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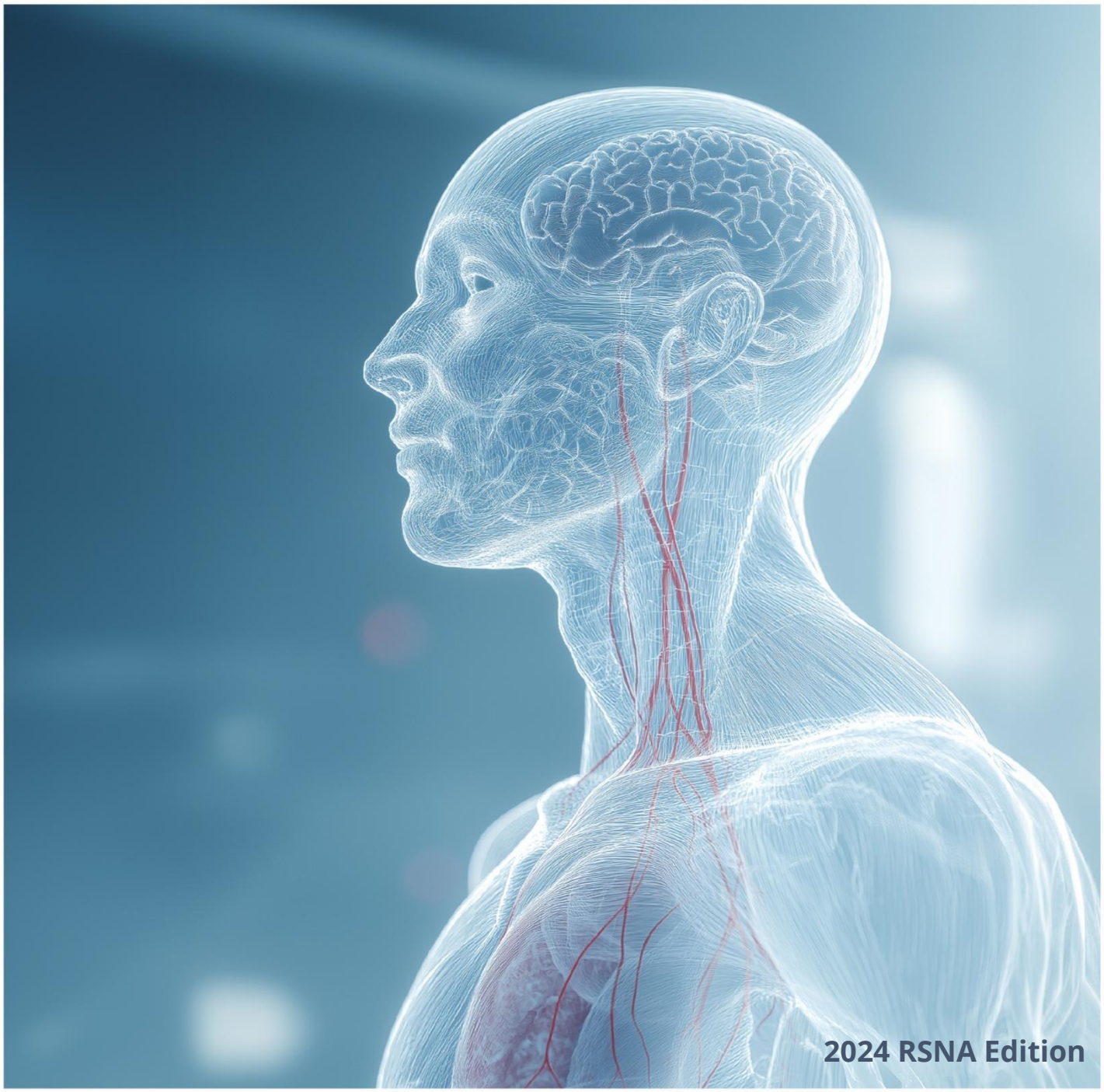

Issue Highlights

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Machine learning based diagnosis of Alzheimer's disease using volumetric analysis of gray and white matter

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1. Introduction

Alzheimer's disease (AD), a primary degenerative disease of the brain, is characterized by progressive deterioration of memory and other cognitive functions, as well as behavioral and other disorders. As per the World Health Organization (WHO) experts, AD is the primary cause of dementia among older individuals. The incidence of the AD exhibits a positive correlation with progressing ages. Currently, clinical presentation and psychological examinations are the primary methods used to diagnose AD. However, as compared to the gold-standard neuropathological diagnosis, the diagnosis of AD exhibits lower specificity (70%) and sensitivity (70%) (1). Numerous studies have been conducted to identify biomarkers for Alzheimer's disease (AD) (2, 3), along with various imaging techniques that employ magnetic resonance imaging (MRI) and positron emission tomography (PET) (4, 5).

Multiple MRI scans of the brains of AD patients have found abnormalities in the gray matter (GM) region. In contrast to healthy control (HC), AD patients had significantly reduced GM volume, decreased total brain volume, and larger ventricles (6-8). During the initial phases of the disease, there was a noticeable reduction in GM volume in specific areas of the brain. This mostly affected the medial temporal structures, such as the hippocampus, amygdala, and entorhinal cortex, as well as the posterior cingulate gyrus and medial thalamus on both sides (9-11). In response to the progression of the disease, abnormal brain areas spread to the frontal and parietal lobes of the brain (12, 13).

Measuring brain volume is an essential task in neurological and psychiatric research. The variations in GM, WM, and cerebrospinal fluid (CSF) volume can be used to identify physiological processes, medical conditions, or severity of an illness (14, 15). The main uses of brain volume measurement in neurological sciences include diagnosis, disease monitoring, and the evaluation of neurodegenerative disease treatment like AD (16-18). Thus, the assessment of brain volume is an essential initial stage in the majority of neuroimaging research. MRI is a precise technique for quantifying the volume of organs or structures.

Brain volume quantification in MR images can be carried out using manual, semi-automated, or fully automated approaches. For manual volume calculation of individual brain compartments from MRI data, two commonly used techniques are stereology and manual tracing (19, 20). Volumetric measurements must be exact and precise for both reliability and reproducibility. Automated methods are becoming increasingly important in brain volume studies, as manual estimation is time-consuming and labor-intensive (21).

The objective of the study was to evaluate the brain volume in HC individuals and patients with mild AD using deep learning network. Additionally, the study aimed to evaluate the performance of this model using machine learning classifiers.

2. Materials and methods

2.1 MRI data

This study employed 3T MRI scans from participants enrolled in the Alzheimer's Disease Neuroimaging (ADNI) – Phase 3. These scans were obtained from the ADNI (22) public website (http://www.loni.ucla.edu/ADNI/). This study included baseline MRI scans from 39 HC subjects and 39 individuals with a diagnosis of mild AD. The mean age was 70.90±7.20 years and the age range varied between 60 to 80 years across all subjects. Each subject underwent the acquisition of high-resolution T1-Weighted MRI scans using a sagittal 3D MP-RAGE sequence on a Siemens scanner. In this study, scans were obtained in the early phase of ADNI3 when availability was limited to the slice thickness of 1.2 mm with Siemens scan. The details of the MR parameters are shown in table 1.

2.2 Deep learning model and parameters

The current study utilized a cascaded weakly supervised confidence integration network (CINet) developed by United Imaging Intelligence, Shanghai, China (23) to quantify the volume of GM and WM regions through brain MR image parcellation. This deep learning-based tool can segment brain regions into sub-regions and quantify those regions.

2.2.1 Confidence network

A confidence network is first trained to predict confidence that assesses the quality of the label at each instant in order to properly utilize images with weak labelling. The weakly labeled images form a dataset $\{(X_1, Y_1), (X_2, Y_2),\ldots,(X_i, Y_i)\}$, where Xi represents the i^{th} image in the dataset (the input data), Yi corresponds to the label associated with Xi and Wi refers to the weak label map for the image Xi. Figure 1 depicts the confidence network's architecture. The network is provided with an unlabeled image and its weak label map. The discrepancies between the weak labels and the actual labels are used as a training metric. The output of the network can be considered a measure of confidence for the process of making inferences about the weak labels of the input image. The confidence network can be used to assess the data with weak labels once it has been trained.

2.2.2 CINet and loss function

V-Net is indeed a well-known deep learning model designed specifically for the segmentation of 3D medical images. Three improvements were implemented to the fundamental framework of V-Net with the aim of detecting variations in volume. First, as illustrated in figure 1, V-Net was divided up into two subnetworks. Only intermediate variables connected to one of the sub-networks are accessible during the training phase. The second adjustment involves substituting all the convolution operations in the second sub-network with 1*1*1 convolutions. The field of view can remain consistent at this point. The final change is to choose a patch at random from the first sub-output networks to serve as the second sub-input. The CINet framework is depicted in figure 2.

The atlas dataset is a collection of high-quality, labeled brain images used as a reference or guide for training segmentation models. Each image in the atlas dataset is paired with a corresponding ground truth label that delineates the structures of interest within the brain. The primary purpose of the atlas dataset is to provide a robust reference for training and validating the segmentation model (CINet). The atlas data is used in the fine-tuning phase of training CINet after it has been initially trained on a weakly labeled dataset. For atlas dataset $\{(M_1, L_1), (M_2, L_2),\ldots,(M_k, L_k)\}$ and the weakly labeled dataset $\{(X_1, Y_1, C_1), (X_2, Y_2, C_2),\ldots(X_i, Y_i, C_i)\}$, two different loss function were utilized in the training stage, where C_i is the confidence map for X_i, indicating the reliability of the weak label. Here, the confidence map Ci as masks by setting a threshold (i.e., α) to select parts of the image to enhance the performance of the segmentation network. The proposed loss is defined as follows:

$$Loss = \sum_x [C(x) > \alpha] * CrossEntropy(CINet(X), Y)(x) \quad (1)$$

Table 1: Details of MR Data. GR = Gradient Echo, IR = Inversion Recovery, TE = Echo time, TI: Inversion time, TR: Repetition time

Acquisition Plane: Sagittal	**Pulse Sequence:** GR/IR
Acquisition Type: 3D	**Slice Thickness:** 1.2 mm
Coil: Phase-array	**TE:** 3.0 ms
Field strength: 3 T	**TI:** 900 ms
Flip Angle: 9 degrees	**TR:** 2300 ms
Matrix Size: 240 x 256 x 170	**Pixel Spacing:** 1.1 mm x 1.1 mm
Manufacturing Model: Prisma Fit	

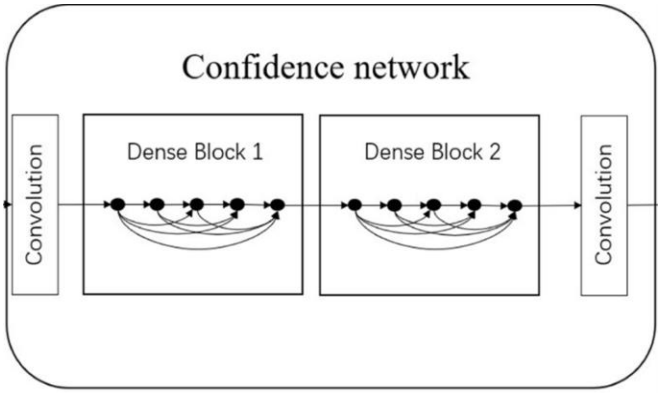

Figure 1: The architecture of the confidence network (Figure adopted from Xiao et al. (2019) (23))

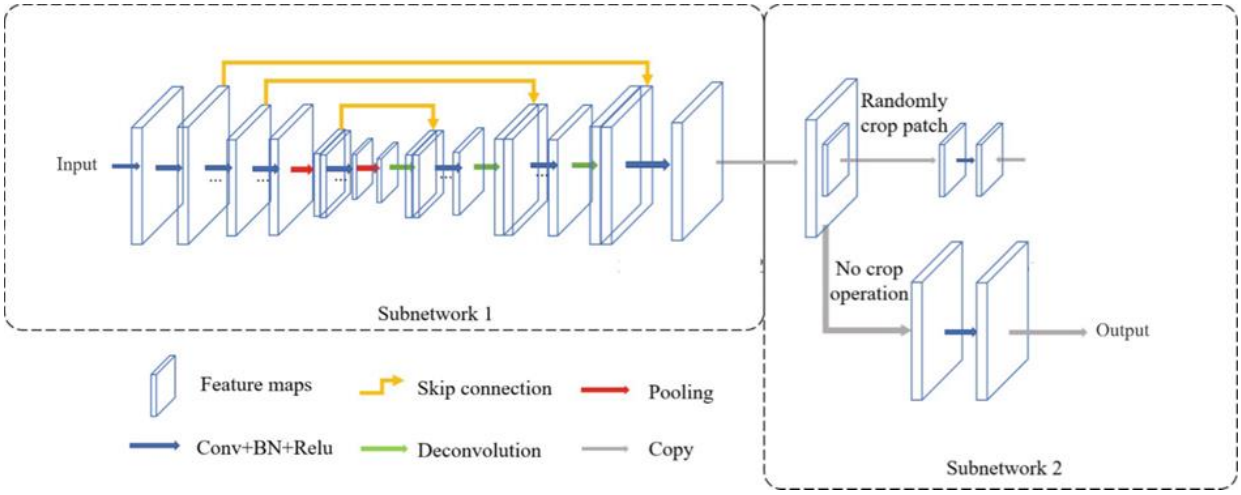

Figure 2: CINet framework (Figure adopted from Xiao et al. (2019) (23))

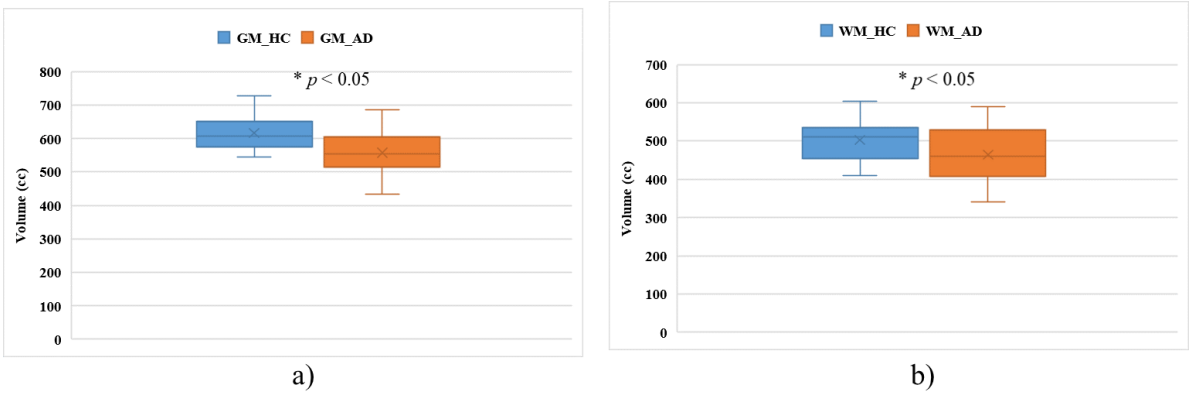

Figure 3. Box plots for GM and WM volumes of healthy and AD subjects

2.3 Statistical analysis

The statistical analyses were carried out using MedCalc for Windows, version 12.2.1 (MedCalc Software in Mariakerke, Belgium). The volumes of GM and WM in HC and individuals with mild AD were compared, and the statistical significance of the results was evaluated using a paired sample t-test with a p-value of less than 0.05.

Moreover, the model's diagnostic performance was assessed using machine learning methods, particularly linear discriminant analysis (LDA), linear support-vector machine (SVM), and Gaussian SVM classifier. These machine learning techniques were employed to assess the performance of the model through classifying between individuals with HC and those with mild AD. The sensitivity, specificity, accuracy and area under the receiver-operating characteristic curve (AUC) were measured to evaluate the performance of the classification.

3. Results

The mean ± SD of GM volume was 616.85 ± 49.67 cc for HC patients and 557.71 ± 62.73 cc for mild AD patients. For HC patients, the mean WM brain volume was 503.30 ± 58.21 cc, while for mild AD subjects, it was 464.72 ± 70.60 cc. Both GM and WM volume values for HC showed significant ($p < 0.05$) higher than mild AD subjects. Figure 3 shows the boxplots distribution of the GM and WM brain volume of HC and mild AD subjects.

The supervised machine learning classifiers were given the inputs of GM and white matter WM volumes, which were then classified into HC and mild AD classes. The performance of this two-class classification, involving GM and WM volumes, was evaluated using three different classifiers. The Gaussian SVM classifier demonstrated the highest performance with sensitivity of 75.00 ± 1.06%, specificity of 76.67 ± 1.87%, accuracy of 75.10 ± 2.05% and AUC of 0.77 using the combination of GM and WM volumes. The classification performance obtained using only GM and WM volume is shown in figure 4.

4. Discussions

AD is indeed a degenerative neurological condition characterized by a progressive decline in cognitive function, which significantly impacts various aspects of daily life. An effective method for early detection is high-resolution 3D MRI, which enables the assessment of alterations in the amount of gray and white matter in the brain. AD is mostly attributed to the gradual deterioration of both white and gray matter, in contrast to the typical aging process.

Numerous brain MRI investigations have revealed anomalies in the GM of AD patients. According to a number of studies, measuring the gray and white matter volume with an MRI can successfully identify AD in its early stages (24, 25). A study found that the automated assessment of GM volume using MRI was able to effectively distinguish between those who are in normal health and those who have AD (26). A number of investigations have been conducted to examine the use of automated artificial intelligence (AI)-based volume measurement for the early detection of AD.

The researchers employed a convolutional neural network (CNN) to partition the brain into regions containing GM and WM, as well as calculate the volumes of these regions, in a cohort of AD and HCs (27). Additionally, individuals with moderate cognitive impairment can be identified based on abnormalities identified in both gray and white matter volume (28). Another study found that patients with AD showed larger ventricles, considerably less whole brain volume, and lower global GM volume than normal controls.

In this study, we utilized a deep learning method known as CINet, as described in section 2.3, to precisely determine the volumes of GM and WM. The findings indicated that the brain volume of GM and WM in healthy subjects were considerably higher than in individuals with mild AD, with a statistical significance level of $p < 0.05$. Our study showed that individuals with AD in the early stages exhibited a more significant decline in brain volume compared to a control group with similar characteristics. The use of the CINet for brain parcellation allows not only accurate brain region segmentation but also precise estimation of different brain region volumes for diagnostic assessment. The combination of the volumes of GM and WM yielded to an accuracy of 75.10 % in classifying two separate categories.

The use of the CINet combined V-Net algorithm for GM and WM volume measurement in early-stage AD has several advantages over traditional manual segmentation methods. Firstly, the automated algorithm is faster and more efficient, completing the processing within 15 seconds. This rapid speed provides a notable advantage, especially in clinical environments, as it allows for more frequent measurements over time. Secondly, the algorithm has shown high levels of accuracy and reliability, which minimizes the risk of human

error and variability. The proposed method may enhance accuracy or precision in volumetric measurements, potentially due to superior image processing techniques, more precise anatomical atlases, or advanced statistical approaches.

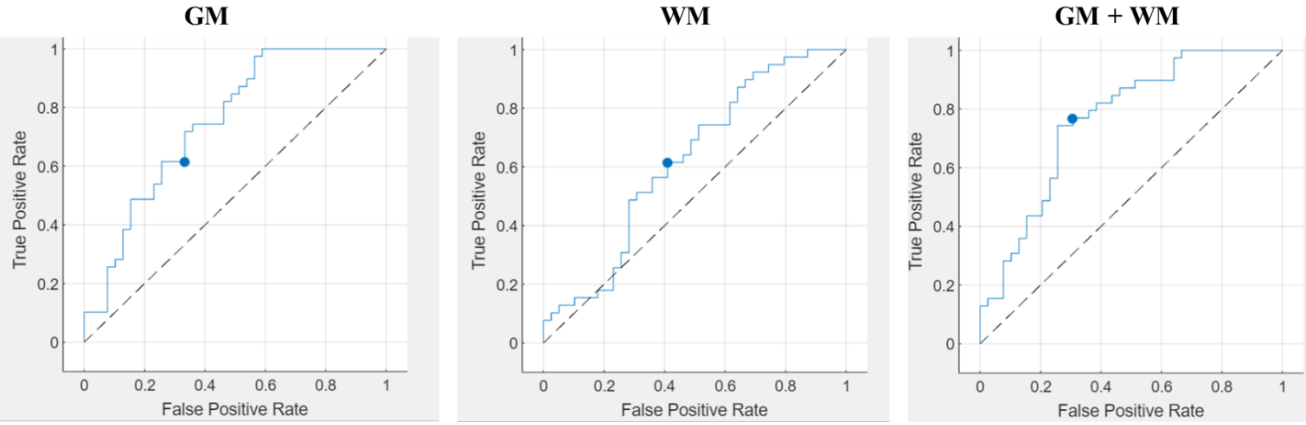

Figure 4: ROC graphs for the two-class classification using GM, WM and combination of GM, WM volumes

5. Challenges and limitations

Despite the potential of automated AI-based volume assessment utilizing high-resolution 3D MRI for early detection and treatment of AD, there are still certain challenges and limitations. Limited access to high-quality MRI images may impact the effectiveness of this technique. Large datasets of MRI scans from both healthy people and AD patients are needed for researchers to establish precise algorithms for measuring gray and white matter volume. Although MRI is an accurate means of detecting alterations in the amount of gray and white matter associated with AD, it is not a precise measure of cognitive performance. It is essential to compare automated AI-based volume assessment to other markers of cognitive impairment in order to ensure accuracy and application in clinical practice.

6. Conclusion

The study findings indicate a significant decline in the amount of GM and WM regions among individuals diagnosed with mild AD. The proposed classification methodology achieved an accuracy of 75.10% and AUC of 0.77 in the classification of HC and mild AD subjects using the combination of GM and WM volumes.

7. Data availability

The data supporting the findings of this study are available from the ADNI database and can also be obtained from the corresponding author.

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