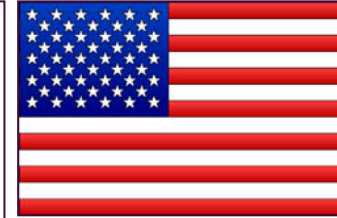


# Global Correlations: What You Don't Know Will Hurt You

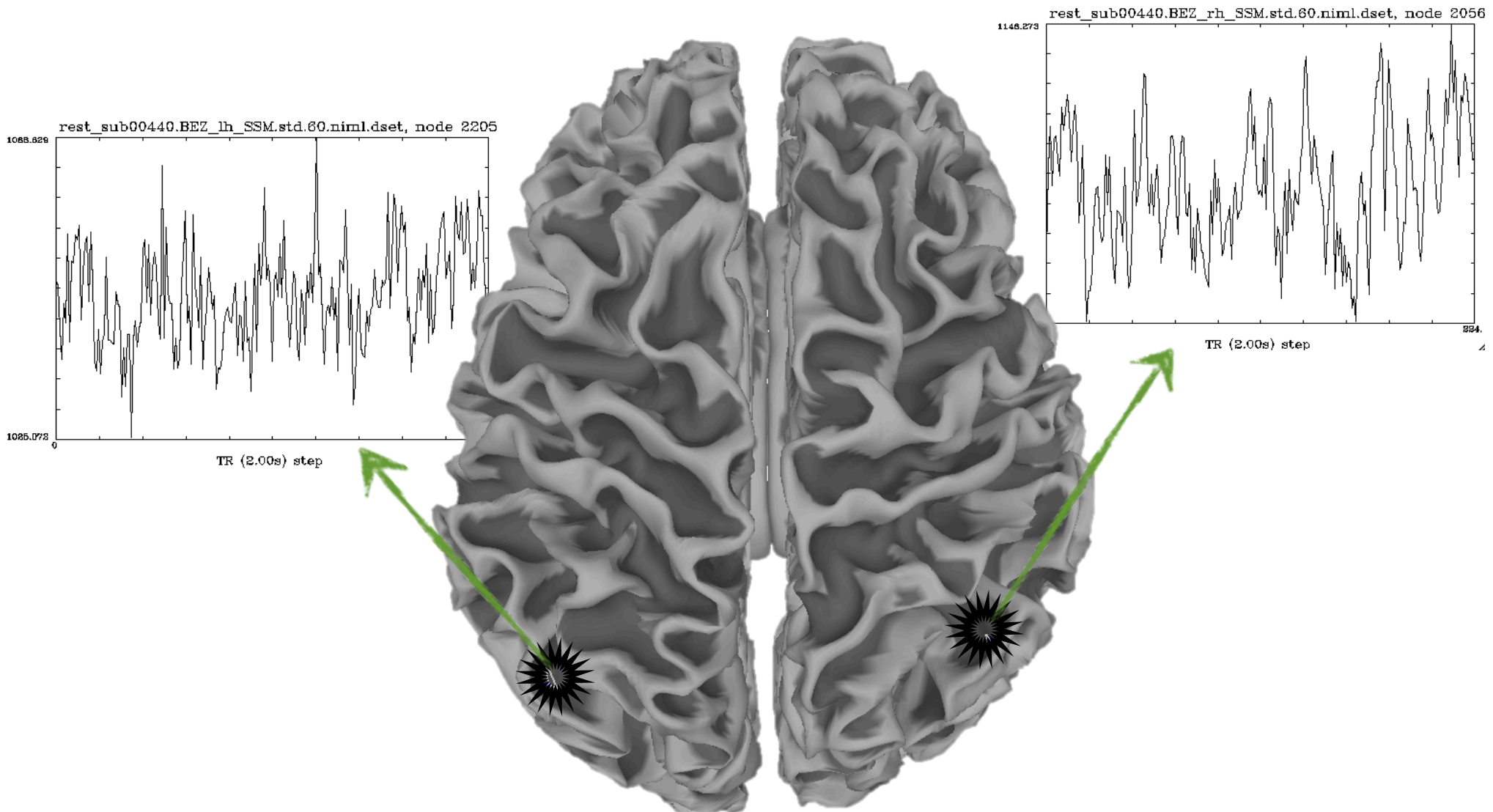
Ziad S Saad, PhD

SSCC / NIMH & NINDS / NIH / DHHS / USA /  
EARTH



# Resting state

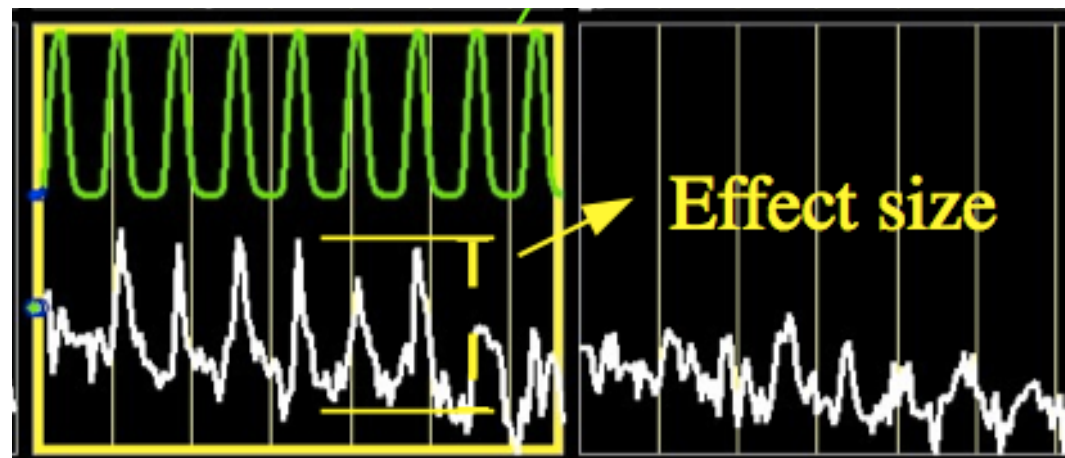
BOLD signal fluctuations **during undirected** brain activity



# Resting state

BOLD signal fluctuations **during undirected** brain activity

There is **no model for signal**, such as expected response in task FMRI



# Resting state

BOLD signal fluctuations **during undirected** brain activity

There is **no model for signal**, such as expected response in task FMRI

Resort to **describing relationships** between brain regions

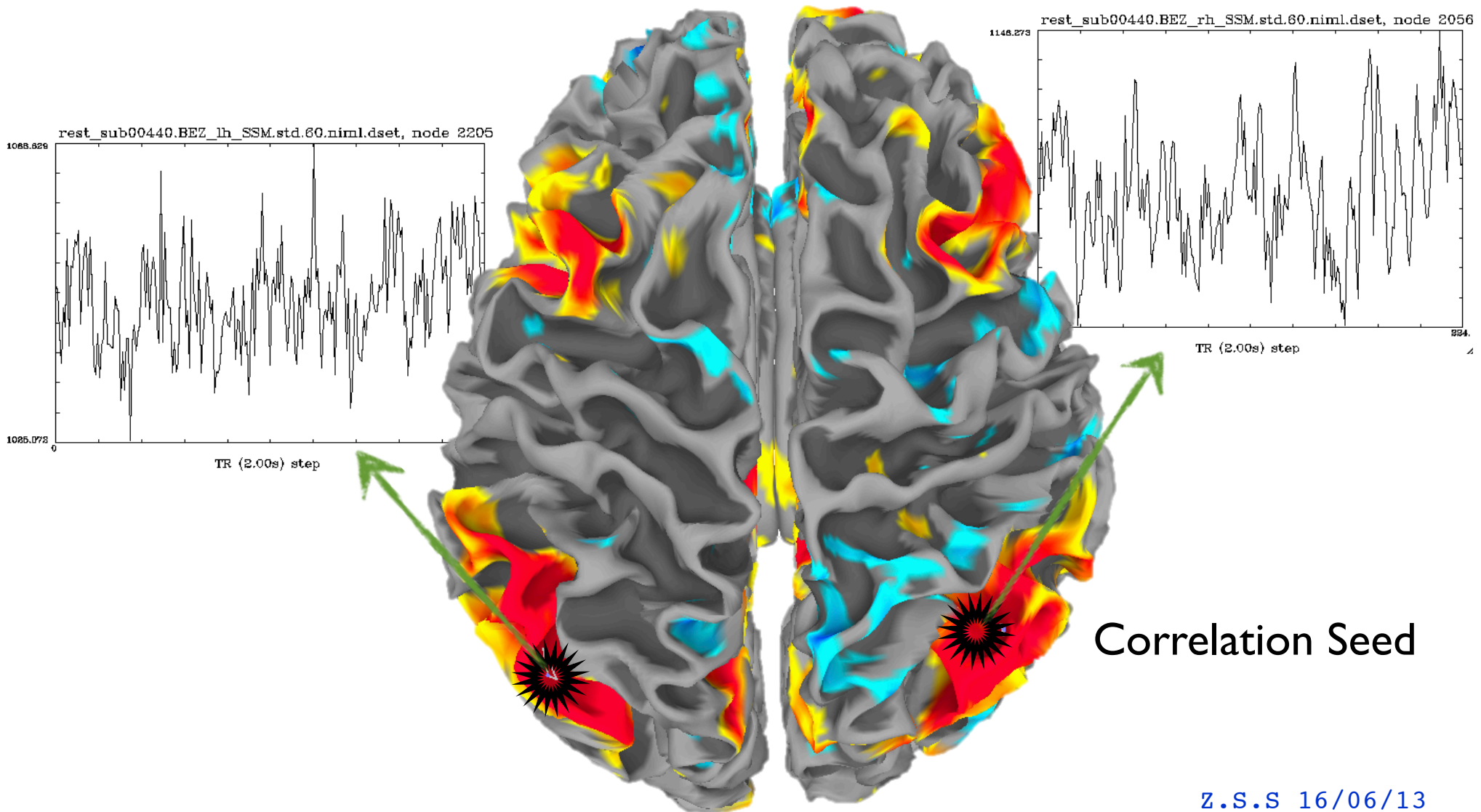
Correlation matrices, graph theory, functional/effective/\* connectivity

Factoring data into space $\otimes$ time components in statistically interesting ways (PCA, ICA)



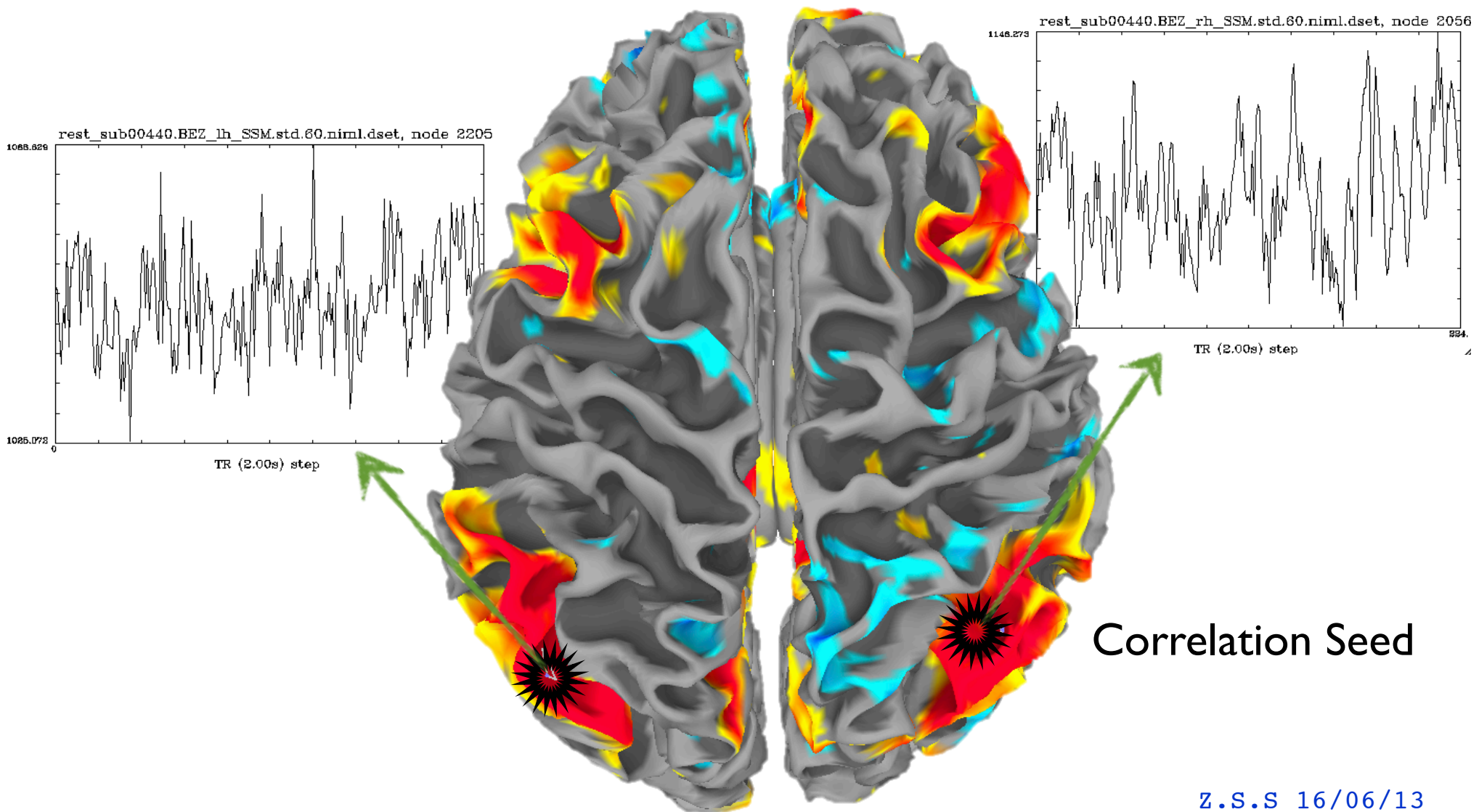
# Resting state

Resort to **describing relationships** between brain regions



# Resting state

Interpret **correlation strength as proxy** for brain function coupling between regions



# The magic of resting state (Biswal 95)

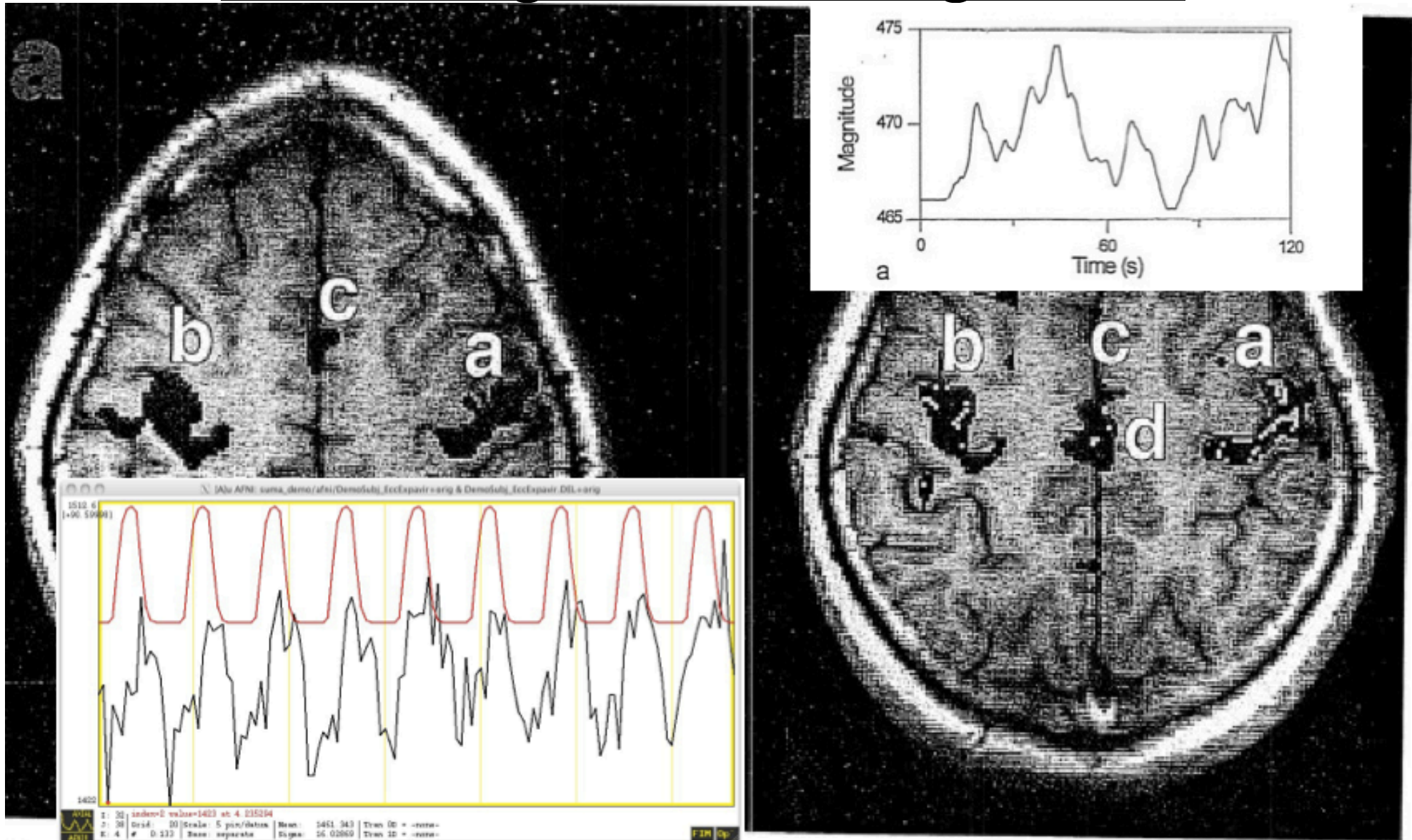
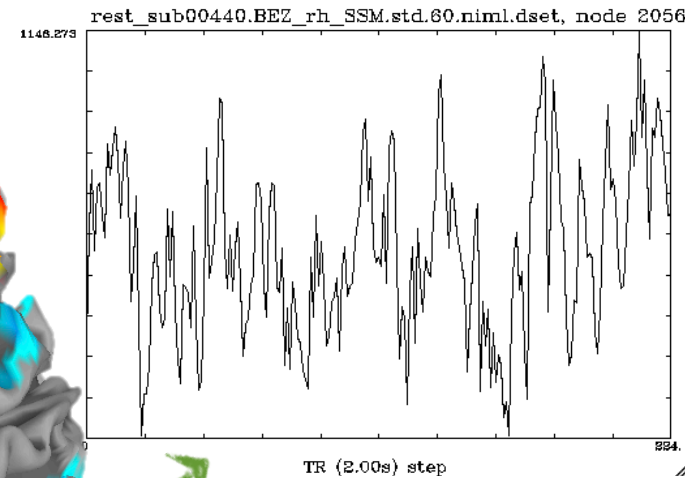
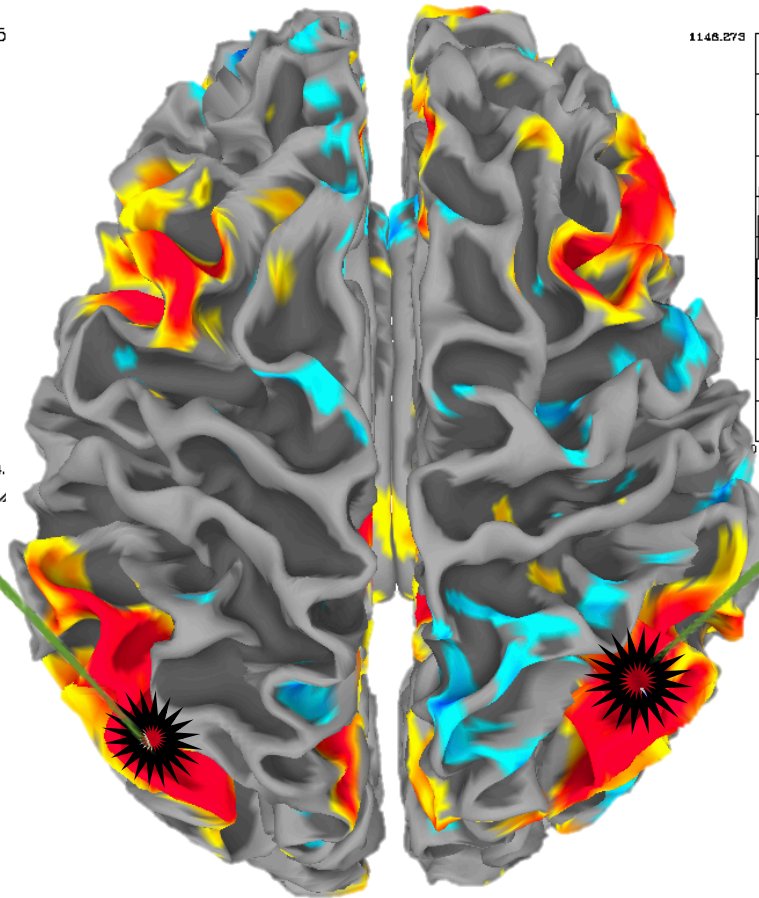
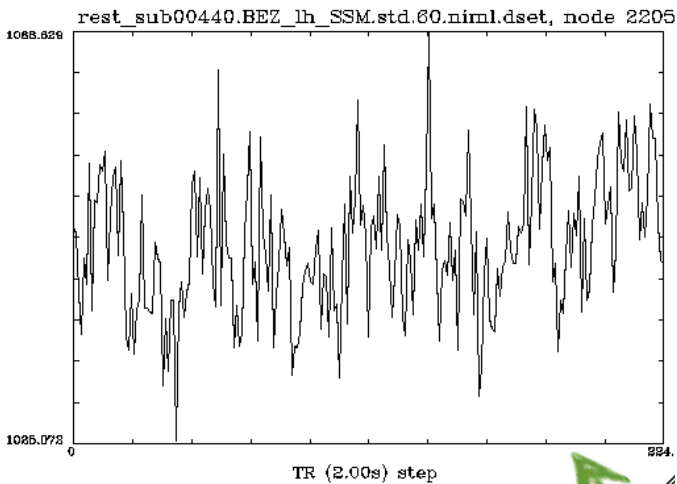


Fig. 3. (Left) FMRI task-activation response to bilateral left and right finger movement, superimposed on a GRASS anatomic image. (Right) Activation response using the methods of this paper. See text for assignment of labeled regions. Red is positive correlation, and yellow is negative.



# Resting state PROBLEM

Neuronally driven **BOLD fluctuations of interest**  
AND  
Fluctuations from respiration, heart beat, motion



# The fount of our troubles

We have **no model for signal**

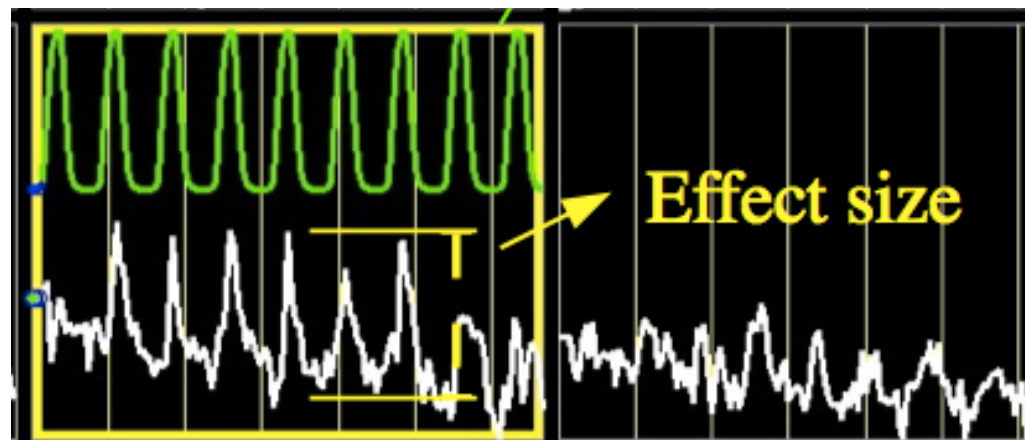
Nothing like the expected response (regressors) of task FMRI

We have **no good models for noise**

We have some, but they're far from perfect

**Effect size** (as correlation) is a spatially **varying function of noise** (fluctuations of no interest)

- Noise can bias correlations up, or down depending on the noise's spatial covariance
- In task FMRI by contrast, noise affects variance of effect size estimate



# The fount of our troubles

Difficult to attach meaning to effect size in RS-FMRI

Effect is like an SNR measure, affected by changes in both signal (numerator) and noise (denominator)

For example more motion → more noise → more correlation (bias) → group differences

Weak but consistent bias → significant difference

Some sources have brain-wide (global) effects on correlation distribution (e.g. ETCO<sub>2</sub> , motion, etc.)

# Sources of bias

- Head motion ([Van Dijk, 2012](#)) ([Power, 2012](#))
- Physiological “Noise”
  - Respiratory or cardiac cycles ([Glover, 2002](#))
  - Non-stationarity of breathing and cardiac rhythms ([Birn, 2006](#)) ([Shmueli, 2007](#)) ([Chang, 2009](#))
- Hardware instability ([Jo, 2010](#))
- Anatomical bias
- Pre-processing



# Adjusting brain-wide nuisances

- Model noise effect on time series and project
  - Motion estimates
  - Retroicor/RVT/etc requires simultaneous recordings of cardiac and respiratory cycles  
(Glover 2002; Birn 2006; Shmueli 2007; Chang 2009)
  - Nuisance signals estimates from dataset
  - Tissue-based nuisance regressors  
(Beckmann 2004; Fox 2009; Behzadi 2007; Beall 2007, 2010; Jo 2010, 2013; Kundu 2012; Bright 2013; Boubela 2013)
- Group level adjustments
  - Covariates for motion, brainwide levels of correlation  
(Van Dijk 2012; Satterthwaite 2012; Saad 2013; Yan 2013)

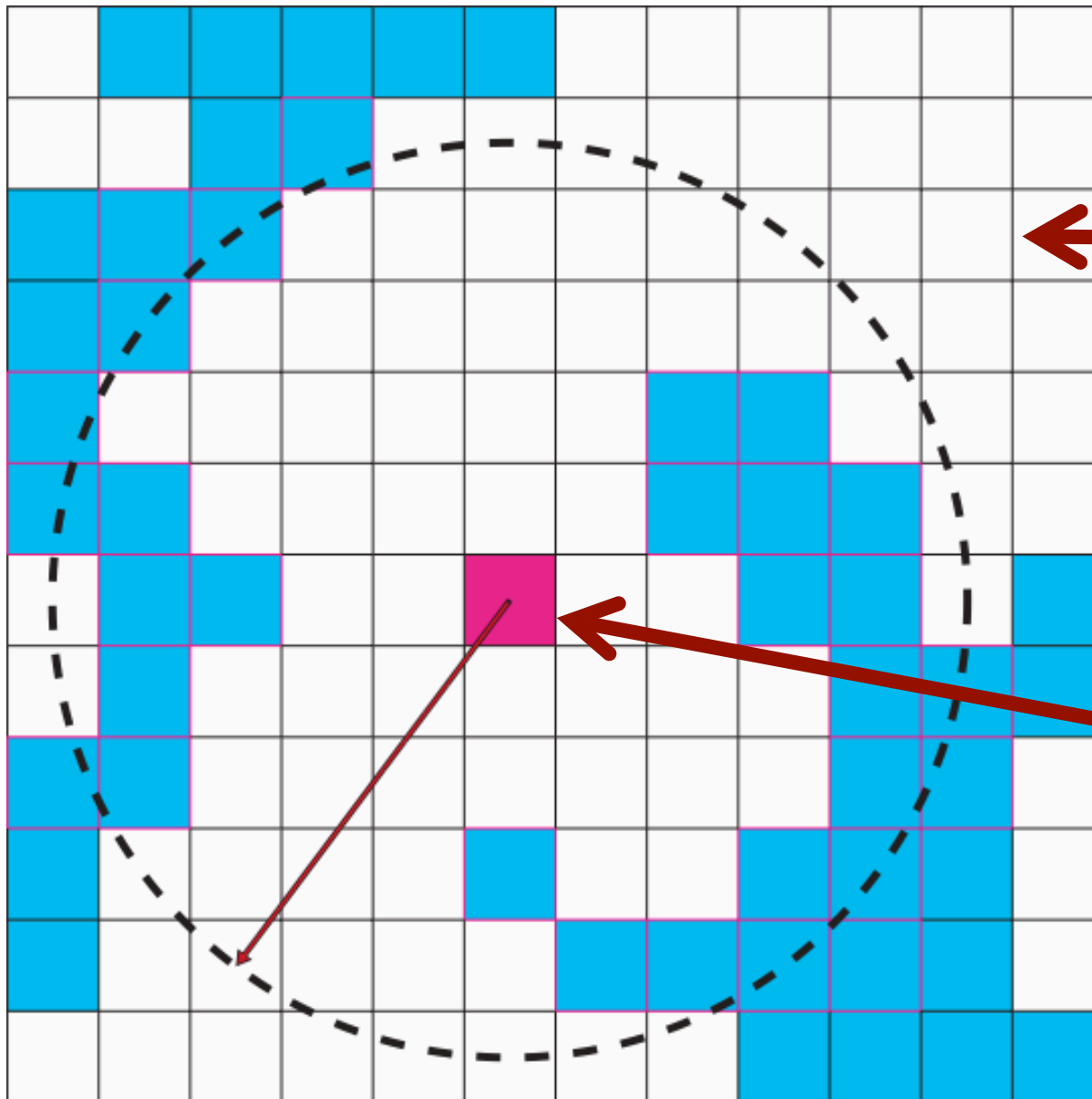
# Tissue-based nuisance regressors

- **Avoid Projecting Fluctuations of Interest**
- OK to sample nuisance signals from regions whose fluctuations are not correlated with the *fluctuations of interest* in the regions of interest
- Should not project time series containing aggregates of fluctuations of interest, even if they contain contribution from noise
  - Sagittal sinus voxels might allow sampling of aliased heart rate, HOWEVER they also exhibit BOLD fluctuations of interest from the regions being modeled (Jo, 2010)

# And why not?

- Because you end up **differentially biasing** the correlation matrices of your groups, and considerably distorting group differences
- Best explained with GSRreg because math is straight forward.
  - What follows applies whether or not noise exists or differs between groups

# ANATicor – Tissue Based but *not* GM

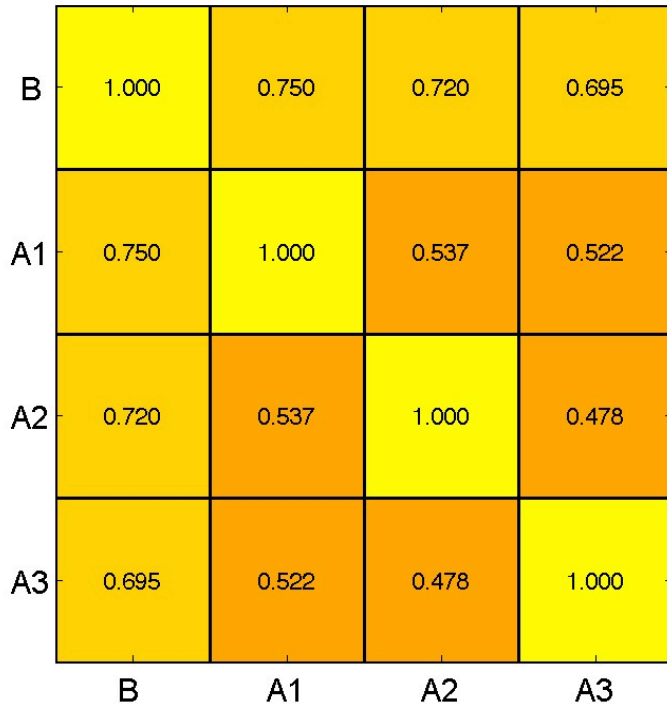


Eroded WM  
mask (Wme)

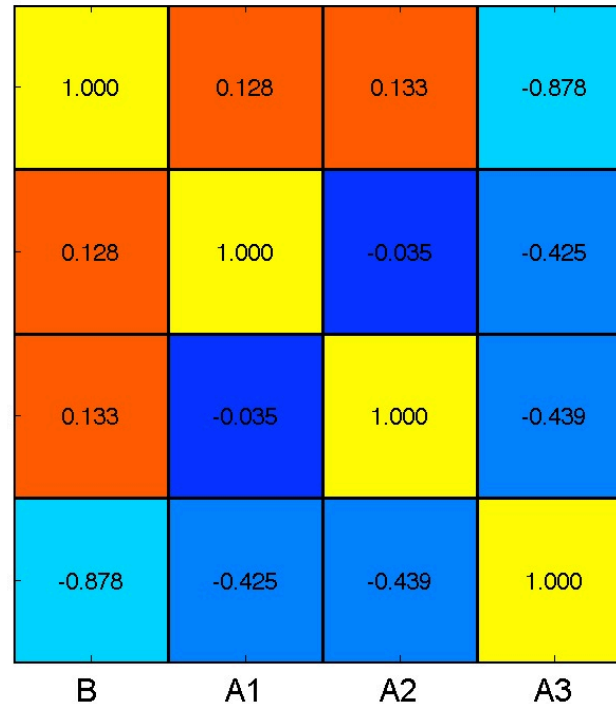
Average over  
WMe voxels  
inside 25mm  
radius

# Why not GSReg ?

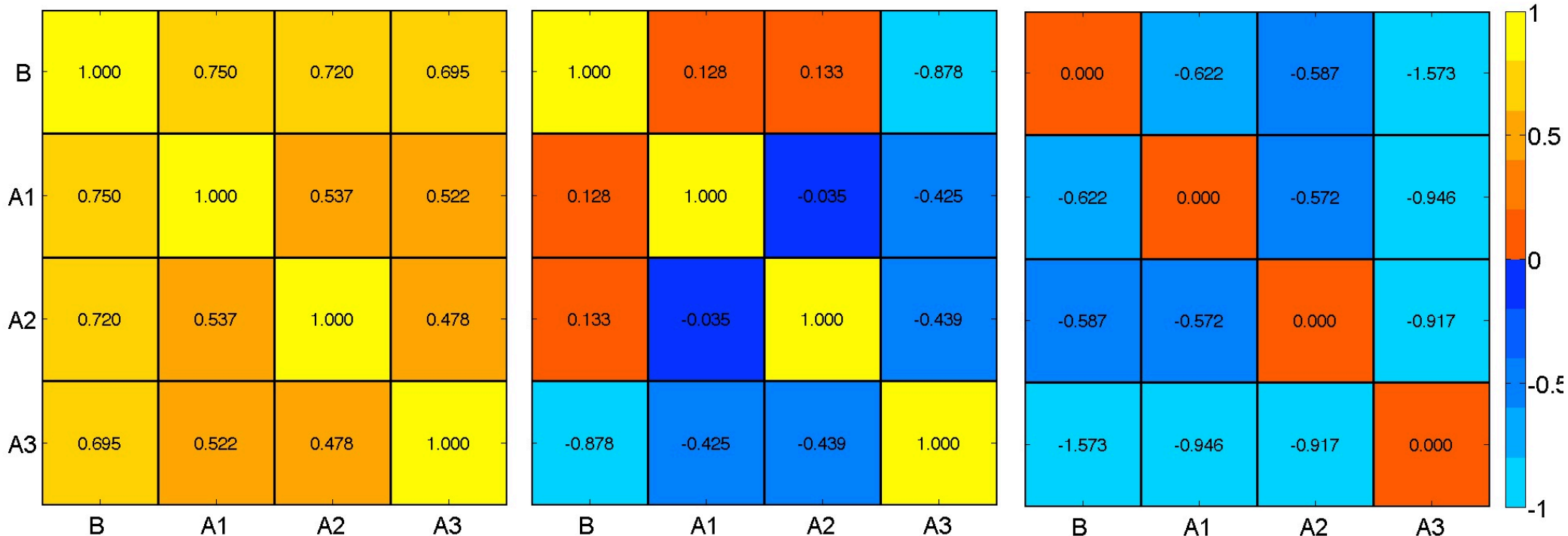
Original ( $R$ )



After GSReg ( $S$ )



$S - R$



Bias **will vary** by region pair

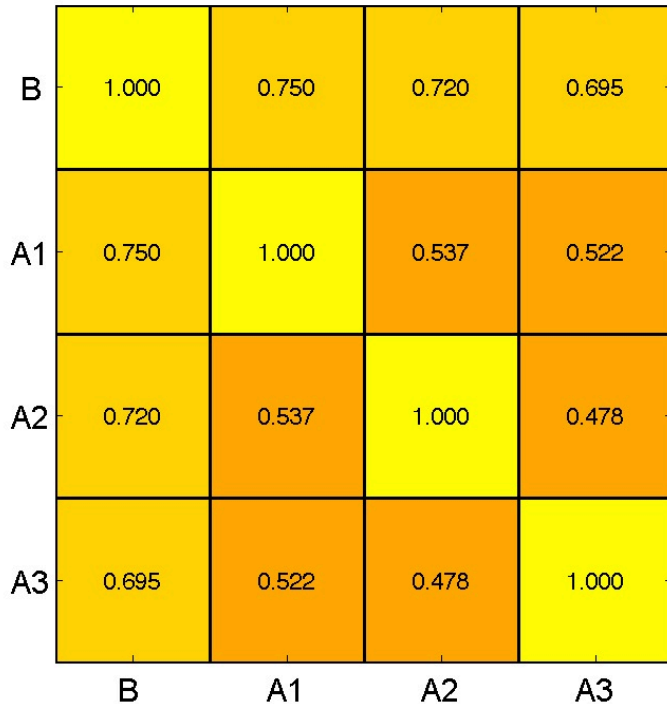
AND

Entirely dependent on initial covariance matrix  $P$

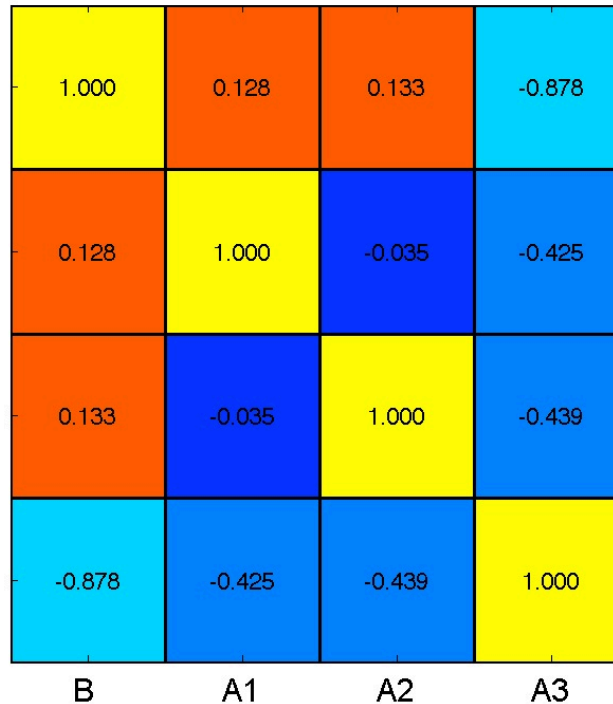
(therefore your grouping variable)

# Why not GSReg ?

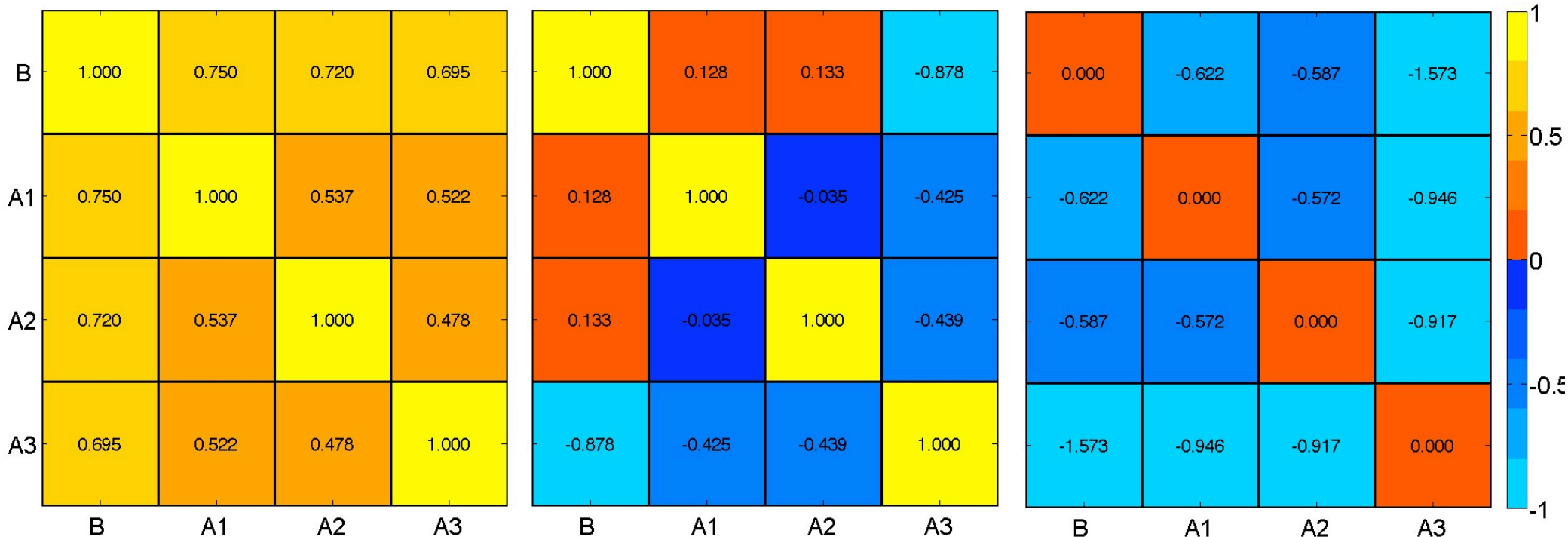
Original ( $R$ )



After GSReg ( $S$ )



$S - R$



For any FMRI time series (not just simulations)

$$S - R = (P - (P11^T P)/(1^T P 1)) * \sigma_Q \sigma_Q^T - P * \sigma_P \sigma_P^T$$

$S-R$  is constant for group with same cov. matrix  $P$

( $Q$  is also a sole function of  $P$ ) (Saad, 2013)

# Are biased estimates useful?

Region pair dependent **biasing is OK** if:

Not interpreting correlations between regions as those between the sampled BOLD signals and by extension neuronal signals

Not just about interpretability of negative correlations ([Murphy, 2008](#); [Weissenbacher, 2009](#); [Cole, 2010](#))

Two strongly correlated regions after GSReg DOES NOT imply regions were strongly correlated before GSReg

Using correlations after GSReg as some feature space for parcellation, classification, etc



# Are biased estimates useful?

Region pair dependent **biasing is OK** if:

Not interpreting correlations between regions as those between the sampled BOLD signals and by extension neuronal signals

Not just about interpretability of negative correlations (Murphy, 2008; Weissenbacher, 2009; Cole, 2010)

Two strongly correlated regions after GSReg DOES NOT imply regions were strongly correlated before GSReg

Using correlations after GSReg as some feature space for parcellation, classification, etc

Region pair dependent **biasing is problematic** if:

Comparing two groups with different signal covariance structures

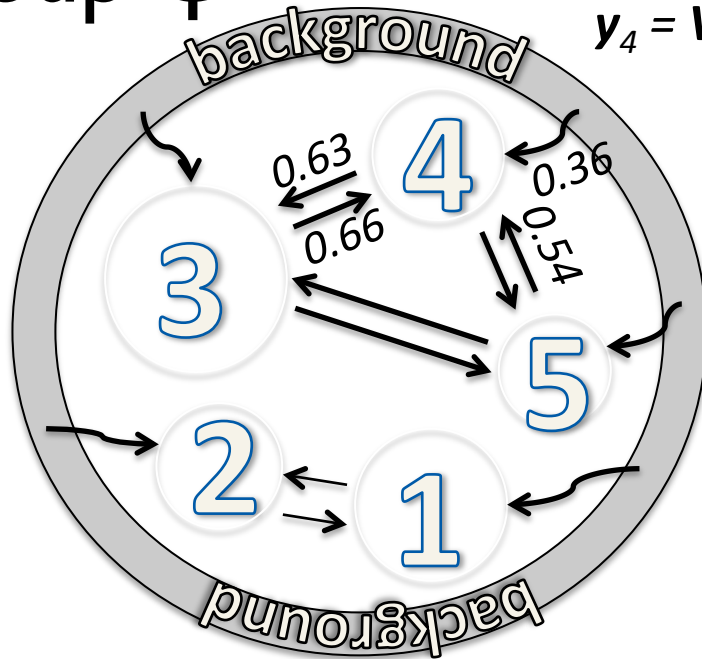
$$\mathbf{S} - \mathbf{R} = (\mathbf{P} - (\mathbf{P}\mathbf{1}\mathbf{1}^T\mathbf{P})/(\mathbf{1}^T\mathbf{P}\mathbf{1})) * \boldsymbol{\sigma}_Q\boldsymbol{\sigma}_Q^T - \mathbf{P} * \boldsymbol{\sigma}_P\boldsymbol{\sigma}_P^T$$

$\mathbf{S}-\mathbf{R}$  is constant for group with same cov. matrix  $\mathbf{P}$

**$\mathbf{S}-\mathbf{R}$  will differ between groups with different  $\mathbf{P}$**

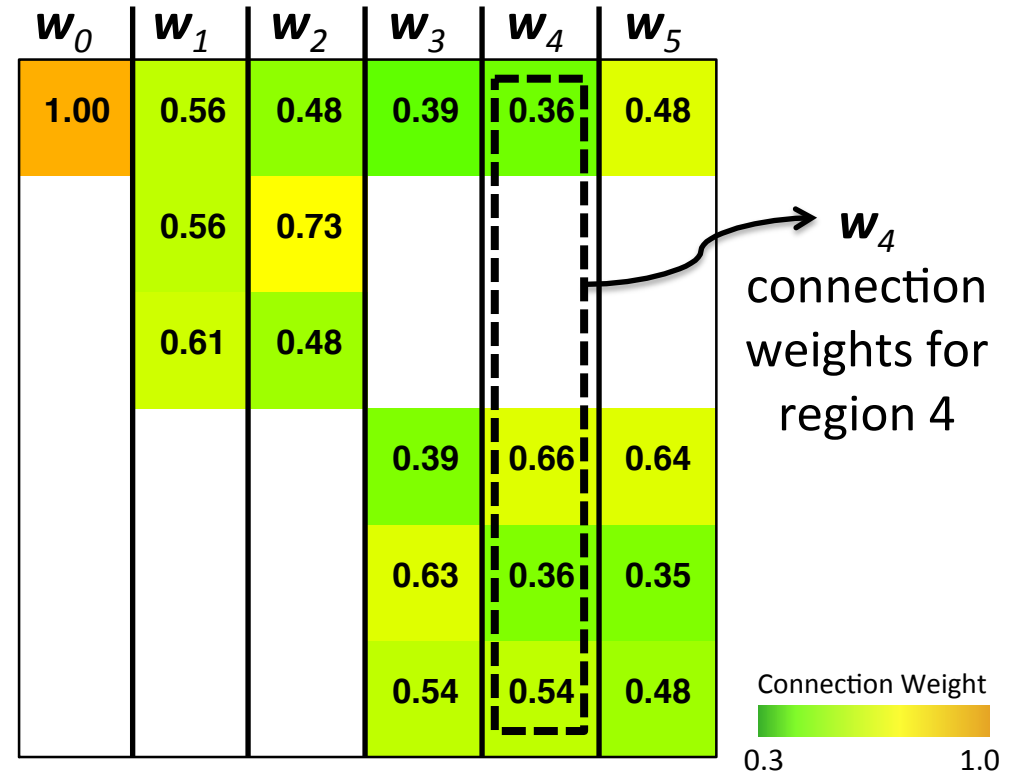
# An illustrative model

Group  $\psi$



Observed signal from region 4:

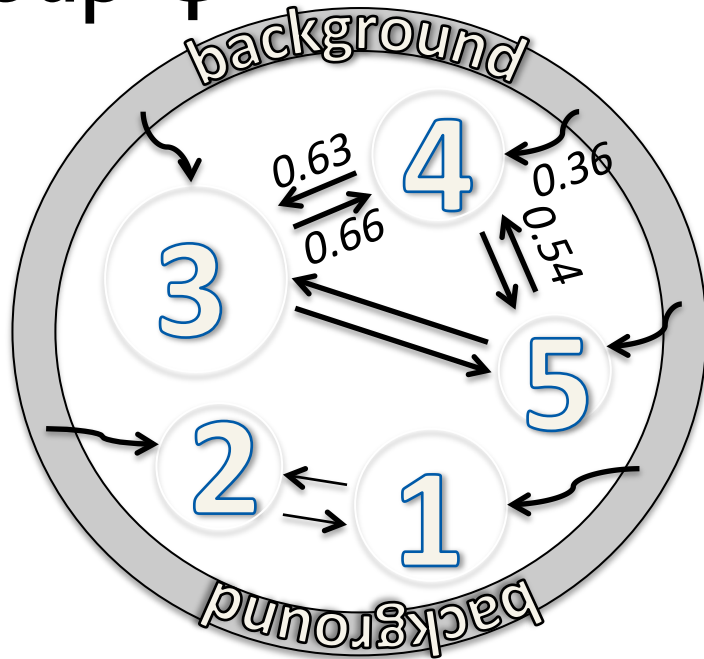
$$y_4 = V w_4 + e = 0.36 v_0 + 0.66 v_3 + 0.36 v_4 + 0.54 v_5 + e$$



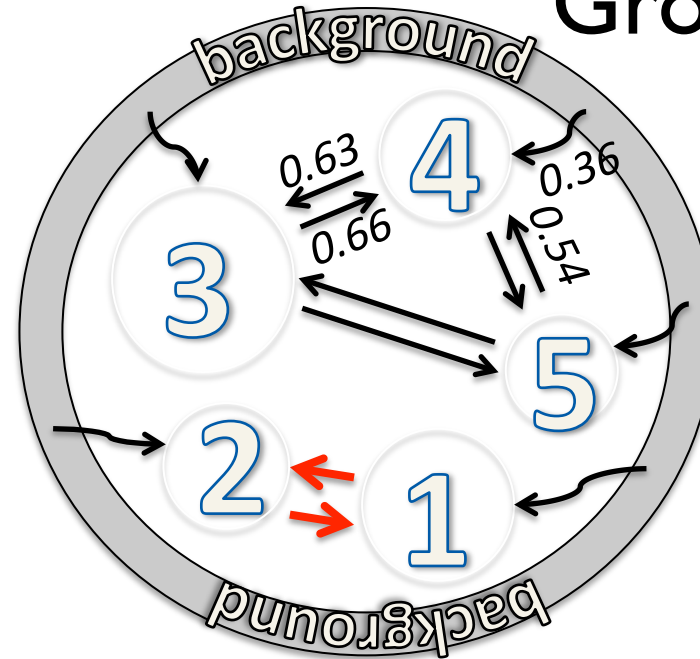
In simulations 9 regions + background were used

# Comparing Groups

Group  $\Psi$



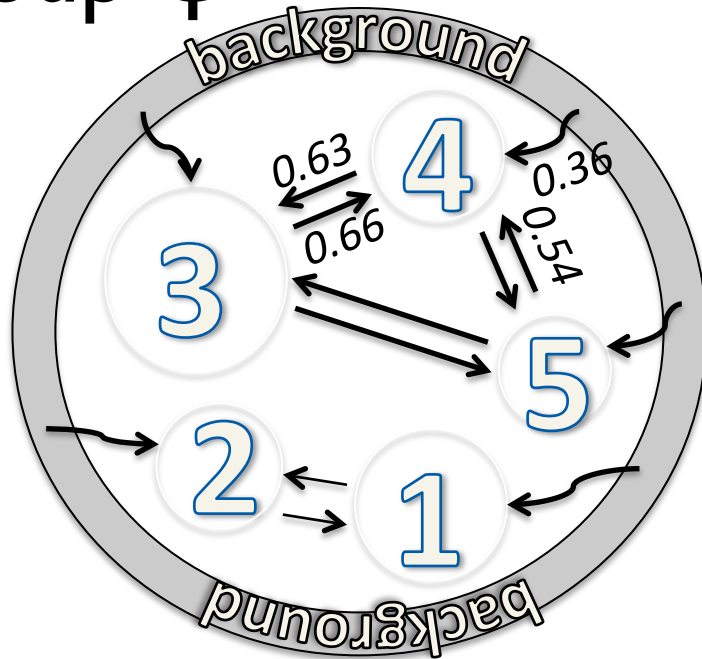
Group  $\Psi_L$



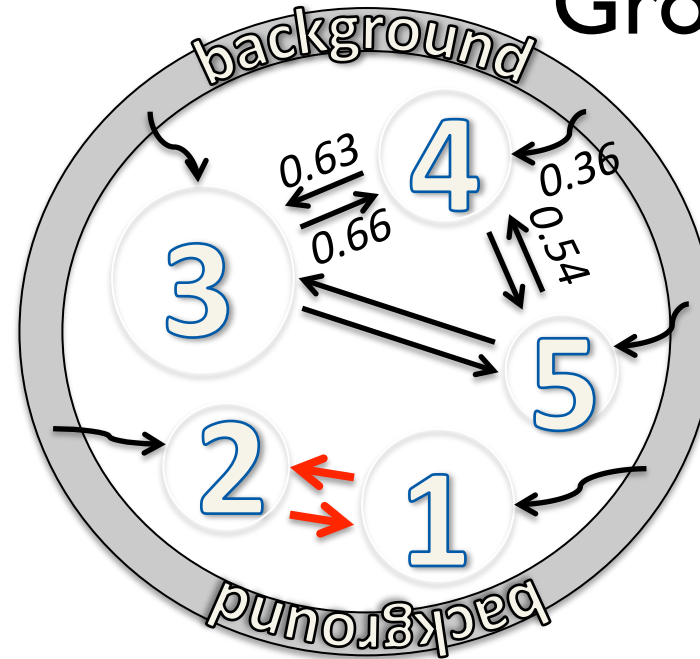
Increased connection  
between regions 1 and 2 only

# Comparing Groups

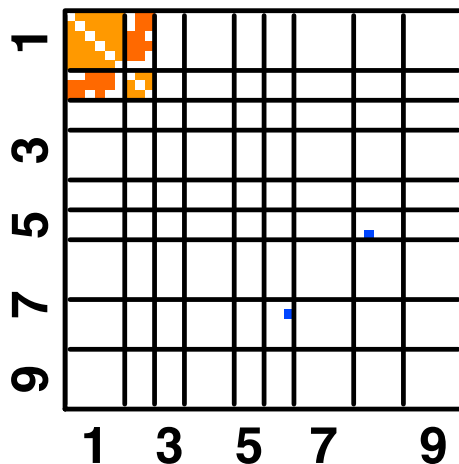
Group  $\psi$



Group  $\psi_L$



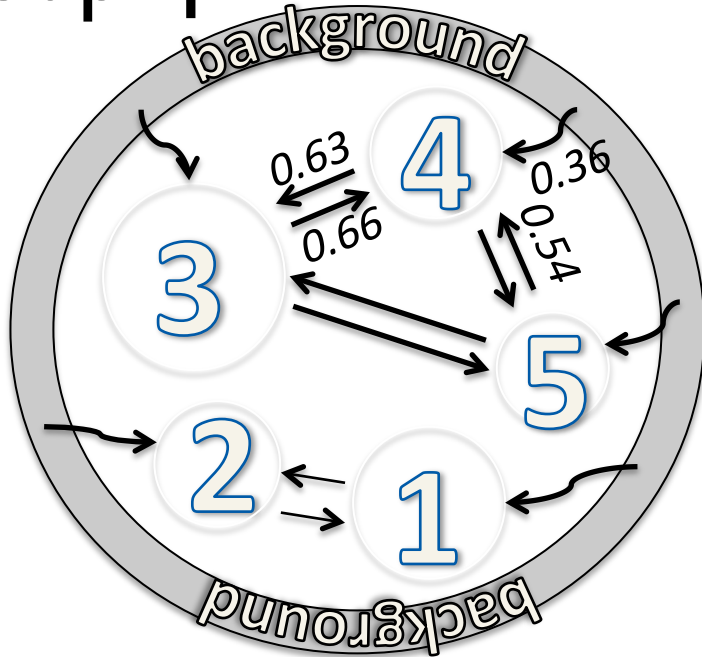
$\psi_L - \psi$  Base



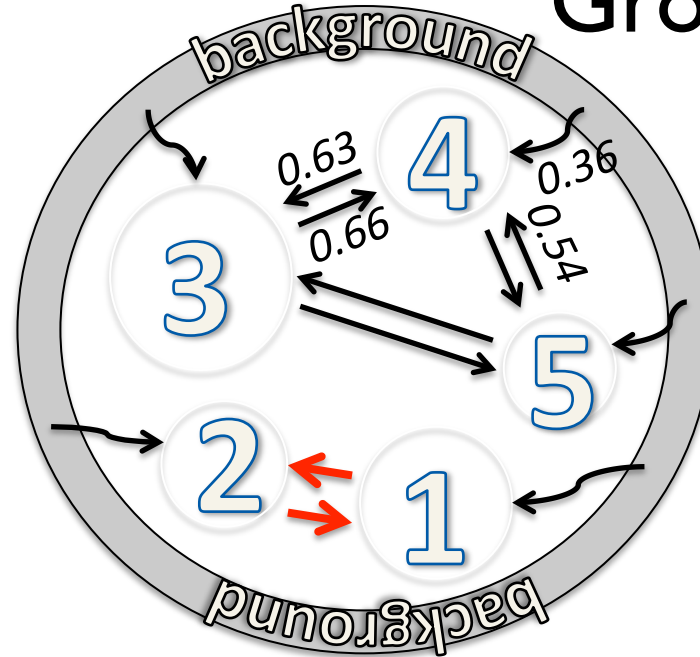
Difference confined  
to two regions

# Comparing Groups

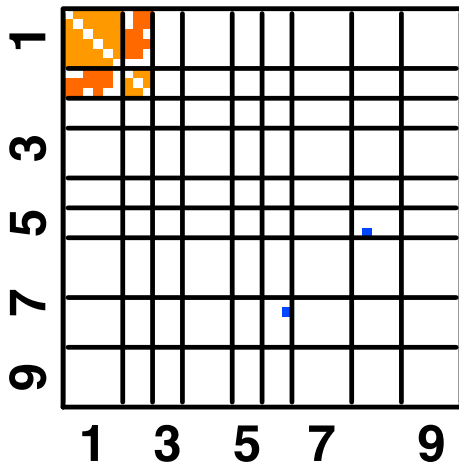
Group  $\psi$



Group  $\psi_L$



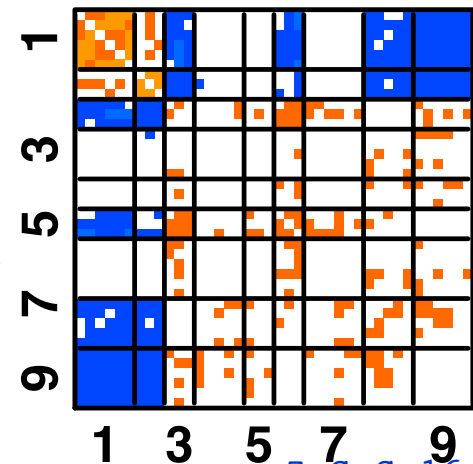
$\psi_L - \psi$  Base



Difference confined  
to two regions

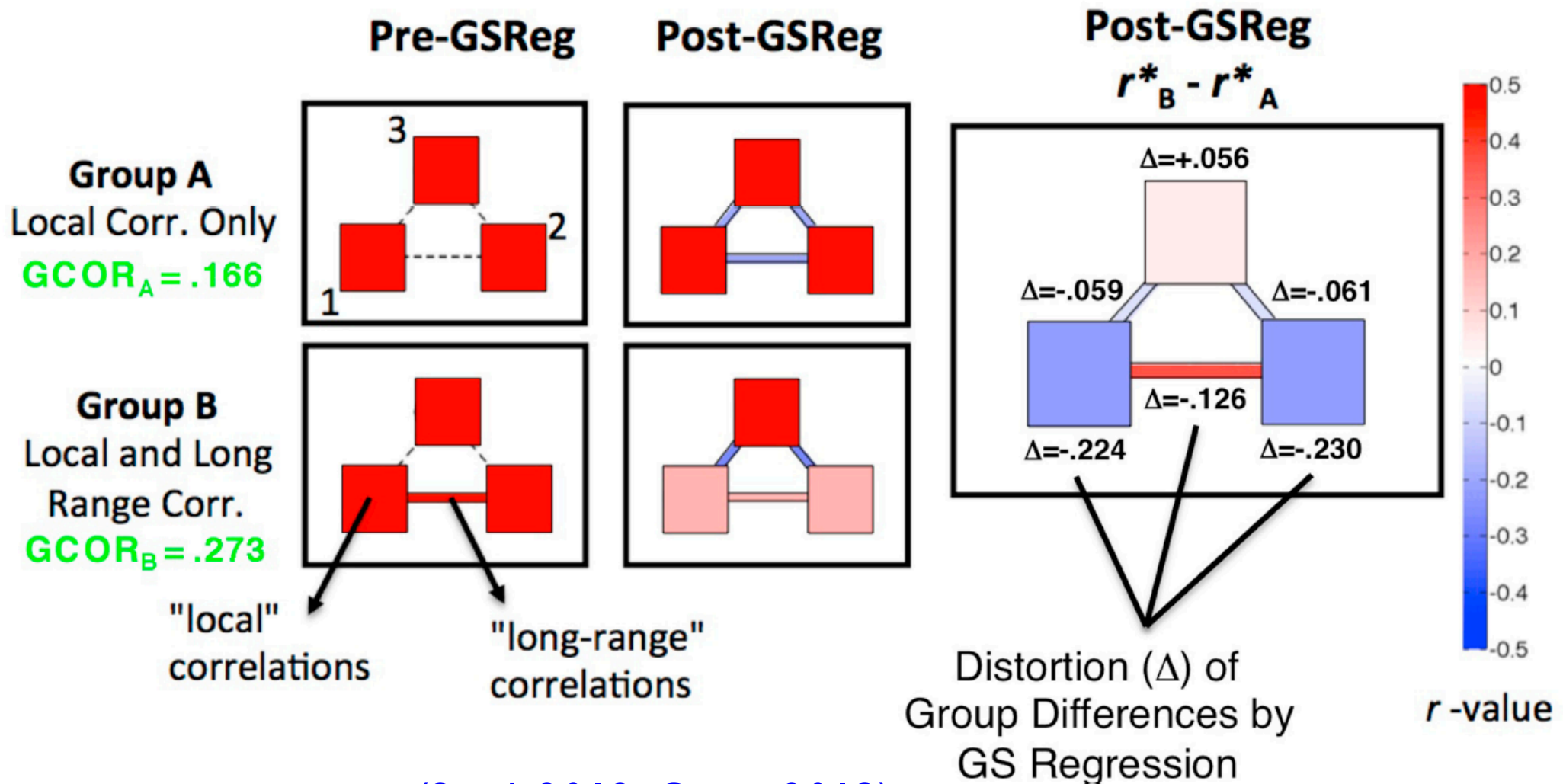
Ends up all  
over the place

$\psi_L - \psi$  GSReg



# Distortion of long/short range correlations

Contrast of correlations between groups A and B  
 'long-range' correlations in Group B only



(Saad, 2012, Gotts 2013)

# Comparing Groups with GSReg

One seeks and hopes for differences in covariance/correlation structures between groups.

Using GSReg means each group will be biased **DIFFERENTLY** for different region pairs.

- Even in the absence of noise difference, you can find group correlation **differences** in places where **none existed before**.
  - OK if you're teaching a classifier to differentiate between the two groups.
  - NOT OK if interpreting correlation differences to evoke correlation differences of neuronally induced BOLD signal between these regions.

With noise previous problems remain

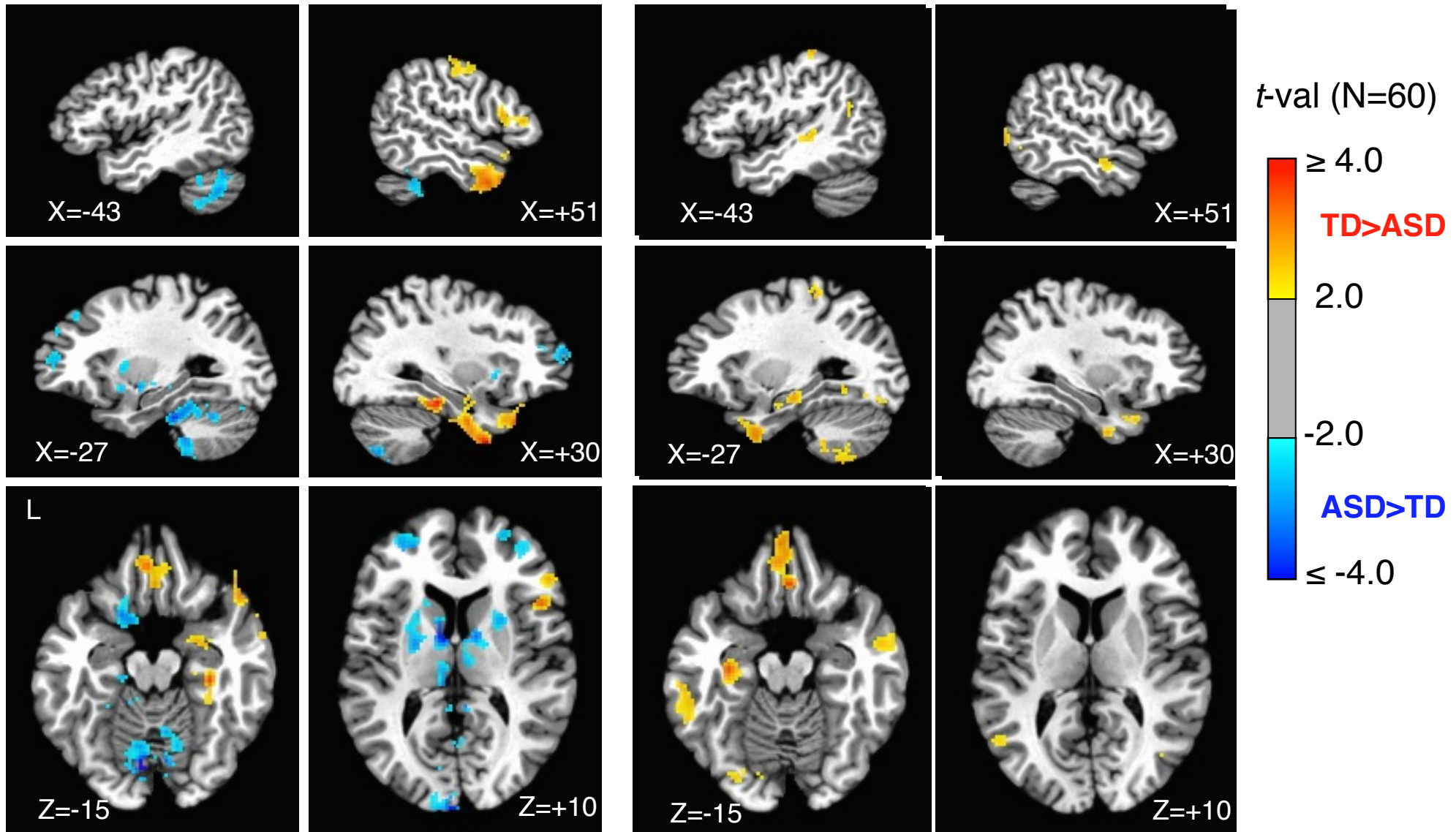
- However bias now depends on the covariance structures of noise and signals of interest though we can't tell them apart.
- Interaction between GSReg projection effects and grouping variable remains



# SAME holds with empirical data

+ **GS Regression**

**ANATICOR** (Jo, 2010)



(Gotts, 2013)

Z.S.S 16/06/13

# SAME holds with empirical data

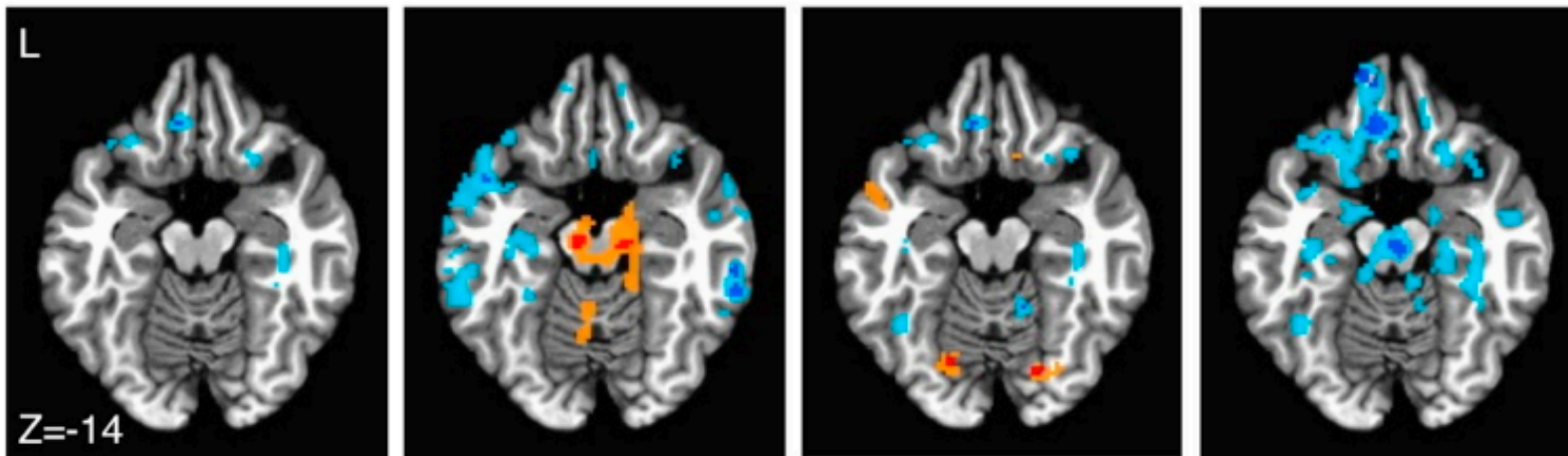
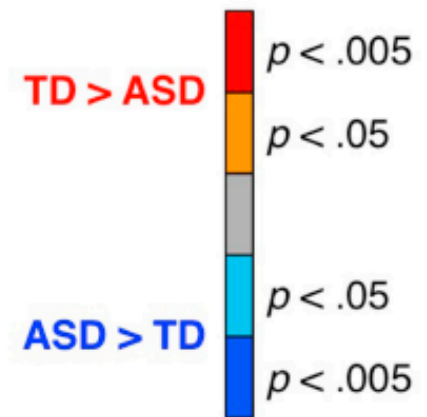
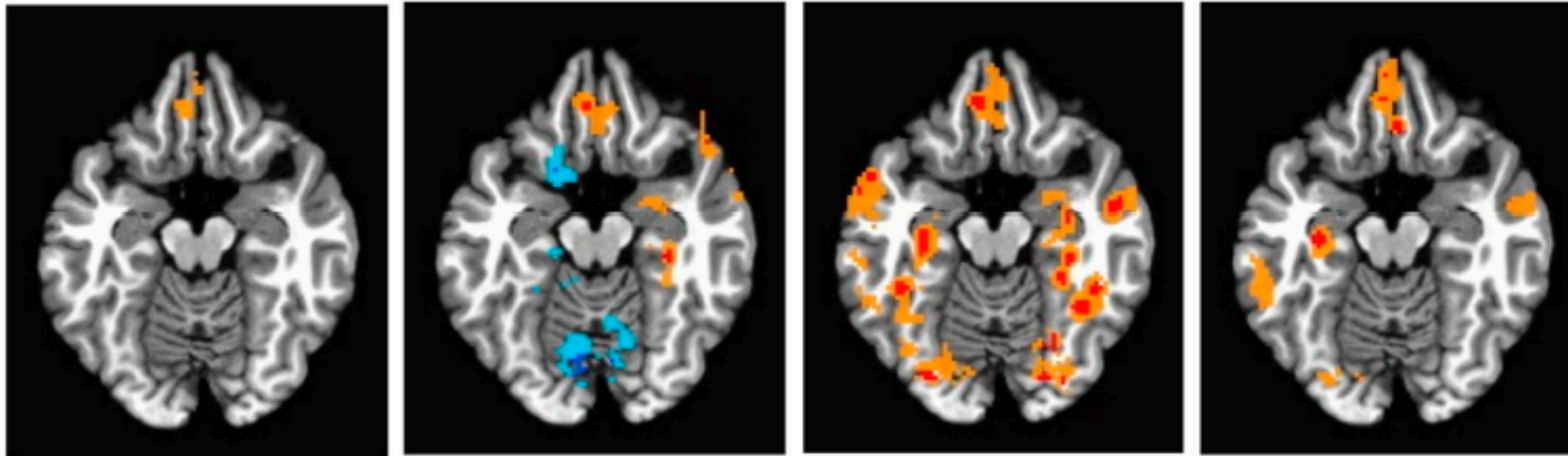
Basic Model

+ GS Regression

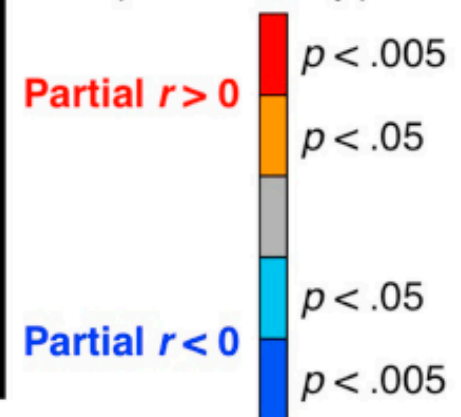
+ GCOR

ANATICOR

Group *t*-tests



Correlation with SRS (ASD Group)



(Gotts, 2013)

# It is not just GSR

- Nuisance regressors **correlated with fluctuations of interest** in regions of interest (not the noise) will cause the same problems.
- Non-gray matter averages may be comparable to GSReg (partial voluming with grey matter)
  - Averaging over small regions of eroded non-gray matter tissue are advantageous (Jo, 2010, 2013)
- Decomposition methods that cannot separate BOLD (fluctuations of interest) from noise also problematic.

# The Siren's Song

What of results being more stable after GSR?

There is a denoising component to the approach and bias is consistent for consistent covariance structure

- However, interpretation of correlations is now difficult (Cole, 2010)
- Interaction effect with grouping variable completely ignored
- Differences can get spread in unknown ways
- Tests of processing methods should always **consider group comparisons**

What of GSReg for motion compensation?

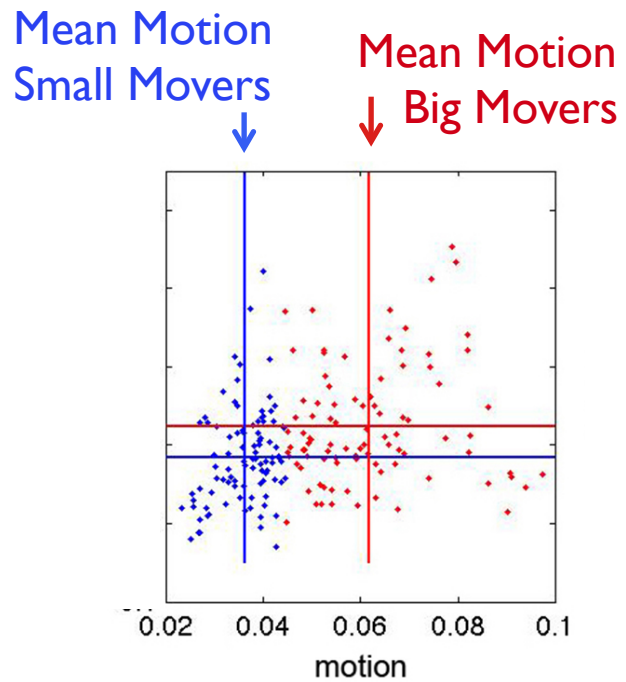
Some denoising effect → reducing residual variance and motion-based group differences

However, caveats from above remain

AND are we actually compensating for motion?

# Grouping Based on Motion

FCON 1000: Cambridge\_Buckner

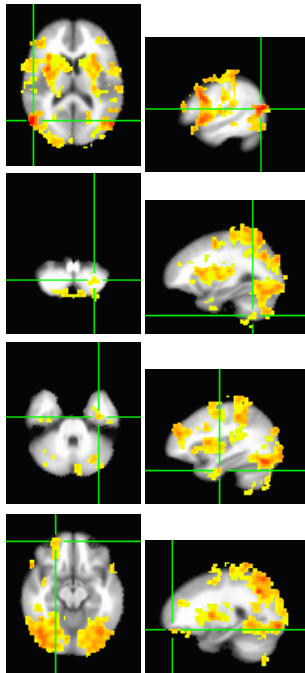


# Grouping Based on Motion

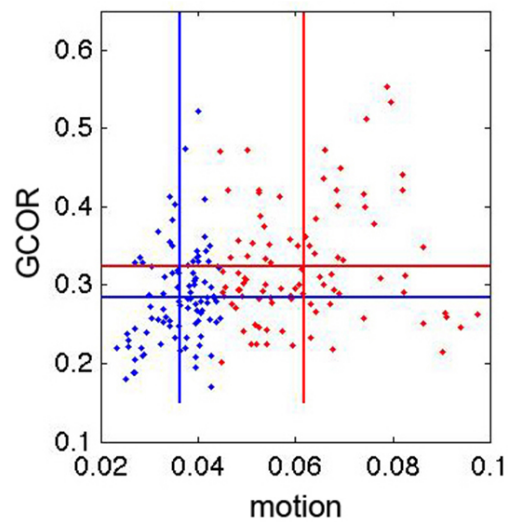
FCON 1000: Cambridge\_Buckner

$\beta_1$  Base

Largest 4 Clusters



4 clusters





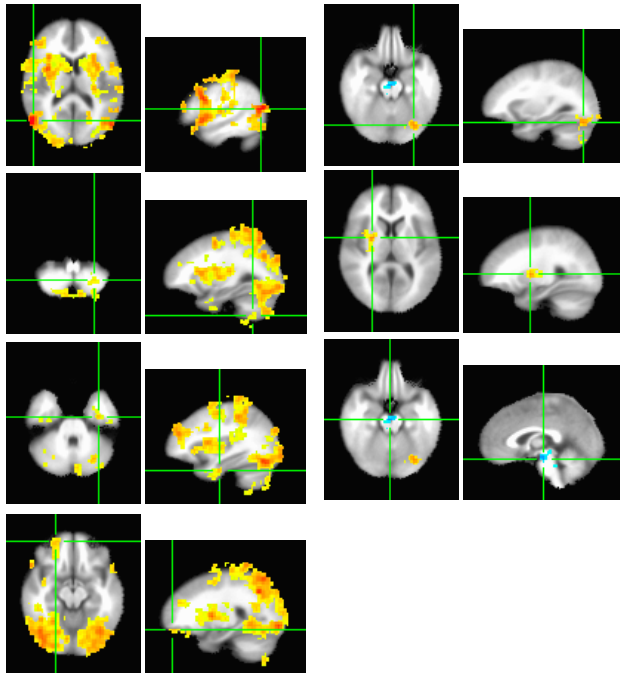
# Grouping Based on Motion

FCON 1000: Cambridge\_Buckner

$\beta_1$  Base

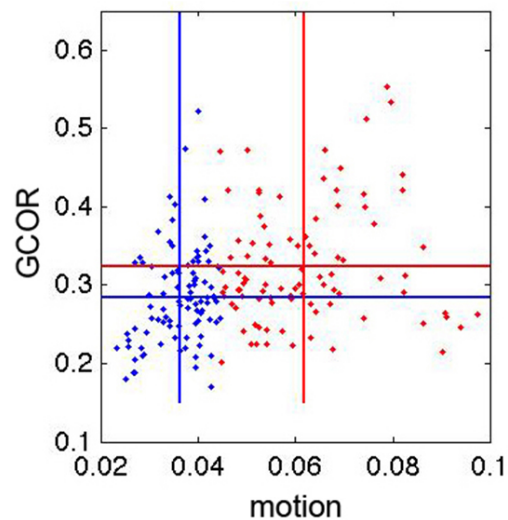
$\beta_1$  GSReg

Largest 4 Clusters



4 clusters

3 clusters



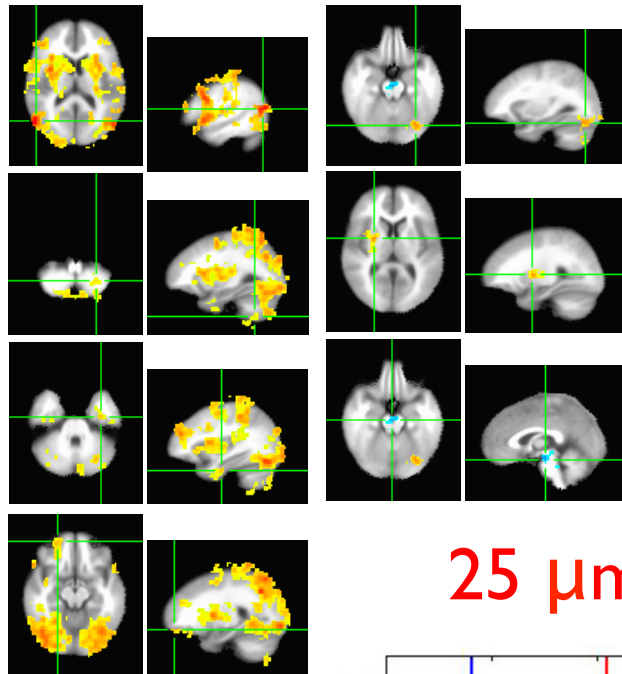


# Grouping Based on Motion

FCON 1000: Cambridge\_Buckner

$\beta_1$  Base

$\beta_1$  GSReg



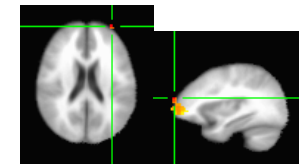
Largest 4 Clusters

4 clusters

FCON 1000: Beijing\_Zang

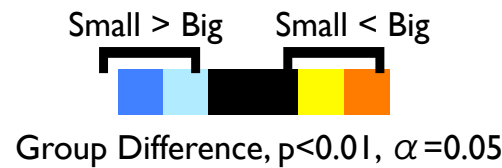
$\beta_1$  Base

$\beta_1$  GSReg



1 cluster

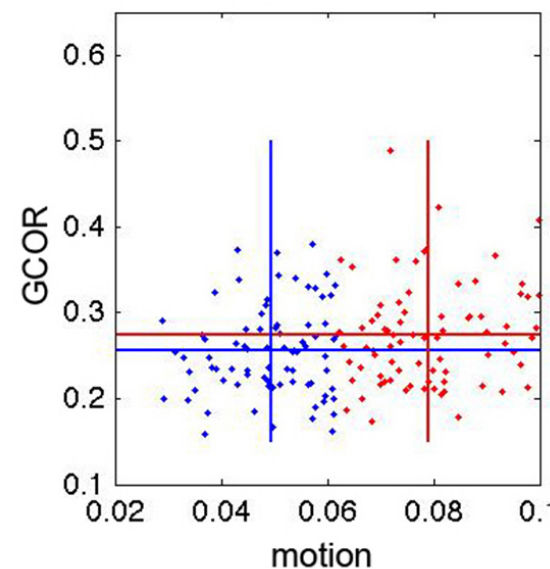
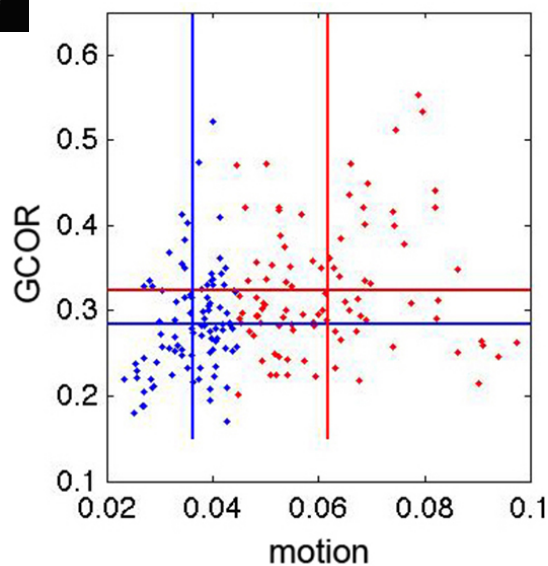
0 clusters



More Motion  
More Motion Difference  
**Much less group difference!**

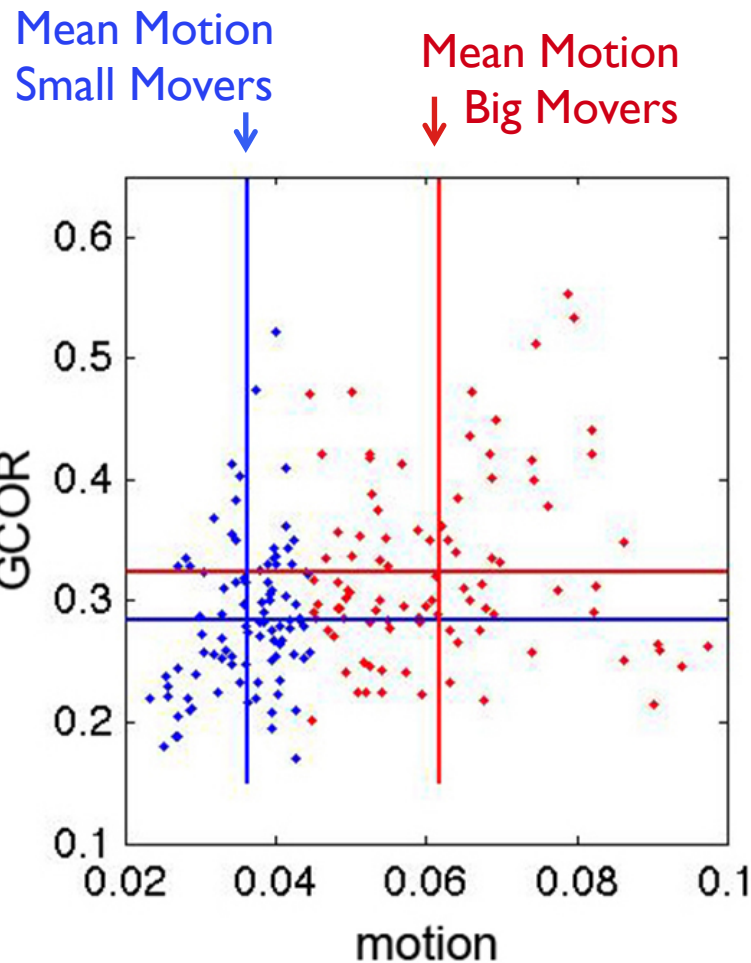
25  $\mu\text{m}/\text{TR}$

29  $\mu\text{m}/\text{TR}$

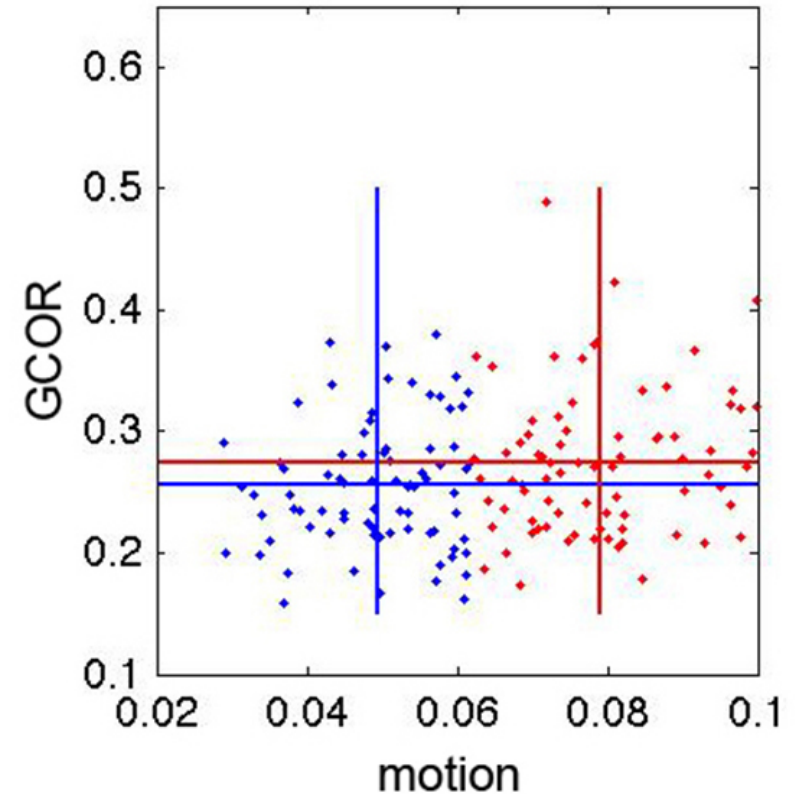


# Grouping Based on Motion

The average correlation of every voxel with every other voxel in the brain



FCON 1000: Cambridge\_Buckner



FCON 1000: Beijing\_Zang

Note weak correlation between motion and GCOR ( $R^2=11\%$  Cambridge,  $4.3\%$  Beijing)

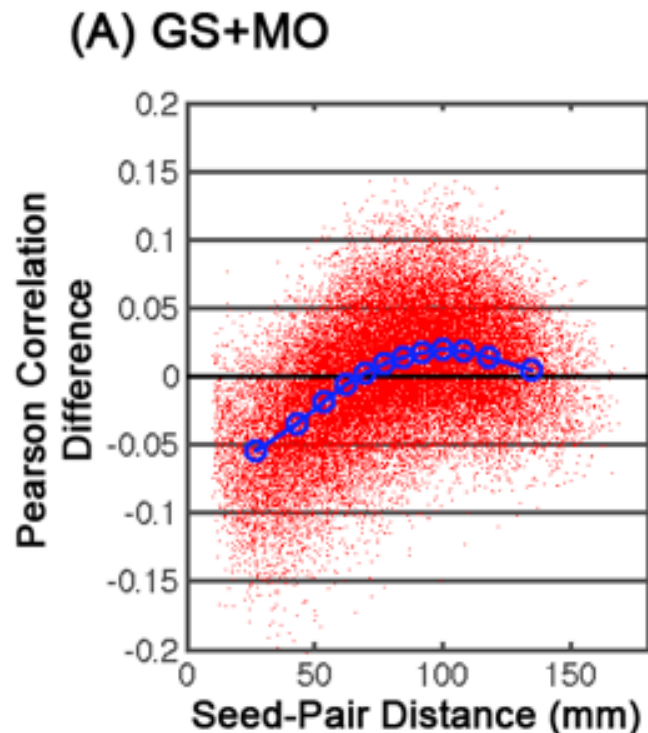
# Can GSReg help with motion?

Censoring (scrubbing) high motion samples changes inter-regional correlations in distance dependent manner.

→ suggests effect of motion on correlations depends on distance between regions (Power et al. 2012)

→ importance of censoring high motion

Data generously made public by Power & Coauthors 2012



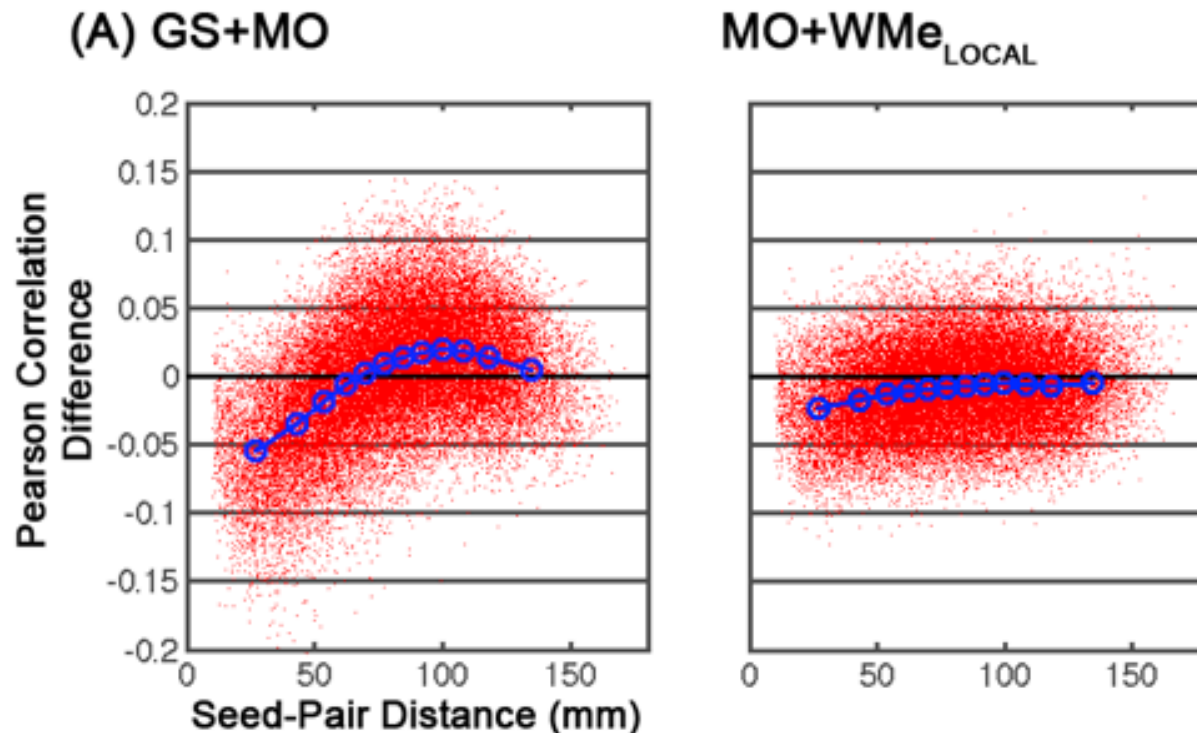
# Can GSReg help with motion?

Censoring (scrubbing) samples of high motion changes inter-regional correlations in a distance manner.

→ suggests effect of motion on correlations depends on distance between regions (Power et al. 2012)

→ importance of censoring high motion

Less dependence without GSReg



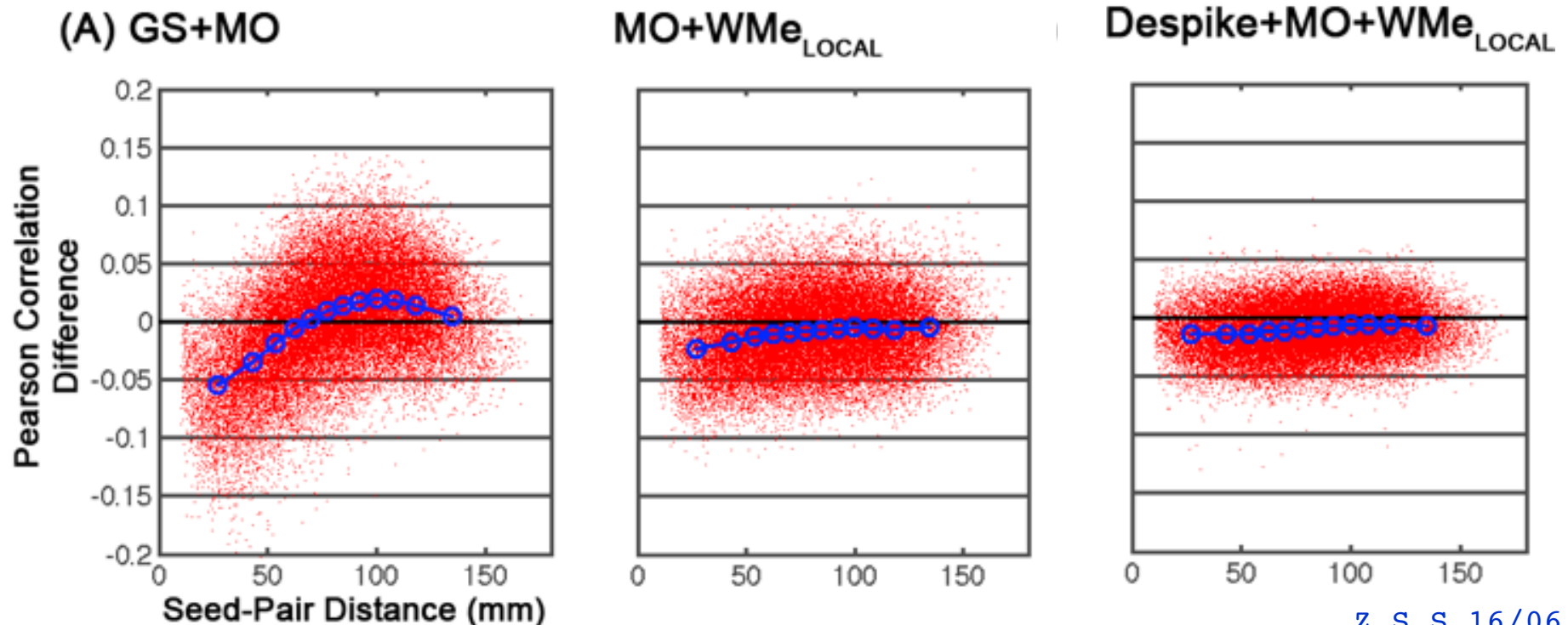
# Can GSReg help with motion?

Censoring (scrubbing) samples of high motion changes inter-regional correlations in a distance manner.

→ suggests effect of motion on correlations depends on distance between regions (Power et al. 2012)

→ importance of censoring high motion

Least dependence



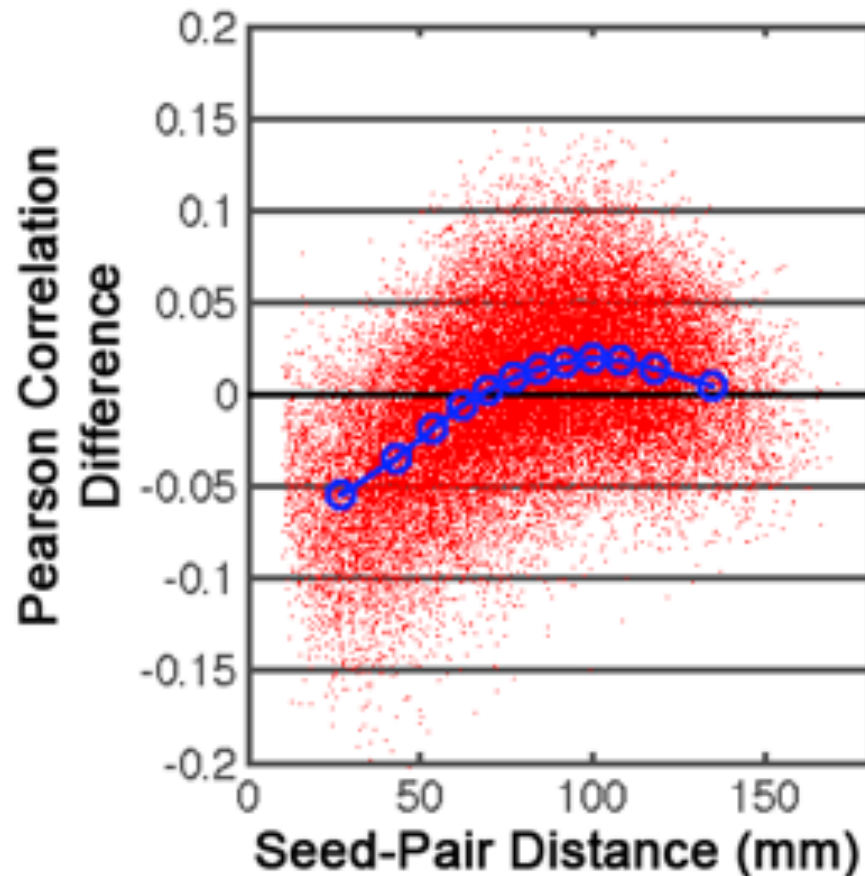


# Can GSReg help with motion?

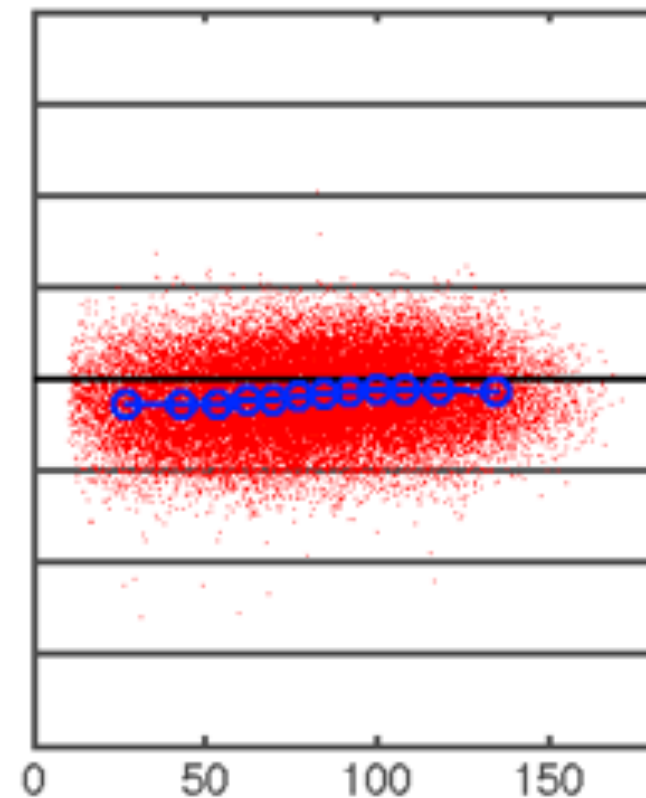
- GSReg → Correlation more sensitive to motion
- Correlation more sensitive to censoring (Jo, 2013)

Improved denoising largely eliminates distance dependent bias

**(A) GS+MO**



**Despiking+MO+WMe<sub>LOCAL</sub>**



# Sampling nuisance TS regressors

- Sample noise without aggregating over regions with fluctuations of interest
  - Erode white matter masks to avoid partial voluming
  - Avoiding regions with fluctuations of interest (Anderson 2011)
  - Local eroded white matter masks improve denoising without increasing DOFs (Jo, 2010, 2013)
- Use decomposition methods that can separate BOLD from non BOLD fluctuations of interest (Kundu, 2012, Bright, 2013)  
or attempt to identify noise components (Beckmann 2004, Beall 2010, Boubela, 2013)
- Use noise models RICOR/RVT/etc. (Glover 2000; Shmueli 2007; Birn 2008; Chang 2009)



# Brain-wide correlation adjustments?

- If subject to subject variations in brain-wide correlations exist, why not correct for them?
- Consider GCOR, the average over the entire correlation matrix of every voxel with every other voxel (Saad, 2013)
  - Measure would be costly to compute if one had to estimate the entire correlation matrix first.
  - However estimating GCOR is trivial:

$$\begin{aligned}\gamma &= 1/(M^2N) \mathbf{1}^T \mathbf{U}^T \mathbf{U} \mathbf{1} \\ &= 1/N \mathbf{g}_u^T \mathbf{g}_u,\end{aligned}$$

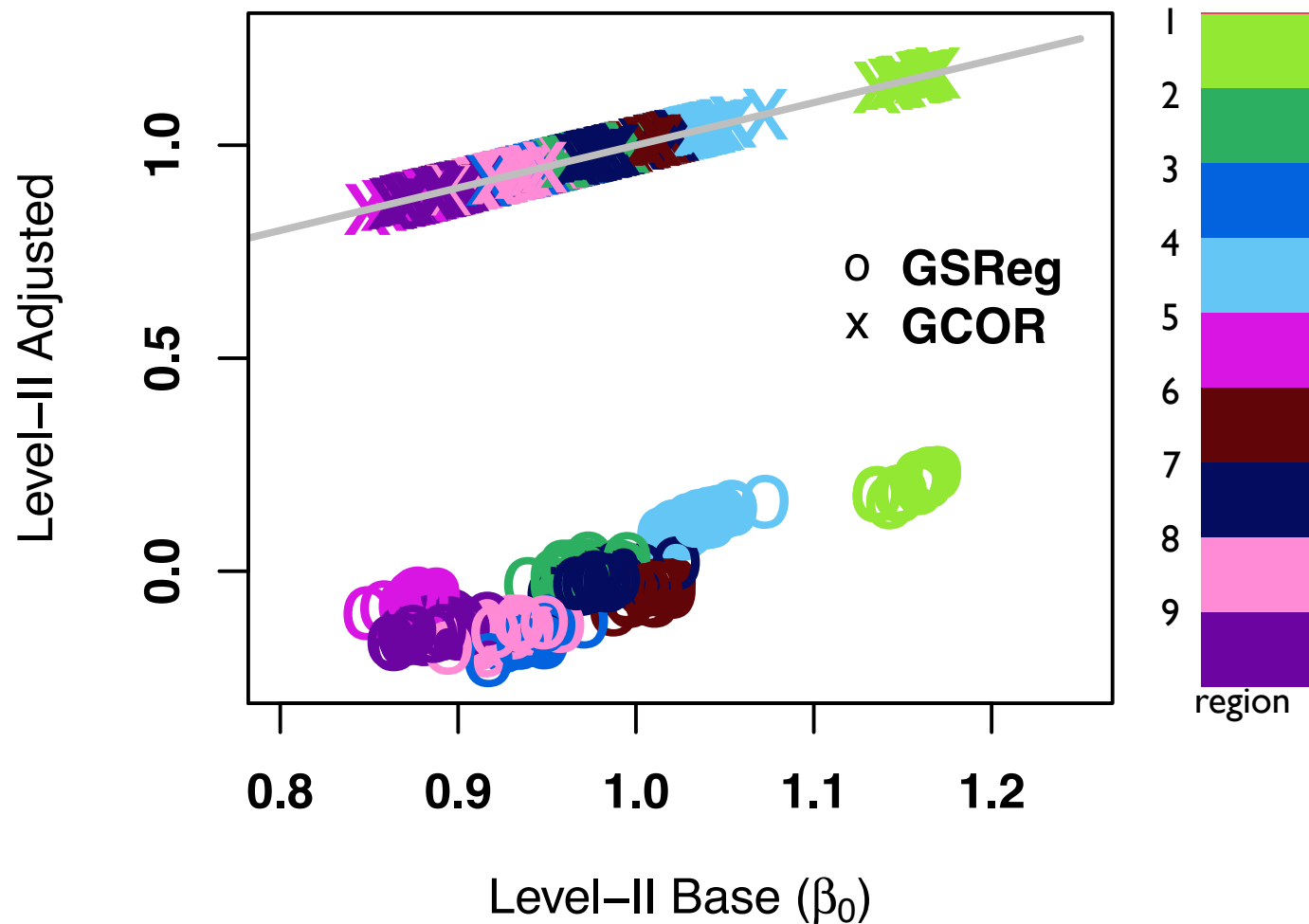
$\mathbf{g}_u$  is the average of all ( $M$ ) unit variance time series of length  $N$  in matrix  $\mathbf{U}$

# GCOR as group level covariate

- Using models described earlier, we consider group level correlation (differences) from three models:
  - No adjustment:  $r_{i,j} = \beta_0 + \beta_1 x$
  - GSReg at level I:  $s_{i,j} = \beta_0 + \beta_1 x$
  - GCOR as covariate:  $r_{i,j} = \beta_0 + \beta_1 x + \beta_2 \gamma + \beta_3 x \gamma$

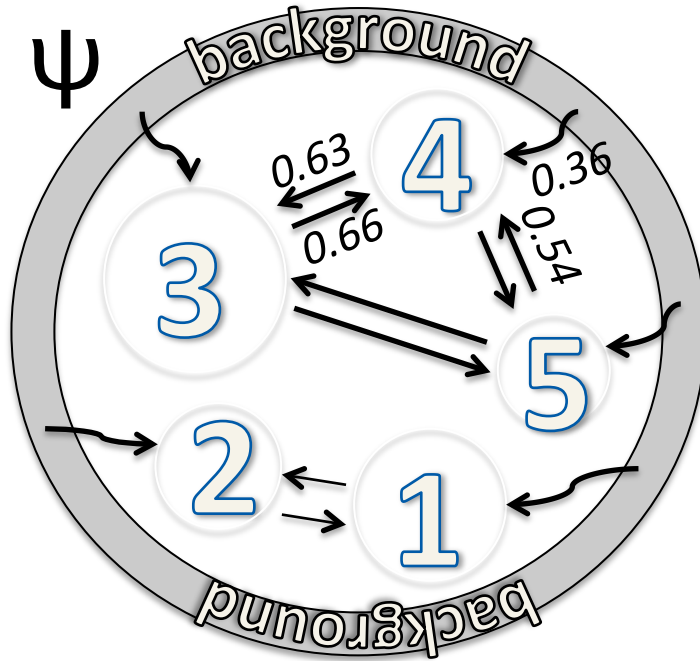
# Less bias than with GSReg for 1 sample tests

Mean Correlations with Region 1

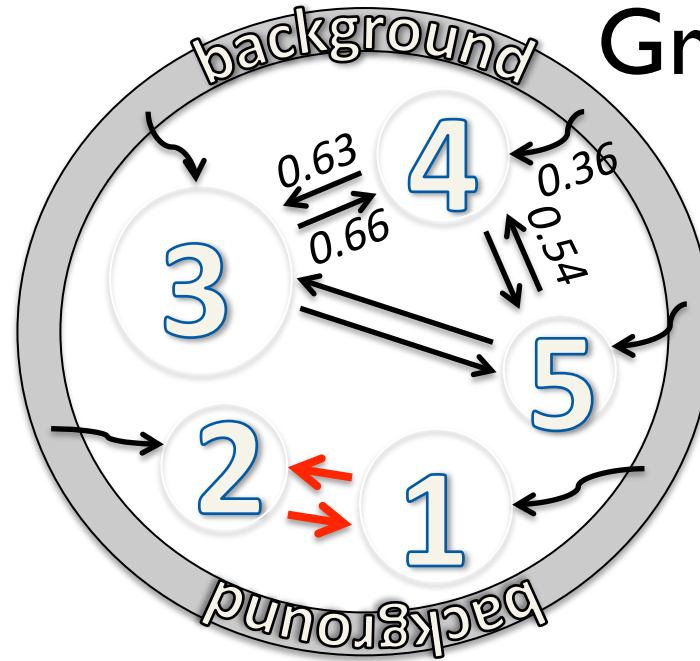


# Comparing Groups

Group  $\Psi$



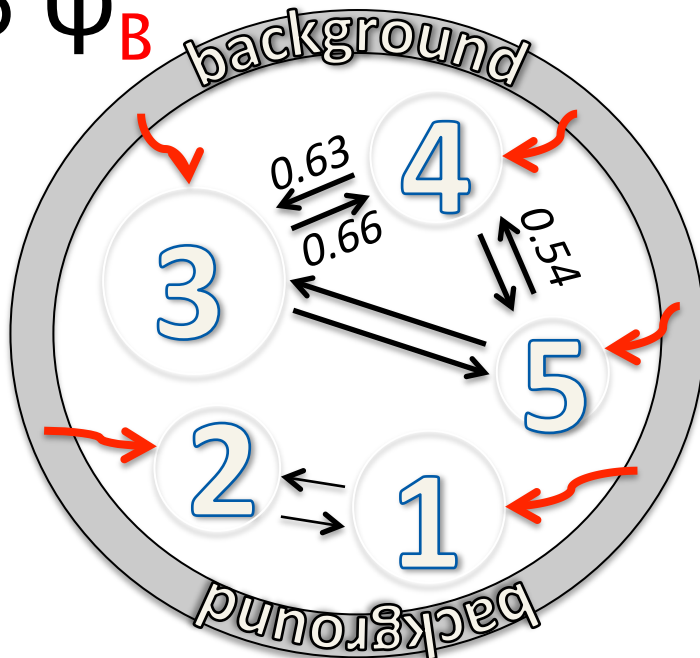
Group  $\Psi_L$



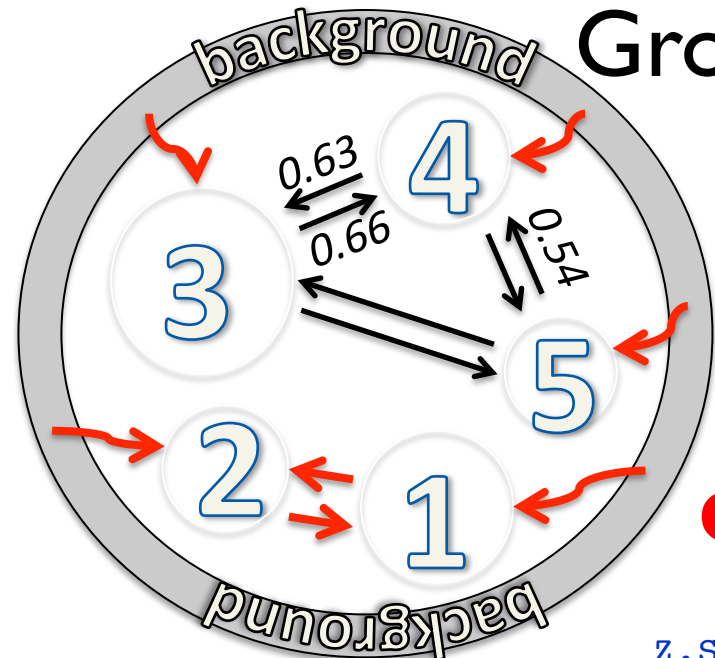
**More  
Local**

Group  $\Psi_B$

**More  
Backg.**

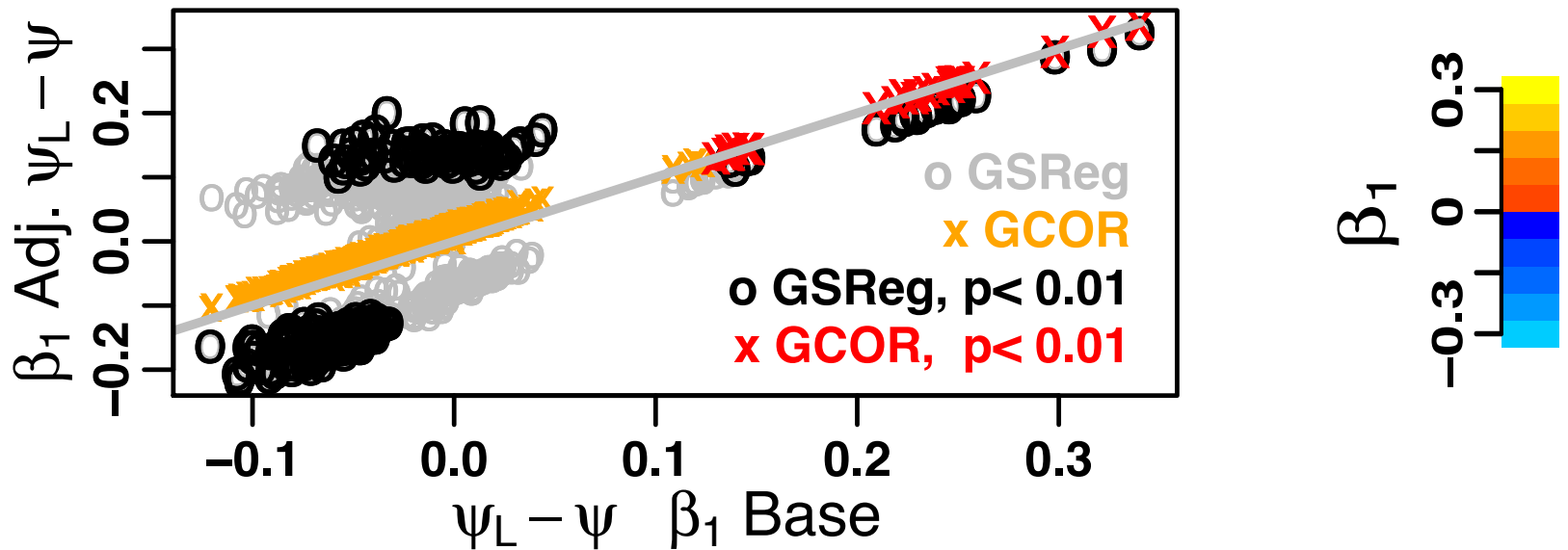
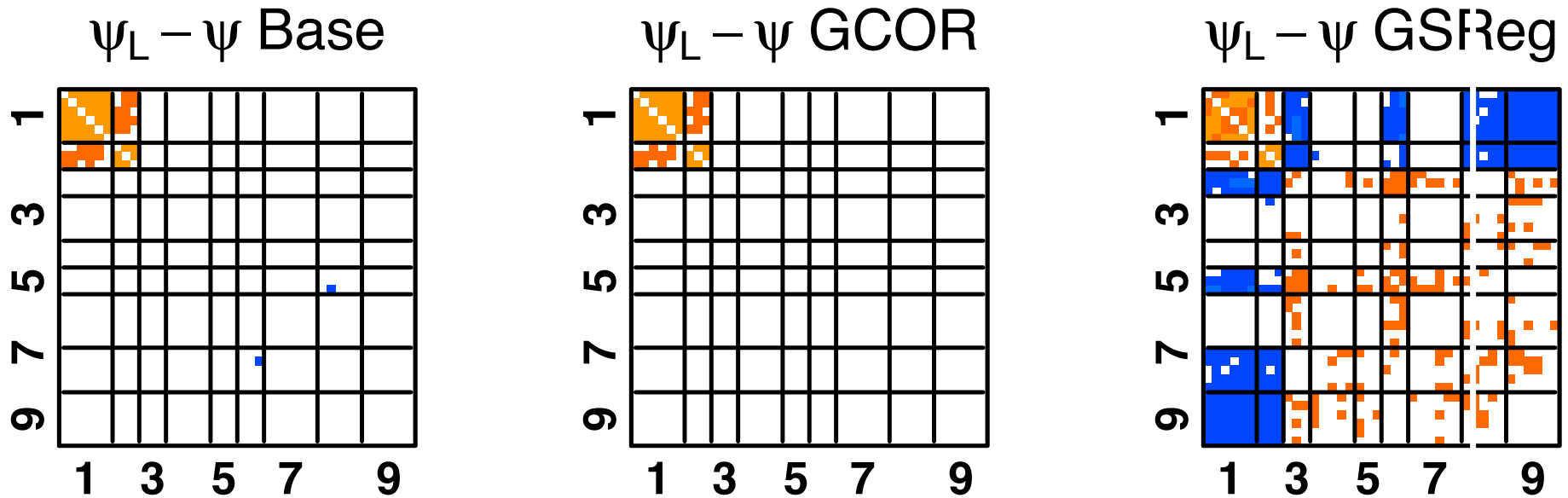


Group  $\Psi_{BL}$

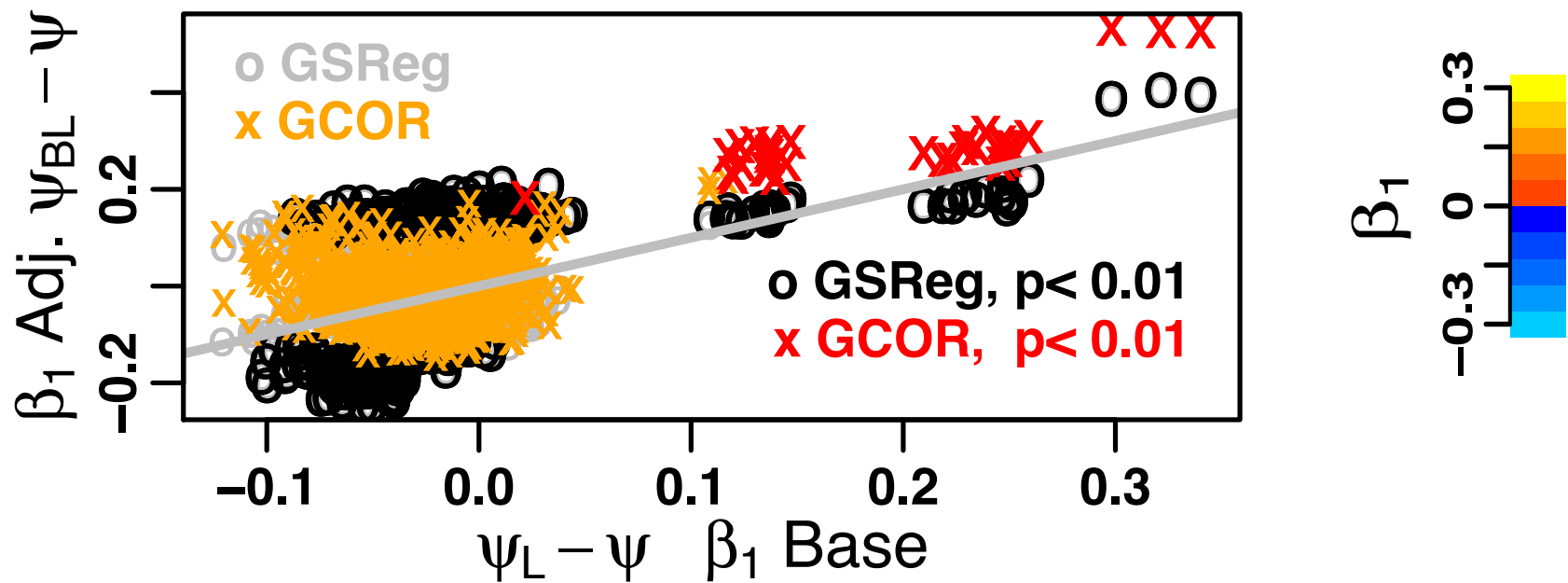
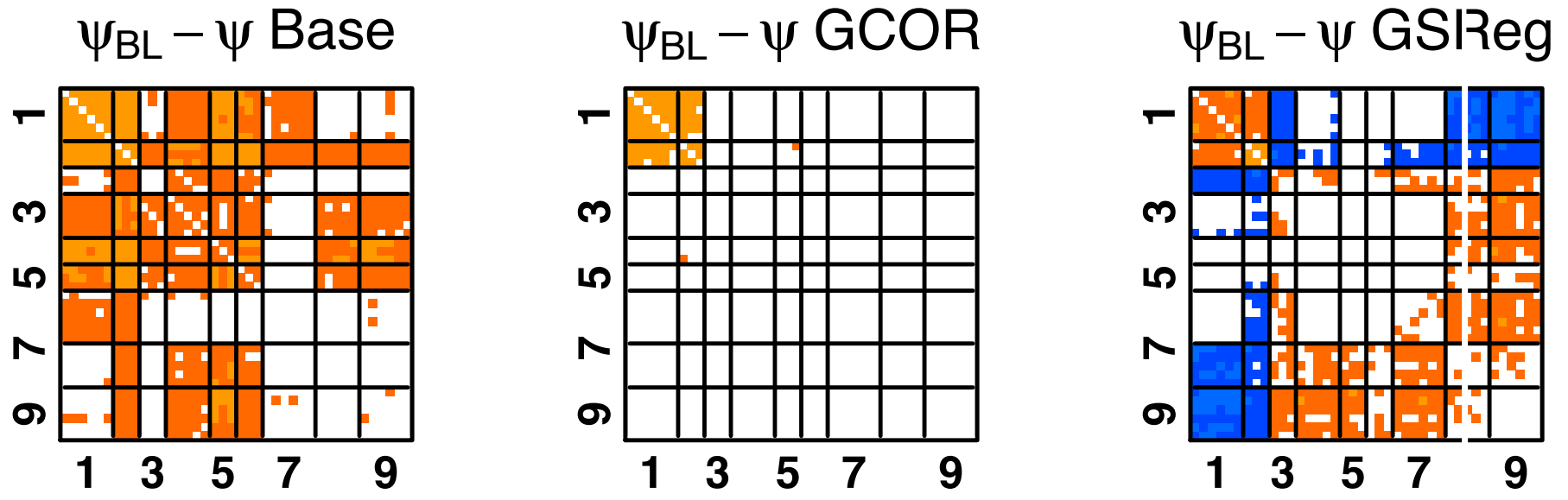


**More  
Cowbell**

# Group Contrast, Only Local Change



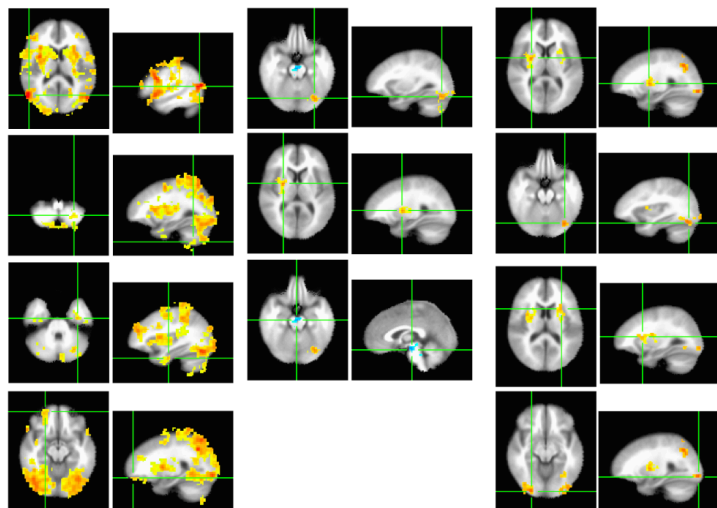
# Group Contrast, Local & Backg. Change



# GCOR and *Motion* Grouping

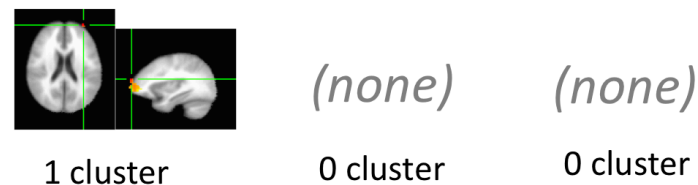
FCOR 1000: Cambridge\_Buckner

$\beta_1$  Base     $\beta_1$  GSReg     $\beta_1$  GCOR



FCOR 1000: Beijing\_Zang

$\beta_1$  Base     $\beta_1$  GSReg     $\beta_1$  GCOR

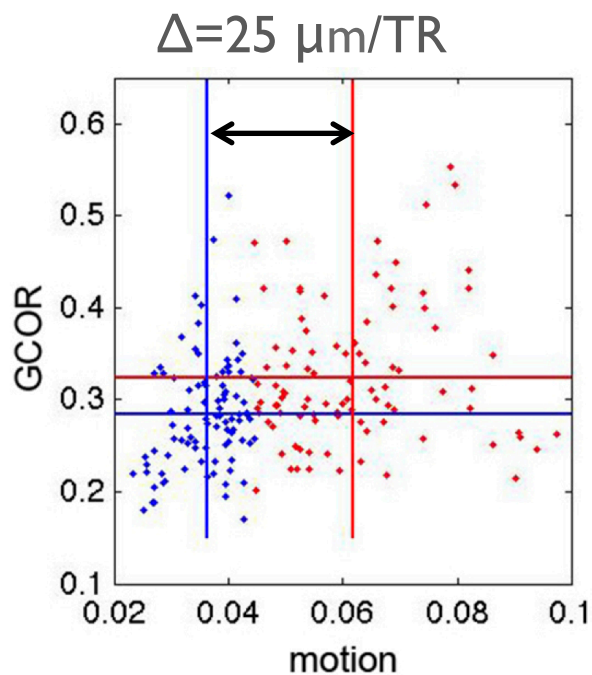


Largest 4 Clusters

Small > Big    Small < Big



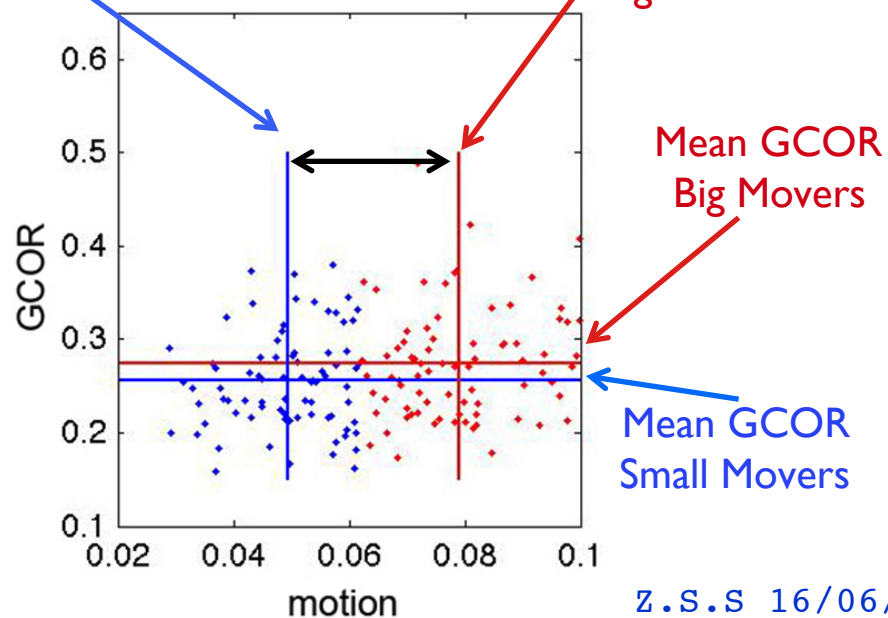
Group Difference,  $p < 0.01$ ,  $\alpha = 0.05$



Mean Motion  
Small Movers

$\Delta = 29 \mu\text{m/TR}$

Mean Motion  
Big Movers





# GCOR as Group Level Covariate

Correlations less biased with GCOR, than GSReg.

- when GCOR has low correlation with grouping variable

Level-II tests conservative

- Less likely to detect difference as grouping variable and covariate correlation increases

Adjustment outside of level II test is NOT recommended

- There is always potential for **interaction effect with group**
- 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 driven by correlations of interest?
  - contrast sign might even get reversed

# Conclusions

- Stay away from regions with Fluctuations of Interest
- GSReg and its variants are bad for group comparisons
- One MUST consider interactions of method with grouping variable
  - Generative models clarify matters since there is no base truth
- GCOR is very simple to compute and is useful to assess global correlation levels
- Use of GCOR and comparable measures is better than GSReg
  - However, their interaction with grouping variable can confound interpretation

**Use should be as last resort**

- Use them as covariates and consider interaction terms
- Separate covariate modeling prior to level-II not recommended
- Risks of false negatives
- Centering issues

# Conclusions

The best approach remains with careful denoising

- motion parameter estimates
- physiological measurements
- local estimates of nuisance signals from eroded white matter
- denoising decompositions in as far as they can dissociate nuisance estimates from signal fluctuations of interest

Look at your data

# Acknowledgments

Robert Cox  
Gang Chen  
Steve Gotts  
Hang Joon Jo  
Alex Martin  
Rick Reynolds

Kelly Barnes  
Catie Chang  
Carlton Chu  
  
Jonathan Power  
and coauthors  
for releasing data

