Voxel Based Morphometry and TBSS in PSP and MSA

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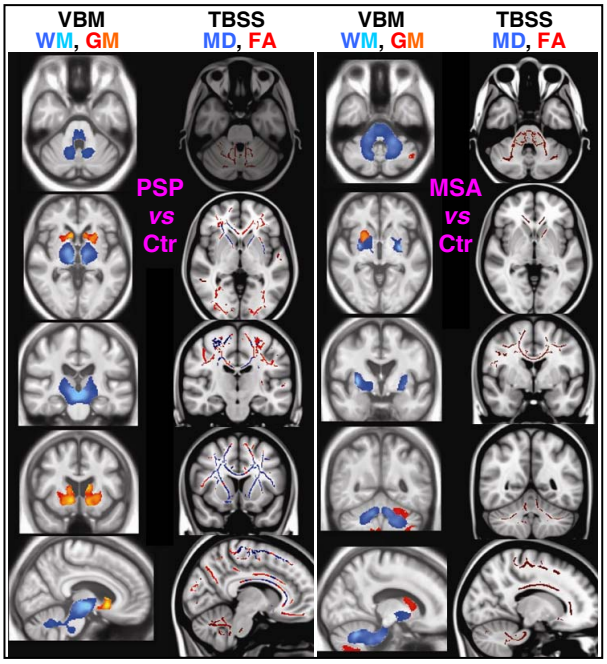
Purpose. Voxel based morphometry (VBM)[1] and Tract Based Spatial Statistics (TBSS)[2] have been separately used in both progressive supranuclear palsy (PSP)[3-4] and multiple system atrophy (MSA) [5-6] and TBSS in PSP [7-8]. We applied these 2 complementary techniques on the same group of patients to assess the relative topography of pathological changes in these neurodegenerative diseases without an *a priori* assumptions on the brain regions affected.

Methods. *Patients/MRI.* 20 controls (Ctr), 18 PSP, and 10 MSA patients were scanned on a Siemens 3T Tim Trio. 3DMPRAGE had TR/TE/TI= 2200/2.9/900ms, flip angle 10°, acquisition matrix 256x256x 208 partitions, isotropic 1.1mm spatial resolution. DWI used double echo SE-EPI (55 2mm slices; TR/TE=6800/91ms, matrix 96x96, isotropic 2mm in-plane resolution), 64 diffusion weighting directions with b = 1000 s/mm^2 (2 averages) plus 6 averages with b = 0 s/mm^2. Clinical examinations included the Golbe's PSP Rating scale (PSPRS)[36]. *Image processing.* VBM was performed in SPM8 similarly to [9], in brief: (i) Unified segmentation including bias correction and normalisation [38]; (ii) DARTEL [39] to generate group specific template; (iii) non linear warping of separate grey matter (GM) and white matter (WM) tissue classes to this template space with 'modulation' to account for expansion/contraction associated with the warping; (iv) smoothing with 6mm Gaussian kernel; (v) separate analysis of resulting GM and WM segments with an ANCOVA model to compare groups that included age and total intracranial volume as covariates. TBSS [2] was performed as advised on the FSL website for fractional anisotropy (FA), mean, axial and radial diffusivity (MD, AD, RD). *Statistical analysis.* For VBM we used uncorrected voxelwise p-values at a threshold of 0.001 and accounted for multiple comparisons with a non-stationary correction for significant clusters at $p<0.05$. For TBSS we p-values were corrected for multiple comparisons with threshold-free cluster enhancement (TFCE) at a significance level of 0.05. Voxels were significant group differences were found were tested for correlation with disease duration and clinimetric scores.

Results. Significant suprathresold clusters for Ctr *vs* PSP and Ctr *vs* MSA are shown in the **Figure**. As expected WM, GM and FA were found to decrease in patients *vs* Ctr, while MD was increased.In PSP significant GM reduction was seen in the striatum, dorsal thalamus, globus pallidus, subthalamus, midbrain tegmentum, the superior cerebellar peduncle (SCP) and its decussation, dentate nuclei plus WM reduction in the cerebellum. In MSA the head of caudate, anterior and posterior putamen and the posterior limb of the internal capsule (IC) and external capsule, pontine base, middle cerebellar peduncle (MCP) and cerebellar showed significant reductions. TBSS revealed significantly reduced FA in the PSP group in the SCP and its decussation, anterior limb of IC as well as extensive frontal and parieto-occipital WM changes. MD increase was found in the anterior 2/3 of the corpus callosum, anterior limb of IC, and frontal white matter. In MSA there was reduced FA in deep cerebellar WM, inferior cerebellar peduncles, MCP, pontocerebellar crossing fibres, corticospinal tracts (at the level of the pons), right SCP, body of the corpus callosum (mid portion and forceps minor) and corticospinal tract in the precentral gyrus. Direct comparison of the PSP and MSA groups did not reveal any statistically significant differences with either VBM or TBSS. Disease severity in PSP as measured by the PSPRS correlated with midbrain atrophy and disease duration with FA reduction in parietal WM. The PSPRS score also correlated with MD increase in the frontal WM and anterior corpus callosum (data not shown).

Discussion. Our results are in line with previous observations [3-8]. This study confirms that VBM and TBSS can detect disease-specific topography of PSP and MSA pathology during life. TBSS showed involvement of frontal WM tracts in both PSP and MSA and more extensive involvement of WM in the parieto-occipital lobes in PSP in areas where VBM did not show any differences compared to controls. Extensive frontal and parieto-occipital WM changes in fractional anisotropy and mean diffusivity were found in PSP, which were less extensive in MSA. The lack of significant differences between PSP and MSA may be an effect of the small group numbers and/or the fact that both PSP and MSA exhibit local brain atrophy and are thus individually more different *vs* Ctr than *vs* each other.



Conclusions. Marked subcortical WM changes particularly in PSP were not evident on VBM indicating that more subtle findings may be detectable during life using analysis of DWI data compared to standard high-resolution structural MRI. Frontal WM tract disruption in PSP correlates with disease severity and duration and has potential as a prospective biomarker.

References. 1. Ashburner, Neuroimage 2000;11:805; **2.** Smith, Neuroimage 2004 ; 23(S1) :208; **3.** Josephs, Mov Disord 2011;26(3):493; **4.** Price, NeuroImage 2004;23(2):663; **5.** Specht, Archives of neurology 2003;60(10):1431; **6.** Minnerop, Mov Disord 2010;25(15):2613. **7.** Knake, Mov Disord 2010; 25(9):1232; **8.** Saini, Neuroradiology 2012;54(7):771; **9.** De Vita, AJNR 2013; 34(9):1723.