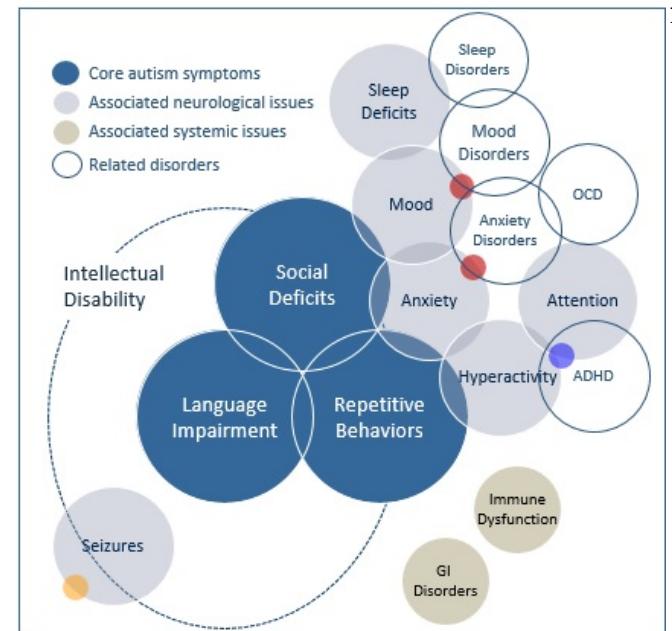


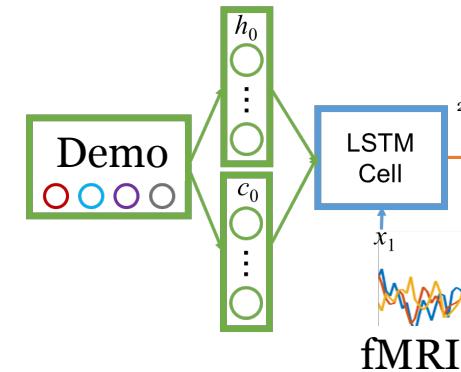
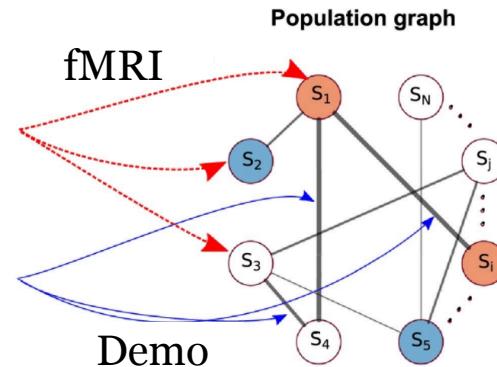
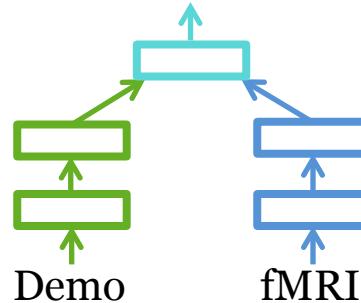
The Challenge of Learning from fMRI of Heterogeneous Psychiatric Disorders

- fMRI used to characterize pathophysiology of psychiatric disorders, e.g. autism spectrum disorder (ASD)
- ASD is extremely heterogeneous
- Early studies impose homogeneity
 - Restrict gender, age, etc.
 - Smaller datasets
 - Poor generalization of results
- Recent large open datasets (ABIDE)
 - Highly heterogeneous
 - Poor classification accuracy of ASD/Control



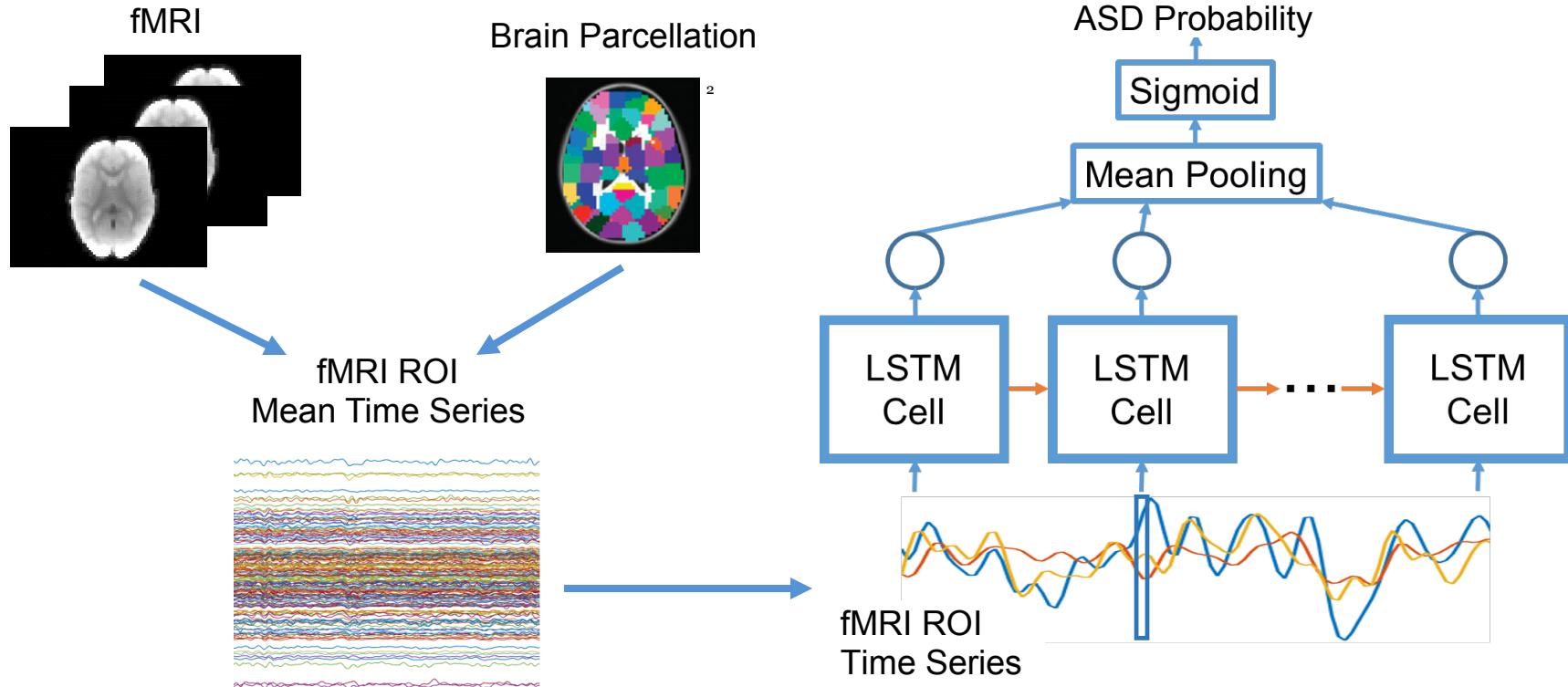
Include Demographic Information to Mitigate Heterogeneity Problem

- Non-imaging, scalar variables easy to obtain: Age, sex, IQ, ...
- Many ways to incorporate demographic variables

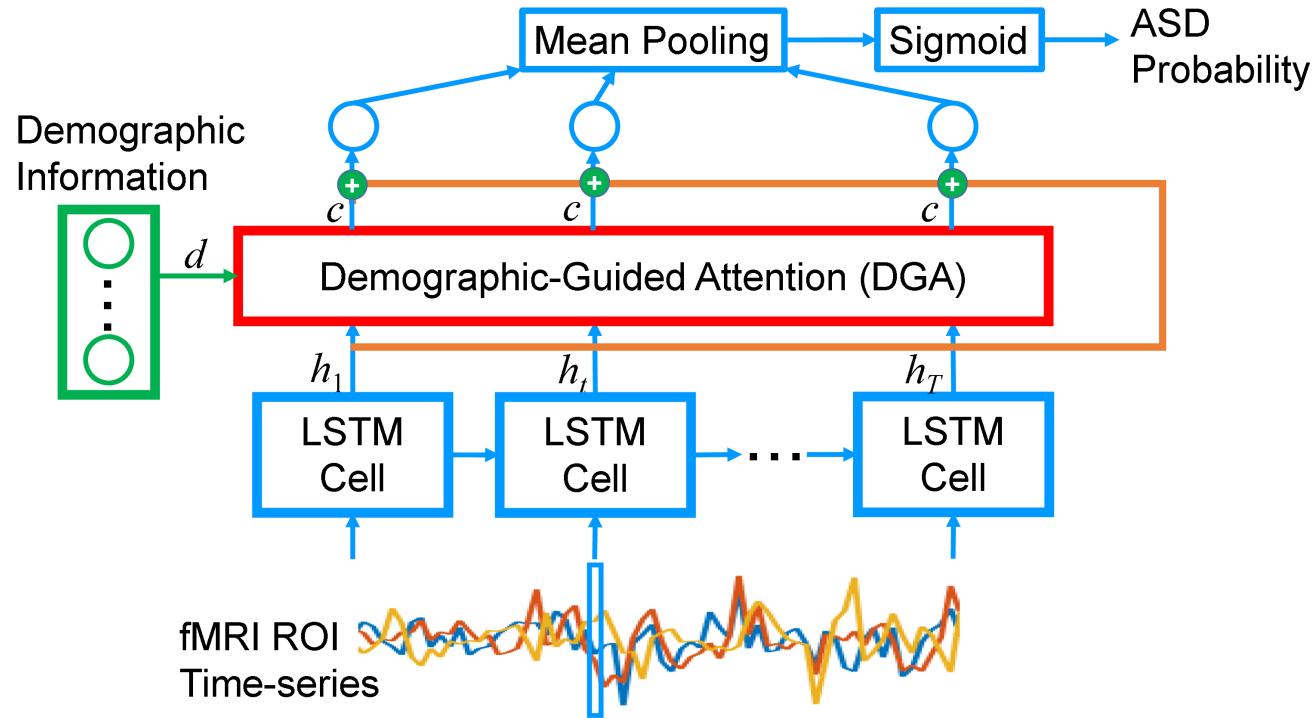


- No approach aims to modulate differences in neurological mechanisms
- We model heterogeneous functional network patterns using a demographic guided attention + RNN model for fMRI

Baseline LSTM Network for fMRI Time-series Data¹



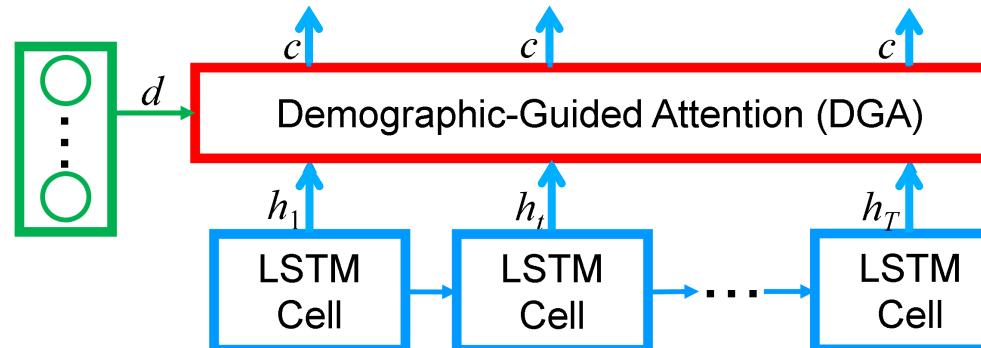
Proposed Demographic-Guided Attention Network



Generalized Attention Mechanism Based on Demographic and fMRI Information

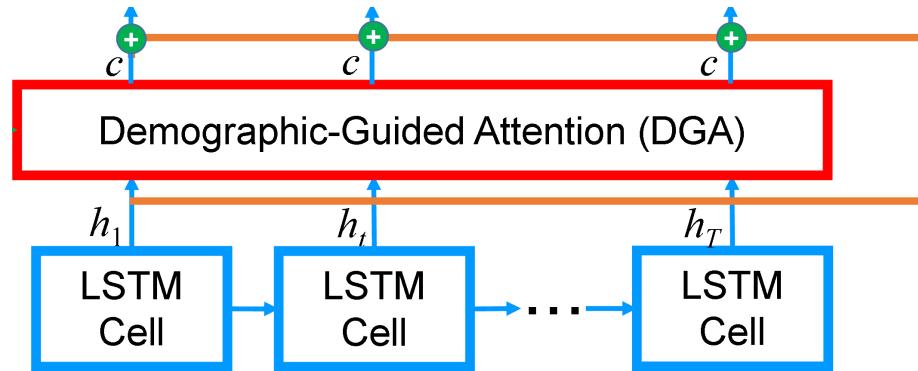
- Query: Demographic information d
- Key and value: LSTM output h_t
- Scaled dot product attention computes context c :

$$c = \text{att}(d, \{h_t\}) = \sum_{t=1}^T \text{softmax} \left[\underbrace{(W_q d)^T}_{\text{Query}} \underbrace{(W_k h_t)}_{\text{Key}} / \sqrt{m} \right] \underbrace{W_v h_t}_{\text{Value}}$$



Model Neurological Heterogeneity with Residual Connection between LSTM and Attention Outputs

- Use context to bias LSTM output
→ Change focus on LSTM nodes based on demographic information



- For multiple attention heads:
 - Process each head k output $c_k + h_t$ with separate FC layer
 - Take maximum score

Model Greater Neurological Heterogeneity with Multiple Attention Heads and Query Diversity Loss

- Single head: same demographics → same neuropathophysiology
- Multiple heads to model greater heterogeneity
- *Query Diversity Loss*: encourage K different attention heads to capture different underlying neuropathological modes:

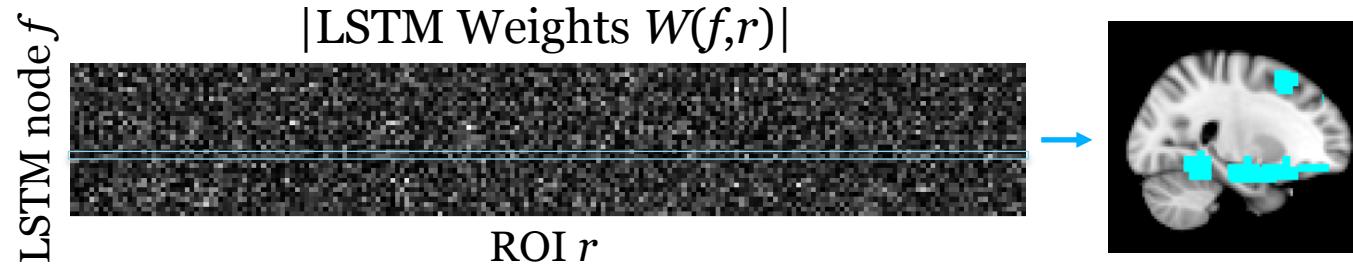
$$L_{QD} = \sum_{i=1}^N \sum_{j=1}^{K-1} \sum_{k=j+1}^K \left| \frac{q_{ij}^T q_{ik}}{\|q_{ij}\| \|q_{ik}\|} \right| \quad \begin{aligned} q_{ij} &= W_{q_j} d_i \\ &= \text{Query vector for subject } i, \\ &\quad \text{attention mode } j \end{aligned}$$

Cosine proximity

- Total loss: $L = L_C + \lambda L_{QD}$
- \swarrow Binary cross-entropy \searrow 0.5 in experiments

Interpretation of Demographic-Guided Attention as Neuropathological Heterogeneity

- LSTM node f : represents functional network
 - Assign membership by large LSTM weights of ROI inputs¹



- LSTM output $h(f)$: signal for functional network f
- Demographic information provides context for deciding which functional networks are important for ASD classification
 - $c(f)$: demographic-guided attention to functional network f
 - Observe correlation between $d(i)$ and $c(f)$ across subjects

Datasets and Preprocessing

- Resting-state fMRI from multisite ABIDE I Dataset
- 3 Datasets from 3 prior publications
 - DS1¹: N = 1100, CCS Pipeline, CC200 atlas
 - DS2²: N = 1035, CPAC Pipeline, CC200 atlas
 - DS3³: N = 860, CPAC Pipeline, HO atlas
- Standardize ROI mean time-series, resample at 2s interval
- Training: augment x10 by randomly cropping 3 min windows
- Inference: predict using all 3 min windows
- Demographic data: gender, age, handedness, full IQ, verbal IQ, performance IQ, eye status
 - Standardized to [-1,1]

Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

Published results

Orig[†] [9]

LSTM [5]

DFuse [7]

DInit [6]

DGA1-C

DGA2-C

DGA1

DGA2

DGA2-QDL

DS1

Identifying Autism from Resting-State fMRI
Using Long Short-Term Memory Networks

Nicha C. Dvornek¹(✉), Pamela Ventola², Kevin A. Pelphrey³,
and James S. Duncan^{1,4,5}

DS2

Identification of autism spectrum disorder using deep learning and the ABIDE dataset

Anibal Sólón Heinsfeld ^a, Alexandre Rosa Franco ^{b, c, d}, R. Cameron Craddock ^{f, g}, Augusto Buchweitz ^{b, d, e}, Felipe Meneguzzi ^{a, b}(✉)

DS3

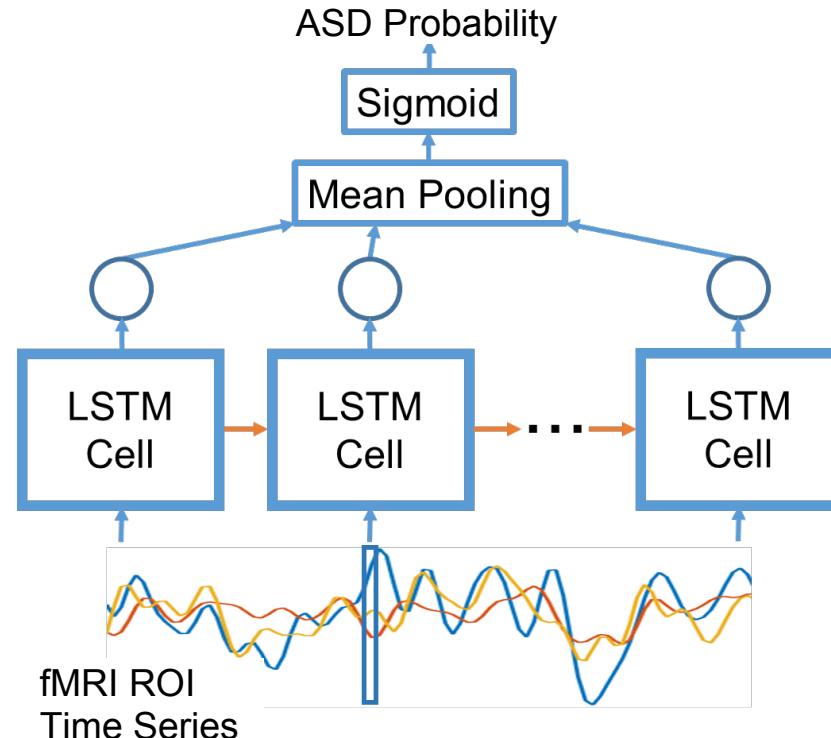
Deriving reproducible biomarkers from multi-site resting-state data: An Autism-based example

Alexandre Abraham ^{a, b}(✉), Michael P. Milham ^{e, f}, Adriana Di Martino ^g, R. Cameron Craddock ^{e, f}, Dimitris Samaras ^{c, d}, Bertrand Thirion ^{a, b}, Gael Varoquaux ^{a, b}

Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

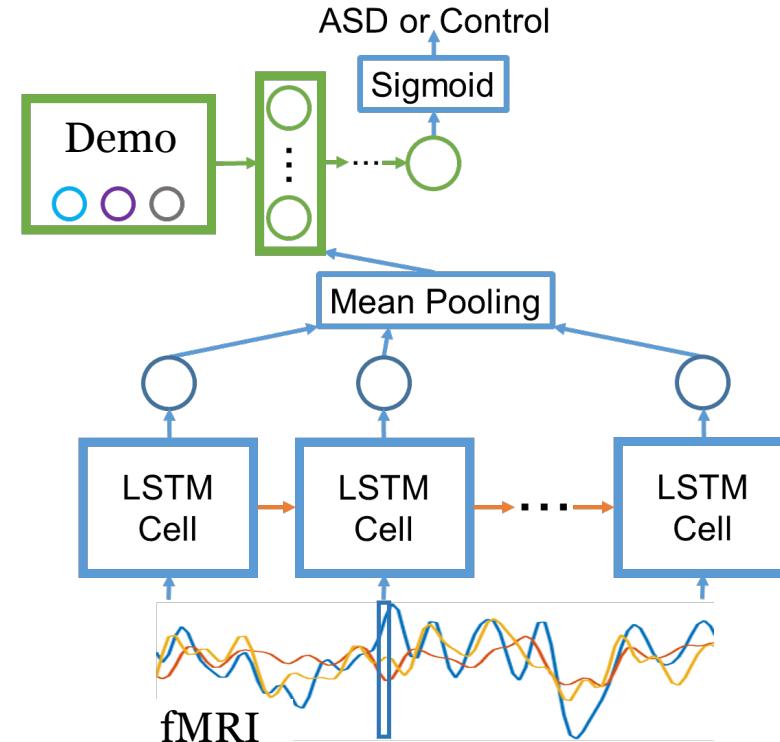
Baseline LSTM – no demographic information¹



Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

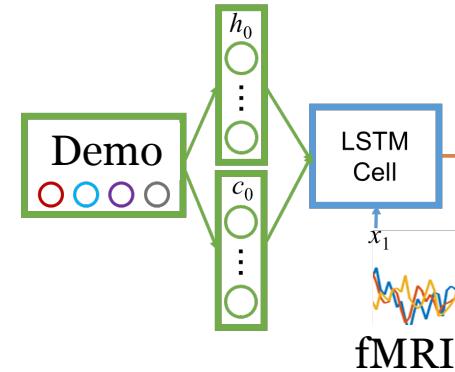
LSTM + late fusion
of demographic
information¹



Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

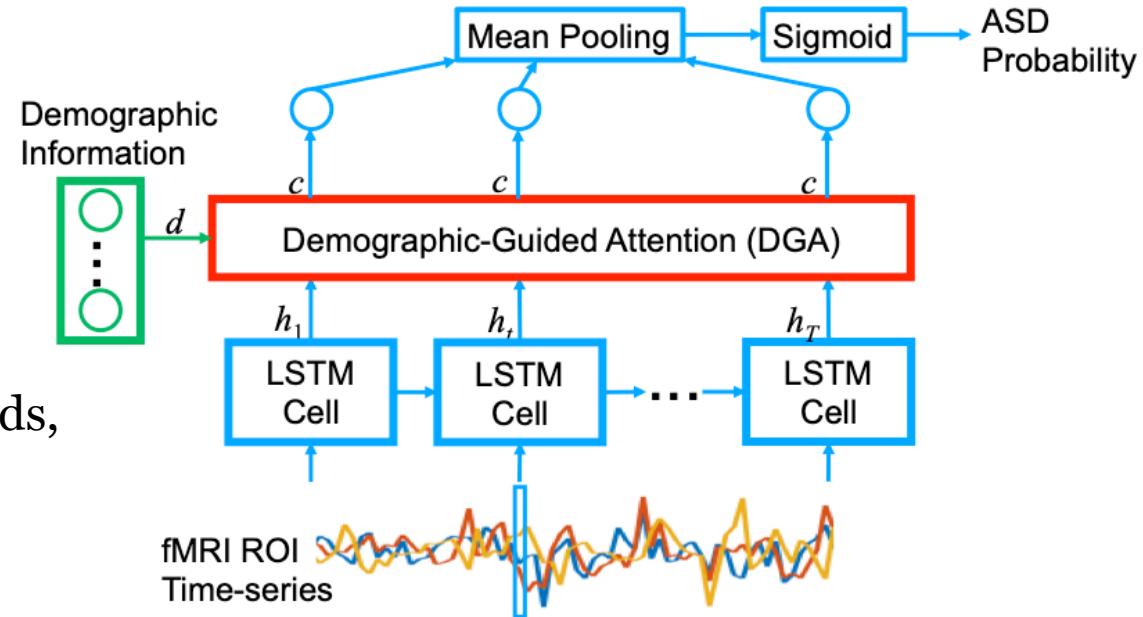
LSTM + state
initialization via
demographic
information¹



Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

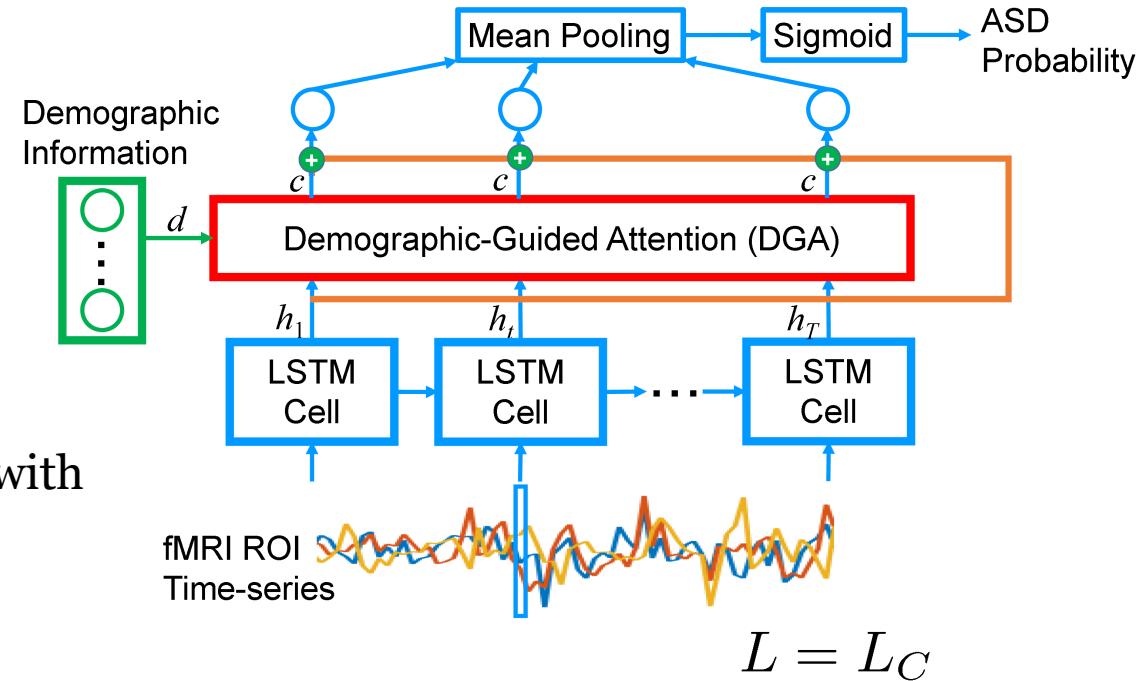
LSTM + DGA
with 1 or 2 heads,
context alone
(no residual
connection)



Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

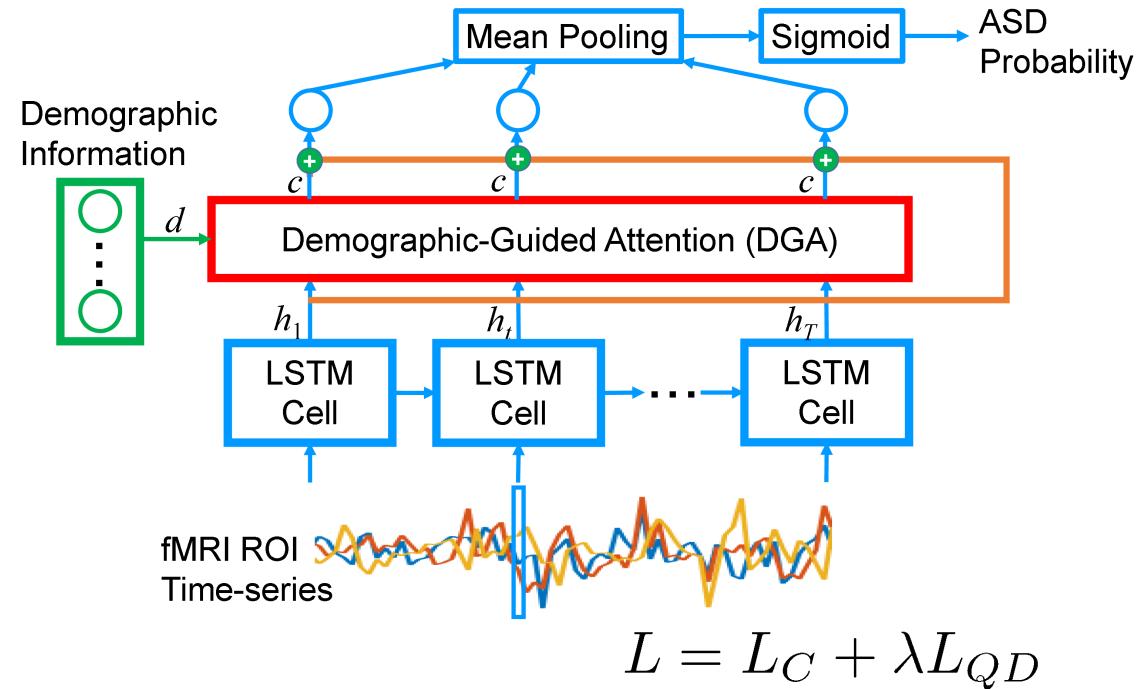
LSTM + DGA with
1 or 2 heads
(with residual
connection)



Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

Full model



Classification of ASD vs. Healthy Control: Methods Compared

Model
Orig [†] [9]
LSTM [5]
DFuse [7]
DInit [6]
DGA1-C
DGA2-C
DGA1
DGA2
DGA2-QDL

Evaluation of implemented models

- Leave-one-site-out (LOSO) cross-validation (CV), repeated 5 times
- Averaged performance measures for each site across CV runs
- Paired two-tailed t-tests to compare models

DS2 Classification Results

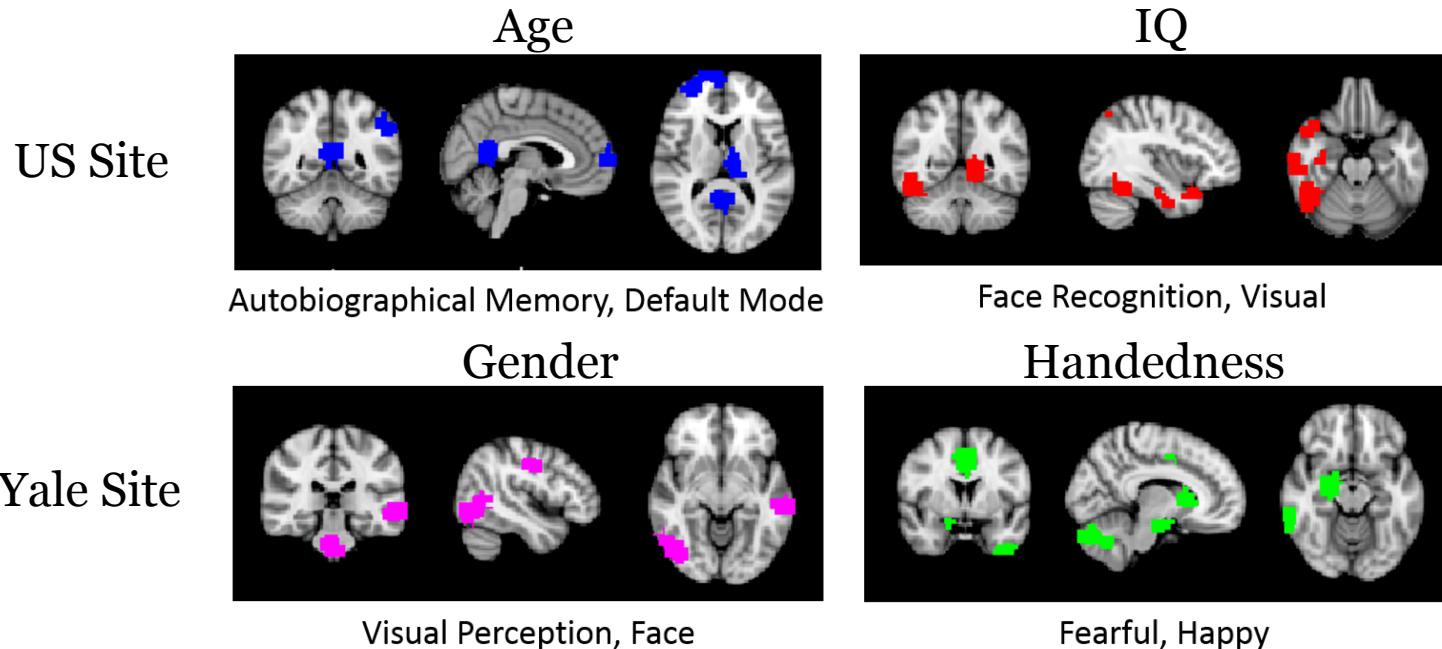
Table 2: DS2 Classification Results (N = 1035, 48.8% ASD)

Model	Leave-One-Site-Out				Weighted by # Subjects/Site		
	Mean (Std) ACC (%)	Mean (Std) TPR (%)	Mean (Std) TNR (%)	Mean (Std) AUC	Mean (Std) ACC (%)	Mean (Std) TPR (%)	Mean (Std) TNR (%)
Orig [†] [9]	65 (1.5)	69 (2.6)	62 (2.7)	-	65.4 (1.3)	68.1 (2.6)	62.3 (2.6)
LSTM [5]	63.6 (0.5)	55.2 (1.6)	71.9 (0.6)	0.709 (0.006)	65.6 (0.6)	58.2 (1.7)	72.7 (0.9)
DFuse [7]	65.5 (0.9) *	57.1 (0.6)	73.5 (1.6)	0.713 (0.006)	67.2 (0.6)	61.2 (1.2)	72.8 (1.0)
DInit [6]	65.8 (0.8) *	58.1 (0.4)	72.9 (1.4)	0.720 (0.009)	67.5 (1.1) *	61.8 (1.6) *	72.9 (3.2)
DGA1-C	65.6 (1.7) *	61.1 (1.6)	69.6 (1.1)	0.713 (0.011)	66.8 (1.6)	64.1 (2.0) *	69.3 (1.9)
DGA2-C	65.8 (0.9) *	52.6 (2.4)	78.3 (1.7) *	0.719 (0.009)	67.2 (1.2) *	55.9 (2.4)	78.0 (0.8) *
DGA1	66.1 (1.5) *	61.3 (2.5) *	70.4 (1.4)	0.719 (0.011)	67.4 (1.7) *	63.6 (2.3) *	70.9 (1.7)
DGA2	65.5 (1.0) *	54.3 (1.5)	76.5 (1.4) *	0.716 (0.015)	67.1 (1.4)	57.6 (1.3)	76.1 (2.3) *
DGA2-QDL	66.4 (0.4) *	58.0 (1.9) *	74.2 (2.0)	0.722 (0.006)	67.4 (0.5) *	61.3 (1.7) *	73.1 (1.9)

* Higher compared to LSTM with no demographics ($p < 0.05$)

† Taken from literature, reflects 1 round of LOSO CV

Networks with Demographic-guided Heterogeneity of Functional Processing



Different modes of response for functional network modulated by demographics may point to different mechanisms of ASD pathophysiology

Conclusions

- What we did:
 - Novel demographic-guided attention mechanism for modeling heterogeneity in neuropathophysiology
 - Achieved higher ASD classification performance on several ABIDE datasets under different preprocessing pipelines using LOSO CV
- What this means:
 - Improved generalization to data from new imaging sites
 - Different neural mechanisms may explain in part difficulty in classification and conflicting ASD literature
- What's next:
 - Include other phenotypic information (e.g., genetic, behavior scores)
 - Deeper analysis of changes in functional network patterns

Thank you!

- NIH Grants R01 MH100028 and R01 NS035193
- Contact: nicha.dvornek@yale.edu

