PAPER 1

PROBLEM

Alzheimer's Disease Progression for Real-World Clinical Applications

Most machine learning approaches are either **single-task** or single-**modality models**

Most of those approaches are trained on a **single dataset**

OBJECTIVE

Our goal is to predict the progression of Alzheimer's Disease 12 months from the first patient visit (baseline visit).

We propose a novel multimodal multi-task deep learning model to predict AD progression by analyzing longitudinal clinical and neuroimaging data from multiple cohorts

In this paper we focus on the task of modeling the trajectory of AD over time as measured by three cognitive tests (CDRSB, ADAS-COG12, MMSE) using a multimodal approach that uses cognitive scores, genomic, demographic, and imaging data as input

CDRSB: accurately stage severity of Alzheimer dementia and mild cognitive impairment (MCI)

ADAS-COG12: a brief neuropsychological assessment used to assess the severity of cognitive symptoms of dementia

MMSE: is a set of 11 questions that doctors and other healthcare professionals commonly use to check for cognitive impairment (problems with thinking, communication, understanding and memory)

Using MRI features from a 3D convolutional neural network with other data modalities including clinical and demographic information**" age, race, ethnicity, gender, marital status, income, education, and employment.**", to predict the future trajectory of patients.

Methods

DeepAD: a multimodal multitask deep neural network for personalized prediction of disease progression and diagnosis

adversarial loss: It is a binary classifier that differentiates between ground truth data and generated data predicted by the generative network

to alleviate the study specific imaging bias, in particular the inter-study domain shifts.

Sharpness-**Aware** Minimization: optimization technique is applied to further improve model generalization.

A multi-modal GRU-based RNN was used to integrate longitudinal clinical information and crosssectional tabular imaging features for classifying the MCI patients into converter to AD or not-converter to AD [15]. MinimalRNN

3D MR images are fed into a 3D dense convolutional neural

A stacked denoising auto-encoder approach was used to extract features from clinical and genetic data, and a 3D CNN for MRIs to categorize patients into different stages of the disease

A regularization loss based on mutual information [14], was adopted to minimize the undesirable effects of the possible study-specific biases.

NOTE:" models using extracted neuroimaging features from 3D convolutional neural network outperform the same models when applied to MRI-derived volumetric features"

NOTE" Specifically, our model takes in as input a single 3D MR image (H x W x T x C) and D length vector containing the concatenation of cognitive scores, genomics, and demographic information at the baseline visit to predict the interpolated CDRSB, MMSE and ADAS-COG12 at month 12"

<u>Neural Network design:</u>

Two main networks

The first is an encoder a, which learns an effective representation of the clinical information.

The second is a combined network that consists of three subnetworks: feature extraction network f, endpoint prediction network g, and domain adaptation network h.

The feature extraction: designed by stacking four layers including a 3D convolutional layer, a 3D batch normalization layer, a leaky ReLU layer, and a 3D max-pooling layer followed by two dense blocks respectively with 6 and 12 dense layers.

The dense layer is composed of 6 layers including a 3D batch normalization layer, a leaky ReLU layer, and a 3D convolution layer, where this set of 3 layers is repeated twice

The transition layer is composed of a 3D batch normalization layer, a leaky 3 ReLU layer, a 3D convolution layer, and a 3D average pooling layer

The endpoint prediction network g is a single dense block with 16 dense layers.

domain adaptation network h: a single dense block with 16 dense layers, a leaky ReLU layer, a 3D average pooling layer, and a linear layer **encouraged** to output a uniform prediction for all imaging sites

DATASETS

5548 participants with **34731** total visits from the Alzheimer's Disease **Neuroimaging Initiative (ADNI)** and **six internal studies** including A,B,C,D,E and F

Study	Abbreviation	Number of patients		
-	-	CN	MCI	AD
Anon_A	A	-	-	374
Anon_B	B	-	-	66
Anon_C	C	-	-	197
Anon_D	D	-	702	-
Anon_E	E	-	240	437
Anon_F	F	-	271	341
ADNI	ADNI	272	490	185

Summary of datasets: Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; AD Alzheimer's disease. to test whether MR imaging, PET, other biological markers and clinical, and neuropsychological assessment can be combined to measure the progression of AD. For up-to-date information, see **http://adni.loni.usc.edu.** For each patient we have the following modalities: • Demographic: Age, Sex, Diagnosis, Education level, and BBMI • Genomic: APOE4 • Cognitive scores: CDRSB, MMSE, ADAS-COG12, and FAQ • Imaging: Raw 3D MRI image

RESULTS

DeepAD+Clinc is better

endpoint	study	Linear regression	DeepAD-Clin	DeepAD-MRI	DeepAD-MRI+Clin
CDRSB	in-study	0.17	0.15	0.12	**0.22**
	out-study	0.12	0.11	0.08	**0.17**
MMSE	in-study	0.09	0.09	0.14	**0.18**
	out-study	**0.13**	0.10	0.03	0.10
ADAS-COG12	in-study	0.06	0.06	0.11	**0.15**
	out-study	0.06	0.07	**0.08**	**0.08**

	Method-modality	CDRSB	MMSE	ADAS-COG12
MMST	Regression-Clin+Volumetric	0.18	0.17	0.09

Paragraph

most machine learning approaches developed for prediction of disease progression are **either single-task or single-modality models**, which cannot be directly adopted to our setting involving multi-task learning with high dimensional images. Moreover, most of those **approaches are trained on a single dataset**, which cannot be generalized to other cohorts We propose a novel **multimodal multi-task deep learning model** to predict AD progression by analyzing longitudinal clinical and neuroimaging data from **multiple cohorts**. Our proposed model integrates high dimensional MRI features from a 3D convolutional neural network with other data modalities, including clinical and demographic information, to predict the future trajectory of patients. Our model employs an adversarial loss to alleviate the studyspecific imaging bias, in particular the inter-study domain shifts. In addition, a Sharpness-Aware Minimization (SAM) optimization technique is applied to further improve model generalization. The proposed model is trained and tested on various datasets in order to evaluate and validate the results. Our results showed that 1) our model yields significant improvement over the baseline models, and 2) models using extracted neuroimaging features from 3D convolutional neural network outperform the same models when applied to MRI-derived volumetric features