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Intrastriatal gradient analyses of 18F-FDOPA PET scans for differentiation of Parkinsonian disorders

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ABSTRACT

Aim: L -3,4-dihydroxy-6–18F-fluorophenylalanine (18F-DOPA PET may be used to distinguish subjects with Parkinsonism from those with symptoms not originating from impaired dopaminergic transmission. However, it is not routinely utilized to discriminate Idiopathic Parkinson's disease (IPD) from Atypical Parkinsonian Disorders (APD). We investigated the potential of FDOPA PET to discriminate between IPD and APD, with a focus on the anterior-to-posterior decline in het striatum, considered to be more specific for IPD.

Materials and methods: 18F-DOPA PET data from a total of 58 subjects were retrospectively analyzed. 28 subjects had idiopathic Parkinson's disease (14 male, 14 female; age at scan 61 +- 11,5), 13 atypical Parkinsonian disease (7 male, 6 females; age at scan: 69,6 +- 6,4) and 17 were controls (6 male, 11 female; age at scan 65,3 +-8,6). Regional striatal-to-occipital ratio's (RSOR's) were calculated, as well as multiple in-line VOI's from the caudate nucleus to the posterior part of the putamen. The linearity of anteroposterior decline was determined by a linear regression fit and associated R squared values. ROC curves were calculated to assess the diagnostic performance of these measurements. Data contralateral to the clinically most affected side were used for analysis.

Results: ROC curve analysis for differentiation between controls and Parkinsonism patients showed the highest AUC for the caudate nucleus-to-posterior putamen ratio (AUC = 0.930; $p < 0.00$) and for the R squared value for the linear regression fit (AUC = 0.948; $p = 0.006$). For discrimating IPD from APD, the highest AUC was found for the caudate nucleus-to-anterior putamen ratio (0.824; $p < 0.001$)

Conclusions: Subregional analysis of the striatum in F-DOPA PET scans may provide additional diagnostic information in patients screened for a presynaptic dopaminergic deficit. A more linear decrease from the head of the caudate nucleus to the posterior putamen was present in patients with IPD, although this feature did not have additional diagnostic value over the RSOR analysis.

1. Introduction

Parkinson's disease (PD) is a slowly progressive degenerative disorder associated with the loss of dopaminergic neurons, mainly in the substantia nigra pars compacta. The loss of these nigrostriatal projection neurons and a resulting decrease of striatal dopamine release accounts for many of the clinical features. PD is one of the most prevalent neurodegenerative diseases, affecting 1% of the population over 50 years old (Gilmore, 1984). Most patients show signs of motor dysfunctions characterized by bradykinesia, rigidity, and tremor, often with unilateral onset. Motor signs are levo-dopa responsive . No perfect ante mortem diagnostic test exists as yet and currently, the most reliable diagnostic method is the strict use of published clinical criteria and follow up by a movement disorder specialist (Schrag et al., 2002; Gibb and Lees, 1989). Nevertheless, the accuracy of the clinical diagnosis of idiopathic Parkinson's disease continues to be a challenge, with autopsy studies showing misdiagnosis rates up to one quarter of cases (Hughes et al., 1993; Rajput et al., 1991). Most often, the incorrect diagnosis of idiopathic Parkinson's disease (IPD) can be attributed to the presence of other neurodegenerative diseases, often coined atypical Parkinsonian disorders (APD), such as Multiple Systems Atrophy (MSA) or Progressive Supranuclear Palsy (PSP) (Schrag et al., 2002). Given

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that the evolution, treatment and prognosis of patients with different kinds of neurodegenerative diseases may differ (Barclay and Lang, 1997; Wenning et al., 1997; Dhawan et al., 2002), correct diagnosis is of major importance both in clinical practice and in research.

While 18F-FDG PET may show characteristic patterns of hypometabolism in different Parkinsonian disorders (Walker et al., 2018), presynaptic dopaminergic imaging convincingly demonstrates impaired dopaminergic function, but is not routinely utilized to discriminate IPD from APD. Presynaptic dopaminergic imaging, most often ^{123}I-FP-CIT dopamine transporter (DAT) SPECT, has been performed to demonstrate the loss of striatal presynaptic dopamine transporters in nigrostriatal neurons that is associated with degenerative parkinsonism. In IPD, such presynaptic dysfunction is the primary cause of disease, while in APD it may be secondary to postsynaptic cell loss. Using visual and quantitative reading, subjects with Parkinsonism can be distinguished from those with symptoms not originating from impaired dopaminergic transmission, such as essential tremor and drug induced Parkinsonism. These latter conditions are not associated with a presynaptic dopaminergic defect (Brooks, 1998). Although substriatal analysis revealed significant differences within the Parkinsonian disorders, accurate differentiation was hampered by considerable overlap (Joling et al., 2017). PET ligands such as L-3,4-dihydroxy-6–18F-fluorophenylalanine (18F-DOPA), may be better suited to differentiate IPD from APD, because of its potential to quantify presynaptic dopaminergic functioning and its superior spatial resolution in comparison to SPECT Striatal-to-occipital ratio's (SOR) are currently used in routine clinical practice to discriminate healthy or non-dopamine deficient symptomatic subjects from Parkinsonian patients. This approach is considered to be sufficiently sensitive and supportive for a diagnosis of IPD, even in its early stages. The potential of ^{18}F-DOPA PET to differentiate between IPD and APD has not extensively been studied and has been limited to subregional VOI analysis within the striatum (Jaimini et al., 2013). This latter approach, however, may not be fully reproducible, as these regions are not well defined anatomically. Therefore, we investigated the diagnostic value of substriatal VOI analysis as well as multiple in-line VOI's from the caudate nucleus to the posterior part of the putamen.

2. Methods

2.1. Subjects characteristics

F-DOPA PET data from a total of 58 subjects were retrospectively analyzed (for subject characteristics, see Table 1). 28 subjects had idiopathic Parkinson's disease (14 male, 14 female; age at scan 61 +- 11,5), 13 atypical Parkinsonian disease (7 male, 6 females; age at scan: 69,6 +- 6,4) and 17 were controls (6 male, 11 female; age at scan 65,3 +− 8,6). All underwent F-DOPA PET scans as part of their clinical evaluation. The atypical Parkinsonian group consisted of patients with MSA (n = 2), PSP (n = 4), CBD (n = 3), DLB (n = 3), and SCA-3 (n = 1). In control subjects, which were scanned as part of their neurological evaluation (e.g. doubtful diagnosis of IPD), symptoms were in essence not considered to be due to dopamine deficiency. All patients were diagnosed by specialists from the Neurology Movement Disorder unit of the University Hospital of Groningen, according to clinical criteria and with at least 2 years of clinical follow up.

Table 1
Subject characteristics. APD, atypical Parkison disease; IPD, idiopathic Parkinson's disease; H&Y, Hoehn and Yahr Scale.

	Control = 17	APD = 13	IPD = 28
Age [mean in years (± SD)]	65.35 (± 8.63)	69.61 (± 6.42)	61.04 (± 11.53)
Sex (female: male)	11: 6	6: 7	14: 14
Symptom duration [mean in years]	–	2538 (± 2.03)	2.14 (± 2.35)
Age of diagnosis	–	70.3 (± 6)	60.4 (± 11)
H&Y score	–	2.38 (± 0.76)	1.83 (± 0.7)

2.2. Image acquisition

Patients were allowed to continue antiParkinsonian medication, with the exception of catechol-O-methyl transferase inhibitors. All patients fasted for a minimum of four hours and were pretreated with 2.5 mg/kg of carbidopa orally. Sixty minutes later, subjects received intravenously 200MBq of 18F-DOPA. After ninety minutes the tracer administration, one static 3D acquisition of 6 min was performed on a Siemens HR+ camera (Siemens, Erlangen, Germany), according to the standard operating procedures protocol of the University Hospital of Groningen. Image data were reconstructed using iterative methods (ordered subsets expectation maximization) and corrected for attenuation.

2.3. Image analysis

Employing PMOD version 3.8, PET images were spatially normalized to a standard template and 2 predefined sets of volumes of interest (VOIs) were applied to the normalized images. Values from PET were calculated in both standardized and patient spaces.

The first VOI set consisted of the caudate nucleus (CN), anterior putamen (AP), posterior putamen (PP) and whole putamen (Fig. 1A). The second was formed by 9 multiple in-line spherical VOIs (with a radius of 2 mm) through the striatum from anterior-to-posterior (Fig. 1B). Both sets included the occipital cortex region as reference, assuming that this region presents nonspecific uptake for this tracer. Striatal-to-occipital (SOR) ratios were calculated by dividing each region with the averaged occipital value. For the first set, the following regional striatal-to-occipital ratio's (RSORs) were calculated: CN-to-AP, CN-to-PP and AP-to-PP; for the second set, 9 spherical in-line VOIs were placed from the caudate nucleus to the posterior part of the putamen. The linearity of anteroposterior decline (slope) was determined by a linear regression fit and associated R squared values. Data contralateral to the clinically most affected side were used for analysis.

2.4. Statistical analysis

Statistical analysis of our data was processed by IBM SPSS statistics 23 (64 bits). Using one sample t-tests, all values were firstly compared between the data acquired from the PET in the standardized space and in the patient original space to validate the efficiency of the normalization process. The Shapiro-Wilk test was used to verify the presence of a normal distribution of the datasets. RSORs, slope and R squared were compared between each group using ANOVA test. Sensitivity and specificity of all values were calculated by the construction of receiver operator characteristic (ROC) curves and their respective areas under the curve (AUC) in a two-step method. First, the subjects were divided in controls (=17) and Parkinsonian patients (=41) and the optimal cutoff values was obtained from the ROC curves. Then, Parkinsonian patients were separated in two distinct groups, APD and IPD, and similarly, optimum cutoff values were acquired.

3. Results

The transition of data from patient space into standard space did not result in significant VOI value changes (t-test, $p > 0.05$), except for the CN SOR in the control group. For the purpose of clarity, the subsequent results shown in the study were derived from the data of the standardized PET images. All SORs, RSORs, slope and R squared were significantly different between controls and subjects with Parkinsonism, with the exception of the SOR CN when comparing controls to APD (p = 0.319, ANOVA). When analyzing the IPD and APD groups, the highest SOR means of the IPD and the APD were the caudate nucleus

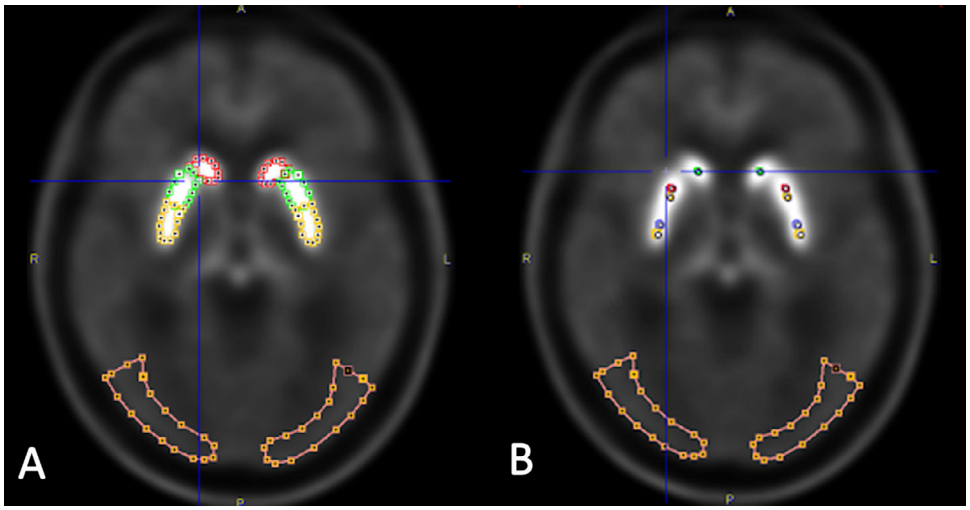

Fig. 1A. Axial section of the template used for the spatial normalization of the images showing the striatum bilaterally covered by 3 different VOIs (caudate nucleus, anterior putamen and posterior putamen) and the occipital reference region. B. Axial section of the template used for the spatial normalization of the images showing the striatum bilaterally covered by 9 multiple in-line spherical VOIs and the occipital reference region.

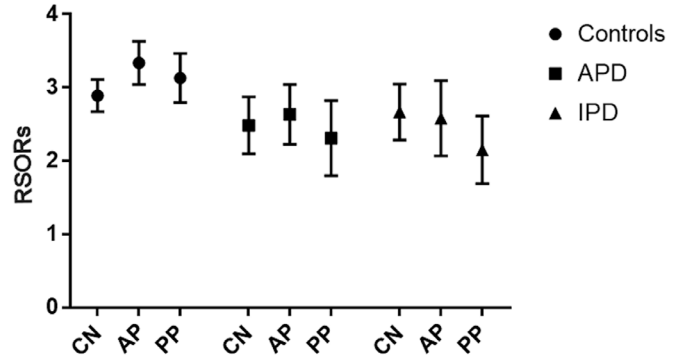

Fig. 2. SOR values of controls, APD and IPD patients. The posterior putamen is most affected in APD and IPD, but the anterior putamen is relatively spared in APD.

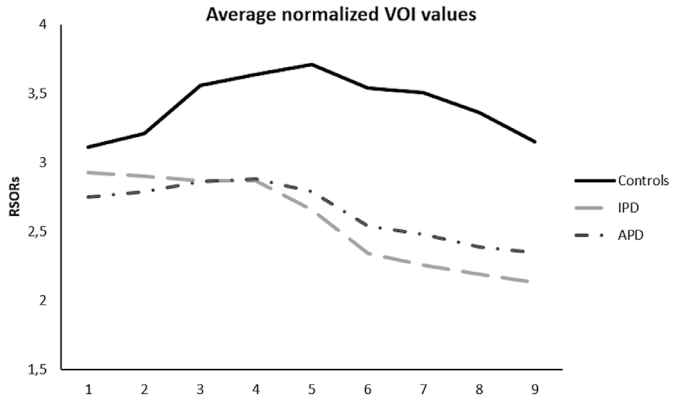

Fig. 3. Mean values of all 9 in-line spherical VOIs for each group, from the head of the caudate nucleus to the posterior part of the putamen.

(2.66) and anterior putamen (2.63) respectively, and the posterior putamen was lowest in both groups (IPD: 2.15; APD: 2.31). No significant differences were observed between the SOR's in both groups ($p > 0.05$, ANOVA, Fig. 2). RSORs showed significant differences in all groups, except for the RSOR of AP to PP between APD and IPD ($p = 0.194$), table 2. Despite a small significant difference in mean age between patients with IPD and APD, no significant correlations were found between age and SOR values in these groups ($p > 0.05$). Pearson's r was 0.27, 0.33 and 0.36 for the CN, AP, and PP in IPD and −0.21, −0.23, −0.32 in APD respectively.

In the regression analysis, we observed a higher tendency for the striatal uptake values of the IPD group to fit in a linear pattern, as can be seen in Fig. 3. The IPD group showed the highest R squared values, suggesting that a linear pattern, in this case a gradual anterior to posterior decline of RSOR values in the striatum, is more present in this group when compared to the APD and the control group.

ROC curve analysis for differentiation between controls and Parkinsonism patients showed highest area under the curve for the CN to PP ratio (AUC = 0.930; $p < 0.00$) and for the R squared value for the linear regression fit (AUC = 0.948; $p < 0.006$ – Table 3). For differentiation between IPD and APD, the highest AUC was the CN to AP ratio (0.824; $p < 0.001$ – Figs. 4 and 5). As might be expected, we found that if patients with three or more years of evolution of the disease were excluded from the analysis, the AUC for separating IPD and APD AUC increased to 0.867.

Table 2
SOR, striatal-to-occipital ratio; RSOR, regional-striatal-to-occipital ratio; regions with highest values are underlined for each group.

	Group Mean (SD) Controls	APD	IPD	ANOVA (p value) Controls vs APD	Controls vs IPD	APD vs IPD
SOR CN	2.89 (0.22)	2.48 (0.39)	2.66 (0.38)	*0.01*	0.32	0.06
SOR AP	3.33 (0.29)	2.63 (0.4)	2.58 (0.51)	*0.00*	*0.00*	0.72
SOR PP	3.13 (0.33)	2.31 (0.51)	2.15 (0.46)	*0.00*	*0.00*	0.28
RSOR CN to AP	0.87 (0.03)	0.94 (0.06)	1.04 (0.09)	*0.00*	*0.00*	*0.00*
RSOR CN to PP	0.92 (0.05)	1.1 (0.12)	1.26 (0.19)	*0.00*	*0.00*	*0.00*
RSOR AP to PP	1.07 (0.05)	1.16 (0.1)	1.2 (0.13)	*0.02*	*0.00*	0.19
Slope	−0.001 (0.04)	0.06 (0.05)	0.12 (0.07)	*0.00*	*0.00*	*0.00*
R Squared	0.12 (0.16)	0.55 (0.31)	0.77 (0.22)	*0.00*	*0.00*	*0.00*

Table 3
AUC, area under the curve.

	AUC Controls vs Parkinsonism	APD vs IPD
SOR CN	.650	.646
SOR AP	.923	.456
SOR PP	.911	.398
RSOR CN to AP	.915	.824
RSOR CN to PP	.930	.799
RSOR AP to PP	.846	.651
Slope	.907	.794
R Squared	.948	.772

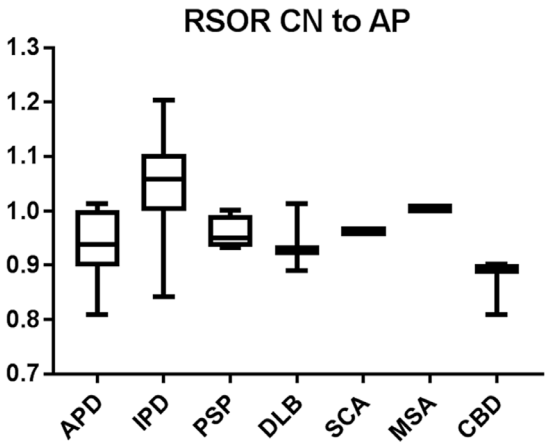

Fig. 4. Boxplot of regional striatal-to-occipital uptake values from the caudate nucleus relative to the anterior putamen of APD and IPD. On the right the values of the individual APD groups are displayed.

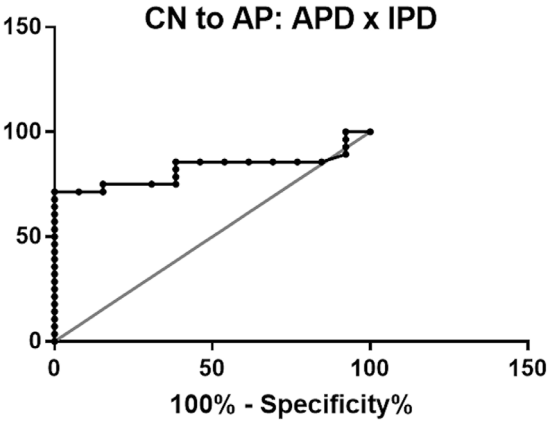

Fig. 5. ROC curve for differentiation between AUC = 0,824; Std. Error = 0,06; 95% confidence interval = 0,7 to 0,92; *p* value = <0,001.

4. Discussion

Our data support the previous notion that the depletion of F-DOPA uptake in both patients with idiopathic Parkinson's disease and patients with atypical Parkinsonism preferentially affects the posterior part of the putamen (Jaimini et al., 2013). Additionally, in our analysis a more linear decrease from the anterior to the posterior part of the putamen was present in patients with Parkinsonism than in those without. This linearity was more evident in patients with IPD in comparison to those with atypical Parkinsonism. In patients with atypical Parkinsonism, the anterior part of the putamen may be relatively spared whereas the caudate nucleus may be relatively more affected, which is reflected by a significantly lower CN-to-AP ratio in comparison to IPD.

The preferential presynaptic dopaminergic decline of the posterior putamen in IPD is caused by predominantly affected ventrolateral parts of the substantia nigra and its striatal projections (Fearnley and Lees, 1991). As the disease progresses, this decline may expand to the remaining striatum, while the rate of decline stays equal in striatal subregions (Bruck et al., 2006). Atypical Parkinsonian disorders such as MSA and PSP, may show this gradient evolution to a lesser degree (Wenning et al., 1997; Burn et al., 1994), thus reflecting a more general post-synaptic (striatum) deficit. Jaimini et al. previously attempted to discriminate APD patients from IPD patients, based on this regionally specific decrease in FDOPA uptake (Jaimini et al., 2013). They showed that the intrastriatal ratio of the caudate-to-posterior putamen and caudate-to-whole putamen may be useful for this differentiation. However, as there is no anatomic definition of the posterior and the anterior putamen, this approach may not be fully reproducible and less sensitive to subtle changes in the posterior part of the putamen. We, therefore, to remove bias due to arbitrary definition of the posterior putamen, deepened this analytic approach by dividing the striatum in anatomic sub-regions, by adding multiple in-line spherical volumes of interest through the striatum and analyzing the linear fit of the anterior-to-posterior dopaminergic function decline. Indeed, IPD patients tended to have a more linear decrease from the anterior-to-posterior putamen, but this did not show a higher diagnostic accuracy than the RSOR analysis.

4.1. Limitations

A limitation of the current analysis is the heterogeneity of the atypical Parkinsongroup, which consisted of patients with MSA, DLB, PSP, DLB and SCA-3, which may have obscured disease specific metabolic disturbances (Piccini et al., 2001). Less heterogeneity may have led to an improved diagnostic accuracy in selected cases. In addition, no post-mortem verification of the clinical diagnosis was obtained. To reduce the potential for error, a minimum follow-up of 2 years by a neurologist specialized in movement disorders was required for our analysis. A small but significant age difference was present between the IPD and APD group. This may have resulted in different SOR values, although this is not particularly relevant for our analysis, as the age related decline is assumed to be relatively homogenously present in the whole striatum. In our sample, no significant correlations between age and SOR values were detected in patient groups, with observed correlation coefficients unlikely to generate regional striatal differences. Other factors that may have influenced the outcomes of the analysis include clinical symptoms which have been shown to influence uptake of F-DOPA, such as tremor dominance (Pikstra et al., 2016) (not significant in our series, data not shown), and the UPDRS scores (particularly motor scores), which have not been included in the current analysis. Finally, the sample sizes in this analysis were relatively small, however comparable to other studies in this field (Jaimini et al., 2013; Jokinen et al., 2009)

5. Conclusions

Subregional analysis of the striatum in F-DOPA PET scans may provide additional diagnostic information in patients screened for a presynaptic dopaminergic deficit. In our analysis, the posterior putamen was the region with the highest diagnostic accuracy for the differentiation of subjects with and without Parkinsonism. In addition, in APD, the anterior putamen was spared relative to the caudate nucleus, resulting in a lower caudate nucleus-to-anterior putamen ratio. A more linear decrease from the head of the caudate nucleus to the posterior putamen was present in patients with IPD, although this feature did not have additional diagnostic value over the RSOR analysis.

CRediT authorship contribution statement

Gilles N. Stormezand: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Lumi T. Chaves:** Conceptualization, Formal analysis, Writing - original draft. **David Vállez García:** Methodology, Visualization. **Janine Doorduin:** Conceptualization, Formal analysis. **Bauke M. De Jong:** Conceptualization, Formal analysis. **Klaus L. Leenders:** Conceptualization, Formal analysis. **Berry P.H. Kremer:** Supervision. **Rudi A.J.O. Dierckx:** Conceptualization, Supervision, Writing - original draft.

Declaration of Competing Interest

The authors declare that thay have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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