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WHITE MATTER DIFFERENCES BETWEEN MULTIPLE SYSTEM ATROPHY (PARKINSONIAN TYPE) AND PARKINSON'S DISEASE: A DIFFUSION TENSOR IMAGE STUDY

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Abstract—The clinical differential diagnosis between the Parkinson variant of multiple system atrophy (MSA-P) and Parkinson's disease (PD) is difficult in early stages. To identify objective markers for differential diagnosis, we combined the novel tract-based spatial statistics (TBSS) and region of interest (ROI) analyses for the first time to investigate three groups (15 MSA-P, 20 PD patients and 20 controls) with diffusion tensor imaging data. By TBSS, we performed pairwise comparisons of fractional anisotropy (FA), mean diffusivity, radial diffusivity (RD) and axial diffusivity maps. The clusters with significant differences between MSA-P and PD were used as ROIs for further analyses. FA/RD values in bilateral corticospinal tract (CST) and left anterior thalamic radiation (ATR) in MSA-P were significantly different from PD or controls, and significantly correlated with clinical data. These findings indicated that the abnormalities of left ATR and bilateral CST were specific for MSA-P relative to PD or controls, and seemed to be promising for differential diagnosis. Furthermore, it may be useful for severity assessment of MSA-P.

Key words: diffusion tensor imaging, multiple system atrophy, Parkinson's disease, region of interest, tract-based spatial statistic.

INTRODUCTION

Multiple system atrophy (MSA) is a neurodegenerative disease that can be divided into two clinical subtypes according to whether MSA has predominant cerebellar symptoms (MSA-C) or predominant parkinsonian symptoms (MSA-P) (Gilman et al., 2008). MSA-P has similar symptoms and signs to Parkinson's disease (PD), especially in the early stages. Early differentiation between MSA-P and PD has important prognostic and therapeutic implications. During the past decade, several tools have been developed to address this issue. In conventional magnetic resonance imaging (MRI), the typical radiographic changes such as ''slit-like'' marginal hyperintensity of the putamen and ''hot-cross bun'' sign in pontine images, usually appear at the advanced stage of this disease. Thus, many researchers have recently focused on other non-invasive technologies, such as diffusion weighted image (DWI) and diffusion tensor image (DTI).

Studies comparing DWI changes found higher apparent diffusion coefficients (ADC) or lower fractional anisotropy (FA) values in regions associated with clinical symptoms, such as pons, cerebellum, middle cerebellar peduncle (MCP) and putamen in MSA-P than in PD or controls (Schocke et al., 2004; Nicoletti et al., 2006; Ito et al., 2007; Kollensperger et al., 2007). In theory, DTI can provide more precise details on tissue microstructure than DWI (Mori and Barker, 1999). DTI exploits the random diffusion motion of water molecules *in vivo* (Moseley, 2002), and reveals important information about the status of neuronal fiber tracts that is not evident on conventional MRI. Several measures can be extracted from DTI analyses, including FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). FA is considered a valid measure of white matter structural integrity, sensitive to anomalies in axonal density, diameter, myelination and coherence of directional alignment of fibers within white matter tracts (Pierpaoli and Basser, 1996; Le Bihan et al., 2001), while MD represents a directionally independent measure of the average diffusivity that reflects the degree of myelination, interstitial space and axonal density (Norris, 2001). AD measures diffusion parallel to the white matter tracts. RD appears to reflect diffusion perpendicular to white matter tracts. It is recommended to use multiple diffusion tensor measures to better characterize the tissue microstructure (Alexander et al., 2007).

Previous DTI studies have used conventional MRI to set region of interest (ROI) in intracranial structures that

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Abbreviations: ADC, apparent diffusion coefficients; ATR, anterior thalamic radiation; CST, corticospinal tract; DTI, diffusion tensor image; DWI, diffusion weighted image; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; MCP, middle cerebellar peduncle; MD, mean diffusivity; MSA, multiple system atrophy; PD, Parkinson's disease; ROI, region of interest; SLF, superior longitudinal fasciculus; TBSS, tract-based spatial statistic analysis; UPDRS, Unified Parkinson's Disease Rating Scale.

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are vulnerable in MSA or PD and related to the clinical symptoms, then obtained quantitative data for further analyses. They have demonstrated significant reduction of FA values in MCP, pontine and cerebellar white matter, and putamen in MSA-P compared with PD (Ito et al., 2007; Nilsson et al., 2007; Nair et al., 2013).

The novel tract-based spatial statistics (TBSS) method which combines the strength of both voxel-based and tractography-based analyses has received more attention recently (Smith et al., 2006). It does not require smoothing and allows for higher spatial comparability. Furthermore, it is available for the alignment and registration of major fiber bundles between different subjects, so as to achieve more accurate group comparisons. This approach is appropriate for DTI group analyses focusing on deep white matter fiber tracts (Smith et al., 2004; Woolrich et al., 2009). In recent studies, TBSS has been shown to improve sensitivity for detecting white matter diffusion changes, even with relatively small sample size ($n < 30$) (Focke et al., 2008; Yeh et al., 2009).

However, TBSS has rarely been performed in patients with MSA. One study reported significantly different ADC values in the vicinity of the putamen between PD and MSA-P patients via TBSS algorithm (Cnyrim et al., 1997). Hence, it is hypothesized that the combined use of TBSS and ROI is more accurate for characterizing differences between MSA-P and PD.

After detecting specific micro-structural white matter alterations using the TBSS method, we performed a more detailed investigation of the alteration using the ROI method. Correlation between diffusion indices and clinical data was tested by ROI methods.

EXPERIMENTAL PROCEDURES

Subjects

DTI scans were initially acquired from 18 patients with MSA-P. However, two patients were excluded due to large motion artifacts, and one patient was discarded because of the presence of infarction. Therefore, a total of 15 MSA-P patients (13 out of 15 patients fulfilled the criteria for 'probable MSA' and two were classified as 'possible MSA') (Gilman et al., 2008), 20 age- and sex-matched patients with PD (Hughes et al., 1992) and 20 age- and sex-matched healthy volunteers were included in the final analyses (see Table 1). All these subjects were selected randomly by our experienced movement disorder specialist. Patients with MSA-P and PD were assessed using the motor part of Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn–Yahr (H-Y) scale. Patients with MSA-P were also assessed by Unified Multiple System Atrophy Rating Scale (UMSARS), as it was conducive to classification. The study was approved by our regional research ethics committee. Written informed consent was obtained from all participants. All cases were recruited from Nanjing Brain Hospital, from January 2011 to August 2013.

Table 1. Demographic and behavioral characteristics of the included participants

Characteristics	MSA-P ($n = 15$)	PD ($n = 20$)	Control ($n = 20$)	P^*
Age at DTI, mean (SD)	59.87 (7.20)	64.20 (7.37)	59.95 (4.88)	0.124
Gender (male: female)	9:6	11:9	10:10	0.840
Disease duration at DTI, median (range)	2 (1–5)	5 (1–8)	NA	0.048
H–Y, median (range)	2 (1–3)	2 (1–4)	NA	0.090
UPDRS motor score, median (range) (off medication)	28 (10–40)	32 (11–44)	NA	0.356

HY: Hoehn and Yahr scale; UPDRS: Unified Parkinson Disease Rating Scale; NA: not applicable; SD: standard deviation.

MRI protocol

DTI was performed on a 3-Tesla Siemens Verio scanner with an 8-channel radio frequency coil, using a single-shot spin-echo diffusion-weighted echo-planar pulse sequence at 3-mm section thickness with no gap (TR/TE = 8800/88 ms; acquisition matrix = 128 × 128). Thirty diffusion-weighted volumes with gradient encoding applied in 30 non collinear directions and $b = 1000$ s/mm^2 were used to image the entire brain with a 23-cm square field of view (resolution = 1.8 mm × 1.8 mm × 3 mm). T1 and T2 weighted images were also obtained with no diffusion gradient ($b = 0$ s/mm^2), as the latter is conducive to further exclusion of other organic diseases such as tumors, infarction and hydrocephalus.

Image analysis

Images were processed and analyzed using the FSL (FMRIB Software Library, FMRIB, Oxford, UK) software package (Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012). First, the FDT (FMRIB's Diffusion Toolbox) ''eddy_correct'' function was used to reduce distortion and the effect of head movement. After that, a brain mask was created from the first b_0 image using the BET (Brain Extraction Tool) (the fractional intensity threshold is 0.2). Finally, we computed the diffusion maps using the FDT tool ''dtifit'' to fit the tensor model at each voxel.

Voxelwise analysis was conducted using the FSL tool ''TBSS''. Data were projected on a common pseudoanatomical skeleton, therefore smoothing could be avoided, and we could carry out the voxelwise statistics without matching every voxel in different subjects. All subjects' FA data were first aligned to the FMRIB58_FA standard-space image using the nonlinear registration tool. Next, the TBSS script created the mean FA image, and skeletonized it using a protocol that searches and labels the skeleton voxels with maximum FA intensity along the perpendicular direction (breadth) of a white matter tract. To make sure that gray matter, ventricle and cerebrospinal fluid were not included, a threshold of 0.2 was set. Finally, the registered FA images were projected onto the skeleton before running the voxelwise cross-subject stats. The MD, RD and AD images were performed in the same way as described above without the initial registrations.

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