Radiotracer imaging of dopamine transporters and presynaptic dopamine synthesis in parkinsonian syndromes

Nicolaas Paul L G Verhoeff

PET Centre and Schizophrenia and Continuing care Division, Centre for Addiction and Mental Health and University of Toronto. Toronto, Ontário, Canadá

Introduction

The prevalence of idiopathic Parkinson's disease (IPD) is 84-164 per 100,000 for Caucasians, whereas the annual incidence is 8.7-20 per 100,000.[1] Both figures increase with age. These figures show that IPD is and will be one of the major neurological causes of morbidity, especially with an increasing mean age of the population. The development of possible pharmacological treatments to retard the progression of IPD, such as selegiline and dopamine (DA) agonists rather than L-DOPA, has increased the need for a reliable outcome measure to assess progressive loss of the dopaminergic (DAergic) system, to monitor the efficacy of treatment and to diagnose the disease during the preclinical phase so that treatments can be implemented before irreversible loss of DAergic neurons occurs.[2] The preclinical phase in IPD may be as long as 20-40 years. Neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) provide such objective outcome measures.[3-5] The presynaptic site can be labeled with probes for the DA transporter (DAT) or the synthetic enzyme aromatic l-amino acid decarboxylase ("DOPA decarboxylase").

[^{123}I]ßCIT SPECT as marker for IPD

With [^{123}I]2ß-carbomethoxy-3ß-(4–iodophenyl)tropane ([^{123}I]ßCIT or [^{123}I]RTI-55) SPECT, acceptable clinical-epidemiologic characteristics of a preclinical marker of later onset of IPD, showing clinical-pathological relevance to the process, have been met.[3,4,6,7] [^{123}I]ßCIT SPECT imaging of DAT may be useful for: (1) diagnosing early or pre-symptomatic stages of IPD, (2) monitoring progression severity in IPD over time, (3) assessing the efficacy of putative neuroprotective agents, (4) revealing the extent of striatal involvement in IPD and other parkinsonian syndromes, and (5) following growth or rejection of fetal tissue transplanted into IPD patients (see below).

Correlation with neuronal cell counts or dopamine levels

As mentioned above, decreased DAT densities have been observed in putamen and caudate nucleus in IPD patients, closely paralelling losses of DA.[8,9] Both the decrease of tissue DA levels and [^{3}H]2ß-carbomethoxy-3ß-(4–fluorophenyl) tropane ([^{3}H]ßCFT or [^{3}H]WIN-35,428) binding to the DAT showed similar medial to lateral gradients in the striatum and more severe losses in the putamen compared to the caudate (Kaufman and Madras 1991; Kish et al. 1988). [^{123}I]ßCIT SPECT studies performed in IPD patients have confirmed the relative selective loss of DAT in the putamen.[11-14]

Sensitivity and specificity, and positive and negative predictive values for IPD

Hemiparkinson patients demonstrate reduced striatal uptake contralateral and ipsilateral to motor symptoms suggesting [^{123}I]ßCIT may be sensitive to preclinical changes in DAT.[11,12,15,16] The V_3" (e.g. the ratio of {striatum-occipital cortex} over occipital cortex during a state of equilibrium), the putamen/caudate ratio and the contralateral/ipsilateral ratio for putamen and caudate were significantly reduced in 28 IPD patients compared with 27 healthy controls.[14] Discriminant function analysis using V_3" for ipsilateral and contralateral caudate and putamen correctly classified 54 of the 55 cases; when age-correction of the data was performed, all cases were correctly identified. Age-corrected V_3" in the putamen contralateral to the side of sign onset provided a particularly good group separation with only 18% unaccounted variance. Similar analyses for the putamen/caudate ratio and the contralateral/ipsilateral ratio for putamen and caudate correctly classified 96% and 80% of the subjects, respectively.

Correlation with onset of symptomatic IPD and with severity of symptoms

[^{123}I]ßCIT SPECT in five IPD patients showed greater losses in the striatum contralateral to the side of the body with initial symptoms.[12] In eight early IPD patients with exclusively hemiparkinsonism, [^{123}I]ßCIT striatal uptake was reduced by about 53% contralateral and by 38% ipsilateral to the clinically symptomatic side, when compared with eight age and sex matched healthy subjects (Marek et al. 1996). The reduction in [^{123}I]ßCIT uptake was greater in the putamen than in the

caudate. These data were confirmed independently in 15 early untreated IPD patients[17] and in 16 early untreated IPD patients,[18] and indicate that [123I]ßCIT SPECT may be useful in identifying individuals with developing DAergic pathology prior to the onset of motor signs.

In 28 L-DOPA-responsive IPD patients, the degree of abnormal striatal uptake of [123I]ßCIT, expressed as both ipsilateral and contralateral V_3" in both putamen and caudate, was significantly correlated with the total Unified Parkinson's Disease Rating Scale (UPDRS) score and with the Hoehn-Yahr stage.[14] Both UPDRS motor subscores and bradykinesia were strongly correlated with the V_3" measures. The uptake in the putamen was relatively more reduced than in the caudate. Also, the asymmetry (based on the side where the parkinsonian signs started) was larger in the putamen than in the caudate. These findings have been repoduced in small groups of IPD patients discriminated as early (Hoehn and Yahr scores 1-2) and late IPD patients (Hoehn and Yahr scores 2.5-4; disease history > 10 years),[19] 1995), in 34 previously untreated IPD patients (Hoehn and Yahr scores 1-3),[20] and in a large group of 113 IPD patients (Hoehn and Yahr scores 1-5).[21]

Differential diagnosis

It has been suggested that the elevation of the caudate/putamen ratio and marked asymmetry of [123I]ßCIT activity may be useful in distinguishing IPD from atypical parkinsonian syndromes such as multiple system atrophy (MSA)[6,13,22] as these would usually show a more uniform and symmetrical loss of DAergic activity both involving the caudate and putamen, reflected in reduced 6-[18F]fluoro-L-DOPA ([18F]FDOPA) uptake in both nuclei.[23] This was observed to some extent with [123I]ßCIT SPECT in nine MSA patients and four progressive supranuclear palsy (PSP) patients compared to 113 IPD patients, but not sufficiently to differentiate IPD from MSA or PSP.[21] Also, posterior putamen/caudate ratios by [11C]ßCFT PET allowed discrimination of six PSP patients from six IPD patients.[24] The differential diagnosis between IPD on the one hand and MSA on the other hand can be further improved by adding imaging with presynaptic markers such as [18F]FDOPA PET[25] [123I]ßCIT SPECT[26] to DA D_2 receptor (D_2R) imaging. With both [123I]ßCIT and [123I]IBZM SPECT in 50 unselected patients with parkinsonian syndromes, both sensitivity and specificity were 86%.

Other markers for IPD

Similar findings as for [123I]ßCIT SPECT were observed with [11C] ßCIT PET in nine IPD patients when compared with three healthy controls.[27] However, because of the short half-life of 11C, only the first part of a prolonged accumulation process could be visualised. Therefore, ßCIT may be better suited for SPECT studies than for PET.

With SPECT using the N-fluoropropyl, methyl ester of ßCIT, i.e. [123I]FPCIT, the loss of striatal DAT was measured in five non-medicated IPD patients versus five healthy controls.[28] Assayed at 3 hours after the intravenous injection of [123I]FPCIT, the patients showed reduced signal in both caudate nucleus and putamen. The ratios of specific to nonspecific uptake were consistently 2.5-fold lower than for [123I]ßCIT. However, when expressed as a percentage of the uptake ratio found in healthy controls the decrease in the IPD patients was similar for both tracers. An elaboration of the [123I]FPCIT SPECT study in six early IPD patients (Hoehn and Yahr score 1-2), 12 patients with advanced IPD (Hoehn and Yahr score 2.5-4; disease history > 10 years), and six healthy age-matched controls revealed that the specific to non-specific striatal uptake ratios correlated with the Hoehn and Yahr stage.[29] Progression of IPD evolved apparently more rapidly in the putamen than in the caudate nucleus based on the relatively higher uptake of the latter area in early IPD. For all 21 early-stage and drug-naive IPD patients, striatal [123I]FPCIT ratios were lower than those in 14 healthy controls with more reductions in the putamen than in the caudate nucleus and more reductions contralateral than ipsilateral to the side with the most severe symptoms; the subgroup with hemi-IPD showed DAT loss even on the ipsilateral side.[30,31] However, in this early IPD group no significant correlations were found between striatal [123I]FPCIT ratios and disease severity. One can conclude that (1) [123I]FPCIT allows a significant discrimination between IPD patients and age-matched controls, (2) [123I]FPCIT seems as good as [123I]ßCIT for this purpose, and (3) the faster kinetics of [123I]FPCIT allow a one day protocol, which is a clear advantage over [123I]ßCIT. One caveat is that with [123I]FPCIT only a transient or peudo-equilibrium is reached versus a prolonged equilibrium with [123I]ßCIT.

This caveat was addressed in another recent study which also compared [123I]ßCIT versus [123I]FPCIT SPECT in six IPD patients versus five healthy controls.[32] The major conclusions were the following. (1) The nonspecific uptake of [123I]FPCIT was greater than [123I]ßCIT. (2) Whereas the striatal and occipital activity of [123I]ßCIT was very stable over 18-27 h p.i. (less than 1%/h washout), the striatal and occipital activity of [123I]FPCIT showed significant washout over 3-6 h p.i.(5%-8%/h). This was corroborated by plasma analysis showing elimination rates of 13%-20%/h for [123I]FPCIT. (3) The striatal V_3" values of [123I]FPCIT gradually increased and became stable 3-6 h p.i., and the differences between the IPD patients and controls were greater with [123I]FPCIT than with [123I]ßCIT, consistent with the faster brain washout of [123I]FPCIT and the resultant transient equilibrium state, which resulted in an overestimation of DAT density by [123I]FPCIT in the controls. (4) The primary metabilite of [123I]FPCIT is the carboxylic acid, similar to that of [123I]ßCIT. (5) [123I]FPCIT SPECT is sensitive to striatal DAT reductions in IPD patients and may provide useful data for clinical purposes. (6) [123I]FPCIT may not provide the accurate DAT quantitation required for some clinical studies, as in the evaluation of IPD progression. However, the last point contradicts another study in 12 mildly affected IPD patients, concluding that [123I]FPCIT SPECT can provide quantitative descriptors of presynaptic DAergic function comparable to those obtained with [18F]FDOPA PET.[33] In 10 IPD patients with decreased striatal uptake compared to the controls, age-corrected striatal distrubution volume ratios correlated

negatively with the UPDRS composite motor ratings.[34]

A profound reduction of uptake was shown with SPECT using [123I]2ß-carbomethoxy-3ß-(4-fluorophenyl)-n-(1-iodoprop-1-en-3-yl)nortropane ([123I]altropane or [123I]IACFT) in the posterior putamen with relative sparing of the caudate nuclei in eight IPD patients compared to seven controls.[35] These results are congruent with [125I]altropane data in normal versus IPD human brain post mortem.[36] The high selectivity and rapid striatal accumulation of [123I]altropane may allow for accurate DAT quantification in less than 2 h and [123I]altropane SPECT may be an additional effective clinical marker for IPD.[35]

The question remains which marker would be more important to establish the status quo in vivo of the nigrostriatal pathway: one that assays the surviving neurons, like the markers discussed above, or a DA analogue, like [18F]FDOPA, that might be a better measure for the functional status of the surviving neurons.[37] However, DA turnover is increased in animals with nigrostriatal lesions and in postmortem parkinsonian brain. As a result of this enhanced turnover, an increased proportion of radiometabolites may leave the brain of parkinsonian patients, exaggerating the deficits in these patients when measured with [18F]FDOPA.[6] The assumption at present is that the number of DAT per nerve terminal remains constant in IPD, so that a ligand for the DAT can directly visualise the number of remaining nerve terminals. However, at present it cannot be excluded that as the loss of DAergic neurons reaches a critical threshold, the remaining neurons may compensate by decreasing the amount of DAT per terminal in order to maintain synaptic DA at a certain level.[38] A PET study demonstrated that apomorphine decreased the striatal [11C]L-DOPA influx rate in early IPD but not in advanced IPD patients.[39] This suggests that the DAergic presynaptic inhibitory feedback regulation is intact in early IPD but diminished in advanced IPD patients.

Aging

Another question remains regarding the optimum age correction for comparison of striatal DAT in IPD patients versus controls. Aging is associated with a gradual degeneration of DAergic neurons and an accompanying loss of transmitter and transporter. A decrease of about 10%/decade has been described for DAT in postmortem samples.[40,41] SPECT with [123I]ßCIT, [123I]FPCIT and [123I]altropane in healthy volunteers showed comparable age-related striatal DAT declines of 7.6-9.6%/decade, [30,35,42] whereas PET with [11C]ßCFT, [18F]FPCIT and [11C]d-threo-methylphenydate showed declines of 4.6-7.7%/decade.[34,43,44] However, the age-related DAT decline may be more rapid during young adulthood and less rapid throughout middle age so that nonlinear functions may be more optimal than linear functions to descibe this.[45] In addition, early IPD patients did not show any age-associated DAT decline with [123I]FPCIT SPECT, in contrast to healthy controls.[30,46] These issues pose additional challenges for age correction in striatal DAT imaging.

Cortical dopamine transporters in IPD

In nine non-demented, non-depressed IPD patients, with mild marked side-to-side asymmetry in motor impairment, the clinical motor asymmetries significantly correlated in the clinically expected direction to asymmetries in neocortical (especially frontal) [11C]nomifensine uptake.[47] This suggests that monoamine neocortical denervation might play a direct role in motor impairment in IPD.

Experimental therapies

Firstly DAT and secondly D_2R PET or SPECT can be used in future to create homogeneous patient groups for clinical trials exploring both medical and surgical experimental therapies. In parkinsonian patients, possible additional damage in the connections forming the striato-thalamo-cortical circuit might occur.[48] This is the clinical basis for therapies with NMDA receptor NR_{2B} subunit antagonists,[49] AMPA receptor antagonists such as NBQX, $alpha_2$–adrenergic receptor agonists such as clonidine, and muscarinic receptor antagonists such as dexetimide, either alone or in combination, with or without apomorphine or other DA (D_1R) agonists.[48] In a rat model, 6-OHDA was used to lesion the median forebrain bundle, resulting in a complete and irreversible destruction of the nogrostriatal pathway. When glial cell-line-derived neurotrophic factor (GDNF) was injected ipsilaterally above the substantia nigra and immediately before the unilateral 6-OHDA injection, it prevented both the 6-OHDA-induced reduction of DAT, measured by [11C]IPCIT PET in the ipsilateral striatum, and the development of amphetamine-induced rotations.[50] Therefore, GDNF may be useful for the treatment of IPD. One PET study was done in a unilateral IPD rat neurotransplantation model.[51] In the lesioned striatum, the [11C]ßCFT binding ratio was reduced to 15-30% of the intact side. After DA neuronal transplantation, behavioral recovery occurred only after the [11C]ßCFT binding ratio had increased to 75-85% of the intact side. Therefore, DAT imaging could be a useful addition to placebo-controlled clinical trials evaluating the effect of fetal nigral transplantation in IPD.[52]

Conclusion

Imaging of the presynaptic DAergic nigrostriatal neurons with SPECT or PET has been shown to be of value in detecting IPD at a very early (probably even presymptomatic) stage, in monitoring the severity of IPD and, combined with D_2R imaging, in differentiating parkinsonian syndromes. These techniques are being used in clinical trials to evaluate neuroprotective properties of medications that may inhibit the rate of progression of IPD and could also be used for such studies in other parkinsonian syndromes.

The synthesis of this article was supported by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Affective Disorders and by a Postdoctoral Research Fellowship Award from the Ontario Mental Health Foundation to Nicolaas Paul LG Verhoeff.

References

1. Speelman JD. Parkinson's disease and stereotaxic neurosurgery [thesis]. Amsterdam: University of Amsterdam; 1991. p. 11-58.
2. Hauser RA, Zesiewicz TA. Management of early Parkinson's disease. Med Clin North Am 1999;83:393-414.
3. Verhoeff NPLG. Ligands for neuroreceptor imaging by single photon emission tomography (SPET) or positron emission tomography (PET). In: Murray IPC, Ell PJ, editors. Nuclear Medicine in Clinical Diagnosis and Treatment. 2nd Edition. New York: Churchill Livingstone; 1998. p. 521-62.
4. Verhoeff NPLG. Radiotracer imaging of dopaminergic transmission in neuropsychiatric disorders. Psychopharmacology 1999;147:217-49.
5. Booij J, Tissingh G, Winogrodzka A, van Royen EA. Imaging of the dopaminergic neurotransmission system using single-photon emission tomography and positron emission tomography in patients with parkinsonism. Eur J Nucl Med 1999;26:171-82.
6. Innis RB. SPECT Imaging of Dopamine Terminal Innervation: Potential Clinical Tool in Parkinson's disease. Eur J Nucl Med 1994;21:1-5.
7. Verhoeff NPLG, Booij J, Innis RB, Van Royen EA. Neuroreceptor ligand imaging by SPECT in Parkinsonian syndromes. In: De Deyn PP, Dierckx RA, Alavi A, Pickut BA, editors. A textbook of SPECT in Neurology and Psychiatry. London: John Libbey Publishers; 1997. p. 149-65.
8. Hirai M, Kitamura N, Hashumoto T, Nakai T, Mita T, Shirakawa O, et al. [^{3}H]GBR-12935 binding sites in human striatal membranes: binding characteristics and changes in parkinsonians and schizophrenics. Jpn J Pharmacol 1988;47:237-43.
9. Kaufman MJ, Madras BK. Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's diseased striatum. Synapse 1991;9:43-9.
10. Kish SJ, Shannak K, Hornykiewics O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. N Engl J Med 1988;318:876-80.
11. Brücke T, Kornhuber J, Angelberger P, Asenbaum S, Frassine H, Podreka I. SPECT imaging of dopamine and serotonin transporters with [^{123}I]ß-CIT. Binding kinetics in human brain. J Neural transm [GenSect] 1993;94:137-46.
12. Innis RB, Seibyl JP, Scanley BE, Laruelle M, Abi-Dargham A, Wallace E, et al. Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in parkinson disease. Proc Natl Acad Sci USA 1993;90:11965-9.
13. Marek KL, Seibyl JP, Zoghbi SS, Zea-Ponce Y, Baldwin RM, Fussell B, et al. [^{123}I[ß-CIT SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. Neurology 1996;46:231-7.
14. Seibyl JP, Marek KL, Quinlan D, Sheff K, Zoghbi S, Zea-Ponce Y, et al. Decreased SPECT [^{123}I]ß-CIT striatal uptake correlates with symptom severity in idiopathic Parkinson's disease. Ann Neurol 1995;38:589-98.
15. Asenbaum S, Pirker W, Angelberger P, Bencsits G, Pruckmayer M, Brücke T. [^{123}I]ß-CIT and SPECT in essential tremor and Parkinson's disease. J Neural Transm 1998;105:1213-28.
16. Ichise M, Kim YJ, Ballinger JR, Vines D, Erami SS, Tanaka F, et al. SPECT imaging of pre- and postsynaptic dopaminergic alterations in L-dopa-untreated PD. Neurology 1999;52:1206-14.
17. Wenning GK, Donnemiller E, Granata R, Riccabona G, Poewe W. ^{123}I-beta-CIT and ^{123}I-IBZM-SPECT scanning in levodopa-naive Parkinson's disease. Mov Disord 1998;13:438-45.
18. Tissingh G, Bergmans P, Booij J, Winogrodzka A, van Royen EA, Stoof JC, et al. Drug-naive patients with Parkinson's disease in Hoehn and Yahr stages I and II show a bilateral decrease in striatal dopamine transporters as revealed by [^{123}I]ß-CIT SPECT. J Neurol 1998;245:14-20.
19. Vermeulen RJ, Wolters ECh, Tissingh G, Booij J, Stoof JC, Janssen AGM, et al. [^{123}I]-ß-CIT binding with SPECT in controls, early and late Parkinson's disease. Nucl Med Biol 1995;22:985-91.
20. Muller T, Farahati J, Kuhn W, Eising EG, Przuntek H, Reiners C, et al. [^{123}I]ß-CIT SPECT visualizes dopamine transporter loss in de novo parkinsonian patients. Eur Neurol 1998;39:44-8.
21. Brücke T, Asenbaum S, Pirker W, Djamshidian S, Wenger S, Wober C, et al. Measurement of the dopaminergic degeneration in Parkinson's disease with [^{123}I]ß-CIT and SPECT. Correlation with clinical findings and comparison with multiple system atrophy and progressive supranuclear palsy. J Neural Transm Suppl 1997;50:9-24.
22. Seibyl J, Marek K, Sheff K, Innis R. [I-123]ß-CIT brain SPECT imaging of dopamine transporters in Parkinson's disease and Parkinson syndrome [abstract]. J Nucl Med 1996;37:134P.
23. Brooks DJ, Ibanez V, Sawle GV, Playford ED, Quinn N, Mathias CJ, et al. Differing patterns of striatal ^{18}F-DOPA uptake in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Ann Neurol 1990;28:547-55.
24. Ilgin N, Zubieta J, Reich SG, Dannals RF, Ravert HT, Frost JJ. PET imaging of the dopamine transporter in progressive supranuclear palsy and Parkinson's disease. Neurology 1999;52:1221-6.
25. Antonini A, Leenders KL, Vontobel P, Maguire RP, Missimer J, Psylla M, et al. Complementary PET studies of striatal neuronal function in the differential diagnosis between multiple system atrophy and Parkinson's disease. Brain 1997;120: 2187-95.
26. Tatsch K, Kerner M, Linke R, Schwarz PD, Mozley PD, Hahn K. Combined analysis of the pre- and postsynaptic dopaminergic system for improved discrimination between idiopathic and non-idiopathic parkinsonian syndromes [abstract]. J Nucl Med 1998;39:124P.
27. Laihinen AO, Rinne JO, Nagren KA, Lehikonen PK, Oikonen VJ, Ruotsalainen UH, et al. PET Studies on Brain Monoamine Transporters with Carbon-11-ß-CIT in Parkinson's Disease. J Nucl Med 1995;36:1263-7.
28. Booij J, Tissingh G, Winogrodzka A, Boer GJ, Stoof JC, Wolters ECh, et al. Practical benefit of [^{123}I]FP-CIT SPET in the demonstration of the dopaminergic deficit in Parkinson's disease. Eur J Nucl Med 1997;24:68-71.
29. Booij J, Tissingh G, Boer GJ, Speelman JD, Stoof JC, Janssen AGM, et al. [^{123}I]FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;62:133-40.
30. Tissingh G, Booij J, Bergmans P, Winogrodzka A, Janssen AG, van Royen EA, et al. Iodine-123-N-?-fluoropropyl-2ß-carbomethoxy-3ß-(4-iodophenyl)tropane SPECT in healthy controls and early-stage, drug-naive Parkinson's disease. J Nucl Med 1998;39:1143-8.
31. Booij J, Hemelaar JTGM, Speelman JD, de Bruin K, Janssen AGM, van Royen EA. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [^{123}I]FPCIT SPECT. J Nucl Med 1999;40:753-61.
32. Seibyl JP, Marek K, Sheff K, Zoghbi S, Baldwin RM, Charney DS, et al. Iodine-123-ß-CIT and iodine-123-ß-FPCIT SPECT measurement of dopamine transporters in healthy subjects and Parkinson's patients. J Nucl Med 1998;39:1500-8.
33. Ishikawa T, Dhawan V, Kazumata K, Chaly T, Mandel F, Neumeyer J, et al. Comparative nigrostriatal dopaminergic imaging with iodine-123-ß CIT-FP/SPECT and fluorine-18-FDOPA/PET. J Nucl Med 1996;37:1760-5.
34. Kazumata K, Dhawan V, Chaly T, Antonini A, Margouleff C, Belakhlef A, et al. Dopamine transporter imaging with fluorine-18-FPCIT and PET. J Nucl Med 1998;39:1521-30.

35. Fischman AJ, Bonab AA, Babich JW, Palmer EP, Alpert NM, Elmaleh DR, et al. Rapid detection of Parkinson's disease by SPECT with altropane: a selective ligand for dopamine transporters. Synapse 1998;29:128-41.
36. Madras BK, Grasz LM, Fahey MA, Elmaleh D, Maltzer PC, Liang AY, et al. Altropane, a SPECT or PET imaging probe for dopamine neurons: III. Human dopamine transporter in postmortem normal and Parkinson's diseased brain. Synapse 1998;29:116-27.
37. Brooks DJ. Functional imaging in relation to parkinsonian syndromes. J Neurol Sci 1993;115: 1-17.
38. Gordon I, Weizman R, Rehavi M. Modulatory effect of agents active in the presynaptic dopaminergic system on the striatal dopamine transporter. Eur J Pharmacol 1996;298:27-30.
39. Ekesbo A, Rydin E, Torstenson R, Sydow O, Längstrom B, Tedroff J. Dopamine autoreceptor function is lost in advanced Parkinson's disease. Neurology 1999;52:120-5.
40. Zelnik N, Angel I, Paul SM, Kleinman JE. Decreased density of human striatal dopamine uptake sites with age. Eur J Pharmacol 1986;126:175-6.
41. De Keyser J, Ebinger G, Vauquelin G. Age-related changes in the human nigrostriatal dopaminergic system. Ann Neurol 1990;27:157-61.
42. Van Dyck CH, Seibyl JP, Malison RT, Laruelle M, Wallace E, Zoghbi SS, et al. Age-Related Decline in Dopamine Transporter Binding in Humane Striatum with [^{123}I]ß-CIT SPECT. J Nucl Med 1995;36:1175-81.
43. Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley SJ, et al. Dopamine transporters decrease with age. J Nucl Med 1996;37:554-9.
44. Rinne JO, Sahlberg N, Ruottinen H, Nagren K, Lehikoinen P. Striatal uptake of the dopamine reuptake ligand [^{11}C]ß-CFT is reduced in Alzheimer's disease assessed by positron emission tomography. Neurology 1998;50:152-6.
45. Mozley PD, Kim HJ, Gur RC, Tatsch K, Muenz LR, McElgin WT, et al. Iodine-123-IPT SPECT imaging of CNS dopamine transporters: nonlinear effects of normal aging on striatal uptake values. J Nucl Med 1996;37:1965-70.
46. Booij J, Bergmans P, Winogrodzka A, Speelman JD, Wolters EC. Imaging of dopamine transporters with [^{123}I]FP-CIT SPECT does not suggest a significant effect of age on the symptomatic threshold of disease in Parkinson's disease. Synapse 2001;39:101-8.
47. Marie RM, Barre L, Rioux P, Allain P, Lechevalier B, Baron JC. PET imaging of neocortical monoaminergic terminals in Parkinson's disease. J Neural Transm Park Dis Dement Sect 1995;9:55-71.
48. Wichmann T, Vitek J, DeLong MR. Parkinson's Disease and the Basal Ganglia: Lessons from the Laboratory and from Neurosurgery. Neuroscientist 1995;1:236-44.
49. Verhagen Metman L, Blanchet PJ, van den Munckhof P, Del Dotto P, Natte R, Chase TN. A trial of dextromethorphan in parkinsonian patients with motor response complications. Mov Disord 1998;13:414-7.
50. Sullivan AM, Opacka-Juffry J, Blunt SB. Long-term protection of the rat nigrostriatal dopaminergic system by glial cell line-derived neurotrophic factor against 6-hydroxydopamine in vivo. Eur J Neurosci 1998;10:57-63.
51. Brownell AL, Livni E, Galpern W, Isacson O. In vivo PET imaging in rat of dopamine terminals reveals functional neural transplants. Ann Neurol 1998;43:387-90.
52. Freeman TB, Vawter DE, Leaverton PE, Godbold JH, Hauser RA, Goetz CG, et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. N Engl J Med 1999;341:988-92.

Correspondência: Nicolaas Paul L.G. Verhoeff
Clinical Research Fellow Psychiatry - Centre for Addiction and Mental Health, Clarke Site, PET Centre
250 College Street - Toronto, Ontário - M5T 1R8 - Canadá
Tel.: (00xx1) (416) 535-8501, r. 6456 - Fax: (00xx1) (416) 979-6936 - E-mail: pverhoeff@camhpet.on.ca