Divergent expression of regional metabolic topographies in Parkinson’s disease and normal ageing

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Summary

We have used [¹⁸F]fluorodeoxyglucose (FDG) with PET to identify regional metabolic covariance patterns associated with Parkinson’s disease and normal ageing. In this study we utilized these patterns as metabolic markers to assess the relative roles of these processes in the progression of parkinsonism. We studied 37 Parkinson’s disease patients and 20 normal volunteer subjects with FDG/PET to calculate regional metabolic rates for glucose. We applied the Parkinson’s disease and normal ageing regional covariance patterns separately to these data to compute the expression of both these markers in each subject on an individual case basis. The measured expression of the normal ageing pattern provided an estimate of subject age, based entirely upon the FDG/PET data. The normalized difference between this metabolic estimate and chronological age (Δ) was then computed, where Δ = (metabolic age – real age)/(real age).

We found that Δ values were negative and significantly reduced in the Parkinson’s disease cohort compared with normal subjects (P < 0.005) indicating a consistent underestimation of chronological age by FDG/PET in parkinsonism. In the Parkinson’s disease group, Δ correlated negatively with disease duration (r = –0.38, P < 0.04); extrapolation of this linear relationship to Δ = 0 yielded an estimate of the mean preclinical period of 4.5 years. These findings suggest that the Parkinson’s disease process is likely to be associated with a progressive disruption of the normal age-metabolism relationship, rather than with an exaggeration of the normal ageing process. Our metabolic data also suggest that the preclinical period in Parkinson’s disease is of relatively short duration.

Keywords: Parkinson’s disease; ageing; glucose metabolism; PET

Abbreviations: FDG = [¹⁸F]fluorodeoxyglucose; FDOPA = [¹⁸F]fluorodopa; GMR = global metabolic rate for glucose; H and Y = Hoehn and Yahr (scores); rCMRGlc = regional cerebral metabolic rate for glucose; UPDRS = Unified Parkinson’s Disease Rating Scale; Δ = normalized difference between estimated age based on rCMRGlc and real age

Introduction

Degeneration of the nigrostriatal dopamine system occurs in both normal ageing and Parkinson’s disease. However, the temporal relationship of these two neurodegenerative processes is unknown. Because of topographic differences in the distribution of nigral cell loss in normal ageing and Parkinson’s disease (Fearnley and Lees, 1991), it has been suggested that the two processes are spatially and temporally independent and perhaps additive (Calne 1994; Lee et al., 1994; Schulzer et al., 1994). Additionally, correlations between nigral dopamine cells counted at post-mortem and duration of symptoms have suggested that, in contrast to normal ageing, Parkinson’s disease may evolve through a nonlinear process characterized by relatively increased dopaminergic attrition at early stages of the illness (Fearnley and Lees, 1991). These conclusions were in accord with an earlier post-mortem study quantifying striatal dopaminergic innervation with a vesicular monoamine transporter binding ligand (Scherman et al., 1989). Measurements of dopaminergic function at the time of death have also been used to determine the length of the parkinsonian preclinical period, i.e. the interval between the start of the disease process and the first appearance of clinical symptoms. Nonetheless,
differences in the inferred relationships between the duration of clinical symptoms in life and measurements of dopaminergic activity in post-mortem samples have led to substantial disparities in the estimates of this interval. Scherman et al. (1989) suggested that the preclinical period is ~20–30 years. By contrast, Fearnley and Lees (1991) proposed that the pathological loss of dopaminergic neurons begins only ~5 years before disease onset. Indeed, the conclusions of these post-mortem studies may be limited by cross sectional design with an inherent bias toward cases of long duration and greater clinical involvement, as well as technical and biological differences in the dopaminergic indices quantified in each of these investigations.

Alternatively, longitudinal comparisons of the progression of nigrostriatal dopaminergic dysfunction in normal ageing and Parkinson’s disease have been undertaken with PET. Using [18F]fluorodopa (FDOPA) to quantify nigrostriatal dopaminergic function, Vingerhoets et al. (1994) studied 16 Parkinson’s disease patients on two occasions separated by an average of 7 years. These authors estimated a twofold increase in the rate of cell loss compared with 10 normal control subjects. Linear regression analysis of their longitudinal data produced estimates of the preclinical period of 40–50 years; non-linear fitting reduced this value to 10–15 years. More recently, Morrish et al. (1996) performed a similar longitudinal FDOPA/PET investigation studying 17 Parkinson’s disease patients of shorter clinical disease duration who were scanned twice over an average of 15 months. These authors estimated that the preclinical period was considerably shorter than had been suggested in the earlier PET study, with estimates based upon linear extrapolation of ~3 years. The disparities between these two longitudinal studies may stem from technical differences. Importantly, between-study differences in the duration of disease at the time of the first scan may impact heavily on the estimation of the preclinical period, especially if the illness progresses in a non-linear fashion. Moreover, in these studies estimates of the preclinical period based on longitudinal PET measurements rely on extrapolations over time periods longer than the interval between the two sequential scans. This may compromise the accuracy of these estimates, especially in situations where the rate of progression is highly variable and where disease progression may not be strictly linear. Additionally, FDOPA/PET may not be an optimal method to compare rates of nigrostriatal degeneration in normal ageing and Parkinson’s disease, given the relative insensitivity of striatal dopa decarboxylase measurements to the dopaminergic attrition associated with senescence (Sawle et al., 1990; Eidelberg et al., 1993; Ishikawa et al., 1990a, b; Morrish et al., 1996; also cf. Kish et al., 1995).

Neurodegenerative processes such as parkinsonism and normal ageing can also be quantitatively assessed using [18F]fluorodeoxyglucose (FDG) and PET to measure regional rates of glucose utilization. We have employed a statistical model of regional metabolic covariation to identify abnormal brain topographies in Parkinson’s disease and related disorders (Eidelberg et al., 1990, 1994, 1995a–c). This algorithm, known as the Scaled Subprofile Model (Moeller et al., 1987; Moeller and Strother, 1991; Alexander and Moeller, 1994) is a form of principal component analysis which identifies patterns of regional covariation in brain metabolism data. Through modifications of the functional imaging data prior to performing the principal component analysis, scaled subprofile model analysis both characterizes the regional covariance structure of subject groups and measures the expression of the obtained regional covariance patterns in individual subjects. In this way, scaled subprofile model provides a means of comparing the expression of these patterns in different populations and of examining their relationship with independent clinical descriptions such as disease severity and subject age.

In a recent FDG/PET study, we used Scaled Subprofile Model analysis to identify specific covariance patterns as metabolic markers of the normal ageing process (Moeller et al., 1996). We identified two related patterns, both correlating significantly with subject age in independently studied populations of normal volunteers (Moeller et al., 1996). In spite of coarse similarities, the topography of the ageing patterns was quantitatively different from that previously identified as a metabolic marker for Parkinson’s disease (Eidelberg et al., 1990, 1994, 1995a, 1996). Because of the specificity of these covariance patterns for normal ageing and parkinsonism as discrete entities, we sought to utilize them as separate metabolic markers to determine the relationship between these two processes in the evolution of Parkinson’s disease.

In this study we used FDG/PET to measure regional glucose metabolism in 37 Parkinson’s disease patients. We applied an algorithm described by us previously (Eidelberg et al., 1995a, b; Moeller et al., 1996) to compute the individual expression of the covariance patterns associated with Parkinson’s disease and normal ageing in each of these patients on a case-by-case basis. By quantitatively examining the relationship between pattern expression and disease duration in Parkinson’s disease patients, we were able to demonstrate a progressive disruption of the normal relationship between chronological age and metabolism with the evolution of the disease process. Moreover, the results of this analysis suggest that the parkinsonian preclinical period is likely to be of relatively short duration.

Material and methods

Subjects

We studied 37 idiopathic Parkinson’s disease patients without dementia [24 men and 17 women; age 58.8 ± 10.9 years; disease duration 6.9 ± 5.4 years; composite Unified Parkinson’s Disease Rating Scale (UPDRS 3.0) motor scores (items 19–31; Fahn et al., 1987) 14.1 ± 11.9 (mean ± SD)]. A diagnosis of Parkinson’s disease 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 abnormalities, or ataxia; and did have a convincing response to levodopa (≥20% change in composite UPDRS motor scores). In all patients family histories were negative for neurodegenerative illnesses. The patients ranged in clinical severity according to their 'off'-state (off medication for ≥24 h) Hoehn and Yahr (H & Y) scores (Hoehn and Yahr, 1967): 26 patients had mild disease (Stage I–II); six patients had moderate disease (Stage III); and five had severe disease (Stages IV–V). Twenty patients [H & Y 1.5 ± 0.6; UPDRS 9.7 ± 4.4 (mean ± SD)] had disease duration of five years or less; the remaining 17 patients [H & Y 2.9 ± 1.5; UPDRS 19.3 ± 15.6 (mean ± SD)] had symptoms and signs of longer duration. High-field strength T2-weighted MRI (echo time ≥80 ms; repetition time ≥1500 ms; field strength ≥1.0 T) disclosed normal putaminal signal in all cases studied (35/37); visually evident cortical or subcortical atrophy was absent. We also studied 20 normal volunteer subjects [10 men and 10 women; age 47.0 ± 17.1 years (mean ± SD)] recruited by advertisement among the hospital personnel of North Shore University Hospital and the spouses of Parkinson's disease patients from local support groups. The following exclusion criteria were used: (i) a history of neurological or psychiatric illness; (ii) prior exposure to neuroleptic agents or drug use; (iii) a medical history of hypertension, cardiovascular disease or diabetes mellitus; and (iv) an abnormal neurological examination.

PET
The patients and volunteers fasted overnight prior to FDG/PET scanning. All medications were discontinued at least 24 h before PET was conducted. At the time of PET study, all patients were rated quantitatively according to the H & Y, and UPDRS scales. PET studies were performed using the Superpett 3000 tomograph (Scanditronix, Essex, Mass., USA). The performance characteristics of this instrument have been described elsewhere (Robeson et al., 1993). This four-ring BaF2 time-of-flight, whole body tomograph acquires 14 PET slices with z-axis gantry translation of one half-ring distance every 30 s. Each slice is 8 mm thick and reconstructed with a transaxial resolution of 8 mm (full width at half maximum). Ethical permission for these studies was obtained from the Institutional Review Board of North Shore University Hospital. Written consent was obtained from each subject following a detailed explanation of the procedures in accordance with the declaration of Helsinki.

Subjects and patients were positioned in the scanner in a custom moulded headrest (Alpha Cradle, Smithers Medical, Tallmadge, Ohio, USA) (Kearfott, 1984) with three-dimensional laser alignment with reference to the orbitomental line. The quantitative PET techniques employed in this study are identical to those described previously. We calculated global and regional metabolic rates for glucose (GMR and rCMRGlc, respectively) in all FDG/PET studies using autoradiographic scans (Phelps et al., 1979; Takikawa et al., 1993) acquired for 20 min beginning 35 min post-injection, with estimated mean normal rate constants [k1 = 0.1056, k2 = 0.1584, k3 = 0.0904; k4 was fixed at 0.0068 (Dhawan et al., 1989; Robeson et al., 1993)]. To facilitate comparisons with our previous metabolic data, we chose a lumped constant of 0.42.

Region of interest analysis was performed on 256×256 PET reconstructions using a SUN microcomputer (490 SPARC Server; Sun Microsystems, Mountain View, Calif., USA) with Scan/VP software (Spetsieris et al., 1993). In order to apply the patterns reported previously for normal ageing and Parkinson's disease to individual subject rCMRGlc data, we defined 26 (13 per hemisphere) standardized cortical and subcortical grey matter regions of interest and two cerebellar and two brainstem regions of interest as described elsewhere (Eidelberg et al., 1994,1995a; Moeller et al., 1996). Regions of interest were defined interactively on reconstructed PET slices by visual inspection with reference to a standard neuroanatomical atlas (Talairach and Tournoux, 1988), and MRI or CT when available. Mean region of interest size ranged between 40 pixels for the caudate nucleus to 220 pixels for the lateral frontal and temporal cortical regions (1 pixel = 4 mm2). To reduce partial volume effects, we calculated 'peak' rCMRGlc values by averaging the upper 20% of region of interest pixel values (Rottenberg et al., 1991). Whenever anatomical regions straddled contiguous PET slices, rCMRGlc was calculated by weighting the component region of interest values by the number of thresholded pixels on each slice. The GMR was calculated as the mean of the rCMRGlc values weighted by the total number of thresholded pixels in each region of interest. To reduce inter-subject variability, regional metabolic measurements were normalized by global values (rCMRGlc/GMR).

Regional covariance analysis
In previous studies we used Scaled Subprofile Model to identify unique patterns of regional metabolic covariation associated with Parkinson's disease (Eidelberg et al., 1990, 1994) and normal ageing (Moeller et al., 1996). The mathematical properties of the Scaled Subprofile Model, its statistical assumptions and computational procedures have been described in detail elsewhere (Moeller et al., 1987; Moeller and Strother, 1991; Alexander and Moeller, 1994). In this study we computed Scaled Subprofile Model subject scores for the previously identified Parkinson's disease and ageing covariance patterns (reflecting the expression of each pattern in individual subjects) from the metabolic data obtained in each of the 37 Parkinson's disease patients and the 20 control subjects. The computational procedure for calculating the subject score for a known covariance pattern from individual subject rCMRGlc data has been described elsewhere (Eidelberg et al., 1995a, b; Moeller et al., 1996).
We refer to this application of Scaled Subprofile Model as Topographic Profile Rating. Topographic Profile Rating provides a measure of the degree to which an individual subject expresses any given covariance pattern in their brain FDG/PET (rCMRGlc) data.

To calculate subject scores for the Parkinson’s disease-associated covariance pattern (Subject Score$_{PD}$) by Topographic Profile Rating, we used the region weights reported previously (Topographic Profile I in Eidelberg et al., 1994; also see Eidelberg et al., 1995a). In computing the expression of the ageing-associated patterns (Subject Score$_{AGE}$), we used region weights for the ageing-related covariance pattern identified previously in this cohort of normal volunteers (Topographic Profile B in Moeller et al., 1996). Subject scores for this pattern correlated significantly with chronological age in this normal group and accurately predicted age on an individual subject basis in 130 other normal subjects scanned independently in a different tomograph. Additionally, these subjects’ scores were highly reproducible in the 22 normal subjects who underwent repeated FDG/PET imaging (Moeller et al., 1996). We note that a related ageing-pattern (Topographic Profile A; Moeller et al., 1996) also correlated significantly with chronologically age in the currently reported normal sample. However, this pattern which was extracted from an entirely different independent rCMRGlc dataset, and accounted for relatively less ageing variance in the 20 normal subjects reported here. It was therefore not employed as a metabolic ageing marker in this study.] To facilitate comparison with a metabolic ageing marker, we have previously reported a significant linear relationship between Subject Score$_{AGE}$ and chronological age (age$_{REAL}$) in this normal volunteer cohort (see fig. 3A in Moeller et al., 1996). Having computed Subject Score$_{AGE}$ by Topographic Profile Rating in the Parkinson’s disease patients, we used this linear function to derive an estimate of age based solely upon the expression of the normal ageing pattern in each subject’s FDG/PET image. We designated this estimated metabolic age as age$_{MET} = (1.15 \times \text{Subject Score}_{AGE} + 0.047) \times 10^3$. In turn, we used age$_{MET}$ and age$_{REAL}$ values to calculate a normalized measure of the difference between estimated metabolic age and true chronological age. We designate this deviation as $\Delta = \frac{\text{age}_{MET} - \text{age}_{REAL}}{\text{age}_{REAL}}$. In normal subjects, age$_{MET}$ should approximate age$_{REAL}$, i.e. $\Delta \approx 0$. In an acceleration of the normal ageing process, age$_{MET}$ should be greater than age$_{REAL}$ and $\Delta > 0$. In a pathological neurodegenerative process, the normal age–metabolism relationships may become disrupted by the progressive appearance of disease-related metabolic topographies. In this case age$_{MET}$ may underestimate age$_{REAL}$ ($\Delta < 0$). A formal mathematical model is presented in the Appendix relating chronological age to Subject Score$_{AGE}$ under normal and pathological conditions.

In this study we computed $\Delta$ in each of the 37 Parkinson’s disease patients and 20 normal control subjects. These values were compared in the two groups using Student’s t tests. We computed Pearson product-moment correlation coefficients to examine the relationship between $\Delta$ and disease duration and severity in the Parkinson’s disease patient cohort. Between-group comparisons and clinical correlations were considered significant when $P < 0.05$. In addition, we computed the average duration of the parkinsonian preclinical period by extrapolating the line relating $\Delta$ and disease duration in Parkinson’s disease patients to the expected mean value for normal subjects ($\Delta = 0$). This procedure provided an estimate of the mean time elapsed from an initial departure from the normal age–metabolism line to the onset of clinical symptoms. All statistical analyses were carried out using SAS software (SAS Institute, Cary, NC, USA).

**Results**

**Covariance pattern for Parkinson’s disease**

The mean individual expression of the covariance pattern associated with Parkinson’s disease (Subject Score$_{PD}$) was significantly elevated in the Parkinson’s disease cohort compared with age-matched normal controls ($P < 0.04$). We found that in the patient cohort these subject scores correlated significantly with H & Y scores, UPDRS composite motor ratings, patient age and disease duration ($r \geq 0.44$, $P < 0.01$ for all correlations; Fig. 1). Disease duration correlated significantly with H & Y scores ($r = 0.69$, $P < 0.001$) and with UPDRS composite motor ratings ($r = 0.52$, $P < 0.01$), but not with patient age ($r = 0.22$, $P = 0.18$).
Covariance pattern for normal ageing

The individual expression of the covariance pattern associated with the normal ageing process (Subject Score\textsubscript{AGE}) correlated significantly with chronological age in the Parkinson’s disease patient and normal control cohorts ($r = 0.58$ and $= 0.75$, $P < 0.001$ for the two samples, respectively). We did not observe a significant difference in the slope of the regression line correlating Subject Score\textsubscript{AGE} with chronological age in normal subjects [$4.8 \times 10^{-4} \pm 1.0 \times 10^{-4}$ (mean $\pm$ SEM)] and the slopes of analogous correlation lines computed in Parkinson’s disease patient cohorts with symptoms of either long ($> 5$ years) or short ($\leq 5$ years) duration [$7.8 \times 10^{-4} \pm 1.9 \times 10^{-4}$ and $9.0 \times 10^{-4} \pm 3.2 \times 10^{-4}$ (mean $\pm$ SEM), respectively].

Parkinsonism and normal ageing

After computing individual subject scores for the Parkinson’s disease and normal ageing covariance patterns, we used these values to compute $\Delta$ for each subject. A scatter diagram of $\Delta$ values in normal subjects and Parkinson’s disease patients is presented in Fig. 2. We found that in normal subjects the mean $\Delta$ approximated zero, the expected value for the control mean (see above). In the Parkinson’s disease cohort, the mean $\Delta$ was negative and was significantly reduced compared with normal controls ($P < 0.005$). The $\Delta$ values in the Parkinson’s disease patient group correlated negatively with disease duration ($r = -0.38$, $P < 0.04$; Fig. 3) and with severity ($r = -0.39$, $P < 0.02$ and $r = -0.32$, $P = 0.05$ for H & Y, and UPDRS ratings, respectively), but not with patient age ($r = 0.08$ n.s.). These findings indicate a progressive underestimation of patient age with advancing disease duration and severity, when the normal ageing pattern is considered. This suggests that rather than arising through an accentuation of the normal ageing process, the clinical manifestations of Parkinson’s disease appear to emerge through a pathological disruption of the normal age–metabolism relationships.

Additionally, we estimated the length of the preclinical period in the Parkinson’s disease cohort by extrapolating the line correlating disease duration and $\Delta$ to the point of departure from the normal age–metabolism line ($\Delta = 0$). In this analysis, the preclinical period was estimated as $4.5 \pm 3.1$ years (mean $\pm$ SEM; Fig. 3). This suggests that the preclinical period in Parkinson’s disease may be of relatively short duration.

Discussion

In this study we demonstrate that Parkinson’s disease is not associated with an exaggeration of the normal ageing process. In our prior investigation of normal ageing (Moeller et al., 1996), we identified a specific regional metabolic covariance pattern which was highly correlated with subject age in two independent normal volunteer cohorts studied on different tomographs. By using this pattern as a marker for the normal ageing process, we were able to determine that advancing Parkinson’s disease is associated with a progressive underestimation of patient age based upon the expression of the normal ageing pattern. Indeed, had the process reflected an accentuation of the normal ageing process, our method would have led to an overestimation of patient age by the scan data and not the opposite. Our results are therefore consistent with histopathological evidence for differences in the topography
of nigrostriatal degeneration in Parkinson’s disease and normal ageing (Fearnley and Lees, 1991). Thus, although Parkinson’s disease and normal ageing bear certain clinical, neurophysical and neurochemical similarities (e.g. Evarts et al., 1981; Teravainen and Calne, 1983), it is unlikely that the manifestations of Parkinson’s disease can be ascribed simply to an accentuation of the normal ageing process (Agid et al., 1989; Wolters and Calne, 1989).

The topography of the specific regional metabolic covariance patterns associated with Parkinson’s disease and normal ageing has been discussed previously (Eidelberg et al., 1994; Moeller et al., 1996). The covariance pattern associated with Parkinson’s disease is characterized by the presence of lentiform and thalamic hypermetabolism covarying with relative cortical metabolic decrements in primary and association motor regions. This pattern is consistent with autoradiographic findings in experimental animal models of association motor regions. This pattern is reproducible across populations (Eidelberg et al., 1990) and its expression in individual patients is correlated with independent clinical indices of disease severity (Eidelberg et al., 1995a, b) as well as objective neurochemical markers such as striatal FDOPA uptake (Eidelberg et al., 1990, 1994b) and its expression in individual patients is correlated with independent clinical indices of disease severity (Eidelberg et al., 1995a, b) as well as objective neurochemical markers such as striatal FDOPA uptake (Eidelberg et al., 1990, 1994b). The current observations of abnormal increases in the expression of this covariance pattern in Parkinson’s disease patients, as well as the significant correlations with independent measures of disease severity, support the validity of this covariance pattern as a suitable metabolic marker for assessing the parkinsonian disease process (cf. Eidelberg et al., 1990, 1994, 1995a).

By contrast, the functional–anatomical basis for the covariance patterns associated with normal ageing is less well understood. Though qualitatively similar to the Parkinson’s disease pattern in exhibiting reciprocal metabolic covariation between the basal ganglia and motor association cortices, the normal ageing and Parkinson’s disease patterns are sufficiently different from a topographical standpoint to be considered independent (Moeller et al., 1996). Additionally, in contrast with the Parkinson’s disease pattern, the patterns associated with normal ageing have not been clearly linked to measurable decrements in nigrostriatal dopaminergic function. Comparative dopaminergic imaging with FDOPA/PET may not be helpful in this respect, given the absence of a major ageing effect with this tracer (Sawle et al., 1990; Eidelberg et al., 1993; Ishikawa et al., 1996a, b). Indeed, a direct association between the expression of the normal ageing covariance pattern and dopaminergic attrition cannot be ascertained until rigorous comparative studies are performed with age-sensitive dopaminergic tracers, such as the dopamine transporter binding ligands (e.g. Volkow et al., 1994; Van Dyck et al., 1995; Ishikawa et al., 1996b). Nonetheless, we have found the metabolic covariance patterns associated with normal ageing to be highly reproducible within subjects as well as predictive of chronological age on a prospective basis across independent cohorts scanned on different tomographs (Moeller et al., 1996). Thus, these patterns constitute useful and robust markers for assessing the normal ageing process, even in the presence of a superimposed pathological neurodegenerative condition.

The results of this study support the notion that the normal ageing and parkinsonian disease processes are not only topographically distinct (Fearnley and Lees, 1991), but are also temporally dissociated. Rather than accentuating the normal ageing process, parkinsonism is associated with a distinct disease-related metabolic topography whose expression increases with advancing symptomatology (Eidelberg et al., 1990, 1994, 1995a). In this study, we found that this evolution occurs concurrently with a progressive disruption of the normal age–metabolism relationship. We found that with increasing disease duration and severity, the metabolic marker for normal ageing progressively underestimates the true age of the patient. This finding contrasts with the prediction based upon the hypothesis of accelerated ageing in parkinsonism wherein the normal ageing marker would be progressively overexpressed in the Parkinson’s disease brain leading to a consistent overestimation of patient age based upon cerebral metabolism.

This progressive disruption of the normal age–metabolism relationship occurs concomitantly with the evolving manifestation of an abnormal metabolic topography associated with the parkinsonian disease process. Based upon our data, it appears that, with advancing disease, overall brain glucose utilization becomes increasingly influenced by the expression of this abnormal topography (Eidelberg et al., 1994). Concomitantly, the metabolic substrates of the normal ageing process are rendered functionally irrelevant. From this standpoint, the normal ageing and parkinsonian disease processes in Parkinson’s disease patients appear to evolve separately, and their expression may diverge over time.

We extended our method of covariance analysis to calculate the duration of the preclinical period. In this cross-sectional analysis we estimated the average time in the Parkinson’s disease cohort between the departure from the normal age–metabolism line (Δ = 0) and the onset of symptoms. By this approach, the estimated mean preclinical period was 4.5 years, suggesting a relatively short latency for the parkinsonian disease process. Our metabolic estimate of the preclinical interval accords closely with the conclusions of post-mortem cell counting studies in Parkinson’s disease and normal ageing (Fearnley and Lees, 1991). Additionally, our FDG/PET findings support the conclusions of prior in vivo dopaminergic imaging studies. Morrish et al. (1996) utilized a longitudinal approach with serial FDOPA/PET imaging to estimate the length of the preclinical period by linear extrapolation to the normal mean value for striatal radiotracer uptake. Although the error of this estimate was not reported, their calculated preclinical period of 3.1 years is not substantially different from our own estimates based upon cross-sectional FDG/PET
data. Thus, in spite of major differences in radiotracer selection, experimental design and analytical procedure, both studies yielded convergent estimates to suggest that, in Parkinson’s disease, the preclinical period is of relatively short duration. Nonetheless, we emphasize that substantial errors exist in estimates of the preclinical period derived through PET imaging. Indeed, our mathematical model involves linear and non-linear aspects of network expression with respect to age which may be differentially altered in the presence of disease (see Appendix). Variations in these respective components may yield a wide range of estimates for the preclinical period in parkinsonism and other neurodegenerative disorders. More accurate estimates of Δ and the preclinical period will require a larger cohort of patients and controls ideally studied on a tomograph of greater resolution and sensitivity.

The precise neurochemical correlate of our metabolically determined preclinical period is not fully understood. In the previously reported longitudinal FDOPA/PET studies (Vingerhoets et al., 1994; Morrish et al., 1996), the start of the preclinical period was determined by extrapolating the line relating striatal FDOPA uptake to disease duration backward to the time when radiotracer uptake was at the normal mean value. In our study, the beginning of this period was estimated to be the time when a pathological disruption of the normal age–metabolism relationship began to occur. Nonetheless, the pathophysiological basis for this metabolic disruption is unknown. The onset of clinical parkinsonism is associated with an ~30% loss of nigral dopaminergic cell bodies (Fearnley and Lees, 1991) and a 50% decline in striatal dopa decarboxylase activity and dopamine transporter binding (Brooks et al., 1990; Takikawa et al., 1994; Eidelberg et al., 1995b; Ishikawa et al., 1996a, b). How this dopaminergic threshold is reached in the course of the parkinsonian disease process is a topic of speculation (Langston, 1990; Koller, 1992; Calne et al., 1994). The current findings reject the possibility that the clinical threshold is reached by an acceleration of the normal ageing process. Rather, it is conceivable that the disruption of the normal age–metabolism relationship at the start of the preclinical period parallels a pathogenic influence which abruptly moves the dopamine cell survival curve away from the apparent linear function characterizing normal age-related nigrostriatal dopaminergic attrition (Schulzer et al., 1994). Indeed, using the general event model proposed by these authors, we found that our data are consistent with a pathogenic influence of relatively high intensity occurring ~5 years prior to disease onset at a mean age 60 years.

However, it is to be borne in mind that these findings are equally consistent with an ongoing neurodegenerative process which progressively interferes with nigrostriatal dopaminergic function over a protracted period. In this context, the parkinsonian disease process may actually begin to evolve prior to the start of the neurochemically or metabolically determined preclinical period. Indeed, the time of inception of this process cannot be inferred from the reported PET data. Because of the potential for compensatory expression of striatal dopa decarboxylase activity in the face of low level dopaminergic attrition (Ishikawa et al., 1996a; also cf. Kish et al., 1995), mild degrees of nigrostriatal dopaminergic dysfunction may not be accurately detected by FDOPA/PET methods, nor even perhaps by quantitative dopamine transporter imaging (Ishikawa et al., 1996b). Similar compensatory mechanisms may operate to preserve the normal age–metabolism relationship for an unknown period of time following the initiation of the pathological neurodegenerative process. In this case, the estimated beginning of the preclinical period may represent a primary neurochemical–metabolic threshold beyond which these compensatory metabolic mechanisms begin to fail. During the ensuing time period, lasting perhaps only a few years, unchecked neurodegeneration may lead to a second threshold beyond which clinical signs and symptoms become evident.

Whether construed as an event or a process, Parkinson’s disease is associated with a well-defined preclinical period of apparently short duration. Our study indicates that the beginning of this critical period may be identified by FDG/PET imaging using a regional covariance marker for the normal ageing process. Indeed, identification of this time point in a population at risk for Parkinson’s disease may allow for the duration of the preclinical period to be confirmed on a prospective longitudinal basis. Additionally, disruption of the normal age–metabolism relationship may begin at a time when the degenerative process is rapid, but when clinical symptoms have yet to appear. The onset of the metabolically determined preclinical period may therefore constitute a useful temporal marker for the initiation of neuroprotective therapy in susceptible individuals.

Acknowledgements
We acknowledge the important contributions of Dr Vijay Dhawan, Dr Phoebe Spetsieris and Dr Thomas Chaly to this work. We wish to thank Mr Claude Margouleff for help with the PET studies, Dr Robert Dahl and Mr Ralph Matacchieri for cyclotron support, and Ms Lauren Moran for manuscript preparation. This work was supported by NIH NS RO1–35069 and by generous grants from the National Parkinson Foundation and the Parkinson’s Disease Foundation. David Eidelberg is a Cotzias Fellow of the American Parkinson’s Disease Association.

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In Equation 1, we have assumed that a linear transformation of \( \text{SSF}_{\text{Age}} \) exists (\( a > 0 \)) that is associated with \( K_0 \) and \( K_1 \) values describing specific biological processes. In our model, \( K_0 \) equals the minimal metabolic expression of the ageing network in life in normal subjects. \( K_1 \) equals the positive linear rate of change in the pattern expression with normal ageing. Equation 1 also includes a subject-specific effect which increases as a function of chronological age (\( \text{Age} \times \sigma_{\text{e}} \)), but is not a function of population characteristics. The subject-specific factor (individually proportional to \( \epsilon \)) is assumed to be a normally distributed random variable with mean zero and variance (\( \text{Age} \times \sigma^2 \)).

Model application: cross-sectional design

In the cross-sectional study of metabolic ageing effects in healthy controls and patients with Parkinson’s disease, our hypothesis was that in Parkinson’s disease initial alterations in \( K_0 \) and \( K_1 \) may occur prior to the onset of symptoms. Additionally, following clinical presentation, further changes in \( K_0 \) and \( K_1 \) may occur with increasing disease progression. (We refer to this latter period as ‘post-onset.’) We made two auxiliary assumptions: (i) \( K_0 \) and \( K_1 \) values did not vary across the normal controls; and (ii) the variance of subject-specific effects was the same in both Parkinson’s disease patients and normal subjects.

In our least-squares statistical analysis, the impact of disease on \( K_0 \) and \( K_1 \) was partitioned into between-group and between-patient metabolic effects. The partitioning of effects was as follows:

\[
\text{SSF}_{\text{Age}}^{\text{post}} - \text{SSF}_{\text{Age}}^{\text{pre}} = \delta_2 [\text{Age}_{j0} - \text{Age}_{j1}] + \delta_1 [\text{Age}_{j0} - \text{Age}_{j1}] + \delta_1 [\text{Age}_{j0} - \text{Age}_{j1}] + \delta_1 [\text{Age}_{j0} - \text{Age}_{j1}] + \delta_1 [\text{Age}_{j0} - \text{Age}_{j1}]
\]

in which \( t \) indexes groups (1, controls; 2, patients) and \( j \) indexes subjects within each group. On the left-hand side of Equation 2, \( \text{SSF}_{\text{Age}}^{\text{post}} \) is metabolic age in Subject \( \times \) Group notation, and \( \text{SSF}_{\text{Age}}^{\text{pre}} \) is the average metabolic age of the controls and patients combined. (Without loss of generality, parameter \( a \) of Equation 1 was set to unity.) On the right-hand side, between-group metabolic effects are \( \Delta K_1 \), the average difference in \( K_1 \) between controls and patients (i.e. \( K_{1,\text{post}}^\text{controls} - K_{1,\text{post}}^\text{patients} \)), and \( \Delta K_0 \) the average difference in \( K_0 \) (i.e. \( K_{0,\text{post}}^\text{controls} - K_{0,\text{post}}^\text{patients} \)). The between-patient metabolic effects are \( \Delta K_{1,\text{post}}^\text{between} \), the difference in \( K_1 \) between patient \( j \) and the average patient value (i.e. \( K_{1,\text{post}}^\text{between} - K_{1,\text{post}}^\text{control} \)), and \( \Delta K_{0,\text{post}}^\text{between} \), the corresponding difference in \( K_0 \) (i.e. \( K_{0,\text{post}}^\text{between} - K_{0,\text{post}}^\text{control} \)). In Equation 2, \( K_{1,\text{post}}^\text{control} \) is the normal control value of \( K_1 \); and \( [\text{Age}_{j0} - \text{Age}_{j1}] + [\text{Age}_{j0} - \text{Age}_{j1}] + [\text{Age}_{j0} - \text{Age}_{j1}] + [\text{Age}_{j0} - \text{Age}_{j1}] + [\text{Age}_{j0} - \text{Age}_{j1}] \) is the random component.

the average chronological age of the controls and patients combined, and \( p(t) \) equals \((1 - p)\) for \( t = 1 \) and \((-p)\) for \( t = 2 \), with \( p = N_1/(N_1 + N_2) \), where \( N_1 \) and \( N_2 \) equal, respectively, the number of normal control subjects and Parkinson’s disease patients.

Equation 2 represents a multivariate linear regression equation in which the effect sizes of the between-group and between-patient metabolic ageing factors are a function not only of their respective absolute values, but also of the variances of the associated Subject \( \times \) Group variables. However, the relationship between effect size and statistical power is complicated by the circumstance that the variance of the random component is also a function of Subject \( \times \) Group variables. In this situation, the scaling of \( SSF_{Agej} \) and the Subject \( \times \) Group variables determines statistical power, i.e., the relative percentage variance accounted for by the between-group and between-patient effects compared with the percentage variance accounted for by the random component.

We thus applied the multiplicative scaling factor \( p(t)Age_{\bullet\bullet}[Age_{\bullet\bullet} - Age_{\bullet\bullet}]^{-1} \) to Equation 2 to enhance statistical power. After rescaling, the left hand side of Equation 2 was replaced by

\[
SSF_{Agej} - SSF_{Age\bullet\bullet} = p(t)Age_{\bullet\bullet}[Age_{\bullet\bullet} - Age_{\bullet\bullet}]^{-1}
\]

Subject \( \times \) Group variables multiplying the between-group factors \( \Delta K_1 \) and \( \Delta K_0 \) were replaced, respectively, by \( \delta_2[p(t)Age_{\bullet\bullet}]^{-1} \) and \([Age_{\bullet\bullet}(Age_{\bullet\bullet} - Age_{\bullet\bullet})]^{-1}\). The Subject \( \times \) Group variables multiplying the between-patient factors \( \Delta K_{1j2} \) and \( \Delta K_{0j2} \) were replaced, respectively, by \( \delta_2[p(t)Age_{\bullet\bullet}]^{-1} \) and \( \delta_2[p(t)Age_{\bullet\bullet}(Age_{\bullet\bullet} - Age_{\bullet\bullet})]^{-1} \). Lastly, the Subject \( \times \) Group variable multiplying \( K_{1\bullet\bullet} \) was replaced by \( p(t)Age_{\bullet\bullet} \); and the Subject \( \times \) Group variables multiplying the measurement error were replaced by \( p(t)Age_{\bullet\bullet} \) and \( p(t)(Age_{\bullet\bullet} - Age_{\bullet\bullet})^{-1} \). Between-group and between-patient metabolic ageing effects were estimated separately in a two-step regression analysis. In the first step, the between-group parametric expression \( \Delta K_0 + Age_{\bullet\bullet} \Delta K_1 \) was estimated along with the combined group mean \( K_{1\bullet\bullet} \). Multivariable linear regression was applied to a subset of the cross-sectional data in which controls and patients were excluded whose \( SSF_{Age} \) scores were likely to be unduly influential in determining the between-group effects by virtue of the proximity of their ages to \( Age_{\bullet\bullet} \).

Thus, we excluded control subjects and Parkinson’s disease patients whose ages were within 5 years of \( Age_{\bullet\bullet} \). To enhance the effect sizes of the between-group factors relative to the between-patient factors, we also excluded Parkinson’s disease patients whose clinical duration differed by >5 years from the group mean clinical duration.

In the second-step analysis, the metabolic ageing scores of the patients excluded from the first analysis were predicted on the basis of the first regression estimate of the between-group effects. The second regression analysis was applied to the residuals of all patient scores to estimate the between-patient parameter expressions \( \Delta K_{1j2} \) and \( \Delta K_{0j2} + Age_{\bullet\bullet} \Delta K_{1j2} \) along with the between-group difference in \( \Delta K_1 \). The between-patient effects were modelled as average rates of change in \( K_0 \) and \( K_1 \) multiplied by the specific clinical duration of individual patients.

The first step of the statistical analysis provided a large sample test of the null hypothesis of no preclinical or post-onset effects on the expression of the normal ageing pattern in Parkinson’s disease patients. Specifically, a non-zero coefficient of the covariate \( [Age_{\bullet\bullet}(Age_{\bullet\bullet} - Age_{\bullet\bullet})]^{-1} \) indicates significant \((P < 0.05)\) pathological alterations in \( K_0 \) and/or \( K_1 \) in the Parkinson’s disease group.

The second step of analysis provided separate tests of whether post-onset alterations in \( K_0 \) or \( K_1 \) continued to occur with increasing disease severity, i.e., whether \( \Delta K_{1j2} \) or \( \Delta K_{0j2} + Age_{\bullet\bullet} \Delta K_{1j2} \) differed from zero. In this analytic step, the rates of change were estimated separately for \( K_0 \) and \( K_1 \) as a function of clinical duration. Lastly, the regression intercept provided the statistical test for significant differences in \( \Delta K_1 \). In computing regression statistics, we followed the inclusion/exclusion criteria described above, thereby including 17/20 normal controls and 24/37 Parkinson’s disease patients in the between-group analysis (Step 1). All patients were included in the between-patient analysis (Step 2). In both regression analyses, leverage plots of the Subject \( \times \) Group covariates were used to evaluate the statistical impact of influential data points on parameter estimation.

**Results and comments**

The primary result of this analysis was that Parkinson’s disease patients differed significantly from normal subjects in \( K_0 \) but not in \( K_1 \). Specifically, in the first step of the analysis, the \( \Delta K_0 \) estimate equaled \(0.0054 \pm 0.0025 (P = 0.04)\), indicating a significant decrease in \( K_0 \) in the Parkinson’s disease population. In the second regression step involving Parkinson’s disease patients alone, we estimated that the rate of change of \( K_0 \) with disease duration was \(-0.0021 \pm 0.0004\) per year of illness \((P < 0.0001)\). By contrast, neither \( \Delta K_1 \) nor the rate of change in \( K_1 \) with disease duration were significantly different from zero \((P = 0.28 \text{ and } 0.98, \text{ respectively})\). These modelling results indicate that the reported differences in the macroparameter \( \Delta \) reported in the main text refer specifically to a Parkinson’s disease-related decline in \( K_0 \) and not to a change in \( K_1 \). Our findings suggest that Parkinson’s disease-related alterations in the normal ageing process proceed at a constant rate independent of disease progression. In Parkinson’s disease, the rate of age-related metabolic degeneration does not appear to accelerate with increasing duration of symptoms.