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Cognitive impairment in progressive supranuclear palsy-Richardson's syndrome is related to white matter damage

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ABSTRACT

Introduction: Beside motor symptoms, patients with progressive supranuclear palsy syndrome (PSPs) commonly present cognitive and behavioral disorders. In this study we aimed to assess the structural brain correlates of cognitive impairment in PSPs.
Methods: We enrolled 23 patients with probable PSP Richardson's syndrome and 15 matched healthy controls. Patients underwent an extensive clinical and neuropsychological evaluation. Cortical thickness measures and diffusion tensor metrics of white matter tracts were obtained. Random forest analysis was used to identify the strongest MRI predictors of cognitive impairment in PSPs at an individual patient level.
Results: PSPs patients were in a moderate stage of the disease showing mild cognitive deficits with prominent executive dysfunction. Relative to controls, PSPs patients had a focal, bilateral cortical thinning mainly located in the prefrontal/precentral cortex and temporal pole. PSPs patients also showed a distributed white matter damage involving the main tracts including the superior cerebellar peduncle, corpus callosum, corticospinal tract, and extramotor tracts, such as the inferior fronto-occipital, superior longitudinal and uncinate fasciculi, and cingulum, bilaterally. Regional cortical thinning measures did not relate with cognitive features, while white matter damage showed a significant impact on cognitive impairment (r values ranging from −0.80 to 0.74).
Conclusions: PSPs patients show both focal cortical thinning in dorsolateral anterior regions and a distributed white matter damage involving the main motor and extramotor tracts. White matter measures are highly associated with cognitive deficits. Diffusion tensor MRI metrics are likely to be the most sensitive markers of extramotor deficits in PSPs.

1. Introduction

Beside motor symptoms classically described, patients with progressive supranuclear palsy syndrome (PSPs) commonly present cognitive and behavioral disorders [1].

Previous voxel-based morphometry (VBM) studies of MRI scans demonstrated an association between frontal grey matter (GM) atrophy and deficits of executive functions, social cognition, as well as behavioral changes in PSPs patients. [1–4] Another MR-based technique to evaluate GM damage is cortical thickness measurement. Unlike VBM, cortical thickness evaluation is accurate at the subvoxel level with thickness values being assigned to individual vertices rather than voxels. Furthermore, cortical thickness is less

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susceptible to variations in individual positioning, as the extraction of the cortex follows the GM surface regardless of positional variance. So far, only two studies applied cortical thickness in PSPs. [5,6] Cerebral cortex, especially in frontal areas, was found to be significantly thinned in PSPs patients compared to healthy controls, [5,6] but no significant clinico-anatomical correlations were detected. [5] Several diffusion tensor (DT) MRI studies showed that white matter (WM) damage of corpus callosum, frontal WM tracts and superior cerebellar peduncles (SCPs) contribute to executive deficits [7–9] and apathy [8] in these patients.

The aim of this study was to characterize the patterns of cortical and WM damage in a clinically and neuropsychologically well-characterized sample of PSPs patients using a surface-based method to assess cortical thickness and tract-based spatial statistics (TBSS) to investigate WM tract involvement. We also applied a random forest statistical approach to identify the strongest MRI predictors of cognitive impairment in PSPs at an individual patient level. We hypothesized that PSPs would be associated with focal cortical damage, mainly in frontal regions, and a prominent and distributed WM involvement, in keeping with the underlying frontotemporal lobar degeneration (FTLD)-tau pathology known to occur in this syndrome. [10] We also expected cognition to be significantly influenced by WM damage in these patients, reflecting the disconnection between cortical structures and projection targets.

2. Methods

2.1. Subjects

PSPs patients were recruited at the San Raffaele Scientific Institute from December 2012 to January 2015. Clinical diagnosis was based on patients' history, neurological examination and neuropsychological testing. All patients met the NINDS-SPSP criteria for probable PSP-Richardson's syndrome. [11] PSPs patients with parkinsonian variant were not included. Subjects were excluded if they had: a family history suggestive of an autosomal dominant disease; any other major systemic, psychiatric, or neurological illnesses; substance abuse that could interfere with cognitive functioning; and other causes of focal or diffuse brain damage, including lacunae, and extensive cerebrovascular disorders at routine MRI.Clinical assessment was performed by experienced neurologists with 20 years' experience in clinical neurology, blinded to MRI results. The clinical severity of PSPs was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr (H&Y) stage score, and the Clinical Dementia Rating (CDR) scale (Table 1). Neuropsychological and behavioral assessments were performed by two neuropsychologists unaware of the MRI results (neuropsychological battery is extensively described in the Supplementary methods). Raw cognitive test scores were transformed into Z scores, and the mean Z score was calculated for each cognitive domain (Table 1). Fifteen right-handed, age-matched healthy controls were recruited among spouses of patients and by word of mouth (Table 1). Healthy controls were included if the neurological assessment was normal and their Mini-Mental State Examination (MMSE) score was $\geq$28. They did not perform further neuropsychological tests. Local ethical standards committee on human experimentation approved the study protocol and all subjects provided written informed consent prior to study participation.

2.2. MRI analysis

Using a 3.0 T scanner, the following brain MRI sequences were obtained: T2-weighted spin echo (SE); fluid-attenuated inversion recovery; 3D T1-weighted fast field echo (FFE); and pulsed-gradient SE echo planar with sensitivity encoding and diffusion gradients applied in 32 noncollinear directions. Cortical thickness measurement and DT MRI analysis were performed as previously described. [12] Briefly, cortical reconstruction and estimation of cortical thickness were performed on the 3D T1-weighted FFE images using the FreeSurfer image analysis suite, version 5.3 (http://surfer.nmr.mgh.harvard.edu/). TBSS version 1.2 (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) was used to perform the multisubject DT MRI analysis. Midbrain volumes were obtained from 3D T1-weighted FFE images using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and the Diffeomorphic Anatomical Registration Exponentiated Lie Algebra registration method. [13] MRI acquisition and analysis protocols are extensively described in the Supplementary methods.

2.3. Statistical analysis

Demographic, clinical and cognitive data. Demographic, clinical and cognitive data were reported as means and standard deviations or frequencies and percentages for continuous and categorical variables, respectively. Normal distribution assumption was checked by means of Q-Q plot and Shapiro-Wilks and Kolmogorov-Smirnov tests. Group comparisons were performed using Mann-Whitney *U* test or Pearson chi-square test for continuous (age, education) and categorical variables (sex), respectively.

MRI: between group comparisons. Midbrain volume (mm3) differences between PSPs patients and healthy controls were examined using ANCOVA model, adjusting for age. A vertex-by-vertex analysis was used to assess differences of cortical thickness between controls and PSPs patients, using a general linear model in FreeSurfer. Maps showing between-group differences were generated by thresholding the t-statistic at $p < 0.05$, false-discovery rate (FDR) corrected for multiple comparisons. DT MRI voxelwise statistics were performed to compare mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (axD) and radial diffusivity (raD) between groups using a permutation-based inference tool for nonparametric statistical thresholding ("randomize", part of FSL). The number of permutations was set at 5000. The resulting statistical maps were thresholded at $p < 0.05$, corrected for multiple comparisons at the cluster level using the threshold-free cluster enhancement option. Then, the mean cortical thickness of 34 regions of interest (ROI) per hemisphere and mean DT MRI measures (FA and MD) from WM tracts of interest were compared between groups using ANCOVA models FDR-corrected for multiple comparisons and adjusting for subject's age (see Supplementary methods for further details).

Association between cognitive deficits and MRI findings: random forest analysis. A random forest analysis was used to identify those MRI variables that best predict the PSP cognitive scores (package "randomForest" version 4.5 implemented in R), as previously described. [8] An output of the random forest corresponds to variable importance reported as a ranking: each covariate receives a score according to its ability to predict correctly the patient's outcome when data are permuted. For a better interpretation of the results, variable importance was normalized with respect to the best predictor. For the random forest analysis, MRI measures (i.e., mean cortical thickness values from 34 regions of interest per hemisphere, and mean DT MRI measures from WM tracts) which showed significant correlation with neuropsychological scores were considered. R values (Spearman partial rank-order coefficients) were also reported. For further details see the Supplementary methods.

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