Dynamic Connectivity in Neural Networks Engaged for Emotional Regulation

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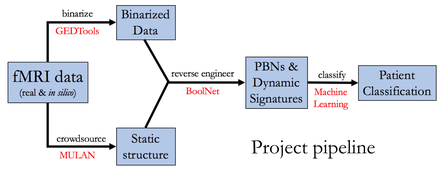
Introduction

Motivation: Abnormalities in **emotional regulation (ER)**, the ability to adjust emotional responses to external stimuli, are implicated in numerous psychiatric disorders, including **Major Depressive Disorder (MDD)** [1]. Functional Magnetic Resonance Imaging (fMRI) measures blood oxygen consumption, serving as an indirect measure of brain activity. Neuroimaging with fMRI has been used in to define the activity of discrete brain regions in the context of neurocognitive tasks [2]. Efforts in functional neuroimaging to characterize the neural presentation of ER deficits have largely focused on static connectivity in functional brain networks [3]. Dynamic neural connectivity, as opposed to the constancy of static connectivity, describes how causal relationships between brain regions change over time. Dynamic connectivity has never been characterized for functional brain networks engaged in ER tasks.

Approach: fMRI data from **typically-developed adolescents** (n = 94) and *in silico* fMRI data (n = 100) from **simTB** (a MATLAB toolbox) were obtained. The data was used to construct probabilistic Boolean networks, from which dynamic signatures were extracted. Later, data from adolescents diagnosed with acute MDD or in remission from MDD will go through the same pipeline.

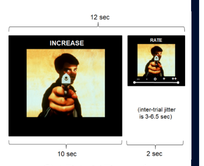


Project pipeline

Methods

• fMRI data collection

Individuals did 4 ER task-runs in a Siemens 3T SKYRA MRI machine. In two tasks they increased emotional response to IAPS images by cognitive reappraisal, and decreased emotional response in the other two. Participants rated the arousal of the images and their ER ability. Pupillometry and electrodermal activity were measured as physiological proxies of emotional response.



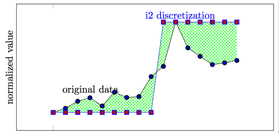
fMRI ER task

• Binarizing fMRI data with TEDIE

Six binarization methods from GEDTools were used to binarize *in silico* and *in vivo* data [4]. The methods were evaluated with the Two-sEep DIscretization Evaluation (TEDIE) [5], which includes:

1) Statistical test (sign test) to eliminate binarizations that introduce new patterns.

2) Mean area between curves (ABC) calculation to test for goodness of binarization fit.



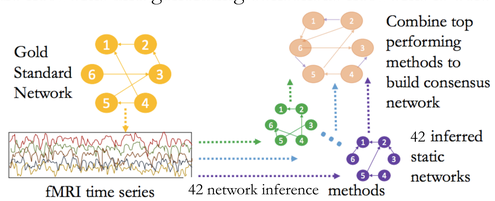
ABC example

• Reverse engineering static networks

MULAN is a MATLAB toolbox [6] that contains 42 reverse engineering methods widely known in the neuroscience community. MULAN can reverse engineer 42 inferred networks for each time series. First MULAN plots the receiver operating characteristic (ROC) curve. If a gold standard network is provided, MULAN can then calculate the area under the curve (AUC) of the ROC curve.

• Generating consensus networks

Consensus networks were generated by taking the mean of the top two methods as determined by the AUC analysis. A graphical summary of the process of reverse engineering static networks and generating consensus networks is below.



• PBNs & Dynamic Signatures

Probabilistic Boolean networks (PBNs) are defined as $G(V, F, \alpha)$, where $V = \{v1, \ldots, vn\}$ represents a set of n brain regions, $F = F1, \ldots Fn$ represents a set of n families of Boolean functions, and $\alpha = \{a1, \ldots an\}$ represents a set of function selection probability vectors corresponding to each family of Boolean functions. Binarized fMRI data and prior knowledge from consensus networks are put into BoolNet, an R package designed to work with Boolean networks and PBNs [7]. A dynamic signature from the resulting PBN is computed.

Results: fMRI data from patients

• Binarizing fMRI data

Method	% Best by TEDIE	% passed stat test	% lowest ABC
eqwidth	0.00%	0.00%	100.00%
kmeans	0.00%	1.06%	0.00%
mean	11.70%	11.70%	0.00%
median	88.30%	100.00%	0.00%
top47	0.00%	0.00%	0.00%

"Best by TEDIE" indicates that the method had the lowest Area Between Curves value of methods that pass the sign test.

Patient fMRI TEDIE results (n = 94)

• Reverse engineering static networks

Representative Examples from real patients S0433NYC (left) and S0022MVK (right) – Threshold = 0.8

Values of these matrices are 1 (green) if brain region corresponding to row i was found to affect the brain region corresponding to column j, and 0 (red) otherwise.

Results: fMRI data from simTB

• Binarizing fMRI data

Method	% Best by TEDIE	% passed stat test	% lowest ABC
eqwidth	0.00%	0.00%	100.00%
kmeans	0.00%	0.00%	0.00%
mean	100.00%	100.00%	0.00%
median	0.00%	100.00%	0.00%
top47	0.00%	100.00%	0.00%

"Best by TEDIE" indicates that the method had the lowest ABC value of methods that pass the sign test. Mean is highlighted in green because it was the method selected for simTB data.

simTB fMRI TEDIE results (n = 100)

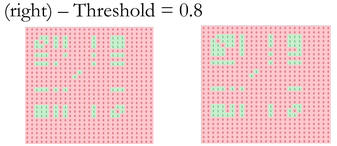
• AUC of ROC curve from MULAN

Top Ten Best Performing Methods by AUC

Methods	BCorrU	BCorrD	BCohF	COH1	BH2D	BH2U	BMITD2	BMITU	BMITD1	PCohF
Mean AUC	0.9900	0.9900	0.9899	0.9897	0.9891	0.9890	0.9889	0.9888	0.9888	0.9734
Number of times in top ten	100	100	100	100	99	100	100	100	100	94

• Reverse engineering static networks

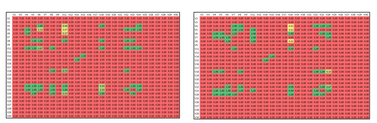
Representative Examples from simTB 003 (left) and simTB 096 (right) – Threshold = 0.8



Values of these matrices are 1 (green) if brain region corresponding to row *i* was found to affect the brain region corresponding to column *j*, and 0 (red) otherwise.

• Dynamic Signatures

Dynamic signatures – representative examples from simTB 003 (left) and simTB 096 (right)



A greener value in *Mij* in these matrices indicates a stronger dynamic connectivity between brain regions *i* and *j*.

Discussion

- By the TEDIE analysis, the best binarization for simTB (*in silico*) data is the mean method, with the uniformity of the *in silico* data making the results conclusive. If PBNs are to be generated from *in vivo* data by concatenating all 4 scans, then the TEDIE analysis indicates that with the median binarization is optimal, although customized binarization methods for each patient may be necessary.
- The mean of BCorrU and BCorrD consensus network perfectly matched our gold standard for all 100 *in silico* patients. This is likely because the gold standard for simTB data is derived from a correlation, not a connectivity, matrix. This reveals a potential limitation of the ability of simTB to validate our pipeline.
- Preliminary dynamic signatures were calculated for the simTB *in silico* data including partial static structures. This was done successfully, but more work will need to be done to meet computational challenges in BoolNet for the number of nodes in the patient data and including all prior network information.

Conclusion and Future Work

The study of functional brain networks engaged for emotional regulation can benefit from a validated pipeline that models dynamic connectivity in fMRI data using PBNs, and our work with *in silico* data has made progress towards classifying real patients based on dynamic connectivity in fMRI scans. Future work will focus on entering real patient data (typically developed, acute MDD, and remitted MDD) into the pipeline. Once dynamic signatures are extracted from real patients, they will be classified into clinically relevant subgroups. The dynamic signatures may also be merged with phenotypic data (age, sex, disease status) to identify clinically relevant dynamic signature phenotypes.

References

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Acknowledgements

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