Diploma thesis

Functional connectivity and memory in Parkinson's disease

submitted by

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Declaration

Hereby I declare, that I have written this diploma thesis fully on my own without any assistance of third parties. Additionally, I confirm that no other sources have been used in formation of the thesis, than those indicated in the thesis itself.

Graz, 12.06.2019 *Judith Pichler eh*

Acknowledgement

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Abstract

Background and Objectives: Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Clinical presentations vary from slight motor impairment to akinesia, progressive neuropsychiatric disorders and cognitive decline. Resting state functional imaging is a rapidly developing research area, and its usage in PD brings major advances, not only in the diagnostic process, but also for understanding the pathophysiology. The aim of this review is to present the current state of research concerning functional connectivity (especially resting state connectivity) alterations measured through functional magnetic resonance imaging (fMRI) in PD. A special focus is given on functional connectivity changes due to cognitive dysfunctions.

Methods: Literature search was conducted via PubMed, Cochrane library (CENTRAL), and Google Scholar in May 2018. Only studies in English language, published between 2008 and 2018, were included for further screening. Overall 44 manuscripts have been included in the review.

Results: The results show a high heterogeneity, due to different resting state approaches used to analyse FC alterations. Medication status and different subtypes of PD also lead to heterogeneous FC results. A variety of approaches was used in the selected manuscripts to examine resting state connectivity: *Seed-based approach*, *independent component analyses*, *principal component analyses*, *graph-based approaches*, *amplitude of low-frequency fluctuation approaches*, *voxel-mirrored homotopic connectivity approaches*, *regional homogeneity approaches* and *multivariate pattern analyses*. This variety of approaches is causative for the fact that comparability of individual studies is poor. The number of PD patients, examined in the selected studies, varies between 16 and 106 subjects. Principally, alterations in resting state connectivity were detected in cortico-striatal-thalamic networks, mostly ascribed to dopaminergic depletion. Considering cognitive decline, alterations were reported within the default mode network, dorsal attention network, fronto-parietal network and ventral attention network, among many other divergent changes.

Discussion and Conclusion: Even if the comparability of studies concerning resting state fMRI data is poor, future studies can lead to a better understanding of the ongoing processes within the brain in PD patients.

Zusammenfassung

Einleitung und Ziele: Die Parkinson-Krankheit ist die zweithäufigste neurodegenerative Erkrankung nach der Alzheimer-Krankheit. In den letzten Jahren wurden große Fortschritte im Bereich der funktionellen Bildgebung in Bezug auf das Erkennen intrazerebraler funktioneller Veränderung bei Parkinsonerkrankten gemacht. Zusätzlich helfen die durch fMRI gewonnenen Erkenntnisse, die zugrundeliegende Pathophysiologie bei der Parkinsonkrankheit besser zu verstehen. Dieses Verständnis kann für die Entwicklung neuer Therapieansätze genutzt werden. Das Ziel dieser Literaturarbeit ist, die neuesten Forschungsergebnisse im Feld der funktionellen Bildgebung, vor allem der *„resting-state“* Bildgebung, bei Parkinsonerkrankten, mit besonderem Augenmerk auf funktionelle Veränderung bei kognitivem Abbau, aufzuzeigen.

Methoden: Für diesen Review wurde die Methode der Literatursuche gewählt. Nach Studien wurde über PubMed, Cochrane library (CENTRAL) und Google Scholar im Mai 2018 gesucht. Nur Studien in englischer Sprache, die zwischen 2008 und 2018 publiziert wurden, wurden für den Review verwendet. Insgesamt wurden 44 Studien analysiert.

Ergebnisse: Die Resultate sind heterogen. Dies ist vor allem den unterschiedlichen Analysemethoden zuzuschreiben. Weiters beeinflussen sowohl der Parkinson-Subtyp, als auch der Medikationsstatus die funktionellen Verknüpfungen im Gehirn und tragen somit auch zur Heterogenität der Studienergebnisse bei. In den analysierten Studien wurden folgende resting-state-Analysemethoden verwendet: *independent component analysis*, *principal component analysis*, seed-based-, *graph-based-*, *amplitude of low-frequency fluctuation-, voxel-mirrored homotopic connectivity-, regional homogeneity-* und *multivariate pattern Methode*. Die Fallzahlen der untersuchten Parkinsonpatientinnen/-patienten variierten zwischen 16 und 106. Grundsätzlich wurden Veränderungen in kortikal-striatal-thalamischen Netzwerken gefunden, die sowohl für Bewegungsstörungen, als auch für nicht motorische Störungen verantwortlich sind. Weitere Veränderungen wurden unter anderem im Default Mode Network, im dorsalen/ventralen Aufmerksamkeitsnetzwerk und im fronto-parietalen Netzwerk, die vor allem bei kognitiven Aufgaben involviert sind, gefunden.

Schlussfolgerungen: Trotz der großen Heterogenität der Studienergebnisse, stellen die *resting-state-connectivity* Analysen eine neue Möglichkeit dar, die funktionellen Vorgänge, die sich bei dieser Krankheit innerhalb des Gehirnes abspielen, besser zu verstehen und dieses Verständnis für die Entwicklung neuer Therapieansätze zu verwenden.

Contents

List of Abbreviations

ACC	Anterior cingulate cortex
ALFF	Amplitude of low-frequency fluctuations
AR	Akinetic-rigid
ATL	Anterior temporal lobe
BGN	Basal ganglia network
BOLD	Blood-oxygenation-level-dependency
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
COMT-inhibitors	Catechol-O-methyltransferase inhibitors
DAN	Dorsal attention network
DBS	Deep-brain-stimulation
DLB	Dementia with Lewy Bodies
dlPFC	Dorsolateral prefrontal cortex
DN	Dentate nucleus
DT-MRI	Diffusion tensor magnetic resonance imaging
EC(M)	Eigenvector centrality (mapping)
EEG	Electroencephalography
ET	Essential tremor
FC	Functional connectivity
FCD(M)	Functional connectivity density (mapping)
fMRI	Functional magnetic resonance imaging
FOG	Freezing of gait
FPN	Fronto-parietal network
FSS	Fatigue severity scale
GABA	Gamma aminobutyric acid
GPe	External globus pallidus
GPi	Internal globus pallidus
HC	Healthy controls
H&Y scale	Hoehn & Yahr scale
ICA	Independent component analysis
ICN	Intrinsic connectivity network
IFG	Inferior frontal gyrus

IPC/L	Inferior parietal cortex/lobe
IPD	Idiopathic Parkinson’s disease
IRBD	Idiopathic rapid-eye-movement behaviour disorder
JCR	Journal citation reports
LB	Lewy Bodies
L-DOPA	Levodopa
LEDD	Levodopa equivalent daily dose
MAO-inhibitors	Monoamine oxidase inhibitors
MCC	Middle cingulate-cortex
MCI	Mild cognitive impairment
MDS-UPDRS	Movement Disorder Society - Unified Parkinson’s Disease Rating Scale
MEG	Magnetoencephalography
MER	Microelectrode recording
MeSH	Medical Subject Headings
MFG	Middle frontal gyrus
MMSE	Mini-mental state examination
MOCA	Montreal cognitive assessment
MPTP	Methyl-phenyl tetrahydropyridine
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
MSA-C	Multiple system atrophy – cerebellar type
MSA-P	Multiple system atrophy – parkinsonian type
MTL/G	Medial temporal lobe (gyrus)
MVPA	Multivariate pattern analysis
NFOGQ	New freezing of gait questionnaire
NMDA	N-methyl-D-aspartate
NMS	Non-motor-symptoms
NPH	Normal pressure hydrocephalus
NSAIDs	Non-steroidal anti-inflammatory drugs
NTD	Non-tremor-dominant
OFC	Orbitofrontal cortex
PCA	Principal component analysis
PCC	Posterior cingulate cortex

PD	Parkinson’s disease
PD-AR	Parkinson’s disease patients with akinetic-rigid subtype
PDD	Parkinson’s disease dementia
PD-(N)A	Parkinson’s disease patients with(out) apathy
PD-(N)CI	Parkinson’s disease patients with(out) cognitive impairment
PD-(N)F	Parkinson’s disease patients with(out) fatigue
PD-(N)FOG	Parkinson’s disease patients with(out) freezing of gait
PD-(N)H	Parkinson’s disease patients with(out) obvious hyposmia
PD-(N)MCI	Parkinson’s disease patients with(out) mild cognitive impairment
PD-(N)TD	Parkinson’s disease patients with (non) tremor dominant subtype
PD-OFF	Parkinson’s disease patients in OFF-medication-state
PD-ON	Parkinson’s disease patients in ON-medication-state
PE	Parameter estimates
PET	Positron emission tomography
PFC	Prefrontal cortex
PHG	Parahippocampal gyrus
PIGD	Postural instability/gait difficulty
PPC	Posterior parietal cortex
PSP	Progressive supranuclear palsy
ReHo	Regional homogeneity
REM	Rapid-eye-movement
ROI	Region of interest
RS	Resting state
RSC	Resting state connectivity
RS-fMRI	Resting state functional magnetic resonance imaging
RSN	Resting state network
RT	Reaction time
rTMS	Repetitive transcranial magnetic stimulation
SFG	Superior frontal gyrus
SMA	Supplementary motor area

SMN	Sensorimotor network
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticularis
SORT	Strength of recommendation taxonomy
SPC/G	Superior parietal cortex/gyrus
SPECT	Single-photon emission computed tomography
SPL	Superior parietal lobe
SSN	Scaled subprofile model
STN	Subthalamic nucleus
TD	Tremor-dominant
TOD	Threshold of olfactory detection
UPDRS	Unified Parkinson’s Disease Rating Scale
VMHC	Voxel-mirrored homotopic connectivity
VN	Visual network
VP	Vascular Parkinsonism
WCST	Wisconsin card sorting test
WD	Wilson disease

Descriptions

Akinesia: Absence or loss of the ability of motor function (voluntary muscle movement). In Parkinson's disease (PD) capriciousness movement is disturbed by inhibition of starting the movement due to akinesia (1-3).

ALFF (Amplitude of low-frequency fluctuations): Resting-state BOLD fluctuations are generally observed in the range between 0.01 and 0.08 Hz frequency. With ALFF this amplitude is calculated (4).

Ataxia: Failure or irregularity of muscular coordination (1-3).

Bradykinesia: Time from starting to finishing the movement is slower than normal. In contrast to hypokinesia, bradykinesia refers more to slowness than to lack of motion (1-3).

Cogwheel phenomenon: This phenomenon is a type of rigidity in which muscles respond with cogwheel-like jolts to the use of steady force in bending the limb (1-3).

DAN (dorsal attention network): DAN is also called the task-positive network and is therefore the anti-correlate to the default mode network (DMN). It consists of the caudal anterior cingulate gyrus, frontal eye fields, dorsolateral prefrontal areas, temporo-occipital junctions, and dorsal occipito-parietal regions (5).

DMN (default mode network): This network is activated when the individual is at wakeful rest. It consists of the posterior cingulate gyrus/precuneus, medial prefrontal region, angular gyrus, and middle/superior frontal gyrus (5).

ECM (Eigenvector centrality mapping): ECM is a special kind of a graph-based approach. To each voxel in the brain a value is attributed (6).

Encephalitis lethargica: atypical form of encephalitis, aka sleeping sickness, with uncertain causes. After the epidemic of encephalitis lethargica in the years after the First World War hardly any cases were reported. This encephalitis causes a parkinsonian like disease in patients (1,2,7-9).

Fatigue: Physical or mental exhaustion, due to different stimuli like stress, medication, illnesses or work (1-3).

FCDM (functional connectivity density mapping): This is an ultrafast method, which generates high resolution functional connectivity maps. It is based on the highly clustered structure of the brain (10).

Festination: A gait in which the patient's trunk and limbs are flexed and stiff and the steps are increasingly short and fast. Walking is reduced to a shuffle, in which the patient tries to avoid falling (1-3).

Hypokinesia: Reduction of spontaneous movement of an affected body part: poverty of movement (1-3).

Hypomimia: A lack of expressive mobility in the face. The face is like a mask. It occurs especially in patients with PD. Diminished animation and movement of the facial muscles are obvious (1-3).

Hypophonia/Microphonia: A weakness in voice due to coordination problems in the vocal muscles (1-3).

Hyposmia: Lack in sensitivity of smell, because of sensorineural disorders (1-3).

ICN (intrinsic connectivity networks): These cerebral functional networks are dynamically interrelated and play an essential role in cognitive processes. The default mode network, the dorsal attention network and the fronto-parietal networks are ICNs (5).

Idiopathic rapid-eye-movement (REM) sleep behaviour disorders (IRBD): IRBD is a primary sleeping-disorder in which patients talk, scream or fall out of bed, because of the loss of the physiological muscle tone (atonia) during REM sleep (1,2,7-9).

Mental rotation test: It is a test to check the ability of rotating mentally represented two-dimensional or three-dimensional compositions (9).

Micrographia: Small, tremulous and cramped handwriting (first noticed by Charcot) (1-3).

Mini-mental state examination (MMSE): Is a screening (max. 30 points), which is used to examine patients with mild to severe cognitive impairment (9).

Odd-man-out: A clinical test to examine cognitive impairment at an early stage. The patient gets to see pictures and must determine the odd one out. Patients, who are not able to accomplish the task, are in greater risk to develop dementia (9).

Paralysis/Palsy: Loss or impairment of motor function, through lesions in the neural or muscular mechanism (primary symptom of corticospinal tract lesions). Due to lesion patterns the clinical presentation may vary. In paralysis strength is also diminished (1,2,7-9).

Persistent homology analysis: This is a multiscale network modelling approach, which shows entire brain network alterations over different threshold values (11).

Pill roll tremor: Is a 4-per-second tremor of the thumb and fingers, which is seen when the hand is in the position of repose. The term "*tremor in the position of repose"* is more accurate than the more common term "*resting tremor*", because in complete relaxation the tremor abolishes (1,2,7-9).

Postural instability: Inability of the patient to keep in balance and not to fall (1-3).

ReHo (regional homogeneity): ReHo analysis states the probability of the time series of one voxel with the time series of the nearest neighbours. It focuses on short distance functional connectivity and gives no insight in the amplitude of the activity (12).

Right and left FPN: It is also stated as control network of the brain and consists of the inferior parietal lobule, the lateral prefrontal cortex, the insula and opercular region, as well as the precuneus (5).

Rigidity: Altered muscle tone, with continuously or intermittently firm and tense muscles. The resistance on passive movement is increased (1).

Seborrhoea: It is an *o*veractivity of the sebaceous glands which causes an oily appearance of the skin (9).

Sensory complaints: There is a wide variety of paraesthesia-like and other sensory complaints. These mainly affect the calves and the abdomen (1,2,7-9).

Shaking palsy: In 1817 James Parkinson was the first to describe Parkinson's disease. He termed it *shaking palsy*, because of the involuntary tremulous motion on the one hand and the loss of muscular power on the other hand. Years later it was renamed Parkinson's disease (1,2,7-9).

Strength of Recommendation Taxonomy (SORT): The aim of this taxonomy is to identify quality, quantity and consistency of evidence (13).

Stroop performance: This is a neuropsychological test, which measures the interference of the reaction time of a task. The patient has to read written colour names (e.g. red, green, blue). It is easier to read colour names, when the names are written in the colour they represent (e.g. green is written in a green colour) – the reaction time is short. In contrast to this, it is harder to read a colour name when the colour name is written in a different colour (e.g. red is written in a blue colour) – the reaction time is longer (9).

Vegetative disorders: These are abnormalities of the vegetative function such as increased sweating, constipation, seborrhoea, disturbance of the sexual function and many more (1,2,7-9).

VMHC (voxel-mirrored homotopic connectivity): Homotopic resting state functional connectivity is quantified between each voxel of one hemisphere through VMHC. Afterwards it is mirrored counterpart in the other hemisphere. This approach presumes symmetric morphology between hemispheres. As this assumption cannot be applied for the “real” human brain, images have to be transformed into models, which present two identical hemispheres, before VMHC can be calculated (14).

VN (visual network): The VN mainly consists of the retinotopic occipital cortex and the temporo-occipital regions, as measured with resting state fMRI (15).

Wisconsin card sorting test: This is a neuropsychological test in which participants have to sort cards (differing in colour, form and number of symbols), but are not told how to sort them. The examiner only gives feedback, if the matches are right or wrong (this criterion is only known to the examiner) (9).

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder associated with progressive impairment of motor functions, as well as with decrease in non-motor functions, such as cognitive deficits or depression. In the last years neuroimaging studies have shown PD related alterations of functional networks and have provided increased knowledge of structural and functional brain changes underlying PD. This review shall give an overview of the current state of research of connectivity changes measured with fMRI in PD patients compared to healthy populations, with the focus on changes of resting state networks. Furthermore, changes in networks and fluctuations in cognition will be compared. Limitations of studies, included in this thesis, are on the one hand the variety of analytical approaches exploring connectivity in resting state and on the other hand the different stages of the disease in which PD patients were examined, rendering a direct comparison of the results impossible. Additionally, the intake of medication (versus non-medicated PD-patients), especially L-DOPA, complicates the comparability of singular studies.

1.1 Basics of Parkinson's disease

1.1.1 Epidemiology, protective and risk factors

The median prevalence of PD in a population aged 65 or more is reported to be 9.5 per 1,000 inhabitants. The lifetime risk for individuals in the USA is estimated to be 2% for men, and 1.3% for women. A definite reason for sex differences remains to be uncovered. Possible hypotheses are higher numbers of traumatic brain injuries in men, higher toxic exposure than in women, neuroprotection by oestrogen in women or X-linkage of genetic risk factors. Thus, PD is the second most common neurodegenerative disease after Alzheimer's disease (16-18). There is a difference in prevalence in the northern hemisphere, where it is the highest, and in the South, such as Africa or Asia, where it is the lowest (1). This paradox may be due to different environmental exposures or variations in individuals. Van Den Eeden et al. (2003) demonstrated in their seminal work, that comparability of studies concerning the incidence of PD may be difficult, because

of methodological issues, such as differences in rates by age, gender, and/or race ethnicity (e.g. the category of the *black population* included in their study both African Americans and individuals form the Caribbean island or African continent, whereas another study (19) rather included individuals of the latter) (20).
The incidence of PD increases with rising age (0.5 per 100,000 per year in the category of 30 to 39 years old, when all ethnic groups and women/men combined; 38.8 per 100,000 in the category of 60 to 69 years; 107.2 (78.4 women and 140.7 men) per 100,000 in the category of 70 to 79 years; 119 (70.7 women and 190.5 men) per 100,000 in the category of 80 to 89 years (20)), with a peaking in the eighth decade, and a slightly decrease (disparately data among different studies exist), especially in the female population, in the oldest age group (>80) (**Figures 1, 2**). This decrease may be due to smaller case numbers in this age group, or due to the pre-existence of comorbidities (e.g. cervical stenosis, osteoarthritic degenerative joint disease or dementia), which complicate the diagnosis of PD. Dementia is an exclusion criterion for the diagnosis of PD, when it is present at the onset of motor symptoms (18,21).

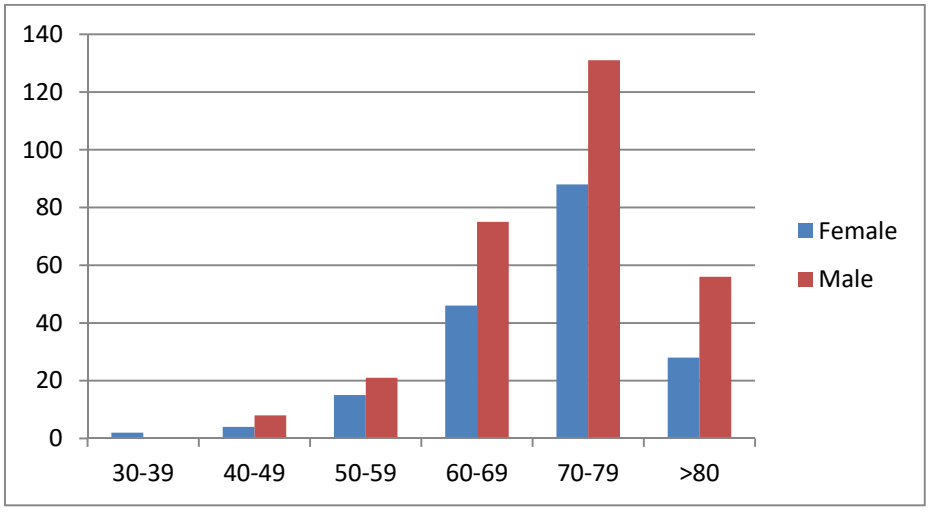


Figure 1: Incidence of PD in non-Hispanic Whites among Northern California population. Total number of female patients: 183; total number of male patients: 291; modified after Van Den Eeden, S. K. et al. (2002) (20)

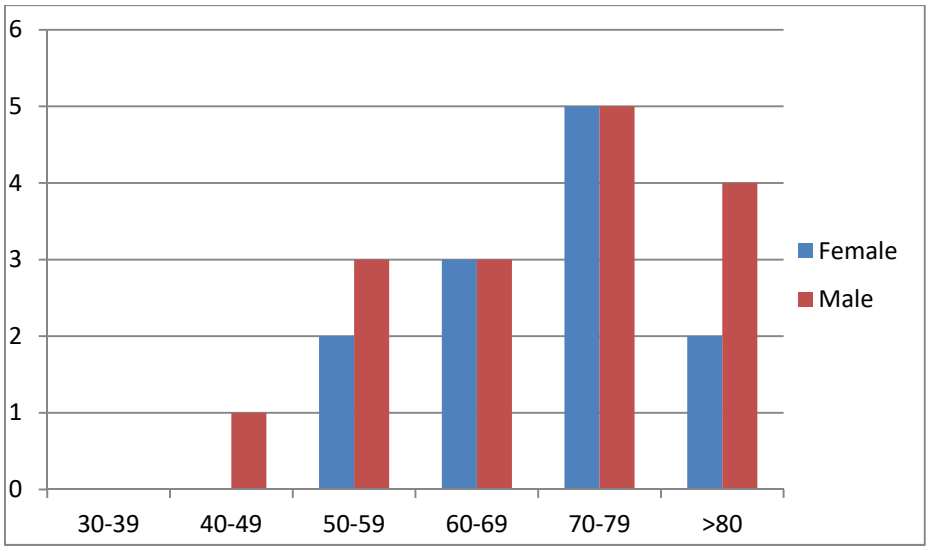


Figure 2: Incidence of PD in black population among Northern California population. Total number of female patients: 12; total number of male patients: 16; modified after Van Den Eeden, S. K. et al. (2002) (20)

The following protective factors of getting PD have been reported: increasing usage of ibuprofen, tobacco smoking or usage of smokeless tobacco (e.g. chewing tobacco), high urate-concentration, coffee and caffeine (maximum protection 3 cups/day), usage of calcium channel blockers and physical activity. In PD commonly substantial glial response, due to activation of microglia appears. Therefore, it is plausible that ibuprofen, which is a non-steroidal anti-inflammatory drug (NSAID), reduces the progression of neuronal degeneration in PD, by depressing the microglial reaction. An association between the usage of other NSAIDs and a reduction of PD risk has not yet been reported, which leads to the assumption that ibuprofen must have specific protective properties (18). The certain cause of the protective role of tobacco-usage is not clear, but may be due to a neuroprotective quality of nicotine, shown in some animal models of PD (18). A role of other tobacco components cannot be excluded. Urates are the end product in the metabolism of purines (e.g. adenosine). It is an antioxidant, which can reduce dopaminergic neuron degeneration (18). Caffeine is an adenosine receptor antagonist and seems to operate as a neuroprotective agent, what is well documented in experimental models of PD (18). Besides the positive effects of caffeine, other constituents of coffee might also contribute. Evidence that arterial hypertension increases the risk of PD is not convincing, but some studies correlate blood lowering drugs (e.g. calcium channel blockers) with a reduction in PD risk

(18). Frequent moderate or intensive physical activity might also operate as a neuroprotective value (18).

The following risk factors for PD have been reported: high milk and dairy consumption, exposure to pesticides, methamphetamine abuses, melanoma patients and traumatic brain injuries (18). The increasing risk due to high dairy consumption is most likely due to the urate-lowering effects of dairy products. The effects of pesticides and other environmental chemicals are based on the similarity of the organic compound p*araquat*, which is used in herbicides, to the metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is converted to a pro-parkinsonian molecule in the body. Methamphetamine damages the dopaminergic neurons in the substantia nigra and creates lesions similar to PD (damage in the dopaminergic neurons of the substantia nigra). The reason of the increasing risk of melanoma patients of getting PD is still unknown. A traumatic brain injury can lead to a breakdown of the blood-brain barrier, a chronic brain inflammation or an alpha-synuclein accumulation in the brain (**Figure 3**) (18,22).

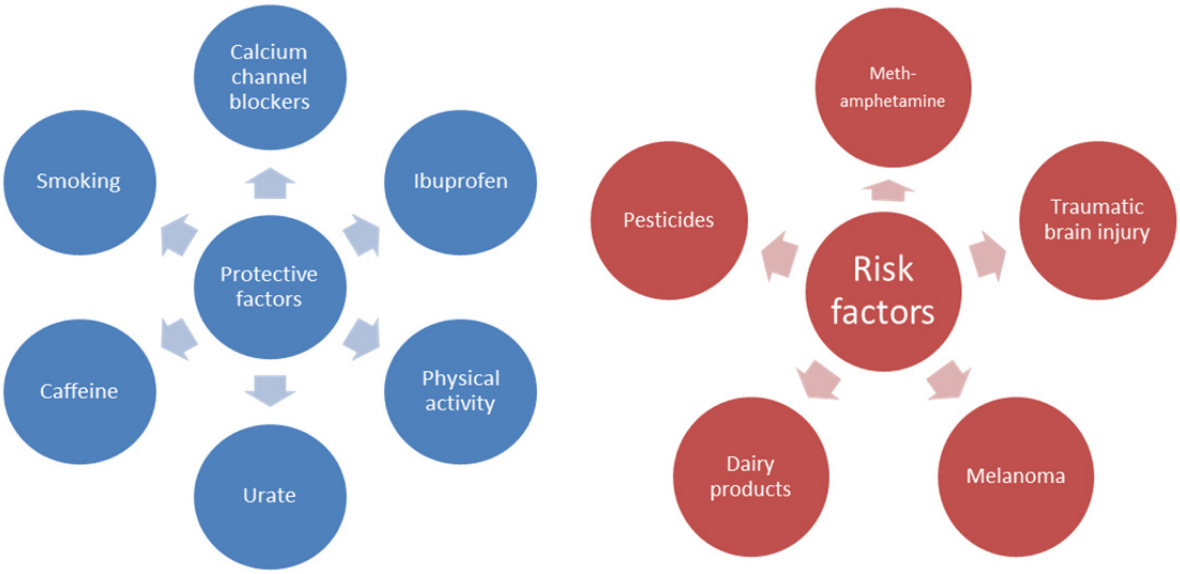


Figure 3: Protective and risk factors of getting PD; modified after Ascherio A.; Schwarzschild, M. A. (2016) (18)

1.1.2 Pathogenesis

PD is a disease characterised by the loss of dopaminergic neurons mainly localised in the substantia nigra pars compacta (SNpc). Symptoms appear, when about 70% of neurons in the SNpc are lost (23).

It is a widespread degenerative illness (second most common neurodegenerative disease after Alzheimer's disease) changing the central nervous system, the peripheral and enteric nervous system in affected people. The disease is the endpoint of changes in the cytoskeleton of special neuronal cells. Especially, nerve cells in components of the motor system and the limbic system show high vulnerability. The mechanisms behind the dissimilar fragility remain unknown (24).

PD occurs sporadically as well as genetically, mostly in combination with additive risk factors, mentioned above. These factors trigger the progressive loss of cells in the SNpc and other pigmented nuclei (loss of melanin). The genetically caused PD can occur as an autosomal dominant inheritance, where there is mostly a mutation in alpha-synuclein, or as an autosomal recessive inheritance with a disturbance in the parkin gene. Alpha-synuclein is a protein, which is normally located in the presynaptic membrane in the brain (25).

Microscopically a depletion of the quantities of melanin in the neurons of the SNpc, a replacement gliosis and eosinophilic cytoplasmic inclusions - so called Lewy bodies - exist (LB). LB are characteristic for PD and mainly consist of alpha-synuclein (25).

In PD the basal ganglia circuit is disturbed, mainly affecting SNpc and afterwards the thalamic nuclei **(Figures 4 and 5)**. Dopamine is necessary to enable the physiological circuit between the basal ganglia and the thalamic nuclei. There are two pathways (direct and indirect) connecting the basal nuclei with the thalami. Typically these two pathways ensure the balance of activation and depression of the thalami and consequently, of smooth movement. The direct pathway is enabled by glutamatergic neurons from the sensorimotor cortex, and by dopaminergic neurons from the SNpc. These activate inhibitory gamma aminobutyric acid (GABA) projections in the striatum proceeding to the internal globus pallidus (GPi) and the substantia nigra pars reticularis (SNpr). These two areas have inhibitory GABA projections. Due to the inhibition of the inhibitory projections of the striatum and GPi, a disinhibition of the thalamic nuclei occurs.

These areas are relevant for capriciousness motor activity. The indirect pathway is inhibited by dopaminergic neurons from the SNpc. Hereafter the external globus pallidus (GPe) is inhibited, which normally inhibits the subthalamic nucleus (STN). The STN activates through a glutamatergic pathway the SNpr and the GPi. These areas are responsible for the inhibition of the thalamus. If there is less dopamine in the SNpc the direct pathway (disinhibition of thalamus) decreases and the indirect pathway (inhibition of thalamus) increases. Both conditions lead to an augmented suppression of the thalamus, hence to a hypokinetic disorder (23,26).
The changes in the SN are accompanied by impressive extranigral pathology, especially changes in the limbic system, decrease of telencephalic cortical functions and dysregulation of autonomic regulative mechanisms (24).

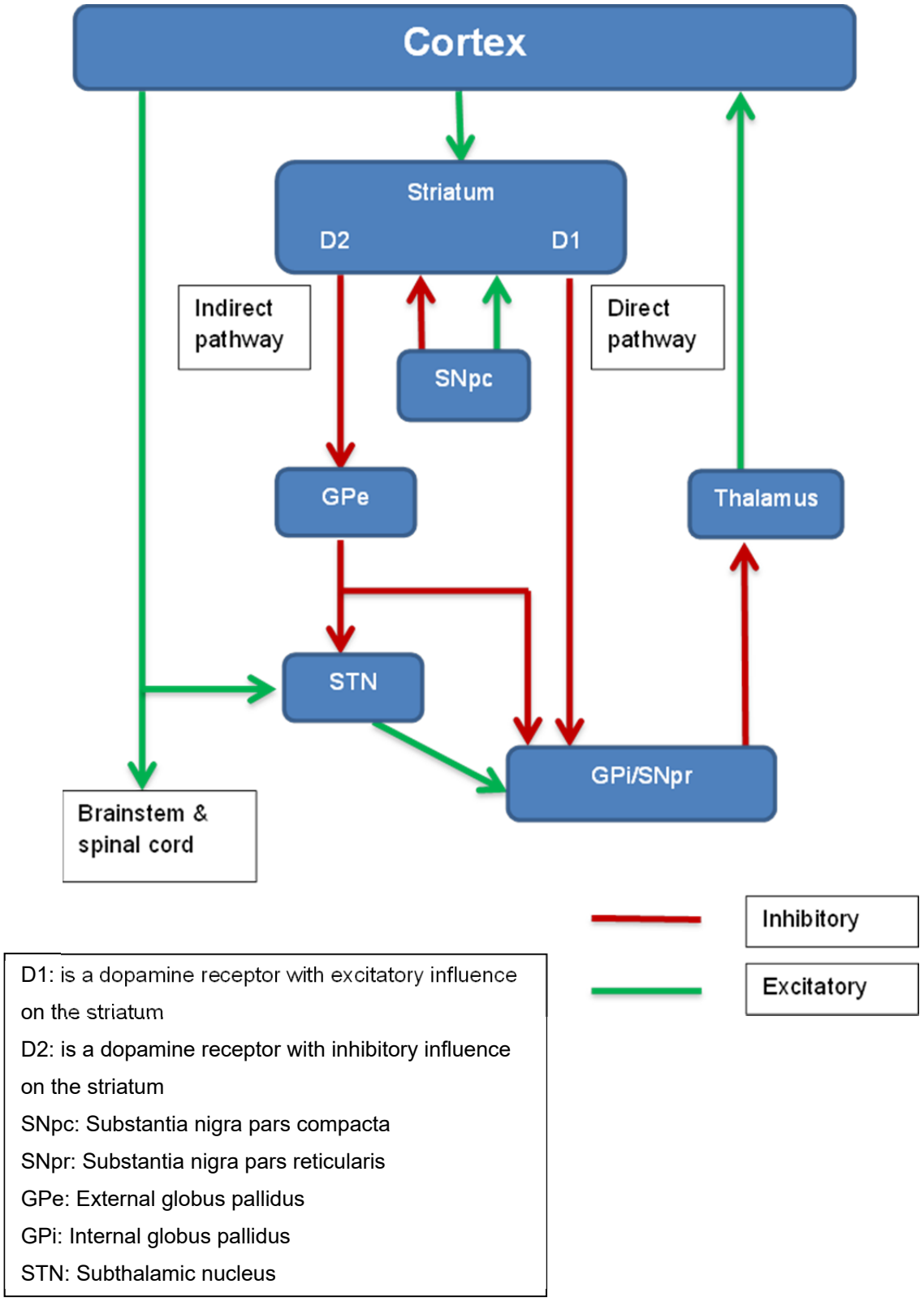


Figure 4: Normal basal ganglia circuit; modified after DeLong, M., Wichmann, T. (2015) (27)

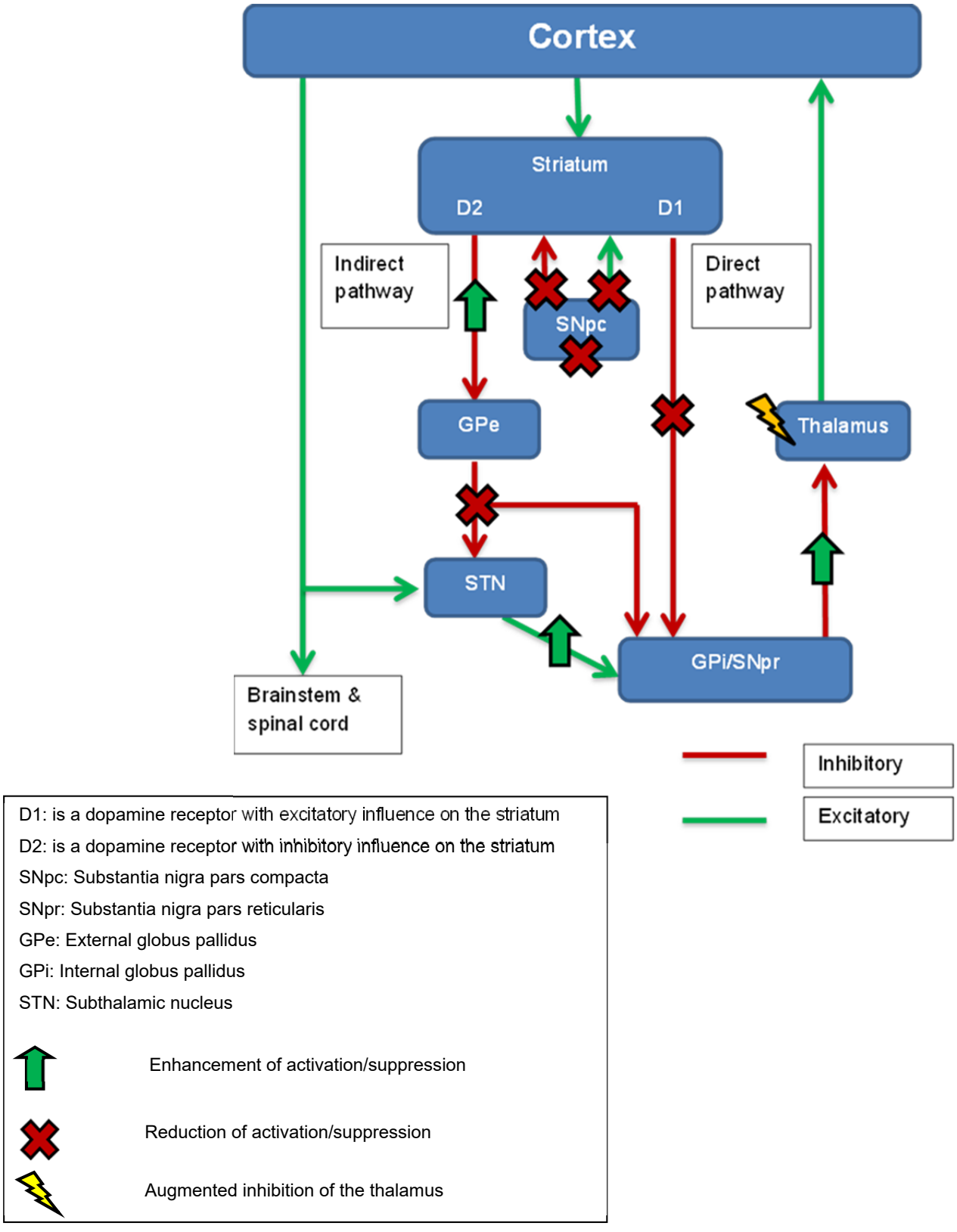
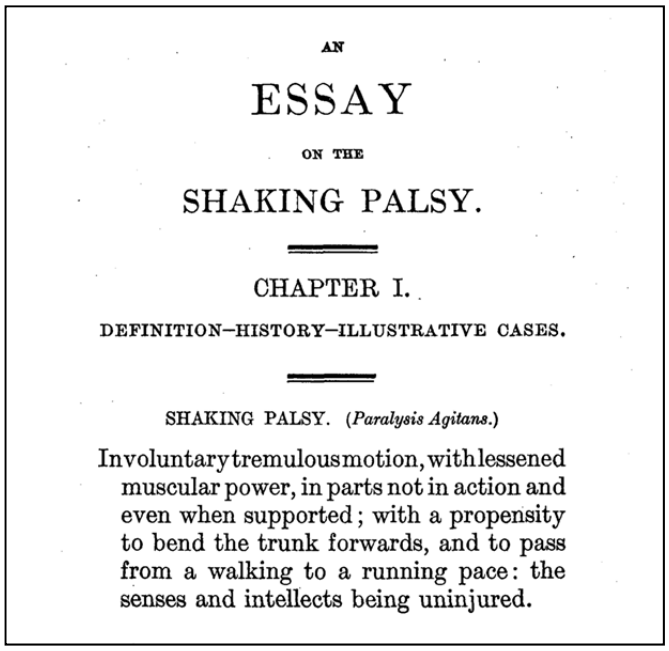


Figure 5: Basal ganglia circuit in a patient with PD; modified after DeLong, M., Wichmann, T. (2015) (27)

1.1.3 Symptoms and progression

James Parkinson described S*haking Palsy* the first time in 1817 (**Figure 6**). His essay contained no referral to rigidity or slowness of motion. Equal lacks can be found in the term *Paralysis agitans*, which appeared for the first time in 1841 in Marshall Hall's textbook *Diseases and Derangements of the Nervous System.*



AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Figure 6: First description of shaking palsy (later PD) by James Parkinson

The cardinal symptoms are hypokinesia and/or bradykinesia (the severest form of these is akinesia), rigidity, resting tremor and postural instability. Initial the symptoms mostly are asymmetrical and/or unilateral (1).

1.1.3.1 **Early symptoms**

Early signs of PD, besides the cardinal motor symptoms (especially tremor), are reported to be: hyposmia, vegetative disorders (e.g. seborrhoea, increased sweating and constipation), depressive complaints and idiopathic rapid-eye-movement (REM) sleep behaviour disorders. This complex of clinical signs might occur years before the motoric cardinal symptoms appear (1,8).
It may be difficult for family members to identify the early symptoms of PD as pathologic symptoms, because they develop slowly and tend to mimic the natural aging process (7).

Hoehn and Yahr (1967) pictured the prevalence of early symptoms of PD in a patient-cohort of 183 participants **(Table 1)** (28).

Tremor	70,5%
Gait disturbance	11,5%
Stiffness	9,8%
Slowness	9,8%
Muscle pain, cramps, aching	8,2%
Loss of dexterity	7,7%
Handwriting disturbance	4,9%
Depression, nervousness or other psychiatric disturbance	4,4%
Speech disturbance	3,8%
General fatigue, muscle weakness	2,7%
Drooling	1,6%
Loss of arm swing	1,6%
Facial masking	1,6%
Dysphagia	0,55%
Paraesthesia	0,55%

Table 1: Initial symptoms and their prevalence in PD; modified after Hoehn, M.M.; Yahr, M.D. (1967) (28)

1.1.3.2 **Motor symptoms**

Hypokinesia refers to poverty of spontaneous movement in affected parts of the body and failure of smooth automatic motion. Mostly the natural swing of the arms during walk is minimized. In contrast to paralysis, strength is not significantly minimized. A patient makes fewer adjustments of position when seated, compared to a healthy person. *Akinesia* is the most extreme variant of hypokinesia. *Bradykinesia* is more entailed to slowness rather than to a lack of movement. The time from onset to perform a movement is longer, compared to a healthy person. The face is like a mask due to a lack of expressive mobility (*hypomimia*). In

addition, PD is characterised by a rapid mumbling, monotonous speech. Normally the blink rate is 12 – 20 / min, in PD patients it is reduced to 5 – 10 / min.
Disorders of postural fixation are accompanied by flexion of the trunk, limbs and the neck. Additionally, *righting reflexes* are also decreased. Patients are not able to make appropriate adjustments to tilting, so a gentle push may cause a fall or start a series of small uncontrolled steps (*festination*) (2,7).
A block of motility, called *freezing*, can occur for seconds (1).
Rigidity is an alteration in the muscle tone, which appears from the start, proceeds throughout the movement and is present in both, extensors and flexors (stronger distinct in flexors). It may only be interrupted to a variable degree by the so called *'cogwheel phenomenon'.* The cogwheel phenomenon is a type of rigidity in which muscles respond with cogwheel-like jolts to the use of steady force in bending the limb. In contrast to spasticity, in rigidity the tendon reflexes are not enhanced and when the limb is released it does not go back in its original position. The term *'lead-pipe'* is also often used in examining rigidity in PD patients. It occurs due to the facts that the limb is nonresponsive and heavy to move and gives smooth resistance no matter how fast the limb is moved.
"Tremor in the position of repose" means that the tremor is dominant when the hand is in repose. The more common term resting tremor is not quite accurate, because complete relaxation may abolish the tremor. Movement eases the tremor momentarily. Fluctuations are seen in this kind of tremor, but its frequency is constant. Typically, it is asymmetrically localised in only one finger or a hand. The characteristical 4-per-seconds tremor, which is also called *pill-roll-tremor* of the thumb and fingers, only appears in half of the patients (2,7).
As the disease progresses, there may occur these effects in all customary activities. For instance handwriting becomes small and cramped (*micrographia*), as first identified by Charcot (**Figure 7**). Writing changes are comparable with speaking changes. The volume level decreases at the end of the spoken sentence. It is called *microphonia* or *hypophonia* (1,7).

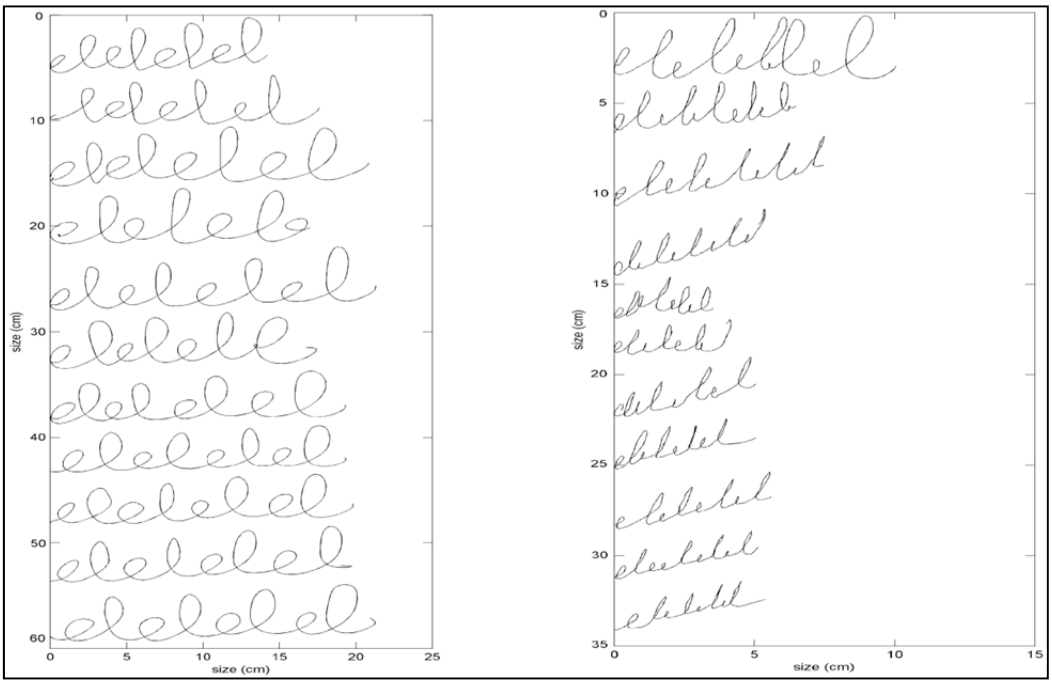


Figure 7: Differences in writing between a healthy person (left in the figure) and a PD patient (right in the figure) (29)

1.1.3.3 **Non-motor symptoms (NMS)**

REM disorders manifest early in the history of PD. Patients tend to paroxysmal shaking, especially in the second half of the night, which may lead to injuries (3). There exist various other NMS, which can be mostly summarised into the category of *autonomic disturbances*. The most prominent dysfunctions are constipation, abdominal pains and cramps, erectile dysfunction and sometimes orthostatic hypotension. *Drooling* may be caused by the reduced frequency of swallowing. *Excessive sweating* may be due to a failure to clean the face adequately *and seborrhoea* claim to be secondary as well, because of the effect of the constant motor activity. More plausible, these symptoms may be due to autonomic dysfunctions (7).

About 50% of the patients with PD are affected by *depression*. Commonly, depression is responsible for faster physical and cognitive impairment. Furthermore, depression has been shown a risk factor for developing dementia in PD (30,31).

The cumulative incidence of Parkinson's disease d*ementia* (PDD) increases with higher age at onset and disease-duration of PD. Further risk factors of developing early PDD are severe extrapyramidal involvement and mild cognitive impairment

(32). PDD leads to reduced quality of life, as well as higher care costs, increased disability and mortality (7,32). Cognitive impairment is caused by specific underactivity in regions of the frontal cortex and the basal ganglia. Primarily, working memory and executive functions are affected by the disease (33). Müller et al. (2013) described that NMS, especially fatigue, depression and sensory complaints, have a more powerful impact on physical and health related quality of life in early and untreated PD, as well as three years after onset, than motor symptoms (34).

1.1.3.4 **Progression**

The progression of PD is characterised by worsening of motor symptoms and complications due to the long-term therapy. In the end-stage of PD, motor and non-motor symptoms persist, which are no longer controllable **(Table 2)**. Autonomic symptoms, such as constipation, abdominal pains and various other sensory sensations, appear. The longer PD persists, the higher the risk of developing dementia gets (7). Increased mortality risk is mostly caused by increasing age and presence of dementia. There is a major heterogeneity in estimated mortality rates, probably due to the variable methodologies and patient selection in different studies. Macleod et al. (2014) showed in a systematic review that the duration from onset of the disease to death varies from 7 to 14 years. Survival of PD patients decreases on average 5% per year of follow-up (high heterogeneity between the studies) (35). Pennington et al. (2010) showed that the most common cause of death in idiopathic Parkinson's disease (IPD) patients is IPD by itself (29%) (IPD patients are more frequently admitted to hospital than healthy populations; show more fragility; depressive complaints increase; more likely to die in a hospital or nursing-home than healthy population), followed by malignancy and ischaemic heart disease (both 12%), pneumonia (11%), cerebrovascular disease (9%) and other conditions (27%) (36). IPD occurs sporadically (non-familial) and leading symptoms are movement disorders. In IPD the pathological correlate has been reported to be a deposition of alpha-synuclein in the brainstem (37). The high pneumonia rates may be due to swallowing problems and thus to an increased aspiration risk (36). Matsumoto et al. (2014) pictured that death in PD patients is commonly caused by swallowing problems,

aspiration pneumonia or asphyxia. Sudden death is the second most common cause of death in PD (38).

Stage I: Unilateral involvement only, usually with minimal or no functional impairment
Stage II: Bilateral or midline involvement, without impairment of balance
Stage III: First sign of impaired righting reflexes
Stage IV: Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated
Stage V: Confinement to bed or wheelchair unless aided

Table 2: Progression-scale modified after Hoehn, M.M.; Yahr, M.D. (2002) (39)

1.1.4 Diagnosis and rating scales

Clinical features, which are based on stringent diagnostic criteria, as well as imaging techniques are used to diagnose PD. Post mortem PD is diagnosed by histological analysis of the basal ganglia (40).

There are two main difficulties in the diagnosis of PD. First, it is challenging to differentiate between typical PD and parkinsonian syndromes and second, distinguishing parkinsonian tremor from other types of tremor (especially essential tremor) appears to be tricky (**Table 3**) (7,41).

Unilateral rest tremor: is highly suspicious for PD
Essential tremor: is bilateral, mostly symmetrical and postural, it worsens with excitement, not able to hold a knife
Intention tremor: it increases when the patient tries to approach a target, due to cerebellar dysfunction
Psychogenic tremor: sudden onset, spontaneous remission, distractibility, no other tremor type probable
Other rare types: physiological tremor, orthostatic tremor, dystonic tremor, Holmes tremor

PD: Parkinson's disease

Table 3: Different tremor types; modified after Boetzel, K et al. (2014) (41)

United Kingdom (UK) Parkinson's Disease Society Brain Bank clinical diagnostic criteria are used in the clinical setting to make a diagnosis of PD (sensitivity up to 90%) **(Table 4)** (42). Historically, motor features like bradykinesia and at least one other motor symptom (such as muscular rigidity, resting tremor or postural instability) have led to the diagnosis PD (Step 1). These motor symptoms are unspecific and do not differentiate IPD from other parkinsonian syndromes. Therefore it is essential to determine if there are other signs, excluding/supporting the diagnosis of IPD (Step 2 and Step 3) (43).

Step 1: diagnosis of parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- Plus at least one more of the following features:
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2: exclusion criteria for Parkinson's disease

One or more of the following points suggest an alternate diagnosis:

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injuries
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- Methyl-phenyl tetrahydropyridine (MPTP) exposure
- Negative response to large doses of levodopa (if malabsorption excluded)
- More than one affected relative (this criterion is generally no longer applied)
- Sustained remission
- Strictly unilateral features after 3 years
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Oculogyric crises
- Supranuclear gaze palsy

• Babinski sign • Cerebellar signs • Presence of a cerebral tumour or communicating hydrocephalus on CT scan or MRI
Step 3: supportive prospective positive criteria for Parkinson's disease Three or more of the following points are required for diagnosis of definite Parkinson's disease: • Unilateral onset • Rest tremor present • Progressive disorder • Persistent asymmetry, affecting mostly the side of onset • Excellent response to levodopa (70-100%) • Severe levodopa-induced chorea • Levodopa response for 5 years or more • Clinical course of 10 years or more

CT: computer tomography; MRI: magnetic resonance imaging

Table 4: UK PD Society Brain Bank clinical diagnostic criteria; modified after Kalia, L.V.; Lang, A.E. (2015) and Hughes, A.J. et al. (1992) (40,42)

To carry out further clinical assessment, the Unified Parkinson's Disease Rating Scale (UPDRS) is the gold-standard. It was originally developed in the 1980s. In 2001 the Movement Disorder Society (MDS) revised the UPDRS into the MDS-UPDRS. There are four main parts in the MDS-UPDRS criteria. The first part includes "non-motor experiences of daily living", the second part contains "motor experiences of daily living", the third part reflects "motor examination" and the fourth part concerns "motor complications". All in all the MDS-UPDRS rates 65 items (several with right/left distribution scores). Each of the questions may be answered with five different responses, which are linked to clinical terms (0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe) **(Table 5)** (44).

Part I	Part II	Part III	Part IV
• Cognitive impairment • Hallucinations and psychosis • Depressed mood • Anxious mood • Apathy • Features of dopamine dysregulation syndrome • Night time sleep problems • Daytime sleepiness • Pain and other sensations • Urinary problems • Constipation problems • Light-headedness on standing • Fatigue	• Speech • Salivation and drooling • Chewing and swallowing • Eating tasks • Dressing • Hygiene • Handwriting • Doing hobbies and other activities • Turning in bed • Tremor • Getting out of bed, car, or deep chair • Walking and balance • Freezing	• Speech • Facial expression • Rigidity of neck and four extremities • Finger taps • Hand movements • Pronation/Supination • Toe tapping • Leg agility • Arising from chair • Gait • Freezing of gait • Postural stability • Posture • Global spontaneity of movement • Postural tremor of hands • Kinetic tremor of hands • Rest tremor amplitude • Constancy of rest tremor	• Time spent with dyskinesia • Functional impact of dyskinesia • Time spent in the OFF state* • Functional impact of fluctuations • Complexity of motor fluctuations • Painful OFF-state dystonia

* OFF-state: patients have a poor response, despite taking medication

Table 5: MDS – UPDRS criteria for the diagnosis of PD; cited from Goetz, C.G. et al. (2007) (44)

Additionally to the assessment of clinical features, imaging techniques, such as MRI, can be used. In IPD changes detected with MRI are unspecific and mostly connected with the normal ageing process. However, brain imaging can be used to detect symptomatic causes, evidence for atypical Parkinsonism or accompanying diseases (1). A routine use of neuroimaging in all patients suspected to PD is not recommended (45).

The Levodopa (L-DOPA) test may confirm the suspected diagnosis of PD. The patient is administered soluble L-DOPA. If there is an improvement of the symptoms, PD is highly probable. Levodopa is the precursor to the neurotransmitter dopamine, which cannot cross the blood brain barrier. Levodopa can cross the blood brain barrier, thus it is used to increase the dopamine levels in PD patients (1).

1.1.5 Differential diagnosis

The distinction between IPD and different variants of Parkinsonism may be challenging, especially in early stages (**Figure 8**). Therefore it is essential using the diagnostic criteria properly. It is estimated that approximately 80% of the diagnosed IPD cases are correct. In up to 20% IPD is misdiagnosed and is only detected post-mortem by autopsy. Most misdiagnoses relate to multiple-system-atrophy (MSA), progressive supranuclear palsy (PSP), Alzheimer's disease and cerebrovascular pathology (40).
IPD occurs sporadically (not familial), the leading symptoms are movement disorders and the pathological correlate is a deposition of alpha-synuclein in the brainstem. Besides secondary forms, which refer to discernible causes, like medication side effects or vascular diseases, Parkinsonian syndromes are late term effects of neurodegenerative disorders (37).

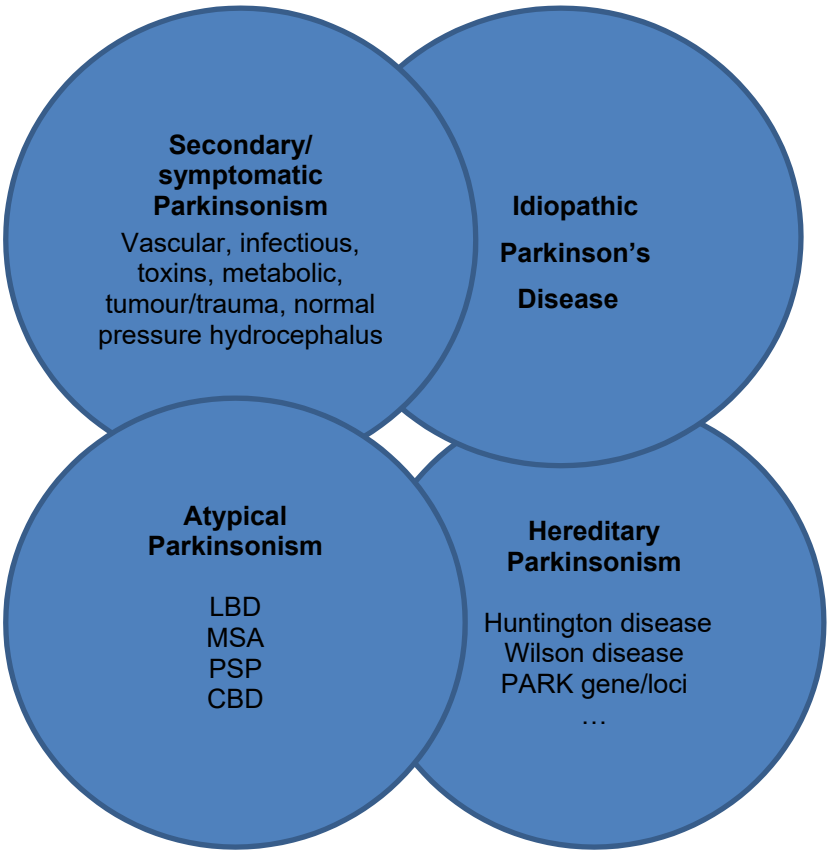


Figure 8: Parkinsonian syndromes; modified after McFarland, N. R. (2016) (46)

In the following sections I will give a short introduction to the most important differential diagnosis of IPD (atypical Parkinsonism, secondary/symptomatic Parkinsonism, hereditary Parkinsonism and essential tremor).

1.1.5.1 **Atypical Parkinsonism**

Atypical parkinsonian syndromes pertain to the field of neurodegenerative disorders. Atypical parkinsonian syndromes are marked by intracellular deposition of amyloidogenic proteins. These syndromes may look like the classical Parkinsonism (IPD), but the cause of the symptoms is different from that of IPD. Therefore it is essential to consider red flags, which may lead to the right diagnosis

(Table 6). Furthermore, it is important to consider atypical parkinsonian syndromes as a notable differential diagnosis when initially diagnosing Parkinsonism (37).

Features predictive of atypical Parkinsonism
Rapid disease progression
Early gait instability, falls
Absence or paucity of tremor
Irregular jerky tremor, myoclonus
Poor/absent response to levodopa

Table 6: Red Flags for differentiating atypical Parkinsonism from PD modified after McFarland, N. R. (2016) (46)

In the following sections I will give a brief introduction into atypical parkinsonian syndromes.

1.1.5.1.1 Lewy Body Disease (LBD)

LBD is an early onset dementia. Clinical criteria for diagnosing LBD besides early onset of dementia are: Parkinsonism parallel to or following dementia onset, cognitive impairment or fluctuations in cognition and relapsing visual hallucinations. Diffuse LB-deposits are found in both, PD dementia and LBD **(Table 7)** (46).

Neuropathology	Aggregates of alpha-synuclein in neuronal somata (Lewy bodies) and processes in typical distribution
Clinical symptoms	Dementia: cognitive impairment with relevance to activities of daily living Additionally one of the following presentations: Parkinsonian syndrome, onset after or at most 12 months before onset of dementia Fluctuations in alertness and attention Repeated visual hallucinations

MRI results	Normal medial temporal lobes → in contrast to Alzheimer's disease Exclude symptomatic causes (e.g. vascular encephalopathy, normal pressure hydrocephalus)

MRI: magnetic resonance imaging

Table 7: Dementia with Lewy bodies; modified after Levin, J. et al. (2016) (37)

1.1.5.1.2 Multiple system atrophy (MSA)

Typical symptoms of MSA are cerebellar and/or parkinsonian signs, as well as autonomic dysfunction. There exist two important phenotypes: a) the Parkinsonian type (MSA-P) and b) the cerebellar syndrome (MSA-C). MSA-P is characterised by symmetrical onset of the symptoms, rapid progression, tremor, frequent rigidity and dyskinesia. MSA-C is characterised by cerebellar limb and gait ataxia, early falls, dysarthria and progressive dementia **(Table 8)** (46).

Neuropathology	Aggregates of alpha-synuclein in cytoplasm of oligodendrocytes and neurons in a typical distribution
Clinical symptoms	Dysautonomia: urinary incontinence, erectile dysfunction, orthostatic hypotension Additionally one of the following points: Parkinsonian syndrome: bradykinesia with rigidity, tremor, or postural instability Cerebellar syndrome: gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
MRI results	Atrophy of putamen, middle cerebellar peduncle, pons, or cerebellum

MRI: magnetic resonance imaging

Table 8: Multiple system atrophy; modified after Levin, J. et al. (2016) (37)

1.1.5.1.3 Progressive supranuclear palsy (PSP)

PSP is the most common form of atypical Parkinsonism. It represents approximately 6% of patients presenting with Parkinsonism. Typical features of the disease are early postural instability, unexplained falls, vertical supranuclear palsy and progressive dementia. The key symptoms, early falls and gait instability, differentiate PSP from other parkinsonian syndromes. Many different PSP-syndromes, such as Richardson syndrome (classical PSP), PSP-parkinsonism, PSP-pure akinesia with gait freezing and others, exist. The criteria for diagnosing PSP include progressive disorder with onset after 40 years, postural instability, significant falls, slowing of vertical saccades or vertical gaze palsy. Although there are many PSP variants the typical features arise in all subgroups, when the disease progresses **(Table 9)** (46).

Neuropathology	Aggregates of 4-repeat tau in astrocytes, oligodendrocytes, and neurons, in typical distribution
Clinical symptoms	**Richardson's syndrome:** symmetric, axial-oriented, akinetic-rigid, levodopa resistant parkinsonian syndrome, with early postural instability and vertical supranuclear gaze palsy **PSP with predominantly parkinsonian symptoms:** asymmetric, limb-predominant; Levodopa-responsive parkinsonian syndrome with late-onset vertical supranuclear gaze palsy **Pure akinesia with freezing of gait:** freezing of gait without rigidity, without tremor, late-onset vertical supranuclear gaze palsy **Corticobasal syndrome (CBS):** at least one cortical symptom and at least one extrapyramidal symptom
MRI results	Midbrain atrophy Frontal lobe atrophy Exclude symptomatic causes

MRI: magnetic resonance imaging; PSP: progressive supranuclear palsy

Table 9: PSP; modified after Levin, J. et al. (2016) (37)

1.1.5.1.4 Corticobasal degeneration (CBD)

The classical presentation of CBD is asymmetrical rigidity, dystonia and ideomotor apraxia, tremor and frontal/cortical dementia. Cortex and basal ganglia are predominantly involved. The asymmetrical involvement is a typical feature and helps differentiating CBD from PSP. CBD has a poor prognosis. Patients die about 7 years after onset. CBD can present in various phenotypes like classic-CBD, frontal behavioural variant, posterior cortical atrophy syndrome, progressive non-fluent/agrammatic aphasia or PSP syndrome. Concerning this mass of phenotypes proper criteria, like insidious onset, gradual progression of more than 1 year, onset in patients aged 50 or more, with a family history or known tau mutations, are essential **(Table 10)** (46).

Neuropathology	Aggregates of 4-repeat tau in astrocytes, oligodendrocytes, and neurons and often swollen achromatic neurons in typical distribution
Clinical symptoms	**Corticobasal syndrome (CBS):** at least one cortical symptom and at least one extrapyramidal symptom **Frontal behavioural-spatial syndrome:** executive dysfunction, behavioural or personality changes, visuospatial deficits **Richardson's syndrome** **Progressive non-fluent aphasia**
MRI results	Parietal lobe atrophy: focal, mostly asymmetric

MRI: magnetic resonance imaging

Table 10: Corticobasal degeneration; modified after Levin, J. et al. (2016) (37)

1.1.5.2 **Secondary/symptomatic Parkinson's disease**

Vascular or arteriosclerotic diseases can cause a syndrome that is similar to IPD, as a result of arteriosclerotic white matter damage. There are different views, if vascular diseases induce a form of PD or not. In elderly patients a coincidence of a vascular factor and IPD is not excludable (1,7).

Drug induced Parkinsonism (DIP) is dominated by hyperkinesia and rigor, resting tremor is hardly seen. A thorough medication history is essential (1).

Encephalitis lethargica, which was an polymorphic epidemic disease in the United States and Western Europe after the First World War, lead in 30%, after a long period of time, to a parkinsonian syndrome (postencephalitic parkinsonism). Although the certain cause is still unknown, some clinicians consider a viral aetiology as the underlying cause. Nowadays, there are hardly cases of encephalitis lethargica documented (1,7,47).

Normal pressure hydrocephalus (NPH) exhibits the cardinal symptoms urinary incontinence, ataxia and cognitive impairment. Especially in older patients with these symptoms NPH should be considered. Underlying correlates for these symptoms are enlarged ventricles, but a normal intracranial pressure. Generally, gait dysfunctions are the earliest symptoms, characterised by slowness, shuffling and broad-based ataxia (48).

1.1.5.3 **Hereditary Parkinsonism**

Wilson disease (WD) occurs in younger patients and additionally shows cerebellar attendant symptoms (1).

Huntington disease is a neurodegenerative disease, which manifests mainly in adulthood, with motor (chorea, rigidity and bradykinesia), cognitive and predominantly psychiatric symptoms (e.g. perseverations, obsessions, and occasionally psychosis) (49).

Another differential diagnosis that has to be considered, when initially diagnosing IPD, is essential tremor. In the following paragraph a short introduction in essential tremor is presented.

1.1.5.4 **Essential tremor (ET)**

The prevalence of PD is much rarer then the prevalence of tremor, which is the most common movement disorder. In contrast to the parkinsonian tremor, which is a resting tremor, the essential tremor is bilateral, postural and mostly symmetrical. If the patient tries to outstretch the arm, the tremor can be seen with amplitude of several centimetres (41).

1.1.6 Therapy

Although there is no method that stops the neurodegeneration underlying PD, methods easing the symptoms are available. There are three main columns, on which the therapy of PD is based: medication, surgery and physical therapy (7).

1.1.6.1 **Pharmacological treatment**

Since the introduction of Levodopa (L-Dopa) in 1960 as a therapy for motor symptoms in PD, it remains the gold-standard (50).
As the disease proceeds and after a usage of L-Dopa for 2-5 years the antiparkinsonian effect decreases, dystonic movement disorders and fluctuation appear in effect. The so called “on-off phenomenon” occurs, in which it comes to a rapid change of states, in which the patient is free of symptoms or nearly completely immobile. Therefore, a therapy with L-Dopa should be protracted, especially in younger patients, by better using dopamine-agonists first (1,7). Other approaches, including oral, transdermal and subcutaneous dopamine agonists, monoamine oxidase inhibitors (MAO-B-inhibitor), catechol-O-methyltransferase inhibitors (COMT-inhibitors) and intrajejunal infusion of L-Dopa should be considered **(Table11)** (50).

Medication	Main benefit	Side effects	Effect mechanism
L-Dopa			
Carbidopa-L-dopa	↓of tremor and bradykinesia; less effect on postural difficulties	Nausea, dyskinesia, orthostatic hypotension, hallucinations, confusion	Striatal dopamine is diminished→ remaining nigral cells are still competent of generating dopamine by taking up its precursor L-dopa
Controlled release carbidopa-L-dopa	May prolong L-dopa effects		Combination with decarboxylase inhibitor (carbidopa or benserazide) helps to reduce peripheral side effects and introduces a greater proportion of L-dopa to the nigral neurons
Dopamine agonists			
Ropinirole Pramipexole	Moderate effects on all aspects; ↓motor fluctuations of L-dopa	Orthostatic hypotension, excessive and abrupt sleepiness, confusion, hallucinations	These have a direct dopaminergic effect on striatal neurons.
Glutamate antagonists			
Amantadine	Smoothing of motor fluctuations	Leg swelling, congestive heart failure, prostatic outlet obstruction, confusion, hallucinations, insomnia	The clear mechanism is unknown, but antagonism of NMDA (N-methyl-D-aspartate receptor) or release of dopamine is presumed.
Anticholinergics			
Benztropine Trihexyphenidyl	Tremor↓, less effect on other features	Atropinic effects: dry mouth, urinary outlet obstruction, confusion, and psychosis	Anticholinergics block the receptor for acetylcholine, thus it is believed, that the activity of neurons

			responsible for smooth movement is increased.
COMT-inhibitors Entacapone	Prolonged effect of L-dopa	Urine discoloration, diarrhoea, increased dyskinesia	These extend the plasma half-life of L-dopa by obviating its breakdown.
MAO-inhibitors Rasagiline Selegiline	↓"off" time, potential neuroprotection Potential neuroprotection	Hypertensive crisis with tyramine-rich foods and sympathomimetics	↑ the availability of dopamine in the neurons by inhibiting monoamine oxidase

L-Dopa: levodopa; COMT: catechol-O-methyltransferase; MAO: monoamine oxidase

Table 11: Commonly used drugs in the treatment of PD; modified after Ropper, A. H. et al. (2014) (7)

New discoveries show the importance of misfolded alpha-synuclein, as well intracellular as extracellular, and its cell-to-cell transfer as a target for therapy. Future orientated therapy may focus on the pathology of alpha-synuclein deposition, its aggregation, its transmission or its degradation (51).

1.1.6.2 **Deep brain stimulation (DBS)**

Frequently, neurosurgery due to PD is conducted in the thalamus, GPi, or subthalamic nucleus (depending on the symptoms), using either lesioning or high frequency DBS (52).

To perform DBS a quadripolar lead is implanted in the target region and an externally programmable implanted pulse generator delivers continuous stimulation, which creates a spherical shape of the electric field around the electrode. The implantation of the electrode is performed in local anaesthesia. The effect of DBS is directly assessed by a neurophysiologist at various locations. This is an important step to get the electrode into an appropriate position. Stimulation of the subthalamic nucleus, especially in patients with advanced PD, who have serious levodopa-induced fluctuations or medication failure after several years, reduces motor impairment and may improve quality of life (53,54).

DBS, conducted through implanted electrodes in the posterior and ventral parts of the subthalamic nucleus or in the internal segment of the globus pallidus, eases all features of the disease. Patients with DBS experience greater responsiveness to L-Dopa therapy and less L-Dopa induced dyskinesia (7).

1.1.6.3 **Nonpharmacological Treatments**

Physical activity is essential to maintain the remaining functions of movement and to adjust the malposition due to the disease. Parts of the concept for PD patients are strength training, balance and gait training, dance interventions, occupational therapy or swallowing therapy. New strategies in physiotherapy consist of short but intensive exercise programs, containing strength, balance, flexibility and aerobic exercises (55).

The following paragraphs give a short overview of the cognitive deficits associated with PD.

1.2 Cognitive deficits associated with Parkinson's disease

Even in early stages of PD cognitive deficits can occur. Most frequently memory dysfunctions, dysexecutive syndrome or visuospatial dysfunctions have been described. Other dysfunctions like attention deficits, learning problems and slowed cognition or bradyphrenia may appear (56).

Mild cognitive impairment (MCI) is common in patients with PD and increases the risk of developing dementia. MCI is a heterogenic term, affecting many aspects of cognition (**Figure 9**) (57).

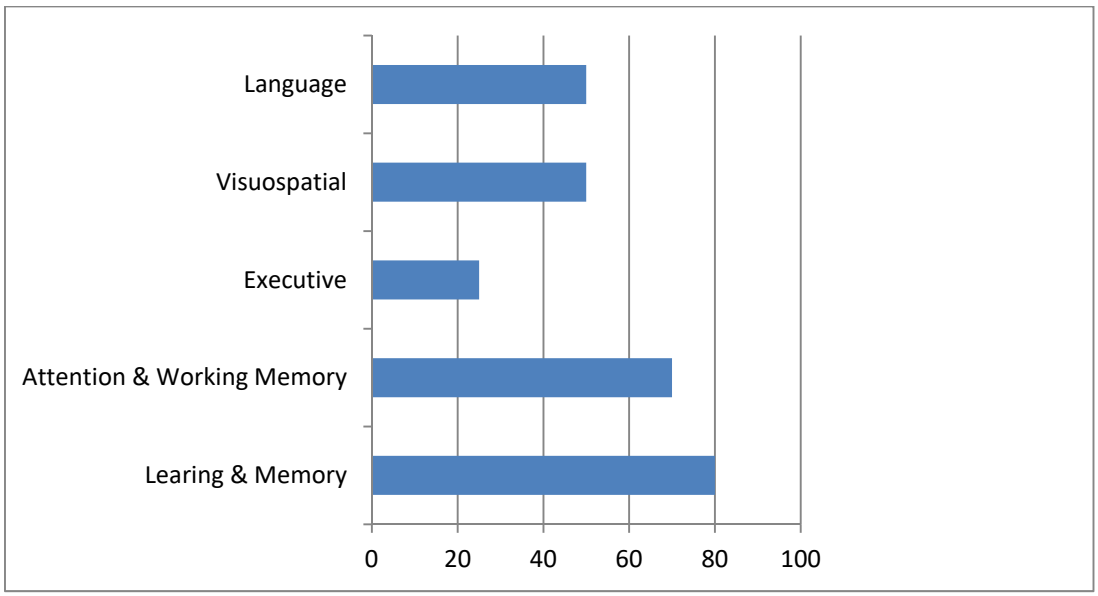


Figure 9: Percentage of different cognition domains affected in PD patients with MCI; modified after Cholerton, B. A. et al. (2014) (57)

1.2.1 Memory

Commonly PD is associated with memory impairment or dementia. Therefore, in the following paragraphs the most important memory subgroups are classified and memory impairment in PD is described.

1.2.1.1 **Classification of Memory**

Sensory memory: it is the shortest term element of memory. Its function is the processing of stimuli received through the five senses. This process is outside of conscious control.

Short-term memory (working memory): The human being is able to focus the conscious awareness on more than one input. Moreover a number of contents of consciousness are ready for delivery on demand for seconds to few minutes simultaneously. It is the ability to remember and process information at the same time. The capacity of this storage is limited up to 5 – 9 inputs. If the inputs have semantic connections, the capacity of the storage increases. Rehearsal and chunking helps to keep the information in memory.

Long-term memory: Information is stored for a long time. This is only possible by the process of learning. Learning leads to an adjustment in the structure of the brain. Neurons can adapt their synapses to the performed activity (50,58). Subdivisions of long-term memory are shown in **Figure 10**.

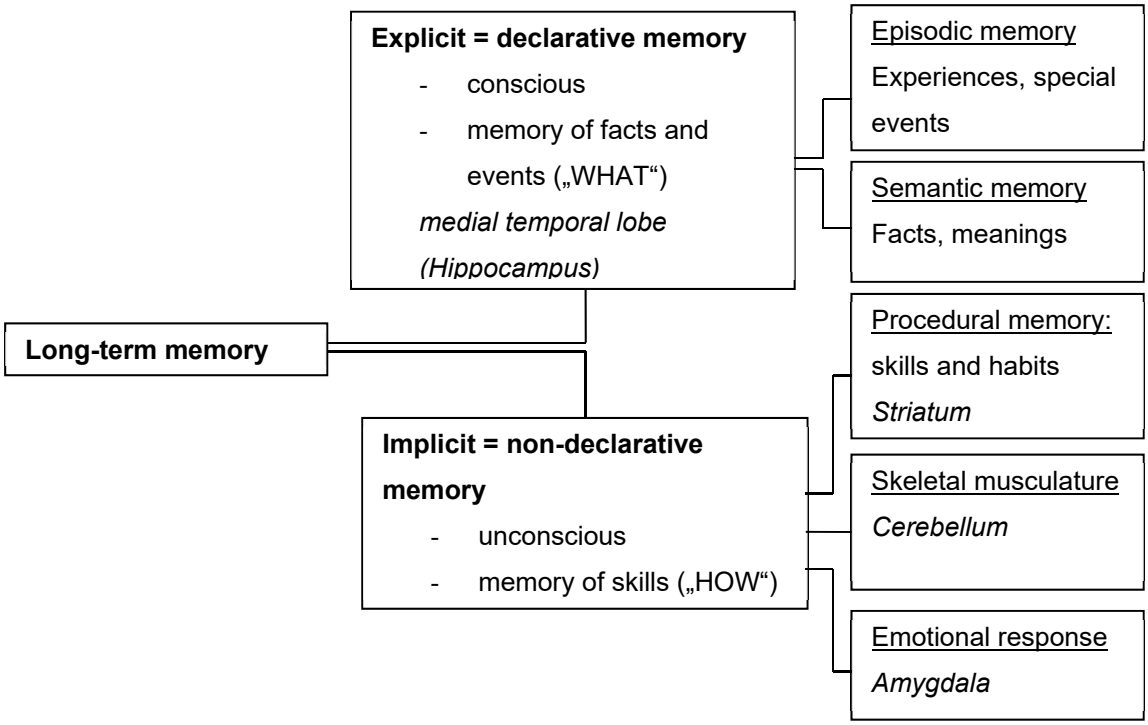


Figure 10: Classification of long-term memory; modified after Behrends, J.C. et al. (2012) and Bear, M.F. et al. (2016) (58,59)

PD patients frequently show impairment in procedural learning. This impairment might be due to executive dysfunctions (1.2.2.). Therefore in the following paragraph procedural memory is described (60).

P*rocedural memory:* This memory is needed for learning complex motor abilities and fixed rules. In reaction to a sensory input, a motor response (procedure) is performed. There are two subcategories, firstly *non-associative learning*, and secondly *associative learning*. *Non-associative learning* is defined as changing in behavioural response, which occurs over time due to a single type of stimulus. A subtype of non-associative learning is *habituation. Habituation* means, learning to ignore a trigger lacking of meaning. For example, we are used to hide noises of cars, when we are working in our office (we heard the noises a hundred times, so that we got used to it). *Associative learning* is defined as alteration of behaviour due to formation of associations between events. A subtype of associative learning is *classical conditioning,* which was discovered in dogs around the turn of the nineteenth century by the Russian physiologist Ivan Pavlov. A stimulus that normally induces a response (unconditioned stimulus) is associated with a second stimulus that normally does not induce this response (conditioned stimulus). In Pavlov's experiment the unconditioned stimulus is the sight of a meat and the response of a dog is salivation. The conditioned stimulus constitutes an added stimulus, such as an auditory one, like the sound of a bell. After repeatedly presenting the meat with ringing the bell, the dog associates the bell-ringing with meat-appearance, so that the dog starts to salivate when the bell rings, despite the meat is not yet there (59).

1.2.1.2 **Memory deficits and Parkinson's disease**

Often, PD is associated with cognitive impairment (see above) or dementia (PDD). The prevalence of cognitive dysfunction varies between different studies, but is estimated to be about 20% - 40%. Cognitive impairment can proceed to dementia, which has high impact on the quality of life and the mortality rates (61).
Mostly, clinical differential diagnosis of PDD, LBD and Alzheimer's disease is difficult **(Table 12)** (62). Cognitive impairment seen in early PD stages is mainly produced by damage in the frontal-lobe area (dopaminergic neuronal loss) and often includes a decrease of executive functions, such as planning and working memory. Lewis et al. (2003) demonstrated in their study that cognitive impairment in PD is related to specific underactivity in regions of the basal ganglia and frontal cortex. Generally, manipulation of information within the working memory is affected (33). Prospective memory, which is the capacity to keep information in memory and carry out intentions in future, is decreased especially in patients with PD and mild cognitive impairment (63). Frequently, procedural memory is impaired in PD. This may be due to the executive (executive dysfunction in PD) involvement in procedural learning (60). Although patients with PDD show symptoms comparable to patients with (mild) cognitive impairment, complexity, range and progression of cognitive and psychiatric symptoms clearly differentiate these two collectives. Dementia onset after diagnosis of PD may vary from a few years to two decades.
Neuroimaging points out that widespread pathological changes as well as specific regional changes underlie early cognitive impairment before PDD develops. In advanced PDD substantial atrophy, especially in the frontal, temporal and occipital cortices and subcortical regions, is observed (64).

Diagnostic criteria

- Diagnosis of PD according to Queen Square Brain Bank Criteria
- PD precedes to dementia onset
- Mini-mental state examination (MMSE) of <26
- Severe cognitive dysfunction that interferes with daily living
- Problems on at least two of the following:
    - Three-word recall (MMSE)
    - Overlapping pentagons (MMSE)
    - Months reversed or sevens backward (MMSE)
    - Lexical fluency
    - Clock drawing
- Absence of major depression, delirium or other abnormalities that disturb diagnosis of PD

Neuropsychological deficits and possible assessments

- Executive: Wisconsin card sorting test, Stroop performance, Odd-Man-Out, verbal fluency (semantic, phonological)
- Working memory: digit and spatial span
- Memory: free and cued recall, auditory verbal learning
- Visuospatial abilities: clock drawing, Benton line orientation, face recognition, fragmented letters
- Assessment:
    - Three-word recall (MMSE)
    - Overlapping pentagons (MMSE)
    - Months reversed or sevens backward (MMSE)
    - Lexical fluency
    - Clock drawing

Psychiatric symptoms (one or more)

- Visual hallucinations
- Psychosis
- Apathy
- Depression
- Anxiety

PD: Parkinson's disease; MMSE: mini-mental state examination

Table 12: Diagnostic criteria, neuropsychological features, and psychiatric symptoms of PDD after Kehagia, A.A. et al. (2010) (64)

1.2.2 Executive function

Executive functions contain the ability of processing relevant information, generating new mental sets, solving problems and planning. If there are changes in an environmental situation, the executive functions are needed to elaborate adaptive behaviour. Damage in the frontal lobes disturbs these functions (56). Executive dysfunction is seen in early PD, whereas global cognitive dysfunction is more likely to be observed in later stages of PD. Cognitive deficits are mainly related to changes in the basal ganglia thalamo-cortical loop, which includes the

prefrontal cortex. Problems in this circuit appear as a fronto-striatal syndrome characterised by executive dysfunction (65). Executive dysfunctions are assessed via standardized tests such as the Wisconsin Card Sorting Test (WCST), Stroop performance or Odd-man-out (66).

1.2.3 Attention and learning

In patients with PD internal control of attention is disturbed, pointing out as a lack in retrieval strategies and non-efficient spontaneous encoding. In addition, procedural learning may also be decreased. For instance patients can gain new motor or mental sets, but they have difficulties in maintaining these against competing alternatives, which is also due to a decrease of internal control of attention. Attentional deficits can be tested for instance with the WCST, the Tower of London test or Stroop performance (56,64).

1.2.4 Slowed cognitive processing/bradyphrenia

The term bradyphrenia means slowing of thinking or cognition. It is characteristical for pathology in the subcortical area. Especially patients with PD show a prolonged thinking time. Subcortical dementia may impress with bradyphrenia and cognitive rigidity. The cognitive slowing increases with enhanced complexity of tasks. Bradyphrenia can be detected with the Tower of London test (64,67).

1.2.5 Visuospatial function

The visuospatial function is the ability to identify, integrate and analyse space. It includes skills such as spatial navigation, perception of distance or mental imagery. A dysfunction in this system can lead to problems in navigating through space or difficulties in discriminating line orientation. Visuospatial dysfunction in PD is more commonly caused by central processing problems than by specific changes in the visuospatial system by itself. A dysfunction in the visuospatial system can be detected via the mental rotation test (56,64,68).

The following paragraphs give an overview of the basics of functional magnetic resonance imaging (fMRI) and highlight the usage of fMRI in PD patients. This functional imaging method can conquer the limitations of structural imaging techniques, which only state the anatomical situation, and show a functional correlate underlying the disease.

1.3 Functional magnetic resonance imaging (fMRI)

To consider functional changes in brain-networks in PD, the following paragraphs introduce basics concerning functional imaging. Additionally, specific attention is paid on resting state fMRI.

1.3.1 Basics of MRI and fMRI

Structural neuroimaging is a class of clinical techniques that provides images of physical structures and gives insight into the distribution of various types of tissue. Magnetic resonance imaging (MRI), a structural neuroimaging technique, uses strong magnetic fields to generate images of biological tissues (it uses series of changing magnetic gradients and oscillating electromagnetic fields, called pulse sequences). The scanner is aligned to the frequency of hydrogen nuclei, which are highly prevalent in the human body. Through the pulse sequence, different tissue properties can be distinguished. A limitation of structural neuroimaging is that it cannot reveal short-term physiological changes by active functioning of the brain. However, functional neuroimaging (as fMRI) can conquer this limitation. Functional MRI is a non-invasive method allowing to map the human brain, its complex functions and connectivity. It enables to examine the interaction of brain regions (i.e. networks) and changes of connectivity over time.
Physiological markers of brain activity, that can be measured, are essential for neuroimaging. There are two main types of markers: On the one hand *direct consequences of neuronal activity* (e.g. changes in electrical potentials or chemical gradients), on the other hand *metabolic correlates of neuronal activity.* Functional MRI is based on the latter. Mostly, fMRI measures the changes in blood oxygenation level dependency (BOLD) over time, which changes rapidly based on activity of neurons in a specific brain region. Thus, it is possible to localise brain

activity within a range of seconds. The mechanism underlying the BOLD effect is based on different magnetic properties of oxygenated (diamagnetic) and deoxygenated haemoglobin (paramagnetic). Whereas diamagnetic matters have a weak repulsion from magnetic field, paramagnetic matters are being weakly attracted by a magnetic field (69).
In response to an external stimuli (sensory, motoric or cognitive) a local increase in blood flow takes place and oxygen consumption in that circumscribed area increases. Thus, oxygen delivery and oxygen consumption are playing a key role for neuronal activity. Simply illustrated, BOLD fMRI works through measuring changes in the total amount of deoxygenated haemoglobin in a voxel over time. Voxels, volume elements, are the basic sampling units of MRI and mostly have a dimension of 2-3 mm^3 (70).
Functional connectivity (FC) implies functional relationships among physiological regions, or regions altered through changes in activation over time, whereby direct or indirect links between singular regions can be detected (71).

1.3.2 Resting state fMRI

Resting state (RS) connectivity (RSC) is utilized to point out synchronous BOLD changes in different brain regions, while the patients are at rest and not adhered to a specific task whilst lying in the scanner. The patients are instructed to rest without falling asleep so that through fMRI, using normal pulse sequences, low frequency oscillation in BOLD signal can be detected. It is essential that physiological fluctuations, due to respiratory or cardiac pulsations, are differentiated from neuronal activity oscillations. As there is no special task used to create a design matrix reflecting the on- and off-phases of a task-based fMRI paradigm during measurement, different approaches to analyse RS fMRI data had to be developed. The most common approaches are: seed based approaches, independent component analysis (ICA) or graph methods. Other methods, but less commonly used, are: clustering algorithms, neural networks and pattern classifiers. One possibility is to identify a seed voxel or a region of interest (ROI), extracting its BOLD signal time course and then searching for brain regions with similar fluctuations over time. One limitation of this approach is the voxel specific time course which can be different from voxel to voxel. Thus, the mean time

course of all voxels from one ROI is used. Even so, this approach may create different patterns of connectivity based on the seed chosen. Alternatively, methods like principal component analysis (PCA) or ICA, where broad patterns of connectivity are identified, are utilized. Concerning graph theory-based approaches, the brain is graphically represented, with nodes (indicating anatomical regions) and edges (indicating relationships between nodes), forming a complex network. Graph methods not only visualise FC-patterns among all elements of the brain, but also give insight into the quantitative characterisation of the global organisation. Two important measures in graph theory are, the *clustering coefficient*, which shows the degree nodes tend to cluster together in a graph, and the *betweenness centrality*, which demonstrates the centrality in a graph stated through shortest paths. Generally, regions which work together in task based approaches also show FC in RS. Thus, brain regions with similar functionality seem to have related patterns of spontaneous BOLD activation. Analysing resting state data, coherent activation particularly in visual, auditory, memory and attentional processes, are found (72-74).

Using RS-fMRI, a variety of connectivity networks can be examined. The default mode network (DMN) has been examined most extensively and consists of the following areas: lateral parietal cortex, posterior cingulate/precuneus, and medial prefrontal cortex. Principally, the DMN is active during rest and shows reduced activation during complex cognitive tasks. Other well described resting state networks are the sensorimotor, visual and attentional networks (73).

RS-fMRI can be used for pre-surgical planning. Clinical applications of RS-fMRI have focused on neuro-oncology, epilepsy-surgery and DBS. Concerning PD RS-fMRI is mainly used as a research tool to increase the understanding of the pathological changes underlying PD (75).

The most common limitations of RS-fMRI studies are: small sample sizes and lack of standardization in past studies, lack of understanding of changes in the baseline of physiological parameters, pharmacological interventions, disease related vascular changes affecting the BOLD signal, or limitations due to analysing methods (especially seed-based approaches) (75).

2 Material and Methods

This diploma thesis is performed as a literature review and has been written at the Medical University of Graz at the Department of Neurology - Division of Neurogeriatrics.

2.1 Structure of the thesis

The main part is structured in two chapters:
Chapter 1: Resting state connectivity in PD
Chapter 2: Connectivity changes in cognitively impaired PD patients
The first part aims to give insight in resting state connectivity changes in PD patients, examined through fMRI. The second part compares studies concerning alterations in cognition in PD patients and the underlying functional connectivity changes detected via fMRI.

2.2 Data sources and search strategy

A systematic literature search was conducted at the 20th of May 2018 via PubMed. Medical Subject Headings (MeSH) were used to figure out the appropriate search-terms (keywords). On Cochrane Central Register of Controlled Trials (CENTRAL) a systematic literature search was conducted at the 22nd of May in 2018. Additionally, a literature search was conducted at the 23rd of May 2018 via Google Scholar. Therefore, keywords were reduced, to create clearly arranged results. The keywords shown in **Tables 13-16** were used for the search in PubMed, Cochrane library (CENTRAL) and Google Scholar. The keywords were connected with the builder ‘AND’ and/or ‘OR’.

2.2.1 PubMed- and Cochrane-search

2.2.1.1 *Resting state connectivity in Parkinson's disease*

On PubMed the search was restricted to "clinical trials", "clinical study", "clinical trial, phase IV", "controlled clinical trial", " multicentre study", observational study", "randomized controlled trial", "validation studies", "abstract availability", "publication dates in the last 10 years" and "human medicine". These limitations reduced the number of initial results from 6565 (this number of results was achieved, when using the search-terms from **Table 13** without filters) to 209. On Cochrane Library the search was restricted to "trials" and "Publication year from 2008 to 2018". These limitations reduced the number of results from 119 (this number of results was achieved, when using the search-terms from **Table 13** without filters) to 87.

OR		OR
• "Parkinson's disease" • "idiopathic Parkinson's disease" • "primary Parkinsonism" • "Parkinsonism" • "paralysis agitans" • "shaking palsy" • "Parkinsonian disorder" • "Parkinsonian disorders"	**AND**	• "functional connectivity" • "functional neuroimaging" • "fMRI" • "functional MRI" • "functional magnetic resonance imaging" • "functional networks" • "resting state" • "DMN" • "default mode network"

fMRI: functional magnetic resonance imaging; DMN: default mode network

Table 13: This table gives an overview of the keywords used for part one for the search in PubMed and Cochrane library (CENTRAL). The keywords in column 1 are connected with the builder 'OR', the same applies for the keywords in column 2. The 2 columns (with the 'OR'-connected keywords) are joined with the builder 'AND'.

2.2.1.2 *Connectivity changes in cognitively impaired Parkinson's diease patients*

On PubMed the search was restricted to "clinical trials", "clinical study", "clinical trial, phase IV", "controlled clinical trial", "multicentre study", "observational study", "randomized controlled trial", "validation studies", "abstract availability", "publication dates in the last 10 years" and "human medicine". These limitations reduced the number of results from 2145 (this number of results was achieved, when using the search-terms from **Table 14** without filters) to 86. On Cochrane Library the search was restricted to "trials" and "Publication year from 2008 to 2018". These limitations reduced the number of results from 60 (this number of results was achieved, when using the search-terms from **Table 14** without filters) to 33.

OR		**OR**		**OR**
• ""Parkinson's disease" • "idiopathic Parkinson's disease" • "primary Parkinsonism" • "Parkinsonism" • "paralysis agitans" • "shaking palsy" • "Parkinsonian disorder" • "Parkinsonian disorders"	**AND**	• "functional connectivity" • "functional neuroimaging" • "fMRI" • "functional MRI" • "functional magnetic resonance imaging" • "functional networks" • "resting state" • "DMN" • "default mode network"	**AND**	• memory" • "cognition" • "dementia" • "cognitive impairment" • "cognitive impairments" • "cognitive deficit" • "cognitive deficits" • "cognitive disorder" • "cognitive disorders" • "mild cognitive impairment" • "mild cognitive impairments" • "cognitive decline"

				• “cognitive declines” • “mental deterioration” • “mental deteriorations”

fMRI: functional magnetic resonance imaging; DMN: default mode network

Table 14: This table gives an overview of the keywords used for part two for the search in PubMed and Cochrane library (CENTRAL). The keywords in column 1 are connected with the builder ‘OR’, the same applies for the keywords in column 2 and 3. The 3 columns (with the ‘OR’-connected keywords) are joined with the builder ‘AND’.

2.2.2 Google Scholar-search

2.2.2.1 *Resting state connectivity in Parkinson’s disease*

On Google Scholar the search was restricted to “publication year from 2008 to 2018”, “English pages” and “all in title”. These limitations reduced the number of results from 31.800 (this number of results was achieved, when using the search-terms from **Table 15** without filters) to 280.

		OR
“Parkinson’s disease”	**AND**	• “functional connectivity” • “fMRI” • “resting state”

Table 15: This table gives an overview of the keywords used for part one for the search in Google Scholar. The keywords in column 2 are connected with the builder ‘OR’. The two columns are joined with the builder ‘AND’.

2.2.2.2 *Connectivity changes in cognitively impaired Parkinson's disease patients*

On Google Scholar the search was restricted to "publication year from 2008 to 2018", "English pages" and "all in title". These limitations reduced the number of results from 135.300 (this number of results was achieved, when using the search-terms from **Table 16** without filters; duplicates included) to 34.

"Parkinson's disease"	**AND**	**OR** • "functional connectivity" • "fMRI" • "resting state"	**AND**	• "memory" • "cognition" • "dementia" • "cognitive impairment" • "cognitive deficit" • "mild cognitive impairment" • "cognitive decline"

fMRI: functional magnetic resonance imaging

Table 16: This table gives an overview of the keywords used for part two for the search in Google Scholar. The keywords in column 2 are connected with the builder 'OR'. The three columns are connected with the builder 'AND'. For each word in column 3, a separate search was conducted (e.g. *"Parkinson's disease" AND ("functional connectivity" OR "fMRI" OR "resting state") AND "memory")*.

Duplicates were detected through scanning the search results from Google Scholar, Cochrane library and PubMed and comparing the result-lists of the singular databases. Consequentially, the detected duplicates were deleted from the results-lists of the Google Scholar search and of the Cochrane search.

Only original studies have been included for further screening (no reviews).

2.3 Data extraction

For the purpose of detecting the most germane studies, the results of the two parts have further been evaluated for title analyses. Therefore, the titles of the results have been copied in a new Microsoft Word® document, using Microsoft Word® 2010. The studies have been classified in *relevant*, *maybe-relevant* or *irrelevant* topic, after working through the titles of all results. Studies have been classified as *irrelevant*, when the titles did not contain at least one of the keywords from each column **(Tables 13-16)**. Additionally, titles with the phrases “Wilson’s disease”, “abstinent smokers”, “geriatric syndrome”, “Anorexia nervosa”, “(progressive) supranuclear palsy (PSP)”, “essential tremor”, “Friedreichs Ataxia”, “Machado-Joseph disease”, “EEG”, “revving-up exercise for sustained weight loss by altering neurological reward and drive (REWARD)”, “acupuncture”, “MEG”, “rat model”, “schizophrenia”, “pain-related fMRI”, “meta-analysis”, “systematic review” and “multiple-system atrophy” were excluded.

Furthermore, the exclusion criterion *“Publication type Journal: Conference Abstract”,* was established during screening the titles and publication types of studies detected via Cochrane library. Only publications from journals have been included for further examination of articles found via Google Scholar search.

The category *maybe-relevant* contains titles which only included one keyword, but nevertheless were content-related.

Furthermore, titles which contained keywords from **Table 14 and 16/column 3** were excluded from the list of studies for part one and added for part two.

A total of 729 titles have been reviewed. Overall 209 titles have been identified to be relevant, 103 titles have been marked as maybe-relevant, 320 to be irrelevant and 97 duplicates have been removed. Additionally, 20 titles which were excluded from the list of studies for part one were added to the list of studies (relevant and maybe-relevant) for part two, and therefore included for abstract screening. Consequently, 228 titles have been marked as relevant and 104 as maybe-relevant. The remaining studies (as well relevant as maybe-relevant titles) have been copied into a new Microsoft Word document for further examination of the abstracts.

A total number of 332 abstracts have been read and 90 abstracts were detected as relevant for the topic. Only fMRI-based studies observing alterations in

functional connectivity in PD compared to a healthy cohort were used for further examination. Additionally, further exclusion criteria are listed in **Table 17**.

Exclusion criteria - Abstracts
• Studies based on EEG[(1)] data • Studies based on MEG[(2)] data • Studies based on PET[(3)] data • Studies based on SPECT[(4)] data • Studies based on MER[(5)] data • Studies based on MRI data (structural imaging, e.g. DT-MRI[(6)]) • Studies based on neuromelanin imaging • Less than n= 15 Parkinson's disease patients included in study • Studies with no healthy control (HC) group • Studies mainly stating drug effects or DBS[(7)] effects on clinical outcome • Studies not considering Parkinson's disease • Studies stating rTMS[(8)] induced alteration in the Tower of London task • Studies mostly concerning cognitive changes/memory impairment analysed via fMRI, were excluded for Part 2 (if not in the list for Part 1, they were added into the list of Part 1) • Paper not in English

[(1)] EEG: Electroencephalography

[(2)] MEG: Magnetoencephalography

[(3)] PET: Positron emission tomography

[(4)] SPECT: Single-photon emission computed tomography

[(5)] MER: Microelectrode recording

[(6)] DT-MRI: Diffusion tensor magnetic resonance imaging

[(7)] DBS: Deep brain stimulation

[(8)] rTMS: Repetitive transcranial magnetic stimulation

Table 17: Exclusion criteria for screening abstracts

Subsequently, the remaining studies were arranged in a Microsoft® Excel® 2010 sheet, including the following points: "title", "authors", "trial type", "number of patients", "used approach for analysis", "main results", "journal" and "impact factor of the journal". The impact factor of a journal is an indicator, which states the annually average number of citations to lately published articles in the journal. The

impact factors of the singular journals, where the studies were published, were detected via Journal Citation Reports (JCR) on the 1st of August 2018. A List with all impact factors of the selected studies is attached in the annex.
*E*xclusion criteria for screening the full-text-studies are listed in **Table 18**. Concerning these exclusion points, 41 studies remained.

Exclusion criteria – Full-text-screening
• Trial not available in English language • Studies only concerning Lewy body dementia • Studies concerning the effects of neurofeedback • Less than 20 study participants (in the PD cohort)* • Studies not concerning resting-state fMRI (only task-based fMRI e.g. writing task/examining micrographia)** • Impact factor <1

*It was decided that the PD-cohort must consist of at least 20 participants, because of the fact that in many studies subgroups of the PD-cohort were formed and so the number of PD patients in the singular subgroups were too low – therefore this adjustment was made.

** This criterion is only applicable for part one

Table 18: Exclusion criteria for screening full-text-studies

It has been decided that only studies comparing resting state changes between PD patients and HCs are further used for part one of the review, for part two, task-based studies are used as well. The purpose of this adjustment is, to improve the comparability between the remaining studies.

Additionally 3 studies, which were either found via screening the reference-lists (76,77) of the selected studies or added by my supervisor (78), were used for performing the review. One study (76) was added, although less than 20 PD patients participated (in this study no subgroups were formed; high impact factor of journal).
In **Table 19** the extraction flow is shown, and in **Figure 11** the extraction-process is visualised in a chart.

Division	Titles to analyse	Relevant titles*	Relevant abstracts	Relevant studies	Additional studies
Resting state connectivity in PD	P: 209 C: 87 G: 280	P: 101 C: 13 G: 118	P: 17 C: 0 G: 51	P: 8 C: 0 G: 24	
Connectivity changes in cognitively impaired PD patients	P: 86 C: 33 G: 34	P: 56** C: 7** G: 37**	P: 5 C: 3 G: 14	P: 1 C: 0 G: 8	+ 3
In total	729	332	90	41 → **44**	

*Relevant Titles also include titles remarked as 'maybe-relevant'

**including titles added from part one

P: PubMed

C: Cochrane Central Register of Controlled Trials

G: Google Scholar

PD: Parkinson's disease

Table 19: Extraction flow of the singular subdivisions

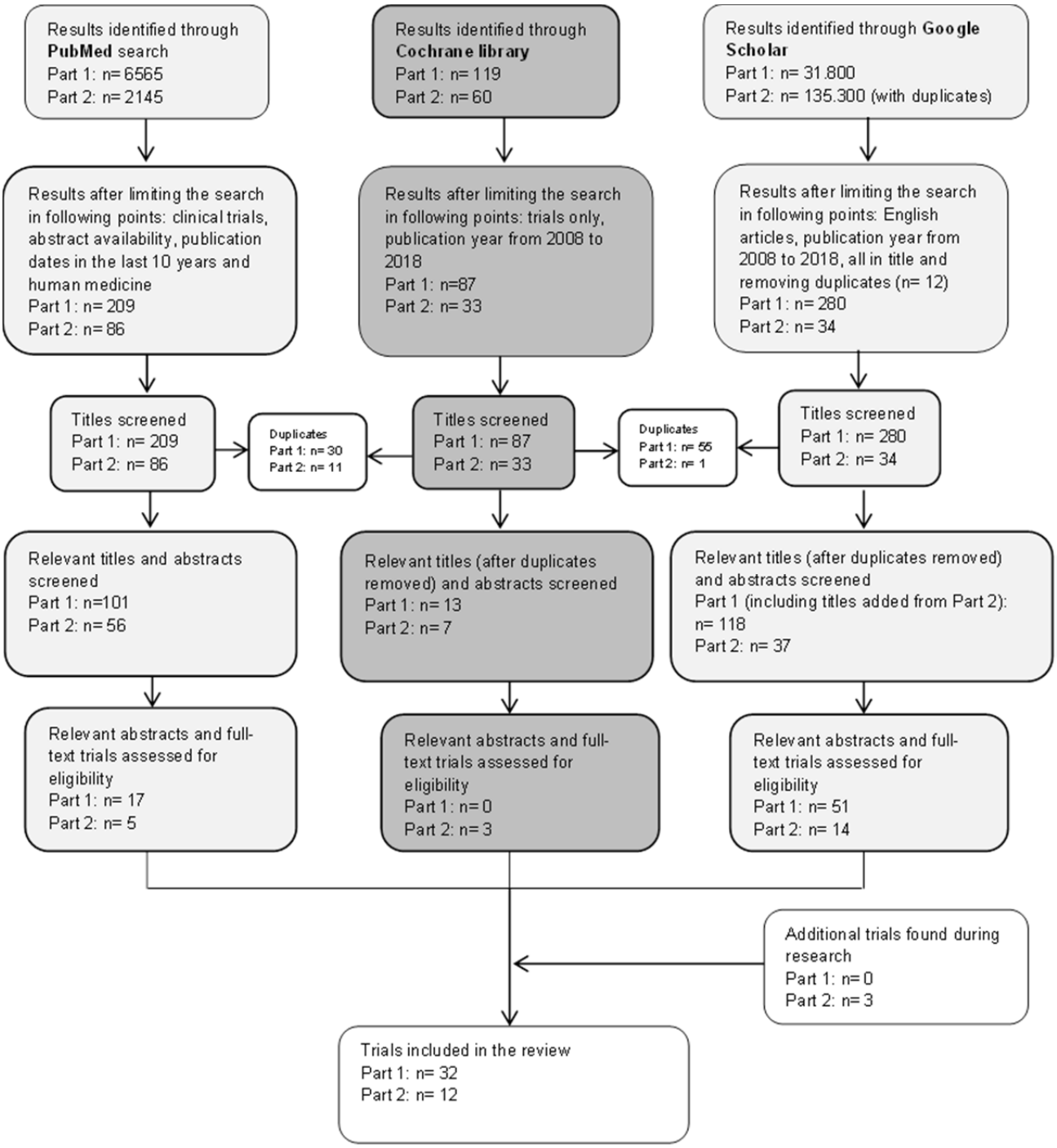


Figure 11: Flow chart of extraction process

Sequentially, the remaining 44 studies were screened concerning the level of evidence for screening recommendations according to the *Strength of Recommendation Taxonomy (SORT)* arranged by Ebell et al. (2004) **(Table 20)** (13). Due to the fact, that all of the selected studies are either case-control studies, cohort studies or cross-sectional studies they have been filed in the *category B – Recommendation based on inconsistent or limited-quality patient-oriented evidence*. Furthermore, on the basis of the issues, these studies cover – mainly medical research issues, which are not yet involved in the clinical routine (means that the patients not yet benefit of these findings) – they have been assigned as *Level 2 quality (limited-quality patient-orientated evidence; no morbidity, mortality or symptom improvement, no cost reduction or change in quality of life)*.

Study quality	**Strength of recommendation**	**Type of publication**
Level 1 – good-quality patient-orientated evidence*	A – Recommendation based on consistent and good-quality patient-oriented evidence	High quality randomized controlled trial All-or-none study**
Level 2 – limited-quality patient-orientated evidence	B – Recommendation based on inconsistent or limited-quality patient-oriented evidence	Retrospective/prospective cohort study (with poor follow-up) Case-control study Case series***
Level 3 – other evidence	C – Recommendation based on consensus, usual practice, opinion, disease-oriented evidence****, or case series for studies of diagnosis, treatment, prevention, or screening.	

* Patient-orientated evidence: measures outcomes that matter to patients, e.g. morbidity, mortality, symptom improvement, cost reduction and quality of life.

** All-or-none study: when the treatment causes a dramatic change in outcomes.

*** Case series or clinical series: these do not employ an analytical design (e.g. cohort studies, case control studies or randomized controlled trials) or a hypothesis testing.

**** Disease-oriented evidence: measures intermediate, physiologic, or surrogate endpoints that may or may not reflect improvements in patient outcomes, e.g. blood pressure, blood chemistry.

Table 20: Strength of Recommendation Taxonomy (SORT) modified after Ebell et al. (2004) (13)

3 Results

3.1 Search Results

Through the methodical search 41 studies were found. Of those studies, 32 belong to the first chapter “Resting state connectivity in Parkinson’s disease” and 9 to the second chapter “Connectivity changes in cognitively impaired Parkinson’s disease patients”. Additionally, three studies, two were detected through screening the reference-lists (76,77) and one was added by my supervisor (78) were added for part two (Part 1: 32 studies; Part 2: 12 studies). The study from Ghahremani et al. (2018) (11) which was primary found during the search for the first chapter, was finally used for chapter one and two.

3.2 Resting state connectivity in Parkinson’s disease

The first part concerning RSC changes in PD is divided into 11 subparts:

1. Hyposmia (2 studies) **(Table 21)**
2. Freezing of gait (FOG) (2 studies) **(Table 22)**
3. Tremor-dominant (TD) or akinetic-rigid (AR) subtype (4 studies) **(Table 23)**
4. TD or postural instability of gait (PIGD) subtype (3 studies) **(Table 24)**
5. Fatigue (3 studies) **(Table 25)**
6. Apathy (1 study) **(Table 26)**
7. Drooling (1 study) **(Table 27)**
8. Different PD stages (3 studies) **(Table 28)**
9. Antiparkinsonian-medication impact (5 studies) **(Table 29)**
10. Motor impairment in general (5 studies) **(Table 30)**
11. FC alterations in general in PD (3 studies) **(Table 31)**

3.2.1 Hyposmia

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication-status
Severe hyposmia and aberrant functional connectivity in cognitively normal Parkinson's disease (79)	Yoneyama, N.; Watanabe, H.; Kawabata, K.	2018	Nagoya University Graduate School of Medicine	30 PD patients (15 with severe hyposmia; 15 with no/mild hyposmia); 15 HCs	Seed-based approach, ICA	PD-ON
Alterations in the limbic/ paralimbic cortices of Parkinson's disease patients with hyposmia under resting-state functional MRI by regional homogeneity and functional connectivity analysis (80)	Su, M.; Wang, S.; Fang, W.	2015	First Affiliated Hospital Chongqing	54 PD patients (38 obvious hyposmia; 16 non/less obvious hyposmia); 22 HCs (age-matched)	ReHo, seed-based approach	PD-OFF

MRI: magnetic resonance imaging; PD: Parkinson's disease; HC: healthy controls; ICA: independent component analysis; ReHo: regional homogeneity; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state

Table 21: Studies analysing RSC in PD patients with hyposmia

3.2.2 Freezing of gait

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Altered resting-state brain activity in Parkinson's disease patients with freezing of gait (81)	Mi, T-M.; Mei, S-S.; Liang, P-P.	2017	Xuanwu Hospital of Capital Medical University (Beijing)	57 PD patients (29 patients with FOG; 28 patients without FOG); 31 HCs	ALFF	PD-ON
Decreased interhemispheric homotopic connectivity in Parkinson's disease patients with freezing of gait: A resting state fMRI study (82)	Li, J.; Yuan, Y.; Wang, M.	2018	First Affiliated Hospital of Nanjing Medical University	54 PD patients (21 PD-FOG; 33 PD-NFOG); 24 HCs (age- and gender-matched)	VMHC, correlation analysis	PD-OFF

PD: Parkinson's disease; HC: healthy control; ALFF: amplitude of low frequency fluctuation; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state; fMRI: functional magnetic resonance imaging; (N)FOG: with(out) freezing of gait; VMHC: voxel mirrored homotopic connectivity

Table 22: Studies analysing RSC in PD patients with freezing of gait

3.2.3 Tremor-dominant or akinetic-rigid subtype

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Disrupted functional connectivity of basal ganglia across tremor-dominant and akinetic/rigid-dominant Parkinson's disease (83)	Guan, X.; Zeng, Q.; Guo, T.	2017	Zhejiang University School of Medicine	106 PD patients (57 PD-TD; 49 PD-AR); 52 HCs	ICA, ECM (global connectivity measure), ROI-based analysis	PD-OFF
Decreased interhemispheric functional connectivity in subtypes of Parkinson's disease (84)	Hu, X.; Zhang, J.; Jiang, X.	2015	Third Military Medical University, Chongqing	50 PD patients (21 TD; 29 AR); 26 HCs	VMHC	PD-OFF
Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease (85)	Baudrexel, S.; Witte, T.; Seifried, C.	2011	Goethe University Frankfurt/Main	31 PD patients; 44 HCs	Seed-based approach, post hoc analyses of motor hand area	PD-OFF
Resting-state functional connectivity of dentate nucleus is associated with tremor in Parkinson's disease (86)	Ma, H.; Chen, H.; Fang, J.	2015	Beijing	50 PD patients (25 TD; 25 NTD); 29 HCs (age-matched)	Seed-based approach	PD-OFF

PD: Parkinson's disease; (N)TD: (non) tremor dominant; AR: akinetic-rigid; HC: healthy control; ICA: independent component analysis; ECM: eigenvector centrality mapping; ROI: region of interest; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state; VMHC: voxel mirrored homotopic connectivity

Table 23: Studies analysing RSC in PD patients with tremor-dominant or akinetic-rigid subtype

3.2.4 Tremor-dominant or postural instability of gait subtype

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Different patterns of spontaneous brain activity between tremor-dominant and postural instability/gait difficulty subtypes of Parkinson's disease: A resting-state fMRI study (87)	Chen, H-M.; Wang, Z-J.; Fang, J-P.	2015	Capital Medical University Beijing	31 PD patients (12 tremor-dominant; 19 postural instability/gait difficulty); 22 HCs (gender- and age-matched)	ALFF	PD-ON
Resting state fMRI reveals increased subthalamic nucleus and sensorimotor cortex connectivity in patients with Parkinson's disease under medication (88)	Shen, B.; Gao, Y.; Zhang, W.	2017	Affiliated Hospital of Nanjing Medical University	31 PD patients; 31 HCs	Seed-based approach	PD-ON

Resting-state functional connectivity of subthalamic nucleus in different Parkinson's disease phenotypes (89)	Wang, Z.; Chen, H.; Ma, H.	2016	Beijing	31 PD patients (19 PIGD; 12 TD); 22 HCs	Seed-based approach	PD-OFF

fMRI: functional magnetic resonance imaging; PD: Parkinson's disease; HC: healthy control; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state

Table 24: Studies analysing RSC in PD patients with tremor-dominant or postural instability of gait subtype

3.2.5 Fatigue

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Alterations in regional homogeneity of resting-state brain activity in fatigue of Parkinson's disease (90)	Li, J.; Yuan, Y.; Wang, M.	2017	First Affiliated Hospital of Nanjing Medical University	49 PD patients (17 with fatigue; 32 without fatigue); 25 HCs (age- and gender-matched)	ReHo	PD-ON
Functional connectivity underpinnings of fatigue in "drug-naïve" patients with Parkinson's disease (91)	Tessitore, A.; Giordano, A.; De Micco, R.	2016	Second University of Naples	40 PD patients (20 with fatigue; 20 without fatigue); 20 HCs (age- and sex-matched)	Single-subject and group-level ICA	PD-OFF
Abnormal resting-state neural activity and connectivity of fatigue in Parkinson's disease (92)	Zhang, J-J.; Ding, J.; Li, J-Y.	2017	First Affiliated Hospital of Nanjing Medical University	49 PD patients (17 with fatigue; 32 without fatigue); 25 HCs	ALFF, seed-based approach	PD-OFF

PD: Parkinson's disease; HC: healthy control; ReHo: regional homogeneity; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state; ICA: independent component analysis; ALFF: amplitude of low frequency fluctuation

Table 25: Studies analysing RSC in PD patients with fatigue

3.2.6 Apathy

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy (93)	Baggio, H.C.; Segura, B.; Garrido-Millan, J.L.	2015	University of Barcelona	62 PD patients; 31 HCs (age-, sex-, and education-matched)	Seed-based approach	PD-ON

PD: Parkinson's disease; HC: healthy control; PD-ON: Parkinson's disease ON medication state

Table 26: Study analysing RSC in PD patients with apathy

3.2.7 Drooling

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
A resting-state fMRI study on early-stage drug-naïve Parkinson's disease patients with drooling (94)	Hou, Y.; Luo, C.; Yang, J.	2016	West China Hospital	30 PD patients (15 "drooler"; 15 non "drooler"); 30 HCs (age- and sex-matched)	Seed-based approach, post-hoc ROI analysis	PD-OFF

fMRI: functional magnetic resonance imaging; PD: Parkinson's disease; ROI: region of interest;

PD-OFF: Parkinson's disease patients in OFF medication state

Table 27: Study analysing RSC in PD patients with drooling

3.2.8 Different Parkinson's disease stages

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Subthalamic nucleus – sensorimotor cortex functional connectivity in de novo and moderate Parkinson's disease (95)	Kurani, A.S.; Seidler, R.D.; Burciu, R.G.	2015	University of Illinois; University of Michigan	39 PD patients (20 de novo/drug-naïve; 19 moderate PD-OFF); 19 HCs	Seed-based approach	PD-OFF
The trajectory of disturbed resting-state cerebral function in Parkinson's disease at different Hoehn and Yahr stages (96)	Luo, C.Y.; Guo, X.Y.; Song, W.	2015	West China Hospital	80 PD patients (28 H&Y stage I; 28 H&Y stage II; 24 H&Y stage III); 30 HCs	ALFF, seed-voxel correlation approach	PD-OFF

Reduced functional connectivity in early-stage drug-naïve Parkinson's disease: a resting-state fMRI study (97)	Luo, C.Y.; Song, W.; Chen, Q.	2013	West China Hospital	52 PD patients; 52 HCs (age- and sex-matched)	Seed-voxel correlation approach, post hoc region-wise FC analysis of amygdala-putamen circuit	PD-OFF

PD: Parkinson's disease; HC: healthy control; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state; H&Y: Hoehn & Yahr; ALFF: amplitude of low frequency fluctuation; fMRI: functional magnetic resonance imaging; FC: functional connectivity

Table 28: Studies analysing RSC in different PD-stages

3.2.9 Antiparkinsonian-medication impact

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach
Functional connectivity in the basal ganglia network differentiates PD patients from controls (98)	Szewczyk-Krolikowski, K.; Menke, R.A.L.; Rolinski, M.	2014	University of Oxford	32 PD patients (19 discovery group; 13 validation group); 19 HCs (age-, sex-matched)	Group-level ICA
Rhythm-specific modulation of the sensorimotor network in drug-naïve patients with Parkinson's disease by levodopa (99)	Esposito, F.; Tessitore, A.; Giordano, A.	2013	University of Naples, University of Maastricht	20 PD patients (10 levodopa administration; 10 placebo administration); 18 HCs (age-matched)	Single-subject and group-level ICA
Altered resting-state functional connectivity of the striatum in Parkinson's disease after levodopa administration (100)	Yang, W.; Liu, B.; Huang, B.	2016	Guangdong General Hospital	22 PD patients; 28 HCs (age- and gender-matched)	Seed-based approach
Dopaminergic basis for impairments in functional connectivity across subdivisions of the striatum in Parkinson's disease (101)	Bell, P.T.; Gilat, M.; O'Callaghan, C.	2015	University of Sydney, University of Queensland	39 PD patients; 40 HCs (age-matched)	Seed-based approach
Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease (102)	Kwak, Y.; Peltier, S.; Bohnen, N.I.	2010	University of Michigan	25 PD patients; 24 HCs (age- and gender-matched)	Seed-based approach

PD: Parkinson's disease; HC: healthy control; ICA: independent component analysis

Table 29: Studies analysing RSC in PD patients with different antiparkinsonian-medication status

3.2.10 Motor impairment in general

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Alteration in the local and global functional connectivity of resting state networks in Parkinson's disease (11)	Ghahremani, M.; Yoo, J.; Chung, J.Y.	2018	Daejeon; Seoul	60 PD patients; 60 HCs (age-matched)	Seed-based correlation analysis, persistent homology analysis	PD-OFF
Altered functional connectivity between precuneus and motor systems in Parkinson's disease patients (103)	Thibes, R.B.; Novaes, N.P.; Lucato, L.T.	2017	Brazil	55 PD patients; 37 HCs	Seed-based approach	PD-ON
Functional connectivity differences of the subthalamic nucleus related to Parkinson's disease (104)	Mathys, C.; Caspers, J.; Langner, R.	2016	University of Duesseldorf	54 PD patients; 55 HCs (matched for age, gender, and within-scanner motion)	Seed-based approach, correlation analysis between motor symptoms and FC	PD-ON
Decreased resting-state interhemispheric functional connectivity in Parkinson's disease (105)	Luo, C.; Guo, X.; Song, W.	2015	Sichuan University	51 PD patients (drug-naïve); 51 HCs (age- and gender-matched)	VMHC	PD-OFF
Parkinson's disease patients show reduced cortical-subcortical sensorimotor connectivity (106)	Sharman, M.; Valabregue, R.; Perlbarg, V.	2013	Paris	36 PD patients; 45 HCs (age-matched)	Seed-based approach	PD-OFF

PD: Parkinson's disease; HC: healthy control; PD-OFF: Parkinson's disease patients in ON/OFF medication state; VMHC: voxel-mirrored homotopic connectivity; FC: functional connectivity

Table 30: Studies analysing motor impairment in general

3.2.11 Functional connectivity alterations in general in Parkinson's disease

Title	Authors	Year	Publication Location	Number of cases and HCs	Approach	Medication status
Discriminative analysis of Parkinson's disease based on whole brain functional connectivity (107)	Chen, Y.; Yang, W.; Long, J.	2015	South China University of Technology; Guangdong General Hospital	21 PD patients (no caffeine, nicotin, alcohol prior to scanning); 26 HCs (age- and sex-matched)	MVPA	PD-OFF

Abnormal functional connectivity density in Parkinson's disease (108)	Zhang, J.; Bi, W.; Zhang, Y.	2015	Third Military Medical University, Chongqing	31 PD patients; 34 HCs	Voxel-wise contrasts of FCD	PD-ON
Parkinson's disease-related spatial covariance pattern identified with resting-state functional fMRI (109)	Wu, T.; Ma, Y.; Zheng, Z.	2015	Beijing	(1) 58 PD patients; 54 HCs (age- and gender-matched) (2) derivation sample (28 PD patients); prospective validation sample (30 PD patients); 26 HCs	ALFF, scaled subprofile model (multivariate spatial covariance technique based on PCA)	PD-OFF

PD: Parkinson's disease; HC: healthy control; PD-ON/OFF: Parkinson's disease patients in ON/OFF medication state; MVPA: multivariate pattern analysis; FCD: functional connectivity density; fMRI: functional magnetic resonance imaging; ALFF: amplitude of low frequency fluctuation; PCA: principal component analysis;

Table 31: Studies analysing RSC alterations in general in PD

3.3 Connectivity changes in cognitively impaired Parkinson's disease patients

The second part, concerning FC changes in cognitively impaired PD patients, is further divided into 3 subparts. In **Tables 32-34** all studies are listed with their titles, first authors, publication year and location, number of cases/HCs (healthy controls) and the used task or rather the used approach for resting state studies.

The three subparts contain:

1. Mild cognitive impairment and cognitive impairment in general (8 studies) **(Table 32)**
2. Memory dysfunctions (3 studies) **(Table 33)**
3. Executive dysfunction (2 studies) **(Table 34)**

3.3.1 Mild cognitive impairment and cognitive impairment in general

Title	Authors	Year	Publication Location	Number of cases and HCs	Task/Approach
Cognitive impairment and resting-state network connectivity in Parkinson's Disease (5)	Baggio, H-C.; Segura, B.; Sala-Llonch, R.	2015	University of Barcelona	65 PD patients; 36 HCs	Resting state analysis (seed-based and ICA)
Resting-state functional connectivity associated with mild cognitive impairment in Parkinson's disease (15)	Amboni, M.; Tessitore, A.; Esposito, F.	2015	University of Salerno and Naples; University of Maastricht	42 PD patients (21 MCI; 21 non-MCI); 20 HCs	Resting state analysis (ICA)
Altered functional connectivity in the default mode network is associated with cognitive impairment and brain anatomical changes in Parkinson's disease (110)	Lucas-Jiménez, O.; Ojeda, N.; Pēna, J.	2016	University of Deusto	37 PD patients; 16 HCs	Resting state analysis (seed-based)
Dynamic functional connectivity in Parkinson's disease patients with mild cognitive impairment and normal cognition (111)	Díez-Cirarda, M.; Strafella, A.P.; Kim, J.	2018	Universtiy of Deusto; University of Toronto	37 PD patients; 26 HCs	Resting state (ICA, dynamic FC analysis, graph theoretical approach)
Abnormal resting-state functional connectivity in posterior cingulate cortex of Parkinson's disease with mild cognitive impairment and dementia (112)	Zhan, Z-W.; Lin, L-Z.; Yu, E-H.	2018	Fujian Medical University	27 PD patients (at different cognitive state); 9 HCs	Resting state analysis (seed-based)
Dysfunction of the default mode network in drug-naïve Parkinson's disease with mild cognitive impairments: A resting-state fMRI study (113)	Hou, Y.; Yang, J.; Luo, C.	2016	University Hospital of Asturias	32 PD patients (14 MCI; 18 cognitive unimpaired); 22 HCs	Resting state analysis (seed-based)
Striatal changes in Parkinson disease: An investigation of morphology, functional connectivity and their relationship to clinical symptoms (78)	Owens-Walton, C.; Jakabek, D.; Li, X.	2018	Canberra Hospital	74 PD patients (34 early PD*; 23 late PD**; 17 PDD); 27 HCs	Resting state analysis (seed-based)
Default-mode network connectivity in cognitively unimpaired patients with Parkinson's disease (76)	Tessitore, A.; Esposito, F.; Vitale, C.	2012	Second University of Naples	16 PD patients; 16 HCs (age- and gender-matched)	Single-subject and group-level ICA

PD: Parkinson's disease; HC: healthy control; ICA: independent component analysis; MCI: mild cognitive impairment; FC: functional connectivity; PDD: Parkinson's disease dementia

* early PD: 5 years or less since diagnosis; ** late PD: more than 5 years since diagnosis

Table 32: Studies analysing MCI/cognition changes via fMRI in PD

3.3.2 Memory dysfunction

Title	Authors	Year	Publication Location	Number of cases and HCs	Task
Compensatory neural mechanisms in cognitively unimpaired Parkinson disease (114)	Poston, K.L.; York Williams, S.; Zhang, K.	2016	Stanford University Medical Centre	31 PD patients (cognitively unimpaired); 23 HCs	Working memory task
Verbal memory in Parkinson's disease: A combined DTI and fMRI study (115)	Lucas-Jiménez, O.; Díez-Cirarda, M.; Ojeda, N.	2015	University of Deusto	37 PD patients; 15 HCs	Verbal memory fMRI paradigm
Diminished activation of motor working-memory networks in Parkinson's disease (77)	Rottschy, C.; Kleiman, A.; Dogan, I.	2013	Aachen; Juelich (Germany)	23 PD patients; 23 HCs (age-, and gender-matched)	Motor working memory task

DTI: diffusion tensor imaging; fMRI: functional magnetic resonance imaging; HC: healthy control;

PD: Parkinson's disease

Table 33: Studies analysing memory-changes via fMRI in PD

3.3.3 Executive dysfunction

Title	Authors	Year	Publication Location	Number of cases and HCs	Task/Approach
Differential functional connectivity alterations of two subdivisions within the right dlPFC in Parkinson's disease (116)	Caspers, J.; Mathys, C.; Hoffstaedter, F.	2017	University of Duesseldorf	39 PD patients; 44 HCs	Resting state analysis (seed-based, whole brain functional connectivity)
Alteration in the local and global functional connectivity of resting state networks in Parkinson's disease (11)	Ghahremani, M.; Yoo, J.; Chung, J.Y.	2018	Daejeon; Seoul	60 PD patients; 60 HCs (age-matched)	Seed-based correlation analysis, persistent homology analysis

dlPFC: dorsolateral prefrontal cortex; PD: Parkinson's disease; HC: healthy control;

Table 34: Studies analysing changes in executive functions via fMRI in PD

4 Discussion

The aim of this review is to clearly point out the latest state of research concerning resting state connectivity changes assessed with fMRI in PD. Studies dealing with connectivity changes in cognitively impaired PD patients are particularly highlighted. Overall 44 studies have been included in the review, covering the topics hyposmia, FOG, TD-/AR-subtype, TD-/PIGD-subtype, fatigue, apathy, drooling, different PD stages, antiparkinsonian-medication impact, motor impairment in general, FC alterations in general in PD, MCI, memory dysfunction, and executive dysfunction. As mentioned above the study from Ghahremani et al. (2018) (11) was employed for part one and two. The number of participants in the included studies varies between 16 and 106 subjects.

4.1 Resting state connectivity in Parkinson's disease

4.1.1 Hyposmia

Yoneyama et al. (2018) (79) and Su et al. (2015) (80) examined connectivity changes in PD patients due to hyposmia. On account of the different approaches used (Regional Homogeneity [ReHo], seed-based analysis, ICA) a direct comparison is not possible. The main results in the Yoneyama et al. paper indicate that in PD patients with hyposmia a diffuse decrease in FC between amygdala and especially the inferior parietal lobule (IPL), lingual gyrus, fusiform gyrus and superior/middle temporal gyrus and an increase in FC within the primary visual networks was predominant. These regions showed a positive correlation, as well with the *"Odor Stick Identification Test for Japanese"* (test for odor-identification performance), as the *"Addenbrooke's Cognitive Examination-Revised"* (test for general cognitive function). Furthermore, a moderate reduction in FC among canonical resting state networks (RSN), within the precuneus network and other networks was detected. Whereas in amygdala highly decreased FC was found, in canonical networks only slightly decreased FC was detected. Maintenance of FC within canonical networks might be crucial for preserving cognitive functions, during disease progression (severe FC reductions around amygdala as a sign for disease-progression) (79). Main results of the Su et al. paper state that hyposmia

patients showed reduced ReHo values in the primary olfactory cortices (including amygdala, olfactory gyrus, anterior olfactory nucleus and piriform cortex) and secondary olfactory structures (e.g. hippocampus, insula). Primary olfactory cortices receive direct olfactory information from the olfactory bulb and transfer this information to secondary olfactory structures. These ReHo alterations inversely correlated with the *"threshold of olfactory detection"* scores. Collectively, decreased FC in primary and secondary olfactory areas of limbic and paralimbic cortices is linked to the presence of hyposmia in PD (80). Both results show that especially brain regions, which are essential for the olfactory system (e.g. amygdala) exhibit a decrease in FC in hyposmia patients.

4.1.2 Freezing of gait

Mi et al. (2017) (81) and Li et al. (2018) (82) investigated alterations in FC due to FOG in PD patients. The results of Mi et al. indicate that FOG in PD patients is associated with altered processing in frontal and parietal regions (prefrontal and posterior parietal cortices are described as the cognitive control network). In PD patients with freezing of gait (PD-FOG) decreased amplitude of low-frequency fluctuations (ALFF) values were found in prefrontal cortex (PFC) (including superior frontal gyrus) and increased ALFF values were found in parietal cortex and anterior cingulate cortex (ACC). The increase in parts of the cognitive control network (especially in the posterior parietal part) might be an attempt to compensate FOG in PD. ALFF values in superior frontal gyrus (SFG) might utilise as a marker for FOG progression (the reduction of ALFF values in SFG becomes more significant with the severity of FOG). Furthermore, enhanced basal ganglia inhibitory output was found, which inhibits processing of data in the thalamus and brainstem. Additionally, the severity of FOG was found to be positively correlated with ALFF values in bilateral globus pallidus and inversely correlated with ALFF values in bilateral sensorimotor regions and thalamus. Reduced ALFF values were found in bilateral Crus I of the cerebellum in PD-FOG compared to PD patients without FOG (PD-NFOG). This finding suggests that cerebellar dysfunctions also play a crucial role in the pathophysiology of FOG in PD (81). Concordantly, Li et al. ascertained decreased voxel-mirrored homotopic connectivity (VMHC) values in IPL, and concluded that this alteration may be a biomarker for PD-FOG patients

(82). Even if different RS-analyses were used, the parietal brain region is emphasised to be elemental in the pathogenesis of FOG in both studies.

4.1.3 Tremor-dominant or akinetic-rigid subtype

Guan et al. (2017) (83), Hu et al. (2015) (84) and Baudrexel et al. (2011) (85) identified RSC differences in PD patients with tremor-dominant subtype (PD-TD) and PD patients with akinetic-rigid subtype (PD-AR). Ma et al. (2015) (86) highlighted RSC alterations in PD-TD only (see below). One of the essential findings in the study of Guan et al. is that PD-AR showed a reduction of FC between occipital lobule, cerebellum posterior lobule and basal ganglia compared to PD-TD. A positive correlation between the FC in occipital lobule and tremor scores and a negative correlation with akinesia/rigidity scores was detected (cerebellum posterior lobule and occipital lobule are important for motor modulation). In PD-TD compared to HCs increased FC between superior frontal lobule, cerebellum posterior lobule and basal ganglia was found. It is hypothesised that in akinesia and rigidity the cortico-striato-thalamic loop and in tremor the striato-thalamo-cortical and cerebello-thalamo-cortical loops play a crucial role. In FOG mainly the occipital and parietal regions are impaired. Patients with PD-AR have a poorer prognosis than patients with PD-TD and are more likely to develop FOG (83). Hu et al. detected a decrease in VMHC values in the precentral gyrus (key region of primary motor areas, responsible for more complex motor behaviour) in PD-AR and a decrease in VMHC values in bilateral posterior lobule of the cerebellum in PD-TD compared to HCs. It is believed that akinesia and rigidity are due to a hypofunction of the putamen-premotor cortex networks and the nigrostriatal dopamine system. Moreover, the precentral gyrus is a part of the bilateral medial frontal cortex, which is believed to be an important hub of the DMN. Early FC disruptions in the DMN might be a precursor for cognitive decline. Therefore it is hypothesised that FC alterations of precentral gyrus in PD-AR might lead to a more rapid progression of cognitive decline. Additionally, a negative correlation between tremor scores and VMHC values in the bilateral cerebellum in PD-TD was found (84). Baudrexel et al. show in turn that PD-TD demonstrated enhanced STN-FC in the hand knob area of M1/S1 and PD-AR in the midline cortical motor regions. It is suggested that the overactivity of FC in the hand knob

area in PD-TD might be due to tremor reflected oscillatory neuronal activity. It has been demonstrated that the amplitude of parkinsonian tremor is closely correlated with the BOLD signal in this area (85). Finally, Ma et al. state as main results, that PD-TD exhibited an increase in dentate-cerebellar connectivity and a reduction in dentato-prefrontal connectivity. The hyperactivity in the cerebellum might play a compensatory role for impairment in the basal ganglia (86).

4.1.4 Tremor-dominant or postural instability of gait subtype

Chen et al. (2015) (87), Shen et al. (2017) (88) and Wang et al. (2016) (89) investigated RSC alterations in PD-TD and PD patients with postural instability of gait subtype (PD-PIGD). Due to different approaches used and different antiparkinsonian drug statuses (Chen et al. and Shen et al. PD-ON, Wang et al. PD-OFF) comparability of the results is poor. The main results in the paper of Chen et al. show that PD-TD demonstrated enhanced ALFF values in bilateral putamen and in cerebellar posterior lobe (might be crucial in the development of PD tremor), and reduced ALFF values in bilateral temporal gyrus and left superior parietal lobule (SPL) compared to PD-PIGD. ALFF values in bilateral cerebellar posterior lobe were found to be positively correlated with tremor scores and ALFF values of bilateral putamen negatively correlated with PIGD scores. Compared to HCs and PD-TD, PD-PIGD exhibited lower ALFF values in bilateral putamen. This impairment might be the basis of difficulties in performing previously learned movements (87). Shen et al. elucidate that in PD-PIGD an increase in FC was detected between STN and sensorimotor cortex. The alterations are motor symptom severity dependent (in PD-ON). They conclude that antiparkinsonian drugs might alternate the hyperdirect pathway and consequently variations in the motor symptoms might be seen (88). Wang et al. state that in PD-PIGD enhanced FC between STN and bilateral occipital lobe (visual cortex) was found and that this alteration positively correlated with PIGD-scores. Furthermore, a decrease in FC between left putamen, pons and STN was found. PD-TD exhibited an enhanced FC between bilateral STN and left cerebellar anterior lobe. FC between STN and cerebellum positively correlated with tremor scores. They draw the conclusion, that these distinguishable functional neural substrates, among different PD-subtypes,

might be the explanation why there is diverse surgical efficiency, seen among different symptoms in different PD subtypes (89).

4.1.5 Fatigue

Li et al. (90), Tessitore et al. (91) and Zhang et al. (92) examined RSC alterations of PD patients with fatigue. Through a ReHo analysis Li et al. found decreased ReHo values in left ACC and right SFG (both essential parts of the cognitive control network) and increased ReHo values in left postcentral gyrus and right inferior frontal gyrus (IFG) in PD patients with fatigue (PD-F) compared to PD patients without fatigue (PD-NF). These regions are normally involved in sensory, motor and cognitive processes and thus might play a role in the pathophysiology of fatigue (90). Tessitore et al. elucidate that a decrease in FC in the supplementary motor area (SMA) (within the sensorimotor network) and an increase of FC in the prefrontal and posterior cingulate cortices (within DMN) in PD-F was predominant (91). Lastly, Zhang et al. state that PD-F exhibited altered FC within the attention network (especially right middle frontal gyrus) and the salience network (especially right midcingulate cortex) (92). These results show that PD-F exhibit alterations in FC, especially within the cognitive control network and within the sensory motor network.

4.1.6 Apathy

Baggio et al. (2015) (93) assessed FC alterations in PD patients with apathy. Especially in the left fronto-striatal circuit, involving the limbic system and ventromedial regions, PD patients with apathy (PD-A) showed decreased FC (probably mediated by dopaminergic loss). These regions, which are hypothesised to be impaired in PD-A, are an essential part of the brain’s motivation and reward system. FC alterations, found in their study, showed a left-sided predominance. The risk of developing apathy might be increased, by the laterality of neuropathological changes. Furthermore, the presence of apathy was related to worse cognitive performance, leading to the hypothesis that there might be an association between apathy and cognitive deficits (93).

4.1.7 Drooling

Hou et al. (2016) (94) examined FC changes in PD patients with a drooling problem. The main findings demonstrate that PD patients with and without drooling exhibited reductions in FC in cortico-striatal loops, compared to HCs (the decrease was more prominent in the posterior than in the anterior putamen). An increase in FC was seen in the relatively unaffected parts of the striatum, mainly in anterior putamen and caudate. This increase might be a compensatory mechanism due to the significant decrease in other parts of cortico-striatal loops. Concerning the drooling phenomenon in PD, a decrease in FC in PD patients with drooling relative to those without drooling was found especially between putamen and bilateral sensorimotor areas, superior/inferior parietal lobules, and areas in the right occipital and temporal lobes. These alterations might play a crucial role in the pathogenesis of drooling in PD. It is considered that drooling rather results of a swallowing problem (in line with the detected FC alterations), than of a hypersecretion of saliva (94).

4.1.8 Different Parkinson's disease stages

Kurani et al. (2015) (95), Luo et al. (2015) (96), and Luo et al. (2013) (97) investigated FC changes in different stages of PD. Kurani et al. state that even in early PD stages FC changes between STN and sensorimotor cortex were present. Early-stage, as well as moderate-stage PD patients, showed an increase in FC between the more affected STN and M1S1 (FC of the less effected STN did not significantly differ from that of HCs) and showed that these alterations positively correlated with the UPDRS motor section. In de-novo PD patients the location in M1S1, which exhibited increased FC, was mainly situated in superior regions, whereas in moderate stage PD patients it was located in more inferior regions. Consequently, they hypothesised that the severity of motor impairments in PD may be due to changes in STN-M1S1 FC. Moreover authors state that the shifting of the location of FC increases in M1S1 regions might be a hint for disease progression (95). The main findings from Luo et al. (2015) demonstrate that regional activity was decreased in the left occipital and lingual regions. Furthermore, FC was reduced between these areas and temporal regions (a negative correlation between these FC alterations and UPDRS-III stages was also

detected). Especially in PD patients at H&Y stage II an increase in FC in the DMN was detected, indicating that patients in this stage exhibited a more highly functioning DMN (96). FC alterations in mesolimbic-striatal circuits and cortico-striatal loops were prominent in early-stage drug-naïve PD patients and were associated with early clinical non-motor features of PD patients, as Luo et al. (2013) state (97). These studies show a wide range of alterations due to PD stages (also regarding the different approaches used). As the disease progresses and as symptoms get worse, FC alterations differ as well.

4.1.9 Antiparkinsonian-medication impact

Szewczyk-Krolikowski et al. (2014) (98), Esposito et al. (2013) (99), Yang et al. (2016) (100), Bell et al. (2015) (101), and Kwak et al. (2010) (102) investigated in their studies FC changes in PD patients due to different medication situations (PD-ON versus PD-OFF). In the BGN reduced FC was found in PD patients, but with levodopa administration this decrease diminished, leading to the hypothesis that this FC decrease is a dopamine-dependent process (98,102). Acute levodopa administration improved FC in the sensorimotor network in PD patients (drug-naïve) (99). Yang et al. elucidate that dopamine depletion in PD patients was less extensive in the ventral part of the striatum, compared to the dorsal part. After levodopa administration, the cortex-striatum connectivity not only increased in the dorsal part but also in the ventral part (mainly in nucleus caudatus, essential for cognitive processes) of the striatum. This led to the notion, that the ventral part was overdosed by levodopa. This overdose of the nucleus caudatus might lead to cognitive dysfunctions in PD after levodopa administration (100). Concordantly, Bell et al. found out that in PD-OFF patients widespread dysfunctions in FC within striatal subdivisions, especially in the posterior regions, were present and that administration of dopaminergic medication improved this FC alterations. Furthermore, in PD-ON patients increased FC in anterior parts of the striatum were detected, similar to the overactivity found in the ventral parts of the striatum in the study from Yang et al. (101). In contrast, Kwak et al. found hyper-connectivity in cortico-striatal networks in PD-OFF patients, which were mitigated by L-DOPA administration. They suggested that dopamine depletion caused this hyper-connectivity in basal ganglia and associated networks (102). These contrary

results might be due to the different methods used in this study, compared to the studies from Yang et al. and Bell et al. These findings suggest that levodopa enhances FC in many brain regions and networks, but it can also lead to overactivity in FC due to an overwhelming effect of dopamine. Consequently, levodopa-administration (as well as administration of other anti-parkinsonian drugs) has to be weighed carefully, because not only the positive effects of levodopa dominate. Conclusively, fMRI can lead to a better understanding of FC changes, caused by medication administration, as well as not intended FC alterations, due to medication side-effects.

4.1.10 Motor impairment in general in Parkinson's disease

Ghahremani et al. (2018) (11), Thibes et al. (2017) (103), Mathys et al. (2016) (104), Luo et al. (2015) (105) and Sharman et al. (2013) (106) assessed FC alterations due to motoric difficulties in PD patients. Ghahremani et al. ascertained, through a seed-based correlation analysis and a persistent homology analysis, from a broad perspective (PCC-connectivity was assessed with 100 ROIs in the entire brain), missing FC between PCC and area 3, which corresponds to the primary somatosensory cortex and gets inputs from sensory fields. Furthermore, they found missing functional connections between the medial PFC connectome ring and somatosensory areas 3-6, which might explain motor and somatosensory impairments in PD (11). Additionally, Thibes et al. (2017) found, through a seed-based approach, decreased FC between PCC and basal ganglia, motor cortex and thalamus. They could not identify the exact regions of the alterations in the motor systems, only one big cluster was found, due to methodological limitations. Conclusively, they assumed that the decrease of FC between PCC (important key hub of DMN) and motor systems might be correlated with processes of planning and motor mental imagery (103). Another study (104) assessed, through a seed-based approach, functional connectivity alterations in STN and showed, through a correlation analysis, whether these alterations correlated with motor symptoms. A positive correlation between motor symptom severity, assessed through UPDRS-III, and FC with STN in a region between superior parietal cortex (SPC) and S1 was found. A negative correlation was found between motor symptom severity and FC between STN and left mid-insula.

Concluding, motor symptom severity in PD might partly be based on insufficient insular processing of sensorimotor information, due to a reduction of FC between STN and insula (104). Luo et al. (2015) (105) investigated with a VMHC-approach connectivity changes in PD. Concordantly, to the studies mentioned above, lower connectivity was found in putamen and cortical regions associated with motor control and sensory processing (105). Finally, Sharman et al. (2013) (106) contrasted anatomical and functional connectivity, especially in the sensorimotor circuits. In sensorimotor connections (especially cortical/subcortical connections with putamen and thalamus) anatomical deficits were most prominent, compared to other cortico-basal and thalamo-cortical circuits. Concordantly, FC reduction in sensorimotor circuit connections within the basal ganglia and between thalamus and basal ganglia was found. Furthermore an increase of FC in the anterior striatum (associative circuit) and ventral striatum (limbic circuit) was found, which might be a system-wide compensatory mechanism due to anatomical deficits (106). Even if different approaches were used, similar brain regions are discovered to be crucial for motor impairments.

4.1.11 Functional connectivity alterations in general in Parkinson's disease

The studies from Chen et al. (2015) (107), Zhang et al. (2015) (108) and Wu et al. (2015) (109) investigated FC alterations in patients with PD (number of PD patients among the different studies varies between 21 and 58 subjects) with different RS approaches (MVPA, seed based correlation analysis/persistent homology analysis and ALFF/scaled subprofile model). Due to the different approaches, the results are not comparable and the studies are only mentioned for the sake of completeness.

4.2 Connectivity changes in cognitively impaired Parkinson's disease patients

4.2.1 Mild cognitive impairment and cognitive impairment in general

The studies from Baggio et al. (2015) (5), Amboni et al. (2015) (15), Lucas-Jiménez et al. (2016) (110), Díez-Cirarda et al. (2018) (111), Zhan et al. (2018) (112), Hou et al. (2016) (113) and Owens-Walton et al. (2018) (78) examined FC alterations by means of various resting state approaches (with reference to **Table 32**) in PD patients with different initial cognitive status. The study from Tessitore et al. (2012) (76) highlights changes in FC, within the DMN, in cognitively unimpaired PD patients and they draw conclusions, regarding the development of cognitive declines. The number of PD patients, examined in the individual studies, varies between 16 and 74 subjects. Through neuropsychological testing patients were classified as PD patients with mild cognitive impairment (PD-MCI) or PD patients without (mild) cognitive impairment (PD-N[M]CI). In **Table 35** neuropsychological tests, used to identify the neuropsychological status of the PD patients in the individual studies, are listed.

Function	**Neuropsychological Tests**
Overall cognitive function	MMSE, MOCA, "Frontal Assessment Battery"
Executive function/attention	"Backward minus forward digit spans", "Trail-Making test", "phonemic fluency", "Stroop Colour-Word test", "Frontal Assessment Battery", "attentional matrices", "Wechsler Adult Intelligence Scale", "Brief Test of Attention", "Clock drawing test", "Corsi block span"
Visuospatial/visuoperceptual function	"Benton's Visual Form Discrimination test", "Judgement of Line Orientation test", "Constructional apraxia test", "copy task of Rey-Osterrieth Complex Figure test", "Clock test", "Incomplete letters from the Visual Object and Space Perception", "Hooper Visual Organisation test"
Memory	"Rey's Auditory Verbal Learning Test" (total learning and 20 minutes free recall), "Hopkins Verbal Learning test", "Brief Visual Memory test"

Language/verbal fluency	Semantic and phonetic fluency tests, “Boston naming test”
Visual learning	“Brief Visual Memory test” (learning and long-term recall performance)
Visual abilities	“Drawing test” (order and copy), “Visual Objects“, “Space Perception Battery” (incomplete letters and cubes)
Verbal learning	“Hopkins Verbal Learning test” (learning and long-term recall performance)
Processing speed	“Trail Making test-A”, “Salthouse Letter Comparison test”

MMSE: mini-mental state examination; MOCA: Montreal cognitive assessment

Table 35: Neuropsychological tests, which were used to assess the neuropsychological states of the PD patients (5,15,76,78,110-113)

Concerning the main results found through resting state functional connectivity analysis, the following findings are essential:

Tessitore et al. found reduced FC of the bilateral inferior parietal cortex (IPC) and right medial temporal lobe (MTL), within the DMN, in cognitively unimpaired PD patients. They hypothesised that these early FC alterations in IPC and MTL, within the DMN, might be associated with developing cognitive impairment in PD (76).

Baggio et al. found in PD-MCI a reduction of FC between the dorsal attention network (DAN) and frontal/insular areas (predominantly right sided), thalami and left striatum, compared to HCs. These FC reductions were also seen when comparing PD-MCI and PD-NMCI, but less extensive. Furthermore, a positive correlation between these FC alterations in the DAN and executive function scores/attention scores was found. Another essential finding from Baggio et al. demonstrates an increase of FC between the DMN and posterior cortical regions (evidence of structural degeneration was also found), corresponding to areas of the left fronto-parietal network (FPN) and the DAN, in PD-MCI compared to HCs and PD-NMCI. A negative correlation between this FC increase in the DMN and visuospatial/visuoperceptual scores was detected. These changes might be due to an interruption of the dynamic coupling mechanisms between these regions.

Concordantly, through a seed-based approach intra- (predominantly in DMN and DAN) and internetwork (predominantly between frontal and right insular FPN nodes and occipital/parietal DAN nodes) connectivity reductions, as well as internetwork connectivity increases (predominantly between midline and

frontal/temporal DMN nodes and posterior DAN nodes) were found. Concordantly, to the study from Tessitore et al., Baggio et al. found reduced within-DMN connectivity in PD-MCI. Furthermore, through a morphological analysis cortical thinning, especially in occipito-parietal regions, predominantly in PD-MCI was found, which was also associated with a decline in visuospatial/visuoperceptual function. The FC increases and morphological changes might be related to cortical dysfunctions, which might lead to progressive cognitive impairment and later on to dementia. The DMN is known as a “task-negative” network, with increasing activity during rest or internally-directed thoughts, whereas the DAN is known as a “task-positive” network, with increasing activity during externally-directed cognitive tasks. The FPN has been appointed to flexibly connect the DMN and the DAN. This connection varies depending on attentional task demands. It is suggested that fronto-insular cortical changes might be crucial for dysfunctions in the executive and attentional system and therefore for the reduction of FC between this area and the DAN (5).

Another study (15) found a decrease in FC between right IPC and PCC, within the DMN (concordantly to the intra-network reductions found by Baggio et al.), in both PD-MCI and PD-NMCI, compared to HCs, whereas a decrease in FC of the bilateral PFC, within the left FPN, was only observed in PD-MCI compared to HCs. These findings suggest that an alteration of FC, within the DMN, is present in all PD patients, neglecting the cognitive situation. Additionally, a reduction of FPN-FC might indicate MCI in PD patients. Furthermore, a positive correlation between visuospatial scores and FC in the left PFC, and as a trend in the right PFC, was detected. These findings indicate a connection between visuospatial dysfunction in PD and alterations in the frontal system (the frontal system is widely connected with posterior visuospatial areas). Further positive correlation was found between memory scores and executive/attentional scores and FC in the left PFC, which leads to the assumption that those alterations in the PFC not only cause memory impairment, but executive/attentional dysfunctions as well (15).

Hou et al. found similar FC alterations, mainly showing a reduction of FC between the DMN and precentral gyrus, middle temporal gyrus (MTG), insula, anterior IPL and middle frontal gyrus (MFG) and between MFG and MTG in PD-MCI compared to HCs. Furthermore, significant FC reductions, within the DMN, especially between hippocampal formation and IFG, between anterior temporal lobe (ATL)

and IFG, and between PCC and posterior IPL, were found in the PD-MCI group compared to HCs. The FC reduction between MFG and MTG showed a positive correlation with attention/working performance and the FC decrease between IFG and hippocampal formation positively correlated with memory function (113). Another study (110) found that FC was decreased between the PCC and bilateral MTL (areas within the DMN) in PD patients compared to HCs. A correlation of verbal and visual memory and FC between the PCC and the left MTL was ascertained. Furthermore, a correlation between visual abilities and FC between the PCC and the right MTL was also detected. Additionally to the FC alterations between these regions, lower grey matter volumes were detected in the posterior regions of the DMN, indicating that the posterior parts of the DMN are more impaired in PD (110).

Díez-Cirarda et al. (2018) investigated RS-FC alterations using different approaches – a graph theoretical approach and a dynamic FC analysis. Through dynamic FC analysis two indexes, including the *mean dwell time* (time spent in the same FC state) and the *number of transitions between states* (number of changes between FC states of each subject), were assessed. Concerning the graph theoretical analysis global parameters assessed were *global efficiency* (effectiveness of the network to convey information through the network) and the *clustering coefficient* (the average of clustering coefficients of every single node in a network). Additionally local parameters assessed were *local efficiency* (effectiveness of transporting information from one node to other close nodes), c*lustering coefficient* (number of existing connections/number of maximal possible connections) and b*etweenness centrality* (demonstrates the degree of which nodes stand between each other and therefore reflects the importance of a node within a network). The *sliding time windows method* was used for temporal dynamic FC analysis (acquired RS-fMRI is divided into windows and subsequently the variation of the FC in these windows is calculated). Through dynamic FC analysis two main FC states, during RS fMRI measurement, were found (first state 22% of the windows: hyper-connective state, showing a positive correlation between somatomotor network and visual network and anti-correlation between cognitive-control network, DMN and cerebellar network; second state 78% of the windows: hypo-connective state, showing modularity in somatomotor network, visual network and DMN). In PD-MCI compared to HCs a decrease in mean dwell

time, as well as higher state transition in the second state were found (no differences between PD-NMCI and HCs were found). These dynamic FC alterations could be one of the underlying causes of MCI, besides the intra-DMN FC reductions, in PD patients. Concerning the graph theoretical approach, PD-MCI exhibited a reduced clustering coefficient in the right precentral gyrus, compared to HCs, and a reduced betweenness centrality in the left paracentral gyrus compared to PD-NCI. These changes, both located in the somatomotor network might be crucial for reduced FC between somatomotor and other networks in PD-MCI (111).

Another study (112) states that PD-MCI exhibited increased FC between PCC and middle frontal gyrus (playing an essential role in executive functions), posterior cerebellum lobe (is essential for advanced cognitive functions, especially for memory and executive functions), middle temporal gyrus (is involved in visual perception, sensory information processing, memory, speech comprehension and emotional activity) and left precuneus (visuospatial imagery, episodic memory retrieval and self-processing operations). This increase in FC might be a resource recruitment attempt, acting as an initial response to MCI in PD patients. Furthermore, as the disease progresses from PD-MCI to PDD, this increase in FC was lost and a reduction of FC between PCC and caudate or thalamus (is essential for episodic memory, executive function, directional attention and working memory; is also called the “classification centre”) arose. Collectively, this loss of compensatory increased FC and the decrease between PCC and thalamus or caudate, might be underlying the progression from PD-MCI to PDD (112).

The last study (78) tried to figure out a connection between morphology, functionality and cognition. They state that caudate nuclei volumes and higher levels of cognitive functions (higher MMSE scores) positively correlated, as well as putamen volumes and higher levels of motor functions. According to the structural changes found in the striatum, functional changes (decreases/increases of FC between caudate nuclei/putamen and several brain regions) were found as well. Interestingly, an increase in FC between caudate nucleus and MFG, SFG and ACC (areas mediating cognitive functions) was found. This alterations lead to the hypothesis that the increase in FC between these areas might be a compensatory mechanism in response to the atrophy, found in PD-MCI, in caudate nuclei (78).

4.2.2 Memory dysfunction

Poston et al. (2016) (114), Lucas-Jiménez et al. (2015) (115) and Rottschy et al. (2013) (77) investigated FC in PD patients (number of participants varies between 23 and 37 subjects) and HCs, while performing either a (motor) working memory task or a verbal memory paradigm **(Table 36)**.

Function	Task
Working memory	**Sternberg working memory task** high-load (5 distinct numbers were presented) and low-load (5 identical numbers were presented); task-accuracy and reaction time (RT) were measured **Motor working memory task** (memorise and retype visually presented sequences)
Verbal memory	**Verbal memory fMRI paradigm** (words presented inside 3 Tesla magnet; paradigm consisted of learning and recognition tasks)

RT: reaction time; fMRI: functional magnetic resonance imaging

Table 36: Tasks used in the individual studies (77,114,115)

In a first study (114), FC alterations in PD patients, either OFF or ON dopaminergic medication, while performing the Sternberg working memory task **(Table 36)**, were assessed. During the working memory task, in either PD-OFF and HCs, load-dependent brain activation of bilateral putamen, bilateral anterior-dorsal insula, bilateral SMA, pre-SMA, dorsal ACC, bilateral SPL, bilateral PFC and bilateral cerebellum was found. Greater load-dependent activation of bilateral putamen, bilateral posterior insula, right SMA, left IPL and left thalamus (cortical, as well as subcortical regions), in PD-OFF compared to HCs, was seen. This hyperactivity in putamen might play a compensatory role, due to the loss of nigrostriatal dopaminergic input, in cognitively unimpaired PD patients, while performing a working memory task. Furthermore, this hyperactivity in putamen was lost when examining the PD-ON group. The dopaminergic therapy caused a worse performance in the Sternberg task (slower RT), which correlated with the loss of hyperactivity in the putamen. Additionally, positive correlation between reduced activation in the bilateral posterior putamen and slower responses on the *"Symbol Digit Modalities Test"* in PD-ON was found (114).

Rottschy et al. (2013) (77) examined alterations in motor working memory networks in PD patients, through a task-based fMRI paradigm. The motor working memory task consisted of an encoding, a direct and indirect recall phase. In PD patients in bilateral putamen, extending to bilateral thalami and temporo-occipital cortex, a decrease in activity was found during the encoding phase. Further decrease in activation was seen in PD, compared to HCs, in bilateral temporal gyrus, bilateral SPC, bilateral dorsal/ventral occipital cortex, bilateral pre- and primary motor cortices, bilateral IFG, right precuneus, medial SPC, bilateral SMA and right IPC during the encoding phase. The immediate-recall-phase in PD patients was characterised by a reduction of activity in the left precentral gyrus, left SMA, bilateral dorsal precentral gyrus, bilateral SPL, left intraparietal sulcus and middle/posterior parts of the left putamen. Finally, PD patients exhibited reduced activity during the long-delay-condition in the left putamen, SPC, precentral gyrus and bilateral SMA, whereas increased activity was present in bilateral posterior parahippocampal gyrus, bilateral cerebellar lobule VIIa, right IFG, posterior midline and left medial SPC. These results show that PD patients exhibited reduced task-related activity, paired with worse performance in the motor working memory task, compared to HCs, in all three phases of the task, but especially in the encoding phase. The encoding phase is essential for stimulus processing and formation of transient motor representations. Action-related spatial stimuli led to less stimulus-driven triggering of activation, within the cortical motor system, in PD patients. Hypo-activation of putamen during encoding, as well as delayed-recall-phase, might be associated with spatial motor working memory impairment and might be associated with dopamine-dependent alterations during the attempt of motor representations. Furthermore, reduced basal ganglia activation might lead to altered transfer of information into the short term storage and alterations of activity in the superior/medial parietal cortices might induce impaired simulation and imagery in PD patients. Concerning the delays in response times, these alterations might be a direct reflection of bradykinesia. The slowing in PD might be due to hypo-activation of putamen, motor and parietal cortices. These areas are all associated with either preparation, as well as execution of voluntary movements. Summarising, the encoding activity decrease might be causal for the encoding-deficits, whereas the recall impairment might be due to impaired motor control, as well as problems in starting and performing the sequence reproduction (77).

In a last study (115) functional correlates of verbal memory and fractional anisotropy (i.e. fibre integrity of a tract) were assessed. Concerning the verbal memory paradigm, PD patients had less hits and more false negatives than HCs. Lower brain activity during the verbal learning paradigm was seen in PD patients, compared to HCs, in the right inferior orbitofrontal cortex (OFC). Activation in right inferior OFC, during the verbal recognition memory task, positively correlated with hits and negatively correlated with false negatives in PD patients. OFC is connected through uncinate fasciculus, a bidirectional white-matter-tract, with temporal lobes. A disruption of the uncinate fasciculus may lead to impairment in the acquisition of learning and memory abilities. Furthermore, correlation between fractional anisotropy of the uncinate fasciculus and the brain activity of the inferior OFC was found. Recognition-memory-impairment in PD might be influenced by fronto-temporal involvement in the learning process. This assumption supports the idea of learning being a fundamental part within the memory process, based on the relation between fractional anisotropy of uncinate fasciculus and brain activation during the learning task. Concluding, impaired memory might be partly due to an altered learning process, and partly due to alterations in orbitofrontal and temporal areas (115).

4.2.3 Executive dysfunction

Caspers et al. (2017) (116) investigated whether the two subdivisions (posterior and anterior region) of the right dorsolateral prefrontal cortex (dlPFC) were disparately impaired in PD and whether there was a dopaminergic modulation effect in FC alterations. While the posterior part of the dlPFC is mostly involved in more basal executive functions, like stimulus integration or working memory, the anterior part is highly associated with more abstract, supervisory functions. A reduction in FC between the posterior right dlPFC and bilateral posterior parietal and left premotor regions in PD-OFF, compared to HCs, was found. Compared to HCs PD-ON exhibited reduced FC between posterior right dlPFC and bilateral medial posterior parietal cortex (PPC) and increased FC between posterior right dlPFC and bilateral dorsomedial SFG (within the dorsomedial PFC). Comparing the two different medication states, PD-ON showed increased FC between posterior right dlPFC and bilateral dorsomedial PFC compared to PD-OFF.

Changes within the dlPFC in PD patients are mainly caused by reduced effectiveness of fronto-striatal projections to the dorsal aspects of the caudate nucleus, affected by dopaminergic depletion in the nigrostriatal pathway. Only in the posterior parts of the dlPFC, which are essential for more basal executive functions, remarkable FC decrease was seen. Consequently, it might be that the more abstract functions depend on the basal functions - hierarchical dependency - and therefore might be impaired as well (116). Concordantly, Ghahremani et al. (2018) (11) ascertained via a ROI-to-ROI explorer (PCC connectivity was assessed with 100 ROIs from the whole brain), that area 46, which corresponds to the dlPFC (important node of the central executive network as mentioned above), was disconnected in the PD group (11).

5 Limitations and Conclusion

Studies covering the topic of connectivity changes in PD are heterogenic in many ways. First, PD presents with many different disease features, which means that there exists a variety of manifestations. Not only the disease duration contributes to this variety, but also subtypes of PD, medication status (e.g. different treatment options, drug-naïve vs medicated, drug-naïve vs OFF-state, LEDD calculation), neuropsychological status, diagnostic process of the disease, other disease/physical status modifying factors (e.g. caffeine, alcohol) and additional comorbidities have to be considered. Second, concerning the recruiting process of the patients, demographic differences (e.g. sex, age, years of education, nationality) have to be noticed, when comparing single studies. Third, patient cohorts are mostly relatively small, so that a generalisation of results is not always possible (even small cohorts are divided into sub-cohorts concerning different PD presentations). Fourth, differences in data pre-processing (e.g. exclusion of first volumes, head motion within the scanner, band-pass filter for reduction of physical nuisance, whole brain regression) lead to a poor comparability of these studies. Fifth, a broad range of functional connectivity analyses (e.g. different task-based approaches) and especially resting state analyses (e.g. seed-based versus data-driven approaches), which make the comparability particularly challenging, is available. Sixth, the matching of the HC groups to the PD groups varies between different studies (e.g. sex, age, education, nationality, and head-motion).
Finally, in some studies PD patients were recruited from the same hospital leading to the notion that patient cohorts among different studies may have been utilized more than once potentially leading to methodological issues.

One limitation of this review might be that only three databases were searched for the most recent literature. Moreover, literature implementing conference publications, dissertations and diploma theses, have not been used for this review since we focused on original articles.

Through analysing FC alterations it might become possible to differentiate different PD-subtypes and use this information for further therapy decisions (DBS or medication). In the last years much progress has taken place in this field. Because

of the fact that many different RS-approaches exist, the comparability of singular studies is poor rendering it essential that in the future more studies of comparable methodological basis are conducted. Finally, future studies shall be carried out with larger numbers of participants, so that a generalisation of the results is feasible.

In conclusion, RS-FC imaging has the potential to improve not only the fundamental research, to better understand the underlying processes of the disease, but also the understanding of the functional alterations caused by antiparkinsonian medication.

6 Annex

6.1 Journals with their impact factor

Journal Name	Impact Factor	First author, year and title
Brain	10,840	(1) Esposito, F.(2013); *Rhythm-specific modulation of the sensorimotor network in drug-naïve patients with Parkinson's disease by levodopa*
Annals of Neurology	10,244	(1) Poston, K.L.(2016); *Compensatory neural mechanisms in cognitively unimpaired Parkinson disease*
Movement Disorders	8,324	(1) Sharman, M.(2013); *Parkinson's disease patients show reduced cortical-subcortical sensorimotor connectivity* (2) Baggio, H.C.(2015) *Resting state frontostriatal functional connectivity in Parkinson's disease related apathy* (3) Tessitore, A.(2016); *Functional connectivity underpinnings of fatigue in drug-naïve patients with Parkinson's disease*
Neurology	7,609	(1) Szewczyk-Krolikowski, K.(2014); *Functional connectivity in the basal ganglia network differentiated Parkinson's disease patients from controls* (2) Tessitore, A.(2012); *Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease*
Journal of Cerebral Blood Flow and Metabolism	6,045	(1) Wu, T.(2015); *Parkinson's disease related spatial covariance pattern identified with resting-state functional MRI*
Human Brain Mapping	4,927	(1) Mathys, C.(2016); *Functional connectivity differences of the subthalamic nucleus related to Parkinson's disease* (2) Luo. C.Y.(2015); *The trajectory of disturbed resting state cerebral function in Parkinson's disease at different Hoehn and Yahr stages* (3) Bell, P.T.(2015); *Dopaminergic basis for impairment in functional connectivity across subdivisions of the striatum in Parkinson's disease* (4) Baggio, H.C.(2015); *Cognitive impairment and resting state network connectivity in Parkinson's disease*
Parkinsonism & Related Disorders	4,721	(1) Li, J.(2018); *Decreased interhemispheric homotopic connectivity in Parkinson's disease patients with freezing of gait: a resting state fMRI study;* Li, J.; Yuan, Y.; Wang, M. (2) Su, M.(2015); *Alterations in the limbic/paralimbic cortices of Parkinson's disease patients with hyposmia under resting-state functional MRI by regional homogeneity and functional connectivity analysis* (3) Lucas-Jiménez, O.(2016); *Altered functional connectivity in the default mode network is associated with cognitive impairment and brain anatomical changes in Parkinson's disease*
Neurobiology of Aging	4,454	(1) Kurani, A.S.(2015); *Subthalamic nucleus sensorimotor cortex functional connectivity in de novo and moderate Parkinson's disease* (2) Luo, C.Y.(2013); *Reduced functional connectivity in early-stage drug-naïve Parkinson's disease: a resting-state fMRI study*
Scientific Reports	4,122	(1) Mi, T-M.(2017); *Altered resting-state brain activity in Parkinson's disease patients with freezing of gait*
Brain Connectivity	3,83	(1) Thibes, R.B.(2017); *Altered functional connectivity between precuneus and motor systems in Parkinson's disease*
NeuroImage-Clinical	3,869	(1) Baudrexel, S.(2011); *Resting state fMRI reveals increased subthalamic nucleus motor cortex connectivity in Parkinson's disease* (2) Díez-Cirarda, M.(2018); *Dynamic functional connectivity in Parkinson's disease patients with mild cognitive impairment and normal cognition*

Journal of Neurology	3,783	(1) Ma, H.(2015); *Resting-state functional connectivity of dentate nucleus is associated with tremor in Parkinson's disease* (2) Hu, X.(2015); *Decreased interhemispheric functional connectivity in subtypes of Parkinson's disease* (3) Amboni, M.(2015); *Resting-state functional connectivity associated with mild cognitive impairment in Parkinson's disease*
Frontiers in Systems Neuroscience	3,79	(1) Kwak, Y.(2010); *Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease*
Frontiers in Aging Neuroscience	3,582	(1) Guan, X.(2017); *Disrupted functional connectivity of basal ganglia across tremor-dominant and akinetic/rigid-dominant Parkinson's disease* (2) Shen, B.(2017); *Resting state fMRI reveals increased subthalamic nucleus and sensorimotor cortex connectivity in patients with Parkinson's disease under medication* (3) Hou, Y.(2016); *Dysfunction of the Default Mode Network in drug-naïve Parkinson's disease with mild cognitive impairments: A resting-state fMRI study*
CNS Neuroscience & Therapeutics	3,495	(1) Chen, H.M.(2015); *Different patterns of spontaneous brain activity between tremor-dominant and postural instability/gait difficulty subtypes of Parkinson's disease: a resting-state fMRI study* (2) Zhang, J.J.(2017); *Abnormal resting state neural activity and connectivity of fatigue in Parkinson's disease* (3) Zhan, Z.W.(2018); *Abnormal resting-state functional connectivity in posterior cingulate cortex of Parkinson's disease with mild cognitive impairment and dementia*
Behavioural Brain Research	3,173	(1) Zhang, J.(2015); *Abnormal functional connectivity density in Parkinson's disease*
Journal of Parkinson's Disease	3,172	(1) Lucas-Jiménez, O.(2015); *Verbal memory in Parkinson's disease: a combined DTI and fMRI study*
Frontiers in Human Neuroscience	2,871	(1) Caspers, J.(2017); *Differential Functional Connectivity alterations of two subdivisions within the right dlPFC in Parkinson's disease*
Journal of Neural Transmission	2,776	(1) Li, J.(2017); *Alterations in regional homogeneity of resting-state brain activity in fatigue of Parkinson's disease*
PLoS One	2,766	*(1) Chen, Y.(2015); Discriminative Analysis of Parkinson's disease based on whole-brain functional connectivity* (2) Yang, W.(2016); *Altered resting-state functional connectivity of the striatum in Parkinson's disease after Levodopa administration;* Yang, W.; Liu, B.; Huang, B. (3) Yoneyama, N.(2018); *Severe hyposmia and aberrant functional connectivity in cognitively normal Parkinson's disease* (4) Rottschy, C.(2013); Diminished activation of motor working-memory networks in Parkinson's disease
Biomed Research International	2,583	(1) Luo, C.(2015); *Decreased resting-state interhemispheric functional connectivity in Parkinson's disease*
Psychiatry Research-Neuroimaging	2,455	(1) Owens-Walton, C.(2018); *Striatal changes in Parkinson disease: An investigation of morphology, functional connectivity and their relationship to clinical symptoms*
Journal of the Neurological Sciences	2,448	(1) Wang, Z.(2016); *Resting-state functional connectivity of subthalamic nucleus in different Parkinson's disease phenotypes*
Neuroscience Letters	2,159	(1) Hou, Y.(2016); *A resting-state fMRI study on early-stage drug-naïve Parkinson's disease patients with drooling*
Journal of Movement Disorders (JMD)	n.a.	(1) Ghahremani, M.(2018); *Alteration in the local and global functional connectivity of resting state networks in Parkinson's disease*

n.a.: not available

Table 37: Impact factors of selected studies with first authors

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