Characterizing neurodegeneration in progressive supranuclear palsy using VBM and SVM classification

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Target audience: Researchers interested in structural brain plasticity and neurodegenerative disease.

Purpose: Progressive supranuclear palsy (PSP) is a neurodegenerative disease with a clinical syndrome including atypical parkinsonism, supranuclear palsy, postural instability, and mild dementia. Neuropathologically, PSP is characterized by the accumulation of tau protein (tauopathy) resulting in neurofibrillary tangles, and affecting both neurons and glial cells[1]. PSP is associated with structural changes in the midbrain that is also called "hummingbird" or "penguin sign". Interestingly, recent studies show PSP effects also on other brain regions predominantly in striatum and insula[2]. To further investigate PSP and structural brain changes caused by this rare disease, patients were investigated by a multi-centric approach within the consortium of fronto-temporal lobar degeneration (FTLD) in Germany.

Methods: A cohort of 19 PSP patients (6 female, age 68.3±7.9 years, mean±stdev) was compared to 19 age- and gender-matched healthy controls (6 female, age 68.0±7.0 years) using T1-weighted images acquired with the MP-RAGE sequence with five different Siemens MAGNETOM® scanners (Allegra, Skyra, Symphony, Trio, Verio).

Voxel-based morphometry (VBM)[3] was performed by computing gray matter density (GMD) images[4] with SPM8 and the VBM8 toolbox. GMD images were generated using the unified segmentation approach and smoothed using a Gaussian kernel of 8 mm FWHM. Voxel-wise statistical analysis was performed using the general linear model implementing a two-sample *t*-test to compare PSP patients with healthy participants controlling for age and brain volume. To correct for multiple comparisons, the significance level was set at $p<0.05$, family-wise error (FWE) corrected threshold on the cluster level[5]. To exclude effects induced by a single center, and to assess between-center variability arising from different location and hardware, statistical analyses were performed repetitively with the "leave one center out" approach and merged to a single map using a conjunction approach.

To differentiate PSP patients from healthy controls, support vector machine (SVM) classification was performed with GMD images using the libSVM software package[6]. Classification accuracy was obtained with cross-validation using the "one leave out" approach by generating a set of 19 models with leaving a patient and a control subject out when building the classifier. Thereafter, it was checked if both remaining data sets were classified correctly. Feature selection was realized with using all gray matter voxels of the brain, and defining a region-of-interest (ROI) with the WFU-PickAtlas selecting the whole striatum, thalamus, and midbrain, as suggested as PSP's core network in the literature[1,2].

Results: Comparing PSP patients with healthy controls (HC), diminished GMD was observed in the brainstem, thalamus, and also in wide regions in the vicinity of putamen and caudate (Fig. 1). Less prominent differences were detected in left and right anterior insulae, lateral orbitofrontal regions and the cerebellum. Investigating the influence of single centers to the observed GMD differences using the conjunction analysis with the "leave one center out" approach, we observed a high concordance in putamen and caudate (yellow), while findings in insulae, orbitofrontal regions and cerebellum might be affected by inter-center variability (Fig. 2).

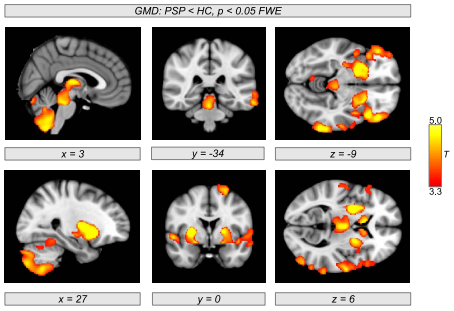

Fig. 1. Sagittal, coronal, and axial brain slices showing significant GMD differences between PSP patients and age- and sex-matched healthy controls (color-coded, $p<0.001$, $k>1000$, controlled for multiple comparisons using FWE-correction with $p<0.05$ on the cluster-level).

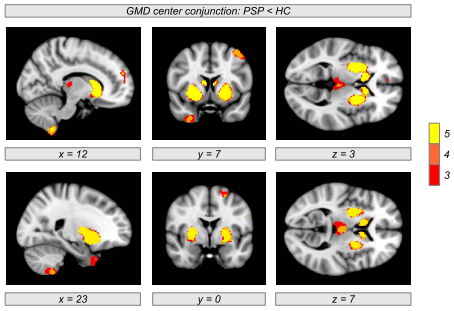

Fig. 2. Orthogonal brain sections showing the overlay of five different analyses using the "leave one center out" approach investigating GMD differences between PSP patients and HC ($p<0.005$ on the voxel-level). Repetitively, five results were obtained with leaving all images of a center out of analysis and finally merged to a single map.

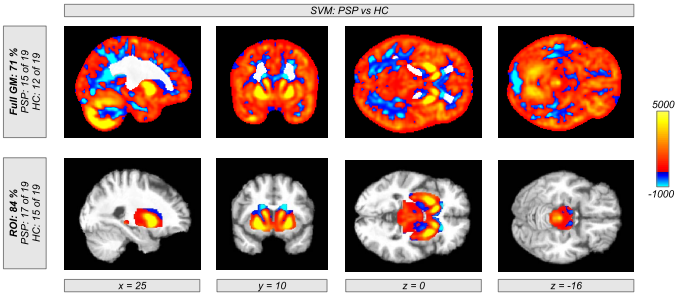

Fig. 3. Weights of voxels most relevant for SVM classification of both groups of PSP patients and healthy controls after SVM training (in red/yellow and blue color, respectively; weights are relative, and have no applicable units). Performing SVM classification with a reduced number of voxels using a region-of-interest (ROI) based approach increased classification accuracy considerably (bottom row) in comparison with the whole brain approach (upper row).

The ROI-based SVM approach focusing on the striatum, thalamus, and midbrain outperformed the classification with all gray matter voxels of the brain (Fig. 3). Both the ROI-based and the full-brain feature selection approach showed a higher sensitivity of disease detection than specificity of correctly classified controls. Relevant voxels for classification are located in brain stem, putamen, and caudate, but also in various cerebellar regions (Fig. 3).

Discussion: Several recent studies are aimed at investigating structural gray matter differences between PSP patients and controls using VBM[7,8,9]. In line with these findings, we show a disease-related GMD decrease using a multi-centric approach in a relatively large cohort. Our results are supported by a recent meta-analytic approach[2] suggesting a role of thalamus and basal ganglia in PSP. Investigating the specific pattern of brain atrophy in PSP patients will be essential for understanding the disease-related underlying neuropathological mechanisms. As expected, brain regions affected by PSP showed also a high relevance for classification when dissociating patients from healthy controls as a precondition for future therapy approaches in the framework of personalized medicine.

Conclusion: Further development of SVM-based classification might complement the radiologist's MRI-based diagnostics for PSP disease detection and characterization. Further biomarkers can even improve disease classification to enable early therapeutic interventions.

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