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Early detection of Alzheimer's disease using structural MRI: A research idea

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Abstract: Alzheimer's disease (AD) is a common progressive neurodegenerative disorder that is not currently diagnosed until a patient reaches the stage of dementia. There is an urgent need to identify AD at an earlier stage, so that treatment can begin early. Structural imaging based on magnetic resonance imaging (MRI) is an integral component of the clinical assessment of patients with suspected AD. Rates of brain atrophy could be assessed in specific regions such as the hippocampus, entorhinal cortex, temporal and parietal lobes, and ventricles. Structural brain MRI is becoming increasingly used in the early diagnostics of AD. Volumetry and pattern recognition techniques for measuring cortical thinning and automated classification approaches that assess the overall pattern of atrophy seem to show promise for the early diagnosis of AD. The study is aimed at developing new pattern recognition techniques and automatic classifiers to reliably detect AD in its early stages. Data used in the preparation of this proposal is supposed to be obtained from the Alzheimer's disease neuroimaging initiative (ADNI) database. Study will begin with pre-processing of MRI images which includes correction of inhomogeneities, de-noising, registration to the stereotaxic space e.g., using a linear transform and cross normalization of the MRI intensity followed by data modulation. Brain tissue will be segmented into white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) by the SMP software. Customized tissue probability maps (TMPs) have to be created for bias correction. For feature reduction and feature selection, datasets will be inserted into a linear support vector machine (SVM). After training a model by a sub-group, cross-validation by another sub-group will be used to achieve SVM parameter optimization. We also try to develop a better classifier e.g. Neural Network for automate classification. It is expected that using structural MRI to predict AD during early stages will allow for diagnosis and treatment before irreversible neurodegeneration and functional impairment have occurred. The aim is to improve the classification accuracy that can be achieved by combining features from different structural MRI analysis techniques.

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1. Introduction

1.1. Definition

Alzheimer's disease (AD) is a neurodegenerative disease of the brain that causes changes in brain functions. AD usually affects people over the age of 65 years, resulting in a progressive decline in memory as well as, thinking, language and learning capacity. Age is the strongest predictor for the development and progression of AD; with the rapidly aging population of our society, AD clearly poses a major health problem (1). The pathophysiology of AD is related to the injury and death of neurons, especially in those areas of the brain involved with memory and learning. AD is the most common form of dementia, accounting for 50% to 75% of all dementia cases, with a greater proportion among older populations. AD should be differentiated from normal age-related declines in cognitive function, which are more gradual and associated with less disability. AD often starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rates. On average, AD

patients live from 8 to 10 years after being diagnosed, although the disease can last for as many as 20 years (1, 2). Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia. MCI is associated with an increased risk for dementia. Such patients are able to live independently, are aware of their memory changes, and typically show problems with delayed recall, although non memory cognitive domains can also be impaired (3, 4).

1.2. Epidemiology of AD

Advances in medical technology have helped increase life expectancy, but age-associated cognitive impairment often diminishes the quality of life for the increasing numbers of older adults. AD is currently the most common form of dementia. In 2005, an estimated 24 million people around the world suffered from dementia. According to the 2010 World Alzheimer report, an estimated 35.6 million people worldwide are living with dementia at a total cost of more than US\$600 billion in 2010, and the

incidence of AD throughout the world is expected to double in the next 20 years (5, 6). By 2040, it is predicted that more than 81 million people worldwide will suffer from dementia. Deaths, because of AD have been rising dramatically while other major causes of death have been on the decline. AD is the sixth leading cause of all deaths in the United States and the fifth leading cause of death in Americans aged 65 years and older. Between 2000 and 2008, deaths due to AD increased by 66% whereas heart disease deaths decreased by 13%, stroke deaths by 20%, and prostate cancer-related deaths by 8% (5, 6).

AD inflicts a terrible toll on patients, their families, and society in general. Most experts agree that treatment is most beneficial if applied early, before significant, potentially irreversible neurodegeneration and functional impairment has occurred (4, 5). Every 69 seconds, one person in America develops AD; by 2050, the time is expected to accelerate to every 33 seconds. Over the coming decades, the baby boom population is projected to add 10 million people to these numbers. By 2050, the incidence of AD is expected to approach nearly a million people per year, with a total estimated prevalence of 11 to 16 million people. Dramatic increases in the numbers of "oldest-old" (those aged 85 years and older) across all racial and ethnic groups will also significantly affect the numbers of people living with AD while the number of Americans aged 65 and over with AD is projected to reach 13.2 million in 2050 compared with 4.5 millions in 2000. If present trends continue, the cost of caring for the expected increase in the number of AD patients will bankrupt public healthcare systems (4, 5).

An estimated 5.4 million Americans have AD; approximately 200,000 65-year-olds with AD comprise the younger onset of AD population. In 2010, nearly 15 million family and other unpaid caregivers provided an estimated 17 billion hours of care to people with AD and other dementias—a contribution valued at more than \$202 billion (4-6). Medicare payments for services to 65+-year-old beneficiaries with AD and other dementias are almost 3 times higher than for beneficiaries without these conditions. Total payments in 2011 for healthcare, long term care, and hospice services for 65+-year-olds with AD and other dementias were estimated to be \$183 billion (not including the contributions of unpaid caregivers) (4-6).

1.3. Diagnosis

1.3.1. Symptoms and signs

AD can affect different people in different ways, but the most common symptom pattern begins with gradually worsening difficulty in remembering new information as the disruption of brain cell

function usually begins in regions involved in forming new memories. As damage spreads, individuals experience other difficulties. The following are warning signs and symptoms of AD (3-5):

- Memory loss that disrupts daily life
- Challenges in planning or solving problems
- Difficulty completing familiar tasks at home, work, or leisure
- Confusion with time or place
- Trouble understanding visual images and spatial relationships
- New problems with words in speaking or writing
- Misplacing things and losing the ability to retrace steps
- Decreased or poor judgment
- Withdrawal from work or social activities
- Changes in mood and personality

1.3.2. Laboratory findings

Lab tests may be done to either categorize dementia or negatively exclude other possible causes of a person's symptoms, such as levels of certain minerals or chemicals in the blood being too high or too low, liver disease, abnormal thyroid levels, or nutritional problems, such as folate or vitamin B12 deficiencies. Some of the most common laboratory tests include the following:

- Complete Blood Count (CBC)
- Serum electrolytes
- Thyroid panel
- Vitamin B12
- Neurosyphilis serology
- ELISA
- Western Blot
- Urine toxicology
- ESR
- EEG

1.3.3. Imaging findings

The methods used for early detection of AD include clinical tests, as well as computerized tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), and cerebrospinal fluid (CSF) biomarkers (5-7). Traditionally, neuroimaging techniques have been categorized as either structural or functional, according to the primary information they provide. However, methods generally used to look at structure can also be altered to observe function (e.g., functional MRI). Similarly, traditional functional methods, such as PET, can also be used to view structure (e.g., amyloid plaque imaging). Commonly used structural methods include CT and MRI. Studies

of brain function are often done using SPECT, with technetium to measure blood flow, or PET, with the 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) tracer to measure glucose metabolism. In clinical practice, imaging studies are usually used to increase diagnostic accuracy to assist with treatment planning. The most recent American Academy of Neurology Practice Parameter guidelines recommend structural neuroimaging with either a non contrast CT or MRI scan in the initial assessment of patients with dementia (7-9).

The advent of computer-based methods for quantitative MRI has allowed for efficient quantification of AD-related atrophy across the brain. MRI offers good contrast between the different soft tissues of the body and provides high-resolution (~1 mm) information, making it especially useful in imaging the brain structure. Gadolinium contrast agents are sometimes used to enhance the visualization of brain lesions. In clinical practice, structural MRI scanning is widely used, and radiologists interpret results based on visual readings (10, 11). However, image analysis programs that quantify regional volumes in MRI have shown that medial temporal or hippocampal atrophy measures can distinguish patients with a clinical diagnosis of AD from controls. Although hippocampal atrophy can predict memory progression, these changes might not be specific to AD and might occur in other dementia disorders (7, 10, and 12).

Current consensus statements have emphasized the need for early recognition and the fact that a diagnosis of AD can be made with high accuracy by using clinical, neuropsychologic, and imaging assessments. Magnetic resonance (MR) or CT imaging is recommended for the routine evaluation of AD. Coronal MR images can be useful for documenting or quantifying atrophy of the hippocampus and entorhinal cortex, both of which occur early in the disease process. Both volumetric and subtraction MR techniques can be used to quantify and monitor dementia progression and rates of regional atrophy. MR measures are also increasingly being used to monitor treatment effects in clinical trials of cognitive enhancers and antidementia agents.

PET and single photon emission CT offer value in the differential diagnosis of AD from other cortical and subcortical dementias and may also offer prognostic value. In addition, PET studies have demonstrated that subtle abnormalities may be apparent in the prodromal stages of AD and in subjects who carry susceptibility genes. PET ligands are in late-stage development for the demonstration of amyloid plaques, and human studies have already

begun. Functional MR-based memory challenge tests are in development as well.

The principal agents used in brain SPECT of patients with AD are $^{99\text{mTc}}$ hexamethyl propyleneamine oxime ($^{99\text{mTc}}$ HMPAO) and $^{99\text{mTc}}$ ethylcysteinate dimer ($^{99\text{mTc}}$ ECD). These agents accurately measure cerebral blood flow and making them valuable in identifying the reduced cerebral blood flow in the temporoparietal region seen in patients with AD (13).

On a perfusion MRI using dynamic susceptibility contrast-enhanced MRI— a method utilizing rapid T2*-weighted imaging of the brain during intravenous injection of a bolus of paramagnetic contrast material— reduced relative cerebral blood volume can be seen in the temporal and parietal regions of patients with AD, which correlates with the cerebral blood flow reduction seen on PET and SPECT. Unlike PET perfusion imaging, MR perfusion imaging takes less time to perform, involves no radiation exposure, and is readily available on any MR unit capable of echo-planar imaging (14).

Diffusion-weighted MRI detects alterations in microscopic water motion within tissues, which is usually measured by the apparent diffusion coefficient value. An increased rate of water diffusion has been reported in the hippocampal gyri of AD patients, likely caused by the disruption of membranes and myelin sheaths combined with the fragmentation of axons and dendrites or by the expansion of extracellular fluid from the inflammatory response (15).

MR brain activation studies that assess the degree of brain activation during memory tasks using a blood oxygenation level-dependent technique offer another promising method for studying AD. Studies of AD patients have shown decreased activation of the left medial temporal lobe during auditory memory tasks and decreased activation of the right parietal region in response to visual memory tasks. Functional MR imaging has proved to be a powerful research technique to aid in identifying regions of the brain activated by particular stimuli and tasks. With this technique, regional brain activity is measured according to local changes in deoxyhemoglobin concentration in response to various stimuli and tasks. In brief, rapid T2*-sensitive imaging, usually gradient-echo echo-planar imaging, is performed during presentation of a stimulus or performance of a specific task and during rest periods. A voxel-by-voxel statistical comparison is then performed with images obtained during the stimulus/task periods versus those obtained during the rest periods, creating a statistical-activation map that can be “thresholded”

and presented as a color overlay on anatomic T1-weighted images (15, 18).

MR spectroscopy is a technique that can monitor the metabolic changes that accompany brain structural changes and therefore would be expected to play a valuable role in the imaging of AD. The presence of senile plaques is associated with neuronal loss that is reflected in a decrease in the neuronal marker N-acetylaspartate. This N-acetylaspartate decrease can be readily detected on MR spectroscopy (16).

1.3.4. Diagnostic criteria

Clinical criteria provide sensitivity of greater than 90% for diagnosing dementia of any type, including AD, in specialized clinical settings such as memory disorders clinics; however they have a specificity of less than 70% for the actual diagnosis of AD (16).

The clinical standards used to diagnose AD were first defined in 1984. These standards require insidious onset; gradual progression of memory deficits; a focus on early deficits of recent memory; and later impairment of orientation, judgment, problem solving, community and home living, and personal care. In addition to a diagnosis of clinically define AD, the diagnoses of probable AD and possible AD can be rendered; both of these diagnoses allow for variations in onset, presentation, and course. The term "probable Alzheimer's disease" refers to memory deficits evident in neuropsychological testing (Mini-Mental State Examination [MMSE] score ≤ 23) and progressive worsening of memory and deficits in two or more cognitive functions, as documented by clinical and neuropsychologic testing.

The cognitive functions discussed thus far are measured by a battery of clinical and psychometric tests, such as the MMSE and clinical dementia rating. Normal cognitive performance scores for the MMSE are greater than or equal to 27.6 (maximum score = 30); for the clinical dementia rating, they are less than 0.5 on a scale of 0–3.

1.4. Study Background

The goal of early MRI studies in AD has been to identify general evidence for brain damage that was specifically associated with AD and with the severity of the clinical symptoms (5, 17). Advances in medical imaging systems have provided a wide spectrum of valuable and complementary information about a patient's pathology, anatomy, and physiology. Information produced by CT, MRI, SPECT, PET, and CSF differs in dimensionality, scale, extent, and biological origin. For example, structural MRI has been successful in the early

detection of the effects of AD on the brain even in earlier stages of the disease when clinical symptoms are not fully expressed and the regional brain damage may be limited. Thus, MRI measurements, primarily in the gray matter (GM), could be sensitive markers of the disease and assist early diagnosis (6, 18).

Volumetric changes to brain structure could be assessed by MRI of specific regions such as the hippocampus, entorhinal cortex, temporal and parietal lobes, and ventricles [12-13]. Current clinical MRI scanners with 1.5T or 3T magnets allow for the acquisition of high resolution digital images of the brain in exquisite structural detail, with excellent tissue contrast and spatial resolution of ≤ 1 mm (4).

1.5. Problem Statement

AD is a common progressive neurodegenerative disorder that is not currently diagnosed until a patient reaches the stage of dementia. A pressing need exists to identify AD at an earlier stage, so that treatment, when available, can begin early (7). According to the World Alzheimer Report 2011, most people living with dementia have not received a formal diagnosis. In high-income countries, only 20-50% of dementia cases have been recognized and documented in primary care. This treatment gap is certainly much greater in low- and middle-income countries, with one study in India suggesting that 90% of such cases remain unidentified. If these statistics are extrapolated to other countries worldwide, it suggests that approximately 28 million of the 36 million people with dementia have not received a diagnosis, and therefore do not have access to treatment, care, and organized support that getting a formal diagnosis can provide.

This is clearly a major concern, given that the world's population is growing older and new cases of dementia and AD are increasing relentlessly; as a result, earlier diagnosis and early intervention are important mechanisms by which the treatment gap can be closed. With increasing life expectancy across the world, the number of elderly people at risk of developing dementia is growing rapidly. The prevalence of dementia rises steeply with age, doubling every 4–5 years from the age of 60, meaning that more than one third of individuals over 80 years of age are likely to develop dementia. AD remains the most common cause of dementia in all age groups (19).

1.6. Study Significance

Pathological processes and brain abnormality in AD can be detected using structural MRI, which is becoming increasingly popular in the early diagnostics of AD (3). Quantitative structural

MRI is sensitive to the neurodegeneration that occurs in mild and preclinical AD, and is predictive of decline to dementia in individuals with mild cognitive impairment. Objective evidence of ongoing brain atrophy is critical for risk/benefit decisions once potentially aggressive, disease-modifying treatments become available. Recent advances have paved the way for the use of quantitative structural MRI in clinical practice, and initial clinical use has been promising (10, 12). Early detection and diagnosis of cognitive impairment confers that early detection and prevention (4, 17, and 20):

- Leads to minimum cognitive decline;
- Helps facilitate treatment or management of coexisting medical conditions that worsen cognitive function;
- Predict of conversion to AD;
- Allows prompt evaluation and treatment of reversible or treatable causes of cognitive impairment;
- Allows potential management of symptoms with medication or other interventions;
- Aids in the management of possible behavioral symptoms.

1.7. Objectives

1.7.1. General objectives

The general objective of the study is to find a method for early detection of AD using structural MRI. In this proposal, “early diagnosis” refers to one’s ability to diagnose AD at a very early stage, before symptoms and clinical signs have reached the stage at which a diagnosis of clinically probable AD can be made according to currently recommended criteria.

1.7.2. Specific objectives

The specific objectives of the proposed study are:

- To improve the latest techniques used in structural MRI for measuring the progression of MCI and early AD;
- To develop methods of extracting quantitative and semi-quantitative data from structural MRI to be applied in early diagnosis of AD;
- To outline new means for feature extraction and feature selection;
- To determine an automated technique for extracting AD-specific data from cross-sectional and serial structural MRI;
- To improve methods for sMRI-based volumetric assessment in ROI;
- To implement a new and more precise classifier to clarify with greater accuracy the

transitional zone between the healthy aging and the first manifestations of AD; and

- To reinforce the place of structural MRI as a powerful biomarker of the stage and intensity of AD.

2. Proposed Methodology

2.1. Research Design

The proposed research is a diagnostic image processing study based on data acquired from structural MRI neuroimaging. It is aimed at developing new pattern recognition techniques to reliably detect AD in its early stages (Fig. 1).

2.2. Research Method

2.2.1. Materials

Data used in the preparation of this proposal were obtained from the Alzheimer's ADNI database (<http://www.loni.ucla.edu/ADNI>). The ADNI is a multi-center study assessing neuroimaging for diagnosis and longitudinal monitoring. The ADNI was launched in 2003, and its primary goal has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in developing new treatments and monitoring their effectiveness as well as reducing the time and cost of clinical trials(4, 6). MRI data were acquired according to the ADNI acquisition protocol. For each subject, we used the MRI scan from the baseline visit when available and from the screening visit otherwise.

Each scan was graded on several separate criteria: blurring/ghosting, flow artifact, intensity and homogeneity, signal-to-noise ratio (SNR), susceptibility artifacts, and gray-white/cerebrospinal fluid contrast. For each subject, we used the MRI scan considered to be the “best” quality scan by the ADNI investigators (12, 21, and 22).

2.2.2. Method

Pattern recognition consists of two major steps. First, features are extracted from the signals in such a way that they represent the signal very well. These features should contain all important information about the image. Then, according to a trade-off between required accuracy and computational cost, a smaller number of meaningful features are selected. The second step focuses on classification. A specific pattern is allocated to a class based on the characteristic features selected for it. In this proposal, the data are first pre-processed, which usually includes de-noising, image normalization,

and the isolation of patterns of interests from background. Then, during the feature extraction and feature selection phase, a group of appropriate

features are obtained. Finally using a good classifier, the data are classified.

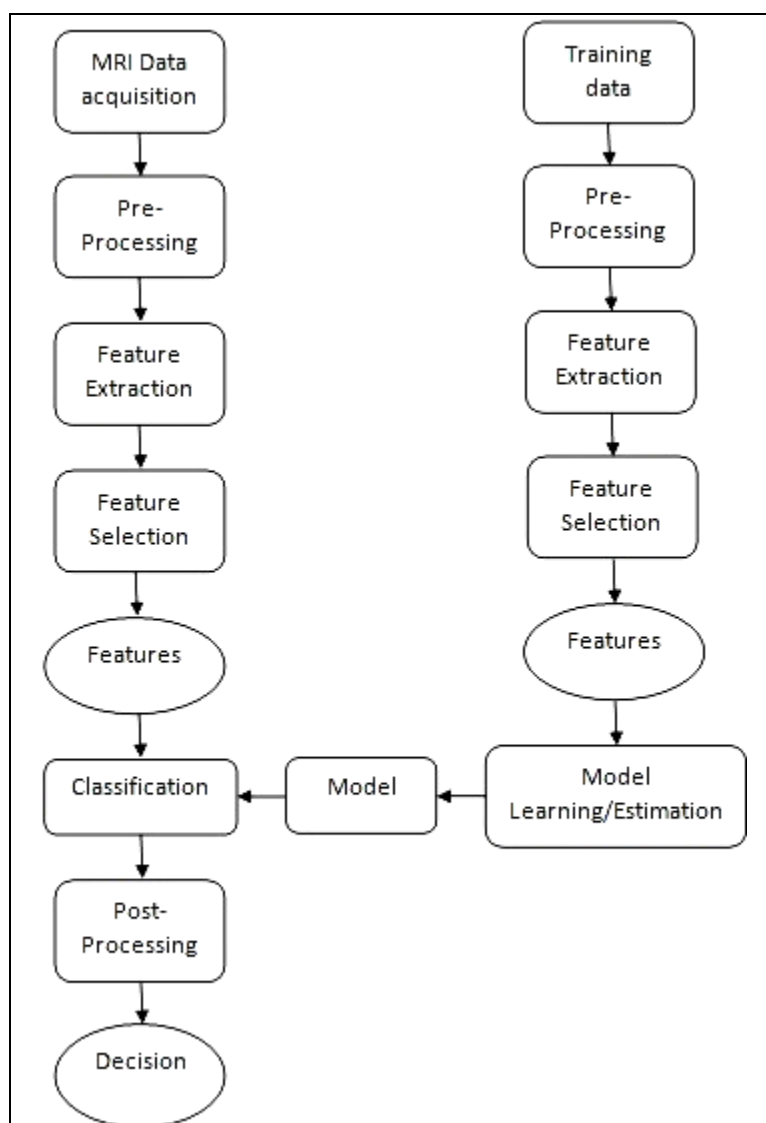


Figure 1. Proposed research design.

In this proposal, preprocessing includes correction of inhomogeneities, registration to the stereotaxic space (e.g., using a linear transform), cross-normalization of the MRI intensity, de-noising, segmentation, and re-sizing of images using special software (e.g., SPM8 or MATLAB). Features (e.g., density) that can be extracted from the MRI include voxel-based, vertex-based, or ROI-based data. In the first category, the features are defined at the level of the MRI voxel. Specifically, the features are the probability of the different tissue classes (grey

matter, white matter, and cerebrospinal fluid) in a given voxel. In the second category, the features are defined at the vertex level on the cortical surface. Cortical thickness in the temporal, parietal, frontal, cingulate, precuneus, cuneus, and entorhinal cortices represents a direct index of atrophy and, thus, is a potentially powerful candidate for assisting in the diagnosis of AD.

Cortical thickness measures can be performed with the Free Surfer image analysis suite. The methods of the third category include only the

hippocampus. Their approach is based on the analysis of the volume and /or shape of the hippocampus. The hippocampus is affected at the earliest stages of the disease and, thus, can be used as a marker of early AD in a vast number of studies. Here, the segmentation of the hippocampus can be performed using SACHA.

Beginning with feature extraction steps, tissue segmentation (WM, GM, and CSF) can be performed by the SMP software. Image normalization is followed using a template. It may be followed by data modulation to maintain a constant total density. For bias correction purposes, customized tissue probability maps (TMPs) can be generated. Smoothing with a smoothing kernel/window is next. Then the image is re-sampled to an acceptable isotropic resolution. For feature reduction, a linear SVM can be used to reduce data to a subset of patterns. Down-sampling is achieved by simple averaging.

A threshold is set to remove CSF and voxels with less than certain intensity. A RIO template is created to remove discarded regions (e.g., cerebellum) from data sets. A linear SVM-based criterion might be used to carry out feature selection. By utilizing estimated weights, vector lengths are reduced. To overcome the disadvantage of the SVM-based approach, which ignores spatial information from adjacent voxels, a modified thresholding can be applied. Cross-validation can be used to achieve SVM parameter optimization. The algorithm is trained by some sub-groups and tested on others. Accumulating additional information and features does not necessarily lead to improved classification performance.

Augmenting the data size increases the dimensionality of the feature space, which can make the classifier unstable and lead to over fitting the data. This problem is well known in machine learning as the curse of dimensionality. However, advances in statistical learning with the development of new machine learning algorithms capable of dealing with high-dimensional data enable the development of new diagnostic tools.

In this study, down-sampling may be achieved via ROI-based measures instead of voxels as input features, principal component analysis, or partial least squares (PLS). In this proposal, we try to extract new features from structural MRI images and better classifiers (e.g., neural network) for automate classification between AD and other dementia. The newly proposed diagnostic criteria for AD must be validated in multiple large data sets, and we will evaluate our result by comparing them with reliable results from the ADNI's database

3. Benefits of the Study

3.1. Benefits to science

Implementation of the proposed study will result in further progress in medical image classification as well as diagnostic imaging techniques used to early detect AD. The following scientific outcomes are expected:

- Implementation of new features from MRI imaging modality;
- Use of artificial intelligence and better classifier
- Improved accuracy of classification and early detection;
- Automated classification;
- In the near future, imaging and cerebrospinal fluid markers of amyloid deposition and glucose metabolism could be integrated with automated assessment of structural markers for optimal diagnosis and monitoring.

3.2. Benefits to society

Improving techniques to detect and diagnose AD early will clearly have social and economic impacts on both healthcare professionals and those affected by AD and their family members. AD is currently diagnosed through longitudinal clinical evaluations, which are available only at specialized dementia clinics, making such evaluations; beyond the financial and geographic reach of most patients. Automated diagnosis tools that can be made available to community hospitals would therefore be very beneficial. Earlier identification of AD may enable earlier treatment and empower people to plan for their future sooner, including financial and legal matters such as:

- Reduction of patient trauma and improvement in quality of life;
- Reduction of the burden on caregivers;
- Access to training, education, and support services for caregivers and family members;
- Shortened terms of hospitalization and reduction of healthcare costs;
- Physicians' and caregivers' awareness of patients who may have difficulty managing their own healthcare, such as when and how to take other prescription medications;
- Reduced anxiety on the part of the affected person and his or her family about the cause of symptoms;
- Allows family members and caregivers to be alert to potential financial mismanagement and scams.

4. Expected Results

It is expected that using structural MRI to predict AD during early stages will allow for diagnosis and treatment before irreversible neurodegeneration and functional impairment have occurred.

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