# AMSF: Attention-based multi-view slice fusion for early diagnosis of Alzheimer's disease

Yameng Zhang  $^1$ , Shaokang Peng  $^2$ , Zhihua Xue  $^3$ , Guohua Zhao  $^4$ , Qing Li  $^5$ , Zhiyuan Zhu  $^6$ , Yufei Gao  $^{\text{Corresp.}\,2}$ , Lingfei Kong  $^{\text{Corresp.}\,1}$ 

Corresponding Authors: Yufei Gao, Lingfei Kong Email address: yfgao@zzu.edu.cn, lfkong@zzu.edu.cn

Alzheimer's disease (AD) is an irreversible neurodegenerative disease with a high prevalence in the elderly population over 65 years of age. The intervention in the early stages of AD is of great significance to alleviate the symptom. Recent advances in deep learning have shown extremely advantages in computer-aided diagnosis of AD. However, most studies only focus on extracting features from slices in specific direction or whole brain images, ignoring the complementarity between features from different angles. To overcome the above problem, attention-based multi-view slice fusion (AMSF) is proposed for accurate early diagonosis of AD. It adopts the fusion of three dimensional global features with multi-view 2D slices features by using an attention mechanism to guide the fusion of slice features for each view, in order to generate a comprehensive representation of the MRI images for classification. The experiments on public dataset demonstrate that AMSF achieves the significant improvements over several previous promissing methods. It indicates that the better solution for AD early diagnosis not only depends on the large scale of dataset, but also the organically combination of feature construction strategy and deep neural networks.

<sup>1</sup> Department of Pathology, Henan Provincial People's Hospital; People's Hospital of Zhengzhou University, Zhengzhou 450003, China, Zhengzhou, China

<sup>&</sup>lt;sup>2</sup> School of Cyber Science and Engineering, Zhengzhou University; SongShan Laboratory, Zhengzhou 450001, China, Zhengzhou, China

<sup>3</sup> Laboratory Animal Center, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, 450052, Henan, China., Zhengzhou, China

<sup>4</sup> Department of Magnetic Resonance Imaging, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450004, China, Zhengzhou, China

State Key Lab of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China, Beijing, China

<sup>6</sup> School of Communication and Information Engineering Chongqing University of Posts and Telecommunications Chongqing 400065, Chongqing, China

1 AMSF: Attention-based multi-view slice fusion for 2 early diagnosis of Alzheimer's disease 3 4 5 Yameng Zhang<sup>1</sup>, Shaokang Peng<sup>2</sup>, Zhihua Xue<sup>3</sup>, Guohua Zhao<sup>4</sup>, Qing Li<sup>5</sup>, Zhiyuan Zhu<sup>6</sup>, 6 Yufei Gao <sup>2,\*</sup> and Lingfei Kong <sup>1,\*</sup> 7 8 9 <sup>1</sup> Department of Pathology, Henan Provincial People's Hospital & People's Hospital of 10 Zhengzhou University, Zhengzhou, Henan, China <sup>2</sup> School of Cyber Science and Engineering, Zhengzhou University, SongShan Laboratory, 11 12 Zhengzhou, Henan, China <sup>3</sup> Laboratory Animal Center, Academy of Medical Sciences, Zhengzhou University, Zhengzhou, 13 14 Henan, China <sup>4</sup> Department of Magnetic Resonance Imageing, The First Affiliated Hospital of Zhengzhou 15 University, Zhengzhou, Henan, China 16 <sup>5</sup> State Key Lab of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, 17 18 Beijing, China 19 <sup>4</sup> School of Communication and Information Engineering, Chongging University of Posts and 20 Telecommunications, Chongqing, Chongqing, China 21 22 Corresponding Author: 23 Lingfei Kong<sup>1,\*</sup> No. 7, Weiwu Road, Zhengzhou, Henan, 450003, China 24 Email address: lfkong@zzu.edu.cn 25 Yufei Gao<sup>2,\*</sup> 26 27 No. 97, Wenhua Road, Zhengzhou, Henan, 450003, China 28 Email address: vfgao@zzu.edu.cn 29 30 **Abstract** Alzheimer's disease (AD) is an irreversible neurodegenerative disease with a high prevalence in 31

the elderly population over 65 years of age. Intervention in the early stages of AD is of great significance to alleviate the symptom. Recent advances in deep learning have shown extreme advantages in computer-aided diagnosis of AD. However, most studies only focus on extracting features from slices in specific direction or whole brain images, ignoring the complementarity between features from different angles. To overcome the above problem, attention-based multi-

- 36 between features from different angles. To overcome the above problem, attention-based multi-
- 37 view slice fusion (AMSF) is proposed for accurate early diagnosis of AD. It adopts the fusion of
- three-dimensional global features with multi-view 2D slice features by using an attention mechanism to guide the fusion of slice features for each view, to generate a comprehensive

- 40 representation of the MRI images for classification. The experiments on the public dataset
- 41 demonstrate that AMSF achieves significant improvements over several previous promising
- 42 methods. It indicates that the better solution for AD early diagnosis is not only depends on the
- 43 large scale of dataset, but also the organic combination of feature construction strategy and deep
- 44 neural networks.

**Keywords**: Alzheimer's disease; magnetic resonance imageing; attention mechanism; multi-view

46 slice fusion

48 Introduction

AD is a neurodegenerative disease with a high prevalence in people over 65 years of age (Reiman et al. 2012). Previous studies have shown that the structural changes in the brain caused by AD can be traced back 20 years before the onset of symptoms in patients (Barthelemy et al. 2020). In the early stages of AD, patients may not notice any significant changes in their brain structure or activity, but some difficulties with memory recall or retention may appear. As AD progresses, it leads to the formation of brain tissue lesions that impair and ultimately destroy neurons responsible for various cognitive functions (Zarei et al. 2013), including deterioration of memory and thinking skills, as well as a decline in physical abilities and independence. Patients with AD may present symptoms such as memory loss, cognitive impairment, language difficulties, and reduced mobility (Gaugler et al. 2022).

The global community is currently confronted with a significant demographic predicament characterized by a rapid expansion in the population of older individuals. As per the United Nations, the proportion of individuals aged 65 years and above in the overall global population is projected to reach 9.7% by 2022, and further escalate to 16.4% by 2050 (ECONOMIC & AFFAIRS. 2023). This unprecedented surge in ageing demographics presents formidable challenges for healthcare systems, given the heightened vulnerability of older adults to chronic and degenerative ailments. Among these conditions, AD stands out as a highly prevalent and debilitating disorder that profoundly impacts the cognitive and functional capacities of countless individuals across the globe.

Mild cognitive impairment (MCI) represents a pivotal transitional phase between normal ageing and dementia, characterized by a discernible cognitive decline that does not significantly impede daily functioning. MCI assumes a critical role as an early intervention window, presenting a valuable opportunity to mitigate or forestall subsequent cognitive deterioration (Wee et al. 2012). Extensive research has established that individuals diagnosed with MCI face a heightened susceptibility to developing AD, with an annual conversion rate ranging from 10% to 15% (Roberts & Knopman 2013). Consequently, the implementation of timely and efficacious medical interventions during the MCI stage holds the potential to safeguard neural cells against further impairment and delay the onset of AD pathology, thereby contributing to a reduction in the mortality associated with this incurable affliction (Odusami et al. 2022).

Neuroimageing serves as a valuable and indispensable tool in the clinical diagnosis of AD, enabling the quantification of structural and functional alterations within the brain that accompany disease progression. Among the diverse array of neuroimageing modalities available, magnetic resonance imageing (MRI) has garnered considerable attention owing to its high spatial resolution and non-invasive characteristics. Through MRI, intricate details regarding brain volume, cortical thickness, white matter integrity, and cerebral blood flow in AD patients can be gleaned. Notably, the advent of deep learning techniques has emerged as a formidable approach

for medical image analysis across a wide range of conditions, encompassing neurodegenerative disorders, orthopaedic ailments, and cancer. Leverageing the intrinsic capacity to automatically learn and extract intricate features from image data through the construction of multilayer neural networks, deep learning methods transcend conventional machine learning approaches by iteratively optimizing models with large-scale data. This obviates the need for manual feature engineering, engenders enhanced diagnostic accuracy, and improves overall diagnostic efficiency.

The integration of deep learning techniques into AD diagnostic research has been instrumental in the development of algorithms aimed at supporting physicians in early diagnosis and prognosis prediction. By harnessing the power of deep learning for MRI analysis, the detection of AD at its nascent stages becomes attainable, thereby augmenting the diagnostic capabilities and precision of healthcare professionals. This, in turn, facilitates the timely implementation of intervention strategies to mitigate further cognitive decline. The exploration of deep learning-based early AD diagnosis holds significant theoretical and practical implications, encompassing the identification of initial brain alterations in AD patients, the enhancement of AD diagnostic efficiency, the amelioration of the quality of life for individuals afflicted by AD, and the advancement of deep learning theory as a whole.

Deep learning has become increasingly prominent in medical image analysis, surpassing conventional machine learning algorithms in various domains (Lian et al. 2020). Notably, its automated feature learning capability from raw data, without the need for human intervention or domain expertise, distinguishes it as a highly advantageous approach. Among the array of deep learning models, Convolutional Neural Networks (CNNs) have demonstrated remarkable success and widespread adoption for medical image analysis. This can be attributed to their proficiency in capturing both spatial and semantic information from images, thereby enabling robust and accurate analysis in the medical field.

Korolev et al. (Korolev et al. 2017) explored the use of 3D CNNs for AD classification and developed two 3D CNN models that achieved comparable results to traditional methods using ADNI data. Cheng et al. (Cheng et al. 2017) employed 3D CNNs for AD classification, but they amalgamated multiple 3D CNNs by training them on MRI data from distinct brain regions and subsequently appending an FC layer to each one. Improved AD diagnosis performance of 3D CNNs was achieved by Zhang et al. (Zhang et al. 2021) through the incorporation of an attention mechanism, which enabled the network to selectively focus on relevant features. Spasov et al. (Spasov et al. 2019) proposed a method to reduce the computational complexity of 3D CNNs by using separable convolution techniques.

Pan et al. (Pan et al. 2022) invented an adaptive interpretable ensemble model (3DCNN+EL+GA) that leverages the power of 3DCNN, ensemble learning and genetic algorithm (GA) for AD classification and biomarker discovery. 246 base classifiers (3DCNN) were trained on a dataset of 246 brain regions and a majority voting scheme was employed to select the optimal combination of base classifiers from the set of classifiers by using GA. Liu et al. (Liu et al. 2020) developed a multi-task deep CNN model that performed both hippocampal segmentation and disease classification tasks simultaneously. They combined a 3D densely connected convolutional network (3D DenseNet) with the hippocampal segmentation results to learn richer features for AD diagnosis.

Khvostikov et al. (Khvostikov et al. 2018) built 3D CNNs for AD classification by extracting hippocampal ROIs from sMRI and DTI data. They also balanced the classes of different sizes by using data augmentation methods and investigated the effect of ROI size on classification results.

Liu et al. (Liu et al. 2018) developed an end-to-end approach for AD classification by extracting local fMRI image patches centred on predefined anatomical landmarks. These patches are applied to capture both the local and global structural features from the images. However, many of these 3D deep learning-based approaches still excessively rely on pre-determined ROIs before the training of the network, which may limit the performance due to the presence of irrelevant features in sMRI for AD diagnosis. Moreover, most of these studies only focus on binary classification, which is not very helpful for determining the stage of the patient's situation.

Each individual's brain exhibits unique characteristics and may possess disease-related features that cannot be fully captured by a single MRI slice. Consequently, the MRI slices of patients may exhibit minimal deviation from those of healthy individuals, making classification challenging. Previous studies have primarily focused on extracting features from specific slices or the entire image, disregarding the features of slices from different views and the complementary nature of features across these slices. Moreover, they have not effectively utilized the comprehensive structural information available in whole-brain MRI scans (Lian et al. 2022). In light of this, Qiao et al. (Qiao et al. 2021) proposed a novel approach for early AD diagnosis based on MRI, which involves extracting fused global features from multi-view slice features. They employed a simple splicing technique to combine the features of multiple slices from the same view. However, it is restricted by an assumption that all slices are of equal importance for the classification task. Different slices may contribute differently to disease features. Therefore, using equal weights for feature fusion may not effectively capture the relevant features, potentially resulting in lower classification accuracy.

Actually, the slices from the same view capture diverse brain regions and exhibit distinct features, essentially representing channel-specific mappings that reflect varying degrees of importance in the slice clusters. Additionally, it is essential to recognize that slices from different locations are not isolated entities but interconnected, collectively forming a comprehensive feature representation of the slice cluster in that specific direction. Hence, when fusing the features of different slices from the same view, it becomes crucial to consider both the significance of the information carried by each slice and the contextual relationship that exists between them. By incorporating these factors into the fusion process, a more robust and informative representation can be achieved, facilitating improved accuracy in capturing essential features for classification tasks, such as early AD diagnosis based on MRI data.

In this dissertation, a novel approach to the early diagnosis of AD called ASMF is proposed. Firstly, the Multi-view Slice-level Feature Extraction (MSFE) method is employed to acquire slice-level features from three distinct views (sagittal, coronal, and cross-sectional) by repeatedly slicing the 3D MRI and leverage three separate 2D sub-networks to extract features from each view. Then, an attention mechanism is incorporated to guide the fusion of slice features for each view, assigning varying weights to individual slices based on their respective importance. Secondly, global features are extracted from the entire MRI images by using a 3D CNN to complement the slice-level features. Finally, the slice-level and global features are fused to generate a more comprehensive feature representation for the classifier. The key contributions of this study can be concluded as follows:

- 1. To address the limitations of relying on feature extraction in a specific direction, this study proposes a novel MSFE-based approach for early diagnosis of AD.
- 2. This is the first study that incorporates the self-attention mechanism and the fusion of multiview features to construct a comprehensive representation of the MRI images for classification.

3. According to the experimental results, the proposed method outperforms other recently published promising approaches.

The remainder of this paper is arranged as follows. The materials and methods are described in Section 2. Section 3 provides experimental results and corresponding discussion. At last, the summary of this study is given in Section 4.

#### 181 182

183

192

193

194

195

196

197 198

199

200

201

202 203

204

205

206

207

208

209

210

211

212 213

214

215

216 217

176 177

178 179

180

#### **Materials & Methods**

In contrast to previous studies that typically rely on a single slice from a specific view for AD 184 diagnosis, we utilize multiple slices from three views of 3D MRI scans to extract features. As 185 shown in Fig. 1, by incorporating information from various slices, we aim to capture the full 186 extent of brain damage caused by AD, accounting for patient heterogeneity. To guide the fusion 187 of slice features, an attention mechanism is employed that assigns different weights to slices 188 based on their relevance for classification. It ensures that the most informative slices contribute 189 more significantly to the diagnostic process. Furthermore, we integrate the slice features from the 190 191 three views with global features extracted from the entire MRI images, resulting in a feature

representation that comprehensively reflects the overall brain state of the patient.

Multi-view slicing feature extraction

To facilitate the analysis of the 3D MRI data, we initially partitioned it into three distinct planes: sagittal, coronal, and transverse planes. Each plane represents a different orientation of the brain and provides unique information about its structural characteristics. To ensure a comprehensive assessment, we extracted a total of 40 slices per view, thereby constructing a robust slice cluster. Figure 2 visually illustrates the resulting set of images, showcasing the diversity and coverage achieved across the different planes. By encompassing multiple slices from each view, our approach captures a broader range of relevant features, enabling a more thorough examination of the brain's structural attributes.

To extract features from each slice of the 3D MRI data, we used a slice-level feature extraction network that takes slice clusters as input. A slice cluster consists of 40 slices from one of three possible views: sagittal (x), coronal (y) or transverse (z), which represent different orientations of the brain structure and contain different types of features. Therefore, we designed a separate Slice Feature Extraction Network (SFEN) for each view. For instance, the sagittal view (x),  $C_x$  denotes the cluster of slices in this direction. Each slice in this cluster has an index i that ranges from 1 to 40. Thus,  $C_x$  can be written as

$$C_{x} = \left[ C_{x}^{1}, C_{x}^{2}, ..., C_{x}^{n} \right]$$
 (1)

where n denotes the number of slices in the x-direction. The feature extraction of the i-th slice in the x-direction can be expressed as

$$T_{x}^{i} = AvgPool(F_{x}(C_{x}^{i}W_{x}^{i})) \tag{2}$$

 $T_x^i = AvgPool(F_x(C_x^i W_x^i))$  (2) where  $F_x$  represents the feature extraction function consisting of multiple blocks containing a 3\*3 convolutional layer, BN layer, activation function ReLU and maximum pooling layer, as shown in Fig. 3. Besides,  $W_x^i$  denotes the convolutional layer weight of the i-th slice in the xdirection,  $T_x$  stands for the features of the cluster of slices in the x-direction after  $F_x$ . Then the slice cluster feature in the x-direction can be expressed as

 $T_{\mathbf{v}} = \left[ T_{x}^{1}, T_{x}^{2}, ..., T_{x}^{n} \right]$ (3) 218

#### Attention-based slice feature fusion

219 220

221

222

223 224

225 226

227

228

229 230

231

232

233 234

235

236

237 238

239

240

241

242

243 244

245

246

247 248

249

250

251

252 253

254

255

256

257 258

To integrate the distinct features within each view (x, y, or z), we leverage the notion of a "slice cluster" comprising 40 slices that possess unique characteristics. These features serve as mappings for specific brain structures observed from their respective perspectives. Notably, these features are not isolated entities, but rather interconnected across various locations within the slice cluster. Consequently, they collectively establish a comprehensive feature representation for the given view. To effectively merge these features, it is imperative to consider both their significance and their interdependencies. To address this, we propose a novel mechanism termed Slices Fusion Attention (SFA). SFA employs self-attention to capture contextual information among the slices and assigns attention weights to each slice based on its relative importance and contribution to the overall feature representation of the view. By incorporating this attention-based weighting scheme, SFA effectively balances the significance of different slices while enriching them with contextual information derived from their interrelationships. Figure 4 provides an illustrative depiction of the structural composition of SFA.

We feed the slice cluster feature  $T_x$  into SFA as input.  $T_x$  has a dimension of 40\*1\*128 and it is obtained by concatenating the features of 40 slices along the channel dimension after applying SFEN. To reduce the number of channels from 128 to 1, we use a 1\*1 convolution layer that compresses  $T_{r}$  into a single-channel feature map. This gives us an aggregated feature that represents the fusion of 40 slices. Next, we apply a Softmax function to  $T_x$  and multiply it with  $S_x$ . This way, we obtain  $S_x$  that contains contextual information between slices weighted by their attention scores. We can write this process as

$$S_{x} = T_{x}^{*} * Softmax(Conv(T_{x}))$$
 (4)

where Conv means 1\*1 convolution operation, and  $T_{\nu}^*$  is obtained by reducing one dimension of  $T_{\chi}$ .

 $S_r$  contains the contextual relationship between different slices, which needs to be assigned to each slice by calculating the slice feature weights of different channels. Firstly,  $S_x$  is expanded by one dimension and the number of channels is reduced by 1\*1 convolution, then BatchNorm and ReLU activation function operations are performed, and the number of channels is raised to the original number by 1\*1 convolution, denoted as

$$A_{x} = Conv(BR(Conv(S_{x}^{'})))$$
 (5)

where  $S_x$  is obtained by adding one dimension to  $S_x$ , and BR denotes the BatchNorm and ReLU activation functions.

 $A_x$  is applied to represent the reweighted channel features that reflect how much each slice contributes to  $S_x$ . To obtain the slice fusion feature that incorporates both channel weights and contextual relationships between slices, we multiply  $A_x$  with  $T_x$  along the channel axis and sum them up. We denote this final output as  $F_x = \sum_{i=1}^{40} T_x^i * A_x^i$ 

$$F_{x} = \sum_{i=1}^{40} T_{x}^{i} * A_{x}^{i}$$
 (6)

### **PeerJ** Computer Science

#### Manuscript to be reviewed

where 40 denotes the number of slices and  $A_x^i$  denotes the i-th channel of weight  $A_x$ . 259 260 261 Global feature extraction The global feature extraction (GFE) component contains four blocks, each encompassing a 262 sequence of operations: a 3D convolutional layer, a 3D batch normalization layer (BN), a 263 264 rectified linear unit (ReLU) activation function, and a 3D maximum pooling layer. Subsequently, 265 a 3D average pooling layer is employed to convert the multichannel features into a vector that encapsulates the global information. Figure 5 provides the structure of GFE. Following the 266 267 acquisition of the global features, adaptive averageing pooling is applied to generate a onedimensional vector. The multi-view slice-level features are then concatenated with the global 268 269 vector. Finally, a fully connected layer is employed to obtain the ultimate classification 270 outcomes. 271 **Dataset and processing** 272 273 The Alzheimer's Disease

(1. 项目研究的目的、意义,突出说明项目实施后对郑州市产业发展 的预期作用; 2. 项目已有技术基础和专利储备描述,包括:本项目研 究的关键技术及难点,现有技术水平,国内外相关的研究开发情况及 知识产权现状,有关的主要论文、专著情况,项目技术实现主要面临 的风险和应对措施,以往承担国家、省级等各类科技计划项目完成情 况等)

- 1. 项目研究目的、意义
- 2. 项目已有技术基础和专利储备
- 2.1 本项目研究的关键技术及难点

漏洞挖掘技术

敏感数据加密技术

动态防御决策技术

2.2 现有技术水平

2.3 国内外相关的研究开发情况

Neuroimageing Initiative (ADNI) dataset (http://adni.loni.usc.edu/) is employed in this study. 274

ADNI provides data processed by standard volumetric analysis methods, including gradient non-275

linearity correction, B1 correction, N3 correction, CAT12 for extraneous tissue removal, 276

alignment and smoothing operations. Then, a total of 351 3D-MRI scans for NC subjects are acquired (301 3D-MRI scans for AD subjects and 331 3D-MRI scans for MCI subjects).

In the experiments, the ADNI data were utilized and underwent several preprocessing steps before being fed into the feature extraction network, as depicted in Fig. 4. Initially, the background information that is unrelated to the classification task was eliminated. Subsequently, the image size was adjusted to 90\*90\*90, and the image density was normalized based on the mean and standard values of the non-zero region. The 3D MRI data were then sliced according to three directions, and for each view, the middle 40 slices were selected. Finally, feature extraction operations were conducted on the obtained slices.

285 286 287

288

297

298

299 300

301 302

303 304

305 306

307

308

309

310

311

312

313

318

277

278 279

280 281

282 283

284

#### **Results and Discussion**

#### **Ablation experiments**

- To investigate the performance of the proposed framework, the indicators of Acc (Accuracy), 289
- 290 Sen (Sensitivity), Spe (Specificity), Pre (Precision) and F1 (F1-score) are employed for
- 291 evaluation. The ablation experiments are conducted with the detailed definition as follows:
- 292 1. 3D: 3D features are only obtained by 3D GFE.
- 2. 2D: only employ 2D features learned by MSFE. 293
- 294 3. 2D+3D: 2D and 3D features are extracted by MSFE and GFE.
- 295 4. SE+2D+3D: the combination of 2D+3D with SE.
- 5. AMSF (SFA+2D+3D): SFA-guided 2D+3D. 296

The results of the ablation experiments are shown in Table 1. It can be seen that the classification accuracy of 3D is the lowest (76.9%). The 2D method provides better performance with the classification accuracy improvement to 89.4%, which is 12.5% higher than 3D. With the help of fused global features, 2D+3D achieves 91.6% Acc better than only using 2D or 3D strategy. However, the inclusion of SE results in a decrease in classification accuracy by 1.8%, suggesting that SE fails to effectively address the imbalanced importance among different slices within the same view for this particular task. At last, it is demonstrated that AMSF reaches the highest accuracy of 94.3%, surpassing that of the 2D+ 3D and SE+2D+3D by 2.7% and 4.5% respectively. It also exceeds in F1 scores, Sen, Spe and Pre. This indicates that SFA effectively integrates contextual relationships between different slices, enabling it to balance their importance within a given view.

The curve of validation loss for each epoch is shown in Fig. 6. It can be seen that during the training process, the training loss decreases continuously in the first 20 epochs and keeps stable. The validation loss declines in the first 10 epochs, then falls in fluctuation before 25 epochs, and finally stabilises after 35 epochs. Figure 7 gives the curve of the accuracy for each epoch. With a zigzag rise before 35 epochs, the validation accuracy reaches saturation. As can be seen in Fig. 8, the classification of AD achieves the highest accuracy (97.0%), indicating that ASMF is more sensitive to the features of AD. The classification accuracy for NC is 95.4% with 4.6%

- 314
- misclassifying NC to MCI. For MCI, it obtains the worst performance (90.4%), as well as an 315
- 8.2% misclassifying MCI to AD. It can be observed that the subtle difference in features between 316
- 317 MCI and AD are formidable to extract, which is still a significant problem in AD diagnosis.

#### Comparison with other methods

- 319 An experimental comparison with previous promising approaches is also arranged, including two
- 320 traditional machine learning-based approaches (JMMP-LRR, Liner SVM) and three deep
- 321 learning-based methods (DemNet, Automatic CL and AdaBoost). The abstracts of these works
- 322 are listed as follows:
- 1. Automatic CL (Gracias & Silveira 2022): curriculum learning is employed in the early diagnosis of AD based on a 3D CNN network, by incorporating task complexity, cognitive
- test scores, and ROI features, thereby enhancing the accurate classification of MCI.
- Liner SVM (Yuan et al. 2022): Mr cortical and ApoE4 gene features are explored for AD classification and the optimal performance is achieved by an SVM classifier with higher
- 328 sensitivity and specificity.
- 329 3. JMMP-LRR (Sheng et al. 2020): it aims to better alleviate the problem of small-sample, ultra-high-dimensional features, accompany by stable AD classification accuracy.
- JemNet (Billones et al. 2016): an improved 16-layer VGGNet architecture is proposed with
  SOTA (state-of-the-art) classification results of AD vs. MCI vs. NC.
- AdaBoost (Buyrukoğlu 2021): an ensemble learning method is designed for AD diagnosis
  with SOTA performance compared with different ensemble learning methods.
- Table 2 shows the classification results on the ADNI dataset compared with other previous
- promising methods. It can be seen that ASMF achieves the best performance with 94.3%
- classification accuracy, which is 1.6% -7.1% higher than other related works. Surprisingly, only
- by using a small scale of dataset, traditional machine learning-based methods (Linner SVM and
- AdaBoost) surpass the other three deep learning-based approaches. Especially for Linner SVM,
- it outperforms Automatic CL and DemNet without the help of DNNs. Together these results provide important insights into the better solution for AD early diagnosis not only depends on
- the large scale of dataset, but also the organic combination of feature construction strategy and
- 343 deep neural networks.

#### Conclusions

- This study proposes a novel AD diagnosis approach called AMSF to address the limitation of
- relying on the feature extraction in a specific direction. It incorporates multiple slices with feature extraction from different views of 3D MRI images and the fusion of slice cluster features
- from each view achieved through an attention mechanism. Furthermore, the GFE by the 3D
- from each view achieved through an attention mechanism. Furthermore, the GFE by the 3D
- network fusion is combined to obtain a comprehensive MRI feature representation. Based on the AD vs. MCI vs. NC classification tasks on the public ADNI dataset, the experimental results
- 352 demonstrate significant advantages over several SOTA methods. Although the promising
- 353 experimental results achieves, the drawback still exists to be addressed. For example, a dataset
- 354 with a limited size may restrict the generalization of the proposed model for practical
- applications. In future, diverse datasets with large scales are required to enhance the robustness
- and reliability of the method.

357

344

345

358

#### Acknowledgments

- 360 Author Contributions
- 361 S.P. and Y.G provided the idea and experiments; Y.Z, S.P. and Y.G. wrote the contents of the
- article; Y.Z., Z.X., G.Z., Q.L., Z.Z reviewed and edited the manuscript, L.K and Y.G supported
- 363 the study. All authors have read and agreed to the published version of the manuscript.
- 364 Data Availability Statement
- In this study, we used a publicly available MRI dataset: ADNI (http://adni.loni.usc.edu/).
- 366 Acknowledgments
- 367 This work was supported in part by the Nature Science Foundation of China (62006210,
- 368 62001284, 62206252), the Key Scientific and Technology Project in Henan Province of China
- 369 (221100210100), the Key Project of Collaborative Innovation in Nanyang (22XTCX12001), the
- 370 Research Foundation for Advanced Talents of Zhengzhou University (32340306).
- 371 Conflicts of Interest
- 372 The authors declare no conflict of interest.

373374375

359

#### References

376377

378

379

380

381 382

383

384

385

386 387

388

389

390

396

397

- Barthelemy NR, Li Y, Joseph-Mathurin N, Gordon BA, Hassenstab J, Benzinger TLS, Buckles V, Fagan AM, Perrin RJ, Goate AM, Morris JC, Karch CM, Xiong C, Allegri R, Mendez PC, Berman SB, Ikeuchi T, Mori H, Shimada H, Shoji M, Suzuki K, Noble J, Farlow M, Chhatwal J, Graff-Radford NR, Salloway S, Schofield PR, Masters CL, Martins RN, O'Connor A, Fox NC, Levin J, Jucker M, Gabelle A, Lehmann S, Sato C, Bateman RJ, McDade E, and Dominantly Inherited Alzheimer N. 2020. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. *Nat Med* 26:398-407. 10.1038/s41591-020-0781-z
- Billones CD, Demetria OJLD, Hostallero DED, and Naval PC. 2016. DemNet: A Convolutional Neural Network for the detection of Alzheimer's Disease and Mild Cognitive Impairment. 2016 IEEE Region 10 Conference (TENCON). p 3724-3727.
- Buyrukoğlu S. 2021. Improvement of Machine Learning Models' Performances based on Ensemble Learning for the detection of Alzheimer Disease. 2021 6th International Conference on Computer Science and Engineering (UBMK). p 102-106.
- Cheng D, Liu M, Fu J, and Wang Y. 2017. Classification of MR brain images by combination of multi-CNNs for AD diagnosis. Ninth international conference on digital image processing (ICDIP 2017): SPIE. p 875-879.
- 394 ECONOMIC UNDF, and AFFAIRS. S. 2023. World population prospects 2022: Summary of 395 results: UN.
  - Gaugler J, James B, Johnson T, Reimer J, Solis M, Weuve J, Buckley RF, and Hohman TJ. 2022. 2022 Alzheimer's disease facts and figures. *Alzheimers & Dementia* 18:700-789.
- Gracias C, and Silveira M. 2022. Curriculum learning for early Alzheimer's Disease diagnosis.
  Annu Int Conf IEEE Eng Med Biol Soc 2022:4777-4780.
  10.1109/EMBC48229.2022.9871601
- Khvostikov A, Aderghal K, Benois-Pineau J, Krylov A, and Catheline G. 2018. 3D CNN-based
  classification using sMRI and MD-DTI images for Alzheimer disease studies. arXiv
  preprint arXiv:180105968.

419

420

421

422

423

424

425

426

427

437

438

439

440

441

442

443

444 445

446

- 404 Koroley S. Safiullin A. Belyaey M. and Dodonova Y. 2017. Residual and plain convolutional 405 neural networks for 3D brain MRI classification. 2017 IEEE 14th international symposium 406 on biomedical imageing (ISBI 2017): IEEE. p 835-838.
- 407 Lian C, Liu M, Pan Y, and Shen D. 2022. Attention-Guided Hybrid Network for Dementia 408 Diagnosis With Structural MR Images. IEEE Trans Cybern 52:1992-2003. 409 10.1109/TCYB.2020.3005859
- 410 Lian C, Liu M, Zhang J, and Shen D. 2020. Hierarchical Fully Convolutional Network for Joint 411 Atrophy Localization and Alzheimer's Disease Diagnosis Using Structural MRI. IEEE 412 Trans Pattern Anal Mach Intell 42:880-893. 10.1109/TPAMI.2018.2889096
- 413 Liu M, Li F, Yan H, Wang K, Ma Y, Alzheimer's Disease Neuroimageing I, Shen L, and Xu M. 414 2020. A multi-model deep convolutional neural network for automatic hippocampus 415 segmentation and classification in Alzheimer's disease. Neuroimage 208:116459. 416 10.1016/j.neuroimage.2019.116459
- 417 Liu M, Zhang J, Adeli E, and Shen D. 2018. Landmark-based deep multi-instance learning for brain disease diagnosis. Med Image Anal 43:157-168. 10.1016/j.media.2017.10.005 418
  - Odusami M, Maskeliunas R, and Damasevicius R. 2022. An Intelligent System for Early Recognition of Alzheimer's Disease Using Neuroimageing. Sensors (Basel) 22. 10.3390/s22030740
  - Pan D, Luo G, Zeng A, Zou C, Liang H, Wang J, Zhang T, Yang B, and Initiative AsDN. 2022. Adaptive 3DCNN-Based Interpretable Ensemble Model for Early Diagnosis of Alzheimer's Disease. IEEE Transactions on Computational Social Systems.
    - Qiao H, Chen L, and Zhu F. 2021. A Fusion of Multi-view 2D and 3D Convolution Neural Network based MRI for Alzheimer's Disease Diagnosis. Annu Int Conf IEEE Eng Med Biol Soc 2021:3317-3321. 10.1109/EMBC46164.2021.9629923
- 428 Reiman EM, Quiroz YT, Fleisher AS, Chen K, Velez-Pardo C, Jimenez-Del-Rio M, Fagan AM, 429 Shah AR, Alvarez S, Arbelaez A, Giraldo M, Acosta-Baena N, Sperling RA, Dickerson B, 430 Stern CE, Tirado V, Munoz C, Reiman RA, Huentelman MJ, Alexander GE, Langbaum 431 JB, Kosik KS, Tariot PN, and Lopera F. 2012. Brain imageing and fluid biomarker 432 analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in 433 the presentilin 1 E280A kindred: a case-control study. Lancet Neurol 11:1048-1056. 434 10.1016/S1474-4422(12)70228-4
- 435 Roberts R, and Knopman DS. 2013. Classification and epidemiology of MCI. Clin Geriatr Med 436 29:753-772. 10.1016/j.cger.2013.07.003
  - Sheng J, Shao M, Zhang Q, Zhou R, Wang L, and Xin Y. 2020. Alzheimer's disease, mild cognitive impairment, and normal ageing distinguished by multi-modal parcellation and machine learning. Sci Rep 10:5475. 10.1038/s41598-020-62378-0
  - Spasov S, Passamonti L, Duggento A, Lio P, Toschi N, and Alzheimer's Disease Neuroimageing I. 2019. A parameter-efficient deep learning approach to predict conversion from mild cognitive impairment to Alzheimer's disease. Neuroimage 189:276-287. 10.1016/j.neuroimage.2019.01.031
  - Wee CY, Yap PT, Zhang D, Denny K, Browndyke JN, Potter GG, Welsh-Bohmer KA, Wang L, and Shen D. 2012. Identification of MCI individuals using structural and functional connectivity networks. Neuroimage 59:2045-2056. 10.1016/j.neuroimage.2011.10.015
- 447 Yuan Z, Yao X, and Bu X. 2022. Classification of Alzheimer's Disease Using Conventional Machine Learning Methods with Cortical and Genetic Characteristics. 2022 IEEE 2nd 448 449 International Conference on Power, Electronics and Computer Applications (ICPECA). p. 450 303-306.
- 451 Zarei M, Beckmann CF, Binnewijzend MA, Schoonheim MM, Oghabian MA, Sanz-Arigita EJ, 452 Scheltens P, Matthews PM, and Barkhof F. 2013. Functional segmentation of the 453 hippocampus in the healthy human brain and in Alzheimer's disease. Neuroimage 66:28-454 35. 10.1016/j.neuroimage.2012.10.071

### **PeerJ** Computer Science

#### Manuscript to be reviewed

,	Zhang J, Zheng B, Gao A, Feng X, Liang D, and Long X. 2021. A 3D densely connected
;	convolution neural network with connection-wise attention mechanism for Alzheimer's
,	disease classification. Magn Reson Imageing 78:119-126. 10.1016/j.mri.2021.02.001
1	

Figure 1. The framework of AMSF.

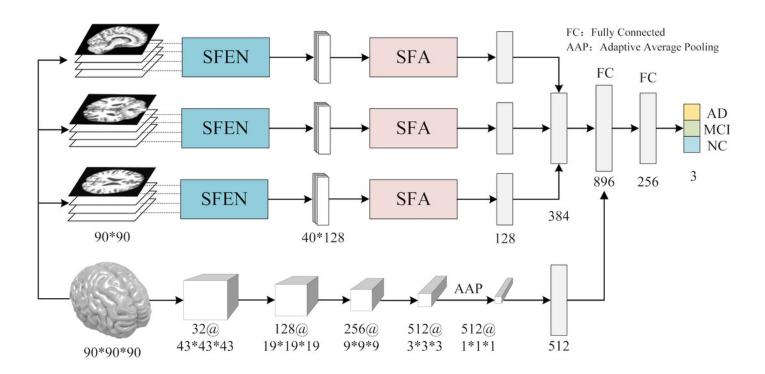


Figure 2. 3D MRI data slicing in three directions.

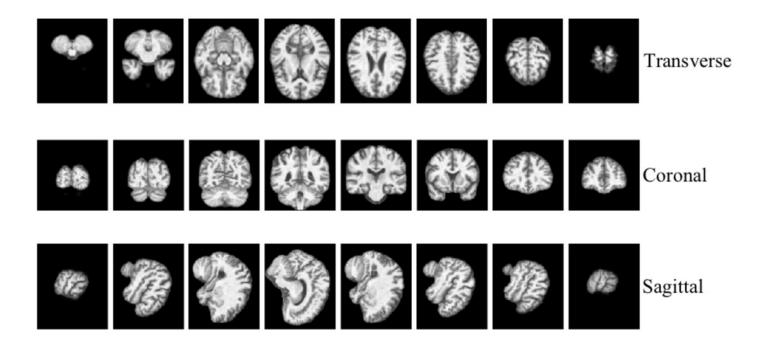


Figure 3. The architecture of SFE.

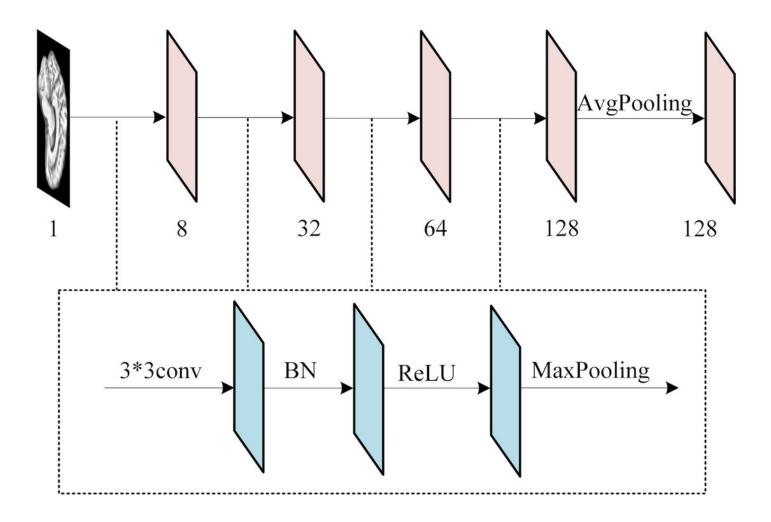
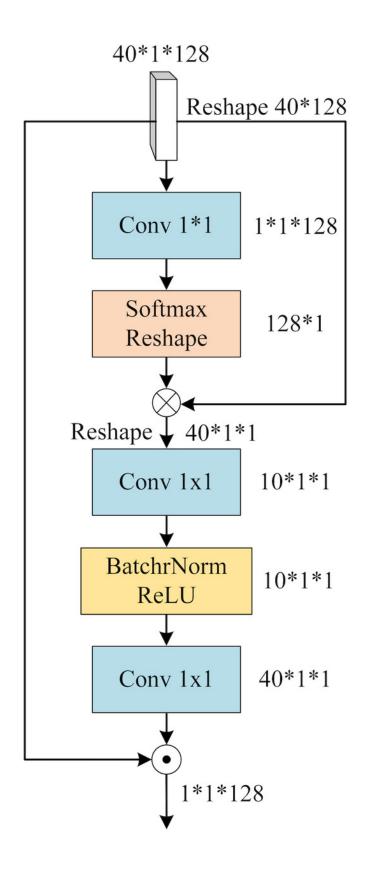


Figure 4. The architecture of SFA.



- Matrix multiplication
- Multiply by channel and add up

Figure 5. The structure of GFE network.

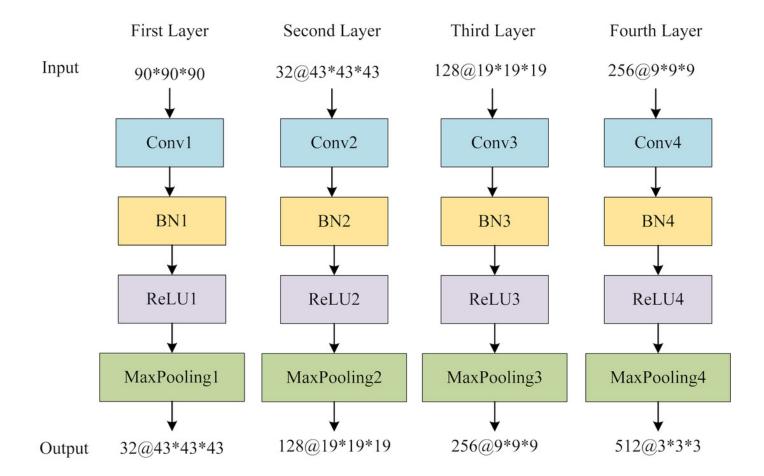


Figure 6. The curve of validation loss of AMSF.

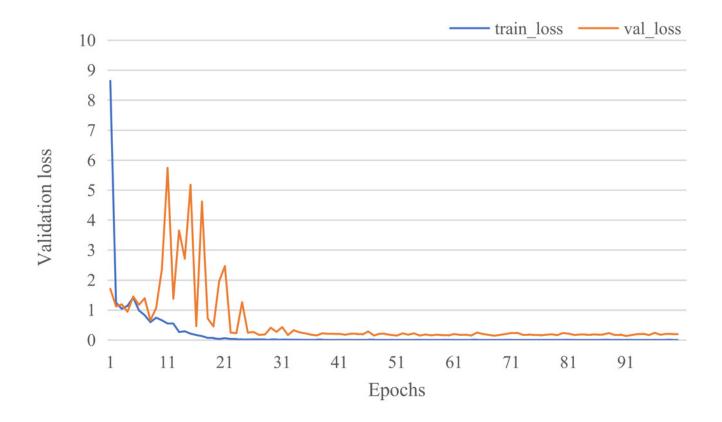


Figure 7. The curve of accruracy of AMSF.

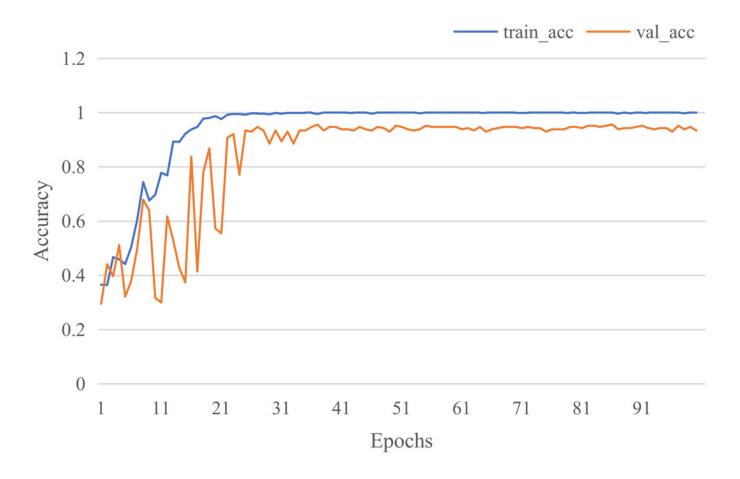
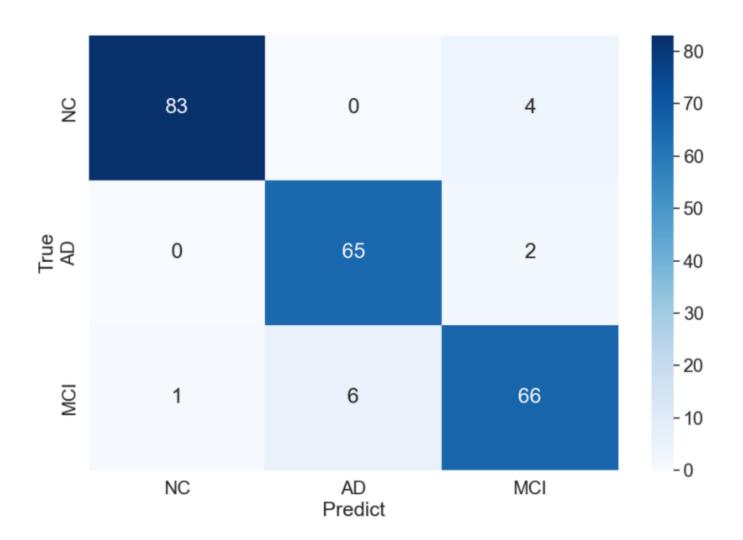


Figure 8. Confusion matrix of of AMSF in ablation experiment.



### **PeerJ** Computer Science

Manuscript to be reviewed

Table 1(on next page)

Table 1. Results of ablation experiments.

### **PeerJ** Computer Science

#### 1 **Table 1.** Results of ablation experiments.

Methods	Acc (%)	Sen (%)	Spe (%)	Pre (%)	F1 (%)
3D	76.9	76.6	88.7	77.2	76.7
2D	89.4	90.2	94.8	90.8	89.8
2D+3D	91.6	91.6	95.9	92.2	91.3
SE+2D+3D	89.8	89.6	95.1	89.6	89.5
AMSF	94.3	94.2	97.1	94.2	94.1

### PeerJ Computer Science Manuscript to be reviewed

#### Table 2(on next page)

Table 2. The comparison results with other previous methods for AD vs. MCI vs. NC classification.

1 Table 2. The comparison results with other previous methods for AD vs. MCI vs. NC classification.

2	Methods	Category with the number of samples	Acc(%)
3	Automatic CL	AD: 95,MCI: 207,NC: 104	87.2
	JMMP-LRR	AD: 24,MCI: 24,NC: 24	89.0
4	DemNet	AD: 300,MCI: 300,NC: 300	91.9
_	Linner SVM	AD: 34,MCI: 45,NC: 21	92.0
5	AdaBoost	AD: 85,MCI: 193,NC: 111	92.7
6	AMSF (ours)	AD: 301,MCI: 331,NC: 351	94.3