Preoperative Cognitive Profile Predictive of Cognitive Decline after Subthalamic Deep Brain Stimulation in Parkinson's Disease

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Abstract

Cognitive decline represents a severe non-motor symptom of Parkinson's disease (PD) that can significantly reduce benefits of subthalamic deep brain stimulation (STN DBS). Here, we aimed to **describe expected post-surgery cognitive decline and** identify pre-surgery cognitive profile associated with faster post-surgery cognitive decline in STN DBS treated PD patients. A retrospective observational study of 126 PD patients treated by STN DBS combined with oral dopaminergic therapy followed for 3.54 years on average (SD = 2.32) with repeated assessments of cognition was conducted. Pre-surgery cognitive profile was obtained via a comprehensive neuropsychological examination. Data were analyzed using exploratory factor analysis for pre-surgery cognitive profile extraction and Bayesian generalized linear mixed models for description of the longitudinal cognitive outcome. Overall, we observed a mild annual cognitive decline of 0.90 points from a total of 144 points in the Mattis Dementia Rating Scale (95% posterior probability interval (PPI) [-1.19, -0.62]). Pre-surgery executive deficit predicted the rate of post-surgery cognitive decline (b = -0.39, 95% PPI [-0.63, -0.15]). The predictive utility of pre-surgery executive deficit resulted from summing small effects of several single test scores. **Exploratory analysis of electrode localisation did not yield any statistically clear results. Overall, our data imply that mild average annual post-surgery cognitive decline in PD patients treated with STN DBS with high inter-individual variability. However, patients with worse long-term cognitive prognosis can be identified via pre-surgery examination of executive functions.**

Keywords: Parkinson's disease, deep brain stimulation, cognition, longitudinal, latent variable analysis

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Introduction

Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) is an advanced symptomatic treatment of Parkinson's disease (PD) that can successfully reduce motor symptoms and improve patients' quality of life (Armstrong & Okun, 2020; Bratsos et al., 2018). On the other hand, prior research revealed considerable heterogeneity in cognitive outcomes after STN DBS with a small to moderate post-surgery decline in verbal fluency and equivocal results for other cognitive domains (Combs et al., 2015; Mehanna et al., 2017; Parsons et al., 2006). The ability to predict which patients are likely to develop post-surgery cognitive decline can thus prove useful for patient selection and for guiding post-surgery patient monitoring. In this article, we aim to describe **annual rate of long-term post-surgery cognitive decline after STN DBS in PD as well as** pre-surgery cognitive profile extractable from clinically available neuropsychological evaluation that **predicts faster post-surgery decline**.

When describing longitudinal post-surgery cognitive decline, the majority of prior studies employed pre-test/post-design with change scores as their dependent variable (Gruber et al., 2019; Kim et al., 2014) or estimated dementia-free survival time (Barbosa et al., 2024; Bove et al., 2020; Kishore et al., 2019). When conversion to dementia is an outcome, studies do not estimate annual rate of post-surgery decline but the time it takes to reach clinically salient cognitive deficit. On the other hand change scores have a drawback of confounding true change with measurement error (Singer & Willett, 2003). Furthermore, the focus on change scores allows researchers to estimate group-level post-surgery changes describing their sample but ignores patient-level variability which is necessary to generalize findings beyond the sample (Yarkoni, 2020). In this study, we leverage the fact that our data set includes three or more observations in large enough number of patients to estimate both group-level post-surgery cognitive

decline to describe our sample as well as patient-level variability to provide predictions for other similar samples.

With regards to predicting post-surgery cognitive decline from patients' pre-surgery cognitive profile, studies addressing th**is** task can be broadly divided to two groups, randomized controlled trials (RCT*s*) and long-term observational studies. In a typical RCT, patients are randomized to treatment and placebo groups and outcomes are compared in a full factorial design (**representing the estimand of interest** as interactions between group and time of assessment) (Schüpbach et al., 2007). Courtesy of their experimental control RCTs allow for causal inference and are well suited for providing guidelines for patient selection. However, even though RCTs are regarded as a gold standard for causal inference, it is ethically unacceptable to deny DBS treatment for PD patients for longer time intervals than necessary. Long-term (i.e., more than three years after surgery) outcomes can thus be best described by observational studies. While observational studies usually do not allow for causal inference and are not well suited for guiding patient selection due to a lack of proper control group and resulting collider bias (Cinelli et al., 2022), they are well suited for description of patients' long-term outcomes. Longitudinal observational studies can serve as a basis for selecting high-risk STN DBS treated patients that would benefit from increased monitoring.

Previous longitudinal observational studies reported that PD patients treated with STN DBS showing pre-surgery deficit in executive functions **or poorer memory** are at risk of faster post-surgery cognitive decline or developing dementia (Bove et al., 2020; Gruber et al., 2019; Jahanshahi et al., 2022; Kim et al., 2014; Kishore et al., 2019; Smeding et al., 2009). However, previous studies aimed at identifying any possible pre-surgery predictors of post-surgery cognitive decline accepting high false positive error rates **and effect sizes inflation** in the process. In this study, we complement prior findings by identifying a sparse solution to the problem of identifying pre-surgery cognitive profile that is predictive of long-term post-surgery cognitive decline in naturalistic clinical settings. In other words, we aim to describe a minimal significant

pre-surgery cognitive profile that predicts higher rate of post-surgery cognitive decline in a sample derived from everyday clinical practice.

In a typical observational study aiming to determine pre-surgery risk factors of post-surgery cognitive decline the authors employ the following two-step procedure. In the first step, a series of separate univariate analyses for each potential predictor is conducted to pre-select variables for further analysis. In the second step, predictors that achieved an arbitrary threshold (e.g., $p < 0.05$) are used to predict the cognitive decline in a subsequent multiple regression model (Bove et al., 2020; Gruber et al., 2019; Kim et al., 2014; Smeding et al., 2009). This procedure **was named "univariable screening" in biomedical statistics literature and was shown to systematically overestimate effect sizes (Zwet, 2019; Zwet & Cator, 2021). In this article, we show that it** can **also** lead to false positive error rates that are magnitudes higher than the expected nominal five percent.

One way to overcome shortcomings **of univariable screening is to use partially pooling estimators of the effects associated with each predictor. This can be achieved via regularizition of multiple regression coefficients (Zwet, 2019). In this, regularizing technique of choice is** the Bayesian Lasso regression, a method developed for identifying small amount of significant predictors out of a larger pool of possible predictors such as results from a comprehensive neuropsychological battery (Park & Casella, 2008).

Another way to achieve sparsity in prediction of post-surgery cognitive decline is to reduce the number of potential predictors. In the context of neuropsychological assessment this can be accomplished straightforwardly via a latent variable approach such as factor analysis that statistically extracts commonalities across several cognitive tasks. Added benefit of employing such a procedure to pre-surgery predictors is that latent variable approaches can reduce the impact of the task impurity problem – the observation that any cognitive task involves several cognitive functions at once (Burgess, 2014; Whitney & Hinson, 2010).

Overall, in this study we aimed to **describe annual post-surgery cognitive**

decline on group- and patient-level as well as derive a sparse solution to the task of identifying pre-surgery cognitive profile predictive of long-term post-surgery cognitive decline in STN DBS treated PD patients. In other words, instead of identifying any pre-surgery cognitive variables that can be predictive of post-surgery decline, we aimed to identify only the most likely predictive ones. To this end, we asked the following research questions: *RQ1)* What is the size of expected long-term rate of cognitive decline after STN DBS in PD patients? *RQ2)* What is the pre-surgery cognitive profile that is predictive of long-term post-surgery cognitive decline in STN DBS treated PD? To answer these questions, we analyzed data of retrospectively sampled longitudinally followed STN DBS treated PD patients with a single pre-surgery comprehensive neuropsychological assessment and up to five post-surgery cognitive screening assessments.

Materials and methods

Participants

The data of all patients diagnosed with idiopathic PD following United Kingdom Parkinson's Disease Society Brain Bank Criteria (Hughes et al., 1992) that underwent cognitive evaluation for STN DBS treatment at General University Hospital in Prague between years 2000 and 2020 were retrospectively gathered from clinical records and considered for inclusion in the study. **Patients were selected for DBS treatment via selection criteria mirroring the CAPSIT-protocol (Defer et al., 1999), consequently p**atients with atypical parkinsonian syndromes, dementia, depression at the time of pre-surgery assessment (according to an independent psychiatric evaluation), recurrent psychotic conditions or a gait disorder despite optimal dopaminergic therapy during pre-surgery assessment were not implanted and were thus not included in the study. Furthermore, only patients who underwent pre-surgery and at least one post-surgery assessment were included. All included patients were treated via continuous bilateral STN DBS in conjunction with dopaminergic therapy. Bilateral STN DBS implantation was performed as previously described (Jech et al., 2006; Jech et al., 2012; Ugosik et al., 2011). All patients provided signed informed consent and the

study was approved by the General University Hospital Ethics Committee in Prague, Czech Republic.

Assessments

All patients underwent a comprehensive pre-surgery assessment including neuropsychological and neurological examinations. The patients were followed up post-surgery with similar examination protocol at varying time intervals according to their options. Post-surgery, patients were first contacted one year after the surgery and every two years afterwards. The pre-surgery assessment was performed with the usual dopaminergic therapy (ON medication). In the post-surgery assessment, patients were examined in the ON medication condition and STN DBS ON with optimal stimulation parameters.

Pre-surgery neuropsychological measures

The neuropsychological assessment was arranged analogously to the standard International Parkinson and Movement Disorder Society (MDS) neuropsychological battery at Level II for mild cognitive impairment in Parkinson's disease (PD-MCI) (Bezdicek, Sulc, et al., 2017; Litvan et al., 2012). The battery consisted of 10 tests in 5 cognitive domains: (i) attention: Trail Making Test, part A (TMT-A) (Bezdicek et al., 2012; Bezdicek, Stepankova, et al., 2017; Partington & Leiter, 1949) and dot color naming condition from Prague Stroop Test (PST-D) (Bezdicek, Lukavsky, et al., 2015) for sustained visual attention; (ii) executive functions: Trail Making Test, part B (TMT-B) (Bezdicek et al., 2012; Bezdicek, Stepankova, et al., 2017; Partington & Leiter, 1949) for set shifting, and Tower of London task (TOL) (Michalec et al., 2017; Shallice, 1982) for planning; (iii) language: Similarities (Sim.) from Wechsler Adult Intelligence Scale, third revision (WAIS-III) (Wechsler, 2010) for conceptualization, and category verbal fluency test (CFT, category Animals) (Nikolai et al., 2015) for speeded word production; (iv) working memory: Digit Span backward (DS-B) from WAIS-III (Wechsler, 2010) and Spatial Span backward (SS-B) from Wechsler Memory Scale, third edition (WMS-III) (Wechsler, 2011) for auditory and spatial working memory respectively; and (v) memory: Rey Auditory Verbal Learning Test delayed recall

(RAVLT-DR) (Bezdicek et al., 2014; Frydrychová et al., 2018) for explicit verbal learning and memory, and WMS-III Family Pictures delayed recall (FP-DR) for visuo-spatial memory (Wechsler, 2011). Furthermore, we administered the following tests beyond the battery: Prague Stroop Test, naming color of neutral words (PST-W) and interference condition (i.e., naming color of contrasting color words, PST-C) for sensitivity to interference (Bezdicek, Lukavsky, et al., 2015), Controlled Oral Word Association Test (COWAT, letters K + P) (Nikolai et al., 2015) for mental flexibility, and WMS-III letter-number sequencing (LNS) (Wechsler, 2011) for working memory. Finally, anxiety was assessed with the State-Trait Anxiety Inventory for the state (STAI-X1) and trait (STAI-X2) anxiety (Spielberger et al., 1983).

Longitudinal neuropsychological measures

Patients' longitudinal cognitive state was assessed pre-surgery and post-surgery with MDS battery at Level I using Mattis Dementia Rating Scale, second edition (DRS-2) (Bezdicek, Michalec, et al., 2015; Jurica et al., 2001). DRS-2 is a routinely employed cognitive screening measure in PD that has been shown to have acceptable discriminative performance for PD-MCI in Czech population with both sensitivity estimated to be around 0.8 (Bezdicek, Michalec, et al., 2015; Mazancova et al., 2020). Furthermore, subjective depressive symptoms were assessed with Beck Depression Inventory, second edition (BDI-II) (Beck et al., 1996; Ciharova et al., 2020) at each assessment. BDI-II was not used for pre-surgery exclusion due to depression which was instead ascertained by an independent neuropsychiatric evaluation.

Neurological examination

Patients' motor state was assessed with part three of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) in medication ON and medication OFF state during the pre-surgery levodopa test. Scores of patients who underwent the older version of the Unified Parkinson's Disease Rating Scale (UPDRS III) were converted to the MDS-UPDRS III scale using the method described by Hentz et al. (2015). The levodopa equivalent daily dose (LEDD) was calculated at each assessment time-point according to Tomlinson et al. (2010).

Theoretical and empirical estimands

Following the framework of Lundberg et al. (2021), in this section we link our research questions to explicit targets of inference (i.e., the theoretical estimands) and to observable data (i.e., the empirical estimads). Within this framework, the theoretical estimand consists from two components, a unit-specific quantity and the target population. Regarding our *RQ1* , the patient-specific quantity of interest was the difference between expected post-surgery cognitive performance compared to expected cognitive performance one year before. We aimed to describe this quantity at two levels: (i) the current sample and (ii) the population of patients selected for DBS treatment via the CAPSIT-protocol criteria. The patient-specific quantity for *RQ2* was the difference between expected annual post-surgery cognitive decline per unit change in pre-surgery performance in a single latent cognitive factor/test score with other factor/test scores are being held constant. This quantity was described for sample only. Empirical estimands consisted of the same quantities as theoretical estimand conditional on patient being selected to the study (based on geographical and exclusion criteria described above).

Statistical analysies

Deriving pre-surgery cognitive profile

Latent cognitive factors were extracted from the data via an exploratory factor analysis (EFA) with varimax rotation using ordinary least squares to find the minimum residual solution (Harman & Jones, 1966). We opted for the orthogonal varimax rotation because: (i) extracting orthogonal factors can be statistically advantageous in later steps of our analysis due to reducing multicollinearity, and (ii) in the framework of PD-MCI, it is considered desirable to describe patients' cognitive profile by factors or tests that are independent of each other (Litvan et al., 2012).

All pre-surgery cognitive tests listed above were entered into EFA as input variables (see Supplementary Materials for the exact processing pipeline). Missing

observations were multiply imputed using a parametric bootstrap via the "missMDA" R package to create one hundred imputed data sets We then computed EFA with three up to eight factors via the "psych" R package (Josse & Husson, 2016; R Core Team, 2022; Revelle, 2022) using each imputed data set. Within each imputed data set, factor scores for each patient were calculated using the regression method (Thomson, 1951).

We based the number of extracted factors on a combination of the root-mean-square error approximation (RMSEA), Tucker-Lewis Index (TLI), and consistency of each factor model across imputations. TLI is a measure of a goodness-of-fit such that higher values of TLI imply better fit and values exceeding 0.90 are considered to indicate a good model fit. On the other hand, RMSEA is a measure of badness-of-fit such that lower values imply better fit with values less than 0.08 indicating an adequate model fit (Browne & Cudeck, 1992). A model was considered consistent if the model identified similar factors across imputed data sets.

Describing and predicting post-surgery cognitive decline

Longitudinal data were analyzed using Bayesian generalized linear mixed models (GLMMs). GLMMs overcome the issue **of confounding measurement error with true change described above** by estimating both group-level (i.e., "fixed effect") as well as patient-level (i.e., "random effect") parameters. Furthermore, modelling patient-level effects results in partial pooling of parameter estimates (shifting parameter estimates towards each other), which reduces the influence of outliers and facilitates reliable group-level inference (Gelman et al., 2012; Tuerlinckx et al., 2006).

To describe the rate of post-surgery cognitive decline, we estimated a GLMM with longitudinal DRS-2 performance as an outcome predicted by the time after surgery on the group-level and correlated patient-specific intercepts and slopes on the patient-level. Since the group-level slope of this model represents the expected rate of cognitive decline after STN DBS, it constituted the **statistical estimate of the first version of the** empirical estimand for *RQ1* **(i.e., the expected annual cognitive decline in the sample). To arrive at the statistical estimate of the second version of the empirical estimand for *RQ1* (i.e., the expected annual**

cognitive decline in a population of patients selected for surgery using CAPSIT-protocol criteria) we used the model to predict expected post-surgery cognitive decline at one year intervals using both group- and patient-level parameters. To evaluate suitability of the linear model we compared it to an equivalent non-linear model that estimated post-surgery cognitive trajectory via tensor product smooths (Wood et al., 2012). Both models were fitted using non-informative improper flat priors to ensure that their parameters are informed primarily by the data.

Two GLMMs were estimated to evaluate predictive utility of pre-surgery cognitive profile. The longitudinal DRS-2 performance was predicted on a group-level by post-surgery time slopes varying by either patients' pre-surgery cognitive tests' scores (the "test scores" model) or patients' pre-surgery latent cognitive factors' scores extracted from the EFA reported above (the "factor scores" model). Both models further included correlated patient-level intercepts and slopes. To check robustness of our findings we compared the results to estimates of GLMMs that also included group-level effects of age, LEDD and BDI-II (and their interaction with the time after surgery) to adjust for potentially confounding effects of aging, dopaminergic medication, and depressive symptoms.

Since previous long-term studies demonstrated that a subset of PD patients treated with STN DBS can develop dementia which may lead to heavy tails in the data distribution of cognitive test scores, we modelled the data distribution with Student-t instead of Gaussian likelihood. Furthermore, because the outcome DRS-2 has a maximum of 144 points which is achieved by a large proportion of healthy people (Bezdicek, Michalec, et al., 2015), we used the right-censored version of Student-t to account for the ceiling effect. Models' likelihoods had following specification:

$$P(DRS_i = DRS_{max}) = 1 - T(\vartheta, \mu_i, \sigma), for DRS_i \in N_{max}, N_{max} = \{i : drs_i = drs_{max}\}$$

$$DRS_i \sim\ t(\vartheta, \mu_i, \sigma), for DRS_i \in N_1, N_1 = \{i : drs_i < drs_{max}\}$$

$$\mu_i = \alpha + \delta_{time} time_i + \sum_{j=1}^{m} (\beta_{predictor[j]} predictor_{[j]i} + \delta_{predictor[j]} time_i predictor_{[j]i}) + \bar{\alpha}_{id[i]} + \bar{\delta}_{id[i]} time_i$$

$i = 1 \ldots n$, where n is the total number of assessments across all patients, m is the total number of pre-surgery predictors, DRS_{max} is the maximal attainable score in DRS-2 (i.e., a raw score of 144), $T()$ is the Student-t cumulative distribution function, $t()$ is the Student-t probability density function, $time_i$ is the time from surgery at assessment i, $predictor_{[j]i}$ is the pre-surgery cognitive score in the predictor (i.e., either a test or latent factor) j of the patient evaluated at assessment i, and the remaining terms denote model parameters. E**mpirical e**stimands relating to $RQ2$ comprised of the two sets of $\delta_{predictor[j]}$ representing the expected prognostic value of single pre-surgery cognitive tests and latent cognitive factors.

We specified equivalent prior distributions for model parameters of both the "test scores" and the "factor scores" models. We used the Bayesian Lasso priors for all group-level parameters barring the intercept. This prior is the Bayesian equivalent of the Lasso method for performing variable selection and allows for fitting models with a large number of potentially collinear predictors All remaining parameters were given weakly informative priors to ensure that models' estimates fall within the range of measurable values of the outcome (see https://github.com/josefmana/dbs_cogPRED for the R and Stan code).

Exploratory analysis of electrode localisation association with cognitive decline

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Model description and statistical testing

Effects were described by medians and 95% highest density posterior probability intervals (PPIs) of corresponding model parameters. A 95% PPI can be interpreted such that a given parameter lies within this interval with 95% probability. Models were compared via the expected log pointwise predictive density (ELPD) computed via the leave-one-out cross-validation (LOO-CV) as approximated by the Pareto-smoothed importance sampling (PSIS) (Vehtari et al., 2015). The ELPD difference ($ELPD_{dif}$)

and its 95% frequentist confidence interval (CI) were used to decide whether predictive performance of compared models statistically significantly differs (i.e., the 95% CI excludes zero). To identify influential observations, we calculated a Pareto-k diagnostic and looked for observations with Pareto-k > 0.7 which can be considered problematic (Bürkner et al., 2020; Vehtari et al., 2015).

Evaluating false positive error rates

To validate the assumption that our analysis provides lower false positive rates than the commonly used two-step procedure we conducted series of simulations with a data set structure equivalent to that observed in our data. Patients' outcome was generated as a normally distributed random variable with unit standard deviation and mean depending on average annual rate of cognitive decline and patient-specific random deviations. Moreover, for each patient we generated a set of potential predictors including either seven independent variables, twenty-three independent variables or twenty-three covaried variables representing our analysis of the predictive utility of seven latent cognitive factors and twenty-three observed cognitive test scores respectively. Covariance structure in the case of covaried predictors was based on the structure of the battery described above with predictors that represented test measures belonging to the same superordinate task having Pearson's correlation of 0.7 (thus sharing approximately half of the variance) and zero otherwise (see Figure S5 in Supplementary materials). The simulations were set-up such that there was no effect of any predictor on the outcome. Subsequently, we generated one hundred data sets which were then fitted via the two-step procedure and Bayesian Lasso. For each procedure, the number of statistically significant interactions between time and any of the predictors were recorded to estimate the amount of false positive errors these procedures produce under the null hypothesis.

Transparency and openness

All GLMMs were fitted using via Stan's (version 2.21.0) build-in Hamiltonian Monte Carlo sampler accessed via R version 4.2.0 using package "brms" (Bürkner, 2017; R Core Team, 2022; Stan Development Team, 2020). Four parallel chains were run each

for 2,500 iterations for each GLMM. The first 500 iterations served as a warm-up and were discarded. Convergence was checked numerically by inspection of the Rs and visually by inspection of trace plots. We used R packages "tidyverse" and "dplyr" for data operations, "tidybayes" for operation with model posteriors, and "DiagrammeR, "ggplot2" and "patchwork" for plotting (Iannone, 2022; Pedersen, 2020; Wickham, 2016). This study's design and its analysis were not pre-registered. The data are not publicly available due to privacy or ethical restrictions. The computer code used in our data analysis as well as synthetic data and replicable code for simulations to estimate false positive error rates can be accessed at https://github.com/josefmana/dbs_longCOG.

Results

Characterizing the sample

A total of 200 patients with PD who underwent cognitive evaluation for STN DBS between 2000 and 2020 were identified by a retrospective search of local database in General University Hospital in Prague and a total of 126 patients met inclusion criteria (see Figure 1). All included patients were Caucasians and were speaking Czech as their primary language. Baseline demographic and clinical characteristics as well as stimulation parameters of the sample are presented in Table 1 and baseline cognitive characteristics are presented in Table 2. Mean duration of a follow-up after the surgery was 3.54 years (SD = 2.32, median = 3.07, range = 0.72–11.38) with a median number of 3 assessments per patient (range = 2–6) (see also Figure 2).

Table 1

Clinical characteristics of the sample of included patients

	N	Md	Min-Max	M	SD
Baseline characteristics					
Age at surgery (years)	126	58	40-76	57.25	7.96
Education (years)	117	13	10-23	14.26	2.91
Sex (males)	83 (66 %)	-	-	-	-
Disease duration at surgery (years)	125	11	4-30	11.67	4.05
LEDD (mg)	114	1614	400-4138	1696.88	672.33
Levodopa test (% response)	93	54	20-81	52.64	12.81
MDS-UPDRS III (ON medication)	105	21	7-46	21.78	7.57
MDS-UPDRS III (OFF medication)	100	45	24-81	45.79	10.93
Stimulation parameters[1]					
Current right (mA)	67	2.1	0.6-4.3	2.14	0.71
Current left (mA)	67	2.3	1.0-3.9	2.35	0.68
Voltage right (V)	59	3.0	1.4-5.3	3.00	0.65
Voltage left (V)	59	2.9	0.5-5.7	2.87	0.74
Pulse duration right (ţs)	126	60.0	52.0-120.0	73.98	17.14
Pulse duration left (ţs)	126	60.0	30.0-120.0	71.57	16.15
Frequency right (Hz)	126	130.0	60.0-210.0	128.42	12.44
Frequency left (Hz)	126	130.0	60.0-160.0	127.89	11.14

[1]Each measurement of each electrode considered independently. For stimulation parameters, column N indicate number of patients with current/voltage mode of stimulation. N: number of observations; Md: median; M: mean; SD: standard deviation; MDS-UPDRS III: Movement Disorder Society Unified Parkinsons Disease Rating Scale, motor part; LEDD: levodopa equivalent daily dose; Levodopa test: a percentage change of the MDS-UPDRS III score from medication OFF to medication ON state during the levodopa test as described in the main text; V: Volts; mA: milliampere; s: microseconds; Hz: Hertz.

Table 2

Pre-surgery neuropsychological measures of included patients

Test	N	Md	Min-Max	M	SD
DRS-2 (range 0-144)	126	141	129-144	139.77	3.68
BDI-II (range 0-63)	122	8	0-28	9.28	5.95
STAI-X1 (range 20-80)	104	37	23-63	38.27	8.66
STAI-X2 (range 20-80)	104	39	22-62	39.52	8.11
TMT-A (secs)	125	41	18-122	43.15	15.85
TMT-B (secs)	124	102	39-334	119.01	54.96
DS-F (range 0-16)	113	8	5-16	8.94	2.02
DS-B (range 0-14)	113	6	2-11	6.21	1.80
LNS (range 0-21)	97	8	2-13	7.85	2.46
SS-F (range 0-16)	110	8	4-14	7.54	1.74
SS-B (range 0-16)	110	7	2-11	6.97	1.69
TOL (range 0-108)	118	78	46-90	74.93	9.81
PST-D (secs)	124	13	8-20	13.09	2.37
PST-W (secs)	124	15	10-25	15.72	2.97
PST-C (secs)	124	28	14-57	29.35	9.15
COWAT (total words)	125	32	12-57	32.35	9.05
CFT (words/min.)	89	22	3-39	22.55	7.10
Sim. (range 0-28)	94	22	8-28	21.61	4.35
RAVLT-IR (range 0-75)	108	44	20-64	43.80	8.39
RAVLT-B (range 0-15)	108	5	0-8	4.71	1.45
RAVLT-DR (range 0-15)	108	8	3-14	8.37	2.49
RAVLT-Rec50 (range 0-50)	105	46	33-50	45.10	3.49
RAVLT-Rec15 (range (0-15)	107	14	9-15	13.32	1.54
FP-IR (range 0-64)	74	32	15-55	32.04	10.21
FP-DR (range 0-64)	74	32	13-55	31.91	9.97

N: number of observations; Md: median; M: mean; SD: standard deviation; DRS-2: Dementia Rating Scale, second edition; BDI-II: Beck Depression Rating Scale, second edition; STAI-X1: State-Trait Anxiety Inventory, the state version; STAI-X2: State-Trait Anxiety Inventory, the trait version; TMT-A: Trail Making Test, part A; TMT-B: Trail Making Test, part B; DS-F: Digit Span forward; DS-B: Digit Span backward; LNS: letter-number sequencing; SS-F: Spatial Span forward; SS-B: Spatial Span backward; TOL: Tower of London task; PST-D: Prague Stroop Test, dot color naming; PST-W: Prague Stroop Test, word color naming; PST-C: Prague Stroop Test, interference condition; COWAT: Controlled Oral Word Association Test; CFT: category fluency test; Sim.: Similarities; RAVLT-IR: Rey Auditory Verbal Learning Test, immediate recall; RAVLT-B: Rey Auditory Verbal Learning Test, recall of the interference set; RAVLT-DR: Rey Auditory Verbal Learning Test, delayed recall; RAVLT- Rec50: Rey Auditory Verbal Learning Test, delayed recognition from 50 items (15 correct answers + 35 distractors); RAVLT-Rec15: Rey Auditory Verbal Learning Test, delayed recognition, number of correctly identified from 15 items; FP-IR: Family Pictures, immediate recall; FP-DR: Family Pictures, delayed recall; Secs: seconds; Total words: word count in two minutes (one minute per each letter P and K); words/min.: word count in one minute time limit.

Pre-surgery cognitive profile

Detailed summaries of the fit statistics of all EFA models are presented in the Supplementary material (see Table S1 and Figure S1). Most importantly, raising the number of factors from six to seven resulted in a clear improvement. Out of the one hundred imputed data sets, the six-factor model showed good fit according to RMSEA in 96 cases and it showed good fit according to the TLI in 76 cases. On the other hand, the seven-factor model showed good fit according to RMSEA in 99 cases and good fit according to TLI in 97 cases. Moreover, the seven-factor model was more consistent across imputations. Finally, while the eight-factor resulted in the best fit statistics, factors identified by this model were often substantially loaded on by only a single cognitive test score (with a factor loading above 0.3) which impedes theoretical interpretation of such factors. Consequently, the seven-factor model was retained for subsequent analyses. On average, the seven factors accounted for a total of 54.8 % of variance (SD = 0.8 %) and corresponded to seven cognitive functions: 1) executive functions/attention (EF/Att.) was loaded on primarily by PST tasks, TMT tasks, verbal fluency tests and TOL, 2) episodic memory (EM) was loaded on primarily by indexes of RAVLT except for the recall of interference list (RAVLT-B), 3) verbal working memory (VWM) was loaded on primarily by Digit Span tasks, LNS and Similarities, 4) visuospatial memory (VM) was loaded on primarily by indexes of the Family Pictures test, 5) set shifting (SS) was loaded on primarily by TMT tasks and RAVLT-B, 6) anxiety (An.) was loaded on primarily by STAI, and 7) spatial working memory (SWM) was loaded on primarily by Spatial Span tasks (see Table 3).

Table 3

Summary of factor loadings

	EF/Att.	EM	VWM	VM	SS	An.
TMT-A	-0.26 (0.10)	0.05 (0.03)	0.09 (0.08)	-0.16 (0.11)	-0.38 (0.28)	-0.08 (0.05)
TMT-B	-0.30 (0.09)	-0.08 (0.04)	-0.31 (0.10)	-0.12 (0.11)	-0.53 (0.20)	-0.02 (0.05)
DS-F	0.05 (0.04)	-0.01 (0.03)	0.67 (0.09)	-0.04 (0.05)	-0.02 (0.09)	-0.08 (0.03)
DS-B	0.27 (0.05)	0.12 (0.03)	0.63 (0.07)	-0.05 (0.07)	0.05 (0.08)	0.08 (0.03)
LNS	0.19 (0.06)	0.06 (0.04)	0.49 (0.10)	0.14 (0.10)	0.20 (0.10)	-0.21 (0.09)
SS-F	0.05 (0.04)	0.06 (0.03)	0.19 (0.09)	0.10 (0.14)	0.03 (0.14)	-0.12 (0.06)
SS-B	0.04 (0.04)	-0.06 (0.04)	0.18 (0.09)	0.32 (0.12)	0.13 (0.09)	-0.26 (0.07)
TOL	0.38 (0.07)	0.02 (0.04)	0.07 (0.06)	0.14 (0.08)	0.25 (0.22)	0.06 (0.05)
PST-D	-0.76 (0.04)	-0.01 (0.03)	-0.11 (0.05)	-0.06 (0.05)	-0.19 (0.09)	-0.02 (0.03)
PST-W	-0.83 (0.04)	-0.05 (0.03)	-0.30 (0.05)	-0.14 (0.05)	-0.06 (0.09)	0.01 (0.04)
PST-C	-0.52 (0.06)	-0.06 (0.03)	-0.27 (0.05)	-0.14 (0.07)	-0.18 (0.15)	-0.01 (0.04)
COWAT	0.43 (0.06)	0.24 (0.04)	0.12 (0.04)	0.10 (0.09)	0.14 (0.09)	0.04 (0.05)
CFT	0.37 (0.10)	0.24 (0.05)	-0.05 (0.09)	0.30 (0.09)	0.28 (0.13)	-0.12 (0.06)
Sim.	0.14 (0.05)	0.10 (0.04)	0.48 (0.08)	0.04 (0.08)	0.16 (0.12)	-0.09 (0.07)
RAVLT-IR	0.26 (0.05)	0.79 (0.04)	0.09 (0.06)	0.03 (0.07)	0.13 (0.07)	0.05 (0.04)
RAVLT-B	0.15 (0.05)	0.18 (0.04)	0.28 (0.08)	0.13 (0.08)	0.38 (0.26)	-0.03 (0.05)
RAVLT-DR	0.05 (0.04)	0.74 (0.03)	-0.02 (0.04)	0.07 (0.05)	0.04 (0.06)	0.12 (0.03)
RAVLT-Rec50	0.07 (0.04)	0.68 (0.03)	0.15 (0.05)	0.11 (0.06)	-0.04 (0.07)	-0.02 (0.03)
RAVLT-Rec15	-0.11 (0.04)	0.48 (0.04)	0.04 (0.05)	0.24 (0.09)	0.02 (0.06)	-0.04 (0.05)
FP-IR	0.22 (0.09)	0.30 (0.08)	-0.01 (0.09)	0.70 (0.14)	0.13 (0.08)	-0.13 (0.08)
FP-DR	0.24 (0.07)	0.26 (0.08)	-0.01 (0.08)	0.72 (0.13)	0.14 (0.07)	-0.13 (0.08)
STAI-X1	0.00 (0.03)	-0.05 (0.03)	-0.09 (0.05)	-0.05 (0.06)	-0.03 (0.04)	0.79 (0.13)
STAI-X2	0.05 (0.03)	0.14 (0.04)	-0.04 (0.04)	-0.12 (0.07)	0.06 (0.05)	0.69 (0.10)
Proportion Var	0.11 (0.02)	0.10 (0.01)	0.08 (0.01)	0.07 (0.01)	0.06 (0.02)	0.06 (0.01)
Cumulative Var	0.11 (0.02)	0.21 (0.02)	0.30 (0.02)	0.37 (0.02)	0.43 (0.02)	0.49 (0.02)

Values represent mean (SD) across one hundred imputations. Factor loadings used for interpretation (|loading| $>$ 0.30) are printed in bold. TMT-A: Trail Making Test, part A; TMT-B: Trail Making Test, part B; DS-F: Digit Span forward; DS-B: Digit Span backward; LNS: letter-number sequencing; SS-F: Spatial Span forward; SS-B: Spatial Span backward; TOL: Tower of London task; PST-D: Prague Stroop Test, dot color naming; PST-W: Prague Stroop Test, word color naming; PST-C: Prague Stroop Test, interference condition; COWAT: Controlled Oral Word Association Test; CFT: category fluency test; Sim.: Similarities; RAVLT-IR: Rey Auditory Verbal Learning Test, immediate recall; RAVLT-B: Rey Auditory Verbal Learning Test, recall of the interference set; RAVLT-DR: Rey Auditory Verbal Learning Test, delayed recall; RAVLT-Rec50: Rey Auditory Verbal Learning Test, delayed recognition from 50 items (15 correct answers + 35 distractors); RAVLT-Rec15: Rey Auditory Verbal Learning Test, delayed recognition, number of correctly identified from 15 items; FP-IR: Family Pictures, immediate recall; FP- DR: Family Pictures, delayed recall; STAI-X1: State-Trait Anxiety Inventory, the state version; STAI- X2: State-Trait Anxiety Inventory, the trait version; Secs: seconds; Total words: word count in two minutes (one minute per each letter P and K); words/min.: word count in one minute time limit. Proportion Var: Proportion of variance in data accounted for by each factor (column); Cumulative Var: Cumulative variance accounted for by each factor and factors that preceded it (columns to the left); EF/Att.: Executive functions/Attention; EM: Episodic memory; VWM: Verbal working memory; VM: Visuospatial memory; SS: Set shifting; An: Anxiety; SWM: Spatial working memory.

Describing post-surgery cognitive decline

Both descriptive longitudinal GLMMs converged within a specified number of iterations ($\hat{R}s \leq 1.01$). All observations had Pareto-k below 0.7 implying that the results are not likely to be biased by influential outliers.The linear and non-linear models showed tight correspondence up to approximately five years post-surgery after which the non-linear model predicted a slightly faster rate of cognitive decline than the linear model (see Figure 3). The difference in estimated predictive performance between these models did not reach statistical significance ($ELPD_{dif} = 1.64$, 95% CI [-2.13, 5.41]). Based on the linear model, there was an average post-surgery decline of 0.90 DRS-2 points/year (95% PPI [-1.19, -0.62]) from an average pre-surgery DRS-2 performance of 140.34 out of 144 points (95% PPI [139.61, 141.07]).

Predicting post-surgery cognitive decline

Both predictive longitudinal GLMMs converged within a specified number of iterations ($\hat{R} \leq 1.02$) with all observations having Pareto-k below 0.7. Patients with lower verbal working memory or set shifting showed relatively impaired pre-surgery performance on DRS-2 while there was no cognitive test that clearly indicated pre-surgery impairment in DRS-2 performance (see Tables S2 and S3 in Supplementary materials). Patients with lower pre-surgery executive functions/attention performance showed faster post-surgery cognitive decline (see Figure 4). Pre-surgery executive functions/attention performance that was one standard deviation below sample average was associated with additional 0.39 DRS-2 points post-surgery annual decline (95% PPI [-0.63, -0.15]). There was no single cognitive test that clearly indicated faster-than-average post-surgery cognitive decline (all 95% PPIs included zero). Notably, both models generated similar predictions for majority of included patients (see Figure S2 in Supplementary material). The only difference in terms of model predictions was that the "cognitive tests" model showed marginally better fit to outlying observations which coupled with the fact that it also showed marginally higher Pareto-k values (see Figure S6 in Supplementary material) indicates that the "cognitive tests" model exhibited less regularization than the "cognitive functions" model. Adding

group-level effects of age, LEDD and BDI-II did not reveal any substantial deviation from these results (see Figures S3 and S4 in Supplementary material).

Evaluating false positive error rates

Results of simulations used to estimate false positive rates of the two-step procedure and the Bayesian Lasso are summarised in Supplementary Materials Figure S6. Overall, the Bayesian Lasso showed almost no false positives across simulation settings whereas the false positive rates of the two-step procedure ranged from 14 to 57 of analyses including at least one false positive. In the case of our data structure, the false positive rates were attenuated when all twenty-three predictors covaried or when we reduced the number of predictors to seven independent variables.

Discussion

In the present study, we analyzed retrospectively sampled data of longitudinally followed 126 PD patients after STN DBS surgery and described their post-surgery cognitive performance. We observed a mild post-surgery cognitive decline (*RQ1*) that was faster in patients with lower pre-surgery executive functions/attention (*RQ2*) compared to the rest of the sample. Instead of aiming to identify any pre-surgery cognitive variables that can be potentially predictive of post-surgery cognitive decline, we aimed to identify only these variables that are the most likely to be truly predictive. To achieve this goal, we applied the Bayesian Lasso and factor analysis to decrease false positive error rates of our analysis.

According to our data and model, the expected average annual rate of cognitive decline after STN DBS in PD assessed via DRS-2 reaches 0.90 from a total of 144 points which represents slower rate than in previous reports (Castrioto et al., 2022; Gruber et al., 2019; Schupbach, 2005; Smeding et al., 2009). These differences can stem from study-specific variables such distinct demographic and clinical characteristic of investigated cohorts, details of selection process for STN DBS or the number of patients followed. However, the results generally correspond with prior findings of gradual but rather mild cognitive decline in PD patients after STN DBS. The effect decreased in size but persisted after adjusting for age, LEDD and depressive symptoms implying

that neither withdrawal of dopaminergic medication nor cognitive symptoms associated with depression are likely candidates for explaining away all observed post-surgery cognitive decline.

In the present study, lower performance on the latent factor of executive functions/attention (EF/Att.) was reliably predictive of post-surgery cognitive decline. Similarly, previous studies suggested that patients with executive deficit (operationalized as a performance on tasks such as Stroop test, TMT, Wisconsin Card Sorting Test and verbal fluency test) are at a high risk of developing dementia and experiencing fast cognitive decline after STN DBS surgery (Bove et al., 2020; Kishore et al., 2019; Smeding et al., 2009). On the other hand, unlike previous studies which singled out pre-surgery test scores that ought to be the most predictive of post-surgery cognitive decline, our findings indicate that it is the combination of small predictive utilities of several test scores that provides the best prognostic value for cognitive decline after STN DBS. The predictive performance of test-level pre-surgery cognitive profile likely results from a combination of small effects of the test scores that also happen to load on the executive function latent factor (compare Figure 4 and Table 3). Aggregating results from multiple executive tests to gauge cognitive prognosis of STN DBS patients is therefore likely be superior to interpreting each test score independently (compare to Miyake et al., 2000).

Constraints on Generality

Following contemporary best practices of psychological science we next discuss generalizability of our findings (Simons et al., 2017). Compared to previous research our models allow for broader generalizations of the findings across STN DBS treated PD patients because GLMMs account for interindividual heterogeneity and intraindividual homogeneity (Gelman et al., 2012; Yarkoni, 2020). However, several constraints of generality still apply to our findings.

Due to a lack of a control group, we cannot discern the causal effect of DBS from the effect of disease progression. Consequently, we limit our conclusions to STN DBS treated patients that were selected for treatment using similar exclusion criteria as

those applied in this study (see exclusion criteria above). The lack of control group also limits application of our findings for selection purposes. Since our sample comprised of patients already selected for STN DBS treatment, the estimates could exhibit distortion due to the collider bias if generalized to a larger population of PD patients (Cinelli et al., 2022). We thus advise against using our findings as a basis for patient selection for STN DBS. Instead, practitioners should base their decision for STN DBS treatment on the current best practices (Armstrong & Okun, 2020) and use our findings to single out patients who could benefit from more monitoring.

Another generality constraint stems from the selection of measures used in the current study. Most importantly, there was a lack of visuo-spatial tasks in pre-surgery examination. Moreover, the cognitive outcome was evaluated by DRS-2 which although suitable for cognitive screening of global cognition does not appear to have utility in evaluating single cognitive functions in PD (Lopez et al., 2021).

Finally, the results of the EFA analysis can be disputed from several points of view. The EF/Att. factor was loaded on by timed test scores and could thus be better characterized as processing speed instead. We decided to follow the naming convention established in the methods section of our article, however, the lack of time-independent executive tests constitutes a clear limitation of our data set. Moreover, several latent factors identified by the EFA were test-specific (e.g., the visuospatial memory was specific to the Family Pictures test). This issue was most pronounced in the case of verbal working memory factor which was loaded on not only by the prototypical measures of working memory capacity but also by Similarities test of WAIS-III. Some of the identified latent factors can thus represent test-specific commonalities instead of latent cognitive functions. Incidentally, these shortcomings seem to affect the EF/Att. factor the least. Notably, all three of these limitations were also observed in other recent studies that applied latent variable approach to clinically used comprehensive neuropsychological batteries in PD (Chung et al., 2021; Specketer et al., 2019). The phenomena observed in EFA results of our study may thus at least partially stem from the contemporary practice of building neuropsychological batteries according to expert

consensus and warrant further investigation of a latent structure of such batteries.

Limitations and future directions

A major limitation of our study is the moderate number of missing values. To alleviate this limitation, we applied a multiple imputation technique with high number of imputations which has been shown to provide reasonable interval estimates in the Bayesian models. However, missing data still lowered estimation precision of effects of those latent cognitive factors that were identified less consistently across imputed datasets (set shifting and spatial working memory). Another way missing data might have influenced our findings is the survivorship bias which could have led to overly optimistic estimates of the post-surgery cognitive decline rate.

Next, our results are limited to evaluating pre-surgery cognitive profile predictive of post-surgery cognitive decline. While we adopted this approach for parsimony's sake, other non-cognitive features such as demographic or clinical characteristics will likely significantly improve prediction. On the other hand, several recent studies claimed that cognitive outcomes of STN DBS are influenced by the location of stimulating electrode in STN (John et al., 2021; Petry-Schmelzer et al., 2019; Reich et al., 2022). Further research investigating causal effect of electrode placement on longitudinal cognitive outcome will add a level of explanation that is missing from the current study.

Despite these limitations, our results provide actionable information about the PD patients who are selected for STN DBS treatment based on current best practices. Based on our results, clinicians can preferentially monitor patients with a pre-surgery executive functions/attention deficit. Moreover, the cognitive profile identified in our study can serve to select within STN DBS treated patients suitable candidates for prospective clinical trials investigating effects of strategies to mitigate cognitive decline such as cognitive training, reprogramming of stimulation parameters or further DBS using a secondary target (Cappon et al., 2022).

Conclusions

Our findings imply that STN DBS in combination with oral dopaminergic therapy is a safe treatment option from a cognitive standpoint as it was associated with

only mild annual post-surgery cognitive decline. Pre-surgery executive functions/attention deficit appears to have a prognostic value for risk stratification with regards to development of the post-surgery cognitive decline. Based on our models and data, we recommend considering aggregated pre-surgery results from multiple executive tests to estimate cognitive prognosis of PD patients treated with STN DBS rather than evaluating single test scores separately. Future studies may follow-up by evaluating alternatives to factor analysis for estimating the aggregate executive score in everyday clinical practice.

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Conflict of interest

Nothing to report.

Ethical statement

The study was approved by the General University Hospital Ethics Committee in Prague, Czech Republic. All Participants provided informed consent.

Data availability

The data that support the findings of this study are not currently publicly available due institutional regulations protecting patient clinical data but are available from the corresponding author on request (may require data use agreements to be developed). The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The computer code used in our analysis as well as supplementary presentation of our results can be accessed at https://github.com/josefmana/dbs_longCOG.

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Figure 1

Patients inclusion/exclusion flowchart.

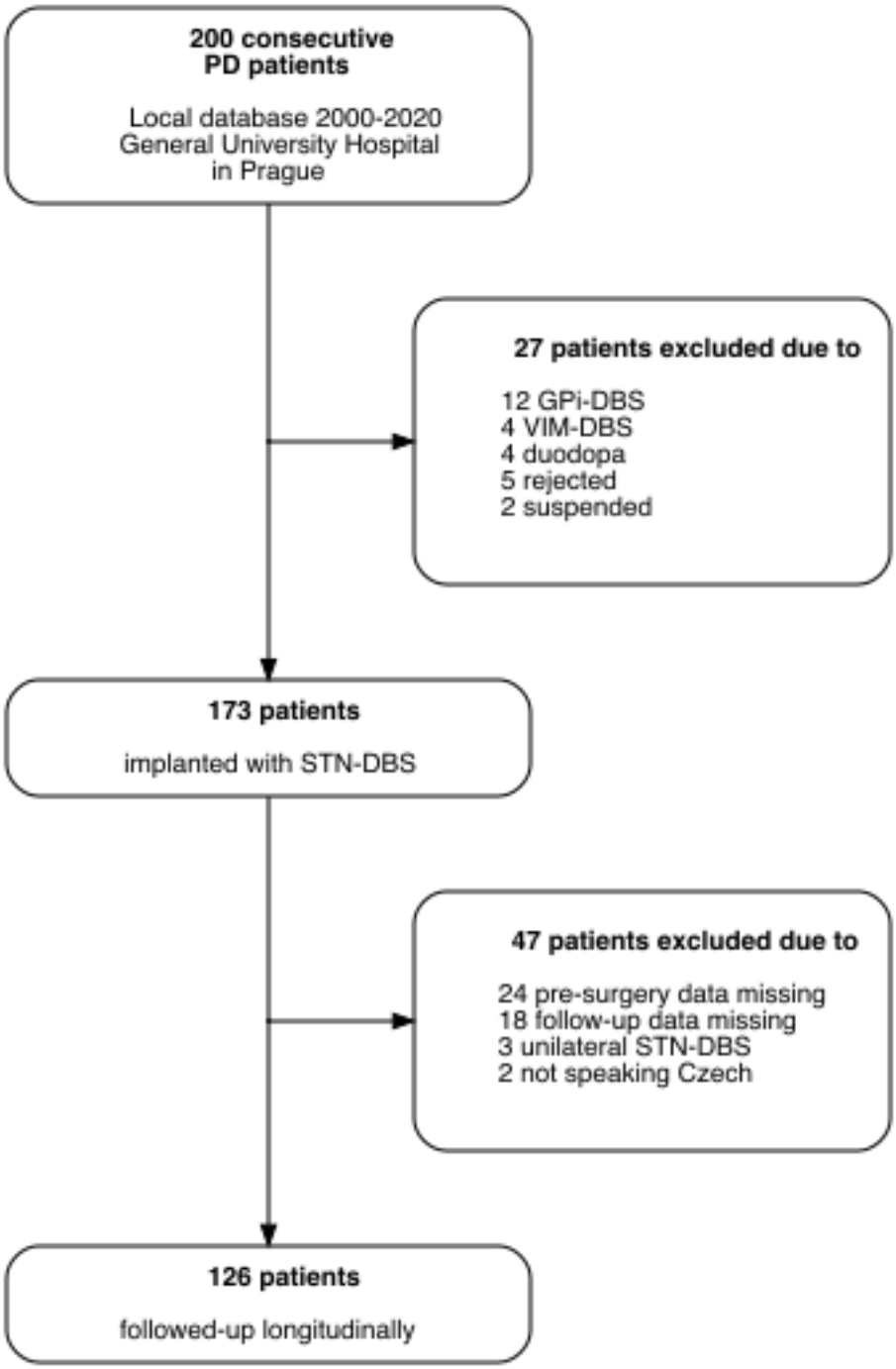

Figure 2

Distribution of assessments. Distribution of (A) follow-up years and (B) number of assessments per patient for N = 126 patients. Negative values on horizontal axis in (A) represent pre-surgery assessments.

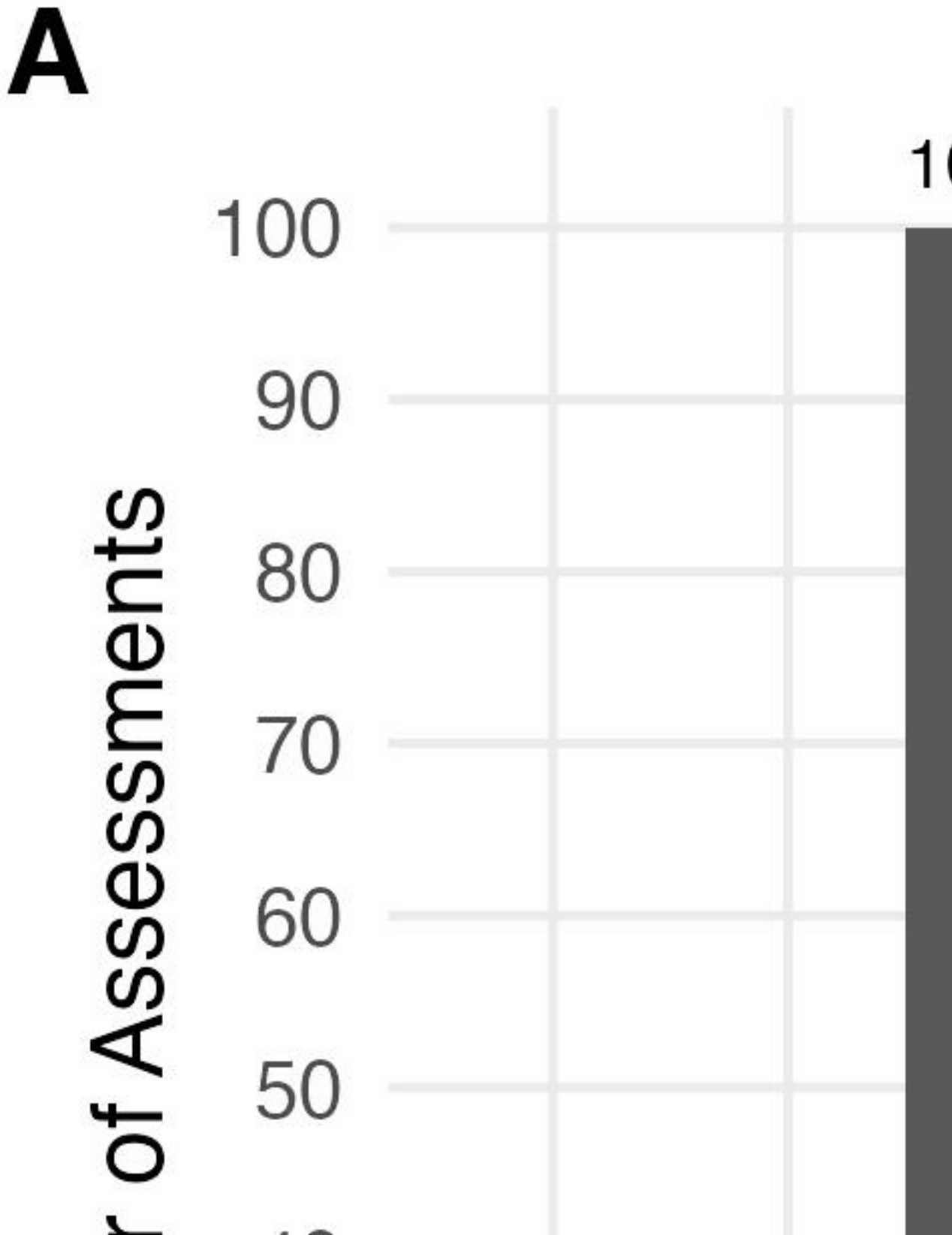

Figure 3

Comparison of linear versus non-linear models of the longitudinal cognitive trajectory.

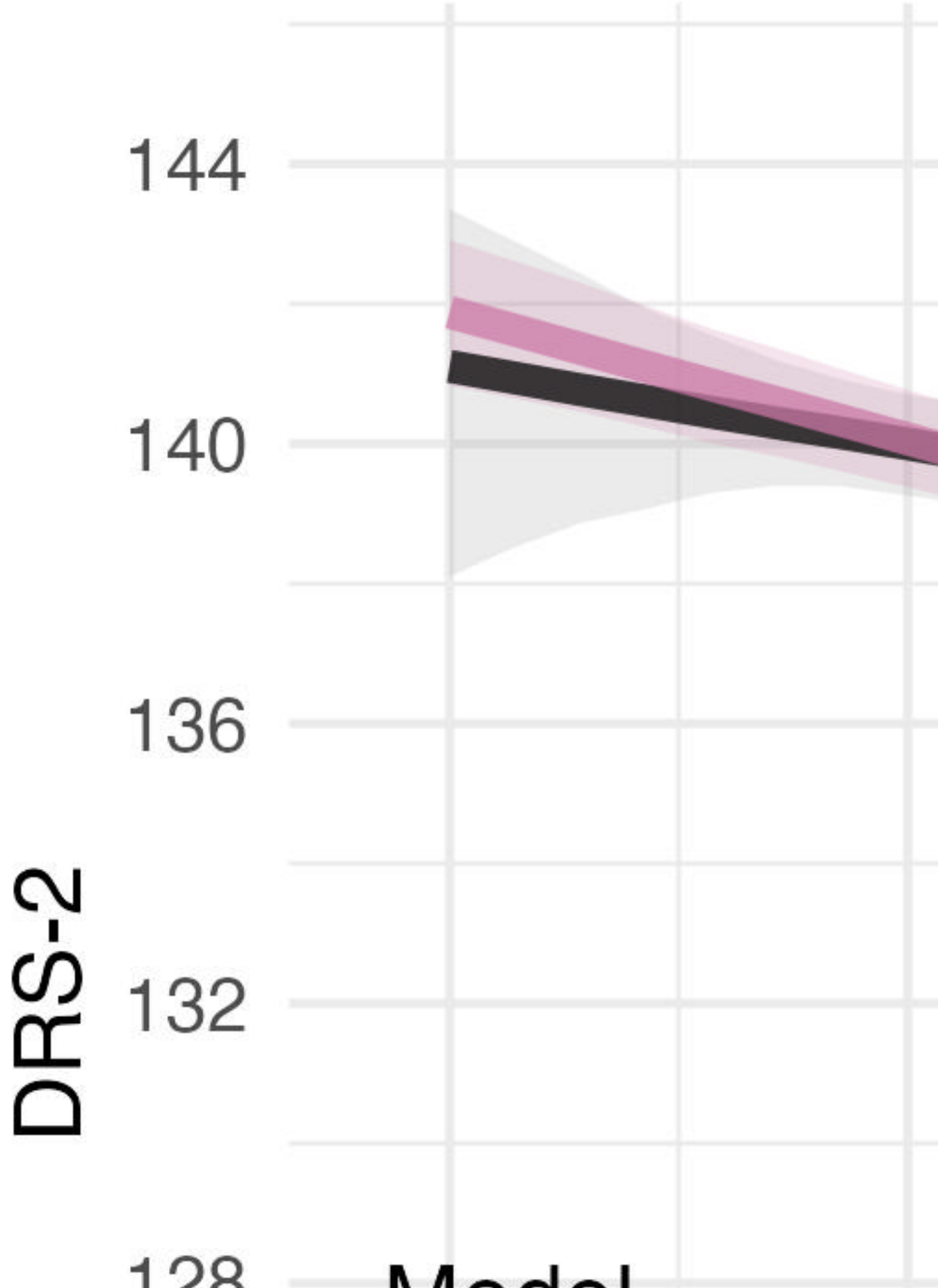

Figure 4

Interaction terms of the "test scores" (A) and the "factor scores" (B) models predicting post-surgery cognitive decline. Acronyms are explained in the text.