8

Neuroimaging in Parkinson's Disease

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Neuroimaging has provided insight into the pathophysiology and natural history of Parkinson's disease (PD) and has emerged as a tool to monitor disease progression and to assess new potentially neuroprotective or neurorestorative therapies for PD. Diverse imaging methods have been successfully applied to neurological disorders. While technology like functional magnetic resonance imaging or magnetic resonance spectroscopy has been especially useful in assessing stroke, multiple sclerosis and epilepsy (1–3), in vivo neuroreceptor imaging using single photon emission tomography (SPECT) and positron emission tomogrpahy (PET) have so far been most valuable in assessing PD. SPECT and PET use specific radioactively labeled ligands to neurochemically tag or mark normal or abnormal brain chemistry. Recent advances in radiopharmaceutical development, imaging detector technologies, and image analysis software have expanded and accelerated the role of imaging in clinical research in PD, in general, and neurotherapeutics, in particular. In this overview we will focus on developments in neuroreceptor imaging in PD.

IMAGING TECHNOLOGY

Both PET, also called dual photon emission tomography, and SPECT are sensitive methods of measuring in vivo neurochemistry (4,5). The choice of imaging modality is ultimately determined by the specific study questions and study design. While, generally PET cameras have better resolution than SPECT cameras, SPECT studies may be technologically and clinically more feasible, particularly for large clinical studies and in clinical practice. PET studies may benefit from greater flexibility in the range of radiopharmaceuticals that can be tested, but SPECT studies have the advantage of longer half-life radiopharmaceuticals necessary for some studies.

The strengths and limitations of in vivo neuroreceptor imaging studies depend on the imaging technology utilized to measure brain neurochemistry and the ligand or biochemical marker used to tag a specific brain neurochemical system. The properties of the radiopharmaceutical are the most crucial issue in developing a useful imaging tool for PD. Some of the key steps in development of a potential radioligand include assessment of the brain penetration of the radioligand, the selectivity of the radioligand for the target site, the binding properties of the radioligand to the site, and the metabolic fate of the radioligand. These properties help to determine the signal-to-noise ratio of the ligand and the ease of quantitation of the imaging signal. While ligands targeting neuronal metabolism have been used successfully to study PD patients, this review will focus on dopaminergic ligands (6). Specific markers for the dopaminergic system including ^{18}F-DOPA (7–12), ^{11}C-VMAT2 (13–15), and dopamine transporter (DAT) ligands (16–22) (Fig. 1) have been widely used to evaluate patients with PD.

Dopamine ligands are useful to assess PD in so far as they reflect the ongoing dopaminergic degeneration in PD. In the study most directly correlating changes in dopamine neuronal numbers and imaging outcomes there is good correlation between dopamine neuron loss and ^{18}F-DOPA uptake, although conclusions are limited by a small sample size of five subjects (12). Numerous other studies have shown that the vesicular transporter and dopamine transporter are reduced in striatum in postmortem brain from PD patients (23–25). In turn numerous clinical imaging studies have shown reductions in ^{18}F-DOPA, ^{11}C-VMAT2, and DAT ligands uptake in PD patients and aging healthy subjects consistent with the expected pathology of PD and of normal aging. Specifically these imaging studies demonstrate asymmetric, putamen greater than caudate loss of dopaminergic uptake that is progressive (26–28) (Table 1). In addition both ^{11}C-VMAT2 and DAT ligands demonstrate reductions in activity with normal aging (13,29).
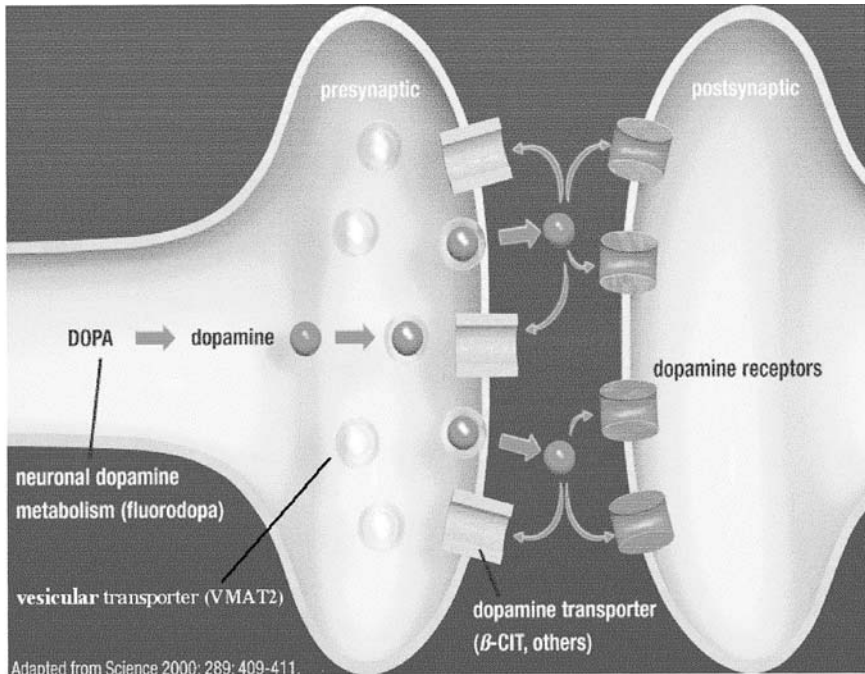
FIGURE 1 Idealized dopamine synapse showing targets for radiopharmaceutical in PD. (See color insert.)

TABLE 1 Comparison of Dopamine Presynaptic Ligands in PD Studies

	[^{123}I]β-CIT	^{11}C-VMAT2	^{18}F-DOPA
Target	DA transporter	Vesicular transporter	DA turnover
Bilateral reduction in hemi-PD	Yes	Yes	Yes
Correlates with UPDRS in cross section	Yes	Yes	Yes
Annual reduction change with aging (% loss from baseline)	0.8–1.4%	0.5%	No
Annual progression (% loss from baseline)	6–13%	10%	7–12%

Imaging with ^{18}F-DOPA, ^{11}C-VMAT2, and DAT ligands target different components of the presynaptic nigrostriatal neuron. The mechanism of each of these ligands has been elucidated in preclinical studies. Imaging with ^{18}F-DOPA depends on conversion of ^{18}F-DOPA by aromatic amino acid decarboxylase and uptake and trapping of ^{18}F-dopamine into synaptic vesicles. Studies in 1-methyl-4-Phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys have shown a correlation between the ^{18}F-DOPA uptake and both dopaminergic neuron number in the substantia nigra and dopamine levels in the striatum (30). The vesicular monoamine transporter acts to sequester newly synthesized or recovered monoamines (dopamine, serotonin, norepinephrine, and histamine) from the cytosol into the synaptic vesicles, thereby protecting the neurotransmitters from catabolism by cytosolic enzymes and packaging them for subsequent exocytotic release (31). VMAT2 ligand uptake is reduced in two commonly used rodent models of PD the 6-hydroxydopamine–treated rat and the MPTP-treated mouse (32,33). DAT, a protein on the nerve terminal, is responsible for reuptake of dopamine from the synaptic cleft. In MPTP-treated monkeys the loss of DAT paralleled that of dopamine in the striatum, and in MPTP monkeys treated with nigral implants recovery of behavioral function was correlated with changes in DAT imaging (34,35).

During the past decade, several DAT ligands have been developed and used to assess PD and related disorders. Table 2 provides a more detailed comparison of the properties of these ligands. This comparison both illustrates the increasing choice of radioligands available and underscores the distinction of those ligands that enable easy quantification of the imaging signal. DAT imaging agents are cocaine analogs with nanomolar affinity at the DAT (36–41). These ligands are chemically modified to alter

TABLE 2 Characteristics of SPECT Dopamine Transporter Radioligands

SPECT tracer	[123I]β-CIT	[123I]FP-CIT	^{99m}Tc-TRODAT	[123I]Altropane
Time to peak uptake	Protracted, 8–18 h	Rapid, 2–3 h	Rapid, 2–3 h	Rapid, 0.5–1 h
Washout phase	Prolonged	Prolonged	Intermediate	Rapid
DAT binding affinity	1.4 nM Ki	3.5 nM Ki	9.7 nm Ki	6.62 nM IC50
DAT:SERT selectivity	1.7:1	2.8:1	26:1	28:1
SPECT target:background tissue ratio	High	High	Low	Low

the rapid metabolism of cocaine at the ester linkage to provide more in vivo stability of the parent compound. Nonetheless, the kinetic properties of DAT radiotracers are quite different with regard to plasma protein binding, permeability across the blood-brain barrier, binding affinity, selectivity for the dopamine transporter, and elimination. These differences are crucial to the applications of the DAT ligand for imaging (42). For example, while a given DAT tracer may distinguish PD from healthy controls based on the qualitative appearance of striatal uptake, the ability to distinguish the longitudinal changes in severity of PD may be more difficult for tracers with relatively poorer signal-to-noise properties (lower specific to nonspecific brain uptake) (Table 2). The quantitative properties of the radiotracer must be well understood to assess disease progression. Specifically, does the imaging signal provide a measure that is related to Bmax, the density of DAT, and/or the integrity of dopamine neurons? For some tracers absolute quantitation of the DAT signal may require invasive methods involving full kinetic modeling, while other DAT tracers have a pharmacokinetic profile, which simplifies the methods for signal quantification. For example, the unusual binding kinetics of $[^{123}I]\beta$-CIT, with a protracted period of stable specific radiotracer uptake in the brain and extremely slow elimination from the DAT sites in striatum, permit reproducible quantitative determination of DAT density using a simple tissue ratio method (19,43). For DAT tracers with faster washout from specific binding sites, this simple ratio technique will overestimate the density of binding sites in healthy striatum relative to PD (44), although these tracers may permit better visual discrimination of diseased from control cases.

Of the DAT SPECT tracers in development, $[^{123}I]\beta$-CIT, $[^{123}I]$FP-CIT, $[^{123}I]$-altropane, and $[^{99m}Tc]$-TRODAT have been the most widely evaluated dopamine transporter agents for SPECT imaging (18,20,45) and ^{18}F-CFT (WIN 35,428) for PET (46,47). None of these tracers is commercially available as yet in North America, although one tropane derivative of cocaine (FP-CIT, DATSCAN®) is available as a $[^{123}I]$-labeled tracer in Europe.

PD DIAGNOSIS ACCURACY

The diagnosis of PD is currently based primarily on clinical judgment. However, the variability of disease presentation, progression, and response to medications often makes diagnosis uncertain. Prevalence studies of parkinsonism suggest a diagnostic accuracy of 80% after examination and application of clinical diagnostic criteria (48–50). Long-term clinicopathological studies evaluating the diagnostic accuracy of PD demonstrate that the diagnoses most commonly mistaken for PD are progressive supranuclear

palsy (PSP) and multisystem atrophy (MSA) (51,52). However, early in the course of PD the diagnoses most commonly mistaken for PD include essential tremor, vascular parkinsonism, drug-induced parkinsonism, and Alzheimer's disease (53,54). It is estimated that diagnosis is incorrect in as many as 35% of those initially diagnosed as PD by generalists (55). In addition, symptoms of parkinsonism are relatively common in elderly subjects, making the diagnosis most challenging in this population. Subtle extrapyramidal signs on neurological evaluation are common in the elderly, with recorded prevalences of 32% (56) and 35% (57). Prevalence estimates for clinically evident parkinsonism in similarly aged subjects are much lower at around 3%. Neurologists with specialized training in parkinsonism are able to make the diagnosis of PD with higher accuracy than generalists as demonstrated by a follow-up study of the DATATOP cohort in which the diagnosis of PD was changed in only 8.1% of subjects at 6-year follow-up and by a study of movement disorder specialists in the United Kingdom demonstrating sensitivity of 91.1% for diagnosis of PD compared to the diagnosis based on pathology (58,59).

In vivo imaging holds the promise of improving diagnostic accuracy by providing an in vivo assessment of the nigrostriatal dopaminergic system early in disease. While comparison of imaging and pathology helps to confirm the validity of the imaging studies, it also highlights questions for which imaging studies may provide unique and otherwise unobtainable data. For example, in vivo imaging studies with either ^{18}F-DOPA/PET or [^{123}I]β-CIT/SPECT demonstrate a reduction in ligand uptake of approximately 50–70% in the putamen in PD subjects (20,60). The reduction in dopamine terminal function or DAT density and the pattern of striatal degeneration is consistent with the reduction in substantia nigra pars compacta neurons of greater than 80% and of putamenal dopamine content of 95% in PD brains (61–63). However, these imaging studies have shown at or near the threshold of diagnosis of PD a reduction in putamenal ^{18}F-DOPA or DAT activity of 40–60% rather than 80–90% as suggested by pathology studies (64–66). These imaging data acquired from early PD patients have clarified the natural history of disease, led to longitudinal studies on the rate of disease progression (as indicated below), and provide further impetus to develop therapies to protect the remaining 50% of dopaminergic neurons not yet affected at disease onset.

PD DIFFERENTIAL DIAGNOSIS AND SEVERITY

The first questions of an imaging ligand is whether it reliably distinguishes between subjects with and without known pathology (a marker for disease trait) and whether the changes in the imaging outcomes correlate with

disease severity (a marker for disease state). In several studies both dopamine and vesicular transporter ligands and ^{18}F-DOPA discriminated between individuals with PD and healthy subjects with a sensitivity of >95% (11,13,20,67–69). These studies take advantage of the relatively greater dopaminergic loss in the putamen to enhance the discriminant function. Furthermore, the reduction in both dopamine and vesicular transporter and ^{18}F-DOPA imaging activity correlated with well-defined clinical rating scales of PD severity (16,20,28,70). Interestingly when specific PD symptoms are compared, the loss of dopaminergic activity measured by imaging correlated with bradykinesia but not with tremor (20,71). Cross-sectional studies show that severity of bradykinesia measured by clinical scales reflects the severity of the nigrostriatal dopamine neuron loss. Therefore, in vivo dopaminergic imaging provides a biomarker both for the presence of disease and for the severity of the pathological process.

In clinical practice, diagnosis is often difficult at the onset of symptoms. In studies focused on early PD patients, at the threshold of their illness, in vivo imaging demonstrated a 40–60% reduction in DAT or F-DOPA activity in the putamen contralateral to the symptomatic side. PD generally presents as a unilateral motor disorder and progresses during a variable period of 3–6 years to affect both sides although frequently remaining asymmetric (72). The unilateral motor presentation reflects the asymmetric dopaminergic pathology, which is in turn demonstrated by in vivo dopaminergic imaging (11,65,66).

Imaging may also be useful in special diagnostic situations such as psychogenic, drug-induced, traumatic, or vascular parkinsonism in distinguishing these syndromes without a presynaptic dopamine deficit from PD and other related disorders (73,74). A more difficult diagnostic problem is the distinction between the more specific diagnosis of PD and other related neurodegenerative disorders categorized as Parkinsonism or Parkinson's syndrome. The more common etiologies of Parkinson's syndrome are PSP, MSA, cortical basal ganglionic degeneration, and diffuse Lewy body disease, which may account for about 15–20% of patients with apparent PD. Parkinsonism is characterized by significant nigrostriatal neuronal loss, which is demonstrated by reduction in in vivo presynaptic dopaminergic imaging. While the severity of DAT or ^{18}F-DOPA loss does not discriminate between PD and other causes of Parkinson's syndrome, the pattern of loss in Parkinson's syndrome is less region specific (putamen and caudate equally affected) and more symmetric than PD. This strategy discriminates between PD and other causes of Parkinson's syndrome with a sensitivity of about 75–80% (75–77). In addition, the more widespread pathology associated with Parkinson's syndrome may be reflected in abnormalities in post-synaptic dopamine receptor imaging and in metabolic imaging which are

not seen in PD. Therefore the pattern of presynaptic dopaminergic loss may be coupled with postsynaptic dopamine receptor imaging or metabolic imaging to distinguish PD from other related Parkinsonian syndromes (78,79).

PARKINSON'S DISEASE PROGRESSION

The rate of clinical progression of PD is highly variable and unpredictable (72). In clinical studies several clinical endpoints for progressive functional decline in PD have been used including Unified Parkinson's Disease Rating Scale (UPDRS) in the "defined off" state or after drug washout up to 2 weeks, time to need for dopaminergic therapy, or time to development of motor fluctuations (80–84). Clinical rating scales are extremely useful, but ratings may be investigator dependent and are frequently confounded by changes in symptomatic treatment. Pathological studies investigating rate of progression have been limited and rely entirely on cross-sectional data (62,63). These studies have in general considered patients with severe illness of long duration. In vivo imaging studies provide the opportunity to evaluate patients longitudinally from early to late disease using an objective biomarker for dopaminergic degeneration.

In several studies neuroreceptor imaging of the nigrostriatal dopaminergic system has been used as a research tool to monitor progressive dopaminergic neuron loss in PD. In longitudinal studies of PD progression both ^{18}F-DOPA and DAT imaging [β-CIT(2β-carboxymethoxy-3β(4-iodophenyl)tropane) and CFT] using both PET and SPECT have demonstrated an annualized rate of reduction in striatal ^{18}F-DOPA, ^{18}F-CFT, or [^{123}I]β-CIT uptake of about 6–13% in PD patients compared with 0–2.5% change in healthy controls (85–89). Similar findings have been reported for VMAT2 imaging (K. Frey, personal communication, 2002) (Fig. 2).

Evidence from studies of hemi-PD subjects provide further insight into the rate of progression of disease. In early hemi-PD there is a reduction in ^{18}F-DOPA and DAT uptake of about 50% in the affected putamen and of 25–30% in the unaffected putamen. Since most patients will progress clinically from unilateral to bilateral in 3–6 years, it is therefore likely that the loss of these in vivo imaging markers of dopaminergic degeneration in the previously unaffected putamen will progress at about 5–10% per annum (11,65).

Imaging has also been used to monitor progression of PD in patients receiving fetal substantia nigral transplants for PD. Several studies during the past several years show an increase in ^{18}F-DOPA uptake with follow-up of 6 months to 6 years posttransplant (90,91). The change in ^{18}F-DOPA
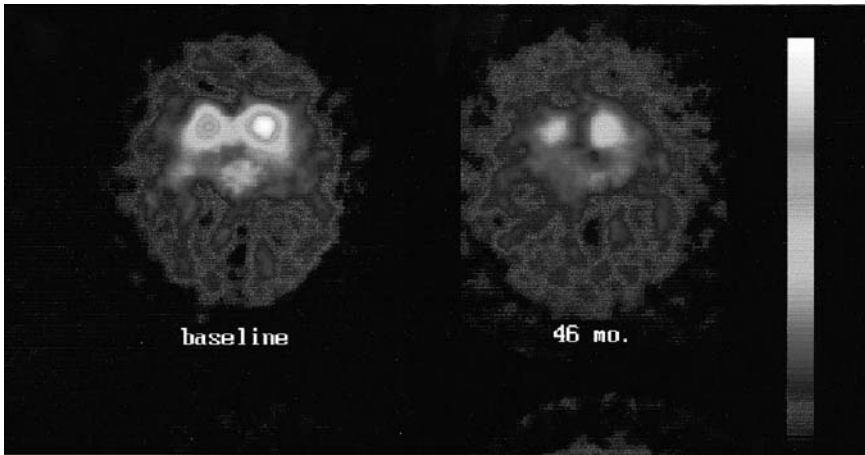
FIGURE 2 SPECT [^{123}I]β-CIT images from a patient with PD 2 years after diagnosis and 46 months later and from an age-matched healthy subject. Note the asymmetric reduction in [^{123}I]β-CIT uptake more marked in the putamen than caudate in the patient and the progressive loss of activity. Levels of SPECT activity are color-encoded from low (black) to high (yellow/white). (See color insert.)

uptake has been correlated with postmortem survival of grafted dopaminergic nigral cells (92).

The most important role of longitudinal imaging studies is to provide a tool to assess objectively potential neuroprotective and restorative therapies for PD. Imaging studies assessing progression of disease have provided data to estimate sample sizes required to detect slowing of disease progression due to study drug treatment. The sample size required depends on the effect of the disease-modifying drug and the duration of exposure to the drug. The effect of the drug is generally expressed as the percent reduction in rate of loss of the imaging marker in the group treated with the study drug versus a control group. More specifically, imaging studies have sought a reduction of between 25 and 50% in the rate of loss of ^{18}F-DOPA or [^{123}I]β-CIT uptake (i.e., a reduction from 10% to 5–7.5% per year). The sample size needed to detect a 25–50% reduction in the rate of loss of F-DOPA or β-CIT uptake during a 24-month interval ranges from approximately 30 to 120 research subjects in each study arm (85,93).

These data support the use of dopamine neuroreceptor imaging to assess the effects of potential neuroprotective drugs in PD, but there are several caveats in the study design and interpretation of these studies.

1. It must be acknowledged that imaging outcomes in studies of PD patients are biomarkers for brain activity, but are not true surrogates for drug effects in PD patients (94). These investigational drugs may have effects on dopamine neurons unrelated to slowed neuronal degeneration and may have effects outside the dopaminergic system.
2. The rate of change in imaging outcomes used to measure disease progression is slow, reflecting the slow clinical progression in PD and requiring the duration of these progression studies to be at least 18–24 months. In a recent study evaluating potential disease modifying effects of Neuroimmunophilin A, the study duration of 6 months resulted in an equivocal outcome necessitating a second, longer study to clarify the drug effects (95).
3. Progressive loss in brain dopaminergic imaging activity also occurs in aging healthy individuals, though at a rate approximately one-tenth that of PD patients (13,29).
4. The reliability of the imaging outcomes must be assessed. Recent test-retest studies using current technology and analyses methodology show good test-retest reproducibility of approximately 3–5% for ^{18}F-DOPA or VMAT2 studies and 5–7% for β-CIT SPECT (95–97).
5. Imaging outcomes of disease progression may be confounded by pharmacological effects of the study drug. In preclinical studies evaluation of the effect of dopamine agonists and antagonists and levodopa suggest possible regulation of both the DAT and dopamine turnover (32,98). The relevance of these studies to human imaging studies is questionable due to short duration of exposure to drugs, suprapharmacological dosing, and species differences. In another approach to assess regulation, in one of the few clinical studies comparing imaging ligands within subjects, 35 PD patients and 16 age-matched controls imaged with ^{11}C-methylphenidate (a dopamine transporter ligand), ^{18}F-DOPA and ^{11}C-dihydrotetrabenazine (a vesicular transporter ligand), demonstrated reduction in DAT which is greater than vesicular transporter which is greater than F-DOPA uptake. These data suggest that differential regulation of these imaging targets might occur in a progressively denervated striatum (14). These data were also consistent with the presumed upregulation of dopamine turnover in normal aging reflected in the lack of change in ^{18}F-DOPA imaging in aging healthy subjects (99). Other studies have more directly assessed the potential short-term regulation of imaging ligands by common PD medications. Available data does

not show regulation of DAT ligands or ^{18}F-DOPA uptake by levodopa or dopamine agonists. In the CALM-PD CIT study there was no significant change in β-CIT uptake after 10 weeks of treatment with either pramipexole (1.5–4.5 mg) or levodopa (300–600 mg) consistent with previous studies evaluating levodopa and selegiline effects after 6–12 weeks (100–102). In a similar study treatment with pergolide for 6 weeks also showed no significant changes in [^{123}I]β-CIT striatal, putamen, or caudate uptake, but an insignificant trend toward increased [^{123}I]β-CIT uptake (103). Data assessing RTI-32, another DAT ligand, demonstrated significant reductions from baseline in striatal DAT after 6 weeks of treatment with both levodopa and pramipexole, but also with placebo, and this pilot study could not detect differences between the treatment and placebo (104). There was no effect on ^{18}F-DOPA uptake in a study of five patients with restless legs syndrome who had been treated with levodopa (105). While these clinical studies do not demonstrate significant regulation of the DAT or ^{18}F-DOPA uptake, they do not exclude a significant short-term treatment-induced change in DAT, nor do they address the possibility that pharmacological effects may emerge in long-term studies.

Despite these caveats in interpretation of imaging results, neuroreceptor ligand biomarkers have become an increasingly useful method to assess the potential disease modifying effects of experimental drugs for PD. Several candidate drugs, including coenzyme Q10, a mitochondrial agent, neuroimmunophilin A, a potential growth factor, riluzole, a glutamatergic drug, CEP 1347 and CTCH 346, antiapoptotic agents, and pramipexole and ropinirole, dopamine agonists, have been or are in ongoing clinical studies of neuroprotection (80–82,84,106–108). Several other drugs are in preclinical testing as we seek the ''holy grail'' of neuroprotection.

Recently two similar studies compared the effect of initial treatment with a dopamine agonist [pramipexole (CALM-PD CIT) or ropinirole (REAL-PET)] or levodopa on the progression of PD as measured by [^{123}I]β-CIT or ^{18}F-DOPA imaging. These two clinical imaging studies targeting dopamine function with different imaging ligands and technology both demonstrate slowing in the rate of loss of [^{123}I]β-CIT or ^{18}F-DOPA uptake in early PD patients treated with dopamine agonists compared to levodopa. These studies evaluated two related, predominantly D2 dopamine receptor agonists, suggesting that the results may indicate a class effect. The relative reduction in the percent loss from baseline of [^{123}I]β-CIT uptake in the pramipexole versus the levodopa group was 47% at 22 months, 44% at 34

months, and 37% at 46 months after initiating treatment. The relative reduction of ^{18}F-DOPA uptake in the ropinirole group versus the levodopa group was 35% at 24 months. These data suggest that treatment with the dopamine agonists pramipexole and ropinirole and/or with levodopa may either slow or accelerate the dopaminergic degeneration of PD. Furthermore, these studies demonstrated that in vivo imaging can be used effectively to assess potential disease modifying drugs in well-controlled, blinded clinical studies (102,109)

In the CALM-PD CIT and REAL-PET studies there was no correlation between the percent change from baseline in the imaging outcome and the change from baseline in UPDRS at 22–24 months. There are several explanations for the lack of correlation between [^{123}I]β-CIT or ^{18}F-DOPA uptake and UPDRS in longitudinal studies. First, the UPDRS is confounded by the effects of the patient's anti-Parkinson medications both acutely after initiating therapy and with ongoing treatment. Even evaluation of the UPDRS in the "defined off" state or after prolonged washout does not eliminate the long-term symptomatic effects of these treatments (83,110). Second, in early PD the temporal patterns for rate of loss of DAT or ^{18}F-DOPA and the change in UPDRS may not be congruent. This is most evident in the preclinical period when the imaging outcomes are reduced by 40–60% prior to diagnosis. In the CALM-PD study the loss of striatal [^{123}I]β-CIT uptake from baseline was significantly correlated ($r = -0.40$; $p = 0.001$) with the change in UPDRS from baseline at 46-month evaluation, suggesting that the correlation between clinical and imaging outcomes begins to emerge with longer monitoring (102). These data suggest that particularly in early PD, clinical and imaging outcomes provide complementary data and that long-term follow-up will be required to correlate changes in clinical and imaging outcomes. Slowing the loss of imaging outcomes in PD is relevant only if these imaging changes ultimately result in meaningful, measurable, and persistent changes in clinical function in PD patients.

PRECLINICAL PARKINSON'S DISEASE

Neuroreceptor imaging studies provide a window into the preclinical period of PD, the time during which neurodegeneration has begun, but symptoms have not yet become manifest. Preclinical identification of affected subjects is particularly important if intervention exists that may prevent the progression of disease. The most extensive preclinical imaging data are from studies imaging patients with hemi-PD. In several imaging studies there is a significant reduction in putamen DAT or ^{18}F-DOPA uptake of

about 25–30% in the "presymptomatic" striatum in these patients who are known to progress to bilateral disease (11,65,66).

Progression studies also elucidate the preclinical period of PD. For example, given the assumption that progression is linear, it is possible to back extrapolate from sequential imaging data and reported symptom duration to estimate the level of reduction in dopaminergic activity at symptom onset and the duration of the preclinical phase of PD (Fig. 3). Data from longitudinal imaging studies using both ^{18}F-DOPA and DAT imaging have been remarkably consistent with estimated disease onset at 70–75% of normal dopaminergic activity and a preclinical phase of 4–8 years (99,102). Interestingly these data are consistent with estimates of duration of the preclinical phase from pathology studies of 4.7 years derived from cross-sectional data (111). While the data available to calculate estimates of the preclinical phase must be viewed as preliminary, data acquired using different imaging methods measuring different components
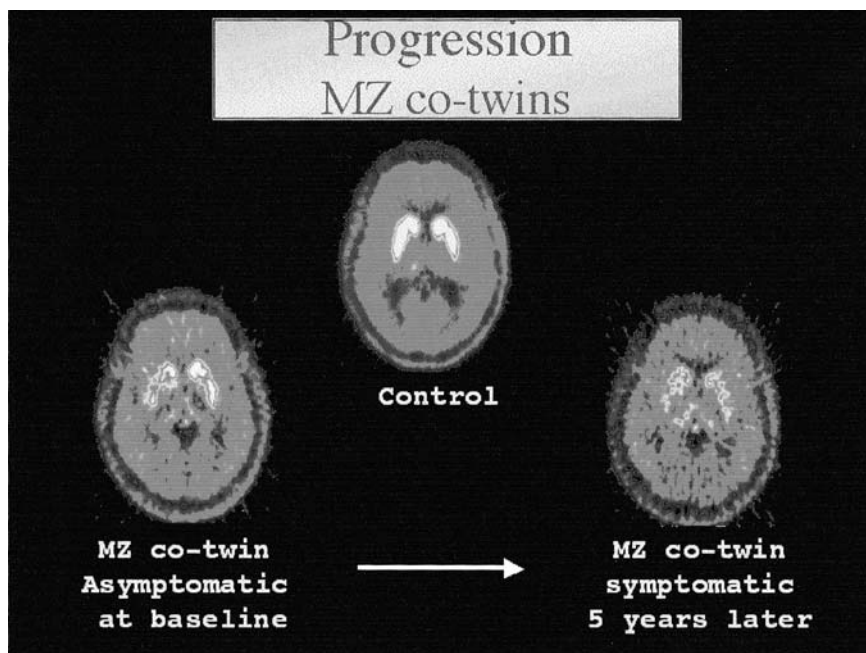
FIGURE 3 Presymptomatic loss of ^{18}F-DOPA in the asymptomatic co-twin of a PD patient. Note that the asymptomatic co-twin shows mild reduction in ^{18}F-DOPA at baseline that has worsened abnormality at 5-year follow-up associated with onset of symptoms. (Courtesy of D. Brooks, London, UK.) (See color insert.)

of the dopaminergic system and data from an independent pathology study suggest a relatively brief preclinical phase of less than a decade for PD. These data influence our understanding of disease etiology and development of strategies for disease screening and treatment. For example, if preclinical disease is relatively short, repetitive screening might be required to identify affected individuals in an at-risk population. Furthermore, as potential preventive or restorative therapies are developed, these treatments might be directed to the time period from onset of degeneration to onset of symptoms.

Other studies of the pre-clinical period have focused on potential at-risk individuals for PD such as family members or unaffected twins of PD patients. In studies of familial PD in several well-characterized kindreds 11 of 32 asymptomatic relatives were found to have reduced ^{18}F-DOPA uptake, and three of these subjects subsequently developed symptomatic PD (112). Several asymptomatic co-twins who also showed a reduction in ^{18}F-DOPA activity later developed symptoms of PD (Fig. 3), although the concordance rate for monozygotic and dyzygotic twins remains uncertain (113). Sporadic cases also have been reported of individuals imaged as presumed healthy subjects with mildly abnormal ^{18}F-DOPA uptake who later developed definite PD (114). Preclinical identification of subjects with PD forces us to reexamine our clinical definitions of disease. The recent identification of genes that confer the PD phenotype in familial PD will provide an opportunity to evaluate an at-risk population both clinically and with sequential imaging studies (115,116). As additional genetic markers are discovered, imaging will play an essential role in assessing neurodegeneration and possibly in redefining clinical disease onset.

FUTURE DIRECTIONS

Neuroimaging has provided key insights into the natural history of PD and has become a necessary if not sufficient test to assess potential new disease-modifying therapies for PD. While this review has focused on presynaptic dopamine ligands, several additional directions for imaging in PD have emerged or are under active study. Several postsynaptic dopamine imaging ligands have been used to study the postsynaptic dopaminergic receptors in PD (117–119), although quantitative information has been limited by relatively low sensitivity of the ligands available and has been complicated by uncertainty regarding endogenous dopamine binding to the receptor target. Postsynaptic dopamine receptor imaging studying dopamine release is a novel approach to using imaging to assess function particularly in studies involving cell-replacement therapy (120).

While dopamine degeneration is a crucial feature of PD, it is clear that there is widespread degeneration in the brain in PD and that many clinical manifestations of PD are likely not due to dopamine deficiency. Ligands for nondopaminergic targets have been and are being developed to investigate nondopaminergic manifestations of PD and to better understand the cause of PD and of dyskinesias. Some examples include recent data suggesting that uptake of a serotonin (5HT1A) receptor ligand 11C-Way100635 is reduced in the cortex of PD patients with associated depression, but not those without depression (121). Furthermore the reduction in 11C-Way100635 uptake correlates with tremor scores, suggesting that tremor may be related to serotonin deficiency. Ligands directed at the SP/neurokinin (NK1) receptor show reduction in thalamic uptake in dyskinetic but not in nondyskinetic PD patients, suggesting that this ligand may be a tool to help understand dyskinesias (122). In addition, imaging studies showed a reduction in acetylcholine activity in PD patients in cortex, and imaging of microglial activation has been demonstrated in cortex in Alzheimer's disease, and this approach may also be useful to understand the underlying pathology in PD (123).

The role of brain imaging in PD will continue to expand as new imaging targets emerge and additional disease-modifying drugs are developed. As simpler tools to identify preclinical at-risk individuals become available, neuroreceptor imaging will be widely used to establish and monitor the onset and progression of disease. As treatments become available that target the mechanisms that initiate and subsequently promote the course of disease progression, precise information about an individual's neurochemical status will be essential to optimize clinical management.

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