

# Neuroimaging and Therapeutics in Movement Disorders

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**Summary:** In this review, we discuss the role of neuroimaging in assessing treatment options for movement disorders, particularly Parkinson's disease (PD). Imaging methods to assess dopaminergic function have recently been applied in trials of potential neuroprotective agents. Other imaging methods using regional metabolism and/or cerebral perfusion have been recently introduced to quantify the modulation of network activity as an objective marker of the treatment response. Both

imaging strategies have provided novel insights into the mechanisms underlying a variety of pharmacological and stereotaxic surgical treatment strategies for PD and other movement disorders. **Key Words:** Movement disorders, Parkinson's disease, Huntington's disease, Tourette's syndrome, dystonia, positron emission tomography (PET), magnetic resonance imaging (MRI).

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## INTRODUCTION

Movement disorders are a group of syndromes characterized by an impairment of the regulation of voluntary motor activity without deficits of force, cerebellar function, or sensation. This class of neurological diseases includes hypokinetic disorders associated with a slowing of movements such as Parkinson's disease (PD), as well as hyperkinetic disorders characterized by involuntary abnormal movements such as Huntington's disease (HD), torsion dystonia, and tic disorders. Generally, the clinical manifestations of movement disorders result from dysfunction of the basal ganglia. Although histopathologic studies reveal specific neurodegenerative changes in some of these diseases (e.g., PD and HD), the pathologic basis for many movement disorders remains unknown. Various neuroimaging techniques have been used to visualize pathological changes in these disorders. Radiotracer imaging techniques using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging can be used to evaluate and quantify changes in specific neurochemical systems.<sup>1,2</sup> Alternatively, disease-related changes in local

brain function can be assessed with generalized tracers for regional cerebral metabolism and blood flow.<sup>3,4</sup>

Brain imaging in movement disorders was originally introduced to visualize the pathological changes associated with different clinical syndromes.<sup>5</sup> Subsequently, these techniques have been used in longitudinal studies designed to assess disease progression<sup>6,7</sup> and the effects of potential neuroprotective strategies.<sup>8-10</sup> Lately, functional imaging has also been applied in the objective assessment of symptomatic treatment responses.<sup>11-14</sup> In addition to providing an objective descriptor of the treatment response, brain imaging can also link clinical outcome to alterations in regional brain function.<sup>15</sup>

In this review, we describe functional neuroimaging strategies to evaluate and monitor therapeutic interventions for movement disorders. Because PD is the most common and broadly studied of these disorders, this review will focus on the use of imaging to assess treatment options for this condition.

## DOPAMINERGIC IMAGING IN PARKINSON'S DISEASE: NEUROPROTECTION TRIALS

PET and SPECT assessments of nigrostriatal dopaminergic function have been a traditional focus of imaging studies in parkinsonism and other movement disorders. Presynaptic dopaminergic imaging can be conducted using the following approaches: 1. [<sup>18</sup>F]-fluorodopa (FDOPA) PET to eval-

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uate the uptake and conversion from fluorodopa to fluorodopamine by the aromatic acid decarboxylase (AADC); 2. [ $^{11}\text{C}$ ]-dihydrotrabenazine (DTBZ) PET to assess the density of monoamine-containing synaptic vesicles; and 3. a variety of radiolabeled cocaine derivatives [e.g., [ $^{123}\text{I}$ ]-2 $\beta$ -carbomethyl-3 $\beta$ -(4-iodophenyl) tropane ( $\beta$ -CIT)] to quantify the expression of the dopamine transporter (DAT), which facilitates the release and reabsorption of dopamine in the nigrostriatal intersynaptic cleft. The relative merits of these agents have been summarized elsewhere.<sup>1,2</sup>

Radiotracer imaging of the presynaptic nigrostriatal dopaminergic system has been used to assess the rate of disease progression deterioration in PD. FDOPA PET and  $\beta$ -CIT SPECT show a 4% to 13% yearly reduction in baseline putamen uptake compared with 0–2.5% in healthy controls in longitudinal studies.<sup>6,7</sup> This technique has also been used to estimate the duration of the pre-clinical period of PD using a linear regression analysis.<sup>16</sup> Striatal FDOPA measurements correlate with dopamine cell counts measured in postmortem specimens<sup>17,18</sup> and striatal DAT binding decreases with age in healthy volunteers and PD patients.<sup>19–21</sup>

The precise determination of neuroprotective treatment effects represents a major challenge in current movement disorders therapeutics. Although well established in clinical trials for PD, clinical rating scales like the Unified Parkinson's Disease Rating Scale (UPDRS)<sup>22</sup> may not be sufficiently sensitive to detect subtle changes in rates of progression, as are likely to be encountered in neuroprotective trials. Moreover, clinical ratings reflect long-term symptomatic effects, which are apt to persist following protracted medication washout.<sup>9</sup>

Imaging assessment of presynaptic nigrostriatal function has been used for evaluation of disease progression in PD patients (see above) and may therefore provide a useful adjunct to clinical assessment in assessing disease progression in pharmacologic therapeutic trials of potential neuroprotective agents.<sup>2</sup> Two large randomized, blinded studies have employed imaging to investigate disease progression in patients receiving dopamine agonists relative to those treated with levodopa. In both studies, imaging based descriptors of neuroprotection diverged from the clinical outcome measures. The CALM-PD study investigated early treatment with levodopa *versus* pramipexole.<sup>10</sup> It was found that PD patients receiving levodopa did better clinically, although they experienced more motor complications. The REAL-PET study disclosed similar results in a comparison of levodopa with ropinirole. By contrast, presynaptic dopaminergic imaging with  $\beta$ -CIT SPECT (CALM-PD) and FDOPA PET (REAL-PET) revealed slower declines with agonist treatment. Similarly, in the subsequent ELLDOPA trial,<sup>9</sup> subjects treated with high-dose levodopa had the best clinical outcome even following up to 4 weeks of medication washout, despite a more rapid

decline in putamen DAT binding as measured by  $\beta$ -CIT SPECT.<sup>9</sup>

These trials reveal discrepancies between the clinical assessment and radiotracer-based imaging of the presynaptic dopaminergic system, and raise the question of comparability of these measures as neuroprotection outcome variables. Even though most imaging descriptors of nigrostriatal dopaminergic function correlate with independent disease severity measures (see Ravina et al.<sup>2</sup> for review), these techniques do not directly assess the number or density of nigral dopaminergic neurons. Moreover, these radiotracer-based imaging methods require simplifying assumptions for the acquisition and analysis of data. Thus, the results of these imaging studies may be affected by factors other than the primary biological process under study.

A critical issue in this regard is the occurrence of possible temporal up- and downregulation of neuropeptides and receptors that can affect the results of imaging studies. A study comparing FDOPA, DTBZ, and a DAT ligand, in the same PD subjects revealed a relative upregulation of AADC and downregulation of DAT.<sup>23</sup> This suggests that surviving neurons may synthesize more dopamine but perhaps also take up less from the synaptic cleft. Dopaminergic treatment can change the amount of available dopamine at the synaptic level, which may differentially influence the regulation of AADC and DAT. Although a number of studies have not revealed an effect of dopaminergic treatment on presynaptic dopaminergic imaging measures,<sup>8,24,25</sup> other evidence suggests that dopaminergic treatment can affect these parameters in PD patients.<sup>26,27</sup> Specifically, Guttman et al.<sup>27</sup> reported a decline in DAT binding after treatment with levodopa, which was not significant after pramipexole treatment. Similar treatment effects in the CALM-PD study could have contributed to the differences in imaging measures that were observed with the pramipexole and levodopa treatment groups. Further investigations with larger numbers of patients will be required to characterize time-dependent changes in the regulation of neuropeptides or receptors that might occur with treatment. Indeed, the optimal duration of medication washout before imaging will need to be determined before further studies of this sort can be pursued effectively.

Lastly, the evaluation of disease progression in PD with radiotracer imaging has relied upon the notion that pathology is limited to the nigrostriatal neurons. This assumption may be overly restrictive given that other neural pathways are likely to be involved with disease progression, even at early clinical phases of the illness.

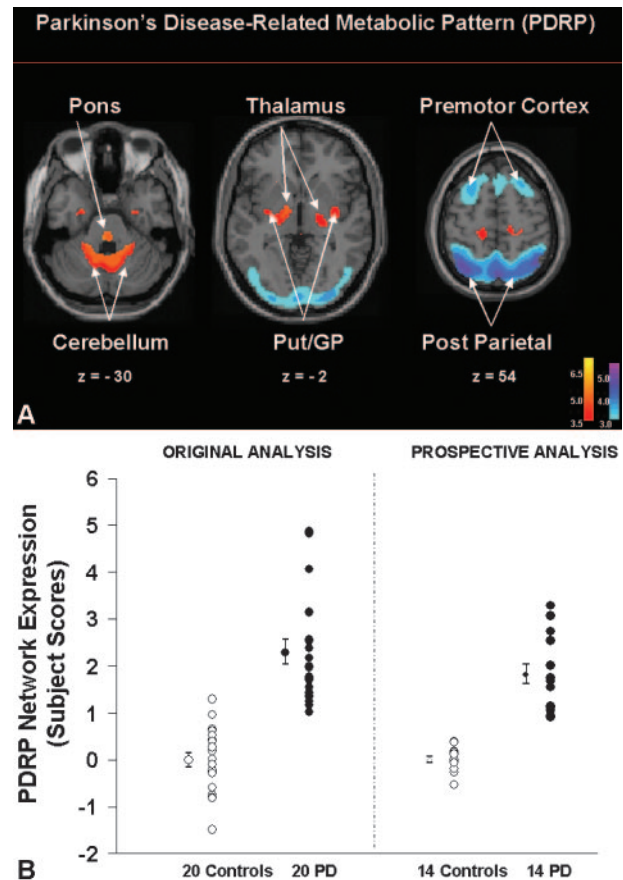
Dopaminergic imaging with PET has also been used to assess the efficacy of embryonic cell transplantation for PD. The presence of increases in putamen FDOPA uptake after transplantation is consistent with graft surviv-

al.<sup>28,29</sup> These localized changes may underlie the development of post-transplantation dyskinesia in some patients.<sup>30</sup> Additionally, graft function has been directly demonstrated using PET imaging and <sup>11</sup>C-raclopride (RAC) displacement methods.<sup>31</sup> Nonetheless, the meaning of these post-transplantation changes on PET is unclear given that motor performance does not necessarily improve in these patients (e.g.,<sup>32</sup>). Whereas the ultimate clinical role of embryonic dopamine cell transplantation for PD is unclear, imaging methodologies are likely to provide useful biomarkers in future trials of cell-based therapies.<sup>33</sup>

### METABOLIC BRAIN NETWORKS IN PARKINSON'S DISEASE

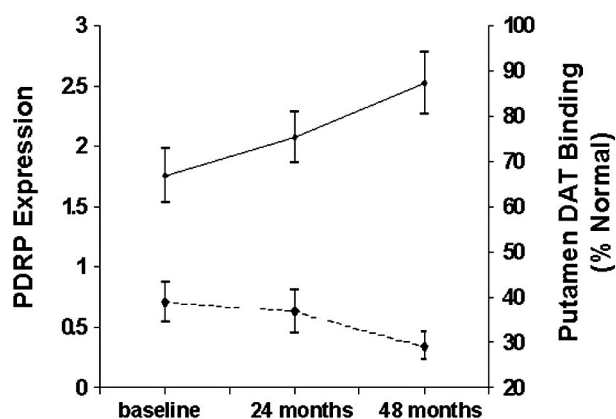
PD patients exhibit characteristic changes in regional glucose utilization on PET studies conducted with [<sup>18</sup>F]-fluorodeoxyglucose (FDG) in the resting state.<sup>3,34</sup> Formal multiregion, multisubject network approaches using principal components analysis (PCA)<sup>3,35</sup> have been employed to identify patterns of regional metabolism that are associated with PD<sup>3,36</sup> and other movement disorders (e.g., Huntington's Disease,<sup>37</sup> torsion dystonia,<sup>38,39</sup> Tourette syndrome).<sup>40</sup> PCA extracts multiple, statistically independent components that account, singly or in combination, for the majority of the variability in the regional PET data. The technique also quantifies the expression of these patterns in individual subjects.<sup>41,42</sup>

Specific criteria have been developed to determine whether one or more patterns are "disease-related," i.e., have significantly different expression in patients relative to controls.<sup>36,38</sup> For instance, employing this mathematical-statistical approach, we identified a specific regional metabolic network in PD patients scanned in the resting state with FDG PET.<sup>3</sup> This PD-related covariance pattern (PDRP) was characterized by increased glucose metabolism of the lentiform nucleus, thalamus, and brainstem as well as decreased glucose metabolism of the lateral premotor cortex and the supplementary motor area (SMA). This characteristic pattern (FIG. 1A) 1) has been validated in multiple populations of unmedicated PD patients<sup>4,36,43</sup>; 2) can be detected early in the disease course<sup>34</sup>; and 3) correlates consistently with disease severity and duration.<sup>3,44</sup> We also found that PDRP activity correlates with nigrostriatal dopamine deficiency as determined by [<sup>18</sup>F]-fluorodopa PET<sup>34,45</sup> and with internal pallidal (Gpi) single unit activity recorded during surgery.<sup>46</sup> Blinded prospective PDRP calculations show that this pattern not only discriminates PD patients from normal subjects (FIG. 1B),<sup>36</sup> but can also distinguish between patients with PD and atypical parkinsonian syndromes.<sup>3,4,34</sup> Additionally, preliminary results from a longitudinal PET study of early stage PD conducted at our center suggest that PDRP expression may also be



**FIG. 1.** A: Parkinson's disease-related metabolic pattern. This pattern of regional metabolic covariation was identified by network analysis of [<sup>18</sup>F]-fluorodeoxyglucose (FDG) PET scans from 20 PD patients and 20 age-matched normal volunteer subjects.<sup>14,123</sup> This PDRP (representing the first principal component, which accounted for 20.7% of the subject  $\times$  voxel variation) was characterized by pallidal, thalamic, pontine, and cerebellar hypermetabolism associated with metabolic decrements in the lateral premotor and posterior parietal areas. The display represents voxels that contribute significantly to the network at  $p = 0.001$ , and that were demonstrated to be reliable by bootstrap estimation ( $p < 0.0001$ ). [Voxels with positive region weights (metabolic increases) are color coded from red to yellow; those with negative region weights (metabolic decreases) are color coded from blue to purple. The numbers under each slice are in millimeters, relative to the anterior-posterior commissure line.] B: Prospectively computed PDRP scores accurately discriminate subjects by blinded network analysis. *Left:* PDRP expression (subject scores) in the 20 PD patients (filled circles) and 20 control subjects (open circles) described above. Network activity was significantly increased in the PD cohort ( $p < 0.00001$ ). *Right:* In a prospective individual case analysis (see text), we computed the expression of the PDRP (see panel A) in 14 subsequent PD patients (filled circles) and 14 control subjects (open circles). These computations were conducted using an automated routine that was blind to diagnostic category.<sup>38,41</sup> As in the original analysis, prospectively computed PDRP scores were significantly elevated in the disease group ( $p < 0.00001$ ).

sensitive to disease progression (FIG. 2). These results suggest that network imaging with FDG PET may have certain advantages in clinical trial settings: 1) FDG PET is becoming commonplace in North American, European, and Japanese medical centers. Although the tech-

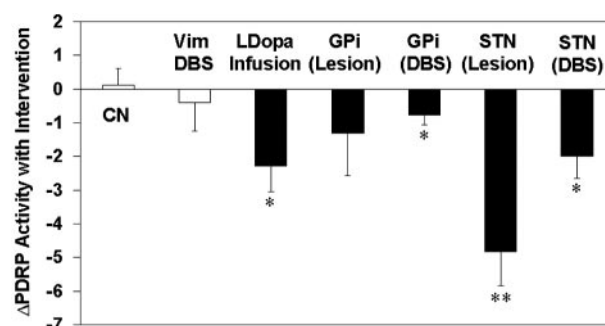


**FIG. 2.** Longitudinal changes in early stage PD: dopaminergic loss and network evolution. *Top:* Mean expression of the PD-related metabolic covariance pattern (PDRP, see FIG. 1A) at baseline, and at the second (24 months) and third (36 months) time points as part of our longitudinal FDG PET study of early stage Parkinson's disease (solid line). PDRP values increased significantly over time ( $p < 0.005$ ; repeated measures ANOVA). *Bottom:* Mean putamen DAT binding measured by [ $^{18}\text{F}$ ]-fluoropropyl  $\beta\text{CIT}$  PET in the same PD patients scanned longitudinally at the three time points (dashed line). DAT binding was expressed as percentage of the normal mean value for 15 age-matched control subjects. Unlike the longitudinal increases that occurred with PDRP expression, DAT binding declined over time ( $p < 0.04$ , reading a minimum of 30% normal for the putamen).

nology has focused upon oncology uses, brain imaging of neurodegenerative conditions can be performed conveniently employing the same imaging platforms. Indeed, pattern analysis can be performed remotely on images transferred electronically from remote sites.<sup>13,14</sup> 2) Prospective quantification of network activity can be performed on a case by case basis,<sup>41</sup> even using scans of cerebral perfusion obtained using less expensive imaging devices such as SPECT.<sup>4</sup> This methodology may ultimately be applicable to perfusion-based magnetic resonance imaging (MRI)<sup>47</sup>, thereby totally eliminating the need for tracer injections and radiation exposure. 3) Network approaches may be useful in quantifying the effects of therapy by scanning subjects before and after treatment (see below). Given the capacity of metabolic imaging to assess multiple networks in single subjects, this technique may be able to parse out motor and nonmotor treatment effects on brain function.<sup>43,48</sup>

### Network modulation by therapy

Network quantification during therapeutic interventions for PD may provide an objective means of assessing treatment effects on brain function. This imaging approach may be particularly useful in screening new agents for symptomatic therapy in that network modulation during treatment can be detected with sample sizes as small as seven subjects. Initial assessments of treatment responses employing this network approach were conducted in patients undergoing stereotaxic surgical interventions. Significant declines in PDRP activity were



**FIG. 3.** Network modulation with antiparkinsonian interventions. Bar graph illustrating relative changes in the expression of the PD-related metabolic covariance pattern ( $\Delta$ PDRP; see text), during antiparkinsonian therapy with levodopa infusion,<sup>54</sup> and unilateral ventral pallidotomy,<sup>11</sup> pallidal and STN DBS,<sup>12,15</sup> and subthalamotomy<sup>13</sup> (filled bars). For the surgical interventions,  $\Delta$ PDRP reflects changes in network activity in the operated hemispheres. With levodopa infusion, the PDRP changes were averaged across hemispheres. [The control data (open bars) represent: 1)  $\Delta$ PDRP values in the unoperated contralateral hemispheres (CN) of the surgical patients scanned in the unmedicated state; and 2) PDRP changes with unilateral Vim thalamic stimulation for tremor-predominant PD<sup>53</sup>]. [Asterisks represent  $p$  values with respect to the untreated condition (paired Student's  $t$  test). \*:  $p < 0.01$ ; \*\*:  $p < 0.005$ ].

first observed following unilateral pallidotomy.<sup>11</sup> Subsequent studies investigating the effects of deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi),<sup>12</sup> ablation of the subthalamic nucleus (STN),<sup>13,14</sup> and STN DBS,<sup>15</sup> revealed significant suppression of PDRP network activity as a common feature of these interventions (FIG. 3). Indeed, unilateral surgery resulted in significant reductions in PDRP expression in the ipsilateral hemisphere, and network modulation was not present contralateral to intervention. In most cases, the degree of network reduction correlated significantly with improvement in standardized motor ratings,<sup>12,13</sup> suggesting the potential role of this approach in the objective assessment of treatment effects in a blinded trials setting. Even though all these interventions suppressed the PDRP, there were differences in magnitude of PDRP reduction, depending upon the surgical target (GPi, STN, or Vim thalamic) or mode of treatment (ablation or DBS). In agreement with the general clinical impression that STN is superior to GPi as a treatment target,<sup>49,50</sup> the magnitude of PDRP suppression was higher for interventions involving the former structure. The finding that PDRP expression is not altered by Vim DBS for severe PD tremor is also consistent with prior studies suggesting different mechanisms underlying the akinetic-rigid and tremulous manifestation of the disease<sup>51,52</sup> in PD patients undergoing Vim DBS for intractable PD tremor.<sup>53</sup> Significant reductions in PDRP expression have also been observed following pharmacological intervention. Comparison of FDG PET scans before and during levodopa infusion revealed a significant reduction of PDRP expression during treatment.<sup>54</sup> As in the surgical interven-

tions, reductions in PDRP scores correlated with clinical improvement measured in standardized motor rating scales. Interestingly, the degree of PDRP suppression observed during levodopa infusion was similar in magnitude to that encountered with STN DBS<sup>15</sup> (FIG. 3). This observation is consistent with human and animal studies suggesting mechanistic similarities between the two forms of treatment.<sup>55</sup> In aggregate, these results indicate that the expression of disease-related brain networks may constitute a useful biomarker for objectively assessing outcomes in trials of new treatment approaches for PD and other movement disorders.

FDG PET has been used in other investigations to assess regional changes in glucose utilization occurring with levodopa treatment<sup>56</sup> as well as with STN DBS.<sup>57</sup> Rather than network analysis, these studies used statistical parametric mapping (SPM) to localize mean treatment effects subsequent to the two interventions. Although useful in identifying brain regions affected by therapy, this approach does not use regional covariation to quantify the network-wide changes that might occur during treatment. Comprehensive imaging investigations using PET in conjunction with different analytical tools will be of value in assessing the comparative efficacy of new and established treatments for PD.

Network analysis of imaging data can also be used to identify specific metabolic topographies associated with different manifestations of disease such as tremor and akinesia.<sup>51</sup> Additionally, we used PCA to characterize patterns associated with visuospatial and memory function in PD,<sup>43,48</sup> as well as affective symptoms. We found<sup>48</sup> that mnemonic functioning correlated with a specific metabolic pattern involving parietal decrements, covarying with increases in temporal cortex, pons, and cerebellum. By contrast, dysphoria in PD patients was associated with metabolic decrements in dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortex. A subsequent FDG PET study<sup>43</sup> used network analysis to demonstrate that brain metabolism in PD could be segregated into two discrete (orthogonal) networks, relating respectively to motor and nonmotor disease manifestations. The first pattern correlated with clinical ratings for bradykinesia and was topographically similar to the previously characterized PDRP. The second pattern was characterized by relative ventromedial frontal, hippocampal, and striatal hypometabolism, as well as mediodorsal thalamic hypermetabolism. Scores for this pattern correlated significantly with indices of executive function.<sup>43</sup> These studies emphasize the versatility of the network approach in clinically applied brain imaging. By quantifying the activity of multiple networks in single resting state images, this method can allow investigators to assess the differential effects of treatment on parallel neural systems using simple, widely available, and potentially automated scanning routines.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of parkinsonian syndromes on clinical grounds, even if considered to be “gold standard,” may be limited, especially at early disease stages.<sup>58–62</sup> It may be argued that the inadvertent inclusion of atypical “look alikes” may not impact the results of large-scale randomized blind studies. However, given that up to 30% of patients enrolled may not have classical PD<sup>63</sup> even with rigid inclusion criteria in early disease stages,<sup>61</sup> one can only assume that the assessment of treatment effects would be improved by eliminating heterogeneous cohorts of variant patients from all treatment arms. Correct diagnosis early in disease is also important for the patients themselves because prognosis<sup>64–66</sup> and treatment options<sup>67–72</sup> can differ substantially between patients with PD and patients with atypical parkinsonian syndromes.

Various imaging techniques for differential diagnosis have been employed.<sup>5</sup> These include imaging of glucose metabolism using FDG PET; imaging of presynaptic dopaminergic function with presynaptic ligands;<sup>34,73–76</sup> imaging of the postsynaptic dopaminergic D2-receptor binding with [<sup>123</sup>I]-(S)-2-hydroxy-3-iodo-6-methoxy-[(1-ethyl-2-pyrrolidinyl)methyl] benzamide (IBZM) SPECT and raclopride PET;<sup>77–79</sup> imaging of cardiac sympathetic denervation,<sup>80,81</sup> as well as various MRI techniques.<sup>82–84</sup>

Examples of the use of these methods have appeared in the literature of the past decade. Presynaptic dopaminergic imaging has been shown to differentiate between patients with parkinsonian syndromes on one side, and healthy control subjects and essential tremor patients on the other.<sup>34,73–76</sup> Postsynaptic dopamine D2-receptor imaging may help in distinguishing between PD and atypical parkinsonian syndromes.<sup>77–79</sup> Imaging of the cardiac sympathetic system reveals denervation in PD patients, even in early disease stages, and may differentiate between patients with multiple system atrophy (MSA) and PD.<sup>80,81</sup> However, these techniques are not generally able to discriminate between the various atypical parkinsonian syndromes.

Several MRI techniques have been employed for differential diagnosis in parkinsonian syndromes. Even though routine MRI shows characteristic changes as an atrophic putamen and a hyperintense rim of the putamen in MSA patients, these changes are observed in only half of subjects suspected as having this diagnosis.<sup>82</sup> Recent MRI studies have revealed decreases of the apparent diffusion coefficient of the putamen in MSA patients<sup>83</sup> as well as decreases in the magnetization transfer ratio in regions of neuronal degeneration in MSA and progressive supranuclear palsy (PSP) patients.<sup>84</sup> These noninvasive methods may ultimately prove helpful in differentiating these syndromes from PD.

Evaluation of regional glucose utilization with FDG PET has revealed characteristic metabolic patterns for the different parkinsonian syndromes. As described above, clinical PD is characterized by a distinctive metabolic pattern involving increased activity in the putamen/globus pallidus, thalamus, cerebellum, and brainstem, as well as relative reductions in cortical motor regions.<sup>3,34,85,86</sup> Characteristic patterns have been associated with other parkinsonian syndromes. MSA is characterized by metabolic decreases in the lentiform nucleus and cerebellum.<sup>87–92</sup> By contrast, PSP is associated with decreased metabolism in midline frontal cortical areas and the brainstem.<sup>74,93–95</sup> Corticobasal ganglionic degeneration (CBGD) is associated with relatively reduced glucose metabolism in many cortical areas, including the insula and in the basal ganglia of the hemisphere contralateral to the most affected side.<sup>96–98</sup>

Results of an ongoing study<sup>99</sup> have shown that these characteristic patterns can prospectively distinguish between patients with PD, MSA, PSP, CBGD, and healthy age-matched control subjects. In a large cohort of patients who underwent FDG PET imaging for purposes of differential diagnosis of parkinsonian disorders at North Shore University Hospital between 1995 and 2001, a probable/likely clinical diagnosis was achieved at follow-up by blind review undertaken independently by two movement disorder specialists. Blind reading of the scans by either visual inspection or a single subject statistical parametric mapping (SPM) approach were compared in terms of their ability to conform with an ultimate diagnosis achieved at follow-up. Overall, correct imaging diagnosis was obtained in about 90% of all subjects using the SPM approach and in about 84% by blind visual inspection of the FDG scans.<sup>99</sup> These results emphasize the excellent potential of FDG PET imaging to augment clinical assessments in the evaluation of subjects for potential enrollment in pharmaceutical trials for PD.

#### METABOLIC NETWORKS IN OTHER MOVEMENT DISEASES: POTENTIAL SURROGATE MARKERS FOR CLINICAL TRIALS

In contrast to PD where PET and SPECT techniques can provide quantitative descriptors of dopaminergic dysfunction, other movement disorders are not associated with specific, localized neurochemical abnormalities that can be measured *in vivo*. However, the quantification of disease-related patterns of glucose metabolism may provide unique data regarding diagnosis and treatment effects in situations in which other imaging approaches are lacking or insufficient. Indeed, we have used FDG PET to describe unique metabolic networks associated with Huntington's disease,<sup>37,100</sup> idiopathic torsion dystonia,<sup>38,39</sup> and Tourette syndrome.<sup>40,101</sup>

#### Huntington disease

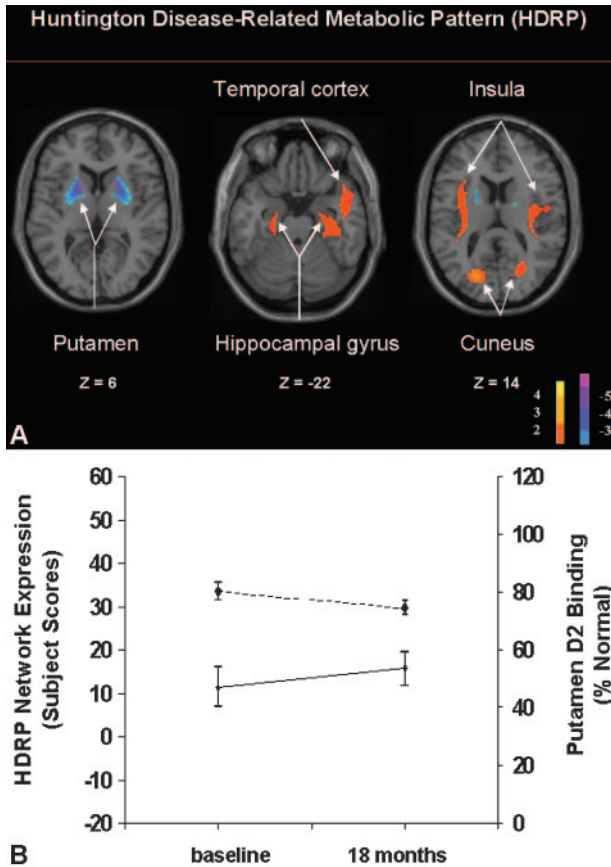
Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressively worsening abnormalities of movement and cognition. While investigating the glucose metabolism in HD patients, we identified an HD-related pattern (HDRP). HDRP is characterized by caudate and putaminal hypometabolism but also includes mediotemporal metabolic reductions as well as relative metabolic increases in the occipital cortex (FIG. 4A). Assessment of presymptomatic HD gene carriers revealed that HDRP expression is not only elevated before the development of clinical symptoms, but may also be increased significantly at a time when striatal D<sub>2</sub> receptor binding is still normal.<sup>37</sup> Results of an ongoing longitudinal study show that HDRP expression is also a valuable measure for disease progression in HD patients (FIG. 4B).<sup>100</sup> It is currently not known whether HDRP expression is more sensitive to advancing neurodegeneration in the preclinical period than either striatal D<sub>2</sub> binding<sup>102</sup> or MRI-based measures of local atrophy.<sup>103</sup> Quite possibly, the most accurate assessment of disease progression in the preclinical period of HD will be achieved with multiple imaging approaches in combination.<sup>104</sup>

#### Torsion dystonia

Torsion dystonia is a movement disorder characterized by sustained muscle contractions with twisting and repetitive movements or abnormal postures. Although primary torsion dystonia (PTD) is linked to several genetic mutations,<sup>105</sup> there is no consistent histopathology associated with this disorder. Nonetheless, our FDG PET studies revealed a reproducible pattern associated with primary dystonia.<sup>38,39,106</sup> This torsion dystonia-related pattern (TDRP) is characterized by hypermetabolism of the basal ganglia, cerebellum, and SMA (FIG. 5A).<sup>38</sup> Whereas this characteristic pattern was initially identified in affected PTD patients,<sup>106</sup> its presence was subsequently confirmed in genotyped subjects, even without clinical manifestations.<sup>38,39,107</sup> Further studies revealed subtle behavioral impairments in nonmanifesting DYT1 carriers,<sup>108</sup> as well as abnormalities in brain activation responses during movement and nonmotor learning. It is therefore possible that TDRP expression can represent an endophenotype for dystonia, which may be useful in gene identification in at risk populations (FIG. 5B). The clinical spectrum of dystonia may indeed be broader than previously suspected,<sup>109</sup> with separate structural/functional abnormalities underlying the motor and nonmotor manifestations of the disorder.<sup>110,111</sup> How genotypic and phenotypic patterns are altered by the treatment of dystonia, particularly DBS, is a topic of ongoing investigation.

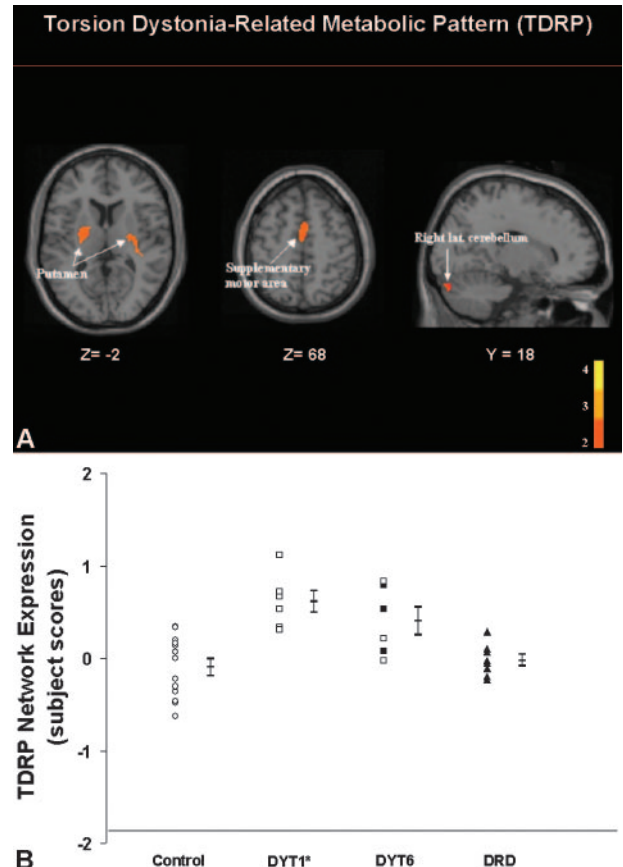
#### Tourette syndrome

Gilles de la Tourette's syndrome (TS) is a movement disorder characterized by multiple motor and vocal tics



**FIG. 4.** A: Huntington's disease-related metabolic pattern (HDRP). This pattern of regional metabolic covariation was identified by network analysis of [<sup>18</sup>F]-fluorodeoxyglucose (FDG) PET scans from 10 presymptomatic HD gene carriers and 20 age-matched normal volunteer subjects. This HDRP (representing the first principal component, which accounted for 18% of the subject × voxel variation) discriminated carriers from controls ( $p < 0.0001$ ) and was characterized by relative metabolic decreases in the striatum, associated with increases in the temporal cortex, insula, and occipital association cortex. [The display represents voxels that contribute significantly to the network at  $p = 0.01$ . Voxels with positive region weights (metabolic increases) are color coded from red to yellow; those with negative region weights (metabolic decreases) are color coded from blue to purple. The numbers under each slice are in millimeters, relative to the anterior-posterior commissure line.] B: Preclinical progression of HDRP: dopaminergic loss and network evolution. *Bottom*: Mean expression of the HD-related metabolic covariance pattern (HDRP, see panel A) in preclinical gene carriers scanned at baseline and at 18 months as part of our longitudinal FDG PET study (solid line). HDRP values increased significantly over this time period ( $p < 0.03$ ; paired  $t$  test). *Top*: Mean RAC binding in the same preclinical HD cohort scanned at baseline and at 18 months (dashed line). Striatal D2 receptor binding was abnormally reduced at both time points ( $p < 0.001$  relative to gene negative controls). RAC binding declined significantly between the two time points ( $p < 0.05$ ; paired  $t$  test).

of varying intensity. Despite its well-known clinical presentation, the histopathology and the underlying physiologic mechanisms mediating the clinical manifestations of TS are unknown. An early network analysis of FDG PET data in TS<sup>40</sup> revealed the disease-related metabolic patterns. One pattern was characterized by metabolic



**FIG. 5.** A: Torsion dystonia-related metabolic pattern (TDRP). This pattern of regional metabolic covariation was identified by network analysis of [<sup>18</sup>F]-fluorodeoxyglucose (FDG) PET scans from nonmanifesting DYT1 gene carriers and control subjects (see text). This TDRP was characterized by bilateral covarying metabolic increases in the putamen, extending into the globus pallidus (GP), the SMA, and the cerebellar hemisphere. Subject scores for this pattern discriminated the DYT1 carriers from controls ( $p < 0.002$ ). The display represents voxels that contribute significantly to the network at  $p = 0.001$ . Voxels with positive region weights (metabolic increases) are color coded red. B: TDRP activity in dystonia genotypes (prospective FDG/PET study). Scatter diagram of torsion dystonia-related pattern subject scores computed prospectively in six new nonaffected DYT1 gene carriers, six DYT6 gene carriers, seven dopa-responsive dystonia (DRD) patients, and 13 control subjects. Subject scores were abnormally elevated in DYT1 ( $p < 0.001$ ) and DYT6 carriers ( $p < 0.007$ ), but not in DRD patients ( $p = 0.4$ ). The error bars indicate subgroups standard errors of the mean. Circles, normal controls; squares, subjects with genotypes associated with primary torsion dystonia; triangles, DRD patients; open symbols, clinically nonmanifesting subjects; filled symbols, affected dystonia patients.

increases in the lateral premotor and supplementary motor association cortices and the midbrain, perhaps secondary abnormal spontaneous movements occurring during PET imaging. The second pattern was characterized by metabolic decreases in the caudate and thalamus, with less pronounced decrements in the lentiform nucleus and the hippocampus. This network correlated significantly with Tourette Syndrome Global Scale (TSGS) ratings. Importantly, this TS-related topography has recently

been identified in a subsequent group of patients scanned on a modern tomograph. A voxel-based network analysis of these FDG PET data<sup>101</sup> confirmed that this pattern predicted TSGS ratings, indicating its potential as a surrogate marker for this condition in future clinical trials. This may be particularly relevant in movement disorders such as TS in which fully objective treatment markers are not available.

#### OTHER IMAGING APPROACHES POSSIBLY APPLICABLE TO MONITOR TREATMENT

Investigations have been conducted to assess changes in brain activation responses during therapy. These imaging studies have been conducted with <sup>15</sup>O-water (H<sub>2</sub><sup>15</sup>O) PET and functional MRI methods during a variety of interventions such as dopaminergic therapy (apomorphine,<sup>112</sup> levodopa<sup>113,114</sup>) and DBS.<sup>115</sup> These studies have been reviewed recently.<sup>116,117</sup> Despite the elegance of this approach, the demands of experimental control of task performance during dynamic imaging make this strategy less desirable for the study of treatment effects in large populations. The assessment of brain activation responses with treatment requires the performance of specified motor and/or cognitive tasks in different treatment and, thus, changes of brain perfusion or BOLD signal during task performance are dependent on factors such as movement frequency and force<sup>118,119</sup> as well as cognitive load.<sup>120</sup> These parameters are particularly difficult to control in a motorically impaired patient population. Moreover, task equivalence within subjects across treatment conditions is necessary if the activation comparisons are truly to reflect the inherent effects of therapy on brain function. Nonetheless, carefully controlled activation studies may shed light on the mechanisms by which different therapeutic strategies modulate neural circuitry during motor performance and learning.<sup>121,122</sup> Indeed, network analysis of these data has revealed reproducible patterns of regional activation that may be used to assess the effects of therapy on higher order motor functioning.<sup>123</sup>

#### FUTURE DIRECTIONS

New imaging methodologies are emerging<sup>124</sup> that may be useful in the quantitative assessment of potential neuroprotective agents. Recent MRI studies in parkinsonian syndromes have revealed changes in the apparent diffusion coefficient<sup>83</sup> and the magnetization transfer ratio,<sup>84</sup> perhaps reflecting aspects of the underlying pathological features of these conditions. Such techniques may provide interesting biomarkers for neurodegenerative processes that may be suitable for neuroprotective trials. Diffusion tensor imaging<sup>124</sup> has revealed microstructural changes in the white matter of DYT1 gene carrier in the subgyral white

matter of the sensorimotor cortex.<sup>110</sup> This suggests that abnormal anatomical connectivity in cortical-subcortical pathways may be important in determining whether carriers are more or less likely to develop clinical signs of disease, and may be the basis for variable penetrance in some inherited neurological conditions.<sup>107</sup> Similar mechanisms may be involved in other movement disorders in which conventional methods have failed to reveal consistent functional or anatomical abnormalities.

Perfusion-weighted MR imaging<sup>124</sup> represents another emerging imaging method with potential promise in the assessment of disease progression and treatment effects. Because cerebral blood flow and metabolism are generally coupled in neurodegenerative disorders, changes in cerebral perfusion may be used as a simple noninvasive, radiation-free alternative to PET and SPECT for network quantification in the resting state (e.g.,<sup>4</sup>). Although appealing, more research is needed to determine the ultimate utility of these methods in the context of clinical trials.

#### SUMMARY

Functional neuroimaging has contributed greatly to our understanding of the pathophysiology and natural history of the movement disorders. Recently, these methodologies have generated a variety of imaging-based biomarkers for the assessment of both symptomatic and neuroprotective therapies for this class of neurological disease. Although the quantification of dopaminergic function with imaging has shown great promise in clinical trials for PD, this approach may be less appropriate for other movement disorders in which other neurotransmitter systems may be involved. In this review, we demonstrate the use of alternative metabolic imaging strategies for the objective measurement of treatment effects in PD. In addition to providing novel imaging biomarkers for motor and nonmotor manifestations of PD, this general approach may be of value in the determination of treatment outcomes in other movement disorders in which a specific neurochemical pathology is not precisely known.

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