

# Brain MRI changes in Parkinson's disease

*A cross sectional study*

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## **Abstract**

### **Background**

Cognitive impairment is common even in newly diagnosed Parkinson's disease (PD), and characteristically involves executive and visuospatial functions with deficits also in the memory domain. There is an increased risk of dementia associated with the diagnosis of PD, with an almost sixfold increased risk of becoming demented compared with subjects without PD.

The morphologic changes of grey and white matter which accompany cognitive impairment in early PD, and dementia in PD are incompletely understood.

The first study to compare whole brain atrophy in PD versus other types of dementia was published in 2004, showing that the pattern of grey matter loss in PD and PDD was different from the changes found in AD. Occipital atrophy was found in the PDD group and frontal volume loss in PD without dementia. No difference in grey matter volume was found between PDD and DLB patients. The studies that have been published since, have in part confirmed these results, but also conflicting results have been found. No studies have previously looked at white matter hyperintense lesions in MR images of PD patients and their impact on dementia in PD.

### **Hypotheses**

The frequency and extent of white matter T2 hyperintense lesions (WMH) are associated with dementia in PD.

The pattern of grey matter atrophy in PD is different from atrophy in normal ageing, patients with PDD and PD with mild cognitive impairment.

Grey matter atrophy in patients with PDD differs from the pattern of atrophy in patients with Alzheimer's disease but not from patients with Dementia with Lewy Bodies.

Patients with PD who develop dementia early in the disease diagnosis have more grey matter atrophy than patients who develop dementia late in the disease course.

## **Subjects**

Patients were recruited by doctors in the outpatient clinics of the Department of Neurology, Department of Geriatric Medicine and the Department of Old Age Psychiatry at Stavanger University Hospital in the period from 2001 to 2005. One group was recruited from an ongoing longitudinal study, the Parkinson-study of Rogaland, during their annual follow up (n= 17). Another group consisted of consecutive patients with PD with and without dementia. Patients with Alzheimer's disease and DLB were also recruited. Healthy elderly volunteers were recruited from Stavanger and the surrounding district.

## **Methods**

After a clinical assessment including evaluation of cognition, motor symptoms and psychiatric symptoms patients were diagnosed according to established diagnostic criteria for PD and dementia. Healthy controls completed a brief interview and a mini mental state evaluation (MMSE). All patients and controls completed an MRI examination with the same imaging protocol, in the same MRI machine.

Images were analysed for white matter hyperintense lesions (WMH) using a semi-quantitative visual rating scale. Unbiased whole brain image analysis with voxel based morphometry (VBM) was used for the evaluation of grey matter differences between groups.

## **Results**

We found that white matter hyperintense lesions in T2 weighted series on MRI are not increased in number or extent in the total PD group, but they were increased in PDD compared to non-demented PD subjects.

We found atrophy in PDD both in cortical and sub cortical grey matter compared to healthy subjects and non-demented subjects with PD. A novel finding was atrophy in grey matter observed in patients with MCI and PD compared to subjects with PD and

intact cognition, indicating that even the early cognitive changes in PD are associated with morphological brain changes.

The overall pattern of grey matter changes in PDD differed from that in AD and DLB, although overlapping regions of atrophy exists. In our study, DLB patients had more atrophy in parietal and occipital areas compared with PDD patients.

We found that patients with PD who developed dementia early had a different pattern of atrophy than those who developed dementia late in the course.

## **Conclusion**

We found that there is no increase in WMH in PD compared to controls. The more severe changes found in PDD however, suggests that in some patients WMH may contribute to cognitive impairment.

Our grey matter findings are in line with other studies, supporting the hypothesis that morphological changes in the cortex contribute to dementia in PD. We found grey matter structural changes associated with cognitive impairment in PD, thus cognitive impairment early in PD are not entirely based on functional changes. Differences found between DLB and PDD shed light on the ongoing discussion whether DLB and PDD are different diseases or represent stages on a continuum of Lewy body disease.

The results of the studies included in this thesis, gives valuable new information about structural changes accompanying PD both in white matter and grey matter, and our results give rise to new hypotheses for future imaging studies of PD. Challenges for future studies will be to find which brain changes that reliably can predict development of dementia in PD.

## List of abbreviations

**DLB** - Dementia with Lewy Bodies

**LB** – Lewy bodies

**PDD** - Parkinson's disease with dementia

**VBM** - Voxel based morphometry

**AD** - Alzheimer's disease

**3D** -Three dimensional

**MRI** - Magnetic resonance imaging

**MMSE** - Mini mental state examination

**CSF** - Cerebro spinal fluid

**SPECT** - Single photon emission computed tomography

**FP-CIT** - iodine I 123-radiolabeled 2beta-carbomethoxy-3beta-( 4-iodophenyl)-N-(3-fluoropropyl) nortropane

**DSM-IV** - Diagnostic and Statistical Manual of Mental Disorders

**NINCDS – ADRDA** - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association

**NPI** - The Neuropsychiatric Inventory

**MADRS** - Montgomery Asberg Depression Rating Scale

**FSPGR** - Fast spoiled gradient recalled echo

**SPM2** - Statistical parametric mapping

**TR** - Repetition time

**TE** - Echo time

**TI** - Inversion time

**FFE** - Fast field echo



**FLAIR** - Fluid Attenuation Inversion Recovery

**FWE** - family wise error

**UPDRS** –Unified Parkinson’s Disease rating Scale

**rCBF** - regional cerebral blood flow

**mAChRs** - muscarinic acetylcholine receptors

**QOL** - quality of life

**ChAT** - choline acetyltransferase

**MDS** – Movement Disorder Society

**DAT** – dopamine transporter imaging

**MIBG** - Metaiodobenzylguanidine

**CT** - Computer tomography

## List of publications

1. **Beyer MK**, Aarsland D, Greve OJ, Larsen JP. *Visual rating of white matter hyperintensities in Parkinson's disease*. *Mov Disord* 2006;21(2):223-9.
  
2. **Beyer MK**, Janvin CC, Larsen JP, Aarsland D. An MRI study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel based morphometry. *J Neurol Neurosurg Psychiatry* 2007;78(3):254-9.
  
3. **Beyer MK**, Larsen JP, Aarsland D. Grey matter atrophy in Parkinson's disease with dementia and Dementia with Lewy Bodies. Accepted for publication in *Neurology* March 2007
  
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# 1. Introduction

## 1.1 Magnetic Resonance Imaging (MRI)

### 1.1.1 History of MRI

The physical phenomenon of nuclear magnetic resonance (NMR) was first discovered by Isidor I Rabi in 1938.<sup>1</sup> He was awarded the 1944 Nobel Prize in Physics for his method for recording the magnetic properties of atomic nuclei. (<http://nobelprize.org>) Felix Bloch and Edward Purcell are considered to be the inventors of magnetic resonance imaging (MRI), for which they were awarded the Nobel Prize in Physics in 1952. (<http://nobelprize.org>) It was not until the 1970s the principle of nuclear magnetic resonance could be used to make images of the body. In 1973, Paul Lauterbur, a chemist at the State University of New York, Stony Brook, produced the first NMR image.<sup>2</sup> Peter Mansfield, a physicist working in Nottingham, England, further developed the utilisation of gradients in the magnetic field. Mansfield's work showed how fast MR imaging could be achieved.<sup>3</sup> In 2003 Mansfield and Lauterbur were awarded the Nobel Prize in Medicine for their pioneering contributions, which later led to the application of magnetic resonance in medical imaging.

### 1.1.2 Principles of MRI

In MRI the magnetic properties of the hydrogen nuclei of the body are utilised. Hydrogen nuclei contain only one proton, and are therefore often referred to as protons. All MRI used in clinical medicine utilise the NMR from the hydrogen nucleus. Hydrogen nuclei give the best NMR signals, and are the most common

atomic nuclei in the body.<sup>4</sup> Similar to a bar magnet, the hydrogen nucleus has a magnetic moment and an associated magnetic field. In the natural state these magnetic dipoles are randomly oriented. When the protons are placed in a powerful magnetic field, as in a MRI machine, these little dipoles align with the external magnetic field. They either align parallel or anti parallel with the direction of the magnetic field. There is an overweight of protons that align parallel to the magnetic field, but only as little as 1 proton per million. This results in a net magnetic moment parallel to the magnetic field, created by the sum of the individual protons' magnetic moments. The protons that are aligned parallel to the external magnetic field have lower energy than the anti-parallel protons.<sup>5</sup> When they are exposed to a signal of electromagnetic radiation, they generate a signal, the NMR. The NMR that is the basis for creating images are thus signals generated in the body and detected in an antenna /coil which is placed around the protons, i.e. the patient.

The electromagnetic radiation that can produce NMR must have the same frequency as the spin of the atomic nucleus, the resonance frequency (RF). In clinical MRI the RF is usually in the so called radio-frequency area. RF stimulation causes the nuclei to absorb energy, and lifts them to an excited state. In order to return to the lower energy state the excess energy of the nuclei is released to the surrounding tissue.<sup>5</sup>

Following RF pulsing, the strength and origin of the magnetic signals can be determined by magnetic field gradients that are superimposed on the magnetic field in the MR machine. This spatial information can be encoded electronically and reconstructed into a cross-sectional image.<sup>6</sup> Each cross sectional MR image is based on a matrix of numbers, each assigned a shade of grey. The numerical value of each voxel (i.e. picture elements in three dimensions) in the image represents the intensity of the NMR emanating from the tissue following a RF pulse. Depending on the RF pulse(s) and the sampling time of the signal, different contrasts between tissue classes can be depicted.<sup>7</sup> Image contrast is created by using a selection of image acquisition parameters that weights signal by e.g. T1, T2 or no relaxation time ("proton-density images"). MR images have good tissue contrast which means the ability of

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differentiation between tissue types is good. There is also good differentiation between normal and pathologic tissue.

### *T1 contrast*

After an RF pulse stimulation, the protons are “excited” for a short time, but the added energy diminishes and after a while the protons have regained their original (lower) energy level. This process depends on the protons’ ability to align with the external magnetic field, which differs for different tissue types. For example in lipids protons will relax faster than protons in water, or in molecules that are much larger.<sup>5</sup> In the time period of returning to lower energy state, the NMR signal will gradually decay and disappear. The T1 relaxation time is the time it takes for 63% of the protons to align with the external field of magnetisation. A sampling of the NMR signals in a T1 relaxation gives T1 weighted images. T1 time is tissue class dependent, and one of the reasons why MR images have good tissue contrast. In the brain, T1-weighting causes the nerve connections of white matter to appear white, and the congregations of neurons of grey matter to appear grey, while cerebrospinal fluid appears dark.<sup>4, 5</sup>

### *T2 contrast*

The T2 weighted images are obtained after a refocusing of the spins in the x-y direction following a 180 ° RF pulse. T2 relaxation is caused by reduction in magnetisation in the X -Y plane, also called transverse relaxation. This is caused by in-homogeneity of the magnetic field on a molecular level, leading to a dephasing of the protons with decay of the transverse magnetisation. T2 relaxation time describes how fast the decay of the NMR is because of T2 relaxation. T2 time is longer in pure water than tissues or liquids containing protein.<sup>5</sup> The contrast of "white matter," "grey matter" and "cerebrospinal fluid" is reversed using T2 imaging compared to T1 imaging. See figure 1, below.

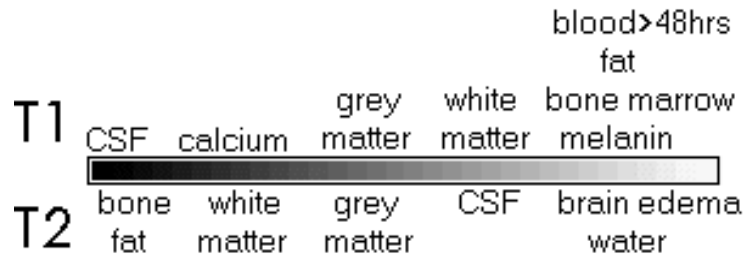


Figure 1. Relative brightness levels for different material in T1 and T2 weighted scans. Courtesy of C. Rorden, Associate professor, University of South Carolina.

### *Volumetric MRI*

The ability to acquire high-resolution three-dimensional (3D) imaging in MRI is the result of technical improvements and rapid scan techniques. Low flip angle gradient-echo imaging is one method to do this, which I will not describe in detail. Through this method thin slices can be obtained, with voxel-size of 1x1x1 millimeters. An advantage of 3D MRI is the ability to get detailed images of complex anatomical structures, like the brain.

#### **1.1.3 Structural Imaging**

Computer tomography (CT) and MRI are two methods for obtaining images of the structure of the brain. CT uses ionising radiation (x rays) that are potentially harmful for the patient, while no unwanted side-effects of MRI are so far discovered.

Other advantages with MR images are that different sequences that can be applied in MRI reveals information about properties of the tissue being imaged. The discrimination between grey and white matter can be excellent e.g. in T1 weighted images, and this enables us to perform studies where different tissue classes can be segmented and treated separately. A combination of good T1 contrast between grey and white matter and a volumetric MR uptake of the brain gives us the opportunity to study structural differences between patients or groups of patients that are not



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obvious by visual inspection. This can be done using a region of interest (ROI) approach where the investigators, based on a hypothesis, make measurements in specific areas of the brain. Another approach is the unbiased methods in which a data-based analysis is performed. This kind of analyses can be used both to test certain hypotheses, but they can also be performed without a pre-specified hypothesis and point the attention of the investigators to structural differences that have not previously been found. There are a number of different software available to perform such analyses e.g. Statistical parametric mapping (SPM) (<http://www.fil.ion.ucl.ac.uk/spm>), Freesurfer<sup>8</sup>, Brainvoyager (<http://www.brainvoyager.com/>) and Analyze (<http://www.mayo.edu/bir/>). The choice of method is guided by the hypotheses of the study, but also the availability and cost of using the different methods will influence the choice of method. The quality of the images will also decide which programmes can be used for image analysis.

Disadvantages of MRI especially for studies of elderly and demented patients, or patients with movement disorders, are the movement artefacts produced when the patient is unable to lie still in the machine. This in combination with the prolonged scanning time for MR imaging may lead to acquisition of useless data. The noise in the scanner can be a problem as well, in addition to the limited space that may lead to a feeling of claustrophobia. Because of this and the unfamiliar setting for the patient, some dementia patients get agitated and cannot complete the imaging. Imaging with modern CT scanners now only take seconds to complete a scanning of the brain, while a typical MRI will take at least 15 minutes. Despite these disadvantages MRI is the method of choice for most structural imaging studies of the brain for research purposes.

### 1.1.4 MRI findings in normal ageing of the brain

#### *Grey matter*

Global thinning of the cerebral cortex has been found to start by middle age (third decade of life), and age-associated patterns of atrophy have been identified.<sup>9</sup> Prominent atrophy of the prefrontal cortex with relative sparing of temporal and parahippocampal cortex has been found in independent studies of normal ageing.<sup>9-11</sup> The preservation of temporal and parahippocampal structures is consistent with the functional importance of the thalamo-limbic circuits in sensory integration, arousal, emotion, and memory. Later-maturing cortical regions are thought to be more vulnerable to age-related morphologic changes.<sup>11</sup> Atrophy of subcortical structures like the striatum has also been shown in healthy adults.<sup>12</sup> Local areas of accelerated loss in normal ageing are also found bilaterally in the insula, superior parietal gyri, central sulci, and cingulate sulci.<sup>10</sup> Conflicting findings exist regarding the interaction of age with sex for grey matter atrophy. One study found no regionally specific effects,<sup>10</sup> while another group found greater cortical thickness in some regions in females relative to males independent of differences in brain or body size.<sup>13</sup>

In a longitudinal study, decreases in cross-sectional whole-brain, temporal lobe, and hippocampal volumes and increase in ventricular volume is found with increasing age, with the most marked changes occurring after 70 years of age. The increase after 70 years of age is found to be particularly marked in the ventricles and the hippocampi.<sup>14</sup> Longitudinal change in atrophy of normal ageing often comes from studies where elderly are used as healthy controls, and reported annual percentage loss ranges from 0.2<sup>15</sup> to 0.4-0.5 %.<sup>16</sup>

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## *White matter*

The structural integrity of myelin sheaths deteriorates during normal ageing, especially in the late-myelinating association regions and may result in "disconnection" of widely distributed neural networks.<sup>17</sup> Age-related decline in frontal white matter (WM), the posterior limb of the internal capsule and the genu of the corpus callosum is found using diffusion tensor imaging.<sup>18</sup> The same study showed that temporal and posterior WM was relatively preserved, suggesting that some fibre populations are more vulnerable to age-related degeneration than others. Deep white matter hyperintensities (WMH) are common on T2 weighted and fluid attenuated inversion recovery (FLAIR) images of elderly people. Gliosis, loss of myelin and loss of fibres are found in WMH histopathologically,<sup>19</sup> and even in normal appearing white matter on MRI, damage associated with WMH is detectable.<sup>20</sup> Combined MRI and pathology studies of WMH suggest that in vivo MRI is less sensitive than post mortem analyses to detect WMH,<sup>21</sup> and propose that they originate from chronic hypoperfusion injury.<sup>22</sup>

### **1.1.5 MRI in neurodegenerative diseases/dementia**

Alzheimer's disease is the neurodegenerative disease that is most studied with neuroimaging methods. In the classical study by Jobst et al medial temporal lobe atrophy was found in CT scans of AD patients.<sup>23</sup> This has later been confirmed in studies using MRI.<sup>24</sup> Combined volumetric measures of the amygdala and septal area were found to distinguish patients with AD from normal control subjects with 93% accuracy.<sup>25</sup> None of these methods are so far widely used for diagnosing AD in a clinical setting although it has been argued that it could be feasible.<sup>26</sup>

Asymptomatic persons from families with autosomal dominant AD had cortical grey matter loss in the preclinical stages in the medial temporal lobes, posterior cingulate and temporoparietal cortical areas.<sup>15</sup> Volumetric analysis of the hippocampus and

entorhinal cortex showed that both persons with mild cognitive impairment (MCI) and early AD had volume reductions in these two areas,<sup>27</sup> and in a VBM study grey matter loss has been demonstrated in persons with MCI that resemble those seen in early AD<sup>28</sup> This shows that there are available methods to detect preclinical stages of the disease, and therapeutic intervention can be applied if available.

Neuroimaging investigations may be helpful in the diagnosis of dementia with Lewy bodies (DLB) the second most common neurodegenerative dementia.<sup>29</sup> Significant differences between DLB and AD on MRI have been reported. The most typical finding is the preservation of the hippocampus and medial temporal lobe volume in DLB in comparison with AD.<sup>24, 30</sup> These differences are based on group studies and cannot reliably differentiate between DLB and AD on an individual level, demonstrated by the rather low sensitivity (38%) reported<sup>31</sup>. Other changes, such as atrophy of the putamen<sup>32</sup>, basal forebrain<sup>33, 34</sup>, white-matter lesions<sup>35</sup>, and rates of progression of whole-brain atrophy<sup>36</sup> are even less specific and not helpful in the diagnosis of individual patients.

In a recent study involving the largest sample to date, using automated voxel-based technique without specifying an a-priori area of interest, a signal pattern involving focal atrophy of several areas, including substantia innominata, hypothalamus, and dorsal midbrain<sup>37</sup> was found in DLB, indicating that this pattern of atrophy combined with a relative preservation of medial temporal lobes, is suggestive of DLB.

However, these were group data and there is large degree of overlap between individuals in the AD and DLB groups. Sensitivity and specificity values were not reported. Thus, structural MRI cannot reliably distinguish between DLB and AD.

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## 1.2 Parkinson's disease (PD)

### 1.2.1 PD without dementia

#### *Epidemiology*

Parkinson's disease (PD) is a common neurodegenerative disorder of the elderly characterised by tremor, rigidity and slowness of movements. It was first described by James Parkinson in 1817 in his "An Essay on the Shaking Palsy". The prevalence of PD is 100 to 150 patients per 100 000 inhabitants in Western Europe<sup>38-40</sup> and USA<sup>41</sup> and the prevalence increases with increasing age. Incidence rates for PD are shown to increase from 0.3 per 1000 person-years in subjects aged 55 to 65 years, to 4.4 per 1000 person-years for those aged  $\geq$  85 years.<sup>42</sup> The number of individuals with PD over age 50 in Western Europe's 5 most and the world's 10 most populous nations is expected to double reaching between 8.7 and 9.3 million by 2030.<sup>43</sup>

Conflicting results have been published about the prevalence in developing countries compared to western countries. Some find PD to be less prevalent in the developing countries e.g. China<sup>44</sup> and Bolivia<sup>45</sup>, while recent studies found no difference in the prevalence of idiopathic PD in Brazil<sup>46</sup> or China<sup>47</sup> compared to western countries. Gender distribution is almost equal, although some have reported a slight male preponderance.<sup>48</sup>

#### *Etiology of PD*

The etiology of PD is not known but it is generally believed to be a multi-factorial disease process in which genetic, environmental, occupational and lifestyle factors individually and collectively play a significant role.<sup>49, 50</sup>

There is considerable evidence suggesting that genetic factors can influence susceptibility to PD,<sup>51-53</sup> especially in young onset PD. In late onset idiopathic PD however, the influence of genetics is found to be low, ~2 % for the LRRK2 gene<sup>51</sup>

Numerous environmental conditions are found to influence the risk of developing PD, and interaction between genetic polymorphisms and these environmental factors may be important for the development of idiopathic PD.<sup>54</sup>

Midlife adiposity,<sup>55</sup> infrequent bowel movements,<sup>56</sup> and postmenopausal estrogen use<sup>57</sup> have been found to be associated with increased risk of PD. Childhood well water drinking,<sup>58</sup> exposure to certain pesticides,<sup>59, 60</sup> and rural residence may also increase PD risk,<sup>61</sup> but clear links between rural living and increased risk of PD has not been established.<sup>62</sup> In contrast, smokers and coffee drinkers have a lower risk of PD<sup>63</sup> although smoking does not seem to influence the course of disease.<sup>64</sup>

### *Neuropathology of PD*

PD is characterised by loss and gliosis of the dopaminergic neurons of the substantia nigra pars compacta and the presence of intracellular inclusions called Lewy bodies (LB).<sup>65</sup> Lewy neurites (LN), which are located in the axonal processes of neurons, indicate degenerating neurons present in PD patients.<sup>66</sup> Poorly myelinated or unmyelinated projection neurons with long axons are predisposed to PD related pathology.<sup>67</sup> Neuron loss and LB are not restricted to the SN, but are also found in the dorsal motor nucleus of vagus, nucleus basalis of Meynert, and in the locus ceruleus, and in cortical neurons in PD brains.<sup>68</sup> A characteristic topographic spread of LB pathology in the brain has been proposed by Braak<sup>69</sup> starting in the brain stem and progressing through 6 stages of the disease eventually spread to the neocortex. According to this theory, in stage 1-2 the LB pathology is confined to the medulla/pontine tegmentum and anterior olfactory structures. Stage 3-4 is characterised by initially subtle, but later severe changes of the substantia nigra and other nuclei of the basal mid- and forebrain including limbic structures. The disease is thought become clinically manifest during these stages. A 60 % to 80 % loss of dopaminergic terminals is needed to induce parkinsonian symptoms.<sup>70, 71</sup> Stages 5-6 are considered to be the final stages, when lesions appear in the neocortex.<sup>67</sup> The duration of the preclinical stage of PD is unknown, but may last for 6-8 years.

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## Neurochemical dysfunction

PD is a multi-system disorder that not only affects nigral dopaminergic nerve cells. Also other transmitter systems are affected. Reduced activity in cholinergic, nor-adrenergic, serotonergic and glutamatergic transmitter systems have also been found<sup>72</sup> Post mortem and in vivo studies of PD patients have found reductions in cholinergic activity in PD patients compared to normal controls and AD patients,<sup>73</sup> and dysfunction of the cholinergic system in the frontal cortex of patients with PD has been found to be associated with dementia.<sup>73, 74</sup>

Several neuropathological criteria for PD exist. Those proposed by Gelb<sup>75</sup> are as follows:

- Substantial nerve cell depletion with accompanying gliosis in the substantia nigra
- At least 1 Lewy body in the substantia nigra or in the locus ceruleus
- No pathological evidence for other diseases that produce Parkinsonism (e.g. progressive supranuclear palsy, multiple system atrophy, cortical–basal ganglionic degeneration).

## *Diagnosis of PD*

Parkinsonism is defined as the presence of bradykinesia/akinesia, rigidity, postural instability and tremor.<sup>76</sup> Parkinsonism is found not only in idiopathic PD, although this is the most common cause of parkinsonism, and therefore misdiagnosis may occur. Important differential diagnoses to idiopathic PD are drug induced parkinsonism, Wilson's disease, vascular and other neurodegenerative diseases like multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).<sup>77</sup>

The diagnosis of PD is based on clinical examination. To improve the diagnostic accuracy of the clinical diagnosis, criteria have been developed. The Stavanger PD diagnostic criteria differentiate between clinical definite, probable and possible PD to enhance sensitivity while retaining good specificity.<sup>78</sup> The diagnosis of clinical definite idiopathic PD requires asymmetrical presentation and the patient must have

tremor. In addition at least two of the following symptoms are required: rigidity, bradykinesia or postural abnormality. Good to excellent response to dopaminergic agents is required and at disease onset no atypical signs should be present and CT or MRI of the brain is without major pathology.

For a diagnosis of clinical probable idiopathic PD two of the cardinal symptoms must be present, and no more than one atypical feature is allowed: (1) dementia or clinically relevant autonomic failure at disease onset, (2) symmetrical disease presentation, (3) moderate response to dopaminergic treatment, or (4) other atypical signs or symptoms that indicate another parkinsonian disorder.

For a diagnosis of clinical possible PD the patients must fulfil at least two of the four cardinal symptoms and the response to dopaminergic treatment should at least be moderate. Mild to moderate dementia and autonomic failure is allowed.

The United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria, are probably the most widely used criteria.<sup>79</sup> The criteria described by Gelb are also widely used, and include neuropathologic criteria for a diagnosis of definite PD.<sup>75</sup>

Clinical criteria have limitations in terms of diagnostic accuracy. Even in specialised centres, at least 15 % of patients with a diagnosis of PD did not fulfil strict clinical criteria for the UK Brain Bank criteria.<sup>80</sup>

## **1.2.2 Cognitive impairment in PD**

### *Epidemiology*

Cognitive impairment is common even in newly diagnosed PD, affecting 25-30% of patients.<sup>81,82</sup> The pattern of cognitive deficits seen among these patients suggests that sub-groups of patients based on cognitive ability might be identifiable even in the early stages of disease, probably reflecting regional differences in the underlying



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neuropathological processes.<sup>82</sup> Cognitive impairment characteristically involves executive and visuospatial functions<sup>83</sup> with deficits also in the memory domain.<sup>81</sup>

### *Neuropathology of cognitive impairment in PD*

The neuropathologic/morphologic changes that accompany cognitive impairment in early PD are not known, but some functional changes have been found. In an fMRI study of working memory signal intensity reductions in specific striatal and frontal lobe sites in patients with cognitive impairment were found compared with those patients who were cognitively unimpaired. Cognitive deficits in PD are thus accompanied by neural changes that are related to, but distinct from, those changes that underlie motor deficits in these patients.<sup>84</sup>

Another fMRI study showed decreased efficiency of prefrontal cortical information processing in the hypo-dopaminergic state and showed that dopaminergic therapy improved the physiological efficiency of this region.<sup>85</sup>

A PET study showed that reduced [18F] fluorodopa uptake in PD in the caudate nucleus (and frontal cortex) is related to impairment on neuropsychological tests measuring verbal fluency, working memory, and attention reflecting frontal lobe function.<sup>86</sup>

These studies convincingly show that the dopaminergic system is associated with cognitive impairment in PD. They point to dysfunction in specific structures of the brain and to dysfunction of the dopaminergic system. However, these results do not exclude the possibility of more generalised changes in early PD with cognitive impairment or dysfunction in other transmitter systems.

### *Diagnosis of cognitive impairment in PD*

The term mild cognitive impairment (MCI) describes a transitional state between the cognitive changes of ageing and the earliest clinical manifestations of dementia.<sup>87</sup>

The prevalence of MCI in adults older than 65 years ranges from 3% to 19 % in

epidemiological studies. Some of them remain stable or return to normal, while more than half progress to dementia within a period of 5 years.<sup>88</sup>

The most widely used diagnostic criteria of mild cognitive impairment are those proposed by Petersen;<sup>89</sup> (a) complaint of defective memory, (b) normal activities of daily living, (c) normal general cognitive function, (d) abnormal memory function for age, and (e) absence of dementia. Recently MCI divided into subtypes has been proposed<sup>90</sup> with the idea that subtypes of MCI can predict conversion to different types of dementia.<sup>91</sup> Although diagnostic criteria for MCI have not been validated for PD, recent studies have employed Petersen's criteria and found that in a study of patients with long duration of PD, over 50 % of the non demented subjects fulfilled these criteria<sup>92</sup> and 62 % of them developed dementia over a 4 year period.<sup>93</sup> Thus, the presence of MCI in PD seems to identify patients with a high risk of developing dementia.

### **1.2.3 Dementia in PD**

#### *Epidemiology*

There is an increased risk of dementia associated with the diagnosis of PD,<sup>94</sup> with an almost six fold increased risk of becoming demented compared with subjects without PD.<sup>95</sup> In cross-sectional studies, the prevalence is approximately 30%.<sup>96</sup> In two longitudinal studies the reported cumulative prevalence of PDD was as high as 83%<sup>97</sup> and 78 %.<sup>98</sup>

Predictive factors for developing dementia in PD are age, severity of motor symptoms and cognitive impairment.<sup>41, 95</sup> PD patients who develop postural instability and gait disorder (PIGD) during the course of the disease also have a highly increased risk for subsequent dementia. These findings raise the question whether these motor symptoms and dementia share common or parallel neuropathology.<sup>99</sup> Early hallucinations and akinetic-dominant PD are associated with

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an increased risk of dementia,<sup>98</sup> but duration of PD and age at onset of PD are not predictive of dementia development.<sup>94, 100</sup>

Patients with dementia in PD have more neuropsychiatric symptoms,<sup>101</sup> including cognitive fluctuations, visual and auditory hallucinations, depression, and sleep disturbance.<sup>97</sup> Dementia in PD has wide-ranging effects on quality of life of patients and caregivers, prognosis including the risk of nursing home admission and clinical management,<sup>102</sup> and thus should become an important target in the treatment of the disease.

### *Diagnosis of dementia in PD*

Dementia in PD (PDD) is characterised by executive dysfunction, visuospatial dysfunction, cognitive and motor slowing, impaired memory retrieval, and behavioural symptoms.<sup>83, 102, 103</sup> Dementia in PD is often considered a sub-cortical dementia, although recent evidence show that the syndrome is heterogeneous and that both cortical and subcortical features occur.<sup>104</sup> There are currently no specific and operationalised criteria for dementia in PD. According to the DSM IV criteria, PDD is diagnosed as “dementia due to other medical condition “. In brief, dementia is defined as the development of multiple cognitive deficits manifested by both memory impairment and one or more of the following disturbances aphasia, apraxia, agnosia and disturbance of executive functioning. These deficits cause significant impairment in social or occupational functioning and representing a significant decline from a previous level of functioning, and do not occur exclusively during the course of a delirium. No specific criteria for PDD are listed, but the typical features and the differential diagnoses are described.<sup>103</sup>

Diagnostic criteria for dementia in PD are currently being developed by a Task Force recruited by the Movement Disorder Society (MDS), based on a comprehensive literature review.<sup>105</sup> These new criteria include criteria for probable PDD and possible PDD. PD is diagnosed according to the UK Brain Bank criteria as one of two core features. The second core feature is a dementia syndrome with insidious onset and slow progression, developing within the context of established PD and diagnosed by

history, clinical and mental examination, defined as impairment in more than one cognitive domain, representing a decline from premorbid level, with deficits severe enough to impair daily life (social, occupational or personal care), independent of the impairment ascribable to motor or autonomic symptoms.

### *Causes of dementia in PD*

The cause of dementia in PD is incompletely understood but it is thought to be a multifactorial process involving multiple neuronal populations both cortical and subcortical.<sup>102, 106</sup> Most recent neuropathological studies suggest that cortical and limbic Lewy bodies are the pathological changes associated with dementia in PD,<sup>107; 108-110</sup> and that LB pathology in frontal and limbic areas correlate with the severity of dementia in PD.<sup>111</sup> However, there are cases with PDD with rather mild LB involvement,<sup>108</sup> and vice versa: some patients have marked cortical LB involvement but without dementia.<sup>112</sup> Therefore, other factors than the absolute number of Lewy bodies in the neocortex and limbic system may influence the development of cognitive impairment in PD. Alzheimer type changes, in particular amyloid plaques may contribute,<sup>113</sup> although they are found to be modest<sup>110</sup> and not sufficient to fulfil the diagnostic criteria for AD.<sup>109, 114</sup> The impact of vascular pathology for PDD is less studied. Although vascular changes are common in older people, they are not common in PD, and do not seem to be important for the development of dementia in PD.<sup>115, 116</sup>

The variety of clinical and pathological features of PDD indicates that the syndrome is heterogeneous with individual differences. For example, more morphological changes were reported in PD patients developing dementia early in the disease compared to those with a late dementia.<sup>117</sup>

Neurochemical deficits are also thought to have an impact on the development of dementia in PD, with loss of cholinergic, dopaminergic, and noradrenergic innervation.<sup>73, 118</sup> Cholinergic markers such as Acetylcholine esterase is more reduced in the cortex of patients with PD than of patients with mild AD<sup>119</sup> and choline acetyltransferase is more reduced in PDD compared to patients with DLB.<sup>117</sup> In

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summary, the main pathology underlying dementia in PD is Lewy-body-type degeneration with associated cellular loss in cortical and limbic structures and cortical cholinergic deficits. Further studies are needed to improve our knowledge about the causes of dementia in PD, and future studies should focus on in-vivo investigations as most previous studies have been based on the neuropathology of end-stage PD.

### 1.2.4 Related dementias

#### *Dementia with Lewy Bodies*

DLB is reported by many as the second most common type of dementia after Alzheimer's disease<sup>120</sup> Clinically DLB is characterised by progressive cognitive impairment, recurrent episodes of confusion, attention deficits, parkinsonism and visual hallucinations.<sup>29</sup>

DLB is characterised by cortical, limbic and brainstem Lewy Bodies, usually in combination with Alzheimer type changes.<sup>121</sup> There is limited knowledge about the relationship between neuropathological findings and the clinical symptoms in DLB, and even less is known about the relation between in-vivo findings and the clinical phenotype.

The diagnostic accuracy of DLB has been poor<sup>122</sup> with low sensitivity of the first diagnostic criteria.<sup>123</sup> New pathologic and clinical criteria are introduced to improve the accuracy of the diagnosis.<sup>29</sup> Features suggestive of DLB now include REM sleep behaviour disorder and severe neuroleptic sensitivity. Recently visualisation of the striatal dopamine transporter is shown to aid in this distinction,<sup>124</sup> and has been included in the revised criteria for DLB. Whether these criteria have improved diagnostic sensitivity remains to be seen.

The dementia profile of DLB is similar to that of dementia in PDD,<sup>125</sup> and the distinction between them is based on the relative timing of dementia and

parkinsonism.<sup>29</sup> Patients presenting with less than 1 year of parkinsonism prior to dementia are diagnosed with DLB, whereas patients with > 1 year duration of parkinsonism prior to dementia are diagnosed with PDD. DLB can be difficult to distinguish from AD in early dementia. However, few studies have compared brain changes in PDD with DLB brain changes, although in a recent neuropathology study, differences were found in the severity of morphological and neurochemical changes.<sup>117</sup>

### *Alzheimer's disease*

Alzheimer's disease (AD) is the most frequent cause of dementia and incidence rates increases with age.<sup>126</sup> The typical symptoms of AD are insidious in onset and consist of progressive impairment of memory typically accompanied by aphasia, agnosia and apraxia, leading to impaired activities of daily living. In addition alterations in mood, and behavioural functions are common, like decline in emotional control or motivation and changes in social behaviour.<sup>103</sup>

Increased risk of AD is associated with age and the apolipoprotein E e4 genotype. Educational level is inversely associated with the risk of dementia, and some find an increased risk for AD in women.<sup>126</sup>

AD is characterised histopathologically by neuron loss and extracellular amyloid deposits and intra-neuronal neurofibrillary tangles in the brain.<sup>127, 128</sup> The disease usually begins in entorhinal cortex and hippocampus, and subsequently involves temporal and parietal association areas.<sup>127</sup>

The most commonly used clinical criteria for the diagnosis of AD, are the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association (NINCDS-ADRDA) criteria,<sup>129</sup> with good sensitivity (92%) and moderate specificity (65 %).<sup>130</sup> The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and ICD 10 criteria are other commonly used clinical criteria.

(<http://www.who.int/classifications/apps/icd/icd10online/> )

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## 1.3 Imaging in Parkinson's disease and in dementia associated with PD

### 1.3.1 Imaging in PD

#### *Structural imaging techniques*

There is no single measure or imaging characteristic that is sensitive and specific for the diagnosis of PD. Therefore routine diagnostic imaging in patients with suspected idiopathic PD is done to exclude other potential causes of parkinsonism such as vascular parkinsonism, and may help in distinguishing PD from other neurodegenerative syndromes with parkinsonism like MSA and PSP.

Studies have tried to find characteristic abnormalities to differentiate between Parkinson disease and its differential diagnoses. Pathology thought to be typical of MSA like putaminal hypointensity, lateral slit like hyperintensity and cerebellar abnormalities have also been shown in PD. However, these changes were always considered to be mild. Brainstem and putaminal atrophy was only seen in MSA.<sup>131</sup> A similar study did not confirm these results, but showed that measurement of the middle cerebellar peduncle differed between PD, normal controls and MSA patients.<sup>132</sup> The most recent attempt to develop a diagnostic tool for PD used a 3 tesla (T) MRI scanner and visualised neuromelanin-containing neurons in the brainstem locus ceruleus and substantia nigra pars compacta of healthy volunteers and patients with PD. In PD patients, the signal intensity in the locus ceruleus and substantia nigra pars compacta was greatly reduced, suggesting depletion of neuromelanin-containing neurons.<sup>133</sup> Whether this method can differentiate between PD and other diseases with parkinsonism remains to be shown.

Diffusion tensor imaging of the olfactory tract have shown promising results in distinguishing PD patients from normal controls,<sup>134</sup> but more and larger studies are

needed to confirm their results, and to see if this method can serve as a biomarker in PD.

### *Functional imaging techniques*

Novel functional imaging techniques are increasingly used in studies of PD for the evaluation of disease progression, disease severity, and to assess the effect of therapeutic intervention. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) using dopamine tracers are among the most frequently used techniques.

In PD patients the first perfusion SPECT studies did not find perfusion deficits compared to controls<sup>135, 136</sup> while later studies have found brain hypoperfusion in the frontal lobes<sup>137</sup> and multiple brain areas.<sup>138</sup> Improved imaging techniques and methods of analysis may explain these differences, while differences in cognitive functioning might influence the results although they were all classified as not demented.

With dopamine transporter (DAT) imaging by SPECT, and different ligands such as [123I]beta-CIT, loss of dopamine transporter in PD is depicted as a marker of loss of presynaptic dopaminergic neurons.<sup>139</sup> This method is useful for differentiating PD from other parkinsonian syndromes,<sup>140</sup> and DLB from AD.<sup>141</sup> It may also aid in the discrimination between diseases that both have dopamine transporter loss like PD and MSA through quantification of midbrain DAT signal,<sup>142</sup> but these results awaits confirmation by other studies.

Functional imaging of the heart using the radionuclide Metaiodobenzylguanidine (MIBG), which is a specific marker for noradrenergic transporters, is significantly reduced in PD.<sup>143</sup> This method, which until now have mostly been used in Japan, have also been shown to differentiate between LB related and non LB related dementia with a high sensitivity ( 95 %) and specificity (87 %),<sup>144</sup> and may thus aid in differential diagnosis of patients with dementia.



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### 1.3.2 MRI findings in PD with cognitive impairment and dementia

#### *Region of interest based methods.*

The first MRI studies of neurodegenerative diseases mainly involved the examination of specific structures thought to be most affected in the disease. In an early study, morphological measurements of the brain in 68 PD patients were done and compared to healthy controls. The authors concluded that dementia in PD is not associated with any specific pattern of MRI abnormalities.<sup>145</sup> A subsequent study showed that PDD patients had hippocampal atrophy, and that this patient group had hippocampal volumes smaller than AD patients. PD patients without dementia also had hippocampal atrophy, but less pronounced than the PDD group.<sup>146</sup> Later studies have confirmed the finding of hippocampal atrophy in both PD groups,<sup>147</sup> but it has not been found to be more severe than in AD patients.<sup>148</sup> A pattern of the severity of hippocampal atrophy has been proposed; (Control < PD < PDD < DLB < AD) suggesting progressive hippocampal volume loss in PD.<sup>149</sup> Atrophy of the amygdala and prefrontal cortex has also been shown in PDD.<sup>147, 150</sup>

In addition studies have reported caudate atrophy in AD and PDD but not PD, suggesting that caudate atrophy is part of a general brain atrophy rather than being regionally specific.<sup>151</sup>

#### *Methods for assessing volumetric and regional changes using unbiased methods.*

The first study to compare whole brain atrophy in PD versus other types of dementia was published in 2004<sup>152</sup> showing that the pattern of grey matter loss in PD and PDD was different from the changes found in AD. They found occipital atrophy in the PDD group and frontal volume loss in PD without dementia. The AD group had more temporal lobe atrophy, including the hippocampus and parahippocampal gyrus compared with the PDD group. No difference in grey matter volume was found between PDD and DLB patients. Their results in PD patients were confirmed, while

the changes found in PDD differed in another study. They did not find occipital atrophy in PDD, rather they found widespread atrophy of the limbic/paralimbic system and the temporal lobe, dorsolateral prefrontal cortex and the parahippocampal gyrus.<sup>153</sup> A third VBM study, which did not include the whole brain<sup>154</sup> found that the hippocampus, thalamus and anterior cingulate are the regions most affected in PDD. Each of these studies involved rather small samples and therefore further studies are needed to confirm their findings and add to the knowledge about grey matter changes in PD.

### *Longitudinal studies*

Few studies have addressed the longitudinal brain changes in PD using imaging.

A study by Paviour showed the annual overall atrophy rate of PD to be 0.6-0.7%,<sup>16</sup> while other investigators found annual percentage loss of 0.8 %.<sup>155</sup> The annual rate of atrophy found in PDD was 1.1 %.<sup>156</sup> In comparison, in DLB the atrophy rate was found to be 1.4 %. In this study the rate of atrophy in DLB was not found to be significantly different from AD.<sup>36</sup> A annual atrophy rate of about 2 % per year has been found in patients with AD.<sup>15</sup> An accelerating atrophy with increasing severity of dementia has been suggested for AD, vascular dementia and DLB<sup>36, 157</sup> but this has not been found in PD/PDD.<sup>156</sup> The pattern of general atrophy rate among the neurodegenerative diseases is thus similar to that of hippocampal atrophy: Control  $\leq$  PD < PDD < DLB < AD.

The studies above did not look at the regional differences in atrophy during the follow up period. One longitudinal VBM study has looked at regional differences in grey matter volume loss in PD patients with and without dementia with disease progression. They found a widespread decrease in limbic and paralimbic regions in non-demented patients. Neocortical volume reduction was the most relevant finding in patients with dementia.<sup>158</sup> Based on this study the authors suggested that the neocortex is the substrate for dementia in PD. This was a small study (19 subjects) and had a short follow up time (25 months). Future studies should include more patients followed for a longer period.

The impact of T2 WMH lesion progression on global cognitive performance has recently been studied. The authors found a 0.07 % increase of WMH volume in PDD patients, but no association with this increase and change in global cognitive performance.<sup>159</sup>

## 2. Hypotheses

1. The frequency and extent of white matter T2 hyperintense lesions (WMH) are associated with dementia in PD.
2. The pattern of grey matter atrophy in PD is different from atrophy in normal ageing, and is associated with the severity of cognitive impairment.
3. Grey matter atrophy in patients with PDD differs from the pattern of atrophy in patients with Alzheimer's disease but not from patients with Dementia with Lewy Bodies.
4. Patients with PD who develop dementia early in the disease diagnosis have more grey matter atrophy than patients who develop dementia late in the disease course.

## **3. Methods**

### **3.1 Subjects**

#### **3.1.1 Patients**

Patients were recruited by doctors in the outpatient clinics of the Department of Neurology, Department of Geriatric Medicine and the Department of Old Age Psychiatry at Stavanger University Hospital in the period from 2001 to 2005. One group was recruited from an ongoing longitudinal study, the Parkinson-study of Rogaland, during their annual follow up (n= 17). Another group consisted of consecutive patients with PD with and without dementia, and patients with Alzheimer's disease and DLB. They were diagnosed as described below.

#### **3.1.2 Controls**

Healthy elderly volunteers were recruited from Stavanger and the surrounding district after information in meetings arranged by local clubs for the retired, meetings for patients and relatives of patients with either dementia or PD. Some volunteers also recruited others and some healthy controls were relatives of my friends or colleagues. They were interviewed for information about medication, education, previous illness including psychiatric illness, and a mini mental state examination (MMSE) was done.<sup>160</sup>

### 3.1.3 Inclusion/exclusion criteria

#### *Inclusion criteria*

Patients were included after all information about the patient was evaluated by an old age psychiatrist (DAa) and the patient was found to fulfil the diagnostic criteria of PD, PDD, AD or DLB (see below), and agreed to participate after the procedure was explained in full. Clinical assessments were, performed by a study neurologist and/or a psychiatrist with experience in neuropsychiatric research. Cognitive assessments were performed by a trained research nurse.

#### *Exclusion criteria*

We excluded patients with any neurological or psychiatric disease other than PD, AD or DLB that could potentially be the cause of their dementia. (e.g. significant cerebrovascular disease, space occupying intracranial lesion, uncompensated hypothyroidism or vitamin B12 deficiency, substance abuse, or other severe psychiatric illness (e.g. schizophrenia).

Focal lesions affecting grey matter led to exclusion from the VBM studies. The MRI scans were thus checked before inclusion of a patient or control person. Those who had structural abnormalities in the brain affecting grey matter were excluded from VBM analysis. Subjects with marked tremor or dyskinesia which interfered with the imaging session were also excluded from the VBM studies because the scans could not be correctly segmented into grey matter, white matter and cerebro spinal fluid (CSF). Some of these patients were included in the study of white matter hyperintensities, since for this visual rating we used T2 weighted images and for these sequences some patient movement was not critical for the evaluation of the lesions.

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## 3.2 Clinical assessments

### 3.2.1 Cognition

A semistructured interview using the DMS IIIR or DSM IV criteria for dementia<sup>103, 161</sup> as a guide was administered. All patients performed a MMSE, a brief and widely used cognitive screening test. The MMSE assesses orientation, learning, short term memory, concentration and higher cortical functions through an interview containing 30 questions/tasks. It is mainly used to differentiate between cognitively intact, and cognitively impaired patients.<sup>160</sup> In addition, patients completed the Dementia Rating Scale<sup>162</sup> or the CAMCOG, the cognitive battery of the CAMDEX.<sup>163</sup> These more comprehensive screening instruments include a more detailed assessment of executive functions than MMSE.

### 3.2.2 Motor and psychiatric measures

**Motor symptoms :** The clinical evaluation of motor symptoms consisted of the motor subscale of the Unified PD Rating Scale (UPDRS),<sup>164</sup> including the Hoehn & Yahr scale.<sup>165</sup>

**Psychiatric symptoms:** Psychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI),<sup>166</sup> a structured care-giver based clinical interview designed to elicit psychiatric symptoms in subjects with brain damage and cognitive impairment. In addition, depression was assessed by a psychiatrist or a research nurse using either the Montgomery Åsberg Depression Rating Scale (MADRS)<sup>167</sup> or the NPI. The main purpose of the psychiatric assessment was two-fold: First to seek information for the diagnosis of DLB, i.e. visual hallucinations, and second to differentiate between depression-induced cognitive impairment and dementia.

### **3.2.3 Supplemental tests**

As part of a routine dementia work up a clinical examination, the history of previous physical or psychiatric diseases was recorded and a physical examination including a neurological examination was performed. Routine blood analysis, including thyroid status, folate and cobalamine status was done on all patients. If there was a clinical indication ECG and supplemental tests like a chest x –ray, or perfusion SPECT of the brain was done. To ascertain the diagnosis of DLB, dopamine transporter imaging was performed on 11 patients with a clinical diagnosis of DLB.

## **3.3 Diagnostics**

### **3.3.1 Diagnosis of PD**

For the diagnosis of PD the diagnostic criteria from Stavanger were used.<sup>78</sup> These criteria are described in detail in section 2.1.5. Patients with clinically significant cognitive impairment at disease onset were excluded, to avoid diagnostic overlap with DLB.

### **3.3.2 Diagnosis of MCI in PD**

A Diagnosis of MCI was made according to a modified version of the criteria proposed by Petersen<sup>89</sup> Impaired performance on neuropsychological tests was defined as 1.5 standard deviations (SD) or more below the mean of the control group. Impaired performance on one, two or all three tests was required for a diagnosis of MCI. The three neuropsychological tests used were; the multiple choice version of the Benton Visual Retention Test, (BVRT)<sup>168</sup> the Judgement of Line Orientation test (JLO)<sup>169</sup> and the Stroop Word Test (SWT).<sup>170</sup>



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Through a caregiver-based interview, information about memory complaints or other cognitive complaints was collected. If cognitive impairment was present, but not serious enough to affect activities of daily living the patients were classified as having MCI.<sup>93</sup>

### **3.3.3 Diagnosis of dementia in PD**

In this study the diagnosis of PDD was made in a patient fulfilling PD criteria who also fulfilled criteria for dementia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM III –R)<sup>161</sup> or (DSM IV) criteria for dementia<sup>103</sup> based on the clinical interview and cognitive assessment, given that no other plausible explanation for the dementia syndrome was found. Patients were examined by a psychiatrist and a research nurse, both experienced in dementia evaluation. Patients with a notable cognitive impairment before or within 1 year after onset of PD were not included in the PDD group.

### **3.3.4 Diagnosis of DLB and AD**

Dementia diagnoses were made after a clinical interview with the patient and a caregiver and supported by neuropsychological testing and supplementary tests including brain imaging to exclude other causes of cognitive decline. AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association (NINCDS – ADRDA) criteria for a diagnosis of probable AD,<sup>129</sup> and probable DLB was diagnosed according to the criteria suggested by the third report of the DLB Consortium.<sup>29</sup>

## 3.4 MRI and image analysis

### 3.4.1 MRI imaging protocol

All patients and healthy elderly volunteers are scanned at Stavanger University Hospital, department of Radiology. The first healthy elderly were scanned in December 2001 in a Phillips gyroscan NT intera, Release 8.1 MRI machine (Philips Medical Systems, Best, the Netherlands). This was later upgraded to release 10.3.1, which was an upgrade of the platform for the operating system, and had no effect on the image quality. All patients and controls are imaged in the same MRI scanner. The following imaging protocol was used; A coronal T1- weighted 3D fast spoiled gradient recalled echo (FSPGR), resulting in 124 coronal slices (repetition time(TR) 12,4 ms, echo time (TE) 4,2 ms, inversion time (TI) 650 ms, matrix 256x192, slice thickness 1,6 mm). In addition the following sequences were acquired (Sagittal T1, axial dual fast field echo (FFE), coronal T2 fluid attenuation inversion recovery (FLAIR). The same head position and imaging protocol was used for all the participants of this study. Our imaging protocol was mainly composed of our standardised protocol for brain imaging with an additional 3D series created after a protocol used for VBM studies in Newcastle General Hospital, England. This led to a total scan time in the machine of ~30 minutes. Because we observed that tremor tended to increase during scanning, we acquired the volumetric sequence first.

### 3.4.2 Visual rating of white matter T2 hyper-intense lesions

Several methods exist for the evaluation of white matter T2 hyperintense lesions in MRI images. We have used the semiquantitative method published by Scheltens in 1993<sup>171</sup> which was one of the first methods after Fazekas<sup>172</sup> to try to give a measure for the load of lesions. I was taught the method of Scheltens by Emma Burton, PhD, Wolfson Research Centre, Institute for Ageing and Health, Newcastle General

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Hospital, UK, who had research experience in using this method. We used the scoring sheets obtained from Newcastle. Two radiologists did the rating of WMH in a blinded manner. A proportion of the images were rated twice during the same session for the evaluation of intra rater reliability. Both raters rated each scan two times with a time interval of 1-2 weeks between ratings. These ratings were used to establish our inter-rater reliability. Through consensus sessions we decided on the results of each patient, also blinded regarding name, diagnosis and age etc. These results were then used in the group analyses for the load of WMH.

Periventricular WMH was scored according to the following criteria;

Absence of lesions give a 0 score,  $\leq 5$  mm lesion = score 1, and score 2 is rated if the lesion is  $> 5$ mm. Hyperintensities exceeding 10 mm were scored as lobar white matter changes.

WMH located in the deep and subcortical white matter was rated according to the following criteria;

Score 0 = no abnormalities

Score 1 = lesions less than 3mm,  $\leq 5$  lesions,

Score 2 = lesions  $< 3$ mm, 6 or more lesions,

Score 3 = lesions 4-10 mm,  $\leq 5$  lesions

Score 4 = same as 3, but 6 or more lesions

Score 5 = lesions  $> 11$ mm,  $> 1$  lesion

Score 6 = confluent lesions.

These rating criteria were applied to regions of the deep white matter (frontal, parietal, occipital, and temporal), and also for the basal ganglia and infra-tentorial foci of WMH.

For the statistical analysis, the SPSS statistics package, version 11.5 (SPSS for Windows, Release 11.50 (6 Sep 2002) SPSS Inc)) was used. Differences between groups on continuous variables were first assessed using bivariate analyses, 1-way analysis of variance (ANOVA) with post hoc Scheffes test to determine group differences. For the non-parametric data a Kruskal Wallis test was used followed by a post hoc Mann Whitney U test, or a chi-square test was used when appropriate. Multivariate regression analyses were performed to assess the relationship between WMH and cognition in PD after controlling for potential confounding variables. These potentially confounding variables included age, sex, education, Hoehn & Yahr stage, cerebrovascular risk factors. For cognition the MMSE score was used as a measure.

This was the first time we used the rating scale of Scheltens,<sup>171</sup> therefore we needed to assess our reliability. Several methods are developed to evaluate reliability. We used the intraclass correlation coefficient (ICC) for the evaluation of intra – and inter rater reliability. The ICC is considered as poor when below 0.4, fair to good between 0.4 and 0.75, and excellent for values above 0.75.<sup>173</sup>

### **5.4.3 Voxel Based Morphometry (VBM)**

In 2000 VBM was introduced as a method for analysing whole brain structural images.<sup>174</sup> Although even prior to this the method had been described.<sup>175</sup>

Morphometric methods attempts to automatically identify neuroanatomical differences, using VBM the analyses are among groups of brains.

To prepare the images for statistical analyses a series of pre-processing steps must be done. The “optimised ” VBM was developed to improve the spatial normalisation of the images, and to better remove non-brain tissue during segmentation.<sup>10</sup> This approach has later been widely used. We have used this approach in the VBM studies included in this thesis, and the description of image pre-processing below refers to this method, which is also shown in the flow chart below (Figure 2).

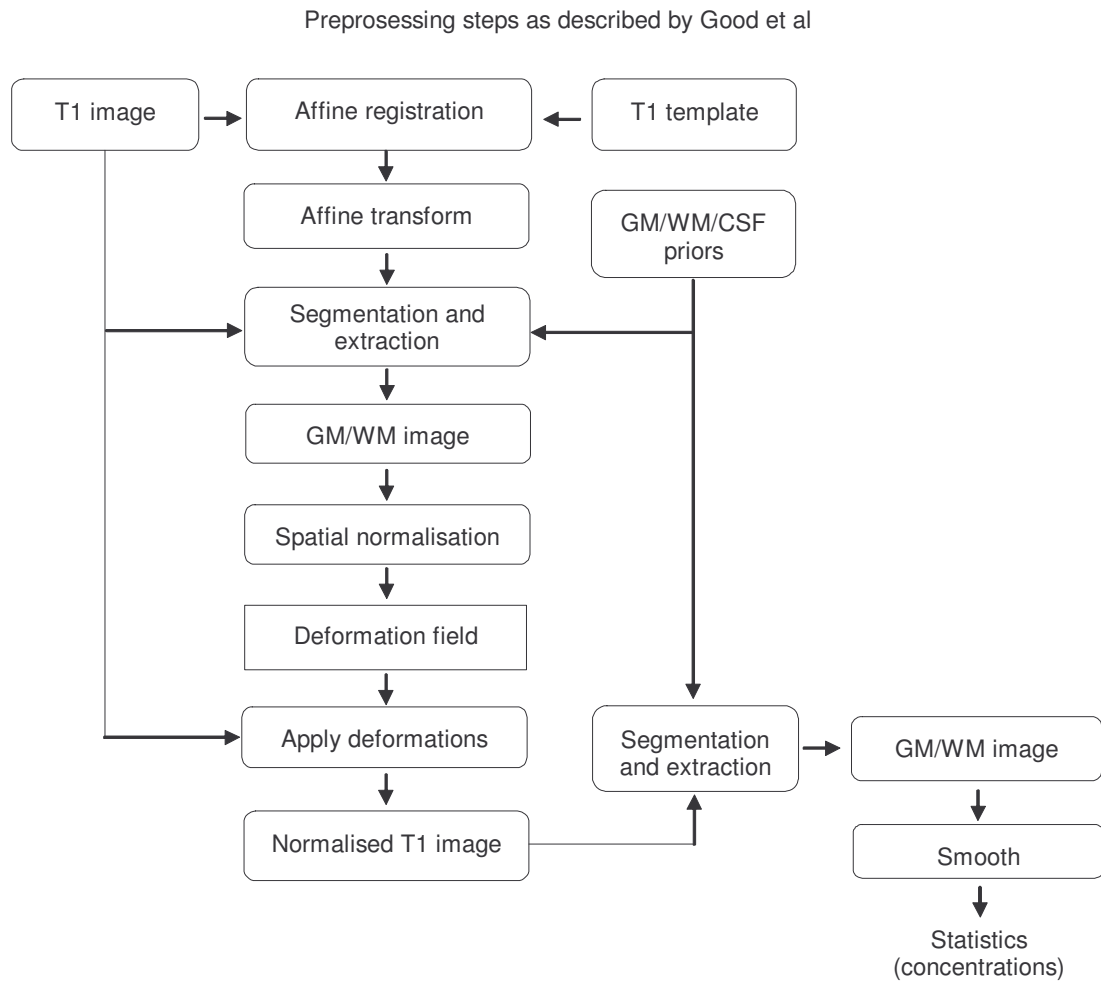


Figure 2. Flow chart describing the steps of pre-processing MR images in VBM.

### *Template creation and pre-processing steps*

For SPM2 customised templates based on all the patients and controls in the study are created. This is important when studying older people with brain atrophy and larger ventricles that make them different from templates provided with the software, which are usually based on younger persons. An example of this is the illustration below, which shows the difference between our customised template and the template from SPM2.

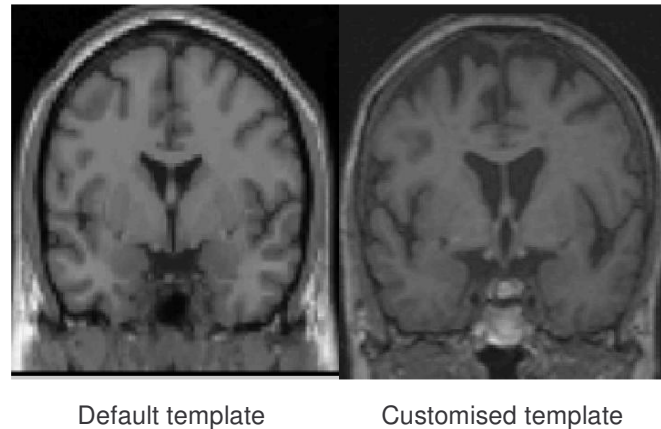


Figure 3. Left: The image shows the default template of SPM based on younger persons Right: the customised template created for this study based on all patients and healthy controls. Note that the size of the ventricles and the width of the sulci are larger in the customised template, based on older persons.

We created a study specific T1 template image (based on all the patients and controls in our study), and a study specific grey matter template/prior probability map. The templates are made by averaging the spatially normalised tissue class images from all included subjects of the study.

The first pre-processing steps include the creation of customised templates. T1 images of each patient were normalised to the T1 Template of SPM2 using an affine only cut-off. After normalising, images were averaged and then smoothed with an 8 mm kernel, creating the T1 template. We then normalised the original images to the customised T1 template using a 25 mm cut off. The normalised images were then segmented and smoothed with an 8 mm kernel. The smoothed grey matter images were then averaged creating the study specific grey matter template. The resolution of the normalised images was high with 1.5mm isotropic voxels. These templates were used in the optimised VBM protocol in the following manner;

The original images were segmented and the grey matter images were normalised to the customised grey matter template. The resulting deformations from the normalisation of grey matter to the grey matter template were used to normalise the original T1 images before the final segmentation. Segmented images were then

smoothed with a 12 mm kernel. The resulting smoothed images were used in the statistical analysis.

Spatial transformations are applied to the images so that they all conform to a standard brain.

Smoothing of the images conditions the data so that they conform more closely to a Gaussian field model, i.e. if you want to make statistical inferences about the regionally specific changes

### *Statistics in VBM*

Voxel based morphometry uses mass-univariate tests for comparing whole brain images. Each voxel is analysed using any standard (univariate) statistical test. That means that there is a single variable at each voxels in the analysis.<sup>176</sup> The resulting statistical parameters from these analyses are assembled into an image –the Statistical Parametric Map (SPM). Standard statistical procedures are done within the framework of the general linear model.

SPM has been used and developed mainly for analysis of functional imaging data, but with VBM structural data can also be analysed. To be able to apply voxel based analysis of imaging data, spatial transformations are applied to the images so that they all conform to a standard brain. This is called normalisation, and this facilitates the reporting of the results in a conventional way. The smoothing of the images conditions the data so that they conform more closely to a Gaussian field model. The Gaussian Random Field determines the number of independent statistical tests which makes it possible to correct for multiple comparisons. The smoothing also renders the data more normally distributed, increasing the validity of parametric statistical tests.<sup>176</sup>

After analysing the images, SPM shows regions where grey matter concentration differs significantly among groups. This is if unmodulated images are analysed.

### *MNI and Talairach space*

The co-ordinates of the significant peak voxels ( i.e. the voxel that has the highest z/T score among the voxels surviving the threshold) are in MNI space. MNI space is an internationally distributed brain template from Montreal Neurological Institute, Canada based on 152 normal brains that is used as standard template brain for SPM2. (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) The co-ordinate system of MNI space differs from another brain template, the Talairach template brain.<sup>177</sup> Both templates can be used to find the localisation of significant voxels in SPM. There are also conversion algorithms from MNI to Talairach space, which I have used in my publications with VBM (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) Having found the localisation of the peak significant voxel using either MNI or Talairach space, the anatomic name of the area where this voxel is situated can be found using either an atlas<sup>177</sup> or using one of several online anatomical atlases e.g. Talairach Daemon.<sup>178</sup>



## 4. Results

Table 1. This overview provides the demographic characteristics of the different patient groups who took part in the present study. All mean values are shown with the standard deviations in parenthesis.

	PD no dementia	PDD	AD	DLB	Healthy controls
Subjects (n)	19/20 <sup>g</sup>	15 /16 <sup>a</sup>	21	18	20
Female (n) / male (n)	11 / 9	5 / 10	16 / 5	9 / 9	10 / 10
Mean age (years)	72.5 (8.5)	73.3 (6.5)	75.1 (9.2)	78.3 (5.8) <sup>b</sup>	73.6 (6)
MMSE score	28.2 (2.1)	19.3 (4.7)	20.0 (5.0)	19.4 (4.9)	29.6 (0.7) <sup>c</sup>
Education (years)	11.0 (3.6)	9.9 (3.6)	8.2 (2.2)	8.3 (2.1)	12.1 (4.3) <sup>d</sup>
Hoehn & Yahr stage	2.4 (0.6)	3 (0.5) <sup>e</sup>	-	2.4 (1.6)	NA
PD duration (years)	12.0 (6.3)	12..3 (7.5)	NA	3,6 (1.8)	NA
PD years prior to dementia	NA	9.9 (7.2)	NA	0.5 (0.5)	NA
Duration of dementia (years)	NA	1.9 (1.1) <sup>f</sup>	2.9 (1.4) <sup>f</sup>	3.7 (2.2) <sup>f</sup>	NA

NA = non applicable

<sup>a</sup> One of the patient included in paper 1 and 2 was excluded from paper 3 and 4 (see discussion).

<sup>b</sup> The DLB group was significantly older than the PDD (p=0.036) and control (p=0.028) groups.

<sup>c</sup> The MMSE score in the PDD group was lower than in the PD without dementia - and control groups.

<sup>d</sup> Education was longer in the control group than in AD (p<0.001 ) and DLB (p=0.002) groups.

<sup>e</sup> A higher H & Y stage in PDD patients than in PD patients was observed.

<sup>f</sup> Dementia duration was shorter in PDD than in AD (p=0.03) and in DLB (p=0.007) groups.

<sup>g</sup> Only 19 PD patients in paper 1, as one was recruited after the analyses for this paper.

## 4.1 Results paper 1

Overall, WMH did not differ between PD and control subjects. However, compared to the non-demented patients, the PDD group had significantly higher level of WMH in the deep white matter ( $p=0.01$ ) and in the peri-ventricular areas ( $p=0.03$ ). WMH in the deep white matter was the only variable which was significantly associated with MMSE score ( $p=0.02$ ) and explained 38 % of the variance in the multivariate linear regression analysis. Our findings suggest that WMH in the deep white matter may to some degree contribute to dementia in PD.

## 4.2 results paper 2

### 4.2.1 PDD versus controls.

Patients with PDD had reductions in grey matter concentration in the limbic lobes (amygdala) and both temporal lobes, compared with the control group. On the left side there was also reduced grey matter density in the frontal lobe, limbic lobe (cingulate and hippocampus) and brainstem red nucleus. On the right side there was reduced grey matter density in the middle occipital gyrus. When we included age, gender and PD duration as covariates in ANCOVA the results were unchanged. There were no areas where controls had more grey matter atrophy than patients with PDD. Using a small volume correction and correcting for multiple comparisons the bilateral reduction of grey matter in the middle temporal gyrus and amygdala, and also the left brainstem red nucleus were significant at  $p \text{ FWE} < 0.05$ .

### 4.2.2 PDD compared with PD without dementia

In PDD there were areas of significant grey matter reduction in frontal lobes, limbic, parietal and temporal lobes bilaterally. On the right side there was also reduced grey

matter density in the pulvinar of the thalamus. The results did not change when age, gender and duration of PD were included as covariates in ANCOVA.

There were no areas where non-demented patients had more grey matter atrophy than patients with PDD.

### **4.2.3 Group comparison of PD with and without MCI.**

PD patients with MCI had reduced cortical grey matter density compared with cognitively intact PD in the left middle frontal gyrus, precentral gyrus and in the left superior temporal lobe and right inferior temporal lobe. The findings were not significant after small volume correction and correction for multiple comparisons. When we analysed with age and gender as covariates in ANCOVA the differences were no longer significant, but when we analysed with duration of PD as covariate the same changes in grey matter were found as in the ANOVA. PD without MCI did not have any areas of more grey matter atrophy than PD with MCI.

## **4.3 Results paper 3**

### **4.3.1 Comparison of PDD and DLB patients**

We found more pronounced cortical atrophy in DLB than in PDD in the temporal, parietal and occipital lobes. Using age as a covariate, there were areas of reduced grey matter in the temporal, parietal and occipital lobes, with increased atrophy in patients with DLB relative to PDD ( $p$  uncorrected  $< 0.001$ ). Changes were found bilaterally in the inferior parietal lobule and in the precuneus. Areas with increased atrophy only in the right hemisphere were in the insula, inferior temporal gyrus and in the lentiform nucleus. Areas of increased atrophy found only in the left hemisphere

were in the angular gyrus, cuneus, and in the superior occipital gyrus (See figure 4). There were no areas with more atrophy in PDD than DLB.

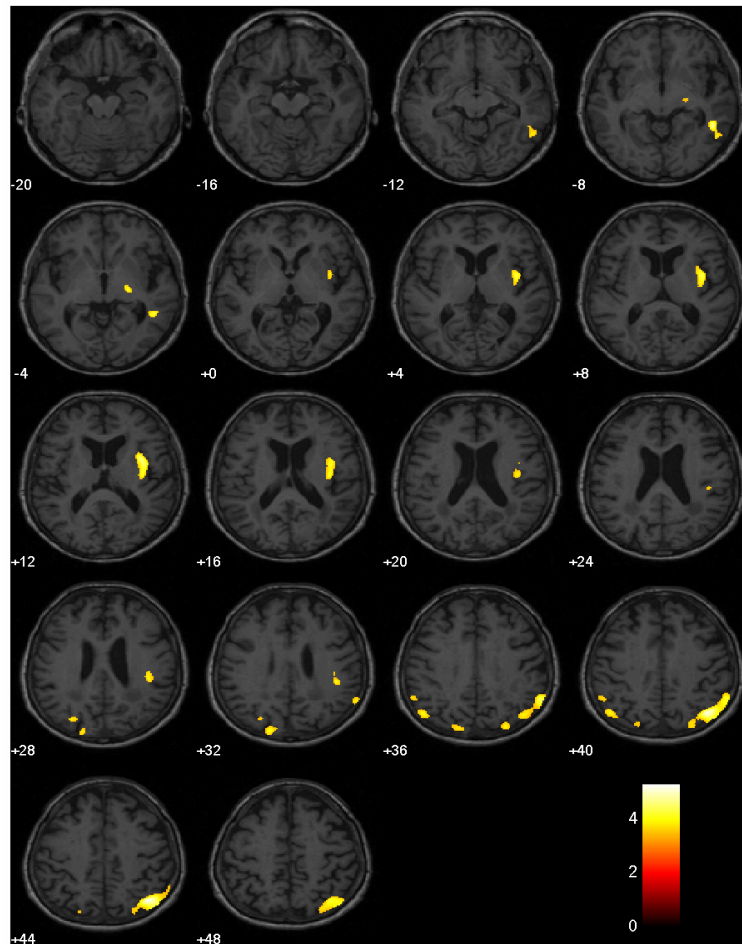


Figure 4. The figure shows the areas of grey matter atrophy in the DLB group compared to the PDD group. These are outlined as yellow areas overlaid on a structural MR image of the brain.

### 4.3.2 Comparison of PDD and AD patients

AD patients had reduced grey matter concentrations in the temporal lobes bilaterally, including the amygdala, compared to PDD. Compared with PDD, AD patients had reduced grey matter concentrations in the amygdala and middle temporal gyrus bilaterally ( $p$  uncorrected  $< 0.001$ ). There were also reduced grey matter

concentrations in the right insula and postcentral gyrus. Left sided grey matter reductions were found in the hippocampus and middle occipital gyrus

#### 4.4 Results paper 4

The early dementia group had areas of more atrophy than the group with late dementia. The areas of reductions in grey matter volume were bilaterally in the medial frontal gyrus, and in the right precuneus, and on the left side in the inferior parietal lobule, superior frontal gyrus and middle temporal gyrus. In the group with long disease duration prior to dementia we found symmetrical grey matter volume reduction in the inferior frontal gyrus bilaterally.

In the unmodulated images, the group with early dementia had more atrophy than the group with late dementia in the striatum (right caudate, left putamen), in the left precentral gyrus, left middle temporal gyrus and in the right red nucleus. The late dementia group had symmetrical reduction in grey matter in the insula bilaterally compared to the early dementia group.

## **5. Discussion**

### **5.1 Main findings**

1. We have shown that white matter hyperintense lesions in T2 weighted series on MRI are not increased in number or extent in the total PD group compared to a control group. However, they were increased in number and extent in PDD compared to non-demented PD subjects.
2. We found atrophy in PDD both in cortical and sub cortical grey matter compared to healthy subjects and non-demented subjects with PD. A novel finding was reduction in grey matter observed in patients with MCI and PD compared to subjects with PD and intact cognition. This finding indicates that even the early cognitive impairment in PD is associated with morphological changes.
3. The overall pattern of grey matter changes in PDD differed from that in AD and DLB, although overlapping regions of atrophy exists. DLB patients have more atrophy in parietal and occipital areas compared with PDD patients.
4. We found that patients with PD who develop dementia early have a different pattern of atrophy than those who develop dementia late in the course.

### **5.2 Methodology**

#### **5.2.1 Patient selection**

Patients for this study were mainly recruited at the outpatient clinics of the department of Old Age psychiatry and the Department of Neurology. Some were recruited from the outpatient clinic of the Department of Geriatric Medicine. These

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are the three main centres of referral for patients with PD and neurodegenerative diseases in our region. Even patients living in nursing homes attend the outpatient clinics, and all patients with PD have their follow up at the Department of Neurology. Compared to other samples of patients with AD, PDD and DLB, our groups are rather similar with regard to age, gender and MMSE,<sup>154, 179</sup> although differences in duration of the disease exist. This suggests that our samples do not differ markedly from the overall populations of patients with AD, DLB and PDD.

One source of selection bias is the fact that the patients had to be able to complete the MRI scanning, and those who had suffered from stroke or had lesions of grey matter were not included. This may have led to the selection of the patients with less vascular disease and tremor. However, also the healthy controls had the same exclusion criteria regarding lesions. For future studies patients with previous stroke could be included since there exists methods to overcome this problem by masking out the lesions, e.g.<sup>180</sup> Patients with marked tremor will be a continuing problem for MRI scanning because it creates movement artefacts.

### *Impact of groups differences*

The groups of patients included differed with regard to age, gender and education (see table 1) which may have influenced our results.

A correlation between age and rate of atrophy has been shown for normal controls,<sup>156</sup> but in AD and DLB groups, variance in the rate of atrophy was more influenced by baseline MMSE than age.<sup>36</sup> In PD patients no association between cognitive scores at baseline or age, and rates of atrophy was found, while atrophy was inversely correlated with UPDRS motor score at baseline in PDD patients.<sup>156</sup> To my knowledge, no gender specific differences of atrophy in PD or DLB have been shown. In healthy elderly, more brain atrophy was found in male than female subjects with ageing.<sup>181</sup> In AD perfusion differences have been shown between male and female patients,<sup>182</sup> and female patients with AD have been found to have less atrophy than men.<sup>183</sup> Increased atrophy has been shown in AD patients with more

education.<sup>183</sup> The association between length of education on atrophy in PD/PDD and DLB is unknown.

In some comparisons where only one of the possible confounds was different, we could include this as a covariate in the analysis. When more than one variable differed, a correction could not be done due to the small groups with low statistical power. The groups were however perfectly matched for MMSE, which is the most important factor. One may argue that since the MMSE is dominated by items assessing memory and language, it may not be the optimal method to match for overall severity of dementia between the groups. However, there is no consensus regarding the optimal method of matching different dementia groups, and the MMSE is the most common variable used for matching groups in dementia studies. In summary, although the groups were well matched regarding level of dementia, a possible bias due to demographic differences cannot be excluded.

### *Cross sectional study*

This study is a cross sectional study. Accordingly, rate of atrophy and causality cannot be firmly established. However, there are good reason to believe that the more severe atrophy observed is causally related to differences in cognition, since several of the affected areas are implicated in cognitive functioning. We had planned to do follow up scans, but many of the patients died not long after the first scanning and we considered the number of surviving patients to be too low. Future studies should scan PD patients at the time of diagnosis and follow them with annual clinical assessment and a follow-up scan after 2-3 years. We have incorporated this design in our new and ongoing study.



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## 5.2.2 Diagnostics

### *Diagnosis of PD*

The clinical diagnosis of PD is not 100% accurate, even by experienced clinicians. However the positive predictive value of the clinical diagnosis of idiopathic PD by movement disorder specialists in the UK was as high 98 % using the UK Brain Bank criteria.<sup>184</sup> In this study, all PD patients were diagnosed by neurologists with a special interest in movement disorders, using explicit criteria for PD.<sup>78</sup> These criteria were designed in order to achieve both high sensitivity (possible PD) and specificity (clinical definite PD). Only patients with a diagnosis of clinical probable or clinical definite idiopathic PD were included in this study. In another project from our hospital, all brains of patients with the clinical diagnosis of PD were confirmed as Lewy body PD by neuropathological examination.<sup>109</sup> Since the same movement disorder specialists are involved in the clinical diagnosis and follow-up of PD in the two projects we expect the diagnostic accuracy to be high.

### *Diagnosis of AD and DLB*

The diagnoses of AD and DLB were based on clinical examination and thus misdiagnosis may occur. We took care to ensure good diagnostic accuracy, however. All patients were assessed using a comprehensive battery of clinical examination, including standardised instruments for cognitive, psychiatric and neurological symptoms. The clinical examinations were performed by experienced and trained clinicians, psychologists, and research nurses and the final diagnoses were made by an experienced clinician based on all available information, including longitudinal follow-up evaluations after the scans were performed (not reported in the papers). For AD, the NINCDS – ADRDA<sup>129</sup> criteria were used, which have shown good diagnostic accuracy with neuropathological diagnosis.<sup>130, 185</sup>

The DLB diagnosis was made according most recent criteria from the DLB Consortium<sup>29</sup>. Only subjects with probable DLB were included. The previous criteria

for DLB by the DLB Consortium have shown low sensitivity in several studies but generally they have provided excellent specificity.<sup>120, 186</sup> Thus, when a diagnosis of DLB is made, it is usually correct. To further ascertain the diagnosis, in some cases a DAT SPECT scan was performed. This examination is shown to have high sensitivity and specificity for a diagnosis of DLB versus AD,<sup>124, 187</sup> and is included as a supportive feature in the revised criteria for DLB<sup>29</sup>. To differentiate between PDD and DLB only subjects with several years of pure movement disorder prior to dementia were included in the PDD group. This is demonstrated in the observation that the mean duration of PD was 12 years, with less than 2 years duration of dementia (see table 1). Due to lack of pathological confirmation of the diagnoses we cannot exclude the possibility that subjects with diagnoses other than DLB and AD were included.

### *Cognitive and neuropsychiatric assessment*

The assessment of cognition varied somewhat between diagnostic groups. This is due to the fact that subjects were recruited from different study populations. However, for all patients, standardised psychiatric and cognitive assessments using scales with established reliability and validity were administered.

### *MCI and dementia in PD*

Criteria for MCI in PD have not yet been validated, and this is a novel concept. We used a modified version of the criteria for MCI in the general population, but our criteria may not have been strict enough. We only had three neuropsychological tests, and impairment only in one test was sufficient to get a classification of MCI. This will lead to a risk for a false positive diagnosis. Nevertheless, patients with PD-MCI had more atrophy than those without MCI. There is a need to establish criteria for MCI in PD and a battery of tests to diagnose MCI in PD. Further support to our diagnosis of MCI was provided in a recent prospective follow-up study, demonstrating that subjects with PD and MCI, diagnosed with the criteria mentioned

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above, had a higher risk of developing dementia than non-demented PD patients without MCI.<sup>93</sup>

Pathological criteria for PDD do not exist, and thus we have to rely on a clinical diagnosis. Clinical criteria for dementia in PD have only very recently been proposed. In our study, we required a firm diagnosis of PD, and dementia according to DSM-III-R or DSM IV. The DSM-III-R was used in the Rogaland PD cohort for consistency throughout the study. Our definition is in accordance with previous recommendations,<sup>120</sup> and does not differ markedly from the recently proposed criteria for PDD (<sup>105</sup>In press). The accuracy of the diagnosis of dementia in PD as well as DLB is supported by the fact that all these patients are followed regularly at the outpatient clinic for participation in other research projects, and a rate of decline in PDD similar to that in AD has been observed.<sup>188</sup>

One patient with PDD was included in the first two papers, but then not included in the last two. We followed these patients over time, and this patient had at one point a variation in test scores that led to discussion about the diagnosis of PDD. Therefore we chose not to include her for the last two papers. She later had test scores indicating that it was correct to include her in the PDD group in the first two papers. In the first paper 19 patients were included in the PD group. This was because the analyses for this study were done before inclusion for the VBM studies were finished.

### **5.2.3 Scanning technique**

MRI scanning techniques are constantly improving and knowledge about the different possibilities increase through studies. When we started this project our main focus was to create a protocol for imaging that was fast enough for the patients to be able to complete. Especially the volumetric sequence is time consuming, but also the most important in our project. Thickness of slices is one of the ways to reduce scanning time. This study has 1.6 millimetre slices, while most studies now use 1x1x1 millimetre isotropic voxels in their protocol. Improved techniques using

parallel imaging allows this to be done in 5-6 minutes now, while our volumetric series took more than 9 minutes. This will improve the image quality of future studies, and might affect the results.

#### **5.2.4 Statistics/VBM**

##### *Group size and choice of method:*

Larger groups are an advantage when studying PD since grey matter loss seems to be less than for AD patients. Very few studies had been published on this topic when we started, and one of the results of this work is that for these patients larger groups should be collected  $n > 30$  or perhaps more. One of the reasons for this could be that PD patients are more heterogeneous both clinically and concerning brain atrophy than AD patients. Another possibility is that there is less annual brain atrophy, as has been shown by longitudinal studies<sup>156</sup> and more sub cortical changes as has been shown pathologically.<sup>117</sup> Larger groups are thus needed, which necessitates either multi-centre studies or longer duration of data collection.

Future research should compare different methods to evaluate grey matter loss/cortical atrophy. We chose VBM based on recommendations, and the availability of experienced users to guide us. It is free software, widely used for imaging studies, and only requires Matlab as a platform, which we could acquire at a low cost. Since then a lot of other imaging software has been used world wide by other investigators in the study of atrophy or regional changes in the brain.<sup>15, 189</sup> Many of these methods are developed on campus and are not freely available to the imaging community, and others are quite expensive to purchase.

##### *Presentation of VBM results*

Modulation of images used for VBM was introduced with the paper by Good et al in 2000.<sup>10</sup> Before that studies using VBM were unmodulated images ie showing

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differences in tissue concentration in structural MRI. Unmodulated results have been confirmed using a different imaging method for the same images e.g.<sup>190</sup>

Modulated images shows regional cerebral volume differences.<sup>10</sup> Many papers only report modulated images in their results, others report both, and some report only unmodulated results. The choice of which results to report is a matter of constant debate in the SPM e-mail list, where researchers post questions, and get answers and viewpoints from colleagues. (<http://www.fil.ion.ucl.ac.uk/spm/support>) Depending on who you ask, the answers may vary. In the papers of this thesis we mostly present unmodulated results. Future studies will have to resolve this question, maybe by neuropathologic confirmation of VBM findings or confirmation of results through other imaging approaches e.g. ROI analyses or other whole brain analyses.

### *Presentation of uncorrected results*

In VBM several hundred thousand voxels may be included in the analysis of two independent groups. Therefore a number of false positive voxels will appear at a statistical threshold of  $p < 0.001$ . To correct for this a Bonferroni correction could be performed, but since neighbouring voxels are not independent, but rather are highly correlated, the Bonferroni correction will be too conservative. (<http://imaging.mrc-cbu.cam.ac.uk/imaging/>) In addition, analyses in VBM are done on smoothed images (so that they are normally distributed), which make the data in each voxel more correlated with the neighbouring voxels. In addition it is not possible to find out how many independent observations there are, therefore the Random Field theory is used to determine the Z-threshold in SPM. Two methods for correction of results exist within the SPM2 software package, family wise error (FWE) and false discovery rate (FDR). FWE is also considered to be a harsh method of correction, and little is published on the use of FDR for correction in VBM studies. There is a continuing debate about this. For future studies of dementia using VBM, providing that there are prior hypotheses about expected changes, uncorrected results can be published,<sup>191</sup> but larger studies are recommended to possibly avoid this issue.

### *Method for the evaluation of WMH*

The method by Scheltens has been validated and used in several studies.<sup>35, 192</sup> It has also been found to have significant agreement with quantitative volumetric measurement of age-related white matter changes,<sup>193</sup> although a similar but smaller, study found the opposite.<sup>194</sup> We chose to use it instead of more recent visual rating methods e.g.<sup>195</sup> which has not become widely used even though they are argued to be better than the older ones.<sup>194</sup> Automated methods have recently been developed for the evaluation of volume of lesions.<sup>196</sup> Our images did not meet the requirements for use in these computerised methods mainly because our FLAIR images were coronal slices and the interslice gap was too big.

The changes in white matter due to ageing have not been the focus of attention in the same way as grey matter changes. With the more widespread use of new imaging techniques like diffusion tensor imaging, I think this will change in the years to come.

## 5.3 Results

### **5.3.1 White-matter lesions**

We found an association with increased load of WMH in PDD compared to PD, which was a novel finding. Increased WMH burden has consistently been found to be associated with impaired cognition and mental slowing,<sup>197, 198</sup> and with other types of dementia.<sup>35</sup> Often, increased WMH are associated with cerebrovascular disease, but this is not found in PD. Our finding of a low level of WMH in PD is in line with previous research showing that risk factors for cerebrovascular disease are reduced in PD compared to controls.<sup>199</sup> A previous record-based study from our group did not find that risk-factors for vascular disease were associated with dementia in PD.<sup>116</sup> Thus other mechanisms may lead to increased WHM in patients with PDD e.g. hypotension or some other common mechanism associated with advanced disease.

The more severe changes found in PDD suggests however that in some patients, WMH may contribute to cognitive impairment.

### **5.3.2 Atrophy**

#### *Relationship of imaging findings and neuropathology in PD*

With whole brain analysis methods like VBM the regional tissue concentration differences throughout the brain can be compared between groups. Neuropathology studies can not work as detailed as this covering all brain regions. Therefore to directly compare atrophy in MRI with load or distribution of Lewy body pathology or Alzheimer pathology in the brain is difficult. This kind of comparison would work better in defined regions of interest of smaller structures, like the hippocampus. Thus whole brain image analysis can indicate which brain regions that can be interesting to study with neuropathology. Additional advantages of imaging are the possibilities to study changes early in course and to follow patients longitudinally, whereas pathology is confined to end-stage disease.

#### *Relationship of atrophy to cognitive changes in PD*

Our grey matter findings are in line with other studies, supporting the hypothesis that morphological changes in the cortex contribute to dementia in PD. The affected areas are previously shown to be involved in cognitive processes. We found grey matter structural changes associated with cognitive impairment in PD, thus cognitive impairment early in PD are not entirely based on functional changes.

#### *Cortical atrophy in PDD compared to DLB and AD*

The regional differences between PDD and AD are consistent with the reported clinical differences in cognitive profile with more executive dysfunction and

impaired attention in PDD and more memory impairment and problems with orientation in AD.<sup>200</sup>

Differences found between DLB and PDD shed light on the ongoing discussion whether DLB and PDD are different diseases or represent stages on a continuum of Lewy body disease. Although clinical and pathological similarities exist, our findings are in line with several recent studies demonstrating different brain changes, which may relate to the subtle clinical differences reported in detailed studies.

### *Clinical implications of findings*

Our findings provide new knowledge in understanding the relationship between cognitive impairment and brain changes in PD, and how these contrast with other related neurodegenerative disorders. Our results support the notion that cognitive impairment is a consequence of morphological brain changes of PD, rather than solely being the effect of long term medication, functional changes, or concomitant AD or vascular pathology. Due to a large inter-individual overlap, and time consuming analyses, current methods for the analysis of structural MRI can provide only limited information in the differential diagnosis of individual patients with dementia. Future studies with new and refined methods, will hopefully provide more diagnostic and prognostic information about the risk of future cognitive decline in patients with PD.



## 6. Conclusions

The results of the studies included in this thesis, gives valuable new information about structural changes accompanying PD both in white matter and grey matter, and our results can give rise to new hypotheses for future imaging studies of PD.

Challenges for future studies will be to design larger longitudinal studies which can follow the MRI brain changes in PD along with the clinical and cognitive functions.

Another challenge will be to find out which symptoms of cognitive impairment that reliably can predict development of dementia, and to find the associated brain changes.

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# Paper I



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## **Visual Rating of White Matter Hyperintensities in Parkinson's Disease**

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### Abstract

Dementia is a common complication of Parkinson's disease (PD), but the cause is incompletely understood. In previous studies, dementia has been associated with an increase in hyperintense lesions in the cerebral white matter. The aim of this study was to explore whether white matter hyperintensities (WMH) on cerebral magnetic resonance imaging (MRI) are associated with dementia in PD. For this study, 35 patients with PD, 16 with dementia (PDD) and 19 without (PDND), and 20 control subjects were recruited. MRI scans of patients and controls were rated for WMH, blind to diagnosis, using the Scheltens visual rating scale. Both bivariate and multivariate statistical analyses were carried out. Cerebrovascular risk factors, education, gender, or age were similar across groups. Compared with the PDND group, the PDD group had significantly higher level of WMH in the deep white matter and in the periventricular areas. WMH in the deep white matter was the only variable that was associated significantly with Mini-Mental State Examination score and explained 38% of the variance in the multivariate linear regression analysis. Our findings suggest that WMH in the deep white matter may contribute to dementia in PD.

Key words: Parkinson's disease; dementia; MRI; white matter hyperintensity; cerebrovascular risk factor; visual rating



# Paper II





## PAPER

# A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry

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To view supplementary tables, see <http://jnnp.bmj.com/supplemental>

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**Background:** Dementia is common in Parkinson's disease, but the underlying brain pathology is not yet fully understood.

**Aim:** To examine the changes in the brain of patients with Parkinson's disease with mild cognitive impairment (MCI) and dementia, using structural magnetic resonance imaging.

**Methods:** Using voxel-based morphometry, the grey matter atrophy on brain images of patients with Parkinson's disease and dementia (PDD; n = 16) and Parkinson's disease without dementia (PDND; n = 20), and healthy elderly subjects (n = 20) was studied. In the PDND group, 12 subjects had normal cognitive status and 8 had MCI. Standardised rating scales for motor, cognitive and psychiatric symptoms were used.

**Results:** Widespread areas of cortical atrophy were found in patients with PDD compared with normal controls (in both temporal and frontal lobes and in the left parietal lobe). Grey matter reductions were found in frontal, parietal, limbic and temporal lobes in patients with PDD compared with those with PDND. In patients with PDND with MCI, areas of reduced grey matter in the left frontal and both temporal lobes were found.

**Conclusion:** These findings show that dementia in Parkinson's disease is associated with structural neocortical changes in the brain, and that cognitive impairment in patients with PDND may be associated with structural changes in the brain. Further studies with larger groups of patients are needed to confirm these findings.

Cognitive impairment and neuropsychiatric symptoms are common in patients with Parkinson's disease, and most patients with Parkinson's disease who survive >10 years after the onset of Parkinson's disease will eventually develop dementia (PDD).<sup>1</sup> The dementia profile of PDD is characterised by executive, visuospatial and attentional impairment, suggesting that frontostriatal changes are the main causes of dementia in patients with Parkinson's disease.<sup>2–3</sup> In addition, a substantial proportion of patients with Parkinson's disease have mild cognitive impairment (MCI) without fulfilling dementia criteria, even early in the course of disease.<sup>4–5</sup> Preliminary evidence suggests that these mild cognitive changes represent the early stages of dementia.<sup>6–7</sup>

The few existing studies of Parkinson's disease using structural magnetic resonance imaging (MRI) techniques have not consistently shown a specific pattern of atrophy in patients with PDD. In a study measuring hippocampal volumes,<sup>8</sup> patients with Parkinson's disease with and without cognitive impairment had more hippocampal atrophy than healthy age-matched controls. Another volumetric study found reduction in volume of both hippocampus and amygdala in patients with PDD and patients with Parkinson's disease without dementia (PDND) compared with normal controls.<sup>9</sup> These findings were confirmed in a recent study using visual rating of the medial temporal lobes. There were no significant differences in hippocampal atrophy in patients with PDD compared with those with PDND.<sup>10</sup> Patients belonging to both Parkinson's disease groups, however, showed more hippocampal atrophy than the control group.

In a study using voxel-based morphometry (VBM), neocortical atrophy has also been reported in patients with PDD. VBM is an automated, unbiased method for voxel-wise comparison of anatomical data from high-resolution MRI. The method is fairly new, introduced in 2000,<sup>11</sup> and compares the density of grey or white matter between groups of individuals. In patients with PDD, reduced grey matter volume in temporal and occipital lobes, right frontal and left parietal lobes were found, together with subcortical areas.<sup>12</sup> Similar but less widespread atrophy was reported in a recent study, which also found hippocampal atrophy in patients with PDD.<sup>13</sup>

Changes in MRI have also been reported in patients with PDND using VBM. Reduced volumes in the right frontal lobe,<sup>12</sup> temporal lobe and hippocampus,<sup>13</sup> and limbic and parahippocampal atrophy have been found.<sup>14</sup>

Two longitudinal studies have recently been published on the rates of atrophy in patients with Parkinson's disease versus controls. Whole-brain atrophy rates were significantly increased in patients with PDD compared with those with PDND and controls.<sup>15</sup> No increase in atrophy in patients with PDND compared with normal controls was found. Another longitudinal study using VBM found progressive decreases in the grey matter volume in limbic, paralimbic and temporo-

**Abbreviations:** ANCOVA, analysis of covariance; ANOVA, analysis of variance; FWE, family-wise error; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PDD, Parkinson's disease with dementia; PDND, Parkinson's disease without dementia; SPM, statistical parametric mapping; SVC, small volume correction; VBM, voxel-based morphometry

**Table 1** Characteristics of participants

	PDD	PDND	Controls	p Value
Participants	16	20	20	NA
Female/male	6/10	11/9	10/10	0.56
Mean age	73.5 (6.5)	72.5 (8.5)	73.3 (6.3)	0.9
Mean MMSE score	19.4 (4.6)	28.2 (2.1)	29.6 (0.7)	<0.001*
Mean education (years)	10.2 (3.6)	11.0 (3.6)	12.1 (4.3)	0.31
Mean H&Y stage	3.0 (0.6)	2.4 (0.6)	NA	0.008†
Mean duration of PD (years)	12.3 (7.5)	12.0 (6.3)	NA	0.38

H&Y stage, Hoehn & Yahr stage; MMSE, Mini Mental State Examination; NA, non-applicable; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PDND, Parkinson's disease without dementia.

\*Significantly lower mean value in PDD compared with PDND and controls.

†Higher H&Y stage in PDD compared with PDND.

Standard deviation is given in parentheses.

occipital regions in patients with PDND, and, neocortical grey matter loss was found in patients with PDD.<sup>16</sup>

No MRI studies of patients with Parkinson's disease and MCI have, to our knowledge, yet been reported. Thus, whether structural changes exist in patients with Parkinson's disease and MCI, and whether the previously reported cortical and hippocampal atrophy is present in all patients with PDND or only in a subgroup with MCI is not clear.

To explore these issues, we investigated structural brain MRIs of patients with Parkinson's disease with and without MCI and dementia and healthy elderly volunteers using VBM.

We hypothesised that patients with PDD would have more pronounced cortical atrophy than controls and patients with PDND, and that those with Parkinson's disease with MCI would show more atrophy than those with Parkinson's disease with intact cognition. On the basis of the cognitive profile of PDD and previous MRI studies, we further hypothesised that these changes in the brain would involve frontal, limbic and temporal lobes, including the medial temporal cortex.

## PATIENTS AND METHODS

### Case-finding and diagnostic procedures

The patients were recruited from an ongoing epidemiological study (sample 1).<sup>17</sup> In addition, consecutive patients referred to outpatient clinics of the Department of Neurology or the Department of Geriatric Psychiatry, Stavanger University Hospital, Stavanger, Norway, were included (sample 2). A diagnosis of Parkinson's disease was made by a neurologist, according to explicit criteria.<sup>18</sup> The minimum requirement for a diagnosis of Parkinson's disease was at least two of the cardinal signs (akinesia, rigidity, resting tremor or postural abnormalities) and a moderate response to a dopaminergic agent. Staging of Parkinson's disease was carried out according to the Hoehn and Yahr scale.<sup>19</sup> Sample 1 has been followed up prospectively with a 4-year interval in 1993, 1997 and 2001 and

then assessed annually. The autopsy diagnosis in the first 22 patients, 2 of whom participated in the current MRI study, was consistent with a diagnosis of Lewy-body Parkinson's disease.<sup>20</sup>

### Diagnosis of dementia

The diagnosis of dementia was based on a semistructured interview with the patient and a care giver following the Diagnostic and Statistical Manual of Mental Disorders-III-R criteria for dementia<sup>21</sup> (sample 1) or Diagnostic and Statistical Manual of Mental Disorders IV (sample 2).<sup>22</sup> All patients completed the Mini-Mental State Examination (MMSE).<sup>23</sup> In addition, sample 1 completed the Dementia Rating Scale.<sup>24</sup> Patients with an MMSE score  $\geq 16$  completed a neuropsychological battery consisting of (1) the multiple-choice version of the Benton Visual Retention Test,<sup>25</sup> the Judgement of Line Orientation Test<sup>26</sup> and the Stroop Word Test.<sup>27</sup> These neuropsychological tests were selected to identify cognitive deficits typically occurring in Parkinson's disease,<sup>28</sup> and were as much as possible independent of motor abilities. The tests were administered by a neuropsychologist, and scored according to conventional procedures outlined in the test manuals. A detailed description of the test battery is made elsewhere.<sup>5</sup> Sample 2 completed the Cambridge Cognitive Examination, the cognitive section of the Cambridge Mental Disorders of the Elderly Examination.<sup>29</sup> To qualify for a diagnosis of dementia, the interview and the cognitive rating scales had to be compatible with a diagnosis of dementia. The final diagnosis was made by one of the authors (DA) on the basis of all available information except the MRI scan. Further details of the clinical assessment of sample 1 can be found in Tandberg *et al.*<sup>30</sup> and Aarsland *et al.*<sup>31</sup> Psychiatric symptoms were assessed using the Neuropsychiatric Inventory<sup>32</sup> in all patients with Parkinson's disease with cognitive impairment to detect cognitive impairment secondary to psychiatric syndromes such as depression.

**Table 2** Characteristics of patients with Parkinson's disease without dementia

	MCI	No MCI	p Value
Participants	8	12	NA
Female/male	5/3	6/6	0.47*
Mean age (years)	77.4 (7.4)	69 (8)	0.057
Mean MMSE score	25.9 (2.9)	29.4 (0.5)	0.007
Mean education (years)	8.4 (1.5)	12.5 (3.6)	0.013
Mean H&Y stage	2.6 (0.8)	2.3 (0.4)	0.52
Mean duration of PD (years)	10.8 (3.7)	14.1 (7.1)	0.52

H&Y stage, Hoehn and Yahr stage; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NA, non-applicable; PD, Parkinson's disease.

\*Fishers exact test.

Standard deviation is given in parentheses.

### Mild cognitive impairment

MCI was defined according to the criteria proposed by Petersen *et al*<sup>33</sup>: impaired performance (ie,  $\geq 1\frac{1}{2}$  standard deviation (SD) below the mean of a control group matched with the PDND group for age, sex and education) on one, two or all three neuropsychological tests. In addition, information regarding memory problems or other subjective cognitive deficits was gathered by means of the care giver-based dementia interview and the mentation item from the mental subscale of Unified Parkinson Disease Rating Scale.<sup>34</sup> MCI was diagnosed if cognitive impairment on testing and from the interview was not severe enough to affect activities of daily living, and thus the criteria for dementia were not met. For a more detailed description of the MCI diagnosis, see Janvin *et al*.<sup>7</sup>

### Control group

Healthy elderly controls were recruited from the local Parkinson interest group, elderly people from local clubs for retired people and from relatives of patients with Parkinson's disease or other neuropsychiatric disorders. The controls had no active neurological or psychiatric disorder. They had no cognitive deficits, and were not taking drugs that could affect their cognition. A minimum MMSE score of 28 was required. Written consent was obtained from all patients and controls, and the study was approved by Regional Committee for Medical Research Ethics, University of Bergen, Bergen, Norway.

### Exclusion criteria

Patients with other known brain disorders apart from Parkinson's disease, Parkinsonism due to antipsychotic or other drugs, or a history of schizophrenia or bipolar disorder were not included. To avoid inclusion of patients with dementia with Lewy bodies, patients with clinical signs of cognitive impairment during the first year after onset of Parkinson's disease were excluded according to the International Consensus Criteria.<sup>35</sup> We checked the standard sequences of the MRI scans (T1, dual fast field echo (FFE) and T2 flair) before the inclusion of a patient or control, and those who had structural abnormalities in the brain affecting the grey matter were excluded from VBM analysis. Patients with marked tremor, which interferes with the imaging session and produces movement artefacts, were also excluded.

### Magnetic resonance imaging

The subjects were scanned at the Department of Radiology, Stavanger University Hospital, in the period from December 2001 to June 2005, in a 1.5-T Phillips Gyroscan NT intra release 8.1 (Phillips Medical Systems, Best, The Netherlands). The software of the machine was upgraded in the autumn of 2003, to Release 10. This has not affected the quality of the images, which has been stable throughout the study. We performed a structural MRI series with a T1-weighted three-dimensional fast, spoiled gradient recalled echo (TR 12.4 ms, TE 4.2 ms, TI 650 ms, matrix 256×192, slice thickness 1.6 mm).

### Image analysis

Standard sequences (T1, dual FFE, T2 flair) were examined to visualise focal lesions of grey matter that might lead to exclusion of patients from the study. These sequences were not used for statistical image analysis in this study, but results on visual rating of white matter hyperintensities can be found in Beyer *et al*.<sup>36</sup>

### VBM preprocessing

The optimised VBM protocol of Good *et al*<sup>37</sup> was applied for the preprocessing of the images, including creating a study-specific T1 template image (based on all the patients and controls in our

study) and a study-specific grey matter template/prior probability map. The preprocessing steps have already been described in detail by others.<sup>12–37</sup> The first preprocessing step includes the creation of the customised templates. T1 images of each patient were normalised to the T1 template of statistical parametric mapping (SPM)2 using an affine only cut-off. After normalising, images were averaged and then smoothed with an 8 mm kernel, creating the T1 template. Normalising the original images to the customised T1 template using a 25 mm cut-off created the customised grey matter template. The normalised images were then segmented and smoothed with an 8 mm kernel. The smoothed grey matter images were then averaged, creating the study-specific grey matter template. These templates were used in the optimised VBM protocol in the following manner: the original images were segmented and the grey matter images were normalised to the customised grey matter template. The resulting normalisation parameters were used to normalise the original T1 images before the final segmentation. Segmented images were then smoothed with a 12 mm kernel. The resulting smoothed images were used in the statistical analysis.

### Statistical analyses

The smoothed images from the preprocessing steps were analysed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK (<http://www.fil.ion.ucl.ac.uk/spm>)). Smoothed images that are used to show regional changes in grey matter, above that occurring globally, are referred to as unmodulated images.

The following VBM analyses of grey matter were performed: for unmodulated images, we statistically assessed differences in grey matter between groups using one-way analysis of variance (ANOVA). We also performed analyses where age, sex and duration of Parkinson's disease were included as covariates in analysis of covariance (ANCOVA). For all analyses, the whole brain was analysed. As we had a prior hypothesis about the localisation of change, significance levels for t statistics were set at  $p < 0.001$  uncorrected. All the results are presented at the voxel level.<sup>38</sup> In addition, we performed a small volume correction (SVC) using the WFU PickAtlas software V.2,<sup>39,40</sup> and corrected for multiple comparisons using p family-wise error (FWE)  $< 0.05$ . The SVC reduces the number of voxels entering the statistical computation by defining a region of interest. The correction for multiple comparisons is based on the number of voxels in the region of interest.

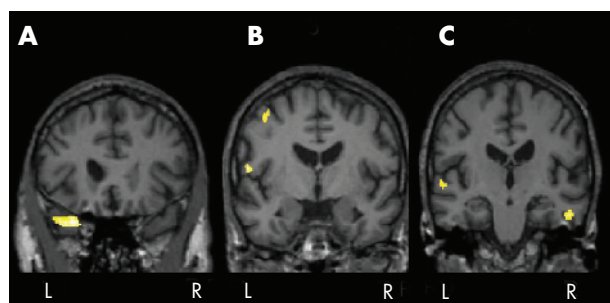
The coordinates obtained for the peak voxels—that is, the anatomical location with maximal grey matter loss in each significant cluster—were transferred into Talairach space using Matthew Brett's mni2tal routine (<http://www.mrc-cbu.cam.ac.uk/imaging/index.html>).

The anatomical locations of the peak voxels were then found using The Talairach Daemon Client.<sup>41</sup> The results given by the Talairach Daemon were verified from the *Co-planar stereotaxic atlas of the human brain*.<sup>42</sup> Data were analysed on a personal computer using Windows XP Professional V.5.1 and Matlab 6.5.2 and SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>).

Group statistics were analysed using SPSS for Windows V.12.0.1. Differences between groups on continuous variables with normal distribution were assessed using one-way ANOVA with retrospective Scheffe's test to determine group differences. For the non-parametric data a Kruskal–Wallis test was used, followed by a retrospective Mann–Whitney U test, or a  $\chi^2$  test, when appropriate, using  $p < 0.05$  as significant.

### RESULTS

A total of 56 participants were included: PDD (sample 1,  $n = 3$ ; sample 2,  $n = 13$ ), PDND (sample 1,  $n = 14$ ; sample 2,  $n = 6$ )



**Figure 1** Areas of reduced grey matter in the analysis of unmodulated images of patients with Parkinson's disease with mild cognitive impairment (MCI) compared with those who had no cognitive impairment. The figure shows areas of regional changes in grey matter, above that occurring globally, in patients with Parkinson's disease without dementia and MCI. Significant changes are found in the (A) left superior temporal gyrus, (B) left frontal lobe (precentral gyrus) and (C) right temporal lobe (inferior temporal gyrus) and left temporal lobe (superior temporal gyrus) at  $p < 0.001$  uncorrected. L, left side, R, right side.

and normal controls ( $n = 20$ ). Table 1 presents the demographic and clinical characteristics. We found no significant differences in age, education, duration of illness or sex between the three groups. As expected, patients with PDD had a lower MMSE score and a higher Hoehn and Yahr stage than those with PDND. The mean duration of dementia in the PDD group was 1.7 (SD 0.8) years. In the PDND group, 12 subjects had normal cognitive status and 8 had MCI (5 were impaired on 1 test, 2 on 2 and 1 on all 3 tests; table 2). The patients with MCI had a lower mean duration of education ( $p = 0.013$ ; table 2) and a non-significant trend towards higher age ( $p = 0.057$ ). As expected, patients with MCI had a lower MMSE ( $p = 0.007$ ) compared with those with a normal cognitive status (table 2).

Eight patients were recruited for MRI, but not included in the study. Two patients became agitated during the scanning, two patients had movement artefacts, three had clinically unrecognised structural lesions, such as a cortical infarction or a post-traumatic lesion, and one patient could not be scanned in the correct head position. One control was excluded because of claustrophobia. Mean (SD) time between clinical testing and MRI scanning was 69 (19.8) days for sample 1 and 40 (23.1) days for sample 2.

### MRI changes in patients with PDND and PDD

#### Patients with PDD versus controls

Patients with PDD had reductions in grey matter concentration in the limbic lobes (amygdala) and both temporal lobes, compared with the controls. On the left side, there was also reduced grey matter density in the frontal lobe, limbic lobe (cingulate and hippocampus) and brain stem red nucleus. On

the right side, there was reduced grey matter density in the middle occipital gyrus (see supplemental table A at <http://jnnp.bmjournals.com/supplemental>). When we included age, sex and Parkinson's disease duration as covariates in ANCOVA, the results were unchanged. We found no areas where controls had more grey matter atrophy than patients with PDD. Using an SVC and correcting for multiple comparisons, the bilateral reduction in grey matter in the middle temporal gyrus and amygdala, and also in the left brain stem red nucleus, was significant at  $p_{FWE} < 0.05$ .

#### Patients with PDD compared with those with PDND

In patients with PDD, there were areas of marked grey matter reduction in the frontal lobes, limbic, parietal and temporal lobes bilaterally. On the right side, there was also reduced grey matter density in the pulvinar of the thalamus (see supplementary table B at <http://jnnp.bmjournals.com/supplemental>). The areas surviving SVC with correction for multiple comparisons using FWE are marked with an asterisk in the table. The results did not change when age, sex and duration of Parkinson's disease were included as covariates in ANCOVA.

There were no areas where patients with PDND had more grey matter atrophy than patients with PDD.

#### Patients with PDND compared with normal controls

Patients with PDND had a cluster of reduced grey matter in the right superior temporal gyrus compared with normal controls. The result was unchanged when covariates were included, but was not significant after SVC and correction for multiple comparisons. Normal controls did not have any areas of more grey matter atrophy than PDND.

#### Group comparison of patients with PDND with and without MCI

Patients with Parkinson's disease with MCI had reduced cortical grey matter density compared with those with cognitively intact Parkinson's disease in the left middle frontal gyrus, precentral gyrus, left superior temporal lobe and right inferior temporal lobe (fig 1, table 3). The findings were not significant after SVC and correction for multiple comparisons. When we analysed with age and sex as covariates in ANCOVA, the changes were no longer present, but when analysed with duration of Parkinson's disease as covariate the same changes in grey matter were found as in the ANOVA. Patients with Parkinson's disease without MCI did not have any areas of more grey matter atrophy than patients with Parkinson's disease with MCI.

### DISCUSSION

We studied grey matter changes in patients with Parkinson's disease with MCI and dementia using structural MRI and VBM.

**Table 3** Anatomical location of areas of reduced grey matter in patients with Parkinson's disease with mild cognitive impairment compared with no cognitive impairment

Cluster size	Voxel level	Anatomical location	x	y	z	T score
420	L	Superior temporal	-30	21	-28	5.31
103	L	Precentral gyrus	-58	-5	11	4.75
75	R	Inferior temporal	55	-20	-21	4.49
79	L	Superior temporal	-62	-22	3	4.27
107	L	Precentral gyrus	-42	-5	56	4.08
	L	Middle frontal	-39	3	58	3.74

L, left; R, right.

The coordinates x, y and z refer to the anatomical location, indicating standard stereotactic space as defined by Talairach and Tournoux.<sup>42</sup> Only clusters  $> 200 \text{ mm}^3$  are included. In this table, all reported voxels are  $p$  uncorrected  $< 0.001$ .

The main finding was the widespread reduced density of cortical grey matter in patients with PDD compared with controls and patients with PDND. Frontal, temporal and limbic lobes, including the medial temporal cortex, were affected in patients with PDD, in accordance with our hypothesis. They also had reduced grey matter concentration in the parietal cortices and the right thalamus when compared with patients with PDND. We found grey matter reduction in the hippocampus (right side) and amygdala (bilaterally) in the PDD group. This confirms the results from previous studies with different methods of MRI analysis.<sup>9–12</sup>

Our results are similar to but not identical with, those reported in a previous study using VBM.<sup>12</sup> In that study, patients with PDD showed bilateral frontal, temporal and occipital grey matter volume loss relative to controls, whereas the changes between PDND and PDD groups were confined to the occipital lobes. There are several possible explanations for these differences. The patients with PDD in the two studies were comparable with regard to age and overall severity of dementia as measured with the MMSE, but the PDD group in the previous study had a markedly shorter disease duration compared with our cohort. Thus, that cohort had a later age at onset of Parkinson's disease, and an earlier and more rapid cognitive decline than our cohort. Dementia early in the course of Parkinson's disease has often been shown to represent other brain disorders,<sup>43</sup> and preliminary data indicate differential changes in the brain underpinning dementia occurring within the first 10 years after the onset of Parkinson's disease compared with after >10 years.<sup>44</sup> Different underlying changes in the brain related to differences in the time to develop dementia may therefore explain the MRI findings in these two studies. Another possible explanation is the higher statistical power in the previous study due to a larger sample size ( $n = 83$ ) than in our study ( $n = 56$ ). This hypothesis is supported by a recent report finding less widespread neocortical atrophy with an even smaller sample size ( $n = 42$ ).<sup>13</sup> The small sample size of the groups studied limits the possibility of generalising from these results.

Another potential explanation for the contrasting results among these studies may be the differential selection process of patients; about half of our sample was recruited from a community-based study and the rest from patients referred to outpatient clinics, compared with samples based on only referrals to specialist clinics in the other studies. In line with this, the patients with Parkinson's disease in the Spanish study<sup>45</sup> were younger than the patients in our study. There were also differences in sex distribution, although sex-specific differences in MRI in Parkinson's disease have not been shown. Finally, information of the detailed cognitive profile in the two studies was not available. Despite similar overall dementia severity, differences in the cognitive profile—for example, relative severity of frontal, visuospatial and memory type cognitive disturbances—were observed in groups of patients with Parkinson's disease and PDD,<sup>4–46</sup> which may be related to differences in the severity and distribution of cortical atrophy.

As motor disease severity in Parkinson's disease was greater in the PDD group than the PDND group, the differences observed in cortical atrophy may be merely associated with the different motor disease stage. When controlling for Hoehn & Yahr stage in the analysis of patients with PDND versus those with PDD, we still found the same areas of atrophy. This indicates that our findings cannot be explained entirely by the increased motor disease severity in PDD.

A novel finding was the cortical grey matter reduction in patients with PDND with MCI compared with patients with Parkinson's disease with normal cognition.

Several studies have shown that cognitive impairment, in particular executive and attentional dysfunction, is common even in patients with PDND.<sup>4–46</sup> In contrast with a previous study,<sup>12</sup> which reported widespread cortical changes also in patients with PDND, we found only minimal differences in patients with PDND compared with controls. However, when the patients with PDND were classified into groups with or without MCI, we found areas of grey matter atrophy in the MCI group compared with the cognitively intact group. These results were in accordance with our hypothesis.

In this study, the grey matter atrophy in Parkinson's disease with MCI was found in the ANOVA, and in the ANCOVA with Parkinson's disease duration as covariate, whereas the differences were not present when age was entered as a covariate. This could be due to the low power with 8 v 12 patients in the compared groups, and even lower degrees of freedom with a covariate in the analysis, or that atrophy is due to the age difference between groups. However, as changes were found in some of the same areas as in the PDD group, but less widespread, this may indicate that MCI in Parkinson's disease is associated with cortical atrophy and may represent early dementia. Similar results from other studies using VBM and volumetry in subjects without Parkinson's disease with MCI support our view. Atrophy in areas that are involved early in Alzheimer dementia, such as the hippocampus and temporal neocortex,<sup>47–48</sup> and in the hippocampal region and cingulate gyri<sup>49</sup> has been reported.

The main limitations of this study is the small sample size, particularly of patients with Parkinson's disease with MCI, the possibility of selection bias, as a proportion of the patients with Parkinson's disease were referrals to outpatient hospital clinics, and the lack of pathological confirmation of the clinical diagnosis of Parkinson's disease in most cases.

Future imaging studies and clinicopathological studies with adequate sample size are needed to further explore the relationship between specific cognitive deficits and the underlying brain correlates in Parkinson's disease, and to see whether MRI can contribute in the early diagnosis of dementia in Parkinson's disease.

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# **Paper III**





Beyer, M. K.; Larsen, J. P; Aarsland, D., Grey matter atrophy in Parkinson's disease with dementia and Dementia with Lewy Bodies. Preprint. Published in *Neurology* 2007;69:747-754. Copyright © 2007 American Academy of Neurology. Abstract only. Full-text not available due to publisher restrictions.

## **Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies**

Mona K. Beyer, MD; Jan P. Larsen, MD, PhD; Dag Aarsland, MD, PhD

### **ABSTRACT**

**Background:** The nosologic relationship between dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD) is continuously being debated. We conducted a study using voxelbased morphometry (VBM) to explore the pattern of cortical atrophy in DLB and PDD.

**Methods:** Seventy-four patients and healthy elderly were imaged (healthy elderly n= 20, PDD n =15, DLB n = 18, and Alzheimer dementia [AD] n = 21). Three dimensional T1-weighted MRI were acquired, and images analyzed using VBM. The following diagnostic criteria were used: criteria proposed by the third report of the DLB Consortium for DLB, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association criteria for AD, and Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for dementia in PDD.

**Results:** Overall dementia severity was similar in the dementia groups. We found more pronounced cortical atrophy in DLB than in PDD in the temporal, parietal, and occipital lobes. Patients with AD had reduced gray matter concentrations in the temporal lobes bilaterally, including the amygdala, compared to PDD. Compared to DLB, the AD group had temporal and frontal lobe atrophy.

**Conclusion:** We found that despite a similar severity of dementia, patients with dementia with Lewy bodies (DLB) had more cortical atrophy than patients with Parkinson disease with dementia (PDD), indicating different brain substrates underlying dementia in the two syndromes. Together with previous studies reporting subtle clinical and neurobiologic differences between DLB and PDD, our findings support the hypothesis that PDD and DLB are not identical entities, but rather represent two subtypes of a spectrum of Lewy body disease.

# **Paper IV**



## Grey matter atrophy in early versus late dementia in Parkinson's disease.

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## **Abstract**

### **Background**

There is considerable heterogeneity within patients with Parkinson's disease (PD) regarding time from onset of PD to dementia. Age, mild cognitive impairment and severity of parkinsonism are the main factors influencing the time from onset of disease to dementia in PD. We compared grey matter atrophy using magnetic resonance images (MRI) of patients with PD who developed dementia early and late in the disease course.

### **Methods**

Fifteen patients diagnosed with PD who developed dementia before (n=9) or after (n=6) 8 years duration of PD were included. They were diagnosed according to established criteria for PD and dementia, and rated using standardized scales assessing motor, cognitive and psychiatric symptoms. We then compared MRI of the groups with Voxel Based Morphometry (VBM).

### **Results**

Despite similar age and severity of dementia and parkinsonism, the group with early dementia had more atrophy than the group with late dementia in some areas (the striatum (right caudate, left putamen), in the left precentral gyrus, left middle temporal gyrus and in the right red nucleus). The late dementia group had symmetrical reduction in grey matter in the insula bilaterally compared to the early dementia group.

### **Conclusion**

Our results indicate that the early development of dementia in PD is associated with more severe degeneration of cortical and sub-cortical structures.

**Key words:** Parkinson's disease, dementia, MRI, atrophy.

## Introduction

Recent longitudinal studies indicate that the majority (up to 80%) of older patients with Parkinson's disease (PD) also eventually develop dementia.[1] Parkinson's Disease Dementia (PDD) is a distressing condition characterized by parkinsonism, executive, visuo-spatial and attentional impairment.[2, 3] Visual hallucinations and REM sleep behavior disorder (RBD) are also common in PDD,[4, 5] [6] resulting in major difficulties for clinical management.

Studies of the neuropathology and neurochemistry of PD have shown that Lewy bodies are mainly located in the substantia nigra and other brainstem nuclei,[7] with a resulting extensive loss of striatal dopaminergic neurons[8] and neocortical cholinergic innervation[9, 10] which are greater in patients with concurrent cognitive impairment. The consensus from neuropathological studies focusing upon PDD is that diffuse cortical Lewy bodies are the main substrate of dementia in these patients.[11, 12] Limbic Lewy bodies were thought to be associated with dementia in PD,[13] but a later study has shown an association between limbic lewy bodies and visual hallucinations and no relation to severity or duration of dementia.[14]

There is considerable heterogeneity within PD patients[15] including time from onset of PD to dementia. The mean duration of PD from onset to development of dementia is 10-12 years, but some develop dementia after 6-7 years or less, while others develop dementia after 15 years or more.[16] Age, mild cognitive impairment and severe parkinsonism are the main factors influencing the time from onset of disease to dementia in PD.[17, 18] Visual hallucinations and male gender have also been identified as clinical predictors of PDD.[19] In particular, motor symptoms other than tremor, such as postural and gait disturbances, have been found to be associated with a shorter time to dementia,[20] indicating an association between pathologies underlying cognition and certain motor symptoms.

A recent neuropathological study reported different brain changes underlying dementia occurring early (ie before 9.5 years after onset of PD) compared to later in the course of the disease.[21] Imaging studies have found more cortical atrophy in PDD versus PD.[22, 23] However, to our knowledge, no study has explored whether pattern and degree of atrophy differs in PD patients with early and late

occurring dementia. Such knowledge would aid in the understanding of the etiology of dementia in PD, the clinical heterogeneity of PD, and to the relationship of PDD and dementia with Lewy bodies (DLB).

We compared brain MRI from two groups of PDD where one group developed dementia early in the course ie. before or including 8 years of PD duration, while the second group developed dementia after more than 8 years of PD duration. Our hypothesis was that patients with dementia early in the disease course, have more atrophy than patients with dementia occurring late.

## **Methods**

### **Case-finding and diagnostic procedures**

Fifteen patients with PDD referred to the Department of Neurology, and the Department of Geriatric Psychiatry at Stavanger University Hospital, Norway comprised the study group.

### **Diagnosis of PD and dementia**

A diagnosis of PD was made by a neurologist specialized in movement disorders according to explicit criteria.[24] A minimum requirement for a diagnosis of PD was two or more of the four cardinal signs for PD (i.e. resting tremor, bradykinesia, rigidity, and postural instability), and the response to a dopaminergic agent should be at least moderate.

Diagnosis of PDD was made in a patient fulfilling PD criteria who also fulfilled criteria for dementia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for dementia due to PD[25]. Patients were examined by a psychiatrist and a research nurse both trained in neuropsychiatry. A clinical medical examination and routine laboratory tests were also performed. To qualify for a diagnosis of dementia, the interview and the cognitive rating scales had to be compatible with a diagnosis of dementia. Patients with a notable cognitive impairment before or within 1 year after onset of PD were not included, to exclude patients with DLB.[26]. Staging of PD was carried out according to the UPDRS motor sub-scale[27] and Hoehn & Yahr scale.[28] All patients performed Mini mental state examination (MMSE), a brief cognitive screening test[29]. In addition, patients completed the Dementia Rating Scale[30] or the CAMCOG, the cognitive battery of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX).[31]

Age at diagnosis of PD and time of onset of clinically significant cognitive impairment indicating dementia was based on a detailed interview of the patient or caregiver. In addition case-notes from the departments were carefully studied. This assessment was done independent of and blind to the imaging results. The time from PD diagnosis to onset of dementia varied from 3 to 28 years, and the median was 8 years. Patients were classified as early dementia if dementia occurred 8 years or less before PD diagnosis (n=9), and late dementia if dementia occurred later than 8 years after PD diagnosis (n=6).

## **Magnetic Resonance Imaging**

Patients were scanned at the Department of Radiology, Stavanger University Hospital in the period from December 2001 to June 2005, in a 1.5 T Phillips Gyroscan NT intera, Release 8.1 MRI machine ( Philips Medical Systems, Best, The Netherlands) A software upgrade of the machine was done in the fall 2003, to release 10. The quality of the images has been stable throughout the study. We performed a structural MRI series with a T1- weighted three dimensional (3D) fast spoiled gradient recalled echo (FSPGR), (TR 12.4 ms, TE 4.2 ms, TI 650 ms, matrix 256 x 192, slice thickness 1.6 mm).

## **Image analysis**

The optimised VBM protocol of Good et al [32] was applied for the preprocessing of the images. The preprocessing steps are already described in a previous paper.[23] The resulting smoothed images were used in the statistical analysis.

## **Statistical analysis**

Smoothed images from the pre-processing steps were analyzed using statistical parametric mapping (SPM2) (Wellcome Department of Cognitive Neurology, London, UK (<http://www.fil.ion.ucl.ac.uk/spm>)). Data were analysed on a PC using windows XP professional, version 5.1 and Matlab 6.5.2 (Mathworks, Natick, MA).

The following voxel-based analyses of grey matter were performed:

Differences in grey matter between groups were assessed statistically using a two sample t-test, analysing the whole brain. Significance levels for t - statistics were set at  $p < 0.001$  uncorrected for



multiple comparisons. All results are presented at the voxel level.[33] Smoothed, modulated images were also analysed. The co-ordinates obtained for the peak voxels, ie the anatomic location with maximal grey matter loss within each significant cluster, were transferred into Talairach space using Matthew Brett's mni2tal routine (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>).

The anatomic locations of the peak voxels were found using The Talairach Daemon Client[34]. The results given by the Talairach daemon were verified by the Co-planar Stereotaxic Atlas of the Human Brain[35]. When discrepancies in the location of peak voxels were found, the manually detected anatomic locations were reported.

Group statistics were done using the SPSS for windows, version 13.0 (SPSS for Windows, Release 13.0 (1 Sep 2004) SPSS Inc). Differences between groups were assessed using Mann Whitney U test, or a chi-square test was used when appropriate, using  $p < 0.05$  as statistically significant.

## Results

There were no significant differences between the early and late dementia groups regarding age, education, severity or duration of dementia, severity of parkinsonism or drug treatment, although the late dementia group had a numerical lower MMSE score (Table 1). There were more females and the age at onset was younger in the late dementia group than the early dementia group (Table 1).

The early dementia group had areas of more atrophy than the group with late dementia. The areas of reductions in gray matter volume were bilaterally in the medial frontal gyrus, and in the right precuneus, and on the left side in the inferior parietal lobule, superior frontal gyrus and middle temporal gyrus. In the group with long disease duration prior to dementia we found symmetrical gray matter volume reduction in the inferior frontal gyrus bilaterally.

In the unmodulated images, the group with early dementia had more atrophy than the group with late dementia in the striatum (right caudate, left putamen), in the left precentral gyrus, left middle temporal gyrus and in the right red nucleus. (Table 2, Figure 1)The late dementia group had symmetrical reduction in gray matter in the insula bilaterally compared to the early dementia group. (Table 2, Figure 1)

## Discussion

The main finding of this study is that PD patients who developed dementia early in the disease course had areas of more atrophy than PD patients who developed dementia late in course, consistent with our hypothesis. These differences could not be explained by differences in clinical features such as severity of dementia or parkinsonism or age. The findings are in line with a recent neuropathology study who found more morphological brain pathology (plaques and  $\alpha$ -synuclein) in the group with shorter duration of PD prior to dementia.[21] In addition we found a symmetrical reduction in gray matter in the insula bilaterally in the long duration PDD group.

Structural imaging studies have previously shown atrophy of similar areas as those found in the current study; the right caudate nucleus,[22] the left middle temporal, left precentral gyrus[23] and putamen[36] in PDD patients, although conflicting results have been reported.[37] The novel finding in this study is that this atrophy is more pronounced in some areas in patients who develop dementia early in the disease.

We found symmetrical gray matter reductions in the insula in the group with 8 years or more duration of PD prior to dementia. This confirms the results of a previous VBM study of patients with PDD,[22] and a longitudinal VBM study of PDD patients where bilateral insula reductions were found.[38]

The structures with more atrophy in those with early dementia in our study have previously been found to be related to cognitive and neuropsychiatric features. The basal ganglia are not only involved in motor function, but are also engaged in cognitive functions.[39, 40] A PET study of PDD patients showed decreased uptake of 18F-dopa in the caudate and mesolimbic structures compared to non-demented PD patients, suggesting that dementia in PDD is related to reduced function in these areas.[41]

There is a remarkable inter-individual variation in the course of PD, both regarding motor[42] and cognitive decline[16] and age at onset of PD.[15] The relationship of age and age at onset with clinical course is complex. Age at disease onset was the main predictor of motor decline, indicating a slower and more restricted pathologic disease process in patients with young-onset PD.[43] In contrast, age but not age at onset, was associated with time to dementia after adjustment for the overall effect of age on the risk of dementia in non-PD subjects.[16] In our study the patients in the early dementia group were older at PD debut than the late dementia patients. There were also numerical differences

in age at scanning, but this was not significant, and no association between age and rates of atrophy in PD has been found.[44] We did not attempt to disentangle the relationship between age and age at onset with time to dementia.

Neuropathological heterogeneity in PD has been reported, although the pathological variability underlying the clinical heterogeneity is not known in detail.[15] Together with a recent neuropathological study [21], our findings suggest that a differential degeneration of cortical and subcortical structures is underpinning the variation in time to develop dementia. Braak hypothesized a systematic progression of Lewy pathology emerging in the brain stem and subsequently involving basal forebrain and finally neocortex.[45] Our findings indicate that although the overall pattern may be valid, there are clinically significant variations in the regional progression of the pathology, with more rapidly progressing atrophy in some patients. In contrast, neurochemical changes may play a larger role in the group with late onset dementia, consistent with the findings in the autopsy study [21]. The factors regulating this differential disease progression, in part related to age, needs to be further explored in future studies.

Our study has methodological limitations that need to be addressed. The study groups are small, and differed on some demographic and clinical variables. Thus, our findings should be interpreted with caution, and larger groups are needed to confirm our results. The diagnosis of PD was clinical, and thus misdiagnosis may occur. However, neuropathological verification of PD diagnoses from our hospital have been demonstrated[12]. Finally, this was a cross-sectional study, and the time from onset of PD to dementia was based on a clinical interview of patient and caregiver, and thus recall bias cannot be ruled out. It is however unlikely that this introduced a systematic bias that would affect the results.

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**Table 1**

**Clinical and demographic characteristics of the groups according to timing of dementia and parkinsonism**

	<b>PD ≤ 8 years</b>	<b>PD &gt; 8 years</b>	<b>P (Mann Whitney)</b>
<b>N</b>	9	6	-
<b>Gender male/female</b>	8/1	2/4	0.047*
<b>Age</b>	74 (69-84)	69.5 (62-82)	0.46
<b>Education (years)</b>	9 (7-17)	7.5 (7-17)	0.69
<b>MMSE</b>	21 (13-25)	18 (10-24)	0.39
<b>UPDRS</b>	40 (29-45)	39.5 (18-60)	0.714
<b>H&amp;Y</b>	3.0(2-4)	3.0 (2.5-4)	0.514
<b>Dementia duration (years)</b>	2 (1-3)	2 (1-5)	0.753
<b>Duration of PD (years)</b>	6(5-10)	19.5 (12-30)	0.001
<b>Age of PD debut</b>	67(59-78)	53 (32-67)	0.015
<b>L-dopa dose (mg)</b>	600 (400-800)	925 (500-1200)	0.18

Median (range)

Fishers exact test

Duration of PD = duration from PD diagnosis, not start of symptoms

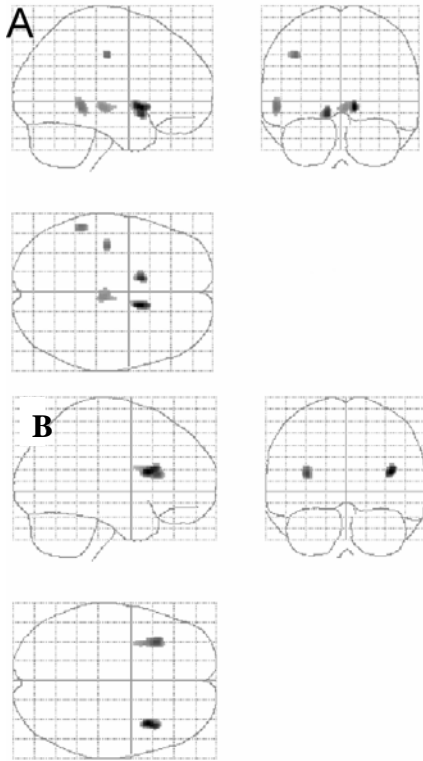
**Table 2****Brain areas showing significant differences between groups**

Areas with reduced gray matter in patients with $\leq 8$ years PD duration					
Talairach Coordinate			Structure	Cluster size	Z score
x	y	z			
12	10	-5	R caudate nucleus	144	3.97
-12	10	-10	L putamen	104	3.75
-39	-16	37	L precentral gyrus	60	3.47
-55	-40	-3	L middle temporal gyrus	104	3.44
3	-21	-4	R brainstem, red nucleus	101	3.34
Areas with reduced gray matter in patients with $> 8$ years PD duration					
x	y	z	Structure	Cluster size	Z score
38	15	15	R insula	189	4.49
-33	21	13	L insula	194	4.01

All peak voxels are  $p < 0.001$  uncorrected. Only clusters larger than  $200 \text{ mm}^3$  /60 voxels are shown.

**Figure 1**

- A) Areas of reduced gray matter in patients with  $\leq 8$  years of PD duration prior to dementia**  
**B) Areas of reduced gray matter in patients with  $>8$  years of PD prior to dementia development**



Results shown on glassbrain, where areas of atrophy are shown as gray and black clusters ( $p < 0.001$  uncorrected).