Assessment of Disease Severity in Parkinsonism with Fluorine-18-Fluorodeoxyglucose and PET

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Fluorine-18-fluorodeoxyglucose (FDG) and PET have been used to identify an abnormal regional metabolic covariance pattern in Parkinson's disease (PD). To examine the potential use of this covariance pattern as a metabolic imaging marker for PD, we describe the Topographic Profile Rating (TPR), which is a method for calculating subject scores for this pattern in individual PD patients. We then assess the relationship between these metabolic measures and objective independent disease severity ratings. **Methods:** Two independent groups of PD patients were studied with FDG-PET. Group A consisted of 23 patients (mean age 60.2 ± 12.2; mean Hoehn and Yahr stages 2.4 ± 1.3) and Group B had 14 patients (mean age 49.0 ± 12.1; mean Hoehn and Yahr stage 3.2 ± 1.2). The regional cerebral metabolic rates for glucose (rCMRGlc) in all patients in each group were measured. TPR was used to calculate subject scores for the disease-related covariance pattern on a patient-by-patient basis. **Results:** In both PD patient groups, subject scores correlated with Hoehn and Yahr disease severity ratings (Group A: $r = 0.59$, $p < 0.004$; Group B: 0.57, $p < 0.04$), quantitative ratings for bradykinesia (Group A: $r = 0.63$, $p < 0.002$; Group B: $r = 0.61$, $p < 0.03$), rigidity (Group A: $r = 0.59$, $p < 0.004$; Group B: $r = 0.59$, $p < 0.04$), but not with tremor. **Conclusion:** These findings indicate that regional metabolic covariance patterns are robust imaging markers of disease severity. FDG-PET may be useful clinically in assessing parkinsonian disability and disease progression.

Key Words: Parkinson's disease; glucose metabolism; positron emission tomography; fluorodeoxyglucose

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Parkinson's disease (PD) is characterized by a presynaptic nigrostriatal dopamine dysfunction. This abnormality may be quantified in living patients with ^{18}F-fluorodopa (FDOPA) and PET (*1,2*). Because striatal uptake rate constants for FDOPA (K_i^{FD}) correlate with objective ratings of disease severity as well as nigral dopaminergic cell counts (*2–4*), FDOPA/PET provides a useful imaging marker of the PD process. However, kinetic PET measurements of striatal K_i^{FD} are technically demanding, and have limited practical applicability in a broad clinical setting (*5*). Moreover, striatal K_i^{FD} is a neurochemical indicator of underlying nigrostriatal dopaminergic pathology which is insensitive to changes in a pharmacologic state. As such, this technique is generally not suitable for assessing the effects of antiparkinsonian pharmacotherapeutic interventions.

In contrast to striatal K_i^{FD}, PET measurements of regional brain metabolism (rCMRGlc) with ^{18}F-fluorodeoxyglucose (FDG) may provide a more versatile alternative as an imaging marker for the diagnosis and assessment of PD. In a recent FDG-PET study of a combined group of 22 PD patients and 20 age-matched normals, we used the Scaled Subprofile Model (SSM) to identify a significant disease related regional metabolic covariation pattern or topographic profile (*6*). This profile (Topographic Profile 1) was characterized by lentiform and thalamic hypermetabolism covarying with hypometabolism of the medial and lateral premotor cortical areas as well as the parieto-occipital association area—a metabolic topography consistent with experimental animal models of parkinsonism (*7,8*). We found that individual subject scores for this profile, representing the quantitative contribution of the profile to the patient's overall brain metabolism, correlated significantly with independent objective clinical ratings of disease severity. Topographic Profile 1 correlated closely with a similar disease related covariance pattern identified by us previously in an earlier SSM analysis of a separate sample of PD patients and normals studied with a different tomograph (*2,6*).

In this study we examined the potential clinical applicability of Topographic Profile 1 as an imaging marker of PD. We used a modification of SSM to calculate subject scores for this topographic profile directly from individual patient FDG-PET data. Calculated subject scores for Topographic Profile 1 correlated with parkinsonian disability in each of two discrete patient samples studied with tomographs of different spatial resolution.

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TABLE 1
Regional and Global Metabolic Rates for Glucose (mg/min/100g)

	Normal (n = 20)		PD_1 (n = 11)		PD_2 (n = 12)	
	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)
Cerebellum	7.46	(1.06)	5.88	(0.75)	5.94	(1.16)
Pons	5.05	(0.87)	3.83	(0.66)	3.78	(0.79)
Midbrain	5.83	(1.17)	3.97	(0.74)	3.81	(1.01)
Caudate	7.91	(1.25)	6.04	(1.02)	5.84	(1.31)
Lentiform	8.61	(1.19)	6.75	(1.28)	6.62	(1.32)
Thalamus	7.74	(1.09)	6.15	(1.39)	5.74	(1.06)
Med. temporal	6.07	(1.14)	3.94	(0.93)	4.04	(1.00)
Lat. temporal	7.52	(1.32)	5.43	(1.09)	4.90	(1.39)
Operculum	8.70	(1.38)	6.41	(1.51)	5.64	(1.40)
Sup. temporal	9.02	(1.50)	6.69	(1.27)	6.37	(1.42)
Med. frontal	7.96	(1.26)	5.73	(1.19)	5.14	(1.42)
Lat. frontal	8.71	(1.44)	6.51	(1.30)	5.69	(1.50)
Occipital	10.16	(1.51)	7.41	(1.11)	7.04	(1.79)
Parieto-occipital	9.76	(1.50)	7.65	(1.17)	6.45	(1.76)
Inf. parietal	8.48	(1.28)	6.24	(1.10)	5.82	(1.57)
Paracentral	7.81	(1.08)	5.70	(1.19)	5.13	(1.15)
Whole brain	8.30	(1.19)	6.28	(1.08)	5.84	(1.28)

PD_1 = mild Parkinson's disease (Hoehn and Yahr I–II) and PD_2 = moderate–advanced Parkinson's disease (Hoehn and Yahr III–V).

MATERIALS AND METHODS

Patients and PET

Group A. We studied 23 classical PD patients (13 male and 10 female; age 60.2 ± 12.2 yr; mean Hoehn and Yahr score 2.4 ± 1.3) (H&Y) (*9*). A diagnosis of PD was made if the patient had pure parkinsonism without a history of known causative factors, such as encephalitis or neuroleptic treatment, did not have early dementia, supranuclear gaze palsy or ataxia but did have a convincing response to levodopa. In all patients, family history was negative for neurodegenerative illnesses. In all patients T_2-weighted MRI (echo time ≥80 msec; repetition time ≥1,500 field strength ≥1.0T) disclosed normal basal ganglia signal; cortical and subcortical atrophy was absent. These patients were selected with a wide range of clinical involvement. Eleven patients had mild parkinsonism (H&Y I–II), and 12 patients had moderate-severe disability (H&Y III–IV). These PD patients are entirely different from the 22 patients who were employed by us for the identification of Topographic Profile 1 (*6*).

Patients fasted overnight prior to FDG-PET scanning. In all patients, antiparkinsonian medications were discontinued at least 12 hr before PET was conducted. At the time of the PET study, all patients were rated quantitatively according to the H&Y scale and the Unified Parkinson Disease Rating Scale (UPDRS 3.0) (*10*). PET studies were performed using the Superpett 3000 tomograph (Scanditronix; Essex, MA) at North Shore University Hospital, Manhasset, NY. The performance characteristics of this instrument have been described elsewhere (*11*). This four-ring BaF_2 time-of-flight, whole-body tomograph acquires 14 PET slices with Z-axis translation. Each slice is 8 mm thick and reconstructed with a transaxial resolution of 8 mm (FWHM). Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital/Cornell University Medical College. Written consent was obtained from each subject following a detailed explanation of the procedures.

Patients were positioned in the scanner using the Laitinen stereoadapter (*12*) with three-dimensional laser alignment with reference to the orbitomeatal (OM) line. A cylindrical tube filled with ^{68}Ge was placed in the field of view to provide internal calibration for each slice. All studies were performed with the subject's eyes open in a dimly lit room and minimal auditory stimulation. The FDG-PET technique employed to calculate rCMRGlc has been described by us in detail (*6,13*).

Region of interest (ROI) analysis was performed on 256 × 256 PET reconstructions using a SUN microcomputer (490 SPARC Server; Sun Microsystems, Mountain View, CA) with Scan/VP Software (*14*). We defined 26 (13 per hemisphere) standardized cortical and subcortical gray matter ROIs and two cerebellar and two brainstem ROIs. ROIs were defined interactively on reconstructed PET slices by visual inspection with reference to a standard neuroanatomical atlas (*15*) and MRI. To reduce partial volume effects, we calculated peak rCMRGlc values by averaging the upper 20% of ROI pixel values (*16*). Whenever anatomical regions straddled contiguous PET slices, rCMRGlc was calculated by weighting component ROI values by the number of thresholded pixels on each slice. Mean rCMRGlc data for Group A patients and 20 normal subjects (mean age 47.0 ± 17.1 yr) are given in Table 1.

Group B. We studied 14 other classical PD patients (13 male, 1 female; mean age 49 ± 12 yr; mean H&Y score 3.2 ± 1.2). The clinical characteristics of these patients have been presented previously (*6*). These patients were entirely different from the 22 patients used in the identification of Topographic Profile 1 (*6*), and from the subsequent 23 patients constituting Group A described above. These PD patients were studied while on antiparkinsonian medications with FDG-PET using the PC4600 PET tomograph (slice thickness 10 mm; transaxial resolution 10 mm FWHM) at Memorial Sloan Kettering Cancer Center, New York, NY (*17*). All patients were rated quantitatively at the time of the PET study according to the H&Y scale and a modified version of the Cornell-UCLA scoring system in which bradykinesia, rigidity and tremor were each rated on a composite 0–4 scale (*2,18*). The FDG-PET procedures for rCMRGlc calculation have been previously de-

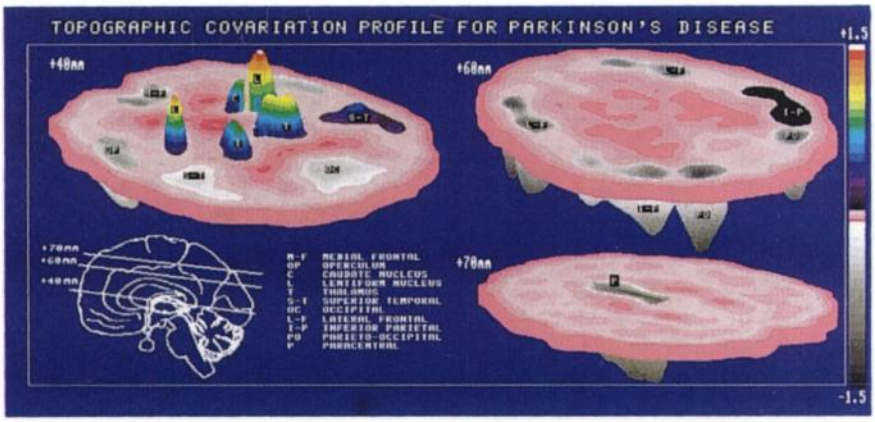

FIGURE 1. Isometric display (*6,14*) of the region weights for Topographic Profile 1 on representative transverse brain slice acquired approximately 40, 60 and 70 mm above the orbitomeatal line. The insert (lower left) indicates the positions of the midlines of these transverse slices on a standardized parasagittal two-dimensional display. Relative hypermetabolism (color scale) of the lentiform nuclei and thalamus is shown on the bottom slice (upper left). Relative hypometabolism (grey scale) of the lateral frontal, inferior parietal and parieto-occipital areas is evident on the upper slices (right).

scribed (*2*). To facilitate the comparison of rCMRGlc data obtained for Group A and Group B patients, we used similar ROI placement procedures for both sets of PET studies. However, because of the lower resolution of the tomograph used for the Group B studies, a composite ROI including both caudate and lentiform nuclei was adopted for those analyses. The remaining ROIs defined for both Group A and B PET scans occupied analogous positions relative to the OM line. Mean rCMRGlc data for these 14 PD patients also have been previously reported (*2*).

Topographic Profile Rating: Rationale and Computational Procedure

In previous studies we used SSM to identify disease-related topographic covariance profiles from combined rCMRGlc datasets obtained from patients and controls, blind to group membership (*2,6,19*). The mathematical properties of this model and its statistical assumptions have been described elsewhere (*19–21*). In contrast to combined group analyses for the identification of significant topographic profiles, SSM computational procedures can also be used to calculate subject scores for a predetermined topographic profile on a patient by patient basis. We refer to this clinical application of SSM as Topographic Profile Rating (TPR). We selected Topographic Profile 1 (Fig. 1) as a potential imaging marker for disease severity in PD (*6*), and used it to calculate subject scores for this profile from the individual patient rCMRGlc data. This procedure was conducted separately for each of the PD patients comprising both Group A and B. In the TPR computational procedure, subject scores were calculated for Group A and B patients in nearly an identical fashion. Because Topographic Profile 1 was determined on the same tomograph as that employed in the Group A studies, these patients were analyzed using separate region weights for the caudate and lentiform nuclei. Because of the lower resolution of the tomograph employed in the Group B studies, composite basal ganglia ROI data were used with averaged caudate-lentiform profile region weights.

TPR provides a measure of the degree to which an individual subject expresses any given topographic profile in their brain FDG-PET (rCMRGlc) data. This determination is made relative to a reference rCMRGlc dataset obtained either from another patient or normal control subject, or from mean rCMRGlc data acquired across a population of normals, patients or both. In TPR, rCMRGlc data (from ROIs or individual pixels) from the unknown subject and the reference are log-transformed and subtracted. The subject score of the unknown relative to the reference is determined by using a multivariate linear regression analysis to predict the regional differences from the corresponding region weights of the topographic profile. The resulting regression coefficient quantifies the difference in topographic profile expression between the unknown subject and the reference, i.e., the relative subject score. In this study, the calculated subject scores were used to predict disease severity on an individual basis.

The particular rCMRGlc dataset used as a reference is not critical provided that the same reference is used for intersubject comparisons or longitudinal studies of individual subjects. In this study we performed the analysis using Topographic Profile 1 region weights (*6*), and Group A and B rCMRGlc datasets. We chose as reference the mean rCMRGlc values from the combined sample of 42 PD patients and normals used to identify Topographic Profile 1 in the original SSM analysis (*6*). This reference was selected to provide a common baseline for subject scores derived in the original SSM analysis and in the subsequent TPR analyses.

Regional measures of glucose metabolism and calculated subject scores for Topographic Profile 1 were correlated with clinical ratings in each group of PD patients, using Pearson product moment correlation coefficients. The following clinical parameters were used in these correlations: H&Y ratings of overall disease severity and individual ratings for bradykinesia, rigidity and tremor. All statistical analyses were carried out using SAS.

RESULTS

Glucose Metabolism

Absolute rCMRGlc and whole-brain normalized rCMRGlc values did not correlate with clinical ratings in either of the two patient groups.

Topographic Profile Rating

Group A. Calculated subject scores for these 23 patients correlated with individual H&Y disease severity ratings ($r = 0.59$, $p < 0.004$; Fig. 2A, left) and with UPDRS ratings for rigidity ($r = 0.59$, $p < 0.004$) and bradykinesia ($r = 0.63$, $p < 0.002$; Fig. 2A, right); subject scores did not correlate significantly with tremor scores ($r = 0.24$, ns).

Group B. Calculated subject scores for these 14 patients correlated significantly with H&Y scores ($r = 0.57$, $p < 0.04$; Fig. 2B, left), and with quantitative ratings for rigidity ($r = 0.59$, $p < 0.04$) and bradykinesia ($r = 0.61$, $p < 0.03$; Fig. 2B, right), but not tremor ($r = 0.28$, ns).

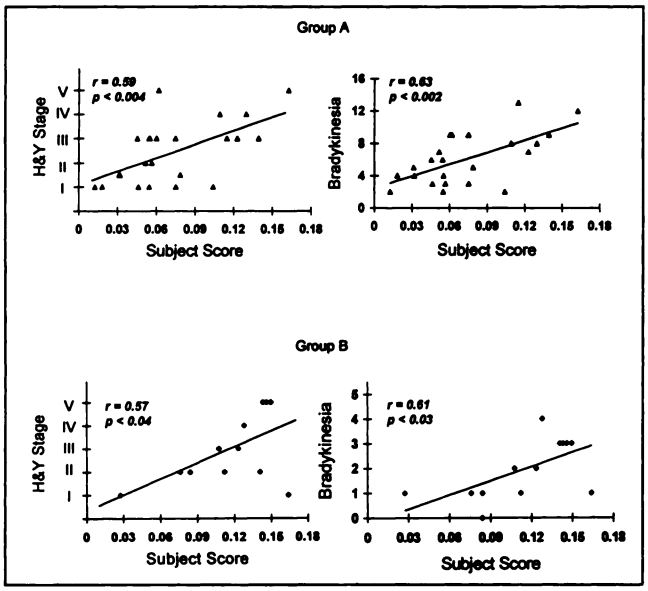

FIGURE 2. Correlation in PD patients between subject scores for Topographic Profile 1 and standardized clinical ratings of disease severity (left: H&Y scores; right: quantitative bradykinesia ratings). Group A and Group B correlations appear in Figures 2A and B, respectively. In both patient groups, significant positive correlations were found between the calculated subject scores and the clinical disease severity ratings.

DISCUSSION

In this report, we demonstrated that regional metabolic data obtained through FDG-PET may be used as an imaging marker of parkinsonian disease severity. Topographic Profile 1 is characterized by abnormal increases in basal ganglia and thalamic metabolism and associated with premotor and parietal cortical metabolic reduction. Accordingly, it can be used as a metabolic probe to quantify precisely its representation in the functional brain images of individual subjects. Thus, SSM methods are not limited to the identification of biologically relevant topographic profiles, but may have a clinical application in the objective gauging of the severity of parkinsonism and related disorders.

Under different scanning conditions, TPR produced similar correlations between subject scores and independent measures of clinical disability. Specifically, the Group A and Group B FDG-PET scans differed from one another in several important ways: (a) The tomographs used in the two groups were of markedly different spatial resolution and camera design: that used in the Group A studies was a whole-body scanner of higher spatial resolution than the brain dedicated instrument used for the Group B studies; and (b) The scanning protocol for image functionalization (i.e., converting raw counts to metabolic values on a pixel-by-pixel basis) was different in the two patient groups: individually calculated kinetic rate constants (k_1–k_3) were used to calculate rCMRGlc in Group B scans (*2*), while mean population rate constants were used in the autoradiographic equation for Group A metabolic calculations (*6,11,13*).

Additionally, clinical measurements of disease severity in the two groups differed in the following ways: the pharmacologic states of the patients in the two groups differed: all Group A patients were off antiparkinsonian medication at the time of PET, while the majority (12 of 14) Group B patients had PET scans on medication; different PD rating scales were used for clinical assessment in the two patient groups: the complete motor UPDRS was used in rating the Group A patients, while an abbreviated modification of the Cornell-UCLA scale (*18*) was employed in the Group B ratings. In spite of these technical differences, calculated Topographic Profile 1 subject scores accounted for similar variance in quantitative clinical scores in both groups ($R^2 \sim$ 35–40%). These results indicate that TPR subject scores are a robust marker of disease severity relatively independent of PET instrumentation, scanning protocols and clinical rating scales. Equally important, this metabolic measure correlates with clinical disability in both medicated and unmedicated states, suggesting its potential applicability in the assessment of antiparkinsonian pharmacotherapy with PET. Indeed, levodopa infusion studies in parkinsonian primates and PD patients have revealed significant reductions in basal ganglia and thalamic hypermetabolism with treatment (*22,23*). This suggests the potential applicability of Topographic Profile 1 subject scores as useful markers of successful pharmacologic intervention with likely decreases in subject scores in patients undergoing dopaminergic therapy. In addition, we found that the magnitude of clinical correlations with the calculated subject scores was similar to that reported by us for analogous correlations with striatal K_i^{FD} (*3*). Moreover, as in our earlier studies of clinical metabolic correlations in PD, we found no relationship between subject scores for disease-related topographic profiles and tremor ratings (*2,6*). We attribute this to potential nondopaminergic mechanisms subserving parkinsonian tremor (*24*), as supported by the absence of correlation between tremor ratings and striatal K_i^{FD} (*2,3*).

Our findings suggest that FDOPA and FDG-PET techniques may yield comparable results as imaging markers of parkinsonian disease severity. FDOPA/PET methods are costly, technically demanding and have been limited to few centers (*5*). Apart from the specialized radiochemistry necessary for production (*25*), this technique also requires long kinetic scanning protocols, which may be uncomfortable for patients with advanced disease. Although methodological simplifcations have been described and validated (*3,26,27*), the most accurate correlations with disease severity can be achieved with arterial blood sampling and high pressure liquid chromatography (HPLC) (*3*). Additionally, precise quantitation of nigrostriatal dopaminergic function with FDOPA/PET may be hampered by endogenous amino acids (*28*) as well as concurrently administered dopaminergic agents, their metabolites or both (*29*). These technical limitations may be less constraining in other ap-

proaches to the quantification of nigrostriatal function, such as the use of ^{123}I(1*R*)-2β-carbomethoxy-3β-(4-iodophenyl)tropane] ([^{123}I]β-CIT) with SPECT, for the imaging of presynaptic dopamine reuptake sites (*28*). In spite of these limitations, direct nigrostriatal imaging is a useful, straightforward method of demonstrating the presence of presynaptic lesions in living patients. These imaging methods have been proven useful in early disease detection (*4*) and in the evaluation of fetal tissue implants (*31,32*). They may also be appropriate for longitudinal studies of the natural history of disease progression (*33,34*) and the comparative long-term assessment of neuroprotective strategies. They are, however, unsuited for assessing the functional consequences of modifications in pharmacologic state, as would be desirable in testing the efficacy of new dopaminergic agents for the treatment of PD.

Our results indicate that TPR applied to FDG-PET data has utility comparable to quantitative FDOPA/PET imaging for most of the clinical indications listed above. As an indirect functional marker of the nigrostriatal dopamine system, this technique can be used to determine the integrity of this system at baseline and to assess progression over varying time periods. Mild PD is characterized by clinical and metabolic asymmetries (*2,6,9*); therefore, SSM analysis of left-right differences in regional glucose metabolism may be used for early diagnosis. In an SSM analysis of 10 H&Y Stage I PD patients and 10 age-matched normals, we demonstrated that subject scores for a significant covariance pattern of regional asymmetries discriminated early patients from age-matched normals with an accuracy comparable to striatal K_i^{FD} (*35*). FDG-PET and TPR analysis may have the added utility of differentiating atypical drug-resistant patients from their drug-responsive counterparts (*1,6,13*), and perhaps of objectively gauging the efficacy of antiparkinsonian therapies.

In conclusion, Topographic Profile 1 is a useful, robust imaging marker of the parkinsonian disease process. Because of the greater availability of FDG-PET in clinical research centers, metabolic brain imaging with TPR techniques may be a useful alternative to the more technically demanding FDOPA/PET methods. Recent simplified methods for the estimation of rCMRGlc further increases the applicability of FDG-PET techniques for the study of large clinical cohorts (*36*). To the extent that regional cerebral blood flow and glucose metabolism are coupled in PD (*37*), TPR may also be applicable to cerebral perfusion mapping with other widely available imaging modalities such as SPECT. Additionally, these functional imaging techniques may have analogous clinical applicability in the study of other neurodegenerative disorders including the dementias.

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