Integrating Genetic Information for Early Alzheimer's Diagnosis through MRI Interpretation

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***Abstract*— Early detection of Alzheimer's disease (AD) is crucial, yet predicting AD in the mild cognitive impairment stage remains challenging. Integrating biological data from genomics and neuroimaging can provide valuable insights into early detection and treatment. Although recent deep learning studies have shown promise in AD prediction tasks, they often lack the interpretation of multimodal data interactions. Therefore, there is a need for further research on deep learning methods that can effectively integrate and interpret multimodal biological data for AD diagnosis and prediction. This study proposes a novel approach for identifying regions where interactions occur in sMRI (structural MRI) and genetic information and for detecting discriminative features in AD progression. Through the use of an attention mechanism and contrastive loss, it effectively models the inter-relationships between these modalities, leading to a more accurate understanding of AD. Our proposed method achieved remarkable performance, with an accuracy of 92%. Additionally, through model interpretation, we were able to identify genetic and brain feature associations in AD progression. This integrating study provides an effective and interpretable approach for AD diagnosis and prediction.**

***Clinical relevance*— This study provides a interpretable approach to AD prediction by integrating imaging and genetic data. By capturing the interplay between imaging and genetic data, the model provides valuable clinical interpretations and enhances its predictive capabilities. This integration also enables the identification of critical biomarkers and signatures for early detection and intervention in AD.**

I. Introduction

Alzheimer's disease (AD) is a debilitating and progressive neurological disorder that affects millions of people worldwide. Early detection of AD is critical for effective management and treatment, as the disease can lead to significant cognitive impairment. Magnetic resonance imaging (MRI) is a widely used diagnostic tool for AD, but its accuracy can be limited in the early stages of the disease. Integrating genetic information into MRI interpretation may enhance the accuracy of AD diagnosis and provide understanding of pathology, but this approach has not yet been fully explored. In this paper, we propose a novel method for integrating genetic information into MRI analysis to improve AD diagnosis accuracy.

Neuroimaging and genomics are important tools for the early detection and treatment of AD. Single-nucleotide polymorphisms (SNPs) associated with AD pathology have been identified [1], [2], and structural MRI (sMRI) identifies regions of the brain associated with AD pathology, such as brain atrophy and white matter lesions [3]. Due to the complexity of AD, however, the connection between genetic factors and the brain is not well understood, and an integrated approach can provide a more biological understanding of the pathology [4]. But earlier analysis was based on manual feature extraction, which relies on prior knowledge, and may not capture non-linear associations.

Recently, deep learning (DL) methods have been successfully applied to AD classification using sMRI or genetic data [5]. DL algorithms can provide effective integration strategies, enabling accurate clinical prediction and representation of biological data [6]. However, while multimodal studies in AD show promising performance [7]–[10] , they have not demonstrated the exploration of data interactions, which is crucial for fully benefiting from multimodal learning. Furthermore, most DL methods using sMRI still rely on predefined regions. Consequently, there is a need for sophisticated methods that can automatically capture features related to AD between different modalities and within each modality, providing investigative data interaction and more accurate AD prediction.

To address these issues, we propose a deep learning model that (i) achieves high accuracy, (ii) automatically learns the gene influential regions of the brain related to AD (no need for extracting hand-crafted features), and (iii) incorporates them for interpretability. To achieve these objectives, we propose a masked convolution layer that automatically extracts only the regions of interest and an attention mechanism to combine local-specific information from two modalities in an interpretable manner. Using our model, we can provide a clear interpretation of the relationship between local regions of MRI and genes. Additionally, we employ a contrastive learning framework to ensure consistency of information between the genetic global feature and MRI global feature of the same individual.

Our study represents a pioneering effort in identifying the regions influenced by genes and brain images through the application of a DL approach. The key contributions of our work can be summarized as follows:

- Providing insights into the genetic underpinnings of the AD progression, by identification of gene-influencing regions of the brain.
- Providing efficient interpretable architectures using attention mechanism to relate local MRI regions to genetic information, and utilizing gene transformer encoder, identify SNPs that may be associated with AD.

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- Exploiting masked convolutions, which is able to efficiently focus on AD relevant regions of the MRI data.
- Adopting a contrastive framework, which captures individual-specific characteristics, to provide understanding of the different features in patients.

II. Related work

Our study of related work focuses on exploring deep learning techniques that leverage both genetic data and medical images to improve AD classification. We pay particular attention to methods designed for multi-modal data analysis.

Genetic-medical image integrated study: The importance of integrating genome with the medical image has been attributed by some existing researches. Kirchler et al. [11] identify subsets of genes whose levels of expression in a tissue sample correlate with morphological characteristics, by transfer learning. Taleb et al. [12] aligns fundus images and genetic modalities in the feature space using contrastive learning. Ash et al. [13] associate features of tissue images with genomic markers based on autoencoders and correlation analysis.

DL models using multi-modality in AD: There are some works that show that multi-modal data can be critical to developing a the high-performing DL. Ying et al. [7] improve decision accuracy in an AD classification by incorporating. Venugopalan et al. [8] propose data integration by concatenating intermediate features. Prabhu et al. [9] integrate MRI and electronic health record in AD progression prediction using decision level integration. Golovanevsky et al. [10] connected to genetic, MRI, and clinical data using cross-modal attention. However, unlike our method, these methods did not connect local interactions within modalities.

III. Deep learning model for integrating genetic information and MRI

This study aims to develop a model that combines brain and gene data to accurately predict the AD during the mild cognitive impairment (MCI) stage. The model also focuses on learning the interactions between the two types of data in an understandable way. The overall model structure is illustrated in Figure 1, consisting of three main blocks: the data block, the attention-based feature fusion block, and the contrastive individual feature learning block. In the data block, local features are extracted from MRI and genetic data. The attention-based feature fusion block is responsible for learning the relationship between the extracted features from both modalities. Finally, the contrastive individual feature learning block ensures consistency between the two modalities by using contrastive loss. This step helps the model align and match corresponding features from brain and gene data, further enhancing the accuracy of AD progression prediction. In this section, we first describe the organization of our data and introduce the notations we use (Section III-A). Next, we explain our approach to extracting local features from each data source (Section III-B), followed by our method for fusing the data to make predictions (Section III-C). Additionally, we describe our global contrastive learning method that enhances patient consistency (Section III-D).

A. Data and notation

Before proceeding further, we describe the input data and our notation. It included AD, MCI, and normal patients; progressive MCI (pMCI) and stable MCI (sMCI) were differentiated based on whether patients in the MCI stage had been converted to AD for three years. In our model, we sample 10 MRI slices continuously from the center of the sagittal plane. We denote $x_m = \{m_1, m_2, ..., m_{10}\}$ be a sequence of slices, where m_k represent k-th MRI slice($1 \leq k \leq 10$).

The gene dataset consists of 620,000 SNP for each person. SNP is genetic variation that occurs "minor" in a single nucleotide. We selected the top 128 SNPs that have the greatest impact on AD disease using linear regression. In our implementations, each SNP is encoded as one of four integers, 3, 2, 1, 0, which represent four cases of "major+major", "major+minor", "minor+minor" and "missing" respectively. Hereafter, we refer encoded SNP as just "a gene" for convenience. Let $x_g = \{g_1, g_2, ..., g_{128}\}$ be a sequence of 128 genes for a person, where g_n is n-th gene ($1 \leq n \leq 128$).

B. Data block

Our key idea in designing the network is that there must be a close correlation between each gene and local regions of a brain in causing AD disease. Before learning the correlation, our model extracts local information from each modality. To capture this, we designed a data block with two local feature encoders, $\mathscr{E}_m$ for MRI and $\mathscr{E}_g$ for genes, which encode information from each modality.

$\mathscr{E}_m$ takes 10 MRI slices as inputs to extract local features. Since an MRI image contains lots of noisy regions (background or tissues), we propose the use of the masked residual layer to ensure that $\mathscr{E}_m$ concentrates on the only relevant regions of the brain. Let f_m^l denote the MRI feature after l-th layer of $\mathscr{E}_m$. A masked residual layer computes output feature as follows:

$$f_m^{l+1} = (f_m^l + \text{residual}(f_m^l)) \odot m^l, \tag{1}$$

where $\odot$ is a element-wise multiplication, and residual is a *residual network* made up of two convolutional layers with batch normalization and LeakyReLU activation. m^l is a mask in l-th layer, which is computed by another small convolutional network. This mask has same spatial shape as f_m^l, and is computed by using *mask network* which takes f_m^l as an input. The mask network has same architecture as residual network, except for exploiting sigmoid function as last activation. We exploit five masked residual layers in $\mathscr{E}_m$.

$\mathscr{E}_g$ takes the sequence of 128 genes to compute features for each genes. $\mathscr{E}_g$ consists of an gene embedding layer followed by five transformer encoder layers [14]. We exclude positional encoding in order not to be constrained by the order of genes In addition, in order to ensure that each genes contains sufficient information about classes, we implement an auxiliary classifier $\mathscr{C}_g$ at the end of the gene encoder,

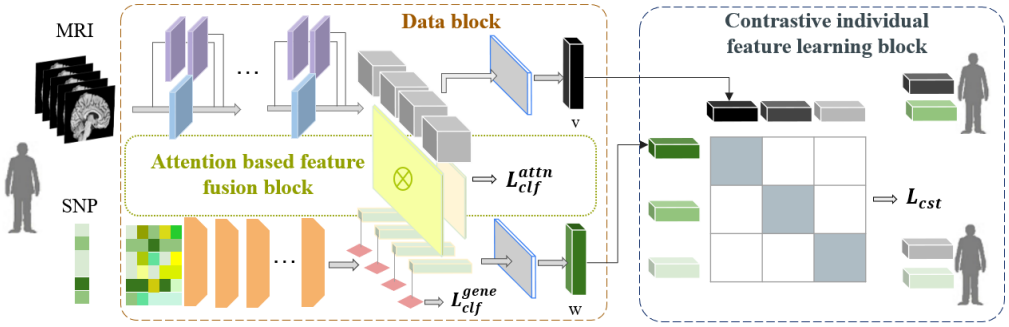


Fig. 1: Model overview: The three parts of the proposed model.

which learns with the binary cross entropy for the prediction result using each feature.

$$\mathscr{L}_{\text{clf}}^{\text{g}} = -\sum_{n=1}^{128} \sum_{\{y^{(i)},g_n\}} \left(y^{(i)} \log \mathscr{C}_g(g_n) + (1-y^{(i)}) \log(1-\mathscr{C}_g(g_n)) \right) \tag{2}$$

where $y^{(i)}$ is whether i-th person is on stage of sMCI or pMCI.

C. Attention based feature fusion block

The attention-based feature fusion block is designed to capture the local relationships between the MRI features and each gene. By adopting the attention mechanism, the model can focus on the most relevant parts of the input data to improve accuracy. In this study, we adopt the attention mechanism to learn the relationship between the two modal features. Let G be the matrix where each row represents g_n, and M be the matrix where each row represents m_k. Then, the output of attention attn is computed as follows:

$$\text{attn} = \text{softmax}\left(GM^T\right) M \tag{3}$$

In order for this relationship to capture sufficient information about MCI, we add another MCI classifier trained with the following loss term:

$$\mathscr{L}_{\text{clf}}^{\text{attn}} = -\sum_{\{y,\text{attn}\}} \left(y \log \mathscr{C}_{\text{attn}}(\text{attn}) + (1-y) \log(1-\mathscr{C}_{\text{attn}}(\text{attn})) \right) \tag{4}$$

D. Contrastive individual feature learning block

While attention mechanisms enable the learning of relationships between the local features, ensuring that the genetic global feature is consistent with the MRI global feature of the same person is essential. In other words, we aim to guide our network to learn *global consistency* between MRI and genetic information when they originate from the same person. To accomplish this, we compute global feature vectors for each modality and maximize their mutual information. Let v, w be the global MRI feature and global genetic feature of a person, respectively. We maximize the mutual information by exploiting the InfoNCE loss, which approximates the upper bound of negative mutual information [15].

$$\mathscr{L}_{\text{cst}} = -\sum_{\{v,w\}} \log \frac{\exp\left(\text{sim}\left(w,v\right)\right)}{\sum_{v' \neq v} \exp\left(\text{sim}\left(w,v'\right)\right)} \tag{5}$$

where $\text{sim}(\cdot,\cdot)$ is a cosine similarity function. The global features v and w are computed by encoding the MRI and genetic local features, respectively.

E. Overall loss function

The overall loss function for training our network as follows:

$$\mathscr{L}_{\text{overall}} = \lambda_{\text{clf}}^{\text{attn}} \mathscr{L}_{\text{clf}}^{\text{attn}} + \lambda_{\text{clf}}^{\text{g}} \mathscr{L}_{\text{clf}}^{\text{g}} + \lambda_{\text{cst}} \mathscr{L}_{\text{cst}} \tag{6}$$

where $\lambda_{\text{clf}}^{\text{attn}}, \lambda_{\text{clf}}^{\text{g}}$ and λ_{cst} are hyperparameters for adjusting the effect of each loss term. In our experiment, we set them to $1.0, 1.0$ and 0.5 respectively.

IV. Experiments

A. Datasets description

We use the ADNI stage 1 dataset (adni.loni.usc.edu), which contains T1w MRI images and a GWAS total of 836 people (208 sMCI, 237 pMCI, 179 AD, and 212 normal). For MRI, bias correction, linear registration using the ICMB MNI 152, and skull stripping were performed. For the GWAS data, quality preprocessing was performed using the Plink tool [16].

B. Performance Evaluation

Dataset was split into training (70%), validation (15%), and test (15%) subsets. PyTorch 1.13 was used for training on an NVIDIA GeForce RTX 3090 GPU. Adam optimizer was employed with a learning rate of 1e-4. Training consisted of a maximum of 10,000 steps with a batch size of 8.

Table I presents the results of our proposed method, comparing the attention-based method (Atten) and the concat method ($h = [w;v]$). The performance was further enhanced by incorporating contrastive learning. Additionally, we evaluated the Gene Transformer Encoder (Gene TrE) and MRI Mask Encoder (MRI maskE) by removing the mask and using a linear encoder, demonstrating their contribution to improved performance in contrastive learning and attention fusion. Table II demonstrates the superior performance of our model compared to existing studies that utilized sMRI and SNP data for the given task.

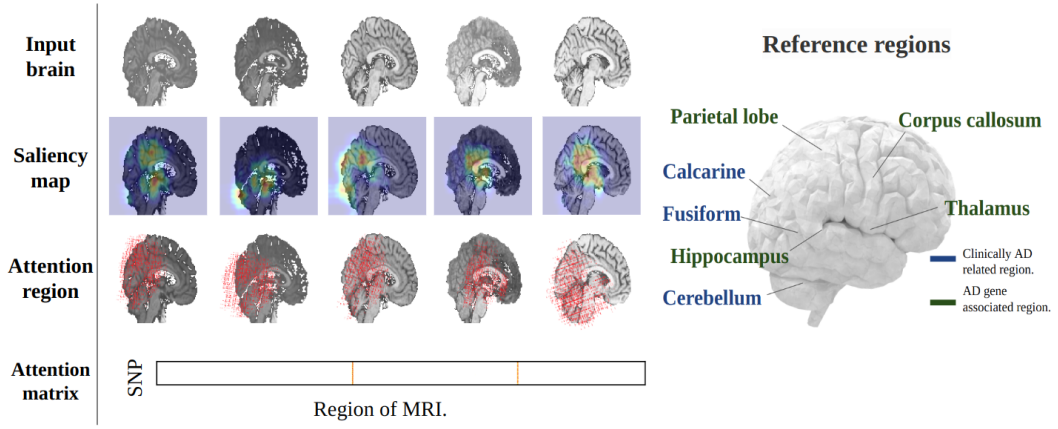


Fig. 2: Discriminative region and attention region associated with AD.

TABLE I: Evaluation proposed method for pMCI vs sMCI.

Method	Acc	Sen	Spc
Proposed Contrastive + Attn(Gene +TrE, MRI +mask)	**0.92**	**0.89**	**0.95**
Concat(Gene +TrE ; MRI +mask)	0.87	0.84	0.88
Attn(Gene +TrE, MRI +mask)	0.90	0.88	0.93
Contrastive + Attn(Gene, MRI +mask)	0.87	0.79	0.94
Contrastive + Attn(Gene +TrE, MRI)	0.90	0.87	0.95
Contrastive + Attn(Gene, MRI)	0.86	0.82	0.91

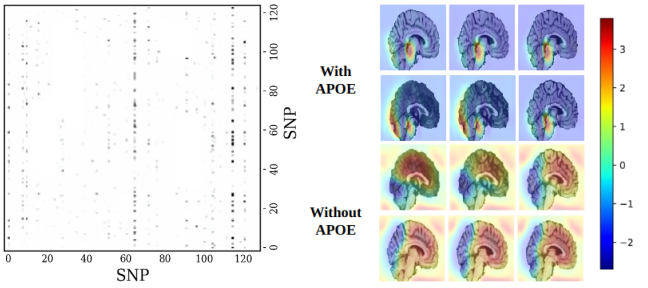
TABLE II: Evaluation compared other studies.

TASK	Study	Data	Method	AUC
pMCI vs sMCI	[17]	SNP(20 SNPs) sMRI(Extracted feature)	FNN	0.83
	[18]	SNP(40 SNPs.) sMRI(Extracted feature)	RF	0.82
	Our	**SNP(128 SNPs) sMRI**	**Attention + Contrastive**	**0.91**
AD vs MCI vs CN	[19]	SNP (486 SNPs) sMRI(ROI region)	CNN	0.80
	Our	**SNP(128 SNPs) sMRI**	**Attention + Contrastive**	**0.95**
AD vs CN	[7]	SNP (15 SNPs) sMRI	CNN+ MLP	0.93
	Our	**SNP(128 SNPs) sMRI**	**Attention + Contrastive**	**0.96**

C. Interpretation

1) Identifying the discriminative regions for AD progression: In order to identify regions that are most indicative of AD progression, we generate saliency maps (Fig. 2 "Saliency map") highlighting the input image regions that are most important for the model's prediction through gradient tracking. The highlighted region is associated with the prodromal AD region, such as the hippocampus, parietal lobe, and corpus callosum [20], demonstrating model's ability focus on disease associated region.

2) Finding highly correlated brain regions with genes.: Our attention fusion approach enables us to selectively focus on informative and relevant features, leading to accurate



(a) Genetic self-attention map. (b) Feature map without APOE.

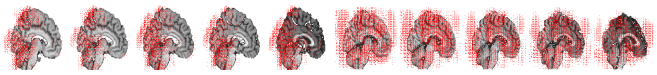
Fig. 3: Genetic influence in AD progression.

TABLE III: A influential SNP confirmed gene self attention.

Idx.	SNP	Related Gene	Function
114	rs8067676	Unknown	Unknown
65	rs2123060	DLGAP2	Neuronal signaling synapse organization
120	rs12961741	Unknown	Unknown
127	APOE4 [23]	APOE4	Neuronal signaling neuroinflammation
9	rs2345493 [24]	KCNS3	potassium channel control.

predictions in AD progression. By examining the attention map visualization, as shown in Figure 2, we gain valuable insights into the specific regions of the brain that exhibit concentrated attention. To further identify these regions, we visualize the gradients of the attention map with respect to the input image in the "Attention region" of Figure 2. Remarkably, these identified regions align with AD-associated genes such as fusiform, calcarine, and cerebellum [21], [22]. This finding suggests that our attention-based approach effectively captures the parts of the brain that are genuinely affected in AD.

3) Exploring the associated SNP.: While APOE4 has been extensively investigated in the context of AD, we confirm that other genes are also significantly influential by viewing the attention map in the gene encoder, as displayed in Figure 3a. The pattern is observed in most patients, and we identify relatively highlighted genes as in Table III. some of which are known to be associated with AD and some are not.



(a) pMCI (b) sMCI

Fig. 4: Discriminative global features of progression AD.

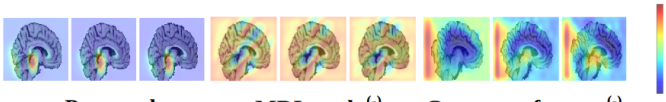


Fig. 5: Impact of components on capturing relevance regions.

Furthermore, to investigate the influence of a significant gene, we trained our model without the APOE4 gene, since that is an established genetic risk. As shown in Figure 3b, this model's MRI encoder feature map highlights irrelevant regions containing noise, demonstrating that gene information contributes to the capture of discriminative features.

4) Investigating contribution brain region of the global feature.: Global consistency enables the capture of the individual-specific features of both MRI and genetic data. Figure 4 shows the attribute MRI regions of global features in pMCI and sMCI, via gradient calculation. In pMCI, the gradient region is concentrated in the parietal lobe, which is associated with AD pathology and the attention fusion region. whereas in sMCI, the gradient is evenly distributed, confirming the absence of a particular contribution region. These demonstrate that global consistency effectively represents individual-specific characteristics and establish a link between genetic features and brain in AD progression.

D. Ablation study

We assessed the impact of the MRI mask and gene transformer encoder. To assess the ability to detect disease-related regions, we analyzed the MRI feature map. Figure 5 highlights the importance of accurately capturing discriminative regions, where MRI feature maps primarily focus on noisy regions instead of disease-related regions. Not only do these components enhance model performance, but they also significantly induce model to focus on associated region.

V. Conclusion

In this paper, we present an interpretable multimodal method that not only achieves high performance but also offers interpretability through the integration of multimodal data. The model's outputs reveal that the attention fusion actually learns by focusing on specific brain regions known to be associated with genetic information. Furthermore, differences in global consistency between classes confirm the regions that are relevant to AD progression. Gene transformer encoders provide influential SNP features as well. The results of this study enhance our comprehension of the genetic influence on the brain in the progression of AD, and provide insights into the pertinent genetic and brain features.

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