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ORIGINAL ARTICLE

Predictive potential of pre-operative functional neuroimaging in patients treated with subthalamic stimulation

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Abstract
Purpose The aim of this study was to investigate the predictive potential of pre-operative regional cerebral blood flow (rCBF) in the pre-supplementary motor area (pre-SMA) and clinical factors in Parkinson's disease (PD) patients treated with subthalamic nucleus (STN) stimulation.
Methods Ten patients underwent rCBF SPECT and motor Unified Parkinson's Disease Rating Scale (UPDRS) pre- and post-operatively during stimulation at 5 and 42 months. Statistical parametric mapping (SPM) was used to extract rCBF values in the pre-SMA because it is related with motor improvement. Post-operative outcomes included motor response to stimulation and percent improvement in UPDRS. Pre-operative predictors were explored by correlation test, linear regression and multivariate analyses.
Results Higher pre-operative rCBF in the pre-SMA and younger age were associated with favourable outcomes at 5 and 42 months. Pre-operative rCBF results were significantly associated with baseline clinical factors.
Conclusion This study shows that PD patients with younger age have higher rCBF values in the pre-SMA and better outcome, thus giving the rationale to the hypothesis that STN stimulation could be considered early in the course of disease.

Keywords Parkinson's disease · Subthalamic stimulation · Predictive potential · rCBF · Pre-SMA

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Introduction

High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) has gained widespread acceptance and is now regarded by many as the surgical treatment of choice for patients with an advanced form of Parkinson's disease (PD) who meet strict criteria for treatment of this type [1]. According to general recommendations [2], these include age under 70 years at time of surgery, a levodopa-responsive form of PD characterized by disabling on-off phenomena and levodopa-induced dyskinesia, the absence of abnormal cerebral MRI findings, dementia and psychiatric disorders. Therefore, the mean delay before STN DBS has been shown to be currently 14 years after diagnosis [3], when medical treatment no longer controls motor symptoms and quality of life is already severely impaired [4].

In order to prevent psychological degradation and maintain quality of life, especially in young patients facing a long course of disease, it has been suggested that neurosurgery could be performed earlier after the diagnosis of PD [4–6]. Indeed, the majority of clinical studies have shown that outcomes from STN DBS tend to be better in

patients with younger age at time of surgery [4–10]. Moreover, a favourable outcome from DBS has been also observed in patients with shorter disease duration, lower motor Unified Parkinson's Disease Rating Scale (UPDRS) and motor symptoms responsive to L-dopa [7–12]. However, there is no general consensus as yet on the use of STN DBS in younger parkinsonian patients. Indeed, results of two clinical studies failed to detect statistically significant correlations between age at time of operation and post-operative results [13, 14]. Besides, prediction of greatest beneficial response to STN DBS in younger patients has been observed mainly in the short term [4, 5, 7–9], and the mechanisms underlying the influence of age on post-operative outcome have not been fully clarified [15].

Positron emission tomography studies and covariance analyses applied to single photon emission computed tomography (SPECT) imaging data have opened up the challenging opportunity to study the neural networks underlying recovery of motor function related to STN DBS. Results of functional imaging studies comparing the stimulators on with the stimulators off conditions at rest [16] or during motor tasks [17, 18] have shown that improvement of motor performance is mainly related to regional cerebral blood flow (rCBF) increases in the rostral part of the pre-supplementary motor area (pre-SMA). Similarly, several follow-up studies performed in the on and off stimulation conditions have highlighted that this cortical area plays a crucial role in recovery of motor function during long-term treatment with STN DBS [19, 20]. In line with results of these studies, it has been suggested that a careful evaluation of the correlation between pre-operative functional parameters in strategical regions of the brain such as the rCBF in the pre-SMA and post-operative clinical outcome measures could provide important information concerning a possible role of such parameters in predicting outcomes from DBS [15, 19]. However, no studies have been made to investigate the role of pre-operative functional imaging with respect to predictors of response to surgery [15].

The main aim of the present study was to investigate the predictive potential of pre-operative rCBF in the pre-SMA in PD patients treated with bilateral long-term STN DBS in order to identify characteristics of the candidate who may receive the greatest benefit from surgery. Along with rCBF in the pre-SMA, the predictive role of several pre-operative clinical factors including age at time of surgery was also investigated. The predictive potential was evaluated at 5 and 42 months after DBS implants to test whether prediction of clinical improvement in the short term was confirmed in the long term. Relationships between pre- and post-operative clinical and functional imaging data were also analysed to provide novel insights into the mechanisms underlying the influence of the function in the pre-SMA and age on post-operative outcomes in this population.

Materials and methods

Patient selection and surgical procedure

The clinical characteristics of PD patients have been described previously [19]. Ten consecutive patients with medically intractable PD who underwent DBS implantation in 1999 at our hospital were included in the study (4 women, 6 men, mean age: 64±4 years, mean disease duration: 15±5 years, range of disease duration: 6–22 years). All patients were right-handed. The side prevalence of motor symptoms was left in one patient, bilateral in two patients and right in seven patients. Bilateral implantation of electrodes in the STN was performed only in the presence of clinically diagnosed idiopathic PD as defined by the UK Parkinson's Disease Society Brain Bank [21], disabling motor fluctuations despite all drug therapies, an age of <70 years, a response to levodopa greater than 30%, normal cerebral MRI findings, the absence of significant cognitive impairment as ascertained by means of the Mini-Mental State Examination with a cut-off value of 24/30 (mean value ± SD=27.8±1.4), major ongoing psychiatric illness and dopaminergic treatment-induced psychosis in the 6-month period preceding surgery. The exclusion criteria were neurological signs suggestive of secondary forms of parkinsonism and the presence of other significant medical illnesses [2]. The procedure for bilateral implantation of STN electrodes conformed to the previously published procedure [22, 23]. There were no serious complications due to surgery. In all patients continuous monopolar stimulation was applied bilaterally. Stimulator settings remained substantially stable during the course of the study. The mean values of voltage intensity, frequency stimulation and the pulse width used at 5 and 42 months after surgery were as follows: 2.8±0.4 V (range: 2.3–3.7 V) and 2.9±0.5 V (range: 2–3.7 V); 140±12 Hz (range: 135–185 Hz) and 144±16 Hz (range: 130–185 Hz); 85±34.5 μs (range: 60–210 μs) and 93±44 μs (range: 60–210 μs). Written informed consent was obtained from all subjects according to the Declaration of Helsinki. The Ethics Committee of our institution approved the study.

Assessment of pre- and post-operative clinical parameters

Clinical evaluation included the motor UPDRS [19]. Evaluation was performed pre-operatively within 1 week prior to the surgical procedure and post-operatively at 5 and 42 months. Pre-operatively the patients were evaluated in a defined "medication off state" without intake of PD

medication for at least >12 h and "medication on state" when the best clinical response was obtained following their usual dose of L-dopa. At the time of surgery, the mean UPDRS motor stimulation on score was 64±4 and mean baseline percent improvement in UPDRS motor score (calculated as: L-dopa responsiveness = medication off scores – medication on scores/medication off scores × 100) was 35±3. The mean administered dose of L-dopa before DBS was 1.440±465 mg/day. Post-operatively all patients were tested in the stimulation on and medication off condition. The mean motor UPDRS at 5 and 42 months after DBS were 48±12 and 41±9, respectively. The mean improvements in UPDRS motor scores from the pre- to the post-operative conditions at 5 and 42 months (calculated as medication off scores at baseline – medication off and stimulation on scores at optimized follow-up/medication off scores at baseline × 100) were 26 and 36%, respectively. The mean administered dose of L-dopa decreased at a value of 897±189 and 655±155 at 5 and 42 months, respectively.

Assessment of pre- and post-operative rCBF in the pre-SMA

Along with clinical evaluation, PD patients underwent rCBF three times, once pre-operatively in the off medication state and two times post-operatively, i.e. in the stimulation on and medication off condition at 5 and 42 months, respectively [19]. In summary, SPECT images were acquired 30 min after an intravenous dose (740 MBq in all scanning conditions) of ^{99m}Tc-ethyl cysteinate dimer (ECD) (bicisate, Neurolite, DuPont Merck Pharmaceutical Co., Billerica, MA, USA) using a triple-head rotating gamma camera (PRISM 3000, Picker International Inc., Cleveland, OH, USA) equipped with ultra-high-resolution fan beam collimators.

Images were analysed for regionally specific effects using statistical parametric mapping (SPM) developed at the Wellcome Functional Imaging Laboratory (http://www.fil.ion.ucl.ac.uk./spm/) implemented in MATLAB, version 5.3 (The MathWorks, Inc., Natick, MA, USA) [24]. After conversion from Interfile into Analyze format using the ImageJ software (http://rsb.info.nih.gov./ij/), all images were spatially realigned to the first one of the series in order to compensate for position changes. All brain images were then spatially transformed into the standard stereotactic space. The default spatial normalization procedure employed was based on a bilinear interpolation method, involving a 12-parameter linear affine transformation and a non-linear three-dimensional deformation to match each scan to a generic SPECT template. A resulting voxel size of 2×2×2 mm was used. The normalized images were smoothed with an isotropic 13-mm kernel.

A covariance analysis was performed to extract regions whose increases in rCBF from the pre- to the post-operative conditions at 5 and 42 months correlated significantly with improvement in motor function. To assess specific effects of this covariate on rCBF, individual UPDRS motor scores during each scanning condition were introduced into the design paradigm. Importantly, the effect of age on rCBF was also taken into account by introducing this factor as confounding covariate in the study design. After specifying the appropriate design matrix, image intensity was normalized between subjects to prevent inter-subject variability in tracer uptake from masking regional changes. To this end, the proportional scaling technique was performed. Global blood flow was normalized by scaling across the entire data set to a grand mean of 50 ml/100 ml per minute (normalization by scaling to average whole-brain activity). The grey matter threshold was set to the default value of 0.8. These analyses produced a t statistic for each voxel, which constituted the statistical parametric map $SPM_{\{t\}}$. The $SPM_{\{t\}}$ map was then transformed to the unit normal distribution to give a Gaussian field or $SPM_{\{Z\}}$. The level of significance of areas of rCBF changes was assessed by the spatial extent (k) and peak height (u) of their foci using estimations based on the theory of Gaussian fields. It is noteworthy that for the sake of brevity, relative perfusion increases or decreases as compared to the mean brain uptake were conventionally referred to as "rCBF" without meaning that these values really express rCBF; rather they reflect a regional deviation from the mean brain uptake of ^{99m}Tc-ECD. Results of statistical analysis showed that a significant relationship between individual motor UPDRS scores and rCBF ($p<0.0001$, z-score = 3.68) was present in the right pre-SMA (x=6, y=4, z=62; spatial extent of cluster = 141 voxels) [19].

In the present analysis, individual rCBF values in the pre-SMA for each scanning condition were extracted using exactly the irregular volume of interest (VOI) resulting from the significant correlation cluster (Fig. 1). The mean values of rCBF in the pre-SMA in the pre- and post-operative conditions at 5 and 42 months were 0.168±0.03, 0.234±0.03 and 0.258±0.03, respectively. The mean improvements in rCBF from the pre- to the post-operative conditions at 5 and 42 months (calculated as rCBF medication off and stimulation on values at optimized follow-up – rCBF medication off values at baseline/rCBF medication off values at baseline × 100) were 39 and 53%, respectively.

Statistical analysis

Data were obtained from all ten patients for the analysis at 5 and 42 months after DBS implants. As a first step, we examined the predictive value of pre-operative parameters.

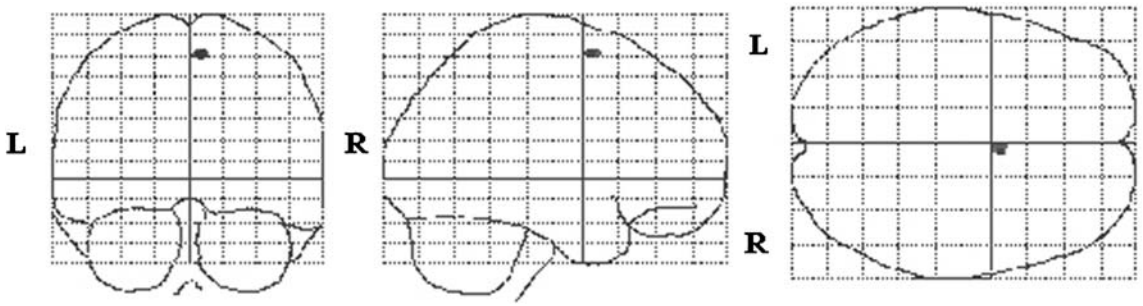

Fig. 1 rCBF increases in the right pre-SMA related to improvement in motor function (motor UPDRS) from pre- to post-operative on-stimulation conditions at 5 months and 4 years follow-up after the application of VOI function in SPM, with a sphere (radius = 5 mm) centred on peak voxel [peak z-score = 3.68 (p=0.0001 uncorrected); location: x=6, y=4, z=62]

They included: (1) pre-operative "medication off" rCBF in the pre-SMA, (2) age at time of surgery, (3) pre-operative UPDRS motor "medication on" scores, (4) disease duration and (5) baseline percent improvement in UPDRS motor scores using each patient's typical doses of levodopa. The post-operative outcome measures were considered: (1) the response to stimulation evaluated by UPDRS motor stimulation on/medication off scores at 5 and 42 months and (2) the percent improvement in motor UPDRS scores from the pre- to the post-operative conditions at 5 and 42 months, respectively. All pre-operative factors potentially influencing post-operative outcomes at 5 and 42 months after DBS were separately explored by univariate analysis Pearson correlation test and linear regression analyses. Then, a multivariate model including all significant variables at univariate analysis and using a forward stepwise procedure was performed to identify which pre-operative factors could effectively predict the post-operative outcome of patients with PD treated with STN DBS.

As a second step, we investigated the mechanisms underlying the predictive potential of pre-operative parameters. For this purpose, a univariate analysis Pearson correlation test was used to evaluate the relationship within all pre-operative data. Then, we investigated the relationship within pre- and post-operative rCBF values and between these values and percent improvements in rCBF from the pre- to the post-operative conditions. Finally, we examined if percent improvements in rCBF from the pre- to the post-operative conditions were associated with both percent improvements in UPDRS motor scores from the pre- to the post-operative conditions and post-operative UPDRS motor scores. The associations between post-operative motor UPDRS scores and percent improvements in UPDRS motor scores were also investigated. All continuous variables were expressed as means ± SD or as percent. A p value of 0.05 was considered significant. Analyses were done using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Predictive factors for bilateral STN stimulation at 5 months after DBS implants

Results of the Pearson test showed that the pre-operative rCBF values in the pre-SMA presented a negative correlation with post-operative UPDRS motor scores (p=0.0001, r=−0.981) (Fig. 2a) and a positive correlation with percent improvement in UPDRS motor scores from the pre- to this post-operative condition (p=0.0001, r=0.983) (Fig. 2b). Among clinical variables, a positive correlation with post-operative UPDRS motor scores and a negative correlation with percent improvement in UPDRS were observed for age (p=0.0001, r=0.96; p=0.0001, r=−0.92) (Fig. 2c, d), pre-operative UPDRS motor scores (p=0.0001, r=0.944; p=0.001, r=−0.889) and disease duration (p=0.01, r=0.742; p=0.01, r=−0.759). The baseline percent improvement in motor scores showed a negative correlation with UPDRS motor scores (p=0.015, r=−0.739) and a positive correlation with percent improvement in UPDRS motor scores (p=0.009, r=0.774).

At univariate linear regression analysis, the pre-operative rCBF in the pre-SMA was significantly associated with both the post-operative UPDRS motor scores at 5 months (R^2=0.96, F=202, p=0.0001, β=−0.98) and percent motor improvement from the pre- to the post-operative condition (R^2=0.96, F=222, p=0.0001, β=0.98). A significant association with post-operative outcomes was also found for age at time of surgery (R^2=0.92, F=94, p=0.0001, β=0.96; R^2=0.84, F=44, p=0.0001, β=−0.92), pre-operative UPDRS motor scores (R^2=0.8, F=65, p=0.0001, β=0.94; R^2=0.8, F=30, p=0.001, β=−0.88), baseline percent improvement in UPDRS motor scores (R^2=0.546, F=9.6, p=0.01, β=−0.739; R^2=0.599, F=12, p=0.009, β=0.77) and disease duration (R^2=0.55, F=9.79, r=0.014, β=0.74; R^2=0.57, F=10, p=0.01, β=−0.75). In a multivariate model including all the significant variables at univariate analysis and using a forward stepwise procedure, we found

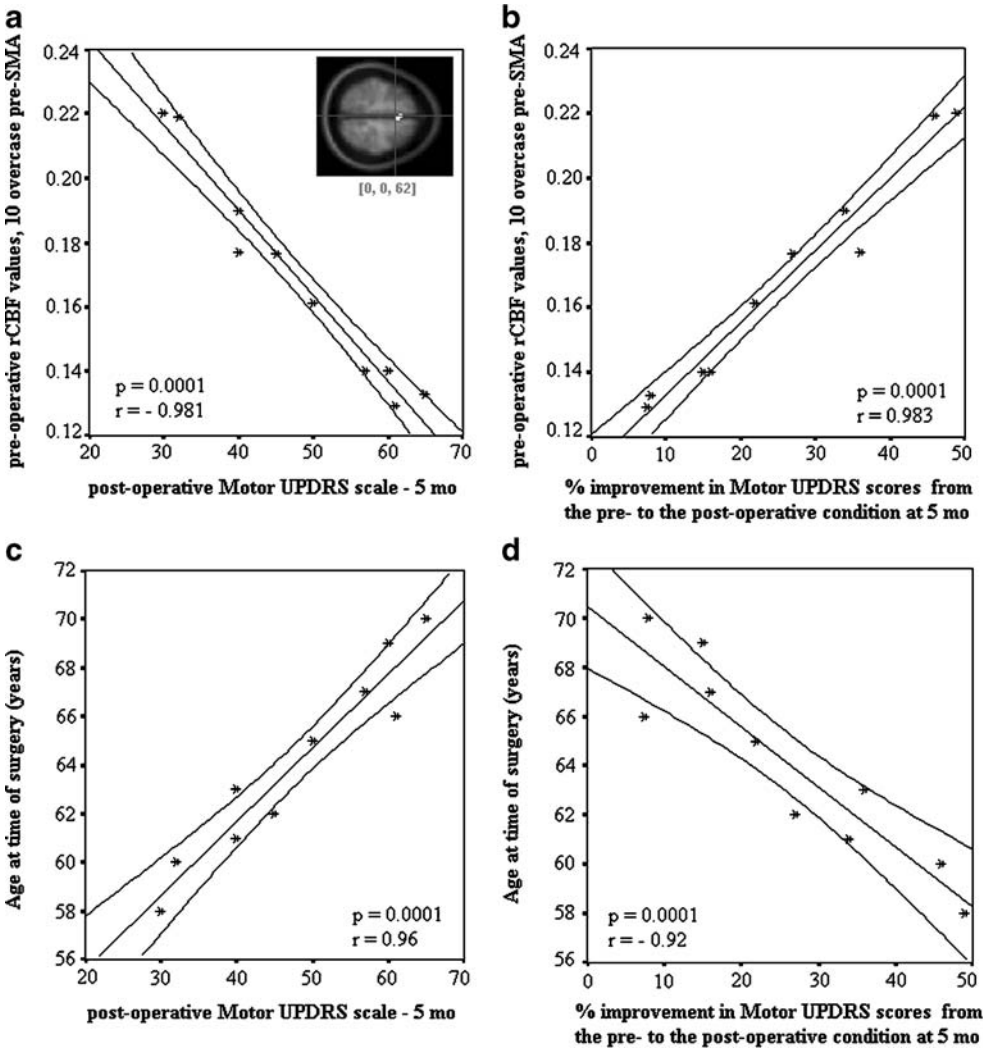

Fig. 2 **a** rCBF increases in the pre-SMA superimposed on a normalized T1-weighted MRI image and relationship between rCBF values in this cortical area for the pre-operative off drug condition, as measured by the VOI function in SPM, and individual motor UPDRS scores for the post-operative off drug/on stimulation condition at 5 months. **b** Relationship between rCBF values in the pre-SMA for the pre-operative off drug condition and percent improvements in motor UPDRS scores from the pre- to the post-operative off drug/on stimulation condition at 5 months. **c** Relationship between age at time of surgery and motor UPDRS scores for the post-operative off drug/on stimulation condition at 5 months. **d** Relationship between age at time of surgery and percent improvements in motor UPDRS scores from the pre- to the post-operative off drug/on stimulation condition at 5 months. *Pre-SMA* rostral part of the supplementary motor area

that only the association of pre-operative rCBF in the pre-SMA remained significant independently from post-operative UPDRS motor scores and percent improvement in UPDRS motor scores from the pre- to this post-operative condition. If the pre-operative rCBF variable was excluded from the model, we found that among all clinical variables the age at time of surgery presented a significant association with post-operative outcomes.

Predictive factors for bilateral STN stimulation at 42 months after DBS implants

At univariate analysis Pearson test, the pre-operative rCBF in the pre-SMA showed a negative correlation with post-operative UPDRS motor scores at 42 months (p=0.0001, r=−0.96) (Fig. 3a) and a positive correlation with percent improvement in UPDRS motor scores from the pre- to the post-operative condition at 42 months (p=0.0001, r=0.971) (Fig. 3b). A positive correlation with post-operative UPDRS motor score and a negative correlation with percent improvement from the pre- to this post-operative condition were observed for age at time of surgery (p=0.0001, r=0.958; p=0.001, r=−0.924) (Fig. 3c, d), pre-operative UPDRS motor scores (p=0.0001, r=0.954; p=0.0001, r=−0.907) and disease duration (p=0.035, r=0.668; p=0.02, r=−0.687). The baseline percent improvement in UPDRS motor scores showed a negative correlation with UPDRS motor scores at 42 months (p=0.0001, r=−0.965) and a positive correlation with percent improvement in UPDRS motor scores from the pre- to the post-operative condition at 42 months (p=0.0001, r=0.931).

At univariate linear regression analysis, the pre-operative rCBF in the pre-SMA was significantly associated with UPDRS motor scores at 42 months (R^2=0.92, F=97.27, p=0.0001, β=−0.96) and percent motor improvement from the pre- to the post-operative condition (R^2=0.94, F=132.324, p=0.0001, β=0.97). A relationship with both post-operative outcomes was also present for age at time of surgery (R^2=0.9, F=90, p=0.0001, β=0.95; R^2=0.85, F=46.4, p=0.0001, β=−0.92), pre-operative UPDRS motor

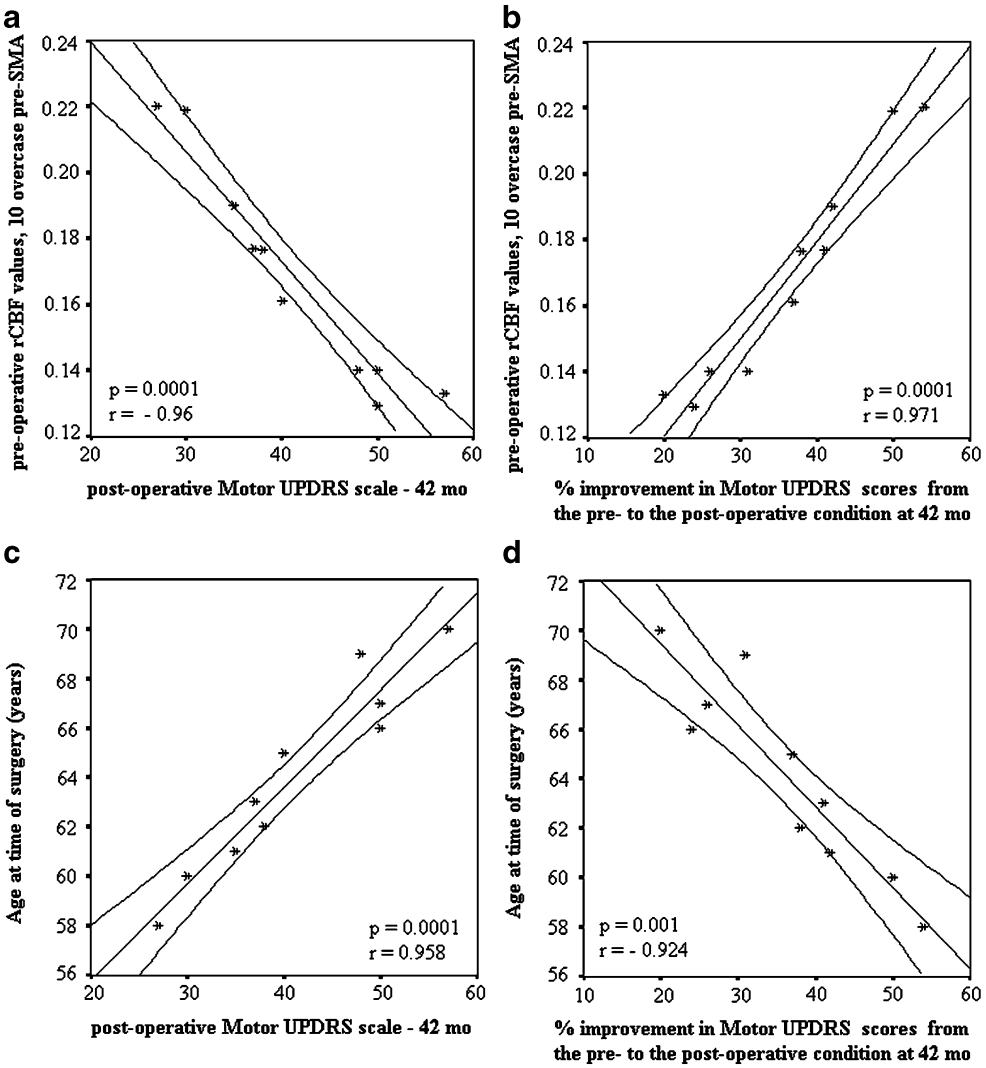

Fig. 3 **a** Relationship between rCBF values in the pre-SMA for the pre-operative off drug condition and motor UPDRS scores for the post-operative off drug/on stimulation condition at 42 months. **b** Relationship between rCBF values in the pre-SMA for the pre-operative off drug condition and percent improvements in motor UPDRS scores from the pre- to the post-operative off drug/on stimulation condition at 42 months. **c** Relationship between age at time of surgery and motor UPDRS scores for the post-operative off drug/on stimulation condition at 42 months. **d** Relationship between age at time of surgery and percent improvements in UPDRS scores from the pre- to the post-operative off drug/on stimulation condition at 42 months. *Pre-SMA* rostral part of the supplementary motor area

scores (R^2=0.89, F=81.2, p=0.0001, β=−0.95; R^2=0.82, F=36.9, p=0.0991, β=−0.9), disease duration (R^2=0.45, F=6.46, p=0.035, β=0.67; R^2=0.47, F=7.1, p=0.02, β=−0.68) and baseline percent improvement (R^2=0.642, F=14, p=0.005, β=−0.801; R^2=0.849, F=20, p=0.002, β=0.849). In the multivariate model including all the significant variables at univariate analysis, only the association of pre-operative rCBF in the pre-SMA remained significant independently from post-operative UPDRS motor scores and percent improvement in UPDRS motor scores from the pre- to this post-operative condition. If the pre-operative rCBF variable was excluded from the model, the age of patients at time of surgery and baseline percent improvement in UPDRS motor score results were significantly associated with post-operative outcomes.

Correlation within pre-operative variables

Results of the Pearson test showed that the pre-operative rCBF in the pre-SMA presented a negative correlation with age at time of surgery (p=0.0001, r=−0.937) (Fig. 4a), pre-operative UPDRS motor scores (p=0.0001, r=−0.91) (Fig. 4b) and disease duration (p=0.007, r=−0.787) (Fig. 4c). A positive correlation was present between pre-operative rCBF and baseline percent improvement in UPDRS motor scores (p=0.008, r=0.777) (Fig. 4d). Among clinical pre-operative variables, a significant positive correlation was found between the age of patients at time of surgery and both the pre-operative UPDRS motor scores (p=0.0001, r=0.988) (Fig. 5a) and disease duration (p=0.03, r=0.683) (Fig. 5b). A negative correlation was present between the age at time of surgery and baseline percent improvement in UPDRS motor scores (p=0.03, r=−0.679) (Fig. 5c).

Correlation between pre- and post-operative rCBF values, percent improvement in rCBF, post-operative motor UPDRS scores and percent improvement in motor UPDRS

Concerning the analysis of data at 42 months, we found that the pre-operative rCBF in the pre-SMA was significantly

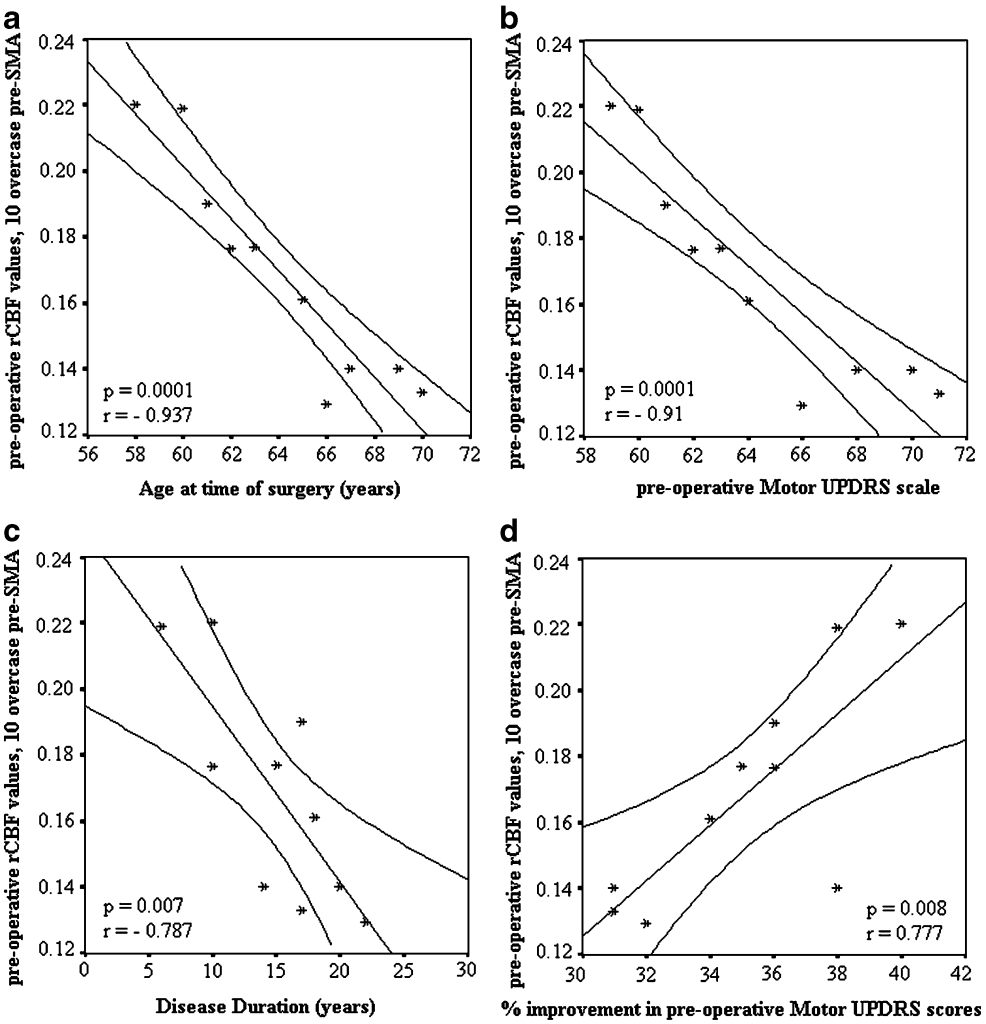

Fig. 4 **a** Relationship between pre-operative rCBF values in the pre-SMA and age at time of surgery. **b** Relationship between rCBF values in the pre-SMA and motor UPDRS scores for the pre-operative off drug condition. **c** Relationship between rCBF values in the pre-SMA and disease duration for the pre-operative off drug condition. **d** Relationship between rCBF values in the pre-SMA and percent improvements in motor UPDRS scores for the pre-operative off drug condition. *Pre-SMA* rostral part of the supplementary motor area

associated with post-operative rCBF values at 42 months (p=0.0001, r=0.964) (Fig. 6a). The pre- and post-operative rCBF values in the pre-SMA at 42 months presented a significant negative relationship with percent improvement of rCBF in the pre-SMA from the pre- to the post-operative condition at 42 months (p=0.0001, r=−0.928; p=0.003, r=−0.829) (Fig. 6b, c), which also presented a significant negative correlation with percent improvement in UPDRS motor scores from the pre- to the post-operative condition at 42 months (p=0.001, r=−0.869) (Fig. 6d) and a positive correlation with post-operative UPDRS motor scores at 42 months (p=0.002, r=0.853) (Fig. 6e). A significant negative relationship was found between the post-operative UPDRS motor scores at 42 months and percent improvement of UPDRS motor scores from the pre- to the post-operative condition at 42 months (p=0.0001, r=−0.989) (Fig. 6f).

Similarly, we found that the pre-operative rCBF in the pre-SMA was significantly associated with post-operative rCBF values at 5 months (p=0.001, r=0.868). A trend was present toward a negative association between pre-operative rCBF values and percent improvement of rCBF at 5 months (p=0.05, r=−0.65). The percent improvement of rCBF in the pre-SMA from the pre- to the post-operative condition at 5 months presented a significant negative correlation with percent improvement in UPDRS motor scores from the pre- to this post-operative condition (p=0.02, r=−0.687) and a trend toward a positive relationship with UPDRS motor scores at 5 months (p=0.06, r=0.6). A significant relationship was found between the post-operative UPDRS motor scores at 5 months and percent improvement of rCBF in the pre-SMA from the pre- to the post-operative condition at 5 months (p=0.0001, r=−0.99).

Discussion

This study was undertaken to define predictive factors for the outcome of treatment for PD by continuous bilateral stimulation of the STN in order to identify characteristics of the candidate who may receive the greatest benefit from surgery. To address this issue we evaluated the predictive

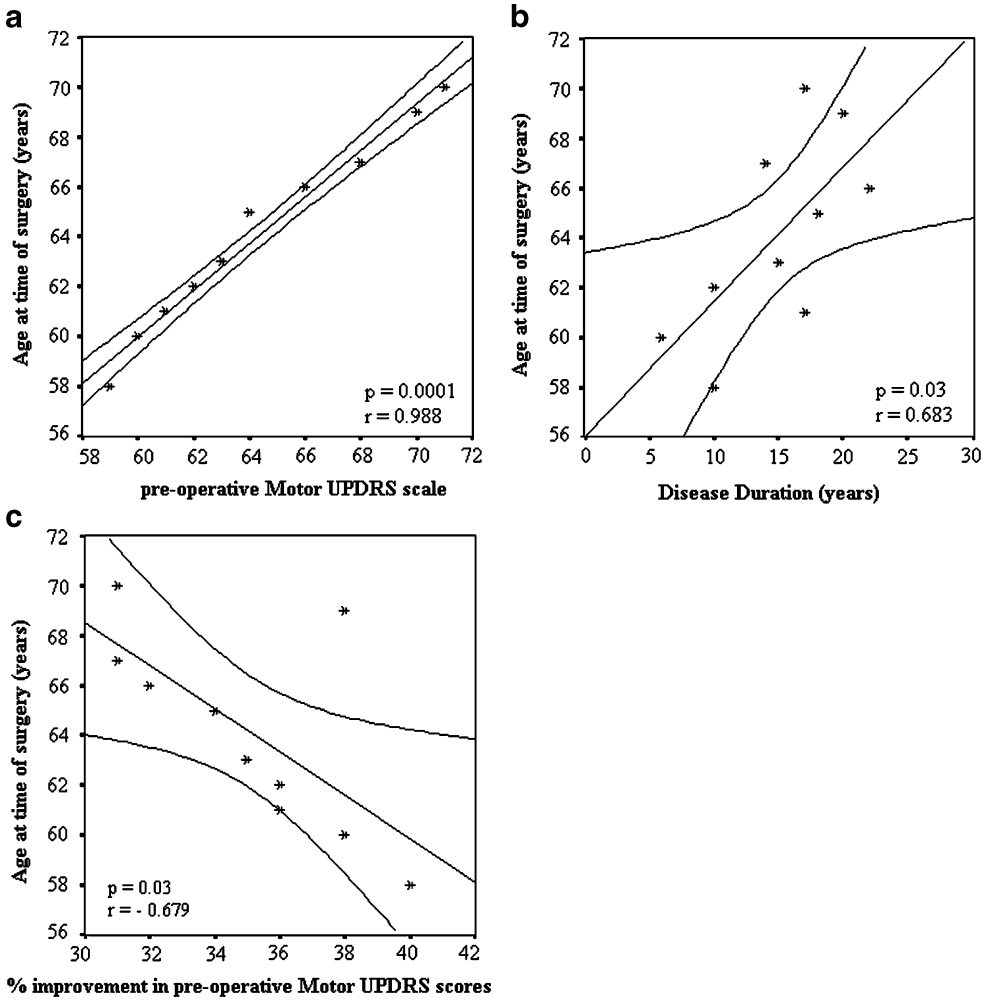

Fig. 5 **a** Relationship between age at time of surgery and pre-operative motor UPDRS scale. **b** Relationship between age and disease duration at time of surgery. **c** Relationship between age at time of surgery and baseline percent improvement in motor UPDRS scores

value of pre-operative rCBF in the pre-SMA and clinical parameters including age at time of surgery, pre-operative UPDRS motor medication on scores, disease duration and baseline percent improvement in UPDRS motor scores. The reason to investigate the potential for the rCBF in the pre-SMA (Fig. 1) to predict patients' outcome was supported by the role of this cortical area in the recovery of motor function during STN DBS [16–20]. In this group of ten patients, who were rigorously selected and followed after 4 years of treatment, we found that the outcome of neurosurgery at 5 and 42 months was markedly dependent upon the pre-operative rCBF values in the pre-SMA and, among clinical variables, the age and L-dopa response at time of surgery. Indeed, results of uni- and multivariate analyses clearly showed that parkinsonian patients presenting higher rCBF values and younger age at time of surgery were characterized by higher UPDRS motor scores and percent improvement of motor performance in the short- as well in the long-term treatment with STN DBS. Results of this study showed that also the L-dopa responsiveness was a reliable predictor of favourable response for the long-term outcome of treatment by STN DBS, e.g. the higher the L-dopa responsiveness the higher the clinical benefit from STN DBS at 4 years. Concerning the study of mechanisms underlying the predictive potential, we found that patients with higher rCBF values in the pre-SMA at time of surgery were those with younger age, higher L-dopa responsiveness and pre-operative motor performance, and shorter disease duration. Interestingly, we also found that patients with higher pre-operative rCBF values in the pre-SMA presented with higher rCBF values at 42 months and that both these parameters were negatively associated with percent improvement in rCBF from the pre- to the post-operative condition at 42 months. Besides, we found that the percent improvement in rCBF in the pre-SMA from the pre- to the post-operative condition at 42 months was negatively associated with percent improvement in motor performance and UPDRS motor scores at 42 months after surgery and that these two parameters were negatively correlated. Similar relationships were also found at 5 months after DBS.

The most important finding of the current study was that rCBF in the the pre-SMA is a key predictor of good response to STN DBS. Importantly, since age strongly

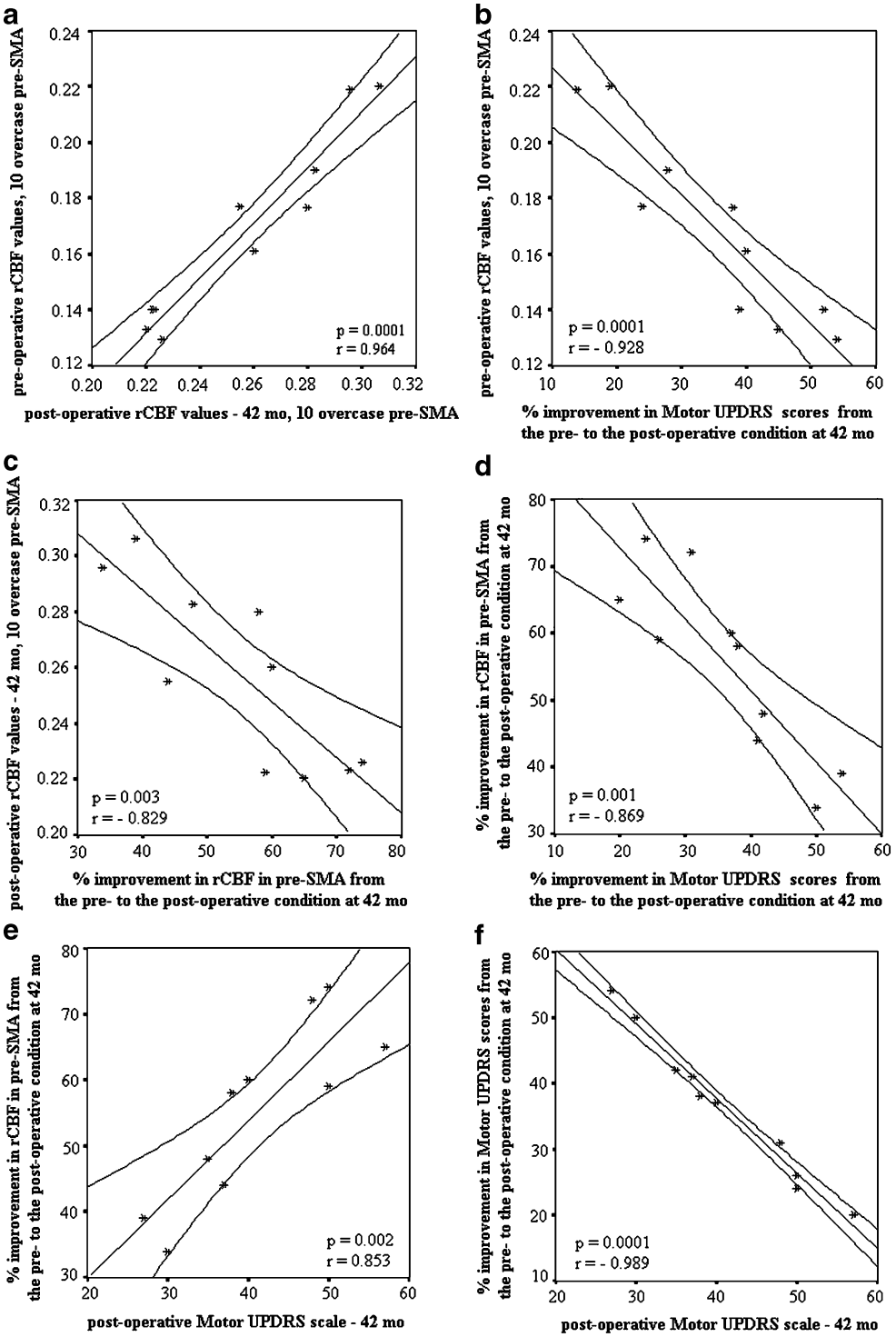

Fig. 6 **a** Relationship between rCBF values in the pre-SMA for the pre-operative off drug condition and for the post-operative off drug/on stimulation condition at 42 months. **b** Relationship between rCBF values in the pre-SMA for the pre-operative off drug condition and percent improvements in rCBF in the pre-SMA from the pre- to the post-operative off drug/on stimulation condition at 42 months. **c** Relationship between rCBF values in the pre-SMA for the post-operative off drug/on stimulation condition at 42 months and percent improvements in rCBF in the pre-SMA from the pre- to the post-operative off drug/on stimulation condition at 42 months. **d** Relationship between percent improvements in rCBF in the pre-SMA from the pre- to the post-operative off drug/on stimulation condition at 42 months and percent improvements in motor UPDRS scores for the pre-operative off drug condition at 42 months. **e** Relationship between percent improvements in rCBF in the pre-SMA from the pre- to the post-operative off drug/on stimulation condition at 42 months and post-operative off drug/on stimulation condition at 42 months. **f** Relationship between percent improvements in motor UPDRS scores for the pre-operative off drug condition at 42 months and post-operative off drug/on stimulation condition at 42 months. *Pre-SMA* rostral part of the supplementary motor area

affects rCBF, the rCBF data of parkinsonian patients were corrected for age to avoid the confounding effect of this parameter. Although no study has been performed investigating the influence of the brain on outcome of PD patients treated with STN DBS, the superior motor response observed in patients with higher pre-operative rCBF values in the pre-SMA is consistent with the crucial role of this high order motor cortical area in PD and STN DBS [16–20]. Along with rCBF, the present results showed that age and pre-operative L-dopa responsiveness are key predictors of favourable outcome for STN DBS. This finding is consistent with results of previous clinical studies obtained in a larger series showing that PD patients with younger age and better pre-operative response to medication tend to be highly responsive to STN DBS [7–12]. Combined rCBF and clinical factors suggest that PD patients with younger

age, higher L-dopa responsiveness and rCBF in the pre-SMA have a better outcome for STN DBS, thus giving further support to the evidence that this surgical therapy could be considered early in the course of the disease [4–6].

Concerning the rationale for the predictive potential of rCBF in the pre-SMA, results of correlation within pre-operative variables suggest that the greater benefit from STN DBS observed in PD patients with younger age (Fig. 4a), higher motor scores at time of surgery (Fig. 4b), shorter disease duration (Fig. 4c) and good response to medication (Fig. 4d) is strictly related to a more preserved function of the pre-SMA. Accordingly, results of correlation between pre- and post-operative rCBF values, percent improvement in rCBF, post-operative motor UPDRS scores and percent improvement in motor UPDRS show that in younger patients with high pre-operative rCBF values in the pre-SMA small increases in rCBF due to DBS are sufficient to reach high post-operative rCBF values (Fig. 6a–c), which are related to both high improvements in motor performance and UPDRS scores in the years after surgery (Fig. 6d–f). On the contrary, in older patients with low pre-operative rCBF values larger increases in rCBF due to stimulation are necessary to reach post-operative rCBF values that are lower than those observed in younger patients with a better functioning pre-SMA (Fig. 6a–c) and thus related to lower post-operative improvement in motor performance and UPDRS scores (Fig. 6d–f). Therefore, the STN DBS is likely to produce a greater and faster clinical effect in younger parkinsonian patients because it works on residual cortical neurons whose function is relatively less compromised than that observed in older PD patients. These findings are largely supported by our understanding of current models of the function of the basal ganglia motor circuit [25–27], the pathological changes and the compensatory mechanisms that progressively occur in PD [28–30], as well as the neural mechanisms underlying the therapeutic effect of STN DBS [19, 31–33]. Particularly, it is noteworthy that younger PD patients are characterized by a more isolated dopaminergic lesion and more effective compensatory mechanisms and that both result in a better functioning pre-SMA at the time of surgery [32, 34, 35]. Furthermore, it is well known that success of a brain therapy generally tends to correlate with degree of residual function within surviving target neurons and that a normal function demands that neurons work at a rather high capacity which is more easily reached by such therapy if their function is not completely compromised [36, 37].

Limitations of this study must be mentioned. Further investigations with a larger series and with instrumentation characterized by a higher spatial resolution are needed to confirm the predictive potential of rCBF in the pre-SMA. Although our clinical results are in line with those reported by the majority of studies investigating the predictive potential of pre-operative clinical parameters in PD patients treated with STN DBS, there are at least two studies in which the predictive role of age was not evident [13, 14]. Besides, prediction of greatest beneficial response to STN DBS in younger patients has been observed mainly in the short term and further studies are needed to confirm this effect in the long term.

In summary, the present results assessed by means of rCBF SPECT suggest that PD patients presenting at time of surgery at a younger age and high L-dopa responsiveness tend to have a favourable outcome after STN DBS because of a better preserved function in the pre-SMA. This finding may add further support to the evidence that neurosurgery could be also considered earlier after the diagnosis of PD in order to prevent psychological degradation and maintain quality of life, especially in young patients facing a long course of the disease. Furthermore, as previously proposed [15], our findings also suggest that, along with clinical measurements, the activity in cortical motor areas of crucial importance in PD should be also taken into consideration as a valuable marker of the candidates who may receive the greatest benefit from surgery.

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