Volumetric Brain MRI changes in Parkinson's disease

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Aims and objectives

Parkinson's disease (PD) is a common progressive neurodegenerative disorder usually affecting people older than forty years and its incidence is progressively increasing with advancing age(1).

Idiopathic Parkinson's disease (PD) is commonly defined as a hypokinetic movement disorder. It is the second most common neurodegenerative disorder following Alzheimer's disease(2).

It is characterized by four cardinal features bradykinesia, rigidity, resting tremors and postural instability. Previously, it was regarded as a pure motor disease, PD is now considered a multisystem brain disease with various non motor aspects including cognitive dysfunction(3), behavioral, autonomic, sleep related dysfunctions, sensory and sensorimotor dysfunctions(4).

Cognitive dysfunction in Parkinson’s disease is ranging from mild cognitive impairment to genuine dementia(5). Mild cognitive impairment (MCI) is defined as a transitional stage between cognitive changes of normal aging and early dementia or a stage during which subjects experiencing subtle cognitive deficits with largely intact cognition and activities of daily living(6).

MCI is characterized by different clinical and etiological heterogeneity. Parkinson's disease mild cognitive impairment is defined as impairment of at least one domain of neuropsychological tests respecting individual complaints(7).

Incidence of MCI in Parkinson's disease ranges between 19% to 36% based on neuropsychological tests and neuroimaging research. Mild cognitive impairment in Parkinson's disease may progress to dementia in 24% to 31% of patients(8).

Identifying individuals who are predisposed to develop cognitive impairment in PD at early stages will allow physicians to better assess and detect potential neuroprotective or neurorestorative therapies and secondary prevention efforts of dementia might be expected to have their greatest impact during the earliest phases of the disease process(9).

The striatum, i.e. the caudate and putamen, is the major input structure of the basal ganglia complex and is an essential part of neural networks involved in motor and nonmotor function(10). In Parkinson's disease there is severe impairment of its function, that causes loss of the neuromodulatory influence of ventral midbrain dopamine producing neurons with disruption of the balance of multiple corticostriatal circuits(11).

It is unclear whether PD also produces gross morphological, i.e. volumetric, changes in the striatum(11). Motor and non-motor (cognitive and behavioral) dysfunction may in part
reflect anatomical changes at the level of the putamen (motor) and caudate (oculomotor, cognitive and behavioral). Several previous studies using MRI reported decreased or non significant volume differences for striatal structures using manual or semi-automated tracing methods (12-14).

Hence the aim of this research was to investigate the role of Volumetric brain MRI in PD patients with and without dementia and related these structural changes to global cognitive status and memory performance. Early diagnosis of PD-MCI (Parkinson's Disease Mild Cognitive Impairment) may lead to prevention of PDD (Parkinson's Disease related Dementia) or even recovery into normal cognition and so decrease the burden on medical health service.
Methods and materials

Twenty participants (drug naive patients of Parkinson's disease) meeting the criteria of United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (UKPDSBBCDC) were participated in this study.

Participants (13 female and 7 male) were recruited from neuropsychiatry department, Tanta university hospital. The volunteers represent cognitively intact Parkinson's disease patients (PD-NC) and Parkinson's disease with mild cognitive impairment (PD-MCI) patients aged above 20 years.

The control group comprised ten healthy volunteers matched to the whole PD sample for age, level of education and sex.

Exclusion criteria:

1) Patients with other causes of Parkinsonism like secondary Parkinsonism, patients with evident dementia and advanced systemic disease affecting cognition like hepatic impairment and renal impairment.

2) Neuroradiological screening excluded two patients and one control participant due to moderate to severe white matter disease and another three PD subjects were excluded due to motion corrupted MR images.

Methodology, diagnostic criteria and assessment:

I: Mini-Mental State Examination (MMSE)(15)

II: Parkinson's Disease Cognitive Rating Scale (PD-CRS)(16)

1. 'Subcortical-type' cognitive items:

   - Attention/executive functions:

   - Verbal fluency (VF) and cognitive flexibilityfunctions:

   - Verbal memory functions:

   - Visuoconstructional skills /Clock drawing /Visuospatial functions:

2. 'Cortical-type' cognitive items:

   - Confrontation naming:

   - Visuoperceptual skills/Copy of a clock:
III: Hoehn and Yahr scale (HY scale)(17)

**Neuroimaging (volumetric MRI):**

MRI data preprocessing:

A semiautomatic method was used as it combine the automatic techniques with a prior operator knowledge of the grey matter location, anatomical boundaries, and shape. This method uses the powerful and flexible capability of deformable models.

Image acquisition and postprocessing:

Images were acquired with a 1.5-tesla General Electric scanner (GE Medical Systems, Milwaukee) with quadrature head coil (8 channel). Sedation was needed for five patients (for uncooperative patients and involuntary movements)

Using a three-dimensional magnetization prepared rapid acquisition Fourier transform spoiled gradient-recalled acquisition sequence was used that resulted in a coronal series of contiguous 1.5 mm images throughout the brain perpendicular to the anterior commissure-posterior commissure line and averaged after off-line motion correction. Standard neuroanatomical landmarks (such as the orbits, sulci and the commissures) were used to correct for possible deviations in any of the orthogonal planes. The following parameters were used for the spoiled gradient recalled images: echo time (TE) =3 msec, repetition time (TR)=25 msec, repetition=1, nutation angle=45°, field of view=24 cm, acquisition matrix=256×256×124, voxel dimensions=0.9375×0.9375×3 mm, resolution 1mm×1mm ×1 mm). This protocol resulted in high-spatial-resolution images with excellent gray white matter contrast, and it was used for measuring by means of manual tracing of specific gray matter (hippocampus, caudate, putamen and DLPF cortex) and third ventricle regions of interest.

Volumetric analysis of the hippocampus, caudate nucleus, putamen and Dorsolateral prefrontal cortex (DLPFC) was performed using 3D Slicer version 4.2.2-1 software which is a multiplatform, free an open source software package for visualization and medical image computing developed by Harvard University and approved for medical research.

The grey matter and the third ventricle were segmented in a semi-automatic way by tracing their outlines manually, and the software was preset not to exceed the outlines of the region of interest by assigning the MR numbers of the tissues subject of study. After each of the slices of the brain with the nuclei or regions of interest were segmented, a quantification process was run which rendered the volume of the structure in focus as well as a 3 dimensional graphical model of it. The data is validated by comparison with SPL-PNL brain atlas (developed by Talos et al.2008)(18).

**Measurement of the hippocampal volume ROI analysis:** Tracing of the hippocampus started rostrally where the hippocampus first appears below the amygdala and ended posteriorly in the section where the crura of the fornices depart from the lateral wall of the
lateral ventricles. The hippocampus included the dentate gyrus, the hippocampus proper and the subicular complex

**Putamen ROI:** Tracing of the putamen began in first slice in which the putamen was clearly separated from the head of the caudate by the anterior limb of the internal capsule. Tracing continued on sequential slices for as long as a clearly distinguishable patch of grey matter was visible below the corona radiata. The globus pallidus and anterior limb of the internal capsule served as the medial border and the external capsule as the lateral border. Care was taken to ensure the claustrum was excluded.

**Caudate nucleus ROI:** The caudate was divided into two parts, head and body, which were traced separately. Tracing of the head of the caudate began in the first slice in which the internal capsule clearly separates the caudate from the putamen and in which the cavity of the lateral ventricle was visible.

The boundary between the caudate head and body was defined, in the coronal view, as the first slice in which the interventricular foramen was present, i.e. when the cavities of the lateral and third ventricle were seen to be continuous.

The medial border of the caudate was the cavity of the lateral ventricle. The lateral and superior borders of the caudate were the white matter of the internal capsule and corona radiata, respectively.

**Dorso-lateral prefrontal cortex (DLPFC) ROI:** The adopted anatomical landmarks for areas 9 and 46 (plus transitional areas 9-8, 9-45, 46-10, and 46-45), area 9 is consistently located in the superior frontal gyrus, whereas area 46 can be found in the middle frontal gyrus. Tracing start on the slice located immediately anterior to the most rostral one where corpus callosum could be seen. Tracing was performed from posterior to anterior and continued until the most anterior slice where the superior and middle frontal gyrus could be distinguished, until the slice immediately posterior to the first one where the frontal pole could be visualized, since this region has been previously adopted as the anterior border of DLPFC. This landmark corresponds approximately to the cytoarchitectonic border between Brodmann's area 10 and 9.

Afterwards, a line was traced from the tip of the superior frontal gyrus to the bottom of the superior frontal sulcus, in order to delineate the medial and lateral portions of area 9. The medial and lateral parts of area 9 are located on the medial and lateral hemisphere surfaces respectively, and they differ by their fine cytoarchitectonic features. The volume of the medial portion was subtracted from the total to calculate the DLPFC volume.

**Third ventricle ROI measurement:** It is a median cleft between the two thalami and is bounded laterally by them and the hypothalamus. Its anterior wall is formed by the lamina terminalis. There are two protrusions on the anterior surface of the third ventricle: supra-optic recess (above the optic chiasm) and the infundibular recess (above the pituitary stalk). It communicates with the lateral ventricles via the foramen of Monro.
(interventricular foramen) and with the fourth ventricle via the aqueduct of Sylvius (cerebral aqueduct).
Results

The study was conducted on 20 patients with Parkinson's disease and 10 healthy matched volunteers as a control group.

Grey matter volumes which included right and left caudate, left putamen, and left hippocampus were significantly lower in PD patients than control group. Also dorso-lateral prefrontal cortex was lower in PD patient than control but insignificant. Third ventricular dilatation was markedly affected in PD patients than control (p=0.0001). Grey matter atrophy was observed in left hemisphere than right which is opposite to the control (table 1).

Positive correlation when comparing grey matter volumes with MMSE. While negative correlation when comparing with third ventricular volume in parkinson's group, but this correlation was insignificant (table 2).

{*Significant (P<0.05) r=Correlation Coefficient*}

There was negative insignificant correlation between both putamen, hippocampus, DLPFC and severity of disease according to Hoehn and Yahr staging scale of the studied patients with PD, also third ventricular dilatation increase progressively with increase severity of disease (table 3).

There was positive significant correlation between left DLPFC and Right putamen and total score of PD-CRS which mean that the subcortical items affected more in PD patient (table 4,5).

Case: a Parkinson’s diseased male patient aged 55 year complains of 4 year onset of both right tremor and bradykinesia dominant complaints, Hoehn and Yahr scale equals 2, MMSE=29\30, PD-CRS =123\134 affected mainly in working memory

Volumetric MRI show mild grey matter atrophy in the left hemisphere and third ventricular enlargement relative to control subjects (figure 2, 3).
**Table 1:** Mean volume of grey matter at different sites and third ventricle of the studied patients with Parkinson’s disease (PD) and the control group.

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<table>
<thead>
<tr>
<th></th>
<th>Patients with Parkinson's disease (n=20)</th>
<th>Control group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>3rd ventricle</td>
<td>0.74</td>
<td>0.530</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>1.35</td>
<td>0.827</td>
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<tr>
<td>Right hippocampus</td>
<td>1.57</td>
<td>0.613</td>
</tr>
<tr>
<td>Left putamen</td>
<td>1.67</td>
<td>0.142</td>
</tr>
<tr>
<td>Right putamen</td>
<td>2.57</td>
<td>0.104</td>
</tr>
<tr>
<td>Left caudate</td>
<td>0.120</td>
<td>0.171</td>
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<tr>
<td>Right caudate</td>
<td>0.318</td>
<td>0.077</td>
</tr>
<tr>
<td>3rd ventricle volume</td>
<td>-0.353</td>
<td>0.127</td>
</tr>
</tbody>
</table>

**Table 2:** Correlation between studied volumes and total scores of Mini Mental State Examination (MMSE).
### Table 3: Correlation between studied volumes and severity of disease (Hoehn and Yahr staging scale).

<table>
<thead>
<tr>
<th>Volume of grey matter at different sites &amp; 3rd ventricle</th>
<th>Severity of disease according to Hoehn and Yahr staging scale of the studied patients with PD (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Right caudate</td>
<td>0.015</td>
</tr>
<tr>
<td>Left caudate</td>
<td>0.094</td>
</tr>
<tr>
<td>Right putamen</td>
<td>-0.075</td>
</tr>
<tr>
<td>Left putamen</td>
<td>-0.070</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>-0.046</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>-0.163</td>
</tr>
<tr>
<td>R. DLPFC</td>
<td>-0.075</td>
</tr>
<tr>
<td>L. DLPFC</td>
<td>-0.142</td>
</tr>
<tr>
<td>3rd ventricle volume</td>
<td>0.155</td>
</tr>
</tbody>
</table>

### Table 4: Correlation between studied volumes and total scores of Parkinson Disease Cognitive Rating Scale (PD-CRS) among the studied patients with Parkinson's disease (PD) and the control group.

<table>
<thead>
<tr>
<th>Studied Volumes</th>
<th>PDCRS total scores of the study subjects (n=30)</th>
<th>Patients with Parkinson's disease (n=20)</th>
<th>Control group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Right caudate</td>
<td>0.018</td>
<td>0.939</td>
<td>0.372</td>
</tr>
<tr>
<td>Left caudate</td>
<td>-0.162</td>
<td>0.496</td>
<td>0.755</td>
</tr>
<tr>
<td>Right putamen</td>
<td>0.487</td>
<td>0.029*</td>
<td>0.389</td>
</tr>
<tr>
<td>Left putamen</td>
<td>0.153</td>
<td>0.518</td>
<td>0.076</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>0.388</td>
<td>0.091</td>
<td>-0.312</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>0.342</td>
<td>0.140</td>
<td>-0.109</td>
</tr>
<tr>
<td>R. DLPFC</td>
<td>0.418</td>
<td>0.067</td>
<td>0.205</td>
</tr>
<tr>
<td>L. DLPFC</td>
<td>0.504</td>
<td>0.023*</td>
<td>0.208</td>
</tr>
<tr>
<td>3rd ventricle volume</td>
<td>-0.254</td>
<td>0.279</td>
<td>-0.247</td>
</tr>
</tbody>
</table>
Table 5: Correlation between right putamen and left DLPFC and total scores of Parkinson's Disease Cognitive Rating Scale (PD-CRS) among the studied patients with Parkinson's disease (PD)

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**Fig. 1:** volumetric MRI tracing bilateral caudate and DLPFC, and third ventricle

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**Fig. 2:** volumetric MRI tracing bilateral putamen nuclei and hippocampi

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Conclusion

Parkinsonism is a neurological syndrome characterized by tremors, bradykinesia, rigidity, and postural instability(1).

The continuing evolution of new techniques for imaging the central nervous system has produced significant advances in the investigation of patients with neurodegenerative disorders and in our understanding of basal ganglia function. Although magnetic resonance imaging (MRI) has made possible the correlation of structural abnormalities identified in vivo with specific neurologic syndromes such as parkinsonism, changes in cerebral function do not always parallel changes in structure (4).

When comparing grey matter volume in PD patients and control subjects using volumetric MRI, the result is significantly lower in PD patients than in the control subjects. Grey matter volume which include right and left caudate (p=0.0001), left putamen (p=0.004) and left hippocampus (p=0.011) are significantly lower in PD patients than control. This means affection of different cognitive loops that are interconnected, also dorso-lateral prefrontal cortex are lower in PD patient than control but insignificant.

Third ventricular dilatation is markedly affected in PD patients than in the control (p=0.0001) and there is a negative correlation between third ventricular volume and recall more manifest in PD patients than control. It is also mentioned by Camicioli et al (19) and Apostolova et al (20) who studied ventricular dilatation and brain atrophy in patients with Parkinson's disease with incipient dementia and found that there was ventricular enlargement in non-amnestic MCI type which include visuospatial (unprompted clock drawing) and attention and executive dysfunction than in control subjects.

Regarding psychometric study, MMSE used as screening test to exclude demented PD patient and comparing Parkinson's disease non demented patients (PD ND) or patients with PD-MCI with the control group. It is found that PD patient are more affected regarding attention and calculation (mean = 4.05±1.05) when comparing them with the control group (mean = 4.30±0.67).

Most of PD patients show non-amnestic MCI subtypes when comparing them with the control subjects matched with Janvin et al (5). Regarding the total score of mini-mental state examination (MMSE) of PD patient and control group, no significant difference is found. This is matching with the results detected by Pennanen, (21).

There is a negative insignificant correlation between both putamen, hippocampus and DLPFC and severity of disease according to Hoehn and Yahr staging scale of the studied patients with PD (P>0.05), also third ventricular dilatation increase progressively with increase severity of disease manifested more in stage III as mentioned by Beyer et al (22) and Nishio et al (23) who studied the magnetic resonance imaging of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based.
morphometry and found that, there is a corticolimbic grey matter loss in Parkinson's disease without dementia.

Apostolova et al (20) and Pitcher et al (11) studies found that there was a negative significant correlation between right and left putamen, right and left hippocampus and right and left DLPFC and severity of disease according to Hoehn and Yahr staging scale of the studied patients with PD. This significant correlation is due to sample size, interslice gap and using 3 tesla MRI device but most of their patients were medicated and PD-MCI patients are more liable to the medication side effects than PD-NC and PDD and control.

There is a positive significant correlation between left DLPFC($r=0.504$, $p=0.023$) and right putamen($r=0.487$, $p=0.029$) and total score of PD-CRS so executive function affected more in PD patients ,while in control group left caudate correlate positively with PD-CRS coincides with Apostolova et al (20) who studied grey matter volume and ventricular changes in Parkinson's disease mild cognitive impairment. While grey matter volume of left putamen, right and left hippocampus, right and left caudate and right DLPFC show positive but insignificant correlation with the total score of PD-CRS.

**CONCLUSION:**

Volumetric MRI has the potential to evaluate, in a noninvasive fashion, structural changes in PD and could potentially be a useful indicator of PD in the early stage and correlated with the severity of clinical findings. Early diagnosis of PD-MCI may lead to prevention of PDD or even recovery into normal cognition and so decrease the burden on medical health service.

**Recommendation:**

PD-CRS should be applied to every PD patient to detect cognitive impairment and prevent its progression and helps in patient follow up.

Volumetric MRI region of interest analysis should be applied to every patient even with normal cognition to be a base for follow up and so early detection of any cognitive impairment and matching it with neuropsychological tests.

**Limitation of this study** is time consuming protocol of MR volumetry, also relatively low number of cases decrease the power of statistical analysis. Larger sample size and longitudinal study are needed to confirm our findings.
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