ALZHEIMER’S DISEASE CLASSIFICATION USING ATTENTION MECHANISM AND GLOBAL AVERAGE POOLING ON A CONVOLUTIONAL NEURAL NETWORK

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DEDICATION

To the utmost important people in my life.

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ABSTRACT

The robustness of Convolutional Neural Network (CNN) architecture as the innovative technology has led to the surge of research adoption for Alzheimer’s disease (AD) classification. CNN is replacing the conventional machine learning methods to assist and support experts in diagnosing AD. However, the performance of conventional CNN architecture in classifying AD class and Normal Control (NC) class is hindered by its behaviours that require a large-scale dataset. Nonetheless, the major hindrance in the AD domain is limited amount of dataset. Therefore, previous studies have adopted data-centric enhancement modules such as pre-processing techniques, data augmentation, and transfer learning strategies to improve the classification performance of CNN. Yet, these modules alone are still struggling to offer sound accuracy of classification of the disease due to CNN's overfitting issue and behaviour which is insensitivity to the local position information, also known as spatial invariance. A recent trend in this domain is the merge of an attention mechanism with CNN to enhance the classification performance. This is done by identifying and extracting the salient discriminative features of MRI images. However, the generalization ability is still hindered due to validity of one specific dataset found among many research works. This research then proposes a novel attention-based CNN model (AGap-CNN), that employs the global average pooling (GAP) to reduce the number of learning parameters to be used for classification by Softmax. The AGap-CNN combines the attention mechanism with the GAP layer for classification at the model header to enhance the classification performance of CNN and improve the generalization capability of the network. The AGap-CNN was validated on two benchmark datasets of OASIS and ADNI. Furthermore, in further analysing the network performance, the AGap-CNN was compared to the existing state-of-the-art methods. The proposed AGap-CNN model outperformed the existing state-of-the-art methods for the OASIS and ADNI datasets with 99.22% and 100% average validation accuracy, respectively. In other words, the proposed AGap-CNN model works with acceptable accuracy, sensitivity, and specificity in classifying AD class and NC class for both benchmark datasets of OASIS and ADNI dataset.

ABSTRAK

Kekukuhan struktur *Conventional Neural Network* (CNN) sebagai teknologi canggih telah membawa kepada lonjakan penggunaan penyelidikan untuk klasifikasi penyakit Alzheimer (AD). CNN menggantikan kaedah konvensional *Machine Learning* untuk membantu pakar dalam mendiagnosis AD. Walau bagaimanapun, prestasi struktur CNN konvensional dalam mengklasifikasikan kelas AD dan kelas Kawalan Normal (NC) dihalang oleh cirinya, yang memerlukan data berskala besar. Halangan utama dalam domain AD ialah jumlah data yang terhad. Kebanyakan kajian telah menerima pakai modul peningkatan berpusatkan data seperti teknik pra-pemprosesan, penambahan data, dan strategi pembelajaran pemindahan untuk meningkatkan prestasi klasifikasi CNN. Walau bagaimanapun, semua modul ini masih bergelut untuk menawarkan ketepatan klasifikasi CNN yang bagus disebabkan oleh isu CNN yang terlalu bagus (*overfitting*) dan sifat CNN yang tidak sensitif kepada ciri yang dikenali sebagai *spatial invariance*. Trend terkini dalam domain ini adalah menggabungkan mekanisme perhatian dengan CNN untuk meningkatkan prestasi klasifikasi dengan mengenal pasti dan mengekstrak ciri diskriminatif yang menonjol bagi imej MRI. Walau bagaimanapun, ia masih terhalang kerana keupayaan generalisasi disebabkan beberapa kerja sedia ada hanya di sahkan pada set data tertentu.Penyelidikan ini mencadangkan model CNN berasaskan perhatian baharu (AGap-CNN), menggunakan *Global Average Pooling* (GAP) untuk mengurangkan bilangan parameter pembelajaran yang akan digunakan untuk pengelasan oleh fungsi *Softmax*. AGAp-CNN menggabungkan mekanisme perhatian dengan lapisan GAP untuk pengelasan pada kepala model CNN bagi keupayaan generalisasi rangkaian. AGAp-CNN disahkan pada dua set data penanda aras OASIS dan ADNI. Tambahan pula, AGap-CNN dibandingkan dengan kaedah terkini yang sedia ada untuk menganalisis prestasi rangkaian dengan lebih lanjut. Model AGap-CNN yang dicadangkan mengatasi kaedah terkini yang sedia ada untuk set data OASIS dan ADNI dengan purata ketepatan pengesahan 99.22% dan 100%, masing-masing. Dalam erti kata lain, model AGAp-CNN yang dicadangkan berfungsi dengan ketepatan, kepekaan dan kekhususan yang boleh diterima dalam mengklasifikasikan kelas AD dan kelas NC untuk kedua-dua set data penanda aras kumpulan data OASIS dan ADNI.

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AD	-	Alzheimer's disease
Aβ		β-amyloid peptide
CT	-	Computed Tomography
PET	-	Positron Emission Tomography
MRI	-	Magnetic Resonance Imaging
SPECT	-	Single-Photon Emission Computed Tomography
CAD	-	Computer-Aided Diagnosis
ML	-	Machine Learning
DL	-	Deep Learning
ANN	-	Artificial Neural Network
NC	-	Normal Control
MCI	-	Mild Cognitive Impairment
SVM	-	Support Vector Machine
CNN	-	Convolutional Neural Network
MMSE	-	Mini-Mental State Examination
MoCA	-	Montreal Cognitive Assessment
sMRI	-	Structural Magnetic Resonance Imaging
3D	-	Three-Dimensional
OPLS	-	Orthogonal Projections To Latent Structures
GLCM	-	Grey Level Co-Occurrence Matrix
CSF	-	Cerebrospinal Fluid
GPU	-	Graphics Processing Unit
ReLU	-	Rectified Linear Unit
FC	-	Fully Connected
2D	-	Two-Dimensional
ROI	-	Region Of Interest
GM	-	Gray Matter
MNI	-	Montreal Neurological Institute
TF-CNN	-	Tensorflow CNN
OASIS	-	Open Accese Series Of Imaging Studies

WM	-	White Matter
AMS-MEM	-	Adaptive Mean Shift Modified Expectation-Maximization
2D-ABF	-	2D Adaptive Bilateral Filter
AHA	-	Adaptive Histogram Adjustment
RNN	-	Recurrent Neural Network
LSTM	-	Long-Short Term Memory
BGRU	-	Bidirectional Gated Recurrent Units
1D	-	One-Dimensional
DNN	-	Deep Neural Network
SPM	-	Statistical Parametric Mapping
DARTEL	-	Diffeomorphic Anatomical Registration Exponentiated Lie Algebra
CapsNet	-	Capsule Network
DSC	-	Depthwise Separable Convolution
NLP	-	Natural Language Processing
NMT	-	Neural Machine Translation
CBAM	-	Convolution Block Attention Module
GAP	-	Global Average Pooling
ADNI	-	Alzheimer’s Disease Neuroimaging Studies
NIH	-	National Institutes Of Health
NIA	-	National Institutes On Aging
NIfTI	-	Neuroimaging Informatics Technology Initiative
HA	-	Hippocampal Absence
HP	-	Hippocampal Presence
Conv. Block	-	Convolution Blocks
Conv. Layer	-	Convolutional Layer
BN	-	Batch Normalization
CDR	-	Clinical Dementia Rating

LIST OF SYMBOLS

$e^{c_i^s}$	-	Standard Exponential Function For Element-Wise Summation
i	-	Spatial Location
n	-	Number Of Channels (Spatial Location)
α_i^s	-	Attention Coefficient At Spatial Location i Of Convolution Block
$\boldsymbol{\mathcal{F}}^{\boldsymbol{s}}$	-	Local Feature Vectors At Convolution Block s
f_i^s	-	Local Feature Vectors At Convolution Block s
y_c	-	The Actual Class Label
p_c	-	The Softmax Probability For The c^{th} Class
M	-	Number Of Class

CHAPTER 1

INTRODUCTION

1.1 Problem Background

In World Alzheimer Report 2021, Alzheimer's Disease International (ADI) reported over 55 million people are living with dementia globally, and the number is estimated to escalate to 78 million people by the year 2030 [3]. Dementia, also known as 'major neurocognitive disorder' is a term to describe people who suffer from cognitive impairment, i.e., memory loss, deterioration in thinking and reasoning function, and significant change in behavioural abilities severely to such an extent affects one's daily routine and social autonomy. To be more specific, it may exhibit symptoms or early warning signs such as progressive memory decline regarding recent events, inability to recognize familiar faces, difficulty making decisions and judgements, searching for words, lost in directions, times and places, and language problems. Also, psychological symptoms such as anxiety, social withdrawal, irritability, and depression are often associated with the prior symptoms.

It has been stated in the report, the common causes of dementia are highly related to brain-related diseases, i.e., Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and young-onset dementia. However, due to the rising of the world population ageing [4], Alzheimer's disease (AD) is the most common cause, accounting for 60% to 80% of dementia cases. Furthermore, since AD has often been diagnosed during the late stage of the disease; thus, older people over 65 years old are the most at risk. Alzheimer's disease (AD) is an irreversible neurodegenerative disease, progressively changes the brain morphologies due to the degeneration of the brain cells. This happened because the normal cognitive functions have been blocked by the presence of two significant pathologies, which are the extracellular plaque deposits of the β-amyloid peptide (Aβ) and the flame-shaped neurofibrillary tangles of the microtubule-binding protein tau [5] in the brain leads to dysfunction of cognitive, reduction of specific neuron and destruction of the synapse.

Up to the present, there is still no treatment that can fully cure Alzheimer's disease. The current treatment focuses more on slowing the progression of AD symptoms, reducing the build-up of the β-amyloid peptide (Aβ) and tau protein by prescribing the patients. For instance, US Food and Drug Administration (FDA) recently has approved Aduhelm (aducanumab), a new medicine to treat patients with AD [6]. Alongside the drug treatment, creating a supportive environment for the patients is a part of the treatment to sustain their life. In order to provide appropriate treatment for the patients, an early, accurate, and timely diagnosis of AD by medical practitioners is vital. It is the very first step in a long process, which requires comprehensive and attentive medical evaluations involving a multidisciplinary team of healthcare professionals, i.e., primary care physicians, medical experts, and radiologists.

Conventionally, clinical assessment and laboratory tests are run on the patients following initial assessment from the primary care practitioner. It involves a medical history and physical examination, cognitive assessment, blood test, and neuroimaging scans. Following the preliminary assessment (i.e., physical examination, cognitive assessment, and blood tests), brain neuroimaging scans are usually performed on patients to assess and diagnose AD progression and severity by using non-invasive neuroimaging modalities such as computed tomography (CT) scan, positron emission tomography (PET), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT). Among the modalities, MRI is often used since it is the safest modality, produces no radiation that can be harmful to the patients compared to other modalities. Furthermore, MRI scans show the changes of specific parts of the brain structure: 1) degeneration of the hippocampus, 2) ventricle enlargement, and 3) cerebral cortex shrinkage can be assessed, thus can facilitate experts in characterizing AD. Nevertheless, diagnosing AD involves a long process that can last years, requiring thorough interventions and professional knowledge.

Over the past decade, an automated analysis system, otherwise known as a computer-aided diagnosis (CAD) system, has been widely used to assist and support medical experts in diagnosing AD based on MRI scans. Often, CAD systems in this domain are highly related to the utilization of conventional machine learning (ML) and deep learning (DL)-based techniques in identifying, predicting, and detecting the pattern of AD. In early year, conventional ML techniques have shown promising results in classification of AD subjects from others classes of subjects i.e. normal control (NC) and mild cognitive impairment (MCI), utilizing powerful classifiers such as support vector machine (SVM) [7-11], artificial neural network (ANN) [8, 12, 13], etc. Due to the hand-crafted feature extraction, conventional ML techniques were seemed incompatible and impracticable to be used within that time, incurs high computational resources and times.

Therefore, researchers have begun to utilise DL-based techniques in diagnosing AD since it has become a recent trend in the medical image analysis area. To date, the trend in the AD domain has shown the surge in utilizing convolutional neural network (CNN) architecture among the existing studies for potential application, i.e., classification of AD and NC subjects based on the MRI data. The trend may be due to the capability of CNN in extracting the subtle low-level and high-level features end-to-end from the high-dimension input image without any prior feature selection and less dependent on image pre-processing. The performance of existing CNN-based models in the whole process classification task are primarily affected by the nature of MRI data and the configuration of CNN architecture, which often lead to the misclassification [14, 15]. Also, the misclassification may due to the existing CNN-based models disregard the significance of the spatial and salient information of MRI images [16]. Nevertheless, there is still room for discussion and investigation to further enhance the high-performing CNN models for AD classification, including several enhancement modules choices and critical implementations for alternatively handling the MRI data and CNN architecture.

1.2 Problem Statement

Often, medical experts diagnose AD by running clinical assessments on the patients, as well with the assisting of MRI. High-resolution T1-weighted MRI sequences are able to distinguish the anatomical boundaries and detect the structural changes in the brain [17]. However, experts with vital knowledge and a lot of experience are required to analyse MRI visually, i.e., the abnormal brain changes (atrophy), which may be scarce. Sometimes, there is a possibility of being prone to errors in diagnosis due to human error factors such as stress, fatigue, heavy workload, and cognitive bias affecting the performance of experts, thus leading to diagnostic errors. According to [18], diagnostic errors by the radiologists contributed approximately 75% of all the medical errors, and about 74% of diagnostic errors were caused by cognitive factors [19].

Therefore, to support and assist experts in diagnosing AD, prior studies began to employ an automated analysis system, i.e., a CAD system. CAD systems in this domain have been developed by using the recent technology advancement: conventional machine learning-based technique and deep learning-based technique, aiming to assist experts in making-decision (AD classification) task. Conventional machine learning-based technique has shown promising results but exceptionally high maintenance due to the complex processes requiring manual feature extraction [20] with expert's intervention and relatively time consuming [21]. Hence, recent trend in this domain is utilizing deep learning-based techniques since it become the cutting-edge technology in medical images domain due to its robustness in image classification, segmentation and detection tasks [22].

The most dominantly used of deep learning algorithm for AD classification is CNN [22, 23], performing well in image classification and having revolutionised performance of conventional machine learning techniques. CNN-based techniques highly depend on the nature of data i.e., requiring the large-scale and high-quality image of MRI data, and optimal neural network architecture to achieve a good classification performance. However, the performance of CNN architecture in classification task of AD is hindered by the small amount of MRI data with low quality image but high-dimensionality. Therefore, existing researchers improved the performance by introducing modules such as MRI pre-processing [24], transfer learning strategy, data augmentation and incorporating advanced modules. However, all these modules still struggling to offer a good accuracy of classification of the disease.

The degradation of MRI images quality due to the artefacts, i.e., inhomogeneity, motion, and scanner-specific variations [25] may affect the performance of CNN architecture in AD disease classification. Hence, MRI pre-processing techniques have been applied, although some studies conceded the CNN architecture can perform well without the pre-processing [26, 27]. With the advancement of deep learning, some of the pre-processing techniques have become less critical [28]. Moreover, several limitations of the techniques have been emphasized such as poor generalization in which often require to be tuned to work on different brain morphologies and acquisition sequences, and requiring manual intervention [29, 30]. Therefore, most of the studies perform no to minimal pre-processing techniques in their works [16, 23], as well improving their models with the implementation other modules.

MRI data provided by the databases are insufficient for training a deep learning-based model by means of CNN architecture. So, every study tried to develop solutions to tackle the major issue regarding the limited amount of data: 1) transfer learning strategy; 2) adopting data augmentation. Commonly, pre-trained network on natural images (ImageNet) has been adopted for transfer learning, i.e., fine-tuning the last few layers with MRI images, which is sufficient to achieve better classification performance. However, according to [31], this behaviour might change depending on the application at hand. It might lead to the negative transfer issue since transfer learning only works if the initial and target problems of both models are similar. Although pre-trained network alone is good to use yet some researchers improve with varies techniques such as layer-wise transfer learning, and associating data augmentation and advanced modules with the transfer learning strategy.

Data augmentation often involves the geometric transformation such as rotation and flipping. However, these geometric transformations might degrade the spatial normalization of the MRI data [16, 32]. Local position information is significant in training medical images; thus, the geometric transformations are inapplicable to augment the data, especially in the AD domain, where the information from hippocampal region is high importance and such transformations may remove the information. Since, most of the enhancement modules are data-centric i.e., enhancing the classification performance by improving the MRI data, yet, the driven data-centric on classification module subjects to the CNN architecture as a backbone in offering good classification. Hence, researchers improve the classification performance with enhancing the CNN architecture by integrating advanced modules with the architectures such as depth-wise separable convolution (DSC), Capsule Network (CapsNet) and dilated causal convolution module.

Although these modules have improved the CNN architecture, yet stuck in the low performance due to the compact and slow algorithm thus, incurring the requirement to depend on high computational resources. Also, the high performance might be hindered by the behaviour of CNN architecture, which incapable to preserve and exploit the local spatial information due to spatial invariance and object of interest is relatively small. Hence, recent trend in AD classification is incorporating attention module within CNN architecture. In handling medical images, particularly MRI images, local spatial position information is significant to exploit and preserve in making-decision tasks [33].The loss of information of the salient region may lead to misclassification and misdiagnosis. Even though attention mechanism has slightly improved the performance of CNN architecture in AD classification application, but CNN architecture tends to be overfitting due to the utilization of FC layers, thus hindering the classification performance of AD.

1.3 Research Objective

The main objective of this research is to improve the classification performance of a deep learning-based model by enhancing the CNN architecture to assist and support experts in diagnosing AD. The specific objectives are:

(a) to develop a novel attention-based deep learning model, using modify VGG-16 architecture as baseline network, attention mechanism and global average pooling (GAP) layer for classification application based on the enhanced local features extracted.

(b) to classify normal control (NC) subject and AD subject based on (a) by investigating the best configuration of implementing the global average pooling (GAP) layer for prediction.

(c) to validate and compare the performance of the proposed technique on benchmark datasets known as Alzheimer's Disease Neuroimaging Initiative (ADNI) & Open Access Series of Imaging Studies (OASIS) with existing methods.

1.4 Research Scope

The scope of this research covers all aspects that are considered as follows:

a) All the relevant subjects selected in this research are provided by two large databases: Alzheimer's Disease Neuroimaging Initiative (ADNI) and Open Access Series of Imaging Studies (OASIS). Relevant subjects are verified and categorized based on Clinical Dementia Rating (CDR) score. A CDR score greater than zero indicates subjects with AD symptoms, whereas normal subjects (NC) have a CDR score of zero. The age and gender of the subjects are also significant demographic characteristics in this research to choose relevant subjects. Therefore, males and females were included and distributed equally in this research, with the average age range between 65 to 74 years old.

b) The downloaded OASIS MRI data were obtained from the latest cohort, OASIS T1-weighted sequence MRI data was collected using Siemens Vision 1.5T scanner (Siemens Medical Solutions USA, Inc). The downloaded ADNI MRI data of relevant subjects were captured using standard 1.5 Tesla screening baseline T1-weighted sequence via volumetric 3D MPRAGE protocol.

c) 3D MRI scans were sliced into three view projections (i.e., axial, sagittal, and coronal). Only a single view projection was used in this research, i.e., the sagittal view. Also, the slice selection was performed manually to select MRI image slice consists a better view of the hippocampus.

d) The salient features (i.e., hippocampus) have been preserved and extracted using an attention mechanism incorporated with modified VGG16, one of the CNN architecture variants for the subsequent classification task. An attention map was used to visualize the salient features captured by the attention mechanism.

e) Global average pooling (GAP) layer was used over the features map captured by the attention mechanism to reduce the number of learning parameters in enhancing the classification performance of the AD and NC subjects.

f) MRI data fitted into the proposed AGap-CNN model are without undergoing pre-processing and augmentation. In addition, layer-wise transfer learning also has been adopted to support the training process of the proposed model.

(d) The result achieved from the proposed method was compared with other existing state-of-the-art CNN-based models (i.e., Inception-V4 and standard VGG architecture) and CNN-Attention-based model, including visual attention and convolutional block attention, to validate the performance of the proposed method against existing methods.

1.5 Research Significance

The significance of this research is as follows:

a) A new CNN-based model with the integration of attention mechanism was developed to capture the salient features, i.e., the hippocampus of the brain for discriminating AD subjects and NC subjects. The designated model was based on the soft attention mechanism and VGG-16 architecture as a baseline network.

b) A new method to further improve the classification performance of AD and NC subjects based on the features (i.e., hippocampus) captured by the attention module and further classified by the GAP layer was developed as an alternative to existing methods that depends on standard enhancement modules such as data augmentation, transfer learning, and other advanced modules.

1.6 Thesis Outline

This thesis is organised as follows:

a) Chapter 2 provides an overview of diagnosing AD based on medical perspective and computer-aided diagnosis (CAD) system as a tool to assist experts in making-decision task i.e., classification of AD and NC class. Also, critical review on the specific topics of classification of AD including an overview of existing CNN-based techniques in this domain, the recent enhancement and advancement methods such as pre-processing, data augmentation, transfer learning and advanced modules.

b) Chapter 3 explains the methodologies and research flow adopted in this study starting from the dataset used, dataset preparation, pre-trained network, the application of deep learning model development to classify the AD and NC class, the performance evaluation metrics, and the experimental setup.

c) Chapter 4 presents the results and discussion of the experiments conducted using the proposed methodologies described in Chapter 3. A critical analysis of the finding is also presented.

d) Chapter 5 presents the conclusion of this research, the limitation of study and the recommended future works that can improve upon the findings.

applications, such as in object detection and semantic segmentation in image. The idea of implementation attention mechanism and GAP layer on the FCN to further segment, extract and exploit the local feature of the images effectively, as well classify the disease accurately is a good initiative to enhance the classification performance. Also, the subtle difference and high similarity between the classes (AD class and NC class) issue can be addressed by introducing the idea in the near future. With FCN properties where it is known to be good at segmentation, thus makes it suitable to be applied for future works especially in improving AD and NC classification problems.

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LIST OF PUBLICATIONS

a) **Abd Hamid, N.A.**, Shapiai, M.I., Batool, U., Sarban Singh, R.S., Mohammed Amin, M.K., Elias, K.A., "Incorporating Attention Mechanism in Enhancing Classification of Alzheimer's Disease", *New Trends in Intelligent Software Methodologies, Tools and Techniques*. 2021, Vol. 337, page no. 496-509.