Diplomarbeit

White matter lesions in Parkinson's disease/ Marklagerhyperintensitäten bei Morbus Parkinson

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Lukas Gattermeyer

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Assoz.-Prof.in Priv.-Doz.in Dr.in med.univ. Petra Schwingenschuh

sowie

Dr. med.univ. Sebastian Franthal

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Graz, am 23.04.2021 *Lukas Gattermeyer, eh*

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List of Abbreviations

AchE……acetylcholine esterase
AD……Alzheimer's disease
ADC……..apparent diffusion coefficient
APOE-4……..……..apolipoprotein E4
ARIC……Atherosclerosis Risk in Communities
ASPS……Austrian Stroke Prevention Study
BAI……..……Beck Anxiety Inventory
BBB……...…….blood-brain barrier
BDI(-II)……Beck Depression Inventory(-II)
BG……basal ganglia
BMI……body mass index
BP……..……...blood pressure
CAA……cerebral amyloid angiopathy
CADASIL..…cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAMCOG……Cambridge Cognition Examination
CASCADE……..Cardiovascular Determinants of Dementia study
CCSI(T)……Cross-Cultural Smell Identification (Test)
CDR……..Clinical Dementia Rating
CERAD…….……Consortium to Establish a Registry for Alzheimer's Disease
CHIPS……...Cholinergic Pathways Hyperintensities Scale
CI……confidence interval
CIND……cognitive impairment no dementia
cm……..……centimetres
cm^3……..…..cubic centimetres
CMB……...…….cerebral microbleeds
CN……..……control negative
COMT……..……..catechol-O-methyltransferase
COWAT……Controlled Oral Word Association Test
COX-2……...……..cyclooxygenase-2
CP……..control positive
CREDOS……..Clinical Research Center for Dementia of South Korea

CSF……..cerebrospinal fluid
CSVD……...cerebral small vessel disease
CT…….computed tomography
CV RF……..cardiovascular risk factor(s)
CVD…….cardiovascular disease
CWMH……..confluent WMH
DAD……...Disability Assessment for Dementia
DAT……..…….dopamine transporter
DBP……diastolic blood pressure
DBS……...deep brain stimulation
DD……..……...dopaminergic denervation
DLB……...dementia with Lewy bodies
DM…….diabetes mellitus
DNA…….……..deoxyribonucleic acid
DTI……..……diffusion tensor imaging
DWI……...……diffusion-weighted imaging
DWMH……...……..deep WMH
FA……...……..fractional anisotropy
FAB……...……..Frontal Assessment Battery
FCSRT……...free/cued recall selective reminding test
FLAIR……..fluid attenuated inversion recovery
FOG……..freezing of gate
FOG-Q……..Freezing of Gate-questionnaire
FP-CIT……..…….fluoropropyl-carbomethoxy-iodophenyl-nortropane
FR score……..Framingham risk score
GABA……..……..gamma-aminobutyric acid
GBA……..……glucocerebrosidase
GDS……..Geriatric Depression Scale
GRE……..gradient-recalled echo
H&Y……Hoehn and Yahr (stage)
HC……..…….healthy controls
HC-IC…….healthy controls with intact cognition
HC-MCI……healthy controls with MCI
hcy……...……...homocysteine

HDL……..……..high density lipoprotein
HDRS……..Hamilton Depression Rating Scale
HR……..……hazard ratio
HVLT……...Hopkins Verbal Learning Task
Hz……....hertz
IADL……Instrumental Activities of Daily Life
IL-8……..interleukin 8
IMT……...……...intima-media thickness
IPD……..……idiopathic Parkinson's disease
IQR……...interquartile range
ITF…… infratentorial foci of hyperintensity
LADIS……Leukoaraiosis and Disability in the Elderly
LDL……low density lipoprotein
L-dopa……...……..levodopa
LE……...……...lower extremity
LED……levodopa equivalent dose
LRRK2 (gene)……leucine-rich repeat kinase 2 (gene)
m……..metres
MAO-B……...……..monoamine oxidase-B
MAP……..mean arterial pressure
max……...…….maximum
MCI……..mild cognitive impairment
MD……...…….mean diffusivity
MDS……...…….Movement Disorder Society
MELAS…..Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes
mg……..……milligrams
MHC II……..……major histocompatibility complex II
MHz……..……megahertz
MIBG...……...……..(123I-)metaiodobenzyl-guanidine
min……..……minimum
mL……...……..millilitres
mmHg……millimetres of mercury
MMSE……Mini-Mental State Examination
mm^3……..…….cubic millimetres

MoCA……..Montreal Cognitive Assessment
MPTP……..……1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR……magnetic resonance
MRA……..magnetic resonance angiography
MRI……magnetic resonance imaging
msec……...……...milliseconds
MTA……...medial temporal atrophy
MTI…….magnetisation transfer imaging
MTR…….magnetisation transfer ratio
n.a……..not available
NC……...……..normal controls
NFL……light subtype of the neurofilament protein
N-MCI…….neurodegenerative MCI
NMDA……..……N-methyl-D-aspartate
NMS…….Non-Motor Symptoms Questionnaire
nOH……...……neurogenic OH
NOTCH3 (gene)……neurogenic locus notch homolog protein 3 (gene)
NPI……...……..Neuropsychiatry Inventory
OH……..……orthostatic hypotension
OR……..……...odds ratio
PARK2 (gene)……..parkin RBR E3 ubiquitin protein ligase (gene)
PD…….(idiopathic) Parkinson's disease
P-d……...……proton density
PDD……..……..Parkinson's disease dementia
PD-IC……...……PD patients with intact cognition
PD-MCI……..…….Parkinson’s disease mild cognitive impairment
PDND…….Parkinson's disease no dementia
PDQ-39……..Parkinson's Disease Questionnaire
PDSS……...……..Parkinson's Disease Sleep Scale
PET……...……..positron emission tomography
PFS……...……Parkinson Fatigue Scale
pg……...picograms

PIGD……..……..postural instability and gait difficulty
PIGF…….placental growth factor
PON1 (gene)……paraoxonase-1 (gene)
ppm……..parts per million
PSP……..……progressive supranuclear palsy
PVH……...…….periventricular hyperintensities
PVL…...…….periventricular lesions
PVS……...…….perivascular space(s)
r……...…….Pearson's correlation coefficient
RARE……...……rapid acquisition with relaxation enhancement
RBD……...…….REM sleep behaviour disorder
RCPM……Raven's Coloured Progressive Matrices
REM……...……..rapid eye movement
RF……..……risk factor(s)
r_s……Spearman's correlation coefficient
RSS……..Rotterdam Scan Study
s……..second(s)
SBP……..systolic blood pressure
SCNA (gene)……...……...synuclein alpha (gene)
SCOPA-COG…….Scales for Outcomes in Parkinson's disease-COGnition
SD……...…….standard deviation
SH…….supine hypertension
SLP……...…….status lacunaris in the putamen
SNP……...……...single nucleotide polymorphism
SOB……...……sum of the box
SPECT……...….single photon emission computerised tomography
SPPB……Short Physical Performance Battery
SSLI……...…….striatal silent lacunar infarction
STIR……...……...short time inversion recovery
STN……..subthalamic nucleus
STRIVE……..standards for reporting vascular changes on neuroimaging
SVD……...……..small vessel disease
sVEGFR-1……..soluble vascular endothelial growth factor receptor-1
T……..Tesla

TD……tremor dominant
TE……time to echo
TI……..……..time after inversion
TIA……...……...transient ischaemic attack
TMT-A/B……Trail Making Test part A/B
TR……time of repetition
TS……...……...total score
UE……...……..upper extremity
UPDRS……...……...Unified Parkinson's disease rating scale
VaD……..vascular dementia
VADAS-Cog……Vascular Dementia Assessment Scale cognitive subscale
VEGF……..……vascular endothelial growth factor
VMAT2……...……type 2 vesicular monoamine transporter
V-MCI……vascular MCI
VP……...……..vascular parkinsonism
WMC……...……...white matter changes
WMD……white matter disease
WMH……..white matter hyperintensities
WML……..white matter lesions

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Zusammenfassung

Ziel

Erstens, eine systematische Suche der gegenwärtigen Literatur betreffend Marklagerhyperintensitäten bei Patientinnen und Patienten mit Morbus Parkinson durchzuführen. Zweitens, das Volumen von Marklagerhyperintensitäten zwischen Patientinnen und Patienten mit Morbus Parkinson und gesunden Kontrollpersonen zu vergleichen und Korrelationen der Volumina von Marklagerhyperintensitäten mit klinischen Parametern bei Patientinnen und Patienten mit Morbus Parkinson zu explorieren.

Methoden

Als erster Teil dieser Arbeit wurde eine systematische PUBMED Suche durchgeführt, um relevante Studien zu identifizieren, die über Marklagerhyperintensitäten bei Patientinnen und Patienten mit Morbus Parkinson berichten. Für den zweiten Teil wurden 141 Patientinnen und Patienten aus der longitudinalen Datenbank für Bewegungsstörungen in Graz (PROMOVE) und 141 gesunde, dem Alter und Geschlecht entsprechende Kontrollpersonen aus der Austrian Stroke Prevention Family Study-Kohorte in eine Querschnittsstudie mit eingeschlossen. Alle Teilnehmerinnen und Teilnehmer wurden einer 3.0 T MRT-Untersuchung inklusive FLAIR-Sequenzen unterzogen. Die Volumina der Marklagerhyperintensitäten wurden mithilfe einer halbautomatischen, Schwellenwert-basierten Technik bestimmt und die Resultate zwischen Parkinson- und Kontrollgruppe verglichen. Überdies durchlief die Parkinson-Gruppe eine umfassende klinische Evaluierung (MDS-UPDRS, Non-Motor Symptoms Questionnaire, Geriatric Depression Scale, neuropsychologische Testbatterie CERAD).

Ergebnisse

Die gegenwärtige Literatur, die über Marklagerhyperintensitäten bei Patientinnen und Patienten mit Morbus Parkinson berichtet, zeigt insgesamt recht heterogene Resultate, auch wenn sich einige konsistente Ergebnisse wie eine Zunahme der kognitiven Beeinträchtigung mit Anstieg der Läsionslast finden. In der hier vorliegenden Querschnittsstudie unterschied sich weder das Gesamtvolumen der Marklagerhyperintensitäten noch jenes im tiefen Marklager oder in den periventrikulären Regionen signifikant zwischen der Parkinson- und der

Kontrollgruppe. Betreffend die Volumina fanden sich auch keine signifikanten Unterschiede zwischen den Geschlechtern, weder innerhalb noch zwischen den beiden Gruppen. In der Parkinson-Gruppe korrelierten alle drei Volumina signifikant negativ mit der Punkteanzahl im MMSE, mit dem CERAD-TS1 und TS2 sowie dem CERAD Gedächtnis-Score, in beiden Gruppen außerdem positiv mit dem Alter. Es fanden sich keine signifikanten Korrelationen in der Parkinsongruppe zwischen den Volumina und MDS-UPDRS-Ergebnissen, NMS, GDS, Krankheitsdauer, Hoehn-und-Yahr-Stadium und Levodopa-Äquivalenz-Dosis.

Schlussfolgerungen

Die Volumina der Marklagerhyperintensitäten unterscheiden sich nicht zwischen Parkinson-Patientinnen und Patienten und gesunden Kontrollpersonen, ungeachtet des Geschlechts. Die Läsionslast nimmt in beiden Gruppen mit dem Alter zu. Überdies korrelieren bei Morbus Parkinson die Läsionsvolumina mit kognitiver Dysfunktion. Um einen möglichen Effekt von Marklagerhyperintensitäten auf motorische und nicht-motorische Symptome aufzudecken, sollten sich zukünftige Studien bei Morbus Parkinson auf mögliche Beziehungen zwischen Marklagerhyperintensitäten und spezifischen motorischen und nicht-motorischen Symptomen anstatt auf globale Bewertungsskalen fokussieren.

Abstract

Objective

First, to review the existing evidence for an association of white matter hyperintensities (WMH) with clinical parameters and markers of disease progression in Parkinson's disease (PD). Second, to compare WMH volumes between PD patients and healthy controls (HC) and to investigate correlations of WMH volumes with clinical parameters in PD patients.

Methods

For part one of this thesis, a systematic PUBMED search was performed to identify relevant studies reporting on WMH in PD patients. For part two, 141 PD patients from the prospective, longitudinal registry on movement disorders in Graz (PROMOVE) and 141 age- and sex-matched healthy controls from the Austrian Stroke Prevention Family Study cohort were included in a cross-sectional study. All participants underwent cerebral 3.0 T MRI comprising FLAIR sequences. WMH volumes were determined using a semi-automated, threshold-based technique and results were compared between PD patients and healthy controls. Furthermore, extensive clinical assessment was performed in all PD patients, including MDS-UPDRS, Non-Motor Symptoms Questionnaire (NMS), Geriatric Depression Scale (GDS) and the CERAD neuropsychological test battery.

Results

The current literature reporting on WMH in PD patients reveals overall rather heterogenous results, although there are some consistent findings like a cognitive decline with increasing WMH burden. In this present cross-sectional study, neither total, deep or periventricular WMH volume differed significantly between PD patients and controls. There were no significant differences in WMH volumes between females and males in inter- and intragroup comparisons, either. Total, deep and periventricular WMH correlated significantly negatively with MMSE score, CERAD-TS1, CERAD-TS2 and CERAD memory score in PD patients and positively with age in both groups. MDS-UPDRS total and sub-scores, NMS, GDS, disease duration, Hoehn and Yahr stage and levodopa equivalent dose did not correlate significantly with any WMH volume in PD patients.

Conclusion

White matter hyperintensity volumes do not differ between PD patients and healthy controls, irrespective of sex. WMH burden increases with higher age both in PD patients and healthy controls. Moreover, total, deep and periventricular WMH volume correlate with cognitive dysfunction. In order to expose a possible effect of WMH on motor or other non-motor symptoms, future studies in PD patients should focus on possible relations between WMH and more specific motor and non-motor items rather than global scores of impairment.

1 Introduction

1.1 Parkinson's Disease

1.1.1 Definition and epidemiology

"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" (1). These are the words James Parkinson chose in 1817 in "An Essay on the Shaking Palsy" (1) to describe the malady which was later named after him, Parkinson's disease. In today's literature, Parkinson's disease (PD) is usually hallmarked by its characteristic features hypo- and bradykinesia, resting tremor, postural instability and rigidity (2).

PD is one of the most common neurodegenerative diseases. Its worldwide prevalence increases with age, ranging from 41/100000 in the age group from 40 to 49 years, up to 1903/100000 in individuals older than 80 years (3). Considering differences according to geographic locations, a meta-analysis by Pringsheim et al. (3) found that, in the age group of individuals from 70 to 79 years, prevalence of PD was significantly lower in Asia (646/100000) than in Europe/Australia/North America (1602/100000). Prevalence of PD in Asia was lower in all other age groups compared to the other regions, too, although not statistically significant. Regarding sex differences, the worldwide prevalence tended to be slightly higher in males than in females in most age groups, but the difference was statistically significant only in the group of individuals aged 50 to 59 years (134/100000 in males vs. 41/100000 in females) (3).

According to a systematic review and meta-analysis performed by Hirsch et al. (4), overall incidence rates of Parkinson's disease were 37.55/100000 person-years in females ≥ 40 years and 61.21/100000 person-years in males ≥ 40 years. In both genders, incidence rates increased with age (in females, from 3.26/100000 person-years at age 40-49 to 103.48 at age 80+; in males, from 3.57/100000 person-years at age 40-49 to 258.47 at age 80+). While most studies found a peak of incidence between the age of 70-79 in females, incidence rates in males kept growing after the age of 80 years. Incidence rates were significantly higher in males than in females at age 60-69 years (58.22 vs. 30.32/100000 person-years)

and at age 70-79 years (162.58 vs. 93.32/100000 person-years). Moreover, incidence rates were higher in males in all other age groups, too, although statistically insignificant (4). In African Americans, the incidence of PD is but one-quarter of the incidence in whites. Moreover, incidence might be higher in rural regions than in urban ones (2).

1.1.2 Clinical symptoms and natural history of disease

The hallmark characteristics of PD are hypo-/bradykinesia, resting tremor, rigidity and postural instability (2).

The term *bradykinesia* characterises a slowness of voluntary movement. This condition becomes evident in PD patients both as an increased reaction time and a reduced velocity of movement (i.e., the time from beginning to completion of movement). Bradykinesia is largely independent from rigidity, as precise stereotactic brain lesions in PD patients can resolve rigidity while not affecting bradykinesia. *Hypokinesia* (or, in its extreme manifestation, *akinesia*) connotes a diminution of spontaneous movements. Differentiating hypokinesia from paralysis, strength is significantly diminished in the latter but not in the former. Hypokinesia becomes apparent in PD patients as a poverty of movement, leading to a reduction of normal, automatic, habitual movements like crossing the legs, swinging of the arms when walking or putting the hand to the face. As an early sign of PD, the frequency of blinking can be reduced (from the usual rate of 12-20/min to 5-10/min). Drooling occurs since saliva is secreted more quickly than it can be swallowed in hypokinetic patients. Other features of hypokinesia include hypomimia (“masked facies”, due to reduced facial expressive mobility), a monotonic, fast and mumbling speech and a soft voice (2,5).

Tremor describes an involuntary, rhythmic and oscillatory movement. Generally speaking, tremor occurs when muscles with reciprocal innervation contract alternatingly or irregularly synchronously. The parkinsonian tremor is coarse and rhythmic, its frequency 3 to 5 Hz. Most frequently, the tremor affects one or both hands and forearms. Jaw, lips, tongue, eyelids or feet can also be affected. Tremor in PD is almost always asymmetrical and, in the beginning, often completely one-sided. Since the tremor emerges when the limb is in a resting position and can be momentarily suppressed by voluntary movement, it is also

referred to as repose or resting tremor. During walking and under emotional stress, the tremor might be intensified. In PD patients, the tremor most frequently presents as alternating flexion and extension or abduction and adduction of the fingers or the hand. Alternating pronation and supination of hand and forearm can be seen, too. The typical “pill-rolling” tremor of PD patients emerges from flexion and extension of the fingers combined with adduction and abduction of the thumb. It occurs in approximately 50% of PD patients. The so-called cogwheel phenomenon (Negro sign) describes a ratchet-like interruption of resistance sensed by an examiner when the limb is moved passively. It is usually attributed to the concurrence of tremor and rigidity. This effect can be exaggerated by asking the patient to use the opposite arm in a motor task, e.g., to draw circles in the air (Froment sign) (2,6).

Rigidity is defined as an altered muscle tone where the muscles are firm and tense at all times or intermittently. A low threshold for involuntary continual contractions of the muscles is present during the majority of the waking state, also when the patient is relaxed. When a limb is moved passively, rigidity presents as an even and uniform resistance during the whole range of movement (like in bending a lead pipe). Spasticity, on the other hand, is characterised by an initially increased resistance when moving the limb passively, followed by a sudden loss of resistance (clasp-knife phenomenon). Furthermore, in contrast to spasticity, rigidity does not depend on the velocity of movement. While the tendon reflexes are enhanced in spasticity, they are not in rigidity. When a limb is released, a spastic one recovers to its original position while a rigid one does not. Rigidity is most pronounced in muscles sustaining a flexed posture (flexor muscles of trunk and limbs), but it is also present in extensor muscles groups. While it seems to be strongest in large muscle groups, rigidity also frequently involves the facial muscles, the tongue and the laryngeal muscles (2,5).

Postural disorder or instability in Parkinson’s disease becomes, for instance, evident as a posture where the trunk, the limbs and the neck are involuntarily flexed. Moreover, anticipatory and compensatory righting reflexes are considerably hampered. This results in the patients failing to appropriately adjust their posture to tilting or falling and to move from a reclining to a standing position. Gently

pushing a patient might induce a fall or festination (several small corrective steps, beyond control of the patient) (2,5).

These features of PD can affect all daily activities in the course of the disease. The handwriting of the patient becomes tremulous, cramped and very small (micrographia). Eating a meal consumes a lot of time since each bite has to be swallowed before the next one can be taken. The patients show a shuffling gait and often lose balance. Moreover, festination occurs frequently, making the patient seem to be chasing the centre of gravity of his body with the small, quick steps to prevent a fall. An obstacle like a door threshold can lead to a “freezing” of the patient in place. Due to the immobility and rigidity of the facial musculature, the patients have difficulty to shave or put on lipstick (2).

Muscular power is usually normal or almost normal in large muscles, even though patients can perceive muscular weakness. However, power is somewhat reduced in small muscles. PD patients can also suffer from dystonia (e.g., jaw clenching, clawing of the toes), often causing pain. Some patients show an extreme forward flexion of the spine followed by severe stooping (camptocormia), which seems to constitute a form of axial dystonia. The Myerson sign can be present in PD patients; it describes the inability of patients to suppress blinking when tapped on the glabella. Upward gaze and convergence are often affected in PD patients, too (2).

Apart from the typical motor symptoms described above, PD patients can also be affected by various non-motor symptoms (2).

Deficits in sensory perception are a possible non-motor feature of PD, with hyposmia being the most common sensory disturbance. Vision malfunctions are manifold and comprise, inter alia, decreased contrast sensitivity and colour discrimination, dry eyes, hampered convergence and stereopsis (7).

Drooling due to swallowing with a reduced frequency was already mentioned earlier. Paresthetic complaints and discomfort, which are located most frequently in the abdomen and the calves, can occur. Another typical non-motor symptom is seborrhoea, which might be caused by insufficient cleaning of the face. Although disproportional sweating is often traced back to the continuous motor activity in PD patients, it is probably induced by an autonomic disturbance. Autonomic dysfunction is also responsible for obstipation, abdominal pains and cramps, joint

aches and erectile dysfunction (2). Some patients experience orthostatic hypotension and syncope (2), which could be caused by a loss of cells in the sympathetic ganglia (8). Urinary complaints, like urinary urgency, nocturia, and urge incontinence, are most frequently produced by overactivity of the detrusor (9).
PD patients are often affected by dementia. Its frequency varies in studies and lies around 10-15% of all patients. However, the prevalence of dementia in PD patients increases with age and disease duration and reaches about 65% in patients above the age of 80 years (2,10). In their 2005 systematic review, Aarsland, Zaccai and Brayne found an even higher prevalence of dementia in PD patients (24.5% up to 31.1%) (11). Moreover, mild cognitive impairment is already present in about 25% of PD patients in Hoehn and Yahr stage 1 (12).
Apart from dementia, PD patients can also show several other psychiatric symptoms, including mood disturbances (primarily depression), psychosis and confusion (visual hallucinations, delusions, agitation, aggression, paranoia), and sleep disorders. The latter comprises both disturbed sleep during night-time and excessive somnolence during daytime (13). REM sleep behaviour disorder (RBD) is another form of sleeping disturbances in PD. In this disorder, the patient continues to be able to move during REM sleep (7).

The natural history of Parkinson's disease is rather variable. The mean period of time from disease onset to a chairbound condition lies around 7.5 years. However, up to 10% of patients show a relatively mild and slowly progressive course of disease and maintain a quite stable state for 10 years or more. Moreover, the natural history of PD might be therapeutically modulated to some degree (2).
At disease onset, the symptoms usually develop gradually. Early symptoms are often overlooked or misinterpreted as pertaining to the natural aging process by the patients or their relatives (2).
Hoehn and Yahr (14) examined 183 patients with idiopathic PD and found tremor to be the most frequent initial symptom in those patients (see Table 1). While the characteristic tremor is still frequently cited as the initial symptom, family members in many cases indicate to have noticed slowness of movement beforehand. As common early features, the patient's voice may turn soft and monotonous, pain in the back, neck, shoulders or hips may occur, or the patient may feel weak in general (2). Non-motor symptoms, like olfactory impairment, depression and

anxiety, obstipation, or RBD, can precede the typical motor symptoms of PD by years or even decades (7). Modest stiffness and a slowness of movement (like the reduced swinging of one arm when walking) often pose the first motor symptoms noticeable. A reduced frequency of blinking can also be an early symptom (2). Tremor and rigidity, the latter relatively rarely being an early symptom of PD, typically affect one limb or one side of the body earlier, and then spread out to the other one. The tremor, however, usually stays asymmetrical to some degree. With the progression of the disease, increasing rigidity can superpose and attenuate the intensity of the tremor (2).

As the disease proceeds further, the impairment of daily activities like eating, handwriting, walking or maintaining one's balance heavily increases. In advanced stages, dementia becomes a frequent feature of PD. However, if dementia arises at an early stage, Lewy body disease should be taken into account. Disturbed upward gaze and convergence also tend to appear in later stages; if they manifest early or very markedly, one should consider progressive supranuclear palsy (PSP) as an alternate diagnosis. Similarly, postural dysfunction is more typical for advanced PD, but emerges early in PSP. A very pronounced autonomic dysfunction should be recognised as a possible feature of multiple system atrophy (2).

Initial symptom	**Number of patients (n=183)**
Tremor	129 (70.5%)
Gait disturbance	21 (11.5%)
Stiffness	18 (9.8%)
Slowness	18 (9.8%)
Muscle pain, cramps, aching	15 (8.2%)
Loss of dexterity	14 (7.7%)
Handwriting disturbance	9 (4.9%)
Depression, nervousness, or other psychiatric disturbance	8 (4.4%)
Speech disturbance	7 (3.8%)
General fatigue, muscle weakness	5 (2.7%)
Drooling	3 (1.6%)
Loss of arm swing	3 (1.6%)
Facial masking	3 (1.6%)
Dysphagia	1 (0.5%)
Paraesthesia	1 (0.5%)

Table 1. Frequency of initial symptoms in Parkinson's disease patients adapted from Hoehn and Yahr 1967 (14).
The average number of initial symptoms per patient was 1.4.

1.1.3 Pathophysiology

Parkinson's disease is a neurodegenerative disease of the basal ganglia, which consist of the striatum (caudate nucleus and putamen), the pallidum (globus pallidus externus/lateralis and globus pallidus internus/medialis), the nucleus subthalamicus and the substantia nigra (pars compacta and pars reticulata).
The striatum (especially the putamen) receives input from the cerebral cortex and the pigmented neurons originating from the pars compacta of the substantia nigra. The globus pallidus internus and the pars reticulata (non-pigmented) of the substantia nigra, on the other hand, are the main output nuclei of the functional system (5).
From the striatum/putamen, two major efferent pathways exist: the direct and the indirect efferent system. The direct system consists of projections from the putamen to the globus pallidus internus, and from there further on to the pars reticulata of the substantia nigra. Projections from the putamen to the globus pallidus externus and from there to the nucleus subthalamicus, which has reciprocal connections with the globus pallidus externus, comprise the indirect system. The nucleus subthalamicus then projects to the globus pallidus internus and the pars reticulata. The pars reticulata and the globus pallidus internus share the same input and output patterns and can be, hence, seen as a functional unit; similar considerations apply to the subthalamic nucleus and the globus pallidus externus. The output nuclei (globus pallidus internus and pars reticulata) finally project to the ventrolateral and ventroanterior nuclei of the thalamus. From there, fibres reach the premotor cortex and then the motor cortex, thus closing a cortical-striatal-pallidal-thalamic-cortical motor loop (5).
Simply put, the basal ganglia's function during an intended or projected movement is to facilitate one combination of activities and to suppress all other ones which are not necessary at the moment. For this purpose, there exist both an excitatory (the direct pathway) and an inhibitory (the indirect pathway) functional structure in the basal ganglia (5).
Glutamatergic neurons from the sensorimotor cortex and dopaminergic neurons from the pars compacta of the substantia nigra (via D1 dopamine receptors in the striatum) projecting to the striatum activate the direct pathway (see Figure 1a). This leads to an inhibition of the globus pallidus internus via the release of the

neurotransmitter GABA (gamma-aminobutyric acid), which in turn disinhibits the ventrolateral and ventroanterior thalamus by reducing GABA-ergic output from the globus pallidus internus to the thalamus. Hence, thalamocortical drive is increased and movements initiated by the cortex are promoted (5).

The indirect pathway, on the other hand, is activated by glutamatergic cortico-striatal neurons and inhibited by dopaminergic nigro-striatal projections (originating in the pars compacta) through D2 dopamine receptors. Activation of the indirect pathway in the putamen causes GABA-ergic neurons to inhibit the globus pallidus externus, which in turn disinhibits the nucleus subthalamicus (reduced GABA release in pallido-subthalamic projections). Hence, subthalamic drive (glutamate) to the globus pallidus internus and substantia nigra pars reticularis is increased, leading to an enhanced thalamic inhibition. This causes a decrease of thalamocortical input to the motor cortex, thus hampering volitional movements.

In summary, increased conduction through the direct pathway decreases pallidothalamic inhibition and hence leads to hyperkinesia, while increased conduction through the indirect pathway increases pallidothalamic inhibition, causing hypokinesia (5).

In Parkinson's disease, the main pathophysiological event is the loss of dopaminergic neurons in the pars compacta of the substantia nigra (see Figure 1b). Therefore, the direct pathway is less activated via D1 receptors, while the indirect pathway is less inhibited via D2 receptors. Reduced activity in the direct pathway and enhanced activity in the indirect pathway consequently augment inhibition of the thalamus and hence diminish the cortical motor area's excitation. This causes the characteristic parkinsonian motor symptoms (5).

Another neurotransmitter that plays a role in the pathophysiology of PD is acetylcholine. Its highest concentration within the basal ganglia is in the striatum. Acetylcholine seems to have a mainly excitatory effect on the origin neurons of both the direct and indirect pathway in the putamen. It was suggested that there is a functional equilibrium in the striatum between this excitatory effect of acetylcholine and an inhibitory effect of dopamine. Loss of dopaminergic neurons might disinhibit acetylcholine synthesising neurons, hence shifting the equilibrium towards the acetylcholine effects. This theory explains the antiparkinsonian effect of anticholinergic agents, which restore the dopamine to acetylcholine ratio (5).

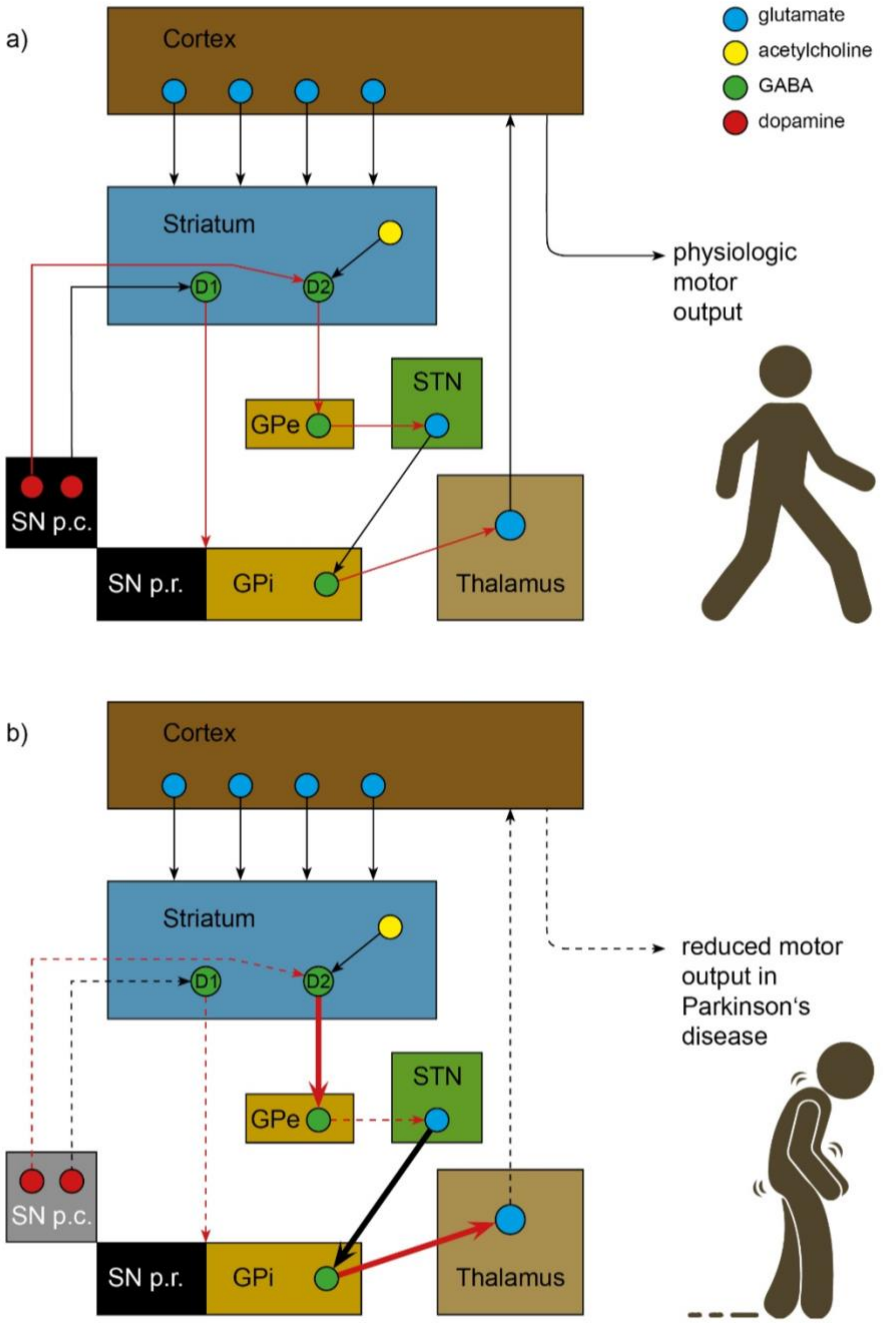

Figure 1. Physiological and pathophysiological processes in the basal ganglia adapted from Ropper, Samuels and Klein (5).

a) Physiological conditions.
b) Pathophysiological cascade in Parkinson's Disease, caused by dopaminergic cell loss in the substantia nigra, pars compacta.

Black lines denote excitatory neurons, *red lines* denote inhibitory neurons.
Bold lines indicate an increased activity in the pathway, *dotted lines* indicate a reduced activity in the pathway.

Abbreviations: GABA → gamma-aminobutyric acid; D1 → dopamine D1 receptors; D2 → dopamine D2 receptors; SN p.c./SN p.r. → substantia nigra, pars compacta/pars reticularis; GPi/GPe → globus pallidus internus/externus; STN → subthalamic nucleus.

Considering the cause of nigral cell loss, aging seems to play an important role but it cannot explain the whole extent of cell depletion in PD (2). While there is a decrease of nigral cells from a maximal 425000 to 200000 at the age of 80 years, PD patients only have 30 percent or less of the number of pigment neurons age-matched controls have (2,15). MPTP is a neurotoxin that binds to the extraneural monoamine oxidase, which transforms it to a toxic metabolite. This metabolite is taken up into dopaminergic nigral neurons and causes their destruction, leading to parkinsonian symptoms. In analogy to this mechanism, other environmental toxins could play an aetiological role in PD. The prevalence of the disease is, for instance, marginally higher in industrialised regions and in agrarian areas where organophosphates are frequently utilised (2,16,17). In their relatively recent publication, Ascherio and Schwarzschild (18) provide an overview of factors possibly increasing or decreasing, respectively, the risk for developing PD. After reviewing recent longitudinal studies, they concluded that pesticides, melanoma, high milk and dairy consumption and traumatic brain injury raise the risk for PD, while tobacco consumption, coffee and caffeine use, higher serum urate concentrations, physical activity, ibuprofen and calcium channel blockers can offer some protection from PD (18).

The loss of pigmented neurons in the substantia nigra macroscopically becomes evident as a visible paleness. Histopathologically, PD is characterised by a pronounced depletion of cells in the substantia nigra and other pigmented nuclei like the dorsal motor nucleus of the vagal nerve and the locus coeruleus. The perished cells are replaced with gliosis. Of the cells which are still alive, some are reduced in their melanin content, and many contain characteristic cell inclusions, termed Lewy bodies. Lewy bodies, eosinophilic cytoplasmic inclusions which are enclosed by a subtle halo, are found in almost all brains of patients suffering from idiopathic PD. The main component of these Lewy bodies is α-synuclein, which can be found as an integral part of the nucleus and the synapse in its soluble unfolded form. If present in high quantities, however, it aggregates into filaments and constitutes a major element of the Lewy body. Other proteins involved in the formation of Lewy bodies are ubiquitin and tau. Many gene mutations alternating the metabolism of these proteins, especially of α-synuclein, have been identified in familial forms of PD. These mutations can lead to increased production, instability,

misfolding or insufficient removal of α-synuclein by the proteasomal system and hence to its accumulation, potentially resulting in dopaminergic cell death. Prominent mutations found in familial PD affect, for example, the SCNA gene (coding for α-synuclein), the PARK2 gene (parkin) and the LRRK2 gene (leucine-rich repeat kinase 2) (2).

According to the neuropathological Braak staging system, Lewy body pathology, the histopathological hallmark of PD, is a process that affects wide parts of the nervous system and spreads out through anatomically connected regions in a certain sequence. The regions affected the earliest are the anterior olfactory structures, the dorsal motor nucleus of the vagus, and parts of the enteric nervous system (19). Originally published in 2003, Braak et al. (20) organise the ascending progression of the characteristic inclusion bodies (globular Lewy bodies in perikarya, thread or spindle-like Lewy neurites in cell-processes) and related lesions in six stages. Advancing of the process to a higher stage not only includes involvement of new regions, but also lesions in previously affected areas becoming more severe. In stage 1, the dorsal IX/X motor nucleus, the intermediate reticular zone and the anterior olfactory nucleus are affected. The caudal raphe nuclei, the gigantocellular reticular nucleus and the coeruleus-subcoeruleus complex are involved in stage 2. While stage 3 comprises progression to the midbrain (especially the pars compacta of the substantia nigra), stage 4 is characterised by the appearance of prosencephalic lesions (temporal mesocortex, allocortex). Stages 5 (high order sensory association areas of neocortex and prefrontal neocortex) and 6 (first order sensory association areas of neocortex and premotor areas) mark the most advanced phases of the disease (20).

1.1.4 Diagnostic tools and classifications

The diagnosis of Parkinson's disease is primarily a clinical one. The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria are widely used for this purpose and are presented in Table 2 (21).

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria
Step 1: Diagnosis of Parkinsonian syndrome
• Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) • And at least one of the following: ○ 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

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3: Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Table 2. UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (21).

Abbreviations:
CT……..computed tomography
Hz…….....Hertz
MPTP……1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Differential diagnoses of idiopathic Parkinson's disease include other neurodegenerative diseases like progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies and corticobasal syndrome. Moreover, normal-pressure hydrocephalus and essential tremor can clinically resemble PD. If parkinsonism begins very rapidly, viral encephalitis, Creutzfeldt-Jakob disease, postinfectious or paraneoplastic conditions or exposure to neuroleptic drugs (including metoclopramide) should be considered as possible causes (2). Controversy exists regarding the diagnosis "vascular parkinsonism", also referred to as "arteriopathic" or "arteriosclerotic" Parkinson's disease. This condition is attributed to atherosclerotic white matter lesions or to damage to the substantia

nigra due to vascular disease. Clinically, vascular parkinsonism is often associated with the term “lower half” parkinsonism, which is characterised by the predominance of falling, shuffling gait and stickiness on turning over other features. Moreover, tremor is absent and responsiveness to L-dopa is lacking or minimal. In MRI, these patients show extensive white matter changes in both hemispheres of the brain (2,22).

The revised version of the Unified Parkinson’s Disease Rating Scale, sponsored by the Movement Disorder Society (MDS-UPDRS) (23), is a commonly used tool for the clinical assessment of PD. The scale consists of four parts:

- I: Non-motor Experiences of Daily Living
- II: Motor Experiences of Daily Living
- III: Motor Examination
- IV: Motor Complications

The scale comprises a total of 65 items, and each one is rated from 0 to 4 (0=normal, 1=slight, 2=mild, 3=moderate, 4=severe), yielding a separate score for each part and a total score. Part I consists of 13 items and is subdivided in two sections (IA: 6 questions, rated by investigator, IB: 7 questions, self-administered questionnaire, assessed by patient, possibly with the help of a caregiver). Part II comprises 13 questions and is a self-administered questionnaire. Part III contains a total of 33 scores based on 18 items (some items are rated separately for left and right side or for different body regions). It is implemented by the investigator, who should remark the patient’s antiparkinsonian medication and whether the examination is performed in on or in off state. Furthermore, part III also rates if dyskinesias were present during examination and if they had an impact on the ratings. Moreover, Hoehn and Yahr stage is determined. Part IV includes 6 items and is assessed by the rater. Table 3 presents all 65 items assessed in the MDS-UPDRS (23).

Part	Items of the MDS-UPDRS
IA	1.1 Cognitive impairment 1.2 Hallucinations and psychosis 1.3 Depressed mood 1.4 Anxious mood 1.5 Apathy 1.6 Features of dopamine dysregulation syndrome
IB	1.7 Sleep problems 1.8 Daytime sleepiness

	1.9 Pain and other sensations 1.10 Urinary problems 1.11 Constipation problems 1.12 Light headedness on standing 1.13 Fatigue
II	2.1 Speech 2.2 Saliva and drooling 2.3 Chewing and swallowing 2.4 Eating tasks 2.5 Dressing 2.6 Hygiene 2.7 Handwriting 2.8 Doing hobbies and other activities 2.9 Turning in bed 2.10 Tremor 2.11 Getting out of bed, a car, o a deep chair 2.12 Walking and balance 2.13 Freezing
III	3.1 Speech 3.2 Facial expression 3.3 Rigidity (neck, right/left UE, right/left lower extremity LE) 3.4 Finger tapping (right/left) 3.5 Hand movements (right/left) 3.6 Pronation-supination movements of hands (right/left) 3.7 Toe tapping (right/left) 3.8 Leg agility (right/left) 3.9 Arising from chair 3.10 Gait 3.11 Freezing of gait 3.12 Postural stability 3.13 Posture 3.14 Global spontaneity of movement (body bradykinesia) 3.15 Postural tremor of the hands (right/left) 3.16 Kinetic tremor of the hands (right/left) 3.17 Rest tremor amplitude (right/left UE, right/left LE, lip/jaw) 3.18 Constancy of rest tremor
IV	4.1 Time spent with dyskinesias 4.2 Functional impact of dyskinesias 4.3 Time spent in the off state 4.4 Functional impact of fluctuations 4.5 Complexity of motor fluctuations 4.6 Painful off-state dystonia

Table 3. Items assessed in the MDS-UPDRS (23).

Abbreviations:
LE…….lower extremity
MDS-UPDRS…….Movement Disorder Society- Unified Parkinson's disease rating scale
UE……...upper extremity

In addition to clinical assessment, the diagnosis of PD can be supported by imaging techniques. Functional, scintigraphy-based imaging techniques like positron emission tomography (PET) and single photon emission computerised tomography (SPECT) using various ligands and tracers offer several diagnostic

possibilities in PD. First of all, these methods are used to assess the functional integrity of presynaptic nigrostriatal projections. Techniques for this purpose include 18-F-dopa PET (reduced striatal 18-F-dopa-uptake in PD), methods measuring presynaptic dopamine transporter (DAT) availability (only found in dendrites and axons of dopaminergic neurons, hence reduced in PD), and 11-C-dihydrotetrabenazine PET (binds to the type-2 vesicular monoamine transporter (VMAT2), which transports monoamines from the cytoplasm to secretory vesicles in dopaminergic neurons; reduced in PD). Moreover, PET and SPECT can be utilised to detect subclinical dysfunction in individuals who are at (genetic) risk for PD, to measure progression of the disease and the impact of presumably neuroprotective agents on it, and to explore the impairment of non-dopaminergic pathways. Furthermore, magnetic resonance imaging (MRI) can primarily help to exclude some secondary causes of parkinsonism, like vascular or structural lesions, and atypical parkinsonian syndromes (24).
Post mortem, the diagnosis of idiopathic Parkinson's disease can be secured histopathologically (21).

The Hoehn and Yahr scale (14) is widespread in use for measuring the degree of severity and the progression of Parkinson's disease. It assigns PD patients to one of five stages according to clinical disability (see Table 4).

Stage	Definition
I	Unilateral involvement only, usually with minimal or no functional impairment.
II	Bilateral or midline involvement, without impairment of balance.
III	First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.
IV	Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.
V	Confinement to bed or wheelchair unless aided.

Table 4. The Hoehn and Yahr scale (14).

According to Jankovic et al. (25), PD can be sub-divided in different clinical phenotypes. Using the original UPDRS, they calculated an average global tremor score as the mean of nine items (right and left arm tremor defined by history, tremor at repose of face, lips, or chin and of all four limbs, action or postural tremor of both arms rated by the investigator). Moreover, they also defined a score for

symptoms of postural instability and gait difficulty (PIGD) by calculating the mean of five other original UPDRS-items (freezing, falling, walking difficulty by history, gait and postural instability by examination). By calculating a ratio between these scores (mean tremor score/mean PIGD score), PD patients can be assigned to a tremor dominant (TD) group (ratio ≥ 1.5) or a PIGD group (ratio < 1.5). In the original paper by Jankovic et al., PIGD patients showed more severe postural and gait difficulties, body bradykinesia, poorer posture and more difficulty in rising from a char than their TD counterparts. Moreover, occupational disability, intellectual impairment, depression, lack of motivation and impairment in the activities of daily live were more pronounced in the PIGD group. There was no difference between the groups in performance on neuropsychiatric tests. The TD group not only showed more severe tremor at rest, but also more intense action-postural tremor than PIGD patients. Gait and postural disturbances, rigidity and dystonia were more probable to exist at onset of the PIGD than the TD subtype. Moreover, PIGD symptoms and bradykinesia at onset were associated with rapid disease progression (25).

The calculation of the type-determining ratio was later adapted to the revised MDS-UPDRS. Mean tremor score is now calculated using eleven (2.10, 3.15, 3.16, 3.17, 3.18), mean PIGD score using five MDS-UPDRS items (2.12, 2.13, 3.10, 3.11, 3.12). Optimal cut-offs were determined as a TD/PIGD ratio of ≥ 1.15 for the TD phenotype and ≤ 0.90 for the PIGD phenotype. The indeterminate group comprises patients with a ratio between 0.90 and 1.15 or with a zero in both numerator (tremor score) and denominator (PIGD score) (26).

In PD patients, the incidence of dementia is increased by up to six times compared to non-PD individuals, with older age, mild cognitive impairment (MCI) at baseline, PIGD symptoms and akinetic-rigid type constituting risk factors. Hallmarks of Parkinson’s disease dementia (PDD) include deficits in memory, executive and visuo-spatial functions, attention and behavioural symptoms (apathy, hallucinations, affective alterations). In order to differentiate PDD from dementia with Lewy bodies (DLB), the MDS recommends diagnosing PDD when dementia occurs in the course of established PD. DLB, on the other hand, should be diagnosed when dementia manifests prior to the development of parkinsonism or within one year of it (27).

In 2007, the MDS published criteria for the diagnosis of probable and possible PDD. Basically, to diagnose probable PDD in patients with established PD, deficits in at least two of four cognitive domains (attention, executive functions, visuo-spatial functions, memory) must be present, and these deficits need to be serious enough to impair normal functioning. The exact features of PDD and diagnostic criteria for probable and possible PDD can be found in the original publication by Emre et al. (27).

Mild cognitive impairment is common in non-demented PD patients (mean prevalence of 26.7%). Number and types of cognitive domain deficits are rather heterogenous, with non-amnestic, single domain impairment being the most prevalent form. The frequency of mild cognitive impairment in PD (PD-MCI) grows with age, disease severity and disease duration, and it constitutes a risk factor for progression to PDD (28). The MDS diagnostic criteria for PD-MCI can be found in the publication by Litvan et al. (29). In summary, PD-MCI can be diagnosed in established PD patients when there is a gradual decrease in cognitive abilities, with impairments found either on a scale of global cognitive abilities or in formal neuropsychological testing. Moreover, these cognitive deficits should not be severe enough to affect functional independence (29).

1.1.5 Therapeutic options

In the first place, treatment of Parkinson's disease aims to relief symptoms. Currently, there are no therapies that are undisputedly able to halt or reverse the neurodegeneration in PD. While drugs are the mainstay in treatment of PD, there are also some surgical methods (2).

L-dopa (or levodopa) is the drug that bears the most effectiveness in the treatment of PD, even in advanced stages of the disease. Levodopa is a precursor of dopamine. The remaining nigral cells use levodopa to synthesise dopamine, which can then act on the intact neurons in the striatum. However, in the course of time, the beneficial effect of levodopa diminishes and paradoxical and excessive movements (dyskinesias) can emerge. Levodopa is usually combined with a decarboxylase inhibitor (benserazide or carbidopa) which does not reach the central nervous system. These agents inhibit the decarboxylation of levodopa to dopamine in peripheral tissues, allowing more levodopa to reach the neurons of

the substantia nigra. Moreover, peripheral side effects of levodopa and dopamine, like hypotension, confusion, or nausea, are diminished (2).
Catechol-O-methyltransferase (COMT) inhibitors like entacapone block the degradation of levodopa and hence prolong its plasma half-life and effect duration.
Dopamine agonists, like ropinirole and pramipexole, exert a direct dopaminergic effect on striatal neurons. Dopamine agonist are, however, less effective in controlling parkinsonian symptoms than levodopa. Moreover, they can cause motor and cognitive side effects, especially in high doses and in older patients. Dyskinetic motor complications, on the other hand, occur less frequently than with levodopa (2).
Anticholinergic drugs, like benztropine or trihexyphenidyl, can be particularly useful to control tremor, but have little effect on the other typical parkinsonian motor symptoms. Typical (atropinic) side effects of these drugs are confusion, psychosis, dry mouth and urinary outlet obstruction (2).
The NMDA glutamate antagonist amantadine can ameliorate tremor, hypokinesia and postural disturbances. It may also reduce levodopa-related dyskinesias.
Rasagiline and selegiline pertain to the group of monoamine oxidase-B (MAO-B) inhibitors. These agents presumably reduce oxidative stress in dopaminergic neurons, hence exerting a neuroprotective effect. For this reason, it is often recommended to initiate MAO-B inhibitors in early stages of the disease. Moreover, MAO-B inhibitors can also smoothen levodopa-induced motor fluctuations and ameliorate the main Parkinson symptoms (2).
Neuroprotective effects in PD have also been suggested for ropinirole, pramipexole, and levodopa (2).
Surgical measures are performed stereotactically guided and combined with the implantation of electrodes (deep brain stimulation, DBS). The electrodes are positioned in the ventral and posterior parts of the nucleus subthalamicus or in the internal segment of the globus pallidus. DBS can reduce levodopa-induced dyskinesias and enhance levodopa-responsiveness. A bilateral stimulation of the nucleus subthalamicus can improve all features of PD, including bradykinesia, except disturbed gait and balance. Regarding the mode of action of DBS, the high-frequency electrical impulses are presumed to disturb local neuronal activity, hence functionally equivalenting an ablative lesion (2).

Ancillary treatments, like exercise programs and physical therapy, usage of walking aids and speech exercises, can be of great value for PD patients. Fludrocortisone or midodrine can ameliorate hypotensive episodes, and focal dystonias can be addressed with local botulinum toxin injections (2).

1.2 White Matter Lesions

1.2.1 Definition and epidemiology

White matter lesions (WML) are bilateral, mostly symmetrical hyperintensities on T2-weighted cerebral MR images and are frequently found in elderly people. Various different terms have been in use for describing these lesions, most frequently including the following: leukoaraiosis, white matter lesions, white matter hyperintensities (WMH), white matter changes (WMC), leukoencephalopathy and white matter disease (WMD) (30).

WMH of widely varying extent are present in more than half of all elderly people (31,32). Das et al. (33) recently reviewed the major population-based studies of WMH in healthy subjects, which found a baseline WMH prevalence between 65-96% (32,34-36). Among those, the Austrian Stroke Prevention Study (31,36) showed the lowest prevalence of WMH (65%, mean age 60 years), while the Cardiovascular Health Study (34) found the highest one with 96% (mean age 74 years). This finding is consistent with the fact that WMH prevalence and degree increase with age (32,37). In a study including 243 healthy, relatively young individuals (16-65 years, mean age 36.95 ± 13.45 years) (38), WMH prevalence was only 5.3%. Participants free of WMH had a median age of 34.5 years while individuals with WMH had a median age of 57.0 years. The age group > 55 years had the tenfold prevalence of WMH compared to the group ≤ 55 years; age and WMH significantly correlated (38). Furthermore, some studies found that women tended to have a higher degree of WMH (32,34).

Evidence is strong that WMH are a predictor for the risk of stroke, dementia and mortality and thus represent a marker for increased cerebrovascular risk (39). However, histopathological substrates of WMH are heterogenous (40) and their pathogenesis is not fully understood yet (40,41). These aspects will be discussed in detail in chapters 1.2.4 and 1.2.5.

Generally speaking, WMH are seen as a consequence of cerebral small vessel disease (CSVD). This term describes a group of pathological processes of numerous aetiologies affecting the small cerebral arteries, arterioles, venules and capillaries. The two most common types of CSVD are age-related and hypertension-related SVD (type 1 CSVD; also referred to as arteriolosclerosis or vascular risk-factor-related SVD) and cerebral amyloid angiopathy (type 2;

sporadic and hereditary). Less prevalent types include inherited or genetic SVD (type 3; for example, CADASIL and Fabry's disease), inflammatory and immunologically mediated SVD (type 4), venous collagenosis (type 5) and other SVD (type 6; for example, post-radiation angiopathy). The sequelae of CSVD on brain parenchyma predominantly involve subcortical structures and include, besides WMH, lacunar infarcts, large haemorrhages, microbleeds and others. Owing to the lack of the ability to visualise small vessels in vivo, WMH and lacunar infarcts, which are detectable in standard neuroimaging methods, have been employed as markers of CSVD (41).

As is the case with WMH, a plethora of synonyms have been used in scientific literature to describe the other markers and consequences of SVD. Hence, this inconsistency in reporting SVD lesions handicaps cross-study comparisons and scientific work on risk factors, pathophysiology, pathological backgrounds and clinical implications. Therefore, Wardlaw et al., representing an international working group from the Centres of Excellence in Neurodegeneration, have published the "Standards for reporting vascular changes on neuroimaging (STRIVE)", providing standardised terms and definitions for the six key lesion types of SVD visible in MRI (30). The results of their effort are reflected in Table 5.

Standardised term of lesion type	**Definition**
Recent small subcortical infarct	Neuroimaging evidence of recent infarction in the territory of one perforating arteriole, with imaging features or clinical symptoms consistent with a lesion occurring in the previous few weeks.
Lacune of presumed vascular origin	A round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) of between 3 mm and about 15 mm in diameter, consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole.
White matter hyperintensity of presumed vascular origin	Signal abnormality of variable size in the white matter that shows the following characteristics: hyperintensity on T2-weighted images such as fluid-attenuated inversion recovery, without cavitation (signal different from CSF). Lesions in the subcortical grey matter or brainstem are not included in this category unless explicitly stated. If deep grey matter and brainstem hyperintensities are also included, the

	collective term should be subcortical hyperintensities.
Perivascular space	Fluid-filled spaces that follow the typical course of a vessel as it goes through grey or white matter. The spaces have signal intensity similar to CSF on all sequences. Because they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel.
Cerebral microbleed	Small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects.
Brain atrophy	A lower brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction. Thus, infarction is not included in this measure unless explicitly stated.

Table 5. Standardised terms and definitions of the six key lesion types of CSVD adapted from Wardlaw et al. 2013 (30).

Abbreviations:
CSF…….cerebrospinal fluid
CSVD……..…...cerebral small vessel disease
MRI……..…magnetic resonance imaging

1.2.2 Imaging

As stated in Table 5, the term white matter hyperintensity (or white matter lesion) describes an area of varying extent within the cerebral white matter which is characterised by a high signal intensity in T2-weighted magnetic resonance images. In the absence of contraindications, MRI is the mainstay of detecting WMH and the remaining key lesions of SVD, both in routine clinical setting and in research. MRI shows a higher sensitivity and specificity for detecting the majority of SVD lesions than computed tomography (CT) (30).

Due to its clinical importance in the field of WMH and neuroimaging in general, the general techniques of MRI will be discussed in the following chapters. Fluid attenuated inversion recovery (FLAIR) sequences were used in conducting this study and hence will be elaborated, too.

1.2.2.1 General MRI techniques

Magnetic resonance imaging (MRI) is an imaging technique that uses strong magnetic fields and radio frequency signals to generate images of organs and structures within the human body. Unlike most other imaging techniques, MRI can selectively utilise different tissue characteristics as a source of contrast, such as characteristics of fluid movement, spectroscopic effects related to molecular structure and, most importantly, specific magnetic characteristics. Simply put, MRI ultimately depicts the level of magnetisation of tissues induced by an external magnetic field, based on the physical processes described in the following chapters (42).

1.2.2.1.1 Basic physical principles

The quintessential basis for producing an MRI image is the presence of atomic nuclei with specific magnetic properties. Only isotopes with an odd number of protons and neutrons function as small magnets (and are thus magnetisable by an external field) and show a magnetic moment. Each particle in an atomic nucleus has an intrinsic angular momentum, also known as spin. Pairs of protons and neutrons align in a way that leads to a cancellation of their spins, resulting in a net spin of zero. However, if there is an odd number of particles in the nucleus, not all spins are cancelled, and the nucleus will show a net spin characteristic (42). Since the atomic nucleus is an electrically charged particle, this net spin produces a magnetic moment with a certain direction. The chemical element showing magnetic properties which is most frequently used in conventional MRI is hydrogen-1, found mainly in water; its nucleus consists merely of a single proton. Thanks to the high tissue density of the specific magnetic isotope hydrogen-1 and its high relative magnetic sensitivity, hydrogen emits a very strong radio frequency signal (see below). High relative sensitivity means that hydrogen-1 produces a strong signal compared to other nuclei which are present in equal concentration (42).

When there is no magnetic field present, the magnetic hydrogen nuclei are randomly oriented, and no magnetic net effect is generated. However, as soon as the nuclei (i.e., the patient) are placed in a strong external magnetic field (i.e., within the bore of the MRI system), some of them align in the direction of the field, resulting in a magnetisation of the tissue parallel to the field. This effect is also

known as longitudinal magnetisation and its quantity depends, aside from the density of nuclei in the tissue and their magnetic sensitivity, very much on the strength of the external magnetic field generated by the coils of the MRI system: The stronger the field, the more protons align in its direction and the stronger is the magnetisation (42).

In addition to longitudinal magnetisation, the magnetic field also causes the atomic nuclei (hydrogen-1) to take on a resonant characteristic. This means that the nuclei absorb and re-emit radio frequency signals at a specific frequency, much like a radio receiver; this phenomenon is called nuclear magnetic resonance: After the parallel alignment with the magnetic field, the nuclei do not remain in a fixed position. As a consequence of the interaction between the external magnetic field and the spinning momentum of the nuclei, the magnetic moment starts to precess (oscillate) about the axis of the magnetic field. This process called precession is often compared to a child's spinning top, which starts to wobble after a few seconds. In this case, the interaction happens between the earth's gravitational field and the spinning momentum of the spinning top (42).

The precession rate (cycles per second), also called resonance frequency or Larmor frequency, lies in the radio frequency range; it is what makes a nucleus sensitive to an external radio frequency signal with the exact same frequency. The Larmor frequency is characteristic for each specific nuclide and increases with the strength of the magnetic field (in Tesla, T). For hydrogen-1, the Larmor frequency is 42.58 MHz/T. In addition, the Larmor frequency of a magnetic nucleus is also influenced by molecular structure. This effect on the resonance frequency is called chemical shift and is used to determine the chemical composition of tissues (MR spectroscopy). To give an example: The chemical shift in resonance frequency between fat and water is approximately 3.3 ppm, resulting in a difference of 210 Hz at 1.5 Tesla (the proton's basic resonance frequency at 1.5 T is 64 MHz). This effect can also be used to specifically suppress fat or water components in images using special radio frequency pulses (spectral presaturation) (42).

1.2.2.1.2 Excitation, saturation and relaxation

Radio frequency coils are used to transmit energy to the tissue, generate a measurable signal and then receive these signals (42).

The first step in acquiring a signal from the magnetised tissue is to apply energy to it. This happens when the radio frequency coils send pulses of energy with a frequency matching the Larmor frequency into the tissue. This energy is then partially absorbed by the magnetised, precessing protons, which causes them to lose their parallel alignment with the magnetic field and to flip into the transverse plane of the field. Therefore, the nuclei are now in an unnatural, excited state, which is richer in energy. This process is also known as excitation and causes a magnetisation in the transverse plane (transverse magnetisation). At the same time, the radio frequency pulse reduces longitudinal magnetisation to zero, a status called saturation (42).

Duration and strength of the pulse determine the angle the magnetisation is flipped. As described above, pulses with a 90° flip angle are very commonly used. In certain techniques, however, 180° flip angles or flip angles below 90° are applied (42).

In the excited state the precessing motion of the resting state is converted into a spinning motion around the longitudinal axis of the magnetic field. It is this spinning motion around the field's axis during transverse magnetisation that generates a radio frequency signal, which is then picked up by the radio frequency coils and used to produce an image. The frequency of the radio signal produced matches the rate the magnetic nuclei are spinning in (42).

Once a nucleus has been flipped to the excited state, it will be urged by the magnetic field to realign with it, thus, to return to a lower state of energy, resulting in a re-growth of longitudinal magnetisation. This requires the excited nucleus to transfer its excess energy to either other nuclei or to the general structure of the material. This process is called relaxation. The time required for the transfer of energy and thus relaxation depends on the physical characteristics of the tissue (and on the magnetic field strength). Therefore, the relaxation time (or rate) is one of the primary sources of contrast between different (physiologic or pathologic) tissues in MR images (42).

1.2.2.1.3 T1, T2, P-d

Relaxation can be separated into two sub-processes: the regrowth of longitudinal magnetisation and the decrease of transverse magnetisation. Both sub-processes can be used independently to produce contrast in an MR image. The selection of

the primary source of contrast is called weighting and is controlled by certain protocol factors, which will be discussed in the next chapter. In general terms, it can be said that the level of magnetisation (either longitudinal or transverse) of the tissue at the time of taking the MR image determines the brightness of the tissue in the image: The more intense the magnetisation is, the brighter the tissue appears in the image (42).

Saturated tissue shows a longitudinal magnetisation of zero and consequently appears dark in MR images. The recovery of longitudinal magnetisation increases the brightness of the picture. This relaxation process after saturation happens at an exponential rate and the time required is characteristic for each tissue. Due to the exponential nature of this process, it cannot be established precisely when the longitudinal magnetisation reaches its maximum. Therefore, the tissue-specific longitudinal relaxation time (usually referred to as T1) is defined as the time required for the longitudinal magnetisation to reach 63% of its maximum. After three T1 intervals, the longitudinal magnetisation has regained 95% of its maximum and can be considered as fully recovered. Tissues with short T1 values like fat regain longitudinal magnetisation quickly, thus appearing brighter in T1-weighted images than tissues with long T1 values like fluids. The T1 value is related to the naturally occurring molecular motion of the molecules surrounding the protons: If the proton resonant frequency and the frequency of the molecular motion match, the relaxation process is facilitated. Large molecules like fat are characterised by a relatively slow molecular movement and therefore match the proton resonant frequency better than water, which consists of small molecules showing a faster molecular movement. This explains why tissues high in fat are characterised by short T1 values whereas tissues with high water content show long T1 values (42).

As previously described, a 90° radio frequency pulse flips the magnetised protons in the transverse plane, generating unstable transverse magnetisation. The successive exponential decay of the transverse magnetisation happens at a tissue-specific relaxation rate. The time required for a tissue to lose 63% of its maximal transverse magnetisation is usually referred to as transverse relaxation time or T2. In T2-weighted images, the difference in T2 values of specific tissues is used to produce contrast: Tissues with short T2 values like fat lose their transverse magnetisation, i.e., become darker, more quickly than tissues with long

T2 values like fluids. As a result, tissues with long T2 values appear brighter in T2-weighted images (42).
When the magnetic moments of the protons are flipped into the transverse plane, they also point in the same direction within this plane, they are in phase. This being in phase generates a net transverse magnetisation. The relaxation of transverse magnetisation is caused by the dephasing of the protons. The dephasing of protons is the result of two different effects: The first one, spin-spin-interactions, is the transfer of energy between the spinning nuclei. It causes a relatively slow decline in transverse magnetisation (dephasing); these spin-spin-interactions are responsible for the tissue-specific T2 values (42).
The second reason for the dephasing of protons are inhomogeneities within the magnetic field, for instance due to the presence of materials with different magnetic susceptibilities (a property determined by the orbital electrons which defines a material's ability to become magnetised within a magnetic field). These inhomogeneities in field strength cause a slight difference in local Larmor frequency and thus a very rapid dephasing of the protons. That means that those inhomogeneities often mask the T2 characteristics of a tissue. This real relaxation time, which is much shorter than the T2 values would indicate, is referred to as T2*. The so-called spin echo technique is a means of separating the T2 and T2* characteristics of a tissue (42).
The third important tissue characteristic serving as a source of contrast is proton density (P-d) or proton concentration. The more magnetic protons a tissue contains, the higher is the maximum level of magnetisation that can be induced in this tissue (42).

1.2.2.1.4 Imaging cycle

In order to acquire an MR image, a certain imaging cycle needs to be repeated many times. The number of cycles and the duration of each cycle determine the total time required for the acquisition of an image. Each imaging cycle can be divided into two phases: a longitudinal and a transverse magnetisation phase. While tissue specific T1 values are responsible for producing contrast during the longitudinal magnetisation phase, T2 contrast emerges in the transverse magnetisation phase. Proton density contrast is present in both phases but is most of the time concealed by T1 and T2 contrast. The duration of the phases and the

transfer of contrast from the longitudinal to the transverse phase define how the image is weighted, i.e., which tissue characteristic (T1, T2, P-d) is the main source of contrast (42).

The adjustable values of two protocol factors – TR (Time of Repetition) and TE (Time to Echo) – determine the duration of the two phases and hence the weighting of the MR image. TR describes the duration of the longitudinal magnetisation phase and is defined as the period between saturation (the beginning of longitudinal relaxation) and the (next) 90° excitation pulse, which converts the regrown longitudinal magnetisation to the signal producing transverse magnetisation. Thus, the value of TR can be selected in a way that produces an MR image which shows the tissue specific differences in longitudinal relaxation rate (T1 contrast). Since longitudinal relaxation takes more time than transverse relaxation, TR is also the time required for a full imaging cycle (42).

TE is the duration of the transverse magnetisation phase and characterises the period between excitation, when transverse relaxation begins, and the echo event, the moment when a radio frequency signal is generated and magnetisation is finally measured for producing image contrast. The adjustment of TE allows to produce MR images whose primary source of contrast are differences in transverse relaxation rate (T2 contrast) (42).

In order to produce a T1-weighted image, TR must be set to a value corresponding to a point in time where significant T1 contrast between tissues is present. This is the case relatively early in the relaxation process. To avoid T2 contrast distorting the T1 characteristics of a tissue, a short TE value has to be selected. Summarising, the creation of a T1-weighted image requires short TR values (around 500 msec) as well as short TE values (around 15-20 msec) (42).

The difference in magnetisation level is the source of contrast in P-d-weighted pictures. Since P-d contrast is heavily masked by T1 contrast in early phases of relaxation, it becomes apparent only in its later phases when T1 contrast diminishes and the tissue reaches its maximum level of longitudinal magnetisation. Therefore, relatively long TR values are necessary for producing a P-d-weighted picture. Like in T1-weighted images, short TE values are necessary for reducing effects of T2 characteristics (42).

To produce a T2-weighted image, as little as possible T1 contrast should be transferred to the transverse magnetisation phase. This is realised by using long

TR values. As a result, the transverse phase begins at the maximum level of magnetisation determined by PD, followed by a gradual decay of transverse magnetisation depending on the tissue specific T2 values. TE needs to be set to a value which coincides with a point in time when there is significant T2 contrast between tissues. This applies especially in relatively late phases of transverse relaxation. In conclusion, T2-weighted images are generated by selecting both long TR values (around 2000 msec) and long TE values (around 120 msec) (42).
Since longitudinal magnetisation is a radio frequency silent condition, the signal is always generated during transverse magnetisation, regardless of the weighting of the image. As described previously, the echo event marks the point in time when radio frequency signals are measured. This echo event can be triggered in two ways: either by applying an additional radio frequency pulse or a gradient pulse to the tissue. Therefore, two basic categories of imaging methods exist, the spin echo imaging methods and the gradient echo imaging methods. The latter uses magnetic field gradients, that is, changes in field strength from one point in the field to another, to produce the echo event; this method allows to apply radio frequency pulses less than 90°, therefore adding the flip angle as an adjustable protocol factor. The main advantage of gradient echo methods is that they enable a faster image acquisition than spin echo methods; however, most of these gradient echo methods do not produce good T2-weighted images (42).
Spin echo methods are the basis for the FLAIR-sequence and will hence be discussed in more detail. Moreover, methods combining the advantages of the gradient echo and the spin echo technique have been developed (42).

1.2.2.1.5 Spin echo imaging method

As described in chapter 1.2.2.1.3, the dephasing of protons and thus the decay of transverse magnetisation is caused by spin-spin-interactions (T2 contrast) and magnetic field inhomogeneities (T2* contrast). The spin echo imaging process allows to annihilate the predominant T2* characteristics and to use the pure T2 characteristics of tissue to produce an MR image (42).
After being excited by the 90° radio frequency pulse and the following rapid dephasing of the magnetic moments due to T2* characteristics, the protons are randomly rotating in the transverse plane. In spin echo methods, a 180° pulse is then applied to those protons, causing them to reverse the direction of their

rotation around the axis in the transverse plane. While initially the fast protons are located behind the slower protons, the faster ones start to catch up with the slower ones and ultimately the protons come back into phase. As a result, the transverse magnetisation reappears and produces a distinct radio frequency signal, the echo event. Since the dephasing due to the tissue characteristics (T2) is irreversible, the transverse magnetisation cannot grow back to its initial maximum. The level of transverse magnetisation reached after the 180° pulse corresponds solely to the actual T2 characteristics of the tissue. After reaching this T2-dependent maximum level of magnetisation, the protons begin to dephase once again and transverse magnetisation decays. In multi-echo imaging, a series of 180° rephasing pulses is applied within one cycle. As a result, multiple echo events with different TE values are generated and both P-d- and T2-weighted images can be produced in the same acquisition (42).

To sum up, a basic pulse sequence of the spin echo method consists of a 90° excitation pulse, followed by a 180° rephasing pulse. TE marks the time between the excitation pulse and the echo event, therefore the interval between the 90° and the 180° pulse is ½ TE (42).

The radio frequency signals generated at the echo event are picked up by radio frequency coils. In order to attribute the numerous signals to a specific position within the body, the region to be imaged is first divided into slices, which are then subdivided into columns and rows. The resulting volume elements, or voxels, represent the smallest units in the imaging process and are thus paramount to image quality and detail resolution. Each voxel is an independent, collective source of radio signals and corresponds to a picture element, or pixel, in the final MR image. The intensity of the signal emitted by a certain voxel determines the brightness of the associated pixel. The slices and voxels are created by applying a number of magnetic field gradients in different dimensions and at specific times during the imaging cycle. This leads to slightly different resonant frequencies as well as phase shifts of the rotating nuclei throughout the body or region. This process causes the signals of each voxel to exhibit a specific combination of frequency and phase shift and thus allows an exact local allocation. The final process after the collection of the signals is the reconstruction of the actual image using mathematical methods (42).

1.2.2.2 Inversion recovery and FLAIR

Inversion recovery is a special spin echo imaging method which is used to produce images with high T1 contrast. Moreover, it enables to selectively suppress signals from specific tissues like fat or fluid. In inversion recovery pulse sequences, an additional 180° radio frequency pulse is applied to the tissue prior to the standard spin echo pulse sequence (90° excitation pulse followed by 180° rephasing pulse). The time span between the 180° inverting pulse and the 90° excitation pulse is termed “Time after Inversion” (TI) and is an adjustable protocol factor. Its adjustment allows to specifically suppress a certain type of tissue (see below) (42).

This initial 180° pulse inverts the direction of the longitudinal magnetisation. As a result, the regrowth of the longitudinal magnetisation does not start from zero, but rather from a negative value. Therefore, the total longitudinal relaxation time is much longer than in normal spin echo sequences and a higher level of T1 contrast can evolve (42).

The suppression of specific tissues is usually performed to diminish artefacts or to rise the contrast between tissues. Tissues that emit intense signals and hence appear very bright, such as fat in T1-weighted images and fluid in T2-weighted images, can obscure other tissues or pathologies. In certain inversion recovery methods, the particular T1 characteristics of fat and fluids are used to suppress either of them. The T1 values of fat (around 260 msec) and fluids (around 2000 msec) mark the outer limits of the range of T1 values found in tissues (42). Consequently, fat regains its longitudinal magnetisation after the inversion pulse much faster than other tissues, making it pass earlier through the zero level. To suppress the signal from fat, the 90° excitation pulse needs to be applied when the longitudinal magnetisation of fat is at zero, which means that no transverse magnetisation can be generated, and fat appears dark in the image. This requires TI to be set to a relatively short value, therefore this method is known as Short Time Inversion Recovery (STIR). In order to allow longitudinal magnetisation to regrow properly, relatively long TR values (approximately 1500-2000 msec) are necessary (42).

In T2-weighted images, an equivalent process is used to selectively suppress fluids. Fluids are characterised by long T1 values; therefore, the longitudinal

magnetisation is at zero relatively late after the inversion pulse. Long TI values are required to suppress the signals from fluids, making the fluids appear dark in images. Because of the long TI values used, very long TR values are inevitable (5000-6000 msec). As this causes long acquisition times, this method is usually combined with fast acquisition techniques (42).

Using inversion recovery sequences to suppress signals from cerebrospinal fluid and other tissues had been originally described by Bydder and Young in 1985 (43). However, Hajnal et al. and De Coene et al. were the first to use inversion recovery to suppress CSF combined with long TE values, therefore producing heavily T2-weighted images (44-46).

Since many pathologic processes, like multiple sclerosis or infarction, increase the T2 relaxation time of tissues, T2-weighted spin echo sequences are very frequently used in brain imaging (47,48). In conventional spin echo techniques, however, the possible degree of T2-weighting is markedly limited by the CSF signal: The signal produced by the brain tissue decreases much faster than the CSF signal; furthermore, the motion of the liquor and partial volume effects generate artefacts and therefore worsen image quality. To overcome this problem, Hajnal et al. (45) nulled the CSF signal using inversion recovery sequences. They found that, at 1.0 T, an inversion time (TI) of 2100 msec eliminates the CSF signal; with a TI within a range of 600 msec on either side of this number, useful attenuation of CSF signal can be achieved. Combining this finding with a long TE (240 msec) allowed creating heavily T2-weighted images (45). This technique was shortly thereafter referred to as “fluid attenuated inversion recovery” or “FLAIR” (44,46).

Using the FLAIR technique in healthy individuals revealed several regions within normal white matter which showed a higher signal intensity than surrounding white or grey matter. Among these regions were the centrum semiovale, posterior internal capsule, parietopontile tract, occipitothalamic radiation, brain stem and the cerebellum. In subependymal regions, a possible explanation for this finding might be the transudation of CSF, increasing the tissue specific T2 relaxation times. In regions more distant from the ventricular system, the high signal intensity might be caused by the presence of unmyelinated or sparsely myelinated fibres. These

regions of normal, high signal white matter can be mistaken for pathologic conditions in heavily T2-weighted cerebral MR images (45).
De Coene et al. (44) compared MR images of various brain lesions acquired using FLAIR sequences to images taken with standard T2-weighted spin echo sequences. The lesions studied included vascular disease, benign and malign tumours, infectious and metabolic diseases, white matter diseases and cases of ventricular enlargement. To sum up, they found that overall, more lesions were visible in the FLAIR sequences. Moreover, conspicuity of the vast majority of lesions was better in FLAIR sequences and the lesion extent was assessed better in most cases, too. For instance, in cases of vascular disease of the brain, additional and more extensive deep white matter lesions and periventricular lesions were depictable in the FLAIR sequences compared to the conventional T2-weighted sequences. They concluded that the FLAIR technique is especially useful in depicting a wide range of lesions in regions of the brain where CSF artefacts or partial volume effects between grey and white matter hinder the diagnosis in conventional T2-weighted sequences. This applies primarily in the periphery of the cerebral hemispheres, around the basal cisterns, in the brainstem and at grey white matter interfaces as well as in periventricular regions. In addition, the heavy T2 weighting of FLAIR sequences can visualise lesions invisible in conventional sequences (44).
One major drawback of the original FLAIR sequences are their long acquisition times (44,45,47). These long acquisition times are caused by the long TIs and TRs which are necessary to null CSF and to allow other tissues to regain longitudinal magnetisation (47). As a result, these sequences are prone to artefacts caused by patient motions and unsuppressed CSF flowing in from neighbouring slices (49). To overcome this problem, several fast image acquisition techniques have been developed, including, for instance, the RARE sequence (rapid acquisition with relaxation enhancement) (50), a multi-echo imaging method, and the so called “fast FLAIR” pulse sequence presented by Rydberg et al. (47).

1.2.2.3 White matter lesions in MRI – sequences, locations, grading

As mentioned previously, WMH appear hyperintense in T2-weighted MRI sequences including FLAIR (30). WMH can be best depicted by FLAIR sequences: Thanks to the annihilation of CSF signal, even periventricular or

perisulcal WMH become clearly recognisable. In addition, FLAIR sequences help to differentiate between WMH and lacunes since the core of lacunes usually behaves like liquor (51). While WMH appear hyperintense also in P-d-weighted images, they produce an isointense or hypointense signal in T1-weighted images, depending on the grade of pathological alterations and sequence parameters; however, their T1 signal is not as hypointense as liquor (30). Furthermore, WMH are also characterised by hyperintensity in T2*-weighted sequences (52). Wardlaw et al. (30) recommended in their STRIVE position paper to include, e.g., for clinical or extensive epidemiological studies, at least the following fundamental sequences in the examination of CSVD: axial DWI (diffusion-weighted imaging), FLAIR, T2-weighted, and T2*-weighted GRE (gradient-recalled echo) or susceptibility weighted imaging, and T1-weighted imaging (30). The recommended sequences and their purpose are summarised in Table 6.

Sequence	Purpose
T1-weighted	Important for discriminating lacunes from dilated perivascular spaces; for discriminating grey from white matter, and for studying brain atrophy
DWI	The most sensitive sequences for acute ischaemic lesions; positive for up to several weeks after cerebrovascular event
T2-weighted	To characterise brain structure; to differentiate lacunes from white matter hyperintensities and perivascular spaces; to identify old infarcts
FLAIR	To identify white matter hyperintensities and established cortical or large subcortical infarcts; to differentiate white matter lesions from perivascular spaces and lacunes
T2*-weighted GRE	To detect haemorrhage, cerebral microbleeds, siderosis; for measurement of intracranial volume

Table 6. Essential sequences and their purpose in the examination of CSVD adapted from Wardlaw et al. 2013 (30).

Abbreviations:
CSVD…….cerebral small vessel disease
DWI…….diffusion-weighted imaging
FLAIR…….fluid attenuated inversion recovery
GRE……...gradient-recalled echo

According to their location, WMH are typically classified as hyperintensities of the periventricular or of the deep white matter (30,53-55). Periventricular WMH can present on MRI as “caps”, “pencil-thin lining”, “bands” or smooth “halos” of high T2 signal intensity; irregular periventricular WMH reach into the deep white matter. Deep/subcortical WMH, on the other hand, can be graduated in “punctate”, “early confluent” and “confluent” (51,55). Exact definitions of these terms have been

established in the LADIS (Leukoaraiosis and Disability in the Elderly) study and are cited in Table 8 (56). These different degrees of WMH reflect different pathological findings (57,58) as well as different risks of progression (31,36); a more in-depth discussion of both aspects will follow in the upcoming chapters. Apart from periventricular and deep white matter regions, hyperintensities are also found in the brainstem and in subcortical grey matter structures, like the basal ganglia. However, these lesions should not be subsumed under the category of white matter hyperintensities unless explicitly indicated (30).

WMH can be analysed and assessed using a vast number of qualitative (visual rating) (59-64) and quantitative (computational analysis) (65-69) methods (30). Visual rating scales frequently used with MRI (62) include the Manolio scale (64), the Fazekas and Schmidt scale (also known as Fazekas scale) (55,70) and the Scheltens scale (71). Another visual rating scale for MRI was employed by Erkinjuntti and colleagues (72). Wahlund et al. (59) presented a scale employable to both CT and MRI that is characterised by nearly equivalent sensitivity, aside from certain regions like the parieto-occipital and infratentorial areas (59).
In the hands of a rater with expertise, visual rating scales are relatively quick and reliable; moreover, no sophisticated or costly post-processing instruments are necessary (73). The Fazekas and Scheltens scales, which were originally created for rating WMH cross-sectionally, exhibit good intra- and interobserver agreement for the measurement of WMH at a certain point in time; in addition, their results have been shown to correlate closely with volumetric assessments (62,73). Disadvantages of visual rating scales include that they have a high time consumption and a ceiling effect and that they use relatively wide categories for severity (73). Hence, they are not well suited for measuring change in white matter lesion severity (61).
Semi-automated and automated quantitative methods, on the other hand, allow measuring the exact volume of WMH and therefore enable the most accurate and fastest quantification of WMH burden and progression (73).

The Manolio scale assesses the overall volume of periventricular and subcortical WMH by comparing it to eight template studies with successively increasing WMH load, from hardly detectable WMH (grade 1) to extensive, confluent changes (grade 8); studies without WMH are labelled as grade 0, those with alterations

even more pronounced than grade 8 as grade 9 (64). The Scheltens scale takes into account the different locations of WMH and provides four sum scores in a semiquantitative way: Periventricular hyperintensities, lobar white matter hyperintensities, basal ganglia hyperintensities and infratentorial foci of hyperintensity are each further divided into anatomical subregions and then rated separately and given points according to the number and extent (in millimetres) of WMH and confluency (71). The specific regions and the scoring system are outlined in Table 7.

The Scheltens scale – visual rating of signal hyperintensities	
Periventricular hyperintensities (PVH 0-6)	
caps occipital 0 / 1 / 2 frontal 0 / 1 / 2 bands lateral ventricles 0 / 1 / 2	0 = absent 1 = ≤ 5 mm 2 = > 5 mm and < 10 mm*
Lobar white matter hyperintensities (WMH 0-24)	
frontal 0 / 1 / 2 / 3 / 4 / 5 / 6 parietal 0 / 1 / 2 / 3 / 4 / 5 / 6 occipital 0 / 1 / 2 / 3 / 4 / 5 / 6 temporal 0 / 1 / 2 / 3 / 4 / 5 / 6	0 = no abnormalities 1 = < 3 mm, n ≤ 5 2 = < 3 mm, n > 6 3 = 4-10 mm, n ≤ 5 4 = 4-10 mm, n > 6 5 = > 11 mm, n > 1 6 = confluent
Basal ganglia hyperintensities (BG 0-30)	
Caudate Nucleus 0 / 1 / 2 / 3 / 4 / 5 / 6 Putamen 0 / 1 / 2 / 3 / 4 / 5 / 6 Globus Pallidus 0 / 1 / 2 / 3 / 4 / 5 / 6 Thalamus 0 / 1 / 2 / 3 / 4 / 5 / 6 Internal capsule 0 / 1 / 2 / 3 / 4 / 5 / 6	
Infratentorial foci of hyperintensity (ITF 0-24)	
Cerebellum 0 / 1 / 2 / 3 / 4 / 5 / 6 Mesencephalon 0 / 1 / 2 / 3 / 4 / 5 / 6 Pons 0 / 1 / 2 / 3 / 4 / 5 / 6 Medulla 0 / 1 / 2 / 3 / 4 / 5 / 6	

Table 7. The Scheltens scale adapted from Scheltens et al. 1993 (71).
*Periventricular hyperintensities exceeding 10 mm are per definition scored as lobar white matter hyperintensities.
n = number of lesions

Abbreviations:
BG……basal ganglia
ITF…….. infratentorial foci of hyperintensity
PVH…….periventricular hyperintensities
WMH……...white matter hyperintensities

The Fazekas scale, similarly, differentiates between WMH surrounding the ventricles and WMH located in the deep white matter (55). The Fazekas scale (55) and exact definitions of its grades of deep WMH (56) are collated in Table 8.

The Fazekas scale			
Location	**Fazekas grade**	**Extent**	**Definition**
Deep white matter hyperintensities	0	Absent	
	1	Punctate foci	Single lesions < 10 mm Areas of grouped lesions < 20 mm in any diameter
	2	Beginning confluence of foci	Single lesions between 10-20 mm Areas of grouped lesions > 20 mm in any diameter No more than connecting bridges between individual lesions
	3	Large confluent areas	Single lesions or confluent areas of hyperintensity ≥ 20 mm in any diameter
Periventricular hyperintensities	0	Absent	
	1	Caps or pencil-thin lining	
	2	Smooth halo	
	3	Irregular periventricular WMH extending into the deep white matter	

Table 8. The Fazekas scale adapted from Fazekas et al. 1987 (55) and Pantoni et al. 2005 (56).

Abbreviations:
WMH……white matter hyperintensities

1.2.2.4 WML in other diagnostic techniques

In computed tomography images, white matter changes appear as areas of decreased density, i.e., they appear hypodense (30,74,75).
In 1986 and 1987, respectively, Hachinski, Potter and Merskey (74,75) pointed out the necessity of a “neutral term” to describe the changes in white matter observed on CT and MRI, considering the fact that many different causes might underlie those heterogenous abnormalities. Hence, they proposed the descriptive term “leuko-araiosis” and defined it as “a diminution of the density of representation of the white matter” (74,75). The neologism leukoaraiosis is composed of the two Greek roots “leuko-“ (“white”) and “araiosis” (“rarefaction”) (74,75). “Leukoaraiosis” was introduced at a time when the majority of studies was conducted with CT;

thus, some authors take the view that the term should only be used for describing the CT lesions (41).
The STRIVE group proposed the terms “white matter hypoattenuation” or “white matter hypodensities” for describing the lesions on CT. However, they recommended the use of CT for imaging of CSVD and WMH, respectively, solely in large-scale epidemiological studies or if magnetic resonance imaging is lacking or too costly (30).

New quantitative MRI techniques like diffusion tensor imaging (DTI) and magnetisation transfer imaging (MTI) indicate that the tissue damage associated with WMH is not limited to the lesions visible in conventional MRI sequences but rather also affects normal appearing white matter, making WMH only the “tip of the iceberg” of a diffuse pathological process (52,76).
DTI assesses both the direction and magnitude of diffusion of water in the axons’ cytoplasm and, in doing so, gives insight into the microstructural integrity of cerebral tissue. Water diffusion in cerebral tissue is limited by lipid bilayers and other cell structures; hence, it shows an anisotropy, and the highest diffusivity exists in the orientations of the axons (76,77). Parameters obtained from DTI include fractional anisotropy (FA), indicating the divergence of the in vivo water mobility from absolute isotropic diffusion, and mean diffusivity (MD), quantifying the magnitude of the water molecule’s diffusion (52,78).
MTI is a technique that gives information about the composition of cerebral tissue. Protons which are tied to large molecules (like myelin lipids or proteins) are not depictable in standard MRI sequences due to their specific relaxation characteristics. MTI, on the other hand, allows to indirectly quantify the amount of bound protons. By mapping a parameter called magnetisation transfer ratio (MTR), MTI enables a semi-quantitative evaluation of tissue alterations (76,79).
Several studies (80-83) have found an increase of MD and a decrease of FA and MTR in WMH when compared to normal appearing white matter, which points towards pathological processes involving increased water content and mobility as well as loss of myelin and axons (52). Maniega et al. (83) concluded that these imaging data suggest that WMH have decreased structural integrity in comparison with surrounding normal appearing white matter. They showed that MD differentiated best between normal appearing white matter and WMH, identifying

94.6% of the lesions. Moreover, they also found that the level of deterioration of normal appearing white matter was strongly associated with the severity of WMH: The higher the Fazekas score was, the stronger were the increase of MD and the decrease of FA and MTR in normal appearing white matter. This relationship was maintained independently of distance from the WMH and after accounting for age, gender, and self-reported vascular risk factors. They concluded that these results indicate that pathologic changes of the cerebral tissue sprawl beyond the zones of apparent WMH. Furthermore, their finding that MD increases in normal appearing white matter already with the lowest Fazekas score indicates that a change in water mobility in the interstitium could represent an early trait of white matter pathology in the senescent brain (83). Maillard et al. (84) observed that “FA measures of white matter integrity surrounding WMH decline in proximity to WMH” (84) and introduced the term “white matter hyperintensities penumbra” to describe this circumstance. Furthermore, they found that “generalized white matter integrity is a function of the overall WMH load” (84): With increasing total WMH burden, the white matter damage was more generalised, also affecting regions very far from WMH. These findings suggest, as described previously, that WMH are an indicator for a process sprawling beyond the region of tissue damage visible in conventional FLAIR sequences (84). Substantiating the concept of WMH penumbra, Maniega et al. (83) also showed that alterations of the normal appearing white matter locally correlate with distance from the WMH, reporting a decrease of MD and an increase of MTR with growing distance from the WMH (83).

Apart from imaging methods, several studies (85-87) have also investigated CSF biomarkers as potential in vivo diagnostic tools of WMH and SVD. Sjögren et al. (85) studied a group of 22 patients with Alzheimer’s disease (AD), 9 patients with subcortical dementia and 20 normal controls and split them into individuals with no or only punctate WMH and individuals with moderate to severe WMH; they found elevated levels of the light subtype of the neurofilament protein (NFL) in CSF of individuals with moderate to severe WMH compared to individuals with mild (punctate) or no WMH (also after correction for age, gender, and degree of cognitive impairment). When opposing individuals with any signs of WMH to those without such signs, a similar result was obtained, with NFL being increased in the group with signs of WMH. They found, however, no difference in levels of tau or

beta-amyloid 42 between these groups (85). While the latter are important CSF biomarkers of Alzheimer's disease (88), NFL is present predominantly in large myelinated axons (89); hence, its increase in CSF of individuals with WMH may represent degeneration of axons of highly myelinated neurons (85). In the LADIS study, Jonsson et al. (86) examined 53 non-demented elderly individuals and split them into three groups according to WMH severity, using the Fazekas scale; also, volumetric assessment of WMH was performed. They found that CSF NFL levels increased significantly with increasing rank on the Fazekas scale and that WMH volume correlated positively with CSF NFL levels (86). CSF sulfatide concentration, which is a marker of myelin injury (90), showed a slight increase in subjects with moderate or severe WMH, even though the association was not strong. No significant difference in Alzheimer's disease biomarkers between the groups was detected (86). These results support the findings of Sjögren et al. (85), suggesting that "NFL is a marker for axonal damage in response to small vessel disease in the brain" (86), and that "this manifestation may be distinct from or earlier than the neurodegenerative process seen in AD, as reflected by the lack of association between WMLs and AD biomarkers" (86). Results of a recent study by Osborn et al. (87) further corroborate these findings: In a population of community dwelling elderly individuals without dementia or stroke, they observed that higher CSF NFL levels were associated with increased WMH. Moreover, they also found lower beta-amyloid 42 levels to be associated with WMH. Osborn et al. developed a combined model, wherein both NFL and beta-amyloid 42 contributed to unique variance in WMH (3.2% and 4.3%, respectively). According to the authors, these findings yield "evidence of the co-occurrence of at least 2 distinct pathways for WMHs among older adults, including amyloid deposition and axonal injury" (87).

1.2.3 Risk factors for the development of WMH

Other than increasing age (32,37,38) and female sex (32,34), several (cardiovascular) risk factors for the development of WMH have been identified. A plethora of studies found hypertension to be associated with WMH (34,66,91-94). The LADIS Study (94), for instance, yielded that hypertension (≥ 140/90 mmHg), along with age and lacunar strokes, is a main risk factor for WMH. They found an increasing frequency of hypertension with increasing WMH grade on the Fazekas

scale in individuals without a stroke history (94). The Cardiovascular Determinants of Dementia (CASCADE) study (91), a European multicentre study, investigated the association of current and previous blood pressure levels, hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg or use of antihypertensive drugs) and WMH in 1625 non-demented individuals (65 to 75 years old). Both higher systolic (SBP) and diastolic blood pressure (DBP) (current as well as preceding values) showed an association with an elevated risk of severe periventricular and subcortical WMH. Furthermore, in comparison with constant DBP in the course of time, both a decrease as well as an increase of DBP showed an association with an elevated risk for severe periventricular WMH. The authors explained this phenomenon by the fact that the periventricular white matter is an arterial border zone and hence might be especially vulnerable to hypoperfusion due to drops in blood pressure. Moreover, they found that an increasing SBP elevated the risk for severe WMH. Finally, hypertension was strongly associated with severe WMH, with individuals who were hypertensive even though treated with antihypertensive drugs having the highest risk for severe WMH (91).

Another risk factor that is strongly positively associated with the presence and extent of WMH is smoking (34,66,94-97). Gons et al. (97) showed that mean WMH volume was higher in both present and ex-smokers than in subjects who had never smoked. Moreover, using diffusion tensor imaging, they also found that not only WMH but also normal appearing white matter were characterised by higher MD values in former and current smokers. However, MD and FA values in normal appearing white matter of individuals who had stopped smoking more than 20 years ago were similar to the values of individuals without a history of smoking. The authors therefore concluded that smoking, on the one hand, damages the white matter's microstructural integrity, and, on the other hand, that this damage is repairable if smoking is stopped (97).

Research results concerning the role of hypercholesterolaemia as a potential risk factor for WMH have been somewhat conflicting: While some studies found a positive association between hypercholesterolaemia and WMH (94) or WMH progression (98), respectively, others failed to do so (96,99). Khan et al. (96) found that hypercholesterolaemia was a risk factor for isolated lacunar infarction but not

for lacunar infarctions combined with more severe WMH (Fazekas grade 3) (96). Moreover, a study performed by Jimenez-Conde et al. (99) yielded that patients with acute ischaemic stroke who also suffered from hyperlipidaemia exhibited a lower WMH burden at the time of the incident; the authors concluded that hyperlipidaemia might protect against CSVD (99).

Similarly, some studies identified diabetes mellitus as a risk factor for WMH (98,100) while others did not (66,96,101,102). Like with hypercholesterolaemia, Khan et al. (96) showed that diabetes mellitus was associated with isolated lacunar infarctions but not with lacunar infarctions in the presence of severe WMH (96). A recent study performed by de Bresser et al. (101) revealed that patients with diabetes mellitus showed a specific shape and distribution of WMH, even though there was no difference in WMH volume detectable when compared to a control group (101).

Associations of WMH with different markers of atherosclerosis have been found, too. Several studies identified ultrasonographic carotid intima-media thickness (IMT) as a potential risk factor for WMH (103-105). De Leeuw et al. (106) reported a positive association of the number of plaques in the carotid artery with the severity of periventricular WMH but not with subcortical WMH; neither did they find a significant association between IMT and periventricular ($p=0,09$) or subcortical ($p=0,68$) WMH (106). Moreover, atherosclerosis of the aorta at middle age is a risk factor for the presence of periventricular WMH roughly 20 years later but not for subcortical WMH (107).

Additionally, associations of WMH with atrial fibrillation (108-110), elevated plasma total homocysteine levels (98,111), albuminuria (112,113), moderate to severe obstructive sleep apnoea (114), heart failure (115) and reduced cerebral perfusion in patients with heart failure (116) have been reported.

Apart from those risk factors, WMH have also been shown to have a high heritability (117-119). For instance, a study on monozygotic twins aged 68 to 79 yielded a heritability of WMH volume of 71% (117), a more recent monozygotic twin study showed a high heritability especially of deep WMH (118). In a family-based sample of healthy individuals taken from the Framingham Heart Study, Atwood et al. found a high heritability of WMH, too (55%) (119).

A number of mostly rare monogenic diseases are accompanied by WMH, including, inter alia, CADASIL ("Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy"), homocystinuria, MELAS ("Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes") and Fabry disease (120).

Considering the rarity of these monogenic diseases, the genetic background of WMH assumedly lies in the slight effects of a number of genes and their interactions with each other and environmental determinants. These candidate genes have been evaluated for single nucleotide polymorphisms (SNPs) and through genome-wide association studies. Possible candidates include cholesterol-regulation and atherosclerosis-related genes (for instance, the apolipoprotein E gene), hypertension-related genes (coding for enzymes involved in the renin-angiotensin system), genes pertaining to the homocysteine metabolism, genes related to neuronal regeneration and genes associated with oxidative stress (120).

The Austrian Stroke Prevention Study investigated several candidate genes: They found that the epsilon 2/epsilon 3 genotype of apolipoprotein E was more prevalent in individuals (above 50 years and free of neuropsychiatric disorders) who showed imaging signs of CSVD (early confluent or confluent WMH or lacunes) compared to individuals free of such imaging signs (121). Furthermore, they presented evidence that a certain haplotype (B haplotype) of the promoter region of the angiotensinogen gene might predispose for WMH and lacunes (122). Elderly individuals with a certain polymorphism of the paraoxonase (PON1) gene (the LL PON1 genotype at position 54) trended to have a higher WMH load and a more frequent progression of WMH, too (123). In addition, an increased risk of WMH in hypertensive patients was associated with common variants of the NOTCH3 gene (124); mutations of this gene are causative for CADASIL (125).

1.2.4 Pathogenesis of CSVD and WMH

As mentioned previously, a wide variety of aetiopathogeneses can underlie cerebral small vessel disease, with arteriolosclerosis (type 1) and cerebral amyloid angiopathy (CAA, type 2) being the most common forms (41). However, the exact pathogenetic mechanisms and their link to brain parenchyma lesions like WMH

are heterogenous and not fully elucidated and different explanatory approaches coexist and intertwine (40,41,76,126,127).

In CAA, congophilic, βA4 immunoreactive amyloid protein aggregates in the walls of small to mid-sized arteries and arterioles in the leptomeningeal space and the cerebral cortex; capillaries and veins are partially affected, too. CAA can ultimately result in dilation and disruption of the vessels, focal wall fragmentation, blood extravasation, microaneurysmal dilatation and occlusion of the lumen (41,128,129). CAA is not only a typical pathological finding in Alzheimer's disease (130,131) but is also very common in unselected populations, its frequency increasing with age (132). Lesions found to be associated with CAA include, inter alia, large lobar haemorrhages (133), microbleeds on MRI (134) and WMH (135,136).

The histopathology of arteriolosclerosis, or age-related and vascular risk-factor-related SVD (type 1), unveils smooth muscle cell loss from the tunica media, deposition of fibro-hyaline material, luminal narrowing and thickened vessel walls. Arteriolosclerosis is a highly prevalent and systemic disease. Kidneys and retinas can be involved, too, and it is associated with ageing, diabetes and particularly hypertension (hence the term hypertensive small vessel diseases) (41,137). Other pathological alterations seen in arteriolosclerosis include "distal manifestations of atherosclerosis (microatheroma) and the presence of elongated and dilated vessels (microaneurysms)" (41).

The pathogenetic mechanisms linking SVD with (brain) parenchyma damage are heterogenous and not fully elucidated yet (41). A synopsis of the presumed pathophysiological sequence leading from SVD to brain injury, adopted from Pantoni (41), is given in Figure 2. The pathological alterations in small vessels can cause both ischaemic and haemorrhagic sequelae; it is, however, unclear why some vessel ruptures lead to extensive haemorrhage and others only to micro haemorrhage (41). In CAA, increased thickness of the vessel wall might be a risk factor for microbleeds rather than macrobleeds (138).

WMH are most often hypothesised to be of ischaemic origin, with several other pathogenetic mechanisms in discussion to be contributing to their development (see below) (127,139).

According to Pantoni (139), an ischaemic origin of WMH is put forward by the following facts:

I. Considering the aspect of blood supply, the brain's white matter is a border zone. Consequently, it is especially vulnerable to abrupt decreases of cerebral blood flow in case of low systemic blood pressure or regional circulatory disruptions.
II. WMH are associated with vascular risk factors and disease, especially hypertension (34,35) (see also chapter 1.2.3).
III. In pathological examinations, arteriolosclerosis is often detected in regions corresponding to radiological WMH, and these regions show a rarefaction of white matter comparable to that in the marginal zones of true infarcts (140).
IV. Individuals with WMH show an elevated risk of vascular events and mortality at follow-up (39,141,142).
V. White matter constituents (oligodendrocytes and myelinated axons) are characterised by a high vulnerability to ischaemia (143,144).
VI. PET observations revealed an elevated oxygen extraction rate in WMH (145).

(List taken and adapted from Pantoni 2002 (139))

The narrowing of the vessel lumen in SVD possibly causes a condition of chronic hypoperfusion of the cerebral white matter, which ultimately results in degeneration of myelinated fibres due to recurring selective oligodendrocyte death (41), representing a type of uncompleted infarct or selective necrosis (41,140).
In addition, changes in small vessels might cause an impairment or loss of autoregulation. This would lead to the white matter being more susceptible to reductions of blood flow during periods of low systemic blood pressure, which would be especially deleterious for the white matter given its terminal type of blood supply (139).
Furthermore, acute occlusion of a small vessel could happen, causing focal and acute ischaemia followed by total necrosis of the tissue (41). This mechanism, put forward by Fisher in 1965 (146,147) is hypothesised to cause lacunar infarcts (41).
Another mechanism that could be involved in the formation of WMH is periventricular venous collagenosis, as described by Moody et al. (148). Periventricular venous collagenosis is frequently found in individuals older than 60 years and considered a noninflammatory, degenerative alternation. It is characterised by an "extraordinary wall thickening in the periventricular veins with

multiple concentric rings of collagen" (148), leading to narrowing of the lumen and culminating in occlusion. Venous obstruction results in diminished perfusion pressure, blood-brain barrier (BBB) impairment of the venules and dysfunctional venous drainage, which can ultimately cause chronic ischaemia, brain oedema, pseudotumor, infarct and haemorrhage. Periventricular venous collagenosis was found to be strongly associated with leukoaraiosis/WMH, and more pronounced venous alterations correlated with more severe WMH (148).

Another mechanism whose pathogenetic role in CSVD, WMH and their clinical consequences has been in discussion is an increased permeability of the blood-brain barrier (126,149-151). Dysfunction of the cerebral small vessel endothelium (i.e., impairment of the BBB), accompanied by leaking of plasma constituents into the vessel wall and the adjacent cerebral tissue, might lead to neuronal and glial injury; hypertension and diabetes mellitus could be factors contributing to the vascular leakage. Components of the plasma that could potentially produce the actual perivascular injuries include plasmin and other proteases, environmental toxins in the blood, infectious noxae or changed electrolyte levels in the interstitium (149). Diagnostic methods that have been used to assess BBB permeability include imaging methods (contrast CT, contrast MR, PET) and biochemical methods (CSF/serum albumin ratio) (126). A systematic review and meta-analysis conducted by Farrall and Wardlaw (126) revealed that BBB permeability increased in normal ageing and further rose with mounting WMH burden (and in patients with dementia, especially vascular dementia). Skoog et al. (152) found that CSF/serum albumin ratio was elevated before the beginning of dementia and that there was no relation to the degree of severity of dementia, suggesting that BBB dysfunction is present at an early stage of the disease (152). Another study (153) found that individuals with lacunar stroke (as a discrete clinical marker of CSVD) have, compared to individuals with cortical stroke, "a diffuse background increase in BBB permeability in the white matter, evident as increased signal after gadolinium in white matter and CSF" (153). Even though this finding does not allow the conclusion that BBB dysfunction is causative of the small vessel alterations and damage of the parenchyma, it can be said that elevated BBB permeability is detectable when SVD first shows clinical symptoms (153). This hypothesis is also corroborated by the changes of MRI biomarkers (83) described in chapter 1.2.2.4.

Additionally, some studies indicate that inflammatory processes play a pathogenetic role in CSVD and WMH. A post mortem study (154) found that, in the brains of deceased patients who had suffered from chronic cerebral ischaemia, COX-2 immunoreactivity was upregulated in microglia. The authors concluded that these microglia could play a role “in tissue repair or inflammation-mediated cell responses” (154). Simpson et al. (155) examined the microglial response in WMH and normal white matter immunohistochemically, investigating markers of microglial activation and proliferation. They found a higher number of activated microglia (identified by the expression of MHC II, CD40 and B7-2) in periventricular WMH than in normal white matter of controls or in deep WMH, and, in addition, a higher microglial expression of a replication licensing protein in periventricular compared to deep WHM. According to the authors, these findings indicate that periventricular WMH represent a more proliferation-permissive milieu than deep WMH. Moreover, they concluded that the two types of WMH might differ in pathogenesis as the increased activation of microglia in periventricular WMH might represent activation of the immune system triggered by BBB dysfunction (155). Furthermore, they also found evidence substantiating the concept of WMH only being the “tip of the iceberg” of a more diffuse pathology (52,76,83,84): The microglia in normal white matter from individuals showing WMH in their brain expressed significantly more MHC II than those in normal white matter from WMH-free individuals (155).

In two case reports, Brown et al. (156,157) found histopathological evidence that DNA fragmentation was more prevalent in WMH than in surrounding normal white matter, indicating apoptosis, primarily of oligodendrocytes, as another possible pathogenetic factor of WMH (156,157).

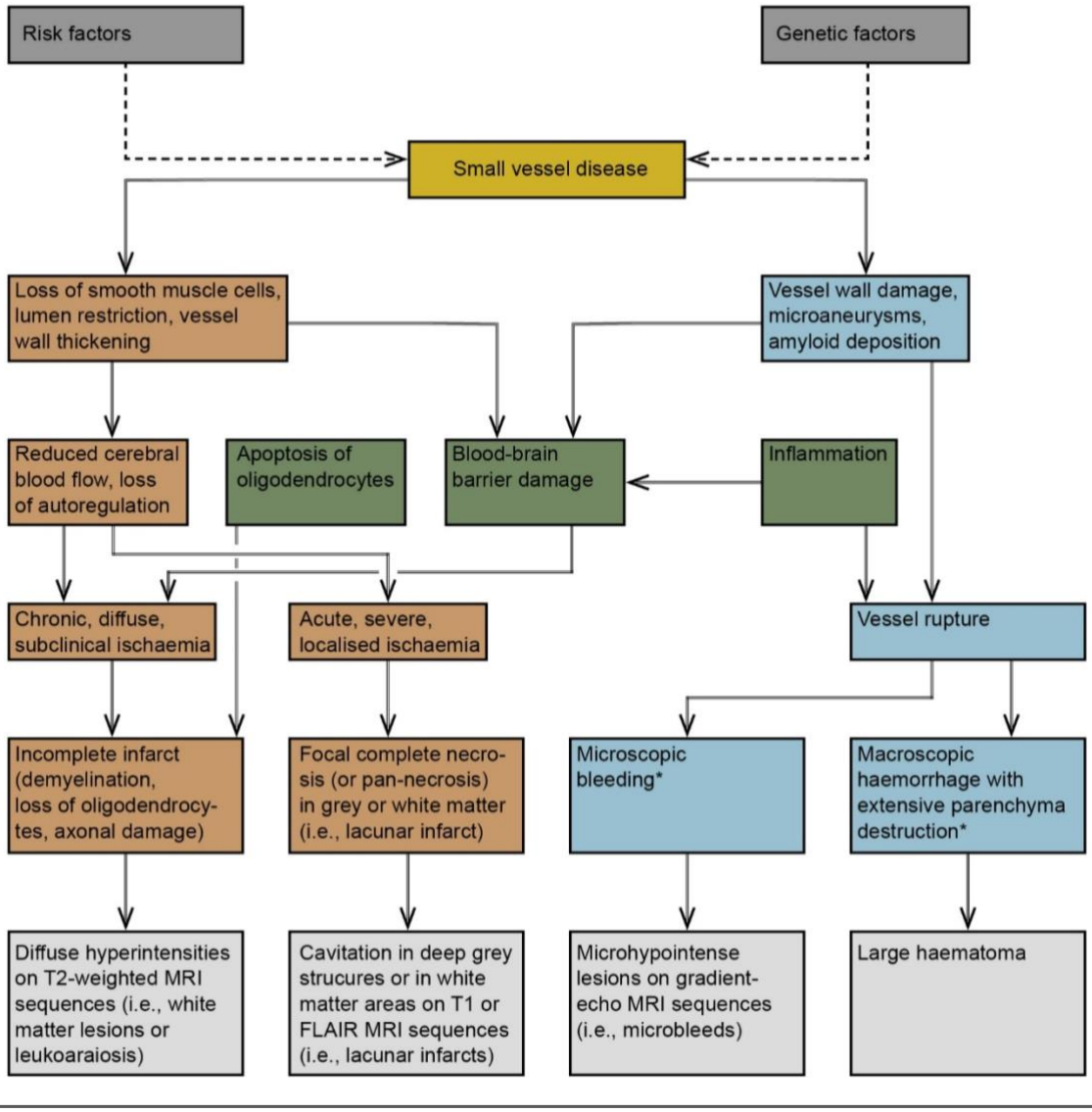

Figure 2. Synopsis of the cascade leading to brain parenchyma damage in CSVD adopted from Pantoni (41).

*based on the hypothesis by Greenberg et al. (138).

Abbreviations:
CSVD…….cerebral small vessel disease
FLAIR…….fluid attenuated inversion recovery
MRI…….magnetic resonance imaging

1.2.5 Histopathology of WMH

Studies investigating the histopathology of WMH are usually performed using formaldehyde fixed brain tissue and post-mortem MRI. Collectively, these studies reveal a quite heterogenous histopathology of WMH (40).

Fazekas et al. conducted two histopathological studies of WMH (57,58), characterising the different types of WMH as outlined in the Fazekas scale (55).

The brains of patients who had received a cerebral MRI prior to death were fixed in formalin, followed (in some cases) by a post-mortem MRI, then cut in axial slices and histopathologically stained with haematoxylin-eosin, Masson's trichrome and the Klüver Barrera technique for myelin (57,58).

Periventricular WMH (PVH) represented only by pencil-thin lining were not examined in this study (58).

Periventricular caps along the frontal horns presented as pale regions in myelin-stained sections, indicating a decrease in myelin content which was caused by a "loose organization of finely textured fibers" (58). Moreover, Fazekas et al. found large tortuous venules in periventricular caps; however, no arteriolosclerotic changes of the vessel walls were evident. Discontinuous ependymal lining and subependymal gliosis characterised the bordering wall of the ventricle (58). Smooth halos of hyperintensities along the ventricular bodies showed similar alterations, i.e., irregular or partially disrupted ependyma and a margin of gliosis adjacent to the ventricle. The latter was, however, found in areas with intact ependymal lining, too. Furthermore, these changes were accompanied by a broader zone of myelin reduction, particularly around venous structures. In a few cases enlarged perivascular spaces and thickened arterioles surrounded by injured tissue were demonstrable (58).

Differing from caps and halos, irregular PVH corresponded to "patchy, in part confluent, areas with varying extent of fiber loss and reactive gliosis" (58). Central cavities, representing lacunar infarcts, were evident in some patches of larger extent. Fibrohyalinosis and lipohyalinosis, leading to a wall thickening of small arteries and arterioles, were also present (58).

Histopathological findings in punctate WMH primarily included periarteriolar and perivenous demyelination. Other alterations were circumscribed areas of demyelination, perivenous oedema, periarteriolar fibrosis and heterotopic ganglion cells. Arterial walls were thickened due to hyalinosis and fibrosis and often enclosed by large perivascular spaces and adjacent atrophic neuropil. No areas of infarction were detectable (57).

Early confluent hyperintensities of the deep white matter presented as "widespread perivascular rarefaction of myelin, mild to moderate fiber loss, and

varying extents of gliosis" (58). Furthermore, small perivascular cavities were found in larger WMH in some instances (58).
Confluent deep WMH showed ischaemic tissue damage similar to irregular PVH, consisting of "irregular, relatively well demarcated areas of incomplete parenchymal destruction with focal transitions to true infarcts" (58).

In view of these different histopathological findings, Fazekas et al. concluded that altered periventricular fluid dynamics might be the pathophysiological cause of caps and smooth halos. The different grades of deep WMH as well as irregular PVH, on the other hand, could represent increasing degrees of tissue damage due to ischaemia; hence, deep confluent WMH and irregular PVH ought to be treated jointly (58).

1.2.6 Progression of WMH

The prospective, population-based Rotterdam Scan Study (RSS) evaluated the association of cardiovascular risk factors, WMH at baseline and progression of WMH (158). The semiquantitative Rotterdam Progression Scale, as described in (61), was used to measure progression of WMH. After a mean follow-up of 3.4 years (SD 0.2 years), 27% of the participants had progression of periventricular lesions (PVL), 32% had progression of subcortical WMH and 39% had progression of any WMH. A few participants showed slight regression of WMH. Pronounced progression of subcortical WMH was primarily caused by growth and confluence of hyperintensities while slight progression was mainly due to occurrence of new small WMH. Higher age, increasing baseline WMH severity, baseline lacunar infarcts, higher systolic and diastolic blood pressure as well as current smoking conferred an increased risk of progression of PVL and subcortical WMH. Female sex was only associated with marked progression of subcortical WMH. The youngest age group (60-69 years) and participants free of severe baseline WMH showed the strongest association between progression of WMH and blood pressure. On the other hand, atrial fibrillation, carotid atherosclerosis, homocysteine levels and oxygen saturation were not associated with WMH progression (158).
The Austrian Stroke Prevention Study (ASPS) assessed WMH progression as absent, minor (difference of one to four punctate WMH between baseline and

follow-up MRI) or marked (difference of more than four WMH or advancement to early confluent or confluent WMH) (36). At the three-year follow-up (36), 17.9% of participants showed WMH progression (minor progression in 9.9% and marked progression in 8.1%). Progression risk factors were diastolic blood pressure and baseline early confluent or confluent WMH (36). At the six-year follow-up (31), individuals without WMH or only punctate WMH at baseline showed merely minor progression of WMH. Individuals exhibiting early confluent or confluent WMH on baseline MRI had a median increase in WMH volume of 2.7 cm^3 (IQR 0.5-5.9) and 9.3 cm^3 (IQR 7.1-21.0). Solely baseline WMH grade predicted progression significantly. The authors concluded that early confluent as well as confluent WMH progress and, as a consequence, are more malignant than punctate WMH (31).
In the LADIS study (159) (see also chapter 1.2.7), WMH progression was evaluated by means of a modified version of the Rotterdam Progression Scale after a follow-up of three years. While no progression was detectable in 26% of participants, 21% of participants showed progression of WMH in one region and 53% in two or more regions (159). Regarding different baseline Fazekas grades, 57.3% of individuals with punctate WMH, 89.4% with early confluent WMH and 83.9% with confluent WMH showed progression (160). The bulk of baseline WMH was located in the subcortical white matter, predominantly of the parietal and frontal lobe. Progression was most frequent in frontal and parietal subcortical white matter, too, followed by periventricular white matter. Lacunes and WMH at baseline, history of stroke or diabetes and elevated blood glucose were identified as risk factors for WMH progression (159).
Furthermore, the Cardiovascular Health Study found WMH progression in 28% of subjects after five years and identified smoking and infarct at baseline as risk factors for progression. Moreover, several risk factors for progression only of low grade WMH on initial scan (higher age, elevated HDL-cholesterol, low LDL-cholesterol, elevated diastolic BP) and high grade WMH (use of statins and diuretics), respectively, were detected (161).
The Atherosclerosis Risk in Communities (ARIC) Study yielded a progression of WMH in 23% of subjects; an increase of smoked pack-years was a risk factor for WMH progression (162).
The Framingham Offspring Cohort Study identified hypertension in midlife and smoking in midlife as risk factors for WMH progression (163).

1.2.7 Clinical symptoms and prognostic implications

While the clinical significance of WMH was originally unclear and disputed (41), WMH can nowadays be related to deficits concerning functional status, cognition, mood, motor performances and urinary continence (164). This chapter will focus on one of the most important research projects on this topic, the LADIS ("Leukoaraiosis and Disability in the Elderly") study (56).

This longitudinally designed study was conducted in eleven centres in Europe and included 639 individuals aged 65 to 84 (mean age 74.13 years; 288 men and 351 women) who showed WMH on cerebral MRI. The WMH were graded according to the Fazekas scale (grade 1-3 or mild (285 patients), moderate (196), severe (158) WMH, respectively). However, only deep and subcortical WMH were considered (56). Furthermore, only individuals showing no or only mild disability, defined as none or but one item impaired on the IADL scale (Instrumental Activities of Daily Life) (165), were included in the study (56). Reasons for referral to the study comprised cognitive, motor, psychic or other neurological complaints, minor stroke and incidental CT or MRI findings, as well as volunteering or being a control in other studies. At baseline, the participants underwent cerebral MRI and an investigation of their social background and medical history; moreover, they were evaluated functionally and clinically with various assessment tools. Follow-up consisted of a yearly reassessment of functional and clinical status for three years as well as another cerebral MRI at the end of follow-up after three years to document WMH progression. The main outcome was transition to disability, specified as impairment in at least two items on the IADL scale. Depression, dementia, cognitive impairment, cardiovascular events (TIA, stroke, myocardial infarction) and death from any cause or specific causes represented secondary outcomes (56).

A slight degree of functional impairment, evident both as a decreasing performance on the DAD (Disability Assessment for Dementia) Scale (166) and poorer performance in tests of executive function with increasing WMH severity, was already detectable at baseline in participants with severe WMH (167). After one year, 9% of individuals with mild WMH, 15% of those with moderate WMH and 26% of patients with severe WMH had transitioned to a status of disability (impairment of two or more items on the IADL scale). Patients with severe WMH

had more than the twofold risk of transition compared to patients with mild WMH (OR 2.38, 95% CI 1.29-4.38). This global functional decline was primarily caused by decreasing motor and cognitive functions (168). These findings were further corroborated by the results at the end of follow-up after three years, yielding an annual rate of transition or death of 10.5% (mild WMH), 15.1% (moderate WMH) and 29.5% (severe WMH) and a more than twofold risk of transition or death for patients with severe compared to mild WMH (HR 2.36, 95% CI 1.65-3.81) (169).

In order to investigate cognitive function at baseline, the participants were assessed with a neuropsychological test battery (comprising the Mini-Mental State Examination (MMSE) (170), the VADAS-Cog (171), the Stroop (172) and Trail Making (173) test) whose subtests were assorted by different cognitive domains (174). Participants showing severe WMH scored less well in global tests of cognition and in the following domains: naming, attention, visuoconstructional praxis, executive functions, speed and motor control. Moreover, vascular risk factors influenced the performance on several cognitive domains independently of age, education and WMH severity: Diabetes mellitus affected naming, memory, speed and motor control, attention, executive function whereas arterial hypertension and stroke affected executive function and attention (174). The progression of WMH was related to a deterioration of executive functions (175). Utilising diffusion-weighted imaging, Schmidt et al. (176) discovered that microstructural alterations (changes in the ADC) in normal-appearing brain tissue also interfered independently of WMH volume and cerebral atrophy with speed, executive function and memory (176).

At the end of the three-year follow-up, a total of 90 patients had developed dementia (vascular dementia: 54, AD: 22, AD with vascular component: 12, frontotemporal dementia: 2). Moreover, 147 participants had CIND (cognitive impairment no dementia). The severity of WMH and the presence of diabetes mellitus at baseline were independent predictors for the deterioration of cognition (both dementia and not dementia). Looking closely at dementia subtypes, previous stroke, WMH severity and medial temporal atrophy (MTA) were predictors of vascular dementia while MTA was the sole predictor of AD (177).

Furthermore, depressive symptoms at baseline, rated using the Geriatric Depression Scale (GDS) (178), significantly correlated with the severity of WMH

(179). Krishnan et al. (180) graded periventricular and deep/subcortical WMH separately using the Scheltens scale. They found that both deep and periventricular WMH correlated with depressive symptoms, but the correlation was stronger for deep WMH. In an ordinal logistic regression analysis, however, only deep WMH were a predictor of GDS score while periventricular hyperintensities were not (180). Another sub-study revealed that frontal and temporal rather than occipitoparietal WMH showed a correlation with depressive symptoms (181). In a logistic regression analysis controlled for quality of life, increasing disability and depressive features at baseline, baseline severity of WMH was identified as an independent predictor for depressive symptoms at the one-year follow-up (182). Similarly, WMH burden at baseline also was a predictor for depressive symptoms at two and three years, respectively, as well as incident depression. When the main outcome variable of the LADIS study, the transition to a status of disability, was included in regression models, baseline WMH severity still was a predictor for depressive symptoms at two years but not at three years and not for incident depression, either. The authors hypothesised that transition to disability might also trigger depressive symptoms and hence, as time goes by, mediate the independent relation between WMH and depression (183). Collectively, the results of the LADIS study reinforce the “vascular depression hypothesis” and attribute a pathogenetic role to WMH in depression of the elderly (164).

The LADIS study assessed motor performance (gait and balance) using the Short Physical Performance Battery (SPPB) (184), a timed eight metre walk (to calculate gait velocity) as well as single leg stance time (185). At baseline, increasing severity of WMH (mild/moderate/severe WMH) showed an association with lower SPPB scores, decreasing walking speed and decreasing single leg stance time. Additionally, participants who were physically active had a lower risk of a pathologic score in the SPPB and a better single leg stance time (185). Furthermore, WMH severity was also associated with a history of falls in the year before baseline evaluation, with a rate of falls of 22.2% in the patient group with mild WMH, 31.6% in the patient group with moderate WMH and 37.3% in the patient group with severe WMH (186). Blahak et al. (186) used the Scheltens scale to analyse the relation between motor performance and differentially located WMH. They found an association of falls with PVL as well as frontal and parietal

DWMH, but not with temporal or occipital DWMH, lesions in the basal ganglia nor with infratentorial hyperintensities. In a multivariate analysis, however, only PVL and frontal DWMH sustained a significant association with falls. In addition, severe frontal DWMH but not WMH in other locations were associated with a reduced single leg stance time, i.e., balance ability. The authors concluded that these results corroborate the hypothesis that frontal and periventricular lesions affect the cortico-subcortical circuit for motor control and are therefore responsible for falls and balance dysfunctions associated with WMH (186). Longitudinal data after the three-year follow-up revealed an annual decline in motor function by 2.6% (measured as change of scores on the SPPB in the course of time). When adjusted for motor disturbances at baseline and other confounders, only patients with moderate (-0.22 points on the SPPB per year or -2.3%, respectively) and severe (-0.46 points on the SPPB per year or -4.7%, respectively) WMH deteriorated significantly in gait and balance (187).

Furthermore, the LADIS study found an independent association between severe WMH and urinary urgency (188).

In the standard neurological examination at baseline, an independent association between severe WMH and the following abnormalities was found: fingertap slowing, upper motor neuron signs, gait and stance abnormalities. Furthermore, WMH burden at baseline as well as WMH progression were related to the emergence of fingertap slowing, primitive reflexes (including grasp reflex, palmomental reflex, forced laughing and crying, snout reflex, glabellar tapping), upper motor neuron signs and stance abnormalities during follow-up (189). Moreover, the finding of any abnormality in the neurological examination at baseline was an independent predictor of transition to disability or death, and an increase in the quantity of abnormal findings further elevated the risk. Furthermore, also severe WMH were an independent predictor of disability or death (190).

Further regarding the prognostic implications of WMH, Debette and Markus (39) conducted a systematic review and meta-analysis on longitudinal hospital and general population-based studies investigating the association between WMH and risk of stroke, cognitive decline/dementia and death. They included 46 studies in their systematic review (12 for stroke, 17 for dementia, 19 for cognitive decline, 10

for mortality) and 22 of those in meta-analyses. A meta-analysis including nine studies revealed a significant association between WMH and risk for incident stroke (HR 3.5, 95% CI 2.5-4.9). An association of WMH with incidental dementia of any subtype was only found in a meta-analysis of three population-based studies (HR 2.9, 95% CI 1.3-6.3) but not in a meta-analysis comprising six studies in high-risk populations (HR 1.4, 95% CI 0.9-2.3). Combining both data pools, however, yielded a significant association (HR 1.9, 95% CI 1.3-2.8). Moreover, they found that most studies could associate WMH with worsening global cognitive performance, executive function and processing speed. Risk of death and WMH were associated both in meta-analyses comprising four studies in general populations (HR 2.3, 95% CI 1.9-2.8) and four studies in high-risk populations (HR 1.6, 95% CI 1.01-2.7), respectively. A joint analysis of both data pools yielded a hazard ratio of 2.0 (95% CI 1.6-2.7) (39).

1.2.8 Therapeutic approaches

WMH progression has been proposed as a potential surrogate marker in clinical intervention trials focusing on CSVD (160,191). Thus, several therapeutic approaches exist:

“Vascular care” was effective in slowing WMH progression in AD patients and included lifestyle interventions (weight reduction, dietary advice, exercise, quitting smoking), medication (acetylsalicylic acid, pyridoxine, folic acid), antihypertensive treatment (both lifestyle and drug interventions) and statins (192). Several studies (193-195) have demonstrated a decelerating effect of antihypertensive treatment on WMH progression, substantiated by a recent meta-analysis (196). Moreover, some trials (197-199) found statin usage to slow down WMH progression while others (200,201) failed to do so. A systematic review yielded that physical exercise was related to fewer WMH only in subjects free of advanced disease (202).

1.3 White Matter Lesions in Parkinson's Disease

30-75% of patients suffering from Parkinson's disease show WMH on cerebral MRI (203-205). While a few studies (206,207) found a higher prevalence of WMH on MRI in PD patients compared to healthy controls, others (205,208) did not. A post-mortem study conducted by Jellinger (209) yielded that total cerebrovascular lesions (lacunes, amyloid angiopathy, white matter lesions, old and recent ischaemic infarcts and haemorrhages) were more common in patients suffering from autopsy-proven idiopathic Parkinson's disease (44.0%) than in age-matched controls (32.8%) (209). An autopsy study by Ghebremedhin et al. (210) reported a WML frequency of 26.5% in PD patients, which was higher than in age- and sex-matched controls (13.2%), although insignificantly (p=0.07) (210). On the contrary, another post-mortem study (211) yielded a higher prevalence of SVD pathology (and vascular risk factors) in controls than in autopsy-proven PD patients (211). Some of the symptoms associated with WMH described in chapter 1.2.7, such as gait and postural disturbances and cognitive deficits, are also characteristic for Parkinson's disease. Hence, an effect of concurrent WMH on the clinical presentation of PD patients seems plausible (212).
WMH are primarily suspected to cause or aggravate PD symptoms by disrupting major fibre tracts (212), as outlined in Table 9.

White matter tracts disrupted	Clinical consequences
Periventricular WMH may reflect damage of both periventricular ascending thalamocortical and descending corticospinal fibres	Impaired postural control and gait
Corpus callosum	Impaired bipedal stance and gait functions
Longitudinal fasciculus	Impaired cognitive – including executive – functions
Striato-thalamocortical connections	Impaired executive cognitive and psychomotor functions
Deep frontal forebrain monoaminergic and cholinergic projections	Cortical deafferentation with associated cognitive, mood and motor changes
Brainstem long tract pathways	Impaired postural control and gait

Table 9. Disruption of major tracts by WMH adapted from Bohnen and Albin 2011 (212).

Abbreviations:
WMH…….white matter hyperintensities

In elderly people, the simultaneous occurrence of WMH and subclinical age-associated loss of nigrostriatal dopaminergic innervation might potentially evoke

parkinsonian motor impairments (212). De Laat et al. (213) showed that severe WMH, especially in the frontal and parietal lobes, are associated with mild parkinsonian signs (assessed with the UPDRS motor section) in elderly subjects free of dementia or parkinsonism (213). However, this paper will focus on the presence and clinical consequences of WMH in idiopathic Parkinson's disease.

The main section of this thesis is divided into two parts: The first one (chapter 3.1) represents a systematic search of the current literature on WMH in individuals suffering from Parkinson's disease. The second part (chapter 3.2) constitutes an original cross-sectional study comparing WMH volumes in PD patients and healthy controls and correlating clinical parameters with WMH volumes in PD patients.

2 Methods

2.1 Search strategy

In order to attain a comprehensive overview of the current literature on WMH in Parkinson's disease representing part one of this thesis (chapter 3.1), a systematic search strategy was applied. A PubMed search using the search term cited in Figure 3 yielded a total of 174 results (reference date: 05/09/2020).

(("Parkinson Disease"[Mesh]) AND (("Cerebral Small Vessel Diseases"[Mesh]) OR ("White matter hyperintensities") OR ("White matter lesion*") OR ("White matter disease") OR ("White matter changes") OR ("White matter abnormalities") OR ("Leukoaraiosis") OR ("White matter hyperintensity")))
Figure 3. PUBMED search term.

Studies were considered relevant if they reported data on both WMH in cerebral MRI and, in some way, on their effects on clinical presentation of patients suffering from idiopathic Parkinson's disease. Furthermore, some studies reporting on possible pathophysiological aspects of WMH in PD patients were included, too. Only studies presenting data on patients suffering from idiopathic Parkinson's disease were included; studies focussing predominantly on vascular parkinsonism or other forms of secondary or atypical parkinsonism were excluded. Studies which merely compared prevalence of WMH in secondary parkinsonism and idiopathic PD and did not deliver clinical data on the effects of WMH in idiopathic PD patients were not included. Additionally, studies reporting exclusively DTI or CT data were not considered, either. The same applies to publications focussing on the effects of WMH on other imaging markers in PD patients. Studies investigating certain genetic alterations in PD and WMH were only included if they also compared mutation free or total PD patients with healthy controls.
Studies published in English or German were taken into account for title and abstract screening. Studies published in other languages were only included if English abstracts were available and provided sufficient data.
Some studies have been published which reported solely the incidence of parkinsonism or parkinsonian signs in populations with small vessel disease. These publications were not included since they did not focus on PD populations but rather on VP populations.

Applying this search strategy, a total of 67 studies (49 cross-sectional or case control studies, 18 longitudinal studies) were eligible for this paper after title and abstract screening of the search results. Another 7 publications (all of them cross-sectional or case control studies) were included after a screening of the references of relevant studies and other publications. Hence, a total of 74 studies (56 cross-sectional/case control studies, 18 longitudinal studies) were reviewed in detail.

2.2 Study population

Part two of this thesis (chapter 3.2) represents an original cross-sectional study. A total of 282 subjects (141 PD patients and 141 age- and sex-matched controls, see also Table 13) were included in this study. The 141 PD patients were extracted from the prospective, longitudinal registry on movement disorders in Graz (PROMOVE). Through the movement disorders outpatient clinic at the University Clinic for Neurology Graz, more than 380 individuals have been included in this registry since January 2010. All included individuals were fully informed and provided written consent. The local ethics committee of the Medical University of Graz gave its positive vote, number 21-345 ex 09/10. The study design consists of a baseline examination as well as four follow-ups, comprising clinical assessments, blood testing and image acquisition.
Inclusion and exclusion criteria constituted the following:

General inclusion criteria:

- Verified diagnosis of a movement disorder
- Age of 18 or older
- MMSE score over 24 to be allowed to sign the consent form, otherwise there had to be a solicitor to sign the form

General exclusion criteria:

- Age under 18
- No commitment from the patient or his or her solicitor to sign the consent form
- Patients who did not have a solicitor and the study-doctor declared the patient not to be able to sign the consent form himself or herself

- Patients who undergo a study for experimental medical treatment of their movement disorder

Moreover, subjects had to comply with the following requirements to be included as a patient in this particular study:

- diagnosis of Parkinson’s disease pursuant to the UK Parkinson's Disease Society Brain Bank criteria (21)
- existence of an in-depth neurological and neuropsychological examination at baseline
- availability of an MRI examination at baseline including FLAIR sequences

141 age- and sex-matched healthy controls without first degree relatives with any movement disorder (see Table 13) were recruited from the Austrian Stroke Prevention Family Study, an ongoing community-dwelling aging cohort (31).

2.3 Clinical Assessment

All clinical assessments were performed in off state. In PD patients taking dopaminergic medication, medication was paused on the day of examination.
The LED (levodopa equivalent dose) was established based upon the medication prescribed at the time of assessment (214).
Clinical state and disease severity of PD patients were assessed using the Hoehn and Yahr scale (14) and the Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (23). The MDS-UPDRS sub-scores (I: Non-motor Experiences of Daily Living, II: Motor Experiences of Daily Living, III: Motor Examination, IV: Motor Complications) and an MDS-UPDRS total score were determined.
The Non-Motor Symptoms Questionnaire (NMS) (215,216) was applied for the evaluation of non-motor symptoms. This scale consists of a total of 30 items from nine categories: cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, miscellany (215,216).
The Geriatric Depression Scale (GDS) (178,217,218) was utilised for the detection and assessment of depressive symptoms.

In order to assess cognition, a CERAD-Plus testing was performed on all PD patients. The CERAD ("Consortium to Establish a Registry for Alzheimer's Disease") neuropsychological test battery comprises a test for verbal fluency, the modified Boston Naming Test, the MMSE, a word list memory test, a test for constructional praxis and tests for word list recall and recognition (219). In the CERAD-Plus, this battery is augmented with the Trail Making Test (TMT) parts A and B and a test for phonematic fluency ("s-words"). Furthermore, CERAD total scores were calculated: verbal fluency, modified Boston Naming Test, constructional praxis, word list memory, word list recall and word list recognition discriminability constitute total score 1 (TS1), total score 2 (TS2) is defined as TS1 plus constructional recall (220,221). In addition, a CERAD memory score, which consists of word list recall, word list recognition and constructional praxis recall, was determined (222).

2.4 Imaging

2.4.1 Acquisition

A 3.0 Tesla cerebral MRI scan (Magnetom Prisma Fit or Magnetom Trio, Siemens Healthcare, Erlangen, Germany), using a 12/20 channel head coil, was performed on all individuals in the PD and control group. The MRI protocol included a FLAIR sequence for lesion load quantification with the following sequence-settings: TE=95 msec, TR=10000 msec, TI=2500 msec, flip angle=160°, acquisition matrix= 256 x 192 voxels (rows x columns), slice thickness=3 mm, pixel spacing=1 mm.).

2.4.2 Processing and Analysis

Deep and periventricular white matter hyperintensities on cerebral FLAIR images of PD patients and healthy controls were mapped separately using the software DispImage, an in-house development for manual segmentation on magnetic resonance images. White matter hyperintensities were classified as periventricular (labelled as "2") if they were in immediate contact with the ventricular system in at least one slice. Lesions in the deep white matter without immediate contact to the ventricular system were classified as deep white matter hyperintensities (labelled as "1"). Hyperintensities in the cerebellum or the brain stem were, if present, not taken account of.

The lesions were primarily marked in a “semi-automated”, threshold-based technique (brightness of pixels) by selecting them with a cursor in two-dimensional sectional MRI images. Lesions were manually redrawn if the threshold-based selection did not produce results concurring with visual rating (especially in cases of PVH-caps or pencil thin lining). In this manner, binary lesion mask were obtained. This procedure was repeated in every slice showing a certain white matter hyperintensity/lesion.
Subsequently, the selected pixels were counted and multiplied with the geometric dimensions of a voxel (0.9 x 0.9 x 3 mm) to calculate total, periventricular and deep white matter hyperintensity volume. For this purpose, FSLstats was used, which is part of the FSL library (223-225) (freely available online from https://fsl.fmrib.ox.ac.uk/fsl/fslwiki, accessed 03/02, 2021).
To compensate for different head and brain sizes/volumes amongst the subjects, individual WMH volumes were normalised by division with each subject’s intracranial volume and subsequent multiplication with the intracranial volume of a standard template.

2.5 Statistical analysis

The statistical software SPSS (IBM Statistics for Windows, Version 24, Armonk, NY, USA) was used for statistical analysis. Two-tailed p-values were used for all analyses. A p-value <0.05 was considered statistically significant. Variables were tested for normal distribution with Kolmogorov-Smirnov test and Shapiro-Wilk test. None of the variables was normally distributed. Variables are, with a few exceptions, presented as mean ± SD, median (IQR) and minimum/maximum and are rounded to the first decimal place.
Chi-square test was used to test for differences in sex distribution between patients suffering from Parkinson’s disease and healthy controls. Mann-Whitney U test was used to compare age, total, deep and periventricular WMH volume between PD patients and healthy controls. Mann-Whitney U test was also used to test for inter- and intragroup sex differences in WMH volumes.
Spearman’s rank correlation coefficient (r_s) was used to evaluate correlations between variables.

3 Results

3.1 Systematic literature review

A total of 74 studies (56 cross-sectional/case control studies and 18 longitudinal studies) were included in this review. In Table 10, the results of cross-sectional and case control studies using MRI are collated. In addition, one post-mortem study by Choi et al. (226) was included, too. Table 11 gives an overview of longitudinal studies investigating the relationship between WMH and Parkinson's disease. Furthermore, Table 12 presents quantitative results on WMH volumes of selected studies.

Almost all studies used FLAIR sequences to depict WMH. The abbreviation "PD" refers to idiopathic Parkinson's disease.

3.1.1 Cross-sectional studies

Source [Assessment of WMH] [Magnetic field strength] **Study population**	**Key findings**	**Remarks**
Piccini et al. 1995 (207) [Fazekas scale] [0.5 T] 102 PD patients, 68 healthy controls (HC)	PVH more prevalent and extensive in PD patients than in HC, no difference in DWMH prevalence/extent Significantly shorter disease duration and greater disease severity (H&Y, UPDRS) in PD patients with PVH Significantly greater disease progression index* in PD patients with PVH Higher UPDRS scores for bradykinesia, postural instability, gait difficulty for PD patients with PVH	Exclusion criterion: CV RF *calculated as ratio between Hoehn & Yahr stage and disease duration
Sohn et al. 1998 (203) [Fazekas scale] [1.5 T] 44 PD patients	30% (13 patients) showed WMH (5 DWMH, 8 PVH), mean age of patients with WMH significantly higher than in those without WMH Gait score (UPDRS) significantly higher in patients with WMH in "on" and "off" states, no significant difference in other symptoms Lower responsiveness of bradykinesia score to single dose levodopa/benserazide in patients with WMH, no difference for other symptoms Regression analysis: patient age did not influence severity or levodopa	Patients with structural lesions on MRI other than WMH were excluded

	responsiveness of PD symptoms, presence of WMH was the only significant variable No significant difference in disease progression index between patients with and without WMH	
Kraft et al. 1999 (227) [Fazekas scale] [1.5 T] 30 PD patients*	No significant difference in focal or global WMH scores between the PD patients with/without visual hallucinations	* each 15 with or without a history of visual hallucinations
Tohgi et al. 2001 (228) [Fazekas scale] [0.5-1.5 T] 227 patients with clinical diagnosis of either PD or VP (144 cases without significant infarct, 66 cases with status lacunaris in the putamen (SLP), 17 cases with confluent WMH (CWMH))	↑ age at onset, male-to-female ratio, hypertension, stroke history in patients with CWMH or SLP than in patients without significant infarct 35% of cases with CWMH vs. 73% with SLP vs. 94% without significant infarct had clinical diagnosis of PD Cases with CWMH/SLP showed more frequently Hoehn and Yahr stage ≥ 3 PD-typical characteristics** more frequent in cases without CWMH/SLP Lead pipe rigidity, short-stepped gait and gait freezing more frequent in CWMH/SLP cases Patients without PD-typical symptoms** (→ probable diagnosis of VP) more frequent in cases with SLP (26%) and CWMH (40%) than no significant infarct (8%)	**asymmetric 4- to 6-Hz resting tremor and cogwheel rigidity and good response to levodopa
Beyer et al. 2006 (229) [Scheltens scale] [1.5 T] 35 PD patients, of those 16 with dementia (PDD) and 19 without dementia (PDND); 20 elderly HC	No difference in WMH between PD patients and HC PDD patients had significantly more DWMH and PVH than PDND patients; most DWMH were located in frontal and parietal regions Total and frontal DWMH were more severe in HC than in PDND patients Multivariate linear regression analysis: DWMH was the only variable significantly associated with MMSE score and accounted for 38% of MMSE score variance; PVH, age, education and presence of CV RF were not associated with MMSE score	All 22 autopsies performed in deceased PD patients up to the date of publication pathologically confirmed idiopathic Lewy-body-PD
Derejko et al. 2006 (230) [Wahlund scale] [not specified] 60 PD patients	31.7% had at least one vascular risk factor No significant difference between groups (vascular RF vs. no vascular RF) in Wahlund scale or clinical parameters 55% of patients had WMH	Vascular risk factors: arterial hypertension, diabetes mellitus 1 and 2, plasma cholesterol, cardiovascular diseases, alcohol abuse, smoking

	No significant differences in clinical parameters or vascular RF between PD patients with or without WMH	
Marshall et al. 2006 (231) [Scheltens scale] [1.5 T] 11 PDD patients (including 2 patients with DLB), 14 HC	PDD patients had more severe mean summed PVH and DWMH than HC Simultaneous presence of mild to moderate WMH did not have a significant effect on cortical AchE activity in PDD patients	Overall, only mild to moderate WMH were present in this small study population
Acharya et al. 2007 (205) [Wahlund scale] [1.5 T] 36 PD patients, 43 HC	Total WMH severity scores did not differ between patients and HC; proportion of subjects with WMH was not different between groups (75% of PD patients, 67% of HC) Positive correlation between WMH score and age in PD patients (r=0.42) and HC (r=0.44) WMH score did not correlate significantly with total UPDRS, UPDRS III, sub-score A or sub-score B (insignificant trend for correlation with sub-score B, p=0.09) PD patients: WMH score correlated positively with number of steps (r=0.41) and walking time (r=0.52) to complete gait task, however, not with cadence In HC, only steps correlated significantly with WMH (r=0.36)	Dementia was an exclusion criterion Examinations in “on” state Sub-score A: UPDRS III sub-scores for tremor, rigidity, bradykinesia, facial expression Sub-score B: sub-scores for speech and axial impairment Adjustment for age eliminated correlations
Meyer et al. 2007 (232) [Wahlund scale, semi-automated quantitative method] [1.5 T] 52 HC, 73 MCI patients (30 N-MCI, 35 V-MCI, 8 PD-MCI including DLB patients), 41 dementia patients (19 AD, 17 VaD, 5 PDD/DLB)	HC, PDD and PD-MCI did not differ in WMH parameters PDD/PD-MCI patients were pooled and then grouped into PD patients with vascular features (vascular RF, history of TIA/stroke; n=6) and those without (n=7) PD patients with vascular features had more depressive symptoms and more severe WMH than PD patients without vascular features	N-MCI= neurodegenerative mild cognitive impairment V-MCI=vascular MCI PD-MCI=Parkinson’s disease MCI VaD=vascular dementia Possible DLB patients were included in PD-MCI and PDD groups
Sławek et al. 2008 (233) [Wahlund scale] [1.5 T]	No significant differences in WMH severity or number of vascular RF (except ischaemic heart disease between I and III)	Group I: no cognitive disability Group II: mild cognitive impairment Group III: dementia

60 PD patients, split into 3 groups according to cognitive status (n=17/25/18)		
Lee et al. 2009 (204) [Manolio scale] [1.5 T] 141 PD patients, further differentiated in a tremor-predominant (TD) and a postural instability and gait difficulty-dominant (PIGD) group (75 and 54 patients, respectively)	40.4% had "distinct" WMH (≥ grade 3) WMH grade correlated significantly with patient age and disease severity (UPDRS total score and parts I-III, H&Y) but not with disease duration WMH grade correlated significantly with UPDRS motor sub-scores for speech, facial expression, rigidity, bradykinesia and, relatively strong, posture and gait subdomains (r=0.475); no significant correlation with combined tremor sub-scores or separate sub-scores for resting/action tremor Significantly longer disease duration and higher WMH grade in PIGD group compared to TD group Multivariate logistic regression: PIGD group independently associated with higher WMH grade (OR=1.306, 95% CI 1.05-1.63) but not with age, gender, disease duration or CV RF	Patients with clinical diagnosis of VP explicitly excluded, MIBG scintigraphy was used to ameliorate diagnostic accuracy of PD, clinical PD diagnosis confirmed in two follow-ups (6/12 months) Clinical assessments during off medication
Dalaker et al. 2009 (234) [semi-automated quantitative method] [1.0-1.5 T] 163 incident, drug-naïve PD patients, 102 age-matched HC PD group: 30 patients classified as PD-MCI and 133 as PD-IC (PD patients with intact cognition)	Higher frequency of diabetes mellitus in PD-MCI compared to PD-IC and controls; no significant difference in other CV RF No significant differences in mean/ median total WMH volume between controls (7.1/2.3 mL), PD-IC (7.3/2.5 mL) and PD-MCI (10.4/5.8 mL) Significant negative correlation between total WMH volume and attention-executive scores in controls (r=-0.277), PD-IC (r=-0.298), PD-MCI (r=-0.527) and total PD sample (r=-0.348) Linear regression: total WMH volume did not predict attention-executive performance in total PD sample anymore; only age, education and sex did No significant differences in spatial distribution of WMH between controls and PD patients nor between WMH distribution and attention-executive performance in total PD sample	PD patients with dementia or depression were excluded
Dalaker et al. 2009 (208) [semi-automated quantitative method]	No significant difference between PD patients and HC in WMH volume nor in WMH volume as a percentage of normalised brain volume	Same underlying study population as in the former publication but different analyses

[1.0-1.5 T] 155 PD patients, 101 age-matched HC	WMH volume significantly negatively correlated with global cognition, attention-executive, visuospatial and memory scores in PD patients and with attention-executive score in HC PD sample: significance was not retained in regression models controlling for various variables; age was a significant explanatory variable in all models, education and sex in some	and slightly differing exclusion criteria
Rodriguez-Oroz et al. 2009 (235) [Wahlund scale] [1.5 T] 89 PD patients (37 PD-IC, 22 PD-MCI, 30 PDD), 30 HC 68 of the PD patients received MRI	PD patients had higher plasmatic homocysteine levels than HC, but they did not predict cognitive status No difference in Wahlund scale between the PD groups after adjusting for age Age and homocysteine levels were associated with Wahlund score, but no after including both variables in a multinomial logistic regression model*	*the authors suggest this might be due to increasing silent vascular events and homocysteine levels with age
Choi et al. 2010 (226) [post-mortem histopathological study] 26 PDD patients and 25 PD-IC patients	When adjusted for age at death, age at PD onset and PD duration, the PDD group had a higher burden of histological white matter lesions (OR for dementia versus positive white matter score 2.6, 95% CI=0.43-16; 73% probability that OR > 1.5, 85% probability that OR > 1.0)	Only subjects with typical PD histopathology included; subjects with concurrent pathologic signs of other cerebral/ neurodegenerative diseases excluded
Lee et al. 2010 (236) [Scheltens scale] [1.5 T] 71 PD patients (11 PD-IC, 25 PD-MCI, 35 PDD)	PDD patients had significantly more WMH in different brain regions, particularly periventricular, and a higher sum score for WMH than PD-IC and PD-MCI; no differences between the latter two groups No association between WMH and CV RF; correlation of WMH severity and increasing number of RF only in infratentorial region WMH sum score significantly correlated with age (r=0.472), total UPDRS score (r=0.336), MMSE (r=-0.475), sum of the box (SOB) scores of the Clinical Dementia Rating (CDR) (r=0.494) and all cognitive domains in a neuropsychological test battery Most cognitive domain scores also correlated with frontal, parietal and occipital but not with temporal WMH scores Linear regression: WMH independently associated with cognitive deficits (MMSE, SOB of CDR) in PD patients	Clinical PD diagnosis confirmed after 6 and 12 months Battery included, amongst others, tests for attention, working memory, language, verbal memory, visuospatial memory and function, reading and word fluency and frontal executive function Regression models adjusted for age, sex, education, disease duration, UPDRS, CV RF

Santangelo et al. 2010 (237) [Scheltens scale] [1.5 T] 12 VP patients, 12 patients with both vascular lesions and dopaminergic denervation (VP+DD), 12 PD patients (no lacunes/WMH but DD)	PD patients had a significantly longer disease duration and lower age at onset than VP and VP+DD patients Significantly more VP and VP+DD patients had vascular RF than PD patients By definition, no vascular lesions in PD patients; VP patients had more WMH in all brain regions, although only statistically insignificant VP+DD patients scored lower on FAB, RCPM and Attentive Matrices, TMT-A, and semantic fluency task than PD patients VP patients performed significantly worse on semantic and phonological fluency tasks and TMT-A than PD patients	Only non-demented patients included All patients had [^{123}I] FP-CIT-SPECT VP → no dopaminergic denervation (DD) in SPECT, but lacunar infarcts/WMH on MRI Evaluations made in "on" state RCPM tests logical abstract thinking → worse performance of patients with WMH in frontal/executive tasks
Bohnen et al. 2011 (238) [automated quantitative method] [3.0 T] 73 PD patients (36 PIGD, 25 TD, 10 intermediate motor phenotype, 2 unclassifiable)	Increased WMH significantly correlated with higher H&Y stages (r_s=0.42) and higher total UPDRS motor scores (r=0.34), and also with axial (r=0.49) and bradykinesia (r=0.30) but not rigidity or tremor sub-scores Multivariate regression with nigrostriatal dopaminergic denervation (striatal VMAT2 binding) and WMH as independent variables and UPDRS total motor and sub-scores as dependent variables: WMH as well as nigrostriatal denervation had significant regression effects on UPDRS total motor score; axial motor impairment: more robust regression for WMH than nigrostriatal denervation; WMH regression effects for bradykinesia borderline significant, not significant for tremor or rigidity sub-scores Significantly higher WMH in PIGD than in TD group, but for both no significant difference to intermediate motor group Individual item analysis of PIGD components: WMH correlated significantly with retropulsion test (r_s=0.40) and walking assessment by history (r_s=0.25) and borderline significantly with gait examination (r_s=0.22) Significant correlation between WMH and UPDRS rating of posture (r_s=0.43) and speech difficulties (r_s=0.23)	Examinations performed in "off" state Nigrostriatal dopaminergic denervation assessed using vesicular monoamine transporter type 2 (VMAT2) – [^{11}C] dihydrotetrabenazine PET Conclusion: "(…) comorbid leucoaraiosis is associated with worsening motor performance independent of the degree of nigrostriatal dopaminergic denervation in Parkinson's disease. In particular, comorbid leucoaraiosis is a greater predictor of axial motor impairment than nigrostriatal dopaminergic denervation."
Petrovic et al. 2012 (239) [Scheltens scale] [1.5 T]	No differences in WMH in any region between total PD patients and HC Significantly more PD patients with depression had total (31 vs. 16 patients)	Dementia was an exclusion criterion All testing performed in "on" state

59 PD patients above 60 years (34 with and 25 without depression), 30 age-matched HC	and frontal (30 vs. 14) DWMH than patients without depression; mean total and frontal DWMH Scheltens score not significantly different PD patients with depression had a significantly higher frequency and mean score for PVH than those without depression and HC PD patients with depression had a significantly higher frequency and mean score for basal ganglia WMH than HC Multivariate regression with Hamilton Depression Rating Scale (HDRS) score as dependent variable: only PVH total score was a significant variable and explained 39% of HDRS variance	Other independent variables in regression analysis: frontal/parietal/ temporal/occipital DWMH, basal ganglia WMH, age, education, CV RF
Shin et al. 2012 (240) [Cholinergic Pathways Hyperintensities Scale (CHIPS); Manolio scale] [3.0 T] 44 PD-IC patients, 87 PD-MCI patients and 40 PDD patients; 41 age- and gender-matched HC	WMH scores in PDD group were significantly higher than in HC group and borderline significantly higher than in PD-MCI (p=0.06) and PD-IC (p=0.06) group; no difference between HC and PD-IC/MCI PDD patients had a significantly higher mean CHIPS score than HC, PD-IC and PD-MCI patients even after controlling for age and education; no significant differences between the other three groups Negative correlation between both CHIPS and WMH score and general cognition (MMSE) (r=-0.28 and r=-0.18) in PD patients Positive correlation between both CHIPS and WMH score and UPDRS motor score (r=0.24 and r=0.20) Both WMH burden and CHIPS score significantly correlated negatively with almost all cognitive subdomains but the correlation was weaker for WMH in most subdomains Correlation coefficients of CHIPS score were significantly higher than those of general WMH scores in attention (backward digit span) and executive functions (contrasting programme and go-no-go test) subdomains Multivariate linear regression in PD patients: Significant and independent negative correlation of CHIPS score with contrasting programme and forward digit span and of WMH score with contrasting programme	The cholinergic system, which arises from the basal forebrain, likely plays an essential part in cognitive performance. CHIPS: visual rating scale to grade WMH in cholinergic pathways Disease duration differed significantly between groups (PDD > PD-MCI > PD-IC) Vascular RF did not differ between groups Regression adjusted for vascular RF, age, education, UPDRS motor scores
Kim et al. 2012 (241)	Patients with OH had a significantly higher mean CHIPS score than those without OH	Head-up tilt-table testing:

[CHIPS] [3.0 T] 87 patients with early PD (25 PD-IC, 48 PD-MCI, 14 PDD) All patients were naïve to dopaminergic drugs	CHIPS score significantly correlated with lowest DBP during tilt (r_s=-0.217) and ∆DBP (r_s=0.245), borderline significance (p=0.069) with ∆SBP (r_s=0.196) Patients with SH had a significantly higher mean CHIPS score than those without SH Significant correlation between CHIPS score and supine SBP (r_s=0.258) Patients with both OH+SH had a higher mean CHIPS score than those with neither OH nor SH Significantly higher mean CHIPS score in PDD patients than in patients with MCI or normal cognition No differences in mean CHIPS scores for dippers vs. non-dippers and arterial hypertension vs. no arterial hypertension, respectively	Orthostatic hypotension (OH): fall in BP of ≥ 20 mmHg systolic and ≥ 10 mmHg diastolic after at least three minutes of tilt Supine hypertension (SH): systolic pressure ≥ 150 mmHg or diastolic pressure ≥ 90 mmHg ∆SBP/∆DBP = difference between supine and tilt SBP/DBP Non-dipping: lack of decrease in BP during the night Neurocirculatory abnormalities (particularly OH and SH) were in turn associated with cognitive deficits
Sławek et al. 2013 (242) [Wahlund scale, Erkinjuntti scale] [1.5 T] 192 PD patients (135 PDND (PD patients without dementia), 57 PDD), 184 age- and sex-matched HC	HC had a higher number of vascular RF than PD patients 41.1%/68.2% of all patients had Wahlund score/Erkinjuntti score of at least 1 PDD patients had significantly higher total and regional scores on both Wahlund and Erkinjuntti scale Significant correlations between Wahlund score and age, age at disease onset, MMSE score, UPDRS part II-IV score, homocysteine level and low vitamin B12 plasma levels; not with vascular RF Significant correlations between Erkinjuntti total score and age, age at onset, number of vascular risk factors, MMSE score, Beck Depression Inventory (BDI), total cholesterol Univariate regression: Wahlund score and DWMH Erkinjuntti score were significantly and independently associated with PDD (amongst other variables) Multivariate regression: Erkinjuntti score for DWMH was the only WMH sub-score that predicted dementia Univariate regression on Wahlund score significant for age, age at disease onset,	PD diagnosis confirmed during follow-ups; no drug-naïve patients The two scales used consider different regions (Wahlund scale assesses white matter and basal ganglia, Erkinjuntti scale PVH and DWMH)

	MMSE; none significant in multivariate analysis Univariate regression on Erkinjuntti score significant for age, disease duration, H&Y stage, Schwab-England activities of daily living scale, MMSE, BDI, number of vascular RF; multivariate analysis: only age significant	
Agosta et al. 2013 (243) [quantitative method] [1.5 T] 15 PD patients with and 14 without GBA mutation, 16 age- and sex-matched HC	No difference in WMH load between PD patients and HC No correlation of WMH with cognitive variables (including MMSE and FAB) or DTI metrics	Glucocerebrosidase (GBA) mutations are a risk factor for idiopathic PD; all carriers were heterozygous
Oh et al. 2013 (244) [Scheltens scale] [3.0 T] 129 newly diagnosed, drug-naïve PD patients	Increasing WMH scores were not associated with history of hypertension, diabetes mellitus, smoking, higher LDL cholesterol and serum homocysteine levels Patients with nocturnal hypertension were older and had more frequently hypertension than those without Significantly higher WMH scores in patient group with nocturnal hypertension than in group with nocturnal normotension* Close correlation between night-time SBP and WMH scores (r=0.3335); multiple linear regression: night-time SBP main contributor to increasing WMH scores (B=0.289) No association between non-dipping and WMH scores*, no correlation between percent of nocturnal mean BP decrease and WMH scores No significant correlation between WMH scores and SD of SBP but significant inverse correlation between increasing WMH scores and nocturnal decline in heart rate (r=-0.2126) and SD of heart rate (r=-0.1807)	Nocturnal hypertension: average night-time blood pressure ≥ 120/70 mmHg Non-dippers: patients with less than 10% nocturnal fall in mean BP BP/heart rate variability: within-subject SD of mean SBP and heart rate during the 24 h measurement period * controlled for age, presence/absence of hypertension and diabetes mellitus, LDL cholesterol and serum homocysteine levels Conclusion of authors: results put forward “a possible role for cardiovascular autonomic dysfunction in vascular brain injury pathogenesis”
Pilleri et al. 2013 (245) [Scheltens scale] [1.5 T]	No difference in mean WMH (sub-)scores between PD patients with or without orthostatic hypotension	

48 PD patients (44 regarded for MRI scorings)	Scheltens scores did not differ between patients with asymptomatic or symptomatic OH	
Melzer et al. 2013 (246) [automated quantitative method] [3.0 T] 109 PD patients (63 PD-IC, 28 PD-MCI, 18 PDD), 32 HC matched to age, sex and years of education	PDD and PD-MCI patients had a higher WMH burden than PD-IC patients and HC, even after covarying for age	Individuals with moderate-severe WMH were excluded
Kandiah et al. 2013 (247) [automated quantitative method] [3.0 T] 91 patients with early PD (H&Y stage 1-2.5; 24 PD-MCI patients and 67 PD-IC patients)	Significantly higher total WMH, PVH and DWMH in PD-MCI patients than in PD-IC patients; regional analysis: significantly higher WMH load in frontal, parietal and occipital areas but only insignificantly higher in temporal area and basal ganglia Logistic regression: log transformed total WMH (OR=2.19), PVH and DWMH significantly higher in PD-MCI (adjusted for age, education, vascular RF) Significant* relationship of increasing total WMH volume and poorer performance on executive function, memory and language tests	PD-MCI patients had a significantly higher frequency of diabetes mellitus 3 WMH severity groups: low WMH (25^{th} percentile), moderate WMH (26-74^{th} percentile), severe WMH (≥ 75^{th} percentile) *after correction for age, education and vascular RF
Herman et al. 2013 (248) [Scheltens scale, 2 different automated quantitative methods] [3.0 T] 110 PD patients (42 TD, 62 PIGD, 6 undetermined) Complete MRI data only for 104 patients	No significant differences between PIGD and TD patients in mean scores on Scheltens scale or in percent of patients with lesions (both total and in specific cerebral regions) WMH (Scheltens scale) significantly correlated with age across nearly all cerebral regions but not with PIGD or TD scores or disease duration WMH in basal ganglia and thalamus were scarce and did not differ between motor subtypes WMHref-cereb: no difference between PIGD and TD WMHref-total: TD group had a significantly higher number of WMH voxels and a significantly higher WMH ratio than PIGD group No differences in either of the three assessment methods between subtypes when comparing 1^{st} WMH quartile (fewest WMH) and 4^{th} quartile (most WMH)	Demented patients and patients who could not walk independently in the "off" state excluded Automated methods differed in their reference used to define and select WMH: one used mean white matter voxel intensity (WMHref-total), the other mean cerebellar white matter voxel intensity (WMHref-cereb) WMH ratio: detected WMH voxel divided by total white matter voxels

	No significant correlation between WMH in any method with number of falls in previous year or Freezing of Gait-questionnaire (FOG-Q)	
Wang et al. 2013 (249) [Scheltens scale] [3.0 T] 63 PD patients (23 PD-IC, 23 PD-MCI, 17 PDD)	PDD patients showed significantly higher DWMH scores than PD-IC and PD-MCI patients, especially in frontal and parietal regions No significant differences in PVH, BG or infratentorial hyperintensities DWMH significantly correlated with age, MMSE, verbal fluency test, orientation, executive function Multiple regression: MMSE score associated with DWMH	
Ham et al. 2014 (250) [Wahlund scale] [3.0 T] 123 PD patients (41 PD-IC patients, 46 PD-MCI, 36 PDD), 49 age- and gender-matched HC	PDD patients had significantly higher WMH scores than HC, PD-IC patients and PD-MCI patients; no significant difference between PD-MCI and PD-IC patients/HC CMB (cerebral microbleeds) were significantly associated with PDD but only before adjusting for WMH as a covariate	In 94 patients, [18F] FP-CIT PET scan was used to confirm PD diagnosis
Kotagal et al. 2014 (251) [automated quantitative method] [3.0 T] 85 PD patients (68 of those H&Y stage ≤ 2.5; 1 PDD patient and 33 PD-MCI patients), grouped according to the simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR score) in 22 patients with low risk and 63	Patients with elevated risk had higher WMH scores, although insignificantly (p=0.076) Multivariable linear regression (controlled for, inter alia, striatal dihydrotetrabenazine activity): elevated risk according to FR score was associated with greater axial motor feature accrual rate, but not with total UPDRS motor score rate Frontal WMH load significantly associated with total and axial feature accrual rate, also after controlling for elevated risk status Frontal WMH load also associated with estimated rate of nonaxial motor progression Multivariable regression for association of frontal WMH and individual items of FR score: female sex, advanced age, elevated SBP associated with higher frontal WMH severity; diabetes and smoking status, antihypertensive use, BMI not	Typical patterns of nigrostriatal dopaminergic denervation in dihydrotetrabenazine PET in all patients Axial motor sub-score was calculated by adding the sum of 5 UPDRS motor items (speech, arising from a chair, gait, postural stability, posture); remaining items= nonaxial Estimated rate of motor features accrued per year= axial and total UPDRS motor scores divided by number of years of PD motor symptoms

patients with elevated risk		
Gallardo et al. 2014 (252) [Fazekas scale] [not specified] 22 PD patients (12 with and 10 without FOG)	In both groups, 50% of patients had WMH The severity of WMH was higher in the group with FOG, although statistically insignificant	Demented patients were excluded
Kim et al. 2015 (253) [Fazekas scale] [3.0 T] 124 PD patients (102 without CMB, 22 with CMB)	Patients with CMB had more severe PVH and DWMH and more lacunar infarcts than patients without CMB CMB were not associated with any cognitive domain after excluding PDD patients	
Liu et al. 2015 (254) [Scheltens scale, semi-automated quantitative method] [3.0 T] 23 PD patients, 23 age-matched HC MRA (time of flight and phase contrast) was used to group subjects into 4 categories (see right-hand column)	70% of HC were category 4, 57% of PD patients were in categories 1 to 3 21 of 23 PD patients had WMH PD patients had significantly higher WMH volumes and Scheltens scores than HC Most PD patients in category 4 and HC had a low WMH volume (< 500mm^3), most PD patients in categories 1 to 3 had a high WMH volume (≥ 500 mm^3) Similar distribution for low (≤ 3) and high (≥ 4) Scheltens score; all PD patients in category 1 had a high Scheltens score	Hypertension and diabetes mellitus were exclusion criteria 1: “complete or local missing transverse sinus and internal jugular veins on the time-of-flight images” 2: “low flow in the transverse sinus and stenotic internal jugular veins” 3: “reduced flow in the internal jugular veins“ 4: “normal flow and no stenosis“
Mak et al. 2015 (255) [semi-automated quantitative method] [3.0 T] 90 mild PD patients (mean H&Y stage 1.9, SD 0.4) comprising 25 PD-MCI patients and 65 PD-IC patients	Significantly higher prevalence of diabetes mellitus and hyperlipidaemia in PD-MCI PD-MCI patients had significantly higher total and periventricular WMH volumes than PD-IC patients*; DWMH volume only insignificantly higher* Comparison of spatial distribution of WMH using voxel-wise lesion probability maps yielded significant differences between PD-IC patients and PD-MCI in widespread cerebral areas (especially periventricular) Spatial distribution of WMH correlated significantly with global cognition (MMSE)** and worse performance on the FAB and Fruit Fluency tasks**	Dementia was an exclusion criterion *corrected for age, gender, education, multiple comparisons **corrected for age, gender, education, vascular RF, multiple comparisons FAB=Frontal Assessment Battery, tests executive function

	No significant voxel-wise relationship between spatial WMH distribution and UPDRS or H&Y stages	Fruit Fluency: a semantic categorisation task
Ham et al. 2015 (256) [Scheltens scale] [3.0 T] 87 non-demented PD patients	Patients with high-grade total WMH had a higher frequency of hypertension and higher UPDRS III scores than patients with low-grade total WMH Patients with high-grade DWMH had a significantly poorer performance in the word Stroop tasks than patients with low-grade DWMH* Patients with high-grade total WMH, DWMH or PVH, respectively, showed cortical thinning in various brain regions compared to patients with low-grade lesions, especially in frontal regions Total WMH/DMWH/PVH scores correlated significantly negatively with mean cortical thickness (r=-0.546/r=-0.507/r=-0.603) and frontal thickness (r=-0.461/r=-0.492/r=-0.516)** Total WMH-related mean cortical thickness correlated significantly with the word Stroop task and DWMH-related mean cortical thickness with word Stroop and semantic COWAT tasks Multiple regression: DWMH- but not PVH-associated frontal thickness exhibited an independent effect on frontal lobe-based executive dysfunction	All patients showed reduced dopamine transporter uptake in the posterior putamen on [18F] FP-CIT PET *after adjustment for age, sex, years of education, MMSE **after adjustment for age, sex, education, MMSE, intracranial volume COWAT=Controlled Oral Word Association Test Author's conclusion: "These data suggest that in patients with PD, DWMHs are closely coupled with decreased cortical thickness in the frontal areas and may lead to declines in executive function."
Janelidze et al. 2015 (257) [Wahlund scale] [3.0 T] 100 PD patients (82 without dementia and 18 with PDD), 38 HC 32 HC and 58 PD patients underwent MRI examination	No difference in total WMH score between groups PD patients: total WMH were associated with higher CSF levels of VEGF, PIGF, IL-8, higher VEGF/sVEGFR-1 ratio and PIGF/sVEGFR-1 ratio; similar results when only looking at PD patients without dementia; no associations between WMH and angiogenesis variables/ratios in HC WMH were associated with CSF NFL levels	In another cohort of the study, pathological WML were associated with higher VEGF CSF levels in PD patients Author's conclusion: elevated levels of angiogenesis biomarkers in PD patients might depend on the hypoxic milieu associated with orthostatic hypotension and WMH
Ham et al. 2016 (258) [Scheltens scale] [3.0 T]	No significant difference in vascular RF between PD patients and HC; significantly higher scores of deep, periventricular and total WMH in PD patients compared to HC Multiple regression*: DWMH correlated significantly negatively with olfactory	All patients showed reduced dopamine transporter uptake in the posterior putamen on [18F] FP-CIT PET

171 non-demented PD patients, 36 age- and sex-matched HC	performance (β=-0.097); borderline insignificant negative correlation between total WMH and CCSI score (β=-0.118, p=0.058); no significant correlation between PVH and CCSI score Multiple regression**: total WMH (β=-0.109) and DMWH (β=-0.153) but not PVH correlated significantly negatively with semantic fluency Binary logistic regression: co-presence of severe DWMH and severe olfactory dysfunction increased the risk for worse performance on semantic fluency task	*adjusted for age, gender, PD duration Olfactory performance graded with Cross-Cultural Smell Identification (CCSI) test **adjusted for age, gender, education, MMSE score
Malek et al. 2016 (259) ["visual reporting", not specified] [1.5 or 3.0 T] 1759 recently diagnosed PD patients (mean disease duration 1.3 years), 842 of which underwent cerebral MRI	Significant association between increasing UPDRS part III score and diabetes and presence of > 2 vascular RF; also, between presence of > 2 vascular RF and cognitive impairment PD patients with WMH had significantly more frequently cognitive impairment than patients with lacunar/territorial infarcts or with no vascular lesions; 44.6% of all patients with WMH had some kind of cognitive impairment; OR for cognitive impairment for WMH patients compared to patients without vascular lesions was 1.88, 95% CI 1.21-2.91 In cases with WMH, the PIGD type was more frequent (61.4%) than in patients with lacunar/territorial strokes (39.1%) or without vascular lesions (42.8%); OR for PIGD for WMH patients compared to patients without vascular lesions was 1.81, 95% CI 1.14-2.88	Clinical diagnosis of dementia at first assessment was an exclusion criterion Mixture of "on" and "off" state motor scorings Functional dopaminergic imaging was used in clinically uncertain cases
Arena et al. 2016 (260) [Scheltens scale] [1.5 or 3.0 T] 60 PD patients	WMH (sub-)scores correlated significantly positively with age at PD onset and age at L-dopa challenge test; negative correlation of both age variables with UPDRS III scores (axial and gait) Higher DMWH scores correlated significantly with poorer response of UPDRS axial impairment scores* to L-dopa (r_s=-0.35); corrected for age at PD onset and age at L-dopa challenge test *comprises "worse performance on ratings for speech, facial expression, neck rigidity, rising from a chair, gait, freezing of gait, postural stability, posture and global spontaneous movements"	Author's conclusion: "Results of present study suggest WMH may affect response to L-dopa on axial function of PD patients, which could be due to either non-dopaminergic (cortico-basal ganglia) motor pathway disruption, or postsynaptic nigrostriatal pathway involvement."
Tokuchi et al. 2016 (261) [Fazekas scale]	WMH prevalence increased with higher age in all 3 groups; > 72% of PD and > 88% of AD patients showed WMH	

[1.5 T] 153 PD patients, 216 AD patients, 103 HC	AD patients had significantly higher PVH and DWMH grades than PD patients Age-dependent decrease in cognitive and in affective functions in AD and PD patients, more severe in AD	
Zhang et al. 2016 (262) [Wahlund scale] [3.0 T] 72 early PD patients (H&Y stage 1-2), (34 with and 38 without SSLI)	PD patients with SSLI had a significantly higher mean WMH score than PD patients without SSLI	SSLI=striatal silent lacunar infarction
Al-Bachari et al. 2017 (263) [Fazekas scale, Wahlund scale, semi-automated quantitative method] [3.0 T] 51 PD patients (21 TD, 24 PIGD, 6 intermediate), 18 CP subjects with CVD, 34 CN subjects Groups matched for age	All WMH scores significantly higher in PD group than in CN group; no significant differences between PD and CP group or between TD and PIGD WMH volume borderline insignificantly higher in PD group compared to CN ($p=0.08$); significantly higher in CP compared to PD group as well as in PIGD compared to TD Higher WMH volume correlated significantly with lower MoCA score in the PD group ($r=-0.39$) and in the TD group ($r=-0.45$)	Exclusion criteria for PD patients: history of TIA/stroke, dementia CVD patients (control positive, CP): TIA or stroke within the previous two years Control negative (CN): no history of CVD or PD
Cioncoloni et al. 2017 (264) [Fazekas scale] [not specified] 16 PD patients (divided in two groups of 8 patients each, one with and one without WMH), 8 age- and weight-matched elderly HC	No difference in UPDRS III score between PD patients with and without WMH PD patients with WMH had a significantly higher mean UPDRS postural stability item score than PD patients without WMH or HC; PD patients without WMH had a significantly higher score than HC PD patients with WMH showed “inability to rescale an effective preparatory postural pattern to known, repeated postural perturbations suggesting impaired sensory-motor strategies in anticipating perturbations. Anticipatory postural patterns remain effective in IPD patients.“	Patients had mild to moderate disease severity and postural instability and no dementia, no unstable CVD Examinations in “on” state “IPD patients” = PD patients without WMH
Jones et al. 2017 (265) [automated quantitative method] [3.0 T]	No significant difference in CV risk score between PD and HC Both groups: higher CV risk significantly related to poorer performance on tasks of executive function, processing speed,	Excluded: patients with severe cognitive impairment, stroke history Examinations in “on” state

67 PD patients, 61 HC	verbal recall, language (the latter only in PD patients) More severe CV risk was related to higher WMH volume (and also periventricular, deep and infracortical WMH volume) in HC but not in PD patients No difference in WMH volume between PD patients and HC except for HC having a greater infracortical WMH volume WMH volume was related to poorer executive functioning scores in HC but not PD No correlation of CV risk or WMH volume (total or regional) with any cognitive domain, LED, measures of mood or PD severity in PD patients	CV risk assessed with Framingham 10-year Cardiovascular Risk Index
Ten Harmsen et al. 2018 (266) [Fazekas scale, Wahlund scale] [3.0 T] 204 PD patients=entire group (2 cohorts with prospectively collected data: cohort 1 (28 patients) and cohort 2 (50 patients); cohort 3 with 126 patients with retrospectively collected data only)	26% of PD patients had neurogenic OH (nOH) Entire cohort: PD patients with OH had significantly higher Fazekas scores (DWMH but not PVH) and higher Wahlund scores (DWMH but not in BG); similar results for cohorts 1 to 3 Ordinal regression in entire cohort: significant association between DWMH (on both scales) and nOH; no significant association between Fazekas PVH or Wahlund BG scores and nOH; age was also significantly associated with WMH but hypertension and cognitive decline, e.g., were not Cohorts 1 & 2: DMWH severity on both scales was significantly negatively associated with FAB but not MMSE score; PVH and BG WMH were associated with neither of the scores; no association between any WMH and abnormal pull test or abnormal tandem gait Cohort 1: change of SBP or DBP within up to 10 min of standing up and WMH did not correlate	In cohort 3, presence or absence of nOH was evaluated only by history taking
Joki et al. 2018 (267) [Fazekas scale] [1.5 T] 50 AD, 50 DLB, 50 PDD, 50 PD patients without dementia, 50 HC	Significantly higher PVH and DWMH scores in AD, DLB and PDD than in HC PD without dementia: PVH significantly lower than in AD, DLB, PDD; DWMH significantly lower than in AD and DLB Higher ratio of severe PVH and DWMH (Fazekas score ≥ 2) in AD, DLB, PDD than in PD without dementia and HC	MTA=medial temporal lobe atrophy “Among all groups, DLB and AD exhibited the most severe WMH, followed by PDD, PDND, and NC, in that order.“ (PDND= PD no dementia, NC=normal controls)

Age- and sex-matched	MTA score correlated significantly with PVH (r=0.46) and DMWH (r=0.36) in the total group	
Lee et al. 2018 (268) [Fazekas scale] [1.5 T] 105 PD patients (38 without WMH, 13 with mild WMH, 33 with moderate WMH, 21 with severe WMH)	Patients with mild, moderate or severe WMH scored significantly higher in UPDRS part III, H&Y scale and FOG-Q than patients without WMH No difference between the four groups in MMSE or in disease duration Patients with severe WMH had significantly lower MoCA and FAB scores than patients without WMH Patients with moderate or severe WMH had significantly more non-motor symptoms than those without or with only mild WMH, assessed by NMS (Non-Motor Symptoms Questionnaire), PDQ-39 (Parkinson's Disease Questionnaire), PDSS (Parkinson's Disease Sleep Scale), BDI, BAI (Beck Anxiety Inventory), NPI (Neuropsychiatry Inventory), PFS (Parkinson Fatigue Scale) Multivariate linear regression: WMH severity correlated significantly with UPDRS part III (r=0.623), H&Y scale (r=0.640), FOG-Q (r=0.494), MoCA (r=-0.339), FAB (r=-0.354), PDQ-39 (r=0.606), BDI (r=0.506), BAI (r=0.351), NPI (r=0.306), PFS (r=0.426)	All patients underwent [18F] FP-CIT PET scan Patients with cerebrovascular incidents or vascular RF (hypertension, diabetes mellitus) or with severe cognitive impairment were excluded Mild WMH: sum Fazekas score of PVH + DWMH=1 Moderate WMH: sum=2 or 3 Severe WMH: sum= 4-6
Ciliz et al. 2018 (269) [Scheltens scale, Wahlund scale] [not specified] 50 PD patients	No significant association between falls and total or regional WMH (Scheltens scale) Wahlund scale: no association between falls and total WMH; left temporal WMH were associated with falls*; frontal WMH of both hemispheres tended towards significant associations	Dementia as an exclusion criterion *Possible explanations, all related to left temporal lobe pathologies: deficits in navigation, memory, orientation, auditory processing, fear conditioning
Stojkovic et al. 2018 (270) [semi-automated quantitative method] [1.5 T] 130 PD patients (23 PDD, 61 PD-MCI, 46 PD-IC; 96 PIGD, 25 TD, 9 not determined)	PDD patients had more frequently arterial hypertension than PD-IC patients PD patients with high vascular risk had significantly higher whole brain WMH volume PDD patients had significantly higher whole brain WMH volume than PD-IC patients Whole brain WMH volume correlated significantly with FOG score (r=0.265) Linear regression: whole brain WMH volume independently associated with performance on attention tests* No associations between frontal WMH volume and cognitive measures	Evaluations in "on" state Vascular risk assessed with FR score *regardless of age, education, sex, disease duration, severity of motor symptoms, FR score **adjusted for age, sex, education, disease duration

	Whole brain WMH volume independently related to PDD (OR=2.188)**	
De Schipper et al. 2019 (271) [automated quantitative method] [3.0 T] 163 PD patients, 218 age- and gender-matched HC	PD patients had significantly higher total WMH, PVH and anterior DWMH volumes than HC; no difference in posterior DWMH volume or white matter microstructure parameters (FA, MD, MTR) Total WMH volume, PVH and posterior DWMH volume increased with age in both groups PD group**: visuospatial functioning related to total WMH volume, postural instability and gait difficulty related to PVH	Visuospatial functioning assessed with SCOPA-COG score (Scales for Outcomes in Parkinson's disease-COGnition) **both remained significant when age was included in the model
Toda et al. 2019 (272) [Scheltens scale] [not specified] 64 PD patients, 20 age- and sex-matched HC	Normal walking: PVH score significantly correlated with walking speed (r_s=-0.35) and stride length (r_s=-0.38); DWMH score not associated with any gait parameter Walking speed and stride correlated with frontal cap (r_s=-0.36/r_s=-0.33) and occipital cap (r_s=-0.34/r_s=-0.38) Calculation task gait: significant correlation between PVH score and walking speed (r_s=-0.37) and stride (r_s=-0.39) Multiple regression: significant negative correlations between frontal cap and walking speed and between occipital cap and stride length, respectively	MMSE <24 was an exclusion criterion Gait was assessed during normal walking and while performing a calculation: walking speed (m/minute), stride length (cm), gait cycle (s), left-right instability (cm), step time variability (%)
Wan et al. 2019 (273) [Scheltens scale] [3.0 T] 137 PD patients (89 PIGD, 38 non-PIGD)	Mean PVH score of 3.5, mean DWMH score of 4.8 PIGD patients had a significantly higher DWMH score in the frontal lobe and the occipital lobe than non-PIGD patients; no difference in other regions DWMH scores of the frontal lobe (r_s=0.18) and the occipital lobe (r_s=0.20) correlated with the axial motor score Multivariate linear regression*: significant association between axial motor score and frontal and occipital DWMH score Univariate logistic regression: PIGD type closely correlated with lower MoCA score and higher frontal DWMH score (OR = 1.59, 95% CI = 1.08-2.34) Multivariable logistic regression: lower MoCA score and higher frontal DWMH score (OR = 1.62, 95% CI = 1.07–2.43) were independent risk factors of PIGD sub-type	*adjusted for PD duration Lacunes and enlarged perivascular spaces were assessed, too
Dunet et al. 2019 (274)	PD-MCI patients had a significantly higher left temporal lobe WMH volume compared to HC and PD-IC patients; no significant	Inclusion criterion for patients and HC: no history of

[Wahlund scale, semiautomated quantitative method, automated quantitative method] [3.0 T] 28 PD patients (13 PD-MCI, 15 PD-IC), 21 HC	difference in WMH volume in other regions or in visual rating score Wahlund score did not correlate with any neuropsychological metrics Total WMH volume estimated by manual segmentation correlated negatively with performance during the second cued recall in the FCSRT (r_s=-0.41) Automated method: performance during second and third free recall correlated negatively with the left prefrontal and left temporal WMH volumes; delayed free recall performance correlated negatively with the left prefrontal and left temporal WMH volumes; left prefrontal WMH volume correlated negatively with Mattis memory sub-score	cardiovascular disease PD patients with dementia excluded FCSRT=free/cued recall selective reminding test, used to assess episodic memory Results independent of age, gender, educational attainment, cardiovascular risk factors, disease duration, dopamine therapy
Shen et al. 2019 (275) [Fazekas scale] [1.5 T] 176 PD patients (40 non-PIGD, 136 PIGD)	PIGD patients had a significantly higher median DWMH score than non-PIGD patients; proportion of moderate to severe WMH was higher in PIGD than non-PIGD; same results in binary regression adjusted for gender In the entire group, PD patients with moderate to severe WMH had significantly higher homocysteine (hcy) levels and lower folate levels than patients with no or mild WMH; patients with PIGD and moderate/severe WMH had the highest homocysteine and the lowest folate levels In entire group, WMH correlated with age (r_s=0.387), smoking (r_s=-0.165), cystatin C (r_s=0.298), folate (r_s=-0.309), hcy (r_s=0.355) Binary logistic regression: age (OR=1.103), folate level (OR=0.826), hcy level (OR=1.124) were significant independent risk factors for WMH ORs of moderate to severe WMH by quintiles of hcy and folate: a higher hcy level was significantly associated with a higher risk for moderate to severe WMH (OR=8.011, 95% CI=2.700-23.767 for patients in highest quintile of hcy levels compared to lowest quintile)* Lower folate levels were significantly associated with a higher risk of moderate to severe WMH (OR=16.81, 95% CI=4.74-59.65 for patients in lowest quintile of folate levels compared to highest quintile)**	History of cerebrovascular disease was an exclusion criterion Non-PIGD=TD and intermediate type combined *adjusted for age, folate, vitamin B12, cystatin C, hypertension, diabetes, alcohol consumption **adjusted for age, hcy, vitamin B12, cystatin C, hypertension, diabetes, alcohol consumption Author's conclusion: "It can be speculated that higher Hcy and lower folate probably played important roles in the development of WMHs and motor heterogeneity in PD."
Markaki et al. 2019 (276)	86 of 100 PD patients showed WMH on MRI	

[information not available] 100 PD patients (50 received lumbar puncture)	Increasing WMH severity showed an independent association with higher age and lower CSF beta-amyloid 1-42	

Table 10. Cross-sectional and case control studies on WMH in PD.

Abbreviations:
AchE……..acetylcholine esterase
AD……..Alzheimer's disease
BAI…….Beck Anxiety Inventory
BDI…….Beck Depression Inventory
BG……..basal ganglia
BMI…….body mass index
BP……...blood pressure
CCSI……...Cross-Cultural Smell Identification
CDR……Clinical Dementia Rating
CHIPS……Cholinergic Pathways Hyperintensities Scale
CI…….confidence interval
cm……centimetres
CMB……cerebral microbleeds
CN……control negative
COWAT……..Controlled Oral Word Association Test
CP……...control positive
CSF……....cerebrospinal fluid
CV RF……....cardiovascular risk factor(s)
CVD……....cardiovascular disease
CWMH……....confluent WMH
DBP……..…diastolic blood pressure
DD……..…dopaminergic denervation
DLB……..…...dementia with Lewy bodies
DTI……diffusion tensor imaging
DWMH……..deep white matter hyperintensities
FA……..fractional anisotropy
FAB……frontal assessment battery
FCSRT……..free/cued recall selective reminding test
FOG……...freezing of gait
FOG-Q……...Freezing of Gait-questionnaire
FP-CIT……...fluoropropyl-carbomethoxy-iodophenyl-nortropane
FR score……...Framingham risk score
GBA……..……glucocerebrosidase
H&Y……Hoehn and Yahr (stage)
HC……..healthy controls
hcy…….homocysteine
HDRS……Hamilton Depression Rating Scale
Hz……...hertz
IL-8……Interleukin-8
IPD…….idiopathic Parkinson's disease
LDL…….low density lipoprotein
L-dopa……...levodopa
LED……levodopa equivalent dose
m……metres
MCI……mild cognitive impairment
MD…….mean diffusivity
MIBG…….(123I-)metaiodobenzyl-guanidine
mL……..millilitres
mmHg……millimetres of mercury
MMSE……Mini-Mental State Examination
MoCA……..Montreal Cognitive Assessment

MRA……...magnetic resonance angiography
MRI…….magnetic resonance imaging
MTA……medial temporal atrophy
MTR…….. magnetisation transfer ratio
NC……..normal controls
NFL……light subtype of the neurofilament protein
N-MCI……neurodegenerative MCI
NMS……..Non-Motor Symptoms Questionnaire
nOH……..……neurogenic OH
NPI…….Neuropsychiatry Inventory,
OH……..orthostatic hypotension
OR……..odds ratio
PD……..Parkinson's disease
PDD……..……Parkinson's disease dementia
PD-IC……PD patients with intact cognition
PD-MCI……....Parkinson's disease mild cognitive impairment
PDND……....Parkinson's disease no dementia
PDQ-39……Parkinson's Disease Questionnaire
PDSS……Parkinson's Disease Sleep Scale
PET……positron emission tomography
PFS……Parkinson Fatigue Scale
PIGD……..postural instability and gait difficulty
PIGF……..placental growth factor
PVH……periventricular hyperintensities
r……..Pearson's correlation coefficient
RCPM……...Raven's Coloured Progressive Matrices
RF……..risk factor(s)
r_s…….Spearman's correlation coefficient
s……..second(s)
SBP……systolic blood pressure
SCOPA-COG…...Scales for Outcomes in Parkinson's disease-COGnition
SD……..standard deviation
SH……..supine hypertension
SLP……...status lacunaris in the putamen
SOB……sum of the box
SPECT……....single photon emission computerised tomography
SSLI……...striatal silent lacunar infarction
sVEGFR-1…….soluble vascular endothelial growth factor receptor-1
T……..Tesla
TD……tremor dominant
TIA……...transient ischaemic attack
TMT-A……Trail Making Test part A
UPDRS……Unified Parkinson's disease rating scale
VaD……..vascular dementia
VEGF……...vascular endothelial growth factor
VMAT2……type 2 vesicular monoamine transporter
V-MCI……...vascular MCI
VP……vascular parkinsonism
WMH……..……white matter hyperintensities
WML……white matter lesions

3.1.2 Longitudinal studies

Source & baseline population	Baseline facts & findings	Follow-up facts & findings
Burton et al. 2006 (277)	No significant difference in baseline WMH between	13 PDD, 14 DLB, 23 AD, 33 HC completed follow-up approximately 1 year later

[automated quantitative method] [1.5 T] 31 PDD, 26 DLB, 32 AD, 39 HC	drop-outs and subjects who completed follow-up No difference in WMH volume between HC and PDD; AD had higher baseline WMH than HC No difference in whole group between subjects with/without hypertension/diabetes mellitus/APOE-4 allele No correlations between baseline WMH and baseline or change in MMSE/CAMCOG score or duration of cognitive decline in any dementia group	Significant total WMH increase in all groups but DLB; WMH progression did not differ significantly between groups; median change in PDD patients: 0.78 mL (range: -0.8–7.5 mL) WMH progression significantly greater in subjects with hypertension than in those without; no difference in progression between subjects with/without diabetes/OH Whole group: WMH progression correlated with age (r_s=0.29) and baseline WMH (r_s=0.26); not significant in individual groups except in HC Demented group: WMH progression did not correlate with duration of cognitive decline, baseline or change in MMSE/CAMCOG score Linear regression in whole group: only baseline WMH significantly predicted WMH progression
González-Redondo et al. 2012 (278) [Scheltens scale] [1.5 T] 111 PD patients	Patients with severe vascular disease (stroke, atherosclerosis, etc.) were excluded At baseline, the population consisted of 39 PD-IC, 46 PD-MCI and 26 PDD patients Prevalence of CV RF did not differ between groups No difference in total Scheltens score or sub-scores between the groups Ordinal logistic regression (controlled for education level, age, UPDRS III, GDS score): no effect of total Scheltens score or any sub-score on cognitive status Linear multiple regression (adjusted for education level, age, GDS score): total Scheltens score did not predict MMSE Frontal WMH score correlated significantly with semantic fluency (r_s=-0.29); significant association also in linear regression model	36 non-demented subjects were re-examined after 12-48 (mean 30) months 3 PD-IC patients progressed to PD-MCI, 1 to PDD 4 PD-MCI patients progressed to PDD Patients with 12-24 months follow-up: none progressed Patients with 24-36 months follow-up: 1 progressed from PD-IC to PD-MCI, 1 from PD-MCI to PDD Patients with 36-48 months follow-up: 2 progressed from PD-IC to PD-MCI, 1 from PD-IC to PDD, 3 from PD-MCI to PDD Association of increasing PVH score and increased conversion to dementia; no association between total score or other sub-scores with progression to PD-MCI or PDD Increase in total WMH score was not associated with change in MMSE (p=0.054) (adjusted for age) Increasing frontal WMH sub-score did not significantly affect changes in semantic verbal fluency

	(adjusted for age, educational level, GDS score); subjects with severe frontal WMH had a significantly lower semantic fluency score than those with no, mild or moderate WMH	
Rektor et al. 2012 (279) [Scheltens scale] [1.5 T] 57 PD patients		Follow-up after 4 years as patient examination (26 patients), review of medical records (13 patients) or death register (18 patients) 18 patients died in follow-up period (group 1), 39 survived (group 2) At baseline, patients in group 1 were significantly older and had a higher total WMH score than patients in group 2 Baseline WMH score and age did not correlate in either group
Kandiah et al. 2014 (280) [automated quantitative method] [3.0 T] 97 PD patients	26 PD-MCI patients, 71 PD-IC patients PDD patients excluded	Clinical and neuropsychological examinations repeated every 6 months for 2 years (in “on” state); mean duration of follow up 17.5 months 16 PD-IC patients progressed to PD-MCI 8 PD-MCI patients progressed to PDD (all of them males) Baseline CV RF did not differ between PD-IC, PD-MCI, PDD (status at follow-up) Logistic univariate regression: Baseline total WMH and PVH significantly predicted conversion from PD-IC to PD-MCI; however, significance was lost in multivariate analyses correcting for age, CV RF and hippocampal volume Logistic univariate regression: Baseline total WMH, PVH and DWMH predicted conversion from PD-MCI to PDD; however, significance was lost in multivariate analyses (adjusted for age, CV RF, hippocampal volume) PD-IC patients with high WMH had a significantly lower disease-free survival than those with low WMH
Sunwoo et al. 2014 (281) [automated quantitative method, CHIPS] [3.0 T]	[18F] FP-CIT PET: decreased dopamine transporter uptake in posterior putamen in all patients 46 patients were classified as PD-IC, 65 as PD-MCI	Follow-up: neuropsychological test after a minimum of 24 months 22 of 65 PD-MCI patients converted to PDD (after a mean follow-up of 29.8 months) PD-MCI converters and non-converters did not differ in baseline number of CV RF

111 PD patients		Baseline WMH volume and CHIPS score were significantly higher in converters than in non-converters Logistic regression in PD-MCI: WMH volume (OR=1.616, 95% CI=1.126-2.317) and CHIPS score (OR=1.084, 95% CI=1.022-1.150) showed an independent association with conversion to PDD 18 of 46 PD-IC patients converted to PD-MCI (mean follow-up of 28.8 months) PD-IC converters and non-converters did not differ significantly in baseline number of CV RF, WMH volume or CHIPS score WMH volume/CHIPS score correlated significantly with decline in MMSE (r=0.380/r=0.336), semantic fluency (r=0.276/r=0.298) and Stroop test scores (r=0.386/r=0.285) in PD-MCI patients No correlations between WMH volume/CHIPS score and cognitive decline in PD-IC patients
Lee et al. 2016 (282) [Fazekas scale] [1.5 T] 132 PD patients	Patients with MMSE ≤ 10 were excluded 96 non-demented, 36 PDD patients Baseline PDD patients had significantly more frequently Fazekas ≥ 2 than non-PDD patients No difference between demented and non-demented PD patients in vascular risk factors Multivariate logistic regression: association between WMH grade and dementia became insignificant (corrected for age, postural instability, education level) Considering only the 96 non-demented patients, patients with Fazekas ≥ 2 had a higher frequency of hypertension, azotaemia and brain vessel stenosis than patients with Fazekas score < 2	Only the 96 non-demented PD patients were included in the longitudinal study Neuropsychological tests were repeated every three to twelve months Median follow-up of the 96 non-demented patients was 59.2 months Univariate analysis: Fazekas grade ≥ 2 was associated with occurrence of dementia (HR=2.669, 95% CI=1.323-5.385) This relationship became insignificant in multivariate analyses adjusting for various confounders
Moccia et al. 2016 (283)	Only newly diagnosed PD patients included	Follow-up examinations after 24 and 48 months; motor examinations in “off” state

[Wahlund scale] [1.5 T] 63 PD patients	18 PIDG, 27 TD, 18 indeterminate phenotype PIGD patients had a significantly higher WMH total score than TD patients Patients with intermediate phenotype did not differ in WMH score from PIGD or TD patients	At two-year follow-up, WMH score was only insignificantly higher in PIGD patients (p=0.059) At four-year follow up, WMH score was significantly higher in PIGD patients compared to TD patients Logistic regression: higher WMH score was associated with an increased probability of being PIGD phenotype during the study period (OR=2.743, 95% CI=1.137-7.802) Subjects with intermediate phenotype who developed PIGD or TD phenotype did not differ in WMH score from those who did not
Foo et al. 2016 (284) [Fazekas scale, Rotterdam Progression Scale] [3.0 T] 73 PD patients	Only patients with mild PD (H&Y stage <3) without dementia were included SVD: apart from WMH, lacunes and PVS (and their progression= development of new lesions) were also assessed	Follow-up after 18 months 59 patients had SVD-no-progression, 14 had SVD-progression Over 18 months, SVD-progression group showed decline in MMSE, executive functions and episodic memory compared to SVD-no-progression group Mean global thickness in left and right hemisphere at baseline did not differ between the two groups; SVD-progression group had significant cortical thinning at baseline in the left parahippocampal gyrus At follow-up, the group with SVD progression had a significant increase of cortical thinning in the left frontal and bilateral parietal regions compared to the SVD-no-progression group Higher cortical thinning in the progression group after 18 months was significantly associated with higher motor, global cognition, episodic memory and executive functions impairment At baseline, the progression group had significantly more left nucleus accumbens and left amygdala atrophy than the no-progression group At follow-up, the progression group had significantly more atrophy of the caudate nucleus
Compta et al. 2016 (285) [Wahlund scale] [3.0 T] 38 PD patients, 12 HC	19 PDND, 19 PDD patients HC and PD patients did not differ in CV RF A significantly higher proportion of PDD patients had moderate-to-severe WMH (Wahlund score > 1) in the parieto-occipital	PDND patients were followed-up every six months for 18 months Higher proportion of dementia-converters vs. non-converters in group with CSF Aβ levels < 500 pg/mL and moderate-to-severe parieto-occipital WMH compared to other constellations 3 PD patients died after follow-up (2 PDD, 1 PDND who converted to PDD) and were

	region compared to HC and PDND patients PD patients (PDND + PDD) with moderate-to-severe parieto-occipital WMH had significantly lower CSF Aβ levels, lower MMSE scores and higher age compared to those with none-to-mild parieto-occipital WMH Binary logistic regression: association between parieto-occipital WMH and lower CSF Aβ levels remained significant (adjusted for age, MMSE, dementia at baseline, APOE-4, CV RF, comorbidities)	brain donors; all 3 had CSF Aβ levels < 500 pg/mL and moderate-to-severe parieto-occipital WMH at baseline
Blume et al. 2017 (286) [semi-automated quantitative method] [1.5T] 40 PD patients	All patients underwent deep brain stimulation (DBS) of the subthalamic nucleus (STN); no demented patients included Assessments in “on” state 26 PD-MCI, 14 PD-IC patients WMH volume significantly correlated with age and presence of CV RF	17 patients had a follow-up within three years (mean 21 months); significant decline in verbal fluency, Trail Making Test A, Block Design Test (visual-constructive function) Patients who converted to PDD within three years (n=10) had a significantly higher baseline WMH volume compared to non-converters; difference was even higher when comparing patients who converted to PDD within one year of surgery (n=4) to non-converters Multivariate regression: WMH volume was significantly associated with conversion to PDD within three years Linear regression: cognitive decline was significantly associated with WMH volume after correcting for age
Ong et al. 2017 (287) [automated quantitative method] [3.0 T] 77 PD patients	Only non-demented patients included 65 PD patients without diabetes mellitus (PD-no DM), 12 PD patients with diabetes mellitus (PD-DM) No baseline difference in global cognitive scores between the two groups PD-DM patients had significantly higher total WMH and PVH volume compared to PD-no DM	Follow-up: clinical and neuropsychological re-assessments every 6 months for 36 months (in “on” state), re-MRI at study end 51 PD-no DM and 11 PD-DM patients included in longitudinal analyses PD-DM patients worsened significantly more in MMSE and MoCA scores than PD-no DM patients (mean follow-up 29.08 months) PD-DM patients had a higher increase in total WMH volume, PVH and DWMH volume, although statistically not significant

Dadar et al. 2018 (288) [automated quantitative method] [3.0 T] 365 de novo PD patients, 174 age-matched HC	All participants were cognitively normal at baseline Baseline WMH volume did not significantly differ between PD patients and HC No association between baseline WMH and baseline cognitive measures Threshold for discriminating high from low WMH was set at 5 cm^3	Patients were yearly re-examined, mean follow-up of 4.09 years Controlled for age, baseline WMH volume correlated significantly with MoCA score decline rate in PD patients (r=-0.145) but not in HC Longitudinal cognitive status was significantly associated with baseline WMH volume in PD patients (β=0.216) but not HC Cognitive decline was greater in PD patients with high WMH burden Survival analysis with two-point drop in MoCA score as terminal event: PD patients with high WMH burden had a significantly lower 4-year survival rate than PD patients with low WMH burden or HC with high WMH; no difference between PD patients with low WMH and HC with low WMH or between HC with high or low WMH burden Only in PD patients, baseline WMH had a significant negative effect on global cognition, memory and visuospatial skills (independent of age) Significant decrease in mean whole-brain cortical thickness in PD patients with low and high baseline WMH but not in HC; higher decrease in the latter group, especially in the right frontal lobe; thinning of this region correlated with poorer HVLT performance at one-year follow-up (r=-0.335)
Chahine et al. 2019 (289) [automated quantitative method] [not specified] 141 PD patients, 63 HC	All PD patients were newly diagnosed and dementia free, and showed dopamine deficit on SPECT Vascular risk was assessed with the modified Framingham Risk Score (minus smoking) No difference between PD patients and HC in CV RF or WMH volume PD patients: vascular risk score significantly associated with total WMH volume, frontal and temporal WMH volume HC: vascular risk score significantly associated only with temporal WMH	134 PD patients (median follow-up 731 days) and 61 HC (median follow-up 761 days) underwent follow-up and were included in longitudinal analyses Vascular risk score was inversely associated with annual change in MoCA score both in PD patients (β=-0.040) and in HC In HC, WMH were not associated with any longitudinal measures of cognition Global (β=-0.029, 95% CI -0.058, -0.0001) and occipital (β=-0.041, 95% CI -0.080, -0.001) WMH volume was significantly inversely associated with annual rate of change in MoCA score Temporal WMH volume was significantly inversely associated with annual rate of change in HVLT-delayed recall (β=-0.034, 95%CI -0.065, -0.003)

	No associations between cognitive measures and WMH in HC PD patients: global, temporal and parietal WMH significantly inversely associated with HVLT-delayed recall (Hopkins Verbal Learning Task) and WMH in all regions except occipital associated with HVLT-recognition	
Grey et al. 2019 (290) [manual quantitative method] [1.5 T] 47 PD patients	At baseline, all participants were cognitively normal	Two-year follow-up included clinical examinations and cerebral MRI; 34 PD patients completed follow-up After two years, 11 patients had developed PD-MCI, while 23 remained PD-IC Compared to PD-IC, PD-MCI patients had significantly higher values for PVH volume at follow-up, PVH change, total WMH volume at follow-up and total WMH volume change; baseline PVH or total WMH volume did not differ between PD-IC and PD-MCI The two groups did not differ in baseline, follow-up or change of DWMH volume
Chung et al. 2019 (291) [CREDOS scale, Fazekas scale, Scheltens scale] [not specified] 268 de novo PD patients	[18F] FP-CIT PET: all patients exhibited decreased dopamine transporter uptake in posterior putamen 198 patients had only minimal WMH, 70 had moderate to severe WMH (according to CREDOS scale) PD patients with moderate to severe WMH had higher age and UPDRS-III scores compared to those with minimal WMH Patients with moderate to severe WMH had a higher Scheltens score in periventricular, lobar, basal ganglia and infratentorial regions than those with minimal WMH Patients with moderate to severe WMH had a higher prevalence of both hypertension and diabetes	Follow-up visits were every three months for at least three years PD patients with moderate to severe WMH had a higher risk of becoming demented than patients with minimal WMH (HR 2.565, 95% CI 1.442-4.629) Over the course of the follow-up period, the group with moderate to severe WMH needed significantly higher doses of dopaminergic medications (serving as a marker of disease progression in early stages) than the patients with minimal WMH in order to control PD symptoms 25 of 70 PD patients with moderate to severe and 27 of 198 with minimal WMH developed freezing of gait (FOG) during follow-up; FOG might serve as a marker for more advanced PD stages Kaplan-Meier analysis (starting from PD symptom onset): PD patients with moderate to severe WMH had a higher risk of developing FOG than the PD patients with minimal WMH Cox proportional hazard model: PD patients with moderate to severe WMH had a higher risk of developing FOG than patients with

	mellitus than those with minimal WMH The TD subtype was less frequent in the group with moderate to severe WMH compared to the one with minimal WMH No differences in sex, disease duration, CCSIT, BDI, MMSE scores between the groups Higher decrease of dopamine transporter uptake in all sub-regions of the striatum in moderate to severe WMH group than minimal WMH group	minimal WMH (HR 3.292, 95% CI 1.791-6.048) (adjusted for age at PD onset, sex, levodopa equivalent doses, dopamine transporter uptake in posterior putamen)
Pozorski et al. 2019 (292) [automated quantitative method] [3.0 T] 29 PD patients, 42 HC	Participants with MMSE <27 were excluded; examinations performed in "off" state PD patients had a significantly higher MAP both in standing and supine position than HC A higher proportion of HC had a history of smoking compared to PD patients No difference between PD patients and HC in total WMH volume Regression analyses: higher WMH volume and poorer performance in tests of executive function were significantly associated in PD patients and HC, but relationship was stronger in PD patients No difference between PD patients and HC in spatial WMH distribution in voxel-wise analyses Voxel-wise analysis: significant association between poorer executive function and bilateral frontal and parietal DWMH in PD patients; association between impaired memory and WMH in genu of	One follow-up visit (including MRI) after 18 months; 71 participants (29 PD patient and 42 HC) completed follow-up PD patients had a significantly higher standing MAP averaged across the two visits than HC No difference in change of total WMH volume over 18 months (∆WMH) between PD patients and HC (controlled for age, sex, education, average supine MAP, time between visits, pack-years) Regression analyses: no associations between cognitive change and ∆WMH Regression analysis: a higher increase of WMH was significantly associated with a higher increase of UPDRS motor sub-score in PD patients (β=0.423) but not in HC Longitudinal voxel-wise analyses: no differences between PD patients and HC

	corpus callosum and surrounding white matter in PD patients	
Park et al. 2019 (293) [Fazekas scale] [3.0 T] 271 PD patients	PDD patients and patients who directly converted from PD-IC to PDD were excluded 106 PD-IC patients, 165 PD-MCI patients Remark: high basal ganglia PVS and hypertension also independently predicted cognitive decline	During the mean follow-up of 59.8 months, participants were classified as cognitive converters (n=52) or non-converters (n=219) 18 PD-IC patients converted to PD-MCI, 88 were non-converters 34 PD-MCI patients converted to PDD, 131 were non-converters Converters (all PD patients) had more frequently severe baseline WMH (total Fazekas score > 3) than non-converters; the same applies to PD-MCI patients who converted to PDD vs. those who did not Univariate logistic regression (all patients): amongst others, severe WMH predicted cognitive conversion (OR=4.6, 95% CI=2.3-9.1) Multivariate logistic regression (all patients): amongst others, severe WMH independently predicted cognitive conversion (OR=3.1, 95% CI=1.4-7.1) Univariate logistic regression (PD-IC): severe WMH predicted conversion to PD-MCI (OR=3.8, 95% CI=1.1.-13.6) Univariate logistic regression (PD-MCI): severe WMH predicted conversion to PDD (OR=4.9, 95% CI=2.2-11.3) Multivariate logistic regression (PD-MCI): severe WMH independently predicted conversion to PDD (OR=4.9, 95% CI=1.9-13.0)
Hanning et al. 2019 (294) [CHIPS, semi-automated quantitative method] [1.5 T] 108 de novo PD patients, 102 age- and sex-matched HC	At baseline, all PD patients were drug-naïve Patients with a stroke history were excluded At baseline, 79 PD patients were classified as PD-IC and 29 as PD-MCI At baseline, 89 HC were classified as HC with intact cognition (HC-IC) and 13 as HC with MCI (HC-MCI) No significant differences in CV RF between PD-IC and PD-MCI, although PD-MCI patients tended to have more frequently arterial hypertension	Follow-up assessments were performed after 24 months; during the period, all patients had received dopaminergic medication 15 PD-IC patients converted to PD-MCI, 10 PD-IC patients converted to PDD, 8 PD-MCI patients converted to PDD 54 PD-IC and 15 PD-MCI remained cognitively stable, i.e., did not convert; 6 PD-MCI patients improved to PD-IC PD converters had more frequently hypertension than PD non-converters, although statistically insignificant (p=0.09) No significant differences in baseline WMH volume/CHIPS score between PD converters and PD non-converters,

	No significant differences in WMH presence or volume/CHIPS score between PD-IC and PD-MCI, although PD-MCI tended to have a higher WMH burden	although PD converters tended to have a higher global WMH burden Multivariable logistic regression*: baseline global WMH presence or volume/CHIPS score not associated with baseline cognitive status; neither global WMH presence or volume nor CHIPS score predicted conversion to a more impaired cognitive status in PD patients; moreover, no significant findings in HC *adjusted for age, gender, education, relative brain parenchyma volume

Table 11. Longitudinal studies on WMH in PD.

Abbreviations:
AD……..Alzheimer's disease
APOE-4……....apolipoprotein E4
BDI……Beck Depression Inventory
CAMCOG……..Cambridge Cognition Examination
CCSIT……Cross-Cultural Smell Identification Test
CHIPS……Cholinergic Pathways Hyperintensities Scale
CI……confidence interval
cm^3……..cubic centimetres
CREDOS……...Clinical Research Center for Dementia of South Korea
CSF……cerebrospinal fluid
CV RF……cardiovascular risk factors
DBS……..…….deep brain stimulation
DLB……..…..dementia with Lewy bodies
DWMH……deep white matter hyperintensities
FOG……freezing of gait
FP-CIT……fluoropropyl-carbomethoxy-iodophenyl-nortropane
GDS……Geriatric Depression Scale
H&Y……Hoehn and Yahr (stage)
HC……...healthy controls
HC-IC……..healthy controls with intact cognition
HC-MCI……..healthy controls with MCI
HR……...hazard ratio
HVLT……...Hopkins Verbal Learning Task
MAP……mean arterial pressure
mL……millilitres
MMSE……..Mini-Mental State Examination
MoCA……...Montreal Cognitive Assessment
MRI……...magnetic resonance imaging
OH……..…orthostatic hypotension
OR……odds ratio
PD……Parkinson's disease
PDD……..Parkinson's disease dementia
PD-DM…….PD patients with diabetes mellitus
PD-IC……...PD patients with intact cognition
PD-MCI……Parkinson's disease mild cognitive impairment
PDND……...Parkinson's disease no dementia
PD-no DM……PD patients without diabetes mellitus
PET…….....positron emission tomography
pg…..picograms
PIDG……postural instability and gait difficulty
PVH……..periventricular hyperintensities
PVS……..perivascular space(s)
r……Pearson's correlation coefficient
r_s……..……Spearman's correlation coefficient

SPECT…….single photon emission computerised tomography
STN……..subthalamic nucleus
SVD……..small vessel disease
T……Tesla
TD……tremor dominant
UPDRS…….Unified Parkinson's disease rating scale
WMH…….white matter hyperintensities

3.1.3 Quantitative results of selected studies

Source	Mean ages	Quantitative results
Dalaker et al. 2009 (234)	HC (65.7 years) PD-IC (65.5 years) PD-MCI (69.4 years)	HC: mean total WMH volume 7.1 mL PD-IC: mean total WMH volume 7.3 mL PD-MCI: mean total WMH volume 10.4 mL
Melzer et al. 2013 (246)	HC (70.1 years) PD-IC (64.0 years) PD-MCI (71.0 years) PDD (73.7 years)	HC: median total WMH volume 1.2 mL PD-IC: median total WMH volume 1.0 mL PD-MCI: median total WMH volume 6.4 mL PDD: median total WMH volume 10.5 mL
Kandiah et al. 2013 (247)	PD-IC (63.39 years) PD-MCI (68.99 years)	PD-IC: mean total WMH volume 4.09 mL PD-IC: mean PVH volume 2.66 mL PD-IC: mean DWMH volume 1.44 mL PD-MCI: mean total WMH volume 8.2 mL PD-MCI: mean PVH volume 6.04 mL PD-MCI: mean DWMH volume 2.16 mL
Liu et al. 2015 (254)	HC (64.1 years) PD (62.6 years)	HC: mean total WMH volume 0.776 mL HC: median total WMH volume 0.265 mL PD: mean total WMH volume 5.827 mL PD: median total WMH volume 0.502 mL
Mak et al. 2015 (255)	PD-IC (63.4 years) PD-MCI (69.4 years)	PD-IC: mean total WMH volume 4.2 mL PD-IC: mean PVH volume 3.1 mL PD-IC: mean DWMH volume 1.1 mL PD-MCI: mean total WMH volume 12.3 mL PD-MCI: mean PVH volume 10.1 mL PD-MCI: mean DWMH volume 2.0 mL
Al-Bachari et al. 2017 (263)	CN (67.4 years) CP (70.1 years) PD (69.0 years) PIGD (70.0 years) TD (67.9 years)	CN: median total WMH volume 1.41 mL CP: median total WMH volume 10.44 mL PD: median total WMH volume 4 mL PIGD: median total WMH volume 8.03 mL TD: median total WMH volume 1 mL
Stojkovic et al. 2018 (270)	PD-IC (61.50 years) PD-MCI (65.62 years) PDD (70.61 years)	PD-IC: mean total WMH volume 0.43 mL PD-IC: mean frontal WMH volume 0.22 mL PD-MCI: mean total WMH volume 1.15 mL PD-MCI: mean frontal WMH volume 0.48 mL PDD: mean total WMH volume 2.01 mL PDD: mean frontal WMH volume 1.01 mL
De Schipper et al. 2019 (271)	HC (65.0 years) PD (64.8 years)	HC: mean total WMH volume 4.8 mL HC: mean PVH volume 2.2 mL HC: mean anterior DWMH volume 0.03 mL HC: mean posterior DWMH volume 1.7 mL PD: mean total WMH volume 8.8 mL PD: mean PVH volume 3.6 mL

		PD: mean anterior DWMH volume 0.2 mL PD: mean posterior DWMH volume 1.6 mL
Dunet et al. 2019 (274)	HC (76.7 years) PD-IC (78.1 years) PD-MCI (81.8 years)	HC: mean total WMH volume 9.2 mL PD-IC: mean total WMH volume 8.2 mL PD-MCI: mean total WMH volume 18.1 mL
Burton et al. 2006 (277)	PDD (74.9 years)	PDD: mean total WMH volume 6 mL
Sunwoo et al. 2014 (281)	PD-MCI converters (to PDD; 74.32 years) PD-MCI non converters (71.51 years)	PD-MCI converters: mean total WMH volume 14.421 mL PD-MCI non converters: mean total WMH volume 5.18044 mL
Blume et al. 2017 (286)	Total group (61.8 years) PD-IC/MCI after 3 years (60.5 years) PDD after 3 years (65.8 years)	Total group: mean total WMH volume 14.0 mL PD-IC/MCI after 3 years: mean total WMH volume 8.8 mL PDD after 3 years: mean total WMH volume 29.6 mL
Ong et al. 2017 (287)	PD-no DM (64.4 years) PD-DM (67.41 years)	PD-no DM: mean total WMH volume 5.8 mL PD-no DM: mean PVH volume 4.02 mL PD-no DM: mean DWMH volume 1.78 mL PD-DM: mean total WMH volume 9.76 mL PD-DM: mean PVH volume 7.29 mL PD-DM: mean DWMH volume 2.48 mL
Dadar et al. 2018 (288)	HC (60.07 years) PD (60.51 years)	HC: mean total WMH volume 7.66 mL PD: mean total WMH volume 6.93 mL
Hanning et al. 2019 (294)	PD-IC (64 years) PD-MCI (63 years)	PD-IC: median total WMH volume 0.5 mL PD-MCI: median total WMH volume 1.0 mL

Table 12. Quantitative results on WMH volumes of selected studies.

Abbreviations:
CN……control negative
CP……control positive
DWMH…….deep white matter hyperintensities
HC……healthy controls
mL……millilitres
PD……Parkinson's disease
PDD……Parkinson's disease dementia
PD-DM…….PD patients with diabetes mellitus
PD-IC……...PD patients with intact cognition
PD-MCI……Parkinson's disease mild cognitive impairment
PD-no DM……...PD patients without diabetes mellitus
PIGD……postural instability and gait difficulty
PVH…….periventricular hyperintensities
TD……tremor dominant
WMH…….white matter hyperintensities

3.2 Cross-sectional study

3.2.1 Demographic, clinical and imaging characteristics

A total of 282 individuals were included in this study. The population consisted of 141 Parkinson's disease patients and 141 age- and sex-matched healthy controls. Baseline demographic, clinical and imaging characteristics of the study population are given in Table 13. Demographic and imaging data was available in all PD patients and controls. Clinical data was missing in some PD patients (for exact numbers, see Table 13).

3.2.1.1 Demographic characteristics

There was no significant difference in mean age between patients with Parkinson's disease (62.9 years) and healthy controls (63.0 years). The youngest PD patient was 30.9 years old, the oldest 81.1 years. HC ranged from 38.5 to 81.3 years. Both groups consisted predominantly of men: 73.8% of PD patients and 71.6% of HC were male. The groups did not differ significantly in sex.

3.2.1.2 Clinical characteristics of PD patients

Mean and median disease duration were 4.4 and 2.7 years, respectively. Disease duration ranged from 0.05 years up to 25.8 years.
Median Hoehn and Yahr stage was 2. 79.3% of PD patients were classified as Hoehn and Yahr stage 2 (n=111), while 22 patients were Hoehn and Yahr stage 1. Only a minority of PD patients was stage 3 (n=5) or stage 4 (n=2); no patients in stage 5 were included.
78.0% of PD patients (n=110) took regular dopaminergic medication at the time of clinical examinations; in these cases, medications were paused on the day of examination for the sake of better comparability. LED ranged from 0.0 mg up to 1880 mg. Mean and median LED were 292.0 mg and 205.0 mg, respectively.
Both mean and median MMSE score were 28 points. The lowest MMSE score was 18 (n=1), while 26 patients (18.6%) scored the maximum 30 points. 135 patients (96.4%) reached a score of 24 points or more, 123 patients (87.9%) scored at least 27 points.

Median MDS-UPDRS total score was 43 points, ranging from 14 to 134 points (mean score: 46.5 points). Descriptive statistics of other clinical scores are given in Table 13.

Characteristics	PD patients (n=141)*	HC (n=141)	p-value
Age in years			0.927[a]
mean ± SD	62.9 ± 10.2	63.0 ± 10.0	
median (IQR)	65.2 (15.8)	65.2 (15.3)	
min/max	30.9/81.1	38.5/81.3	
Sex			0.688[b]
male:female	104:37	101:40	
percentage male	73.8%	71.6%	
Disease duration in years			
mean ± SD	4.4 ± 4.9	n.a.	
median (IQR)	2.7 (4.2)	n.a.	
min/max	0.05/25.8	n.a.	
Difference clinical examination – MRI in days			
mean ± SD	-1.3 ± 14.3	n.a.	
median (IQR)	0.0 (0.0)	n.a.	
min/max	-105.0/42.0	n.a.	
MDS-UPDRS total score			
mean ± SD	46.5 ± 20.6	n.a.	
median (IQR)	43.0 (23.0)	n.a.	
min/max	14.0/134.0	n.a.	
MDS-UPDRS part 1			
mean ± SD	6.6 ± 4.5	n.a.	
median (IQR)	6.0 (7.0)	n.a.	
min/max	0.0/24.0	n.a.	
MDS-UPDRS part 2			
mean ± SD	10.0 ± 6.2	n.a.	
median (IQR)	9.0 (7.0)	n.a.	
min/max	0.0/42.0	n.a.	
MDS-UPDRS part 3			
mean ± SD	29.7 ± 13.7	n.a.	
median (IQR)	27.5 (14.0)	n.a.	
min/max	6.0/86.0	n.a.	
MDS-UPDRS part 4			
mean ± SD	0.2 ± 1.3	n.a.	
median (IQR)	0.0 (0.0)	n.a.	
min/max	0.0/12.0	n.a.	
Hoehn & Yahr stage			
mean ± SD	1.9 ± 0.5	n.a.	
median (IQR)	2.0 (0.0)	n.a.	
min/max	1.0/4.0	n.a.	
mode	2.0	n.a.	
Non-Motor Symptoms Questionnaire			
mean ± SD	7.1 ± 4.4	n.a.	
median (IQR)	7.0 (6.0)	n.a.	
min/max	0.0/21.0	n.a.	
Geriatric Depression Scale			

mean ± SD	2.6 ± 2.4	n.a.	
median (IQR)	2.0 (3.0)	n.a.	
min/max	0.0/11.0	n.a.	
LED in mg			
mean ± SD	293.0 ± 339.9	n.a.	
median (IQR)	205.0 (363.0)	n.a.	
min/max	0.0/1880.0	n.a.	
MMSE			
mean ± SD	28.0 ± 2.0	n.a.	
median (IQR)	28.0 (2.0)	n.a.	
min/max	18.0/30.0	n.a.	
CERAD-TS1			
mean ± SD	79.9 ± 11.1	n.a.	
median (IQR)	82.0 (15.0)	n.a.	
min/max	43.0/98.0	n.a.	
CERAD-TS2			
mean ± SD	89.2 ± 12.7	n.a.	
median (IQR)	91.5 (17.0)	n.a.	
min/max	45.0/109.0	n.a.	
CERAD memory score			
mean ± SD	35.2 ± 4.6	n.a.	
median (IQR)	36.0 (7.0)	n.a.	
min/max	21.0/41.0	n.a.	
Total WMH in mm^3			0.502[a]
mean ± SD	6933.3 ± 7419.7	5591.9 ± 5961.0	
median (IQR)	4555.2 (8568.1)	3766.5 (4651.6)	
min/max	35.4/35602.1	57.6/36590.2	
Deep WMH in mm^3			0.312 [a]
mean ± SD	1654.5 ± 3008.1	1758.9 ± 3000.5	
median (IQR)	363.4 (1648.9)	502.9 (1548.7)	
min/max	0.0/18001.6	0.0/15243.2	
Periventricular WMH in mm^3			0.164 [a]
mean ± SD	5278.8 ± 5262.7	3834.4 ± 3995.7	
median (IQR)	3801.9 (6892.5)	2986.6 (2677.5)	
min/max	35.4/24812.2	0.0/30800.9	

Table 13. Demographic, clinical and imaging characteristics of PD patients and HC.

*full dataset (n=141) only available for the following parameters: age, sex, total WMH, deep WMH, periventricular WMH, disease duration, difference clinical examination – MRI, Geriatric Depression Scale, LED
number of PD patients with data for other parameters: MDS-UPDRS parts 1-4 and total score (n=140), Hoehn & Yahr stage (n=140), Non-Motor Symptoms Questionnaire (n=137), MMSE (n=140), CERAD-TS1, TS2 and memory score (n=120)
[a]Mann-Whitney U test
[b]Chi-square test

Abbreviations:
CERAD……..Consortium to Establish a Registry for Alzheimer's Disease
HC……..healthy controls
IQR…….interquartile range
LED……levodopa equivalent dose
max……maximum
MDS-UPDRS……Movement Disorder Society-Unified Parkinson's disease rating scale
mg……..milligrams
min…….minimum

mm^3……cubic millimetres MMSE……Mini-Mental State Examination MRI……magnetic resonance imaging n.a……..not available PD……..Parkinson's disease SD……..standard deviation TS1/2……total score 1/2 WMH……..white matter hyperintensities

3.2.1.3 WMH volume in PD patients and healthy controls

All study participants showed WMH at least to some degree. Mean/median total white matter hyperintensity volume was higher in PD patients (6933.3 mm^3/4555.2 mm^3) than in healthy controls (5591.9 mm^3/3766.5 mm^3). However, this difference was not statistically significant (p=0.502). Total WMH volume ranged from 35.4 mm^3 to 35602.1 mm^3 in PD patients and from 57.6 mm^3 to 36590.2 mm^3 in HC. Similarly, mean/median periventricular white matter hyperintensity volume in PD patients tended to be higher (5278.8 mm^3/3801.9 mm^3) than in controls (3834.4 mm^3/2986.6 mm^3). This difference did not reach statistical significance, either (p=0.164). PVH volume ranged from 35.4 mm^3 to 24812.2 mm^3 in PD patients and from 0.0 mm^3 to 30800.9 mm^3 in HC. A total of two HC did not show any PVH. Mean/median total deep white matter hyperintensity volume was slightly higher in healthy controls (1758.9 mm^3/502.9 mm^3) compared to PD patients (1654.5 mm^3/363.4 mm^3), although statistically insignificant, too (p=0.312). DWMH volume ranged from 0.0 mm^3 to 18001.6 mm^3 in PD patients and from 0.0 to 15243.2 mm^3 in HC. 19 PD patients and 15 HC did not show any DWMH on MRI.
Table 14 shows WMH volumes stratified by sex. There were no statistically significant differences in total, deep or periventricular white matter hyperintensity volume between male and female PD patients or between male and female healthy controls. Moreover, when combining PD patients and controls, male and female individuals did not differ in any WMH volume parameter, either. A comparison of male PD patients with male healthy controls and of female PD patients with female healthy controls, respectively, yielded no statistically significant differences, either.

Group	Parameter	male	female	p-value
PD patients	Mean total WMH volume in mm^3 ± SD	7343.9 ± 7931.9	5779.1 ± 5677.1	0.583[a]

	Median total WMH volume in mm^3 (IQR)	4440.0 (9045.9)	4555.2 (7471.8)	
	Mean DWMH volume in mm^3 ± SD Median total WMH volume in mm^3 (IQR)	1687.0 ± 3224.7 368.9 (1457.7)	1562.9 ± 2329.5 363.4 (2118.1)	0.385[a]
	Mean PVH volume in mm^3 ± SD Median PVH volume in mm^3 (IQR)	5656.9 ± 5662.9 3732.1 (7800.5)	4216.2 ± 3792.5 3810.8 (6347.6)	0.394[a]
HC	Mean total WMH volume in mm^3 ± SD Median total WMH volume in mm^3 (IQR)	5305.5 ± 5463.6 3773.1 (4154.2)	6315.0 ± 7089.8 3512.8 (6814.0)	0.934[a]
	Mean DWMH volume in mm^3 ± SD Median total WMH volume in mm^3 (IQR)	1481.6 ± 2519.4 511.8 (1278.4)	2459.1 ± 3916.9 375.5 (3872.3)	0.918[a]
	Mean PVH volume in mm^3 ± SD Median PVH volume in mm^3 (IQR)	3824.5 ± 4025.4 2991.0 (2544.6)	3859.1 ± 3970.3 2902.4 (3453.0)	0.866[a]
Combined	Mean total WMH volume in mm^3 ± SD Median total WMH volume in mm^3 (IQR)	6339.6 ± 6887.9 3999.1 (6148.2)	6057.5 ± 6413.5 4047.9 (7183.8)	0.760[a]
	Mean DWMH volume in mm^3 ± SD Median total WMH volume in mm^3 (IQR)	1585.8 ± 2893.5 429.8 (1363.4)	2028.4 ± 3262.9 374.4 (2225.5)	0.612[a]
	Mean PVH volume in mm^3 ± SD Median PVH volume in mm^3 (IQR)	4754.1 ± 4997.8 3316.7 (4645.3)	4030.7 ± 3864.5 2986.6 (4328.7)	0.508[a]

Table 14. Mean and median WMH volumes stratified by sex.

[a]Mann-Whitney U test, male vs. female intra-group

Inter-group comparisons (Mann-Whitney U test):

- male PD patients vs. male HC: total WMH volume (p=0.418), DWMH volume (p=0.198), PVH volume (p=0.173)
- female PD patients vs. female HC: total WMH volume (p=0.927), DWMH volume (p=0.943), PVH volume (p=0.775)

Abbreviations:
DWMH……..deep white matter hyperintensities
HC…….healthy controls
IQR……interquartile range
mm^3……..cubic millimetres
PD…….Parkinson's disease
PVH……..periventricular hyperintensities
SD…….standard deviation
WMH…….white matter hyperintensities

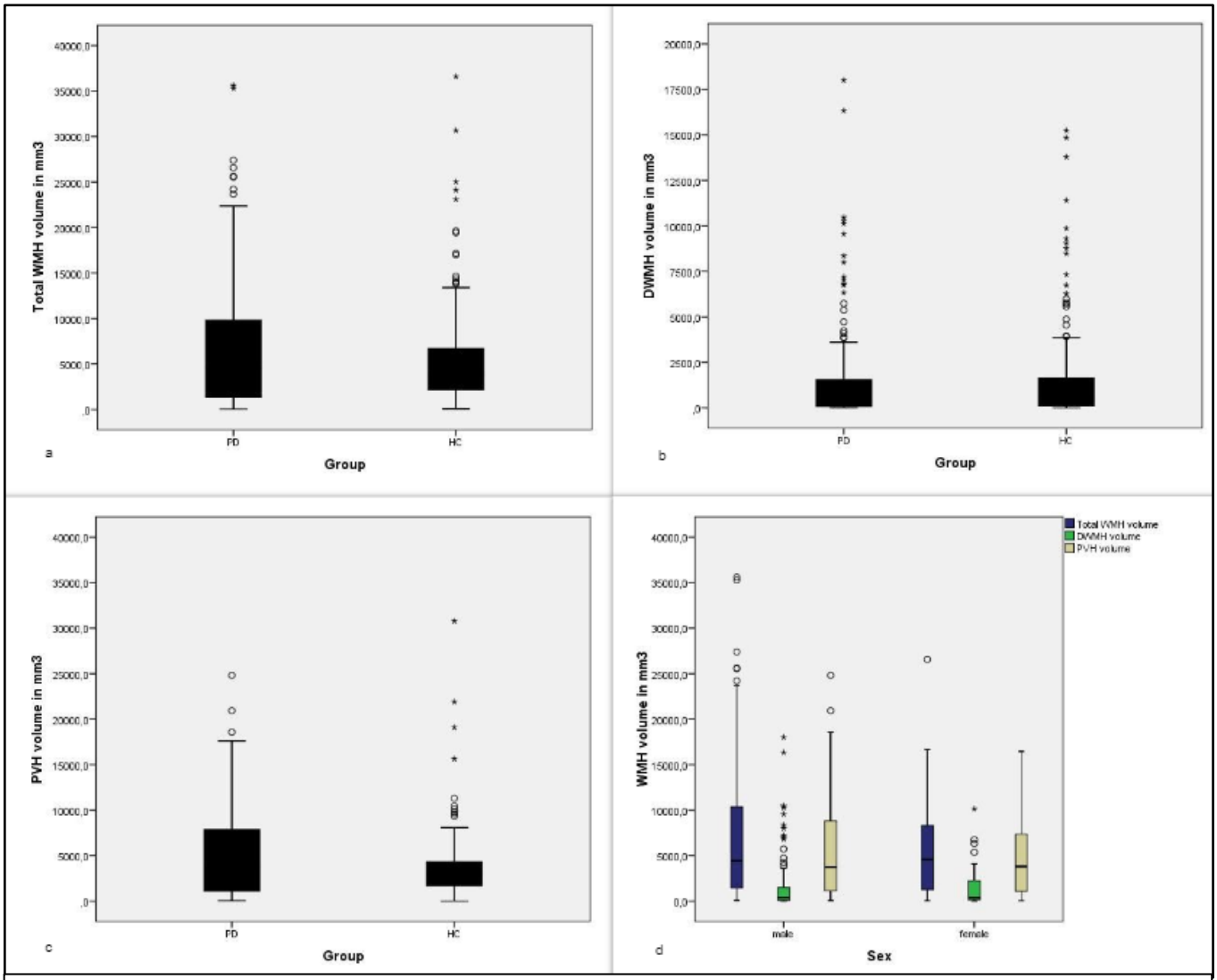

Figure 4. Distribution of WMH volumes visualised as boxplots.

a) Total WMH volume in PD patients and HC
b) DWMH volume in PD patients and HC
c) PVH volume in PD patients and HC
d) Total, deep and periventricular WMH volume in male and female PD patients

Mind the different scaling used in case of DWMH volumes. Circles represent statistical outliers (distance to the box (first/third quartile) of 1.5 to 3 times the interquartile range), asterisks represent extreme statistical outliers (distance to the box of more than 3 times the interquartile range).

Abbreviations:
DWMH……deep white matter hyperintensities
HC……...healthy controls
mm^3…….cubic millimetres
PD……Parkinson's disease
PVH……periventricular hyperintensities
WMH……white matter hyperintensities

3.2.2 Correlation analyses

Table 15 shows Spearman correlation coefficients of total, deep and periventricular white matter hyperintensity volume with various clinical parameters in PD patients.

There were highly significant negative correlations between total WMH volume and MMSE (r_s=-0.234, p=0.005), CERAD-TS1 (r_s=-0.323, p=0.000), CERAD-TS2 (r_s=-0.341, p=0.000) and CERAD memory score (r_s=-0.301, p=0.001). No significant correlations were found between total WMH volume and disease duration, MDS-UPDRS total and sub-scores, Hoehn & Yahr stage, Non-Motor Symptoms Questionnaire (r_s=0.144, p=0.094), Geriatric Depression Scale or LED, respectively.

Significant negative correlations were also found between deep WMH volume and MMSE (r_s=-0.215, p=0.011), CERAD-TS1 (r_s=-0.328, p=0.000), CERAD-TS2 (r_s=-0.337, p=0.000) and CERAD memory score (r_s=-0.276, p=0.002). Deep WMH volume did not correlate significantly with disease duration, LED (r_s=0.149, p=0.079) or any other clinical score.

Similarly, there were significant negative correlations between periventricular WMH volume and MMSE (r_s=-0.210, p=0.013), CERAD-TS1 (r_s=-0.313, p=0.000), CERAD-TS2 (r_s=-0.332, p=0.000) and CERAD memory score (r_s=-0.300, p=0.001). There were no significant correlations between periventricular WMH volume and any of the other parameters.

WMH volumes correlated significantly and strongly with each other: total WMH volume with deep WMH volume (r_s=0.721, p=0.000) and periventricular WMH volume (r_s=0.975, p=0.000), as well as deep WMH volume and periventricular WMH volume (r_s=0.599, p=0.000), respectively.

Age correlated highly significantly with total WMH volume (r_s=0.399, p=0.000), deep WMH volume (r_s=0.338, p=0.000) and periventricular WMH volume (r_s=0.399, p=0.000) in PD patients. Similarly, age and total WMH volume (r_s=0.379, p=0.000), deep WMH volume (r_s=0.402, p=0.000) and periventricular WMH volume (r_s=0.333, p=0.000) correlated significantly in healthy controls.

Moreover, in PD patients, there were also significant correlations between age and Hoehn & Yahr stage (r_s=0.333, p=0.000), MMSE (r_s=-0.349, p=0.000), CERAD-

TS1 (r_s=-0.559, p=0.000), CERAD-TS2 (r_s=-0.560, p=0.000) and CERAD memory score (r_s=-0.468, p=0.000).

Disease duration correlated significantly with MDS-UPDRS total score (r_s=0.371, p=0.000), MDS-UPDRS part 1 (r_s=0.215, p=0.011), MDS-UPDRS part 2 (r_s=0.323, p=0.000), MDS-UPDRS part 3 (r_s=0.307, p=0.000), MDS-UPDRS part 4 (r_s=0.182, p=0.031), Hoehn & Yahr stage (r_s=0.290, p=0.001) and LED (r_s=0.441, p=0.000). There were no significant correlations between disease duration and cognitive scores (MMSE, CERAD-TS1, CERAD-TS2, CERAD memory score), Non-Motor Symptoms Questionnaire, Geriatric Depression Scale or age.

Apart from disease duration, LED also significantly correlated with MDS-UPDRS total score (r_s=0.376, p=0.000), MDS-UPDRS part 1 (r_s=0.198, p=0.019), MDS-UPDRS part 2 (r_s=0.267, p=0.001), MDS-UPDRS part 3 (r_s=0.308, p=0.000), MDS-UPDRS part 4 (r_s=0.249, p=0.003), Hoehn & Yahr stage (r_s=0.319, p=0.000) and Non-Motor Symptoms Questionnaire (r_s=0.245, p=0.004). No significant correlations were found between LED and WMH volumes, age, Geriatric Depression Scale or cognitive scores.

Parameter	**Total WMH volume**	**p-value**	**Deep WMH volume**	**p-value**	**PVH volume**	**p-value**
Age	**0.399****	0.000	**0.338****	0.000	**0.399****	0.000
Disease duration	-0.035	0.680	0.061	0.474	-0.050	0.552
MDS-UPDRS total score	0.113	0.186	0.138	0.105	0.093	0.273
MDS-UPDRS part 1	0.124	0.145	0.090	0.292	0.108	0.204
MDS-UPDRS part 2	0.055	0.517	0.096	0.258	0.045	0.598
MDS-UPDRS part 3	0.100	0.241	0.113	0.184	0.100	0.241
MDS-UPDRS part 4	-0.048	0.576	0.086	0.310	-0.100	0.237
Hoehn & Yahr stage	0.134	0.115	0.106	0.211	0.124	0.143
Non-Motor Symptoms Questionnaire	0.144	0.094	0.101	0.238	0.124	0.149
Geriatric Depression Scale	0.121	0.153	0.068	0.423	0.102	0.229
LED	0.134	0.114	0.149	0.079	0.118	0.163
MMSE	**-0.234****	0.005	**-0.215***	0.011	**-0.210***	0.013
CERAD-TS1	**-0.323****	0.000	**-0.328****	0.000	**-0.313****	0.000
CERAD-TS2	**-0.341****	0.000	**-0.337****	0.000	**-0.332****	0.000
CERAD memory score	**-0.301****	0.001	**-0.276****	0.002	**-0.300****	0.001

Table 15. Spearman correlation coefficients of WMH volumes with clinical markers in PD patients.

*significant at the 0.05 level (two-tailed)
**significant at the 0.01 level (two-tailed)

Abbreviations:
CERAD……Consortium to Establish a Registry for Alzheimer's Disease
LED……..levodopa equivalent dose
MDS-UPDRS…...Movement Disorder Society-Unified Parkinson's disease rating scale

MMSE……...Mini-Mental State Examination PD……..Parkinson's disease PVH……...periventricular hyperintensities TS1/2……total score 1/2 WMH…….white matter hyperintensities

4 Discussion

Constituting part one (chapter 3.1) of this paper, a comprehensive systematic review of the current literature covering WMH in PD patients was conducted (presented in Tables 10, 11 and 12). While there are some consistent findings in the literature, research results are overall quite heterogenous. Possible reasons for this heterogeneity are, inter alia, discussed in the following.
Furthermore, part two of this paper (chapter 3.2) represents an original study aimed to cross-sectionally compare the extent of white matter lesions in FLAIR MRI sequences of patients suffering from Parkinson's disease to healthy subjects. Moreover, correlation analyses of WMH volumes and clinical parameters were performed in the PD group.
In the upcoming chapters, both parts will be brought together: The original cross-sectional results presented in chapter 3.2 and their underlying methods will be related to and compared with the findings and methods of existing literature outlined in chapter 3.1.

4.1 Methods

4.1.1 Study population and clinical assessment

With a total of 282 individuals (141 PD, 141 HC) included, this analysis is one of the largest cross-sectional studies investigating WMH in PD patients yet.
The PD and the HC group were equal in size and very well matched in age and sex. With a mean age of 62.9 and 63.0 years, respectively, our study population was relatively young. As is generally the case (3), PD patients were predominantly males.

Overall, the PD population in this study was characterised by a relatively mild disease severity: 95% of PD patients were in Hoehn and Yahr stage ≤ 2, no patients in stage 5 were included. This might be explained by the facts that the patients were relatively young and that they were recruited in an ambulatory setting, where visits of patients confined to bed are fairly scarce. Correspondingly, median disease duration was relatively short (2.7 years), although with a wide range (from 0.05 to 25.8 years). Disease severity and duration vary quite a lot in

the current literature, too, with several studies only including patients with mild or early/de novo PD (241,244,247,251,255,259,262,283,284). This could contribute to heterogenous study results to some extent.

In order to avoid an effect of medication on clinical status and to guarantee equal conditions for all patients, dopaminergic medication was paused on the day of examination. Concerning this important aspect, the methodology of studies presented in Tables 10 and 11 is quite differing. Examinations were conducted both in “on” (205,237,239,264,265,270,280,286,287) and in “off” (204,238,283,292) state. The large-scale study by Malek et al. (259) included a mixture of “on” and “off” state ratings. Quite a few publications did not provide detailed information on this topic.

Widely accepted tools were used for the clinical assessment of the participants. The MDS-UPDRS and its sub-scores were utilised to rate the clinical symptoms of PD patients. This scale was also predominantly applied in previous studies.
PD patients were not distinguished in PIGD- and TD-phenotypes according to Stebbins et al. (26). Jankovic et al. (25), however, found that the PIGD phenotype was associated, for instance, with more postural and gait difficulties, body bradykinesia, intellectual impairment and depression than the TD phenotype. WMH in non-PD populations are associated with similar symptoms (180,185,187,189) and Bohnen and Albin have suggested an effect of concurrent WMH on clinical presentation in PD patients (212). Hence, it is conclusive that several studies have shown that the PIGD phenotype is associated with a higher WMH burden than non-PIGD phenotypes (204,238,259,263,273,275,283). As a consequence, future studies should consider differentiating between different clinical PD phenotypes. Moreover, exploring the relation between different WMH locations and PD phenotypes could deliver further pathophysiological insight.

Considering that up to 25% of PD patients suffer from PD-MCI already in Hoehn and Yahr stage 1 (12) and dementia prevalence in PD patients generally ranges around 24.5 to 31.1% (11), general cognitive status in this PD population was relatively well preserved (mean and median MMSE 28 points, 87.9% ≥ 27 points, lowest score 18), even though dementia was no exclusion criterion as in many other studies (205,237,248,274,292). The good cognitive status of this population could also be a consequence of the primarily ambulatory setting of patient

inclusion. Moreover, patients with a MMSE ≤ 24 points required a solicitor to sign the consent form, which might have represented a barrier for these patients to be regarded for the cohort.

In this study, MMSE score and CERAD scores were used to evaluate the cognitive status in PD patients. In the current literature, a wide variety of neuropsychologic tests and assessments tools has been applied (see also Tables 10 and 11). Moreover, many studies grouped the patients in demented or non-demented individuals. For this purpose, furthermore, different criteria have been in use over the course of time. These methodical differences represent further plausible causes for inhomogeneous study results and hamper comparability. A clear stratification in PD-IC, PD-MCI and PDD patients according to published MDS criteria (27,29) could have allowed a more direct comparison to the results of other studies in this case.

The relation between cardiovascular risk factors/disease and WMH in the general population is underlined by many studies (34,39,94,158,159,163). Similar results, at least for certain risk factors, were found in PD patients in some cases (232,251,256,270,275,291). It seems, however, that the part of publications failing to show an association between WMH and cardiovascular risk factors or disease in PD patients (230,233,236,240,242,244,258,265) slightly prevails. In some populations, prevalence of cardiovascular risk factors was even higher in healthy controls than in PD patients (242) or higher cardiovascular risk was related to a higher WMH burden in healthy controls but not in PD patients (265). However, several publications (207,265,268,274,278,294) listed the presence of vascular risk factors or of severe vascular disease like stroke as exclusion criteria, which could bias the effect of WMH in PD patients and therefore explain some of the heterogeneity of study results. It has been shown, apart from this, that more severe WMH in PD patients are associated with nocturnal hypertension (244) and orthostatic hypotension (241,266), which might be caused by cardiovascular autonomic dysfunction (244). Gathering information on cardiovascular risk factors and neurocirculatory dysfunctions in PD patients could provide new insights into the pathophysiology of WMH in PD patients in future studies.

4.1.2 Imaging

As in the preponderant majority of the studies reviewed herein, FLAIR sequences were used to evaluate the extent of WMH. This imaging technique enabled a very clear depiction and distinction of WMH in most cases. Even small, periventricular and perisulcal WMH were generally easily definable, as described elsewhere (44,51). A drawback of this technique, however, are its relatively long acquisition times (44,45,47). As a result, movement artefacts hampered assessment and delineation of WMH in some patient's MR images. This might have led to an over- or underestimation of WMH volume in those few cases since either artefacts could have been mistaken for WMH or smaller WMH might not have been detected properly.

Another factor that might contribute to heterogenous findings concerning WMH in PD patients in the literature are the different field strengths used for image acquisition. While early investigations mostly used 1.5 T scanners, studies published in the last decade were performed with 3.0 T scanners for the most part. Moreover, some studies cited in Tables 10 and 11 used scanners with different field strengths or did not provide any information on field strength. By providing better image quality and hence easier and more precise WMH assessment, the usage of higher field strengths might have an influence on both the visual and volumetric rating of WMH extent. The present study was conducted with a 3.0 T scanner.

DTI methods were not used in this study, hence literature specifically covering this field was not reviewed. De Schipper et al (271), however, additionally provided DTI data in their publication and found no difference in white matter microstructural parameters (FA, MD, MTR) between PD patients and healthy controls even though PD patients had a higher WMH burden.

4.1.3 Assessment of WMH

A semi-automated, threshold-based, volumetric technique was used for identifying and delineating regions of interest (i.e., PVH and DWMH) in this study. Advantages of this method are that it enables a very accurate, fairly objective determination of WMH volume free of ceiling effects and that it is also easily applicable for measuring WMH progression (73). The threshold-based

identification of regions of interest per se was fast and easy to implement. In lesions where this method did not produce satisfying results, however, manual delineation of WMH, especially of thin or low-volume ones, in several section planes was quite time-consuming and, due to technical constraints, partially imprecise. However, this manual correction compensated for inaccuracies of threshold-based lesion selection, which were in some cases gross and might have passed unnoticed in a fully automated method. Having said this, the manual selection of lesions in the first place and even more their manual delineation might have led to a certain loss of objectivity compared to a fully automated method. Manual delineation was especially problematic in the case of thin hyperintensities alongside the lateral walls of the ventricles (equivalent to “pencil-thin lining”). This issue was greatly aggravated in a few patient’s MR images by movement artefacts. Selection of lesions in the deep white matter, on the other hand, usually could be performed without greater issues. Furthermore, periventricular and deep white matter hyperintensities tended to merge in the regions of the frontal and occipital horns in severe cases. Hence, establishing a clear-cut demarcation between periventricular and deep white matter lesions was problematic and somewhat arbitrary in those instances. Moreover, other lesions might have been falsely classified as WMH. This could happen, e.g., if only the hyperintense rim of a lacune but not the lacune itself is depicted in a single section plane (due to the predetermined slice thickness). Despite these minor drawbacks and sources of errors, this method was, in summary, particularly flexible, and it provided an exact and reasonably objective quantification of WMH burden.

As demonstrated in Tables 10 and 11, a variety of rating scales and quantitative methods has been used for the assessment of WMH. Even though these methods have been shown to correlate (62,73), this wide variety could very likely be a major factor contributing to the heterogeneity in research results. The increased use of volumetric, quantitative methods in recent years could improve inter-study comparability. However, this might compromise comparability to older studies only utilising visual rating techniques. While visual rating scales are limited by ceiling effects and relatively wide categories, they are cost effective, independent of post-processing techniques and, in the hands of a trained rater, quick (73). For this present study, each slice of a patient’s MR image was processed manually for

semi-automated quantification. Hence, in my opinion, the additional time required for a simultaneous implementation of a visual rating scale like the Fazekas scale probably would have been acceptable. Such a bimodal approach might guarantee the best possible comparability to both past and future studies.

4.2 Results

4.2.1 WMH volumes

White matter hyperintensities were highly prevalent in this study population: All PD patients (mean age of 62.9 years) and healthy controls (mean age of 63.0 years) showed WMH at least to a minimal degree. Previous studies (31,34) have shown that WMH are very frequently found in healthy elderly individuals, too. In younger, healthy populations, however, the prevalence of WMH is lower (38). Consistently, both studies in general populations (32,37) and PD populations (203-205,236,242,248,249,261,266,271,275-277,285,286,291) have shown an increase of WMH burden with age. Further corroborating these results, in this study we found close positive correlations between WMH volumes and age both in PD patients and healthy controls. Correlations with age were strong for all volumetric parameters in PD patients (total WMH volume: r_s=0.399; DWMH volume: r_s=0.338; PVH volume: r_s=0.399) as well as in HC (total WMH volume: r_s=0.379; DWMH volume: r_s=0.402; PVH volume: r_s=0.333). Consequently, age appears to be one of the strongest risk factors for the presence of WMH not only in general but also in PD populations. However, it has to be kept in mind that possible confounders like cardiovascular risk factors and disease were not accounted for in this study.

In PD patients, mean and median total WMH volume amounted to approximately 6,93 mL/4,56 mL, with mean/median DWMH volume accounting for 1,65 mL/0,36 mL and mean/median PVH volume for 5,28 mL/3,80 mL, respectively. These volumes concur with results of previous studies (outlined in Table 12) and are located in the medium range of WMH volumes determined in these publications. The same applies to mean/median total WMH volume (5,60 mL/3,77 mL), mean/median DWMH volume (1,76 mL/0,50 mL) and mean/median PVH volume (3,83 mL/2,99 mL) in healthy controls.

Total, deep or periventricular white matter hyperintensity volume did not differ significantly between Parkinson's disease patients and healthy controls. This finding is consistent with the majority of previous studies (205,208,229,232,239,243,257,265,288,289,292), which failed to demonstrate a significant difference in WMH burden between PD patients and HC, too. Total and periventricular WMH volume, however, tended to be higher in PD patients than in HC. This difference, although statistically insignificant, should not pass unnoticed since several studies (206,207,254,258,271) have found a higher WMH burden in PD patients than in HC. Further research is needed to elucidate possible pathophysiological causes of these differences; a promising approach might be, in my opinion, to further research the role of neurocirculatory dysfunctions as mentioned in chapter 4.1.1.

While female sex was associated with a higher WMH burden in some studies in general (32,34) and PD populations (251), we did not find any significant differences in WMH volumes between males and females in inter- and intragroup comparisons. In their study including 268 de novo PD patients, Chung et al. (291) did not find any sex differences between patients with minimal WMH and moderate to severe WMH, either.

4.2.2 Correlation analyses with clinical parameters

We found no significant correlation between any WMH volume and disease duration in PD patients. While an early study found a significantly shorter disease duration in PD patients with PVH (207), this finding could neither be reproduced in other publications since (204,248,268,291) nor in this present study.
Similarly, we did not detect a significant correlation between WMH volumes and Hoehn and Yahr stage. However, higher WMH burden was related to higher Hoehn and Yahr stages in several precedent studies (204,207,238,268). The circumstance that our study population was characterised by relatively low Hoehn and Yahr stages and fairly short disease durations might have contributed to the lack of correlation in this case.

Neither total WMH, DMWH nor PVH volume correlated significantly with MDS-UPDRS total score or parts 1-4. Similarly, Acharya et al. (205) did not find a significant correlation between WMH score and total UPDRS score or UPDRS part

3 and Cioncoloni et al. (264) could not detect a significant difference in UPDRS part 3 score between PD patients with or without WMH. Nevertheless, the large majority of studies showed an increase in clinical symptoms overall and motor symptoms in particular with increasing WMH burden, evident as significant relations between (total) WMH volume/scores and UPDRS total score (204,236) or part 3 (204,238,240,242,256,268,291,292), respectively. The lack of correlations between WMH volumes and MDS-UPDRS total score and particularly the motor sub-score in this present study might also be due to the fact that we included ambulatory patients in mostly early Hoehn and Yahr stages. Possibly, the effect of WMH in PD patients on clinical motor symptoms only comes into effect in later stages of the disease. Moreover, we did not investigate possible correlations between WMH volumes and specific MDS-UPDRS items or clusters of items rating related symptoms. Piccini et al. (207), for example, found higher bradykinesia, postural instability and gait difficulty UPDRS scores in patients with PVH compared to those without PVH (207). Similarly, more recent studies reported significant relations between PVH and postural instability (271) or gait impairment (271,272). While Sohn and Kim (203) only found an association between higher gait score and WMH burden, Lee et al. (204) reported significant positive correlations of WMH with higher ratings of speech, facial expression, rigidity, bradykinesia and posture and gait items but not with tremor items. The study by Bohnen et al. (238) yielded comparable results: WMH correlated significantly with bradykinesia, axial, posture and speech difficulties but not with rigidity or tremor sub-scores. Another recent publication demonstrated higher ratings of the postural stability item in patients with WMH (264). Furthermore, some studies found significant positive correlations of frontal (251) or frontal and occipital (273) DWMH burden with axial motor features in general. In addition, freezing of gait was related to higher WMH loads in some studies (268,270,291), too. In summary, these results substantiate the possible role of WMH in the clinical manifestation of PD as the PIGD phenotype as discussed in chapter 4.1.1. Consequently, future studies should focus on the effect of WMH on specific motor symptoms rather than global scores of motor impairment.

WMH volumes did not correlate significantly with non-motor symptoms (NMS, MDS-UPDRS part 1) in our population. Studies investigating the effect of WMH on

non-motor symptoms other than cognitive dysfunction or depressive symptoms are relatively scarce. Lee and colleagues (204) found a significant positive correlation between WMH grade and UPDRS part 1. A more recent study reported more severe non-motor symptoms in patients with moderate or severe WMH compared to patients with no or only mild WMH (268); they found significant associations of moderate or severe WMH with NMS, PDQ-39, PDSS, BAI, NPI and PFS. Moreover, WMH severity correlated significantly with PDQ-39, NPI and PFS (268). Ham et al. (258) reported a significant negative correlation between DWMH and olfactory performance. Chung et al. (291), however, did not find a difference in the Cross-Cultural Smell Identification Test between patients with moderate to severe and minimal WMH. Furthermore, an early study by Kraft and colleagues (227) failed to prove a difference in WMH score between PD patients with or without visual hallucinations.

Data on the possible role of WMH in the manifestation of depression or depressive symptoms in PD patients is sparse and diverging. Petrovic et al. (239) found a higher frequency of total and frontal DWMH and PVH in PD patients with depression compared to those without; moreover, depressed patients were characterised by higher PVH scores and PVH total score was independently associated with HDRS (239). Two other studies (242,268) reported a significant positive correlation between WMH burden and BDI. Opposingly, Jones and colleagues (265) did not find a significant correlation of WMH volume with BDI-II or other measures of mood and Chung et al. (291) could not detect a difference in BDI between PD patients with moderate to severe or minimal WMH, respectively. In accordance with the latter findings, we could not reproduce significant correlations of total, deep or periventricular WMH with symptoms of depression either. The fact that we utilised a different assessment tool (the Geriatric Depression Scale) should not pose an issue since previous studies reported diverging results even though they all primarily used the BDI. Reasons for the heterogenous results might be differences in demography and cognitive performance between the study populations. One explanatory approach might be that Jones and colleagues excluded patients with severe cognitive impairment (265), the study population in the publication by Chung and colleagues consisted of de novo PD patients (291), and this present study population was characterised

by a relatively well preserved cognitive function, too. However, also two out of three studies showing an association between WMH and depressive symptoms excluded patients with severe cognitive impairment (239,268). In addition, Meyer et al. (232) reported that PD patients with vascular features, like a history of TIA/stroke or presence of cardiovascular risk factors, had both more severe WMH and depressive symptoms than the patients without such vascular features (232). This finding somewhat substantiates the “vascular depression hypothesis” briefly discussed in chapter 1.2.7. In conclusion, further research is required to elucidate the role of WMH in the expression of depressive symptoms in PD patients and the effect of comorbid cardiovascular disease.

A few studies explored the effect of WMH on the response of parkinsonian symptoms to levodopa. Sohn and Kim (203) found that bradykinesia symptoms (finger taps, hand movements, rapid alternating hand movements, leg agility, body brady- and hypokinesia) in PD patients with WMH responded less to a single dose of levodopa/benserazide than in those without WMH (203). In the study by Arena et al. (260), higher DWMH scores correlated negatively with responsiveness of UPDRS axial impairment scores (comprising global spontaneous movements, posture, postural stability, freezing of gait, gait, arising from a chair, neck rigidity, facial expression, speech) to levodopa (260). In a recent publication, the patients with moderate to severe WMH required higher dosages of dopaminergic medications than those with minimal WMH in order to control PD symptoms (291). Jones et al. (265), on the other hand, could not detect a significant correlation between LED and total WMH volume. In our study population, we could not establish a significant correlation between levodopa requirement (measured in LED) and any WMH volume, even though nearly four fifths (78.0 %) of our patients regularly used dopaminergic drugs. There was, however, a trend towards a positive correlation between DWMH volume and LED ($p=0.079$). Furthermore, we did not investigate the effect of WMH on levodopa doses required to control specific parkinsonian symptoms, especially bradykinesia or axial impairment. As might be expected, there were significant positive correlations between LED and disease duration, MDS-UPDRS total score and parts 1-4, Hoehn and Yahr stage and Non-Motor Symptoms Questionnaire. LED did not correlate significantly with GDS or cognitive scores.

Evidence is strong and consistent that white matter hyperintensity burden is related to cognitive dysfunction in PD patients. Numerous cross-sectional studies reported an increase of total WMH burden from PD-IC to PD-MCI and PDD, respectively (236,242,246,247,250,255,270,282), and several longitudinal studies have shown that baseline WMH burden is a risk factor for cognitive decline (280-282,288,291,293). In some populations, both DWMH and PVH independently were higher in PD patients with poorer cognitive status (229,247,267). Others specifically found either a higher DWMH (249), PVH (255) or parieto-occipital (285) WMH burden in PD-MCI or PDD patients. Only few studies (232,233,257,278) failed to detect an increase of WMH loads from PD-IC to PD-MCI and PDD or from PD-MCI to PDD, respectively. In this present study, we did not stratify our study population into distinct groups according to cognitive status (i.e., PD-IC, PD-MCI, PDD). Hence, comparability to these publications cited above is somewhat hampered. Considering that mean and median MMSE score was 28 and that 96,4% of patients had a MMSE score of 24 points or higher, the majority of patients would have probably fallen into the categories of PD-IC or PD-MCI. Nevertheless, we found significant negative correlations between MMSE score and total (r_s=-0.234), deep (r_s=-0.215) and periventricular (r_s=-0.210) white matter hyperintensity volume. We did, however, not correct these correlations for age, which correlated significantly with both cognitive scores and WMH volumes and hence might confound our results to a certain degree. Nonetheless, several other studies found associations or correlations between MMSE and total (236,240,242,249), deep (229) or parieto-occipital (285) WMH, too. These results are substantiated by publications reporting significant correlations between WMH and other tools measuring global cognition (208,263,268). Only few studies failed to show significant relations between total (277,278) or deep (266) WMH and MMSE score in PD populations. However, two of those (266,278) found associations of WMH to poorer performance in more specific cognitive domains instead. There are, to my best knowledge, only very few studies (265,277) who could not relate WMH to any sort of cognitive dysfunction or decline in PD patients; moreover, Burton et al. (277) only performed analyses in a small population consisting of HC, PDD, DLB and AD patients.

Apart from assessing global cognitive status with the MMSE, we also performed more sophisticated neuropsychological testing in our study population by means of the CERAD neuropsychological test battery and calculating CERAD total and memory scores (see chapter 2.3). We found strong negative correlations between total/deep/periventricular WMH volumes and both CERAD-TS1 (r_s=-0.323/-0.328/-0.313) and CERAD-TS2 (r_s=-0.341/-0.337/-0.332) in PD patients. Moreover, we also found a significant correlation between increasing total/deep/periventricular WMH volume and poorer performance on tests of memory, assessed as the CERAD memory score (r_s=-0.301/-0.276/-0.300). This result is in line with several other studies reporting significant relations between higher WMH burden and worse performance on tests of memory (208,236,247,274,288). Aside from memory performance, we did not, however, separately look into other cognitive subdomains. Numerous studies reported negative correlations or associations between higher total or, in one case (249), only deep WMH and poorer performance in tests of attention (237,270), executive functions (247,249,292), or both (208,236,240). Several studies specifically showed negative correlations between WMH and poorer results in semantic/verbal fluency tests (236,237,249,258,278) or the FAB (237,266,268). Furthermore, negative correlations were found between WMH burden and lower scores in tests of visuospatial function (208,236,271). Apart from that, deficits in tests of language (236,247) or orientation (249) were related to increased WMH in some populations, too. Most of these results regarding cognitive subdomains refer to total WMH volumes; Wang et al. (249) and Ten Harmsen et al. (266) only found significant correlations with DWMH but not PVH, Ham et al. (258) with total and deep WMH, and one study (278) referred to frontal WMH. In summary, WMH have been shown to correlate with poorer performance across a wide range of cognitive domains in PD patients. Analysing the effects on different cognitive subdomains of WMH, especially if differentiated according to their localisation, could provide further insight into pathophysiological mechanisms of cognitive deterioration in PD patients. Taking into consideration the well documented relations between WMH and cognitive deterioration in both PD and general populations, observing and managing the risk factors for the development of WMH (as discussed in chapter 1.2.3) appear to be particularly recommendable in patients suffering from Parkinson's disease. However, since the effect of cardiovascular risk factors on

WMH in PD patients is not fully elucidated yet, more research is needed in this field. Nonetheless, possible therapeutic approaches, as briefly addressed in chapter 1.2.8, might include antihypertensive treatment, statins and lifestyle interventions like physical exercise and weight loss. Research is also needed to evaluate the effect of WMH risk factor management in PD patients.

4.3 Conclusions

In conclusion, research results concerning WMH in PD patients are overall quite heterogenous. In our study, however, we were able to further substantiate the evidence that WMH volumes do not differ significantly between Parkinson's disease patients and healthy controls. Regarding subjects included, this cross-sectional study is one of the largest in this field, yet. Nevertheless, unlike many previous papers we could not find significant correlations of WMH with motor impairment or non-motor symptoms other than cognitive dysfunction. This might be due to our relatively young study population in rather early disease stages. Moreover, we only looked into global scores of motor impairment or non-motor symptoms. Further studies should rather focus on the effect of WMH on specific motor and non-motor items.
Furthermore, we demonstrated that increased WMH volume, irrespective of its exact location, correlates with both higher age and poorer cognitive performance in PD patients. Hence, possible risk factors for the development of WMH should be minded carefully and, if possible, eliminated. Future studies should evaluate the effect of WMH risk factor management in PD patients.

5 References

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