

**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 behavioral 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 $604bn globally in 2010 and it is expected to rise around $1tr 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., 2015). 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., 2015). 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., 2015). 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).

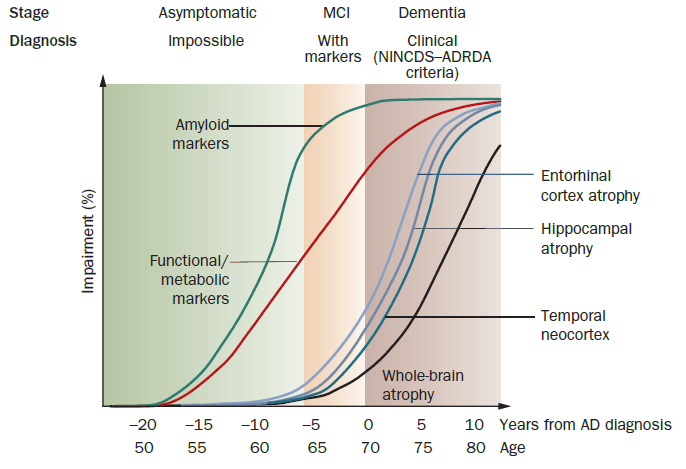
***Pathophysiology.*** The pathophysiology of the AD can be related the formation of amyloid β (Aβ) plaques and tau fibrils as a result of protein aggregation (Golde et al., 2000, Selkoe, 2001). These can also promotes the neurofibrillary structure of the brain due to insoluble plaques in extracellular spaces (Spielmeyer et al. 1922). In addition, disease also has strong genetic connections with apolipoprotein E (APOE), which is a crucial risk factor for AD that make individuals more susceptible to have AD (Fernandez-Miranda et al., 1997).

***Diagnosis and Monitoring***.

At the other hand, co-morbidies (i.e. cerebrovascular disease) and hippocampal sclerosis are very common at this age, which makes diagnosis really complicated, in addition to that Alzheimer’s disease have many characteristics in common with other molecularly defined 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.

Making a diagnosis of Alzheimer’s disease is really challenging, because in the prodromal stage patients have not only subtle cognitive symptoms, as they also are in the dementia phase (Knopman et al., 2001). That causes misdiagnoses clinically (%35), that patients with negative Aβ PET scans were misdiagnosed as having Alzheimer’s disease, and also co-morbidies and hippocampal sclerosis aid to the difficulty of the judgement (Salloway et al., 2014). In England, there was a study introduced to find the cases who are in the high risk group such as people older than 75, with that said age is the most significant factor for dementia, and people with high vascular risk, Parkinson’s disease and learning impairment which 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 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, symptoms’ similarity 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).

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 barrier between blood and brain, binding Aβ (Mathis et al., 2002). In the past ten years studies with PiB helped people radically to understand the correlation between Aβ accumulation and cognitive decline and neuro-degeneration at the preclinical, prodromal and dementia phases of Alzheimer’s disease. The studies show that deposition 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 dementia, caused by Alzheimer’s disease (Rowe et al., 2013, Villemagne et al., 2013). 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 Alzheimer’s disease 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

### Use of Big Data Techniques

## Image Processing

### Brain Segmentation

### 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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