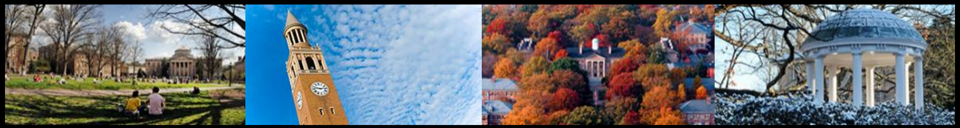

Resting-state brain network construction and network-based disease classification

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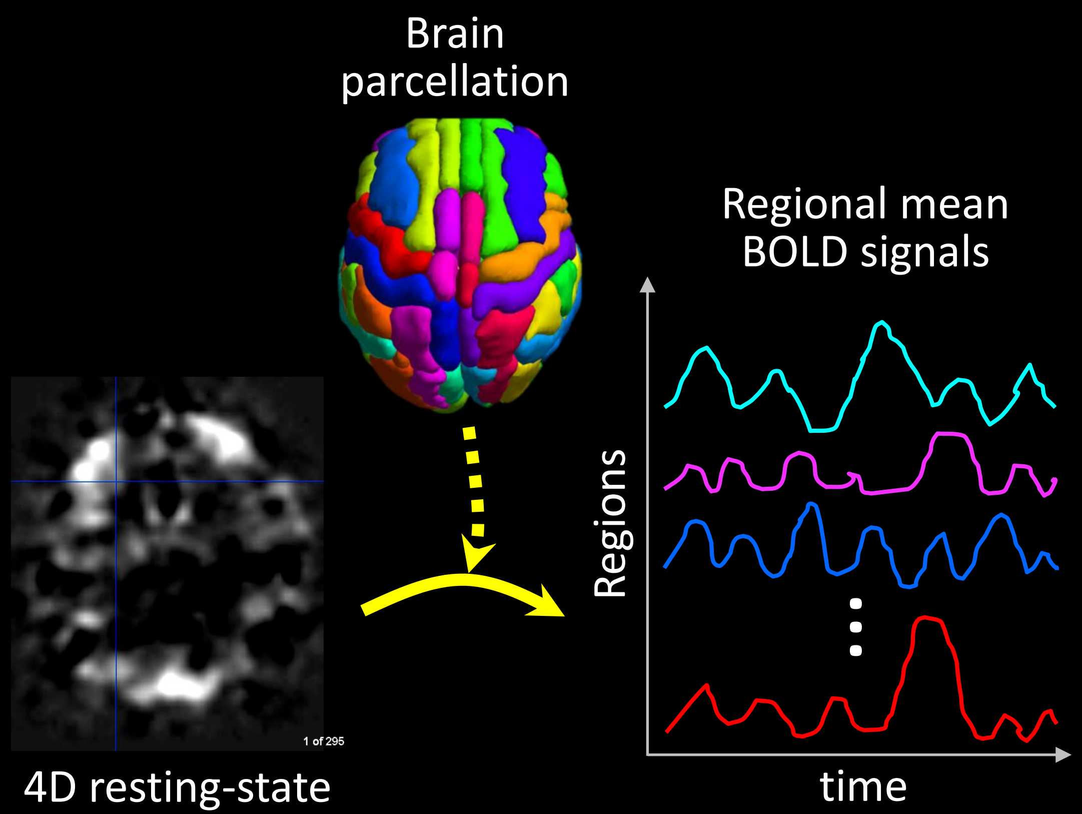
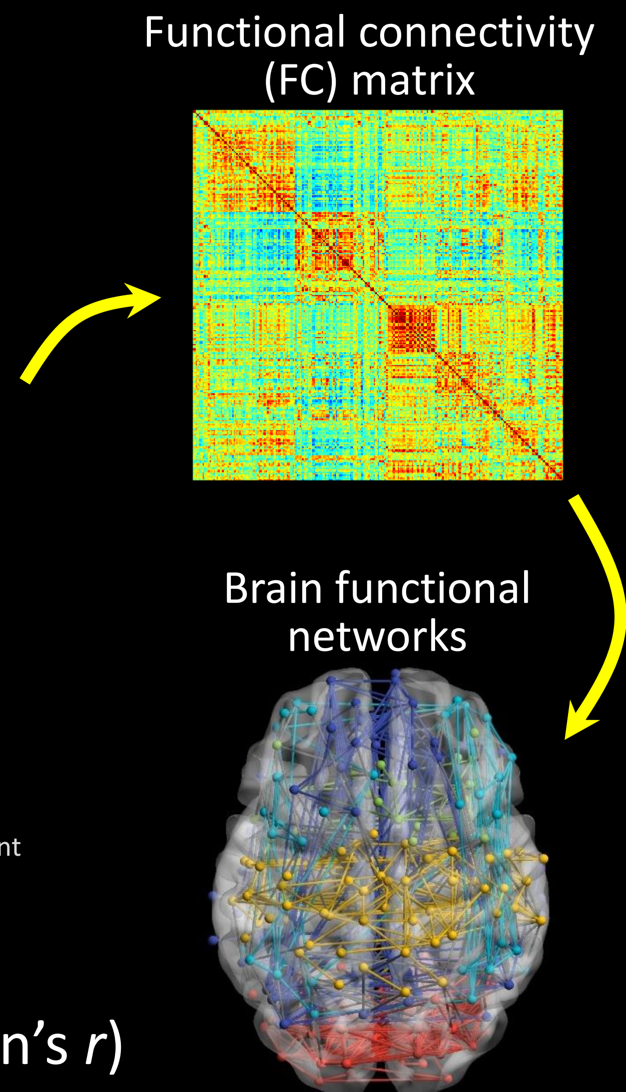
COI disclosure

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation

Static Brain Functional Network Construction



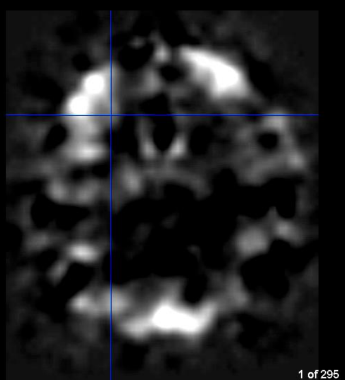
BOLD: blood-oxygenation-level-dependent



- Pairwise connections
- Simple linear relationship (Pearson's *r*)

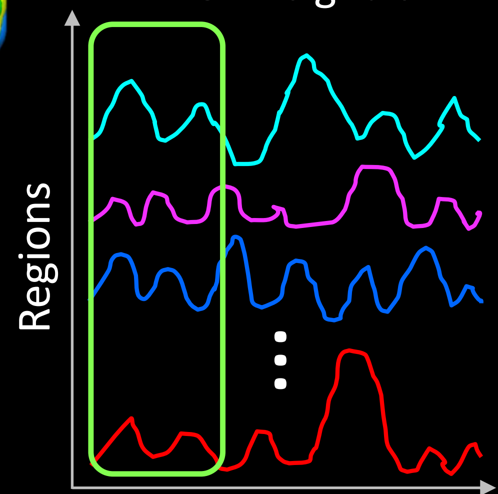
Dynamic Brain Functional Network Construction

Brain parcellation



4D resting-state fMRI data

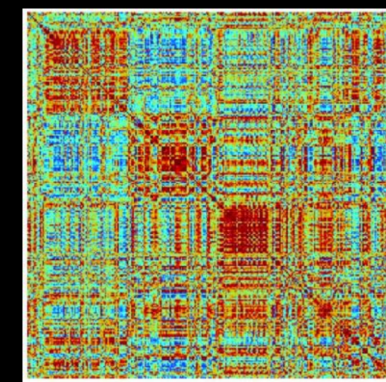
Regional mean BOLD signals



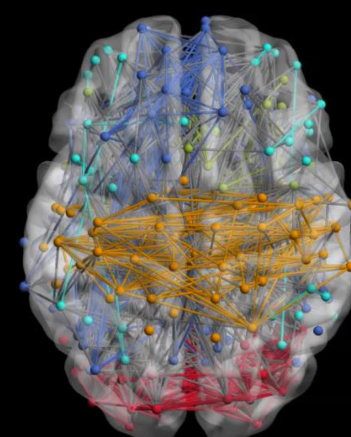
time

BOLD: blood-oxygenation-level-dependent

"Dynamic" functional connectivity matrix

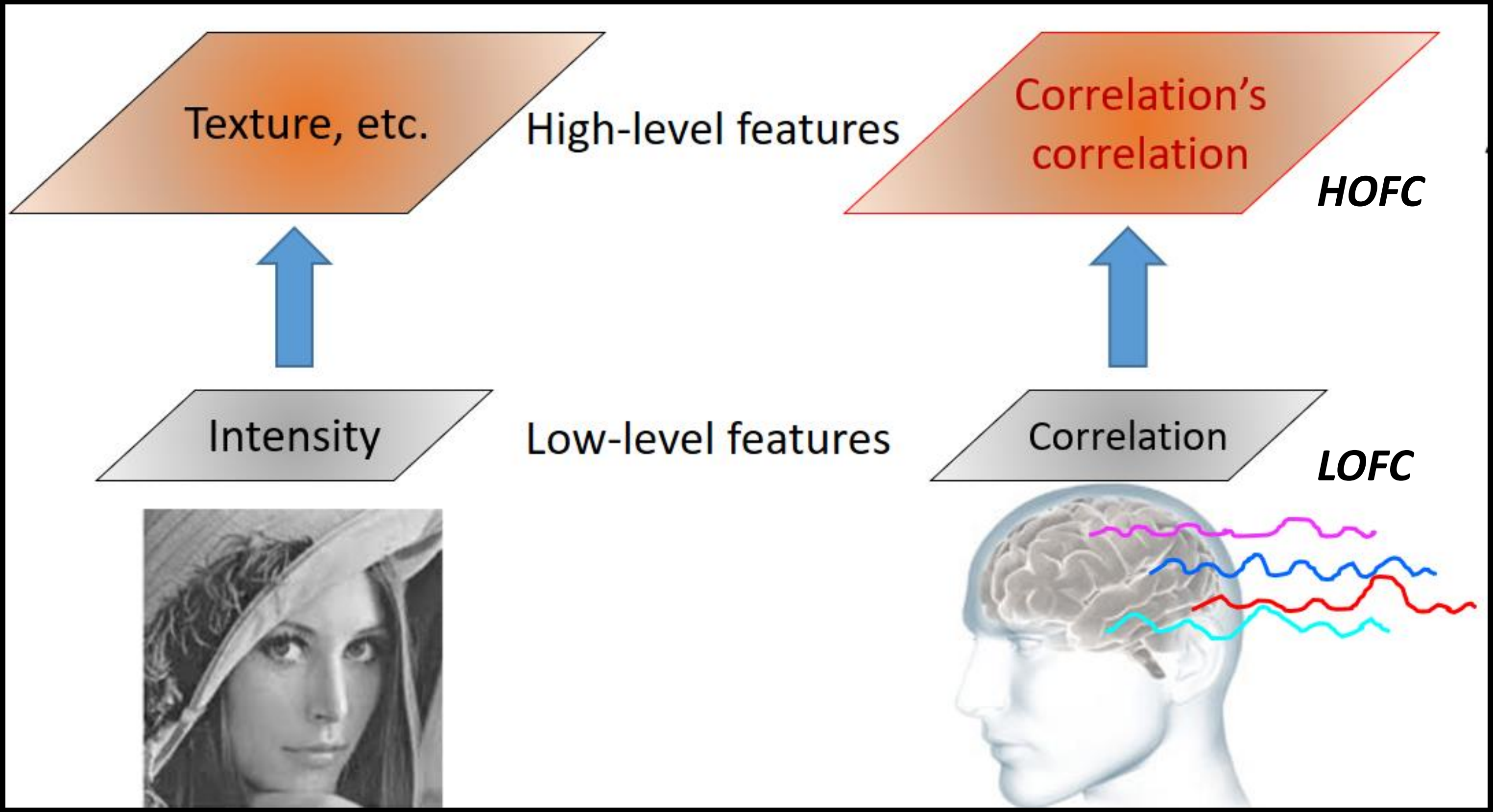


"Dynamic" brain functional networks

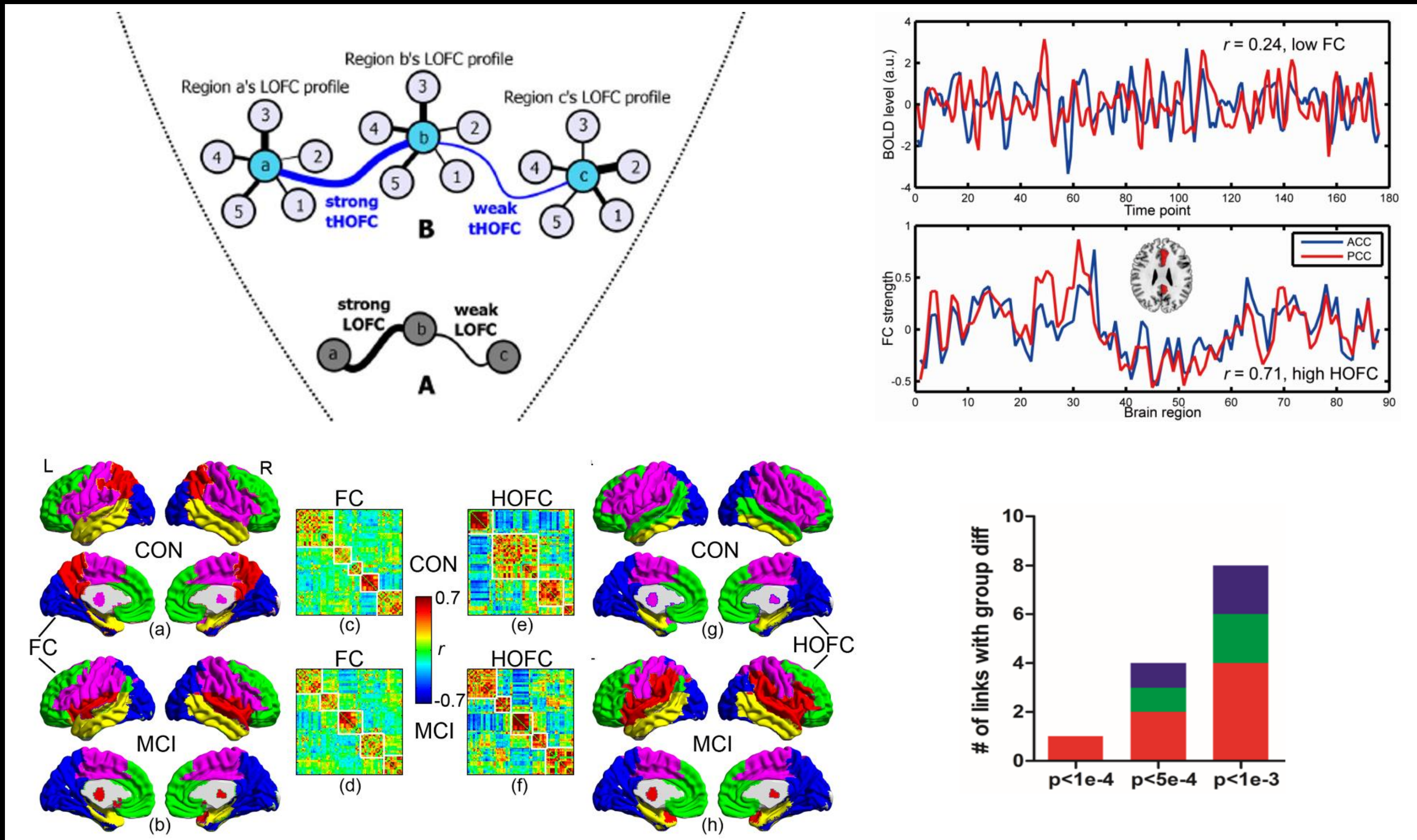


- More information brought up
- New dimension (time) created
- Few analysis methods

From Low- to High-Order Functional Connectivity (HOFC)



High-order FC based on Topological Profiles (tHOFC)



tHOFC (topographical info-based HOFC): Zhang et al., J Alzheim Dis 2016; Zhang et al., Neuroinformatics 2019
Zhang et al., CNI 2017 (extended to inter-frequency HOFC)
Jia et al., CNI 2017 (consciousness level classification and recovery prediction)
Zhao et al., Front in Hum Neurosci 2018 (autism diagnosis)

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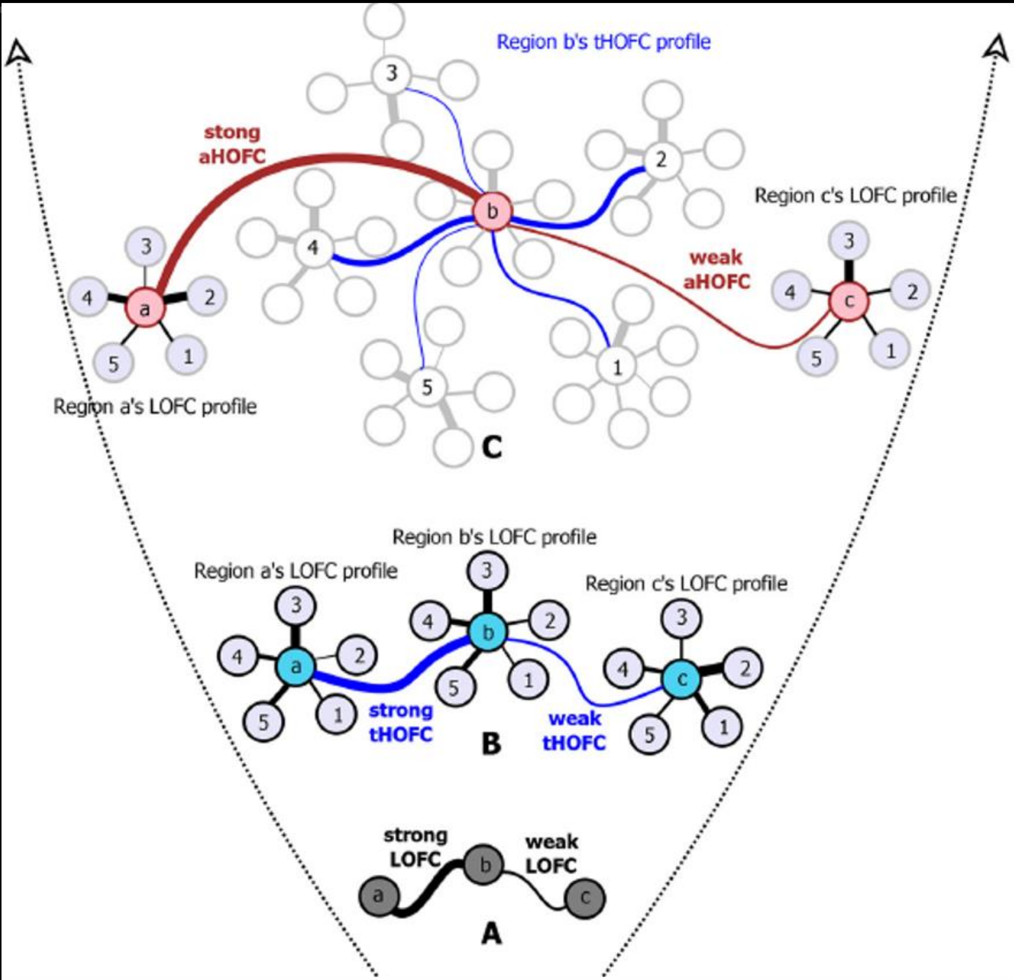
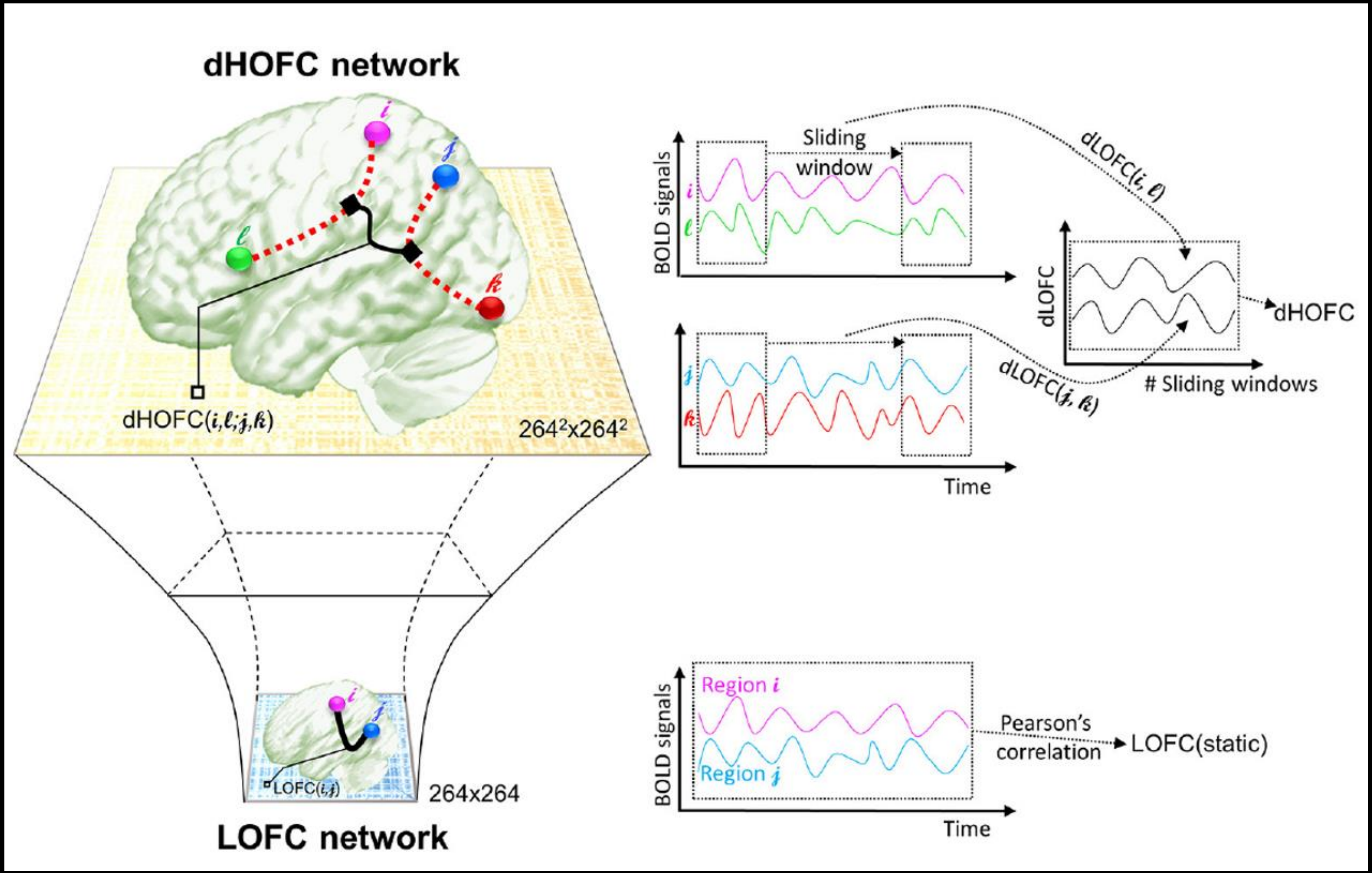
Associated High-order FC (aHOFC)



Method	ACC (%)	AUC	SEN (%)	SPE (%)
SN_L	66.1	0.614	55.2	76.7
SN_H	71.2	0.741	70.0	72.4
SN_A	**72.9**	**0.816**	**70.0**	**75.9**
$SN_L + SN_H + SN_A$	**83.1**	**0.875**	**79.3**	**86.7**

aHOFC (associated HOFC): Zhang et al., Sci Rep 2017
Hybrid HOFC: LOFC + tHOFC + aHOFC

High-order FC based on Functional Dynamics (dHOFC)



Chen et al., Hum Brain Mapp 2016
Chen et al., MICCAI 2016
Chen et al., Neuroinform 2017
Zheng et al., J Affect Disord 2019 (major depression diagnosis)
Liu et al., MICCAI 2016; Brain Imag Behav 2018 (survival prediction)

Early Mild Cognitive Impairment classification performance

Method	ACC	AUC	SEN	SPE
LOFC (part)	0.6271	0.6598	0.6552	0.6000
LOFC (PC)	0.6610	0.6138	0.5517	0.7667
Sparse dFC	0.7966	0.7920	0.7586	0.8333
dHOFC	0.8644	0.9000	0.8621	0.8667
LOFC + dHOFC	0.8814	0.9299	0.8621	0.9000

Test-retest reliability of HOFC metrics

TABLE 1 | Differences among LOFC and various HOFC metrics.

	Input	Output	Test-retest reliability
LOFC	BOLD signals	Temporal synchronization, functional coherence	Fair-to-good; nearly all connections have fair or better reliability. Within-network connections have better reliability; high-level cognitive function-related connections have better reliability.
tHOFC	Regional LOFC topographical profiles	To what extent two regions share similar LOFC topographical profiles	Fair-to-good; similar to LOFC reliability, but with reduced reliability at within-network connections. Better reliability at inter-network connections (esp. between high-level cognition and primary regions).
aHOFC	Both regional LOFC and regional tHOFC topographical profiles	To what extent topographical LOFC modulates topographical tHOFC	Fair-to-good; similar to LOFC reliability, but with further reduced reliability at within-network connections. Better reliability at inter-network connections.
dHOFC	Dynamic, time varying LOFC time series between two brain regions	Temporal synchronization of two time-varying LOFC time series among four brain regions	Fewer connections have fair or better reliability. Strong (within-network and modulatory) connections have fair-to-moderate reliability. Between-network connections have poor reliability. Shorter window length produces better reliability.

BOLD, Blood-oxygen-level dependent; LOFC, low-order functional connectivity; tHOFC, topographical similarity-based high-order functional connectivity; aHOFC, associated HOFC; dHOFC, dynamics-based HOFC.

Zhang et al., Front Neuroscience 2017

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Summary

“Correlation of correlation” generates high-order functional connectivity (HOFC), which characterizes higher-level brain functional interactions and supplements traditional (low-order) FC.

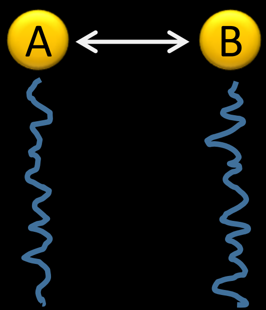
Using both HOFC and LOFC could improve disease diagnosis accuracy.

From one-to-one to one-to-all relationship

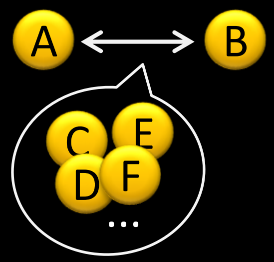
- Instead of only calculating pairwise relationship, one-to-all relationship could be more meaningful

$$\min_{\boldsymbol{W}} \frac{1}{2} \parallel \boldsymbol{X} - \boldsymbol{XW} \parallel_F^2 + \lambda \parallel \boldsymbol{W} \parallel_1 \;\; \text{s. t. } W_{ii} = 0, \forall i = 1, \dots, n$$

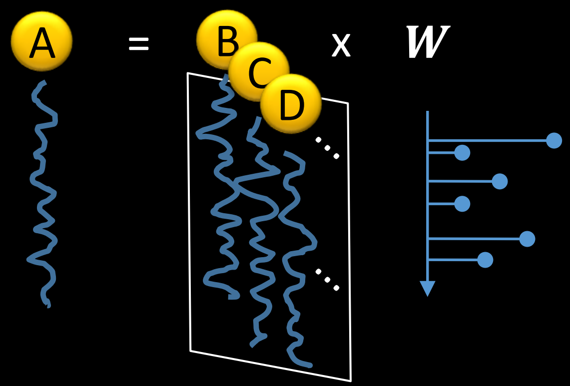
Pairwise FC

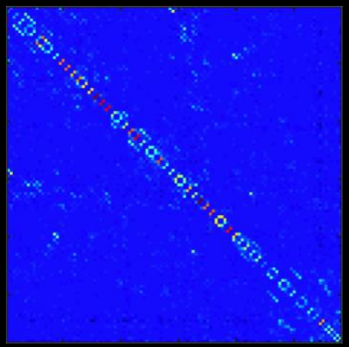


Partial correlation



Sparse representation (SR)

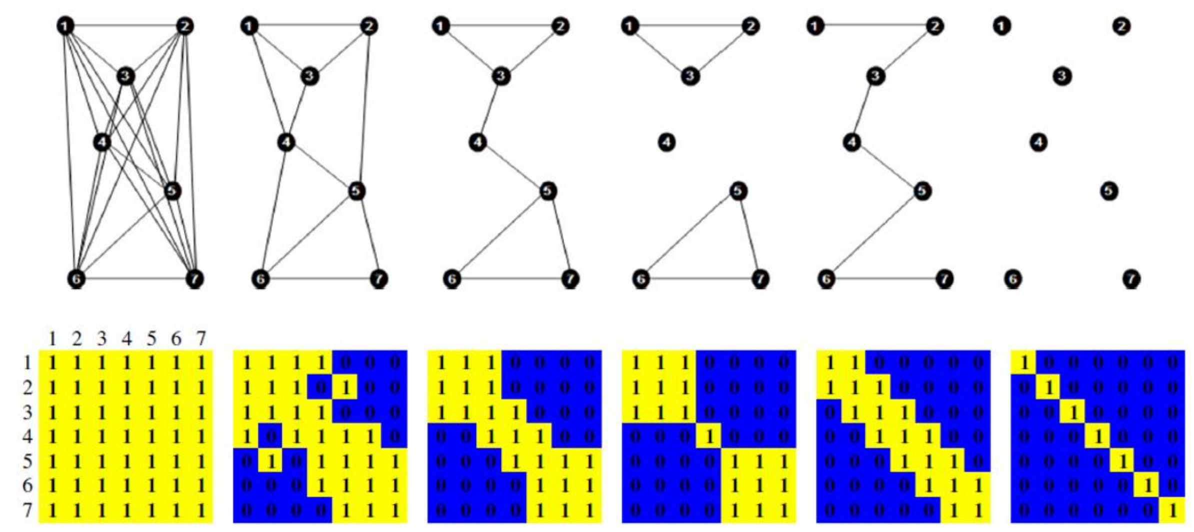




- Remove noise, sparse network
- Biologically meaningful sparse network is more important

Sparse Low-Rank (SLR)-based Brain Network Construction

Incorporate a low-rank prior into SR-based network modeling to achieve modular structure



(a) rank=1 (b) rank=6 (c) rank=4 (d) rank=3 (e) rank=7 (f) rank=7

$$\min_{W} \frac{1}{2} \| \boldsymbol{X} - \boldsymbol{XW} \|_F^2 + \lambda_1 \| \boldsymbol{W} \|_1 + \lambda_2 \| \boldsymbol{W} \|_*$$

Trace norm

Comparison on classification performance and the number of involved features for 4 different methods. The last column shows the mean ± standard deviation of the feature numbers used in all 91 LOO runs. The bold numbers indicate the best results for the accuracy, sensitivity and specificity, respectively.

Method	Accuracy (%)	Sensitivity (%)	Specificity (%)	#Features
Pearson's correlation (PC)	69.23	71.11	67.39	45.1 ± 8.0
Sparse representation (SR)	71.43	71.11	71.74	60.4 ± 7.9
Low-rank (LR)	79.12	80.00	78.26	62.5 ± 4.0
Sparse low-rank (SLR)	**89.01**	**86.67**	**91.30**	72.4 ± 3.3

Qiao et al., NeuroImage, 2016

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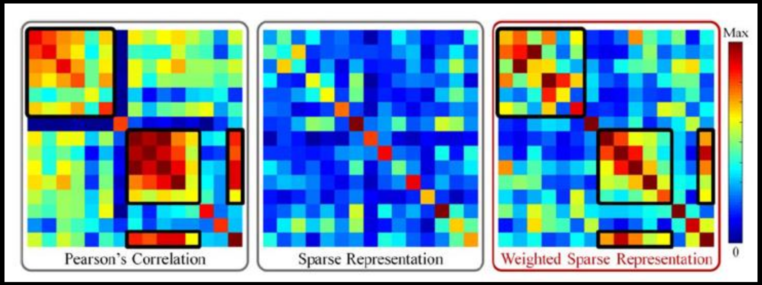
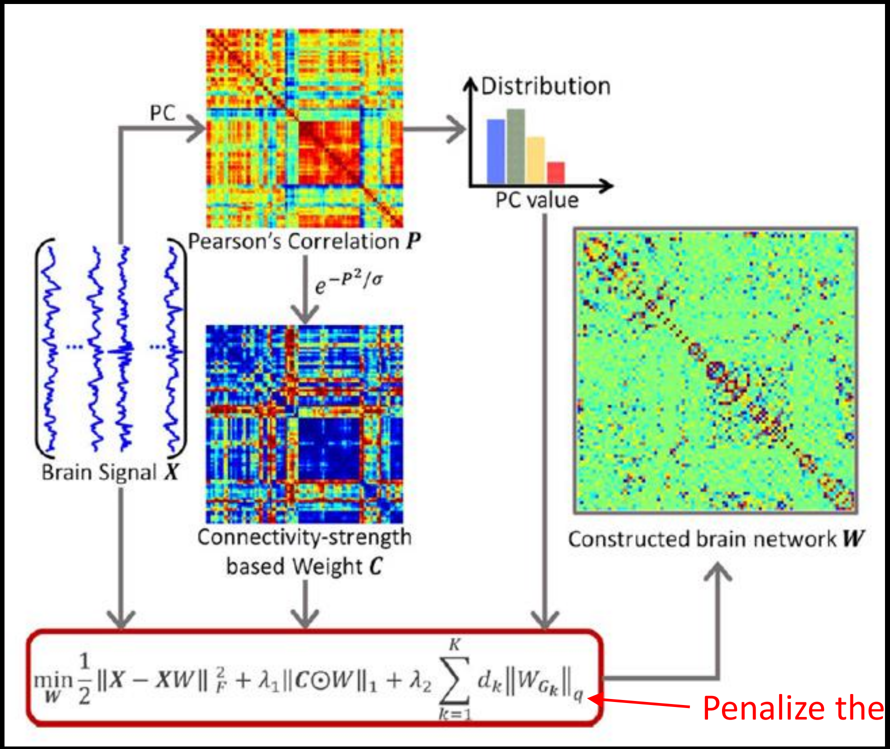
Weighted Sparse Group Representation (WSGR)

The constructed networks feature sparsity, connectivity, and group structure





Penalize the FC group with higher FC strength

Yu and Zhang et al., Hum Brain Mapp 2018

Summary

Brain network construction can be achieved by measuring one-to-all relation among multiple regions, which is more complex than one-to-one relation between two regions.

By integrating biologically meaningful constraint into sparse representation (SR), the resultant network could have many good properties, such as reduced noise and enhanced structures.

BrainNetClass (v1.0)

A user-friendly toolbox for advanced network construction and classification

Problems: Most of the studies still use pairwise Pearson's r to build brain network due to lack of toolbox for advanced network modeling. While group-level comparison still dominate the field, individualized diagnosis is highly desired. The clinicians have data and domain knowledge, but have limited machine learning and neuroimage computing knowledge.

Download: https://github.com/zzstefan/BrainNetClass
Details: https://arxiv.org/abs/1906.09908

References

[1] Chen, X., Zhang, H., Gao, Y., Wee, C.Y., Li, G., Shen, D., Alzheimer's Disease Neuroimaging, I., 2016. High-order resting-state functional connectivity network for MCI classification. Hum Brain Mapp 37, 3282-3296.

[2] Qiao, L., Zhang, H., Kim, M., Teng, S., Zhang, L., Shen, D., 2016. Estimating functional brain networks by incorporating a modularity prior. NeuroImage 141, 399-407.

[3] Zhang, Y., Zhang, H., Chen, X., Liu, M., Zhu, X., Lee, S.-W., Shen, D., 2019. Strength and Similarity Guided Group-level Brain Functional Network Construction for MCI Diagnosis. Pattern Recognition, 88, 421-430.

[4] Zhang, H., Chen, X., Zhang, Y., Shen, D., 2017. Test-retest reliability of "high-order" functional connectivity in young healthy adults. Frontiers in Neuroscience, 11:439.

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[7] Yu, R., Zhang, H., An, L., Chen, X., Wei, Z., Shen, D., 2017. Connectivity strength-weighted sparse group representation-based brain network construction for MCI classification. Human Brain Mapping, 38(5): 2370-2383.

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[9] Zhou, Z., Chen, X., Zhang, Y., Qiao, L., Yu, R., Pan, G., Zhang, H., Shen, D., 2019. Brain network construction and classification toolbox (BrainNetClass). arXiv:1906.09908.

(BrainNetClass-v1.0 uses libsvm-3.23 and SLEP-4.1 toolboxes)

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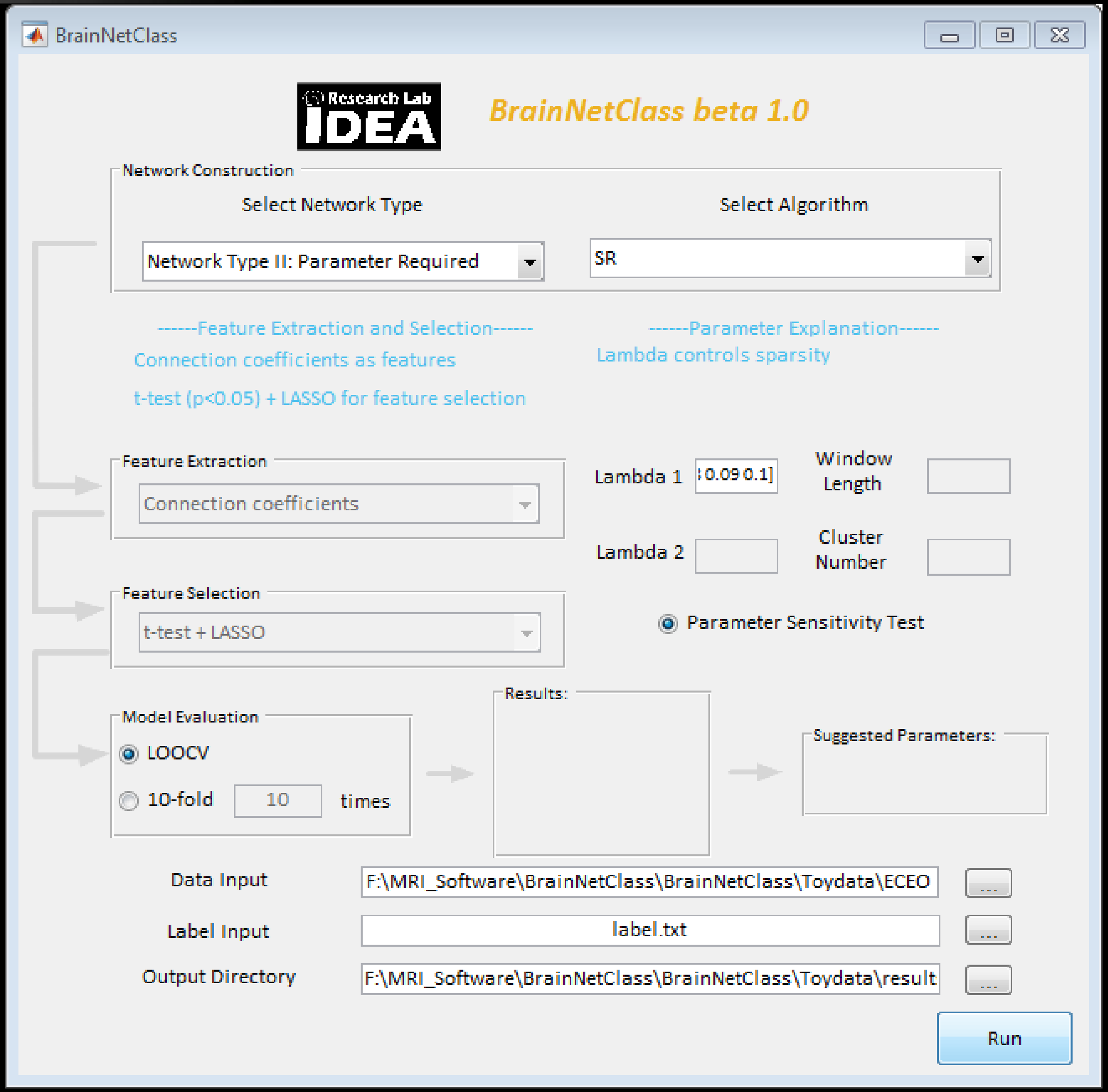
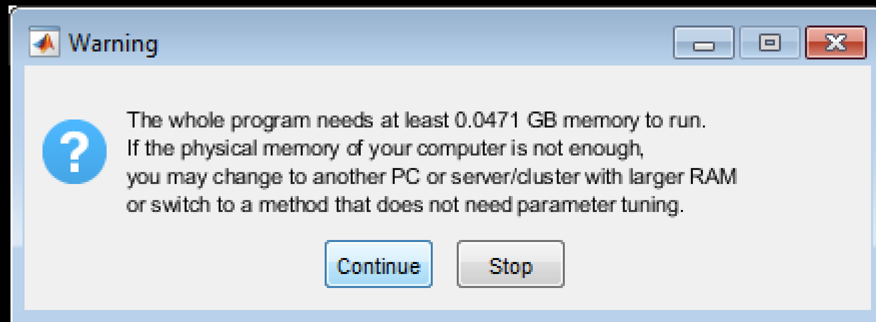
BrainNetClass - Setup



BrainNetClass - Running



>>
Begin network construction
.
..
Network construction finished
Begin process 10%...
Begin process 20%...
Begin process 30%...
Begin process 40%...
Begin process 50%...
Begin process 60%...
Begin process 70%...
Begin process 80%...
Begin process 90%...
Begin process 100%...
Testing set AUC: 0.42
Testing set Sens: 50.00%
Testing set Spec: 60.00%
Testing set Youden: 10.00%
Testing set F-score: 52.63%
Testing set BAC: 55.00%
Begin parameter sensitivity test
End parameter sensitivity test

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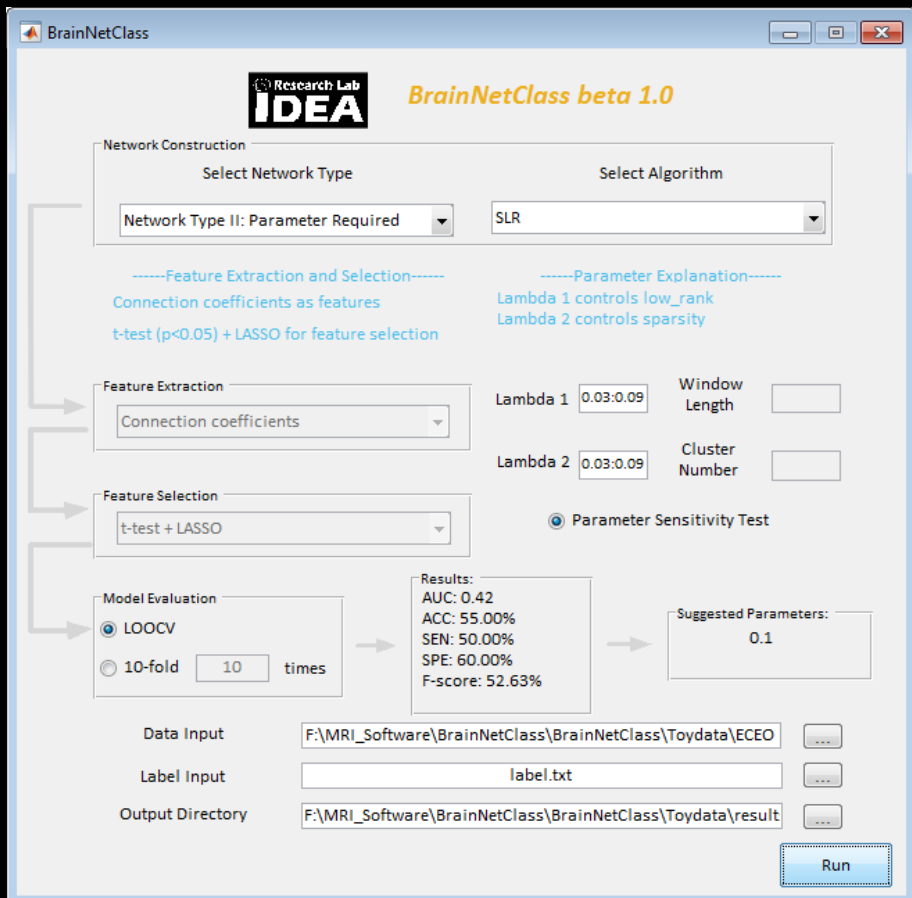
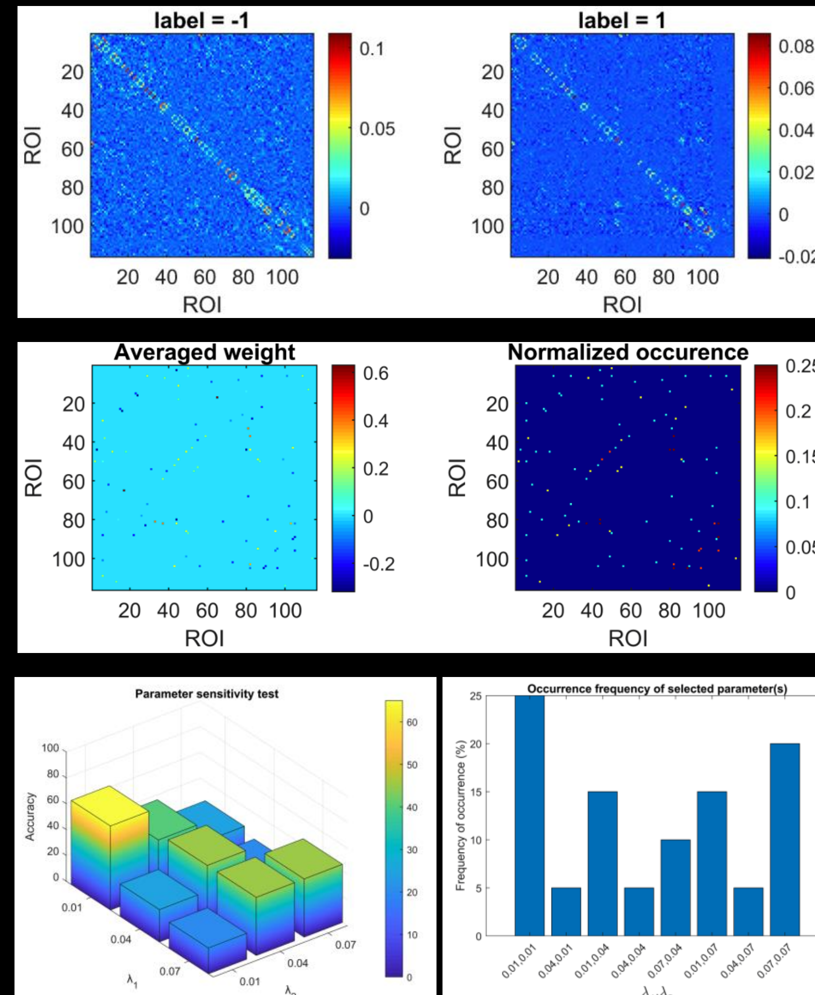
BrainNetClass – Results (Toy Data)





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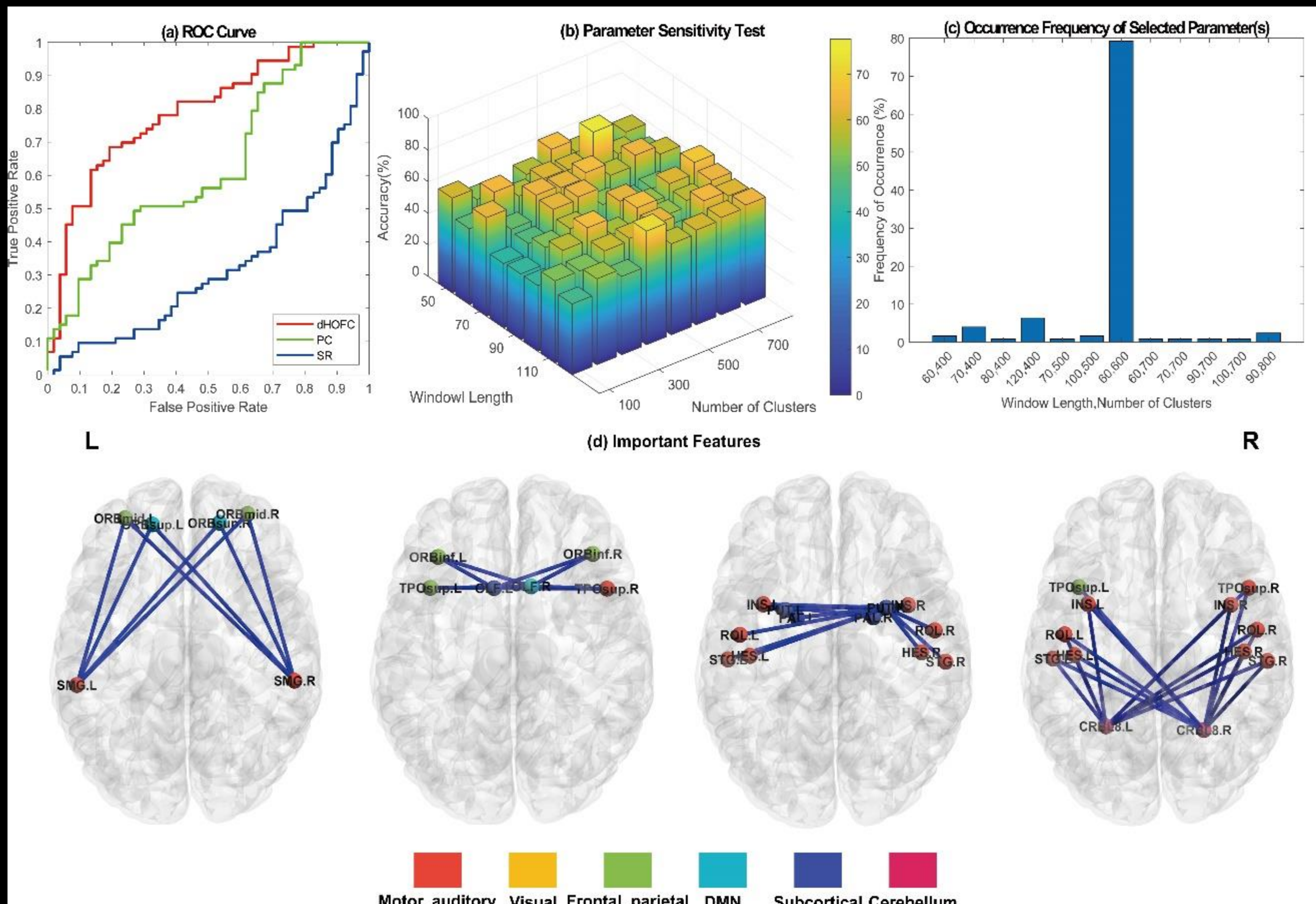
BrainNetClass – Results (Real FMRI Application)



Classification performance of BD (n=52) / MDD (n=73) by using dHOFC, PC, SR

	AUC	ACC	SPE	BAC	SEN	F-score
dHOFC	0.7900	72.00%	65.38%	71.05%	76.71%	76.19%
PC	0.6243	50.40%	38.46%	48.68%	58.90%	58.11%
SR	0.3203	39.20%	25.00%	37.16%	49.32%	48.65%

BrainNetClass - Summary

- A easy-to-use pipelined brain network construction and classification toolbox.
- Options from many state-of-the-art brain functional network construction methods (11 methods).
- Comprehensive interpretable results for classification model assessment.
- Basic and clinic neuroscience application orientated without losing machine learning rigor.
- Matlab-based, GUI interfaced, thus easy to be integrated with many existing neuroscience tools.

https://github.com/zzstefan/BrainNetClass

https://arxiv.org/abs/1906.09908

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Thank you!

IDEA (Image Display, Enhancement and Analysis Laboratory)

www.med.unc.edu/bric/ideagroup

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