Dopamine denervation in the functional territories of the striatum: a new MR and atlas-based 123I-FP-CIT SPECT quantification method

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Abstract

Current quantification methods of ^{123}I-FP-CIT SPECT rely on anatomical parcellation of the striatum. We propose here to implement a new method based on MRI segmentation and functional atlas of the basal ganglia (MR-ATLAS) that could provide a reliable quantification within the sensorimotor, associative, and limbic territories of the striatum. Patients with Parkinson's disease (PD), idiopathic rapid eye movement sleep behavioral disorder (iRBD) and healthy controls underwent ^{123}I-FP-CIT SPECT, MRI, motor, and cognitive assessments. SPECT data were corrected for partial volume effects and registered to a functional atlas of the striatum to allow quantification in every functional region of the striatum (nucleus accumbens, limbic, associative, and sensorimotor parts of the striatum). The MR-ATLAS quantification method proved to be reliable in every territory of the striatum. In addition, good correlations were found between cognitive dysexecutive tests and the binding within the functional (limbic) territories of the striatum using the MR-ATLAS method, slightly better than correlations found using the anatomical quantification method. This new MR-ATLAS method provides a robust and useful tool for studying the dopaminergic system in PD, particularly with respect to cognitive functions. It may also be relevant to further unravel the relationship between dopaminergic denervation and cognitive or behavioral symptoms.

Keywords: Parkinson's disease, idiopathic rapid eye movement sleep behavioral disorder, 123I-FP-CIT SPECT, DATSCAN, striatum

Introduction

[123I] N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane single-photon emission computed tomography (^{123}I-FP-CIT SPECT) is a well-validated radiopharmaceutical that binds to the membrane dopamine transporter strongly expressed in dopaminergic neuron terminals in the striatum. It is used in clinical practice to support the diagnosis of diseases characterized by presynaptic dopaminergic denervation like Parkinson's disease (PD). ^{123}I-FP-CIT binding quantification relies on fully-automated or semi-automated methods that have already proven their usefulness and validity (Koch et al. 2005; Tossici-Bolt et al. 2006; Nobili et al. 2013; Brogley 2019). Numerous methods offer a parcellation of the striatum separating nuclei of the striatum (caudate nucleus vs. putamen) or subregions of the putamen (e.g. anterior and posterior putamen) (Koch et al. 2005; Brogley 2019). Nonetheless, the regions defined accordingly do not take into account the anatomo-functional organization of the striatum in sensorimotor, associative, and limbic territories based on their cortical afferents (Yelnik et al. 2007; Choi et al. 2017). Yet, histology-based MR atlases have been created and designed to allow an accurate delineation of these functional regions (Yelnik et al. 2007). Here, we propose a new MR and atlas-based method (MR-ATLAS) that will allow for the quantification of ^{123}I-FP-CIT SPECT in functional territories of the striatum and may be useful for research purposes. To prove its relevance and validity, we tested this method in healthy controls, patients with PD and idiopathic rapid eye movement sleep behavioral disorder (iRBD), considered to be a prodromal phase of parkinsonism (Postuma et al. 2019) and compared it to a validated quantification method (Koch et al. 2005) using correlations between methods and correlations with clinical scores.

Material & Methods

Population

Forty-six patients with Parkinson's disease (PD), 21 patients with iRBD and 21 healthy age-matched controls were enrolled in the ICEBERG study. Briefly, PD patients were consecutively recruited since November 2015 according to the following criteria: age ≥ 18 years, "possible", "probable" or "defined" PD according to the UKPDSBB criteria (Hughes et al. 1992), disease duration ≤ 4 years at the time of inclusion. Exclusion criteria included the absence of dopaminergic loss in ^{123}I-FP-CIT SPECT, Parkinsonism secondary to neuroleptics or atypical Parkinsonism, and neuroleptic treatment 6 months prior to inclusion in the study. Diagnosis of iRBD patients was confirmed by polysomnography and had a normal neurological examination notably without Parkinsonism. Finally, the control subjects were healthy volunteers with a normal neurological examination and no symptom or sign of PD. Patients and controls were matched for age and sex at recruitment. Additional exclusion criteria at inclusion were a Mini Mental Status Examination (MMSE) < 26, the presence of an active psychiatric disorder, a life expectancy below one-year, legal protection (guardianship, curatorship), or contraindication to MRI. All procedures performed in this study were in accordance with the ethical standards of the institutional and French national research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the local ethic committee *Comité de Protection des Personnes (CPP)* "Ile-de-France VI" (IRB:2014-A00725-42 / 48-14). Informed consent was obtained from all individual participants included in the study.

Each participant underwent motor assessment using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scale. For PD participants, this was performed in a "OFF" period, i.e. after at least 12h dopaminergic treatment discontinuation (Goetz et al. 2008). We then calculated an MDS-UPDRS III Rigid Akinetic subscore for each patient and each hand side (sum of the 5 segmental akinesia scores and of the 2 limbs rigidity scores: from 0 to 28 points for each hand side). A short cognitive assessment was also performed including the Frontal Assessment Battery (FAB) (Dubois et al. 2000) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005).

Imaging Acquisition

SPECT data were collected using the ^{123}I-FP-CIT tracer (DATSCAN®). PD patients did not interrupt their medication before the SPECT acquisition. One hour after ingestion of a single dose of Lugol, 185 MBq (169.2 ± 8.5 MBq, 138-192 MBq) of ^{123}I-FP-CIT were injected. The acquisition began approximately 180 min (mean ± standard deviation: 187 ± 11 min, range: 169-229 min) after the injection. The acquisition consisted of 120 projections acquired in 30 minutes on a hybrid Discovery NM/CT 670 Pro scanner (GE Healthcare™, Milwaukee, 2-head imager equipped with low-energy / high-resolution collimators) coupled with a high-resolution computed tomography (CT). All data were reconstructed using an iterative algorithm that includes motion detection and correction, then post-filtered (low pass filter: order = 4, cut-off frequency = 0.35 cm^{-1}) and finally corrected for attenuation using the Chang method (μ = 0.12 cm^{-1}) (Chang 1978).

Magnetic resonance imaging (MRI) data were collected using a 3 Tesla PRISMA FIT Siemens™ scanner (gradient amplitude 80 mT/m, 64-channel receive head coil). The anatomical T1-weighted (T1w) images were acquired using a Magnetization Prepared 2 Rapid Acquisition Gradient Echoes sequence (MP2RAGE, TR: 5000.00ms, TE: 2.98ms, TI: 700 & 2500ms, voxel size = 1x1x1mm^3).

Data Processing

A schema of neuroimaging processing is provided in Supplementary Material (Supplementary Figure 1).

Regions of Interest (ROI) creation

^{123}I-FP-CIT SPECT, CT, and MRI data were transformed into Nifti. The T1w images were segmented according to two methods: 1) using the CAT12 software (www.neuro.uni-jena.de/cat/) as an SPM

toolbox (SPM12: www.fil.ion.ucl.ac.uk/spm/software/spm12/) for the cerebral cortex, white matter and cerebrospinal fluid (CSF); 2) the FSL FIRST toolbox (Patenaude et al. 2011) for basal ganglia (nucleus accumbens, caudate nucleus, putamen, and globus pallidus) and thalamus. Note that the globus pallidus and the thalamus were segmented only for purposes of partial volume correction (see below). Basal ganglia functional territories were then individually created using a 2-step registration procedure: 1) a rigid registration followed by an affine deformation between the 3D T1w images of each participant and that of the reference subject of the YeB atlas (Yelnik et al. 2007); and 2) a nonlinear registration step between the previously obtained image (step 1 of the registration) and the FIRST segmented T1w images (after binarization of the accumbens, caudate, putamen, globus pallidus, and thalamus regions of interest [ROIs]) using the SPM 'Old Normalize' procedure. Thus, for each participant, we defined individual ROIs in the native space corresponding to the following structures or regions: the functional territories (sensorimotor, associative, and limbic) of the caudate nucleus and putamen, as well as the nucleus accumbens, the internal and external globus pallidus and the thalamus (Figure 1B).

Partial Volume Effects correction

Rigid registration was performed with SPM between the CT and the T1w images of each subject and applied to the ^{123}I-FP-CIT SPECT image. Thanks to the previously obtained segmentations of the basal ganglia, cerebral cortex, white matter, and CSF, five compartments were individually created to perform the partial volume effects correction (PVEc) according to the iterative Yang method (region-based voxel-wise correction - RBV) (Yang et al. 1996; Thomas et al. 2011) (number of iterations = 7). For every participant the full width at half maximum (FWHM) at the center of the field of view was calculated according to the source-to-collimator distance (radius), after measurement using a phantom, identic in the 3 dimensions (8.83 ± 0.28 mm, range = 8.52 – 10.08mm). This individual FWHM was then used to perform PVE correction using spatially variant resolution (according to the radius of the acquisition) for each participant. A white matter compartment, a CSF compartment, and

three gray matter compartments were defined according to human post-mortem dopaminergic quantification data (Gerlach et al. 1996): high-density dopamine gray matter (accumbens, caudate, putamen), intermediate-density dopamine gray matter (internal globus pallidus) and low-density dopamine gray matter (thalamus, cerebral cortex) (Figure 1A).

Quantitative normalization

Finally, the intensity of the signal was normalized to the average signal intensity obtained in the occipital lobe using the AAL template (Tzourio-Mazoyer et al. 2002), according to the standard procedure used in the literature (O'Brien et al. 2004), to obtain striatal binding ratio (BR). The transformation of the AAL template to the single-subject space was performed by adding 2 deformation fields: 1) from the whole T1w image of the single-subject used to create the AAL template (Tzourio-Mazoyer et al. 2002) to the mean MNI space obtained using Segmentation and Geodesic Shooting integrated in CAT12 (Ashburner and Friston 2011) and 2) the reverse deformation field calculated from every T1w images of each participant to the mean MNI space obtained using Segmentation and Geodesic Shooting integrated into CAT12. The mean value of each ROI was then extracted for each hand side (left/right) and for each participant (total putamen [mean of the whole ROI], total caudate, nucleus accumbens, sensorimotor putamen, associative putamen, limbic putamen, sensorimotor caudate, associative caudate, limbic caudate), as well as volume-weighted mean metaROIs (mean of limbic regions, mean of associative regions and mean of sensorimotor regions; the nucleus accumbens being included in the limbic region) for correlations with clinical scores (Figure 1B). As a whole, the BR was estimated in the native space for every participant. This method will be referred to as MR-ATLAS.

Validation of the method

To validate our method, we compared the obtained values with a more conservative, non-MRI-dependent approach (linear deformation on a ^{123}I-FP-CIT template [computed in a standard anatomic space, in the Talairach coordinate system, defined by MRI images of a single healthy control subject], without PVE correction, followed by segmentation into three compartments of the caudate image, putamen anterior and posterior, and quantitative normalization on the occipital lobe: BRASS (Hermes Medical Solution) method (Koch et al. 2005)).

The statistical analyses were performed using the SPSS® software (IBM® SPSS® Statistics version 23, 2015). We then looked at the distribution of the values in each region, and in each group, using both quantification methods and tested the noise by calculating coefficients of variations in each region for the 3 groups pooled together and the control group. Group differences of mean ^{123}I-FP-CIT BR values across striatal regions were tested for each quantification method using ANOVAs with Bonferroni corrected posthoc assessments. We also performed direct comparisons between the MR-ATLAS and the BRASS quantification methods in the pooled three groups of participants using intraclass-coefficient correlations, Pearson correlations and Bland-Altman plots in two ROIs: (i) in the total caudate nuclei (obtained using both methods), and (ii) in the sensorimotor territory of the putamen (obtained using the MR-ATLAS approach) and the posterior portion of the putamen using the BRASS method (since the sensorimotor territory of the putamen represented the large majority of the posterior putamen: Figure 1B). We also tested the diagnosis performance of the MR-ATLAS method and performed area under curve (AUC) calculations of receiver operating characteristic (ROC) curves to compare the ability of the MR-ATLAS and BRASS method to distinguish between the different groups of patients (PD vs. healthy controls; PD vs. iRBD; iRBD vs. healthy controls). And finally, to illustrate the relevance of the quantification in striatal functional territories, we chose the most robust clinical conditions and tested the relationships with motor and cognitive scores and mean regional ^{123}I-FP-CIT BR values using Pearson correlation coefficients amongst the PD group only (to avoid any group effect that would bias the correlation). Due to strong laterality hypotheses regarding the correlations with motor scores, the Rigid Akinetic subscore of each hand side was

tested with the contralateral ^{123}I-FP-CIT striatal BR obtained within the limbic, associative, and sensorimotor striatal metaROIs using the MR-ATLAS approach and the anatomical BR obtained using the BRASS method. On the other hand, due to the lack of strong laterality hypotheses regarding the correlations with cognitive scores, these correlations were tested with the pooled bilateral limbic, associative, and sensorimotor striatal metaROIs (volume-weighted mean metaROIs: see above) using the MR-ATLAS approach and the bilateral anatomical BR obtained using the BRASS method. Correlations with detailed subregions of the YeB atlas are provided in Supplementary Material.

Results

Details regarding the demographic and clinical characteristics of the patients are illustrated in Table 1. Beyond disease characteristics, there were no significant differences between groups except for a female over-representation in the healthy control group.

Comparison between the two quantification techniques

Quantification results using the MR-ATLAS method in every striatal region are illustrated in Figure 2. In every region, there was a significant group effect (One Way ANOVAs, $p< 0.001$). Post-hoc differences (Bonferroni corrected) are illustrated in Figure 2. Briefly, there was a significant posthoc difference in every region and between every group except between the healthy control group and the iRBD group in bilateral nuclei accumbens, bilateral limbic parts of the caudate nuclei, and the right total and associative caudate nucleus. Quantification results using the BRASS method are illustrated in Figure 3. In every region, there was a significant group effect (One Way ANOVAs, $p< 0.001$). Posthoc differences (Bonferroni corrected) are illustrated in Figure 3. There was a significant difference between the three groups in every striatal region. The magnitude of the coefficients of variation were similar in magnitude between the two methods (Supplementary Figure 2). Moreover,

in the MR-ATLAS method, the smallest regions thought to be more subject to artefacts (eg Accumbens) did not evidence a higher variability of BR (Supplementary Figure 2).

We then tested the direct relationships between the two methods: the Bland-Altman plots of the two quantifications methods are illustrated in Figure 4 and show good consistency, with almost all values within the limits of agreement. Besides the Bland-Altman plots displayed a global increase in BR values with the MR-ATLAS method and a trend to have an increasing difference with the highest BR values within a region. The intraclass correlation coefficients (ICC) for single values were either good or excellent (Koo and Li 2016), and highly significant (ICC values for the posterior putamen: left = 0.89, right = 0.86; and the caudate nucleus: left = 0.77, right = 0.79, all p-values < 0.001). All Pearson linear correlations were also significant (r correlation coefficients for the posterior putamen: left = 0.95; right = 0.93; and the caudate nucleus: left = 0.86, right = 0.87, all p-values < 0.001, Supplementary Figure 3).

Diagnostic performances

Both the MR-ATLAS and the BRASS methods had comparable diagnostic performances (AUC values) to distinguish the three clinical groups: PD vs. healthy controls, PD vs. iRBD and iRBD vs. healthy controls (Supplementary Figure 4).

Correlation with clinical scores

To validate the interest of the MR-ATLAS method, we then correlated within the PD patients the Rigid Akinetic subscore of each hand side with the contralateral ^{123}I-FP-CIT striatal BR obtained within the limbic, associative, and sensorimotor striatal metaROIs using the MR-ATLAS approach and the anatomical BR obtained using the BRASS method. The correlation matrices are illustrated in Figure 5. The correlation coefficients were higher within the sensorimotor striatal territories for the MR-ATLAS method and within the posterior putamen for the BRASS method. Correlation matrices with detailed subregions are illustrated in Supplementary Figure 5.

Finally, correlations with cognitive scores proved to be significant only for the FAB and not for the MoCA test (Figure 6). Regarding the correlations of BR obtained with the MR-ATLAS approach, all the functional striatal regions were significantly correlated to the FAB scores but the limbic striatum was the most strongly correlated region (correlation coefficients comparisons: correlations with associative vs. correlations with limbic territories of the striatum: z=2.76, p 0.003; correlations with sensorimotor vs. correlations with limbic territories of the striatum: z=1.95, p 0.025). Using the anatomical parcellation of the BRASS method, the FAB score was significantly correlated to the BR in the caudate nucleus and posterior putamen, the caudate nucleus being the most strongly correlated. Correlation matrices with detailed subregions are illustrated in Supplementary Figure 6.

Discussion

We propose here a new ^{123}I-FP-CIT SPECT quantification method based on MR-registration, PVE correction, and striatal atlas functional segmentation, that allows quantification in every functional region of the striatum (nucleus accumbens, limbic, associative and sensorimotor parts of both the caudate nucleus and the putamen: Figure1B). The choice of the PVE correction was dictated by the involvement of small size brain structures close to the CSF (eg nucleus accumbens) which were quantified in the MR-ATLAS method. These structures are indeed much more influenced by PVE than bigger structures. This method has both proven to be reliable and to be a relevant tool to explore the non-motor aspects of the dopaminergic system.

Indeed, our method provided consistent BR values (that ranged between 4 and 9) across participants and striatal regions as provided by the distribution in healthy control subjects (Figure 2). As expected, values were significantly lower in PD patients than in healthy control subjects, following an anteroposterior gradient (i.e. the largest differences between the two groups were found in the posterior putamen, i.e. the sensorimotor putamen, rather than in the nucleus accumbens, or the limbic/associative parts of the caudate nucleus (Nandhagopal et al. 2009). As expected, the patients

with iRBD had intermediate BR values between healthy controls and PD patients (Figure 2) (Iranzo et al. 2017). The largest differences between iRBD and PD patients were observed in the sensorimotor territory of the striatum, as expected regarding the lack or paucity of motor symptoms in iRBD patients (Figure 2) (Nandhagopal et al. 2009). These results were consistent with those observed using the BRASS method (Figure 3). Also, BR values obtained using the MR-ATLAS method were highly consistent with those obtained with the BRASS method (Figure 4). The Bland-Altmann plots also underlined that the MR-ATLAS method systematically increased the BR values. Since the MR-ATLAS integrated PVEc, this in line with previous dopamine PET studies where PVEc proved to systematically increase the BR values (Rousset et al. 2000; Mawlawi et al. 2001; Martinez et al. 2003; Smith et al. 2019) (Figures 2, 3 and 4), but where PVEc was not coupled to the use of a striatal atlas functional segmentation. PVEc is thus likely to explain in the Bland-Altman plots (Figure 4) 1) the global increase in BR values and 2) the trend to have an increasing difference with the highest BR values within a region (Martinez et al., 2003; Mawlawi et al., 2001; Rousset et al., 2000; Smith et al., 2019). Besides, the study by Koch et al. (2005) showed that striatal DAT binding computed with the automated BRASS method was underestimated by ~25 % compared to the manual method in native space. This may also increase the apparent differences in striatal DAT binding values between the MR-ATLAS and BRASS methods: the MR-ATLAS method might correct the BR values decreases of the BRASS method. As a whole, these results demonstrate the validity of this new MR-ATLAS quantification method.

Beyond its validity, this new method provided an opportunity for new clinico-radiological explorations in PD especially for the non-motor aspects of the dopaminergic system. Indeed, in PD patients the rigid and akinetic symptoms were more strongly correlated with the BR values of the striatal sensorimotor territories using the MR-ATLAS method and the posterior putamen using the BRASS quantification method, with equivalent correlation coefficients between the two methods (Figure 5 and supplementary Figure 5). Besides, strong relationships were found between cognitive performances measured using the FAB test and the presynaptic dopaminergic denervation in the

limbic territory of the striatum using the MR-ATLAS method, whereas correlations with the associative and sensorimotor territories of the striatum were weaker (Figure 6). For its part, the BRASS method provided significant correlations with the caudate nucleus and the posterior putamen (Figure 6). Finally, no correlation was found with the MoCA test. These correlations with motor and cognitive scores illustrated that the use of a histology-based MR atlas of the striatum provided consistent results with the expected brain functions involved in the striatal territories. Indeed, first, the correlation with akinetic and rigid symptoms was as expected more significant within the sensorimotor striatum. Second, there was a lack of correlation with scores at the MoCA test, which was not surprising since this test was a global cognitive test, expected to be less dependent on the striatum (Firbank et al. 2017; Chen et al. 2017). Finally, the MR-ATLAS quantification approach even provided a better understanding of the neuroanatomical bases of the frontal cognitive symptoms in PD patients as measured with the FAB: the correlation with the anatomical parcellation obtained by the BRASS method provided atypical results (caudate nuclei and posterior putamen), whereas the correlation with the MR-ATLAS method suggested that these functions were more underpinned by the striatal limbic areas than the striatal associative (and sensorimotor) areas. This result can be explained by the fact that the correlation was mostly driven by the Conflicting Instructions and Go-No Go subscores of the FAB (Supplementary Figure 7), cognitive tasks that mostly depends on cognitive inhibitory control and goal-directed behaviors (Dubois et al. 2000; Kopp et al. 2013) and involves the cingulate cortex (Menon et al. 2001; Nieuwenhuis et al. 2003; Løvstad et al. 2012; Shenhav et al. 2013; Luijten et al. 2014; Morris et al. 2016), itself connected to the limbic part of the striatum (Beckmann et al. 2009; Torta and Cauda 2011; Morris et al. 2016; Marquand et al. 2017; Choi et al. 2017; Palomero-Gallagher et al. 2019). In addition, the ventral striatum has also proven to be involved in “cold cognitive functions” such as reasoning processes (Donoso et al. 2014). This result illustrates the interest of this new MR-ATLAS method for future research on the dopaminergic system, especially regarding its behavioral and cognitive aspects. Further developments and studies could also involve BR quantification in other brain structures, outside of the striatum, together with

the MR-ATLAS method as well as the use of another dopaminergic or metabolic tracer such as fluorodeoxyglucose.

Our study has some limitations. The use of a single low-resolution SPECT image for each participant limited the validation of our method. Indeed, a second ^{18}F-DOPA PET or ^{123}I-FP-CIT SPECT image would have allowed a test-retest validation. Besides, the over-representation of females in our healthy control group could also have biased the group comparisons, even if it could not have biased the cross-methods and intra-PD group assessments. Given the low SPECT resolution, one would have expected difficulties for reliable quantification in small areas such as striatal subregions and particularly the nucleus accumbens (mean volume = 6% of the total striatum). No reasonable Gold Standard in our study could demonstrate the definite validity of the values obtained in this area. Nonetheless, there was no significant difference in BR variance in healthy controls between the different subregions of striatum obtained using the MR-ATLAS method (Levene's test ANOVA 2 factors [hand side and subregion]; F = 0.81; p=0.65) as well as similar coefficients of variation compared to other striatum subregions. Given segmentation differences (anatomical vs. functional), we could not directly compare the striatal BR values from the BRASS and MR-ATLAS methods. This may have introduced a bias and have negatively limited the value of comparisons between the two methods. Nonetheless, as discussed throughout the Manuscript, these direct comparisons remained highly acceptable. So the actual theoretical direct comparison may give better results. Nonetheless, this prevented us to directly compare the two methods in the anterior parts of the striatum where the segmentation methods were too different. Furthermore, the evidence of significant group differences in the expected direction even in the smallest regions (Figure 2) suggests that the BR values obtained in this area were not the pure result of artifacts and noise.

The complexity of the MR-ATLAS method and the necessity of an MRI were obvious limiting factors for implementation in clinical routine. Nonetheless, the method proposed here relied on free and open access software. As a consequence, the compilation of the functions used here was

theoretically feasible and could provide a time-consuming but fully automatic individual quantification method. However, such an implementation would be more relevant and feasible on hybrid SPECT-MR scanners. Even if not directly tested here, there is neither theoretical nor practical limitation that could prevent the application of this MR-ATLAS method to PET imaging. Implemented on a hybrid PET-MR scanner, this method might be able to provide quantitative values in the same striatal regions as detailed here for ^{18}F-FDOPA or another PET dopaminergic tracer.

Conclusion

To conclude, we proposed a new ^{123}I-FP-CIT SPECT quantification method that has proven its validity and enabled BR quantification in several nuclei and functional striatal territories. This method may also prove useful for studying PD and the dopaminergic system, in particular concerning cognitive and behavioral functions.

References

Ashburner J, Friston KJ (2011) Diffeomorphic registration using geodesic shooting and Gauss-Newton optimisation. Neuroimage 55:954–967. https://doi.org/10.1016/j.neuroimage.2010.12.049

Beckmann M, Johansen-Berg H, Rushworth MFSS (2009) Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. J Neurosci 29:1175–90. https://doi.org/10.1523/JNEUROSCI.3328-08.2009

Brogley JE (2019) DatQuant: The future of diagnosing Parkinson disease. J Nucl Med Technol 47:21–26. https://doi.org/10.2967/jnmt.118.222349

Chang L-T (1978) A Method for Attenuation Correction in Radionuclide Computed Tomography. IEEE Trans Nucl Sci 25:638–643. https://doi.org/10.1109/TNS.1978.4329385

Chen B, Wang S, Sun W, et al (2017) Functional and structural changes in gray matter of parkinson's disease patients with mild cognitive impairment. Eur J Radiol 93:16–23. https://doi.org/10.1016/j.ejrad.2017.05.018

Choi EY, Ding SL, Haber SN (2017) Combinatorial inputs to the ventral striatum from the temporal cortex, frontal cortex, and amygdala: Implications for segmenting the striatum. eNeuro 4:. https://doi.org/10.1523/ENEURO.0392-17.2017

Donoso M, Collins AGE, Koechlin E (2014) Foundations of human reasoning in the prefrontal cortex. Science (80-) 344:1481–1486. https://doi.org/10.1126/science.1252254

Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: A frontal assessment battery at bedside. Neurology 55:1621–1626. https://doi.org/10.1212/WNL.57.3.565

Firbank MJ, Yarnall AJ, Lawson RA, et al (2017) Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. J Neurol Neurosurg Psychiatry 88:310–316. https://doi.org/10.1136/jnnp-2016-313918

Gerlach M, Gsell W, Kornhuber J, et al (1996) A post mortem study on neurochemical markers of dopaminergic, GABA-ergic and glutamatergic neurons in basal ganglia-thalamocortical circuits in Parkinson syndrome. Brain Res 741:142–52

Goetz CG, Tilley BC, Shaftman SR, et al (2008) Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 23:2129–2170. https://doi.org/10.1002/mds.22340

Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson ' s disease : a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184. https://doi.org/10.1136/jnnp.55.3.181

Iranzo A, Santamaría J, Valldeoriola F, et al (2017) Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol 82:419–428. https://doi.org/10.1002/ana.25026

Koch W, Radau PE, Hamann C, Tatsch K (2005) Clinical testing of an optimized software solution for an automated, observer-independent evaluation of dopamine transporter SPECT studies. J Nucl Med 46:1109–1118

Koo TK, Li MY (2016) A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 15:155–163. https://doi.org/10.1016/j.jcm.2016.02.012

Kopp B, Rösser N, Tabeling S, et al (2013) Performance on the Frontal Assessment Battery is sensitive to frontal lobe damage in stroke patients. BMC Neurol 13:179. https://doi.org/10.1186/1471-2377-13-179

Løvstad M, Funderud I, Meling T, et al (2012) Anterior cingulate cortex and cognitive control: Neuropsychological and electrophysiological findings in two patients with lesions to dorsomedial prefrontal cortex. Brain Cogn 80:237–249.

https://doi.org/10.1016/j.bandc.2012.07.008

Luijten M, Machielsen MWJ, Veltman DJ, et al (2014) Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. J. Psychiatry Neurosci. 39:149–169

Marquand AF, Haak K V., Beckmann CF (2017) Functional corticostriatal connection topographies predict goal-directed behaviour in humans. Nat Hum Behav 1:1–9. https://doi.org/10.1038/s41562-017-0146

Martinez D, Slifstein M, Broft A, et al (2003) Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: Amphetamine-induced dopamine release in the functional subdivisions of the striatum. J Cereb Blood Flow Metab 23:285–300. https://doi.org/10.1097/01.WCB.0000048520.34839.1A

Mawlawi O, Martinez D, Slifstein M, et al (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D2 receptor parameter measurements in ventral striatum. J Cereb Blood Flow Metab 21:1034–1057. https://doi.org/10.1097/00004647-200109000-00002

Menon V, Adleman NE, White CD, et al (2001) Error-related brain activation during a Go/NoGo response inhibition task. Hum Brain Mapp 12:131–143. https://doi.org/10.1002/1097-0193(200103)12:3<131::AID-HBM1010>3.0.CO;2-C

Morris LS, Kundu P, Dowell N, et al (2016) Fronto-striatal organization: Defining functional and microstructural substrates of behavioural flexibility. Cortex 74:118–133. https://doi.org/10.1016/j.cortex.2015.11.004

Nandhagopal R, Kuramoto L, Schulzer M, et al (2009) Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. Brain 132:2970–2979.

https://doi.org/10.1093/brain/awp209

Nasreddine Z, Phillips N, Bédirian V, et al (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nieuwenhuis S, Yeung N, Van Den Wildenberg W, Ridderinkhof KR (2003) Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. Cogn Affect Behav Neurosci 3:17–26. https://doi.org/10.3758/CABN.3.1.17

Nobili F, Naseri M, De Carli F, et al (2013) Automatic semi-quantification of [123 I]FP-CIT SPECT scans in healthy volunteers using BasGan version 2: Results from the ENC-DAT database. Eur J Nucl Med Mol Imaging 40:565–573. https://doi.org/10.1007/s00259-012-2304-8

O'Brien JT, Colloby S, Fenwick J, Williams ED (2004) Dopamine Transporter Loss Visualized With FP-CIT. Arch Neurol 61:919–925

Palomero-Gallagher N, Hoffstaedter F, Mohlberg H, et al (2019) Human Pregenual Anterior Cingulate Cortex: Structural, Functional, and Connectional Heterogeneity. Cereb Cortex 29:2552–2574. https://doi.org/10.1093/cercor/bhy124

Patenaude B, Smith SM, Kennedy DN, Jenkinson M (2011) A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56:907–922. https://doi.org/10.1016/j.neuroimage.2011.02.046

Postuma RB, Iranzo A, Hu M, et al (2019) Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 142:744–759. https://doi.org/10.1093/brain/awz030

Rousset OG, Deep P, Kuwabara H, et al (2000) Effect of partial volume correction on estimates of the influx and cerebral metabolism of 6-[18F]fluoro-L-dopa studied with pet in normal control and

parkinson's disease subjects. Synapse 37:81–89. https://doi.org/10.1002/1098-2396(200008)37:2<81::aid-syn1>3.0.co;2-%23

Shenhav A, Botvinick MM, Cohen JD (2013) The expected value of control: An integrative theory of anterior cingulate cortex function. Neuron 79:217–240

Smith CT, Crawford JL, Dang LC, et al (2019) Partial-volume correction increases estimated dopamine D2-like receptor binding potential and reduces adult age differences. J Cereb Blood Flow Metab 39:822–833. https://doi.org/10.1177/0271678X17737693

Thomas BA, Erlandsson K, Modat M, et al (2011) The importance of appropriate partial volume correction for PET quantification in Alzheimer's disease. Eur J Nucl Med Mol Imaging 38:1104–1119. https://doi.org/10.1007/s00259-011-1745-9

Torta DM, Cauda F (2011) Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. Neuroimage 56:2157–2172. https://doi.org/10.1016/j.neuroimage.2011.03.066

Tossici-Bolt L, Hoffmann SMA, Kemp PM, et al (2006) Quantification of [123I]FP-CIT SPECT brain images: An accurate technique for measurement of the specific binding ratio. Eur J Nucl Med Mol Imaging 33:1491–1499. https://doi.org/10.1007/s00259-006-0155-x

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273–289

Yang J, Huang SC, Mega M, et al (1996) Investigation of partial volume correction methods for brain FDG PET studies. IEEE Trans Nucl Sci 43:3322–3327. https://doi.org/10.1109/23.552745

Yelnik J, Bardinet E, Dormont D, et al (2007) A three-dimensional, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data.

Neuroimage 34:618–638. https://doi.org/10.1016/j.neuroimage.2006.09.026

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GB, AK, JA, OJ, RV, SFV, GM, MV declare no conflict of interest related to this work.

Availability of data and material

Not applicable

Code availability

On demand to the corresponding author: gathers publicly available codes (see Methods for details).

Authors' contribution

NV conceived the presented methodological pipeline, contributed to data collection, performed analyses and wrote the manuscript.

GB contributed to data collection and to the writing of the manuscript.

M-OH, AK, JCC, GM, SL, MV and DG contributed to the design of the study, data collection and to the writing of manuscript.

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Ethics approval/Consent to participate

The study was approved by the local ethic committee Comité de Protection des Personnes (CPP) "Ile-de-France VI" (IRB:2014-A00725-42 / 48-14). Informed consent was obtained from all individual participants included in the study.

Consent for publication

All the authors have read and agreed with current content of the submitted manuscript.

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Figures Legends

Figure 1

A: Single subject's (healthy control) raw T1-weighted MRI (left) and ^{123}I-FP-CIT SPECT (right) images after rigid coregistration. ^{123}I-FP-CIT SPECT image after partial volume effect correction (middle).

B: Illustration of the functional striatal parcellation performed using YeB atlas (Yelnik et al. 2007). 3D view (top) and coronal render (bottom).

Figure 2 Striatal subregions quantification using the MR-ATLAS quantification method. Red dots=PD patients. Blue dots=iRBD patients. Green dots=healthy controls. Large bars = median. Small bars = 25th and 75th percentile. *: $p<0.05$ using Bonferonni correction.

Figure 3 Striatal subregions quantification using the BRASS quantification method. Red dots=PD patients. Blue dots=iRBD patients. Green dots=healthy controls. Large bars = median. Small bars = 25th and 75th percentile. *: $p<0.05$ using Bonferonni correction.

Figure 4 Bland-Altman plots between the quantification obtained using the BRASS method and the MR-ATLAS method. Difference between the two methods = $BR_{MR\text{-}ATLAS}$ - BR_{BRASS}. Red dots=PD patients. Blue dots=iRBD patients. Green dots=healthy controls.

Figure 5 Matrices of correlations amongst PD patients between the MDS UPDRS III Rigid Akinetic subscore OFF of each hand side and the contralateral ^{123}I-FP-CIT striatal BR obtained within the

limbic, associative and sensori-motor substriatal subregions using the MR-ATLAS approach and the anatomical BR obtained using the BRASS method.

Figure 6 Matrices of correlations amongst PD patients between the cognitive scores (MoCA and FAB) and the ^{123}I-FP-CIT striatal BR obtained within the limbic, associative and sensori-motor substriatal subregions using the MR-ATLAS approach and the anatomical BR obtained using the BRASS method.

Table 1. Clinical and demographic characteristics of the population. To test group differences, ANOVAs were performed for continuous variables and X^2 for categorical variables

	Healthy controls	iRBD	PD	Statistics
Number	21	21	46	
Age (years), mean +/- SD	63.0±8.2	66.7±7.9	62.2±10.1	p = 0.18
Education level (years), mean +/- SD	6.4±1.0	6.6±1.2	6.2±1.2	p = 0.51
Gender, m/f	5/16	17/4	27/19	**p = 0.001**
Laterality, R/L	21/0	20/1	42/4	p = 0.37
MDS UPDRS III OFF, mean +/- SD	6.8±2.1	13.3±3.4	34.6±1.8	**p < 0.001**
MDS UPDRS III Rigid Akinetic subscore OFF (right), mean +/- SD	1.9±2.5	3.9±2.7	9.8±4.7	**p < 0.001**
MDS UPDRS III Rigid Akinetic subscore OFF (left), mean +/- SD	2.4±2.4	4.5±3.2	10.4±4.3	**p < 0.001**
PD duration (years), mean +/- SD	NA	NA	3.8±2.1	
RBD, yes	NA	21/21	13/46	
RBD duration (years), mean +/- SD	NA	6.3±4.1	3.1±1.0	
Levodopa Equivalent Daily Dose (mg), mean +/- SD	NA	NA	128.5±196.8	
Montreal cognitive Assessment (MoCA), mean +/- SD	27.8±2.1	26.7±3.4	27.6±1.8	p = 0.22
Frontal Assessment Battery (FAB), mean +/- SD	16.9±1.2	16.0±1.4	16.2±1.8	p = 0.162