = 1200 s/mm^2; 60 directions; 6 non-DW images; 60 axial slices; TR = 20 R-R intervals. DW-data were motion/ distortion corrected followed by appropriate re-orientation of the diffusion encoding vectors[6] prior to single tensor fitting providing anisotropy and diffusivity indices (fractional anisotropy FA, mean diffusivity MD, axial diffusivity L1 and radial diffusivity RD) in *ExploreDTI*[7]. **Cognitive Data Acquisition:** Three behavioural measures were acquired from each participant: choice reaction time (CRT)[8], mental rotation[9] and intelligence quotient (IQ)[10]. These tests were chosen as previous studies have found DTI-performance correlations using them[8,11,12]. **Stability Testing:** Stability was assessed using a bootstrapping procedure where a 'leave 4 out' procedure was used for the *N*=24 participants. For each of 100 iterations, a unique set of 4 participants was randomly eliminated from the total of 24. The skeletonization-projection was performed for the remaining 20 participants, prior to voxelwise cross-subject permutation-based non-parametric GLM statistics by *randomize*[13](1000 permutations) with TFCE-based inference (p = 0.05). Both behaviour-microstructure correlation and hemispheric asymmetry analyses were performed for each iteration, yielding 100 TBSS results. **Cross Correlation:** To aid in visualization, for a given slice location, the skeletonised and thresholded t-statistic maps were binarized and collapsed into a single vector comprising zeros (not significant) or ones (significant correlation / asymmetry) and a cross-correlation (CC) matrix of the 100 vectorized results was performed. This CC-matrix was then re-ordered using the Fiedler vector of the normalized Laplacian formed from the CC-matrix[14]. Behavioural and diffusions measurements were checked for outliers and their influence on the stability of results determined.

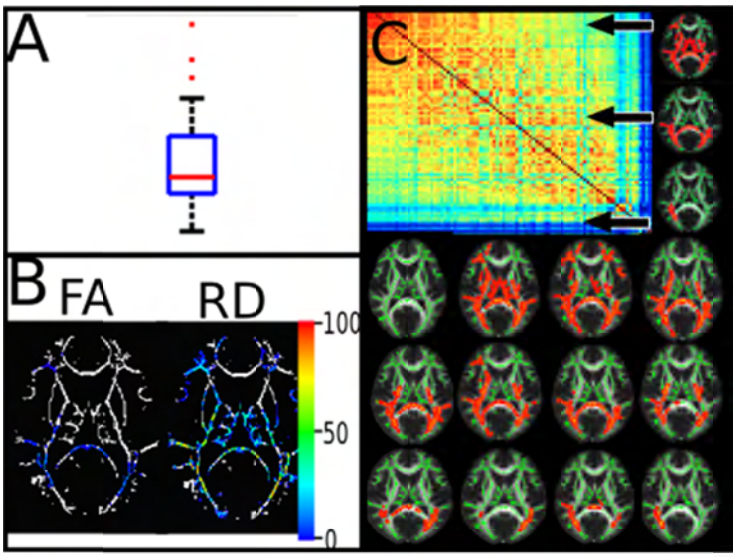

Fig 1: Bootstrapping results from CRT-RD/FA correlations A) Box-plot of CRT scores' B) Probability of significant correlation being found in voxel; C) Cross-correlation in RD for 100 samples with example slices from the (top, mid, bottom) of the matrix.

RESULTS: The bootstrapping procedure reveals a large variability of results when correlating task-performance with FA and RD – even within task, and despite the fact that the group of 20 subjects in each iteration was drawn from the same pool of 24 subjects. Space prohibits us for showing all results from the other behavioural measures here – so we focused on CRT-RD correlations. Figure 1C shows the wide array of results obtained. Figure 1B shows that the probability of getting a significant FA-CRT and RD-CRT correlation in a voxel ranges from 0-89% and is very heterogeneous across the skeleton. The majority of the voxels appear significant less than 50% of the time (less than chance). We took a closer look at the behavioural measures, and 3 participants were deemed to be outliers (see boxplot in Fig. 1A). However, we found no significant effect of these individuals within the resampling results. Moreover, looking at the cross-correlation of skeletal-diffusion values within a slice detected outlier in RD, but again this outlier did not appear to be driving the variability of the CRT-RD correlation results. Results from hemispheric asymmetry analyses were found to be far more stable. Fig 2 shows results for FA, and even when selecting iterations from the top, mid or bottom of the sorted cross-correlation matrix, the results are largely consistent with little variation along the skeleton.

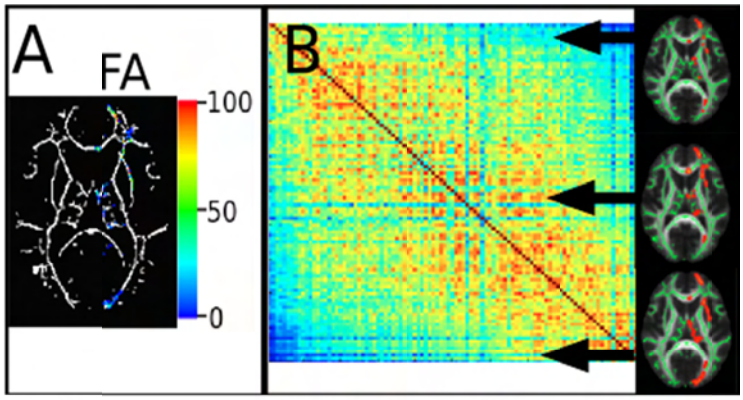

Fig 2: Bootstrapping results from CRT-diffusion measurements. A) Probability of significant finding; B) Cross-correlation in FA for 100 samples with example slices from the (top, mid, bottom) of the matrix.

DISCUSSION: Tract based spatial statistics provides a unique tool to assess brain connectivity. However, the number of participants required to produce stable correlation maps is unknown. Importantly, we showed using a resampling method that for three different behavioural measures the stability for a literature average number of participants (*N*=20) was low.

REFERENCES: 1. Jones DK.2008 *Cortex* **44:**936-; Kanai R, Rees G. 2011.*Nat Rev Neurosci.* **12:**231-; 3. Johansen-Berg H. 2010. *Curr Opin Neurol.* **23:**351-; 4. Smith SM *et al.* 2006. *NeuroImage* **31**:1487-; 5. Smith SM *et al.* 2009 *NeuroImage* **44:**83-; 6. Leemans *et al.* 2009. *MRM* **61:**1336-; 7. Leemans A *et al.* 2009. Proc. ISMRM, Hawaii.p.3536; 8. Tuch DS *et al.* 2005 *PNAS* **102:**12212-; 9. Peters *et al.*1995 *Brain Cogn.* **28:**39-; 10.Cattell R. 1967. *Br J Educ Psychol.* **37**:209; 11. Wolbers *et al.* 2006 *NeuroImage* **32:**1450-; 12. Schmithorst VJ *et al.* 2005 *Hum Brain Mapp.***26**:139-; 13. Nichols TE *et al.* 2002 *Hum Brain Mapp.* **5**:1-; 14. Barnard ST *et al. ACM/IEEE Conf Supercomputing* 1993.