

Review

PET and SPECT functional imaging studies in Parkinsonian syndromes: from the lesion to its consequences

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Functional imaging techniques provide major insights into understanding the pathophysiology, progression, complications, and differential diagnosis of Parkinson's disease (PD). The dopaminergic system has been particularly studied allowing now early, presymptomatic diagnoses, which is of interest for future neuroprotective strategies. The existence of a compensatory hyperactivity of dopa-decarboxylase at disease onset has been recently demonstrated in the nigrostriatal and also extrastriatal dopaminergic pathways. Modification of dopamine receptors expression is observed during PD, but the respective contribution of dopaminergic drugs and the disease process towards these changes is still debated. Abnormalities of cerebral activation are seen and are clearly task-dependent, but the coexistence of hypoactivation in some areas and hyperactivation in others is also now well established. Such hyperactivation may be compensatory but could also reflect an inability to select appropriate motor circuits and inhibit inappropriate ones by PD patients. Interestingly, dopaminergic medications or surgical therapy reverse such abnormalities of brain activation.

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Introduction

Functional imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) significantly help in understanding the pathophysiology and evolution and aid the differential diagnosis of Parkinson's disease (PD). These techniques also provide a better understanding of the effects of medical or surgical treatment. The aim of this review is to provide an up to date account of the different contributions of functional imaging to PD.

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Search strategy and selection criteria

Data for this review were identified by searches of Medline and Current Contents using the search terms “Parkinson”, “Parkinsonism”, “Parkinsonian syndromes”, “PET”, “SPECT”, “functional imaging”, and “deep brain stimulation”. References were also identified from relevant articles and through searches of the author's files. Only papers published in English were reviewed.

Parkinson's disease

Dopaminergic system dysfunction at the presynaptic level

[¹⁸F]-Dopa PET studies

Motor consequences of the dopaminergic degeneration. [¹⁸F]-6-fluoro-L-Dopa radiotracer uptake reflects the dopaminergic nerve density but at the same time, the activity of the aromatic amino acid decarboxylase enzyme (AADC) that converts dopa into dopamine and the storage of dopamine (Firnau et al., 1987). This radiotracer allows the study of the integrity of the presynaptic dopaminergic system in the nigrostriatal and also the mesolimbic and mesocortical dopaminergic pathways. In PD, a major reduction of striatal [¹⁸F]-Dopa uptake is consistently observed, which reflects degeneration of the dopaminergic nigrostriatal pathways (Brooks et al., 1990a,b; Broussolle et al., 1999; Leenders et al., 1986; Morrisch et al., 1998; Vingerhoets et al., 1997). This reduction of uptake is well correlated with neuronal degeneration as demonstrated by pathological studies (Snow et al., 1993a). However, at disease onset, false negative cases have been reported due to the compensatory upregulation of AADC in preserved dopaminergic terminals, which implies that at this stage of the disease, [¹⁸F]-Dopa underestimates the degenerative process (Ribeiro et al., 2002). This is not the case using dopamine transporter ligands such as ⁷⁶Br-FE-CBT, because dopamine transporters activity is not regulated like dopadecarboxylase (Ribeiro et al., 2002). This study and others shows that DAT imaging is more sensitive than [¹⁸F]-Dopa to detect dopaminergic degeneration especially in early-stage PD (Lee et al., 2000; Ribeiro et al., 2002). When the disease is more advanced, this upregulation disappears. The reduction of striatal [¹⁸F]-Dopa uptake is not homogeneous in the striatum and a clear

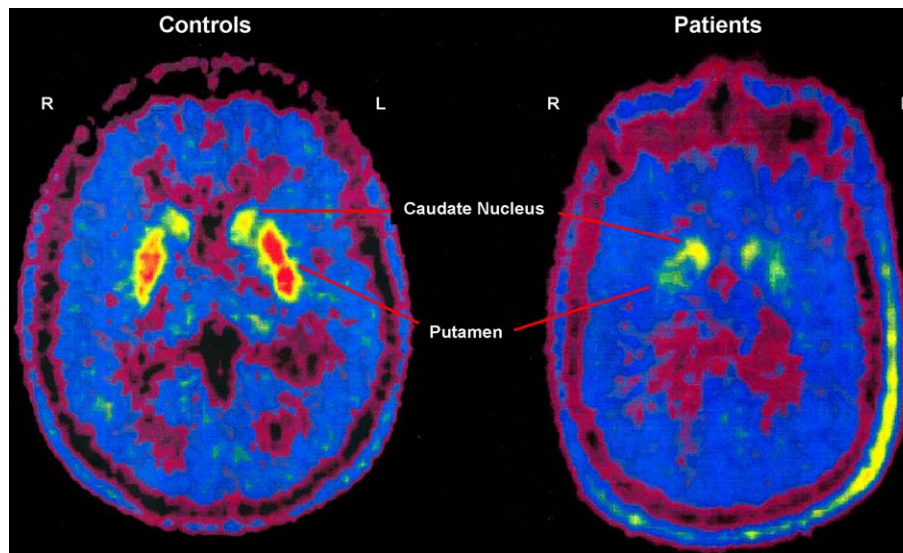


Fig. 1. This figure illustrates the major reduction of striatal [^{18}F]-Dopa uptake in Parkinson's disease (right part) compared to normal subjects (left part). The reduction of [^{18}F]-Dopa uptake predominates in the putamen while the caudate nucleus is relatively spared. R: right; L: left.

antero-posterior gradient is described, the caudate being less affected than the anterior putamen and the anterior putamen less than the posterior putamen (Fig. 1) (Brooks et al., 1990a,b; Broussolle et al., 1999; Leenders et al., 1986; Morrish et al., 1998; Vingerhoets et al., 1997). Furthermore, the striatal reduction of [^{18}F]-Dopa uptake is asymmetrical and correlated with the asymmetry of the motor signs (Brooks et al., 1990a,b; Broussolle et al., 1999; Leenders et al., 1986; Morrish et al., 1998; Vingerhoets et al., 1997). Thus, [^{18}F]-Dopa PET allows for the positive diagnosis of parkinsonian syndromes even in presymptomatic stages of the disease as demonstrated in twins studies and in familial PD (Burn et al., 1992; Piccini et al., 1997a, 1999a).

There is also clear evidence of a significant inverse correlation between [^{18}F]-Dopa uptake and the degree of motor disability and disease progression (Figs. 2 and 3) (Brooks et al., 1990b; Vingerhoets et al., 1994a; Morrish et al., 1996; Broussolle et al., 1999; Nurmi et al., 2001). Moreover, although other mechanisms exist, the presence of motor fluctuations is partly correlated with the reduction of putaminal [^{18}F]-Dopa uptake, suggesting a role for altered storage capacity in dopaminergic terminals in the pathophysiology of motor fluctuations (de la Fuente-Fernandez et al., 2000). The consequen-

ces of levodopa or apomorphine, a potent D1 and D2 dopamine agonist, administration on [^{18}F]-Dopa uptake vary in different stages of the disease. In early stages of the disease, levodopa administration reduces striatal [^{18}F]-Dopa uptake, whereas in late stages, the uptake remains unchanged or increases (Ekesbo et al., 1999; Torstenson et al., 1997). The explanation is that at disease onset, levodopa intake may stimulate dopaminergic autoreceptors and consequently reduce AADC activity and thus [^{18}F]-Dopa uptake. More recently, extrastriatal [^{18}F]-Dopa uptake has been studied and, at disease onset, an increase of dorsolateral prefrontal cortex, anterior cingulate, and pallidal radiotracer fixation has been shown that is not found in more advanced disease (Kaasinen et al., 2000; Rakshi et al., 1999; Whone et al., 2003a). This may suggest that at disease onset, there is either compensatory hyperactivity of dopa-decarboxylase in the mesocortical dopaminergic pathway because nigrostriatal degeneration, or that the uptake of [^{18}F]-Dopa, is into serotonergic terminals. In advanced PD, the degeneration of dopaminergic pathways is more global, which explains the absence of any increase in extrastriatal [^{18}F]-Dopa uptake (Kaasinen et al., 2000; Rakshi et al., 1999; Whone et al., 2003a).

Cognitive performance and dopaminergic degeneration. Cognitive deficits are frequently present in PD. In particular, attention

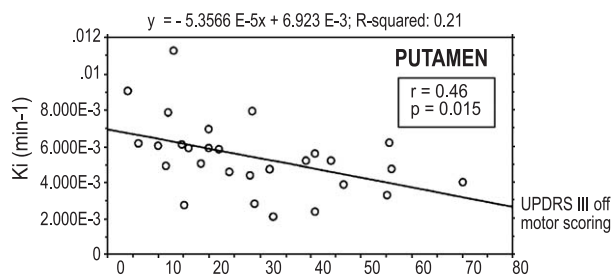


Fig. 2. This histogram illustrates the inverse correlation between the severity of parkinsonian motor symptoms reflected by the UPDRS motor score and the putaminal [^{18}F]-Dopa uptake. The more severe the disability (and high the UPDRS motor score), the less important Ki index value. Ki: index of [^{18}F]-Dopa uptake. UPDRS: Unified Parkinson's Disease Rating Scale.

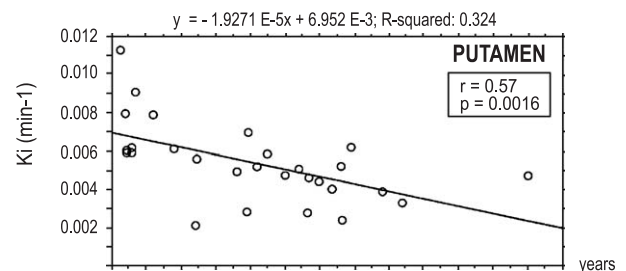


Fig. 3. This histogram illustrates the inverse correlation between the duration of Parkinson's disease severity and the putaminal [^{18}F]-Dopa uptake. The longer the duration of the disease, the smaller the Ki index value. Ki: index of [^{18}F]-Dopa uptake.

and memory deficits and impairment of executive functions are common and can lead to a frontal subcortical dementia (Dubois and Pillon, 1997). The existence of correlations between these deficits and dopaminergic neuronal degeneration is still a matter of debate. A link between the reduction of [^{18}F]-Dopa and [^{11}C]-Nomifensine uptake in the caudate but not putamen and dysexecutive syndrome has been suggested by some studies (Broussolle et al., 1999; Holthoff-Detto et al., 1997; Marié et al., 1999; Rinne et al., 2000). A recent study demonstrated a positive correlation between the reduction of [^{18}F]-Dopa uptake in the frontal cortex and deficits observed during tasks of verbal fluency and immediate or working memory (Rinne et al., 2000). Recently, relative differences in dopaminergic function in the whole brain were investigated in PD patients with and without dementia (Ito et al., 2002). A significant reduction of [^{18}F]-Dopa uptake in the cingulate, ventral striatum, and caudate nucleus was noted in the group of PD patients with dementia compared to the group without, which suggests that dementia in PD is associated with impaired mesolimbic and striatal dopaminergic function. However, deficiencies in other neurotransmitter systems contribute to the cognitive deficits in PD as suggested by the lack of efficacy of levodopa replacement therapy in improving all aspects of cognitive performance and by other experimental data (Dubois et al., 1990).

Sleep disorders and dopaminergic degeneration. Sleep abnormalities in PD are frequent and consist mostly of rapid eyes movement (REM)-associated behavioral disorders, periodic leg movements, or daytime sleepiness (Arnulf et al., 2000). Few functional imaging data are available on the role of dopaminergic depletion in sleep problems. A recent study showed no relationship between deficits in the pre- and post-synaptic mesostriatal dopaminergic pathway and sleep disorders but an inverse correlation between mesopontine [^{18}F]-Dopa uptake and sleep problems (Hilker et al., 2003a). Thus, the reduction of REM sleep duration and abnormal REM sleep behaviors are associated with increased mesopontine [^{18}F]-Dopa uptake that probably reflects an upregulation of AADC in nondopaminergic monoaminergic brainstem neurons that are normally silent during REM sleep (Hobson et al., 1975). However, this hypothesis is still debated as a SPECT study demonstrated a reduction of the striatal uptake of a dopamine transporter in subjects with idiopathic REM sleep disorders (Eisen-sehr et al., 2000). In this study, it was stated that the sleep problems were due to excessive inhibition of midbrain extrapyramidal areas that promote REM sleep (Pahapill and Lozano, 2000).

Dopaminergic degeneration and hereditary forms of PD. In familial PD, about 25% of asymptomatic members presented abnormal reduction of putaminal [^{18}F]-Dopa uptake (Piccini et al., 1997a). Another study performed in twins, of which only one had Parkinsonism, showed that 55% of nonsymptomatic monozygotic twins had abnormal [^{18}F]-Dopa uptake and 18% of dizygotic twin (Piccini et al., 1999a). In the last decade, several genes and loci have been associated with familial forms of PD (Dekker et al., 2003a). Among these mutations, the most important in terms of number of affected patients are the Parkin gene mutations (PARK 2) that are responsible for an autosomal recessive form of PD that differs from idiopathic PD. The age of onset is younger, focal dystonia is frequent at onset, and progression is slow (Khan et al., 2003; Lohmann et al., 2003). Functional imaging of the dopaminergic system has been used in these hereditary forms of PD to look for specific abnormalities that could distinguish them from idiopathic disease.

In PARK 1, an autosomal dominant form of PD related to the α -synuclein gene mutation, striatal [^{18}F]-Dopa uptake is reduced with an anteroposterior gradient that is similar to idiopathic PD (Samii et al., 1999). In PARK 6, another autosomal recessive form of PD, the decrease of striatal [^{18}F]-Dopa uptake is more uniform than in idiopathic disease (Khan et al., 2002a). In PD associated with Parkin gene mutations, the decrease of striatal [^{18}F]-Dopa uptake is more pronounced in the posterior putamen but less asymmetrically than in idiopathic PD, and it is not correlated with the severity of motor symptoms nor with the type of mutation (Broussolle et al., 2000; Hilker et al., 2001; Portman et al., 2001; Thobois et al., 2003a). In addition, in a given family, the reduction of [^{18}F]-Dopa uptake is correlated with the number of mutated alleles; heterozygotic asymptomatic carriers of Parkin gene mutations have abnormal striatal [^{18}F]-Dopa uptake (Hilker et al., 2002a; Portman et al., 2001). The lack of clinical-imaging correlation in Parkin patients suggests the existence of dopaminergic post-synaptic compensatory mechanisms, but until now, the results of the few PET studies using [^{11}C]-Raclopride, a D2 receptor ligand, have failed to demonstrate any upregulation of these receptors and rather showed a more pronounced downregulation of D2 receptors than in PD without Parkin gene mutation (Hilker et al., 2001; Portman et al., 2001; Scherfler et al., 2004). Finally, dopaminergic degeneration in patients with Parkin gene mutations is slower than in idiopathic PD patients, which fits well with the more “benign” clinical course of this disease (Khan et al., 2002b). In PARK 7, another autosomal recessive form of PD associated with mutations of the DJ-1 gene, functional imaging studies show a symmetrical reduction of striatal [^{18}F]-Dopa uptake that is similar to that described in PARK 2 (Bonifati et al., 2003; Dekker et al., 2003b). In conclusion, despite clinical differences, the abnormalities of striatal [^{18}F]-Dopa uptake are very similar to those described in idiopathic PD and are not discriminative enough for routine differential diagnosis.

Evaluation of graft in Parkinson's disease. Since the 1980s, intrastriatal transplantation of human embryonic mesencephalic tissue has been used to treat PD (Lindvall et al., 1989). Striatal [^{18}F]-Dopa uptake clearly increases after the transplantation, which is well correlated with the survival of grafts observed in post-mortem (Kordower et al., 1995; Nakamura et al., 2001a; Olanow et al., 2003; Remy et al., 1995; Sawle et al., 1992). The capacity for storage and release of the dopamine by transplants has been confirmed using [^{11}C]-Raclopride (Piccini et al., 1999b). Furthermore, the existence of dyskinesias after transplantation has been associated with greater [^{18}F]-Dopa uptake in the ventral putamen, which is less affected by dopaminergic denervation (Ma et al., 2002).

PET and [^{18}F]-Dopa for monitoring neuroprotection in PD. The role of PET in assessing any potential neuroprotective effect of antiparkinsonian drugs is still a matter of debate, but the approach appears promising (Brooks, 2003; Marek et al., 2003; Morrish, 2003). The objective is to demonstrate that a tested drug can slow the natural progression of dopaminergic degeneration. Using PET and [^{18}F]-Dopa, it has been demonstrated that ropinirole, a dopamine agonist, reduces the rate of dopaminergic neuronal loss by about 30% compared to levodopa at 2 years (Whone et al., 2003b). Using SPECT and β -CIT, a dopamine transporter ligand, it has been shown that pramipexole, another dopamine agonist, reduces dopaminergic cell loss by 40% compared to levodopa (Parkinson Study Group, 2002). However, these results have to be interpreted with caution, because there was no placebo group, some patients receiving dopamine agonists were also treated with levodopa, and

there was no clear correlation between the functional imaging data and clinical evolution (Morrish, 2003).

Nevertheless, the data are encouraging and functional imaging presently remains the only way to monitor a potential neuroprotective action of a treatment in vivo.

Other presynaptic dopaminergic ligands and radiotracers

Several dopamine transporter radiotracers such as [¹⁸F] or [¹¹C]-WIN-35428, [¹¹C]-CIT-FE, [¹²³I]-β-CIT (SPECT), [¹¹C]-methylphenidate, and [¹¹C]-RTI-32 are taken up less well into the striatum of patients with PD; results are consistent with [¹⁸F]-Dopa studies (Frey et al., 1996; Frost et al., 1993; Guttman et al., 1997; Innis et al., 1991). Similar results have been found with [¹¹C]-CFT, a tropan, but an additional 52% reduction of uptake in the orbitofrontal cortex at disease onset has also been observed (Ouchi et al., 1999). The SPECT radiotracer [¹²³I]-β-CIT shows a good correlation between the reduction of striatal uptake, symptoms severity, and stage of PD (Seibyl et al., 1995). However, the best correlation is obtained for axial signs and for bradykinesia whereas no correlation exists between [¹²³I]-β-CIT uptake and tremor (Brucke et al., 1997; Pirker, 2003). In addition, as [¹⁸F]-Dopa, [¹²³I]-β-CIT is also able to detect subclinical dopaminergic cell loss (Berendse et al., 2001). However, in contrary to [¹⁸F]-Dopa, [¹²³I]-β-CIT binding is not influenced by either chronic or acute administration of dopaminergic medications even in early PD, showing that the DAT is not down or upregulated by these drugs (Frey et al., 2001; Innis et al., 1999).

[¹¹C]-nomifensine, a ligand of dopamine reuptake sites, shows a reduction of striatal uptake compared similar to [¹⁸F]-Dopa, which reflects the degree of neuronal loss (Brooks et al., 1990b).

[¹¹C]-dihydrotetabenazine is a vesicular monoamine transporter radiotracer. Recently, Lee et al. (2000) compared striatal uptake of three different radiotracers, [¹¹C]-dihydrotetabenazine—a vesicular monoamine transporter ligand, [¹¹C]-methylphenidate, which labels the plasma membrane-bound dopamine transporter and [¹⁸F]-Dopa in early and advanced PD patients. They demonstrated that the putaminal uptake of [¹⁸F]-Dopa is greater than that of [¹¹C]-dihydrotetabenazine, but [¹¹C]-methylphenidate uptake is lower. These observations suggest that in the striatum of patients with PD, the activity of aromatic L-amino acid decarboxylase is upregulated and the plasma membrane DA transporter is probably downregulated to compensate for dopaminergic degeneration. [¹¹C]-dihydrotetabenazine binding probably reflects the density of dopaminergic terminals more precisely.

Dopaminergic system dysfunction at the postsynaptic level

[¹¹C]-Raclopride PET studies

To study postsynaptic dopamine receptors [¹¹C]-Raclopride, a low affinity dopaminergic D2 receptor ligand has been used in most PET studies. In de novo, drug-naïve PD patients, [¹¹C]-Raclopride binding is either normal or increased in the putamen and normal in the caudate nucleus (Dentresangle et al., 1999; Rinne et al., 1993). This increase of the putaminal binding at disease onset is usually interpreted as a compensatory mechanism involving receptor upregulation, but this remains debated. Indeed, some animal histological studies show that major and almost complete dopaminergic degeneration is necessary to upregulate dopaminergic receptor expression (Robinson and Whishaw, 1988). In advanced PD, [¹¹C]-Raclopride binding normalizes in the putamen and most often decreases in the caudate (Antonini et al., 1994; Brooks et al., 1990b, 1992; Den-

tresangle et al., 1999; Turjanski et al., 1997). This reduction of ligand binding may reflect either disease progression or an effect of dopaminergic medication. It is very difficult with the long half-life of dopamine agonists to separate drug-induced receptor changes (such as internalization) from simple competitive modification of [¹¹C]-Raclopride binding (Antonini et al., 1994; Laruelle, 2000; Muriel et al., 1999). The histological data do not help answer these questions as the striatal D2 receptor density has been reported to be either normal or decreased in 6[OH]-dopamine or MPTP lesioned animals and in PD patients treated with dopaminergic medication (Bokobza et al., 1984; Guttman et al., 1986). Thus, the significance of these modifications of D2 receptor expression in late PD remains unknown.

Interestingly, the combined use of [¹¹C]-Raclopride and [¹⁸F]-Dopa has demonstrated that in PD patients, the amount of released dopamine after methamphetamine challenge (measured indirectly via [¹¹C]-Raclopride displacement) is proportional to the density of dopaminergic terminals (measured by the [¹⁸F]-Dopa uptake) (Piccini et al., 2003).

In an experiment comparing fluctuating and nonfluctuating patients, synaptic dopamine release was found to be faster and of greater amplitude in patients with motor fluctuations, which indicates a greater turnover of dopamine when fluctuations appear (de la Fuente-Fernandez et al., 2001a). Tedroff et al. (1996) found that after levodopa intake, [¹¹C]-Raclopride binding was reduced by 10% at disease onset and 20% in more advanced PD, which suggests an upregulation of dopamine synthesis and release and a reduction of the storage and reuptake mechanisms in late disease. Another study in healthy subjects and also, although to a lesser extent, in PD patients has demonstrated that the execution of a simple motor task is accompanied by dopamine release as reflected by a displacement of [¹¹C]-Raclopride (Goerendt et al., 2003). Using the ability of endogenous dopamine to compete for [¹¹C]-Raclopride binding, substantial release of endogenous dopamine in the striatum of PD patients in response to placebo has also been observed, explaining one of the possible mechanisms underlying this phenomenon (de la Fuente Fernandez et al., 2001b).

Finally, several groups have recently investigated modifications of striatal dopamine release in response to stimulation of the subthalamic nucleus (STN). Indeed, such endogenous dopamine release after STN stimulation had been observed in rats, parkinsonian or not, using microdialysis techniques (Bruet et al., 2001). This phenomenon may be related to the glutamatergic connections of the STN with the substantia nigra pars reticulata, which in turn sends GABAergic projections to the substantia nigra pars compacta. However, the microdialysis findings have not been replicated in humans using PET and [¹¹C]-Raclopride. In other words, no modification of striatal [¹¹C]-Raclopride binding was observed after STN stimulation (Hilker et al., 2003b; Strafella et al., 2003a; Thobois et al., 2003b).

Other post-synaptic dopaminergic ligands

[¹¹C]-SCH23390, a D1 receptor ligand, is normally taken up in the putamen of de novo drug-naïve PD patients and its binding may either be normal or reduced in more advanced and treated patients (Shinotoh et al., 1993; Turjanski et al., 1997). In addition, Turjanski et al. (1997) found no differential of D1 and D2 receptor expression with dyskinesias, which means that dyskinesias are not related to simple modifications of dopaminergic receptor density but to more complex changes in functioning downstream of them and to nondopaminergic mechanisms (Chase and Oh, 2000).

The expression of D2 and D3 receptors has been followed by the dopaminergic ligand, [^{11}C]-FLB 457. They are reduced in the anterior cingulate, dorsolateral prefrontal and temporal cortex and the thalamus in late stage PD, suggesting lesions of the mesolimbic dopaminergic pathways that may be involved in the cognitive and emotional deficits in PD patients (Kaasinen et al., 2000, 2003).

In addition, in idiopathic drug-naïve PD patients, the striatal binding of [^{123}I]-iodobenzamide (IBZM), a SPECT ligand of dopamine D2 receptors, is normal (Schwarz et al., 1993). As for the [^{11}C]-Raclopride, dopaminergic drugs modify IBZM binding. However, in contrary to [^{11}C]-Raclopride, IBZM binding is only reduced by dopaminergic agonists, but not by levodopa (Schwarz et al., 1996). This implicates the need to stop the dopaminergic agonists before doing an IBZM SPECT.

Functional consequences of the dopaminergic depletion: PET activation studies

At rest

The consequences of dopaminergic medication on cerebral blood flow at rest have been investigated. Some studies showed no modifications of brain activation while others rather found a global increase of cerebral activity (Leenders et al., 1985; Montastruc et al., 1987). Interestingly, the response to levodopa at rest depends on the duration of exposure to levodopa. PD patients chronically treated by levodopa have decreased regional cerebral blood flow in the ventrolateral prefrontal and sensorimotor cortex, but drug-naïve patients have no levodopa-induced modification of cerebral activation (Hershey et al., 2003a). The significance of these changes of response to levodopa remains uncertain but could mean that long-term levodopa treatment modifies the function of the thalamocortical projections, at rest.

During the execution of a manual motor task

During the execution of a freely chosen unilateral motor task, the activation (i.e., the regional cerebral blood flow) was reduced in PD compared to normal subjects in the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate that are, respectively, the main output projections of the basal ganglia to the motor, associative, and limbic loops (Jahanshahi et al.,

1995; Playford et al., 1992). Conversely, the primary motor, parietal and lateral premotor cortices were normally activated. Apomorphine administration normalized the activation profile when patients turned on (Jenkins et al., 1992). More recent studies have demonstrated an higher activation of a lateral cerebello-parieto-premotor circuit in PD compared to healthy subjects while the activation was reduced in a mesial SMA-cingulate circuit (Rascol et al., 1997; Sabatini et al., 2000; Samuel et al., 1997a). Circuits showing increased activation are more implicated in externally cued motor tasks (Jahanshahi et al., 1995). These studies also demonstrated that the reduction of SMA activation involves anterior SMA while its caudal part is more activated than in controls (Sabatini et al., 2000). Furthermore, the primary motor cortex, both ipsi- and contralateral to a motor task, may also be more activated in PD than in normal subjects even in early stages of the disease (Figs. 4 and 5) (Sabatini et al., 2000; Thobois et al., 2000). These abnormal activation patterns are highly dependent of task. During an externally cued, sequential, and repetitive motor task, the SMA is normally activated in PD while the activation of the primary motor cortex and the cerebellum is reduced (Turner et al., 2003). In contrast, lesser activation of the SMA is observed in PD during a task that requires attentional and selection processes (Rowe et al., 2002). The complexity of a task has to be taken into account. During a sequential motor task of increasing complexity, activation of the SMA, for example, can be greater than in controls if the sequence is long (Catalan et al., 1999). To summarize, the abnormalities of SMA activation in PD consist of normal or increased activation in automatic or complex sequential motor tasks but reduced activation in internally triggered or attention-demanding tasks.

Thus, abnormalities of cerebral activation in PD are clearly dependent on the type of motor task, which is important when comparing results from different studies. This conclusion suggests that PD patients have difficulties to activate motor programs that correspond to the type of task they are performing normally. Furthermore, the interpretation of the changes in the so-called compensatory motor pathways is still debated. Making an analogy with what has been described during the recovery period after stroke, the abnormal recruitment could be considered compensatory (Chollet et al., 1991). This idea is supported by a recent study showing that the lateral premotor cortex, whose activation is

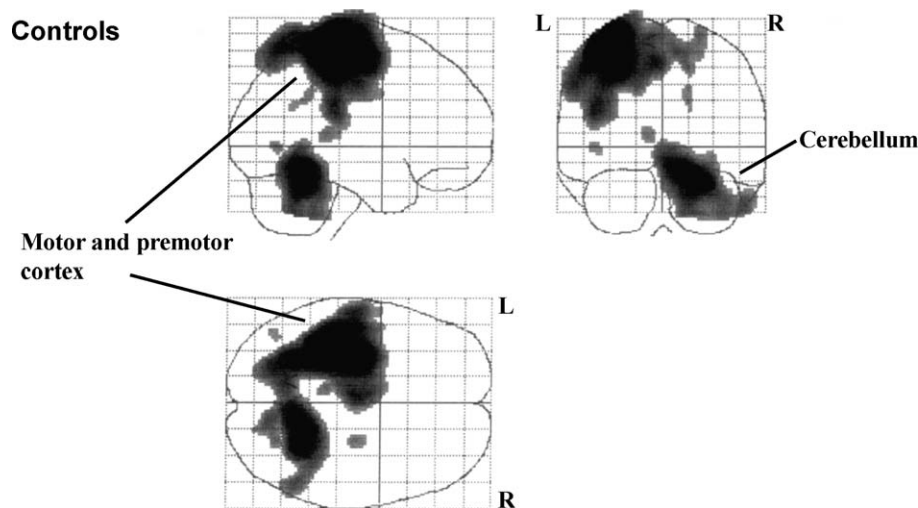


Fig. 4. PET [H_2^{15}O] activation study, healthy subjects. Brain areas activated during the execution of a sequential, predefined, manual motor task with a joystick and the right hand. The main activated areas are the left motor, premotor and parietal cortex, and the right cerebellum. L: left; R: right.

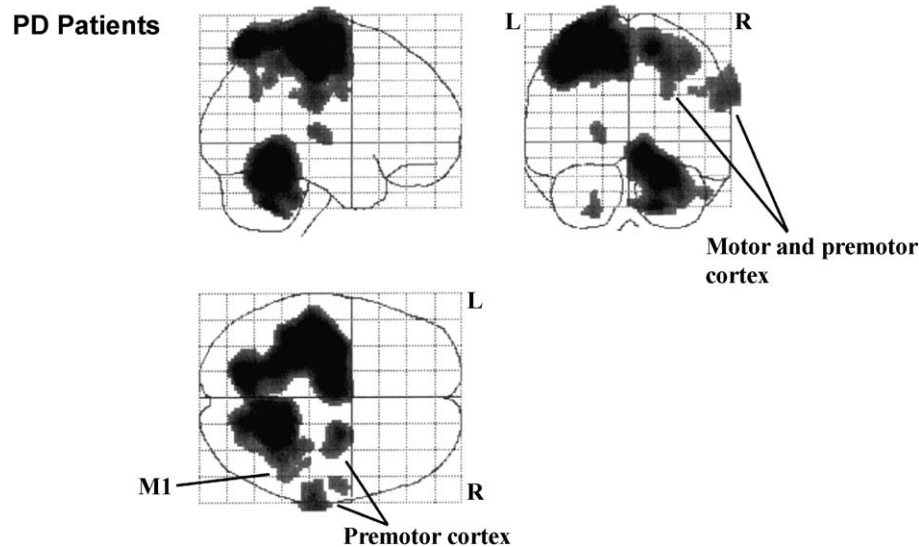


Fig. 5. PET [H_2^{15}O] activation study, right hemiparkinsonian patients. Brain areas activated during the execution of a sequential, predefined, manual motor task with a joystick and the right akinetic hand. The main activated areas are the left motor, premotor and parietal cortex, and the right cerebellum. In addition, contrary to that is observed in controls, an ipsilateral activation of the primary and premotor cortex is noted. L: left; R: right.

increased compared to controls, is activated when visual stimuli are presented to PD patients to improve their gait (Hanakawa et al., 1999). However, other hypothesis can be made, for example, the higher activations in PD patients may represent an inability to inhibit inappropriate motor circuits and to select an appropriate one (Boecker et al., 1999). Finally, a relationship between abnormal activations and the occurrence of dyskinesias has been suggested but cannot explain the additional activations observed at disease onset in nondyskinetic patients (Rascol et al., 1994, 1998; Thobois et al., 2000).

During speech

Dysarthria is a major and disabling problem in PD. Few functional imaging studies have looked at this aspect of motor disability in PD patients. In a recent PET study, the brain activation profile was analyzed during a speech production task before and after speech therapy with the Lee Silverman Voice Treatment (LSVT) (Liotti et al., 2003). Here again, the abnormalities of cerebral activation appeared specific for the task and comprised a higher activation of primary motor and premotor cortex before treatment. After LSVT, these increased activations disappeared and normal activations of the insula, caudate, and putamen were observed (Liotti et al., 2003).

Consequences of surgical treatments on the cerebral activation patterns

In the last 20 years, there has been a resurgence of interest in surgical treatments for PD, either by lesion or deep brain stimulation. According to the classical model of basal ganglia dysfunction in PD, deep brain stimulation or lesioning of the internal pallidum (GPi) or subthalamic nucleus should reverse the inhibitory output of GPi to the thalamus and consequently improve cortical activation (DeLong, 1990). After pallidotomy and during execution of a manual motor task, the activations of SMA and DLPFC are normalized (Grafton et al., 1995; Samuel et al., 1997b). Pallidal stimulation induces increased activation of the SMA and anterior cingulate (Fukuda et al., 2001a). STN stimulation also increases

activations of the rostral SMA, DLPFC, anterior cingulate, thalamus, and putamen (Ceballos-Baumann et al., 1999; Limousin et al., 1997; Strafella et al., 2003b; Thobois et al., 2002). The improvement of activations in the SMA and anterior cingulate cortex are observed even at low, clinically ineffective (60 Hz) frequencies of stimulation, while the improvement of DLPFC activation is only found at a high, clinically effective (130 Hz) frequency (Strafella et al., 2003b). In parallel with restoration of normal activation, a reduction of the recruitment of compensatory pathways and in particular of the ipsilateral primary motor, lateral premotor, and parietal cortices has also been observed (Ceballos-Baumann et al., 1999; Limousin et al., 1997; Thobois et al., 2002). Similar simultaneous improvement of mesial premotor cortex activation and reductions in the lateral premotor cortical circuitry has been shown after levodopa challenge (Haslinger et al., 2001). The type of motor task has also to be taken into consideration when considering responses in the SMA. In the studies of Limousin et al. (1997) and Ceballos-Baumann et al. (1999), who used a freely moving joystick task, SMA activation improved after STN stimulation. In contrast, in another study, that used an externally cued, repetitive, and sequential task, SMA activation decreased after STN stimulation (Thobois et al., 2002). Despite these differences, the results clearly show a restoration of normal cortical activation patterns, which supports the hypothesis of an inhibitory effect of STN stimulation on the STN and Gpi output. However, the effects of STN stimulation at rest conflict with those found during motor execution. Recently, Hershey et al. (2003b) observed that STN stimulation at rest increased pallidal and thalamic activation and reduced frontal (including SMA), parietal, and temporal cortex activation, which suggests an excitatory effect on STN output neurons, that increases inhibition of thalamocortical projections, ultimately decreasing cortical blood flow.

The effects of STN stimulation on parkinsonian dysarthria have also been investigated (Pinto et al., 2004). In clinical practice, STN stimulation usually does not improve or sometimes worsens speech intelligibility and/or articulation (Rousseaux et al., 2004; Santens et al., 2003). However, this point remains debated as other studies

showed that STN stimulation can improve speech function, which is different from intelligibility (Gentil et al., 2003; Pinto et al., 2003). In this study, off medication and with stimulation off, parkinsonian dysarthria was associated with a lack of primary motor cortex and cerebellar activation, but the superior premotor cortex, SMA, and DLPFC were more activated than in controls, which is a very different pattern from that usually found during a manual motor task. STN stimulation improved speech and suppressed these abnormalities of activation restoring normal cerebellar and primary motor cortex activations and reducing SMA overactivation (Fig. 6). These studies again demonstrate that abnormalities of brain activation in PD are task-dependent and are differentially influenced by stimulation.

The role of the cerebellum in the genesis of parkinsonian tremor has been described in a study showing that the improvement of tremor in patients with implanted thalamic electrodes was associated with a reduction of cerebellar activation (Deiber et al., 1993). This is in line with the increased cerebellar blood flow found in PD patients with prominent tremor (Duffau et al., 1996).

Finally, 18 months after a mesencephalic dopaminergic cell graft, a normalization of SMA and DLPFC activation was found during motor task execution, which shows that the transplant is functional and can restore physiological striatocortical circuitry in PD (Piccini et al., 2000).

Cognitive performance in Parkinson's disease

The consequences of PD and the effects of dopaminergic drugs on cognitive function have been studied in several PET and fMRI studies. Performance of a spatial memory task is associated with a reduction of pallidal activation, which is in keeping with a disruption of a frontostriatal pathway (Owen et al., 1998). In a spatial and planning working memory task, contrary to what is observed during

a motor task, PD patients off medication show an increased activation of the prefrontal (especially the right DLPFC), parietal, and cingulate cortex (Cools et al., 2002; Mattay et al., 2002). Additional recruitment of cortical areas has also been demonstrated during motor sequence learning and trial-and-error sequence learning when PD patients perform the same task equally to controls (Mentis et al., 2003; Nakamura et al., 2001b). Indeed, motor sequence learning in PD, compared to healthy subjects, is associated with bilateral rather than unilateral DLPFC, premotor, and precuneus cortex activation and additional cerebellar activation (Mentis et al., 2003; Nakamura et al., 2001b). In contrast, striatum activation is reduced. Dopaminergic medication reduces and normalizes the prefrontal activation compared to off medication state during a working memory task (Cools et al., 2002; Mattay et al., 2002). Interestingly, the higher cortical recruitment in off levodopa condition correlated with errors in task performance whereas the improvement of a motor task is associated with increased cerebral activation (Mattay et al., 2002). However the cognitive status of the patients has to be considered. Indeed, during a working-memory paradigm, PD patients with cognitive decline rather show decreased activation of the prefrontal cortex and caudate nucleus compared to cognitively preserved patients (Lewis et al., 2003). During implicit learning of motor sequences, levodopa may have a deleterious effect in non-demented PD patients (Feigin et al., 2003). This effect of levodopa is associated with an increased activation of the premotor cortex and a reduction of activation of the association occipital cortex (Feigin et al., 2003). Opposite results have been found after internal pallidum stimulation with the same kind of task. Indeed, pallidal stimulation improves sequence learning concomitantly with increased activation of the premotor, occipital, and DLPFC cortex compared to off-stimulation condition (Fukuda et al., 2002). During a planning task, PD patients show reduced caudate activation but increased hippo-

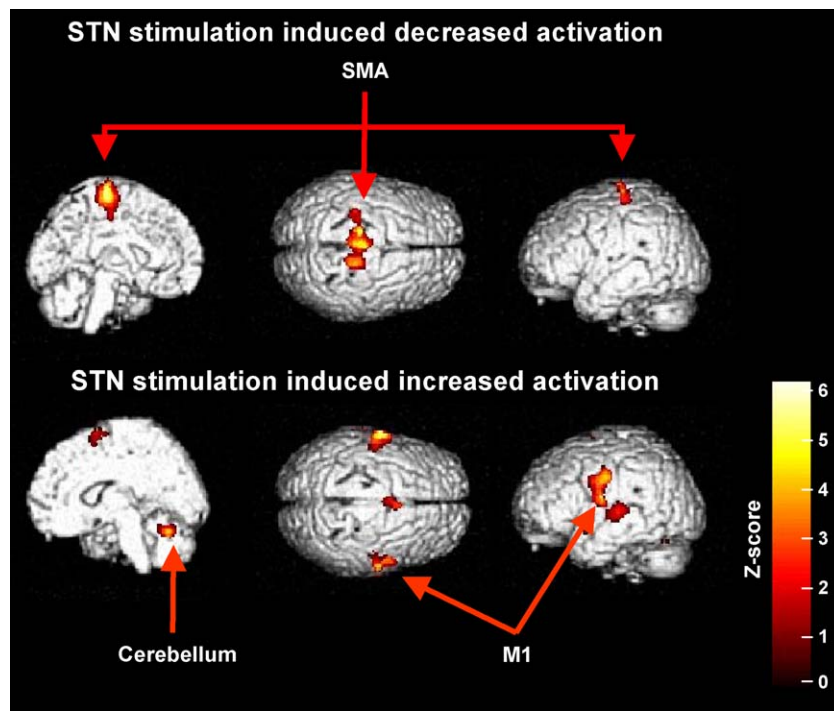


Fig. 6. PET [H_2^{15}O] activation study. Effects of bilateral subthalamic nucleus (STN) stimulation during speech production in Parkinson's disease. During this kind of task, STN stimulation induces a decreased activation of the SMA and increases the activation of the primary motor cortex and cerebellum. M1: primary motor cortex; SMA: supplementary motor area. Areas of activation are superimposed on a brain MRI.

campal activation, which can be interpreted as “a switch to declarative memory because of the insufficient working memory capacity within the frontostriatal system” (Dagher et al., 2001).

To summarize, cognitive symptoms in PD are associated with supplementary, possibly compensatory recruitment of brain areas to balance for abnormal functioning of the basal ganglia.

Stimulation of the STN does not significantly influence cognitive function of PD patients (Ardouin et al., 1999). However, certain specific tasks can be impaired by STN stimulation, in particular verbal fluency (Pillon et al., 2000). This phenomenon has recently been studied by PET. The authors found that STN stimulation reduces activation in a frontotemporal network (inferior frontal, temporal cortex, and insula) involved in the verbal fluency task (Schroeder et al., 2003). In addition, during a Stroop task, STN stimulation reduces activation of the anterior cingulate (Schroeder et al., 2002). These results demonstrate that although STN stimulation does not impair overall cognitive performance in Parkinson's disease, subtle changes may occur, associated with modifications of cerebral activation.

Metabolism studies in Parkinson's disease: [¹⁸F]-deoxy-glucose

Most of the PET [¹⁸F]-deoxy-glucose (FDG) studies have revealed normal striatal metabolism in PD, which differentiates PD from other parkinsonian syndromes, such as progressive supranuclear palsy (PSP) or multiple system atrophy (MSA) (Antonini et al., 1997; Eidelberg et al., 1993). However, by analyzing regional metabolic covariance patterns, metabolic abnormalities have been found in a specific network in PD. Hypometabolism has been found in the lateral and mesial premotor cortex and thalamic metabolism is normal or increased (Antonini et al., 1998; Eidelberg et al., 1990). With a voxel-based analysis, Lozza et al. (2002) recently observed pallidal and putaminal hypermetabolism in PD that was correlated with the degree of bradykinesia, which, at least for the pallidum, is in keeping with the hyperactivity of the internal pallidum predicted by the classical pathophysiological model of PD. In advanced PD patients with cognitive decline, a reduction of temporoparietal metabolism is noted, which is comparable to what found in Alzheimer's disease (Frackowiak et al., 1981; Kuhl et al., 1984). However, this is not specific for cognitive deficit, as such hypometabolism has also been observed in nondemented PD patients (Hu et al., 2000; Mentis et al., 2002). Depression correlates with low anterior cingulate and orbitofrontal cortex metabolism, which suggests that the metabolic abnormalities of mood and cognitive disorders are different (Mentis et al., 2002). The effect of dopaminergic medications has been recently assessed (Berding et al., 2001). In both on and off states, hypometabolism is found in the caudate nucleus, frontal, parietal, and temporal cortices. In addition, in the on state, orbitofrontal and thalamic hypometabolism is more pronounced than in the off state. The authors interpreted this levodopa-induced hypometabolism by the deleterious effect it has on learning procedures (Gotham et al., 1988). All the studies indicate that the results of FDG PET studies have to be interpreted cautiously since the clinical differential diagnosis between PD and other parkinsonian syndromes is difficult and the presence or absence of cognitive decline is an important differentiating feature.

The consequences of surgical procedures on brain metabolism in PD have also been assessed. Pallidal stimulation increases cortical and reduces thalamic and lenticular nucleus metabolism and thus normalizes the metabolic abnormalities previously described (Fukuda et al., 2001b). After unilateral subthalamotomy, an

ipsilateral reduction of the internal pallidal, substantia nigra pars reticulata, and thalamus metabolism is found (Su et al., 2001). Finally, both subthalamic nucleus stimulation and levodopa reduce hypermetabolism in the lenticular nucleus and improve metabolism in the associative prefrontal cortex (Hilker et al., 2002b).

Contributions of other ligands and radiotracers to the understanding of the pathophysiology of PD

More recent radiotracers allow newer insights into understanding the in vivo pathophysiology of PD, in particular, the causes of neuronal death, nondopaminergic lesions, and the basis of motor complications.

Opioid transmission and PD: [¹¹C]-diprenorphine

[¹¹C]-Diprenorphine binds to opioid receptors (enkephalin and dynorphine). In patients with dyskinesia, ligand uptake is reduced in the striatum, thalamus, and anterior cingulate and is increased in the prefrontal cortex. Conversely, uptake is normal in nondyskinetic patients (Piccini et al., 1997b). These results are in accordance with the increased level of pre-proenkephalin B expression in striatal neurons projecting to the GPi via the direct pathway in parkinsonian macaques and patients with dyskinesias (Henry et al., 2003). Indeed, the reduction of [¹¹C]-diprenorphine binding in dyskinetic patients may be due to increased endogenous opioid transmission that competes with ligand uptake in the direct pathway. As the direct striato-internal pallidum pathway uses opioids as a cotransmitter with GABA, the increase in endogenous opioid release implies increased inhibition of the GPi, which consequently will increase thalamocortical output and may then lead to dyskinesias.

Inflammation and PD: [¹¹C]-PK-11195

This ligand binds to peripheral benzodiazepine receptors, which are expressed in activated microglia and allows the study of microglial activation implicated in the pathophysiology of PD (Benavides et al., 1988; Wullner and Klockgether, 2003). In PD, the uptake of [¹¹C]-PK-11195 is increased in the substantia nigra and pallidum, but not in the striatum (Banati et al., 2000). In multiple system atrophy, an additional increase of uptake is found in the prefrontal cortex and putamen (Gerhard et al., 2003). In both cases, the results support a role for inflammation in the degeneration of dopaminergic neurons.

Serotonergic function and PD: [¹¹C]-WAY-100635 and [¹¹C]-McGN5652

[¹¹C]-WAY-100635 is a serotonergic radiotracer. Uptake is reduced in the raphe in PD patients with and without depression, while the uptake is reduced in the cortex only in depressed patients (Doder et al., 2000). The role of serotonergic lesions in the depression of PD is important. The reduction of radiotracer uptake in the raphe is correlated with tremor severity, which supports the idea that the pathophysiology of tremor is not purely dopaminergic as already suggested by other authors (Doder et al., 2003; Vingerhoets et al., 1997). [¹¹C]-McN5652 is a radiotracer that binds to serotonin transporters and has been combined with a dopamine transporter radiotracer, [¹¹C]-WIN35428. This study showed reduced striatal binding of both radiotracers, which correlated with stage of the disease (Kerenyi et al., 2003). However, the topography of the abnormalities was different for both radiotracers. The reduction of serotonin ligand binding predominated in the caudate nucleus and was not related to the severity of clinical signs.

Cholinergic function and PD: [¹¹C]-PMP and [¹²³I]-IBVM

Cholinergic lesions are found in the forebrain in PD associated with dementia (Whitehouse et al., 1983). Functional imaging studies also demonstrated cholinergic deficits in PD patients. PD patients without dementia have reduced binding in the parietal and occipital cortex as shown by SPECT and [¹²³I]-IBVM, an acetylcholine transporter radiotracer. On the other hand, PD patients with dementia show a global reduction of cortical binding indicating extensive lesions similar to those in Alzheimer's disease (Kuhl et al., 1996). Cortical acetylcholinesterase activity is reduced in PD patients with and without dementia compared to controls (Bohnen et al., 2003). Furthermore, acetylcholinesterase activity was lower in PD with and without dementia compared to Alzheimer disease patients except in the temporal cortex (Bohnen et al., 2003). These results suggest that as for Lewy body dementia, inhibitors of acetylcholinesterase should be effective in treating cognitive decline and associated behavioral disorders.

Differential diagnosis between PD and other parkinsonian syndromes

In contrast to Parkinson's disease, the clinical diagnosis of parkinsonian syndromes is often difficult at onset but becomes easier after several years. Thus, functional imaging could be useful in differentiating different types of parkinsonism in the early stages.

Multiple system atrophy

In striatonigral degeneration FDG PET shows a marked hypometabolism of 64% in the caudate nucleus and 54% in the putamen compared to normal subjects (De Volder et al., 1989). In addition, hypometabolism is also noted in the frontal cortex and the cerebellum. Striatal hypometabolism clearly distinguishes idiopathic PD from MSA (Eidelberg et al., 1993). In olivopontocerebellar atrophy, a reduction of metabolism in the vermis and cerebellar hemispheres is found that fits well with the characteristic presentation with cerebellar signs (Rosenthal et al., 1988). Dopaminergic presynaptic radiotracers such as [¹⁸F]-Dopa or [¹²³I]-β-CIT are not reliable in the differential diagnosis of idiopathic PD and MSA although the reduction of uptake is usually more homogeneous without relative sparing of the caudate nucleus in MSA (Antonini et al., 1997; Brooks et al., 1990a,b; Brucke et al., 1997). In addition, the progression of dopaminergic lesions in PD assessed by [¹²³I]-β-CIT appears faster than in atypical parkinsonism (Pirker et al., 2002). The study of dopaminergic receptor expression differentiates MSA from PD more readily. In MSA, in contrast to untreated PD, a significant reduction of the striatal binding of [¹¹C]-Raclopride is noted, which suggests a degeneration of D2 receptors (Antonini et al., 1997; Brooks et al., 1992). However, as previously mentioned, [¹¹C]-Raclopride binding is reduced in idiopathic PD patients taking dopaminergic drugs, indicating that in late PD, some overlaps exist between MSA and PD, making a reliable differential diagnosis difficult. Similar results have been obtained with IBZM, which showed a normal binding to dopamine D2 receptors in idiopathic PD but a reduced binding in MSA (Schulz et al., 1994). However, as previously mentioned, dopamine agonists can reduce IBZM uptake in PD (Schwarz et al., 1996). Thus, a withdrawal of the agonists for

several weeks is requested to reliably differentiate idiopathic PD from MSA using IBZM (Schwarz et al., 1996). In addition, a similar reduction has been found with the D1 receptor ligand [¹¹C]-SCH-23390 (Shinotoh et al., 1993).

Progressive supranuclear palsy

Studies using PET and [¹⁸F]-FDG or the oxygen 15 method show reduced metabolism in the frontal cortex and striatum in PSP, but this pattern does not clearly differentiate it from MSA (Blin et al., 1990; D'Antona et al., 1985; De Volder et al., 1989; Foster et al., 1988; Goffinet et al., 1989). In the presynaptic dopaminergic system, several PET studies have shown a major reduction of striatal [¹⁸F]-Dopa and [¹¹C]-WIN35428, a dopamine transporter ligand, that is identical in caudate and putamen (Brooks et al., 1990a; Broussolle et al., 1999; Ilgin et al., 1999; Leenders et al., 1988). This homogeneous reduction may constitute a good criterion for separating PD from PSP because there is less overlap between PD and PSP than between PD and MSA though the matter is still debated (Brooks, 1998; Brucke et al., 1997; Burn et al., 1994). PET or SPECT using ligands of dopaminergic D2 receptors consistently show reduction of striatal binding, which is consistent with the reduction of receptor expression found post-mortem in PSP (Baron et al., 1986; Bokobza et al., 1984; Brooks et al., 1992; Van Royen et al., 1993). This dopaminergic post-synaptic degeneration may be a good way of separating idiopathic PD from PSP. But in late-stage idiopathic PD patients on dopa agonist drugs, [¹¹C]-Raclopride binding is also reduced making it difficult to differentiate PSP and treated PD (Brooks et al., 1992; Dentresangle et al., 1999; Rinne et al., 1993; Turjanski et al., 1997). IBZM also shows a reduction of D2 receptors density in PSP (Schwarz et al., 1993). However, with IBZM, dopamine agonists have to be stopped to correctly differentiate PD from PSP (Schwarz et al., 1996). In addition, it remains impossible to distinguish MSA from PSP using radiotracers, which limits their use in clinical practice (Brooks et al., 1992; Schwarz et al., 1993). Finally, radiotracers of cholinergic transmission may be useful in distinguishing PD from PSP. Indeed, cortical cholinergic innervation seems to be more impaired in PD compared to PSP, whereas thalamic cholinergic innervation is only reduced in PSP (Shinotoh et al., 1999).

Corticobasal degeneration

In corticobasal degeneration, FDG PET studies show asymmetrical hypometabolism in the striatum, thalamus, and parietal cortex, which predominates in the hemisphere contralateral to the most affected hemibody (Blin et al., 1992; Eidelberg et al., 1991; Sawle et al., 1991a). Striatal [¹⁸F]-Dopa uptake is also markedly and asymmetrically reduced and affects the putamen and the caudate nucleus to the same extent (Sawle et al., 1991a). However, this asymmetrical reduction of [¹⁸F]-Dopa uptake is also found in idiopathic PD and thus is not useful for differentiating PD from corticobasal degeneration (CBD). In addition, at disease onset, [¹⁸F]-Dopa uptake may be within normal limits in CBD and PD (Laureys et al., 1999).

Dopa-responsive dystonia

The differential diagnosis between Dopa-responsive dystonia (DRD) and juvenile forms of PD, in particular, related to muta-

tions of the parkin gene, may sometimes be difficult from a clinical point of view. In this case, functional imaging is very useful, showing in DRD a normal or only slightly reduced striatal [¹⁸F]-Dopa uptake (Sawle et al., 1991b; Snow et al., 1993b). Recently, an increase in striatal [¹¹C]-Dihydrotetraabenazine binding has been found in DRD, which may reflect the decrease of intravesicular concentration of dopamine and/or an increase in neuronal firing (de la Fuente Fernandez et al., 2003). Evidence for increased dopamine turnover has been found by measuring variations of [¹¹C]-Raclopride binding after levodopa challenge (de la Fuente Fernandez et al., 2003).

Iatrogenic or toxic parkinsonian syndromes

In this section, we will discuss only the parkinsonian syndromes secondary to neuroleptic intake or to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication.

Post-MPTP parkinsonism

In clinically asymptomatic subjects who ingested MPTP, PET and [¹⁸F]-Dopa demonstrated a reduction of radiotracer uptake indicating a dopaminergic degeneration (Calne et al., 1985). Ten years after intoxication, clinically evident parkinsonian signs were manifested in 50% of initially asymptomatic patients and striatal [¹⁸F]-Dopa uptake was reduced in all patients (Vingerhoets et al., 1994b). This result demonstrates that after a toxic insult, the degeneration of dopaminergic neurons may progress. However, the topography of such lesions is different from that in idiopathic PD, with a symmetrical reduction of [¹⁸F]-Dopa uptake without an anteroposterior gradient (Snow et al., 2000).

Post-neuroleptics parkinsonism

This represents the most frequent drug-induced parkinsonian syndrome and is sometimes a difficult issue in clinical practice. This is notably the case in previously treated elderly patients who had received neuroleptics and then developed a parkinsonian syndrome indistinguishable from idiopathic PD. In this situation, PET or SPECT using dopamine transporter radiotracers or [¹⁸F]-Dopa usefully differentiate the two disorders. In the case of post-neuroleptic parkinsonism, the presynaptic dopaminergic system is intact, in contrast to PD (Burn and Brooks, 1993). In addition, in cases of persistent neuroleptic intake, the study of dopamine receptors shows a competitive reduction of D2 dopamine receptor ligand binding (Farde et al., 1992).

Conclusion

Functional imaging techniques have provided major insights and a better understanding of PD. The interpretation of the data has, of course, to take into account multiple factors such as compensatory mechanisms or effects of the medications themselves, which can modify the results. Nevertheless, they allow early diagnoses of dopaminergic degeneration and are useful to separate PD from others parkinsonian syndromes or differential diagnoses like essential tremor. They also can be used to monitor the natural progression of the disease and the effect of putative neuroprotective treatments on this progression. In the future, the availability of neuroprotective agents will reinforce the interest for early diagnosis in PD.

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