Exploiting of Machine Learning Paradigms in Alzheimer's disease

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Abstract: - The importance of using machine learning techniques in the field of medical imaging technologies have increased in both research and clinical care over the recent years. So, detecting Alzheimer's disease in precise way and early phase is essential for patient care. Researchers have been dedicating their efforts to evaluate compulsive changes that happen in the brain through the process of Alzheimer's disease by neuroimaging techniques. Neuroimaging is becoming a progressively beneficial tool in understanding the pathogenesis of AD progress. Moreover neuroimaging playing an essential role in detecting AD using machine learning paradigms. Several machine learning techniques like Support Vector Machines, Artificial Neural Network, Deep Learning, K-Nearest Neighbour, K-means and Naive Bayes have been proposed to classify AD and to build CAD systems capable of detecting Alzheimer's at any stage. This paper is aim to present the medical aspects of AD, give review of AD biomarkers especially neuroimaging biomarkers and its techniques and finally presents a state-of-the-art review of the researches achieved on AD diagnosis.

Key-Words: - Alzheimer's disease, Biomarker, Neuroimaging technologies, deep learning, K-Nearest Neighbor (KNN), Support Vector Machine (SVM), Neural Networks (NNs).

1. Introduction

Alzheimer's disease (AD) is one of the most serious diseases that destroy the brain and classified as the most widespread type of dementia According to Alois Alzheimer, Alzheimer's disease is a physical disease that affects the brain [1, 2]. In Alzheimer's disease procedure, proteins are created in the brain in order to form two main components: plaques and tangles. This process may leads to damage the connections between nerve cells. In addition to, Alzheimer's patient have a shortage of some significant chemicals in their brain. When there is some problems of them, the chemical messengers are not send the signals through the region of the brain. [3].

Alzheimer's disease is one of the greatest interesting disease for doctors in order to recognise it before reaching to the critical stage if patients themselves do not recognize the warning signs [4]. Although Alzheimer's disease is not a alleviate disease recently, the progression of the disease can occur slowly down if detected at an early or mild stage. With the advance of AD, there are changes causes in the brain and can be detected. From a bio-marker viewpoint, the changes of AD are: progressive build-up of the beta-amyloid protein fragments (plaques) outside the neurons, and the presence of twisted strands of the tau protein (tangles) inside neurons, in the brain [2]. These changes eventually cause damage to, and death of, neurons [5].

The rest of the paper is organized as follows: Section 2 provides the medical aspects of Alzheimer's disease. Section 3 discusses the biomarkers of AD and gives a comparative study of neuroimaging techniques. Section 4 provides analysis of machine learning techniques in AD. Section 5 gives discussion about the pervious analysis and finally section 6 gives conclusion of the paper including future works.

2. Medical aspects of Alzheimer's disease

Alzheimer's disease is a growing brain disease [1, 2]. There are two main neuropathological characteristics that discriminate Alzheimer's disease from any disease in the brain: neurofibrillary tangles (NFTs) and senile plaques (SPs). SPs composed of beta amyloid (Aβ) peptides and NFTs composed of hyper phosphorylated tau protein [6]. Ultimately when Alzheimer's disease was at latest stages, neurons are damaged or destroyed. In addition to the patient wasn't capable to achieve the basic physical activities such as swallowing and walking. People in the final stages of the disease are bed-bound and require very special care all the time. Alzheimer's disease is a circumstance in which the neurons doesn't work well and the connection between all neurons are loss.

2.1. Stages of Alzheimer's disease

The progression of AD comprises of three different stages:

(a) Preclinical Alzheimer's disease: In the preclinical AD stage [7], individuals have quantifiable changes in the brain, CSF, and/or blood (biomarkers).

(b) Mild Cognitive Impairment: Mild Cognitive Impairment (MCI) [7] is an intermediate stage between normal and AD. The MCI patients have mild memory and cognitive problems; however they are capable of executing daily activities. The two different types of MCI are non-amnestic Mild Cognitive Impairment (naMCI) and Amnestic Mild Cognitive Impairment (aMCI). Studies proved that from 10% to 20% of people age sixty-five or older have MCI.

(c) Alzheimer's disease: This is the most critical stage, where the person is incapable of performing day to day activities because of loss of memory and reduction in thinking ability and changes in behaviour. Figure 1 show the stage of Alzheimer's disease.
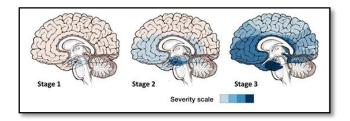

Fig.1: Stages of Alzheimer's disease

2.2. AD symptoms

AD affects people in differing ways. The most mutual symptom pattern starts with inability to recollect new information. This symptom occurs because the first neurons to die and malfunction are usually neurons in brain regions involved in forming new memories [7, 8]. In figure 2 symptoms of AD are shown.
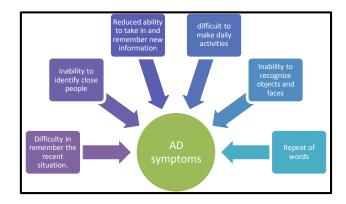

Fig.2 Alzheimer's symptoms

2.3. Regions affected by AD

Due to the pathological changes in the different areas of brain before the appearance of AD symptoms, it's important to detect the AD in early condition and predicate the dangerous conditions.

a- Hippocampus

The hippocampus is the first region of the brain that affected by AD [9]. It is lies under the medial temporal lobes. The structure of it like a seahorse, and there is one on each side of the brain above the ears as show in figure 3.
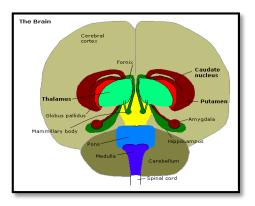
Fig.3: Region affected by AD

b- Amygdala

The amygdala is lied in the medial temporal lobe, inside the hippocampus. Like the hippocampus, the amygdala is a paired structure, with one located in each hemisphere of the brain. The amygdala is considered main component of the neural network system which responsible of memory and the reactions during each situation [10].

c- Entorhinal Cortex

The location of Entorhinal Cortex is lied under the hippocampus, in the ventromedial surface of the temporal lobe. The main functions of it are: construction of memory, retrieval and extinction as part of circuit involved. Entorhinal Cortex is the essential part affected when the patient in Mild Cognitive Impairment stage [11].

d- Putamen

The putamen is located beside the thalamus and in the front of amygdala. It is responsible of controlling the signs and movement of the limbs by a complicated feedback loop. The putamen is a structure in the forebrain [12].

e- Thalamus

The thalamus is a paired entity of gray matter located in the forebrain which is superior to the midbrain, near the core of the brain, with nerve fibers projecting out to the cerebral cortex in all directions. For more medical aspects see reference [12].

2.4.AD statistics

According to Alzheimer's Association in the United States, the ratio of deaths in Alzheimer's disease is reached to 60% all over the world between those age from 65 and older. In addition to, studies proved that between 2000 and 2015, AD is considered the first dementia which recorded the highest mortality rate reached to 123 percent [13]. Table 1 will show the future of AD according to Alzheimer's Association studies.

Table 1: Population with Alzheimer's Dementia, 2010 to 2050

Year	Description
In 2010	There were an estimated 454,000 new cases of Alzheimer's dementia
By 2025	The number of people age sixty-five and older with Alzheimer's dementia is projected to reach 7.1 million
By 2050	The number of people age sixty-five and older with Alzheimer's dementia may grow from 5.5 million to a projected 13.8 million, except the development of medical breakthroughs to prevent, slow, or cure AD.

3. AD biomarkers

In recent years, there has been a great amount of studies about the AD biomarkers field [14- 16]. According to Mueller et al., 2005 [17], an ideal AD biomarker should be able to detect features of the Pathological processes. Also, it should be able to detect AD in an early stage and differentiate it from other dementias, easy to achieve an accurate diagnosis, economical and adaptable in routine clinical practice. There are four biomarkers used in AD researches: biochemistry, genetics, neurophysiology, and neuroimaging. Figure 4

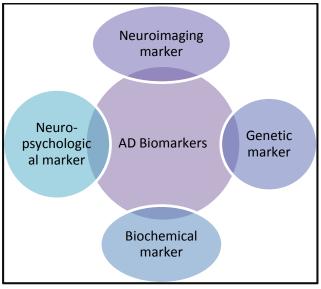presents the different types of biomarkers used in AD studies.

Fig.4: Different biomarkers of Alzheimer's disease.

3.1. Neuroimaging marker

Neuroimaging biomarkers [15] have effective role in the early diagnosis of Neurological diseases such as Alzheimer's disease (AD). Studies have proved that imaging techniques are responsible for the prediction of AD in its three stage: NC, MCI and AD. Neuroimaging techniques can be categorized as structural and functional. The main structural imaging techniques are: Computed tomography (CT) [18, 19] and Magnetic resonance imaging (MRI) [18-20]. The main functional imaging are: Positron emission tomography (PET) [21, 22], Single photon emission computed tomography (SPECT) [21, 22] and Functional MRI (fMRI) [20].

3.1.1. Study on medical imaging technologies

Medical Imaging Technologies (MITs) are non-invasive methods for investigating and testing the brain without making surgery. It used to aid in making an accurate diagnosis or give correct treatment of different medical conditions. There are many medical imaging techniques; every technique has different risks and benefits. Table 2 shows comparison between medical imaging techniques.

3.2.Genetic marker

Genetic biomarker [14] is very complex which is depending on whether Alzheimer disease is in early stage or in late stage. To date, single gene mutations of one of three known genes are known to cause familial AD. These genes are amyloid precursor protein on chromosome 21, presenilin-1 on chromosome 14, and presenilin-2 on chromosome 1. Late-onset AD, which comprises the vast majority of cases, is more complicated and a single causative gene has yet to be identified.

3.3.Biochemical marker

For early diagnosis of AD, the two biochemical markers [14]: cerebrospinal fluid (CSF) and peripheral blood have been estimated by cross-sectional and longitudinal studies [11]. CSF biomarkers for AD can be divided into basic or nonspecific, core or specific, and novel biomarkers". The nonspecific or basic biomarkers are useful to rule out important differential diagnoses. On the other hand, core or specific biomarkers reflect the central molecular pathogenesis of AD.

3.4.Neuropsychological markers

In Neuropsychological approach [14, 23], the electrical brain activities are recorded in the form of frequencies and analysed using signal processing techniques. This technique is based on both spatial and temporal resolutions and can potentially identify dementia even in early stages.

4. Analysis of machine learning (ML) techniques in AD diagnosis

In the recent years, ML play potential role in the field of medical care and researches. Therefor it is promising in the area of early and accurate diagnosis of Alzheimer's disease. Understanding the patient brain changes may take a great efforts from the physicians and waste the time especially in the critical cases. Integration ML techniques with medical imaging technologies will help detect AD at an early stage before irreparable damage has been done.

Based on machine learning techniques: deep learning [24, 25], support vector machine[30, 31] and hybrid techniques, table 3, table 4 and table 5 respectively give extensive literature survey on image processing phase, classifier data sets, purpose, image modality and different stages of AD which is used for detecting abnormalities in Alzheimer's disease.

5. Results and discussion

From the table 3, table 4 and table 5, it was observed that the most researches are concentrated on hybrid techniques of feature extraction and classification techniques to get superior and good accuracy for early diagnosis of Alzheimer's disease. For early, accurate and precise detection of AD, the authors developed computer aided diagnosis systems (CADs) classification through using several machine learning techniques. These systems applied using several of imaging techniques like: MRI, PET, SPECT and DIT. Many of these algorithms were spotlight in their studies on MRI due to its powerful medical imaging technology that is used in AD detection, and extraction of effective structural MRI bio-markers of AD has become an active research area in this field.

Most of these systems are focused on diagnosis AD in all stage: normal control (NC), mild cognitive impairment (MCI) and AD. In [28], [29] and [34] the authors used binary classification (AD vs. HC), (AD vs. MCI) and (MCI vs. HC) while in [26, 27], the authors used binary and multi-classification (HC vs. MCI vs. AD).

In this comparison, deep learning techniques like: autoencoder, 3D-Convolution Neural Network (3D-CNN) and Capsule Network, Support Vector Machine (SVM) and hybrid techniques (K-nearest neighbor (KNN) [37], Random forest (RF) [35], artificial neural network (ANN)) [36] and are used for good classification.

In [30] and [31] authors confirmed that Support vector machine (SVM) was one of the most efficient classification methods in ML and it has been used successfully in several AD and MCI imaging studies. While the recent researchers in [32] and [33] introduced two versions of SVM. First, the kernel SVMs (KSVMs) which is the extension of the original linear SVMs. The KSVMs allows one to fit the maximum-margin hyperplane in a transformed feature space compared with the original SVM. Second, The multiple kernels SVM (MK-SVM) which permits the combined analysis of different imaging modalities. They have all found the multimodal MK-SVM to be significantly more accurate than the single modality SVM.

According to [36] and [37], KNN is one of the good classifier. KNN has a simpler model structure, which makes it the faster classifier for low-level classification applications of the two classes, having low dimensional features which affected with increasing the training datasets which enhances its

Performance. By comparing SVM classifier and KNN classifier, it was notice that SVM classifier has the better performance, but it is a little bit more complex and slower than KNN.

Deep learning technique is one of ML techniques that able to overcome the problems in other techniques. Comparing deep learning with other techniques, it is observed that deep neural networks (DNN) and specifically convolutional NN (CNNs) have become popular now due to their good generalization capacity and available GPU Hardware needed for parameter optimization [26]. Also, 3D-Capsule Networks (CapsNets) one of the deep learning techniques has achieved a big success in AD detection. According to [29], CapsNets can effectively handle robust image transitions and rotations and has the capability of fast learning even for small datasets. Also, CapsNet is capable of handling large datasets with low training turns and small sample sizes, which is the reason for its success. It was noted that, an ensemble method using 3D-CapsNets and CNN with 3D-autoencoder increased the detection performances comparing to Deep-CNN alone. In short, the CapsNet is efficient in providing spatial relationship between the features of the image and understanding changes in shape, size, position, orientation, luminance, perspective, etc. Combination of different techniques of deep learning such as autoencoder, Convolutional CNNs, and CapsNet [29] can increase accuracy and efficiency.

In this study, more datasets are used in order to classify between healthy patients and AD patients like: The OASIS (Open Access Series of Imaging Studies) datasets, AD Neuroimaging Initiative (ADNI) data sets and EDSD framework.

- OASIS: the goal of OASIS is to present the opportunity to access a significant database of neuroimaging and processed imaging data. All data is available via www.oasis-brains.org [39].

- ADNI: the objective of ADNI is to check whether the imaging techniques can be combined to measure the development of mild cognitive impairment (MCI) and early AD [40].

- EDSD framework(The European DTI Study on Dementia): EDSD is a multicentre framework created to study the diagnostic accuracy and inter-site variability of DTI (Diffusion tensor imaging) in patients with manifest and prodromal Alzheimer's disease (AD)

Table 2: comparison between medical imaging technologies

Technique	Features	Benefits	Risks
Computed Tomography (CT)	Depend on X-rays which used to create 3D images for the inside part of the brain by passing the beams through the head from many angels and create the brain picture	• Fast, and painless. • Resolution is high • Easy view of veins.	• Difficult to detect the tumours • The contrast is very low when soft tissue contrast is low.
Magnetic Resonance Imaging (MRI)	• uses a magnetic field and radio waves to create itemized images of tissues and organs • MRIs utilize robust magnets which produce a strong magnetic field that forces protons in the body to align with that field	• Non-invasive and painless. • Without ionizing radiation. • High spatial resolution. • Easy to blind and ability to measure flow and velocity with advanced technique. • Good soft tissue contrast.	• Relatively low sensitivity. • Long scan and post processing time • Difficult to detect the tumours. • Relatively expensive.
Positron Emission Tomography (PET)	• provide information about the metabolism of a disease • Isotopes used in PET imaging are decayed by positron emission	• Provides functional information that is often highly accurate and specific. • Good tissue specific contrast. • Can check how far a cancer has spread and how well the treatment is working.	• Relatively low spatial resolution. • High cost • May cause some people to feel claustrophobic, which may mean sedation is required.
Single Photon Emission Computed Tomography (SPECT)	• provide information about the metabolism of a disease • relies on drugs that are labelled with atoms that emit at least one gamma ray when they decay		

Table 3 deep learning for AD diagnosis

Algorithm	Datasets	Purpose / Technique	Image modality	AD classification
Jyoti Islam etal. (2018) [24]	OASIS	Developed a deep convolutional neural network that learned features directly from the input sMRI and classify the current AD stage.	MRI	NC- MCI- AD
Siqi Liu etal. (2015) [25]	ADNI	designed a novel diagnostic framework with deep learning architecture to aid the diagnosis of AD	MRI- PET	NC- MCI- AD
Alexander Khvostikov etal (2018) [26]	ADNI	Proposed new algorithm based on a 3D-convolutional NN and sMRI and DTI modalities fusion on hippocampus ROI using data from the (ADNI) database	MRI- DIT	AD vs. NC AD vs. MCI MCI vs. NC
Adrien Payan (2015) [27]	ADNI	Developed new algorithm using deep learning methods (autoencoder and 3D-convolution neural network) to predict AD status based on an MRI scan of the brain	MRI	HC vs. AD vs. MCI AD vs. HC AD vs. MCI MCI vs. HC
Silvia Basaia etal (2018) [28]	ADNI	Built a deep learning algorithm (that can predict the individual diagnosis of AD and the development of AD in MCI patients based on a single cross-sectional brain structural MRI scan	MRI	Binary Classification
K.R. Kruthika etal (2018) [29]	ADNI	Proposed a CBIR system using 3D Capsule Network, 3D- Convolution NN and 3D-autoencoder technology for early detection of Alzheimer's	MRI	Binary Classification

Table 4 support vector machine for AD diagnosis

Algorithm	Datasets	Purpose / Technique	Image modality	AD classification
P. Padilla etal. (2012) [30]	ADNI	Presented a novel computer-aided diagnosis (CAD) technique for the early diagnosis of the Alzheimer's disease (AD) using SVM.	SPECT, PET	NC
Christian Salvatore etal. (2015) [31]	ADNI	Proposed a machine learning method by SVM able to extract spatially distributed multivariate diagnostic biomarkers from structural MR brain images to be used for the early and accurate diagnosis of AD	MRI	NC
Zhang etal. (2015) [32]	OASIS	Developed a hybrid eigenbrain based CAD system that can not only detect AD from NC, but also detect brain regions that related to AD by using K-SVM	MRI	NC- MCI- AD
Martin Dyrba etal (2015) [33]	EDSD framework	Developed a framework using machine learning classification of multimodal multicenter diffusion-Tensor and Magnetic Resonance Imaging Data by using MK-SVM	MRI- DIT	NC- MCI- AD
Elaheh Moradi etal. [34]	ADNI	Developed an approach by LDS and SVM to predict conversion to AD within MCI patients by combining machine learning approaches including feature selection for selecting most relevant voxels corresponding to AD within MRI data.	MRI	MCI- AD

Table 5 Hybrid techniques for AD diagnosis

Algorithm	Datasets	Purpose / Technique	Image modality	AD classification
J. Ramírez etal. (2010) [35]	(Virgen de las ves)	Proposed a complete CAD system using random forest for the early detection of the AD by means of supervised SPECT image classification	SPECT	NC
Neha etal. (2017) [36]	ADNI	Proposed a method for classifying MRI into (NC), Mild (MCI) and Alzheimer's disease (AD) using SVM, ANN and KNN	MRI	NC- MCI- AD
Taqi etal. (2017) [37]	ADNI	Presented a new methodology of invariant interest point descriptor for Alzheimer disease classification by using KNN-SVM	MRI	NC
K R Kruthika etal (2018) [38]	ADNI	Built classification system for AD by the swarm intelligence feature selection and multiclassifier (SVM-KNN Naïve Bayes)	MRI	MCI vs. HC

6. Conclusion and future work

This paper focused on the medical aspects of Alzheimer's disease, its stages, symptoms, concluded AD biomarkers and concentrated on neuroimaging biomarker which aids the physicians in early and accurate diagnosis of Alzheimer's disease. The paper presented a two comparative study: first, between the different medical imaging modalities like CT, MRI, PET and SPECT from advantages and disadvantages. Second, between machine learning techniques used in AD detection. This comparison spot light on image processing techniques, datasets, imaging techniques and AD classification and found that using hybrid techniques give better accuracy and good performance. So, developing computer aided diagnosis (CAD) system using hybrid machine learning techniques in diagnosis Alzheimer's disease will give superior results in the future.

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