Nucleus basalis of Meynert predicts cognition after deep brain stimulation in Parkinson's disease

Dorothee Kübler, Sophie Katharina Wellmann, Jakob Kaminski, Cornelia Skowronek, Gerd-Helge Schneider, Wolf-Julian Neumann, Kerstin Ritter, Andrea Kühn

Citation details
Kübler D, Wellmann SK, Kaminski J, Skowronek C, Schneider GH, Neumann WJ, et al. Nucleus basalis of Meynert predicts cognition after deep brain stimulation in Parkinson's disease. Parkinsonism & Related Disorders. Elsevier BV; 2022;94: 89-95.
DOI: 10.1016/j.parkreldis.2021.12.002

Nucleus basalis of Meynert predicts cognition after deep brain stimulation in Parkinson's disease

Dorothee Kübler, MD[1]; Sophie Katharina Wellmann[1]; Jakob Kaminski, MD[2]; Cornelia Skowronek, MD[1]; Gerd-Helge Schneider, MD[3]; Wolf-Julian Neumann, MD[1]; Kerstin Ritter, PhD* [2,4]; Andrea Kühn, MD* [1,4,5,6,7].

*equal contribution

[1] Movement Disorder and Neuromodulation Unit, Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany

[2] Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany

[3] Department of Neurosurgery, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany

[4] Berlin Center for Advanced Neuroimaging, Bernstein Center for Computational Neuroscience, Berlin, Germany

[5] Exzellenzcluster NeuroCure, Charité - Universitätsmedizin Berlin, Berlin, Germany

[6] Berlin School of Mind and Brain, Humboldt - Universität zu Berlin, Berlin, Germany

[7] Deutsches Zentrum für Neurodegenerative Erkrankungen, Berlin, Germany

Corresponding author:

Dorothee Kübler, Department of Neurology, Movement Disorder and Neuromodulation Unit, Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany, dorothee.kuebler@charite.de.

Number of words

Abstract: 250

Text: 3227

Tables and figures

Tables: [1] Comparison of clinical scores and scales before and 1 year after chronic STN-DBS.

Figures: [1A-B] Visualization of the basal forebrain nuclei (Figure 1A), Correlation normalized NBM volumes and the percentage of change in the cognitive screening scores before and 1 year after chronic STN-DBS (Figure 1B). [2A-B] Summary plot (Figure 2A) and beeswarm plot (Figure 3B) of the mean SHAP values. [3] Force plots showing the individual contributions of features in four patients with small to marked improvement or deterioration of general cognitive abilities.

References: 33

Keywords: Parkinson's disease, deep brain stimulation, cognition, nucleus basalis of Meynert, basal forebrain

Financial Disclosure / Conflicts of Interest

AAK reports honoraria and non-financial support from Medtronic, honoraria from Boston Scientific, Ipsen Pharma and Abbott. GHS reports honoraria for lectures by Medtronic, Boston Scientific and Abbott. CS, DK, JK, KR, SKW and WJN have nothing to disclose.

Study Funding

CS, DK and JK are supported by the BIH-Charité Clinician Scientist Program funded by the Charité-Universitätsmedizin Berlin and the Berlin Institute of Health. KR acknowledges support from the German Research Foundation (DFG, 389563835; TRR 265/A07; CRC 1404/A05), and the Brain & Behavior Research Foundation (NARSAD grant, USA). WJN holds grants from the German Research Foundation (DFG, 424778381), the Bundesministerium für Bildung und Forschung (iDBS FKZ01GQ1802), and a BIH/Wellcome Trust SPOKES Fellowship as well as a HERTIE Excellence in Clinical Neuroscience Fellowship. AAK is supported by the German Research Foundation (DFG, TRR 295, KU 2261/13-1 and EXC 2049/1).

Highlights

- Subthalamic DBS in Parkinson's disease (PD) was associated with cognitive decline in few cases.
- Cognitive decline in PD is highly relevant in terms of quality of life of patients and caregivers.
- Nucleus basalis of Meynert (NBM) is a simple non-invasive predictor for cognitive development in PD.
- We used a regression model and random forests with other prognostic factors in this retrospective study.
- We show that NBM volume is predictive of cognitive outcome 1 year after subthalamic DBS.

Abstract

Introduction

Subthalamic DBS in Parkinson's disease has been associated with cognitive decline in few cases. Volume reduction of the nucleus basalis of Meynert (NBM) seems to precede cognitive impairment in Parkinson's disease. In this retrospective study, we evaluated NBM volume as a predictor of cognitive outcome 1 year after subthalamic DBS.

Methods

NBM volumes were calculated from preoperative MRIs using voxel-based morphometry. Cognitive outcome was defined as the relative change of MMSE or DemTect scores from pre- to 1 year postoperatively. A multiple linear regression analysis adjusted for the number of cognitive domains affected in the preoperative neuropsychological testing and UPDRS III was conducted. To account for other variables and potential non-linear effects, an additional machine learning analysis using random forests was applied.

Results

55 patients with Parkinson's disease (39 male, age 61.4±7.5 years, disease duration 10.8±4.7 years) who received bilateral subthalamic DBS electrodes at our center were included. Although overall cognition did not change significantly, individual change in cognitive abilities was variable. Cognitive outcome could be predicted based on NBM size (B=208.98, p=0.022*) in the regression model ($F(3,49)=2.869$; R^2 of 0.149; p=0.046*). Using random forests with more variables, cognitive outcome could also be predicted (average root mean squared error between predicted and true cognitive change 11.28±9.51, p=0.039*). Also in this model, NBM volume was the most predictive variable.

Conclusion

NBM volume can be used as a simple non-invasive predictor for cognitive outcome after DBS in Parkinson's disease, especially when combined with other clinical parameters that are prognostically relevant.

Introduction

Patients with Parkinson's disease (PD) show heterogenous courses in both the motor and non-motor domains. In terms of cognition, many PD patients exhibit mild cognitive impairment (PD-MCI)[1] which can proceed to dementia (PD-D) with an increasing impact of cholinergic pathology[2]. The transition from PD-MCI to PD-D and the interplay of different pathologies is still unclear.

Deep brain stimulation in the subthalamic nucleus (STN-DBS) is a well-established therapy for the treatment of PD motor symptoms [3,4]. A comprehensive evaluation of possible contraindications is of course mandatory prior to DBS surgery. As the main risk factors for cognitive deterioration after STN-DBS are higher biological age[5] and preexisting cognitive deficits[6], only patients up to approximately 70 years with exclusion of are eligible for this type of therapy.

In the studies that led to FDA approval of STN-DBS, cognitive symptoms in PD patients with STN-DBS did not differ from PD patients under best medical treatment nor was there a significant change from before to after DBS surgery. The long-term incidence (3 years) of PD-D in patients with STN-DBS is comparable with that under best medical treatment[7]. In a meta-analysis on cognitive sequelae of STN-DBS including 612 patients from 8 different studies[8], however, small negative effects have been seen in executive functions, verbal learning and memory and moderate negative effects in semantic and phonemic verbal fluency.

Despite these good results, in clinical practice, few patients show a sustained deterioration on a global cognitive level[9] following STN-DBS although PD-D was ruled out by the current gold standard of neuropsychological assessment and although these patients improved as expected in terms of motor symptoms. Therefore, we must aim at identifying risk factors for such negative cognitive sequelae that are highly relevant for the quality of life of patients.

As the pathological hallmark of progressive cognitive deterioration in PD is of cholinergic nature, a measure with high sensitivity in early stages, when no or minor cognitive symptoms are present, is needed. The cholinergic basal forebrain is a highly promising non-invasive biomarker for cognitive abilities in patients with PD. It consists of four cholinergic groups of cells aligned above the optic nerves of both hemispheres named Ch1, 2,3 and Ch4 with Ch4 being the biggest of its nuclei, referred to as the nucleus basalis of Meynert (NBM)[10]. The NBM consists of 90% of cholinergic neurons and is currently being studied as a possible DBS target for Alzheimer's disease Lewy body dementia and PD-D[11,12]. The size and functional integrity of the basal forebrain and its NBM are closely intercorrelated and have been studied in detail in Alzheimer's disease[13,14] and two recent MRI studies have investigated the NBM as a possible predictor of cognitive decline in PD: Ray and colleagues[15] have investigated the MRIs of 168 PD patients from the Parkinson's Progressive Marker's Initiative (PPMI) and found that NBM volume was predictive of cognitive change as measured by the MoCA score in a 2-year period in de novo PD patients. Participants in this study with lower-than-expected NBM volumes at baseline were

shown to have a 3.5-fold greater risk of becoming cognitively impaired during a 5-year period. In another study on 304 PD patients from the PPMI[16], not only NBM volume but also its mean diffusivity, an MRI marker for lesioning, could predict the development of cognitive impairment in a 3-year period. Interestingly, in this study, PD patients with normal cognition who developed cognitive impairment disposed of higher axial (gait) scores stressing the relationship of axial motor symptoms and cognition.

In sum, the NBM seems to fulfill the criteria of a sensitive non-invasive predictor. To our knowledge, however, there are no studies that have investigated the NBM volume for the prediction of cognitive decline after STN-DBS.

The goal of this retrospective study was to evaluate whether the volume of the NBM can be used as a predictor of cognitive outcome of PD patients 1 year after the implantation of STN-DBS electrodes.

Methods

Patients and cognitive testing

Clinical and imaging data were retrospectively collected. All patients gave their written informed consent and the ethics committee of the Charité - Universitätsmedizin Berlin approved all study procedures. Patients with PD who received DBS electrodes at the Charité - Universitätsmedizin Berlin were included if they

1) received bilateral electrodes in the STN (in order to avoid a mixture of trajectories)
2) had a useable preoperative MRI and
3) a cognitive test both pre- and 1 year postoperatively.

At both timepoints, the Unified Parkinson's Disease Rating Scale (UPDRS) was additionally applied in order to characterize non-motor and motor aspects (UPDRS I and II) and motor complications (UPDRS IV). The motor examination (UPDRS III) was conducted with and without dopaminergic medication preoperatively (Med ON / Med OFF) and with and without STN-DBS postoperatively (Med ON Stim ON / Med ON Stim OFF / Med OFF Stim OFF / Med OFF Stim ON). Health-related disability was assessed by the Bain and Findley Activities of Daily Living (ADL) scale and a screening for symptoms of depression was conducted with the Beck Depression Inventory (BDI-II).

Neuropsychological assessment was conducted by a neuropsychologist and comprised the domains attention and attention switching, naming, visual and verbal short-term and episodic memory and executive functions. For this study, we extracted the number of cognitive domains reported to be affected. As the additional neuropsychological evaluation was conducted mainly for clinical purposes, patients completed different neuropsychological screening tests: The widely used Mini-Mental State Examination (MMSE, maximum 30 points) or the DemTect (maximum 18 points, adjusted for age). Both tests assess memory, language, visual construction, concentration and executive function and were conducted during Med ON or Med ON Stim ON. Cognitive development after STN-DBS was calculated as the relative change of MMSE or DemTect scores from pre- to 1 year postoperatively.

Imaging

For MRI analysis, preoperative images from either a 1.5 or 3 T Siemens or Philips scanner were used. Basal forebrain volumes were extracted from T1-weighted images acquired with an MPRAGE sequence in 130-208 slices with a slice thickness of 0.9 or 1 mm (n=75) with contrast agent originally acquired for surgical planning. Voxel-based morphometry was applied by means of the open-source toolbox CAT12 (http://141.35.69.218/cat), an extension for SPM12 (http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB (version 2019a). After segmentation with visual quality check, normalization in MNI space and smoothing, a homogeneity check was

conducted after which 5 MRIs were discarded due to MR sequences differing significantly from the rest (resulting n=70). NBM and Ch1-3 volumes (Figure 1A) were calculated with the atlas developed by Zaborszky and colleagues[17] implemented in the Anatomy toolbox (version 2.2). It is based on probabilistic anatomical maps derived from histological delineation of the cholinergic basal forebrain nuclei in ten human brains and comprises the regions Ch4 corresponding to the NBM and Ch1-3 corresponding to the surrounding smaller cholinergic nuclei.

Volumes of the basal forebrain depend highly on the individual total intracranial volume (TIV), which in turn depends on age and sex. In order to account for this interdependency, the ratio between NBM and Ch1-3 volumes and TIV was calculated (normalized TIV and Ch1-3 volume). Since disease severity has also an influence on the size of brain structures, the regression model was additionally corrected for the preoperative UPDRS III without dopaminergic medication (Med OFF).

Statistical analysis

Statistical analyses were performed using SPSS (IBM, version 25). Clinical characteristics are reported as mean ± SD (range). Comparisons of pre- and postoperative findings were conducted using paired two-sample t-tests as Kolmorogov-Smirnov tests revealed that clinical data was normally distributed. Correlations were calculated according to Pearson. In order to predict cognitive development after STN-DBS based on preoperative NBM volume, a multiple linear regression analysis adjusted for the number of cognitive domains affected and disease severity (UPDRS III Med OFF) was conducted.

Machine learning analysis

Since there is a large overlap between the risk factors for an overall postoperative cognitive deficit and cognitive deterioration in PD, an additional machine learning analysis was performed to allow for predictions on the single-subject level. We investigated the predictive performance of the demographic and clinical variables sex, age, disease duration, Levodopa equivalent dose (LED, the amount of Levodopa needed by the patients to control motor symptoms), PD motor subtype and preoperatively available imaging data (NBM/TIV, Ch1-3/TIV). As the duration and the narcosis regimen applied during surgery can also influence cognitive outcomes[18], these were considered, too. To predict cognitive change after DBS, we applied random forest regression and feature importance was assessed using Shapley Additive exPlanations (SHAP). For further details, please see supplementary material.

Results

Clinical scores and outcome

Of the 70 patients with suitable MRI data, 55 PD patients fulfilled the inclusion criteria of bilateral STN-DBS and available MMSE (n=49) or DemTect scores (n=6). 39 of them were male and 16 female. The average age was 61.4 ± 7.5 years, disease duration was 10.8 ± 4.7 years. 21 patients had an equivalent, 20 an akinetic-rigid and 14 a tremor-dominant motor type. Patients included in this study were operated between 04/2014 and 12/2018. Time between pre- and postoperative testing was 14.9 ± 2.8 months and 12.3 ± 1.9 months between DBS surgery and postoperative testing.

In the neuropsychological assessment conducted before DBS surgery, the number of impaired cognitive domains was 1.3 ± 1.3. 19 patients did not show any signs of MCI, 13 patients had one domain affected, 13 patients had two domains affected, five patients had three domains affected and another five patients had 4 domains affected.

Clinical scores and scales pre- and 1 year postoperatively and their respective significance level in terms of a change are depicted in Table 1. After STN-DBS, the UPDRS III improved significantly by 40 ± 32% (Med OFF vs. Med OFF Stim ON, p<0.001**) or 14 ± 58% (MedON vs. Med ON Stim ON, p=0.006**) respectively. Postoperatively, without dopaminergic medication, the UPDRS III improved by 39 ± 34% with STN-DBS switched on (Med OFF Stim OFF 42.7 ± 16.7, p<0.001**). LED was reduced significantly by 55 ± 30% (p<0.001**). Health-related disability as measured by the UPDRS II and the ADL also improved significantly by 13 ± 60% (p=0.001**) and 21 ± 88% (p<0.001**). A small improvement of 7 ± 65% (p=0.021*) was also seen in symptoms of depression as measured by the BDI-II. No difference was detected when comparing the UPDRS I (patient-reported non-motor symptoms) pre- and postoperatively.

General anesthesia and intubation for DBS surgery was necessary in 10 of the 55 patients. 30 patients underwent general anesthesia and intubation for intraoperative imaging only. All patients were intubated for the second operation with implantation of the impulse generator several days later.

Despite the wide range of preexisting cognitive states the mean cognitive outcome 1 year after STN-DBS surgery was stable: There was no significant change in MMSE scores (see Table 1) and a slight improvement in the DemTect from 14.3 ± 2.8 preoperatively to 15.2 ± 2.5 postoperatively (11 ± 29%, p=0.037*). The individual change in cognitive abilities after STN-DBS, however, varied widely between patients 1 year after STN-DBS. 24 patients did not show any change of their cognitive abilities, 16 deteriorated (up to 20%) and 15 improved (up to 50%) (see also Figure 1B).

Imaging parameters and correlation with cognitive outcome

Mean TIV was 1386.08 ± 133.03 cm^3 (1039.77-1716.35), mean NBM volume 0.94 ± 0.12 cm^3 (0.70-1.32) and mean Ch1-3 volume 1.04 ± 0.12 cm^3 (0.80-1.32).

Pearson's correlations between normalized NBM volume (ratio between NBM and TIV) and the relative change in cognitive scores pre- and 1 year postoperatively were significant (NBM volume: r=0.300, p=0.026*; normalized NBM volume: r=0.343, p=0.010*, see Figure 1B). Without the three patients with marked cognitive improvement, however, the correlation fails to reach the significance level (r= 0.242, p=0.084).

A multiple linear regression model adjusted for the number of cognitive domains affected preoperatively and disease severity (UPDRS III Med OFF) was calculated in order to predict cognitive development 1 year after STN-DBS based on NBM size relative to TIV. We found a significant regression (F(3,49)=2.869; p=0.046*) with an R^2 of 0.149. The cognitive outcome was significantly influenced by the NBM/TIV ratio (non-standardized regression coefficient B=208.98, p=0.022*) but not by the number of cognitive domains affected (p=0.390) nor UPDRS III Med OFF (p=0.288).

For the random forest regression based on all available variables, the average RMSE of the independent test data was 11.28±9.51 percentage points between the predicted and true cognitive change (p=0.038*). When averaging the SHAP values across all subjects and models, the normalized NBM volume was most predictive (Figure 2A) and larger NBM volumes were associated with a better cognitive outcome after DBS (Figure 2B). Other variables that contributed either positively or negatively to the prediction were UPDRS III Med OFF, disease duration, duration of intubation, normalized Ch1-3 volume, and LED pre DBS. From Figure 2B, it can be seen that for UPDRS III Med OFF, lower feature values seem to positively influence the prediction of cognitive outcome and that longer disease duration resulted in a worse cognitive outcome except for some individual cases in which a short disease duration had a negative effect. In Figure 3, we show the individual contributions of features on a single-subject level for four example cases.

Discussion

Cognitive decline in PD in general and after DBS in particular is not only highly relevant in terms of quality of life of patients and caregivers. In the framework of precision medicine, its risk should guide clinicians when making therapeutic decisions. We found that smaller NBM size is associated with unfavorable cognitive outcome one year after STN-DBS. This is the first study that has shown the NBM volume to be predictive of cognitive performance after DBS surgery. Our results are consistent with other studies on medically treated PD patients that have shown the integrity of the basal forebrain to be an early predictor of disease related cognitive decline[15,16,19]. As expected from previous work[20], normalized NBM volume in our cohort had a higher predictive value for global cognitive abilities than the one of Ch1-3.

Overall, a highly significant motor benefit from STN-DBS and reduction of dopaminergic therapy, similar to the large clinical trials[3,4], were seen and ADL capacities improved with STN-DBS. Importantly, cognitive abilities were stable after but there were large interindividual differences one year after surgery. Some patients deteriorated although preoperative cognition seemed normal. Apparently, the quantitative preoperative cognitive assessment alone cannot predict the outcome after STN-DBS and additional biomarkers are needed to identify patients at risk for cognitive deterioration. It is known that qualitative cognitive differences are also important: Abboud and colleagues have shown that the type of MCI can predict DBS outcomes in PD and suggest detailed cognitive testing to stratify a patient's risk[21]. Aybek and colleagues described poorer executive scores[7] and Bove and colleagues lower frontal scores[22] associated with a higher risk for the development of dementia after STN-DBS in PD. Based on our results, preoperative assessment of NBM volume could help to predict potential cognitive decline after STN-DBS. However, it has to be considered that normalized NBM volume was only able to predict a small portion of the variability. Larger cohorts are needed to estimate NBM volumes that help to define patients at risk for cognitive decline.

In the additional machine learning analysis, we showed that using all variables of interest, cognitive change can be predicted with an average precision of 11 percentage points. Also in this model, the leading predictor was normalized NBM volume followed by the preoperative UPDRS III Med OFF which reflects disease severity and disease duration. Higher normalized NBM volume and lower UPDRS III Med OFF led to better cognitive outcomes. Contrary to other studies[7,22], age at surgery and preexisting cognitive deficits in the neuropsychological test set did not have much influence on the cognitive outcome in this explorative analysis. Of course, our cohort is already selected because higher biological age and dementia are exclusion criteria for DBS surgery. Due to the limited sample size, our results need to be validated in larger prospective study samples.

Contrary to our expectations, the classic motor phenotype of PD being differentially associated with cognitive impairment had not much influence on the cognitive outcome in our cohort. This might have several reasons: Subtypes are a currently being discussed[23], may change in the

course of the disease[24] and patients with substantially advanced PD or a diffuse-malignant phenotype[23] are not operated on and are therefore not part of this study.

We also investigated the influence of the heterogenous surgical and anesthesiologic procedures. One year after DBS surgery, the total duration of intubation and consequent general anesthesia ranked fourth in predicting cognition in our data-driven approach. This finding is supported by previous studies that have shown the length and depth of narcosis to have a negative influence on postoperative cognitive outcomes[18]. Moreover, the trajectory of STN electrodes, their distance to the striatum and penetration of the caudate nucleus were found significant cofactor sfor cognitive decline after DBS[25] which were not analyzed in our patients.

A recent autopsy study on 25 postmortem brains of PD-MCI patients by Knox and colleagues, however, found a broad variety of pathological changes including α-synuclein and cholinergic pathology as well as cerebral amyloid angiopathy[26]. Therefore, it could be interesting to look further into other pathologies like white matter lesions and their underlying risk factors and into the size and integrity of other non-cholinergic structures discussed to play a role in cognition in PD like the nucleus accumbens[27] and the pulvinar[28].

Limitations and strengths

The main limitation of this study is its retrospective design with MRI data from different scanners and different cognitive not PD specific screening scores within the cohort. However, preoperative imaging data homogeneity was checked both visually and with SPM12 and thus verified twice to be sufficient for VBM analysis. Regarding the different cognitive scores, the DemTect was only taken if there was no MMSE scores available from the pre- and 1 year postoperative assessment and relative changes were calculated. Of note, Pearson's correlation between normalized NBM volume and relative change in MMSE stays significant after exclusion of the patients with DemTect ($r=0.289$, $p=0.044$*). Other shortcomings are the relatively short study period and the lack of a control group of PD patients without DBS but with other types of surgery as the prevention of misattribution of cognitive decline to DBS therapy is crucial. Nevertheless, the NBM seems to be a simple non-invasive predictor for the cognitive development in presurgical PD patients, especially when combined with other parameters. As a cerebral MRI is part of the clinical routine for ruling out contraindications for electrode implantations and a prerequisite for stereotactic planning, this non-invasive method could help to better stratify the cognitive risk of DBS surgery and/or chronic stimulation.

Conclusion

Our study supports the importance of the NBM volume as a predictor for cognitive development in PD patients undergoing STN-DBS. Nevertheless, we are fully aware of the small amount of variability of the postoperative cognitive outcome explained by NBM size. Therefore, we are currently conducting a prospective study investigating patients with PD that underwent STN-DBS aiming at validating and extending the presented retrospective findings (registered on www.clinicaltrials.gov under the number NCT03982953). Amongst other putative predictors of

cognitive decline, this study comprises a tablet-based neuropsychological test battery that takes into account different cognitive domains and will also take into account possible stimulation effects and lead trajectories. The overarching goal is to improve assessment of individual risk factors of STN-DBS in order to guide patients with PD to the appropriate therapy with optimal success.

Acknowledgements

We thank all patients for their consent to include their clinical and imaging data in this study. CS, DK and JK are fellows of the Clinician Scientist Program funded by the Charité-Universitätsmedizin Berlin and the Berlin Institute of Health. This program was headed by Prof. Duška Dragun to allow physicians to pursue a parallel career in academic research. With great sadness, we have received the news that Prof. Dragun passed away on December 28th 2020. We dedicate this publication to her as a mentor, role model and excellent scientist.

Authors' Roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

D Kübler: 1A-C, 2A-C, 3A
SK Wellmann: 1B-C, 2B
J Kaminski: 1A, 3B
C Skowronek: 1A, 3B
GH Schneider: 1C, 3B
WJ Neumann: 1A, 2C, 3B
K Ritter: 1A-C, 2 A-C, 3A
AA Kühn: 1A, 1B, 2C, 3B

Figure legends

Figure 1: Visualization of the basal forebrain nuclei according to the probabilistic atlas by Zaborszky and colleagues on axial slices. The NBM (Ch4) is shown in green and the surrounding summarized nuclei Ch1-3 in red (Figure 1A). Pearson's correlation between nucleus basalis of Meynert (NBM) volume in relation to the total intracranial volume (TIV) and the percentage of change in the cognitive screening scores before and 1 year after chronic STN-DBS (Figure 1B). When leaving the patients with no cognitive change out of this analysis, the results were still significant (NBM volume: r=0.365, p=0.044*; normalized NBM volume: r=0.462, p=0.009*).

Figure 2: Summary plot (Figure 2A) and beeswarm plot (Figure 2B) of the mean SHAP values for all 11 features included in the model. While Figure 2A shows the global importance of each feature by taking the mean of the absolute SHAP values, Figure 2B shows the SHAP values depending on the feature values. The influence of low (blue) and high (red) feature values on the model output are depicted.

Feature Description: Normalized NBM Volume: Ch4/TIV, UPDRS III Med OFF: disease severity score without dopaminergic medication, Disease Duration: years from symptom onset until DBS, Duration of Intubation: hours of general anesthesia and intubation during STN-DBS electrode and impulse generator implantation, Normalized Ch1-3 Volume: Ch1-3/TIV, LED pre DBS: Levodopa equivalent dose before DBS surgery, Age: at DBS surgery, Duration of Surgery: summed up for both operations, Affected Neuropsychological Domains: number of domains affected in neuropsychological assessment, Sex: biological sex, Motor Type: equivalent, akinetic-rigid or tremor-dominant motor type.

Figure 3: Force plots showing the individual contributions of features in four cases of male patients with good motor improvement from our cohort. MMSE (Mini-Mental State Examination) scores are given on the left for each case (pre- > postoperative). One year after DBS surgery, case 1 showed a very good cognitive improvement and case 2 showed a moderate cognitive improvement. Case 3 showed a slight deterioration in overall cognitive abilities and case 4 showed a marked deterioration in cognition.

Feature Description: Numbers indicate the raw values of Disease Duration: years from symptom onset until DBS, Intubation: hours of general anesthesia and intubation during STN-DBS electrode and impulse generator implantation, NBM Volume: normalized nucleus basalis of Meynert (NBM) volume, LED: Levodopa equivalent dose before DBS surgery, UPDRS: disease severity score (UPDRS III points) without dopaminergic medication, Age: in years at DBS surgery, Ch1-3 Volume: normalized Ch1-3 volume.

Supplementary methods

Machine learning analysis

In order to predict cognitive change after DBS, we applied random forest regression and feature importance was assessed using Shapley Additive exPlanations (SHAP). For further details, please see the supplements. in which subsets of the data were used to build uncorrelated decision trees and then the outcomes of the single decision trees were averaged[29,30]. Here, we used the default values of 100 trees and the RandomForestRegressor function of scikit-learn in python[31] (version 3.0). To avoid overfitting and obtain a realistic estimate of generalizability, we split the data 1000 times randomly into training (80%) and test (20%) data and report averages of the root mean squared error (RMSE). The RMSE indicates the deviation between the actual (i.e., measured) and the predicted cognitive change of the subjects in the test sets. As cognitive change is measured here in %, the RMSE corresponds to the percentage points between actual and predicted cognitive change. Significance was tested with a permutation test. To assess feature importance, SHapley Additive exPlanations (SHAP) were calculated using the TreeExplainer backend of the SHAP library (https://github.com/slundberg/shap). SHAP is a recent game theoretic approach that allows to compute the individual contributions of features in a machine learning model by fairly distributing the outcome of the model (i.e., the prediction score) among the features[32]. The TreeExplainer has recently been shown to provide optimal explanations in several medical machine learning problems[33]. We calculated the SHAP values for each of the models and averaged them for each subject across models. To get global explanations, we additionally averaged the SHAP values across subjects.

References

[1] I. Litvan, J.G. Goldman, A.I. Tröster, B.A. Schmand, D. Weintraub, R.C. Petersen, B. Mollenhauer, C.H. Adler, K. Marder, C.H. Williams- Gray, D. Aarsland, J. Kulisevsky, M.C. Rodriguez- Oroz, D.J. Burn, R.A. Barker, M. Emre, Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines, Movement Disord. 27 (2012) 349–356. https://doi.org/10.1002/mds.24893.

[2] G.M. Halliday, J.B. Leverenz, J.S. Schneider, C.H. Adler, The neurobiological basis of cognitive impairment in Parkinson's disease, Movement Disord. 29 (2014) 634–650. https://doi.org/10.1002/mds.25857.

[3] F.M. Weaver, K. Follett, M. Stern, K. Hur, C. Harris, W.J. Marks, J. Rothlind, O. Sagher, D. Reda, C.S. Moy, R. Pahwa, K. Burchiel, P. Hogarth, E.C. Lai, J.E. Duda, K. Holloway, A. Samii, S. Horn, J. Bronstein, G. Stoner, J. Heemskerk, G.D. Huang, for the C. 468 S. Group, Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease: A Randomized Controlled Trial, Jama. 301 (2009) 63–73. https://doi.org/10.1001/jama.2008.929.

[4] W.M.M. Schuepbach, J. Rau, K. Knudsen, J. Volkmann, P. Krack, L. Timmermann, T.D. Hälbig, H. Hesekamp, S.M. Navarro, N. Meier, D. Falk, M. Mehdorn, S. Paschen, M. Maarouf, M.T. Barbe, G.R. Fink, A. Kupsch, D. Gruber, G.-H. Schneider, E. Seigneuret, A. Kistner, P. Chaynes, F. Ory-Magne, C.B. Courbon, J. Vesper, A. Schnitzler, L. Wojtecki, J.-L. Houeto, B. Bataille, D. Maltête, P. Damier, S. Raoul, F. Sixel-Doering, D. Hellwig, A. Gharabaghi, R. Krüger, M.O. Pinsker, F. Amtage, J.-M. Régis, T. Witjas, S. Thobois, P. Mertens, M. Kloss, A. Hartmann, W.H. Oertel, B. Post, H. Speelman, Y. Agid, C. Schade-Brittinger, G. Deuschl, E.S. Group, Neurostimulation for Parkinson's Disease with Early Motor Complications, New Engl J Medicine. 368 (2013) 610–622. https://doi.org/10.1056/nejmoa1205158.

[5] T. Nimura, K. Nagamatsu, T. Ando, A. Matsumoto, K. Hisanaga, T. Tominaga, An investigation into the effects and prognostic factors of cognitive decline following subthalamic nucleus stimulation in patients with Parkinson's disease, J Clin Neurosci. 44 (2017) 164–168. https://doi.org/10.1016/j.jocn.2017.06.018.

[6] K.A. Mills, K. Donohue, A. Swaminathan, J.-M. Leoutsakos, G. Smith, J. Brandt, Neuropsychological predictors of patient-reported cognitive decline after deep brain stimulation in Parkinson's disease, J Clin Exp Neuropsyc. 41 (2018) 1–10. https://doi.org/10.1080/13803395.2018.1526889.

[7] S. Aybek, A. Gronchi- Perrin, A. Berney, S.C. Chiuvé, J. Villemure, P.R. Burkhard, F.J.G. Vingerhoets, Long- term cognitive profile and incidence of dementia after STN- DBS in Parkinson's disease, Movement Disord. 22 (2007) 974–981. https://doi.org/10.1002/mds.21478.

[8] T.D. Parsons, S.A. Rogers, A.J. Braaten, S.P. Woods, A.I. Tröster, Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis, Lancet Neurology. 5 (2006) 578–588. https://doi.org/10.1016/s1474-4422(06)70475-6.

[9] L. Puy, M. Tir, M. Lefranc, H. Yaïche, O. Godefroy, P. Krystkowiak, Acute Dementia After Deep Brain Stimulation in Parkinson Disease, World Neurosurg. 119 (2018) 63–65. https://doi.org/10.1016/j.wneu.2018.07.197.

[10] A.K.L. Liu, R.C.-C. Chang, R.K.B. Pearce, S.M. Gentleman, Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer's and Parkinson's disease, Acta Neuropathol. 129 (2015) 527–540. https://doi.org/10.1007/s00401-015-1392-5.

[11] M. Nazmuddin, I.H.C.H.M. Philippens, T. van Laar, Electrical stimulation of the nucleus basalis of meynert: a systematic review of preclinical and clinical data, Sci Rep-Uk. 11 (2021) 11751. https://doi.org/10.1038/s41598-021-91391-0.

[12] J. Pasquini, D.J. Brooks, N. Pavese, The Cholinergic Brain in Parkinson's Disease, Mov Disord Clin Pract. 8 (2021) 1012–1026. https://doi.org/10.1002/mdc3.13319.

[13] I. Kilimann, M. Grothe, H. Heinsen, E.J.L. Alho, L. Grinberg, E.A. Jr., G.A.B. dos Santos, R.E. da Silva, A.J. Mitchell, G.B. Frisoni, A.L.W. Bokde, A. Fellgiebel, M. Filippi, H. Hampel, S. Klöppel, S.J. Teipel, Subregional Basal Forebrain Atrophy in Alzheimer's Disease: A Multicenter Study, J Alzheimer's Dis. 40 (2014) 687–700. https://doi.org/10.3233/jad-132345.

[14] H. Hampel, M.-M. Mesulam, A.C. Cuello, M.R. Farlow, E. Giacobini, G.T. Grossberg, A.S. Khachaturian, A. Vergallo, E. Cavedo, P.J. Snyder, Z.S. Khachaturian, The cholinergic system in the pathophysiology and treatment of Alzheimer's disease, Brain. 141 (2018) 1917–1933. https://doi.org/10.1093/brain/awy132.

[15] N.J. Ray, S. Bradburn, C. Murgatroyd, U. Toseeb, P. Mir, G.K. Kountouriotis, S.J. Teipel, M.J. Grothe, In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's disease, Brain. 141 (2018) 165–176. https://doi.org/10.1093/brain/awx310.

[16] J. Schulz, G. Pagano, J.A.F. Bonfante, H. Wilson, M. Politis, Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson's disease, Brain. 141 (2018) 1501–1516. https://doi.org/10.1093/brain/awy072.

[17] L. Zaborszky, L. Hoemke, H. Mohlberg, A. Schleicher, K. Amunts, K. Zilles, Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain, Neuroimage. 42 (2008) 1127–1141. https://doi.org/10.1016/j.neuroimage.2008.05.055.

[18] R. Hou, H. Wang, L. Chen, Y. Qiu, S. Li, POCD in patients receiving total knee replacement under deep vs light anesthesia: A randomized controlled trial, Brain Behav. 8 (2018) e00910. https://doi.org/10.1002/brb3.910.

[19] F. Gargouri, C. Gallea, M. Mongin, N. Pyatigorskaya, R. Valabregue, C. Ewenczyk, M. Sarazin, L. Yahia- Cherif, M. Vidailhet, S. Lehéricy, Multimodal magnetic resonance imaging investigation of basal forebrain damage and cognitive deficits in Parkinson's disease, Movement Disord. 34 (2019) 516–525. https://doi.org/10.1002/mds.27561.

[20] M.J. Barrett, S.A. Sperling, J.C. Blair, C.S. Freeman, J.L. Flanigan, M.E. Smolkin, C.A. Manning, T.J. Druzgal, Lower volume, more impairment: reduced cholinergic basal forebrain grey matter density is associated with impaired cognition in Parkinson disease, J Neurology Neurosurg Psychiatry. 90 (2019) 1251. https://doi.org/10.1136/jnnp-2019-320450.

[21] H. Abboud, D. Floden, N.R. Thompson, G. Genc, S. Oravivattanakul, F. Alsallom, B. Swa, C. Kubu, M. Pandya, M. Gostkowski, S. Cooper, A.G. Machado, H.H. Fernandez, Impact of mild cognitive impairment on outcome following deep brain stimulation surgery for Parkinson's disease, Parkinsonism Relat D. 21 (2015) 249–253. https://doi.org/10.1016/j.parkreldis.2014.12.018.

[22] F. Bove, V. Fraix, F. Cavallieri, E. Schmitt, E. Lhommée, A. Bichon, S. Meoni, P. Pélissier, A. Kistner, E. Chevrier, C. Ardouin, P. Limousin, P. Krack, A.L. Benabid, S. Chabardès, E. Seigneuret, A. Castrioto, E. Moro, Dementia and subthalamic deep brain stimulation in Parkinson disease: A long-term overview, Neurology. 95 (2020) e384–e392. https://doi.org/10.1212/wnl.0000000000009822.

[23] S.-M. Fereshtehnejad, Y. Zeighami, A. Dagher, R.B. Postuma, Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression, Brain. 140 (2017) 1959–1976. https://doi.org/10.1093/brain/awx118.

[24] R. Erro, M. Picillo, S. Scannapieco, S. Cuoco, M.T. Pellecchia, P. Barone, The role of disease duration and severity on novel clinical subtypes of Parkinson disease, Parkinsonism Relat D. 73 (2020) 31–34. https://doi.org/10.1016/j.parkreldis.2020.03.013.

[25] K. Witt, O. Granert, C. Daniels, J. Volkmann, D. Falk, T. van Eimeren, G. Deuschl, Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial, Brain. 136 (2013) 2109–2119. https://doi.org/10.1093/brain/awt151.

[26] M.G. Knox, C.H. Adler, H.A. Shill, E. Driver- Dunckley, S.A. Mehta, C. Belden, E. Zamrini, G. Serrano, M.N. Sabbagh, J.N. Caviness, L.I. Sue, K.J. Davis, B.N. Dugger, T.G. Beach, Neuropathological Findings in Parkinson's Disease With Mild Cognitive Impairment, Movement Disord. 35 (2020) 845–850. https://doi.org/10.1002/mds.27991.

[27] V. Planche, F. Munsch, B. Pereira, E. de Schlichting, T. Vidal, J. Coste, D. Morand, I. de Chazeron, P. Derost, B. Debilly, P.-M. Llorca, J.-J. Lemaire, A. Marques, F. Durif, Anatomical predictors of cognitive decline after subthalamic stimulation in Parkinson's disease, Brain Struct Funct. 223 (2018) 3063–3072. https://doi.org/10.1007/s00429-018-1677-2.

[28] K. Matsuura, M. Maeda, M. Satoh, K. Tabei, T. Araki, M. Umino, H. Kajikawa, N. Nakamura, H. Tomimoto, Low Pulvinar Intensity in Susceptibility-Weighted Imaging May Suggest Cognitive Worsening After Deep Brain Stimulation Therapy in Patients With Parkinson's Disease, Front Neurol. 10 (2019) 1158. https://doi.org/10.3389/fneur.2019.01158.

[29] L. Breiman, Random Forests, Mach Learn. 45 (2001) 5–32. https://doi.org/10.1023/a:1010933404324.

[30] A. Liaw, M. Wiener, Classification and Regression by random Forest, R News 2/3. (2002) 18–22.

[31] A. Abraham, F. Pedregosa, M. Eickenberg, P. Gervais, A. Mueller, J. Kossaifi, A. Gramfort, B. Thirion, G. Varoquaux, Machine learning for neuroimaging with scikit-learn, Front Neuroinform. 8 (2014) 14. https://doi.org/10.3389/fninf.2014.00014.

[32] S. Lundberg, S.-I. Lee, A Unified Approach to Interpreting Model Predictions, Arxiv. (2017).

[33] S.M. Lundberg, G. Erion, H. Chen, A. DeGrave, J.M. Prutkin, B. Nair, R. Katz, J. Himmelfarb, N. Bansal, S.-I. Lee, From local explanations to global understanding with explainable AI for trees, Nat Mach Intell. 2 (2020) 56–67. https://doi.org/10.1038/s42256-019-0138-9.

	pre DBS	1 year post DBS	p
UPDRS I	8.8 ± 6.6	8.2 ± 5.5	0.542
UPDRS II	14.1 ± 7.8	11.0 ± 7.0	0.001**
UPDRS III	Med OFF 44.2 ± 14.4	Med OFF Stim ON 25.0 ± 12.7	< 0.001**
UPDRS III	Med ON 23.1 ± 12.0	Med ON Stim ON 18.3 ± 11.5	0.006**
UPDRS IV	8.8 ± 5.9	4.1 ± 4.5	0.001**
LED	1242 ± 542	512 ± 326	< 0.001**
ADL	17.5 ±13.3	11.9 ± 10.9	< 0.001**
BDI-II	11.4 ± 6.5	9.6 ± 6.1	0.021*
MMSE	29.0 ± 1.2	28.8 ± 1.8	0.247
DemTect	14.3 ± 2.8	15.2 ± 2.5	0.037*

Table 1: Comparison of clinical scores and scales before and 1 year after chronic STN-DBS.

Abbreviations: UPDRS: Unified Parkinson's Disease Rating Scale, Med ON/OFF: with or after washout of indivdual dopaminergic medication, Stim ON/OFF: with STN-DBS switched on and off, LED: Levodopa equivalent dose, ADL: Activities of Daily Living scale, BDI-II: Beck Depression Inventory, MMSE: Mini-Mental State Examination, STN-DBS: bilateral deep brain stimulation in the subthalamic nucleus.

Figure 2

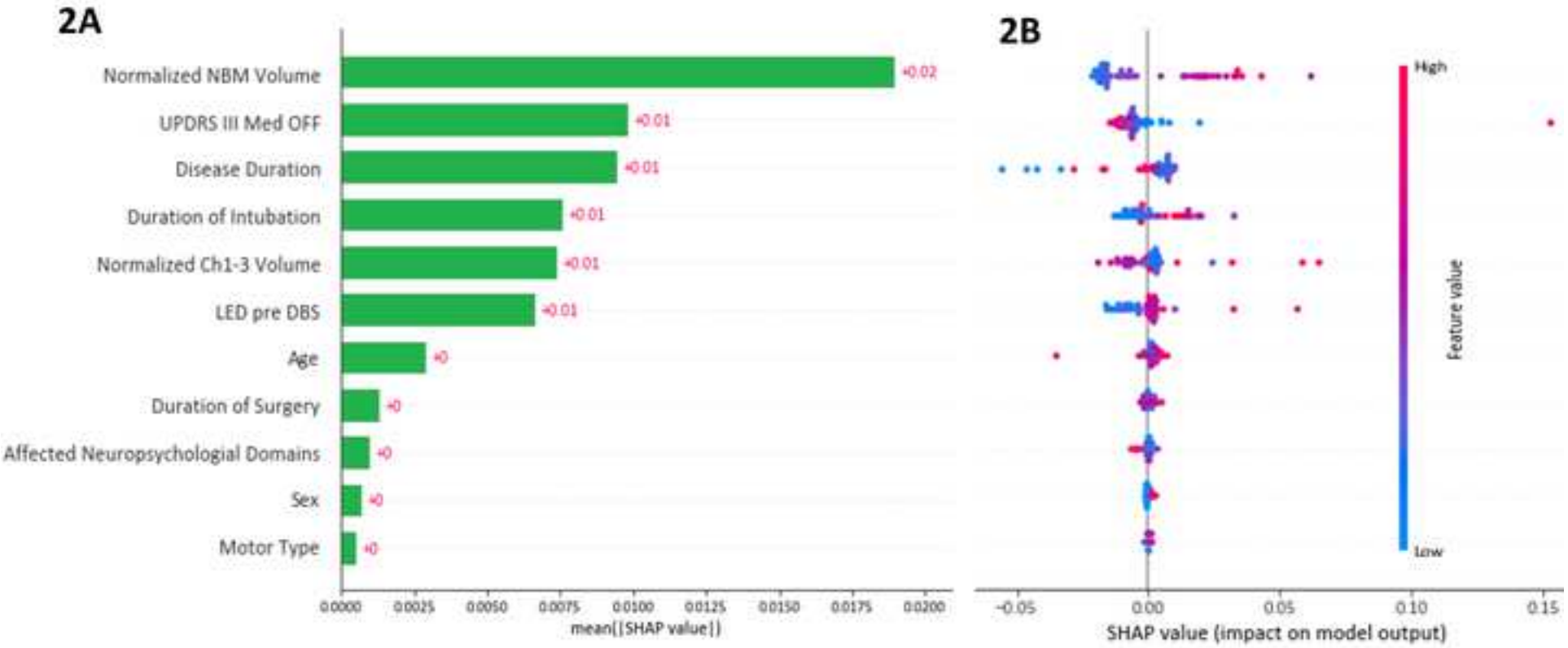

Figure 3

Click here to access/download;Figure(s);Figure_3.tiff