PAPER

Disease progression continues in patients with advanced Parkinson's disease and effective subthalamic nucleus stimulation

R Hilker*, A T Portman*, J Voges, M J Staal, L Burghaus, T van Laar, A Koulousakis, R P Maguire, J Pruim, B M de Jong, K Herholz, V Sturm, W-D Heiss, K L Leenders

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*The first two authors contributed equally to this work.

See end of article for authors' affiliations

Correspondence to: Dr R Hilker, Department of Neurology, University Hospital, Joseph-Stelzmann-Strasse 9, 50924 Cologne, Germany; hilker@pet.mpin-koeln.mpg.de

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Objectives: Glutamate mediated excitotoxicity of the hyperactive subthalamic nucleus (STN) has been reported to contribute to nigral degeneration in Parkinson's disease (PD). Deep brain stimulation of the STN (STN DBS), in its role as a highly effective treatment of severe PD motor complications, has been thought to inhibit STN hyperactivity and therefore decrease progression of PD.
Methods: In a prospective two centre study, disease progression was determined by means of serial ^{18}F-fluorodopa (F-dopa) positron emission tomography (PET) in 30 patients with successful STN DBS over the first 16 (SD 6) months after surgery.
Results: Depending on the method of PET data analysis used in the two centres, annual progression rates relative to baseline were 9.5–12.4% in the caudate and 10.7–12.9% in the putamen.
Conclusions: This functional imaging study is the first to demonstrate a continuous decline of dopaminergic function in patients with advanced PD under clinically effective bilateral STN stimulation. The rates of progression in patients with STN DBS were within the range of previously reported data from longitudinal imaging studies in PD. Therefore this study could not confirm the neuroprotective properties of DBS in the STN target.

Deep brain stimulation of the subthalamic nucleus (STN DBS) is a highly effective and increasingly used treatment for patients with advanced Parkinson's disease (PD). Marked off-time reduction of severe motor fluctuations and disappearance of levodopa induced dyskinesias after dosage reduction of antiparkinson medication are the main features of this intervention.[1] In the hands of experienced and specialist teams, STN DBS has proved to be a safe surgical procedure with an acceptable rate of side effects and surgical risks.[2]

Several recent papers have confirmed a long term motor benefit of STN DBS in patients with advanced PD.[3–7] Such a sustained motor benefit may possibly reflect slowing of disease progression, since a neuroprotective effect of STN stimulation has been hypothesised previously,[8] based on the rationale that the large number of glutamatergic efferents from the STN to the dopaminergic neurones in the substantia nigra pars compacta (SNc) become overactive in the abnormal parkinsonian basal ganglia network.[9] Glutamatergic STN mediated excitotoxicity has been implicated as an aetiological factor in the progressive decline of intact dopamine neurones in the SNc.[10] It was postulated that the reduction of STN neuronal hyperactivity by inhibition of high-frequent stimulation might slow or even halt the progression of neurodegeneration in PD.[8 10] In fact, chemical lesioning of the STN has been shown to prevent degeneration of the nigrostriatal dopaminergic pathway in the 6-hydroxydopamine rat model.[11–13]

These pathophysiological considerations have led to the suggestion that DBS in the STN target may offer a novel neuroprotective approach in PD. However, this requires objective investigation of disease progression in STN stimulated PD patients. Serial functional imaging studies with positron emission tomography (PET) or single photon emission computed tomography (SPECT) have been used previously to quantify presynaptic dopaminergic function in human subjects.[14–16] Here we report the results of the first prospective study on the progression of PD after successful STN DBS measured with ^{18}F-fluorodopa (F-dopa) PET.

PATIENTS AND METHODS

Clinical evaluation of patients and surgical procedure

A total of 30 patients with advanced PD (19 men, 11 women; mean age (SD) 59.8 (7.2) years; mean disease duration 12.6 (4.2) years; mean Hoehn and Yahr stage[17] off-drug 3.6 (0.5); 26 akinetic rigid PD, 4 tremor dominant PD) were consecutively recruited during the years 1999–2003 after obtaining written informed consent according to the Declaration of Helsinki. The patients were prospectively followed up at two centres—the neurological departments of Cologne University, Germany, and Groningen University, the Netherlands. The local ethics committees of both medical faculties approved the study. We diagnosed PD according to the UK Parkinson's Disease Society Brain Bank criteria,[18] and indication for STN DBS according to the CAPSIT-PD protocol,[19]—that is, presence of parkinsonian symptoms refractory to medication, such as severe levodopa associated on-off fluctuations, peak dose dyskinesias, and severe resting hand tremor. All study patients had a clear but short levodopa response and did not show any atypical clinical signs.

We implanted bilateral STN electrodes (Medtronic model 3389, Medtronic, Minneapolis, MN) and impulse generators (Itrel II or Kinetra, Medtronic GmbH) in each patient. Both

Abbreviations: DBS, direct brain stimulation; K_{occ}, influx constant; LEDD, levodopa equivalent daily dose; PET, positron emission tomography; ROI, region of interest; SOR, striatal to occipital ratio; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale

centres followed similar surgical procedures (departments of stereotaxy and functional neurosurgery of Cologne and Groningen universities) described in detail previously.[20 21] The targets were verified intraoperatively by microstimulation (Groningen) and macrostimulation (Groningen, Cologne) and regular neurological monitoring of clinical DBS effects (Groningen, Cologne). We used the Unified Parkinson's Disease Rating Scale (UPDRS)[22] for clinically measuring disease severity before and after surgery as follows.

- Before surgery:
  - in the drug-off condition 12 hours after cessation of antiparkinson medication (''practically defined off'')
  - one to two hours after the oral intake of 150–300 mg soluble levodopa (''best on'').
- After surgery:
  - under continuous STN stimulation (DBS-on condition) six months after electrode implantation
  - at the time of the follow up PET scan (DBS-on condition).

The levodopa equivalent daily dose (LEDD) was calculated on the basis of the following formula[4]: 1 mg of pergolide = 1 mg of lisuride = 1 mg of pramipexole = 2 mg of cabergoline = 5 mg of ropinirole = 10 mg of bromocriptine = 5 mg of apomorphine = 20 mg of dihydroergocriptine = 100 mg levodopa. To assure correct electrode placement in the study sample, only those patients with a favourable stimulation effect—that is, with more than 30% improvement of the UPDRS III score in the DBS-on versus off condition six months after surgery—were included in the PET follow up protocol.

PET data acquisition

Each patient had one baseline scan 4 (SD 6) weeks (range 1–14) prior to STN electrode implantation and one follow up scan at least one year after the beginning of STN DBS with the same PET camera, following the same study protocol. The mean (SD) follow up interval was 16 (6) months (range 12–36). At both study centres, two 24 detector ring scanners (ECAT EXACT HR and ECAT EXACT, Siemens-CTI, Knoxville, TN) were used.[23 24] The patients were positioned supine in a relaxed state with their eyes closed and ears unplugged. To avoid drug interference, the antiparkinson medication was stopped for a minimum of 12 hours prior to the PET scanning procedure (drug-off condition). The follow up scan was performed in the DBS-on and drug-off condition (see table 1 for the DBS parameters). After pretreatment with 100 mg carbidopa to block peripheral dopa-decarboxylase activity, 150–370 MBq of F-dopa was injected intravenously. Following this, at the Cologne centre, all patients ($n = 20$) were scanned with a dynamic series of nine 10 minutes frames over 90 minutes in a three dimensional mode, whereas at the Groningen centre, the first three patients had a static scan protocol which consisted of a single scan from 90–120 minutes after the injection. The remaining seven patients had a dynamic scan protocol with 21 time frames of increasing duration over a period of 120 minutes. Images were corrected for scatter and attenuation. We realigned individual frames from all dynamic scans to get a summed image from 0 to 90 minutes and from 0 to 120 minutes to reduce possible motion artefacts.

PET data analysis

We analysed the data on SUN Sparc 2 workstations (Sun Microsystems, Silicon Valley, CA). For each patient, both PET scans were analysed at the same time following a standardised protocol including one rater blinded for the presence of baseline or follow up PET scans. Four regions of interest (ROIs) were placed on the summed axial F-dopa images, namely the right and left head of the caudate nucleus and the right and left putamen. Reference regions were defined over the occipital cortex. In Cologne, both PET scans were coaligned exactly with standard software (MPI-tool).[25] Then the ROI set was placed by inspection of the coaligned summed images and slightly adapted to the individual basal ganglia anatomy. In Groningen, the PET volume data were first linearly normalised to the Talairach coordinate space using the regional cerebral blood flow (rCBF) template of the SPM99 software package (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Then ROI analysis was based on a standard template fixed in Talairach stereotactic space.

We used two previously validated methods of striatal F-dopa uptake determination, the striatal to occipital ratio (SOR) method (patients from both centres) and the influx constant (K_{occ}) calculated by the multiple time graphical analysis (MTGA) method (patients from Cologne only).[26] For SOR calculation, the mean ROI activity concentration was computed in either static scans or the averaged last two frames of dynamic scans. The SOR index was expressed as:

$$SOR = C_{ROI} - C_{REF}/C_{REF}$$

where C_{ROI} = average ROI activity concentration and C_{REF} = average occipital activity concentration in the occipital reference region. For MTGA analysis, time activity curves of dynamic PET series were plotted with the occipital reference region activity serving as input function resulting in the striatal F-dopa influx constant K_{occ} (min^{-1}) which represents the rate of striatal F-dopa uptake and storage.[27]

Calculation of disease progression and statistical analysis

Right and left striatal F-dopa K_{occ} and SOR values were averaged for each patient. Within each ROI, the annual decline of F-dopa K_{occ} and SOR over the entire study period was calculated as the difference of baseline minus follow up PET data divided by the duration of the individual PET follow up period. For each individual and each ROI, annual progression rates were then expressed as the percentage of baseline K_{occ} and SOR values. Paired Student's *t* test was used to evaluate intraindividual differences between baseline and follow up K_{occ} and SOR values and between UPDRS scores. Statistical significance was accepted at the level of $p<0.05$ (SPSS for Windows 10.0, SPSS UK Ltd, Surrey, England).

RESULTS

At the time of the follow up PET scan, we found a significant clinical improvement caused by STN DBS, that is, a 52% decrease of the drug-off/DBS-on UPDRS motor score compared with the corresponding drug-off baseline value ($p<0.001$; see table 1). The LEDD was significantly reduced by 28% from before surgery to the follow up PET investigation ($p<0.001$; see table 1). A dopamine agonist was also continued in most patients after surgery (agonist medication in 27/30 patients (90%) at baseline and in 24/30 patients (80%) at time of follow up PET). During the follow up period, the drug-off/DBS-on UPDRS motor score at the PET follow up was nearly unchanged from that at the six month follow up ($p = 0.4$, paired *t* test; see table 1). In contrast, a significant improvement occurred in the corresponding drug-on value at six months versus baseline ($p<0.05$; see table 1). However, this was lost at the PET follow up (*v* six month scores $p<0.01$; *v* baseline $p = 0.7$; see table 1). Data on clinical outcome and STN DBS parameters are also summarised in table 1.

Both PET investigations showed a similar F-dopa uptake reduction pattern with the putamen more severely affected than

Table 1 Clinical outcome and STN DBS parameters (n = 30; values are mean (SD))

	Before surgery	After surgery	
	Baseline F-dopa PET	At six month follow up	At follow up F-dopa PET (12–36 months)
UPDRS III score			
Drug-off condition	42.9 (11.4)*	19.4 (9.1)‡**	20.4 (8.4)‡**
Drug-on condition	16.5 (7.6)†¶	13.8 (6.9)§††	16.0 (7.4)§‡‡
LEDD (mg)	935 (384)	611 (288)**	670 (324)**
DBS parameters			
Amplitude (V)	–	3.2 (0.9)	3.4 (0.7)
Pulse width (μs)	–	72.5 (14.3)	72.5 (14.2)
Frequency (Hz)	–	133.9 (10.2)	137.1 (14.5)
Mode	–	Monopolar (n = 58 electrodes) Bipolar (n = 2 electrodes)	Monopolar (n = 58 electrodes) Bipolar (n = 2 electrodes)

*Obtained at least 12 hours after cessation of antiparkinsonian medication (''practically defined off'').
†Obtained after oral intake of 200 mg soluble levodopa (''best on'').
‡Obtained at least 12 hours after cessation of antiparkinsonian medication under continuous STN stimulation (DBS-on).
§Obtained after oral intake of 200 mg soluble levodopa under continuous STN stimulation (DBS-on).
¶Difference between baseline drug-off and drug-on conditions: $p<0.001$ (paired *t* test).
**Difference between drug-off baseline and follow up scores: $p<0.001$ (paired *t* test).
††Difference between drug-on baseline and follow up scores: $p<0.05$ (paired *t* test).
‡‡Difference between drug-on follow up scores: $p<0.01$ (paired *t* test).
DBS, direct brain stimulation; LEDD, levodopa equivalent daily dose; PET, positron emission tomography; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

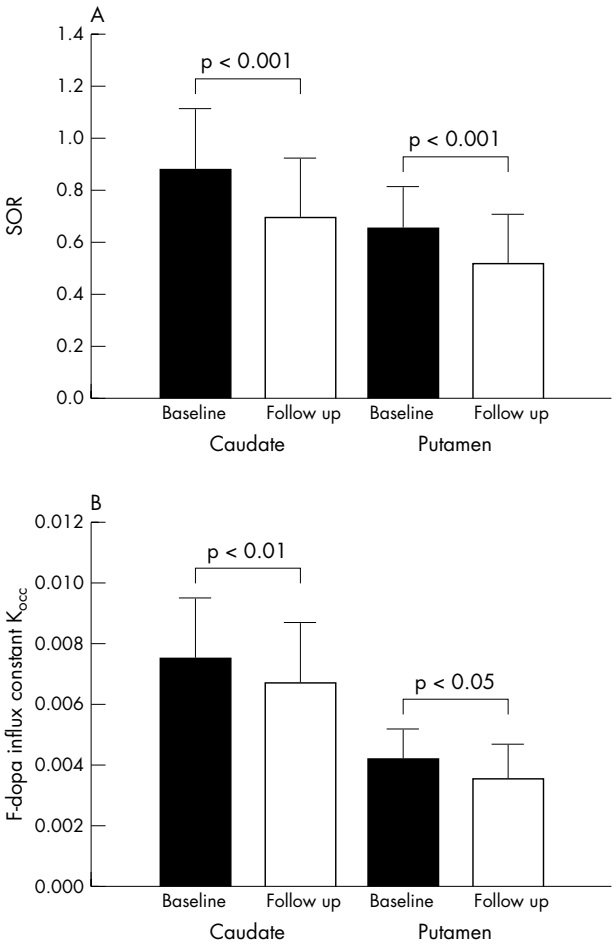

Figure 1 Significant reduction of the striatal F-dopa uptake from baseline to follow up PET calculated with (A) the striatal to occipital ratio (SOR; n = 30) and (B) the F-dopa influx constant (K_{occ}; n = 20) methods. The p values are for mean comparisons with paired *t* test statistics.

the caudate nucleus (table 2). The mean striatal K_{occ} and SOR values decreased significantly during the follow up period (table 2 and fig 1). The annual decline of K_{occ} was 0.00071 (0.00081) min^{-1} in the caudate and 0.00049 (0.00074) min^{-1} in the putamen (table 3). Likewise, SOR values decreased by 0.11 (0.10) per year in the caudate and by 0.08 (0.09) per year in the putamen. These rates of decline were reflected in the annual progression rates relative to baseline given in table 3. Progression data based on SOR values were nearly identical in the two study centres (table 3). No significant correlation was found between PET progression rates determined by either method and the clinical deterioration measured with UPDRS motor scale (data not shown).

DISCUSSION

This prospective, two centre F-dopa PET study is the first to measure disease progression objectively in PD patients with clinically effective bilateral STN DBS. In a total of 30 patients we found a significant decrease of striatal F-dopa uptake over the 16 month follow up period which corresponds to progression rates ranging from 9.5% to 12.9% loss of baseline radiotracer binding per year depending on the approach used for PET data analysis. Therefore, our data are the first to prove a continuing decline in dopaminergic function even in PD subjects with effective STN stimulation.

Our data are in good agreement with disease progression rates reported in previous studies on medically treated PD patients establishing F-dopa PET as a valid tool for measuring the progression of PD.[28–30] For example, Morrish and colleagues found an average annual decline of 12.5% from baseline in the putamen and 4% from baseline in the caudate.[29] More recent single photon emission computed tomography (SPECT) and PET studies using the dopamine transporter ligands [^{123}I]β-CIT and [F]CFT have also reported a 4–12.5% progression from baseline in the caudate nucleus and 8–13.1% in the putamen.[14 31] However, most of these studies investigated PD patients in earlier stages of the disease compared with our STN stimulated cohort. Therefore, our results are the first to show a comparable rate of dopaminergic deterioration in PD patients with a long disease duration and severe motor complications at the time of baseline PET. In line with the studies cited above, we found high interindividual variability in the rates of disease

Table 2 Striatal F-dopa influx constants (K_{occ}) and SOR values at baseline and follow up PET scans (n = 30; values are mean (SD))

	Baseline F-dopa PET		Follow up F-dopa PET	
	K_{occ} (min^{-1})	SOR	K_{occ} (min^{-1})	SOR
Caudate				
Cologne	0.0076 (0.0021)	0.85 (0.20)	0.0067 (0.0020)	0.71 (0.21)†
Groningen	–	0.94 (0.32)	–	0.65 (0.27)‡
Total	0.0076 (0.0021)	0.88 (0.24)	0.0067 (0.0020)**	0.69 (0.23)***
Putamen				
Cologne	0.0042 (0.0010)	0.65 (0.15)	0.0036 (0.0011)	0.55 (0.19)†
Groningen	–	0.68 (0.19)	–	0.49 (0.20)‡
Total	0.0042 (0.0010)	0.66 (0.16)	0.0036 (0.0011)*	0.52 (0.19)***

Difference between total baseline and follow up values: *p<0.05, **p<0.01, ***p<0.001 (paired *t* test).
Length of the follow up period (mean (SD)): †15.6 (3.6) months (n = 20), ‡27.0 (8.8) months (n = 10).
Normal ranges in healthy controls: SOR caudate 1.68 (0.25), SOR putamen 1.69 (0.29) (n = 7, age 56 (9) years); K_{occ} caudate 0.0125 (0.0015) min^{-1}, K_{occ} putamen 0.0126 (0.0013) min^{-1} (n = 16, age 54 (12) years).
K_{occ}, F-dopa influx constant; PET, positron emission tomography; SOR, striatal to occipital ratio.

progression in our STN stimulated patients, reflected in the high standard deviations and 95% confidence intervals. Differences in PET data acquisition and analysis can be mostly disregarded as causal factors in view of the nearly identical results in both study centres. As the two PET scans for each patient were taken in an identical manner with the same PET camera at both centres, methodological differences should not have influenced the percentage baseline progression values. Thus, our data corroborate the high interindividual biological variability in the speed of dopaminergic degeneration even in advanced PD patients.

Our PET data are also in line with two recent long term follow up studies on STN DBS which reported a slight increase in UPDRS motor scores over two and five years, in particular a worsening of axial symptoms subscores such as akinesia, postural instability, and freezing of gait.[5 6] In contrast, Herzog *et al* found no pertinent deterioration of UPDRS scores in their two year follow up of 20 STN DBS patients.[4] However, it has to be kept in mind that clinical data on PD progression are often influenced by hangover effects of medication on the ''drug-off, stimulation-on'' motor performance and also by DBS-on the ''drug-off, stimulation-off'' condition.[32] Therefore the most valuable aspect of our study is the objective monitoring of dopaminergic decline with F-dopa as a PET biomarker. We also found a slight and, with respect to the drug-on data, significant deterioration of the UPDRS scores over time. The absence of correlation of clinical and PET-based progression rates is in line with previous longitudinal F-dopa PET studies in medically treated PD patients.[33] Perhaps the main reason for this is the effective long term control of the signs of dopamine deficiency by STN stimulation in the ''drug-off, stimulation-on'' condition, but our PET data suggest that DBS masks rather than prevents clinical PD progression.

We are aware that our study does not directly disprove a neuroprotective effect of STN DBS due to the small sample size and a lack of randomised design (progression determination in the DBS and a medically treated control group). However, we did not consider this study design for ethical reasons because the empirically well proved symptomatic relief of PD symptoms by STN DBS would have had to be withheld in severely handicapped patients for at least one year. Thus, our data merely verify an ongoing significant loss of dopaminergic function within the first two years of STN stimulation in advanced PD which, however, makes a clinically relevant neuroprotective effect of STN stimulation highly unlikely.

The assumption about neuroprotective properties of STN stimulation was essentially based on its putative blocking of glutamatergic STN hyperactivity, which is considered as an important aetiological factor for excitotoxicity and cell death within the substantia nigra.[8] Although the reasons for the lack of a protective effect of STN DBS remain unclear, our findings can be interpreted as indirect arguments against the neurone inhibiting theory of DBS. Recent PET studies[20 34] that showed a local increase of energy metabolism in the midbrain and the STN target area under effective STN DBS suggesting activation rather than blocking stimulation support this view. Recent animal studies have demonstrated increased glutamate levels in the internal pallidum of normal rats and elevated firing rates of internal pallidum neurones in parkinsonian monkeys during chronic STN stimulation.[35 36] These data on vascular and metabolic activation in the DBS target region and its projection sites suggest that STN stimulation might result in a high-frequent, tonic, and regular neuronal activity pattern (so-called neuronal jamming) that replaces an abnormally synchronised and oscillating basal ganglion firing, characteristic of the parkinsonian state.[37 38] Thus, it is probable that the glutamatergic transmission as well

Table 3 Annual reduction of striatal K_{occ} and SOR values and disease progression rates from baseline (n = 30; values are mean (SD))

	Annual reduction		Annual disease progression from baseline (%)			
	K_{occ} (min^{-1})	SOR	K_{occ}	95% CI	SOR	95% CI
Caudate						
Cologne	0.00071 (0.00081)	0.10 (0.10)	9.5 (12.4)	3.2–14.4	12.2 (12.6)	6.4–18.1
Groningen	–	0.11 (0.10)	–	–	11.8 (10.0)	4.6–18.9
Total	0.00071 (0.00081)	0.11 (0.10)	9.5 (12.4)	3.2.–14.4	12.1 (11.6)	7.7–16.4
Putamen						
Cologne	0.00049 (0.00074)	0.08 (0.09)	10.7 (17.9)	2.5–18.3	12.8 (15.5)	5.5–20.0
Groningen	–	0.08 (0.08)	–	–	11.8 (12.4)	2.9–20.6
Total	0.00049 (0.00074)	0.08 (0.09)	10.7 (17.9)	2.5–18.3	12.4 (14.3)	7.1–17.8

K_{occ}, F-dopa influx constant, SOR, striatal to occipital ratio; CI, confidence interval.

as the excitotoxic drive from STN to the substantia nigra is not diminished by chronic STN stimulation alone.

From a clinical point of view, our PET data may help in maintaining realistic expectations about STN stimulation—that is, there is strong symptomatic relief but not a slowing of disease progression or even a cure of the disorder. The data also highlight the need for careful presurgical assessment of potential DBS candidates with respect to realistic treatment goals and the unchanged progressive character of PD after surgery. However, it has to be kept in mind that our study failed to show mitigation of disease progression in advanced PD patients with STN stimulation only. Our results cannot rule out that STN DBS might have a disease modifying effect in the earlier stages of PD, which might help prevent the development of severe on-off fluctuations and levodopa induced dyskinesias in these patients. Future research is needed on this important question.

In conclusion, this is the first PET study to demonstrate that decline of dopaminergic function in advanced PD continues despite clinically effective bilateral STN stimulation. Therefore, neuroprotective properties of DBS in the STN target could not be confirmed. Nevertheless, it has to be emphasised that STN DBS is a very effective treatment option that offers favourable long term symptomatic relief to advanced PD patients with treatment fluctuations or an otherwise intractable tremor. Further research is needed to investigate whether DBS of subcortical targets may still have a role to play in the more comprehensive neuroprotective treatment for PD.

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Authors' affiliations

R Hilker, L Burghaus, K Herholz, W-D Heiss, Department of Neurology, Medical University of Cologne, Cologne, Germany
A T Portman, T van Laar, R P Maguire, B M de Jong, K L Leenders, Department of Neurology, University Hospital, Groningen, the Netherlands
J Voges, A Koulousakis, V Sturm, Department of Stereotaxy and Functional Neurosurgery, Medical University of Cologne, Cologne, Germany
M J Staal, Department of Neurosurgery, University Hospital, Groningen, the Netherlands
J Pruim, PET Centre, University Hospital, Groningen, the Netherlands
W-D Heiss, Max-Planck-Institute for Neurological Research Cologne, Cologne, Germany

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