The Sources of Bias in Resting State FMRI

Ziad S Saad, PhD

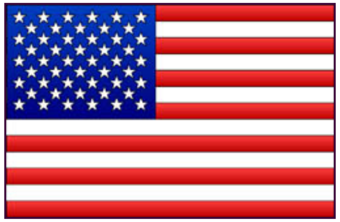
SSCC / NIMH & NINDS / NIH / DHHS / USA / EARTH

The Sources of Bias in Resting State FMRI

No Conflicts Of Interest To Declare

Ziad S Saad, PhD

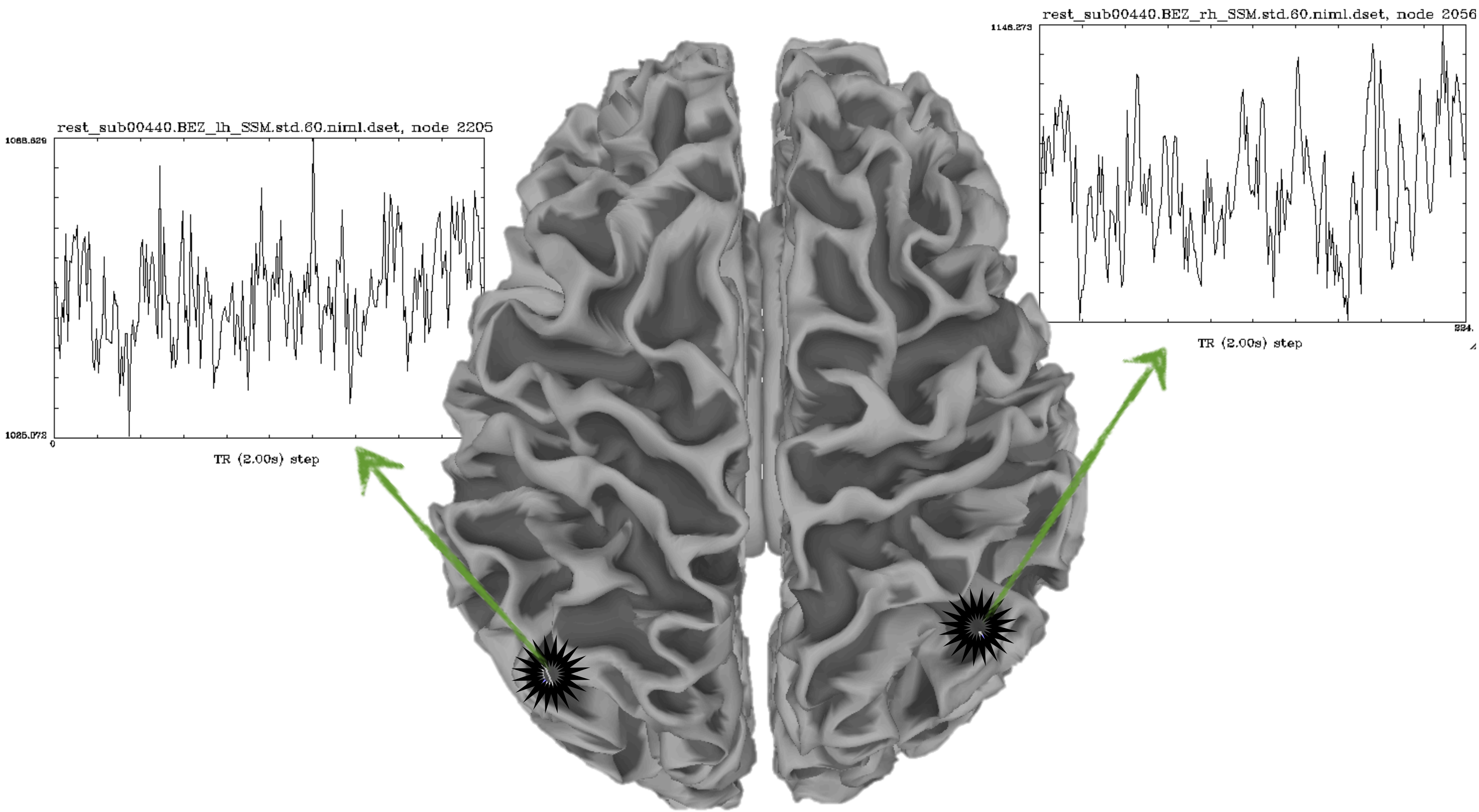
SSCC / NIMH & NINDS / NIH / DHHS / USA / EARTH



Z.S.S 16/06/13

Resting state

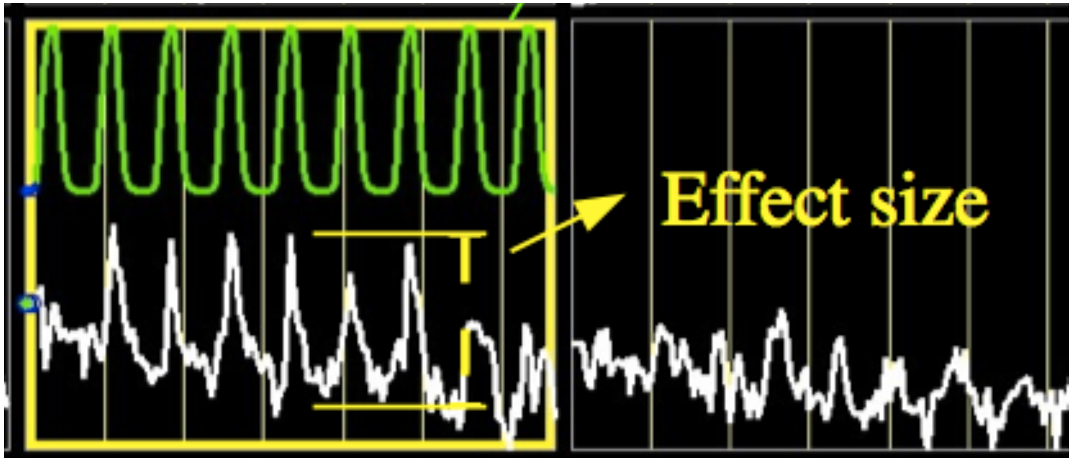
BOLD signal fluctuations during undirected brain activity



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

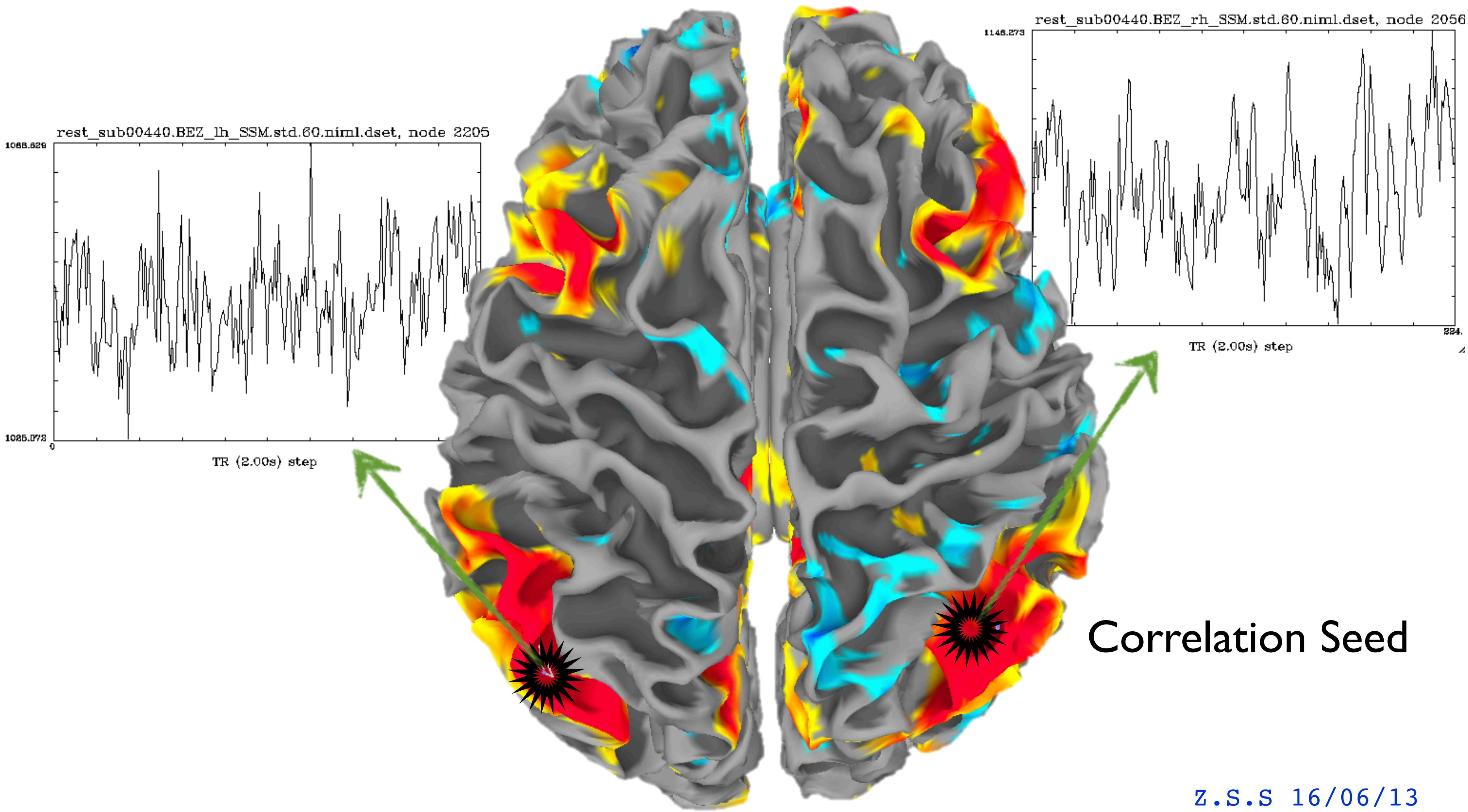
Resort to describing relationships between brain regions

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

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

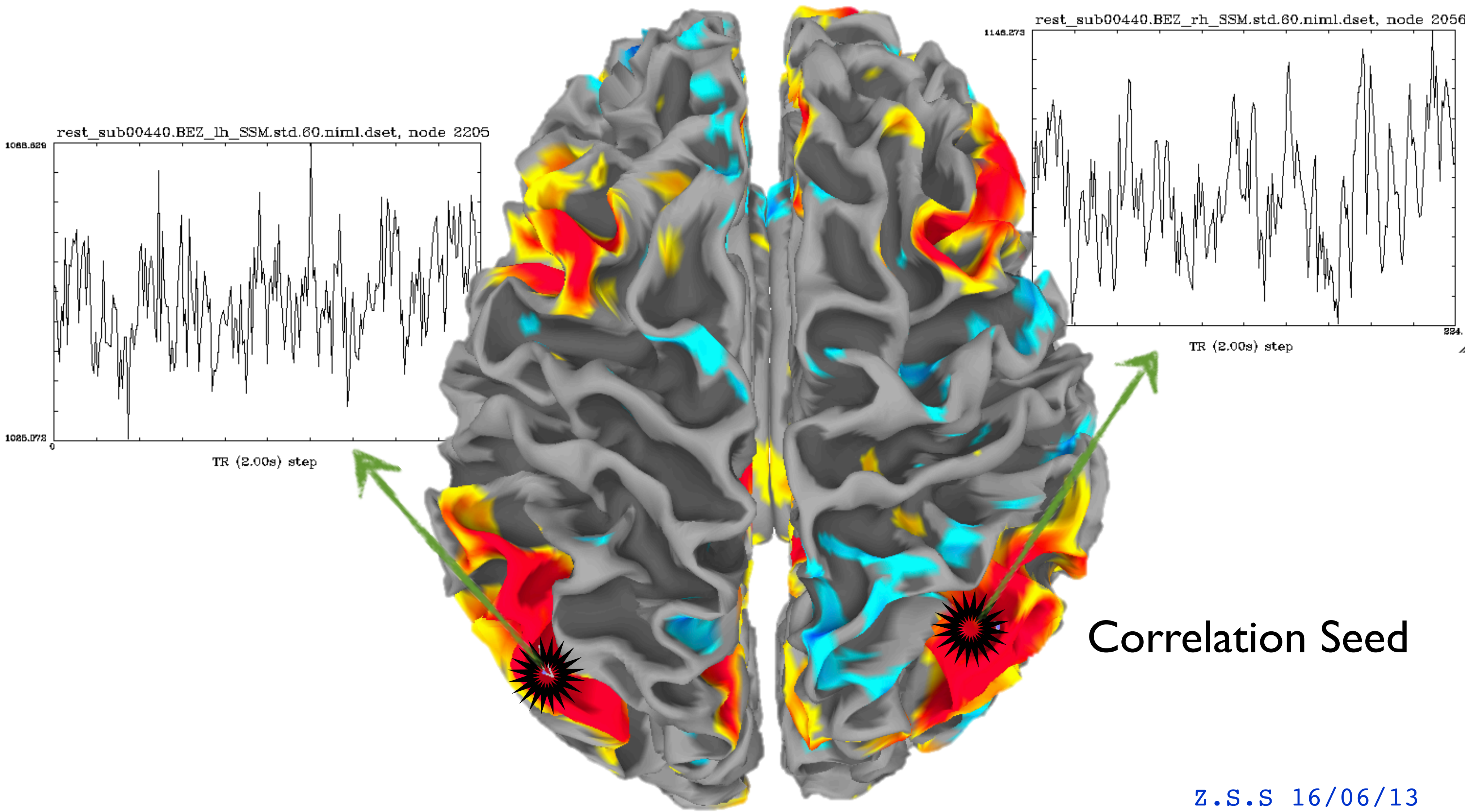
Resting state

Resort to describing relationships between brain regions



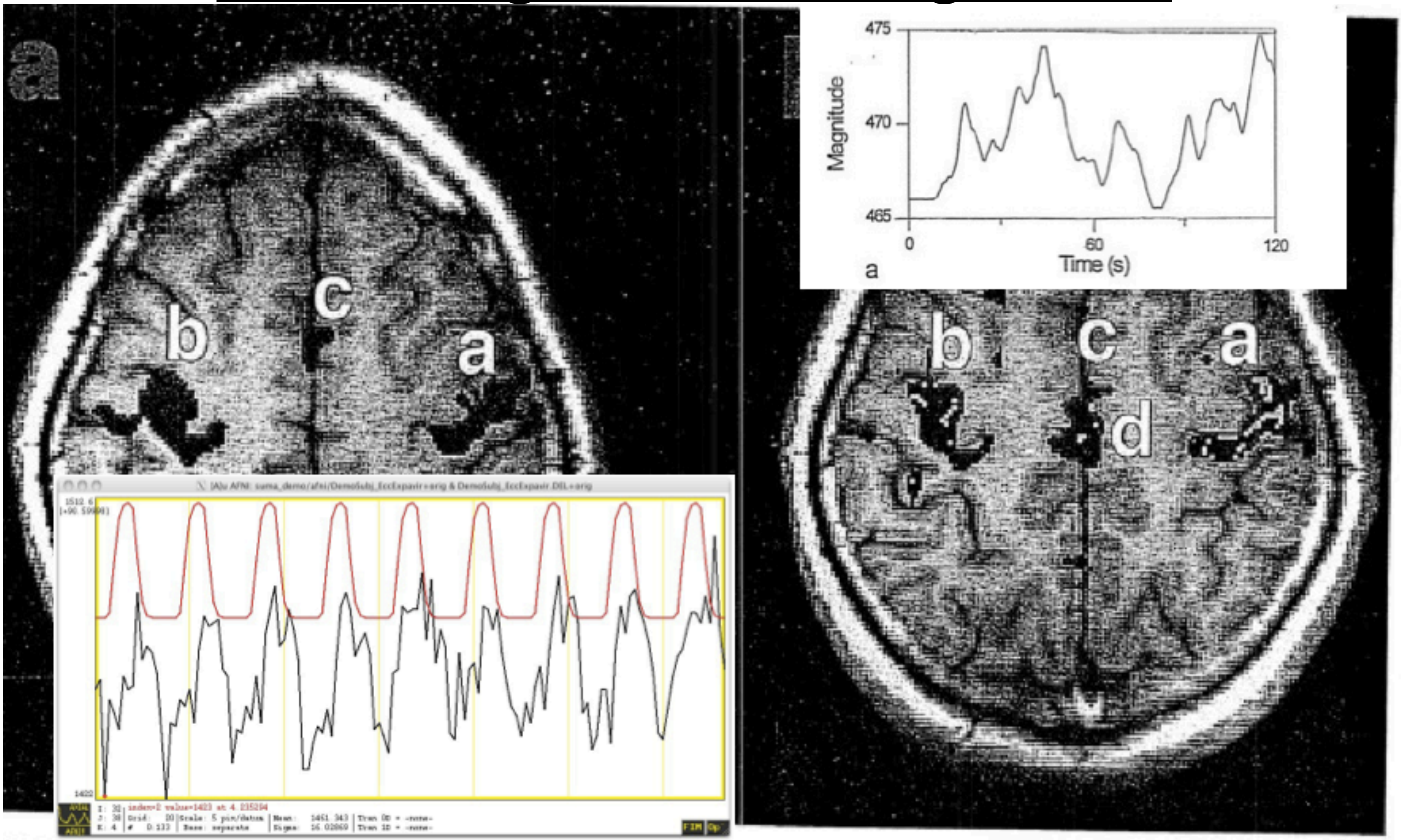
Resting state

Interpret correlation strength as proxy for brain function coupling between regions



Z.S.S 16/06/13

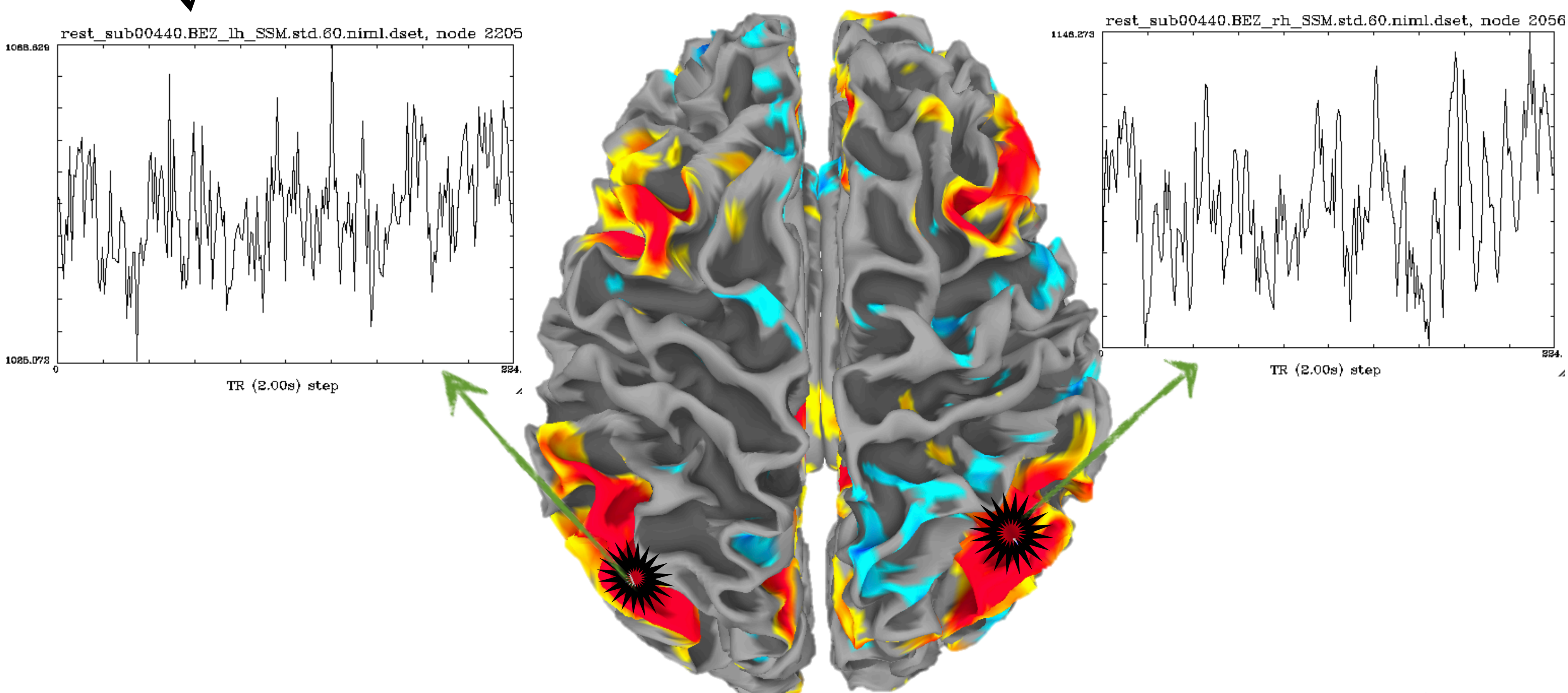
The magic of resting state (Biswal 95)



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

Resting state PROBLEM

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



Z.S.S 16/06/13

The fount of our troubles

We have no model for signal

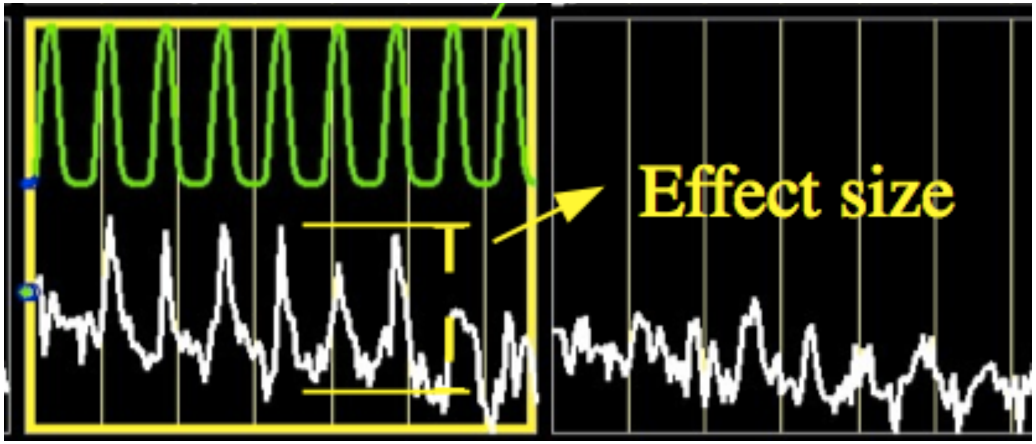
Nothing like the expected response (regressors) of task FMRI

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 amplitude 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 → less *(or more!)* correlation (bias) → group differences

Weak but consistent bias → significant difference

Some sources have brain-wide (global) effects on correlation distribution (e.g. $ETCO_2$, motion, etc.)

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 → less (*or more!*) correlation (bias) → group differences

Weak but consistent bias → significant difference ?

Some sources have brain-wide (global) effects on correlation distribution (e.g. ETCO$_2$, motion, etc.)

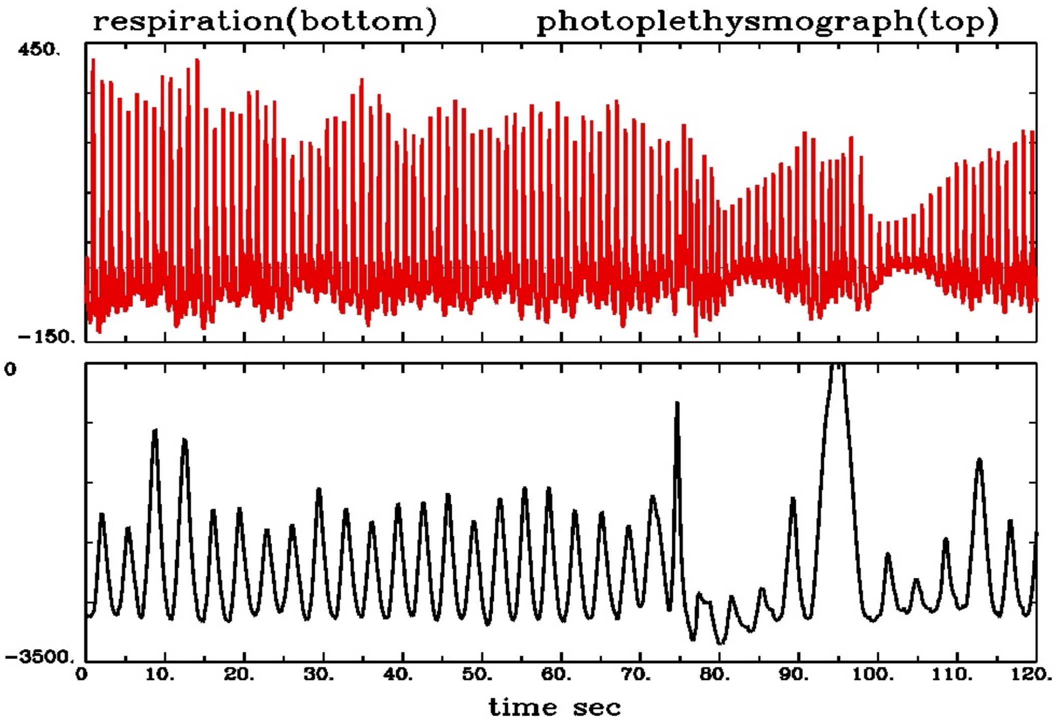
Sources of bias

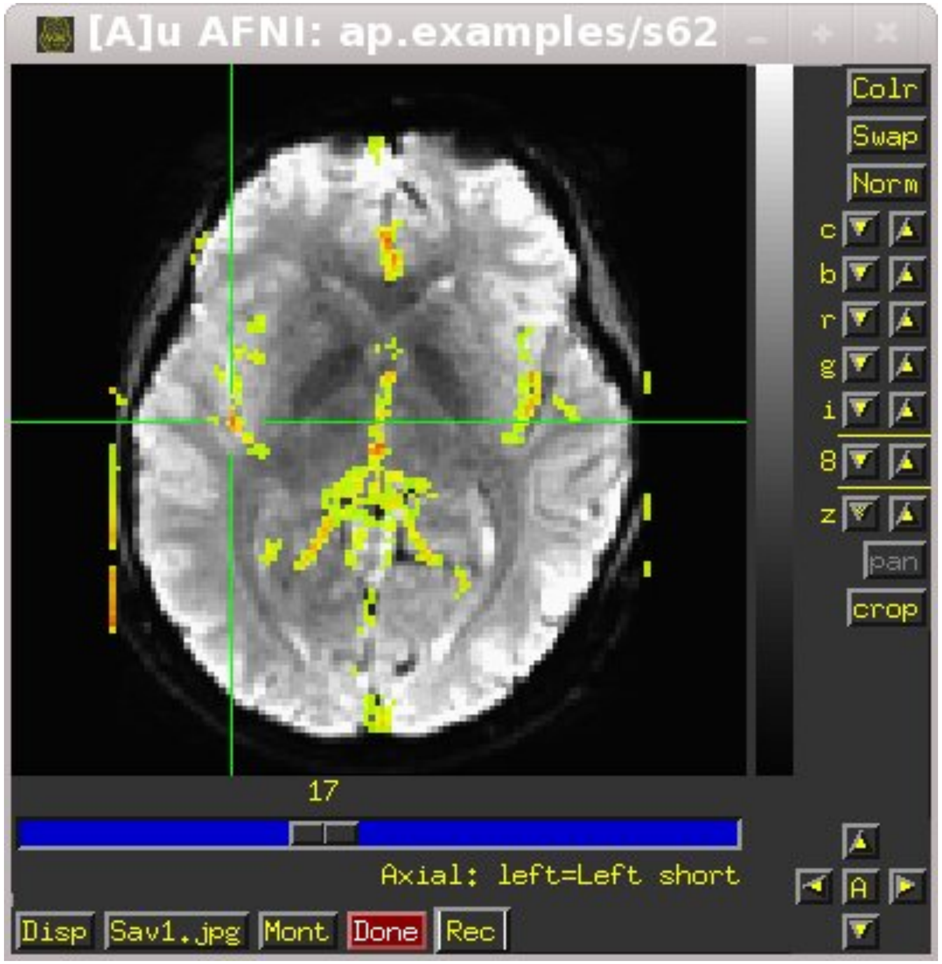
- Head motion (Van Dijk, 2012) (Power, 2012)
- Physiological "Noise"
  - Respiratory or cardiac cycles (Glover, 2002)
  - Non-stationarity of breathing and cardiac rhythms (Birn, 2006) (Shmueli, 2007) (Chang, 2009)
- Hardware instability (Jo, 2010)
- Anatomical bias
- Pre-processing

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

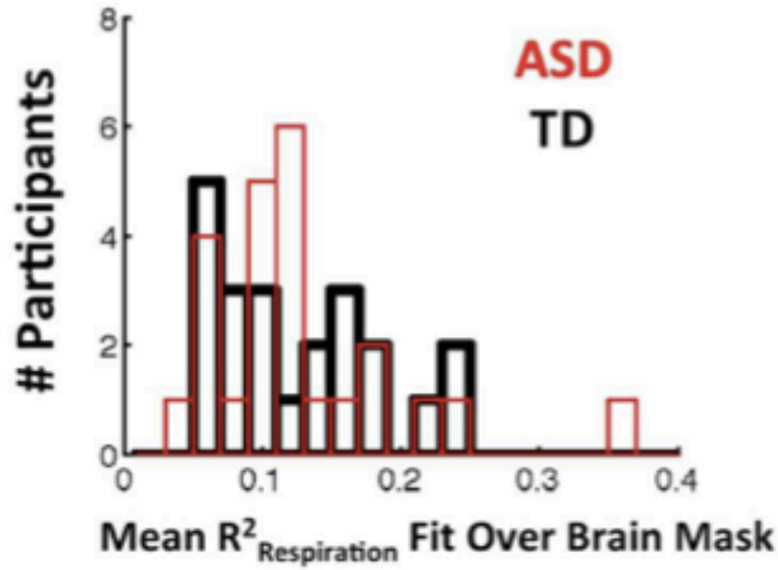
Physiological noise





Bias from physiological noise

MR Signal Variance Accounted for by Respiration Measures



TD – ASD Connectedness, Respiration Not Removed

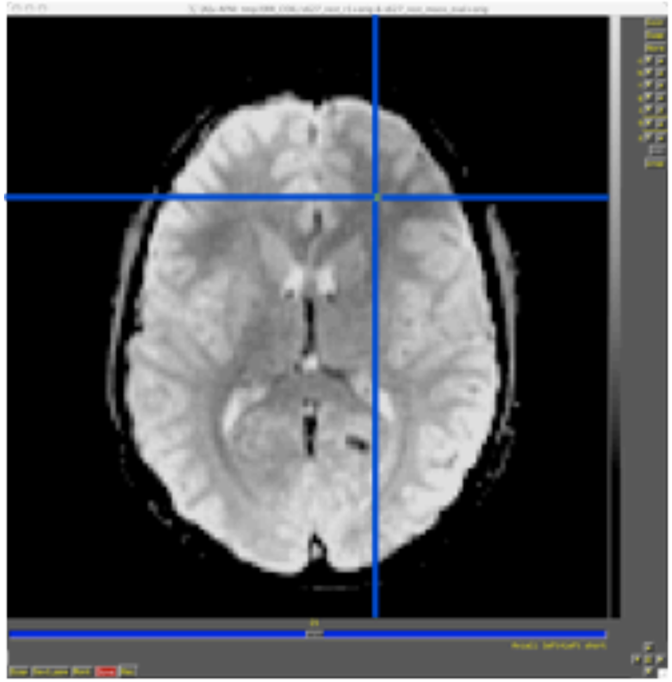
Gotts et al. 2012

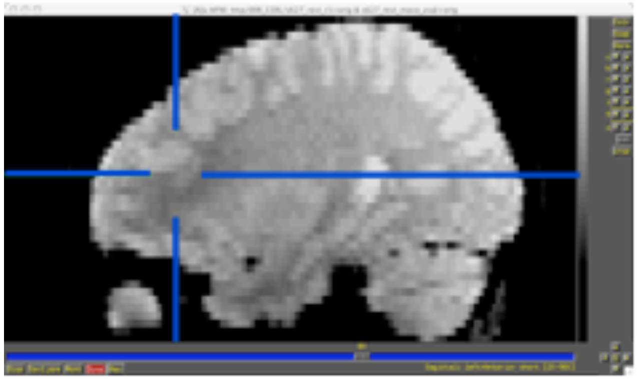
- "All of these results highlight the importance of measuring and removing the effects of respiration in resting-state fMRI studies that compare two groups of participants, particularly if one of these groups involves a clinical population with anxiety symptoms that could alter normal breathing patterns."

Sources of bias

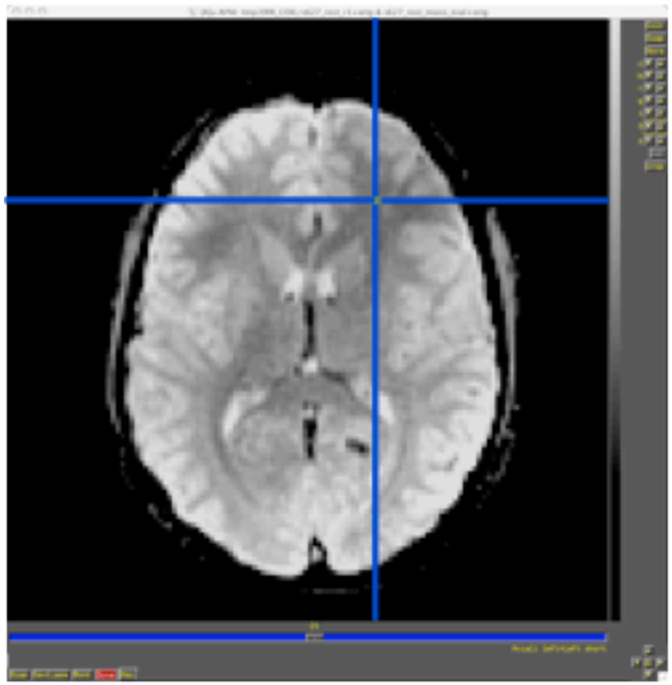
- Head motion (Van Dijk, 2012) (Power, 2012)
- Physiological "Noise"
  - Respiratory or cardiac cycles (Glover, 2002)
  - Non-stationarity of breathing and cardiac rhythms (Birn, 2006) (Shmueli, 2007) (Chang, 2009)
- Hardware instability (Jo, 2010)
- Anatomical bias
- Pre-processing

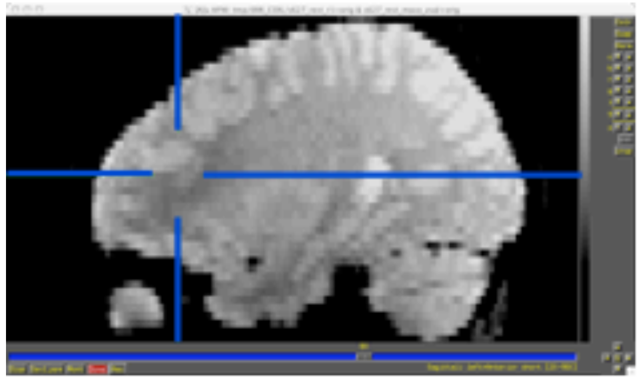
Hardware instability

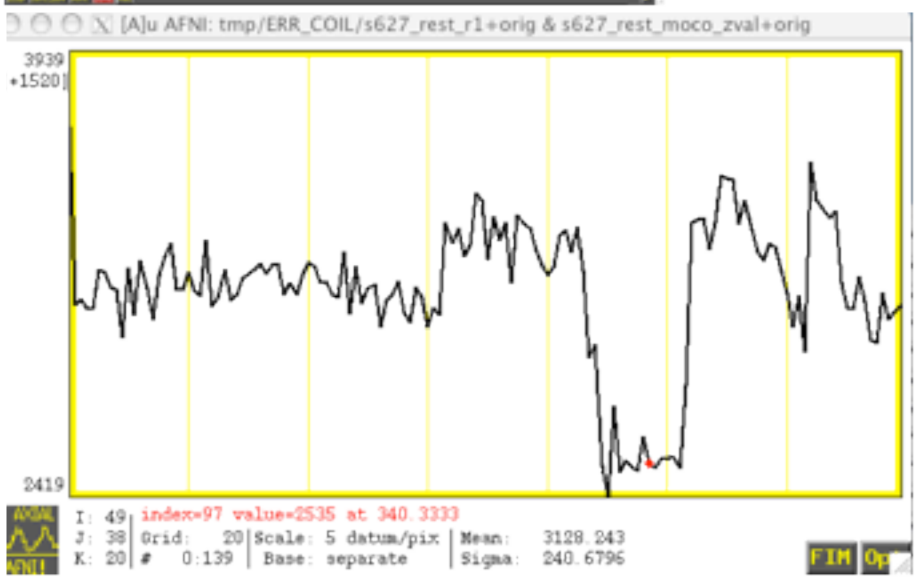




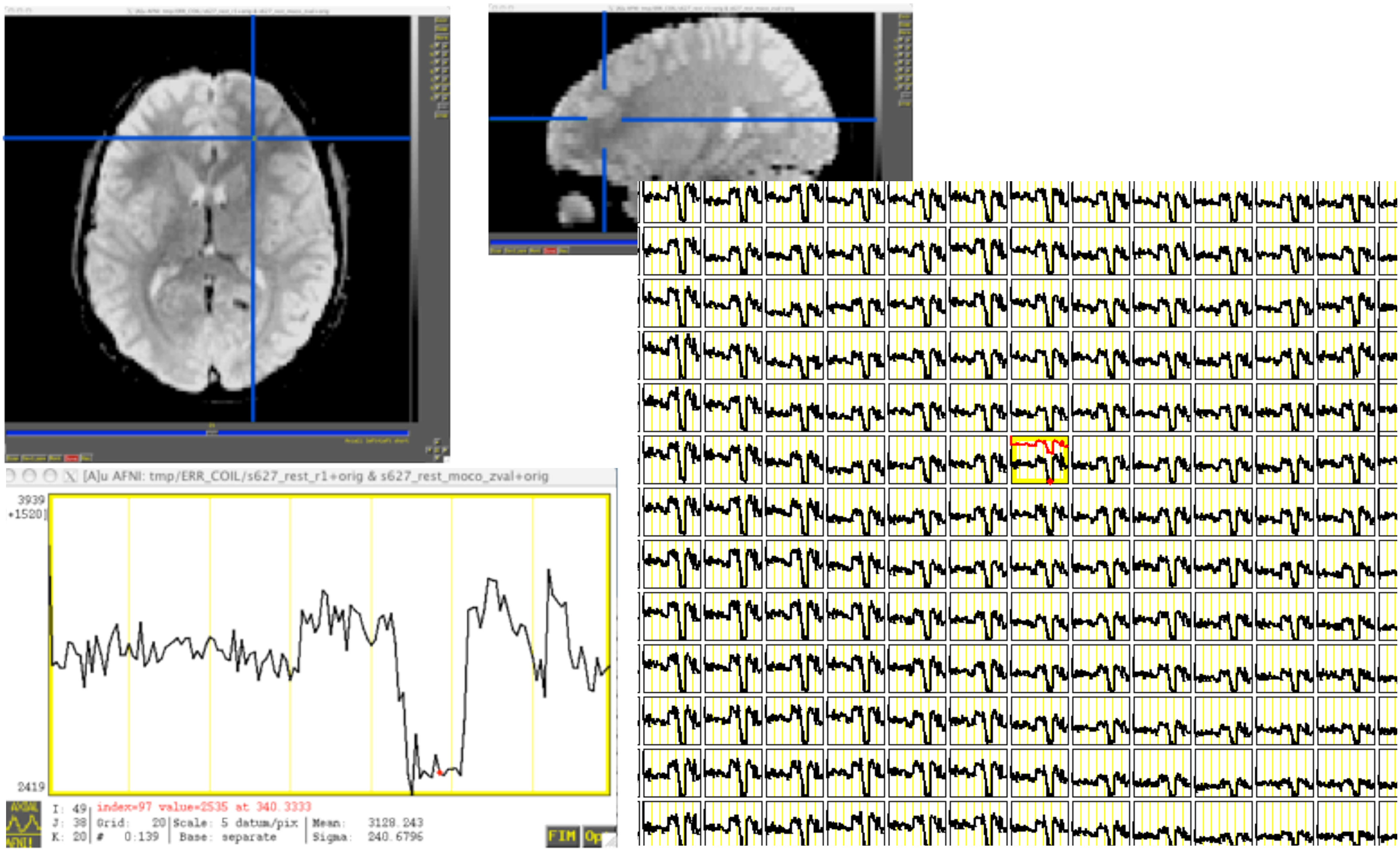
Hardware instability

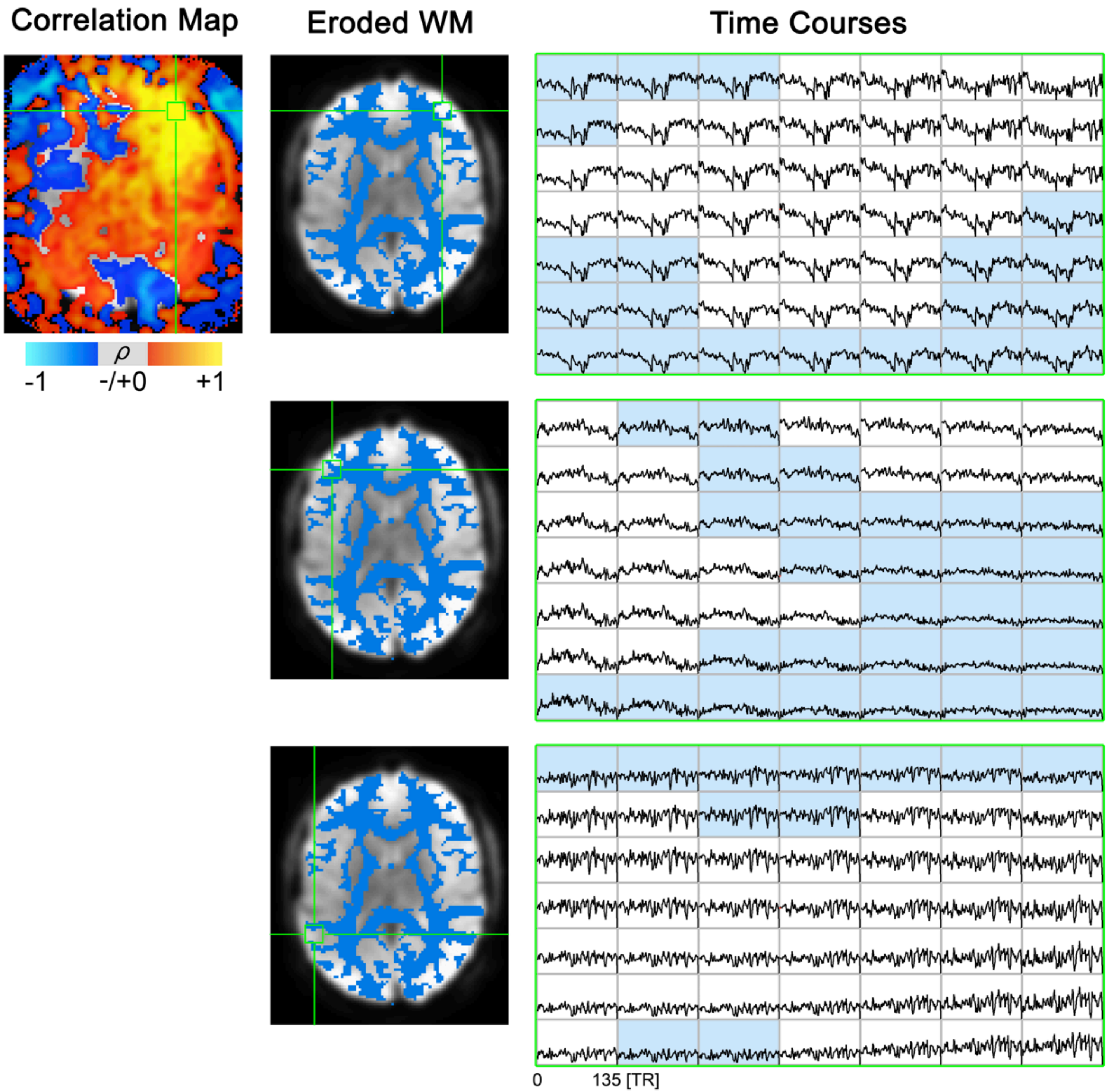






Hardware instability



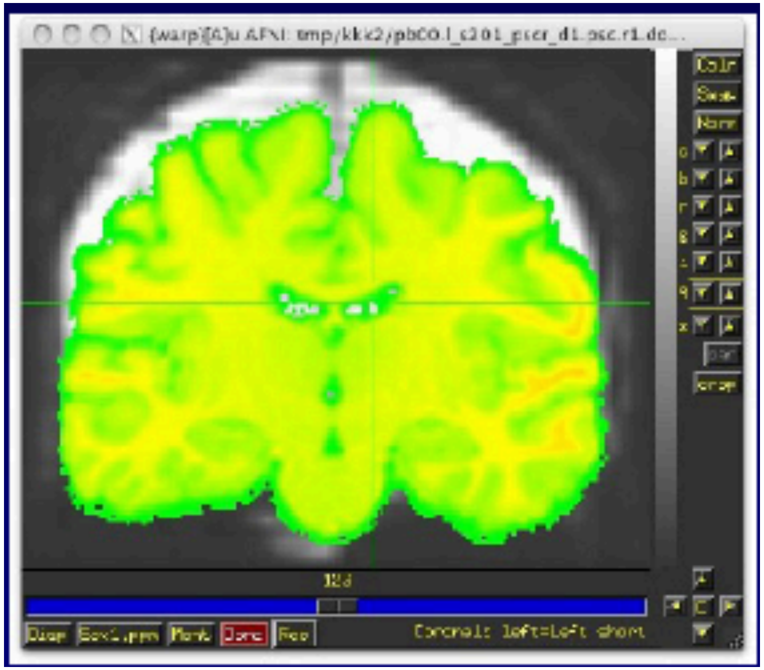


Z.S.S 16/06/13

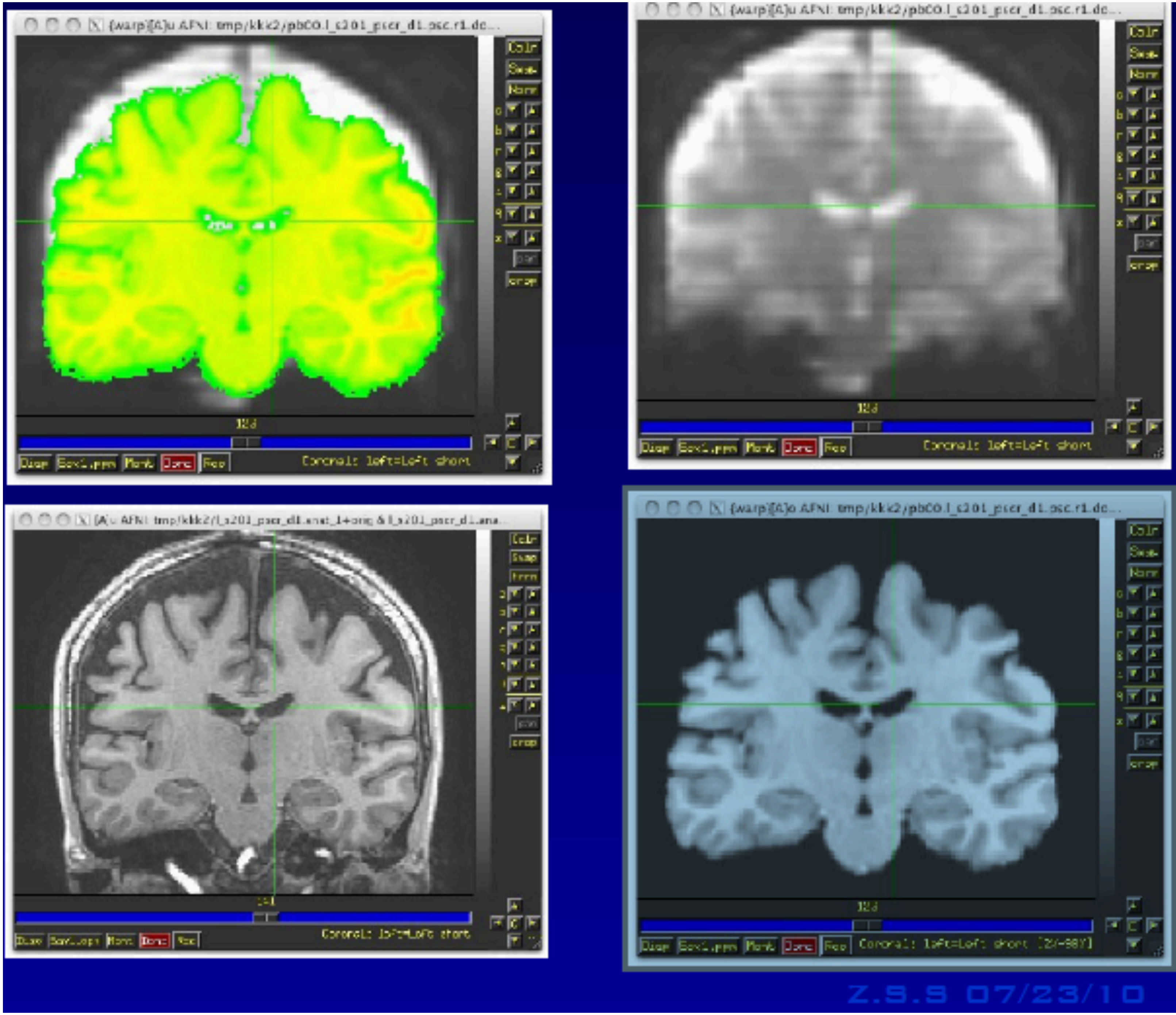
Sources of bias

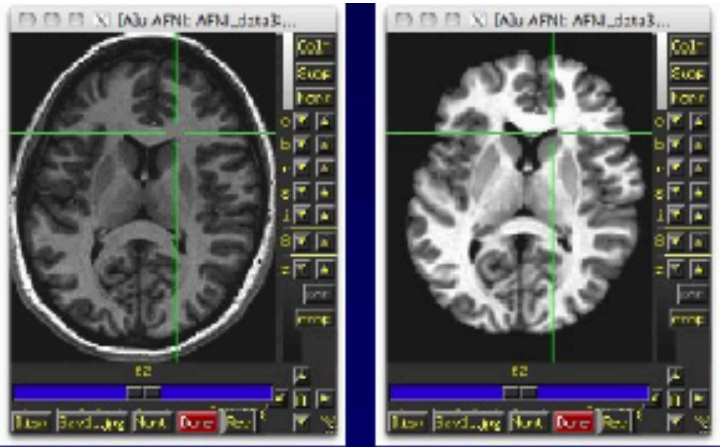
- Head motion (Van Dijk, 2012) (Power, 2012)
- Physiological “Noise”
  - Respiratory or cardiac cycles (Glover, 2002)
  - Non-stationarity of breathing and cardiac rhythms (Birn, 2006) (Shmueli, 2007) (Chang, 2009)
- Hardware instability (Jo, 2010)
- Anatomical bias
- Pre-processing

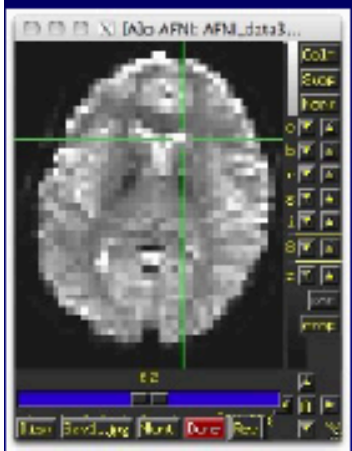
Anatomical Bias



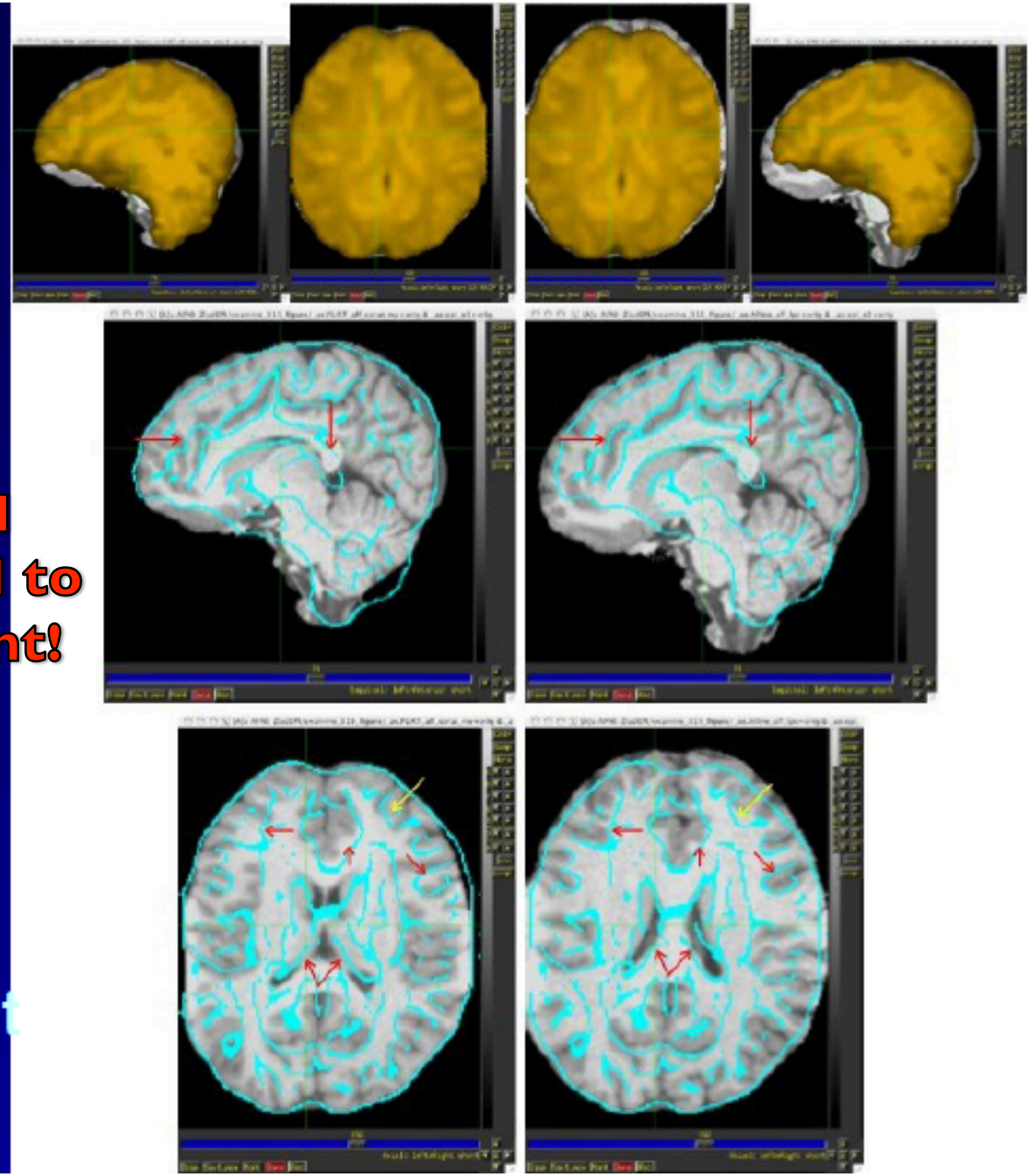
Anatomical Bias







Need Spatial Contrast in EPI to judge alignment!

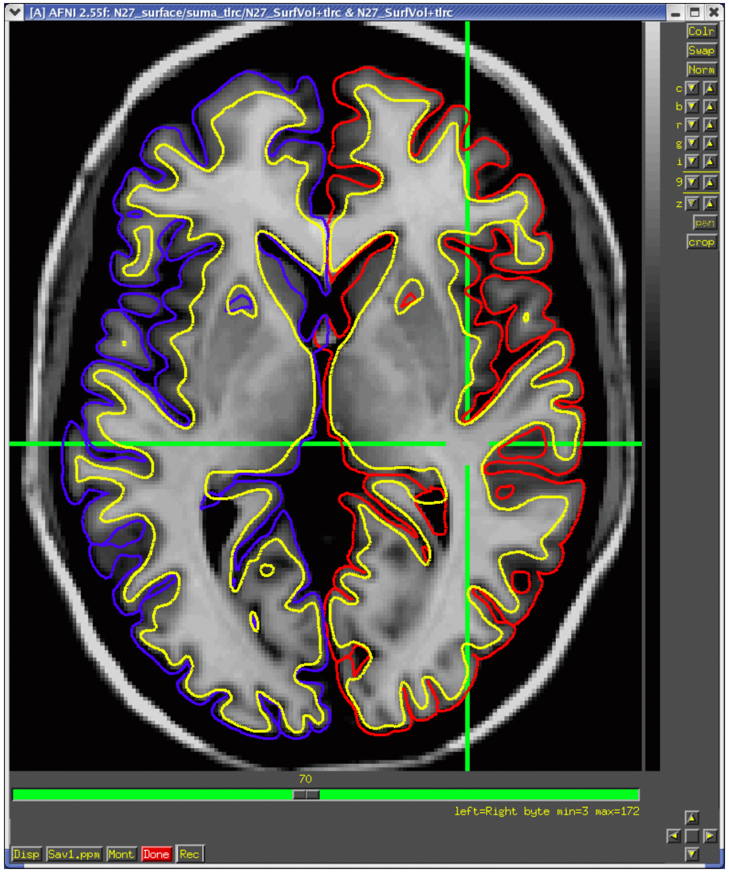


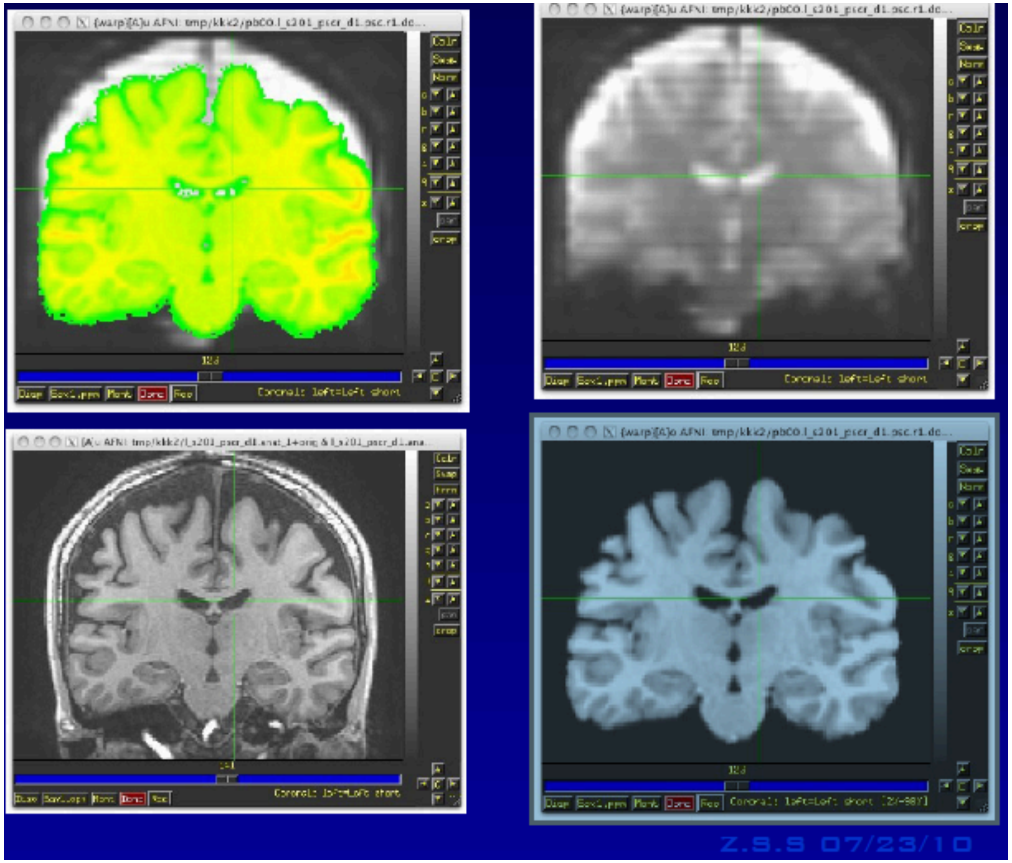
- Cursory checks not enough
- Normally, misalignment errors reduce power

With RS FMRI they can lead to effect differences

Anatomical Bias

- If concerned about systematic differences in anatomy, consider
  - Surface-based analysis with smoothing on the surface, or smooth within gray matter mask only
  - ROI-based analysis with ROIs restricted to gray-matter voxels in each subject





Z.S.S 16/06/13

Adjusting for noise/bias sources

- 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)

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

Tissue-based nuisance regressors

- Avoid Projecting Fluctuations of Interest

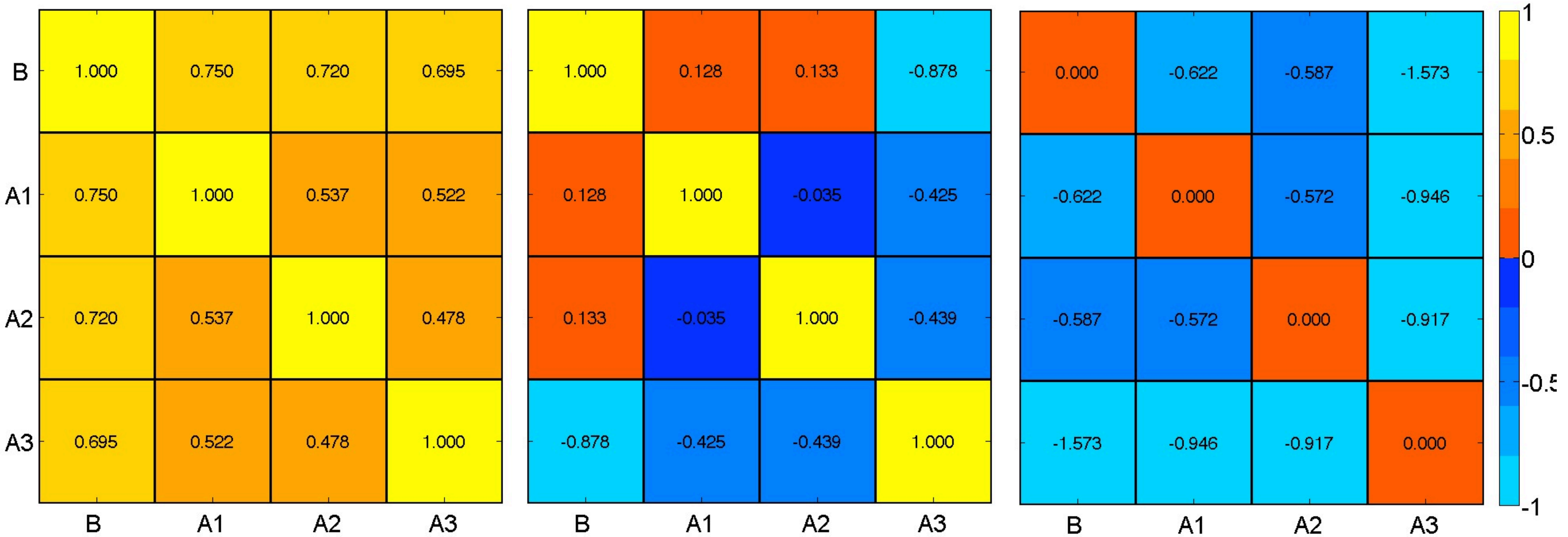
- OK to sample nuisance signals from regions whose fluctuations are not correlated with the *fluctuations of interest* in the regions of interest
- Should not project time series containing aggregates of fluctuations of interest, even if they contain contribution from noise
    - Sagittal sinus voxels 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 GSReg because math is straight forward.
    - What follows applies whether or not noise exists or differs between groups

Why not GSReg ?

Original (*R*) **After GSReg (*S*)** ***S* - *R***



Bias will vary by region pair

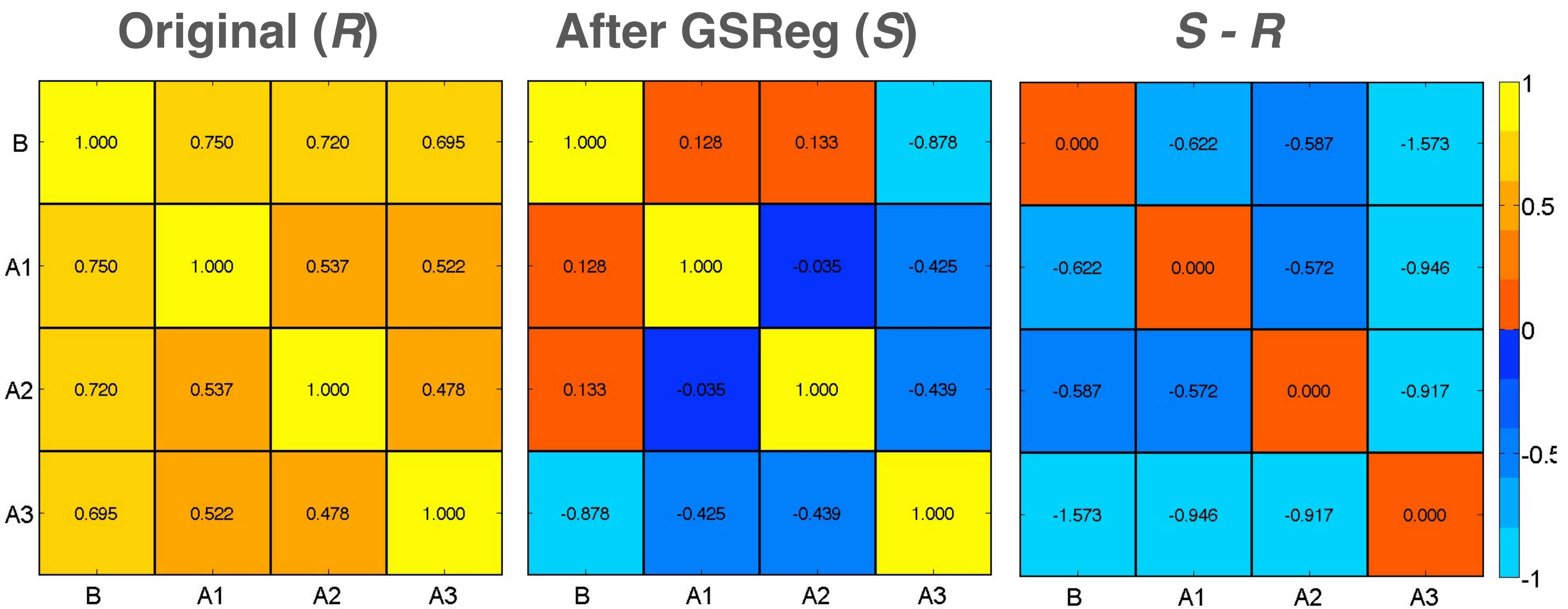
AND

Entirely dependent on initial covariance matrix ***P***

(therefore your grouping variable)

Z.S.S 16/06/13

Why not GSReg ?



For any FMRI time series (not simulations)

$$S - R = (P - (P11^{T}P)/(1^{T}P1)) \; * \; \sigma_Q \sigma_Q^{T} - P * \sigma_P \sigma_P^{T}$$

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 (Craddock, 2009)

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 (Craddock, 2009)

Region pair dependent biasing can be problematic when interpreting connectivity matrix differences:

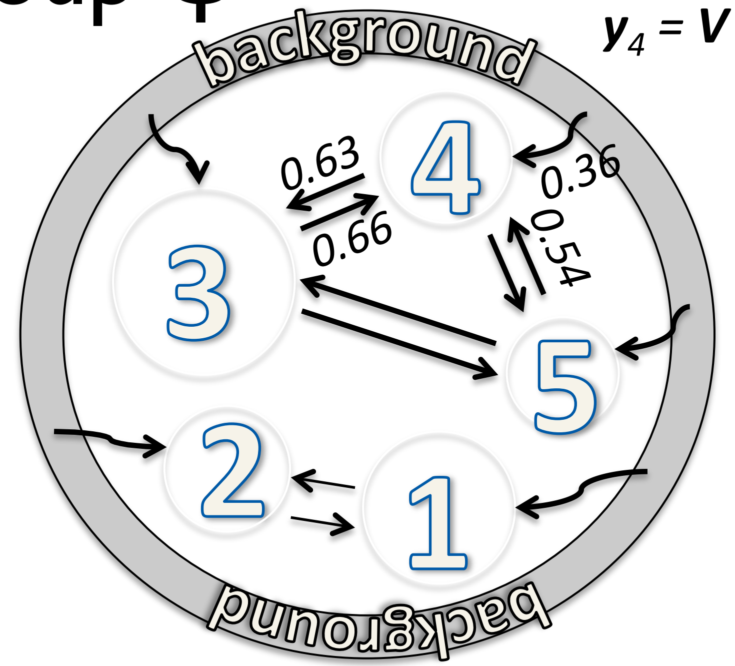
$$\boldsymbol{S} - \boldsymbol{R} = (\boldsymbol{P} - (\boldsymbol{P}\mathbf{1}\mathbf{1}^{\mathsf{T}}\boldsymbol{P})/(\mathbf{1}^{\mathsf{T}}\mathbf{P}\mathbf{1})) * \boldsymbol{\sigma}_{Q}\boldsymbol{\sigma}_{Q}^{\mathsf{T}} - \boldsymbol{P} * \boldsymbol{\sigma}_{P}\boldsymbol{\sigma}_{P}^{\mathsf{T}}$$

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

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

An illustrative model

Group ψ



Observed signal from region 4:

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

w_0	w_1	w_2	w_3	w_4	w_5
1.00	0.56	0.48	0.39	0.36	0.48
	0.56	0.73			
	0.61	0.48			
			0.39	0.66	0.64
			0.63	0.36	0.35
			0.54	0.54	0.48

w_4 connection weights for region 4

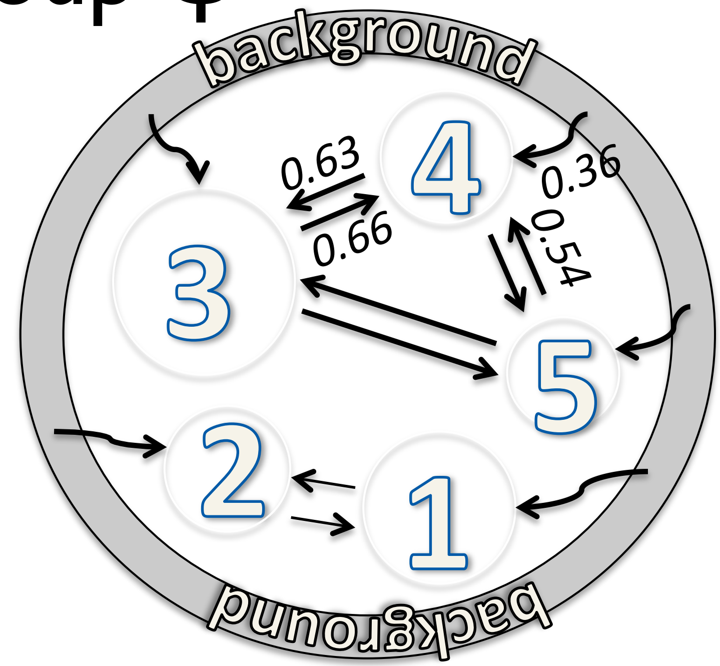
Connection Weight

0.3 1.0

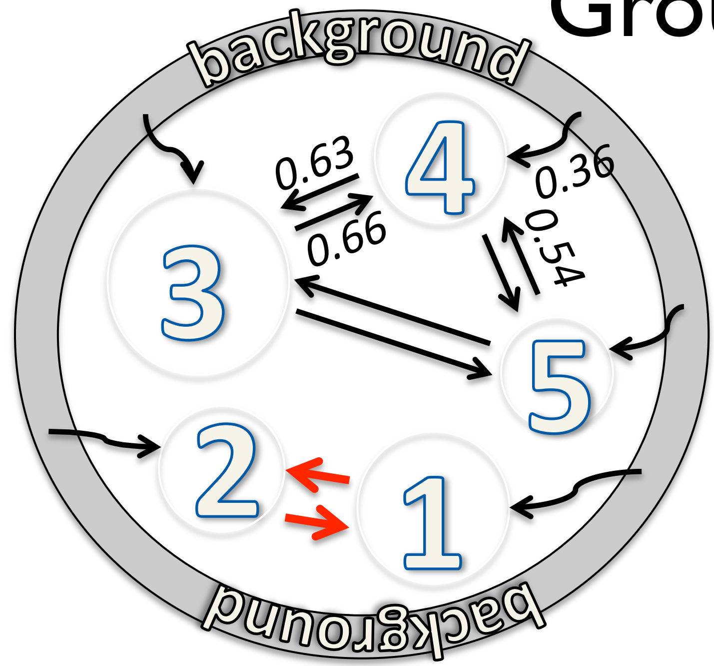
In simulations 9 regions + background were used

Comparing Groups

Group ψ



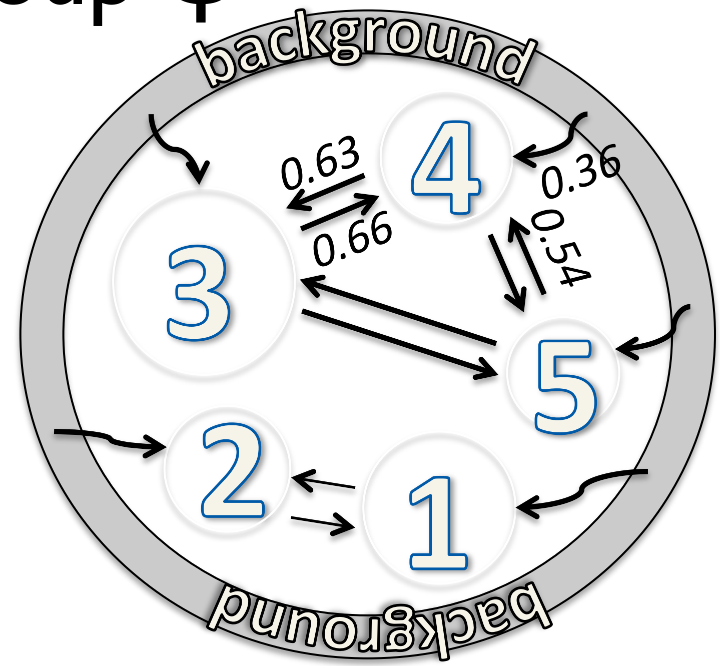
Group ψ_L



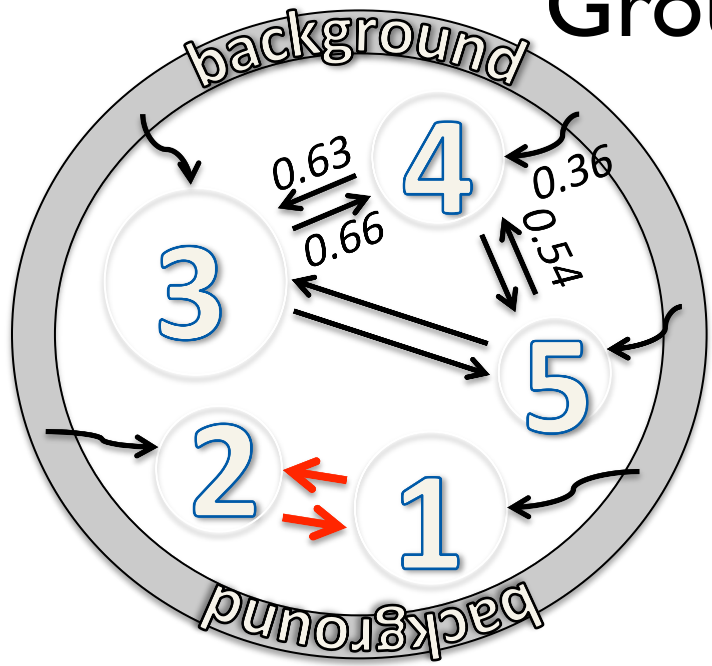
Increased connection
between regions 1 and 2 only

Comparing Groups

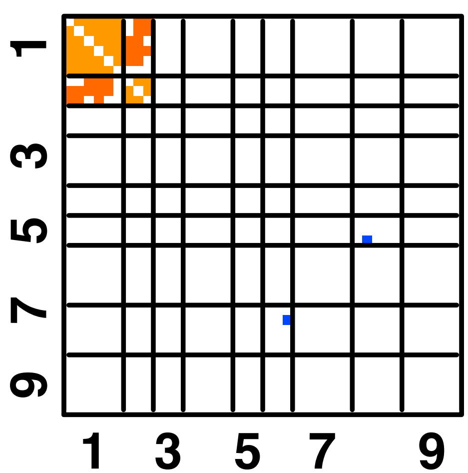
Group ψ



Group ψ_L



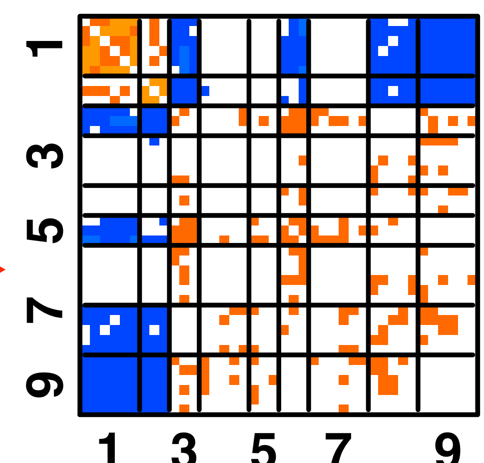
$\psi_L - \psi$ Base



Difference confined to two regions

Ends up all over the place

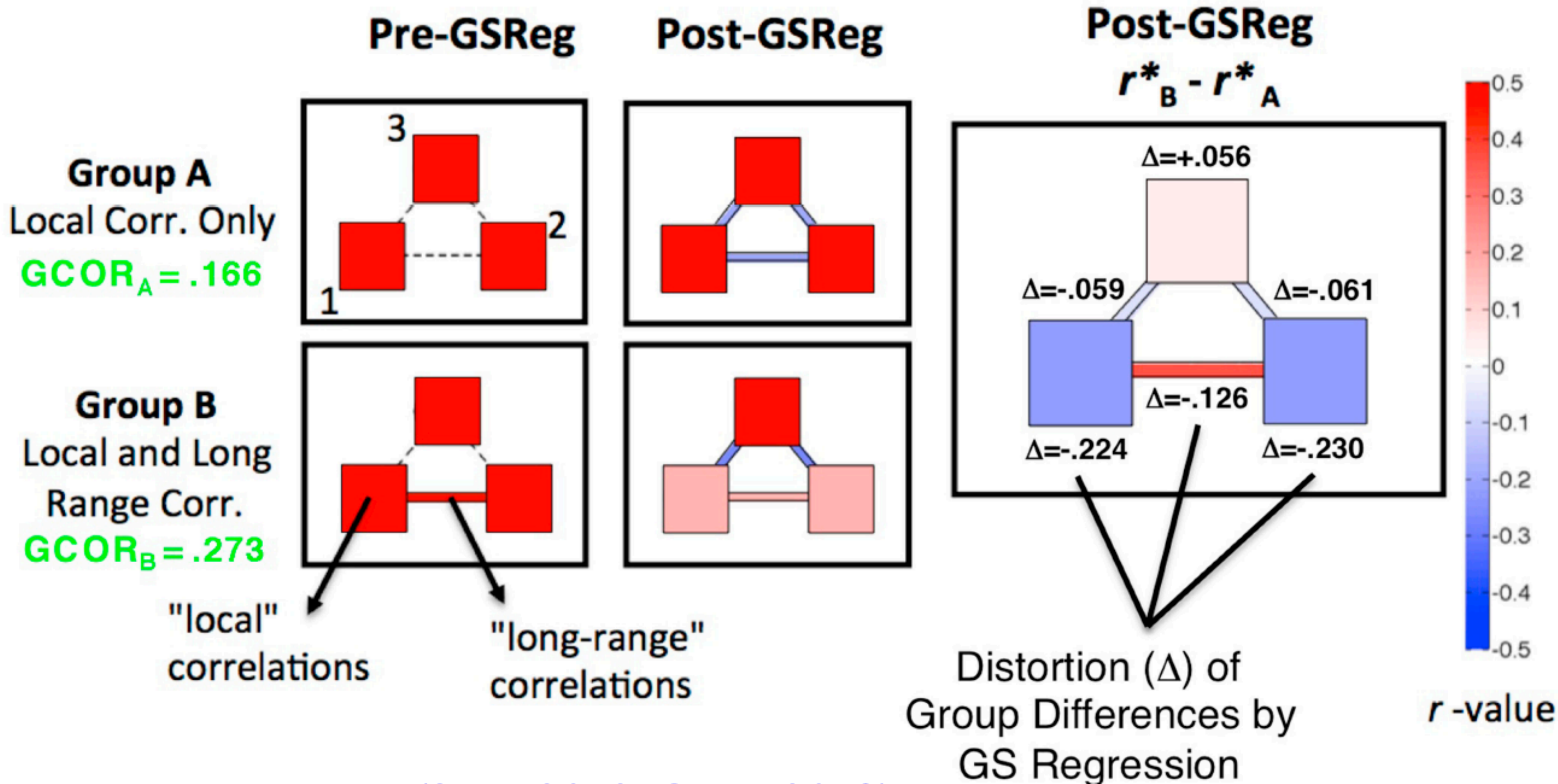
$\psi_L - \psi$ GSReg



Z.S.S 16/06/13

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 could 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.

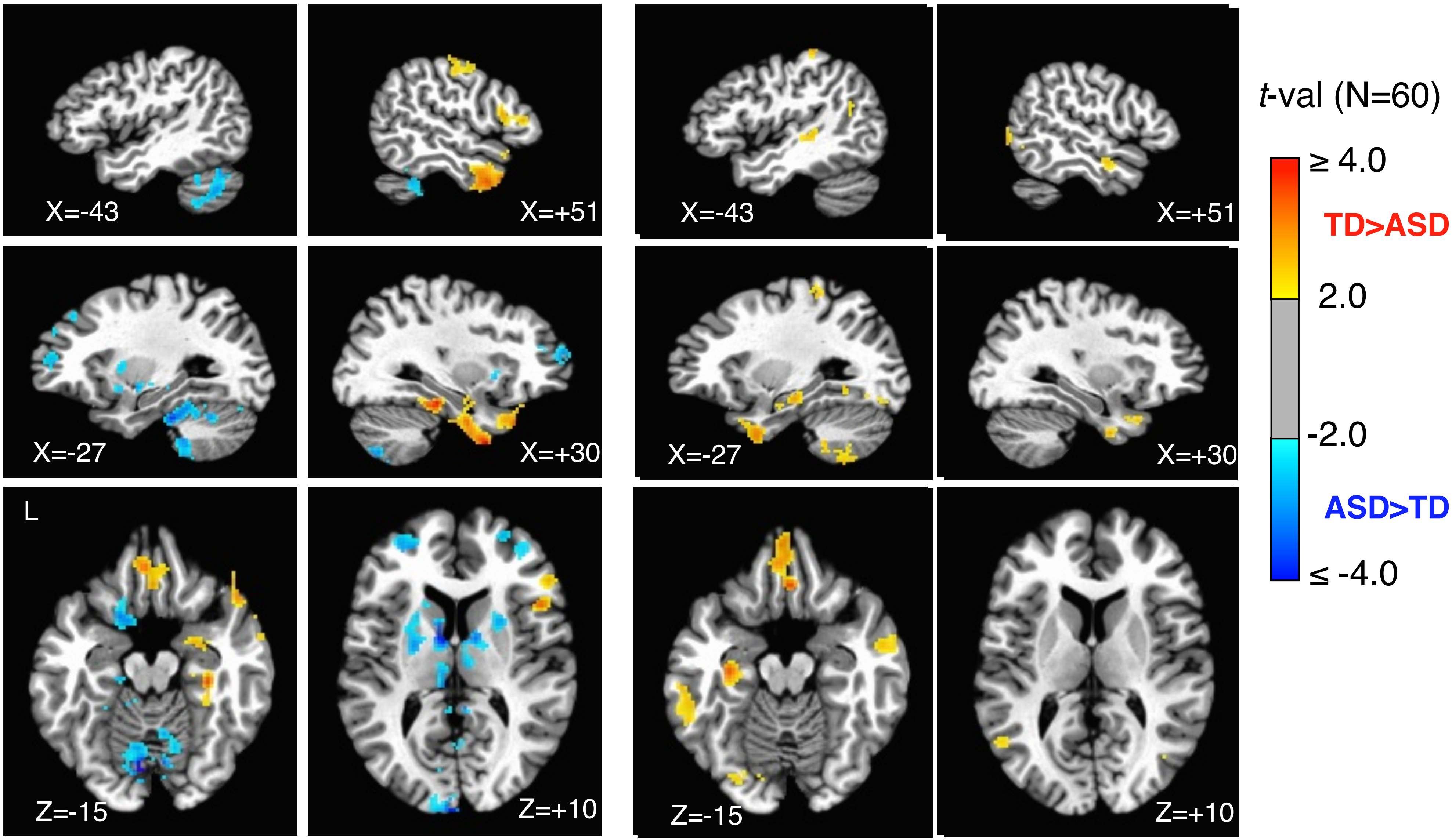
With noise previous problems remain

→ 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

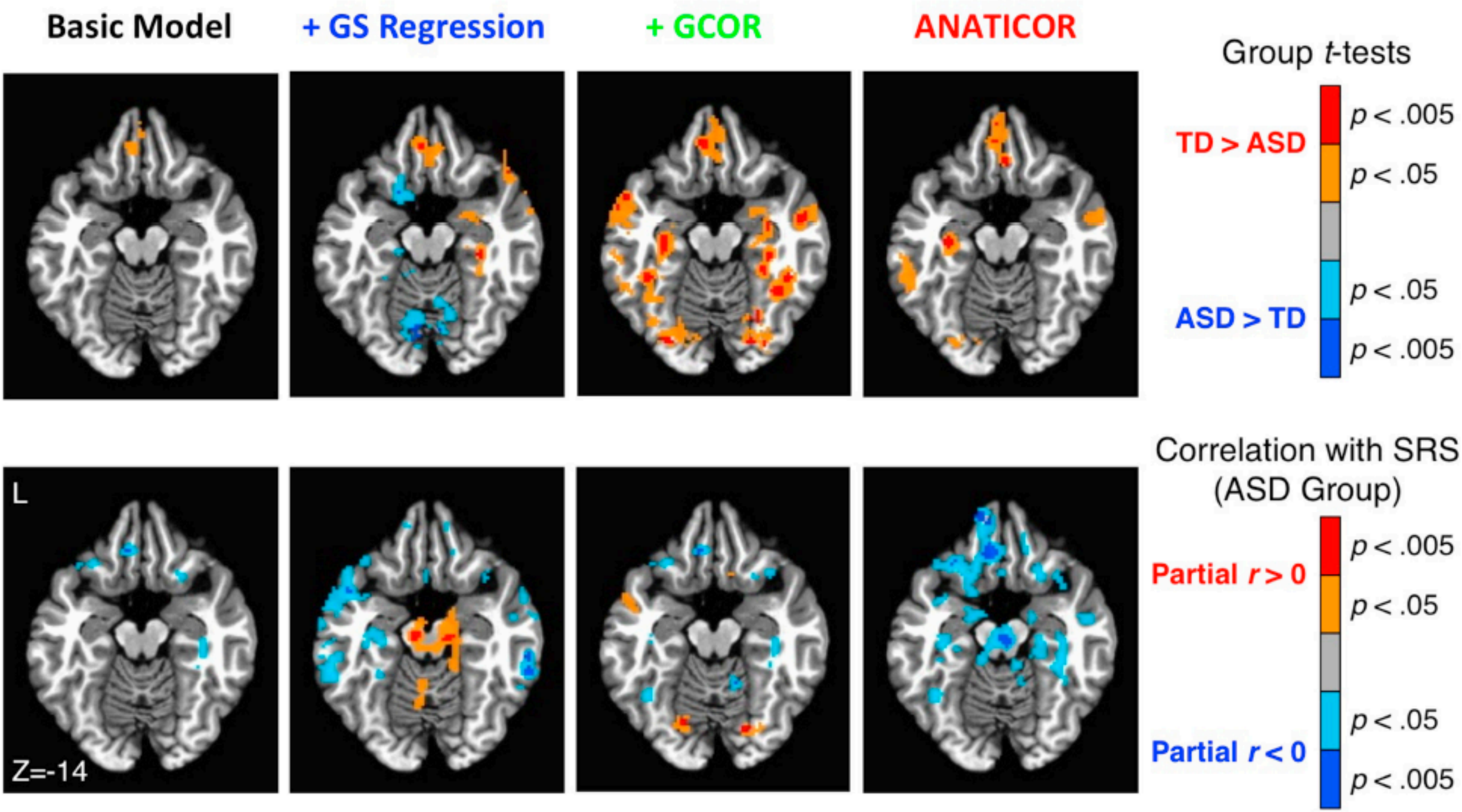
+ GS Regression **ANATICOR** (Jo, 2010)



(Gotts, 2013)

Z.S.S 16/06/13

SAME holds with empirical data



(Gotts, 2013)

It is not just GSR

- Nuisance regressors correlated with fluctuations of interest in regions of interest (not the noise) can cause the same problems.

- Non-gray matter averages may be comparable to GSReg (partial voluming with gray matter)
  - Averaging over small regions of eroded non-gray matter tissue is advantageous (Jo, 2010, 2013)

- Decomposition methods that cannot separate BOLD (fluctuations of interest) from noise also problematic.

There is some denoising with GSR

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

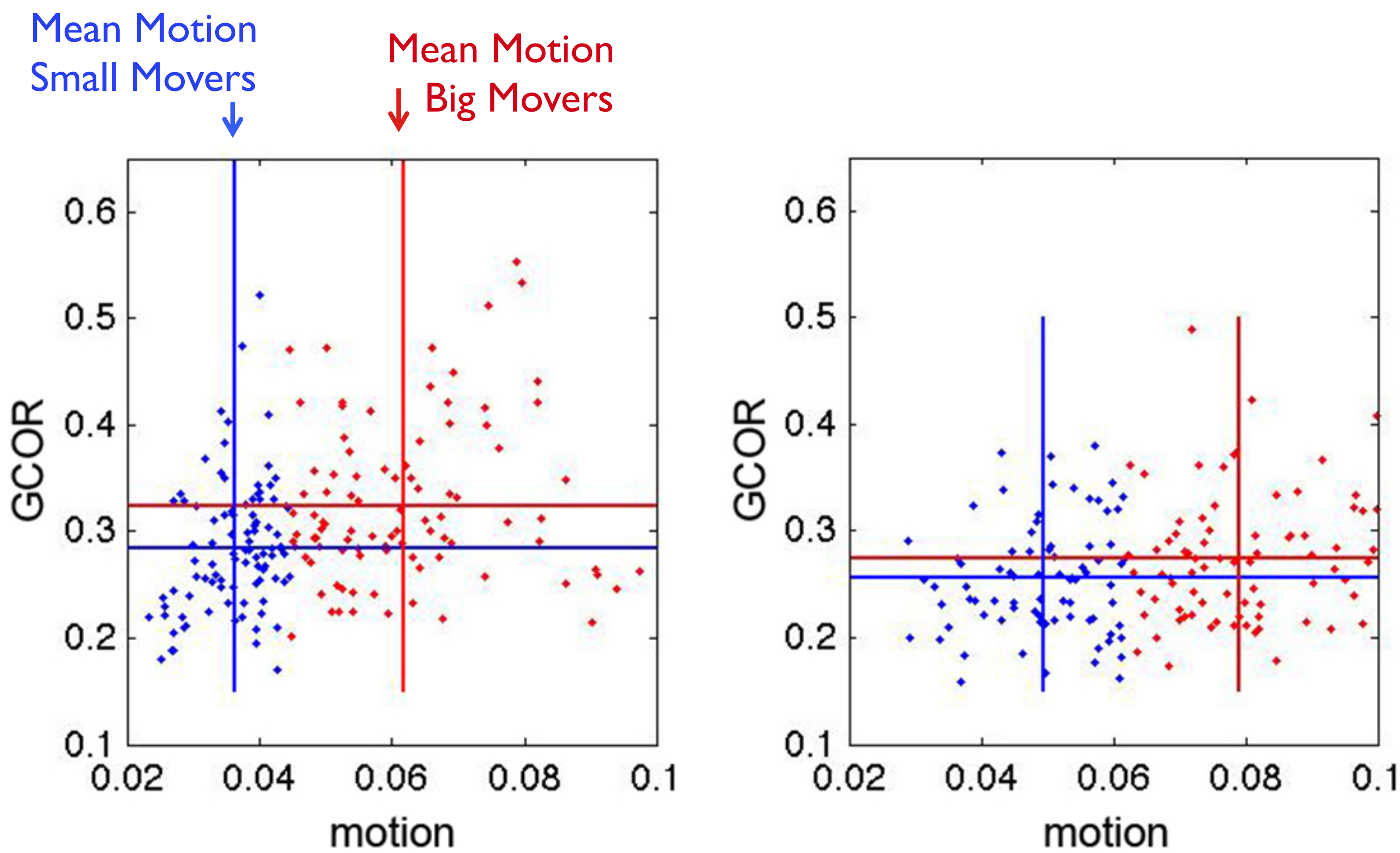
What of GSReg for motion compensation?

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

FCON 1000: Beijing_Zang

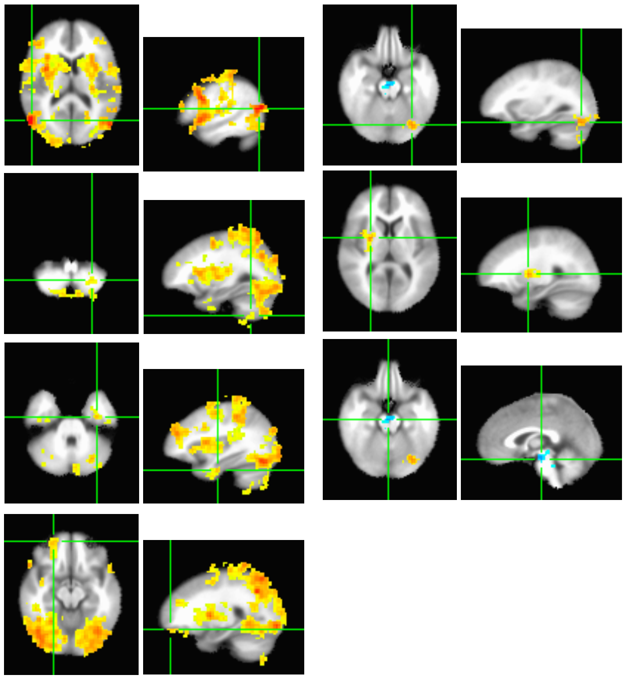
Note weak correlation between motion and GCOR (R^2=11% Cambridge, 4.3% Beijing)

Grouping Based on Motion

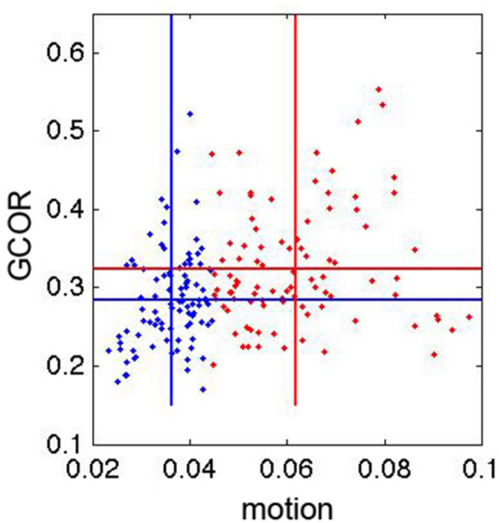
FCON 1000: Cambridge_Buckner

β_1 Base β_1 GSReg

Largest 4 Clusters



4 clusters 3 clusters

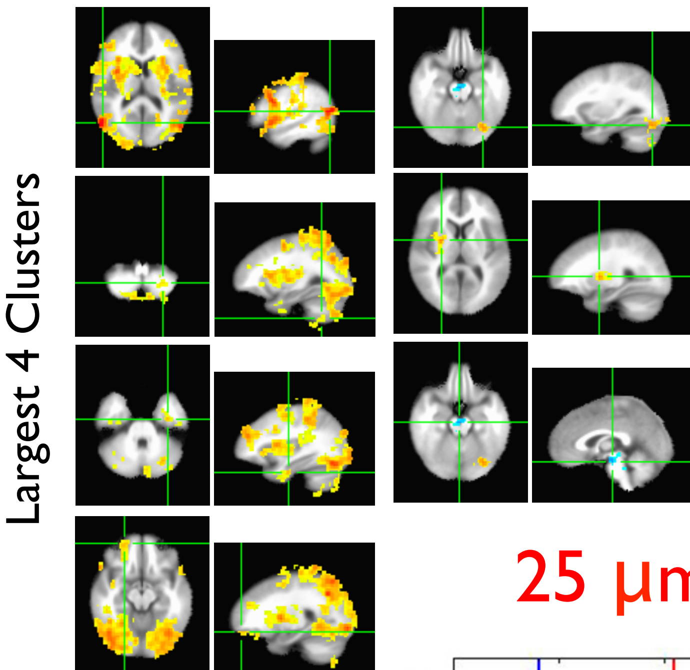


Z.S.S 16/06/13

Grouping Based on Motion

FCON 1000: Cambridge_Buckner

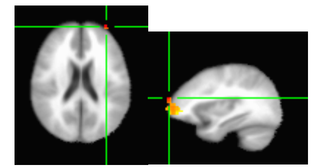
β_1 Base β_1 GSReg



4 clusters

FCON 1000: Beijing_Zang

β_1 Base β_1 GSReg



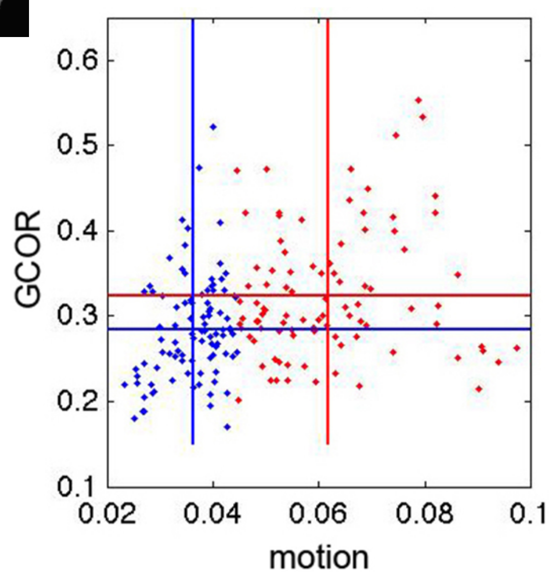
1 cluster

0 clusters

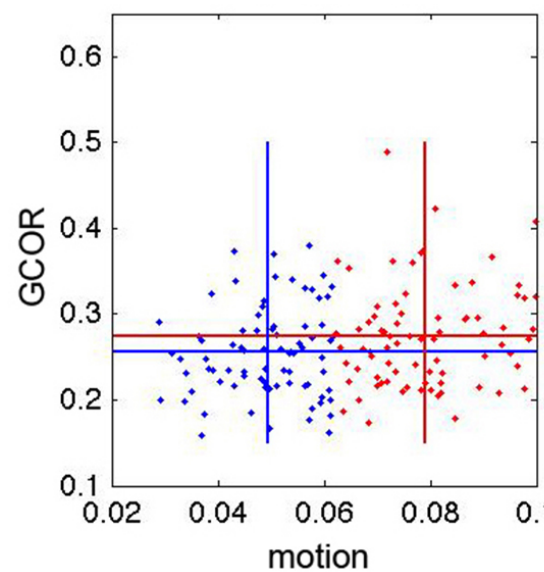
Small > Big Small < Big

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

25 µm/TR



29 µm/TR



(Saad, 2013)

Z.S.S 16/06/13

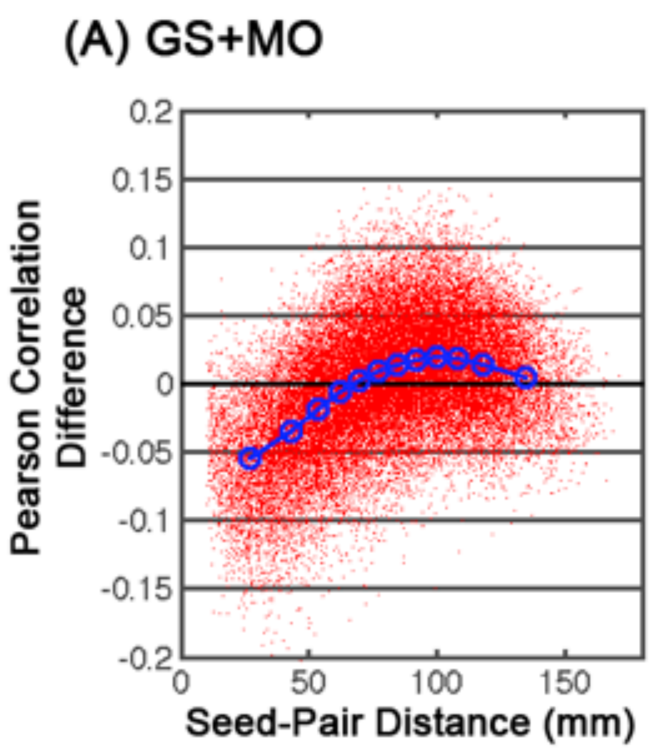
Can GSReg help with motion?

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 et al.



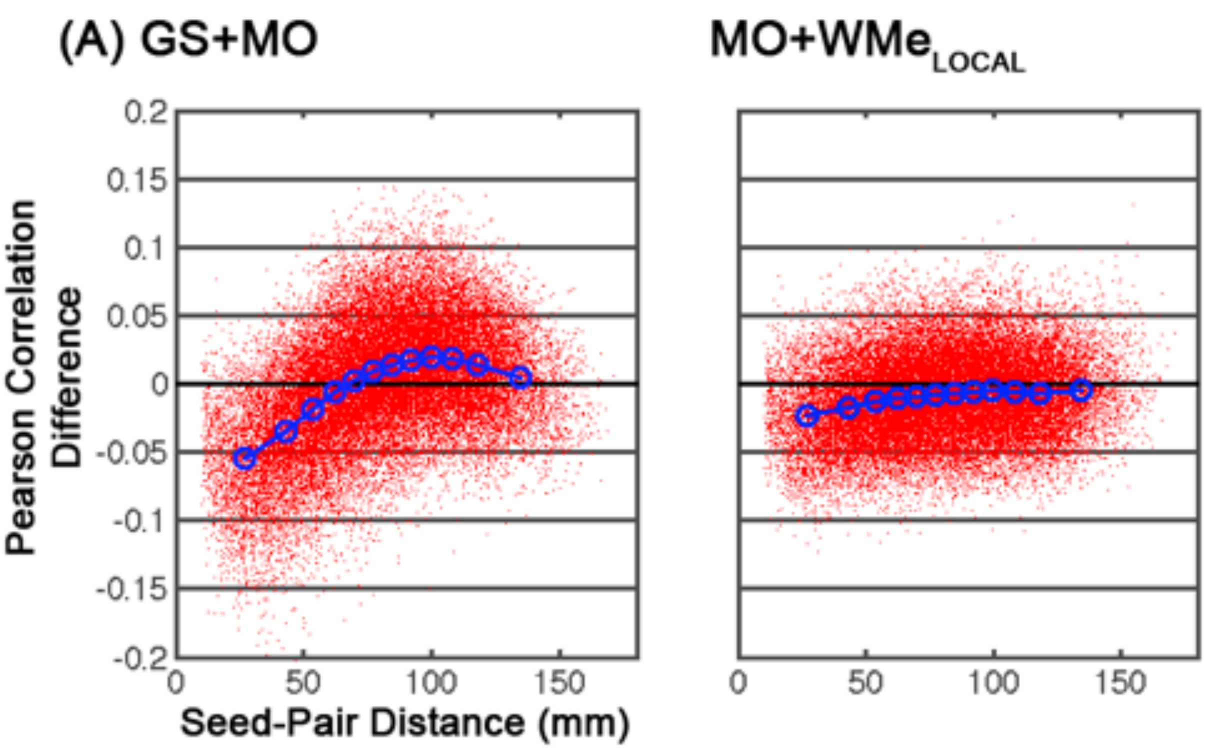
Can GSReg help with motion?

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



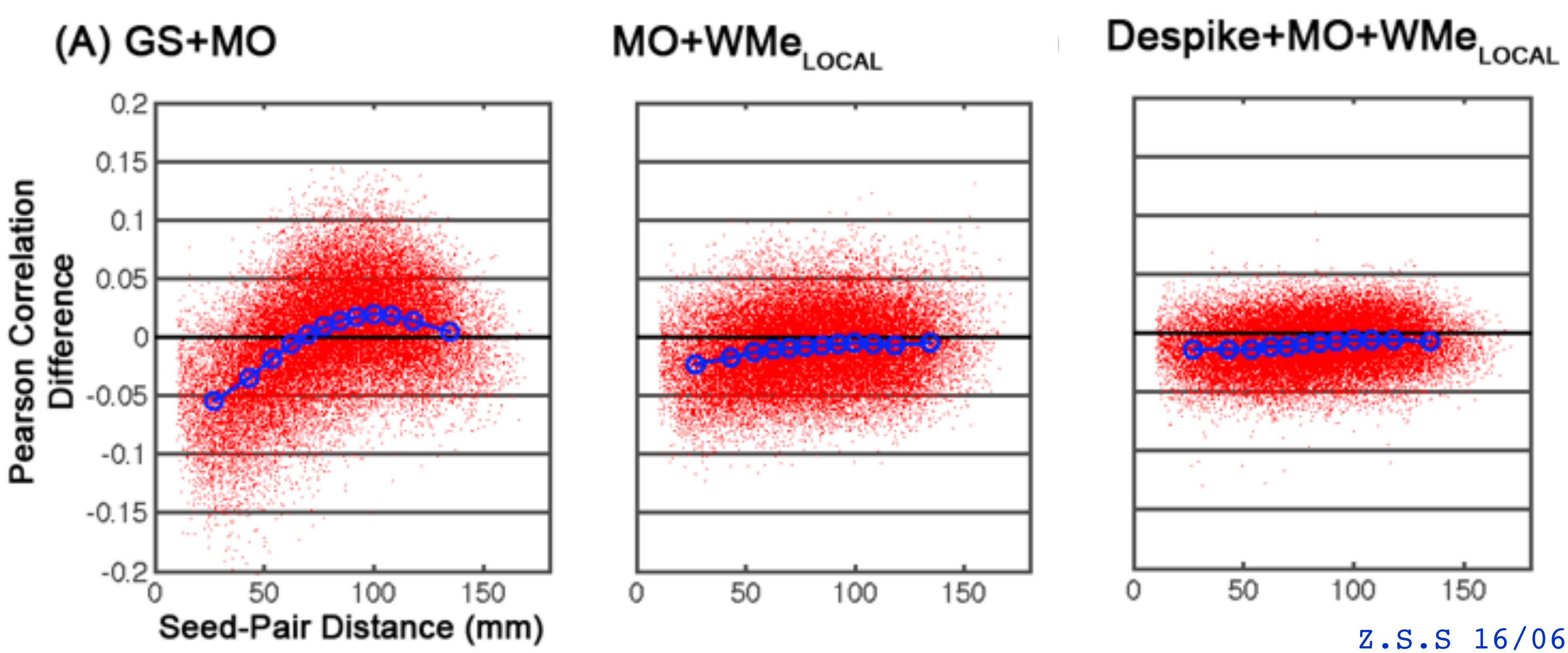
Can GSReg help with motion?

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

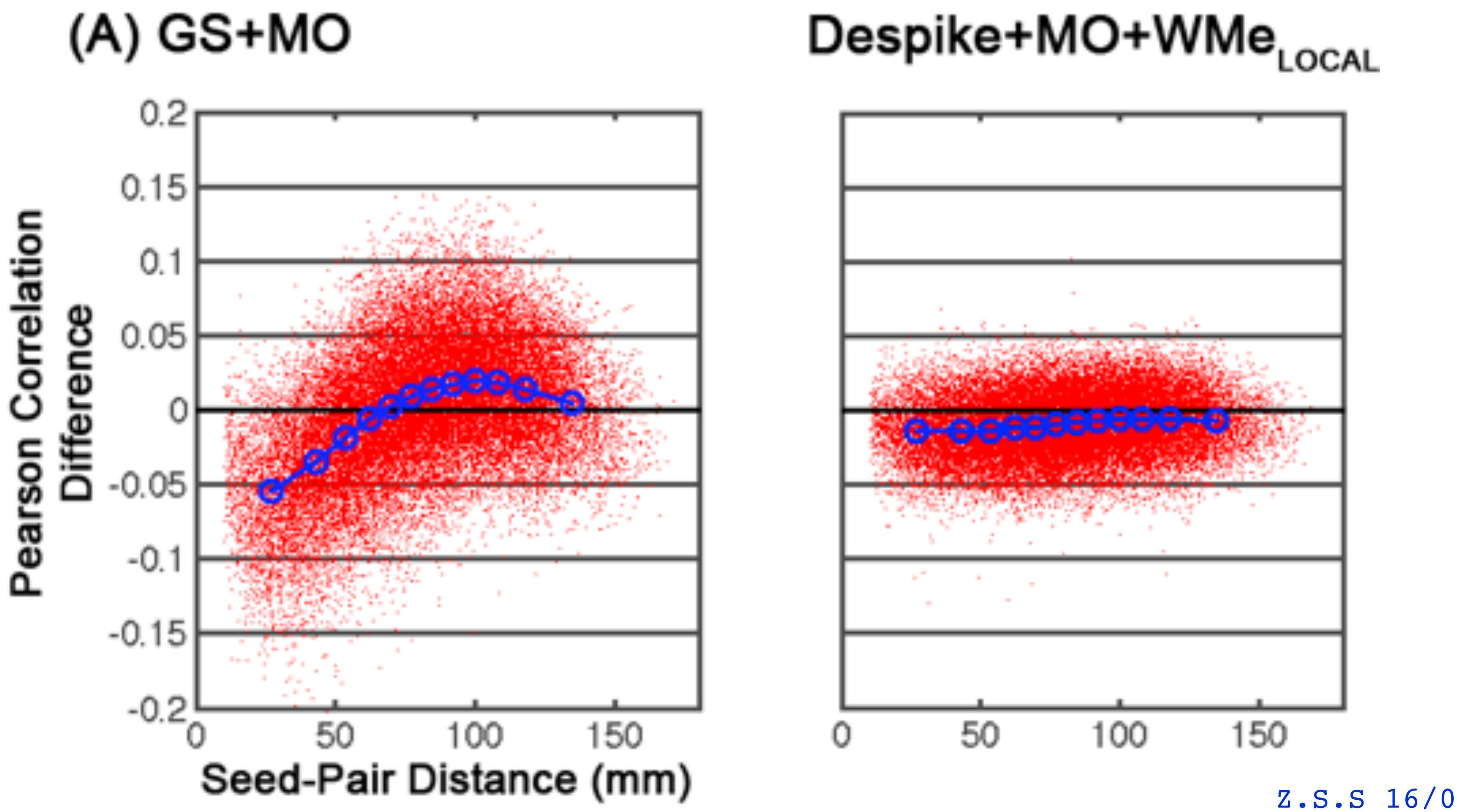


Can GSReg help with motion?

GSReg → Correlation more sensitive to motion
→ Correlation more sensitive to censoring

(Jo, 2013)

Improved denoising largely eliminates distance dependent bias



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:

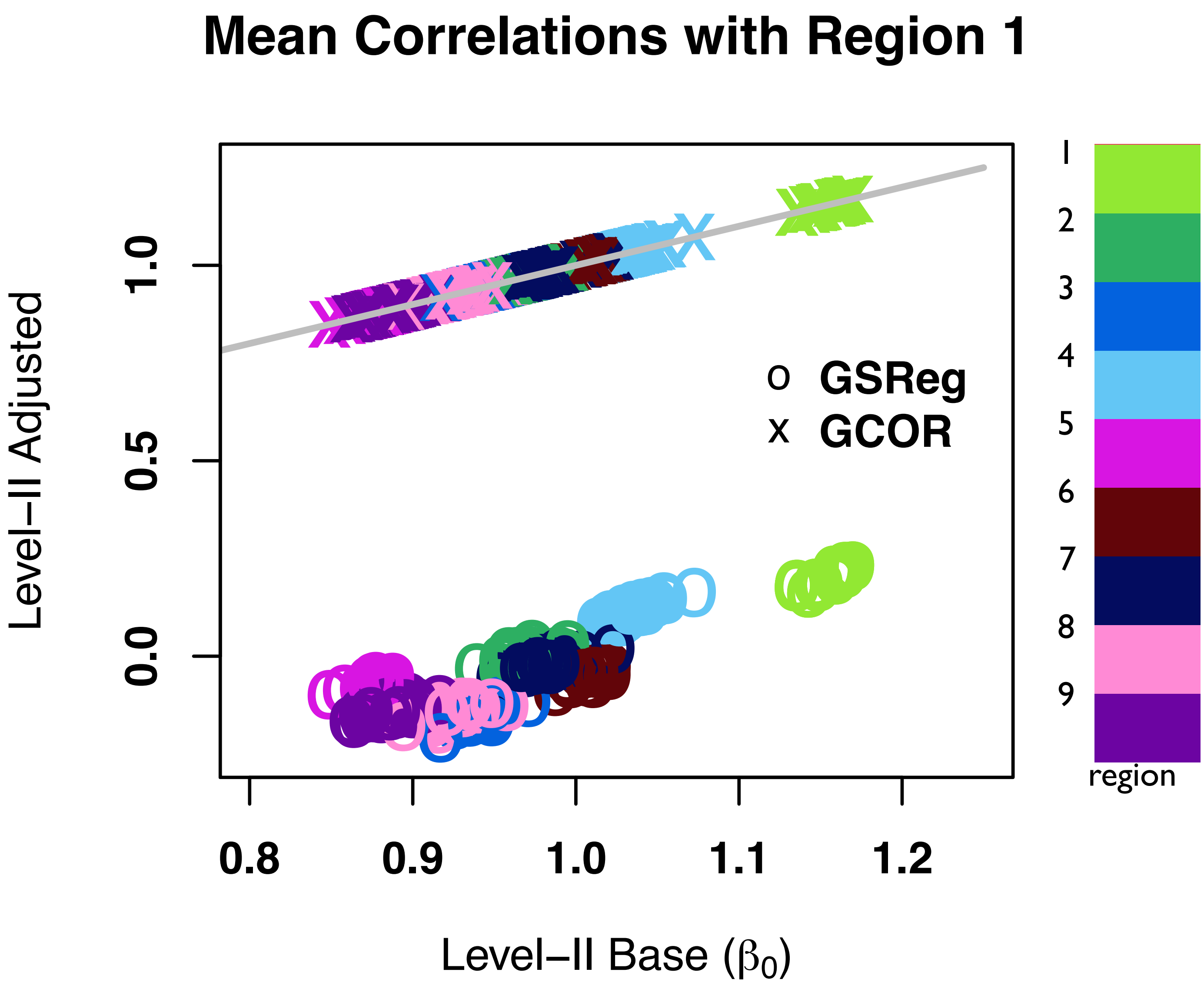
$$\gamma = 1/(M^2 N)\, \mathbf{1}^{\mathrm{T}} \boldsymbol{U}^{\mathrm{T}} \boldsymbol{U}\, \mathbf{1}$$
$$= 1/N\, \boldsymbol{g}_u^{\mathrm{T}}\, \boldsymbol{g}_u,$$

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

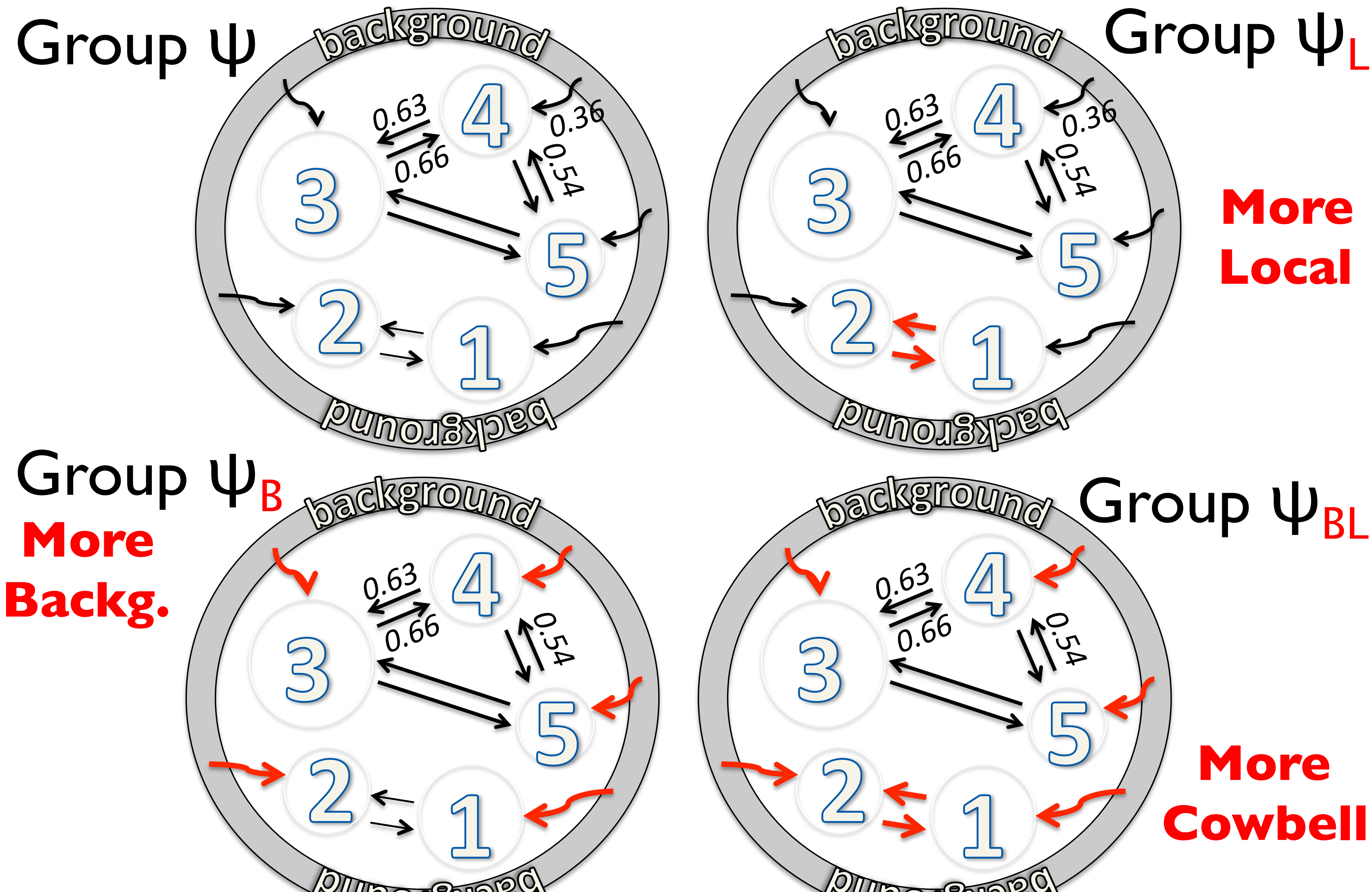
GCOR as group level covariate

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

Less bias than with GSReg for 1 sample tests

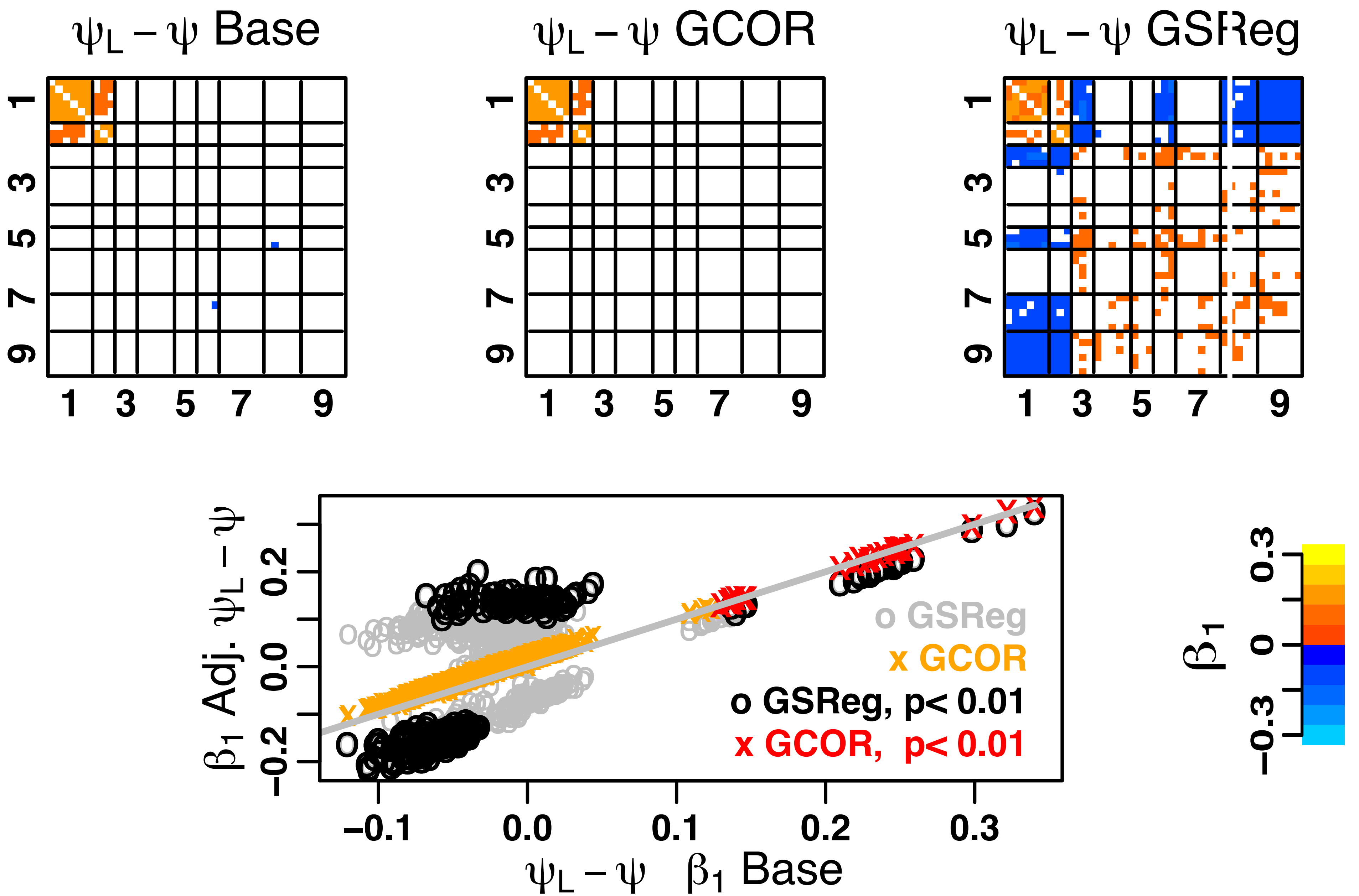


Comparing Groups



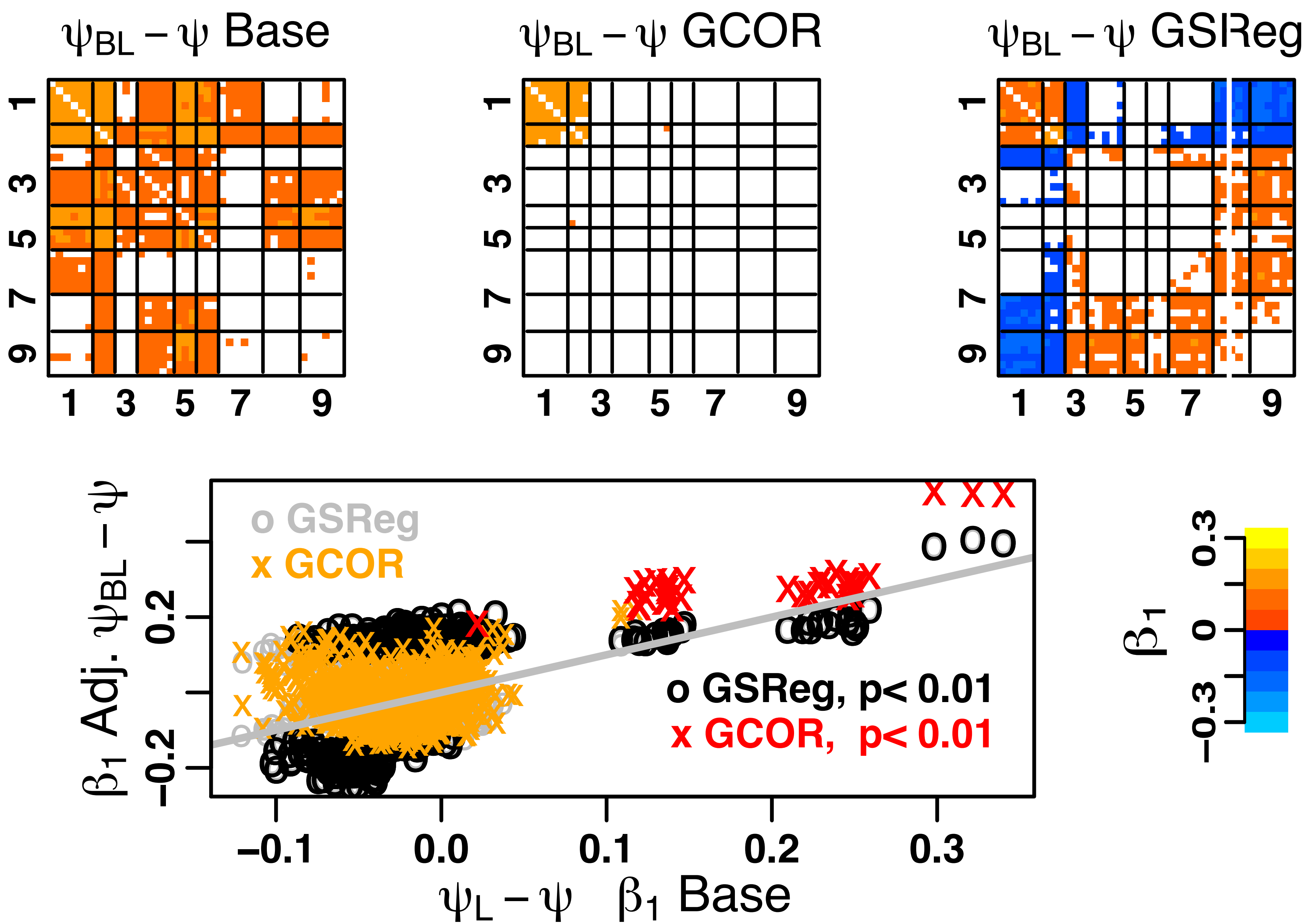
Z.S.S 16/06/13

Group Contrast, Only Local Change



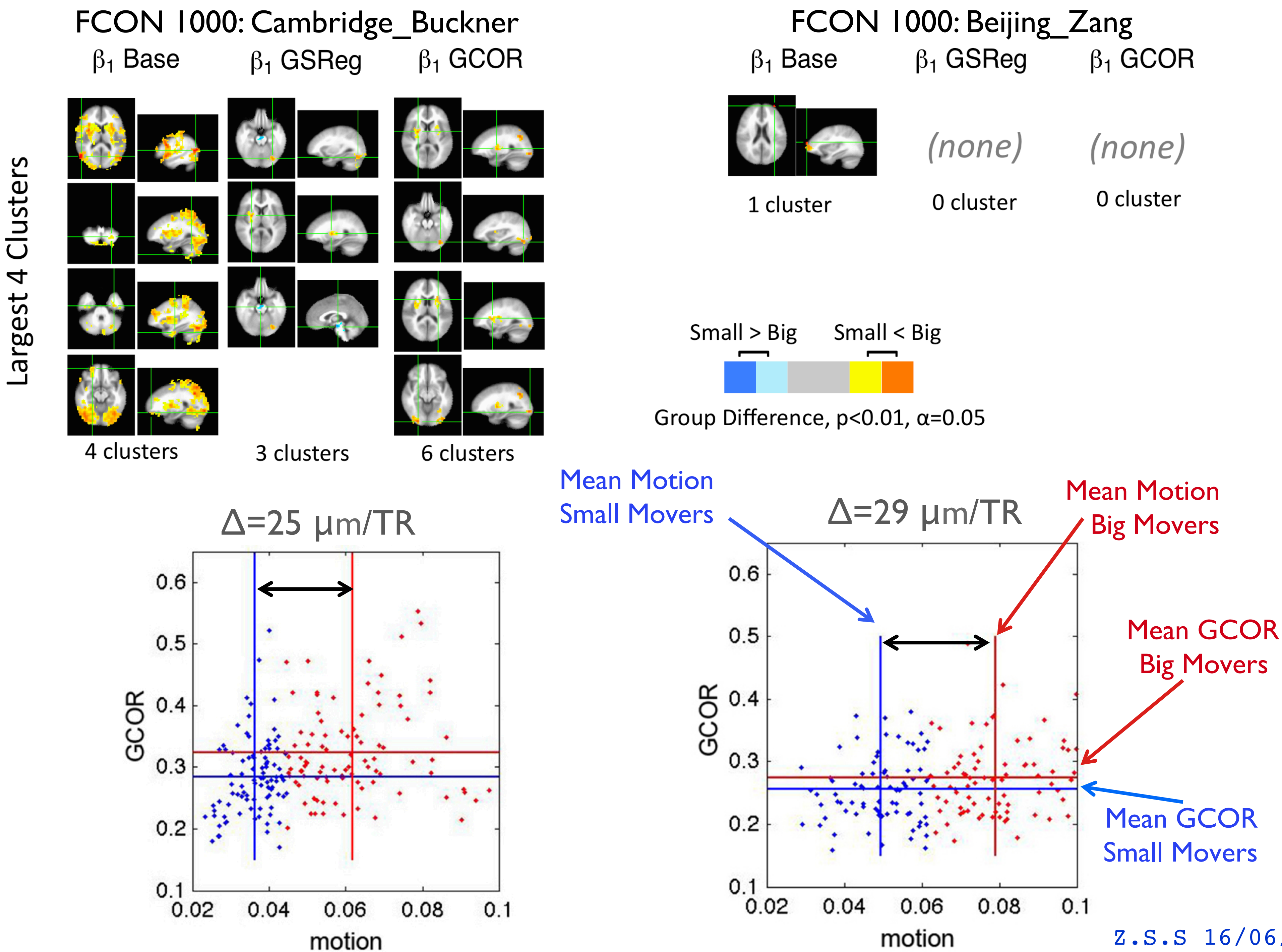
Z.S.S 16/06/13

Group Contrast, Local & Backg. Change



Z.S.S 16/06/13

GCOR and *Motion* Grouping



Z.S.S 16/06/13

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?

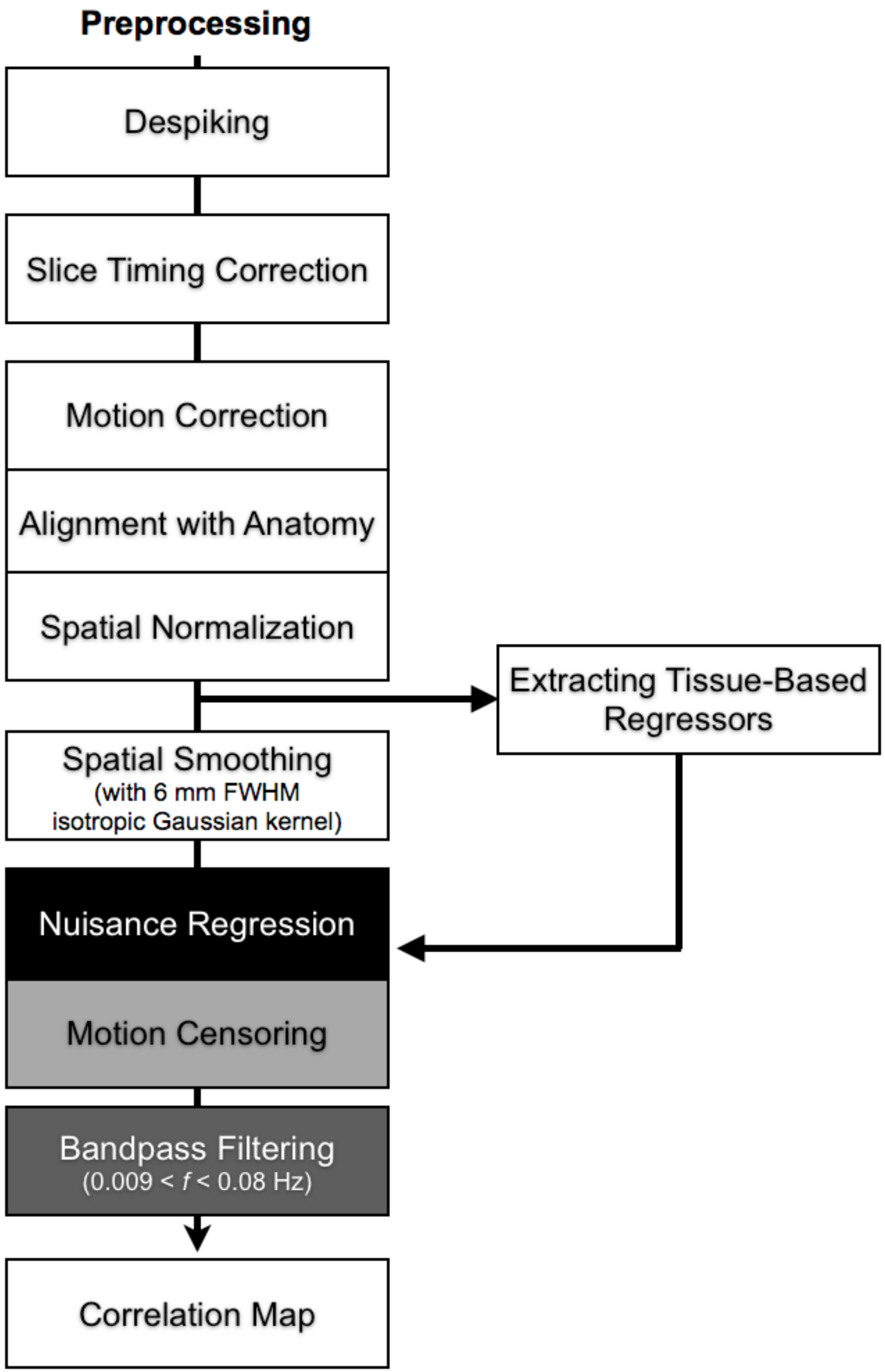
→ contrast sign might even get reversed

Conclusions for Global Corrections

- Stay away from regions with Fluctuations of Interest
- GSReg and its variants are problematic 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 safer 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



RS FMRI processing pipeline

Jo et al. 2013

Single-Subject RS-FMRI Processing

Generate Analysis Pipeline with *afni_proc.py*

```
afni_proc.py -subj_id subj123                          \
  -dsets epi_run1+orig.HEAD                            \
  -copy_anat anat+orig                                 \
  -blocks despike ricor tshift align                   \
          volreg blur regress                          \
  -regress_anaticor                                    \
  -regress_censor_motion 0.2                           \
  -regress_bandpass 0.01 0.1                           \
  -ricor_regs RICOR/r*.slibase.1D
```

See afni_proc.py –h_view for more detailed examples,

Single-Subject RS-FMRI Processing

Generate Analysis Pipeline with *afni_proc.py*

```
afni_proc.py -subj_id subj123 ← Subject ID            \
   -dsets epi_run1+orig.HEAD          ← EPI timeseries \
   -copy_anat anat+orig ← Anatomical                  \
   -blocks despike ricor tshift align                 \
           volreg blur regress                        \
   -regress_anaticor                                  \
   -regress_censor_motion 0.2                         \
   -regress_bandpass 0.01 0.1                         \
   -ricor_regs RICOR/r*.slibase.1D
```

See afni_proc.py –h_view for more detailed examples,

Single-Subject RS-FMRI Processing

Generate Analysis Pipeline with *afni_proc.py*

```
afni_proc.py -subj_id subj123                               \
  -dsets epi_run1+orig.HEAD                                 \
  -copy_anat anat+orig                                      \
  -blocks despike ricor tshift align                        \
          volreg blur regress                               \
  -regress_anaticor                                         \
  -regress_censor_motion 0.2                                \
  -regress_bandpass 0.01 0.1                                \
  -ricor_regs RICOR/r*.slibase.1D
```

← Processing blocks

Use defaults or specify sequence

See afni_proc.py –h_view for more detailed examples,

Single-Subject RS-FMRI Processing

Generate Analysis Pipeline with *afni_proc.py*

```
afni_proc.py -subj_id subj123                                  \
   -dsets epi_run1+orig.HEAD                                   \
   -copy_anat anat+orig                                        \
   -blocks despike ricor tshift align                          \
           volreg blur regress                                 \
   -regress_anaticor                                           \
   -regress_censor_motion 0.2                                  \
   -regress_bandpass 0.01 0.1                                  \
   -ricor_regs RICOR/r*.slibase.1D
```

← Use Local Eroded White Matter for denoising. (Jo el al. 2010)

See afni_proc.py –h_view for more detailed examples,

Single-Subject RS-FMRI Processing

Generate Analysis Pipeline with *afni_proc.py*

```
afni_proc.py -subj_id subj123                                   \
  -dsets epi_run1+orig.HEAD                                     \
  -copy_anat anat+orig                                          \
  -blocks despike ricor tshift align                            \
          volreg blur regress                                   \
  -regress_anaticor                                             \
  -regress_censor_motion 0.2        ← Motion censoring          \
  -regress_bandpass 0.01 0.1          and bandpass filter       \
  -ricor_regs RICOR/r*.slibase.1D
```

See afni_proc.py –h_view for more detailed examples,

Single-Subject RS-FMRI Processing

Generate Analysis Pipeline with *afni_proc.py*

```
afni_proc.py -subj_id subj123                              \
   -dsets epi_run1+orig.HEAD                               \
   -copy_anat anat+orig                                    \
   -blocks despike ricor tshift align                      \
           volreg blur regress                             \
   -regress_anaticor                                       \
   -regress_censor_motion 0.2                              \
   -regress_bandpass 0.01 0.1                              \
   -ricor_regs RICOR/r*.slibase.1D
```

← RICOR+RVT for respiration & cardiac denoising (Glover 2002, Birn 2006)

See afni_proc.py –h_view for more detailed examples,

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, one subject at a time!

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

NIMH
National Institute
of Mental Health

National Institute of
Neurological
Disorders and Stroke