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Positron emission tomography imaging in Parkinson's disease

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Positron emission tomography (PET) neuroimaging techniques provide a useful tool for understanding the complex functional anatomy of the basal ganglia and their disorders. They help to elucidate the pathophysiological mechanisms underlying the degenerative processes and the evolution of symptoms in Parkinson's disease (PD). In this review, the potential role of PET imaging on evaluating the dopaminergic and non-dopaminergic function in PD is discussed along with its use as a biological marker in the differential diagnosis of typical and atypical parkinsonism, in monitoring disease's progression, and in understanding the mechanisms underlying motor fluctuations, drug induced dyskinesias and non-motor symptoms. The role of functional imaging in assessing the efficacy of neuroprotective and restorative strategies, is also discussed. It is concluded that, in the future, if technical and cost limitations are adequately addressed, PET imaging may well provide a valuable adjunct to clinical assessment when evaluating the complications and management of PD.

Key words: **Tomography, emission computed - Parkinson's disease - Radionuclide imaging.**

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized typically by motor features of tremor, rigidity and bradykinesia due to depletion of dopaminergic nigrostriatal neurons and usually results in a significant decline in quality of life for both patients and family and contributes to significant economic and institutional costs on family and society.

PD is uncommon before the age of 40 but affects approximately 1% of patients over the age of 60, with a rising incidence and prevalence thereafter to around 2% in the population over 80 years of age.

The pathology of PD is characterized by neuronal loss accompanied by the formation of Lewy inclusion bodies in different cortical and subcortical areas of the brain.

Brain imaging techniques represent unique tools to investigate *in vivo* the pathogenesis of PD and they can provide insights into its pathophysiology.

Positron emission tomography (PET) uses short-lived radioisotopes bound to specific tracers which, after administration, can be monitored in the brain to obtain structural and kinetic information, such as the distribution of receptors in the brain (Table I). PET in comparison with other brain imaging techniques, provides high sensitivity and high spatial and temporal resolution. On the oth-

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TABLE I.—*Positron emmision tomography techniques in Parkinson's disease.*

PET tracer	Target	Assessment	Use in PD
11C-CFT (WIN35,428)	DAT	Presynaptic dopaminergic system	- Monitoring progression - Differential diagnosis
18F-CFT	DAT	Presynaptic dopaminergic system	- Monitoring progression - Differential diagnosis
11C-methylphenidate (MP)	DAT	Presynaptic dopaminergic system	- Monitoring progression - Differential diagnoses - Motor fluctuations and dyskinesias
11C-nomifensine	DAT	Presynaptic dopaminergic system	- Monitoring progression - Differential diagnosis
11C-RTI32	- DAT - NAT	- Presynaptic dopaminergic system - Noradrenergic System	- Differential diagnoses - Depression
11C-DHTBZ	VMAT2	Presynaptic dopaminergic system	- Monitoring progression - Differential diagnosis - Motor fluctuations and dyskinesias
18F-dopa	AACD	Monaminergic systems: - presynaptic dopaminergic system - noradrenergic system - serotonergic system	- Monitoring progression - Modifying progression - Differential diagnoses - Detection of preclinical PD - Motor fluctuations and dyskinesias - Dementia - Sleep - Drug development - Evaluation of restorative approaches (e.g. fetal mesencephalic cell grafts, GDNF infusion)
11C-SCH23390	D1 receptors	Postsynaptic dopaminergic system	Monitoring progression
11C-FLB457	D2/D3 receptors	Postsynaptic dopaminergic system	Drug development
11C-raclopride	D2/D3 receptors	- Dopamine release - Postsynaptic dopaminergic system	- Monitoring progression - Modifying progression - Differential diagnoses - Motor fluctuations and dyskinesias -Addictive and compulsive behaviour - Drug development - Evaluation of restorative approaches (e.g. fetal mesencephalic cell grafts, GDNF infusion)
11C-PHNO	D3/D2 receptors	- Postsynaptic dopaminergic system - Dopamine release	Monitoring progression?
11C-WAY100635	5-HT1A receptors	Serotonergic system	- Tremor - Depression - Fatigue?

(Table I to be continued)

TABLE I.—*Positron emmision tomography techniques in Parkinson's disease (continues).*

11C-MeN5652	SERT	Serotonergic system	- Depression? - Fatigue?
11C-DASB	SERT	Serotonergic system	- Depression - Motor fluctuations and dyskinesias? - Fatigue?
15-O_2	$rCMRO_2$	Brain metabolism	- Differential diagnosis - Dementia?
15-H_2O	rCBF	Brain metabolism	- Dementia? - Evaluation of restorative approaches?
18F-FDG	Relative regional CMR_{glc}	Brain metabolism	- Differential diagnosis - Dementia - Psychosis - Fatigue?
11C-PMP	AChE	Cholinergic system	Dementia
11C-MP4A	AChE	Cholinergic system	Dementia
11C-NMPB	Postsynaptic muscarinic receptors	Cholinergic system	Dementia
11C-PIB	Fibrillar β-amyloid	β-amyloid plaque load	Dementia
11C-PK11195	Peripheral BDZ sites	Microglial activation	- Monitoring progression - Drug development - Evaluation of restorative approaches?
11C-diprenorphine	μ xand δopioid sites	Opioid system	Motor fluctuations and dyskinesias
11C-deprenyl	Monoamine oxidase B	MAO-B inhibition	Drug development
11C-KW6002	Adenosine A2A receptors	Adenosinergic system	Drug development
11C-SCH442416	Adenosine A2A receptors	Adenosinergic system	Motor fluctuations and dyskinesias?
11C-MHED	NET	Myocardial sympathetic innervation	Cardiac sympathetic denervation
18F-L829165	NK1 receptors	Substance P	Motor fluctuations and dyskinesias
11C-MePPEP	Cannabinoid CB1 receptors	Cannabinoid system	Motor fluctuations and dyskinesias? Depression? Psychosis?
11C-CNS5161	NMDA receptors	Glutamatergic system	Motor fluctuations and dyskinesias?

er hand, the availability of PET is still limited due to high costs and complicated function.

Imaging dopaminergic function in Parkinson's disease

Presynaptic dopaminergic system

The function of presynaptic dopaminergic terminals can be assessed *in vivo* with PET by measuring aromatic amino acid decarboxylase (AADC) activity, dopamine transporter (DAT) availability and vesicular monoamine transporter (VMAT2) density (Figure 1).

The radiotracer 18F-dopa was first described as a marker of presynaptic terminals in 1983.[1] Since then, there have been many descriptions of the use of this tracer in parkinsonism and related disorders. PET with 18F-dopa, after taken up by the terminals of

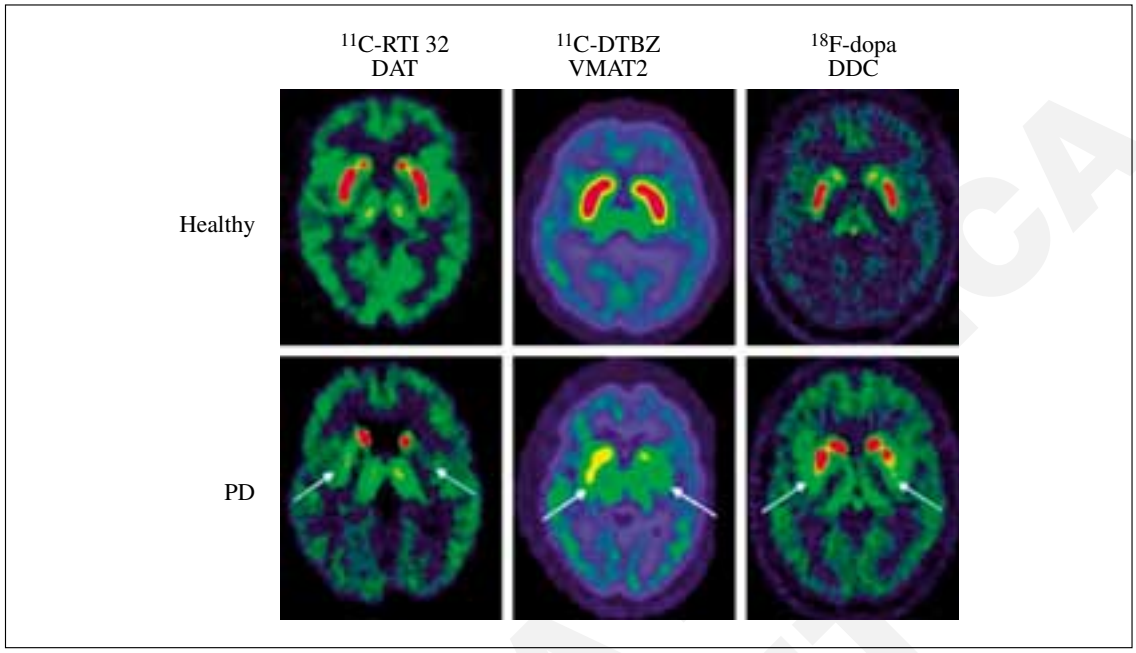

Figure 1.—PET imaging of presynaptic dopaminergic function in healthy controls and early PD.

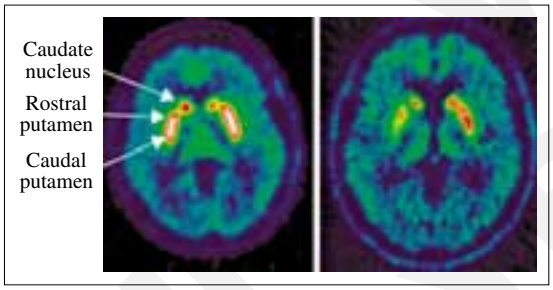

Figure 2.—Transverse 18F-dopa PET images of a healthy control (left) and a patient with idiopathic PD (right). In PD, there is asymmetric loss of uptake of the tracer, and a more pronounced loss in the caudal putamen than in the rostral putamen and the caudate nucleus.

the dopamine projections, monitors conversion of levodopa to dopamine through AACD activity. In PD there is a characteristic gradient of loss of striatal dopamine terminal function with posterior putamen being the most affected (Figure 2). The rate of striatal 18F-dopa accumulation, as measured by PET, therefore directly reflects the activity of AACD in dopamine terminals.[2]

It has been shown that striatal uptake of 18F-dopa in PD correlates with the degree of motor dysfunction. Several studies have described a significant inverse correlation between 18F-dopa uptake and the degree of motor disability as measured by the Unified Parkinson's Disease Rating scale (UPDRS).[3-5]

Interestingly, as has been shown by one study, reductions in 18F-dopa uptake correlate with increased rigidity and bradykinesia but not with increased tremor. The latter suggests that pathways other than the nigrostriatal might be implicated in the expression of this symptom.[6]

The neurodegeneration in PD is not standardized across all areas. At symptom onset, the ventrolateral nigral dopaminergic projections to the dorsal putamen are more affected, whereas the dorsomedial projections to the head of the caudate nucleus seem to be preserved until more advanced disease stages.[7] Likewise, in early cases, the reduction in 18F-dopa uptake is bigger in the putamen than the caudate nucleus.

Furthermore, in early hemiparkinsonian cases, reduction in 18F-dopa uptake is more pronounced in the dorsal posterior putamen contralateral to the affected limbs.[8] As PD progresses and symptoms become bilateral,

there is reduction of 18F-dopa uptake in the ventral and anterior putamen and dorsal caudate. In more advanced stages, the uptake within the ventral head of caudate also falls.

The PET radiotracers 11C-nomifensine, 11C-RTI32, 11C-CFT and 18F-CFT were all developed to bind to DAT to measure its availability.[9-14] These tracers, which also provide a measure of presynaptic dopamine terminal integrity, show similar findings in PD compared to those seen with 18F-dopa PET, and provide a sensitive means of discriminating patients with early PD from healthy subjects.

11C-DHTBZ with PET is a reliable technique of measuring VMAT2 density. It has been shown that 11C-DHTBZ uptake is reduced in the striatum of PD patients, thus providing another marker for evaluating the integrity of presynaptic dopaminergic terminals.[15]

Dopamine release

One of the most fascinating applications of PET is the ability to evaluate synaptic neurotransmitter fluxes in the living human brain. These fluxes are reflected as changes in neuroreceptor availability to radiotracers and PET with 11C-raclopride has been used for this purpose.

11C-raclopride is a marker of postsynaptic dopamine D2 and D3 receptors, and a number of studies have demonstrated its ability to detect *in vivo* changes in synaptic cleft dopamine levels following pharmacological or task challenges. When dopamine binds to D2 receptors, it competes with 11C-raclopride allowing synaptic dopamine levels to be estimated from the changes of the tracer's D2 receptor binding potentials.

It has been estimated that a 10% reduction in availability of D2 receptors for 11C-raclopride binding reflects a five-fold increase in synaptic dopamine levels.[16]

Synaptic dopamine can be increased in the synapse after administering exogenous levodopa or with pharmacological challenges of substances that are known to inhibit/reverse the DAT function, such as methylphenidate,[17] cocaine [18] and amphetamines.[19, 20]

PET techniques with 11C-raclopride have shown that, after administration of methamphetamine, the endogenous release of dopamine is significantly greater in normal subjects when compared to advanced PD patients.[21] In this study, 11C-raclopride binding was reduced in both groups but was significantly smaller in the striatum of PD patients (8% *vs* 17% in the caudate nucleus and 7% *vs* 25% in the putamen). Also, in the group of PD patients, there was a correlation between percentage reduction in putamen 11C-raclopride binding and UPDRS scores. Interestingly, even in advanced PD cases the frontal dopamine release was within the normal range suggesting that reduced striatal rather than frontal release of endogenous dopamine is likely to be most relevant to executive dysfunctions associated with PD.

In addition to pharmacological challenges, *in vivo* endogenous release of DA in healthy subjects has been detected during performances of motor tasks, contributing to the understanding of the complex basal ganglia network.[22, 23]

A recent study using 11C-raclopride PET assessed dopamine release in patients with early PD and normal controls after visuomotor tasks with and without financial rewards according to success.[24] Dopamine release in striatum was only detected in normal controls while both groups showed significant increases in the levels of synaptic dopamine in the prefrontal cortex suggesting that although the capacity to release striatal dopamine during motor tasks is impaired in early PD patients, it is relatively preserved in the prefrontal cortex.

Postsynaptic dopaminergic system

At least five different subtypes of dopamine receptors have been described. They broadly fall into D1-type receptors (D1 and D5), which activate adenyl cyclase, and D2-type receptors (D2, D3 and D4), which either inhibit or have no effect on this enzyme. The striatum contains mainly D1 and D2 receptors and these play a primary role in modulating locomotor function.

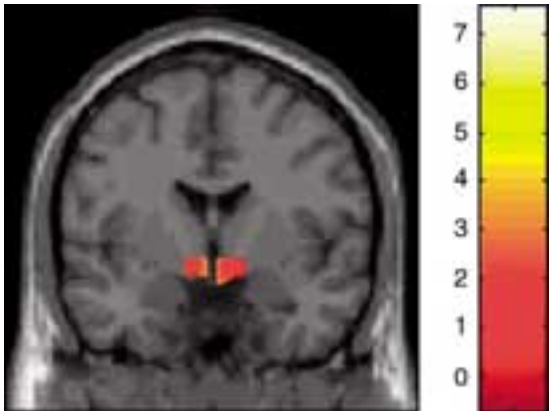

Figure 3.—Coronal section of statistical parametric map. Yellow-red areas represent voxel clusters with significant decreases in 11C-raclopride binding within the hypothalamic region mask in PD patients compared with the group of healthy controls.

11C-raclopride PET studies in *de novo* PD patients have shown 10-20% increases in D2 receptor availability in the putamen contralateral to the more affected limbs while the binding in caudate nucleus seems intact.[25-27] In addition, 11C-raclopride binding inversely correlated with presynaptic 18F-dopa uptake in patients with early disease,[28] suggesting that the mildly upregulated putamen and the normal caudate nucleus D2 binding take place where dopamine terminal function is relatively preserved.

Serial 11C-raclopride PET studies have shown that as disease progresses and PD patients are exposed to dopaminergic therapy, D2 binding normalizes in the putamen, but caudate nucleus binding is reduced by around 20%.[3, 27, 29-31]

PET with 11C-raclopride PET has also been used for the assessment of extrastriatal areas with possible involvement in PD. Findings from a recent study demonstrated that 11C-raclopride uptake in the hypothalamus is significantly reduced in patients with PD when compared with a group of normal controls,[32] suggesting a possible role of dopaminergic dysfunction in the hypothalamus towards the development of sleep, endocrine and autonomic problems often seen in PD (Figure 3).

Whereas increased putaminal 11C-raclopride binding seen in *de novo* patients could correspond to compensatory mechanisms and receptor upregulation, reduction of binding in striatum and hypothalamus in more advanced cases may reflect either disease progression or an effect of chronic exposure to dopaminergic therapy.

PET with 11C-FLB457, another marker of dopamine postsynaptic D2 and D3 receptors, has also been employed to investigate the expression of extratriatal D2 and D3 receptors in PD. Advanced PD patients showed reduced 11C-FLB457 binding in the thalamus, anterior cingulate, dorsolateral prefrontal and temporal cortex,[33, 34] suggesting a possible role of extrastriatal dopamine receptors in the presence of cognitive and emotional deficits seen in PD.

PET with 11C-SCH23390 has been used to evaluate the expression of striatal D1 receptors in PD. In *de novo* hemiparkinsonian patients later shown to be levodopa responsive, 11C-SCH23390 PET showed that putamen D1 receptor availability is generally preserved contralateral to the affected limbs,[35] whereas PD patients who have been exposed to levodopa for several years showed a 20% reduction in striatal D1 receptor binding.[27]

Imaging non-dopaminergic function in Parkinson's disease

In PD, along with the impairment of dopaminergic projections, degeneration of the cholinergic, noradrenergic, and serotonergic systems is taking place. Function of these non-dopaminergic systems can be quantified with PET and possible correlations with motor and non-motor symptomatology can be investigated.

Serotonergic function

The readiotracer 11C-WAY100635 binds specifically to serotonin 5-HT1A receptors. These receptors are expressed both presynaptically, as somatodendritic autoreceptors localized on 5-HT cell bodies in the midbrain raphe nuclei where they inhibit serotonin release, and postsynaptically, on cortical pyramidal neurons and on glia. Midbrain raphe 5-

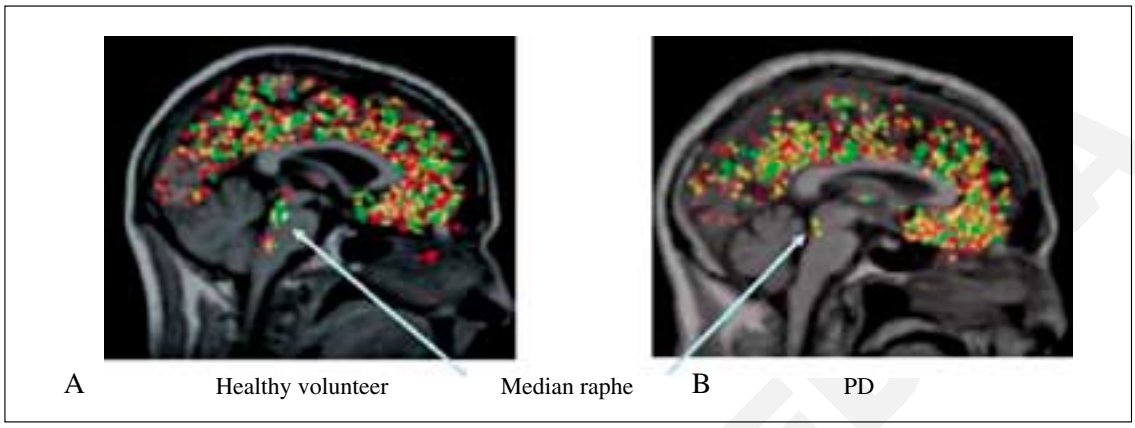

Figure 4.—Sagittal 11C-WAY100635 PET images of a healthy control (A) and PD patient (B) showing reduced median raphe serotonin 5-HT1A binding in PD.

HT1A binding provides a functional measure of serotonergic system integrity and can be measured *in vivo* with 11C-WAY100635 PET. A study using PET with 11C-WAY100635 has shown that the midbrain 5-HT1A binding is reduced by 29% in PD patients when compared with a group of normal controls (Figure 4). Additionally, UPDRS combined tremor scores, but not rigidity or bradykinesia, correlated with decreased 5-HT1A binding in the raphe suggesting an important role for serotonergic neurons in the pathogenesis of tremor.[36]

While the brainstem serotonin neurons have been reported to be affected by the PD, single photon emission computed tomography (SPECT) studies have shown that the striatal serotonin innervation is within the normal range.[37, 38]

11C-DASB and 11C-McN5652 PET are both consistent techniques for assessing the integrity of serotonergic innervation in the striatum and other brain areas. Both radiotracers bind with high specificity and selectivity to the serotonin transporter (SERT) in the serotonin presynaptic terminals. Studies using PET with 11C-McN5652 [39] and PET with 11C-DASB [40] have shown that SERT binding sites in the striatum are only moderately reduced (14-26%) in comparison to the profound dopaminergic denervation (70-80%).

The function of serotonin has proved to be increasingly important in PD as it was observed that serotonin neurons are able to convert exogenous levodopa to dopamine, and store and release dopamine in an activity-dependent manner,[41-44] suggesting a role in the control of motor behaviour and handling of exogenous levodopa.[45, 46] It is hoped that PET techniques will provide more insight into these observations in the near future.

Noradrenergic function

The role of noradrenergic neurons may also be of great importance in PD but there are currently no specific PET markers of noradrenergic function. Reboxetine derivatives were tested as markers of noradrenaline transporter binding but the results were disappointing due to their lipophilicity and associated high nonspecific signals.[47, 48]

11C-RTI32 PET is a marker of both noradrenaline transporter (NAT) and DAT binding. It has been used to evaluate depression in PD patients and will be discussed in the next paragraphs.

Finally, PET with 18F-dopa can also be employed to evaluate the integrity and function of the serotonergic and noradrenergic systems in the brain [49] as presynaptic terminals from both systems contain AADC. However, this use should be limited to structures known to have extensive serotonergic (raphe nucleus) or noradrenergic (*locus coeruleus*) innervation because quantification could be confounded by the greater

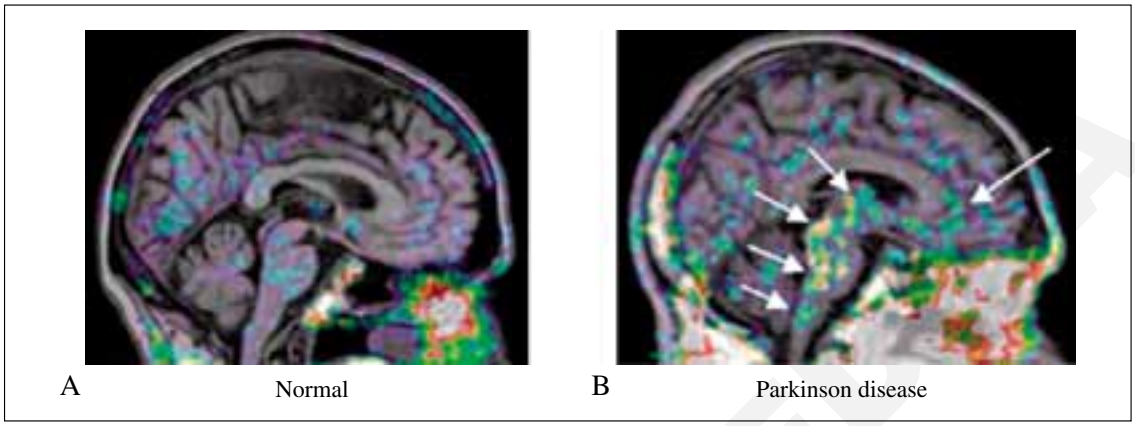

Figure 5.—Sagittal 11C-PK11195 PET images of a healthy control (A) and PD patient (B). Increases of activated microglia are evident in the midbrain, basal ganglia and frontal cortex.

extent of AADC inclusion in dopaminergic terminals.

Cholinergic function

The radiotracers 11C-PMP and 11C-MP4A when used with PET provide a measure of acetylcholinesterase (AChE) levels and can be used for the assessment of integrity and function of cholinergic system. Both radiotracers are acetylcholine analogues that serve as selective substrates for AChE hydrolysis.[50, 51]

PET with 11C-NMPB is a marker of postsynaptic muscarinic receptor availability [52] and its use along with these of 11C-PMP and 11C-MP4A PET can be employed to assess the association between cholinergic deficiency and dementia seen in PD patients (discussed later).

Opioid function

Caudate nucleus and putamen contain high densities of μ, γ and δ opioid receptors.[53] These receptors are located both presynaptically on dopaminergic terminals, where they regulate dopamine release, and postsynaptically on interneurones and medium spiny projection neurons to pallidum terminals.[54, 55]

11C-diprenorphine PET is a non-selective marker of μ, γ and δ opioid sites and its binding has been shown to be sensitive to levels of endogenous opioids.[56]

PET with 11C-diprenorphine has been used in the assessment of levodopa-induced dyskinesias that will be discussed later in this review.

Microglial activation

Microglia constitute 10-20% of white cells in the brain and form its natural defense mechanism. Microglia in normal conditions are in a quiescent state in the central nervous system but can become activated in response to several insults such as trauma, ischemia, inflammation, and neurodegeneration. The mitochondria of activated microglia express peripheral benzodiazepine (BDZ) sites, which may play a role in preventing cell apoptosis through membrane stabilization.

The radiotracer 11C-PK11195, used with PET, is an isoquinoline that binds selectively to peripheral BDZ sites and provides an *in vivo* marker of microglia activation. An 11C-PK11195 PET study in early-stage *de novo* PD patients has shown that the levels of 11C-PK11195 binding in the midbrain contralateral to the clinically affected side were significantly higher in PD patients than in age-matched normal controls. In addition, the increased levels of midbrain 11C-PK11195 binding correlated positively with the motor severity assessed with UPDRS and inversely with DAT availability as measured with 11C-CFT PET.[57] Therefore, the co-localization of increased activated microglia and dopamin-

ergic terminal loss in the affected nigrostriatal pathway in early PD supports a role of microglia activation in disease progression.

Furthermore, in a study where PD patients were examined serially with 11C-PK11195 PET over a period of 18 to 24 months, the authors reported significantly increased 11C-PK11195 binding in the pons, basal ganglia, frontal, and temporal cortical regions, and the levels of microglial activation did not correlate with either disease severity, measured clinically with 18F-dopa PET, or clinical disease duration (Figure 5). Interestingly, the levels of microglial activation remained stable over the two years, while the patients deteriorated clinically.[58] The steadiness of the microglial signal in PD suggests that these cells are activated early in the disease process and may then drive progression. This is supported by postmortem studies which have shown that microglia continue to express cytokine mRNA. 11C-PK11195 PET could provide important information when putative neuroprotective drugs designed to modulate microglial activation in neurodegenerative diseases are being tested.

Imaging of preclinical Parkinson's disease

Populations known to be at risk for developing PD include carriers of genes known to be associated with parkinsonism, relatives of patients with the disorder, elderly subjects with idiopathic hyposmia, and patients suffering from REM sleep behaviour disorders (RBD).

PET with 18F-dopa has been used for the detection of preclinical PD although it is known that the degenerative process might be underestimated in preclinical and early stages of the disease due to the compensatory upregulation of AADC in the preserved terminals.[59]

A study using PET with 18F-dopa, showed that in kindreds with familial PD, 25% of adult asymptomatic family members had dopamine terminal loss in putamen. From these, one third developed clinical parkinsonism within the next five years.[60]

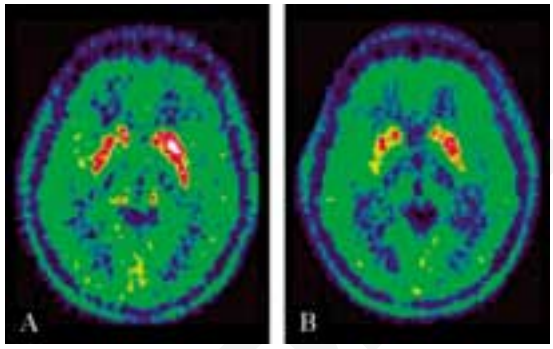

Figure 6.—Transverse 18F-dopa PET images at the striatal level in a patient with PD at baseline (A) and after 2 years follow-up (B).

Abnormal 18F-dopa PET findings for adult asymptomatic co-twins of idiopathic PD patients have also been reported; 18% of asymptomatic dizygotic co-twins and 55% of asymptomatic monozygotic co-twins of patients with idiopathic PD showed significant terminal loss in the putamen. Furthermore, in the same study, these co-twins were followed up over a four-year period with PET. All of the asymptomatic monozygotic co-twins showed a further decrease in putaminal 18F-dopa uptake while two developed clinical parkinsonism over this period. The asymptomatic dizygotic co-twins showed no significant further reductions in their putaminal 18F-dopa uptake.[61]

18F-dopa PET has also been used in the assessment of asymptomatic carriers of a single parkin mutation. It has been reported that these parkin carriers have decreased 18F-dopa uptake in the putamen, caudate nucleus, and ventral and dorsal midbrain when compared with a group of normal controls.[62] However, it remains ascertained whether these subjects will later convert to clinical parkinsonism.

Imaging progression of Parkinson's disease

Monitoring progression

The assessment of PD progression clinically is a challenging process. While motor tests and rating scales are somewhat subjec-

tive and generally biased towards bradykinetic symptoms, most PD patients within the first months of diagnosis will require symptomatic therapy and this effectively masks disease progression.[63]

It is difficult for patients to revert back to the unmedicated state, as washing out the drugs is a complex process and usually achieve partial success in practice due to poor patient tolerance. Also, it has now become clear that a two-week medication washout period after several months of medication is insufficient to represent an unmedicated state.

PET with 18F-dopa potentially provides biomarkers for objectively monitoring disease progression *in vivo* in PD (Figure 6). Several studies have demonstrated a significant inverse correlation between putaminal 18F-dopa uptake and disease progression [4, 5, 64] and the dopaminergic terminal loss seems to correlate closely with the severity of bradykinesia and rigidity.[65]

Furthermore, it has been described that in early PD cases treated with levodopa, the putamen 18F-dopa uptake declines by 6-12% *per annum* whereas caudate uptake falls at a slower rate.[66] Similar rates of decreased putamen dopamine trasporter density have been reported with 18F-CFT PET.[67]

Modifying progression

As PET imaging with 18F-dopa can potentially track the loss of presynaptic dopaminergic terminal function in PD, it also provides potential means of monitoring the efficacy of putative neuroprotective agents.[68]

Dopamine agonists are potent candidates for modifying disease progression as they suppress the production of endogenous dopamine, thus diminishing its oxidative metabolism and free-radical formation.[69] PET with 18F-dopa was used in the two-year double-blind multinational REAL-PET trial where *de novo* PD patients were randomized to ropinerole or levodopa. Reduction in mean putamen 18F-dopa uptake was one third slower over two years in the group taking ropinerole than that taking levodopa. However, symptom improvement as measured by UPDRS were superior for the levodopa group.[70] Similar results have been reported with the use of pramipexole in another trial using SPECT (CALM-CIT),[71] suggesting that treatment with an agonist in early PD may slow the loss of dopamine terminal function.

Finally, in another randomized, double-blind, placebo-controlled trial, PET with 18F-dopa was unable to determine any efficacy of the glutamate release inhibitor riluzole in halting progression of patients with *de novo* PD.[72]

Imaging genetic forms of Parkinson's disease

Over the last fifteen years, several causative genes have been thought implicative in subjects with a family history of PD. These include autosomal recessive mutations in Parkin (PARK2), PINK1 (PARK6) and DJ1 (PARK7) that lead to young PD onset. Mutations in alpha-synuclein (PARK1/4), the gene encoding ubiquitin carboxyhydrolase L1 – UCH-L1 (PARK 5) and leucine rich repeat kinase 2 – LRRK2 (PARK8) are autosomal dominantly inherited, and can also lead to young onset PD. Differentiating between familial and idiopathic PD clinically can be challenging, and post mortem cases provide limited feedback, therefore PET imaging has a valuable role in the diagnoses of these conditions *in vivo*.

Using PET with 18F-dopa, studies have demonstrated similar 18F-dopa uptake reductions between PARK1 and idiopathic PD,[73] PARK 8 and idiopathic PD,[74] whereas PARK2, PARK6 and PARK7 PD are associated with more symmetrical and uniform reduction of 18F-dopa uptake than idiopathic PD.[75-79] Furthermore, parkin PD patients seem to have slower disease progression compared to idiopathic PD as this has been shown by the slower rate of 18F-dopa striatal uptake reduction *per annum*.[75]

PET with 11C-raclopride has shown that in *de novo* parkin PD, the D2 receptor availability in putamen is increased when compared to a group of normal controls (similar

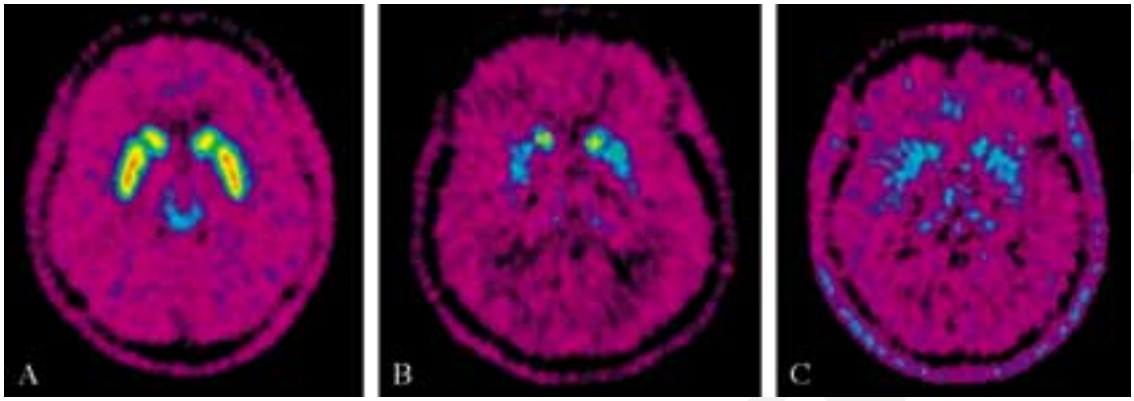

Figure 7.—Transverse 18F-dopa PET images at the striatal level in a healthy control (A) and in patients with idiopathic PD (B) and PSP (C). Note the relative preservation of caudate uptake compared with putamen uptake in the patient with idiopathic PD. In the patient with PSP caudate and putamen are equally affected.

results with idiopathic PD). As disease progresses and levodopa treatment is established, the D2 receptor availability significantly decreases in both putamen and caudate nucleus, whereas in idiopathic PD it normalizes in the putamen and most often decreases in the caudate nucleus.[80] These provide evidence for greater responsiveness to dopaminergic medication among Parkin PD patients than the one observed in idiopathic PD.

Imaging differential diagnoses of Parkinson's disease

A common problem that movement-disorder clinicians encounter when assessing PD patients is that parts of the PD features are shared by several other disorders. PD's differential diagnoses includes essential tremor, vascular parkinsonism, drug induced parkinsonism, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal ganglionic degeneration, dementia with Lewy bodies (DLB), and Alzheimer's disease (AD). From these, MSA and PSP are the most common conditions to be clinically mistaken for PD. While the prognosis and therapeutic management of each of these disorders differs significantly from PD, some of the aforementioned disorders may show mild to moderate response to dopaminergic therapy.

PET imaging techniques are very effective (with approximate sensitivity of 90%) in detecting functional differences between PD, normality, and essential tremor. In the REAL-PET study,[70] 11% of previously untreated patients with clinically classified PD and symptoms of two years or less had entirely normal striatal 18F-dopa imaging both at baseline and at follow up two years later. Patients with essential tremor or vascular parkinsonism would also be expected to have normal 18F-dopa striatal binding.[81, 82]

The use of PET with 18F-dopa also helps to easily differentiate between post-neuroleptics parkinsonism and idiopathic PD as former subjects are demonstrated to have intact dopaminergic terminals.[83]

Using the same technique, several studies have shown that in patients with PSP, MSA, and corticobasal ganglionic degeneration, mean 18F-dopa uptake in the posterior putamen is decreased to concentrations similar to those of patients with PD with similar disease duration, but caudate nucleus uptake is more affected[3, 84-87] (Figure 7).

Studies of PET with 11C-CFT, 18F-CFT, 11C-RTI-32, 11C-nomifensine and 11C-DHT-BZ have shown similar findings in idiopathic PD compared to those seen with 18F-dopa PET, and provide a sensitive means of discriminating patients with early idiopathic PD from healthy subjects. Similar to 18F-dopa PET studies, patients with MSA have reduced binding of 11C-nomifensine in the putamen

(similar to PD) and significantly lower 11C-nomifensine binding in the caudate nucleus when compared to PD patients of similar locomotor disability.[3]

PET with 11C-raclopride also helps to distinguish between PD and, MSA and PSP. In contrast to PD, both PSP and MSA demonstrate a significant loss of putaminal D2-receptor availability.[88-91] However, despite the ability of D2 receptor imaging to distinguish PD from PSP and MSA, decreased binding will be seen in both PSP and MSA, and therefore, D2 imaging alone cannot separate these two from each other.

PET with 18F-FDG and oxygen-15 has been used to quantify resting concentrations of regional cerebral metabolic rate. It has been shown with both techniques that in early PD striatal metabolic activity is increased in the lentiform nucleus contralateral to the affected limb.[92, 93] As disease progresses, decreased caudate nucleus and cortical metabolic activity have been reported.[94-96] Furthermore, in PD with dementia, as it is also seen in patients with AD, there is hypometabolism in posterior parietal and associated temporal areas.[97] However, contrary to AD, in PD with dementia, occipital hypometabolism is seen, which may in part explain the greater degree of visual hallucination in this form of dementia.[98] Dementia in PD will be discussed in a greater extent in later paragraphs. Finally, in contrast to early PD where striatal metabolism is either normal or increased, in PSP and MSA striatal metabolic activity is low.[86, 99-102]

Imaging motor fluctuations and dyskinesias

Patients with PD usually enjoy a stable response to levodopa during the first years of the disease. Unfortunately, a significant proportion will eventually develop motor fluctuations and/or dyskinesias after chronic levodopa treatment. It has been proposed that both presynaptic and postsynaptic dopaminergic systems are dysfunctional in order for these troublesome motor complications to occur, and now the implication of other neurotransmitter systems have started receiving more attention.

PET with 18F-dopa has shown that PD patients with motor fluctuating responses to levodopa had 28% decrease in presynaptic terminal function in putamen compared to PD patients with stable responses to levodopa.[103] However, this terminal loss in putamen cannot be the only responsible factor in the development of motor fluctuations, or in determining the onset of fluctuating responses to levodopa, or the development of involuntary movements.

A more recent study, using PET with the DAT marker 11C-methylphenidate, among other techniques, has suggested that in PD, a decrease in DAT may ultimately result in an increase in dopamine turnover and higher oscillations in synaptic dopamine concentration, thereby act as a predisposing factor to the occurrence of motor complications as disease progresses.[104]

By using PET with 11C-SCH23390 and 11C-raclopride, the role of striatal dopamine D1 and D2 receptor availability has been investigated as a possible cause of levodopa induced dyskinesias, respectively.

The mean caudate nucleus D1, putamen D1 and D2 availability is within normal range in baseline conditions in dyskinetic and non-dyskinetic PD, whereas caudate nucleus D2 binding is reduced by around 15% in each.[27, 105] These observations suggest that changes in striatal postsynaptic receptor availability are not primarily associated with the onset of motor complications.

PET with 11C-raclopride allows indirect monitoring of changes in levels of striatal dopamine release. It has been reported that in PD patients with fluctuating responses to levodopa, after an intravenous levopoda challenge, putaminal 11C-raclopride binding falls by 23%, compared to a 10% fall in putamen of PD patients with stable responses to levodopa. This suggests that exogenous levodopa provokes greater dopamine release in putamen of PD patients with fluctuating responses to levodopa than of PD patients with stable responses to levodopa. Furthermore the reductions in putaminal 11C-raclopride inversely correlate with UPDRS in the

off medication state.[106] Taken all this together, it seems that as the severity of disease advances and as loss of dopamine terminal in PD increases, the striatal control of dopamine release after administration of exogenous levodopa is progressively impaired. This could be due to the fact that the remaining terminals, after administration of exogenous levodopa, increase dopamine synthesis, and the remaining DATs cannot compensate by reuptaking the excess of dopamine, and therefore cannot regulate the release of dopamine back in a physiological range.

Similar results have been reported in another 11C-raclopride PET study involving an oral medication challenge with levodopa.[107] In this study, the authors reported that in the group of PD patients with fluctuating responses to levodopa, the synaptic levels of dopamine were three times higher than in PD patients with stable responses to levodopa, one hour after levodopa administration explaining their more rapid response to medication. By contrast, whereas stable responders maintained the increased dopamine levels four hours after levodopa administration, the synaptic levels in the group of PD patients with fluctuating responses to levodopa dropped to baseline (off) state.

Moreover, in another *in vivo* evaluation of synaptic dopamine release after a single oral dose of levodopa, the presence of dyskinesias positively correlated with the increased levels of dopamine in the synapse. In this study, PD patients experiencing dyskinesias showed significantly decreased levels in putaminal 11C-raclopride binding after oral levodopa administration when compared to a group of PD patients with stable responses to levodopa.[108]

PET with 11C-diprenorphine has been used in order to investigate the role of opioid system in the development of PD dyskinesias.[109] Reductions in both striatal (caudate nucleus and putamen) and extrastriatal (thalamus and anterior cingulate) 11C-diprenorphine binding was reported in PD patients with dyskinesias when compared to stable responders.

Additionally, PET with 18F-L829165 (a selective marker of NK1 site availability), has shown that thalamic NK1 availability is reduced in dyskinetic PD patients while it remained normal in PD patients with stable responses to levodopa.[110]

Taking these last two findings suggest that elevated levels of endogenous peptides may contribute to the appearance of dyskinesias.

Imaging non-motor aspects of Parkinson's disease

PD is increasingly recognized as a non-motor disorder since symptoms such as dementia and depression emerge with disease progression to become dominant in the clinical picture.

Addictive and compulsive behaviour

Dopamine replacement therapy (DRT) is the gold standard in managing PD motor symptoms. Although dopaminergic analogues are indeed highly effective up to a certain level of disease progression, the reported occurrence of addictive and compulsive behaviour after chronic exposure to DRT is now recognized as one of the biggest issues in managing PD. These previously unpredicted drug side-effects can lead to devastating social consequences and require immediate attention.

PET with 11C-raclopride has detected enhanced dopamine release in ventral striatal areas of PD patients with compulsive use of dopaminergic analogues (dopamine dysregulation syndrome – DDS) after an oral levodopa challenge, when compared to a group of PD patients who were taking their medication normally. The ventral striatal dopamine release in DDS patients correlated with "wanting" but not "liking" the medication, suggesting that the sensitization of ventral striatal circuitry is linked to compulsive drug use.[111]

However, this is only one aspect of reported compulsive behaviour as recently there is increasing evidence associating the chronic exposure of DRT in PD to Impulse Control Disorders (ICDs), which commonly involve pathological gambling, compulsive shopping, hypersexuality and compulsive eating.[112] It

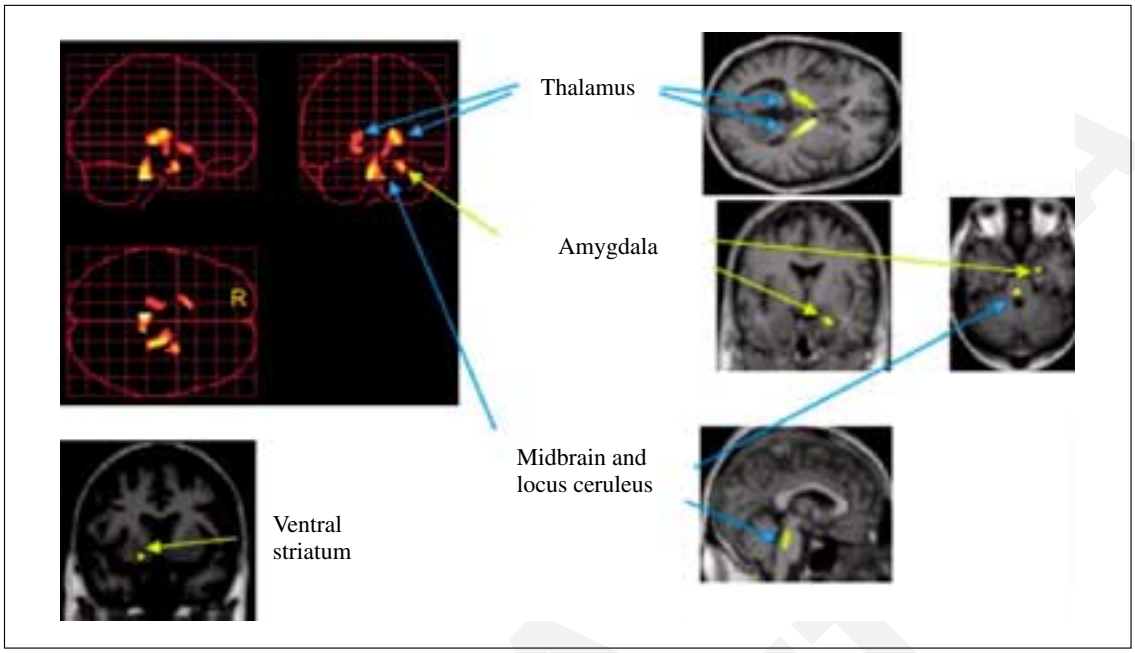

Figure 8.—Statistical parametric maps showing loss of 11C-RTI32 binding in the locus coeruleus, thalamus, ventral striatum and amygdala of depressed compared to euthymic PD cases.

is hoped that PET techniques will help to elucidate the mechanisms underlying these conditions in the near future.

Depression

Depression is a determinant of quality of life in PD with a reported prevalence of up to 45%, depending on different criteria used for the diagnosis.[113] Although the pathophysiology of depression in PD remains uncertain, changes in the serotonergic, noradrenergic and limbic dopaminergic neurotransmission may have a role. On the other hand, reactive depression following the disease's onset cannot be excluded. However, it is possible for the depressive symptoms to precede the onset of motor symptoms during the clinical course of PD.

Changes in the serotonin neurotransmission have been evaluated using 11C-WAY100635 PET [114] and showed that even though there is a 27-30% decrease in 5-HT1A binding in raphe nucleus of PD patients when compared to normal controls, there was no siginificant difference between depressed and euthymic PD patients at serotonin presynaptic level. However, 5-HT1A receptors are also distributed postsynaptically on various cortical regions. In the same study, the group of depressed PD patients showed significant reductions in 5-HT1A binding in the anterior cingulate and superior/medial frontal gyrus when compared with the group of the euthymic PD patients. Taken together, these data suggest that the vulnerability to depression seen in PD is possibly associated with decreased anterior cingulate and frontal cortex areas rather than with presynaptic serotoninergic function.

Changes in noradrenergic and limbic dopaminergic neurotransmission have been studied using PET with 11C-RTI32. PD patients with depression have been reported to have lower 11C-RTI32 binding in locus coeruleus, thalamus and areas of the limbic system including ventral striatum, amygdala and anterior cingulate when compared to a group of non-depressed PD patients (Figure 8). Hence, the severity of anxiety in PD showed an inverse correlation with ^{11}C-RTI 32 binding in most of these regions, whereas

apathy was inversely correlated with the radiotracer binding in the ventral striatum.[115]

In areas with low dopaminergic innervation such as the locus coeruleus, reduced 11C-RTI 32 binding mainly implicates the function of noradrenergic neurons, whereas in other areas a combined involvement of both dopaminergic and noradrenergic pathways is more likely to play a role. These findings suggest an important role of dopaminergic and noradrenergic systems dysfunction in the pathogenesis of depression in patients with PD.

Psychosis

Psychosis, and particularly in the form of visual hallucinations are not uncommon in PD. They generally occur at advanced stages of the disease and are associated with cognitive impairment. However, the mechanisms underlying their appearance remain largely unclear and research is currently limited.

A study in advanced PD cases, using PET with 18F-FDG, has shown that in patients experiencing visual hallucinations the relative regional cerebral glucose metabolic rate is greater in the frontal areas and predominantly in the left superior frontal gyrus, when compared with a group of PD patients without visual hallucinations.[116] This finding suggests that hypermetabolism in the frontal cortex in advanced PD could be a metabolic feature of visual hallucinations in PD.

Dementia

The prevalence of dementia in PD averages around 40% and is significantly higher compared to normal population. Possible reasons include loss of cholinergic projections, loss of mesolimbic and mesocortical dopaminergic projections, direct cortical involvement by DLB disease, coincidence of AD and vascular pathology.

The incidence of dementia in PD has been investigated using PET technology.

Using PET with 18F-FDG, studies have shown a similar pattern of reduced glucose metabolism in frontal, temporal and parietal areas between patients with AD and PD with dementia.[117-119] Using the same technique, it has been reported that patients with PD dementia and DLB disease show similar hypometabolism in the parietal, temporal, occipital and frontal lobes as well as the anterior cingulate when compared with a group of normal controls. However, when patients with DLB disease were directly compared with PD dementia patients the metabolic decrease in anterior cingulate was greater among patients with DLB disease, suggesting a similar pattern of pathology between these two conditions, although anterior cingulate was more involved in DLB disease.[120]

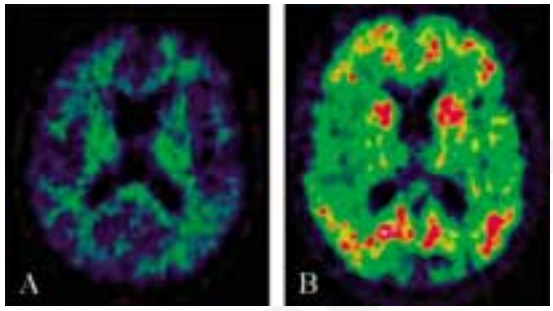

Figure 9.—Transverse 11C-PIB PET images of a PD subject with dementia (A) and a subject with DLB (B). Note the significant amount of amyloid load in the DLB subject.

Using PET with 18F-dopa, the role of dopaminergic projections in PD dementia has been investigated.[121] It has been reported that PD patients with dementia show further 18F-dopa uptake reductions in ventral striatum, the right caudate and the anterior cingulate when compared to a group of non-demented PD patients, suggesting a possible dysfunction of mesolimbic and mesocortical dopaminergic systems.

PET with 11C-PMP and 11C-MP4A has been used in PD patients with dementia to evaluate cortical AChE activity. The total cortical ^{11}C-MP4A binding was reported significantly reduced in demented PD patients when compared with a group of non-demented PD patients. Furthermore these reductions where particularly pronounced in parietal areas.[122] PET with 11C-PMP has shown similar reductions of AChE activity in PD patients with dementia. Additionally, the cortical cholinergic denervation correlated with worse performance on cognitive tests assessing

attentional, memory and executive functions.[51] These findings suggest that PD with dementia is associated with a reduction in cholinergic function and support the usage of AChE inhibitors in PD dementia.

Examining cortical muscarinic receptor binding in PD using PET with 11C-NMPB, was found that increased individual levels of frontal 11C-NMPB uptake correlated with worse performance on the Wisconsin Card Sorting test.[52]

PET with 11C-PIB, a marker of the β-amyloid plaque load, is a useful technique for investigating dementia. In AD there are significant 11C-PIB uptake increases throughout the cortex when compared with normal controls. Recent studies reported similar findings for DLB disease, while amyloid pathology is infrequent in PD with dementia [123-125] (Figure 9). These findings suggest that β-amyloid deposition does not significantly contribute to the pathogenesis of PD with dementia.

Sleep

Sleep disorders are common non-motor manifestations of PD and include a variety of disruptions of nocturnal sleep and inability to maintain normal daytime arousal, leading to impaired daytime performance. Symptomatic excessive daytime sleepiness (EDS) and disruption of nocturnal sleep can occur up to 50% of patients with PD and unfortunately little is known about the pathogenesis of these symptoms.

PET with 18F-dopa has been used in one study to investigate PD patients with a history of sleep disorders. The authors reported a significant inverse correlation between mesopontine ^{18}F-dopa uptake and REM sleep duration, as measured by polysomnography.[126] This finding suggests that increased monoaminergic activity in the mesopontine results in the suppression of nocturnal REM sleep in PD. However, more studies are needed to explore the pathogenesis of the sleep problems in PD.

Fatigue

Chronic fatigue is another common non-motor manifestation in PD with high prevalence during the course of the disease (more than 50%). Unfortunately, there are no PET imaging studies so far in PD patients with chronic fatigue syndrome (CFS), although data showing possible mechanism patterns exist from PET studies in patients with CFS alone.

In one study, using PET with 18F-FDG, although abnormalities were detected in half of the patients with CFS examined compared to a group of normal controls, the technique failed to identify any specific pattern associate with the expression of fatigue symptoms.[127] However, another 18F-FDG PET study reported significant brain stem hypometabolism in CFS.[128]

PET studies using 11C-McN5652 and 11C-WAY100635 have investigated for the involvement of serotoninergic system in the CFS. 11C-McN5652 binding has been reported significantly reduced in the rostral subdivision of the anterior cingulated of subjects with CFS as compared with that in normal volunteers,[129] suggesting that an alteration of serotonergic system in the rostral anterior cingulate plays a key role in pathophysiology of CFS. 11C-WAY100635 PET has shown a widespread reduction in 5-HT1A receptor binding in CFS relative to control subjects. This was particularly marked in the hippocampus bilaterally, where a 23% reduction was observed.[130] These findings suggest that there is evidence of decreased 5-HT1A receptor availability or affinity in CFS. This may be a primary feature of CFS, related to the underlying pathophysiology, or a phenomenon secondary to other processes, such as previous depression, other biological changes or the behavioral consequences of CFS. However specific studies on patients with PD and CFS are needed to address these issues.

Cardiac sympathetic denervation

Orthostatic hypotension is another non-motor symptom that can be present during the clinical course of PD. According to clinical tests, histopathological data and SPECT studies, PD patients have shown decreased cardiac uptake, indicative of myocardial post-

ganglionic sympathetic dysfunction that can cause orthostatic hypotension. The loss of sympathetic innervation can be seen in the heart and other organs, even where cardiovascular reflexes remain intact.

11C-MHED used with PET, is a radiolabelled catecholamine analogue and one of the available tracers for mapping sympathetic neurons. Using this technique in a pilot study, PD patients showed lower 11C-MHED uptake ratios compared to that observed in normal subjects, whereas patients with both PD and orthostatic hypotension had the lowest myocardial signals.[131]

Olfactory function

Hyposmia is a frequent non-motor feature of PD that could precede the appearance of motor symptoms providing a potential marker of subclinical disease.

PET with 11C-CFT has been used to investigate the relationship between nigostriatal dopaminergic denervation and olfactory deficits in PD. Whereas PD patients have worse olfactory function when compared to a group of normal controls, it has been reported that impaired 11C-CFT uptake values in PD patients significantly correlate with worse scores in specific and general smell indentification scores.[132]

This finding in combination with reports from SPECT studies could suggest that olfactory testing and PET imaging may provide a useful tool for screening the risk of developing PD.

Imaging drug development in Parkinson's disease

PET, apart from facilitating the diagnosis of PD and detecting functional changes in different stages of the disease, can provide potential biomarkers to monitor the effects of putative neuroprotective agents, as well as to establish the efficacy of novel therapeutics.

As previously discussed, PET with 11C-PK11195 is an efficient technique to demonstrate microglia activation. It has been suggested that suppression of inflammatory and immune reaction of the brain's neuronal degeneration might slow the progression of PD. Agents such as minocycline agonists could potential suppress microglia activation and 11C-PK11195 provides a biomarker for examining the anti-inflammatory properties of these agents.

Respecting the difficulties and limitations when trying to assess the rate of PD progression, studies have reported that the annual loss of 18F-dopa uptake in putamen ranges from 7 to 12% in early levodopa treated cases.[133]

Riluzole has been proposed to have disease-modifying effects, and its efficacy has been tested on *de novo* PD patients using 18F-dopa with PET. Results showed no difference in progression rates between groups in riluzole and placebo. Also, as discussed earlier, the REAL-PET trial demonstrated a one-third relative slowing of loss of dopamine terminal function in the dopamine agonist treated group when compared to levodopa.[70]

Up to now, there are only few studies that have addressed the direct effects of medications on brain 18F-dopa uptake, and findings have been inconsistent. Undoubtedly, further trials will be needed to assess the direct medication effects on disease progression.

PET imaging can also help to determine the dose-occupancy ratios of novel drugs for pharma and help guide dose selection for Phases I and II trials.[134] Examples include the use of PET with 11C-deprenyl to measure binding of MAO-B inhibitors that act to boost central dopamine levels in PD [135] and the use of PET with 11C-KW6002 to examine adenosine A2A site availability in the presence of varying doses of cold istradefylline, a useful adjunct therapy to levodopa.[136]

A further advantage of PET imaging is that it can examine the downstream effects of novel agents on brain metabolism and pharmacology. In both PD and normal controls, PET with 18F-dopa showed that after administrating the catechol-O-methyl transferase (COMT) inhibitor entacapone with the peripheral dopa decarboxylase inhibitor carbidopa, 18F-dopa uptake was boosted by 50% in normal and early PD subjects, as the

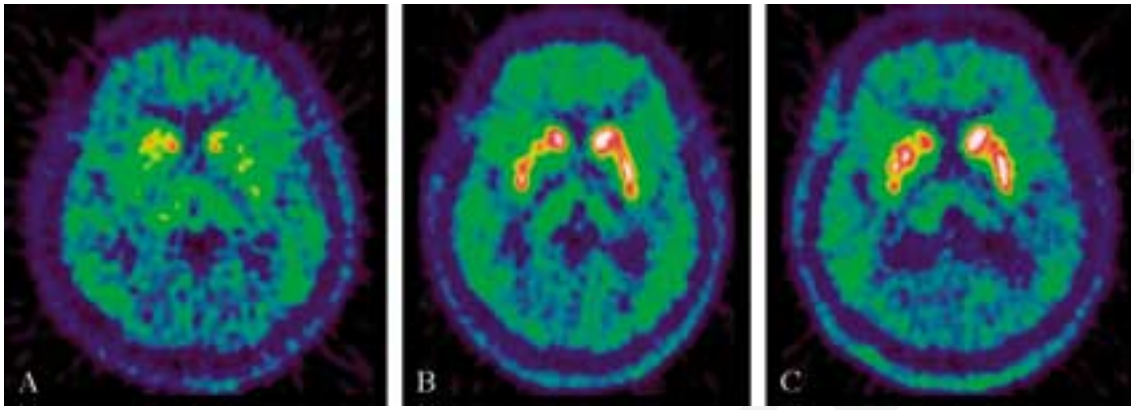

Figure 10.—Transverse 18F-dopa PET images of a PD patient who received striatal transplant with fetal mesencephalic cells, before the transplantation (A), 8 months after transplantation (B) and 21 months after transplantation (C).

medication blocked the peripheral metabolism of the tracer.[137] In advanced PD cases the effect was attenuated possibly due to the reduced ability of these patients to store levodopa in the striatum.[138]

Finally, by using PET with radioligands that compete to postsynaptic dopamine D2 receptors (11C-Raclopride, 11C-FLB457) changes in the neurotransmitter fluxes can be detected. The difference in binding of 11C-raclopride and 11C-FLB457 before and after a drug or behavioural challenge gives an indirect measure of changes in synaptic dopamine levels. 11C-raclopride PET has been used to demonstrate that striatal grafts of foetal dopamine cells in PD patients can release dopamine after an amphetamine challenge.[139]

Imaging restorative approaches in Parkinson's disease

Restorative approaches in PD aim to reverse the biochemical deficiency of the disease by restoring dopamine production in the areas affected. The possible approaches include: transplantation of striatal implants of human and fetal mesencephalic cells, stem cells, gene therapy and direct intrastriatal infusions of nerve growth factors.

Functional imaging provides a means of monitoring the effects of restorative approaches in PD. Using PET with 18F-dopa, several studies have reported increase 18F-dopa uptake by the striatal graft [139-142] (Figure 10). The same technique has demonstrated that following implantation of fetal midbrain cells into the putamen contralateral to their more affected limbs, grafted cells can survive for up to 10 years and they are able to release normal amount of dopamine following a methamphetamine challenge [139] and are able to restore activation of cortical areas responsible for control of movement.[143]

Following these encouraging findings, two major double-blinded trials evaluated the efficacy of human fetal implants in PD.[144,145] Despite the evidence of increased 18F-dopa uptake by the graft, neither of these trials showed significant clinical improvement. However, there were some promising indications that younger, less severe patients could benefit from the transplant. An important issue raised by these two trials was the high incidence of dyskinesias in the transplanted patients. There are imaging reports using 18F-dopa and 11C-raclopride PET, both in favor [146] and against [147, 148] the hypothesis that graft induced dyskinesias could be related to an excessive dopamine production from the graft.

PET with both 18F-dopa and 11C-raclopride has been used to investigate factors affecting the functional outcome after transplantation of fetal mesencephalic cells. Increased 18F-dopa uptake is associated with better long-term survival of the graft while progressive dopaminergic denervation in

areas outside the grafted regions are associated with poor outcome.[148]

Recent reports from animal studies on neuronal transplants implicate the role of the serotonin system and the relative densities of dopamine and serotonin innervations of the grafted striatum in the aggravation of graft-induced dyskinesias.[149, 150] Therefore, investigations of the presence and extent of serotonin innervation in the striatum of patients with graft-induced dyskinesias using PET imaging with ligands for the serotonin transporter may help to clarify this point.

Glial cell line-derived neurotrophic factor (GDNF) is known to protect dopamine neurons in rodents and nonhuman primates against toxins such as the 6-hydroxydopamine or the MPTP. The safety and efficacy of GDNF infusion via catheter into the putamen of PD patients has been investigated using 18F-dopa PET.[151] This confirmed increases in putaminal uptake consistent with improvements in UPDRS subscores in a 12-month follow-up period, suggesting that putamen GDNF infusion is safe and may represent a potential restorative approach for PD. However, following this study, a randomized placebo-controlled study, failed to show consistent clinical benefit from this procedure.[152]

Conclusions and future research

PET imaging techniques can provide an objective approach to assess different aspects of PD. They can be used to investigate subclinical disease, assist in the differential diagnosis, improve the understanding of motor and non-motor complications, monitor disease progression, to aid management, and to evaluate restorative approaches and new therapeutic developments. PET imaging has an increasing role in clarifying the unknown pathophysiology of the disease. Future research with the use of PET should focus on the elucidation of the mechanisms underlying the addictive and impulsive behaviour seen in treated PD patients and other common non-motor symptoms such as fatigue, sleep and depression. Furthermore, there is a need to further explore motor symptoms and complications that patients experience after years of disease progression and chronic exposure to dopaminergic therapy.

With the development of modern PET radiotracers, investigation of the serotoninergic (11C-DASB), cannabinoid (11C-MePPEP), glutamatergic (11C-CNS5161) and adenosinergic (11C-SCH442416) systems, newly developed hypotheses could clarify many of the remaining questions. Also, infiammatory responses to restorative approaches such as graft-transplantation could be monitored using tracers such as the activated microglial marker 11C-PK11195.

However, the development of new radiotracers is needed to increase the biological specificity and to explore various unknown biochemical pathways involved in the pathology of PD. These could include specific PET markers of noradrenergic function, a derivative of 11C-PK11195 for improving sensitivity to inflammation markers, and new tracers that target amyloid deposition as well as tracers able to explore previously untouched pathways of dopaminergic and non-dopaminergic function.

Riassunto

La tomografia a emissione di positroni nel morbo di Parkinson

La tomografia ad emissione di positroni (positron emission tomography, PET) è una tecnica utile nella valutazione e interpretazione della complessa anatomia funzionale dei gangli della base. Questa metodica può inoltre aiutare a chiarire i meccanismi fisiopatologici che sono alla base del processo degenerativo e della evoluzione dei sintomi nel Morbo di Parkinson. In questa review sarà discusso il ruolo potenziale delle imagini PET nella valutazione della funzione dopaminergica e non-dopaminergica nel contesto del Morbo di Parkinson, l'uso della PET come marker biologico nella diagnosi differenziale del parkinsonismo tipico e atipico, nel monitorare la progressione della malattia e nel chiarire i meccanismi alla base delle fluttuazioni motorie, le discinesie e i sintomi non motori. Sarà inoltre discusso il ruolo delle immagini funzionali nella valutazione della efficacia delle strategie neuroprotettive e neurorestorative nel Morbo di Parkinson. In futuro, se i costi lo permetteranno, la PET potrebbe rappresentare un'aggiunta consid-

erevole alla valutazione clinica di routine per facilitare la comprensione delle complicazioni della terapia e la gestione dei pazienti parkinsoniani.

Parole chiave: Tomografia ad emissione di positroni - Morbo di Parkinson - Medicina nucleare.

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