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Hyperconnective and hypoconnective cortical and subcortical functional networks in multiple system atrophy

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ABSTRACT

Introduction: In multiple system atrophy (MSA), the organization of the functional brain connectivity within cortical and subcortical networks and its clinical correlates remains to be investigated.
Methods: Whole-brain based 'resting-state' fMRI data were obtained from 22 MSA patients (11 MSA-C, 11 MSA-P) and 22 matched healthy controls, together with standardized clinical assessment and video-oculographic recordings (EyeLink®).
Results: MSA patients vs. controls showed significantly higher ponto-cerebellar functional connectivity and lower default mode network connectivity ($p < .05$, corrected). No differences were observed in the motor network and in the control network. The higher the ponto-cerebellar network functional connectivity was, the more pronounced was smooth pursuit impairment.
Conclusion: This functional connectivity analysis supports a network-dependent combination of hyper- and hypoconnectivity states in MSA, in agreement with adaptive compensatory responses (hyperconnectivity) and a function disconnection syndrome (hypoconnectivity) that may occur in a consecutive sequence.

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1. Introduction

Multiple system atrophy (MSA) is characterized by a variable combination of autonomic dysfunction, parkinsonism, cerebellar ataxia, and pyramidal symptoms [1,2]. Neuronal loss is strongly associated with alpha-synuclein accumulation in the cerebellum, pons, basal ganglia, as well as frontal and primary motor cortices [2,3]. By use of structural imaging modalities such as volumetry and diffusion weighted imaging, patterns of specific brain atrophy and white matter changes in MSA could be mapped [4–6]. However, although 'resting-state' functional magnetic resonance imaging (fMRI) has emerged as an advanced approach to the analysis of spatially distributed patterns of intrinsic functional connectivity networks over the last years [7], merely very few 'resting state' fMRI studies have been performed in MSA, so far [8–10].

In the present study, we aimed to investigate functional connectivity changes in MSA patients compared with matched healthy controls using 'resting-state' fMRI. Based on the topography of abnormal aggregation of alpha-synuclein protein as well as the clinical presentation of MSA patients [2,3], we hypothesized that MSA-related pathology was associated with altered functional connectivity in disease-specific networks, i.e. the subcortical ponto-cerebellar network, the cortical motor network, and the default mode network; as a control, we also investigated the dorsal attention network that we did not expect to be affected. Further, we hypothesized that possible ponto-cerebellar network alterations might be associated with clinical and behavioral measures, e.g. video-oculographically captured eye movement disturbances as a valuable and robust measure of complex forms of human behavior [11,12].

2. Materials and methods

2.1. Study population

The study was approved by the Ethical Committee of the University of Ulm, Ulm, Germany (reference #88/11), and all subjects

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provided written informed consent. Standardized clinical-neurological examinations were undertaken in all patients by two movement disorder specialists resulting in a diagnosis of 19 patients with probable MSA and three with possible MSA according to the current standardized consensus criteria for MSA [13]. Twenty-two MSA patients (11 MSA-C, 11 MSA-P) were compared with 22 matched healthy controls. Groups did not differ in age and gender as assessed by Fisher's exact test for categorical variables (gender) and the two-sample unpaired *t*-test. Clinical features and demographics of all subjects included in the analysis are summarized in (Table 1).

2.2. MRI data acquisition

Functional 'resting-state' MRI data were acquired at a 1.5T clinical MRI scanner (Symphony Siemens, Erlangen, Germany) using a BOLD contrast sensitive gradient echo-planar sequence (30 transversal slices, $3.27 \times 3.27 \times 3.00\ mm^3$ voxels, $64 \times 64 \times 30$ matrix, TE = 28 ms, TR = 3080 ms, flip angle 90°, 120 vol). Whole-brain-based structural data were acquired using a high-resolution 3-D T1-weighted magnetization-prepared gradient echo image (MPRAGE) sequence (144 sagittal slices, no gap; $1.0 \times 1.2 \times 1.0\ mm^3$ voxels; $256 \times 192 \times 256$ matrix; TE = 4.2 ms; TR = 1600 ms).

2.3. 'Resting-state' fMRI data analysis

Functional imaging data were analyzed using an extension module for intrinsic functional connectivity data analysis [14] within the framework of the *Tensor Imaging and Fiber Tracking* (TIFT) software package [15]. This module has been used in previous studies [16–19]. Processing of 'resting-state' fMRI data followed a standardized protocol [14,16]. The analysis steps included: (i) quality control and head movement correction, (ii) resampling to a cubic 1 mm grid, (iii) deformation to MNI stereotaxic space using a study-specific template (computed from all 44 subjects), (iv) spatial smoothing using a 7 mm full-width at half maximum Gaussian filter, (v) de-meaning and voxel-wise removal of linear trends, and (vi) temporal bandpass filtering ($0.01 < f < 0.08$ Hz). The networks were computed using the "seed-based" approach. According to our hypothesis, the following networks were defined using bilateral voxel-seeds according to previous studies [14]: (1) pontocerebellar network (pons; MNI $x = \pm 11$; $y = -32$; $z = -39$), (2) motor network (motor cortex; $x = \pm 27$; $y = -27$; $z = 68$), (3) default mode network (posterior cingulum; $x = 0$; $y = -57$; $z = 26$), and (4) as a control network that was not expected to be alterated, the dorsal attention network (frontal eye fields; $x = \pm 30$; $y = -9$; $z = 54$). The resulting brain maps, i.e. functional networks, were voxel-wise transformed using Fishers r-to-z transformation, and globally thresholded for $|z(r)| \geq .40$. A detailed description of the data processing is given in Supplementary file 1.

2.4. Video-oculographic data acquisition and postprocessing

Eye movements were video-oculographically recorded using a binocular EyeLink I® system (SR Research Ltd., Osgoode, ON, Canada) in our certified oculomotor laboratory. The stimuli comprised smooth pursuit eye movements in horizontal direction (sinusoidal target motion, amplitude ±20°, $f = 0.375$ Hz, 6 cycles). The smooth pursuit recordings were analyzed using the software package *OculoMotor Analysis* in order to quantify the shape of saccadized smooth pursuit by investigating the prevalence of 'catch-up' saccades that are typically present in MSA as a correlate of ponto-cerebellar dysfunction [20]. Further details of the data acquisition and analysis have been published previously [16,20].

2.5. Statistical analysis

Functional connectivity differences between MSA patients and controls were analyzed using two-sided parametric unpaired Student's *t*-test for unequal variance [17]. The functional connectivity brain maps were corrected for multiple comparisons at a 5% level using the false discovery rate (FDR) approach, followed by a parametric correlation-based clustering procedure that discarded isolated clusters not exceeding the minimum size of 216 voxels at cubic 1 mm resolution. Possible relationships between network-based functional connectivity measures (connectivity maps) and the clinical and behavioral parameters were studied by use of the non-parametric Spearman rank order correlation coefficient. All statistical analyses followed a standardized procedure with thresholds obtained from independent Monte-Carlo analysis [17].

3. Results

3.1. Altered functional connectivity in MSA

Using the seed-based correlation analysis, all investigated functional connectivity networks were consistently identified for all subjects, i.e. MSA-C, MSA-P patients and controls, as illustrated in the Supplementary Fig. 1. The controls' functional connectivity networks were similar to previous 'resting-state' fMRI studies [21,22].

Functional connectivity in the ponto-cerebellar network was significantly higher in MSA patients compared with controls, but functional connectivity was lower along the midline cores, i.e.

Table 1
Demographic and clinical variables are shown as mean (±SD), min—max.

Parameter	MSA	healthy controls	p
Subjects (number)	22	22	–
Gender (male:female)	8:14	9:13	1.000[a]
Age (years)	65.2 (±7.8), 50-76	66.4 (±6.3), 53 - 80	.594[b]
Duration of disease (months)	45.3 (±22.3), 13–71	–	–
Age of onset (years)	61.2 (±8.6), 44-74	–	–
MSA-C: MSA-P (male:female)	(3:8): (5:6)	–	–
Smooth pursuit eye movement performance [21] (sum of catch-up saccades; N = 16, °)	−67.5 (±67.5), -135-0	–	–
UPDRS III[c] motor examination	42 (±12), 22-69	–	–
Hoehn and Yahr	3.5 (±0.9), 1.5–5		
Levodopa equivalent dose (mg)	296.2 (±353.4), 0-1022		

MSA, multiple system atrophy.
[a] Fisher's exact test for MSA versus healthy controls.
[b] Two-sample unpaired *t*-test for MSA patients versus healthy controls.
[c] Unified Parkinson's Disease Rating Scale, part III, motor examination.

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