

**Designing a tool for early diagnosis for dementia from neuroimaging data using machine learning**

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# Abstract

# Acknowledgment

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# Introduction

## Dementia

Dementia is a cumulative term for a variety of changes that affect brain physiology, those effect person’s daily activities by causing long term and often progressive diminishing on capability of thinking and remembering (Burns and Iliffe, 2009). In addition to these symptoms, there are emotional disturbances, difficulty on speech and motivational decrease (Burns and Iliffe, 2009). For diagnosis there should be distortions on person’s mental functioning and one expected to have a significant decrease than projected due to aging (Budson et al., 2016). Until late 19th century, dementia had a vague description and a simple clinical concept, that at that time it can described as anyone who had lost their ability to think and reason (Berrios, 1987). Moreover, the term was also used for defining the mental illnesses and incapacities those can be reversible by right treatment (Berrios, 1987). In several studies, it is stated that there is no known cure for dementia (Iliffe et al., 2009). However, there are some medications that could help people where disease is at mild to moderate stage, but overall expectation of positive feedback is unlikely (Comission de la transparence, 2012). Despite the challenges of diagnosis and treatment of dementia, Zaccai et al. (2006) are believed that population-focused experiments can break the existing walls of biological indicators for cognitive and behavioural changes, and can provide further information for clinical and neuropsychological developments (Zaccai et al., 2006).

### Epidemiology

Since the population on the Earth is growing old, dementia has become one of the biggest concerns globally, which causes a significant burden for the people themselves besides their families and social and health care groups (Prince et al., 2014). Estimated population with dementia is 135 million within 2050, and the cost of care calculated as $604 billion globally in 2010 and it is expected to rise around $1 trillion by 2050 (Prince et al., 2014). The majority of dementia patients are diagnosed with Alzheimer’s disease, followed by vascular dementia and Lewy body dementia (Bermejo-Pareja et al., 2008). Out of 10-15 thousand patients, 5-8 thousand of them are suffering from Alzheimer’s disease (Bermejo-Pareja et al., 2008). Another study carried out that 0.4% of world’s total population (26.6 million) is diagnosed by Alzheimer’s in 2006, and with its expanding rate, currency of AD will increase three times and the number of people suffering to be quadrupled by 2050 (Brookmeyer et al., 2007).

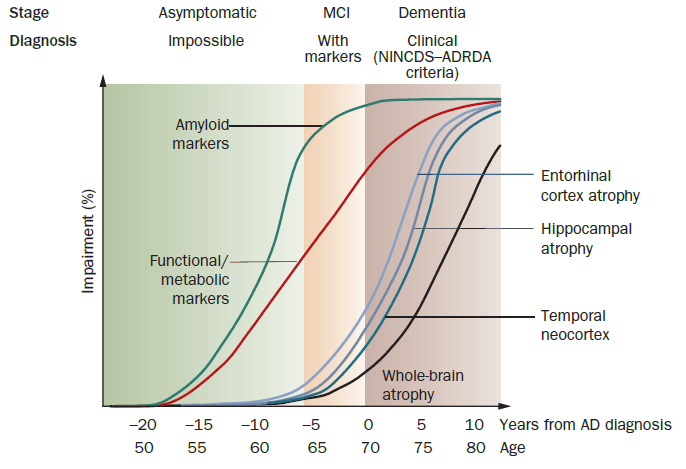
### Alzheimer’s disease (AD)

Alzheimer’s disease is a neuro-degenerative disorder, which affects multiple brain areas, and demonstrates a progressive disease course with broad range of symptoms changes within the individual patient (Masters et al., 2015a). Disease symptoms are usually spotted in frontal and temporal lobes of the brain tissue, then it spreads to the other areas of the cortex (Masters et al., 2015a). The incidence rate of the disease amongst the population with the age over 65 years old ranges between 10-30% based on gender and ethnicity (Bachman et al., 1993). The disease progresses and spreads exponentially within the brain cells of more than 90% of the patients, which are generally varies between the age of 80-90 years (Masters et al., 2015a). Average duration of the AD is approximately 10 years after diagnosis, yet the initiation of symptoms extends the duration over two decades (Evans et al., 2003).

***Pathophysiology.*** The pathophysiology of the AD can be related the formation of amyloid β (Aβ) plaques and tau fibrils as a result of protein aggregation (Golde et al., 2000, Selkoe, 2001). These accumulation of insoluble plaques in extracellular spaces promote the formation of neurofibrillary structure of the brain (Spielmeyer et al. 1922). In addition, disease also has strong genetic connections via increased production of apolipoprotein E (APOE), which is a crucial risk factor for AD that make individuals more susceptible to disease (Fernandez-Miranda et al., 1997). In overall, these changes in the brain physiology result synaptic and neuron loss, and also decrease in the production of neurotransmitters which are the chemical messengers of neural cells (Masters et al., 2015a). The interrupted communications between the brain cells, or complete loss of these cells can cause the condition called brain atrophy, which is also known as “shrinkage” of the brain (Pini et al., 2016).

***Diagnosis and Monitoring***. Diagnosis of Alzheimer’s disease can be challenging for physicians, since patients in the late stages can develop dementia addition to cognitive symptoms (Knopman et al., 2001). In England, there was a study introduced to find the cases who are in the high risk group such as people older than 75, since age is the most significant factor for dementia, and people with high vascular risk, Parkinson’s disease and learning impairment, were effected either in wrong way or right way by the policy (Bamford et al., 2007). The policy emphasized memory assessment of people who may or may not have the symptoms, which raised the stress of the patients and questioned itself as if it is cost effective (Iliffe et al., 2009). As stated before diagnosing either dementia and Alzheimer’s disease can be difficult due to subject not accepting that he/she forgets at their earlier stages, similarity of symptoms with memory loss that comes with normal ageing process and diversity of other indications as well, for example uncertainty on making decisions and hassle to find the words whilst speaking (Kostopoulou et al., 2008). On the other hand, co-morbidies (i.e. cerebrovascular disease) and hippocampal sclerosis are very common within the age range of AD, which makes diagnosis really complicated, in addition to that Alzheimer’s disease have many characteristics in common with other neuro-degenerative diseases, for example Parkinson’s disease (Duncan et al., 2014). With all the symptoms and the progress of sickness brings one question upfront, which is Alzheimer’s disease is a normal part of aging or it is a discrete disease process.

Aβ PET imaging contains a technique (Pittsburgh compound B (PiB)) that uses radioactive analogue of the fluorescent amyloid dye thioflavin-T, which goes through the blood-brain barrier (BBB), binding Aβ (Mathis et al., 2002). In the past ten years, studies with PiB helped people to understand the correlation between Aβ accumulation and cognitive decline, neuro-degeneration and dementia phases of Alzheimer’s disease (Masters et al., 2015b). The studies show that accumulation of Aβ starts years before dementia and being followed by cognitive decline and brain atrophy, and also in long term studies Aβ PET is a significant marker on forecasting the progression from mild cognitive impairment to Alzheimer’s disease (Rowe et al., 2013, Villemagne et al., 2013). That causes clinical misdiagnoses (%35), that patients with negative Aβ PET scans were misdiagnosed as having Alzheimer’s disease, moreover co-morbidies and hippocampal sclerosis makes it difficult to judge and diagnose (Salloway et al., 2014). Hippocampal volume is measured by the neuronal counts, in early, mild stages of AD Hippocampal volume is already decreased 15-30% whereas, in a converting type of Mild Cognitive Impairment which turns into AD on later stages, the volume is decreased by 10-15% (Shi et al., 2009). However, atrophy values vary with the progression of the severity of AD, in contrast as shown in Figure 1 Aβ markers are more likely to be effected than structural markers to conversion of MCI to mild stages of AD (Sluimer et al., 2008).



**Figure 1: Difference of the changes between the biomarkers during the advance of Alzheimer’s disease.**

Theoretical model of biological markers in Alzheimer’s disease, X axis indicates the ages of the patients and years before/after their diagnosis of Alzheimer’s disease, Y axis shows the percentage changes of the biological markers whereas lines indicates the biological markers including; Amyloid marker (green), Funtional/metabolic markers (red), Entorhinal cortex atrophy (light blue), Hippocampal atrophy (purple), Temporal neocortex (blue) and Whole-brain atrophy (black). On the graph, green layout parts are the stage that there are no symptoms exist whereas, orange part indicates mild cognitive impairment and brown part is where all the samples are diagnosed with Alzheimer’s disease. Figure is obtained from Frisoni et al. (2010).

## Image processing on Diagnosis

# Objective

# Methods

## Data Handling

Data was consist of T1-weighted MR images which was in nii format, gathered from ADNI. ADNI is the short form of the Alzheimer’s disease Neuroimaging Initiative, which was established in 2004, and their goal to conduct better solutions on Alzheimer’s disease by investigating and confirming the biomarkers for clinical purposes (Weiner et al., 2015). In dataset there were 479 patients and in total 1314 MRI images. There were 415 healthy person images, 657 images of who are suffering from mild cognitive impairment and 242 images of people who are diagnosed as Alzheimer’s disease.

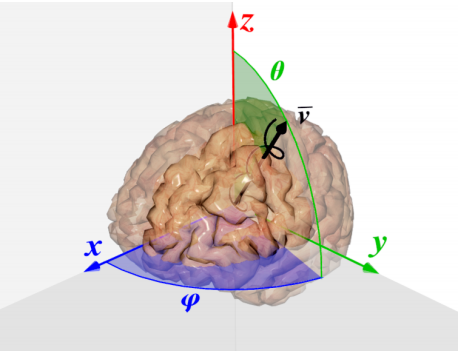
### Use of Big Data Techniques

## Image Processing

In this part, effectiveness of Spherical Brain Mapping on texture measures on prediction of MCI patients’ conversion rate to AD (Martinez-Murcia et al., 2016). Since MR images are used frequently on diagnosis of AD by inspecting the decrease of the grey matter and white matter, yet decay is mainly been seen in the grey matter tissue (Baron et al., 2001, Misra et al., 2009).

### Spherical Brain Mapping

Spherical Brain Mapping (SBM) is a technique that focuses on the spherical coordinates of the brain and convert brain image from 3D to 2D map (Martinez-Murcia et al., 2016). Central point of the MRI image set as a base point and a mapping vector (v) of length of N created and populated for each angles covering the brain (Figure 2). After getting Vθ,ϕ populated with each voxel by the mapping vector v there can be some formulas applied to get certain values such as brain surface or thickness of the tissue.



**Figure 2: Computation of the mapping vector**

Illustration of populating the mapping vector v, as the angles θ and ϕ embraces the brain on every angle, with that there won’t be any missing point in the output of the model.

* First parameter is the brain surface. Surface can be calculated as it is the sum of every last tissue voxel of each Vθ,ϕ. With this calculation tissue loss on the surface or worsening on structural model can be observed
* Other calculation used for finding the thickness of the tissue. This is calculated by differentiating the every last point of each vectors by the starting point of their first, long term short distance between the starting point and the ending point. With that calculation thickness of white matter and grey matter can be obtained.

### Add all the other image processing methods here

## Machine Learning

### Support Vector Machine

### Add all the other machine learning techniques here

# Results

## Results for each methods used

## Method 2

# Discussion

# Conclusion

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