Global Correlation (GCOR) Correction for Group Analysis in Resting-State FMRI

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Two Corrections For Brain-wide Correlation Differences

1- Global Signal Regression (GSReg):

- Project brain-wide average timeseries as nuisance regressor
- Change in correlation matrices before (***R***) and after (***S***) GSReg

$$S - R = (P - (P\mathbf{1}\mathbf{1}^T P)/(\mathbf{1}^T P \mathbf{1})) * \sigma_Q \sigma_Q^T - P * \sigma_P \sigma_P^T$$

With ***P*** and ***Q*** being full voxel-to-voxel covariance matrices before and aver GSReg, respectively. ***Q*** is a function only of ***P***

S-R is constant for group with same cov. matrix ***P*** (Saad, 2013)

S-R will differ between groups with different ***P***

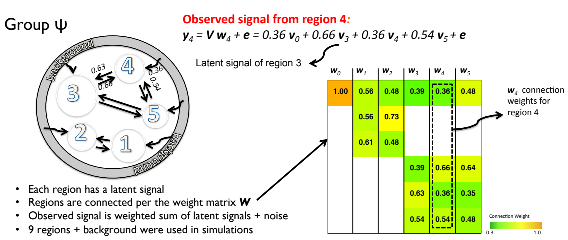
2- Global Correlation (GCOR):

- Use per-subject average of correlation matrix as covariate at level II test
- GCOR, the average of the entire correlation matrix ***R***, is easily computed by:

$$\gamma = 1/(M^2 N)\ \mathbf{1}^T U^T U\ \mathbf{1} = 1/N\ g_u^T g_u,$$

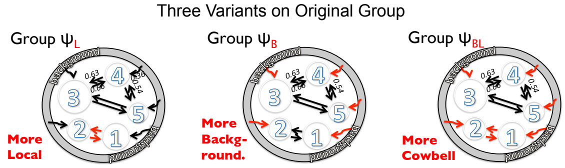
Where g_u is the average of all (M) unit variance time series of length N in matrix U

Generative Models For Groups with Different Connectivity



- Each region has a latent signal
- Regions are connected per the weight matrix ***W***
- Observed signal is weighted sum of latent signals + noise
- 9 regions + background were used in simulations

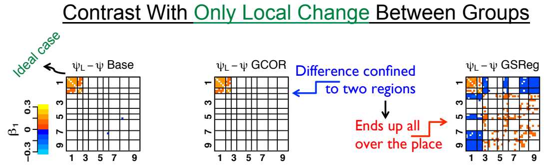
Three Variants on Original Group



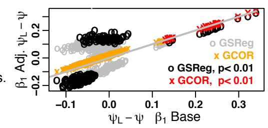
Consider group level correlation differences with three levell II models:

Base (No global adjustments) :	$r_{i,j} = \beta_0 + \beta_1 x$
GSReg at level I:	$s_{i,j} = \beta_0 + \beta_1 x$
GCOR as covariate: with overall mean centering	$r_{i,j} = \beta_0 + \beta_1 x + \beta_2 \gamma + \beta_3 x \gamma$

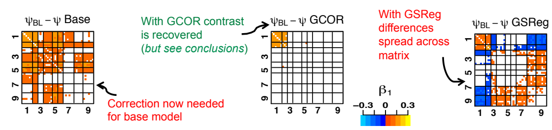
Contrast With Only Local Change Between Groups



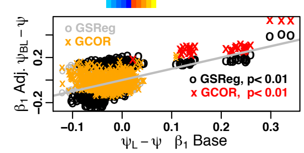
Correlation differences with GCOR are more linearly dependent on initial correlation differences. This becomes less so as correlation between GCOR and grouping variable increases. (Saad, 2013 for details)



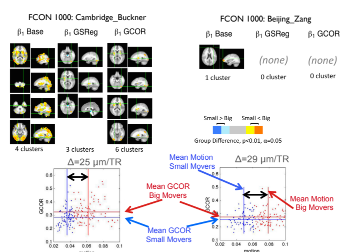
Contrast With Background & Local Change Between Groups



Contrast is recovered with GCOR but not with GSReg.
However GCOR can also bias correlations in a manner that depends on the initial covariance structure, as GSReg does. (Saad, 2013)



Application In Empirical Data: Grouping by Motion



Both GSReg and GCOR reduced difference.

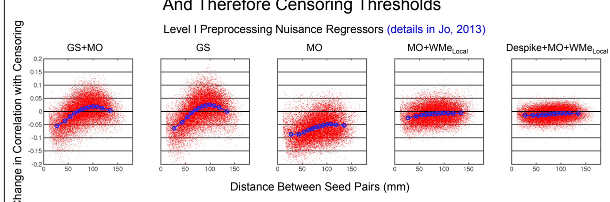
- However, this does not confer validity on GSReg.
- GSReg bias problems hidden in this contrast.
  - See Gotts et al. 2013 for group comparisons between ASD & TD

Is motion behind Base contrast results?

- Weak motion and GCOR correlation: (R^2= 11% Camb., 4.3% Beijing)
- Larger motion + Larger D in Beijing, BUT much less difference than Cambridge contrast

Correlations With GSReg Are More Sensitive to Motion And Therefore Censoring Thresholds

Level I Preprocessing Nuisance Regressors (details in Jo, 2013)



Data Generously Contributed by Power and Coauthors (Power, 2012)

QR code provides link to script for full reproduction of plots above

Conclusions

Of GSReg And Its Variants:

- Time series directly derived from fluctuations of interest should not be projected from the data
- Resultant correlations hard to relate to those of neuronal fluctuations reflected in BOLD signal
- This is particularly troublesome when comparing groups with differing connectivity profiles
- GSReg makes correlations more sensitive to motion and therefore to censoring levels
- These effects are not confined to these simulations, see Gotts et al 2013 for empirical parallels

Of GCOR:

- Correlations at the group level are less biased with GCOR, compared with GSReg.
- Level-II tests are conservative with GCOR as a covariate
  - Less likely to detect difference as grouping variable and covariate correlation increases
- Adjustment outside of level II test is NOT recommended
  - Must consider Interaction effect with group
  - Must consider correlation with grouping variable
  - GCOR (and other params. (Yan 2013)) depend on noise AND/OR inter-regional correlations of interest

    →contrast results very likely depend on covariate centering

    •Centering at overall mean makes sense if GCOR is driven by noise.

    •What if it is also (or solely) driven by correlations of interest?

    → contrast sign might even get reversed

In Short:

At the very least, GCOR, which is very simple to compute, is useful to assess global correlation levels.

While it is better than GSReg for adjusting global correlation differences, it should only be used as a last resort, and included as a covariate in level II test.

The best approach for correcting noise induced global correlations remains with careful denoising, including physiological corrections.

References:

Gotts et al 2013: The perils of global signal regression for group comparisons: A case study of Autism Spectrum Disorders

Jo et al 2013: Effective Preprocessing Procedures Virtually Eliminate Distance-Dependent Motion Artifacts in Resting State FMRI

Saad et al 2013: Correcting Brain-Wide Correlation Differences in Resting-State FMRI

Power et al 2012: Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion.

Yan et al 2013: Standardizing the intrinsic brain: Towards robust measurement of inter-individual variation in 1000 functional connectomes

For related OHBM 2013 posters, papers, data, and processing scripts: http://afni.nimh.nih.gov/pub/dist/HBM2013