Cognitive deficits in mild Parkinson's disease are associated with distinct areas of grey matter atrophy

Article in Journal of neurology, neurosurgery, and psychiatry · October 2013
DOI: 10.1136/jnnp-2013-305805 · Source: PubMed

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Cognitive deficits in mild Parkinson’s disease are associated with distinct areas of grey matter atrophy

Elijah Mak,1 Juan Zhou,2 Louis C S Tan,1,3 Wing Lok Au,1,3 Yih Yian Sitoh,4 Nagaendran Kandiah1,3

ABSTRACT

Background and objectives The neuroanatomical substrates underlying cognitive impairment in Parkinson’s disease (PD) remain poorly understood. To address this gap, we compared the grey matter atrophy patterns in PD patients with mild cognitive impairment (PD-MCI) with PD patients having no cognitive impairment (PD-NCI), and examined relationships between atrophic regions and cognitive performance in specific domains.

Methods 90 non-demented PD patients (mean age 64.95±7.54 years, Hoehn and Yahr=1.88±0.39) were classified using formal diagnostic criteria as PD-MCI (n=23) or PD-NCI (n=67). Grey matter volume differences were examined using voxel-based morphometry on structural MRI, and multivariate linear regressions were employed to assess the relationships between cognitive performance in specific domains and atrophic regions.

Results Patients with PD-MCI had lower global cognition scores compared with PD-NCI (Mini Mental State Examination: 26.9 vs28.4, p=0.011; Montreal Cognitive Assessment: 24.5 vs 27.0, p<0.001). The PD-MCI group demonstrated significantly poorer performance on executive function, attention, memory and language abilities. Patients with PD-MCI had reductions in grey matter volumes in the left insular, left superior frontal and left middle temporal areas compared to PD-NCI. Multiple regressions controlling for age, education and cardiovascular risk factors revealed significant positive correlations between left insular atrophy and executive–attention dysfunction.

Conclusions Domain specific cognitive impairment in mild PD is associated with distinct areas of grey matter atrophy. These regions of atrophy are demonstrable early in the disease course and may serve as a biomarker for dementia in PD.

INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disorder typically characterised by motor symptoms including tremor, rigidity, bradykinesia and postural instability. In recent times, however, PD is increasingly recognised not solely as a movement disorder, but as a multi-system disease affecting cognitive and behavioural domains, even in early clinical stages.1 2 The prevalence of dementia in PD ranges from 30% to 90% depending on stage of PD.3 PD patients have been demonstrated to have a sixfold increased risk for the development of dementia compared to non-PD elderly subjects.4 While dementia is frequently a late feature of PD, subcortical cognitive dysfunction can be found early in the disease course, such that PD patients experiencing quantifiable cognitive dysfunction without meeting the criteria for dementia are defined as PD with mild cognitive impairment (PD-MCI).5 6

Taken together, these studies demonstrate that cognitive deterioration is a frequent and progressively incapacitating feature of PD.

Although cognitive impairment is fairly common in PD, patients have diverse cognitive impairment profiles with variable progression rates to dementia.7 In view of the complex clinical picture, the underlying brain pathology leading to cognitive deficits in PD is still poorly understood. As such, the use of neuroimaging analysis to delineate the various risk factors and identify structural differences would confer more insight to current theories. At present, there is much to be elucidated with regard to the aetiology of cognitive impairment in PD. Theories point to striatal dysfunction and global neurotransmitter system deficits while pathological explanations implicate Lewy body degeneration and Alzheimer-type changes.8 9 In this regard, structural MRI is gaining increasing recognition as a viable platform for identification of imaging biomarkers in PD. Despite the lack of consensus due to conflicting results, previous voxel-based morphometric studies have demonstrated that grey matter (GM) atrophy in the limbic system, including the amygdala, hippocampal and parahippocampal cortices is strongly associated with dementia in PD.10 11 The heterogeneity in the progression of dementia in PD is a ripe avenue for further research aiming to identify individual differences and structural biomarkers. Concerted efforts and corroborations of research findings would help to elucidate the pathophysiological mechanisms of cognitive deterioration in PD, and assist in the evaluation of disease treatment and progression.

At present, findings on brain atrophy in non-demented PD patients are inconclusive. This heterogeneity in findings could be due, in part, to cognitively heterogeneous groups of patients, particularly in studies wherein patients with MCI were not distinguished from those with normal cognition. While a few studies have demonstrated atrophy in the medial temporal lobes, amygdala, frontal regions and cerebellum, others have reported no significant GM reductions in non-demented PD populations.10 12–15 To systematically study the pattern of GM atrophy in mild PD and its impact on specific cognitive domains, we employed the recent Movement Disorder Society (MDS) Task Force criteria to classify PD patients to have MCI or to be...
cognitively normal. We hypothesised that PD-MCI patients will have greater impairment in executive function and attention span related to GM atrophy in the frontal lobe.

METHODS

Subjects
The present study included 90 mild PD patients (64.95 ±7.54 years old, disease duration of 5.2±3.91 years, Hoehn and Yahr=1.88±0.39) recruited from August 2011 to March 2012 from a tertiary neurology centre. PD was diagnosed by neurologists trained in movement disorders according to the National Institute of Neurological Disorders and Stroke (NINDS) criteria. Literate PD patients aged between 50 and 90 years with mild PD, defined by Hoehn and Yahr stages of 1–2.5 were included. Patients with dementia, or serious medical and psychiatric co-morbidities were excluded. Demographic, clinical and vascular risk factor data were collected, and a comprehensive clinical assessment was conducted to ascertain cognitive status and functional ability. Motor function was evaluated using the Unified PD Rating Scale (UPDRS) motor scoring. The study was approved by the Centralised Institutional Review Board in Singapore and informed consent was obtained from patients or their legal caregivers.

Neuropsychological assessment
Cognitive performance was evaluated by trained psychologists using a standardised neuropsychological battery. Global cognition was evaluated using the Mini Mental State Examination (MMSE)17 and Montreal Cognitive Assessment (MOCA). As per the recommendations of the MDS Task Force 2012, specific cognitive domains including memory, executive function, visuospatial function, language and attention/working memory were also assessed. Memory was assessed using a Word-List Immediate, Delayed and Recognition Recall; executive function was evaluated with the Frontal Assessment Battery (FAB) and the 10-point clock drawing test; visuospatial function was assessed with a figure copy test and number of errors made on a Maze test; language was assessed with a 20-point object naming test and semantic fluency; attention/working memory was assessed with digit span, colour trails 2 and time taken on a Maze test.20–22 Performances on individual tasks were z-scored. Subsequently, performance index in each cognitive domain was derived from the corresponding averages. To qualify for MDS level 2 criteria for PD-MCI, performance on the suggested five cognitive domains (attention/working memory, executive, language, memory, and visuospatial) were analysed. Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains were required. Impairment was defined as test performance 1.5 SD below appropriate norms. PD patients who did not fulfil criteria for PD-MCI or PD-dementia were classified as PD-NCI (no cognitive impairment).

Image acquisition
All subjects underwent MRI on a 3 Tesla GE scanner system. A high-resolution T1-weighted MP-RAGE (axial acquisition, 176 slices, matrix size=256 x 256, voxel size=1.0 x 1.0 x 1.0 mm3, TE=3.2 ms, TR=7 ms, TI=850 ms, flip angle 8°, field of view 256×256 mm2) was acquired for all patients. Both clinical testing and MRI scanning were done on the same day for all patients.

Image analysis
Optimised voxel-based morphometry (Statistical Parametric Mapping software; SPM8) in MATLAB 2010 was utilised to perform whole-brain voxel-wise statistical analysis of GM volume. First, segmentation of the brain tissues was conducted in original space using the analysis of likelihood of each voxel of the brain images to be classified as GM, white matter (WM) or cerebrospinal fluid. Second, to create the customised group-specific template, the T1 high-resolution structural GM images for all participants were averaged after normalising to the standard Montreal Neurological Institute (MNI) stereotactic space. The segmented GM images using the customised template were then modulated and smoothed using an 8-mm kernel to improve signal to noise and ensure that the assumptions underlying Gaussian random fields theory were met. To examine brain regions with significant group differences in GM volumes, a two-sample t-test between PD-MCI and PD-NCI was performed and significant clusters were reported by thresholding at p<0.001, uncorrected, with minimum cluster size of 172 voxels. Age, gender and total intracranial volume (TIV) were included as nuisance variables.

Statistical analysis
Group comparisons of demographics and neuropsychological variables were performed using STATA12. Differences between groups on normally distributed continuous variables (age, Hoehn and Yahr, duration of PD) were assessed using the Student t test. The distribution of education years and cognitive performances did not follow a normal distribution, so the non-parametric Mann–Whitney test was used. χ2 tests were used on categorical variables (gender and vascular risk factors). Significance level of all tests was set at p<0.05.

To examine the correlation between GM volume and domain-specific cognitive functions in PD-MCI, we defined a set of regions of interest with reduced GM volume in PD-MCI compared to PD-NCI. Then, we extracted the subject-level mean GM volumes for these identified clusters from the modulated and smoothed GM maps using the Marsbar toolbox for SPM8 toolbox.24 Multiple regression analyses were performed to estimate the extent to which GM volume at the identified regions of interest contributed to the variance in performances in each cognitive domain (executive function, attention, memory, visuospatial ability and language) across all PD patients. Separate models were created for each region, with GM volume as the dependent variable. All regression analyses were controlled for age, education years, cardiovascular risk factors, gender and total brain volume.

RESULTS

Demographics and neuropsychological assessments
A total of 90 participants were included: PD-MCI (N=24) and PD-NCI (N=66). Table 1 presents the demographic and clinical characteristics. Age was significantly different between the two groups (p=0.002). The mean disease duration was 4.83 (SD 2.7) years in the PD-MCI group and 5.32 (SD 4.27) in the PD-NCI group (p=0.971). We found no significant differences in gender, education and Hoehn and Yahr stages. The incidence of diabetes mellitus (p=0.003) and hyperlipidaemia (p=0.048) was significantly higher in the PD-MCI compared to the PD-NCI group, while other cardiovascular risk factors (hypertension and smoking) were not significantly different. None of the patients were on acetylcholinesterase inhibitors and the levodopa equivalent dose was not significantly different between the two groups (510 vs 558 mg, p=0.728). As expected, patients with PD-MCI had lower global cognition scores compared with PD-NCI (MMSE: p=0.011; MOCA: p<0.001). With the exception of visuospatial ability, the PD-MCI group had significantly lower performance compared to PD-NCI patients.
PD-MCI had more GM volume than patients with PD-NCI at the same threshold (table 2). For all three regions, the volumes were significantly lower among PD-MCI patients (table 3). The left insular region was most atrophic, followed by the left superior frontal gyrus and left medial temporal gyrus. Compared to mean volumes in the PD-NCI group, 83% of PD-MCI subjects demonstrated reduced volumes in all three regions.

**GM atrophy correlated with reduced cognitive functions in PD patients**

Regression analyses controlling for age, education years and cardiovascular risk factors revealed significant correlations between GM volumes in the previously identified regions of interest and performance across several cognitive domains. Reduced GM volume at the left insular gyrus was associated with disruptions in executive function and attention; the left middle temporal gyrus atrophy was associated with decreased executive function, attention and memory performance; and the left superior frontal gyrus was solely associated with attention (table 4).

**DISCUSSION**

The specific neuroanatomical changes underlying preclinical cognitive impairment in mild stages of PD have not been comprehensively evaluated. In this prospective study, we examined GM volume changes in mild PD patients with and without MCI. Consistent with our hypothesis that patients with PD-MCI will demonstrate impairment in executive–attention related to atrophy in frontal lobe, our findings demonstrate reduced GM volume in the left insular, left superior frontal and left middle temporal areas in patients with PD-MCI compared to PD-NCI. We also identified significant associations between deficits in specific cognitive domains and specific areas of GM volume loss among our patients with mild PD. Insular atrophy was significantly associated with impaired executive function and attention; the left middle temporal gyrus atrophy was associated with impaired executive function, attention and memory; and the superior frontal gyrus atrophy was solely associated with impaired attention.

These novel findings add to the growing literature of structural abnormalities underlying cognitive deficits in early PD. Several studies evaluating patterns of brain atrophy among PD patients with established dementia have demonstrated extensive loss of GM in the insular, middle temporal and frontal areas. In the current study we found GM atrophy in similar brain regions at the stage of PD-MCI. This suggests that atrophy of specific GM regions begins early in the course of PD cognitive impairment and thus may emerge as a biomarker for PD dementia. More

**Table 1** Demographic and neuropsychological characteristics of Parkinson’s disease (PD) patients with no cognitive impairment (PD-NCI) and PD patients with mild cognitive impairment (PD-MCI)

<table>
<thead>
<tr>
<th></th>
<th>PD-MCI (N=24)</th>
<th>PD-NCI (N=66)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Age, years (mean, SD)</td>
<td>68.99 (6.09)</td>
<td>63.48 (7.53)</td>
<td>0.002*</td>
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<td>Gender, female (%)</td>
<td>25</td>
<td>28.79</td>
<td>0.723**</td>
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<td>Education, years (mean, SD)</td>
<td>9.40 (3.52)</td>
<td>10.88 (3.10)</td>
<td>0.055***</td>
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<td>Clinical information</td>
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<td></td>
<td></td>
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<tr>
<td>Hoehn and Yahr (mean, SD)</td>
<td>1.81 (0.44)</td>
<td>1.91 (0.37)</td>
<td>0.324*</td>
</tr>
<tr>
<td>Duration of PD, years (mean, SD)</td>
<td>4.83 (2.70)</td>
<td>5.32 (4.27)</td>
<td>0.971*</td>
</tr>
<tr>
<td>UPDRS-Motor (mean, SD)</td>
<td>19.96 (8.55)</td>
<td>17.44 (7.02)</td>
<td>0.159*</td>
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<td>Vascular risk factors (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>33.33</td>
<td>7.81</td>
<td>0.003**</td>
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<tr>
<td>Hypertension</td>
<td>50</td>
<td>31.25</td>
<td>0.103**</td>
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<td>Hyperlipidaemia</td>
<td>54.17</td>
<td>32.30</td>
<td>0.048**</td>
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<td>Smoking</td>
<td>25</td>
<td>23.44</td>
<td>0.878**</td>
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<td>Global cognition</td>
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<td>MMSE (mean, SD)</td>
<td>26.91 (2.47)</td>
<td>28.36 (1.62)</td>
<td>0.011*</td>
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<tr>
<td>MOCA (mean, SD)</td>
<td>24.5 (2.43)</td>
<td>26.99 (2.87)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Cognitive domains (standardised z scores)</td>
<td></td>
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<td></td>
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<tr>
<td>Executive function</td>
<td>−0.95 (1.39)</td>
<td>0.41 (1.40)</td>
<td>0.002***</td>
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<td>Attention</td>
<td>−1.87 (2.36)</td>
<td>0.75 (1.76)</td>
<td>0.000***</td>
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<td>Memory</td>
<td>−0.61 (1.44)</td>
<td>0.21 (1.60)</td>
<td>0.010***</td>
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<tr>
<td>Visuospatial ability</td>
<td>−0.13 (1.38)</td>
<td>0.04 (1.78)</td>
<td>0.207***</td>
</tr>
<tr>
<td>Language</td>
<td>−1.00 (1.60)</td>
<td>0.40 (1.46)</td>
<td>0.000***</td>
</tr>
</tbody>
</table>

*p value from t-test, **p value from the χ² test, ***p value from a Mann–Whitney test, all significance set to p<0.05.

MMSE, Folstein Mini-Mental State Exam, range: 0–30; MOCA, Montreal Cognitive Assessment, range: 0–30; UPDRS: Unified Parkinson’s Disease Rating Scale; Executive function: FAB and clock; Attention: cite; Memory: immediate and delayed recall; Visuospatial ability: cite; Language: verbal fluency.

demonstrated significantly poorer performance on executive functioning, attention, memory and language abilities (table 1).

**Reduced GM volume in frontal and temporal regions in PD-MCI compared to PD-NCI**

At a threshold of p<0.001 (uncorrected for multiple comparisons, cluster extent 172 contiguous voxels), patients with PD-MCI had reductions in GM volumes in the left insular, left superior frontal and left middle temporal areas compared to PD-NCI (figure 1). We found no areas where patients with PD-MCI had more GM volume than patients with PD-NCI.

**Figure 1** Areas of reduced grey matter volume in patients with Parkinson’s disease (PD) and mild cognitive impairment compared with patients with PD and no cognitive impairment. Significant reductions in grey matter volume are found in: (A) left superior frontal gyrus (LSFG); (B) left medial temporal gyrus (LMTG); and (C) left insular (LI) area at p<0.001 uncorrected cluster size 172. L, left side.
importantly, the left insular area was associated with impaired executive function, attention and language abilities; the left middle temporal area was associated with impaired executive function, attention and memory; and the left superior frontal area was solely associated with impaired attention. In a previous study, atrophy of the insular region was associated with executive dysfunction, and in conjunction with findings from our study, suggests that atrophy of the left insular area may have a major impact on executive function among patients with mild PD.29 Other studies investigating cerebral changes in relation to cognitive impairment in PD have demonstrated that the hippocampal atrophy and WM damage are associated with cognitive impairment in PD.30 31 Our findings add to the literature on the specific brain changes in the pathophysiology of cognitive impairment in PD. While patients with PD-MCI had a higher prevalence of diabetes mellitus and hyperlipidaemia, based on existing literature it is unlikely that these two vascular risk factors had an influence on cognitive performance.32

The insular, middle temporal gyrus along with the ventral stream of the fronto-parietal pathways have been demonstrated to have an important role in working memory and executive function.33 This ventral stream is activated during attention shifting, interference resolution and strategic organisation.34 Our finding of the significant association between insular-middle temporal gyrus atrophy with executive and attention deficits among patients with PD-MCI suggests early disruption to the ventral fronto-parietal pathway as a likely mechanism for the cognitive impairment seen in PD.

The strengths of this study include the use of new robust criteria to define PD-MCI and the relatively large sample size with both structural brain measures and comprehensive neuropsychological assessments. However, our study was limited by absence of PD patients with established dementia and healthy controls.

| Table 2  | Anatomical locations of areas of reduced grey matter in patients with Parkinson’s disease with mild cognitive impairment compared with no cognitive impairment |
|------------------|---------------------------------|------------------|------------------|------------------|
| Brain regions    | Hemisphere | Cluster size | Cluster in GM (%) | X    | Y    | Z    | T score |
| Insular          | L          | 760          | 98.89             | −36  | 20   | −9   | 4.26    |
| Middle temporal  | L          | 241          | 85.48             | −44  | −4   | −17  | 4.09    |
| Superior frontal g | L          | 667          | 99.29             | −12  | 48   | 25   | 4.02    |

L, left. The coordinates X, Y and Z refer to the anatomical location, indicating standard stereotactic space as defined in Montreal Neurological Institute (MNI) space. All reported voxels were p<0.001, uncorrected, with minimum cluster size of 172 voxels. Cluster in GM represents the percentage of voxels within the identified cluster belonging to grey matter (GM).

| Table 3  | Grey matter volume of the three regions of interest among PD-MCI and PD-NCI patients |
|------------------|---------------------------------|------------------|------------------|------------------|
| Brain regions    | PD-MCI Mean | SD | PD-NCI Mean | SD | p Value |
| Left insular     | 0.54          | 0.07 | 0.60          | 0.05 | <0.001 |
| Left middle temporal gyrus | 0.39          | 0.03 | 0.43          | 0.03 | <0.001 |
| Left superior frontal gyrus | 0.36          | 0.03 | 0.32          | 0.04 | <0.001 |

MCI, mild cognitive impairment; NCI, no cognitive impairment; PD, Parkinson’s disease.
for comparison. This constraint prevented us from exploring the associations between atrophy and cognitive dysfunction across different cognitive stages. The higher age in the PD-MCI group compared to the PD-NCI subjects may have contributed to the greater atrophy in brain regions in the PD-MCI group. Despite correcting for age difference in our statistical model, we acknowledge that the findings have to be interpreted taking into consideration the age difference. Another limitation is that our results from GM analyses did not persist after correction for multiple comparisons. Nevertheless, this study has identified specific areas of GM atrophy which are robustly correlated to deficits in specific cognitive domains. These findings will need to be confirmed in larger prospective studies. The correlation between the degrees of atrophy in these three regions with the stage of PD will also need to be studied in larger cohorts.

In summary, within a group of non-demented mild PD patients, we demonstrated distinct GM atrophy patterns in the PD-MCI group compared to the PD-NCI group. We also showed an association between the regions of GM atrophy and impairment in executive function, attention, memory and language function. With growing recognition of PD-MCI as a clinically significant condition in PD, our findings warrant the continued concerted efforts to validate biomarkers of neurodegeneration associated with MCI. The early delineation of PD-MCI from PD-NCI will elucidate the processes underlying cognitive decline in PD. Further longitudinal research is needed to examine whether these regions continue to contribute to cognitive dysfunction as the disease progresses. Structural MRI can potentially emerge as a sensitive and reliable neuroimaging biomarker for dementia in PD.

Contributors NK contributed to the design of the study, statistical analysis, interpretation of the data and drafting of the manuscript. EM contributed to statistical analysis, interpretation of the data and drafting of the manuscript. JZ contributed to statistical analysis, interpretation of the data and revising the manuscript for intellectual content. WLA, YYS and LCST contributed to revising the manuscript for intellectual content.

Funding This research was supported by the Singapore National Research Foundation and was administered by the Singapore Ministry of Health’s National Medical Research Council.

Competing interests NK has received honoraria and CME sponsorship from Lundbeck, Novartis and Eisai. He has also received research funding from the Singapore Health Foundation, Media Development Authority of Singapore, National Medical Research Council of Singapore and Biomedical Research Council of Singapore. LCST has received research support from the Singapore Millennium Foundation and funding for conference travel from GlaxoSmithKline Pte Ltd.

Patient consent Obtained.

Ethics approval This study was approved by the Centralised Institutional Review Board in Singapore.

Provenance and peer review Not commissioned; externally peer reviewed.

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*J Neurol Neurosurg Psychiatry* 2014 85: 576-580 originally published online October 16, 2013
doi: 10.1136/jnnp-2013-305805

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