HUMAN Connectome PROJECT

Washington University in St. Louis
SCHOOL OF MEDICINE

Resting State Analysis II

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Overview: Head motion

- Metrics of motion artifact (Power et al., 2014)
  - Timeseries plots
  - Distance-dependent artifact
  - Motion-group differences
- Denoising strategies: Pros and Cons
  - Censoring (aka scrubbing)
  - Global Signal Regression
  - Low-pass temporal filter

Overview: Physiological noise regression

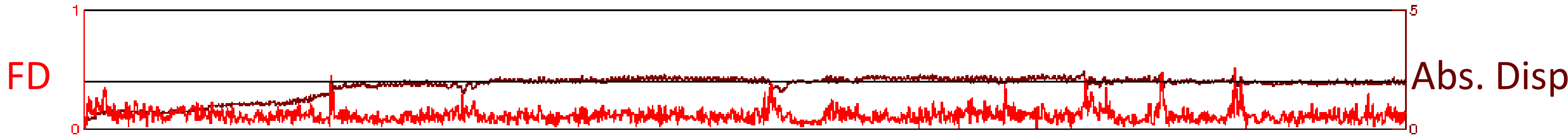
- Physiological Denoising
  - RETROICOR
  - RVHRCOR
  - PNM
- Addressing physiological noise with FIX

Overview: Individual RSNs

- Identifying individual subject RSNs using supervised classifier

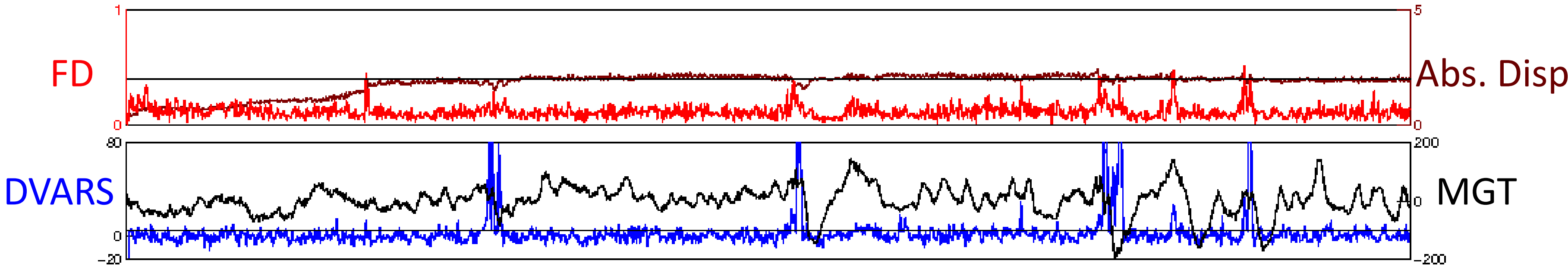
Let’s get moving!

Quantifying Head Motion



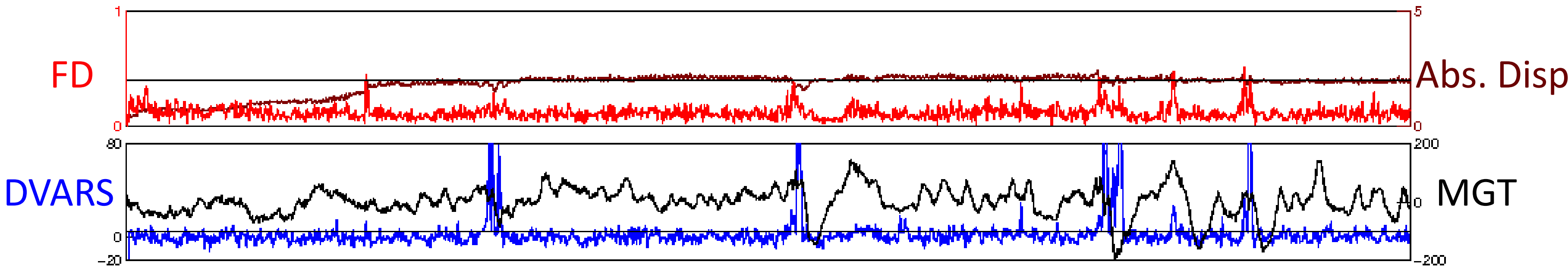
- Absolute displacement (dark red)
  - Motion relative to *beginning of scan*
- Frame Displacement (FD; bright red)
  - Motion relative to *previous time point*

QC Measures related to motion



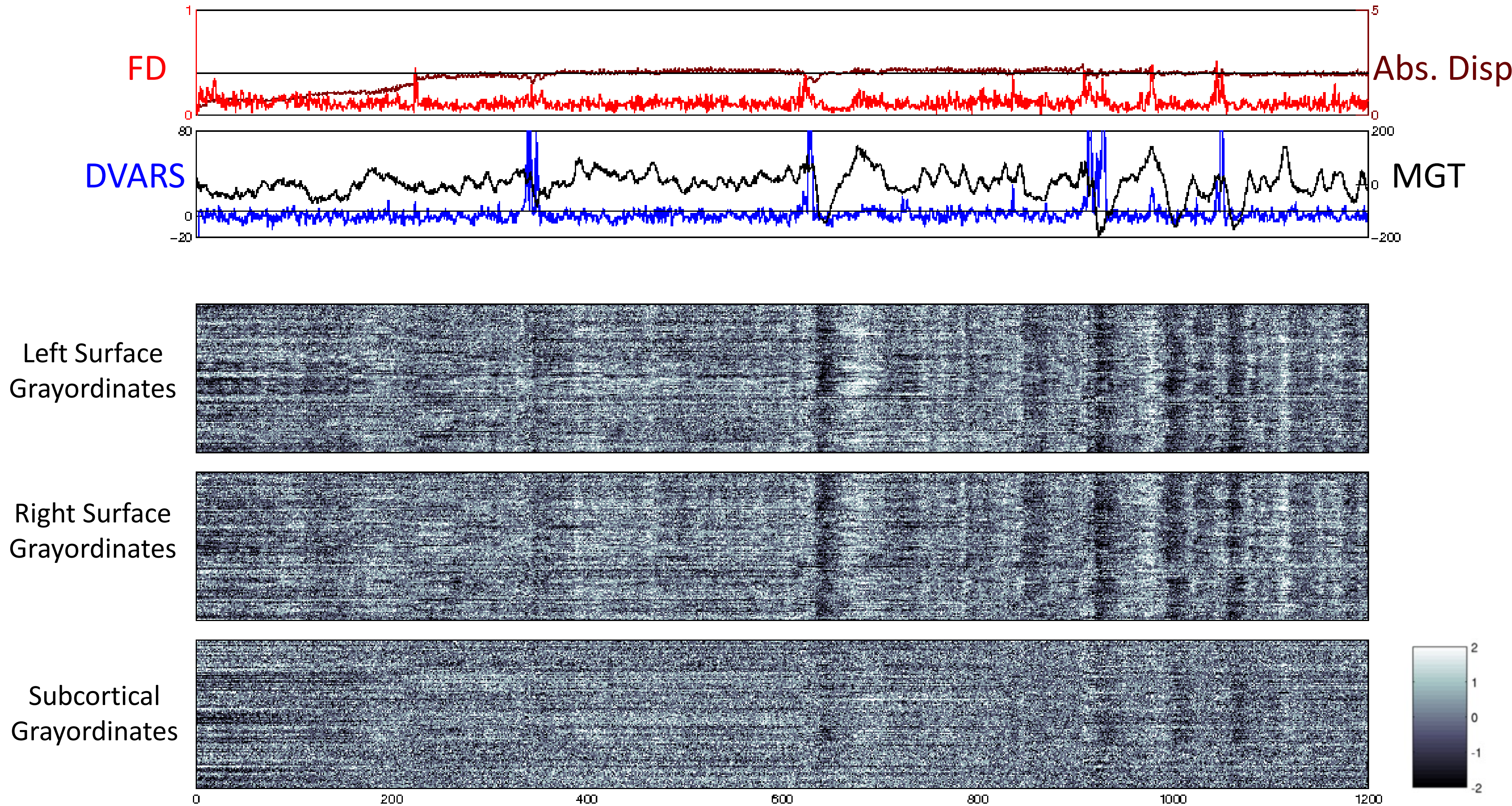
- DVARS (blue)
  - *Var*iance of Backward *D*erivative
  - Change in image relative to *previous time point*
  - DVARS correlated with FD
    - Power et al. 2014: r = 0.69
    - HCP MPP timeseries: r = 0.34

Mean Grayordinate Timeseries



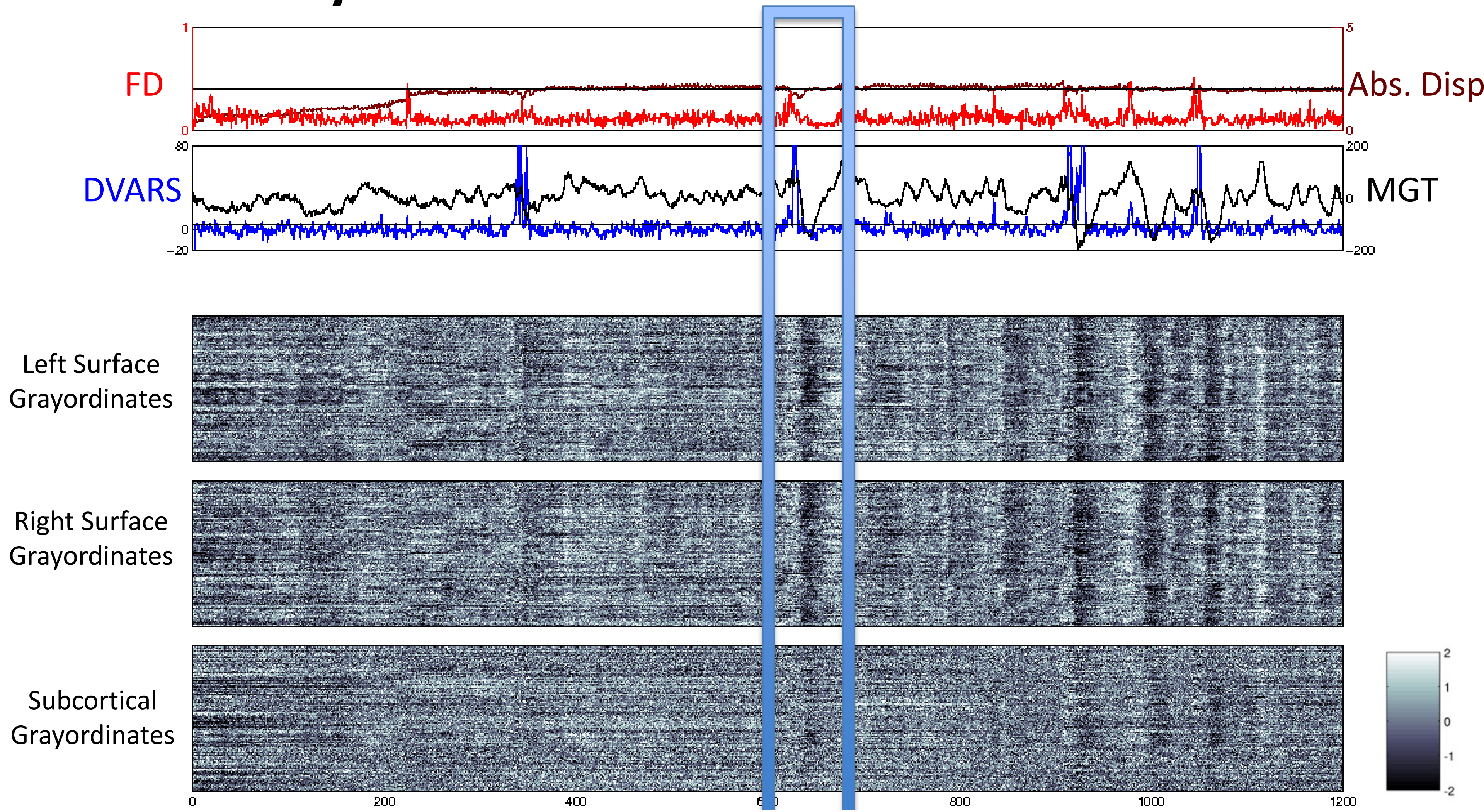
- MGT (black)
  - *M*ean *G*rayordinate *T*imeseries
  - Mean across grayordinates at each time point
- In CIFTI grayordinate data, MGT can be proxy for global signal
  - Power et al., 2014: correlation between whole-brain signal and gray matter mask is r=.99
  - In HCP data: correlation between MGT in CIFTI and whole-brain in NIFTI was r=.93

Grayordinate Timeseries Plots



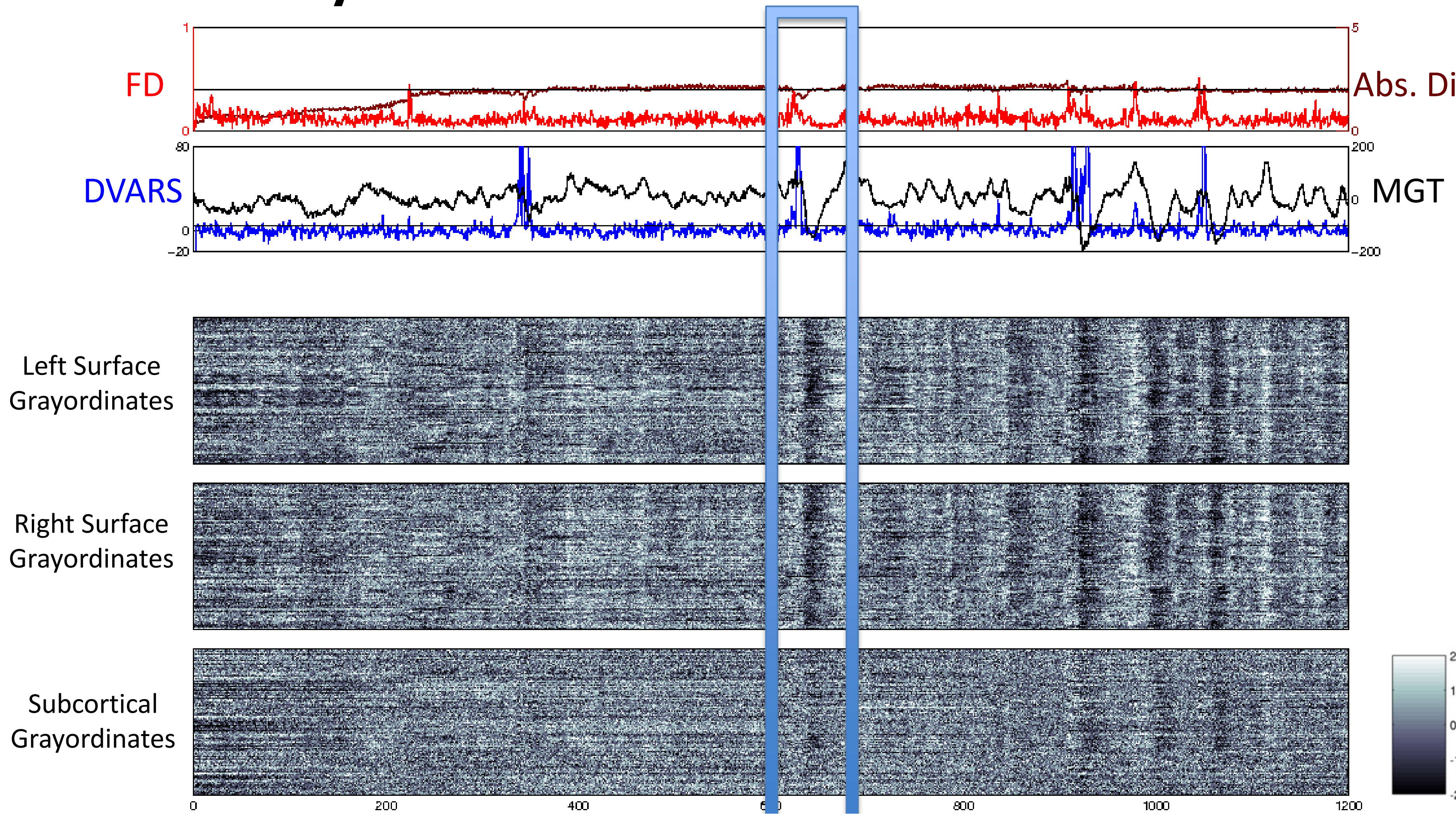
- "Grayplots"
  - Standardize rfMRI timeseries at each grayordinate
  - Grayscale range from -2 to +2

Grayordinate Timeseries Plots



- Two aspects obvious
  - Spatially-localized bands
  - Globally-distributed bands

Grayordinate Timeseries Plots

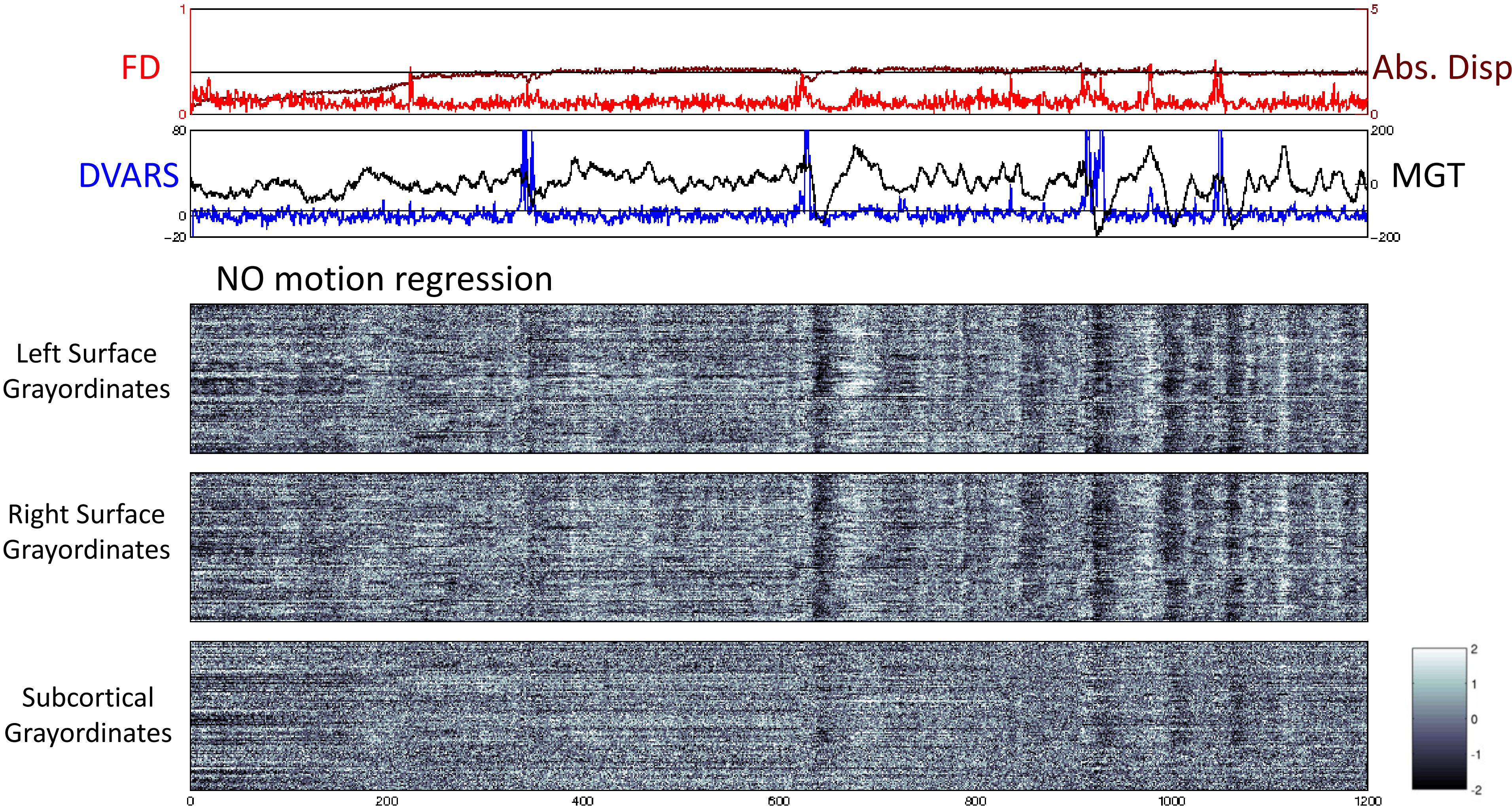


- Some bands relate to head motion (likely noise)
- Some bands lack clear relationship to head motion (noise or signal)

Let's keep moving!

- Denoising by regressing motion parameters
  - In HCP rfMRI data, 17.8% of variance explained by regressing 24 motion parameters
    - 6 rigid-body parameters
    - 6 backward derivatives
    - squares of those 12

Grayordinate timeseries plots

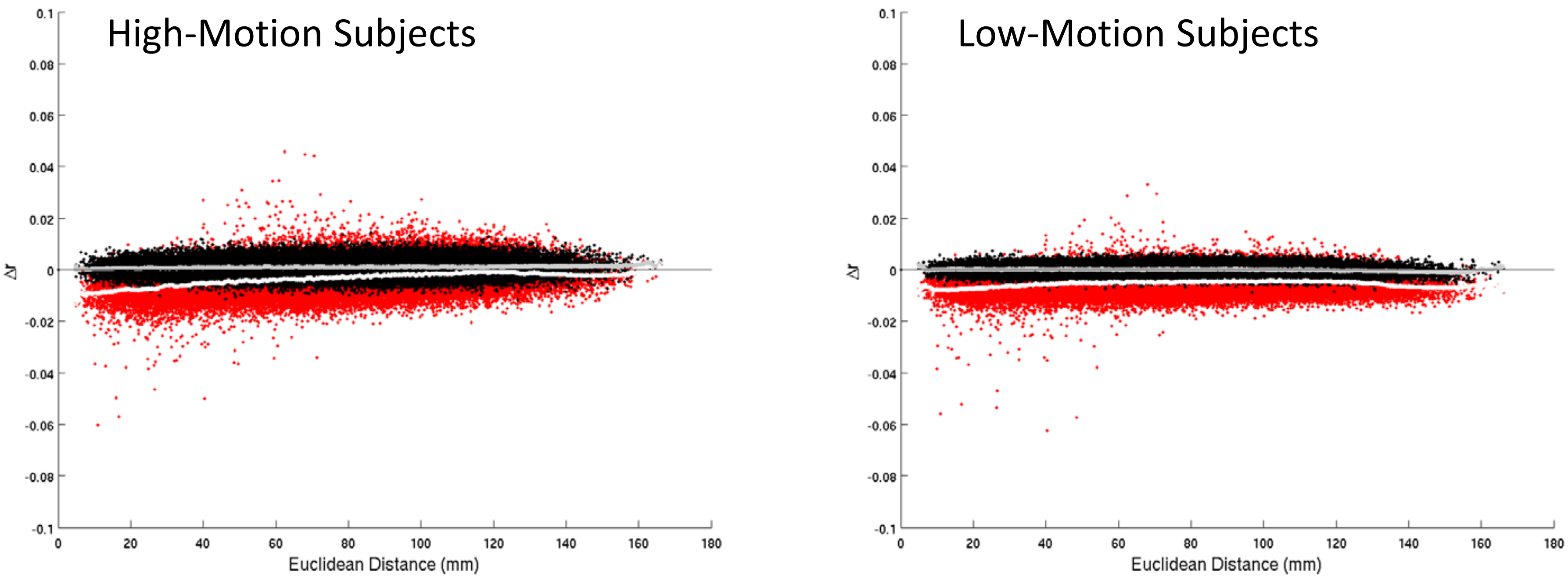


- 24 motion regressors
  - Remove lots of spatially-localized bands
  - Leaves global bands

Censoring

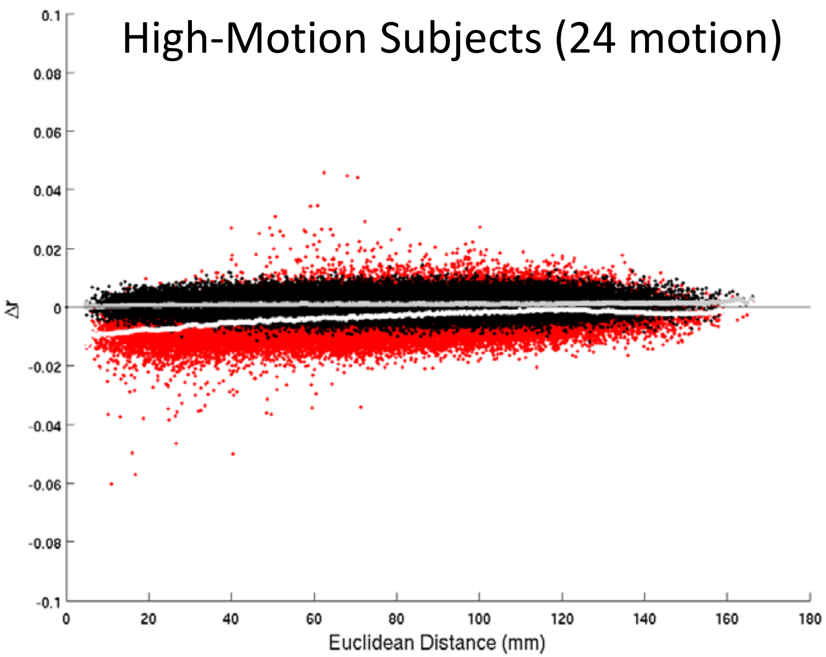
- What if we treat high-motion time points as "outliers"?
  - Simply drop them from analyses!
  - Look at difference between correlations with and without high-motion time points
- Thresholds for censoring in current analysis
  - FD > 0.4mm
  - DVARS > 4.8 (after median-centering)

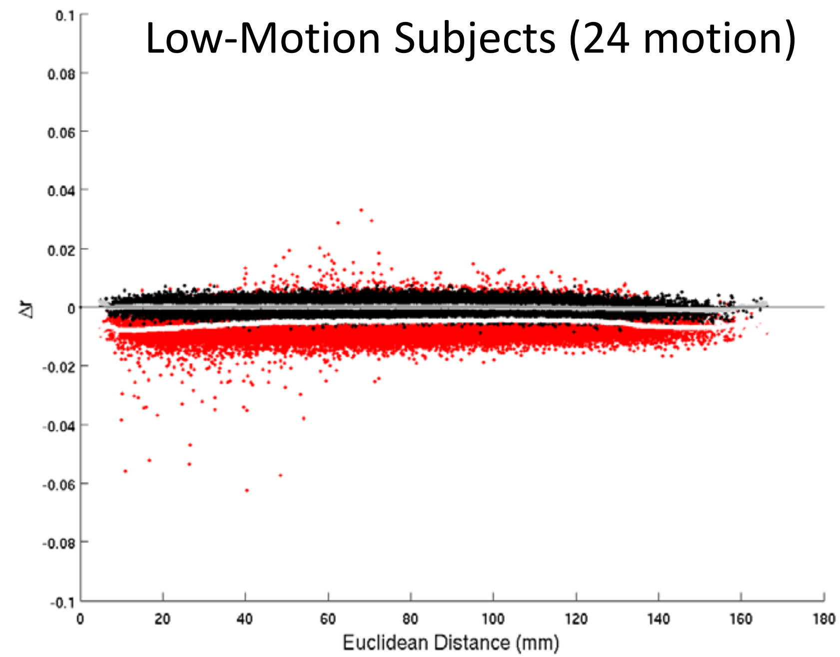
Distance-dependent artifact



- Delta-R plots: change due to censoring as function of distance between nodes
  - Y-axis shows Delta-R (change in correlation between censored and uncensored data)
  - X-axis is distance between nodes being correlated
  - Red cloud after censoring high-motion time points
  - Black cloud after censoring same number of random time points

Distance-dependent artifact





- Censoring high-motion time points reveals two types of motion artifact…
  - "Global shift": reduces correlations at all distances
  - Distance-dependent artifact: reduces correlations more for short-distance connections

Motion-group differences

- “Global shift” and distance-dependent artifact left behind after 24-motion regressors
- Does censoring + 24-motion regressors eliminate motion artifact?
- If so, perhaps we might not expect correlations for low-motion and high-motion subjects to differ
  - N.B. high- and low-motion groups may have real connectivity differences in addition to artifactual differences due to motion (e.g., Zeng et al, 2014)

Motion-group differences

- Procedure:
  – Divided participants into high-, medium- and low-motion groups
    - Gender-match (61 participants in each group)
  – Create parcellated connectomes
    - 333 cortical parcels (Gordon et al. 2014)
    - 19 subcortical Freesurfer anatomical parcels
  – Compute motion-group differences (t-tests)
    - Number of significant edges out of 61776 total edges
    - Set alpha to 300xBonferroni (~15 edges)

Motion-group differences

HIGH PASS		Pre-Censored			Post-Censored	
Condition	Low vs. High	Med vs. High	Low vs. Med	Low vs. High	Med vs. High	Low vs. Med
24-Motion	10525***	88*	14	7578***	49*	16*

- Very large number of differences between low- and high-motion groups
- Censoring leaves substantial motion-group differences

Censoring : PROS

- Power and colleagues (2012, 2014) showed stronger benefits from censoring
  - May remove distance-dependent motion artifact
  - May reduce motion-group differences

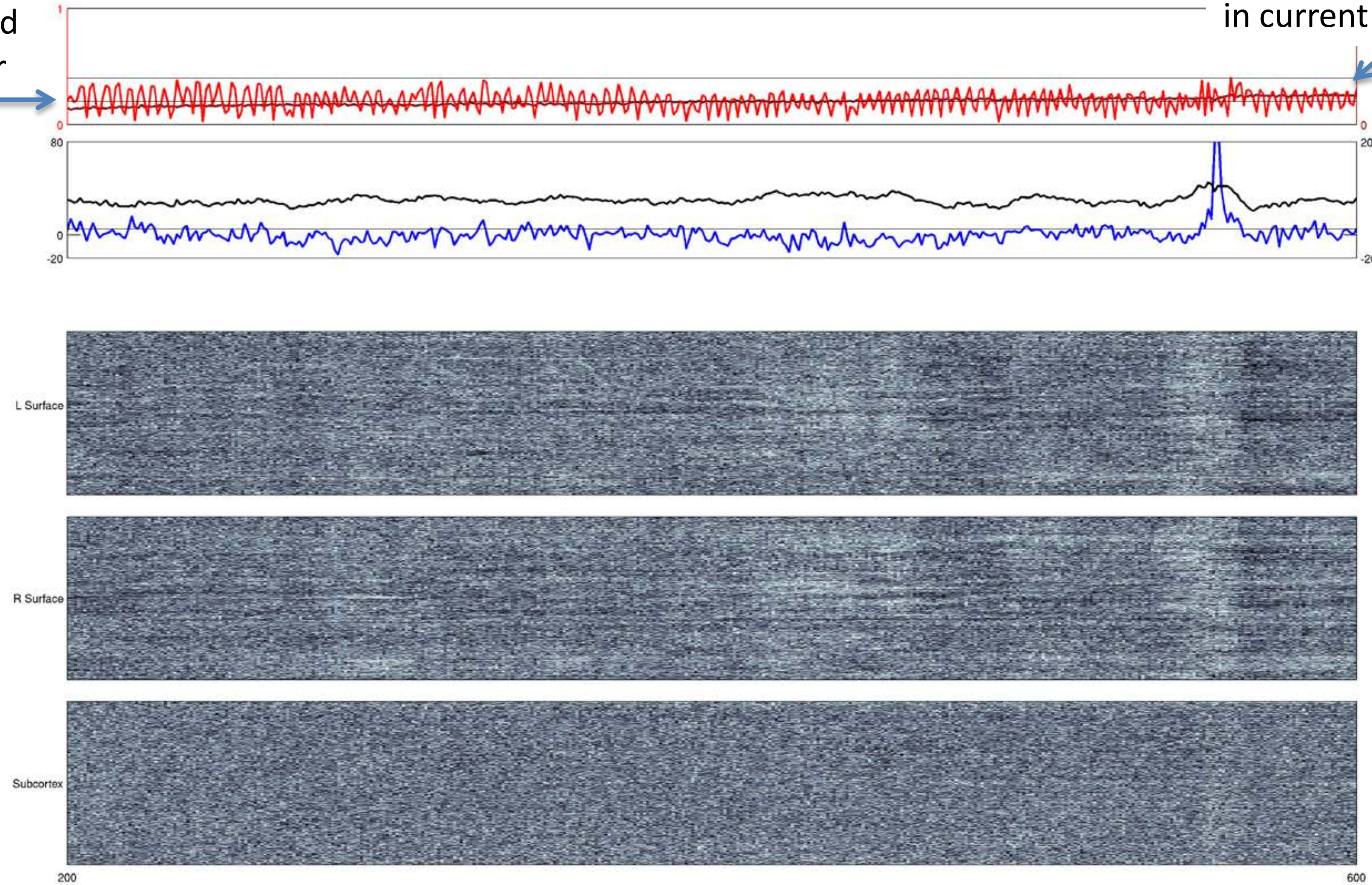
Issues with FD estimates

- However… at this point, censoring HCP data doesn't strongly reduce group differences
  - FD estimates have cyclic fluctuations
  - Censoring difficult because magnitude of cyclic fluctuations in FD varies across individuals

Issues with FD estimates

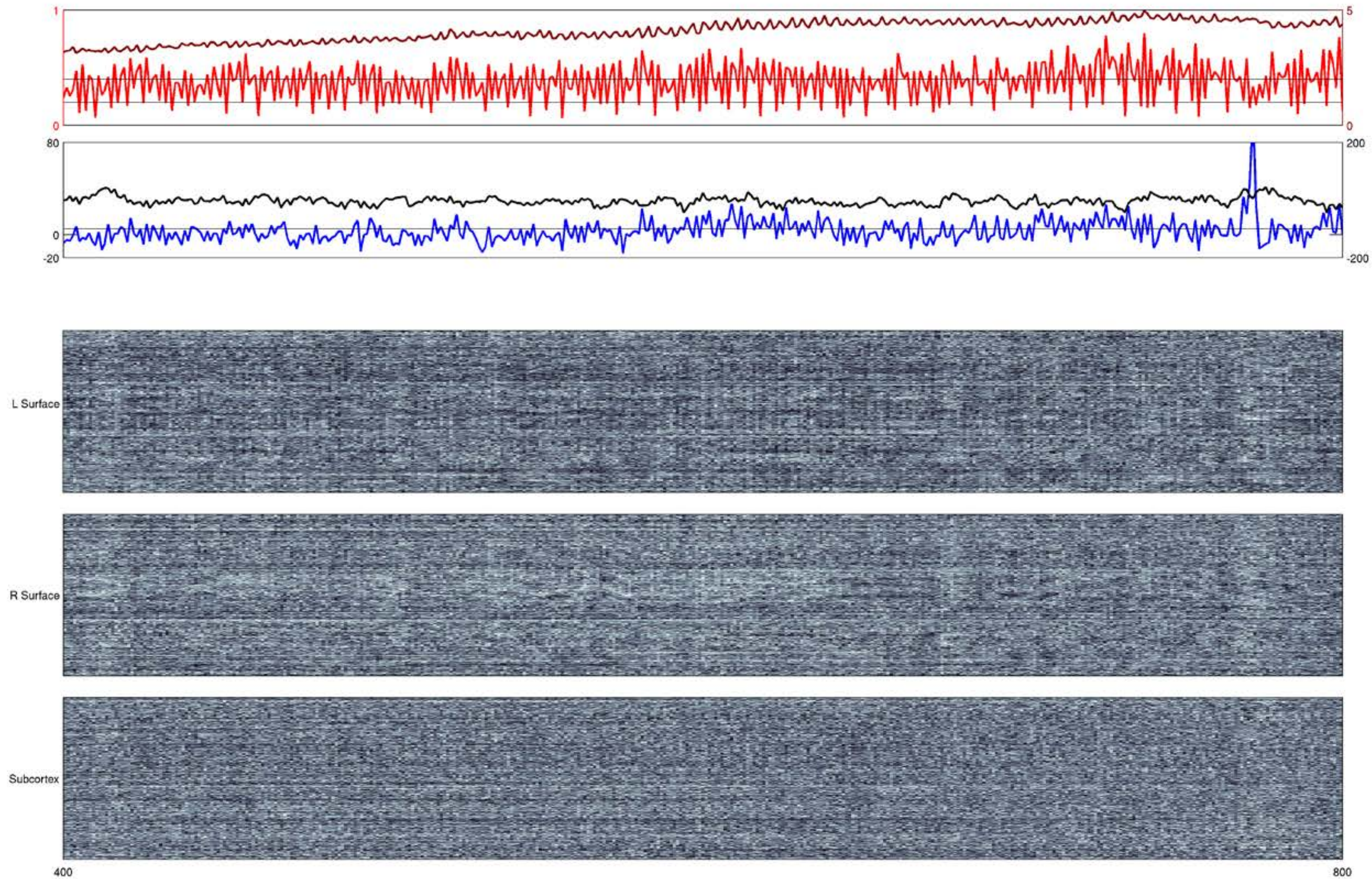
FD > 0.2mm suggested by Power

FD > 0.4mm used in current analyses



- Cyclic fluctuations *in* head motion / FD estimates
  - FD fluctuations often at same frequency as respiratory measures
  - Sometimes FD fluctuations not clearly mirrored in grayordinate BOLD signal

Issues with FD estimates



- Participant at 66th percentile of mean FD
- Spikes in DVARS are often easier to identify

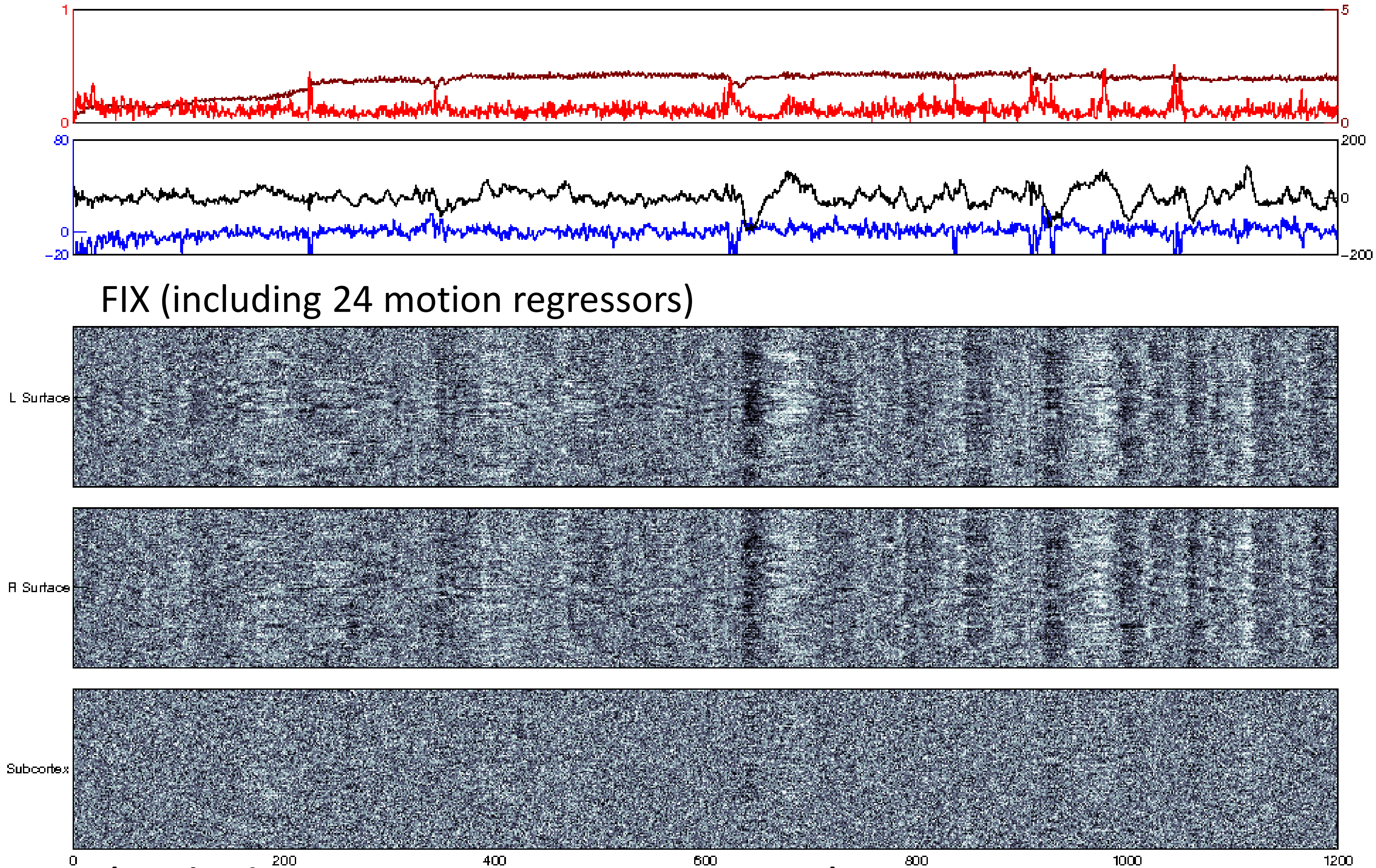
Censoring : CONS

- Censoring increases variance of estimates
  - May only be problematic with less than 5 minutes of data after censoring (Yan et al. 2013)
- Frequency-based measures (e.g., ALFF and fALFF) don't work with censored data

ICA-FIX Denoising

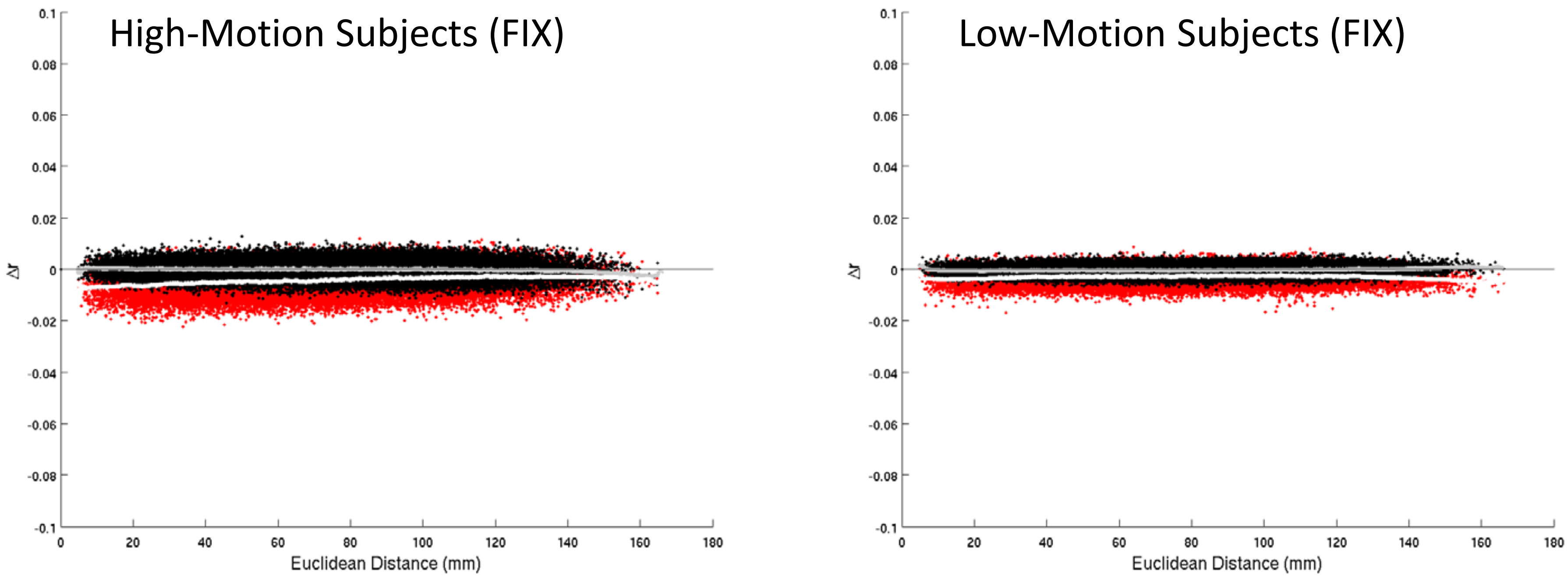
- Motion artifact remains after 24 motion
- Censoring left artifact behind
- Can FIX address the artifact that is left behind?
- FIX pipeline removes
  - 24 motion regressors
  - Unique variance in noise components
    - Variance unrelated to signal components

Grayordinate timeseries plots: FIX



- FIX (including 24 motion regressors)
  - Removes or reduces more spatially-specific bands
  - which reduces intensity of some global bands

Distance-dependent artifact: FIX



- FIX reduces global shift (in low-motion group)
- FIX reduces distance-dependent effect

Motion-group differences

HIGH PASS		Pre-Censored				Post-Censored	
Condition	Low vs. High	Med vs. High	Low vs. Med		Low vs. High	Med vs. High	Low vs. Med
24-Motion	10525***	88*	14		7578***	49*	16*
FIX-Denoised	8790***	120*	23		7459***	74*	50*

- Small reductions in motion-group differences using FIX

ICA-FIX denoising: PROS

- Reduces motion artifact and other noise
- Automated classification of signal vs. noise ICs
- High accuracy of classification in HCP data

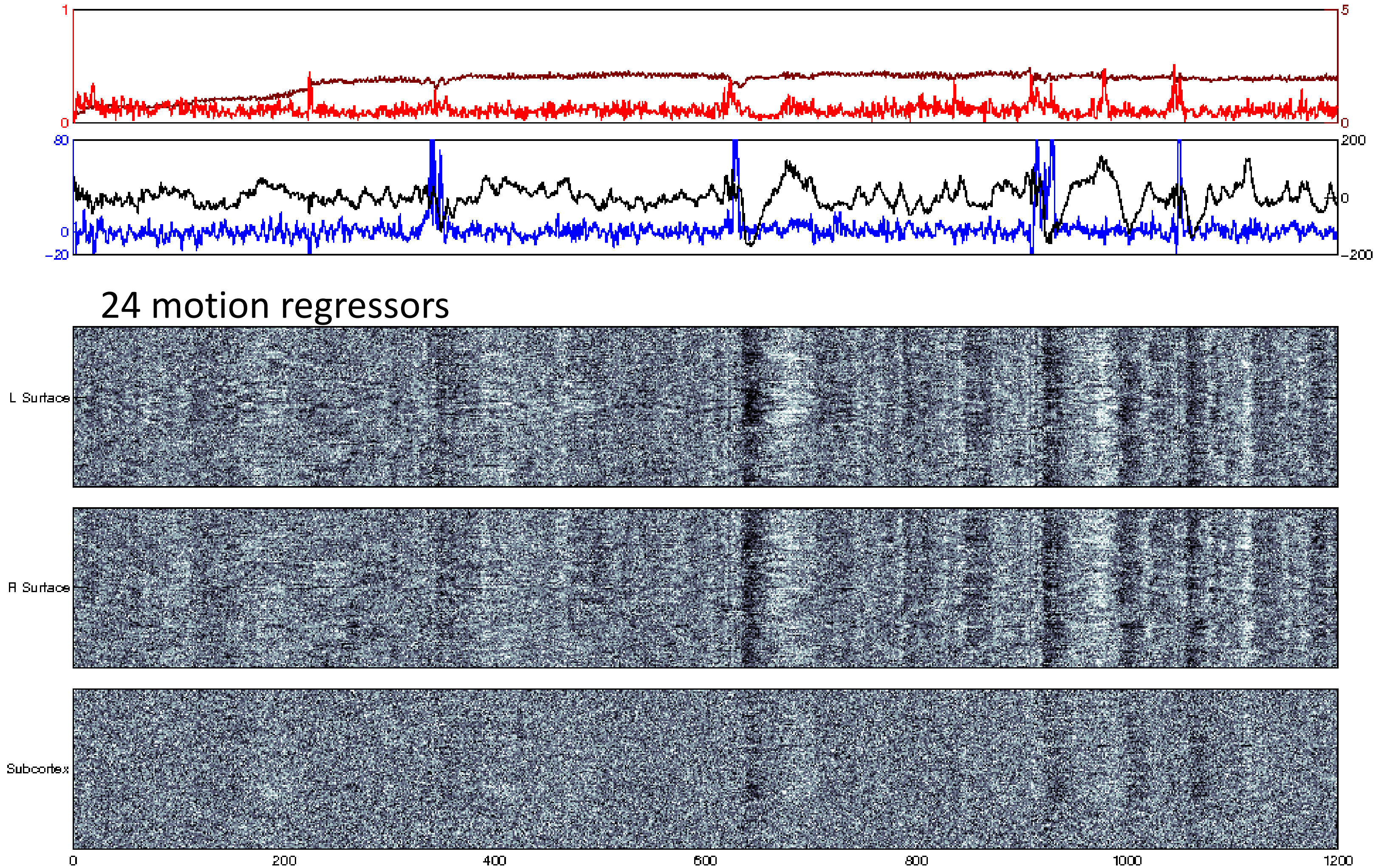
ICA-FIX denoising: CONS

- Signal and noise sources may not be well separated with lower number of time points
  - Not an apparent issue with HCP rfMRI data (1200 time points) but could be an issue with other data
- ICA not well-suited to identifying global signal
  - Assumption of ICA: components are spatially independent
  - Global = not spatially independent

Global signal regression

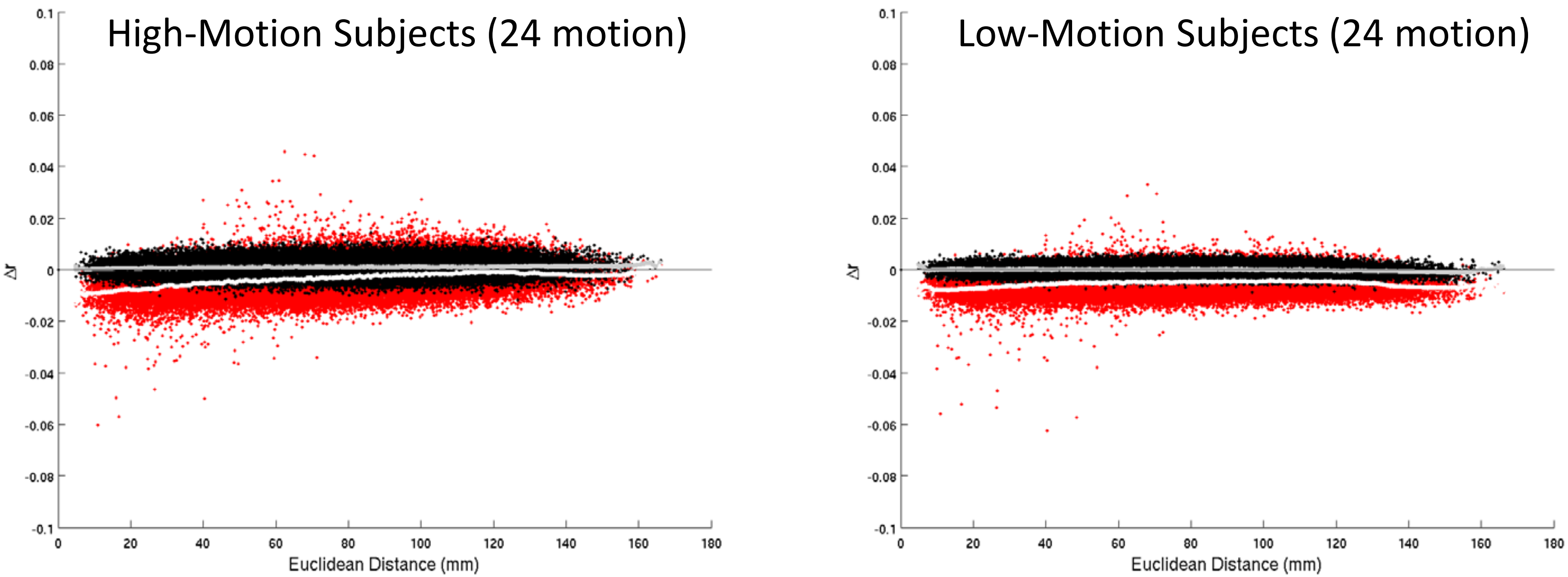
- What about a method that directly addresses global bands?
- Global signal regression may remove widely-distributed sources of noise
  - Respiration and cardiac activity (Birn et al, 2006)
  - Motion-related artifact (Power et al, 2014)

Grayordinate timeseries plots



- MGTR + 24 motion regressors
  - Eliminates global bands nearly entirely
  - Leaves spatially-specific bands behind

Distance-dependent artifact



- MGTR reduces global shift
- MGTR doesn’t reduce distance-dependent □R

Motion-group differences

HIGH PASS		Pre-Censored			Post-Censored	
Condition	Low vs. High	Med vs. High	Low vs. Med	Low vs. High	Med vs. High	Low vs. Med
24-Motion	10525***	88*	14	7578***	49*	16*
FIX-Denoised	8790***	120*	23	7459***	74*	50*
24-Motion + MGTR	240***	13	6	109***	8	1

- Substantial decrease in motion-group differences using MGTR!

Global Signal Regression: PROS

- Can remove physiological noise
- Reduces several metrics of motion artifact, especially group-differences

Global Signal Regression: CONS

- GS may contain real neural signal
  - Synchronized neural activity across whole brain (dePasquale et al., 2010; Popa et al, 2009; Scholvinck et al., 2010)
- Spatial relationship with global signal is higher in certain brain regions
  - Suggests there may be a real neural signature

Global Signal Regression: CONS

- Rebuttal (Power et al., 2015)
  - Yes, GSR will remove any global neural signal that exists!
  - Motion and physiological noise may be larger proportion of global signal
  - Spatial relationship with global signal stronger in high-motion participants

Global Signal Regression: CONS

- GSR can induce anticorrelation (Murphy et al., 2009; Saad et al., 2012)
- Rebuttal (Power et al., 2015)
  - Yes, GSR can induce anticorrelation!
    - However, induced anticorrelation goes down as number of nodes in network model goes up
  - Motion and physiological noise likely induce worse artifactual changes in connectivity

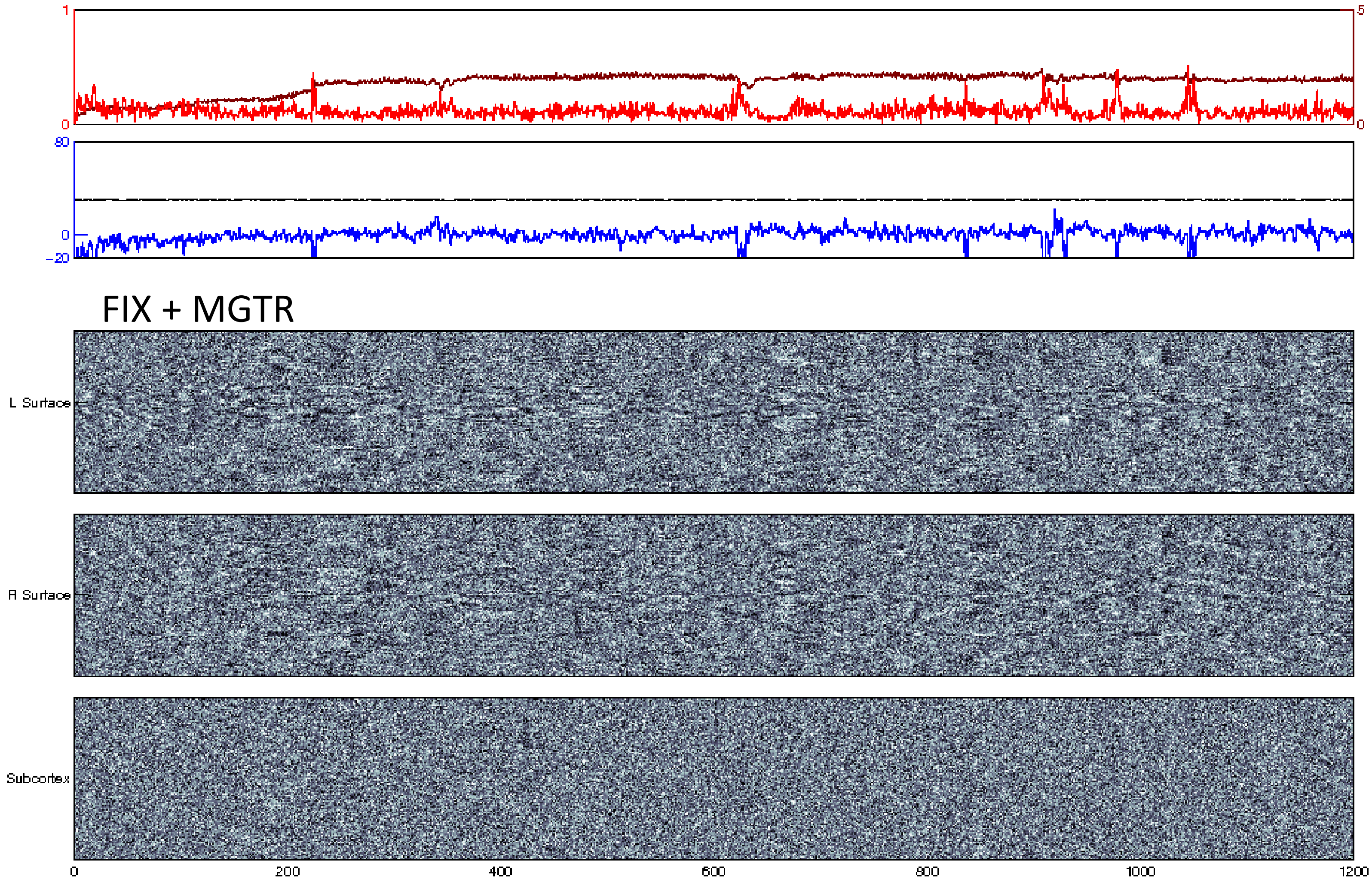
Global Signal Regression: CONS

- Saad et al. 2012; Gotts et al., 2013: If groups differ in GS, GSR increase group-differences in anticorrelation
- Rebuttal (Power et al., 2015)
  - In real data, GSR reduces group differences between high- and low-motion groups, rather than increasing them

FIX + MGTR

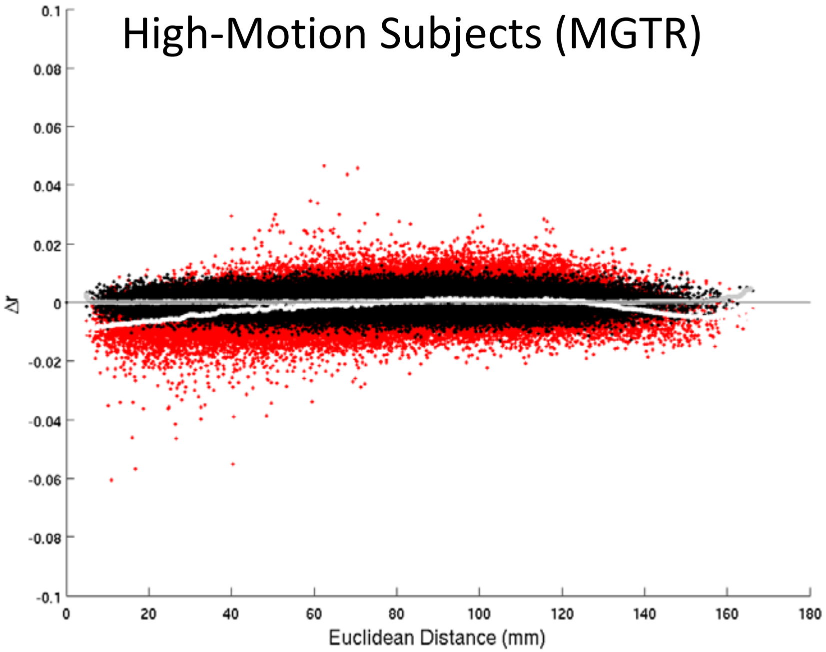
- FIX and MGTR methods may be complementary
  - FIX: Spatially-specific noise components
  - MGTR: Global signal

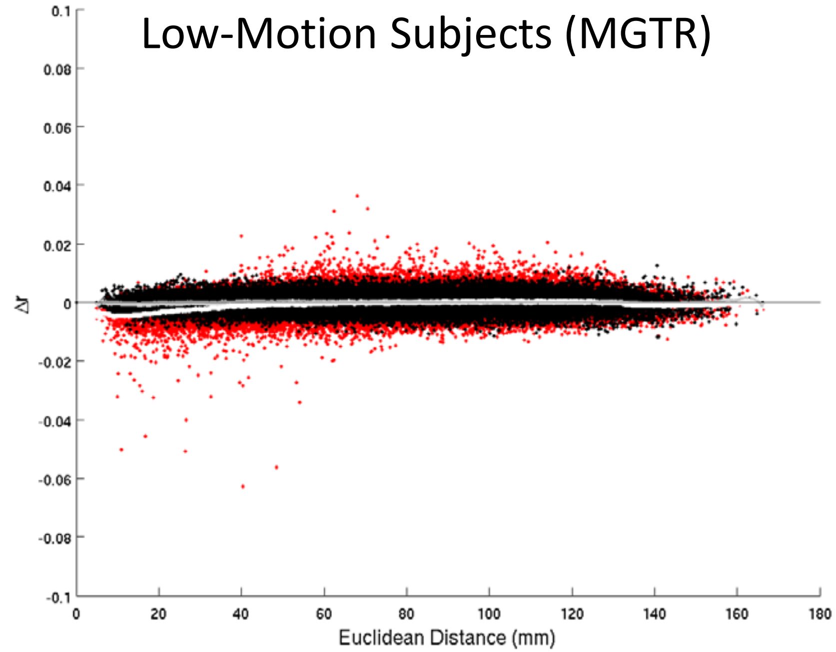
Grayordinate timeseries plots



- FIX + MGTR + 24 motion regressors
  - MGTR eliminates global signal
  - FIX removes additional spatially-specific noise

Distance-dependent artifact





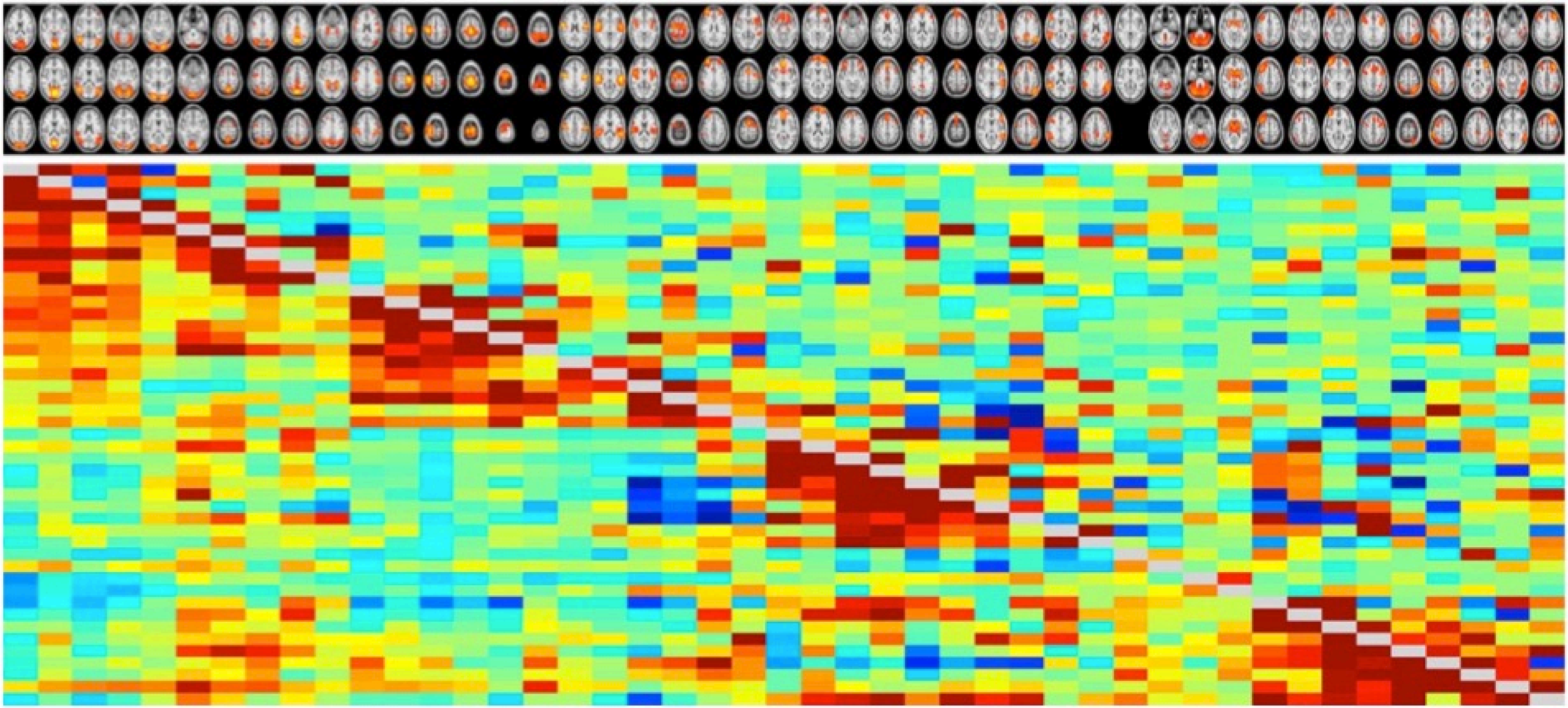
- MGTR eliminates global shift
- FIX reduces distance-dependent artifact

Motion-group differences

HIGH PASS		Pre-Censored			Post-Censored	
Condition	Low vs. High	Med vs. High	Low vs. Med	Low vs. High	Med vs. High	Low vs. Med
24-Motion	10525***	88*	14	7578***	49*	16*
FIX-Denoised	8790***	120*	23	7459***	74*	50*
24-Motion + MGTR	240***	13	6	109***	8	1
FIX+MGTR	235***	32*	16	174***	25	13

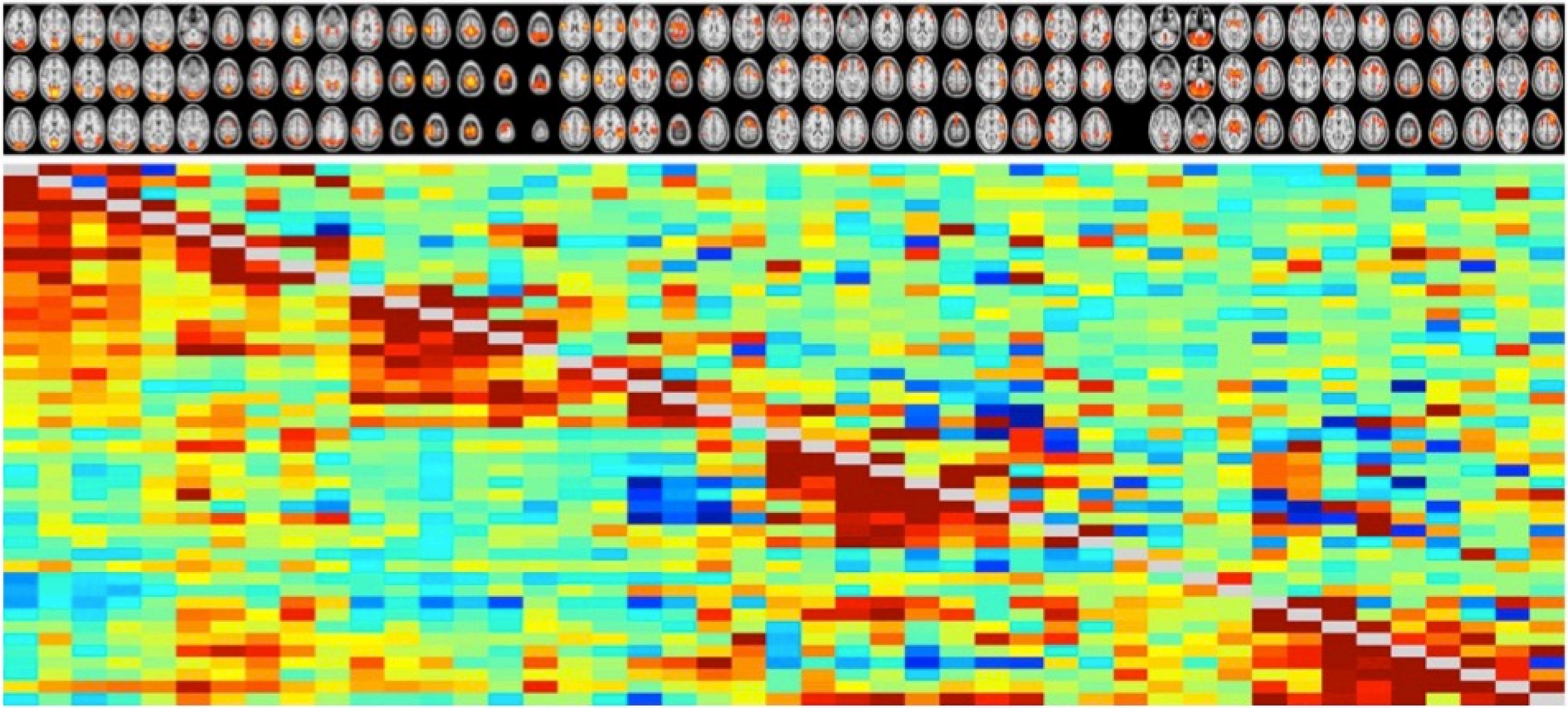
- FIX+MGTR does not reduce motion-group differences compared to MGTR

Partial Correlation Netmats



- Will be discussed in greater detail in next lecture
- Primary goal is to estimate direct connections (i.e., partial out all possible indirect pathways)

Partial Correlation Netmats



- Potential secondary benefit: Partialling all other timeseries should remove any artifact contained in those parcels
  - Should reduce influence of motion-related global signal…
  - However, Yan et al. (2013) found that partial correlation netmats showed motion-group differences unless GSR was conducted first

Partial Correlation Netmats

HIGH PASS		Pre-Censored	
Condition	Low vs. High	Med vs. High	Low vs. Med
24-Motion	39***	30***	18
FIX-Denoised	28**	14	9
24-Motion + MGTR	43***	25**	20
FIX+MGTR	25**	11	12

- Substantial decrease using partial correlations
- FIX reduces motion-group differences
- MGTR does not affect motion-group differences

Low pass temporal filter

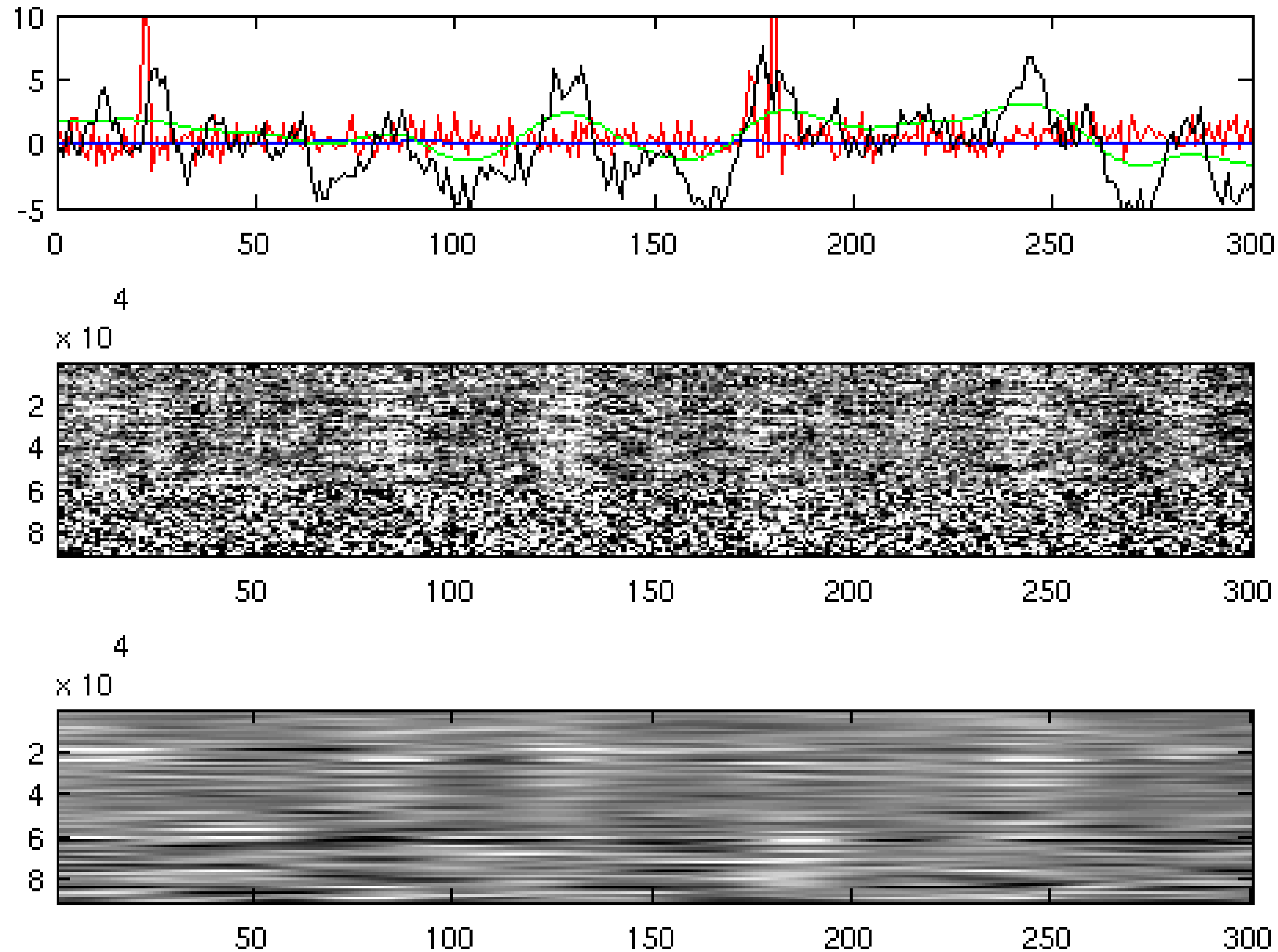
- Let’s slow down a bit…

Time series after low pass filter

Red: unfiltered DV
Blue: filtered DV
Black: unfiltered GS
Green: filtered GS

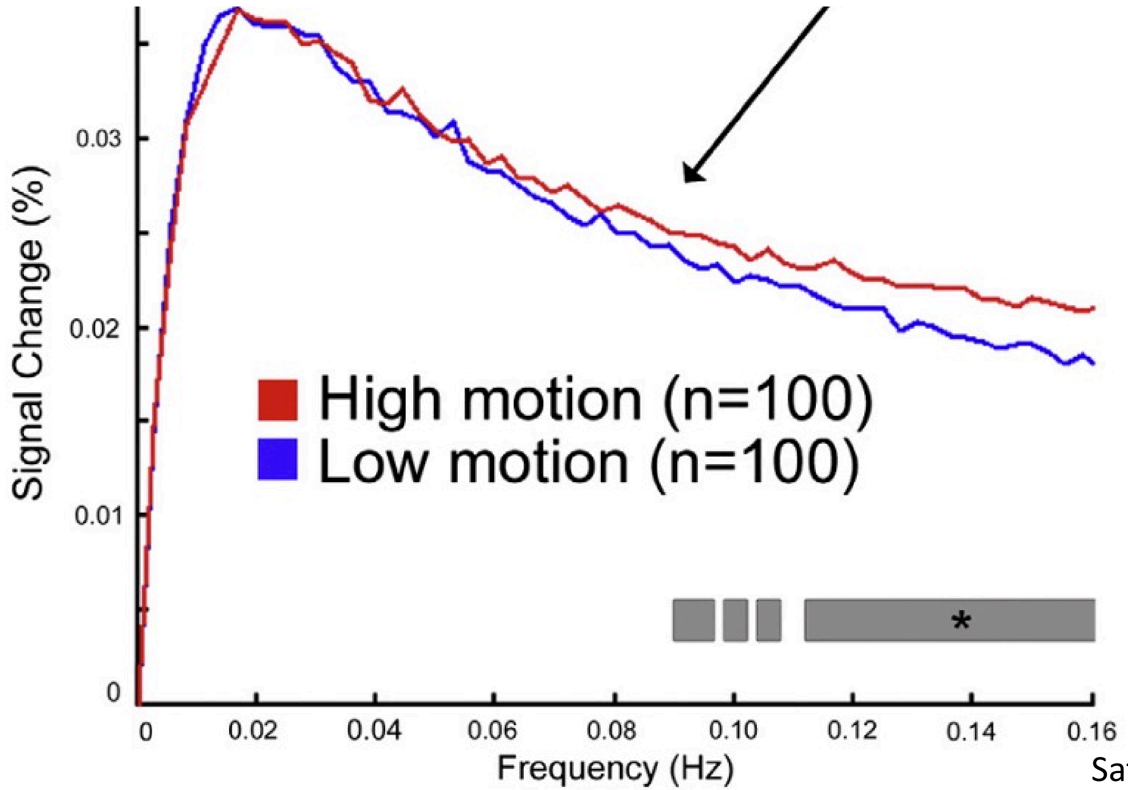
Unfiltered time series

Filtered time series



- Low-pass filtering loses a lot of temporal information
  - What is that information being removed?

Low pass filter: PROS



Satterthwaite et al. (2013)

- Motion-group differences in magnitude spectra constrained to *f* > 0.08Hz
  - after motion regression, GSR, and spike regression (similar to censoring)

Motion-group differences

BAND PASS	Pre-Censored			Post-Censored		
Condition	Low vs. High	Med vs. High	Low vs. Med	Low vs. High	Med vs. High	Low vs. Med
24-Motion	4102***	38*	3	2342***	47*	12
FIX-Denoised	3117***	55*	12	2217***	46	11
24-Motion + MGTR	383***	15	8	122***	17*	2
FIX+MGTR	192***	31	15	180***	22	14

- Without MGTR: Low pass filtering reduces motion-group differences
- With MGTR: Little to no benefit of low pass filtering

Low pass filter: PROS

- Cordes et al. (2001): Physiological artifact also exists disproportionately above f = 0.10Hz
- However, FIX-ICA denoising removes apparent noise at those frequencies

Low pass filter: CONS

- There may be real signal at high-frequencies!
  - Niazy et al. (2011): discussed earlier
  - Boubela et al. (2013)

RSNs at high-frequencies

Boubela et al. 2013

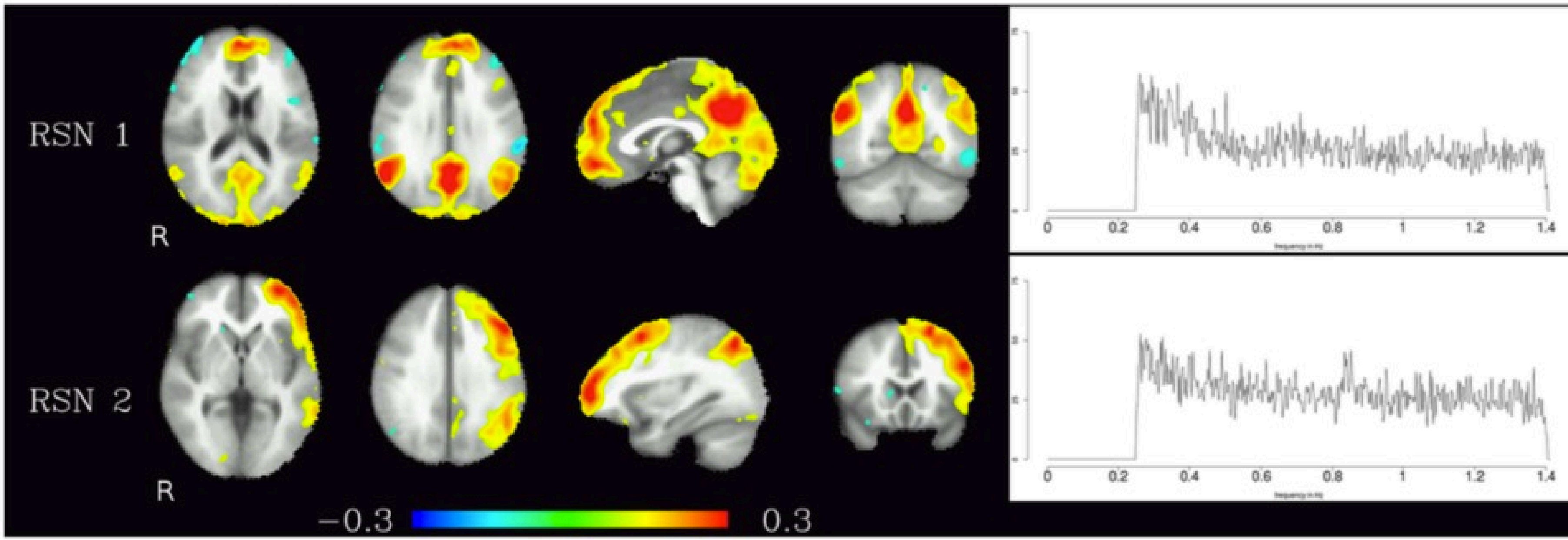


FIGURE 2 | Temporal ICA components representing high-frequency fluctuations in brain regions commonly associated with resting-state networks. Figure layout as in **Figure 1**.

- High-pass filter limited data to *f* > 0.25Hz
- Identified two ICs that overlapped with typical RSNs

RSNs at high-frequencies

Boubela et al. 2013

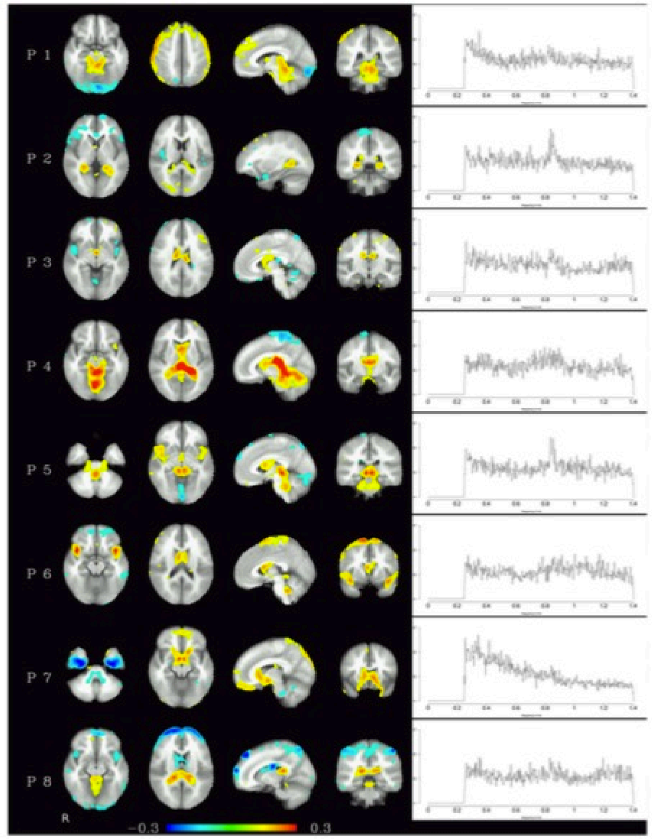


FIGURE 1 | Temporal ICA components attributed to pulsation in ventricles and large blood vessels. Left: maps thresholded at 0.1 (weights in the mixing matrix). Right: frequency spectra corresponding to the ICA components represented on the left.

- Also found quite a bit of noise components too!

Throwing the baby out with the bathwater

- Much of the controversy is essentially about
  - Throwing the baby (real signal of neural origin) out
  - with the bathwater (artifact)
  - Throwing babies out is a bad thing!

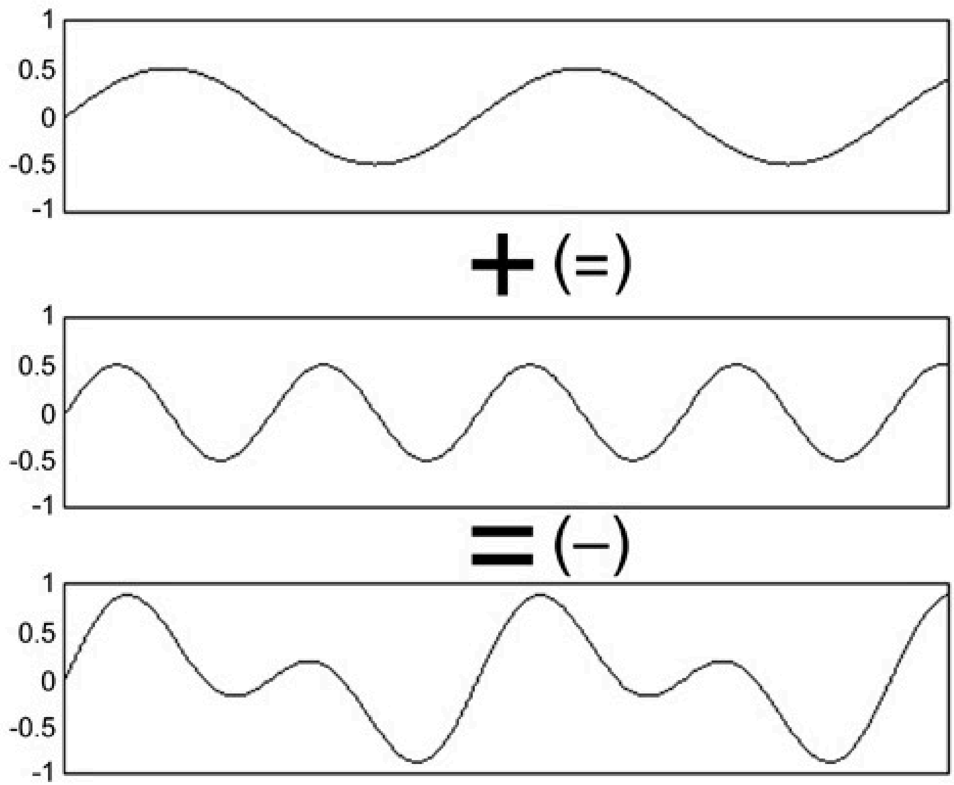
Throwing the baby out with the bathwater

- What if the baby turns out not to be *your* baby?
  - Higher-frequencies may show motion-group differences (Satterthwaite et al. 2013)
  - Increased motion may increase correlation with GS in some regions more than others (Power et al., 2015)

Physiological noise

- Let’s take a deep breath and move on…

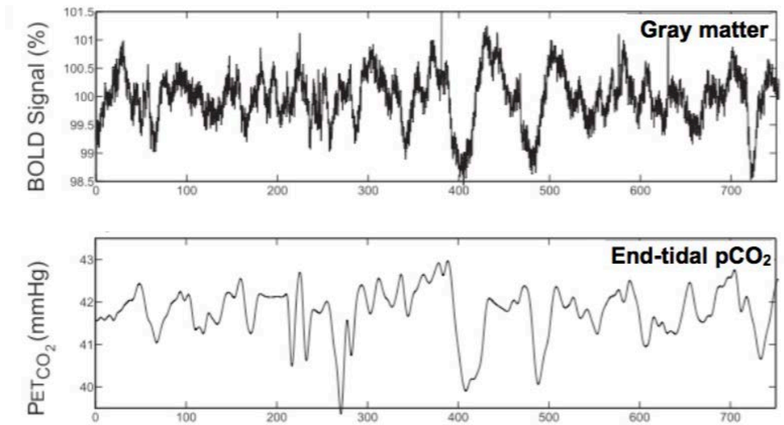
Physiological denoising: RETROICOR



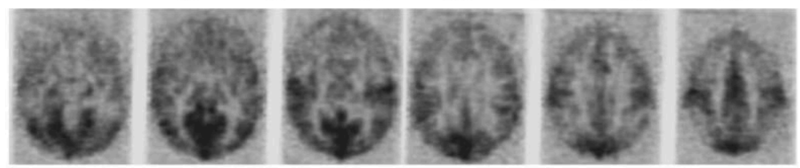
- Artifact due to cardiac-related pulsations and respiratory motion
- Physiological responses modeled as low-order Fourier series
  - sin and cos waves
  - Reflect frequency and phase of cardiac and respiratory recordings at time of image acquisition

Additional effects of physiological noise

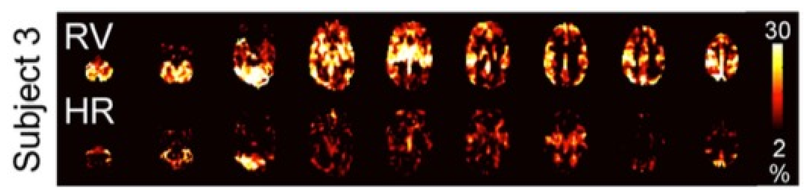
Wise et al, 2004



Birn et al, 2006

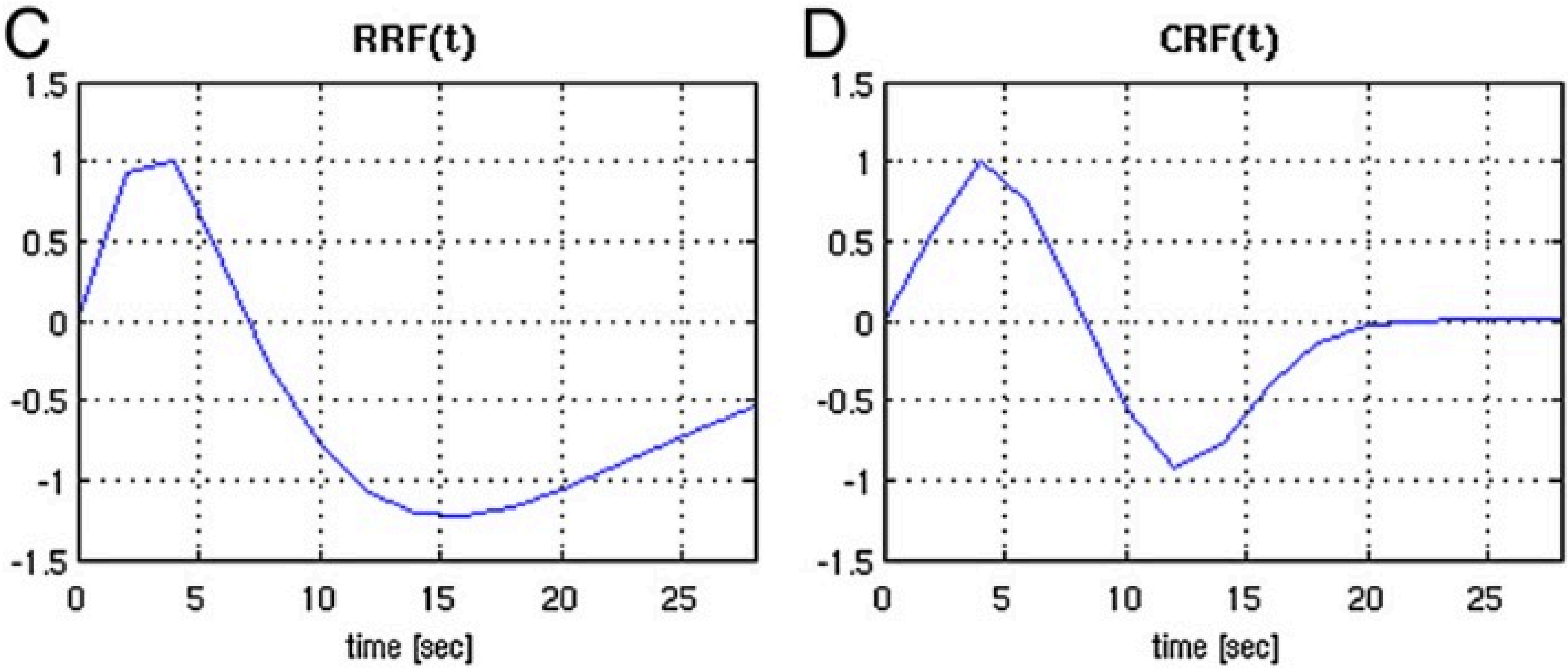


Chang et al, 2009



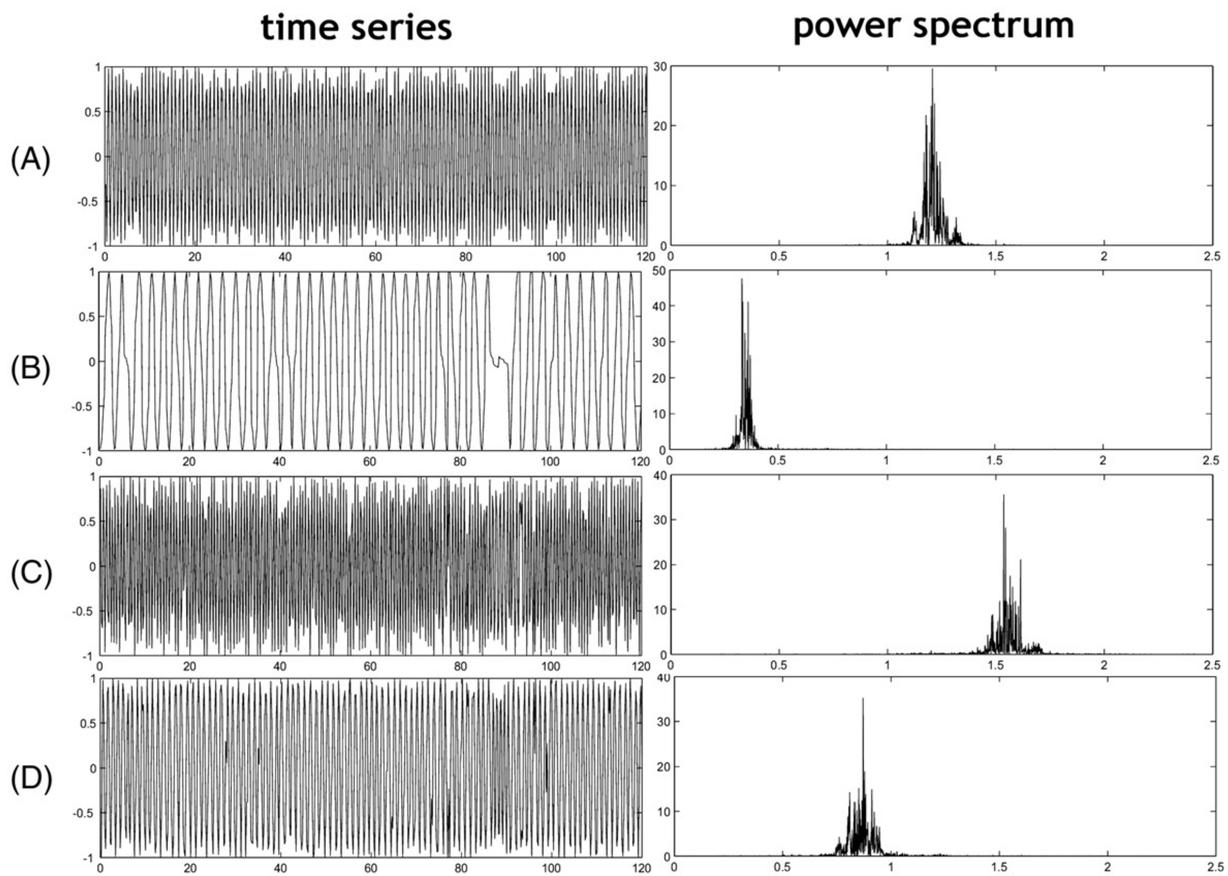
- End-tidal CO_2 concentration (and RVT) strongly related to gray matter signal (Birn et al., 2006; Wise et al., 2004)
- Heart rate fluctuations affect BOLD signal (Chang et al, 2009)

Physiological denoising: RVHRCOR



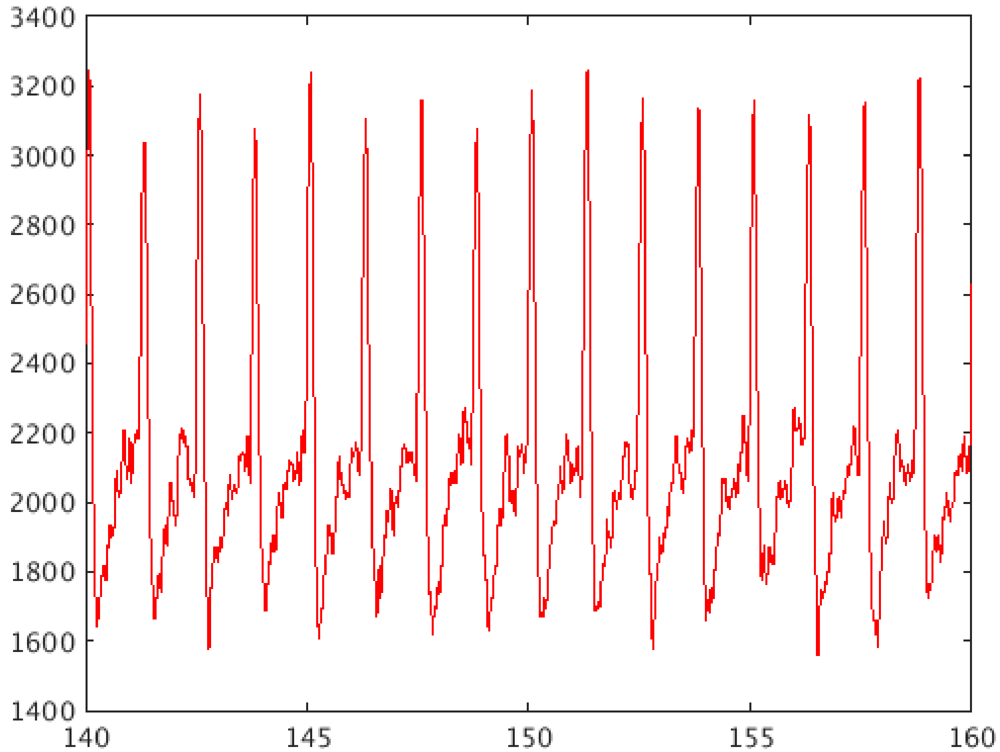
- These influences tend to be low-frequency
- Respiration volume (RV) convolved with "respiratory response function"
- Heart rate (HR) convolved with "cardiac response function"

Physiological denoising: PNM



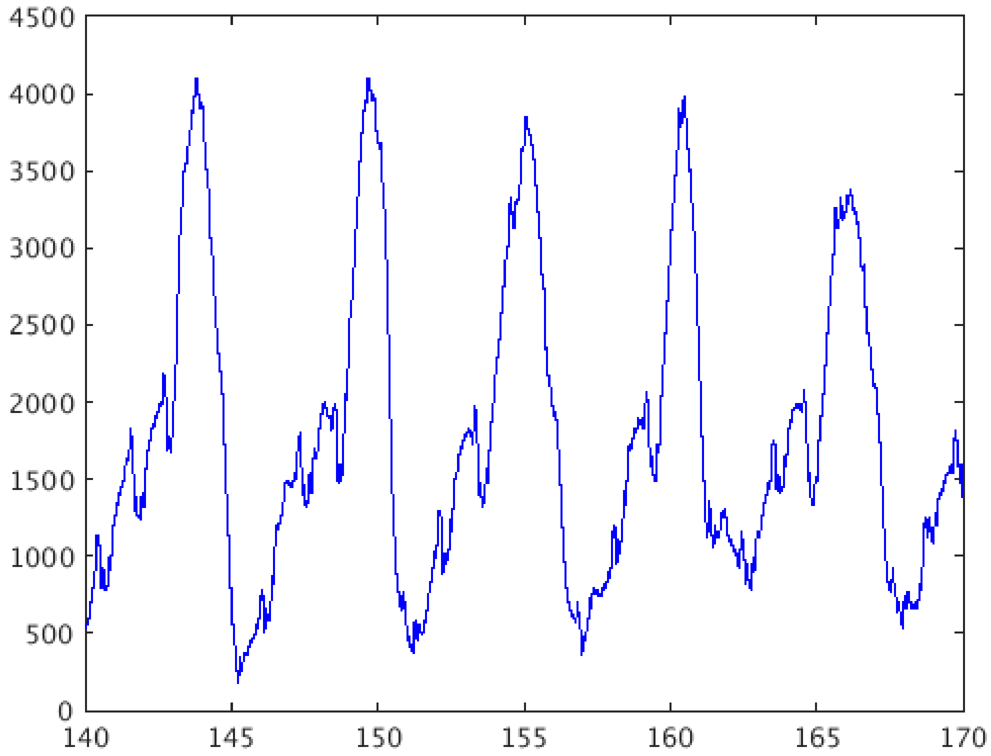
- Allows combination of:
  - RETROICOR regressors
  - Cardiac x Respiratory interaction regressors
  - RVHRCOR regressors
  - CSF regressor

PNM example: Good



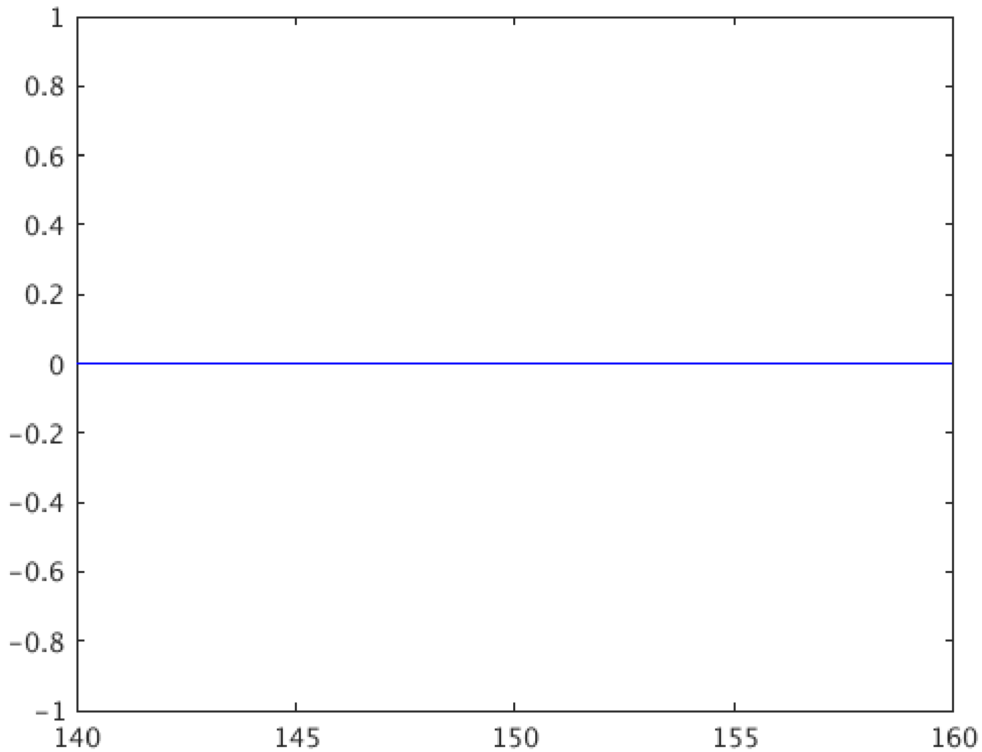
- Some participants produced clean respiratory and pulse ox traces

PNM example: Bad



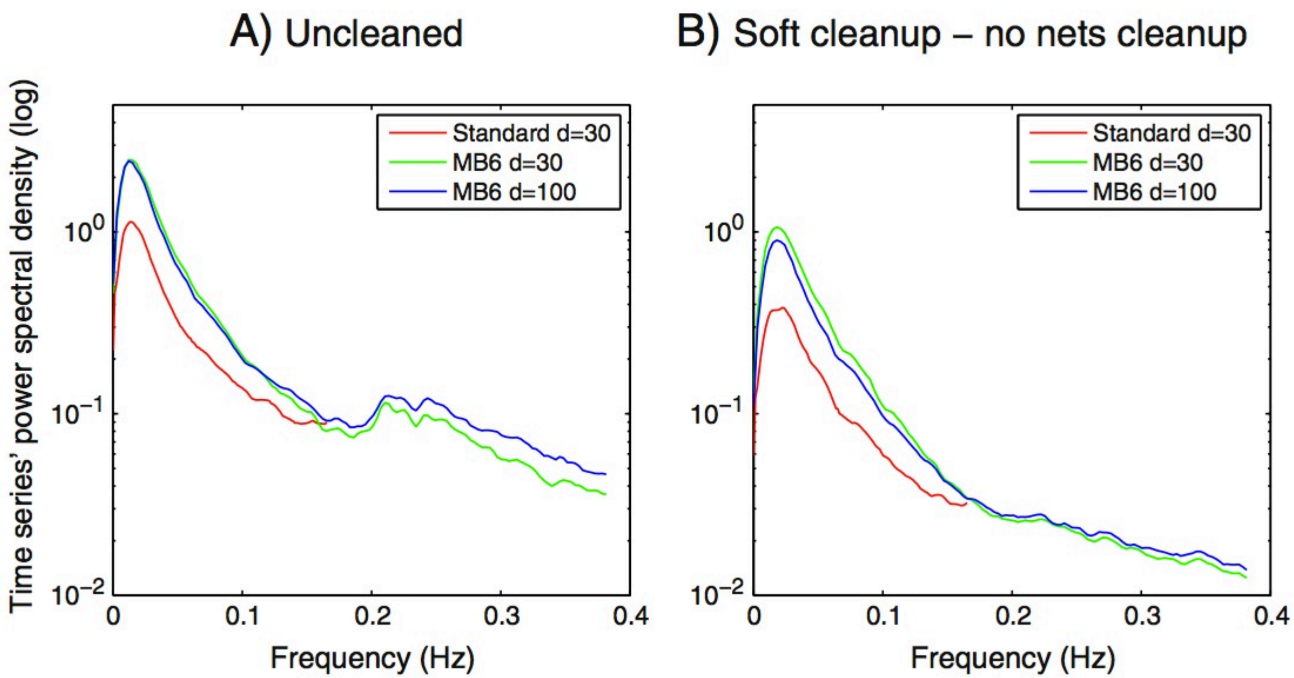
- Some physiological traces are exceptionally noisy, hit ceiling and/or floor, or drop out

PNM example: Impossible



- Some participants are missing physiological monitoring due to malfunction

Addressing physio with FIX



- FIX classifies physiological artifact as noise
  - Based on frequency and spatial location
- Physiological noise removed by regressing artifact timeseries

Addressing physio with FIX

- However, physiological noise may be…
  - globally distributed (not fully decomposed by ICA)
  - lower-frequency (less likely labeled as noise)
- Additional physiological denoising might be helpful
  - if you don’t want to do GSR / MGTR

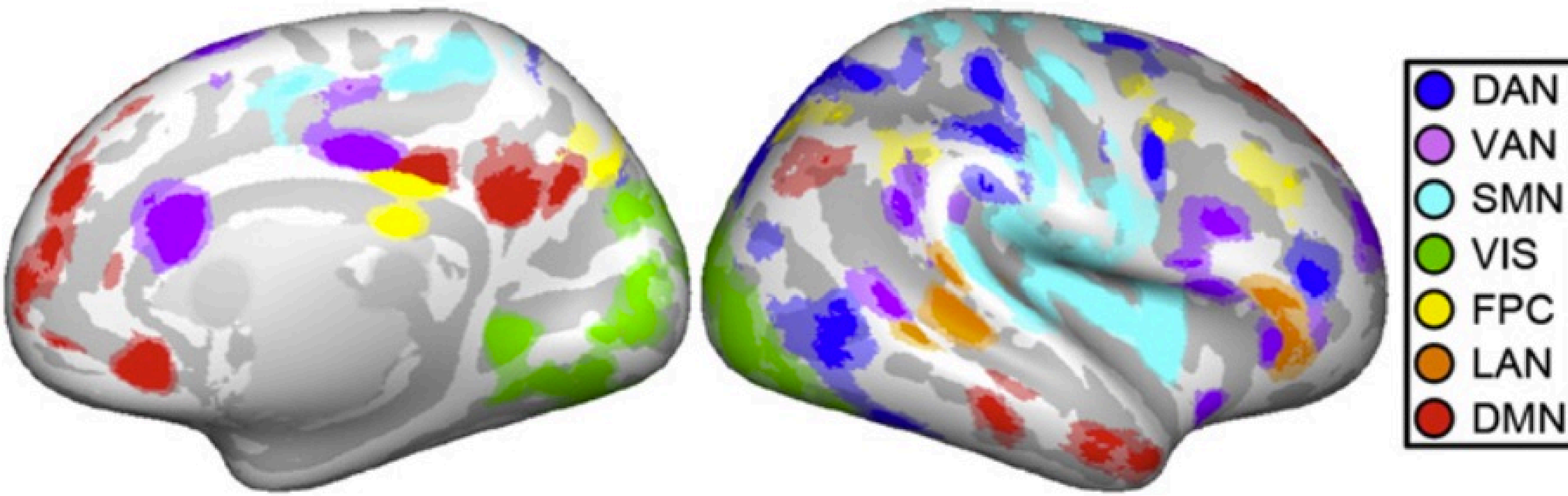
Addressing physio with FIX

- Combining physiological regression with FIX may be a bit tricky
  - FIX before physio regression: change physio noise so it's no longer fit by physio regressors
  - Physio regression before FIX: change noise ICs so they are no longer correctly classified
- If you really want to try physiological regression in addition to FIX…
  - Identify FIX noise ICs separately
  - Combine FIX and physio regressors simultaneously into single denoising model

Switching gears…

- Hacker et al. (2013)
  - Goal: Compute extent and shape of known RSNs classes in individual participants
    - RSNs should be fairly similar across people
    - However, individual differences are likely to relate to psychologically meaningful variables

Multi-Layer Perceptron: RSN classes

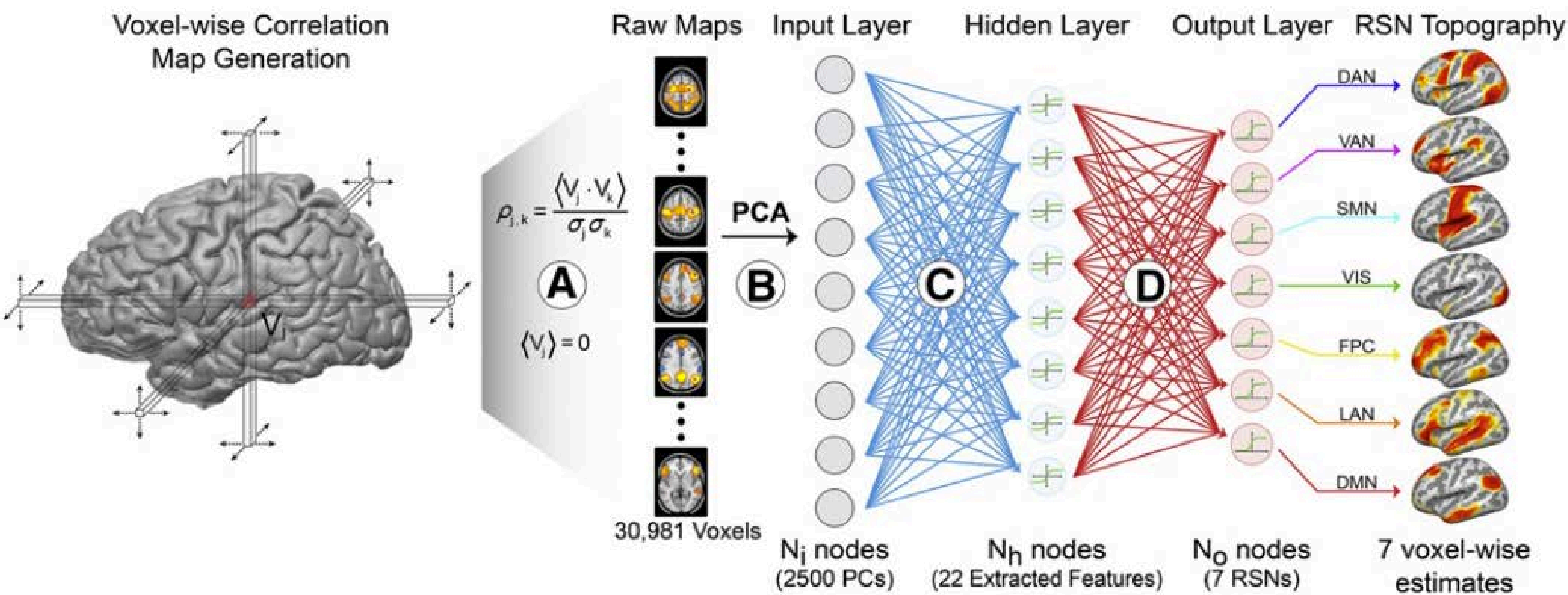


- Step 1: Define RSN classes
  - Conceptually similar to templates for dual regression
  - Defined 7 distinct RSNs using 169 ROIs from meta-analysis of task-fMRI activity (Dosenbach et al. 2007)

Choosing a template

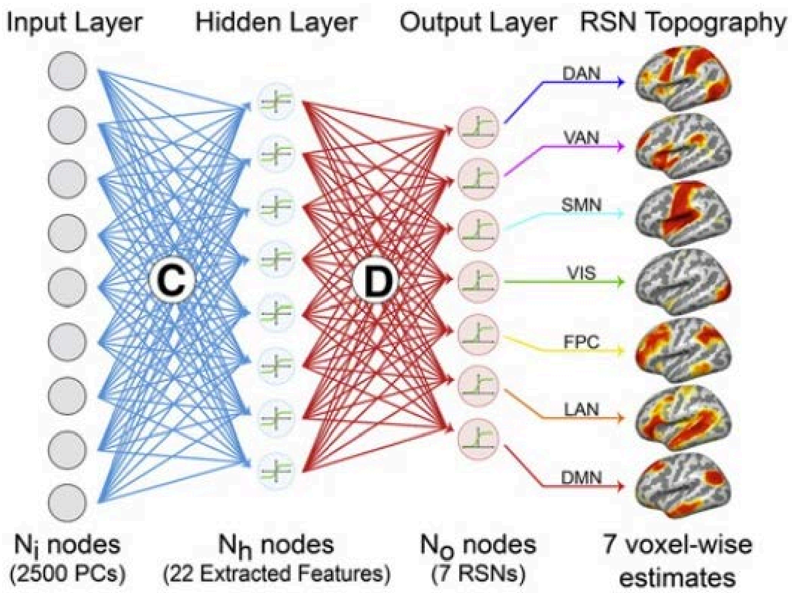
- Seed-based functional connectivity
  - Biased by seed choice
  - Avoid bias by choosing every seed in brain (Cohen et al., 2008)
  - Or bias with intent!
    - seeds via a more robust method (e.g., meta-analysis)
- ICA templates
  - Lots of statistical benefits
  - Interpretation of group components required
    - Some components may be group-level noise

Multi-Layer Perceptron: Classifier



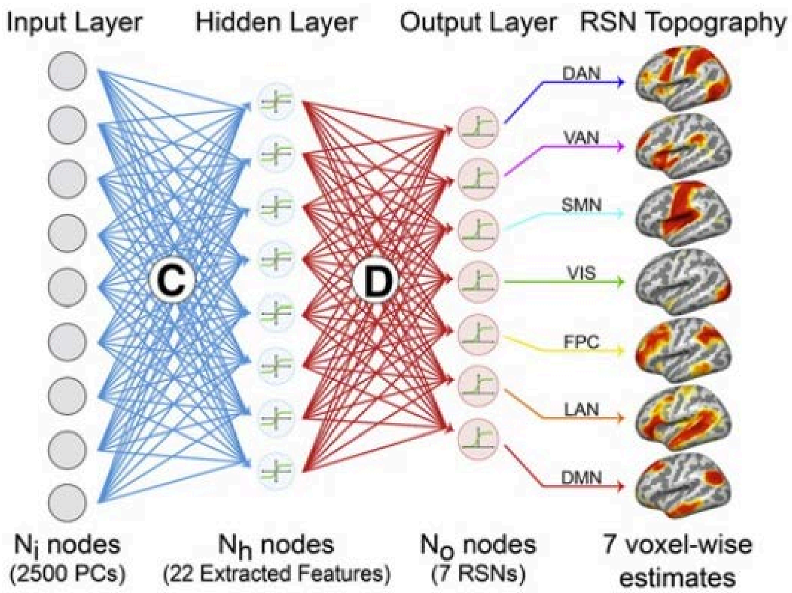
- Step 2: Design neural network classifier
- Inputs:
  - Whole-brain corr maps -> gray matter mask -> PCA reduction (2500 components)
- Feed-forward neural network:
  - 22 hidden layer nodes: Reflect learned features that map PCs to RSNs
  - 8 output nodes (7 RSNs + 1 nuisance): reflects confidence of membership in each class

Multi-Layer Perceptron: Training



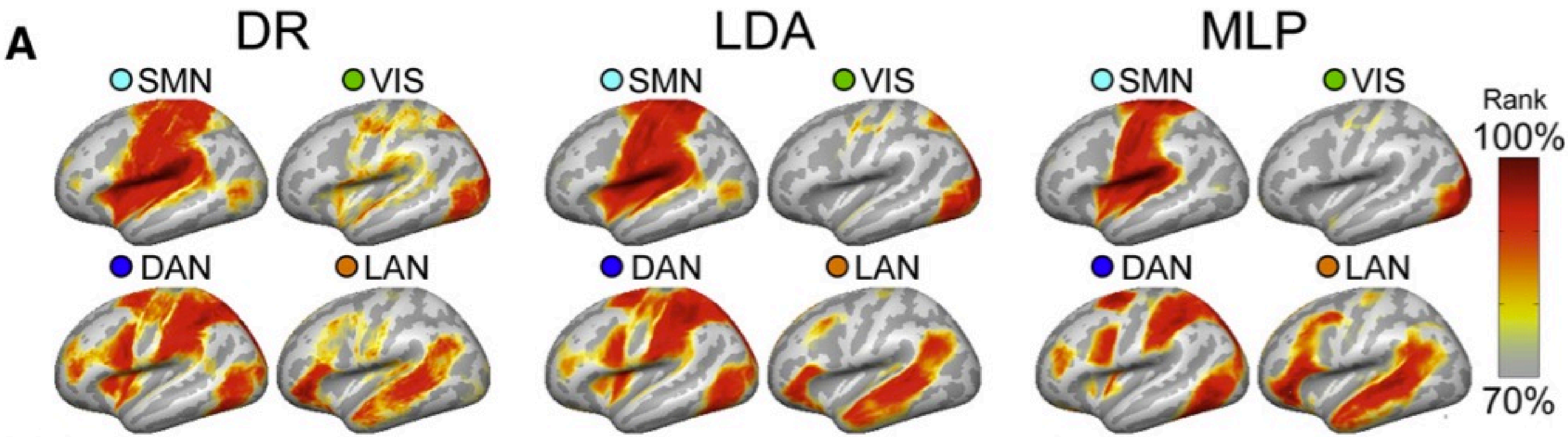
- Step 3: Train network
- Output nodes compared to a priori labels
  - Feed-forward network sets output node values
  - Compared to a priori label for seed: '1' for correct RSN, '0' for incorrect RSNs
  - Yields estimate of error at each output node

Multi-Layer Perceptron: Training



- Error estimates modify weights via back-propagation
  - weights between output layer and hidden layer (D)
  - weights between hidden layer and input layer (C)
- Training iterations continue until classification accuracy asymptotes for all RSNs
  - or if MLP begins to overfit to training set
- Learned weights are fixed after training

Multi-Layer Perceptron: Performance



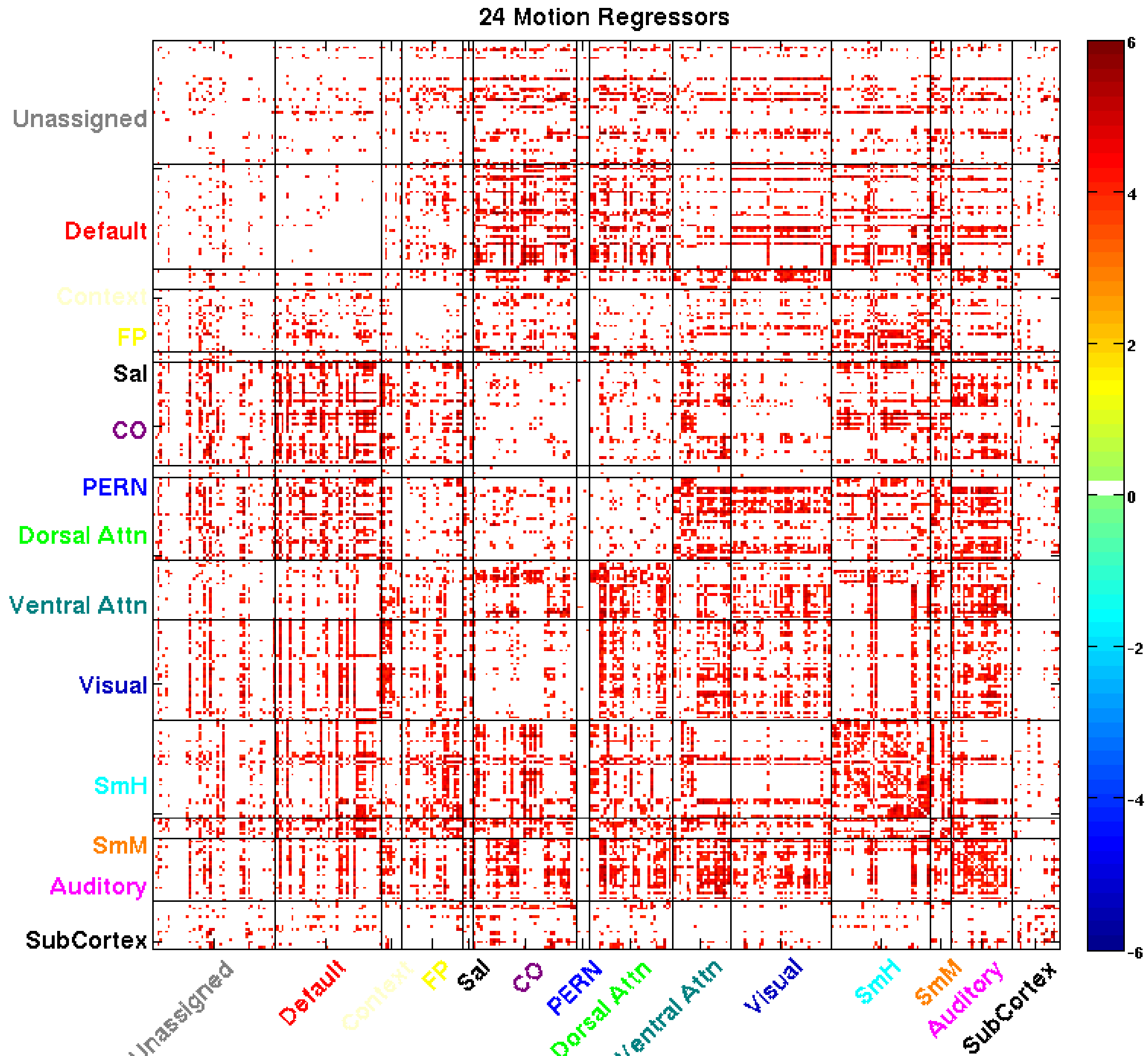
- Step 4: Test MLP
- Procedure:
  - Extracted corr maps from a priori ROIs in individuals
  - Tested classification performance using trained MLP
  - Compared to performance of dual regression (DR) and linear discriminant analysis (LDA)
- Results:
  - MLP classified networks more distinctly than DR or LDA
    - less spatial overlap between networks
    - lower correlation between RSN estimates for different networks

Extending MLP

- Neural networks will one day rule the world
- In the meantime, we can train MLP to perform other classification tasks
  - Instead of classifying entire networks, classify individual parcels vs. adjacent / surrounding areas
- Train MLP to utilize additional inputs / features
  - Structural features: myelin, curvature
  - Task fMRI activation

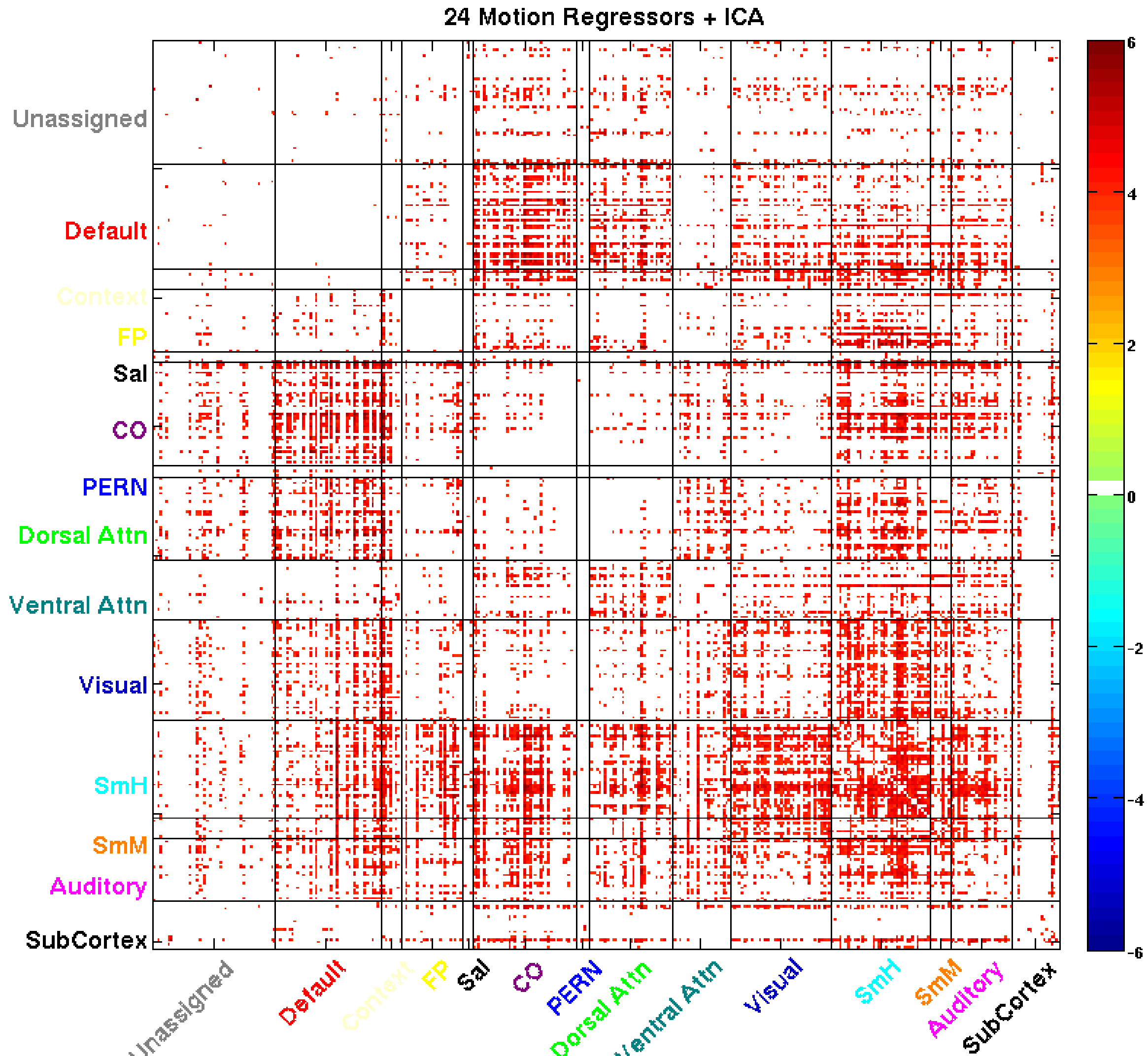
Mahalo!

Networks showing motion-group differences



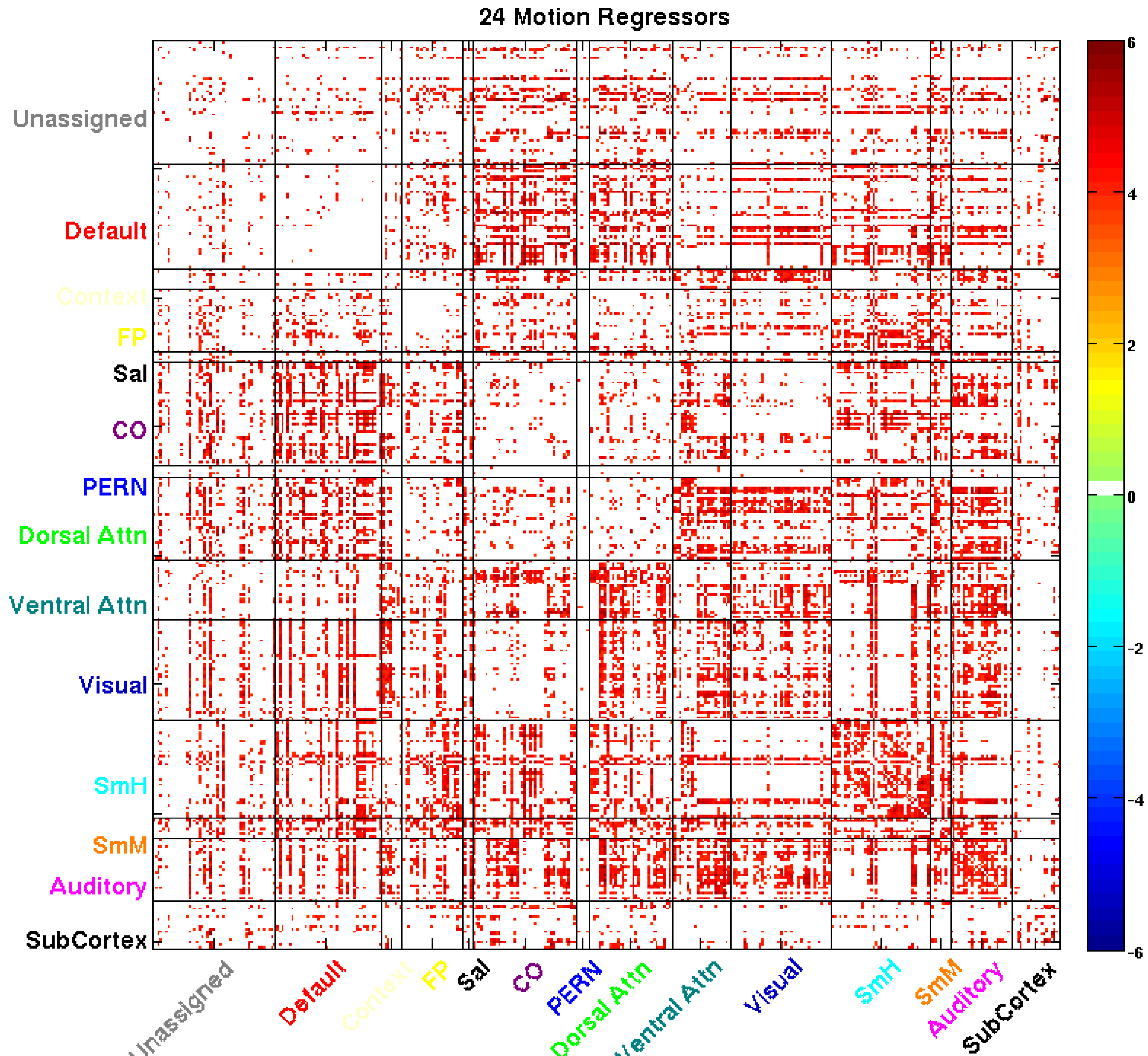
- After 24-motion regressors:
  - motion-group differences between most networks across whole brain
  - High-motion group has more similarity between regions than low-motion

Networks showing motion-group differences



- After FIX ICA-Denoising:
  - motion-group differences with default remain stable
  - motion-group differences with somatomotor strengthen

Networks showing motion-group differences



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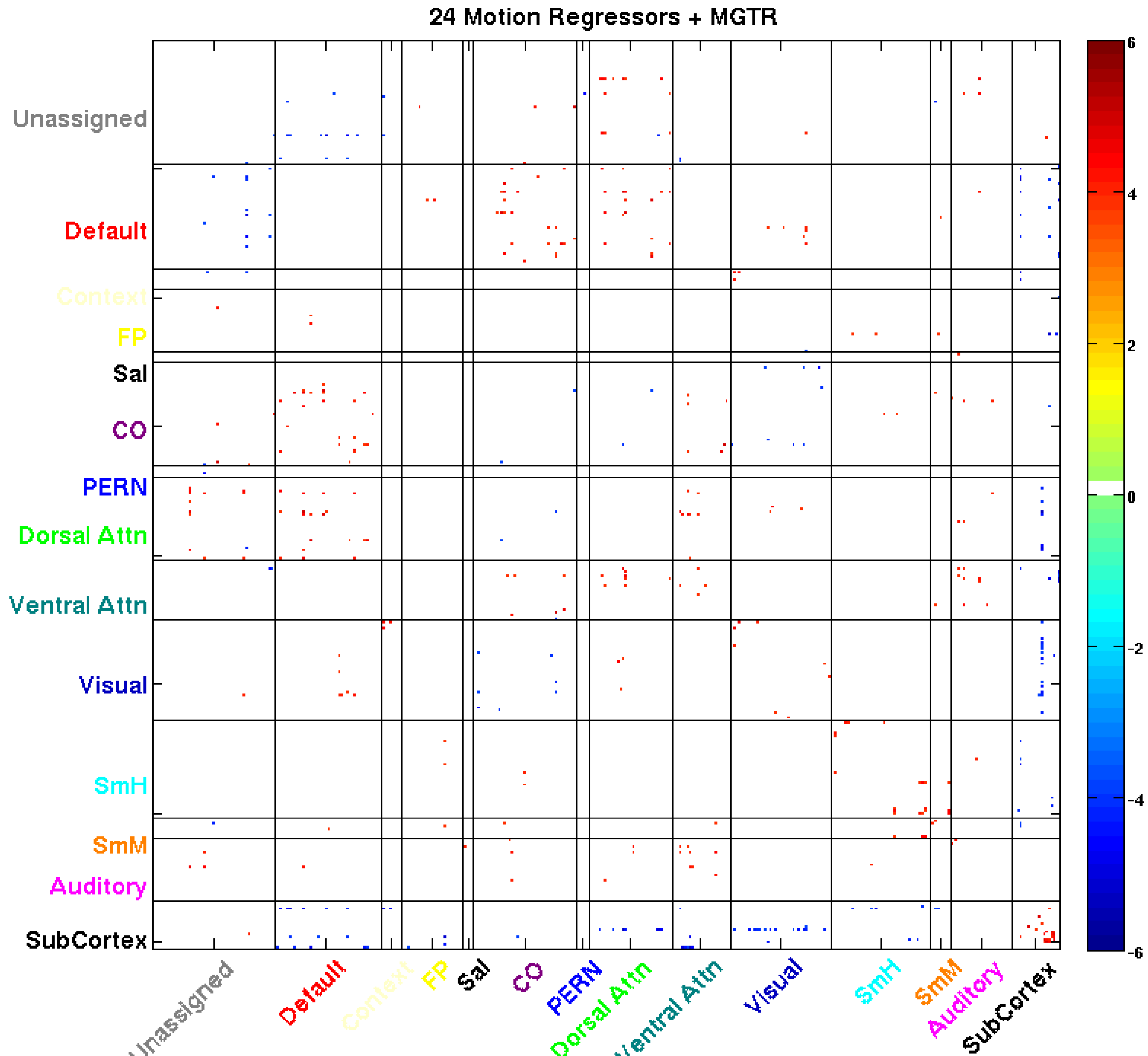
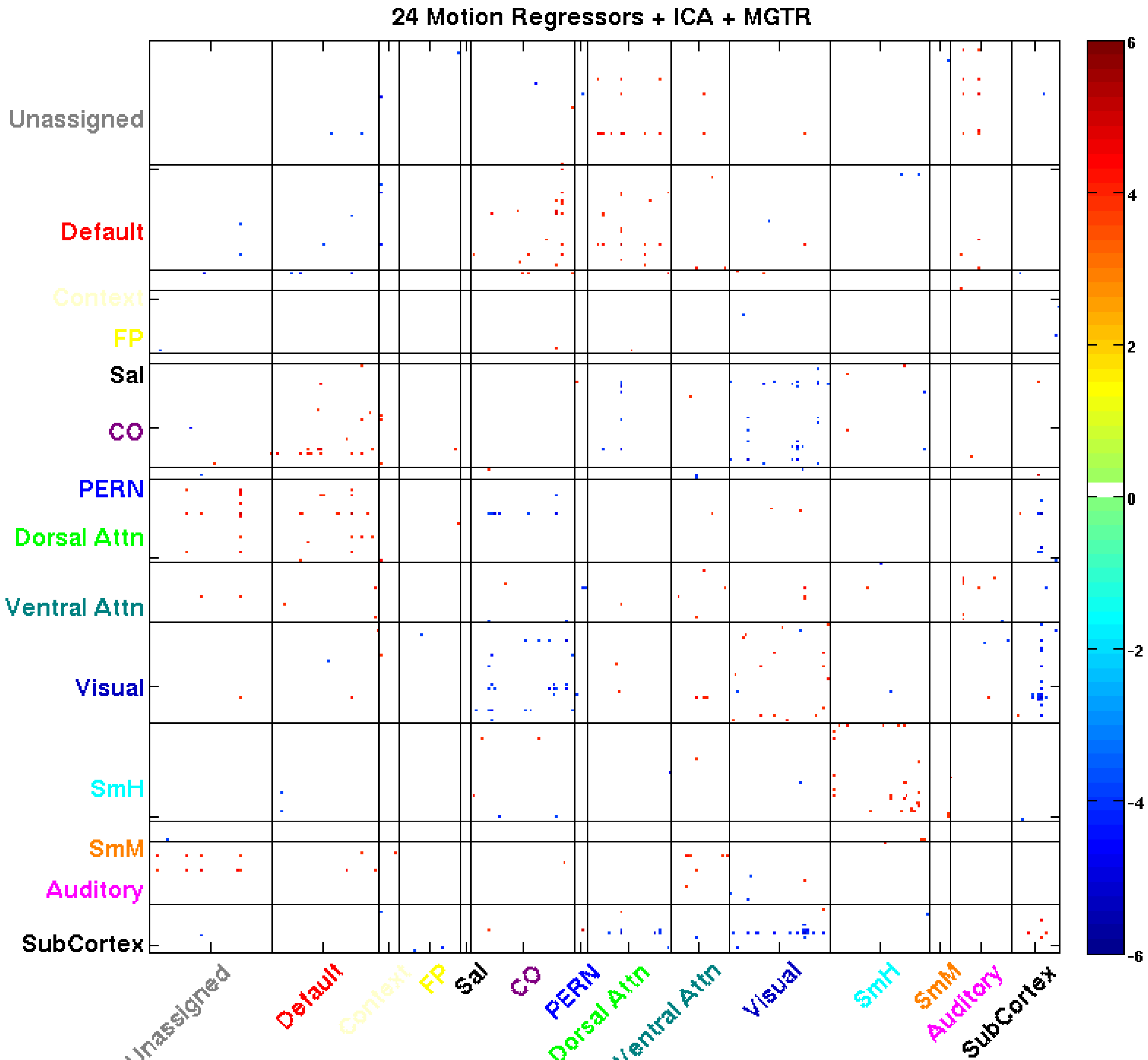


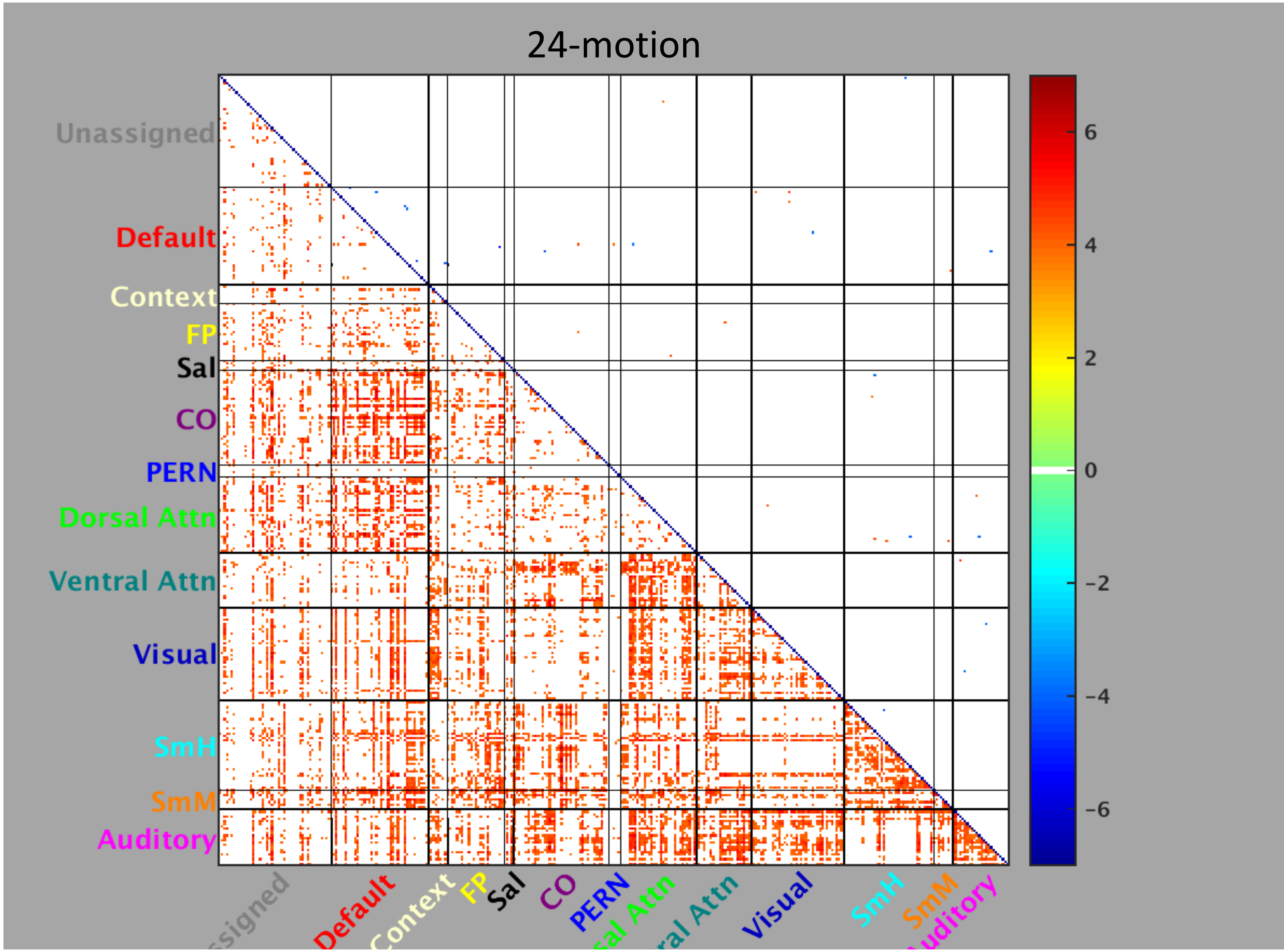
- MGTR + 24 motion:
  - motion-group differences dramatically reduced
  - remaining differences involve default with CO and Dorsal Attn

Networks showing motion-group differences



- FIX data after MGTR:
  - differences in different parcels within same networks
  - additional (negative) differences between Visual and CO

Partial Correlation Netmats



- Partial correlation matrices are very similar at each denoising stage:
  - After 24-motion, few motion group differences (however, more than chance)
  - After FIX, motion-group differences increase at some edges, decrease at others
  - FIX+MGTR does not show appreciable differences to FIX only