Alzheimer’s Disease (AD) is the most common form of dementia in the elderly, and the prevalence of AD increases with age. It is the fourth leading cause of death among adults in the Western world. An estimated 35.6 million people worldwide were living with dementia in 2010. This number is estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050.

While the aetiology of AD remains unknown, the disease is characterized by accumulation of extracellular plaques composed of amyloid beta protein (Aβ) and intracellular neurofibrillary tangles consisting of hyperphosphorylated tau in the brain parenchyma, followed by extensive neurodegeneration. Traditionally, the diagnosis of AD has been based on cognitive symptoms, though requiring histopathologic confirmation for a definitive diagnosis. However, with recent advances in neuroimaging, the diagnostic criteria for AD have been revised to include evidence from imaging. Still, the diagnosis of AD is difficult to confirm due to overlapping symptoms with other disorders and the fact that patients often have mixed pathologies. Neuroimaging has the potential to effectively differentiate disorders and identify the various pathologies. With the progress of imaging technology and the wide access to scanners, the role of imaging has become increasingly important in the diagnosis of AD.

The temporal ordering of biomarkers associated with AD is relatively well-established (see Figure 1). For instance, the accumulation of Aβ can be detected by positron emission tomography (PET) years before symptoms appear, and before any structural changes can be detected using magnetic resonance imaging (MRI). However, structural imaging markers are considered more sensitive to change after the first symptoms appear. While the relatively cheap and non-invasive MRI is routinely used for excluding other causes of neuropsychological symptoms, such as tumours or strokes, PET with a radioactive tracer that targets amyloid, is currently perceived as the gold standard for detecting Alzheimer’s pathology in patients with dementia. However, recent research shows that the accumulation of Aβ is highly associated with age, and symptom free individuals have been found to have abundant accumulations of Aβ in the brain. In addition, PET is very expensive, which limits its general use in the clinic.

Even though macroscopic changes to the brain seem to occur later than accumulation of Aβ (see Figure 1), the progression of atrophy is closely correlated with the progression of symptoms. At patients’ first contact with the health care system, cerebral atrophy has already started. Thus, localized atrophy is generally a better marker than Aβ for disease progression in the transition phase between symptom onset and the established clinical diagnose. The accumulation of Aβ has already reached a plateau at the symptom onset (see Figure 1). Therefore, extensive research is carried out to develop imaging and image processing for accurate measurements of localized atrophy in order to diagnose AD and monitor the disease progression.

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Structural MRI, primarily T1- and T2-weighted images, has been used to assess cerebral atrophy in the past two decades. During the past 10 years, the technology for quantifying atrophy has progressed rapidly. For example, ten years ago, the standard method for hippocampal volumetry was to calculate the volume from manual delineations of consecutive image slices at relatively low resolutions. Since then, automatic methods have gained widespread use owing to their increasing robustness and accuracy when used with high resolution images. Today, automatic methods for measuring hippocampal subfields are on the verge of becoming sufficiently accurate and reliable to be used as highly sensitive markers for neurodegeneration, with the potential for improvement in diagnosis and prediction.

Typical structural alterations measured in AD are grey matter densities, anatomical deformations, cortical thickness, and the volumes of key structures, such as the hippocampus.
Recently, the sensitivity and accuracy of such structural features were thoroughly studied\(^7\). Results revealed that classical approaches for measuring these features have limitations in terms of their ability to predict AD among individuals with mild symptoms. Prediction accuracies achieved using a single method were less than 65% for all reviewed methods. Accordingly, these methods lack reliability and accuracy when applied on multi-centre studies or in a clinical setting. Accordingly, efforts must be placed in the identification of more sensitive features and more robust feature extraction methods for structural MRI.

In 2012, CFIN’s neuro-image analysis laboratory in a collaboration with researchers at Montreal Neurological Institute (MNI) and Centre National de la Recherche Scientifique (CNRS) in Bordeaux, published methods for predicting AD using hippocampus volumetry\(^8\) and cortical thickness\(^9\) (see Figure 2). We demonstrated that the improvement of such structural feature extraction methods significantly improves classification and prediction accuracy in AD. Using only cortical thickness features from a baseline MRI scan we were able to predict the development of AD in individuals suffering from mild cognitive impairment (MCI) within a three year window with an accuracy of 74% (see Figure 3). This is the best prediction accuracy achieved so far using a single imaging feature. Combining the structural features with clinical and neuro-psychological data may yield even higher accuracies.

Using a new concept of grading the hippocampus and the entorhinal cortex (ERC) using a library of labelled images, we were able to automatically classify AD patients and age-matched controls with an accuracies in the range of 90% -

**Figure 2**
Progression of cortical atrophy in patients with MCI. At three years prior to AD diagnosis, cortical atrophy is present in only few specific regions, such as the parahippocampal gyrus and the precuneus. However, one year later, the atrophy pattern is much more evident and continues to spread across the cortex. Notice how the sensory-motor and visual cortices are spared throughout the course of the disease. Adapted from\(^4\) and based on data from the ADNI study (http://adni.loni.ucla.edu/).

**Figure 3**
Performance of AD prediction using cortical thickness from baseline MRI. The “Conversion” shows the known conversion from MCI to AD (149 converted after three years). The accuracy, specificity, and sensitivity show the performance of predicting AD within X months from baseline among all the MCI patients (N=283). The three years prediction yields an accuracy of 74% with sensitivity of 64% and specificity of 84%\(^9\). Based on data from the ADNI study (http://adni.loni.ucla.edu/).
93%6,10 (see Figure 4). The grading concept can be applied in all areas where brain structures are modified by a pathological process.

More consistent and accurate measurements can be obtained from longitudinal data acquired over at least six months. With the MNI and CNRS, we are now developing methods11 that utilize longitudinal imaging data for detecting subtle structural changes and identifying specific atrophy patterns with the aim of predicting the disease and possibly improve patient stratification and AD subtype classification.

Looking forward, we expect to obtain reliable measurements of hippocampal subfields and investigate these in relation to cortical atrophy. The structural measurements will be combined with properties of cerebral vascular flow obtained from perfusion MRI for examining a hypothesis of capillary dysfunction in AD proposed recently by researchers at CFIN12. This has the potential to contribute significantly to understanding the aetiology of AD.

References