Original Article
Striatal dopamine correlates to memory and attention in Parkinson's disease

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Abstract: Parkinson's disease (PD) is clinically characterized by motor symptoms, however, specific cognitive impairments are common and poorly understood. This study was designed to assess whether cognitive performances are related to dopamine active transporter (DAT) availability in non-demented PD subjects. Fifty-four non-demented PD patients were enrolled. They underwent [99mTc] TRODAT-1 SPECT/CT and a comprehensive neuropsychological battery including attention/executive and memory tests. Multiple linear regression controlling the effect of age, disease duration and education was applied. The significance level was set at *P* values of < 0.02. After controlling the effect of age, disease duration and education, lower scores in Rey's Auditory-Verbal Learning Test (RAVLT)/immediate recall were significantly related with lower uptake values in the less affected striatum and more affected caudate. Lower scores in RAVLT/short-term recall were also significantly associated with lower uptake values in the more affected caudate and reduced performance in Trail Making Test part B was related with reduced DAT values in the less affected anterior putamen. Our findings suggest that reduced DAT availability in both caudate and putamen is related to reduced performances in some memory and attention/executive tasks. Nigrocaudate dysfunction is related to lower memory performance while dopamine depletion in the anterior putamen is related to poorer attention performance. If the dopaminergic defects can mostly explain all the cognitive symptoms or this phenomenon just co-occur with other anatomical and biochemical changes remains unknown. Further studies in larger patient samples are required to clarify this issue.

Keywords: Parkinson disease, cognition, radionuclide imaging, DATscan, attention, memory

Introduction

Parkinson's disease (PD) is clinically characterized by motor symptoms, however specific cognitive impairments in executive function, attention, visuospatial skill, and even memory are common [1, 2]. The "frontal" dysfunction can be present since the first stages [2, 3] and the set-shifting and suppressing attention deficits are among the first cognitive domains to show impairment in PD [3-5]. Non-negligible episodic memory deficits, especially in learning/encoding, are common [6] and have been described in early PD subjects [7]. Executive/attentional deficits are probably primary in relation to deficits in other cognitive domains. That is, impairment of memory, learning, visuospatial func-

tions, and verbal fluency is secondary to attention and executive dysfunction [8].

About 30% of PD subjects have mild cognitive impairment (MCI) in the early stages of the disease [6, 9, 10]. Mild cognitive impairment in PD (PD-MCI) is associated with increasing age, disease duration, and disease severity. Moreover, PD-MCI predicts the development of dementia, which can occur in up to 80% of PD patients over the long term [10].

Dopamine active transporter (DAT), which is located in the presynaptic terminal of the dopaminergic projection and it is responsible for dopamine re-uptake, is a marker of dopamine innervation. Thus, [99mTc] TRODAT-1, which binds to DAT, can be used to image the dopaminer-

gic system [11]. Besides [99mTc] TRODAT-1 SPECT, other SPECT and PET methods have been used to evaluate dopaminergic function. Exemples include [123I] FP-CIT SPECT (also known as DaTSCAN™ or DaTscan™) and [18F] F-Dopa PET [12]. The commercial availability of the tracer and the more rapid binding kinetic, which allows much earlier imaging (4 hours) after administration, are possible advantages of using [99mTc] TRODAT-1 SPECT [12, 13]. In clinical practice, DAT imaging can assist the differentiation between conditions with and without presynaptic dopaminergic deficit, which is a hallmark of neurodegenerative parkinsonism. Thus, DAT imaging has an important function on diagnostic accuracy in movement disorders presenting with tremor and/or parkinsonism [14].

A role of dopamine nigrostriatal dysfunction in PD cognitive deficits has been suggested by both PET studies with [18F] F-Dopa and SPECT studies with [123I] FP-CIT [15, 16], however, there are no studies on cognitive performances and [99mTc] TRODAT-1 SPECT. The putamen is thought to be predominantly involved in motor functions and is closely linked with the supplementary motor cortex. The caudate nucleus, however, is connected with the dorsolateral prefrontal cortex and the lateral orbitofrontal cortex, and it has been believed to be mainly involved in cognition in PD [5].

Considering the fact that previous studies have found conflicting results on cognitive performances and striatal dopaminergic function, and the lack of studies on cognition and [99mTc] TRODAT-1 SPECT, this study was designed to assess whether neuropsychological performances are related to DAT availability in non-demented PD subjects.

Materials and methods

Subjects

Fifty-four parkinsonian patients referred to the Department of Neurology of the Federal University of Health Sciences of Porto Alegre were enrolled in the study. Inclusion criteria were the following: (1) diagnostic of Parkinson's disease according to United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria [17]; and (2) [99mTc] TRODAT-1 SPECT imaging within 1 year of evaluation.

Exclusion criteria were the presence of: (1) clinical signs satisfying the criteria of possible atypical parkinsonisms, (2) secondary or iatrogenic parkinsonism, (3) dementia according to last consensus criteria [18], (4) significant cerebral lesions at the magnetic resonance imaging and/or computed tomography (CT) or severe concomitant disease that might explain the presence of cognitive disturbances, (5) use of anticholinergics, and (6) previous PD surgery. All participants gave written informed consent, and the study was approved by the local ethics committee.

Motor symptoms were assessed by UPDRS-III scale [19]. A comprehensive neuropsychological examination was performed during the effect of dopaminergic treatment (in the on state). The cognitive and neuropsychiatric domains assessed were (1) attentional/executive functions (by Trail Making Test Part A [TMT:A] and Part B [TMT:B], Trail Making Test: Part B minus Part A [TMT:B-A] [20], phonological fluency task [FAS], category fluency task [animals] [21], and Frontal Assessment Battery [FAB] [22]); (2) memory (by immediate and delayed recall of Rey's Auditory-Verbal Learning Test [RAVLT] [23]); and (3) depressive symptoms (by Beck Depression Inventory [BDI] [24]). A global cognitive assessment was also performed by Mini-mental State Examination (MMSE) [25] and Montreal Cognitive Assessment (MoCA) [26].

SPECT studies

[99mTc] TRODAT-1 SPECT/CT was performed as described previously [27]. Images were acquired 4 hours after the injection of 740 MBq (20 mCi) of [99mTc] TRODAT-1 (produced by the Institute of Nuclear Energy Research-INER, Taiwan) using a dual-head gamma camera (Siemens Medical System, USA) with fan-beam hole collimators. For each scan, a total of 128 projection angles were made over 360 degrees, 128×128 matrix, 30 seconds/projection, and step-and-shoot mode in a circular orbit. Image data were reconstructed by standard filtered back projection using a Butter-worth filter (cutoff frequency 0.40 Nq), and attenuation was corrected using the Chang method (0.12 cm-1). After reconstruction and attenuation correction, the final slice thickness was 3.32 mm.
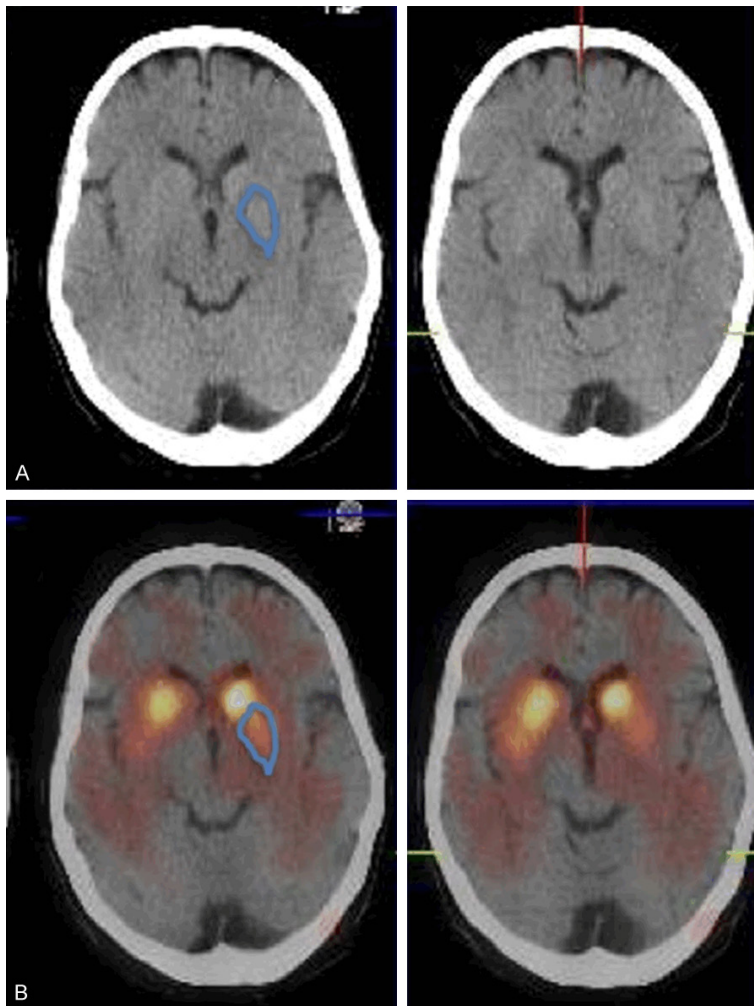
Figure 1. [99mTc] TRODAT-1 SPECT/CT images before (A) and after (B) DAT imaging fusion. The figure represents the 2 consecutive transverse slices showing the highest tracer accumulation in the basal ganglia. The activities in the striatal areas and in the occipital areas (background) were measured by manually delineated regions of interest (ROI) by a nuclear medicine physician. The ROIs were placed using anatomical reference based on CT scans. In this image, a ROI was placed over left putamen.

differences in angle, size, and distance between the interested structures. The region of interest created in the striatal areas was used as a template in the occipital. Eight specific circular ROIs (striatum, caudate, anterior and posterior putamen of both hemispheres) and a polygonal ROI for the occipital cortex were used. Specific binding was estimated to evaluate DAT density/affinity by measuring the mean specific activity in the basal ganglia region, calculated by subtracting the mean counts in the striatal area of interest (e.g., striatum [STR]) from the mean counts in the occipital as background (BKG) and dividing the result by the mean counts in the background [(STR-BKG)/BKG]. This method has been validated in previous studies [28] and has been used in Brazilian studies [29]. DAT densities were calculated for the more affected and less affected striatum, caudate and anterior/posterior putamen. An anterior and posterior ROI were drawn on the putamen at its midpoint. The more affected putamen and caudate were defined as the contralateral ones to the side of the body with prevalence of motor symptoms, while the less affected putamen and caudate were defined as the ipsilateral ones. The reliability between observers of our manually delineated ROI was tested in a previous work conducted by Silva et al. [27], one of the authors of this study.

Statistical analysis

Demographic, clinical and neuropsychological characteristics, and regional DAT densitiy values were expressed by mean ± standard deviation (SD) for normal distribution or median and interquartile range for asymmetrical distribution.

DAT reconstructed images were evaluated in the 2 consecutive transverse slices showing the highest tracer accumulation in the basal ganglia (**Figure 1**). The activities in the striatal areas and in the occipital areas were measured by manually delineated regions of interest (ROI) by a nuclear medicine physician who was blind to the clinical data. The ROIs were placed using anatomical reference based on CT scans. Templates (established and optimized using the data of a control group) were used for defining the total activity in the striatal areas. The size and shape of the templates were adjusted to fit individuals and corrected for anatomical

Table 1. Clinical and neuropsychological features in non-demented PD patients

Non-demented PD subjects (n = 54)	
Age, years	58.6 ± 13.3 [28, 80]
Age at onset, years	52.1 ± 14.3 [17, 78]
Disease duration, years§	4 (2, 6) [2, 25]
UPDRS-III	28.2 ± 16 [5, 63]
H&Y (1/1.5/2/2.5/3)	6/2/29/12/5
Lateralization (right/left)	53/1
Sex (women men)	26/28
Initial symptom (tremor/rigidity or slowness/micrographia)	35/14/5
Location of first symptom (right/left/bilateral)	32/18/4
Motor Subtype (T/AR/MX)	17/35/2
Family history (yes/no)	9/45
L-dopa treatment (yes/no)	52/2
L-dopa daily dose, milligrams	556.7 ± 254.3 [150, 1250]
Education, years	8.7 ± 4.9 [0, 22]
MMSE§	29 (28, 30) [20, 30]
MoCA§	26 (24, 27) [13, 30]
FAB	15 ± 3 [4, 18]
BDI§	8 (6, 14.7) [1, 38]
Categorical fluency (animals)	15.6 ± 4.5 [5, 28]
Phonological fluency task (FAS)	30.2 ± 12.9 [10, 81]
RAVLT-immediate recall (sum of A1 to A5)	32.1 ± 10.9 [11, 59]
RAVLT-short-term recall (A6)	6.7 ± 2.9 [1, 13]
RAVLT-delayed (long-term) recall (A7)	5.8 ± 3.3 [0, 14]
TMT:A§	79 (60.5, 94.2) [37, 300]
TMT:B	143 ± 76.7 [50, 300]
TMT:B-A§	40 (15, 70) [0, 249]

T, PD tremor-dominant group; AR, PD akinetic-rigid group; MX, PD mixed group; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; FAB, Frontal assessment battery; BDI, Beck depression inventory; RAVLT, Rey's auditory verbal learning test; TMT:A, Trail making test: part A; TMT:B, Trail making test: part B; TMT:B-A, Trail making test: part B minus part A. Values in mean + SD [minimum, maximum] for normal distribution. Values in median (interquartile range) [minimum, maximum] for asymmetrical distribution (§).

Correlations between neuropsychological measures and DAT availability for each ROI were assessed by Pearson correlation. The significance level was set at a more stringent P values of < 0.02. Multiple linear regression was applied to control the effect of the age, disease duration and education.

Results

Table 1 shows clinical and neuropsychological features in this sample of 54 non-demented PD subjects. The mean age was 58.6 ± 13.3 years (n = 54) and the median disease duration was 4. Fifty-two percent were men and 54% were Hoehn-Yahr Scale (H&Y) 2. The most common initial symptom was tremor (65%) followed by rigidity/slowness (26%). Sixty-five percent of patients were classified as akinetic/rigid subtype, 31% were tremor-dominant subtype and only 4% were mixed subtype (according to Schiess calculation) [30]. Only 9 patients had positive family history and only 2 patients were not using L-dopa treatment. Using MoCA cutoff score of 25, fifty-seven percent (57%) had positive screening for mild cognitive impairment (MCI) [31, 32].

DAT availability in striatum, caudate, and anterior/posterior putamen (more and less affected) is shown in Table 2.

Correlations between cognitive performances and DAT availability showed that in these non-

Table 2. DAT density/availability in non-demented PD patients

	Subjects (54)
Striatum (more affected)	0.40 ± 0.20
Striatum (less affected)	0.45 ± 0.24
Anterior putamen (more affected)	0.27 ± 0.22
Posterior putamen (more affected)	0.16 ± 0.17
Anterior putamen (less affected)	0.44 ± 0.29
Posterior putamen (less affected)	0.24 ± 0.25
Caudate (more affected)	0.53 ± 0.32
Caudate (less affected)	0.61 ± 0.33

Values in mean ± SD.

demented PD patients lower scores in RAVLT/immediate recall were significantly related with lower DAT density values in the less affected striatum (r = 0.382, P = 0.009), less affected caudate (r = 0.463, P = 0.001) and more affected caudate (r = 0.384, P = 0.008). Lower scores in RAVLT/short-term recall were also related with lower DAT availability in the less affected caudate (r = 0.406, P = 0.006) and more affected caudate (r = 0.411, P = 0.005). Reduced performance in TMT:B was significantly related with reduced DAT density values in the less affected anterior putamen (r = -0.477, P = 0.008). Lower scores in categorical fluency test (animals) were significantly related with lower DAT density values in the less affected caudate (r = 0.421; P = 0.003). No significant correlation was found between DAT availability and other neuropsychological scores. The degree of depression, evaluated by the BDI score, did not show any significant correlation with [99mTc] TRODAT-1 uptake in any of the examined striatal areas.

Except for TMT:B, lower education was significantly related with worst performance in cognitive tests (P < 0.01). No significant correlation was found between disease duration and cognitive performance. Age was significantly associated with RAVLT/immediate recall (r = -0.415; P = 0.004), RAVLT/short-term recall (r = -0.355, P = 0.017) and RAVLT/delayed recall (r = -0.348; P = 0.018), but not with other cognitive performances.

Disease duration was significantly correlated with DAT availability in the less affected striatum (r = -0.436; P = 0.001), but not in the more affected side. Age was not significantly associated with DAT densities. UPDRS-III total score was significantly associated with less affected caudate DAT values (r = -0.460; P < 0.001), but not with other striatal regions.

After multiple linear regression controlling the effect of age, disease duration and education, lower scores in RAVLT/immediate recall were significantly related with lower uptake values in the less affected striatum (parameter estimation = 14.42, P = 0.01) and more affected caudate (parameter estimation = 10.75, P = 0.01; **Figure 2**). Lower scores in RAVLT/short-term recall were also significantly associated with lower uptake values in the more affected caudate (parameter estimation = 3.08, P = 0.01; **Figure 3**) and reduced performance in TMT:B was related with reduced DAT values in the less affected anterior putamen (parameter estimation = -179.41, P = 0.01; **Figure 4**).

Discussion

This study was designed to assess the presynaptic dopaminergic innervation and its relationships with cognitive performances in non-demented PD patients. An analysis of the relationship between striatal DAT availability and cognitive functions suggests that reduced DAT availability in both caudate and putamen is related to reduced performances in some memory and attention/executive tasks. A relation between nigrostriatal dopaminergic dysfunction and cognition in PD has been already reported in previous studies [5, 16, 33, 34], however, [99mTc] TRODAT-1 SPECT/CT has never been used for this purpose. Our data suggest a relation between caudate uptake and memory subtests of RAVLT (immediate recall and short-term recall). This correlation indicates that the weaker the dopaminergic activity the poorer the memory performance in PD subjects. In previous studies a connection between the caudate presynaptic function and the performance in tests measuring memory was found in PD [5, 35, 36]. However, other studies have failed to demonstrate the association between caudate dopaminergic function and memory performance [16, 33, 34]. Caudate dopaminergic hypofunction has been widely associated with frontal/executive dysfunction in patients with PD [15, 16, 33, 34], thus implicating nigrocaudate dopamine depletion in these cognitive deficits. The results of this study and previous studies suggest, however, that the
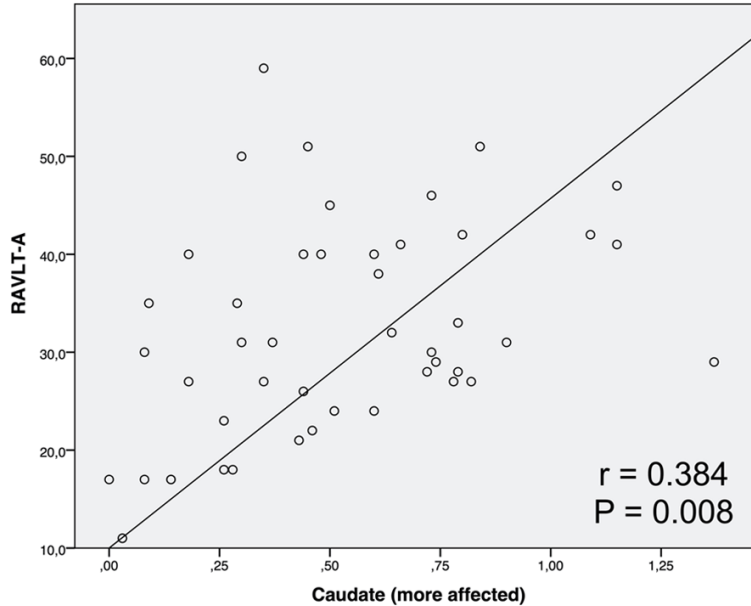
Figure 2. Positive correlation between RAVLT-A (immediate recall) and DAT availability in the more affected caudate.

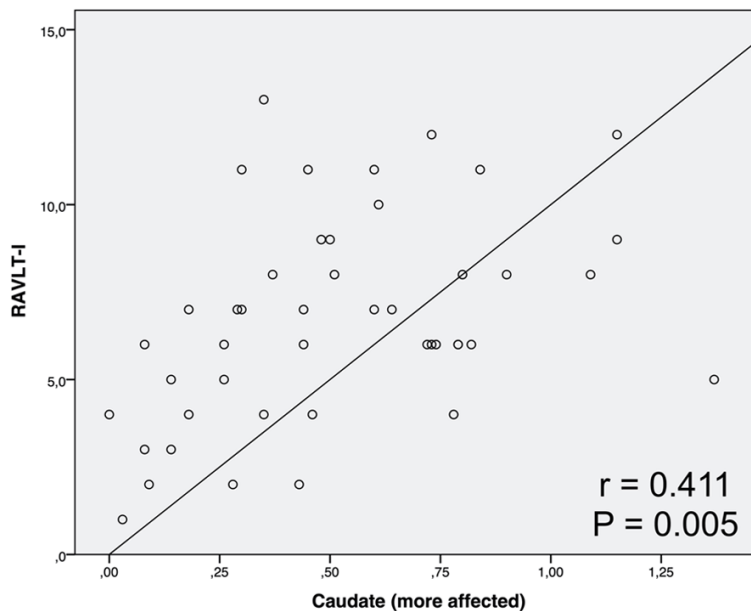**Figure 3.** Positive correlation between RAVLT-I (short-term recall) and DAT availability in the more affected caudate.

cholinergic deficit and Alzheimer's pathology are possible explanations for that [8]. These phenomena could co-occur in PD patients and independently contribute to memory impairment but it has been argued that executive/attentional deficits are primary in relation to deficits in other cognitive domains and that impairment of memory, learning, visuospatial functions, and verbal fluency is a consequence of attention and executive dysfunction [8, 37]. We hypothesize that poorer memory performances could be related to attention impairment due to nigrostriatal dopamine depletion. In fact, we found a negative correlation between TMT:B (a shifting attention test) and DAT values in the less affected anterior putamen. This correlation indicates that the lower the dopaminergic activity the higher the time to perform TMT:B. All of our patients were evaluated in the on state, so we do not believe that akinesia has influenced the results. To avoid the possible influence of motor speed, some authors have used TMT:B-A score. TMT:B-A is interesting, because this test is usually used in PD as an index of cognitive flexibility to switch attention between two competing tasks independently of the time to link letters and numbers. Unfortunately, we did not find any significantly correlation between TMT:B-A and DAT availability. Although the putamen might be predominantly involved with motor behavior and the caudate nucleus more related with behavioral and cognitive functions [38], our study found a correlation between attention/executive function and dopaminergic activity in the less affected putamen. The association between cognitive perfor-

reduced dopaminergic activity in the caudate nucleus is not only related to the classic frontal lobe functions but is also associated with the tests measuring verbal memory. Nonetheless, the mechanisms to explain memory impairment in PD are probably more complex. Frontostriatal dysfunction, hippocampal atrophy [5],
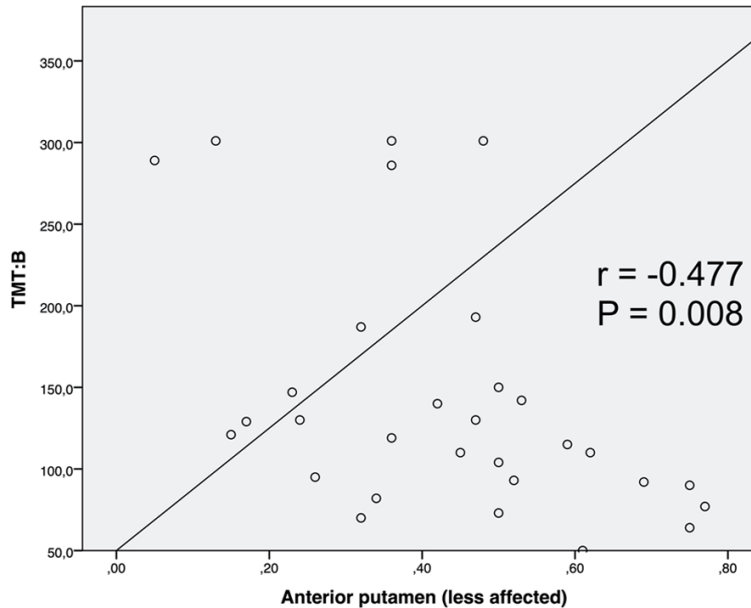
Figure 4. Negative correlations between TMT:B and DAT availability in less affected anterior putamen.

mances and DAT putaminal availability has been previously described [16, 39, 40], although most of the studies have only demonstrated the association between caudate uptake and cognition [5, 15, 33, 34]. We believe that both structures play a role in cognition with a prevalent involvement of caudate. In addition, we found that UPDRS-III total score was significantly associated with less affected caudate DAT values, but not with other striatal regions, corroborating the concept that putamen is not the only striatal subregion involved in motor control.

After multiple linear regression controlling the effect of age, disease duration and education, we did not find significant correlation between verbal fluency and DAT availability, which is in line with results from previous SPECT and PET studies [16, 33, 41]. This finding might be explained by a more predominant dysfunction in the mesocortical dopaminergic pathway instead of the nigrostriatal dopaminergic pathway. The mesocortical dopaminergic involvement in the modulation of verbal fluency has been suggested by Rinne et al., who found a positive correlation between frontal dopaminergic activity and verbal fluency tasks [33]. Paschali et al., in the same way, found an association between left frontal lobe perfusion and verbal fluency tests, but not with striatal dopaminergic activity [41].

As previously described, no significant association between the degree of overall cognitive impairment (e.g., MoCA or MMSE) of patients and presynaptic function was found [33], supporting the concept that dysfunction of the dopamine system has an impact just in some specific cognitive domains.

The decrease of FAB score in PD has been considered attributable to frontostriatal circuit impairment [37] and was associated with lower DAT striatal availability in a previous study [16]; however, in agreement with Jokinen et al., we did not find an association between FAB and striatal dopamine function [5]. In non-demented PD subjects, not only frontostriatal circuit impairment but also parietal lobe dysfunction, especially left inferior parietal lobule and left supramarginal gyrus impairment, may be associated with decreased FAB score. Patients with PD may have frontal lobe dysfunction, but the decreased FAB score may be caused not by progressed frontal lobe dysfunction but by parietal lobe dysfunction added to their preexisting frontal lobe impairment [42]. This could be an explanation for the lack of association between FAB and [99mTc] TRODAT-1 striatal uptake in the present study.

The main limitation of our study is the absence of a control group. Nevertheless, previous controlled studies have found similar results [5, 33, 34].

In conclusion, our findings suggest that reduced DAT availability in both caudate and putamen is related to reduced performances in some memory and attention/executive tasks. If the dopaminergic defects alone can predominantly explain all the cognitive symptoms or this phenomenon co-occur with other anatomical and biochemical changes remains unknown. Further studies in larger patient samples are required to clarify this issue.

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References

[1] Gomperts SN. Lewy body dementias: dementia with lewy bodies and parkinson disease dementia. Continuum (Minneap Minn) 2016; 22: 435-63.

[2] Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E and Obeso JA. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. Lancet Neurol 2009; 8: 1128-39.

[3] Dubois B and Pillon B. Cognitive deficits in Parkinson's disease. J Neurol 1997; 244: 2-8.

[4] Dujardin K, Degreef JF, Rogelet P, Defebvre L and Destee A. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol 1999; 246: 783-8.

[5] Jokinen P, Bruck A, Aalto S, Forsback S, Parkkola R and Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. Parkinsonism Relat Disord 2009; 15: 88-93.

[6] Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, Burn D, Barone P, Pagonabarraga J, Allcock L, Santangelo G, Foltynie T, Janvin C, Larsen JP, Barker RA and Emre M. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology 2010; 75: 1062-9.

[7] Bronnick K, Alves G, Aarsland D, Tysnes OB and Larsen JP. Verbal memory in drug-naive, newly diagnosed Parkinson's disease. The retrieval deficit hypothesis revisited. Neuropsychology 2011; 25: 114-24.

[8] Aarsland D, Bronnick K and Fladby T. Mild cognitive impairment in Parkinson's disease. Curr Neurol Neurosci Rep 2011; 11: 371-8.

[9] Pfeiffer HC, Lokkegaard A, Zoetmulder M, Friberg L and Werdelin L. Cognitive impairment in early-stage non-demented Parkinson's disease patients. Acta Neurol Scand 2014; 129: 307-18.

[10] Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA and Emre M. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. Mov Disord 2012; 27: 349-56.

[11] Sasannezhad P, Juibary AG, Sadri K, Sadeghi R, Sabour M, Kakhki VRD and Alizadeh H. 99mTc-TRODAT-1 SPECT imaging in early and late onset parkinson's disease. Asia Ocean J Nucl Med Biol 2017; 5: 114-119.

[12] Ba F and Martin WR. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. Parkinsonism Relat Disord 2015; 21: 87-94.

[13] Kung HF, Kim HJ, Kung MP, Meegalla SK, Plossl K and Lee HK. Imaging of dopamine transporters in humans with technetium-99m TRODAT-1. Eur J Nucl Med 1996; 23: 1527-1530.

[14] Kagi G, Bhatia KP and Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry 2010; 81: 5-12.

[15] Bruck A, Portin R, Lindell A, Laihinen A, Bergman J, Haaparanta M, Solin O and Rinne JO. Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. Neurosci Lett 2001; 311: 81-4.

[16] Pellecchia MT, Picillo M, Santangelo G, Longo K, Moccia M, Erro R, Amboni M, Vitale C, Vicidomini C, Salvatore M, Barone P and Pappatà S. Cognitive performances and DAT imaging in early Parkinson's disease with mild cognitive impairment: a preliminary study. Acta Neurol Scand 2015; 131: 275-81.

[17] Gibb WR and Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745-52.

[18] Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E and Dubois B. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22: 1689-707.

[19] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A,

Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ and LaPelle N; Movement Disorder Society UPDRS Revision Task Force. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UP-DRS): scale presentation and clinimetric testing results. Mov Disord 2008; 23: 2129-70.

[20] Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Arch Clin Neuropsychol 2004; 19: 281-8.

[21] Tombaugh TN, Kozak J and Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol 1999; 14: 167-77.

[22] Dubois B, Slachevsky A, Litvan I and Pillon B. The FAB: a frontal assessment battery at bedside. Neurology 2000; 55: 1621-6.

[23] Ivnik RJ, Malec JF, Tangalos EG, Petersen RC, Kokmen E and Kurland LT. The auditory-verbal learning test (AVLT): norms for ages 55 years and older. Psychol Assess 1990: 304-12.

[24] Beck AT, Ward CH, Mendelson M, Mock J and Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-71.

[25] Folstein MF, Folstein SE and McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.

[26] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL and Chertkow H. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695-9.

[27] Silva N Jr, Szobot CM, Shih MC, Hoexter MQ, Anselmi CE, Pechansky F, Bressan RA and Rohde LA. Searching for a neurobiological basis for self-medication theory in ADHD comorbid with substance use disorders: an in vivo study of dopamine transporters using (99m)Tc-TRODAT-1 SPECT. Clin Nucl Med 2014; 39: e129-34.

[28] Krause KH, Dresel SH, Krause J, Kung HF and Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 2000; 285: 107-10.

[29] Shih MC, Franco de Andrade LA, Amaro E Jr, Felicio AC, Ferraz HB, Wagner J, Hoexter MQ, Lin LF, Fu YK, Mari JJ, Tufik S and Bressan RA. Higher nigrostriatal dopamine neuron loss in early than late onset Parkinson's disease?-a [99mTc]-TRODAT-1 SPECT study. Mov Disord 2007; 22: 863-6.

[30] Schiess MC, Zheng H, Soukup VM, Bonnen JG and Nauta HJ. Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. Parkinsonism Relat Disord 2000; 6: 69-76.

[31] Memória CM, Yassuda MS, Nakano EY and Forlenza OV. Brief screening for mild cognitive impairment: validation of the Brazilian version of the Montreal cognitive assessment. Int J Geriatr Psychiatry 2013; 28: 34-40.

[32] Martinelli JE, Cecato JF, Bartholomeu D and Montiel JM. Comparison of the diagnostic accuracy of neuropsychological tests in differentiating Alzheimer's disease from mild cognitive impairment: can the montreal cognitive assessment be better than the cambridge cognitive examination? Dement Geriatr Cogn Dis Extra 2014; 4: 113-21.

[33] Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M and Solin O. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol 2000; 57: 470-5.

[34] Nobili F, Campus C, Arnaldi D, De Carli F, Cabassi G, Brugnolo A, Dessi B, Morbelli S, Sambuceti G, Abbruzzese G and Rodriguez G. Cognitive-nigrostriatal relationships in de novo, drug-naive Parkinson's disease patients: a [I-123]FP-CIT SPECT study. Mov Disord 2010; 25: 35-43.

[35] Holthoff VA, Vieregge P, Kessler J, Pietrzyk U, Herholz K, Bonner J, Wagner R, Wienhard K, Pawlik G and Heiss WD. Discordant twins with Parkinson's disease: positron emission tomography and early signs of impaired cognitive circuits. Ann Neurol 1994; 36: 176-82.

[36] Holthoff-Detto VA, Kessler J, Herholz K, Bonner H, Pietrzyk U, Wurker M, Ghaemi M, Wienhard K, Wagner R and Heiss WD. Functional effects of striatal dysfunction in Parkinson disease. Arch Neurol 1997; 54: 145-50.

[37] Zgaljardic DJ, Borod JC, Foldi NS and Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. Cogn Behav Neurol 2003; 16: 193-210.

[38] Bhatia KP and Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 1994; 117: 859-76.

[39] Muller U, Wachter T, Barthel H, Reuter M and von Cramon DY. Striatal [123I]beta-CIT SPECT and prefrontal cognitive functions in Parkinson's disease. J Neural Transm (Vienna) 2000; 107: 303-19.

[40] Duchesne N, Soucy JP, Masson H, Chouinard S and Bédard MA. Cognitive deficits and stria-

tal dopaminergic denervation in Parkinson's disease: a single photon emission computed tomography study using 123iodine-beta-CIT in patients on and off levodopa. Clin Neuropharmacol 2002; 25: 216-24.

[41] Paschali A, Messinis L, Kargiotis O, Lakiotis V, Kefalopoulou Z, Constantoyannis C, Papathanasopoulos P and Vassilakos P. SPECT neuroimaging and neuropsychological functions in different stages of Parkinson's disease. Eur J Nucl Med Mol Imaging 2010; 37: 1128-40.

[42] Matsui H, Udaka F, Miyoshi T, Hara N, Tamura A, Oda M, Kubori T, Nishinaka K and Kameyama M. Frontal assessment battery and brain perfusion image in Parkinson's disease. J Geriatr Psychiatry Neurol 2006; 19: 41-5.