PET and movement disorders

DAVID J BROOKS, RICHARD SJ FRACKOWIAK

From the MRC Cyclotron Unit, Hammersmith Hospital and Institute of Neurology, National Hospital for Nervous Diseases, London, UK

SUMMARY In this paper the use of PET for determining the patterns of disruption of both regional cerebral metabolism, and the pre- and post-synaptic dopaminergic systems, associated with movement disorders is reviewed. That the various akinetic-rigid syndromes result in distinctive PET findings is shown, making functional imaging valuable in their differential diagnosis. PET may also be useful for detecting the presence of sub-clinical disease in Huntington’s disease and other inherited movement disorders.

Positron emission tomography (PET) provides a non-invasive means of quantitatively measuring regional cerebral energy metabolism and blood flow, and of assessing the integrity of a number of neurotransmitter systems in patients. As such it is ideally suited for the study of the effects of cerebral diseases associated with movement disorders on regional cerebral function. We have been involved in PET studies on patients with movement disorders through collaboration with Professor CD Marsden and his clinical colleagues, initially at The Maudsley Hospital and Institute of Psychiatry, and more recently at the Institute of Neurology and National Hospitals. In this paper we intend to review the various patterns of regional cerebral metabolic changes associated with akinetic rigid syndromes and the dystonias. We will also discuss disturbances of the integrity of the dopaminergic system that have been detected with PET tracers in movement disorders. Finally, we will consider the future use of PET to study disturbances in the normal patterns of regional cerebral activation in diseases presenting with disorders of movement.

In order to make measurements with PET a tracer tagged with a positron-emitting isotope is administered to a subject either intravenously, or by inhalation. The subject is then scanned, and axial tomographic slices of regional cerebral tracer accumulation are obtained. This tracer accumulation can be related to cerebral metabolism, blood flow, or binding site concentrations by appropriate mathematical models. Positron-emitting isotopes include $^1$O, $^{15}$C, $^{18}$F, and $^{39}$Br. These are short lived and prepared on-site by a cyclotron. Molecules suitable for use as a PET tracer can then be labelled with these isotopes. Table 1 details some PET tracers commonly used in the study of movement disorders.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half Life</th>
<th>Tracer</th>
<th>Biological Application*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{15}$O</td>
<td>2.03 mins</td>
<td>$^1$O, $^{15}$O</td>
<td>Blood Flow</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.4 mins</td>
<td>$^{11}$C-SCH-23390</td>
<td>Oxygen utilisation</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.4 mins</td>
<td>$^{11}$C-methylpiperone</td>
<td>D receptors</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.4 mins</td>
<td>$^{11}$C-raclopride</td>
<td>D receptors</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.4 mins</td>
<td>$^{11}$C-nomifensine</td>
<td>D receptors</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.4 mins</td>
<td>$^{11}$C-deprenyl</td>
<td>D uptake sites</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-2-fluoro-deoxyglucose (FDG)</td>
<td>Glucose utilisation</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-6-Dopa</td>
<td>Dopamine storage</td>
</tr>
<tr>
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<td>110 mins</td>
<td>$^{18}$F-fluoromethylpiperone</td>
<td>D receptors</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-fluorospiperone</td>
<td>D receptors</td>
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<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-diprenorphine</td>
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<tr>
<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-methylspiperone</td>
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<td>110 mins</td>
<td>$^{18}$F-raclopride</td>
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<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-nomifensine</td>
<td></td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-rotenone</td>
<td></td>
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<tr>
<td>$^{18}$F</td>
<td>110 mins</td>
<td>$^{18}$F-spiroperidol</td>
<td></td>
</tr>
<tr>
<td>$^{39}$Br</td>
<td>16 hours</td>
<td>$^{39}$Br-bromospiperone</td>
<td></td>
</tr>
</tbody>
</table>

*D = Dopamine. MAO = Monoamine oxidase.

To data, the PET studies performed on patients with a movement disorder have fallen into two main categories: First, under resting conditions, the changes in regional cerebral metabolism and blood flow associated with Parkinson’s disease, progressive supranuclear palsy, multiple system atrophy, Huntington’s chorea, dystonia, and Wilson’s disease have been reported. These changes make it possible, to a major extent, to distinguish between these various diseases and to detect sub-clinically affected patients with Huntington’s disease. Secondly, PET has been used to assess the integrity of the pre-and post-synaptic components of the dopaminergic system in the above movement disorders. These disrupt the nigrostriatal and efferent striatal pathways in different ways, and so produce varying patterns of dysfunction of the dopaminergic system. The findings of these various PET studies are reviewed below.
PET and movement disorders

Regional cerebral metabolic changes in movement disorders

(a) Parkinson’s disease

The pathology of Parkinson’s disease is Lewy body associated degeneration of the substantia nigra compacta and other pigmented brain stem nuclei. The majority of Parkinson’s disease patients have normal intellectual function, but those 20% that have dementia may show degeneration of the nucleus basalis of Meynert (NBM), Alzheimer-like changes, or cortical Lewy body disease at necropsy. There have been a number of PET studies on regional cerebral metabolism and blood flow in Parkinson’s disease. Using 18FDG, it has been shown that in clinically bilateral Parkinson’s disease, striatal glucose utilisation is generally normal.1,2 Cortical glucose utilisation, however, tends to be globally reduced and may show an Alzheimer-type pattern of disruption, with the posterior parietal cortex being most affected.2 Rougemont et al3 showed that in spite of a good clinical response to levodopa, Parkinson’s disease patients did not show a significant change in their striatal or cortical glucose utilisation following therapy. This lack of change in striatal glucose utilisation after levodopa is not surprising.18FDG uptake primarily reflects activity of synaptic terminals. As dopaminergic terminals make up only 10% of striatal neurons, even a 50% increase in dopaminergic function will only result in a 5% increase in striatal energy utilisation. Such a change in striatal glucose utilisation would be difficult to detect with PET.

In animals, lesioning the nigra results in a transient rise in pallidal glucose utilisation which persists for about three months.4 This is thought to reflect increased activity in strio-pallidal efferents as a result of release from the inhibitory effects of the nigrostriatal system. Miletich et al5 have shown that in patients with hemiparkinsonism, early into their disease, utilisation of glucose is raised in the contralateral lenticular nucleus, presumably as a consequence of similar strio-pallidal disinhibition.

Wolfson et al6 have studied regional cerebral oxygen utilisation (rCMRO2) and blood flow (rCBF) in patients unilaterally and bilaterally affected by Parkinson’s disease. In the bilaterally affected subjects both mean striatal and cortical oxygen utilisation were depressed by 7–10%, while rCBF was depressed by 20%. The Alzheimer-like pattern of posterior parietal metabolic dysfunction in Parkinson’s disease noted by Kuhl et al,7 was not seen by Wolfson et al, who found a global depression of cortical function. Such global depression would be more likely to result from loss of function of the nucleus basalis of Meynert, with its diffuse cortical projections, than from Alzheimer’s disease. By contrast, unilaterally affected Parkinson’s disease patients, with early disease, showed a mean increase of 12% in contralateral basal ganglia oxygen utilisation. This finding is reminiscent of the increased contralateral striatal rCMRGlut reported by Miletich et al8 in his hemiparkinsonian group, and again suggestive of the initial presence of strio-pallidal disinhibition in Parkinson’s disease. Interestingly contralateral frontal cortical rCMRO2, and rCBF were focally depressed in Wolfson’s patients with unilateral disease suggesting that selective disruption of the mesofrontal projection fibres had also occurred. Perlmutter et al9 reported a similar depression of contralateral mesofrontal cortex rCBF in the group of eleven patients with hemiparkinsonism.

As with regional cerebral glucose utilisation,3 levodopa therapy appeared to have little effect on cerebral oxygen utilisation in Parkinson’s disease in spite of a good clinical response to treatment.5 There is debate, however, about the effects of levodopa therapy on rCBF. Perlmutter and Raichle10 found no change in mean rCBF after treatment, whereas Leenders et al,8 using higher doses of medication, have reported global increases in rCBF within one hour of receiving oral levodopa. Subsequently rCBF fell to normal after several weeks of therapy, however, in spite of a continued clinical response to levodopa. This finding, and the observation that the levodopa induced rCBF increases could be blocked by prior administration of domperidone, a peripheral dopamine receptor blocker, suggests that the blood flow increases following levodopa administration are the result of a peripheral action of levodopa on cerebral vasculature.

To summarise, the metabolism of the basal ganglia is normal, or slightly depressed, in patients with bilateral Parkinson’s disease, while contra-lateral basal ganglia metabolism may be increased in unilaterally affected patients with early disease. Cortical function is globally depressed, the medial frontal and posterior parietal areas being particularly affected. Levodopa therapy has no significant effect on cortical or striatal metabolism at clinically effective doses.

(b) Huntington’s disease (HD)

The pathology of HD consists of fall-out of spiny neurones from the striatum, pallidum, and dentate nuclei. Patients present with chorea, an akinetic-rigid syndrome, and a so-called subcortical dementia where memory and concentration are impaired in the absence of significant apraxia or agnosia. CT brain scans are normal in early disease, but later show atrophy of the heads of the caudate nuclei and frontal cortex.

Several PET studies of regional cerebral glucose utilisation in patients with HD have been reported. Kuhl et al7 first demonstrated reduced caudate rCMRGlut in early HD in the absence of caudate atrophy on CT. Their subjects who were not demented had normal cortical glucose utilisation, but those with...
metabolism subjects be concluded, HD be low, elevated striatal system in three " at risk " of HD with chorea raises hypometabolism, even in the absence of chorea. Since hypometabolism correlates with degree of locomotor dysfunction. Among subjects " at risk " of HD there is a 38%–91% concordance between demonstration of an abnormal PET scan and the identification of subjects carrying the HD gene using DNA polymorphism studies.

(c) Progressive supranuclear palsy (PSP)
PSP, or Steele-Richardson-Olszewski (SRO) syndrome, is characterised clinically by axial rigidity, a supranuclear vertical gaze palsy, striatal bulbar dysfunction, and " sub-cortical " dementia. Pathologically, neuronal fall-out and neurofibrillary tangles with straight filaments are found in the bas ganglia, cerebellum, and brain-stem nuclei. The cerebral cortex appears to be spared. PSP can be very difficult to diagnose with certainty on clinical grounds alone as a variety of other conditions such as multiple system atrophy, Creutzfeld-Jakob disease, encephalitis lethargica, sub-cortical gliosis, cortical degeneration, and multi-infarct disease, can all produce akinetic-rigid syndromes with supranuclear gaze palsy. " Sub-cortical " dementias can also be mimicked by early Pick's and Alzheimer's disease, and isolated thalamic and caudate lesions. As a consequence most PET studies on PSP await pathological validation.

D'Antona et al. compared the regional cerebral glucose utilisation of six PSP subjects with that of eight controls. The PSP subjects showed a significant reduction of mean frontal cortical metabolism, with lesser reductions of rCMRGLu in other cortical areas. Two of their six subjects, however, did not clearly have PSP as these patients had only mild akinetic-rigid syndromes and isolated restricted up-gaze in association with their dementia of subcortical type. This illustrates the difficulty in making a clinical diagnosis of PSP. Leenders et al. measured regional cerebral blood flow and oxygen utilisation in five patients with probable PSP. The CBF images of one of their patients are shown in Fig 1. Like D'Antona et al., these workers found a global decrease in cortical metabolism, the frontal cortex being most severely affected. The degree of frontal cortical hypometabolism correlated with disease duration, but not with individual patient's WAIS scores.

Foster et al. used PET to study 14 subjects probably affected by PSP. Glucose utilisation was significantly reduced in the striatum, thalamus, and pons, and in all cortical regions, but particularly the frontal region. Cerebellar function was spared. Clin-
Fig 1  Regional cerebral blood flow in a progressive supranuclear palsy patient and a normal control. There is a global reduction of rCBF in the PSP subject.

There are few reports of the use of PET in patients with MSA. Rosenthal et al studied regional cerebral glucose utilisation in thirty patients with pontocerebellar (OPCA) degeneration. Their subjects had primarily cerebellar degeneration, a minority having evidence of pyramidal dysfunction. Out of thirty, fourteen had a familial disorder. These authors found that locomotor dysfunction correlated better with levels of cerebellar and brainstem hypometabolism, than with the degree of atrophy on CT scan. Preliminary data on six subjects with MSA and a akinetic rigid syndrome have not shown a clear correlation between striatal hypometabolism and locomotor dysfunction.

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(d) Multiple system atrophy (MSA)
This condition may present as an akinetic rigid syndrome, poorly responsive to levodopa, autonomic failure, and pontocerebellar dysfunction, and is often known as Shy-Drager syndrome (SDS). Pathologically neuronal fall-out and gliosis are found in the basal ganglia, brain-stem and cerebellar nuclei, and the intermediolateral columns of the spinal cord. Anterior horn cell disease and an axonal neuropathy may also be present. MSA is not associated with Lewy body or neurofibrillary tangle formation. Unlike PSP patients intellect is preserved in MSA cases. It remains unclear if the akinetic-rigid and pontocerebellar (OPCA) variants of MSA are part of a spectrum, or if they represent separate conditions.

(e) Wilson’s disease (WD)
This recessively-inherited condition is thought to arise from impaired biliary excretion of copper. As a consequence copper is deposited in cerebral grey matter, particularly the striatum, and results in cystic degeneration. CT brain scans generally show cortical atrophy, a minority revealing additional low attenuation lesions in the basal ganglia. PET scans, however, consistently reveal reduced glucose utilisation in the striatum, the putamen being worst affected.

rCMR-Glu is also globally depressed in the cortex, fronto-
parietal regions being most impaired. Studies on the
effect of treatment on PET cerebral measures of
function have not yet been reported, although striatal
CT lesions are known to be reversible on occasion.23

(f) **Dystonia**
Stoessl et al22 measured rCMRGlut in sixteen patients
with idiopathic torticollis. Eleven of their subjects had
pure torticollis, and four had additional tremor or
writer's cramp. No consistent regions of altered
cerebral metabolism were identified. Two other sub-
sequent studies have reported both normal and
increased contralateral striatal glucose metabolism in
idiopathic focal dystonia.22,51 Perlmutter and Raichle26
have reported a case of post-traumatic paroxysmal
hemidystonia whose attacks lasted a few seconds, and
occurred every few minutes. CT scan findings were
normal, but oxygen utilisation was reduced and blood
flow was elevated in the striatum contralateral to the
affected limbs. Such a pattern suggests that preferen-
tial aerobic glycolysis was occurring in the affected
striatum; this has been reported in foci of epilepsy
partialis continua (EPC).52 Interestingly this patient’s
paroxysmal dystonia, like EPC, responded to pheno-
ytoin treatment.
In a further study these authors measured rCBF
under resting conditions in seven hemidystonic
patients.50 Three subjects had paroxysmal dystonia
(two post-traumatic and one familial), while four had
idiopathic dystonia. Five out of seven of these patients
showed no resting rCBF abnormalities, but two had
raised rCBF in the putamen contralateral to their
affected limbs. These preliminary studies are
encouraging, as they suggest PET is capable of
detecting functional abnormalities in some dystonias
in the absence of an obvious structural lesion on CT.

(g) **Summary**
The patterns of regional cerebral metabolic dysfunc-
tion associated with various movement disorders are
summarised in table 2.

**Regional neuropharmacological changes in movement
disorders**

(a) **Parkinson’s disease** (PD)
18F-6-fluorodopa (F-dopa), when given intravenously,
is transported across the blood-brain barrier by the
neutral aminoacid carrier and stored as F-dopamine
and its metabolites in the terminals of nigro-striatal
neurones.28 As a consequence, striatal 18F activity
following F-dopa administration provides a measure
of striatal dopamine storage capacity. Garnett et al,29
and Nahmias et al,30 published the first PET reports on
striatal 18F-dopa administration. Their subjects had
hemiparkinsonism, and were young with early disease.

PET showed normal 18F uptake in the caudate, but
bilaterally reduced uptake in the putamen, the uptake
contralateral to the affected limbs being the more
depressed. Such a finding indicates that in patients
with hemiparkinsonism there is invariably subclinical
involvement of the ipsilateral striatum. It also sug-
gests that putamen, rather than caudate, is the site of the
dysfunction that is responsible for the locomotor
problems of Parkinsonian patients. Reduced 18F
uptake in contralateral putamen was found whether
the subjects had primarily tremor or rigidity of their
affected limbs, suggesting that both tremor and
rigidity can arise from putaminal dysfunction.

Leenders et al31 studied F-dopa uptake in two
patients with Parkinsonian patients with bilateral
disease, one group with early disease and a sustained
response to levodopa, and a second severely affected
group with on-off fluctuations. All the Parkinson’s disease
patients showed reduced striatal 18F uptake compared to
controls, though the controls were significantly
younger. On-off patients had lowest levels of striatal
18F uptake. Interestingly, while normal subjects con-
tinuously accumulated striatal 18F activity over the
three hours following F-dopa administration, the
Parkinson’s disease patients showed a plateauing of
tracer uptake. This finding suggests that although the
transport of 18F-dopa into the striatum of Parkinson’s
disease patients remains normal, the ability of the
striatum to store 18F-dopamine is impaired. In a
second publication, the same authors compared the
degree of locomotor dysfunction with the accumula-
tion of 18F in the striatum in their Parkinson’s disease
patients.32 Parkinsonian rigidity correlated with a
decline in striatal 18F-dopa uptake, but surprisingly
Leenders et al did not find a correlation between
striatal 18F-uptake and severity of tremor.

The S or (+) isomer of 1-C-nomifensine (1-C-NMF)
binds to sites of dopamine re-uptake on the nigro-
striatal nerve terminals in the caudate and putamen,
and to sites of noradrenaline re-uptake sites in the
ventral thalamus.33 Using a racemic mixture of 1-C-
NMF, Tedroff et al34 studied striatal tracer uptake in
six Parkinson’s disease patients and seven control
patients. Using a [11C]-labeled dopamine PET trac-
er, they were able to quantify the uptake of [11C]-
NMF in both striatal regions. They found normal
uptake in the caudate, whereas the uptake in the
putamen was reduced in their Parkinsonian patients.

They also found a relationship between the rate of
uptake of [11C]-NMF in the putamen and the severity
of their symptoms of Parkinson’s disease. This finding
suggests that the decreased uptake of 18F-dopa in the
putamen is a consequence of the loss of nigro-
striatal neurones.28

Table 2 **Changes in regional cerebral metabolism associated
with movement disorders**

<table>
<thead>
<tr>
<th>Region</th>
<th>Parkinson’s disease (uni)</th>
<th>Parkinson’s disease (bilat)</th>
<th>HD</th>
<th>PSP</th>
<th>MSA</th>
<th>WD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>CL or N</td>
<td>N or ↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Putamen</td>
<td>CL or N</td>
<td>N or ↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Thalamus</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>CL ↓</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

CL = contralateral. N = normal.
The three younger Parkinson’s disease subjects appeared to have reduced striatal $^{11}$C-NMF uptake compared to controls of a similar age, and the two primarily hemiparkinsonian subjects showed a greater reduction of $^{11}$C-NMF uptake in striatum contralateral to their affected limbs. However, the specific signal from racemic $^{11}$C-NMF was small, making discrimination between Parkinson’s disease patients and controls difficult. A recent study, using pure (+) $^{11}$C-NMF, has shown a significant fall in both caudate and putamen tracer uptake in Parkinson’s disease compared with age-matched controls.35 This finding is of interest as it implies that not only do Parkinsonian patients fail to store dopamine adequately in the striatum, but they also are unable to reaccumulate it normally after it is released. An inability to re-accumulate dopamine in the striatum may contribute to the development of the on-off phenomenon in Parkinson’s disease, as in this situation a sustained clinical response to levodopa will require a constant delivery of the drug to the striatum. Several studies have demonstrated that on-off responses to oral levodopa in Parkinson’s disease can be improved by the use of intravenous infusions of levodopa.

Post-synaptic striatal dopamine D$_2$ receptors can be imaged with PET tracers such as $^{11}$C-methylspiperone ($^{11}$C-MSP), $^{18}$F-flusperideone, and $^{76}$Br-bromospiperone ($^{76}$Br-BSP). Leenders et al first demonstrated a similar striatal distribution of $^{18}$F-dopa and $^{11}$C-MSP in a normal volunteer. They then studied striatal $^{11}$C-MSP uptake in four untreated and five treated PD patients.36 The untreated patients had similar striatal:cerebellar (s/c) ratios of tracer uptake to age-matched controls, suggesting normal levels of striatal D$_2$ receptors were present. The treated Parkinson’s disease subjects had reduced tracer s/c ratios, implying that levodopa therapy may have led to down-regulation of their striatal D$_2$ receptors. Rutgers et al studied striatal $^{11}$C-MSP uptake in thirteen hemiparkinsonian patients. They found that striatal tracer uptake was symmetrical suggesting that levels of D$_2$ receptors are preserved in Parkinson’s disease. Hagglund et al also reported normal striatal $^{11}$C-MSP binding in six Parkinsonian patients. Those patients who were primarily hemiparkinsonian again
Fig 3 Regional cerebral \( ^{11}C\)-nomifensine binding in a normal subject and a patient with multiple system atrophy (Shy Drager syndrome). High \( ^{11}C\) uptake is seen in the caudate, putamen, and thalamus of the normal subject. Impaired \( ^{11}C\) uptake is seen in the striatum of the MSA patient, but uptake is preserved in the thalamus.

showed no consistent asymmetry in striatal \( ^{11}C\)-MSP binding. From these studies it can be concluded that although nigro-striatal fibres are damaged in Parkinson's disease, post-synaptic D2 receptors are preserved, explaining the good response of Parkinson's disease patients to levodopa. Further studies are required to establish whether levodopa therapy truly leads to down-regulation of D2 receptors.

(b) MPTP-induced Parkinsonism

MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), when given intravenously, crosses the blood-brain barrier and is converted to MPP\(^+\) by monoamine oxidase B in glial tissue. MPP\(^+\) is then transported into dopaminergic neurons via the dopamine re-uptake mechanism where it results in neuronal death and levodopa responsive Parkinsonism. Hartvig et al.\(^{42}\) have studied the kinetics of distribution of \( ^{11}C\)-MPTP in primate brain. This tracer is rapidly taken up and retained in cortex, striatum, thalamus, and mid-brain. The MAO-A inhibitor, clorgyline, has no effect on \( ^{11}C\)-MPTP uptake but pargyline, a non-specific MAO-A and B inhibitor, induces rapid \( ^{11}C\)-MPTP washout. This suggests that uptake and conversion of MPTP to MPP\(^+\) occurs within minutes in glial tissue, and it is MPP\(^+\) and not MPTP that is retained by brain tissue. If MPTP to MPP\(^+\) conversion is blocked by pargyline, the \( ^{11}C\)-MPTP is rapidly washed out. Nomifensine, a dopamine re-uptake site blocker, has no immediate effect on \( ^{11}C\)-MPTP uptake kinetics. This implies that \( ^{11}C\) activity is initially trapped as glial rather than neuronal \( ^{11}C\)-MPP\(^+\), and that neuronal MPP\(^+\) accumulation via the dopamine re-uptake pathway is a far slower process.

Chiueh et al.\(^{45}\) very elegantly used MPTP treated monkeys to validate PET measurements of striatal \( ^{11}F\)-dopa uptake as a measure of striatal dopamine storage capacity. In vivo primate striatal \( ^{11}F\)-dopa uptake was reduced and paralleled postmortem striatal dopamine content, and correlated inversely with rigidity. MPTP exposed human subjects have also been shown to have reduced striatal \( ^{11}F\)-dopa uptake.\(^{43}\)

Perlmuter et al.,\(^{44}\) using PET and \( ^{11}F\)-fluspirerone, have reported up-regulation of striatal D2 receptors in an MPTP-exposed patient. This implies that in man, while MPTP attacks nigrostriatal dopaminergic neurons, it spares striatal efferents. Leenders et al.\(^{31}\)
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confirmed this by unilaterally lesioning a primate with MPTP. The affected striatum showed reduced uptake of \textsuperscript{11}C-nomifensine, a marker of dopamine re-uptake sites on nigrostriatal terminals, but showed raised \textsuperscript{11}C-raclopride binding, a marker of post-synaptic D\textsubscript{2} receptor integrity.

(c) Progressive supranuclear palsy (PSP)

Both pre- and post-synaptic dopaminergic systems have been investigated with PET in this poorly levodopa responsive akinetic rigid syndrome. Striatal \textsuperscript{18}F-dopa uptake in PSP subjects is diminished to the same degree as in levodopa-responsive Parkinson's disease,\textsuperscript{19} and correlates with the degree of frontal cortical hypometabolism present in these patients. Contrary to the findings in Parkinson's disease, levels of striatal D\textsubscript{2} receptors appear to be diminished in PSP. Baron et al\textsuperscript{45} compared striatal \textsuperscript{3}Br-bromospiperone (BSP) binding in seven PSP patients and seven age-matched control subjects. BSP is a D\textsubscript{2} receptor marker, and striato-cerebellar ratios of the uptake of this tracer at 4 hours were significantly depressed in PSP subjects. Such a finding would in part explain the lack of response of PSP subjects to levodopa.

(d) Multiple system atrophy (MSA)

These patients are poorly responsive to levodopa. The integrity of the presynaptic dopaminergic system in MSA patients has been studied with PET.\textsuperscript{35,46} Figure 2 shows PET images of striated \textsuperscript{18}F-dopa uptake in a normal subject and a patient with multiple system atrophy. Both Parkinson's disease and MSA patients show impairment of striatal uptake of \textsuperscript{18}F activity following \textsuperscript{18}F-dopa administration. Putamen function is equally severely affected in both these conditions, but unlike Parkinson's disease, where caudate function is relatively spared,\textsuperscript{29,30} 50% of MSA subjects show equally impaired caudate and putamen \textsuperscript{18}F-dopa uptake.\textsuperscript{39} The involvement of caudate in MSA, and relative sparing of caudate in Parkinson's disease, is likely to reflect the different pathologies of these two conditions. In MSA striatal degeneration occurs, while in Parkinson's disease the substantia nigra compacta is primarily involved. Although both caudate and putamen are severely affected in MSA, it is putamen rather than caudate dysfunction that correlates with locomotor disability in MSA patients.\textsuperscript{35,46} Such a finding is in line with current theories of basal ganglia function.\textsuperscript{49} The putamen receives direct input from the supplementary motor cortex, while the caudate receives input from frontal association areas. As such the caudate is less likely to play a direct role in motor control.

Figure 3 shows PET images of (+)—\textsuperscript{11}C—nomifensine uptake in a normal subject and a MSA patient. Striatal \textsuperscript{11}C-nomifensine binding is diminished in MSA\textsuperscript{35,46} suggesting that fall-out of dopamine re-uptake sites occurs in parallel with diminished striatal dopamine storage capacity. Such a finding may simply reflect a loss of nigro-striatal nerve terminals. To date no data on post-synaptic dopamine D\textsubscript{2} receptor status in MSA have been reported. In view of the poor levodopa responsiveness of these patients, and the presence of striatal degeneration at post-mortem, one would expect a low density of striatal D\textsubscript{2} sites to be present.

(e) Huntington's disease (HD)

Leenders et al\textsuperscript{12} studied the integrity of the pre- and post-synaptic dopaminergic system in one case of early Huntington’s disease. Their subject had normal striatal \textsuperscript{18}F-dopa uptake, implying an intact nigro-striatal pathway was present, but reduced striatal \textsuperscript{11}C-methylspiperone binding, suggesting a reduced density of post-synaptic D\textsubscript{2} dopamine receptors had resulted. These findings would fit in with the known pathology of HD where fall-out of spiny striatal neurones is seen, but the nigro-striatal pathway is spared. Hagglund et al\textsuperscript{40} have examined striatal \textsuperscript{11}C-MSP binding in a case of HD. These authors also found reduced \textsuperscript{11}C-MSP striatal uptake in their patient.

(f) Dystonia

This is a highly heterogeneous condition and may result from lesions in the striatum, pallidum, ventral thalamus, and mid-brain. In idiopathic torsion dystonia, which is frequently familial, it is common to find no abnormalities either at post-mortem, or on structural imaging. Leenders et al\textsuperscript{48} have PET scanned a series of six dystonic patients. Three had idiopathic hemidystonia, one acquired hemidystonia, and two had torticollis. The four hemidystonic subjects showed impaired contralateral striatal \textsuperscript{18}F-Dopa uptake, and the two subjects with torticollis had bilaterally impaired striatal \textsuperscript{18}F-dopa uptake. The hemidystonic patients were not typical of idiopathic torsion dystonia, however, in that all subjects had extrapyramidal rigidity between dystonic spasms. Further studies are required to determine if functional lesions of the nigro-striatal pathway are a consistent finding in idiopathic torsion dystonia.

(g) Summary

The patterns of striatal dysfunction of the dopaminergic system associated with various movement disorders are summarised in table 3.

The future of PET in movement disorders

This paper has reviewed the potential of PET for identifying the varying patterns of disruption of
on movement disorders have concerned the dopaminergic system. With the current availability of PET markers of the opiate and serotoninergic systems, and in the future glutamatergic and peptidergic markers, our understanding of the neuropharmacological changes associated with movement disorders is likely to expand rapidly.

References


PET and movement disorders


