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Subthalamic stimulation improves quality of life of patients aged 61 years or older with short duration of Parkinson's disease

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Complete List of Authors:	<p>Dafsari, Haidar; University Hospital Cologne, Department of Neurology; King's College Hospital, National Parkinson Foundation International Centre of Excellence</p> <p>Reker, Paul; University Hospital Cologne, Department of Neurology</p> <p>Silverdale, Monty; Salford Royal Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Department of Neurology and Neurosurgery</p> <p>Reddy, Prashanth; King's College Hospital, National Parkinson Foundation International Centre of Excellence</p> <p>Pilleri, Manuela; "Villa Margherita" Hospital of Arcugnano-Vicenza, Department of Neurology</p> <p>Martinez-Martin, Pablo; Carlos III Institute of Health, National Center of Epidemiology and CIBERNED</p> <p>Rizos, Alexandra; King's College Hospital, National Parkinson Foundation International Centre of Excellence</p> <p>Perrier, Estelle; University Hospital Cologne, Department of Neurology</p> <p>Weiss, Luisa; University Hospital Cologne, Department of Neurology</p> <p>Ashkan, Keyoumars; King's College Hospital, National Parkinson Foundation International Centre of Excellence</p> <p>Samuel, Michael; King's College Hospital NHS Foundation Trust</p> <p>Evans, Julian; Salford Royal Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Department of Neurology and Neurosurgery</p> <p>Visser-Vandewalle, Veerle; University Hospital Cologne, Department of Stereotaxy and Functional Neurosurgery</p> <p>Antonini, Angelo; IRCCS San Camillo, Department of Neurology</p> <p>Ray-Chaudhuri, K.; King's College Hospital, National Parkinson Foundation International Centre of Excellence; King's College London, Institute of Psychiatry, Psychology and Neuroscience</p> <p>Timmermann, Lars; University Hospital Cologne, Department of Neurology; University Hospital Giessen and Marburg, Campus Marburg, Department of Neurology</p>
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For Peer Review

Neuromodulation (Clinical Research)

Subthalamic stimulation improves quality of life of patients aged 61 years or older with short duration of Parkinson's disease

Haidar Salimi Dafsari^{1, 2*}, Paul Reker^{1*}, Monty Silverdale³, Prashanth Reddy², Manuela Pilleri⁴, Pablo Martinez-Martin⁵, Alexandra Rizo², Estelle Perrier¹, Luisa Weiß¹, Keyoumars Ashkan², Michael Samuel², Julian Evans³, Veerle Visser-Vandewalle⁷, Angelo Antonini^{4, 6}, K. Ray-Chaudhuri^{2, 8}, Lars Timmermann^{1, 9},
On behalf of EUROPAR and the IPMDS Non Motor PD Study Group.

¹ Department of Neurology, University Hospital Cologne, Cologne, Germany

² National Parkinson Foundation International Centre of Excellence, King's College Hospital, London, United Kingdom

³ Department of Neurology and Neurosurgery, Salford Royal Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, United Kingdom

⁴ Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, Italy

⁵ National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain

⁶ Department of Neurosciences (DNS), Padova University, Padova, Italy

⁷ Department of Stereotaxy and Functional Neurosurgery, University Hospital Cologne, Cologne, Germany

⁸ Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

⁹ Department of Neurology, University Hospital Giessen and Marburg, Campus Marburg, Germany

* These authors contributed equally to this work

Corresponding Authors:

Dr. Haidar S. Dafsari

Department of Neurology

University Hospital Cologne

Kerpener Str. 62

50937 Cologne, Germany

Tel.: +49-(0)221-478-4014

E-mail: haidar.dafsari@uk-koeln.de

Or

Dr. Paul Reker

Department of Neurology

University Hospital Cologne

Kerpener Str. 62

50937 Cologne, Germany

Tel.: +49-(0)221-478-4014

E-mail: paul.reker@uk-koeln.de

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Abstract

Objectives: The optimal timing of subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease (PD) is a topic of ongoing debate. In patients with short disease duration an improvement of quality of life (QoL) has been demonstrated for patients aged younger than 61 years. However, this has not been systematically investigated in older patients yet.

Material and Methods: From four centers (Cologne, London, Manchester, Venice) we identified 'older patients' aged 61 years or older with short (≤ 8 years) or longer disease duration and compared quality of life (QoL), motor impairment, complications, medication requirements, and MMSE on baseline and 5 months after surgery.

Results: Mean age/disease duration in 21 subjects with shorter disease duration were 65.5/6.3 years compared to 66.8/14.6 in 33 subjects with longer disease duration. The short disease duration group was affected by less baseline motor complications ($p=0.002$). QoL in the short/longer disease duration group improved by 35/20% ($p=0.010/p=0.006$), motor complications by 40/44% ($p=0.018/p<0.001$) and medication requirements by 51/49% (both $p<0.001$). MMSE remained unchanged in both groups.

Conclusion: Patients aged 61 years or older benefited from STN-DBS regardless of short (≤ 8 years) or longer (> 8 years) disease duration. Our results contribute to the debate about DBS selection criteria and timing and call for prospective confirmation in a larger cohort.

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1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment option for patients with Parkinson's disease (PD) improving motor symptoms¹ and quality of life (QoL)²⁻⁵. In recent years, the expansion of the traditional indication for DBS by intervention at earlier stages of PD has emerged as a major topic of debate⁶⁻⁸.

In the EARLYSTIM study, a randomized, controlled trial with relatively young patients (mean age 52.9 years) with short disease duration (mean 7.3 years) and short duration of motor complications (≤ 3 years), STN-DBS was superior to best medical treatment regarding quality of life (QoL), motor function and medication requirements⁶. An inclusion criterion in this study was age < 61 years. However, 'older patients', aged 61 years or older, form a majority of the PD population⁹. Previous studies have not provided evidence for an improvement of quality of life in older patients with PD undergoing bilateral STN-DBS¹⁰ and the effects of subthalamic neurostimulation in the subpopulation of older patients with short duration of PD remain to be investigated.

In spite of their possible suitability, neurostimulation might not be considered for these patients due to a rather high degree of uncertainty regarding its benefits and complications. We thus analyzed baseline characteristics and outcome parameters of this subpopulation of patients aged 61 years or older with short disease duration (≤ 8 years) and compared results to patients with the same age and longer disease durations of PD (> 8 years). We hypothesized that patients aged 61 years or older experience a significant QoL improvement after STN-DBS with no difference in effect sizes for groups of patients with short and longer disease duration.

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2. Methods

2.1. Study Design

For this post-hoc analysis of prospective data collected between August 2011 and January 2015, we screened the databases in four European DBS centers (Cologne, London, Manchester, Venice; IPMDS Non-Motor PD Study Group – DBS Section) for patients aged ≥ 61 years at surgery who underwent bilateral STN-DBS due to motor complications or medication refractory PD tremor.

To categorize our cohort of older patients aged ≥ 61 years into two groups, one with short and another with longer disease duration, we chose 8 years or less at surgical intervention as a cut-off for disease duration based on the mean baseline disease duration of the neurostimulation group in the EARLYSTIM trial which was 7.3 (± 3.1) years⁶. A cut-off based on disease duration was chosen as the onset and duration of motor fluctuations had not been systematically recorded in our database.

2.2. Patients and surgical procedures

PD diagnoses were based on UK Brain Bank criteria¹¹ and eligibility for bilateral STN-DBS had been verified at each center by an experienced multidisciplinary team. This involved exclusion of clinically relevant psychopathology or neuropsychological deficits, confirmation of levodopa responsiveness and exclusion of surgical contraindications.

All patients underwent bilateral subthalamic lead implantation in a single session. The STN was targeted visually by stereotactic MRI, assisted by intraoperative electrophysiological mapping according to established procedures at each center. Final lead positions were determined clinically and confirmed by postoperative imaging. The subcutaneous impulse generator was implanted either in the same session or shortly thereafter. Stimulation and adjustment of medication was

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commenced within few days after completion of surgical procedures at the discretion of the movement disorder specialists in each center.

2.3. Clinical assessments

The main outcome of this analysis was QoL change from preoperative baseline to postoperative follow-up rated with the Parkinson's Disease Questionnaire-8 (PDQ-8) which has previously been used for patients with PD and STN-DBS^{12, 13}. The PDQ has been recommended by the ad hoc Task Force of the Movement Disorders Society as an instrument to assess quality of life in patients with PD¹⁴ and previously been used as a primary endpoint in various large DBS trials^{2, 5, 6}. Domains of the PDQ comprise mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort with higher scores indicating lower quality of life. All results are reported as PDQ-8 summary index (PDQ-8 SI)¹⁵.

Motor impairment was assessed preoperatively in levodopa challenge tests as per clinical routine and documented with the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) and its revised version (MDS-UPDRS part 3; 47 and 7 patients, respectively)¹⁶.

Postoperative motor impairment was assessed with heterogeneous instruments in patients in clinical ON states with neurostimulation plus medication (MedON/StimON). Of the 54 patients, the MDS-UPDRS was available for 7 patients and the UPDRS for 31 patients. In the remaining 16 patients, motor impairment was assessed with the Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's disease (SPES/SCOPA) which was deducted from the UPDRS and strongly correlates with it^{17, 18}. The overall clinimetric properties of the SPES/SCOPA and UPDRS, including their inter- and intra-rater reliability, are good and the construct validity of the SPES/SCOPA referenced to the UPDRS is also good based

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on correlations between corresponding components of the two scales, such as motor impairment¹⁷. Based on previously published conversion methods^{19, 20}, here we report motor impairment ratings as MDS-UPDRS part 3 scores to enable comparisons across patients and simplify the interpretation of data.

For motor complications, the heterogeneous rating instruments were harmonized by comparing percentages of their maximum scores as there is no validated conversion method of SCOPA-motor complications to the (MDS)-UPDRS motor complications section.

Accordingly, tremor items of available scales were summarized as percentages of their maximum score to provide “tremor sub-scores” (UPDRS part III items 20 and 21, MDS-UPDRS part 3 items 3.15–3.18, and SPES/SCOPA motor examination, items 1 and 2).

Furthermore, we calculated the levodopa equivalent daily dose (LEDD) according to the formulae previously published by Tomlinson et al.²¹.

All patients underwent neuropsychological assessment as routine for their centers, using various tests which differed amongst centers. For a general cognitive measure, we only present the Mini-Mental State Examination (MMSE) results as this was found to be a common factor amongst the operating centers in this study.

2.4. Adverse events

Adverse events (AE) were extracted from databases/patient files and codified according to the following criteria: any event leading to death, disability or prolonged or new hospitalization with serious health impairment was considered serious AE (SAE). As an exception, scheduled hospitalizations for DBS follow-up were not considered serious. Mild, moderate or severe AE were categorized according to their extent of interference with normal function and their consequences, with moderate

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AE possibly interfering with normal activity and leading to the consideration of medical intervention or close follow-up and severe AE posing a substantial risk to the patient's health and requiring medical intervention or close follow-up.

2.5. Statistical analysis

After analyzing the normality of distribution with Shapiro-Wilk tests, baseline features of the short and longer disease duration groups were compared using the Mann-Whitney U test. The relationship between disease duration and preoperative motor impairment (OFF) was explored using Spearman correlation analysis. Additionally, to confirm this analysis, a median split of preoperative motor impairment was used to compare disease duration in patients with high and low motor impairment. In the main statistical analysis, we analyzed QoL changes intra-group from baseline to follow-up employing the Wilcoxon signed-rank test with Bonferroni-correction for the two comparisons. Additionally, we explored changes of motor impairment, motor complications, LEDD, and MMSE at follow-up as secondary outcomes. In order to better illustrate the magnitude of change at follow-up, Cohen's effect size was calculated for each outcome and categorized into "small" (effect size: 0.20 – 0.49), "moderate" (effect size: 0.50 – 0.79) and "large" (effect size: ≥ 0.80)²².

3. Results

3.1. Baseline

From our databases we identified 54 consecutive patients fulfilling the age inclusion criterion (≥ 61 years): 21 patients in the short disease duration group with a mean age and disease duration of 65.5 (± 6.3) and 6.3 (± 1.2) years and 33 patients in the longer disease duration group with 66.8 (± 3.2) and 14.6 (± 6.7) years.

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Baseline assessment was carried out shortly before surgery (mean: 6.2 ± 9.4 days, 95% confidence interval [CI]=3.4–9.0). Baseline motor complications ($p=0.002$) were significantly higher in the longer disease duration group. Other characteristics did not differ significantly, although values for motor impairment and tremor sub-scores were higher in the short disease duration group. In our cohort, no significant relationship was found for disease duration and motor impairment in Spearman correlation and median split analyses.

Baseline characteristics are presented in the *Table 1*, age distribution in *Figure 1*.

3.2. Follow-up

Follow-up assessments were carried out approximately 5 months after surgery (mean: 156 days ± 41.7 , CI=143.3–167.8). QoL significantly improved in both groups (short disease duration group: $p=0.010$; longer disease duration group: $p=0.006$; see *Table 2* and *Figure 2*). As expected, motor impairment significantly improved in the comparison of preoperative MedOFF to postoperative MedON/StimON (short disease duration group: $p<0.001$; longer disease duration group: $p<0.001$) while no significant change was found between preoperative MedON and postoperative MedON/StimON (both $p>0.05$).

Furthermore, while MMSE did not change significantly in either group, other exploratory outcomes, such as LEDD and motor complications, significantly improved in both groups (see *Table 2*).

Effect sizes were ‘moderate’ for QoL and ‘large’ for LEDD reduction and motor examination (comparing preoperative MedOFF and postoperative MedON/StimON) in both groups. For motor complications, they were ‘small’ in the short disease duration, but ‘large’ in the longer disease duration group.

In both groups, tremor was significantly reduced with a relative change of about 50%.

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3.3. Adverse events

AE and serious AE (SAE) are listed in detail in *Table 3*. SAE frequency was comparable in both groups (2 SAE/9.5% in the short, 4 SAE/12.1% in the longer disease duration group). The occurrence of AE per age group is shown in *Table 4*. No statistically significant difference in the frequency of AE could be observed with regard to age although the small number of patients older than 71 years potentially distorts the analysis.

In the short disease duration group, in one patient surgical revision of the implantable pulse generator became necessary due to impaired wound healing. This occurred in two patients of the longer disease duration group. One patient in the longer disease duration group suffered from severe and prolonged postoperative confusion which led to psychiatric hospitalization and intensified neuroleptic treatment. One patient in the short disease duration group experienced a transient delirious state. Delirium occurred after activation of ventral contacts, required temporary treatment in an intensive care unit and resolved completely after reprogramming and adjustment of medication. The removal of a suprapubic catheter and surgery for adenoma of the prostate in one patient in the longer disease duration group were unrelated to PD.

For non-serious AE the general distribution and profile did not differ between the groups with the exception of falls and dyskinesia which occurred more frequently in the longer disease duration group. In around 10% of patients in both groups gait disorders were observed.

4. Discussion

Bilateral STN-DBS in patients aged ≥ 61 years improved QoL and motor symptoms, irrespective of short (≤ 8 years) or longer (> 8 years) disease duration of PD. These

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findings resemble studies of younger patients with neurostimulation after short disease duration⁶ and of older patients matching the traditional selection profile in terms of a longer disease duration^{1, 2, 5}.

4.1. Baseline characteristics and DBS outcomes

Considering the minimally important difference for the PDQ-8 SI (5.8 – 7.4 points)²³, patients in both groups experienced relevant QoL improvement. Effect sizes for QoL were ‘moderate’ and for motor impairment ‘large’, supporting a robust and meaningful change. Few studies have investigated QoL outcomes stratified by age and disease duration. Derost et al. analyzed QoL outcomes in two age groups with a cut-off at 65 years¹⁰ and reported negative results in the older compared to the younger group for specific PDQ domains (‘Stigma’, ‘Cognition’, ‘Communication’, ‘ADL’, and ‘Mobility’). However, the authors did not provide information whether absolute changes of PDQ total and domain scores changed significantly after surgery in each group. Other studies assessing age-dependent QoL outcomes after STN-DBS only reported negative results for correlation analyses between QoL outcome and age at intervention and also did not report the absolute QoL changes for different age groups including patients aged 61 years or older^{24, 25}. As regards disease duration and QoL outcome, previous studies including patients with limited disease duration (<10 years)²⁶ and at early disease stages⁶ included relatively young patients aged <55, respectively <61 years. Therefore, as age may be a crucial confounding factor, the comparability of our results with these studies seems very limited.

The greater extent of baseline motor complications in the longer disease duration group was to be expected as a result of later disease stage and the marked postoperative improvement resulted in a ‘large’ effect size. In contrast, although a

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significant improvement was also observed in the short disease duration group, its effect size was only 'small'.

The analysis of tremor sub-scores showed a significant improvement of about 50% in both groups (see *Table 2*). Interestingly, baseline tremor scores were about twice as high in the short disease duration group. Thus, the impact of tremor reduction was particularly meaningful for these patients and supports the indication for DBS treatment in this group despite lower scores for motor complications.

In our cohort, the frequency of AE, especially of surgical complications, did not exceed the rates commonly reported²⁷.

4.2. Age and disease duration

Both the application of STN-DBS at short disease duration stages of PD and in older patients are topics of vivid debate^{6, 7, 28-30}.

The concept of early neurostimulation has been criticized due to medical, socioeconomic and scientific concerns²⁸ and many patients are cautious about undergoing early DBS²⁹. On the other hand, the authors of the EARLYSTIM study proposed their strategy as a possibility to prevent social, occupational and professional withdrawal and prolong the phase of good QoL at a critical point in the disease course^{6, 7, 30}.

Age has repeatedly been implied as a negative predictor for DBS outcomes, e.g. surgical complications³¹, motor functions³², QoL and axial signs^{10, 33}. However, recently its role as a rigid exclusion criterion was questioned when similar complication rates were reported between elderly (>75 years) and younger patients³¹ although this study focused on all targets, not just STN. Randomized, controlled trials report no influence of age on motor improvement as a statistically independent factor

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in STN-DBS³⁴. Surgical complications seem to depend mainly on comorbidities, for which age serves as a surrogate³⁵.

Consequently, in our cohort of older patients the perioperative risk may rise with increasing comorbidities at higher age and particularly in patients aged between 60 to 70 years more years of disease duration until DBS could result in a loss of years with good QoL.

4.3.Looking beyond age and disease duration – the need for better surrogates

Higher age and longer disease duration at surgery are associated with more non-dopaminergic motor phenomena³⁶. Postoperatively, with progressing disease these symptoms gradually limit DBS efficacy^{1, 37}.

Generally, the response to medical and surgical treatment seems to depend on the interplay of age, disease duration and clinical phenotype. This also becomes apparent in our cohort: Despite a significantly longer disease duration in the corresponding group, motor impairment and QoL at baseline were comparable in both groups, seemingly suggesting a faster progression of parkinsonian symptoms in the short disease duration group. However, in our cohort, we did not find a significant relationship between disease duration and motor impairment in correlation and median split analysis. Instead, this apparent mismatch might in part result from the relatively higher, albeit statistically not significant, tremor sub-scores in the short disease duration group. This higher tremor sub-score might also explain the fact that higher motor impairment and yet less motor complications were observed in this group. These findings point to tremor as an important phenotypic characteristic in the evaluation of surgical candidacy in older patients with short disease duration.

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Age and disease duration rather seem to serve as surrogates for factors detrimental to DBS outcomes, such as comorbidities, axial signs and cognitive impairment. Except for comorbidities, which correlate mainly with age³⁵, their development might be more reliably associated with the individual disease characteristics. Subtypes of PD could offer better outcome predictions than mere demographic features such as chronological age.

4.4. Limitations

Our results need to be interpreted with caution due to a number of limitations.

Despite the involvement of four DBS centers, the size of our short disease duration group was rather small. This in turn may indicate the clinical underrepresentation of older patients with DBS and short disease duration of PD. The relative underrepresentation of women in the short disease group is in line with previous studies which have reported that men seem to be undergoing DBS earlier than women³⁸ which may be based on patients' wishes, position in society³⁹ and an underrepresentation in referrals for DBS surgery⁴⁰. The high variability of clinical data is likely explained by the small sample size, especially in the short disease duration group which as discussed may be more prone to a higher degree of clinical heterogeneity in stages of shorter disease duration. Further studies including more patients are needed to investigate this issue.

The cognitive assessment is limited as the MMSE is not a disease specific instrument and therefore has limited utility in PD.

Although the concept of our study investigating DBS outcomes such as QoL, motor functions, medication requirements in older patients with short disease duration, somehow echoes the concept of the EARLYSTIM study, it is important emphasize basic methodological differences: Above all, the EARLYSTIM study was a large,

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randomized and controlled prospective trial. In the EARLYSTIM study, a main inclusion criterion was ≤ 3 years duration of motor fluctuations to enable inclusion of patients at early stages of disease progression. As the duration of motor fluctuations had not been systematically recorded in our databases, we cannot confirm disease progression stages based on the same designated cut-off as in the EARLYSTIM study. However, a short disease duration based on a 8 year cut-off seemed to be a sensible approach to approximate this criterion as motor complications do not occur in $>90\%$ for dyskinesia and $>85\%$ for motor fluctuations during the first five years of the disease⁴¹.

The lack of a best medical treatment group, the unblinded clinical assessments, and the inclusion criteria based on disease duration instead of duration of motor complications and the retrospective character highly limit the comparability of our study with EARLYSTIM. Furthermore, due to the shorter observation period in our study, e.g., AE counts cannot be directly compared between the studies.

Due to the design of our database as a prospective, but non-interventional longitudinal observation, only clinical ON states (MedON/StimON) were recorded at the follow-up assessments. MedOFF/StimON values were thus not available, limiting the analysis of the pure stimulation effects on QoL and motor outcomes. The LEDD reduction and the comparison of postoperative MedON/StimON to the preoperative MedOFF and MedON scores observed in our cohort were, however, well within the range of previous studies^{1, 2, 5, 6}.

A longer follow-up will need to address the long-term outcome, especially the development of non-dopaminergic, non-motor, and axial symptoms. From our relatively short follow-up, we cannot predict the durability of QoL improvements. Although the alleviation of especially appendicular motor symptoms by STN-DBS is known to be quite sustainable, comorbidities and the factors mentioned above may

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reduce the differences between surgical management at different disease stages and medical treatment in an older cohort.

To conclude, our study provides preliminary evidence for a potential benefit of subthalamic neurostimulation after short disease duration in an older PD subpopulation.

However, this group of older patients with short disease duration might rather epitomize the impact of individual disease type and health status than that of demographic features on DBS outcomes. This emphasizes the need to look beyond demographical features in determining surgical candidacy.

Although due to its exploratory character no general recommendations can be derived from our study, it adds another piece to the puzzle of patient selection for neurostimulation.

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Author's Roles

Haidar Salimi Dafsari, study concept and design, data acquisition, statistical analysis concept and execution, drafting of the manuscript
Paul Reker, study concept and design, data acquisition, statistical analysis concept and execution, drafting of the manuscript
Prashanth Reddy, data acquisition, critical review of the manuscript
Monty Silverdale, data acquisition, critical review of the manuscript
Manuela Pilleri: data acquisition
Pablo Martinez-Martin: statistical analysis execution and review, critical review of the manuscript
Alexandra Rizos, data acquisition, critical review of the manuscript
Estelle Perrier: data acquisition, critical review of the manuscript
Luisa Weiß: data acquisition, critical review of the manuscript
Keyoumars Ashkan: surgical intervention, critical review of the manuscript
Michael Samuel: data acquisition, critical review of the manuscript
Julian Evans: surgical intervention, critical review of the manuscript
Veerle Visser-Vandewalle: surgical intervention, critical review of the manuscript
Angelo Antonini: data acquisition, critical review of the manuscript
K. Ray Chaudhuri: study concept and design, data acquisition, critical review of the manuscript
Lars Timmermann: study concept and design, data acquisition, critical review of the manuscript

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Running title: "STN-DBS in age ≥61 years with short PD duration"

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Table 1 – Baseline characteristics

	Short disease duration (n = 21)	Longer disease duration (n = 33)	p [‡]
Sex (male/female)	17/4 (81/19%)	18/15 (54.5/45.5%)	
Age at intervention (years ±SD, range)	65.5 (±6.3)	66.8 (±3.2)	n.s.
Disease duration at surgery (years)	6.3 (±1.2)	14.6 (±6.7)	< 0.001[†]
PDQ-8 Summary Index	34.8 (±20.7)	32.2 (±10.9)	n.s.
Motor impairment (MDS-UPDRS part 3) Med OFF	46.4 (±16.8)	44.4 (±14.65)	n.s.
Med ON	25.1 (±11.5)	24.6 (±10.49)	n.s.
Tremor (% of maximum tremor score)	22.9 (±23.7)	10.1 (±10.8)	n.s.
Motor complications (% of maximum score)	28.3 (±27.6)	49.3 (±20.0)	0.002*
LEDD (mg)	1029.0 (±607.6)	1212.5 (±470.6)	n.s.
MMSE	29.2 (±0.9)	28.6 (±1.4)	n.s.

Abbreviations: LEDD = levodopa equivalent daily dose; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; MMSE = Minimal Mental State Examination; PDQ-8 SI = 8-item Parkinson's Disease Questionnaire Summary Index

‡ Mann-Whitney U test

† Significantly shorter disease duration of Parkinson's disease in corresponding group

* Significantly less motor complications in the short disease duration group

n.s.: not significant (p > 0.05)

Table 2 – Outcome parameters at follow-up and comparison with baseline												
	Short disease duration (n = 21)						Longer disease duration (n = 33)					
	Baseline	Follow-up	Δ	Relative change (%)	p	Effect size [†]	Baseline	Follow-up	Δ	Relative change (%)	p	Effect size [†]
PDQ-8 Summary Index	34.8 (±20.7)	22.5 (±15.7)	- 12.3	-35.3	0.010 ‡	0.59	32.2 (±10.9)	25.9 (±11.1)	- 6.3	- 19.6	0.006 ‡	0.58
Motor impairment (MDS-UPDRS part 3)	MedOFF: 46.4 (±16.8)	25.0 (±13.9)	21.4	-46.1	<0.001	1.27	MedOFF: 44.4 (±14.7)	28.8 (±7.9)	15.6	-35.2	<0.001	1.06
	MedON: 25.1 (±11.5)		0.1	-0.4	n.s.	0.00	MedON: 24.6 (±10.5)		- 4.2	17.0	n.s.	0.40
Tremor Scores (% of maximum tremor score)	22.9 (±23.7)	10.4 (±15.4)	- 12.5	- 54.6	0.004	0.53	10.1 (±10.8)	5.2 (±6.8)	- 4.9	- 48.5	0.037	0.45
Motor complications (% of maximum score)	28.3 (±27.6)	17.1 (±21.5) ^Φ	- 11.2	-39.6	0.018	0.41	49.3 (±20.0)	27.5 (±23.3)	- 21.8	-44.2	< 0.001	1.09
LEDD (mg)	1029.0 (±607.6)	500.4 (±302.9)	- 528.6	-51.4	< 0.001	0.87	1212.5 (±470.6)	623.3 (±300.4)	- 589.2	-48.6	< 0.001	1.25
MMSE	29.2 (±0.9)	29.2 (±1.2) ^Φ	0	0	n.s.	0	28.6 (±1.4)	28.7 (±1.6)	0.1	0.3	n.s.	0.07

Abbreviations: **LEDD** = levodopa equivalent daily dose; **MDS-UPDRS** = Movement Disorders Society – Unified Parkinson’s Disease Rating Scale; **MMSE** = Minimal Mental State Examination; **PDQ-8 Summary Index** = 8-item Parkinson’s Disease Questionnaire Summary Index

Scores for motor complications are presented as percentage of maximum scores to allow comparison across different rating scales. Maximum score for motor complications is 20 points in the UPDRS part IV (maximum score of the entire part IV is 23, but items 40-42 with a maximum score of 3 relate to non-motor symptoms and were excluded), 24 points in the MDS-UPDRS part 4 and 12 points in the SPES/SCOPA part C.

Δ Absolute change (Baseline – Follow-up)

‡ Wilcoxon signed-rank test with Bonferroni-correction for Type I error of main outcome (PDQ-8 Summary Index)

† Effect sizes: "small" (0.20-0.49), "moderate" (0.5-0.79) and "large" (>0.80)

Φ Follow-up motor complications score and MMSE each missing in one patient of the shorter disease duration group (n = 20)

|| Follow-up motor impairment and motor complications score each missing in one patient of longer disease duration group (n = 32)

n.s.: not significant (p > 0.05)

Table 3 - Adverse Events

Event	Short disease duration (n = 21)		Longer disease duration (n = 33)	
	No. of events	No. of patients with event (%)	No. of events	No. of patients with event (%)
Serious adverse events	2	2 (9.5)	4	4 (12.1)
Death	0	0	0	0
Life-threatening event	0	0	0	0
Event related to medication	0	0	0	0
Event related to surgery or device	1	1 (4.8)	3	3 (9.1)
Postoperative confusion	0	0	1	1 (3.0)
Impaired wound healing [¶]	1	1 (4.8)	2	2 (6.1)
Event related to stimulation	1	1 (4.8)	0	0
Transient delirious state ^Φ	1	1 (4.8)	0	0
Event related to Parkinson's disease	0	0	0	0
Other [‡]	0	0	1	1 (3.0)
Adverse events				
Mild	14	11 (52.4)	23	16 (48.5)
Moderate	15	9 (42.9)	24	16 (48.5)
Severe	1	1 (4.8)	9	8 (24.2)
Moderate or severe				
Dyskinesia	1	1	7	6
Gait disorder	2	2	3	3
Worsening of mobility	0	0	1	1
Depression	0	0	0	0
Impulse control disorder	0	0	1	1
Pain	1	1	2	2
Hypersalivation	1	1	0	0
Falls	1	1	4	4
Motor fluctuations	1	1	1	1
Anxiety	0	0	2	2
Hypomania	0	0	1	1
Dopamine withdrawal syndrome	1	1	2	2
REM behaviour disorder	1	1	1	1
Cognitive disturbance	0	0	1	1
Daytime sleepiness	1	1	0	0
Dysarthria	1	1	2	2
Subcutaneous seroma/hematoma	1	1	0	0
Postoperative confusion	1	1	2	2
Disturbed wound healing	1	1	1	1
Paraesthesias due to device	0	0	0	0
Gastrointestinal disorder	1	1	0	0
Infections (excl. device related)	1	1	1	1
Sexual function/fertility disorders	0	0	1	1
Other	0	0	0	0

[¶] Impaired wound healing around the implantable pulse generator in these patients required surgical revision

[‡] The removal of a suprapubic catheter and surgery for adenoma of the prostate in one patient were unrelated to PD

^Φ Disorientation, confusion and mania after activation of contact 0 required transient sedation and surveillance on Intensive Care Unit, resolved completely after adjustment of medication and stimulation

Table 4 - Adverse events per age group						
Age group	No. of patients	No. of events (%)				
		Total	Mild	Moderate	Severe	Serious
61 - 65	26	38	13 (34.2)	17 (44.7)	5 (13.2)	3 (7.9)
66 - 70	22	39	17 (43.6)	15 (38.5)	5 (12.8)	2 (0.1)
71 - 75	6	15	7 (46.7)	7 (46.7)	0 (0)	1 (6.7)
Sum	54	92	37 (40.2)	39 (42.4)	10 (10.9)	6 (6.5)

Table 4 lists all adverse events per age group. Percentages refer to the total of each age group and the sum of all events respectively.

Figure 1 – Distribution of patients according to age group and disease duration at surgery

Figure 1 shows that age in both the short disease duration group (red) and the longer disease duration group (grey) ranged from 61 to 75 years. The majority of patients in our cohort were between 61 to 70 years of age at surgery.

Figure 2 – Box and line plots of quality of life in patients aged 61 years or older with short and longer disease duration

Figure 2 illustrates a significant improvement of quality of life in patients aged ≥ 61 years with short (≤ 8 years, 2a) and longer disease duration (> 8 years, 2b) at deep brain stimulation surgery.

Big black stars and p-values indicate significant changes. Outliers are indicated with small circles (between 2 to 3 SD).

Members of the Non-motor Parkinson's Disease Study Group (NM-PD-SG) of the International Parkinson's Disease and Movement Disorders Society (IPMDS):

Steering Committee:

- Kallol Ray-Chaudhuri; Professor, FRCP (Edin) FRCP (Lond) DSc, MD (King's College London, London, United Kingdom; Chair)
- Angelo Antonini; Professor, MD/PhD (IRCCS Hospital San Camillo, Venice, Italy)
- Pablo Martinez-Martin; Professor, MD/PhD (Carlos III Institute of Health, Madrid, Spain)
- Per Odin; Professor, MD/PhD (Klinikum-Bremerhaven, Germany, and Skane University Hospital, Lund, Sweden)
- Anette Schrag; MD/PhD (University College London, London, United Kingdom)
- Daniel Weintraub; Professor (Associate), MD/PhD (University of Pennsylvania, Philadelphia, PA, USA)

Standing Members:

- Paolo Barone; Professor, MD/PhD (University of Naples, Italy)
- David J Brooks; Professor, MD/PhD, D.Sc., F.R.C.P., F.Med.Sci. (University College London, London, United Kingdom)
- Richard G. Brown; Professor, MD/PhD, MPhil (King's College London, London, United Kingdom)
- Peter Jenner; Professor, MD/PhD, D.Sc. (King's College London, London, United Kingdom)
- B Jeon; Professor, MD/PhD (Seoul National University Hospital, Seoul, Korea)
- Kelly Lyons; Professor, MD/PhD (University of Kansas Medical Center, Kansas City, KS, USA)
- Nicola Pavese; Professor (Associate), MD/PhD (Aarhus University Hospital, Århus, Denmark, and Imperial College London, London, United Kingdom)
- Marios Politis; MD/PhD, MSc, DIC (King's College London, London, United Kingdom)
- Ronald B. Postuma; Professor (Associate), MD, MSc (McGill University, Montreal, Canada)
- Anthony Schapira; Professor, MD/PhD, DSc, FRCP, FMedSc (University College London, London, United Kingdom)
- Fabrizio Stocchi; Professor, MD/PhD (IRCCS, San Raffaele Rome, Rome Italy)
- Lars Timmermann; Professor, MD/PhD (University Hospital Cologne, Cologne, Germany)
- Yoshio Tsuboi; Professor, MD/PhD (Fukuoka University, Fukuoka, Japan)

Managerial and Coordination

- Alexandra Rizos; PhD (King's College Hospital, London, United Kingdom)
- Antoniya Todorova; MD/PhD (King's College Hospital, London, United Kingdom)