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# UNIVERSITÀ DEGLI STUDI DI TORINO

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# Subthalamic deep brain stimulation: clinical and neuropsychological outcomes in mild cognitive impaired parkinsonian patients

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## Abstract

*This observational study reports the long-term follow-up of 184 Parkinson's disease (PD) patients treated with subthalamic deep brain stimulation (STN-DBS), retrospectively analyzing the outcomes of subjects with pre-surgical mild cognitive impairment (MCI) compared to those of patients with normal cognition. Patients were divided into PD-MCI or normal cognition groups at baseline, and then compared after 1, 3, 5 and >5 years of follow-up. Subjects assessed by outpatient clinical follow-up evaluation, not performing a complete clinical and neuropsychological follow-up assessment, were separately considered and rated according to their functional autonomy in daily living activities. The MCI prevalence at baseline was 23 %, increasing to 34 % at 1 year and over 40 % after 3 years. Dementia progressively affected more than 30 % of subjects after a median time of 6 years in the PD-MCI group and 11 years in the normal cognition group (p: 0.028). The mortality risk was slightly higher in PD-MCI patients. Outpatient clinical evaluations showed a progressive increase of subjects completely dependent in the activities of daily living, which ranged from the 11 % at 3 years to 23 % at 5 years and 31 % at >5 years. MCI can be frequently observed in PD patients, possibly influencing the outcome of surgical therapy. Our findings confirm the sustained long-lasting efficacy of STN-DBS on motor functions in both PD-MCI and normal cognition subjects. PD-MCI patients showed a more precocious cognitive impairment, as expected by natural history studies, but no case of dementia was observed early after surgery.*

## Keywords

Parkinson's disease. Dementia. Mild cognitive impairment. Deep brain stimulation. Subthalamic nucleus.

## Introduction

Mild cognitive impairment (MCI) can be observed since the onset of Parkinson's disease (PD) [1, 3], representing the initial phase of PD cognitive impairment and an important risk factor for the development of Parkinson's-associated dementia (PD-D) [4].

As suggested by the recent formulation of specific Movement Disorder Society (MDS) criteria for PD-MCI, an early identification of PD cognitive deficits could be particularly relevant for the long-term prognosis of PD; this could be especially relevant in patients' candidates to surgical therapies such as subthalamic nucleus deep brain stimulation (STN-DBS). In fact, long-term follow-up studies on STN-DBS treated patients [5, 7] demonstrated that stimulation efficacy could be limited by the progressive development of neuropsychological alterations, even though few data have been reported on the long-term STN-DBS outcomes in relation to the baseline

cognitive performances. The majority of follow-up studies focused only on patients reaching the long-term evaluation, without considering subjects who developed dementia or died after a variable period of time after DBS.

In a recent review on DBS for PD, facing the issue of patient selection, Bronstein et al.<sup>[8]</sup> reported that best results could be observed in patients with advanced PD and excellent L-Dopa response, younger age, no or few axial non-L-Dopa-responsive motor symptoms, no or very mild cognitive impairment. However, no data have been reported yet about the presence of the PD-MCI in predicting the long-term outcomes of STN-DBS subjects.

This study analyzes the role of PD-MCI in patients treated with STN-DBS. We retrospectively divided 184 patients into PD-MCI and normal cognition groups, following the criteria suggested by Litvan et al.<sup>[1]</sup>, with the aim of evaluating whether the pre-surgical PD-MCI feature may influence the long-term cognitive and motor outcomes.

## Methods

All 184 PD patients treated with STN-DBS at our Centre between 1998 and 2010 were included in the study. Subjects were selected according to the Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (CAPSIT-PD)<sup>[9]</sup> and STN-DBS bilateral surgery was performed following the procedure previously described elsewhere<sup>[10]</sup>.

A complete Unified Parkinson's disease Rating Scale (UPDRS) examination was performed at baseline (before STN-DBS), both in "OFF-condition" (at least 12 h after the last levodopa dose) and in "ON-condition" (at least 40 min after a levodopa challenge dose, consisting in 1.5 times the usual morning dose). In addition, the UPDRS-III axial subscore was calculated by the sum of items 18 (speech), 22 (neck rigidity), 27 (arising from a chair), 28 (posture), 29 (gait) and 30 (postural stability). A periodical clinical and neuropsychological CAPSIT-PD assessment, performed during a brief hospitalization, was proposed to each subject at 1, 3, 5 and >5 years (or more frequently according to the medical needs) in four conditions: Stimulation ON/Medication OFF; Stimulation OFF/Medication OFF; Stimulation OFF/Medication ON; Stimulation ON/Medication ON. Some patients underwent clinical outpatient evaluations only, basing on their familial needs or logistical problems. These subjects were then classified as completely independent, partially dependent or completely dependent in the ADL, taking into account the patients' autonomy in bathing, dressing, toileting, transferring, feeding and continence<sup>[11]</sup> in relation to the cognitive status and to the parkinsonian motor symptoms.

All PD patients were evaluated with a standardized battery of cognitive tests previously described<sup>[12]</sup>. Visuo-spatial reasoning was evaluated<sup>[12]</sup> by means of the Raven Colour Matrices (PM 47)<sup>[13]</sup>; verbal and spatial short-term memory were assessed by means of the validated versions of the Italian Bi-syllabic Words Repetition test (BWR) and Corsi's Block Tapping test (CBT)<sup>[14]</sup>. The assessment of verbal learning was achieved by means of the Paired Associate Learning (PAL)<sup>[15]</sup>, a Wechsler Memory Scale subtest. Frontal lobe executive functions, including the development of abstract concepts and the shift of attentional and motor sets, were assessed by means of the Trail Making B<sup>[16]</sup>. In addition, patients were administered the Phonemic and Category Verbal Fluency

tasks<sup>[14, 17]</sup>. Age and education appropriate normative data were used to evaluate the neuropsychological tests. In order to obtain comparable categorical data each test was rated as: normal performances, limited performances, moderate impairment, severe impairment, according to the scoring reported by Aybeck et al.<sup>[18]</sup>. Depression was evaluated by means of the Beck Depression Inventory (BDI), a 21-item self-rated scale<sup>[19]</sup>. The activities of daily living (ADL) functional impairment due to neuropsychological deficits were evaluated by means of a clinical diagnostic interview, administered to patients and caregivers by a trained neuropsychologist at each neuropsychological evaluation, taking into account the UPDRS-II score in “ON-condition”. PD-MCI was retrospectively defined as moderate or severe impairment on at least two neuropsychological tests and cognitive deficits not sufficient to interfere significantly with functional independence, in accordance with the Level-I of MDS criteria<sup>[20]</sup>. PD-D was defined according to the MDS criteria<sup>[21]</sup> as impairment in more than one cognitive domain with a decline from premorbid level and deficits severe enough to impair daily life, independently from the impairment ascribable to motor or autonomic symptoms. *Table 1* reports a complete list of clinical and demographic variables at baseline, including the number of patients fulfilling the criteria for PD-MCI (23 %) and normal cognition (77 %); in case of pre-surgical missing data (10 subjects), patients were excluded from the analysis. The study was approved by the local ethical committee, and a written informed consent was signed by all patients included.

**Table 1:** Demographic and clinical data at the pre-surgical baseline evaluation.

Total		Normal cognition	MCI	p
Baseline evaluation				
Number of patients	174	134 (77 %)	40 (23 %)	
Gender (M/F)	104/70 (59.8 %/40.2 %)	78/56 (58.2 %/41.8 %)	27/13 (67.5 %/32.5 %)	0.390
Age at onset (years)	46.40 ± 7.30 (24–59)	46.39 ± 7.01 (24–59)	45.53 ± 7.72 (26–57)	0.765
Age at DBS (years)	60.31 ± 6.72 (37–70)	60.32 ± 6.12 (40–70)	59.74 ± 8.21 (37–70)	0.856
Disease duration (years)	13.91 ± 4.75 (7–28)	13.93 ± 4.78 (7–28)	14.21 ± 4.90 (6–25)	0.207
Motor fluctuation duration (years)	5.86 ± 3.92 (1–23)	5.85 ± 4.04 (1–23)	6.29 ± 3.57 (1–19)	0.207
LEDD (mg/day)	1,063.59 ± 409.73 (100–2,435)	1,061.94 ± 357.04 (100–2,300)	1,118.78 ± 459.87 (325–2,435)	0.706
UPDRS I	1.64 ± 1.48	1.68 ± 1.47	1.58 ± 1.47	0.641
UPDRS II OFF	22.73 ± 7.27	21.83 ± 7.11	24.78 ± 7.74	0.005*
UPDRS II ON	7.68 ± 5.38	7.18 ± 5.55	9.30 ± 5.28	0.013*
UPDRS III OFF	47.51 ± 15.61	46.40 ± 15.43	53.07 ± 12.88	0.005*
UPDRS III ON	16.91 ± 8.23	15.76 ± 7.84	20.27 ± 8.07	0.001*
UPDRS III OFF axial subscore	20.60 ± 7.02	19.70 ± 6.93	23.30 ± 6.63	0.014*
UPDRS III ON axial subscore	8.57 ± 4.17	7.95 ± 4.02	10.45 ± 4.07	0.001*
UPDRS IV	7.97 ± 3.64	7.89 ± 3.65	8.50 ± 3.42	0.419
UPDRS V OFF	3.46 ± 0.99	3.29 ± 0.99	3.89 ± 0.83	0.001*
UPDRS V ON	2.62 ± 0.81	2.05 ± 0.79	2.31 ± 0.62	0.047*
UPDRS VI OFF	0.49 ± 0.20	0.50 ± 0.23	0.39 ± 0.19	0.003*
UPDRS VI ON	0.87 ± 0.14	0.84 ± 0.22	0.83 ± 0.23	0.601
Beck depression inventory	12.80 ± 7.83	12.72 ± 7.66	13.67 ± 8.25	0.312

Column “p” reports the “p value” of the differences between “normal cognition” and “PD-MCI” patients.

\* Significant difference (p<0.05).

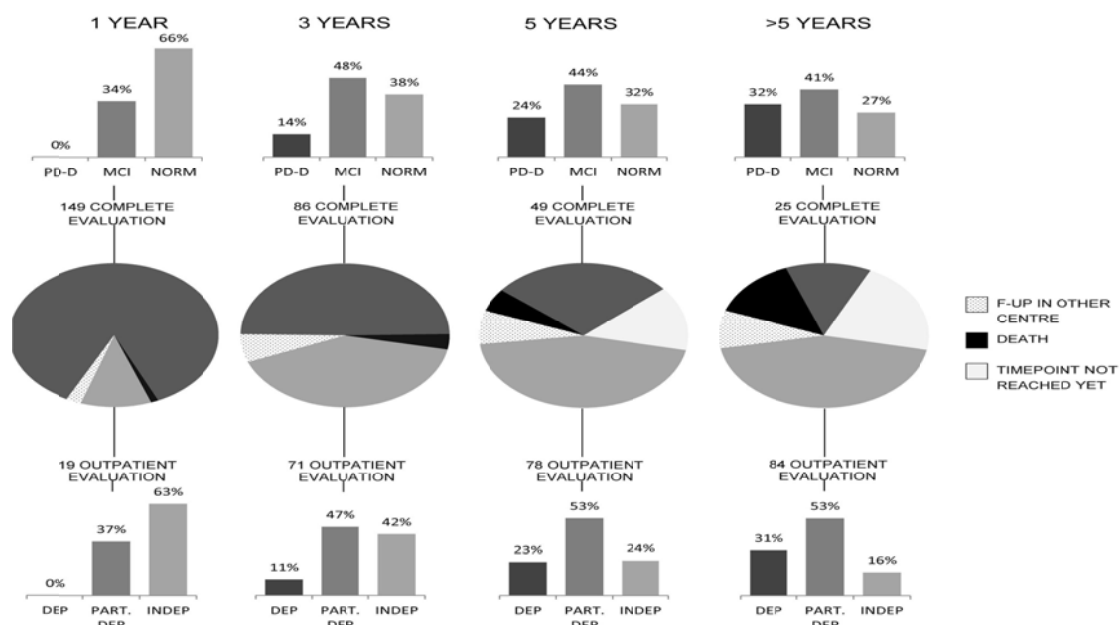
## Statistical analysis

Descriptive statistics (mean, SD and range) were used for continuous variables, while categorical variables were described as percentages of subjects falling in each group. The median

disease duration at PD-D development was estimated by Kaplan–Meier survival analyses; time to event was censored at the end of follow-up, and differences in the estimated survival distribution were examined with the log-rank test. Binary logistic regression was used for correlation with baseline clinical and neuropsychological features; Wilcoxon and Friedman non-parametric tests were used for the comparison of follow-up data within the same group. A multivariate Cox proportional hazard regression model was conducted to estimate the risk of PD-D and the mortality risk in relation to different baseline features, while controlling for relevant covariates. UPDRS subscores were included in the model; in addition, some demographic or clinical variables potentially correlated with PD-D and mortality risk, as age at disease onset, disease duration and gender, were also included as covariates. Moreover, a repeated measures general linear model (GLM) was applied for the comparison of outcomes between groups. All p values reported are two-tailed, and a probability (p) value <0.05 was considered statistically significant. The analyses were performed using PASWStat 18 for Windows, considering all the follow-up data available at January 2014.

## Results

As shown in *Table 1*, complete baseline clinical and neuropsychological data were available for 174/184 patients; a detailed analysis of all subjects evaluated at each follow-up has been reported (*Fig. 1*), including the number of deaths and the subjects evaluated only at outpatient clinic, not receiving therefore a complete CAPSIT-PD and neuropsychological follow-up assessment.



**Fig. 1** Number of patients with a complete follow-up evaluation or only outpatient clinical evaluation: patients with a complete follow-up assessment were divided into normal cognition, PD-MCI and PD-D, while subjects with outpatient clinical data were divided into dependent, partially dependent or completely independent in the activities of daily living.

## Baseline demographic and clinical characteristics.

The criteria for PD-MCI were fulfilled by 23 % of patients at baseline (*Table 1*), while no subject was affected by dementia. PD-MCI patients showed higher scores of UPDRS-II, -III, -V, axial subscores (both in OFF and ON condition) and lower scores of UPDRS-VI in OFF condition (*Table 1*). Gender, age at the disease onset, age at surgery and levodopa equivalent daily dose (LEDD) were similar in PD-MCI and normal cognition patients.

Follow-up evaluations: PD-D and PD-MCI rates and estimated time to dementia development.

As shown in *Fig. 1*, no case of PD-D was observed at the first follow-up, while 14 % of subjects developed PD-D at 3 years and this percentage rose to 32 % at >5 years.

The effects of STN-DBS surgery on PD-MCI and normal cognition group were compared for each neuropsychological test between baseline and 1 year after surgery, observing no significant changes for the majority of tests. The only exception was represented by the Phonemic Verbal Fluency, which showed a more marked decrease in the group of normal cognition patients (*Table 2*).

**Table 2** Neuropsychological assessment in PD-MCI and normal cognition groups: baseline versus 1-year follow-up scores.

Baseline	1 year	p
<b>Raven Colour Matrices—PM47</b>		
Normal 28.12 ± 4.108	28.33 ± 3.766	0.441
MCI 25.98 ± 5.276	25.32 ± 4.956	
<b>Bi-syllabic Words Rep. test—BWT</b>		
Normal 4.47 ± 0.789	4.22 ± 0.772	0.932
MCI 3.98 ± 0.740	3.84 ± 0.602	
<b>Corsi's Block Tapping test—CBT</b>		
Normal 4.43 ± 0.797	4.29 ± 0.852	0.995
MCI 4.14 ± 0.774	4.00 ± 0.913	
<b>Paired Associate Learning—PAL</b>		
Normal 11.98 ± 2.932	11.31 ± 2.925	0.140
MCI 10.29 ± 3.372	10.57 ± 3.060	
<b>Trail Making B—TMB</b>		
Normal 182.35 ± 118.379	207.84 ± 138.369	0.993
MCI 290.54 ± 168.652	306.33 ± 184.837	
<b>Phonemic Verbal Fluency</b>		
Normal 43.30 ± 15.422	33.12 ± 13.449	0.002*
MCI 30.69 ± 12.330	30.41 ± 13.991	
<b>Category Verbal Fluency</b>		
Normal 21.03 ± 5.572	18.85 ± 8.401	0.345
MCI 16.78 ± 4.868	16.02 ± 3.941	

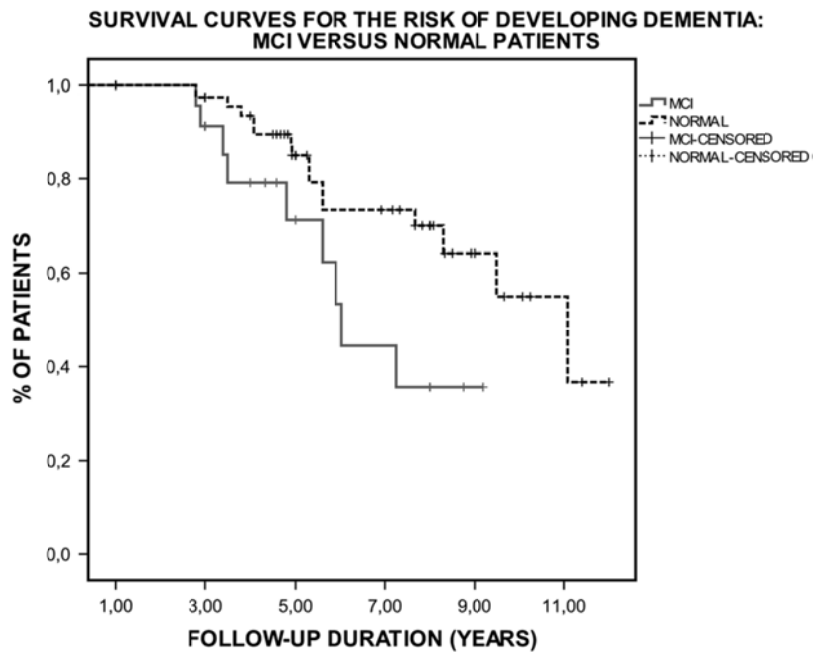
Column "p" reports the "p value" of the differences between "normal cognition" and "PD-MCI" patients

\* Significant difference (p<0.05).

After the first year, 34 % of subjects were classified as PD-MCI and this percentage rose to over 40 % after the 3-year evaluation (*Fig. 1*). Clinical outpatient report analyses demonstrated a

similar trend with a progressive increase of patients requiring assistance in daily living activities (Fig. 1).

The estimated time to dementia development was 9.5 years for the entire cohort of subjects with a significant difference between patients with PD-MCI and normal cognition at baseline (p: 0.028): PD-MCI patients had a median time to PD-D of 6.03 years compared to the 11.08 years of patients with normal baseline cognition (Fig. 2).

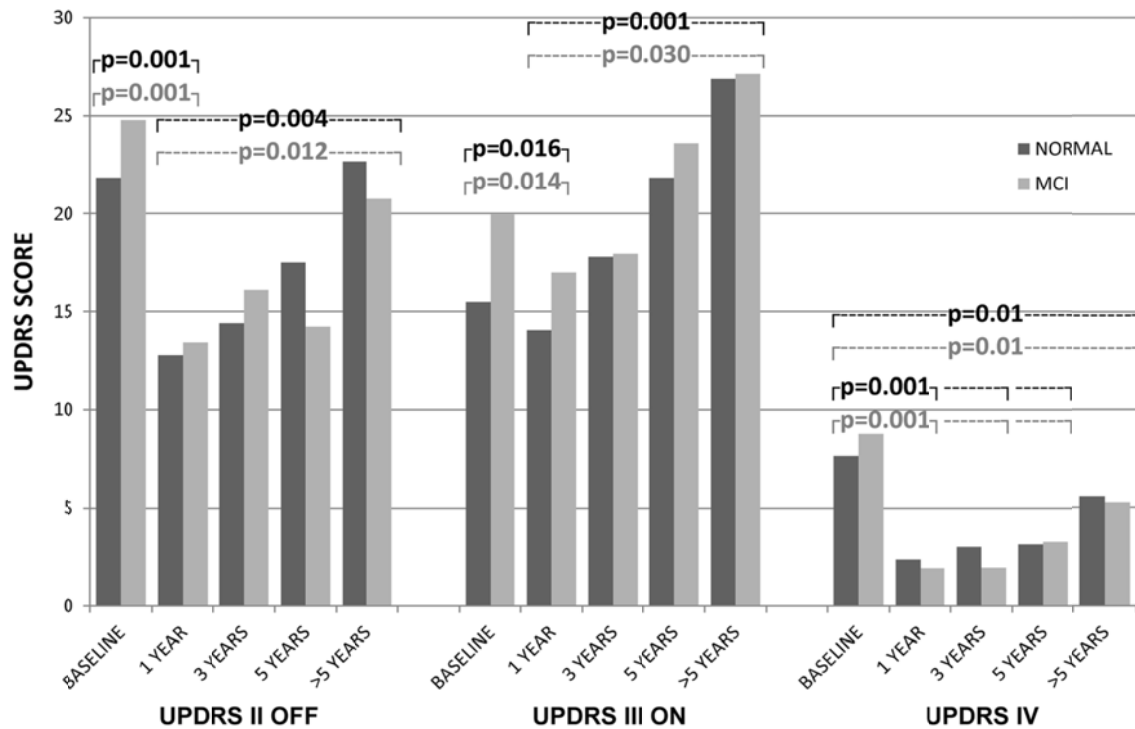


**Fig. 2** A significantly higher risk of developing PD-D was observed for PD-MCI (solid line) versus normal cognition (dashed line) patients.

### **Follow-up evaluations: activities of daily living, motor performances and complications of therapy**

No significant difference was observed between the two groups in UPDRS-II, -III and -IV outcomes during follow-up. As shown in Fig. 3, the ADL functions represented by UPDRS-II significantly improved between baseline and 1 year (OFF condition) in both groups, returning to the basal score values only after more than 5 years. Conversely, UPDRS-II in ON condition progressively worsened since the third year of follow-up in both groups (p: 0.004 for PD-MCI group; p: 0.001 for Normal Cognition group).





**Fig. 3** A significant improvement was observed in UPDRS-II in OFF condition after surgery, both for PD-MCI and normal cognition patients, followed by a slow gradual worsening that reached the statistical threshold after C5 years. After an initial improvement, the UPDRS-III score in ON condition worsened in both groups after C5 years of follow-up. UPDRS-IV showed a sustained and long-lasting improvement in both groups.

Motor performances, represented by the UPDRS-III scores, exhibited a similar trend, with a post-surgical significant improvement of STIM-ON/MED-ON versus MED-ON basal condition and a progressive moderate worsening, since the fifth year of follow-up (Fig. 3).

On the other hand, motor complications (UPDRS-IV) showed a long-lasting significant amelioration in both groups with a marked improvement after surgery and only a minimal worsening in the following clinical assessment that did not reach the basal score, even after >5 years of follow-up.

### Prognostic factors of PD-D

The baseline UPDRS-I score was found to be directly associated to the risk of developing dementia (HR: 1.466; p: 0.043), while a trend was observed for older age at DBS surgery (HR: 1.1; p: 0.093) and higher UPDRS-III score in ON condition (HR: 1.09; p: 0.065). Gender, age at disease onset, other UPDRS subscores did not reveal a relevant predictive value.

### Mortality rate

The overall mortality rate was ~15 % with moderate (p: 0.084) differences between the two groups: 16/134 (11.94 %) subjects with normal baseline cognition died during follow-up compared to 10/40 (25 %) subjects with PD-MCI. No patients died during the surgical procedure or because of related complications. A detailed analysis of the causes of death during follow-up is reported in Table 3. The mortality rate was associated with older age at disease onset (HR: 1.17; p: 0.016) and higher pre-surgical UPDRS-I and -II scores in OFF condition (HR: 1.43; p: 0.049 and HR:1.13; p:

0.033 respectively); higher score of UPDRS-III in ON condition showed a trend, not reaching the significance threshold (p: 0.062).

**Table 3** Mortality and causes of death

Causes of death	1 year	3 years	5 years	>5 years	Total
Pneumonia	1	2	1	7	11
Sepsis			1	3	4
Myocardial infarction	1			2	3
Cancer		2		1	3
Intestinal obstruction			1	2	3
Pulmonary thromboembolism				2	2
Total	2	4	3	17	26

## Discussion

This study reports the retrospective clinical and cognitive analysis of a large sample of parkinsonian patients treated with STN-DBS, comparing the clinical outcomes, mortality rate and conversion rate to PD-D in patients with PD-MCI and normal cognition.

PD-MCI criteria were fulfilled by 23 % of patients at the time of surgery; these data are in accordance with Broeders et al.<sup>[22]</sup> who described a 35 % prevalence of PD-MCI in newly diagnosed PD patients, and Muslimovic et al.<sup>[23]</sup> who reported a precocious and specific pattern of cognitive impairment since the disease onset.

None of the PD-MCI patients of our cohort developed dementia within the first year after surgery, suggesting that STN-DBS may not worsen a pre-existing mild cognitive impairment. In addition, the long-term outcome of motor functions and therapy complications was similar between the two groups, even though PD-MCI subjects showed higher UPDRS-II, -III, -V and lower UPDRS-VI baseline scores.

Comparing PD-MCI and normal cognition groups, no different neuropsychological outcomes were observed after the first year of surgery apart from Phonemic Verbal Fluency, which showed a more marked worsening in normal cognition subjects. This finding could be probably explained by the significant differences already evident at the baseline evaluation between the two groups: Phonemic Verbal Fluency alteration is a well-known STN-DBS specific side effect<sup>[24]</sup>, and it is likely that PD-MCI patients showed less evident modifications after surgery, since already impaired in this specific task.

On the other hand, we observed a significantly higher incidence of PD-D in patients with PD-MCI, confirming the data reported for the general PD population<sup>[25]</sup>: the percentage of PD-D gradually increased after the first year of follow-up, reaching the value of 14 % at 3 years and 32 % at >5 years, with UPDRS-I score representing the only independent prognostic risk factor. A similar

trend was observed in the percentage of outpatient subjects requiring assistance in the ADL, partly due to the cognitive status and partly to the parkinsonian motor symptoms.

The estimated time to PD-D conversion was 11 years for the normal cognition group and 6 years for the PD-MCI group. These findings might resemble those described by the natural history PD studies<sup>[22, 25, 26]</sup>, although only few data are currently available on the long-term follow-up of PD-MCI patients: Janvin et al.<sup>[25]</sup> described a PD-MCI conversion rate to PD-D of 62 % in a 4-year follow-up study, while Broeders et al.<sup>[22]</sup> reported a 26 % conversion rate to PD-D over a 5-year follow-up, in a cohort of naïve patients. Nevertheless, no reliable comparison can be made with the general PD population, since STN-DBS patients represent a highly selected cohort of PD subjects. Mortality rate showed a similar trend, rising to 25 % in PD-MCI patients compared to 12 % in the normal cognition group, possibly indicating a different incidence of severe complications or a different disease progression between the two groups.

Taken together, these data seem to suggest that STN-DBS surgery has beneficial effects both in PD-MCI and in normal cognition patients with a different incidence of PD-D. Moreover, we observed that our cohort of PD-MCI patients had higher baseline score of UPDRS-II and -III and lower UPDRS-VI scores; it is questionable whether a more precocious surgical approach should have been proposed, to provide a longer symptomatic STN-DBS beneficial effect and prevent the development of severe motor complications<sup>[27]</sup>.

Contrasting neuropsychological data have been reported on PD patients treated with STN-DBS: some studies suggested that cognitive outcomes might follow the natural history of the disease<sup>[5, 28]</sup>, whereas others reported an increased risk of dementia early after surgery<sup>[29, 30]</sup>.

At the present time, no clear indications exist for the STN-DBS selection in MCI patients, although this condition is very frequent in PD subjects candidates to surgery<sup>[26, 31]</sup>.

In conclusion, our study seems to confirm the safety and beneficial effects of STN-DBS surgery on motor functions also in PD-MCI patients with some predictable differences in the long-term cognitive outcomes. The main study strength is represented by the comprehensive analysis of short- and long-term follow-up outcomes of an entire cohort of STN-DBS subjects, while the principal limitations are: (a) the neuropsychological battery used, which was chosen before 1998, when there was no general consensus on the type of testing to establish cognitive impairment in PD subjects<sup>[8]</sup>, (b) the partial data collected in patients with outpatient clinical evaluations and (c) the retrospective analysis of data, which require confirmation by further prospective longitudinal studies.

## **Acknowledgments**

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## **Conflicts of interest**

Prof. Lopiano Leonardo has received honoraria for lecturing from Medtronic. Dott. Maurizio Zibetti and Prof. Michele Lanotte received travel grants for attending scientific congresses from Medtronic.

Dott. Aristide Merola, Laura Rizzi, Carlo Alberto Artusi, Alberto Romagnolo, Mario Giorgio Rizzone and Andrea Bernardini declare no conflict of interests.

### **Ethical standard**

The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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