

Presenting symptoms, biomarkers and underlying brain changes in pre-dementia Lewy body and Alzheimer's disease

Eirik Auning



Faculty of Medicine, University of Oslo

Department of Geriatric Psychiatry, Akershus University Hospital

2014

© Eirik Auning, 2015

*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 2076*

ISBN 978-82-8264-988-9

All rights reserved. No part of this publication may be reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard.
Print production: John Grieg AS, Bergen.

Produced in co-operation with Akademia Publishing.
The thesis is produced by Akademia Publishing merely in connection with the thesis defence. Kindly direct all inquiries regarding the thesis to the copyright holder or the unit which grants the doctorate.

“ Our knowledge
is a little island
in a great ocean of
nonknowledge ”

Isaac Bashevis Singer

Contents

Acknowledgement	8
List of publications	9
Abstracts of the publications	10
List of other publications	12
Abbreviations	13
1.0 Clinical definitions	15
1.1 Cognitive impairment	15
1.2 Pre-dementia, pre-clinical, prodromal	15
1.3 Mild cognitive impairment	15
1.4 Subjective cognitive impairment	17
1.5 Activities of daily living	17
1.6 Dementia	17
1.7 Depression	19
1.8 Biomarker	20
2.0 Overarching themes	22
3.0 Lewy body disease	24
3.1 Introduction	24
3.2 Dementia with Lewy bodies (DLB)	25
3.2.1 Clinical criteria	25
3.2.2 Molecular pathology	27
3.2.3 Neuropathology	28
3.2.4 Diagnosis	30

3.2.5	The prevalence and incidence of DLB	32
3.2.6	Clinical features preceding DLB	33
3.2.7	Genetic contributions in DLB	35
3.2.8	Potential biomarkers in DLB	35
3.3	Parkinson's disease (PD)	39
3.3.1	Introduction	39
3.3.2	Diagnostic criteria	39
3.3.3	Pathogenesis	41
3.3.4	Clinical features	41
3.3.5	Treatment of motor symptoms	42
3.3.6	Cognitive impairment	42
3.3.6.1	The prevalence and incidence of PD dementia (PDD)	42
3.3.6.2	Mild cognitive impairment in PD	42
3.3.6.3	Variations in the course of cognitive impairment in PD	44
3.3.6.4	Clinical risk factors for early cognitive decline in PD	44
3.3.6.5	Genetic contributions to cognitive impairment in PD	44
3.3.6.6	Biomarkers predicting cognitive impairment in PD.....	45
3.4	Treatment/management of DLB and PDD.....	53
3.4.1	Introduction	53
3.4.2	Cognitive impairment	53
3.4.3	Motor symptoms	53
3.4.4	Neuropsychiatric symptoms	53
3.4.5	Sleep problems	53
3.4.6	Autonomic dysfunction	54

3.4.7 Non-pharmacological treatment	54
4.0 Alzheimer's disease	55
4.1 Introduction	55
4.2 Prevalence and incidence of Alzheimer's disease	55
4.3 Diagnostic criteria	56
4.4 Pathogenesis	56
4.5 Clinical features	59
4.5.1 Cognitive impairment	59
4.5.2 Neuropsychiatric symptoms	59
4.5.3 Somatic symptoms	60
4.6 Biomarkers in Alzheimer's disease	61
4.6.1 Genetics	61
4.6.2 Structural MRI	62
4.6.3 Cerebrospinal fluid (CSF)	63
4.6.4 PET based imaging	63
4.6.5 Conclusion	64
4.7 Treatment	64
5.0 Depression in the elderly	68
5.1 Introduction	68
5.2 Late life depression	69
5.3 Risk factors, prevalence and incidence of depression	69
5.4 Biomarkers of depression in the elderly	73
5.5 Depression and cognitive impairment	74
5.6 Treatment	76

6.0 Aims of the study	78
7.0 Methods	79
7.1 Design	79
7.2 The subjects	79
7.2.1 DemVest study	79
7.2.2 MCI-study Ahus	79
7.3 Diagnostic procedures and clinical assessment	81
7.3.1 DemVest-study	81
7.3.2 MCI-study Ahus	81
7.4 Biomarkers for the Ahus cohort (paper 2 and 3).....	82
7.4.1 Cerebrospinal fluid	82
7.4.2 FluoroDeoxyGlucose - Positron Emission Tomography (FDG-PET)	82
7.4.3 Dopamine Transporter Scan	83
7.4.4 Magnetic resonance imaging	83
7.4.5 Neuropsychological assessment	83
7.5 Statistics	84
7.6 Ethical considerations	84
8.0 Discussion	86
8.1 Main findings	86
8.2 Paper 1	86
8.3 Paper 2	89
8.4 Paper 3	93
8.5 Methodological issues and limitations	97

8.6 Conclusions and future directions for research	98
9.0 References	100
10.0 Papers I-III	

Acknowledgement

I am grateful for this opportunity given me to immerse myself in research and to be able to submit this thesis.

It all started when my main supervisor, Dag Årslund, appeared “out of nothing” and asked why I was not already involved in research. Dag's long track record and standing in the field of dementia and geriatric psychiatry research made the choice easy, an opportunity not to be missed. Furthermore, Dag's enthusiasm, drive and encouragement made me quickly realize that a Ph.D. degree was achievable and that completion largely relied upon my own effort and dedication. Although not always present in person, he was easily available by mail, phone or Skype, giving clear advice and direction on how to proceed when needed. Additionally, I have learned from his remarkable ability to build professional relations with collaborating researchers and research groups.

Similarly, I have been fortunate to come in contact with my co-supervisor, Tormod Fladby, head of the Neurology clinic at Ahus and a renowned dementia researcher. He has over the years established a competent research group at Ahus and is currently leading several multicenter projects. I extend my gratitude to him and my good colleagues at the Neurology clinic. Furthermore, I would like to thank all my fellow co-writers at collaborating hospitals and institutions.

I am also indebted to my superior Terje Røst, the head of the Department of Geriatric Psychiatry at Ahus, who has established research as a key priority in our department's strategic plans. Without his support it would not have been possible to complete this thesis. Furthermore, I would also like to extend my appreciation to Lisbeth Kristoffersen, the leader of the Geriatric Psychiatry outpatient clinic, for giving me the necessary flexibility to combine research and clinical work.

I would like to thank my family for invaluable support in this process and for being patient and understanding during periods of heavy work. Especially my wife, Marit, deserves credit as the accepting and easygoing person she is.

Finally, I am grateful to all patients and caregivers who have participated in this study. Hopefully it was not all sacrifice, but also of some benefit to the individual.

This dissertation was financed by the Department of Geriatric Psychiatry, Ahus, and a grant from the University of Oslo, Institute of clinical medicine, Ahus campus.

List of publications

1. Auning E, Rongve A, Fladby T, Booij J, Hortobágyi T, Siepel FJ, Ballard C, Aarsland D. Early and presenting symptoms of dementia with Lewy bodies. *Dement Geriatr Cogn Disord*. 2011;32(3):202-8.
2. Auning E, Krohn Kjærvi V, Selnes P, Aarsland D, Haram A, Bjørnerud A, Hessen E, Esnaashari A, Fladby T. White matter integrity and cognition in Parkinson's disease. *BMJ Open* 2014;4(1)e003976.
3. Auning E, Selnes P, Grambaite R, Šaltytė Benth J, Haram A, Løvli Stav A, Bjørnerud A, Hessen E, Hol PK, Muftuler løndalen A, Fladby T, Aarsland D. Neurobiological correlates of depressive symptoms in people with subjective and mild cognitive impairment. *Acta Psychiatr. Scand*. **131**, 139-147.

Abstracts of the publications

Paper 1: Early and presenting symptoms of dementia with Lewy bodies

Background/Aims:

To explore the presenting and early symptoms of dementia with Lewy bodies (DLB).

Method:

Patients with mild dementia fulfilling diagnostic criteria for DLB (n = 61) and Alzheimer's disease (AD) (n = 109) were recruited from outpatient dementia clinics in western Norway. At diagnosis, caregivers were asked which symptom had been the presenting symptom of dementia.

Results:

Caregivers reported that memory impairment was the most common presenting symptom in DLB (57%), followed by visual hallucinations (44%), depression (34%), problem solving difficulties (33%), gait problems (28%), and tremor/stiffness (25%). In contrast, 99% of AD caregivers reported impaired memory as a presenting symptom, whereas visual hallucinations were a presenting symptom in 3% of the AD cases.

Conclusion:

DLB should be suspected in pre-dementia cases with visual hallucinations.

Paper 2: White matter integrity and cognition in Parkinson's disease: a cross-sectional study

Objective:

We used diffusion tensor imaging (DTI) to test the following hypotheses: (1) there is decreased white matter (WM) integrity in non-demented Parkinson's disease (PD), (2) WM integrity is differentially reduced in PD and early Alzheimer's disease (AD) and (3) DTI changes in non-demented PD are specifically associated with cognitive performance.

Methods:

This study included 18 non-demented patients with PD, 18 patients with mild cognitive impairment due to incipient AD and 19 healthy elderly normal control (NC) participants in a cross-sectional design. The participants underwent DTI, and tract based spatial statistics was used to analyze and extract radial diffusivity and fractional anisotropy. Correlations between scores from a battery of neuropsychological tests and DTI were performed in the PD group.

Results:

Patients with PD had significant differences in DTI in WM underlying the temporal, parietal and occipital cortex as compared with NC. There were no significant differences between the PD and AD groups in the primary region of interest analyses, but compared with NC there was a tendency for more anterior changes in AD in contrast to more posterior changes in PD. In a secondary whole-brain analysis there were frontoparietal areas with significant differences between AD and PD. In patients with PD, there were significant correlations between DTI parameters in WM underlying the prefrontal cortex and executive and visuospatial abilities.

Conclusions:

In early, non-demented PD we found reduced WM integrity underlying the temporal, parietal and occipital cortices. In addition, WM integrity changes in prefrontal areas were associated with executive and visuospatial ability. These findings support that DTI may be an important biomarker in early PD, and that WM changes are related to cognitive impairment in PD.

Paper 3: Neurobiological correlates of depressive symptoms in people with subjective and mild cognitive impairment

Objective

To test the hypothesis that depressive symptoms correlate with Alzheimer's disease (AD) type changes in CSF and structural and functional imaging including hippocampus volume, cortical thickness, white matter lesions, Diffusion Tensor Imaging (DTI) and **Fluoro-Deoxy-Glucose Positron Emission Tomography** (FDG-PET) in patient with subjective (SCI) and mild (MCI) cognitive impairment.

Methods

In 60 patients depressive symptoms were assessed using the Geriatric Depression Scale. The subjects underwent MRI, 18F-FDG PET imaging and lumbar CSF extraction.

Results

Subjects with depressive symptoms (n=24) did not have more pathological AD biomarkers than non-depressed. Uncorrected there were trends towards larger hippocampal volumes ($p=0.06$), less orbital WM damage measured by DTI ($p=0.10$) and higher orbital glucose metabolism ($p=0.02$) in the depressed group. The findings were similar when SCI and MCI were analyzed separately.

Similarly, in patients with pathological CSF biomarkers (i.e. pre-dementia AD, n=24), we found that correlations between scores on GDS and CSF A β 42 and P-tau indicated less severe AD-specific CSF changes with increasing depression.

Conclusion

Depressive symptoms are common in SCI/MCI, but are not associated with pathological imaging or CSF biomarkers of AD. Depression can explain cognitive impairment in SCI/MCI or add to cognitive impairment leading to an earlier clinical investigation in pre-dementia AD.

List of other publications

1. Aarsland D, Auning E, Buter T. DaTSCAN in early diagnosis of dementia with Lewy bodies: reviewing the evidence. *Dementia Europe*, issue 3, 2011.
2. Auning E, Krohn Kjærvik, Aarsland D. Kognitiv svikt hos pasienter med Parkinson's sykdom. *Best Practice*, nr. 6, mai 2011.
3. Rongve A, Auning E, Aarsland D. Forekomst og risikofaktorer ved demens. *Medisinsk informasjon*, (3) 2011.
4. Rongve A, Auning E, Ehrst U, Aarsland D. Psykose ved Parkinson's sykdom. *Tidsskr Nor Laegeforen*. 2012 Jan 24;132(2):155-8.
5. Auning E, Rongve A, Aarsland D. Tidlige symptomer ved demens med Lewy-legemer. *Best Practice*, nr. 10, mai 2012.
6. Auning E, Rongve A, Aarsland D. Parkinson's disease dementia and dementia with Lewy bodies – epidemiology, risk factors and biomarkers. *Norsk epidemiologi*, (2)22:2012.
7. Selnes P, Aarsland D, Bjørnerud A, Gjerstad L, Wallin A, Hessen E, Reinvang I, Grambaite R, Auning E, Kjærvik VK, Due-Tønnessen P, Stenset V, Fladby T. Diffusion tensor imaging surpasses cerebrospinal fluid as predictor of cognitive decline and medial temporal lobe atrophy in subjective cognitive impairment and mild cognitive impairment. *J Alzheimers Dis*. 2013;33(3):723-36.
8. Grambaite R., Hessen E., Auning E., Aarsland D., Selnes P., Fladby T. Correlates of subjective and mild cognitive impairment: depressive symptoms and CSF biomarkers. *Dement Geriatr Cogn Dis Extra*. 2013;3(1):291-300.
9. Rongve, Arvid; Auning, Eirik; Haram, Astrid; Aarsland, Dag. Dementia in Parkinson's Disease. I: Tröster A (Editor). *Clinical Neuropsychology and Cognitive Neurology of Parkinson's Disease and Other Movement*. Oxford University Press 2014 ISBN 978-0-19-981237-0.
10. Haram, Astrid; Hessen, Erik; Auning, Eirik; Stav, Ane Løvli; Boeve, Bradley F.; Eliassen, Carl F Andestad; Rugland, Eyvind; Esnaashari, Abdolreza; Fladby, Tormod & Aarsland, Dag (2014). Clinical Correlates of RBD in Early Parkinson Disease. *Journal of Alzheimers Disease & Parkinsonism*. ISSN 2161-0460.
11. Stav, Ane Løvlie; Aarsland, Dag; Johansen, Krisztina Kunszt; Hessen, Erik; Auning, Eirik; Fladby, Tormod (2015). Amyloid- β and α -synuclein cerebrospinal fluid biomarkers and cognition in early Parkinson's disease. *Parkinsonism and related disorders* in print.

Abbreviations and definitions

A β	Amyloid Beta
ADL	Activities of daily living
AD	Alzheimer's disease
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy bodies
DR	Radial diffusivity
DTI	Diffusion tensor imaging
GWAS	Genome wide association study
FA	Fractional anisotropy
FDG-PET	Fluorodeoxyglucose- positron emission tomography
ICD-10	International classification of diseases 10 th edition
LB	Lewy bodies
Lewy body dementia	Clinical diagnosis. Includes DLB and PDD
Lewy body disease	Pathological diagnosis. Includes PD, DLB and PDD
LDD	Late life depression
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PDD	Parkinson's disease dementia
MCI	Mild cognitive impairment, i.e. objectively measured cognitive impairment, but only slight reduction in ADL (no dementia).
MMSE	Mini Mental State Examination

PET	Positron emission tomography
P-tau	Phospho-tau
ROI	Region of interest
RBD	REM sleep behavior disorder
SCI	Subjective cognitive impairment, i.e. subjective complaints, but intact cognition and ADL.
SD	Standard deviation
SPECT	Single Photon Emission Computed Tomography
TBSS	Tract-based spatial statistics
T-tau	Total-tau
UPDRS	Unified Parkinson's disease Rating Scale
VH	Visual hallucinations
WM	White matter
WML	White matter lesions

1.0 Clinical definitions

1.1 Cognitive impairment

The word “cognition” comes from the Latin (and partly Greek) verb “cognosco” which can be translated to “with knowledge”. In a broader sense the concept of cognition involves higher mental processes including reasoning and problem-solving ability, memory, attention, orientation and language. Cognitive impairment refers to deficits in a person's ability to execute these mental processes by various reasons.

1.2 Pre-dementia, pre-clinical, prodromal

The pre-dementia stage is understood as the phase where the degenerative process has begun, but where cognitive impairment is too mild to meet established criteria for dementia (**Textbox 4**). The pre-dementia phase can further be subdivided in a pre-clinical phase where no clinical signs of neurodegenerative disease are evident and a pre-dementia clinical phase where only slight symptoms have emerged. The latter term is equivalent to *a prodrome*, or prodromal symptoms, which originates from the Greek word prodromos (precursor) and means early, often non-specific symptoms of disease.

The pre-dementia phase has long been unrecognized and seen as unimportant. Recent evidence strongly suggest that dementia subtypes, including Alzheimer- and Lewy body disease, may start decades before onset of obvious signs of cognitive impairment and that other symptoms, including depression and affection of the peripheral and autonomic nervous system, can be prodromal signs of disease.

This new insight has urged a reclassification of the traditional concept of dementia (see section 1.6).

1.3 Mild cognitive impairment

The term mild cognitive impairment (MCI) is now widely accepted as a state encompassing the earliest features of cognitive impairment before functional impairment is evident (only slightly impaired) with an increased risk of a later conversion to dementia (Petersen *et al.*, 2009). The first MCI criteria (Petersen *et al.*, 1999), focusing on AD, defined MCI as a state of memory complaints, objective measured memory impairment, essentially normal performance in other cognitive domains and with preserved Activities of Daily Living (ADL-) functions (not demented) (see section 1.5). A later revision and broader conceptualization by Winblad *et al.* (Winblad *et al.*, 2004), emphasized that patients with MCI could also convert into other dementia subgroups, not only AD, and that other cognitive domains than memory could be affected. The Winblad criteria broadly divide MCI in amnesic (affection in the memory domain only) and non-amnesic (affection of other domains than memory, i.e. language, executive or visuospatial ability and attention) and further in single or multiple domains (**textbox 1**).

The prevalence of MCI has recently been estimated to about 14-18 % in people 70 years or older (Petersen *et al.*, 2009), and the annual dementia conversion rate is about 10-15 % from

referral sources including memory clinics. In epidemiological studies, the conversion rates are lower and in the 6-10 % range per year (Petersen *et al.*, 2009). The different conversion rates in different clinical settings emphasize an important issue in trying to define at risk populations; although MCI is believed to be a prodrome of dementia, it is a heterogeneous concept constituting other conditions including normal aging, depression or other brain disorders and cognitive impairment may not progress and can even be reversible (**text box 2**).

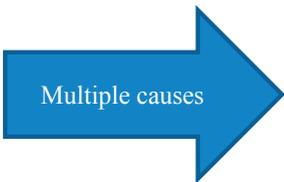
Text box 1:

General criteria for mild cognitive impairment (MCI) (Winblad et al. 2004)

1. Not normal, not demented (Does not meet criteria (DSM IV, ICD 10) for a dementia syndrome)
2. Cognitive decline
 - Self and/or informant report and impairment on objective cognitive tasks and / or
 - Evidence of decline over time on objective cognitive tasks
3. Preserved basic activities of daily living / minimal impairment in complex instrumental functions

Text box 2:

Heterogeneity of the clinical presentation of mild cognitive impairment (MCI) and potential multiple etiologies (Winblad et al. 2004)

<p><u>Clinical presentations:</u></p> <p>MCI amnesic, single domain MCI amnesic, multiple domains</p> <p>MCI non-amnesic, single domain MCI non-amnesic, multiple domains</p>	 <p>Multiple causes</p>	<p><u>Possible etiologies :</u></p> <p>Degenerative Vascular Metabolic Traumatic Psychiatric Other ?</p>
--	--	--

1.4 Subjective cognitive impairment

In an effort to select patients even earlier in the disease process and before irreversible signs of disease are evident, the term subjective cognitive impairment (SCI) has recently been suggested as a pre-MCI stage, a condition with only subjective and subtle cognitive impairment on a SCI-MCI-dementia continuum (Reisberg and Gauthier, 2008). This state is even more heterogeneous than the MCI stage, but still with higher dementia conversion rates than the base annual incidence rates of AD and other dementias of around 1-2 % (Mayeux and Stern, 2012; Mitchell *et al.*, 2014).

Due to the lack of common standards in defining patients with SCI and an attempt to define consensus on terminology, a conceptual framework including research criteria for subjective cognitive decline (a proposed new term replacing SCI) in pre-MCI has recently been proposed (Jessen *et al.*, 2014).

This new way of defining at risk populations has opened up the field to substantial research efforts including implementation of various biomarkers for diagnostic purposes and monitoring of medical trials (see also sections 3.2.8, 3.3.6.6 and 4.6).

1.5 Activities of daily living (ADL)

In the context of neurodegenerative brain disorders, one has traditionally equated the term cognitive impairment and “dementia”, which indicates a rather advanced disease stage including impaired ADL (**text box 3**). ADL can be defined as routine activities that people do every day without the need for assistance. Basic ADLs include eating, dressing, bathing, toileting (continence) and walking (transferring).

Text box 3:

Definition of Activities of Daily Living (ADLs) (MedicineNet.com Medical Dictionary):

- ADLs refer to daily self-care activities within an individual's place of residence, in outdoor environments or both.

- ADLs include activities such as feeding ourselves, bathing, dressing, grooming, work, homemaking and leisure. The ability or inability to perform ADLs can be used as a very practical measure of ability/disability in many disorders.

1.6 Dementia

Dementia can be translated into being without “mind” or “sense” and has been known since antiquity. Before the beginning of modern dementia research around the 20th century, dementia encompassed all conditions causing severe mental disability, including psychiatric disorders and delirium caused by reversible somatic disease. Often it was equated with normal aging, hence the commonly used term “senile dementia”. Traditionally the term dementia refers to a

variety of conditions of different etiology and is as such a syndrome of cognitive decline where Alzheimer's disease (AD), Lewy body disease (LBD) and cerebrovascular disease are the most common causes. According to the World Health Organization's (WHO) international classification of diseases (ICD-10, 10th edition), dementia is characterized by memory loss, impairment of other cognitive functions including judgment, planning and reasoning, clear consciousness (as opposed to delirium), a decline in emotional control or motivation (including emotional lability, irritability, apathy and coarsening of social behavior) and impaired ADL-functions (**textbox 4**). To ensure that the symptoms are of a chronic nature, the duration must be at least 6 months. Of note, a few conditions are potentially reversible including vitamin deficiencies (vitamin B1, B2, B12), normal pressure hydrocephalus, encephalitis (Borelia, Lues,) and even drug side effects, and are thus per definition not dementia. The ICD-10 criteria are primarily based upon typical symptoms seen in AD. The prevalence of the five most common causes of dementia account for about 95 % of all cases and are listed in **table 1**.

Textbox 4:

Definition of the dementia syndrome according to the ICD-10 research criteria

1. Impairment of memory and other cognitive functions (judgment, planning, thinking, abstraction)

Mild: Decline in cognitive abilities affects a person's capacity to cope with everyday activities, but the individual is not dependent upon others.

Moderate: Decline in cognitive abilities makes the individual dependent upon others in daily living.

Severe: Decline in cognitive abilities makes the individual dependent on continuous care

2. Clear consciousness

3. Impairment in emotional control or motivation or change in social behavior in at least one of the following:

- Emotional stability
- Irritability
- Apathy
- Coarsening of social behavior

4. Duration of cognitive decline at least six months

In light of the past decades recognition of a pre-dementia phase and subsequent redefinition of the clinical characterization of cognitive disorders, the newly published fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has replaced the term "dementia" with "minor and major neurocognitive disorder". DSM-5 now recognizes that

dementia is on a continuum from MCI, in DSM-5 labelled “minor cognitive impairment”, an initial stage without significant changes in a person’s ability to manage ADL-functions to more profound deficits that interfere with independence, i.e. “major cognitive impairment”. This is an important distinction because it promotes attention also to early clinical features of dementia and encourages a higher research focus on pre-dementia stages.

DSM-5 also includes Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) (see section 3.0) for the first time, referring to it as "major or mild neurocognitive disorder with Lewy Bodies" and “major or mild neurocognitive disorder due to Parkinson's disease” respectively.

Accordingly, the new criteria focus less on memory and recognize that the different dementia subtypes have different presentations including deficits in other cognitive domains.

Table 1: Prevalence of different dementia subtypes (Aarsland et al. 2008)

Dementia subtype	Percentages of subjects having subtypes of dementia
Alzheimer's disease	60-70 %
Dementia with Lewy bodies	15-20 %
Vascular dementia	5-30 % (depending on definition)
Frontotemporal dementia	5-15 % (> 65 years of age; until 50% < 65 years of age).
Parkinson's disease dementia	3-6 %
Alcoholic dementia	2-10 %

1.7 Depression

Depression can refer to a symptom of low mood, but is also a clinical diagnosis fulfilling a set of operationalized criteria. The latter is an umbrella term for different mood (affective) disorders including major depression ,dysthymia, cyclothymia, recurrent brief depression, bipolar disorder and seasonal affective disorder. Mood disorders often accompany medical conditions and can be secondary to a diversity of disorders including organic brain disease, cancer, vitamin deficiencies and drug effects.

Diagnostic criteria for a major depressive episode (MDD) according to ICD- 10 (**text box 5**) consist of 3 key depressive symptoms and 7 associated symptoms. The three key symptoms are

1) persistent low mood or sadness, 2) loss of interest or pleasure and 3) fatigue, and at least two of them must be present most days, most of the time for at least two weeks. In addition the episode is not attributable to psychoactive substance use or an organic mental disorder. Associated symptoms are 1) sleep problems, 2) poor concentration or indecisiveness, 3) poor appetite, 4) suicidal thoughts, 5) agitation or retardation, 6) guilt or self-blame and 7) low self-esteem.

A major depressive episode is typically subdivided in mild, moderate and severe depression. A diagnosis of mild depression requires at least 4 symptoms (minimum 2 key symptoms), moderate depression at least 6 symptoms (minimum 2 key symptoms) and severe depression at least 8 symptoms (including all 3 key symptoms). Severe depression can be with or without psychotic symptoms. Minor depression is thus defined as a “sub-threshold” depressive state with clinical relevant symptoms not fulfilling diagnostic criteria for major depression. Thus, depression has a variety of clinical manifestations and, not surprisingly, also a multitude of possible explanations. Depression can run in families and impose an increased genetic risk, some people may be at higher risk due to personality traits, traumatic events including accidents may be precipitating causes and serious medical illness can trigger depression directly or be a consequence of associated stress.

With regard to neurological disorders, a bidirectional relationship has been proposed between depression and (among others) cerebrovascular brain disease (e.g. stroke), epilepsy, AD and Parkinson's disease (PD) (Kanner, 2005; Thomas *et al.*, 2004). That means that these patients are not only at increased risk of developing depression, but also that depression in itself increases the risk of certain neurological disorders. For possible mechanisms and associations between depression, neurodegenerative disease and cognition, see section 5.5.

1.8 Biomarker

A “biomarker” is the short form of “biological marker” and can be defined as a characteristic that is (ideally) “objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or a pharmacological response to a therapeutic intervention“. There is a variety of biomarkers in use in medicine today, for instance different blood test, ultrasound, imaging, and even by definition clinical symptoms such as hallucinations, depression, etc. Often several biomarkers in combination are needed for optimal diagnosis and treatment or in order to find underlying disease mechanisms of specific conditions. Typically each biological system (nervous system, gastro-intestinal system, etc.) has its own set of biomarkers that is adapted for optimal disease control or measurement of biological activity. Selection of an ideal biomarker or sets of biomarkers will thus depend on the nature of the desired study. An ideal biomarker should be reproducible, have high sensitivity and specificity (> 80%), provide a rapid response and be non-invasive and cost-effective (Mayeux, 2004). In science, where the goal often is exploratory research, biomarkers will not always meet all of these criteria.

Textbox 5:

Severity criteria of a major depressive episode according to the ICD-10

A. General criteria:

- The depressive episode must last at least two weeks
- The episode is not attributable to use of psychoactive substances or an organic mental disorder
- No former hypomanic or manic episode as part of a bipolar disorder

B. Presence of at least two of the following three symptoms:

- Clearly abnormal depressive mood for the subject, present during most of the day and almost every day, which is altered very little by environmental circumstances and which persists for at least two weeks
- Marked loss of interest or of the ability to enjoy activities that were previously pleasurable
- Lack of vitality or increased fatigability

C. One or more symptoms from the list must be present so that the sum total is at least four:

- Loss of confidence and self-esteem and feelings of inferiority
- Disproportionate self-blame and feelings of excessive guilt or inadequacy
- Recurrent thoughts of death or suicide or any suicidal behavior
- Complaints about or a decrease of the ability to concentrate and think, accompanied by a lack of decision and vacillation
- Changes of psychomotor activity, with agitation or inhibition
- Sleep alterations of any kind
- Changes of appetite (decrease or increase), with corresponding weight change

Mild depressive episode:

Two or three of the symptoms of criteria B are present, in addition to symptoms of criteria C until there is a minimum of total 4 symptoms. A person with a mild episode is probably capable of continuing with the majority of their activities.

Moderate depressive episode:

At least two of the symptoms of criteria B are present; in addition to symptoms of criteria C until there is a minimum total of 6 symptoms. A person with a moderate episode will probably have difficulties continuing with their ordinary activities.

Severe depressive episode:

There must be 3 symptoms of criteria B, in addition to symptoms of criteria C until there is a minimum of 8 symptoms. People with this type of depression present marked and distressing symptoms, mainly the loss of self-esteem and feelings of guilt or worthlessness. Suicidal thoughts and actions are common, and a number of somatic symptoms are present. Psychotic symptoms can appear, such as hallucinations, delusions, psychomotor retardation or severe stupor. In this case, it is called a severe depressive episode with psychotic symptoms. Psychotic phenomena such as hallucinations or delusions may or may not be mood-congruent.

2.0 Overarching themes

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are common and debilitating dementia syndromes accompanied by parkinsonism and a range of other psychiatric, sleep and autonomic disturbances. The overall negative impact on the individual patient and caregiver, as well as the health-related costs of Lewy body dementia (i.e. DLB and PDD) are even higher than those of AD (Bostrom *et al.*, 2007a; Bostrom *et al.*, 2007b; Rongve *et al.*, 2014; Vossius *et al.*, 2011), and diagnosis and treatment of the diversity of neuropsychiatric symptoms related to the disease are particularly challenging. Disease mechanisms are unknown, but aggregated Lewy bodies (LB) containing alpha-synuclein are believed to play a central role in the pathogenesis (see also section 3.0). Giving individualized treatment as early as possible is a clinical priority, preferably in the pre-dementia phase before irreversible brain damage has occurred, but there are few available studies and validated guidelines are lacking.

AD is the most common form of dementia, with core pathological hallmarks of amyloid deposits and neurofibrillary tangles, and clinical and pathological features overlap with DLB and PDD, especially in end-stage disease (see also sections 3.0 and 4.0). As for DLB and PDD, treatment options for AD are limited. The overall cost of dementia disease for society is high and expected to rise considerably the next decades. Development of disease-modifying therapies is thus urgently needed.

In contrast to the situation in AD and PD, the pre-dementia phase of DLB is almost unexplored, and there exists no consensus criteria for DLB-mild cognitive impairment (DLB-MCI). Given the known diversity of clinical DLB features, the non-demented phase is probably heterogeneous and complex (see also section 3.2.6 and figures 1 and 3).

It has become increasingly clear that PD has a long pre-motor period, the most prevalent and best documented symptoms being gastrointestinal (constipation) and olfactory dysfunction, REM sleep Behavior Disorder (RBD) and neuropsychiatric symptoms such as depression (see section 3.3.4.2). Despite the fact that MCI is prevalent in early (including untreated) PD (see section 3.3.6.2), it is unclear whether cognitive impairment is an antecedent of motor PD (Sanchez-Ferro *et al.*, 2013). Further, it is not known whether depression is common in pre-dementia DLB (Fritze *et al.*, 2011). This is a relevant question since depression can precede AD and PD by several years and is also known to be a risk factor in development of cognitive impairment and dementia (see also sections 5.5 and 8.4). Similar studies have not been performed with DLB as an outcome.

Since both DLB and PDD are synucleinopathies (see section 3.2.2), it is not surprising that they share common features (Lippa *et al.*, 2007). Widely accepted is the Braak staging system for PD that proposes a pathologic progression from the enteric nervous system, olfactory bulb and the lower parts of the brain stem (i.e. medulla oblongata) with subsequent rostral distribution involving the substantia nigra and finally cortical areas (bottom-up pathological progression) (Braak *et al.*, 2003) (see sections 3.2.3 and 3.3.3). In DLB, alpha-synuclein positive Lewy bodies (LBs) are typically more abundant in cortical areas, and parkinsonism develops later in the disease process. Although the mechanisms of disease development is unknown, a top-down pathological progression (i.e. cortical involvement first) rather than the bottom-up progression as suggested by Braak *et al.* for PD may be a more common pattern in DLB (Langston, 2006; Parkkinen *et al.*, 2008). In addition to the similarities between DLB and PDD, there are

also overlapping features between Lewy body dementia and AD that need to be disentangled. This thesis aims to further this understanding. Our main focus will be on Lewy body disease since less is known about the existing pathophysiology and early clinical features compared to AD. Important research questions asked in this thesis include (**figure 1**):

- What are the earliest and most prevalent clinical symptoms in DLB ? Is depression an early presentation in DLB (paper 1) ?
- What role does depression have as an early marker of neurodegenerative disease (papers 1 and 3) ?
- Is depression in subjective cognitive impairment (SCI) and MCI associated with neurobiological correlates of early AD pathology (paper 3) ?
- What is the potential relevance of white matter disintegrity in pre-dementia Lewy body disease ? Are these changes related to cognitive impairment (paper 2) ?

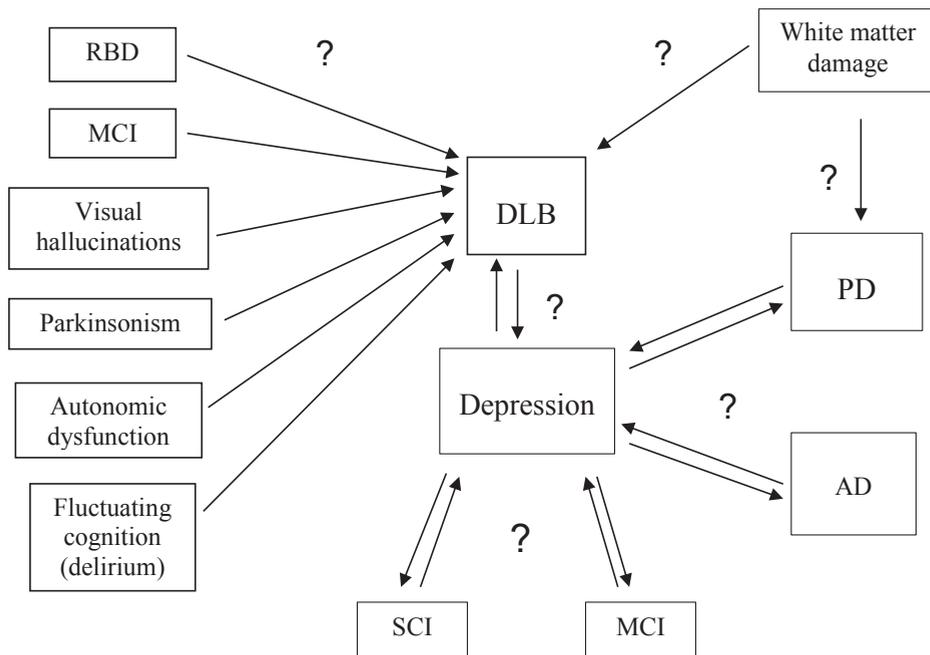


Figure 1:
 Single arrow indicates increased probability for a certain condition to lead to another. Double arrows indicate a bidirectional relationship, i.e. increased probability that one condition will lead to another and vice versa. Question marks represent research hypothesis raised in this thesis. RBD=REM sleep behavior disorder. MCI=mild cognitive impairment. DLB=dementia with Lewy bodies. PD=Parkinson's disease. AD=Alzheimer's disease. SCI=Subjective cognitive impairment.

3.0 Lewy body disease

3.1 Introduction

James Parkinson's (1755 - 1824) "essay on the shaking palsy" written in 1817, was the first clinical description of a patient group characterized by motor symptoms such as slowing of movement, tremor and flexed posture. The essay was based on only six cases that James Parkinson had observed in his own practice in London or around his neighborhood. The essay was meant to encourage research, and about 60 years later the influential French neurologist Jean-Martin Charcot (1825 - 1893) working at the Salpetriere hospital in Paris saluted Parkinson for his observations and suggested the name Parkinson' disease (PD). Charcot recognized that cardinal symptoms of PD were tremor, rigidity, bradykinesia and postural instability and classified the disorder as a "neurosis", meaning a neurologic disease of unknown origin. This established PD as a recognized medical disorder.

In 1912, the German born American neurologist Friedrich Heinrich Lewy (1885-1950), who studied under Alois Alzheimer (1864 -1915) in Munich at that time, discovered that abnormal aggregates of intracytoplasmatic proteins could be found in the brainstem of PD patients (including the dorsal vagal nucleus, but also the nucleus basalis of Meynert in the basal forebrain), now better known under the eponym of Lewy bodies (LB). In 1919 the Russian neuropathologist Konstantin Tretiakoff (1892 – 1958) found LBs in the substantia nigra of PD patients, at present the hallmark of idiopathic PD.

In his original description James Parkinson himself stated that the "intellect was preserved". Although Friedrich Lewy described significant cognitive impairment in PD patients, it was merely seen as an incidental finding, and for decades PD was regarded as a disease with pure motor dysfunction. From 1960 and later more sensitive immunocytochemical methods could detect LBs also in cortical and limbic structures in patients with dementia both with and without typical motor symptoms. Typical symptoms such as visual hallucinations, disorientation, autonomic dysfunction and cognitive impairment in addition to parkinsonian motor symptoms were described and linked to autopsy confirmed presence of cortical LBs (Okazaki *et al.*, 1961). Similar histopathological changes were also seen in the peripheral nervous system (Kosaka *et al.*, 1976;Kosaka *et al.*, 1984).

Another key development was the detection of the neurotransmitter dopamine and its relevance for PD and the remarkable efficacy of dopaminergic drugs in the treatment of motor symptoms (Carlsson, 2002;Olanow and Schapira, 2013). In the absence of cortical senile plaques and neurofibrillary tangles typically seen in Alzheimer's disease (AD), a distinct and new dementia subtype was starting to emerge with a diversity of symptoms affecting several brain structures and transmitter systems. Thus, the first clinical criteria for dementia with Lewy bodies (DLB) (McKeith *et al.*, 1996) and a decade later the clinical, diagnostic criteria for dementia associated with PD (PDD) were proposed (Emre *et al.*, 2007).

There has been much debate about whether these two disorders are different, but the common view now is that similarities dominate, and that the relative timing of dementia and motor symptoms is the major difference. Lewy body disease (LBD) has thus been proposed as an umbrella term for PD, PDD and DLB, the latter subsequently named Lewy Body dementias

(Lippa *et al.*, 2007). A Movement Disorders Society commissioned task force has recently initiated a redefinition of the criteria for PD, PDD and DLB (Berg *et al.*, 2014) (see also section 8.3), proposing that DLB should be included as a subtype of PD.

Increased knowledge of LBD progression will provide patients and caregivers with an explanation to the diversity of symptoms often seen years before onset of dementia. In addition, greater insight into disease mechanisms will help facilitate future administration of targeted disease-modifying medication before irreversible brain damage occurs.

In this section I will attempt to address the important features of cognitive impairment in LBD. Despite similarities between DLB and PDD, I will describe the current known risk factors and epidemiology separately. I will review highlights from the current status of both established and potential future biomarkers, such as clinical features, genetics, cerebrospinal fluid (CSF) and imaging parameters. Finally, a brief outline of the treatment options in Lewy body dementia is presented together. This review is partly overlapping with a recent publication (Auning *et al.*, 2012, Norsk epidemiologi), but has been expanded and updated.

3.2 Dementia with Lewy bodies (DLB)

3.2.1 Clinical criteria

The original DLB criteria (McKeith *et al.*, 1996) had low sensitivity (20-80 %), but high specificity (80-100 %) (McKeith *et al.*, 2005), i.e. a lot of DLB cases were missed, but when a diagnosis was made it was most often correct. The revised criteria included a pathological dopamine transporter single photon emission computed tomography (SPECT) using ioflupane (123I) or other ligands (Dopamine transporter scan) and REM-sleep Behavior Disorder (RBD) as suggestive features to increase sensitivity (McKeith *et al.*, 2005) (**text box 6**).

According to the revised criteria DLB is defined by the presence of dementia together with two of three core symptoms:

(1) Parkinsonism, (2) typically well-formed and persistent visual hallucinations and (3) fluctuating cognition and/or consciousness. A probable DLB diagnosis can also be made with only one core symptom together with one or more suggestive features like RBD, neuroleptic hypersensitivity or pathologic Dopamine transporter scan. A diagnosis of possible DLB can be made with only one core or suggestive feature. In addition, the consensus criteria list a number of supporting clinical features like frequent falls, psychotic and depressive symptoms and autonomic failure.

The revised clinical criteria await further systematic validation, but seem to be more sensitive than the previous criteria. In a study by Aarsland *et al.*, the number of cases diagnosed with probable DLB increased by 25 % using the new compared to the old criteria (Aarsland *et al.* 2008b), and the sensitivity and specificity has been found to increase if RBD is added as a core feature (sensitivity 90%) and cognitive fluctuation excluded (specificity 85%) in advanced disease (Ferman *et al.*, 2011).

However, in a large multi-center study were 2861 patients with final clinical diagnoses (of neurodegenerative disease) were compared systematically with subsequent neuropathology diagnoses, the sensitivity for a clinical diagnosis of DLB was low (32,1 %), but sensitivity high (> 95 %) (Nelson *et al.*, 2010).

Textbox 6:

Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB) (McKeith et al. 2005)

1. Central features (essential for a diagnosis of possible or probable DLB):

- Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function
- Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression
- Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

2. Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB):

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous features of parkinsonism

3. Suggestive features (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features are sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.):

- REM sleep behavior disorder
- Severe neuroleptic sensitivity
- Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

4. Supportive features (commonly present but not proven to have diagnostic specificity):

- Repeated falls and syncope
- Transient, unexplained loss of consciousness
- Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence
- Hallucinations in other modalities
- Systematized delusions
- Depression
- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
- Abnormal (low uptake) MIBG myocardial scintigraphy
- Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is less likely

- In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
- In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
- If parkinsonism only appears for the first time at a stage of severe dementia

6. Temporal sequence of symptoms

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

Furthermore, evidence suggested that the core symptoms of parkinsonism, visual hallucinations and fluctuating cognition added little to the diagnosis in severe dementia. DLB was most often misdiagnosed as AD, which is in accord with the mixed AD pathology in the majority of DLB cases (see section 3.2.3).

3.2.2 Molecular pathology

LBs are intraneural, cytoplasmic, eosinophilic inclusions and found in neuronal cell processes they are called Lewy neurites (or intraneuritic LBs). They are traditionally classified in a brainstem (classical) and a cortical type, each type with distinct histopathological features (Wakabayashi *et al.*, 2013). LBs in the substantia nigra is regarded the hallmark of idiopathic PD. Furthermore, the association between the extent of LB pathology and clinical symptoms is well established (Ballard *et al.*, 2013) although some individuals have severe alfa-synuclein pathology at autopsy but not the typical symptoms of Lewy body disease (LBD) (Parkkinen *et al.*, 2008). LBs accompanied by neuronal loss are characteristic of all forms of LBD.

LBs consist of more than 90 molecules, mainly proteins of the ubiquitin-proteasome system (involved in protein degradation) and alfa-synuclein, but their exact functions are poorly understood. Increased expression of alfa-synuclein has been shown to inhibit synaptic recluster and subsequently inhibit neurotransmitter release in the synaptic cleft (Nemani *et al.*, 2010). The biological function of alfa-synuclein is thus believed to be involved in neural plasticity. Recent evidence suggest that alfa-synuclein can spread directly from cell to cell leading to neurodegeneration (Luk *et al.*, 2012), and a hypothetical model of alfa-synuclein toxicity includes increased oxidative stress, disruption of axonal transport and synaptic dysfunction, inhibition of the ubiquitin proteasome system and mitochondrial dysfunction (Irwin *et al.*, 2013; Olanow and Brundin, 2013).

Alfa-synuclein seems to play a key role in the pathogenesis of several conditions, and thus the term alfa-synucleinopathy is increasingly being used (**table 2**).

Table 2: The alfa-synucleinopathies

Condition	Clinical features
Parkinson's disease	Tremor, rigidity, bradykinesia and gait disturbance
Parkinson's disease dementia	Development of dementia in established (at least one year) Parkinson's disease.
Dementia with Lewy bodies	Dementia prior to parkinsonism (at least one year); visual hallucinations, fluctuating cognition, REM sleep behavior disorder
Multiple system atrophy	Parkinsonism, autonomic dysfunction, ataxia, minimal effect of L-dopa
Pure autonomic failure	Orthostatic hypotension, visual disturbances, sexual dysfunction, sweating
Idiopathic REM sleep behavior disorder	Acting out dream content during REM sleep

3.2.3 Neuropathology

The gold standard when diagnosing Lewy body dementias (and other dementias) is autopsy. A neuropathological diagnosis of DLB and PD is based on the widespread finding of LB both in the central and peripheral nervous system. In contrast to previous staining methods with hematoxylin/eosin and ubiquitin immunohistochemistry, LBs and Lewy neurites are now directly detected with immunohistochemical staining of alfa-synuclein (McKeith *et al.* 2005). This new method has increased sensitivity and specificity significantly.

Historically, several staging systems in Lewy body disease have been proposed. One of the earlier classifications differentiated between three DLB subgroups based solely on the localization of LBs, namely brainstem, transitional (intermediate between brainstem and cortical) and (diffuse) cortical predominant (Kosaka *et al.*, 1984). This broad classification has also been adopted in the current semi quantitative assessment of LB density and distribution in DLB (McKeith *et al.*, 1996). However, the underlying pathology in DLB is often mixed with typical AD pathology (amyloid and neurofibrillary tangle deposits). With increasing LB pathology in the brain, the likelihood of a typical DLB phenotype increases. Concomitant AD-type pathology, on the other hand, decreases the probability of the clinical syndrome of DLB and increases the likelihood of a mixed DLB and AD phenotype. In contrast, AD pathology seems to be less prominent in PDD, although the presence of cortical amyloid beta 42 (A β 42) are associated with progression of dementia also in PDD (Siderowf *et al.*, 2010). The new pathologic criteria propose to take into account not only LB pathology but also concomitant AD-related pathology to assess the probability that the neuropathologic findings can explain the clinical syndrome of DLB (McKeith *et al.*, 2005).

In 2003 Braak *et al.* proposed a pathological staging scheme for PD with ascending caudal-rostral progression with increasing severity throughout the brain starting in the peripheral nervous system and lower medulla oblongata and ultimately involving the entire cortex (Braak *et al.*, 2003). Stage 1-2 includes the dorsal vagal motor nucleus, anterior olfactory structures and eventually the entire enteric nervous system (olfactory and autonomic symptoms may present). Stage 3-4 involve the basal forebrain and mesocortex (where typical motor symptoms occur) and stage 5-6 the neocortex (frequently associated with cognitive symptoms). This staging system is currently widely accepted in PD, but is in contrast to the spread of LBs in DLB, which per definition has earlier cortical involvement. Despite a proposal by Beach *et al.* to unify the staging systems to allow for the classification of all subjects with LB disorders, the need for further refinement of the neuropathological criteria (for DLB) is clear (Beach *et al.*, 2009) (**see also table 3**).

It is at present unclear whether LB pathology is toxic or neuroprotective. Indeed, up to 30 % of elderly patients have LBs at autopsy, but not the clinical syndrome of LB dementia, so-called incidental LBD (Halliday *et al.*, 2011a; Parkkinen *et al.*, 2005). One explanation could be that these patients would eventually develop symptoms had they lived longer, and evidence in support of this hypothesis indicates that predilection sites for LBs in these cases are similar to those seen in early stage PD (Del *et al.*, 2002).

Of note, LBs and alfa-synuclein related pathology are found in up to 60 % of AD cases, and 3 out of 4 DLB patients also have AD pathology (although usually with less neurofibrillary tangles) (Halliday *et al.*, 2011a; Hamilton, 2000; Iseki, 2004), but how the different pathologies affect the other is not known. The Amygdala seems especially vulnerable in cases with AD and

mixed pathology (Hamilton, 2000). The comorbid role of cardiovascular factors is at present also poorly understood.

Interestingly, in an autopsy study of 1720 subjects, 83% (of 248 cases with alfa-synuclein positive autopsy) showed a distribution pattern compatible with the current staging systems (Parkkinen *et al.*, 2008). However, 55 % of the subjects with abundant alfa-synuclein pathology (Braak stage 5-6) remained cognitively intact which raises doubts whether the actual disease process is measured in all cases. In addition, 17% of cases deviated from the suggested caudo-rostral progression suggesting that alternative routes are perhaps more relevant in DLB.

Table 3: Staging of Lewy body pathology

Reference	Staging
Kosaka et al., 1984	<p><u>Group A:</u> Diffuse type of LBD involves cerebral cortex, basal ganglia, diencephalon and brainstem.</p> <p><u>Group B:</u> Transitional type between group A and C.</p> <p><u>Group C:</u> Involves brainstem and diencephalon.</p>
Braak et al. 2003	<p><u>Stages 1-2:</u> Pathology confined to lower medulla oblongata, olfactory bulb and enteric nervous system.</p> <p><u>Stages 3-4:</u> Pathology in the substantia nigra, midbrain and basal forebrain.</p> <p><u>Stages 5-6:</u> Pathology in the cortex.</p>
Beach et al. 2009	<p><u>Stage 1:</u> Pathology in olfactory bulb only.</p> <p><u>Stage 2a:</u> Brainstem predominant involvement.</p> <p><u>Stage 2b:</u> Limbic predominant involvement.</p> <p><u>Stage 3:</u> Brainstem and limbic roughly equally involved.</p> <p><u>Stage 4:</u> Neocortical involvement.</p>

3.2.4 Diagnosis

A main challenge in diagnosing DLB is making an accurate and early diagnosis. There is evidence that DLB patients have a more rapid decline, need more resources, have poorer quality of life and higher mortality as compared to AD (Bostrom *et al.*, 2007a; Bostrom *et al.*, 2007b; Williams *et al.*, 2006). In addition, a diversity of symptoms can probably precede the clinical syndrome of DLB (see also section 3.2.6 and figure 3), making it essential for the physician in charge to be able to make informed decisions, educate the patient and caregiver and plan the best course of management as early as possible.

At present, there is evidence that DLB is underdiagnosed (Toledo *et al.*, 2013) and that the clinical DLB criteria has low sensitivity in a clinical setting, low to moderate sensitivity in research settings, but overall high specificity when a diagnosis of probable DLB can be made (see section 3.2.1).

In order to increase sensitivity, a structured assessment of the core and suggestive features of DLB is recommended. Parkinsonism can be identified by a routine clinical examination or preferably by using the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale (Fahn *S et al.*, 1987) or the validated short version (Ballard *et al.*, 1997). Of note, parkinsonism is present in only about 75 % of DLB cases (Hanson and Lippa, 2009; McKeith, 2007), and subjects without motor symptoms are less likely to be considered for the diagnosis. Visual hallucinations affect around 60-80 % of patients with DLB (Ferman and Boeve, 2007) and can be evaluated with the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994). The most difficult symptom to reliably evaluate in clinical practice is fluctuating cognition which affects around half of the DLB patients. The 2005 consensus criteria for DLB recommends using at least one formal measure when searching for fluctuating cognition, and the Clinician Assessment of Fluctuation Scale or The Mayo Fluctuation Composite Scale can be used for this purpose (McKeith *et al.* 2005). Of note, these scales define different aspects of cognitive fluctuation and await further validation.

The Mayo Sleep Questionnaire is a structured and validated instrument used to screen for a wide range of sleep disturbances including RBD (Boeve *et al.*, 2011). RBD is characterized by vivid and often frightful dreams and a tendency to “acting out” dream content (e.g. moving limbs including hitting/kicking the bed partner, screaming, etc.) during REM sleep and is suggestive of a DLB disorder. A bed partner is asked to elaborate by use of a semi-structured interview. A tentative diagnosis of RBD can be confirmed by polysomnography. A pathologic [¹²³I]FP-CIT SPECT (Dopamine transporter scan) can increase the sensitivity and specificity in separating DLB from AD, even in cases without clinical parkinsonism (see also section 3.2.8.6).

Importantly, neuropsychological deficits in DLB are heterogeneous and (eventually) affect all domains, and memory problems do not preclude a diagnosis of DLB. However, there is evidence that early visuospatial dysfunction is more prominent in pure DLB and early memory problems more pronounced in pure AD, and that mixed DLB and AD pathology increases the probability of similar clinical phenotypes (Yoshizawa *et al.*, 2013) (see also section 3.2.3).

Clinical and biomarker changes in DLB and PDD are overall similar, but there are subtle differences, especially in early disease, including early features that per definition are slightly

Table 4: Studies reporting the prevalence of dementia with Lewy bodies

Study	Number in study	Number with dementia	Number with DLB	DLB ³ /all dementia %	Criteria
Yamada et al., 2001	3715 ¹	142	4	2.8	1996
Herrera et al., 2002	1656 ¹	118	2	1.7	1996
Harvey et al., 2003		185 ²		6.5	1996
Takada et al., 2003		275 ²		2.2	1996
Rahkonen et al., 2003	601 ¹	137	30	21.9	1996
Sambook et al., 2004		766 ²		3.0	1996
Yokota et al., 2005		464 ²		4.0	1996
Shinagawa et al., 2007		483 ²		11.0	1996
Molero et al., 2007	2438 ¹	196	4	2.0	1996
Gascon-Baiarri et al., 2007	1754 ¹	165	15	9.1	2005
Fernandez Martinez et al., 2008	1931 ¹	108	10	9.2	1996
Aarsland et al., 2008		196 ²		15.8	2005
Arslantas et al. 2009	3100 ¹	262	0	0	1996
Kim et al., 2011	1673 ¹	351	2	0.6	1996
Yoshida et al. 2011		126 ²		8.7	1996
Alladi et al., 2011		347 ²		8.9	2005
Dimitrov et al. 2012	540	39	2	5.1	2005

¹ Population-based prevalence ² Clinic-based prevalence ³ Dementia with Lewy bodies

different (Aarsland *et al.*, 2009b;Johansen *et al.*, 2010;Lippa *et al.*, 2007). In DLB there is less resting tremor and asymmetry, a more rapid progression of motor symptoms and a poorer response to levodopa as compared to PDD. DLB patients are usually reported to have more frequent visual hallucinations and fluctuating cognition and in mild dementia more severe executive impairment than in PDD. Finally, although considerable overlap, there seems to be more early and extensive AD plaque pathology in DLB compared to PD and PDD.

Of note, at the stage of severe dementia a distinction between the different dementia subtypes is almost impossible due to extensive brain damage and the considerable overlap in symptoms. In addition most DLB cases have comorbid AD changes at autopsy with less likelihood of detecting the clinical syndrome of DLB with increasing AD pathology. Additionally, there is evidence that a synergistic relationship between LB and AD pathology exist (Galpern and Lang, 2006;Irwin *et al.*, 2013).

3.2.5 The prevalence and incidence of DLB

Few community-based epidemiological studies have focused on DLB and few have applied the new 2005 clinical diagnostic criteria.

In the first review of epidemiological studies in DLB, only 7 prevalence and incident studies were included (Zaccai *et al.*, 2005). It was concluded that the prevalence of DLB ranged from 0 to 5% with regard to the general population (> 65 years) and from 0 to 30.5% of all dementia cases. A large part of this variation was probably due to methodological differences.

Since 2005, new diagnostic criteria for DLB have been published and the awareness of the clinical syndrome of DLB has been raised considerably. In a recent review 28 prevalence and 3 incidence studies were identified (Vann Jones and O'Brien, 2014), but the majority (about 80 %) still used the original 1996 criteria. The largest prevalence studies are shown in **table 4**. The mean prevalence of DLB in the whole population over 65 was estimated to 0.36%, or one in 270 people, with a wide range from 0 - 21.9 %. 4.2 % of cases with dementia were estimated to be DLB, but prevalence rates varied considerably between studies. In studies implementing the 2005 criteria, the prevalence rates ranged from 0 - 1.2 % in the general population (> 65 years) and 0-9.7 % in those with dementia. In two population-based studies, the probable and possible DLB cases were added resulting in an increase in prevalence numbers from 9.7 - 30.5 % and 9.1 - 12.7 % in all dementia cases respectively (Gascon-Bayarri *et al.*, 2007;Stevens *et al.*, 2002).

In clinical settings the prevalence rates for DLB were overall higher, with an average of 7.5 % of all dementia cases, ranging from 2.2 – 24.7 %. Using the 2005 criteria, both population and clinical based studies had higher prevalence rates than compared to the original 1996 criteria. Still, the mean prevalence numbers are probably an underestimation since four studies (three clinic-based, one population-based) specifically looking for DLB, including a neurological examination, had considerably higher rates (range 16-24 %). In one of these, the DemVest study in Western Norway, the revised 2005 criteria was applied on a referral cohort to old age psychiatry and geriatric medicine clinics, including all referrals with a first time diagnosis of mild dementia (defined as a Mini Mental State Examination (MMSE) score of 20 or more). In 196 patients, 15.8% of cases with mild dementia were diagnosed with probable DLB and 20% with possible and probable DLB combined (Aarsland *et al.*, 2008).

Population incidence studies report 0.57 - 1.4 % new DLB cases for every 1.000 persons per year and annual incidence rates in the 3.2-4.5 % range (Matsui *et al.*, 2009, (de Lau *et al.*, 2004;Lopez-Pousa *et al.*, 2004;Miech *et al.*, 2002;Perez *et al.*, 2010).

3.2.6 Clinical features preceding DLB

Very few studies have explored the early, pre-dementia stages of DLB, but evidence is emerging to suggest that several possible starting points and trajectories can lead to the pathological and clinical syndrome of DLB (**figure 3**). This is in accord with the more extensive evidence found to support a long pre-dementia period in AD and pre-motor phase in PD (see also sections 3.3.4.2 and 4.0).

MCI has been shown to precede AD with an annual conversion rate of about 10-15% (Petersen *et al.*, 2009), but the pre-dementia stage of DLB is at present undefined and essentially unexplored. A clinicopathological study of eight MCI patients with subsequent autopsy-proven LBD showed that RBD preceded MCI in six cases with a median of 12 years (Molano *et al.*, 2010). The cognitive domains most frequently affected at the pre-dementia stage were attention, executive and visuospatial functioning. Memory was less frequently impaired. The same cognitive pattern was seen in another study with a similar design (Jicha *et al.*, 2010). In a recent study including 337 MCI patients, patients with non-amnesic MCI were more likely to develop DLB and those with amnesic MCI more likely to develop probable AD (Ferman *et al.*, 2013). Parkinsonism, visual hallucinations and delirium were also shown to be early features in contrast to the MCI-stage of AD, which is dominated by memory problems. In another autopsy proven study, visual hallucinations were seen as the best positive predictor and the absence of visuospatial impairment the best negative predictor of a later diagnosis of DLB versus AD (Tiraboschi *et al.*, 2006). Similarly, in a recent study visual hallucinations were found to be highly specific for a pathological diagnosis of DLB (Toledo *et al.*, 2013).

In the DemVest study, higher frequencies of RBD and Excessive Daytime Sleepiness (EDS) in mild DLB were found compared to normal controls and mild AD patients. RBD started on average seven years (range 0.5-35 years) before dementia was diagnosed in 39 patients, indicating a strong association (unpublished data from the DemVest study). This long-duration preclinical phase was also demonstrated in another study (Claassen *et al.*, 2010). In a recent study 80 % of males with an initial diagnosis of RBD eventually developed a parkinsonian disorder over a 16 year follow-up (Schenck *et al.*, 2013).

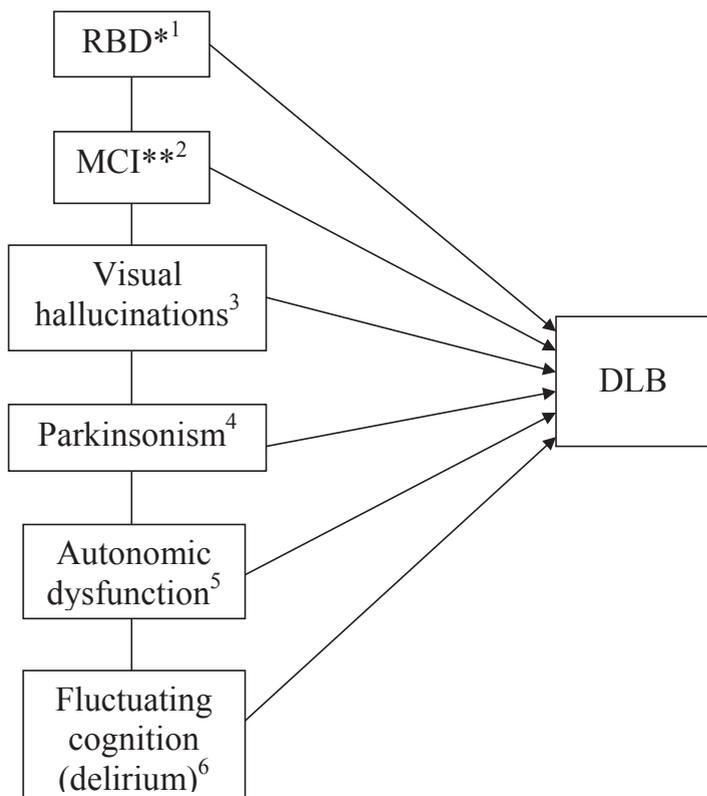
Pure Autonomic Failure (PAF) is restricted clinically to the peripheral nervous system and includes orthostatic hypotension, constipation, olfactory dysfunction and urinary incontinence. Autonomic symptoms has been shown to be the initial presentation in both DLB and PD (Postuma *et al.*, 2013), and a positive [¹²³I]FP-CIT SPECT in PAF supports the hypothesis of a common etiology (Tolosa *et al.*, 2007).

Chiba *et al.* found that non-motor symptoms such as olfactory dysfunction, constipation, increased salivation and RBD was increased in DLB compared to AD (Chiba *et al.*, 2012).

Finally, a recent retrospective study suggest that a history of suspected delirium is more often associated with a later diagnosis of DLB than AD (Vardy *et al.*, 2014).

Figure 3:

Potential presenting symptoms in dementia with Lewy bodies



* REM sleep behavior disorder

** Mild cognitive impairment

1 Claassen *et al.*, 2010, Boot *et al.*, 2012, Schenk *et al.*, 2013

2 Molano *et al.*, 2010, Jicha *et al.*, 2010

3 Tiraboschi *et al.*, 2006, Toledo *et al.*, 2013

4 Jicha *et al.*, 2010

5 Tolosa *et al.*, 2007, Chiba *et al.*, 2012

6 Vardy *et al.*, 2014

3.2.7 Genetic contributions in DLB

Causal genes are rare in the common types of neurodegenerative diseases. More common are gene mutations or single nucleotide polymorphisms (SNPs) associated with an increased risk of disease. Established genetic causes for AD include rare autosomal dominant mutations in the genes coding for Presenilin1, Presenilin 2 and Amyloid Precursor Protein (APP) (Goate *et al.*, 1991; Levy-Lahad *et al.*, 1995; Schellenberg *et al.*, 1992). The genetics of DLB are largely unexplored, but two autosomal dominant genes (alpha-synuclein and LRRK2) and three recessive genes (PINK1, PARK2 and PARK7) are causal disease genes found in familial PD (Nuytemans *et al.*, 2010).

Most DLB cases occur sporadically, although families have been described as having several members diagnosed with DLB with gene alterations in different locations, some of which overlap with PD and others with AD (Kurz *et al.*, 2006). Cousins of DLB patients have a 2.3 fold increased risk of developing DLB compared to members of the general population (Nervi *et al.*, 2011). Traditional genetic studies have identified multiplications (Chartier-Harlin *et al.*, 2004; Singleton *et al.*, 2003) and mutations in the gene encoding alpha-synuclein (Polymeropoulos *et al.*, 1997; Yamaguchi *et al.*, 2005; Zarranz *et al.*, 2004) and beta-synuclein (Ohtake *et al.*, 2004). Genetic mutations known to be risk factors of early onset familial AD, like Presenilin 1 and 2, have also been identified in DLB (Meeus *et al.*, 2012). As in PD, mutations in the gene coding for glucocerebrosidase (GBA, an enzyme involved in lysosome activity) is known to increase the risk for DLB (Nalls *et al.*, 2013).

The ApoE ϵ 4 allele is the strongest genetic risk factor for developing AD, but in DLB there are conflicting results regarding APOE as a risk factor (Singleton *et al.*, 2002; Tsuang *et al.*, 2013). Conversely, the ApoE ϵ 2 allele has recently been shown to be a possible protective factor also in DLB (Berge *et al.*, 2014). A recent, large neuropathologically proven study involving 667 DLB cases and 2624 controls showed that the APOE, alpha-synuclein and SCARB2 (Scavenger Receptor class B, member 2) loci are strongly associated with DLB (Bras *et al.*, 2014). The SCARB2 gene is a known PD-reported locus and encodes a lysosomal protein, and the affection of the GBA and SCARB2 loci suggest a dysfunction in lysosomal function in DLB.

Genome-wide association studies (GWAS) have not yet been presented for DLB, but it is to be hoped that in the near future more of the underlying disease mechanism and risk factors will be revealed.

3.2.8 Potential biomarkers in DLB

Due to the relatively low sensitivity of the consensus criteria for DLB, the need for reliable biomarkers is evident. A complicating factor is the heterogeneous brain pathology in DLB and the considerable overlap between neuropathological changes and clinical presentation in DLB and AD.

A standard computerized tomography (CT) or magnetic resonance imaging (MRI) is used in the routine clinical examination of cognitive impaired patients (i.e. to exclude secondary causes of dementia). The development of biomarkers is vastly growing, and in this section, present and some promising and potential future biomarkers are presented, see also **table 5**.

Diffusion Tensor Imaging (DTI) is presented in section 3.3.6.6.

3.2.8.1 Structural MRI including computer-based analyzes

MRI is a non-invasive technique that uses a magnetic field and pulses of radio wave energy to create detailed images of organs and structures inside the body. A powerful magnetic field temporarily realigns hydrogen atoms in the body and the radio waves cause these aligned atoms to produce faint signals, which are then used to create cross-sectional MRI images (slices). FreeSurfer is a freely available software package that can create computerized models of the brain based on MRI data (<http://surfer.nmr.mgh.harvard.edu/>) including measurements of cortical thickness and volumes and other morphological properties.

There is generally more global (grey matter) atrophy in AD compared to DLB, and among established biomarkers for AD is atrophy of the medial temporal lobe (hippocampus) (Bloudek *et al.*, 2011; Hansson *et al.*, 2006). The same pattern can also be seen in DLB, but typically the hippocampus is less damaged. Comparable patterns have been shown with Hippocampus subfield imaging (including subiculum, CA1 and entorhinal cortex), but it cannot be used to separate DLB from AD on an individual level (Mak *et al.*, 2014). This is also in accord with the relative preservation of memory in DLB on neuropsychological testing compared to AD. Furthermore, the midbrain including the substantia innominata (and the nucleus basalis of Meynert where F. Lewy first documented LBs) has shown greater atrophy in DLB as compared to AD (Kantarci *et al.*, 2012a; Whitwell *et al.*, 2007). The latter is highly involved in cholinergic transmission and can explain the greater cholinergic deficits found in Lewy body disease. Comparisons of grey matter atrophy between DLB and PDD seems variable and often similar patterns can be seen (Mak *et al.*, 2014).

Advancements in imaging processing using automatic whole-brain segmentation techniques extracted from structural MRI (e.g. by use of FreeSurfer), allows for a more none-biased approach (not regions of interest driven). Lebedev *et al.* recently conducted a multivariate MRI classification of cortical thickness demonstrating an 82 % sensitivity and 85 % specificity in separating DLB and AD patients (Lebedev *et al.*, 2013). The finding that DLB patients have a more occipital and posterior affection compared to the more temporal affection in AD is consistent with several other structural imaging studies (Mak *et al.*, 2014).

White matter hyperintensities or lesions (WML) and a special variant of MRI, Diffusion Tensor Imaging (DTI), are discussed in section 3.3.6.6 (Biomarkers of cognitive impairment in PD).

3.2.8.2 Cerebrospinal fluid (CSF) and plasma

CSF is a colorless fluid surrounding the brain and spine functioning as a buffer or shock absorber, but also offering immunologic and nourishing properties. About 500 ml of CSF is produced in the choroid plexus (situated in the roof of the third ventricle) each day and recirculated within the ventricular system. CSF is constantly being reabsorbed and only about 100-160 ml is present at any given time in the subarachnoid space. Lumbar puncture (or spinal tap) and extraction of CSF gives the opportunity to analyze for abnormalities in a fluid standing in direct contact with the brain and the central nervous system.

CSF amyloid beta 1-42 (A β 42) and phospho-tau are established biomarkers in AD and contributes to an early diagnosis with a sensitivity and specificity of around 85 % (Hansson *et al.*, 2006). These markers cannot at present separate AD from DLB although lower levels of A β 40 and A β 42 have been shown in DLB and PDD compared to controls (Bibl *et al.*,

2006;Parnetti *et al.*, 2008). In a recent study, the level of concomitant AD pathology in DLB correlated to A β 42, but not tau (Brunnstrom *et al.*, 2013).

Reduced levels of alfa-synuclein in the CSF of DLB patients compared to that of those with AD have recently been demonstrated (Ballard *et al.*, 2010), but most studies are small and routine measurement of alfa-synuclein has proven technically difficult. In a recent meta-analysis comprising 13 studies and 2728 patients, CSF alfa-synuclein concentrations were lower in DLB compared to AD (Lim *et al.*, 2013). These findings are promising, but more confirmatory studies are needed in order to incorporate alfa-synuclein as a good and valid biomarker for DLB.

There are currently no blood markers in DLB.

3.2.8.3 Electroencephalography (EEG)

Slowing of the EEG rhythm is a frequent finding in AD and other dementias, and several studies have shown a more pronounced slowing in DLB patients. These early studies have, however, included few patients, and larger studies have not been able to reproduce the findings (Londos *et al.*, 2003). More recently, a longitudinal study including 50 DLB, 50 AD and 40 PDD patients with early dementia (≥ 20 on the MMSE), concluded that EEG could discriminate between AD and DLB (Bonanni *et al.*, 2008). In a systematic review of the diagnostic utility of EEG in early onset dementia (< 65 years) involving 12 studies and 965 patients with different dementia subtypes, it was concluded that slow wave activity was more prominent in DLB (Micanovic and Pal, 2014). At present more confirmatory studies are needed in the older age groups before EEG can serve as a reliable biomarker for DLB.

3.2.8.4 Myocardial scintigraphy

Autonomic dysfunction involving the cardiovascular system is common in DLB, and myocardial scintigraphy with (123)I-metaiodobenzylguanidine (MIBG) enables the quantification of post-ganglionic cardiac sympathetic innervation. Several studies have demonstrated reduced cardiac uptake in DLB compared to AD patients, and the 2005 diagnostic criteria has included a pathologic (123) I-MIBG cardiac scintigraphy as a "supportive" diagnostic feature, based on limited evidence. A recent meta-analysis involving 46 studies and 2680 patients concluded that AD and DLB (and PD) could be discriminated with a high level of accuracy (King *et al.*, 2011).

However, cardiac heart disease and diabetes can also cause an abnormal myocardial scintigraphy, and pathology must be interpreted with care, especially in the elderly with comorbid somatic disease.

3.2.8.5 Perfusion SPECT

Single-photon emission computed tomography (SPECT) is a nuclear medicine imaging technique that can measure among others cortical blood flow, tumor spread, infection and thyroid activity, providing 3D biological information. A radioisotope (radionuclide, an atom with an unstable nucleus, ultimately emitting gamma rays) is attached to a specific ligand (creating a radio ligand) and usually injected intravenously in the patient. The radioligand binds to biological tissue depending on the quality and properties of the ligand, and a gamma camera can thus detect the ligand concentration. Several ligands are used to measure blood flow, one commonly used ligand is ^{99m}Tc hexamethylpropyleneamineoxime. Dopamine transporter scan is a specific form of SPECT targeting dopamine producing neurons in the basal ganglia, the

ligand most frequently studied is ^{123}I -2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT), (see section 3.2.8.6 below).

Radiolabelled tracers used in SPECT to measure regional, cortical blood flow have shown a typical pattern of reduced perfusion in temporoparietal areas in AD. In DLB a pattern of occipital and parietal hypoperfusion is more common, often referred to as the “horse-shoe sign” (Lobotesis *et al.*, 2001), at present a supportive feature in the diagnosis of DLB (McKeith *et al.*, 2005). Relatively few studies with small samples have assessed the precision of cerebral SPECT as a biomarker for DLB, and available results are conflicting, indicating the need for multicenter studies for better diagnostic accuracy.

3.2.8.6 Dopamine transporter imaging

The most convincing evidence exists for Dopamine transporter scan where a soluble radioactive isotope, most often containing ioflupane (^{123}I) (^{123}I]FP-CIT SPECT), is injected intravenously in the patient. About 3 hours later a gamma camera is used to visualize the uptake in the brain (Booij *et al.*, 1999). Ioflupane has a high binding affinity for presynaptic dopamine transporters which is especially enriched in the striatum (part of the basal ganglia). In cases of reduction of dopaminergic neurons in the substantia nigra, the visualization of dopamine transporters is greatly reduced.

These findings were first demonstrated in PD, but can now also be seen in preclinical cases of nigro-striatal degeneration including multiple system atrophy, progressive supranuclear palsy and DLB. This means that DLB patients without clinically detectable parkinsonism can now be identified (Walker *et al.*, 2007), whereas the scans of patients with AD are normal.

In a large pivotal multicenter study, Dopamine transporter scan demonstrated a sensitivity of 78% and a specificity of 90% in distinguishing probable DLB from AD (McKeith *et al.*, 2007). Recent findings suggest that Dopamine transporter scan could be of even greater clinical relevance in identifying patients with possible DLB. In a 12-month longitudinal study no patients with possible DLB and a normal scan at baseline had developed probable DLB at the follow-up examination. In contrast, 63% (12 of 19) of subjects with an abnormal scan had probable DLB at follow-up, a significant difference (O'Brien *et al.*, 2009). Thus, Dopamine transporter scan can help to identify DLB at an early stage, before the full clinical syndrome has developed.

3.2.8.7 PET based imaging

In Positron Emission Tomography (PET) a radioactive tracer (drug) is used to evaluate the biological activity in various tissues and organs. The tracer can be injected intravenously, swallowed or inhaled and different radioisotopes can be used depending on the preferred uptake in different tissues or organs. Fluorodeoxyglucose-positron emission tomography (FDG-PET) uses glucose to measure metabolic activity, N-11C-methyl-4-piperidyl acetate can be used to investigate cholinergic pathways, 18-fluorodopa to assess the dopaminergic system and Pittsburgh compound B (PIB) and 18 F-labelled compounds, such as 18 F-Flutemetamol, to assess amyloid load. In contrast to SPECT, PET-based imaging is more expensive and not easily available.

Consistent with perfusion SPECT findings, FDG-PET has also shown the typical pattern of occipital hypometabolism with relative preservation of the posterior cingulate (as opposed to AD, the so-called positive cingulate island sign) (Kemp and Holmes, 2007), and the same cortical pattern has been linked to visual hallucinations in DLB (Kantarci *et al.*,

2012b;Pernecky *et al.*, 2008). The pattern of occipital hypometabolism is also typical for PDD, but the sensitivity and specificity is at present too low to recommend FDG-PET in the clinical routine.

Most studies using amyloid imaging have focused on AD using ¹¹C-Pittsburgh compound-B (PIB). Typical predilection sites for amyloid in AD are pre-frontal and temporoparietal cortices. Studies in DLB have been variable, but amyloid retention seems to be less than in AD, but overall higher than in PDD and NC (Donaghy *et al.*, 2015). DLB has been shown to have increased amyloid retention in 80 % of cases while infrequent in PDD (Edison *et al.*, 2008). At present the diagnostic use of amyloid PET in Lewy body disease is not established, but amyloid deposits are associated with faster cognitive decline (DLB) and progression to dementia (PD) as compared to normal controls (Halliday *et al.*, 2011b).

Biomarkers in Lewy body dementia are summarized in **table 5**.

3.3 Parkinson's disease

3.3.1 Introduction

Parkinson's disease (PD) is a chronic, idiopathic, neurodegenerative disease that affects not only movement, but also includes a range of non-motor features such as autonomic dysfunction, sleep problems and neurobehavioral symptoms. PD is the second most common progressive neurodegenerative disorder after Alzheimer's disease (AD) and worldwide an estimated 7-10 million people are believed to be affected (Parkinson's Disease Foundation: Statistics on Parkinson's. Retrieved from http://www.pdf.org/en/parkinson_statistics. (2013)).

The age-adjusted incidence is estimated to about 13.5 per 100.000 person-years and an age-related prevalence of about 115 per 100.000 populations. The frequency of PD is about 1.3 cases per 100 000 people younger than 45 years of age, 3100 per 100.000 in the 75–85 age group, and 4300 per 100.000 in those older than 85 years (de Lau and Breteler, 2006). The prevalence of PD is expected to rise dramatically over the next decades due to the aging of the population.

3.3.2 Diagnostic criteria

PD is a clinical diagnosis defined by the gradual occurrence of motor symptoms such as rigidity (stiffness), bradykinesia (slowness of movements), resting tremor, and postural and gait disturbances, usually with unilateral onset, progressing to bilateral symptoms overtime. Rest tremor is the presenting symptom in over 70 percent of cases and postural and gait disturbance usually develop later in the disease process. The “pill rolling” rest tremor of idiopathic PD is most noticeable when the body part is not engaged in purposeful movement.

The most widely accepted clinical criteria for the diagnosis of PD are those introduced by the UK PDS Brain Bank Diagnostic Criteria (Hughes *et al.*, 1992) and National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for Parkinson's disease (Gelb *et al.*, 1999) (**text box 7**). Typically, the clinical diagnosis is based on the presence of cardinal motor symptoms, associated and exclusionary symptoms and response to levodopa.

Text box 7:

Criteria for the diagnosis of Parkinson's disease (Gelb et al. 1999)

Group A features: Characteristic of Parkinson disease:

- Resting tremor
- Bradykinesia
- Rigidity
- Asymmetric onset

Group B features: suggestive of alternative diagnoses (features unusual early in the clinical course):

- Prominent postural instability in the first 3 years after symptom onset
- Freezing phenomena in the first 3 years
- Hallucinations unrelated to medications in the first 3 years
- Dementia preceding motor symptoms or in the first year after diagnosis
- Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
- Severe symptomatic dysautonomia unrelated to medications
- Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Criteria for possible diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A are present; at least 1 of these is tremor or bradykinesia **and**
either none of the features in group B is present **or**
symptoms have been present for less than 3 years and none of the features in group B is present **and**
either substantial and sustained response to levodopa or a dopamine agonist has been documented **or**
patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for probable diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A are present **and**
none of the features in Group B is present (note: symptom duration of at least 3 years is necessary to meet this requirement) **and**
substantial and sustained response to levodopa or a dopamine agonist has been documented

Criteria for definite diagnosis of Parkinson disease:

All criteria for possible Parkinson disease are met **and**
histopathological confirmation of the diagnosis is obtained at autopsy

3.3.3 Pathogenesis

The defining hallmark of PD is the finding of Lewy bodies (LBs) in the substantia nigra (see sections 3.2.2 and 3.2.3 for details) including loss or degeneration of dopamine-producing neurons. The preferential loss of dopaminergic neurons eventually leads to the typical motor syndrome, and pathological and neuroimaging studies suggest that between 50-70% of substantia nigra neurons have degenerated at that point (Cheng *et al.*, 2010). This means that the neurodegenerative process in PD is at a rather advanced stage when clinical motor symptoms are evident.

There are five genes associated with familial PD (causal genes) including alfa-synuclein, PARK2, PINK1, DJ-1 (PARK7) and LRRK2. These familial cases are found in only 1-2 % of PD cases. In addition, there are associated genes that do not directly cause, but contribute to disease susceptibility (Spatola and Wider, 2014). Although causal mechanisms in PD are rare, evidence suggest that environmental factors including exposures to pesticides, drug abuse and chronic low-level inflammation of the brain due to aging are contributing. Smoking and caffeine intake can possibly offer protective properties (de Lau and Breteler, 2006).

Braak et al. developed a staging scheme of LB pathology in PD suggesting that the disease spreads from the medulla, enteric nervous system and the olfactory bulb and ascends in a predictable manner eventually involving the entire neocortex (Braak *et al.*, 2003) (se section 3.2.3). It is well established that clinical symptoms, both motor and non-motor, are associated with the regional distribution and extent of LB pathology (Braak *et al.*, 2005;McKeith *et al.*, 2005)

3.3.4 Clinical features

3.3.4.1 Motor symptoms

The typical motor symptoms are described in section 3.3.2.

3.3.4.2 Non-motor symptoms

There is a broad spectrum of non-motor symptoms (NMS) in PD (Aarsland *et al.*, 2009c), and although they can be present in all stages of disease, they are especially problematic as the disease progresses. Most patients with PD also describe NMS symptoms at the time of diagnosis.

There are typically four domains affected including neuropsychiatric symptoms (depression, anxiety, psychosis and apathy), autonomic dysfunction (orthostatic hypotension, urinary urge/incontinence, constipation/fecal incontinence, sexual dysfunction, etc.), sensory disorders (olfactory dysfunction, pain syndromes, abnormal sensation) and sleep problems (insomnia, REM sleep Behaviour Disorder (RBD), restless legs syndrome, day time sleepiness). Neuropsychiatric and behavioral symptoms are especially common in PD and were found in 89% of patients in one study, with depression (58%), apathy (54%), anxiety (49%), and visual -hallucinations (44%) emerging as the most common symptoms (Aarsland *et al.*, 2007a).

It has also become increasingly recognized that a number of NMS can precede the traditional motor symptoms and clinical diagnosis of PD, including constipation, RBD, olfactory dysfunction and depression (Postuma *et al.*, 2012), and that PD may start even decades before evident motor features. Although the underlying mechanisms of NMS, including pathological and biochemical substrates, are poorly understood, there is (according to the Braak staging

system, see section 3.2.3) evidence that early spread of Lewy bodies, before involvement of the basal ganglia and central nervous system (stages 1-2), may be involved. Conducting large, prospective studies in the future assessing potential premotor manifestations can help define the non-motor stage of PD.

NMS can be potential sensitive, clinical biomarkers, leading to an earlier focus on a parkinsonian phenotype, but a major challenge is the present low specificity.

3.3.5 Treatment of motor symptoms

Since the genetic and molecular basis of PD is largely unknown, all therapeutic strategies are at present purely symptomatic.

The mainstay of treatment of motor symptoms in PD has since the 1960's been dopamine replacement therapy, with L-Dopa being the gold standard. However, chronic L-Dopa use is associated with problematic side-effects including debilitating dyskinesias, and alternative medical treatments strategies are being researched (Stayte and Vissel, 2014). These include drugs targeting adenosine, serotonin, glutamate and adrenergic receptors and also calcium channel blockers, anti-inflammatory drugs and gene therapies.

For patients experiencing serious side-effects or diminishing effects of dopamine replacement therapy, Deep Brain Stimulation (DBS), may be an alternative. In DBS, an electrode is surgically implanted in the subthalamic nucleus, globus thalamus or ventral intermediate nucleus, providing continuous high frequency electrical stimulation.

For general treatment of non-motor symptoms in DLB and PDD, see section 3.4.

3.3.6 Cognitive impairment

3.3.6.1 The prevalence and incidence of Parkinson's disease dementia (PDD)

One common complication in PD is PDD, and the Movement Disorder Society Task Force has proposed diagnostic criteria to be used in clinical practice (Dubois *et al.*, 2007a) (**Text box 8**).

The prevalence of PDD is estimated to be about 5% of all cases of dementia (Aarsland *et al.*, 2008). Several cross-sectional epidemiological studies have reported that the proportion of PD patients who have dementia is approximately 30% (Aarsland *et al.*, 2005; Riedel *et al.*, 2010). Cross-sectional studies, however, underestimate the proportion of people with PDD, since mortality in PD is influenced by dementia.

Longitudinal studies have reported a six times higher risk of developing dementia in PD compared to people without PD of the same age. The incidence of dementia in cross-sectional PD cohorts is 100 per 100,000 patient-years. Consequently, a very high cumulative proportion of up to 80% with dementia has been reported among PD patients (Aarsland *et al.*, 2003; Hely *et al.*, 2008). A lower incidence has been reported for the first years after diagnosis. In a longitudinal study based on an incidence PD-cohort, a dementia incidence of 30 per 100,000 person-years was reported (Evans *et al.*, 2011) and slightly less than 50% of the cohort had developed dementia eight years after the diagnosis. The mean time-period to diagnosis with dementia was 6.2 years.

3.3.6.2 Mild cognitive impairment in PD

The term MCI is now well established as a precursor of dementia in AD, but remains an area of research in DLB and PD.

About 20-25% of PD patients without dementia have mild cognitive impairment (PD-MCI) (Aarsland *et al.*, 2010), and even at the time of diagnosis MCI is observed in 15-20%,

including non-treated patients (Aarsland *et al.*, 2009a). Recently the Movement Disorders Society commissioned a task force which proposed the first clinical consensus criteria for MCI in PD (Litvan *et al.*, 2012). The cognitive profile in PD is heterogeneous, and it has recently been demonstrated that impairments of visuospatial functions and memory occur in addition to the well-known attentional and executive deficits (Bronnick *et al.*, 2011). More importantly, the early cognitive changes in PD seem to predict subsequent development of dementia. To date, three studies have published longitudinal data on PD-MCI patients (Janvin *et al.*, 2006; Pedersen *et al.*, 2013; Williams-Gray *et al.*, 2009a).

Text box 8

Diagnostic procedures for Parkinson's Disease Dementia (PDD) - Recommendations from the Movement Disorder Society Task Force (Dubois *et al.*, 2007) :

- A diagnosis of Parkinson's disease (PD)
- PD developed prior to the onset of dementia
- Decreased global cognitive efficiency - Mini Mental Status Examination (MMSE) below 26 (level 1 testing *)
- Cognitive deficits severe enough to impact daily living
- Impairment in at least two of the following domains and proposed screening tests (level 1):
 - a) Attention - Serial 7's of the MMSE, months reversed within 90 seconds
 - b) Executive function – Lexical fluency within 60 seconds (words beginning with S), Clock drawing test
 - c) Visuo-constructive ability - MMSE pentagons
 - d) Memory impairment - 3-word recall of the MMSE

Supportive features:

Apathy, depressed or anxious mood, hallucinations, excessive daytime sleepiness

Diagnosis of probable PDD uncertain:

Comorbidities including depression delirium or any other abnormality that can cause significant cognitive impairment make the diagnosis uncertain. Furthermore, if the time interval between motor and cognitive symptoms is uncertain, differentiation between dementia with Lewy bodies and PDD can be difficult.

*Level 1 equals screening tests as opposed to a more detailed neuropsychological assessment

Janvin et al. concluded that non-amnesic MCI was strongly associated with development of dementia 4 years later (odds ratio 8.3%), and Pedersen et al. found that a diagnosis of MCI versus non-MCI had a relative risk of dementia of 39.2 at 3 years. A 5 year follow up of the CampaIGN study incident cohort (Williams-Gray *et al.*, 2009a), including 126 PD patients, found that age ≥ 72 years, semantic fluency and inability to copy an intersecting pentagons figure (a task in the Mini Mental Status Examination (MMSE)) were significant predictors of dementia risk. Furthermore, a polymorphism in the catechol-O-methyltransferase (COMT) gene, involved in dopamine metabolism in the pre-frontal cortex, was associated with executive dysfunction, but not conversion to dementia. In contrast, patients with a genetic variant in the gene containing the microtubule-associated protein tau gene (MAPT, H1 haplotype) were strongly associated with an increased dementia risk. One interpretation of these findings is that frontal-type deficits are more related to dopaminergic lesions (causing executive, but more mild cognitive deficits), whereas the more posterior cognitive deficits may be associated with structural pathologies such as temporo-parietal Lewy bodies and plaque pathology (associated with semantic memory and visuospatial dysfunction, leading to a more rapid decline and dementia). Further studies are needed to test this “dual syndrome hypothesis”, and although conclusions cannot be drawn due to a cross-sectional design, recent data published from the ICICLE-PD study support these main findings (Nombela *et al.*, 2014) (see also section 8.3).

3.3.6.3 Variations in the course of cognitive impairment in PD

There is a wide variation in the time from onset of PD to dementia. Whereas some patients develop dementia within a few years of the diagnosis, others do not show signs of dementia for more than 20 years (Aarsland *et al.*, 2007b). Similarly, there is a variation in the rate of cognitive decline in PD. The mean rate of cognitive decline in PD is approximately 1 point per annum on the MMSE (Aarsland *et al.*, 2004), but for unknown reasons there is large inter- and intra-individual variation in the rate of decline. As reported above, a slower rate of decline occurs in the early stages of the disease. Typically, in an individual PD patient, a period of no or very little decline is followed by an inflexion point after which a much more rapid decline occurs, with large inter-individual variation in the time-period to this inflexion point (Aarsland *et al.*, 2011a; Johnson and Galvin, 2011). After the onset of PDD, the progression to the terminal stage of the illness is less variable, and there is an average of 3 years with increasing disability leading to death, whatever the age of onset (Kempster *et al.*, 2010). Identifying predictors of time to diagnosis of dementia and of the rate of cognitive decline is thus a key clinical and research priority.

3.3.6.4 Clinical risk factors for early cognitive decline in PD

A shorter time to dementia is associated with older age at diagnosis of PD, non-tremor dominant motor subtypes with significant postural instability and gait disturbances (PIGD-subtype) (Evans *et al.*, 2011; Halliday and McCann, 2010; Williams-Gray *et al.*, 2009a). In addition, visual hallucinations, RBD (Boot *et al.*, 2012; Postuma *et al.*, 2009; Williams-Gray *et al.*, 2009a) and olfactory dysfunction (Baba *et al.*, 2012) are associated with a shorter time to the development of dementia. MCI as a predictor of cognitive decline in PD is reviewed in section 3.3.6.2.

3.3.6.5 Genetic contributions to cognitive impairment in PD

Several studies have reported a familial association between dementia and PD, suggesting that genetic factors influence the emergence of cognitive impairment and dementia in PD (Kurz *et*

al., 2006). Despite the progress in identifying genes that cause or increase the risk of PD the specific genetic contribution to cognitive impairment in PD is not known (Singleton *et al.*, 2013).

The H1 and H1p haplotypes of the tau-associated microtubule associated protein tau (MAPT) have been found to be significantly associated with PDD with significant odds ratios ranging from 1.35 to 3.7 (Goris *et al.*, 2007;Nombela *et al.*, 2014;Seto-Salvia *et al.*, 2011), although not consistently. Furthermore, combining genomewide association studies (GWAS) from both AD and PD have recently provided insights into genetic pleiotropy (defined as a single gene or variant being associated with more than one distinct phenotype, i.e. shared pathobiology). In a recent large GWAS involving almost 90.000 subjects, single nucleotide polymorphisms (SNPs) were identified and it was concluded that the MAPT locus was a site of genetic overlap associated with both AD and PD (Desikan *et al.*, 2015).

Alfa-synuclein gene mutations and duplications may lead to cognitive impairments and dementia (Chartier-Harlin *et al.*, 2004;Polymeropoulos *et al.*, 1997), but remains a rare cause of familial PD.

PD patients with GBA mutations have more frequent and severe cognitive impairments when compared to sporadic cases of PD (Neumann *et al.*, 2009), and GBA mutation status may be an independent risk factor for cognitive impairment in patients with PD (Alcalay *et al.*, 2012;Sidransky *et al.*, 2009) These findings have recently been confirmed in a prospective study of newly diagnosed PD patients where the increased risk of progression to dementia was 5 times greater in those with a GBA mutation compared to those without (Winder-Rhodes *et al.*, 2013).

Other typical PD mutations such as LRRK2 and Parkin-mutations do not seem to be associated with the development of cognitive impairment (Alcalay *et al.*, 2010). However, neuropathologic features of LRRK2-associated PD have been linked to cortical LB formation, and it is possible that cognitive impairment in Parkin-carriers only becomes apparent after a long disease duration (Alcalay *et al.*, 2014;Poulopoulos *et al.*, 2012). Furthermore, mutations of the COMT gene are associated with dopamine related cognitive deficits, such as reduced attention, but do not seem to be associated with increased risk of dementia (Hoogland *et al.*, 2010;Williams-Gray *et al.*, 2009a) (see also section 3.3.6.2).

Finally, inconsistent results have been found regarding the associations between APOE genotype and butyrylcholinesterase-K genotypes and the risk of dementia (Kurz *et al.*, 2009;Lane *et al.*, 2009;Nombela *et al.*, 2014;Williams-Gray *et al.*, 2009b).

3.3.6.6 Biomarkers of cognitive impairment in PD

For a general introduction to different biomarkers, see section 3.2.8.

Several different biomarkers, including genetics, EEG, CSF, MRI, SPECT, PET and even serum, have been associated with cognitive impairment in PD, and several longitudinal studies have been reported (Bohnen *et al.*, 2011;Chen-Plotkin *et al.*, 2011;Dujardin *et al.*, 2004;Klassen *et al.*, 2011;Siderowf *et al.*, 2010). However, larger multicenter studies with robust and a priori defined cut-off points are necessary before these markers can be implemented in clinical practice.

3.3.6.6.1 MRI including computer-based analyzes

MRI has been proposed as a tool for predicting cognitive impairment and dementia in PD, similar to its common use in AD.

Most studies have used structural MRI and shown that atrophy of the temporoparietal lobe, entorhinal cortex, hippocampus, prefrontal cortex and posterior cingulate cortex (Burton *et al.*, 2004; Kenny *et al.*, 2008; Lyoo *et al.*, 2010; Song *et al.*, 2011; Weintraub *et al.*, 2011) are associated with PDD. Similar, but less marked, changes have also been identified in PD-MCI (Beyer *et al.*, 2007; Song *et al.*, 2011). In a large multicenter study it was recently found that PD-MCI was associated with widespread cortical atrophy and both anterior (superior frontal) and posterior (temporoparietal) cognitive deficits. There was even some atrophy in the right inferior temporal lobe of cognitively normal patients suggesting that cortical thinning can be an early biomarker of cognitive decline in non-demented PD (Pereira *et al.*, 2014b). Moreover, an AD-like pattern of atrophy (hippocampus, temporoparietal cortex) was recently found to be related to cognitive performance in PD, and it was suggested that these changes might be used to predict a global cognitive decline in non-demented patients over a 2-year follow-up period (Weintraub *et al.*, 2012).

However, in a recent review of the literature it was concluded that MRI, although there were MRI detectable grey (and white) matter atrophy across all stages of PD, could not serve as a valid biomarker and that more longitudinal studies are necessary (Duncan *et al.*, 2013). Other promising MR techniques are also emerging, including functional MRI, MR perfusion imaging with arterial spin labeling and MR spectroscopy, but more confirmatory studies with longitudinal design are needed (Duncan *et al.*, 2013).

WML

White matter hyperintensities or lesions (WML), also termed leukoaraiosis, are small lesions of high intensity within periventricular and deep subcortical WM, normally seen on T2-weighted MRI or fluid-attenuated inverted recovery (FLAIR) sequences, and are thought to result from small vessel disease. Small vessel disease comprises different pathological processes, the most common being arteriolosclerosis which affect deep white matter (WM) arterioles. In the general population the prevalence of WML ranges from 11-21% in adults aged around 64 to 94% at age 82 (Garde *et al.*, 2000; Ylikoski *et al.*, 1995) and predict an increased risk of cerebrovascular disease, including stroke (hazard ratio 3.3, 95% confidence interval 2.6 - 4.4), dementia (1.9, 1.3 -2.8), and death (2.0, 1.6 -2.7) (DeBette and Markus, 2010).

Despite an increased risk of dementia in the general population, the role of WML in cognitive impairment and progression to dementia in LBD is unclear and studies have been inconclusive. Importantly, methodological problems including heterogeneity of study populations, concomitant cerebrovascular burden and different MRI protocols (i.e. visual rating scales versus automated protocols) have made comparisons across studies challenging.

WML comparisons (including periventricular hyperintensities) in AD, vascular dementia, DLB and normal aging have shown more extensive lesions in all dementia subtypes (Barber *et al.*, 1999), and in imaging studies of patients with established PD, WML were seen across all stages of disease (Beyer *et al.*, 2006; Burton *et al.*, 2006). In a longitudinal study comparing patients with AD, PDD, DLB and normal controls, WML burden at baseline was greater in AD, but cognitive decline was similar between groups (Burton *et al.*, 2006). More severe WML load in advanced disease (PDD), typically associated with deep WM and periventricular involvement, correlated to cognitive parameters including the MMSE and impairments in attention, visuospatial, memory and executive functions (Beyer *et al.*, 2006; Lee *et al.*, 2010; Santangelo *et al.*, 2010).

Of note, in early PD including PD-MCI, no significant WML load differences compared to normal controls and no association between WML load and cognitive impairment (attention-executive functions) were seen (Dalaker *et al.*, 2009).

Taken together, the role of WML in neurodegeneration is unclear. These findings suggest an interaction between the effects of age and WML in PD or merely that cognitive effects of comorbid WMLs are more easily detectable in advanced disease (PDD). Underlying mechanisms are unknown, but possibly direct damage to neuronal networks or an interaction between WMLs and other regional structures are involved. Since WML load seems to increase the risk of cognitive impairment only in the general population, one can speculate that the effect of WMLs is less important once cognitive deterioration has begun. A more sensitive measure of WM integrity is diffusion tensor imaging, see below.

Diffusion tensor imaging

A special variant of MRI is Diffusion Tensor Imaging (DTI). DTI measures the diffusion of water in biological tissue and is a technique where the integrity and orientation of WM and WM tracts (tractography) can be visualized and evaluated (Le, 2007). Anisotropy reflects the directionality of diffusion (i.e. diffusion along axons and fiber bundles), as opposed to isotropy, which implies identical properties in all directions. Fractional anisotropy (FA), a measure of how strongly directional the local tract structure is, typically measures high in intact WM tracts because water tends to move parallel rather than perpendicular to fiber bundles. A measure of diffusivity in the perpendicular plane is the radial diffusivity (DR), and increased DR is characteristic of WM damage. Tractography essentially follows the primary eigenvector of diffusion from one voxel to the next.

Still, there has not been a satisfactory solution to alignment of FA images from multiple subjects in a way that allows for valid conclusions in the subsequent voxelwise analysis.

Tract Based Spatial Statistics (TBSS) is a new technique that aims to improve the sensitivity, objectivity and interpretability of analysis of multi-subject diffusion imaging studies by aligning all images creating a “mean FA skeleton” which represents the centers of all tracts common to the group (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>).

Over the last few years we have seen a proliferation of DTI studies in a wide range of neurodegenerative disorders including AD and Lewy body disease (LBD). When this thesis was planned, however, very few studies using DTI in PD, none that had focused on DTI and early cognitive impairment in LBD and no studies directly comparing PD and AD had been published.

In a recent meta-analysis focusing on parkinsonian syndromes it was concluded that DTI shows promise as a candidate biomarker (including differentiating PD from atypical parkinsonian syndromes and detecting early WM changes), but that these preliminary findings need confirmation in larger cohorts (Cochrane and Ebmeier, 2013). Furthermore, most studies were small and based on a region of interest approach, no studies presented correlations between PD severity and cognition and no longitudinal results were presented. Focusing on PD, 4 studies found reduced FA in frontal WM compared to normal controls, and preliminary findings in PDD and DLB were somewhat mixed, but primarily with FA reductions in WM in temporo-occipital and posterior cingular areas. (Cingulum is known as a collection of WM fibers projecting from the cingulate gyrus to the entorhinal cortex. The posterior cingulum is typically related to cognitive functions, the anterior part probably more to emotion, including apathy and depression).

More recently, Kamagata et al. found that FA was significantly lower in patients with PDD (n=15) than in normal controls (n=15) in both the anterior and posterior cingulate WM fiber tracts and similarly in the anterior cingulate for PD (n=15) (Kamagata *et al.*, 2012). MMSE and FA values of the anterior cingulate fiber tracts correlated ($r = 0.633$, $p < .05$) in patients with PDD. Hattori et al. enrolled patients with PD cognitively normal (n = 32), PD-MCI (n = 28), PDD (n = 25), DLB (n = 29) and normal controls (n =40) finding reduced FA in several major tracts in PD-MCI, PDD, DLB, but not PD cognitively normal. Grey matter and cerebral perfusion was also assessed, and results suggested a common disease progression with functional alteration (hypoperfusion) followed by structural alterations in which WM alteration preceded gray matter atrophy (Hattori *et al.*, 2012).

Conversely, a study by Meltzer et al. showed that WM integrity was compromised also in PD cognitively normal (n=63) and that these alterations increase with disease progression (Melzer *et al.*, 2013). Importantly, these microstructural changes were associated with executive function, attention and memory. Similar findings have recently been reproduced in two other studies (Theilmann *et al.*, 2013;Zheng *et al.*, 2014).

In the first study comparing AD (n=35) and DLB (n=36) using TBSS, it was concluded that DLB patients had a specific pattern of reduced FA in parieto-occipital tracts, and that changes were more diffuse in AD (Watson *et al.*, 2012).

There have also been attempts to detect early WM changes using TBSS analysis in 64 asymptomatic first degree relatives of patients with PD (30 mutation carriers), who carry the G2019S mutation in the LRRK2 gene, but with negative result (Thaler *et al.*, 2014).

In conclusion, using DTI subcortical WM tract degeneration is detectable early in LBD and may precede changes observed on conventional structural MRI (Duncan *et al.*, 2013).

See further discussion in section 8.4 (paper 2).

3.3.6.6.2 Electroencephalography (EEG)

Quantitative electroencephalography (QEEG) studies suggest that low-frequency background rhythm is associated with cognitive impairment in PD, and that QEEG measures can predict future risk of developing dementia (Klassen *et al.*, 2011).

On the other hand, in a previous study EEG could discriminate between AD and DLB based primarily on posterior leads, but patients with PDD exhibited the same abnormalities in less than half of the DLB cases (Bonanni *et al.*, 2008), suggesting low specificity in separating the different LBDs.

3.3.6.6.3 PET-based imaging

Reduced glucose metabolism in both frontal and parietal cortex measured by FDG-PET has been found to be associated with cognitive decline in PD-MCI (Huang *et al.*, 2008). More specifically, hypometabolism in the temporal cortex has been associated with verbal memory, frontal cortex with executive dysfunction and parietal cortex with visuospatial dysfunction (Jokinen *et al.*, 2010). A recent longitudinal study suggested that early metabolic changes in visual association and posterior cingulate cortices could predict incident dementia in PD (Bohnen *et al.*, 2011).

For amyloid-based PET, see section 3.2.8.7.

3.3.6.6.5 Perfusion SPECT

Cross-sectional studies using SPECT have reported hypoperfusion in lateral parietal and frontal cortices in PD patients without dementia, which correlated with cognitive impairment (Firbank *et al.*, 2003). Bilateral hypoperfusion in posterior parietal lobes and in the right occipital lobe were seen in PD-MCI, which differed from the pattern seen in non-PD-MCI (Nobili *et al.*, 2009). Perfusion has also been shown to aid in the prediction of cognitive decline in PD (Dujardin *et al.*, 2004).

3.3.6.6.6 Cerebrospinal fluid (CSF) and plasma

It has been reported that A β 42 levels were lower and total-tau and p-tau were higher or normal in PDD patients compared to PD patients without dementia and controls (Montine *et al.*, 2010). Likewise, a prospective study indicated that lower baseline A β 42, but not total-tau and phospho-tau (181p), was associated with a more rapid cognitive decline (Siderowf *et al.*, 2010). Detailed analyses of several splice variants of A β showed that early PD patients displayed significant reductions not only of CSF A β 42, but also A β 40 and A β 38. These reductions were associated with memory impairment (i.e. PD-MCI), but not with executive-attentional or visuospatial dysfunction (Alves *et al.*, 2010). Similar findings in PDD and DLB suggest that amyloid pathology contributes to cognitive impairment in LBD, and that there is an interaction and overlap with typical pathology seen in AD (Brunnstrom *et al.*, 2013; Mollenhauer *et al.*, 2006).

Of great interest is the association between LBD and alpha-synuclein. Patients with PD and DLB have shown lower monomeric CSF alpha-synuclein levels than patients with AD and controls (Mollenhauer *et al.*, 2011), but in a recent meta-analysis involving 2728 patients, lower CSF alpha-synuclein could only separate DLB from AD. No significant difference was found between DLB and PD or other neurodegenerative conditions (Lim *et al.*, 2013). Moreover, correlations between cognitive status and lower CSF alpha-synuclein have been reported in DLB (Ballard *et al.*, 2010), but at present not in PD. Conversely, alpha-synuclein oligomers or phospho-alpha-synuclein (129p) in CSF have been reported to be higher in patients with PD compared to patients with AD or controls (Tokuda *et al.*, 2010). Of note, in the DATATOP study with up to 8 years follow-up of more than 300 unmedicated PD patients, CSF alpha-synuclein predicted better preservation of cognitive functions (Stewart *et al.*, 2014).

In a recent systematic review it was concluded that neither CSF nor plasma alpha-synuclein was a reliable biomarker in diagnosing PD, with CSF alpha-synuclein in the 71-94 % and 25-53 % range with regard to sensitivity and specificity respectively (Malek *et al.*, 2014). Conversely, measurements in peripheral solid tissues were more promising and in case of colonic mucosa, submandibular salivary glands and skin biopsies showed moderate sensitivity and high specificity (80-100%) in detecting alpha-synuclein. Furthermore, epidermal growth factor has been shown to predict cognitive decline in PD (Chen-Plotkin *et al.*, 2011).

In conclusion, findings from CSF studies confirms the heterogenous biology involved in PD including overlapping features with typical AD pathology. Currently CSF biomarkers cannot be used in clinical practice.

Biomarkers in Lewy body dementia are summarized in **table 5**.

Table 5: Biomarkers in Lewy body dementia

Modality		DLB	PDD	Comment
SPECT	Dopamine Transporter (FP-CIT SPECT)	DLB patients without clinically detectable parkinsonism can be identified (Walker <i>et al.</i> , 2007). Pathological scan can predict DLB (O'Brien <i>et al.</i> , 2009)	Significantly reduced uptake in striatum (nucleus caudatus and putamen) relative to NC and AD (never clinically indicated)	Diagnostically useful for distinguishing DLB from AD/NC and essential tremor and neuroleptic induced parkinsonism from DLB, PDD, MSA, PSP and CBD.
	Perfusion	Global cortical hypoperfusion relative to NC. Some evidence for reduced occipital lobe perfusion relative to AD (horse shoe sign) (Lobotesis <i>et al.</i> , 2001).	Similar findings for DLB and PDD with more parieto-occipital affection compared to NC (Rossi <i>et al.</i> , 2009). Perfusion has been shown to aid in the prediction of cognitive decline in PD (Dujardin <i>et al.</i> , 2004).	Occipital hypoperfusion is indicative of DLB or PDD (but specificity is low)
MRI	Atrophy	Diffuse pattern of global GM atrophy compared to NC. Generally less GM atrophy including MTL than AD (Mak <i>et al.</i> , 2014)	Detectable GM atrophy across all stages of PD, but less MTL atrophy than AD (Duncan <i>et al.</i> , 2013) AD-like pattern of atrophy (including MTL) can possibly predict cognitive decline in PD (Weintraub <i>et al.</i> , 2012)	MTL preserved supports diagnosis of DLB. No MTL atrophy or just general atrophy is not diagnostically helpful.
	Diffusion Tensor Imaging	DLB patients show a specific pattern of reduced FA (WM damage) in parieto-occipital tracts with more diffuse changes in AD (Watson <i>et al.</i> , 2012).	A recent meta-analysis concludes that DTI is a promising biomarker in PD and PDD (evaluation of WM integrity). (Cochrane and Ebmeier, 2013)	A possible future biomarker in early LBD and may precede changes observed on conventional structural MRI (Duncan <i>et al.</i> , 2013)

CSF	Amyloid and tau	Typical AD changes (lower A β 42 and higher total-tau and p-tau than NC) are also seen in DLB (Brunnstrom <i>et al.</i> , 2013)	Typical AD changes (lower A β 42 and higher total-tau and p-tau than NC) are also seen in PDD (Mollenhauer <i>et al.</i> , 2006). Lower A β 42 has been shown to predict PDD (Siderowf <i>et al.</i> , 2010)	Similar findings in PDD and DLB suggest that amyloid pathology contributes to cognitive impairment in LBD.
	Alfa-synuclein	Patients with DLB have shown lower monomeric CSF alfa-synuclein levels than patients with AD and NC (Lim <i>et al.</i> , 2013; Mollenhauer <i>et al.</i> , 2011)	Patients with PD and DLB have shown lower monomeric CSF alfa-synuclein levels than patients with AD and NC (Mollenhauer <i>et al.</i> , 2011), and may predict preservation of cognitive function (Stewart <i>et al.</i> , 2014)	Alfa-synuclein is a promising biomarker for LBD, but sensitivity and specificity is currently too low to be used in the clinical routine.
EEG		A longitudinal study including DLB, AD and PDD patients with early dementia (≥ 20 on the MMSE), concluded that EEG could discriminate between AD and DLB (Bonanni <i>et al.</i> , 2008)	Low-frequency background rhythm is associated with cognitive impairment in PD, and can predict future risk of dementia (Klassen <i>et al.</i> , 2011).	At present more confirmatory studies are needed before EEG can serve as a reliable biomarker for LBD.
Myocard scinti-graphy (MIBG)		A recent meta-analysis involving 46 studies and 2680 patients concluded that AD, DLB and PD could be discriminated with a high level of accuracy (King <i>et al.</i> , 2011).	A recent meta-analysis involving 46 studies and 2680 patients concluded that AD, DLB and PD could be discriminated with a high level of accuracy (King <i>et al.</i> , 2011).	A pathological scintigraphy is listed as a supportive feature in the 2005 DLB consensus criteria. Pathology is also seen in the elderly with comorbid heart disease and diabetes.

PET	Glucose metabolism	Generalized low uptake, but typical pattern of occipital hypometabolism with relative preservation of the posterior cingulate (as opposed to AD) (Kemp and Holmes, 2007)	Generalized hypometabolism, but typically more occipital involvement (Jokinen <i>et al.</i> , 2010). Early metabolic changes in visual association and posterior cingulate cortices could predict incident dementia in PD (Bohnen <i>et al.</i> , 2011).	Supportive diagnostic feature for DLB. Could distinguish FTD with reduced dopamine transporter uptake from LBD.
	Amyloid	Amyloid retention seems to be less than in AD, but overall higher than in PDD and NC (Donaghy <i>et al.</i> , 2013).	No difference in deposition between PDD, PD, and NC (Donaghy <i>et al.</i> , 2013).	At present the diagnostic use of amyloid PET in LBD is not established. May help identify patients for treatment with anti-amyloid agents in the future.
Genetics		Most DLB cases occur sporadically, but genetic alterations overlap with AD and PD. GWAS-studies have not yet been published.	Alfa-synuclein, LRRK2, PINK1, PARK2 and PARK7 are causal disease genes found in familial PD (Nuytemans <i>et al.</i> , 2010).	The specific genetic contribution to cognitive impairment in PDD and DLB is not known.

DLB = dementia with Lewy bodies. PDD = Parkinson's disease dementia. SPECT = Single photon emission computed tomography. FP-CIT SPECT = ^{123}I -2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl) nortropane SPECT. NC = Normal control. AD = Alzheimer's disease. MSA = Multiple system atrophy. CBD = Corticobasal degeneration. PSP = Progressive supranuclear palsy. MRI=magnetic resonance imaging. CSF = Cerebrospinal fluid. EEG = Electroencephalography. PET=positron emission tomography. GM = grey matter. MTL=Medial temporal lobe. LBD=Lewy body disease. MIBG= (123) I-metaiodobenzylguanidine. FTD=frontotemporal dementia

3.4 Treatment/management of DLB and PDD

3.4.1 Introduction

Focusing on cognitive impairment, treatment is challenging for several reasons. First, there exists no curative treatment and thus per definition all interventions are directed against alleviating symptoms. Second, symptoms in DLB and PDD are often heterogeneous, involving a multitude of transmitter systems and organs and the patients are often frail. Thus, side effects are common and symptomatic targeting of one symptom will often affect and worsen others. This will present the physician with difficult priorities and tradeoffs in which one problem solved may create another. Third, there exist few randomized controlled trials and validated guidelines.

Adequate treatment of concomitant somatic disease should always have first priority as it can cause delirium and add to Neuropsychiatric symptoms (see also section 3.3.4.2), and non-pharmacological interventions are generally the treatment of choice. For details see (Ballard *et al.*, 2013).

3.4.2 Cognitive impairment

A recent Cochrane review concluded that acetylcholinesterase inhibitors are beneficial in PDD (Rolinski *et al.*, 2012), but most often with modest effects on cognition, neuropsychiatric symptoms and ADL. Similar evidence exists for DLB (McKeith *et al.*, 2000;Mori *et al.*, 2012). Despite mixed results (including no effect on motor and cognitive scores, but possible effect on global scores), a recent meta-analysis concluded that Memantine may be of benefit in Lewy body disorders (Matsunaga *et al.*, 2015).

3.4.3 Motor symptoms

Dopamine replacement therapy is well established and effective in PD (see section 3.3.5). No studies focusing on PDD exist, but some evidence from uncontrolled studies suggests benefit in DLB (Ballard *et al.*, 2011b;Mori *et al.*, 2012). However, these medications are typically not as effective as in PD and the propensity to exacerbate neuropsychiatric symptoms such as hallucinations must be taken into consideration.

3.4.4 Neuropsychiatric symptoms

Non-pharmacological interventions, including support, cognitive therapy and education to staff and caregiver should always be the cornerstone in treating neuropsychiatric symptoms (see also section 3.4.7).

Antipsychotic medication should ideally be avoided given the neuroleptic hypersensitivity about 50 % of these patients experience. Visual hallucinations and psychosis can be treated by screening and treating co-morbid somatic disease, reducing dopamine-based therapies or starting the patient on an acetylcholinesterase inhibitor. In severe cases of psychosis an atypical antipsychotic should be considered, the most convincing evidence exist for clozapine (Rongve *et al.*, 2012).

Depression is common in both PDD and DLB but evidence for the efficacy of antidepressants is scarce as patients with dementia most often are excluded from trials (Ballard *et al.*, 2013). There is, however some evidence that antidepressants in PD is useful (Richard *et al.*, 2012).

3.4.5 Sleep problems

Educating the patient, caregiver and staff on sleep hygiene is important as sleep disruption is common. RBD can be treated with melatonin, clonazepam or low dose quetiapine (Aurora *et*

al., 2010), and safety for the patient (and bed partner) must be secured for instance by padding the bed or floor and removing potential dangerous objects.

3.4.6 Autonomic dysfunction

Orthostatic hypotension can be alleviated using compression stockings and/or salt tablets or reducing antihypertensive or other medication affecting blood pressure. Anticholinergic medication should be avoided as they can induce a diversity of side effects including delirium. Stool softeners can be used for obstipation, and pain killers such as paracetamole with rather few side effects may be tried in first line treatment of pain.

3.4.7 Non-pharmacological treatment

There exists no systematic evidence for the use of non-pharmacological treatment in LBD, but information and regular support, appropriate activities including social interaction and follow-up of patient and caregiver is important. There is some evidence that coping strategies for visual hallucinations (Diederich *et al.*, 2003) and cognitive behavioral therapy for depression (Dobkin *et al.*, 2011) in PD are effective.

4.0 Alzheimer's disease

4.1 Introduction

In 1907 Alois Alzheimer described the case of Auguste Deter, a 51 year old woman who a few years earlier presented with rapid deteriorating memory and progressive behavioral symptoms. During the course of her illness her husband was eventually unable to care for her at home and brought her in 1901 to the Institution for the mentally ill and for epileptics in Frankfurt, Germany. There she was examined by Dr. Alzheimer, and after her death in 1906 he performed an autopsy and noticed that the patient's cerebral cortex looked atrophied, with widening of the sulci. He also found histopathological changes including neurofibrillary deposits and amyloid plaques which are now the hallmarks of Alzheimer's disease (AD). The pathological findings and the early age of onset made Auguste Deter's condition unique, and she became the first patient diagnosed with what was later called AD dementia in recognition of Alzheimer's pioneering work. Recently it was discovered that she had a mutation in the gene encoding Presenilin 1, a well known cause of early onset AD (Muller *et al.*, 2013).

AD is typically characterized by early impairment of memory and later by additional affection of other cognitive domains and a gradual decline in ADL-functions ultimately leading to death. Since dementia is common and will increase (see below), and is a highly debilitating syndrome, the overall negative impact on the individual patient and the caregiver, as well as the health-related costs for society, is already very high and will increase dramatically. Current AD therapies are limited to symptomatic drugs and offer a moderate, but temporary improvement or stabilization of cognitive decline in selected patients. The underlying disease, however, is not targeted. Due to the expected increase in AD patients, there is an urgent need for continuous search for better understanding of the underlying disease mechanisms and for curative or disease-modifying treatment.

4.2 Prevalence and incidence of Alzheimer's disease

AD is the most common neurodegenerative disease and accounts for the majority (about 70 %) of about 70.000 people in Norway and 35-40 million worldwide that are currently estimated to suffer from dementia, a number expected to more than double towards 2050 due to the aging of the population (Hjort and Waaler, 2010;Prince *et al.*, 2013). About 60 % of people with dementia live in developed countries with middle or low income, and this proportion is expected to rise to around 70 % in 2040 (Ferri *et al.*, 2005). However, there are some indications that the incidence is decreasing slightly in high income countries, probably partly due to better treatment of cardiovascular risk factors and rising education, and thus the increase in number of people with dementia might be slightly lower (Langa KM, 2015).

The prevalence increases exponentially with age, doubling with every 5 years increase above the age of 65, rising from 3% among those 65-74 years of age to almost 50% among those 85 or older (Mayeux and Stern, 2012;Zhu and Sano, 2006). In 2005 it was estimated that the one-year incidence of dementia worldwide was 4.6 million (one new case every 7 seconds) (Ferri *et al.*, 2005). Similarly, in a study involving more than 2300 people initially free of AD, it was found that 95 out of 642 persons further examined, had developed AD during a mean 4 years follow-up. Calculated incidence rates were substantial and about 14 times higher among participant above 85 years of age compared to those between 65-69 (Hebert *et al.*, 1995).

4.3 Diagnostic criteria

In 1984 the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) published diagnostic criteria for AD which has been widely used since and still is the current definition according to ICD-10 (McKhann *et al.*, 1984). These criteria are accurate with an average sensitivity and specificity of 81 % and 70 % respectively (Knopman *et al.*, 2001). As reflected in the 1984 criteria, AD has traditionally been considered a pure clinical diagnosis which could only be confirmed by autopsy (“dual clinicopathological classification”), but the last decades research advances and development of reliable biomarkers in AD have modified this view. AD is still considered a clinical diagnosis, but it is now recognized that AD has a long, symptomatic pre-dementia phase (and even preclinical, biomarker-positive) and that in vivo biomarkers can help in diagnosis even before patients are demented. This has led to a revision of the original criteria for dementia due to AD (McKhann *et al.*, 2011) (**table 5**) and incorporation of the term MCI due to AD (Aarsland *et al.*, 2011b; Albert *et al.*, 2011). The new criteria include clinical criteria for AD dementia and MCI to be used by all healthcare providers without access to relevant biomarkers and criteria incorporating the use of biomarkers for research purposes. Although pathologic evaluation for the presence of amyloid-beta ($A\beta$) plaques and tau protein still is required for a definitive diagnosis, recent diagnostic criteria identify biomarkers that can increase sensitivity and specificity in the diagnosis of underlying AD. Main AD biomarkers include brain amyloid $A\beta$ represented by low CSF $A\beta$ and amyloid retention on PET and biomarkers of neuronal degeneration or injury represented by CSF tau (total-tau and phosphorylated tau), decreased fluorodeoxyglucose (FDG) uptake on PET in temporoparietal cortex and atrophy of the medial, basal and lateral temporal lobe and medial parietal lobe on structural magnetic resonance imaging (**table 6**). At present these biomarkers are not recommended in the clinical routine because of their limited access and standardization, the current high sensitivity and specificity of the clinical criteria and lack of validation of the new criteria.

Of note, all patients who met criteria for probable AD by the old (1984-) criteria, would meet the current criteria for probable AD dementia shown in **table 7**. (See also sections 1.6 and 4.6).

4.4 Pathogenesis

The two core pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles, but what causes AD and the exact mechanisms involved are unknown. The pathological changes typically begin in the entorhinal cortex and Hippocampus and then proceed to other cortical areas, resulting in increasing neuron damage and death (Braak and Braak, 1996). The amyloid cascade hypothesis, although challenged and revised, still offers a main framework for the understanding of AD progression (Karran *et al.*, 2011). The hypothesis postulates that abnormal cleavage of the Amyloid Precursor Protein (APP) (β -secretase [BACE1] pathway) leads to abnormal fibrillation and aggregation of $A\beta$ in contrast to the normal, non-amyloidogenic (α -secretase) pathway in which $A\beta$ is not formed. After extracellular cleavage by the β -secretase, the γ -secretase cleaves within the transmembrane region of APP to generate a number of isoforms of 36-43 amino acid residues in length. The two most common isoforms

are A β 1-40 and A β 1-42, the former being the most common, but the latter most fibrillogenic and associated with disease.

Table 6: Biomarkers for examination of AD-MCI and AD dementia*

<p>Biomarkers of Aβ deposition:</p> <ul style="list-style-type: none">- CSF Aβ42- PET amyloid imaging
<p>Biomarkers of neuronal injury:</p> <ul style="list-style-type: none">- Elevated CSF total/phosphorylated tau- Hippocampal volume or medial temporal atrophy on magnetic resonance imaging (volume or visual rating)- Rate of brain atrophy- FDG-PET (including temporoparietal changes)- SPECT (similar, but poorer accuracy than FDG-PET)(Herholz, 2011)

* McKhann et al., 2011, Albert et al. 2011. AD-MCI = Alzheimer's disease – Mild Cognitive Impairment, A β = Amyloid beta, CSF = Cerebrospinal fluid, PET = Positron Emission Tomography, FDG = Fluorodeoxyglucose, SPECT = Single Photon Emission Tomography

Amyloid is thought to be deposited in the extracellular brain tissue either causing AD or contributing to toxic effects on the surrounding neurons. The hypothesis also postulates that the microtubule-associated protein tau, the main constituent of neurofibrillary tangles, aggregates due to toxic effects from amyloid deposits (Ballard *et al.*, 2011a). The protein tau is located principally in axons, and hyperphosphorylation leads to detachment of tau from microtubules, degradation of microtubules and consequently neuronal death.

Since studies of disease modifying treatment targeting amyloid has been unsuccessful have been unsuccessful, the original hypothesis has been challenged (Lee *et al.*, 2004). A competing hypothesis postulates that amyloid deposits aggregate merely as a consequence of other causal events (i.e. neuronal stress) and as such can be seen as a possible side effect and down-stream marker (with possible protective properties) in AD pathogenesis.

In clinical practice and in research settings, measuring proteins related to amyloid and tau metabolism is incorporated in the diagnostic criteria (see section 4.6) and remains an important diagnostic tool.

It is estimated that around 70 % of the risk of developing AD can be attributed to genetics, but causal genes are rare, especially in late onset AD (after 65 years) (Ballard *et al.*, 2011a). Early onset AD affects about 1-5 % of all AD cases and is usually linked to familial aggregation and autosomal dominant mutations in the genes coding for Presenilin 1, Presenilin 2 and APP (Bekris *et al.*, 2010). A number of risk genes have also been identified, most consistently associated with late onset AD is ApoE (Bekris *et al.*, 2010) (see section 4.6.1).

Table 7: General criteria for dementia and core clinical criteria for probable AD dementia*:

<p>1. General criteria for dementia are fulfilled when there are cognitive or neuropsychiatric symptoms that</p> <ul style="list-style-type: none"> - interfere with the ability to function at work or at usual activities <i>and</i> - represent a decline from previous levels of functioning and performing <i>and</i> - are not explained by delirium or major psychiatric disorder - Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. - The cognitive or behavioral impairment involves a minimum of two of the following domains: <ul style="list-style-type: none"> a) Impaired ability to acquire and remember new information b) Impaired reasoning and handling of complex tasks and poor judgment c) Impaired visuospatial abilities d) Impaired language functions (speaking, reading, writing) e) Changes in personality, behavior or comportment
<p>2. Probable AD dementia is diagnosed when the patient meets criteria for dementia described above and the following characteristics:</p> <ul style="list-style-type: none"> a) Insidious onset. Symptoms have a gradual onset over months to years b) Clear-cut history of worsening of cognition by report or observation <i>and</i> c) The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: <ul style="list-style-type: none"> - Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain - Non-amnestic presentations including: <ul style="list-style-type: none"> - Language presentation - Visuospatial presentation - Executive dysfunction
<p>3. The diagnosis of probable AD dementia should not be applied when there is evidence of substantial concomitant cerebrovascular disease, core features of Dementia with Lewy bodies other than dementia itself, prominent features of behavioral variant of frontotemporal dementia, prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia or evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.</p>

* McKhann et al., 2011

4.5 Clinical features

AD progression can (broadly) be divided in the following stages: pre-dementia (further subdivided in an asymptomatic and a prodromal phase), mild, moderate and severe dementia stages (end stage). Each stage has typical clinical features, but there is a gradual decline with no distinct boundaries between the different stages as the disease progresses. There are also large inter-individual differences in the clinical presentation, and neuropsychiatric symptoms such as anxiety and depression may be prodromal symptoms of disease (McKhann *et al.*, 2011; Sperling *et al.*, 2011).

4.5.1 Cognitive impairment

Early memory loss is frequently the first clinical sign in AD, often seen years before a definite diagnosis of dementia can be made. AD-MCI can be defined as a state of subjective and/or informant based cognitive impairment, objective signs of impairment in any domain and relatively intact activities of daily living not fulfilling criteria for dementia (Petersen *et al.*, 2009) (see also section 1.3). AD-MCI is typically characterized by early memory complaints (amnestic MCI), and language, executive and visuospatial functions are relatively spared. Non-amnestic MCI is characterized by a subtle decline in functions not related to memory (executive function, language, attention and visuospatial ability), and may be a forerunner to other dementias than AD, including DLB (Molano *et al.*, 2010).

As the disease progresses and cortical involvement increases, memory is typically worsened and impairment of other cognitive abilities becomes evident (mild AD dementia, roughly MMSE > 20). Symptoms in this phase include confusion and difficulties in orientation, poor judgment often leading to bad decisions, loss of initiative and spontaneity, mood and personality changes and overall increasing difficulties in maintaining ADL-functions.

In moderate stage AD (roughly MMSE between 10-20) typical symptoms seen are language, reading and writing problems, shortened attention span, difficulties in recognizing friends and family members, inability in learning new things, reduced mental flexibility and difficulties in handling unexpected events.

In end stage AD, the patients are generally incapacitated with severe or total loss of verbal skills, ability to remember or process information. Patients at this stage are often confused about past and present, frequent falls often render patients to the bed and they are in need of full time care in nursing homes.

4.5.2 Neuropsychiatric symptoms

Neuropsychiatric symptoms, also known as Behavioral and Psychiatric Symptoms of Dementia (BPSD), are the result of complex brain processes involving multiple transmitter systems. As many as 80-97 % of demented patients may have BPSD during the course of the disease, and it can exacerbate cognitive and functional impairment (Gauthier *et al.*, 2010) (**table 8**).

The spectrum of BPSD includes depression, anxiety, aggression, restlessness, agitation, psychosis including delusions and hallucinations, wandering and screaming. (see sections 5.5 and 8.4), Depression is common in both MCI and AD dementia with prevalence rates as high as 50 % (Lee and Lyketsos, 2003; Lee *et al.*, 2007) and is described in more detail in section 5.5.

Of note, the relationship between depression and cognitive impairment is complex. Depression has been shown to be a risk factor for dementia (Barnes and Yaffe, 2011), but depression occurring temporally close to cognitive impairment and dementia may also represent prodromal signs of the dementing process itself or a psychological reaction to being ill. In a diagnostic perspective, late life depression (LLD) is often underreported, partly because of the different

clinical presentation compared to depression in the young (including more prominent agitation, less sadness and more somatic complaints such as gastrointestinal distress, fatigue or insomnia in LLD) and lack of consensus criteria for LLD. Furthermore, the diagnostic precision is even lower when assessing comorbid depression and cognitive impairment. For further discussion of these matters, see section 8.4 (paper 3).

Taken together, BPSD can be present early in the disease process and even be a risk factor of dementia, but typically BPSD are more frequent and severe as the disease progresses.

4.5.3 Somatic symptoms

As the disease reaches moderate and severe stages, gradually involving the entire cortex, there are also considerable somatic complications. These include perceptual-motor problems (trouble seeing and moving in three dimensional space, arising from chair, setting the table, etc.), reduced appetite and weight loss, seizures, visual impairment, delirium, autonomic dysfunction including bowel or urinary incontinence, dizziness, orthostatic hypotension and sleep problems.

Table 8: Types of behavioral and psychological symptoms of dementia (BPSD) *

Psychological or psychiatric symptoms	Behavioral symptoms
Delusions	Aggression (physical or verbal)
Hallucinations	Agitation (hoarding, pacing, screaming)
Anxiety (worrying, shadowing the caretaker)	Apathy or indifference
Depression or dysphoria	Disinhibition (socially and sexual inappropriate behavior)
	Repetitive motor activities (wandering, rummaging)
	Waking and getting up at night

*Based on modified neuropsychiatric inventory-Q categories

4.6 Biomarkers in Alzheimer's disease

At present, only symptomatic treatments for AD exist, and much effort has therefore been made to develop drugs which slow or halt the disease process, so far without much success. A major challenge is to separate symptomatic effects from true disease-modifying effects, and surrogate biomarkers that can objectively measure the characteristic features of AD, and hence act as indicators of underlying disease and disease progression, are urgently needed. The existing diagnostic tests of AD are mostly based on neuropsychological assessment (see also table 7), but it remains inadequate for early detection and differentiation of AD from other types of dementia.

A multitude of different candidate biomarkers of disease progression in AD have therefore been investigated, and there have been major advances in developing CSF markers and imaging techniques that can diagnose AD (and other dementia subtypes) at the MCI (and even SCI) and early dementia stage. The most valid biomarkers have been incorporated in the new AD dementia and AD MCI criteria (Albert *et al.*, 2011;McKhann *et al.*, 2011) (**table 6**).

At present there are two main categories of biomarkers used in the investigation of AD based on the biology that is measured: biomarkers of A β accumulation represented by low CSF A β metabolites and amyloid retention on PET and what is believed to be more “downstream” markers including elevated CSF tau, decreased fluorodeoxyglucose (FDG) uptake on PET and atrophy of the medial temporal lobe (Hippocampus) and parietal cortex on structural MRI. Based on these findings, Jack *et al.* have proposed a hypothetical dynamic model of AD progression (adapted in the recent revised diagnostic criteria for AD) that relates disease stage to biomarker abnormalities (Jack, Jr. *et al.*, 2010a). In this model, amyloid biomarkers first become abnormal, before tau-mediated neuronal injury, brain injury and ultimately memory and other cognitive and clinical symptoms.

In this section, an outline of the most important biomarkers will be reviewed. Basic biomarker characteristics are described in section 3.0.

4.6.1 Genetics

AD is broadly divided in early (before the age of 65) and late onset. Early onset AD is often a rare autosomal dominant, familial disease (so-called Mendelian families, i.e. a single-gene disease, due to an error or mutation in one of the 25 000 genes in the human genome). The known genes that cause mendelian forms of dementia are autosomal dominant with high penetrance accounting for 1-5 % of all AD cases, typically presenting in the late 40's or early 50's, and is caused by mutations in the genes encoding Amyloid Precursor Protein (APP), Presenilin1 and Presenilin 2 (Loy *et al.*, 2014;Rongve *et al.*, 2013).

The APP, Presenilin 1 and Presenilin 2 genes share the same biological pathways, i.e. causing increased production of A β 1-42 and other A β metabolites which are the main constituent of amyloid plaques found in the AD brain.

The more common late onset AD occurs after the age of 65 and is assumed to be a polygenic and multifactorial disease of unknown origin. In clinical practice the two major types of AD are indistinguishable, but early onset is typically more severe and has a more rapid course.

Inadequate clearance of amyloid beta is believed to contribute also in late onset AD.

Several potential genes have been linked to an increased risk of AD, i.e. in a genetically complex manner, but the only established susceptibility gene in late AD is APOE. Individuals with two *ApoE* $\epsilon 4$ alleles have a more than seven times increased risk of developing AD

compared to those with *ApoE* $\epsilon 3/\epsilon 3$ alleles (Corder *et al.*, 1993). The $\epsilon 2/\epsilon 2$ and $\epsilon 3/\epsilon 4$ alleles represent intermediate risk for a later AD development. In a recent and large study involving more than 17.000 subjects, it was demonstrated that double APOE $\epsilon 4$ alleles increased risk of AD 35 times as compared to double *ApoE* $\epsilon 3/\epsilon 3$ alleles, making APOE the strongest susceptibility gene to date (Genin *et al.*, 2011). However, since only 50% of individuals with AD carry an APOE $\epsilon 4$ allele, other genetic factors must contribute to risk for disease. After APOE, the best-validated gene modulating late-onset AD risk is the sortilin-related receptor 1 (*SORL1*) gene (Rogaeva *et al.*, 2007).

Additionally, since 2009 genome-wide association studies (GWAS) have identified several genetic variations associated with AD, among them *CLU*, *PICALM 1* and *TREM2* (Lambert *et al.*, 2013; Rongve *et al.*, 2013). Only a small portion of these risk genes have been replicated in other studies, and these variants contribute only slightly to an increased risk of disease, with much lower effect sizes than APOE (odd ratio < 2). In GWAS studies large sample sizes are essential, and it is likely that as sample sizes continue to grow, additional risk loci will be revealed. Taking advantage of this method, a recent study combined several large GWASs involving 300.000 subjects to identify single nucleotide polymorphisms (SNPs) and associations between AD, C-reactive protein and plasma lipid levels (specifically triglycerides, high- (HDL) and low-density lipoproteins (LDL)). It was demonstrated a polygenetic overlap between AD, inflammation and plasma lipids in support of the hypothesis that the latter influence AD pathogenesis (Desikan RS *et al.*, 2015).

Taken together, there are only three known genes causing AD, and mutation in the Presenilin 1 gene is the most common, accounting for about 60 % of cases (Janssen *et al.*, 2003; Raux *et al.*, 2005). The second most common form of familial AD is mutations or duplication of the gene encoding APP which account for about 20-25 % of AD cases (about 15 % of cases caused by mutations) (Janssen *et al.*, 2003; Raux *et al.*, 2005; Rovelet-Lecrux *et al.*, 2006). Since mutations in Presenilin 2 are rather rare, initial screening for APP and subsequently Presenilin1 is the most common approach when examining families at risk. In clinical practice, testing for other risk genes, possibly with the exception of APOE, is at present not recommended.

4.6.2 Structural MRI

See sections 3.2.8.1 and 3.3.6.6.1 for further details.

The hallmark MRI biomarker for AD is medial temporal lobe atrophy particularly in the hippocampus. Atrophy in the hippocampus and entorhinal cortex is associated with progression of memory impairment and an increased risk of AD (Apostolova *et al.*, 2006; Mungas *et al.*, 2005) and the average hippocampal volume reduction is 20 % – 25 % in AD and 10 % – 15 % in MCI (Shi *et al.*, 2009).

MRI is widely used in the examination of potential AD, but the lack of a standardized methodology for measurement of hippocampal volumes has limited the incorporation of this biomarker into clinical practice. However, scales such as the Scheltens scale (Scheltens *et al.*, 1992) are increasingly used and accurate considering age and other confounders are taken into account (Pereira *et al.*, 2014a), whereas computer-based approach, which are more accurate, are yet not feasible for use in clinical practice.

Diffusion Tensor Imaging (DTI) is presented in more detail in section 2.3.6.6, and is a promising biomarker both in LBD and AD. DTI has become a leading method in identification of white matter integrity reductions in several brain regions of persons with AD and MCI

compared to normal controls suggesting that these changes occur early in the disease process (Medina *et al.*, 2006; Selnes *et al.*, 2013; Stebbins and Murphy, 2009; Zhang *et al.*, 2007). Increased mean diffusivity and decreased fractional anisotropy values have been reported in AD and MCI in parietal and temporal areas, including the hippocampal region, but also in frontal regions, specifically in cingulum posterior, corpus callosum, fasciculus longitudinalis superior and fasciculus uncinatus. Moreover, DTI as a marker of tissue microstructure, appears to be a more sensitive marker of hippocampal integrity than macrostructural measurements with MR volumetry (Clerx *et al.*, 2012). At present, DTI is not used in the clinical routine, but reserved for research purposes.

4.6.3 Cerebrospinal fluid (CSF)

Characteristic changes in the CSF of AD patients are the reduction of A β 1-42 and the increase in total-tau and phospho-tau. Reduced CSF A β 1-42 is one of the first detectable biomarkers in AD disease progression and can be observed years or even decades before evident symptoms of cognitive decline (Jack, Jr. *et al.*, 2013). CSF A β 1-42 levels show high sensitivity (78%-100%) in detecting AD dementia, but since the same pattern can be seen in different disorders including LBD, vascular and frontotemporal dementia, there is insufficient specificity (47%-81%) in differentiating AD patients from other dementias (Blennow and Hampel, 2003; Blennow *et al.*, 2010; Skogseth *et al.*, 2011).

Elevated total-tau is not specific for AD, but rather a marker of unspecific neuronal damage, and hence specificity is insufficient to separate AD, vascular dementia, frontotemporal dementia, stroke and traumatic brain injury (Skogseth *et al.*, 2011). However, total-tau can separate AD patients from normal controls with high sensitivity (84 %) and specificity (91 %) (Blennow, 2004).

Phospho-tau better reflects pathology in AD (i.e. the phosphorylation state of protein tau in the build up of neurofibrillary tangles) with high specificity (92 %) and sensitivity (80 %) in separating AD patients from normal controls (Blennow and Hampel, 2003).

A better accuracy in differentiating between AD and controls can be obtained by combining the main CSF biomarkers (A β 38, A β 40, A β 42, total-tau and phospho-tau) (Duits *et al.*, 2014; Hampel *et al.*, 2014; Tapiola *et al.*, 2009), but at present it is not recommended using these markers alone in differentiating between AD and other subgroups of dementia (Hansson *et al.*, 2006; Skogseth *et al.*, 2011).

Furthermore, large longitudinal studies have shown that an AD biomarker profile (low A β 42, high total-tau and phospho-tau) can separate SCI and MCI patients who will progress to dementia (with high degree of accuracy for amnesic MCI with up to 95 % sensitivity) from normal controls and stable MCI (Hansson *et al.*, 2006; Mattsson *et al.*, 2009; Visser *et al.*, 2009).

4.6.4 PET based imaging

Using 18F-FDG PET, typical patterns of hypometabolism have been described in AD dementia in the hippocampi and medial temporal lobes, posterior cingulate, precuneus and lateral temporoparietal cortex, sparing the sensorimotor and visual cortex. Similar, but milder changes are seen at the MCI stage. 18F-FDG-PET can discriminate with high sensitivity and specificity patients with AD dementia from normal controls, and the most reliable early changes are seen in the posterior cingulate cortex and precuneus, areas with high positive and negative predictive value also in predicting conversion from MCI to AD dementia (Drzezga *et al.*, 2005; Herholz *et al.*, 2002; Kadir *et al.*, 2012; Minoshima *et al.*, 1997; Mosconi *et al.*, 2007).

Using PET scanning with the 11C-labeled Pittsburgh compound B (PiB-PET), a benzothiazole derivative of Thioflavin T, allows for the estimation of amyloid levels in the living brain.

Amyloid-PET has shown high sensitivity in detecting AD dementia in a series of pathology proven studies, and about 50 % of MCI patients have positive scans, especially those with multiple cognitive domain affection (Vandenberghe *et al.*, 2013;Wolk *et al.*, 2009). Brain amyloid can be detectable decades before onset of dementia (Jack, Jr. *et al.*, 2010b) and may be a valuable future biomarker as it allows for the direct measure of the efficacy of anti-amyloid therapies.

4.6.5 Conclusion

AD is still a clinical diagnosis, but biomarkers can increase sensitivity and specificity, especially if different biomarkers are used in combination.

In separating AD from normal controls, there is now solid evidence for biomarkers such as MRI (typically Hippocampus atrophy), FDG-PET (typically reduced metabolism in temporoparietal regions) and amyloid-PET (high retention of ligand in frontal and temporoparietal cortices). MRI and FDG-PET measures can also be used to predict transition from MCI to AD dementia. Furthermore, there is solid evidence that lower A β 42 and higher phospho-tau in CSF can differentiate between AD and healthy subjects and that pathologic CSF can predict a future transition (from SCI/MCI) to AD dementia. In the rather few cases of autosomal dominant inherited AD, genetic testing is valid and the investigation of choice. Biomarker differences between AD and other dementias, however, are less clear cut and, with the exception of Dopamine transporter scan, cannot at present be used at an individual level (see also section 3.2.8.). The most common biomarkers currently used in AD are shown in **table 9**.

4.7 Treatment

At present there are only symptomatic therapies available for AD. The standard medical treatment for cognitive impairment include acetylcholinesterase inhibitors (Donepezil, Rivastigmine and Galantamine) and a partial *N*-methyl-D-aspartate (NMDA) antagonist (Memantine). The acetylcholinesterase inhibitors are licensed for mild to moderate AD (MMSE 10-26) and have a modest effect on cognition (1.5-2 points on the MMSE over 12 months) including some effects on function and global outcome (Birks and Flicker, 2006;Birks *et al.*, 2009;Loy and Schneider, 2006). Memantine is licensed for moderate to severe AD and has significant benefits on cognition, function, global outcome and possibly neuropsychiatric symptoms (agitation, aggression) over 6 months (McShane *et al.*, 2006). There is some evidence that combination therapy (acetylcholinesterase inhibitor and Memantine) may be of benefit (Lopez *et al.*, 2009).

In BPSD, after concomitant somatic disease has been treated or excluded, the first line treatment is non-pharmacological interventions including psychosocial/psychological counseling and interpersonal and environmental management (Ballard *et al.*, 2013;Gauthier *et al.*, 2010). Psychotropic medications, including neuroleptics, antidepressants, anxiolytics and anti-epileptic drugs are extensively being used in clinical practice, but most studies have demonstrated no or limited efficacy (Ballard *et al.*, 2013;Gauthier *et al.*, 2010). There is some evidence that cognitive training in mild disease is beneficial (Yu *et al.*, 2009) and also other non-pharmacological approaches are effective and also other non-pharmacological approaches are effective (Testad *et al.*, 2014).

Finding disease-modifying drugs that can slow or reverse the progression of AD are important and intensive research efforts are being made. However, at present no drugs has demonstrated efficacy in phase three trails (Ballard *et al.*, 2011a;Schneider *et al.*, 2014).

Table 9: Biomarkers in Alzheimer's disease

Modality		SCI or MCI stages	AD dementia	Comment
Genetics	Familial genes (APP, PRESENILIN 1 and 2)			Early onset AD is a rare autosomal dominant, familial disease caused by mutation in APP, PRESENILIN 1 and 2 (1-5 % of AD cases)
	Risk genes (i.e. APOE)			Genes linked to an increased risk of late onset AD, which is assumed to be a polygenic and multifactorial disease of unknown origin.
MRI	Atrophy	The average hippocampal volume reduction is 10 – 15 % in MCI compared to controls (Shi F. et al., 2009)	The average hippocampal volume reduction is 20 – 25 % in AD compared to controls (Shi F. et al., 2009)	The hallmark MRI biomarker for AD is medial temporal lobe atrophy particularly in the hippocampus.
	Diffusion Tensor Imaging	Changes in parietal and temporal areas, but also in frontal regions (Selnes <i>et al.</i> , 2013)	Changes in parietal and temporal areas, but also in frontal regions (Selnes <i>et al.</i> , 2013)	Can predict conversion from MCI to AD dementia. At present only recommended for research purposes.
CSF	Amyloid	Reduced A β 42 can be seen decades before symptoms of AD (Jack CR. et al. 2013)	High sensitivity (78%-100%) in detecting AD dementia, but insufficient specificity (47%-81%) (Blennow K. et al., 2003)	No combination of the main AD CSF biomarkers are recommended in differentiating between AD and other subgroups of dementia (Skogseth RE et al., 2011).

CSF	Tau (Phospho-tau, total-tau)	An AD biomarker profile can separate SCI and MCI patients who will progress to dementia with high degree of accuracy from normal controls and stable MCI (Visser PJ, 2009, Matsson N. et al., 2009).	Phosphorylated tau shows high specificity (92 %) and sensitivity (80 %) in separating AD patients from normal controls (Blennow and Hampel, 2003)	No combination of the main AD CSF biomarkers are recommended in differentiating between AD and other subgroups of dementia (Skogseth RE et al., 2011).
PET	Glucose metabolism	Similar, but milder changes as compared to AD dementia are seen at the MCI stage (Kadir <i>et al.</i> , 2012, Mosconi <i>et al.</i> , 2007)	Hypometabolism have been described in the hippocampi and medial temporal lobes, posterior cingulate, precuneus and lateral temporoparietal cortex (Kadir <i>et al.</i> , 2012, Herholz <i>et al.</i> , 2002)	High positive and negative predictive value in separating AD dementia from controls and in predicting conversion from MCI to AD dementia (Kadir <i>et al.</i> , 2012).
	Amyloid	About 50 % of MCI patients have positive scans, especially those with multiple cognitive domain affection (Wolk <i>et al.</i> , 2009).	High sensitivity in detecting AD dementia in a series of pathology proven studies (Vandenberghe <i>et al.</i> , 2013;Wolk <i>et al.</i> , 2009).	At present the diagnostic use of amyloid PET in LBD is not established. May help identify patients for treatment with anti-amyloid agents in the future.

SCI – Subjective Cognitive Impairment, MCI – Mild Cognitive impairment, AD – Alzheimer's disease, APP – Amyloid Precursor Protein, MRI – Magnetic Resonance Imaging, Aβ42 – Amyloid Beta 1-42, PET – Positron Emission Tomography

5.0 Depression in the elderly

5.1 Introduction

A feeling of sadness and low mood is something most people will experience during life, but symptoms are most often elusive, will usually not effect daily functioning and is thus not necessarily considered an illness. In contrast, clinical depression is defined according to core criteria including a persistent state of sadness, loss of interest and fatigue and accompanying symptoms such as sleep problems, indecisiveness and suicidal thoughts (see section 1.7). Depression is common in all age groups, but especially in the very old, and represents a considerable burden for the individual and society. The latest global burden of disease study from 2010 concluded that depressive disorders were among the leading causes of years lived with disability (YLDs), second only to cardiovascular disease (Ferrari *et al.*, 2013). MDD contributed not only to suicide, but also to an increased risk of ischemic heart disease. In 2001 WHO proclaimed that neuropsychiatric disorders accounted for 4 out of the 10 leading causes of disability worldwide with depression ranked 4th. It was estimated that depression would jump to second place by the year 2020, second only to ischemic heart disease. There is broad consensus that depression leads to disability and reduced quality of life (Papakostas *et al.*, 2004).

Table 10: Symptoms related to late life depression¹²

Hypochondriasis
More somatic complaints (often related to the gastro-intestinal tract)
Agitation and irritability
Less guilt
Less sexual interest
Cognitive complaints
Psychomotoric retardation
Sleep disturbances
Less sadness
Poor concentration
Fatigue
Anhedonia and social withdrawal
Less likely to have a family history of depression

¹ Based on Hegeman *et al.*, 2012, Wilkins *et al.*, 2009, Lavretsky *et al.* 2002 and Ellison *et al.*, 2012.

² As compared to depression in the young

5.2 Late life depression

Late life depression (LLD) is often defined as a major depressive episode in an older adult above 65 years of age and encompasses both first lifetime episodes and known depression re-occurring in older life. LLD is a heterogeneous disorder, and the symptomatology is often different compared to depression in the young (see table 10). In a meta-analysis including 11 studies and 2000 patients, it was found that older depressed people more often presented with hypochondriasis, somatic complaints (most often from the gastrointestinal tract) and agitation compared to younger patients (Hegeman *et al.*, 2012). Furthermore, older people demonstrated less guilt and sexual interest. Older people more often present with irritability, anhedonia and social withdrawal and somatic and cognitive complaints, sleep disturbances, fatigue, poor concentration and psychomotoric retardation are often prominent (Ellison *et al.*, 2012;Hegeman *et al.*, 2012;Lavretsky and Kumar, 2002;Wilkins *et al.*, 2009).

Because the elderly can have numerous distressing ailments, subsyndromal depression (minor depression not meeting established criteria for major depression) is more common, and symptoms of depression may be overlooked because of the assumption that symptoms are merely related to somatic disease or normal age related decline. However, physical discomforts or normal aging alone are not likely to be the only cause of depression, but often becomes clinically relevant when it coexistent with other stressful life events such as loss of spouse and loneliness, impairment of mobility and economic worries. Using age-related symptom scales taking into account the often unusual clinical presentation can therefore assist in the diagnosis of LLD and is relevant for screening purposes in addition to the established criteria (see sections 1.7 and 8.4).

Although there is evidence that the efficacy in treating LLD is similar to depression in the young, LLD seems to have a more chronic course, a worse prognosis and a higher relapse rate (Kok *et al.*, 2012;Mitchell and Subramaniam, 2005). Since LLD severely impacts both quality as well as length of life (Baldwin *et al.*, 2006;Penninx *et al.*, 1998), it should be taken seriously and treated promptly.

5.3 Risk factors, prevalence and incidence of depression

Major depression (MDD) is one of the world's most debilitating and frequent disorders with 12-month prevalence numbers around 5-6 % and lifetime prevalence around 13 % in the general adult population (Barnes and Yaffe, 2011).

Population studies focusing on unipolar depression have rather consistently shown that women are more affected than men regardless of race, socio-economic status and nationality (Alexopoulos, 2005;Kuehner, 2003). Other risk factors include a history of depression, genetic susceptibility, negative life events including poverty and bereavement, poor health status and sleep disturbances (Cole and Dendukuri, 2003;Foland-Ross *et al.*, 2013) .

The diagnostic criteria for major depression are applicable both for LLD and depression in the young, but as mentioned the clinical presentation often differs affecting prevalence numbers in the two broadly divided groups. In addition, a large body of literature exist on the prevalence of LLD, but less is known about incidence rates of depression above the age of 70.

1-4 % of the elderly population suffers from MDD with incidence rates around 0.15 % (Alexopoulos, 2005). Both prevalence (Palsson *et al.*, 2001) and incidence (Teresi *et al.*, 2001) rates double after the age of 70-85, and the prevalence is higher in medical settings than in the

community. About 10-12 % of patients admitted to hospital and 6-9 % of primary-care patients suffered from MDD in addition to symptoms of subthreshold (minor) depression (see below) (Alexopoulos, 2005). Among nursing home residents, prevalence number for MDD are in the 12-14 % range (Alexopoulos, 2005).

When planning for long-term care of depressed patients, longitudinal incidence studies are the method of choice. Interestingly, two large cross-sectional studies from Norway, HUNT 2 and HUNT 3, involving all adult inhabitants above 45 years in the county of Nord-Trøndelag (n=16517) were examined with an 11 year interval from 1995-97 to 2006-08 (Solhaug *et al.*, 2012). HUNT 2 was considered baseline and HUNT 3 follow-up, and the population was subdivided in 5-year age cohorts and interviewed with the Hospital Anxiety and Depression scale (HADS-D). Overall, the participation rate was 69 % and 54 % in HUNT 2 and HUNT 3 respectively. As shown in **table 11**, the authors concluded that there was an increase in depression rates in all cohorts above 76-years at follow-up, with the largest increase in the oldest cohort (9.6 % in the 86-90 year group). Additionally, incidence rates increased with age with the highest incidence in the oldest. Incidence rates in the 65-69 and 70-74 age groups were around 10 % and almost 15 % in the 75-79 age group compared to around 5 % below the age of 60. The phenomenon that depression seems to increase with age in the oldest age group was also shown in another longitudinal study (Heikkinen and Kauppinen, 2004), but can also represent cohort effects (the oldest participants in HUNT was born in the early 1920s, during the interwar period). Of note, although symptom scale-based studies indicate higher prevalence rates of depression with age, epidemiological studies based on formalized diagnostic criteria (i.e. DSM and ICD) have shown a decrease in prevalence of major depressive disorder with age (Scott *et al.*, 2008). This contrast can be explained by the different clinical presentation of depression in old age compared to the younger and that formalized criteria are less sensitive in detecting depression in the old (see section 5.2). A similar conclusion was drawn in a recent systematic review of incidence of late life depression (Buchtemann *et al.*, 2012).

Minor depression is a subthreshold state not meeting established criteria for major depression, and prevalence rates are estimated to 0-18 % depending on the definition of depression and population studied (Blazer, 2003; Polyakova *et al.*, 2014) (**table 12**). Although not fulfilling established criteria for major depression, this condition is associated with an increased risk of not only major depression, but also suicide and substance abuse (Polyakova *et al.*, 2014). As such, minor depression can be regarded as a prodromal state of a later conversion to a more serious and debilitating depressive disorder. Furthermore, minor depression is probably more prevalent among the elderly in a primary care setting than major depression, and clinically relevant symptoms up to 36 % are recorded (Heun *et al.*, 2000; Luppá *et al.*, 2012).

Table 12: Studies reporting the prevalence of minor depression without MCI in people 55 years and older

Study	Design, number in study	Diagnostic criteria	Prevalence of minor depression
Vilalta-Franch et al. (2012)	Community-based, 451	DSM-IV	Point prevalence 16.8 %
Grabovich et al. (2010)	Primary care, 745	DSM-IV	Point prevalence 6.9 %
Park et al. (2010)	Community-based, 714	DSM-IV research criteria	Point prevalence 5,5 %
Steffens et al. (2009)	Community-based, 851	DSM-IV	12-months prevalence 13.5 %
Mossaheb et al. (2009)	Community-based, 331	DSM-IV	Point prevalence 10.7 %
Mechakra-Tahiri et al. (2009)	Community-based, 2670	DSM-IV	Point prevalence 9.5 %
Kramer et al. 2009	Nursing home residents, 97	DSM-IV	Point prevalence 14.4 %
Han et al. (2008)	Medical inpatients, 281	DSM-IV	Point prevalence 18.1 %
Preville et al. (2008)	Community-based, 2798	DSM-IV	12-months prevalence 5.7 %
Norton et al. (2006)	Community-based, 2877	DSM-IV	Point prevalence 14.8 %
Licht-Strunk et al. (2005)	Primary care, 5686	DSM-IV	Point prevalence 10.2 %
Heun et al. (2000)	Community-based, 287	DSM-III	Point prevalence 0 %, Life time prevalence 23 %

MCI: Mild Cognitive Impairment, DSM: Diagnostic and Statistical Manual of Mental Disorders

Cognitive impairment is a common symptom in LLD. Similarly, behavioral and psychological symptoms of dementia are common, and depression is especially prevalent among these symptoms (Lee and Lyketsos, 2003) (see also section 5.5). Prevalence rates differ according to the population and also by the definition of depression, but in MCI 20 % of patients have been found to have major depression and 17-27 % minor depression (Gabryelewicz *et al.*, 2004;Kumar *et al.*, 2006). In a recent study examining the prevalence of depression among SCI, MCI and demented patients referred to a memory or outpatients clinic, it was found that 37 % were depressed according to the Cornell score of depression in dementia (Knapskog *et al.*, 2014). Depression in dementia is associated with negative outcomes such as earlier admission to nursing homes, higher morbidity and mortality rates, reduced quality of life and difficulties in performing ADL's (Dorenlot *et al.*, 2005;Starkstein *et al.*, 2005).

Table 11: Prevalence of depression with age (Solhaug *et al.*, 2012)

Years at baseline	Age at follow-up	Depression baseline (HUNT 2)	Depression follow-up (HUNT 3)
45 - 49	56 – 60	9.7 %	10.1 %
50 - 54	61 – 65	11.1 %	9.4 %
55 - 59	66 - 70	12.1 %	9.5 %
60 - 64	71 - 75	11.9 %	12.3 %
65 - 69	76 - 80	11.6 %	15.0 %
70 - 74	81 - 85	11.9 %	15.7 %
74 - 79	86 - 90	11.3 %	20.9 %

HUNT: The Nord-Trøndelag Health Survey (Helseundersøkelsen i Nord-Trøndelag)

5.4 Biomarkers of depression in the elderly

At present MDD remains a clinical diagnosis defined according to operationalized criteria (see section 1.7). However, over the last decades a large body of evidence has accumulated and points to a diversity of contributing factors and pathways including the effects of pro-inflammatory cytokines, oxidative stress, serotonergic dysfunction, endocrine and genetic factors and metabolic dysregulation (Felger and Lotrich, 2013; Lopresti *et al.*, 2014; Schmidt *et al.*, 2011; Schneider and Prvulovic, 2013).

The roles of noradrenaline, dopamine and serotonin (5HT) have long been the basis for pharmacological intervention and are pivotal in the understanding of pathogenic mechanisms in depression (Baldessarini, 1975; Schildkraut, 1965). The serotonin hypothesis postulates lower levels of 5HT both in plasma and in the brain involving 5HT at multiple levels including abnormal serotonin transporter binding, abnormalities in the metabolism of the precursor tryptophan and effects at receptor and cell level. Similarly, the catecholamine hypothesis suggests that lower concentrations of noradrenaline and dopamine at different levels facilitate depression. There is also evidence that anxiety and depression share pathophysiology, the most consistent common abnormality has been found to be hyperactivity within the amygdala, and that also the transmitter GABA is involved in common pathways (Martin *et al.*, 2009; Mohler, 2012). Since underlying mechanisms are unclear, what ultimately strengthens the role of serotonin and other transmitters in the neurobiology of depression is the effect of serotonin reuptake inhibitors (SSRIs) and other antidepressants (Kok *et al.*, 2012).

There are no known causal genes in depression, but major depression is moderately inheritable and several known polymorphisms, mostly related to monoaminergic (i.e. noradrenaline, dopamine and serotonin) transmission, are known to increase the risk (Levinson, 2006). Among targets for genetic research include the serotonin transporter promoter region (5-HTTLPR), genes related to neurotoxicity (including effects involving the hypothalamic-pituitary (HPA-) axis) and neuroprotection (including brain-derived neurotrophic factor, BDNF). In the largest GWAS to date including 9240 subjects with MDD and 9519 controls, no significant associations to single-nucleotide polymorphisms (SNPs) were found due to low sample size (Ripke *et al.*, 2013). The high prevalence of MDD suggests that power issues are critical in the detection of genetic effects typical for complex traits. The role of personality (e.g., personality traits like neuroticism, extraversion, openness to experience and conscientiousness), which is also known to be important in the etiology of depression, complicates these matters further (Klein *et al.*, 2011).

Vascular depression has been suggested as a subtype of depression affecting people in late life. The vascular depression hypothesis originated from the findings that patients with late life depression (LLD) had higher WML load compared to early onset depression and that high WML load was associated with neuropsychological deficits and poor treatment outcomes (Sneed and Culang-Reinlieb, 2011). Of note, there seems to be a bidirectional relationship between cardiovascular disease and LLD, i.e. cardiovascular risk factors (represented by the surrogate marker WML) (see also section 3.3.6.6.1) is associated with depression, but also conversely, depression is associated with hypertension, diabetes, stroke etc. (Gothé *et al.*, 2012). The role of WML in the etiology of depression is, however, poorly understood, but potential mechanisms include inflammation (and possibly increased oxidative stress and higher levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor), HPA-axis

hyperactivity, atherosclerosis and reduced brain perfusion, typically in subcortical areas (Gothe *et al.*, 2012).

In addition, there have been considerable efforts to find neuroanatomical markers of depression by means of imaging techniques. There seems to be consensus that the orbitofrontal cortex, anterior cingulate and Hippocampus are central structures often implicated in depression (Benjamin and Steffens, 2011;Enache *et al.*, 2011;Gothe *et al.*, 2012) (see also section 5.5).

In conclusion, the clinical syndrome of depression is probably multicausal, and there is a clear need for development of biomarkers to make more accurate diagnosis, finding more reliable tools for evaluation of treatment and to better understand disease mechanisms. The heterogeneous nature of depressive symptoms is a major challenge in this regard, and there is probably no single biomarker, but more likely a panel of biomarkers that can contribute to a better understanding of the neurobiology involved.

5.5 Depression and cognitive impairment

The understanding of the neurobiology of depression in cognitive disorders is limited, but a number of proposed mechanisms appear to be similar in both depression and neurodegenerative disease, including LBD and AD (Benjamin and Steffens, 2011;Enache *et al.*, 2011;Gothe *et al.*, 2012).

Neuropsychological dysfunctions are often present in MDD and have been shown to contribute independently to poor functional outcome. But it has been less clear whether cognitive deficits in recurrent MDD are independent or a consequence of mood state. In a recent meta-analysis psychomotor speed, attention, visual learning and memory and executive functioning were significantly impaired in first-episode MDD compared to NC (Lee *et al.*, 2012). It was further concluded that attention and executive deficits were not associated with clinical variables of illness severity, in contrast to deficits in psychomotor speed and memory, suggesting that the former may function as important trait-markers.

Importantly, studies have shown a high prevalence of depression in both MCI (Panza *et al.*, 2010) and dementia cohorts (Lyketsos and Olin, 2002), and it seems to be more common in LBD (Fritze *et al.*, 2011) and vascular dementia (Castilla-Puentes and Habeych, 2010) than AD. Depression is the most common comorbidity in AD and dementia in general and prevalence numbers are in the 30-50 % range including both minor and major depressive states (Lee and Lyketsos, 2003). Similarly the prevalence of post-stroke depression has ranged from 30-50 %, typically peaking 3-6 months after the stroke (Robinson, 2003). Depression in AD present slightly different from in non-demented elderly, and diagnostic criteria for comorbid depression and AD dementia have been proposed (Olin *et al.*, 2002). Loss of interest and dysphoria are the most common symptoms of depression in AD, but the severity of signs and symptoms may be less than in non-demented. Other criteria including appetite, pessimism, worthlessness and low self-esteem vary considerably depending on the study sample.

In meta-analyses there is evidence that mid-life and late life depression increases (doubles) the risk for a later development of dementia, with an estimated 10-15 % of AD cases potentially attributed to depression (Byers and Yaffe, 2011;Ownby *et al.*, 2006). A 25 % reduction in

depression prevalence could potentially result in 800.000 fewer AD cases worldwide. Furthermore, there is also evidence that LLD not only increases the risk but represents a prodrome of dementia (Byers and Yaffe, 2011), but studies are conflicting. Depression has also been shown to increase conversion to AD in subjects with MCI (Enache *et al.*, 2011), but whether concomitant depressive symptoms in MCI and dementia accelerate neurodegeneration is unclear. Importantly, patients with PD have been found to have higher odds ratios for a prior history of depression preceding the onset of PD compared to control subjects (Leentjens *et al.*, 2003; Nilsson *et al.*, 2001), but the role of depression in the underlying pathology of PD is uncertain. Depression is also reported as a supportive feature in DLB (McKeith *et al.*, 2005), but as in PD, little is known about the predictive properties of depression and underlying mechanisms.

Overall, there seems to be a bidirectional relationship between MDD and several common neurological disorders including PD, AD, cerebrovascular disease (stroke), multiple sclerosis and epilepsy. This does not imply that the one causes the other or vice versa, but that common mechanisms are operant in both cases and facilitate each other. These mechanisms are at present poorly understood. Of note, depressive disorders in neurological disorders often present with atypical signs and symptoms and can fail to meet established criteria.

Among the most studied neuroanatomical structures involved in depression is the Hippocampus, and evidence strongly support an association between MDD and reduced Hippocampal volume (Benjamin and Steffens, 2011; McKinnon *et al.*, 2009). Hippocampus is also central in neurocognitive disorders and may be a common link.

The vascular depression hypothesis states an association between depression and WMLs as well as cerebrovascular risk factors (Sneed and Culang-Reinlieb, 2011). WMLs are believed to be caused by small vessel disease affecting subcortical brain perfusion. More important than WML load (count and size of lesions), is seemingly the localization, and the past decade has revealed a correlation between LLD and WMLs in mainly frontal subcortical regions (Greenwald *et al.*, 1998; MacFall *et al.*, 2001; O'Brien *et al.*, 2006; Videbech *et al.*, 2004). WMLs have also been associated with an increased risk of cognitive impairment and dementia (DeBette and Markus, 2010). Interestingly, the LADIS study evaluated the longitudinal influence of depressive symptoms on cognition in independent older people (n=639), accounting for the severity of WMLs. Depression was shown to be a predictor of cognitive impairment (MCI and dementia) at follow-up, independent of the effect of the severity of WMLs and medial temporal lobe atrophy (Verdelho *et al.*, 2013) Thus, the role of WMLs in depression and cognitive impairment is not fully understood, but evidence suggest that cerebrovascular factors may initiate, but not necessarily be the driving force as neurodegeneration accelerates (See also sections 3.3.6.6.1 and 8.4).

Neural deficits in frontal regions have also been shown for depressed patients with other imaging techniques including DTI (Sexton *et al.*, 2009) and functional MRI (fMRI) (Ebmeier *et al.*, 2006). Other areas are also implicated, and in a recent study it was found that depressive symptoms in AD patients were associated with cortical thinning in temporal and parietal regions (Lebedeva *et al.*, 2014). It was also suggested that protein pathology (total-tau) in these areas may contribute to the development of depressive symptoms. Overall however, the association between CSF, depression and degree of AD-related pathology is unclear (Enache *et al.*, 2011). Of note, in mild AD and LBD, depression was associated with cortical thinning in

prefrontal and temporal areas and antidepressant use was associated with parahippocampal thinning (Lebedev *et al.*, 2014). The latter is in contrast to the finding that treatment with antidepressants can induce hippocampal cell proliferation and neurogenesis (Pilar-Cuellar *et al.*, 2013), and could explain the low efficacy of antidepressants in cognitively impaired elderly. Finally, studies have shown that a previous history of depression or coexistent depression and AD, increased the likelihood of an autopsy-proven diagnosis of AD (Rapp *et al.*, 2006; Rapp *et al.*, 2008). Similar findings have been shown using amyloid-PET (Butters *et al.*, 2008). Interestingly, in a recent clinical-pathologic cohort study, 1764 older persons without cognitive impairment at baseline were followed for almost 8 years until autopsy (Wilson *et al.*, 2014). Evaluation included assessment of depressive symptoms, and in 582 cases neuropathological examination to quantify β -amyloid plaques, tau tangle density, neocortical LBs, hippocampal sclerosis and cerebral infarcts were performed. Both MCI and dementia were associated with higher depressive scores, but only comorbid depression and dementia with a more rapid cognitive decline. Furthermore, there were no associations between depressive scores and biomarkers of neurodegeneration. An interpretation of these findings is that depression accelerates cognitive impairment, but traditional biomarkers of dementia are unrelated, suggesting alternative etiologies.

To conclude, the neural mechanisms underlying both dementia and depressive disorders and the interaction between the two are complex. Clarification is important in order to improve future assessment and diagnosis, early intervention and treatment.

LLD is often accompanied by cognitive impairment, making diagnosis and treatment challenging. The etiology of LLD is not known, but probably involves fronto-subcortical neuronal networks, cerebrovascular factors and inflammation. The low efficacy of antidepressants in demented patients, necessitates more targeted interventions.

Cognitive impairment can be secondary to depression, but depression can also be a prodrome and risk factor of dementia. In general, there seems to be a bidirectional relationship between depression and neurological disorders including stroke, epilepsy, PD and AD. This interdependence means that depression imposes an increased risk of a later development of several common neurodegenerative disorders, but also vice versa.

The determination of the temporal relationship between depression and cognitive impairment is important, but not always possible in a clinical setting. If depression pre-dates cognitive impairment, although cognitive deficits improve, but do not completely resolve after remission of LLD, depression is the likely primary diagnosis (Alexopoulos, 2005). Conversely, cognitive impairment is the most likely diagnosis if it pre-dates depression and persists after successful treatment of depression.

5.6 Treatment

Both major and minor depression need to be treated as the latter also increases the risk of major depression, substance abuse and suicide (Polyakova *et al.*, 2014).

In all cases a thorough medical examination including blood tests and subsequent treatment of primary somatic causes of depression is essential before any specific measures are introduced. The main treatment options for depression are social interventions including physical activity, psychotherapy, antidepressant medication and Electroconvulsive Treatment (ECT). The indication and efficacy of treatment of LLD and depression in the young is basically similar (Kok *et al.*, 2012; Mitchell and Subramaniam, 2005), but there is evidence of widespread

undertreatment of LLD probably because of doubts about the efficacy and fear of adverse effects. Medical treatment should never be the only intervention, but be combined with psychological modalities.

Of note, probably the most serious risk of LLD is mortality. Depressed older people can die either from worsening of an accompanying medical illness or by suicide. The risk of suicide among elderly is high in most countries and especially high in older men (Mitty and Flores, 2008). Health care professionals and others therefore need to raise their awareness to the signs and symptoms of depression in the elderly as the consequences of ignorance can be high.

Psychotherapy has proven effective in the treatment of LLD, and in a meta-analysis no differences were seen between individual or group format or between cognitive behavioral therapy (CBT) and other types of interventions (Cuijpers *et al.*, 2006). The evidence for psychotherapy in demented patients with depression is weak, but some studies indicate effects in patients with mild cognitive impairment (Kurz *et al.*, 2012; Wilkins *et al.*, 2009).

Physical activity can alleviate depressive symptoms in elderly depressed, but may not be appropriate for all groups, including the cognitively impaired and the severely somatic ill (Arean and Niu, 2014). In addition, further research need to be conducted on the long-term effects of physical exercise.

Of note, most studies on antidepressants have been conducted in younger populations, but response rates in LLD seem comparable in elderly with or without comorbid medical illnesses (Gill and Hatcher, 2000; Kok *et al.*, 2012). Before selecting an antidepressant it is particularly important to avoid worsening of medical conditions due to adverse events and/or dangerous interactions. Thus, the tricyclic antidepressant should best be avoided in the oldest (newer class antidepressants, including SSRIs, are in any case first choice). The evidence supporting antidepressants in the demented is in general weak (Banerjee *et al.*, 2011; Gill and Hatcher, 2000; Nelson and Devanand, 2011).

In cases of severe, psychotic, or refractory depression, ECT is warranted. Most studies have been performed on elderly without cognitive impairment, but there is evidence that ECT is equally effective and well tolerated in depressed patients with MCI or dementia (Hausner *et al.*, 2011).

Of note, depression is often a recurrent disorder. It is therefore essential that patients are followed up by health care professionals also in the vulnerable period succeeding the initial successful treatment of the acute episode. Systematic evidence for the optimal post-depression management is sparse.

6.0 Aims of the study

The overall objective of this thesis was to investigate early, clinical features of dementia and to find potential biomarkers that could help explain underlying disease mechanisms. Our main focus has been on Lewy body disease since little is known about the early features of disease in this patient group.

Specific objectives of this thesis include:

In patients with mild dementia (paper 1):

- 1) to retrospectively explore presenting and early, clinical symptoms of DLB.

In early, non-demented PD patients (paper 2):

- 2) use DTI to test the hypothesis that there is decreased WM integrity compared to NC.
- 3) use DTI to test the hypothesis that WM integrity is differentially reduced in PD and early AD.
- 4) test the hypothesis that DTI changes are specifically associated with cognitive performance.

In SCI and MCI patients (paper 3):

- 5) test the hypothesis that depressive symptoms correlate with AD type changes in CSF.
- 6) test the hypothesis that depressive symptoms correlate with AD type changes in structural imaging including hippocampus volume, cortical thickness, WML and DTI.
- 7) test the hypothesis that depressive symptoms correlate with AD type changes in FDG-PET.

7.0 Methods

7.1 Design

Both the Dementia study in Western Norway (DemVest) and the MCI-study at Akershus University Hospital (AHUS) are longitudinal cohort-studies, using a variety of biomarkers and diagnostic techniques. The projects include patients with early, pre-dementia (SCI and MCI) states (AHUS) and early dementia (DemVest). Participants are recruited from the referrals to clinical routine service in university-based hospitals.

In all papers of this thesis, a cross-sectional design has been used, although the longitudinal design of the overall project is relevant for diagnostic and strengthens diagnostic accuracy. In addition, in paper 1 we used a retrospective technique asking caregivers if certain symptoms had ever occurred between onset of disease and the time of assessment (**text box 9**).

7.2 The subjects

7.2.1 DemVest study

In the first paper, patients referred between 2005-2007 to 5 outpatient clinics of geriatric psychiatry and geriatric medicine in Rogaland and Hordaland counties were screened for a first time diagnosis of mild dementia according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV, 4th edition). The neurology clinics in the area were asked to refer such patients to the study. From 2007 only early DLB and PDD patients were recruited. In paper 1 only patients with a diagnosis of DLB (n=61) and AD dementia (n=109) were included. All patients underwent a clinical examination including standardized clinical rating scales (see section 7.3). “Mild dementia” was defined as a MMSE score > 19 or Clinical Dementia Rating (CDR) = 1. Patients with acute delirium or confusion, terminal illness, a recently diagnosed major somatic illness, previous bipolar disorder or a psychotic disorder were excluded. Patients were recruited for brain donation, and results for the first 36 cases coming to autopsy have shown that all patients with a clinical diagnosis of probable DLB had limbic and/or cortical Lewy bodies.

7.2.2 MCI-study Ahus

In the second and third paper, patients with SCI, MCI and recently diagnosed PD were recruited from referrals to a university-hospital based memory clinic and neurology outpatient clinic. These are the only memory and neurology clinics in the area, and general practitioners have for a long time been encouraged to refer people with early memory problems. Inclusion criteria for both groups were age 40-79, and for patients included from the memory clinic impaired cognition (SCI or MCI) for at least 6 months. Exclusion criteria for both groups were impaired activities of daily living (i.e. dementia), a previous diagnosis of a (major) psychiatric disorder, cancer, drug abuse, solvent exposure, anoxic brain damage or other severe physical disease which could influence cognition. Subjects underwent standardized clinical examination, blood tests, MRI including DTI, FDG-PET and lumbar puncture with CSF extraction. All PD patients had pathological Dopamine transporter scans ($[^{123}\text{I}]\text{FP-CIT}$ SPECT). The total number of inclusions is 22 SCI, 56 MCI, 18 PD and 19 NC.

Text box 9

Eliciting presenting and early symptoms of dementia with Lewy bodies and Alzheimer's disease dementia according to the DemVest study protocol (paper 1)* :

Presenting Symptoms

Caregivers were interviewed by a trained research clinician regarding the presenting symptoms of dementia using a scripted list of symptoms (more than one answer was possible):

- Reduced memory
- Problem solving difficulties
- Depression
- Visual hallucinations
- Gait problems
- Tremor, stiffness
- Tendency to fall
- Language problems
- "Other"

Symptoms during course of disease

Caregivers were also asked whether symptoms had ever occurred between onset and time of assessment:

- Tremor or stiffness
- Gait problems/problems with balance or falling
- Visual hallucinations
- Delirium or fluctuations of consciousness.

*The answers were further explored with detailed questioning by the clinician and recorded as present or absent. The final diagnosis was not known at the time of administering this questionnaire.

In the second paper all 18 PD patients with available data were included. As a comparison group, 18 subjects with MCI and pathological CSF (low AB42 and/or high p-tau) (i.e. AD-MCI according to research criteria (Dubois *et al.*, 2007b)), were individually matched for age, gender and level of education to the PD patients and included. In addition, 19 non-demented control subjects were recruited from spouses or relatives of the patients with AD-MCI on the basis of a clinical interview by a neurologist and neuropsychological tests administered by a trained neuropsychologist. Cognitive normality was ensured by T-scores ≥ 40 on tests of memory, executive functioning and visuospatial ability (see section 7.4.5 below).

In the third paper we included all available patients with SCI (n=22) and MCI (n=38) and used the Geriatric Depression Scale (see section 7.3.2 below) to divide the cohort into those with and without depressive symptoms.

7.3 Diagnostic procedures and clinical assessment

7.3.1 DemVest-study

All included patients had a thorough somatic examination including a battery of blood tests. The diagnosis of dementia was made according to the Diagnostic and Statistical Manual for Mental Disorders 4th edition (DSM-4) based on interview with patient and caregiver in addition to the clinical and biomarker evaluation program. The diagnosis for AD dementia was made according to The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann, et al., 1984). DLB was diagnosed according to the revised consensus criteria (McKeith, et al., 2005) based on a number of clinical rating scales focusing on the core DLB features. PDD was diagnosed according to the recommendations from the Movement Disorder Society Task Force (Emre, et al., 2007) (text box 8). The clinician completed the Clinician Dementia Rating scale (CDR), range 0 – 3, 0 meaning no cognitive impairment, 0.5 mild cognitive impairment or very mild dementia, 1 mild dementia, 2 moderately severe dementia and 3 severe dementia (Morris, 1997). ADL were assessed using the Rapid Disability Rating Scale-2 (Linn & Linn, 1982). The clinical diagnosis was made by two of the researchers taking into account all available information and the diagnosis was revised annually. Study nurses administered a neuropsychological test battery including the Mini Mental Status Examination (MMSE) (Folstein *et al.*, 1975) and met regularly to ensure consensus and harmonisation of the conduct of the study program.

7.3.2 MCI-study Ahus

All included patients underwent a thorough somatic examination including a battery of blood tests. All patients with PD (Paper 1) were examined by a neurologist with training in movement disorders and met the criteria of probable PD (3 of 4 features: asymmetric onset, bradykinesia, rigidity and resting tremor) (Gelb *et al.*, 1999) (text box 7). To further support the PD diagnosis, all participants had a pathological single photon emission computer tomography using an ioflupane (123I) biomarker (DaTSCAN). Standardized rating scales of motor function (Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale) (Fahn and Elton, 1987) and Hoehn and Yahr staging were performed by trained research physicians (Hoehn and Yahr, 1967).

The Stepwise comparative status analysis (STEP) combines psychiatric and neurologic status examination to identify common dementia symptoms by which regional brain symptom profiles can be determined (Wallin *et al.*, 1996). Furthermore, the Clinical Dementia Rating Scale (CDR) is a six item questionnaire (including memory, orientation, judgment and problem-solving, community affairs, home and hobbies and personal care) and was used to exclude people with dementia (Berg, 1988).

Cognitive staging (paper 2 and 3) in SCI and MCI was performed according to the Global Deterioration Scale (GDS) (Auer and Reisberg, 1997) after a clinical interview of patient and a relative and the use of the following screening tests: MMSE (Folstein *et al.*, 1975), STEP parameters 13-20 (memory, abstract thinking, visuospatial ability, language, sensory aphasia, visual agnosia and apraxia) (Wallin *et al.*, 1996), I-Flex (fluency, interference and numeral-letter items) (Royall *et al.*, 1992) and Cognistat (memory, including cued recall, and executive

functions) (Kiernan *et al.*, 1987). Cognitively normal patients were classified as GDS 1. Patients reporting subjective cognitive impairment in addition to scoring above published cutoff on all screening tests (including 28 or higher on MMSE), were classified as GDS 2 (Subjective Cognitive Impairment, SCI), whereas patients scoring below cutoff were classified as GDS 3 (MCI). Patients who scored GDS>3, CDR >0.5 or > 1 in sum of STEP variables 13-20 were classified as demented and excluded as previously described (Nordlund *et al.*, 2005).

In paper 3 (and 2) we used the 15-item Geriatric Depression Scale (Sheikh JI and Yesavage JA., 1986; Brown, L. M. and J. A. Schinka, 2005) with 5/6 as cutoff for the evaluation of depressive symptoms. The questions are on a yes/no basis and is a valid and reliable measure of depression both in the elderly and in populations with MCI (Marc LG *et al.*, 2008) (Debruynne *et al.*, 2009). Of the 15 items, 10 indicate the presence of depression when answered positively, while the rest (question numbers 1, 5, 7, 11, 13) indicate depression when answered negatively. Scores of 0-4 are considered normal; 5-8 indicate mild depression; 9-11 indicate moderate depression and 12-15 indicate severe depression.

7.4 Biomarkers for the Ahus cohort (papers 2 and 3)

7.4.1 Cerebrospinal fluid

CSF extraction by lumbar puncture in the L3/L4 or L4/L5 intervertebral space was performed and analyzed according to protocol at a standardized time and as previously described (Fjell *et al.*, 2008). CSF p-tau was considered pathological if ≥ 80 ng/L, A β 42 if ≤ 550 ng/L and t-tau if > 450 ng/L (age 50–69) or 500 ng/L (age ≥ 70) (Sjogren *et al.*, 2001).

7.4.2 FluroDeoxyGlucose – Positron Emission Tomography (FDG-PET)

18F-FDG PET/CT imaging was performed with a Siemens Biograph 16 PET/CT scanner. Subjects fasted for at least 4 hours prior to imaging (water only), and plasma glucose had to be ≤ 8 mmol/L for FDG to be injected. After 10 minutes rest with eyes closed, subjects had an intravenous bolus of 200 +/-10 MBq 18F-FDG injected and rested for 45-60 minutes before scanning. For each subject, FDG-PET frames were registered to the corresponding intensity-normalized MRI volume. PET activity was averaged within each ROI defined on the MRI and normalized to activity within the brainstem.

7.4.3 Dopamine Transporter Scan

Dopamine transporter imaging was performed by intravenous injection of 185 MBq [123 I] FP-CIT (supplied by GE Healthcare), and SPECT images were acquired 3 h after injection. Images were acquired with 2-headed gamma camera (Infinia Hawkeye 4) in a procedure that lasted approximately 30 min. 10-30 minutes before 123I-FP-CIT administration, we gave every patient a thyroid-blocking preparation (200 mg i.v. sodium perchlorate) to stop local uptake of the ligand. The raw image data were reconstructed on a VISION workstation (Sophia medical/GE) using FBP (Filtered back projection) reconstruction, Butterworth filter, order 6, cut off 0.30 and no attenuation correction. Reconstructed images were initially analyzed visually by a nuclear medicine physician. In addition, volume-of-interest based semi-quantification of regional DAT striatal binding was undertaken calculating the Total Striatal Binding Potential Index (BP) and the Asymmetry Index (AI) using Dr. Durval Costa's method (reference area for BP %: ≥ 60 % and for AI > 10 %). The relationship between the uptake in striatum compared to the occipital cortex (ratio 1) and the relationship between the uptake in

putamen and nucleus caudatus (ratio 2) was calculated using the Dr. Freiberg Bispebjerg Hospital method (reference area for ratio $1 \geq 2.0$ and for ratio $2 \geq 0.8$). (European Association of Nuclear Medicine (EANM) procedure guidelines for Brain neurotransmission SPECT using ^{123}I -labelled dopamine transporter ligands. www.eanm.org) (Booij *et al.*, 1999).

7.4.4 Magnetic resonance imaging

MRI scans were obtained using a Siemens Espree 1.5 T system. For structural imaging (cortical thickness and volumetry) a T1-weighted (3D) magnetization prepared rapid gradient echo (MPRAGE) sequence was used. The protocol also included 2D axial fluid-attenuated inversion recovery (FLAIR) images.

For post-processing of imaging data (cortical reconstruction and volumetric segmentation) Freesurfer version 4.5.0 was used. This labels cortical sulci and gyri, and thickness values are calculated in the ROIs.

The Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL) version 4.1 was used for standard registration calculations and DTI analyzes. Tract-Based Spatial Statistics (TBSS) was used for voxel-wise statistical analysis of the DTI variables (FA, DR). WM ROIs based on the Freesurfer WM parcellations were extracted for FA and DR. The processing stream includes segmentation of the subcortical WM and deep gray matter volumetric structures and parcellation of the cortical surface.

7.4.5 Neuropsychological assessment

All neuropsychological tests were performed by a neuropsychologist within three months of baseline examination and consisted of a battery of tests covering all 5 cognitive domains (memory, attention, executive, language, and visuospatial domains). The following tests were applied in paper 2:

Trail making test (TMT)

TMT measures visual scanning, processing speed, mental flexibility and executive functions (Spreeen and Strauss, 1998). The TMT consist of two parts, but only TMT-B was used. In TMT-B the examinee is required to connect number and letters (1-A-2-B-3-C, etc.) on a piece of paper, and the time is recorded.

Controlled Oral Word Association Test – FAS (COWAT-FAS)

The COWAT-FAS is a measure of letter fluency (Reitan and Wolfson, 1985), and the participants are given one minute to say out loud as many words as possible within one minute starting with the letters “F”, “A” and finally “S”. The total number of words is recorded.

Rey Complex Figure Test (RCFT)

The RCFT consists of a copy trail, followed by a recall trial after 3 and 30 minutes (Meyers and Meyers, 1995). Only the copy trail was executed, which is a measure of visuospatial ability.

Rey Auditory Verbal Learning Test (RAVLT)

RAVLT is a measure of learning and episodic memory (Schmidt M, 1996). 15 different words are read to the examinee five times, and the number of correctly repeated words is recorded and summoned in a total score. Scores for both short (immediate) and delayed (30 minutes) recall are recorded.

Color-Word Interference Test (CWIT)

The CWIT from Delis-Kaplan Executive Function System (D-KEFS) measures selective attention and ability to inhibit a dominant and automatic verbal response (Delis et al., 2001). The CWIT includes four subtests: 1) Color naming, 2) Word reading, 3) Inhibition (i.e. determining colours of the ink of inconsistently coloured names) and 4) Inhibition/switching (i.e. switching between naming colours of the ink of inconsistently coloured names and reading words).

7.5 Statistics

SPSS/PASW statistics versions 18 and 20 were used for all analyzes and $p = 0.05$ was considered statistically significant. Significance at trend-level was defined as $0.05 < p < 0.10$. For the comparisons of demographic and clinical data, Chi-square test, independent sample T-test and Mann-Whitney U-test were used as appropriate. Kolmogorov-Smirnov test for normality was used to assess if variables were normally distributed. Demographic and clinical characteristics of patients were described as means and standard deviations (SD) or frequencies and percentages.

In paper 2 we used one-way analysis of variance (ANOVA) to compare the pre-dementia PD group to AD-MCI and HC. The DTI WM ROI variables were normally distributed (after the effects of age and sex had been corrected by regression analysis), and hence one-way ANOVA (with a priori planned contrast AD vs. NC and PD vs. NC including polynomial linear trends) was used to compare the three groups. The Pearson's correlation method (for normally distributed data) was used to compare neurocognitive test data in three domains with DTI variables in a priori selected brain regions. The effects of sex and age on the DTI parameters were corrected by linear regression before correlations were determined.

In paper 3 Hippocampus volume, cortical thickness, DTI and FDG-PET variables were adjusted for age and sex by a linear regression model before a multivariate analysis of variance (MANOVA) was performed for simultaneous comparison with cognitive impairment (SCI or MCI) as factors in the model together with depressed/non-depressed (independent variables). Post-hoc comparisons were done by ANOVA. Analyses stratified by CSF were defined as secondary and were performed by including CSF (pathological or not) in addition to cognitive classification (SCI or MCI) as factors into the MANOVA model together with depressed/non-depressed (independent variables) and interaction between the two. Bonferroni adjustment for multiple tests was applied for primary analyses only.

7.6 Ethical considerations

In Norway the first committees for research ethics were established in 1977 (Lahlum and Ruyter, 2012). The precipitating cause was the 1975 revised World Medical Association's declaration of Helsinki that stated that "any experiment involving human beings (...) must be submitted to an especially appointed, independent committee for review, comment and guidance". Further laws and regulations were implemented in 2006 (Research Ethics Act) and 2009 (Health Research Act). In all studies where people are involved there is a balance between disadvantages for the individual participant and the benefits for future patients and society. The DemVest-study and the MCI-study were approved in advance by the Data Inspectorate of Norway and the Regional Committee for Medical and Health Research Ethics (REK number DemVest 2010/0633, REK numbers MCI-project Ahus 2011/99 (PD) and 2013/150). All patients and healthy control subjects received detailed oral and written information and written

approval was obtained before inclusion. All participants could withdraw from the study at any time without explanation. Patient's ability to make informed decisions on their own behalf were assumed and secured by involvement of caregivers. Having mild dementia was assumed not to significantly affect that ability.

The projects did not raise any major ethical concerns, but some of the procedures were both time-consuming and strenuous for the participants. The neuropsychological evaluation often lasted half a day, and imaging, including MRI and PET, was obtained at neighboring hospitals which increased travelling distances. In addition, all patients were encouraged to perform a lumbar puncture and CSF extraction. This is not part of the clinical routine, but often preferable given the diagnostic sensitivity and specificity especially in AD-MCI cases. All patients were given detailed information about potential risks and complications in advance (which in general are regarded as minor), including post puncture headache, back pain and localized bleeding (Wright *et al.*, 2012).

Of note, all study-specific procedures were free of charge and travelling expenses (and to a certain extent work-related costs) were refunded.

Many of the participants expressed gratitude and a sense of security that they could reach project assistants at convenience and that they benefitted from the regularly and thoroughly conducted examination. Other health issues not directly related to the project were diagnosed and dealt with at the appropriate health care level.

8.0 Discussion

8.1 Main findings

The main goal of this thesis has been to explore the earliest clinical and biological changes in LBD and AD with a special emphasis on LBD. More specifically, investigate presenting clinical features in early DLB, WM changes associated with cognition in early non-demented PD and find potential neurobiological substrates for depressive symptoms in patients with SCI and MCI. In articles 1 and 2, more established knowledge regarding AD has been used to contrast findings in LBD.

Summarizing our main observations, we found that DLB patients most often present with memory problems and visual hallucinations, that WM changes can be seen early and are associated with cognitive impairment in PD and that minor depression in SCI and MCI patients attending a memory clinic are associated with cognitive impairment and may be the earliest features of neurodegenerative disease.

8.2 Paper 1

At the time of publishing this paper, very few studies had focused on pre-dementia DLB.

We found that the most common presenting symptoms in DLB were memory impairment (57 % of cases) and visual hallucinations (VH) (44 %). In contrast 99 % of AD patients presented with memory problems and almost none with VH (3%). It is well established that memory impairment is an early and central feature in AD. Conversely, memory impairment is less common and less pronounced in the early stages of DLB relative to impaired visuospatial and executive skills (Ferman *et al.*, 2013; Yoshizawa *et al.*, 2013).

In a pivotal study, the first prospective study of the pre-dementia stage of DLB, Molano *et al.* followed 8 MCI patients until death with subsequent autopsy-proven LBD (Molano *et al.*, 2010). 7 patients developed DLB prior to death, one patient remained mildly cognitively impaired. All 8 patients also had parkinsonian symptoms, 7 had RBD and 6 had experienced VH and fluctuating cognition. A main finding was that REM sleep behavior disorder (RBD) preceded cognitive symptom onset by a median of 10 years (2–47 years) and a MCI diagnosis by a median of 12 years (3–48 years). The cognitive domains most frequently affected were attention, visuo-construction and executive ability, but also memory problems were recorded. Conversely, memory was the most common presenting symptom in our study, although other domains were not specifically researched (other than problem solving ability as a substitute for executive functioning). The sensitivity of caregivers retrospectively detecting memory impairment (and other domains) is subject to recall bias and is probably variable (Noe *et al.*, 2004), but suggested to be good reporting early cognitive deficits (Naismith *et al.*, 2011). Furthermore, reported impairment of memory does not necessarily reflect an isolated single-domain amnesic deficit. Other domains, especially attention which is commonly affected in LBD, are also likely to affect memory thus raising the question of reduced specificity and over-reporting of memory impairment. Furthermore, memory does not only have to be linked to medial temporal lobe pathology (as typical seen in AD), but may also be secondary to executive dysfunction. The observed high prevalence of early memory impairment in the present cohort, regardless of underlying pathology, is nevertheless an interesting finding and

relevant for clinicians, who should consider DLB as a differential diagnosis also when memory impairment is an early complaint.

44 % of DLB patients presented with VH, a core symptom in the clinical consensus criteria (McKeith *et al.*, 2005). It is likely that such a symptom would be more accurately reported than cognitive impairment because of the peculiar nature of its presentation. On the other hand, VH may be under-reported by the patients due to feelings of shame and guilt.

In another pivotal study, Tiraboschi *et al.* wanted to determine the best clinical predictors (among VH, extrapyramidal signs (EPS) and visuospatial impairment) of a later autopsy-proven diagnosis in 23 DLB and 95 AD cases (Tiraboschi *et al.*, 2006). It was retrospectively found that DLB was best predicted by VH (seen only in 22 % of all DLB cases, positive predictive value 83 %). In contrast, although not a core feature, visuospatial impairment was the best negative predictor of DLB at autopsy (negative predictive value 90 %). In conclusion, a recent history of VH was the most specific clinical sign of DLB (99 % specificity) and visuospatial impairment the most sensitive (74 %). Of note, only 26 % of DLB patients had a history of EPS and only 13 % had both EPS and VH. These findings are in accord with our finding that VHs are common and early features of DLB. Similarly, 25-30 % of the patients in our study reported that EPS (tremor, stiffness and gait problems) was the presenting symptom, suggesting that VH precede motor symptoms. Informant-based assessment tools such as the Neuropsychiatric Inventory (NPI) can be useful both for screening for VH and assessing their severity and frequency (Cummings *et al.*, 1994).

The biological substrate of VH is not established, but there is an association between Lewy body deposition in the temporal lobe and VH (Harding *et al.*, 2002). Furthermore, evidence suggest an association between VH and deficits in cortical acetylcholine (Ballard *et al.*, 2000), and VH may therefore respond well to acetyl cholinesterase inhibitors (McKeith *et al.*, 2004). There is mounting evidence to suggest that VH in Lewy body disease can occur after lesions in all parts of the visual pathway, from the retina to the occipital cortex, and both increased and decreased metabolic activity have been documented (Archibald *et al.*, 2009;Boecker *et al.*, 2007;Pernecky *et al.*, 2008). In a recent study, DLB patients and normal controls were presented with simple visual stimuli during functional MRI (fMRI) with subsequent arterial spin labelling. It was concluded that higher (V5), but not lower (V1, V2, V3), visual areas, particularly in occipito-parietal regions, appear abnormal in DLB (Taylor *et al.*, 2012). Similarly, in another recent study using resting state FMRI, there were no differences in connectivity in the primary visual cortex (V1) between DLB, AD and normal controls (Kenny *et al.*, 2012). These findings suggest that the underlying brain changes associated with VH are complex and involving higher order visual pathways.

FMRI has also been used to explain impaired visual processing in PD patients with VH suggesting that these patients are creating their own false images (Meppelink *et al.*, 2009). Clinically, the patients with VH often have more profound visuo-perceptual dysfunction compared to those without hallucinations (Mosimann *et al.*, 2004), and also deficits in attention have been reported (Collerton *et al.*, 2005).

Finally, there is mounting evidence that DTI can reveal WM damage in DLB, and that common predilections sites include the visual pathways (Kantarci *et al.*, 2012b;Watson *et al.*, 2012), but at present no DTI study has focused on early Lewy body disease and potential associations to VH.

Depression can precede AD dementia and PD by several years, i.e. be a prodromal symptom, and is also known to be a risk factor in development of cognitive impairment and dementia (See also sections 5.0 and 8.4). Conversely, the prevalence and role of depression in pre-dementia DLB is not known, but recently a history of depression was shown to be more common in DLB than in normal controls (Boot *et al.*, 2013).

In this study depression was reported as the third most common presenting symptom (in 34 % of DLB cases), and similar prevalence rates were seen in AD (38 %). However, the method of eliciting depressive symptoms has weaknesses, and a diagnosis of depression according to ICD-10 cannot be made. Although answers were explored by detailed questioning by the clinician (see text box 9), all depressive symptoms were collected retrospectively, making validation according to established criteria difficult. Furthermore, included patients were mildly demented, and although caregivers added valuable information, depression in itself will often induce secondary cognitive impairment in the patient, adding to the symptoms of dementia, including memory loss. However, depression is a known prodrome in AD and it is reasonable to conclude that (minor) depressive symptoms probably are present also in the early stages of DLB. Of note, as discussed in more detail later, depressive symptoms may also represent psychological reactions to the experience of the earliest signs of neurodegeneration. It is thus not surprising that the different dementia subtypes share depression as an early reaction to disease. The neurobiology of depression in DLB needs further investigation, and one method is to evaluate depressive symptoms and biomarkers in SCI/MCI cohorts followed longitudinally (see also discussion of paper 3 in section 8.4).

After publication of this paper, a few other studies have focused on early symptoms in DLB. In a retrospective study of prodromal symptoms it was concluded that patients with DLB (n=34) exhibited higher prevalence rates of RBD, olfactory dysfunction, constipation and increased salivation at onset compared to AD (n=32) and normal controls (n=30) (Chiba *et al.*, 2012).

Toledo *et al.* examined biomarker correlates of 22 autopsies (from the Alzheimer's Disease Neuroimaging Initiative (ADNI)) including clinical data, imaging, neuropsychological profiles and CSF. It was found that VHs were a strong predictor of coincident DLB (100% specificity) and a more severe dysexecutive profile suggested coincident DLB (80 % sensitivity and 83 % specificity) (Toledo *et al.*, 2013).

Finally, in the second prospective study of pre-dementia DLB, Ferman *et al.* followed 337 patients with MCI until a clinical diagnosis of DLB (n=49) or AD (n=162). Autopsy-confirmation of the clinical diagnosis was available in a subgroup. Non-amnesic MCI progressed more often to probable DLB and amnesic MCI more often to probable AD, and 88 % of DLB cases included attention and/or visuospatial deficits at baseline (Ferman *et al.*, 2013).

To conclude, recent studies confirm our findings that the pre-dementia phase of DLB has multiple clinical starting points and that VH and MCI are common prodromes of the full DLB syndrome.

Of note, our findings suggest that a top-down clinical progression rather than the bottom-up pathological progression as suggested by Braak *et al.* for PD may be a more common pattern in DLB. Despite differences in the relative timing of clinical features and neuropathology between PD and DLB, there has recently been an initiative to redefine diagnostic criteria for PD, proposing to omit the "1-year rule" and incorporate DLB as a PD subtype (see section 3.2.3 and further discussion in section 8.3 (paper 2)).

8.3 Paper 2

At the time of planning this thesis, few studies had focused on white matter (WM) integrity in Lewy body disease (LBD), and very few had focused on WM using diffusion tensor imaging (DTI). Furthermore, no DTI studies of early, non-demented PD including comparisons to AD and associations to neuropsychological tests had been published. In AD, some promising results regarding DTI and early WM affection suggested that DTI could be a potential sensitive biomarker (Selnes *et al.*, 2013). Whether this was the case also in early LBD was uncertain. We therefore included newly diagnosed PD patients without dementia and compared them to pre-dementia AD and normal controls.

Main findings of this paper include WM affection in temporal, parietal and occipital cortices in early PD without dementia as compared to controls. Some of these WM changes also related to neuropsychological testing. Furthermore, differences between pre-dementia PD and AD could be detected using whole-brain analysis. The exact neurobiology of early cognitive impairment in PD is not known, but these findings offer some insight into pathological mechanisms.

DTI is a rather new MRI technique that basically measures the movement of protons when biological tissue is introduced to a magnetic field (gradient). In most of its applications this movement of protons is most sensitive to the general mobility of water molecules depending on factors in the tissue including temperature, viscosity and larger molecules. This movement of water molecules will be hindered by biological/microstructural barriers such as cell membranes, myelin and cell organelles. See section 3.3.6.6.1 for more details.

This brings forth an important and debatable question: what exactly is measured by DTI and can we use it as a biomarker of neurodegenerative disease?

DTI has proven useful in examining tissue where diffusivity is anisotropic (i.e. directionally unequal), and there is increasing evidence that DTI can function as a surrogate marker for various pathological processes including WM integrity (Jones *et al.*, 2013). There is to some extent a correlation between WML and DTI parameters (Zhan *et al.*, 2009), and DTI is also probably a more sensitive method of evaluating WM integrity than conventional MRI (Assaf and Pasternak, 2008; Cochrane and Ebmeier, 2013; Duncan *et al.*, 2013). Thus, in the present study we regard DTI as surrogate marker of WM affection.

However, despite the increasing use of DTI as a biomarker also in neurodegenerative disease it is important to be aware of the limitations and that such an “indirect” method of measuring potential pathophysiological processes must be interpreted with caution.

Furthermore, different artifacts including physiologic noise and image artifacts as well as the analytic method used, may complicate diffusion parameters and their biologic interpretation (Basser and Jones, 2002).

Our findings suggest that DTI can differentiate between WM affection in early PD versus controls, but also potentially between early PD and AD. The latter is questionable since we did not find any significant changes in the pre-planned region of interest (ROI) based analyzes, but only in some regions using a whole brain approach. Also, a main limitation in the present study is the rather low sample size and these findings must therefore be interpreted with caution.

Our main finding, that WM affection is present in early PD, however, is consistent with recent and larger studies (see also section 3.3.6.6.1 for a more detailed review). Indeed, we and others have found correlations between DTI abnormalities and cognitive measures including microstructural changes associated with executive function, attention and memory (Melzer *et al.*, 2013;Theilmann *et al.*, 2013;Zheng *et al.*, 2014) supporting the role of DTI as a promising biomarker of early cognitive decline in PD.

The past decade's advances in neuropathology, genetics and epidemiology have increased our understanding of the neurobiology involved in LBD. Clinical risk factors for cognitive decline in PD include older age of onset of PD, non-tremor dominant motor subtypes, REM sleep behavior disorder, olfactory dysfunction and visual hallucinations (see section 3.3.6.4), and a variety of biomarkers are associated with cognitive decline in LBD (see sections 3.2.8 and 3.3.6.6). Cortical Lewy bodies and Lewy neurites are the most significant correlates of dementia in PD (Irwin *et al.*, 2012), but in contrast to AD there are no reliable biomarkers at present in use in the clinical routine to predict cognitive impairment and dementia in LBD. A multimodal biomarker approach combining different techniques is probably needed to disentangle the different aspects of cognitive decline in PD including visual hallucinations. There are, however, some areas of research that are encouraging, and worth discussing.

Like in AD, a prodromal MCI stage predicts a later conversion from PD to PDD, affecting several domains, especially attention, executive and visuo-constructive abilities (see section 3.3.6.2). Neuropsychological deficits including impaired semantic fluency and pentagon copying, have been shown to predict PDD (Williams-Gray *et al.*, 2009a), and this pattern may offer some insight into the underlying pathology as impairments in semantic fluency (memory) and pentagon copying (visuospatial ability) are thought to represent temporal and parietal lobe dysfunction respectively. This “posterior cortical LB pathology” is believed to predict a more rapid progression to dementia in PD and is possibly related to cholinergic loss. In contrast, defects in dopaminergic transmission affect fronto-striatal pathways resulting in working memory and executive impairment, but seem to less often progress to dementia. This is also known as the “the dual syndrome hypothesis” (Kehagia *et al.*, 2013), and it signifies an important, but controversial, hypothesis in the understanding of cognitive impairment in PD. Posterior cortical defects in PD/PDD can to some extent be assessed using different imaging techniques including structural MRI, DTI, FDG-PET and amyloid-PET, but diagnostic sensitivity and specificity is at present too low to be used in the clinical routine for the diagnosis of LBD (see section 3.3.6.6). Our results indicate that early WM affection in PD is not related to memory, but possibly to executive and visuospatial deficits and prefrontal involvement. However, the study sample is too small to draw definite conclusions and follow-up studies to confirm the importance of these findings are needed.

Of note, the MMSE is commonly used around the world as a screening instrument for cognitive dysfunction and it is a sensitive tool for separating moderate and severe dementia from persons without dementia. However, the MMSE is less sensitive in the differentiation between MCI and mild dementia and for detection of cognitive impairment in LBD (Hoops *et al.*, 2009). The use of more advanced neuropsychological tests in the differentiation between SCI, MCI and dementia in this cohort could have increased the validity of our findings.

The CamPaIGN study (Williams-Grey *et al.*, 2009) further postulates an association between these “posterior” neuropsychological deficits and gene alterations in the MAPT H1/H1 haplotype which is implicated in the buildup of isoforms of tau. The exact role of tau in LBD is

unknown, but a recent study strengthens the hypothesis that an interaction between tau and alpha-synuclein can occur through cross-seeding (i.e. direct interaction between misfolded proteins) of tau to promote alpha-synuclein aggregation (Guo *et al.*, 2013). Other possible genetic associations to dementia in PD include GBA mutations and possibly APOE, but not COMT genotypes (which are associated with “anterior deficits” related to dopamine-dependent fronto-striatal pathways) (see also section 3.3.6.5).

“The dual syndrome hypothesis” was further supported by recent findings in the ICICLE-PD study (Nombela *et al.*, 2014) where 168 participants with early PD and 85 normal controls underwent clinical, neuropsychological and fMRI assessments and genotyping for three polymorphisms commonly related to cognitive impairment in PD (COMT, MAPT and APOE). It was concluded that task-specific regional activations in PD (assessed with fMRI) were linked to genetic variation, i.e. COMT to executive functions, MAPT to visuospatial and APOE to memory tasks respectively.

Up to 50 % of PDD cases have concomitant amyloid and tau pathology sufficient for a secondary AD diagnosis (Irwin *et al.*, 2013), and decreased levels of A β 42 have been shown to predict future PDD (Siderowf *et al.*, 2010). This confirms the heterogeneous nature of PD including overlapping features with AD and possibly synergistic effects between the two. A recent prospective study over 18 months involving 27 non-demented PD patients combined CSF A β 42, neuropsychological tests (“posterior cortical based” including verbal learning, semantic fluency and visuo-perception) and structural MRI. At follow-up all participants without baseline biomarker abnormalities remained non-demented whereas all with abnormalities in all three biomarkers progressed to dementia, with intermediate risk for those showing abnormalities in one or two biomarker types (Compta *et al.*, 2013). Abnormal MRI-findings included limbic- and posterior cortical thinning.

Despite the central role of Lewy bodies in the pathogenesis of LBD and promising preliminary results, so far the sensitivity and specificity of CSF (and plasma) alpha-synuclein have been too low to reliably diagnose PD and predict disease progression.

WM was long thought to be passive tissue, but is now known to consist of myelin producing glia cells that actively modulate neural signaling including support and protection of neurons and maintaining of homeostasis.

A surrogate marker for WM disintegrity is white matter lesions (WMLs) which can be defined as areas of high intensity in WM observed on T2-weighted MRI. WMLs, especially those in the deep WM, are believed to be caused by small vessel disease and have been shown to increase the future risk of stroke, dementia and death in the general population (DeBette and Markus, 2010). There is also increasing evidence that small vessel disease is linked to incipient AD (Snowdon *et al.*, 1997; Stenset *et al.*, 2006), but the role in LBD is unclear.

Although WMLs can be seen in all stages of PD, including PDD, and are associated with cognitive impairment, there exists no evidence to conclude that WMLs accelerate neurodegeneration. Similarly, the role of cardiovascular risk factors and PD is poorly understood. Our results, however, suggest that cardiovascular risk factors, including hypertension, diabetes, hypercholesterolemia and WMLs cannot aid in the differentiation between early AD, PD and controls. It is of major interest to investigate the role of cardiovascular risk factors and WM affection in PD (and AD) since these are potential preventable and/or reversible factors available for treatment.

Of note, WMLs represented as smooth periventricular lining probably have another etiology than those clearly separated from the ventricles, so-called deep WMLs. The former are associated with loss of ependymal lining of the ventricles, gliosis and lack of hypoxia-induced

inflammatory tissue damage and is probably unrelated to small vessel disease in contrast to the latter (especially when they present as punctuate lesions and not beginning confluent or confluent abnormalities)) which are associated with a low progression rate (O'Brien, 2014). Deep WMLs are associated with chronic hypoxia or episodic hypoperfusion, and can as such be regarded as “incomplete” infarcts. Indeed, there can be a number of other etiological factors to WMLs affecting cognition other than vascular including toxic and metabolic leukoencephalopathies, neoplasms, infections, mitochondriopathies and immune related disease (Weidauer *et al.*, 2014). Further studies on the different representation of WMLs types are needed in order to understand the possible pathogenic role of different WM involvement in neurodegeneration.

Interestingly, no previous DTI study has focused on early Lewy body disease and potential associations to visual hallucinations. We found early signs of occipital WM affection that could signify the earliest signs of visual pathway affection, but larger cohorts followed longitudinally are required to elucidate the neurobiology of visual hallucinations in PD.

Future research will also be facilitated by higher field strength MRI (7-11 Tesla) and greater congruity in MRI protocols which will enable multicenter studies.

To our knowledge no DTI study focusing on early PD with a longitudinal design has yet been published, which is needed before conclusions regarding DTI as a biomarker in PD can be drawn.

Finally, recent recognition of non-motor symptoms (both early and late) has raised awareness of PD as a neuropsychiatric disorder, and the present understanding and classification of LBD has thus been debated. An area of controversy is the distinction between DLB and PDD, in practice to distinct disorders separated by the “one year rule” (McKeith *et al.*, 2005). In addition, there are currently two classification systems in use for the assessment of Lewy body pathology, i.e. Braak's staging system for PD and McKeith's staging system for DLB including criteria for mixed LB and AD pathology (Braak *et al.*, 2003, McKeith *et al.*, 2005) (see also section 3.2.3). Furthermore, the present criteria for PD focus on motor symptoms and non-motor symptoms, including pre-motor symptoms, cognitive impairment and dementia, are largely neglected (except that early dementia is an exclusion criterion for PD). A recently convened task force has therefore proposed to redefine current criteria for PD (Berg *et al.*, 2014). Among proposals are that early pre-motor features should be termed “prodromal” or “pre-clinical”, suggestion of omitting the “1-year rule” (i.e. dementia is no longer an exclusion criterion in PD) and that core clinic-pathologic criteria of the motor syndrome accompanied by neurodegeneration in substantia nigra and alfa-synuclein deposition remain the gold standard of PD diagnosis. The current staging systems for LBD have not been proposed to be revised at present awaiting further understanding of the underlying disease mechanisms and disease progression.

To summarize, no single marker is presently able to predict progression of cognitive decline in PD with good reliability and validity. We and others have shown that DTI changes characterize early stages of cognitive affection in both AD and Lewy body disease (Cochrane and Ebmeier, 2013; Selnes *et al.*, 2013), but the best approach in predicting dementia in PD is at present by using a combination of biomarkers rather than a single biomarker.

Furthermore, there is reason to believe that DTI abnormalities reflect axonal integrity and that diffusivity changes in AD may be directly related to AD neuropathology (Selnes *et al.*, 2013). Whether this is the case in LBD remains an important research question.

The considerable overlap between neuropathological changes and clinical presentation in DLB and AD has so far made it difficult to find biomarkers able to distinguish between the disorders. Like in AD, affected cognition in Lewy body disease may be characterized by amyloid dysmetabolism, but also by a multitude of other pathological factors including alfa-synuclein, suggesting a generalized neuronal disease (Ferrer *et al.*, 2012).

In the present study, we have shown that DTI can potentially differentiate between normal controls, pre-dementia AD and PD and that WM affection is an early event in PD pathogenesis. DTI is thus a promising biomarker in predicting conversion to dementia in PD and also in the differentiation between AD and LBD in general. It remains to be seen whether this rather new technique will offer sufficient sensitivity and specificity to be a valid tool in diagnosing Lewy body disease and prediction of disease progression in the future. Hopefully more specific changes can be found with larger groups followed longitudinally.

8.4 Paper 3

Due to the high prevalence rates of concomitant depression in cognitive disorders and the future growth of the elderly population, there is a need for a better understanding of the neurobiology involved with the ultimate goal of modifying or preventing disease.

As described in more detail in section 5.0, the relationship between major depression and AD is complex. Depression can be a prodrome of AD, increase the risk of dementia and is a common neuropsychiatric symptom in all stages of AD. Moreover, the concomitant prevalence of depression and dementia is probable even higher in Lewy body dementia and vascular dementia than in AD (Castilla-Puentes and Habeych, 2010;Enache *et al.*, 2011). Depression is also a common pre-motor symptom in PD (Postuma *et al.*, 2012), but little is known about the prevalence of depression in the pre-dementia phase of DLB despite the fact that depression is included as a supportive feature in the DLB consensus criteria (McKeith *et al.*, 2005). Despite some evidence to support an increased risk of AD dementia in subjects with concomitant MCI and depression (Enache *et al.*, 2011), little is known about the underlying mechanisms.

We hypothesized that minor depressive symptoms, a sub-threshold depressive state not fulfilling formalized criteria for major depression, in SCI and MCI would correlate with typical AD-type changes in CSF and imaging parameters. On the contrary, our main finding was that depression correlated with less changes associated with neurodegeneration. An explanation for this, and in contrast to the above mentioned association between major depression and established AD, may be that minor depressive states are elusive and have no or only subtle impact on the neurodegenerative process. It seems that minor depressive symptoms can explain cognitive impairment in this group of patients attending a memory clinic.

Several challenges have been described using self-report scales for depression in the elderly (Yesavage *et al.*, 1982). A main explanation is probably that the symptomatic phenomenology may differ between depression in the young and in the elderly. Potential sources of error previously reported are among others a too strong focus on somatic symptoms which are common in the elderly for other reasons than depression, complex response formats which exclude the cognitively impaired and questions about the future. In addition there are several significant comorbidities in late life depression, including sleep disturbances, grief, frailty and drug interactions affecting symptomatology.

In the present study we used the short version of the Geriatric Depression Scale (GDS15), which is an established test for depression in the elderly living in different environments (Marc LG *et al.*, 2008) including patients with MCI (Debruyne *et al.*, 2009)(Marc LG *et al.*, 2008). Although adapted to elderly populations, it is not diagnostic and cannot replace clinical judgment and use of established criteria for depression, but rather help the clinician in deciding whether further comprehensive investigation is necessary.

In the original study by Scheik *et al.* (Sheikh JI and Yesavage JA, 1986), the GDS15 was found to have a rather high sensitivity (92 %) and specificity (89 %). In a later systematic review of 21 studies, cutoff values of 5/6 (six studies) or 6/7 (seven studies) and a diagnosis of major depression according to DSM-IV or ICD-10 were most often used as “gold standard”. Mean sensitivity (80.5 %) and specificity (75.0 %) were found to be considerably lower than in the original study (Wancata *et al.*, 2006).

Since no validation study of the Norwegian version of the GDS15 has been conducted, sensitivity and specificity are unknown, but probably comparable to the other European countries included in the review. The rather low specificity of the GDS15 increases the probability of including patients having symptoms not related to depression, which partly could explain the negative result in the present study. Specificity could have been raised by using a higher cutoff value, but the present level is well established for screening purposes. Similarly, a lower cutoff would increase sensitivity, but lower specificity. This was demonstrated in a study by Friedman *et al.* involving 960 functionally impaired, but cognitively intact community-dwelling primary care elderly. It was shown that sensitivity increased from 81 % to 89 % using 5/6 as cutoff compared to 6/7. Similarly, specificity varied from 75 % with a cutoff of 6/7 to 65 % with a cutoff of 5/6 (Friedman *et al.*, 2005).

In the present study, patients were screened for depression using the GDS15 followed by a clinical examination to see if diagnostic criteria for major depression according to ICD-10 were fulfilled. The latter patients were excluded, but some misdiagnosis (i.e. inclusion of presumed minor depression when in fact major depression) contaminating the analyses cannot be excluded.

Minor depression is common in the elderly with prevalence numbers in the 0-18 % range (Polyakova *et al.*, 2014). Several of the included studies have only used one single diagnostic instrument and a single clinical examination which could explain the wide variety in prevalence rates.

Risk factors for minor depression are similar to those in major depression (see section 5.3), except that data on age and gender are inconclusive (Polyakova *et al.*, 2014). There is also evidence that patients with minor depression are at increased risk of developing major depression (MDD), substance abuse and even suicidal behavior (Polyakova *et al.*, 2014), complications that suggest that this “minor” condition also deserves attention. However, studies on the co-existence of minor depression and MCI are rare, as depressive patients most often are excluded from MCI studies and vice versa. Available studies suggest that almost half of MCI patients in hospital-based settings exhibit depressive symptoms, but prevalence rates vary due to methodological differences (Panza *et al.*, 2010). Studies on comorbid MCI and minor depression are rare, and only two studies were found using established criteria. Gabryelewicz *et al.* (hospital-based) and Kumar *et al.* (community-based) found prevalence rates for comorbid minor depression and MCI of 26.5 % and 17.2 % respectively (Gabryelewicz *et al.*, 2004; Kumar *et al.*, 2006). In the hospital-based sample about 46 % of MCI patients had minor and major depression combined which is comparable to our findings of 40 % minor depression in SCI and MCI (and exclusion of major depression). Of note, we only used the GDS15 as

screening instrument and conducted only one clinical examination which could have resulted in a lower estimate of prevalence. Another weakness in our study is the fact that ICD-10 does not contain a diagnostic category for minor depression in contrast to DSM-IV.

Inclusion of patients with major depression in this study might have shown more pronounced changes, but was an exclusion criterion since core criteria for MCI dictates ruling out comorbidities including depressive, vascular, traumatic, neurologic or medical comorbidities that could imitate cognitive impairment (Albert *et al.*, 2011). As mentioned in section 1.3, MCI has an annual dementia conversion rate of about 10-15 % (Petersen *et al.*, 2009), but it may not harbor early signs of neurodegeneration, and the concept of SCI is even more heterogeneous with annual conversion rates in the 6-7 % range (Reisberg and Gauthier, 2008). Since international consensus criteria for SCI until recently have been lacking (see below), similar exclusion criteria as for MCI were used.

Recently Jessen *et al.* proposed multiple points that should be described in studies on SCI patients in order to select patients with increased risk of dementia and to facilitate multi-center comparisons (Jessen *et al.*, 2014). Risk factors raising the likelihood of a pre-clinical AD state in SCI are among others onset of SCI the last 5 years, affection of memory, concerns (worries) associated with SCI, age at onset > 60 years, confirmation of cognitive decline by an informant in addition to APOE genotype and biomarker evidence for AD. Our SCI patients fulfilled the first three points and the average age was 60 years, but other biomarkers typically seen in AD were only randomly present. The SCI inclusion criteria used in this paper would thus probably lower the probability that the SCI patients represent pre-dementia states compared to the proposed criteria.

Similarly, one can argue that the 40 year age cut is too low and that it is unlikely that 40-50 year olds have SCI (or MCI) due to AD or other dementias. This is an additional source of insignificant findings in this paper. On the other hand, all MCI classifications were based on established criteria, and despite sub-optimal sensitivity and specificity in predicting dementia, it is at present a pertinent approach for defining at risk populations.

Pooling SCI and MCI patients together can be seen as a limitation in this study as the two conditions constitute different likelihoods of a future conversion to dementia and often reflect different etiologies. On the other hand, both conditions are dementia risk states and finding relevant associations to biomarker pathology as soon as possible is a priority. Since SCI can be seen as a pre-MCI state, AD biomarker pathology in the combined group, or even in an isolated SCI group, would be an important finding and worth examining. Analyzing SCI and MCI separately did not, however, reveal any significant correlations, but the number of patients included in these analyses was limited. Of note (and as mentioned in section 8.3), the MMSE is less sensitive in the differentiation between MCI and mild dementia than between normal cognition and moderate/severe dementia. A more thorough examination with a battery of neuropsychological test would better discriminate between dementia and risk groups such as SCI and MCI. However, since the demarcation between SCI, MCI and dementia is not sharp it makes pooling of SCI and MCI relevant, but the number of patients included should ideally be higher in order to increase the probability of significant findings.

In an effort to increase the likelihood that the underlying disease (in SCI and MCI) indeed reflect a neurodegenerative disorder, we included a subgroup with concomitant depression and pathological CSF biomarkers, but also in this cohort depressed had less pathology. Secondary

depression due to psychosocial stress (not necessarily related to neurodegeneration) may also be a plausible explanation for our findings.

One major obstacle in finding underlying pathology in concomitant depression and cognitive impairment is the present classification of depression and especially the classification of depression in dementia. This is not unexpected since both disorders are heterogeneous in nature. Although there has been progress in the development of biomarkers in dementia, including CSF and imaging parameters, very few biomarkers can be used in a clinical setting, and with regard to depressive states even less is available. Thus, despite progress in developing biomarkers in dementia and depression, the diagnostic precision is still low, and biomarkers are at present mostly reserved for research purposes. In addition, depression has different, age-dependent clinical phenotypes not reflected in the current criteria. Late life depression (LLD) is characterized by sub-syndromal symptoms and atypical presentation such as vegetative signs (including weight loss and anorexia, insomnia, inattention and fatigue), somatization and cognitive impairment, which can lead to underreporting of depression in the elderly (Alexopoulos, 2005). Focusing on cognitive impairment, an unresolved question is whether these atypical symptoms in LLD constitute a different type of depression with another etiology than in younger people. If that is the case, the atypical and sub-syndromal presentation in a (large) subgroup of elderly depressed could possibly be secondary to neurodegeneration and have other underlying mechanisms than “classic” symptomatology. Indeed, the concept of apathy in this regard is relevant as there are overlapping presentation in depressive states and dementia. Apathy can be defined as a state of indifference, or the suppression of emotions such as concern, excitement, motivation and/or passion and is the most prevalent neuropsychiatric syndrome in dementia affecting 19-76 % of patients (Tagariello *et al.*, 2009). Furthermore, evidence suggests that apathy increases the risk of dementia in MCI (Robert *et al.*, 2006). Could it be that atypical presentation and sub-threshold depression in the elderly are mistakenly interpreted as somatic complications or even “normal” aging, and that some of these symptoms (i.e. apathy and/or depression) in reality reflect prodromes and neuropsychiatric symptoms of neurodegeneration? Developing diagnostic consensus criteria that encompass both “traditional” depression, depression in the elderly, atypical presentation including apathy and criteria for depression in dementia are thus needed. At present, provisional diagnostic criteria for depression in AD and diagnostic criteria for apathy have been proposed, but are currently only used for research purposes (Olin *et al.*, 2002; Robert *et al.*, 2009).

To conclude, our results suggest that minor depression is common and the driving force responsible for the cognitive impairment in this SCI/MCI cohort and not caused by neurodegenerative changes. Despite the negative association between minor depression and imaging and CSF parameters, it is possible that the subgroup with pathologic CSF and depressive symptoms are at increased risk of a faster progression to dementia. One can speculate that minor depression in these cases represents a prodrome of dementia and as such an important symptom that may bring these patients earlier to the memory clinic. Follow-up studies are needed to determine the significance of these findings. Statistically, most of the cases of SCI and MCI converting to dementia will be cases of AD, but since MCI probably is a pre-dementia stage also in Lewy body disease, some will also convert to Lewy body dementia. This can shed light on depression as a potential biomarker also in non-AD cases.

8.5 Methodological issues and limitations

A cross-sectional approach was used in all 3 papers and thus conclusions regarding causality cannot be drawn. In paper 1, a retrospective technique was used which introduces a prevalence-incidence bias (Neyman bias) (Grimes and Schulz, 2002). Even if standardized questionnaires are used it is impossible to answer questions from the past with total accuracy. This fact will likely affect the results.

It is important to critically evaluate the sensitivity and specificity of the clinical criteria for DLB and AD. The 1996 consensus criteria for DLB (McKeith *et al.* 1996) had high specificity (80-100 %), but low sensitivity (20-60 %) and thus the 2005 criteria incorporated Dopamine transporter scan, RBD and neuroleptic sensitivity as suggestive features to improve sensitivity. Although no systematic evaluation of the new criteria has been conducted, the specificity using the new criteria is believed to be generally good when a diagnosis of probable DLB can be made. Similarly, the 1984 criteria for probable AD are reliable with more than a dozen clinical-pathological studies showing an average sensitivity of 81% and specificity of 70% (McKhann *et al.*, 2011). In paper 1, only probable DLB (2005 DLB criteria) and probable AD (1984 AD criteria) were included, and the high specificity was confirmed in the 36 cases at present submitted to autopsy (of 10 with a clinical diagnosis of DLB, 8 had pathological verification, and 11 of 13 with a clinical diagnosis of probable AD were confirmed at autopsy (T. Hortobágyi, personal communication)). In paper 2 all AD diagnoses were strengthened by CSF biomarkers. Furthermore, the PD diagnosis was determined according to established criteria (Gelb) and all patients had been followed in the clinic for some time and had a pathological Dopamine transporter scan ([¹²³I]FP-CIT SPECT) strengthening the diagnosis. With these procedures the diagnostic accuracy of PD is expected to be high, although some misdiagnosis may occur.

Selection bias may occur in referral based cohorts since it is likely that SCI and MCI patients recruited from a hospital based memory clinic are not completely representative of the general SCI and MCI population. For instance, there is a chance that patients and caregivers coming to the memory clinic are more resourceful (e.g. higher educated with more insight into disease processes and on average with better performance on cognitive tests) and that depressive and cognitive symptoms in this group are differently expressed compared to other social groups who may not seek medical assistance at an early stage. For instance, depression scores may be less than the average in the general population because of better coping strategies (including better socio-economic resources) or conversely more pronounced because they are usually highly functioning and may be more sensitive to change and the suffering caused by illness. What impact these matters may have had on the present results is difficult to conclude, but a potential limitation to be aware of. In addition, it is possible that MCI and also PD and dementia patients who are referred may differ clinically from similar groups in the general population, for example by being more atypical, having more co-morbidity or more personality disorders.

The heterogeneous nature of SCI and MCI has been discussed in more detail under section 8.4 and could explain why we could not find any associations between minor depression and AD-related pathology in these groups.

As mentioned (in section 1.8), an ideal biomarker should have sensitivity and specificity above 80 %. These criteria are currently not fulfilled by the biomarkers used in this thesis. For instance, DTI indices are thought to reflect axonal bundle microstructure, but their relationship to pathophysiology is debatable (Assaf, 2008). A continuous effort to improve biomarker sensitivity and specificity through technical innovation, replication of findings and autopsy-proven diagnosis is essential and may improve sensitivity and specificity and thereby their diagnostic accuracy.

Another issue worth mentioning is the relative small sample sizes employed in the current thesis. It has been claimed that many conclusions drawn from biomedical research are false due to small sample sizes (Button *et al.*, 2013;Ioannidis, 2005). The lower the statistical power of a study (due to either low sample size, small effect size or both), the lower the probability that significant findings are actually true. The obvious solution is ideally to participate in multicenter studies to raise the number of participants. Another issue is that true effect sizes are seldom (never) known in neuroscience. Metaanalyses, which can provide an optimal starting point for estimates of effect size, power calculations and study design are not always available in experimental research.

8.6 Conclusions and future directions for research

In this thesis we have found that DLB patients present with memory impairment and Visual hallucinations before parkinsonism. This is important as early memory problems not always indicate AD. Similar to AD and PD, DLB patients probably also have depressive symptoms prior to diagnosis. Furthermore, we found that white matter damage is an early event in PD without dementia and that DTI could potentially serve as a biomarker to differentiate between LBD and AD. Larger, confirmatory studies are however needed before DTI can serve as a reliable biomarker in clinical practice. Finally, we found that depressive symptoms are common in SCI and MCI patients seeking help at the memory clinic, but minor depression was not associated with AD-related pathology. Cognitive impairment in SCI and MCI could be related to depression, or depression could potentially signal early and subtle neurodegenerative changes motivating these patients for a prompt clinical investigation. Our findings are a reminder that depressive symptoms should always be considered when cognitive impairment and neurodegenerative disease is suspected.

The ultimate goal of all neurodegenerative research is to develop (curative) neuroprotective or disease-modifying therapies. Predicting future cognitive impairment in at risk populations as early as possible is an important research priority and finding valid biomarkers including clinical features, genetics, neuropathology, CSF and imaging parameters for better understanding of disease mechanisms with subsequent refinement of clinical diagnostic criteria and development of new treatment targets are important priorities. Given the complexity of the various disease manifestations in cognitive disorders, a multimodal approach is most likely to yield success.

The vast majority of biomarker studies (including neuroimaging) in LBD (and AD) are cross-sectional, small and focusing on established disease. In the future, larger, longitudinal studies focusing on known risk factors, including SCI/MCI, autonomic symptoms, RBD and visual hallucinations are needed. Similarly, to disentangle the role of depression, elderly patients with depressive disorders should be monitored with selected biomarkers (neuroimaging, markers of

cerebrovascular disease, genetics and immunology in addition to measuring depressive symptoms) and monitored to detect cognitive impairment. Furthermore, there is a need for a better understanding of the differences and similarities between late life depression, comorbid depression and dementia and the role of apathy in neurodegeneration. As most depressive patients will not develop dementia, a better characterization of the clinical and biological features which represent risk factors for dementia development is a key clinical challenge. Such knowledge can only be achieved by conducting longitudinal studies using careful, comprehensive and standardized clinical and biomarker measurements.

10.0 References

- Aarsland, D., K. Andersen, J. P. Larsen, A. Lolk, and P. Kragh-Sorensen, 2003, "Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study," *Arch. Neurol.* **60**, 387-392.
- Aarsland, D., K. Andersen, J. P. Larsen, R. Perry, T. Wentzel-Larsen, A. Lolk, and P. Kragh-Sorensen, 2004, "The rate of cognitive decline in Parkinson disease," *Arch. Neurol.* **61**, 1906-1911.
- Aarsland, D., K. Bronnack, J. P. Larsen, O. B. Tysnes, G. Alves, and Norwegian ParkWest study group, 2009a, "Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study," *Neurology* **72**, 1121-1126.
- Aarsland, D. *et al.*, 2010, "Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis," *Neurology* **75**, 1062-1069.
- Aarsland, D., M. Emre, A. Lees, W. Poewe, and C. Ballard, 2007a, "Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology* **68**, 80.
- Aarsland, D., J. T. Kvaloy, K. Andersen, J. P. Larsen, M. X. Tang, A. Lolk, P. Kragh-Sorensen, and K. Marder, 2007b, "The effect of age of onset of PD on risk of dementia," *J. Neurol.* **254**, 38-45.
- Aarsland, D., E. Londos, and C. Ballard, 2009b, "Parkinson's disease dementia and dementia with Lewy bodies: different aspects of one entity. [Review] [0 refs]," *Int. Psychogeriatr.* **21**, 216-219.
- Aarsland, D., L. Marsh, and A. Schrag, 2009c, "Neuropsychiatric symptoms in Parkinson's disease. [Review] [94 refs]," *Mov. Disord.* **24**, 2175-2186.
- Aarsland, D., G. Muniz, and F. Matthews, 2011a, "Nonlinear decline of mini-mental state examination in Parkinson's disease," *Mov. Disord.* **26**, 334-337.
- Aarsland, D., A. Rongve, T. Fladby, I. Testad, M. Kivipelto, and B. Winblad, 2011b, "[New diagnostic criteria for Alzheimer disease]. [Norwegian]," *Tidsskr. Nor. Laegeforen.* **131**, 2224-2225.
- Aarsland, D., A. Rongve, S. P. Nore, R. Skogseth, S. Skulstad, U. Ehrt, D. Hoprekstad, and C. Ballard, 2008, "Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria," *Dementia & Geriatric Cognitive Disorders* **26**, 445-452.
- Aarsland, D., J. Zaccai, and C. Brayne, 2005, "A systematic review of prevalence studies of dementia in Parkinson's disease. [Review] [59 refs]," *Mov. Disord.* **20**, 1255-1263.

- Albert, M. S. *et al.*, 2011, "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's & Dementia* **7**, 270-279.
- Alcalay, R. N. *et al.*, 2014, "Cognitive and motor function in long-duration PARKIN-associated Parkinson disease," *JAMA Neurology* **71**, 62-67.
- Alcalay, R. N. *et al.*, 2012, "Cognitive performance of GBA mutation carriers with early-onset PD: The CORE-PD study," *Neurology* **78**, 1434-1440.
- Alcalay, R. N. *et al.*, 2010, "Self-report of cognitive impairment and mini-mental state examination performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease," *Journal of Clinical & Experimental Neuropsychology: Official Journal of the International Neuropsychological Society* **32**, 775-779.
- Alexopoulos, G. S., 2005, "Depression in the elderly. [Review] [144 refs]," *Lancet* **365**, 1961-1970.
- Alves, G. *et al.*, 2010, "CSF amyloid-beta and tau proteins, and cognitive performance, in early and untreated Parkinson's disease: the Norwegian ParkWest study," *Journal of Neurology, Neurosurgery & Psychiatry* **81**, 1080-1086.
- Apostolova, L. G., R. A. Dutton, I. D. Dinov, K. M. Hayashi, A. W. Toga, J. L. Cummings, and P. M. Thompson, 2006, "Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps.[Erratum appears in Arch Neurol. 2007 Sep;64(9):1360-1]," *Arch. Neurol.* **63**, 693-699.
- Archibald, N. K., M. P. Clarke, U. P. Mosimann, and D. J. Burn, 2009, "The retina in Parkinson's disease. [Review] [226 refs]," *Brain* **132**, 5-45.
- Arean, P. A. and G. Niu, 2014, "Choosing treatment for depression in older adults and evaluating response. [Review]," *Clin. Geriatr. Med.* **30**, 535-551.
- Assaf, Y., 2008, "Can we use diffusion MRI as a bio-marker of neurodegenerative processes?," *Bioessays* **30**, 1235-1245.
- Assaf, Y. and O. Pasternak, 2008, "Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. [Review] [93 refs]," *J. Mol. Neurosci.* **34**, 51-61.
- Auer, S. and B. Reisberg, 1997, "The GDS/FAST staging system," *Int. Psychogeriatr.* **9**, Suppl-71.
- Auning E. *et al.*, 2012, "Parkinson's disease dementia and dementia with Lewy bodies – epidemiology, risk factors and biomarkers." *Norsk Epidemiologi* **22** (2) s. 233-242
- Aurora, R. N. *et al.*, 2010, "Best practice guide for the treatment of REM sleep behavior disorder (RBD).[Erratum appears in J Clin Sleep Med. 2010 Apr 15;6(2):table of contents]," *Journal of Clinical Sleep Medicine* **6**, 85-95.

- Baba, T. *et al.*, 2012, "Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study," *Brain* **135**, 1-9.
- Baldessarini, R. J., 1975, "The basis for amine hypotheses in affective disorders. A critical evaluation," *Arch. Gen. Psychiatry* **32**, 1087-1093.
- Baldwin, R. C., A. Gallagley, M. Gourlay, A. Jackson, and A. Burns, 2006, "Prognosis of late life depression: a three-year cohort study of outcome and potential predictors," *Int. J. Geriatr. Psychiatry* **21**, 57-63.
- Ballard, C., D. Aarsland, P. Francis, and A. Corbett, 2013, "Neuropsychiatric symptoms in patients with dementias associated with cortical Lewy bodies: pathophysiology, clinical features, and pharmacological management. [Review]," *Drugs & Aging* **30**, 603-611.
- Ballard, C., S. Gauthier, A. Corbett, C. Brayne, D. Aarsland, and E. Jones, 2011a, "Alzheimer's disease. [Review]," *Lancet* **377**, 1019-1031.
- Ballard, C., E. L. Jones, E. Londos, L. Minthon, P. Francis, and D. Aarsland, 2010, "alpha-Synuclein antibodies recognize a protein present at lower levels in the CSF of patients with dementia with Lewy bodies," *Int. Psychogeriatr.* **22**, 321-327.
- Ballard, C., Z. Kahn, and A. Corbett, 2011b, "Treatment of dementia with Lewy bodies and Parkinson's disease dementia. [Review]," *Drugs & Aging* **28**, 769-777.
- Ballard, C., I. McKeith, D. Burn, R. Harrison, J. O'brien, K. Lowery, M. Campbell, R. Perry, and P. Ince, 1997, "The UPDRS scale as a means of identifying extrapyramidal signs in patients suffering from dementia with Lewy bodies," *Acta Neurol. Scand.* **96**, 366-371.
- Ballard, C., M. Piggott, M. Johnson, N. Cairns, R. Perry, I. McKeith, E. Jaros, J. O'brien, C. Holmes, and E. Perry, 2000, "Delusions associated with elevated muscarinic binding in dementia with Lewy bodies," *Ann. Neurol.* **48**, 868-876.
- Banerjee, S. *et al.*, 2011, "Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. [Review]," *Lancet* **378**, 403-411.
- Barber, R., P. Scheltens, A. Gholkar, C. Ballard, I. McKeith, P. Ince, R. Perry, and J. O'brien, 1999, "White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging," *Journal of Neurology, Neurosurgery & Psychiatry* **67**, 66-72.
- Barnes, D. E. and K. Yaffe, 2011, "The projected effect of risk factor reduction on Alzheimer's disease prevalence. [Review]," *Lancet Neurology* **10**, 819-828.
- Basser, P. J. and D. K. Jones, 2002, "Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. [Review] [107 refs]," *NMR Biomed.* **15**, 456-467.
- Beach, T. G. *et al.*, 2009, "Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction," *Acta Neuropathol. (Berl)*. **117**, 613-634.

- Bekris, L. M., C. E. Yu, T. D. Bird, and D. W. Tsuang, 2010, "Genetics of Alzheimer disease. [Review]," *Journal of Geriatric Psychiatry & Neurology* **23**, 213-227.
- Benjamin, S. and D. C. Steffens, 2011, "Structural neuroimaging of geriatric depression. [Review]," *Psychiatr. Clin. North Am.* **34**, 423-435.
- Berg, D. *et al.*, 2014, "Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease," *Mov. Disord.* **29**, 454-462.
- Berg, L., 1988, "Clinical Dementia Rating (CDR)," *Psychopharmacol. Bull.* **24**, 637-639.
- Berge, G., S. B. Sando, A. Rongve, D. Aarsland, and L. R. White, 2014, "Apolipoprotein E 2 genotype delays onset of dementia with Lewy bodies in a Norwegian cohort," *Journal of Neurology, Neurosurgery & Psychiatry* **85**, 1227-1231.
- Beyer, M. K., D. Aarsland, O. J. Greve, and J. P. Larsen, 2006, "Visual rating of white matter hyperintensities in Parkinson's disease," *Mov. Disord.* **21**, 223-229.
- Beyer, M. K., C. C. Janvin, J. P. Larsen, and D. Aarsland, 2007, "A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry," *Journal of Neurology, Neurosurgery & Psychiatry* **78**, 254-259.
- Bibl, M., B. Mollenhauer, H. Esselmann, P. Lewczuk, C. Trenkwalder, P. Brechlin, E. Ruther, J. Kornhuber, M. Otto, and J. Wiltfang, 2006, "CSF diagnosis of Alzheimer's disease and dementia with Lewy bodies," *J. Neural Transm.* **113**, 1771-1778.
- Birks, J. and L. Flicker, 2006, "Donepezil for mild cognitive impairment. [Review] [18 refs]," *Cochrane Database of Systematic Reviews*. (3):CD006104, 2006. CD006104.
- Birks, J., E. J. Grimley, V. Iakovidou, M. Tsolaki, and F. E. Holt, 2009, "Rivastigmine for Alzheimer's disease. [Review] [105 refs][Update of Cochrane Database Syst Rev. 2000;(4):CD001191; PMID: 11034705]," *Cochrane Database of Systematic Reviews*. (2):CD001191, 2009. CD001191.
- Blazer, D. G., 2003, "Depression in late life: review and commentary. [Review] [295 refs]," *Journals of Gerontology Series A-Biological Sciences & Medical Sciences* **58**, 249-265.
- Blennow, K., 2004, "Cerebrospinal fluid protein biomarkers for Alzheimer's disease. [Review] [148 refs]," *NeuroRx* **1**, 213-225.
- Blennow, K. and H. Hampel, 2003, "CSF markers for incipient Alzheimer's disease. [Review] [89 refs]," *Lancet Neurology* **2**, 605-613.
- Blennow, K., H. Hampel, M. Weiner, and H. Zetterberg, 2010, "Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. [Review] [159 refs]," *Nature Reviews Neurology* **6**, 131-144.

- Bloudek, L. M., D. E. Spackman, M. Blankenburg, and S. D. Sullivan, 2011, "Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. [Review]," *Journal of Alzheimer's Disease* **26**, 627-645.
- Boecker, H., A. O. Ceballos-Baumann, D. Volk, B. Conrad, H. Forstl, and P. Haussermann, 2007, "Metabolic alterations in patients with Parkinson disease and visual hallucinations," *Arch. Neurol.* **64**, 984-988.
- Boeve, B. F. *et al.*, 2011, "Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort," *Sleep Medicine* **12**, 445-453.
- Bohnen, N. I., R. A. Koeppe, S. Minoshima, B. Giordani, R. L. Albin, K. A. Frey, and D. E. Kuhl, 2011, "Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study," *J. Nucl. Med.* **52**, 848-855.
- Bonanni, L., A. Thomas, P. Tiraboschi, B. Perfetti, S. Varanese, and M. Onofri, 2008, "EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up," *Brain* **131**, 3-705.
- Booij, J., T. G. Hemelaar, J. D. Speelman, B. K. de, A. G. Janssen, and E. A. van Royen, 1999, "One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [¹²³I]FPCIT SPECT," *J. Nucl. Med.* **40**, 753-761.
- Boot, B. P. *et al.*, 2012, "Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study," *Ann. Neurol.* **71**, 49-56.
- Boot, B. P. *et al.*, 2013, "Risk factors for dementia with Lewy bodies: a case-control study," *Neurology* **81**, 833-840.
- Bostrom, F., L. Jonsson, L. Minthon, and E. Londos, 2007a, "Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease," *Alzheimer Disease & Associated Disorders* **21**, 150-154.
- Bostrom, F., L. Jonsson, L. Minthon, and E. Londos, 2007b, "Patients with Lewy body dementia use more resources than those with Alzheimer's disease," *Int. J. Geriatr. Psychiatry* **22**, 713-719.
- Braak, H. and E. Braak, 1996, "Evolution of the neuropathology of Alzheimer's disease. [Review] [53 refs]," *Acta Neurol. Scand. Suppl.* **165**, 3-12.
- Braak, H., T. K. Del, U. Rub, R. A. de Vos, E. N. Jansen Steur, and E. Braak, 2003, "Staging of brain pathology related to sporadic Parkinson's disease," *Neurobiol. Aging* **24**, 197-211.
- Braak, H., U. Rub, E. N. Jansen Steur, T. K. Del, and R. A. de Vos, 2005, "Cognitive status correlates with neuropathologic stage in Parkinson disease," *Neurology* **64**, 1404-1410.
- Bras, J. *et al.*, 2014, "Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies," *Hum. Mol. Genet.* **23**, 6139-6146.

- Bronnick, K., G. Alves, D. Aarsland, O. B. Tysnes, and J. P. Larsen, 2011, "Verbal memory in drug-naive, newly diagnosed Parkinson's disease. The retrieval deficit hypothesis revisited," *Neuropsychology* **25**, 114-124.
- Brown, L. M. and J. A. Schinka, 2005, "Development and initial validation of a 15-item informant version of the Geriatric Depression Scale," *Int. J. Geriatr. Psychiatry* **20**, 911-918.
- Brunnstrom, H., O. Hansson, H. Zetterberg, E. Londos, and E. Englund, 2013, "Correlations of CSF tau and amyloid levels with Alzheimer pathology in neuropathologically verified dementia with Lewy bodies," *Int. J. Geriatr. Psychiatry* **28**, 738-744.
- Buchtemann, D., M. Lippa, A. Bramesfeld, and S. Riedel-Heller, 2012, "Incidence of late-life depression: a systematic review. [Review]," *J. Affect. Disord.* **142**, 172-179.
- Burton, E. J., I. G. McKeith, D. J. Burn, M. J. Firbank, and J. T. O'Brien, 2006, "Progression of white matter hyperintensities in Alzheimer disease, dementia with lewy bodies, and Parkinson disease dementia: a comparison with normal aging," *Am. J. Geriatr. Psychiatry* **14**, 842-849.
- Burton, E. J., I. G. McKeith, D. J. Burn, E. D. Williams, and J. T. O'Brien, 2004, "Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls," *Brain* **127**, 4-800.
- Butters, M. A. *et al.*, 2008, "Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B," *Alzheimer Disease & Associated Disorders* **22**, 261-268.
- Button, K. S., J. P. Ioannidis, C. Mokrysz, B. A. Nosek, J. Flint, E. S. Robinson, and M. R. Munafo, 2013, "Power failure: why small sample size undermines the reliability of neuroscience.[Erratum appears in *Nat Rev Neurosci.* 2013 Jun;14(6):451]," *Nature Reviews Neuroscience* **14**, 365-376.
- Byers, A. L. and K. Yaffe, 2011, "Depression and risk of developing dementia. [Review]," *Nature Reviews Neuroscience* **7**, 323-331.
- Carlsson, A., 2002, "Treatment of Parkinson's with L-DOPA. The early discovery phase, and a comment on current problems. [Review] [38 refs]," *J. Neural Transm.* **109**, 777-787.
- Castilla-Puentes, R. C. and M. E. Habeych, 2010, "Subtypes of depression among patients with Alzheimer's disease and other dementias," *Alzheimer's & Dementia* **6**, 63-69.
- Chartier-Harlin, M. C. *et al.*, 2004, "Alpha-synuclein locus duplication as a cause of familial Parkinson's disease," *Lancet* **364**, 1167-1169.
- Chen-Plotkin, A. S. *et al.*, 2011, "Plasma epidermal growth factor levels predict cognitive decline in Parkinson disease," *Ann. Neurol.* **69**, 655-663.
- Cheng, H. C., C. M. Ulane, and R. E. Burke, 2010, "Clinical progression in Parkinson disease and the neurobiology of axons," *Ann. Neurol.* **67**, 715-725.

- Chiba, Y., H. Fujishiro, E. Iseki, K. Ota, K. Kasanuki, Y. Hirayasu, and K. Satoa, 2012, "Retrospective survey of prodromal symptoms in dementia with Lewy bodies: comparison with Alzheimer's disease," *Dementia & Geriatric Cognitive Disorders* **33**, 273-281.
- Claassen, D. O., K. A. Josephs, J. E. Ahlskog, M. H. Silber, M. Tippmann-Peikert, and B. F. Boeve, 2010, "REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century," *Neurology* **75**, 494-499.
- Clerx, L., P. J. Visser, F. Verhey, and P. Aalten, 2012, "New MRI markers for Alzheimer's disease: a meta-analysis of diffusion tensor imaging and a comparison with medial temporal lobe measurements," *Journal of Alzheimer's Disease* **29**, 405-429.
- Cochrane, C. J. and K. P. Ebmeier, 2013, "Diffusion tensor imaging in parkinsonian syndromes: a systematic review and meta-analysis. [Review]," *Neurology* **80**, 857-864.
- Cole, M. G. and N. Dendukuri, 2003, "Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. [Review] [42 refs]," *Am. J. Psychiatry* **160**, 1147-1156.
- Collerton, D., E. Perry, and I. McKeith, 2005, "Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations," *Behavioral & Brain Sciences* **28**, 737-757.
- Compta, Y. *et al.*, 2013, "Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study.[Erratum appears in *Parkinsonism Relat Disord.* 2013 Nov;19(11):1071-2]," *Parkinsonism & Related Disorders* **19**, 717-724.
- Corder, E. H., A. M. Saunders, W. J. Strittmatter, D. E. Schmechel, P. C. Gaskell, G. W. Small, A. D. Roses, J. L. Haines, and M. A. Pericak-Vance, 1993, "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families," *Science* **261**, 921-923.
- Cuijpers, P., S. A. van, and F. Smit, 2006, "Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. [Review] [52 refs]," *Int. J. Geriatr. Psychiatry* **21**, 1139-1149.
- Cummings, J. L., M. Mega, K. Gray, S. Rosenberg-Thompson, D. A. Carusi, and J. Gornbein, 1994, "The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia," *Neurology* **44**, 2308-2314.
- Dalaker, T. O., J. P. Larsen, M. G. Dwyer, D. Aarsland, M. K. Beyer, G. Alves, K. Bronnick, O. B. Tysnes, and R. Zivadinov, 2009, "White matter hyperintensities do not impact cognitive function in patients with newly diagnosed Parkinson's disease," *Neuroimage* **47**, 2083-2089.
- de Lau, L. M. and M. M. Breteler, 2006, "Epidemiology of Parkinson's disease. [Review] [114 refs]," *Lancet Neurology* **5**, 525-535.

- de Lau, L. M., P. C. Giesbergen, M. C. de Rijk, A. Hofman, P. J. Koudstaal, and M. M. Breteler, 2004, "Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study," *Neurology* **63**, 1240-1244.
- Debette, S. and H. S. Markus, 2010, "The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. [Review] [87 refs]," *BMJ* **341**, c3666.
- Debruyne, H., B. M. Van, B. N. Le, M. Aries, K. Audenaert, P. P. De Deyn, and S. Engelborghs, 2009, "Is the geriatric depression scale a reliable screening tool for depressive symptoms in elderly patients with cognitive impairment?," *Int. J. Geriatr. Psychiatry* **24**, 556-562.
- Del, T. K., U. Rub, R. A. de Vos, J. R. Bohl, and H. Braak, 2002, "Where does parkinson disease pathology begin in the brain?," *Journal of Neuropathology & Experimental Neurology* **61**, 413-426.
- Delis et al., 2001. Delis and Kaplan executive functions system: examiner's manual. The Psychological Corporation.
- Desikan RS et al., 2015, "Genetic overlap between Alzheimer's disease and Parkinson's disease at the MAPT locus." *Mol Psychiatry*. Feb 17. doi:10.1038/mp.2015.6. [Epub ahead of print].
- Desikan RS et al., 2015, "Polygenic Overlap Between C-Reactive Protein, Plasma Lipids and Alzheimer's Disease." *Circulation*. 2015 Apr 10. [Epub ahead of print]
- Diederich, N. J., V. Pieri, and C. G. Goetz, 2003, "Coping strategies for visual hallucinations in Parkinson's disease," *Mov. Disord.* **18**, 831-832.
- Dobkin, R. D., M. Menza, L. A. Allen, M. A. Gara, M. H. Mark, J. Tiu, K. L. Bienfait, and J. Friedman, 2011, "Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial," *Am. J. Psychiatry* **168**, 1066-1074.
- Donaghy, P., A. J. Thomas, and J. T. O'Brien, 2015, "Amyloid PET Imaging in Lewy body disorders," *Am. J. Geriatr. Psychiatry* **23**, 23-37.
- Dorenlot, P., M. Harboun, V. Bige, J. C. Henrard, and J. Ankri, 2005, "Major depression as a risk factor for early institutionalization of dementia patients living in the community," *Int. J. Geriatr. Psychiatry* **20**, 471-478.
- Drzezga, A., T. Grimmer, M. Riemenschneider, N. Lautenschlager, H. Siebner, P. Alexopoulos, S. Minoshima, M. Schwaiger, and A. Kurz, 2005, "Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET," *J. Nucl. Med.* **46**, 1625-1632.
- Dubois, B. *et al.*, 2007a, "Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. [Review] [70 refs]," *Mov. Disord.* **22**, 2314-2324.

- Dubois, B. *et al.*, 2007b, "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. [Review] [143 refs]," *Lancet Neurology* **6**, 734-746.
- Duits, F. H. *et al.*, 2014, "The cerebrospinal fluid "Alzheimer profile": easily said, but what does it mean?," *Alzheimer's & Dementia* **10**, 713-723.
- Dujardin, K., L. Defebvre, A. Duhamel, P. Lecouffe, P. Rogelet, M. Steinling, and A. Destee, 2004, "Cognitive and SPECT characteristics predict progression of Parkinson's disease in newly diagnosed patients," *J. Neurol.* **251**, 1383-1392.
- Duncan, G. W., M. J. Firbank, J. T. O'Brien, and D. J. Burn, 2013, "Magnetic resonance imaging: a biomarker for cognitive impairment in Parkinson's disease?," [Review]," *Mov. Disord.* **28**, 425-438.
- Ebmeier, K., E. Rose, and D. Steele, 2006, "Cognitive impairment and fMRI in major depression. [Review] [48 refs]," *Neurotoxicity Research* **10**, 87-92.
- Edison, P. *et al.*, 2008, "Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography," *Journal of Neurology, Neurosurgery & Psychiatry* **79**, 1331-1338.
- Ellison, J. M., H. H. Kyomen, and D. G. Harper, 2012, "Depression in later life: an overview with treatment recommendations. [Review]," *Psychiatr. Clin. North Am.* **35**, 203-229.
- Emre, M. *et al.*, 2007, "Clinical diagnostic criteria for dementia associated with Parkinson's disease. [Review] [179 refs]," *Mov. Disord.* **22**, 1689-1707.
- Enache, D., B. Winblad, and D. Aarsland, 2011, "Depression in dementia: epidemiology, mechanisms, and treatment," *Current Opinion in Psychiatry* **24**, 461-472.
- Evans, J. R., S. L. Mason, C. H. Williams-Gray, T. Foltynie, C. Brayne, T. W. Robbins, and R. A. Barker, 2011, "The natural history of treated Parkinson's disease in an incident, community based cohort," *Journal of Neurology, Neurosurgery & Psychiatry* **82**, 1112-1118.
- Fahn S *et al.*, 1987, Florham Park, MacMillan Health Care Information, pp 153-163)
- Felger, J. C. and F. E. Lotrich, 2013, "Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. [Review]," *Neuroscience* **246**, 199-229.
- Ferman, T. J. and B. F. Boeve, 2007, "Dementia with Lewy bodies. [Review] [191 refs]," *Neurol. Clin.* **25**, 741-760.
- Ferman, T. J. *et al.*, 2011, "Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies," *Neurology* **77**, 875-882.
- Ferman, T. J. *et al.*, 2013, "Nonamnesic mild cognitive impairment progresses to dementia with Lewy bodies," *Neurology* **81**, 2032-2038.

- Ferrari, A. J., F. J. Charlson, R. E. Norman, S. B. Patten, G. Freedman, C. J. Murray, T. Vos, and H. A. Whiteford, 2013, "Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010," *PLoS Medicine / Public Library of Science* **10**, e1001547.
- Ferrer, I., I. Lopez-Gonzalez, M. Carmona, E. Dalfo, A. Pujol, and A. Martinez, 2012, "Neurochemistry and the non-motor aspects of PD. [Review]," *Neurobiol. Dis.* **46**, 508-526.
- Ferri, C. P. *et al.*, 2005, "Global prevalence of dementia: a Delphi consensus study," *Lancet* **366**, 2112-2117.
- Firbank, M. J., S. J. Colloby, D. J. Burn, I. G. McKeith, and J. T. O'Brien, 2003, "Regional cerebral blood flow in Parkinson's disease with and without dementia," *Neuroimage* **20**, 1309-1319.
- Fjell, A. M. *et al.*, 2008, "Morphometric changes in the episodic memory network and tau pathologic features correlate with memory performance in patients with mild cognitive impairment," *Ajnr: American Journal of Neuroradiology* **29**, 1183-1189.
- Foland-Ross, L. C., M. G. Hardin, and I. H. Gotlib, 2013, "Neurobiological markers of familial risk for depression. [Review]," *Current Topics in Behavioral Neurosciences* **14**, 181-206.
- Folstein, M. F., S. E. Folstein, and P. R. McHugh, 1975, "'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician," *J. Psychiatr. Res.* **12**, 189-198.
- Friedman, B., M. J. Heisel, and R. L. Delavan, 2005, "Psychometric properties of the 15-item geriatric depression scale in functionally impaired, cognitively intact, community-dwelling elderly primary care patients," *J. Am. Geriatr. Soc.* **53**, 1570-1576.
- Fritze, F., U. Ehrt, H. Sonnesyn, M. Kurz, T. Hortobagyi, S. P. Nore, C. Ballard, and D. Aarsland, 2011, "Depression in mild dementia: associations with diagnosis, APOE genotype and clinical features," *Int. J. Geriatr. Psychiatry* **26**, 1054-1061.
- Gabryelewicz, T., M. Styczynska, A. Pfeffer, B. Wasiak, A. Barczak, E. Luczywek, W. Androsiuk, and M. Barcikowska, 2004, "Prevalence of major and minor depression in elderly persons with mild cognitive impairment--MADRS factor analysis," *Int. J. Geriatr. Psychiatry* **19**, 1168-1172.
- Galpern, W. R. and A. E. Lang, 2006, "Interface between tauopathies and synucleinopathies: a tale of two proteins. [Review] [129 refs]," *Ann. Neurol.* **59**, 449-458.
- Garde, E., E. L. Mortensen, K. Krabbe, E. Rostrup, and H. B. Larsson, 2000, "Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study," *Lancet* **356**, 628-634.

- Gascon-Bayarri, J. *et al.*, 2007, "Prevalence of dementia subtypes in El Prat de Llobregat, Catalonia, Spain: the PRATICON study," *Neuroepidemiology* **28**, 224-234.
- Gauthier, S., J. Cummings, C. Ballard, H. Brodaty, G. Grossberg, P. Robert, and C. Lyketsos, 2010, "Management of behavioral problems in Alzheimer's disease. [Review] [221 refs]," *Int. Psychogeriatr.* **22**, 346-372.
- Gelb, D. J., E. Oliver, and S. Gilman, 1999, "Diagnostic criteria for Parkinson disease. [Review] [71 refs]," *Arch. Neurol.* **56**, 33-39.
- Genin, E. *et al.*, 2011, "APOE and Alzheimer disease: a major gene with semi-dominant inheritance," *Mol. Psychiatry* **16**, 903-907.
- Gill, D. and S. Hatcher, 2000, "WITHDRAWN: Antidepressants for depression in medical illness. [Review] [148 refs][Update of Cochrane Database Syst Rev. 2000;(4):CD001312; PMID: 11034712]," *Cochrane Database of Systematic Reviews.* (4):CD001312, 2000. CD001312.
- Goate, A., M. C. Chartier-Harlin, M. Mullan, J. Brown, F. Crawford, L. Fidani, L. Giuffra, A. Haynes, N. Irving, and L. James, 1991, "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," *Nature* **349**, 704-706.
- Goris, A. *et al.*, 2007, "Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease," *Ann. Neurol.* **62**, 145-153.
- Gothe, F., D. Enache, L. O. Wahlund, B. Winblad, M. Crisby, J. Lökk, and D. Aarsland, 2012, "Cerebrovascular diseases and depression: epidemiology, mechanisms and treatment. [Review]," *Panminerva Med.* **54**, 161-170.
- Greenwald, B. S., E. Kramer-Ginsberg, K. R. Krishnan, M. Ashtari, C. Auerbach, and M. Patel, 1998, "Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression," *Stroke* **29**, 613-617.
- Grimes, D. A. and K. F. Schulz, 2002, "Bias and causal associations in observational research," *Lancet* **359**, 248-252.
- Guo, J. L. *et al.*, 2013, "Distinct alpha-synuclein strains differentially promote tau inclusions in neurons," *Cell* **154**, 103-117.
- Halliday, G. M., J. L. Holton, T. Revesz, and D. W. Dickson, 2011a, "Neuropathology underlying clinical variability in patients with synucleinopathies. [Review]," *Acta Neuropathol. (Berl.)* **122**, 187-204.
- Halliday, G. M. and H. McCann, 2010, "The progression of pathology in Parkinson's disease. [Review] [61 refs]," *Ann. N. Y. Acad. Sci.* **1184**, 188-195.
- Halliday, G. M., Y. J. Song, and A. J. Harding, 2011b, "Striatal beta-amyloid in dementia with Lewy bodies but not Parkinson's disease," *J. Neural Transm.* **118**, 713-719.

- Hamilton, R. L., 2000, "Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry," *Brain Pathol.* **10**, 378-384.
- Hampel, H. *et al.*, 2014, "Perspective on future role of biological markers in clinical therapy trials of Alzheimer's disease: a long-range point of view beyond 2020. [Review]," *Biochem. Pharmacol.* **88**, 426-449.
- Hanson, J. C. and C. F. Lippa, 2009, "Lewy body dementia. [Review] [45 refs]," *Int. Rev. Neurobiol.* **84**, 215-228.
- Hansson, O., H. Zetterberg, P. Buchhave, E. Londos, K. Blennow, and L. Minthon, 2006, "Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study.[Erratum appears in *Lancet Neurol.* 2006 Apr;5(4):293]," *Lancet Neurology* **5**, 228-234.
- Harding, A. J., G. A. Broe, and G. M. Halliday, 2002, "Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe," *Brain* **125**, 2-403.
- Hattori, T., S. Orimo, S. Aoki, K. Ito, O. Abe, A. Amano, R. Sato, K. Sakai, and H. Mizusawa, 2012, "Cognitive status correlates with white matter alteration in Parkinson's disease," *Hum. Brain Mapp.* **33**, 727-739.
- Hausner, L., M. Damian, A. Sartorius, and L. Frolich, 2011, "Efficacy and cognitive side effects of electroconvulsive therapy (ECT) in depressed elderly inpatients with coexisting mild cognitive impairment or dementia," *J. Clin. Psychiatry* **72**, 91-97.
- Hebert, L. E., P. A. Scherr, L. A. Beckett, M. S. Albert, D. M. Pilgrim, M. J. Chown, H. H. Funkenstein, and D. A. Evans, 1995, "Age-specific incidence of Alzheimer's disease in a community population," *JAMA* **273**, 1354-1359.
- Hegeman, J. M., R. M. Kok, R. C. van der Mast, and E. J. Giltay, 2012, "Phenomenology of depression in older compared with younger adults: meta-analysis. [Review]," *Br. J. Psychiatry* **200**, 275-281.
- Heikkinen, R. L. and M. Kauppinen, 2004, "Depressive symptoms in late life: a 10-year follow-up," *Archives of Gerontology & Geriatrics* **38**, 239-250.
- Hely, M. A., W. G. Reid, M. A. Adena, G. M. Halliday, and J. G. Morris, 2008, "The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years," *Mov. Disord.* **23**, 837-844.
- Herholz, K., 2011, "Perfusion SPECT and FDG-PET. [Review]," *Int. Psychogeriatr.* **23**, Suppl-31.
- Herholz, K. *et al.*, 2002, "Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET," *Neuroimage* **17**, 302-316.
- Heun, R., A. Papassotiropoulos, and U. Ptok, 2000, "Subthreshold depressive and anxiety disorders in the elderly," *European Psychiatry: the Journal of the Association of European Psychiatrists* **15**, 173-182.

- Hjort, P. F. and H. T. Waaler, 2010, "[Dementia towards 2050]. [Norwegian]," *Tidsskr. Nor. Laegeforen.* **130**, 1356-1358.
- Hoogland, J., R. M. de Bie, C. H. Williams-Gray, D. Muslimovic, B. Schmand, and B. Post, 2010, "Catechol-O-methyltransferase val158met and cognitive function in Parkinson's disease," *Mov. Disord.* **25**, 2550-2554.
- Hoops, S., S. Nazem, A. D. Siderowf, J. E. Duda, S. X. Xie, M. B. Stern, and D. Weintraub, 2009, "Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease," *Neurology* **73**, 1738-1745.
- Huang, C., P. Mattis, K. Perrine, N. Brown, V. Dhawan, and D. Eidelberg, 2008, "Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease," *Neurology* **70**, t-7.
- Hughes, A. J., S. E. Daniel, L. Kilford, and A. J. Lees, 1992, "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases," *Journal of Neurology, Neurosurgery & Psychiatry* **55**, 181-184.
- Ioannidis, J. P., 2005, "Why most published research findings are false," *PLoS Medicine / Public Library of Science* **2**, e124.
- Irwin, D. J., V. M. Lee, and J. Q. Trojanowski, 2013, "Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. [Review]," *Nature Reviews Neuroscience* **14**, 626-636.
- Irwin, D. J. *et al.*, 2012, "Neuropathologic substrates of Parkinson disease dementia," *Ann. Neurol.* **72**, 587-598.
- Iseki, E., 2004, "Dementia with Lewy bodies: reclassification of pathological subtypes and boundary with Parkinson's disease or Alzheimer's disease," *Neuropathology* **24**, 72-78.
- Jack, C. R., Jr. *et al.*, 2013, "Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers," *Lancet Neurology* **12**, 207-216.
- Jack, C. R., Jr., D. S. Knopman, W. J. Jagust, L. M. Shaw, P. S. Aisen, M. W. Weiner, R. C. Petersen, and J. Q. Trojanowski, 2010a, "Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade," *Lancet Neurology* **9**, 119-128.
- Jack, C. R., Jr. *et al.*, 2010b, "Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease," *Brain* **133**, 3336-3348.
- Janssen, J. C., J. A. Beck, T. A. Campbell, A. Dickinson, N. C. Fox, R. J. Harvey, H. Houlden, M. N. Rossor, and J. Collinge, 2003, "Early onset familial Alzheimer's disease: Mutation frequency in 31 families," *Neurology* **60**, 235-239.
- Janvin, C. C., J. P. Larsen, D. Aarsland, and K. Hugdahl, 2006, "Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia," *Mov. Disord.* **21**, 1343-1349.

- Jessen, F. *et al.*, 2014, "A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease," *Alzheimer's & Dementia* **10**, 844-852.
- Jicha, G. A., F. A. Schmitt, E. Abner, P. T. Nelson, G. E. Cooper, C. D. Smith, and W. R. Markesbery, 2010, "Prodromal clinical manifestations of neuropathologically confirmed Lewy body disease," *Neurobiol. Aging* **31**, 1805-1813.
- Johansen, K. K., L. R. White, S. B. Sando, and J. O. Aasly, 2010, "Biomarkers: Parkinson disease with dementia and dementia with Lewy bodies. [Review] [151 refs]," *Parkinsonism & Related Disorders* **16**, 307-315.
- Johnson, D. K. and J. E. Galvin, 2011, "Longitudinal changes in cognition in Parkinson's disease with and without dementia," *Dementia & Geriatric Cognitive Disorders* **31**, 98-108.
- Jokinen, P., N. Scheinin, S. Aalto, K. Nagren, N. Savisto, R. Parkkola, J. Rokka, M. Haaparanta, M. Roytta, and J. O. Rinne, 2010, "[¹¹C]PIB-, [¹⁸F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia," *Parkinsonism & Related Disorders* **16**, 666-670.
- Jones, D. K., T. R. Knosche, and R. Turner, 2013, "White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI," *Neuroimage* **73**, 239-254.
- Kadir, A., O. Almkvist, A. Forsberg, A. Wall, H. Engler, B. Langstrom, and A. Nordberg, 2012, "Dynamic changes in PET amyloid and FDG imaging at different stages of Alzheimer's disease," *Neurobiol. Aging* **33**, 198-14.
- Kamagata, K., Y. Motoi, O. Abe, K. Shimoji, M. Hori, A. Nakanishi, T. Sano, R. Kuwatsuru, S. Aoki, and N. Hattori, 2012, "White matter alteration of the cingulum in Parkinson disease with and without dementia: evaluation by diffusion tensor tract-specific analysis," *Ajnr: American Journal of Neuroradiology* **33**, 890-895.
- Kanner, A. M., 2005, "Depression and the risk of neurological disorders," *Lancet* **366**, 1147-1148.
- Kantarci, K. *et al.*, 2012a, "Focal atrophy on MRI and neuropathologic classification of dementia with Lewy bodies.[Erratum appears in *Neurology*. 2012 Sep 4;79(10):1072 Note: Murray, Melissa M [corrected to Murray, Melissa E]]," *Neurology* **79**, 553-560.
- Kantarci, K. *et al.*, 2012b, "Multimodality imaging characteristics of dementia with Lewy bodies," *Neurobiol. Aging* **33**, 2091-2105.
- Karran, E., M. Mercken, and S. B. De, 2011, "The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. [Review]," *Nature Reviews. Drug Discovery* **10**, 698-712.
- Kehagia, A. A., R. A. Barker, and T. W. Robbins, 2013, "Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. [Review]," *Neurodegenerative Diseases* **11**, 79-92.

- Kemp, P. M. and C. Holmes, 2007, "Imaging in dementia with Lewy bodies: a review. [Review] [63 refs]," *Nucl. Med. Commun.* **28**, 511-519.
- Kempster, P. A., S. S. O'Sullivan, J. L. Holton, T. Revesz, and A. J. Lees, 2010, "Relationships between age and late progression of Parkinson's disease: a clinico-pathological study," *Brain* **133**, 6-62.
- Kenny, E. R., A. M. Blamire, M. J. Firbank, and J. T. O'Brien, 2012, "Functional connectivity in cortical regions in dementia with Lewy bodies and Alzheimer's disease," *Brain* **135**, 2-81.
- Kenny, E. R., E. J. Burton, and J. T. O'Brien, 2008, "A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia," *Dementia & Geriatric Cognitive Disorders* **26**, 218-225.
- Kiernan, R. J., J. Mueller, J. W. Langston, and D. C. Van, 1987, "The Neurobehavioral Cognitive Status Examination: a brief but quantitative approach to cognitive assessment," *Ann. Intern. Med.* **107**, 481-485.
- King, A. E., J. Mintz, and D. R. Royall, 2011, "Meta-analysis of 123I-MIBG cardiac scintigraphy for the diagnosis of Lewy body-related disorders," *Mov. Disord.* **26**, 1218-1224.
- Klassen, B. T., J. G. Hentz, H. A. Shill, E. Driver-Dunckley, V. G. Evidente, M. N. Sabbagh, C. H. Adler, and J. N. Caviness, 2011, "Quantitative EEG as a predictive biomarker for Parkinson disease dementia," *Neurology* **77**, 118-124.
- Klein, D. N., R. Kotov, and S. J. Bufferd, 2011, "Personality and depression: explanatory models and review of the evidence. [Review]," *Annual Review of Clinical Psychology* **7**, 269-295.
- Knapkog, A. B., M. L. Barca, and K. Engedal, 2014, "Prevalence of depression among memory clinic patients as measured by the Cornell Scale of Depression in Dementia," *Aging & Mental Health* **18**, 579-587.
- Knopman, D. S., S. T. Dekosky, J. L. Cummings, H. Chui, J. Corey-Bloom, N. Relkin, G. W. Small, B. Miller, and J. C. Stevens, 2001, "Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology* **56**, 1143-1153.
- Kok, R. M., W. A. Nolen, and T. J. Heeren, 2012, "Efficacy of treatment in older depressed patients: a systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. [Review]," *J. Affect. Disord.* **141**, 103-115.
- Kosaka, K., S. Oyanagi, M. Matsushita, and A. Hori, 1976, "Presenile dementia with Alzheimer-, Pick- and Lewy-body changes," *Acta Neuropathol. (Berl)*. **36**, 221-233.

- Kosaka, K., M. Yoshimura, K. Ikeda, and H. Budka, 1984, "Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease?," *Clin. Neuropathol.* **3**, 185-192.
- Kuehner, C., 2003, "Gender differences in unipolar depression: an update of epidemiological findings and possible explanations. [Review] [132 refs][Erratum appears in *Acta Psychiatr Scand.* 2003 Dec;108(6):406]," *Acta Psychiatr. Scand.* **108**, 163-174.
- Kumar, R., A. F. Jorm, R. A. Parslow, and P. S. Sachdev, 2006, "Depression in mild cognitive impairment in a community sample of individuals 60-64 years old," *Int. Psychogeriatr.* **18**, 471-480.
- Kurz, A., A. Thone-Otto, B. Cramer, S. Egert, L. Frolich, H. J. Gertz, V. Kehl, S. Wagenpfeil, and K. Werheid, 2012, "CORDIAL: cognitive rehabilitation and cognitive-behavioral treatment for early dementia in Alzheimer disease: a multicenter, randomized, controlled trial," *Alzheimer Disease & Associated Disorders* **26**, 246-253.
- Kurz, M. W., G. Dekomien, O. B. Nilsen, J. P. Larsen, D. Aarsland, and G. Alves, 2009, "APOE alleles in Parkinson disease and their relationship to cognitive decline: a population-based, longitudinal study," *Journal of Geriatric Psychiatry & Neurology* **22**, 166-170.
- Kurz, M. W., A. M. Schlitter, J. P. Larsen, C. Ballard, and D. Aarsland, 2006, "Familial occurrence of dementia and parkinsonism: a systematic review. [Review] [67 refs]," *Dementia & Geriatric Cognitive Disorders* **22**, 288-295.
- Lahlum, E. and K. W. Ruyter, 2012, "The establishment of ethical committees for medical research," *Tidsskr. Nor. Laegeforen.* **132**, 1486-1489.
- Lambert, J. C. *et al.*, 2013, "Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease," *Nat. Genet.* **45**, 1452-1458.
- Lane, R., Y. He, C. Morris, J. B. Leverenz, M. Emre, and C. Ballard, 2009, "BuChE-K and APOE epsilon4 allele frequencies in Lewy body dementias, and influence of genotype and hyperhomocysteinemia on cognitive decline," *Mov. Disord.* **24**, 392-400.
- Langa M, "Is the risk of Alzheimer's disease and dementia declining?" *Alzheimers Res Ther.* Mar 26;7(1):34. doi: 10.1186/s13195-015-0118-1. Epub ahead of print.
- Langston, J. W., 2006, "The Parkinson's complex: parkinsonism is just the tip of the iceberg. [Review] [25 refs]," *Ann. Neurol.* **59**, 591-596.
- Lavretsky, H. and A. Kumar, 2002, "Clinically significant non-major depression: old concepts, new insights. [Review] [123 refs]," *Am. J. Geriatr. Psychiatry* **10**, 239-255.
- Le, B. D., 2007, "The 'wet mind': water and functional neuroimaging. [Review] [196 refs]," *Physics in Medicine & Biology* **52**, R57-R90.
- Lebedev, A. V., M. K. Beyer, F. Fritze, E. Westman, C. Ballard, and D. Aarsland, 2014, "Cortical changes associated with depression and antidepressant use in Alzheimer and

- Lewy body dementia: an MRI surface-based morphometric study," *Am. J. Geriatr. Psychiatry* **22**, 4-13.
- Lebedev, A. V., E. Westman, M. K. Beyer, M. G. Kramberger, C. Aguilar, Z. Pirtosek, and D. Aarsland, 2013, "Multivariate classification of patients with Alzheimer's and dementia with Lewy bodies using high-dimensional cortical thickness measurements: an MRI surface-based morphometric study," *J. Neurol.* **260**, 1104-1115.
- Lebedeva, A., E. Westman, A. V. Lebedev, X. Li, B. Winblad, A. Simmons, L. O. Wahlund, D. Aarsland, and Alzheimer's Disease Neuroimaging Initiative, 2014, "Structural brain changes associated with depressive symptoms in the elderly with Alzheimer's disease," *Journal of Neurology, Neurosurgery & Psychiatry* **85**, 930-935.
- Lee, H. B. and C. G. Lyketsos, 2003, "Depression in Alzheimer's disease: heterogeneity and related issues. [Review] [107 refs]," *Biol. Psychiatry* **54**, 353-362.
- Lee, H. G., G. Casadesus, X. Zhu, A. Takeda, G. Perry, and M. A. Smith, 2004, "Challenging the amyloid cascade hypothesis: senile plaques and amyloid-beta as protective adaptations to Alzheimer disease. [Review] [25 refs]," *Ann. N. Y. Acad. Sci.* **1019**, 1-4.
- Lee, J. S., G. G. Potter, H. R. Wagner, K. A. Welsh-Bohmer, and D. C. Steffens, 2007, "Persistent mild cognitive impairment in geriatric depression," *Int. Psychogeriatr.* **19**, 125-135.
- Lee, R. S., D. F. Hermens, M. A. Porter, and M. A. Redoblado-Hodge, 2012, "A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. [Review]," *J. Affect. Disord.* **140**, 113-124.
- Lee, S. J., J. S. Kim, J. Y. Yoo, I. U. Song, B. S. Kim, S. L. Jung, D. W. Yang, Y. I. Kim, D. S. Jeong, and K. S. Lee, 2010, "Influence of white matter hyperintensities on the cognition of patients with Parkinson disease," *Alzheimer Disease & Associated Disorders* **24**, 227-233.
- Leentjens, A. F., M. Van den Akker, J. F. Metsemakers, R. Lousberg, and F. R. Verhey, 2003, "Higher incidence of depression preceding the onset of Parkinson's disease: a register study," *Mov. Disord.* **18**, 414-418.
- Levinson, D. F., 2006, "The genetics of depression: a review. [Review] [135 refs]," *Biol. Psychiatry* **60**, 84-92.
- Levy-Lahad, E., W. Wasco, P. Poorkaj, D. M. Romano, J. Oshima, W. H. Pettingell, C. E. Yu, P. D. Jondro, S. D. Schmidt, and K. Wang, 1995, "Candidate gene for the chromosome 1 familial Alzheimer's disease locus," *Science* **269**, 973-977.
- Lim, X., J. M. Yeo, A. Green, and S. Pal, 2013, "The diagnostic utility of cerebrospinal fluid alpha-synuclein analysis in dementia with Lewy bodies - a systematic review and meta-analysis. [Review]," *Parkinsonism & Related Disorders* **19**, 851-858.

- Lippa, C. F. *et al.*, 2007, "DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. [Review] [87 refs]," *Neurology* **68**, 812-819.
- Litvan, I. *et al.*, 2012, "Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. [Review]," *Mov. Disord.* **27**, 349-356.
- Lobotesis, K., J. D. Fenwick, A. Phipps, A. Ryman, A. Swann, C. Ballard, I. G. McKeith, and J. T. O'Brien, 2001, "Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD," *Neurology* **56**, 643-649.
- Londos, E., U. Passant, A. Brun, I. Rosen, J. Risberg, and L. Gustafson, 2003, "Regional cerebral blood flow and EEG in clinically diagnosed dementia with Lewy bodies and Alzheimer's disease," *Archives of Gerontology & Geriatrics* **36**, 231-245.
- Lopez, O. L., J. T. Becker, A. S. Wahed, J. Saxton, R. A. Sweet, D. A. Wolk, W. Klunk, and S. T. Dekosky, 2009, "Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease.[Erratum appears in *J Neurol Neurosurg Psychiatry*. 2009 Sep 1;80(9):1056]," *Journal of Neurology, Neurosurgery & Psychiatry* **80**, 600-607.
- Lopez-Pousa, S., J. Vilalta-Franch, J. Llinas-Regla, J. Garre-Olmo, and G. C. Roman, 2004, "Incidence of dementia in a rural community in Spain: the Girona cohort study," *Neuroepidemiology* **23**, 170-177.
- Lopresti, A. L., G. L. Maker, S. D. Hood, and P. D. Drummond, 2014, "A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers," *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **48**, 102-111.
- Loy, C. and L. Schneider, 2006, "Galantamine for Alzheimer's disease and mild cognitive impairment. [Review] [135 refs][Update of Cochrane Database Syst Rev. 2004;(4):CD001747; PMID: 15495017]," *Cochrane Database of Systematic Reviews*. (1):CD001747, 2006. CD001747.
- Loy, C. T., P. R. Schofield, A. M. Turner, and J. B. Kwok, 2014, "Genetics of dementia. [Review]," *Lancet* **383**, 828-840.
- Luk, K. C., V. Kehm, J. Carroll, B. Zhang, P. O'Brien, J. Q. Trojanowski, and V. M. Lee, 2012, "Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice," *Science* **338**, 949-953.
- Luppa, M., C. Sikorski, T. Luck, L. Ehreke, A. Konnopka, B. Wiese, S. Weyerer, H. H. König, and S. G. Riedel-Heller, 2012, "Age- and gender-specific prevalence of depression in latest-life--systematic review and meta-analysis. [Review]," *J. Affect. Disord.* **136**, 212-221.
- Lyketsos, C. G. and J. Olin, 2002, "Depression in Alzheimer's disease: overview and treatment. [Review] [68 refs]," *Biol. Psychiatry* **52**, 243-252.

- Lyoo, C. H., Y. H. Ryu, and M. S. Lee, 2010, "Topographical distribution of cerebral cortical thinning in patients with mild Parkinson's disease without dementia," *Mov. Disord.* **25**, 496-499.
- MacFall, J. R., M. E. Payne, J. E. Provenzale, and K. R. Krishnan, 2001, "Medial orbital frontal lesions in late-onset depression," *Biol. Psychiatry* **49**, 803-806.
- Mak, E., L. Su, G. B. Williams, and J. T. O'Brien, 2014, "Neuroimaging characteristics of dementia with Lewy bodies. [Review]," *Alzheimer's Research & Therapy* **6**, 18.
- Malek, N., D. Swallow, K. A. Grosset, O. Anichtchik, M. Spillantini, and D. G. Grosset, 2014, "Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson's disease - a systematic review," *Acta Neurol. Scand.* **130**, 59-72.
- Marc, L. G., P. J. Raue, and M. L. Bruce, 2008, "Screening performance of the 15-item geriatric depression scale in a diverse elderly home care population," *Am. J. Geriatr. Psychiatry* **16**, 914-921.
- Martin, E. I., K. J. Ressler, E. Binder, and C. B. Nemeroff, 2009, "The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. [Review] [142 refs]," *Psychiatr. Clin. North Am.* **32**, 549-575.
- Matsunaga, S., T. Kishi, and N. Iwata, 2015, "Memantine for Lewy body disorders: systematic review and meta-analysis," *Am. J. Geriatr. Psychiatry* **23**, 373-383.
- Mattsson, N. *et al.*, 2009, "CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment," *JAMA* **302**, 385-393.
- Mayeux, R., 2004, "Biomarkers: potential uses and limitations. [Review] [16 refs]," *NeuroRx* **1**, 182-188.
- Mayeux, R. and Y. Stern, 2012, "Epidemiology of Alzheimer disease. [Review]," *Cold Spring Harbor Perspectives in Medicine*: **2**, 2012.
- McKeith, I., 2007, "Dementia with Lewy bodies and Parkinson's disease with dementia: where two worlds collide. [Review] [20 refs]," *Practical Neurology* **7**, 374-382.
- McKeith, I., S. T. Del, P. Spano, M. Emre, K. Wesnes, R. Anand, A. Cicin-Sain, R. Ferrara, and R. Spiegel, 2000, "Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study," *Lancet* **356**, 2031-2036.
- McKeith, I. *et al.*, 2007, "Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study," *Lancet Neurology* **6**, 305-313.
- McKeith, I. G. *et al.*, 2005, "Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.," *Neurology* **65**, 1863-1872.

- McKeith, I. G. *et al.*, 1996, "Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. [Review] [49 refs]," *Neurology* **47**, 1113-1124.
- McKeith, I. G., K. A. Wesnes, E. Perry, and R. Ferrara, 2004, "Hallucinations predict attentional improvements with rivastigmine in dementia with lewy bodies," *Dementia & Geriatric Cognitive Disorders* **18**, 94-100.
- McKhann, G., D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, 1984, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," *Neurology* **34**, 939-944.
- McKhann, G. M. *et al.*, 2011, "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's & Dementia* **7**, 263-269.
- McKinnon, M. C., K. Yucel, A. Nazarov, and G. M. MacQueen, 2009, "A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. [Review] [68 refs]," *Journal of Psychiatry & Neuroscience* **34**, 41-54.
- McShane, R., S. A. Areosa, and N. Minakaran, 2006, "Memantine for dementia. [Review] [79 refs][Update of Cochrane Database Syst Rev. 2005;(3):CD003154; PMID: 16034889]," *Cochrane Database of Systematic Reviews*. (2):CD003154, 2006. CD003154.
- Medina, D., L. DeToledo-Morrell, F. Urresta, J. D. Gabrieli, M. Moseley, D. Fleischman, D. A. Bennett, S. Leurgans, D. A. Turner, and G. T. Stebbins, 2006, "White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study," *Neurobiol. Aging* **27**, 663-672.
- Meeus, B. *et al.*, 2012, "DLB and PDD: a role for mutations in dementia and Parkinson disease genes?," *Neurobiol. Aging* **33**, 629.
- Melzer, T. R., R. Watts, M. R. MacAskill, T. L. Pitcher, L. Livingston, R. J. Keenan, J. C. Dalrymple-Alford, and T. J. Anderson, 2013, "White matter microstructure deteriorates across cognitive stages in Parkinson disease," *Neurology* **80**, 1841-1849.
- Meppelink, A. M., B. M. de Jong, R. Renken, K. L. Leenders, F. W. Cornelissen, and L. T. van, 2009, "Impaired visual processing preceding image recognition in Parkinson's disease patients with visual hallucinations," *Brain* **132**, 11-93.
- Meyers and Meyers. Rey complex figure test and recognition trail. Psychological Assessment Resources, 1995
- Micanovic, C. and S. Pal, 2014, "The diagnostic utility of EEG in early-onset dementia: a systematic review of the literature with narrative analysis. [Review]," *J. Neural Transm.* **121**, 59-69.

- Miech, R. A., J. C. Breitner, P. P. Zandi, A. S. Khachaturian, J. C. Anthony, and L. Mayer, 2002, "Incidence of AD may decline in the early 90s for men, later for women: The Cache County study," *Neurology* **58**, 209-218.
- Minoshima, S., B. Giordani, S. Berent, K. A. Frey, N. L. Foster, and D. E. Kuhl, 1997, "Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease," *Ann. Neurol.* **42**, 85-94.
- Mitchell, A. J., H. Beaumont, D. Ferguson, M. Yadegarfar, and B. Stubbs, 2014, "Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis," *Acta Psychiatr. Scand.* **130**, 439-451.
- Mitchell, A. J. and H. Subramaniam, 2005, "Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. [Review] [71 refs]," *Am. J. Psychiatry* **162**, 1588-1601.
- Mitty, E. and S. Flores, 2008, "Suicide in late life. [Review] [17 refs]," *Geriatr. Nur. (Lond.)* **29**, 160-165.
- Mohler, H., 2012, "The GABA system in anxiety and depression and its therapeutic potential. [Review]," *Neuropharmacology* **62**, 42-53.
- Molano, J. *et al.*, 2010, "Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study," *Brain* **133**, 2-56.
- Mollenhauer, B., J. J. Locascio, W. Schulz-Schaeffer, F. Sixel-Doring, C. Trenkwalder, and M. G. Schlossmacher, 2011, "alpha-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study.[Erratum appears in *Lancet Neurol.* 2011 Apr;10(4):297]," *Lancet Neurology* **10**, 230-240.
- Mollenhauer, B., C. Trenkwalder, A. N. von, M. Bibl, P. Steinacker, P. Brechlin, J. Schindehuetter, S. Poser, J. Wiltfang, and M. Otto, 2006, "Beta-amyloid 1-42 and tau-protein in cerebrospinal fluid of patients with Parkinson's disease dementia," *Dementia & Geriatric Cognitive Disorders* **22**, 200-208.
- Montine, T. J. *et al.*, 2010, "CSF Abeta(42) and tau in Parkinson's disease with cognitive impairment," *Mov. Disord.* **25**, 2682-2685.
- Montorio, I. and M. Izal, 1996, "The Geriatric Depression Scale: a review of its development and utility. [Review] [50 refs]," *Int. Psychogeriatr.* **8**, 103-112.
- Mori, E., M. Ikeda, K. Kosaka, and S. Donepezil-DLB, I, 2012, "Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial," *Ann. Neurol.* **72**, 41-52.
- Morris, J. C., 1997, "Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type," *Int. Psychogeriatr.* **9**, Suppl-6.
- Mosconi, L., M. Brys, L. Glodzik-Sobanska, S. S. De, H. Rusinek, and M. J. de Leon, 2007, "Early detection of Alzheimer's disease using neuroimaging. [Review] [93 refs]," *Exp. Gerontol.* **42**, 129-138.

- Mosimann, U. P., G. Mather, K. A. Wesnes, J. T. O'Brien, D. J. Burn, and I. G. McKeith, 2004, "Visual perception in Parkinson disease dementia and dementia with Lewy bodies," *Neurology* **63**, 2091-2096.
- Muller, U., P. Winter, and M. B. Graeber, 2013, "A presenilin 1 mutation in the first case of Alzheimer's disease," *Lancet Neurology* **12**, 129-130.
- Mungas, D. *et al.*, 2005, "Longitudinal volumetric MRI change and rate of cognitive decline," *Neurology* **65**, 565-571.
- Naismith, S. L., M. Pereira, J. M. Shine, and S. J. Lewis, 2011, "How well do caregivers detect mild cognitive change in Parkinson's disease?," *Mov. Disord.* **26**, 161-164.
- Nalls, M. A. *et al.*, 2013, "A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies," *JAMA Neurology* **70**, 727-735.
- Nelson, J. C. and D. P. Devanand, 2011, "A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. [Review]," *J. Am. Geriatr. Soc.* **59**, 577-585.
- Nelson, P. T., G. A. Jicha, R. J. Kryscio, E. L. Abner, F. A. Schmitt, G. Cooper, L. O. Xu, C. D. Smith, and W. R. Markesbery, 2010, "Low sensitivity in clinical diagnoses of dementia with Lewy bodies," *J. Neurol.* **257**, 359-366.
- Nemani, V. M., W. Lu, V. Berge, K. Nakamura, B. Onoa, M. K. Lee, F. A. Chaudhry, R. A. Nicoll, and R. H. Edwards, 2010, "Increased expression of alpha-synuclein reduces neurotransmitter release by inhibiting synaptic vesicle recluster after endocytosis," *Neuron* **65**, 66-79.
- Nervi, A. *et al.*, 2011, "Familial aggregation of dementia with Lewy bodies," *Arch. Neurol.* **68**, 90-93.
- Neumann, J. *et al.*, 2009, "Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease," *Brain* **132**, 7-94.
- Nilsson, F. M., L. V. Kessing, and T. G. Bolwig, 2001, "Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study," *Acta Psychiatr. Scand.* **104**, 380-386.
- Nobili, F. *et al.*, 2009, "Amnesic mild cognitive impairment in Parkinson's disease: a brain perfusion SPECT study," *Mov. Disord.* **24**, 414-421.
- Noe, E., K. Marder, K. L. Bell, D. M. Jacobs, J. J. Manly, and Y. Stern, 2004, "Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia," *Mov. Disord.* **19**, 60-67.
- Nombela, C. *et al.*, 2014, "Genetic impact on cognition and brain function in newly diagnosed Parkinson's disease: ICICLE-PD study," *Brain* **137**, 10-58.

- Nordlund, A., S. Rolstad, P. Hellstrom, M. Sjogren, S. Hansen, and A. Wallin, 2005, "The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition," *Journal of Neurology, Neurosurgery & Psychiatry* **76**, 1485-1490.
- Nuytemans, K., J. Theuns, M. Cruts, and B. C. Van, 2010, "Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. [Review] [313 refs]," *Hum. Mutat.* **31**, 763-780.
- O'Brien, J. T., 2014, "Clinical significance of white matter changes. [Review]," *Am. J. Geriatr. Psychiatry* **22**, 133-137.
- O'Brien, J. T. *et al.*, 2006, "White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: the LADIS study," *Am. J. Geriatr. Psychiatry* **14**, 834-841.
- O'Brien, J. T., I. G. McKeith, Z. Walker, K. Tatsch, J. Booij, J. Darcourt, M. Marquardt, C. Reiningger, and DLB Study Group, 2009, "Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies," *Br. J. Psychiatry* **194**, 34-39.
- Ohtake, H. *et al.*, 2004, "Beta-synuclein gene alterations in dementia with Lewy bodies," *Neurology* **63**, 805-811.
- Okazaki H, Lipkin LE, Aronson SM., 1961, Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadripareisis in flexion. *J Neuropathol Exp Neurol*, **20**:237-44
- Olanow, C. W. and P. Brundin, 2013, "Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder?. [Review]," *Mov. Disord.* **28**, 31-40.
- Olanow, C. W. and A. H. Schapira, 2013, "Therapeutic prospects for Parkinson disease. [Review]," *Ann. Neurol.* **74**, 337-347.
- Olin, J. T., I. R. Katz, B. S. Meyers, L. S. Schneider, and B. D. Lebowitz, 2002, "Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. [Review] [128 refs][Erratum appears in Am J Geriatr Psychiatry 2002 May-Jun;10(3):264]," *Am. J. Geriatr. Psychiatry* **10**, 129-141.
- Ownby, R. L., E. Crocco, A. Acevedo, V. John, and D. Loewenstein, 2006, "Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis," *Arch. Gen. Psychiatry* **63**, 530-538.
- Palsson, S., L. Larsson, E. Tengelin, M. Waern, S. Samuelsson, T. Hallstro, and I. Skoog, 2001, "The prevalence of depression in relation to cerebral atrophy and cognitive performance in 70- and 74-year-old women in Gothenburg. The Women's Health Study," *Psychol. Med.* **31**, 39-49.
- Panza, F. *et al.*, 2010, "Late-life depression, mild cognitive impairment, and dementia: possible continuum?. [Review] [83 refs]," *Am. J. Geriatr. Psychiatry* **18**, 98-116.

- Papakostas, G. I., T. Petersen, Y. Mahal, D. Mischoulon, A. A. Nierenberg, and M. Fava, 2004, "Quality of life assessments in major depressive disorder: a review of the literature. [Review] [64 refs]," *Gen. Hosp. Psychiatry* **26**, 13-17.
- Parkkinen, L., T. Kauppinen, T. Pirttila, J. M. Autere, and I. Alafuzoff, 2005, "Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia," *Ann. Neurol.* **57**, 82-91.
- Parkkinen, L., T. Pirttila, and I. Alafuzoff, 2008, "Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance," *Acta Neuropathol. (Berl)*. **115**, 399-407.
- Parnetti, L., P. Tiraboschi, A. Lanari, M. Peducci, C. Padiglioni, C. D'Amore, L. Pierguidi, N. Tambasco, A. Rossi, and P. Calabresi, 2008, "Cerebrospinal fluid biomarkers in Parkinson's disease with dementia and dementia with Lewy bodies," *Biol. Psychiatry* **64**, 850-855.
- Pedersen, K. F., J. P. Larsen, O. B. Tysnes, and G. Alves, 2013, "Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study," *JAMA Neurology* **70**, 580-586.
- Penninx, B. W., J. M. Guralnik, C. F. Mendes de Leon, M. Pahor, M. Visser, M. C. Corti, and R. B. Wallace, 1998, "Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age," *Am. J. Cardiol.* **81**, 988-994.
- Pereira, J. B. *et al.*, 2014a, "Influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs," *J. Intern. Med.* **275**, 317-330.
- Pereira, J. B., P. Svenningsson, D. Weintraub, K. Bronnick, A. Lebedev, E. Westman, and D. Aarsland, 2014b, "Initial cognitive decline is associated with cortical thinning in early Parkinson disease," *Neurology* **82**, 2017-2025.
- Perez, F., C. Helmer, J. F. Dartigues, S. Auriacombe, and F. Tison, 2010, "A 15-year population-based cohort study of the incidence of Parkinson's disease and dementia with Lewy bodies in an elderly French cohort," *Journal of Neurology, Neurosurgery & Psychiatry* **81**, 742-746.
- Perneckzy, R., A. Drzezga, H. Boecker, A. O. Ceballos-Baumann, O. Granert, H. Forstl, A. Kurz, and P. Haussermann, 2008, "Activities of daily living, cerebral glucose metabolism, and cognitive reserve in Lewy body and Parkinson's disease," *Dementia & Geriatric Cognitive Disorders* **26**, 475-481.
- Petersen, R. C., R. O. Roberts, D. S. Knopman, B. F. Boeve, Y. E. Geda, R. J. Ivnik, G. E. Smith, and C. R. Jack, Jr., 2009, "Mild cognitive impairment: ten years later. [Review] [63 refs]," *Arch. Neurol.* **66**, 1447-1455.
- Petersen, R. C., G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, 1999, "Mild cognitive impairment: clinical characterization and outcome.[Erratum appears in Arch Neurol 1999 Jun;56(6):760]," *Arch. Neurol.* **56**, 303-308.

- Pilar-Cuellar, F. *et al.*, 2013, "Neural plasticity and proliferation in the generation of antidepressant effects: hippocampal implication. [Review]," *Neural Plas.* **2013**, 537265.
- Polyakova, M., N. Sonnabend, C. Sander, R. Mergl, M. L. Schroeter, J. Schroeder, and P. Schonknecht, 2014, "Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review. [Review]," *J. Affect. Disord.* **152-154**, 28-38.
- Polymeropoulos, M. H. *et al.*, 1997, "Mutation in the alpha-synuclein gene identified in families with Parkinson's disease," *Science* **276**, 2045-2047.
- Postuma, R. B., D. Aarsland, P. Barone, D. J. Burn, C. H. Hawkes, W. Oertel, and T. Ziemssen, 2012, "Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. [Review]," *Mov. Disord.* **27**, 617-626.
- Postuma, R. B., J. F. Gagnon, A. Pelletier, and J. Montplaisir, 2013, "Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies," *Mov. Disord.* **28**, 597-604.
- Postuma, R. B., J. F. Gagnon, M. Vendette, M. L. Fantini, J. Massicotte-Marquez, and J. Montplaisir, 2009, "Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder," *Neurology* **72**, 1296-1300.
- Poulopoulos, M. *et al.*, 2012, "Clinical and pathological characteristics of LRRK2 G2019S patients with PD," *J. Mol. Neurosci.* **47**, 139-143.
- Prince, M., R. Bryce, E. Albanese, A. Wimo, W. Ribeiro, and C. P. Ferri, 2013, "The global prevalence of dementia: a systematic review and metaanalysis. [Review]," *Alzheimer's & Dementia* **9**, 63-75.
- Rapp, M. A., M. Schnaider-Beeri, H. T. Grossman, M. Sano, D. P. Perl, D. P. Purohit, J. M. Gorman, and V. Haroutunian, 2006, "Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression," *Arch. Gen. Psychiatry* **63**, 161-167.
- Rapp, M. A., M. Schnaider-Beeri, D. P. Purohit, D. P. Perl, V. Haroutunian, and M. Sano, 2008, "Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression," *Am. J. Geriatr. Psychiatry* **16**, 168-174.
- Raux, G., L. Guyant-Marechal, C. Martin, J. Bou, C. Penet, A. Brice, D. Hannequin, T. Frebourg, and D. Campion, 2005, "Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update," *J. Med. Genet.* **42**, 793-795.
- Reisberg, B. and S. Gauthier, 2008, "Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. [Review] [61 refs]," *Int. Psychogeriatr.* **20**, 1-16.
- Reitan and Wolfson, 1985. *The Halstead-Reitan Neuropsychological Test Battery.* Neuropsychology Press.

- Richard, I. H. *et al.*, 2012, "A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease," *Neurology* **78**, 1229-1236.
- Riedel, O. *et al.*, 2010, "Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease," *J. Neurol.* **257**, 1073-1082.
- Ripke, S. *et al.*, 2013, "A mega-analysis of genome-wide association studies for major depressive disorder," *Mol. Psychiatry* **18**, 497-511.
- Robert, P. *et al.*, 2009, "Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders," *European Psychiatry: the Journal of the Association of European Psychiatrists* **24**, 98-104.
- Robert, P. H., C. Berr, M. Volteau, C. Bertogliati, M. Benoit, M. Sarazin, S. Legrain, B. Dubois, and s. PreAL, 2006, "Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: a one-year follow-up study," *Clinical Neurology & Neurosurgery* **108**, 733-736.
- Robinson, R. G., 2003, "Poststroke depression: prevalence, diagnosis, treatment, and disease progression. [Review] [103 refs]," *Biol. Psychiatry* **54**, 376-387.
- Rogaeva, E. *et al.*, 2007, "The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease," *Nat. Genet.* **39**, 168-177.
- Rolinski, M., C. Fox, I. Maidment, and R. McShane, 2012, "Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. [Review]," *Cochrane Database of Systematic Reviews* **3**, CD006504.
- Rongve, A., D. Arsland, and C. Graff, 2013, "[Alzheimer's disease and genetics]. [Review] [Norwegian]," *Tidsskr. Nor. Laegeforen.* **133**, 1449-1452.
- Rongve, A., E. Auning, U. Ehr, and D. Arsland, 2012, "[Psychosis in Parkinson's disease]. [Review] [Norwegian]," *Tidsskr. Nor. Laegeforen.* **132**, 155-158.
- Rongve, A., C. Vossius, S. Nore, I. Testad, and D. Aarsland, 2014, "Time until nursing home admission in people with mild dementia: comparison of dementia with Lewy bodies and Alzheimer's dementia," *Int. J. Geriatr. Psychiatry* **29**, 392-398.
- Rossi, C., D. Volterrani, V. Nicoletti, G. Manca, D. Frosini, L. Kiferle, E. Unti, F. P. De, U. Bonuccelli, and R. Ceravolo, 2009, "'Parkinson-dementia' diseases: a comparison by double tracer SPECT studies," *Parkinsonism & Related Disorders* **15**, 762-766.
- Rovelet-Lecrux, A. *et al.*, 2006, "APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy," *Nat. Genet.* **38**, 24-26.
- Royall, D. R., R. K. Mahurin, and K. F. Gray, 1992, "Bedside assessment of executive cognitive impairment: the executive interview," *J. Am. Geriatr. Soc.* **40**, 1221-1226.

- Sanchez-Ferro, A., J. Benito-Leon, E. D. Louis, A. J. Mitchell, J. A. Molina-Arjona, R. Trincado, A. Villarejo, and F. Bermejo-Pareja, 2013, "Rate of cognitive decline in premotor Parkinson's disease: a prospective study (NEDICES)," *Mov. Disord.* **28**, 161-168.
- Santangelo, G., C. Vitale, L. Trojano, G. D. De, L. Bilo, A. Antonini, and P. Barone, 2010, "Differential neuropsychological profiles in Parkinsonian patients with or without vascular lesions," *Mov. Disord.* **25**, 50-56.
- Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS), 1986, recent evidence and development of a shorter version. In Brink TL, editor. *Clinical gerontology: a guide to assessment and intervention*. New York: Haworth Press.
- Schellenberg, G. D., T. D. Bird, E. M. Wijsman, H. T. Orr, L. Anderson, E. Nemens, J. A. White, L. Bonnycastle, J. L. Weber, and M. E. Alonso, 1992, "Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14," *Science* **258**, 668-671.
- Scheltens, P., D. Leys, F. Barkhof, D. Huglo, H. C. Weinstein, P. Vermersch, M. Kuiper, M. Steinling, E. C. Wolters, and J. Valk, 1992, "Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates," *Journal of Neurology, Neurosurgery & Psychiatry* **55**, 967-972.
- Schenck, C. H., B. F. Boeve, and M. W. Mahowald, 2013, "Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series," *Sleep Medicine* **14**, 744-748.
- Schildkraut, J. J., 1965, "The catecholamine hypothesis of affective disorders: a review of supporting evidence. [Review] [110 refs]," *Am. J. Psychiatry* **122**, 509-522.
- Schmidt, H. D., R. C. Shelton, and R. S. Duman, 2011, "Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. [Review]," *Neuropsychopharmacology* **36**, 2375-2394.
- Schmidt M., 1996. Rey auditory and verbal learning test. A handbook. Western Psychological Services.
- Schneider, B. and D. Prvulovic, 2013, "Novel biomarkers in major depression. [Review]," *Current Opinion in Psychiatry* **26**, 47-53.
- Schneider, L. S. *et al.*, 2014, "Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. [Review]," *J. Intern. Med.* **275**, 251-283.
- Scott, K. M. *et al.*, 2008, "Age patterns in the prevalence of DSM-IV depressive/anxiety disorders with and without physical co-morbidity," *Psychol. Med.* **38**, 1659-1669.

- Selnes, P. *et al.*, 2013, "Diffusion tensor imaging surpasses cerebrospinal fluid as predictor of cognitive decline and medial temporal lobe atrophy in subjective cognitive impairment and mild cognitive impairment," *Journal of Alzheimer's Disease* **33**, 723-736.
- Seto-Salvia, N. *et al.*, 2011, "Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes," *Arch. Neurol.* **68**, 359-364.
- Sexton, C. E., C. E. Mackay, and K. P. Ebmeier, 2009, "A systematic review of diffusion tensor imaging studies in affective disorders. [Review] [99 refs]," *Biol. Psychiatry* **66**, 814-823.
- Shi, F., B. Liu, Y. Zhou, C. Yu, and T. Jiang, 2009, "Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies," *Hippocampus* **19**, 1055-1064.
- Siderowf, A., S. X. Xie, H. Hurtig, D. Weintraub, J. Duda, A. Chen-Plotkin, L. M. Shaw, D. Van, V, J. Q. Trojanowski, and C. Clark, 2010, "CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease," *Neurology* **75**, 1055-1061.
- Sidransky, E. *et al.*, 2009, "Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease," *N. Engl. J. Med.* **361**, 1651-1661.
- Singleton, A. B. *et al.*, 2003, "alpha-Synuclein locus triplication causes Parkinson's disease," *Science* **302**, 841.
- Singleton, A. B., M. J. Farrer, and V. Bonifati, 2013, "The genetics of Parkinson's disease: progress and therapeutic implications. [Review]," *Mov. Disord.* **28**, 14-23.
- Singleton, A. B. *et al.*, 2002, "Clinical and neuropathological correlates of apolipoprotein E genotype in dementia with Lewy bodies," *Dementia & Geriatric Cognitive Disorders* **14**, 167-175.
- Sjogren, M. *et al.*, 2001, "Tau and Abeta42 in cerebrospinal fluid from healthy adults 21-93 years of age: establishment of reference values," *Clin. Chem.* **47**, 1776-1781.
- Skogseth, R. E., T. Fladby, E. Mulugeta, and D. Aarsland, 2011, "[Biomarkers in spinal fluid of patients with dementia]. [Review] [Norwegian]," *Tidsskr. Nor. Laegeforen.* **131**, 2235-2238.
- Sneed, J. R. and M. E. Culang-Reinlieb, 2011, "The vascular depression hypothesis: an update," *Am. J. Geriatr. Psychiatry* **19**, 99-103.
- Snowdon, D. A., L. H. Greiner, J. A. Mortimer, K. P. Riley, P. A. Greiner, and W. R. Markesbery, 1997, "Brain infarction and the clinical expression of Alzheimer disease. The Nun Study," *JAMA* **277**, 813-817.
- Solhaug, H. I., E. B. Romuld, U. Romild, and E. Stordal, 2012, "Increased prevalence of depression in cohorts of the elderly: an 11-year follow-up in the general population - the HUNT study," *Int. Psychogeriatr.* **24**, 151-158.

- Song, S. K., J. E. Lee, H. J. Park, Y. H. Sohn, J. D. Lee, and P. H. Lee, 2011, "The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status," *Mov. Disord.* **26**, 289-296.
- Spatola, M. and C. Wider, 2014, "Genetics of Parkinson's disease: the yield. [Review]," *Parkinsonism & Related Disorders* **20**, Suppl-8.
- Sperling, R. A. *et al.*, 2011, "Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's & Dementia* **7**, 280-292.
- Spreen and Strauss, 1998. *A compendium of neuropsychological tests, second edition: administrations, norms and commentary.* Oxford University Press.
- Starkstein, S. E., R. Jorge, R. Mizrahi, and R. G. Robinson, 2005, "The construct of minor and major depression in Alzheimer's disease," *Am. J. Psychiatry* **162**, 2086-2093.
- Stayte, S. and B. Vissel, 2014, "Advances in non-dopaminergic treatments for Parkinson's disease. [Review]," *Frontiers in Neuroscience* **8**, 113.
- Stebbins, G. T. and C. M. Murphy, 2009, "Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. [Review] [94 refs]," *Behavioural Neurology* **21**, 39-49.
- Stenset, V., L. Johnsen, D. Kocot, A. Negaard, A. Skinningsrud, P. Gulbrandsen, A. Wallin, and T. Fladby, 2006, "Associations between white matter lesions, cerebrovascular risk factors, and low CSF Abeta42," *Neurology* **67**, 830-833.
- Stevens, T., G. Livingston, G. Kitchen, M. Manela, Z. Walker, and C. Katona, 2002, "Islington study of dementia subtypes in the community," *Br. J. Psychiatry* **180**, 270-276.
- Stewart, T., C. Liu, C. Ghingina, K. C. Cain, P. Auinger, B. Cholerton, M. Shi, J. Zhang, and Parkinson Study Group, 2014, "Cerebrospinal fluid alpha-synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort," *Am. J. Pathol.* **184**, 966-975.
- Tagariello, P., P. Girardi, and M. Amore, 2009, "Depression and apathy in dementia: same syndrome or different constructs? A critical review. [Review] [25 refs]," *Archives of Gerontology & Geriatrics* **49**, 246-249.
- Tapiola, T., I. Alafuzoff, S. K. Herukka, L. Parkkinen, P. Hartikainen, H. Soininen, and T. Pirttila, 2009, "Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain," *Arch. Neurol.* **66**, 382-389.
- Taylor, J. P., M. J. Firbank, J. He, N. Barnett, S. Pearce, A. Livingstone, Q. Vuong, I. G. McKeith, and J. T. O'Brien, 2012, "Visual cortex in dementia with Lewy bodies: magnetic resonance imaging study," *Br. J. Psychiatry* **200**, 491-498.

- Teresi, J., R. Abrams, D. Holmes, M. Ramirez, and J. Eimicke, 2001, "Prevalence of depression and depression recognition in nursing homes," *Social Psychiatry & Psychiatric Epidemiology* **36**, 613-620.
- Testad, I., A. Corbett, D. Aarsland, K. O. Lexow, J. Fossey, B. Woods, and C. Ballard, 2014, "The value of personalized psychosocial interventions to address behavioral and psychological symptoms in people with dementia living in care home settings: a systematic review.[Erratum appears in *Int Psychogeriatr.* 2014 Jul;26(7):1099]," *Int. Psychogeriatr.* **26**, 1083-1098.
- Thaler, A. *et al.*, 2014, "A voxel-based morphometry and diffusion tensor imaging analysis of asymptomatic Parkinson's disease-related G2019S LRRK2 mutation carriers," *Mov. Disord.* **29**, 823-827.
- Theilmann, R. J., J. D. Reed, D. D. Song, M. X. Huang, R. R. Lee, I. Litvan, and D. L. Harrington, 2013, "White-matter changes correlate with cognitive functioning in Parkinson's disease," *Frontiers in neurology* [electronic resource]. **4**, 37.
- Thomas, A. J., R. N. Kalaria, and J. T. O'Brien, 2004, "Depression and vascular disease: what is the relationship? [Review] [124 refs]," *J. Affect. Disord.* **79**, 81-95.
- Tiraboschi, P., D. P. Salmon, L. A. Hansen, R. C. Hofstetter, L. J. Thal, and J. Corey-Bloom, 2006, "What best differentiates Lewy body from Alzheimer's disease in early-stage dementia?," *Brain* **129**, 3-35.
- Tokuda, T., M. M. Qureshi, M. T. Ardah, S. Varghese, S. A. Shehab, T. Kasai, N. Ishigami, A. Tamaoka, M. Nakagawa, and O. M. El-Agnaf, 2010, "Detection of elevated levels of alpha-synuclein oligomers in CSF from patients with Parkinson disease," *Neurology* **75**, 1766-1772.
- Toledo, J. B. *et al.*, 2013, "Clinical and multimodal biomarker correlates of ADNI neuropathological findings," *Acta Neuropathologica Communications* **1**, 65.
- Tolosa, E., T. V. Borgh, E. Moreno, and DaTSCAN Clinically Uncertain Parkinsonian Syndromes Study Group, 2007, "Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study," *Mov. Disord.* **22**, 2346-2351.
- Tsuang, D. *et al.*, 2013, "APOE 4 increases risk for dementia in pure synucleinopathies," *JAMA Neurology* **70**, 223-228.
- Vandenberghe, R., K. Adamczuk, P. Dupont, K. V. Laere, and G. Chetelat, 2013, "Amyloid PET in clinical practice: Its place in the multidimensional space of Alzheimer's disease. [Review]," *NeuroImage Clinical* **2**, 497-511.
- Vann Jones, S. A. and J. T. O'Brien, 2014, "The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies.[Erratum appears in *Psychol Med.* 2014 Mar;44(4):684]," *Psychol. Med.* **44**, 673-683.

- Vardy, E., R. Holt, A. Gerhard, A. Richardson, J. Snowden, and D. Neary, 2014, "History of a suspected delirium is more common in dementia with Lewy bodies than Alzheimer's disease: a retrospective study," *Int. J. Geriatr. Psychiatry* **29**, 178-181.
- Verdelho, A. *et al.*, 2013, "Depressive symptoms predict cognitive decline and dementia in older people independently of cerebral white matter changes: the LADIS study," *Journal of Neurology, Neurosurgery & Psychiatry* **84**, 1250-1254.
- Videbech, P., B. Ravnkilde, L. Gammelgaard, A. Egander, K. Clemmensen, N. A. Rasmussen, A. Gjedde, and R. Rosenberg, 2004, "The Danish PET/depression project: performance on Stroop's test linked to white matter lesions in the brain," *Psychiatry Res.* **130**, 117-130.
- Visser, P. J. *et al.*, 2009, "Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study," *Lancet Neurology* **8**, 619-627.
- Vossius, C., J. P. Larsen, C. Janvin, and D. Aarsland, 2011, "The economic impact of cognitive impairment in Parkinson's disease," *Mov. Disord.* **26**, 1541-1544.
- Wakabayashi, K., K. Tanji, S. Odagiri, Y. Miki, F. Mori, and H. Takahashi, 2013, "The Lewy body in Parkinson's disease and related neurodegenerative disorders. [Review]," *Mol. Neurobiol.* **47**, 495-508.
- Walker, Z., E. Jaros, R. W. Walker, L. Lee, D. C. Costa, G. Livingston, P. G. Ince, R. Perry, I. McKeith, and C. L. Katona, 2007, "Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy," *Journal of Neurology, Neurosurgery & Psychiatry* **78**, 1176-1181.
- Wallin, A., A. Edman, K. Blennow, C. G. Gottfries, I. Karlsson, B. Regland, and M. Sjogren, 1996, "Stepwise comparative status analysis (STEP): a tool for identification of regional brain syndromes in dementia.[Erratum appears in *J Geriatr Psychiatry Neurol* 1997 Apr;10(2):90-1]," *Journal of Geriatric Psychiatry & Neurology* **9**, 185-199.
- Wancata, J., R. Alexandrowicz, B. Marquart, M. Weiss, and F. Friedrich, 2006, "The criterion validity of the Geriatric Depression Scale: a systematic review. [Review] [72 refs]," *Acta Psychiatr. Scand.* **114**, 398-410.
- Watson, R., A. M. Blamire, S. J. Colloby, J. S. Wood, R. Barber, J. He, and J. T. O'Brien, 2012, "Characterizing dementia with Lewy bodies by means of diffusion tensor imaging," *Neurology* **79**, 906-914.
- Weidauer, S., M. Nichtweiss, and E. Hattingen, 2014, "Differential diagnosis of white matter lesions: Nonvascular causes-Part II. [Review]," *Clinical Neuroradiology* **24**, 93-110.
- Weintraub, D., N. Dietz, J. E. Duda, D. A. Wolk, J. Doshi, S. X. Xie, C. Davatzikos, C. M. Clark, and A. Siderowf, 2012, "Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease," *Brain* **135**, 1-80.

- Weintraub, D., J. Doshi, D. Koka, C. Davatzikos, A. D. Siderowf, J. E. Duda, D. A. Wolk, P. J. Moberg, S. X. Xie, and C. M. Clark, 2011, "Neurodegeneration across stages of cognitive decline in Parkinson disease," *Arch. Neurol.* **68**, 1562-1568.
- Whitwell, J. L. *et al.*, 2007, "Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease," *Brain* **130**, 3-19.
- Wilkins, C. H., J. Mathews, and Y. I. Sheline, 2009, "Late life depression with cognitive impairment: evaluation and treatment. [Review] [29 refs]," *Clinical Interventions In Aging* **4**, 51-57.
- Williams, M. M., C. Xiong, J. C. Morris, and J. E. Galvin, 2006, "Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease," *Neurology* **67**, 1935-1941.
- Williams-Gray, C. H. *et al.*, 2009a, "The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort," *Brain* **132**, 11-69.
- Williams-Gray, C. H., A. Goris, M. Saiki, T. Foltynie, D. A. Compston, S. J. Sawcer, and R. A. Barker, 2009b, "Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease," *J. Neurol.* **256**, 493-498.
- Wilson, R. S., A. W. Capuano, P. A. Boyle, G. M. Hoganson, L. P. Hizek, R. C. Shah, S. Nag, J. A. Schneider, S. E. Arnold, and D. A. Bennett, 2014, "Clinical-pathologic study of depressive symptoms and cognitive decline in old age," *Neurology* **83**, 702-709.
- Winblad, B. *et al.*, 2004, "Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. [Review] [0 refs]," *J. Intern. Med.* **256**, 240-246.
- Winder-Rhodes, S. E., J. R. Evans, M. Ban, S. L. Mason, C. H. Williams-Gray, T. Foltynie, R. Duran, N. E. Mencacci, S. J. Sawcer, and R. A. Barker, 2013, "Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort," *Brain* **136**, 2-9.
- Wolk, D. A. *et al.*, 2009, "Amyloid imaging in mild cognitive impairment subtypes.[Erratum appears in *Ann Neurol.* 2009 Jul;66(1):123 Note: DeKoskym, Steven T [corrected to De-Kosky, Steven T]]," *Ann. Neurol.* **65**, 557-568.
- Wright, B. L., J. T. Lai, and A. J. Sinclair, 2012, "Cerebrospinal fluid and lumbar puncture: a practical review. [Review]," *J. Neurol.* **259**, 1530-1545.
- Yamaguchi, K., E. J. Cochran, J. R. Murrell, M. H. Polymeropoulos, K. M. Shannon, R. A. Crowther, M. Goedert, and B. Ghetti, 2005, "Abundant neuritic inclusions and microvacuolar changes in a case of diffuse Lewy body disease with the A53T mutation in the alpha-synuclein gene," *Acta Neuropathol. (Berl)*. **110**, 298-305.

- Yesavage, J. A., T. L. Brink, T. L. Rose, O. Lum, V. Huang, M. Adey, and V. O. Leirer, 1982, "Development and validation of a geriatric depression screening scale: a preliminary report," *J. Psychiatr. Res.* **17**, 37-49.
- Ylikoski, A., T. Erkinjuntti, R. Raininko, S. Sarna, R. Sulkava, and R. Tilvis, 1995, "White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home," *Stroke* **26**, 1171-1177.
- Yoshizawa, H., J. P. Vonsattel, and L. S. Honig, 2013, "Early neuropsychological discriminants for Lewy body disease: an autopsy series," *Journal of Neurology, Neurosurgery & Psychiatry* **84**, 1326-1330.
- Yu, F. *et al.*, 2009, "Cognitive training for early-stage Alzheimer's disease and dementia. [Review] [35 refs]," *J. Gerontol. Nurs.* **35**, 23-29.
- Zaccai, J., C. McCracken, and C. Brayne, 2005, "A systematic review of prevalence and incidence studies of dementia with Lewy bodies. [Review] [31 refs]," *Age & Ageing* **34**, 561-566.
- Zarranz, J. J. *et al.*, 2004, "The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia," *Ann. Neurol.* **55**, 164-173.
- Zhan, W., Y. Zhang, S. G. Mueller, P. Lorenzen, S. Hadjide metriou, N. Schuff, and M. W. Weiner, 2009, "Characterization of white matter degeneration in elderly subjects by magnetic resonance diffusion and FLAIR imaging correlation," *Neuroimage* **47**, Suppl-65.
- Zhang, Y. *et al.*, 2007, "Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease," *Neurology* **68**, 13-19.
- Zheng, Z., S. Shemmassian, C. Wijekoon, W. Kim, S. Y. Bookheimer, and N. Pouratian, 2014, "DTI correlates of distinct cognitive impairments in Parkinson's disease," *Hum. Brain Mapp.* **35**, 1325-1333.
- Zhu, C. W. and M. Sano, 2006, "Economic considerations in the management of Alzheimer's disease. [Review] [112 refs]," *Clinical Interventions In Aging* **1**, 143-154.