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Olfactory performance acts as a cognitive reserve in non-demented patients with Parkinson's disease

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ABSTRACT

Objective: To explore whether olfactory performance acts as a cognitive reserve in non-demented patients with Parkinson's disease (PD).
Methods: Patients with non-demented PD ($n = 119$) underwent T1-weighted MRI and olfactory identification tests. According to their olfactory performance, PD patients were subdivided into three groups of high score (PD-H, $n = 38$), middle score (PD-M, $n = 48$), and low score (PD-L, $n = 33$). We investigated the pattern of gray matter (GM) density according to olfactory performance using voxel-based morphometry (VBM) and analyzed the correlation between GM density and olfactory performance.
Results: No significant differences in demographic characteristics were observed among the groups. A neuropsychological test showed that cognitive deficits in verbal memory function were more severe in the PD-L group than in the PD-H group. However, a VBM analysis revealed that patients in the PD-H group possessed significantly decreased GM density in the bilateral temporal areas, orbitofrontal areas, mesiofrontal areas extending into the cingulate gyrus, and prefrontal areas, compared with patients in the PD-L group. No areas exhibiting a significant difference in GM density were observed between the PD-H and PD-M groups. Olfactory performance in patients with PD was negatively correlated with both the brain GM volume and intracerebral volume; in particular, GM density in the caudate nucleus and putamen exhibited a negative correlation with olfactory performance.
Conclusions: Our data show that a high olfactory performance may compensate GM volume loss in order to minimize the exhibition of cognitive impairment and thus may act as a cognitive reserve in non-demented patients with PD.

Impairment of olfactory function, a common non-motor symptom in patients with Parkinson's disease (PD), may precede the development of parkinsonian motor symptoms. Pathological studies have suggested that together with the enteric plexus, the olfactory system may act as an induction site for α-synuclein, and result in neuropathological changes in the olfactory system early in the course of PD [1,2]. In terms of prognostic significance, olfactory performance seems to be closely related to other non-motor features such as autonomic, sleep, or neuropsychiatric dysfunction, rather than the nigral motor system [3,4]. Of these, recent studies have demonstrated that more severe olfactory impairment was associated with poorer performance in verbal memory and frontal executive tasks, and that diminished olfactory performance in the early course of PD was associated with increased risk for ongoing cognitive decline [5–7]. These data imply that olfactory performance in the early stage of PD may play a modulating role in cognitive performance.

Cognitive reserve (CR) refers to the individual's capacity to withstand pathological changes in order to minimize symptomatology, and thus modulate the threshold of clinical manifestations. Standard proxies for CR include education, intelligence quotient, literacy, occupational complexity, or leisure activities. Brain reserve, a passive component of reserve capacity, has been estimated using brain size or neuronal count [8]. Among patients with Alzheimer's disease (AD) or amnestic mild cognitive impairment (MCI), those with a higher CR display a more severe brain volume deficit, cerebral perfusion or metabolism deficit, and a higher beta amyloid load compared with those with a lower CR [8,9], and there is a negative correlation between reserve capacity and neuroanatomical integrity [10]. Thus, at a particular level of AD pathology,

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individuals with a higher CR are less likely to manifest the clinical symptoms of dementia, but may show a more rapid progression of dementia after the diagnosis of AD.

In the present study, we investigated the pattern of gray matter (GM) density according to olfactory performance using voxel-based morphometry (VBM) and analyzed the correlation between GM density and olfactory performance, to explore whether olfactory performance acts as a CR in patients with non-demented PD.

1. Methods

1.1. Subjects

The participants were 119 non-demented PD patients recruited consecutively between January 2008 to September 2012 at a university hospital. Odor identification was assessed with a Cross-Cultural Smell Identification (CCSI) test [11], which uses 12 pads that release odors when scratched; a high score indicates good olfactory performance. According to the tertile distribution of CCSI scores, subjects with PD were divided into three groups: high score group (CCSI score, ≥ 9, $n = 38$; PD-H), middle score group ($4 <$ CCSI score < 9, $n = 48$; PD-M), and low score group (CCSI score, ≤ 4, $n = 33$; PD-L). PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank [12]. To ensure clinical diagnostic accuracy, only patients who displayed decreased dopamine transporter uptake in the posterior putamen on a [18F]FP-CIT PET scan were included in this study. Motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS-III), and total medication dosages were calculated in levodopa equivalents. Visual hallucination was defined as "repetitive involuntary images of people, animals, or objects" that were experienced as real during the waking state, using the caregiver-based structured interview of the Neuropsychiatric Inventory [13], which was administered by a trained neuropsychologist. The self-rated Beck Depression Inventory (BDI) was used to assess depressive symptoms in patients with PD [14].

The Seoul Neuropsychological Screening Battery (SNSB) [15] was used to evaluate cognitive performance. For these, the quantifiable tests comprised the digit span (forward and backward), the Korean version of the Boston Naming Test, Rey Complex Figure Test (copying, immediate and 20-min delayed recall, and recognition), Seoul Verbal Learning Test (immediate recall, 20-min delayed recall, and recognition), phonemic and semantic Controlled Oral Word Association Test, go-no-go test and contrasting program, and Stroop Test (word and color reading of 112 items during a 2-min period). Abnormal cognitive performance in each cognitive subdomain was defined as a score below the 16th percentile of the norm.

The exclusion criteria for all subjects included: (1) the presence of focal brain lesions, diffuse white matter hyperintensities, or multiple lacunes in the basal ganglia by MRI; (2) compatible clinical diagnostic criteria for probable PD dementia [16] or parkinsonism plus syndromes; (3) history of drugs causing parkinsonism (antipsychotics, gastrointestinal kinetics, antiepileptic drugs, or L-type calcium channel blockers); (4) history of head trauma, nasal fracture, rhinitis, sinusitis, nasal polyp, or history of a recent common cold. Possible medical comorbidities were also excluded by laboratory tests, including thyroid function test, vitamin B12 and folic acid levels, and VDRL test. Healthy age- and gender-matched elderly volunteers were used as controls for the VBM analysis ($n = 50$, age $= 68.7 \pm 4.6$ yr, number of men $= 24$, education duration $= 9.0 \pm 5.8$). Control subjects had no active neurological disorders, no cognitive complaints, and a minimum score of 28 on the Korean version of the Mini-Mental State Examination (K-MMSE). Informed consent was obtained from all patients and control subjects. This study was approved by the Institutional Review Board of our hospital.

1.2. MRI acquisition

All scans of healthy controls and patients with PD were acquired using a Philips 3.0-T scanner (Philips Intera; Philips Medical System, Best, Netherlands) with a SENSE head coil (SENSE factor = 2). Head motion was minimized with restraining foam pads provided by the manufacturer. A high-resolution T1-weighted MRI volume data set was obtained from all subjects, using a 3D T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224×256 matrix; 256×256 reconstructed matrix with 182 slices; 220 mm field of view; $0.98 \times 0.98 \times 1.2$ mm^3 voxels; TE, 4.6 ms; TR, 9.6 ms; flip angle, 8°; and slice gap, 0 mm.

1.3. VBM of gray matter

VBM was conducted using DARTEL [17] in SPM8 software (Institute of Neurology, University College London, UK). A group of GM templates was generated from controls and patients with PD, to which all individual GM was spatially normalized. Spatially normalized GM maps were modulated by the Jacobian determinant of the deformation field to adjust volume changes during nonlinear transformation [18]. The modulated GM maps were smoothed using a 6-mm full-width half-maximum isotropic Gaussian kernel. In order to obtain the intracerebral volume, we performed segmentation of the normalized whole brain MR image into three compartments (GM, white matter, and cerebrospinal fluid), and the intracerebral volume was represented by the sum of the GM, white matter, and cerebrospinal fluid volumes. The total GM volume did not differ among the groups (control, 597 ± 59 cc; PD-H, 593 ± 38 cc; PD-M, 598 ± 48 cc; PD-L, 609 ± 33 cc). Regional volume differences were determined using one-way analysis of variance (ANCOVA) at every voxel in the GM from PD patients and healthy controls, where age and K-MMSE were included as covariates in the analysis of covariance. When analyzing GM density between PD subjects, the disease duration of PD, K-MMSE, and education levels were also included as covariates in ANCOVA. Additionally, using a multiple regression model of covariance with age, disease duration, education duration, and K-MMSE, we searched for a region-specific pattern of GM loss in which GM density correlated with olfactory performance. Statistical significance was determined at an uncorrected $p < 0.001$ with a cluster size >200 mm^3 in the PD group comparison and multiple regression analysis, or a cluster size >100 mm^3 in comparison between controls and PD patients.

1.4. Statistical analysis

One-way analysis of variance followed by post hoc comparisons was used to assess group differences in demographic and neuropsychological characteristics of the PD subjects. The χ^2 test was used for categorical variables. Pearson's correlation was conducted to evaluate the relationship between CCSI scores and intracerebral or GM volume. Statistical analyses were performed using commercially available software (SPSS, Version 13.0), and a two-tailed $p < 0.05$ was considered statistically significant.

2. Results

2.1. Demographic characteristics

The demographic characteristics of the patients are shown in Table 1. No significant differences in age, gender, education level,