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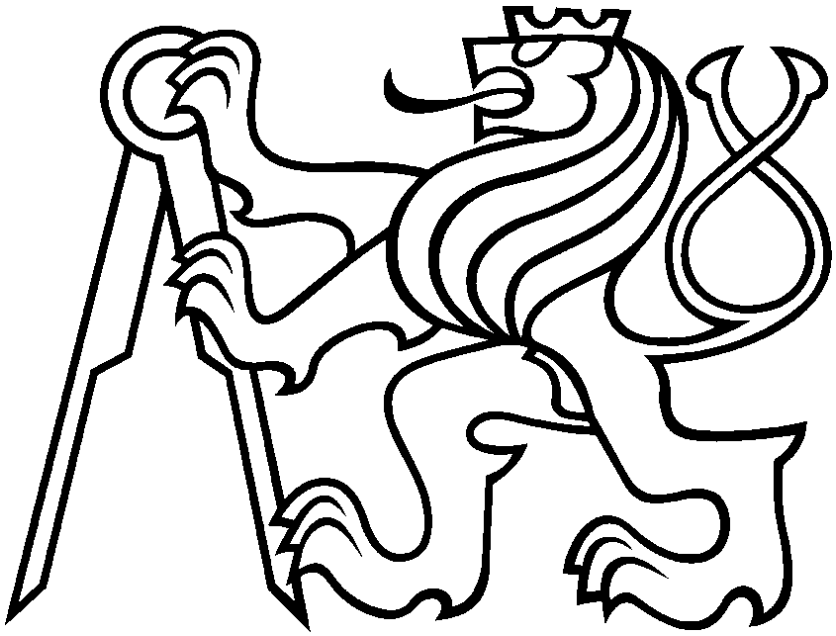

Doctoral Thesis Statement

Czech Technical University in Prague
Faculty of Biomedical Engineering
Department of Biomedical Informatics

Christiane Malá

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

Ph.D. Program: Biomedical and Clinical Technology
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The work was produced in a combined Ph.D. study at the Department of Biomedical Informatics of the Faculty of Biomedical Engineering of the CTU in Prague.

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Inhalt

1. Introduction 1
2. State of the art 2
2.1 Rapid Eye Movement Sleep Behaviour Disorder 2
2.1 Parkinson disease 3
2.2.1 Symptoms and epidemiology 3
2.2.2 Pathophysiology of Parkinson disease 3
2.6 Image Processing and data analysis 5
2.6.1 Voxel Based Morphometry (VBM) 5
2.6.2 Deformation Based Morphometry (DBM) 5
2.6.3 Surface Based Morphometry (SBM) 5
3. Aim of the thesis 6
4. Methods 7
4.1 Cognitive and Motor tests 7
4.2 Processing of the results of cognitive and motor data 9
4.3 Image pre-processing 9
4.4 Voxel Based Morphometry, Deformation Based Morphometry and Surface Based Morphometry 10
4.6 Statistical processing of data 10
5. Results 11
5.1 Goal 1: Definition of a preprocessing pipeline for MR image analysis 11
5.1.1 Processing pipeline for detection of neuromelanin in substantia nigra 11
5.1.2 Processing pipeline for VBM, DBM and SBM 12
5.2 Goal 2: Correlation of brain morphology with cognitive test performance in PD and iRBD patients 13
5.2.1 Subjects 13
5.2.2 Correlation of cognitive tests with brain morphology 13
5.3 Goal 3: The influence of impaired DTC on the correlation of brain morphology and Dual task cost parameters in PD 19
5.3.1 Subjects and division into subgroups 19
5.3.2 Morphological brain analysis 20
6 Discussion 22
7 Thesis achievements 25
7.1 Scientific summary of results of the study 25
7.2 Project funding, publications, conferences 26
7.3 Additional activities and achievements during PhD studies 27

Publications of author 28
References 29
Summary 33
Resumé 34

1. Introduction

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]. 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.

2. State of the art

To fully understand all aspects of this work, this chapter will give a basic overview of indispensable knowledge about the background of PD and RBD, standard cognitive testing and medical image-analysis.

2.1 Rapid Eye Movement Sleep Behaviour Disorder

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 [5]. 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 [6] . 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.

The minimal diagnostic criteria for RBD proposed by the International Classification of Sleep Disorders (ICSD)-242 are the following [7]:

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 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. 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. [8]

2.1 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.

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].

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

- Bradykinesia
- Tremor
- Rigidy
- Postural deformities, instabilities and freezing

Additionally, the following non-motor symptoms can be observed in patients with PD [9]:

- Mental health problems
- Falls and potential fractures
- Sleep disturbance
- Autonomic disturbance
- Pain

The highest risk factor for development of PD is age. Parkinson Disease is rare in people younger than 50 years [10].

2.2.2 Pathophysiology of Parkinson disease

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. [10]

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. [11]

Motor control is a complex process which involves several brain regions and different neurotransmitters (Fig. 2.1). 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.

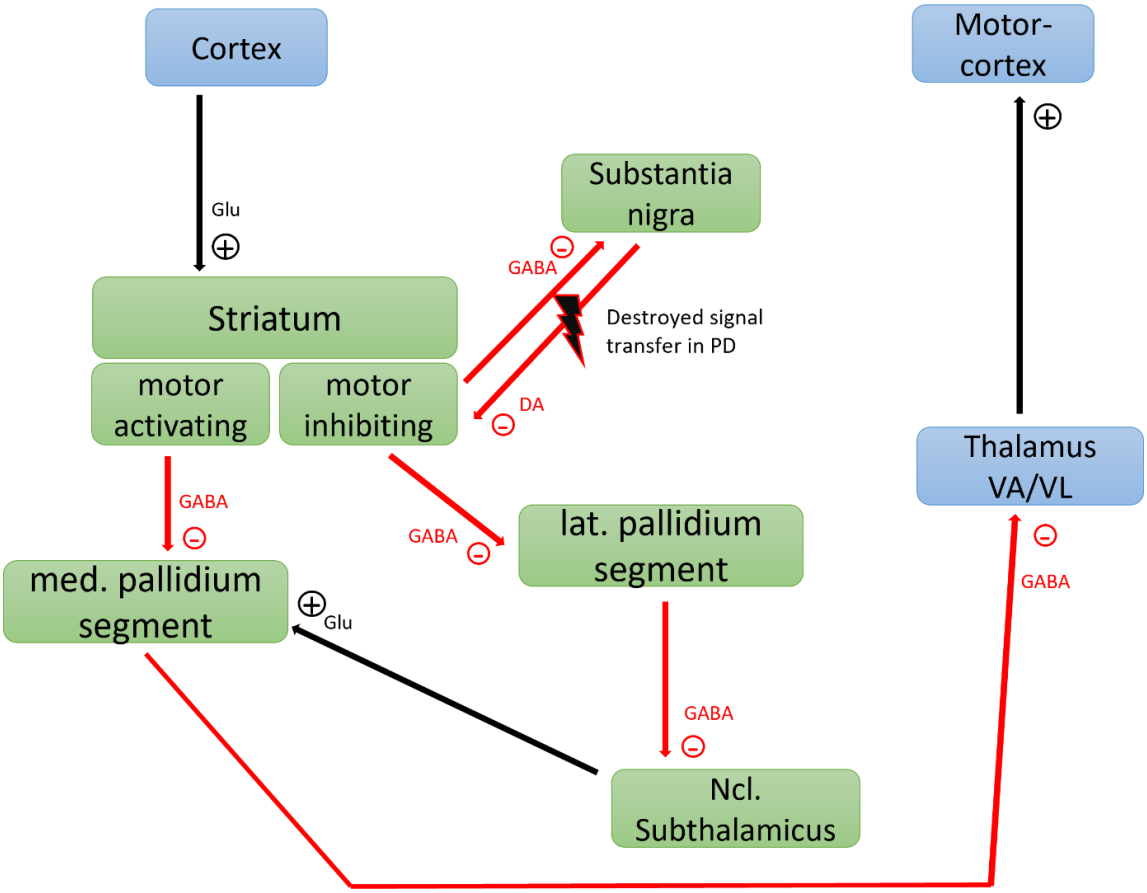

Figure 2.1: Motor regulating circuits in brain with inhibiting (-) and activating (+) pathways and responsible neurotransmitters. DA-Dopamin, GABA – gamma amino buteryc acid, GLU – Glutamat, green: parts of basal ganglia, blue: regions outside basalganlia interacting with basalganlia

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. Several clearly defined preprocessing steps including segmentation, spatially normalization and smoothing are necessary to perform VBM. 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.

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. Technically it is done by mapping the subject's brain to a standard template brain by three-dimensional nonlinear normalization routines. 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. The derivates of the deformation fields – called Jacobian determinant- are used for statistical analysis. [12]

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.

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.

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	• Letter-Number-Sequencing • Trail-Making-Test Version A
executive functions	• Prague Stroop Test (colors) • Prague Stroop Test (interference) • Trail-Making-Test Version B • Verbal Fluency (animals/clothes)
language	• Verbal Fluency (K) • Verbal Fluency (action verb) • Verbal Fluency (vegetables)
episodic memory	• Ray-Auditory-Verbal-Learning Test (Total recall 1-5) • Ray-Auditory-Verbal-Learning Test (Trial 6) • Ray-Auditory-Verbal-Learning Test (delayed recall) • Ray-Auditory-Verbal-Learning Test (recognition) • Memory-for-Intensions-Screening Test (event-based) • Memory-for-Intensions-Screening Test (time-based) • Memory Binding Test (Total Cued Recall) • Memory Binding Test (Paired Recall Pairs) • Memory Binding Test (Total Delayed Paired Recall) • Memory Binding Test (Delayed Paired Recall Pairs) • Memory Binding Test (Total Free Recall) • Memory Binding Test (Total Delayed Free Recall)
visuospatial functions	• Clock Drawing Test • Montreal Cognitive Assessment (cube)
speed of processing/psychomotor speed	• Grooved Pegboard Test (left hand) • Grooved Pegboard Test (right hand) • SDMT • Prague Stroop Test (Dots) • Prague Stroop Test (Words)

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 (picture 4.1).

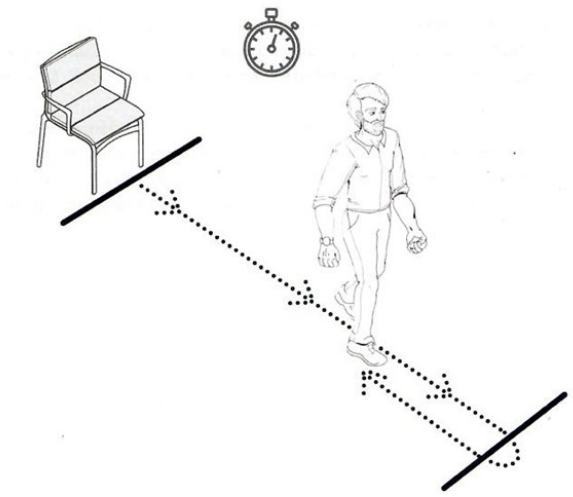

Figure 4.1: Scheme of TUG test

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.

The total MoCa score and MDS-UPDRS-III value was determined using the standard protocols [13, 14].

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).

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.

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):

$$DTC = \frac{DTvalue - STvalue}{STvalue} \quad \text{(E4.1)}$$

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 segmentation was done by Hammers atlas [15] as this atlas provides the most suitable division of brain regions for our purpose.

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.

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 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).

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).

4.6 Statistical processing of data

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 [16] 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".

5.2Goal 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. [17].

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 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 5.1 depicts the significant clusters in PD, Figure 5.2 results for iRBD.

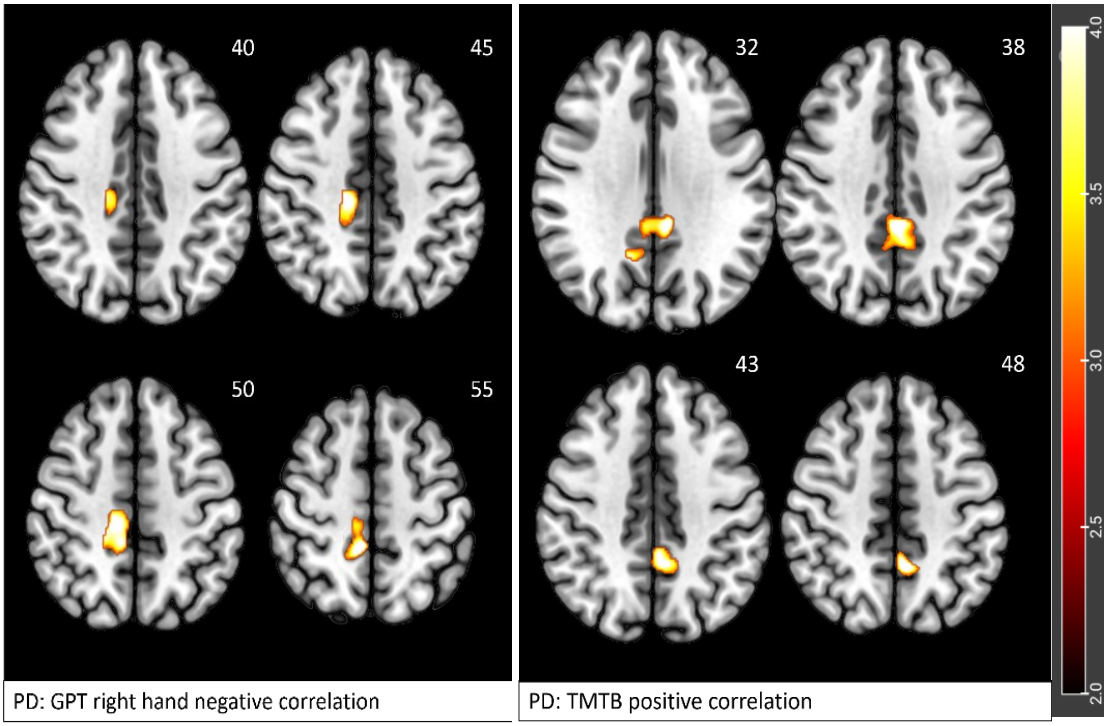

Figure 5.1: Correlation between cognitive performance and brain morphology in PD, analyzed with VBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right).

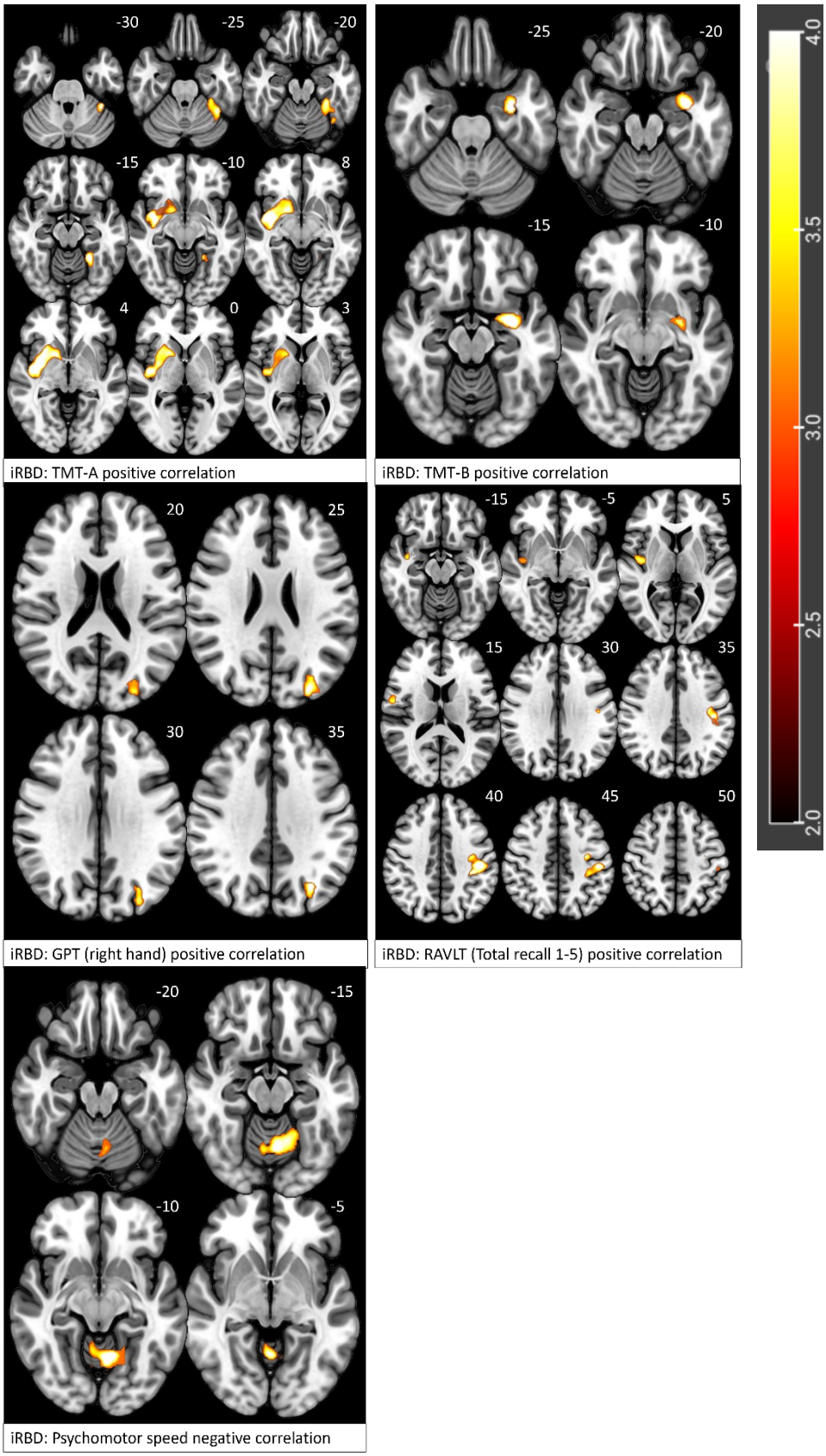

Figure 5.2: Correlation between cognitive performance and brain morphology in iRBD, analyzed with VBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic 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 5.2.

Table 5.2: 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	-0.033	0.852
	Right Insula*	0.366	0.003	-0.123	0.482
	Right Nucleus Accumbens*	0.364	0.003	0.012	0.943
	Left Nucleus Accumbens*	0.364	0.004	-0.062	0.725
	Left Putamen*	0.365	0.004	-0.074	0.671
	Left Precentral Gyrus*	0.330	0.009	-0.176	0.311
	Left Insula*	0.311	0.014	-0.130	0.456
GPT (left hand)					
	Right Insula*	0.434	<0.001	-0.174	0.318
GPT (right hand)					
	Right Insula*	0.314	0.013	-0.265	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	-0.262	0.128
	Right Insula*	0.402	0.001	-0.272	0.115
	Left Brainstem*	0.354	0.002	-0.279	0.105
	Right Superior Parietal Gyrus	0.376	0.003	-0.369	0.029
	Right Brainstem*	0.373	0.003	-0.249	0.149
	Right Nucleus Accumbens	0.357	0.004	-0.480	0.004
	Right Precentral Gyrus	0.362	0.004	-0.541	0.001
	Left Insula*	0.352	0.005	-0.274	0.112
	Left Nucleus Caudate*	0.354	0.005	-0.254	0.141
	Right Nucleus Caudate*	0.348	0.006	-0.230	0.184
	Left Inferior Lateral Parietal Lobe	0.343	0.006	-0.345	0.043

		iRBD		HC	
		r	*p*	*r*	*p*
	Left Precentral Gyrus	0.335	0.008	-0.348	0.040
	Right Posterior Temporal Lobe*	0.328	0.009	-0.219	0.206
	Right Cuneus*	0.327	0.010	0.199	0.253
	Left Postcentral Gyrus	0.327	0.010	-0.552	0.001
	Right Lingual Gyrus*	0.322	0.011	0.149	0.349
	Right Inferior Lateral Parietal Lobe*	0.307	0.015	-0.237	0.170
	Right Fusiform Gyrus*	0.295	0.020	-0.064	0.717
	Left Posterior Temporal Lobe*	0.293	0.021	-0.198	0.255
	Left Superior Parietal Gyrus*	0.274	0.031	-0.140	0.424
Psychomotor speed (PCA component)					
	Left Cerebellum*	-0.390	0.002	-0.043	0.804
	Left Anterior Temporal Lobe, Med. Part*	-0.360	0.004	-0.101	0.562
	Left Insula*	-0.310	0.014	0.104	0.551

* Significant correlation in iRBD but not in HC

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.

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. 5.3).

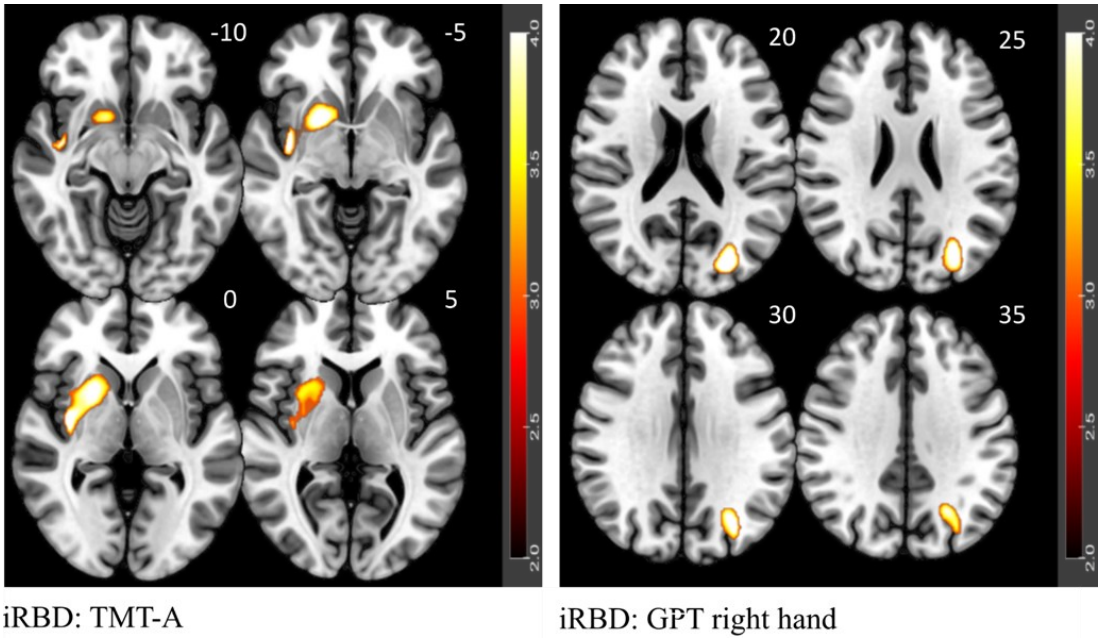

Figure 5.3: Correlation between cognitive performance and brain morphology analyzed with DBM, Highlighted significant clusters thresholded at p <0.05 at cluster level, corrected for family wise error. Color scale represents decimal logarithm of p-level. Z-coordinates in the Montreal Neurologic Institute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

Surface-based-morphometry

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.

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].

5.3Goal 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 5.3). Patients with a cognitive impairment (defined by MoCa < 24) were excluded.

Table 5.3: 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 5.4.

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

Table 5.4: 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 ($p < 0.014$).

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 5.4. 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 5.5. 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.

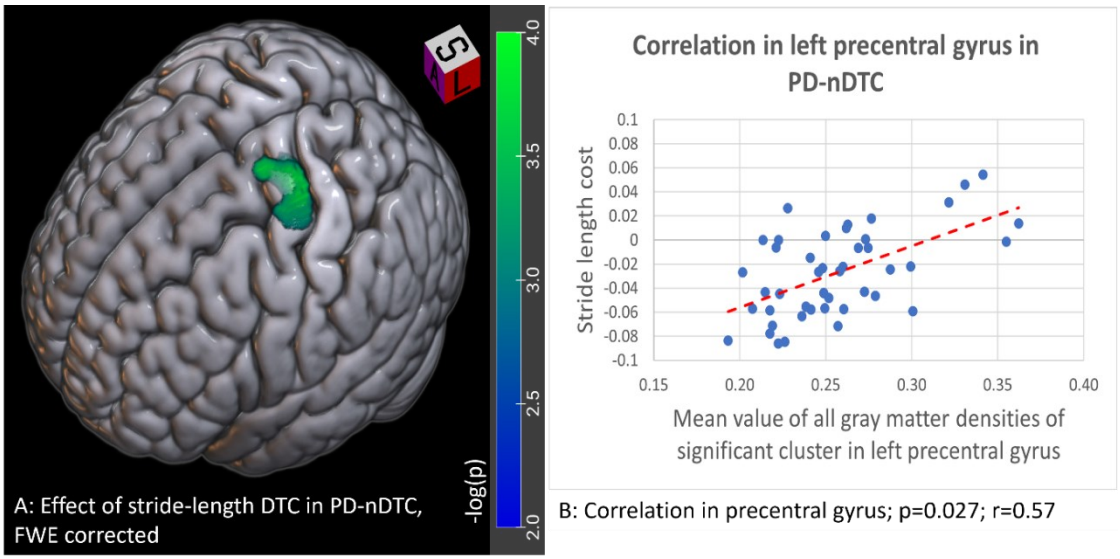

Figure 5.4: Results of correlation analysis of brain morphometry with dual task cost of gait parameters for Parkinson`s disease patients with normal DTC. A: Significant cluster in left precentral gyrus for a positive correlation with stride length cost in PD-nDTC, p=0.027. B: Correlation of gray matter density with stride length cost values within the cluster in left precentral gyrus..

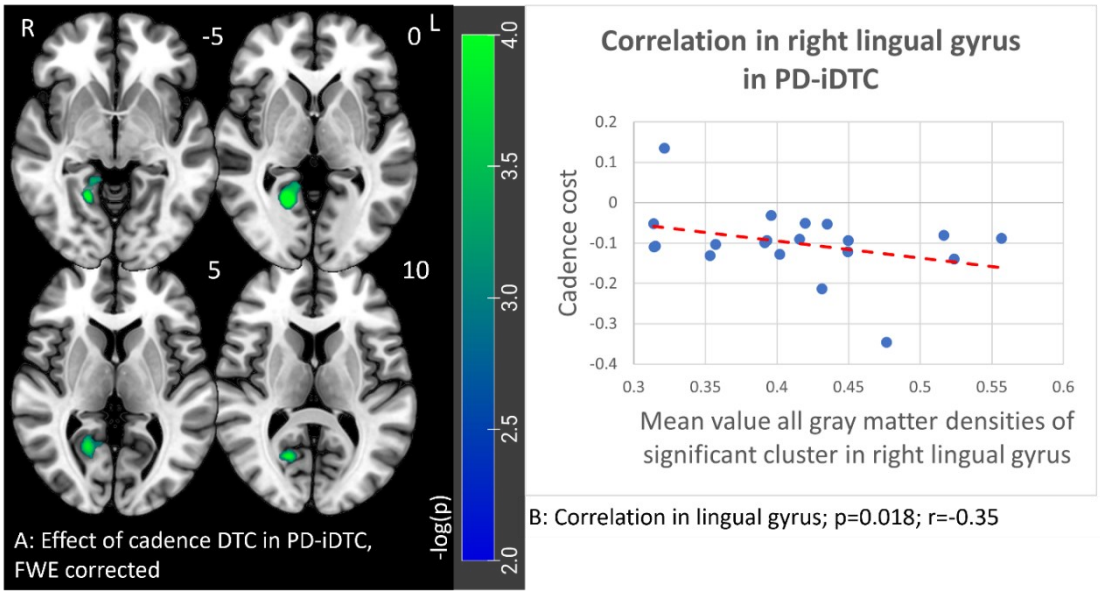

Figure 5.5: Results of correlation analysis of brain morphometry with dual task cost of gait parameters for Parkinson`s disease patients with impaired DTC. A: Significant cluster in right lingual gyrus for a negative correlation with cadence cost in PD-iDTC, p = 0.018. Z-coordinates in the Montreal Neurologic Institute space (in millimeters) are indicated next to each slice (top right) B: Correlation of gray matter density with cadence cost values within the cluster in right lingual gyrus.

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 [18–20]. 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 [20]. 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 [21, 22] the here presented results point predominantly to brain regions connected to memory deficits which are common in iRBD [21]. 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 [23]. Indeed, impaired visuospatial abilities in iRBD were shown to be connected with parietal regions in previous studies Pereira et al. [24] or Rahayel et al. [18]. 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 [21, 25]. For iRBD patients an association between verbal learning/memory and disruptions in temporal, occipital and insular regions was described previously [18, 22].

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 [26]. 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. [27], 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 [28].

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 [29] Regarding cadence cost our study differs from some previous published results in which PD patients showed also increased cadence [30, 31]. One explanation could be the association of this increase with longer disease duration [30] while our patients are in a relatively early disease stage. The increased dual task costs in gait parameters are consistent with previous research [32].

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 [33] 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. [33] 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 Thesis achievements

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 several different subjects for the Bachelor and Master study programs Biomedical Technology (English and Czech), Biomedical engineering, Informatics and Cybernetics in Healthcare and Physiotherapy:

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 student's 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, FBMI, CTU

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, FBMI, CTU

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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Summary

Parkinsons disease (PD) massively influences all day life of the patients and their families. Mainly known for its motor symptoms as bradykinesia, rigidity, tremor and freezing of gait the disease causes also non-motor symptoms as autonomic dysfunction, mental health problems and, later on, also cognitive deficits.

For early onset of treatment is it crucial to diagnose this neurodegenerative disease as early as possible. Several precursors, preceding motor-symptoms by years, were identified through intensive research in the last decades. One scientifically proven disease preceding diagnosis of Parkinson Disease is the idiopathic Rem-Sleep-Behavior-Disorder (iRBD). Patients suffering from this sleep disorder, characterized by the loss of REM-sleep muscle atonia, get diagnosed with a probability of up to 90% with a neurodegenerative disorder from the class of α-synucleopathies within 14 years.

The assessment of patients cognitive and motor abilities with the help of standardized tests is a relatively quick and low-cost possibility of diagnostic for neurodegeneration compared to difficult and high-cost medical imaging.

The aim of the thesis was to find possible connection between morphological changes in brains of patients with iRBD and PD with their cognitive and motor performance. Therefore, in a first step, a suitable picture processing pipeline was developed using T1 weighted MR brain images.

Voxel-based, deformation-based and surface-based morphometry analysis was conducted in the programs SPM12/CAT12 to find possible correlations between cognitive and motor performance and brain morphology.

The main findings are:

1. For iRBD the performance in cognitive tests TMTA, TMTB, GPT and RAVLT1-5 correlate with brain morphology.
2. For PD the performance in cognitive tests TMTB and GPT correlate with brain morphology.
3. Correlation analysis of gait parameters with brain morphology suggests an involvement of different brain regions in dual task performance in PD patients with normal Dual task cost and patients with increased Dual task cost.

The results of this study can help to detect morphological brain changes earlier and more cost effective than with MR brain scans and support other diagnostic steps. Additionally, it shows that cognitive performance in diagnostics of iRBD and PD is an important factor.

Resumé

Parkinsonova choroba (PD) masivně ovlivňuje každodenní život pacientů a jejich rodin. Nemoc je známá především svými motorickými příznaky, jako jsou bradykineze, rigidita, třes a strnulost chůze, ale způsobuje i nemotorické příznaky, jako jsou autonomní dysfunkce, psychické problémy a později i kognitivní deficity.

Pro včasné zahájení léčby je zásadní diagnostikovat toto neurodegenerativní onemocnění co nejdříve. V posledních desetiletích bylo díky intenzivnímu výzkumu identifikováno několik prekurzorů, které o několik let předcházejí motorickým příznakům. Jedním z vědecky prokázaných onemocnění předcházejících diagnóze Parkinsonovy nemoci je idiopatická porucha spánku a chování (iRBD). Pacienti trpící touto poruchou spánku, která je charakterizována ztrátou svalové atonie v REM-spánku, dostanou do 14 let s pravděpodobností až 90 % diagnózu neurodegenerativního onemocnění ze třídy α-synukleopatií.

Hodnocení kognitivních a motorických schopností pacientů pomocí standardizovaných testů je relativně rychlou a levnou možností diagnostiky neurodegenerace ve srovnání s náročným a nákladným lékařským zobrazováním.

Cílem práce bylo zjistit možnou souvislost mezi morfologickými změnami v mozku pacientů s iRBD a PD a jejich kognitivní a motorickou výkonností. Proto byla v prvním kroku vyvinuta vhodná sestava pro zpracování obrazu pomocí T1 vážených MR snímků mozku.

V programech SPM12/CAT12 byla provedena morfometrická analýza založená na voxelech, deformacích a povrchu s cílem nalézt možné korelace mezi kognitivní a motorickou výkonností a morfologií mozku.

Hlavní zjištění jsou následující:

1. U iRBD koreluje výkon v kognitivních testech TMTA, TMTB, GPT a RAVLT1-5 s morfologií mozku.
2. U PD koreluje výkon v kognitivních testech TMTB a GPT s morfologií mozku.
3. Korelační analýza parametrů chůze s morfologií mozku naznačuje zapojení různých oblastí mozku do výkonu duálních úkolů u pacientů s PD s normálními náklady na duální úkoly a u pacientů se zvýšenými náklady na duální úkoly.

Výsledky této studie mohou pomoci odhalit morfologické změny mozku dříve a nákladově efektivněji než pomocí MR mozku a podpořit další diagnostické kroky. Navíc ukazuje, že kognitivní výkonnost je v diagnostice iRBD a PD důležitým faktorem.