Published in final edited form as:

Ann N Y Acad Sci. 2011 June ; 1228: 93–108. doi:10.1111/j.1749-6632.2011.06025.x.

PET/CT in diagnosis of movement disorders

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Abstract

Molecular imaging with PET offers a broad variety of tools supporting the diagnosis of movement disorders. The more widely applied PET imaging techniques have focused on the assessment of neurotransmitter systems, predominantly the pre- and postsynaptic dopaminergic system. Additionally, PET imaging with [¹⁸F] fluorodeoxyglucose has been extensively used to assess local synaptic activity in the resting state and to highlight local changes in brain metabolism accompanying changes in neural activity in movement disorders. PET imaging has provided us with diagnostic agents as well as tools for evaluation of novel therapeutics, and has served as a powerful means for revealing *in vivo* changes at different stages of movement disorders and within the course of an individual patient's illness.

Keywords

PET/CT; movement disorders; Parkinson's disease

Introduction

Imaging with positron emission tomography (PET) represents a valuable clinical and research tool to visualize pathological changes in movement disorders. During the past decade, PET imaging has provided us with diagnostic agents as well as tools for evaluation of novel therapeutics, and has served as a powerful means for revealing *in vivo* changes at different stages of movement disorders.

The use of computed tomography (CT) in modern PET/CT scanners provides additional value to PET methodology. Technically, CT scanning allows accurate attenuation correction, and constitutes a superior substrate compared to PET alone for coregistration. In addition to its technical superiority for attenuation correction, the CT scan also provides help in excluding structural abnormalities as secondary causes of movement disorders.

The discovery of several radiopharmaceuticals useful for assessment of movement disorders has enormously simplified the clinical management of patients (Table 1). Emphasis has been placed on imaging of the dopaminergic system (Supporting Fig. S1), as well as other

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Conflicts of interest

The authors declare no conflicts of interest.

neurotransmission systems, which are affected in several movement disorders. Additionally, PET imaging with [^{18}F] fluorodeoxyglucose ([^{18}F]FDG) has been extensively used to assess local synaptic activity in the resting state and to highlight local changes in brain metabolism accompanying movement disorders. This paper reviews PET findings in the major movement disorders (Table 2 and Fig. 1), including

- Parkinson's disease;
- essential tremor;
- atypical parkinsonisms (multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration);
- Huntington's disease;
- ataxia; and
- dystonia.

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting 1% of individuals of age 65–70 years, and 3% of individuals over age 80 years.¹ Typical neuropathological alterations in PD are Lewy body inclusions and loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in progressive neuronal death in the nigrostriatal pathways and ultimately in the alteration of cortico-striatopallido-thalamocortical circuits.² Histopathological lesions in PD precede the development of symptoms by several years, leading to motor disturbances after approximately 50–70% of dopaminergic neurons are lost.³

Clinically, PD is characterized by the presence of resting tremor, bradykinesia, rigidity, and postural instability. Other clinical criteria supporting PD diagnosis are the response to dopaminergic treatments, asymmetrical onset of symptoms, and the absence of atypical signs suggesting other forms of parkinsonism.⁴

Imaging of the dopaminergic system in PD

Dopamine synthesis—The PET tracer 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine ([^{18}F]DOPA) has been used in PD studies to evaluate the first step in dopaminergic transmission, namely dopamine synthesis, which takes place in the presynaptic dopaminergic neurons. [^{18}F]DOPA is taken up into neurons by an active transport system and is converted to [^{18}F]dopamine by aromatic amino-acid decarboxylase (AADC), which represents the rate-limiting step in dopamine synthesis in dopaminergic neurons (Supporting Fig. S1). As such, [^{18}F]DOPA uptake reflects the synthetic ability of dopaminergic neurons to produce dopamine through AADC.

Several studies demonstrated a significant reduction of [^{18}F]DOPA striatal uptake in PD patients compared to control subjects.^{5,6} The reduction is more severe in the putamen than in the caudate nucleus, and most prominent in the caudal parts of the putamen⁵ (Figs. 1 and 2). [^{18}F]DOPA uptake correlates with clinical disease severity and with disease progression, with 8–9% annual decline in uptake rate constant in the putamen and 4–6% decline in caudate nucleus of clinical PD patients.^{6,7}

Potential disadvantages to the use of [^{18}F]DOPA PET in the evaluation of dopaminergic system integrity are that the method may underestimate the severity of nigrostriatal loss due to upregulation of AADC activity, in particular, at early stages of disease. Additionally,

tracer uptake may increase in patients undergoing treatment with dopaminergic medications.⁸

Dopamine storage in synaptic vesicles—The dopamine produced at the synaptic level is stored in synaptic vesicles by the type-2 vesicular monoamine transporter (VMAT2), which is responsible for translocating monoamine neurotransmitters from the cytoplasm into vesicles (Supporting Fig. S1). In the central nervous system, VMAT2 is expressed exclusively by monoaminergic neurons. Over 95% of striatal VMAT2 transporters are associated with dopaminergic terminals and striatal VMAT2 density is a linear function of the nigrostriatal neuron number.⁹ PET radiotracer [¹¹C]dihydrotetrabenazine ([¹¹C]DTBZ) is a specific ligand of VMAT2 and is used as an *in vivo* marker of nigrostriatal dopaminergic system integrity. Studies with [¹¹C]DTBZ PET showed the expected pattern of decreased uptake in the corpus striatum in PD patients compared to control subjects, involving preferentially the putamen.^{10,11} [¹¹C]DTBZ uptake is not affected by synaptic dopamine levels or dopaminergic agents, which makes the tracer one of the best available radioligands to examine dopaminergic system integrity.¹⁰

Dopamine transporters—Dopamine transporters (DAT) are located in the presynaptic dopaminergic nerve terminal. Dopamine reuptake through the DAT is the primary mechanism of dopamine removal from the region of the synaptic cleft (Supporting Fig. S1). A decrease in DAT density indicates decreased amount of presynaptic terminals that produce dopamine. Among many DAT-specific tracers used in PET and single photon emission computed tomography (SPECT) imaging, the cocaine analogs, 2β-carbomethoxy-3β-[4-[¹²³I]iodophenyl] tropane ([¹²³I](3-CIT) and *N*-β-fluoropropyl-2β-carbomethoxy-3α-4-[¹²³I]iodophenyl nortropine ([¹²³I]FP-CIT), are the most widely used in clinical practice due to their affinity to DAT and ability to assess decreased DAT density, which may precede clinical symptoms in PD. Therefore, the loss of nigrostriatal dopaminergic neurons in PD is mirrored by striatal DAT reductions, which can be evaluated by a variety of [¹¹C] or [¹⁸F] ligands.^{12,13} Quantitative evaluation of DAT plays an important role in clinical practice and is based on measurements of the tracer binding potential, defined as the ratio of uptake in a striatal region of interest to that of a brain area devoid of specific binding (usually cerebellum or occipital lobe).¹⁴

PET studies evaluating DAT availability, particularly with *N*-(3-[¹⁸F]fluoropropyl)-2β-carbomethoxy-3α-(4-iodophenyl) nortropine ([¹⁸F]FP-CIT)¹² and 2β-carbomethoxy-3α-(4-[¹⁸F]fluorophenyl) tropane ([¹⁸F]CFT),¹³ showed a reduction of striatal tracer uptake in PD patients compared to control subjects, affecting primarily the putamen and to a lesser extent the caudate nucleus. The reduction is typically more severe in the striatum contralateral to the earliest and most affected body side.^{12,13,15,16} Striatal DAT levels, particularly in the putamen, correlate with disease severity¹⁵ and decrease with PD progression.¹⁶

DAT imaging is useful in the management of patients with parkinsonian symptoms, and to support the clinical decision process in cases with uncertain diagnosis, particularly in the differential diagnosis between presynaptic and nonpresynaptic parkinsonism, and in cases of dubious symptoms.⁵

The effect of dopaminergic treatment on striatal DAT tracers uptake has been the object of investigation and controversy. Several SPECT and PET studies performed with different DAT tracers did not demonstrate significant effects of dopaminergic medications on DAT density,¹⁷ suggesting no interference between dopaminergic treatments and DAT tracers uptake. Further studies are needed to specifically examine possible interactions.

Dopamine receptors—Dopamine released into the synaptic cleft binds mainly to the postsynaptic striatal D₂ receptors (Supporting Fig. S1), and the binding capacity of these receptors can be measured by several PET tracers. One such tracer is [¹¹C]raclopride. PET studies with [¹¹C]raclopride showed that striatal dopamine D₂ binding to the postsynaptic dopaminergic receptors was either normal or increased in PD patients.¹⁸ This increase has been interpreted as a compensatory reaction to the reduction of striatal dopaminergic terminals.¹⁸ D₂ receptor upregulation is most evident at early stages and contralateral to the clinically most affected side,¹⁹ and is usually the site of onset in PD. On the other hand, the increase in postsynaptic D₂ receptor binding could also be due to loss of endogenous dopamine, thereby unloading the post-synaptic receptors and ultimately increasing uptake of [¹¹C]raclopride or similar PET tracers in these receptors.

D₂ receptor imaging is widely used for the differential diagnosis of parkinsonism, since uptake is typically normal or increased in patients with PD, whereas patients with other forms of parkinsonism, such as multiple system atrophy and progressive supranuclear palsy show reduced tracer uptake.^{20,21}

Chronic pharmacologic treatment may reduce D₂ receptor availability, probably due to downregulation. It should be noted that in contrast, dyskinesia, a common motor symptom after chronic levodopa therapy, is not directly associated with D₁ or D₂ receptor density, as shown by a PET study using [¹¹C]SCH23390 and [¹¹C]raclopride, which demonstrated no differences in mean caudate and putamen D₁ and D₂ binding between dyskinetic and nondyskinetic treated PD patients.²²

Metabolic imaging in PD

In addition to loss of dopaminergic neurons, damage to subcortical structures alters the functional connectivity across brain regions in a disease-specific manner. A recent meta-analysis of quantitative [¹⁸F]FDG PET studies revealed widespread cortical hypometabolism in PD.²³ Nonquantitative [¹⁸F]FDG PET studies using normalization to the global gray matter activity consistently showed a pattern of relative cortical hypometabolism, particularly involving temporoparietal regions and increased metabolism in the putamen, globus pallidus, thalamus, brainstem, central cerebellum, white matter, and primary sensory-motor areas of PD patients (Fig. 3).^{24,25} Conversely, hypermetabolism is seen in subcortical structures and is evidenced by increased neuronal firing rates in animal models of PD.²⁶ However, caution is necessary because relative metabolic increases may be artifactual due to normalization of the global gray matter mean, which is reduced in PD patients, as demonstrated in several quantitative [¹⁸F]FDG PET studies.²⁷

Cerebral metabolic rate of glucose (CMR_{glc}) in primary and associative visual cortex, occipitotemporal area, orbitofrontal cortex, and anterior cingulate gyrus is inversely correlated with motor impairment on clinical scales,²⁸ which may represent an effect on the cortex of dopaminergic deficits in the striatum.²⁹ Moreover, a recent double-tracer study in early-stage PD patients using [¹²³I]FP-CIT and [¹⁸F]FDG PET demonstrated that CMR_{glc} in premotor, dorsolateral prefrontal, anterior prefrontal, and orbitofrontal cortices, was significantly correlated with putaminal dopaminergic dysfunction,³⁰ confirming the connection between striatum and frontal cortex.²⁹

Formal network approaches using principal component analysis identified a PD-specific metabolic network characterized by relative hypermetabolism in the lentiform nucleus, thalamus, and brainstem, in conjunction with hypometabolism in the lateral premotor cortex and supplementary motor area.²⁴ This pattern correlated with clinical impairment, was modulated by PD therapy, and discriminated PD patients from normal subjects and from atypical parkinsonian syndromes with high accuracy.^{25,31–33} [¹⁸F]FDG PET imaging has

advantages over dopaminergic tracers, especially for clinical trials. First, [^{18}F]FDG is widely available in most PET centers, including those without an onsite cyclotron. Second, the method allows one to quantify the effects of therapy, including reversible changes in brain metabolism.

Other tracers in PD: neuroinflammation

While there are currently no tracers that bind Lewy body inclusions *in vivo*, the glial reaction to the presence of pathology can be detected with PET. Microglial cells are normally in a resting state, but become activated in response to any local disturbance, such as inflammation, trauma, ischemia, tumor, and neurodegeneration.³⁴ In PD, the loss of dopamine neurons is linked with activation of microglia within the substantia nigra, which might in turn promote degeneration of nigral neurons as the disease progresses.³⁵

Mitochondria of activated microglia express peripheral benzodiazepine sites that bind the PET tracer [^{11}C](1-(2-chlorophenyl)-*N*-methylpropyl)-3 iso-quinoline-carboxamide ([^{11}C]PK11195). PET imaging with [^{11}C]PK11195 showed higher tracer uptake in midbrain,³⁶ striatum, pallidum, and frontal cortex of PD patients compared to age-matched healthy subjects.³⁷ Moreover, midbrain [^{11}C]PK11195 binding was inversely correlated with DAT levels in the posterior putamen and positively correlated with the severity of motor impairment.³⁶

Longitudinally, PD patients showed increases in [^{11}C]PK11195 binding in the meso-basal gangliathalamo-cortical loop and in extrastriatal regions, especially in the occipital cortex. These findings are consistent with the observation that microglial activation, besides providing an immediate immune response, may trigger a cascade of inflammatory events that promote neurodegeneration.³⁷ Due to its capability to show progression effects, PET with [^{11}C]PK11195 represents a promising *in vivo* imaging technique for early detection and evaluation of neuroinflammation before and after therapy in PD.

Essential tremor

Essential tremor (ET) is the most common movement disorder, characterized by postural and kinetic tremors that most frequently occur in hands, arms, head, and neck. Tremor may occur at the beginning of, or during, voluntary movements (initial or kinetic tremor) or at the end of the movement (intentional tremor).³⁸

Imaging studies show that the nigrostriatal dopaminergic system is relatively preserved in ET. Two multicenter studies using SPECT with DAT tracers demonstrated DAT reductions in parkinsonism but not in ET, reflecting a preserved dopaminergic system integrity in the latter condition.^{39,40} However, several ET patients with initial postural tremor develop resting tremor and accompanying dysfunction of the dopaminergic system. A [^{18}F]DOPA PET study reported a 50% reduction of tracer uptake in the striatum of nine out of 11 patients with resting tremor, compared to only two out of 12 patients with postural tremor in parkinsonism.⁴¹

Atypical parkinsonism

The differential diagnosis of parkinsonian syndromes from PD and from each other may be difficult, especially at early disease stages when the potential for misdiagnoses is the greatest.^{4,42} In PD clinical trials, the inclusion of atypical parkinsonism in lieu of PD is a hindrance to the assessment of treatment effects, as atypical parkinsonian patients may not respond to therapy and therefore confound results. Moreover, in clinical practice, correct and

early diagnosis is fundamental as both prognosis and treatment options can differ substantially between PD and atypical parkinsonism.⁴²

Multiple system atrophy

Multiple system atrophy (MSA) is the most common among atypical parkinsonian disorders, and the most frequently misdiagnosed. MSA is clinically characterized by the combined presence of parkinsonism, autonomic dysfunction, cerebellar ataxia, and pyramidal symptoms.⁴³ Parkinsonism (typically akinesia, rigidity, postural tremor) prevails in 80% of patients (MSA-P subtype) and cerebellar ataxia (ataxia, dysarthria, oculomotor cerebellar symptoms) in 20% of patients (MSA-C subtype).

PET imaging of the dopaminergic system in MSA—Dopaminergic degeneration typical of PD is present also in MSA. [¹⁸F]DOPA studies generally report severe reductions of striatal uptake in MSA (30% in putamen and 10% in caudate nucleus) compared to healthy subjects.^{5,21,44,45} [¹⁸F]DOPA uptake in the posterior putamen is more severely reduced than in anterior putamen or caudate nucleus, reaching levels similar to PD.⁵ As in PD, there is a significant correlation between the decrease in putaminal [¹⁸F]DOPA uptake and disease severity in MSA.²¹

The usefulness of [¹⁸F]DOPA-PET for the differential diagnosis of parkinsonism remains under debate. While some studies have shown that MSA patients present with more severe impairment of caudate dopaminergic nerve terminals than PD patients (suggesting a role for [¹⁸F]DOPA putamen/caudate ratios in the differential diagnosis of parkinsonisms),⁵ in other studies [¹⁸F]DOPA measurements did not distinguish between PD and MSA.⁴⁴

[¹¹C]DTBZ PET studies of the VMAT2 showed severe reductions of striatal monoaminergic terminals in MSA patients compared to controls, with reductions of 40–60% in both caudate and putamen.^{46,47} A comparison of MSA-P and MSA-C subtypes demonstrated that [¹¹C]DTBZ uptake was significantly impaired in the putamen of MSA-P patients,⁴⁷ PET studies of dopamine D₂ receptors using both [¹¹C]raclopride and [¹⁸F]desmethoxyfallypride revealed reduced striatal binding in MSA in comparison with controls,^{48,49} (a finding that was present already at early disease stages). D₂ receptor binding is also reduced in MSA in comparison with PD patients,^{45,49} thus facilitating the discrimination between MSA and PD.²¹ This finding is consistent with the neuropathological differences between PD and MSA: neurodegeneration in PD involves only dopaminergic presynaptic neurons, while MSA is characterized by more widespread degeneration, involving both presynaptic and postsynaptic neurons. As the effectiveness of dopaminergic therapy is associated with the integrity of striatal postsynaptic dopamine receptors, D₂ receptor PET imaging could be a useful tool to predict dopaminergic responsiveness in MSA.

[¹⁸F]FDG PET imaging in MSA—[¹⁸F]FDG PET studies in MSA showed significant metabolic decreases in the striatum, particularly in the putamen, as well as in the brainstem and cerebellum, when compared to both normal subjects and patients with PD (Fig. 3).^{24,25,50–52} CMRglc reductions affect the cerebellum, brainstem, and striatum at the early stage of MSA, and then spreads to the cerebral cortex at later stages.^{51,52} [¹⁸F]FDG PET findings of striatal hypometabolism in MSA suggest that, besides postsynaptic dopaminergic system degeneration, feedback mechanisms within the motor loop may modulate striatal energy metabolism. There is a strong correlation between clinical symptoms and hypometabolism.⁵³

[¹⁸F]FDG PET can be used for differentiating MSA from PD due to bilateral hypometabolism in the putamen of patients with MSA.²⁵ Additionally, patients with MSA-P subtype show more pronounced striatal hypometabolism, whereas MSA-C-subtype patients

exhibit cerebellar hypometabolism, which may help to distinguish between these forms of MSA.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is an akineticrigid syndrome clinically characterized by the combination of early postural instability, supranuclear vertical gaze palsy, parkinsonism not responsive to levodopa treatment, and dementia.⁵⁴

PET imaging of the dopaminergic system in PSP—Degeneration of nigrostriatal dopaminergic pathways has been reported in PSP as well as in PD, but with a different specific pattern.⁵ Striatal [¹⁸F]DOPA uptake is reduced in PSP patients, with similar uptake reductions in the putamen and caudate, reflecting loss of nigrostriatal dopaminergic terminals.⁵ As compared to PD, PSP patients show significant reduction of [¹⁸F]DOPA uptake in caudate nucleus.⁵

Although PSP patients show symmetrical and profound DAT loss in the whole striatum, as previously mentioned for MSA, [¹⁸F]DOPA DAT imaging is of limited value in the differential diagnosis of PSP, PD, and atypical parkinsonism.⁵⁵ On the other hand, D₂ receptor imaging improves the differential diagnosis between PSP and PD. While striatal dopamine D₂ binding is either normal or increased in PD patients, several PET studies reported reduced [¹¹C]raclopride binding in PSP patients, with a 24% and 9% reduction in the caudate nucleus and putamen, respectively.⁴⁸

[¹⁸F]FDG PET imaging in PSP—[¹⁸F]FDG PET studies in PSP patients show diffuse reductions in CMRglc, mostly involving the frontal cortex, particularly at the level of midline frontal areas, basal ganglia, and brainstem (Fig. 3),⁵⁶ and additionally involving the anterior cingulate, motor and premotor cortex, striatum, and thalamus.^{25,57} Hypometabolism correlates with general intelligence scores and performance on tests, stratified by disease duration⁵⁸ and locomotor function.⁵⁸ The mechanisms underlying cortical metabolic reduction in the frontal areas in PSP are under debate. Degeneration of noradrenergic, serotonergic, and dopaminergic projections may contribute to diffuse cortical hypofunction, while frontal hypometabolism in PSP is more likely due to degeneration of pallidal projections to frontal regions.

The specific pattern of hypometabolism in the brainstem and frontal cortex in PSP discriminates this disorder from PD and atypical parkinsonism.²⁵

Corticobasal degeneration

Corticobasal degeneration (CBD) is an adult-onset progressive neurodegenerative disorder characterized by cortical and basal ganglionic degeneration. The cardinal manifestations of CBD include motor symptoms that are typically asymmetric at early stages and similar to those seen in PD (i.e., rigidity, bradykinesia, tremor). Patients with advanced disease show a progressive decline of cognitive function. There is no significant response to levodopa and dopamine agonists in CBD patients.⁵⁹

PET imaging of the dopaminergic system in CBD—[¹⁸F]DOPA PET studies performed in early CBD patients show more severe reductions of tracer uptake in the putamen, while uptake in the caudate nucleus is relatively preserved.⁶⁰ Patients with more advanced disease show impairments of striatal [¹⁸F]DOPA uptake in the caudate nucleus to similar levels as in the putamen; with a predominance contralateral to clinical signs.⁶¹ Interestingly, dopaminergic degeneration in CBD is more asymmetrical and less pronounced than in MSA and PSP.⁵⁵

Postsynaptic D₂ receptor imaging seems to be of lower clinical value for CBD than in other parkinsonian syndromes (like MSA or PSP), since striatal D₂ receptor binding in CBD patients is either normal⁶² or decreased compared to controls,⁶³ with values more often in normal range than in MSA and PSP.

[¹⁸F]FDG PET imaging in CBD—On [¹⁸F]FDG PET, CBD patients present with asymmetrical hypometabolism, affecting the hemisphere contralateral to the first and most affected limbs (Fig. 3).^{61,64} Parietotemporal, prefrontal, and motor cortex, as well as basal ganglia and thalamus, are particularly affected in CBD. While CBD and other parkinsonian disorders have many common clinical features, the presence of unilateral cortical and unilateral balanced striatal (caudate nucleus/putamen) hypometabolism is specific to CBD patients differentiating it from PSP or PD.^{25,65}

PET imaging of other neurotransmission systems—PET studies using [¹¹C]diprenorphine investigated striatal opioid receptor density in patients with PD, MSA, and PSP, and showed a significant binding reduction in the caudate nucleus and putamen of PSP patients, and in the putamen of MSA patients, as compared to PD and normal controls.⁶⁶ A PET study in PSP patients using [¹¹C]flumazenil, a marker of neuronal integrity, demonstrated a 20% reduction of benzodiazepine receptors in the anterior cingulate cortex of PSP patients, which was accompanied by a significant reduction of [¹⁸F]FDG uptake.⁶⁷ Finally, a PET study using [¹¹C]MP4A (an indicator of acetylcholinesterase activity), demonstrated a significant reduction of cortical tracer uptake in PD patients and a prominent reduction of thalamic uptake in PSP patients, as compared to normal controls.⁶⁸

Overall, these studies demonstrated that multi-modality PET imaging with tracers targeting different neurotransmission systems, including, but not limited to, those for the dopaminergic system, could be of great relevance to the differential diagnosis of parkinsonism.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive loss of capacity in movement control, cognition, and emotional regulation.

The primary genetic cause of HD is an expansion of a trinucleotide cytosine–adenine–guanine (CAG) in the IT15 gene on chromosome 4 and the number of CAG repeats is a major determinant of age of onset of HD.⁶⁹ The characteristic neuropathological finding in HD is the selective striatal neuronal degeneration of small to medium size spiny neurons, beginning in the dorsal medial head of the caudate with subsequent progression to the ventrolateral striatum. Less pronounced neuronal loss has been observed in other subcortical and cortical structures.⁷⁰ Brain atrophy of the striatum and neocortex following neuronal loss is evident several years prior to a diagnosis of HD.

PET imaging of the dopaminergic system in HD

D₂ receptors ligands ([¹¹C]raclopride, [¹⁸F]fluoroethylspiperone) and D₁ receptors ligands ([¹¹C]SCH23390) have been extensively used to examine HD patients because the medium spiny neurons express these receptors. PET studies using the selective dopamine D₁ and D₂ receptor antagonists [¹¹C]SCH23390 and [¹¹C]raclopride demonstrated > 40% reduced striatal D₁ and D₂ receptor binding in HD patients compared to normal controls.⁷¹ Such reductions in dopamine D₁ and D₂ receptor availability could represent loss of functioning receptors on intact but dysfunctional striatal neurons, as well as loss of receptors secondary

to death of striatal neurons. Reductions of D₁ and D₂ receptor availability are strongly related to increasing illness duration and performance on several cognitive tasks.⁷² Longitudinal PET studies in HD patients demonstrated a mean annual decrease in D₁ and D₂ receptor binding of 5% and 3.2%, respectively.^{73,74}

Similar to clinically symptomatic HD patients, the majority of asymptomatic HD mutation carriers show D₁ and D₂ receptors loss, with a mean reduction of up to 50% of striatal binding as compared to normal controls,⁷⁵ as well as longitudinal decreases of D₁ and D₂ receptor binding.⁷⁴

[¹⁸F]FDG PET imaging in HD

Since the first [¹⁸F]FDG PET studies in the 1980s, a large body of literature has accumulated showing diffuse cortical decreases in glucose use, preceding tissue loss, in HD patients.⁷⁶ The presence of striatal hypometabolism is a consistent finding in HD patients, who also show reduced cortical CMRglc, involving in particular, the frontal and temporal lobes (Fig. 4).^{76,77} Reduced [¹⁸F]FDG uptake correlates with motor and functional abnormalities.⁷⁸

Similar metabolic reductions in striatum, frontal, and temporal lobes were observed in presymptomatic HD mutation carriers.⁷⁹ Moreover, presymptomatic carriers present with thalamic hypermetabolism, which may represent a compensatory reaction to early neuronal loss.⁸⁰

Longitudinal [¹⁸F]FDG PET studies in HD demonstrated significant CMRglc reductions over time in several cortical regions, including mostly frontal, temporal, parietal lobes, and striatum.^{77,81} Similar longitudinal effects were reported in presymptomatic HD subjects, with decreases in striatal metabolism as much as 2.3–7.6% per year, which were accompanied by a parallel increase in the expression of the HD-related pattern.^{77,82} Overall, metabolic reductions are an early feature of HD, preceding the clinical onset of HD symptoms by many years.

Novel PET tracers in Huntington's disease

Based on postmortem findings of reduced type 1 cannabinoid receptor (CB1) levels in HD brains, a few PET studies with the highly selective, high-affinity CB1 radioligand *N*-[2-(3-cyano-phenyl)-3-(4-(2-[¹⁸F]fluorethoxy)phenyl)-1-methylpropyl]-2-(5-methyl-2-pyridyloxy)-2-methylpropanamide ([¹⁸F]MK-9470)⁸³ demonstrated a profound and widespread reduction of CB1 availability in the gray matter of the cerebrum, in cerebellum and brainstem of HD patients, including those at early symptomatic stages of disease.⁸³

GABA receptor density is also reduced in striatum of HD patients, as demonstrated by [¹¹C]flumazenil PET studies.⁸⁴ PET with [¹¹C]flumazenil showed reduced binding in the caudate nucleus and normal values in the putamen of symptomatic, as well as of presymptomatic HD carriers.⁸⁴

Finally, consistent with post-mortem findings of activated microglia in HD brains, several PET studies reported significant increases in [¹¹C]PK11195 binding in the striatum, frontal, and parietal regions of symptomatic and presymptomatic HD gene carriers.⁸⁵ Higher striatal [¹¹C]PK11195 binding correlated with lower D₂ receptors availability on [¹¹C]raclopride and with a higher CAG repeat length.⁸⁵

Ataxia

The term “ataxia” is used as a synonym for cerebellar syndrome, and includes several cerebellar signs (i.e., postural and gait abnormalities, extremities ataxia, tone abnormalities, tremor, dysarthria, oculomotor abnormalities). Ataxias can be divided into congenital, hereditary, and sporadic forms. Nonhereditary ataxias include idiopathic late-onset cerebellar ataxia, whose diagnosis derives from the exclusion of genetic and secondary causes of cerebellar degeneration. This paper focuses on the hereditary forms, for which functional imaging has been used for diagnostic purposes.

Hereditary ataxias are clinically characterized by slowly progressive gait disturbances, poor motor coordination of limbs, speech and ocular movements, and cerebellar atrophy. Hereditary ataxias are classified (according to the modality of genetic transmission and to the mutation responsible for the disorder) into autosomal dominant, autosomal recessive, X-linked, and mitochondrial forms.

Autosomal dominant cerebellar ataxias, also known as spinocerebellar ataxias (SCA), are the most common ataxias, and consist of a clinically, pathologically, and genetically heterogeneous group of neurodegenerative disorders that share clinical characteristics of deterioration in gait and balance, and various combinations of cerebral, extrapyramidal, bulbar, spinal, and peripheral nervous system involvement.⁸⁶ Several different subtypes of SCA exist according to the mutation causing the disease. The most SCA common type is SCA3, also known as Machado–Joseph disease. Less frequent types of SCA are SCA1, SCA2, SCA6, SCA7, and SCA8, followed by other types with lower prevalence (<http://www.geneclinics.org>). Clinical manifestations in these types may include neuropathies and memory impairment among other symptoms. The mutation basis for all these SCA subtypes is an expanded trinucleotide repeat sequence within the coding regions of the involved genes.⁸⁷

Other forms of hereditary ataxia include X-linked hereditary ataxia, and ataxia associated with mitochondrial disorders, such as MERRF (myoclonic epilepsy with ragged red fibers), NARP (neuropathy, ataxia, and retinitis pigmentosa), or Kearns–Sayre syndrome.

PET imaging of the dopaminergic system in ataxia

[¹⁸F]DOPA PET studies demonstrate reduced striatal tracer uptake in SCA6 patients, with reduced [¹⁸F]DOPA uptake in both the caudate nucleus and putamen, to similar levels as in patients with parkinsonism.⁸⁸ [¹⁸F]DOPA findings suggest that subclinical nigrostriatal dysfunction may be present in SCA patients, resulting in subtle extrapyramidal signs in some cases.

SPECT and PET studies with DAT tracers confirm the involvement of the nigrostriatal dopaminergic system in some SCA patients.⁸⁹ Striatal [¹¹C]dMP (DAT ligand) binding potential was found to be markedly reduced in SCA2 and SCA3 patients, with a reduction of striatal tracer uptake involving the caudate nucleus and putamen (both in SCA2 and SCA3).⁸⁹ Interestingly, the loss of DAT is less severe in SCA3 patients, suggesting that the dopaminergic system could be more sensitive to SCA2 mutations.⁸⁹ Absent or minimal dopaminergic impairment has been described in other types of hereditary ataxia (SCA1 and SCA6).⁸⁹

Finally, D₂ receptors imaging studies using [¹¹C]raclopride show integrity of the postsynaptic dopaminergic system in patients with SCA1, SCA2, and SCA3, revealing no differences in striatal D₂ receptor availability between SCA patients and normal controls.⁹⁰

[¹⁸F]FDG PET imaging in ataxia

[¹⁸F]FDG PET studies in patients with different types of ataxia syndromes (sporadic or hereditary) consistently report hypometabolism of cerebellar hemispheres, cerebellar vermis, and brainstem.⁹¹ Cerebellar hypometabolism is a consistent feature of hereditary autosomal dominant ataxia, and is present in almost all SCA types. In addition to cerebellar hypometabolism, SCA1 patients show significant hypometabolism in the brainstem compared to controls.⁸⁹ Hypometabolism in the cerebellum and pons/brainstem is also a frequent finding in symptomatic, as well as asymptomatic, SCA2 carriers who present with additional hypometabolism of parahippocampal gyrus, and frontal, and parietal cortices.^{89,92} In SCA3, decreased CMRglc extends from cerebellar midline structures to the adjacent pons and midbrain, and then on to the occipital cortex.^{89,92} In addition to cerebellar hypometabolism, SCA6 patients show reduced CMRglc in the brain-stem, basal ganglia, and frontal, temporal, and occipital cerebral cortices.⁹² These results are, however, not consistent across studies.⁸⁹

In conclusion, [¹⁸F]FDG PET imaging is useful for the early detection of SCA, and, as such, it may be of use in the identification of subjects suitable for both therapeutic intervention and to establish the timing of treatment and efficacy of response perhaps years before clinical presentation.

Dystonia

Dystonia is a syndrome characterized by sustained muscle contractions causing distorted voluntary movements or abnormal postures. Dystonia encompasses a wide spectrum of clinical entities including focal and generalized forms. Dystonias may also be divided into primary (unknown etiology) and secondary forms.⁹³ The specific cause of primary dystonias is usually unknown, although it has become clearer that they are likely to have a genetic basis. The secondary forms result from specific factors such as exposure to certain medications, lesions of the basal ganglia, or trauma.

The most prevalent form of hereditary dystonia is early-onset generalized dystonia, resulting from the DYT1 mutation, a GAG deletion within the coding area for torsinA on chromosome 9q34.⁹³ Another less frequent form of primary torsion dystonia is associated with a DYT6 mutation, linked to chromosome 8q21–22.⁹³ Both mutations are inherited via autosomal dominant transmission with reduced penetrance. Clinical manifestations of dystonia are present in 30% of DYT1 and up to 60% of DYT6 mutation carriers.

Dopa-responsive dystonia (DRD) is another form of idiopathic torsion dystonia characterized by early onset and diurnal fluctuations. Clinical features include dystonia, variable degrees of parkinsonism, and an excellent and sustained response to levodopa.⁹³ DRD is inherited as an autosomal dominant trait with reduced penetrance and is associated with mutations in the guanosine triphosphate cyclohydrolase 1 gene.⁹³ Although DRD comprises a minority of patients with dystonia, it is of considerable diagnostic importance because of the excellent response to treatment.

PET imaging of the dopaminergic system in dystonia

The neurochemical basis of primary dystonia is currently unknown. However, multiple lines of evidence support the role of dopaminergic neurotransmission abnormalities in the manifestation of symptoms. PET imaging with [¹⁸F]DOPA shows that the uptake rate constant is within normal range in DRD patients,⁹⁴ indicating that aromatic l-amino acid decarboxylase activity is not affected in this disorder.⁹⁴ Moreover, as compared to controls, DRD patients show increased [¹¹C]DTBZ binding in both the caudate nucleus and putamen,⁹⁴ which may be related to decreased competition for tracer binding from

endogenous dopamine, or alternatively to elevated cell activity, or a combination of the two. Similar results were obtained with [^{11}C]dMP PET, demonstrating striatal DAT radiotracer uptake within the normal range in DRD.⁹⁴ Presynaptic dopaminergic imaging is therefore a practical approach to differentiate dystonia patients from parkinsonism, as DRD patients generally have normal uptake levels while PD patients show striatal uptake reductions.^{5,94}

Several studies have reported decreased striatal D₂ receptor availability in different forms of dystonia. In focal dystonia, PET imaging demonstrates a significant decrease of [^{18}F]spiperone binding in the putamen, with a mean reduction of 29%.⁹⁵ Reduced [^{11}C]raclopride binding was found also in hereditary dystonia, affecting both dystonia-manifesting and dystonia-non-manifesting DYT1 mutation carriers.⁹⁶ The striatal D₂ receptor loss reported in clinically unaffected DYT1 carriers suggests that postsynaptic dopaminergic deficits could be a trait feature of DYT1 dystonia, but not sufficient *per se* for symptoms to arise. Alternatively, clinical penetrance may be determined by the degree to which striatal binding is reduced in mutation carriers, suggesting that clinical signs in DYT1 carriers could emerge only after greater loss of striatal D₂ receptor binding.

[^{18}F]FDG PET imaging in dystonia

On [^{18}F]FDG PET, dystonia patients typically show increased metabolism in the lentiform nucleus, basal ganglia, and associated outflow pathways to the sensorimotor cortex along with regions involved in motor performance.^{97,98} Interestingly, these metabolic abnormalities were present both in clinically silent and symptomatic carriers, as well as in symptomatic carriers when involuntary dystonic movements were suppressed during sleep. This suggests that this metabolic pattern, like the D₂ receptor abnormality, could be a trait feature of DYT1 carrier status.⁹⁸ Clinically silent carriers of the DYT6 mutation showed a different metabolic pattern characterized by CMRglc reductions in the putamen, cerebellum,⁹⁹ and in the upper brainstem extending to the thalamus.⁹⁷ In addition, clinically affected DYT6 carriers showed metabolic increases in the supplementary motor area and parietal association regions.⁹⁷

DRD patients show a distinct metabolic pattern characterized by relative increases in the dorsal midbrain, cerebellar vermis, and supplemental motor area, evidencing covarying decrements in the putamen, lateral premotor, and motor cortical regions.¹⁰⁰ This metabolic pattern is not expressed in dystonia gene carriers of the DYT1 or DYT6 gene mutation,¹⁰⁰ thereby supporting the hypothesis of a different pathophysiology for DRD. Metabolic alterations in DRD patients share some features of both PD and torsion dystonia, as metabolic decreases in the lateral premotor region is a consistent feature of PD,²⁴ while metabolic increases in supplemental motor area is a feature of PTD.^{98,99}

In conclusion, metabolic abnormalities in dystonia could be useful to identify potential gene carriers among family members of dystonia patients, and to assess mechanisms of therapeutic interventions.

Supporting information

Additional supporting information may be found in the online version of this paper.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH/NIA Grants AG032554 and AG035137 and the Alzheimer's Association.

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Figure 1. Illustration of the main findings in movement disorders with presynaptic (left) and postsynaptic dopaminergic (middle), and [^{18}F]FDG PET imaging.

Figure 2. [^{18}F]DOPA PET scans of a representative normal subject, a patient with PD, and a patient with atypical parkinsonism (progressive supranuclear palsy [PSP]). Image courtesy of Angela Cistaro, PET Center IRMET, Turin, Italy.

Figure 3.
[^{18}F]FDG PET scans of a representative cognitive normal individual (NL, left) and of four patients, each with a different movement disorder (from left to right): Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD).

Figure 4. $[^{18}\text{F}]\text{FDG}$ PET scans of a representative patient with HD (right) compared to a control subject (left).

Table 1

Radiotracer ligands used in PET investigations of movement disorders described in this chapter

Radiotracer ligand	Function measured
[¹⁸ F]DOPA	Dopamine synthesis through amino-acid decarboxylase, and storage
[¹¹ C]DTBZ	Type 2 vesicular monoamine transporters
[¹¹ C]dMP, [¹⁸ F]FE@CIT, [¹⁸ F]FP-CIT, [¹⁸ F]FECNT, [¹⁸ F]CFT	Presynaptic dopamine transporters
[¹¹ C]SCH23390	Postsynaptic dopamine D ₁ receptors
[¹¹ C]raclopride, [¹⁸ F]desmethoxyfallypride, [¹⁸ F]spiperone, [¹⁸ F]fluoroethylspiperone	Postsynaptic dopamine D ₂ receptors
[¹⁸ F]FDG	Regional cerebral metabolic rate of glucose
[¹¹ C]PK11195	Activated microglia – neuroinflammation
[¹¹ C]diprenorphine	Opioid receptors
[¹¹ C]flumazenil	Benzodiazepine receptors
[¹¹ C]MP4A	Acetylcholinesterase activity
[¹⁸ F]MK-9470	Type 1 cannabinoid receptor

Table 2

Summary table of PET findings in the major movement disorders using the most common tracers

Disease	Presynaptic dopaminergic ligands	Postsynaptic dopaminergic ligands	Functional ligands ([¹⁸ F]FDG)
Parkinson's disease	↓ caudate nucleus, ↓↓ putamen	= or ↑ striatum	↓ frontal, temporoparietal cortices, = or ↑ basal ganglia, thalamus
Multiple system atrophy	↓ caudate nucleus, ↓↓ putamen	↓ striatum	↓ striatum (MSA-C), ↓ cerebellum (MSA-C), ↓ cortex (advanced stages)
Progressive supranuclear palsy	↓↓ caudate nucleus, ↓↓ putamen	↓ striatum	↓ midline frontal regions, ↓ basal ganglia and brainstem
Corticobasal degeneration	Asymmetrical ↓ striatum (= ↓ caudate nucleus, ↓ putamen)	= or ↓ striatum	Asymmetrical ↓ cerebral hemisphere contralateral to affected side (↓ cortex, striatum, thalamus)
Huntington's disease	= striatum	↓↓ striatum	↓↓ striatum, ↓ frontal and temporal cortex
Hereditary ataxias	↓ striatum	= striatum	↓↓ cerebellum; brainstem and cortical regions differently ↓ in SCA types
Dystonia	= striatum	↓ striatum	DYT1: ↑ basal ganglia, cerebellum and supplementary motor area; DYT6: ↓ putamen, cerebellum, brainstem, thalamus, ↑ parietal association regions and supplementary motor area; DRD: ↓ putamen, motor/premotor cortex, ↑ midbrain, cerebellar vermis, and supplementary motor area