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Imaging of olfactory bulb and gray matter volumes in brain areas associated with olfactory function in patients with Parkinson's disease and multiple system atrophy

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ABSTRACT

We explored if magnetic resonance imaging sequences might aid in the clinical differential diagnosis of idiopathic Parkinson's disease (IPD) and multiple system atrophy (MSA). We measured the volumes of the olfactory bulb, the olfactory tract, and olfaction-associated cortical gray matter in 20 IPD patients, 14 MSA patients, and 12 normal subjects, using high-resolution magnetic resonance imaging sequences in combination with voxel-based statistical analysis. We found that, compared to normal subjects and MSA patients, the volumes of the olfactory bulb and tract were significantly reduced in IPD patients. The gray matter volume of IPD patients decreased in the following order: the olfactory area to the right of the piriform cortex, the right amygdala, the left entorhinal cortex, and the left occipital lobe. Further, the total olfactory bulb volume of IPD patients was associated with the duration of disease. The entorhinal cortical gray matter volume was negatively associated with the UPDRS III score.

Conclusion: Structural volumes measured by high-resolution magnetic resonance imaging may potentially be used for differential diagnosis of IPD from MSA.

1. Introduction

The incidence of olfactory dysfunction in patients with idiopathic Parkinson's disease (IPD) is very high. It is not clear why this is the case. Olfactory dysfunction is rather rare in multiple system atrophy (MSA) patients. Braak [1] believed that IPD was a synucleinopathic disease featuring formation of Lewy bodies and Lewy neural processes in the brain. IPD commences in the medulla, and the first lesion occurs in the olfactory region and the lower portion of the brainstem. Olfactory loss is one of the earliest presentations of IPD patients. The pathological study of Braak et al. showed that the olfactory bulb and the anterior nucleus of the olfactory system, the dorsal nucleus of the vagus nerve, and the rostral intermediate reticular belt, are the first regions to exhibit Lewy body degeneration in IPD patients [2,3]. The retrospective pathological study of Beach [4], who studied 328 cases of IPD, Lewy body dementia, and Alzheimer's disease, showed that although alpha-synuclein levels in the olfactory epithelium of IPD patients exhibited no pathological change, positive staining for alpha-synuclein in the olfactory bulb and tract was both very sensitive and specific for diagnosis of IPD. The autopsy study of Hawkes et al. revealed that neuronal loss in the anterior olfactory nucleus was significant in patients with IPD. This suggested the existence of a strong association between changes in the olfactory bulb and IPD-associated olfactory dysfunction [5]. Therefore, the presence of an olfactory disorder may contribute to early diagnosis of IPD. Huisman et al. [6] found that the numbers of dopaminergic neurons in the olfactory bulb increased significantly in patients with IPD. Also, Pearce et al. [7] found that the numbers of neurons in the region of the anterior olfactory nucleus decreased significantly in IPD patients. Hawkes et al. [8] showed that the volume of the olfactory bulb was reduced in PD patients, compared with normal subjects. However, Mueller [9] reported that the volumes did not differ. Further study is required. In addition, anatomical studies revealed inclusion bodies and nerve fiber aggregation in olfaction-associated cortical structures (including the entorhinal cortex and the amygdale) of IPD patients, suggesting that olfactory disorders in such patients may be associated with impairment of olfaction-related CNS functions. Naroa et al. [10] showed that the volumes of the piriform cortex and gray matter of the amygdala were reduced in IPD patients, compared to

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normal subjects. Kenny et al. [11] found that the volume of entorhinal cortical gray matter was reduced in patients with IPD-associated dementia.

No Chinese study has yet measured the volumes of the olfactory bulb and olfaction-associated cortical regions in IPD patients. The aim of the present study was to use high-resolution magnetic resonance imaging (MRI) to measure the volumes of the olfactory bulb and olfactory tract in patients with IPD and MSA, to ask if significant differences were evident between these two groups; to analyze (voxel-by-voxel) the morphologies of olfaction-associated cortical gray matter in; explore whether it was possible to determine disease duration by studying the olfactory systems of both types of patients; and to explore the causes of olfactory impairment in IPD patients.

2. Subjects and methods

2.1. Subjects

Twenty patients diagnosed with PD using the UK Brain Bank criteria were selected from those who attended our Neurology Department from September 2009 to February 2010 [12]. Fourteen MSA patients were diagnosed in the same interval using current guidelines [13], of whom 9 had type P MSA and 5 type C. No patient had experienced brain trauma or rhinitis, and none had a history of sinusitis or a mental illness. All MMSE scores were over 24. Patients with brain tumors, lacunar infarctions, or other organic diseases were excluded by reference to conventional MR scans. The control group consisted of healthy volunteers matched in terms of age, with MMSE scores over 24, without brain trauma, rhinitis, or histories of sinusitis or mental illness. All participants gave written informed consent.

2.2. Methods

2.2.1. Clinical evaluation

The following scales were used for clinical assessment: The Hoehn–Yahr scale to grade the severity of Parkinsonian syndrome; a uniform scale measuring motion in PD patients (the UPDRS III scale); the UPDRS scale yielding total scores; and the MMSE and MOCA scales scoring cognitive functioning. The severity of MSA disease was evaluated using the motion-evaluating section of the uniform MSA instrument (UMSARS II), and the complete UMSARSA. All evaluations were performed by experienced physicians.

2.2.2. MRI

We used a 1.5 T Phillips platform. The following scans were performed on all participants: (1) Olfactory scanning using a 3D-TSE sequence. The parameters were a TR of 4.0 s, a TE of 250 ms, FLIP 90°, a slice thickness of 0.6 mm, no interval between scans, coronal imaging perpendicular to the plate or skull base, and a layer resolution of 0.5 × 0.45; (2) 3D-T1 structural scanning using the T1FFE sequence. The parameters were a TR of 24 ms, a TE of 6 ms, FLIP 30°, an FOV of 230 mm, and a slice thickness of 2 mm. Depending on skull size, 135–145 layers were obtained.

2.2.3. Procedures after imaging

(1) Measurement of olfactory volume was performed on the post-processing workstation of the Phillips platform using the method of Mueller [14]. The olfactory bulb and tract were automatically outlined on every layer by the software, and the volume of each olfactory bulb was calculated by summing the bulb area in every layer multiplied by the length of the olfactory bulb and tract. This work was performed by a neuroscience physician blinded to patient history and clinical assessments. (2) Volume VBM analysis of olfaction-associated gray matter evident in each voxel was performed using the VBM function of the SPM8 imaging package of MatLab 7.1 [15].

All data were format-converted using MRIcro software. Formatted imaging data for each subject were justified using the T1 model in SPM software and spatially normalized. The brain was divided into three sections: The gray and white matter and the CSF. These brain regions were subjected to density justification using both the warping and non-warping features of spatial normalization nonlinear transformation, and next underwent Gaussian smoothing. The voxel values of all sections were summed to form the brain volume subject to density imaging. Differences in gray matter voxel values among groups were compared, as were the probabilities that each voxel value increased or decreased among groups. The summed voxel values are the K values. We used the nonlinear conversion method of the Canada Montreal Neurological Institute, featured in MNI software, to convert Talairach coordinates to a form useful for determination of brain area. Each region of the brain was anatomically delimited using x, y, and z co-ordinates (unit: mm) and relevant brain regions were similarly defined.

Table 1
The clinical characteristics of the patients and control subjects.

	IPD group (n = 20)	MSA group (n = 14)	Normal control (n = 12)
Age (yrs)	59.9 ± 9.1	62.3 ± 8.9	59.9 ± 9.6
Duration (yrs)	6.7 ± 1.7	5.2 ± 1.2	–
Score of left side limb function	13.0 ± 4.6	–	–
Score of left side limb function	11.1 ± 4.0	–	–
UPDRS III score	34.3 ± 9.0	–	–
UPDRS total score	40.9 ± 7.3	–	–
H–Y scales	2.1 ± 0.4	–	–
MMSE score	28.8 ± 1.6	28.6 ± 1.8	28.9 ± 1.5
MOCA score	17.8 ± 6.0	19.8 ± 5.9	22.9 ± 3.8
UMSARS score	–	24.9 ± 7.8	–
UMSARS II score	–	35.1 ± 8.2	–

Table 2
The comparation of the volume of olfactory bulb and tract in IPD, MSA and normal control groups.

Volume of olfactory bulb and tract	IPD group	MSA group	Normal control	p value
Left side volume (mm^3)	27.3 ± 5.6	39.2 ± 2.3	38.1 ± 3.8	0.000[a]
Right side volume (mm^3)	27.8 ± 5.4	37.1 ± 4.9	37.8 ± 5.1	0.000[a]
Total volume (mm^3)	55.1 ± 10.7	73.8 ± 9.1	75.9 ± 8.4	0.000[a]

[a] IPD vs. Normal control, IPD vs. MSA, the left right side and total olfactory volume are significantly different.