Parkinson's Disease
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Chapter 4

Striatal FDOPA uptake and cognition in advanced non-demented Parkinson’s Disease: a clinical and FDOPA-PET study

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Submitted
Abstract

Parkinson’s disease (PD) is often accompanied by cognitive impairments in several cognitive domains. These are thought to result from deficient frontal lobe functioning secondary to striatal dopamine depletion. PET studies in PD have revealed relationships between striatal FDOPA uptake and cognitive functioning, as well as motor functioning.

This study sought to determine the nature of the relationship between cognition and striatal dopaminergic functioning in patients with advanced PD. FDOPA-PET was assessed in 28 patients and successive PET data were correlated with neuropsychological test scores. In both, putamen and caudate FDOPA uptake was significantly correlated with cognition. Putamen FDOPA uptake showed the strongest relationship to executive functioning (flexibility), while caudate FDOPA uptake appeared to correlate most strongly with the organizational aspects of executive functioning in memory processes and fluency. The non-executive memory functions were not correlated with striatal FDOPA uptake.

In conclusion, previously reported associations between striatal FDOPA uptake and cognition in PD are replicated in a group of advanced PD patients: it appears to be the executive functions that are related to striatal dopaminergic functioning. The caudate may be more important in the mental components of executive functioning, while the putamen may be more important in the motor components of executive functioning.

Introduction

PD is a neurodegenerative disorder of unknown etiology, characterized by progressive loss of dopaminergic neurons in the nigrostriatal pathway. PD is clinically featured by its motor symptoms consisting of an insidious (asymmetric) onset of bradykinesia, rigidity and (rest) tremor. However, PD is also often accompanied by cognitive impairments. Cognitive deficits are found in several domains including memory and the executive functions. Executive functions are typically impaired, which itself results in deficient cognitive switching, impaired concept formation and response-inhibition, and impaired planning abilities. Impaired fluency performance is another example of impaired executive functioning in PD since frontally mediated searching strategies are needed for optimal performance. Deficits in the executive functions can negatively influence other cognitive domains too. Most importantly, memory profiles show that in PD, the executive components of memory performance are disturbed, while the non-executive storage components are relatively intact. PD patients experience problems in the organizational strategies needed for the encoding and retrieval of new information, but not in the storage of information.
In sum, cognitive impairments, as they are found in PD, can be seen as the result of deficient executive functioning, which results in impaired executive functioning, and subsequently broader cognitive dysfunctioning.

A possible explanation for the cognitive deficits can be found in the striatal connections with the frontal lobes. Positron Emission Tomography (PET), using the radiotracer 6-L(18F)-fluorodopa (FDOPA), provides a means of quantifying the loss of striatal dopaminergic terminal function in vivo in PD. Specific striatal FDOPA uptake reflects nigrostriatal dopamine storage capacity and enzymatic decarboxylase activity in surviving neurons. According to the current model of basal ganglia organization, dopaminergic connections between the caudate nucleus and frontal areas are more strongly related to cognition and less strongly related to motor function. On the contrary, putaminal FDOPA uptake has been related to motor function in both early and advanced PD patients, but until recently not to cognition, although Marie et al. reported an inverse correlation between putamen [11C]nomifensine uptake and associative learning. Most studies have shown that diminished (posterior) putamen FDOPA uptake correlates with clinical severity of PD motor symptomatology.

This study was performed to determine whether striatal FDOPA uptake is related to cognitive functioning in a sample of advanced PD patients. While previous FDOPA-PET studies on cognition in PD patients involved early or heterogeneous (both early and advanced patients) samples of patients, our study included only moderately to severely advanced PD patients.

The nature of these relationships between striatal dopamine uptake and cognitive functioning was studied to find an answer to the following questions: first, are these deficits mainly related to the dopaminergic function in the caudate, the putamen, or both? Second, are the cognitive deficits in advanced PD restricted to the executive functions or do they also include non-executive cognitive processes?

**Methods**

**Patients**

28 right-handed PD patients with moderately to severely advanced disease (modified Hoehn & Yahr Staging in off-medication condition: 2.5 (n = 1), 3 (n = 13), 4 (n = 9), 5 (n = 5)) participated in the study. There were 15 men and 13 women (age 60 ± 7.4 years, disease duration 11.8 ± 4.5 years) (see also table I). All patients had idiopathic PD following the criteria of the UK Parkinson’s Disease Society Brain Bank criteria and showed sustained levodopa responsiveness. They were recruited from our outpatients’ Movement Disorder Unit between October 1999 and July 2003. All patients suffered from severe pharmacotherapy resistant tremor or intractable motor fluctuations, despite optimal antiparkinsonian treatment (levodopa and dopamine agonists; n = 28; amantadine, n = 6; anticholinergics, n = 5) and were suitable candidates for bilateral Deep Brain Stimulation (DBS) of the thalamus (thalamus-DBS, n = 3) or subthalamic...
nucleus (STN-DBS, n = 25) respectively. On a 1 (elementary school not finished) to 7 (university degree) Dutch scale for education the patients’ median score was 4 (SD 1.4).

All patients gave their informed consent prior to study inclusion according to the declaration of Helsinki.

### Procedure

Preoperatively all patients were clinically and neuropsychologically evaluated following the Core Assessment Program for Surgical Intervventional Therapy in Parkinson’s Disease (CAPSIT-PD). Additional inclusion and exclusion criteria were: a positive levodopa response (at least 30% improvement of the motor part (III) of the Unified Parkinson’s Disease Rating Scale (UPDRS III), no depression (Montgomery and Asberg Depression Rating Scale (MADRS), score < 19) or recent psychiatric illness, no demen-

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### Table 1 Clinical characteristics and striatal FDOPA uptake values of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Mean (± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>11.8 (4.5)</td>
<td>3-20</td>
</tr>
<tr>
<td>UPDRS part III score *</td>
<td>45.6 (14.2)</td>
<td>24-74</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr Staging *</td>
<td>3.5 (0.8)</td>
<td>2.5-5</td>
</tr>
<tr>
<td>Medication (LEDD) **</td>
<td>1179 (732)</td>
<td>450-3250</td>
</tr>
<tr>
<td>FDOPA uptake putamen ***</td>
<td>0.64 (0.19)</td>
<td>0.29-0.98</td>
</tr>
<tr>
<td>-women</td>
<td>0.72 (0.18)</td>
<td>0.32 – 0.98</td>
</tr>
<tr>
<td>-men</td>
<td>0.58 (0.19)</td>
<td>0.29 - 0.88</td>
</tr>
<tr>
<td>FDOPA uptake caudate ***</td>
<td>0.83 (0.29)</td>
<td>0.41-1.41</td>
</tr>
<tr>
<td>-women</td>
<td>0.90 (0.27)</td>
<td>0.45 – 1.41</td>
</tr>
<tr>
<td>-men</td>
<td>0.78 (0.30)</td>
<td>0.41 – 1.19</td>
</tr>
</tbody>
</table>

* in off-medication condition;  
** LEDD = Levodopa Equivalent Daily Dose: levodopa dose (100 mg) x 1 (added with 0.2 x levodopa dose if using entacapone with each dose) + (slow release levodopa x 0.7) + bromocriptine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100.  
*** Reference values FDOPA uptake, UMC Groningen. Healthy volunteers (n = 10, age 56 ± 19 years): 1.69 ± 0.29 (putamen), 1.68 ± 0.25 (caudate), PD (n = 18, age 64 ± 6 years, disease duration 9 ± 3 years): 0.79 ± 0.1 (putamen), 1.07 ± 0.19 (caudate)
tia (Mattis Dementia Rating Scale, score > 130), and no abnormalities on cerebral MRI suggestive of atypical parkinsonism.

All clinical, neuropsychological and FDOPA-PET assessments were performed on separate successive days during hospitalisation for 2-4 days within 3-6 months prior to planned surgery (bilateral thalamus-DBS or STN-DBS). Antiparkinsonian medication was kept unchanged during a period of at least 2 weeks prior to every assessment. The UPDRS part III score was assessed in the off-medication condition (after withholding regular antiparkinsonian drugs for 12 hours overnight) by the same investigator (ATP). The neuropsychological testing was performed in the medication-on condition following the recommendations of CAPSIT-PD. All subjects were scanned in the medication-on condition.

**Neuropsychological Tests**

Neuropsychological tests included measures for memory, executive functioning, fluency, and psychomotor speed. **Memory** was tested with the memory scale of the Mattis Dementia Rating Scale (MDRS) and the 15 Words Test (15WT) Learning Score (sum score of 15 words that were presented 5 times) and Recall score (words remembered after a 20 minute delay). The recognition score of the 15WT was used to further explore the nature of the possible relationships between memory and striatal FDOPA uptake. **Executive functioning** was tested with the Odd Man Out (OMO) test for cognitive switching, the Stroop Color-Word Card divided by the Stroop Color Card (interference index), and the time needed on the Trailmaking B divided by the time needed on the Trailmaking A (cognitive switching). **Fluency** performance was measured with several versions including two categorical tests (Animals and Professions, 1 minute each), and three letter Fluency tests.

**PET data acquisition and analysis**

All PET measurements were performed at the UMCG PET Center on a Siemens ECAT Exact HR+ (n = 13) or ECAT 951 (n = 15) scanner. Subjects were positioned supine in a resting state with their eyes closed and ears unplugged. After pretreatment with 2 mg/kg carbidopa to block peripheral dopa-decarboxylase activity, 180 ± 33 MBq of FDOPA was intravenously injected over 1 minute with an infusion pump. All subjects were measured following a static or dynamic protocol with identical time range for data analysis. The static protocol consisted of 1 single scan from 90-120 minutes post-injection, while the dynamic protocol consisted of 21 time frames with increasing duration over 120 minutes: then the last 2 frames (2 x 900 sec.) were averaged to create an equivalent volume to the static scan. Linear normalization with SPM99 was used to align the measured volume data to a rCBF template fixed in Talairach coordinate space. Region of interest (ROI) analysis was based on a standardized template fixed in Talairach coordinate space. This template, consisting of 6 ROIs (putamen, caudate and occipital lobe on both sides) was used to sample the volume data and compute mean ROI activity concentration.
Specific FDOPA uptake was expressed as a striato-occipital ratio (SOR) index following the equation: 
\[
\text{SOR index} = \frac{C_{\text{ROI}}}{C_{\text{REF}}}
\]
\[
C_{\text{ROI}} = \text{average (left and right) ROI activity concentration},
\]
\[
C_{\text{REF}} = \text{average occipital activity in the occipital reference region}.
\]

Statistical analyses
Since patients were scanned on two different scanners, t-tests (p ≤ 0.05) for all variables were performed to exclude differences between type of scanner used. No significant differences were found. All variables were tested for normality with the Shapiro-Wilk test. Sex, H&Y, Ledd-score, MDRS memory, Stroop III/II and OMO total scores were not normally distributed, all others were. Often, non-parametric tests are used when non-normally distributed variables are concerned to decrease the chance of false-positives. However, non-parametric tests have major disadvantages, as they lose valuable data information such as the absolute value of (test) scores and they increase the chance of false negatives. Therefore, all statistical tests were performed parametrically, and the results of the parametric tests were reported. To ensure that no false positives were reported, non-parametric tests were performed for those variables that were not normally distributed to check and justify the parametric results. If, in these cases, the non-parametric result lost significance compared to the parametric result, this was indicated in table 2 and 3.

Hypothesis-driven analyses
All cognitive variables were converted to Z-scores using mean values and standard deviations. Composite cognitive scores (i.e. mean Z-scores) were formed for memory (MDRS memory scale, 15 WT Learning score, and 15 WT Recall score), executive functioning, and fluency. Since recognition was not used in a composite score, it did not need to be converted to a standard score and the raw score was used. In this way, the number of correlations to be studied was limited to 6 and it was not necessary to perform a multiple comparisons correction. To justify this approach, each correlation itself was provided with a 95% confidence interval, so as to indicate its accuracy as an estimate of the correlation in the population. Because the direction of the correlations was predictable based on previous literature on the subject, it was justified to perform one-tailed correlational analyses. One-tailed correlations between mean FDOPA uptake values (combined left and right putamen; combined left and right caudate) and the composite scores for memory, executive functioning and fluency were performed.

Further explorative analyses
Two-tailed correlations (Pearson’s r) between sex, UPDRS part III off-medication condition score and illness duration and striatal FDOPA uptake and cognition were assessed. Again, each correlation itself was provided with a 95% confidence interval, so as to indicate its accuracy as an estimate of the correlation in the population. Partial correlations were also used to explore the relationship between memory and striatal uptake, corrected for the influence of executive functioning to investigate the relationship of non-executive components of memory with FDOPA uptake.
## Results

Striatal FDOPA uptake values of the study PD group were lower than the PD norm group (see Table 1). Female subjects showed higher putamen FDOPA uptake compared to males. Significant relationships between the illness variables, sex, psychomotor speed and some of the cognitive variables (memory) and FDOPA uptake were found (see Table 2). Putamen FDOPA uptake was not significantly related to the UPDRS part III off-medication score. Hypothesis-driven analyses: all correlations between FDOPA uptake and cognitive composite scores were significant, except for the correlation between putamen uptake and the memory score (see Table 2 and figure 1). Interestingly, the correlation between caudate uptake and the memory summary score lost significance when corrected for

### Table 2 One-tailed correlation coefficients between sex, disease duration, motor score, and cognition with striatal FDOPA uptake

<table>
<thead>
<tr>
<th></th>
<th>Putamen</th>
<th></th>
<th>Caudate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R (p)</td>
<td>Conf. int. 95 %*</td>
<td>R (p)</td>
<td>Conf. int. 95 %*</td>
</tr>
<tr>
<td>Sex</td>
<td>.38 (.024)</td>
<td>.01,.66</td>
<td>.20 (ns)</td>
<td>-.19,.53</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>.37 (.026)</td>
<td>.00,.65</td>
<td>.40 (.017)</td>
<td>.03,.67</td>
</tr>
<tr>
<td>UPDRS part III score **</td>
<td>.062 (ns)</td>
<td>-.32,.43</td>
<td>.39 (.012)</td>
<td>.02,.67</td>
</tr>
<tr>
<td>Memory</td>
<td>ns</td>
<td></td>
<td>.41 (.027)</td>
<td></td>
</tr>
<tr>
<td>Executive functions</td>
<td>.44 (.010)</td>
<td>.08,.70</td>
<td>.37 (.010)</td>
<td>.00,.65</td>
</tr>
<tr>
<td>Fluency</td>
<td>.32 (.048)</td>
<td>.09,.70</td>
<td>.44 (.010)</td>
<td>.08,.70</td>
</tr>
</tbody>
</table>

ns = not significant; * 95 % confidence interval; ** in off-medication condition
the influence of executive functioning. Recognition of learned verbal material was not related to either putamen or caudate uptake. Non-parametric supported all parametric findings.

**Discussion**
Putamen and caudate FDOPA uptake in our study group were lower than in our PD norm group, and also within the lower range of those stated in the literature, probably because of more advanced disease status. In our study putaminal FDOPA uptake was not significantly related to the clinically evaluated level of motor dysfunction (as assessed by the UPDRS part III), although the correlation was in the expected negative direction. Caudate FDOPA uptake was related to motor dysfunction. These inconsistent results may be caused by the fact that UPDRS III scores were measured in off-medication condition, while FDOPA-PET was measured in on-medication condition. However, since this study was aimed at the relationships between cognition and FDOPA uptake, UPDRS on-medication scores were not measured.
Hypothesis-driven analyses

Caudate FDOPA uptake was related to cognition. These relationships were expected, based on a. previous PD literature on caudate dopaminergic function and cognition, b. findings in other patient groups such as patients with Huntington’s disease and caudate hemorrhage, and c. findings in healthy subjects. In PD, caudate dopaminergic function has been linked to tests measuring executive function and memory. In particular the interference effect on the Stroop test has been associated with caudate dopaminergic function in addition to measurement of cognitive switching that included reward for the right response. However, measurements of cognitive switching that did not include reward (i.e. WCST) have not revealed significant relationships with caudate FDOPA uptake in PD. Similarly, memory has not been consistently related to caudate FDOPA uptake or may only show this relationship in more advanced patients. Rinne et al. reported memory to be related to frontal FDOPA uptake but not to caudate FDOPA uptake. Fluency performance was studied in two larger FDOPA-PET studies with interesting results: Broussolle et al. concluded that fluency is independent from striatal FDOPA uptake, and Rinne et al. found fluency to be related to frontal but not to striatal uptake.

Our main finding compared to previous studies is the association found between putamen FDOPA-uptake and executive functioning. This is a surprising finding, since previous reports and neuroanatomical findings suggest that the putamen is involved in motor functioning but not in cognition. However, other authors have also suggested an association between FDOPA uptake in the putamen and cognitive processing using comparable paradigms (FDG-PET and [123]I-b-CIT SPECT, respectively), in addition to findings with other paradigms.

In our patients, putamen FDOPA uptake was related to executive functioning and fluency, but not to memory. It should be noted that, as addressed in the introduction, the measures for memory and fluency also concern executive functioning since they reflect cognitive searching strategies and organization of verbal material. However, different aspects of executive functioning can be distinguished from each other; our variable “executive functioning” concerned mostly mental flexibility, while the others concerned the organization of behavior. Putamen FDOPA uptake was related to the “flexibility” factor in executive functioning. Monchi et al offer a possible explanation for this finding with their activation study in which they investigated brain activation patterns during neuropsychological testing instead of relying on correlational analyses. They concluded that the putamen was activated during actions that followed a cognitive switch, i.e. actions according to specific behavioural rules. The mental components of this cognitive switch were unrelated to putamen activity. Since most neuropsychological tests require such a motor response after mental switching, it may be this motor component of test performance that is related to putamen FDOPA uptake. Indeed, our tests (e.g. Trail Making Test and OMO Test) and those of Lozza et al required motor actions after cognitive switching while some of the studies that did not find a relation

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between putamen FDOPA uptake and neuropsychological test behaviour did not include tests that require motor actions after cognitive switching. However, results are not consistent, some authors did include such a test but did not find putaminal FDOPA uptake related to them. Also, the relationship between putamen and cognition found in the study of Müller et al did involve tests with an action component, but not specifically an action after switching.

**Explorative analyses**

The analysis of the nature of cognitive deficits showed interesting results. When exploring memory functioning in these patients, it appears that it are the executive components of memory are deficient and related to FDOPA uptake. Other authors have also reported this memory profile in PD patients. Our results confirm this cognitive profile in two ways. First, learning and recall of new verbal material requires organizational skills in structuring the information and searching for information. These are the executive stages of memory processes mostly mediated by the frontal cortex (in interaction with the temporal cortex). The consolidation of learned material is thought to rely more on temporal lobe function, and can be measured by the recognition score. When newly learned material is not recalled, but is recognized, consolidation is intact. Our results showed that recognition of verbal material (non-executive) was not related to caudate FDOPA uptake, while learning and recall of information (executive) was. Secondly, the results are confirmed since the relationships between verbal learning and recall and caudate FDOPA uptake lost significance when corrected for the influence of executive functioning with partial correlational analyses. The methodological aspects of the study should be considered in the interpretation of the study results. The FDOPA uptake in the striatum was lower in our patient study group as compared to previous studies with de novo patients. However, it should be noted, that although the mean striatal FDOPA uptake was low, the range of values was sufficient for a correlation analysis. Finally, our analyses were not corrected for multiple comparisons. Although most of the correlations would not have remained significant after a conservative correction for multiple comparisons, the present results, in the light of previous literature, confirm the a priori hypothesis of negative correlations between FDOPA uptake and cognition in the striatum. Confidence intervals were provided to show the chances of false positives for each correlation individually. Furthermore, scatter plots were provided to provide a detailed view on the data.

In conclusion, three main inferences can be made about the association between striatal FDOPA uptake and cognition, based on these data on non-demented PD patients. First, putamen FDOPA uptake was more related to mental flexibility (i.e. cognitive switching), which may represent difficulty performing the actions after cognitive switching during test performance. Second, caudate FDOPA uptake was related to executive functioning, fluency perfor-
mance and the organizational aspects of memory (i.e. cognitive organization). Third, neither putamen nor caudate FDOPA uptake was related to the non-executive (storage) aspect of memory. Therefore, it appears to be the executive functions that are related to striatal dopaminergic functioning. The caudate may be more important in the mental components of executive functioning, while the putamen may be more important in the motor components of executive functioning.

Acknowledgements
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References


