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COMPUTERIZED TOOLS: A SUBSTITUTE OR A SUPPLEMENT WHEN DIAGNOSING ALZHEIMER'S DISEASE?

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Computerized Tools: a Substitute or a Supplement when Diagnosing Alzheimer's disease?
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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A mis padres y a mis hermanos.

A mis abulos, tíos y primos.

“The boy believes he will be a proper I, a proper fellow, only when he has become a man; the man thinks, only in the other world will he be something proper”

Max Stirner, The Ego and its Own

ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia in the elderly characterized by difficulties in memory, disturbances in language, changes in behavior, and impairments in daily life activities. By the time cognitive impairment manifests, substantial synaptic and neuronal degeneration has already occurred. Therefore, patients need to be diagnosed as early as possible at a preclinical or presymptomatic stage. This will be important when disease-modifying treatments exist in the future.

The main focus of this thesis is on the study of structural neuroimaging in AD and in prodromal stages of the disease. We emphasize the use of statistical learning for the analysis of structural neuroimaging data to achieve individual prediction of disease status and conversion from prodromal stages. The main aims of the thesis were to develop and validate computerized tools to identify patterns of atrophy with the potential of becoming markers of AD pathology using structural magnetic resonance imaging (sMRI) data and to develop a segmentation tool for Computed Tomography (CT).

Using automated neuroanatomical software we measured multiple brain structures that were given to statistical learning techniques to create discriminative models for prediction of presence of disease and conversion from prodromal stages. Building statistical models based on sMRI data we investigated optimal normalization strategies for the combination of structural measures such as cortical thickness, cortical and subcortical volumes **(Study I**). A baseline model was created based on the optimal normalization strategy and combination of structural measures. This model was used to compare the discrimination ability of different statistical learning algorithms (decision trees, artificial neural networks, support vector machines and orthogonal partial least squares (OPLS)). Additionally, the addition of age, years of education and APOE phenotype was added to the baseline model to assess the impact on discrimination ability **(Study II)**. The OPLS classification algorithm was trained on the baseline model to produce a structural index reflecting information about AD-like patterns of atrophy from each individual's sMRI data. Additional longitudinal information at one-year follow-up was used to characterize the temporal evolution of the derived index **(Study III)**. Since total intracranial volume (ICV) remains a morphological measure of interest and CT is today widely used in routine clinical investigations, we developed and validated an automated segmentation algorithm to estimate ICV from CT scans **(Study IV)**.

We believe computerized tools (automated neuroimaging software and statistical discriminative algorithms) have significantly enriched our knowledge and understanding of associated neurodegenerative pathology, its effects on cognition and interaction with age. These tools were mainly developed for research purposes but we believe all accumulated knowledge and insights could be translated into clinical settings, however, that is a challenge that remains open for future studies.

LIST OF SCIENTIFIC PAPERS

I. Westman, E., **Aguilar**, C., et al., 2013. Regional magnetic resonance imaging measures for multivariate analysis in Alzheimer's disease and mild cognitive impairment. Brain Topography, Volume 26, Issue 1, p. 9-23.

II. **Aguilar**, C., Westman, E., et al., 2013. Different multivariate techniques for automated classification of MRI data in Alzheimer's disease and mild cognitive impairment. Psychiatry Research: Neuroimaging, Volume 212, Issue 2, p. 89-98.

III. **Aguilar**, C., Muehlboeck, S., et al., 2014. Application of a MRI based index to longitudinal atrophy change in Alzheimer disease, mild cognitive impairment and healthy older individuals in the AddNeuroMed cohort. Frontiers in Aging Neuroscience. doi: 10.3389/fnagi.2014.00145.

IV. **Aguilar**, C., Edholm, K., et al. 2015. Automated CT-based segmentation and quantification of total intracranial volume. European Ragiology, doi: 10.1007/s00330-015-3747-7 (epub ahead of print).

Publications not included in thesis

Pereira JB, Cavallin L, Spulber G, **Aguilar** C, et al., 2013. Influence of age, disease onset and ApoE4 on visual medial temporal lobe atrophy cut-offs. Journal of Internal Medicine. Volume 275, Issue 3, p. 317-330.

Lebedev AV, Westman E, Beyer MK, Kramberger MG, **Aguilar** C, et al., 2013. Multivariate classification of patients with Alzheimer's and dementia with Lewy bodies using high-dimensional cortical thickness measurements: an MRI surface-based morphometric study. Journal of Neurology. Volume 260, Issue 4, p. 1104-1015.

CONTENTS

LIST OF ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognition
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRDA	Alzheimer's Disease and Related Disorders Association
ANN	Artificial neural networks
ANOVA	Analysis of variance
APOE	Apolipoprotein E
APP	Amyloid precursor protein
BACE 1	Beta-site APP cleaving enzyme 1
BET	Brain extraction tool
CDR	Cognitive Dementia Rating
CSF	Cerebrospinal fluid
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DSM	Diagnostic Statistical Manual
EM	Expectation maximization
$f(X)$	Unknown function of $X = X_1, X_2, X_3, \ldots$
FDG	Fluordeoxyglucouse
GDS	Geriatric depression scale
GM	Gray matter
HU	Hounsfield unit
ICV	Intracranial volume
InnoMed	Innovative Medicines
$L\big(Y, f(X)\big)$	Loss function
MCI	Mild cognitive impairment
MCI-c	MCI converter
MLE	Maximum-likelihood estimation
MLME	Maximum-likelihood mixture estimation
mm	Millimeters

mm^3	Cubic millimeters
MMSE	Mini mental state examination
MPRAGE	Magnetization Prepared Rapid Acquisition with Gradient Echo
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mSV	Millisievert
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
OPLS	Orthogonal PLS
PCA	Principal component analysis
PET	Positron emission tomography
PLS	Partial least squares
P-tau	Phosphorylated tau
$R[f]$	Expected risk
$R_{gua}[f]$	Guaranteed risk
RSS	Residual sum-of-squares
sMRI	Structural MRI
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric maps
SVM	Support vector machines
TICV	Total ICV
Trees	Decision trees
T1-w	T1-weighted
VC	Vapnik-Chervonenkis
WM	White matter
WMCs	White-matter changes

1 AGING AND ALZHEIMER'S DISEASE

Global increased life expectancy has implied a rising elderly population and created new challenges associated with a greater frequency of brain disorders due to aging, particularly of dementia cases [1], [2]. Consequences from suffering biological and cognitive degeneration include frailty, weakness, shortened life expectancy and loss of independence. Dementia can be defined as an acquired syndrome producing brain dysfunction (cognitive impairment, deterioration of intellect and personality changes) as part of aging due to cell death caused by brain disease [3]. The most common cause of dementia is Alzheimer's disease (AD), followed by vascular dementia, Lewy body dementia, frontotemporal dementia and Parkinson's disease.

1.1 NEUROPATHOLOGY OF ALZHEIMER'S DISEASE

The concept of AD as a unique entity originated from observations of severe dementia in the elderly accompanied by histomorphological changes: neuritic plaques, *neurofibrillary tangles* and granulovacuolar degeneration [4]. Like other neurodegenerative diseases, AD is fundamentally a disorder of altered protein folding and aggregation [5], specifically amyloid beta (Aβ) and tau proteins [6]. Misfolded proteins aggregate together leading to a buildup of cellular gunk that causes damage inside or outside cells, eventually consuming entire brain regions [7]. Discovery and characterization of amyloid fibril (neuritic) plaques and cerebrovascular *angiopathy* in post-mortem brain studies of diseased patients prompted the development of an Aβ peptide cascade hypothesis for the study of the pathogenesis of AD [8]–[10].

Aβ is a 38-43 amino acid-long peptide that is cleaved out from the transmembrane protein amyloid precursor protein (APP) by sequential endoproteolysis by beta-site APP cleaving enzyme 1 (BACE 1)/β-secretase and presenilin/γ-secretase complexes. APP can also undergo non-amyloidogenic proteolysis by α-secretase. Aβ monomers undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form *amyloid fibrils*. These fibrils deposit outside neuronal cells in dense formations known as senile or neuritic *plaques*, in less dense aggregates known as diffuse plaques, and in the walls of small blood vessels in a process called amyloid angiopathy. Tau protein is a microtubule-associated protein expressed in neurons. Tau protein stabilizes microtubules in the cell cytoskeleton and is normally regulated by phosphorylation. Abnormal hyperphosphorylation of tau protein (P-tau) in AD results in the loss of tau function causing inhibition and disruption of microtubules [11]. In addition, changes in conformation transform the unfolded monomer to a structured polymer, causing neurofibrillary tangle formation and synapse loss [12], [13].

The degenerating aging process involves the accumulation of structural damage and a deficient metabolic balance mechanism. Aging renders the brain vulnerable to Aβ neurotoxicity which starts to accumulate in the absence of neuritic pathology as part of normal aging [14]. Likewise, accumulation of neurofibrillary tangles in medial temporal lobe structures, like the entorhinal cortex, occurs as part of normal aging and is not specific for AD

[15]. While elderly individuals show AD-like changes, such as neuritic tau pathology in neocortical regions, some maintain their mental performance [16]–[18]. This generated the idea of an asymptomatic *prodromal* stage characterized by increased Aβ accumulation in the brain. Accumulated evidence from research suggests the pathology underlying AD begins to develop 10-20 years prior to cognitive impairment [19]–[21]. Since pathology precedes cognitive impairment, it follows that the onset of initial symptoms (dysfunction of episodic memory) may develop when a threshold level of neuronal and synaptic loss is reached, starting in the entorhinal cortex and hippocampus, in parallel with neurofibrillary tangle formation and gliosis.

The recognition of an irreversible and rapid progressive loss of cognitive abilities in patients suffering dementia, as opposed to normal age-related decline, together with the idea of a major loss of brain tissue [22], [23], elicited a systematic study and characterization of the stages leading to dementia and premature death. The usually precise pathway of tau pathology follows a predictable topographic pattern from the entorhinal cortex via the hippocampus to neocortical association areas and, to subcortical nuclei [24], [25]. In contrast, Aβ deposition is more diffuse and less predictable, usually beginning in the neocortex and later progressing to allocortical regions expanding anterogradely into regions that receive neuronal projections from already affected brain areas. At autopsy, all clinically defined AD cases display huge amounts of amyloid deposits and widespread tau pathology, as well as, massive white matter breakdown due to disconnection of widely distributed neuronal networks [26].

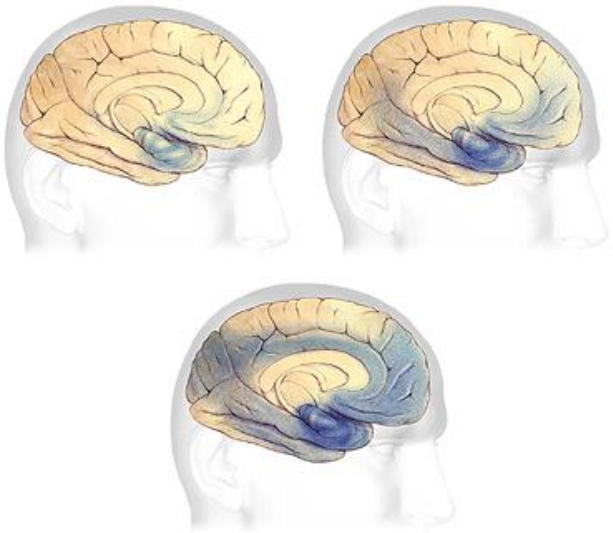
The degenerative gross structural changes and the assessment of distribution and progression patterns of amyloid deposition and neurofibrillary tangles resulted in a chronological description of the temporal evolution of atrophy that characterizes patients suffering from AD [27]. Culminating in the establishment of a time sequence relationship in the cascade of events: brain diseases (such as AD) cause gradual neuronal loss, which causes progressive brain dysfunction, which results in progressive cognitive impairment, which culminates in dementia. It can be thought of as a sequence of pathophysiological stages: preclinical (asymptomatic and with biomarker evidence suggestive of pathology), prodromal (subtle cognitive decline and/or subjective memory report) and dementia [28].

Structural neuroimaging using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) allows visualization of tissue atrophy which tightly follows the distribution of neurofibrillary staging of AD (Figure 1): initial transentorhinal stage affecting the transentorhinal and entorhinal cortices, limbic stage spreading to the hippocampus and amygdala, and isocortical stage affecting the neocortical association areas of the brain [29].

The clinical approach is based on core comprehensive neurological examinations and clinical interviews (neuropsychological examinations). But recent research diagnostic criteria has shifted from purely clinical and neuropsychological to include brain imaging and other biomarker measures [21], [30], [31]. AD diagnosis in the preclinical stage is thus supported by biomarkers of Aβ accumulation (CSF/PET), neurodegeneration (CSF [32]), neuronal

activity (functional MRI), neuronal loss (structural MRI [33]) and synaptic dysfunction (FDG-PET).

Figure 1 Typical pattern of neurofibrillary progression through the course of AD



Alzheimer's association, www.alz.org

1.2 MODULATORS OF PHENOTYPIC EXPRESSION

Modulators of the neuropathological and neurodegenerative cascade could have either genetic or environmental bases affecting the rate of accumulation of brain pathology or the time at which the pathological changes express themselves clinically.

Aging not only increases the risk of other comorbidities (e.g. infectious diseases, cancer, ischemic heart disease, stroke, type 2 diabetes and others), but also exacerbates and reinforces the effect of other risk factors (e.g. tobacco use, unhealthy diet, physical inactivity and alcohol abuse). Age is the main risk factor for AD, followed by inheritance of the apolipoprotein E (APOE) ε4 allele [34]. A number of risk and protective factors have been proposed in association with late-onset of dementia and AD [35]. The proposed risk factors can be categorized into vascular and metabolic: cerebrovascular lesions, diabetes mellitus and pre-diabetes [36], [37]; midlife positive but late-life negative: hypertension [38]; lifestyle: smoking and high alcohol intake; diet, saturated fat and low B vitamins; others: traumatic brain injury and depression. The proposed protective factors can be categorized into psychosocial: high levels of education and of complexity of work, rich social network and social engagement; lifestyle: physical activity and moderate alcohol intake; diet: Mediterranean diet, vitamins B_6 and B_{12}, antioxidants vitamins and vitamin D. Suggesting compensatory and adaptive mechanisms can modulate the effect of degenerative aging processes. Already today, early primary prevention starting in midlife has been implemented since it may be the most effective intervention [39].

1.2.1 Aging and neuropathology

Although the neuropathological hallmarks of AD can be observed in post-mortem studies of brains from early- and late-onset AD patients [40], individuals in the oldest age group, age over 80 years at time of death, without a diagnosis of dementia showed pathological features of AD [41]. Atrophy is considered a proxy of neuronal loss, axodendritic pruning and reduced synaptic density, thus reflecting both AD-like pathology and degeneration in the course of normal aging, which correlates with cognitive impairment and dementia [42]. Thus, in the oldest old, neuropathological confirmation of demented patients becomes harder since the same burden of pathological features may be found in persons of the same age who do not have dementia [43], [44]. These neuropathological features in demented patients seemed to remain relatively constant with increasing age, so that the ability to monitor dementia progression reaches a plateau [45]. Finally, the association between dementia and pathological features is stronger in younger patients suffering AD most probably due to the lack of studies on the oldest old in both normal aging and AD [46].

1.2.2 APOE and AD pathogenesis

APOE protein is encoded by its homonym gene located on chromosome 19 and has three alleles: ε2, ε3 and ε4. The APOE ε4 allele is correlated with increased risk and earlier disease onset in a dose-dependent fashion [47], [48]. Heterozygous ε4 carriers have intermediate risk compared with homozygous carriers, while APOE ε2 has an associated protective effect and seems to retard AD pathology [48]. The molecular mechanisms behind this indicate the APOE isoforms differential regulation of both extracellular and intracellular Aβ clearance in the brain, which in turns regulate fibrillization of Aβ and the levels of soluble Aβ in a isoform-specific fashion [49], [50].

In MCI patients, carriers of the ε4 allele have a higher risk of rapid progression to dementia [51], [52]. A mechanistical explanation follows from evidence that healthy elderly carrying the ε4 allele show decreased cognition and decreased gray and white matter volumes in the medial temporal cortex [53]–[57]. Moreover, there seems to be an interaction between APOE and age influencing the phenotypic expression; in very-old patients carriers of the ε4 allele there is a decrease in sensitivity of cognitive and imaging measures [58].

1.2.3 Education and brain reserve

According to the cognitive reserve hypothesis [59], individuals with higher cognitive reserve should be able to tolerate more severe degrees of pathology, that is, preserved cognitive function even when appreciable burden of pathology is present. Possible mechanisms are that larger brains may tolerate more loss before functional impairment occurs (passive view) [60], and that brain connectivity may be more diverse and efficient enhancing the ability to alternate compensatory brain networks (active view) [59]. Individual variation in education and related cognitive experiences together with individual developmental differences may lead to greater redundancy in neural circuits involved in cognition. This increased redundancy may be caused by neuroplastic effects (synaptogeneis and neurogenesis) driven by exposure

to enriched environments, ultimately modifying the effect of AD pathology on cognition [61]. However, such neural substrate for brain reserve remains elusive. Contradictory studies showed sMRI evidence in favor of increase reserve due to education, and lack of association between greater cortical thickness and higher education [62], [63].

1.3 MILD COGNITIVE IMPAIRMENT

Identification of the shift between early cognitive changes associated with dementia and those associated with normal aging still remains elusive [64]–[70]. Thus, attention has been directed to the identification and characterization of a clinical population of elderly at high risk of developing dementia manifesting symptoms of cognitive impairment, known as mild cognitive impairment (MCI). However, MCI is not synonymous with early dementia since patients can regress, stay the same or progress to dementia.

There is a continuum from normal aging to dementia and MCI is thought to represent the intermediate stage [71], [72]. MCI is a very heterogeneous group to study since diseases other than AD could have a prodromal stage [65], and different clinical subtypes exist [73]–[75]. MCI classification is determined by concepts of normal aging and dementia; as such, MCI is not a fixed concept, but rather a movable one that changes as dementia knowledge improves. Traditionally thought as a prodrome to AD, it was restricted to reflect problems in memory [76]. In a broader sense, the term includes any subtle impairment of cognition but insufficient to qualify as dementia. This may constitute impairment (decrease of at least 1.5 standard deviations below age norms) in one or more domains from attention, executive function, learning and memory, language, perceptual-motor, and social cognition. An important risk factor in progression from MCI to dementia is the presence of neuropsychiatric symptoms, in particular symptoms of depression [77], [78].

Medial temporal lobe atrophy present in patients with MCI seems to be a sensitive marker in identifying those who will progress to dementia [79]–[81]. In particular, measure of hippocampal volume on MRI has been proposed as a marker of incipient memory decline and predictor of progression to dementia [82], [83]. The most challenging distinction is between normal aging and MCI rather than MCI and AD, since while cognitive tests and neurological measures are useful, the final determination relies on the clinician’s judgment. In research settings, the operationalization of the criteria contributes to differences among studies.

In AD, several studies have revealed that separate cognitive components are affected independently, thus giving rise to AD subgroups: memory, executive, visuospatial and language [30], further motivating the heterogeneous presentation of the disease and its prodromal stage. Thus, a combination of well-defined clinical subtypes, neuroimaging measures and putative etiology would be useful in prediction of progression [84].

1.4 EVALUATION OF COGNITIVE FUNCTION

Numerous cognitive tests can be used for clinical and research purposes to assess cognitive function, monitor cognitive decline and establish dementia diagnosis. The Mini-Mental State

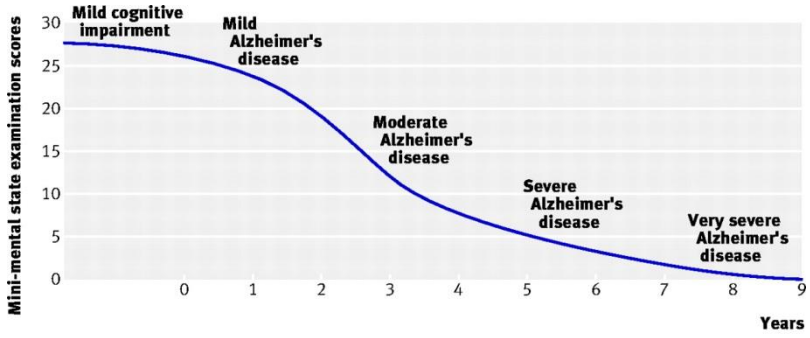
Examination (MMSE) is the most commonly used test for assessment of global cognitive function to screen for dementia, see Figure 2.

The MMSE is a short and straightforward cognitive test that allows a rapid scan of cognitive functioning [85], screening domains of orientation, attention and memory, concentration, language and praxis. It was not designed to detect demented patients (for instance, mood assessment is excluded), and there is no substantial evidence supporting baseline MMSE alone identifies MCI patients who will develop dementia [86].

The Alzheimer's Disease Assessment Scale – cognition (ADAS-cog) is a specialized and more detailed assessment of cognitive impairment in areas shown to decline in AD [87]. It has been frequently used as the gold standard for assessing treatment response in AD pharmacological trials.

The Cognitive Dementia Rating (CDR) is a severity rating scale (0 = normal, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia) and not a diagnostic instrument [88], [89]. Patients with a score of 0.5 may meet the criteria for MCI, but may also represent very mild dementia.

Figure 2 Cognitive function deterioration and its relationship to AD severity



Mild cognitive impairment: Complaints of memory loss, intact activities of daily living, no evidence of Alzheimer's disease
Mild Alzheimer's disease: Forgetfulness, short term memory loss, repetitive questions, hobbies, interests lost, impaired activities of daily living
Moderate Alzheimer's disease: Progression of cognitive deficits, dysexecutive syndrome, further impaired activities of daily living, transitions in care, emergence of behavioural and psychological symptoms of dementia
Severe Alzheimer's disease: Agitation, altered sleep patterns, assistance required in dressing, feeding, bathing, established behavioural and psychological symptoms of dementia
Very severe Alzheimer's disease: Bedbound, no speech, incontinent, basic psychomotor skills lost

Burns Alistair, Iliffe Steve. Alzheimer's disease BMJ 2009; 338 :b158

2 IMAGING ALZHEIMER'S DISEASE

Neuroimaging (imaging of the brain) stands as one of the most important tools to study the brain *in vivo*. It became clinically relevant and an integral part of differential diagnosis in brain disorders with the advent of tomographic techniques such as computed tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI). When the clinical diagnosis is reasonably certain, routine imaging examinations are not likely to be necessary [90]. However, atypical cases with rapidly progressive symptoms show an increase incidence of neuroimaging findings and potentially treatable lesions. This idea is based on the view that the observed changes in cognitive function are caused by structural and functional changes in the brain.

2.1 COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are imaging techniques carried out *in vivo* in both human and animal studies. CT is an *ionizing radiation* medical imaging technique that has commonly been extensively used in clinical routines for visualization of internal organs and cavities thanks to its high degree of anatomical detail [91]. It became an important tool to supplement x-rays and ultrasound and has been used for preventive medicine and screening purposes [92], [93]. CT as a routine clinical imaging technique enables identification and delineation of cerebral infarcts, tumors, subdural fluid and hydrocephalus. CT readings, visual assessment of brain scans performed by trained neuroradiologists, when performed on a heterogeneous group of patients with varied cognitive, behavioral and neurological symptoms, support clinical impressions and may influence treatment strategy.

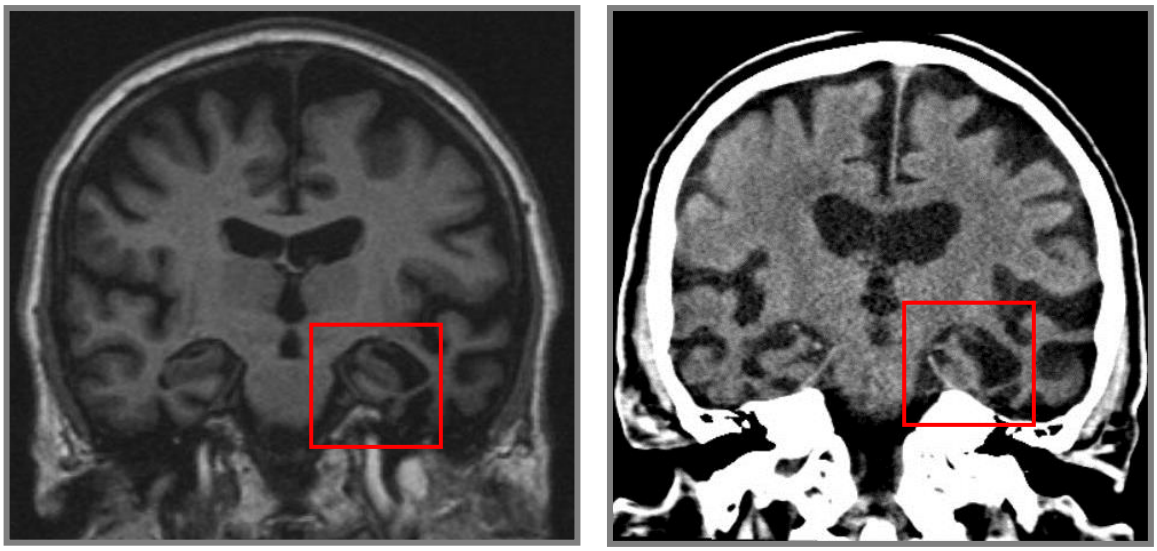
The Swedish National Guidelines for the diagnosis and management of dementia disorders recommend that CT/MRI should be performed in a basic workup to support medical treatment decisions [94]. Given the availability, cost-effectiveness and swift acquisition of CT imaging, it remains a widely used modality in specialist clinics for initial evaluation of patients with dementia [95], [96]. In a memory clinic setting, the latest multidetector row CT technology was shown to yield reliable radiological information comparable with that obtained from MRI [91].

MRI is a noninvasive medical imaging technique that provides better contrast of soft tissue than CT. It is a *non-ionizing radiation* technique that relies on strong magnetic fields to enable the visualization of internal structures with millimetric resolution. Three image contrasts exist: T1-weighted, T2-weighted and proton density. In studies of neuroanatomical structure, T1-weighted (T1-w) is used because it provides good contrast of soft tissue. The possibility to visualize and quantify regional and whole brain tissue shrinkage from **structural magnetic resonance imaging** (sMRI) made it the best established measurement for detection and tracking of AD [97]–[102]. Volume of hippocampus became the best validated marker of memory decline [82], being included in the diagnostic criteria for AD

[30], [103], and showing a distinctive pattern different from normal aging [104]–[108]. However its low specificity for AD makes it inappropriate to rule out other diagnosis that also display atrophy in the medial temporal lobes, such as those caused by non-AD dementing disorders: Parkinson's disease, vascular dementia, hippocampal sclerosis, frontotemporal degeneration, and neurofibrillary tangle-only degeneration [109]–[112].

Success and acceptance of neuroimaging stems from its ability to detect structural changes closely related to cognitive symptoms [84], [113], such as the ventricular structures, hippocampus, amygdala, thalamus and entorhinal cortex [114]; also providing evidence of progression from MCI to AD. While quantification of atrophy requires careful and time-consuming manual tracing, a simple and quick visual assessment by a trained neuroradiologist is sufficient to obtain an impression of global brain atrophy, and observe predictable patterns of mediotemporal and parietal atrophy, see Figure 3 [115]–[118].

Figure 3 Visual assessment of mediotemporal lobe atrophy (*Courtesy of Lena Cavallin*)



T1-weighted Magnetic Resonance Computed Tomography

2.2 AUTOMATED NEUROIMAGING PIPELINES

The development of automated neuroimaging pipelines (e.g. FreeSurfer http://surfer.nmr.mgh.harvard.edu, FSL http://www.fmrib.ox.ac.uk/fsl, and SPM http://www.fil.ion.ucl.ac.uk/spm) enables among others the processing of high-resolution 3D T1-w MR images and measurement of cortical thickness, cortical surface and subcortical volumes across multiple regions of the brain. These developments instigated a change in paradigm: from relying solely in regions of interest manually delineated or global/regional brain tissue volume, neuroscientist began the search for **patterns of atrophy** on sMRI by detecting *group differences* [119]–[121].

Quantification of cortical thickness and regional brain volumes could potentially improve diagnosis and early diagnosis if regions that proved more informative and sensitive to disease-related changes were identified, and could even outperform clinical and cognitive measures. The first regions to show consistent specificity of AD were located in the temporal lobe (hippocampus, entorhinal cortex, fusiform cortex, inferior temporal and middle temporal cortices), and global measures (ventricular volumes and whole-brain volume) although relevant were less prominent [122], [123]. Nevertheless, many cognitively normal elderly people display evidence of pathology that is asymptomatic, including presence of amyloid burden, prompting the question as to whether evidence of preclinical AD can be observed at very early stages of the disease process. This remains elusive, given that reductions in cognitive abilities like processing-speed, executive function and episodic memory are common among elderly people [124]–[126].

Unfortunately, current evidence indicates that significant age-associated decrease in global (whole-brain and ventricular volumes) and regional (temporal lobe and hippocampus) brain volumes can be observed and quantified, and there is evidence of increased acceleration of atrophy with increasing age [127]. After only one year, cortical (temporal and prefrontal cortices) and subcortical reductions, and ventricular expansions were already evident in the healthy elderly [128]. Thus, presence of atrophic changes does not necessarily reflect a latent AD process. Although in aging and AD the hippocampus and entorhinal cortex are affected, medial temporal lobe structures are relatively more prominently affected in AD [129]. In normal aging, the medial temporal lobe structures are relatively spared and most of the age-associated cortical atrophy is most prominent in prefrontal, lateral parietal and sensorimotor regions [130]. Since brain atrophy in AD-prone regions can be seen in normal aging, early diagnosis of dementia with a high sensitivity will most likely result in low specificity. Age inevitably affects brain structures independently of AD, not necessarily related to an ongoing neurodegenerative disease, resulting in part of late life cognitive decline left largely unexplained [131].

Group-based univariate statistics at regional or voxel level offer limited sensibility when differences between populations are due to complex combinations of several brain structures. While it may be possible to say that Alzheimer's patients have smaller hippocampi than controls, it is difficult to deduce that an individual is in the early stages simply by examining hippocampal volume, or any given number of structures in this fashion. No information at the individual level is obtained. Hence, a growing interest in statistical learning methods to overcome the limits of univariate analysis and capture relationships among all measures has begun.

2.3 INDIVIDUAL CLASSIFICATION BASED ON STATISTICAL LEARNING

Eventually, the diagnostic utility of sMRI was demonstrated after the **individual classification** of Alzheimer's disease versus cognitively normal aging became feasible and reliable. It was the integration of neuroscience, statistical learning and neuroimaging that led to the application of support vector machines to MRI for individual diagnosis [132]. This first

study successfully classified gray matter from T1-w MR scans of pathologically proven AD patients from those of cognitively normal elderly individuals (up to 96% accuracy). A number of studies followed for AD classification, MCI classification and progression, and normal aging progression [133]–[143].

Similarly to the group-based analysis, variables of importance for the classification of AD and cognitively normal individuals were medial temporal lobe structures (hippocampus, amygdala, entorhinal cortex, parahippocampal gyrus, inferior and superior temporal gyri, cingulum), isthmus cingulate and ventricular volumes as reported for OPLS [144], [145], SVM [135]–[137] and linear discriminant analysis [146].

Moreover, the use of statistical learning techniques not only allows the integration of information from multiple brain structures and combination of volumes and cortical thickness measures in a principled manner. Statistical learning techniques also allow the creation of a single quantitative value for each individual with discriminative power reflecting the presence of disease-like patterns of brain atrophy [135], [136], [147] and age-associated patterns of brain atrophy [138]. The high discriminative power of disease-specific patterns of atrophy is not surprising, what has become of greatest research value has been the individual discrimination of MCI from cognitively normal individuals carried out in cross-sectional and longitudinal studies [137], [148], [149]. Structural neuroimaging has shown that there are significant individual differences in cognitive decline, progression to AD and neurodegeneration [150], bringing new insights into different pathophysiological processes underlying AD [151].

The marriage between statistical learning and neuroimaging gave birth to an explosion of statistical methods being applied based on sMRI to overcome not only statistical limitations but also methodological issues such as multicenter studies, multiscanner acquisitions, multiprotocol scanning, and multiple data fusion [152], [153]. The quest for imaging neuropathology *in vivo* was initially driven by better visualization, then more accurate measures and better statistics and has finally been driven by data integration and individual's risk estimation and individualized diagnosis.

3 STATISTICAL LEARNING

Begot by the need of experimental scientists to fit theoretical models from limited noisy data and make predictions, linear regression was realized by the method of least squares [154]. Soon after, many other methods based on linear models were proposed, such as linear discriminant analysis, logistic regression and generalized linear models [155], [156]. Advances in computing technology made it possible to introduce non-linear models like classification and regression trees, and generalized additive models [157], [158].

3.1 ESTIMATION OF A FUNCTIONAL RELATIONSHIP

Modeling is part of most research devoted to quantify relationships among variables of some process. Quantification of a process may mean determining the degree of association between a dependent variable and explanatory variables, or estimating the many parameters of a *theoretical mathematical model* for a system. For instance, the most general relationship between a *dependent variable* **Y** and several *explanatory variables* **X** (**X** = X_1, X_2, X_3, …) can be mathematically expressed as

$$Y = f(X) + \epsilon \qquad 4.1$$

A fixed and unknown function *f* represents the *systematic information* that the explanatory variables provide about the dependent one; and ϵ is a random *error term* with zero mean. The whole purpose of *statistical learning* is to estimate a functional relationship (Equation 4.1) from the observed data, in order to make **predictions** and **inference**.

Statistical learning methods can be classified as either *parametric* or *non-parametric*. Parametric methods are characterized by assuming a priori a functional form, simplifying the estimation problem to that of fitting a set of parameters. While non-parametric methods avoid the assumption of a particular functional form covering a wider range of relationships among the variables.

Variables can be classified as either *quantitative* (continuous) or *qualitative* (categorical). Examples of quantitative variables include age, height and weight, while examples of qualitative variables include gender, diagnosis and marital status. Statistical learning problems with a quantitative dependent variable are commonly referred to as *regression* problems, while those involving a qualitative one are referred to as *classification* problems.

The accuracy of a prediction depends on two types of error: one is *reducible error*, given that the functional relationship is unknown and must be estimated. This error can be diminished by choosing a suitable function. The second is *irreducible error* stemming from the fact that the dependent variable is assumed to be a random variable, generating variability that does not depend on the explanatory variables, thus this cannot be estimated, and it affects prediction.

Statistical learning methods are designed to decrease the reducible error by a process called **learning**. Formally, learning reduces to an *optimization problem*: find the optimal functional relationship that ensures a good representation of the data without modeling the irreducible error. Associated with every chosen function, there is an *expected risk* $R[f]$ that the estimated functional relationship will also model this error. Learning aims at decreasing this expected risk, also called *generalization error*, to a minimum. The expected risk captures the average *discrepancy* between predictions and true values on unseen data not used during the learning process, thus intuitively assessing the quality of the modeling. Discrepancy is measured by a suitable function for our particular learning problem, known as the loss function $L\big(Y, f(X)\big)$. Mathematically, the expected risk corresponds to the computation of the expectation (average) of the loss function.

$$R[f] = \int L\big(Y, f(X)\big) dP(X, Y) \tag{4.2}$$

A problem associated with the learning processes just described originates from observing that the original formulation of the expected risk (Equation 4.2) demands unseen data, independent from the one used for learning. In reality, when data is scarce, the risk is calculated by minimizing the loss function on the sample data. This risk computed on the data also used for learning is known as the *empirical risk* or training error. In practice, for some cases there are large deviations between the empirical and expected risks due to noisy data and because a theoretical model will never perfectly model a real-life process.

One idea that originated to tackle this problem starts by defining a *guaranteed risk* $R_{gua}[f]$ [159]. A guaranteed risk is an upper bound on the expected risk; it guarantees that with probability (1 - δ), the expected risk will not exceed a fixed quantity.

$$R[f] \leq R_{gua}[f, \delta] \tag{4.3}$$

The Vapnik-Chervonenkis theory shows that when learning from a *finite* amount of training data, the minimization depends on both the training error and the statistical complexity of the function class, or *capacity* [160]. The VC theory predicts that if the capacity of the function class is restricted so that it is small enough in relation to the available amount of data, i.e. *optimal capacity matched to the size of the training set*, then for all functions of that class: with probability of at least 1 – δ, the expected risk is at most equal to the guaranteed risk.

3.2 LINEAR REGRESSION

In the context of empirical science, an experimenter trying to understand a phenomenon may measure various quantities in a system and attempt to *predict* dependent from explanatory variables. If the experimenter has sufficient evidence to assume a priori a linear relationship exists between the variables (*functional form*), then linear regression suffices to determine *linear relationships* between a set of (quantitative) dependent variables and a set of

explanatory variables. This method produces the best linear fit and is known as **ordinary least squares regression**. In the context of linear regression, multivariate regression refers to the case where the goal is to form relationships between several dependent variables and several explanatory variables; and univariate regression when there is only one dependent variable and several explanatory variables.

Mathematically, a linear model can be expressed as

$$f(X) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots \quad 4.4$$

Where $\beta = \beta_0, \beta_1, \beta_2, \cdots$ are the parameters to be estimated from the available data by a statistical learning method. Associated with every model, the error term ϵ prevents a perfect prediction of dependent from explanatory variables. In particular, assuming a linear model, the general linear relationship becomes

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \epsilon \quad 4.5$$

In the context of regression, the most common and intuitive loss function is the **squared loss** of *residuals* $L\big(Y, f(X)\big) = \big(Y - \hat{Y}\big)^2$. Defining, $\hat{Y}$ as the prediction of dependent from explanatory variables, and the *residual sum of squares*, $RSS = e_1^2 + e_2^2 + \cdots + e_n^2$, where $e_i^2 = (y_i - \hat{y}_i)^2$. RSS measures the amount of variability left unexplained after performing the regression. One finds that the least squares approach to linear regression is a realization of statistical learning that chooses to minimize the squared loss of residuals.

Measuring a large of number of explanatory variables is often done in the hope that some of them may contain relevant variability to explain the process of interest even if some make little contribution. However, having a large number of variables may introduce systematic variation unrelated to the dependent variable, and may often constitute the major part of the observed variation. Moreover, in the case of *multicollinearity* (two or more explanatory variables related to one another) or a small number of observations and a large number of explanatory variables, the regression problem becomes overdetermined. As the number of explanatory variables increases, the data appear cloudy, unclear and redundant, making it difficult to determine how each variable is separately associated with the dependent one.

3.3 PRINCIPAL COMPONENT ANALYSIS

A simple and non-parametric standard tool in data analysis, principal component analysis (PCA), solves this problem by extracting relevant information by *reducing complex data to a lower dimension*. PCA helps identify a set of variables, also known as *components*, that optimally capture the variability present in the explanatory variables. One of the main assumptions behind this technique is that *large variance corresponds to the dynamics of interest while low variance represents noise.*

A rationale for *dimension reduction*, that is producing a number of components less than the number of explanatory variables, is as follows. An equation with many components is typically more flexible than one containing fewer, with the disadvantage that estimating its components would be more easily influenced by noise (random errors) present in the data. That is, having more components allows for a better fit of the data, at the expense of noise also being modeled. When the model is applied on unseen data to make predictions, it turns out that more mistakes are made, bigger generalization error, than applying a model with fewer components less influenced by noise.

3.4 PARTIAL LEAST SQUARES

When the goal is to *predict* a set of dependent variables and the number of observations is small compared to the number of explanatory variables or there is *multicollinearity*, a simultaneous decomposition, *dimension reduction*, of explanatory and dependent variables might be optimal. Partial least squares (PLS) regression finds components that best predict the dependent variable. Each component is a *linear combination* of all explanatory variables, and relates them to the dependent variable using ordinary least squares regression.

PLS regression generalizes PCA and multiple linear regression by forming components that capture most of the variability that is useful for prediction, while reducing the dimensionality of the regression by using fewer components than the number of explanatory variables. Each component is constrained to be uncorrelated with each other, that is, they are said to be orthogonal to each other, solving the multicollinearity problem. However, the issue of deciding the optimal number of components to keep remains; therefore it is necessary to apply additional customized criteria.

3.5 ORTHOGONAL PLS

A method related to PLS, orthogonal PLS (OPLS), extends PLS by applying *cross-validation* as a customization criterion to determine the optimal number of components and, by separating the predictive and orthogonal components, to facilitate model interpretation [161]–[165]. OPLS unlike PLS keeps the *correlated variation*, related to class separation, in the first predictive component. And all *uncorrelated variation*, unrelated to class separation, in orthogonal components. The rationale is that by removing uncorrelated variation prior to data modeling, interpretability improves and the predictive ability should improve as well. In cases where large uncorrelated variation is present, PLS is forced to include all that variation in each PLS component, while OPLS extracts all correlated variation into one PLS component.

3.6 LINEAR CLASSIFICATION

So far, this presentation has focused on regression problems, the other major category is **classification** problems. Most concepts and ideas translate directly to classification problems where the dependent variable is no longer quantitative but qualitative; the objective being to estimate a function that predicts class label. The average number of *misclassifications*

intuitively appears as an appropriate loss function to compute the expected risk for classification problems. Thus, the loss function $L(Y, f(X))$ should correspond to a function that indicates when a misclassification is done $Y \neq \hat{Y}$. This simple function is appropriately called the *indicator function* $I(Y, f(X))$

$$I(Y, f(X)) = \begin{cases} 1 \; if \; Y \neq \hat{Y} \\ 0 \; if \; Y = \hat{Y} \end{cases} \tag{4.6}$$

In classification problems, correlated variation from a trained OPLS model corresponds to variation that separates the groups and non-correlated variation corresponds to variation that combines the groups [166].

An algorithm to solve linearly separable classification problems was devised by applying the idea of optimal capacity tuning by constructing hyperplanes, also known as linear classifier:

$$f(X) = w_1 X_1 + w_2 X_2 + \cdots + b \tag{4.7}$$

Notice the similarity to Equation 4.4, they are identical since a linear relationship is also assumed here. It was recognized that finding the parameters $w_1, w_2, \cdots, b$ that maximizes the margin is equivalent to finding training examples closest to the class boundary. Maximizing the margin between training examples and class boundary is equivalent to optimizing the capacity of the classification function to match the size of the training set. Those examples closest to the class boundary are called the supporting patterns, or *support vectors*, of the decision function. The training algorithm for optimal margin classification is known as **Support Vector Machines** (SVM) [167]. Although multicollinearity is not a problem for this method, the presence of noise can make the boundary between the classes overlap, rendering the problem non-separable. In such cases, the algorithm can be modified and allow some support patterns to be misclassified [168].

3.7 MAXIMUM-LIKELIHOOD ESTIMATION

A fundamental problem in statistical inference, namely that of *recovering the parameters for a given parametric statistical distribution*, is briefly presented. The best known criterion for parameter estimation is known as maximum-likelihood estimation (MLE) [169]. MLE can be formally stated as maximizing the expected *log-likelihood* of the data, such that when the resulting set of parameters are plugged into the model it yields maximum probability for the given data. MLE is very fundamental since any variable can be thought of as a random variable following a (un-)known statistical distribution.

Maximum-likelihood mixture estimation (MLME) finds the mixture of *n* distributions from a specified parametric probability family that best fits the expected log-likelihood of the data. The best-known statistical technique for MLME is the **Expectation Maximization** (EM) algorithm. The algorithm converges to a *local maximum* by iteratively increasing the log-

likelihood of the data to the model; at convergence the log-likelihood remains constant. EM works by iteratively applying Expectation and Maximization steps. In the Expectation step, the expected value of the data for each model given the current parameters is computed. In the Maximization step, the current parameters are updated based on maximum likelihood of the data.

The most common family of statistical distributions is the *exponential family*. Members of this family include Gaussian, Poisson, Binomial and Multinomial distributions [170]. In the Maximization step of the EM algorithm, the expected log-likelihood is maximized to obtain a better fit of the parameters. For a regular exponential family this equates to finding the unique parameter that minimizes the expected value of a corresponding regular *Bregman divergence* [171], [172]. And it has been shown that this minimizer is just the expectation of the random variable X [172]. Thus, the problem of MLE for a given regular exponential family corresponds to minimizing the expected Bregman divergence of the family, simplifying the computationally intensive maximization step of the EM algorithm and resulting in a general *soft-clustering* algorithm [172].

3.8 CLUSTERING

Clustering refers to a broad class of methods for *discovering unknown subgroups in data*. In this setting there are only explanatory variables, and since there is no associated dependent variable, the previous classification and regression methods are not applicable. Clustering seeks to partition the datainto distinct groups, where members of a group are similar to each other, while members of different groups are different, dissimilar to each other. Clustering simplifies data: from a sample of N observations to a sample of M subgroups. The optimization problem can formally be defined as minimizing the within-cluster variation.

Among the different categories of techniques employed in clustering, there are methods that operate on a dissimilarity matrix, such as sum-of-squares methods; and mixture models, which model the probability density function as a sum of individual statistical distributions, such as clustering applying MLME.

4 AIMS OF THE THESIS

The main interest of this thesis was the analysis and individual classification of Alzheimer's disease, MCI and normal aging populations based on structural neuroimaging. In particular, we aimed to evaluate and validate automated tools that have a potential diagnostic role based on structural image analysis of the brain.

Development of classification methods requires several methodological choices. The specific aims of this thesis were:

Study I	To evaluate different combinations of brain measurements and different normalization approaches to determine the optimal choice for individual classification of AD and prediction of MCI conversion at one-year follow-up.
Study II	To evaluate different statistical techniques for individual classification of AD and prediction of MCI conversion one year later, and the effect of age, education and APOE genotype to determine the optimal classification algorithm.
Study III	To characterize the longitudinal information condensed into a structural index derived from a statistical classifier to evaluate its validity as marker of atrophy change and disease progression over a year.
Study IV	To develop and validate an automated CT-based segmentation algorithm for quantification of total intracranial volume that demonstrates reliability, reproducibility and robustness.
Preliminary studies	Apply the proposed segmentation algorithm in a big sample of cognitively normal and demented elderly individuals, and extend the proposed methodology to obtain estimates of brain tissue and CSF volumes.

5 METHODOLOGY

5.1 ETHICAL CONSIDERATIONS

These studies were approved by ethical review boards in each participating country, and the participants have been informed and given written consent for inclusion.

5.2 STUDIES I-III

Subjects

Data was downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla. edu/ADNI, PI Michael M. Weiner). A total of 699 subjects were included in the study (AD = 187, MCI = 287 and cognitively normal = 225). ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public–private partnership (www.adni-info.org).

Data also originated from the AddNeuroMed project, part of InnoMed (Innovative Medicines in Europe), a European Union program designed to make drug discovery more efficient. A total of 348 subjects were included in the study (AD = 119, MCI = 119 and cognitively normal = 110); a subsample of 214 subjects with a one-year follow-up was also included (AD = 62, MCI = 73 and cognitively normal = 79). The project is designed to develop and validate novel surrogate markers in AD and includes a human neuroimaging strand [173], [174] which combines MRI data with other biomarkers and clinical data. Data was collected from six different sites across Europe: University of Kuopio, Finland, University of Perugia, Italy, Aristotle University of Thessaloniki, Greece, King's College London, United Kingdom, University of Lodz, Poland, and University of Toulouse, France.

MRI data

Data acquisition for the AddNeuroMed study was designed to be compatible with the ADNI project [175]. The imaging protocol for both studies included a high resolution sagittal 3D T1-w Magnetization Prepared Rapid Acquisition with Gradient Echo (MPRAGE) volume (voxel size $1.1 \times 1.1 \times 1.2$ mm^3) and axial proton density/T2-weighted fast spin echo images. The MPRAGE volume was acquired using a custom pulse sequence specifically designed for the ADNI study to ensure compatibility across scanners. Full brain and skull coverage was required and detailed quality control carried out on all MR images according to the AddNeuroMed quality control procedures [173], [174].

Inclusion criteria

For ease of comparison, the inclusion criteria for subjects enrolled in the ADNI and AddNeuroMed projects are presented in Table 1.

Table 1 Inclusion criteria

	ADNI	AddNeuroMed
Alzheimer's disease		
MMSE	20-26	12-28
CDR	> 0.5	> 0.5
GDS	< 6	-
Age	-	> 65
ADRDA/NINCDS	Yes	Yes
DSM-IV	-	Yes
Mild cognitive impairment		
MMSE	24-30	24-30
CDR	0.5	0.5
GDS	< 6	<= 5
Age	-	> 65
Cognitively normal		
MMSE	24-30	-
CDR	0	0

ADNI = Alzheimer's Disease Neuroimaging Initiative, MMSE = mini mental state examination, CDR = cognitive dementia rating, GDS = geriatric depression scale, ADRDA = Alzheimer's disease and related disorders association, NINCDS = national institute of neurological and communicative disorders and stroke, DSM = diagnostic statistical manual.

Automated neuroimaging pipeline

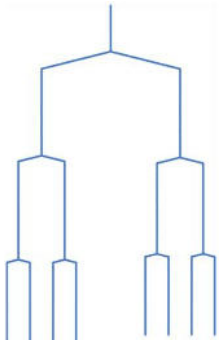
FreeSurfer is an image analysis suite that takes as input one or several T1-w images. It removes all non-brain tissue before automatic segmentation of the subcortical white matter and deep gray matter volumetric structures, including amygdala, hippocampus, caudate, putamen and ventricles. After creation of a cortical model further processing of the cerebral cortex produces representations of cortical thickness not restricted to the voxel resolution of the original data, thus capable of detecting submillimeter differences. These procedures have been validated and are properly documented in its website (http://surfer.nmr.mgh.harvard.edu).

Pre-processing of structural measures

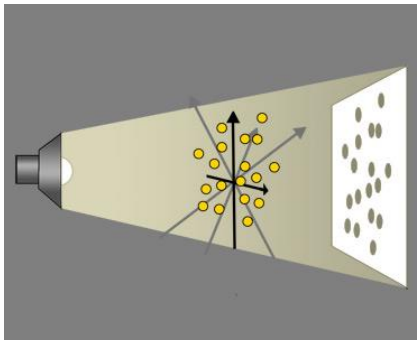
Variables were mean centered (zero mean) and scaled to have unit variance by dividing it by its sample standard deviation. Scaling may be necessary since the variables with highest variance would influence the performance of techniques based on squared Euclidean distance. Given that the average distance measure over all pairs of observations is $E[D] = \frac{1}{N^2}\sum_i \sum_j D(X^i, X^j) = \sum_k E[d_k]$, where $E[d_k] = \frac{1}{N^2}\sum_i \sum_j d_k(X_k^i, X_k^j)$ is the average distance on the k-th variable. For the squared Euclidean distance, the average distance on the k-th variable becomes $E[d_k] = \frac{1}{N^2}\sum_i \sum_j (X_k^i - X_k^j)^2 = 2 \cdot \sigma^2$, that is twice the sample estimate of the variance of the k-th variable. *The relative importance of each variable is proportional to*

its variance. Scaling every variable by dividing it by the sample standard deviation causes each of them to contribute equally.

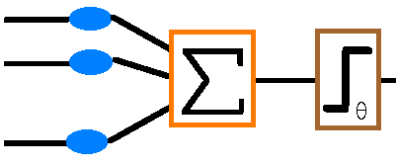
Figure 4 Illustration of statistical learning techniques considered in this thesis.



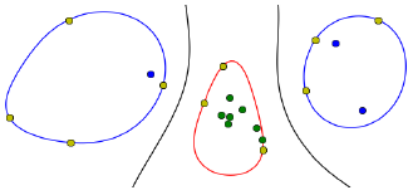
Decision trees



Orthogonal partial least squares



Artiticial neural networks



Support vector machines

Statistical learning techniques

Four classification techniques were considered taking all structural measures derived from FreeSurfer as explanatory variables and clinical diagnosis as dependent variable (demented vs. non-demented), see Figure 4.

An implementation of decision trees (Trees) part of the WEKA machine learning software was used [176]. This family of techniques works by finding arbitrarily complex Boolen functions (YES/NO): a decision tree breaks the classification problem down into a set of choices (if-then rules). A greedy algorithm builds the tree by choosing the most informative variables based on information theory criteria [177].

An implementation of artificial neural networks (ANN), multilayer perceptron, part of the WEKA machine learning software was used [176] . An artificial neural network is a non-linear statistical model inspired from the nervous system. Taking a neuron as the processing unit of the brain, Rosenblatt proposed a hypothetical nervous system: the perceptron [178].

The implementation of the Support Vector Machines (SVM) based on the LIBSVM library was used [179]. This implementation solves the soft-margin classifier and allows for non-linear mapping of the input variables to a higher dimensional space thanks to the dual kernel

representation, allowing for misclassification and modeling of non-linear relationships among the input variables.

The OPLS implementation included in the statistical package SIMCA was used (Umetrics AB, Umeå, Sweden) as a supervised (classification) multivariate data analysis method.

Model validation via cross-validation

Cross-validation is a statistical technique for validating a predictive (classification) model which involves constructing a number of parallel models. Each time a new model is created, part of the data is left out to estimate predictive accuracy on unseen data; this process is repeated for all possible permutation of the data. A 10-fold cross-validation was applied through all studies [180].

5.3 STUDY IV

Subjects

Eighteen patients (8 women and 10 men; mean age of 73 years) referred to a local Memory Clinic (Karolinska University Hospital, Huddinge) were retrospectively selected. From all who had undergone imaging examination of the brain in the context of memory investigation, we selected those who were scanned using both CT and MRI, or were scanned twice the same day using CT. Patients with other pathologies, such as intracranial tumors or infarcts were excluded.

CT and MRI data

The imaging protocol included an axial CT scan (GE Medical Systems, LightSpeed VCT) without intravenous contrast (detector area, 20 mm x 0.625 mm; voxel size, 0.4199 x 0.4199 x 2.5 mm^3; effective radiation dose, 1.7 mSv). The MRI acquisition (1.5 Tesla scanner; Siemens, Avanto) included a T1-w MPRAGE coronal pulse sequence (TR, 1910 ms; TE, 3.14 ms; flip angle, 15 degrees; voxel size, 0.449 x 0.449 x 1.4 mm^3).

All subjects were scanned using the same protocol. Full coverage was required with at least one slice totally above and one totally below to ensure full coverage of total intracranial cavity. As quality control, each scan was visually inspected to assess whole brain coverage and that no major artifacts were present.

Hounsfield scale

The Hounsfield Unit (HU) scale is a linear transformation of the original linear attenuation coefficient measurement. One advantage of using a normalized unit system like the HU scale is that irrespective of the machine and energy used, the radiodensity of water is defined as 0 HU, and that for air as -1000 HU. Hence, every substance has a unique CT number in the Hounsfield scale. Table 2 shows examples of common substances and its corresponding value in the HU scale.

Table 2 Hounsfield scale

Substance	**HU**
Air	-1000
Lung	-500
Fat	-100 to -50
Water	0
CSF	+15
WM	+20 to +30
Blood	+30 to +45
GM	+37 to +45
Bone	+3000 (dense bone)

CSF: cerebrospinal fluid, WM: white matter, GM: gray matter.

Automated MRI pipeline

Structural MRI images were skull-stripped using the Brain Extraction Tool (BET) from FSL. This method uses a deformable surface model that is fitted to the brain surface. The original images were cropped using **fslroi** from FSL to remove the neck. The pre-processed images were fed into **sienax** from FSL for neuroimaging segmentation.

Automated CT segmentation algorithm

Automated segmentation on CT was based on soft-clustering the accumulated histogram of pixel's intensity values by fitting a mixture of two binomial distributions applying MLME. The following algorithm was implemented based on open-source libraries for reading DICOM medical files (Grassroots DICOM – http://gdcm.sourceforge.net), programming real-time computer vision applications (OpenCV – http://opencv.org) and writing interpreted scripts (Lua – http://www.lua.org).

Proposed algorithm (see Figure 5):

1. Axial CT images were read and pixel intensity information extracted (Step I).
2. Two new images are derived based on hard thresholding: (1) brain tissue and cerebrospinal fluid (CSF) information with pixel intensities in the range -50 to 200 HU, and (2) bone information with pixel intensities greater than 200 HU.
3. The interior of the skull is traced from each slice by applying binary operations. Starting at the level of the eyeballs, information from the previously traced slice was used to estimate a region-of-interest and correctly extract the brain tissue, and at the same time remove parts of the eyeballs and connecting veins.
4. The intensity information from all slices is aggregated into a single histogram representing the probability distribution of all pixel's intensity (within the range -50 to 200 HU) composed of two separate frequency curves: CSF and brain tissue (Step II).
5. Maximum-likelihood mixture estimation is applied to obtain the parameters of a mixture of two binomial distributions resulting in a robust estimation of the maximum and minimum intensities with a significant probability of belonging to the fitted distribution (Step III).
6. All pixel intensity is restricted to lie between these minimum and maximum intensities and the resulting mask is eroded and dilated using an elliptical structural element (Step IV).

Statistical analysis

Agreement was assessed by quantification of volume differences and average volumes for repeated measures as part of a Bland-Altman analysis [181], and illustrated in a Bland-Altman plot; statistical significance of the presence of bias was computed based on a one-sample Student's t-test [182].

The degree of correlation was determined by computing the Pearson's correlation coefficient to test for linear correlation between the average volumes among different segmentation approaches.

5.4 PRELIMINARY STUDIES

Subjects

Ten patients from the previous study who underwent imaging examination of the brain in the context of memory investigation, and who were scanned twice the same day using CT were selected for validation of a regional segmentation algorithm.

Additional data also included two hundred forty-eight subjects (24 demented and 224 non-demented; 147 women and 101 men) of 85 years-of-age, born between 1923 and 1924, part of a population-based cohort (Gothenburg, Sweden) who had undergone CT imaging examination of the brain.

CT data

The imaging protocol included an axial CT scan (General Electric's Medical Systems, LightSpeed VCT) without intravenous contrast (detector area, 20 mm x 0.625 mm; voxel size, 0.4199 x 0.4199 x 5.0 mm^3; effective radiation dose, 1.7 mSv).

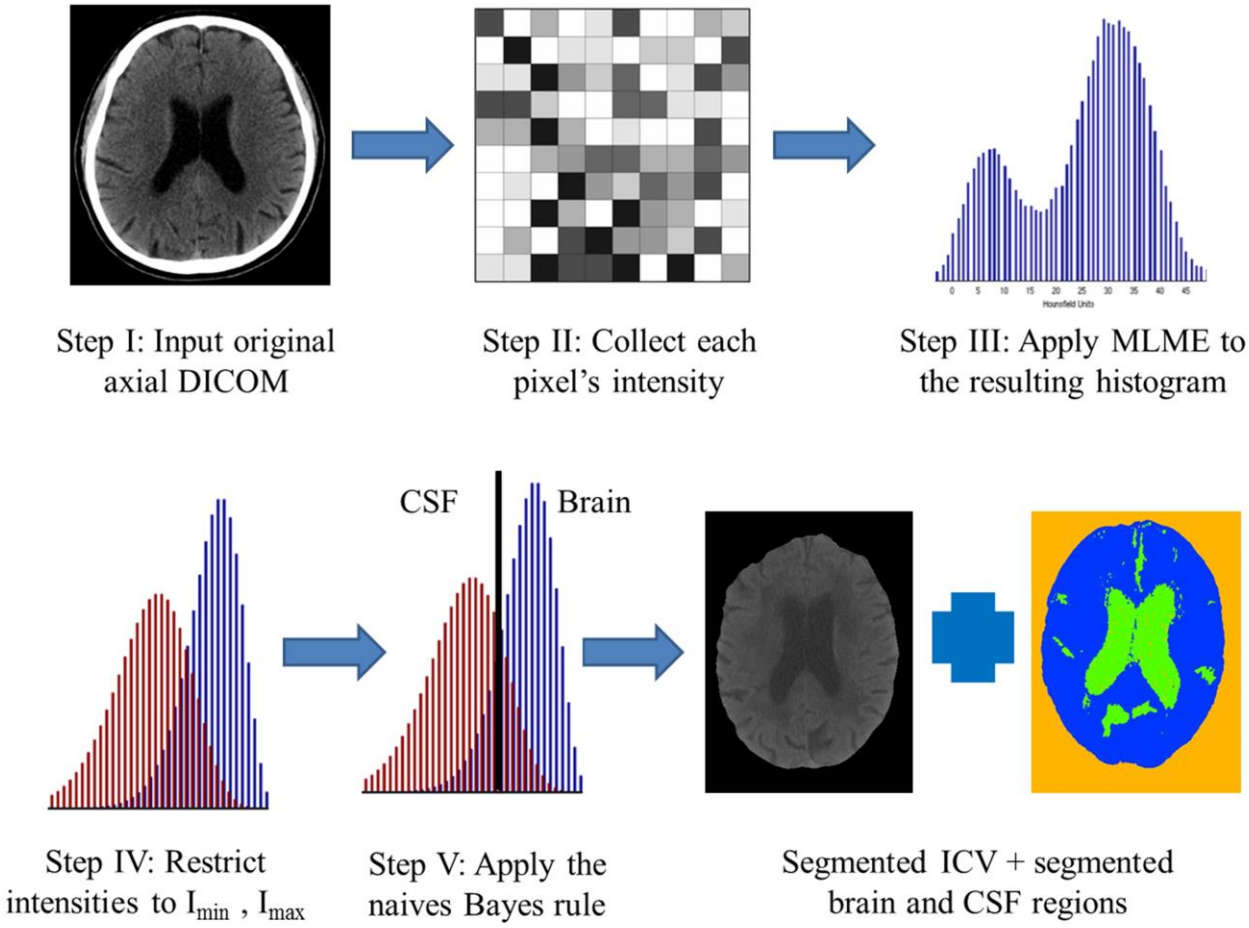
All subjects were scanned using the same protocol. As quality control, each scan was visually inspected to assess whole brain coverage and that no major artifacts were presents.

Automated CT regional segmentation algorithm

The segmentation algorithm proposed in the previous section works by modeling the accumulated intensity histogram as a mixture of two binomial distributions: one modeling CSF and another modeling brain tissue (Step III). Successful MLME results in the estimation of four parameters: two constants that weight the contribution from each distribution, and two parameters that correspond to the expectation parameter or probability for each binomial distribution.

Thus, as result of the MLME we obtain a probability model for the intensity distribution considering two random variables: pixels from CSF and pixels from brain tissue. Based on the naïve Bayes classification rule: for each intensity value select the distribution that is most probable and assign that class label (Step V). The algorithm is extremely efficient since only intensity values are considered, thus it is enough to construct a look-up table to segment a whole image.

Figure 5 Diagram of the proposed segmentation algorithm.



Our proposed algorithm takes as input an axial CT head scan (Step I), and by aggregating all pixel intensity values creates an accumulated histogram (Step II), which is then model using Expectation Maximization as a mixture of two binomial distributions (Step III). From the estimated parameters the maximum and minimum intensities can be robustly estimated to obtain a segmentation mask containing brain tissue and CSF (Step IV). Additionally, one can apply a Naive Bayes classifier and obtain a segmentation mask for brain tissue only and CSF only (Step V).

6 RESULTS

Development and longitudinal validation of a structural index from statistical models of AD-like patterns of atrophy (Studies I-III)

Several brain measures obtained by automated segmentation and parcellation of sMRI brain scans were used to train discriminative models for individual prediction of AD and conversion from prodromal stages. Among the methodological considerations faced when training discriminative models covered in these studies were: an optimal normalization strategy, an optimal combination of structural measures, the best discriminative learning technique and the influence of APOE genotype. A structural index reflecting information about AD-like of atrophy was derived from a baseline model based on the OPLS classification algorithm. And the temporal evolution of the derived index was assessed using one-year longitudinal information.

Optimal normalization strategy

In order to achieve optimal discriminative patterns of atrophy, brain measures need to be properly normalized. In study I, a significantly better discrimination of AD patients from cognitively healthy individuals was obtained for raw cortical thickness measures compared to normalized measures: 85.5% accuracy for raw measures, 83.5% accuracy for normalization by ICV and 83.7% accuracy for normalization by mean cortical thickness. In single region analysis, significantly better results were obtained when cortical volumes were normalized: 83.5% accuracy for normalization by ICV vs. 81.8% accuracy for raw volumes.

Optimal combination of brain structures

The best hierarchical model combining two different measures incorporated cortical and subcortical measures: 89.8% accuracy for subcortical volumes + cortical thickness, and 88.6% accuracy for subcortical volumes + cortical volumes. Normalization had no effect on these models. Combining three different measures did not significantly improve the prediction accuracy either, although the best overall model included raw cortical thickness + normalized cortical volumes + normalized subcortical volumes, resulting in 91.5% accuracy. Additionally, for individual MCI prediction of conversion to AD at 18-month follow-up, a hierarchical model combining subcortical volumes + cortical volumes or cortical thickness measures resulted in 77% of the MCI converters (MCI-c) correctly classified as AD.

Best discriminative learning technique

Optimal discrimination can also be influenced by the technique chosen to build statistical models. In study II, a baseline model was created based on the optimal normalization strategy and optimal combination of structural measures found in study I. Further, this model was used to compare the discrimination ability of different statistical learning techniques. The resulting discriminative models seemed to be equally accurate: 81.8% accuracy for Trees, 84.9% accuracy for ANN, 83.6% accuracy for SVM, and 84.5% accuracy for OPLS.

Likewise, classification of MCI-c as AD resulted in good discrimination: 85.7% for Trees, 81.0% for ANN, 85.7% for SVM, and 81.0% for OPLS. As expected, the hippocampus was the top ranked relevant feature for classification irrespectively of the classifier or whether feature selection was performed.

Addition of modulators of phenotypic expression

Further, addition of age, education level or APOE phenotype to the baseline model did not significantly improved prediction accuracy. Rather, if age was added to the model the performance of Trees became significantly reduced ($P < 0.005$), and if education was added to the model the performance of Trees was also significantly reduced ($P < 0.05$). Moreover, selecting the top most relevant measures did not result in better accuracy, nor did treating the variables differently using multi-kernel learning or hierarchical learning significantly improve performance when compared to the baseline model.

AD-like patterns of atrophy condensed into a structural index

From study I and II we showed that it was possible to build statistical models to find highly discriminative patterns of atrophy. But an atrophy score capturing the signature of these AD-like patterns of atrophy would facilitate clinical interpretation. In study III, the OPLS classification algorithm was trained on the baseline model to produce a structural index reflecting information about AD-like patterns of atrophy. We demonstrated high discrimination of AD patients from cognitively normal individuals at baseline: 84% specificity and 91% sensitivity. We observed that the AD-like patterns consisted of several relevant brain regions such as: the hippocampus, entorhinal cortex, amygdala, temporal lobe, superior temporal gyrus, inferior lateral ventricle, middle temporal gyrus, fusiform gyrus, inferior temporal gyrus and parahippocampal gyrus.

Temporal evolution of a structural index

As expected for an index reflecting AD-like atrophy, the AD group had the highest scores, followed by MCI-c, stable MCI and the cognitively normal group. All diagnostic groups showed higher scores over time, although AD patients showed the fastest rate (One-way ANOVA $P = 0.044$). The increase in scores over time improved classification accuracy due to a better sensitivity at the expense of reduced specificity: at baseline the sensitivity was 81% and the specificity was 90%; at one-year the sensitivity was 92% and the specificity was 75%. The oldest old individuals with normal cognition showed a high frequency of scores typical of AD-like atrophy (> 0.5) and had a significantly faster rate of cognitive (MMSE, Mann-Whitney $p = 0.05$) and structural (Mann-Whitney $p = 0.028$) decline. MCI patients that converted to AD within one-year presented scores non-significantly different from the AD-group (two-sided T-test $p = 0.76$), with the exception of three patients with normal scores (< 0.5). Finally, stratification of MCI patients into carriers vs. non-carriers of the APOE ε4 allele showed that carriers had higher scores ($P = 0.013$) and were more cognitively impaired compared to non-carriers (ADAS1, $P = 0.017$; CDR-sum, $P = 0.013$).

Intracranial volume estimation from Computed Tomography scans (Study IV)

Although MRI offers better brain tissue contrast, and is the preferred research imaging technique, CT is today widely used in routine clinical investigations. Since ICV remains a morphological measure of interest, in study IV we aimed to develop and validate an automated segmentation algorithm to estimate ICV from CT scans.

Our developed automated segmentation algorithm achieved successful segmentation to the degree of intensity variability seen in our sample, and good agreement with manual delineation set as gold standard (Student t-test one-tailed, paired means, $P = 0.011$). Moreover, the developed algorithm showed less variability in the estimation of ICV compared to manual tracing (F statistics = 0.004, $P < 10^{-7}$). There was a high correlation between our segmented volumes on CT and those segmented from MRI (Pearson's $r = 0.92$; linear regression $R^2 = 0.84$). We also observed low variability in volumes estimated on repeated acquisitions: a Bland-Altman analysis showed a non-significant bias of -1.5 mL (one-sample Student's t-test, one-tail, $p = 0.76$).

Preliminary studies: estimation of brain and CSF volumes from brain parenchyma

In study IV we presented a segmentation algorithm designed to successfully estimate ICV by modeling the intensity information in CT head scans. However, ICV alone does not offer any relevant diagnostic information. Both brain and CSF volumes are clinically relevant measures of cognition and the ratio between them appeared to be a sensitive measure of atrophy [183]–[185].

Validation of regional segmentation of brain parenchyma

In this preliminary study we aimed to extend the algorithm presented in study IV to obtain estimates of brain and CSF volumes from segmented brain parenchyma. As an initial approach we tested the hypothesis that a naïve Bayes classifier suffices to obtain good separation of brain tissue and CSF.

The naïve Bayes classifier was applied to patients having repeated CT acquisitions resulting in successful segmentation to the degree of intensity variability seen in our sample, and showing low variability in volumes estimated on repeated acquisitions, see Table 3.

Application of brain volume segmentation on a big sample of elderly individuals

Further, brain volume estimation was applied on a larger dataset of 248 individuals aged 85 who had undergone CT examinations, see Table 4. Volumes of total ICV for the whole cohort resulted in gender differences, men having larger volumes compared to women (One-tail Student's t-test, $p = 0$). Similarly, men had larger total brain volume (One-tail Student's t-test, $p = 0$) and CSF volumes when compared to women (One-tail Student's t-test, $p \sim 0$).

Table 3 Regional volumes from 10 patients scanned twice the same day.

	Brain Tissue		CSF	
Volume [milliliters]	Baseline	Replicate	Baseline	Replicate
	593	595	666	669
	1048	1051	134	124
	1116	1093	96	118
	997	967	143	164
	1211	1198	307	321
	1149	1120	236	263
	1235	1201	250	276
	873	874	137	133
	1061	1060	68	64
	834	819	370	399
Mean	1012	998	241	253
[SD]	[197]	[189]	[178]	[180]

Brain tissue and CSF volumes obtained by extending the proposed algorithm for automated CT segmentation on 10 patients with a replicate the same day. Brain Tissue: GM + WM, GM: gray matter, WM: white matter, CSF: cerebrospinal fluid, CT: computed tomography, SD: standard deviation.

Table 4 Estimated brain volumes from 248 individuals.

[milliliters]	Male	Female	Non-demented	Demented
TICV	1472 ± 114	1277 ± 99	1359 ± 138	1337 ± 177
Brain	1218 ± 114	1077 ± 111	1139 ± 129	1093 ± 149
CSF	255 ± 76	200 ± 78	220 ± 83	244 ± 66

Data is reported as mean ± SD. Two hundred forty-eight 85-year-olds born between 1923-1924 part of a population-based study. TICV: Total intracranial volume, CSF: cerebrospinal fluid, SD: standard deviation.

Effect of white-matter changes on segmented volumes

After stratification of the scans into those having white-matter changes (WMCs) based on visual assessment by a trained neuroradiologist, there was an association of larger CSF volumes when WMCs were present compared to absence of them (One-tail Student's t-test, $p = 0.002$). However, the association of larger CSF volumes with the presence of WMCs was only significant in the female group (One-tail Student's t-test, $p = 0.0002$). Also in non-demented women, the presence of WMCs was associated with larger CSF volumes (One-tail Student's t-test, $p = 0.0004$). The presence of WMCs did not significantly change the observation that demented women had smaller CSF volumes compared to non-demented (One-tail Student's t-test, $p = 0.0008$).

ICV comparison for two population-based cohorts

A previous study reported ICV averages for a population-based cohort of 85-year-olds born 1901-1902 [186]. The population cohort in these preliminary studies consisted of 85-year-olds born 20 years apart compared to the publication by Skoog; see Table 5 for a comparison of average ICV for these two cohorts.

In both cohorts, men had larger ICV compared to women, moreover demented people had an associated smaller ICV. Worthy of note, there was a more balanced number of demented and non-demented participants recruited in the publication by Skoog compared to the cohort used for these studies.

Table 5 Comparison of two population-based cohorts born 20 years apart.

TICV [milliliters]	**Cohort I**	**Cohort II**
Non-demented	(135)	(224)
	1268 ± 160	1359 ± 138
Demented	(104)	(24)
	1201 ± 165	1337 ± 177
Male	(74)	(101)
	1349 ± 164	1472 ± 114
Female	(165)	(147)
	1189 ± 140	1277 ± 99

Data is reported as mean ± SD; number of subjects is stated in parentheses. Cohort I corresponds to two hundred thirty-nine 85-year-olds born between 1901-1902 (*Skoog et al., NEJM 328 (1993) 153-158*). Cohort II corresponds to two hundred forty-eight 85-year-olds born between 1923-1924. TICV = total intracranial volume, SD = standard deviation

7 DISCUSSION

Development and longitudinal validation of a structural index from statistical models of AD-like patterns of atrophy (Studies I-III)

Neuroimaging studies for individual classification of AD patients from cognitively normal aging and prediction of conversion of MCI patients show considerable variability. This could reflect methodological differences in scanning parameters, design of statistical analysis or diagnostic criteria. Besides, there are also differences due to the sample, younger versus older populations or small versus big number of individuals. Finally, differences due to genetic, ethnical, social and environmental factors should not be ignored.

Normalization of volumes by ICV and optimal combination of brain measures in AD

It has been confirmed that patterns of atrophy as markers of disease were not only more sensitive than single regions of interest analysis but also more specific [142]. This study also demonstrated that registration, a preprocessing step, can influence the classification results. Moreover the use of gray matter (GM), white matter and CSF maps could lead to worse results compared to only using GM maps.

Given that GM appeared to be the most prominent marker of AD pathology, in study I we determined the optimal normalization approaches and the optimal combination of measures of GM atrophy that better classify AD patients and better predict MCI conversion. The hypothesis was that regional volumetric measures should be normalized by total ICV, and a combination of normalized volumes and un-normalized cortical thickness measures would generate the most accurate predictions. Besides division, it is possible to regress out ICV and remove its effect altogether, however removing all variance associated with ICV from regional brain volumes may also remove volume differences linked to protective or compensatory mechanisms such as brain reserve, since having a larger brain can have a protective effect against dementia onset.

For individual classification of AD patients from normal aging individuals, study I confirmed that normalized cortical thickness measures yield significantly lower prediction accuracies compared to raw cortical thickness measures [187]. And that volume normalization by division by ICV should be applied even when multivariate modeling is performed since this may facilitate interpretation and comparison between individuals [188]. For optimal discrimination, the combination of cortical and subcortical measures resulted in the best prediction accuracy. Thus it is not patterns of cortical reduction alone but optimally combined with patterns of subcortical atrophy that could become a reliable marker of AD pathology. The optimal combination of cortical and subcortical measures was done in a hierarchical fashion because this approach treats each type of measure independently. In cases of overlapping information, OPLS considers only variation not already provided by other measures [189].

The approach taken in study I had several limitations. The ADNI data originated from a multi-center study where different scanners were used, however, a sequence customized to ensure compatibility across scanners was used. The FreeSurfer pipeline was used to obtain regional measures deeming our results not applicable to studies using GM maps or other pipelines. The ADNI sample may not be representative of the general population, however several studies make use of it facilitating comparison with other groups.

Linear and non-linear classifiers for individual classification in AD

Previous studies demonstrated accurate individual classification by training linear classifiers and a recent review showed that SVM became the most popular and validated statistical learning technique in AD research studies [132], [135], [142], [144], [145], [152]. As an alternative to SVM we have proposed the use of OPLS for studies of individual classification, however, other techniques do exist. Therefore, in study II we aimed to assess the classification ability of different statistical learning techniques for individual classification of AD and prediction of MCI conversion at one-year follow-up. We also studied the effect of age, education and APOE genotype (ε4 carriers vs non-carriers) to determine the optimal learning technique.

In particular, we investigated whether classification performance could be improved by considering three non-linear classifiers: gaussian SVM, Trees and ANN. We speculated that adding age and education to our models, or adding APOE genotype information could enhance prediction accuracy. Finally, we hypothesized that considering all variables simultaneously would allow the model to capture widespread AD-like patterns of atrophy as opposed to selecting the top most informative ones.

The statistical learning techniques considered in study II were equally accurate in their discrimination ability for AD classification; however, they differ in their ability to predict conversion from MCI to AD. Worse performance in prediction of conversion was observed in Trees, probably due to the intrinsic variable selection performed as part of the learning. This provided support to our idea that keeping all variables rather than a selected set would increase discrimination ability. Also, limitations in the data, such as clinical diagnosis, inclusion/exclusion criteria, segmentation algorithm employed, should have a greater effect on individual classification rather than the classifier chosen to build the statistical model. This has also been concluded later when a review of the literature was carried out: the quality of the data rather than the statistical learning technique chosen has a higher impact on individual classification in AD [152]. These results support our view that extracting relevant information from structural neuroimaging demands statistical learning techniques capable of modeling patterns of atrophy. Moreover, the regions selected as most relevant overlapped among the considered classifiers. We found that hippocampus remained the single most relevant measure strongly associated with dementia diagnosis [190]. Contrary to our initial hypothesis, the addition of age, education level or APOE phenotype did not significantly improve classification accuracy. A potential explanation for this finding may be that for a linear

classifier such as OPLS, addition of other variables besides the ones derived from sMRI had a marginal effect since patterns of brain atrophy were stronger predictors of AD in and of itself.

Assessment of an MRI-based index for individual classification in AD

The study of the temporal evolution of patterns of atrophy in longitudinal studies is a necessary step in the validation of a potentially relevant clinical biomarker; for instance, convergence to a definite prediction over time should be demonstrated. However, such analysis requires the simultaneous study of all measures since each individual region follows its own trajectory over time. To ease the complexity burden and simplify interpretation, structural indices describing disease patterns were constructed [138], [140], [147], [191], [192].

In study III we extended the analysis of discriminative patterns of atrophy from studies I and II by deriving an MRI-based index reflecting AD-like patterns of atrophy. Our results revealed that diagnostic groups could be differentiated based on their average scores. Although all groups showed increased atrophy over time, the AD group displayed an accelerated rate thus giving support to the idea that AD unlike normal aging is characterized by an accelerated loss of brain tissue mainly in medial temporal lobe structures [129]. The increase in sensitivity at the expense of reduced specificity was previously reported and thought to be due to a convergence of phenotypic expression of AD pathology, and an accumulation of AD-like atrophy in cognitively normal individuals over time [41], [43], [44]. Another reason may be that brain regions vulnerable to the normal aging process are already evident after only one-year and overlap with those vulnerable to AD, such as the default mode network [128], [150]. We reported a group of oldest old individuals with normal cognition and high scores typical of AD patients. No further conclusions can be derived about this group since knowledge about AD pathology has been derived from populations of elderly people not representative of the oldest old [45], [46], [58]. MCI patients carrying the APOE ε4 allele displayed greater atrophy and more cognitive impairment supporting the idea they are not only at a higher risk of developing dementia, but also expressed a phenotype more typical of AD patients [53]–[56].

An important limitation of study III was the very short follow-up (one year), and that no definite diagnosis of AD was obtained. Also, there was no additional biomarker information to support diagnosis and we did not consider alternative summary scores for longitudinal cognitive performance besides averaging [193], [194].

These three studies demonstrated that statistical learning provides a promising way for individual patient classification in a fully automated and unbiased fashion. Open questions not covered in this thesis were the integration of additional clinical, biochemical and genetic information, as well as how early can AD be detected?

Intracranial volume estimation from computed tomography scans (Study IV)

Despite the fact that for research purposes MRI is the most popular neuroimaging modality, in primary care CT remains widely used for dementia investigations [95]. Therefore, we have aimed to tackle the problem of automated ICV estimation from CT head scans demanding high accuracy, reliability, reproducibility and robustness.

We developed an automated segmentation algorithm by fitting the parameters of the joint intensity distribution of brain tissue and CSF applying the EM algorithm [172]. Our proposed automated segmentation algorithm achieved successful segmentation to the degree of intensity variability seen in our sample, and in good agreement with manual delineation set as gold standard. This confirmed our initial hypothesis that modeling of the intensity information would be enough for adequate segmentation and was probably due to the high contrast between brain parenchyma and skull. There was also high correlation with volumes estimated from MRI, suggesting that estimation of ICV from accurate segmentation of CT head scans is feasible. The low variability in repeated acquisitions supports our idea that automated and unbiased measures of brain volumes should be preferred.

Limitations of our approach are that only a limited number of patients were considered, however patients with repeated acquisitions on CT and MRI modalities are highly uncommon. Also, beam-hardening and partial volume artifacts were not corrected for, which may reduce the size of the intracranial cavity. Finally, no spatial information was collected to refine the segmentation, a popular approach among MRI-based algorithms.

Preliminary studies: estimation of brain and CSF volumes from brain parenchyma

Although the impact of brain pathology on the risk of dementia is modified by ICV in demented old patients [123], [195], ICV does not correlate well with cognitive function [183]. Estimation of brain and CSF volumes has shown better association with cognition and thus would be of clinical relevance.

In these preliminary studies, we aimed at extending the segmentation algorithm proposed in study IV. Our results confirmed accuracy of our segmentation algorithm on estimates of brain and CSF volumes by application of the Naïve Bayes classifier. Although, there was a larger variance in these volumes compared to the variance found in estimating ICV. However, there was good agreement between repeated measures on the same individual. Additionally, a larger dataset of demented and non-demented patients was processed by our proposed algorithm and estimates of ICV, CSF and brain volumes were compared to a similar cohort of patients born 20 years before. Comparing the volumes between the two cohorts born 20 years apart, we could observe similar trends in the data: $ICV_{men} > ICV_{women}$ and $ICV_{non\text{-}demented} > ICV_{demented}$.

Limitations of our approach include a lack of a gold standard to assess the accuracy of our approach, but this would require very time-consuming manual tracing that would be necessary as final validation. Also, we observed differences in the estimated CSF volumes if

WMCs were present, suggestive of a potential partial volume artifact that should be accounted for. Finally, spatial information should be collected in order to refine the segmentation, and although that should help to better delineate the CSF-brain tissue boundary, it most probably would increase the computational complexity. Besides, the clinical utility of such refinement needs to be evaluated to determine its added value.

As proof of concept we have extend our segmentation algorithm to estimate brain and CSF volumes, however, the presence of WMCs could potentially have biased our results and we speculate that spatial information may be necessary to achieve more detailed refinement. Future work should focus on demonstrating the association of brain volume estimates and cognitive function, as well as longitudinal evaluation to demonstrate if this technique is sensible enough and adequate to track changes in time.

8 CONCLUSIONS AND FUTURE PERSPECTIVES

Brain atrophy changes are part of normal aging and perhaps AD is the result of accumulated negative assaults resulting in an accelerated and ordered pathological spreading leading to impaired cognition. However, even if the disease maintains its predictive progression, there is enough individual variability associated with the maintenance of cognitive function indicative of a reduction in the effects of AD pathology that such factors deserve further study [196]–[198].

The main contributions from this thesis are:

- Determination of an optimal combination of brain measures to model patterns of atrophy typical of AD.
- Simplification of the interpration of complex statistical models by deriving an MRI-based index to estimate the individual's risk(s) of developing AD.
- Characterization and longitudinal validation of a structural index that reflects patterns of AD-like brain atrophy.
- Development and validation of a segmentation algorithm for accurate estimation of ICV.
- Development of a segmentation algorithm of the brain parenchyma by modeling the joint intensity distribution of brain and CSF tissue.

The studies contained in this thesis applied computerized tools to the problem of AD diagnosis, achieving accurate individual prediction of disease status and conversion from prodromal stages. Key in the identification and validation of patterns of atrophy is the observation that changes in cognitive function are caused by structural and functional changes in the brain. However, several challenges remained to facilitate the integration of such tools in clinical practice [199]–[202]. At the same time, computerized tools that are unbiased and automated should be preferred and substitute time-consuming and error-prone user-dependent methods. Besides, the knowledge and understanding brought about neurodegenerative pathology is only a part of the big picture, and needs to be complemented by studies that look to elucidate the neuronal/histological substrates of cognitive reserve to shed light on the biological mechanisms behind mental resilience [203]; so that protective and detrimental factors can be linked to specific etiology.

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