Tract-Based Spatial Statistics: Voxelwise Analysis of Multi-Subject Diffusion Data

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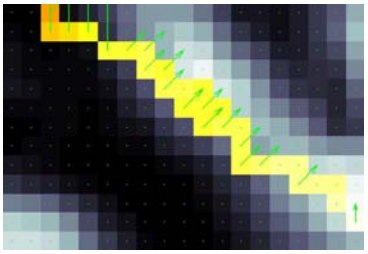
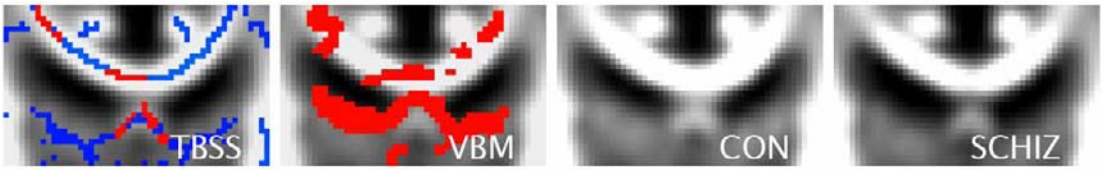
INTRODUCTION There has been much recent interest in using magnetic resonance diffusion imaging to provide information about anatomical connectivity in the brain. Many imaging studies are starting to use diffusion-derived fractional anisotropy (FA) images in voxelwise ("VBM-style") statistical analyses [1,2] in order to localise brain changes related to development, degeneration and disease. However, optimal analysis is compromised by the use of standard registration algorithms; there has not to date been a satisfactory solution to the question of how to align FA images from multiple subjects in a way that allows for valid conclusions to be drawn from the subsequent voxelwise analysis. Furthermore, the arbitrariness of the choice of spatial smoothing extent has not yet been resolved [3]. Here we present a new method that aims to solve these issues via *a*) carefully tuned nonlinear registration, followed by *b*) projection onto an alignment-invariant tract representation (the "mean FA skeleton"). We refer to this new approach as Tract-Based Spatial Statistics (TBSS). TBSS aims to improve the sensitivity, objectivity and interpretability of analysis of multi-subject diffusion imaging studies. TBSS is implemented as part of FSL [www.fmrib.ox.ac.uk]; the nonlinear registration used is IRTK [www.doc.ic.ac.uk/~dr/software].

OVERVIEW OF TBSS Strengths of VBM-style analyses are that they are fully automated, simple to apply, investigate the whole brain, and do not require pre-specifying/localising regions/features of interest. Limitations include problems caused by alignment inaccuracies, and the lack of a principled way for choosing smoothing extent [3]. Tractography-based approaches have opposite advantages and disadvantages. They can overcome alignment problems by working in the space of individual subjects' tractography results, and for similar reasons do not necessarily require pre-smoothing. However, such approaches do not allow the whole brain to be investigated, and generally require user-intervention in order to define the tracts. In TBSS, we attempt to bring together the strengths of each approach. We aim to solve the alignment and smoothing issues, while being fully automated, investigating the "whole" brain - not requiring pre-specification of tracts of interest. This is achieved by estimating a "group mean FA skeleton", which represents the centres of all fibre bundles that are generally common to the subjects involved in a study. Each subject's FA data is then projected onto the mean FA skeleton in such a way that each skeleton voxel takes the FA value from the *local centre* of the nearest relevant tract, thus hopefully resolving issues of alignment and correspondence. To summarise:

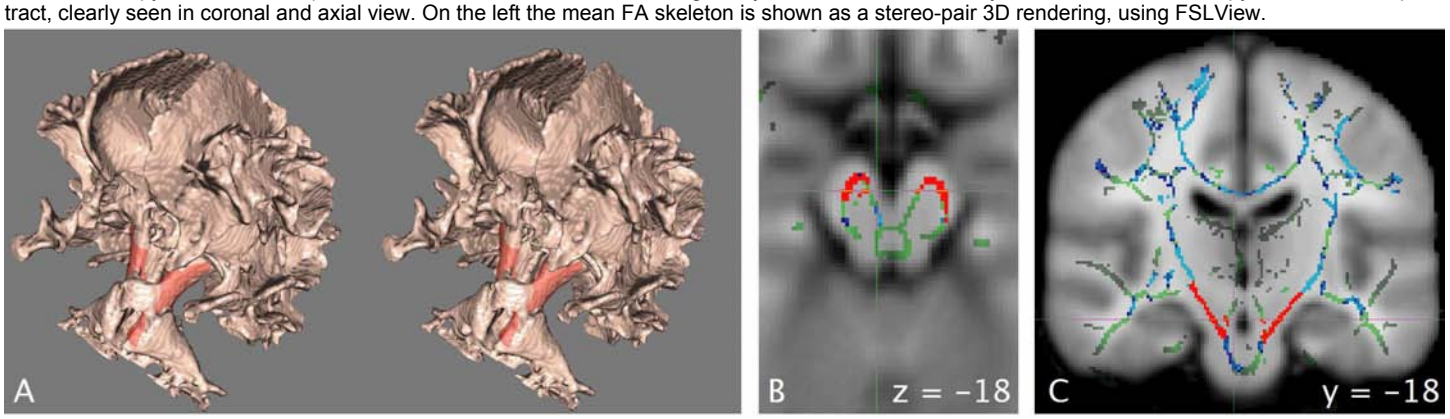


- Identify a common registration target and align all subjects' FA images to this target using nonlinear registration. At this stage, perfect alignment is not expected or required.
- Create the mean of all aligned FA images and apply "thinning" (non-maximum-suppression perpendicular to the local tract structure), to create a skeletonised mean FA image. Threshold this (typically between 0.2 and 0.3) to suppress areas of low mean FA and/or high inter-subject variability.
- Project each subject's (aligned) FA image onto the skeleton, by filling the skeleton with FA values from the nearest relevant tract centre. This is achieved, for each skeleton voxel, by searching perpendicular to the local skeleton structure for the maximum value in the subject's FA image.
- Carry out voxelwise statistics across subjects on the skeleton-space FA data.

EXAMPLE – SCHIZOPHRENIA Data: 33 schizophrenics and 36 age-matched controls: 1.5T, 12 directions, 13 repeats, isotropic 2.5mm. We carried out control-patient voxelwise statistics using both nonlinear-aligned and TBSS-preprocessed data. Inference was carried out using cluster-size thresholding, with clusters defined by t>3; the null distribution of the max (over space) cluster size was built up over 5000 permutations. We thresholded the resulting clusters at p<0.05, corrected for multiple comparisons. TBSS found reduced FA in patients in right-superior, medial and anterior corpus callosum, superior and right-inferior fornix and in long assocation fibres near the junction of the right superior and inferior longitudinal fasciculi. In the majority of these areas the VBM-style analysis also found a difference, though with reduced localisation precision. However, in addition, several spurious results were generated by the VBM-style analyses, for example, just below the ventricles, as seen in the figure. It is clear from inspecting the mean FA images for the controls and schizophrenics that while the corpus callosum is well aligned between the two groups, the lower edge of the ventricles is not, due to larger ventricles in the patient group. This has caused a result that could easily be misinterpreted as a group difference in FA in the VBM-style analysis. TBSS did not show this spurious effect, as it was not sensitive to the between-group shift. For the significant TBSS result in the fornix, we confirmed, through looking at the skeleton-projection vectors, that this result was not spurious, i.e., that any inter-subject movement in the fornix was correctly dealt with via the final projection of FA maximum onto the skeleton.



EXAMPLE – ALS Data: 13 ALS patients, 20 controls, acquired as above. After TBSS preprocessing, we carried out two analyses. In the first, using only the patients, we correlated FA with each patient's ALSFRS, the standard measure of disability in ALS (t>2, p<0.05 corrected). In the second, we tested where FA was significantly reduced in ALS compared with controls, after regressing out the effect of age (t>1, p<0.05 corrected). The figure shows in blue where FA is reduced in ALS compared with controls - the majority of the mean FA skeleton shows reduction, including most of the corpus callosum and pyramidal/corticospinal tracts. Red shows where FA is negatively correlated with disability; this is confined to the pyramidal/corticospinal tract, clearly seen in coronal and axial view. On the left the mean FA skeleton is shown as a stereo-pair 3D rendering, using FSLView.



[1] Ashburner et al., NeuroImage 11:805-821, 2000. [2] Büchel et al., Cerebral Cortex 14:945-951, 2004. [3] Jones et al., NeuroImage 26:546-554, 2005.