EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | CBIS Center for Biomedical Imaging Statistics

Statistical Approaches for Exploring Brain Connectivity with Multi-Modal Neuroimaging Data

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INTRODUCTION

Two main classes of brain imaging:

- Functional: commonly measured by **fMRI**
- Structural: measured by diffusion tensor imaging (**DTI**)

Functional Connectivity (FC) measures the temporal coherence between the BOLD signal (a proxy for brain activity) of spatially remote brain locations.

- **FC network**: a set of functionally connected brain regions
- FC networks can be identified from fMRI data.
- **Independent Component Analysis (ICA)** is a popular *data-driven* method for extracting FC networks, and has several advantages over other techniques.

Structural Connectivity (SC) measures the anatomical connections between brain areas

- **Probabilistic tractography** estimates the SC distribution in the brain based on DTI data.

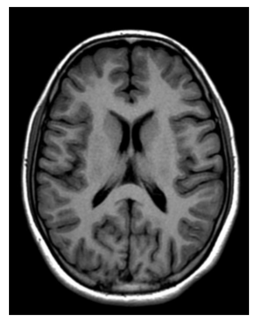
FC analysis excludes information about the underlying structural connectivity in the brain, yet it is thought that structural fiber tracts facilitate inter-regional interactions in brain activity.

Why combine information across modalities (i.e. fMRI and DTI)?

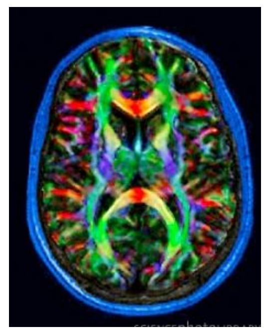
1. **To better understand the relationship between brain structure and function.** FC is usually, but not always accompanied by strong SC[3]
2. **To characterize pathophysiology of disease.** Many disorders exhibit disruptions in FC and/or SC (e.g. Multiple Sclerosis, Stroke, Alzheimer's Disease)

•**Our Goal:** develop statistical methods that combine FC and SC, and provide a convenient framework to conduct statistical inference

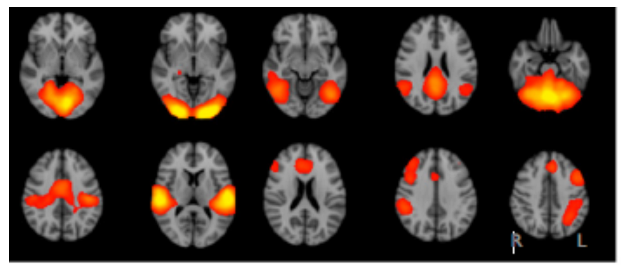
Functional pipeline | **Structural pipeline**



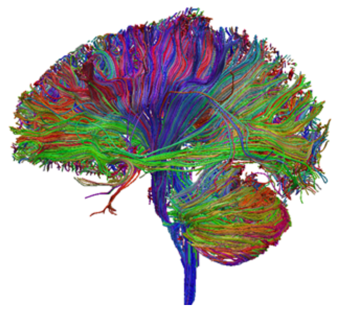
fMRI data



DTI data



Identify FC networks[1] via group ICA[2]



Estimate SC via probabilistic tractography

Goal: combine structure and function

sSC measure

CBIS website:
http://web1.sph.emory.edu/bios/CBIS/

METHODS

Research Questions:

1. What is the strength of SC underlying FC networks estimated by data-driven methods like ICA ?
2. Due to the stochastic nature of ICA, results vary. Can SC be used to inform the reliability of FC networks estimated by ICA?

We propose a novel measure of the strength of SC (**sSC**) underlying an FC network:

$$\theta_\ell = \frac{\sum_{j,k\in\Omega_\ell} [p_{jk} - (\bar{p}_j + \bar{p}_k)/2]}{\sum_{j,k\in\Omega_\ell} [1 - (\bar{p}_j + \bar{p}_k)/2]}$$

Estimated by:

$$\hat{\theta}_\ell = \frac{\sum_{j,k\in\Omega_\ell} [N_{jk} - (\bar{N}_j + \bar{N}_k)/2]}{\sum_{j,k\in\Omega_\ell} [N - (\bar{N}_j + \bar{N}_k)/2]}$$

where:

Ω_ℓ: set of voxels in IC ℓ

p_{jk}: probability of SC between voxels j and k within IC ℓ (max: 1)

$\bar{p}_j$: average probability of SC between voxel j and rest of brain

N_{jk}: # of streams connecting voxels j and k in IC ℓ

$\bar{N}_j$: avg # of streams that pass through voxel j and the rest of the brain

N: total # of streams initiated in the probabilistic tractography procedure

- The **sSC measure** represents the above-baseline strength of SC underlying an FC network.
- We divide by the maximum possible value to standardize and make comparable between FC networks of different sizes

Inference Framework

If we consider the $\binom{V}{2}$x1 vector, $\mathbf{N}^*$, as the set of N_{jk} for all voxel pairs (j,k), we can express $\hat{\theta}_\ell$ as a function of $\mathbf{N}^*$

if $\mathbf{N}^* = \begin{pmatrix} N_{12} \\ N_{13} \\ \vdots \\ N_{V-1,V} \end{pmatrix}$ then $\hat{\theta}_\ell = \left(\frac{(\boldsymbol{C}_\ell - \boldsymbol{A})\boldsymbol{N}^*}{b - \boldsymbol{A}\boldsymbol{N}^*}\right)$ where: $\boldsymbol{A} = \frac{(V_\ell - 1)}{2(V-1)} \sum_{j\in\Omega_\ell} \boldsymbol{C}_j$, $b = \frac{V_\ell(V_\ell - 1)}{2}$,

$\boldsymbol{C}_\ell$ and $\boldsymbol{C}_j$ are binary indicator vectors

V=# voxels in brain, V_ℓ=# voxels in IC ℓ

We assume $\mathbf{N}^*$ ~ MVN($\boldsymbol{\mu}$, $\boldsymbol{\Sigma}$) where $\boldsymbol{\Sigma}$ is a $\binom{V}{2}$x $\binom{V}{2}$ variance-covariance matrix with elements $cov(N_{jk}, N_{j'k'})$

- Estimation of $\boldsymbol{\Sigma}$ is difficult because it is high-dimensional and has spatial dependencies.
- We can model $cov(N_{jk}, N_{j'k'})$ as a function of distance using a parametric semivariogram model.
- Once $\boldsymbol{\Sigma}$ is estimated, we can estimate $Var(\hat{\theta}_\ell)$ by the Delta method:

$$Var(\hat{\theta}_\ell) \simeq \left[\frac{(\boldsymbol{C}_\ell - \boldsymbol{A})\boldsymbol{\mu}}{b - \boldsymbol{A}\boldsymbol{\mu}}\right]^2 \left[\frac{(\boldsymbol{C}_\ell - \boldsymbol{A})\boldsymbol{\Sigma}(\boldsymbol{C}_\ell - \boldsymbol{A})'}{[(\boldsymbol{C}_\ell - \boldsymbol{A})\boldsymbol{\mu}]^2} + \frac{\boldsymbol{A}\boldsymbol{\Sigma}\boldsymbol{A}'}{[b - \boldsymbol{A}\boldsymbol{\mu}]^2} - 2\frac{[-(\boldsymbol{C}_\ell - \boldsymbol{A})\boldsymbol{\Sigma}\boldsymbol{A}']}{[(\boldsymbol{C}_\ell - \boldsymbol{A})\boldsymbol{\mu}][b - \boldsymbol{A}\boldsymbol{\mu}]}\right]$$

Hypothesis testing:

1. Does an FC network have above-baseline sSC?

Hypotheses and test statistic:

$H_0 : \theta_\ell = 0$ vs. $H_1 : \theta_\ell > 0$

$$T^* = \frac{\hat{\theta}_\ell}{\sqrt{\hat{Var}(\hat{\theta}_\ell)/n}} \sim N(0,1)$$

2. Does sSC differ between two FC networks?

Hypotheses:

$H_0 : \theta_\ell = \theta_{\ell'}$ vs. $H_1 : \theta_\ell \neq \theta_{\ell'}$

Use permutation test (permute network id within subject) to evaluate

3. Does sSC of an FC network differ between subject groups?

Hypotheses and test statistic:

$H_0 : \theta_{\ell,1} = \theta_{\ell,2}$ vs. $H_1 : \theta_{\ell,1} \neq \theta_{\ell,2}$

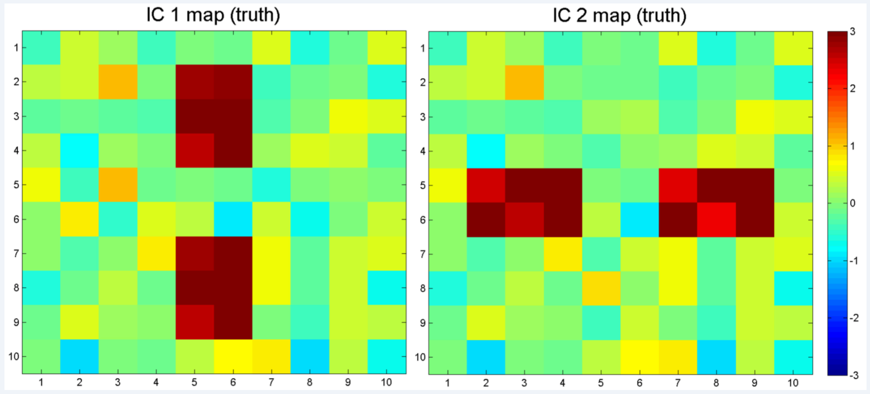
$$T^* = \frac{\hat{\theta}_{\ell,1} - \hat{\theta}_{\ell,2}}{\sqrt{\frac{\hat{Var}(\hat{\theta}_{\ell,1})}{n_1} + \frac{\hat{Var}(\hat{\theta}_{\ell,2})}{n_2}}} \sim N(0,1)$$

Non-parametric alternative: use permutation test (permute group id)

SIMULATION STUDIES

We simulate a 10x10 voxel brain slice with 2 FC networks.

True source signal maps:



- We test 4 conditions, 300 simulation runs each.

- Steps: generate fMRI data, run group ICA to estimate FC network maps, and generate $\mathbf{N}^*$ to estimate SC. Estimate $\boldsymbol{\Sigma}$ by fitting an empirical semivariogram, and calculate $Var(\hat{\theta}_\ell)$ for use in hypothesis testing. Compare to results using a bootstrap variance estimator.

Simulation Results:

Table 1: *Results based on 300 simulation runs*

	Sample size	Noise level	θ	$s\hat{S}C$ mean (SD)	Theoretical SE (SD)	Bootstrap SE (SD)	Cov. Prob. I* (Theoretical)	Cov. Prob. II* (Bootstrap)
IC 1	20	Low	0.3077	0.3081 (0.0091)	0.0083 (0.00035)	0.0093 (0.0016)	92.6	94.3
		High	0.3077	0.3074 (0.0104)	0.0093 (0.00043)	0.0105 (0.0018)	91.6	94
	50	Low	0.3077	0.3084 (0.0061)	0.0053 (0.00019)	0.0060 (0.00063)	90.7	93.7
		High	0.3077	0.3078 (0.0069)	0.0059 (0.00023)	0.0068 (0.00071)	91	94.7
IC 2	20	Low	0.64	0.6405 (0.0120)	0.0112 (0.00041)	0.0115 (0.0018)	93.3	93
		High	0.64	0.6389 (0.0134)	0.0126 (0.00040)	0.0127 (0.0020)	94.6	93.6
	50	Low	0.64	0.6409 (0.0080)	0.0071 (0.00019)	0.0074 (0.00073)	90.7	93
		High	0.64	0.6394 (0.0088)	0.0080 (0.00017)	0.0082 (0.00081)	93.7	93

* Coverage probabilities I: Based on Wald-type CI using theoretical SE. Coverage probabilities II: Bootstrap percentile confidence interval.

a b c

a) Estimator of sSC shows low bias in all conditions.
b) Theoretical variance term tends to slightly underestimate the variance of sSC. The bootstrap estimator performs well.
c) Coverage prob. is close to 95% using the theoretical and bootstrap terms.

Conclusion: we recommend using the bootstrap estimator of variance when V is large, in order to avoid estimating Σ

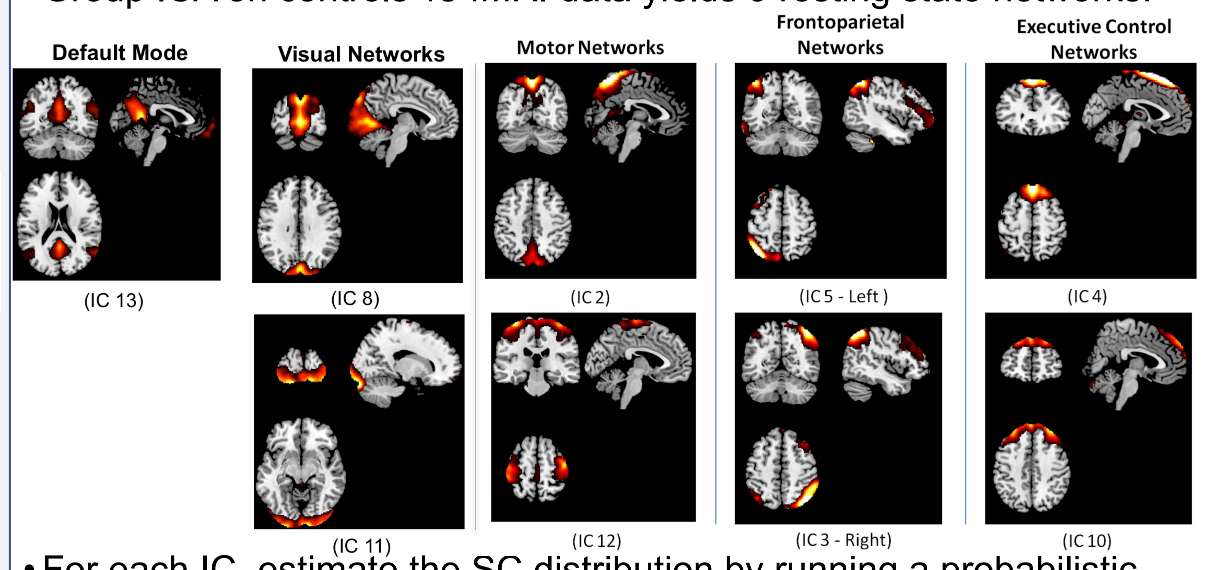
DATA APPLICATION

Data

- resting-state fMRI and DTI scans for 20 subjects with Major Depressive Disorder (MDD) & 20 healthy controls
- Studies of MDD do not agree about the mechanism of connectivity disruption, and the pathology is unclear[4]

Analysis

- Group ICA on controls' rs-fMRI data yields 9 resting state networks:



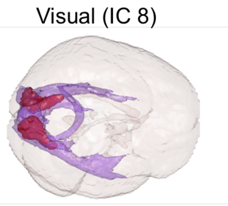
- For each IC, estimate the SC distribution by running a probabilistic tractography procedure, initiating N=5000 streams from each voxel in the IC mask.

Results:

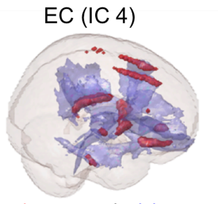
Table 2: *Results of hypothesis testing for controls*

IC		Mean($\hat{\theta}_\ell$)	SD($\hat{\theta}_\ell$)	Bootstrap CI	Bootstrap p-value
2	motor	0.0071	0.0013	(0.0066, 0.0077)	0.0000
3	FP	0.0081	0.0010	(0.0077, 0.0086)	0.0000
4	**EC**	**0.0048**	0.0004	(0.0046, 0.0049)	0.0000
5	FP	0.0077	0.0008	(0.0074, 0.0081)	0.0000
8	**visual**	**0.0098**	0.0014	(0.0092, 0.0103)	0.0000
10	EC	0.0052	0.0008	(0.0048, 0.0055)	0.0000
11	visual	0.0085	0.0009	(0.0082, 0.0089)	0.0000
12	motor	0.0058	0.0005	(0.0056, 0.0060)	0.0000
13	DMN	0.0078	0.0016	(0.0071, 0.0085)	0.0000

Visual (IC 8)



EC (IC 4)



red=IC mask, blue=SC
(p=0 from permutation test for difference between ICs)

The strength of SC is positively associated with the reliability of ICs

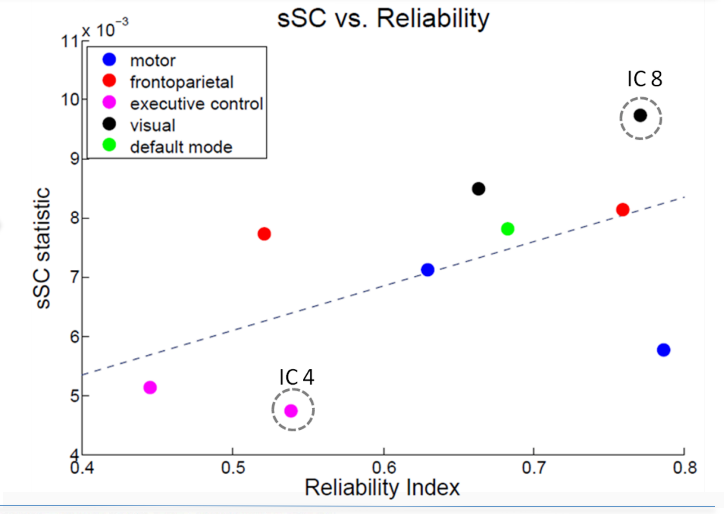


Table 3: *Results of hypothesis testing for MDD vs. controls*

IC		Controls Mean(sSC)	Controls SD(sSC)	MDD Mean(sSC)	MDD SD(sSC)	Bootstrap CI (mdd - con)	Bootstrap p-value	Permutation test p-value
2	motor	0.0071	0.0013	0.0070	0.0012	(-0.0009, 0.0005)	0.702	0.698
3	FP	0.0081	0.0010	0.0079	0.0012	(-0.0009, 0.0005)	0.525	0.562
4	EC	0.0048	0.0004	0.0047	0.0004	(-0.0003, 0.0002)	0.820	0.825
5	FP	0.0077	0.0008	0.0072	0.0010	(-0.0011, -0.0001)	0.018	0.054
8	visual	0.0098	0.0014	0.0095	0.0016	(-0.0012, 0.0007)	0.639	0.608
10	EC	0.0052	0.0008	0.0053	0.0008	(-0.0003, 0.0006)	0.451	0.475
11	visual	0.0085	0.0009	0.0080	0.0008	(-0.0010, 0.0000)	0.084	0.077
12	motor	0.0058	0.0005	0.0060	0.0007	(-0.0002, 0.0006)	0.277	0.299
13	DMN	0.0078	0.0016	0.0073	0.0012	(-0.0015, 0.0003)	0.251	0.252

Within normal FC networks, there is no difference in strength of SC between MDD and control groups

CONCLUSIONS

- The proposed sSC measure combines info from the fMRI and DTI modalities
- sSC can be used to inform the reliability of networks estimated by ICA

REFERENCES

1. Smith et al., 2009
2. Calhoun et al., 2009
3. Damoiseaux & Greicius, 2009
4. Northoff et al., 2011