IMAGING OF DOPAMINE IN PD AND IMPLICATIONS FOR MOTOR AND NEUropsychiatric MANIFESTATIONS OF PD

Raúl de la Fuente-Fernández*

Section of Neurology, Hospital A. Marcide, Complejo Hospitalario Universitario de Ferrol (CHUF), Ferrol, Spain

INTRODUCTION

Parkinson’s disease (PD) has traditionally been defined according to its motor manifestations. Bradykinesia, rigidity, and resting tremor are the core clinical features and reflect the degree of dopamine depletion in the putamen (1, 2). Recent years have seen an increasing interest in neuropsychiatric manifestations of the disease, some of which are likely related to dopamine depletion in the caudate nucleus and nucleus accumbens (NAcc). In fact, a putamen-caudate-accumbens gradient of dopamine depletion, with dysfunction of the corresponding frontostriatal loops, followed by dopamine depletion in the frontal cortex, has been proposed to explain the sequential occurrence of motor symptoms and a great variety of neuropsychiatric manifestations (3). In addition to the clinical picture observed during the “off” medication state, there are also treatment-related motor and non-motor alterations. Dopaminergic (DA) therapies are able to normalize motor function and may also help to correct neuropsychiatric symptoms during the early stages of the disease. In the long-term, however, these therapies are often associated with motor and non-motor complications. Dyskinesias and impulse control disorders (ICDs) are only two examples. There is compelling evidence to suggest that dyskinesias are due to treatment-related abnormalities occurring in the frontostriatal motor loop (4, 5). Likewise, treatment-related abnormalities in the frontostriatal cognitive and limbic loops could be responsible for ICDs. This short review article will cover some of the most relevant contributions of dopamine radiotracer neuroimaging to the understanding of motor and neuropsychiatric manifestations of PD.

PET ASSESSMENTS OF DOPAMINERGIC FUNCTION

A number of positron emission tomography (PET) radiotracers can be used to assess the DA system. Presynaptically, (6), (1) [18F]-fluorodopa uptake provides an estimate of the activity of the enzyme dopa-decarboxylase, (2) plasma membrane dopamine transporter (DAT) radioligands (e.g., [11C]-methylphenidate) provide an estimate of DAT site density, and (3) vesicular monoamine transporter type 2 (VMAT2) radioligands (e.g., [11C]-dihydrodopetamine) provide an estimate of VMAT2 site density. Postsynaptically, [11C]-raclopride (a D2/D3 receptor antagonist) is the radioligand most frequently used to estimate the density of dopamine D2/D3 receptors in the striatum, where receptor concentrations are high. For extrastriatal areas (e.g., frontal cortex), where D2/D3 receptor concentrations are low, raclopride does not provide an optimal signal-to-noise ratio. Here, high-affinity D2/D3 antagonists such as [18F]-fallypride and [11C]-FLB-457 are better biomarkers (7, 8). A major advantage of raclopride is its susceptibility to displacement by dopamine (5, 9). This allows comparisons between baseline and postactivation scans in order to estimate the amount of dopamine released after the activation of the DA system (e.g., after levodopa challenge). In contrast, the ability of high-affinity radiotracers to quantify dopamine release in extrastriatal areas seems to be limited.

DEGENERATION OF DOPAMINE PATHWAYS IN PD

Post-mortem biochemical studies have shown that PD has a characteristic gradient of dopamine depletion in the striatum (1, 2). The putamen is the most affected region, followed by...
dorsal caudate (d-Caud), ventral caudate (v-Caud), and NAcc. Longitudinal PET studies have confirmed in vivo such a progressive putamen-caudate gradient of DA dysfunction (10), although specific subregions of the ventral striatum were not evaluated. In all likelihood, this gradient of dopamine depletion reflects the sequential degeneration of the nigrostriatal and mesolimbic dopamine pathways. Presumably, the mesocortical dopamine pathway would be affected last, which would lead to cortical dopamine depletion.

Based on the striatal gradient of dopamine depletion, three major anatomical and functional frontostratal loops are predicted to be sequentially affected in PD (3): first, the motor loop, which connects cortical motor areas (including the supplementary motor cortex and the primary motor cortex) with the putamen; second, the cognitive loop, which connects the dorsolateral prefrontal cortex (DLPFC) with the dorsal caudate nucleus (d-Caud); and third, a “complex” limbic loop, with connections (i) between the orbitofrontal cortex (OFC) and the v-Caud nucleus (v-Caud), and (ii) between the anterior cingulate cortex (ACC) and the NAcc (11–14). Over time, these frontostratal loop dysfunctions caused by dopamine depletion in the striatum would be further complicated by cortical dopamine depletion secondary to degeneration of the mesocortical dopamine pathway – the direct DA projection to the frontal cortex. The degree of frontal DA dysfunction might follow a gradient similar to that proposed for the striatum (i.e., DLPFC > OFC > ACC) (15).

Dopamine neurons of the mesocortical pathway have unconventional characteristics, including lack of DAT and D2 autoreceptors (16), which may limit their capability to undergo regulatory adaptations.

**DOPAMINE AND MOTOR MANIFESTATIONS OF PD**

A distinction should be made between DA dysfunction “off” and “on” medication.

**STRIATAL DOPAMINERGIC DYSFUNCTION DURING THE “OFF” MEDICATION STATE**

A recent multi-tracer longitudinal PET study has demonstrated in vivo that DA dysfunction in PD is particularly severe in the putamen (17). Using a VMAT2 marker ([11C]dihydrorotenazebine – DTBZ), it was estimated that some 70% of DA terminals must be lost before the first motor symptoms occur (Figure 1), which agrees with post-mortem estimates of striatal dopamine depletion (80%) (1, 2). Different radiotracers offer, however, somewhat different pictures (6). Thus, DAT radioligands tend to give more severe estimates of DA dysfunction, probably reflecting compensatory downregulation of DAT sites in an attempt at maintaining normal synaptic dopamine levels. In contrast, fluorodopa uptake is relatively upregulated in PD, which may also represent a compensatory mechanism. In consequence, there is a consensus that VMAT2 radioligands probably provide more accurate estimates of DA dysfunction (6), although VMAT2 binding may be also subject to some degree of regulation (18). In general, bradykinesia and rigidity scores (but not tremor scores) correlate with the nigrostriatal DA deficit (19, 20). Imaging markers of DA dysfunction may not distinguish between idiopathic and monogenic parkinsonism (21).

Dynamic PET studies with raclopride have revealed a number of adaptations that occur in surviving DA terminals during the symptomatic phase of PD. Among all the mechanisms involved in the dopamine release-reuptake cycle, alterations of a parameter,
namely the dopamine release rate, has been identified as the most important risk factor for the development of treatment-related motor complications (4). Specifically, patients with early PD who will go on to develop motor complications (fluctuations and dyskinasias) have a higher dopamine release rate than those who will remain stable responders (9). This between-group difference increases over time, being particularly prominent once motor complications become clinically relevant (5). At that time, fluctuators and dyskinetics release very large amounts of dopamine during the first hour after oral administration of levodopa. The abnormal increase in levodopa-related dopamine release will lead to (i) dyskinesias (reflecting large swings in synaptic dopamine levels), (ii) fluctuations (whenever the dopamine release reuptake is not efficient enough to maintain adequate presynaptic dopamine levels for the following release-reuptake cycles), or (iii) a combination of the two. In contrast, stable responders show a more physiologic and sustained dopamine release process, maintaining adequate synaptic dopamine levels during hours following levodopa challenge. It should be emphasized that although PD patients with motor complications have an increase in the release of dopamine during the first hour after levodopa administration, it does not mean that the overall synaptic levels of dopamine reach above normal levels in PD. Levodopa treatment does normalize vesicular dopamine levels in surviving striatal DA terminals but the overall synaptic levels of dopamine remain below normal due to the profound loss of striatal DA terminals (4, 5). In keeping with this notion, dyskinetics often have residual parkinsonism during the “on” medication state.

Interestingly, neurophysiologic studies using transcranial magnetic stimulation methods show that the differential pattern of putaminal dopamine release (and the corresponding differential pattern of putaminal dopamine receptor stimulation) observed in patients with motor complications and stable responders has a correlate in the frontostriatal motor loop (24). Thus, while levodopa treatment is able to restore normal plasticity in the primary motor cortex of stable responders, primary motor cortex plasticity dramatically declines in patients with motor complications. As there is some indication that differential patterns of dopamine release may also occur in other striatal structures (caudate and accumbens), the possibility exists that plasticity changes occurring in the corresponding frontostriatal loops (i.e., cognitive and limbic loops) could play a role in the pathogenesis of a number of neuropsychiatric manifestations of PD. For example, ICDSs could be related to a relative overactivity of the loops connecting the v-Caud nucleus with the OFC (v-Caud-OFC loop) and the NAcc with the ACC (NAcc-ACC loop) has been implicated in the pathogenesis of pathological gambling (32) and compulsive DA medication use (33). These observations are in keeping with the reported increase in amphetamine-induced release of dopamine in the striatum of non-PD impulsive individuals, as estimated by [18F]-fallypride binding changes (34). Interestingly, while raclopride PET studies show that pathological gambling is associated with an increase in the release of dopamine in the ventral striatum (32), dopamine D2/D3 receptor availability (as estimated by [11C]-FLB-457 PET) is increased in the ACC (35), suggesting that the mesocortical dopamine pathway may indeed be underactive. ICDSs could therefore be associated with increased DA tone in the ventral striatum and decreased DA tone in the ACC. As mentioned earlier, evidence from fluorodopa PET studies suggest that the mesocortical dopamine pathway is overactive in early PD (29), perhaps as a compensatory mechanism for striatal dopamine depletion. Hence, the...
DA underactivity observed in the ACC of PD patients with pathological gambling could be also compensatory for the excess of DA tone in the ventral striatum.

**Depression and apathy**

In contrast to PD patients with pathological gambling, who have altered striatal and cortical DA homeostasis, with increased DA tone in the ventral striatum and low DA tone in the ACC (35), PD patients with apathy have reduced DA tone in both striatum (ventral and dorsal striatum) and prefrontal cortex (36). Thus, as predicted by the PDFCD model, apathy is associated with low DA tone in the dorsolateral prefrontal, orbitofrontal, and ACC loops (Figure 2). The model also predicts that depression and anxiety are clinical predictors of apathy and may also reflect DA dysfunction. In fact, mood and anxiety fluctuations sometimes mirror DA tone changes in PD patients with motor fluctuations (37, 38), although “on” medication depression can also occur. There is some evidence that dopamine function may be also altered in non-PD individuals with depression (39, 40). This may be particularly true of melanchoic depression, which is typically characterized by anhedonia (41). Naturally, other DA and non-DA factors may also contribute to depression and anxiety in PD. The amygdala, for example, which is known to play an important role in anxiety disorders (42), can undergo DA denervation as well as direct PD-related pathological changes (43, 44).

**Psychosis**

The development of psychosis represents a later PDFCD stage, where DA dysfunction affects not only the striatum (dorsal and ventral striatum) but also the direct DA projection to the frontal cortex (i.e., the mesocortical dopamine pathway) (45). The DA tone can be optimal (0), too low (negative values) or too high (positive values). The direct DA projection to the frontal cortex seems to be initially upregulated (29), but with limited capability to increase further the DA tone in response to DA treatment because it lacks dopamine transporter sites and dopamine D2 autoreceptors (16). ICDs = impulse control disorders. Adapted from Ref. [3].

![FIGURE 2 | Parkinson’s disease related frontostriatal cognitive dysfunction (PDFCD) staging with region-specific dopaminergic (DA) tone. Predicted stage-specific DA function, both “off” and “on” medication (OFF and ON), is shown for dorsal caudate (d-Caud), ventral caudate (v-Caud), nucleus accumbens (NAcc), and frontal cortex. Although no distinction is made between the frontal regions corresponding to the different frontostriatal cognitive loops (i.e., dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex), a gradient of DA dysfunction may be also present in the mesocortical dopamine pathway (11). The DA tone can be optimal (0), too low (negative values) or too high (positive values). The direct DA projection to the frontal cortex seems to be initially upregulated (29), but with limited capability to increase further the DA tone in response to DA treatment because it lacks dopamine transporter sites and dopamine D2 autoreceptors (16). ICDs = impulse control disorders. Adapted from Ref. [3].](image-url)

| Normal | d-Caud | v-Caud | NAcc | Frontal | Symptoms |
|--------|--------|--------|------|---------|----------|
|        | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | None |
| **Stage I** | (OFF) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Executive dysfunction / Fatigue |
|         | (ON)  | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ICDs |
| **Stage IIa** | (OFF) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Depression / Anxiety |
|          | (ON)  | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Depression / ICDs |
| **Stage IIb** | (OFF) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Apathy / Anxiety / Pain |
|           | (ON)  | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Depression / Hallucinations |
| **Stage III** | (OFF) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Apathy / Dementia |
|           | (ON)  | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | ![DA](image-url) | Apathy / Psychosis |
Frontostriatal loops may be relatively overactive during the “on” medication state, which would explain why, as with dyskinasias, decreasing the dose of DA drugs is often helpful for ameliorating hallucinations and psychosis. Taking into account that the DA tone in the frontal cortex is mostly determined by dopamine D1 receptors (46–48) and that hallucinations and psychosis are especially associated with the use direct dopamine D2 agonists (49, 50), it seems reasonable to conclude that PD-psychosis is likely associated with a relative hyperdopaminergic D2 tone in the NAcc. Interestingly, [18F]-FLB-457 binding in the ACC decreases as PD progresses (15), which could suggest a compensatory increase in the activity of the direct DA projection to that frontal area. In addition to striatal and cortical DA dysfunction, cortical alpha-synuclein pathology can be a major determinant for the onset of psychosis.

CONCLUDING REMARKS

Dopamine radiotracer neuroimaging has greatly contributed to increase our understanding of motor and neuropsychiatric manifestations of PD. It is becoming increasingly clear that many of the clinical manifestations observed during the “on” state are not the result of an average hyperdopaminergic tone, but are due to the presence of large swings in synaptic dopamine levels. This mechanism explains dyskinasias and may also apply to ICDs and psychosis. Further research is needed to better characterize the progression of DA dysfunction and plasticity changes in different frontal regions and the corresponding clinical correlates.

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