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Tract-based spatial statistics of the olfactory brain in patients with multiple sclerosis

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ABSTRACT

Purpose: To investigate diffusion tensor abnormalities, e.g. fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD), in olfactory structures of multiple sclerosis (MS) patients using diffusion tensor imaging (DTI).
Methods: Institutional review board-approved prospective study on 30 MS patients and 12 healthy controls investigated with MRI including DTI. Central olfactory structures were labelled on each patient's and healthy contro''s DTI volume. The diffusion tensor was determined in the central olfactory structures in MS patients. Tract-based spatial statistics (TBSS) was used to quantify the streamlines outgoing from the olfactory structures and to quantify changes in FA, MD, and RD within olfactory structures. These brain changes were correlated with olfactory function measured as TDI (Threshold, Discrimination, Identification) scores in patients and compared to our own reference group of 30 healthy volunteers.
Results: Central olfactory structures in the MNI (Montreal Neurological Institute) data volume comprise 4808 voxels (4808 mm^3). TFCE (Threshold-free cluster enhancement) and cluster analysis of patients identified a total of 127 voxels in one cluster with a significantly decreased FA ($p < 0.05$) and none for MD and RD within olfactory structures compared to healthy controls. The correlation with the age-normalised Identification subscore of the TDI score increased the significant number of voxels with decreased FA to 208 voxels, with increased MD to 370 and with increased RD 364 voxels at the same region.
Conclusion: The decrease in FA and increase of MD and RD correlate with the degree of identification impairment of olfactory function in MS patients and clusters of abnormalities were identified on a MNI data volume.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system resulting in demyelination. Magnetic resonance imaging (MRI) is useful in detecting MS-typical lesions; however, the poor association between clinical extent and radiological visible involvement was discussed previously [1]. It was suggested that the so-called normal-appearing brain tissue (NABT) is affected by the disease too [2]. Diffusion tensor imaging (DTI) measures the Brownian motion of water molecules and its directional prevalence. The directional prevalence is reduced in MS lesions as well as in NABT [3]. This reduced directionality of water motion can be quantified as fractional anisotropy (FA; 1 indicating exclusive diffusion in one direction, 0 indicating no preferred direction of diffusion). Many studies have used FA as a marker for assessing the integrity of neuronal tissue in MS patients. A decreased FA is inherently coupled to an increased mean diffusivity (MD) and an increased radial diffusivity (RD) due to the reduced directionality.

There is evidence that MS patients can experience alterations in olfactory function in the course of the disease [4,5]. Zivadinov et al. report an impaired olfactory function in a considerable number of MS patients as well as a low level of awareness of patients having episodes of smell loss [6]. Previously, it has been discussed whether olfactory impairment is an early hallmark of the disease [7]. However, it seems that especially those aspects of olfactory function are affected which require higher cognitive involvement such as discrimination and identification of odours [8]. It has been reported that the frequency of odour identification impairment was higher for patients with secondary progressive than relapsing–remitting or primary progressive courses [9]. Previous studies indicate that impaired olfactory function correlates with the lesion load in the olfactory brain [10–13].

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However, none of the studies attempted to describe diffusion abnormalities in the entire olfactory brain of MS patients.

Tract-based spatial statistics (TBSS) was developed for voxelwise analysis of DTI data and comparison in multi-subject studies [14,15]. The software allows assessing streamlines in brain structures from the diffusion tensor data. Furthermore, it allows determining the number of streamlines outgoing from a seed point or structure. Threshold-free cluster enhancement (TFCE) cluster analysis uses spatial neighbourhood information from perpendicular voxels to enhance information on the spatial distribution of lesions in white matter pathways [16]. TBSS-based analysis of multiple sclerosis patients indicates that FA is lower in a number of brain regions and has been shown to be useful to localise damage [17].

In this study we used TBSS to determine FA, MD, and RD changes of the olfactory brain of MS patients.

We hypothesised that FA is reduced in patients with impaired olfactory function and quantified clusters with significantly decreased FA in the olfactory brain using MNI coordinates. To check for differences between MS patients and healthy controls we also compared reconstructed streamlines outgoing from the olfactory brain in both groups.

2. Material and methods

For this prospective study, we recruited 30 patients and 12 healthy volunteers for MRI measurements. Our own database of normal olfactory function consisting of a reference group of 30 healthy volunteers was used to compare olfactory performance.

All patients fulfilled the McDonald criteria for MS and were between 18 and 65 years old [18]. All patients underwent neurological examination on the day of magnetic resonance imaging (MRI). Furthermore, they were seen by an ENT specialist for examination of the olfactory system and testing of their olfactory function with the TDI (Threshold, Discrimination, Identification) test.

The exclusion criteria were as follows: severe disability (Expanded Disability Status Scale [19] [EDSS] > 6.5), any disorder other than MS of the olfactory system compromising olfactory performance, pregnancy and MRI-incompatible implants. Previous research indicated that olfactory function can be altered by depression or dementia [20,21]. Only patients with a BDI (Beck's Depression Inventory) [22] score of less than 30 and patients with an MMSE (Mini Mental State Examination) score of more than 24 were included in the study [23]. The following demographic and clinical variables were collected for each patient: gender, age, disease duration, MS phenotype, EDSS, TDI score, BDI and MMSE.

Twelve healthy volunteers with no known disorder of the olfactory system were recruited as control subjects for the MRI measurements. The local ethics committee approved our study. Written informed consent was obtained from all participants.

Table 2
Number of streamlines in the olfactory brain: The label maps of the olfactory brain served as seed points for assessing the outgoing number of streamlines.

	Patients	Controls
Mean	20,686,000	18,946,000
SD	10,439,651	2,036,173
1st quartile	16,583,750	17,616,250
3rd quartile	21,796,250	18,365,000
25–75% width of quartile	5,212,500	748,750

2.1. Olfactory testing

All patients were administered the validated and reliable TDI test (Burghart, Wedel, Germany) on the day of their MRI scan [24,25]. Testing was performed using the 'Sniffin sticks' test kit, which consists of 48 sniffing sticks to determine odour threshold, odour discrimination and odour identification. A score of less than 16 is considered as anosmia, less than 30 hyposmia and more than 30 normosmia. The results were individually normalised using age correction to a published standard of reference [24]. The data were then compared to our own database of normal olfactory function consisting of a reference group of 30 healthy volunteers, recruited and tested by our ENT specialists.

2.2. MRI imaging

Brain scans were acquired on a 1.5-Tesla Siemens Symphony scanner (Erlangen, Germany) using an eight-channel phased-array head coil. The following sequences were acquired during a single session in patients and controls:

(1) A T2/proton density (PD) double echo SE sequence with 3-mm slice thickness was used to quantify visible white matter lesions using axial sections (TR 3070 ms, TE (T2) 107 ms, TE (PD) 18 ms, matrix 256 × 192, FOV 250 mm, percent phase FOV 75%, number of excitations (NEX) 1).
(2) A T1-weighted SE scan with 3-mm slice thickness was acquired to determine relevant anatomy in axial sections (TR 600 ms, TE 14 ms, matrix 256 × 192, FOV 250 mm, percent phase FOV 75%, NEX 2).
(3) DTI was performed using an echo planar spin echo diffusion sequence (TR 6000 ms, TE 109 ms, b = 0 and 21 directions for b = 1000, matrix 128 × 128, FOV 250 mm, number of averages = 3, slice thickness 3 mm). No parallel imaging was used since this technique was not available on the scanner.

2.3. MRI data analysis

Image data were processed using FSL (FMRIB Image Analysis Group, Oxford, England). DTI data were corrected for eddy current distortion and motion. FMRIB's Automated Segmentation Tool (FAST) was used

Table 1
Demographic data and clinical characteristics of patients, healthy controls and olfactory reference group.

	MS patients (n = 30)	MS patients (n = 30)	Healthy controls (n = 12)	Healthy controls (n = 12)	Olfactory testing reference group (n = 30)	Olfactory testing reference group (n = 30)
	Mean	SD	Mean	SD	Mean	SD
Age	40.7	11.7	38.3	11.9	42.4	12.3
Disease duration	5.0	6.7	–	–	–	–
EDSS	3.3	2.1	–	–	–	–
BDI	7.2	6.6	–	–	–	–
MMSE	28.8	1.1	–	–	–	–
TDI	31.5	4.1	–	–	34.5	2.6
T	6.3	1.7	–	–	6.8	2.0
D	12.4	2.4	–	–	13.0	1.8
I	12.8	1.7	–	–	14.6	0.8