Is TBSS more sensitive to Pakinson's Disease pathology than traditional VBM?

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Introduction: Parkinson's disease (PD) is the most common neurodegenerative movement disorder, with effects on widely distributed brain networks. The diversity of such motor and cognitive phenomena reflects the widespread progression of underlying pathologies. Diffusion-weighted imaging (DWI) provides an effective non-invasive tool to investigate pathological changes in the white matter of living neurodegenerative and neuropsychiatric patients.

Many previous DWI studies of PD have taken a region-of-interest (ROI) based approach (e.g. [1]). However, manual ROI based comparison of diffusion measures is subject to inter-rater variability, and moreover, limit the regions in which significant group differences can be found to specified areas. Whole-brain analysis methods allow group comparisons of diffusion measures outside specified ROIs. Approaches used in diffusion studies of PD include voxel-based morphometry (VBM) using statistical parametric mapping (SPM) (e.g. [2]) and skeleton-based analyses such as tract-based spatial statistics (TBSS) [3].

In this study we used TBSS and VBM methods to compare a group of PD patients to an age and gender matched set of controls, and we aimed to determine which of those techniques is most sensitive in detecting early white matter changes in Parkinson's patients.

Methods: 15 patients with PD (age=51-78, mean=66; Hoehn and Yahr stage=1.5-3, median 2) and 15 elderly controls (age=50-75, mean=64) were scanned twice at the MRC Cognition and Brain Sciences Unit (Siemens 3T Trio MR; voxel size 2x2x2mm^3). In one session, 5 sets of diffusion-weighted images were acquired along 12 directions (12x5 data), each set corresponding to a different b-value. In the other session, 2 sets of images were acquired along 30 directions (30x2 data). Data were corrected for motion and eddy currents, skull stripped and fitted to the diffusion tensor model using FSL (www.fmrib.ox.ac.uk/fsl).

TBSS: For each of the two datasets, we searched for differences in fractional anisotropy (FA) and mean diffusivity (MD) across the whole brain between the patient group and controls using TBSS [4]. Individual subjects' FA images were registered to a study-specific template (the most "representative subject") and transformed into standard anatomic space (MNI152), before a mean FA skeleton was generated. The same transformations were then applied to MD images. Voxelwise statistics (with 5000 permutations) indicate on the mean FA skeleton any differences in FA and MD between patients and controls.

VBM: An FA template specific to the study was created using the data from all participants and FSL registration tools. All subjects' FA maps were then transformed to this template using non-linear registration, and the same transformations were applied to the MD maps. The subsequent steps were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The transformed FA and MD maps were smoothed with Gaussian kernels with full width half maximum (FWHM) of 4mm. The statistical significant differences for FA and MD images in controls and patients were assessed with two sample t-tests and an absolute threshold of FA>0.2.This threshold helps to minimise the comparison of different structures and constrain the total number of voxels to be analysed.

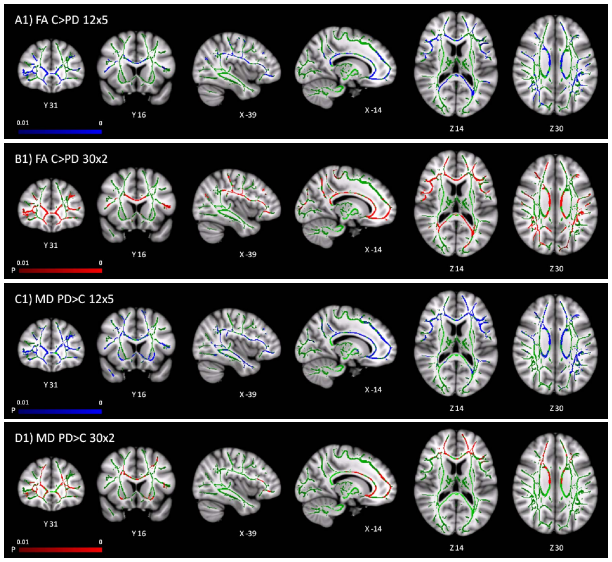

Figure 1 – TBSS: regions of decreased FA (A1 and B1) and increased MD (C1 and D1) in PDs compared to controls. p<0.01 FWE corrected for multiple comparisons. Results shown in blue correspond to the 12x5 acquisition, and in red correspond to the 30x2 acquisition. FA skeleton shown in green.

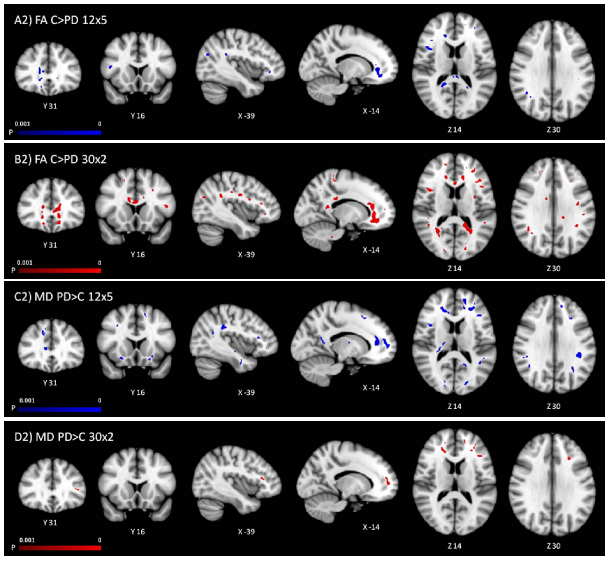

Figure 2 – VBM : regions of decreased FA (A2 and B2) and increased MD (C2 and D2) in PDs when compared to controls. p<0.001 uncorrected. Results shown in blue correspond to the 12x5 acquisition, and in red correspond to the 30x2 acquisition.

Results and Discussion: TBSS was successful in identifying significant widespread group differences in FA and MD between PD patients and controls (Figure 1, p<0.05 FWE). We replicated previous studies by finding reduced FA in the gyrus rectus (olfactory tract), prefrontal white matter, and the corticospinal tract. In addition, we have shown more widespread cortical white matter pathology in PD found in prefrontal white matter, parietal white matter, throughout the length of the corpus callosum, and in the superior corticospinal tract. Increases in MD, similarly a marker of white matter pathology, were found in prefrontal, parietal and temporal white matter, throughout the length of the corpus callosum, in the internal and external capsules, and the superior and inferior corticospinal tract. This suggests that large regions of cortical and subcortical white matter are affected in PD, even in early-to-mid stage patients.

The VBM method found no regions of significantly decreased FA or increased MD in patients that survive FWE or FDR correction for multiple comparisons (p<0.05). Figure 2 shows the uncorrected results with a p-value of <0.001 for the two acquisition schemes. The regions where differences were found largely correspond to the areas identified with the TBSS method. However, the TBSS results are more widespread and statistically significant, suggesting that TBSS is more sensitive to white matter changes in PD patients.

For both VBM and TBSS, the data acquired with a diffusion imaging protocol using more gradient directions (30x2 data) identified more widespread reductions in FA than the dataset acquired with more *b* values (12x5 data). In contrast, the dataset acquired with more *b* values identified more widespread increases in MD. These observations replicate the results of previous work using simulated data [5] but, to the best of our knowledge, had not been shown before with experimental diffusion MRI data.

References: [1] Chan et al, J Neurol Neurosurg Psychiatry, 2007. [2] Karagulle Kendi et al, AJNR Am J Neuroradiol, 2008. [3] Ibarretxe-Bilbao et al, Mov Disord 2010. [4] Smith et al., Neuroimage, 2006. [5] Correia et al, Magnetic Resonance Imaging 2009.