Improving Across-Dataset Schizophrenia Classification with Structural Brain MRI Using Multi-scale Transformer

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Synopsis

Schizophrenia is a neurological disorder that requires accurate and rapid detection for earlier intervention. Previous explorations in artificial intelligence showed overwhelming performance using deep learning in schizophrenia classification, though the generalization remained a challenge. We propose our 3D Multi-scale Transformer (MST) using T1W structural MRI data to detect schizophrenia. By synthesizing reconstructed images at different scales, the transformer-based architecture improves robustness to generalize in unseen data. The proposed method reaches the same-level performance of AUROC to the benchmark mark model in schizophrenia identification, and performs better in all leave-one-site-out generality tests.

Introduction

Schizophrenia is a chronic progressive disorder that affects barely 1% of the population in the United States in 2022. This neuropsychiatric disease may result in disorganized behavior, delusions and other serious symptoms that disable patients' daily functioning. Studies have found its strong dependency on structural abnormalities in the brain such as ventricular enlargement[1].

Neuroimaging research has investigated brain alterations caused by schizophrenia using Magnetic Resonance Imaging (MRI). T1-weighted (T1W) MRI demonstrates differences in the T1 relaxation times of tissues and is widely applied to elucidate progressive changes in the schizophrenic brain [2].

Deep Learning is a computational technique that arose in the past 10 years to support the automated detection of Schizophrenia. While convolutional neural networks have been proved to outperform conventional machine learning models [3][4], the transformer architecture emerged recently uses attention mechanisms to achieve even-better results in medical image analysis and disease classification[5].

We design and propose our 3D Multi-scale Transformer (MST) inspired by the Vision Transformer (ViT) [6] which significantly enhances the across-datasets classification of schizophrenia.

Methods

The architecture of our proposed 3D Multi-scale Transformer is shown in **Figure 1**. Two identical encoders extract features from initial scale input and reconstructed multi-scale input. The encoders are 3D VGG-11BN backbones[7] with five convolutional blocks.

We downsample the input 3D T1W MRI images at a ratio of 2 as the initial scale and input to the first encoder. Then we downsample and upsample the initial images at a ratio of increasing powers of 2 ($\times 2$, $\times 4$, $\times 8$). The images keep the same size after this step,but have larger receptive fields and more dilated information.

The features are fed into a transformer encoder with spatial position embedding and batch normalization removed. To compute the attention, features are projected by 1×1 convolutional layers into three different spaces: 'key' and 'value'; and 'query', separately. Lastly, a linear voting at the decoding stage fuses the output to compute the loss.

We evaluated model performance and generality using 4 datasets from the studies: BrainGluSchi [8], COBRE[9] ,NMorphCH[10] and MCICShare[11]. We tested the overall results using all available data and conducted a leave-one-site-out (LOSO) test to compare the generality. The across-datasets experiments are concluded in **Figure 2**.

The T1-weighted structural MRIs in the 4 studies are gathered in the SchizConnect database (http://schizconnect.org/) and are summarized in **Figure 3A**. All datasets have homogeneous acquisition parameters and characteristics, except the MCICShare which has different MRI sequences and acquisition parameters.

The whole-head T1W scans were registered to the MNI152 unbiased template by robust affine registration [12, 13] . We applied skull-stripping with Brain Extraction Tool[14] before another affine registration of the whole-brain scans. The data preprocessing steps to remove unwanted artifacts and transform the data into a standard formatare are illustrated in **Figure 3B**. All datasets were merged and split into 8:1:1 train/validation/test groups for deep learning analysis. We used a learning rate of 10^{-5} and CrossEntropy loss function. Each input 3D subject was cropped to (128×192×128) and output two scores of probability that correspond to the group label of schizophrenia patients or healthy controls, respectively.

Results

When training and testing on all 4 datasets, our 3D Multi-scale Transformer (MST) model performs better than the state-of-the-art model with an area under the receiver operating characteristic (AUC) of 0.948. When we excluded the MCICShare dataset, our proposed model almost replicated the best existing model performance. The results are compared in **Figure 4**.

Our model outperformed the benchmark model in all leave-one-site-out generality tests, as are shown in **Figure 5**. If training the model using COBRE, NMorphCH and MCICShare datasets and testing on BrainGluschi dataset, the baseline model performance shows a significant drop in terms of the accuracy, sensitivity, specificity and AUC, while our proposed model remains robust towards the unseen dataset. This better generalization could also be revealed via another 3 tests in which our proposed model all beated the benchmark. Specifically, when testing on MCICShare dataset alone, this effect becomes more significant.

Discussion

Generalization is always a formidable challenge in deep learning tasks for MRI image analysis. Current models might have performed extremely well on a regular training-testing pipeline, but those numbers of performance, especially the specificity, unavoidably decreased when switching to an untrained target test. This gap makes the model no longer a potentially automatic diagnostic tool for clinical use, but instead, not convincing until trained with additional data.

Our proposed model solves this problem by raising the idea of multi-scaling at the input stage. This method enables each fundamental element of the image to absorb useful information from adjacent ones, and fuses the features to be more representative. By picking different numbers of the scaling factor, we are able to decide the limit of the receptive field and numbers of images for each encoder. The attention mechanism in the transformer fuses the extracted features and further enhances the predictive ability of this deep learning architecture.

We use the same modality of 3D MRI data, with same-level computational cost, to maintain the model's robustness but significantly improve the generalizability. This approach could improve current MRI research in schizophrenia with various sites, sequences and field strengths.

Summary of main findings:

We propose a 3D Multi-scale Transformer (MST), a new deep learning architecture that improves the across-dataset classification of schizophrenia using T1W structural images.

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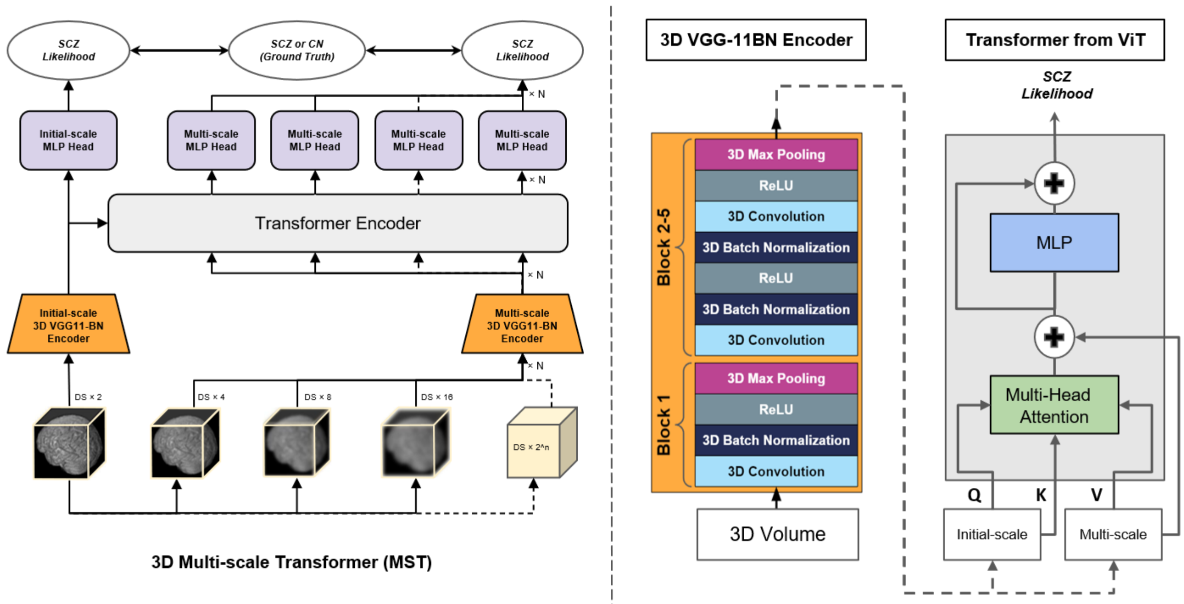


Figure 1

Study design and the 3D Multi-scale Transformer (MST). A 3D-VGG11BN backbone extracts the feature vectors from the multi-scale images with different downsampling and upsampling ratio inputs and feeds them into a Transformer Encoder for schizophrenia classification. The VGG encoder has five blocks containing convolution, batch normalization, and ReLU activation layers. The global-regional attention has the "query" from the local pathway and the pair of "key" and "value" from the global path.

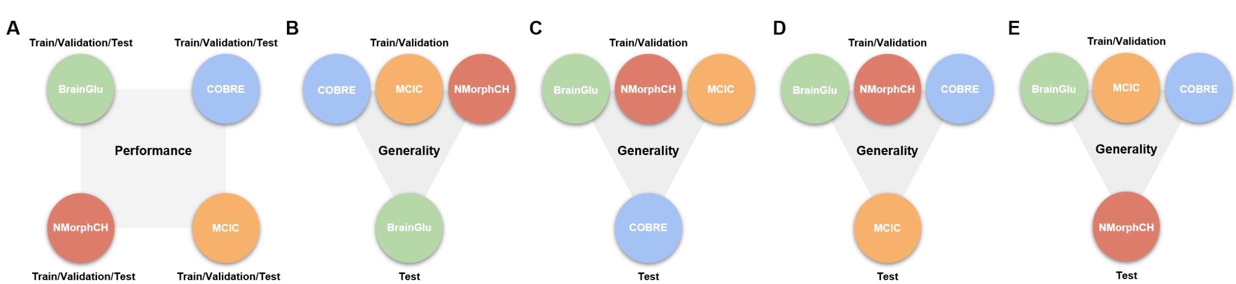


Figure 2 :

Overview of the experimental pipeline.

(A) Model performance test, where the model was trained validated and tested on all datasets.

(B) Model generality tested on the BrainGluSchi dataset

(C) Model generality tested on the COBRE dataset

(D) Model generality tested on the MCICi dataset

(E) Model generality tested on the NMorphCH dataset

A

Scan Parameters	BrainGluSchi	COBRE	NMorphCH	MCIC
Scanner	SIEMENS TrioTim	SIEMENS TrioTim	SIEMENS TrioTim	SIEMENS Sonata/ SIEMENS TrioTim
Field strength	3T	3T	3T	1.5T 3T
Sequence	MPRAGE	MPRAGE	MPRAGE	T1W-TSE
Voxel size (mm)	1.0x1.0x1.0	1.0x1.0x1.0	1.0x1.0x1.0	1.0x1.0x1.0/ 1.0x0.625×0.625
TR/TE (msec)	2530/1.64	2530/1.64	2400/3.16	2530/3.79 12/4.76
Acquisition year	2010 - 2013	2009 - 2013	2008 - 2013	2004 - 2006
Number of normal scans (Train/Validation/Test)	89 (73/8/8)	237 (199/22/16)	111 (89/10/12)	95 (76/9/10)
Number of patient scans (Train/Validation/Test)	86 (70/7/9)	243 (207/23/13)	121 (98/6/17)	109(88/10/11)
Female %	20.3%	24.0%	40.0%	29.5%
Age range (year)	16-66	18-66	19-46	18-61
Age mean ± SD	37.6 ± 13.3	38.3 ± 12.6	32.2 ± 7.6	33.9 ± 11.6

B

Figure 3:

Data structure of the BrainGluSchi, COBRE, NMorphCH and MCIC datasets and preprocessing steps. (A) Sample characteristics and scan parameters of the T1W MR data and the patient demographic information of each dataset. (B) Data preprocessing pipeline to generate the input of different schizophrenia classification deep learning models.

A

Train/Validation/Test dataset: BrainGluSchi, COBRE, NMorphCH

Input	Model	Accuracy (Th = 0.5)	Sensitivity	Specificity	AUC
T1W (whole brain)	Zhang *et al.*, 2022	0.921	0.949	0.946	0.987
T1W (whole brain)	3D MST	0.867	0.923	0.944	0.978

B

Train/Validation/Test dataset: BrainGluSchi, COBRE, MCIC, NMorphCH

Input	Model	Accuracy (Th = 0.5)	Sensitivity	Specificity	AUC
T1W (whole brain)	Zhang *et al.*, 2022	0.829	0.761	0.935	0.921
T1W (whole brain)	3D MST	0.822	0.910	0.855	0.948

Figure 4 :

The schizophrenia classification performance of models in terms of Accuracy (at threshold=0.5), Sensitivity, Specificity and AUC, compared between 3D Multi-scale Transformer and VGG-19BN benchmark.

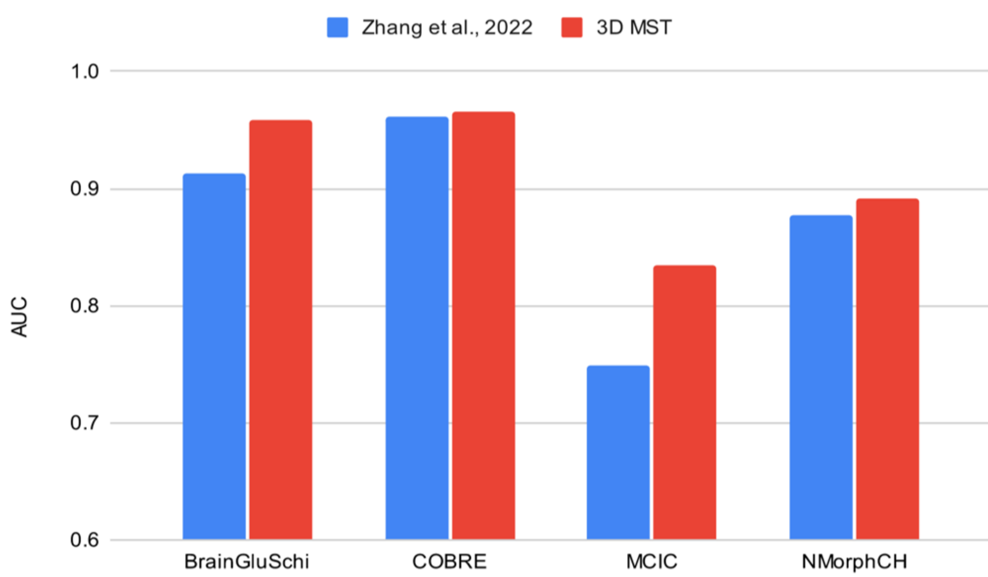
(A) Table quantitatively summarizing the performance on the BrainGluSchi, COBRE, and NMorphCH datasets (B) Table quantitatively summarizing the performance on the BrainGluSchi, COBRE, MCIC and NMorphCH datasets.

Figure 5

A

LOSO Test Dataset	Input	Model	Accuracy (Th = 0.5)	Sensitivity	Specificity	AUC
BrainGluSchi	T1W (whole brain)	Zhang *et al*., 2022	0.822	0.867	0.802	0.913
	T1W (whole brain)	3D MST	0.882	0.889	1.0	**0.958**
COBRE	T1W (whole brain)	Zhang *et al*., 2022	0.793	0.846	1	0.962
	T1W (whole brain)	3D MST	0.897	1.0	0.812	**0.966**
MCIC	T1W (whole brain)	Zhang *et al*., 2022	0.759	0.571	0.962	0.749
	T1W (whole brain)	3D MST	0.667	0.643	0.885	**0.834**
NMorphCH	T1W (whole brain)	Zhang *et al*., 2022	0.586	0.941	0.667	0.877
	T1W (whole brain)	3D MST	0.621	0.824	0.833	**0.892**

B



The leave-one-site-out schizophrenia classification performance in terms of Accuracy (at threshold=0.5), Sensitivity, Specificity and AUC, compared between 3D Multi-scale Transformer and VGG-19BN benchmark.

(A) Table quantitatively summarizing the 4 across-dataset generality test results on the BrainGluSchi, COBRE, MCIC and NMorphCH datasets (B) A bar graph showing the AUC result comparision for each generality test.

Word Limits

The following word limits will apply:

- Title: 125 characters
- Synopsis: 100 words
- Body of the Abstract: 850 words (references not included)
- Summary of Main Findings: 250 Characters (~35 words)
- Figures: up to 5 only
- Figure Captions: 500 characters per caption