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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