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FACULTY OF BIOMEDICAL ENGINEERING

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Correlation of neuroimaging and cognitive parameters in presymptomatic and manifested Parkinson's disease

Korelace zobrazovacích a kognitivních parametrů v presymptomatické a manifestí fázi Parkinsonovy nemoci

Doctoral Thesis

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"Versuche immer das höchstmögliche Ziel zu erreichen, einen Schritt zurück kannst du immer machen"

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Declaration

I hereby declare that I have written this thesis myself as a result of my original research (or as co-author of research papers).

All sources of information have been properly stated and referenced.

In Kladno,

In partial fulfilment of the requirements for the degree of Ph.D.

Abstract

Parkinson Disease (PD) is the second most occurring neurodegenerative disease worldwide. The primarily visible motor symptoms are accompanied by a progressive cognitive decline, which all together brings life changing challenges for the patients. While the disease is still unhealable, it is crucial to detect ongoing neurodegeneration as early as possible.

During the last decade several prodromal biomarkers have been identified, helping with earlier detection of PD. One of them is idiopathic REM-sleep-behavior disorder (iRBD), which occurs up to 15 years before the onset of PD.

The aim of this work is to analyse possible connections between cognitive performance of iRBD and PD patients and their brain morphology. Focusing on early cognitive decline might help to understand the disease progression and help detecting neurodegeneration earlier.

With the help of a unique dataset, consisting of brain MRI and the results of a broad cognitive test battery and detailed gait analysis of iRBD patients, PD patients and Healthy Controls, this work evaluates correlations between morphological changes in patient's brains and cognitive performance.

Several cortical and subcortical brain regions were identified to correspond to cognitive performance in attention, memory, executive functions and psychomotor speed. In a second investigation different compensatory patters for cognitive-motor dual task load for cognitively impaired and non-impaired patients was revealed.

The results of this work imply a cognitive decline connected to morphological brain changes already in the presymptomatic phase of PD. This can help to detect and stage neurodegeneration already earlier than currently, leading to an early start of medication. Thus, helping to slow down disease progression and help patients to maintain a higher quality of life for a longer time.

Keywords: Parkinson Disease, REM-sleep behavior disorder, Voxel-based morphometry, morphological brain changes, cognitive performance, gait analysis

Abstrakt

Parkinsonova choroba (PD) je celosvětově druhým nejčastějším neurodegenerativním onemocněním. Především viditelné motorické příznaky jsou doprovázeny postupným úpadkem kognitivních funkcí, což dohromady přináší pacientům problémy, které jim mění život. I když je stále nevyléčitelná, je zásadní odhalit probíhající neurodegeneraci co nejdříve.

Během posledního desetiletí bylo identifikováno několik prodromálních biomarkerů, které pomáhají při včasnějším odhalení PD. Jedním z nich je idiopatická porucha REM spánku a chování (iRBD), která se vyskytuje až 15 let před nástupem PD.

Cílem této práce je analyzovat možné souvislosti mezi kognitivním výkonem pacientů s iRBD a PD a morfologií jejich mozku. Zaměření na časný pokles kognitivních funkcí by mohlo pomoci pochopit vývoj onemocnění a pomoci odhalit neurodegeneraci dříve.

Pomocí unikátního souboru dat, který se skládá z magnetické rezonance mozku a výsledků široké baterie kognitivních testů a podrobné analýzy chůze pacientů s iRBD, pacientů s PD a zdravých kontrol, tato práce hodnotí korelace mezi morfologickými změnami v mozku pacientů a kognitivním výkonem.

Bylo identifikováno několik kortikálních a subkortikálních oblastí mozku, které odpovídají kognitivnímu výkonu v oblasti pozornosti, paměti, exekutivních funkcí a psychomotorické rychlosti. V druhém šetření byly odhaleny rozdílné kompenzační vzorce pro zátěž kognitivně-motorickým duálním úkolem u pacientů s kognitivním postižením a bez postižení.

Výsledky této práce naznačují, že pokles kognitivních funkcí souvisí s morfologickými změnami mozku již v presymptomatické fázi PD. To může pomoci odhalit a stanovit stadium neurodegenerace již dříve než v současnosti, což by vedlo k včasnému zahájení léčby. Tím přispět ke zpomalení progrese onemocnění a pomoci pacientům udržet si delší dobu vyšší kvalitu života.

Klíčová slova: Parkinsonova nemoc, porucha chování v REM spánku, morfometrie založená na voxelech, morfologické změny mozku, kognitivní výkon, analýza chůze

Content

1. Introduction

Neurodegenerative diseases are one of the most life-impacting diseases in higher age. With progressing cognitive and motor impairment, patients are at higher risk of getting injured by falls or other accidents and overall are more dependent on higher level of care and support for all day routines. The occurrence of progressive neurodegeneration affects not just the patient's life but also the life of their families enormously.

Following Alzheimer's Disease (prevalence of 712 in 100.000), Parkinson Disease (PD) is the second most common neurodegenerative disease worldwide with a prevalence of 94 in 100.000 people [1]. Diagnosed mainly after the onset of motor symptoms like bradykinesia or tremor, the neurodegeneration in this stage is already far progressed. The pre-motor-symptom phase of PD can take up as long as 20 years, including the occurrence of unspecific symptoms such as olfactory dysfunction, depression and anxiety, sleep disorders, autonomic dysfunction and others [2].

An earlier and clearer diagnosis of PD is seen as a crucial challenge in medical research, as it could lead to a start of medication and treatment before neurodegeneration progresses excessively. Interdisciplinary research combining the fields of neurology, psychology, molecular biology, and informatics attempts to deepen the understanding of PD onset and progress and identify reliable biomarkers for early- stage PD.

Idiopathic REM-sleep-behavior-disorder (iRBD), which affects the quality of REM sleep, is one of the few already confirmed PD precursors. It was observed that between 45% and 65% of patients with idiopathic RBD develop a neurodegenerative disease within 10 to 12 years [3, 4].

It is now necessary to connect the knowledge about pathological processes and symptoms of PD with the knowledge about iRBD. This includes changes in brain morphology, detected by MRI brain scans, cognitive decline in different domains, which is detected by standardized cognitive tests as e.g. Montreal Cognitive Assessment (MoCa) and specific impairments in gait parameters, which can be detected by gait analysis. The research question hereby is whether the known pathological changes of these parameters in PD patients are already detectable in iRBD patients and can this lead to new diagnostic options of early-stage PD?

The primary objective of this dissertation is to explore potential correlations between cognitive performance and brain morphology among individuals diagnosed with iRBD and PD. This study is founded upon a comprehensive dataset comprising MRI brain scans, outcomes from a diverse battery of cognitive assessments, and gait analyses conducted on iRBD patients, PD patients, and Healthy Controls (HC). Anticipated findings have the potential to deepen our comprehension of iRBD pathophysiology and facilitate the advancement of more economical and efficient diagnostic techniques for PD, using cognitive and gait assessments.

The first part of this work gives a detailed theoretical overview about Parkinson Disease, iRBD, cognitive and gait tests and current knowledge of correlations between cognitive decline and brain morphology. Additionally, it explains the technical basics for the here used method of morphometry. Afterwards the exact used methodology is described in detail followed by a chapter showing the results, which is divided into the three main goals of the work:

i. Definition of an applicable pre-processing pipeline for Magnetic-Resonance (MR) images
ii. Correlation of brain morphology with cognitive test performance in PD and iRBD patients
iii. The influence of impaired Dual Task on the correlation of brain morphology and Dual task cost parameters in PD

In the latter, the results are discussed, and a conclusion is made.

Thereafter the Author`s publications and additional data is presented in the appendix of the work.

2. State of the art

To fully understand all aspects of this work, this chapter will give a broad overview of knowledge about the medical background of PD and RBD, standard cognitive testing and medical image-analysis. Additionally, this chapter includes an overview of previous results regarding morphological brain changes in RBD and correlations of these changes to standard cognitive tests. Further, the influence of Mild Cognitive Impairment (MCI) in patients on the disease progression and outcome of cognitive tests is explained.

2.1 Rapid Eye Movement Sleep Behaviour Disorder

Idiopathic RBD was shown to be a precursor to different α-synucleopathies with a rate of phenoconversion of up to 82% within a period of 14 years after iRBD diagnosis [5] . This fact makes it to one of the few surely identified and safely diagnosable markers, preceding the onset of PD symptoms by years. On this basis, iRBD can be used to investigate the prodromal phase of neurodegenerative diseases which makes it to a vulnerable tool in Parkinson disease research.

2.1.1 Healthy Rapid-Eye-Movement sleep

The Rapid Eye Movement (REM) sleep phase starts approximately 90 minutes after beginning of the sleep. EEG signal from cortical regions starts to be desynchronized and shows a fast activity pattern, similar but not same as during waking phase. EEG signal from the hippocampal region stays highly synchronized at 4-10Hz theta wave. During this sleeping phase the muscle tone drops down in all body parts except the skeletal muscles which control the eye movement, the middle ear ossicles and muscles responsible for respiration. This leads to the inability of the body to move. Typical for REM sleep is the loss of the ability to control the body temperature; other sympatric activity is supressed as well.

The threshold for disturbance from external signals is increased. From this view it is the deepest sleep phase and environmental disturbances can hardly awake the sleeper. In contrast to this it is most possible for the sleeper to awake spontaneously during REM sleep. From this view REM sleep is the lightest sleep phase. Most people awaking during a REM sleep phase can recall their dreams while this is possible just in 50% of the cases when awaking from other sleep phases.

In the brain the REM sleep phase is characterized by phasic neuronal discharging from **P**ons to Corpus **G**eniculatum laterale and to **O**ccipitalbrain. This can be measured as so called **PGO** waves (Fig. 2.1).

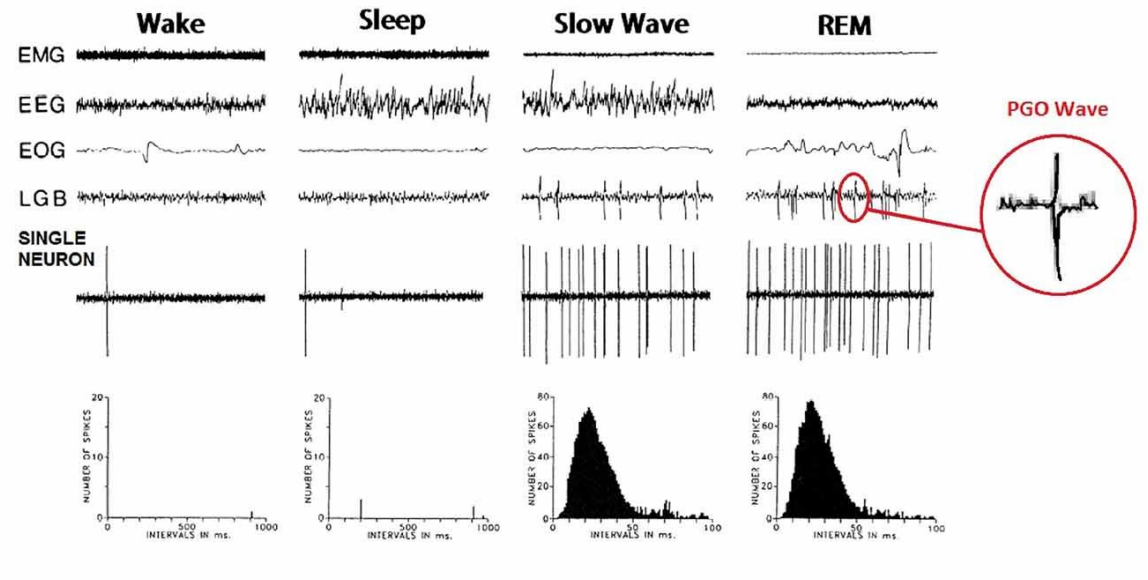


Figure 2.1: Ponto-Geniculo-Occipital (PGO) waves in cats. Measurements of single nonbursting type PGO on-state Neuron, located in the caudolateral peribrachial area (C-PBL) of a cat. Widespread distribution of PGO wave activity correlates with a triggering-neuron transitioning from tonic to high frequency activity. (Image from [1])

2.1.2 RBD symptoms and epidemiology

The REM sleep behaviour disorder is a disorder which is characterized by the loss of physiological atonia of skeletal muscles with abnormal behaviour during dream sleep such as flailing, punching, kicking, vocalisation, self-inflicted injuries or injuries of bed partners [6]. While being common in other sleep phases, these actions should not occur during REM sleep phase. The observed activity seems to be on purpose as if the person tries to protect him/her self and goes as far as jumping out of the bed and running. The reported dreams often contain attacks of animals or insects and the acted-out behaviour fits to the dreamed story. If bed partners try to awake the patient out of the dream, it may happen, that this try is included into the dream and the patient starts to attack the bedpartner. The dream enactment leads often to injuries as bruises, head contusions, hair pulling and fractures of the patient or even its bedpartner. [7]

RBD occurs in approximately 0,5% of general population [8]. The risk increases for older people - of up to 6% of the population older than 70 years [9]. Studies suggest that RBD occurs with around 70-85% predominantly in man, while it stays unclear if the time of disease onset differs between male and female patients [10, 11]. It is discussed, if this number might be too high, as the diagnose in woman may be harder due to less violent sleep enacting.

RBD can be idiopathic or symptomatic caused by neurodegenerative disorders or narcolepsy. Other reasons for RBD are drug- and/or alcohol withdrawal the use of Tricyclic antidepressants or selective serotonin and norephrine reuptake inhibitors [7, 12].

RBD unites a dream disorder and a motor disorder part. Not only do the patients enact their dreams but the dreams are as well unnatural often very aggressive. The reason for this is not yet well understood [13]. As well it is not yet fully clear if RBD involves just “acting out the dreams” or if the dreams are generated according to the movements “dreaming around one’s actions”.

It could be that loss of atonia, and increased locomotor drive leads to limb movements and the dream content could be built around these movements. There exist reported cases of patients dreaming they are attacked while a bedpartner was grabbing the patients arm to stop the fighting behaviour during a dream. This problem can increase the violation against the bedpartner and lead to injuries. It is expected that both directions - acting out the dream and dreaming around an action – can act together and are not exclusive. [12]

2.1.3 Diagnosis and treatment of RBD

The impulse to check for RBD mainly comes from the bedpartners observations who report the typically signs of RBD. Unfortunately, the lack of awareness of RBD among medical doctors often leads to a delay in diagnosis. A study of White et. al. found a mean delay of diagnosis of 8.7 years for 31% of patients with a delayed RBD diagnosis [14].

The most valid diagnostic possibility for RBD is a video Polysomnography (PSG), which the International RBD Study Group sees as mandatory for the diagnosis of RBD [15]. While undoubtedly this technique provides a lot of diagnostic potential, it is rather complicated to achieve for patients as there are not enough sleep laboratories which can provide it.

A quicker and less elaborate possibility is the usage of standardized questionnaires. Here it is important to also include the bedpartner into the interview as the patients might be totally unaware of their behaviour during sleep. The easiest but most inaccurate way is to question the patient based on the International Classification of Sleep Disorders criteria for RBD. A more standardized questionnaire called the Mayo-Sleep-Questionnaire was developed by Boeve and colleagues [16] and showed in general a high sensitivity (100%) and specificity (95%). The advantage is, that this test includes also answers from bedpartners. The most often used questionnaire is the REM Sleep Behavior Disorder Screening Questionnaire, which however relies just on answers from the patient and excludes bedpartner from the interview [17].

The minimal diagnostic criteria for RBD proposed by the International Classification of Sleep Disorders (ICSD)-242 are the following [18]:

A) Presence of REM sleep without atonia (RSWA) on a PSG

B) Repeated episodes of sleep related vocalization and/or complex motor behavior documented on Polysomnogram (PSG) or based on clinical history

C) Absence of epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder

D) Sleep disturbance not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

RSWA shows an abnormally elevated muscle tone during REM sleep. This can be recorded by a polysomnographic examination. The difference between a healthy control and a RBD patient polysomnogram is shown in Figure 2.2 (adapted from [19]):

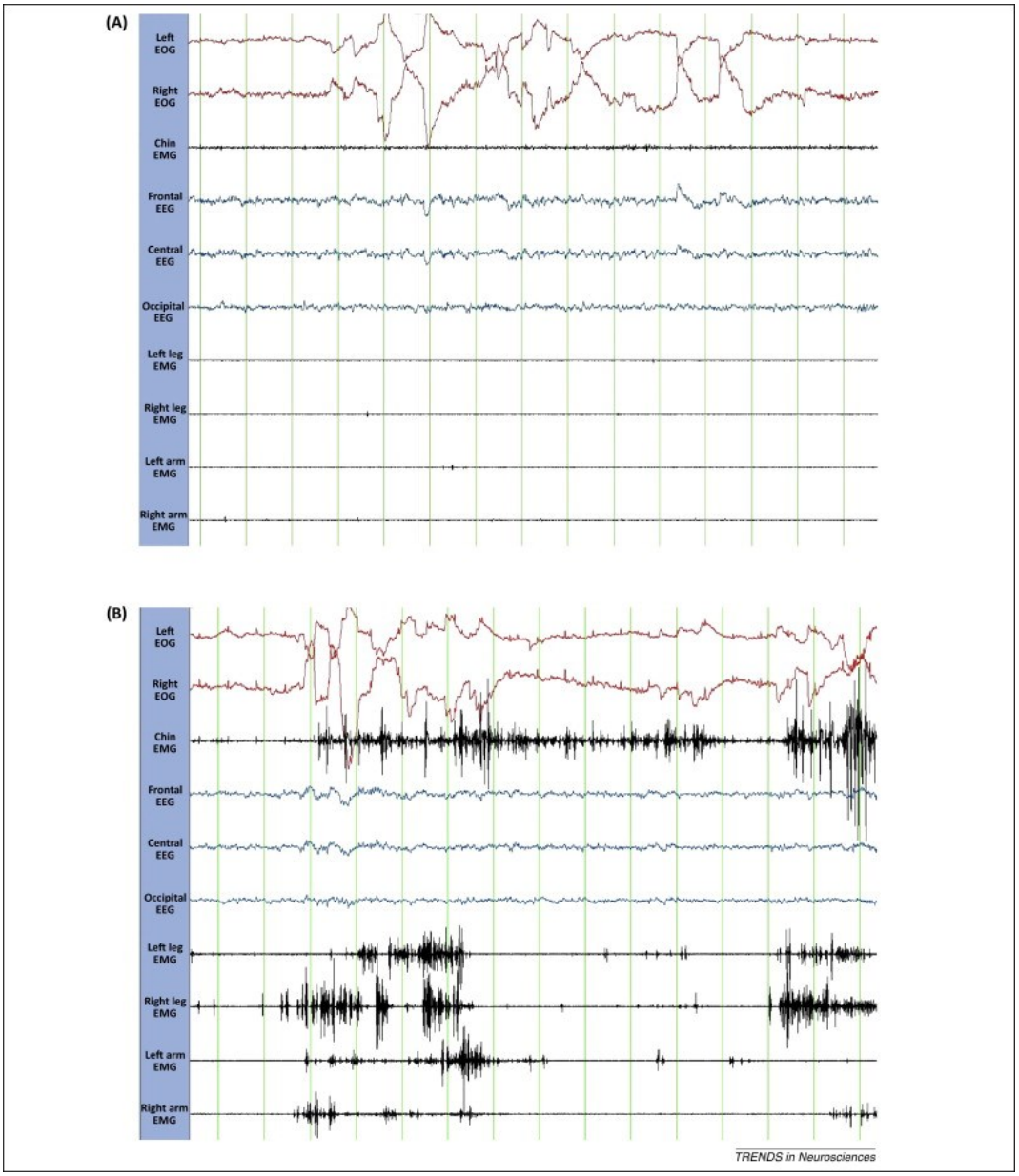


Figure 2.2: Polysomnographic examples of normal rapid eye movement (REM) sleep and REM sleep of a patient with REM sleep behavior disorder (RBD). (A) A 30-s epoch of REM sleep in a control subject shows its three defining features: (i) rapid eye movements on the two electro-oculogram (EOG) leads; (ii) desynchronized electroencephalographic (EEG) activity on frontal, central, and occipital leads; and (iii) atonia on all electromyographic (EMG) leads (chin, legs, and arms). (B) A 30-s epoch of REM sleep in a patient with RBD exhibits the first two features of REM sleep. However, the chin, leg, and arm EMG leads show the excessive muscle activity that characterizes RBD.

Newly emerging technologies as home based PSGs, actigraphy devices (worn on the wrist) or diagnostic applications on the patients smartphone might expand the diagnostic possibilities in the future [20].

The most important role in treatment of RBD takes the avoidance of injuries of the patient and bedpartner. Dangerous objects should be removed from the bed side, sharp corners of furniture should be covered. It might be helpful to put a mattress in front of the bed to avoid injuries by falling out of the bed. Barriers around the bed and between the bedpartners can help as well. In case the patient tends to attack the bedpartner, separated beds or even rooms might be necessary. Useful alarm systems which e.g., recognize stepping the patient out of bed or moving heavily in bed can be purchased and are helpful of detecting enacting episodes especially when the bedpartner sleeps in a different room. Acoustical alarms can awake the patient out of the dreams and so lessen the risk of injuries.

Pharmacologically the symptoms are treated mostly with clonazepam and melatonin [21, 22]. An overview of the medication and side effects is shown in the Table 2.1 below:

Table 2.1: Pharmalogical treatments of iRBD [7, 12]

Drug	**Mechanism**	**Typical Adverse Effects**
Clonazepam	GABA receptor agonist	Sedation, sexual and cognitive dysfunction, respiratory depression
Melatonin	unknown	Sedation
Pramipexole	Dopamin agonist	Sedation, nausea, impulse control disorders
Levodopa	Precursor for neurotransmitter e.g. Dopamin	Hypertension, arrythmias, nausea, disorientation, confusion
Carbamazepine	Anticonvulsant	Nausea, drowsiness, decreased bone marrow function, suicidal thoughts
Donepezil	Acetylcholinesterase inhibitor	Nausea, trouble sleeping, aggression, abnormal heart rhythms, seizures
Galantamine	Acetylcholinesterase inhibitor	Nausea and other gastrointestinal problems
Triazolam	Central Nervous system depressant tranquilizer	Dizziness, coordination problems, euphoria, tiredness
Clozapine	Atypical antipsychotic medication	Muscle stiffness, bed-wetting, central nervous system depression
Quetiapine	Atypical antipsychotic medication	Sleepiness, dry mouth, high blood sugar, seizures

2.1.4 iRBD as an initial state of α-synucleopathies

Idiopathic RBD is known as the most important marker for beginning neurodegenerative processes leading to fully pronounced α-synucleopathies as Parkinson Disease, Dementia with Lewy Body (DLB) and Multi-System atrophy (MSA). Large longitudinal cohort studies of Iranzo et. al. [23] and Schenck et. al. [24] showed a phenoconversion of 81% respectively 91% of iRBD patients to a neurodegenerative disorder or to a diagnosed MCI within 14 years. These numbers of conversion rates were confirmed by a large Meta-analysis of longitudinal studies done by Galbiati et. al. [25] who calculated a risk of conversion of 97% by applying a Kaplan-Meier analysis. Already within the first five years after diagnosis of iRBD a relatively large part of around 30% of followed patients showed a conversion to a clinically defined neurodegenerative disease, rising to about 66% after 7.5 years [26, 27]. This development shows the steady progression of the disease but also gives an idea of a possible time window for medical intervention to stop the progressing degeneration.

While it is unquestioned that iRBD leads with high possibility to a phenoconversion into one of the upper mentioned diseases, it is still highly discussed if there are clear predicting factors which lead to a forecast into which α-synucleopathy iRBD will develop and when conversion will occur. In table 2.2 are summarized risk factors pointing to a short-term phenoconversion in general and to a specific α-synucleopathy.

Table 2.2: Predicting factors of phenoconversion of iRBD in general and into different α-synucleopathies (adapted from [28])

General higher risk of conversion	Conversion to PD	Conversion to DLB	Conversion to MSA
• Presence of RSWA • Several genetic mutations • Reduced ratio of p-tau/tau total • Progressive loss of presynaptic dopamine terminals in striatum • Increased hippocampal perfusion • Cortical thinning in frontal, parietal and occipital cortices • Presence of MCI	• Higher scores of UPDRS III • Presence of hyposmia • Tonic RSWA • EEG slowing in temporal and occipital lobes	• Decline in systolic blood pressure • More pronounced and faster progressing cognitive alternations • Phasic RSWA • Presence of hyposmia • Faster progression of impaired colour vision • Diffuse slowing of electrical activity in EEG	• Presence of urinary symptoms • unpresent Hyposmia

The highest conversion rate of iRBD patients can be seen to a clinically manifested Parkinson`s disease (44%), followed by DLB (25%), other not specified dementia (7%) and MSA (5%). Very low conversion rates of 3% are seen to Alzheimer's dementia (AD), leaving open if

iRBD is really a precursor of AD or if these patients might have developed two neurodegenerative diseases parallel to each other. [25]

This indicates the high importance of further understanding the underlying pathologies of iRBD and the mechanisms of phenoconversion to manifested α-synucleopathies.

2.1.5 Pathophysiology of iRBD

The exact pathogenesis of iRBD is still unclear and seems to be very complex. Lesions in caudal brainstem, affecting the circuits regulating the REM sleep muscle atonia, were identified as the possible starting point for the development of iRBD. This is the same area in which α-synucleopathies start to first appear in central nervous system. This leads to the assumption that α-synuclein pathology starts years before the first motor- and cognitive symptoms appear and iRBD symptoms might be one of the first detectable signs of this pathology. [29]

The motor control circuit inducing muscle atonia in REM sleep phase in healthy persons bases mainly on the inhibiting effect of activated GABA- and Glycin-releasing neurons in reticular nucleus on skeletal motoneurons (Fig. 2.3). This inhibition overlays the activating effect on motoneurons, coming from the motor cortex. The overall effect in this functioning circuit is an induced muscle atonia. In patients with iRBD the inhibiting circuit is damaged. Signals coming from motor cortex to motoneurons are normally processed, which leads to normal muscle movements similar to non-REM sleep and awakeness. [19]

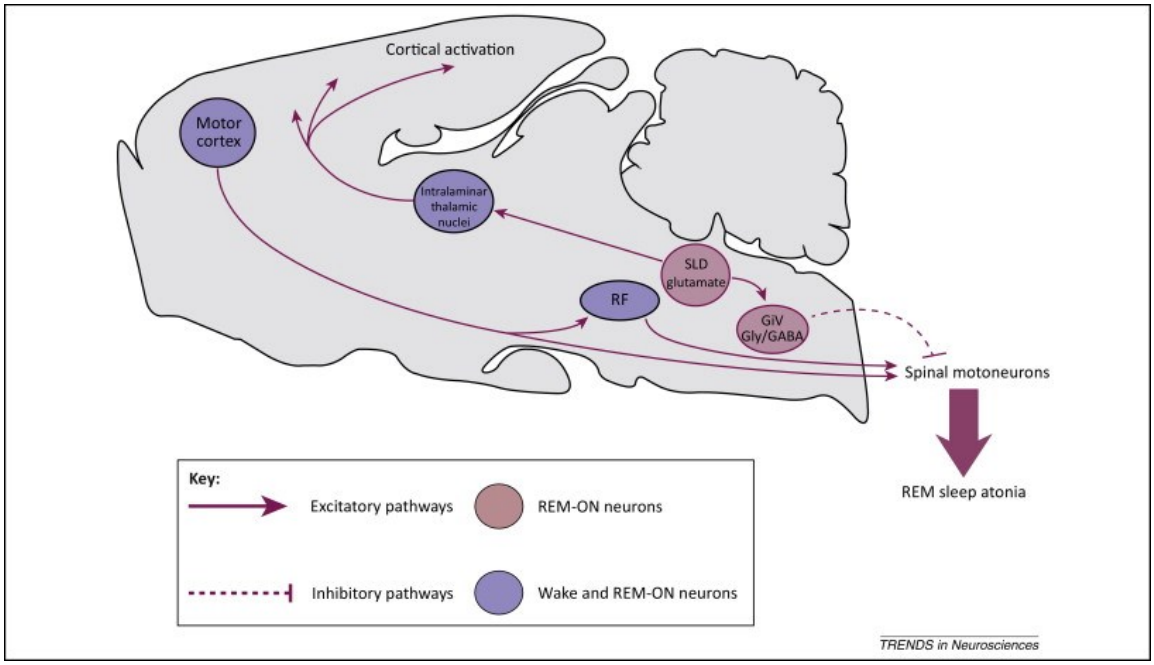


Figure 2.3: Motor control in rapid eye movement (REM) sleep and its role in REM sleep behavior disorder (RBD).

In healthy REM sleep, neurons of SLD activate neurons in GiV which inhibit motor neurons. This leads to atonia during REM sleep. In a second ascending cycle SLD activates cortical motor regions which send activation signals to spinal motor neurons. In healthy patients these signals are blocked by the inhibitory effect of GiV signals. In patients with RBD the SLD-GiV circuit is degenerated and the movement signal from motor cortex are processed in spinal motor neurons which leads to movement during REM sleep. Adapted from [19]

GiV - ventral gigantocellular reticular nucleus; SLD - sublaterodorsal tegmental nucleus

2.1.6 Biomarkers of iRBD

With identifying iRBD as a prodromal stage of fully grown α-synucleopathies and so with recognizing the potential as a predicting factor, several studies tried to identify reliable biomarkers for iRBD diagnosis. The group of Mitchell et. al summarized the results of these studies in an overview of all so far known biomarkers of several categories [30]. This review article was used as a basis for the following summary.

Neurophysiology

The most important neurophysiological marker is the detection of RSWA via visual or automated analysis of video-polysomnography. The presence of lower cyclic alternating patterns in EEG has shown potential of a biomarker as well. The possibility to use of artificial intelligence and machine learning to evaluate PSG and EEG patterns will in future promote these non-invasive diagnostic methods further.

Motor function

The results of upper extremity tap test as well as the analysis of gait parameters as e.g. speed, cadence step variability in single- and dual-task mode have shown differences between iRBD patients and healthy control groups, making these parameters to vulnerable and easily accessible biomarkers. The rising availability of wearable at-home gait analyzing devices will rise the importance of these analysis even more.

Another motor feature which shows potential of differentiating between healthy and iRBD patients is speech analysis. Automatically analyzing systems, build with the help of machine learning algorithms, are able to detect abnormal speech.

Cognition

Standardized cognitive testing has shown the ability to function as a biomarker for iRBD. The cognitive performance of iRBD patients is mainly impaired in the domains of attention, executive function, memory and visuospatial function. For a more detailed overview about cognitive impairment in iRBD see chapter 2.7.

Olfaction

An impaired olfaction was shown to be a reliable biomarker. The Sniffin´Stick test or the UPSIT test are easy to carry out and are at low-cost intensity.

Ophthalmic function

The ability to discriminate colors measured by the Farnsworth-Munsell 100-Hue test and optical coherence tomography showed a potential as a biomarker for iRBD. To validate both methods in iRBD diagnostics, more longitudinal studies are necessary to consolidate the results.

Autonomic functions

Autonomic dysfunction in iRBD include mainly urinary and sexual dysfunction, constipation and cardiovascular deficits. These features can be easily measured by either a questionnaire or medical devices.

Biofluids

The identification of α-synuclein in CSF or in olfactory mucosa was shown to function as a diagnostic and prognostic marker in iRBD. While the CSF test has a higher sensitivity than the nasal swap test, the nasal swap test is by far less invasive.

The identification of further molecular biomarkers is expected due to progress in molecular diagnostics. Some candidates of circulation micro-RNA and proteins were already identified in smaller experimental studies.

Neuroimaging

The radio-nuclear methods of I-FP-SPECT and F-FDG-PET showed both potential in identifying the risk of future phenoconversion.

MRI in connection with picture processing either analyzing special brain regions as e.g. substantia nigra or analyzing general brain atrophy even showed the potential of being a diagnostic marker. For detailed information about morphological brain changes in iRBD see chapter 2.6.

Tissue biopsy

The proof of the presence of α-synuclein in tissues outside the brain as e.g. colon, salvia glands or skin is a promising method to verify an α-synucleopathy. Hereby the skin biopsy is the best tolerated by patients and easiest to perform method of all.

Genetic testing

Up to GBA variants and SNCA 5`varaints have been identified as genetic markers for iRBD mainly having prognostic value with helping to predict phenoconversion.

2.2 Parkinson disease

Parkinson`s disease is one of the most frequently occurring neurodegenerative diseases worldwide. Enormous effort is made to better understand the causes, the pathology and progress of this disease in order to find a possible cure or at least ways to stop progression and higher quality of life of patients.

Thought referred to as one disease, PD presents to be clinically very heterogeneous with a broad spectrum of different motor and non-motor symptoms, different progression patterns and disease duration.

The relatively high incidence in population, the life changing effect of the disease on patients all day live and the complexity of its nature lead to a high focus of research in this field.

2.2.1 Symptoms and epidemiology

Parkinson's disease is a progressive neurological disorder characterized by a large number of motor and non-motor features with early prominent death of doperminergic neurons in the substantia nigra pars compacta [2].

As the second most common neurodegenerative disorder it affects 2-3% of the population aged 65 years and older [31].

It was first described in 1817 by James Parkinson, who published his findings in "An essay on the shaking palsy ". Later, in 1919 scientists found out that patients with Parkinson disease have a loss of cells in the substantia nigra. In 1960 the researchers Ehringer and Hornykiewicz discovered that the concentration of dopamine in the stratum of Parkinson Disease patients is lowered. This observation was the beginning of the dopamine-substitution therapy for Parkinson Disease.

Clinically Parkinson disease is described with the following motor-symptoms:

Bradykinesia

Bradykinesia is the loss of quick and spontaneous movements and the slowing down in activity. The reason is a difficulty in planning, initiation and execution of tasks. It is a basal ganglia disorder.

Tremor

The rest tremor seen in PD patients effects most likely the distal part of an extremity but can also effect the lips, chin, jaw and legs. Mostly the tremor has a frequency of 4-6Hz.

Rigidy

Rigidy is an increased resistance present during a passive movement of a limb. It can be painful.

Postural deformities, instabilities and freezing

Later, in the development of PD, postural deformities often occur primarily within the region of the neck and trunk.

Postural instabilities are characterized by losing the postural reflexes and the freezing is a motor block with the complete loss of movement. Both symptoms are a common course of falls.

Additionally, the following non-motor symptoms can be observed in patients with PD [32]:

- Mental health problems (dementia, depression, psychosis, anxiety, apathy)
- Falls and potential fractures
- Sleep disturbance (hypersomnolence, RBD, restless legs syndrome, inverted sleep-wake cycle, nocturnal akinesia)
- Autonomic disturbance (bowl dysfunction, dysphagia, weight loss, dribbling of salvia, bladder dysfunction, sexual dysfunction, postural hypotension, excessive sweeting
- Pain (disease related dystonia, comorbid joint disorders)

The highest risk factor for development of PD is age. Parkinson Disease is rare in people younger than 50 years [31]. But there is an almost exponential growth of risk after the age of 80 years. Other risk factors are environmental exposures and ethics as well as genetic predispositions [2].

The general mortality in the first decade after onset of symptoms is not increased but rises later up to double of normal mortality.

In most of the population studies, it is shown that Parkinson disease affects men twice as often as woman. But in some studies, there could not be seen any difference between sex. These deviations might be reasoned by the different lifestyle of women and men or the different exposure to environmental factors. As well there might be a protective effect of female sex hormones which is a current topic of research. [31]

The exposure to pesticides or a previous severe brain injury higher the risk for PD, while the use of nicotine or caffeine seems to lower the risk [33].

2.2.2 Pathophysiology of Parkinson disease

The aggregation of, under normal circumstances soluble, α-synuclein, forming neurotoxic Lewy-bodies, is the basic pathology causing process in PD. Research during the last decade identified the start of this process in gastrointestinal tract, connecting the development of PD with regions outside the central nervous system (CNS) [34, 35]. The current understanding of PD progress is the uprising of aggregated α-synuclein from gut via nervus vagus, entering the CNS at Medulla oblongata [36, 37]. A progress into brainstem and midbrain, also affecting locus coeruleus and substantia nigra follows. In this phase, typical motor symptoms start to appear. The degeneration within the brainstem starts in cholinergic and monoaminergic neurons and in neurons of the olfactory system. Later in disease, the limbic system and neocortical brain regions are affected as well [31]. The reasons for the appearance of Lewy- bodies include overproduction of the protein, presence of mutations that lead to misfolding and oligomerization or impairments in molecular pathways which are responsible for degradation of α-synuclein. [38]

The aggregates can be transported inside the cell via axons into other brain regions, they can be excluded out of the cell into the extracellular space and can be taken up by neighboring neurons. This process leads to spreading of the pathology throughout connected brain regions as shown in Figure 2.4. [39]

Considering this theory of progression, the so far identified premotor symptoms of PD as constipation and iRBD [40] follow the axis of transfer of α-synuclein aggregates along nervus vagus into brainstem.

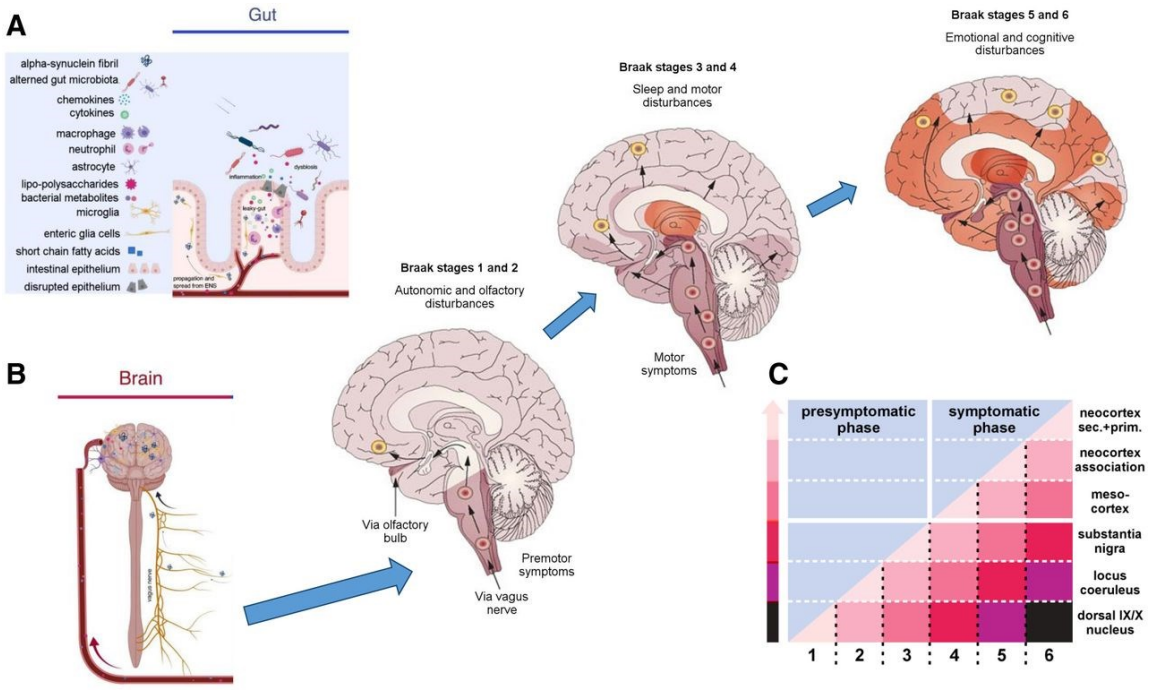


Figure 2.4: Progressivley uprising of demaging α-synuclein aggregates from peripheral nervous system to brainstem, midbrain and subcortical and cortical areas [36]

Parkinson disease is characterized by early prominent death of dopaminergic neurons in the substatia nigra pars compacta (SNpc) and the appearance of α-synuclein accumulations in different brain regions. Applied together, these two neuropathologies are specific for the diagnosis of PD. [31]

The degeneration of doperminergic neurons starts way before the onset of the first motor symptoms. Studies show that before the first motor symptoms occur, approximately 60-70% of neurons in SNpc are already lost. The loss of dopaminergic neurons affects the motor control of the brain negatively, which follows in the typical motor problems of PD patients. [41]

Motor control is a complex process which involves several brain regions and different neurotransmitters (Fig. 2.5). A system of activating and inhibiting pathways interconnecting regions of the Striatum (nucleus caudatus + putamen) and the pallidum, together known as basal ganglia and cortex areas. Functional connected to these regions are the nucleus subthalamicus and sustantia nigra which are parts of the midbrain.

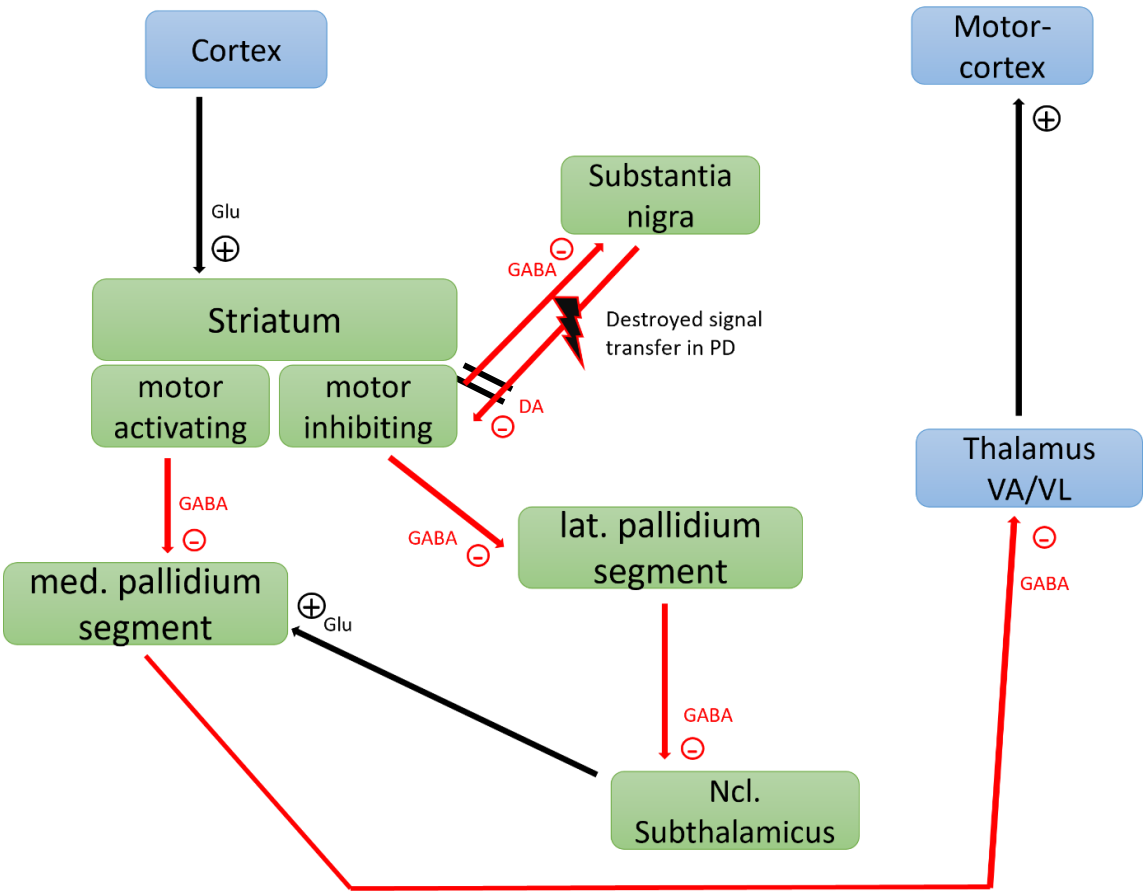


Figure 2.5: Motor regulating circuits in brain with inhibiting (-) and activating (+) pathways and responsible neurotransmitters. DA-Dopamin, GABA – gamma amino buteryc acid, GLU – Glutamat, green: parts of basal ganglia, blue: regions outside basalganlia interacting with basalganlia

The lack of dopamine in PD affects the patients motor abilities significantly. These changes in basalganglia lead to the pathophysiology of tremor, problems with balance and gait.

Genetic mutations, abnormal handling of misfolded proteins by the ubiquitin–proteasome and the autophagy–lysosomal systems, increased oxidative stress, mitochondrial dysfunction and inflammation have been identified as contributing factors in the death of dopaminergic and non-dopaminergic cells in the brains of patients with PD. [40]

2.2.3 Diagnosis of Parkinson Disease

The international Parkinson and Movement Disorder Society released the following criteria for diagnosis of Parkinson disease:

1. Step: diagnosis of parkinsonism
   - Presence of bradykinesia as a slowness of movement and a decrement in amplitude or speed, or progressive hesitations or halts, as movements continued
     - In combination with at least one of: rigidity and/or rest tremor
2. Step: determining Parkinson disease as the cause of parkinsonism with two levels of diagnostic certainty (for full list of clinical diagnostic criteria see [42])

The steady development of medical image analysis and molecular detection methods improved the possibilities of understanding and diagnosis of PD during the last decades enormously.

With the help of the so called DaTscan (I-ioflupane single-photon emission CT) or structural MRI, the changes in the brain structure can be visualized and these techniques can help to differentiate between Parkinson disease and other diseases with similar symptoms. Additionally post-processing image techniques and automated image analyses are more and more common in research and, in future, will improve diagnostics also on clinical level.

During the last few years there were as well identified several genes and genetical abnormalities which can influence the development of PD. An updated overview can be found on: https://www.mdsgene.org/

It is known that the neurodegeneration starts long before the first obvious motor signs. That's why a lot of studies try to find any predictive factors to enable an early diagnosis of PD. The most perspective factor seems to be the appearance of iRBD [27] which was described in chapter 2.1.

2.2.4 Subtypes of Parkinson`s Disease

Although the disease characteristics are very heterogeneous and it is hard to systemize, two sub-types of the disease are currently defined in literature [40]:

1. Body-first-type

   In this type the first symptoms include gut and cardiac dysfunction and later within the progression of the disease, brain dysfunction symptoms begin to occur. A change in the gut-microbiome is discussed as a cause of disease onset for this type.

2. Brain-first-type

   For this disease type the pathology starts in the nigrostriatal system of the brain. The major cause might here be genetic predispositions.

Another subtyping present in literature is the differentiation between two main motor-symptoms [43]:

1. Tremor-dominant-type
2. Postural-instability-gait-difficulty-type (PIGD)

The PIGD-subtype of PD seems to be characterized by a more severe negative effect on activities of daily live, more severe motor and non-motor symptoms and an overall worse prognosis with faster disease progression [44]

2.2.5 Treatment and Outlook

Parkinsons disease, at the moment, is not a disease the medical industry can cure. A treatment of the symptoms with drugs that increase the dopamine concentration or stimulate the dopamine receptors is the common way to help patients to increase their quality of life as long as possible [2]. Almost all PD patients receive the amino acid L-Dopa, which is a precursor to dopamine and can cross the brain-blood-barrier. When taken a long time, the exposure to L-Dopa can cause motor complications [31]. Due to a progression in loosing dopaminergic cells in substantia nigra during ongoing of PD, the positive reaction on L-Dopa decreases throughout disease duration.

As many non-motor symptoms do not respond to a dopamine replacement therapy, often, therapy is expanded by a cholinesterase inhibitor e.g. Clozapine.

A technical breakthrough was the development of the therapy called deep brain stimulation (DBS). Here for an electrode which can emit high frequency electrical stimulations is placed into the patient’s subthalamic nucleus or globus pallidus internus. It helps to reduce motor fluctuations and dyskinesia. Studies showed that the response to DBS is linked to the response of the motor symptoms to a treatment with L-Dopa [45].

Supplementary to pharmaceutical treatment, physiotherapy and speech and language therapy can be very helpful to maintain a higher quality of live for the patient [32]. Additional physiotherapy as well as guided physical activity as e.g. yoga or dance classes can be beneficial as well [40].

Due to the growing group of older people in population and a generally longer life span, the further research on PD can be seen as very important. It must be the highest interest to identify further risk factors, predictive factors, biomarkers and develop new treatments. Therefore, it is necessary to better understand the pathology of PD as it seems to be very complex and can vary case to case. New approaches can be gene therapy, fetal cell transplantation and stem cell therapy. With the newest findings of the oligomerization of α-synuclein and its transport out of cells and into other cells, new immunological approaches for therapy are reasonable [31].

2.3 Cognitive and motor testing

Cognitive and motor ability tests are a well-known method in diagnosis and classification of Parkinson disease and the overall mental state of the patient.

For PD diagnosis several standardized tests are available e.g. Montreal Cognitive Assessment (MoCa), Mini-Mental-State Examination (MMSE) and Unified Parkinson's disease Rating Scale (UPDRS) which are used by psychologists to identify the ongoing and worsening of PD.

A broad range of other standardized tests are available to determine the mental health and assess the cognitive impairment of patients. These tests cover all cognitive domains such as attention, different forms of memory, psychomotorspeed, mental speed, language and visuospatial functions.

For cognitive testing in general, it is necessary to perform them in an undisturbed environment and with just 2 persons – patient and psychologist – in the room. Other persons, especially relatives can disturb the patient's activities. Further the assessment should not be done in an acute or post-acute phase of disease onset as rapidly changes in patients' cognition within these periods can make the results obsolete quickly after.

Several test batteries to assess the cognitive performance of patients are available including standardized tests to evaluate possible impairment in different cognitive domains. Country-related adaptions of the tests, especially for tests including language processing or word memorizing, were developed to maintain the comparability throughout different languages. The following overview is limited to the tests which were used in the study from which the presented dissertation received its data.

The psychologic component of cognitive assessment tests should not be underestimated as the patient's awareness of a poor performance can lead to signs of depression or anxiety. These emotional states can further worsen cognitive abilities. A careful time management and preparing consultations are necessary to receive the necessary results without complicating the patients state. [46]

Typical motor tests assess gait, posture, balance and coordination parameters of PD patients. Standard tests include e.g. UPDRS III Part and Timed-Up-and-Go Test and (TUG) for gait and posture and Finger- Tapping-test for hand coordination [47]. The results of these tests can be enriched by standardized questionnaires about motor impairment in all day life as e.g. Freezing of gait questionnaire [48]. Newer settings can include 3D spatial analysis of gait and movement parameters and add modern artificial intelligence based data analysis [49, 50].

2.3.1 UPDRS

The Unified Parkinson's Disease Rating Scale developed by the Movement Disorder Society (MDS-UPDRS) is a standard test for severity and ongoing of PD and contains of 6 parts with several sub-categories:

- Part I: evaluation of mentation, behaviour and mood
- Part II: self-evaluation of the activities of daily life (ADL) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food
- Part III: clinician-scored monitored motor evaluation
  Talking, mimic, rigidity of neck and upper and lower limbs, finger tipping, movements of hands, movements of feet (tipping) and lower limbs, walking, getting up from a chair, freezing during walking, postural stability, posture, hypokinesia, trembling and amplitude of trembling.
- Part IV: complications of therapy
- Part V: Hoehn and Yahr staging of severity of Parkinson's disease
- Part VI: Schwab and England ADL scale

A revision of the protocol was done in 2008 [51] which is used now as one of the most important tools to PD management.

2.3.2 Timed-Up-and-Go (TUG) -Test

For the test the subject is instructed to get up from a chair, walk a specified distance at freely selectable pace, turn around 180° at a specific turning point, walk back and sit down again (see Fig. 2.6). Parameters as cadence, stride length and speed are measured with the help of a motion sensitive walkway.

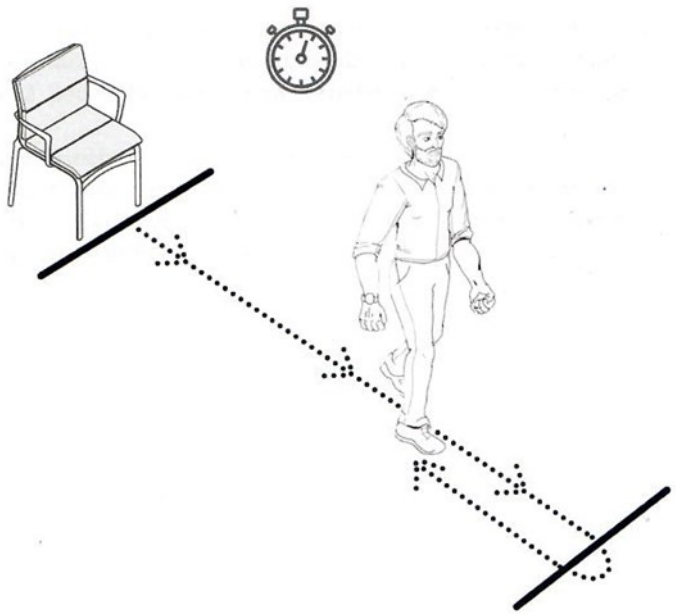


Figure 2.6: Scheme of TUG test

Several parameters influencing the results, need to be considered. Depending on the motor abilities of the patients, it can be necessary that the chair has to have armrests to help the patient get up and sit safely down again. Another critical value can be individual cognitive impairments which can make it difficult for the patients to understand the instructions. A relaxing and calm test environment can help the patients focus on the task. Individual adaptations to the settings, taking into account specific abilities of the tested patient group, can be necessary.

2.3.3 Cognitive tests for the domain Episodic memory

Ray-Auditory-Verbal-Learning-Test (RAVLT)

This test assesses verbal learning and memory of the patient and can be performed from approximately age 6 on. The test consists of several steps which in total give information about the memory span, the ability to learn new things, the susceptibility to interference and the recognition memory of the patient. The basic part of RAVLT is a list of 15 nouns (list A). This list is read out lout with a pause of one second after every word. Immediately after finishing the reading, the patient is asked to repeat all nouns from the list which he remembers. This exact cycle is repeated five times with the task explanation (repeating all remembered nouns) after every cycle, so the patient does not forget the task. The number of correctly remembered words of all five cycles summed up gives the value “RAVLT (Total Recall 1-5)”. After completing Trial 1-

5 an interference list of 15 different nouns is read to the patient (list B) which he must immediately recall. This is followed by the task to again repeat all nouns from list A. The number of correctly remembered words refers to the result “RAVLT (Trial 6)”. As a last task either a story (written or orally) or a matrix of 50 nouns which includes all the words from list A and B and additionally phonetically or semantically similar word is presented to the patient. He needs to identify the words from list A. The number of correct recognized nouns is listed as result “RAVLT (Recognition)”. [46]

It takes approximately 10-15 minutes to complete the whole test. It is commonly known that memory worsens with age. The influence of gender and intelligence on the ability to memorize words is inconsistently described in literature [52, 53]. The absolute results need to be corrected for these influencing variables before using them for any conclusion.

Memory-for-Intentions-Screening-Test (MIST)

The Memory-for-Intensions-Screening test assesses the prospective memory of the patient. This means how well the patient is able to form, maintain and execute future intensions. The patient is given some instructions of what he needs to do in future. Then he is distracted and needs to initiate and execute the task at the correct time. There are time-based tasks e.g. “Tell me in 15 minutes it is time for a break” and event-based tasks e.g. “When I show you a red pen, sign your name on your paper”. The time span between giving the task and the event initiating the task are either 2 or 15 minutes. [54]

Memory-Binding-Test (MBT)

The Memory Binding Test was developed to detect impairments in verbal memory. The MBT consists of 16 pairs of words divided according to superior categories which are again divided into two lists of 16 words each. Each word list is presented with 4 cards with 4 words for each of the lists. The cards are stepwise presented to the patient and with the help of categorical cues (e.g. the categorical cue is a “male name”, and the word Paul is on the card) the patient has to identify the correct word. Categorical cues are spoken sequentially by the examiner and the patient answers with a word from the card. After the administration of the first list, the patient recalls the words categorially. The same procedure is followed to learn the second set of words. The examiner again presents 4 cards with 4 words each, offers the patient superior words, and the patient verbally indicates the words from the card. After learning, again using superordinate words, the patient recalls the second set of words.

After completing this part, the examiner asks the patient to recall the learned words from the first and second sets with the help of superordinate words, creating a pair of words. The patient is then instructed to freely recall the words regardless of their order and position in the list, and the total number of words recalled is counted. After a delay, the examiner again assigns the task of recalling the words regardless of the order, he assigns the arrangement of both lists

with superordinate words. During the test, the number of correct words and any confabulations are monitored. Including the situation when the patient names words from list one while recalling the second list. Thus, the test verifies the memory binding ability of categorical and directly test words. The administration of the first part of the takes about 20 minutes, the second part is usually faster. [55]

The evaluation of the test is done with six values assessing the different variants of recalling:

MBT (Paired recall pairs)

MBT (Total cued recall)

MBT (Total free recall)

MBT (Delayed paired recall pairs)

MBT (Total delayed paired recall)

MBT (Total delayed free recall)

2.3.4 Cognitive tests for the domain Attention/working memory

Letter-Number-Sequencing from Wechsler Adult Intelligence Scale (LNS)

The Letter-Number-Sequencing test is a subtest of the Wechsler Memory Scale III test battery which in total consists of 11 subtests. The LNS is exclusively verbally presented and assesses the working memory of the patients. The therapist reads a list of numbers and letters aloud and the patient is asked to recite these numbers ascending and the letters alphabetically. [46]

The test results are weight by education level and ethnicity via standardized tables. Age doesn't influence the results within a accepted age span for the test (16-89 years). [46]

Trail-Making-Test (version TMT-A)

The Trail-Making-Test assesses attention, mental flexibility, speed of execution and to some parts also motor abilities of the patient.

The patient has to connect randomly located circled numbers from 1-25 on a paper by pencil lines (TMT-A). A time limit of e.g. five minutes can be applied to reduce frustration for severely impaired patients. The time it took the patient to complete the task is the result of the test. [46]

The performance is dependent on age, whereby it is the speed to finish the task which differs more than the accuracy [56]. Education and IQ do as well have an influence on test results of TMT [56] while gender has little to no impact [57].

The motor abilities of the patient, especially in settings in which patients with expected motor impairments are tested, plays a role for test results as well. Even if the cognitive abilities allow the patient to find the correct following number, he needs to be able to stable grab the pencil and draw a stable line between the two numbers.

2.3.5 Cognitive tests for the domain Executive functions

Prague Stroop Test (PST)

The Prague Stroop Test is the for Czech Republic adapted version of the general Stroop Test, modelled after the Victoria Stroop Test version [58]. It assesses the cognitive control, which means how well a person is able to supress a first intention answer and instead answers with a less familiar one [59].

Basically, the test includes four parts beginning with the task to read out loud names of colours printed in black ink. This is followed by a part in which the patient is given a card with colour names printed in different colours, while the colour of the ink does not match the verbal context of the word. Again, the words (colour names) need to be read out loud, independently from the ink (PST words). As third test the subject has to name the colour of different dots (PST dots). During the last part, the patient is given the card from part two, with the task to tell the colour of the word (ink), no matter what the words (colour names) say (PST colours). The difference in time between part 3 and 4 is called PST interference and gives information about the ability to supress the intentional answer and instead produce an answer which needs more cognitive processing. [46]

The test scheme is shown in Figure 2.7.

The whole test duration is approximately five minutes. Especially for the results in the category interference the age needs to be considered as important influence factor [60], while gender and education showed just minor or inconsistent effects on all PST results [61, 60]. Language abilities of the patient play an important role for test results so it is important to use an adapted version for the native language of the patient if possible.

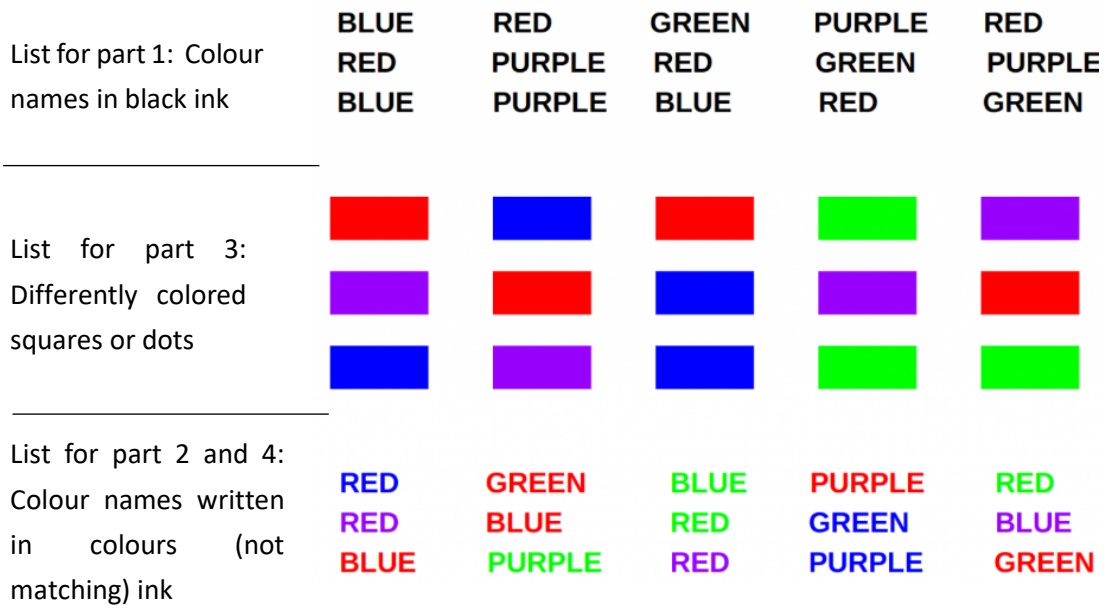


Figure 2.7: The three different lists of Stroop Test (adapted from [59])

PST (colours) and PST (interference) are used to test executive functions, PST (dots) and PST (words) assess processing speed (see chapter 2.3.7).

Trail-Making-Test (version TMT-B)

For detailed and general information about TMT, please see chapter 2.3.4.

For the test version TMT-B the participant has to connect 25 randomly placed circles alternating numbers and letters (1-A-2-B-3-C and so on). This version of the test focuses more on the executive functions of the patient.

Verbal fluency test (VF)

For the detailed description of general Verbal Fluency test see chapter 2.3.8.

During the VF (animal/clothes) test the patient is requested to name nouns out of switching categories – here animal and clothes. This task addresses next to the semantic fluency also executive abilities of the tested subject. [46]

2.3.6 Cognitive tests for the domain Visuospatial functions

Clock-Drawing-Test (CDT)

The clock-drawing tests assesses visual-spacial, constructional and executive abilities of a patient. The assignment includes the drawing of a clock face with the correct location of the numbers and afterwards entering the correct placement of the hour and minute hand for a given time. Besides and empty paper and a pencil, no preparation is necessary. [46]

Age, IQ and education influence the test performance [62, 63] while the influence of gender is less significant [63].

Montreal-Cognitive-Assessment-Test (MoCa) – Subtest cube

The MoCa test (Fig. 2.8) is the golden standard to detect Mild Cognitive Impairment (MCI) in neurodegenerative diseases like Alzheimer`s or Parkinson. It is a simple 10-minutes tests assessing several cognitive domains including e.g visuospatial skills, memory and executive functions. The test is freely available under (www.mocatest.org). [64]

The full MoCa test includes 13 subtasks and is available in 154 languages respectively language versions.

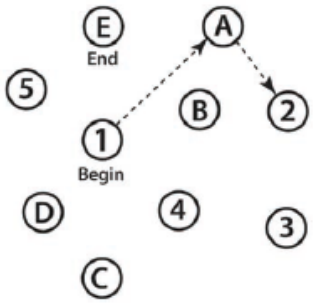
The task of cube drawing includes copying a two-dimensional pattern to a three-dimensional cube. This task detects impairments in visual perception, planning and executive visual and fine motor skills. [64] This subtest is especially potent in detecting MCI in iRBD patients, as visual spatial impairment is one of the earliest symptoms of neurodegeneration in these patients [65].

MoCA
COGNITIVE ASSESSMENT

Version 8.1 English

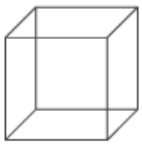
Name:
Education:
Date of birth:
Sex:
DATE:

VISUOSPATIAL / EXECUTIVE — POINTS



[ ]

Copy cube



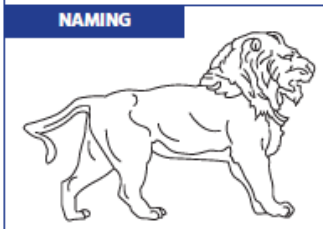
[ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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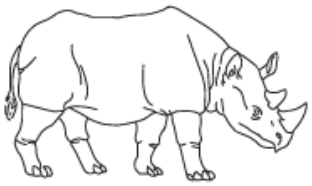

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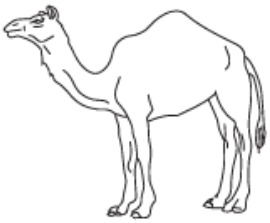


[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1ST TRIAL					
2ND TRIAL					

NO POINTS

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order. [ ] 2 1 8 5 4
Subject has to repeat them in the backward order. [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0**

__/3

LANGUAGE Repeat: I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency: Name maximum number of words in one minute that begin with the letter F. [ ] _____ (N≥11 words)

__/1

ABSTRACTION Similarity between e.g. orange - banana = fruit [ ] train - bicycle [ ] watch - ruler

__/2

DELAYED RECALL — Memory Index Score (MIS)

(MIS)	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
X3							
X2	Category cue						MIS = ____ /15
X1	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Training and Certification are required to ensure accuracy.

MIS: /15
(Normal ≥ 26/30)
Add 1 point if ≤ 12 yr edu

TOTAL __/30

Figure 2.8: The full MoCa Test, English version

2.3.7 Cognitive tests for the domain speed of processing/psychomotor speed

Grooved-Pegboard-Test (GPT)

The Grooved Pegboard Test measures hand-eye coordination and motor speed.

The test is done with a special designed board with 25 slots. The pins can be inserted into the slots just after turning them into the correct position, due to a ridge along one side. The test is done first with the dominant hand, then with the non-dominant hand, giving two results GPT (right hand) and GPT (left hand). The time the patient needs to complete the task is measured and registered as result. It takes approximately 5 minutes to complete the test. [46]

Gender seems to affect the results, probably due to a smaller finger size in women, while handedness does have no influence [66]. Literature shows different results for dependency of GPT on education [66, 53].

Symbol-Digit-Modalities-Test (SDMT)

The SDMT evaluates the patients' abilities in motor speed, divided attention, tracking and visual scanning [46]. The basic principle of the test is to present a patient a coding key consisting of nine abstract symbols which are paired to a number. The patient is asked to train the decoding of the key by writing the correct numbers below the symbols. Afterwards he is given a test document with just the symbols and a blank space below them (Fig. 2.9). The patient needs to correctly fill in the blanks with the correct numbers. [67]

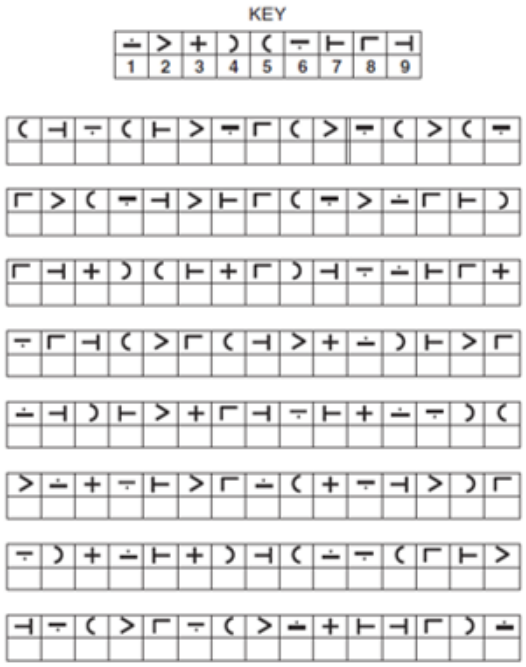


Figure 2.9: Example of SDMT, showing the key between symbols and numbers on top and the task lines with just the symbols below. (adapted from [46])

The number of correctly filled in pairs within a 90 second time frame is taken as the result if the test. It takes approximately five minutes to complete the test. [46]

There seems to be a slight gender difference with women outperforming men in SDMT [68] but IQ and education do have a by far higher influence on the results [69].

Prague Stroop Test (PST)

For the test description see chapter 2.3.5. The subtests PST (dots) and PST (words) assess the processing speed of the patient.

2.3.8 Cognitive tests for the domain Language Assessment

Verbal fluency test (VF)

The Verbal Fluency test assesses the ability of the patient to verbally produce words under a certain restriction. The patient is given a certain amount of time, most often one minute, in which he has to say as many words as possible which fall into the predefined category. Phonemic fluency can be tested by predefining the first letter of the words (in the here used test battery letter “K”). Semantic fluency is assessed by giving a certain parent word group out of which the produced words should be e.g. vegetables or action verbs. As a third possibility the patient can be asked to think of words out of two alternating parent word groups e.g. animal/clothes. The amount of correctly produced words within the given time limit is taken as the test result. [46]

As the whole test is about language processing, it is important to consider specific characteristics of the patient’s native language for example when choosing a definite starting letter for the words.

There is no special preparation necessary. The whole test takes about five minutes. Age and gender have only a slight influence on the results [70] while education level was shown to effect the results dramatically [71, 72].

The subtests VF (K), VF (action verb), VF (vegetables) assess the language abilities while the subtest VF (animal/clothes) addresses more the executive functions of the patient’s cognition and is used in this category (see chapter 2.3.5).

2.4 Impairments in cognitive performance of iRBD and PD patients

Cognitive changes are next to motor symptoms an important sign of Parkinson disease and prodromal stages of it. According to recent research, detectable cognitive impairment occurs already 7-9 years before diagnosis of PD [73]. In a Meta-analysis of Leitner et. al [74], analysing 86 single studies with iRBD patients, it was clearly shown that already patients with this sleep disorder do have a significantly reduced cognitive performance compared to healthy controls.

The most often impaired cognitive domains in PD and iRBD are memory, visual-spatial functions, attention and executive abilities [75, 76].

The presence of RBD in PD has a clear negative influence on cognitive performance. In a comprehensive study with 162 participants it was shown that MCI rate in PD patients with RBD was almost 3 times higher than in PD patients without RBD [77]. In this study, patients with RBD onset before PD diagnosis showed worse results in cognitive tests than patients with RBD onset with or after PD diagnosis. This implicates that RBD duration is important for worsening of cognitive decline.

Figorilli et. al. [78] found a correlation between the severity of cognitive impairment and RSWA parameters in iRBD patients which supports the assumption above.

An overview of impaired cognitive tests in iRBD and PD is visible in Table 2.3.

Table 2.3: Overview of impaired cognitive test results of iRBD and PD patients

Patients	**Cognitive test results**	**Literature**
iRBD vs. HC	MMSE ↓; category fluency test ↓; frontal assessment battery ↓; RAVLT ↓; TMT-B ↓; MoCa ↓	[79–82]
PD-iRBD vs. PD-nRBD	Verbal fluency ↓; word reading ↓; DST ↓; DSpT ↓; TMT-A and TMT-B ↓; Stroop colour ↓; visuo-spatial abilities ↓	[82, 83, 77]
PDnRBD vs HC	Verbal memory ↓; visuo-spatial abilities (cube test) ↓; executive functions (Stroop Colour-Word, TMT-A/B) ↓; attention abilities;	[84, 76, 85]

iRBD – idiopathic REM-Sleep-Behavior-Disorder; HC-Healthy controls; MMSE – Minimal-Mental-State-Examination; RAVLT – Rey-Auditory-Verbal-Learning-Test; TMT-A/B – Trail-Making-Test-Version A/B; MoCa – Montreal-Cognitive-Assessment-Test; DST – Digit Symbol Test; DSpT – Digit Span Test

2.5 Correlation between changes in brain morphology and cognitive performance in iRBD patients

To fully understand the development and worsening of cognitive abilities in iRBD and possible conversion to PD, it is necessary to find the underlaying morphological brain changes. In Table 2.4 an overview about the current knowledge of these correlations is listed.

Table 2.4: Overview of correlations between cognitive tests and brain morphology in iRBD patients

Study	Patients	Cognitive domain	Correlating morphological changes
[86]	iRBD vs. HC	Attention and executive functions	Cortical thinning in • Frontal (medial superior, dorsolateral paracentral, sensorimotor) cortex • Temporal (fusiform, lingual) cortex • Occipital (cuneus) cortex
		Learning and memory	Cortical thinning in • Temporal (pole, anterior superior, posterior lingual, fusiform) cortex • Insular cortex • Occipital (cuneus) cortex Surface expansion • Right hippocampus
		Visuo-spatial abilities	Cortical thinning • Frontal (medial superior, paracentral, prefrontal) cortex • Temporal (middle, posterior lingual, fusiform) cortex • Occipital (cuneus, lateral) cortex Reduced cortical volume • Right lateral occipital cortex Surface expansion • Right hippocampus
[87]	iRBD vs. HC	memory	Cortical thinning • Left superior temporal gyrus • Left caudal middle frontal gyrus • Right superior frontal gyrus • Right lateral occipital gyrus
		Visuo-spatial abilities	Cortical thinning • Left fusiform gyrus • Right supramarginal gyrus
[88]	iRBD vs. HC	Attention/executive	Contraction in • Midbrain • Insula • Partly internal capsula, putamen, pallidum, thalamus, orbitofrontal cortex right temporal lobe
		Visuo-spatial abilities	Contraction in • Left superior culliculus

2.6 Image Processing and data analysis

2.6.1 Voxel Based Morphometry (VBM)

With the help of Voxel Based Morphometry it is possible to compare the relative amount of gray matter (GM), often referred as gray matter density, in a region, between subjects or correlate this amount to different parameters like test results or disease stages. This method is used to statistically analyse differences out of a group of subjects and is not meant for single subject analysis. Several clearly defined preprocessing steps including segmentation, spatially normalization and smoothing are necessary to perform VBM. For accurate segmentation VBM requires medical images which show clear differentiation between different tissue types, which is true for T1-weighted MRI. The MR images are segmented into the different tissue types: gray matter, white matter (WM) and cerebrospinal fluid (CSF). The gray matter segments of all subjects in the study are then normalized (warped) into the same stereotaxic space which is represented by a template image. In the following step the warped gray matter images are smoothed by convolving with a Gaussian Kernel (Fig. 2.10). So, every voxel contains the information of the average amount of gray matter from surrounding voxels. The smoothing step is necessary to remove fine scale structures, which differ from subject to subject so that the analysis detects mainly differences in larger spatial scale. [89]

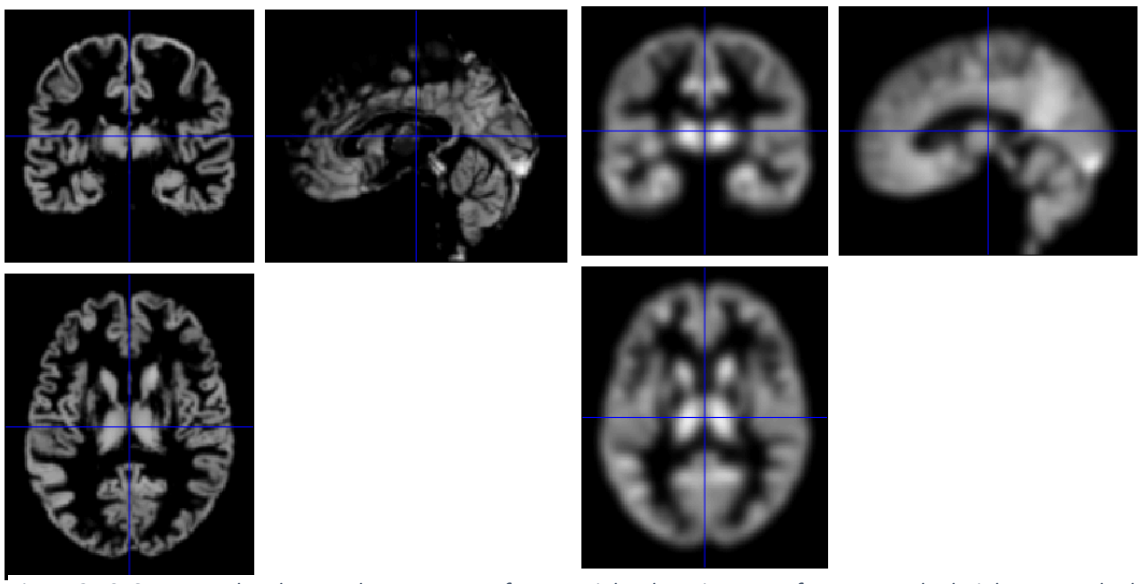


Figure 2.10: Segmented and warped gray matter of a T1-weighted MR image. Left – unsmoothed, right – smoothed with Gaussian kernel

Because of these preprocessing steps VBM is not suitable for classical volume analysis but refers to local gray matter differences in special scale. After finishing of all preprocessing steps, voxel-wise statistical tests, based on standard linear models, are applied. Standard statistical test models like t-test or F-test can be used to test the research hypotheses.

2.6.2 Deformation Based Morphometry (DBM)

Other than VBM the Deformation Based Morphometry detects differences in the shape of the brain regions. A deformation can include a volume change or a position change or both components. Combining this information, the DBM can give a higher sensitivity to detect morphological changes in brains.

Technically it is done by mapping the subject's brain to a standard template brain by three-dimensional nonlinear normalization routines (Fig. 2.11). During this step the brains are adjusted for orientation and transformed to the anatomical space of a template brain. The transformation creates three-dimensional deformation fields for every voxel to match the template. This can be described as the local deformation of the subject's brain needed to match the template brain. The derivates of the deformation fields – called Jacobian determinant- are used for statistical analysis. [90]

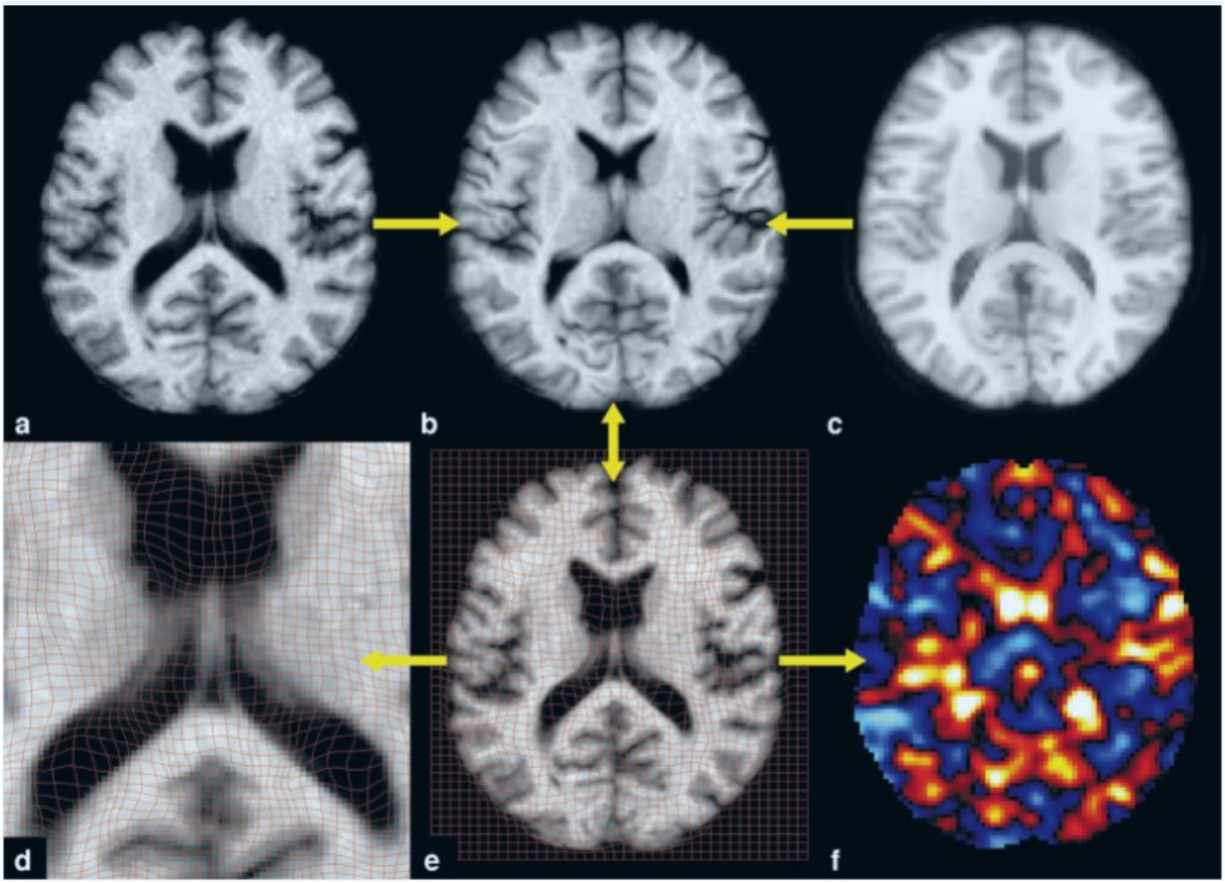


Figure 2.11: Steps of analysis in deformation-based morphometry. An example is shown for a single subject in one axial slice. Adapted from [90]

a) Single object brain

b) Single object brain size and orientation corrected to template brain by applying non-linear normalization

c) Template brain

d) Magnification of ventricular part with the applied deformations visible by deformed grid

e) Overall applied deformations in whole brain, visible by deformed grid lines

f) Coloured deformation visualization by using the local Jacobian determinant as derivative of the field

2.6.3 Surface Based Morphometry (SBM)

The Surface Based Morphometry allows the analysis of several more parameters describing the cortical surface as e.g. cortical thickness, gyrification index, sulcus depth and fractal dimension. The necessary pre-processing can be done parallel to the pre-processing for VBM. This technique allows to analyse morphological changes in brains others than volume and deformation changes and so with complements the possibilities for brain morphometry.

Cortical thickness

The cortical thickness can be described as the distance between the inner cortical surface (labeling the boundary between WM and GM) and the outer cortical surface (labeling the boundary between GM and CSF) as illustrativelz shown in Figure 2.12. As an important biomarker in neurodegenerative diseases as PD, it is an interesting target value for research [91] .

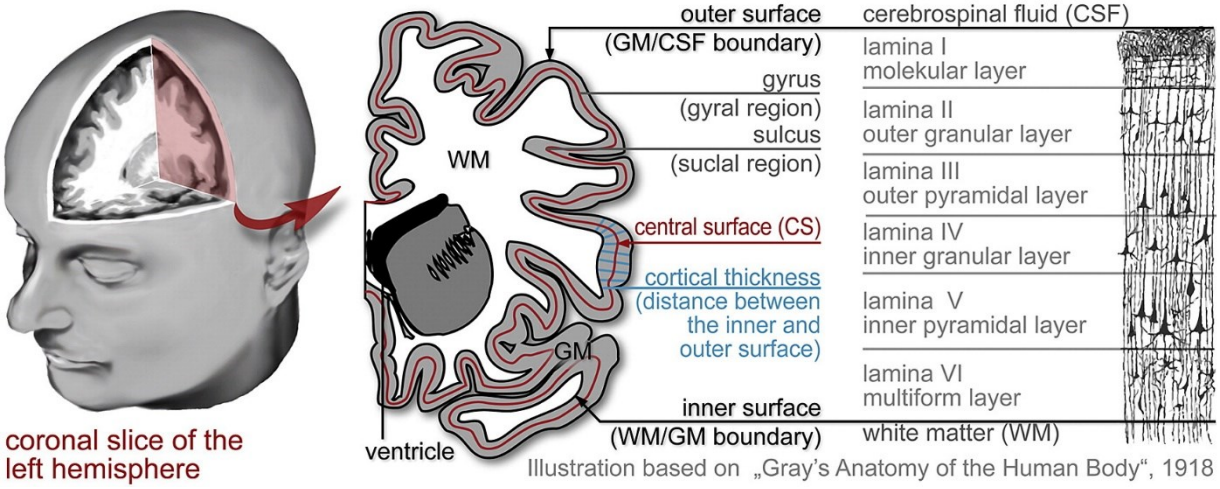


Figure 2.12: Illustration of the cortical macro- and microstructure. The cerebral cortex is a highly folded sheet of gray matter (GM) that lies inside the cerebrospinal fluid (CSF) and surrounds a core of white matter (WM). [92]

The calculation of the cortical thickness is done by a volume-based algorithm called Projection Based Thickness. As a basis the brain structures need to be segmented into GM, WM and CSF which makes this method dependent on the segmentation quality. In a following step the distance of each GM cortical voxel from the inner boundary is calculated. This results in a white matter distance map. The values at the outer GM boundary of this map represent the GM thickness. A back-projection of this outer boundary to the inner boundary results in a GM thickness map. At a 50% level of the relation between WM distance map and GM thickness map the central surface is created. This artificial surface technically is better for further analysis as it contains less topological defects and loses less anatomical detail when smoothed. The smoothing is necessary to remove artefacts and noise. The projection-based algorithm showed better results than e.g. the Laplacian approach when directly compared. [92]

Gyrification index

The local gyrification is calculated on basis of curvature values (Fig. 2.13). These give information about direction changes along the surface. Negative values correspond to sulci and positive to gyri. An averaging of curvature values within a distance of 3mm and transferring the result to an absolute value, reduces the signal to noise ratio. As a final step these absolute mean curvature values are smoothed with a 25mm FWHM kernel. The final gyrification map shows higher values for regions with higher gyrification. The gyrification index reflects this folding geometry with lower values for pointing on sulcus widening. [93]

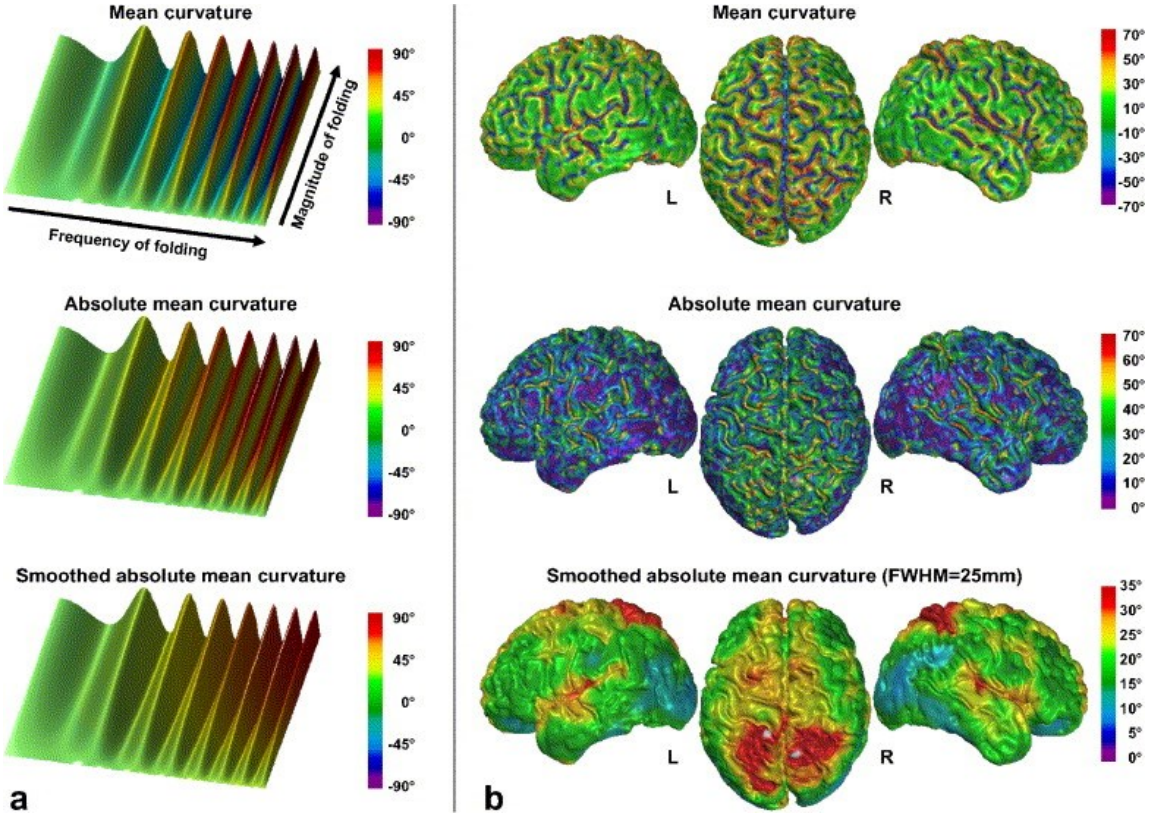


Figure 2.13: Estimation of local gyrification. The left column demonstrates the computation of local gyrification using a simulated folded surface, where the magnitude of the folding increases from proximal to distal and the wavelength from left to right. The calculation of the mean curvature results in large positive values for local maxima (corresponding to gyri) and large negative values for local minima (corresponding to sulci), where curvature values are expressed in degrees. By calculating the absolute mean curvature, all values are converted into positive values. Finally, curvature values are smoothed using a surface-based heat kernel filter with FWHM = 25 mm. The right column illustrates the process of estimating local gyrification on a single subject brain selected from the sample analyzed in this study. In the first step, the mean curvature is calculated using the 3D mesh of the cortical surface. After calculating the absolute mean curvature, all values are transformed into positive values. Final surface smoothing with a heat kernel (FWHM = 25 mm) reveals higher values for areas with pronounced gyrification. (adapted from [92])

Sulcal depth

The square root-transformed sulcal depth is extracted based on the Euclidean distance between the central surface and its convex hull and then transformed using the square root function (Fig. 2.14).

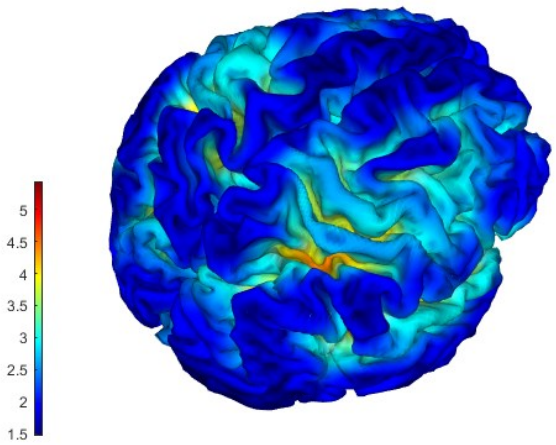


Figure 2.14: Example of sulcus depth map of a whole brain of a subject. Higher values (orange/red) indicate deeper locations.

Fractal dimension (FD)

The fractal dimension is a quantification of the complexity of cortical folding (Fig. 2.15). The approach was described by Yotter et. al. [94]. The complexity value of a locus on brain surface can be seen as a characteristic value for this surface in this localization. Regions with higher FD values show more regularity in their present structures than regions with a lower FD value.

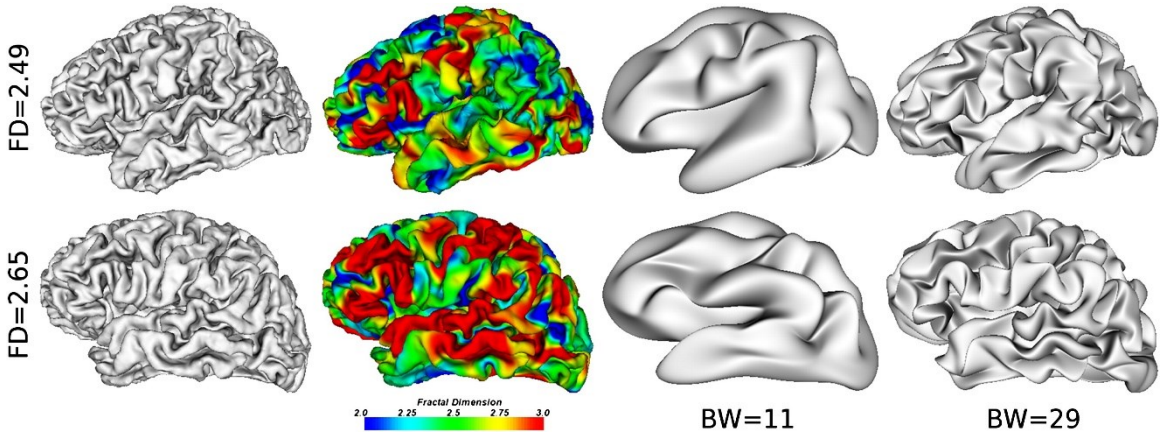


Figure 2.15: Example of Fractal Dimension calculation of two different brain surfaces and two low-pass filtered reconstructions [94]

3. Aim of the thesis

The main goal of the thesis was to describe correlations between brain morphology of PD and iRBD patients and their performance in different cognitive tests. To reach this target the following three subtasks were defined:

Goal 1: **Definition of an applicable processing pipeline for MR images**

- Define a pre-processing pipeline for a series of neuromelanin sensitive MR mid brain images and total brain images for following automatic detection of the amount of neuromelanin in substantia nigra.
- Define a pre-processing pipeline for Voxel-based-, Deformation-based- and Surface-based morphometry analysis of MR whole brain images.

Goal 2: **Correlation of brain morphology with cognitive test performance in PD and iRBD patients**

- Analyse between group differences of brain morphology between Healthy Controls and Patients
- Perform Voxel-based, Deformation-based and Surface-based correlation analysis for the different patient groups with all cognitive tests.

Medical Hypothesis: The morphology of specific brain regions, involved in solving the certain cognitive test tasks, correlates with the performance of the patients in these tests. These correlations will be similar for iRBD patients and PD patients indicating the progress of neurodegeneration from prodromal to manifested disease stage.

Goal 3: **The influence of impaired Dual Task (DT) on the correlation of brain morphology and Dual task cost parameters in PD**

- Analyse between group differences between different gait parameters and between dual-task-costs of these parameters
- Perform Voxel-based, Deformation-based and Surface-based correlation analysis for the different PD patient groups with all dual-task-cost results.

Medical Hypothesis: PD patients with cognitive deficit compensate the additional cognitive-motor dual-task load different than cognitively non-impaired PD patients. Therefor different brain regions should correlate with DT gait performance in these groups.

4. Methods

The work combines a broad field of different methods of the fields psychological and gait assessment, picture processing techniques and statistics to investigate possible correlations between brain morphology and cognitive and motor abilities of the patients. In this chapter the theoretical description of the general methods of chapter 2 is expanded by detailed information about specific characteristics of the procedures used during the study.

4.1 Cognitive and Motor tests

To assess the cognitive abilities of the patients they were evaluated by a complex neuropsychological battery covering six cognitive domains, including 28 different test results (Tab. 4.1):

Table 4.1: Overview about cognitive domains and included tests

Cognitive domain	**Gained test results**
attention/working memory	• LNS • TMT-A
executive functions	• PST (colors) • PST (interference) • TMT-B • VF (animals/clothes)
language	• VF (K) • VF (action verb) • VF (vegetables)
episodic memory	• RAVLT (Total recall 1-5) • RAVLT (Trial 6) • RAVLT (delayed recall) • RAVLT (recognition) • MIST (event-based) • MIST (time-based) • MBT (Total Cued Recall) • MBT (Paired Recall Pairs) • MBT (Total Delayed Paired Recall) • MBT (Delayed Paired Recall Pairs) • MBT (Total Free Recall) • MBT (Total Delayed Free Recall)
visuospatial functions	• CDT • MoCA (cube)

speed of processing/psychomotor speed	• GPT (left hand) • GPT (right hand) • SDMT • PST (Dots) • PST (words)

The tests were completed as by standard protocols (for basic information see chapter 2.3), if necessary with the Czech language adaption [58, 95].

The total MoCa score and MDS-UPDRS-III value was determined using the standard protocols [51, 96].

For HC and iRBD patients the complete test battery results were available. For PD patients just the UPDRS III, MoCa, TMT-A, TMT-B and GPT results could be processed.

For gait data acquisition, all subjects completed an extended Timed Up & Go Test:

1. Get up from a chair
2. Walk 10 meters at the preferred walking speed
3. Turn
4. Walk back
5. Sit down again

TUG was performed twice. For data measurements, a 5.15 m long and 0.9 m wide pressure walkway (Platinum model GAITRite®, CIR System Inc.) was placed 2.43 m from the chair in the middle of the straight gait walkway.

Participants gait was measured under two different settings:

(i) in single task (ST) condition at a normal pace

(ii) in dual task (DT) condition at a normal pace, counting down from 100 in steps of seven

The gait parameters velocity, stride length and cadence where measured.

4.2 Processing of the results of cognitive and motor data

The raw scores of cognitive test results were transformed into z-values based on multiple regression analysis of the results of HC group. The data was corrected for age, gender and education (years in school). Thus, these z-values represent the relative deficit of each participant with respect to age, sex and education-matched healthy controls. The calculation of z-values was performed in R (version 4.2.2)

To reduce the number of single variables and improve the interpretability of the results, a principal component analysis (PCA) with varimax rotation was performed on the raw scores of the total sample. The first six PCA components represent the cognitive domains associative memory, mental speed/executive functions, episodic memory, psychomotor speed, language and visuospatial functions. The factor loadings for PCA can be found in Appendix A.1.

To calculate the influence of the dual task to the gait parameters the Dual-Task-Cost (DTC) was calculated the following for velocity, stride length and cadence (equation E4.1):

$$DTC = \frac{DTvalue - STvalue}{STvalue} \tag{E4.1}$$

4.3 Image pre-processing

The preprocessing and segmentation of T1 weighted images were performed with the Computational Anatomy Toolbox (CAT12) software, version 12.7 (https://neuro-jena.github.io/cat/) implemented in statistical parametric mapping software (SPM, version 6906 – for goal 1+2 and version 7771 – for goal 3; https://www.fil.ion.ucl.ac.uk/spm/) in Matlab (version R2018b; https://www.mathworks.com/). The operation menu of both programs can be seen in Figure 4.1.

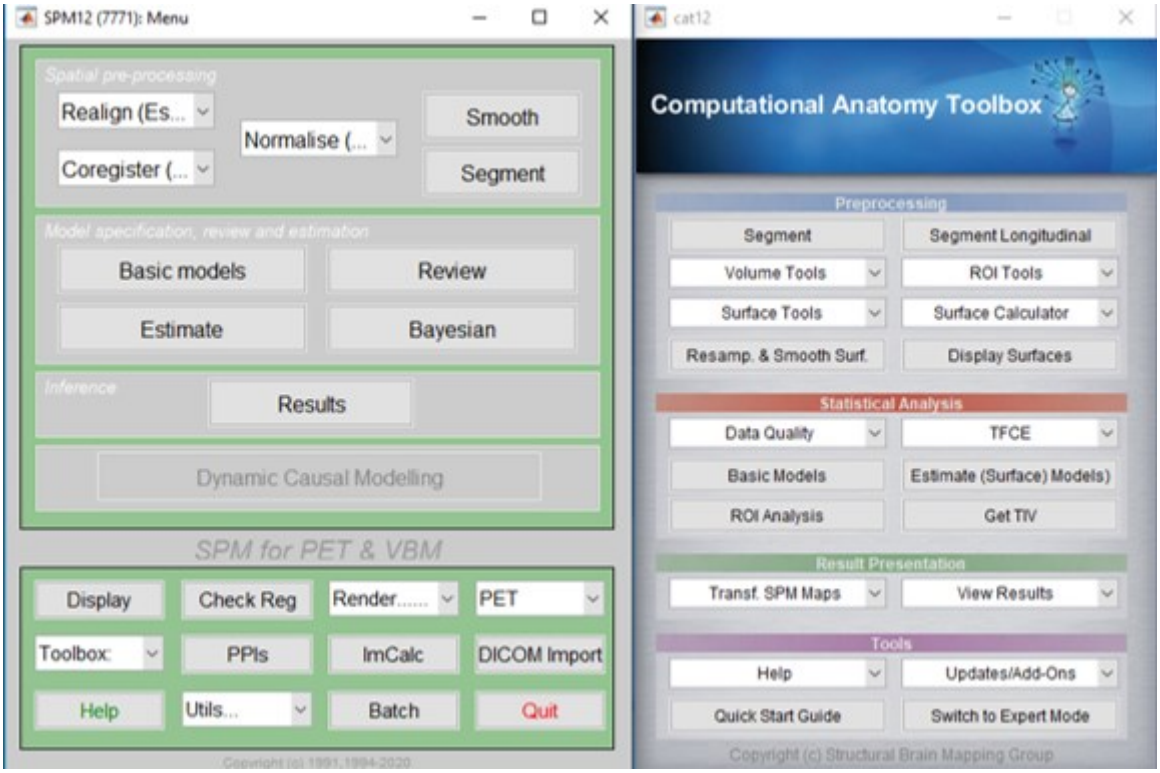


Figure 4.1: SPM12 and CAT12 operation menu windows

The segmentation was done by Hammers atlas [97] as this atlas provides the most suitable division of brain regions for our purpose. A visual quality check was done by reviewing one slice of every brain to find obvious artefacts in the scans and incorrectly oriented images. Data homogeneity was checked by the CAT data quality batch. The quality of segmentation was checked for every T1-weighted image and a minimum of C+ in quality parameters “Resolution”, “Noise”, “Bias” was accepted.

Pre-processing was done with default options in CAT12 and SPM excluding the parameters:

Affine Preprocessing, which was set on “full” and *Power of SPM Inhomogeneity Correction* which was set on “strong” to improve the segmentation quality outcome.

With the help of the batch editor, MR images of all subjects where segmented in one continuous process. During this, brain data were segmented into gray matter, white matter, cerebrospinal fluid and 34 brain regions included in Hammers atlas for each region divided into right and left hemisphere. The absolute size of each of these values was automatically stored in *.mat files for later statistical analysis. A segmentation report was created for every subject which allowed to check for segmentation quality (Fig. 4.2).

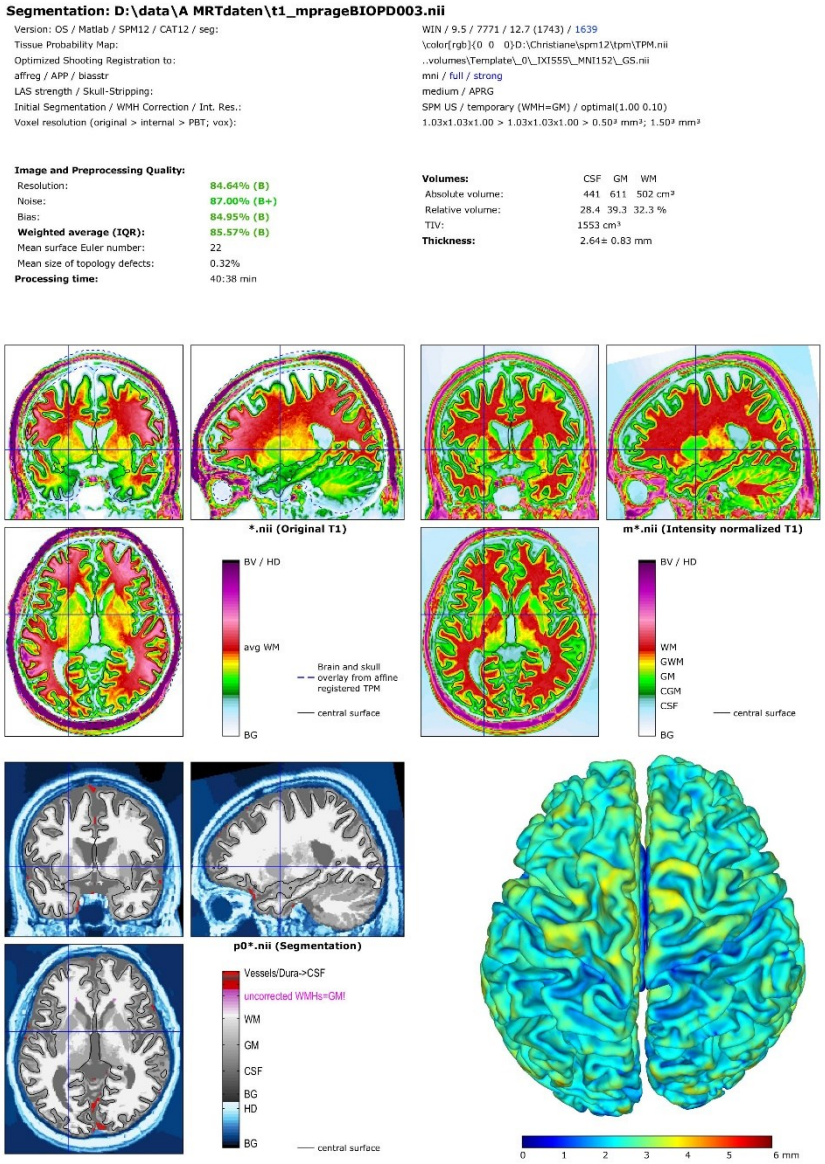


Figure 4.2: Example of the segmentation report of subject BIOPD003

In segmentation protocol the writing options for *Jacobian Determinant* and *Surface and Thickness estimation* were set to "Yes", to not only generate data for VBM but also data needed for DBM and SBM.

Afterwards (next to cortical thickness) the additional surface parameters gyrification index, sulcus depth and complexity (fractal dimension) were extracted using CAT12 – Surface Tools – Extract additional surface parameters.

The smoothing parameters were as following:

VBM - normalized grey matter segments, Gaussian kernel with an 8mm full width at half maximum (FWHM)

DBM - Jacobian determinants, Gaussian kernel with an 8mm FWHM

SBM – meshed central cortical surface data, Gaussian kernel with a 15mm FWHM (Thickness, Sulcus Depth) and 20mm FWHM (gyrification, complexity)

4.4 Voxel Based Morphometry, Deformation Based Morphometry and Surface Based Morphometry

All morphometry analysis were done in CAT12 and SPM12.

To compare brain morphology of two subject groups, the 2-sample-T-test was used. To check for correlations of brain morphology with cognitive performance, the 1-sample-T-test was used.

For VBM Total Intracranial Volume (TIV), age and sex were used as covariates in 2-sample T-test and additionally to this, the z-value of the cognitive test for 1-sample-T-test. In case that PD patients brain morphology was tested for correlations to cognitive performance, results were corrected for UPDRS III results.

Threshold masking was set on "absolute" with a value of 0.1. All other parameters were left on default values.

Except TIV, the same covariates were used also for DBM and SBM.

A batch process (Fig. 4.3) was created, which involved continuous processing of the steps:

- Building of the Basic statistical model
- Estimating the statistical model
- Contrast Manager
- Creating a results report

whilst always taking the output of the previous process as input for the following process. The input for the creation of the basic model were the smoothed data created in preprocessing, depending on analysis type (VBM, DBM, SBM).

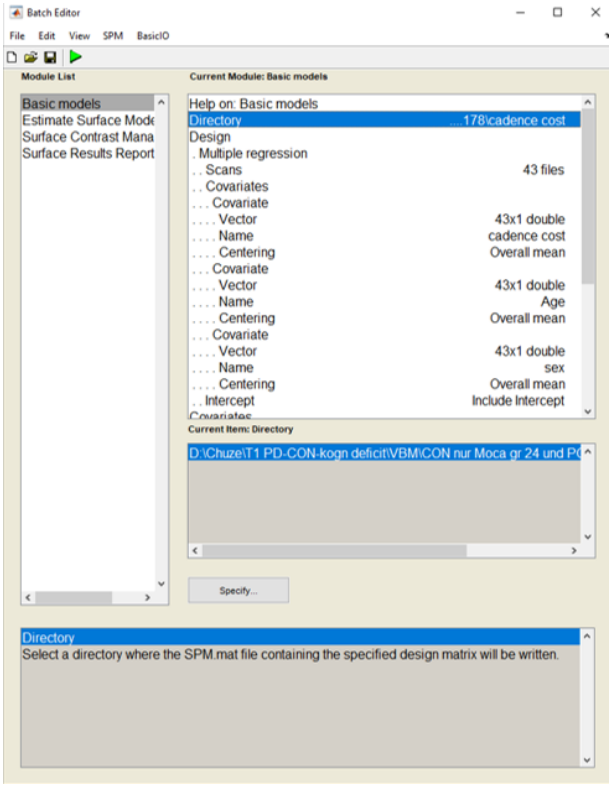


Figure 4.3: Example of a prepared batch including the building of a basic model, model estimation, contrast manager and results report; here for correlation of cadence cost with brain morphology of HC

All models were checked for both possible contrasts. For 1-sample T-test for positive and negative correlation of the parameter with brain morphology and for 2-sample T-test for subject group 1 > subject group 2 and subject group 1 < subject group 2.

The statistical map for correlation analysis and between group comparison was thresholded at $p < 0.05$ statistical level corrected by family-wise error (FWE).

With the SPM.mat file, created for each batch, a Region of Interest Analysis (ROI) was conducted in CAT12. This method reveals differences between subject groups, respectively correlations of whole regions and not clusters which can span through several regions. As basis for the regional division, the results of previous segmentation by Hammers atlas were taken.

4.5 Visualization of Results

For visualisation of VBM and DBM results and determining of the affected brain regions the program MRIcroGL (https://www.nitrc.org/) was used. With the help of CAT12, the T-maps for statistically significant results were transferred to negative decimal logarithm maps. A slice overlay of the SPM/CAT12 -log (p) map, a standard brain MRI “mni152” and the brain atlas “aal” was displayed. With the option “generate cluster table” alle identified clusters were assigned to a brain region.

4.6 Statistical processing of data

The raw data of segmentation, including the GM, WM, CSF absolute values and the absolute size values for all brain regions segmented by Hammers atlas were exported to Excel using a Matlab script. The relative volume of the brain regions was calculated by dividing the raw volume of each region by total intracranial volume of the subject.

Statistical analyses were done in SPSS (Version 26).

The single factor ANCOVA test was used to determine any differences for gray matter volume between subgroups, eliminating the influence of age and sex by using these parameters as covariates.

The correlation between results of cognitive performance and relative size of different brain regions was determined with the bivariant Pearson correlation test.

A linear regression analysis was performed to state regression curves between relative gray matter volume and cognitive performance testing. To determine the significance of the difference between regression slopes between patient groups the p-value was calculated.

For the whole work a statistical level of $p<0.05$ was taken as significant.

5. Results

5.1 Goal 1: Definition of a preprocessing pipeline for MR image analysis

To obtain correct and replicable results from image analysis the development of a task adapted processing pipeline is necessary. Therefore, defined processes for MR image processing for the us available PD and iRBD datasets were created. All picture processing was done in Matlab, as a reliable and through toolboxes expandable program for picture analysis. The open access toolboxes SPM12 and CAT12 were used for advanced picture processing tasks.

5.1.1 Processing pipeline for detection of neuromelanin in substantia nigra

To correctly detect the relatively small and subcortical part of the brain which is necessary for the quantification of neuromelanin (NM), a specific picture processing pipeline was developed. Available initial data included seven repeatedly taken neuromelanin-sensitive T1 and T2 MRI sequences of the mesencephalon in which the substantia nigra (SN), as our region of interest, is located and T1 and T2 sequences of the whole patient's head.

All patient medical images were received packed in .tar format and were unpacked in a first step to make data accessible. This resulted in a list of single images in standard DICOM format for every MRI dataset. For further processing it was necessary to transfer this raw data into NifTI (.nii) format which is used by Matlab and it`s toolboxes. This transferred all single images of one MR sequence into one file without losing any image data.

To ensure the spatial comparability of all patient images, it was necessary to realign the different images. This process spatially adapts all images to the frame of the first image with the help of translation and rotation steps. The patients T1 and T2 MRI images of the whole head were realigned as well as the series of neuromelanin sensitive MRI images of the patient. This resulted in adapted images which are spatially comparable to each other. The data of the necessary adaptations for translation and rotation was stored for every image, which gives information about the extent of the changes which were necessary to undergo.

As the neuromelanin sensitive images of mesencephalon included a series of repetitive pictures of the same condition, an average picture off all seven images was calculated and stored as *nm.nii* file for every patient.

By applying a co-registration of the whole brain MR images with the neuromelanin sensitive images, a combination of anatomical and physiological information was possible. The calculated transformation matrix, which defined the necessary adaptations for co-registration, was saved and later used in further steps.

The T1 images of the whole brain were segmented by Lorio Draganski tissue-probability atlas [98] which was developed for segmentation of subcortical brain structures in MRI. The segmented tissue was then normalized to the SN template. The localization of SN in the

anatomical images was then transformed to NM images, resulting in a defined localization of the patients right and left SN in neuromelanin sequences as well as in T1 images. The so labelled regions could be afterwards used to quantify the amount of neuromelanin in the patient's substantia nigra.

A similar pipeline was used for segmentation of neuromelanin which was part of a research project conducted at our department of Bioinformatics. The results of the project are published in the article "Automatic substantia nigra segmentation in neuromelanin-sensitive MRI by deep neural network in patients with prodromal and manifest synucleinopathy" [p1].

5.1.2 Processing pipeline for VBM, DBM and SBM

For correlation analysis only T1 weighted MR images were used. The raw data was obtained packed in *.*tar* files which were unpacked and the thereout resulting DICOM image series was converted to nifti format **.nii* in SPM12. One nifty file per patient including the whole image series of MRI was obtained by this step.

Afterwards the MR images of patients were segmented in CAT12 which automatically includes the step of normalization and registration to predefined templates. The detailed settings which were used are described in the chapter "4. Methods". The parameters enabling later DBM (calculation of Jacobian determinant) and SBM (Surface and Thickness estimation) where directly done within this fist segmentation process. Modulated and spatially normalized (warped) gray matter maps with the prefix mwp1*.nii, white matter maps with the suffix mwp2*.nii, Jacobian determinants with the preffix wj_*.nii were automatically calculated and saved in the folder *mri*. All left and right surface data files of the datatype *.gii were generated and saved in the folder *"surf"*. The absolute size results for all regions of interest (ROI) according to the chosen Hammers atlas were stored as Matlab files for every patient with the prefix catROI_*.mat in the folder "*label"*. The Matlab file, including the basic results of segmentation data and the segmentation report were stored in the folder *"report".*

The absolute values of gray matter, white matter, cerebrospinal fluid, total intracranial volume, and all segmented brain regions were exported from the according Matlab files described above to Excel. The so generated dataset was used for further statistical analysis.

The step of smoothing of the data preceded the actual VBM, DBM and SBM analysis. The building of the statistical models for these steps is detailed described in the chapter "4. Methods".

5.2 Goal 2: Correlation of brain morphology with cognitive test performance in PD and iRBD patients

A complex morphometric analysis of brain structures including data from HC, iRBD and PD patients was conducted to reveal possible correlations between cognitive performance of the patient groups and their brain morphology.

5.2.1 Subjects

The here used dataset is part of the longitudinal project 'biomarkers in PD (BIO-PD)' aimed at collecting a large representative sample of de-novo PD patients. A detailed protocol of this project was described by Dušek et. al. [99]. Patients were examined at the Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital. Image acquisition was performed on a 3T MRI scanner (Siemens Skyra 3T, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil.

PD was diagnosed according to the clinical diagnostic criteria of the Movement Disorder Society for PD [42] and investigated before starting the pharmacotherapy.

iRBD was diagnosed using video-polysomnography according to the International classification of sleep disorders [100].

The healthy control group was acquired by advertising in the general public. The exclusion criteria for HC were neurological or psychiatric disorders, the use of psychoactive substances, the treatment of oncological or other major somatic illnesses, the presence of sleep disorders, major hearing and vision problems, and cognitive deficit. The HC group was matched in age, education, and sex to be comparable to the iRBD and PD group.

Each participant provided written informed consent. The study received approval from an ethical standards committee on human experimentation and has therefore been performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

All patients and HCs provided written informed consent. The study was approved by the Ethics Committee of the General University Hospital in Prague under the number 11/15.

For the correlation analysis between the results of cognitive tests and brain morphology, all patients with completed cognitive test battery and available and processable MR images were selected out of the total dataset (see Table 5.1).

Table 5.1: Demographic and clinical data of patients for correlation analysis between cognition and brain morphology

	Male sex	Age (years,(SD range))	MoCa (SD range)	MDS - UPDRS III (SD, range)
HC[a]	30/36 (83%)	63.76 (7.15, 51-81)	25.53 (2.01, 19-30)	3.44 (4.36, 0-22)
iRBD[b]	57/63 (90%)	66.73 (6.59, 52-83)	24.21 (2.57, 19-30)	6.37 (5.49, 0-24)
PD[c]	52/86 (60%)	59.85 (11.66, 34-79)	25.12 (2.90, 17-30)	28.84 (12.5, 6-70)
p	*<0.001*	*<0.001*	*0.032*	*<0.001*
Post hoc	a>c, b>c	b>c	a>b	a<c, b<c

Note: HC= Healthy Controls; iRBD= idiopathic Rem-Sleep-Behavior-Disorder; PD= Parkinsons Disease; MoCa= Monteal Cognitive assessment test; MDS-UPDRS III= Movement Disorder Society Unified Parkinson Rating Scale part III;

5.2.2 Between-Group differences in brain morphology

Neither VBM nor DBM, SBM or ROI analysis revealed any significant between group differences for comparison of HC, iRBD and PD. There was a statistical trend for reduced volumes in iRBD and PD compared to HC ($p < 0.05$, uncorrected) which are listed in Table 5.2.

Table 5.2: Regional volumes defined by Hammers atlas with a statistical trend for significant between group differences.

		p (uncorrected)
HC > iRBD		
	Left Cuneus	0.010
	Left Cerebellum	0.024
	Right Cerebellum	0.019
	Left Inferior Lateral Parietal Lobe	0.035
	Right Lingual Gyrus	0.015
	Right Lateral Occipital Lobe	0.032
HC > PD		
	Right Superior Parietal gyrus	0.008
	Left Inferior Lateral Parietal Lobe	0.022
	Left Posterior Temporal Lobe	0.050

5.2.3 Correlation of cognitive tests with brain morphology

Voxel-based-morphometry

The voxel wise correlation analysis between brain morphology and cognitive performance of iRBD and PD patients revealed several significant results.

A positive correlation of clusters was found in iRBD for TMT-A (cluster 1: $p_{FWE}<0.001$; cluster 2: $p_{FWE}=0.026$), TMT-B ($p_{FWE}=0.05$), GPT-right hand ($p_{FWE}=0.043$) and RAVLT 1-5 ($p_{FWE}=0.023$). The component psycho-motor-speed correlates negatively with a cluster in cerebellum in iRBD ($p_{FWE}=0.01$). In PD a cluster covering parts of right and left cingulum and precuneus positively correlates significantly with the results of TMT-B ($p_{FWE}=0.008$). A positive correlation could be shown between right hand GPT results and a cluster in right precuneus, cingulum and paracentral lobe. Figure 5.2 depicts the significant clusters in PD, Figure 5.3 results for iRBD. A detailed overview about correlating cluster localization can be found in Appendix A.2.

The performance in RAVLT 1-5, RAVLT recognition, MBT (total delayed free recall), Stroop words, MIST-eb and the component mental speed/executive functions significantly correlates with clusters in HC (see Appendix A.2).

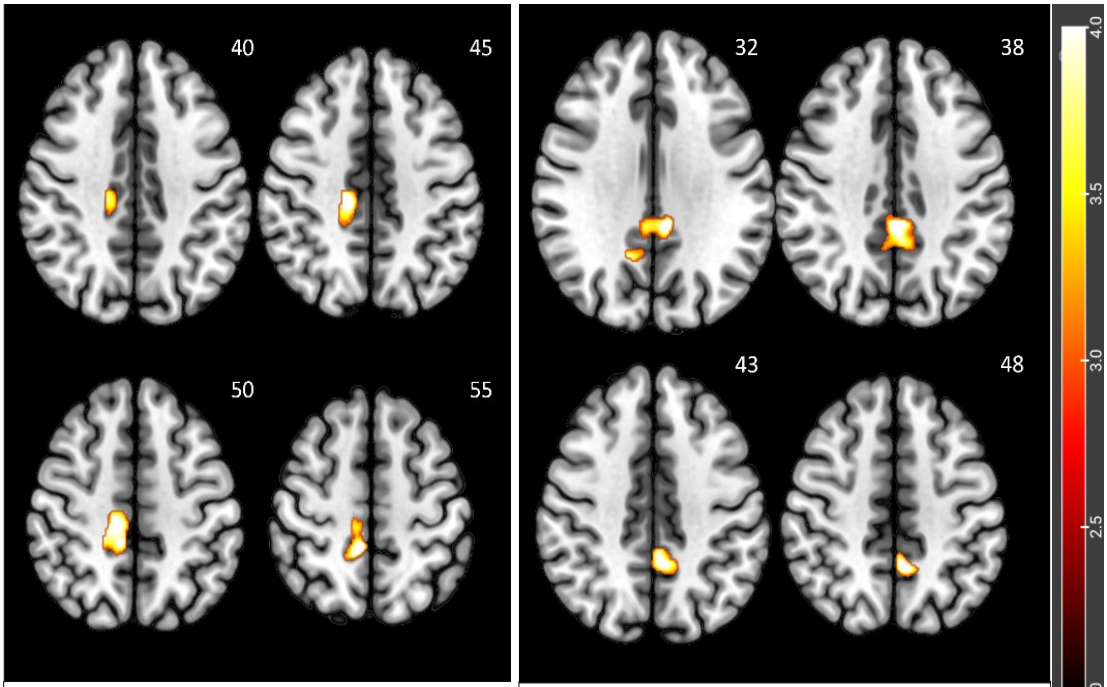


Figure 5.2: Correlation between cognitive performance and brain morphology in PD, analyzed with VBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right).

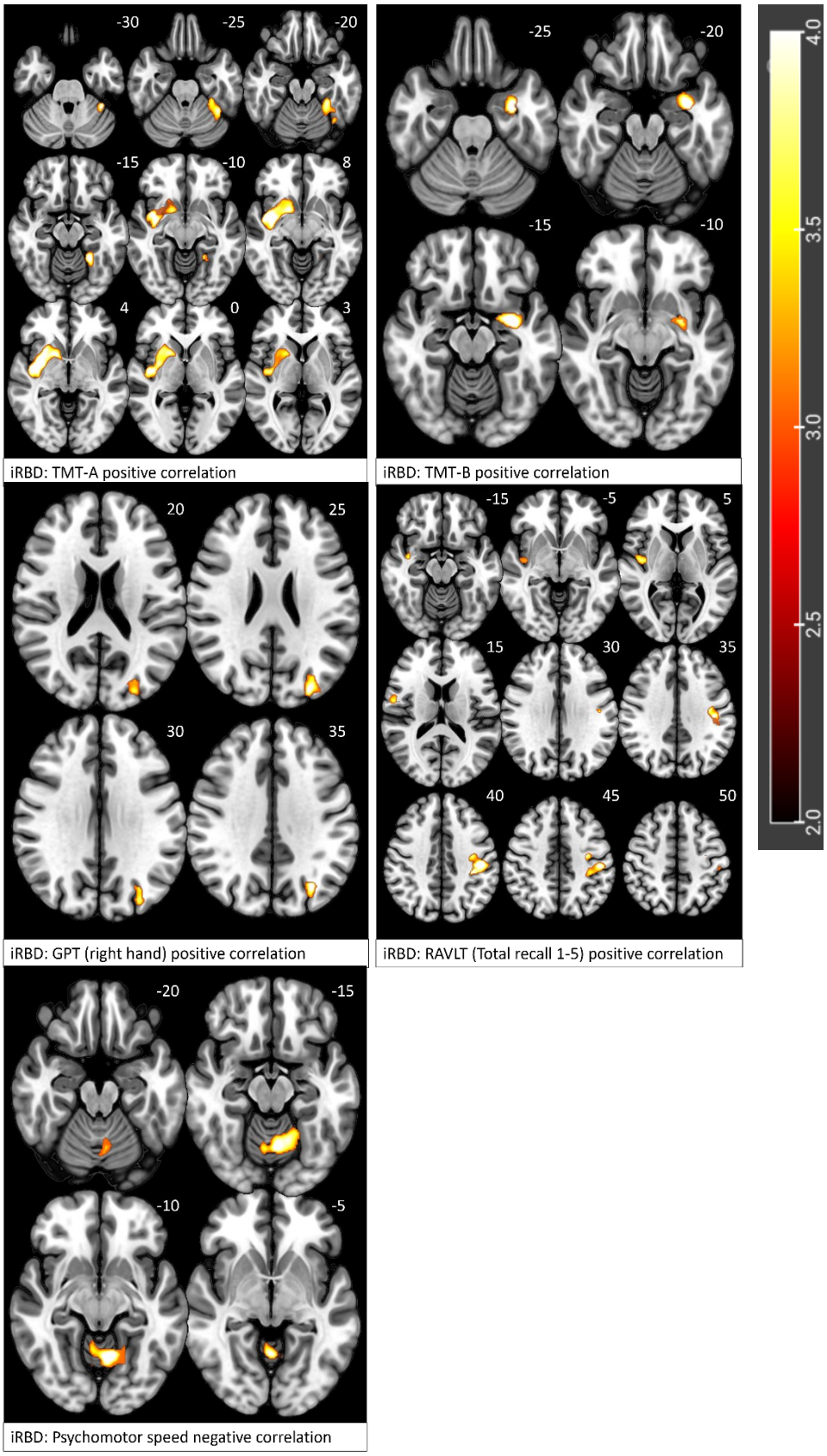


Figure 5.3: Correlation between cognitive performance and brain morphology in iRBD, analyzed with VBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right).

Region of Interest Analysis

Additionally to the cluster analysis, a correlation ROI analysis was conducted to identify brain regions which in total correlate with cognitive performance. The difference hereby is that the clusters in cluster analysis obtain parts of different brain regions while in ROI analysis always just one brain region in total is analyzed. As base for regional division the segmentation by Hammers atlas was used. The results for iRBD can be seen in Table 5.3.

Table 5.3: ROI-based analysis of the correlation between cognitive performance and brain regional volumes segmented by Hammers atlas in iRBD patients, significance level: $p < 0.05$, FDR corrected

		iRBD		HC	
		r	*p*	*r*	*p*
TMT-A					
	Right Putamen*	0.407	0.001	-	0.852
	Right Insula*	0.366	0.003	-	0.482
	Right Nucleus Accumbens*	0.364	0.003	0.012	0.943
	Left Nucleus Accumbens*	0.364	0.004	-	0.725
	Left Putamen*	0.365	0.004	-	0.671
	Left Precentral Gyrus*	0.330	0.009	-	0.311
	Left Insula*	0.311	0.014	-	0.456
GPT (left hand)					
	Right Insula*	0.434	<0.001	-	0.318
GPT (right hand)					
	Right Insula*	0.314	0.013	-	0.124
RAVLT 1-5					
	Right Pallidum *	0.469	<0.001	0.015	0.931
	Left Pallidum*	0.404	0.001	0.113	0.518
	Left Nucleus Accumbens*	0.399	0.001	-	0.128
	Right Insula*	0.402	0.001	-	0.115
	Left Brainstem*	0.354	0.002	-	0.105
	Right Superior Parietal Gyrus	0.376	0.003	-	0.029
	Right Brainstem*	0.373	0.003	-	0.149
	Right Nucleus Accumbens	0.357	0.004	-	0.004
	Right Precentral Gyrus	0.362	0.004	-	0.001
	Left Insula*	0.352	0.005	-	0.112
	Left Nucleus Caudate*	0.354	0.005	-	0.141
	Right Nucleus Caudate*	0.348	0.006	-	0.184

		iRBD		HC	
		r	*p*	*r*	*p*
	Left Inferior Lateral Parietal Lobe	0.343	0.006	-	0.043
	Left Precentral Gyrus	0.335	0.008	-	0.040
	Right Posterior Temporal Lobe*	0.328	0.009	-	0.206
	Right Cuneus*	0.327	0.010	0.199	0.253
	Left Postcentral Gyrus	0.327	0.010	-	0.001
	Right Lingual Gyrus*	0.322	0.011	0.149	0.349
	Right Inferior Lateral Parietal Lobe*	0.307	0.015	-	0.170
	Right Fusiform Gyrus*	0.295	0.020	-	0.717
	Left Posterior Temporal Lobe*	0.293	0.021	-	0.255
	Left Superior Parietal Gyrus*	0.274	0.031	-	0.424
Psychomotor speed (PCA component)					
	Left Cerebellum*	-0.390	0.002	-	0.804
	Left Anterior Temporal Lobe, Med. Part*	-0.360	0.004	-	0.562
	Left Insula*	-0.310	0.014	0.104	0.551

* Significant correlation in iRBD but not in HC

Table 5.4 gives an overview about trends for correlating brain morphology with cognitive performance in PD patients based on regions segmented by hammers atlas. After FDR correction none of the correlations fulfilled the significance level.

Table 5.4: ROI-based analysis of the correlation between cognitive performance and brain regional volumes segmented by Hammers atlas in PD patients, significance level: p < 0.05, uncorrected

		PD	
		r	*p*
TMT-B			
	Left Posterior Orbital Gyrus	0.356	0.002
	Right Lingual Gyrus	0.342	0.004
	Right Posterior Cingular Gyrus	0.319	0.007
	Right Hippocampus	0.316	0.007
	Left Posterior Cingular Gyrus	0.299	0.011
	Left Precentral Gyrus	0.297	0.012*
	Right Posterior Orbital Gyrus	0.290	0.014*
	Right Lateral Orbital Gyrus	0.269	0.024*

Note: * one sided correlation

Regression slope analysis

For all significant correlations of regions and cognitive tests from ROI analysis in iRBD a regression slope comparison between slopes of iRBD and HC was conducted. The size of the left precentral gyrus, the right insula and the right putamen, printed against TMT-A results, showed significantly different regression slopes between iRBD and controls. The detailed results can be seen in Fig. 5.4.

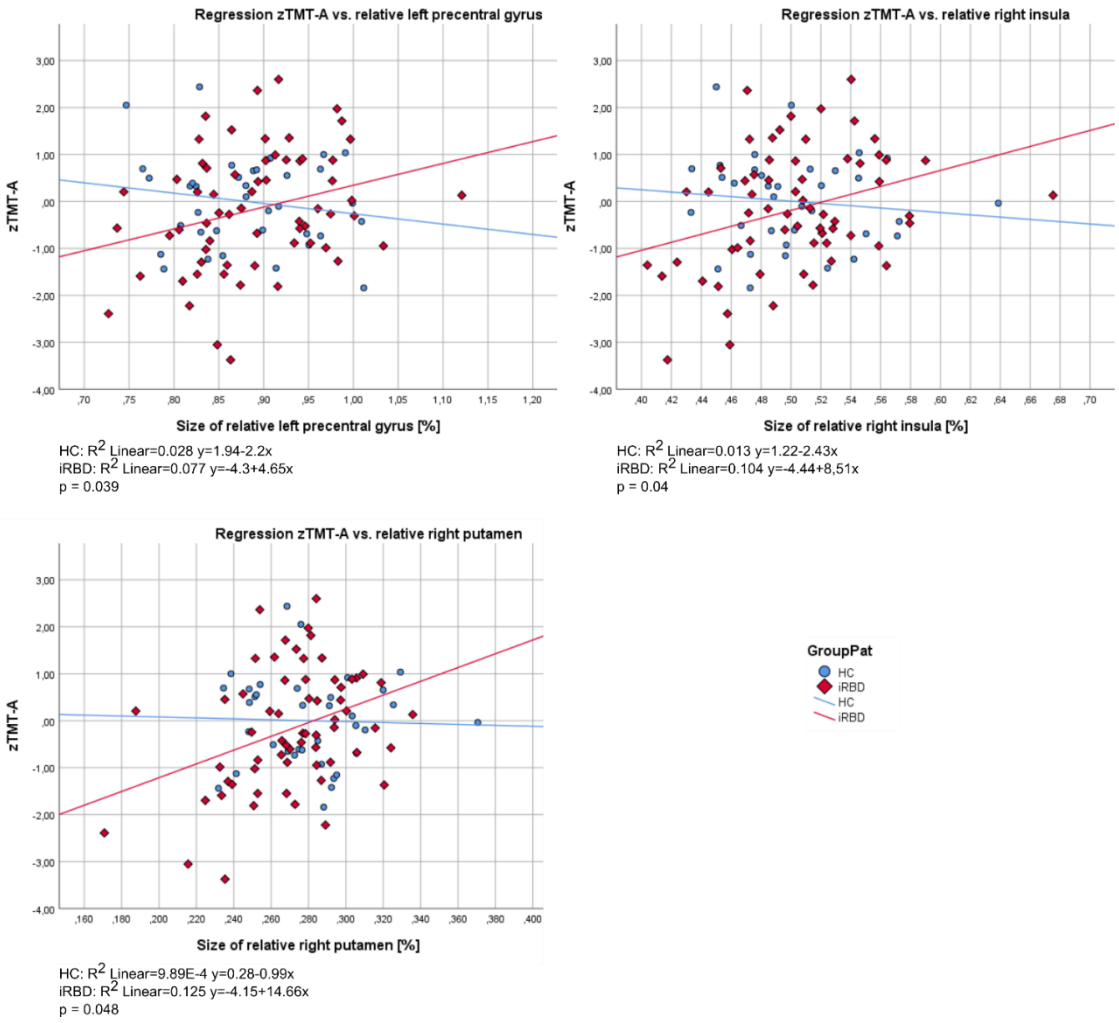


Figure 5.4: Linear regression plots of brain regional volumes associated with the performance of TMT-A. p value for difference of regressions slopes between iRBD and HC is shown in every graph.

Deformation-based-morphometry

Regional cluster deformations correlating with cognitive performance could be shown just for iRBD patients and TMT-A and GPT (right hand). Figure 5.5 shows the significant clusters and Table 10 a more detailed overview of cluster locations. For both cognitive tests the correlating clusters in DBM have a similar location and outspread as in VBM (Tab. 5.5).

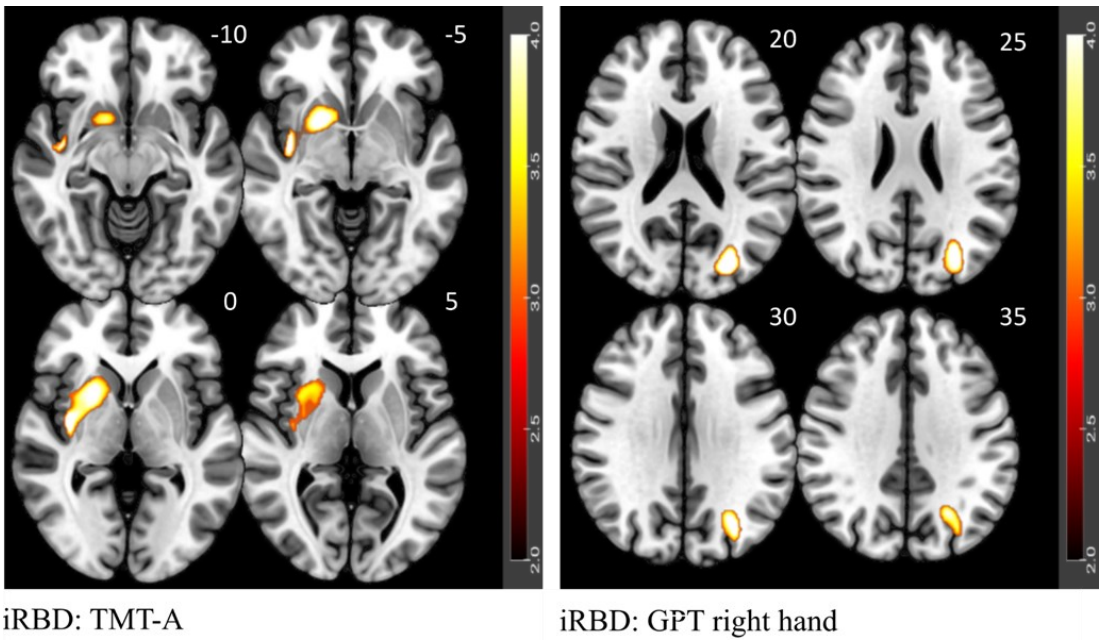


Figure 5.5: Correlation between cognitive performance and brain morphology analyzed with DBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right).

Table 5.5: Detailed information about significant clusters in DBM correlation analysis

	Peak Localisation [mm mm mm]	**T value (Peak)**	**Anatomical region (cluster, aal atlas)**
iRBD vs. TMT-A	38/-8/2	4.88	Right hemisphere: Putamen, Pallidum, Insula, Caudate, Superior Temporal Lobe
iRBD vs. GPT right hand	-27/-83/21	4.98	Left hemisphere: Middle and Superior Occipital Lobe, Superior Parietal Lobe

Surface-based-morphometry

The morphometric parameters cortical thickness, gyrification, sulcus depth and complexity were examined for correlations with cognitive performance in iRBD and PD patients.

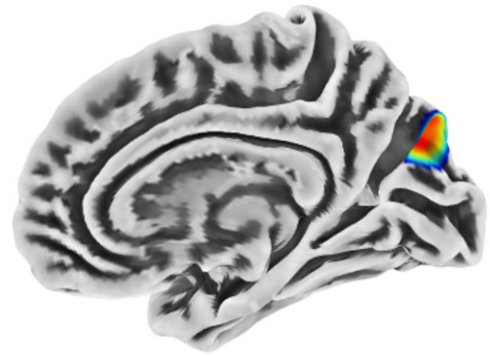
In iRBD, several associations were found. Cortical thickness of right cuneus correlates positively with VF (vegetable) test ($p_{FWE} < 0.001$). A cluster in left precentral gyrus shows a positive correlation between gyrification and LNS ($p_{FWE} < 0.001$) and a cluster in right inferior parietal lobe correlates positively with TMT-B results ($p_{FWE} = 0.043$). Complexity of a cluster in left insula is negatively associated with the PCA component of mental speed/executive functions ($p_{FWE} = 0.02$). The performance in MBT subtests Paired Recall Pairs ($p_{FWE} = 0.001$), Total cued Recall ($p_{FWE} = 0.002$), Total Delayed Paired Recall ($p_{FWE} = 0.002$) and Total Free Recall ($p_{FWE} = 0.003$) correlate positively with complexity within a cluster in right supramarginal region. Figure 5.6 depicts statistically significant clusters found in iRBD.

No correlations were found in PD patients.

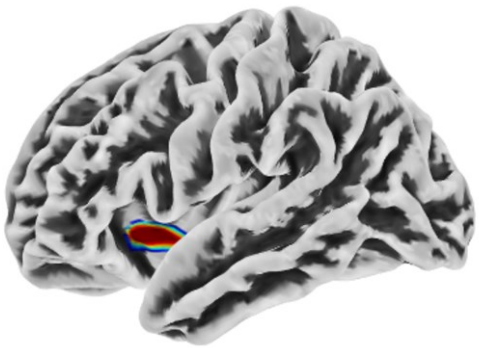
In HC cortical thickness correlates with performance in Stroop words test ($p_{FWE} = 0.031$), gyrification with MBT- Paired Recall Pairs ($p_{FWE} = 0.001$) and MBT – Total Cued Recall ($p_{FWE} = 0.002$). The sulcus depth was significantly associated with performance in MoCa ($p_{FWE} = 0.002$), SDMT ($p_{FWE} = 0.036$), Stroop colour ($p_{FWE} = 0.006$), Stroop words ($p_{FWE} < 0.001$) and the PCA components mental speed/executive functions ($p_{FWE} < 0.001$) and episodic memory ($p_{FWE} = 0.002$).

A more detailed overview about the cluster location in iRBD and HC is listed in Appendix A3.

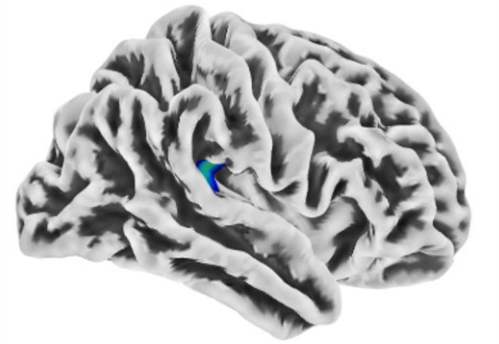
The results of this analysis were published as part of the article "Cortical and subcortical morphometric changes and their relation to cognitive impairment in isolated REM sleep behavior disorder" [p2].



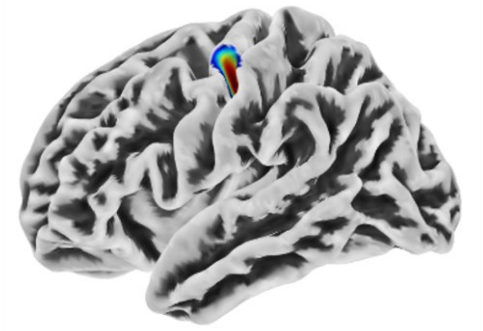
iRBD cortical thickness: VF Vegetables negative correlation



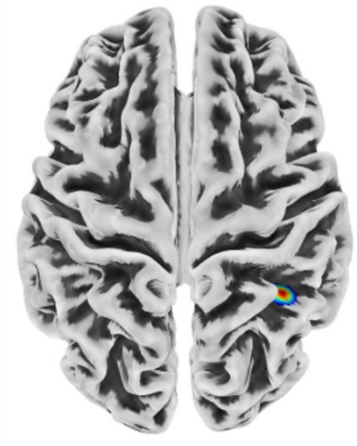
iRBD complexity: mental speed/exec. function neg. correlation



iRBD complexity: MBT Total Cued Recall positive correlation



iRBD gyrification: LNS positive correlation



iRBD gyrification: TMTB positive correlation

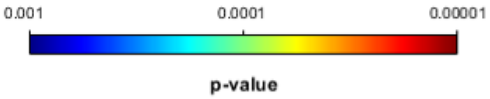


Figure 5.6: Results of Surface-based-morphometry for correlation analysis between cognitive performance and surface brain morphology in iRBD patients

5.3 Goal 3: The influence of impaired DTC on the correlation of brain morphology and Dual task cost parameters in PD

5.3.1 Subjects and division into subgroups

For the correlation analysis between impaired DTC and brain morphology in PD, all participants with completed gait analysis and available and processable MR images were chosen from the dataset described in chapter 5.2.1 (see Table 5.6). Patients with a cognitive impairment (defined by MoCa < 24) were excluded.

Table 5.6: Demographic and clinical data of patients for correlation analysis of impaired DTC with brain morphology

	Male sex	Age (years,(SD range))	MoCa (SD range)	MDS – UPDRS III (SD range)
HC	29/47 (61.7%)	60.4 (9.2, 43-75)	26.5 (1.72, 24-30)	3.0 (3.7, 0-22)
PD	34/64 (53.1%)	58.2 (12.3, 33-81)	26.5 (1.75, 24-30)	28.0 (12.6, 6-70)
p-value	0.44	0.31	0.96	< 0.001

Note: HC= Healthy Control; PD= Parkinson Disease; nDTC= normal DTC; iDTC= impaired DTC; MoCa= Monteal Cognitive assessment test; MDS-UPDRS III= Movement Disorder Society Unified Parkinson Rating Scale part III

To answer the question whether there exists a correlation between severity of gait impairment during execution of a cognitive task and brain morphology in PD, patients were divided into two subgroups.

The first PCA component calculated from DTC parameters linearly combined gait speed cost (multiplication coefficient of 0.8), cadence cost (-0.01) and stride length cost (0.6). It shows a significant difference between PD and HC (p=0.007). The 10th percentile of the first PCA component in HC distinguished PD patients into the subgroups with normal DTC (nDTC) and impaired DTC (iDTC). The characteristics of included patients can be found in Table 5.7.

Because of the small number of subjects in HC-iDTC, I this subgroup was not considered for comparison analysis.

Table 5.7: Demographic and clinical characteristics of the subjects after devision of the dataset into normal DTC and impaired DTC subgroups

	Male sex	Age (years,(SD range))	MoCa (SD range)	MDS - UPDRS III (SD range)
HC-nDTC	27/43 (62.8%)	61.0 (9.3, 43-75)	26.5 (1.8, 24-30)	n/a
PD-nDTC	25/44 (56.8%)	58.6 (12.2, 34-81)	26.6 (1.9, 24-30)	24.3 (9.7, 6-43)
PD-iDTC	11/20 (45%)	57.3 (13.0, 33-81)	26.40 (1.4 , 24-29)	36.2 (14.5, 14-70)
p-value	0.43	0.41	0.93	< 0.001

Between-group differences in gait parameters in our patient dataset were analyzed. Decreased speed ($p < 0.001$) and stride length ($p < 0.001$) were observed in PD patients in single-task-mode, while cadence showed no significant difference.

PD patients had significant different DTC in all parameters: speed cost ($p < 0.007$), cadence cost ($p < 0.29$) and stride length cost ($p < 0.014$).

The results are shown in Figure 5.7.

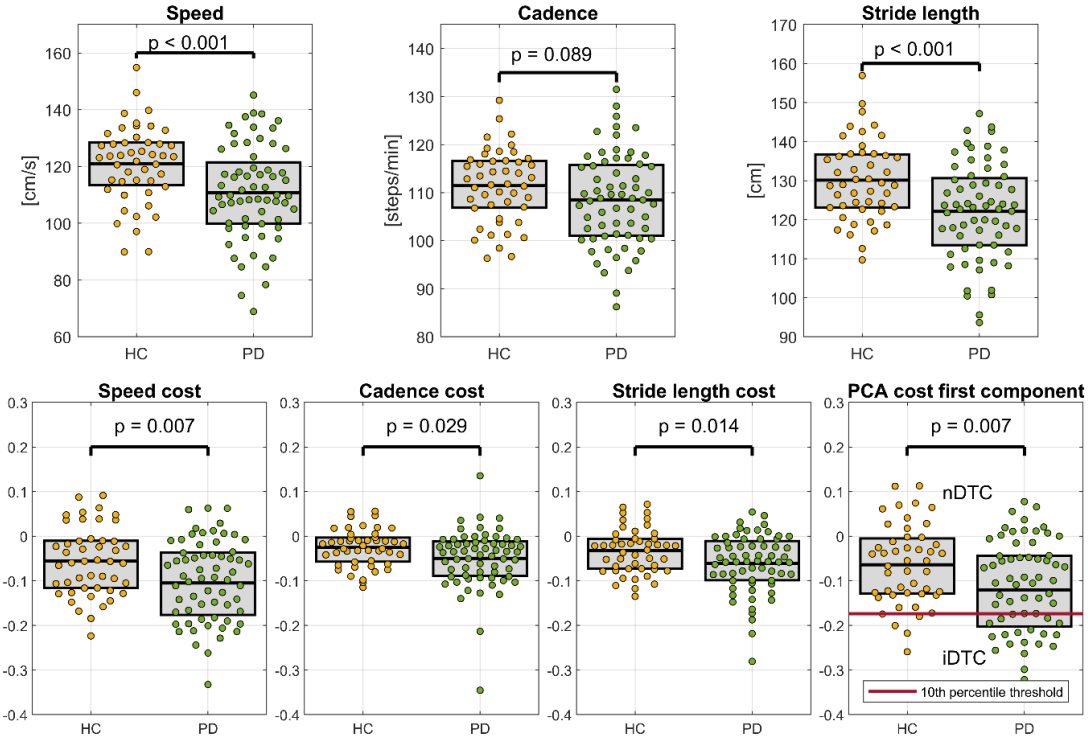


Figure 5.7: Between-Group differences in gait parameters and Dual-Task costs between HC and PD. In the right bottom row figures the first PCA component group difference.

5.3.2 Morphological brain analysis

Comparison of brain morphology between PD-nDTC and PD-iDTC showed no significant differences after FWE correction. Without FWE correction, a cluster in the left frontal inferior pars triangularis had a significantly higher grey matter intensity in PD-nDTC than in PD-iDTC (P_{uncorr}= 0.013).

Correlation analysis between DTC parameters and brain morphology, revealed clear differences between the subgroups in PD.

In PD-nDTC patients, the gait parameter stride length cost positively correlates with a cluster (peak location -21mm/-12mm/78mm) in left precentral gyrus (r= 0.57, p_{FWE}= 0.03) as shown in Figure 5.9. The corresponding cluster in the right hemisphere did not reach a significant level of p_{uncorr} <0.05. Although a cluster in a similarly located area showed a correlation with speed cost, the correlation did not reach significant level after FWE correction (r= 0.51, $p_{uncor\ r}$= 0.02). The cadence cost was not associated with any cluster. Neither in PD-iDTC group nor in HC-nDTC the gray matter density in primary motor cortex correlated with any DTC parameter.

In the PD-iDTC cohort, a cluster in the right lingual gyrus (peak location 20mm/-56mm/-2mm) exhibited a negative correlation with cadence DTC (r = -0.35, p_{FWE} = 0.02) as shown in Figure 5.8. A similar correlation was observed for speed DTC at a significance level just under the border of significance (r = -0.26, p_{uncorr} = 0.06). No significant correlation was detected for stride length cost in the PD-iDTC group. The lingual gyrus did not correlate with any DTC parameters in PD-nDTC subgroup.

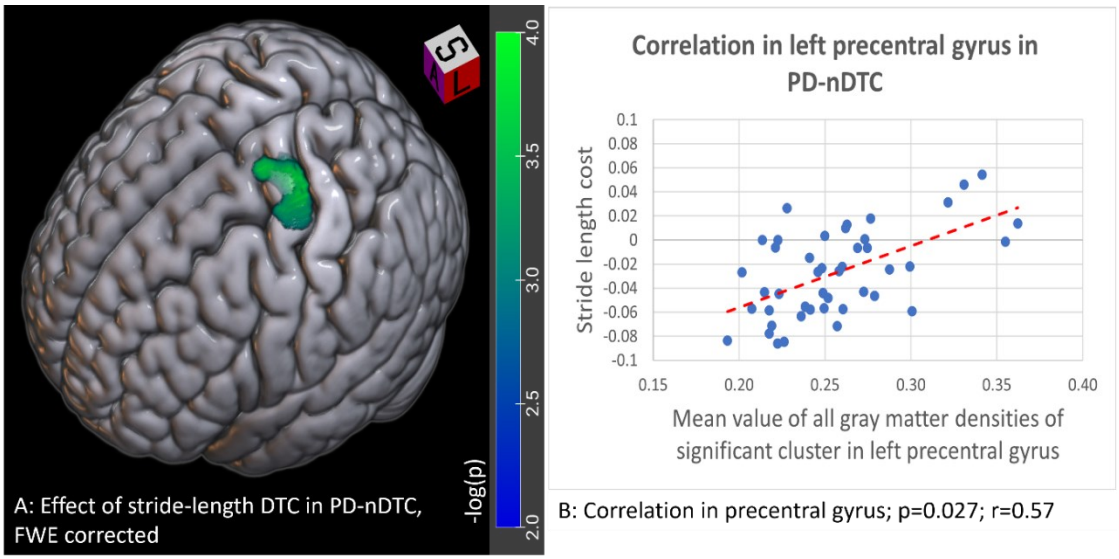


Figure 5.9: Results of correlation analysis of brain morphometry with dual task cost of gait parameters for Parkinson`s disease patients with normal DTC. A: Significant cluster in left precentral gyrus for a positive correlation with stride length cost in PD-nDTC, p=0.027. B: Correlation of gray matter density with stride length cost values within the cluster in left precentral gyrus..

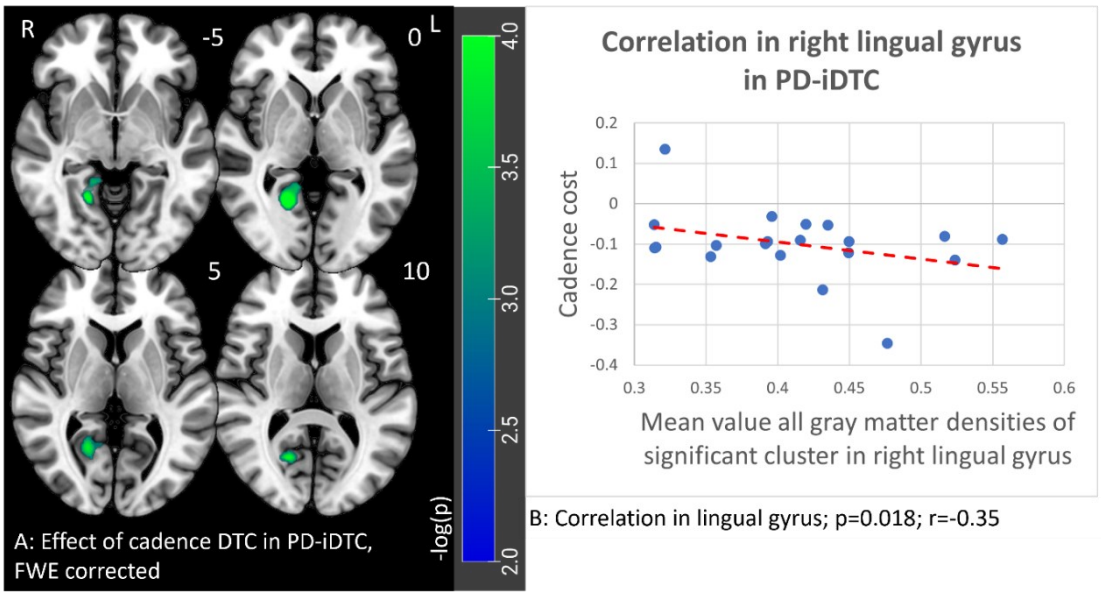


Figure 5.8: Results of correlation analysis of brain morphometry with dual task cost of gait parameters for Parkinson`s disease patients with impaired DTC. A: Significant cluster in right lingual gyrus for a negative correlation with cadence cost in PD-iDTC, p = 0.018. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right) B: Correlation of gray matter density with cadence cost

Within PD-iDTC group the sulcus depth (square root) of two clusters including parts of the right precuneus and isthmuscingulate show a significant negative correlation with velocity DTC (superior cluster p_{FWE}= 0.013; inferior cluster p_{FWE}= 0.001), (see Fig. 5.10). Other surface parameters, namely cortical thickness, gyrification and complexity, did not reveal any significant correlations.

In the PD-nDTC group no surface parameter is associated with any DTC values.

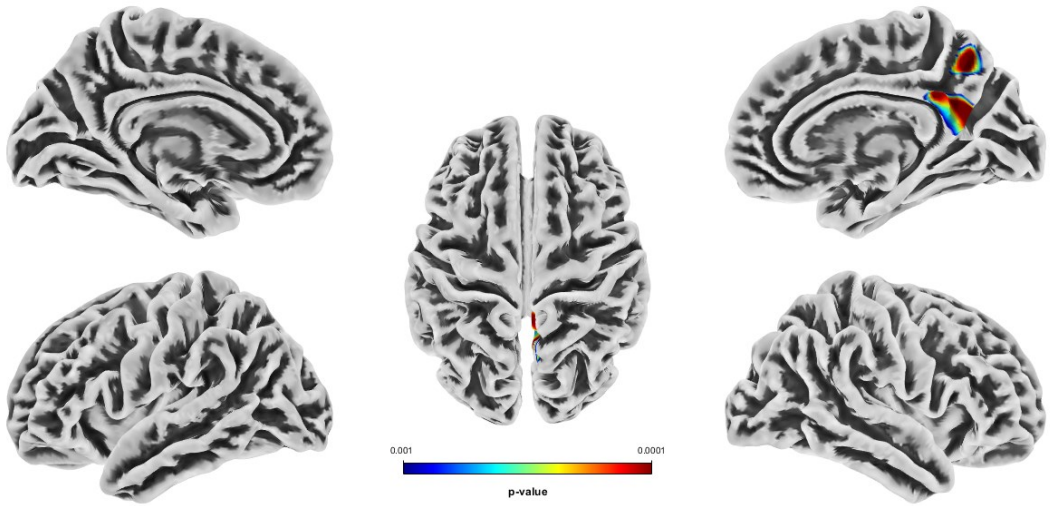


Figure 5.10: Significant clusters in superior right precuneus (p_{FWE}= 0.013) and in inferior precuneus + isthmuscingulate (p_{FWE}= 0.001) for correlation between sulcus depth and velocity cost in PD-iDTC patients.

The results of this analysis were published as part of the article "Impaired dual-task gait in Parkinson's disease is associated with brain morphology changes" [p3].

6 Discussion

The aim of the work was to investigate the presence of correlations between cognitive performance and brain morphology in patients with iRBD and PD.

Under usage of the developed picture processing pipeline, the brain morphology of the patients was compared to the results of a broad cognitive test battery and with results of their dual task gait performance.

Clusters in brain of iRBD patients correlating with the performance of TMT-A, TMT- B, GPT (right hand), RAVLT 1-5 and the PCA component psycho-motor-speed could be identified by voxel-based morphometry. All these findings were iRBD specific and were not present neither in HC nor in PD.

In detail, the performance in TMT-A correlated with a cluster including cortical and subcortical regions of striatum, insula, temporal superior lobe, pallidum and amygdala and a second cluster in cerebellar region. A correlation with a very similar cluster and TMT-A performance was identified also in deformation-based morphometry. This implies not just atrophic changes but also significant changes in shape of these brain regions which are associated with executive and visuospatial functions, motor control and psychomotor speed [86, 101, 102]. Next to working memory, the TMT-A results depend also on the psychomotor speed performance of the subject and in α-synucleopathies this test is a linked mainly with the anatomical structures of basal ganglia [102]. Considering this, the results of this study agree with other publications and confirm the important role of striatum, insula, cerebellum and pallidum in the deficits of psychomotor speed.

The cluster correlating in VBM with TMT-B performance consisted mainly of parts of limbic system (amygdala, hippocampus, parahippocampal region and fusiform gyrus). Even if lower performance in TMT-B is in literature primarily connected with an impairment in executive functions [74, 103] the here presented results point predominantly to brain regions connected to memory deficits which are common in iRBD [74]. An involvement of memory-related structures in performing TMT-B seems logical Under the assumption, that the subject needs to recall the next letter in alphabet or number while remembering the last one.

The performance in GPT (right hand) correlated with regions in occipital and parietal lobe in VBM and DBM analysis. The identified structures play an important role in sensorimotorical and visuomotorical coordination and were shown to be involved in GPT performance [104]. Indeed, impaired visuospatial abilities in iRBD were shown to be connected with parietal regions in previous studies Pereira et al. [87] or Rahayel et al. [86]. So, the results of our analysis support the hypothesis that occipital and parietal regions are responsible for visuomotoric deficits in iRBD as measured by GPT. The role of the occipital region, especially the lingual gyrus, for GPT performance is underpinned by the here detected correlation between the PCA component psychomotor speed, which is mainly loaded by GPT performance) with a cluster involving lingual gyrus.

The correlations detected between temporal and parietal regions with RAVLT 1-5 results are the only ones without any connection to motor abilities in our study. RAVLT tests for performance in memory domain which is the second often impaired in iRBD [74, 105]. For iRBD patients an association between verbal learning/memory and disruptions in temporal, occipital and insular regions was described previously [86, 103].

The detected correlations of surface parameters with cognitive performance can be seen as additional hints of existing connections between brain morphology and cognitive performance. No studies could be found which connect changes in cortical complexity in iRBD patients with any formal outcome. The results shown here can give a first idea of the influence of this surface parameter on cognitive performance. The demonstrated correlation between mental speed/executive function, which is a PCA component mainly influenced by the performance in PST, TMT-A, TMT-B and SDMT, and complexity of a cluster in insular region can point out the role of insula in hand-eye-motor coordination and internal movement motivation in PD which was suggested by previous studies in PD patients [106]. Additionally, it supports the findings of the presented voxel wise analysis which shows a connection of gray matter intensity in insula region with the performance of TMT-A. The identified correlations in gyrification patterns of the primary motor cortex and the inferior parietal lobe with cognitive performance in attention and executive functions remain ambiguous, as the functions of these regions do not inherently influence the abilities required for the administered tests. Again, no similar studies for cortical gyrification analysis in iRBD could be found. For PD patients in later disease stage, changes in gyrification of several cortical regions were shown in a study of Sterling et. al. [107], including also a lowering in gyrification in precentral gyrus – the primary motor cortex – and the inferior parietal lobe which are exactly the regions which correlate in the here presented results.

In PD patients the results of two cognitive tests correlated with brain morphology. The GPT and TMTB test both are connected to gray matter density in a cluster involving the precuneus. As for both tests a certain motor coordination is necessary, this interrelation points to the role of precuneus in visuospatial perception and motor control [108].

In the second part of the study the influence of brain morphology on dual task cost in Parkinson Disease patients was analyzed. This parameter represents a connection between gait and cognitive performance and is known to be increased in PD patients compared to HC (109). In single-task gait the PD patients showed reduced stride length and walking speed compared to the healthy control group. The dual-task cost in all three analyzed parameters - stride length, speed and cadence - was elevated compared to HC.

The results for single-task performance align with previous studies in which PD patients have shown reduced speed and shorter stride length [109] Regarding cadence cost our study differs from some previous published results in which PD patients showed also increased cadence [110, 111]. One explanation could be the association of this increase with longer disease duration [110] while our patients are in a relatively early disease stage. The increased dual task costs in gait parameters are consistent with previous research [112].

Brain morphometric correlation analysis of gait parameters suggests an involvement of different brain regions in dual task performance in PD patients with normal DTC and patients with increased DTC. This supports a recently published study of Johannsson [113] in which a different task prioritization in dual-task performance between cognitively impaired and unimpaired patients is suggested. In this study, patients with normal cognition seemed to focus more on motor task and cognitively impaired patients more on the cognitive task. Similarly to this, the presented results for PD nDTC patients show a positive correlation between the gray matter density in left precentral gyrus with DTC of stride length and speed. Patients with a relatively higher gray matter intensity in a cluster in primary motor cortex tend to have a more normal DTC for these two gait parameters. In contrast to this, in PD-iDTC patients the gray matter density in a cluster in the right lingual gyrus showed a negative correlation with cadence DTC. This part of the brain is involved in visual imagery of numbers and letters and is assumed to be involved in the backwards counting in DT. This is consistent with the findings of Johansson et al. [113] suggesting that cognitively impaired patients focus more on cognitive task.

None of these correlations are present in HC group which implies that they are related to either compensatory mechanisms or brain changes due to neurodegenerative processes. These results suggest different patterns of neuronal degeneration and plasticity in cognitively impaired and non-impaired PD patients.

No between-group difference in gray matter density between nDTC and iDTC in precentral gyrus or lingual gyrus could be detected, leading to the assumption that the observed correlations are not influenced by general atrophy in these brain regions.

7 Conclusions

This chapter summarizes the scientific results of the work and the overall achievements during the PhD studies.

The scientific part of the dissertation originated in a close cooperation of Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague where doc. Petr Dušek, Ph.D contributed the neurological assessment of the patients, doc. Ondřej Bezdiček, Ph.D contributed the cognitive data of the subjects and the group around Prof. MUDr. Evžen Růžička, DrSc. contributed the gait data and the faculty of Biomedical engineering, department of Bioinformatics where the data processing and evaluation was done.

7.1 Scientific summary of results of the study

In the technical part of the work, a medical picture processing pipeline was created which serves as basis for different types of structural brain MRI analysis. Several pre-processing steps ensure e.g. the correct spatial alignment for different picture modalities of the same subject or the reduction of the influence of individual brain anatomical anomalies. Picture series, detecting the amount of neuromelanin in substantia niga, could be analyzed using the developed pipeline. Another application of it is the detection of morphological brain changes within two patient groups or a correlation analysis of a parameter with certain brain morphological characteristics. The created pipeline served as basis for the following steps of the work.

With conducting complex morphological correlation analysis with different cognitive parameters in iRBD and PD patients, this work revealed several significant results in both – the prodromal and manifested phase of PD.

The patient's performance in standardized cognitive tests assessing the domains attention, executive functions and psychomotorspeed were shown to correspond to gray matter density in multiple brain regions in patients with iRBD and PD. Thus, this study confirms previous research and gives new insights into the connection between impaired cognition and brain morphology in iRBD a presymptomatic phase of PD occurring up to 15 years before the confirmed diagnosis of PD. Correlations were identified also for manifested phase of PD and HC giving an interesting insight into a three-step development of these connections in subjects in three different states of disease.

The combination of gait parameters with cognitive outcome in PD revealed an interesting result pointing to possible different compensatory mechanisms or different neuroplasticity in PD patients with and without cognitive impairment.

This work could help to move cognitive decline in the early stages of the development and progress in α-synucleopathies more in focus. The disease-specific connections between morphological brain changes and cognitive performance shown in this work, could be helpful in

assessing the ongoing neurodegeneration with the help of standardized and easily accessible cognitive tests.

Adding cognitive parameters to gait analysis, as done in the second part of correlation analysis, revealed interesting differences between cognitively impaired and unimpaired patients. This exploratory study should motivate to have a closer look on the influence of cognition on motor features in PD in future studies. Hereby it would be especially interesting to also record the cognitive performance of patients while performing cognitive-motor dual task.

Even if PD is mainly seen as a disease with worsening motoric function, this work showed the importance to also investigate patients' cognition to fully understand development and progress of neurodegeneration.

7.2 Project funding, publications, conferences

The project was funded by the Czech Health Research Council, grant No. NU20-04-00327, by the General University Hospital in Prague, MH CZ-DRO-VFN No. 64165, and by the National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) - Financed by the European Union – Next Generation EU.

During my work I published three journal articles concerning the topic of the dissertation in journals with Impact Factor (IF). For the publication in the journal "Neurological Science" with and IF of 3.3 (2022) [p2] and the publication in the "Journal of Neural Transmission" with an IF of 3.3 (2022) [p3] I was the main author. For the publication in the journal "Physiological Research" with an IF of 2.1 (2023) [p1] I acted as co-author.

Additionally, I presented results of my work at the International Conference on e-Health and Bioengineering - EHB 2022 from 17th to 19th of November 2022 in Iasi, Romania in form of a presentation with the title "Short Review of the Use of Brain Morphometry in Gait Impairments Analysis in Parkinson's Disease". My conference proceeding was published in the Conference Book indexed at IEEE [p4].

Several results of the gait study were presented at the conference ESMAC (Annual Meeting of the European Society for Movement Analysis in Adults and Children) from 18th to 23rd of September 2023 in Athens, Greece. My main contribution was an oral presentation with the title "The effect of morphometric brain changes on gait-cognitive impairment of patients with Parkinson's disease" for which I was the main author [p5]. Additionally, I was co-author of two poster presentations with the title "Comparison of spatio-temporal parameters between total gait and steady gait" [p6] and "The effects of cognitive impairment on gait in Parkinson's disease" [p7] for which I acted as co-author. The abstracts of the contributions were published in a special issue of the journal "Gait & Posture"

Next to the publications which were connected to my main topic of dissertation, I supported the publication of a review article dealing with sensors for lower limb Exoskeletons in the journal "Sensors" [p8].

An article about striatal connectivity on which I co-worked is still in review [p9].

In summary I authored or co-authored five journal publications and four conference proceedings and successfully represented FBMI, ČVUT at two international conferences.

7.3 Additional activities and achievements during PhD studies

Next to my scientific contributions, I was actively involved in teaching and students training. I taught the following subjects:

Courses fully taught by me	**Study Program***
Programming in Matlab I	BMT CZ + Eng
Programming in Matlab II	BMT CZ + Eng
Applied Health Informatics	IKZ
Health information sources	IKZ
Basics in Programming and Algorithmisation	BMT Eng
Biological Signals (Workshops)	IKZ + BMT Eng
Seminar to Bachelor Thesis	IKZ
Information Systems in Healthcare (Workshops)	FYT + LDZ
Presentation tools and skills	IKZ
Courses partly taught by me	
Communication technology	BMT CZ+Eng
Information Technology	RA
Virtual Reality and Telemedicine	IKZ
Medical Picture Processing	BMI CZ
Biology (Workshop)	BMT CZ

*IKZ - Informatika a kybernetika ve zdravotnictví; BMT - Biomedicínská technika; LDZ - Laboratorní diagnostika ve zdravotnictví; FYT – Fyzioterapie; RA - Radiologická asistence; BMI - Biomedicínské inženýrství

In the context of teaching the subject Applied Health Informatics, I applied and received a grant under the Projects funding of PPSR 2023 for the project „Expansion of lecture and exercise materials in the field of gerontology/gerontotechnology" for the purchase of an age simulating suit and glasses simulating age-related eye diseases. The suit and glasses since purchase were actively used in teaching of several subjects and propagation activities.

From winter semester 2021/2022 on, I supervised in total 19 students projects within the mandatory subjects Project 1 to 5 for students of the program IKZ, Semester Project 1 for program BMT and yearly project 1 in program BMKI.

Currently I`m supervisor of six Bachelor thesis:

Bachelor program Informatics and Cybernetics in Healthcare, Faculty of Biomedical Engineering, Czech Technical University, Prague

1. Creation of an automatic report in R for the evaluation of DEMAT test results
2. Creation of a training program for evaluating CTG curves for medical professionals
3. Expansion and modification of the application for planning of services of eye-clinic doctors
4. Digitalization of birth documentation

Bachelor program Biomedical Technology, Faculty of Biomedical Engineering, Czech Technical University, Prague

5. Correlation of neuroimaging and sensory parameters in patients with REM Sleep Behavior Disorder (BMT, FBMI, CTU)

Bachelor program Molecular Biology and Biochemistry of Organisms, Faculty of Natural Sciences, Charles University Prague

6. Pathophysiology of Decompression illness and its effects on nervous system

To be best prepared for supervising also neurodivergent students and so with offer as many as possible students an individual supervision of their projects and thesis, I voluntarily attended several courses coping with the topic of supervising students with ADHD and Autismus Sectrum Disorder offered by ELSA (Centre for students with special needs).

I regularly participate in propagation activities of the faculty as e.g. science night, day of open doors or presentation of the faculty to school classes. From winter semester 2023/2024 I organize and supervise the presentation of the study programs IKZ and BMKI at the days of open doors.

I`m honored to have received the Stanislav Hanzl price in November 2023, rewarding students for their excellent performance as well as scientific, professional and other significant activities.

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List of Abbreviations

ADL	Activity of daily life
CAT	Computed Anatomy Toolbox
CDT	Clock Drawing Test
CNS	Central Nervous System
CSF	Cerebro-Spinal Fluid
CT	Computed Tomography
DBM	Deformation Based Morphometry
DBS	Deep Brain Stimulation
DICOM	Digital Communication in Medicine
DLB	Dementia with Lewy Bodies
DT	Dual Task
DTC	Dual Task Cost
EEG	Electroencephalogram
FD	Fractal Dimension
FWE	Family Wise Error
FWHM	Full Width Half Maximum
GM	Gray Matter
GPT	Grooved Pegboard Test
HC	Healthy controls
iDTC	impaired Dual Task Cost
iRBD	idiopathic REM sleep behavior disorder
LNS	Letter Number Sequencing
MBT	Memory Binding Test
MCI	Mild Cognitive Impairment
MIST	Memory for Intentions Screening Test
MMSE	Mini Mental State Examination
MoCa	Montreal Cognitive Assessment
MR	Magnetic Resonance
MSA	Multiple System Atrophy
nDTC	normal Dual Task Cost
NM	Neuromelanin
PD	Parkinson`s Disease
PIGD	posture instability gait difficulty
PSG	Polysomnogram
PST	Prague Stroop Test
RAVLT	Ray Auditory Verbal Learning Test
REM	Rapid-Eye-Movement
ROI	Region of Interest
RSWA	REM Sleep Without Atonia
SBM	Surface Based Morphometry
SD	Standard deviation
SDMT	Symbol Digits Modalities Test
SN	Substantia Nigra
SNpc	Substantia Nigra pars compacta
SPM	Statistical Parametric Mapping
ST	Single Task
TIV	Total Intracranial Volume
TMT-A	Trail Making Test Version A
TMT-B	Trail Making Test Version B
TUG	Timed-Up-And-Go
UPDRS	Unified Parkinson Disease Rating Scale
VBM	Voxel Based Morphometry
VF	Verbal Fluency
WM	White Matter

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Appendix A

A1. Factor loadings for PCA

Table A. 1: Principal components analysis: factor loadings of 28 neuropsychological test scores on six components

	AM	MS/E	EM	PS	L	VisF
MBT (Total Cued Recall)	**0.92**	-0.16	0.16	-0.01	0.13	0.11
MBT (Paired Recall Pairs)	**0.92**	-0.14	0.21	0.00	0.10	0.09
MBT (Total Delayed Paired Recall)	**0.94**	-0.09	0.16	-0.03	0.12	0.05
MBT (Delayed Paired Recall Pairs)	**0.95**	-0.07	0.14	-0.03	0.08	0.04
MBT (Total Free Recall)	**0.70**	-0.09	0.18	0.01	0.31	0.09
MBT (Total Delayed Free Recall)	**0.59**	0.01	0.25	-0.04	0.38	0.12
RAVLT (Trial 6)	0.03	**-0.44**	0.39	-0.05	0.36	0.01
SDMT (total score)	0.18	**-0.63**	0.25	0.04	0.17	**0.42**
PST (Dots)	-0.14	**0.72**	-0.05	0.22	-0.11	-0.22
PST (Interference)	-0.19	**0.46**	-0.31	0.18	-0.14	**-0.46**
PST (Words)	-0.02	**0.77**	-0.04	0.01	-0.13	0.19
TMT-A (total time)	-0.08	**0.57**	-0.11	0.33	0.10	-0.03
TMT-B (total time)	-0.11	**0.52**	-0.15	0.21	-0.16	**-0.43**
RAVLT (Total recall 1-5)	0.24	-0.15	**0.81**	-0.12	0.22	0.11
RAVLT (delayed recall)	0.30	-0.11	**0.78**	-0.11	0.18	0.10
RAVLT (Recognition)	0.34	0.04	**0.72**	-0.22	0.04	0.02
LNS (total score)	0.07	-0.39	**0.59**	0.02	0.01	0.14
GPT (left hand)	0.01	0.10	-0.11	**0.83**	-0.04	-0.20
GPT (right hand)	0.05	0.21	-0.05	**0.85**	-0.02	-0.15
MIST (time-based)	0.20	-0.18	0.36	**-0.58**	0.01	-0.01

VF (latter K)	0.26	-0.30	-0.08	-0.12	**0.55**	-0.08
VF (Action Verb)	0.25	-0.08	0.06	0.21	**0.58**	0.19
VF (Vegetables)	0.16	0.13	0.24	-0.16	**0.74**	0.01
VF (Animals/Clothes)	0.17	-0.38	0.17	0.01	**0.61**	0.19
CDT (total score)	0.00	-0.17	0.08	-0.13	0.26	**0.66**
MoCA (cube)	0.10	0.08	0.01	-0.07	-0.07	**0.71**
MIST (event-based)	0.18	-0.23	0.21	0.25	-0.07	0.24
PST (Colours)	-0.29	0.25	-0.13	0.22	-0.08	-0.36
Proportion Explained	0.28	0.18	0.17	0.13	0.13	0.11

Note: AM = Associative memory; MS/E = Mental speed/Executive functions; EM = Episodic memory; PS = Psychomotor speed; L= Language; VisF = Visuospatial functions

A2. VBM additional data and detailed overviews to goal 2

Table A. 2: Detailed information about significant clusters in VBM correlation analysis for HC, iRBD and PD

	Peak Localisation [mm mm mm]	**Anatomical region (cluster, aal atlas)**
HC vs. RAVLT 1-5	2/38/-6	Left hemisphere: Cingulum Anterior, Olfactory Lobe, Frontal Middle Orb., Caudate Right Hemisphere: Cingulum Anterior, Frontal middle orb. lobe
HC vs. RAVLT Recognition	-45/11/0	Left hemisphere: Putamen, Insula, Frontal inferior orper., Rolandic oper., Temporal superior lobe
HC vs. MBT (Total Delayed Recall)	-2/36/-6	Left hemisphere: Cingulum anterior, Olfactory Lobe, Frontal mid. orb. lobe Right Hemisphere: Cingulum anterior, Frontal mid. Orb. Lobe, Olfactory Lobe, Frontal sup. orb. lobe
HC vs. MIST event based	14/-51/-54	L+R Cerebellum
HC vs. Stroop words	-6/-53/-63	Vermis L+R Cerebellum
HC vs. mental speed/ executive functions	3/-21/-2	Vermis Left hemisphere: Thalamus Right hemisphere: Thalamus, lingual gyrus, Cerebellum
iRBD vs. TMT-A cluster 1	35/-3/-8	Right hemisphere: Putamen, Insula, Temporal Superior Lobe, Pallidum, Caudate, Amygdala
iRBD vs. TMT-A cluster 2	-24/-50/-14	Left hemisphere: Cerebellum, Fusiform, Lingual Gyrus
iRBD vs. TMT-B	-32/-5/-15	Left hemisphere: Amygdala, Hippocampus, Parahippocampal Gyrus, Fusiform Gyrus
iRBD vs. GPT right hand	-32/-71/38	Left Hemisphere: Occipital Middle and Superior Lobe, Parietal Superior and Inferior Lobe
iRBD vs. RAVLT 1-5 cluster 1	-47/-24/42	Left hemisphere: Postcentral Gyrus, Parietal Inferior Lobe, Precentral Gyrus, Supra Marginal Gyrus

	Peak Localisation [mm mm mm]	**Anatomical region (cluster, aal atlas)**
iRBD vs. RAVLT 1-5 cluster 2	38/-6/-12	Right hemisphere: Rolandic Operculum, Insula, Temporal Superior, Heschl, Hippocampus
iRBD vs. Psychomotor speed (PCA component)	-9/-59/-11	Vermis Left hemisphere: Cerebellum, Lingual Gyrus Right hemispere: Cerebellum
PD vs. GPT right hand	6/-41/56	Right hemispere: Precuneus, Cingulum, Paracentral Lobe, Supp. Motor Area, Postcentral Gyrus
PD vs. TMTB	-6/-38/34	Left + right hemisphere: Posterior + Mid. cingulum, Precuneus

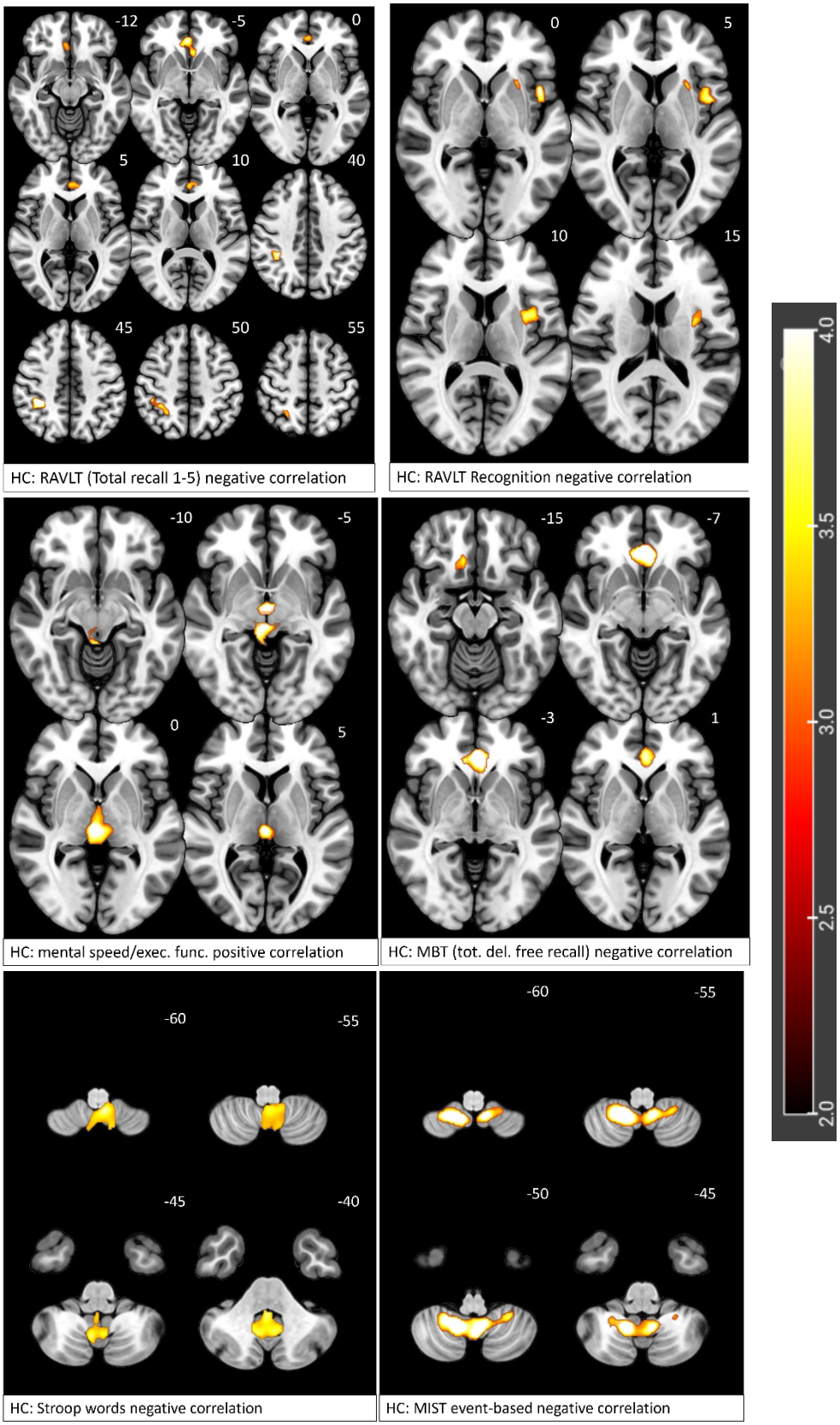

Figure A. 1: Correlation between cognitive performance and brain morphology in HC, analyzed with VBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right).

A3. SBM additional data and detailed overviews to goal 2

Table A. 3: Detailed information about significant clusters in SBM correlation analysis for HC and iRBD

	Peak Localisation [mm mm mm]	**Anatomical region (cluster, DK40 atlas)**
iRBD		
Cortical thickness VF vegetables	3/-75/28	Right hemisphere: cuneus
Gyrification LNS	-34/-16/46	Left hemisphere: precentral gyrus
Gyrification TMTB	39/-46/48	Right hemisphere: inferiorparietal lobe
Complexity MBT (Paired Recall Pairs)	33/-24/19	Right hemisphere: supramarginal gyrus
Complexity MBT (Total Cued Recall)	33/-25/19	Right hemisphere: supramarginal gyrus
Complexity MBT (Total Delayed Paired Recall)	46/-23/12	Right hemisphere: supramarginal gyrus
Complexity MBT (Total Free Recall)	43/-29/12	Right hemisphere: supramarginal gyrus
Complexity Mental speed/executive functions	-34/13/-9	Left hemisphere: insula
HC		
Cortical thickness Stroop words	-25/-72/-5	Left hemisphere: lingual gyrus

	Peak Localisation [mm mm mm]	**Anatomical region (cluster, DK40 atlas)**
Gyrification MBT (Total Cued Recall)	35/-78/19	Right hemisphere: superior-parietal lobe
Gyrification MBT (Paired Recall Pairs)	35/-78/19	Right hemisphere: superior-parietal lobe
Sulcus Depth MoCa	-36/-67/48	Left hemisphere: inferior-parietal lobe
Sulcus Depth SDMT	-36/-4/14	Right hemisphere: rostral-middlefrontal lobe
Sulcus Depth Stroop words	41/-55/51	Right hemisphere: inferior-parietal lobe
Sulcus Depth Stroop colour	-1/-87/-3	Left hemisphere: pericalcarine gyrus
Sulcus Depth Mental speed/executive functions	41/-56/53	Right hemisphere: inferior-parietal lobe
Sulcus Depth Episodic memory	11/-20/40	Right hemisphere: paracentral gyrus

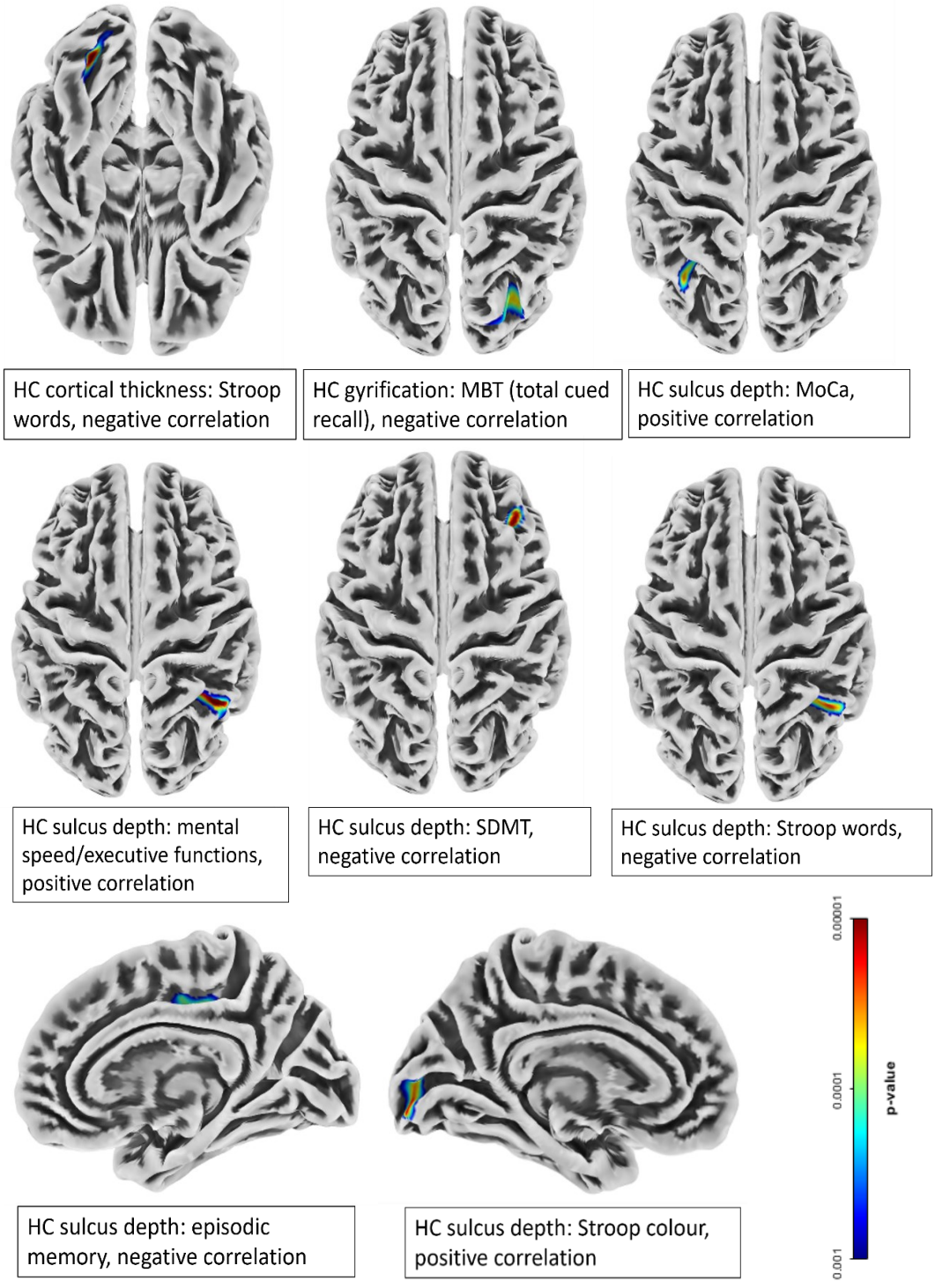

Figure A. 3: Results of Surface-based-morphometry for correlation analysis between cognitive performance and surface brain morphology in HC