Neuroimaging in Parkinson's Disease

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Summary: Parkinson's disease (PD) is a common disorder in which the primary features can be related to dopamine deficiency. Changes on structural imaging are limited, but a wealth of abnormalities can be detected using positron emission tomography, single photon emission computed tomography, or functional magnetic resonance imaging to detect changes in neurochemical pathology or functional connectivity. The changes detected on these studies may reflect the disease process itself and/or compensatory responses to the disease, or they may arise in association with disease- and/or treatment-related complications. This review will focus mainly on neurochemical and metabolic studies and reviews various approaches to the assessment of dopaminergic function as well as the function of other neurotransmitters that may be affected in PD. A number of clinical applications are highlighted, including diagnostic utility, identification of preclinical disease, changes associated with motor and nonmotor complications of PD, and the effects of various therapeutic interventions. **Key Words:** Positron emission tomography, single photon emission computed tomography, functional magnetic resonance imaging, dopamine, monoamines.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, estimated to affect 200–300 per 100,000 population. While other areas of both the central and peripheral nervous system may be affected, [1] the most important pathological finding in PD is the loss of dopaminergic neurons in the substantia nigra that project to the striatum, most often associated with cytoplasmic Lewy bodies. The symptoms of PD do not appear until approximately 50% of the nigral dopamine (DA) neurons have been lost, but the impact on routine structural imaging findings is minimal at this stage. Consequently, structural imaging has in general been unrewarding, although some newer MRI techniques, such as diffuse tensor imaging or shape analysis, are somewhat more promising. Despite the relatively limited structural changes, it is estimated that there is an approximately 80% decline of striatal DA before typical motor symptoms appear, and this has substantial functional effects on the cortical–striatal–pallidal–thalamic–cortical circuitry. PD is therefore an ideal condition for the application of functional imaging techniques, and findings from these will form the thrust of this review. These techniques may not only shed insights into PD and the basis for its complications, but they may also be useful for deriving inferences regarding the role of DA in the normal brain.

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MAGNETIC RESONANCE IMAGING

As already noted, traditional structural imaging does not generally reveal significant reproducible changes in PD. More recently, some investigators have applied diffusion tensor imaging and demonstrated reduced fractional (FA) in the region thought to correspond to ascending nigrostriatal fibers [2], although this finding has not yet been reproduced. One group has demonstrated reduced FA in the substantia nigra itself, with outstanding sensitivity and specificity in caudal regions [3], while others have suggested that FA may be reduced in other regions [4, 5], perhaps representing alterations in white matter integrity or in functional connectivity. Yet another group has suggested that diffusion tensor imaging measures of nigrothalamic connectivity combined with a modified T1 nigral volumetric study have improved sensitivity and specificity for PD [6]. Another recent study used magnetic resonance imaging (MRI) to demonstrate changes in thalamic shape, in the absence of altered volume, in patients with PD [7]. In general, this is an area in its infancy, and findings need to be reproduced before these techniques can be recommended for widespread use in PD.

An area of emerging interest is the application of resting state functional MRI to assess functional con-

nectivity. In PD patients studied off medication, connectivity is reduced in the supplementary motor area, left dorsolateral prefrontal cortex, and left putamen, while connectivity is increased in the left cerebellum, left primary motor, and parietal cortex compared to healthy controls. These findings are at least partially reversed by medication [8]. Another group used this technique to show reduced connectivity between inferior parietal cortex and the posterior putamen, while coupling of this region to the anterior putamen was increased [9]. Yet other investigators have shown that areas active during rest ("default mode network") demonstrate increased activity but reduced connectivity in PD [10].

Functional MRI (fMRI) can of course be used to study activation patterns during the performance of a motor or cognitive task. A full discussion of fMRI studies performed in PD is beyond the scope of this review. It is however of interest that such studies are sensitive to the effects of catechol-*O*-methyltransferase (COMT) polymorphisms that modulate the availability of dopamine in the prefrontal cortex. Reduced activation in frontoparietal networks is seen in subjects with low COMT when performing a planning task [11] and a task sensitive to attentional control [12], with demonstrable interactions between genotype and dopaminergic medication.

Proton magnetic resonance spectroscopy of the striatum has provided variable results in PD itself, but this technique may be useful for differentiating between PD and atypical parkinsonian syndromes, such as multiple system atrophy or progressive supranuclear palsy [13–16], and there may also be changes in the posterior cingulate [17] and pre-supplementary motor area cortex [18]. Phosphorus spectroscopy may also reveal changes that appear to differ between PD and multiple system atrophy [19, 20].

TRANSCRANIAL SONOGRAPHY

Several papers have reported increased echogenicity in the substantia nigra using non-invasive transcranial sonography [21]. This is thought by some authors to be specific for PD (or, more correctly, to be a trait marker, given that echogenicity may be increased in relatives of patients with PD [22], in normal individuals [23], and in those with other disorders thought to predispose to PD, such as rapid-eye-movement sleep behavior disorder and anosmia) [24, 25]. Abnormal echogenicity in normal younger individuals may correspond to impaired dopaminergic function as assessed by positron emission tomography (PET) [26]. However, echogenicity is also increased in subjects with essential tremor [27] and does not change over the course of PD [28], thus its role is still a matter of controversy.

IMAGING DA FUNCTION

Presynaptic function (FIG. 1)

There are 3 basic approaches to studying the integrity of dopaminergic projections. The vesicular monoamine transporter type 2 (VMAT2) is labeled by [^{11}C] dihydrotetrabenazine (DTBZ) (or its [^{18}F]fluoropropyl derivative) and is expressed by all monoaminergic neurons. Thus, a principal disadvantage of VMAT2

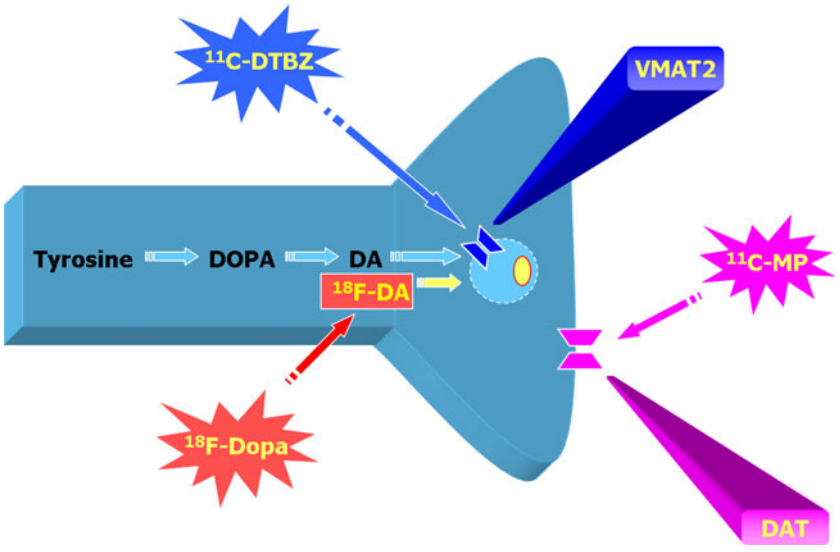

FIG. 1. Cartoon depicting a dopaminergic nerve terminal with 3 different approaches used to assess function *in vivo*. ^{18}F-labeled dopa is taken up by the nerve terminal and decarboxlyated to ^{18}F-labeled dopamine (^{18}F-DA), which is stored in synaptic vesicles. The type 2 vesicular monoamine transporter (VMAT2) is labeled by [^{11}C]dihydrotetrabenzine (^{11}C-DTBZ), while the plasmalemmal dopamine transporter (DAT) is labeled by [^{11}C]-D-*threo*-methylphenidate (^{11}C-MP). Modified with permission from Nandhagopal et al. [120]. (High resolution version of this image is available in the electronic supplementary material.)

imaging is its theoretical lack of specificity for DA as opposed to other monoaminergic neurons. From a practical perspective, however, 90% of VMAT2 binding in the striatum is to DA neurons. A major potential advantage is that, unlike membrane dopamine transporter binding or fluorodopa uptake, DTBZ binding is not thought to be subject to regulatory or compensatory changes in expression. However, VMAT2 binding is subject to competition from endogenous cytosolic DA, so large changes in vesicular DA concentration may alter DTBZ binding [29–31], and it is accordingly an imperfect measure of nerve terminal density. DTBZ PET performed in the "off" medication state nonetheless probably provides a reasonably good (perhaps the optimal) estimate of this parameter, but is currently available at only a few centers worldwide.

The plasmalemmal dopamine transporter (DAT) is selectively expressed by DA neurons, and thus DAT binding is another approach to the estimation of DA nerve terminal density. DAT expression is subject to modification by a number of pharmacological- and disease-related phenomena, and its expression is down-regulated in early disease [32]. The practical importance of this is not clear, however, and DAT binding is a popular and relatively widely available means to assess DA function, especially as a variety of ligands have been developed for use with ^{123}I or even ^{99m}Tc single photon emission computed tomography as well as PET.

6-[^{18}F]fluoro-L-dopa (FD) is an analog of levodopa that is taken up by dopaminergic neurons and converted by L-aromatic amino acid decarboxylase (AADC) to [^{18}F]fluorodopamine (FDA), which is then trapped in synaptic vesicles. FD uptake is therefore also useful as a measure of DA neuron function. FD uptake is not restricted to DA neurons, however, as AADC is expressed in noradrenergic and serotonergic neurons as well [33, 34]. Additionally, much of the radioactivity measured in PET scans reflects vesicular trapping. However, over time there is egress of FDA from synaptic vesicles and subsequent catabolism by COMT and monoamine oxidase. As these metabolites are not trapped, there is a loss of tracer activity which can be used to estimate DA turnover [35, 36]. DA turnover is increased in early PD and continues to increase with disease progression [37, 38] and in association with treatment complications. DA turnover is modulated by expression of the DAT [39].

Measures of postsynaptic function

Dopamine receptors can be studied using a variety of radiolabeled agonist or antagonist ligands. The most widely used ligand for the dopamine D1 receptor is SCH 23390 labeled with ^{11}C. However, although its expression is affected by normal aging [40], there is no evidence of alterations in typical PD (as opposed to conditions such as multiple system atrophy, in which D1 receptor-expressing striatal neurons are affected [41]) nor of any relationship to disease- and treatment-related complications in PD [42, 43], so it has not found widespread use.

A number of ligands have been developed to study the dopamine D2 receptor. High-affinity antagonists, such as spiperone (labeled with either ^{11}C or ^{18}F) or ^{18}F-labeled benperidol [44], bind equally to high- and low-affinity states of the receptor and are not sensitive to occupancy by endogenous DA. In contrast, [^{11}C]raclopride has a lower affinity, and its binding is accordingly affected by changes in the availability of synaptic DA [45, 46]. This can be used to advantage to estimate DA release in response to a variety of pharmacological [47, 48], physical [49–51], or behavioral [52–54] interventions. Higher affinity ligands, such as [^{11}C]FLB 457 or fallypride (labeled with either ^{11}C or ^{18}F) will additionally bind to extra-striatal DA receptors. Although somewhat inconsistent, most studies suggest that they are sensitive to the release of endogenous DA [55–62]. Finally, agonists such as [^{11}C]*N*-propyl-norapomorphine [63] or ^{11}C-labeled PHNO [64] may be used to estimate changes in synaptic DA. Because of its relative selectivity, PHNO may also be useful for visualizing dopamine D3 receptors.

FUNCTIONAL ACTIVITY, METABOLIC NETWORKS, AND CONNECTIVITY

Although not neurochemically specific, the DA denervation of PD leads to widespread alterations in synaptic activity through the cortico–striato–pallidothalamo–cortical loops and beyond. Thus, PD is typically associated with increased glucose metabolism or blood flow in the basal ganglia and thalamus coupled with reductions in the supplementary motor, premotor, and parietal cortex. Glucose metabolism and blood flow are also increased in the pons and cerebellum. This pattern, also referred to as the PD-related profile (PDRP) [65] is distinct from those seen in other disorders resulting in parkinsonism, such as multiple system atrophy (basal ganglia and cerebellar hypometabolism), progressive supranuclear palsy (brainstem and medial frontal cortical hypometabolism) and corticobasal degeneration (asymmetric cortical and basal ganglia hypometabolism) [66]. The pattern seen in PD can not only be used to assist in diagnosis, but it is also sensitive to a variety of therapeutic interventions [67] and to disease progression. This potential application will be discussed further in the following sections.

Glucose metabolism and, particularly because of the better temporal resolution, regional cerebral blood flow are sensitive to activation during the performance of motor or cognitive tasks. Performance of a simple finger

sequence is associated with activation of mesial frontal cortex which is impaired in PD, [68] an abnormality that is reversed with the rapidly acting dopamine agonist apomorphine [69]. Altered patterns of activation may arise not only as a direct result of disease-related deficiencies in function, but also from the engagement of compensatory mechanisms. Thus, the impairment of mesial frontal activation seen with sequential finger movements in PD is coupled with hyperactivation of the premotor and inferolateral parietal cortex [70]. In a similar fashion, whereas performance of a procedural learning (Tower of London) task is normally associated with activation of the dorsal caudate nucleus, in patients with PD, there is a shift to hippocampal circuitry which is usually used for declarative learning (and which is suppressed during performance of the task in healthy individuals) [71].

OTHER NEUROCHEMICAL MARKERS OF INTEREST IN PD

PD affects other monoaminergic systems besides DA. It should be remembered that AADC is expressed in noradrenergic and serotonergic neurons as well as in DA neurons [33, 34], and abnormalities may be seen in PD. More specific markers of serotonergic function include [^{11}C]WAY 100635, which binds to both pre- and postsynaptic $5HT_{1A}$ receptors and [^{11}C]DASB [*N*,*N*-dimethyl-2-(2-amino-4-cyanopheylthio)benzylamine], which is selective for the 5HT transporter. $5HT_2$ receptors can be labeled with [^{18}F]setoperone (which also binds to dopamine D2 receptors) and by [^{11}C]MDL 100,907 or [^{18}F]altanserin. PET ligands for the norepinephrine transporter are in development but not yet well established.

Because of its role in cognitive function, the cholinergic system is of great potential interest in PD. This may typically be labeled with cholinesterase substrates, such as [^{11}C]MP4A (*N*-[^{11}C]methylpiperidin-4-*yl* acetate) or [^{11}C]PMP (*N*-[^{11}C]methylpiperidyl propionate), or with a variety of postsynaptic muscarinic ligands, such as *N*-[^{11}C]methyl-4-piperidyl benzilate ([^{11}C]NMPB). Other neurotransmitter receptor ligands of potential interest in PD are labels for opioid receptors, tachykinin receptors, and adenosine receptors.

PET can be used to assess other non–neurotransmitter related processes relevant to the pathogenesis and/or complications of PD. This includes amyloid deposition (typically with ^{11}C-labeled Pittsburgh compound B [72], but with several analogous agents emerging), microglial inflammation ([^{11}C]PK 11195) [73, 74], and the p-glycoprotein responsible for extrusion of substances from within to outside the blood–brain barrier ([^{11}C] verapamil) [75].

CLINICAL FINDINGS

PD—primary features and diagnosis

By the time patients develop symptoms, it is estimated that they have lost approximately 50% of their nigral DA neurons and approximately 80% of striatal dopamine content. It is therefore not surprising that PD is essentially invariably associated with striking reductions in the uptake of all markers of DA activity. The exception to this is the case of Scans Without Evidence of Dopamine Deficiency (SWEDD), discussed further below. In keeping with known neuropathological [76] and postmortem neurochemical [77] findings, markers of DAT, VMAT2, and FD uptake all show a rostral—caudal gradient, with relative preservation of the caudate and preferential involvement of the posterior putamen (FIG. 2). As PD is typically an asymmetric condition, it is usual to see asymmetric involvement of the striatum on functional imaging. Interestingly, this asymmetry is not necessarily seen in glucose metabolic network abnormalities, which are symmetrically abnormal [78].

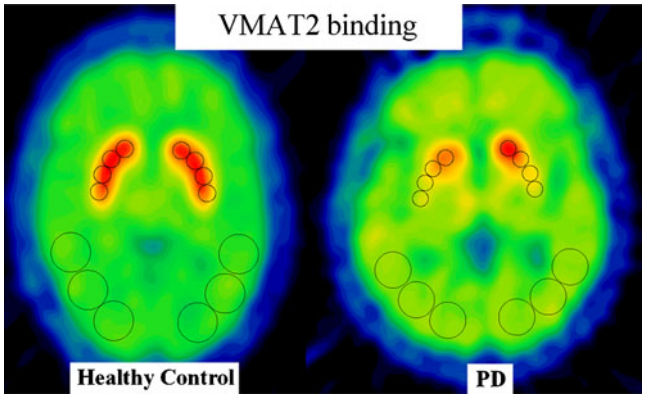

FIG. 2. VMAT2 binding assessed using [^{11}C]dihydrotetrabenazine in a healthy control (left) and a patient with moderate PD (right). Note the asymmetric reduction of tracer uptake in the PD patient, with relative preservation of the caudate nucleus. Circles represent typical regions of interest placed over the caudate, anterior, mid- and posterior putamen, as well as reference regions placed over the parieto-occipital cortex. VMAT = Vesicular monoamine transporter type 2; PD = Parkinson's disease. (High resolution version of this image is available in the electronic supplementary material.)

This pattern of asymmetrical DA denervation with a rostral–caudal gradient, while typical for PD, is not diagnostically specific, as it may also be seen in some patients with multiple system atrophy. However, the latter may be distinguished on the basis of reduced striatal D2 receptors, which are preserved in PD [79], or by the pattern of glucose metabolism, which is reduced in the striatum and cerebellum [66].

Using FD uptake as a marker of DA cell loss, Vingerhoets et al. found that DA loss correlated best with the degree of bradykinesia but not well with the severity of tremor [80]. This is in keeping with the more recent observation of Doder et al. [81], who found that tremor correlated better with brainstem serotonergic innervation as assessed by [^{11}C]WAY 100635 binding.

Progression of PD

DAT, VMAT2, and FD uptake all decline as PD progresses. However, although there is broad relationship between disease severity and severity of imaging abnormalities, studies have generally failed to find a significant correlation between change in motor dysfunction and change in image marker. Whether this reflects the variance inherent in both measurements, persistent effects of medication (typically withheld for several hours prior to the scan), progression of disability arising from non-dopaminergic mechanisms, or other factors is unclear. Nandhagopal et al. [82] reported the findings of 3-tracer PET in a cohort of PD patients (initial N=78) studied on 3 occasions over 8 years. Statistical modeling revealed that the decline in tracer uptake was in all cases described best by an exponential function. As noted in all studies of PD, the posterior putamen was maximally affected from disease onset, while the caudate nucleus was minimally affected. Despite the decline in both, the degree of separation was maintained throughout the course of the illness, while side-to-side asymmetries declined over time. The asymptotes for anterior *versus*. posterior striatal regions were significantly different, but the rates of decline were not. This result suggests that factors responsible for the progression of PD (which affect all striatal subregions to the same degree) may be different from those responsible for its initiation, which are regionally selective. The glucose metabolic pattern or PDRP also progresses with PD [83].

The potential utility of imaging to quantitatively assess the progression of dopaminergic dysfunction has led to great interest in its potential use as a biomarker to assess the effects of potential disease-modifying therapies. However, many of the studies have been plagued by poor agreement between the imaging findings and clinical measures. Studies on the dopamine agonists pramipexole and ropinirole suggested that the decline of DAT binding or FD uptake respectively were slower compared to levodopa therapy, but that the clinical outcome was at least as good and typically better with levodopa [84, 85]. Human fetal transplanation [86] and trophic factor therapy [87] are both associated with improvements in FD uptake in the absence of significant clinical improvement. There may be many reasons for this disparity, but while imaging studies are of unquestioned utility as a biomarker, there is a general consensus that imaging alone cannot be used as a surrogate marker to assess the effects of therapy [88, 89].

An interesting finding that emerged from attempts to use functional imaging for the assessment of disease-modifying therapies was the fairly consistent observation that approximately 15% of patients thought to have PD had normal scans. This phenomenon has become known as SWEDD. These studies were conducted in people with early PD, and it was therefore assumed that some patients with essential tremor had mistakenly been included. While this may indeed be the case, it appears to be an incomplete explanation. Many of the subjects with SWEDD appear to have dystonic tremor which can superficially look very much like early, tremor-predominant PD, [90] but unlike PD, olfaction is preserved, [91] the tremor is not re-emergent on assuming a new posture, and there is no true decrement in the amplitude of repetitive movements [92]. People with SWEDD do not have a convincing response to dopaminergic therapy and do not show the PDRP on glucose PET [93].

Presymptomatic abnormalities

As the symptoms of PD do not develop until striatal DA has been depleted by 80%, functional imaging can, not surprisingly, detect DA dysfunction in asymptomatic individuals. The first demonstration of this was in subjects exposed to the nigral toxin *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, in whom FD uptake was reduced in subjects who were clinically normal [94]. FD PET has also demonstrated abnormalities in asymptomatic twins [95]. In the case of dominantly inherited PD, PET abnormalities have been identified in asymptomatic family members and, by reassigning phenotype, can assist in the identification of the mutation [96, 97].

Motor complications

Within 5 years of starting levodopa treatment, approximately 50% of patients with PD will develop fluctuations in response to medication and/or dyskinesias. While the two problems are not synonymous, they are commonly associated with one another and are thought to be related to changes that occur downstream to striatal DA receptors as a consequence of their pulsatile stimulation. Using changes in [^{11}C]raclopride (RAC) binding to estimate DA release, de la Fuente-Fernandez et al. [98] showed that even while studied at a time when their response to levodopa was stable, those patients who went on to develop motor fluctuations had a large initial increase in DA release following the administration of oral levodopa, followed by a return to baseline within

4 h, whereas those patients who maintained a stable therapeutic response had a relatively smaller but more sustained response. Using this approach, levodopa-induced DA release was shown to increase with disease duration and to be higher in patients with dyskinesias than in those with a stable response (FIG. 3) [99]. An alternate way of estimating DA turnover is from prolonged (4 h) FD scans [100]. DA turnover estimated in this manner is inversely related to expression of the DAT [39], and it is accordingly of interest that patients with dyskinesias appear to have a greater degree of DAT downregulation than do those with a stable response to medication [101]. Downstream changes in response to pulsatile stimulation of denervated DA receptors include the increased expression of neuropeptides. This may explain the reductions in binding of the opioid receptor ligand [^{11}C]diprenorphine reported in PD patients with dyskinesias, presumably reflecting receptor occupancy by endogenous opioids [102].

Gait and postural disturbances are common, particularly in advanced PD, but generally poorly responsive to dopaminergic medication. Recent evidence suggests that a history of falls is associated with cholinergic deficits in the thalamus, presumably reflecting the loss of innervation from the pedunculopontine nucleus, and does not correlate with striatal DA innervation [103].

Cognitive and behavioral complications

Deficits in executive function are common in PD, even in the absence of dementia. Cognitive dysfunction in PD is associated with a glucose metabolic pattern of reduced activity in the frontal and parietal cortex as well as increased activity in the cerebellar vermis [104] and is independent of the PDRP described above and unresponsive to levodopa. Dementia in PD is associated with marked reductions in glucose metabolism in the occipital cortex, a pattern distinct from that seen in Alzheimer disease [105]. PD is also associated with widespread deficits in cholinergic activity, and these are more pronounced in patients with dementia, exceeding the abnormalities seen in Alzheimer disease [106]. A few studies have used ^{11}C-labeled Pittsburgh Compound B to assess amyloid deposition in PD with dementia. For the most part, these studies suggest that amyloid deposition is increased in subjects with Lewy body dementias, but not in those with PD-dementia [107, 108]. Many investigators consider these to represent variations of the same disorder, and this distinction may accordingly be seen as somewhat surprising. Another recent study suggests that amyloid deposition in both Lewy body dementias and PD-dementia is related to expression of the ApoE4 allele [109].

Depression affects approximately 40–50% of patients with PD [110] and may antecede motor dysfunction [111, 112]. It has long been assumed that depression in PD must be related to impaired monoamine transmission, but direct evidence is very limited. There are reductions in the uptake of the mixed DA/norepinephrine transporter ligand [^{11}C]RTI-32 in the thalamus, ventral striatum, locus coeruleus, and amygdala of depressed PD patients *versus* those without depression [113]. Somewhat surprisingly, 5HT transporter binding is increased in the prefrontal cortex of depressed PD patients compared to their non-depressed controls and is positively correlated with depression rating scores in the orbitofrontal cortex, cingulate cortex, and insula [114].

Up to 15% of PD patients will develop some form of impulse control disorder under treatment with dopaminergic agents. These can range from compulsive medication

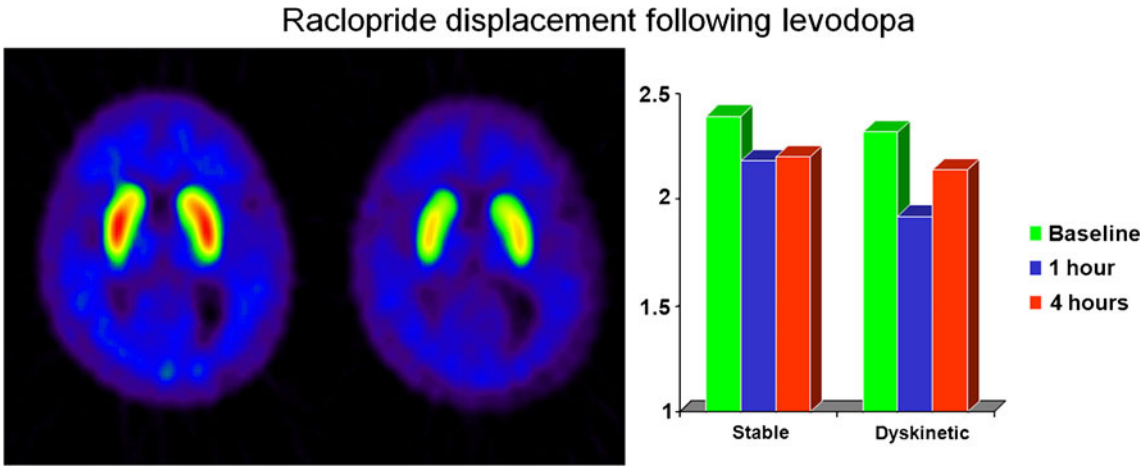

FIG. 3. [^{11}C]raclopride (RAC) binding is subject to competition from levodopa-derived dopamine in patients with PD. The left panel depicts RAC binding at baseline in a patient with PD and following oral administration of levodopa (right). The right panel displays mean putamen RAC binding potential values at baseline and 1 and 4 h following levodopa in patients with a stable response and patients with dyskinesias. Note that the dyskinetic patients have a larger initial decline in RAC binding (representing an increase in synaptic dopamine) but that this is poorly sustained compared to the stable medication responders, who have a smaller but more sustained change in RAC binding. Modified with permission from de la Fuente-Fernandez et al. [94]. (High resolution version of this image is available in the electronic supplementary material.)

use to pathological gambling or shopping, hypersexuality, compulsive eating, or punding, in which people engage in hobbies, hoard, and sort through items or repetitively take instruments apart and reassemble them [115]. Using RAC PET, Evans et al. [116] demonstrated a marked increase in ventral striatal DA release following the administration of oral levodopa to PD patients with the dopamine dysregulation syndrome compared to those without this behavioral complication. Both groups had comparable levels of DA release in the dorsal (motor) striatum. As is seen in other cases of addictive behavior [117], DA release correlated with "drug wanting" rather than the perceived pleasantness of the drug. Steeves et al. [118] used a similar approach to study DA release in PD patients with and without pathological gambling. In this case, the intervention was performance of a computerized gambling task. There was a relatively greater increase in ventral (but not dorsal) striatal DA release (i.e., a greater % change in RAC binding) in the gamblers during performance of the task. However, the interpretation is somewhat hampered by the fact that the baseline RAC binding potentials were lower in the gamblers. The same group has also used fMRI to demonstrate that dopamine agonists impair the relationship between reward prediction error and cerebral blood flow in the orbitofrontal cortex, which mainly reflects a loss of deactivation in response to negative prediction errors [119].

CONCLUDING COMMENTS

While routinely available structural imaging may be of limited use, functional imaging studies can provide great insights into functional connectivity, neurochemical pathology, and pathogenic processes in disorders such as PD, where structural changes may be quite limited. Applications may include diagnosis, preclinical detection, and a better understanding of disease- and treatment-related complications. Such studies can also be used to assess the acute effects of therapeutic interventions and also as a biomarker to assess disease progression and the effects of disease-modifying therapies. In the latter case, however, considerable caution is required, and the findings must be interpreted in conjunction with other clinical measures of disease activity.

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