Journal of Advanced Research in Applied Sciences and Engineering Technology

Journal homepage:
https://semarakilmu.com.my/journals/index.php/applied_sciences_eng_tech/index
ISSN: 2462-1943

Bypassing Pre-processing Method in Alzheimer's Disease Diagnosing using Deep Learning Instance Segmentation

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ARTICLE INFO

Article history:
Received 11 August 2023
Received in revised form 28 December 2023
Accepted 14 January 2024
Available online 12 February 2024

Keywords:
Alzheimer's disease; deep learning; instance segmentation; Mask R-CNN

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that will cause the memory loss of patient and will progressively lead to loss of bodily function that will eventually lead to death. Therefore, diagnosing AD accurately is critical to provide the patients with suitable treatment to delay the progression of AD as well to facilitate the treatment interventions. Recent studies are more dependent on the Deep Learning Semantic Segmentation method to perform the Alzheimer's Disease diagnosis. However, semantic segmentation will segment every single pixel in the images which will affect the precision of the small targets like hippocampal region in MRI images, even though the overall loss is low enough. Therefore, a Deep Learning Instance Segmentation is introduced into the Alzheimer's disease diagnosis field without using any pre-processing method. In this research, the Mask R-CNN will be used to localize the hippocampal region to do the segmentation, and then classified it as AD or NC. The dataset UTM_ADNI_RAW will be used in this study. The proposed method applied on UTM_ADNI_RAW shows the high accuracy of 92.67%. These results show that the proposed method to segment the hippocampal region without requiring pre-processing techniques has a good accuracy in classifying AD and NC subjects. In conclusion, the proposed Mask R-CNN generated a good result on segmenting the hippocampal region without requiring any pre-processing techniques.

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that will cause the memory loss of patient and will gradually cause the function of body loss and eventually lead to death [1]. The average age that detects AD symptoms appear are in between 60 to 65 years old, with some special cases which is the earliest record where the patient at 30 years old age was diagnosed with AD [1].

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https://doi.org/10.37934/araset.39.2.153165

According to Alzheimer’s Disease International (ADI), people that lived with dementia had reached over 50 million all over the world in 2019. The worry is that the number of sufferings from dementia will increase to 152 million by 2050 [1]. It is also predicted that the popularity of the dementia in Malaysia will be 0.126% and 0.454% in 2020 and 2050 respectively [2].

AD can be characterized based on the changing in the features shown, for instance deterioration of hippocampal, cortex shrinkage and enlargement of ventricle. Generally, AD is often diagnosed in late prodromal period due to the slow but progressive onset. Hence, an attentive medical evaluation is required to diagnose Alzheimer’s disease [3]. One of the ways to diagnose AD is observing the thickness of hippocampal region by the experts with rich experiences [2]. To help the doctors and researchers to diagnose AD, two MRI databases have been set up which are Alzheimer’s Disease Neuroimaging Initiative (ADNI) database and Open Access Series of Imaging Studies (OASIS) database [4,5]. Both databases are created based on Clinical Dementia Rating (CDR) with the score of the subject. CDR score of one will be possessed for the subject that having Alzheimer's disease, while CDR score of zero for normal control subject.

Nowadays magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are the tools that play an important role to support doctors in diagnosing patients with AD [2]. Currently, most experts and doctors are still relying on visual assessments to detect the abnormalities of hippocampus manually. Operator dependent on visual analysis of MRI stands a better way to detect the abnormalities when the result is viewed by experiencing experts. However, sometimes the visual analysis of MRI will lead to a diagnosis error due to stress, fatigue, heavy workload, and cognitive bias. This makes the development of computer-aided diagnosis (CAD) systems become so important to assist medical experts in diagnosing Alzheimer’s disease.

Since 2006, deep learning has become universal with breakthroughs in speech recognition. Not only the advent of ImageNet, which is a large visual database with annotated, the rapid development of high-performance parallel computing systems such as graphics processing unit (GPU) clusters, major advances in network architecture and innovations in training strategy design have contributed to the rise of deep learning [6]. One of the hallmark techniques of deep learning is the convolutional neural network (CNN), which consists of a stack of multiple convolutional layers, activation layers, and pooling layers, followed by the addition of several fully connected layers to control the output class. The excellent performance of CNN has prompted many AD-related studies and has been widely used in AD diagnosis [7-26]

Image segmentation is one of the ways to isolate a digital image into numerous regions on the basis of the pixels in different properties. Image segmentation is usually a low-level or pixel-level vision task as the spatial information of an image plays an important role in segmenting different regions semantically. Since segmentation aims to extract meaningful information from images for easier analysis, the way of labelling image pixels can highlight the characteristics of every pixel in an image such as colour, intensity, texture, and so on [27].

There are two main types of deep learning segmentation methods which are semantic segmentation and instance segmentation. The existing work basically consists of two major procedures, which are MRI pre-processing and training of neural network architecture. MRI pre-processing techniques such as skull stripping, bias field correction, and image registration are frequently used to remove the skull boundaries, remove noise or artifacts, and normalize the intensity level. These techniques are adopted to make sure the better accuracy of segmentation performance for diagnosing AD. Besides, various deep learning segmentation methods such as QuickNAT, UG-net, and so on have been proposed to improve the accuracy performance [28,29]. Currently, many deep learning techniques that often depend on MRI pre-processing have been introduced to solve the segmentation problem to get a nice segmentation result. However, there are still have some limitations in existing works:

i. The pre-processing technique is a complicated process that needs to deal with multimodal images (e.g., MRI, CT, PET, and SPECT) to provide the information needed. These techniques also cost a lot of time to prepare the brain images.
ii. Most of the existing deep learning-based methods are more focus on semantic segmentation, leaving a research gap on deep learning instance segmentation.

To overcome the limitations that are stated above, we proposed a novel deep learning-based model without pre-processing techniques, Mask R-CNN, a Deep Learning Instance Segmentation is used as method to segment and classify the hippocampus as AD or NC. We expect our proposed deep learning-based model can capture and segment the hippocampal region of the MRI brain scan image and classify it as AD or NC. We validate the performance of our respective model on a benchmark dataset known as ADNI_RAW_ADNI and compare our performance with previous works.

This paper is organized as follows. In Section 2, we present an overview of an AD study that can help the researchers to understand AD, and how doctors and experts diagnose AD in every patient. This chapter also presents other methods that were proposed by researchers in previous studies to segment the hippocampus and the methodology they utilized in classifying AD. A critical analysis is presented in this chapter to summarize all techniques that have been applied previously for classifying AD and NC. Section 3 will present the proposed method for this research and the method for conducting the investigation and the experiments to fulfil the objectives of this research. This chapter also includes the details of the dataset used in this research, the feature extraction method, and the analysis of the results of every phase of the proposed method. The result will be presented, analysed, and discussed and presents the result's accuracy on classifying the hippocampus in Section 4. Finally, Section 5 concludes the paper with future works.

2. Related Work

2.1 Alzheimer's Disease Neuroimaging Initiative (ADNI)

In order to validate the proposed method, ADNI as a longitudinal multicenter study is designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD). It began in 2004 under the leadership of Dr. Michael W. Weiner. The main objectives of ADNI are to detect AD at pre-dementia stage and identify ways to track the disease's progression with biomarkers, to support advances in AD intervention, prevention, and treatment through the application of new diagnostic methods at the earliest possible stages as the intervention may be most effective at the earliest stages of AD, and to continually manage ADNI's innovative data-access policy, which provides all data without embargo to all scientists in the world.

2.2 MRI Pre-processing

MRI image itself is the main difficulty in diagnosing AD. It contains non-brain tissues that can be considered as noises on MRI images such as skull, eyeball, neck and so on. To prevent the performances of study affected by these non-brain tissues, previous works are more dependent on performing the MRI pre-processing techniques to remove the noises on MRI images so that the training task can be improved. The most common MRI pre-processing techniques that have been applied in previous studies are skull stripping, bias field correction, and image registration.

Skull stripping aims to remove non-brain tissues such as skull and eyes from a brain MRI scan [30]. Bias field correction is used to correct the bias fields caused by the spatial inhomogeneity of the magnetic field [27]. Image registration is required in medical image analysis to aid treatment verification, to improve interventions, or to compare patient's data to anatomical atlases, as it is able to obtain complete information about the patient by combining the data from multiple modalities such as CT, MR, SPECT, or PET [31].

Previous studies also applied various pre-processing techniques to get a better image view for deep learning segmentation tasks. For example, Cao *et al.,* [32], perform anterior commissure (AC)-posterior commissure (PC) correction using MIPA. Then, they resample all images to unify the resolution of the images, followed by intensity inhomogeneity correction through N3 algorithm, and linearly align all images onto a template image. Still, there is an exception on pre-processing application. For example, in order to obtain a segmentation in a short time, Brusini *et al.,* [33] underwent their MRI scans only a couple of pre-processing stages which are resampling and intensity normalization.

2.3 Deep Learning Segmentation for MRI

Image segmentation is to divide an image that belongs to the same object class into a region such as intensity, depth, color, or texture [27]. Image segmentation can be sorting as semantic segmentation for classification problem of pixels with semantic labels or instance segmentation for partitioning of individual objects.

In recent studies, many studies proposed to utilize several convolutional neural networks (CNNs) in the field of image segmentation to analysis the MRI brain scan images. For instance, Cao *et al.,* [32] proposed a multi-task convolutional neural network for joint hippocampus segmentation and clinical score regression. The authors used a 72 x 72 x 72 cropped MR image patches as input data, and the output include probability maps for segmented hippocampus and MMSE scores, estimated by a Dice-like loss function and a mean squared error loss function respectively.

Next, Roy *et al.,* [28] proposed Quick segmentation of NeuroAnaTomy (QuickNAT) which involves three 2D F-CNNs in use on coronal, axial and sagittal views followed by an aggregation step to deduce the final segmentation. The F-CNN used in all three views are enlightened by U-Net architecture.

Pang *et al.,* [34] proposed a novel method based on iterative local linear mapping (ILLM) with representative and local structure-preserved feature embedded. ILLM goals is to enhance the segmentation result iteratively by Space-constrained dictionary update (SCDU), local linear representative (LLR), and signed distance map (SDM) for prediction and segmentation. The dictionary in SCDU is updated by exploiting test MR image and the corresponding SDM image that predicted by previous iteration. Then the updated embedded feature dictionary will be used in LLR to represent the test embedding feature. Finally, the prediction and segmentation will be done by SDM using the coefficients that are calculated in LLR. These procedures of segmentation refinement are repeated iteratively until convergence to get a refined segmentation result.

Shi *et al.,* [29] present a combination of U-Net and generative adversarial network (GAN). A modified U-Net called UG-Net has been used as generative network which is the first part of GAN to produce the per-pixel class prediction of brain MRI. The adversarial network with convolutional neural network will then analyse the expert annotation and the segmentation images generated by generative network in the second part of GAN.

Wang *et al.,* [35] proposed an FCN framework with CRF-RNN layer. Since the FCN experienced a low-resolution result, the method is proposed to improve the pixel-level labelling task's accuracy by retaining an elegant end-to-end framework using the dense CRF that trained as recurrent neural networks (RNN). Since U-Net have shown its remarkable ability to segment biological organs or tissues in different medical images, the proposed model's backbone which is motivated by it is able to precise the segmentation of hippocampus by combines every low layer feature map with corresponding high layer.

Brusini *et al.,* [33] proposed a maximum of three main steps segmentation methods. Each method will perform three orthogonal 2D U-Nets that will perform a first 3D segmentation by taking the original MRI image as input, called as MRI U-Net. Next, a further step is added to MRI U-Net as a second segmentation method which is called Cropped U-Net. Cropped U-Net consists of three orthogonal U-Net, which will use the cropped original MRI images around both left and right hippocampus that preliminarily segmented by MRI U-Net as the input. Finally, a third approach named Shape MRI U-Net is proposed which consists of fitting a statistical shape model to the segmentation obtained from MRI U-Net is proposed. The cropped MRI data and the corresponding fitted shape model will be used as input to three other orthogonal U-Nets employed in this method.

A semi-automatic model that combines a deep belief network (DBN) and Lattice Boltzmann (LB) method was proposed by Liu and Yan [36]. The trained DBN will infer the shape of hippocampus and is used for initialization and is incorporated into LB model for segmentation. An offline training process will be done to train DBN in order to achieve the best parameter values. After the training process, the system will be deployed to perform the automatic segmentation task.

Deng *et al.,* [37] proposed a Pixel2Pixel as the basic architecture GAN model called Res-SEblock-GAN. In this model, a codec structure that is a combination of a residual network and an attention mechanism has been used as generative model, and a CNN that used to discriminate the segmentation result obtained by generative model and expert segmentation results as adversarial network. Thus, the generative model result will be closer to 1 when the segmentation result of the generative model is more realistic, and it is closer to expert segmentation result.

Helaly *et al.,* [38] proposed a DL-AHS framework that comprises five steps. The first step is data acquisition step, where about sixty-four patients with MRI historical scans representing the AD stages are collected from ADNI and NITRIC dataset. Next, in preprocessing step the MIPAV program is used for processing and segmenting both left and right hippocampus for final segmentation performance evaluation. The data augmentation step had been done in step 3 due to the small dataset amount by using DCGAN. This makes the dataset's size become 1500 MRI slices, which 500 for original slices, 500 for left hippocampal slices, and 500 for right hippocampal slices respectively. In step 4, the segmentation steps are done by applying two proposed architectures which are SHPT-Net and RESU-Net. Both proposed architectures are based on U-Net. Finally, according to the DL-AHS steps, the model's performance will then be monitored and reviewed to confirm the effective result and accurate performance.

However, most previous studies are based on semantic segmentation which are U-Net and GAN [39,40]. Semantic segmentation will assign every pixel in an image into a class, while instance segmentation only segments the pixels of specific objects only. This makes the precision of Mask R-CNN higher, as it has region proposal that is from Faster R-CNN as prior support to perform the segmentation. Not only that, but recent studies had also found that the proposed method can't automatically locate the hippocampal region to generate the training set [36]. To overcome this limitation, several studies are used only cropped MRI images instead of full MRI images as input dataset to emphasize the hippocampal region [32,35].

3. Methodology

This section will discuss the research method where the selection of the dataset, the proposed Mask R-CNN for Alzheimer's Disease (AD) segmentation will be discussed in detail. The main objective for the proposed method is to develop a new framework to segment and locate the hippocampal region for Alzheimer's Disease (AD) or Normal Control (NC) using only sagittal projection of MRI images without performing any pre-processing techniques. To fulfil the main objectives, the proposed method contains three stages, which are dataset preparation, setup of deep learning segmentation algorithm for training and testing using labelled MRI data, and the trained model will be deployed onto the whole sagittal MRI dataset to determining the status of patients.

The proposed Mask R-CNN can be divided into two stages. In Stage 1, a lightweight neural network called Region Proposed Network (RPN) scans all FPN top-bottom pathway and proposes regions that may contain objects. Next, anchor as a set of boxes will be used to predefine the position and scale relative to the image. The RPN used these anchors to determine where the feature map should pick up the object, and the size of its bounding box. This ensures that convolution, downsampling, and upsampling will keep features in the same relative positions as objects in the original image. In Stage 2, the ROIAlign has been used to locate the relevant areas of feature map, and generates objects classes, bounding boxes, and an additional branch generating masks for each object in pixel level. Figure 1 shows the proposed methodology of this research.

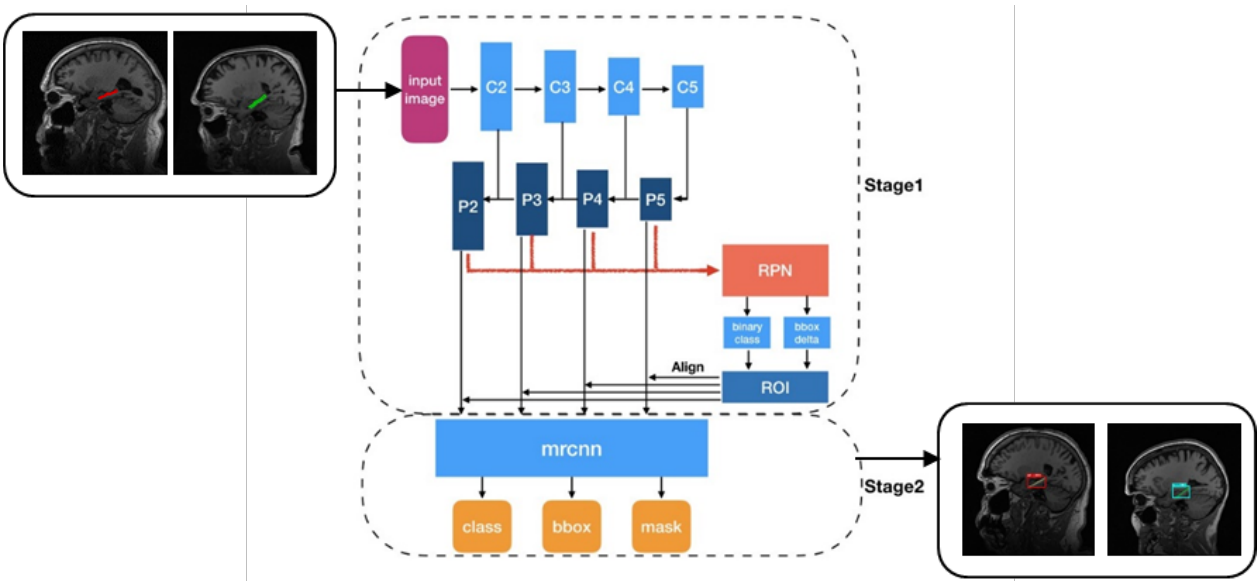


Fig. 1. Proposed methodology

3.1 Dataset Preparation

In this study, we used the ADNI_UTM_RAW dataset obtained from Jia *et al.,* [41] for deep learning-based Alzheimer's disease segmentation. This dataset consists of a total of 1000 subjects obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI), which 500 each in Alzheimer Disease (AD) and Normal Control (NC). All images inside this dataset are from T1-weighted, Magnetization Prepared Rapid Gradient Echo (MPRAGE) series. In order to make sure the better vision of hippocampus thickness can be obtained; only sagittal projection's data are contained in this dataset.

In order to make sure the visual inspection and manual selection easier, the dataset is also converted from medical Dicom (.dcm) format into the Portable Network Graphic (PNG) format by using ImageMagick command line prompt. The dataset is converted into 16-bit PNG-16 format as the data in Dicom format has 16-bit bit depth, this can prevent the image depth information will be lost from data conversion.

The selection of dataset for each subject has been done in three stages to make sure the chosen data represent the best hippocampal region of their corresponding classes. First of all, the manual selection had been done to categorize the sagittal MRI series into hippocampal present (HP) and hippocampal absent (HA) images. In this stage 24 HP MRI slices are selected out of 166-180 slices HA MRI slices. Next, 3-6 middle hippocampal slices that show the best thickness of hippocampus of its selected classes will be chosen for hippocampal labelling in stage 2 and stage 3. The reason of doing the filtering manually is to pick out the best few slices which represent AD and NC. Besides, the selection of dataset in three stages is better choices if compare with selecting those few slices from 166-180 MRI slices. Figure 2 shows a summary of the overview of data selection stage.

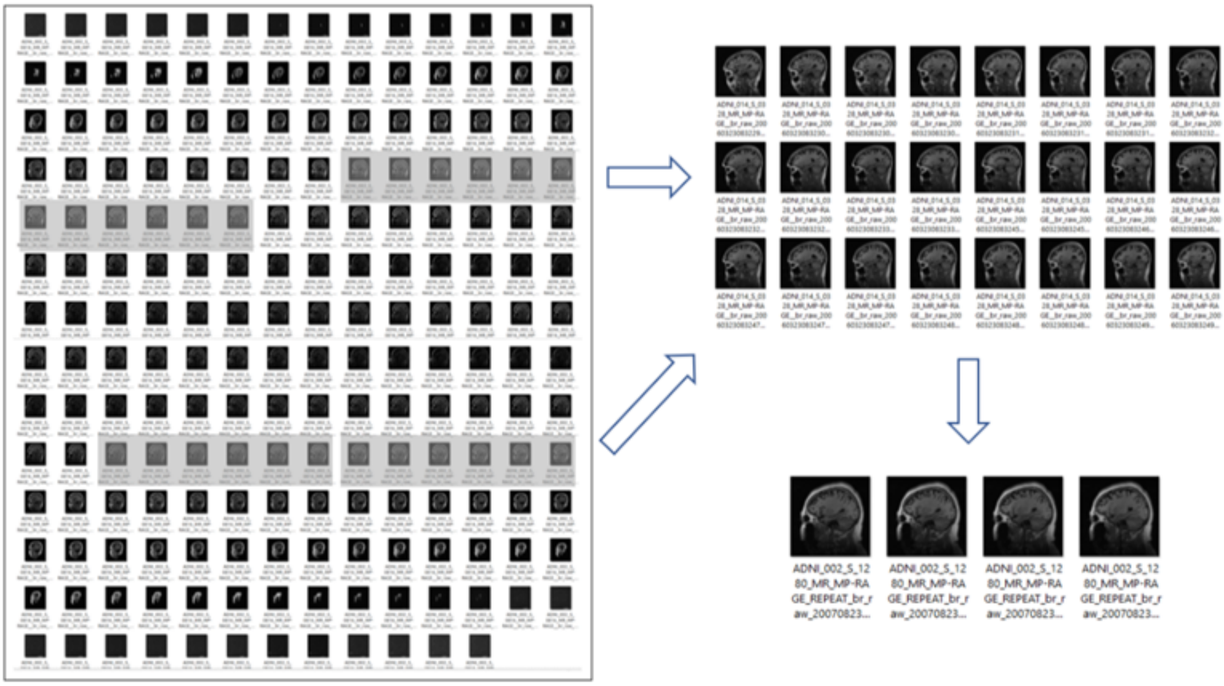


Fig. 2. Overview of data selection stage

The selected dataset as filtered hippocampal slices are then combined as AD and NC classes for labelling. The dataset is labelled using LabelMe. LabelMe is a tool which is a common toolkit for deep learning segmentation research. The labelled area of hippocampal for AD and NC are illustrated in Figure 3. The main characteristics to differentiate AD and NC is by hippocampal thickness. The difference between AD and NC hippocampus can be seen based on Figure 3. The difference of thickness between AD and NC hippocampal can be observed clearly, but in original MRI image, the difference of thickness between both hippocampal is very small. The region of the dataset is validated based on the UTM_ADNI_RAW.

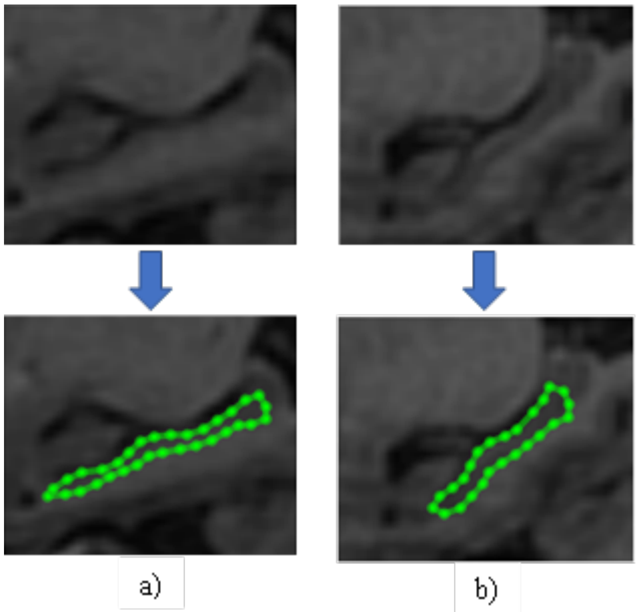


Fig. 3. Hippocampal area labelled (a) AD hippocampus (b) NC hippocampus

3.2 Proposed Mask R-CNN

Most of the previous studies proposed a semantic segmentation method that is mostly based on the U-Net and Generative Adversarial Network (GAN). Therefore, in this study the proposed method utilizes a deep learning instance segmentation model called Mask R-CNN [42] to segment the labelled hippocampal and categorize it as AD or NC without acquiring any pre-processing techniques. Mask R-CNN is a Convolutional Neural Network (CNN) and state-of-the-art in image segmentation. Mask R-CNN is an extension of Faster R-CNN where Faster R-CNN has 2 outputs for each candidate object which are a class label and a bounding-box offset, but Mask R-CNN has an additional third branch as the output which is an object mask [43]. The additional mask output is distinct from the class and box outputs, requiring the extraction of a much finer spatial layout of an object.

3.3 Parameters Setup

The Mask R-CNN will be used to train the model and deployed onto testing images that separated from 1000 subjects' data. The dataset labelled in the previous section are separated into train, validate and test at a 7:1:2 ratio. All these data are converted from medical DICOM format into PNG-16 format. This study is conducted with Linux Mint 19.1 Cinnamon Edition which is a Linux based operating system based on Ubuntu 18.04. The deep learning framework used is Apache Mxnet, a relatively new open-source deep learning software framework with high scalability on multi-GPU. The research is conducted using one NVIDIA GTX 1070 with 8GB VRAM. Finally, a signature deep learning instance segmentation network which is Mask R-CNN with ResNet-50 as backbone will be applied. The training image size in this research will be 256x256. Table 1 shows the description of parameters setup.

Table 1
Description of parameters setup

Parameter(s)	Value
Backbone	ResNet-50
Training image size	256*256
Learning rate	0.0025
Learning rate decay	0.1
Weight decay	0.0001
Momentum	0.9
Batch size	2

3.4 Performance Evaluation

The confusion matrix, which is a general evaluation standard for binary and ternary classification is used to analyse the proposed Mask R-CNN performance. In general, there are specific performance indexes to measure the Mask R-CNN performance, yet in this study common classification-based performance indices are used, which are accuracy, precision, and recall. The confusion matrix is a table that summarizes the success rate of classification model in predicting target images belonging to various classes. There are two axes in confusion matrix which are model predicted and actual label. Table 2 shows the confusion matrix for a classification model predicting. The TP, TN, FP and FN are represented as True positive, True negative, False positive and False negative respectively.

Table 2
The confusion matrix for a classification model predicting

	Model prediction		
Actual loan status		No default (0)	Default (1)
	No default (0)	TN	FP
	Default (1)	FN	TP

There are variant ways to evaluate the performance of our proposed network architecture. Accuracy is one of the ways as the primary evaluation for the binary classification performance between AD and NC. Accuracy is calculated as Eq. (1).

$$accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

In the other hand, the evaluation of the performance can also be done such as Precision and Recall. Precision is defined as the ratio of correct positive predictions to the total predicted positives, recall is defined as the ratio of correct positive predictions to the total positive examples, and accuracy is defined as the ratio of correctly predicted examples by the total examples. The performance metrics for Precision and Recall are calculated as in Eq. (2) and (3).

$$precision = \frac{TP}{TP + FP} \tag{2}$$

$$recall = \frac{TP}{TP + FN} \tag{3}$$

4. Results and Discussion

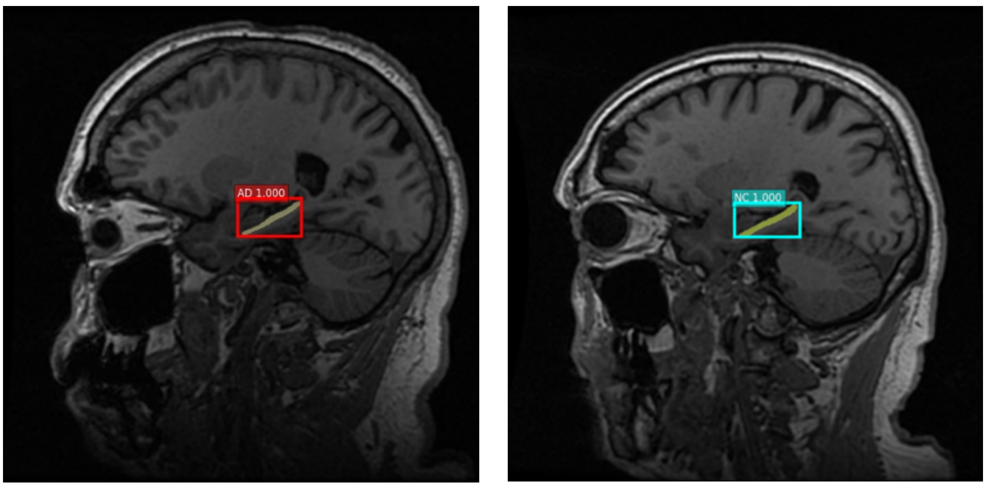
In this study, the Mask R-CNN was trained and tested by simple confusion matrix to analysis the accuracy of classification performance. Next, the accuracy of our trained model was tested to evaluate the performance of our respective network architecture. The proposed method's accuracy performance was compared with the existing methods given in Table 3. The output of the proposed model has been shown in Figure 4.

Table 3 shows that our proposed model obtained 92.67% which has higher accuracy compared with most of the previous studies about 10.77 in Roy *et al.,* [28] to 2.67 in Brusini *et al.,* [33]. However, the proposed Mask R-CNN accuracy is lower than DL-AHS framework by Helaly *et al.,* [38] about 1.67 and 4.33 for SHPT-Net and RESU-Net respectively. Since the proposed methods in previous studies are more based on U-Net and GAN, we believe that we successfully proposed an instance segmentation method into AD diagnosis fields.

Mask R-CNN has the advantage of capturing the hippocampus location and classifying it as AD and NC because of the help of region proposal network (RPN) that inherited from Faster R-CNN. RPN will generate several bounding boxes on the original image in advance, and finally outputs the anchor that is most likely to contain the object, called region of interest (ROI). Only the pixels in ROI region will be classified instead of every single pixels in the MRI image are also one of the reason why our proposed method is more accurate.

Table 3
Model performance for AD NC segmentation

Architecture	Year	Accuracy (%)
Multi-task deep learning (MDL) framework [32]	2018	89.3
QuickNAT [28]	2019	81.9
Iterative local linear mapping (ILLM) [34]	2019	89.67
FCN framework with a CRF-RNN layer [35]	2019	87.31
Shaped MRI U-Net [33]	2020	90
Deep belief network (DBN) [36]	2020	87
Res-SEblock-GAN [37]	2021	89.46
Deep Learning Alzheimer's Disease Hippocampus Segmentation Framework (DL-AHS) [38]	2021	94.34 (SHPT-Net), 97 (RESU-Net)
Proposed Mask R-CNN	2022	92.67



(a) (b)

Fig. 4. Output of Mask R-CNN framework for AD diagnosis (a) AD output (b) NC output

5. Conclusions

In conclusion, we successfully introduced an instance segmentation method based on Mask R-CNN into the AD diagnosis area for classifying AD and NC. Secondly, the proposed method does not utilize pre-processing techniques to the dataset used in order to avoid the changes of information of MRI images. Based on the testing result, we proved that our proposed method is successfully segment the hippocampal region and classified the segmented hippocampal region as AD or NC classes. In future, the attention network will be added into the Alzheimer's disease diagnosis task at the end of the proposed Mask R-CNN to improve our proposed AD segmentation method.

Acknowledgement
This paper is funded by Ministry of Higher Education (MOHE) under Fundamental Research Grant Scheme (FRGS), Registration Proposal No: FRGS/1/2022/ICT11/UTM/02/2 (Attention-Based Fully Convolutional Networks for Lane Detection of Different Driving Scenes - No Vote: R.K130000.7843.5F563)

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