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The harsh realities facing the use of SPECT imaging in monitoring disease progression in Parkinson's disease

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CORRESPONDENCE

The harsh realities facing the use of SPECT imaging in monitoring disease progression in Parkinson's disease

Dr Snow is right to be cautious in his optimism concerning the use of functional imaging markers in neuroprotection studies in Parkinson's disease¹ as storm clouds gather²⁻³ over the methods and interpretation of CALM-PD and REAL-PET. The concerns, however, are not limited to the effect of drug treatment on ligand uptake. Most importantly we need to ask the weight that should be placed on the result of functional imaging studies when they are not supported by the accompanying clinical data. In addition, there are concerns about the ability of the methods for accurately monitoring progression. The key requirements for a PET or SPECT method to be used in assessing progression are sensitivity to clinical change and reproducibility.⁴ There are no data concerning either from the study of Winogrodzka and colleagues,⁵ the authors quoting reproducibility data from Seibyl *et al.*⁶ These data need to be presented for the benefit of the readership. The mean (SD) scan to scan variability in a group (n = 7) of patients with Parkinson's disease was 16.8 (13.3)%. It is surely only in functional imaging that a measurement to measurement variability of $\pm 43\%$ (mean ± 2 SD) could be described as highly reproducible⁵ or excellent.⁶ Sensitivity provides knowledge of the amount a functional imaging marker will change with a given clinical change, and I have yet to be convinced (partly because the data have not been presented) that [¹²³I]β-CIT SPECT can provide the necessary sensitivity to outweigh the very strong influence of scan to scan variability. The problems are compounded in studies of L-dopa versus agonist because within the first year a significant number of patients will leave the study or require supplementary L-dopa. The data of Winogrodzka and colleagues⁵ illustrate this. In one year mean scan to scan change because of progression is 8% of baseline (or about 4% of normal mean), where mean (SD) scan to scan variability (which may be biological or methodological) is 16.8 (13.3)%. If we are looking for a 25% difference in rate of progression between the two study arms over one year (a difference of 2% progression from baseline) we need a technique that gives a more reproducible measurement than $\pm 43\%$. This is the principal problem that needs to be addressed before further "neuroprotection" studies take place using [¹²³I]β-CIT SPECT.

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Authors' reply

We would like to thank Dr Morrish for his comments on our paper.¹ We agree that it would be of interest to present the data of the longitudinal progression of dopaminergic degeneration (as measured by [¹²³I]β-CIT SPECT) in correlation with data on clinical progression. In our study, the patients were drug-naïve when the baseline SPECT scans were obtained. Interestingly, these SPECT data correlated highly with clinical scores (motor UPDRS), which indicate that the SPECT measures may be of value in monitoring progress of nigrostriatal degeneration. Within our study design, however, the patients did not discontinue their dopaminergic drug treatment when the second [¹²³I]β-CIT SPECT scan was done (one year after baseline). Consequently, the UPDRS scores were influenced by dopaminergic drug effects and therefore were not suitable to study correlations with [¹²³I]β-CIT SPECT measures. Nevertheless, as dopamine transporter imaging will only be a relevant tool for monitoring dopaminergic degeneration if it ultimately reflects meaningful changes in clinical function in patients with Parkinson's disease, future studies should investigate this relation carefully. However, there is still debate on how adequate clinical data can be obtained in patients on drug treatment. For example, it is still unclear whether data obtained in the "defined OFF stage" are adequate enough to assess clinical progression (for a discussion, see Marek *et al.*, 2003²).

Concerning the issue of variability and reproducibility of the [¹²³I]β-CIT SPECT technique, we of course agree with Dr Morrish that, for the benefit of future neuroprotection studies, all effort should be made to improve analysis methodology to reduce the variance in imaging outcomes. Variability may be reduced, for example, by quantifying radioligand binding automatically on a voxel by voxel basis (three dimensional).³ Moreover, to reduce variability in SPECT measures for dopamine transporter binding, other tracers than β-CIT

might be of value. For example, FP-CIT SPECT studies in patients with Parkinson's disease have shown reproducibility of the order of 8%.⁴ This high reproducibility may stem from the fact that acquisition can be started as soon as three hours after injection for [¹²³I]FP-CIT,⁵ whereas the optimal time point for acquisition of [¹²³I]β-CIT studies is 20 to 24 hours after injection. Consequently, the counts statistics are better for [¹²³I]FP-CIT than for [¹²³I]β-CIT SPECT studies. Interestingly, a recent preliminary study showed the feasibility of using [¹²³I]FP-CIT SPECT for monitoring dopaminergic degeneration in Parkinson's disease.⁶ Nevertheless, it would be of major importance that further studies focus on minimising the variability in SPECT measures of dopamine transporter binding, and show which radiotracer is optimal for performing progression studies.

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CORRECTIONS

There were two mistakes published in the table of the short report, Sjögren's syndrome associated painful sensory neuropathy without sensory ataxia, by K Mori, M Iijima, M Surgiura *et al.* in the September issue of *JNNP* (2003;74:1320-2): the digit 9 was added to the eleventh column head by accident and the second entry in the final column should read 12, not 2.

The authors of the letter entitled Meningioma of the optic nerve sheath: treatment with hydroxyurea, published in the September issue of *JNNP* (2003;74:1348-50) were listed in the incorrect order. The author order should read as follows: S Paus, T Klockgether, H Urbach, U Schlegel.