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Neuropsychological and imaging profile of patients with Parkinson's disease and freezing of gait

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ABSTRACT

Background: Neuropsychological evaluation with advanced neuroimaging may be a useful tool to determine the anatomical substrates that play crucial role in freezing of gait (FOG) in patients with Parkinson's Disease (PD).
Objectives: To compare the cognitive profile and gray matter (GM) changes (using Voxel Based Morphometry – VBM) between patients with PD with and without FOG (FOG+ve and FOG−ve).
Methods: Seventeen FOG+ve (M:F = 11:6) and 21 FOG−ve (M:F = 11:10) were evaluated clinically and with a structured neuropsychological battery. All patients underwent 3 T MRI. In order to determine areas of GM atrophy, T1W volumetric MRI data of the two groups were compared using VBM and Statistical Parametric Mapping 8.
Results: The mean age of FOG+ve and FOG−ve patients were 56.9 ± 6.6 and 47.4 ± 9.1 years respectively. There was no significant difference in the duration (6.0 ± 4.9 vs 5.2 ± 3.5 years, $p < 0.05$) and stage of PD (Hoehn & Yahr stage: 1.96 ± 0.53 vs 1.78 ± 0.37) between the two groups. Compared to the FOG−ve group, the FOG+ve group had (i) significant impairment in memory, attention, executive and visuospatial functions on neuropsychological tests, and (ii) significant GM atrophy in the right cerebellum (pyramis, declive), left cerebrum (Brodmann area (BA) 21 and 22) and right cerebrum (BA 10 and 6) on VBM analysis.
Conclusions: The FOG+ve group showed widespread involvement of cognition localizing to frontal, temporal (especially left) and parietal areas. VBM analysis showed significant GM atrophy in FOG+ve group in left temporal, right frontal areas (coinciding with that observed in neuropsychological tests) and significant involvement of right cerebellum.

1. Introduction

Patients with Parkinson's disease (PD) show two types of gait disorders: a continuous one, which is more or less consistently present and an episodic or paroxysmal one (Freezing of Gait – FOG), which is present intermittently. FOG refers to paroxysmal events, usually lasting seconds, in which a subject is unable to start locomotion (start hesitation), to turn (turning hesitation), to walk through a doorway, or execute a secondary task [1]. For patients with more advanced PD the prevalence of FOG ranges between 20% and 60% of patients [2,3].

The pathophysiology of FOG remains obscure. It has been suggested that the primary underlying dysfunction is related to the inability to execute a programmed complex motor act and results from a disconnection between the frontal lobe and the basal ganglia [4]. Brain activation studies suggested that the medial fronto-parietal cortex, including the supplementary motor area (SMA), is a crucial higher center for bipedal locomotion in humans and impairment of the basal ganglia–thalamus–SMA loop may be involved in gait impairment and freezing in PD [5]. Fling et al. [6] in their fMRI study reported greater connection in FOG patients

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between the higher-order motor cortex (SMA) with the mesencephalic and cerebellum locomotor regions compared to the subthalamic nucleus (STN). They concluded that this observed pattern of altered connectivity in FOG patients may indicate failure of the central nervous system to compensate for the loss of connectivity between the STN and SMA and reflect a loss of automatic control of gait by the basal ganglia. Since a frontal lobe dysfunction or a disconnection between the frontal lobe and basal ganglia has been implicated in FOG, patients with FOG should undergo evaluation of cognitive functions, especially the frontal executive functions and attention.

Voxel-based morphometry (VBM) is a useful tool to assess the structural integrity of the gray matter. In this study we have explored the alterations of cognition using a neuropsychological battery and alterations in gray matter using VBM, in patients with PD with and without FOG.

2. Methods

Thirty eight patients fulfilling the Queens Square brain bank criteria [7] were recruited. Other inclusion criteria included (i) age $\geq$30 years, (ii) >7 years of formal education, (iii) on stable and optimized dosage of medications for PD for at least 4 weeks before entry to study, and (iv) H&Y stage $\leq$3. The exclusion criteria were: (i) clinically significant comorbidities affecting cognition and limiting gait, and (ii) current major depression (DSM-IV criteria). Patients were classified as having freezing of gait (FOG+ve) if they had a score $\geq$1 on the Freezing of Gait Questionnaire (FOGQ) item 3 [8]. There were 17 FOG+ve and 21 FOG−ve patients.

All patients were evaluated with the following scales: (i) modified H&Y staging, (ii) UPDRS part-III (both in medication OFF and ON stages), (iii) FOGQ (iv) Folstein's Mini-Mental Status Examination (MMSE) scale (v) structured neuropsychological battery (vi) Hamilton Anxiety rating scale (HAM-A) and (vii) Hamilton Depression rating scale (HAM-D). The PD patients were categorized into (i) tremor-predominant type, (ii) akinetic-rigid type, and (iii) mixed type according to the method previously reported by Schrag A et al. [9].

2.1. Neuropsychological assessment

All patients were evaluated using a validated structured neuropsychological battery [10], which included (i) story-immediate and delayed recall, (ii) design construction with immediate and delayed recall, (iii) forward and backward digit span, (iv) forward and backwards spatial span, (v) category and letter fluency, (vi) word list-immediate and delayed recall, (vii) Go−no-go test (viii) Frontal Assessment Battery and (ix) Ten Point Clock Test (TPCT). Edinburgh's handedness inventory was used to assess handedness in all subjects.

2.2. Neuroimaging

MRI images were acquired on a Philips Achieva 3.0 T scanner using a SENSE-32 channel head coil. A high-resolution T1-weighted MRI volume data set of the whole brain with a resolution of $1 \times 1 \times 1$ mm^3 was acquired using an MPRAGE (Magnetization Prepared Rapid Gradient Echo) sequence. All scans were inspected visually for any gross structural abnormalities. Whole brain morphometric comparisons between PD FOG+ve and FOG−ve were done. VBM analysis was done using standard method where images were normalized, segmented and modulated followed by smoothening using Gaussian filter of 8 mm at full width half maximum. These normalized, segmented, modulated, and smoothed GM images with a voxel size of 1 mm^3 were used for further statistical analysis. The group comparisons between patients and controls were performed using Analysis of Covariance (ANCOVA), within the framework of general linear model in SPM8. For all SPM analysis we used age, sex, and ICV as nuisance regressors in the design matrix (confounding covariates) and a priori decided significance level of $p < 0.001$. The coordinates of the significant voxels were converted into Talairach space. The total gray matter (GM), white matter (WM) and intracranial volume (ICV) were generated from the VBM analysis. The total brain volumes (TBV) were calculated as the sum of GM and WM volumes.

2.3. Statistical analysis

The demographic and neuropsychological data was analyzed using SPSS software version 16 and a two-sided p value of <0.05 was taken as significant. For continuous variables, mean and standard deviation and for categorical variables, frequency and percentage was employed. Bivariate correlations were performed by means of Spearman's correlation coefficient, using the FOGQ score and each single cognitive test score as variables.

The Institutional Review Board approved the study and all subjects gave written informed consent.

3. Results

FOG+ve group were older than FOG−ve group (56.9 ± 6.6 years vs 47.4 ± 9.1, $p = 0.001$). Approximately 57.8% of patients were men and all were right handed. The mean FOG score was 13.55 ± 2.94 in the FOG+ve group. The FOG+ve group, compared to the FOG−ve group were more often akinetic-rigid type and less commonly tremor-predominant type, though these differences were not statistically significant (Supplementary Table 1). There was a positive correlation between FOG score and age, duration of PD, H&Y stage and UPDRS motor score.

(A) Neuropsychological profile:

The FOG+ve group, compared to FOG−ve group performed worse on the following cognitive tests: (a) memory (b) executive functions (c) visuospatial function and (d) attentional testing. The details are given in Table 1. A negative correlation between FOG score and design construction, phonemic verbal fluency, word list all trials, Go−no-go test score, FAB total score, FAB item 3 score and TPCT was observed.

(B) Neuroimaging:

Table 2 and Fig. 1 show the comparison of VBM data between the FOG+ve and FOG−ve patients. FOG+ve group showed significant GM atrophy of the right cerebellum (pyramis, declive), left cerebrum [middle temporal gyrus (BA 21 and 22)] and right cerebrum [medial frontal gyrus (BA 10) and precentral gyrus (BA 6)].

(i) Correlation between GM volume and Neuropsychological tests:

In each of the two groups of PD patients, correlation analysis was performed between neuropsychological scores and GM volume at $p < 0.05$ (FDR corrected) with 20 voxels threshold and adjusted for age, sex, TBV and duration of illness. The FOG+ve patients had a positive correlation of the GM volume of the right inferior frontal gyrus (BA 47) with the score of the Design Construction delayed recall test, and the GM volumes of the right occipital lobe and lingual gyrus (BA 18) with the score of Go−no-go test 2 (Supplementary Table 2).

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