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RESEARCH ARTICLE

Physiological Whole-Brain Distribution of [18F]FDOPA Uptake Index in Relation to Age and Gender: Results from a Voxel-Based Semi-quantitative Analysis

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Abstract

Purpose: 6-[^{18}F]fluoro-L-DOPA ([^{18}F]FDOPA), a positron emission tomography (PET) amino-acid tracer of brain decarboxylase activity, is used to assess the brain dopaminergic system. Using a voxel-based semi-quantitative analysis, this study aimed to determine whether a current brain uptake index of [^{18}F]FDOPA, expressed relative to the occipital background level, varies according to age and gender.

Procedures: One hundred and seventy-seven subjects were retrospectively included. A whole-brain statistical parametric mapping analysis of the [^{18}F]FDOPA uptake index in parametric PET images was performed at a voxel threshold of $p < 0.05$ (corrected) and $p < 0.005$ (uncorrected, k cluster > 125).

Results: Striatal uptake indices were influenced by age, negatively for the caudate nucleus and positively for the putamen, as well as by gender, with a lower left putaminal uptake index in women. Extra-striatal uptake indices were influenced by age, negatively for the frontal cortex and brainstem and positively for the occipital cortex and cerebellum, as well as by gender (diffuse increase in women).

Conclusions: The uptake index of [^{18}F]FDOPA exhibited significant physiological variations according to age and gender and should therefore be considered for PET interpretation.

Key words: [^{18}F]FDOPA PET, Quantitative analysis, Age, Gender, Template

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Introduction

6-[^{18}F]fluoro-L-DOPA ([^{18}F]FDOPA) positron emission tomography (PET) has been developed and validated for assessing the integrity of the striatal dopaminergic system [1]. The dopaminergic brain system involves mesocortico-limbic and tubero-infundibular pathways as well as a nigro-striatal pathway exhibiting a higher number of dopaminergic neurons and, consequently, a significant uptake of [^{18}F]FDOPA [2]. After injection, [^{18}F]FDOPA follows the classical steps of catecholamine synthesis. Upon entering the brain cells, [^{18}F]FDOPA exhibits irreversible binding characteristics in the early hours post-injection. It is decarboxylated by aromatic amino acid decarboxylase (AADC), yielding [^{18}F]fluorodopamine, which is retained for several hours within dopamine vesicles and, thereafter, degraded by the successive actions of monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT). The resulting acidic metabolites, [^{18}F]dihydroxyphenylacetic acid and [^{18}F]homovanillic acid, are free to diffuse out of the brain [3, 4]. Several brain cell populations, equipped with AADC, are likely to influence [^{18}F]FDOPA metabolism since this enzyme is directly involved in the synthesis of both dopamine and serotonin and, more indirectly, that of noradrenalin [5].

[^{18}F]FDOPA uptake from striatal regions is currently quantified through a ratio of striatum relative to an occipital cortical background, which can be extracted as an absolute value after subtraction of 1, similarly to that performed for determining the binding potential index [6–9]. This semi-quantitative analysis is that typically performed in clinical routine [1]. A possible approach is to use institution-specific predefined ROIs of the striatum [9], such as those available when using an adaptive template with whole-brain quantitative statistical parametric mapping (SPM) analyses. These ROIs are obtained from an anatomic atlas (WFU-Pickatlas®) spatially normalized to the Montreal National Institute (MNI) SPM template [10]. The additional use of uptake ratios simplifies the analysis of [^{18}F]FDOPA uptake, allowing to overcome the need for blood sampling to quantify nigrostriatal dopamine function while reaching an equivalent diagnostic accuracy to that obtained with dynamic approaches [11]. However, the influences of age and gender on this [^{18}F]FDOPA uptake index remain poorly known, whereas these influences should be accurately assessed before pursuing any further quantitative analysis in patients. Indeed, such influence of age and gender has already been shown to be significant for dopamine transporter (DaT) imaging with [^{123}I]FP-CIT, a dopaminergic tracer currently used with single-photon emission tomography (SPECT) [12]. It should nevertheless be emphasized that the respective molecular targets of these two approaches differ since DaT imaging provides information on the presynaptic vesicular storage of dopamine, whereas [^{18}F]FDOPA PET targets presynaptic aromatic amino acid decarboxylase activity, which transforms L-DOPA into dopamine [1].

Age-related variations in the striatal uptake of [^{18}F]FDOPA, while previously analyzed in several studies, have yielded controversial results [13–16], with an age-related decrease being documented by certain authors [13, 16] but not by others [14, 15]. One study has additionally shown a gender effect with a higher striatal uptake of [^{18}F]FDOPA in women [17]. However, most of these studies were conducted on relatively small sample sizes per age category, with no analysis of extra-striatal changes, whereas a decreased uptake in certain extra-striatal areas on [^{18}F]FDOPA PET may constitute an additional sign of Parkinson's disease [18–20]. In addition, none of these previous studies used a voxel-based semi-quantitative analysis, similarly to that currently performed in clinical routine [13–20]. Such voxel-based approach is mandatory to provide an exhaustive analysis of whole-brain volume [21]. In light of the above, the present study was aimed at determining the evolving pattern of the [^{18}F]FDOPA uptake index with regard to age and gender when analyzed at a voxel-based level on whole brain PET images.

Materials and Methods

Study Population

From January 2013 to December 2015, 762 [^{18}F]FDOPA PET scans were performed in patients referred for a known or suspected neuroendocrine and/or brain tumor. Among the latter, only 177 were ultimately selected for the present analysis on the following basis: (1) absence of any evident brain tumor or neurological disease, or any known history of oncological or dopaminergic brain disorder; (2) absence of dopamine agonist or antagonist treatment, susceptible to interfere with dopamine metabolism [1]; (3) no carbidopa or any other enzyme inhibitor premedication likely to influence striatal and extra-striatal uptake [22]; and (4) conventional acquisitions for brain [^{18}F]FDOPA. This latter criterion implies a time frame for starting brain recording from 81 to 99 min after injection, all subjects being fasted at least 4 h prior to radiotracer injection [1, 9]. In the event where several exams were performed in the same patient, only images from the most recent examination were selected.

All patients from our institution are informed that their medical data can be rendered anonymous and used for scientific purposes. This last statement is clearly conveyed orally and by writing to all patients undergoing a PET scan in our institution. This retrospective study was approved on June 27, 2017 by the local institutional review board (IRB) and the Ethics Committee (CPP Est III).

The 177 retrospectively included subjects were referred to [^{18}F]FDOPA PET for the workup of 71 known neuroendocrine tumors (38 from bowels or lungs as primary location, 29 paragangliomas, 2 VIPomas, 1 insulinoma, and 1 esthesioneuroblastoma) and 106 suspected tumors of various locations: bowels ($n = 42$), adrenal glands ($n = 27$), lungs ($n = 8$), liver ($n = 6$), pancreas ($n = 5$), and others ($n = 18$). The population included 106 (60 %) women, with no difference documented between women and men with regard to age (59.8 ± 14.0 *vs.* 58.5 ± 14.5 years) and injected doses (4.2 MBq (155.4 μCi)/kg ± 0.6 *vs.* 4.4 MBq (162.8 μCi)/kg ± 0.6). Patient distribution is detailed in Table 1 as a function of age and gender.

[^{18}F]FDOPA PET Protocol

[^{18}F]FDOPA was synthesized by electrophilic substitution, using a TracerLab FX synthesizer (General Electric, USA®). Radiochemical yield at the end of synthesis was approximately 20 %, with a radiochemical purity of > 97 %. PET/CT recordings were obtained on a Biograph hybrid system consisting of a six-detector CT for attenuation correction and anatomic localization (Biograph 6 True Point, SIEMENS®). The whole-body PET/CT protocol was initiated 60 min after injection of 4 MBq (148 μCi)/kg of [^{18}F]FDOPA, all subjects being positioned in supine position, with the recording of the CT scan according to the following parameters: voltage 130 kV, intensity 90 mAs, 5-mm slice thickness, rotation time 0.6 s, and pitch of 1. Thereafter, a 3D-PET was recorded with seven bed positions in the caudal to cranial direction, each position lasting 210 s for subjects with < 100 kg of body weight or 240 s for those with > 100 kg. Thereafter, the final position, corresponding to brain recording, was initiated approximately 81 min after [^{18}F]FDOPA injection for subjects < 100 kg of body weight and approximately 84 min for those above this limit. The PET images were reconstructed with an iterative OSEM method (three iterations and eight subsets) and a 5-mm Gaussian post-filter, the images being displayed through 2.8 × 2.8 × 2.8 mm^3 voxels after correction for radioactive decay, scatter, and attenuation.

Whole-Brain SPM Analysis

After a first step consisting of extraction and orientation of the brain PET images using a dedicated software (Inveon Research Workplace by Siemens®, Knockville, USA), a whole-brain analysis was performed at the voxel level using the SPM8 software (Wellcome Department of Cognitive Neurology, University College, London, UK).

All sets of PET images were spatially normalized using an adaptive template through a 2 × 2 × 2 mm^3 voxel size and were further smoothed with a Gaussian filter (8 mm full width at half-maximum). The adaptive template, which is graciously available by asking the authors, was obtained using a specific algorithm provided by SPM and allowed averaging all sets of PET images [10]. Before being averaged, these PET images were primarily normalized through a dedicated template that is freely accessible [23].

Finally, parametric images were obtained by normalizing all voxel intensities through a ratio with mean voxel activities from an occipital cortical reference area, provided by WFU-Pickatlas®, in accordance with the semi-quantitative analysis currently recommended for [^{18}F]FDOPA interpretation [1]. This reference area was extracted from the spatially normalized PET images using the Marsbar® software (Marseille, France). Uptake index parametric images were subsequently obtained at the voxel level by subtracting 1 from the previous parametric images, similarly to that currently performed for DaT imaging [12].

The values of striatal uptake index were thereafter extracted from the spatially normalized PET images with the Marsbar® software (Marseille, France) and by using the regions of interest (ROI) of the caudate and putamen provided by WFU-Pickatlas® [21].

Statistical Analysis

Quantitative variables are expressed as means ± standard deviations and categorical variables as percentages. Analysis of covariance (ANCOVA) tests were performed for between-group comparisons of the quantitative variables. Pearson coefficients were used to determine the correlation between striatal uptake index and age. A $p < 0.05$ was considered as reflecting statistical significance.

For SPM analysis, two statistical analysis models were used within an inclusive mask of gray matter substance: (i) a linear regression model for analyzing the association with age, with gender included in the model as a covariate, and (ii) an ANOVA for assessing the association with gender, with age included as a covariate. SPM (T) maps were obtained at a voxel level with a p voxel significance < 0.05 after corrections performed primarily for multiple comparisons with family-wise error (FWE) and, in the absence of any significant relationship, with a less restrictive level of significance, *i.e.*, p voxel < 0.005 corrected for cluster

Table 1. Patient characteristics

Age (years old)	From 21 to 30 ($n = 9$)	From 31 to 40 ($n = 15$)	From 41 to 50 ($n = 17$)	From 51 to 60 ($n = 46$)	From 61 to 70 ($n = 48$)	From 71 to 80 ($n = 37$)	From 81 to 90 ($n = 5$)
Female gender	6 (67 %)	8 (47 %)	8 (47 %)	29 (63 %)	30 (63 %)	23 (62 %)	2 (40 %)

volume ($k > 125$). The anatomical localization of the most significant clusters was identified using the MNI (Montreal National Institute) atlas.

Results

Whole-Brain SPM Analysis

As shown in Fig. 1, [^{18}F]FDOPA uptake indices were negatively correlated with age in the bilateral caudate as well as in various extra-striatal sites, *i.e.*, diffuse cortical areas including bilateral frontal cortex, bilateral fronto-opercular cortex, bilateral pre and post-central gyri, left insula, the cingulum, limbic cortex, right temporal superior cortex, bilateral thalamus, and brain stem ($p < 0.05$, FWE corrected). In addition, there were positive correlations with age for the bilateral putamen, as well as for the bilateral occipital cortex and cerebellum ($p < 0.05$, FWE corrected).

As shown in Fig. 2, women exhibited a somewhat higher uptake index than men in diffuse cortical areas (frontal-inferior, temporal, right-occiput) and in the cerebellum ($p < 0.005$, $k > 125$), while exhibiting a lower uptake index in the left putamen ($p < 0.005$, $k > 125$).

ROI-Based Analysis of the Striatum

Similarly to that documented with SPM, the ROI method allowed revealing a negative correlation with age for the caudate uptake index ($r = -0.183$ and -0.333 for right and left respectively, $p < 0.02$) and a positive correlation for the putamen uptake index ($r = 0.239$ and 0.204 for right and left respectively, $p < 0.01$). As a consequence of these opposite relationships, no significant relationship with age was documented for the total uptake index measured in the overall striatum ($p = 0.54$).

A further analysis of this impact of age is provided in Fig. 3 through uptake index changes in caudate, putamen, overall striatum, and caudate/putamen ratio among the various decades of age with gender as covariate. These relationships were not perfectly linear with a significant age-related decrease in caudate uptake index and caudate/putamen PBI ratio, mainly starting after the 5th decade and

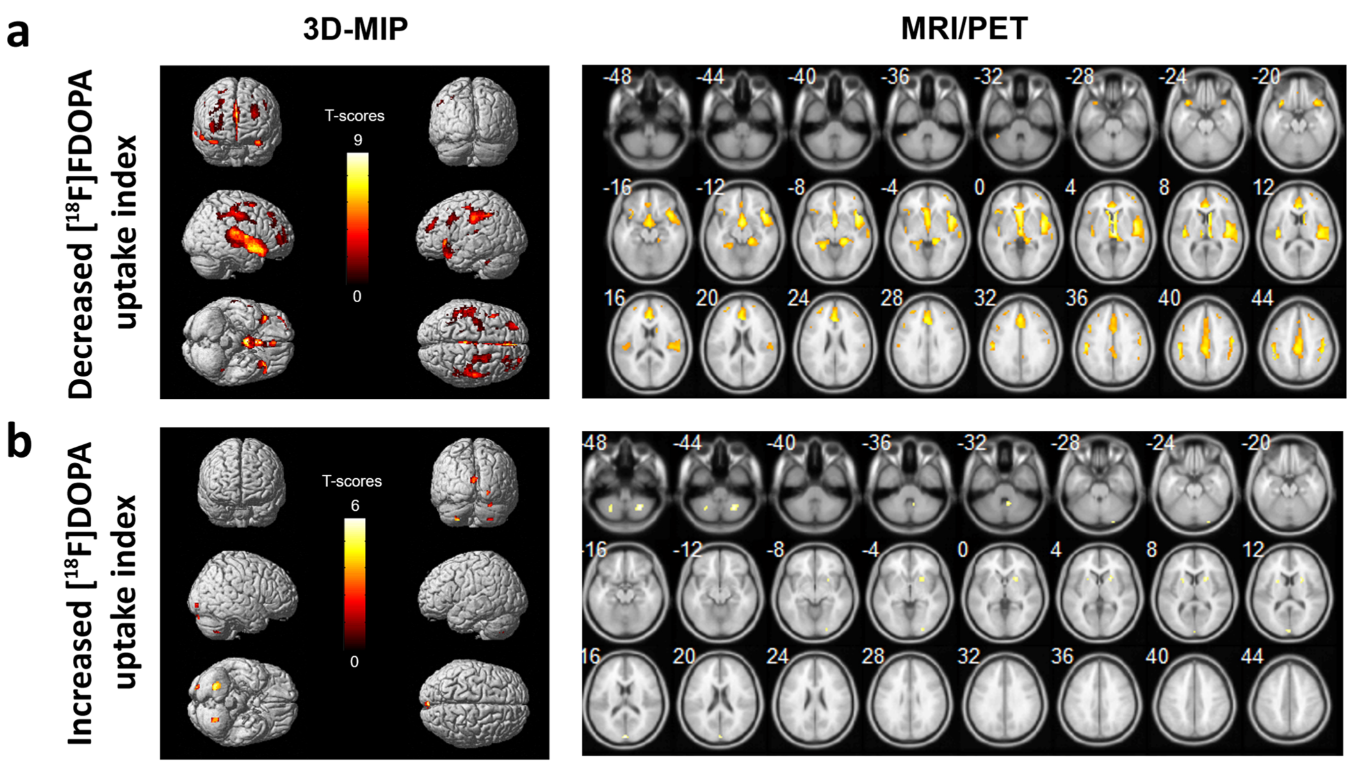

Fig. 1. Results of the SPM linear regression performed in the 177 study patients: anatomical localization of areas of **a** decreased or **b** increased [^{18}F]FDOPA uptake index in relation to age and independently of gender, displayed by means of rendered 3D MIP images (first column) or through a fusion of image slices of a normal MRI set spatially normalized and smoothed with the standard SPM8 template (MRI/PET, second column) ($p < 0.05$, FWE). **a** [^{18}F]FDOPA uptake index was negatively correlated with age in the bilateral caudate as well as in various extra-striatal sites, *i.e.*, diffuse cortical areas including bilateral frontal cortex, bilateral fronto-opercular cortex, bilateral pre- and post-central gyri, left insula, the cingulum, limbic cortex, right temporal superior cortex, bilateral thalamus, and brain stem. **b** In addition, there were positive correlations with age for the bilateral putamen as well as for the bilateral occipital cortex and cerebellum.

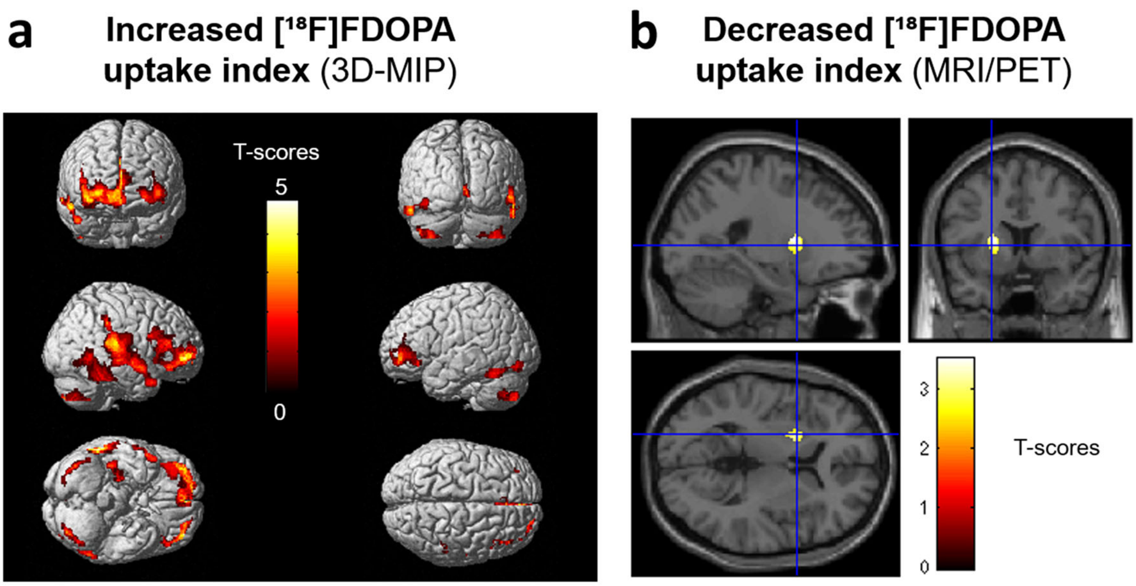

Fig. 2. Results of the SPM *t* test performed in the 177 study patients (106 women). **a** Anatomical localization of areas of changes in [^{18}F]FDOPA uptake index in relation to female gender and independently of age, displayed by means of rendered 3D MIP images showing increased uptake index or **b** through a fusion of image slices of a normal MRI set spatially normalized and smoothed with the standard SPM8 template showing decreased uptake index (MRI/PET) ($p < 0.005$, $k > 125$). **a** Women exhibited a somewhat higher uptake index than men in diffuse cortical areas (frontal-inferior, temporal, right-occiput) and in the cerebellum, as well as **b** a lower uptake index in the left putamen.

with an age-related increase in putamen uptake index reaching a plateau at the 7th decade. Representative examples of the distribution of the [^{18}F]FDOPA uptake index in three different age groups are provided in Fig. 4.

Furthermore, women showed a lower left putamen uptake index than men (uptake index = 1.33 ± 0.18 *vs.* 1.40 ± 0.21, $p = 0.02$). No other significant difference was noted in the caudate or right putamen.

Discussion

In a large population of patients without brain disease and owing to a voxel-based semi-quantitative analysis of the whole-brain volume, this study shows that aging and, to a lesser extent, gender are associated with changes in the physiological distribution of the [^{18}F]FDOPA PET uptake index in both striatal and extra-striatal areas. These changes are pronounced, especially with regard to age, and should therefore be putatively considered when analyzing PET images of patients, particularly when using current methods of semi-quantitative analysis.

The most significant finding of the current study is indeed the age-related changes in the distribution of [^{18}F]FDOPA uptake index. These changes were documented with a correction for multiple comparisons and hence with a high level of statistical significance. It should additionally be pointed out that these changes were linked with the common spatial distribution of the brain atrophy process [24–32]. This process is indeed known to be particularly marked for the caudate nucleus comparatively to the putamen [31, 32], as well as in prefrontal cortex regions including superior and middle frontal gyri [25, 27, 29, 30]. These findings are highly concordant with our results on brain distribution of the age-related decrease in the [^{18}F]FDOPA uptake index. In addition, the decrease in [^{18}F]FDOPA uptake index within frontal, insulo-opercular cortex, and cingulum is in accordance with previous observations with DaT imaging [12].

In contrast, the areas involving temporo-occipital junctions, the putamen, and the cerebellum, namely those showing a relative increased uptake index with aging in the present study, are also known to exhibit a much slower brain atrophy with age [24–28].

It could be postulated that the occipital area, which is currently used as a reference for the computing of the uptake index ratio, is likely to exhibit a slow decrease in [^{18}F]FDOPA uptake with age in keeping with the occipital atrophy process. Thus, areas with an even lower atrophy than occipital atrophy may exhibit a relative increase in uptake index with age, as that documented in the present study.

These different patterns raise the issue of whether these changes in extra-striatal uptake index and thus, in a setting outside of the common dopaminergic system pathways, correspond to actual changes in dopamine innervation. Extra-striatal regions have been reported to have significant dopamine innervation in animals, with the largest amount being documented in the sensorimotor of the neocortex in rodents [33]. This dopamine innervation has also been observed in mouse cerebellum [34].

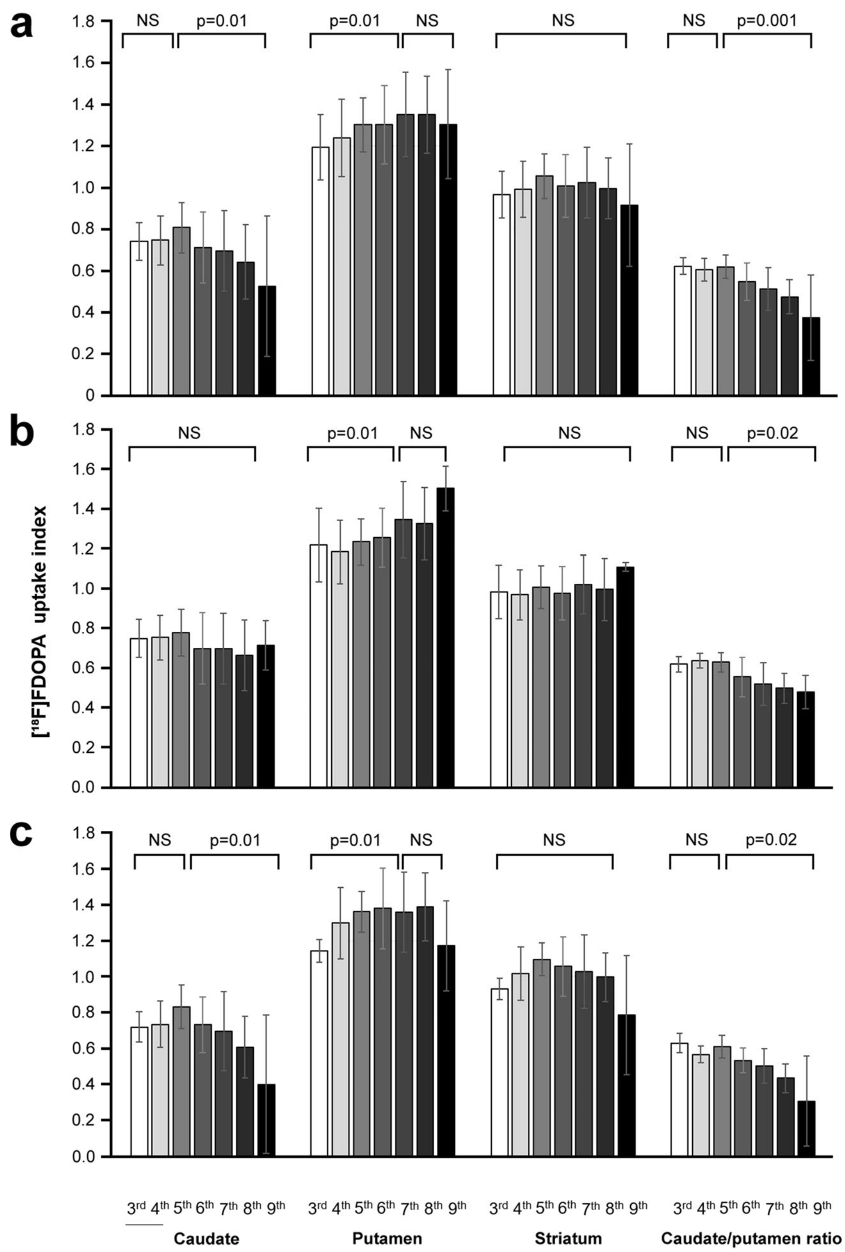

Fig. 3. **a** Striatal uptake index for caudate, putamen, striatum, and caudate/putamen ratio, expressed as means ± standard deviations, according to age decades in the overall study population ($n = 177$) and with adjustment for gender, **b** in only women ($n = 106$) and **c** in only men ($n = 71$), and with the distribution according to age decades and gender as detailed in Table 1. ANCOVA p values are indicated for the evolution with time of the caudate/putamen ratio and of the uptake index within the caudate, putamen, and striatum. These relationships were not perfectly linear with a decrease in caudate uptake index and caudate/putamen uptake index ratio mainly starting after the 5th decade and an increase in putamen uptake index reaching a plateau at the 7th decade.

In keeping with the above, our data show that aging is accompanied by changes in the uptake index within extra-striatal areas and involving the following: (1) a global decrease primarily within the primary sensorimotor system [35] and, thus, in the regions which are the most likely to exhibit marked age-related atrophy and (2) a global increase in areas involved in the involuntary control of movements and known to be much less susceptible to the age-related atrophy process. From a global synthesis standpoint, there is an age-related shift in the brain distribution of uptake index from the motor system of the primary neocortical areas to the occipital areas and cerebellum.

We found a clear impact of age on striatal uptake index, in accordance with that already documented in previous studies [12, 13, 16, 36]. In the present study, however, this impact was characterized by changes in the distribution of the uptake

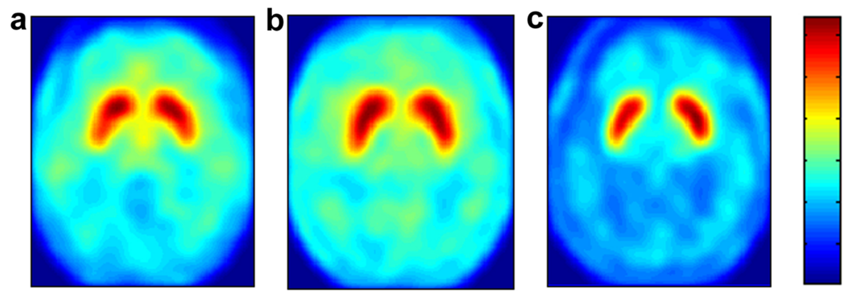

Fig. 4. Representative examples of axial slices of parametric PET images of the [18F]FDOPA uptake index obtained **a** in a 27-year-old man with a caudate uptake index of 0.80 and putamen uptake index of 0.19, **b** in a 56-year-old man with a caudate uptake index of 0.62 and putamen uptake index of 0.17, and **c** in a 79-year-old man with a caudate uptake index of 0.63 and putamen uptake index of 0.42. The caudate/putamen ratio, as well as extra-striatal [18F]FDOPA uptake index, exhibited a global decrease with age.

index, with a decrease in the caudate/putamen ratio over time, whereas the global value of striatal uptake index remained stable throughout the years (Fig. 3). In particular, aging was globally associated with an increase in putamen uptake index and a decrease in caudate uptake index although these relationships with age were not perfectly linear, *i.e.*, the decrease in caudate uptake index starting after the 5th decade and the increase in putamen uptake index reaching a plateau at the 7th decade. These normal changes with age in the caudate/putamen ratio should putatively be considered when using this ratio for diagnostic purposes, namely in early Parkinson's disease or differentiation between Parkinson's disease and atypical parkinsonian syndrome [6, 9].

Certain gender effects were also observed in the present study, although at a much lower significant level than the age-related effects, and only when the correction for multiple comparisons was no longer required. Herein, women exhibited a higher uptake index in diffuse cortical areas, in association with a decrease in left putamen uptake index. This latter observation clearly differs with those of previous studies, although dopamine striatal innervation was assessed using a very different method in these aforementioned reports, *i.e.*, with DaT imaging [12, 36] or with absolute [18F]FDOPA uptake measurement values (Ki value) [17].

The higher diffuse cortical uptake index in women constitutes an original finding, which was obtained owing to the use of a voxel-based analysis of the entire brain. These considerations are further strengthened by the previous observation of higher extra-striatal uptake index in women with DaT imaging [12]. Interestingly, other studies using a voxel-based analysis of brain 2-deoxy-2-[18F]fluoro-D-glucose or 2-[18F]fluorotyrosine PET also reported a higher diffuse metabolism in the female cortex [37–40], possibly due to a higher cerebral blood flow [37, 39] and/or to the effects of estrogen on cerebral metabolism [38]. Such gender differences are documented for many SPECT and PET tracers and have thus been considered to be poorly specific [41].

In addition, as documented through our semi-quantitative voxel-based analysis, female gender was associated with a lower left putamen uptake index. This finding may be relevant for the early diagnosis of parkinsonian syndrome, the putamen being the first striatal structure affected by the loss of dopamine neurons [42, 43]. This neuronal loss, leading to a decrease in uptake index and associated with atrophy, is indeed likely to be detected earlier for the putamen than for the caudate nucleus. This is due to the smaller size of the putamen comparatively to the caudate nucleus and leading to a higher susceptibility to partial volume effect with PET imaging [44].

Our study has several limitations. First, although our study subjects had no known neurological disorder or dopaminergic diseases, most were not healthy since they were initially referred to [18F]FDOPA PET for the workup of known or suspected neuroendocrine tumors. Secondly, our brain imaging data were obtained through a whole-body recording protocol as opposed to a dedicated brain protocol. Therefore, injected activity was as high as 4 MBq (148 μCi)/kg and the recording time centered on the brain area lasted only 3 min, whereas for brain imaging, the recommended parameters are respectively 2 MBq (74 μCi)/kg and 10 min [1], resulting in a slightly lower amount of brain recording counts. Thirdly, the methodological approach used in the present study could be discussed since a more accurate quantification of regional dopamine synthesis and storage by [18F]FDOPA PET would require full pharmacokinetic modeling. As already stated above, the use of ratios oversimplifies the analysis of the brain uptake of [18F]FDOPA and is also likely to provide a high diagnostic accuracy for Parkinson disease [11]. However, it must be recognized that direct comparisons with dynamic approaches of the kinetics of [18F]FDOPA should be planned to provide a more complete analysis of the effects of age and gender on the dopamine metabolism of all brain territories and brain cell populations.

Finally, no correction could be applied for atrophy since brain MRI images were not available for most patients. However, this represents the current routine conditions of [18F]FDOPA analysis and the aim of this study was to determine age and gender effects on [18F]FDOPA uptake index for current conditions of clinical practice. It remains to be determined to what extent the observed age-related changes in the uptake index of [^{18}F]FDOPA may be explained by atrophy of the dopaminergic structures as well as of the occipital cortical reference area. It is therefore likely that our results need to be confirmed by further analyses in other study populations and preferentially in a sufficiently large number of definitely healthy subjects, as well as by using a conventional brain imaging PET protocol along with an additional recording of brain MRI for correcting partial volume effects.

Conclusion

In summary, the present study is the first to highlight age- and gender-related normal changes in uptake index from [^{18}F]FDOPA PET imaging assessed in a large patient cohort and over the entire brain with a voxel-based semi-quantitative analysis. This analysis yielded evidence of a marked reorganization of the brain dopaminergic system with age not only, firstly, in striatal areas and with a progressive decrease of the caudate/putamen ratio but also, secondly, in extra-striatal areas with a shift in uptake index from neocortical to occipital and cerebellar areas. Female gender was also associated with a somewhat higher uptake index in diffuse cortical areas and lower left putaminal uptake index. While the exact mechanisms of these observations remain to be determined, the majority of the age-related changes in uptake index appear to be linked to the distribution of the common brain atrophy process. These physiological uptake index variations according to age and gender are nonetheless marked and therefore should be putatively considered for the semi-quantitative analysis of [^{18}F]FDOPA PET images of patients with parkinsonian syndrome.

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Compliance with Ethical Standards. This retrospective study was approved on June 27, 2017 by the local institutional review board (IRB) and the Ethics Committee (CPP Est III).

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required. Informed consent was obtained from all individual participants included in the study.

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