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Functional Imaging of Cerebral Blood Flow and Glucose Metabolism in Parkinson's Disease and Huntington's Disease

Yilong Ma^{1,2,3} and David Eidelberg^{1,2,3}

¹Center for Neurosciences, Feinstein Institute for Medical Research, North Shore–Long Island Jewish Health System, New York University School of Medicine, Manhasset, NY, USA

²Department of Neurology, New York University School of Medicine, Manhasset, NY, USA

³Department of Medicine, New York University School of Medicine, Manhasset, NY, USA

Abstract

Brain imaging of cerebral blood flow and glucose metabolism has been playing key roles in describing pathophysiology of Parkinson's disease (PD) and Huntington's disease (HD), respectively. Many biomarkers have been developed in recent years to investigate the abnormality in molecular substrate, track the time course of disease progression, and evaluate the efficacy of novel experimental therapeutics. A growing body of literature has emerged on neurobiology of these two movement disorders in resting states and in response to brain activation tasks. In this paper, we review the latest applications of these approaches in patients and normal volunteers at rest conditions. The discussions focus on brain mapping studies with univariate and multivariate statistical analyses on a voxel basis. In particular, we present data to validate the reproducibility and reliability of unique spatial covariance patterns related with PD and HD.

Keywords

Neurodegenerative disorders; Parkinson's disease; Huntington's disease; Cerebral blood flow; Metabolism; Brain mapping; Spatial covariance analysis

Introduction

Pathogenesis of neurodegenerative disorders has been investigated extensively with functional brain imaging of radioligands that bind to relevant neurotransmitters and neuroreceptors as well as general radiotracers for the measurement of regional cerebral blood flow (rCBF) and cerebral metabolic rate of glucose (rCMRglc). Brain imaging of rCBF and rCMRglc can provide signature biomarkers to describe pathophysiological mechanisms and clinical correlates over the whole brain by using either region of interest (ROI) analysis or voxel-based brain mapping. Both univariate and multivariate statistical approaches have been developed for brain mapping analysis after transforming individual images into a standard anatomical space [1–3]. Brain images are also spatially smoothed or

realigned between conditions as part of the preprocessing steps. Statistical parametric mapping (SPM) is a powerful univariate statistical method for detecting localized changes in brain function. By contrast, multivariate methods are more sensitive for assessing systematic changes that reflect potential interactions among a set of functional brain regions of interest.

Network analysis based on principal component analysis (PCA) is one of the versatile multivariate statistical brain mapping methods in neuropsychiatric disorders and normal aging [4–6]. This is a data reduction technique that accounts for variance in the images in decreasing degree of importance; it does so by projecting original images into a series of principal components after removing regional or subject mean from the data. This allows identification of unique 3-D topographic patterns to describe spatial covariation among a set of functionally dependent brain areas. Expressions of each pattern can not only discriminate between different patient groups but also predict behavior performance at rest and activation conditions. By applying this method to [^{18}F]FDG and [^{15}O]H₂O positron emission tomography (PET) images of patients and control subjects, we and others have previously generated specific spatial covariance patterns for a series of neurodegenerative disorders such as Parkinson's disease (PD), Huntington's disease (HD), torsion dystonia, and Alzheimer's disease (AD) [7–10]. A subject score can be computed prospectively on a single case basis and has been shown to correlate with independent measures of disease severity and response to treatment. The applications of this class of approaches have recently been reviewed in detail (see [11]).

Imaging methods based on these approaches have been used extensively in the study of neurodegenerative disorders. For instance, both rCBF and rCMRglc data from PET or single photon emission computed tomography (SPECT) can discriminate among controls, AD, and different forms of dementia as well as identify neural bases of corresponding cognitive dysfunction [12–16]. Imaging variables can serve as objective predictors of AD in individuals with mild cognitive impairment based on unique cerebral lesions related with clinical manifestation and genotype. This type of imaging work has also been pursued in mapping phenotype- or genotype-specific abnormal metabolism in primary torsion dystonia [17, 18] and investigating impaired motor activation response at baseline or after treatment with deep brain stimulations [19–21].

In this review, we discuss brain imaging studies at rest in PD and HD as examples of hypokinetic and hyperkinetic movement disorders, respectively. Both conditions are associated with localized deficits in basal ganglia that cause dysfunction at a systems level across the entire brain by disrupting signal transmission within different components of the cortico-striatopallidal-thalamocortical (CSPTC) circuitry. Because of the limited scope, this article is not meant to provide a systematic review of all the resting state investigations in this area. Instead, we focus on the work over the last decade in developing and validating biomarkers using quantitative measures of regional blood flow and glucose metabolism. Special emphasis will be given to novel applications of multivariate statistical analysis from our laboratory.

Parkinson's Disease

PD results primarily from progressive losses of dopamine neurons in the nigrostriatal system leading to widespread motor symptoms and cognitive impairments. Imaging with PET and SPECT has been widely used to reveal regional abnormality in presynaptic and postsynaptic markers as well as hemodynamic and metabolic brain function in this disorder (e.g., [22]). Previous binding studies based on many radioligands have consistently shown dopamine deficiency and terminal degeneration in caudate and putamen with increased level of dopamine D2 receptors. Here we describe the use of CBF and FDG uptake in establishing clinical correlation in PD and assessing anti-parkinsonian therapies.

Imaging of Pathophysiology

Significant alternations in striatal and cortical function have been demonstrated in primate models of PD induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [23]. rCBF is increased in the globus pallidus but decreased in the caudate, putamen, thalamus, and primary motor cortex. Early investigations in humans with PET have shown that rCBF in striatal areas remains unchanged in PD as compared with the normal population [24], whereas a SPECT perfusion study has revealed that medication-induced hallucinations in PD may be related with significantly lower rCBF in left temporal regions [25]. Measurement of rCBF has limited use in resting states because of its relatively lower signal-to-noise ratio, but is more valuable in studying brain activation response and therapeutic interventions (see below).

PET imaging with 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) provides a more direct measure of brain function by quantifying regional glucose metabolism. The previous animal study on PD has revealed pallidal hypermetabolism with hypometabolism in striatal, thalamic, and motor regions in agreement with rCBF data [23]. In a recent study in primate models of PD, we have observed relative metabolic increases in the ipsilateral globus pallidus and the contralateral cerebellar hemisphere after unilateral MPTP injection [26]. As the most common imaging technique available, this method has been used mainly to distinguish PD from atypical parkinsonism such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) [27–29]. In a systematic analysis of FDG-PET scans from a large cohort of parkinsonian patients, we have used SPM to establish several characteristic patterns of abnormal metabolism for each of these movement disorders relative to age-matched normal controls [30]. A set of disease-specific brain templates and criteria were created for more accurate diagnosis of each entity. Imaging-assisted examination based on single-subject SPM comparison with controls improved the accuracy of differential diagnosis in each individual patient from 75% to 90%. This was achieved by blind comparison of the imaging result with clinical assessment made at two-year follow-up. Additionally, we found that glucose metabolism in PD increased in the dorsal lateral putamen, thalamic, cerebellar, and cortical motor areas with hypometabolism in the parietal cortex.

Brain network analysis—PCA-based network analysis has been successfully applied to identify PD-related covariance patterns associated with motor and cognitive functioning.

The PD-related pattern (PDRP; [7, 31]) was identified on a voxel basis by applying PCA to FDG images acquired at rest from 33 PD patients (age 57 ± 8 years; Hoehn & Yahr stage 2.6) and 33 age-matched normal controls (age 55 ± 13 years). In this analysis, the PDRP represented the first principal component whose expression in individual subjects significantly ($p < 0.0001$) discriminated PD patients from normal controls. Accounting for 21% of subject-voxel variance, this pattern (Fig. 1A) was marked by pallidal, thalamic, pontine, and cerebellar hypermetabolism, covarying with hypometabolism in the lateral premotor cortex, supplementary motor area, and posterior association cortices. This brain network is highly correlated with that reported by us previously [18, 32] and has been validated in the metabolic data from independent imaging centers [33, 34]. It has previously been shown that PDRP scores correlate with pallidal neuronal activity and clinical UPDRS motor ratings in PD patients (e.g., [35–37]).

The PD-related cognitive pattern (PDCP) was identified in the resting-state FDG images of 13 nondemented PD patients (age 59 ± 10 years; Hoehn & Yahr stage 3.2; MMSE = 28.4 ± 2) [38]. The PDCP topography represented the second principal component whose expression in individual subjects was negatively correlated ($R^2 = 0.40$; $p < 0.02$) with performance on the California Verbal Learning Test and other neuropsychological tests of memory and executive function. Accounting for 19% of subject-voxel variance, this pattern (Fig. 1B) showed hypometabolism in the prefrontal, preSMA, and superior parietal cortices and hypermetabolism in the right caudate and bilateral thalamus and cerebellum. This abnormal brain network is in good agreement with that obtained previously with another multivariate network approach based on partial least squares [39].

Both PDRP and PDCP described here are very similar to topographic patterns generated from an early study, which conducted a PCA on ROI data of rCMRglc in a different cohort of PD patients and control subjects [33]. Two orthogonal principal components were detected in this cohort corresponding to PDRP and PDCP, respectively. The PDRP was found to separate the groups and correlate with UPDRS motor ratings in patients, whereas the PDCP correlated only with cognitive performance measures, but not with UPDRS motor scores. These results suggest that topographically distinct brain networks may subserve motor and cognitive dysfunction in PD involving different components within the CSPTC loop.

We have investigated the test–retest reproducibility of PD-related brain networks in the context of clinical trial settings involving distinct patient populations [7]. We first chose control subjects and PD patients who were scanned with both tracers to examine the compatibility of rCBF and rCMRglc data in quantifying network activity of these two abnormal metabolic patterns. We then used within-session H_2O -PET scan pairs in normal controls and several groups of PD patients selected to participate in a longitudinal study or receive levodopa infusion and deep brain stimulations (DBS) at the internal globus pallidus (GPi) and subthalamus (STN), respectively. We also used between-session FDG-PET scan pairs acquired both off and on dopaminergic medications separated by up to two months. To test the within-subject reliability, subject scores of both PDRP and PDCP were computed prospectively from all of these PET scans using an automated algorithm (see [40] for details).

CBF-FDG Correlation—PDRP scores from rCBF and rCMRGlc scans were highly correlated with each other within PD patients (Fig. 2A; $R^2=0.61$; $p<0.001$). The corresponding PDCP scores were also correlated to a high degree in the same PD group (Fig. 2B; $R^2=0.52$; $p<0.001$). In addition, correlations were significant in the combined group of PD patients and healthy volunteers for both PDRP ($R^2=0.62$; $p<0.001$) and PDCP ($R^2=0.48$; $p<0.001$). Normal volunteers had less variability in PDRP or PDCP subject scores with a mean of zero.

We have observed a strong correlation between PDRP scores calculated from CBF and FDG images measured in the same individuals. Likewise, the correlation between CBF and FDG subject scores for PDCP is also highly significant. These results indicate that CBF and FDG uptake over the whole brain are coupled to a high degree and network activity can be reliably quantified with CBF data as has been shown in PD with [99 mTc]-ECD SPECT for imaging cerebral perfusion [41, 42]. This creates the basis for identifying disease-related brain networks in CBF scans obtained using noninvasive arterial spin label imaging methods based on magnetic resonance imaging (MRI) [43–46]. This technique is highly reproducible in normal volunteers and agrees well with measurements from H₂O PET.

Although CBF images can be used to evaluate functional abnormality in PD on a system level, we found that only 50–60% of variability in network activity was shared across the CBF and FDG data (Fig. 2). This suggested that CBF and glucose metabolism may to some degree be uncoupled in PD on a regional level. Indeed, the relatively weaker correlation in the PDCP scores suggests an increase in this uncoupling in regions associated with cognitive dysfunction in PD [38]. This potential dissociation is an ongoing topic of investigation.

Prospective Validation—We observed that subject scores prospectively computed from CBF data discriminated PD and normal groups with a slight difference (Fig. 3). PDRP activity separated both early and late PD patients from controls, whereas PDCP activity discriminated only late PD patients from controls. Network activity was significantly higher in late PD patients than in early PD patients for both PDRP and PDCP. This behavior compared favorably with the results obtained from FDG images in several independent cohorts of patients and controls [7, 31]. However, PDCP activity did not discriminate between early PD and normal groups, reflecting preserved cognitive function in early PD. This is in contrary to PDRP expression, which is more related to motor disability. Indeed, this cross-sectional difference between the PDRP and PDCP networks in relation to disease severity has recently been observed in a longitudinal FDG-PET study of disease progression [47].

Using the same CBF data in Fig. 3, we found a very strong correlation ($p<0.0005$) between PDRP and PDCP network values in the controls ($R^2=0.71$) and all PD patients ($R^2=0.68$). This indicated that both patterns are highly related as a pair of key features of PD pathology although we had shown elsewhere that only PDRP activity correlates moderately with clinical ratings of disease severity. To compare their potential diagnostic value, we performed the ROC analysis on this dataset. As expected, we observed better discrimination between the controls and all PD patients by PDRP [area under the curve (AUC)=0.84] than PDCP (AUC=0.67). We also found that the group separation improved slightly (AUC=0.89)

compared with those of the individual networks by using a linear regression with both network expressions. This shows that a combination biomarker may be more useful in clinical diagnosis and functional assessment of PD in single patients.

We found excellent within-subject reproducibility for PDRP and PDCP subject scores in resting state H₂O PET scans conducted within one hour (Fig. 4). Both subject scores exhibited a very high reliability (intraclass correlation coefficient [ICC] of 0.95 and 95% confidence of interval [CI] of 0.90 to 0.98) in early and advanced PD patients in the absence of any acute treatment, as well as in each subset of patients after levodopa infusion and DBS procedures, respectively. These scores were also highly reproducible (ICC of 0.94 and 95% CI of 0.87 to 0.97) in PD patients scanned over two months by FDG-PET while on dopaminergic medication. This is comparable with high reproducibility shown by within-session CBF measurements made on levodopa, but also agrees with that given by FDG data taken one day apart and off medication from five early-stage PD patients. For comparison, both PDRP and PDCP scores show excellent test–retest reliability in normal controls as well using CBF and FDG scan pairs measured within session.

In addition to PD-related brain networks, we have recently generated specific metabolic covariance patterns for MSA, PSP, and dopa-responsive dystonia to further help differential diagnosis of clinical parkinsonism [18, 40]. This allows us to test the probability of having any one of these conditions by computing the expression of respective brain networks in an individual patient on an automated, high throughput basis. The accuracy of diagnosis at early clinical stages is expected to improve in conjunction with single-subject SPM analysis based on disease-specific brain templates [30]. This approach is currently being validated for diagnostic use.

Therapeutic Interventions

PET imaging of CBF and FDG uptake has been particularly valuable in revealing functional mechanisms of medical and surgical interventions in PD. The specific action of therapy is delivered by either enhancing endogenous dopamine level or modulating different nodes within the CSPTC circuitry. rCBF measurement is proving most useful in charting treatment-mediated brain activation response in PD under task conditions. For example, it has been shown by SPM analysis that STN stimulation decreased motor cortex activity at rest [48] and enhanced movement-related activity of motor-association cortex [49], but suppressed activation of the right orbitofrontal cortex and verbal fluency-associated activation within a left-sided frontotemporal network [50]. These observations help to explain the improved motor function and worsening verbal-fluency performance after STN DBS. Neural bases of impaired sequence learning in PD during disease progression and effective therapies have been explored with both SPM and PCA-based network methods (see review [51]).

We have previously revealed different effects on metabolic brain function after levodopa infusion, DBS at GPi, and ablative lesioning at STN [8, 32, 52, 53]. These interventions consistently restore abnormal glucose metabolism on a regional basis and suppress the PDRP, with the degree of regional change or network modulation correlating with the clinical treatment response. We have recently compared metabolic responses between STN

lesioning and DBS [54]. SPM analysis revealed that metabolism was reduced in the GPi and caudal midbrain but elevated in the posterior parietal cortex by both STN procedures ($p<0.01$). Although reductions in GPi were more evident with lesion, elevations in posterior parietal metabolism were more pronounced with stimulation. Furthermore, we noted that PDRP activity declined significantly ($p<0.02$) with both STN lesioning and stimulation.

In another study, we found that both STN DBS and levodopa therapy [37] were associated with significant ($p<0.001$) metabolic reductions in the putamen/globus pallidus, sensorimotor cortex, and cerebellar vermis, as well as increases in the precuneus (BA 7). The metabolic effects of the two interventions differed in the STN and medial prefrontal cortex, with relative increases with stimulation in the former structure and decreases in the latter. Network quantification disclosed reductions in PDRP activity with both interventions, which correlated with clinical improvement ($p<0.05$). Metabolic increase in the parietal areas and decreases in the cerebellum we observed above agree with an earlier study on STN DBS [55]. We conclude that suppression of pathological brain networks is a critical feature of the treatment response in parkinsonism. Nevertheless, glucose metabolism at a regional level may differ among these interventions.

To demonstrate the independence of the cognitive pattern in PD, we have also examined therapeutic responses of the PDCP network to the treatment modalities described above, which target mainly motor symptoms. Interestingly, we observed that PDCP subject scores did not change significantly before and after these interventions. It is expected that PDCP expression is more sensitive to therapies targeting cognitive symptoms in PD patients. Nonetheless, in a recent study of oral donepezil for PD cognitive symptoms, we found no significant change in PDCP expression with treatment. Further studies using different treatment strategies will be of interest.

Cellular-based transplantation neurosurgery represents a new class of neurorestorative therapies for advanced PD. PET with dopaminergic markers has mainly been used in clinical trials of dopamine cell transplantation and infusion of nerve growth factors. Functional recovery is also been examined by using brain activation paradigms with CBF PET. These aspects have recently been reviewed (e.g., [22]). However, there is some evidence that PET imaging with FDG can also be useful for evaluating the viability of neural grafts. For instance, human differentiated chromaffin cells can be grafted into the caudate nucleus of PD patients [56]. This procedure was capable of generating substantial clinical improvement that was correlated with increased regional glucose metabolism while allowing a 70% decrease in levodopa medications.

Gene therapy is a novel technology capable of restoring functional integrity in PD at advanced stages. One of the promising methods aims to inhibit hyperactivity in STN output by transfection with adeno-associated virus (AAV) containing the gene for glutamic acid decarboxylase (GAD). In a recent animal study, 13 macaques were rendered hemiparkinsonian by right intracarotid MPTP injection [26]. Seven animals were injected with AAV-GAD into the right STN, whereas six received an AAV gene for green fluorescent protein (GFP). Motor ratings were taken over approximately one year followed by FDG-PET and histological examination at the end. The GAD animals exhibited an

increase in glucose utilization in the ipsilateral motor cortex relative to GFP controls ($p<0.001$). Metabolism in this region correlated with clinical ratings at endpoint ($p<0.01$). Histology confirmed GAD expression in treated animals. These findings suggest that STN AAV-GAD is well tolerated and potentially effective in a primate model of PD.

In the first open-label, safety-tolerability dose-escalation trial of this novel intervention we have used FDG-PET to assess the effects of AAV vector delivery of GAD into the STN in PD [57]. Twelve advanced PD patients received unilateral treatment at the right STN and were evaluated at baseline and six months post-surgery. SPM analysis revealed decreases in brain metabolism in the internal globus pallidus and ventrolateral thalamus ipsilateral to AAV-GAD, without any significant changes on the contra-lateral side. Improvements in UPDRS motor ratings correlated with increases in brain metabolism in the primary ($R^2=0.69$; $p<0.001$) and supplementary ($R^2=0.73$; $p<0.001$) motor areas on the side ipsilateral to the AAV-GAD. The results from both animal models and human trials are consistent with imaging studies in other subthalamic surgical therapies for PD, suggesting that STN AAV-GAD therapy is potentially effective in the treatment of advanced PD.

In summary, brain imaging of rCBF and rCMRglc allows identification of signature biomarkers for differential diagnosis of clinical parkinsonism. Multivariate network analysis can generate specific topographic patterns related to motor and cognitive abnormalities, respectively. Recent work has demonstrated that these covariance patterns are highly reliable descriptors of abnormal cerebral blood flow and metabolism underlying PD in a resting state. Both provide objective imaging markers for assessing the time course of disease progression and therapeutic interventions.

Huntington's Disease

HD is a hereditary disorder in which degeneration of neurons in the striatum leads to motor, cognitive, and behavioral dysfunction. The genetic mutation is an unstable expanded DNA trinucleotide [cytosine–adenosine–guanosine (CAG)] repeat whose length predominantly determines the expected age of onset of motor symptoms in affected patients. Prior investigations with MRI have revealed progressively widespread brain atrophy in striatal and selective cortical areas in both presymptomatic and symptomatic HD subjects [58–60]. PET studies have used radiotracers that measure dopamine D1/D2 receptor binding, cerebral blood flow, and glucose metabolism. It has been reported that radiotracer binding to dopamine D1/D2 receptors may be normal or lower in HD mutation carriers in the preclinical period, but is significantly reduced in HD patients [61–63]. Dopamine receptor losses occur mainly in the striatum [64–66] as well as in the cortex [67]. These postsynaptic abnormalities have been shown to correlate with clinical or cognitive symptoms and become more pronounced with progression of HD. In the following sections, we summarize brain imaging studies using both rCBF and rCMRglc measurements.

Evaluation of Pathophysiology

MicroPET technology is increasingly becoming available in exploring cerebral dysfunction in transgenic animal models of HD. One study showed that energy utilization ipsilateral to the lesion in rats was reduced severely one week after intrastriatal excitotoxin injections

[68]. The decrements in energy metabolism were even more prominent five to seven weeks later. This type of imaging techniques has paved the way for evaluating behavior correlates and response to therapies in living animals.

FDG-PET has been employed to investigate abnormal metabolic substrate in both clinically unaffected subjects at risk for HD and symptomatic patients. Striatal glucose metabolism is reported to be normal or reduced in presymptomatic HD (p-HD) individuals [61, 63, 69]. By contrast, striatal hypometabolism is consistently observed in symptomatic HD patients and correlated with different aspects of impaired functional status [70–73]. Thalamic hypermetabolism as well as cortical hypometabolism and hypoperfusion have also been seen in early stage and symptomatic HD patients with PET or SPECT imaging [74–76]. A recent study has shown significantly decreased glucose metabolism in the striatum and temporal and frontal cortical lobes in both preclinical and affected HD subjects [77]. Progressively decreased glucose uptake is seen in the striatum and cortex when assessed longitudinally.

As part of a multimodality longitudinal study, we have acquired FDG-PET and MRI data at baseline and 1.5 years in 12 p-HD gene carriers (CAG repeat length=42±2; age=47±12 years). The time to clinical onset was estimated to be 10±9 years at baseline using a lookup table [78]. We first used SPM analysis to detect local changes in glucose metabolism in the p-HD gene carriers relative to 11 age-matched controls (41±15 years) and between two time points. In addition to confirming the regional abnormalities summarized above, we also revealed hypometabolism in the cingulate cortex as well as hypermetabolism in the cerebellum and occipital cortex (Fig. 5). Altered glucose metabolism was more spread and progressed differently in these anatomical areas of interest over the course of 1.5 years.

We then performed PCA using the combined group of p-HD gene carriers at baseline and normal controls to identify a specific abnormal metabolic topography [79]. We found a significant HD-related covariance pattern (HDRP) as the first principal component accounting for 18% of subject-voxel variance. This pattern was characterized by relative bilateral increases in thalamic, occipital, and cerebellar glucose metabolism associated with bilateral covariate decreases in striatal metabolism (Fig. 6A). Subject scores in the p-HD gene carriers at baseline were elevated ($p<0.05$) as compared with normal controls (Fig. 6B). Region weights of this pattern were highly correlated ($R^2=0.76$; $p<0.0001$) with those reported in the previous HDRP pattern from a different p-HD cohort [80].

We subsequently found that mean subject scores in the p-HD cohort increased further by prospectively calculating the expression of HDRP in each of the asymptomatic gene carriers at follow-up. In addition, HDRP scores at each time point correlated with the estimated years to onset ($R^2>0.66$; $p<0.01$) and caudate D2 receptor binding ($R^2>0.62$; $p<0.01$) measured concurrently in the same cohort. It is of interest to note that on a regional level we observed a strong positive correlation ($R^2>0.7$; $p<0.005$) between dopamine D2 receptor binding and glucose metabolism in caudate and putamen at both time points. This finding supports the notion that abnormal metabolic brain network in HD is related to dopamine D2 receptor loss. However, the brain network can capture aspects of functional abnormality not reflected by impaired neuroreceptor integrity.

In a preliminary study, we have investigated the effect of brain atrophy on metabolic change in preclinical HD. FDG-PET images from the p-HD subjects and controls were corrected for brain atrophy using the coregistered MRI data [81]. Striatal hypometabolism at baseline observed by SPM analysis disappeared to a large extent after atrophy correction. Striatal hypometabolism was present in an enlarging area at the later time point, but appeared mainly in the posterior putamen. These data indicate that striatal hypometabolism reflects mainly the presence of atrophy but begins to decline more quickly as the p-HD subjects move closer to symptom onset.

The HDRP topography generated from FDG images with atrophy correction was similar to that described above but with less hypometabolism in the caudate and putamen, consistent with the SPM analysis. The mean network activity in the p-HD gene carriers was elevated at baseline but did not progress over time. This suggests the existence of a different covariance network after atrophy correction. It remains to be seen whether a unique and new topographic pattern will emerge when these p-HD subjects become symptomatic.

PET imaging of CBF has been primarily utilized to examine abnormal brain activation responses during cognitive tasks in HD. To study the mechanism of this cognitive abnormality in p-HD, we have used H₂O PET to record rCBF in these subjects while they perform a set of kinematically controlled motor sequence learning and execution tasks [82]. We found that sequence learning was impaired in p-HD subjects despite normal motor performance. Activation responses during learning were abnormally increased in the left mediodorsal thalamus and orbitofrontal cortex. Impaired learning performance in these subjects was associated with increased activation in the precuneus. These data suggest that enhanced activation of thalamocortical pathways during motor learning can compensate for striatal degeneration in p-HD. Nonetheless, this mechanism may not be sufficient to sustain a normal level of task performance, even during the presymptomatic stage of the disease.

Assessment of Experimental Therapeutics

Although effective symptomatic treatments are not yet available in HD, there are growing efforts in developing promising new therapies not only to delay the clinical onset but also to slow down the disease progression [41, 83]. This has been focusing on improving energy metabolism with agents such as coenzyme Q and neural grafting with embryonic striatum. FDG-PET can be very useful for studying the efficacy of neuroprotective and therapeutic agents. In R6/2 transgenic HD mice, for example, exponentially decreasing glucose utilization was observed in the striatum, cortex and cerebellum as a function of age [84]. A dose-dependent neuroprotective effect was evident in the striatum by comparing changes in glucose metabolism between cystamine-treated and control animals.

There is evidence that fetal striatal allografts can reverse functional deficits in phenotypic models of HD developed in primates. FDG-PET has been proved valuable in testing the transplantation strategy of striatal fetal tissue in a nonhuman primate model of HD [85]. A recent open-label pilot study has shown some clinical improvement in three out of five HD patients who received bilateral striatal grafts of fetal neurons [86]. Clinical changes in these three patients were associated with a reduction of striatal and cortical hypometabolism, indicating that grafts were able to restore the function of striato-cortical loops. Conversely,

in the two patients not improved by the grafts, striatal and cortical hypometabolism progressed over the two-year follow-up. Further analysis revealed considerable heterogeneity in the anatomic and metabolic profiles of grafted tissue, both within and between HD patients.

By contrast, there has been no benefit on PET indices in a second human transplant trial in which HD patients underwent intrastriatal fetal cell grafting [87]. These patients showed widespread reductions in striatal glucose uptake with no significant change over two years. Whereas striatal D1 receptor binding did not change significantly after transplantation, there was a significant loss of D2 receptor binding. These findings may reflect loss of graft viability and/or disease progression. In addition, there was no significant relationship between changes in PET measures and clinical function. These results demonstrate the usefulness of PET imaging of brain glucose metabolism in understanding the effects of fetal grafts in patients with HD.

DBS may also be a promising alternative for the treatment of motor symptoms in HD based on its effectiveness in the neurosurgical management of PD. A pilot study with bilateral GPi DBS was performed in a HD patient with severe chorea [88]. Stimulation at 40 and 130 Hz improved chorea, but with slight worsening in bradykinesia at 130 Hz. A H₂O PET activation experiment under task conditions showed increased rCBF in motor decision making and execution areas that were more evident at 40 Hz. This suggests that adjustment of stimulation parameters in GPi DBS may have the potential to optimize the motor response in HD and improve chorea without aggravating bradykinesia.

In summary, brain imaging of rCBF and rCMRglc can detect widespread functional abnormality in HD and predict the onset time of motor symptoms even during presymptomatic stages. Progressively abnormal metabolism in presymptomatic HD may be related to neuropsychological dysfunction that is known to precede the onset of motor symptoms. Combining these data with advanced analytic tools will help elucidate the functional basis for the transition from presymptomatic to symptomatic phases of the disease, and for novel treatment approaches.

Conclusion

Measurements of cerebral blood flow and glucose metabolism are valuable in assessing neuronal function and are often associated with clinical and/or behavioral changes in neurodegenerative disorders. Statistical parametric mapping and spatial covariance analysis are complementary tools for quantifying brain function in these disorders on the local and system-wide levels, respectively. In the cases of PD and HD, we have demonstrated the existence of pathological brain networks, which have proven to be reproducible across populations and within individual subjects. Biomarkers based upon these and other pathological brain networks have become simpler to quantify in patients, especially with the greater availability of clinical PET and improved noninvasive MRI-based perfusion methods. Network approaches using images of cerebral blood flow and metabolism are likely to impact on the development of novel therapies for the neurodegenerative disorders.

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A: Parkinson's Disease Related Pattern (PDRP) **B: Parkinson's Disease Cognitive Pattern (PDCP)** **Fig. 1.**

(A) Parkinson's disease-related pattern (PDRP) identified by network analysis of FDG-PET scans from 33 PD patients and 33 age-matched normal volunteers. This covariance pattern was characterized by pallidal, thalamic, pontine, and cerebellar hypermetabolism associated with metabolic decrements in the lateral premotor and posterior parietal areas. PDRP expression (subject scores) for this pattern was increased ($p < 0.00001$) in the PD patients relative to normal subjects. (B) Parkinson's disease cognitive pattern (PDCP) identified by network analysis of FDG-PET scans from 13 nondemented PD patients with mild-moderate motor symptoms. This network was marked by relative hypometabolism of prefrontal, preSMA, and superior parietal regions, associated with cerebellar and thalamic metabolic increases. Subject scores for this pattern correlated significantly with psychometric indices of verbal learning and visuospatial performance. (The display represents voxels that contribute significantly to the network at $p = 0.001$. 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. Both topographic patterns are overlaid on a standard single subject MRI brain template.)

Fig. 2.

Regression analysis revealing significant linear relationships between network scores obtained from concurrent CBF and FDG-PET scans in patients with PD. A: PDRP [$F(1, 34)=52.4, p<0.001$ and $R^2=0.61$]. B: PDCP [$F(1, 34)=35.8, p<0.001$ and $R^2=0.52$]. The same relationships remained after including the normal controls.

Fig. 3.

Disease discrimination by PDRP and PDCP expressions measured by resting-state CBF PET images. Both scores significantly discriminated late PD and early PD or control groups with comparable accuracy ($p < 0.001$). PDRP scores were abnormally elevated while PDCP scores remained unchanged in early PD relative to controls. Subject scores came from a prospective individual case analysis conducted using an automated routine that was blind to diagnostic category. Error bars represent standard errors of the mean.

Fig. 4.

Summary of test–retest reliability showing intraclass correlation coefficient (filled symbols) and 95% confidence of interval (horizontal bars) in normal subjects and PD patients. Data came from CBF scans collected twice within one hour in normals and PD patients at baseline and following medical and surgical therapies (conducted 12 hours off medication for patients) and FDG scans repeated within one hour in normals and over eight weeks in PD patients (on medications).

Fig. 5. Altered glucose metabolism detected by SPM analysis ($p < 0.01$; $T > 2.5$) of FDG-PET scans in 11 presymptomatic HD gene carriers relative to 12 gene-negative normal controls. This abnormality included bilateral hypometabolism in the striatum and cingulate, and hypermetabolism in the bilateral thalamus and cerebella as well as in temporal and frontal cortices. Regions of abnormal metabolism were overlaid on a standard single subject MRI brain template.

A: Huntington's Disease Related Pattern (HDRP) **Fig. 6.**

HD-related spatial covariance pattern (HDRP) identified by network analysis of FDG-PET scans in 11 pre-symptomatic HD gene carriers and 12 gene-negative controls. (A) HDRP overlaid on a standard single subject MRI brain template showing bilateral hypometabolism in the striatum and cingulate, associated with bilateral hypermetabolism in the thalamus and cerebella as well as in occipital and motor cortices. (B) Subject scores in the preclinical HD gene carriers increased at baseline as compared with normal controls and elevated further at 1.5 years. This graph plots the mean and standard error of the mean.