

# **Predictors of dementia after deep brain stimulation in Parkinson´s disease**

## **DISSERTATION THESIS**

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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 identify pre-surgery characteristics that would identify patients with high risk of developing post-surgery cognitive decline. The theoretical part provides a summary of current tools for measuring cognitive functions and a theoretical background linking brain circuits disorders to cognitive dysfunction in PD. In the empirical part, the primary objective is to identify 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 identifikovat předoperační charakteristiky pacientů s vysokým rizikem rozvoje pooperační kognitivní poruchy. V teoretické části jsou shrnutý moderní přístupy měření kognitivních funkcí a teoretické pozadí propojující poruchy mozkových okruhů s kognitivní dysfunkcí u PN. Hlavním cílem empirické části 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 pooperační 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 o progresi nemoci jakožto primárním faktoru 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

## Abbreviations and Definitions

**ADL** activities of daily living

**An.** Anxiety

**BADL** basic activities of daily living

**BDI-II** Beck Depression Inventory, second edition

**BVMT-R** Brief Visuospatial Memory Test

**CAPSIT** Core assessment program for surgical interventional therapies in Parkinson's disease

**CD** cognitively declining

**CFT** category verbal fluency test

**CIFTI** Connectivity Informatics Technology Initiative

**COMT** catechol-O-methyltransferase

**COWAT** Controlled Oral Word Association Test

**CS** cognitively stable

**CTT** classical test theory

**DAG** directed acyclic graph

**DBS** deep brain stimulation

**DS-B** Digit Span backward

**DS-F** Digit Span forward

**DSM-5** Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

**DWI** diffusion weighted imaging

**EF/Att.** executive function/attention

**EFA** exploratory factor analysis

**EM** episodic memory

**ETI** equal-tailed interval

**FA** fractional anisotropy

**FAQ** Functional Activities Questionnaire

**FDR** False Discovery Rate

**FP-DR**, Family Pictures delayed recall

**FP-IR**, Family Pictures immediate recall

**GBA** glucocerebrosidase gene

**GLM** General Linear Model

**GLMM** Generalized Linear Mixed Model

**GPe** external globus pallidus

**GPi** internal globus pallidus

**HC** healthy control

**HDPI** highest density posterior intervals

**HMC** Hamiltonian Monte Carlo

**IADL** instrumental activities of daily living

**IRT** Item Response Theory

**LEDD** levodopa equivalent daily dose

**LNS** letter-number sequencing

**MAO-B** monoamine oxidase-B

**MAPT** microtubule-associated protein tau

**MD** mean diffusivity

**MDRS** Mattis Dementia Rating Scale

**MDS** Movement Disorders Society

**MDS-UPDRS** MDS-Unified Parkinson's Disease Rating Scale

**MMSE** Mini-Mental State Examination

**MNI** Montreal Neurilological Institute

**MoCA** Montreal Cognitive Assessment

**MPRAGE** magnetisation-prepared rapid gradient echo sequence

**MRI** magnetic resonance imaging

**pdir** probability of direction

**PD** Parkinson's Disease

**PDAQ** Penn Parkinson's Daily Activities Questionnaire

**PD-CRS** Parkinson's disease-cognitive rating scale

**PD-D** Parkinson's Disease Dementia

**PD-MCI** Mild Cognitive Impairment in Parkinson's Disease

**PD-NC** Parkinson's Diseases with normal cognition

**PST-C**, Prague Stroop Test, interference condition

**PST-D**, Prague Stroop Test, dot colour naming condition

**PST-W**, Prague Stroop Test, naming colour of neutral words

**RAVLT-B** Rey Auditory Verbal Learning Test, recall of the interference set

**RAVLT-DR** Rey Auditory Verbal Learning Test delayed recall

**RAVLT-IR** Rey Auditory Verbal Learning Test, immediate recall

**RAVLT-Rec15** Rey Auditory Verbal Learning Test, delayed recognition, number of correctly identified from 15 items

**RAVLT-Rec50**, Rey Auditory Verbal Learning Test, delayed recognition from 50 items

**RCT** randomised controlled trials

**RMSEA** root-mean-square error approximation

**ROPE** region of practical equivalence

**RQ** research question

**Sim.** Similarities

**STAI-X1** State-Trait Anxiety Inventory, the state version

**STAI-X2** State-Trait Anxiety Inventory, the trait version

**SS**, set shifting

**SS-B**, Spatial Span backward

**SS-F**, Spatial Span forward

**STN** subthalamic nucleus

**SWM** spatial working memory;

**TE** echo time

**TI** inversion time

**TLI** Tucker-Lewis Index

**TMT-A** Trail Making Test, part A

**TMT-B** Trail Making Test, part B

**TOL** Tower of London

**TR** repetition time

**UPDRS** Unified Parkinson's Disease Rating Scale

**VAT** volume of affected tissue

**VM** visuospatial memory

**VWM** verbal working memory

**WAIS-III** Wechsler Adult Intelligence Scale, third revision

**WMS-III** Wechsler Memory Scale, third edition

# 1 Introduction

## 1.1 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder first described clinically in 1817 by Dr. James Parkinson in a case series of six patients under the name of "Shaking Palsy" (Parkinson, 2002). Between years 1990 and 2016, the age-standardised prevalence rates of PD increased by 21.7% globally causing substantial cost in terms of quality of life and increased death rate (Dorsey, Elbaz, et al., 2018). These data lead several authors to coin the term "*Parkinson Pandemic*" to describe increasing incidence and social cost of PD (Dorsey, Sherer, et al., 2018). PD is rare in people younger than 50 years of age but its prevalence increases with age. Furthermore, relatively more men are diagnosed with PD than women (in ratio approximately that is 1.4:1) (Armstrong & Okun, 2020; Dorsey, Elbaz, et al., 2018).

The defining neuropathological feature of PD is loss of dopaminergic neurons in midbrain's substantia nigra pars compacta and associated insoluble  $\alpha$ -synuclein aggregates called Lewy bodies (Simon et al., 2020). Dopaminergic denervation of substantia nigra's efferent connections to striatum (putamen and nucleus caudatus) of basal ganglia leads to dysregulation of the function of parallel cortico-basal ganglia-thalamico-cortical neural circuits and resulting clinical signs and symptoms (Obeso et al., 2000). Although dopaminergic deficiency within basal ganglia circuits seems to be the major mechanism accounting for most of the core features of PD, other neurotransmitters and brain structures are involved as well contributing to heterogeneity of PD symptomatology (Braak et al., 2003; Kalia & Lang, 2015).

### 1.1.1 Motor and non-motor symptoms

The hallmark of PD is parkinsonism, a clinical syndrome comprising of bradykinesia (i.e., slowness of initiation of voluntary movement) combined with muscular rigidity, rest tremor or postural instability (Hughes et al., 1992; Litvan et al., 2003; Postuma et al., 2015). Supportive criteria for clinical diagnosis of PD include unilateral onset, persistent asymmetry<sup>1</sup>, excellent response to levodopa treatment for five years or more, and progressive long-term clinical course. Although PD is primarily a motor disorder, it is now well established that its symptomatology includes significant non-motor features as well (Kalia & Lang, 2015). Indeed, some non-motor symptoms such as anxiety, depression, sleep disturbances, gastrointestinal dysfunction and 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; Lima et al., 2012).

In this thesis, the focus is on describing and predicting cognitive complications of PD. The ultimate manifestation of cognitive dysfunction in PD is Parkinson's disease dementia (PD-D), a disabling non-motor symptom that afflicts a substantial number of patients, especially at

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<sup>1</sup>However, the signs should not remain strongly lateralised later in disease course as strictly unilateral features after three years from diagnosis belong to exclusion criteria for clinical diagnosis of PD.

later stages of disease progression (Aarsland et al., 2003; Hely et al., 2008). PD-D is defined by a widespread cognitive deficit affecting several cognitive domains that is severe enough to impact patients' daily living (Dubois et al., 2007; Emre et al., 2007; Goetz, Emre, et al., 2008). It is usually associated with behavioural symptoms such as affective changes, hallucinations or apathy as well as high patient and caregiver burden (Emre et al., 2007; Leroi et al., 2012). Although the nigrostriatal dopaminergic pathology responsible for motor PD symptoms is well documented, pathophysiological mechanisms of PD-D remain largely unexplained. Contemporary theories assume that PD-D is caused by dysfunction of several dissociable functional brain circuits, neurotransmitter 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 (Gratwick et al., 2015).

### **1.1.2 Cognitive dysfunction in PD**

One of the most prominent hypotheses of cognitive decline in PD is the dual-syndrome hypothesis of Trevor Robbins and his collaborators (Kehagia et al., 2010, 2012; Robbins & Cools, 2014). This hypothesis distinguishes between two cognitive/motor phenotypes of PD: (i) patients with tremor as a dominant motor sign who show deficit in tests of planning, working memory and executive functions reflecting fronto-striatal dysfunction with profile of slowly progressing mild cognitive impairment in PD (PD-MCI), and (ii) patients with akinesia and gait disorder as dominant motor signs with early deficit in visuo-spatial functions and semantic memory reflecting posterior parietal and temporal dysfunction and rapid progression to PD-D. This distinction was based partially on an observation that conversion to dementia in de novo PD patients during a five-year time period is associated with higher age, MAPT (microtubule-associated protein tau) genotype with cortical Lewy bodies and non-dopaminergic deficits, and ensuing visuospatial and semantic verbal fluency deficit as opposed to fronto-striatal dopaminergic executive dysfunction moderated by catechol-O-methyltransferase (COMT) genotype (Williams-Gray et al., 2009). Recently, the dual-syndrome hypothesis received mixed support from a retrospective study of the Parkinson's Progression Markers Initiative database, whereby although the cognitive profiles extracted by a cluster analysis did not fully coincide with the hypothesis, the posterior cognitive profile was associated with later postural instability, gait disorder and greater dementia risk in a five-year observation interval in de novo PD patients (Summers et al., 2024).

In addition to defining the two general cognitive/motor phenotypes described above, the dual-syndrome hypothesis provides a description of putative neural circuits mechanisms of cognitive decline based on involvement of basal ganglia loops in non-dopaminergic neurotransmitter systems (Kehagia et al., 2012). Similar mapping between neurotransmitter systems and specific cognitive deficits was posited by other theories of cognitive dysfunction in PD and includes dopaminergic executive dysfunction, noradrenergic attention deficits, and acetylcholine related

memory, attention and visuospatial deficits (Fang et al., 2020; Gratwicke et al., 2015). Consequently, well defined cognitive domains and validated cognitive tests should be used for description of cognitive deficits in PD. In both everyday clinical settings as well as research, the gold standard of assessing cognitive functions and diagnosing cognitive dysfunction is the use of standardised neuropsychological tests and complex neuropsychological batteries.

### **1.1.3 Neuropsychologic evaluation**

To guide neuropsychological evaluation of PD patients' cognitive state, the International Parkinson and Movement Disorders Society (MDS) published criteria for PD-D and PD-MCI including recommendations of the structure of neuropsychological batteries that ought to be used for this purpose (Dubois et al., 2007; Litvan et al., 2012). Specifically, the MDS criteria differentiate between level I (abbreviated) and level II (comprehensive) categories of assessment. At level I, abbreviated assessment based on cognitive screening tests such as Mattis Dementia Rating Scale (MDRS), Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) or the Parkinson's disease-cognitive rating scale (PD-CRS) (Folstein et al., 1975; Jurica et al., 2001; Nasreddine et al., 2005; Pagonabarraga et al., 2008) or cognitive testing including less measures than level II is applied. Level I is less diagnostically accurate and thus can lead only to diagnosis of possible PD-MCI or PD-D. However, prior studies indicate acceptable agreement between PD-MCI diagnosis based on level I and level II assessments (Bezdicek, Michalec, et al., 2015; Mazancova et al., 2020; Uysal-Cantürk et al., 2018).

In contrast to the level I assessment, at level II, a comprehensive neuropsychological battery assessing the following cognitive domains each via at least two independent tests is required: (i) attention and working memory, (ii) executive function, (iii) language, (iv) memory, and (v) visuo-spatial function (Bezdicek, Sulc, et al., 2017; Dubois et al., 2007; Litvan et al., 2012). Within this framework, attention and working memory refers to the ability to orient, alert and control information flow through the cognitive system and is linked to fronto-parietal cholinergic and noradrenergic networks; executive function is an umbrella term for high-level cognitive abilities such as planning, problem solving, rule-shifting and response inhibition and is linked to fronto-striatal dopaminergic and noradrenergic networks; language refers to semantic processing including both production and comprehension of human speech and is linked to networks in premotor frontal as well as superior temporal cortical areas and their connections; memory refers to the cognitive processes involved in encoding, storage and retrieval of information and is linked to medial temporal lobe; and visuo-spatial function refers to perception of extrapersonal space and is linked to posterior cortical structures in occipital and parietal lobes (Gratwicke et al., 2015). As any of these domains or their combinations can be impaired in PD, the level II battery allows not only diagnosing PD-MCI or PD-D but also provides means for subtyping the deficit based on patients' cognitive profile (Litvan et al., 2012).

Although the assessment of patients' objective cognitive performance is critical for establishing whether or not a cognitive dysfunction is present, another core feature of both PD-D and PD-MCI definitions is functional independence in terms of activities of daily living (ADLs).

Specifically, if the objective cognitive deficit does not cause substantial deficit in ADLs then PD-MCI can be diagnosed, however, if the objective cognitive deficit leads to substantial ADLs disruption, the diagnosis of PD-D can be considered (Dubois et al., 2007; Litvan et al., 2012). In PD, the major confounding variable when establishing deficit in ADLs is the motor burden of the disease as ADL complaints can be caused by motor rather than cognitive symptoms complicating the diagnostic process (Becker et al., 2020, 2022). This issue can be partially alleviated by distinguishing between basic ADLs (BADLs) such as personal hygiene or dressing oneself, and cognitively demanding instrumental ADLs (IADLs) such as following instructions or doing more than one thing at a time. BADLs can be assessed by tools such as part II of MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS part II) (Goetz, Tilley, et al., 2008) and reflect primarily motor-driven difficulties due to PD. On the other hand, IADLs can be assessed via tools such as Functional Activities Questionnaire (FAQ) (Pfeffer et al., 1982) or PD-specific Penn Parkinson's Daily Activities Questionnaire (PDAQ) (Brennan et al., 2016a, 2016b) and reflect primarily cognitively-driven difficulties due to PD.

## 1.2 Deep brain stimulation

Since the major PD symptoms are caused by loss of dopaminergic cells in substantia nigra pars compacta, the first line of symptomatic treatment 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 doses and their frequency need to increase for equivalent therapeutic effect to be achieved. Moreover, dopaminergic medication-induced complications such as motor and non-motor fluctuations, dyskinesia or psychosis can emerge further decreasing patients quality of life (Kalia & Lang, 2015). At such later stages of the disease, several advanced treatment options exist including deep brain stimulation (DBS), levodopa-carbidopa intestinal gel infusion and subcutaneous infusion of apomorphine (Moore et al., 2020).

DBS is an advanced symptomatic treatment of motor symptoms of PD indicated primarily in patients who experience drug-resistant symptoms, the “wearing-off” phenomenon<sup>2</sup> or dyskinésias (Armstrong & Okun, 2020; Bronstein et al., 2011). The treatment involves neurosurgical procedure whereby electrodes are implanted into selected targets within the brain, then a subcutaneous battery source is implanted which delivers constant or intermittent electricity to the target structure (Lozano et al., 2019). The first cases of successful treatment of PD symptoms via DBS were reported by the Grenoble team of Benabid, Pollak, and their colleagues in the early 1990s (Cavallieri et al., 2024; Limousin et al., 1995; Pollak et al., 1993). The authors selected subthalamic nucleus (STN) as their stimulation target. To this date, STN, together with internal globus pallidus (GPi), is the most common DBS target for motor symptoms reduction in PD (Dallapiazza et al., 2018; Mao et al., 2019). Since this thesis regards STN

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<sup>2</sup>Wearing off is characterised by recurrence of PD symptoms and functional disability occurring immediately before the next medication dose is due.

DBS treated patients specifically, following discussion will focus exclusively on a population of patients treated by STN DBS.

### 1.2.1 Mechanisms of STN DBS

The STN was discovered in 1865 by a French anatomist Jules Bernard Luys (Parent, 2002).<sup>3</sup> It is a relatively small grey matter structure located between diencephalon and basal ganglia enveloped by fibres of the internal capsule. It is composed of glutamatergic projection neurons to both external globus pallidus (GPe) and GPi thus affecting the outcome of basal ganglia circuits to the thalamus (Hamani et al., 2004). More precisely, the classical model of cortico-basal ganglia-thalamico-cortical circuits defines two major projection systems, both of which receive excitatory cortical input (Albin et al., 1989). The “direct” pathway arises from inhibitory striatal neurons and projects monosynaptically to the outcome basal ganglia nucleus, the GPi (or the substantia nigra pars reticulata), which in turn projects to thalamic nuclei. The effect of the “direct” pathway is a pro-kinetic disinhibition of thalamus and its thalamo-cortical excitatory projections. On the other hand, the “indirect” pathway arises from a different set of inhibitory striatal neurons and project to the GPi polysynaptically via STN and GPe leading to an effect opposite to the effect of the “direct” pathway. The push/pull-like action of the two pathways plays an important role in processes such as action selection or scaling of movement parameters (Wichmann & DeLong, 2016). The STN not only receives connections from GPe (via the “indirect” pathway) but also from cortex directly (via the a third, “hyperdirect” pathway) making it a key modulator of cortico-basal ganglia-thalamico-cortical circuits (Nambu et al., 2002).

Although the classical model leads to an elegant explanation of the STN DBS effect on major PD symptoms according to which stimulation acts via inhibiting STN or its efferents and thus effectively down-regulating the “indirect” pathway resulting in a pro-kinetic effect, current theories acknowledge limitations of this useful but simplistic view and bring attention to phenomena such as spatial segregation, temporal dynamics and oscillatory activity of neurons in the circuit (Eisinger et al., 2019). Since this thesis is focused on investigating relatively abstract constructs such as cognitive functions or ADLs and their clinical significance in STN DBS treated PD patients rather than mechanisms of their pathophysiology, for the purposes of this text we identify two primary factors via which STN DBS influences PD symptoms, electrode location and stimulation frequency. Position-wise, there is evidence of somatotopic arrangement and functional dissociation of STN based on its cortical afferents (Bingham et al., 2023; Nambu et al., 2002). Importantly, the STN can be divided into sensorimotor dorsolateral area, and more ventral limbic and associative areas. For the STN DBS to reach optimal motor symptoms reducing effect while avoiding potential adverse cognitive and affective side effects, surgeons aim at stimulating the dorsolateral sensorimotor area preferentially. The

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<sup>3</sup>The STN was named several names during the history of neuroanatomy including the *Luys' body*, *nucleus amygdaliformis*, *corpus subthalamicum*, *discus lentiformis*, *Forel's body*, and *nucleus hypothalamicus*.

reason why stimulating other areas may lead to side effects relates to both location and stimulation frequency. Specifically, it has been theorised that relatively high stimulation frequency of basal ganglia circuits ( $>70$  Hz) has the desirable pro-kinetic (but anti-associative) effect whereas a low frequency stimulation ( $<10$  Hz) has a pro-associative (but anti-kinetic) effect in PD (David et al., 2020). The most commonly employed high frequency stimulation can thus, at least in principle, cause cognitive side effects if applied to the associative area of STN (see Reich et al., 2022).

### **1.2.2 Describing cognitive outcomes after DBS**

DBS successfully reduces motor symptoms as well as medication burden (operationally defined as the levodopa equivalent daily dose, LEDD) (Jost et al., 2023; Tomlinson et al., 2010) and improves patients' quality of life (Bratsos et al., 2018), however, 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; Combs et al., 2015; Mehanna et al., 2017; Parsons et al., 2006; 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; Williams-Gray et al., 2013), they show that substantial subset of STN DBS treated patients experience severe cognitive decline after surgery.

When describing post-surgery cognitive decline, studies can be broadly divided to two groups: (i) randomised controlled trials (RCTs), and (ii) long-term observational studies. In a typical RCT, patients are randomised to treatment and placebo groups and outcomes are compared in a full factorial design (representing the estimand of interest as an interactions between group and time of assessment) (Schüpbach et al., 2007). If the experimental allocation works properly, RCTs allow for causal inference without further statistical adjustments (Pearl, 2009), and are thus well suited for providing guidelines for patient selection.

Albeit RCTs can be regarded as a gold standard for causal inference, they are ethically problematic in the long-term (i.e., more than three years after surgery) due to the need for declining the treatment to patients who would most likely significantly benefited from it. On the other hand, observational studies usually do not allow for causal identification due to the selection bias intrinsic to their data sampling strategy (Cinelli et al., 2022) but they allow researcher to ask questions about long-term post-surgery cognitive trajectories without violating ethical standards. Although the longitudinal observational studies are not well suited to inform patient selection guidelines, they can serve as a basis for selecting high-risk STN DBS treated patients who would benefit from increased monitoring.

### 1.2.3 Predicting cognitive outcomes after DBS

One strategy that can be used within the framework of longitudinal observational study to inform researchers and medical practitioners about potentially high-risk patients is predicting post-surgery outcomes by pre-surgery patient characteristics. Although a large array of pre-surgery patient characteristics could be used to predict later cognitive decline, in medically treated patients with PD, the baseline cognitive profile proved to be especially informative outperforming other demographic, clinical and genetic factors in a large longitudinally followed cohort (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; Levy et al., 2002; 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 neuropsychological assessment of the type described in previous sections. 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 functions 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) while other studies examined the effect stimulation electrodes position within STN as a predictor of post-surgery cognitive decline (Reich et al., 2022).

The majority of prior studies describing and predicting longitudinal post-surgery cognitive decline employed pre-surgery/post-surgery design with change scores as their dependent variable (Gruber et al., 2019; H.-J. Kim et al., 2014; Planche et al., 2018; Reich et al., 2022). 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; Lord, 1956). 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). True score (and by extension true score change) is a concept central to the psychometric classical test theory (CTT) that is used as an interpretation framework in most of the studies reported in this thesis. In CTT, a true score is operationally defined as the expected value of one's scores in a neuropsychological task during a hypothetical “brainwashing” experiment whereby the examined person is brainwashed after finishing the task to remove their memory of responding

and administered the task again repeatedly (Van Bork et al., 2023). 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. In other words, the thesis ought to indicate which cognitive functions are likely to be impaired already at pre-surgery neuropsychologic assessment in patients that go on to show relatively faster post-surgery cognitive decline, and at the same time it should show which cognitive functions are likely to be relatively unimpaired at pre-surgery assessment in patients who enjoy good long-term post-surgery cognitive health.

Secondary aims are to enhance the description of pre-surgery cognitive profile prognostic of post-surgery cognitive decline in STN DBS treated PD patients 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.

To achieve these research goals, I begin by showing that psychologically meaningful differences between patients with and without cognitive impairment can be even in principle observed by studying differences in verbal and non-verbal memory learning curves of PD patients with and without diagnosed PD-MCI (Havlík et al., 2020). Next, I present a longitudinal study that includes data of 126 PD patients repeatedly screened for cognitive dysfunction while being treated by STN DBS (Mana et al., 2024). Discussion regarding this study will comprise the majority of the thesis as it directly addresses its primary research aim. Finally, I build upon the second study by addressing the secondary aims by exploring pre-surgery structural connectivity profile in MRI of patients who experience severe post-surgery cognitive decline (Filip et al., 2024), and relating the objective post-surgery cognitive performance assessed in laboratory settings to patients' subjective difficulty in performing cognitively demanding IADLs (Bezdicek et al., 2022).

The estimates computed in each included study provide valid answers to the research questions under the set of hypotheses that *H1*) Declarative memory deficit profile in PD-MCI varies by modality of memory processes; *H2*) pre-surgery cognitive profile contains information about factors that influence post-surgery cognitive decline in STN DBS treated patients with PD; *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; and *H4*) STN DBS causes a change in self-reported difficulties in IADLs that can be mediated by objective cognitive functioning, affective state, and LEDD.

Following the most recent recommendations of the American Statistical Association on statistical significance (Wasserstein & Lazar, 2016), in majority of presented studies, I do not apply any decision threshold to arrive at conclusions from the data (principle 3), and I share software code used to arrive at results presented in this thesis (principle 4). Study 3 constitutes an exception from this rule as it is based upon analysis of MRI data which is a subfield with a

long tradition of using decision thresholds to bring attention to potentially significant brain areas with respect to an outcome of interest.

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

Declarative memory is one of the cognitive domains that may be impaired even in non-demented PD patients (Bezdicek et al., 2018; Curtis et al., 2019; Domellöf et al., 2015). When taking into account potential mechanisms causing 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; Chiaravalloti et al., 2014), 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. To improve our understanding of this distinction, Study 1 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 and learning curve between PD patients with and without diagnosis of MCI and healthy adults vary according to sensory modality?

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

As discussed in the Introduction section, the STN DBS treatment in PD patients has been associated with heterogenous cognitive outcomes with prior studies reporting findings ranging from small to moderate post-surgery decline in verbal fluency to equivocal results for other cognitive domains (Bucur & Papagno, 2023; 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 guiding post-surgery patient monitoring. 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?

### **2.3 Study 3: Structural and microstructural predictors of cognitive decline in deep brain stimulation of subthalamic nucleus in Parkinson's disease**

Another, increasingly popular modality for predicting post-surgery cognitive decline is pre-surgery profile of anatomy and structural or functional connectivity of patients' brain in MRI (Blume et al., 2017; Costentin et al., 2019; Planche et al., 2018). Consequently, 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?*

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

Whereas studies 1-3 focus on describing patients' in-laboratory cognitive performance, 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. This is the only included study that aimed to address causal questions, in this case, disentangling the total and direct effect of DBS on IADL in Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT) (Defer et al., 1999) protocol selected population of PD patients and estimating the total effect of post-surgery LEDD manipulation on post-surgery self-reported IADLs. 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?*

## 3 Methods

The following section details examined samples, materials and methods, operational definitions of key variables, and statistical models used in each of the presented studies. Across all studies, attention is paid to strictly differentiating inference and prediction (Zhang et al., 2023), and across most studies (with the exception of Study 3), different levels of inference and prediction are employed (Yarkoni, 2020). As these distinctions and strategies are typically not discussed in neuroscience literature, I will now briefly introduce each one of these (see references provided above for more thorough discussion of these topics).

The distinction between inference and prediction is implicitly present in each quantitative study using statistical tools to arrive at its conclusion. Inference refers to statements about parameters whereas prediction refers to statements about unseen observations. As an example, consider the canonical CTT equation, i.e.,  $y = \tau + \epsilon$ . In this equation,  $y$  represents the observed score,  $\tau$  represents the true score, and  $\epsilon$  represents measurement error. Any statistical statements about  $\tau$  (such as frequentist  $p$ -values or Bayesian posterior probabilities of model parameters) consider only uncertainty related to  $\tau$  and constitute inference, whereas statistical statements about  $y$  (such as expected values for new repeats of the sampling procedure) consider uncertainty in both  $\tau$  as well as  $\epsilon$  and constitute prediction. Since inference leads to smaller uncertainty estimates, reporting both inference and prediction results in more transparent presentation of findings than reporting inference only (Zhang et al., 2023).

Further methodological complexity associated with the studies presented in this thesis stems from the fact that in most cases, the datasets include repeated measures of the response variable within patients. Such a hierarchical data structure allows for a straightforward use of multilevel models which estimate both group- and patient-level parameters. Consequently, the inference can be described for group-level parameters and group- and patient-level parameters together, the latter of which is one of the ways to increase generalisability of research findings (Yarkoni, 2020). Furthermore, modelling patient-level parameters results in partial pooling of parameter estimates (shifting parameter estimates towards each other), which reduces the influence of outliers and facilitates more reliable group-level inference (Gelman et al., 2012; Tuerlinckx et al., 2006).

### 3.1 Learning curve in verbal and non-verbal memory of patients with Parkinson's disease

#### 3.1.1 Participants

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). The exclusion criteria were as

follows: PD-D according to MDS criteria (Dubois et al., 2007; Emre et al., 2007), atypical or secondary parkinsonism, severe or unstable depression, psychotic symptoms (hallucinations or delusions) including those caused by medication, and other medical or neurological conditions potentially resulting in cognitive impairment (e.g., history of seizure, stroke or head trauma). 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 test battery described below.

### 3.1.2 Measures

All participants were examined with MoCA screening test for signs of overall cognitive deterioration (Kopecek et al., 2017; Nasreddine et al., 2005). The healthy control group was further examined via a complex test battery (Štěpánková et al., 2015) whereas PD patients underwent a standardized battery for PD-MCI according to the MDS Task Force level II criteria (Bezdicek, Sulc, et al., 2017; Bezdicek, Nikolai, et al., 2017; Litvan et al., 2012). For the purposes of the current study, only the Czech versions of Brief Visuospatial Memory Test (BVMT-R) (Benedict, 1997) and Rey Auditory Verbal Learning Test (RAVLT) (Bezdicek et al., 2014) were analysed.

The BVMT-R is a test of visual and spatial declarative memory consisting of a grid of six figures for the participant to remember and draw after 10 seconds of exposure. The stimulus sheet is presented to the participant three times resulting in three 0-12 scores (maximum two points per figure) representing visuospatial *immediate memory span* (the first trial) as well as visuospatial *learning curve* (difference between successive further trials). The test further includes delayed free recall and delayed recognition trials (Benedict, 1997) which were not analysed in this thesis.

The RAVLT is a test of verbal declarative memory consisting of a list of 15 words presented in five consecutive trials always followed by an immediate recall. Consequently, the data consist of five 0-15 scores (one point for each word correctly recalled) representing verbal *immediate memory span* (the first trial) as well as verbal *learning curve* (difference between successive further trials). The test further includes interfering list recall, post-interference recall, delayed free recall, delayed recognition, and delayed recognition with forced-choice (Bezdicek et al., 2014; Frydrychová et al., 2018) which were not analysed in this thesis.

### 3.1.3 Statistical analyses

RAVLT and BVMT-R data were analyzed using Bayesian generalised linear mixed models (GLMMs) (Gelman & Hill, 2006; McElreath, 2020; Tuerlinckx et al., 2006). 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 modeled 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) (Lewandowski et al., 2009) prior for participant-level correlation matrices.

To evaluate the memory profile of PD patients in RAVLT and BVMT-R, difference between group-specific marginal means across trials (main effects contrasts) was estimated first. Although difference in these marginal means indicates potential memory deficit in some of the groups, it does not indicate whether the deficit is due to impaired *immediate memory span* or impaired *learning curve*. Between-group differences in marginal means of the first trial performance (simple effect contrasts) as a measure of *immediate memory span*, and between-group differences in marginal trends of the logarithmic trial order parameter (interaction contrasts) as a measure of *learning curve* were thus compared next. 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. Marginal means were also compared via percentage in region of practical equivalence (*ROPE*) as an index of effect significance. *ROPE* was set to an interval ranging from  $-0.1$  to  $0.1$  of standard deviation of the outcome variable according to the Czech normative data. 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). Four parallel chains were run each for 2,000 iterations for each GLMM. The first 1,000 iterations served as a warm-up and were discarded. Convergence was checked numerically by inspection of the  $\hat{R}$ s and visually by inspection of trace plots. Full analysis code is available at [https://github.com/josefmana/pd\\_learCUR.git](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

### 3.2.1 Participants

The study involved 126 patients with idiopathic PD following United Kingdom Parkinson's Disease Society Brain Bank Criteria (Hughes et al., 1992) that 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 CAPSIT protocol (Defer et al., 1999), consequently, patients with atypical parkinsonian syndromes, dementia, depression, recurrent psychotic conditions or a gait disorder despite

optimal dopaminergic therapy during pre-surgery assessment were not implanted and were thus not included into the study.

### **3.2.2 Neuropsychological examination**

Pre-surgery neuropsychological assessment examined the following cognitive domains: (i) attention via Trail Making Test, part A (TMT-A) (Bezdicek et al., 2012; Bezdicek, Stepankova, et al., 2017; Partington & Leiter, 1949) and dot colour naming condition from Prague Stroop Test (PST-D) (Bezdicek, Lukavsky, et al., 2015) for sustained visual attention; (ii) executive functions via Trail Making Test, part B (TMT-B) (Bezdicek et al., 2012; Bezdicek, Stepankova, et al., 2017; Partington & Leiter, 1949) for set shifting, Tower of London task (TOL) (Michalec et al., 2017; Shallice, 1982) for planning, Prague Stroop Test, naming colour of neutral words (PST-W) and interference condition (i.e., naming colour of contrasting colour words, PST-C) for sensitivity to interference (Bezdicek, Lukavsky, et al., 2015), and Controlled Oral Word Association Test (COWAT, letters K + P) (Nikolai et al., 2015) for mental flexibility; (iii) language via 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 via Digit Span forward and backward (DS-F and DS-B) from WAIS-III (Wechsler, 2010) as well as letter-number sequencing (LNS) (Wechsler, 2011) and Spatial Span forward and backward (SS-F and SS-B) from Wechsler Memory Scale, third edition (WMS-III) (Wechsler, 2011) for auditory and spatial working memory respectively; and (v) memory via Rey Auditory Verbal Learning Test (RAVLT) (Bezdicek et al., 2014; Frydrychová et al., 2018) 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; Jurica et al., 2001). Moreover, 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. Finally, the levodopa equivalent daily dose (LEDD) was calculated at each assessment time-point according to Tomlinson et al. (2010). All reported assessments were performed in ON medication state pre-surgery, and ON medication as well as ON stimulation state post-surgery.

### **3.2.3 Estimands**

Theoretical estimands linked to each research question of this study and their mapping to statistical estimators according to framework of Lundberg et al. (2021) are presented in Table 1. Regarding *RQ2.1*, the expected cognitive decline was estimated on two levels of generalisation:

(i) the current sample and (ii) a population of patients selected for DBS treatment via the CAPSIT-protocol criteria (Defer et al., 1999). Whereas virtually all previous studies examining long-term cognitive changes after STN DBS constraint their conclusions to sample-level estimates as even studies employing GLMMs elected to report fixed-effects only (Boel et al., 2016; Pal et al., 2022), in this study the hierarchical structure of GLMMs was leveraged to provide both sample- and population-level estimates. To allow for this generalisation, exchangeability between patients selected via CAPSIT criteria is assumed to the extend that can be quantified by patient-level variance estimated from the current sample (see Yarkoni, 2020). Empirical estimands were the same unit-specific quantities as those presented in Table 1, conditional on patient being selected for the study (based on geographical and exclusion criteria described above). Importantly, all three estimands are descriptive, not causal.

Table 1: Mapping of research questions to estimands to quantities to be estimated in the study.

Research question	Estimand (unit specific quantity)	Estimand (population)	Statistical estimator
What is the size of expected long-term rate of cognitive decline after STN DBS in PD patients?	Difference between expected post-surgery cognitive performance and expected cognitive performance $k$ years before	Current sample	$\mu_i = \alpha + \delta_{time} time_i$
What is the pre-surgery cognitive profile that is predictive of long-term post-surgery cognitive decline in STN DBS treated PD patients?	Difference between expected post-surgery cognitive decline of a patient with fixed level of pre-surgery performance across all cognitive factors and expected post-surgery cognitive decline of patients with performance that is one unit smaller in a single cognitive factor but equal to this patient's performance otherwise	CAPSIT-based selected patients Current sample	$\mu_i = \alpha + \delta_{time} time_i + \alpha_{id[i]} + \delta_{id[i]} time_i$ $\mu_i = \alpha + \delta_{time} time_i + \sum_j factor_{[j]i} (\beta_{factor[j]} + \delta_{factor[j]} time_i)$

### 3.2.4 Statistical analyses

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 (Harman & Jones, 1966). All pre-surgery cognitive tests were entered into EFA as input variables. 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 (Thomson, 1951). 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. 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 it identified similar factors across imputed data sets.

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. The group-level slope of this model constituted the statistical estimate of the sample version of the *RQ2.1* estimand (i.e., the expected annual cognitive decline in the sample). To arrive at the statistical estimate of the population version of the *RQ2.1* estimand (i.e., the expected annual cognitive decline in a population of patients selected for surgery using CAPSIT-protocol criteria), the model was used to infer expected cognitive decline at one year post-surgery intervals compared to a pre-surgery assessment using both group- and patient-level parameters. Although both variants of *RQ2.1* are inferential on different levels of generalisation, predictions were also computed to quantify the amount of measurement error in the outcome.

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. Since MDRS scores may include significant outliers, Student-t was used instead of Gaussian measurement error model. Furthermore, because MDRS has a maximum of 144 points which is achieved by a large proportion of healthy people (Bezdicek, Michalec, et al., 2015), the right-censored version of Student-t was used to account for the ceiling effect. Estimands relating to *RQ2.2* comprised of the two sets of interaction coefficients representing the expected prognostic value of single pre-surgery cognitive tests and latent cognitive factors. 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. When presenting results for the second version of *RQ2.1* estimand, medians and 90% equal-tailed posterior probability intervals (ETIs) were reported instead. A 90% ETI can be interpreted such that a given parameter or prediction lies with 5% probability above its upper bound and with 5% probability below its lower bound. Time-dependent parameters are denoted  $\delta$  and time-independent parameters are denoted  $\beta$  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). 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  $\hat{R}$ s and visually by inspection of trace plots. R package "tidyverse" was used for data operations, "tidybayes" was used for operations with model posteriors, and "ggridges," and "patchwork" were used for plotting (Kay, 2023; Pedersen, 2020; Wickham, 2016; Wickham et al., 2019; Wilke, 2024). Full analysis code is available at [https://github.com/josefmana/dbs\\_cogPRED.git](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**

#### **3.3.1 Participants**

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. Exclusion criteria were general contraindications to MRI examination (see Study 2), substantial vascular or space occupying brain lesions or a neurological or psychiatric disorder other than PD and its related complications. 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 ( $\Delta\text{MDRS} = \frac{\text{MDRS}_{\text{post}} - \text{MDRS}_{\text{pre}}}{\text{Years post-surgery}}$  ). Patients with  $\Delta\text{MDRS}$  of -2 or less were labelled as cognitively declining (CD) group, the remaining patients were considered cognitively stable (CS).<sup>4</sup> Furthermore, at each measurement occasion, patients' cognitive state was categorised as possible PD-MCI or PD-NC based on MDRS cutoff 139/140 derived from the Czech normative study as the threshold with the best specificity and sensitivity (both  $\sim .80$  ) (Bezdicek, Michalec, et al., 2015). The cognitive testing was performed in ON medication state pre-surgery, and ON medication as well as ON stimulation state post-surgery.

<sup>4</sup>This choice was based on the reasoning that patient who would score 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.

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  $2.0 \times 2.0 \times 2.0$  mm<sup>3</sup>, TR = 9,000 ms, TE = 94 ms, FA = 90°, single b-value of 1100 s/mm<sup>2</sup>, and 30 directions with 5 additional b0 images, acquired with antero-posterior phase encoding direction. Post-surgery T1w scan with MPRAGE sequence, 1.0 mm isotropic resolution, TR = 2,140 ms, TI = 1,100 ms, TE = 3.93 ms, and flip angle = 15° acquired using a 1.5 T MAGNETOM Avanto scanner (Siemens, Erlangen, Germany) was utilised to estimate position of the DBS electrodes.

### 3.3.2 MRI data processing

For a full MRI data processing pipeline, see the source article (Filip et al., 2024). Shortly, the goal of MRI processing was to (i) transform the raw T1w images from their native space to standardized Montreal Neurological Institute (MNI) space (Grabner et al., 2006) to guide connectivity analyses and estimate subcortical grey matter volumes, (ii) extract structural connectivity metrics from DWI images, and (iii) extract cortical thickness estimates. Pre-processing steps followed the minimal preprocessing pipeline for the Human Connectome Project leading to set of standard Connectivity Informatics Technology Initiative (CIFTI) files in grayordinate space (Glasser et al., 2013). This process resulted in extracting following predictors of interest: (i) fractional anisotropy (FA) and mean diffusivity (MD) as proxies of microstructural connectivity, and (ii) cortical thickness and subcortical grey matter (based on 69 subcortical regions of interest) as proxies of macrostructural integrity. Lastly, Lead-DBS software version 2.5.3 (Horn et al., 2019; Horn & Kühn, 2015) was utilized to determine the position of DBS leads and active contacts with DISTAL subcortical atlas for STN compartmentalization (Ewert et al., 2018). The overlap of volume of affected tissue (VAT) at the time of last recorded cognitive assessment and the entire STN as well as its associative and limbic components separately was calculated, providing three overlap volumes for each side.

### 3.3.3 Statistical analyses

Outcome data were described separately for CS and CD groups. The null hypothesis of zero difference between means of continuous variables was tested using independent samples two-tailed t-tests, and the null hypothesis of stochastic independence of rows and columns in frequency tables of nominal variables was tested using Fisher's exact test. Differences were considered statistically significant if their *q*-value was lower than .05 after adjusting for 5% False Discovery Rate (FDR) (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001). 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 (FA and 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 (i.e., no interaction between the primary predictor and variables from the covariate set was allowed). 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 permutations and FDR correction 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**

#### **3.4.1 Participants**

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 with identical exclusion criteria as in Study 2 and Study 3 (except for the MRI-specific exclusion criteria of Study 3). All PD 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 (Jost et al., 2023; Tomlinson et al., 2010).

#### **3.4.2 Assessments**

Both pre-surgery and post-surgery neuropsychological assessment was performed in accordance with published recommendations (Kubu, 2018) and included cognitive screening via MDRS (Bezdicek, Michalec, et al., 2015; Jurica et al., 2001), screening of depressive symptoms via BDI-II (Beck et al., 1996; Ciharova et al., 2020), and the PDAQ as a measure of IADL. The PDAQ is a brief self-report tool consisting of fifteen items selected by Item Response Theory (IRT)-based statistics from a larger pool of items asking patients about the level of difficulties they experience with cognitively demanding IADLs on a five-point Likert scale ranging from 0 ("cannot do") to 4 ("no difficulty") (Brennan et al., 2016a, 2016b). Finally, during the comprehensive pre-surgery assessment for STN DBS patient selection and post-surgery control assessment, motor function was evaluated via part III of MDS-UPDRS administered by a trained movement disorders neurologist, and psychiatric symptoms were evaluated by a neuropsychiatrist with specialisation in movement disorders to assess risky neuropsychiatric complications. All neuropsychologic assessments were performed in ON medication state pre-surgery, and ON medication as well as ON stimulation state post-surgery. The MDS-UPDRS III was ON as well as OFF medication pre-surgery, and ON as well as OFF stimulation in OFF medication state post-surgery.

### 3.4.3 Causal assumptions

Causal assumptions of Study 4 are represented in the form of a directed acyclic graph (DAG) depicted in Figure 1. Full description of this graphical model is presented in the source article (Bezdicek et al., 2022). 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.<sup>5</sup> The only difference between the model presented in Figure 1 and the source paper is that here I added further edges from the patient node to DBS node as well as all clinical characteristics on top of its edge to PDAQ. This change is meant to represent the assumption that patient-specific time-invariant characteristics (such as disease type or genetic profile) affect not only PDAQ responses but also all the other variables in the model. Nonetheless, adding edges from the patient node did not change the adjustment sets needed to answer the research questions compared to the source article.

Importantly, to answer *RQ4.2* and *RQ4.3*, the back-door criterion can be applied to the DAG presented in Figure 1 to derive *adjustment sets*, i.e., the set of covariates that, if conditioned on, allow for interpretation of statistical modelling results as causal (Cinelli et al., 2022; McElreath, 2020; Pearl, 2009). Applying the back-door criterion, we arrive at adjustment sets presented in panels B and C of Figure 1 for *RQ4.2* and *RQ4.3* respectively. Variables that should be adjusted for in the statistical model are represented by squares and the back-doors that are being closed by these adjustments are depicted as light grey edges in the figure. Although the adjustment set in panel C in Figure 1 does not contain the “item” node, item-level parameters were still included into analysis because they represent competing causes and their inclusion thus will not lead to bias while potentially improving statistical efficiency (see Model 8 in Cinelli et al., 2022).

### 3.4.4 Statistical analyses

The data were analyzed 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 dependend 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 panel B of 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

<sup>5</sup>Note that the decision to exclude 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.

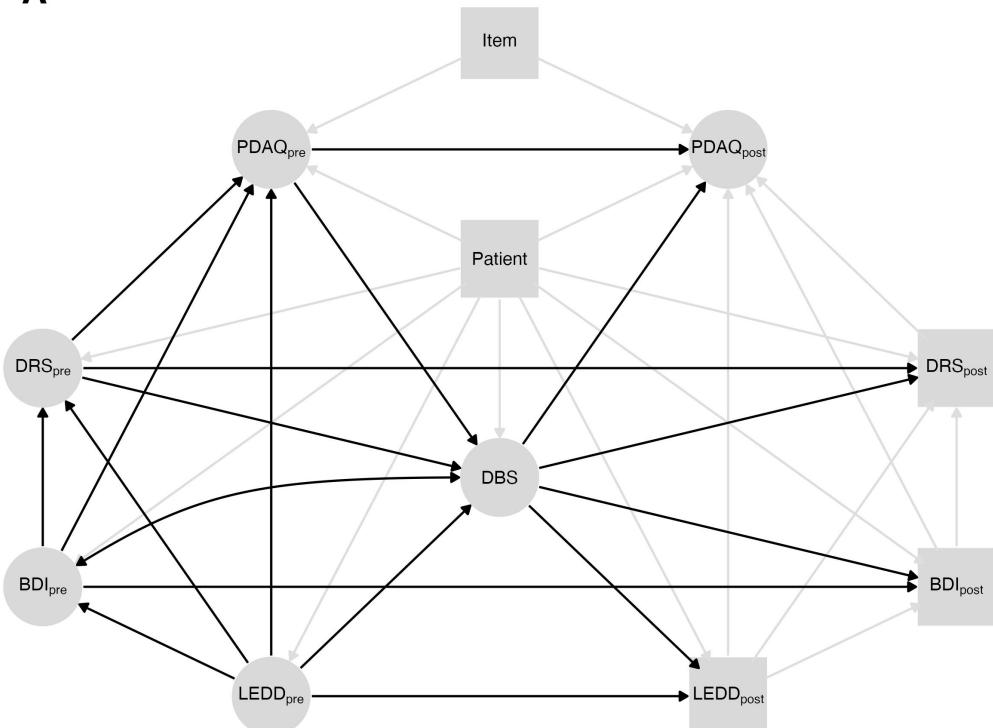
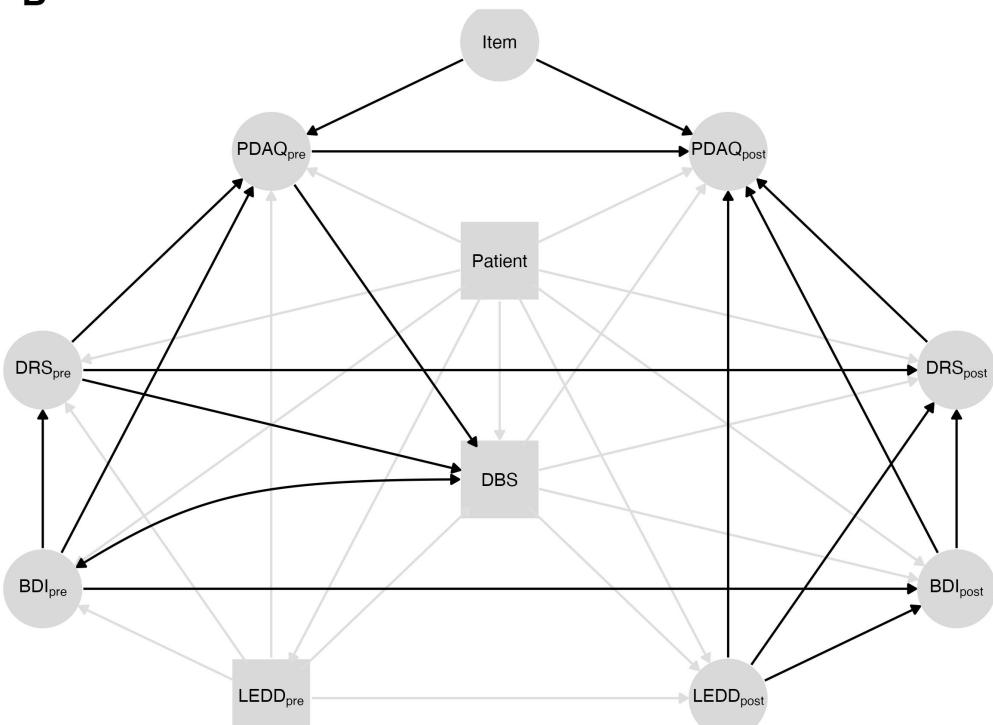
**A****B**

Figure 1: Directed acyclic graph representing causal assumptions of relationships between variables of the Study 4. Panels represent model after adjusting for covariates to extract estimate of direct post-surgery change (A), and total effect of post-surgery LEDD on post-surgery IADL (B). Conditional on the model, black lines represent causal influences that contribute to measured associations whereas grey lines represent causal influences that do not contribute to measured association after adjusting for variables in circles. In both figures, the outcome of interest is the PDAQ<sub>post</sub> variable.

model for *RQ4.2* (i.e., the “*direct effect*” model). Finally, following panel C of 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 modeled using the ordered-logit response function (Bürkner & Vuorre, 2019; Liddell & Kruschke, 2018; McElreath, 2020; also called cumulative logit model or graded response model in the literature, Samejima, 1995). Unlike the rest of included studies that ought to be interpreted in terms of CTT, the model of Study 4 thus constitutes an IRT model (Bürkner, 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 *pdirs*. Further results were presented as posterior predictions of marginalised response probabilities described by their medians and 95% HDPIs. Time-dependent parameters are denoted  $\delta$  and time-independent parameters are denoted  $\beta$  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). Four parallel chains were run each for 2,000 iterations for each GLMM with the first 1,000 iterations being discarded as a warm-up. Convergence was checked numerically by inspection of the  $\hat{R}$ s and visually by inspection of trace plots. R packages “tidyverse,” “tidybayes,” and “patchwork” were used in the same roles as for Study 2 (Kay, 2023; Pedersen, 2020; Wickham, 2016; Wickham et al., 2019). Full analysis code is available at [https://github.com/josefmana/dbs\\_postopIADL.git](https://github.com/josefmana/dbs_postopIADL.git).

## 4 Results

### 4.1 Learning curve in verbal and non-verbal memory of patients with Parkinson's disease

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.

#### 4.1.1 Sample characteristics

In total, 60 HC participants and 60 patients with PD of which 25 were diagnosed with PD-MCI were included into the study. Demographic and clinical characteristics of the sample are presented in Table 2.

Table 2: Demographic characteristics of normative and control sample of Study 1.

	HC (N = 60)	PD-NC (N = 35)	PD-MCI (N = 25)
Age (years)	61.92 ± 3.98	59.43 ± 8.62	62.00 ± 9.71
Education (years)	14.07 ± 2.57	15.87 ± 3.13	13.40 ± 2.89
Sex (% male)	43.33	60.00	56.00
PD duration (years)	-	6.43 ± 6.22	8.64 ± 6.10
LEDD (mg)	-	840.88 ± 805.11	1061.67 ± 653.08
MoCA (range 0-30)	26.32 ± 2.30	26.31 ± 1.64	24.16 ± 3.10
UPDRS III (range 0-132)	-	21.09 ± 12.03	25.96 ± 13.97

BDI-II: Beck Depression Rating Scale, second edition; HC: healthy control group; LEDD: levodopa equivalent daily dose; MoCA: Montreal Cognitive Assessment; N: number of observations; PD: Parkinson's Disease; PD-MCI: Mild Cognitive Impairment in Parkinson's Disease; PD-NC: Normal Cognition in Parkinson's Disease; UPDRS III: Unified Parkinson's Disease Rating Scale, motor part; all values represent mean (standard deviation) for continuous and percentages for nominal variables.

#### 4.1.2 Learning curve analysis

Both models converged to a stationary posterior distribution within specified number of iterations ( $\hat{R}_s < 1.01$ ). The data as well as model fits with uncertainty estimates on group level, group and participant level (i.e., inference), and full model with added measurement error (i.e., prediction) are presented in Figure 2. Inference statistics related to research questions of Study 1 are presented in Table 3. In both, BVMT-R and RAVLT, there was evidence of

main effect existence ( $pdir > .975$ ) that is practically significant ( $< 2.5\%$  in ROPE) implying that patients with PD-MCI experience overall memory deficit in both visuospatial and verbal modalities. Upon closer look, our data and models imply that this deficit is due to *immediate memory span* impairment with relatively unimpaired *learning curve* in visuospatial modality while the reverse is true for the verbal domain whereby PD-MCI patients show only slight impairment in *immediate memory span*, however, there is a clear *learning curve* impairment present (Table 3).

Table 3: Analysis of visuospatial and verbal learning curves

	BVMT-R				RAVLT			
	Median	95% HDPI	pdir	% in ROPE <sup>a</sup>	Median	95% HDPI	pdir	
Recall (Main effect)								
HC-minus-(PD-MCI)	2.50	[1.54, 3.47]	1.000	< 1	2.01	[1.03, 2.99]	1.000	
HC-minus-(PD-NC)	0.07	[-0.82, 0.89]	.553	37.85	0.49	[-0.36, 1.36]	.868	
(PD-MCI)-minus-(PD-NC)	-2.43	[-3.49, -1.33]	1.000	< 1	-1.53	[-2.48, -0.38]	.997	
Immediate memory span (Simple effect on the first trial)								
HC-minus-(PD-MCI)	2.21	[1.13, 3.25]	1.000	< 1	0.84	[-0.02, 1.73]	.970	
HC-minus-(PD-NC)	0.07	[-0.84, 1.06]	.558	33.42	0.32	[-0.46, 1.07]	.795	
(PD-MCI)-minus-(PD-NC)	-2.12	[-3.34, -0.93]	1.000	< 1	-0.52	[-1.51, 0.42]	.857	
Learning curve (Interaction effect)								
HC-minus-(PD-MCI)	0.48	[-0.39, 1.35]	.858	20.60	1.22	[0.60, 1.87]	1.000	
HC-minus-(PD-NC)	-0.03	[-0.81, 0.79]	.531	39.12	0.18	[-0.39, 0.75]	.720	
(PD-MCI)-minus-(PD-NC)	-0.52	[-1.48, 0.48]	.842	19.55	-1.05	[-1.73, -0.36]	.998	

<sup>a</sup>region of practical equivalence was set to one-tenth of normative standard deviation for a median trial, i.e.,  $-0.210$ – $0.210$  for BVMT-R and  $-0.223$ – $0.223$  for RAVLT

BVMT-R: Brief Visuospatial Memory Test - Revised; HC: healthy adult control participants; HDPI: highest density posterior interval; pdir: probability of direction; PD-MCI: Parkinson's disease patients with mild cognitive impairment; PD-NC: Parkinson's disease patients without mild cognitive impairment; RAVLT: Rey Auditory Visual Learning Test; ROPE: region of practical equivalence; comparisons in bold can be regarded as evidence of the existence of an effect ( $pdir > .975$ ).

#### 4.1.3 Manuscript contribution

I was the primary psychometrician of this study. I build, fitted and interpreted all statistical models in this article and wrote part of the methods and all the results section. Together with the main investigator (Mgr. Filip Havlík), I posited the research questions regarding the

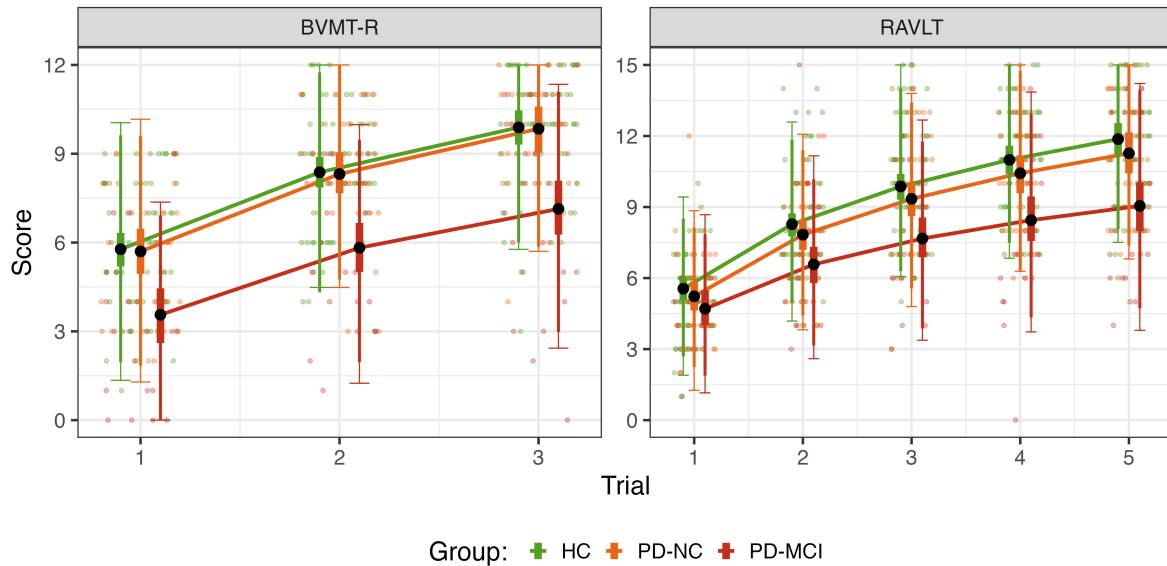


Figure 2: Visuospatial and verbal learning curves of control participants and Parkinson's Disease patients. Lines and black points represent median posterior predictions with 95% highest density posterior intervals from group-level predictions (thick vertical lines), group- and participant-level predictions (thin vertical lines), and full model with added measurement error (error bars). Coloured points represent observed data-points jittered horizontally for visualisation purposes; BVMT-R: Brief Visuospatial Memory Test – Revised; RAVLT: Rey Auditory Visual Learning Test; HC: healthy controls; PD-NC: Parkinson's Disease with normal cognition; PD-MCI: Parkinson's Disease with Mild Cognitive Impairment.

learning curve in PD patients and was involved in writing the draft as well as revisions of this paper.

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

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/ejnn.16521>

### 4.2.1 Sample characteristics

Baseline demographic, clinical and neuropsychological characteristics as well as stimulation parameters of the sample are presented in Table 4. 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 3).

Table 4: Clinical and neuropsychological characteristics of the sample of patients included in Study 2

	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 <sup>a</sup>					
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 (μs)	126	60.0	52.0-120.0	73.98	17.14
Pulse duration left (μs)	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
Pre-surgery cognitive profile					
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	1.8
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	7.1
Sim. (range 0-28)	94	22	8-28	21.61	4.35
RAVLT-IR (range 0-75)	108	44	20-64	43.8	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	45.1	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

<sup>a</sup>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 Parkinson's 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; MDRS: 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 colour naming; PST-W: Prague Stroop Test, word colour 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.

#### 4.2.2 Pre-surgery cognitive profile

In the EFAs, from three up to eight factor solutions for pre-surgery cognitive profile were examined. According to TLI and RMSEA, there was a clear improvement when increasing the number from six to seven factors whereby good TLI (i.e.,  $TLI > .9$ ) increased from 76 to 97, and good RMSEA (i.e.,  $RMSEA < .05$ ) increased from 96 to 99 out of 100 imputed data sets. Moreover, the seven factor solution showed the most consistency of factors across imputations. Finally, even though the eight factor solution had better fit statistics than the seven factor solution, it resulted in factors loaded on substantially (i.e., with a factor loading above 0.3) by only a single cognitive test score which impedes theoretical interpretation of such factors. Consequently, the seven factor solution was retained for further analyses. Summary of factor loadings across imputations is presented in Figure 4. 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

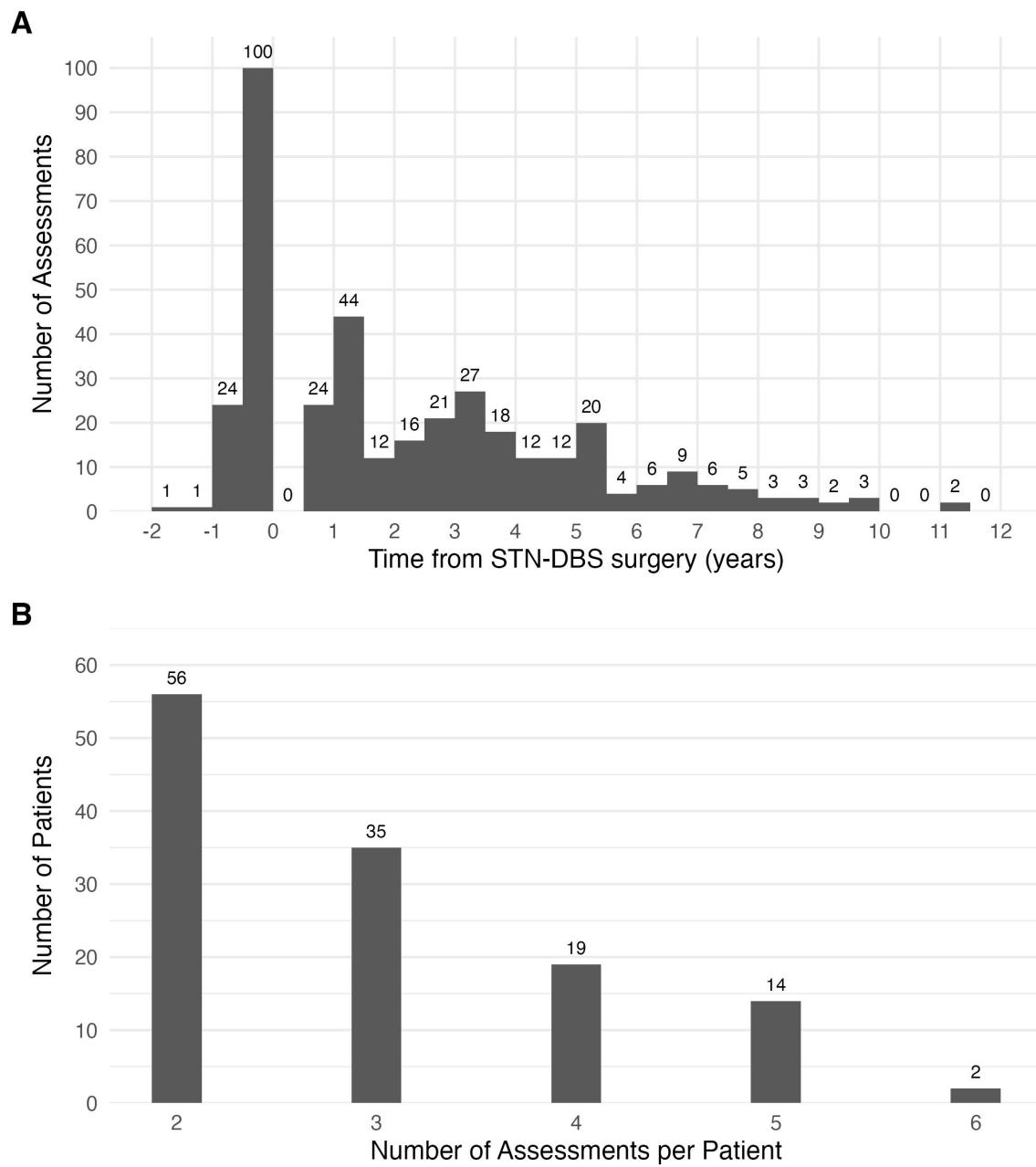


Figure 3: Distribution of assessments. Distribution of (A) follow-up years and (B) number of assessments per patient for  $N = 126$  patients included in Study 2. Negative values on horizontal axis in (A) represent pre-surgery assessments, number of assessments in (B) includes one pre-surgery and various number of post-surgery assessments.

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.

#### 4.2.3 Post-surgery cognitive change description

The descriptive longitudinal GLMM converged to a stationary posterior distribution within specified number of iterations ( $\hat{R}_s < 1.01$ ). 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 0.53 MDRS points/year (95% HDPI [-11.53, 12.15]). This three-level estimate of the rate of post-surgery cognitive decline is further presented in Figure 5 and Table 5 as expected median and 90% ETIs change scores of MDRS after STN DBS surgery.

Table 5: Posterior predictions of cognitive change after STN DBS surgery

Inference <sup>a</sup>			
	Group-level <sup>b</sup>	Population-level <sup>c</sup>	Prediction <sup>d</sup>
Yearly decline <sup>e</sup>			
Intercept	140.34 [139.71, 140.95]	140.35 [135.71, 144.00]	140.37 [132.97, 144.00]
Slope	-0.90 [-1.14, -0.67]	-0.78 [-2.41, 0.52]	-0.73 [-9.24, 7.63]
Contrasts			
Y1-minus-Pre	-1.17 [-1.49, -0.87]	-1.03 [-3.14, 0.67]	-1.09 [-9.45, 7.45]
Y2-minus-Pre	-2.08 [-2.63, -1.55]	-1.87 [-5.60, 1.18]	-2.00 [-10.11, 7.03]
Y3-minus-Pre	-2.98 [-3.77, -2.22]	-2.71 [-8.11, 1.67]	-2.84 [-11.12, 6.35]
Y4-minus-Pre	-3.88 [-4.92, -2.89]	-3.56 [-10.65, 2.13]	-3.76 [-12.04, 5.71]
Y5-minus-Pre	-4.79 [-6.06, -3.56]	-4.41 [-13.23, 2.55]	-4.71 [-12.92, 5.23]

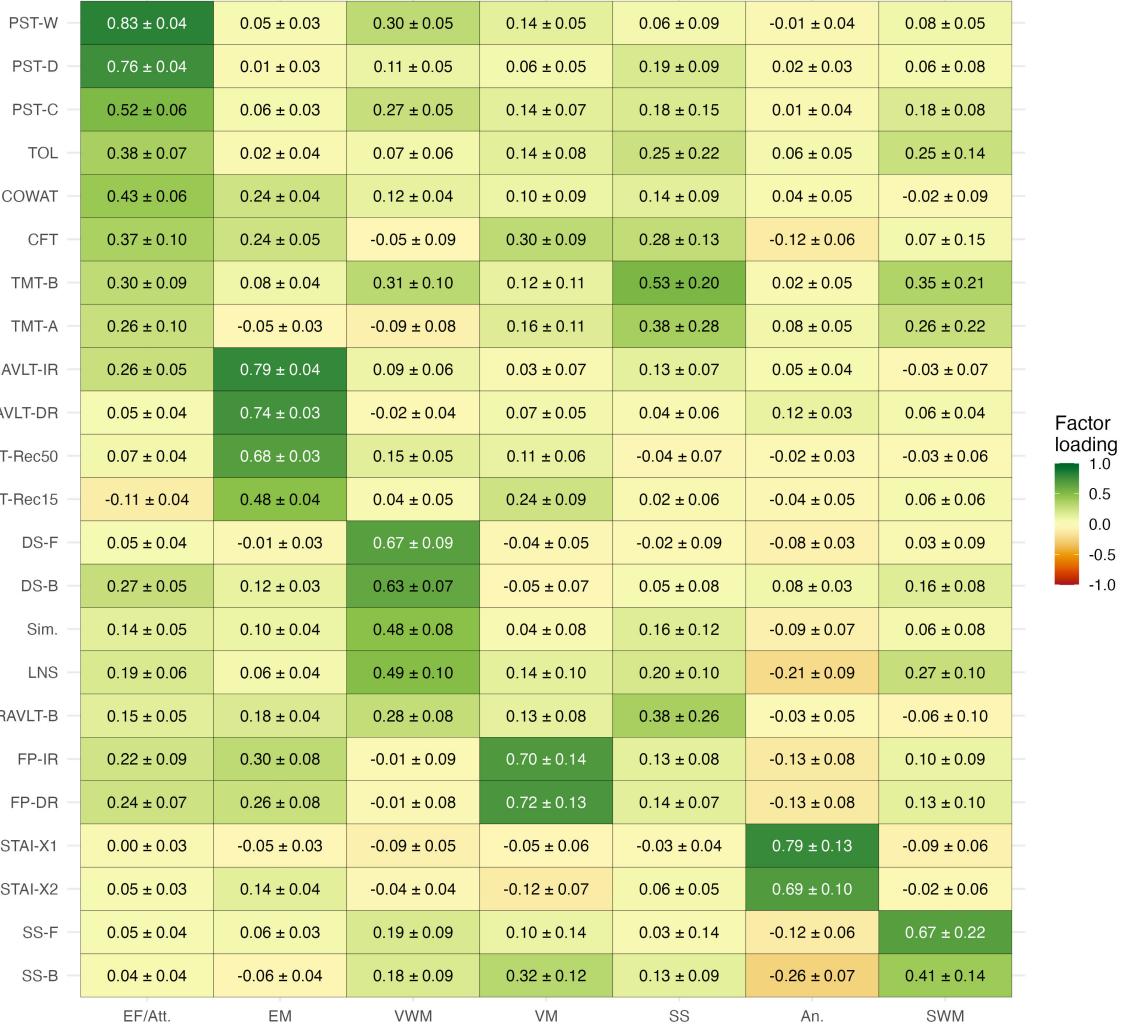


Figure 4: The selected seven factor solution exploratory factor analysis represented as means ± standard deviations of factor loadings across 100 imputed data sets. All variables were scaled such that higher values indicate better performance (or more anxiety in the case of anxiety inventories.)

<sup>a</sup>The columns represent estimation of true score changes before measurement error is added.

<sup>b</sup>Contrasts for the sample version  $RQ1$  estimand predicted by  $\mu_i \sim \alpha + \delta_{time} time_i$

<sup>c</sup>Contrasts for the population version  $RQ1$  estimand predicted by  $\mu_i \sim \alpha + \delta_{time} time_i + \alpha_{id[i]} + \delta_{id[i]} time_i$

<sup>d</sup>Contrasts for model's prediction of the raw score sampled from  $t(\vartheta, \mu_i, \sigma)$

<sup>e</sup>The rows represents expectation of patients' performance at pre-surgery assessment, i.e., 0.3 years before surgery (Intercept), and expected annual Mattis Dementia Rating Scale decline (Slope).

Yi: assessment i years post-surgery; values represent posterior prediction median [90% equal tailed interval (ETI)]; all values were calculated by first generating predictions from the linear descriptive model using parameters specified above and then censoring values higher than 144 or less than 0 before calculating medians and 90% ETIs.

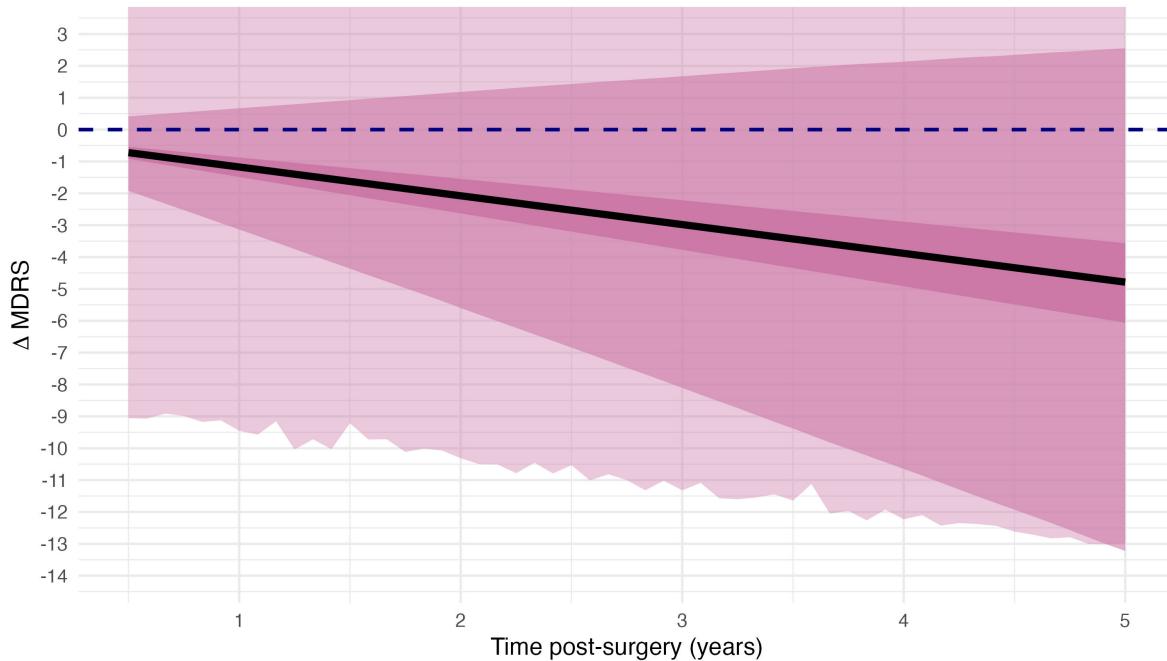


Figure 5: Post-surgery change scores estimates from the descriptive longitudinal model of Mattis Dementia Rating Scale (MDRS) change in patients with Parkinson's disease treated by subthalamic deep brain stimulation. The plot represents estimated change in MDRS with respect to pre-surgery assessment (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).

#### 4.2.4 Post-surgery cognitive change prediction

Both predictive longitudinal GLMMs converged to a stationary posterior distribution within specified number of iterations across all imputed data sets ( $\bar{R}_s < 1.02$ ). Group-level model parameters are presented in Table 6 and Table 7 for the “*test scores*” and “*factor scores*” models respectively. Cross-sectionally, pre-surgery MDRS performance was reliably (i.e., with high posterior probability, compare to Makowski et al. (2019)) predicted by the verbal working memory factor score ( $\beta_{VWM} = -0.87$ , 95% HDPI [-1.64, -0.02],  $pdir = .986$ ) and to a lesser extent by the set shifting factor score ( $\beta_{SS} = -0.69$ , 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 executive function/attention score with high posterior probability ( $\delta_{EF/Att.} = -0.40$ , 95% HDPI [-0.64, -0.14],  $pdir = .999$ ). Figure 6 illustrates how the rate of post-surgery cognitive decline relates to pre-surgery cognitive profile operationalised by cognitive factor scores derived from EFA. Patients with pre-surgery EF/Att. factor scores high relative to the rest of the sample (top-right panel) showed almost no to small long-term decline in MDRS after surgery compared to patients with EF/Att. factor scores low relative to the rest of the sample (top-left panel). There was no cognitive test that would by itself statistically clearly indicate post-surgery MDRS decline.

Table 6: Summary of group-level parameters’ posteriors from the “*test scores*” predictive generalised linear mixed model

Parameter	Median	95% HDPI	pdir
Global intercept ( )			
Intercept	140.16	[139.53, 140.79]	1.000
Baseline correlates ( )			
TMT-A	0.00	[-0.37, 0.37]	.503
TMT-B	-0.23	[-0.85, 0.17]	.867
DS-F	-0.05	[-0.50, 0.27]	.648
DS-B	-0.07	[-0.54, 0.27]	.687
LNS	-0.19	[-0.78, 0.18]	.840
SS-F	-0.05	[-0.51, 0.29]	.648
SS-B	-0.10	[-0.59, 0.23]	.747
TOL	-0.06	[-0.50, 0.28]	.666
PST-D	0.03	[-0.32, 0.47]	.590
PST-W	-0.01	[-0.40, 0.39]	.517
PST-C	-0.32	[-0.94, 0.12]	.919
COWAT	-0.01	[-0.38, 0.36]	.521
CFT	-0.14	[-0.72, 0.22]	.789
Sim.	-0.17	[-0.75, 0.18]	.834

RAVLT-IR	-0.05	[-0.52, 0.29]	.650
RAVLT-B	-0.32	[-0.94, 0.12]	.919
RAVLT-DR	0.05	[-0.29, 0.53]	.656
RAVLT-Rec50	-0.01	[-0.40, 0.36]	.540
RAVLT-Rec15	-0.11	[-0.60, 0.22]	.760
FP-IR	-0.06	[-0.55, 0.30]	.666
FP-DR	-0.04	[-0.51, 0.35]	.611
STAI-X1	0.00	[-0.36, 0.36]	.502
STAI-X2	0.01	[-0.34, 0.39]	.540
Time-dependent parameters ( )			
Time	-0.72	[-1.00, -0.46]	1.000
TMT-A $\times$ Time	-0.09	[-0.34, 0.10]	.825
TMT-B $\times$ Time	-0.16	[-0.48, 0.09]	.897
DS-F $\times$ Time	0.10	[-0.10, 0.33]	.834
DS-B $\times$ Time	0.06	[-0.14, 0.32]	.738
LNS $\times$ Time	0.06	[-0.16, 0.32]	.713
SS-F $\times$ Time	0.25	[-0.05, 0.61]	.951
SS-B $\times$ Time	-0.11	[-0.40, 0.11]	.829
TOL $\times$ Time	-0.05	[-0.28, 0.15]	.696
PST-D $\times$ Time	-0.02	[-0.27, 0.22]	.570
PST-W $\times$ Time	-0.14	[-0.44, 0.09]	.881
PST-C $\times$ Time	-0.10	[-0.37, 0.12]	.818
COWAT $\times$ Time	-0.13	[-0.35, 0.07]	.899
CFT $\times$ Time	-0.02	[-0.25, 0.20]	.582
Sim. $\times$ Time	0.07	[-0.14, 0.34]	.756
RAVLT-IR $\times$ Time	0.01	[-0.23, 0.26]	.544
RAVLT-B $\times$ Time	0.03	[-0.16, 0.25]	.622
RAVLT-DR $\times$ Time	0.07	[-0.13, 0.32]	.764
RAVLT-Rec50 $\times$ Time	-0.03	[-0.28, 0.18]	.640
RAVLT-Rec15 $\times$ Time	0.00	[-0.22, 0.23]	.503
FP-IR $\times$ Time	-0.03	[-0.35, 0.26]	.603
FP-DR $\times$ Time	-0.06	[-0.40, 0.22]	.687
STAI-X1 $\times$ Time	-0.01	[-0.20, 0.18]	.533
STAI-X2 $\times$ Time	0.00	[-0.21, 0.20]	.523

All cognitive predictors were scaled such that negative values mean negative effect of pre-surgery deficit on longitudinal cognitive trajectory.

Median: parameter value point estimate (posterior median); HDPI: highest density posterior probability interval; pdir: probability of direction;  $\times$ : statistical interaction term; 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 colour naming; PST-W: Prague Stroop Test, word colour 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; comparisons in bold can be regarded as evidence of the existence of an effect ( $\text{pdir} > .975$ ).

Table 7: Summary of group-level parameters' posteriors from the “factor scores” predictive generalised linear mixed model

Parameter	Median	95% HDPI	pdir
Global intercept ( )			
Intercept	140.25	[139.62, 140.88]	1.000
Baseline correlates ( )			
EF/Att.	-0.17	[-0.78, 0.32]	.764
EM	-0.16	[-0.73, 0.28]	.768
VWM	-0.87	[-1.64, -0.02]	.986
VM	-0.34	[-1.04, 0.21]	.880
SS	-0.69	[-1.39, 0.02]	.976
An.	-0.04	[-0.59, 0.43]	.589
SWM	-0.29	[-1.03, 0.27]	.845
Time-dependent parameters ( )			
Time	-0.75	[-1.01, -0.50]	1.000
EF/Att. $\times$ Time	-0.40	[-0.64, -0.14]	.999
EM $\times$ Time	0.00	[-0.22, 0.23]	.508
VWM $\times$ Time	0.15	[-0.11, 0.44]	.871
VM $\times$ Time	-0.16	[-0.45, 0.11]	.881
SS $\times$ Time	-0.15	[-0.51, 0.18]	.780

An. $\times$ Time	0.00	[-0.22, 0.21]	.519
SWM $\times$ Time	0.06	[-0.35, 0.42]	.624

All cognitive predictors were scaled such that negative values mean negative effect of pre-surgery deficit on longitudinal cognitive trajectory.

Median: parameter value point estimate (posterior median); HDPI: highest density posterior probability interval; pdir: probability of direction;  $\times$ : statistical interaction term; EF/Att.: Executive function/Attention; EM: Episodic memory; VWM: Verbal working memory; VM: Visuospatial memory; SS: Set shifting; An: Anxiety; SWM: Spatial working memory; comparisons in bold can be regarded as evidence of the existence of an effect (pdir  $> .975$ ).

#### 4.2.5 Manuscript contribution

I administered a portion of post-surgery neuropsychologic assessments, retrospectively sampled data from university hospital database, formulated research questions, analysed data, wrote the original draft of the manuscript as well as its revision. The whole analysis process is documented on this thesis public repository at [https://github.com/josefmana/dbs\\_longCOG.git](https://github.com/josefmana/dbs_longCOG.git) and the revision process is available on the article public repository at [https://github.com/josefmana/dbs\\_cogPRED.git](https://github.com/josefmana/dbs_cogPRED.git).

### 4.3 Structural and microstructural predictors of cognitive decline in deep brain stimulation of subthalamic nucleus in Parkinson's disease

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.

#### 4.3.1 Sample characteristics

Clinical, demographic, and stimulation-related characteristics of the sample as well as statistical comparisons of these characteristics in CS versus CD groups is presented in Table 8. Pre-surgery, the only statistically significant difference regarded patients age whereby the CD group of patients were on average older by circa ten years. No statistically significant pre-surgery difference was detected in either distribution of sex or PD-MCI or average disease duration or MDRS scores between the groups. On the other hand, although there was not a statistically significant difference in follow-up years, statistically significant differences between CS and CD groups were detected in post-surgery MDRS scores and post-surgery PD-MCI distribution (with CD group having lower average MDRS score and higher PD-MCI prevalence). In none of the DBS-related parameters there was a statistically significant difference between

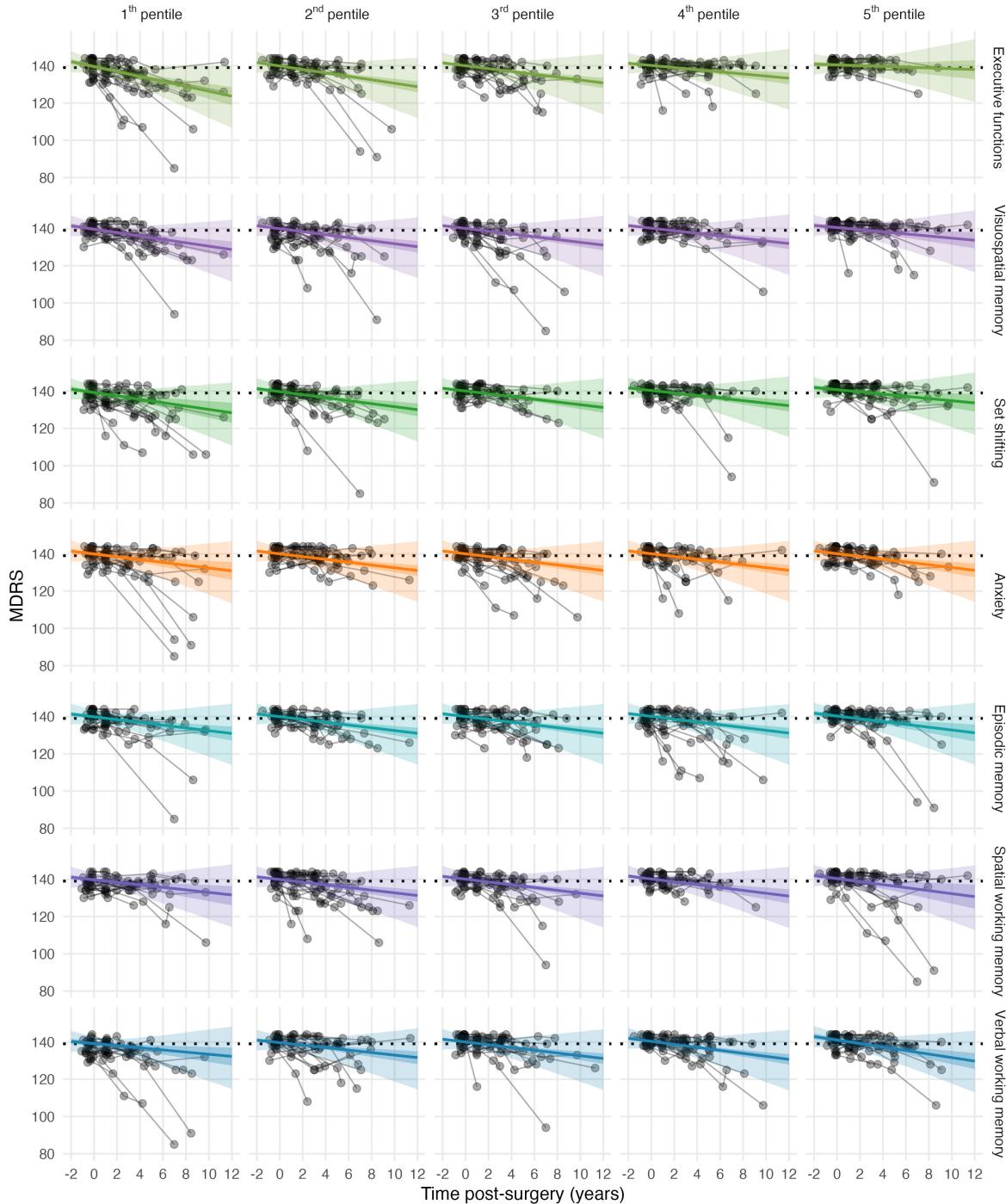


Figure 6: Longitudinal post-surgery cognitive trajectories in patients with Parkinson's disease treated with subthalamic deep brain stimulation stratified by pre-surgery cognitive profile. The sample was repeatedly divided to pentiles (columns) ranging from the lowest (left) to the highest (right) performers based on each pre-surgery cognitive factor (rows) (in the case of Anxiety, patients to the left reported more pre-surgery anxiety than patients to the right). Subsequently, model predictions of Mattis Dementia Rating Scale (MDRS, ordinate) at different post-surgery time lags (abscissa) for each pentile were calculated on three levels of inference related to the MDRS true score: point estimate (dark line), group-level uncertainty estimate (medium saturation ribbon), and population-level uncertainty (light ribbon). The horizontal dotted line is placed at 139 MDRS points which represent mild cognitive impairment cut-off with optimal specificity and sensitivity according to the Czech normative study.

CS and CD patients detected. Nonetheless, CD patients had on average lower total electrical energy delivered to the STN DBS system.

Table 8: Clinical, demographic and stimulation-related characteristics of the sample of patients included in Study 3

	Cognitively stable (N = 52)	Cognitively declining (N = 52)
At pre-surgery examination		
Age (years)	53.65 ± 8.27	63.60 ± 5.42
Sex (% of males)	46.2	70.0
PD duration (years)	10.94 ± 8.27	13.40 ± 5.47
DRS-2 (range 0-144)	139.38 ± 5.06	140.45 ± 2.40
PD-MCI (% of MCI)	34.6	30.0
At the last neuropsychologic examination		
Duration of follow-up (years)	2.35 ± 1.30	2.20 ± 1.47
DRS-2 (range 0-144)	140.29 ± 2.70	132.05 ± 5.54
PD-MCI (% of MCI)	26.9	95.0
ΔDRS-2	0.89 ± 3.49	-4.37 ± 2.11
DBS-related information <sup>a</sup>		
Stimulation mode (monopolar/bipolar/interleaved)	42/7/2	19/0/1
Constant voltage/constant current mode	2/49	4/16
Voltage amplitude (V) <sup>b</sup>	2.45 ± 0.20	2.35 ± 0.65
Current (mA) <sup>b</sup>	2.22 ± 0.70	2.02 ± 0.68
Pulse width (s) <sup>b</sup>	62.25 ± 8.93	63.00 ± 9.00
Frequency (Hz) <sup>b</sup>	127.65 ± 12.89	130.00 ± 0.00
Impedance (kΩ) <sup>b</sup>	1192.35 ± 475.13	1151.30 ± 381.81
Total electrical energy delivered (W) <sup>b</sup>	52.42 ± 32.31	34.61 ± 20.96
Affected volume of STN		
Whole STN (mm <sup>3</sup> )	6.78 ± 11.17	6.43 ± 6.09
Associative subsection (mm <sup>3</sup> )	2.02 ± 4.68	1.81 ± 2.62
Limbic subsection (mm <sup>3</sup> )	1.13 ± 2.19	0.80 ± 0.93

<sup>a</sup>Available for all but one cognitively stable patient and all cognitively declining patients.

<sup>b</sup>Reported values are bilateral averages.

DBS: deep brain stimulation; MDRS: Dementia Rating Scale, second edition;  $\Delta$ MDRS: average annual change in Dementia Rating Scale, second edition score; Hz: Hertz;  $k\Omega$ : kiloohm; mA: milliampere; MCI: mild cognitive impairment; s: microseconds; W: microwatts; PD: Parkinson's disease; PD-MCI: Mild cognitive impairment in Parkinson's disease; q-value: raw p-value after adjusting for 5% false discovery rate (FDR) level; STN: subthalamic nucleus; V: Volts; values are presented as in-sample mean  $\pm$  standard deviation for continuous variables, percentages for demographic categorical variables and frequencies for DBS-related categorical variables.

#### 4.3.2 Magnetic resonance profile of patients experiencing cognitive decline

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 (Table 9). 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.

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Anatomical cluster<sup>b</sup>

Macrostructure (mm/unitless)<sup>c</sup>

Dorsal Stream Visual, Early Visual, Posterior Cingulate, Ventral Stream Visual, Medial Temporal, Primary Visual, Superior Parietal and IPS, Inferior Parietal, Dorsal Stream Visual, Somatosensory and Motor, Early Visual, Posterior Operculum, Early Auditory, Auditory Association, Insular, Putamen

Inferior Parietal, Somatosensory and Motor, Paracentral Lobular and Mid Cingulate, Superior Parietal and Insular, Early Auditory, Insular, Posterior Operculum

Putamen

Paracentral Lobular and Mid Cingulate, Premotor

Inferior Frontal, Insular  
Amygdala  
Caudate

---

Fractional Anisotropy (unitless)<sup>d</sup>

Hippocampus

Hippocampus

Ventral Stream Visual, Medial Temporal, Dorsal Stream Visual, MT+ Complex and neighbouring Visual Area  
Dorsal Stream Visual, Medial Temporal, Early Visual, Ventral Stream Visual, Lateral Temporal, MT+ Complex  
Amygdala

Paracentral Lobular and Mid Cingulate, Posterior Cingulate, Superior Parietal and IPS

Cerebellum

Inferior Frontal

Orbital and Polar Frontal

Cerebellum

Orbital and Polar Frontal, Inferior Frontal, Anterior Cingulate, Insular

Early Auditory, Insular, Posterior Operculum

Early Auditory, Posterior Operculum

Paracentral Lobular and Mid Cingulate, Anterior Cingulate, Posterior Cingulate, Somatosensory and Motor, Dorsolateral Prefrontal, Premotor

Posterior Cingulate, Superior Parietal and IPS

Inferior Parietal

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Mean diffusivity (1,000 × mm<sup>2</sup>/s)<sup>d</sup>

Ventral Stream Visual, Lateral Temporal, Early Visual, Dorsal Stream Visual, MT+ Complex and neighbouring Visual Area  
Ventral Stream Visual, Medial Temporal, Early Visual, Dorsal Stream R Visual, MT+ Complex and neighbouring Visual Area  
Anterior Cingulate, Orbital and Polar Frontal, Paracentral Lobular and Mid Cingulate, Dorsolateral Prefrontal  
Superior Parietal and IPS

Anterior Cingulate, Paracentral Lobular and Mid Cingulate

Orbital and Polar Frontal, Inferior Frontal

Insular, Early Auditory, Posterior Operculum

Early Auditory, Insular, Posterior Operculum

Hippocampus

Hippocampus

Inferior Parietal, Visual cortices, Temporal-Parietal-Occipital Junction, Auditory Association

Temporal-Parietal-Occipital Junction, Inferior Parietal

Diencephalon ventral

Dorsolateral Prefrontal, Inferior Frontal

Posterior Cingulate

Diencephalon ventral

Putamen

<sup>a</sup>values are presented as in-sample mean  $\pm$  standard deviation

<sup>b</sup>Clusters with cortical anatomical localisation based on 22 main cortical segments and parcellation as defined by [@Glasser2016]

<sup>c</sup>Values in mm for cortical thickness and unitless for subcortical grey matter structure volume, the latter was standardised by estimated intracranial volume.

<sup>d</sup>Results based on 46 CS and 16 CD patients

CS: cognitively stable patients; CD: cognitively declining patients; L: left; N: number of observations; q-value: raw p-value after adjusting for 5% false discovery rate (FDR) level; R: right; ROI: number of parcellation regions of interest contained in each cluster.

#### 4.3.3 Manuscript contribution

I administered a majority of post-surgery neuropsychologic assessments, to a small degree assisted with MRI database establishment, pre-processed and check neuropsychologic data, and assisted with original draft writing and revisions during the review process.

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

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.

#### 4.4.1 Sample characteristics

Included patients' characteristics are presented in Table 10. In general, no substantial post-surgery changes can be seen in objective cognitive performance (MDRS), depressive symptoms (BDI-II) or total IADL as measured by the PDAQ sum score. On the other hand, there was a clear LEDD reduction after STN DBS and evidence of STN DBS reducing motor symptoms independently of dopaminergic medication.

Table 10: Demographic, clinical, cognitive, and stimulation characteristics of the sample of Study 4

	Pre-surgery	Post-surgery
Demographic and clinical variables		
Age (years)	55.50 $\pm$ 7.78	56.95 $\pm$ 7.79
Education (years)	14.20 $\pm$ 3.25	-
Sex (% male)	56.25	-
PD duration (years)	11.37 $\pm$ 3.67	-

LEDD (mg)	1819.77 $\pm$ 693.73	833.32 $\pm$ 498.48
Neuropsychological outcomes		
PDAQ (range 0-60)	51.34 $\pm$ 7.49	52.34 $\pm$ 6.35
MDRS (range 0-144)	139.28 $\pm$ 3.62	139.44 $\pm$ 3.33
BDI-II (range 0-63)	10.38 $\pm$ 7.20	9.91 $\pm$ 6.90
Motor outcomes		
Levodopa test (% response)	58.42 $\pm$ 11.79	-
MDS-UPDRS III (medication ON)	18.76 $\pm$ 9.13	-
MDS-UPDRS III (medication OFF)	44.12 $\pm$ 15.05	-
MDS-UPDRS III (stimulation ON) <sup>a</sup>	-	26.25 $\pm$ 10.00
MDS-UPDRS III (stimulation OFF) <sup>a</sup>	-	45.16 $\pm$ 14.04
Stimulation parameters		
Current right (mA)	-	2.24 $\pm$ 0.55
Current left (mA)	-	2.21 $\pm$ 0.60
Pulse duration right ( s)	-	62.81 $\pm$ 8.88
Pulse duration left ( s)	-	63.64 $\pm$ 9.94
Frequency right (Hz)	-	129.06 $\pm$ 18.38
Frequency left (Hz)	-	125.76 $\pm$ 11.73
Impedance right (k $\Omega$ )	-	1298.83 $\pm$ 442.14
Impedance left (k $\Omega$ )	-	1539.40 $\pm$ 1519.69

<sup>a</sup>Post-surgery MDS-UPDRS III testing was done in the OFF medication condition.

BDI-II: Beck Depression Rating Scale, second edition; MDRS: Dementia Rating Scale, second edition; Hz: Hertz; LEDD: levodopa equivalent daily dose; mA: milliamperes; MDS-UPDRS III: Movement Disorder Society Unified Parkinson's Disease Rating Scale, motor part; s: microseconds PDAQ-15: The Penn Parkinson's Daily Activities Questionnaire-15. The values are presented as mean  $\pm$  standard deviation percentage from the whole sample.

#### 4.4.2 Post-surgery IADL change

All GLMMs reported in this section converged to a stationary posterior distribution within specified number of iterations ( $\hat{R}_s < 1.02$ ). Regarding the *RQ4.1*, 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 ( $\delta_{\text{Time}} = 0.18$ , 95% HDPI [-0.11, 0.48],  $p_{\text{dir}} = 0.883$ ). Consequently, without statistically adjusting for competing causes of post-surgery IADL change, the post-surgery probability that an average patient responds to an average PDAQ item with option zero (“cannot do”) decreased by 0.0% (95% HDPI [-0.2, 0.0]), the probability of response one (“a lot”) decreased by 0.1% (95% HDPI [-0.6, 0.1]), the probability of response two (“somewhat”) decreased by 0.6% (95% HDPI [-1.9, 0.6]), the probability of

response three (“a little”) decreased by 3.2% (95% HDPI [-8.6, 2.2]), and the probability of response four (“none”) increased by 4.1% (95% HDPI [-3.1, 10.7]).

Regarding the *RQ4.2*, the main effect of time of assessment in the “*direct effect*” model was positive and of high effect existence probability ( $\delta_{\text{Time}} = 1.09$ , 95% HDPI [0.41, 1.74],  $pdir = 1.000$ ). When potential competing causes measured by MDRS, BDI-II and LEDD were statistically adjusted for, the post-surgery probability that an average patient responds to an average PDAQ item with option zero (“cannot do”) decreased by 0.2% (95% HDPI [-0.4, -0.0]), the probability of response one (“a lot”) decreased by 0.6% (95% HDPI [-1.3, -0.1]), the probability of response two (“somewhat”) decreased by 2.6% (95% HDPI [-5.2, -0.6]), the probability of response three (“a little”) decreased by 17.9% (95% HDPI [-28.5, -7.9]), and the probability of response four (“none”) increased by 21.4% (95% HDPI [8.9, 34.2]).

Panels A and B of Figure 7 present expected pre- and post-surgery response probabilities of an average patient to an average PDAQ item according to the “*descriptive*” and “*direct effect*” models respectively. Coupled with the results presented in previous two paragraphs, the results imply that (i) there is only small and uncertain positive impact of STN DBS on IADL that could be observed in an average patient (as implied by the “*descriptive*” model), however, (ii) the direct causal effect of STN-DBS can be masked by post-surgery changes in competing causes of self-reported IADL difficulty and after accounting for these it appears to be reliably positive and larger than expected by average observational data only (as implied by the “*direct effect*” model), and (iii) the majority of post-surgery change in self-reported IADL is due to an increase of probability that a patient reports “no difficulties” (response four in PDAQ) instead of reporting “a little difficulties” (response three in PDAQ) whereas reporting high level of IADL difficulties is rare in this cohort.

#### 4.4.3 Effect of dopaminergic medication on post-surgery IADL

In the “*total effect*” model, the main effect of the time of assessment was positive with high effect existence probability ( $\delta_{\text{Time}} = 0.84$ , 95% HDPI [0.14, 1.45],  $pdir = 0.993$ ), the main effect of LEDD was positive with high but uncertain probability of effect existence ( $\beta_{\text{LEDD}} = 0.17$ , 95% HDPI [-0.03, 0.39],  $pdir = 0.946$ ), and the Time  $\times$  LEDD interaction was positive with uncertain probability of effect existence ( $\delta_{\text{LEDD}} = 0.16$ , 95% HDPI [-0.16, 0.47],  $pdir = 0.829$ ). Posterior predictions of an average PDAQ item response probabilities by average patient as a function of time of assessment and LEDD are presented in Table 11 and panel C of Figure 7. These results imply that the statistically uncertain improvement in IADL as measured by the “*descriptive*” model can be partially explained by post-surgery LEDD reduction.

Table 11: Expected response probabilities of difficulty in IADL stratified by the time of assessment and levodopa equivalent daily dose derived from the total effect GLMM

LEDD (mg)	P(resp = 0)	P(resp = 1)	P(resp = 2)	P(resp = 3)	P(resp = 4)
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Pre-surgery					
0	0.6 ± 0.5%	2.1 ± 1.4%	8.1 ± 4.2%	45.8 ± 8.5%	43.4 ± 13.5%
500	0.5 ± 0.3%	1.7 ± 1.0%	6.9 ± 3.3%	43.6 ± 8.4%	47.3 ± 12.4%
1,000	0.4 ± 0.3%	1.4 ± 0.8%	5.8 ± 2.6%	41.0 ± 8.2%	51.4 ± 11.3%
1,500	0.3 ± 0.2%	1.2 ± 0.6%	5.0 ± 2.1%	38.1 ± 8.0%	55.4 ± 10.5%
2,000	0.3 ± 0.2%	1.0 ± 0.5%	4.2 ± 1.8%	35.0 ± 8.0%	59.5 ± 10.1%
2,500	0.2 ± 0.2%	0.8 ± 0.4%	3.6 ± 1.7%	32.0 ± 8.2%	63.3 ± 10.2%
3,000	0.2 ± 0.1%	0.7 ± 0.4%	3.1 ± 1.6%	29.0 ± 8.6%	66.9 ± 10.5%
3,500	0.2 ± 0.1%	0.6 ± 0.4%	2.7 ± 1.6%	26.2 ± 9.2%	70.2 ± 11.1%
4,000	0.2 ± 0.1%	0.6 ± 0.4%	2.4 ± 1.6%	23.7 ± 9.7%	73.2 ± 11.7%
4,500	0.1 ± 0.1%	0.5 ± 0.4%	2.2 ± 1.6%	21.4 ± 10.3%	75.8 ± 12.2%
5,000	0.1 ± 0.2%	0.4 ± 0.4%	1.9 ± 1.7%	19.4 ± 10.7%	78.1 ± 12.7%
Post-surgery					
0	0.5 ± 0.3%	1.5 ± 0.9%	6.3 ± 3.0%	42.3 ± 8.3%	49.4 ± 11.8%
500	0.3 ± 0.2%	1.1 ± 0.6%	4.6 ± 2.0%	36.7 ± 8.1%	57.2 ± 10.5%
1,000	0.2 ± 0.1%	0.8 ± 0.4%	3.4 ± 1.5%	30.8 ± 7.9%	64.8 ± 9.7%
1,500	0.2 ± 0.1%	0.6 ± 0.3%	2.5 ± 1.2%	25.3 ± 8.0%	71.5 ± 9.5%
2,000	0.1 ± 0.1%	0.4 ± 0.3%	1.9 ± 1.1%	20.4 ± 8.1%	77.1 ± 9.5%
2,500	0.1 ± 0.1%	0.3 ± 0.3%	1.5 ± 1.0%	16.4 ± 8.2%	81.7 ± 9.5%
3,000	0.1 ± 0.1%	0.3 ± 0.2%	1.2 ± 1.0%	13.2 ± 8.2%	85.3 ± 9.4%
3,500	0.1 ± 0.1%	0.2 ± 0.2%	0.9 ± 0.9%	10.7 ± 8.1%	88.1 ± 9.2%
4,000	0.0 ± 0.1%	0.2 ± 0.2%	0.7 ± 0.9%	8.8 ± 7.9%	90.3 ± 9.0%
4,500	0.0 ± 0.1%	0.1 ± 0.2%	0.6 ± 0.9%	7.3 ± 7.7%	91.9 ± 8.8%
5,000	0.0 ± 0.1%	0.1 ± 0.2%	0.5 ± 0.9%	6.1 ± 7.5%	93.2 ± 8.6%

GLMM: generalised linear mixed model; IADL: instrumental activities of daily living; LEDD: levodopa equivalent daily dose; P(resp = i), probability that a patient responds to any item of The Penn Parkinson's Daily Activities Questionnaire (PDAQ) with the response "i" where "i" represents difficulties in IADL and can take on values 0 = "cannot do," 1 = "a lot," 2 = "somewhat," 3 = "a little," and 4 = "none"; the numbers represent posterior predictions of the ordered-logit GLMM for an average patient to an average PDAQ item presented as posterior mean ± standard deviation.

#### 4.4.4 Manuscript contribution

I administered a portion of post-surgery neuropsychologic assessments, was responsible for data management of the neuropsychological outcomes data, operationalised the research question, defined the causal model, carried out statistical analysis, wrote portions of the article, and presented the results. Consequentially, in this article I share equal contribution with the first author (Prof. Ondrej Bezdicek Ph.D.).

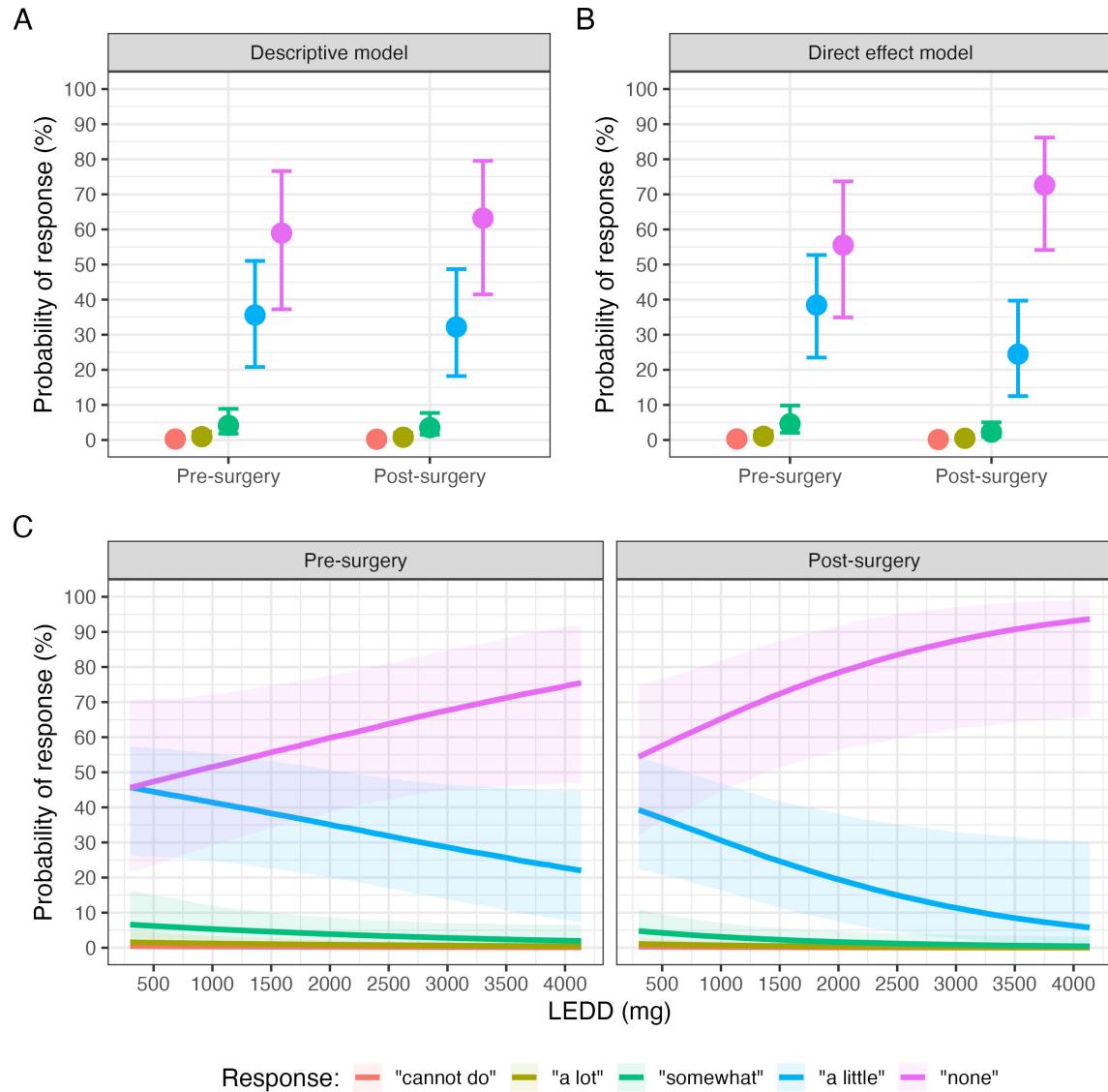


Figure 7: Summaries of the marginal posterior distributions of expected response probabilities to an average item from The Penn Parkinson's Daily Activities Questionnaire (PDAQ) by an average participant pre- and post-surgery according to the “descriptive” model (A), the “direct effect” model (B), and as a function of levodopa equivalent daily dose (LEDD) in the “total effect” model (C). Potential responses to PDAQ items are differentiated by colour, points and lines represent medians, and whiskers and shades represent 95% equal-tailed intervals (ETIs) of posterior distributions.

## 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 memory 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. Specifically, unlike in the previous study, in this thesis there was a statistically reliable *learning curve* deficit in PD-MCI patients' verbal auditory memory and on the other hand, no free recall deficit in PD-NC patients' visuospatial memory was detected. 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. This finding is important for assumptions of Study 2 which is the primary study of this thesis. More precisely, Study 2 asks what pre-surgery cognitive profile is predictive of post-surgery cognitive decline in patients with PD treated by STN DBS. This research question comes with an implicit assumption that differences in pre-surgery cognitive profile that can be detected by neuropsychological testing are psychologically meaningful. Such a psychological meaningfulness would best be demonstrated by comparing patients' cognitive profile to well selected control group. However, acquiring control group in Study 2 research design would be ethically problematic. 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. Finally, the finding that deficit in total immediate recall in auditory verbal learning task such as RAVLT can reflect distinct underlying cognitive mechanisms will prove to be of use when interpreting results of

Study 2 regarding predictive value of pre-surgery memory-related cognitive factors with respect to post-surgery cognitive decline.

## **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*).

### **5.2.1 Describing post-surgery cognitive change**

The expected rate of annual change in cognitive performance after STN DBS in our sample of PD patients was circa 0.90 from total of 144 points in MDRS. Although sample-level uncertainty intervals were tightly clustered around this estimate, population-level inference and prediction uncertainty intervals were considerably wider implying relatively high true score inter-individual heterogeneity and measurement error respectively. Nevertheless, the expected rate of cognitive decline 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; Mangone et al., 2020; Reich et al., 2022; Smeding et al., 2009) whereas other studies appear to observe similar to or larger post-surgery decline than Study 2, however, due to their lack of reporting score changes or regression slopes, they cannot be directly compared to results of this thesis (Boel et al., 2016; Castrioto et al., 2022; Pal et al., 2022; Schupbach, 2005).

### **5.2.2 Predicting post-surgery cognitive change**

In the sample analysed in this thesis, 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). To explain findings relating to the predictive value of pre-surgery executive functions, authors usually refer to the dual-syndrome hypothesis (Kehagia

et al., 2010, 2012). As discussed in the Introduction section, the dual-syndrome hypothesis distinguish two distinct phenotypes in the general PD, the patients with deficits associated with posterior cortical structures (such as visuo-construction skills) indicating high risk of rapid disease progression and short-term conversion to dementia, and the patients with executive function deficits associated with frontal cortical structures indicating slowly progressing dysexecutive syndrome. Since patients from the former group usually fail indication criteria for the STN DBS surgery, STN DBS treated patients tend to be sampled from the latter group and are thus likely to develop slowly progressing fronto-striatal executive impairment.

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; Monchi et al., 2004; Sawada, 2012). The processing speed executive function component may thus be a reliable marker of disease progression sensitive to biological determinants of cognitively high-risk PD.

In contrast to the processing speed component of executive function, the results of predictive value of pre-surgery set shifting factor score are indefinite. The set shifting factor reflected primarily performance in TMT-B, TMT-A, TOL, and RAVLT interference set recall (i.e., RAVLT-B). In accordance with previous research, set shifting and verbal working memory factor reliably predicted pre-surgery MDRS performance cross-sectionally (Lopez et al., 2021). However, neither set shifting nor verbal working memory were predictive of MDRS performance changes longitudinally (compare  $\beta$  and  $\delta$  parameters in Table 7). These findings stay in opposition of the dual-syndrome hypothesis predictions presented above as both set shifting and verbal working memory comprise executive function components linked to fronto-striatal circuitry (Bezdicek et al., 2021; Emch et al., 2019), yet these factors do not seem to be reliably predictive of post-surgery cognitive decline in PD. It needs to be noted, that in our study, the pre-surgery set shifting factor was inconsistently estimated across imputations in EFA (see standard deviations in Figure 4) which increased uncertainty in GLMMs related to it. Nonetheless, both psychometric advances in measuring processing speed-independent executive function components as well as theoretical advances in the dual-syndrome hypothesis will greatly benefit future understanding of cognitive profile related to high risk PD phenotypes for STN DBS.

Finally, recent meta-analysis identified both pre-surgery executive dysfunction as well as poorer pre-surgery memory to be reliably predictive of post-surgery cognitive decline (Jahanshahi et al., 2022). The results of Study 2 corroborate the former but oppose the latter finding of this meta-analysis.<sup>6</sup> Nevertheless, as showed in Study 1, memory profile of PD patients can be further differentiated implying that the discrepancy between our results and conclusions of Jahanshahi et al. (2022) regarding pre-surgery memory predictive value can be explained by future studies examining more granular memory processes.

### **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 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 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. These findings corroborate potential critiques of the dual-syndrome hypothesis explanation for post-surgery cognitive decline raised in discussion of Study 2. More precisely, as stated above, the dual-syndrome hypothesis explanation assumes that patients with primarily posterior cognitive deficits such as visuoconstruction impairments would be excluded from samples treated with STN DBS due to the rapid disease progression. However, Study 3 shows that patient group at high risk of post-surgery cognitive decline show both frontal and posterior structural abnormalities in MRI.

Finally, the involvement of visual cortices in predicting post-surgery cognitive decline may aim our attention to further confounding factors 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.

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<sup>6</sup>The results regarding predictive value of episodic memory are compatible with null hypothesis of no predictive value of pre-surgery episodic memory for post-surgery cognitive decline risk above and beyond information provided by the rest of pre-surgery cognitive profile (see Table 7 and Figure 6).

Overall, the main takeaways from Study 3 are as follows: (i) post-surgery cognitive decline seems to be related to disease progression rather than effects of stimulation itself (however, cf. Reich et al., 2022), (ii) both frontal and subcortical as well as posterior brain structures' structural integrity is lower in pre-surgery assessment of patients with post-surgery cognitive decline, and consequently (iii) in addition to examination of higher order cognitive functions, deficits in perceptual faculties should be measured by neuropsychology assessment for risk stratification of patients with PD considered for STN DBS treatment.

#### **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.<sup>7</sup> 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; Russmann et al., 2004). At the same time, the results of Study 4 imply that lowering LEDD leads to increase in IADL difficulties both pre- and post-surgery (with the effect being possibly marginally larger after STN DBS surgery, see panel C of Figure 7). 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. For this purpose, Table 11 provides expectations of self-rated IADL difficulty response probabilities both pre- and post-surgery at different levels of LEDD.

Overall, Study 4 contributes to the discussion of cognitive decline in patients with PD treated by STN DBS via providing a bridge between objectively measured cognitive performance and

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<sup>7</sup>Since only patients already selected for STN DBS via criteria similar to the CAPSIT protocol (Defer et al., 1999) were included into the analysis, we cannot generalise the findings to other PD patients that may not pass CAPSIT-like inclusion/exclusion protocol without added assumptions such as exchangeability between different subpopulation of PD patients. For this reason, I limit the conclusions to patients that are already suitable for STN DBS treatment according to existing patient selection guidelines.

patients' subjective experience of cognitive impairment affecting their everyday living. As major deficit in IADLs is a core definition feature of PD-D (Dubois et al., 2007; Emre et al., 2007; Goetz, Emre, et al., 2008), the results of this study represent one of the first steps toward objective and fully transparent evaluation of PD-D after STN DBS. The study further differentiates itself from previous investigations of IADL difficulties in PD patients by focusing specifically on effects of STN DBS in a pre-test/post-test paradigm that goes over and beyond previously reported cross-sectional comparisons of IADL difficulties between patients with or without cognitive impairment in objective neuropsychological testing (Becker et al., 2020, 2022; Cholerton et al., 2020; Foster, 2014; Foster & Doty, 2021; Pirogovsky et al., 2014; Rosenthal et al., 2010; Schmitter-Edgecombe et al., 2022).

## 5.5 General Discussion

The results presented in this thesis indicate that there are psychologically meaningful differences in memory profile between patients with and without cognitive impairment (Study 1, Havlík et al., 2020). Regarding the primary research objective, the results demonstrate a slow gradual long-term cognitive decline with high inter-individual variability after STN DBS in PD patients that can be reliably predicted by pre-surgery processing speed component of executive function (Study 2, Mana et al., 2024). Furthermore, patients with PD treated by STN DBS who experience post-surgery cognitive decline show signs of lowered structural integrity of subcortical grey matter as well as frontal and posterior cortical areas in pre-surgery MRI (Study 3, Filip et al., 2024). Finally, STN DBS in PD patients leads to a decrease in self-reported IADL difficulties that is partially masked by LEDD reduction after surgery in a short-term (Study 4, Bezdicek et al., 2022). The primary aim of this thesis was to identify pre-surgery cognitive factors predictive of post-surgery dementia in 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.

### 5.5.1 Dementia in Parkinson's disease

Potential major limitation of this thesis is that it investigated core diagnostic features of PD-D, namely the objective cognitive decline and IADL difficulties, without operationally defining PD-D itself. Prior studies that examined pre-surgery predictors of post-surgery PD-D defined dementia via retrospectively applying Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (Bove et al., 2020) or MDS Task Force clinical diagnostic criteria (Krishnan et al., 2019). However, neither study provides sufficient information for reproduction of their diagnostic algorithm and due to their retrospective design, the validity of diagnosis cannot be fully ascertained. If we were to define PD-D in studies presented in this thesis, we would encounter the same difficulties with diagnostic accuracy due to the retrospective design

as the diagnosis would have to be made *ex post facto* from patients' clinical reports. And since both previously mentioned studies imply that PD-D is rather rare in PD patients after STN DBS in mid- to long-term, any diagnostic inaccuracies can have a relatively large impact on the results.

Another issue that comes about with using PD-D category as the primary outcome variable is a variability in definitions. Specifically, although the MDS Task Force clinical diagnostic criteria and DSM-5 criteria of PD-D agree on most points, they differ in significant ways. The MDS Task Force clinical diagnostic criteria of probable PD-D demand that at least two out of four cognitive domains (attention, executive function, visuospatial functions, and free recall memory) are impaired (Goetz, Emre, et al., 2008), whereas the DSM-5 criteria of probable Major Neurocognitive Disorder due to PD demand that at least one out of six cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition) is impaired (American Psychiatric Association, 2013). The same patient could thus be diagnosed with the Major Neurocognitive Disorder due to PD by DSM-5 while not fulfilling criteria for PD-D according to the MDS Task Force clinical diagnostic criteria.

On the other hand, the MDS Task Force clinical diagnostic criteria and DSM-5 criteria agree on the core features of PD-D, namely the objective cognitive decline with insidious onset and difficulties in cognitively driven activities of daily living that can, but do not need to, be accompanied by behavioural signs and symptoms. Consequently, the focus of this thesis on investigating single core diagnostic features of PD-D could lead to more reliable and generalisable conclusions than retrospectively diagnosing PD-D as the primary outcome would. Importantly, impairment of features investigated in this thesis is necessary (albeit not sufficient) condition for PD-D diagnosis and analysis of these features thus still provides useful information about post-surgery PD-D conversion.

### 5.5.2 Constraints on generality

Severe constraints on generality apply to studies presented in this thesis. 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. However, as implied by for instance the dual-syndrome hypothesis (Kehagia et al., 2010, 2012), these assumptions might be untenable. 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 results due to estimates distortion via the collider bias (Berkson, 1946; Cinelli et al., 2022). Also called Simpson's paradox, this bias refers a phenomenon whereby the sign (or magnitude) of an association flips after statistically

adjusting for a third variable (or set of variables) (Pearl, 2014; Simpson, 1951). Critically for this thesis and all previous studies of this kind, selection processes (such as inclusion of patients based on CAPSIT protocol criteria) result in the same phenomenon if the results are interpreted causally or generalised to a larger population (Deffner et al., 2022; McElreath, 2020). Since the population of patients considered for STN DBS systematically differs from the population of patients selected based on established criteria, I 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).

### 5.5.3 Genetic profiling

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 as well as faster cognitive decline in PD patients (Davis et al., 2016; Sidransky & Lopez, 2012; Szwedo et al., 2016).

Several recent large sample studies implied an important role of GBA mutation in STN DBS treated PD patients. Mangone et al. (2020) re-tested 208 patients (25 of which tested positively for GBA mutation) and observed substantially larger MDRS change scores in GBA mutation carriers (GBA+) ( $M = -3.2$ ,  $SD = 5.1$ ) compared to patients without known genetic mutation ( $M = -1.4$ ,  $SD = 4.4$ ). Pal et al. (2022) published a large sample observational study of STN DBS treated patients with PD including both GBA+ and GBA mutation non-carriers (GBA-) as well as patients with and without STN DBS. The study included 366 subjects across 12 study sites followed for up to 5 years post-surgery. Their results imply that GBA mutation is associated with fast cognitive decline specifically in STN DBS treated patients. Compared to GBA- patients with STN DBS, GBA+ patients with STN DBS showed decline that was circa 1.56 MDRS points/year faster (Pal et al., 2022). Finally, Avenali et al. (2024) recently reported another large scale multicenter study that included 365 patients (73 of which were GBA+) followed for up to 5 years and showed that although GBA+ patients experience faster MDRS post-surgery decline, other clinical markers including motor and neuropsychiatric symptoms are similar between GBA+ and GBA- patients.

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, since the GBA mutation status is patient-specific time-invariant characteristic, the statistical model used in Study 2 does in principle adjust its 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 (see Table 5 and Figure 5). 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). This GBA-associated cognitive profile is 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 (compare  $\beta$  and  $\delta$  parameters in Table 7). Further investigation into GBA association with cross-sectional cognitive profile, structural and functional brain characteristics, and longitudinal change of patients' cognitive profile after STN DBS would thus significantly benefit our understanding of biological mechanisms underlying cognitive side effects of PD and its interplay with STN DBS.

Finally, new projects at the Movement Disorders Center, Department of Neurology at First Faculty of Medicine and General University Hospital in Prague were already commenced that include genetic profiling of patients with PD treated by STN DBS. So far, we tried to replicate results of Pal et al. (2022), however, GBA+ patients demonstrate very similar rate of post-surgery cognitive decline in our dataset (the project and its progress is being documented and is publicly available at [https://github.com/josefmana/dbs\\_coGBA.git](https://github.com/josefmana/dbs_coGBA.git)). Since genetic profiling is becoming more accessible in the clinical research and significant number of patients with PD harbour potentially risky genetic variants (Westenberger et al., 2024), addition of the genotype factor to neuropsychologic theories and prognostic models constitutes an attractive avenue for improving accuracy of risks evaluation of treatment options such as 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, high inter-individual in the rate of post-surgery cognitive decline exists between patients, most likely reflecting distinct PD phenotypes and their underlying genetic variants of patients selected for STN DBS treatment.

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 compared to patients with low risk of developing post-surgery cognitive decline. These results hold in spite of both groups of patients being otherwise equivalent at 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.

Outside the objective cognitive assessment, 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 a balance between 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 to reach the best synergistic effect. 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 component of executive function deficit 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.

## 7 Summary

Cognitive dysfunction represents a severe non-motor symptom of Parkinson's disease (PD) associated with lowered quality of life and high patient and carer burden. Severe cognitive dysfunction is one of the factors that can substantially reduce effectiveness of advanced treatments such as deep brain stimulation (DBS) of subthalamic nucleus (STN). Careful monitoring of potential cognitive side effects of the treatment and ability to predict which patients will develop post-surgery cognitive dysfunction is thus clinically and scientifically relevant. In this thesis, I aim to describe the rate of post-surgery cognitive change, identify pre-surgery cognitive and magnetic resonance imaging (MRI) profiles of patients with high risk of developing post-surgery cognitive decline, and examine the effect of the treatment on cognitively demanding instrumental activities of daily living (IADL) in STN DBS treated patients with PD.

The theoretical part of this thesis presents a brief introduction to epidemiology, pathophysiology and clinical manifestations of PD followed by a discussion of brain circuits theories of cognitive dysfunction in PD, neuropsychological assessment strategies and a brief discussion of DBS as it regards to cognition in PD. The empirical part includes four studies aimed to collectively provide a coherent answer to questions posited above. Methodology used for each study is introduced in detail and links to public projects associated with the studies shared for increased transparency.

In the empirical part, I have shown that STN DBS is largely safe from cognitive point of view as the expected post-surgery cognitive decline amounted to approximately 0.90 our of 144 points yearly decline in Mattis Dementia Rating Scale (MDRS). The rate of post-surgery cognitive decline was below published reliable change cutoffs, however, there was large inter-individual

heterogeneity. Patients with worse pre-surgery performance in tasks reflecting processing speed component of executive function and patients with lower cortical frontal and posterior as well as subcortical structural and microstructural integrity in MRI experienced faster post-surgery cognitive decline. Regarding patients self-reported IADLs, the STN DBS treatment seems to have a neutral to positive effect on them which is moderated by dopaminergic medication reduction.

The findings presented in this thesis have the potential to serve as a basis for identifying patients who could benefit from more monitoring after STN DBS surgery. The combined cognitive profile and MRI results also call into question the exact form of theories used to explain post-surgery cognitive decline in previous studies and suggest potential way to address these issues. Finally, the analysis of IADLs yielded a working hypothesis of STN DBS/dopaminergic medication interaction in affecting cognitively demanding daily tasks that should be submitted to further scrutiny in future research.

## 8 Souhrn

Kognitivní porucha je závažným nemotorickým symptomem Parkinsonovy nemoci (PN) spojeným s nízkou kvalitou života a zvýšenou záteží pro pacienty i pečovatele. Těžká kognitivní dysfunkce je jedním z faktorů, které mohou významně snížit efektivnost pokročilých druhů terapie jakou je např. hluboká mozková stimulace (DBS) subthalamického jádra (STN). Pečlivé monitorování kognitivních nežádoucích účinků léčby a schopnost identifikovat pacienty s vysokým rizikem rozvinutí pooperační kognitivní dysfunkce je tedy klinicky i vědecky relevantní. = této disertační práci si kladu za cíl popsat pooperační kognitivní trajektorii, identifikovat předoperační kognitivní profil a profil v obraze magnetické resonance (MRI) predikující vysoké riziko rozvinutí pooperačního kognitivního deficitu a prozkoumat efekt léčby na kognitivně náročné instrumentální aktivity denního života (IADL) u pacientů s PN léčených STN DBS.

Teoretická část práce obsahuje krátký úvod do epidemiologie, patofyziologie a klinických projevů PN. Následuje diskuze teorií kognitivní dysfunkce u PN na podkladu dysfunkce specifických mozkových okruhů, úvod do metod neuropsychologického testování a krátká diskuze DBS a jejích kognitivních korelatů u PN. Empirická část práce obsahuje čtyři studie zaměřené na poskytnutí odpovědí na výše uvedené výzkumné otázky. V této části detailně představuji metodologii užitou v každé studii spolu s odkazy na veřejně dostupné repozitáře navázané na jednotlivé studie za účelem zvýšení transparentnosti práce.

V empirické části práce ukazuje, že STN DBS lze považovat z kognitivního hlediska za převážně bezpečnou metodu léčby PN. Kognitivní výkon pacientů v souboru se v průměru ročně snižoval o přibližně 0,90 bodu z celkem 144 bodů v Mattisově škále demence, což představuje zhoršování výkonu výrazně nižší než doposud publikované odhady reliabilní, tj. klinicky významné, změny. Zároveň ovšem platí, že mé výsledky ukazují na velkou interindividuální variabilitu v rychlosti kognitivní změny po zahájení léčby STN DBS mezi pacienty. Tato

variabilita lze částečně vysvětlit tím, že pacienti s předoperačně sníženým výkonem v testech odrázejících rychlosť zpracování informace a pacienti s předoperačně sníženou strukturální integritou frontální kůry, posteriorních korových oblastí i subkortikálních struktur dle MRI vykazovali rychlejší vývoj pooperačního kognitivního deficitu. STN DBS léčba se naproti tomu jeví mít neutrální či pozitivní efekt na IADL dle pacientského sebehodnocení. Tento efekt je moderován velikostí pooperační redukce dopaminergní medikace.

Zjištění této disertační práce mají potenciál sloužit jako podklad pro identifikaci pacientů s rizikem rozvoje kognitivního deficitu, kteří mohou profitovat z častějších kontrol kognitivního stavu po zahájení léčby STN DBS. Kombinované výsledky předoperačního kognitivního profilu a profilu v MRI podporují část teorií vysvětlujících pooperační kognitivní úpadek u pacientů s PN, poukazují ovšem také na některé nesrovnanosti a možnosti jak tyto nesrovnanosti využít k pokroku v pochopení kognice u PN. Konečně, analýza pooperačních IADL vedla k postulaci pracovní hypotézy o interakci mezi STN DBS a dopaminergní medikací jako společnými přičinami změn v pacientském vnímání obtíží s kognitivně náročnými aktivitami denního života.

## 9 References

## 10 List of Publications

### 10.1 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: 2.3]

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. [2023 Clarivate IF: 4.1]

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. [2023 Clarivate IF: 1.8]

## 10.2 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. **[2023 Clarivate IF: 3]**

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## 11 Supplement

1. **Mana, J.**, Bezdicek, O., Růžička, F., Lasica, A., Šmídová, A., Klempířová, O., Nikolai, T., Uhrová, T., Růžička, E., Urhošík, 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: 2.3]**
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