Journal of the Neurological Sciences 390 (2018) 231–238

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Reduced gray matter volume is correlated with frontal cognitive and behavioral impairments in Parkinson's disease

Tatsuhiro Terada[a,b,*], Jun Miyata[c], Tomokazu Obi[a], Manabu Kubota[c,d], Miho Yoshizumi[c], Toshiya Murai[c]

[a] Department of Neurology, Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama 886, Aoi-ku, Shizuoka 420-8688, Japan
[b] Department of Biofunctional Imaging, Preeminent Medical Photonics Education & Research Center, Hamamatsu University School of Medicine, Handayama 1-20-1, Higashi-ku, Hamamatsu 431-3192, Japan
[c] Department of Psychiatry, Graduate School of Medicine, Kyoto University,54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
[d] Brain Disorder Translational Research Team, Department of Functional Brain Imaging Research, National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology, Anagawa 4-9-1, Inage-ku, Chiba, 263-8555, Japan

ARTICLE INFO

Keywords:
Behavioral impairment
Frontal assessment battery (FAB)
Frontal cognitive impairment
Frontal systems behavior scale (FrSBe)
Parkinson's disease (PD)
Voxel-based morphometry (VBM)

ABSTRACT

Objective: To identify the brain-volume reductions associated with frontal cognitive and behavioral impairments in Parkinson's disease (PD).
Methods: Forty PD patients without dementia or amnesia (Hoehn and Yahr stage 3) and 10 age-matched controls underwent brain magnetic resonance imaging. Cognitive and behavioral impairments were assessed by using the Frontal Assessment Battery (FAB) and Frontal Systems Behavioral Scale (FrSBe), respectively. We applied voxel-based morphometry to investigate the correlations of regional gray matter volume with FAB, FrSBe, and physical disability.
Results: FAB was significantly lower in PD than in controls. FrSBe was significantly higher after PD onset than before, notably in the apathy subscale. FAB and FrSBe were significantly intercorrelated. In PD patients, left inferior frontal volume was positively correlated with FAB, whereas right precentral volume was negatively correlated with FrSBe total score. The brain volumes in both of these regions were not correlated with the Unified PD Rating Scale III.
Conclusion: Behavioral impairments in PD tended to coexist with progression of frontal cognitive impairment. Regional atrophy within the frontal lobe was associated with both frontal cognitive and behavioral impairments. However, the specific region responsible for behavioral impairment differed from that for frontal cognitive impairment. These associations were independent of physical disability.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons of the substantia nigra; PD is clinically associated with akinesia, tremor, rigidity, and postural instability [1]. In addition to these motor impairments, patients with PD display various cognitive and behavioral impairments, particularly frontal lobe dysfunction, even in the absence of dementia [2]. Previous reports have indicated that the frontal lobe dysfunction in PD might be mediated by frontostriatal circuit dysfunction [2], and recently cortical Lewy bodies have been suggested to be possible substrates for cognitive impairment [1,3]. These results hint at the pathological mechanisms behind the cognitive deficits in PD.

Frontal dysfunction, particularly in the domain of executive function, has been regarded as the primary cognitive impairment in the early stage of PD. However, it has been believed that frontal dysfunction in PD patients does not have a serious effect on daily life [2]. Nevertheless, although individuals with frontal lobe damage might perform within normal limits on screening neuropsychological test batteries, their social and daily behaviors can be impaired [4]. Therefore, when complex and heterogeneous frontal dysfunction is evaluated in PD patients, combined neuropsychological and neurobehavioral assessments are needed to fill the gap between the neuropsychological testing and social and daily behavioral testing. Although some studies have shown that apathy is the predominant behavioral alteration in PD patients [2,5], few measurements are available for assessing apathy in real life, outside the experimental setting.

Several morphologic studies of PD have shown regional cerebral

* Corresponding author at: Department of Neurology, Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama 886, Aoi-ku, Shizuoka 420-8688, Japan.
E-mail address: tatuhiro@hama-med.ac.jp (T. Terada).

https://doi.org/10.1016/j.jns.2018.05.005
Received 18 December 2017; Received in revised form 24 March 2018; Accepted 6 May 2018
Available online 07 May 2018
0022-510X/

atrophy, mainly in the frontal and temporal areas [6,7]. These results support the possibility that there is direct cortical involvement in PD patients with cognitive impairment. Although identifying the specific region responsible for cognitive impairment would provide an important insight into the underlying neural basis of this impairment, the link between cognitive and behavioral deficits in patients with early-stage PD is still unclear. Some studies have investigated the association between frontal dysfunction and brain structural and functional changes in PD patients, but the results have been inconsistent [6,8]. This inconsistency may stem from methodological differences: the patterns of frontal dysfunction may change with disease progression, and inclusion of patients with advanced-stage disease could influence brain imaging and neuropsychological outcomes. In addition, it is always important to control for the effect of physical disability on cognitive and behavioral impairments. However, this effect has not been fully investigated in previous studies.

Our aim here was to investigate frontal cognitive and behavioral disabilities in early-stage PD in a real-life setting, along with their neural correlates. We assessed frontal cognitive impairment in PD patients by using the Frontal Assessment Battery (FAB), which is a brief composite neurocognitive battery designed to evaluate global executive function [9], and the Frontal Systems Behavioral Scale (FrSBe), which captures multifaceted frontal behavioral disorder in real life [10]. To identify the gray matter alterations associated with these frontal cognitive and behavioral impairments, we used voxel-based morphometry (VBM). To exclude the effects of physical impairment, we focused on PD patients at Hoehn and Yahr (HY) stage 3 and excluded patients at the later stages.

2. Materials and methods

2.1. Subjects

Forty subjects with sporadic PD (16 men and 24 women; mean age ± SD, 64.7 ± 8.0 years, mean disease duration 7.4 ± 4.8 years, all right-handed) were recruited from the Shizuoka Institute of Epilepsy and Neurological Disorders (SIEND). Patients were recruited from April 2006 to March 2009. All subjects met the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank [11]. Exclusion criteria were Mini Mental State Examination (MMSE) score of < 24, indicating obvious dementia [12]; Rivermead Behavioral Memory Test (RBMT) score outside the normal range, indicating obvious amnesia; Self-Rating Depression Scale (SDS) score of > 60, indicating obvious depression [13]; cerebrovascular disease; hydrocephalus; brain tumor or traumatic brain injury on brain magnetic resonance imaging (MRI); and meeting the criteria for clinical diagnosis of dementia with Lewy bodies [14]. Furthermore, thirty of forty PD patients including the patients with relatively short disease duration received ^{123}I-MIBG myocardial scintigraphy. None of the patients showed a focal defect in ^{123}I-MIBG uptake, and their delayed H/M ratio of ^{123}I-MIBG uptake were below 2.00, which is cut-off point for differentiating PD from atypical Parkinsonism (mean delayed H/M ratio ± SD, 1.34 ± 0.21; range, 1.07–1.89) [15]. In addition, all patients were followed up for a period of at least six years, and maintained a diagnosis of PD. All patients had not met the criteria for the diagnosis of probable or possible progressive supranuclear palsy [16], corticobasal degeneration [17], and multiple system atrophy [18] during the follow-up period.

Two groups of age-matched healthy controls were recruited (all right-handed) from April 2006 to March 2009. Sixty healthy control subjects (30 men and 30 women; mean age ± SD, 64.4 ± 8.3 years) were recruited for FAB evaluation, and 10 healthy control subjects (5 men and 5 women; mean age ± SD, 67.6 ± 3.2 years) were recruited for VBM analysis. Healthy controls were recruited through personal contacts, which included friends or spouses of patients, but excluded genetically related individuals of the patients. All healthy controls had no neurological problems. They had no history of head injury, psychiatric disease, or serious medical illness or surgery. Their Clinical Dementia Rating was zero, indicating no dementia. No significant differences in age, gender, and behavioral assessment by Clinical Dementia Rating were found between the two control groups.

This study was reviewed and approved by the ethics committee of SIEND. All subjects gave informed consent to participate in the study.

2.2. PD-related physical assessment

All patients were classified by using the HY stage. All subjects met the criteria for HY stage 3 (bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent). Subjects with stage 1 (only unilateral involvement, usually with minimal or no functional disability), 2 (bilateral or midline involvement without impairment of balance), 4 (severely disabling disease; still able to walk or stand unassisted), or 5 (confinement to bed or wheelchair unless aided) were excluded. Thus, all subjects were able to do all activities of daily living with no assistance. PD-related physical impairment in all patients was also evaluated by using the Unified PD Rating Scale III (UPDRS III).

2.3. Frontal cognitive and behavioral evaluation

The FAB is a short neurocognitive battery for the bedside screening of global executive dysfunction. The six subtests of the FAB explore (1) similarity (conceptualization), (2) lexical fluency (mental flexibility), (3) motor series (programming), (4) conflicting instructions (sensitivity to interference), (5) go–no go (inhibitory control), and (6) prehension behavior (environmental autonomy). Each subtest is scored from 0 to 3. The maximum total FAB score obtained by adding the scores in each subscale is 18, and a higher score means better performance. We administered the Japanese version of the FAB to PD patients and age-matched controls; the validity and reliability of this version have been demonstrated [19].

The FrSBe is a 46-item behavior rating scale that captures multifocal real-life frontal behavioral disorder on a questionnaire basis [10]. The reliability and validity of the Japanese version of the FrSBe have been demonstrated to be satisfactory [20]. The FrSBe is designed to assess three major domains of frontal-lobe-mediated behavioral disturbance, namely apathy (14 items), disinhibition (15 items), and executive dysfunction (17 items). We used the family rating of the FrSBe, by a family member who was in regular contact with the patient. Family members were asked to rate each item according to the following 5-point scale: 1 = almost never, 2 = seldom, 3 = sometimes, 4 = frequently, and 5 = almost always. The FrSBe quantified each behavior both before PD onset (retrospective assessment) and after PD onset (current assessment). In each case the total score and three subscale scores—for apathy, disinhibition, and executive dysfunction—were calculated. Raw scores were transformed into standardized T scores adjusted for age and gender, with a mean T score of 50 and standard deviation of 10. Higher scores indicate higher levels of behavioral problems.

2.4. MRI acquisition

Three-dimensional T1-weighted images were acquired on a 1.5-Tesla MRI unit (General Electric Healthcare, Japan) equipped with a standard quadrature head coil. Structural T1 weighted and T2-FLAIR images of all participants were reviewed to exclude potential abnormalities. For the volumetric T1-weighted images, 124 contiguous sagittal sections were obtained by using the following parameters: TR = 17.0 ms, TE = 3.0 ms, flip angle 20°, acquisition matrix = 256 × 192, FOV = 240 mm, section with thickness = 1.3 mm, resolution = 0.9375 mm × 1.25 mm × 1.3 mm.