HBIC COGNEURO WORKGROUP

FMRI FUNCTIONAL CONNECTIVITY

OVERVIEW AND METHODS

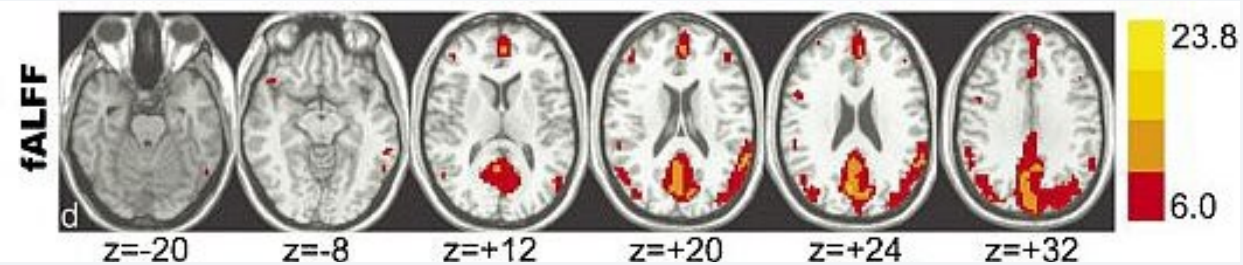
KU MEDICAL CENTER
The University of Kansas

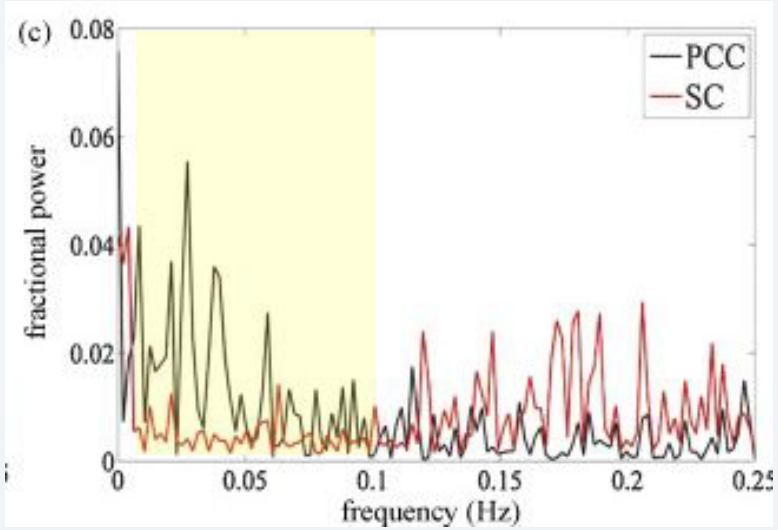
FUNCTIONAL CONNECTIVITY

- Voxel-Based
  - ALFF/fALFF: (fractional) Amplitude of Low-Frequency Fluctuations
  - ReHo: Regional Homogeneity
  - VMHC: Voxel-Mirrored Homotopic Connectivity
- Seed-based
  - SCA: Seed-based Correlation Analysis
  - PPI/gPPI: (generalized) Psychophysiological Interaction
- Network-based
  - Graph Theory
  - Network Degree Centrality
  - GIMME: Group Iterative Multiple Model Estimation
- Software

VOXEL-BASED

- **ALFF/fALFF: (fractional) Amplitude of Low-Frequency Fluctuations**
  - **Description**: Magnitude of slow, spontaneous regional fluctuations in the brain at rest.
  - **Calculate**: At each voxel, band-pass 0.01 - 0.1 Hz, transform time series to frequency domain, obtain power spectrum (square root). Z-transform.
    fALFF: also compute power spectrum from 0-0.25 Hz, calculate ratio of low-frequency to whole range.
  - **Usage**: Magnitudes differ between regions and groups and can be a marker of dysfunction. ALFF, compared to fALFF, is more prone to physiological noise, particularly near the ventricles and large blood vessels, but has higher test-retest reliability.

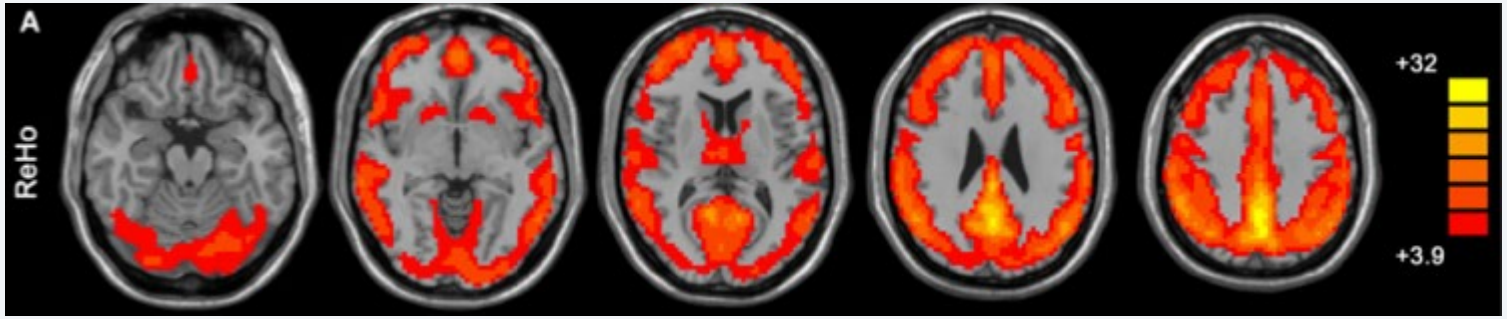


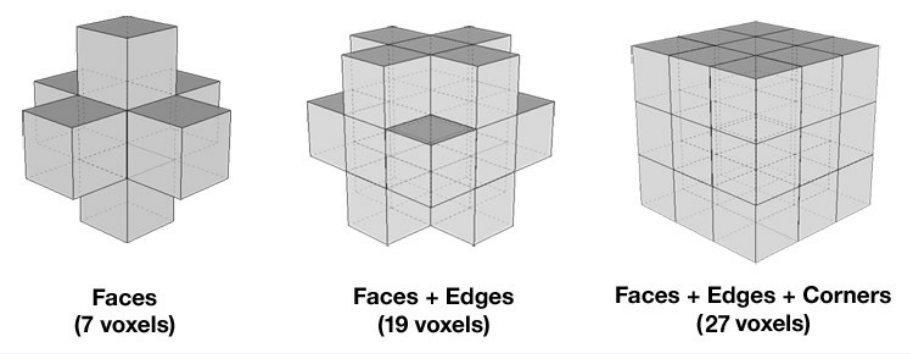


C-PAC https://fcp-indi.github.io/docs/latest/user/alff

VOXEL-BASED

- **ReHo: Regional Homogeneity**
  - **Description**: Synchronization between voxels and their neighbors during **rest or task** (block or slow event-related)
  - **Calculate**: At each voxel, correlate its timeseries with its immediate neighbors. Z-transform.
  - **Usage**: Identify cohesive regions without a priori definitions of ROIs

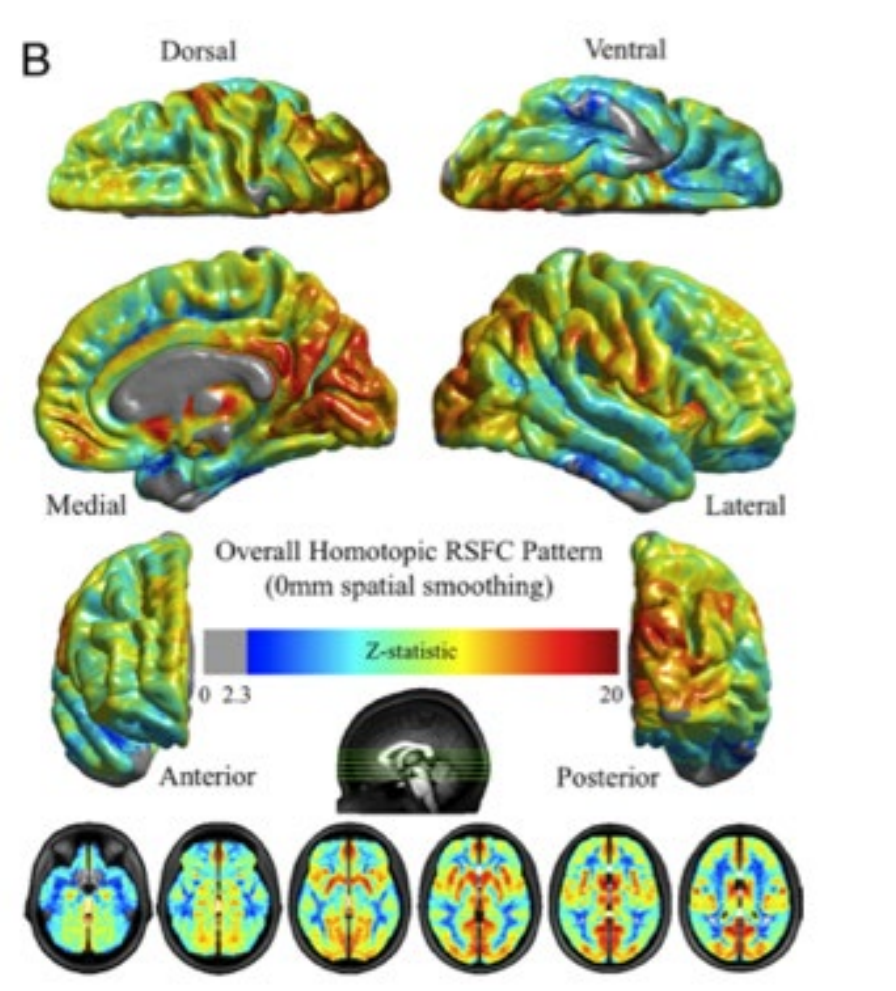




C-PAC https://fcp-indi.github.io/docs/latest/user/reho

VOXEL-BASED

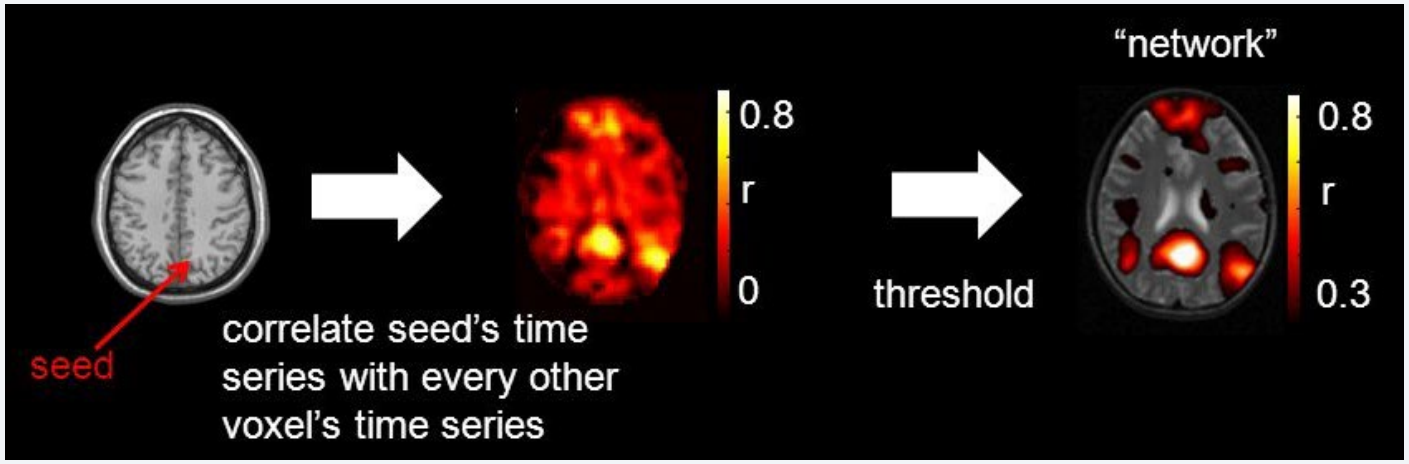
- **VMHC: Voxel-Mirrored Homotopic Connectivity**
  - **Description**: Synchrony between hemispheres
  - **Calculate**: Transform brain to a symmetric template. Correlate each voxel with its homologue in the other hemisphere.
  - **Usage**: Group differences in interhemispheric connectivity between patient/control groups. Indicator of disturbed functional specialization



C-PAC https://fcp-indi.github.io/docs/latest/user/vmhc

SEED-BASED

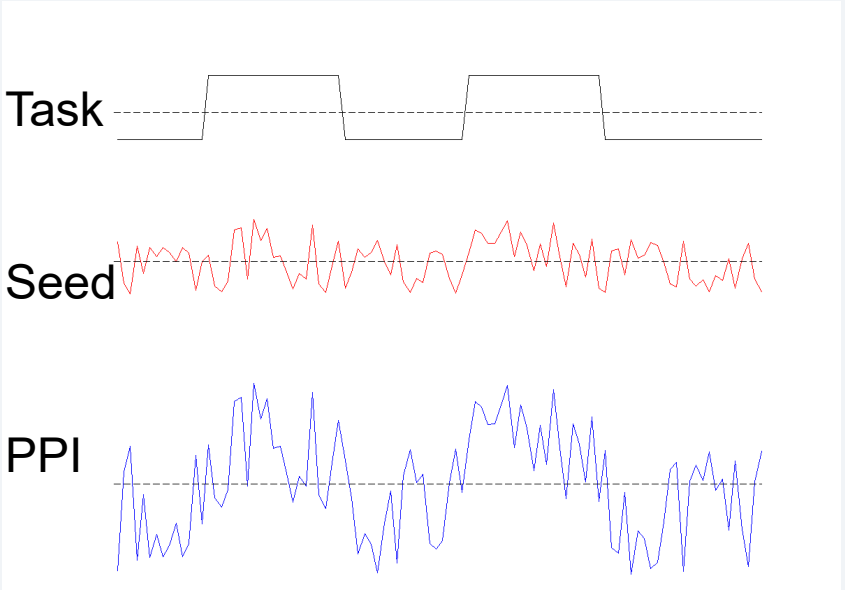
- **SCA: Seed-based Correlation Analysis**
  - **Description**: Whole-brain connectivity (i.e. synchronized activation) to a target voxel/ROI
  - **Calculate**: Extract the timecourse for a single voxel or mean timecourse in an ROI. Correlate its activity with all other brain voxels. Yields a voxel Z-score map that can be thresholded, cluster analysis, etc.
  - **Usage**: Identify network pattern and extent based on connectivity to a hub region



C-PAC https://fcp-indi.github.io/docs/latest/user/sca

SEED-BASED

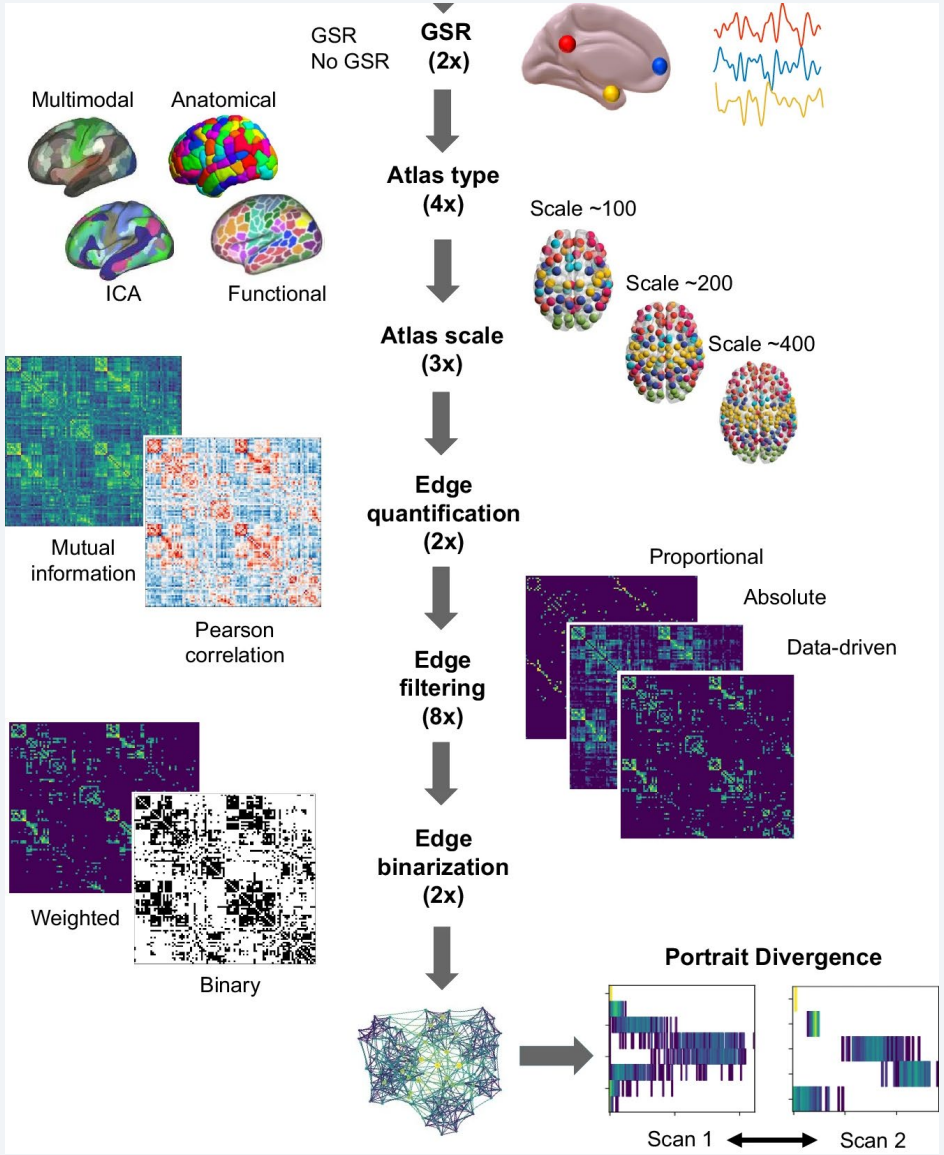
- **PPI/gPPI: (generalized) Psychophysiological interaction**
  - **Description:** how connectivity with a seed changes with psychological context
  - **Calculate:** first-level GLM with predictors: seed timecourse, each psychological context HRF convolved (taskA, taskB, baseline blocks), and the interaction between each psychological regressor and the seed
  - **Usage:** The interaction terms identify voxels whose functional connectivity with the seed changes when a condition is on or off, after accounting for condition-invariant connectivity between the two (the seed regressor), and conjoined baseline changes in activation with condition that are not correlated (the psychological regressor)

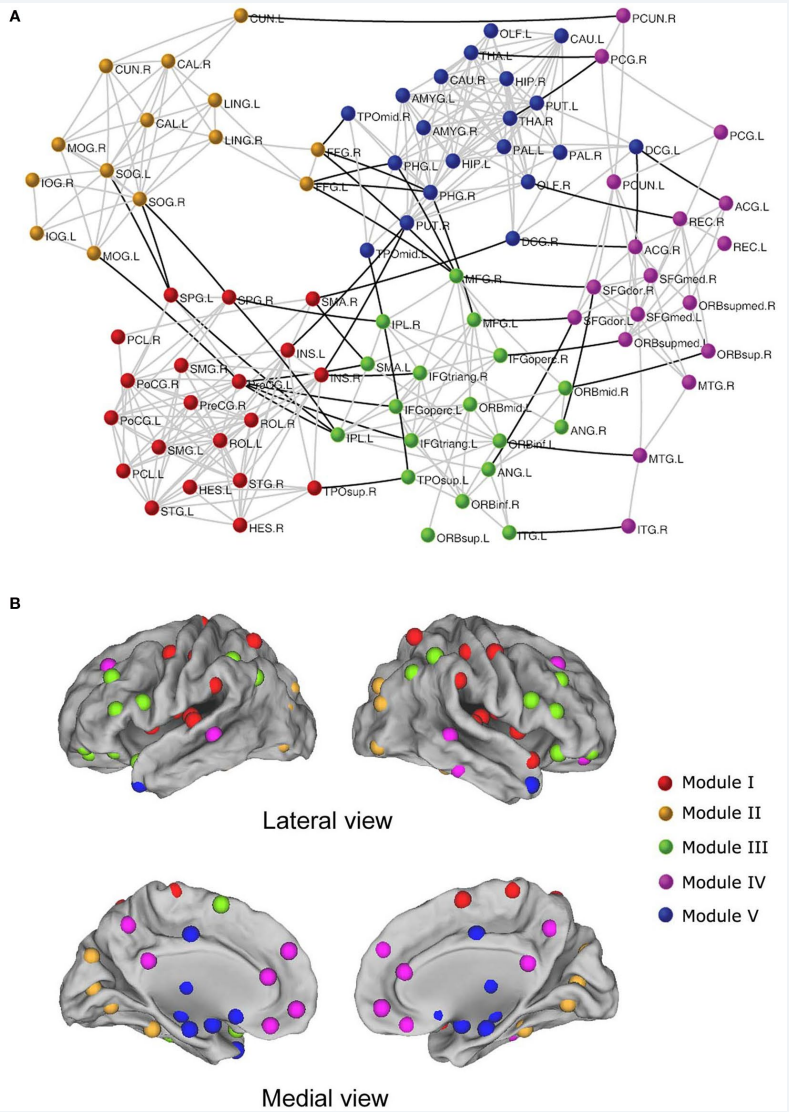


https://web.mit.edu/fsl_v5.0.10/fsl/doc/wiki/PPI.html

NETWORK-BASED GRAPH THEORY

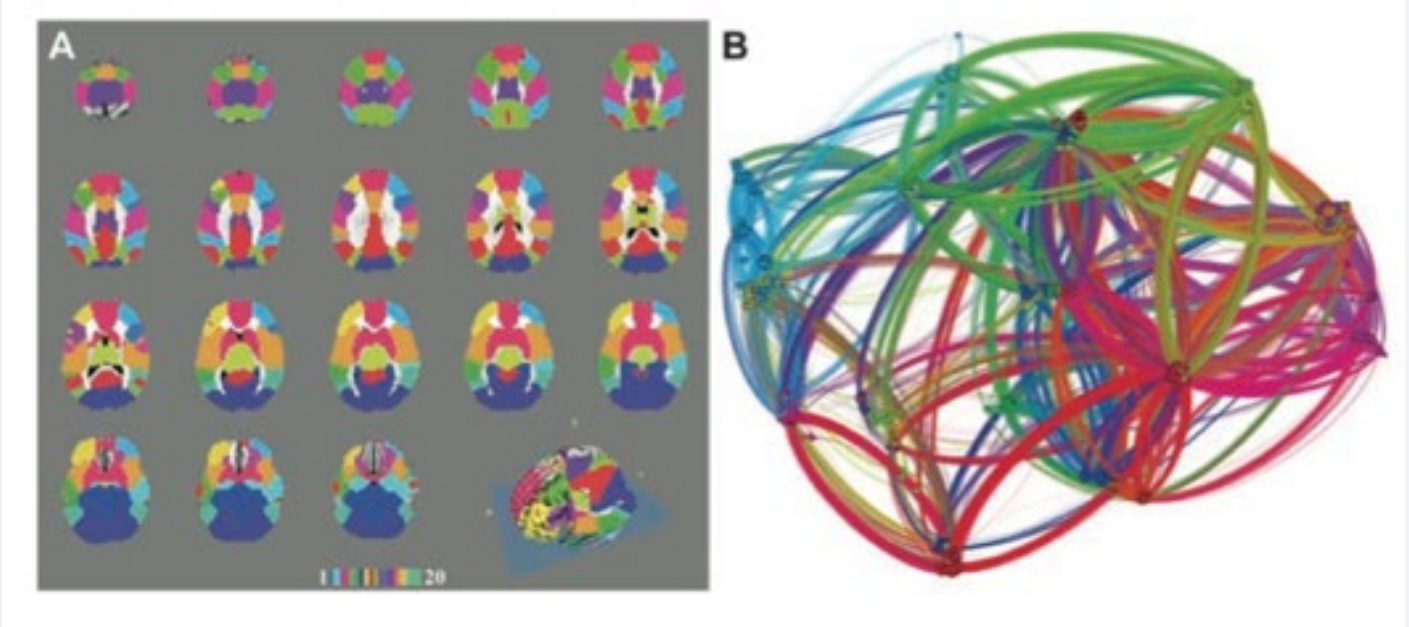
1. Parcellate the brain
2. Cross-correlate timecourses
3. Prune edges
4. Apply graph-theoretical approaches





NETWORK-BASED

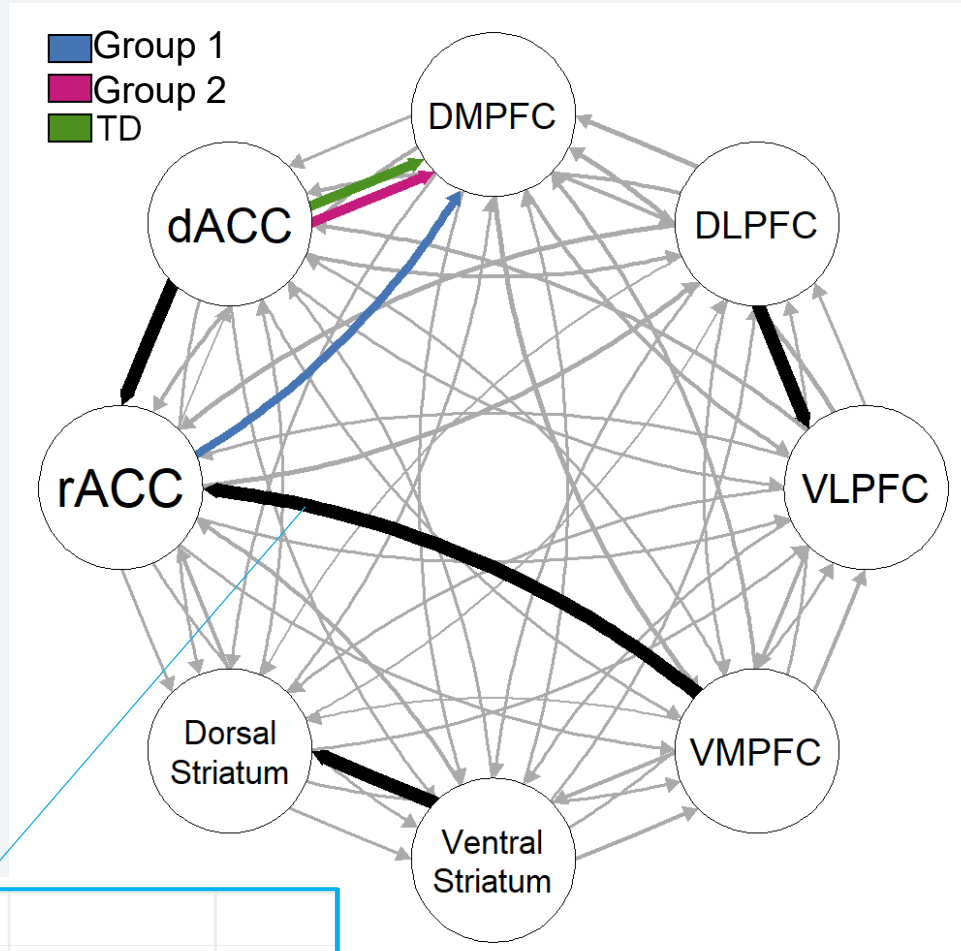
- **Network Degree Centrality**
  - **Description**: Identify regions that are highly interconnected to other regions
  - **Calculate**: Extract timecourses for ROIs from a template. Cross-correlate ROIs (nodes) and threshold the resulting matrix. Count the number of significant connections between a given node and all others.
  - **Usage**: Identify functional networks and their hubs, and changing within/between network connectivity as a function of age/group.

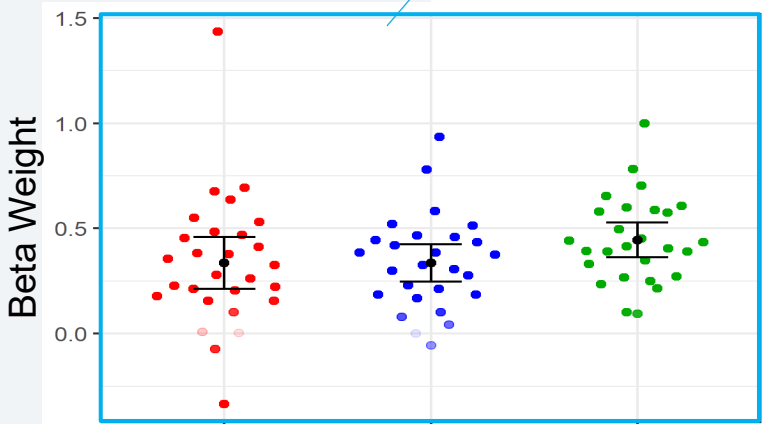


C-PAC https://fcp-indi.github.io/docs/latest/user/centrality

GIMME: GROUP ITERATIVE MULTIPLE MODEL ESTIMATION

- Given a network of ROIs, GIMME identifies **shared & individual** directed connections (contemporaneous & lagged) between nodes to arrive at person-specific time series models.
- First, connections present in greater than 75% of the sample are marked as group-level connections that are included in each individual model. After identifying a full group network, newly sub-threshold connections are pruned.
- Second (optional), sub-group connections are identified similarly to group connections, with the group model as a base. Subgroups can be data driven or specified *a priori.*
- Third, individual models are estimated using the group or subgroup model as a base. Individual connections are added iteratively until excellent fit is achieved. Group/subgroup connections cannot be pruned at this step.





https://tarheels.live/gimme/

GIMME: GROUP ITERATIVE MULTIPLE MODEL ESTIMATION

- **Exogenous factors**: time-varying predictors, e.g. the task condition, can be included as unidirectional predictors. HRF-GIMME (Hemodynamic Response Function) optimizes task-related factors for fMRI with individual estimates of the HRF to be convolved with task. Can show the degree to which, e.g., the relation between ROI1 and ROI2 is modulated by task.
- **A Priori Connections**: can specify in advance which connections to "lock in" to the group or subgroup models.
- **Censoring**: Missing timepoints are tolerated, per-participant
- **Data Recommendations**:
  - **Participants**: Minimum N=10 per subgroup
  - **Nodes**: Recommended 5-15 nodes, up to 3-20 nodes. Higher numbers possible, with costs to computation time
  - **Timecourse**: 200 timepoints accurately recovers path presence & direction. 50 timepoints is sufficient to recover path presence, but not direction.

SOFTWARE

- C-PAC: Configurable Pipeline for the Analysis of Connectomes
  - https://fcp-indi.github.io/docs/latest/user/index
  - Integrated multi-application preprocessing and functional connectivity analysis of resting state fMRI data. Allows branched processing (e.g. Global Signal regression on/off)
- CONN toolbox
  - https://web.conn-toolbox.org/home
  - SPM-based preprocessing and functional connectivity analysis of fMRI data
- XCP-D
  - https://xcp-d.readthedocs.io/en/latest/index.html
  - Takes an fMRIprep dataset directly as input, performs robust denoising (e.g. censoring and motion regression) and outputs parcellated timeseries, connectivity matrices, ALFF, and ReHo
- GIMME
  - https://tarheels.live/gimme/
  - R package to run GIMME analysis on formatted timecourse data
  - gimmefMRI: R package to run GIMME with excel configuration files