Graphical Modeling Approaches for Estimating Brain Networks

BIOS 516

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September 28, 2017

Introduction

- My research focuses on understanding how different parts of the brain work together to drive phenotypic outcomes such as disease status, psychological behavior and so on.
- In particular, I look at brain connectivity or brain networks.
- The tool that I use is called graphical models which has a rich statistical literature & coherent interpretations.
- At a very basic level, graphical model specifies that if two areas of the brain have a high partial correlation, then they are connected, otherwise there is no connection/ edge.
- Currently, I work with continuous imaging outcomes such as PET, fMRI, DTI and so on.

Graphical Models

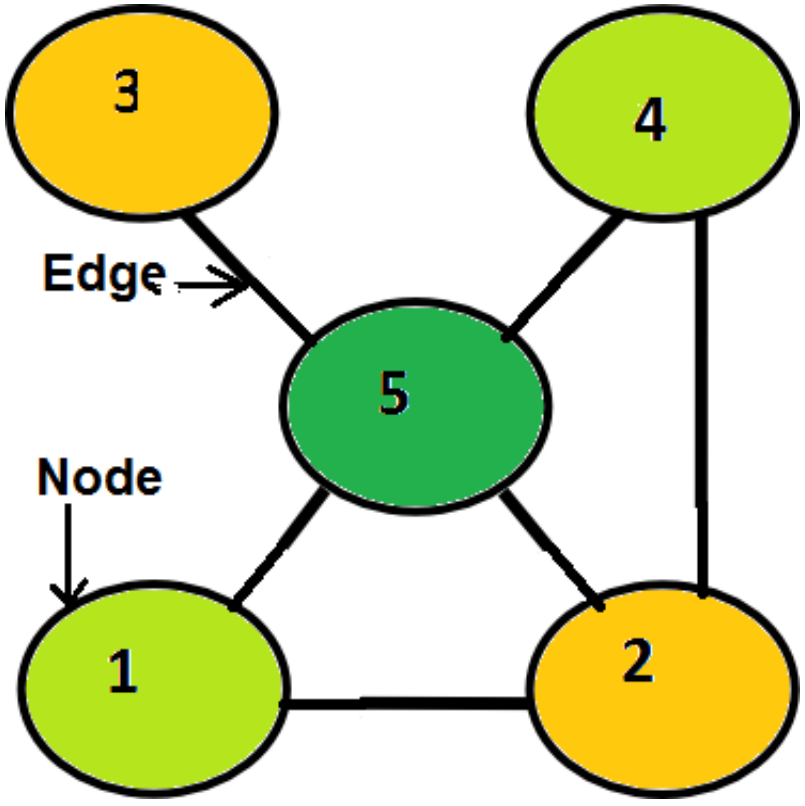


Figure: Visual depiction of an undirected graph. Circles represent nodes or regions of interest in the brain, and straight lines represent edges or connections. An edge corresponds to a high partial correlation.

Graphs

- A graph is defined by the vertex set $V = \{1, \ldots, p\}$ indexing the set of random variables $(X_1, \ldots, X_p)$, and the edge set E.
- *Two types of graphs:* Directed graphs/ Bayesian networks & undirected graphs/ Markov random field (MRF)
- Directed networks specify causal relationships between nodes, whereas undirected networks quantify associations between node pairs.
- We are primarily interested in undirected associations via GGMs which are tools for modeling conditional independence relationships among a collection of nodes

Gaussian Graphical Model or GGM

- Definition: A GGM refers to a set of continuous random variables specified by a Gaussian distribution, which forms a MRF with respect to a graph $G = (V, E)$, with missing edges in E corresponding to zeros on the precision matrix.
- $\mathbf{x} \sim N(0, \Sigma_G)$, with $\Sigma_G^{-1}(i,j) = 0$ for all pairs $(i,j) \notin E$.

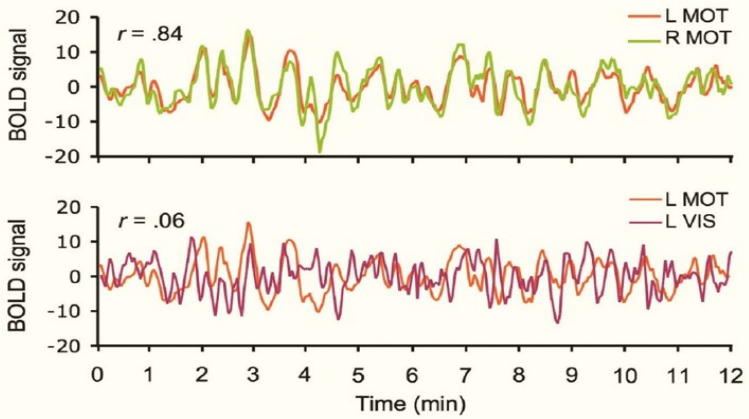
$$\Sigma^{-1} = \begin{pmatrix} \omega_{11} & \omega_{12} & 0 & 0 & \omega_{15} \\ \omega_{21} & \omega_{22} & 0 & \omega_{24} & \omega_{25} \\ 0 & 0 & \omega_{33} & 0 & \omega_{35} \\ 0 & \omega_{42} & 0 & \omega_{44} & \omega_{45} \\ \omega_{51} & \omega_{52} & \omega_{53} & \omega_{54} & \omega_{55} \end{pmatrix} \text{ for the previous example}$$

- Thus for GGMs, graph estimation $\equiv$ determination of structural zeros in the inverse covariance matrix.

GGM and Brain Connectivity

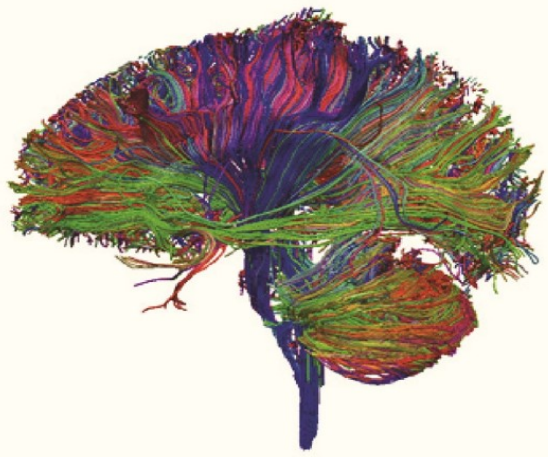
- GGMs can be used to compute brain connectivity
- Mainly, there are two types of connectivity, functional & structural

Functional Connectivity (FC): temporal coherence of activity between remote brain areas



(fMRI data)

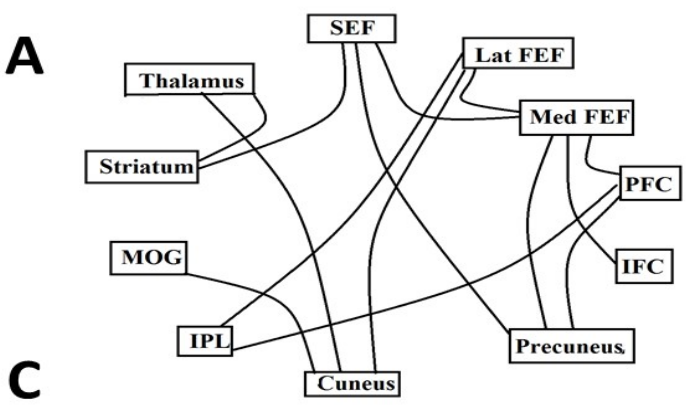
Structural Connectivity (SC): anatomical connections that physically link brain areas

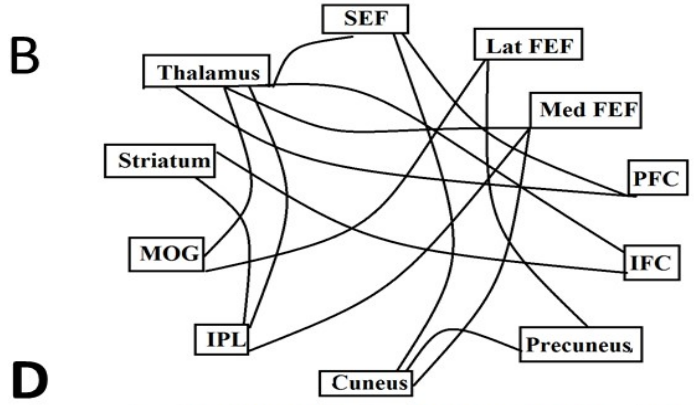


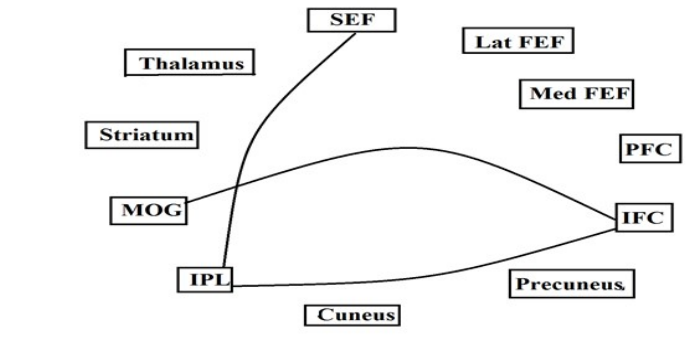
(DTI data)

Figure: Left: fMRI time series; Right: White matter fiber tracts

Functional Connectivity in Saccade Trials







D

	SEF	Lateral FEF	Medial FEF	PFC	IFC	Precuneus	Cuneus	IPL	MOG	Striatum	Thalamus
SEF											
Lateral FEF											
Medial FEF											
PFC											
IFC											
Precuneus											
Cuneus											
IPL											
MOG											
Striatum											
Thalamus											

Figure: Figures display FC which are present in both pro-saccade and fixation (Figure A), connections which are present in pro-saccade blocks only (Figure B), and connections which are present in fixation blocks only (Figure C). Figure D provides a color coded table capturing Figures A, B, & C.

Role of Genes in Brain Networks

- Examine how external epigenetic influences and demographic factors drive such connections in the brain

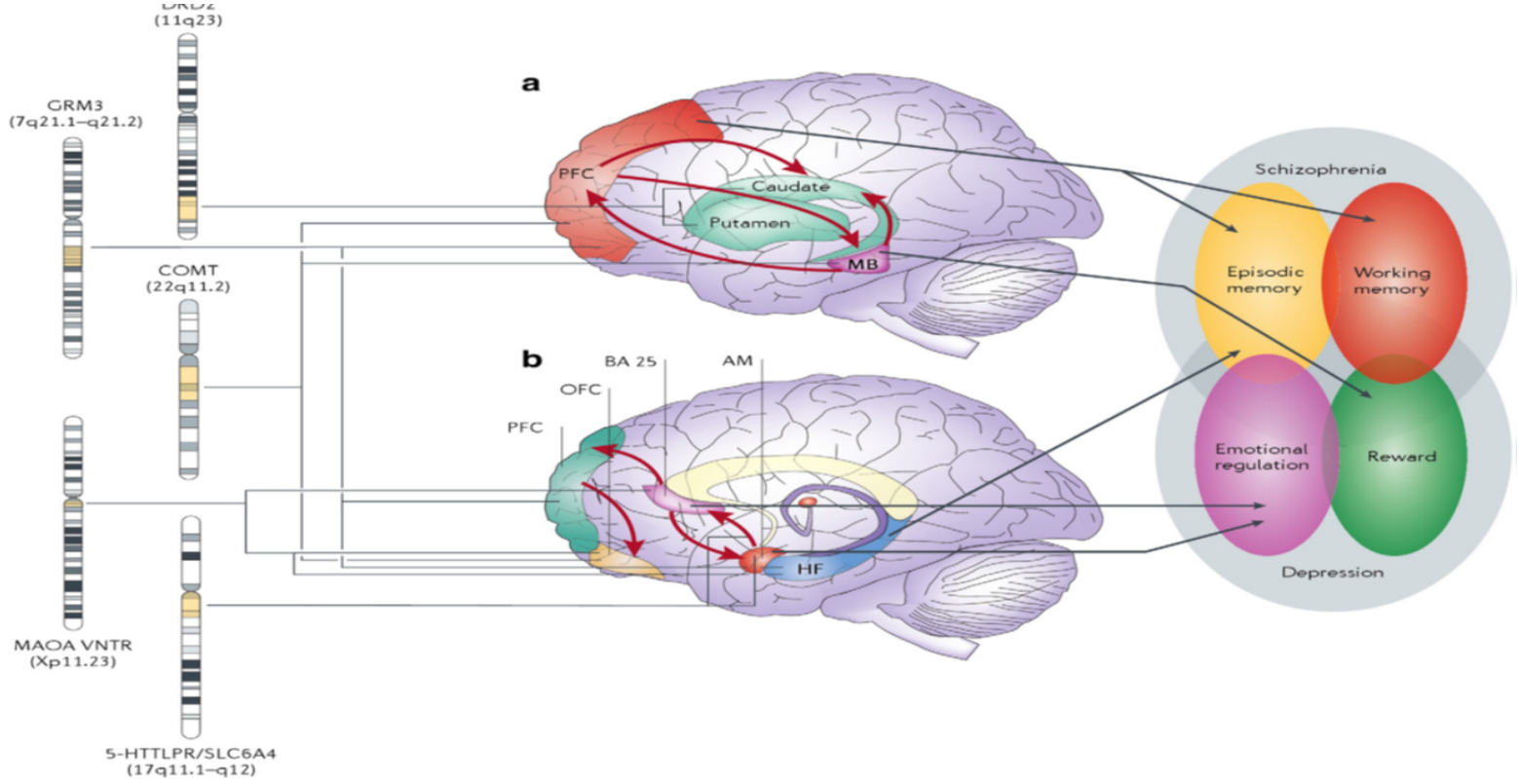


Figure: The complex path from genes to behavior and disease phenotype: mediation through brain circuitry (Tost et. al, 2012).

Motivating PTSD Example

- One of the key questions is why some individuals develop PTSD following trauma exposure while others are resilient
- Role of genetic influences on PTSD risk have been widely recognized
- However, not a lot of progress has been made in identifying causal genetic variants for PTSD.
- Some studies have shown the heritability estimates in the range of 30% to 40%, difficult to replicate these findings
- Likely due to the small effect sizes of the genetic risk factors for PTSD
- More practical to examine how genes alter brain network, which results in system level dysfunction leading to PTSD

Statistical Approaches lacking

- PTSD ex clearly indicates the importance of discovering genetic associations with brain networks
- Some recent developments on finding genetic associations with brain volumes and brain functional activations
- Very limited developments on genetic influences on brain networks - lot of potential!
- Combining imaging and genetic data to design a rich analysis yielding insightful summaries seems to be a meaningful endeavor

Semi-parametric Bayes Graphical Models for Imaging Genetics

- In this article, we model the imaging outcome as a function of genetic & demographic variables.
- We simultaneously (a) infer which genes activate which areas of the brain, (b) estimate the population level brain networks after accounting for external confounding effects, and , (c) infer independent modules in the brain which work together to drive phenotypic outcomes.
- The method assumes that the heterogeneity in the imaging outcome results from inherent genetic and demographic effects, and estimates the brain network after adjusting for these effects, which is common across all subjects.
- Applicable to PET and fMRI data from multiple subjects.

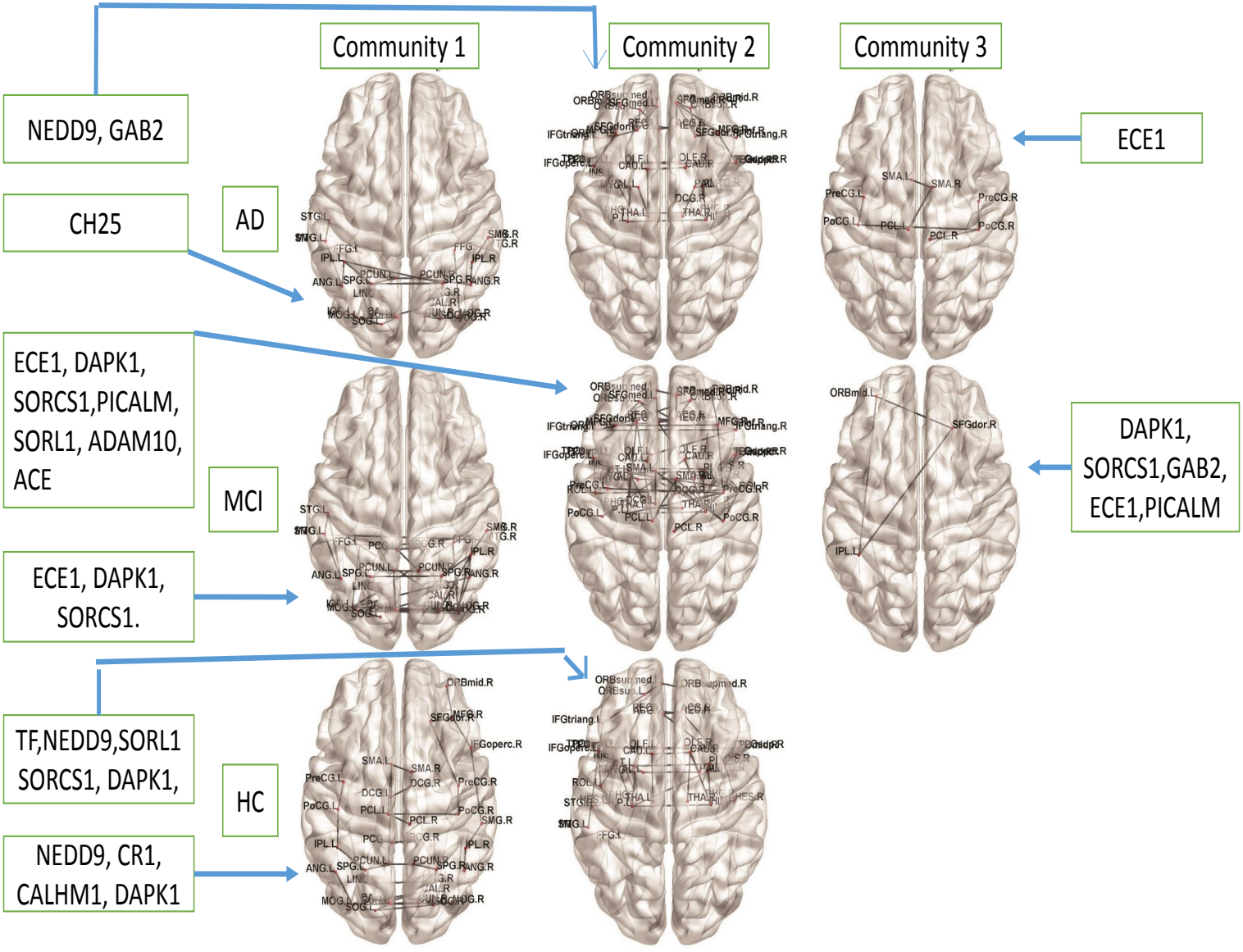


Figure: Brain Networks and Important Genes

Ongoing Work on Imaging Genetics

- Our ongoing work seeks to understand the underlying genetic and demographic causes of connections in the brain.
- Multiple genetic risk variants affect multiple neural systems linked to several psychiatric diseases phenotypes.
- These circuits, in turn, are suspected of mediating the risk for various neuropsychological functions.
- Can help us understand hereditary linkages for diseases.

Ongoing work

- Our proposal seeks to model different connections in the brain as a function of covariates, with it being possible to infer which covariates influence which connections in the brain, and the direction of association.
- We integrate fMRI, genetic & demographic data across subjects, to obtain a distinct brain network for each subject, and population level covariate effects
- Difficult problem to solve, since it involves a large number of model parameters along with multiple brain networks which need to be estimated

Ongoing work

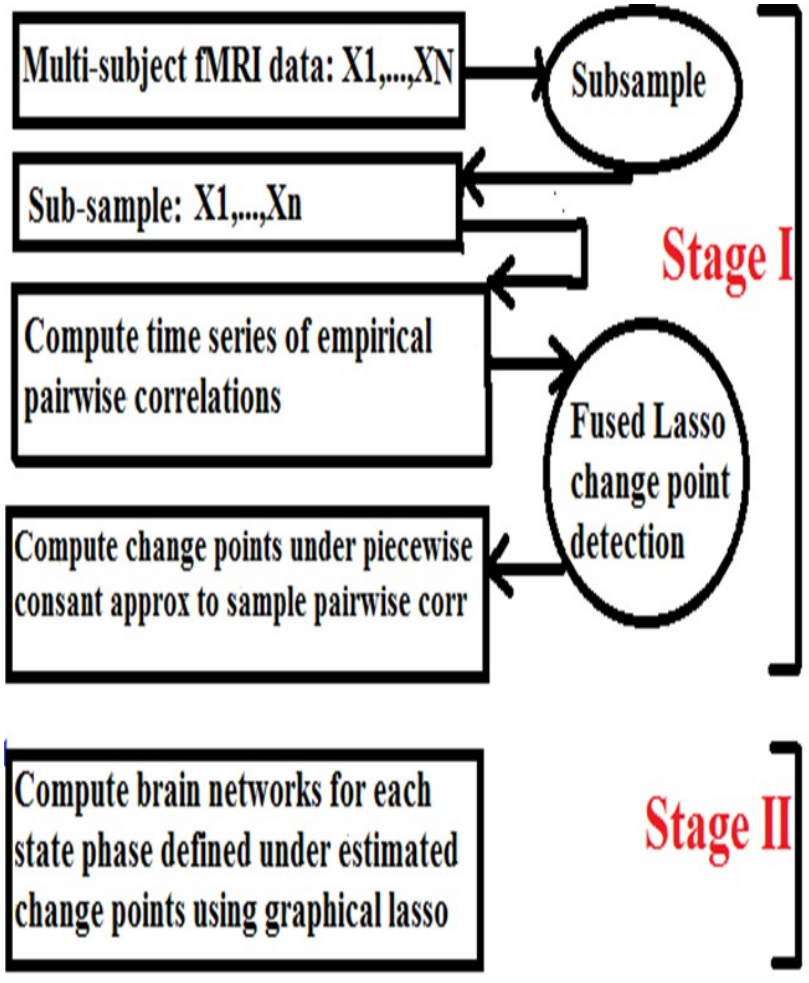
- We develop a dimension reduction approach based on latent scale models (Hoff et. al, 2002)
- The latent scales serve to reduce the dimension and can be modeled using genetic and demographic factors
- Goal is to develop a fast EM algorithm which is at least scalable to a moderate number of brain regions
- We anticipate further speed-ups under parallelization
- Opportunities for computational and methodology development!

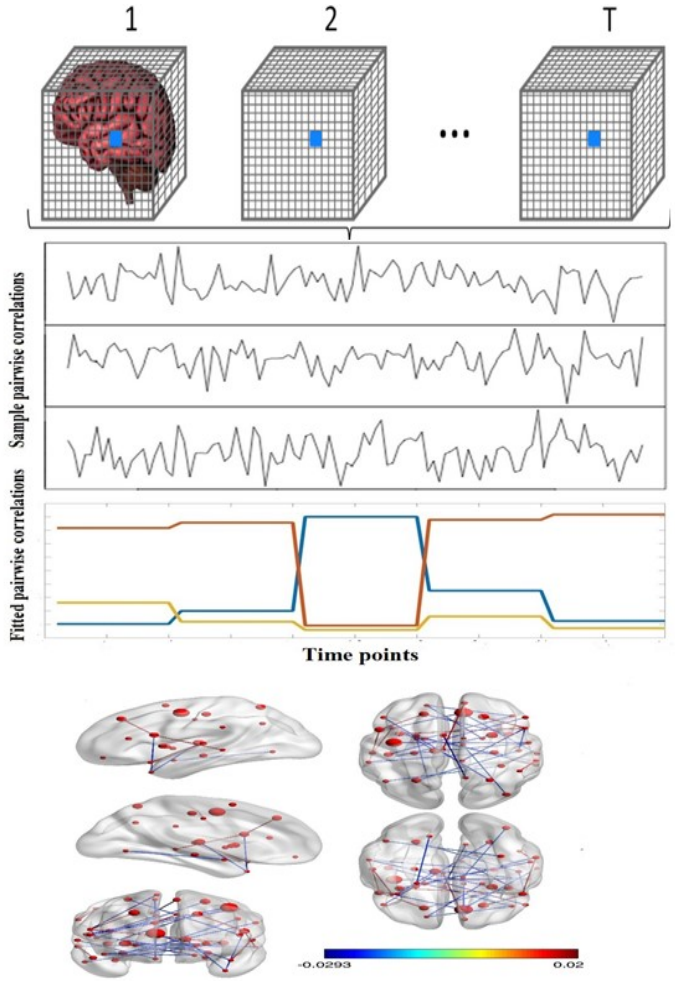
Dynamic Brain Networks using fMRI data

- This project seeks to address the fact that the brain functional network shows fluctuations over time.
- This calls for a dynamic approach for estimating the brain network, where the connectivity can change several times during the scanning session for a subject.
- We propose an approach based on fused lasso which automatically detects group level change points in the network
- The approach divides the scan session into distinct bins, with each such bin having a separate brain network

Dynamic Brain Networks using fMRI data

- The method is fully automated, with both the number and the location of the change points being estimated from the data.





Ongoing Work & Future Goals

- Ongoing work - integrate multimodel brain imaging data (fMRI and DTI) to estimate brain networks
- Develop scalable algorithms which can address voxel-wide, genome-wide analysis
- Branch out to more newer forms of data such as discrete neuronal spike train data

Thank You !