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Voxel-based morphometry and voxel-based relaxometry in multiple system atrophy—A comparison between clinical subtypes and correlations with clinical parameters

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Multiple system atrophy (MSA) is a neurodegenerative disease affecting basal ganglia, brainstem, cerebellum, and intermediolateral cell columns of the spinal cord. Clinically, a cerebellar (MSA-C) and a parkinsonian variant of MSA (MSA-P) are distinguished. We used voxel-based morphometry (VBM) and voxel-based relaxometry (VBR) in 48 MSA patients (32 MSA-C, 16 MSA-P) and 46 controls. In MSA-C, VBM revealed gray matter loss in cerebellum, right thalamus, both putamina and several cortical regions including insular cortex. Gray matter loss in the cerebellum and insular cortex was correlated with disease duration and severity. There was white matter loss in the brainstem, which was correlated with disease duration and severity. VBR analysis in MSA-C showed decreased relaxation rate R2 in cerebellum, pontine brainstem and cortical regions including insular cortex. In MSA-P, gray matter was reduced in cerebellum, dorsal midbrain, both putamina, and several cortical regions including insular cortex. A correlation with disease duration and severity was detected only for some small cortical areas. Direct comparison of MSA-C and MSA-P showed differences only in infratentorial brain regions where structural abnormalities were more pronounced in MSA-C than in MSA-P. In MSA-C, there was a stronger reduction of gray matter in the basal parts of the cerebellum, of white matter in the brainstem and of the relaxation rate R2 in the cerebellum and brainstem.

Keywords: MSA; MSA-C; MSA-P; VBM; VBR

Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset disease characterized by progressive neurodegeneration in various parts of the central nervous system including the basal ganglia, brainstem, cerebellum, and intermediolateral cell columns of the spinal cord (Graham and Oppenheimer, 1969; Quinn, 1989). The neuropathological hallmark of MSA are α-synuclein-positive oligodendroglial cytoplasmic inclusions (GCIs) (Papp and Lantos, 1994). Clinically, MSA patients present with various combinations of parkinsonism, cerebellar ataxia, and autonomic failure, most notably orthostatic hypotension and urinary incontinence. According to the clinical presentation, a parkinsonian (MSA-P) and a cerebellar variant of MSA (MSA-C) are distinguished (Wenning et al., 1994; Schulz et al., 1994).

Magnetic resonance imaging (MRI) has been extensively used to study the brain morphology of MSA patients. Early studies that used subjective rating or region-of-interest- (ROI-)guided planimetric and volumetric approaches defined cerebellar and brainstem atrophy as a prominent structural abnormality of MSA. The striatum consisting of the putamen and caudate nucleus is another brain region that was found to undergo volume loss in MSA. In addition, signal abnormalities in the pons, middle cerebellar peduncles and putamen were observed in a subset of MSA patients (Schulz et al., 1994, 1999; Savoiardo et al., 1999; Schrag et al., 2000). More recently, voxel-based morphometry (VBM) was employed to study the brain morphology of MSA. These studies extended the knowledge of MSA brain morphology by showing additional cortical tissue loss (Specht et al., 2003; Brenneis et al., 2003, 2006; Hauser et al., 2006). However, all VBM studies were done in comparably small groups of either MSA-C or MSA-P patients, so that comparisons of the MSA variants were not

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feasible. Additional information of brain structural abnormalities came from recent MRI studies using diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), magnetization transfer imaging (MTI), and voxel-based relaxometry (VBR) (Seppi et al., 2003, 2006; Eckert et al., 2004; Pell et al., 2004; Specht et al., 2005; Shiga et al., 2005). Voxel-based relaxometry (VBR) is a morphometric method that analyses the relaxation rate R2 (defined as 1/T2) derived from multi-echo T2-weighted images on a voxel-by-voxel basis using the exponential relationship between the actual transverse magnetization and the relaxation rate R2. In principle, decreased R2 indicates increased water content and can therefore provide a measure of tissue atrophy.

In this study we compared brain morphology in MSA-C and MSA-P. To this end, we used VBM and VBR to evaluate MRI's of 48 MSA patients. In addition, we correlated brain morphology with disease duration and severity. Specifically, we wished to address the following questions. (1) What is the brain morphological correlate of the phenotypical differences of the two MSA variants? (2) Does the analysis of T2-weighted images with VBR yield information that complements and extends that derived from VBM? (3) Do VBM and VBR identify structural parameters that can be useful as markers of disease progression?

Methods

Subjects

The study was performed in 48 MSA patients (32 MSA-C, 16 MSA-P, m/f: 27/21, age: 61.2±6.0 years, disease duration: 4.5±2.3 years) and 46 healthy controls (m/f: 22/24, age 58.7±6.1 years). The diagnosis of MSA was made according to established criteria (Gilman et al., 1999). Patient data are given in Table 1. As a measure of disease severity we used disease stages, as previously described: Stage 1=disease onset with onset of gait difficulties, stage 2=loss of independent gait as defined by permanent use of a walking aid or reliance on a supporting arm, stage 3=confinement to wheelchair, as defined by permanent use of a wheelchair (Klockgether et al., 1998).

Table 1
Clinical data

	MSA-C	MSA-C-subgroup	MSA-P	Controls	Control-subgroup
No. of patients	32	16	16	46	16
Age	60.5±6.2	61.6±5	62.8±5.6	58.7±6.1	62.3±4.3
Sex (m/f)	19/13	7/9	8/8	22/24	8/8
Possible/probable MSA	8/24	2/14	2/14	–	–
Disease duration	4.5±2.4	5.9±2.9	4.4±2.3	–	–
Stage 1	10	4	2	–	–
Stage 2	15	8	6	–	–
Stage 3	7	4	8	–	–
Cerebellar symptoms	32	16	8	–	–
Parkinsonism	11	6	16	–	–
Pyramidal signs	4	2	4	–	–
Urinary incontinence	25	11	12	–	–
Orthostatic hypotension	24	12	13	–	–

Stage 0=no gait difficulties, stage 1=disease onset with onset of gait difficulties, stage 2=loss of independent gait as defined by permanent use of a walking aid or reliance on a supporting arm, stage 3=confinement to wheelchair, as defined by permanent use of a wheelchair.

Statistical comparisons were made (1) between MSA-C (n=32) and controls (n=46), (2) between MSA-P (n=16) and a matched subgroup of the controls (n=16, m/f: 8/8, age: 62.3±4.3 years) and (3) between a MSA-C subgroup (n=16) and MSA-P (n=16).

The study was approved by the ethics committee of the Medical Faculty of the University of Bonn. Informed and written consent was obtained from all participants.

Data acquisition

Magnetic resonance imaging measurements were performed using a 1.5 T scanner (Siemens Symphony, Siemens AG, Erlangen, Germany) with the standard head coil. The MRI protocol comprised a sagittal T1-weighted (MPRAGE) sequence (TR 11.08 ms, TE 4.3 ms, FA 15° FOV 230 mm, 256×256 acquisition matrix) yielding 200 sagittal slices and a voxel size of 0.9×0.9×0.9 mm^3. Further, we used an axial multi-echo T2-weighted sequence (TR 5800 ms, TE 15,75,135 ms, FA 180° two excitations, FOV 230, 256×256 matrix, 40 slices) with a voxel size of 0.9×0.9×2.0 mm^3 and a 2 mm gap between slices.

Using the multi-echo T2-weighted images, we calculated new images representing the relaxation rate R2 of each voxel. This was done with the relaxometry option implemented in the Image Control and Evaluation (nICE) software package from Nordic-NeuroLab AS (http://www.Nordicneurolab.no).

Data preprocessing

Image quality was controlled independently by two authors (M.M., K.S.), blinded for group affiliation. Images with artefacts were excluded from further data analysis.

The data of both sequences was comparably preprocessed as described previously (Ashburner and Friston, 2000, 2001; Good et al., 2001a,b; Specht et al., 2003). To prevent mismatch errors each preprocessing step was controlled and verified for each subject and each sequence separately. After defining the anterior commissure in each image as the origin of the individual stereotaxic space, we reoriented all images into the axial view.

The preprocessing of the T1 images was performed according to the previously described protocol (Good et al., 2001b; Specht et al., 2005) using statistical parametric mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/spm2). This procedure optimizes the normalization for the explored tissue type by the use of tissue-specific templates. The variability due to registration errors during the normalization procedure is assumed to be smaller for subcortical structures than for cortical areas (Grachev et al., 1999) and these subcortical areas were a main focus of our study.

In short, the T1-weighted images were segmented into gray- and white-matter probability maps. These maps were normalized to a tissue specific template and the thereby estimated transformations were applied to the original T1 dataset, which was then normalized (1.5×1.5×1.5 mm resampled voxel-size), segmented and smoothed with a 12-mm Gaussian kernel.

To obtain a similarly optimized normalization of the R2 images, we performed a more complex procedure (Specht et al., 2005). This procedure includes the creation of a R2 map template, to which all R2 maps were normalized, with a resampled voxel size of 2×2×2 mm. The data were smoothed with an un-isotropic