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1st Faculty of Medicine

Summary of the dissertation thesis

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Predictors of Dementia after Deep Brain Stimulation in Parkinson's Disease

Kognitivní prediktory konverze do syndromu demence po hluboké mozkové stimulaci u Parkinsonovy nemoci

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

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Abstract

The thesis describes post-surgery cognitive change in patients with Parkinson's disease (PD) treated by subthalamic deep brain stimulation (STN DBS). The aim of the thesis is to select pre-surgery characteristics that would identify patients with high risk of developing post-surgery cognitive decline. Specifically, the primary objective is to derive pre-surgery cognitive and magnetic resonance imaging (MRI) profiles predictive of post-surgery cognitive decline. The secondary objective is to characterise STN DBS effects on cognitively demanding instrumental activities of daily living (IADL). The findings indicate that pre-surgery processing speed deficit and clinically silent structural and microstructural abnormalities in MRI are associated with relatively higher risk of long-term post-surgery cognitive decline. Furthermore, results related to the secondary objective imply that an interplay between STN DBS and post-surgery dopaminergic medication reduction determines short-term post-surgery change in IADL. Overall, the models and data presented in this thesis in conjunction with existing brain circuits theories of cognitive dysfunction in PD lend support to the idea that disease progression is the primary factor leading to cognitive side effects in STN DBS treated patients with PD.

Keywords: Cognitive Impairment, Deep Brain Stimulation, Instrumental Activities of Daily Living, Parkinson's Disease, Risk Stratification

Abstrakt

Překládaná disertační práce popisuje pooperační kognitivní trajektorii pacientů s Parkinsonovou nemocí (PN) léčených hlubokou mozkovou stimulací subthalamického jádra (STN DBS). Cílem práce je definovat předoperační charakteristiky pacientů s vysokým rizikem rozvoje pooperační kognitivní poruchy. Hlavním cílem práce je identifikovat předoperační kognitivní profil a profil abnormit v obraze magnetické resonance (MRI), který reliabilně predikuje pooperační zhoršení kognitivních funkcí. Druhotným cílem je charakterizovat efekt STN DBS na kognitivně náročné instrumentální aktivity denního života (IADL). Prezentovaná zjištění ukazují, že předoperační deficit v rychlosti zpracování informací a klinicky latentní strukturální a mikrostrukturální abnormity v MRI indikují zvýšené riziko rozvoje kognitivního deficitu v dlouhodobém horizontu po zahájení léčby STN DBS. Výsledky řešení druhotného cíle naznačují, že interakce STN DBS a pooperční redukce dopaminergní medikace rozhoduje o pooperační změně IADL. Celkově, modely a data prezentovaná v této disertační práci jsou ve spojení se současnými teoriemi mozkových okruhů vázaných na kognitivní poruchu u PN v souladu s hypotézou, že progrese nemoci je primárním faktorem způsobujícím kognitivní deficit u pacientů s PN léčených STN DBS.

Klíčová slova: hluboká mozková stimulace, instrumentální aktivity denního života, kognitivní porucha, Parkinsonova nemoc, stratifikace rizik

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that significantly increased in prevalence, incidence and societal costs during the last two decades leading some authors to coin the term *"Parkinson Pandemic"* (Dorsey et al., 2018). The defining neuropathological feature of PD is a loss of dopaminergic neurons in the midbrain's substantia nigra pars compacta and associated insoluble-synuclein aggregates called Lewy bodies (Simon et al., 2020). Consequent dysregulation of the function of parallel cortico-basal ganglia-thalamico-cortical neural circuits leads to parkinsonism, the hallmark syndrome of PD comprising of bradykinesia (i.e., slowness of initiation of voluntary movement) combined with muscular rigidity, rest tremor or postural instability (Hughes et al., 1992; Postuma et al., 2015).

Although dopaminergic deficiency within basal ganglia circuits is the major mechanism accounting for the most of the core motor features of PD, other neurotransmitters and brain structures are involved as well contributing to a significant heterogeneity of PD symptomatology (Kalia & Lang, 2015). Indeed, some non-motor symptoms such as cognitive deficit may be present in high proportion of de novo PD patients and even precede classical motor symptoms of PD (Khoo et al., 2013). Contemporary theories assume that cognitive decline in PD is caused by dysfunction of several dissociable functional brain circuits, neurotrasmitter systems, and associated cognitive functions including fronto-striatal executive dysfunction, fronto-parietal attentional dysfunction, mediotemporal memory dysfunction, and visual perceptual dysfunction due to multiple networks pathology including posterior visual cortices (Gratwicke et al., 2015; Kehagia et al., 2012).

Parkinson's disease dementia (PD-D) is a disabling cognitive symptom that afflicts a substantial number of patients, especially at later stages of disease progression (Hely et al., 2008). PD-D is defined by a widespread deficit affecting several cognitive domains that is severe enough to impact patients' daily living (Dubois et

al., 2007). However, patients with PD can show detectable signs of cognitive decline long before converting to PD-D in a stage called mild cognitive impairment in PD (PD-MCI). The International Parkinson and Movement Disorders Society (MDS) criteria for PD-D and PD-MCI differentiate between these two symptoms by defining PD-MCI as a mild cognitive decline that does not interfere with daily living whereas PD-D is defined as a significant cognitive decline leading to difficulties with activities of daily living (ADLs) (Dubois et al., 2007; Litvan et al., 2012). Measuring deficit in instrumental ADLs (IADLs) such as following instructions or doing more than one thing at a time can be especially informative, because PD motor symptoms affect IADLs to a lesser degree than basic ADLs (BADLs) such as self-hygiene (Becker et al., 2020).

The first line of symptomatic treatment of PD consists of supplying dopamine via levodopa preparations, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors (Armstrong & Okun, 2020). However, as the disease progresses, levodopa medication loses on its effectiveness and some type of advanced therapy may be indicated. Deep brain stimulation (DBS) is such an advanced treatment of motor symptoms of PD indicated primarily in patients who experience drug-resistant symptoms, the "wearing-off" phenomenon[1] or dyskinesias (Armstrong & Okun, 2020). The DBS treatment involves neurosurgical procedure whereby electrodes are implanted into selected targets within the brain and then a subcutaneous battery source is implanted which delivers constant or intermittent electricity to the target structure (Lozano et al., 2019). The most common DBS targets in PD are subthalamic nucleus (STN) and internal globus pallidus (GPi) (Mao et al., 2019).

DBS successfully reduces motor symptoms as well as medication burden (operationally defined as the levodopa equivalent daily dose, LEDD) (Tomlinson et al., 2010) and improves patients' quality of life (Bratsos et al., 2018). However,

[1] Wearing off is characterised by recurrence of PD symptoms and functional disability occurring immediately before the next medication dose is due.

considerable heterogeneity in cognitive outcomes after STN DBS was reported by prior studies with a small to moderate post-surgery decline in verbal fluency and equivocal results for other cognitive tests and domains (Bucur & Papagno, 2023; Mehanna et al., 2017; Wang et al., 2021). Estimated dementia incidence rate after STN DBS surgery reaches 35.6–55.4 per 1,000 patient-years (Bove et al., 2020; H.-J. Kim et al., 2014; Krishnan et al., 2019). Even though these estimates do not exceed dementia incidence rate observed in a general PD population treated medically without DBS (Hely et al., 2008), they show that substantial subset of STN DBS treated patients experience severe cognitive decline after surgery. The ability to predict which patients are likely to develop post-surgery cognitive decline can thus prove useful for guiding post-surgery patient monitoring.

Although a large array of pre-surgery patient characteristics could be used to predict later cognitive decline, the baseline cognitive profile proved to be especially informative outperforming other demographic, clinical and genetic factors in a large longitudinally followed cohort of medically treated patients with PD (Phongpreecha et al., 2020). Studies of non-DBS treated patients usually imply predictive role of measures of executive functions, working memory as well as episodic memory for prognosis of later development of PD-MCI or PD-D (T. E. Kim et al., 2014; Phongpreecha et al., 2020).

In this thesis, the primary type of variable used to predict post-surgery cognitive decline is thus the pre-surgery cognitive profile derived from a clinically available neuropsychological assessment. Similarly to data from non-DBS samples, potential cognitive predictors of post-surgery cognitive decline in PD patients treated by STN DBS nominated by previous research include pre-surgery deficits in executive function and poorer memory (Bove et al., 2020; Gruber et al., 2019; Jahanshahi et al., 2022; H.-J. Kim et al., 2014; Krishnan et al., 2019; Smeding et al., 2009). Secondary type of predictor considered in this thesis are magnetic resonance imaging (MRI)-derived measures of brain structural integrity and microstructural connectivity. In this regard, previous studies implied predictive

value of pre-surgery white matter lesions volume, hypointensity in pulvinar thalami, gray matter volume of left nucleus accumbens, and volume of the left lateral ventricle (Blume et al., 2017; Matsuura et al., 2019; Planche et al., 2018).

The majority of prior studies describing and predicting longitudinal post-surgery cognitive decline employed pre-surgery/post-surgery design with change scores as their outcome variable (Gruber et al., 2019; H.-J. Kim et al., 2014; Planche et al., 2018). A change score concept refers to subtracting pre-surgery score from post-surgery score and using this difference as an outcome variable. Although such a modelling strategy can in principle arrive at a correct causal estimate if the model is set up correctly (Y. Kim & Steiner, 2021), it comes with several shortcomings due to poor psychometric properties the change scores have when used to estimate change in noisy data (e.g., Cronbach & Furby, 1970). First of all, this procedure is usually statistically inefficient requiring large sample size for effective estimation (Gelman & Vákár, 2021). More importantly, change scores analysis of longitudinal data confounds true changes with measurement error (Singer & Willett, 2003). In this thesis, patients' true score is estimated directly leveraging the fact that the main dataset includes three or more observations in large enough number of patients to estimate patient-specific post-surgery cognitive trajectories. Moreover, this approach allows for explicit quantification of measurement error as well as patient-level variability improving generalisability of the findings (Yarkoni, 2020).

2. Aims and Hypotheses

The primary aim of this thesis is to describe pre-surgery cognitive profile of STN DBS treated patients with PD that is prognostic of faster long-term post-surgery rate of cognitive decline. Secondary aims are to enhance the description of pre-surgery cognitive profile by describing pre-surgery MRI markers associated with post-surgery cognitive decline, and to breach the gap between the objective cognitive deficit measured in laboratory settings and its impact on everyday life by examining how PD patients' performance of daily living change after initiating STN DBS treatment.

2.1 Study 1: Learning Curve in Verbal and Non-verbal Memory of Patients with Parkinson's Disease

In Study 1 (Havlík et al., 2020) I estimate differences in verbal and non-verbal memory learning curves of PD patients with and without diagnosed PD-MCI to establish that the concept of "cognitive profile" can at least in principle provide psychologically meaningful data. When taking into account potential mechanisms of memory deficits in PD which may be either executive (the retrieval deficit hypothesis) or associative (the associative binding hypothesis) (Bezdicek et al., 2019; Brønnick et al., 2011), we can expect there to be differences in immediate recall (i.e., the *immediate memory span*) and learning over trials (i.e., the *slope* or *learning curve*) PD-related deficits. These differences can vary across modalities (Bezdicek et al., 2019). Study 1 thus aims to address following research questions: *RQ1.1)* How do PD patients with and without diagnosis of MCI differ from healthy adults in their visual and verbal memory immediate memory span? *RQ1.2)* How do PD patients with and without diagnosis of MCI differ from healthy adults in their visual and verbal memory learning curves? *RQ1.3)* Do differences in immediate memory span or learning curve between PD patients with and without diagnosis of MCI and healthy adults vary according to sensory modality? The estimates derived by Study 1 are valid under the following hypothesis: *H1)* declarative memory deficit profile in PD-MCI varies by modality of memory processes.

2.2 Study 2: Preoperative Cognitive Profile Predictive of Cognitive Decline after Subthalamic Deep Brain Stimulation in Parkinson's Disease

In Study 2, I aim to predict cognitive true score changes after STN-DBS leveraging a dataset that includes three or more observations in large enough number of patients to estimate both group-level post-surgery cognitive decline to describe the sample, as well as patient-level variability to provide predictions for other similar samples. Study 2 aims to address following research questions: *RQ2.1)* What is the size of expected long-term rate of cognitive decline after STN DBS in PD patients? *RQ2.2)* What is the pre-surgery cognitive profile that is predictive of long-term post-surgery cognitive decline in STN DBS treated PD patients? The estimates are valid under the following hypothesis: *H2)* pre-surgery cognitive profile contains information about factors that influence post-surgery cognitive decline in STN DBS-treated patients with PD.

2.3 Study 3: Structural and Microstructural Predictors of Cognitive Decline in Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease

I follow the results of Study 2 up with longitudinal examination of STN DBS treated patients with PD that also underwent diffusion weighted imaging (DWI) and structural MRI before surgery. The research question is *RQ3.1)* What is the pre-surgery profile of structural integrity and microstructural connectivity in MRI that is predictive of long-term post-surgery cognitive decline in STN DBS treated PD patients? The estimates are valid under the following hypothesis: *H3)* pre-surgery MRI markers of structural integrity and microstructural connectivity contain information about factors that influence post-surgery cognitive decline in STN DBS treated patients with PD.

2.4 Study 4: The Instrumental Activities of Daily Living in Parkinson's Disease Patients Treated by Subthalamic Deep Brain Stimulation

Study 4 aims to bridge the gap between cognitive deficit detectable by objective cognitive testing and patients' subjective assessment of its impact on everyday living. In Study 4, I aim to document post-surgery IADL changes of PD patients and estimate causal effect of dopaminergic medication level as a potentially relatively simple-to-intervene-on factor to moderate post-surgery IADL. Following research questions are asked in this study: *RQ4.1)* What is the size of change in self-reported IADL one year after STN DBS compared to pre-surgery IADL level in PD patients? *RQ4.2)* What is the size of one-year post-surgery self-reported IADL change that can be attributed to time and STN DBS effects rather than other post-surgery factors? *RQ4.3)* How does one-year post-surgery self-reported IADL change in response to adjusting levels of dopaminergic medication? The estimates are valid under the following hypothesis: *H4)* STN DBS causes a change in self-reported difficulties in IADLs that is partially mediated by objective cognitive functioning, affective state, and LEDD.

3. Materials and Methods

3.1 Learning Curve in Verbal and Non-verbal Memory of Patients with Parkinson's Disease

The study involved 60 patients with PD recruited from the Movement Disorders Center, Department of Neurology at First Faculty of Medicine and General University Hospital in Prague, and 60 age and sex matched healthy adults recruited for the National Normative Study of Cognitive Determinants of Healthy Aging (Štěpánková et al., 2015). All patients were examined in the ON medication state. Patients were further divided into patients with normal cognition (PD-NC) and patients with mild cognitive impairment (PD-MCI) according to their performance on a standardised test battery (Bezdicek, Sulc et al., 2017).

All participants underwent the Czech versions of Brief Visuospatial Memory Test (BVMT-R) (Benedict, 1997; Havlik et al., 2020) and Rey Auditory Verbal Learning Test (RAVLT) (Bezdicek et al., 2014). The BVMT-R is a test of visual and spatial declarative memory and learning whereas the RAVLT test verbal declarative memory and learning consisting of several consecutive trials of recalling a set of figures (BVMT-R) or words (RAVLT). The outcomes of interest in each measure were *free recall* (performance aggregated over all trials), *immediate memory span* (the first trial performance) and *learning curve* (difference between successive further trials).

RAVLT and BVMT-R data were analysed using Bayesian generalised linear mixed models (GLMMs) (McElreath, 2020). Single trial scores were used as outcomes for separate RAVLT and BVMT-R GLMMs with two levels of predictors: (i) natural logarithm of trial order, group (HC, PD-NC and PD-MCI) and their interaction on a group level, and (ii) correlated varying participant-specific intercepts and slopes based on natural logarithm of trial order at the participant level. Outcome variables as well as trial order were treated as continuous and modelled with Gaussian measurement error model for both outcome variables.

Improper flat priors over reals were set-up for population-level parameters, half Student-t priors with 3 degrees of freedom for global intercept and group-level parameters, and non-regularising LKJ(1) prior for participant-level correlation matrices.

Between-group differences in marginal means across all trials (main effects contrasts) were used to compare overall *free recall*, differences in marginal means of the first trial performance (simple effect contrasts) were used to compare *immediate memory spans*, and between-group differences in marginal trends of the logarithmic trial order parameter (interaction contrasts) were used to compare *learning curves*. All estimates were described by their 95% highest density posterior intervals (HDPI) and compared via the probability of direction (*pdir*) as an index of effect existence. The results were interpreted following reporting guidelines for Bayesian analyses as articulated by Makowski et al. (2019). All GLMMs were fitted using via Stan's (version 2.32.2) build-in Hamiltonian Monte Carlo (HMC) sampler accessed via R software for statistical computing version 4.3.3 using package "brms" (Bürkner, 2017; R Core Team, 2024; Stan Development Team, 2020). Full analysis code is available at https://github.com/josefmana/pd_learCUR.git.

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

The study involved 126 patients with idiopathic PD following United Kingdom Parkinson's Disease Society Brain Bank Criteria (Hughes et al., 1992) who underwent surgery for STN DBS treatment at the Movement Disorders Center, Department of Neurology at First Faculty of Medicine and General University Hospital in Prague between years 2000 and 2020 and were repeatedly screened for overall cognitive performance in ensuing years. Exclusion criteria were contingent upon patients being suitable candidates for STN DBS treatment and followed the Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (CAPSIT) protocol (Defer et al., 1999).

Pre-surgery neuropsychological assessment included Trail Making Test, parts A and B (Bezdicek, Stepankova, et al., 2017) for sustained visual attention and set shifting respectively; Prague Stroop Test (Bezdicek, Lukavsky, et al., 2015) dot colour naming (PST-D) for sustained visual attention, and naming colour of neutral words (PST-W) and interference condition (i.e., naming colour of contrasting colour words, PST-C) for sensitivity to interference; Tower of London task (TOL) (Michalec et al., 2017) for planning; Controlled Oral Word Association Test (COWAT, letters K + P) (Nikolai et al., 2015) for mental flexibility; category verbal fluency test (CFT, category Animals) (Nikolai et al., 2015) for speeded word production; Similarities (Sim.) from Wechsler Adult Intelligence Scale, third revision (WAIS-III) (Wechsler, 2010) for conceptualisation; Digit Span forward and backward (DS-F and DS-B) from WAIS-III (Wechsler, 2010) as well as letter-number sequencing (LNS) from Wechsler Memory Scale, third edition (WMS-III) (Wechsler, 2011) for auditory working memory; Spatial Span forward and backward (SS-F and SS-B) from WMS-III (Wechsler, 2011) for spatial working memory; RAVLT (Bezdicek et al., 2014) for explicit verbal learning and memory, and WMS-III Family Pictures (FP) for visuo-spatial memory (Wechsler, 2011). Furthermore, anxiety was assessed with the State-Trait Anxiety Inventory for the state (STAI-X1) and trait (STAI-X2) anxiety (Spielberger et al., 1983). Patients' longitudinal cognitive state was assessed pre-surgery and at several times post-surgery using Mattis Dementia Rating Scale, second edition (MDRS) (Bezdicek, Michalec, et al., 2015). All reported assessments were performed in ON medication state pre-surgery, and ON medication as well as ON stimulation state post-surgery.

Pre-surgery cognitive battery was pre-processed via an exploratory factor analysis (EFA) with varimax rotation using ordinary least squares to find the minimum residual solution. Missing observations were multiply imputed using a parametric bootstrap via the "missMDA" R package to create one hundred imputed data sets. EFA was then computed with from three up to eight factors via the "psych" R package (Josse & Husson, 2016; R Core Team, 2024; Revelle, 2022) using each

imputed data set. Within each imputed data set, factor scores for each patient were calculated using the regression method. The number of extracted factors was based on a combination of the root-mean-square error approximation (RMSEA), Tucker-Lewis Index (TLI), and consistency of each factor model across imputations.

To describe the rate of post-surgery cognitive decline, a GLMM was estimated with longitudinal MDRS 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. To evaluate predictive utility of pre-surgery cognitive profile, further two GLMMs were estimated. Longitudinal MDRS 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 (the *"factor scores"* model). Both models further included correlated patient-level intercepts and slopes. Equivalent prior distributions were specified for model parameters of both the *"test scores"* and the *"factor scores"* models, most importantly the Bayesian Lasso priors for were used all group-level parameters barring the intercept (Park & Casella, 2008).

Estimates were described by full posterior distributions, medians and 95% HDPIs of corresponding model parameters or predictions as appropriate. Time-dependent parameters are denoted δ and time-independent parameters are denoted β throughout. All GLMMs were fitted using via Stan's (version 2.32.2) build-in HMC sampler accessed via R version 4.3.3 using package "brms" (Bürkner, 2017; R Core Team, 2024; Stan Development Team, 2020). Full analysis code is available at https://github.com/josefmana/dbs_cogPRED.git.

3.3 Structural and Microstructural Predictors of Cognitive Decline in Deep Brain Stimulation of Subthalamic Nucleus in Parkinson's Disease

The study involved 72 patients with PD diagnosed according to the criteria defined by the MDS (Postuma et al., 2015) that were indicated for STN DBS.

The examination of cognition (via MDRS) was performed before the STN DBS implantation and then in the years 1, 3 and 5 after the surgery with the last available assessment, i.e. assessment with the longest follow-up duration, being used to calculate the MDRS change per year ($\Delta\text{MDRS} = \frac{\text{MDRS}_{post} - \text{MDRS}_{pre}}{\text{Years post-surgery}}$).

Patients with ΔMDRS of –2 or less were labelled as cognitively declining (CD) group, the remaining patients were considered cognitively stable (CS).[2] The cognitive testing was performed in ON medication state pre-surgery, and ON medication as well as ON stimulation state post-surgery.

Pre-surgery MRI acquisition was performed using a 3T MAGNETOM Skyra scanner (Siemens, Erlangen, Germany). A T1-weighted (T1w) scan was acquired with magnetisation-prepared rapid gradient echo (MPRAGE) sequence, 1.0-mm isotropic resolution, repetition time (TR) = 2,200 ms, inversion time (TI) = 900 ms, echo time (TE) = 2.43 ms, and flip angle = 8°. The protocol further included DWI with voxel size 2.0 × 2.0 × 2.0 mm^3, TR = 9,000 ms, TE = 94 ms, FA = 90°, single b-value of 1100 s/mm^2, and 30 directions with 5 additional b0 images, acquired with antero-posterior phase encoding direction.

To analyse microstructural and macrostructural correlates of pre-surgery cognitive state and post-surgery cognitive decline, two sets of General Linear Models (GLMs) were fitted with region-specific microstructural (fractional anisotropy (FA) and mean diffusivity (MD)) and macrostructural (cortical thickness and subcortical grey matter volume) measures as outcomes, pre-surgery MDRS score or group (CD versus CS) as primary predictors, and age, sex and disease duration as additive covariates. Statistical significance of resulting regression coefficients of primary predictors was decided based on non-parametric analysis as implemented in the Permutation Analysis of Linear Models package with 10,000

[2] This choice was based on the reasoning that patient who would scored at maximal 144/144 points before surgery would with 2 points/year decline reach the optimal threshold for PD-MCI according to the Czech normative study (Bezdicek, Michalec, et al., 2015) at the three-years post-surgery mark.

permutations and False Discovery Rate (FDR) correction (Benjamini & Yekutieli, 2001) over the number of parcels separately for each modality (i.e., FA, MD, cortical thickness and subcortical grey matter volume) (Winkler et al., 2014). Results were considered significant at adjusted q-value < .05 and parcel cluster size equal or above 2 to eliminate singleton cortical parcels.

3.4 The Instrumental Activities of Daily Living in Parkinson's Disease Patients Treated by Subthalamic Deep Brain Stimulation

The study involved 32 patients with PD diagnosed according to the criteria for clinically established PD defined by the MDS (Postuma et al., 2015) that were indicated for STN DBS. All patients were under dopaminergic therapy (i.e., levodopa, dopamine agonist, or a combination of them), and LEDD for each patient was calculated before and after surgery (Tomlinson et al., 2010).

Both pre-surgery and post-surgery neuropsychological assessment included cognitive screening via MDRS (Bezdicek, Michalec, et al., 2015), screening of depressive symptoms via BDI-II (Ciharova et al., 2020), and the Penn Parkinson's Daily Activities Questionnaire (PDAQ) as a measure of IADL (Brennan et al., 2016). All assessments were performed in ON medication state pre-surgery, and ON medication as well as ON stimulation state post-surgery.

Causal assumptions of Study 4 are represented in the form of a directed acyclic graph (DAG) depicted in Figure 1. Briefly, the assumptions are that post-surgery responses to PDAQ are determined by their pre-surgery level, time-locked clinical characteristics (MDRS, BDI-II, LEDD), patient- and item-specific characteristics, and DBS itself which is in turn determined by pre-surgery patient's cognitive, affective and medication profiles, all of which are used by clinicians to decide whether to treat the patient with STN DBS or not. The double-headed arrow between BDI_{pre} and DBS indicates a common cause of these nodes, namely underlying depressive syndrome can both inform the psychiatrist

about contraindication to DBS treatment and increase BDI-II score.[3] Using the back-door criterion (Cinelli et al., 2022; McElreath, 2020), we can infer the *adjustment sets* for *RQ4.2* and *RQ4.3* respectively and adjust for these variables in statistical analysis.

The data were analysed using a set of GLMMs with responses to each item of PDAQ as an outcome, patient-specific and item-specific varying predictors, and a structure of group-level parameters dependent on research question. For *RQ4.1*, only the time of assessment (pre- vs post-surgery) was used to predict mean group-level responses (i.e., the *"descriptive"* model). Following the model in Figure 1, the time of assessment as well as MDRS, BDI-II, LEDD and their interactions with the time of assessment were used to predict group-level responses in model for *RQ4.2* (i.e., the *"direct effect"* model). Finally, the model in Figure 1, the time of assessment, LEDD and their interaction were used to predict group-level responses in model for *RQ4.3* (i.e., the *"total effect"* model). Across all models, the response variable, i.e., the answer to each single PDAQ item on 5-point Likert scale, was modelled using the ordered-logit response function (McElreath, 2020). Student-t priors with zero mean, a scale of 2.5, and 3 degrees of freedom were used for all parameters. Parameters posterior distributions were characterised on the latent logit scale by their medians, 95% HDPIs and *pdir*s. Time-dependent parameters are denoted δ and time-independent parameters are denoted β throughout. All GLMMs were fitted using via Stan's (version 2.32.2) build-in HMC sampler accessed via R version 4.3.3 using package "brms" (Bürkner, 2017; R Core Team, 2024; Stan Development Team, 2020). Full analysis code is available at https://github.com/josefmana/dbs_postopIADL.git.

[3] Note that the decision to exclude a patient from STN DBS treatment for current depression is not based on BDI-II (which is administered by a neuropsychologist at our institution), but by an independent neuropsychiatric evaluation.

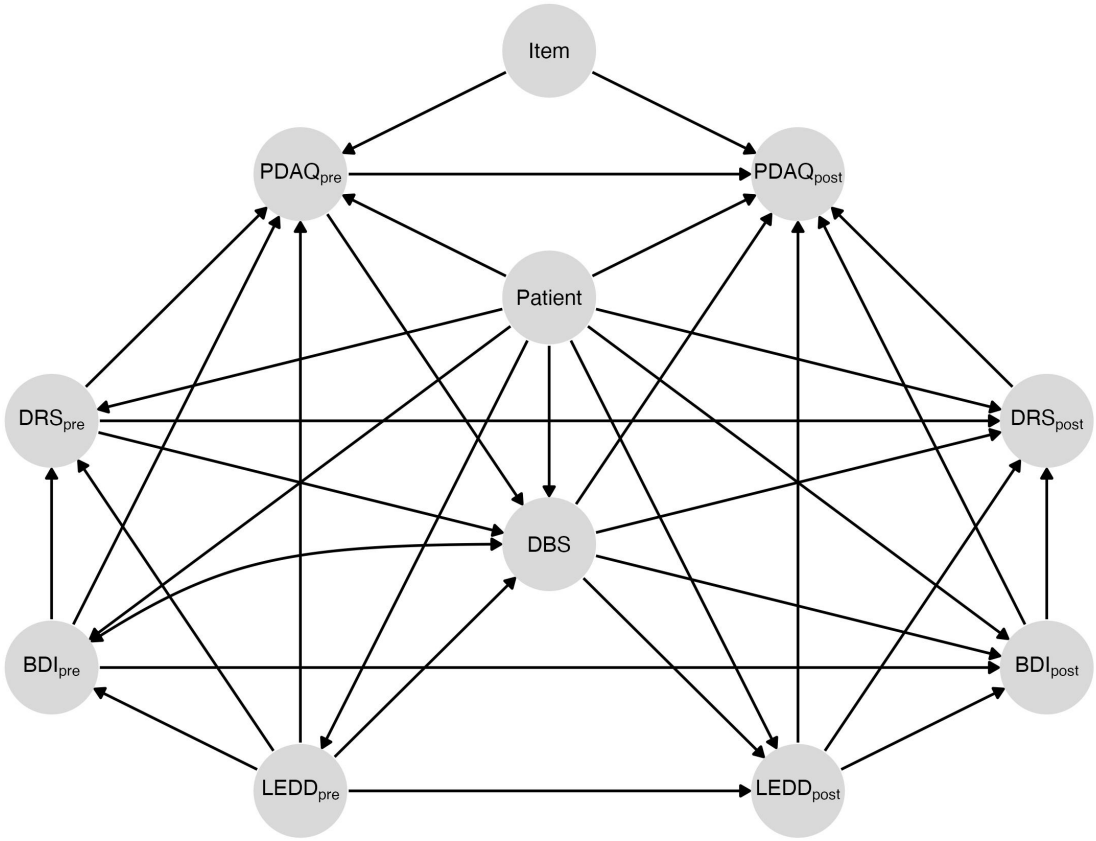

Figure 1
Directed acyclic graph representing causal assumptions of relationships between variables of the Study 4.

4. Results

4.1 Learning Curve in Verbal and Non-verbal Memory of Patients with Parkinson's Disease

In total, 60 HC (61.92 ± 3.98 years old, 14.07 ± 2.57 years of education, 43.33% males), 35 PD-NC (59.43 ± 8.62 years old, 15.87 ± 3.13 years of education, 60% males), and 25 PD-MCI (62.00 ± 9.71 years old, 13.40 ± 2.89, 56% males) participants were included in the study.

We observed strong evidence of effect existence for PD-MCI-related deficit in *free recall* across modalities compared to both HC (BVMT-R: HC-minus-(PD-MCI) = 2.50, 95% HDPI [1.54, 3.47]; *pdir* = 1.000; RAVLT: HC-minus-(PD-MCI) = 2.01, 95% HDPI [1.03, 2.99]; *pdir* = 1.000) and PD-NC (BVMT-R: (PD-MCI)-(PD-NC) = -2.43, 95% HDPI [-3.49, -1.33]; *pdir* = 1.000; RAVLT: (PD-MCI)-(PD-NC) = -1.53, 95% HDPI [-2.48, -0.38]; *pdir* = 1.000). On the other hand, there was no clear evidence of free recall deficit in PD-NC compared to HC (*pdir*s ≤ .868).

The *free recall* deficit in the BVMT-R was driven by *immediate memory span* differences (HC-minus-(PD-MCI) = 2.21, 95% HDPI [1.13, 3.25], *pdir* = 1.000; (PD-MCI)-(PD-NC) = -2.12, 95% HDPI [-3.34, -0.93]; *pdir* = 1.000) but not by learning curve differences (*pdir*s ≤ .858). On the other hand, in the RAVLT it was driven by *learning curve* differences (HC-minus-(PD-MCI) = 1.22, 95% HDPI [0.60, 1.87], *pdir* = 1.000; (PD-MCI)-(PD-NC) = -1.05, 95% HDPI [-1.73, -0.36]; *pdir* = .998) but not immediate memory span differences (*pdir*s ≤ .857).

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

It total, 126 patients were included in the study (57.25 ± 7.96 years of age and 11.67 ± 4.05 years of disease duration at surgery, 14.26 ± 2.91 years of education, 66% males). 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).

Based on TLI (> 0.9), RMSEA (< 0.05), and its highest consistency across imputations, the seven factor model of pre-surgery cognitive profile was retained for further analyses. On average, the seven factors accounted for a total of 54.8 % of variance (SD = 1.1 %) and corresponded to seven cognitive functions: 1) executive function/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.

On the group-level, there was an average post-surgery decline of 0.90 MDRS points/year (95% HDPI [-1.19, -0.62]) from an average pre-surgery MDRS performance of 140.34 out of 144 points (95% HDPI [139.61, 141.07]). After accounting for not only group-level variability but also patient-level variability for generalisation of the inference of the true score change to the CAPSIT-based population of STN DBS treated patients with PD, the estimate reached annual decline of 0.78 MDRS points/year (95% HDPI [-2.68, 0.85]). Finally, when changing the level of analysis from inference to prediction by adding measurement error to the estimates, expected annual post-surgery cognitive decline was 0.65 MDRS points/year (95% HDPI [-13.20, 10.81]). The results of the three level of analysis are graphically depicted in Figure 2.

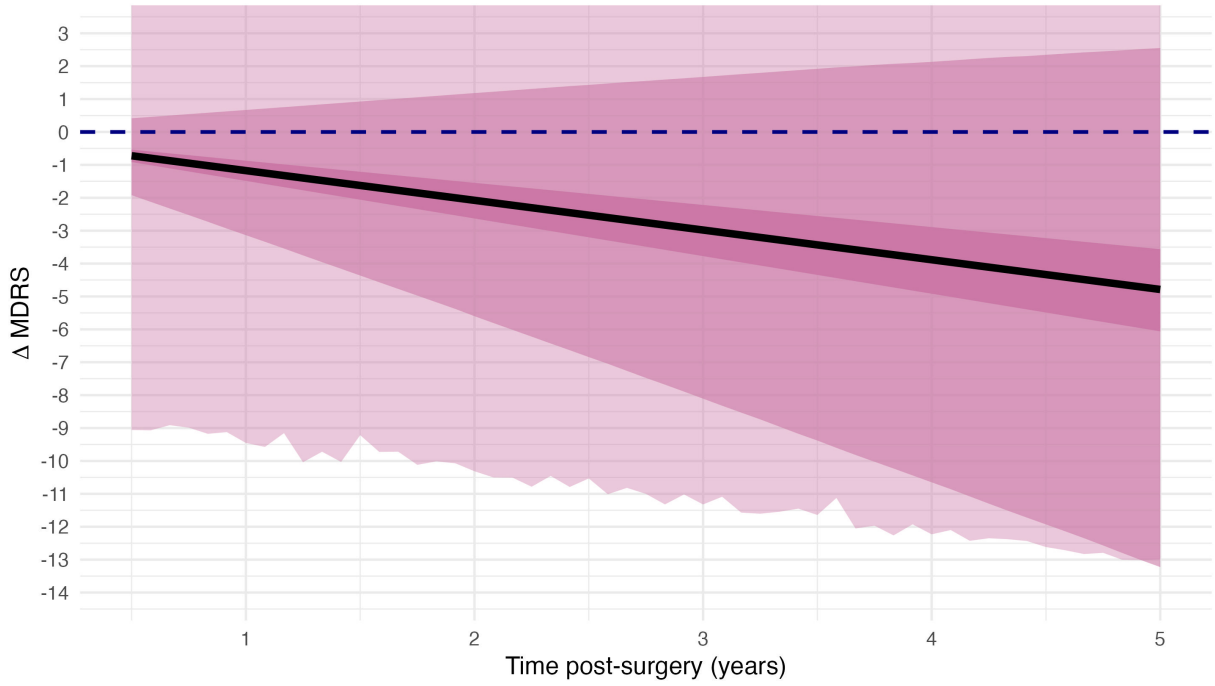

Figure 2

Post-surgery change scores estimates from the descriptive longitudinal model of Mattis Dementia Rating Scale (MDRS) change in patients with Parkinson's disease treated by subthalamic deep brain stimulation. The plot represents estimated change in MDRS with respect to pre-surgery assessment (ordinate) at different time lags from five months to five years post-surgery (abscissa) on three levels: point estimate (black line), inference at group- (dark pink) and population-level (medium pink), and prediction with added measurement error (light pink).

Cross-sectionally, pre-surgery MDRS performance was reliably predicted by the VWM factor score (β_{VWM} = -0.87, 95% HDPI [-1.64, -0.02], *pdir* = .986) and to a lesser extent by the SS factor score (β_{SS} = -0.69, 95% HDPI [-1.39, 0.02], *pdir* = .976). There was no cognitive test that would by itself statistically clearly indicate pre-surgery MDRS impairment. Post-surgery cognitive decline was associated with pre-surgery EF/Att. factor score with high posterior probability ($\delta_{EF/Att.}$ = -0.40, 95% HDPI [-0.64, -0.14], *pdir* = .999). There was no cognitive test that would by itself statistically clearly indicate post-surgery MDRS decline.

4.3 Structural and Microstructural Predictors of Cognitive Decline in Deep Brain Stimulation of Subthalamic Nucleus in Parkinson's Disease

In total, 72 patients split into 52 in the CS group (53.65 ± 8.27 years of age and 10.94 ± 8.27 years of disease duration at surgery, 46.2% males) and 20 in the CD

group (63.60 ± 5.42 years of age and 13.40 ± 5.47 years of disease duration at surgery, 70.0% males) were included.

In the cross-sectional analysis of pre-surgery MDRS, no macrostructural, FA or MD correlate of current pre-surgery cognitive performance was detected. On the other hand, the comparison of longitudinally defined CS and CD groups detected wide-spread differences in cerebral cortex thickness, subcortical structures grey matter volume, FA, and MD. Regarding the macrostructural correlates of post-surgery cognitive decline, CS patients had relatively higher cortical thickness in bilateral inferior parietal, insular, cingulate, sensorimotor, and visual cortices as well as higher volume of both putamina. Regarding the microstructural connectivity, analysis of DWI data detected higher FA in CS patients in medial temporal, inferior parietal, cingulate, and orbito-frontal cortex bilaterally as well as FA in the cerebellum and both hippocampi. The analysis further detected lower MD in CS patients' inferior parietal, orbito-frontal, dorsolateral prefrontal, and temporal cortices as well as both hippocampi and the left putamen. Both MD and FA detected bilateral differences between CS and CD subjects in the occipital cortex.

4.4 The Instrumental Activities of Daily Living in Parkinson's Disease Patients Treated by Subthalamic Deep Brain Stimulation

In total, 32 patients were included in the study (55.50 ± 7.78 years of age and 11.37 ± 3.67 years of disease duration at surgery, 14.20 ± 3.25 years of education, 56.25% males).

The main effect of time of assessment (post-surgery-minus-pre-surgery) in the *"descriptive"* model was positive and of uncertain probability of effect existence (δ_{Time} = 0.18, 95% HDPI [-0.11, 0.48], *pdir* = .883). On the other hand, the main effect of time of assessment in the *"direct effect"* model was positive and of high effect existence probability (δ_{Time} = 1.09, 95% HDPI [0.41, 1.74], *pdir* = 1.000). Figure 3 presents expected pre- and post-surgery response probabilities

of an average patient to an average PDAQ item according to the *"descriptive"* and *"direct effect"* models.

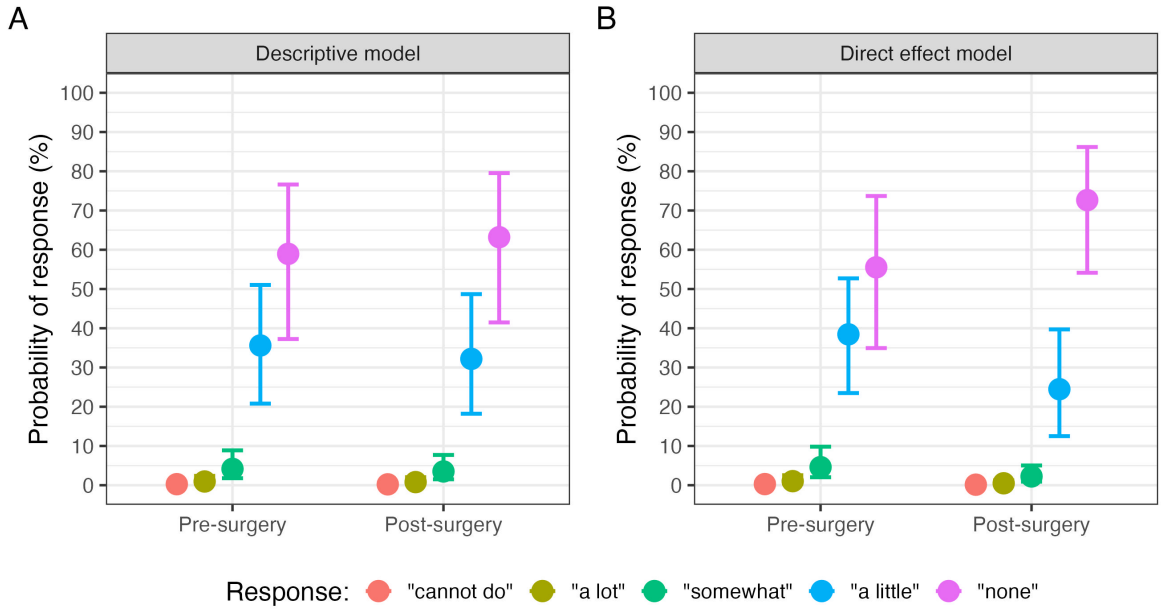

Figure 3

Summaries of the marginal posterior distributions of expected response probabilities to an average item from The Penn Parkinson's Daily Activities Questionnaire (PDAQ) by an average participant pre- and post-surgery according to the "descriptive" model (A), and the "direct effect" model (B). Potential responses to PDAQ items are differentiated by colour, points represent medians, and whiskers represent 95% equal-tailed intervals (ETIs) of posterior distributions.

Finally, in the *"total effect"* model, the main effect of the time of assessment was positive with high effect existence probability (δ_{Time} = 0.84, 95% HDPI [0.14, 1.45], *pdir* = .993), the main effect of LEDD was positive with high but uncertain probability of effect existence (β_{LEDD} = 0.17, 95% HDPI [-0.03, 0.39], *pdir* = .946), and the Time × LEDD interaction was positive with uncertain probability of effect existence (δ_{LEDD} = 0.16, 95% HDPI [-0.16, 0.47], *pdir* = .829). These results imply that the statistically uncertain improvement in IADL measured by the *"descriptive"* model can be partially explained by post-surgery LEDD reduction even though the LEDD itself has only a small statistically uncertain effect.

5. Discussion

5.1 Learning Curve in Verbal and Non-verbal Memory of Patients with Parkinson's Disease

Study 1 demonstrates that memory impairment profile of patients diagnosed with PD-MCI may vary across sensory modalities (*RQ1.3*). Although patients with PD-MCI exhibited overall *free recall* deficit in both visuospatial and auditory verbal free recall as compared to PD patients without MCI and healthy adults, the visuospatial memory deficit was characterised by impaired *immediate memory span* (*RQ1.1*) and relatively intact *learning curve* (*RQ1.2*) whereas the opposite pattern was observed in the auditory verbal memory. Previous study from our research group investigating similar research questions reported PD-related deficit in visuospatial *free recall* (PD-MCI < PD-NC < HC) with no statistically reliable between-group differences in the *learning curve* (the *immediate memory span* as operationally defined in this thesis was not examined in the previous work) (Bezdicek et al., 2019). The results presented here thus do not completely coincide with previous findings. However, some of these discrepancies may stem from the previous study having approximately half of the sample size of Study 1 leading to less precise estimates. Moreover, both studies imply that PD is associated with overall free recall deficit in visuospatial memory, that this deficit is especially pronounced in patients diagnosed with PD-MCI, and does affect the immediate memory span without affecting the learning curve. Finally, Brønnick et al. (2011) concluded that patients with de novo PD already show learning slope deficit in auditory verbal memory compared to healthy adults in a sample of 133 patients and 133 healthy controls further reinforcing the findings of this thesis.

Overall, Study 1 demonstrates that MCI can be associated with differential cognitive profiles in PD. Findings from Study 1 thus serve as a validation of the assumption that different cognitive profiles in neuropsychological

examination imply psychologically meaningful differences corroborating inferences of Study 2.

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

Study 2 shows that although on average the expected post-surgery cognitive decline in patients with PD treated by STN DBS is gradual and rather slow, there exists high inter-individual variability across patients (*RQ2.1*). This inter-individual variability can be partially understood by measuring patients' pre-surgery cognitive profile because pre-surgery executive dysfunction reliably predicts faster rate of post-surgery cognitive decline (*RQ2.2*).

The expected rate of cognitive decline reported here fell below previously estimated reliable change cutoffs for MDRS (Pedraza et al., 2007) implying that STN DBS is relatively safe from cognitive standpoint at least in mid-term (i.e., up to three years post-surgery). Moreover, the rate of post-surgery cognitive decline observed in our sample was relatively lower than most previously reported change scores (Gruber et al., 2019; Smeding et al., 2009).

Pre-surgery executive function/attention (EF/Att.) factor score was reliably predictive of the rate of post-surgery cognitive decline. However, neither any other pre-surgery cognitive factor score nor any single pre-surgery test score reached level of statistical evidence implying effect existence. Similar results were reported in previous studies which suggested that patients with pre-surgery executive deficit (operationally defined as performance on tasks such as Stroop test, Trail Making Test, Wisconsin Card Sorting Test or letter verbal fluency test) are at high risk of developing post-surgery dementia (Bove et al., 2020; Krishnan et al., 2019) and experiencing faster post-surgery cognitive decline (H.-J. Kim et al., 2014; Smeding et al., 2009).

Study 2 thus contributes to a substantial body of evidence implying that pre-surgery executive deficit is reliably predictive of post-surgery cognitive decline

in patients with PD who were selected for STN DBS treatment via current recommended criteria (Armstrong & Okun, 2020; Defer et al., 1999). Yet, it remains unclear which executive function components provide the most information for predicting post-surgery cognitive decline. Study 2 of this thesis can partially address this question courtesy of extracting from data two arguably distinct executive function-related factors in the predictive model. Most importantly, the pre-surgery EF/Att. factor that is according to data and models presented here with high certainty reliably predictive of post-surgery cognitive decline was loaded on primarily by timed test scores. Consequently, this factor may reflect a general processing speed component of executive function rather than any other high-level processes such as planning, problem solving, sensitivity to interference, set-shifting or mental flexibility. Processing speed has been shown to be impaired in clinically cognitively intact patients with PD and it was shown to be the primary executive component impaired in pre-clinical synucleinopathies (Cholerton et al., 2021; Leitner et al., 2024). The processing speed executive function component may thus be a reliable marker of disease progression sensitive to biological determinants of cognitively high-risk PD.

5.3 Structural and Microstructural Predictors of Cognitive Decline in Deep Brain Stimulation of Subthalamic Nucleus in Parkinson's Disease

Study 3 maps post-surgery cognitive decline to widespread pre-surgery changes in macrostructural and microstructural brain characteristics in MRI. Importantly, the study shows that patients at risk of future post-surgery cognitive decline can be identified via relatively lower cortical thickness, smaller subcortical structures' volume, and less anatomical connectivity already at pre-surgery assessment. This holds even though the two groups (i.e., cognitively stable and cognitively declining patients) can be at the pre-surgery point equivalent from neuropsychological point of view. This finding implies that rather than being a side effect of stimulation itself, post-surgery cognitive decline reflects disease progression with latent

structural brain changes present already at time of surgery in the form of weakened structural integrity or brain atrophy.

The brain areas associated with post-surgery cognitive decline were widespread in this study, including the expected sides such as basal ganglia as well as parietal, orbitofrontal and dorsolateral prefrontal cortices. However, several posterior structures were strongly implicated to correlate with post-surgery cognitive decline including both primary visual cortex as well as ventral and dorsal visual streams. The involvement of visual cortices in predicting post-surgery cognitive decline may aim our attention to further confounding factor related to the results of Study 2. Namely, all tests that significantly loaded on the EF/Att. factor with the exception of verbal fluency task are visually guided. On top of considering the processing speed executive function component to play a crucial role in predicting post-surgery cognitive decline in PD patients treated by STN DBS, dissociating perceptual visual processes from higher-order executive function is thus likely also needed to fully characterise cognitive phenotypes of PD.

5.4 The Instrumental Activities of Daily Living in Parkinson's Disease Patients Treated by Subthalamic Deep Brain Stimulation

Study 4 examines post-surgery changes in cognitively demanding IADLs and the possibility to affect these changes via intervening upon dopaminergic medication of patients with PD treated by STN DBS. Based on presented models and data, only a small and uncertain improvement in IADLs can be observed one year post-surgery (*RQ4.1*). However, this may be mainly due to post-surgery changes in competing causes of IADL as after adjusting for the competing causes identified in this study, the expected "unmasked" post-surgery improvement in IADL is statistically reliable (*RQ4.2*). One of these competing causes, the amount of dopaminergic medication operationally defined as LEDD, can be used to affect post-surgery IADLs (*RQ4.3*).

The primary added value of this study comes from disentangling putative total and direct causal effects of STN DBS on self-reported IADLs in carefully selected PD patients. Whereas the direct effect (*RQ4.2*) is large and reliable, its reflection in simple real life observation (i.e., the total effect, *RQ4.1*) is contaminated by STN DBS effects on other variables predictive of IADL change leading to a small and uncertain estimate. Most importantly, one significant and desirable outcome of STN DBS is dopaminergic medication reduction (Molinuevo et al., 2000). At the same time, the results of Study 4 imply that lowering LEDD leads to increase in IADL difficulties both pre- and post-surgery. As a result of these opposing effects whereby STN DBS decreases IADL difficulties directly but indirectly increases it via reducing LEDD, medical professionals may want to carefully consider how much to reduce the LEDD after STN-DBS surgery in PD patients to avoid negative effects on IADL.

5.5 General Discussion

The primary aim of this thesis was to identify pre-surgery cognitive factors predictive of post-surgery cognitive decline PD patients treated with STN DBS. The most relevant answers to this question come from the combination of Study 2 and Study 3 results. On the other hand, Study 1 provides justification for assumptions made by Study 2, and Study 4 expands score of this thesis by examining facets of cognitive functioning that affect patients' everyday functioning.

As is the case with all research, the interpretation of included studies is subject to some constraints on generality. Most importantly, all studies investigating STN DBS outcomes presented here lack control group. Consequently, the results can be safely generalised only to STN DBS treated patients that were selected for treatment using similar exclusion criteria as those applied in studies presented here (i.e., the CAPSIT protocol criteria or their equivalent, Defer et al., 1999). In order to generalise to PD populations defined in a different manner (most importantly a population of candidates for STN DBS), one would have to assert

further assumptions such as exchangeability between patients who pass CAPSIT-like criteria and those that do not. Due to this selection mechanism being applied to samples included in studies presented here, applying the results to guide selection of patients for STN DBS from a larger population of PD patients may lead to unexpected outcomes due to the collider bias (Cinelli et al., 2022). I thus advise against using the findings of this thesis as a basis for patient selection. Instead, the results can be directly used to single out patients who could benefit from more monitoring provided they were already selected for STN DBS treatment via the current best practices (Armstrong & Okun, 2020; Defer et al., 1999).

Finally, a significant patient-specific variable not directly considered in this thesis that garnered much attention lately is patients' genetic profile. Principally, heterozygous mutations in the glucocerebrosidase gene (GBA) have been associated with parkinsonism in general and faster cognitive decline in PD patients with STN DBD specifically (Avenali et al., 2024; Davis et al., 2016; Pal et al., 2022). Since datasets used in this thesis do not include genetic profiling data, the results do not explicitly account for the GBA status of included patients. However, because the GBA mutation status is patient-specific time-invariant characteristic, the statistical models used in Study 2 do in principle adjust their estimates for this factor implicitly via estimating patient-level parameters (McElreath, 2020). Presence of GBA+ patients in the dataset may thus partially explain the large inter-individual variability in true score changes identified by Study 2. Interestingly, GBA mutation in PD was previously associated with deficits in verbal working memory, set-shifting and visuospatial functions in PD (Mata et al., 2016). which is pattern almost identical to cognitive profile that was predictive of pre-surgery MDRS score cross-sectionally but was not predictive of post-surgery MDRS score longitudinally in Study 2. Further investigation into GBA association with cross-sectional cognitive profile, structural and functional brain characteristics, and longitudinal cognitive decline after STN DBS will thus significantly benefit our understanding of biological mechanisms underlying cognitive side effects of PD and its interplay with STN DBS.

6. Conclusions

Under the current guidelines for patient selection, the STN DBS treatment in combination with oral dopaminergic therapy is a relatively safe treatment option from a cognitive standpoint. Longitudinally, most patients do not reach level of cognitive decline that would be considered clinically significant sooner than three or more years post-surgery. Nonetheless, a high inter-individual variability in rate of post-surgery cognitive decline exists, possibly reflecting distinct PD phenotypes and their underlying genetic variants.

The conclusion that it is disease type rather than effect of stimulation as such that is responsible for differences in post-surgery cognitive decline rates between patients follows from the finding that already pre-surgery, the patients who are at risk of experiencing fast cognitive decline show processing speed deficit or widespread structural brain changes. These results hold in spite of a lack of differences in pre-surgery neuropsychologic assessment. However, it needs to be stressed that due to the lack of control group in studies of this thesis, these conclusions remain putative and ought to be subject of falsification attempts in future research.

Moreover, the STN DBS treatment appears to be safe or even beneficial for self-reported functional independence in a short-term. In this thesis, I suggested a push/pull mechanism whereby decrease in cognitively demanding activities of daily living difficulties due to commencing the STN DBS treatment is being counterbalanced by an increase of such difficulties due to dopaminergic medication reduction. Since dopaminergic medication reduction is itself a desirable outcome of STN DBS, achieving optimal results requires medication reduction that is high enough to bring about its intrinsic benefits, yet not too high to outweigh STN DBS benefits for reduction of PD-related post-surgery difficulties in cognitive daily living activities. Future research may more fully characterise the interplay between STN DBS and oral medication as factors influencing cognitively demanding activities of daily living by conducting longer longitudinal

observations as the effect of medication observed in this study could have resulted from large changes of medication levels in short time span rather than from the effect of medication as such.

Overall, this thesis aimed at identifying pre-surgery variables predictive of post-surgery cognitive decline in STN DBS treated PD patients. The results imply a profile of PD with processing speed deficit in tests of executive function and widespread structural brain changes including lower cortical thickness, subcortical volume and decreased anatomical connectivity. The findings presented here can serve as basis of clinical decision making as well as further theoretical development in defining high risk PD phenotypes for STN DBS.

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8. List of Publications

8.1 Publications Related to the Thesis

Mana, J., Bezdicek, O., Růžička, F., Lasica, A., Šmídová, A., Klempířová, O., Nikolai, T., Uhrová, T., Růžička, E., Urgošík, D., & Jech, R. (2024). Preoperative cognitive profile predictive of cognitive decline after subthalamic deep brain stimulation in Parkinson's disease. *European Journal of Neuroscience*, 1–21. https://doi.org/10.1111/ejn.16521 **[2023 Clarivate IF: 2.7]**

Filip, P., **Mana, J.**, Lasica, A., Keller, J., Urgošík, D., May, J., … & Růžička, F. (2024). Structural and microstructural predictors of cognitive decline in deep brain stimulation of subthalamic nucleus in Parkinson's disease. *NeuroImage: Clinical,* 103617. **[2023 Clarivate IF: 3.4]**

Bezdicek, O., **Mana, J.**, Růžička, F., Havlik, F., Fečíková, A., Uhrová, T., … & Jech, R. (2022). The Instrumental Activities of Daily Living in Parkinson's Disease Patients Treated by Subthalamic Deep Brain Stimulation. *Frontiers in Aging Neuroscience, 14,* 886491. **[2022 Clarivate IF: 4.8]**

Havlík, F., **Mana, J.**, Dušek, P., Jech, R., Růžička, E., Kopeček, M., … & Bezdicek, O. (2020). Brief visuospatial memory test-revised: Normative data and clinical utility of learning indices in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 42*(10), 1099-1110. **[2020 Clarivate IF: 2.475]**

8.2 Publications Unrelated to the Thesis

Mana, J., Vaneckova, M., Klempíř, J., Lišková, I., Brožová, H., Poláková, K., … & Bezdicek, O. (2019). Methanol poisoning as an acute toxicological basal ganglia lesion model: evidence from brain volumetry and cognition. *Alcoholism: Clinical and Experimental Research, 43*(7), 1486-1497. **[2019 Clarivate IF: 3.035]**

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