

Striatal dopamine transporters and cognitive function in Parkinson's disease

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Background: Idiopathic Parkinson's disease (PD) is characterized by clinical motor symptoms including hypokinesia, rigidity and tremor. In addition to the movement disorder, cognitive deficits are commonly described. In the present study, we applied FP-CIT SPECT to investigate the impact of nigrostriatal dopaminergic degeneration on cognitive function in PD patients.

Methods: Fifty-four PD patients underwent [¹²³I]FP-CIT SPECT and CERAD (Consortium to Establish a Registry for Alzheimer's Disease) testing. FP-CIT SPECT visualized the density of presynaptic dopamine transporters in both striata, each subdivided into a limbic, executive and sensorimotor subregion according to the atlas of Tziortzi et al (*Cereb Cortex* 24, 2014, 1165). CERAD testing quantified cognitive function.

Results: In the CERAD testing, PD patients exhibited deficits in the domains of semantic memory, attention, visuospatial function, non-verbal memory and executive function. After correction for multiple testing, the performance of the subtests *Figure Recall* and *Trail-Making Test A* correlated significantly with FP-CIT uptake into the ipsilateral executive subregion. The performance of the subtest *Figure Saving* correlated significantly with FP-CIT uptake into the contralateral executive subregion.

Conclusions: The significant correlation between cognitive function and density of nigrostriatal dopamine transporters, as assessed by FP-CIT SPECT, indicate that striatal dopaminergic pathways—primarily the executive striatal subregion—are relevant to cognitive processing in PD.

KEYWORDS

cognitive deficits, dopamine transporters, FP-CIT SPECT, Parkinson's disease

1 | INTRODUCTION

Idiopathic Parkinson's disease (PD) is defined by clinical motor symptoms including hypokinesia, rigidity and tremor, which are mainly caused by a dopaminergic nigrostriatal deficit and are

improved by dopaminergic, anticholinergic or NMDA receptor blocking drugs.¹ More recently, recognition of the relevance of non-motor symptoms, which include depression, psychosis, impulse control disorders, anxiety, sleep disorders and cognitive deficits, has been elucidated. Although the development of newer

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antidepressants, atypical antipsychotics and cholinesterase inhibitors have a positive effect on the non-motor symptoms, therapeutic responses are frequently suboptimal. This remains a major area of unmet therapeutic need.²

A considerable percentage (20%-50%) of patients with PD develop cognitive deficits resulting in mild cognitive impairment (MCI) or dementia in the later stages of the disease.³⁻⁷ Cognitive deficits in PD are explained by the *dual syndrome hypothesis*:^{8,9} PD is characterized as a synucleinopathy with pathogenic aggregation of α -synuclein and the formation of Lewy bodies. This degeneration involves (a) *dopaminergic* and (b) *cholinergic* neurotransmission,¹⁰ thus the term *dual syndrome hypothesis*. The degeneration of both dopaminergic and cholinergic pathways appears to contribute to cognitive deficits in PD. For example, the cholinesterase inhibitor rivastigmine alleviates MCI and dementia in PD.^{1,11} The lack of dopamine results in a fronto-striatal dysexecutive syndrome.⁹ Dopaminergic medication improves verbal fluency, working memory, visuospatial function and executive function in PD patients.¹²⁻¹⁶

The degeneration of the nigrostriatal dopaminergic pathway can be visualized by means of FP-CIT SPECT. Previous studies reported a correlation between striatal FP-CIT binding and cognitive function in selected PD patients: the striatal FP-CIT uptake correlated with executive function in de novo PD patients.¹⁷⁻¹⁹ Striatal FP-CIT binding correlated with attention/working memory, executive and visuospatial function in de novo PD patients with and without MCI.²⁰ Global cognitive function correlated with striatal FP-CIT binding in non-demented PD patients.²¹ Striatal FP-CIT binding also correlated with frontal, executive and visuospatial function in patients with advanced PD and MCI.²² All these studies included selected PD patients (selection criteria: de novo or advanced PD, with or without MCI, non-demented).

In the present study, we applied FP-CIT SPECT to investigate the impact of nigrostriatal dopaminergic degeneration on cognitive function in an unselected cohort of PD patients. Since we aimed to correlate cognitive function with the functional integrity of striatal dopaminergic pathways, we structured the striatum according to the study of Tziortzi et al,²³ which subdivided the striatum into functionally defined subregions—limbic subregion, executive subregion and sensorimotor subregion—based on striato-cortical anatomical connectivity derived from diffusion magnetic resonance imaging and probabilistic tractography in healthy subjects. This connectivity-based parcellation does not match the traditional anatomical, structure-based subdivision of the striatum.

2 | METHODS

2.1 | Subjects

The study involved 54 patients with idiopathic PD (age: 44-85 years, mean $\pm$ SD: 68 $\pm$ 10 years, 18 women, 36 men). PD was diagnosed according to the UK Brain Bank criteria.²⁴ Three patients were at Hoehn and Yahr (H&Y) stage 1, 25 at H&Y stage 2, 11 at H&Y stage 3,

14 at H&Y stage 4 and one at H&Y stage 5. In the “off state” (=without effect of antiparkinsonian medication), the patients reached 19 $\pm$ 7 points (mean $\pm$ SD) in the motor part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). Concerning the predominant motor type, 26 patients belonged to the akinetic-rigid type, 13 patients to the tremor dominant type and 15 patients to the equivalence type. The duration of PD was 3-19 years (8.3 $\pm$ 4.6 years, mean $\pm$ SD).

Patients were excluded from the study if they were taking cholinesterase inhibitors, anticholinergic drugs, serotonin or noradrenalin reuptake inhibitors. Further exclusion criteria included pregnancy or breastfeeding, a partner who was capable of childbearing, current or previous cerebral disease (except PD), psychiatric disorders or severe medical conditions. Antiparkinsonian medication was paused before the CERAD testing since dopaminergic medication influences cognitive function in PD patients.¹²⁻¹⁶

No healthy controls were included in the study. The study protocol was approved by the local ethics committee (Ärztchamber des Saarlandes). All participants gave written informed consent prior to enrolment in the study.

2.2 | [¹²³I]FP-CIT SPECT

Cerebral SPECT imaging of dopamine transporter was performed with the use of ¹²³I-FP-CIT (¹²³I-2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl)nortropan) (DaTscan®, GE Healthcare). After thyroid gland blocking with perchlorate (Irenat®, Alliance Pharma (Ireland) Limited), 185.1 $\pm$ 12.9 MBq ¹²³I-FP-CIT (mean $\pm$ SD) was administered intravenously, followed by 4 hours uptake time to SPECT acquisition. SPECT were performed using a triple-head Siemens Multispect 3 gamma camera (Siemens) equipped with low-energy high-resolution collimators. Data were acquired in a 128 $\times$ 128 matrix covering 120 degrees per camera head, 40 seconds per view. We acquired a total of 120 views. An energy window of 158 keV $\pm$ 15% was applied. SPECT data were iteratively reconstructed by the use of 3D ordered subsets expectation-maximization algorithm (four iterations, 15 subsets, Butterworth filtering 10th order with 0.6 cut-off frequency, voxel size 3.2 $\times$ 3.2 $\times$ 3.2 mm) and attenuation corrected by Chang's method.²⁵ Reconstruction, registration and semiquantitative analysis were automatically performed using DaTQUANT®, (v.1.01, GE Medical Systems Israel), being an established state of the art software for dopamine transporter imaging. With automatically placed, fixed sized volume of interest (VOI) auto-contouring by DaTQUANT®, ¹²³I-FP-CIT uptake was measured for the executive subregion, the limbic subregion and the sensorimotor subregion of both striata. The executive subregion, limbic subregion and sensorimotor subregion were identified by means of the three subdivided striatal connectivity atlas of Tziortzi et al.²³ For all subregions, a subregion-to-background binding ratio was calculated. An automatically drawn VOI in the occipital cortex was used as background.

The measured values in the PD patients were compared to a normal data set provided by the vendor, which was comprised of

196 healthy subjects from the multicenter Parkinson Progression Markers Initiative study.²⁶

2.3 | CERAD testing

The initial version of CERAD, the CERAD-NP test, was developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).²⁷ The CERAD-NP test includes neuropsychological subtests: *Verbal Fluency*, *Modified Boston Naming Test*, *Mini-Mental State Examination*, *Word List (Learning, Recall, Intrusions and Saving)* and *Visuoconstructive Ability (Figures Drawing, Figures Recall and Figures Saving)*. The CERAD-NP test was developed in English; so, for German-speaking people, the Memory Clinic of the University Hospital of Basel (Switzerland) created a German version called the CERAD Plus test.²⁸ In addition to the CERAD-NP test, the CERAD Plus test includes the subtests *Trail-making Test A*, *Trail-making Test B* and *Phonemic Fluency s-words*. All patients in our study underwent the CERAD Plus test. The subtests are explained in detail below:

- **Verbal Fluency:** The subject must name as many animals as possible within 1 minute and is awarded one point for each animal. This subtest examines verbal velocity and capacity, semantic memory, speech, executive function and cognitive flexibility.
- **Modified Boston Naming Test:** 15 drawings of daily objects are shown, which the subject must name within 10 seconds. The maximum score is 15 points (one point for each correctly named drawing). This subtest examines visual perception and reveals word-finding difficulties.
- **Mini-Mental State Examination (MMSE):** The MMSE is often used solely as a screening test for dementia (up to 30 points). It has been integrated into CERAD-NP testing to examine orientation (to person, place and time), memory, attention, calculating capacity and speech.
- **Word List (Learning, Recall, Intrusions, Saving and Recognition):** In the first step (*Word List Learning*), 10 words are read out to the subject, who must memorize them and directly reproduce the words within 90 seconds. This procedure is repeated three times with the same words but with the word order changed (up to 3×10 points). The percentage of words remembered in the three runs altogether is defined as *Word List Saving*. After an interval, in which another subtest is performed, the same words are asked again (*Word List Recall*; up to 10 points). The term *Word List Intrusions* denotes wrongly remembered words, which are produced by the subject although they have not been read out by the examiner. In a further step, 20 words, the 10 words from the first step (old words) and 10 new words, are read out to the subject. The subject has to identify the 10 old words (up to 10 points) and the 10 new words (also up to 10 points, *Word List Recognition*). The subtest *Word List* examines learning capacity and memory for language information.
- **Figure Drawing:** The subject must draw four figures of increasing difficulty (up to 11 points depending on the accuracy of the drawn figure). This subtest examines visuoconstructive ability. After an

interval, in which two other subtests are performed, all four figures must be drawn from memory (*Figure Recall*, up to 11 points). The percentage of figures remembered is defined as *Figure Saving*. These *Figure Recall*/*Figure Saving* subtests investigate non-verbal memory.

- **Phonemic Fluency "s"-words:** Subjects must say as many words as possible beginning with the consonant "s" within 1 minute. For each word, the subject gets one point. This subtest examines strategy-oriented verbal fluency.
- **Trail-making Test A:** The subject must connect neighbouring numbers in ascending order (eg, 1 - 2 - 3 - 4 - 5 etc) by drawing a line between them. The numbers are randomly and widely distributed over a whole page. The examiner measures the time needed for this test which examines psychomotor velocity. **Trail-making Test B:** The subject must connect numbers and letters alternately in ascending order (eg, 1 - A - 2 - B - 3 - C - 4 - D - 5 - E etc) by drawing a line between them. Again, the time needed for this test is measured. The Trail-making Tests A and B and the quotient Trail-making Test B/A reflect the integrity of executive function.

The results of the individual subtests can be expressed in two ways: as an *absolute value* or as a *relative value* (=z-score). The absolute value gives the number of points, that were obtained in a subtest, or the time, which was needed for a subtest (for example in the trail-making tests). The performance (= *absolute value*) of each patient in each subtest was standardized according to a normal population of the same age, sex and educational standard, resulting in a relative value (z-score). The relative value is expressed as a standard deviation (SD) of the mean value of the normal population. For example, a relative value of +1.0 (SD) means that the individual subject is better than 68% of the healthy volunteers of the same age, sex and educational standard. A relative value of -2.0 (SDs) means that the individual subject is worse than 95% of the comparable healthy volunteers, etc. The CERAD testing was performed by a neurologist who was blinded to the results of the FP-CIT SPECT.

2.4 | Statistical analysis

Descriptive data are given as mean and SD. We correlated the 15 subtests of the CERAD testing with FP-CIT uptake in all six studied brain regions—limbic subregion, executive subregion and sensorimotor subregion on both sides—resulting in $15 \times 6 = 90$ correlations. The correlations were corrected for severity of motor symptoms, which was measured by part III (motor part) of the UPDRS. We performed this correction in order to exclude any effects of parkinsonian motor symptoms on the correlations. The correction was calculated using partial correlation analysis for normally distributed data. In the case of not normally distributed data, we used the ordinal regression analysis. Since multiple correlations were calculated from the same data, we performed a correction for multiple testing using the false discovery rate (FDR) after the Benjamini-Hochberg procedure.²⁹

3 | RESULTS

3.1 | Performance of the CERAD testing

The 54 investigated PD patients showed, on average, a normal individual performance—standardized to a normal population of the same age, sex and educational standard—in the subtests Modified Boston Naming Test, Word List Learning, Word List Recall, Word List Intrusions, Word List Saving, Word List Recognition and Phonemic Fluency “s” words (Table 1). All subtests resulting in normal performance study verbal function.

Performance was impaired, compared with a normal population, in the subtests Verbal Fluency, MMSE, Figure Drawing, Figure Recall, Figure Saving, Trail-making Test A and Trail-making Test B. These subtests examine semantic memory, attention, visuospatial function, non-verbal memory and executive function. In no subtest were the 54 PD patients clearly better than the normal population.

TABLE 1 Performance in the single CERAD subtests

CERAD subtest	Mean	SD	Range (min/max)	P-value
Verbal Fluency	-0.54	1.27	-3.40/+2.23	.004
Modified Boston Naming Test	-0.10	1.11	-4.15/+1.51	.593
Mini-Mental State Examination	-1.22	1.69	-8.29/+1.14	<.001
Word List Learning	-0.30	1.23	-4.38/+1.76	.076
Word List Recall	-0.09	1.16	-2.82/+2.47	.488
Word List Intrusions	+0.04	0.98	-2.97/+0.95	.688
Word List Saving	+0.01	1.31	-3.61/+3.56	.862
Word List Recognition	-0.12	1.24	-4.48/+1.23	.415
Figure Drawing	-0.40	1.11	-2.95/+1.26	.017
Figure Recall	-0.68	1.25	-3.82/+1.43	.001
Figure Saving	-0.46	1.04	-3.10/+2.11	.004
Trail-making Test A	-0.71	1.33	-3.44/+2.46	<.001
Trail-making Test B	-0.51	1.13	-2.94/+2.25	.002
Phonemic Fluency s-words	-0.16	1.26	-3.78/+2.16	.568

Note: The column “Mean” contains the mean of the relative values of all 54 PD patients in the individual subtests (mean z-score). A relative value of 0 represents an individual performance which is identical to the average of a normal population with the same age, sex and educational standard. A relative value of -1 represents an individual performance, which is one standard deviation lower than that of the normal population. The column “SD” contains the standard deviation of the relative values of all 54 PD patients in the single subtests. Note: the high standard deviation ≥ 0.98 for all subtests, which indicates high inter-individual variability. Range: The minimum value (min) and maximum value (max) are given (minimum/ maximum). P-value = P-values for the mean z-score being different from zero (t test for one sample).

3.2 | FP-CIT SPECT

The 54 PD patients had a significantly lower FP-CIT uptake into all three subregions (limbic subregion: 1.79 ± 0.28 [mean $\pm$ SD], executive subregion: 2.24 ± 0.29 and sensorimotor subregion: 1.30 ± 0.26 , $n = 108$ each [$n = 108$ due to both sides in 54 PD patients]) than the healthy controls (limbic subregion: $P < .05$, executive subregion: $P < .05$, sensorimotor subregion: $P < .01$, unpaired t test each).

In addition, the FP-CIT uptake can be expressed by relative values (=z-scores) compared to healthy control group. For example, a relative value of +1.0 (SD) means that the FP-CIT uptake is higher than in 68% of the healthy subjects. A relative value of -2.0 (SDs) means that the FP-CIT uptake is lower than in 95% of the healthy subjects. In our PD patients, the relative values (z-scores)—compared to the normal data set provided by the vendor—were -1.92 ± 1.40 (range -4.72 up to +0.76 [minimum up to maximum]) for the limbic subregion, -0.86 ± 1.18 (range -4.55 up to +1.71) for the executive subregion and -2.32 ± 1.78 (range -5.28 up to +1.21) for the sensorimotor subregion ($n = 108$ each).

The following calculations were performed with the absolute values of FP-CIT binding. There was no correlation between age and striatal FP-CIT binding (age vs contralateral limbic subregion: $r = -.05$, $P = .86$, age vs ipsilateral limbic subregion: $r = -.14$, $P = .31$, age vs contralateral executive subregion: $r = -.06$, $P = .78$, age vs ipsilateral executive subregion: $r = -.11$, $P = .49$, age vs contralateral sensorimotor subregion: $r = -.10$, $P = .46$ and age vs ipsilateral sensorimotor subregion: $r = -.14$, $P = .34$). The term “ipsilateral” denotes the striatal subregion ipsilateral to the body side, which was clinically more affected by parkinsonian motor symptoms. Analogous to this, the term “contralateral” means the striatal subregion contralateral to the body side, which was clinically more affected by parkinsonian motor symptoms.

3.3 | Correlation between CERAD testing and cerebral FP-CIT binding

We correlated performance in the individual 15 CERAD subtests, expressed in z-scores, with local FP-CIT binding, as determined by FP-CIT uptake, in six brain areas (limbic subregion, executive subregion and sensorimotor subregion on both sides each). Consequently, we obtained $15 \times 6 = 90$ correlations. These correlations were corrected for severity of motor parkinsonian symptoms, which were measured by the motor part of the UPDRS score. In 14 of these 90 correlations, we found a P-value of $<.05$ ($P < .05$):

- Correlation of FP-CIT uptake in *ipsilateral limbic subregion* with performance of Figure Recall ($r = +.42$, $P = .005$) and Figure Saving ($r = +.48$, $P = .005$).
- Correlation of FP-CIT uptake in *contralateral limbic subregion* with performance of Figure Recall ($r = +.37$, $P = .028$) and Figure Saving ($r = +.41$, $P = .019$).

- Correlation of FP-CIT uptake in *ipsilateral executive subregion* with performance of Word list Recall ($r = +.32$, $P = .030$), Figure Recall ($r = +.48$, $P = .001$), Figure Saving ($r = +.36$, $P = .022$) and Trail-Making Test A ($r = +.49$, $P = .001$).
- Correlation of FP-CIT uptake in *contralateral executive subregion* with performance of Word List Recall ($r = +.35$, $P = .019$), Figure Recall ($r = +.40$, $P = .017$), Figure Saving ($r = +.51$, $P < .001$, Figure 1) and Trail-Making Test A ($r = +.40$, $P = .021$).
- Correlation of FP-CIT uptake in *ipsilateral sensorimotor subregion* with performance of Figure Recall ($r = +.36$, $P = .021$).
- Correlation of FP-CIT uptake in *ipsilateral sensorimotor subregion* with performance of Figure Recall ($r = +.33$, $P = .041$).

The correlation coefficients of FP-CIT uptake in all subregions with performance of Word List Recall were calculated with the partial correlation analysis. For all other calculations coefficients, the ordinal regression analysis was used. The 14 correlation coefficients with a P -value $< .05$ indicate that the performance of the according subtests improved with an increasing FP-CIT uptake in the respective striatal subregion. In the remaining 76 of 90 correlation coefficients, the P -value was equal or higher than .05.

Since we calculated $15 \times 6 = 90$ correlations, we performed a correction for multiple testing by means of the FDR after the Benjamini-Hochberg procedure. This correction for multiple testing disclosed the following three significant correlations ($P < .05$, FDR after the Benjamini-Hochberg procedure):

- FP-CIT uptake in ipsilateral executive subregion vs performance of Figure Recall;
- FP-CIT uptake in ipsilateral executive subregion vs performance of Trail-Making Test A;
- FP-CIT uptake in contralateral executive subregion vs performance of Figure Saving.

4 | DISCUSSION

In our study, PD patients showed a significantly impaired performance in the domains of semantic memory (measured by the subtest Verbal Fluency), attention (Mini-Mental State Examination), visuospatial function (Figure Drawing), non-verbal memory (Figure Recall, Figure Saving) and executive function (Trail-making Test A and Trail-making Test B). Similar cognitive deficits—primarily memory impairment, visuospatial dysfunction, attention/ working memory impairment and executive dysfunction—in non-demented PD patients were reported by previous studies.³⁰⁻³³

The measurement of the density of presynaptic dopamine transporters by means of FP-CIT SPECT enables correlation of cognitive function with the dopaminergic striatal function. We did not subdivide the striatum after anatomical criteria but by functional criteria according to the three subdivided striatal connectivity atlas of Tziortzi et al.²³ Tziortzi et al.²³ applied diffusion magnetic resonance imaging and probabilistic tractography with the aim to obtain striato-cortical anatomical connectivity information. On the basis of this striato-cortical connectivity information, the striatum mainly consists of a limbic subregion, an executive subregion and a sensorimotor subregion. This functional parcellation of the striatum differs from its anatomical structure-based subdivision.

We found in all three striatal subregions—limbic subregion, executive subregion and sensorimotor subregion—a significantly lower FP-CIT uptake in PD patients than in the healthy controls. After correction for multiple testing, there were significant correlations between striatal FP-CIT uptake into the ipsilateral executive subregion and the performance of the CERAD subtests Figure Recall and Trail-Making Test A as well as between striatal FP-CIT uptake into the contralateral executive subregion and the performance of the CERAD subtest Figure Saving. Compared to the healthy control population, the PD patients had a significantly worse performance in the subtests Figure Recall, Figure Saving and Trail-Making Test A. These

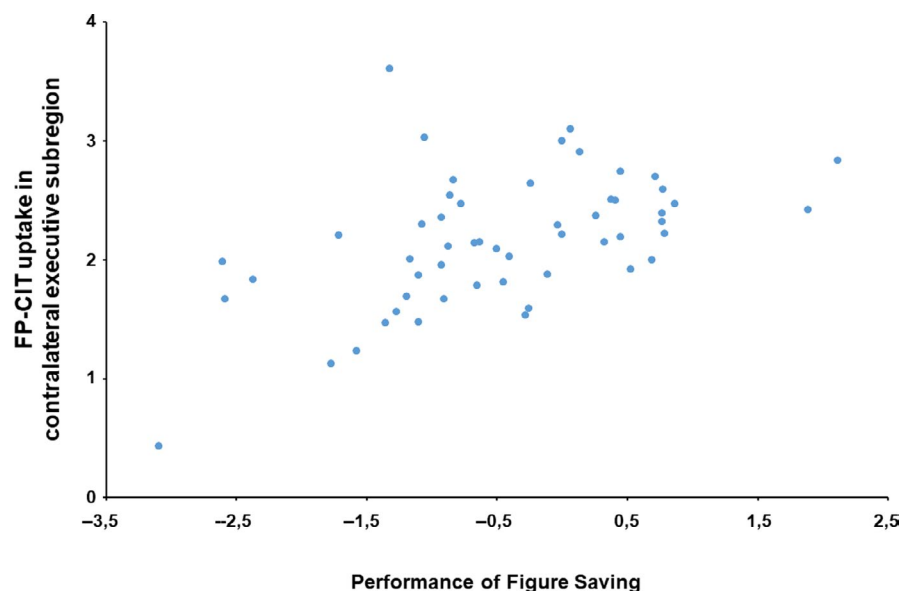


FIGURE 1 Correlation of the CERAD subtest Figure Saving with the FP-CIT uptake in the contralateral executive subregion. Each patient is represented by a blue circle. The performance of Figure Saving is expressed in z-scores (relative values)

data suggest that the impaired dopaminergic function of the ipsi- and contralateral executive subregion may contribute to an impaired performance of non-verbal memory and executive function in PD.

Tziortzi et al²³ found bilaterally symmetric projections of the cortical areas to the striatum. This might explain why we detected significant correlations for both ipsi- and contralateral executive regions and not only for the contralateral executive region. The executive subregion of the striatum receives a strong dopaminergic input from the prefrontal cortex and a smaller dopaminergic input from the parietal lobe.²³ This strong dopaminergic input from the prefrontal cortex, which plays an important role for executive function, may explain the close correlation between FP-CIT uptake into the striatal executive region and performance of executive function (subtest Trail-Making Test A). The parietal lobe is a functionally heterogeneous area, which includes executive, visual, somatosensory and limbic subregions.²³ It might be speculated that the small input from the parietal lobe into the striatal executive region influences the significant correlation between FP-CIT uptake into the striatal executive region vs non-verbal memory (subtest Figure Saving). The significant results according to the executive striatal subregion suggest that impairment of the dopaminergic striatal executive pathways contribute to cognitive deficits in PD.

In PD patients, the other striatal subregions—the limbic subregion and the sensorimotor subregions—also had a significantly lower FP-CIT uptake than in the healthy controls. However, after correction for multiple testing, we could not find any significant correlation between the performance of any CERAD subtest and the FP-CIT uptake into any limbic or sensorimotor subregion. Since the striatal executive subregion overlaps with the limbic and sensorimotor subregion,²³ one would expect significant correlations between cognitive function and the dopaminergic function of the limbic and sensorimotor subregion, too. The reason for this missing correlation is unclear. It can be speculated that in another population of PD patients—for example only PD patients with cognitive deficits (MCI and/or beginning dementia)—several correlations would become more evident.

For some CERAD subtests—Verbal Fluency, Modified Boston Naming Test, Mini-Mental State Examination, Word List Intrusions, Word List Saving, Word List Recognition, Figure Drawing, Trail-making Test B and Phonemic Fluency “s” words—correlation of the performance of the subtest with the FP-CIT uptake of any striatal subregion was not significant ($P > .05$). It might be postulated that these cognitive functions are mainly mediated via transmitters other than dopamine, for example via the transmitter acetylcholine. A previous nuclear medicine study³⁴ reported a significant correlation between the performance of the subtests Modified Boston Naming Test and Word List intrusions vs the acetylcholine receptor binding in cortical areas (right superior parietal lobule) and subcortical areas (left thalamus, right and left posterior subcortical region) in PD patients.

The relevant impact of both dopaminergic and cholinergic neurodegeneration on cognition in PD is reflected by the dual syndrome hypothesis,^{8,9} which is supported by clinical data and nuclear

medicine studies: the cholinesterase inhibitor rivastigmine alleviates MCI and dementia in PD.¹¹ On the other hand, dopaminergic medication improves certain cognitive functions—verbal fluency, working memory, visuospatial function and executive function—in PD patients.^{12–16} FP-CIT studies showed a correlation between striatal FP-CIT uptake and cognitive function—primarily executive and visuospatial function—in PD patients.^{17–22}

In summary, our results show that striatal dopaminergic degeneration—primarily of the executive subregion—contributes to cognitive deficits in PD. Dopaminergic medication appears to be a beneficial therapeutic intervention to improve cognitive deficits in PD.

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CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR CONTRIBUTION

I confirm that all co-authors meet the journal's criteria for authorship and that nobody who meets these criteria has been omitted from the list.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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