



# Neuroimage Analysis for Automated Brain Disease Diagnosis

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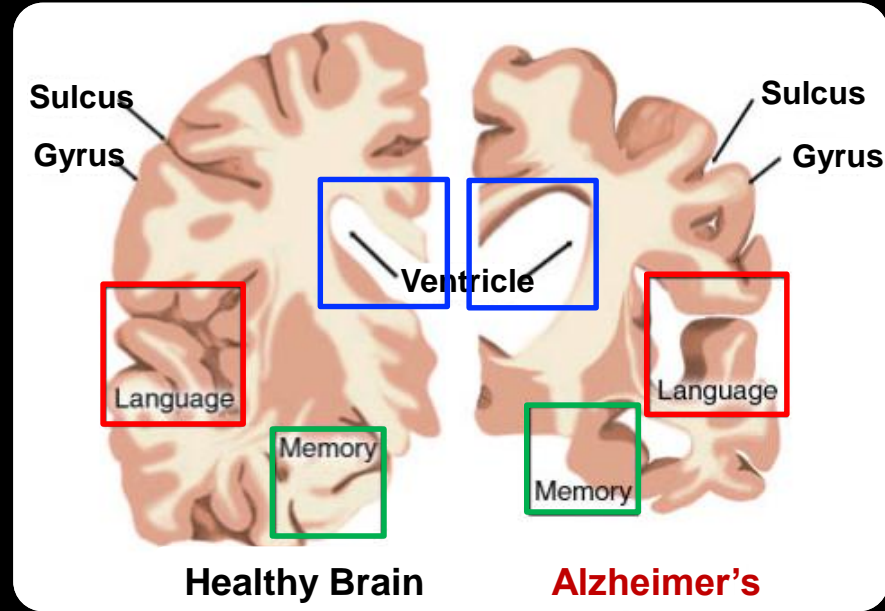
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<http://mingxia.web.unc.edu/>

07-17-2019

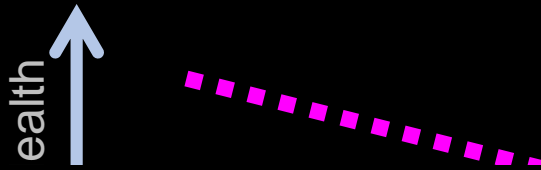
# Background

## Healthy Brain vs. Alzheimer's



# Background

- Alzheimer's Disease (AD)
  - A progressive disease



- Calling Need
  - Developing computer-aided methods for MCI/AD diagnosis

Stable MCI (sMCI)  
Progressive MCI (pMCI)

# Background

## Biomarkers for early diagnosis of AD and MCI

- Structural Magnetic Resonance Imaging (**MRI**)
- FDG-Positron Emission Tomography (**PET**)
- Cerebrospinal Fluid (**CSF**) --- A $\beta$ 42, t-tau

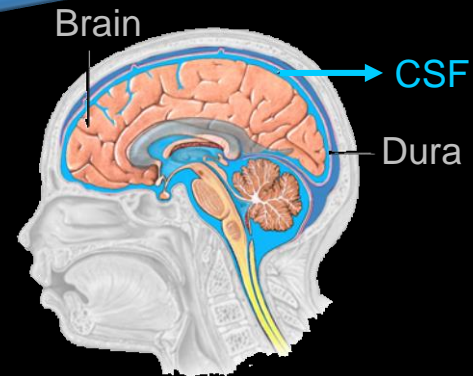
Multi-modal data



MRI

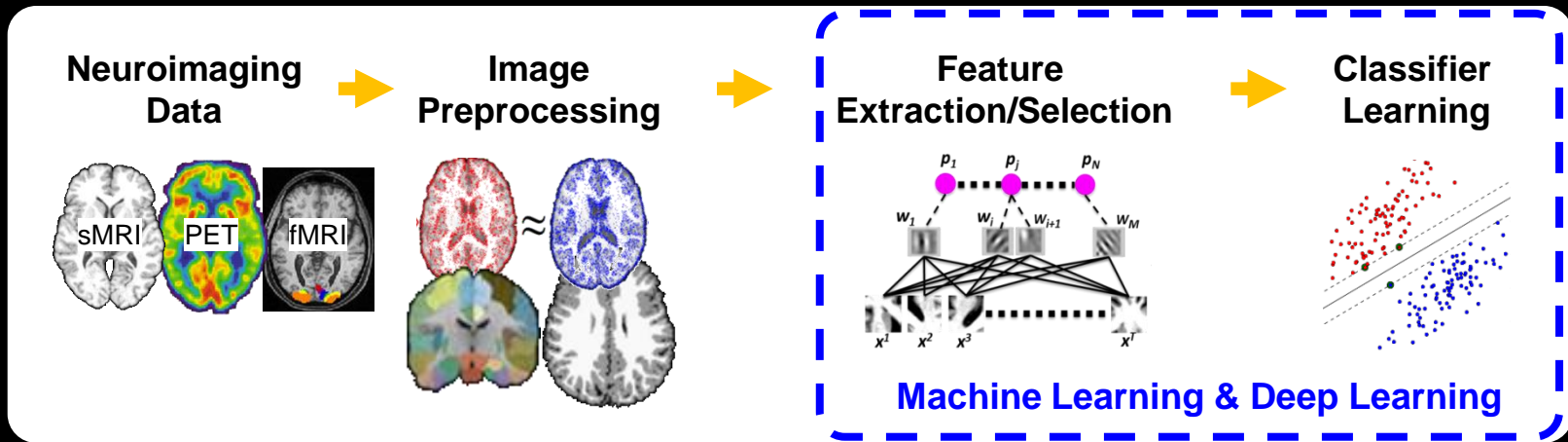


PET



CSF

# Brain Disease Diagnosis – Typical Pipeline



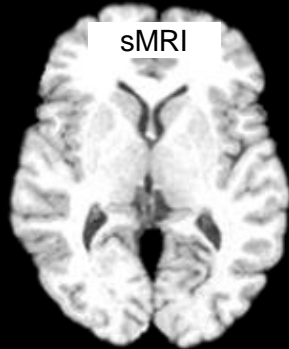
M. Liu, et al., Landmark-based Deep Multi-Instance Learning for Brain Disease Diagnosis, *Medical Image Analysis*, 2018.

M. Liu, et al., Joint Classification and Regression via Deep Multi-task Multi-channel Learning for Alzheimer's Disease Diagnosis. *IEEE Trans. on Biomedical Engineering*, 2018.

# Challenges in Computer-aided Disease Diagnosis

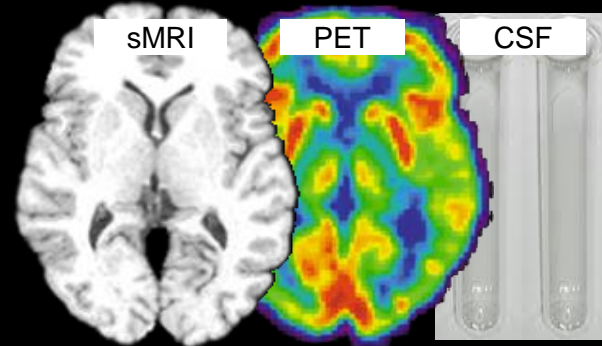
- Effective feature **representation** of neuroimages
- **Missing** multi-modal data
- **Heterogeneous** data at different imaging sites

# Outline



- Structural MRI (sMRI)

Single-modal Neuroimage



- Missing Data
- Multi-modal Data Fusion
- Domain Adaptation

Multi-modal Neuroimage



# Part I. Single-modal Neuroimage Analysis

- Structural MRI based Brain Disease Diagnosis

# Anatomical Landmarks for Structural MRI

- Landmark-based Deep Representation of sMRI

C. Lian, [M. Liu](#), J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

[M. Liu](#), J. Zhang, C. Lian, and D. Shen. *IEEE Trans. on Cybernetics*, 2019.

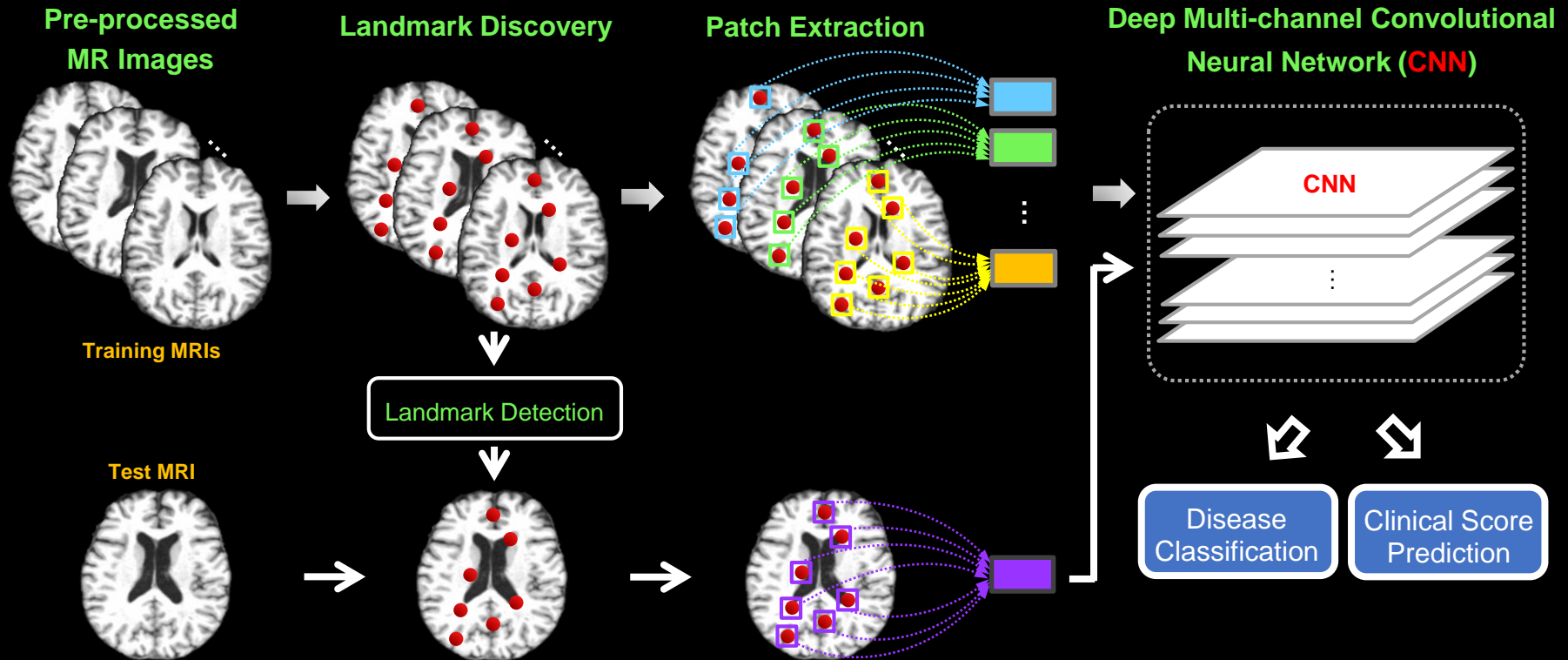
[M. Liu](#), J. Zhang, E. Adeli, and D. Shen. *IEEE Trans. on Biomedical Engineering*, 2019.

[M. Liu](#), J. Zhang, E. Adeli, and D. Shen. *Medical Image Analysis*, 2018.

[M. Liu](#), J. Zhang, D. Nie, P.T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

J. Zhang, [M. Liu](#), and D. Shen. *IEEE Trans. on Image Processing*, 2017.

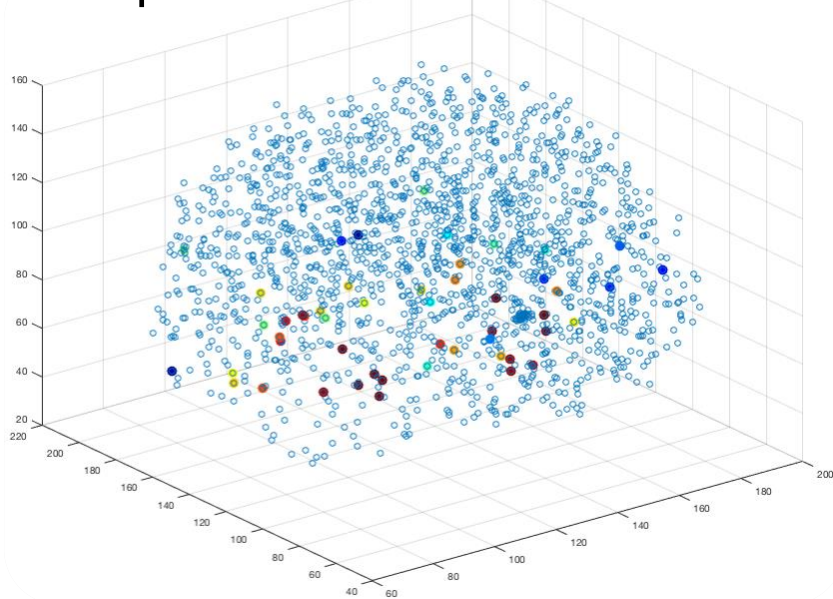
# Anatomical Landmark-based Deep Network



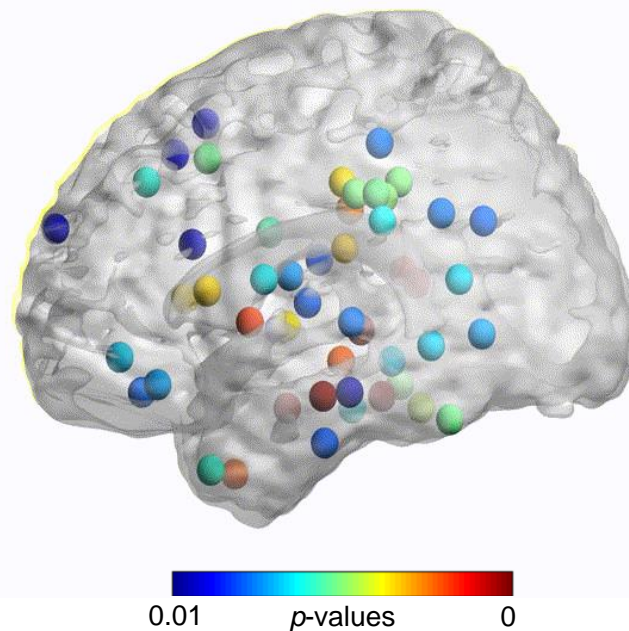
\* Featured Article of IEEE Journal of Biomedical and Health Informatics, 2018

# Anatomical Landmark-based Deep Network

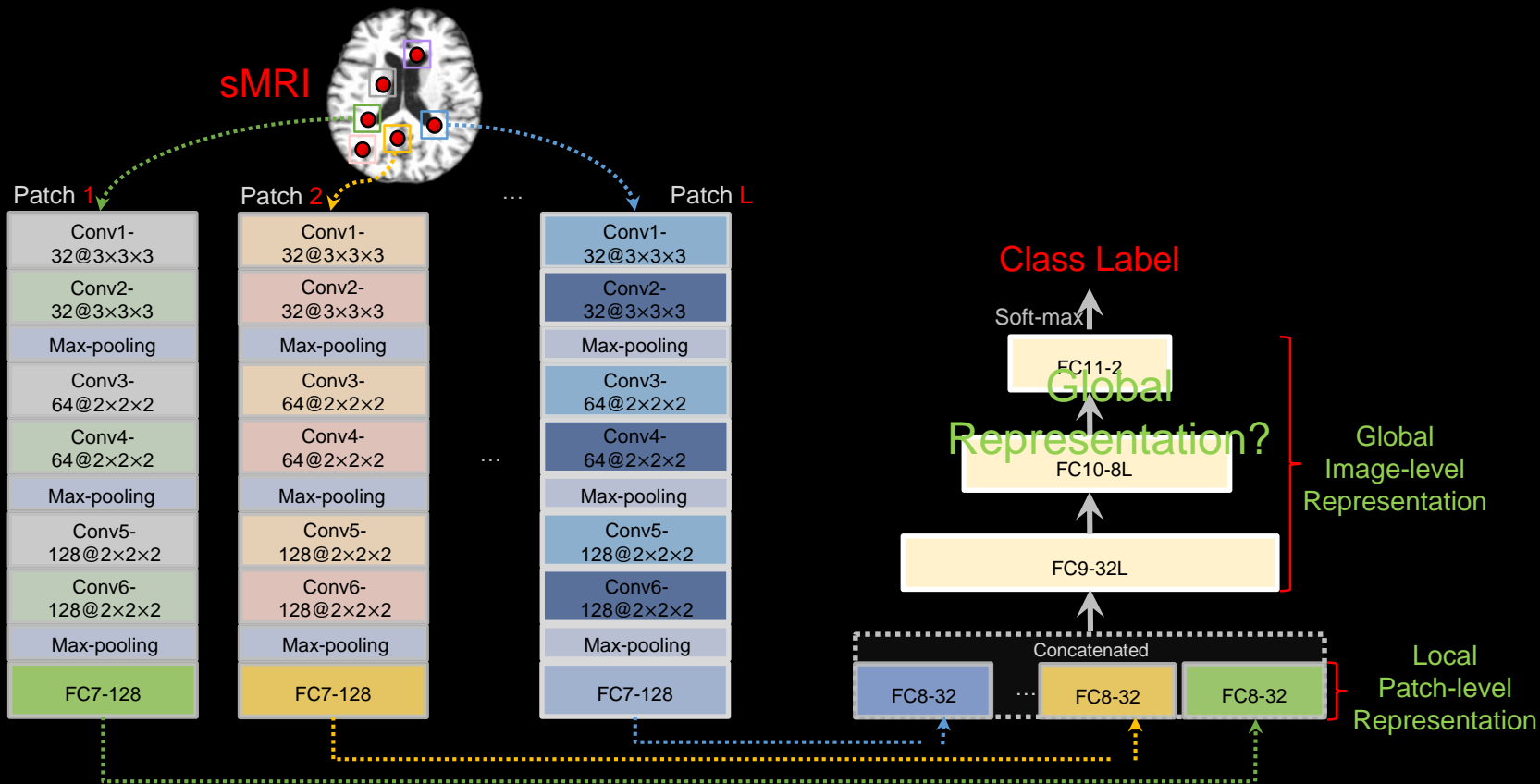
**1,740** landmarks via group comparison between AD and NC



Top 50 landmarks



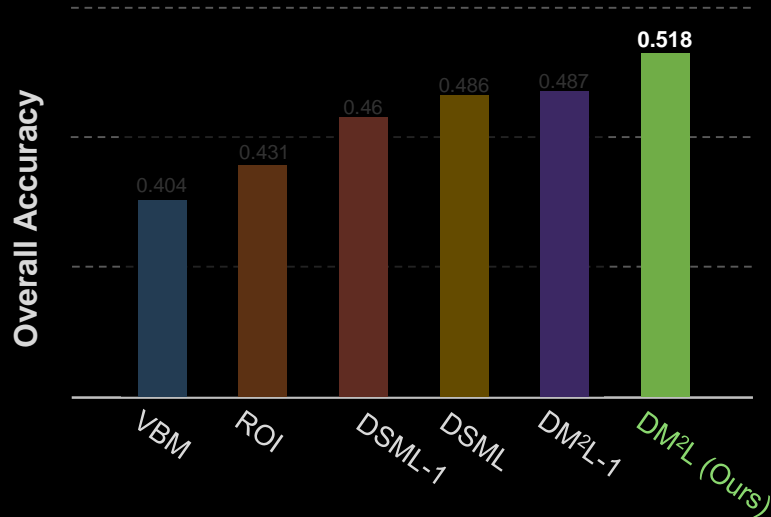
# Landmark-based Deep Network



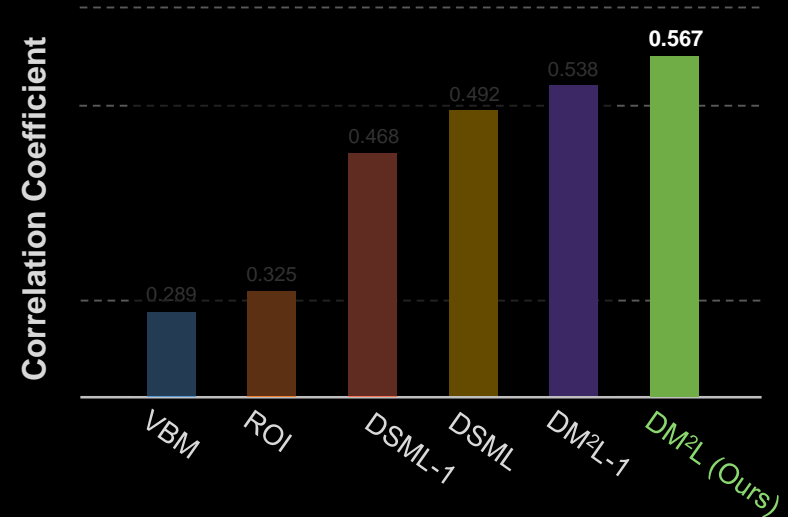
M. Liu, J. Zhang, E. Adeli, and D. Shen. *Medical Image Analysis*, 2018.

M. Liu, J. Zhang, D. Nie, P.T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# Results of Classification and Regression



Classification Results for **AD vs. sMCI vs. pMCI vs. NC**



Regression Results for **MMSE**

# End-to-end Disease Diagnosis with sMRI

- Hierarchical Fully Convolutional network

C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

M. Liu, J. Zhang, C. Lian, and D. Shen. *IEEE Trans. on Cybernetics*, 2019.

M. Liu, J. Zhang, E. Adeli, and D. Shen. *IEEE Trans. on Biomedical Engineering*, 2019.

M. Liu, J. Zhang, E. Adeli, and D. Shen. *Medical Image Analysis*, 2018.

M. Liu, J. Zhang, D. Nie, P.T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

J. Zhang, M. Liu, and D. Shen. *IEEE Trans. on Image Processing*, 2017.

# Hierarchical Network for ROI Identification

- Hierarchical Fully Convolutional Network (H-FCN)
  - Automatically and identify **disease-related ROIs** in the whole sMR image
  - Jointly learn **multi-scale features** and construct a **classification model**

# Hierarchical Network for ROI Identification

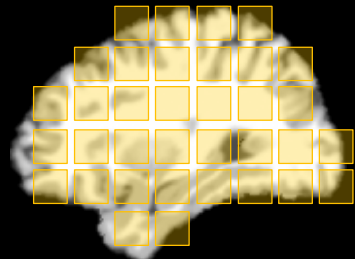


Input:  
sMRI

C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

C. Lian, M. Liu\*, L. Wang, and D. Shen. *MICCAI 2019*.

# Hierarchical Network for ROI Identification



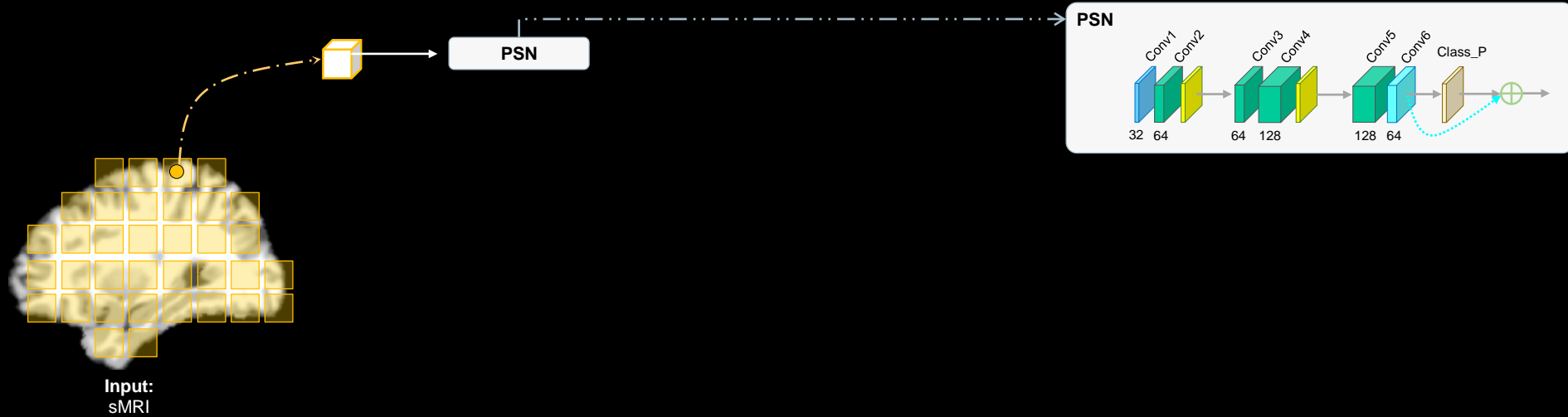
Input:  
sMRI

## 1) Location proposals

C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

C. Lian, M. Liu\*, L. Wang, and D. Shen. *MICCAI 2019*.

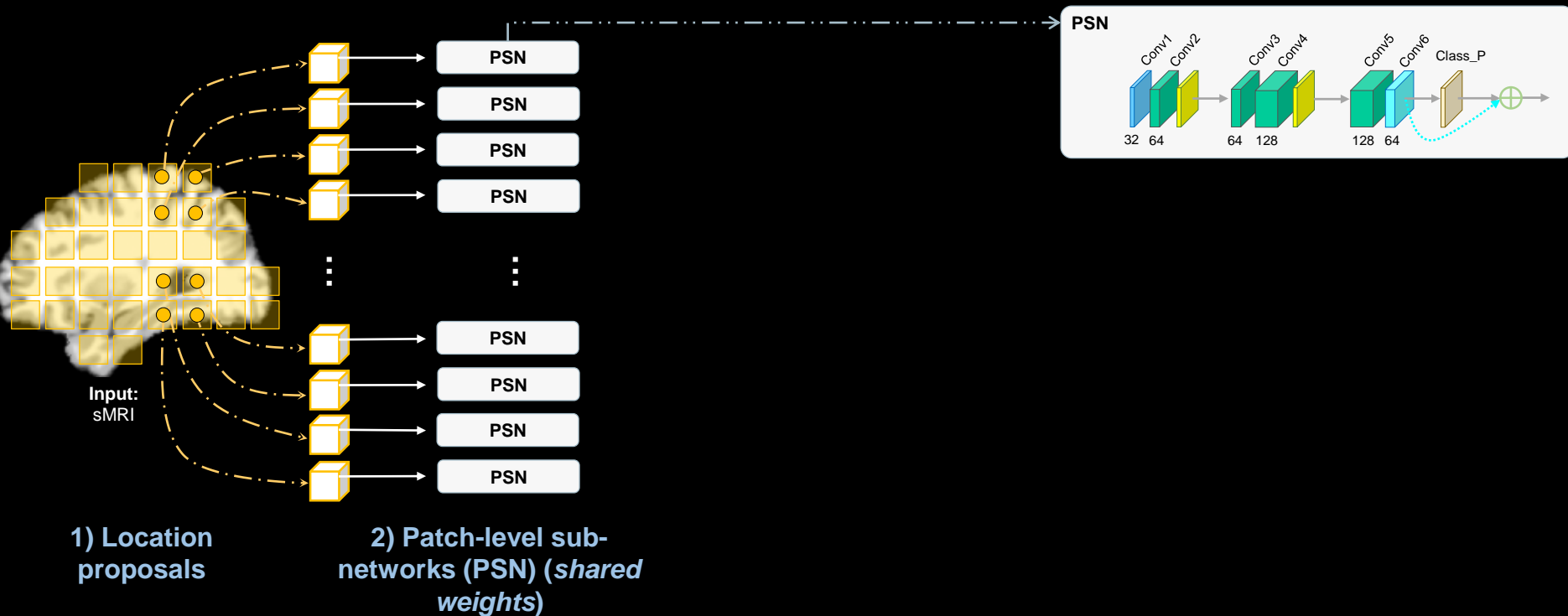
# Hierarchical Network for ROI Identification



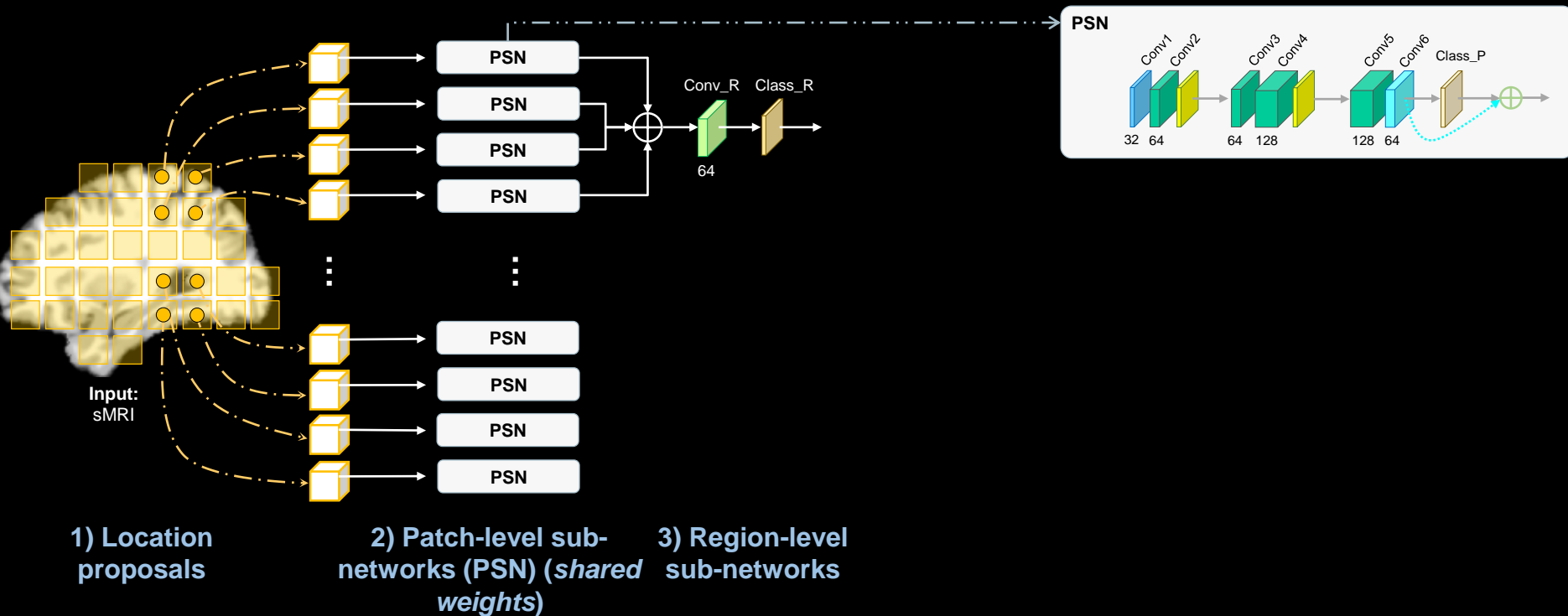
1) Location proposals

2) Patch-level sub-networks (PSN) (*shared weights*)

# Hierarchical Network for ROI Identification



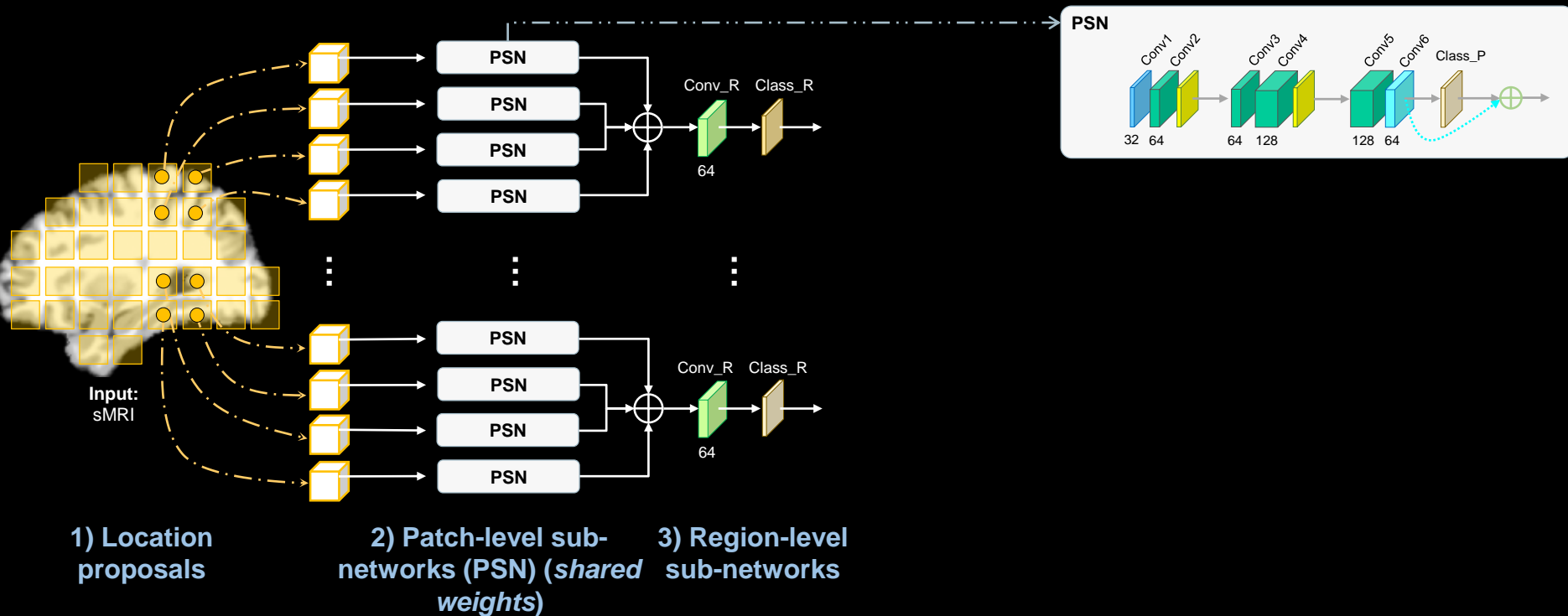
# Hierarchical Network for ROI Identification



C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

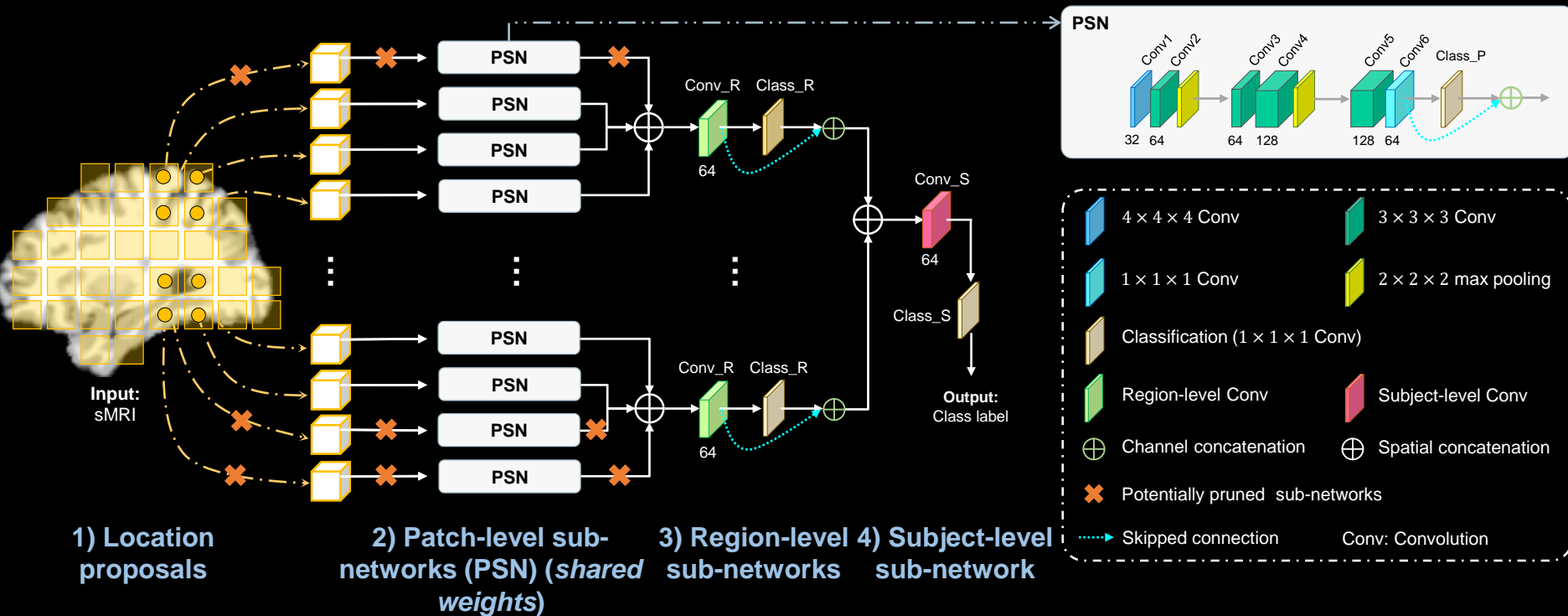
C. Lian, M. Liu\*, L. Wang, and D. Shen. *MICCAI 2019*.

# Hierarchical Network for ROI Identification

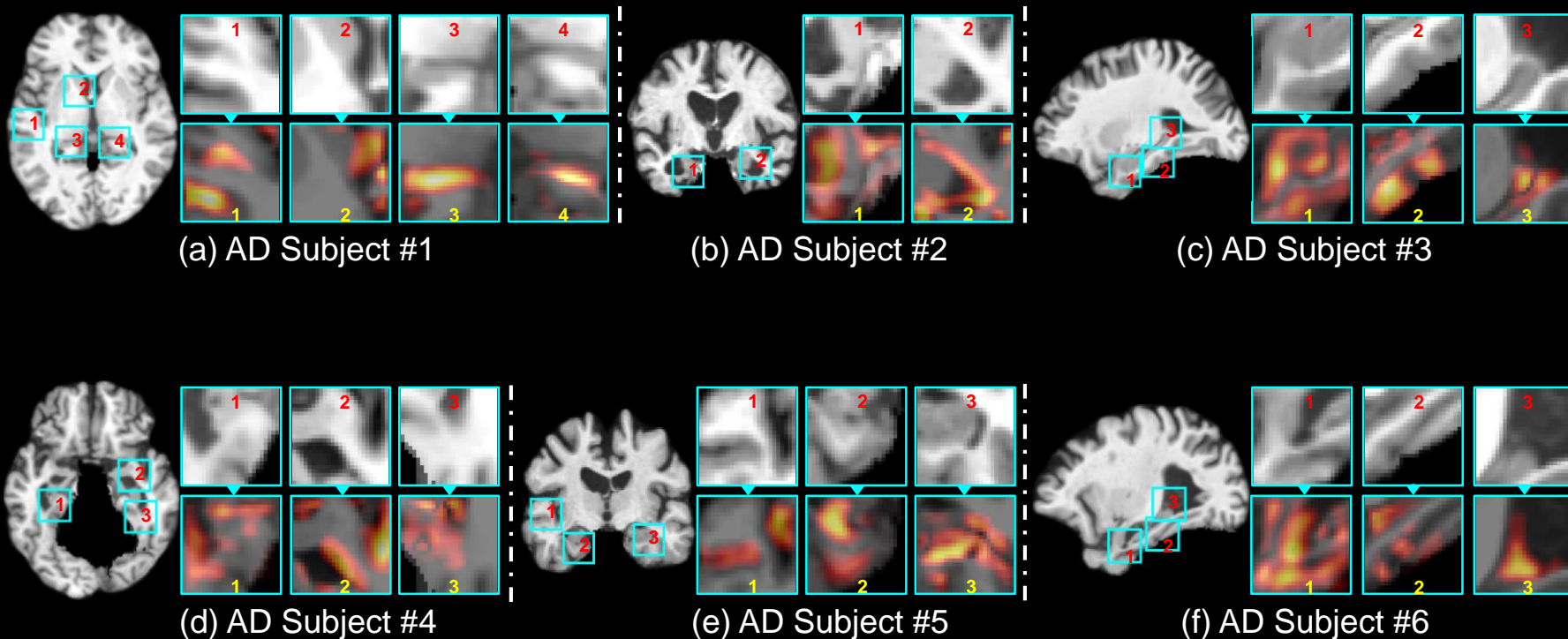


# Hierarchical Network for ROI Identification

**Network Pruning:** To remove less informative regions



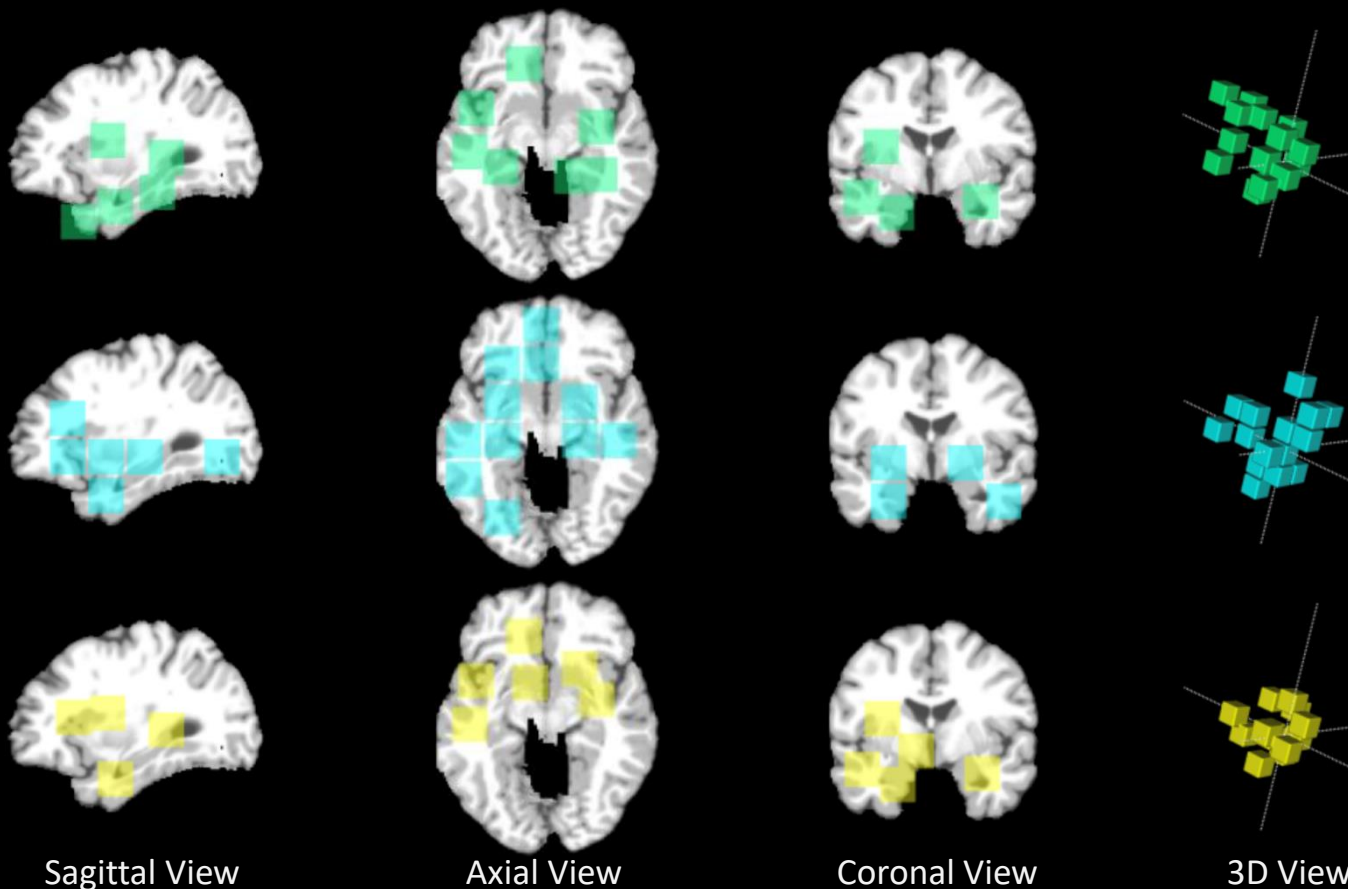
# Identified Voxel-level Discriminative Locations



C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

C. Lian, M. Liu\*, L. Wang, and D. Shen. *MICCAI 2019*.

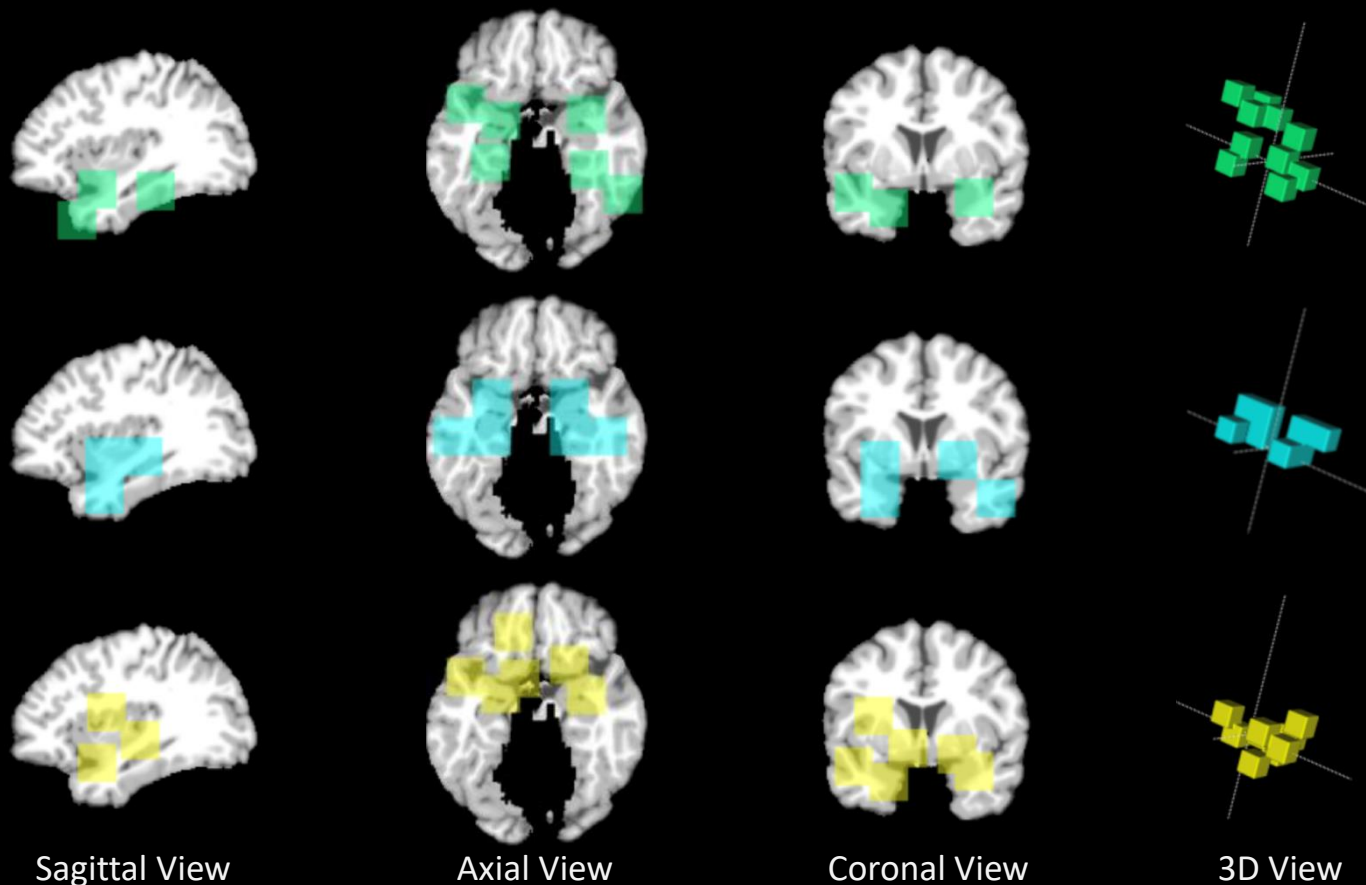
# Identified Patch-level Discriminative Locations



C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

C. Lian, M. Liu\*, L. Wang, and D. Shen. *MICCAI 2019*.

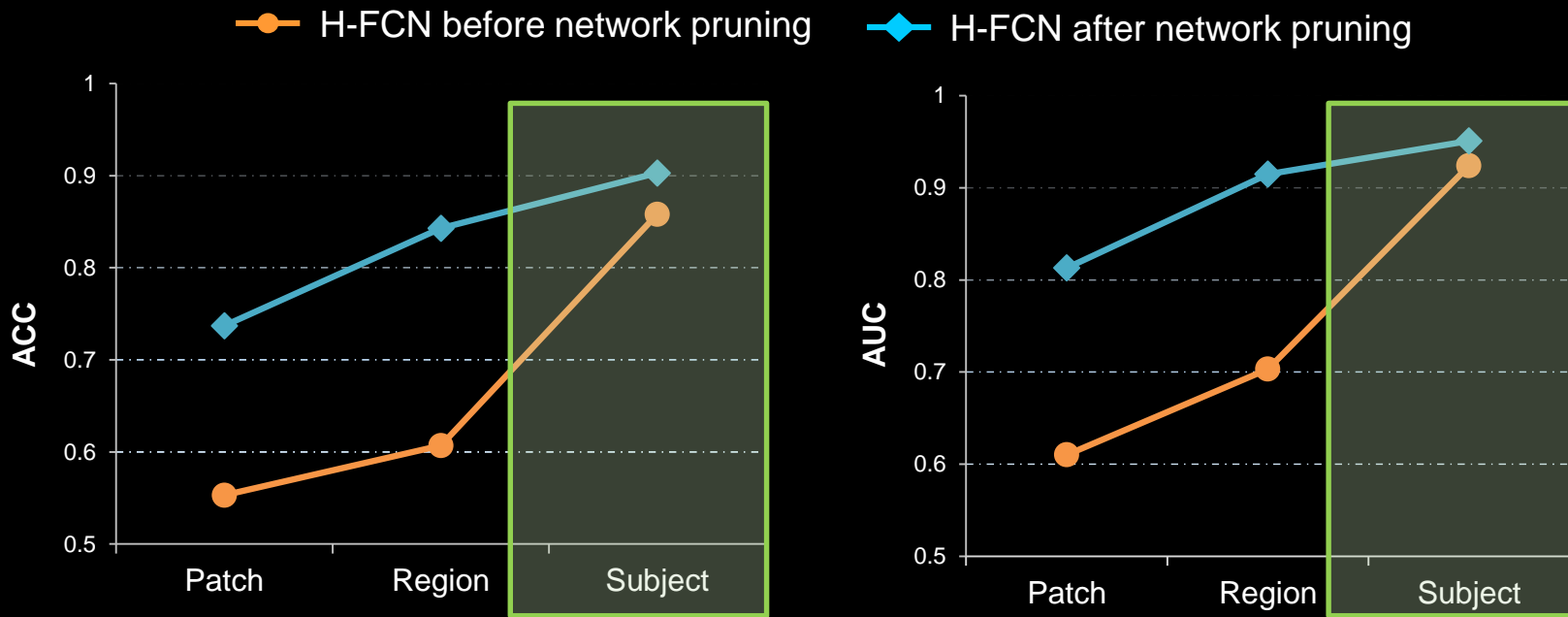
# Identified Region-level Discriminative Locations



C. Lian, M. Liu, J. Zhang, and D. Shen. *IEEE Trans. on Pattern Analysis and Machine Intelligence*, 2019.

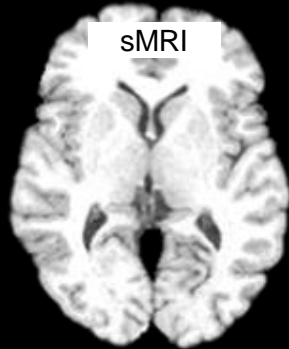
C. Lian, M. Liu\*, L. Wang, and D. Shen. *MICCAI 2019*.

# Classification Results



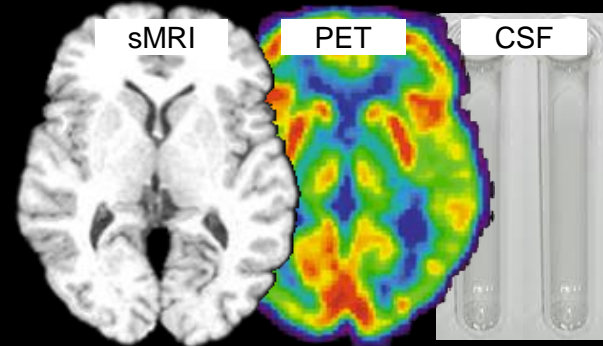
- 1) Global subject-level representation is more useful
- 2) Network pruning promotes the classification performance

# Outline



- Structural MRI (sMRI)

Single-modal Neuroimage



- Missing Data
- Multi-modal Data Fusion
- Domain Adaptation

Multi-modal Neuroimage



## Part II. Multi-modal Neuroimage Analysis

- Multi-modality Fusion for Disease Diagnosis
- Imaging Synthesis for Missing Modalities
- Domain Adaptation for Multi-site Data

# Multi-modality Fusion for Disease Diagnosis

- Hypergraph Learning with Missing Data

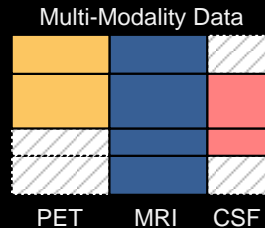
M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *MICCAI*, 2016.

M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *Medical Image Analysis*, 2017.

M. Liu, Y. Gao, P.-T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# Multi-View Data Grouping

- Given **3 modalities** (i.e., MRI, PET and CSF), **6 views** are constructed according to the availability of different modalities

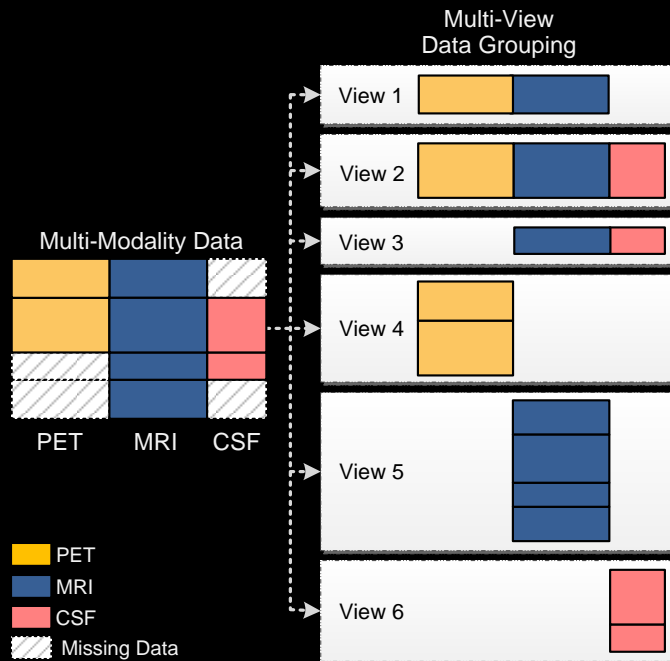


\* MICCAI Young Scientist Award Nomination, 2016

\* MICCAI Travel Award, 2016

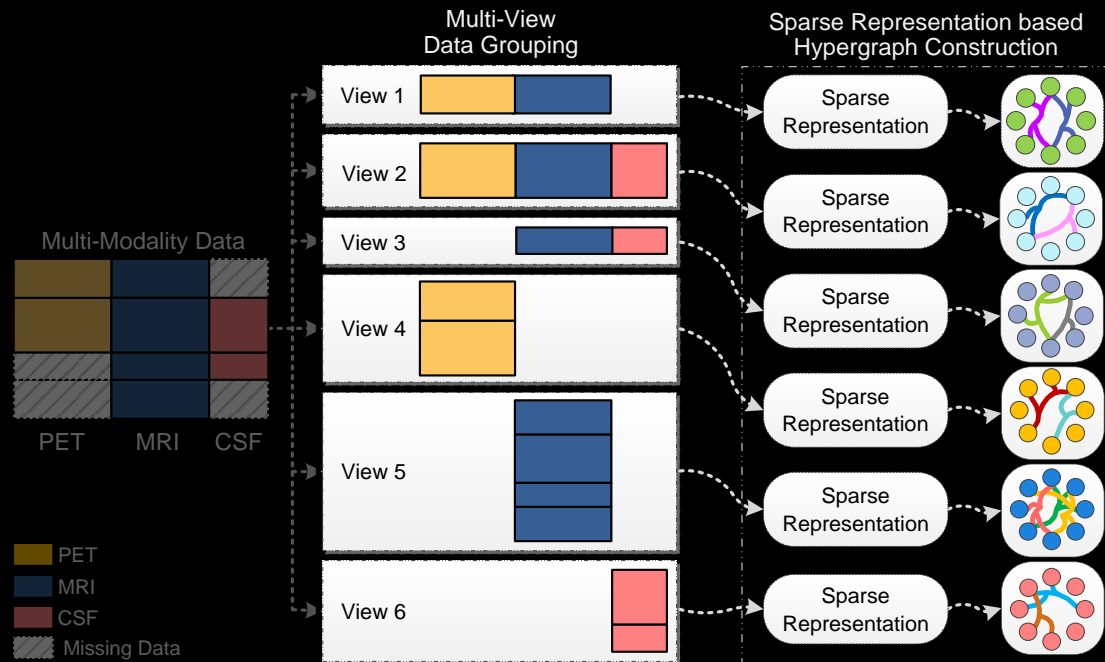
# Multi-View Data Grouping

- Given **3 modalities** (i.e., MRI, PET and CSF), **6 views** are constructed according to the availability of different modalities



# Hypergraph Construction

- Construct multiple hypergraphs, with each hypergraph corresponding to a specific view



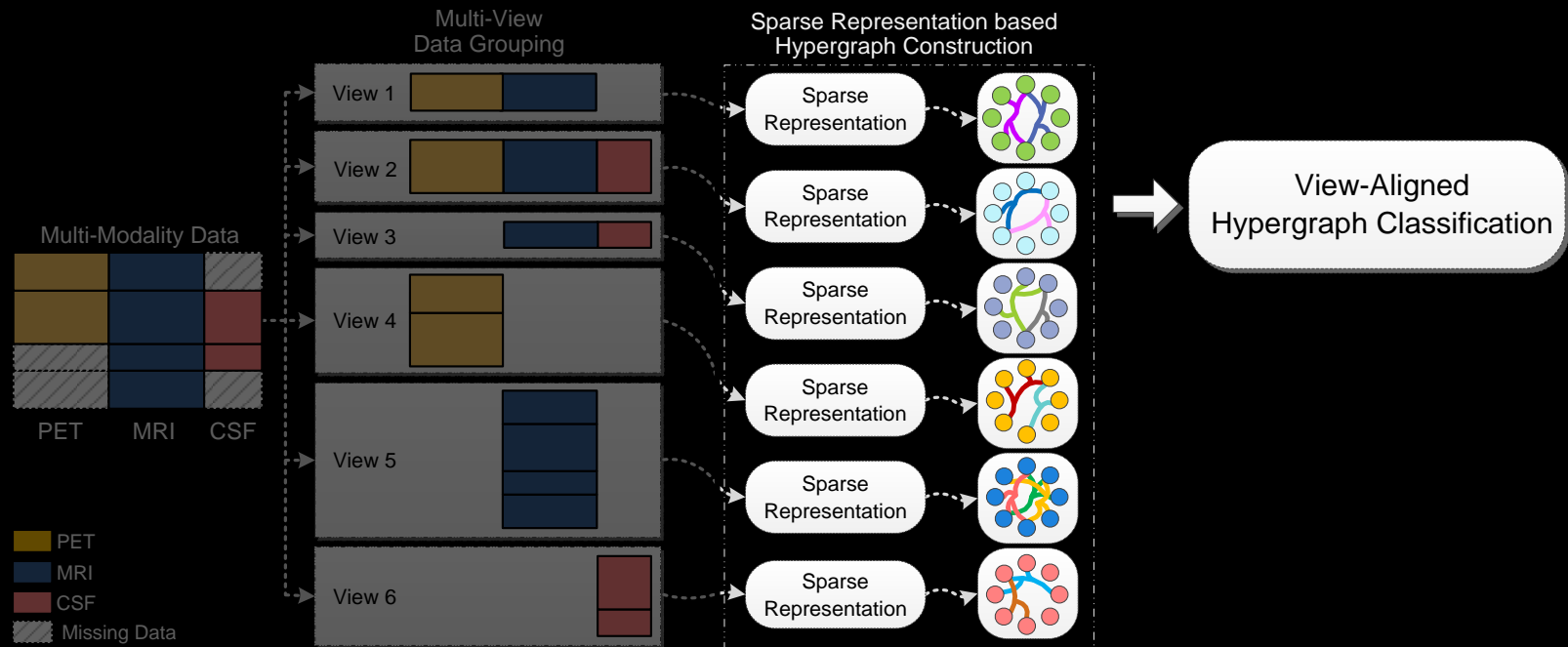
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M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *Medical Image Analysis*, 2017.

M. Liu, Y. Gao, P.-T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# View-Aligned Hypergraph Classification

- A **view-aligned hypergraph classification model** to capture the coherence among different views



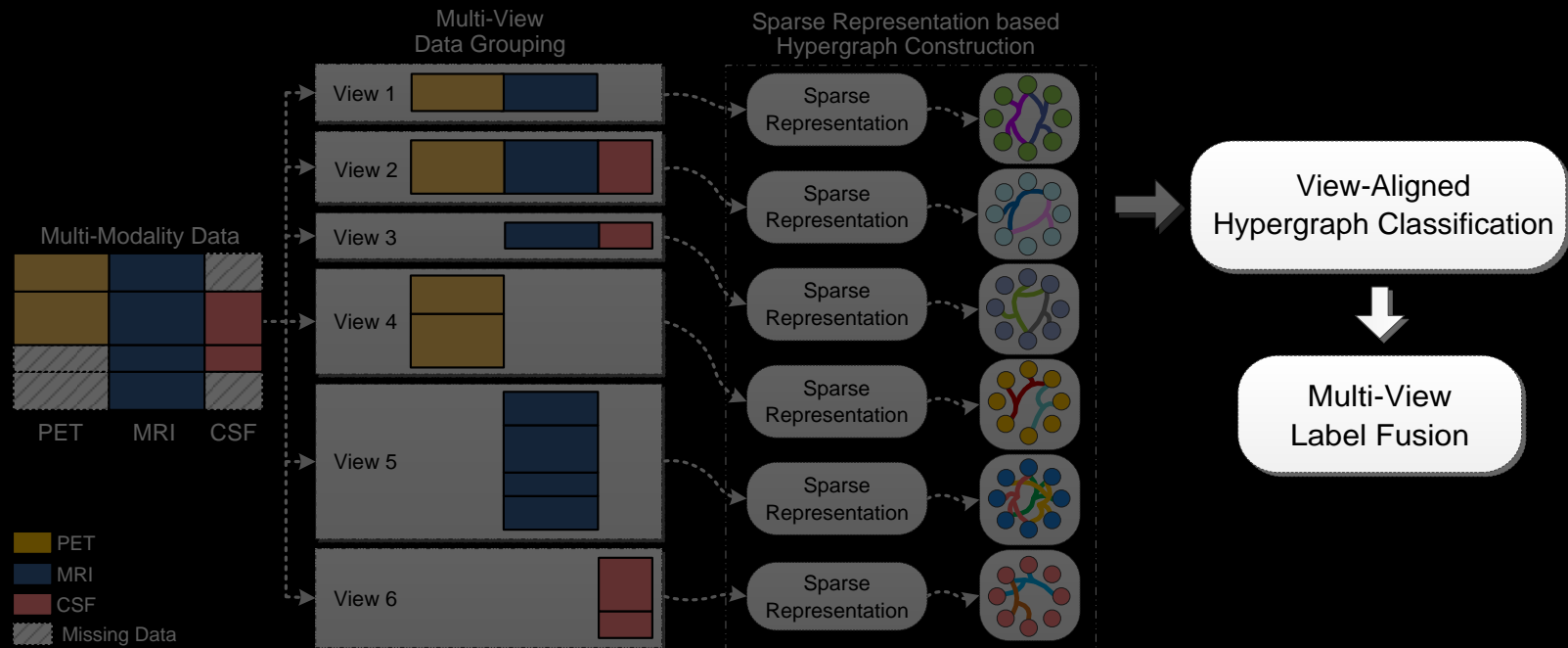
M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *MICCAI*, 2016.

M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *Medical Image Analysis*, 2017.

M. Liu, Y. Gao, P.-T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# Multi-view Label Fusion

- Multi-view label fusion strategy (weighted voting)



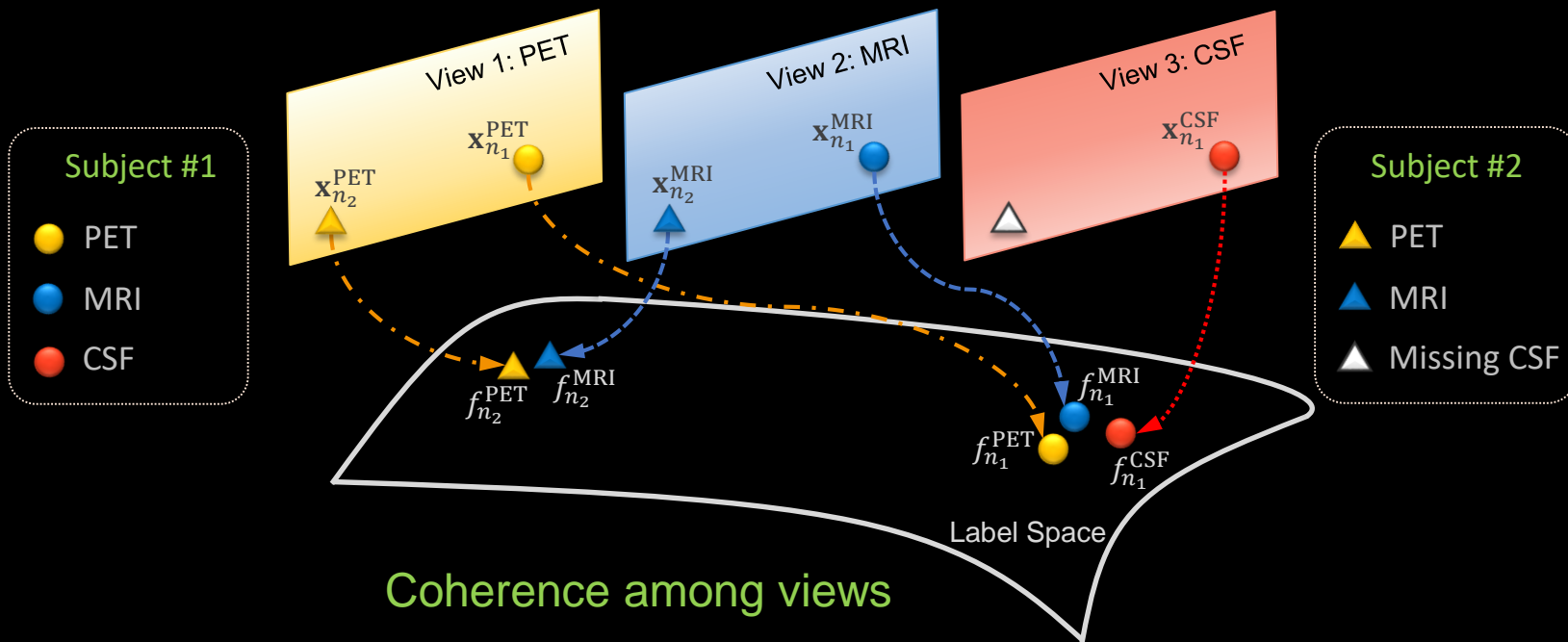
M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *MICCAI*, 2016.

M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *Medical Image Analysis*, 2017.

M. Liu, Y. Gao, P.-T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# View-Aligned Constraint

## View-Aligned Regularizer



M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *MICCAI*, 2016.

M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *Medical Image Analysis*, 2017.

M. Liu, Y. Gao, P.-T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# Step 3: View-Aligned Hypergraph Classification

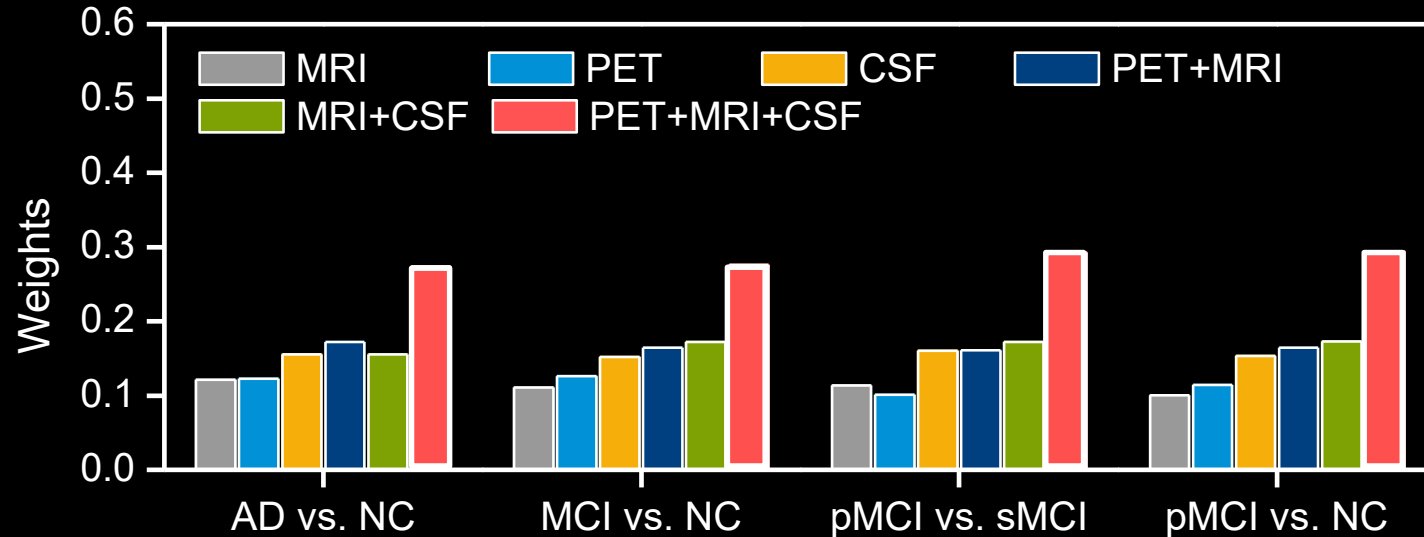
## Formulation of view-aligned hypergraph classification (VAHC)

$$\begin{aligned} \min_{\mathbf{F}, \alpha, \{\mathbf{W}^m\}_{m=1}^M} & \sum_{m=1}^M \|\Omega^m (\mathbf{f}^m - \mathbf{y})\|_2^2 + \sum_{m=1}^M (\alpha^m)^2 (\mathbf{f}^m)^T \mathbf{L}^m \mathbf{f}^m \\ & + \mu \sum_{n=1}^N \sum_{m=1}^M \sum_{p=1}^M \Omega_{n,n}^m \Omega_{n,n}^p (f_n^m - f_n^p)^2 \\ & + \lambda \sum_{m=1}^M \|\mathbf{W}^m\|_F^2 \\ \text{s. t.} & \sum_{m=1}^M \alpha^m = 1, \quad \forall \alpha^m \geq 0; \\ & \sum_{i=1}^{N_e^m} W_{i,i}^m = 1, \quad \forall W_{i,i}^m \geq 0. \end{aligned}$$

View-aligned Regularizer

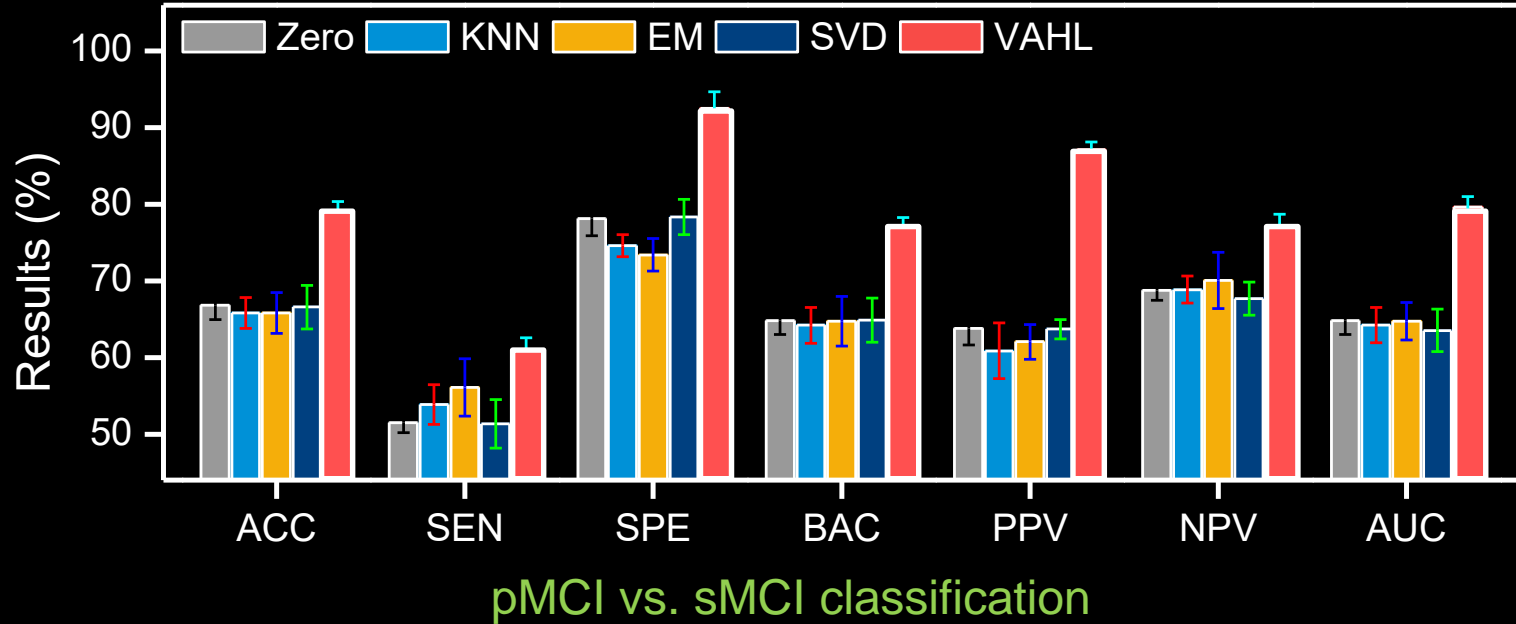
Hypergraph Laplacian matrix  $\mathbf{L} = \mathbf{I} - \Theta$ , and  $\Theta = \mathbf{D}_v^{-\frac{1}{2}} \mathbf{H} \mathbf{W} \mathbf{D}_e^{-1} \mathbf{H}^T \mathbf{D}_v^{\frac{1}{2}}$ .

# Learned Weights for Views



Using all 3 modalities (MRI+PET+CSF) achieves the best results

# Experimental Results



M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *MICCAI*, 2016.

M. Liu, J. Zhang, P.-T. Yap, and D. Shen. *Medical Image Analysis*, 2017.

M. Liu, Y. Gao, P.-T. Yap, and D. Shen. *IEEE Journal of Biomedical and Health Informatics*, 2018.

# Imaging Synthesis for Missing Modalities

- Deep Learning based Automatic PET Synthesis from sMRI

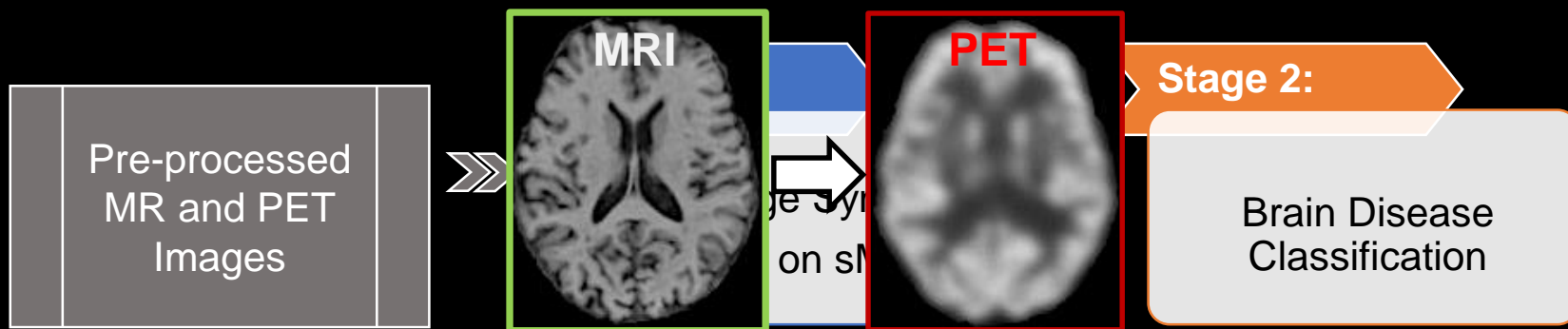
Y. Pan, M. Liu\*, C. Lian, Y. Xia, and D. Shen. *MICCAI*, 2019.

Y. Pan, M. Liu, C. Lian, T. Zhou, Y. Xia, and D. Shen. *MICCAI*, 2018.

Y. Pan, M. Liu\*, C. Lian, L. Yue, S. Xiao, Y. Xia and D. Shen. *ISMRM*, 2019

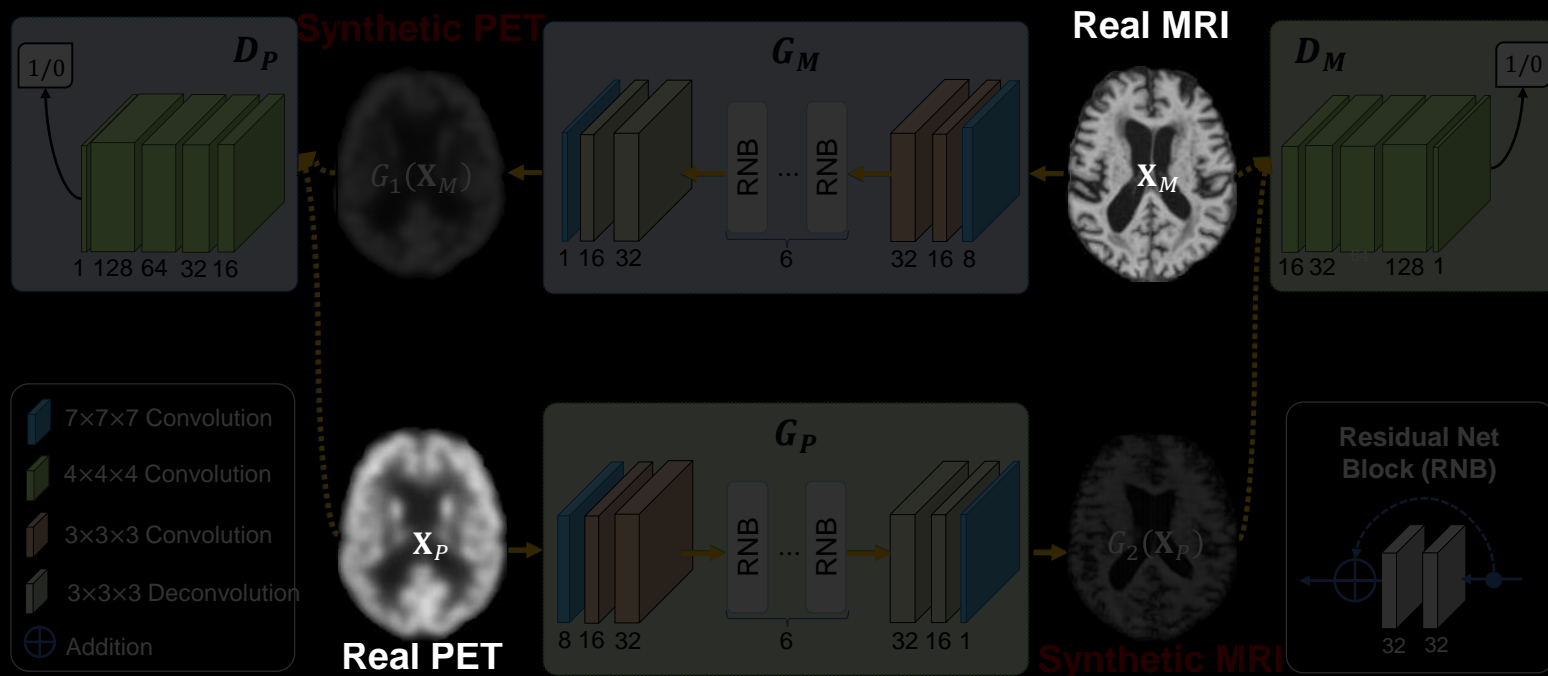
# Hybrid Cycle-GAN for Missing PET Synthesis

- Among 800+ subjects in ADNI, all subjects have sMRI, while only half of them have FDG-PET scans.



Synthesizing Missing PET based on MRI for Brain Disease Diagnosis

# Hybrid Cycle-GAN for Missing PET Synthesis

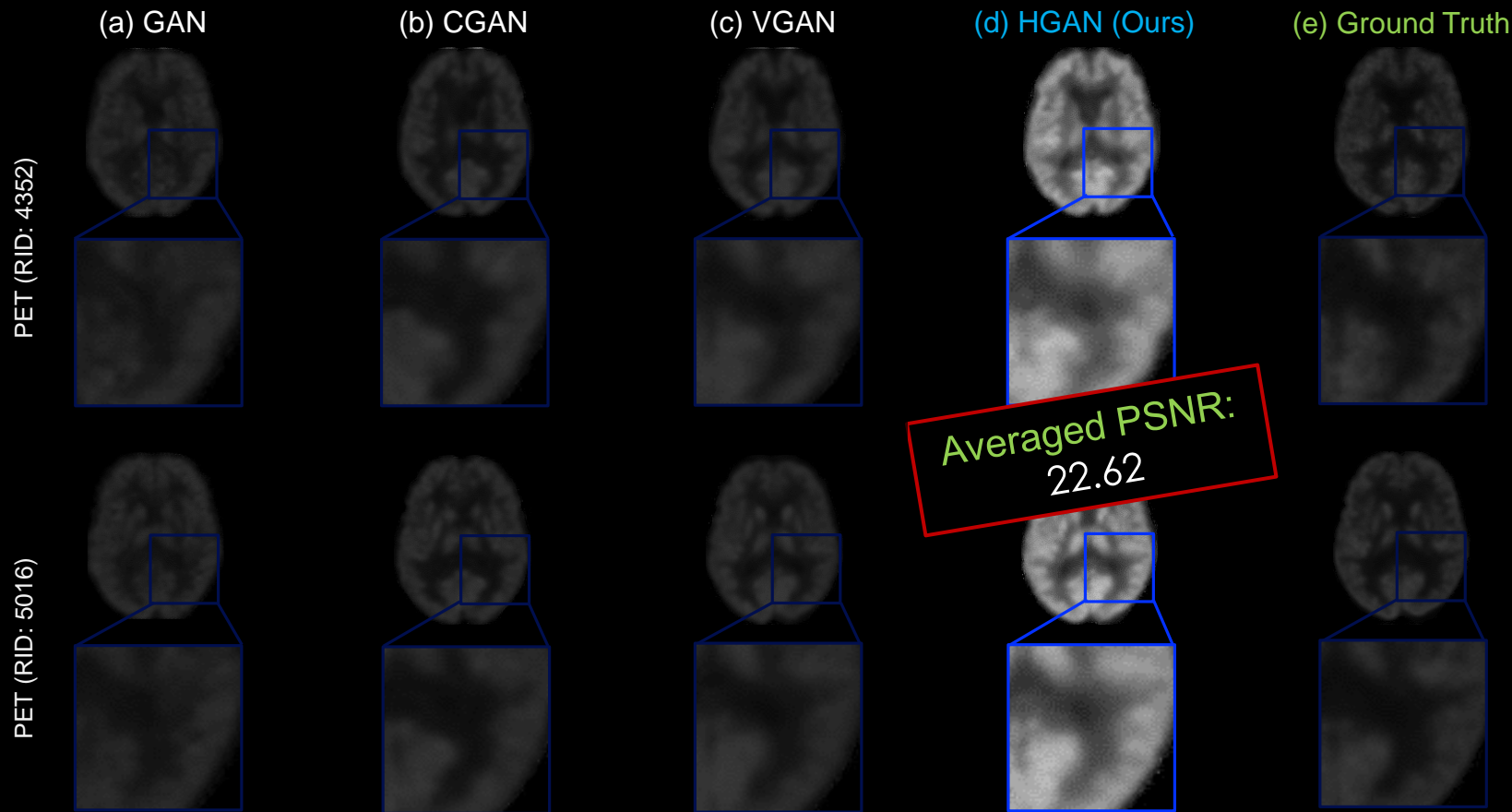


Hybrid cycle-consistent generative adversarial network (**HGAN**) to impute missing PET scans based on sMRI

Y. Pan, M. Liu, C. Lian, T. Zhou, Y. Xia, and D. Shen. *MICCAI, 2018*

Y. Pan, M. Liu\*, C. Lian, L. Yue, S. Xiao, Y. Xia and D. Shen. *ISMRM, 2019*

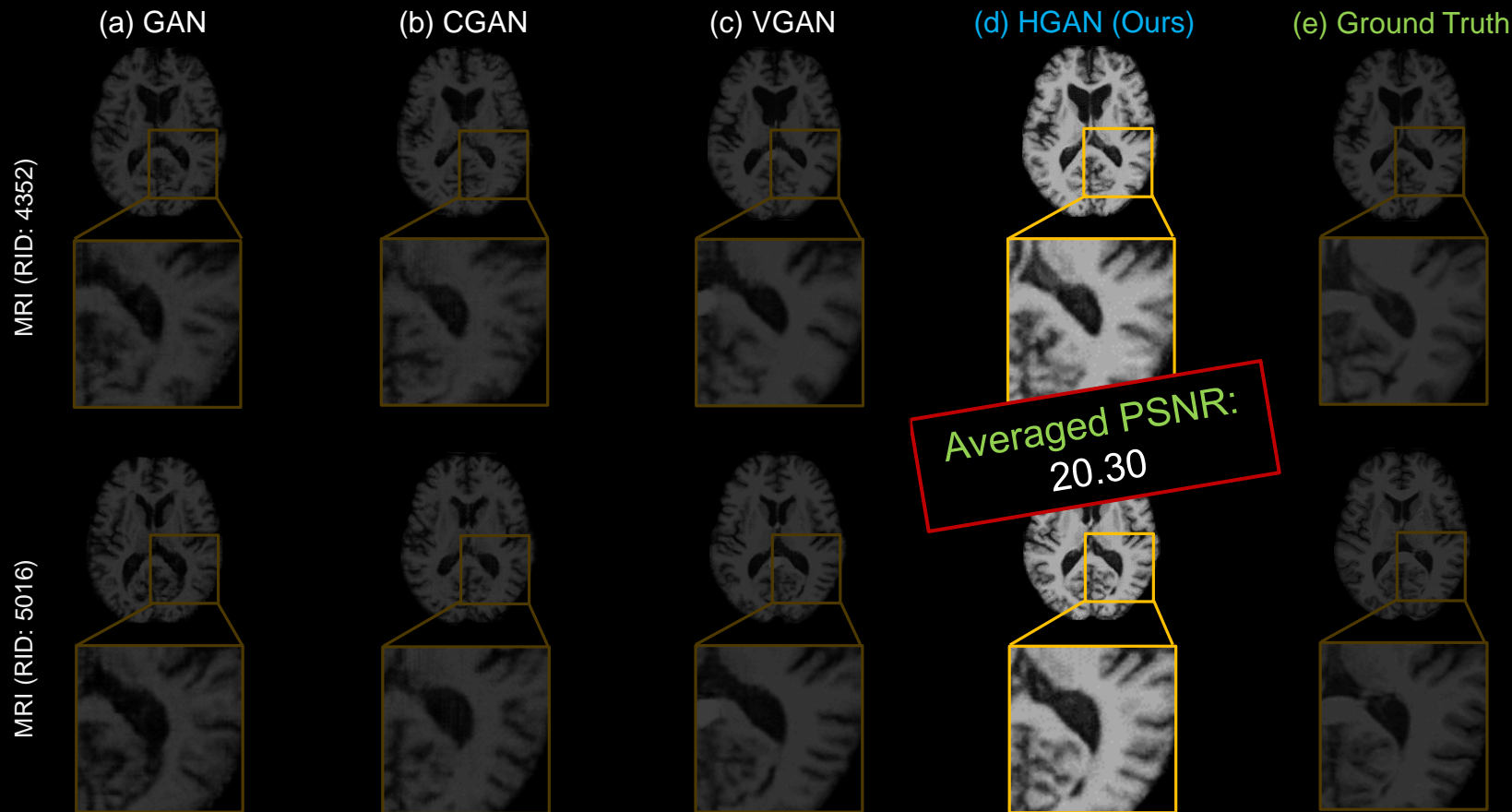
# Synthetic PET Images



Y. Pan, M. Liu, C. Lian, T. Zhou, Y. Xia, and D. Shen. *MICCAI*, 2018

Y. Pan, M. Liu\*, C. Lian, L. Yue, S. Xiao, Y. Xia and D. Shen. *ISMRM*, 2019

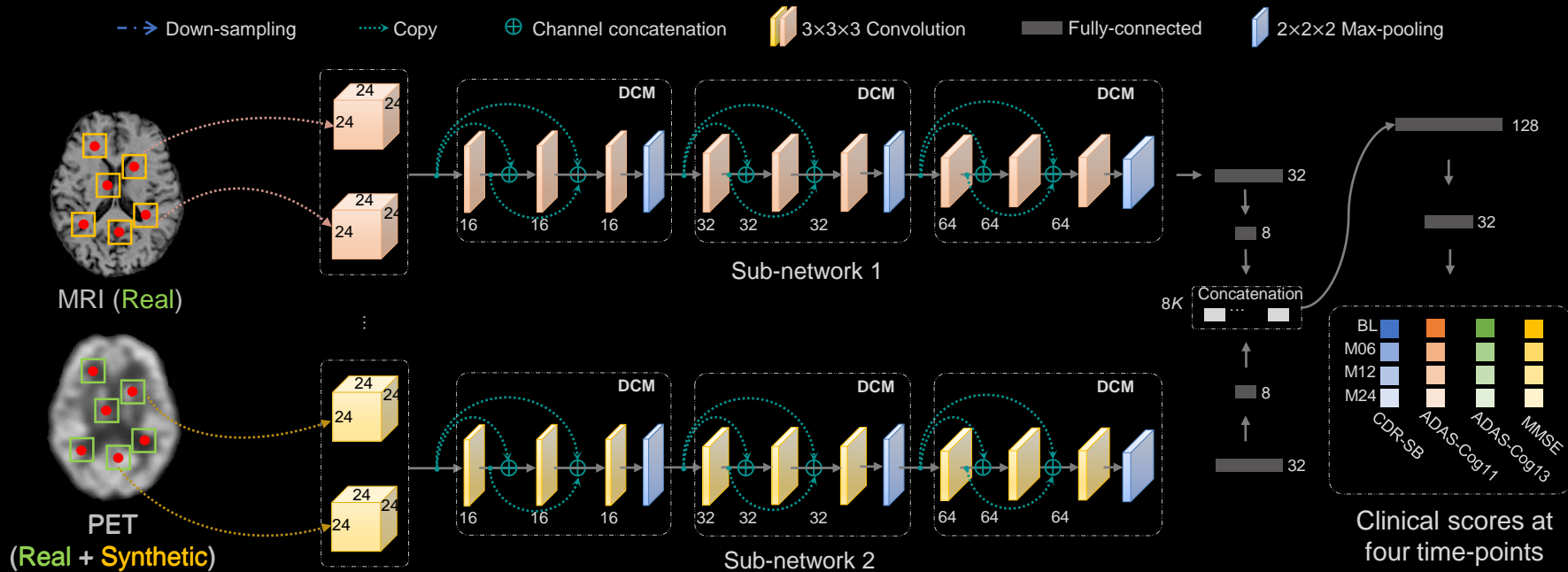
# Synthetic MRI Scans



Y. Pan, M. Liu, C. Lian, T. Zhou, Y. Xia, and D. Shen. *MICCAI*, 2018

Y. Pan, M. Liu\*, C. Lian, L. Yue, S. Xiao, Y. Xia and D. Shen. *ISMRM*, 2019

# Hybrid Cycle-GAN for Missing PET Synthesis

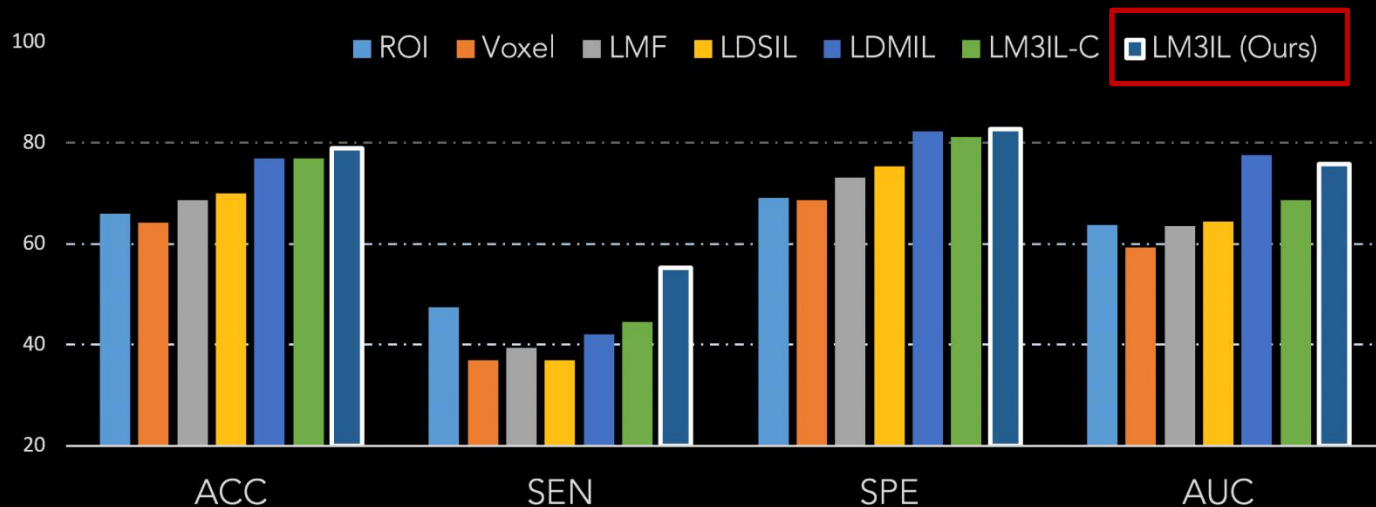


Landmark-based Deep Network for Brain Disease Classification using **MRI and PET (Real+Synthetic)**

Y. Pan, M. Liu, C. Lian, T. Zhou, Y. Xia, and D. Shen. *MICCAI, 2018*

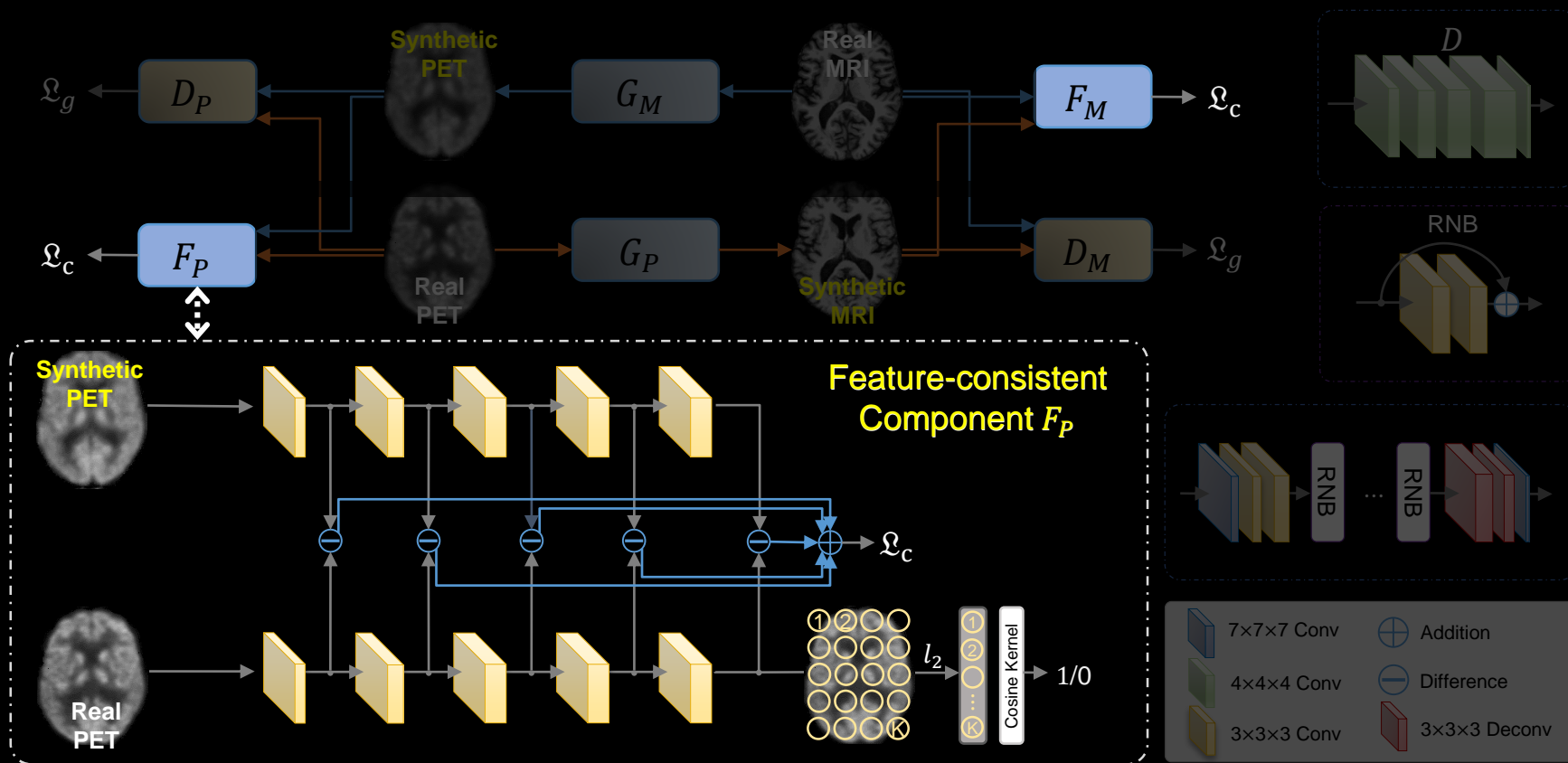
Y. Pan, M. Liu\*, C. Lian, L. Yue, S. Xiao, Y. Xia and D. Shen. *ISMRM, 2019*

# Hybrid Cycle-GAN for Missing PET Synthesis

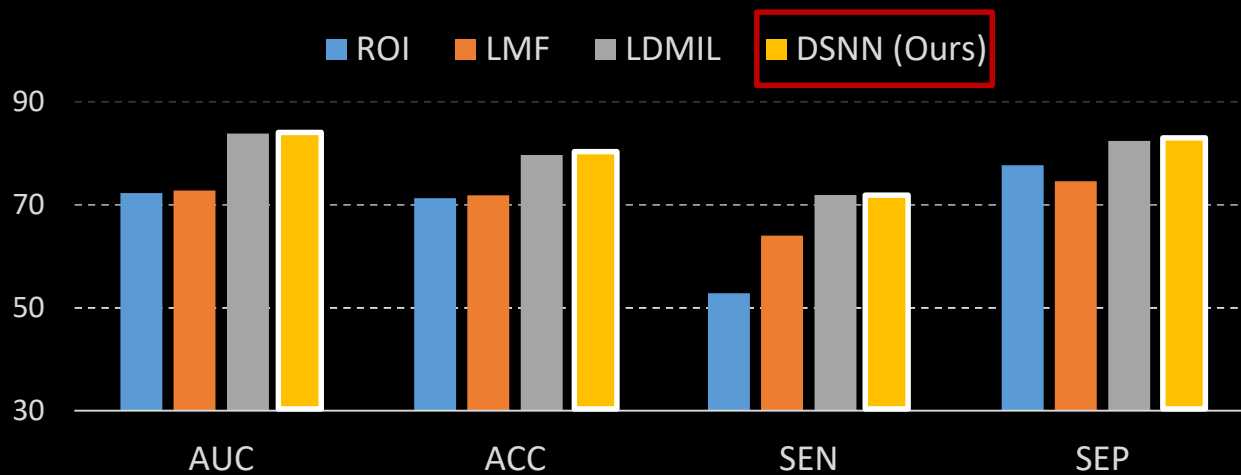


MCI conversion prediction with complete MRI  
and complete (after imputation) PET

# Feature-consistent GAN for Joint PET Synthesis and Classification



# Feature-consistent GAN for Joint PET Synthesis and Classification



MCI conversion prediction with complete MRI  
and complete (after imputation) PET

Generating task-oriented PET scans helps boost performance

# Domain Adaptation for Multi-site Data

- Low-rank Representation for Multi-site Data Adaptation

# Low-rank Representation for Domain Adaptation

ABIDE: 17 imaging sites with resting-state fMRI data

DEMOGRAPHIC INFORMATION OF THE STUDIED SUBJECTS FROM FIVE IMAGING SITES IN THE ABIDE DATABASE. THE VALUES ARE DENOTED AS MEAN±STANDARD DEVIATION. M/F: MALE/FEMALE.

Site	ASD		NC	
	Age	M/F	Age	M/F
Caltech	20.43 ± 8.19	7/2	15.33 ± 5.88	10/2
CMU	14.40 ± 0.00	—	—	—
KKI	16.34 ± 8.34	10/2	15.33 ± 5.88	23/2
NYU	17.59 ± 7.84	66/5	16.49 ± 7.68	79/14
MaxMun	19.33 ± 7.21	13/4	17.96 ± 7.21	—
Leuven	13.40 ± 0.00	21/4	—	—
OHSU	14.40 ± 0.00	—	—	—
Olin	15.39 ± 7.00	1/0	13.44 ± 4.07	1/0
Pitt	19.99 ± 9.77	10/4	17.35 ± 6.95	10/4
SBL	15.84 ± 3.52	1/2	13.44 ± 4.07	5/0
SDSU	15.42 ± 6.75	9/0	18.35 ± 9.02	15/3
Stanford	15.74 ± 6.11	1/7	20.22 ± 8.11	1/7
Trinity	21.00 ± 7.00	—	22.94 ± 8.11	—/0
UCLA	16.27 ± 6.11	—/7	14.61 ± 4.07	—/7
UM	17.05 ± 6.11	—/9	17.35 ± 6.95	—/9
USM	15.77 ± 7.21	30/8	17.34 ± 9.53	21/1
Yale	18.10 ± 7.18	19/2	19.33 ± 9.36	20/6

Scanners

Image Contrast

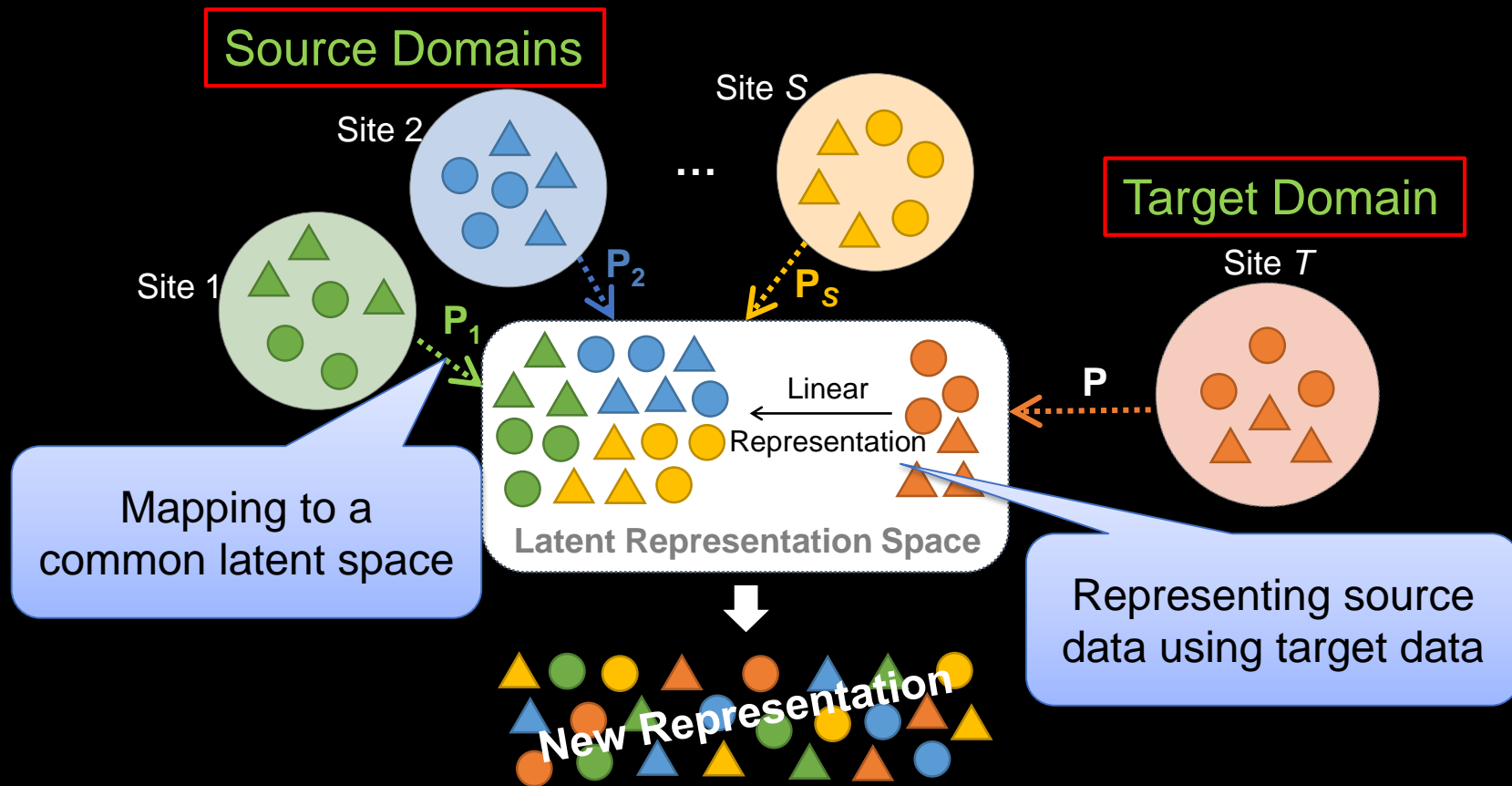
Scanning Parameters

Different Data Distributions

Noise Level

Population

# Low-rank Representation for Domain Adaptation



# Low-rank Representation for Domain Adaptation

Formulation of multi-center low-rank representation (maLRR)

$$\min_{\mathbf{J}, \mathbf{P}, \mathbf{P}_i, \mathbf{Z}_i, \mathbf{E}_{S_i}, \mathbf{E}_{P_i}, \mathbf{F}_i} \|\mathbf{J}\|_* + \sum_{i=1}^K \left( \|\mathbf{F}_i\|_* + \alpha \|\mathbf{E}_{S_i}\|_1 + \beta \|\mathbf{E}_{P_i}\|_1 \right)$$

$$\text{s. t. } \mathbf{P}_i \mathbf{X}_{S_i} = \mathbf{P} \mathbf{X}_T \mathbf{Z}_i + \mathbf{E}_{S_i},$$

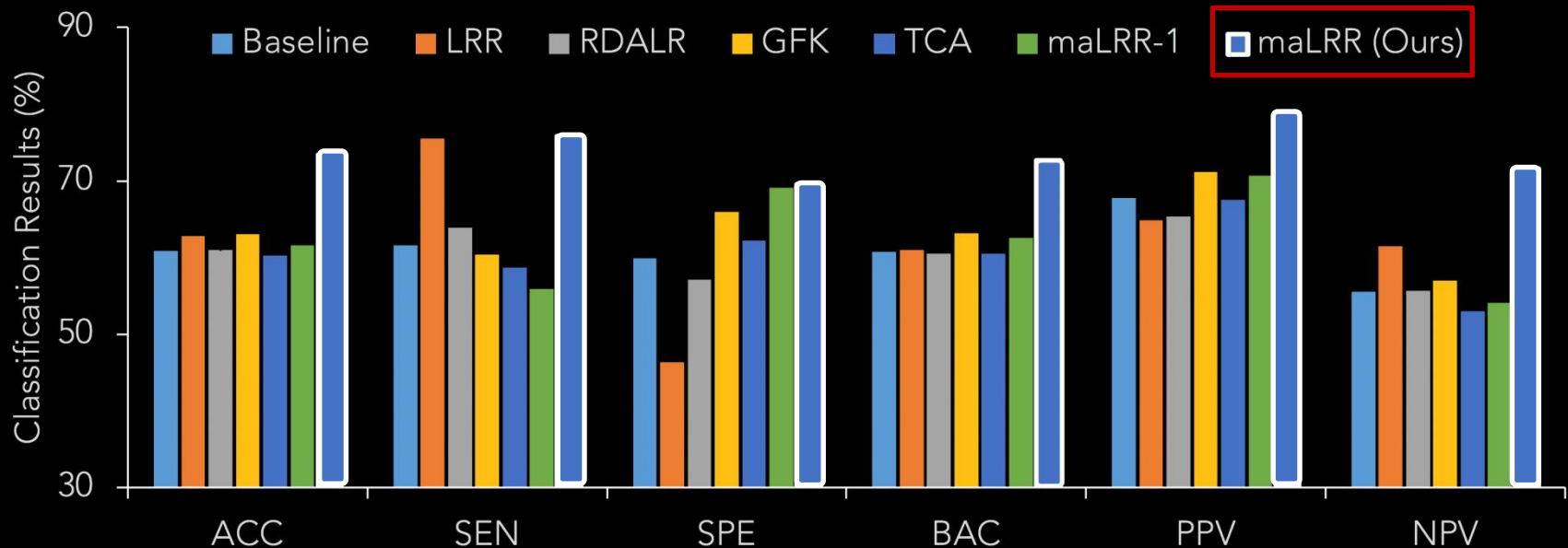
$$\mathbf{P}_i = \mathbf{P} + \mathbf{E}_{P_i}, i = 1, \dots, K$$

$$\mathbf{P} = \mathbf{J}, \mathbf{Z}_i = \mathbf{F}_i, \mathbf{P} \mathbf{P}^T = \mathbf{I}$$

- 1) Mapping to a latent space
- 2) Representing source data using target data

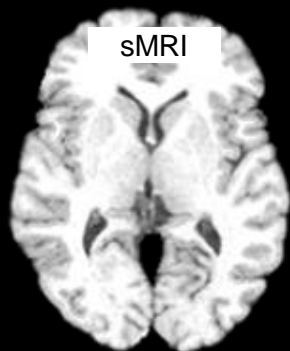
# Low-rank Representation for Domain Adaptation

**ABIDE: 5 imaging sites** with resting-state fMRI data



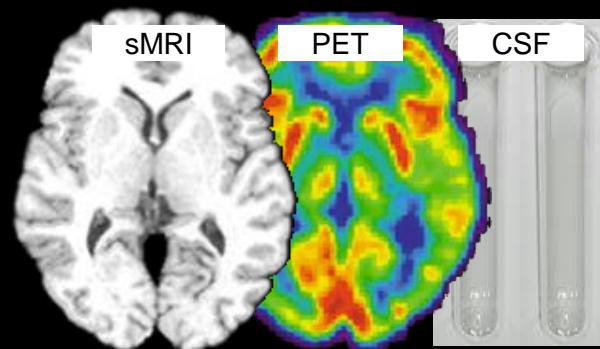
Performance of different methods in the task of **Autism vs. NC** classification, with **NYU** as the target domain and the other **four sites** as the source domains

# Outline



- Structural MRI (sMRI)

Single-modal Neuroimage



- Missing Data
- Multi-modal Data Fusion
- Domain Adaptation

Multi-modal Neuroimage

# Acknowledge

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# Thanks for Your Attention!

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