

BABEȘ-BOLYAI UNIVERSITY CLUJ-NAPOCA
FACULTY OF MATHEMATICS AND COMPUTER SCIENCE
COMPUTER SCIENCE IN ROMANIAN SPECIALIZATION

DIPLOMA THESIS
Alzheimer's Disease Detection

Supervisor

Prof.dr. Horia F. Pop

Author

Ichim Ștefan

2024

Abstract

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1 Introduction

There is no denying that humanity stands at a previously inconceivable point in health-care and medicine, which naturally have led to hindrances in senescence, populations increasingly reaching older stages of life. Furthermore, studies which take into account multiple case scenarios show that population is expected to reach 9.2 billion by the age of 2050, leading to an uprise of 21% in the elderly. [KC and Lutz(2017)]

With that being said, researchers' concern has taken a turn towards diseases occurring at these later parts of human lives, some of them considered treatable while others less so. One of such disorders is Alzheimer's Disease, or AD, considered to be the most likely predecessor of dementia. Alzheimer's Disease is a brain disease, neurodegenerative, which in time diminishes cognitive skills such as memory, thinking and speaking, and in due course even removes the ability of accomplishing simple activities vital to one's daily life. On top of that, it is an incurable disorder, which only underlines even further the reasons why early detection stand of such great importance, so that appropriate actions can be taken by both the medical team and the one diagnosed, along with their relatives and close ones.

1.1 Disease Summary

The brain of a healthy human represents a cluster of neurons by the number of billions which together amount to what actions and reactions we have, through a process of signal propagating. Through our sensory mechanism, which includes hearing and seeing, receptors carry out the tasks of sending signals (Fig 1) using designated channels all the way to the neurons inside the brain, where new specific signals are formed and sent back, resulting in what we call actions. [Sivadas and Broadie(2020)]

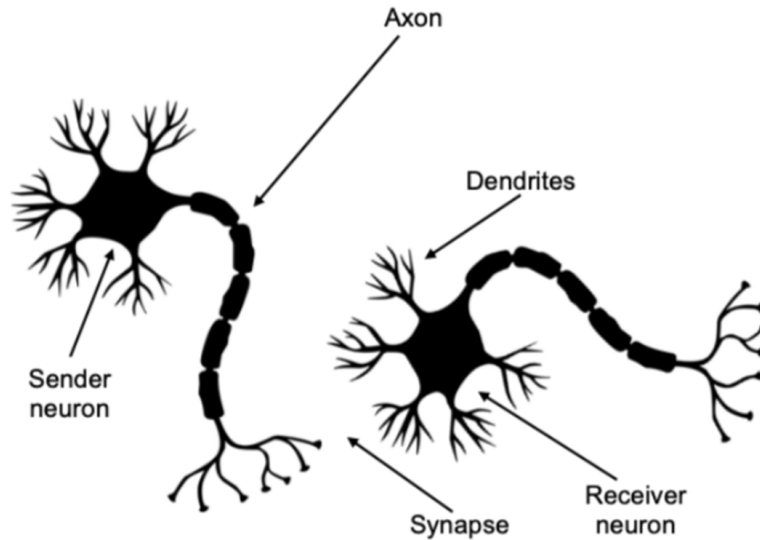


Figure 1: Communication between neurons

Alzheimer's Disease intervenes in this process by gradually decreasing the utility function of each neuron, leading to the atrophy of the brain's proficiencies, as neurons imminently die one by one.

There are three major factors included in the dynamic between AD and neurons. First of all, a key advantage of neurons which many other cells lack, and which accomplishes their long survival, is the ability to repair themselves, form new connections, or changing current ones' magnitude. Secondly, synaptic connections, which solidify the signal transmission process, and lastly the intake of glucose and oxygen necessary for their normal functioning. It is believed these fundamental attributes of a healthy human receive considerable drawbacks upon the disease's presence. [NIH(2024)]

1.2 Causes

While the factors which lead to Alzheimer's Disease are not yet properly understood, past research and studies prove that some of the most commonly met criterias which lead to a diagnostic include genetic inheritance - chances of developing Alzheimer's Disease increase by 30% when another close relative suffers from it [Harvard(2019)], lifestyle and environmental factors.

Genetical Inheritance

Genes represent instructions passed down from generation to generation, which contain information regarding how various cells need to behave. Some roles played by these include defining one's height, or the color of hair and eyes.

Advances in genetic research have led to discover 80 genetic areas that can possibly play a part in AD development [NIH(2019)]. One of the more known genes which raises the risk of Alzheimer's Disease is the apolipoprotein E (APOE) gene, which comes in forms such as ϵ_2 , ϵ_3 , ϵ_4 . A pair of two such APOE genes, one from each parent, gets passed down to the next generation resulting in 6 possible cases. Among them, the (ϵ_4, ϵ_4) combination having the highest risk of AD, only increasing, not guaranteeing it, and in contrast, ϵ_2 provides a higher degree of protection against it.

External Factors

Besides genetical inheritance, researchers have drawn conclusions regarding causes of Alzheimer's Disease to contain a plethora of other outside factors, which we can have a higher influence on. Among these can be found vascular conditions - high blood pressure, heart diseases - and metabolic diseases - obesity and diabetes [NIH(2019)].

1.3 Symptoms

Before beginning the discussion about its effects, a noteworthy fact is that brain structure modifications, whether they may be neurofibrillary tangles or plaques of amyloid, occur several years before any cognitive issues manifest at all, a stage of the disease titled preclinical. With that being said, their presence does not inevitably lead to dementia.

Apart from preclinical stage, AD has been classified into three others: mild, moderate, severe.

Early-stage (Mild)

A person which suffers from early-stage Alzheimer's Disease can still function normally on their own, without mandatory outside benefactors. However, changes appear in memory skills, starting to forget recently gained information, such as names at social gatherings, objects placements and losing the reasoning behind starting certain activities.

It is important to understand these memory setbacks are hardly noticeable by the affected one, more commonly than not leaving it up to their surrounding group of people and friends to pinpoint them and initiate medical visits.

Middle-stage (Moderate)

Here, over the course of many years, cognitive skills start degrading, with the diagnosed person needing increasing help from other people. Previous rare memory losses become the norm, and even more prominent. Not only that, disturbances in emotions begin escalating, some expressed in a stronger tone, while others hardly able to be exhibited at all.

Daily tasks must be simplified to the level the person with Alzheimer's can accomplish them, and as the external attention needed rises, place them in special care centers where experienced caretakers can easily reach out.

Late-stage (Severe)

This final stage of AD is categorized by vital losses in the ability to function at all. Patients stop reacting to outside factors altogether, and even initiating conversations. In due course, pain becomes impossible to verbalize, and as such, hourly check-ups are necessary. [[Alzheimer's Association\(2024a\)](#)]

1.4 Diagnosis Process

AD diagnosis can only be carried out upon gathering a variety of complex data, which includes medical history, assessments of cognitive and physical skills, neurological exams, brain scans, blood tests and cerebrospinal fluid.

Medical history consists of modifications in how the patient behaves over the course of time, past and present medical concerns and even the undergoing medication. Other than these, information about other family members' health conditions is obtained, since, as previously mentioned, genes do play a role in increasing the risk, or protecting against Alzheimer's Disease.

An overall health status is evaluated, involving commonly met questions about diet, blood pressure and pulse, checking the quality of breathing and sample taking for testing.

Cognitive tests' purpose is to express a general view whether memory impairment takes a toll in the daily life of the diagnosed, and to shed light on the awareness of the disease. A number of tests are simple - tasks of remembering sequences of words, or mathematic operations, but there also exist those that take a longer period of time, alongside with raised levels of attention.

The neurological examination typically implies assessing the patient's nervous system, where a physician tries to distinguish between the possibilities of the disease to be a different brain disorder instead of AD - brain tumors or Parkinson's Disease.

Brain imaging is used to form 3D and 2D, functional and structural scans of the brain, through which experts can point out characteristics specific to Alzheimer's Disease. One such mark is the presence of higher concentrations than normal of amyloid beta ($A\beta$ or Abeta), peptides considered the essential part of amyloid plaques. This specific part of the diagnosis process typically serves only as a last resort.

[[Alzheimer's Association\(2024b\)](#)]

1.5 Imaging Modalities Involved in Alzheimer's Disease

Through recent technological advancements, brain imaging's role has shifted to a crucial one. By and large, imaging has expanded into various different modalities, each with their own strengths and weaknesses, but combined lead to a better analysis of AD's effects on the human brain. [[Johnson et al.\(2012\)](#)Johnson, Fox, Sperling, and Klunk]

Amyloid PET

Amyloid Positron Emission Tomography is a non-invasive technique, which locates amyloid plaques. Due to its unavailability and expensive price, this method has not seen much popularity, but there is no denying its accuracy, past studies showing that 96% of the people who had performed an amyloid PET scan and were amyloid positive

had been diagnosed with Alzheimer's Disease.

[Johnson et al.(2012)Johnson, Fox, Sperling, and Klunk]

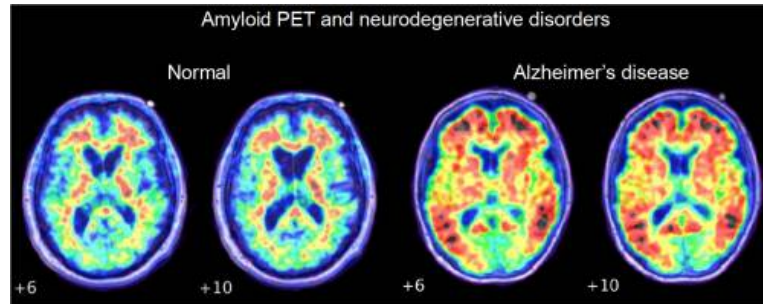


Figure 2: Amyloid PET images

FDG PET

Fluoro-deoxy-D-glucose (FDG) PET showcases synaptic activity, because the brain's primary energy comes from glucose. The Fluorine part of the FDG comes as a consequence of the convenient dynamic it has with Positron Emission Tomography, which easily detects it.

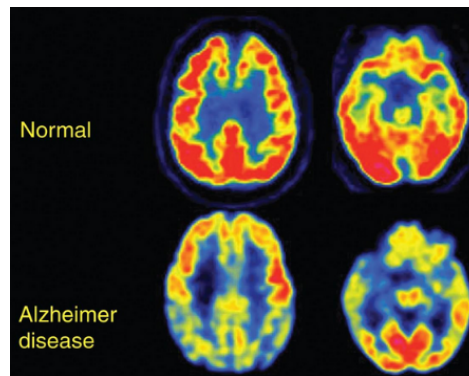


Figure 3: Transitional FDG-PET scans

Structural MRI

Structural Magnetic Resonance Imaging (sMRI) is a non-invasive method applied to observe pathology and anatomy of the brain by emitting radiofrequency pulses in sequences. Its main purpose is to exhibit brain atrophy, associated with shrinking size due to neuron counts declining. One of its drawbacks is that, compared to PET imaging, hallmarks of AD cannot be detected, and also atrophy isn't specific to the disease discussed.

Functional MRI

As the previous method, the functional variant of MRI is non-invasive as well, but, on the other hand, provides scientists a neuronal activity mapping of the brain. A few of them require the patient to perform certain cognitive tasks during the scanning process, and there are also some which need the brain to be found in a specific resting state. Functional MRI's setback is the necessity of lack of motion, and any of the patient's movements could lead to faulty data.

Tasks

An important question to ask before traversing further, is what type of predictions are we demanding from ourselves? As aforementioned, Alzheimer's Disease classifies itself in three stages: Normal Cognition(NC), Mild Cognitive Impairment(MCI) - which further breaks down into progressive MCI and stable MCI, pMCI and sMCI respectively - and Alzheimer's Disease.

These various disease progressions have given birth to a collection of tasks for researchers. There are approaches which classify AD in two - NC vs AD, NC vs MCI, MCI vs AD -, three - NC vs MCI vs AD - and even four classes, including MCI's subclasses. On the other hand, regression problems build the percentage of a specific stage to progress.

Deep Learning

Recent advancements in deep learning, with a higher degree of respect to Convolutional Neural Networks (CNNs) and Recurrent Neural Networks(RNNs), have had main roles in raising the speed and accuracy with which classification or regression task are accomplished.

Before 2013, the most commonly met algorithms included stacked Restricted Boltzmann machines and stacked autoencoders, but ever since, CNNs and RNNs have taken the spotlight, surprising the world with their results, especially when given inputs of MRI or PET [Alsubaie et al.(2024)Alsubaie, Luo, and Shaukat].

Deep Learning's key characteristic is the power to find a hypothesis leading to the desired outcome unbeknownst to the humans of how it is realized, with the drawback of needing a high amount of data and proportionate computational resources.

Artificial Neural Networks

As their name suggests, ANNs consist of a collective of artificial neurons connected between each other. They represent how researchers have tried to emulate the biological neural brain, where the nodes play the role of neurons, and connections, or edges,

between them that of synapses.

Furthermore these neurons are stratified into various layers, through which information passes, notably the initial and last layer have been titled as input and output accordingly, while the ones in-between called hidden layers.

Each neuron's meaning is to receive information and process it in order to be passed to the next layer through the array of synapses. Activation functions take place in the processing stage, in order for non-linearities to be applied to the hypothesis being built.

In the course of multiple iterations, these neurons adapt to the task given by the designer, adaptation formally known as weights.

Convolutional Neural Networks

These types of artificial neural networks are feedforward - input flows only in forward direction, without loops - and exhibit the capacity to extract features automatically. In such networks, convolutional layers and pooling layers represent their main components. Convolutional layers transform the data by passing it through a kernel creating a feature map, and pooling layers finetune network parameters by taking these feature maps and reducing their size. This final product also takes the name of pooled feature map [Li et al.(2021)Li, Liu, Yang, Peng, and Zhou].

Recurrent Neural Networks

RNNs are the other types of neural networks, described best by how information propagates inside it, which compared to the single directioned CNNs, RNNs are bi-directional. This property creates the opportunity of some information to be used in more than just one place, with the justification that evaluations sometimes show improvements in results.

2 Related Work

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