Chapter 1 – General Introduction
Dementia

Worldwide, 35.6 million people have dementia. Every year, there are 7.7 million new cases. The total number of people with dementia is projected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 [1].

Dementia is a syndrome in which there is deterioration in cognitive function beyond what might be expected for normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Impairment of cognition interferes with activities of daily living, in a pattern of progressive decline from a previous level of functioning and ultimately leads to a loss of independence. The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation.

Dementia is caused by a variety of diseases that primarily or secondarily affect the brain. Alzheimer's disease (AD) is the most common cause of dementia, other major forms include vascular dementia (VaD), dementia with Lewy bodies (DLB), and a group of diseases that contribute to frontotemporal dementia (FTD). The boundaries between different forms of dementia are indistinct and mixed forms often co-exist [2].

Dementia is overwhelming not only for the people who suffer from it, but also for their caregivers and families. There is often a lack of awareness and understanding of dementia, resulting in stigmatization and barriers to diagnosis and care. The impact of dementia on caregivers, family and societies can be physical, psychological, social and economic.

There is no treatment currently available to cure dementia or to alter its progressive course. To be able to support and improve the lives of people with dementia and their caregivers and families, it is important to provide information and long-term support. Therefore, one of the principal goals for dementia care is to make a reliable diagnosis as early as possible.

Which problems are clinicians facing?

It has become clear that there are distinct dementia profiles with different cognitive/behavioral syndromes, reflective of different topographical distribution and types of pathology within the brain. Therefore, a comprehensive analysis of patients’ clinical history, cognition and behavior, together with a full neurological examination have been summarized into consensus clinical diagnostic criteria which ought to lead to a high degree of confidence in clinical diagnosis [3-6].

Nevertheless, underlying pathology can be predicted on clinical grounds with only limited accuracy. This is especially true for the differential diagnosis between dementias such as behavioral variant FTD (bvFTD) and AD which show overlapping clinical features, especially in the beginning of the disease, and an enormous heterogeneity within both diagnoses [7,8]. Indeed, an assessment of the currently used clinical core criteria showed that the sensitivity of discriminating between AD and bvFTD of the new criteria proved to be relatively low [9]. Consequently, bvFTD is often misdiagnosed as AD [10,11] and AD as bvFTD [12,13].

Accurate clinical diagnosis of the dementias in life is critical for proper management, assessment of prognosis, and course of treatment. For instance, whereas AD patients may be treated with acetylcholinesterase inhibitors [14] patients with FTD show differing and in some cases unfavorable responses to these drugs [15].
Notwithstanding the treatment consequences, misdiagnosis may also have severe financial impacts and confound the outcome of therapeutic clinical trials.

**Alzheimer's disease**

Alzheimer's disease (AD) is the most common form of dementia, accounting for at least 43% of all dementia cases [1]. Although less prevalent before the age of 65 years, it is still the most frequent cause of early-onset dementia, followed by frontotemporal dementia [16]. The neuropathology of AD is characterized by extracellular amyloid deposits (amyloid plaques) and accumulation of the intracellular hyperphosphorilated tau protein (neurofibrillary tangles) [17,18]. Accumulation of these proteins causes cell death which results in a shrinkage of the total brain volume.

Late-onset AD (arbitrarily defined as first symptoms after 65 years of age) is mainly characterized by episodic memory impairment at time of initial evaluation. Other types of memory, such as factual information, immediate memory, and procedural memory are relatively preserved in the initial stage, but decline when the disease progresses. Deficits in word-finding skills, visuospatial abilities and executive functioning can also occur in the initial phase, or become more prominent during the progression of the disease [3,19,20]. Early-onset AD (symptom onset before 65 years of age) has a distinct clinical profile, especially in the early disease stage: Impairments in the visuospatial-, executive-, and attention domains are commonly observed, while memory is relatively preserved in this subtype of AD [21,22]. Both subtypes of AD are accompanied with a lack of insight (anosognosia), mood disturbances, delusions, hallucinations, vegetative symptoms and aberrant motor disturbances [23]. Next to differences based on age of disease onset, there are marked phenotypic variations in AD patients [24-26]. Even in late-onset AD, in some patients memory symptoms are minimal or absent at presentation. The dominant presenting symptom may be of problems in language [24,27], visuospatial skills [28], motor abilities [29,30], or frontal and executive capacities [31]. These ‘focal’ presentations of AD are particularly problematic for clinicians because memory impairment is traditionally seen as the hallmark of AD. Indeed, non-amnestic presentations would not fulfill conventional clinical criteria [3,4] for AD, so that reliance on such criteria alone would lead to such cases being missed. The existence of ‘atypical’ variants of AD highlights the more general point: not all patients with dementia exhibit a ‘prototypical’ pattern, and diagnostic boundaries may be blurred. For example, the ‘frontal’ symptoms some AD patients exhibit, might potentially be confused with bvFTD.

**Behavioral variant frontotemporal dementia**

The behavioral variant of frontotemporal dementia (bvFTD) is the second most common cause of early onset dementia (<65 years) [32,33]. The syndrome is very heterogeneous, but is mostly characterized by a marked progressive decline in personality and/or behavior. Although the syndrome mostly has a presenile onset, occurrence after the age of 65 accounts for 20-25% of the patients [32]. However, the present rates are likely to be underestimated, since misdiagnoses such as AD or psychiatric disorders are common. The neuropathology of bvFTD can be roughly subdivided in three distinct proteinopathies. Half of the patients suffer from
accumulation of the tau protein. Inclusions of this hyperphosphorilated protein are present in neurons and glial cells of bvFTD patients. Another part of the patients suffers from accumulation of the transactive response DNA-binding protein 43 (TDP-43 protein), and a relatively small part of patients suffers from accumulation of the fused-in-sarcoma protein (FUS protein) [34,35].

Clinically the syndrome can be classified in three behavioral symptoms: the disinhibited syndrome, the apathetic syndrome, and the stereotypic syndrome. Generally, insight is more impaired compared to AD patients, and symptoms such as loss of empathy, idiosyncratic hoarding and collecting, changing in eating behavior, poor hygiene and hyperorality are common. Furthermore, patients often show deficits in cognitive domains of executive function, attention and working memory [32,36].

Neuropsychological testing is an essential component of early detection of bvFTD. However, this can be very challenging due to the heterogeneity of the syndrome. For instance, the general presentation of patients at the time of initial evaluation can differ considerably, and part of the patients perform within the normal range of the traditional tasks [37]. Moreover, while there are differences in the performance of groups of patients with AD and bvFTD on measures of orientation, memory, language, visuomotor function and general cognitive ability, there is still considerable overlap in the performance of these two groups [38]. Thus, even when the most discriminating measures are used, it can be difficult to differentiate between AD and bvFTD. Indeed, contrary to earlier hypotheses and the currently used clinical criteria [6], episodic memory turned out to not discriminate bvFTD from AD patients [39,40], and visuospatial skills only differentiate the atypical visuospatial AD cases from bvFTD [41].

How is magnetic resonance imaging (MRI) helping us?

Structural neuroimaging has dramatically changed our ability to accurately diagnose dementia. The role of neuroimaging extends beyond the detection of potentially treatable causes of dementia (e.g. tumors) to the facilitation of the diagnosis after symptom onset, and shows promise for diagnosis in early or even pre-symptomatic phases. MRI characteristics such as atrophy of the medial temporal lobe, are increasingly used as supportive evidence for a diagnosis of different forms of dementia and some of these characteristics have been incorporated into the clinical guidelines [4,6]. The presence of disproportionate gray matter (GM) atrophy in medial, basal, and lateral temporal lobe, and medial parietal cortex is supportive for a diagnosis of AD, whereas the presence of disproportionate atrophy in medial frontal, orbital–insular and anterior temporal regions help distinguish bvFTD from other conditions. In this way, structural neuroimaging can be helpful in discriminating between normal aging and different forms of dementia and assessments of global cortical atrophy and medial temporal lobe atrophy are of special diagnostic value. These MRI characteristics are detected by the use of visual rating scales [42]. They can be easily used in the daily clinical practice to discover macroscopic brain changes indicative for certain diseases [43-46]. However, many scans differ from the predicted patterns of atrophy, which combined with large between–rater variability results in low sensitivity of these scales. Furthermore, cortical atrophy patterns of AD and bvFTD largely overlap, e.g. frontal atrophy is seen in AD and hippocampal atrophy
does not exclude a diagnosis of bvFTD and even appears in normal aging [24,31,47,48]. Moreover, especially in the beginning of the disease, cortical atrophy may not be visible by eyeballing. More sophisticated analytical methods that could detect and quantify more subtle changes of the brain would be helpful. Ideally, methods should focus on patterns of structural changes and/or altered networks, rather than measuring only specific structures. There are different ways to study the brain with automated quantitative image post-processing techniques by measuring different parts of the brain in more detail (e.g. at voxel level).

The cerebral cortex (the largest part of the brain) contains approximately 15–33 billion neurons, each connected by synapses to several thousand other neurons [49]. These neurons communicate with one another by means of long fibers called axons, which carry trains of signal pulses to distant parts of the brain or body targeting specific recipient cells. Most of the axons are wrapped in a fatty insulating sheath of myelin, which serves to greatly increase the speed of signal propagation. Myelin is white, making the inner parts of the brain filled exclusively with nerve fibers appear as light-colored white matter (WM), in contrast to the darker-colored gray matter (GM) at the outside of the cortex, that marks areas with high densities of neuron cell bodies [50]. Relatively compact clusters of neurons at the heart of the brain also show up as gray matter, bordered by white matter or the ventricles. Because of their location and appearance, these clusters of neurons are often called subcortical or deep gray matter (DGM) structures. These deep gray matter structures are thought to be relay stations in the cortical networks throughout the brain.

By examining the different parts of the brain with quantitative image analysis methods, it is possible to obtain - next to support for differential diagnosis - important information about the different pathophysiological processes in the brain of AD and bvFTD patients.

![Figure 1. Axial MRI scan of the brain, picturing the different parts of the brain.](image)

How do we examine the different parts of the brain with image analysis methods?
Gray matter
In dementia, neurons, the components of gray matter are dying. The consequence is GM loss and shrinkage of the brain. This GM loss, or atrophy, can be quantified and located by automated image analysis methods. Voxel-based morphometry (VBM) is one such automated technique that has grown in popularity since its introduction [51], largely because of the fact that it is relatively easy to use and has provided biologically plausible results. With this technique it is possible to study patterns of atrophy between different forms of dementia and normal aging. VBM involves a voxel-wise comparison of the local concentration of GM between two groups of subjects. The procedure involves segmenting the GM from the native space images, spatially normalizing the images from all subjects into the same stereotactic space and smoothing the GM segmentations. Voxel-wise parametric statistical tests which compare the smoothed GM images from the two groups are performed. Corrections for multiple comparisons are made using the theory of Gaussian random fields or comparable models. VBM has the advantage of being unbiased because it avoids a priori selection of regions. It is an automated technique that eliminates observer variability and analyses 3D volumes at the voxel level and thus can visualize atrophy patterns throughout the whole brain [51]. Using VBM contributes to the understanding of how the brain changes in different forms of dementia and how brain changes relate to characteristic clinical features.

Figure 2. Workflow of VBM analyses.

Next to cortical atrophy, deep gray matter (DGM) structures in the brain can provide important information about the pathological processes in the different forms of dementia. A number of pathological studies have identified DGM atrophy in AD and
bvFTD at autopsy \[52,53\] and there is emerging evidence that compared to AD, generally regarded as a cortical disease, bvFTD patients have more subcortical brain damage \[47,54-56\]. Their involvement in frontostriatal circuits could explain clinical symptoms which are difficult to explain by cortical damage. One of the available tools to study DGM structures is FIRST (FMRIB’s integrated registration and segmentation tool), an automated and robust method for the extraction of the subcortical volumes. Volumes of seven structures can be estimated by registration and segmentation of the structures. FIRST has been shown to give accurate and robust results for the segmentation of subcortical structures and that it performs comparable or better to other automatic methods \[57-59\]. In the discrimination of AD and bvFTD, deep gray matter (DGM) structures have received less attention. However, MRI-based measures of DGM structures could provide important information of the differential distribution of pathology between AD and bvFTD and may explain some of the clinical characteristics typical for these diseases.

![Image](image-url)

**Figure 3.** Segmentation of deep gray matter structures. Colored structures: Yellow: Hippocampus; Turquoise: Amygdala; Green: Thalamus; Light blue: Caudate Nucleus; Pink: Putamen; Dark blue: Globus Pallidus; Orange: Nucleus Accumbens.

**White matter**

In addition to GM damage, altered anatomical connectivity between white matter pathways may play a major role in dementia \[60,61\]. The rapid development of newer neuroimaging techniques, especially Diffusion Tensor Imaging (DTI), has enabled researchers to visualize and quantify the integrity of the WM at the microscopic level, which cannot be seen on conventional MRI methods \[61,62\]. DTI measures water diffusion in white matter tracts and provides details on tissue microstructure. It provides quantitative information regarding white matter tracts and visible and invisible abnormalities. DTI measures differ between dementia and control subjects and seem to correlate with clinical status \[63\]. When analyzing DTI data, the diffusion measures fractional anisotropy (FA) and mean diffusivity (MD) can be obtained \[64\]. FA is the measure of the degree of anisotropy, and ranges from 0 (the diffusion is unrestricted in all directions) to 1 (the diffusion goes in one direction and is fully restricted in all other directions). FA varies substantially by anatomical location, but is also affected by many pathological changes of the WM. Healthy WM shows a relatively high FA value, whereas damaged WM leads to less directionality and consequently, a reduction in FA. MD represents the total mean diffusion within a certain voxel and is often used as a measure of WM tissue alteration in addition to FA.
In addition, two tensor eigenvalues axial diffusivity and radial diffusivity – representing the water diffusivity respectively parallel and perpendicular to the axis of the fiber tract within a voxel of interest – are obtained as specific biological markers of axonal and myelin degeneration [65-67]. To analyze DTI data, Tract-based spatial statistics (TBSS), as part of FSL, can be used [68]. TBSS is a voxel-wise statistical comparison of the FA data between groups, which is a fully automated, observer-independent multi-subject analysis of whole-brain diffusion data. In TBSS analyses, a (group-wise) mean FA tract skeleton is created, which is thought to represent the centers of all WM tracts common to the group under study. By subsequently projecting each subject’s FA image onto the FA skeleton - resulting in individual skeletonized FA data - and feeding this into voxel-wise statistics, differences between groups can be calculated. Many imaging studies have used FA images in voxel-wise statistical analyses, in order to localize brain changes related to development, degeneration and disease. DTI has been used to study normal aging and AD [60,64,69]. But only few DTI studies of bvFTD have been conducted. Furthermore, the direct comparison between AD and bvFTD has been examined even less. Questions like ‘Is the distribution of white matter damage different between bvFTD and Alzheimer’s disease?’ or “Is WM damage secondary to the degeneration of cortical neurons or due to primary pathology occurring in the white matter regions?” remain insufficiently answered. To investigate patterns of WM damage between AD and bvFTD and if these patterns contributes to the differentiation between AD and bvFTD, as well as achieving a better understanding about white matter pathology is therefore a desirable research goal.

![Figure 4. Results of a TBSS voxelwise statistics displaying areas of white matter skeleton (green) with lower FA (red-yellow) values in the frontal areas of the brain.](image.png)

**Combination of image analysis techniques**

So far, no single diagnostic biomarker with sufficient sensitivity and specificity to establish an accurate diagnosis, is available. The combination of different and new imaging techniques will help to discover patterns of alterations in connectivity and structure in the brains of patients with AD and bvFTD. Combining structural data of new imaging techniques can provide us with important new information.

**MRI to study disease progression over time**

Most information about the underlying neuropathology has been studied in cross-sectional designs. Repeated MRI can aid in establishing a diagnosis when brain
abnormalities at baseline are insufficient to reach a conclusion and can be used to track brain changes during the course of the disease. Furthermore, rate of decline is less sensitive for inter-subject variability/ noise in the MRI data than one baseline measurement. Therefore longitudinal MRI studies are expected to enhance power to differentiate between dementias as compared to using a single scan.

**The ultimate goal: Single-subject diagnosis**

The techniques described above are used for group comparisons of different tissue characteristics. However, an ultimate aim of neuroimaging is to identify diagnoses at a single subject level. Pattern recognition techniques or automated classifiers develop and apply algorithms that recognize patterns in data and can classify new patients into different categories. **Pattern Recognition for Neuroimaging Toolbox (PRoNTo)** [70] is a software toolbox based on pattern recognition for the analysis of neuroimaging data. In PRoNTo, brain scans are treated as spatial patterns and statistical learning models are used to identify statistical properties of the data that can be used to discriminate between experimental conditions or groups of subjects (classification models) or to predict a continuous measure (regression models). These automated classifiers can be objective, quantitative and easy to implement and potentially satisfy the requirements of a diagnostic tool for single subjects [71].

**Figure 5.** Performance of support vector machine classification of two groups based on gray matter segmentations.

**Aims of this thesis**

The general aim of this thesis was to find early markers of brain changes associated with specific types of dementia for early (differential) diagnosis and to get more insight in the biological causes of brain changes in AD and bvFTD. The following questions will be answered:

1.) How are patterns of gray matter atrophy linked to a specific diagnosis?
2.) Do white matter integrity measures improve the diagnostic accuracy?
3.) Are MRI derived measures of GM, DGM structures and WM integrity suitable for a diagnostic tool?

Thesis outline
In chapter 2 of this thesis we study how patterns of cortical and deep GM loss are related to different manifestations of AD. In chapter 2.1 we use VBM to detect patterns of GM atrophy in early- and late-onset AD patients compared to age-matched controls, taking into account the potential modulating effect of APOE status. To get more insight in the diagnostic value of GM we validate the 4-point visual rating scale for posterior cortical atrophy through quantitative GM volumetry and VBM, to determine whether its use in clinical practice is justified (chapter 2.2). In chapter 2.3 we investigated volume differences of the subcortical structures between AD, MCI and controls and their predictive value for progression from MCI to AD. In chapter 3 we investigated the role of GM atrophy in AD compared to bvFTD. In chapter 3.1 we investigate if MRI-based measures of DGM structures could provide important information on the differential distribution of pathology between AD and FTD and if they explain some of the clinical characteristics typical of the diseases. Furthermore, we examine if patterns of GM atrophy can serve as a biomarker in single-subject diagnosis (chapter 3.2). In chapter 3.3 we investigated the decline of gray matter over time in different parts of the brain of patients with AD and bvFTD. In chapter 3.4 we investigate the ability of cortical and subcortical GM atrophy in combination with WM integrity to distinguish bvFTD from AD and from controls using VBM, FIRST, and TBSS.
Reference List


