authors say that in order to reduce the number of parameters, the Montreal group selected Ve and q as constants based upon physiologically reasonable criteria. This approach is used by most modelers (including us) because of the limitations inherent in the estimation of multiple parameters with acceptable precision given the current state of the PET art. But once these assumptions and simplifications are made, one must also question how realistic these models are in comprehensively representing underlying physiochemical processes which can be extremely complex. Hav ing agreed to make such assumptions, the least we can do is not to fixate upon a single estimated parameter such as k_3^D.

Transport Ratio

The authors suggest that the blood brain transfer ratio can be determined accurately only in the absence of significant tracer metabolism as is the case with 3OMFD. Nonetheless, our results show that if the metabolic process is incorporated in the model, then there is no reason why the blood brain transfer ratio cannot be determined even with a longer study duration. The question is then which estimate of q is correct. The authors have claimed that "no estimate of q, other than the original one of 2.3, determined as an abscissa intercept, actually meets these requirements." However, it is interesting that in a recent article, these authors reanalyzed their rat kinetic data and estimated the parameters K_1^M and K_1^D to be 0.08 and 0.07, respectively, and go on to state "the value of q in humans may also be close to 1" (*3*). Why did the authors not mention their own article in this letter?

The authors also neglected to refer our work on FDOPA kinetics in the presence of entacapone, a peripheral COMT inhibitor. This material was presented at Brain PET 95 and appeared in the proceedings of that meeting (*4*) and subsequently was published in the *Journal of Cerebral Blood Flow and Metabolism* (*5*). In this study, we found that the use of a erroneously high q value (greater than 1.0) resulted in an incorrect finding regarding the pharmacological effect of entacapone, i.e., the spurious result that this agent reduces striatal DDC activity. It is known that entacapone primarily prolongs the peripheral circulation time of levodopa without any central effect on catechol O-methyl transferase (COMT) or DDC activity. Therefore, the claim by the authors that a use of q value from 0.5 to 3 had minimal effect on k_3 is not applicable to human studies when COMT inhibitors are administered. Moreover, our results are in complete agreement with those of other investigators which also suggest a q value of 1 (*1,6,7*).

How are these different estimates of q to be reconciled? We would like to speculate into a possible source of error in the estimation of the q value of 2.3 in the rat study (*8*). The value of q was obtained from the slope/intercept ratio of a plot of the function: $K_1^*/f^D = K_1^M R + K_1^D$ (Fig. 6, ref. 8). The linear regression is heavily weighted by the last two data points which were acquired toward the end of the experiment. At that time, the error in the HPLC metabolite data is expected to be maximal due to the small fraction of FDOPA present in the plasma. The slope of the line decreases significantly when these last two points are eliminated, yielding an estimate of q value closer to 1.

Partition Volume Ve

Our estimated mean value of Ve^D is lower in frontal cortex as compared to the striatum. The authors have provided several explanations as to why Ve can sometimes exceed 0.8 (binding of 3OMFD to DDC without being metabolized etc.). In our study we did not detect any penalty in the estimates of k_3^D by fitting K_1 and k_2 as independent parameters. This suggests that striatal Ve need not be fixed to other regional values such as that estimated for the frontal cortex. The authors suggest that our estimation of Ve may be artifactually elevated due to diffusion of LNAA from plasma into erythrocytes. However, in our study arterial blood samples were immediately placed in ice and centrifuged within a few minutes of the collection making this possibility unlikely. Moreover, such a diffusion artifact should equally affect both striatum and frontal cortex and does not explain the basic observation that Ve is larger for striatum than for frontal cortex.

Choice of Citations

Our articles focus on the technical issues of the determination and application of striatal DDC activity measurements obtained with FDOPA/PET. These manuscripts were not intended as review articles to document the historical origins of the Patlak plot or as summaries of all the earlier rodent studies. The work of Cummings and his colleagues has been acknowledged in reference 29 of our paper. In that reference the authors cite most of their previous animal studies. The readers of the *Journal of Nuclear Medicine* may refer to these publications should their interest dictate.

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Nigrostriatal Dopaminergic Imaging with Iodine-123-βCIT-FP/SPECT and Fluorine-18-FDOPA/PET

TO THE EDITOR: We read with great interest the study by Ishikawa et al. on SPECT and PET imaging of the dopamine transporter (*1*). They examined 12 patients with Parkinson's disease (PD) and 15 healthy control subjects using both [^{123}I]βCIT-FP/SPECT and [^{18}F]FDOPA/PET. A highly significant correlation was found between the striatal-occipital ratios (SORs) obtained for both ligands. They also reported a significant correlation between the SORs obtained with either SPECT or PET and the severity of motor signs [i.e., the UPDRS score (Pearson correlation coefficients: 0.69 and 0.60, respectively)]. Based on these findings, the authors state that βCIT-FP/SPECT is a useful and simple noninvasive method in the quantification of dopaminergic defects.

Recently, we reported on the use of [^{123}I]FP-CIT ([^{123}I]βCIT-FP) SPECT in various stages of PD (*2*), but we failed to find a significant correlation between UPDRS ratings and SPECT measures. Therefore, we also examined 21 early and nonmedicated patients with PD using the same ligand (data not published). Since age and disease duration may confound the correlation between disease severity and SPECT measures, as has been suggested by others (*3*), we controlled for these variables in the later study.

Again, we found no significant correlation between UPDRS ratings and the SPECT measures.

Unfortunately, Ishikawa et al. do not provide data on the correlation (in the PD group) between: (a) age and SPECT, (b) disease duration and SPECT, (c) age and UPDRS and (d) disease duration and UPDRS. Based on the data presented in their article, we have the impression that the UPDRS ratings are positively and significantly correlated with disease duration (0.69, $p = 0.013$) and not with age. A longer disease duration would allow more degeneration of dopaminergic neurons and might explain the positive and significant correlation between UPDRS ratings and the SPECT measures. It would be interesting to know what the correlations are between the above-mentioned variables and whether the reported significant correlation between UPDRS and SPECT remains significant when controlling for disease duration.

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REPLY: We read with interest the comments of Tissingh and colleagues concerning our article on comparative SPECT and PET imaging of nigrostriatal dopaminergic function (*1*). These readers were apparently unable to duplicate our finding of a significant correlation between the striatal-occipital ratio (SOR) for [^{123}I]FP-CIT and quantitative UPDRS motor ratings. They raise several questions concerning the possibility of a false-positive result emerging through a failure to correct for confounding variables such as patient age and disease duration. We would like to address their concerns.

First, our finding of a significant correlation between parkinsonian disease severity and striatal dopamine transporter binding measured with [^{123}I]FP-CIT conforms well with previously published results utilizing the related cocaine derivative SPECT ligand [^{123}I]βCIT (*2,3*). The reason for the absence of such a correlation in the readers' hands is unclear. In our study, we found that implementing a count thresholding algorithm in the calculation of SOR was critical in reducing noise sufficiently so that this parameter could be used for early diagnosis of parkinsonism and for correlations with disease severity. The clinical scores used as disease severity measures are also important. Our findings in this study and in our previous work (*4,5*) indicate significant correlations between dopaminergic imaging measures and motor ratings (UPDRS items 19–31: 6). The magnitude of correlations between the imaging parameters and disease severity may be weakened by the inclusion of the other clinical domains (mentation, behavior and activities of daily living) of the UPDRS rating system. Furthermore, significant correlations between dopaminergic parameters and UPDRS scores may be difficult to obtain when the latter have a narrow range across patients. Thus, the readers' subsequent study of drug-naive, early-stage patients may not have revealed a significant correlation if the patients were selected within a limited range of motor disability (as might occur close to the time of onset).

Second, the authors appropriately express interest in the possibility of age and duration as confounding variables in the correlations between the SPECT measurements and disease severity. While we did note a small aging effect in normal control subjects, there was no correlation between patient age, UPDRS ratings and either of the dopaminergic imaging parameters [age-UPDRS: $R^2 = 0.02$; age-$SOR^{\beta CIT}$: $R^2 = 0.03$; age-SOR^{FD}: $R^2 = 0.08$. $SOR^{\beta CIT}$ and SOR^{FD} refer to values obtained with [^{123}I]FP-CIT and [^{18}F]fluorodopa, respectively (*1*)]. Controlling for subject age in both groups by regression analysis does not change the accuracy of discrimination between the two groups nor does it change the correlation between the UPDRS ratings and SOR measured either by SPECT or PET imaging ($R^2 = 0.48$, $p < 0.01$ for SPECT correlations; $R^2 = 0.50$, $p < 0.01$ for PET correlations).

Third, the readers express the concern that the correlation between disease severity and SOR may be confounded by the effects of disease duration. We found a highly significant correlation between disease duration and severity ($R^2 = 0.48$, $p < 0.02$): an expected finding in a neurodegenerative disorder. In this vein, we found that in a multiple regression model, predictions of $SOR^{\beta CIT}$ by disease duration and UPDRS motor ratings were interchangeable and of comparable magnitude, respectively, accounting for 40% and 48% of the variability in the SPECT data. Importantly, both clinical variables, when considered in combination, predicted little additional variance in $SOR^{\beta CIT}$ ($R^2 = 52\%$). This suggests that individual differences in disease duration and severity accounted for similar aspects of the variability in the SPECT measure. In this context, "controlling" for disease duration (as the readers have apparently done) is likely to negate any significant correlation with UPDRS severity measures and would not be warranted.

Our results with [^{123}I]FP-βCIT and SPECT indicate that SOR correlates equally with both disease duration and severity as interrelated clinical measures of nigrostriatal degeneration. The comparable findings with both PET and SPECT clearly demonstrate the utility of both imaging techniques as quantitative imaging markers of disease progression in parkinsonism. Nonetheless, the relative sensitivity of the clinical and imaging markers to the neurodegenerative process can be determined only through longitudinal studies conducted at multiple time points in the course of disease.

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