

Noise Models and Correction for fMRI

- an Introduction to the PhysIO Toolbox

Lars Kasper

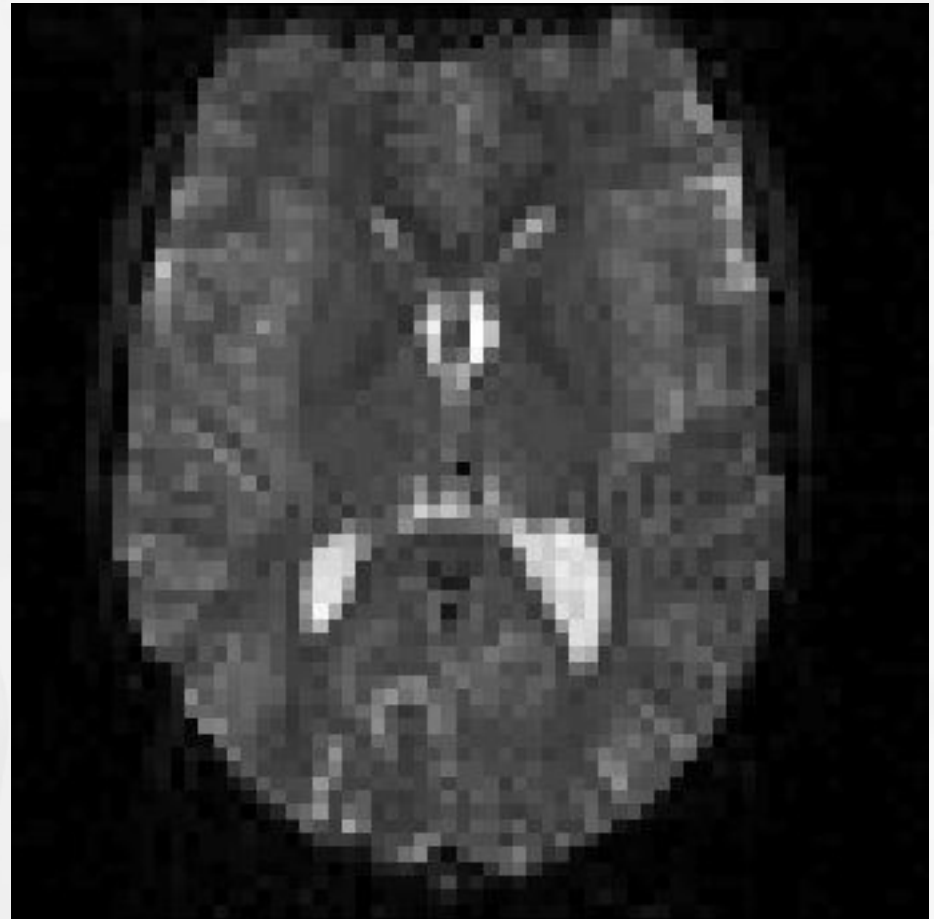
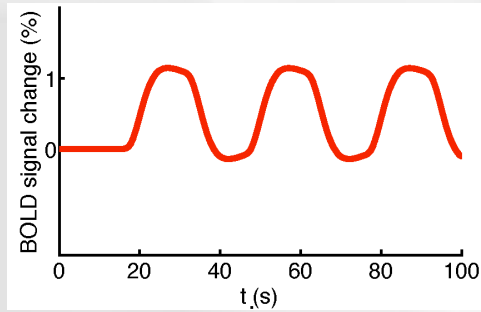
Jan 9th, 2017

MR-Technology Group & Translational Neuromodeling Unit

Institute for Biomedical Engineering
University of Zurich and ETH Zurich



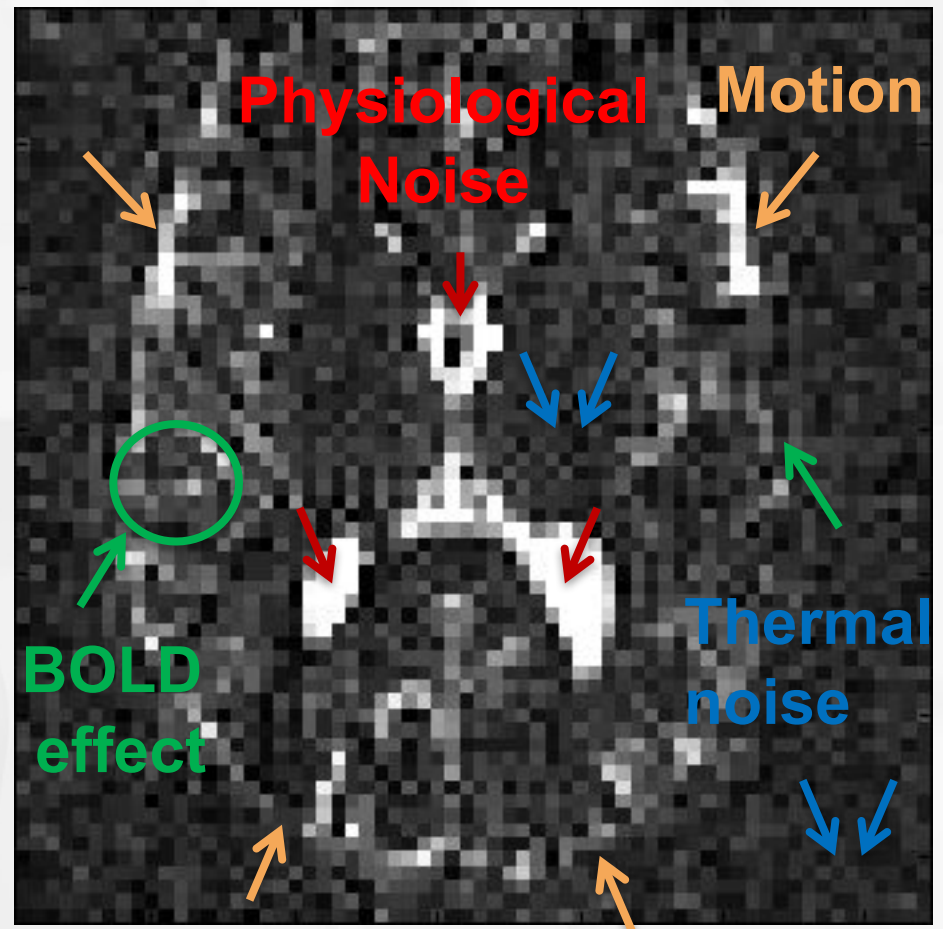
fMRI Data is noisy...



fMRI Data is noisy...



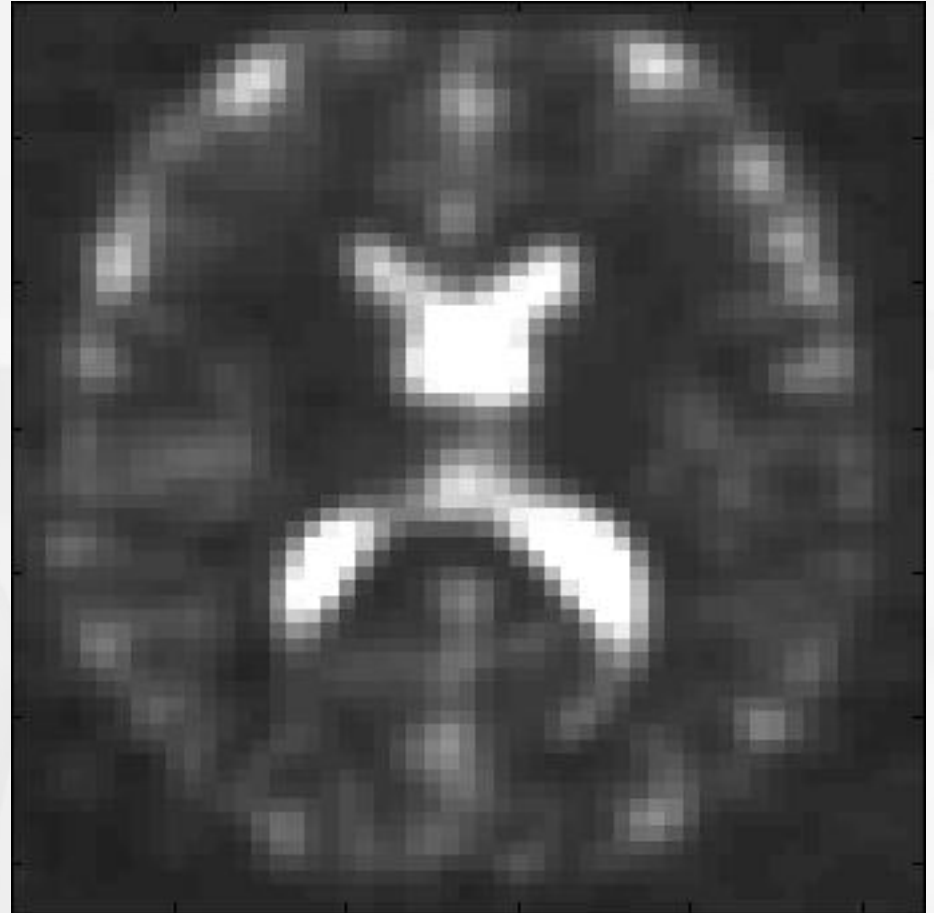
- Interest in fluctuations only: Subtract the mean



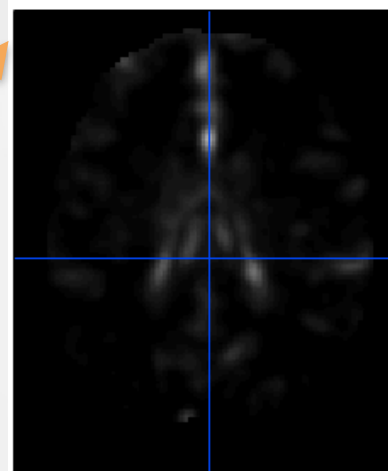
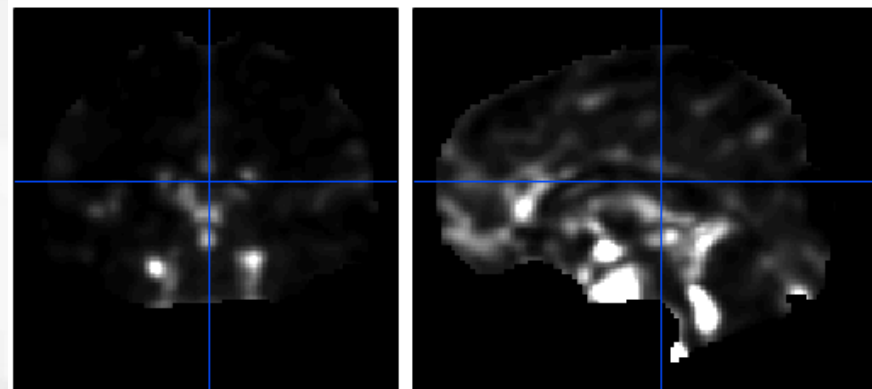
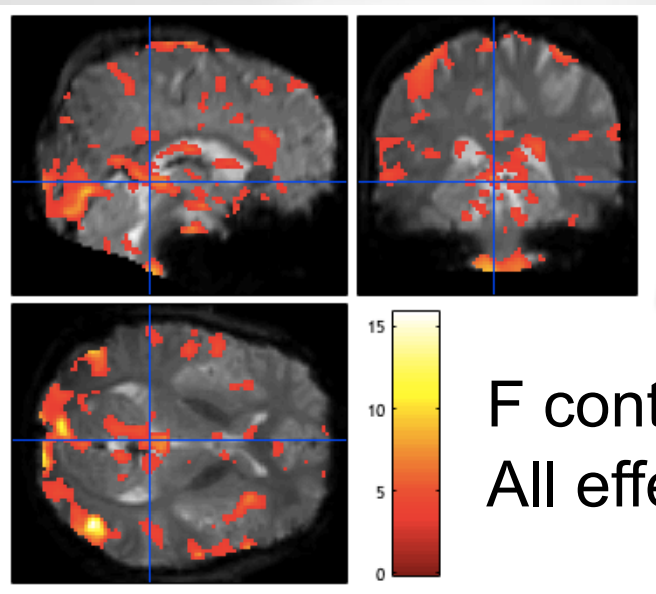
fMRI Data is (still) noisy



- After preprocessing...
- Much better, but still:
some fluctuation



- GLM folder: ResMS image
- Indicates where model incomplete...
- limits sensitivity...



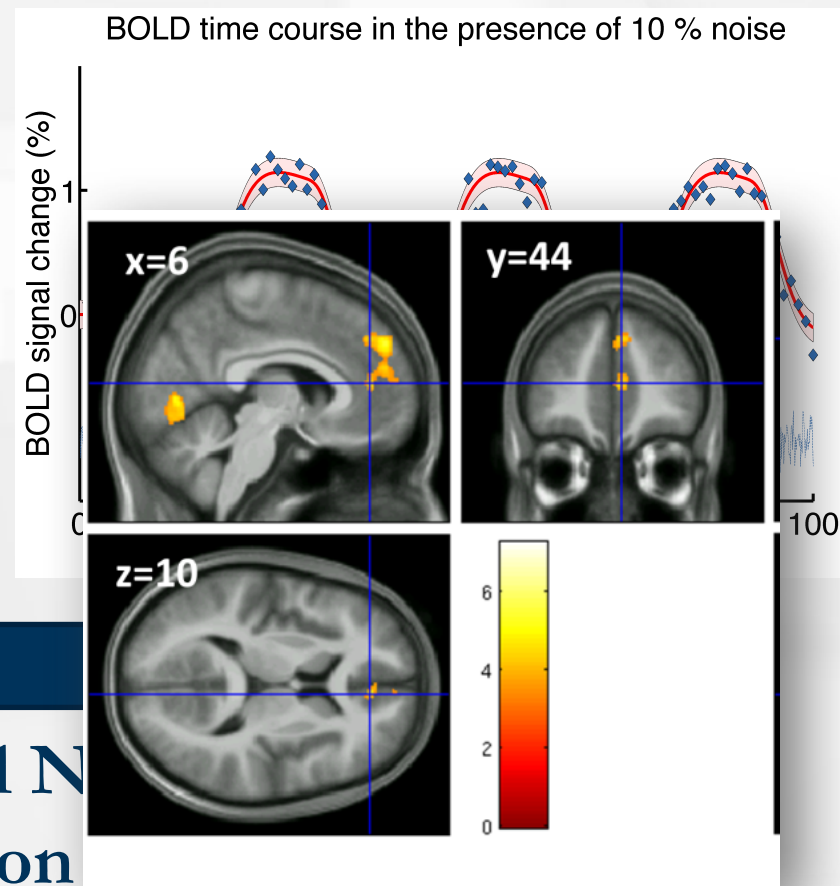
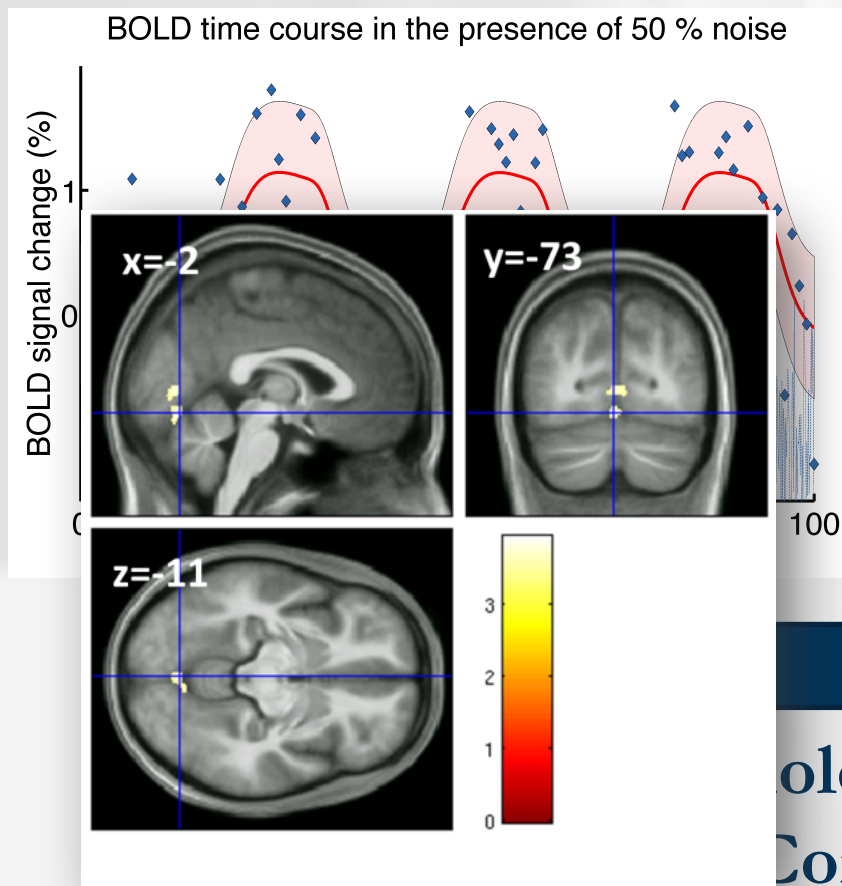
$$\widehat{\sigma^2} = \frac{(Y - X\beta)^2}{N - p}$$

The Goal of Noise Correction



Before

After



Biological Noise Correction



- Toolbox for model-based physiological noise correction in fMRI
- Developed at the Translational Neuromodeling Unit (TNU)
 - Lead programmer: Lars Kasper (TNU, University of Zurich & ETH Zurich)
 - Contributors: Jakob Heinzle (TNU), Steffen Bollmann (KiSpi Zurich)
- Part of the TNU «TAPAS» software suite
- Used at the TNU, in Zurich and beyond by ~50 researchers
 - Iglesias 2013, Neuron; Kasper 2014, NeuroImage; Sulzer 2013, NeuroImage; Hauser 2014, NeuroImage; Grueschow 2015, Neuron; Diaconescu 2017, SCAN
- Download & Example Data:
 - <https://translationalneuromodeling.org/tapas>
 - <https://www.tnu.ethz.ch/en/software/tapas/data.html>



- MRI Time Series Recap and Noise Sources
 - Why de-noising? Structured Noise; Noise Pathways
- Noise Correction Approaches
 - Method: Modeling VS Preprocessing
 - Target: Motion, Cardiac/Breathing Cycle
 - Input: fMRI Data VS Peripheral Measures
- Prospects for Improving Group Statistics
- Limitations
 - Degrees of Freedom; Task-related “noise”; Interoception



- **MRI Time Series Recap and Noise Sources**
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fMRI = Acquiring Movies

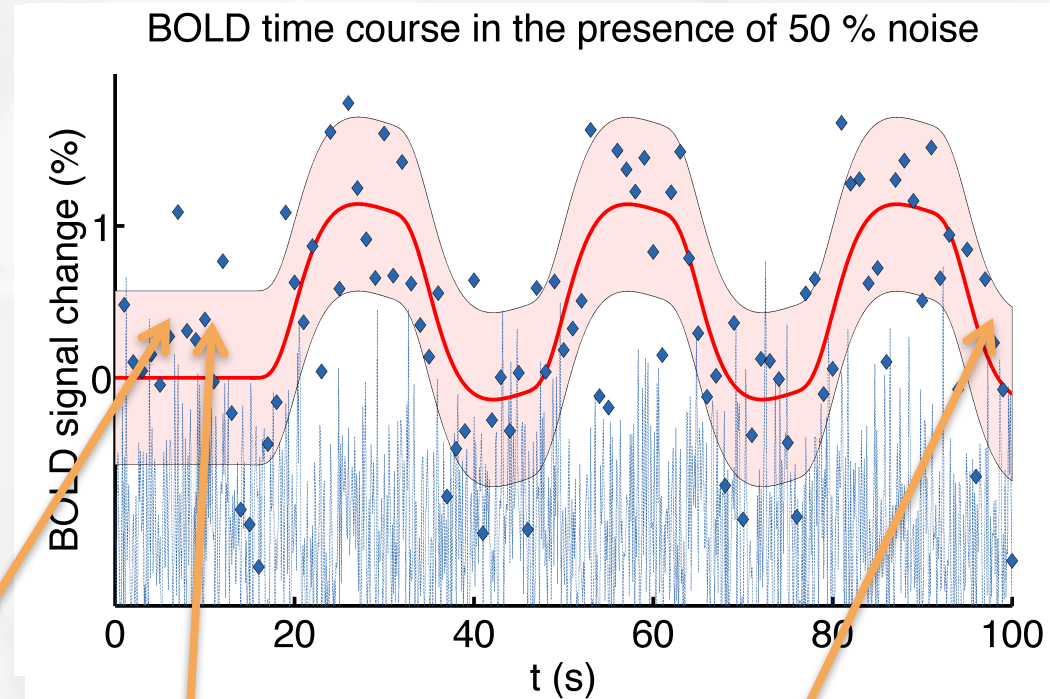


- The Localized Time-series is the Fundamental Information Unit of fMRI

Signal: Fluctuation through Blood oxygen level dependent (BOLD) contrast

Noise: All other fluctuations

- Run/Session: Time Series of Images



scan 1



...



scan N

time

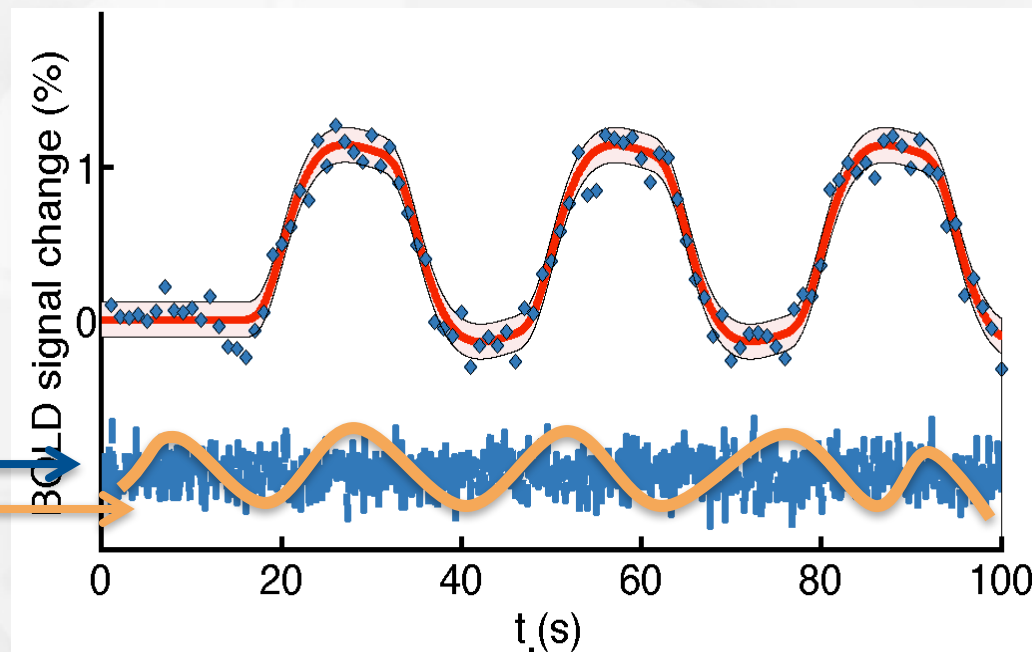
Noise Categories & Reduction



- Thermal Noise
 - temporally uncorrelated
 - reduced SNR → risk of false negatives
 - Remedy: Spatial Smoothing

Noise: All other fluctuations

- “Structured” Noise
 - temporally correlated
 - reduced SNR → risk of false negatives
 - correlated with task → risk of false positives
 - Remedy: Noise modeling (e.g. GLM)



Inference = Signal-To-Noise

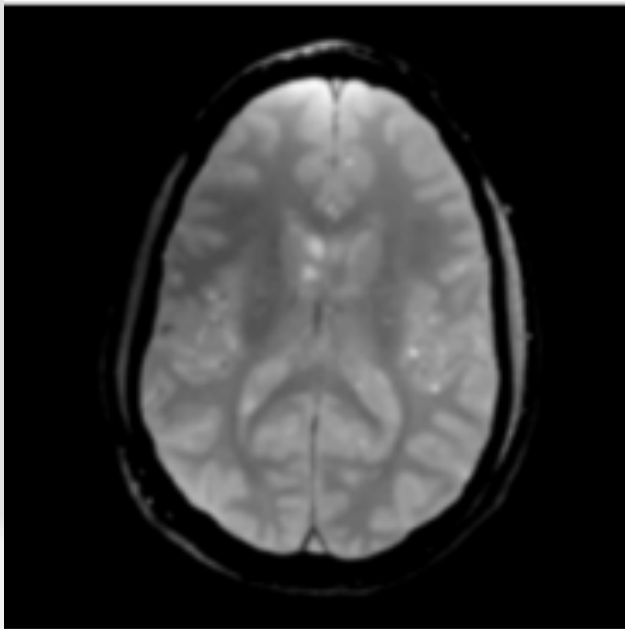
$$t = \frac{\beta}{\sqrt{\hat{\sigma}_\varepsilon^2 (X^T X)^{-1}}} = \frac{\beta \|\mathbf{x}\|}{\hat{\sigma}_\varepsilon}$$

$$F = \frac{N - M}{M_1} \cdot \frac{(\sigma_S^2 + \sigma_N^2) - \sigma_N^2}{\sigma_N^2}$$

Recap: MR Image Encoding



Image Space (m)



y ↑
→ x

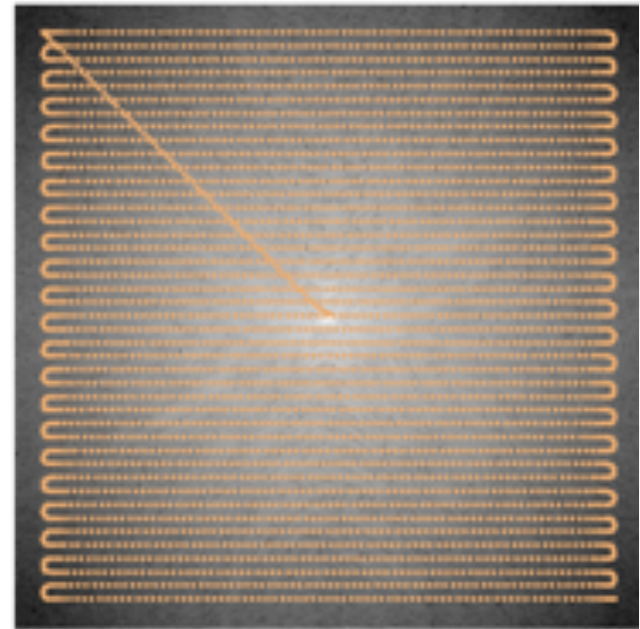
Fourier
Transform
(FT)



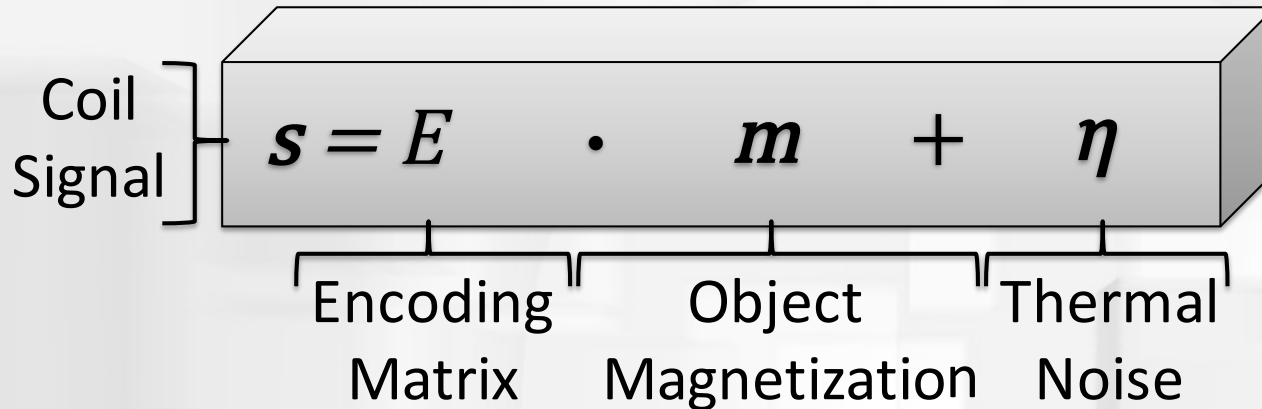
In general:
Image
Encoding

E

k-Space (s)

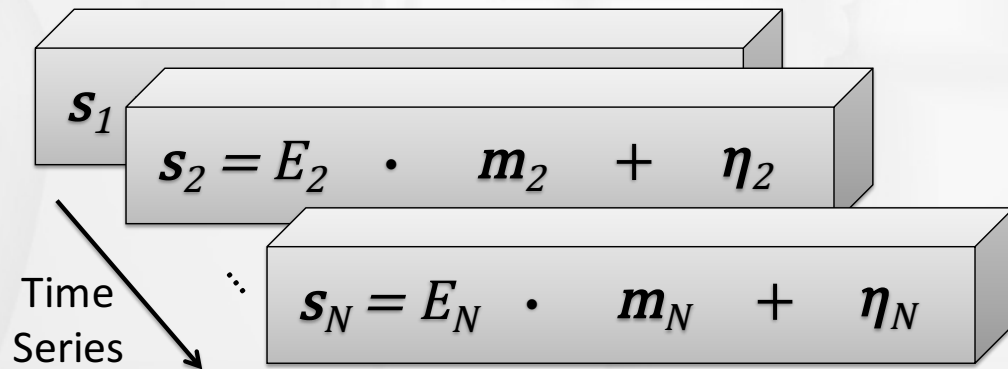


k_y ↑
→ k_x

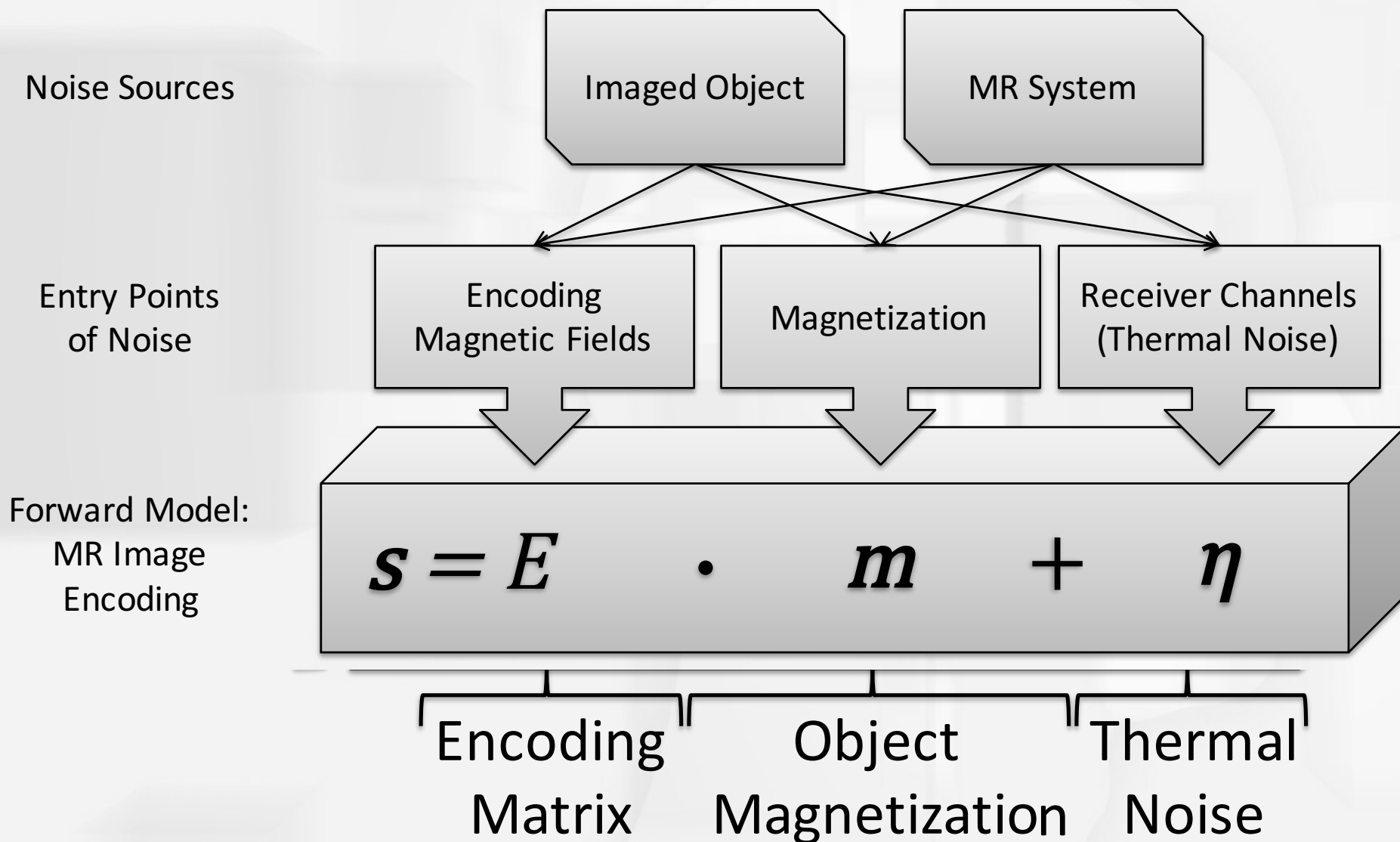


- Image reconstruction is also (often) a GLM, though a huge one, $\sim 100,000$ rows
- Any changes between encodings (images) in encoding matrix (field), object magnetization and thermally induces image noise

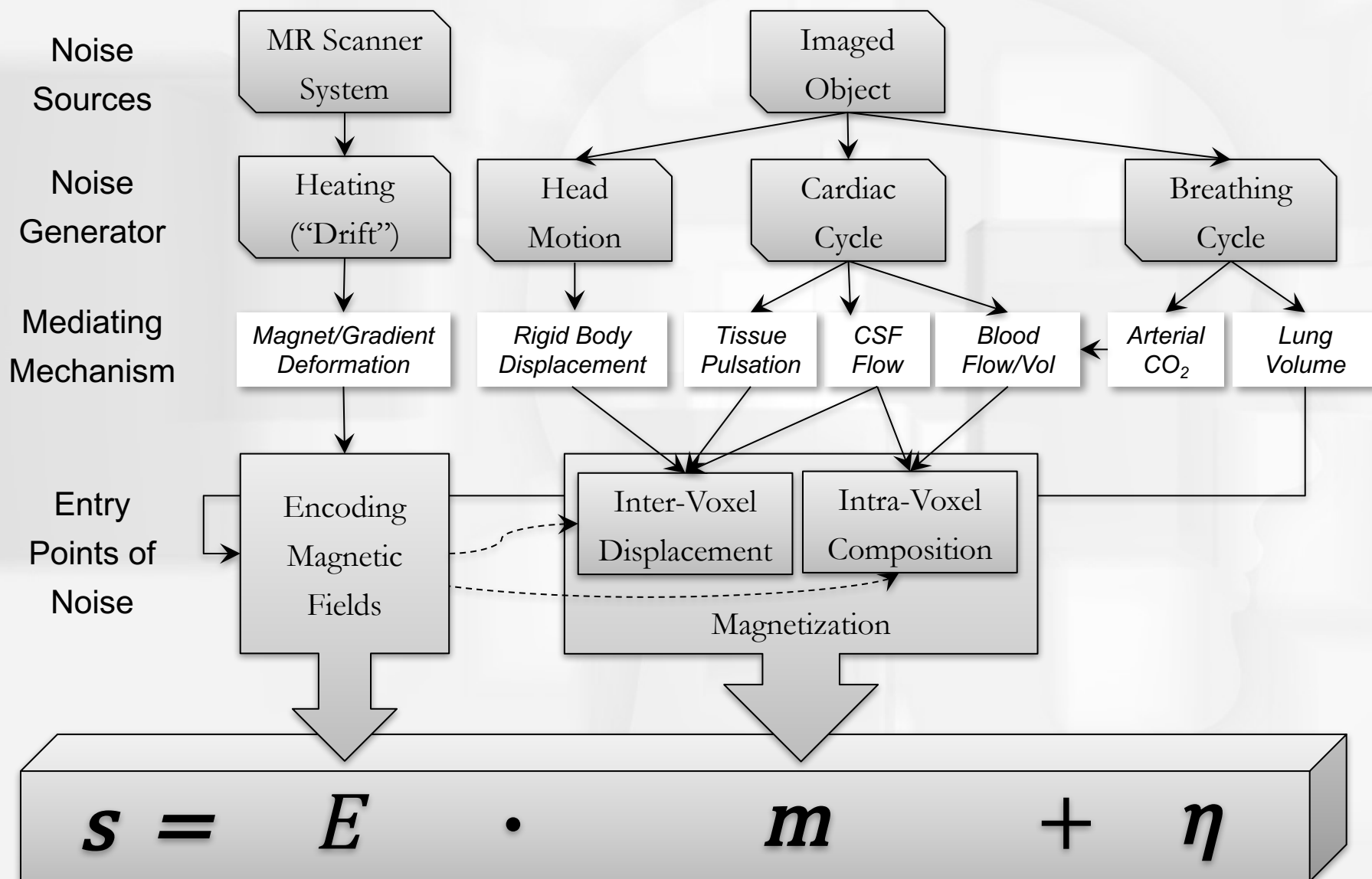
$$\hat{m} = (E^H E)^{-1} E^H s$$



What fluctuates?



Structured Noise in MRI



The Problem: Physiological Noise



- Cardiac effects

- Respiratory effects

The Problem: Physiological Noise



■ Cardiac effects

- Systole:
 - Blood pumped into brain, vessel volume increases: pulsatile vessels
 - CSF pushed down: pulsatile CSF
- Diastole:
 - Vessel volume decreases
 - CSF flows back into “void” brain volume

A Cardiac Cycle in the Brain

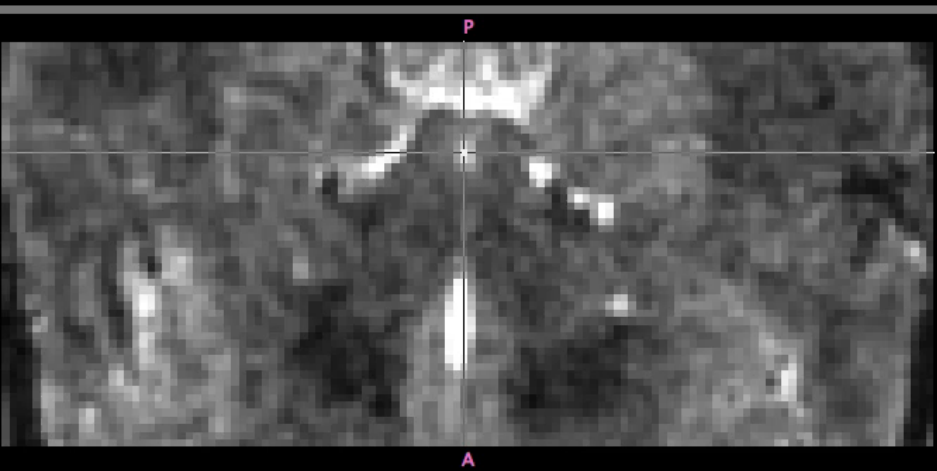
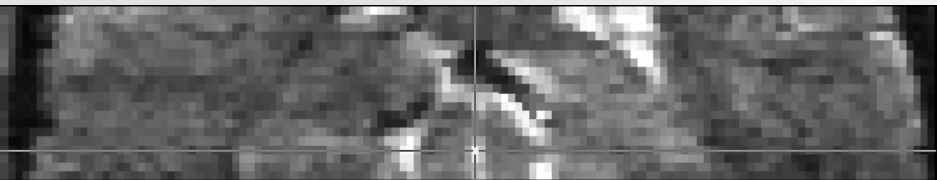


The Problem: Physiological Noise



Triggered High-Resolution fMRI

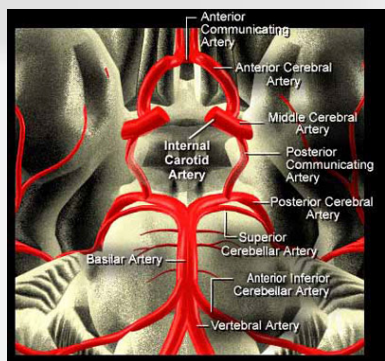
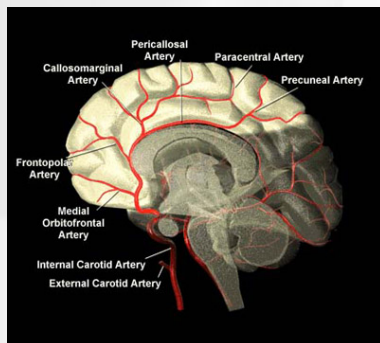
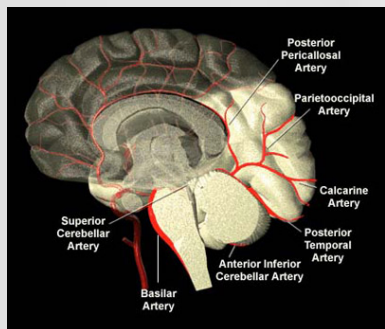
A Cardiac Cycle in the Brain



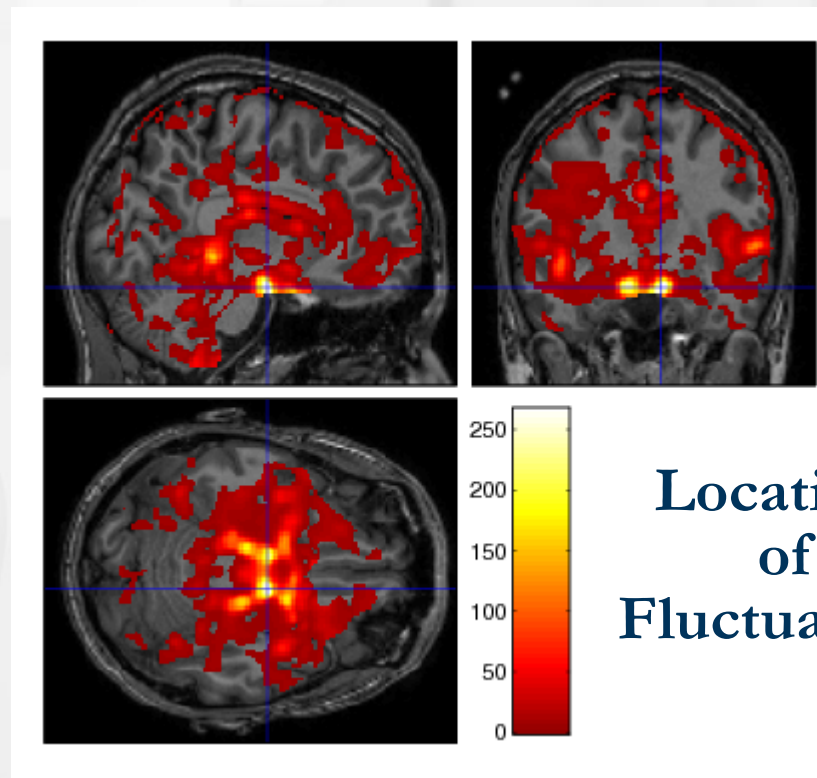
The Problem: Physiological Noise



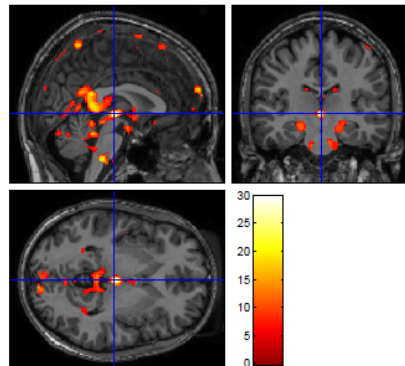
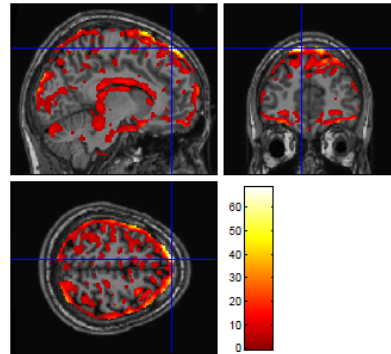
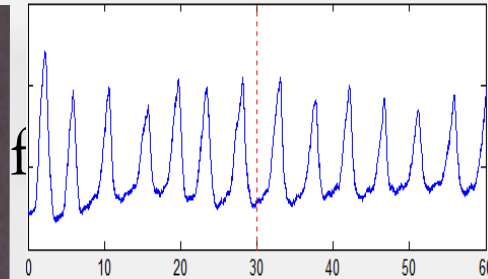
■ Cardiac effects



Vessel Anatomy



The Problem: Physiological Noise



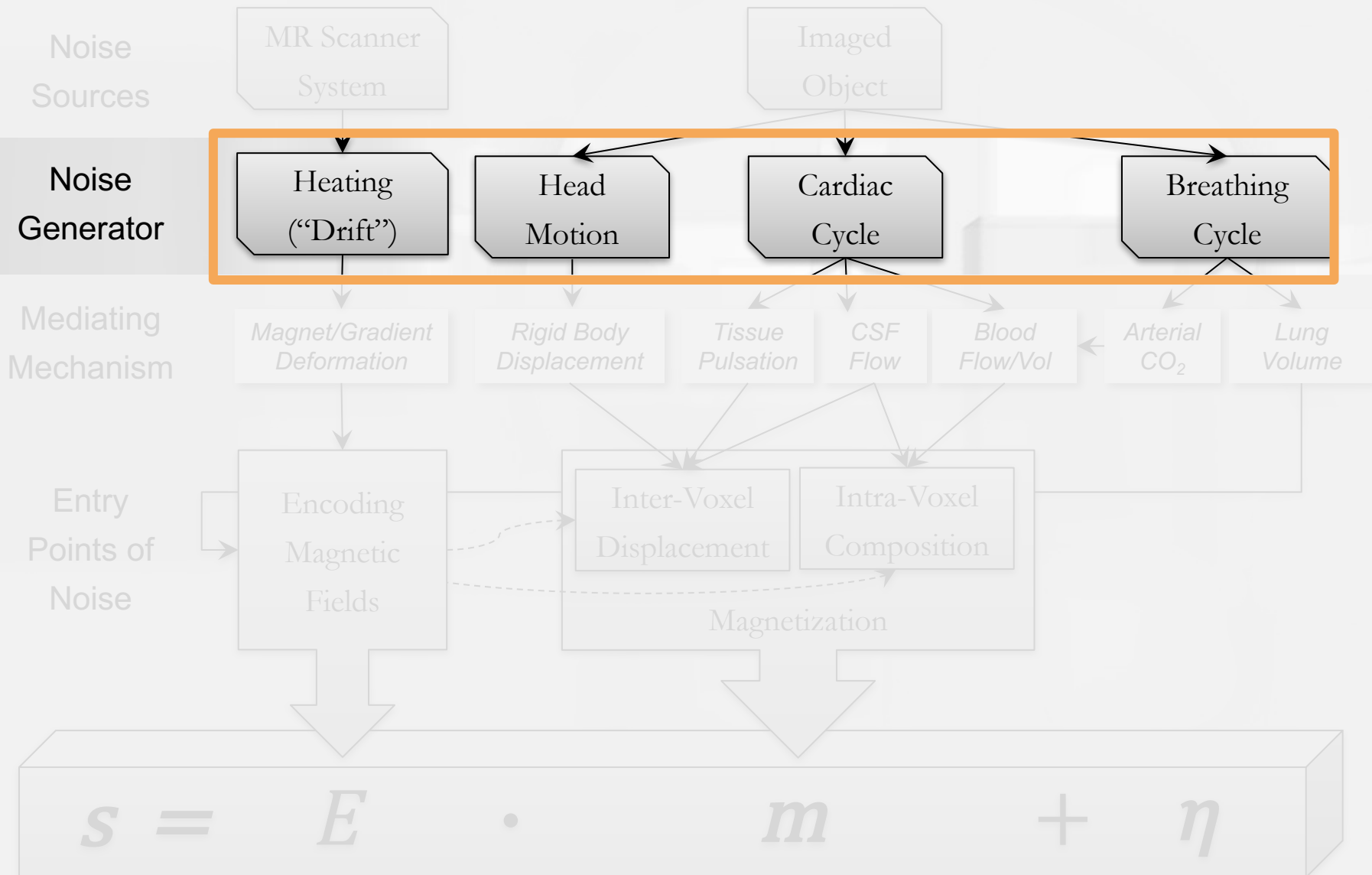
■ Respiratory effects

- Chest (& head) moves with respiratory cycle
- Changes in lung volume change encoding magnetic field for MR
 - Geometric distortion/scaling
- Respiratory-sinus arrhythmia
 - Heart beats faster during inhalation



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Noise Correction Targets



Preprocessing and Limits



■ Acquisition Timing

Temporal Preproc

■ Slice-Timing

■ Subject Motion

Spatial Preproc

■ Realignment

■ Anatomical Identity

Spatial Preproc

■ Co-registration

■ Inter-subject variability

Spatial Preproc

■ Segmentation

■ Thermal Noise

Spatial Preproc

■ Smoothing

■ Physiological Noise

Noise Modeling

■ PhysIO Toolbox

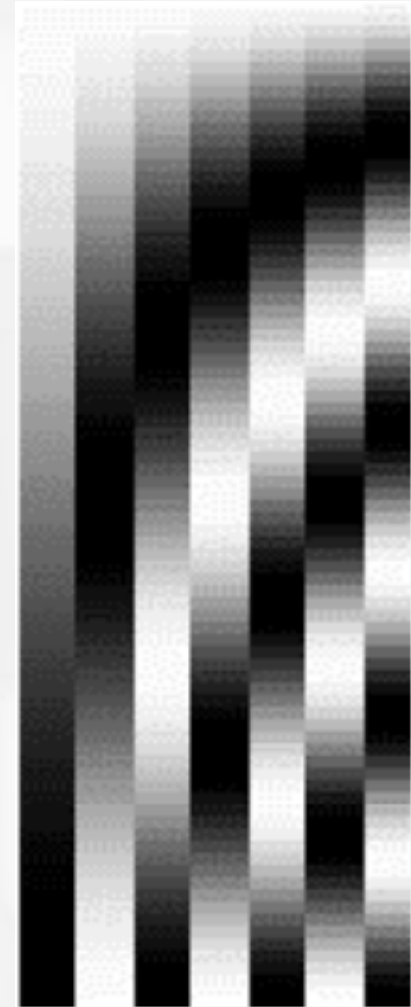
- Discrete Cosine Model (last lecture) of slow oscillations (cycle ≥ 128 s)
- Was: Extra, non-task related columns in design matrix: **nuisance regressors**
- Now: Part of “hidden” preprocessing (high pass filtering)

- Residual forming Matrix

$$K = 1 - X_0(X_0^T X_0)^{-1} X_0^T$$

- With X_0 being the design matrix modeling the confounds
- In fact, GLM in SPM estimates

$$K \cdot \mathbf{y} = K \cdot X \cdot \boldsymbol{\beta} + K \cdot \boldsymbol{\varepsilon}$$



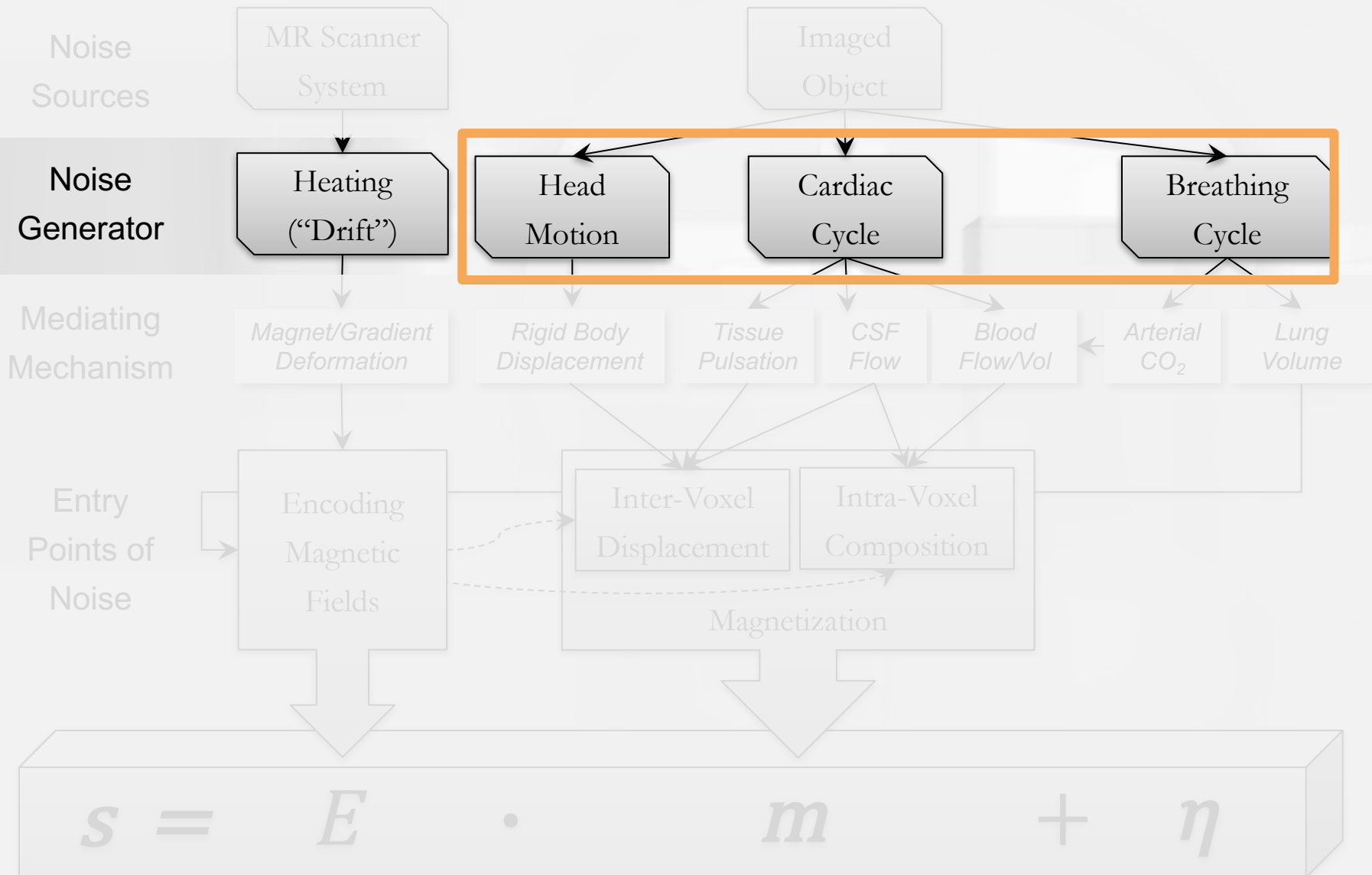


- Modeling:
 - Filters, projections (e.g. to independent components) etc. are all linear operations
 - Combination in one design matrix, together with task
 - Simple test of correction efficacy: F-test on nuisance regressors
- Preprocessing:
 - The data \mathbf{y} entering the GLM is altered $\Rightarrow \mathbf{y}' = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$
 - For non-linear changes of \mathbf{y} or inter-voxel dependencies, alteration outside GLM necessary



- Problem: No inherent measure of efficacy (F-test in GLM), correlation with task regressors undetected
- “Advantage”: No loss of degrees of freedom (sensitivity of F-test)
 - But it is only a hidden loss, statistics for inference is biased, if performed modeling is not incorporated
- Modeling via GLM recommended, if possible
 - Drifts, Motion Regressors
 - RETROICOR, HRV, RVT
 - aCompCor, (ICA)

Noise Correction Targets





- Correction for motion artifacts is actually a combination of Preprocessing and modeling
- Preprocessing cannot correct spin-history effects, intra-volume movements (non-rigid!), small partial volume effects
- Preprocessing:
 - Realignment
 - Motion “Scrubbing”
- Modeling (from estimated realignment parameters)
 - Retrospective Modeling: Motion Regressors
 - Motion Censoring



- Best: Avoid subject motion in the first place
- Better: Use Prospective Motion Correction
- Standard: Perform rigid-body realignment, use parameters as nuisance regressors
 - 6 parameters: translation+rotation
 - 12 parameters: include derivatives (for temporal shifts)
 - 24 parameters: include squared regressors
- 24-parameter model known as Volterra expansion

Friston, MRM, 1996

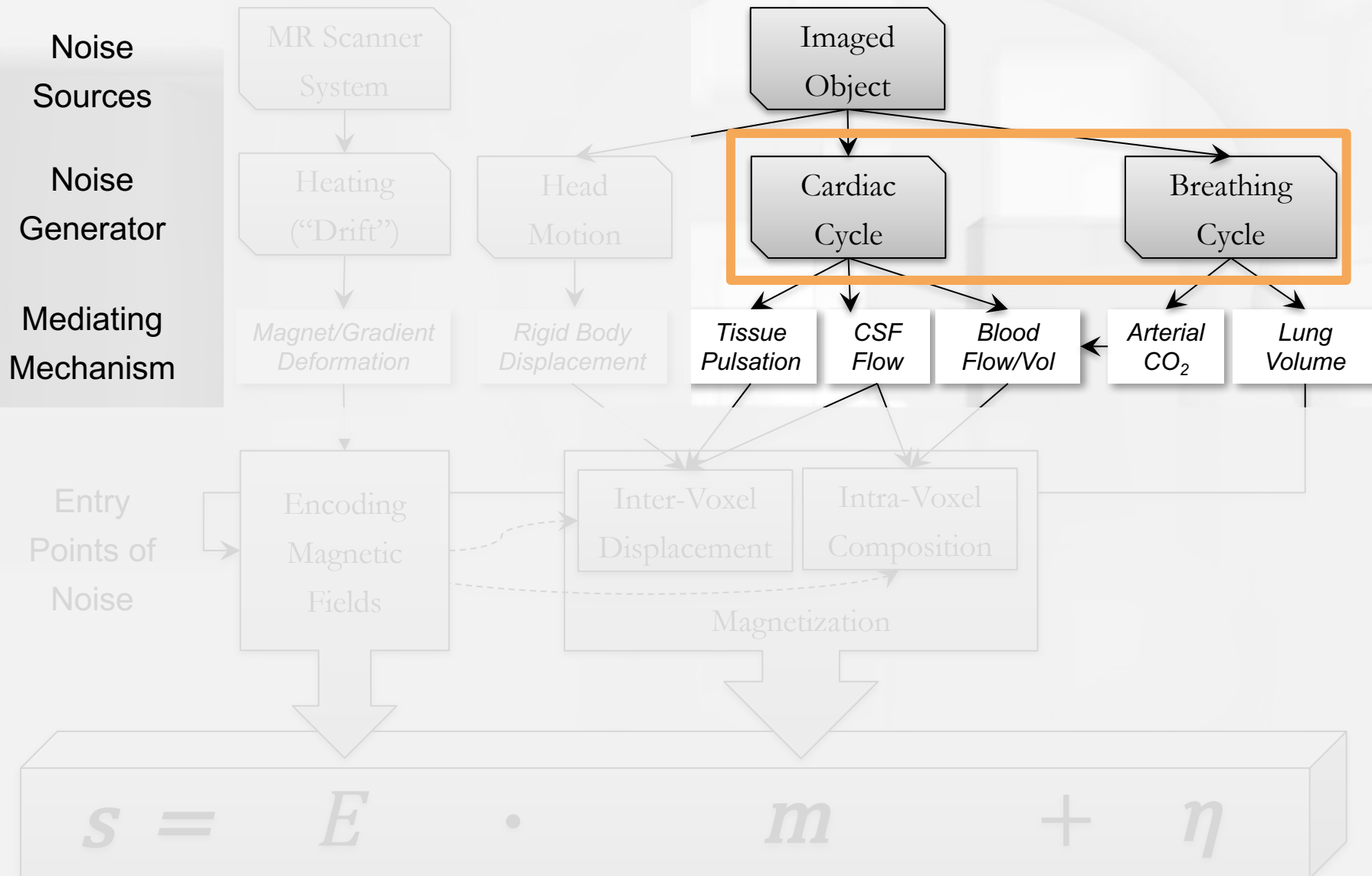
Motion Censoring = “Scrubbing”



- Detect outlier volumes (strong movement, but also spikes, RF flip angle fluctuations)
- Inform the GLM of these bad volumes via stick regressors (zero everywhere else, 1 at volume)
 - Will absorb all variance of that volume
- Problem: Temporal filtering before GLM might create Gibbs ringing of outliers into neighbors
- Alternative: censoring during preprocessing
 - interpolate faulty volume by neighbors

Power, NeuroImage, 2012

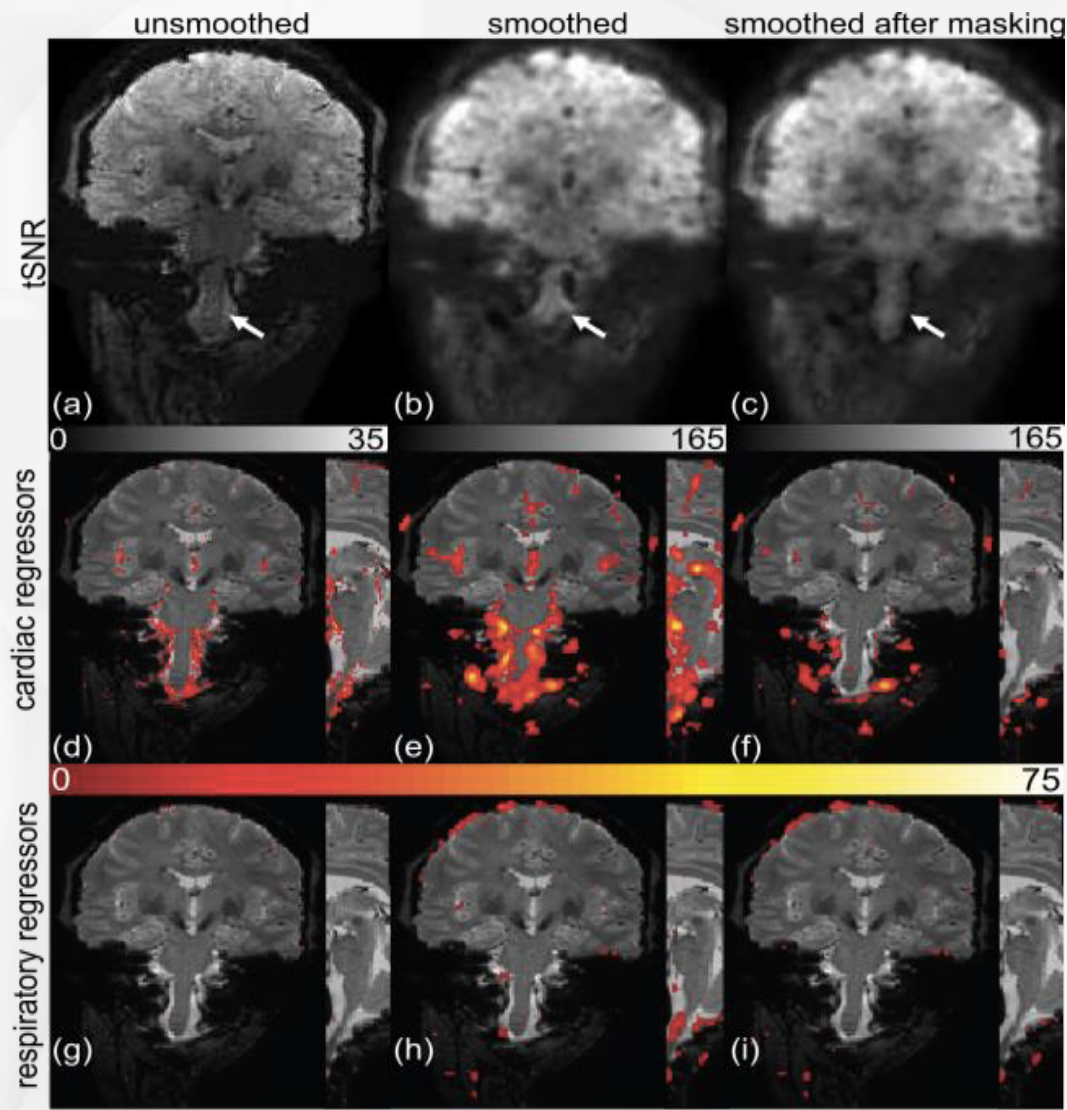
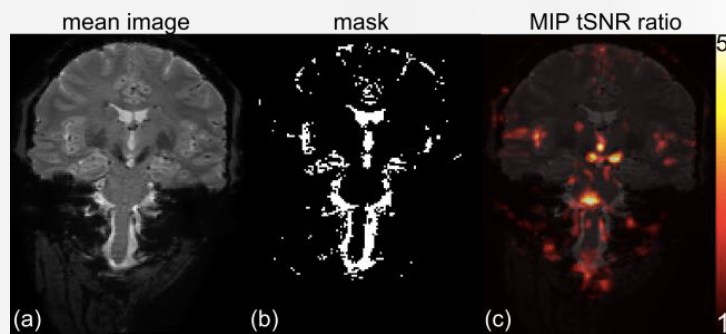
Noise Correction Targets



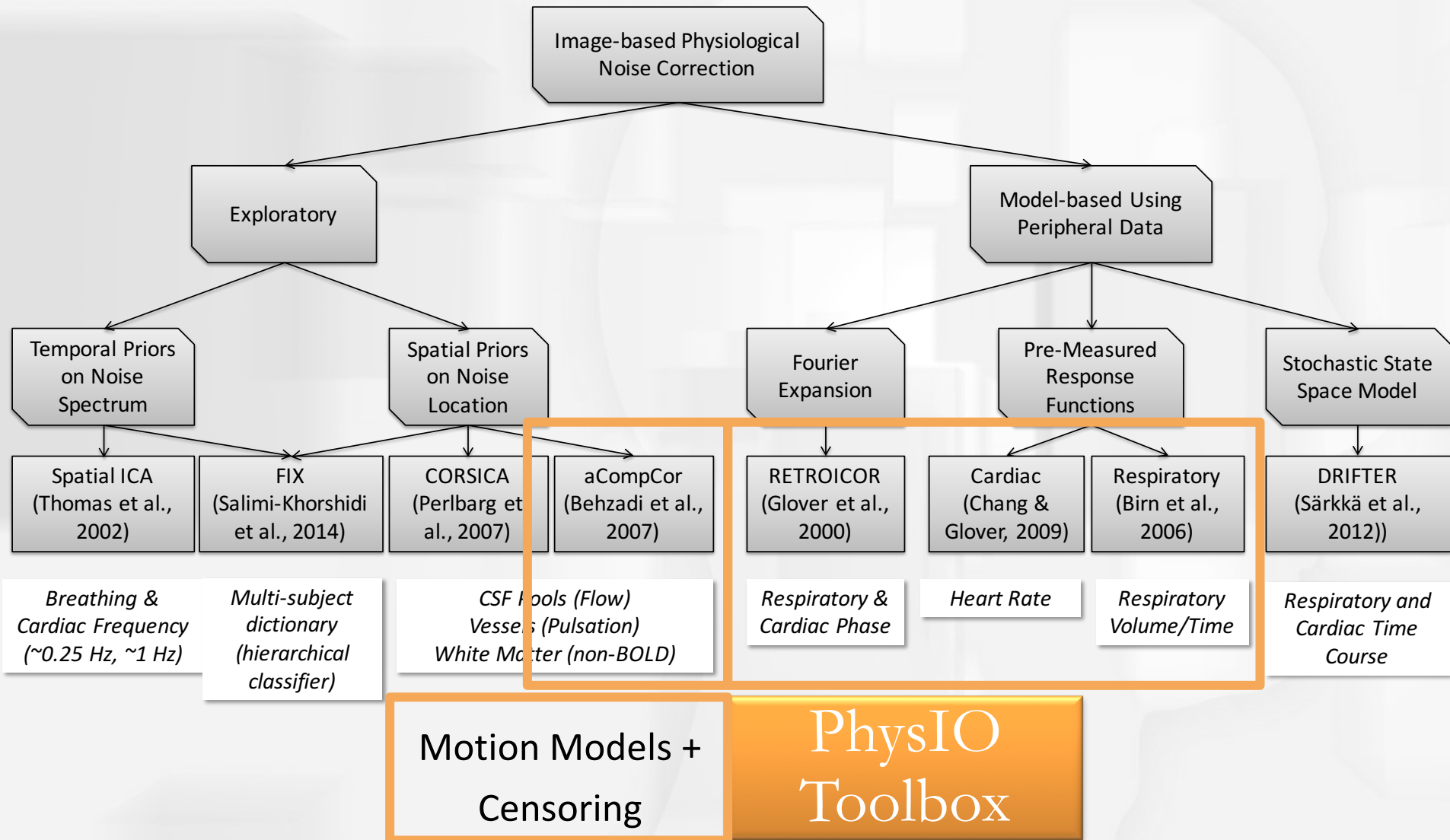
Solution I: Mask it out!



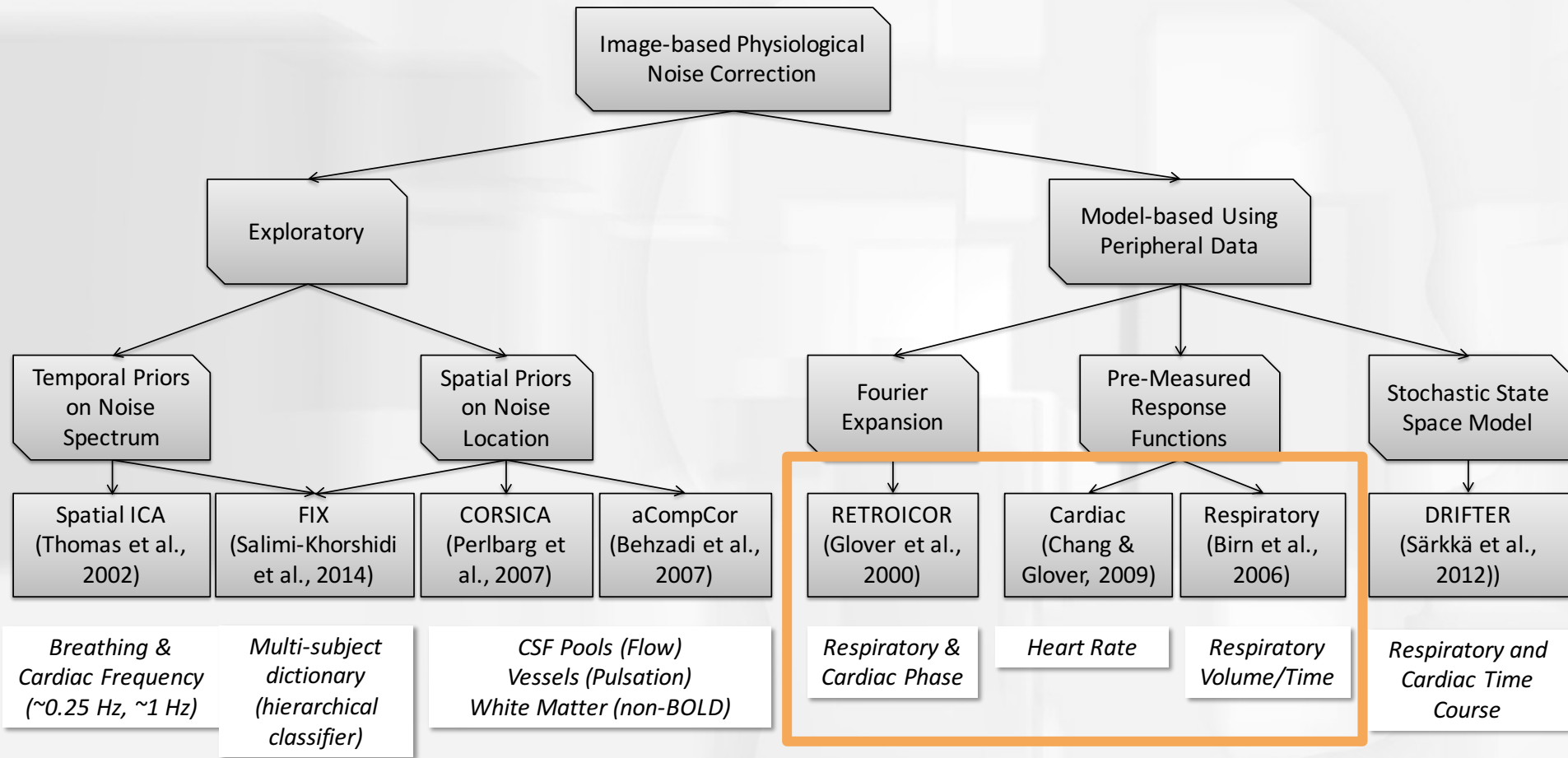
- Physiological noise origins close to, but not *in* gray matter
- High resolution data (1.25mm): mask CSF & vessels, then smooth!
 - *Vionnet 2015, ISMRM*



Solution II: Image-based Correction



Model-based Phys Noise Correction





RETROspective Image CORrection

Cardiac Response Function

Respiratory Response Function

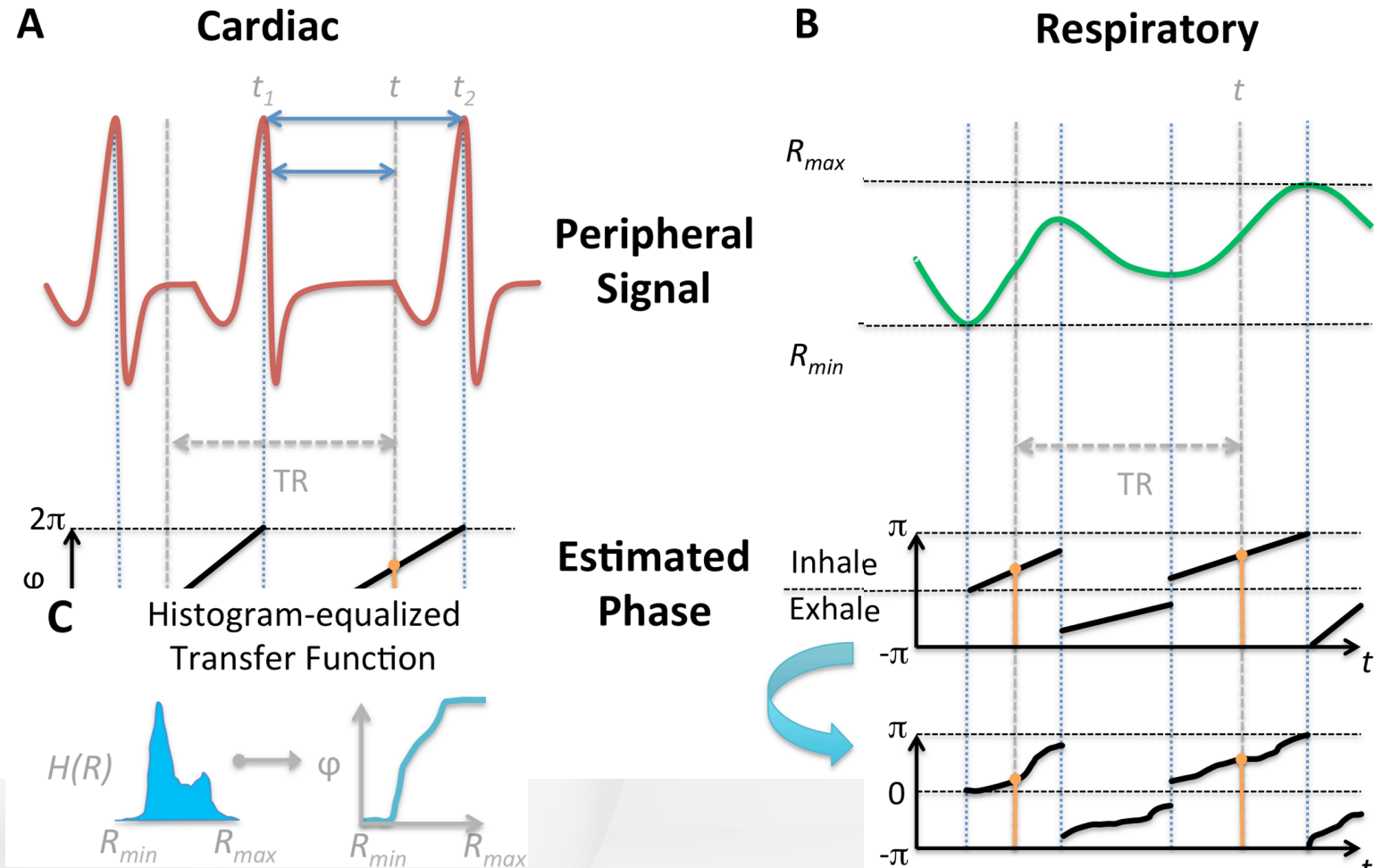
- Cardiac/respiratory phase φ_c φ_r
- Fourier expansion (cosine/sine)
- Heart Rate
- convolved with CRF
- Resp. Volume per Time
- convolved with RRF
- evaluated at 1 time point (slice) per volume = regressor

Noise Modeling



RETROspective Image CORrection

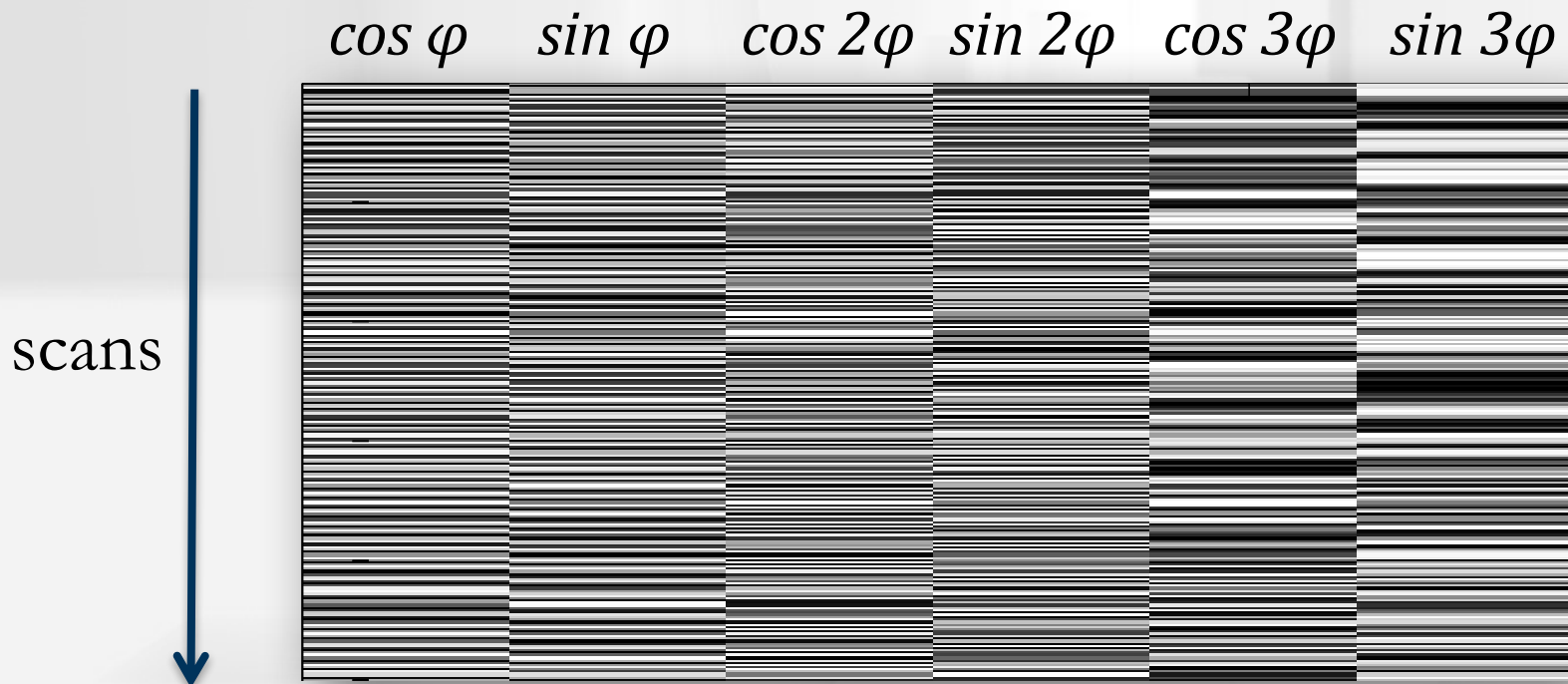
Cardiac/respiratory phase
Function φ_C φ_r Response Function



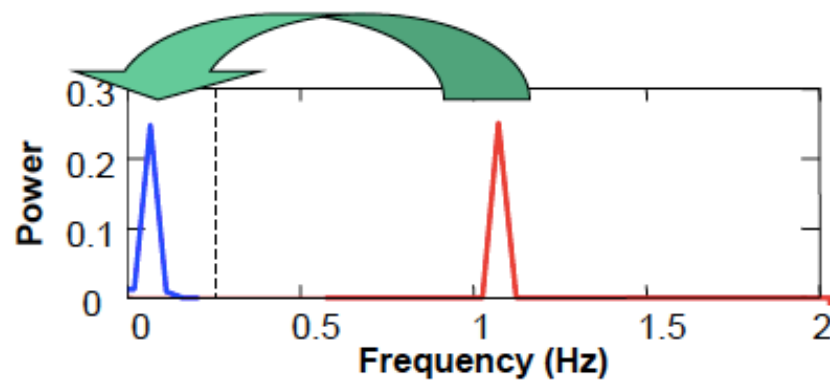
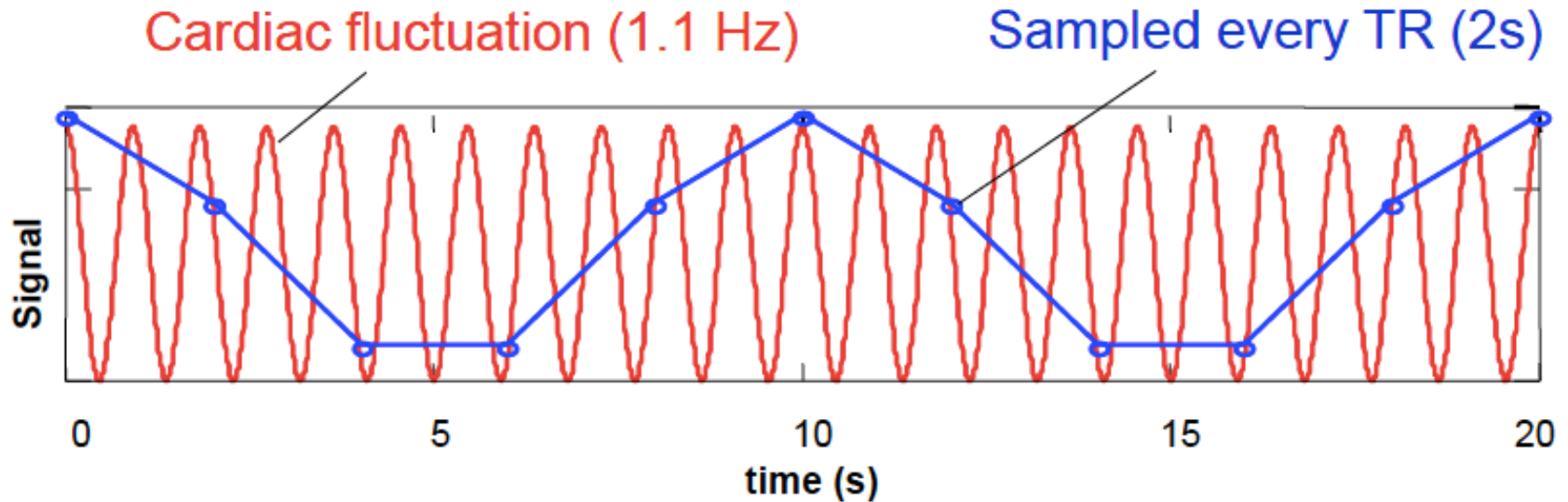
Model: Fourier Phase Expansion



- Cosine and sine to allow for constant phase shifts per voxel
- Higher model orders to account for under-sampling of physiological frequencies with typical TR in fMRI



Aliasing of Physiology



Courtesy: R. Birn, HBM 2015

RETROspective
Image CORrection

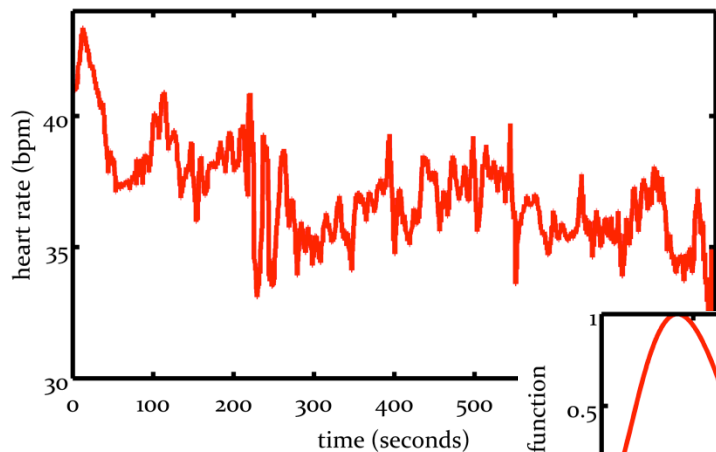
Cardiac Response
Function

Respiratory
Response Function

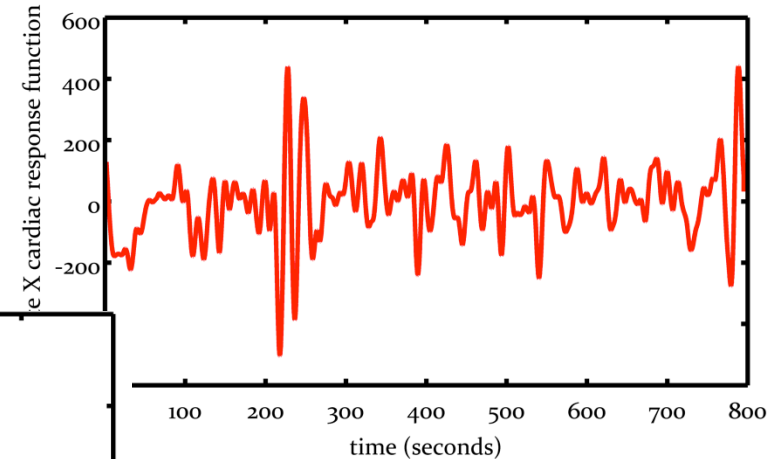
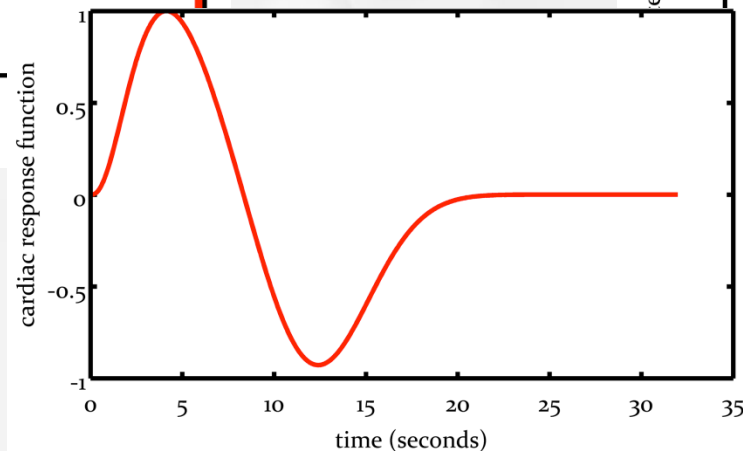
- Heart Rate

- convolved with

- Heart Rate Variability
Response Regressor



CRF



Noise Modeling



RETROspective
Image CORrection

Cardiac Response
Function

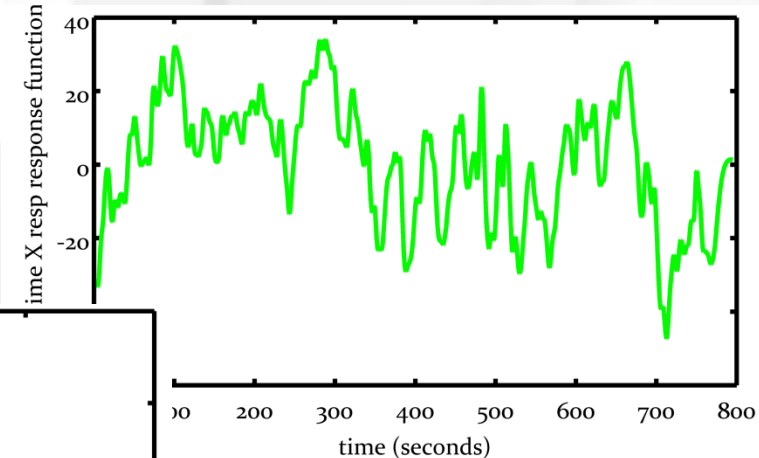
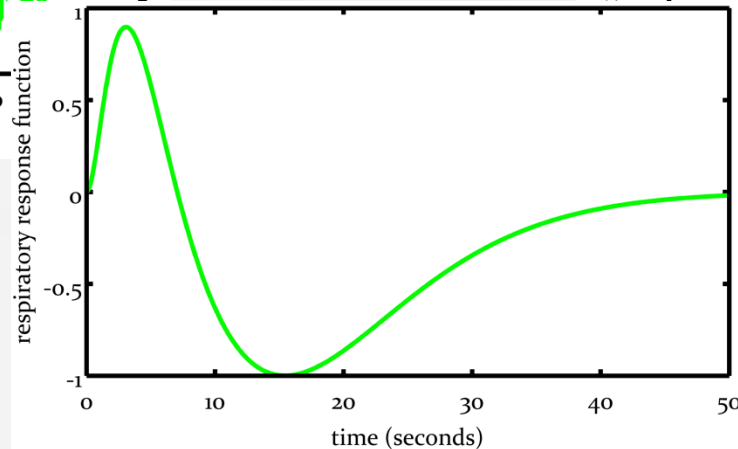
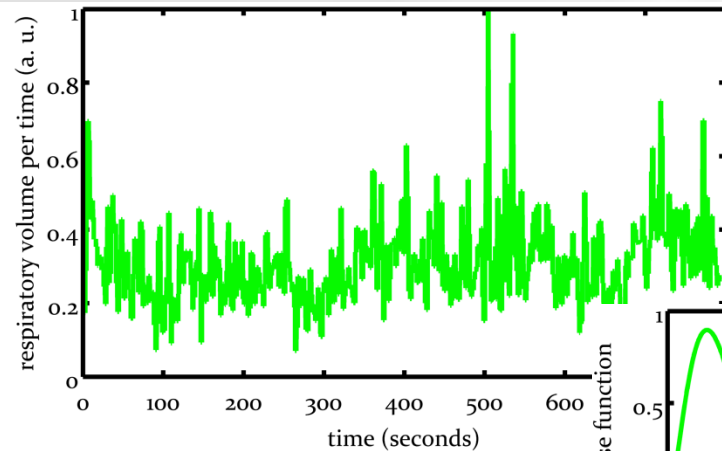
Respiratory
Response Function

■ Respiratory
Volume per Time

■ convolved with

■ Respiratory Volume
per Time Regressor

RRF



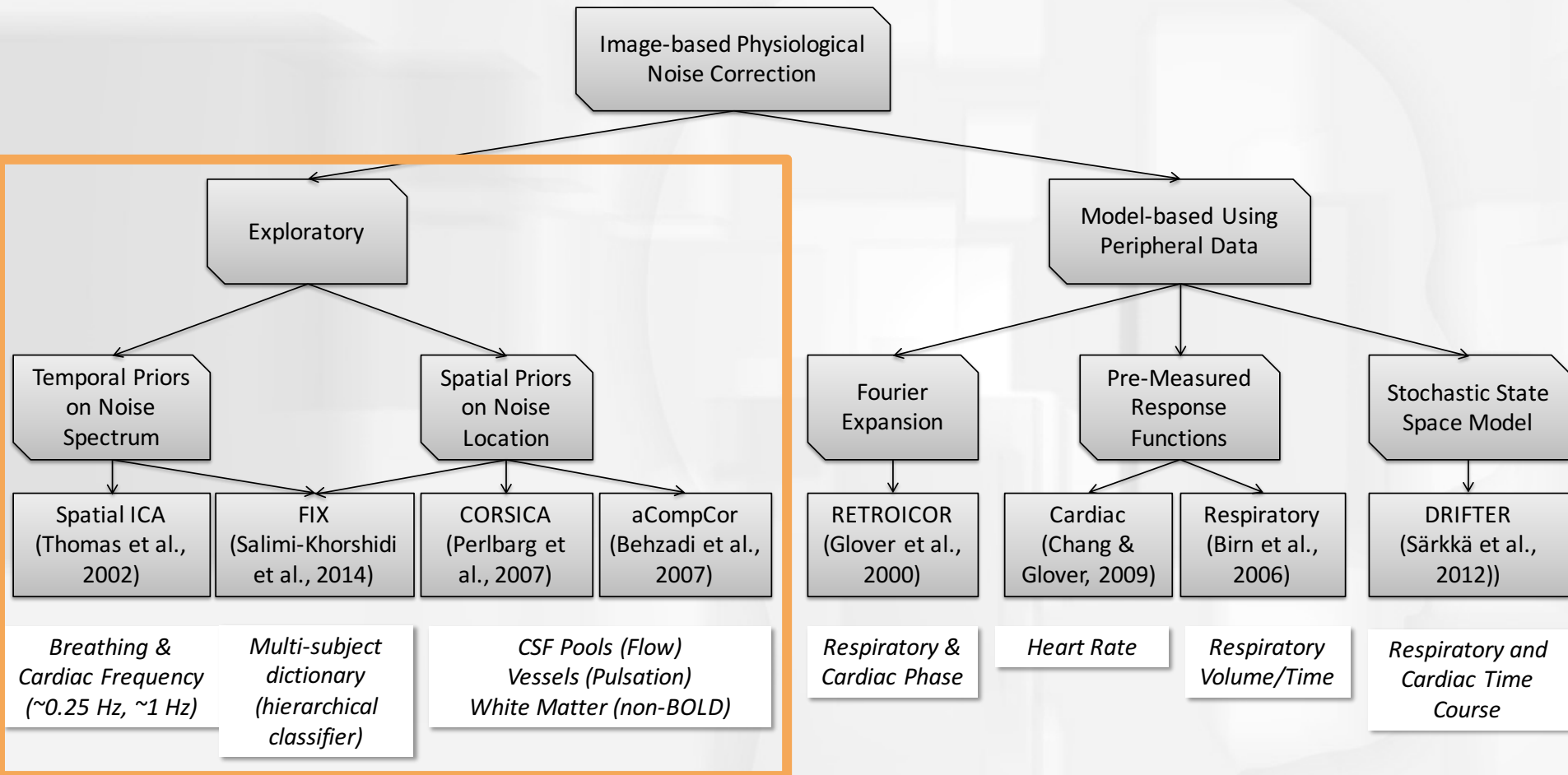


- Assuming convolution of heart rate/respiratory variability time course with unknown response function

$$y = X_r h_r + X_h h_h + \varepsilon$$

Chang, Cunnningham, Glover, 2009

Exploratory Phys Noise Correction





- Use priors about physiological noise to identify noise components (time series)
 - Spatial Priors: Mechanisms of physiological noise implicate physiological noise in CSF, blood vessels
 - Temporal Priors: Knowledge about typical physiological frequency contents (heart ~ 1 Hz, breathing 0.2-0.4 Hz)
 - Note that simple filtering is impossible (cf. aliasing)
 - Population Priors: Use dictionary learning from manually labelled training set of subjects (FIX)

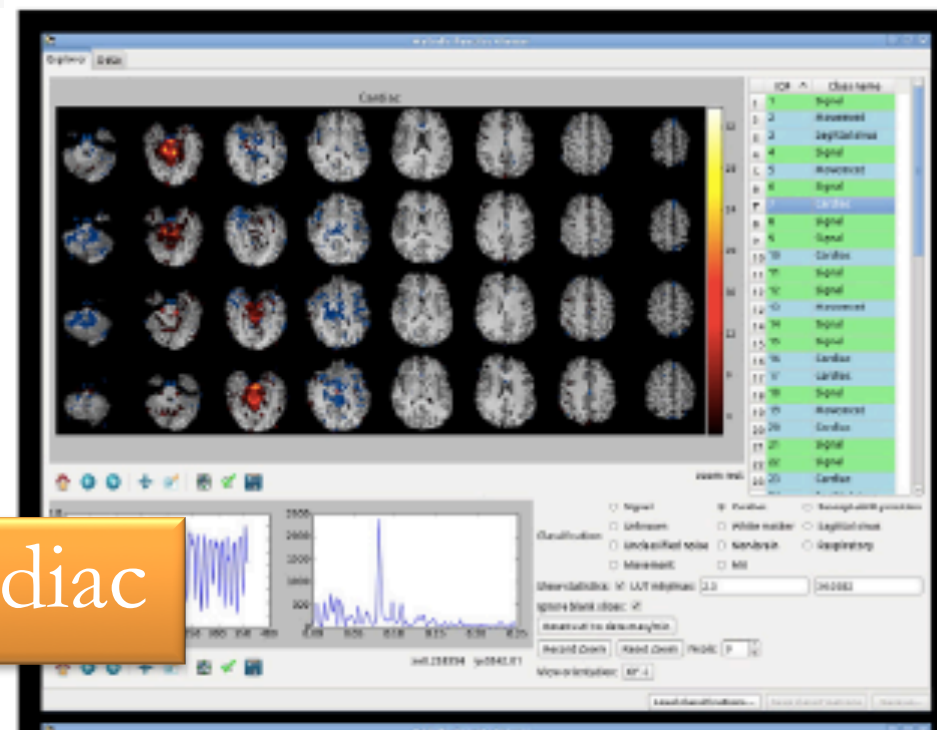
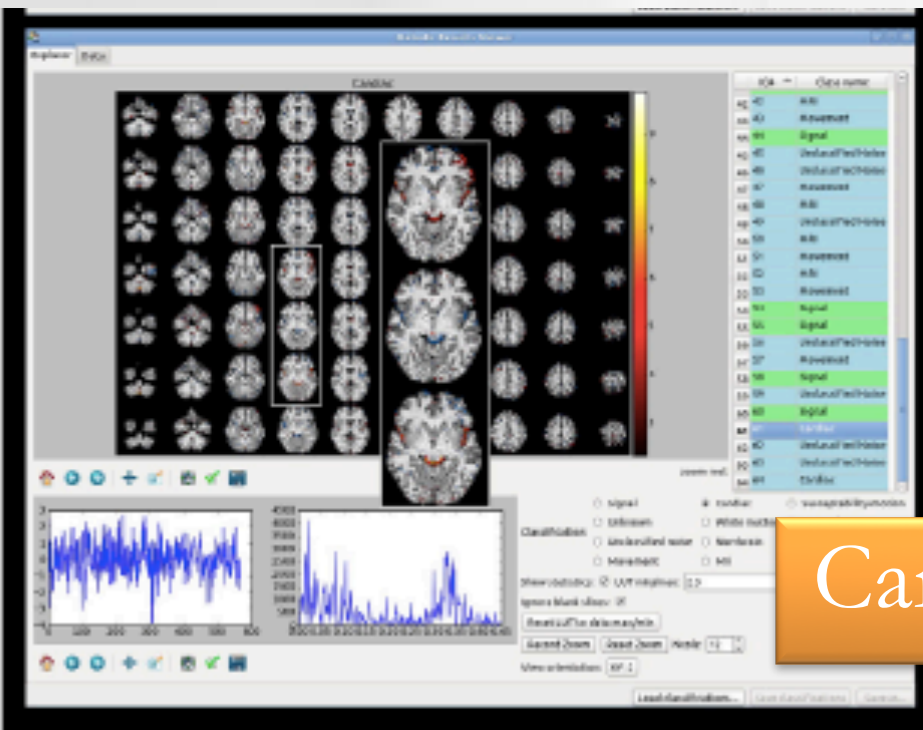


- Methods to extract components (i.e. summarize ROIs/spectra) differ:
 - Maximum variance time series: Principal Component Analysis (PCA) from region of interest (aCompCor, Behzadi 2007)
 - Maximally independent time courses/sites: spatial/temporal ICA, FSL MELODIC, FIX
- aCompCor is basically identical to a seed-based correlation analysis in resting-state fMRI
 - Here: seed is in region-of-no-interest and correlated time series regressed out
 - See resting state analysis for more details

Preprocessing Techniques



- FSL MELODIC, FIX



Cardiac



- Non-linear models
 - DRIFTER: Kalman Filter, Bayesian, *Joint* Stochastic State-space model of peripheral physiology and BOLD
- Identify noise via task test-retest reproducibility
 - PHYCAA: e.g. via high-freq. autocorrelation, anatomy
 - GLMDnoise: PCA of noise regressors
- MEICA: Multi-Echo ICA
 - Use diff. TE-images to decompose proton density from $T2^*$ changes

Särkkä, NeuroImage, 2012

Churchill, NeuroImage, 2012/13

Kay, Front. Neurosc., 2013

Olafsson, NeuroImage, 2015



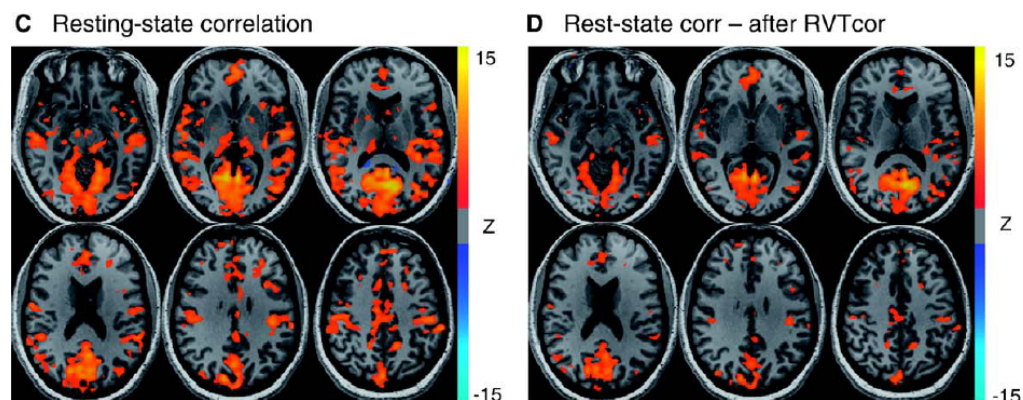
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When? – Literature Evidence



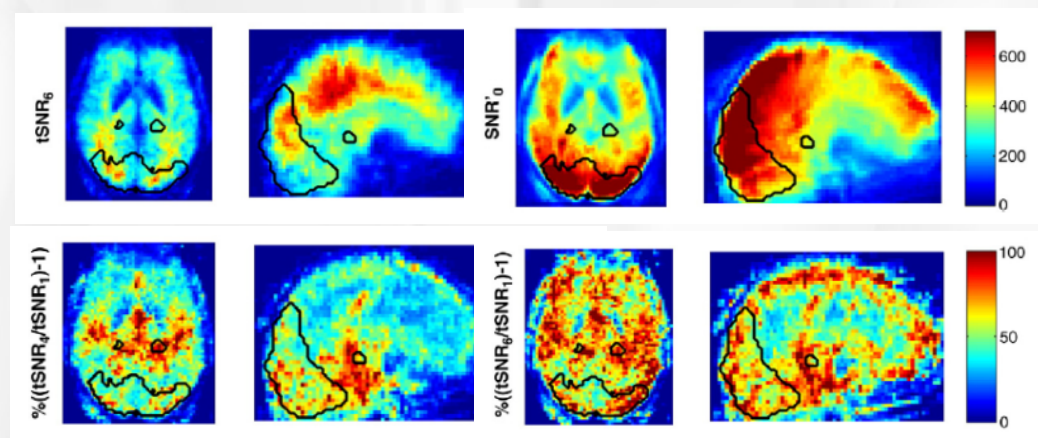
■ Resting-state:

- Birn, R. M. “The Role of Physiological Noise in Resting-state Functional Connectivity.” *NeuroImage* 62, 2012
- Birn, R. M., et al. “Separating Respiratory-variation-related Fluctuations from Neuronal-activity-related Fluctuations in fMRI.” *NeuroImage* 31, 2006



■ Task-based:

- Hutton, C., et al. “The Impact of Physiological Noise Correction on fMRI at 7 T.” *NeuroImage* 57, 2011:





- Physiological noise correction not a default pre-processing step in task-based fMRI
- Reasons
 - Impact on group level fMRI
 - no reports for non-trivial paradigms
 - Existing Toolboxes lack...
 - robust, automatic implementation
 - dealing with variable peripheral data quality



- Hierarchical learning of trustworthiness of advisor over time
- Contrasts: Prediction and Prediction Error about advice



recommendations of adviser were **veridical** (pre-recorded videos from behavioural study)

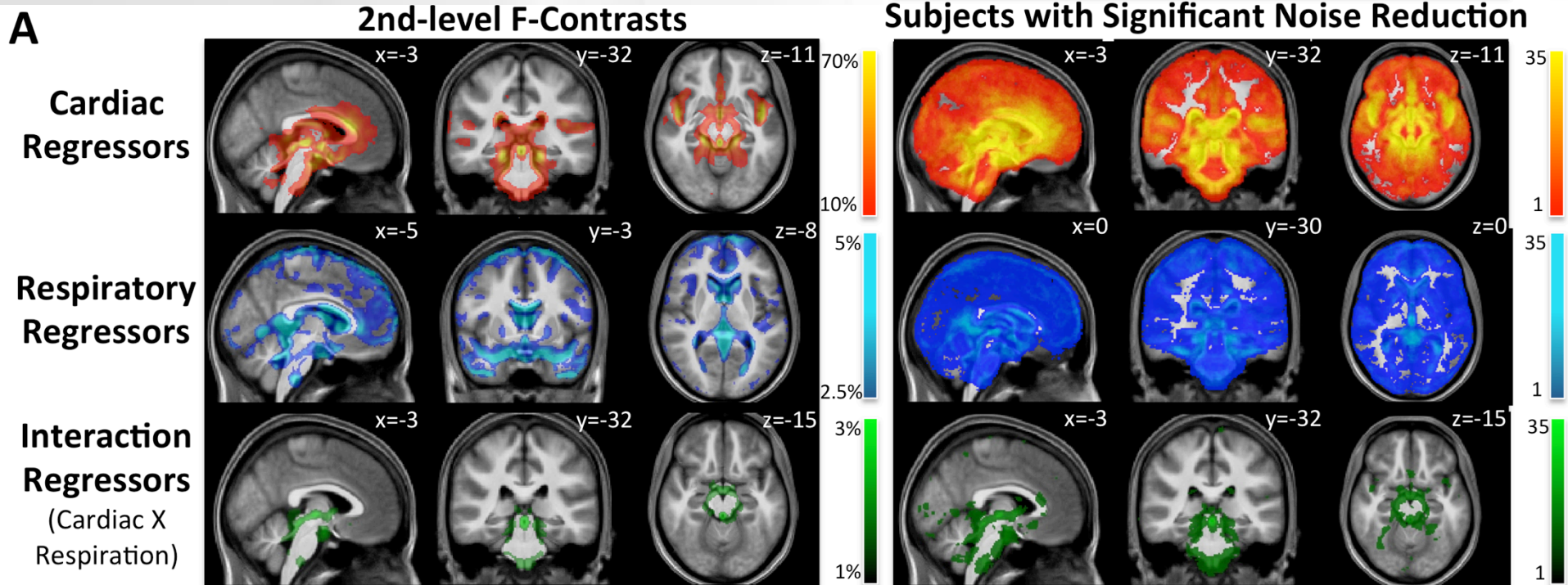
volatility of advice (changing intentions of adviser through incentive structure)

interactive, gender-matched (**40** male subjects)

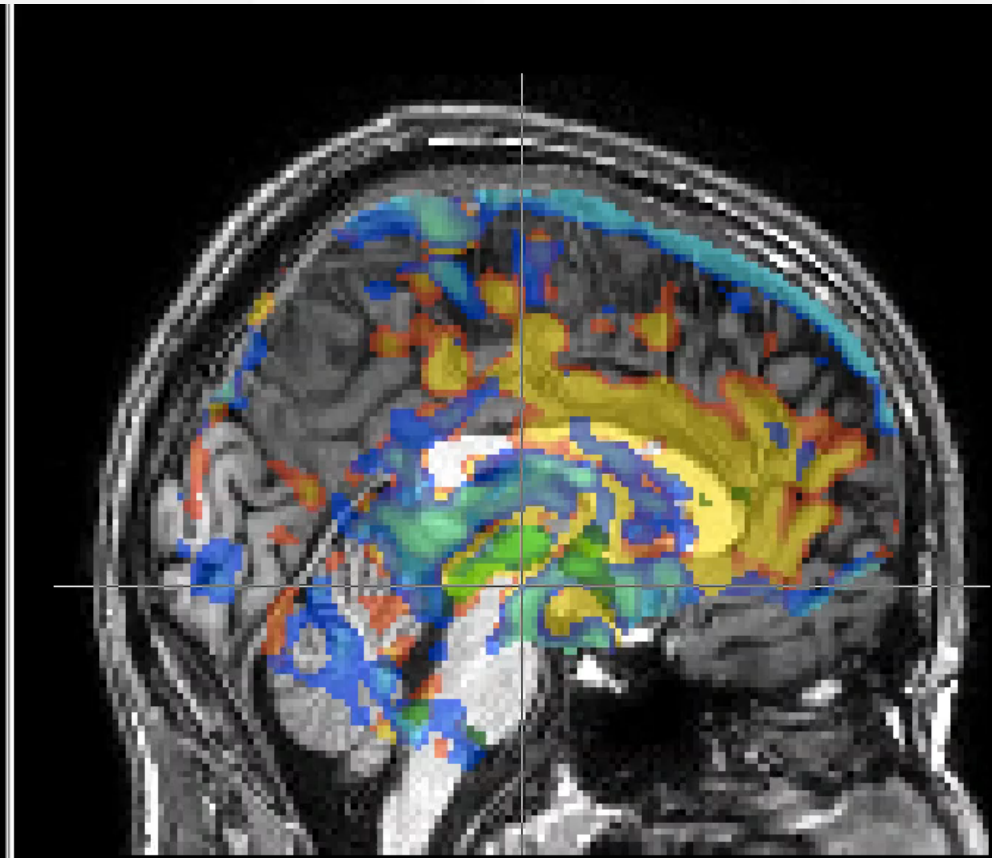
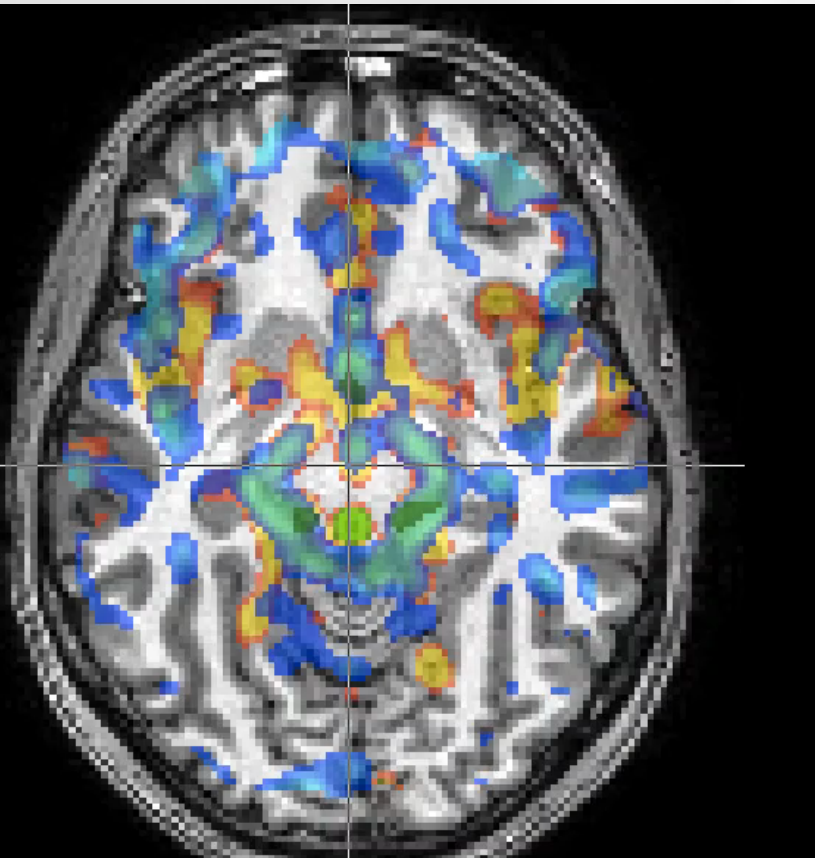
fMRI design: Philips Achieva 3T
TR/TE 2500/36ms, 2 x 2 x 3 mm³

Diaconescu et al, 2014, PLoS Comp. Biol.

- Andreea Diaconescu (TNU): Social Learning Experiment 2012-2014, (N=35)
- F-contrast: Where does physiological noise model explain significant variance?

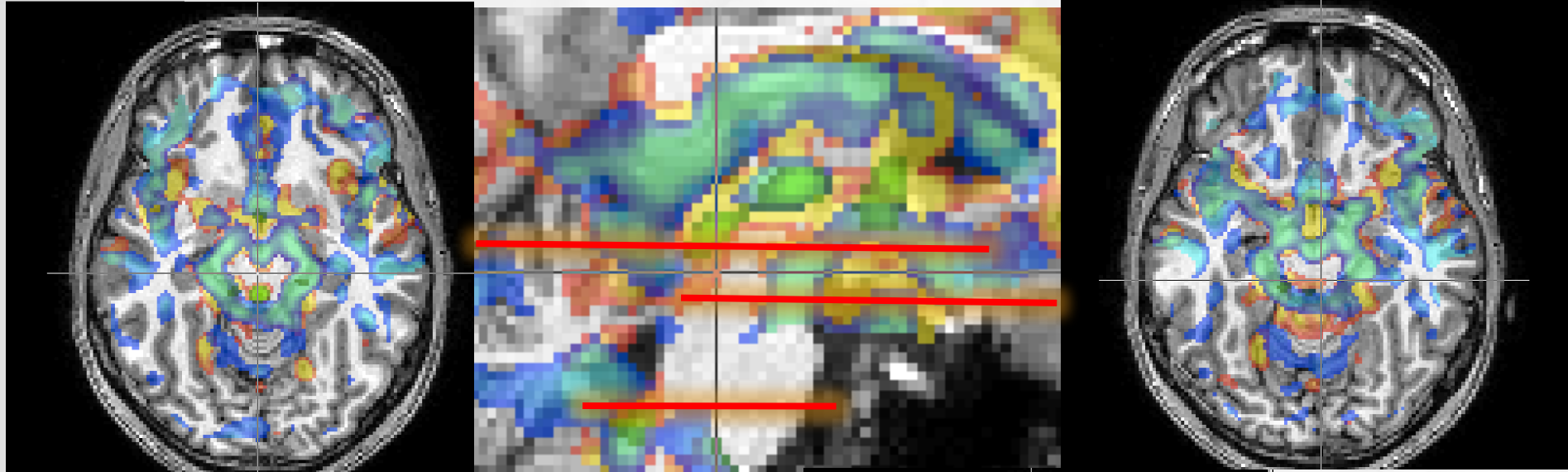


- cardiac (red), respiratory (blue), cardXresp (green)

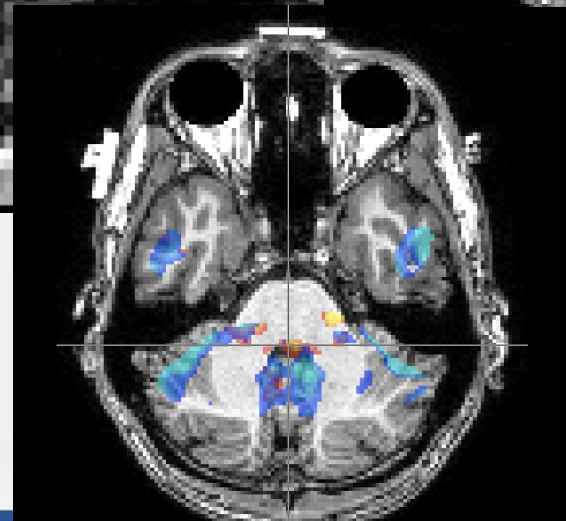


- VTA (DA)

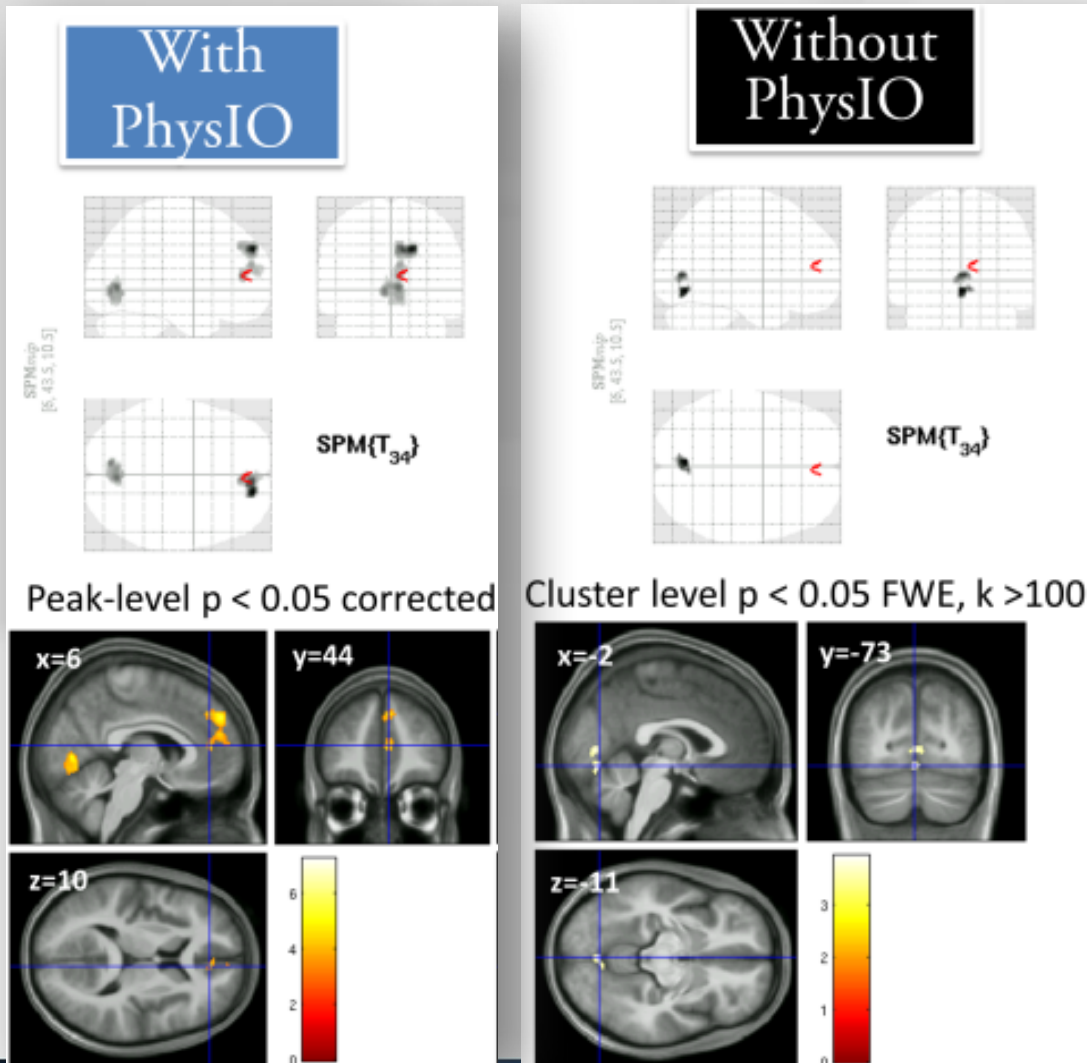
- Raphe Nuclei (5-HT)



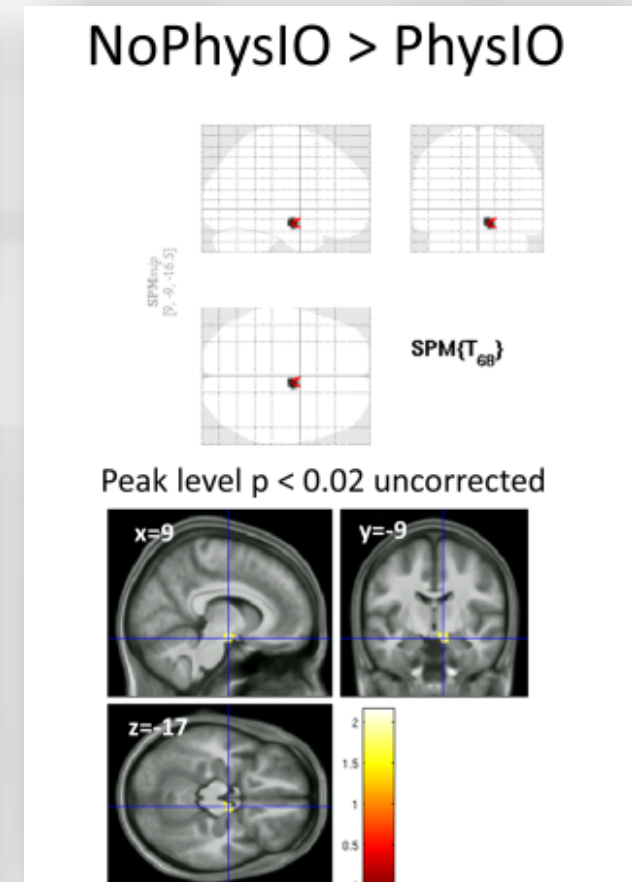
- Locus coeruleus (NA)



Higher Sensitivity

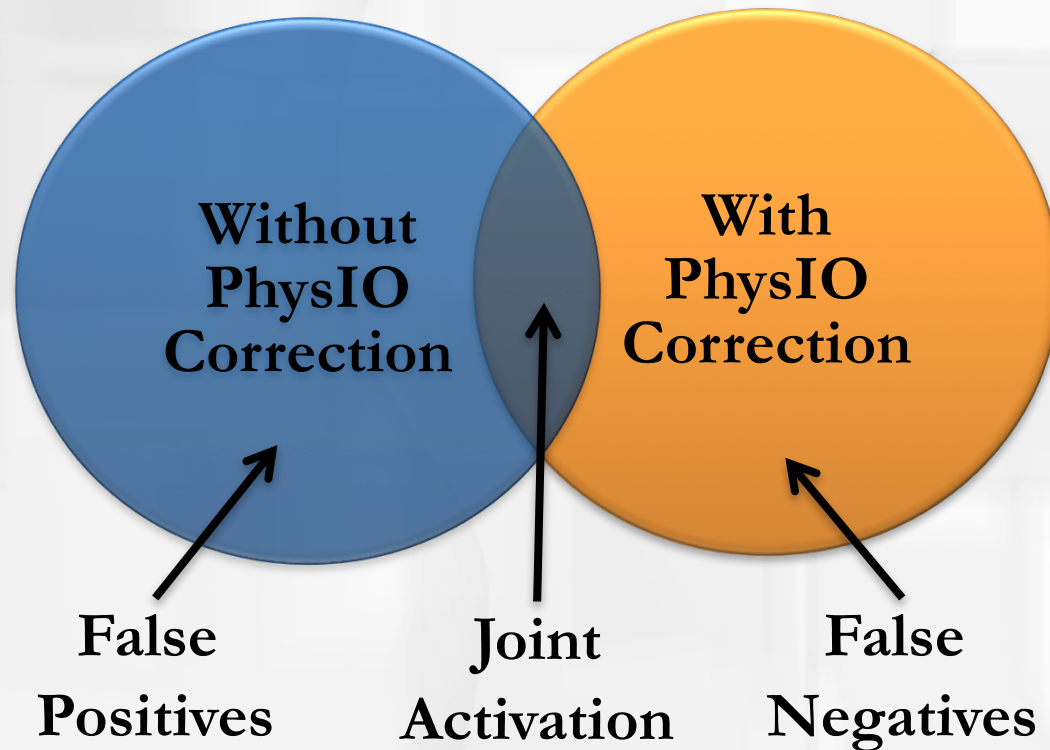


False Positives



2nd level t-contrast
Social Prediction Error

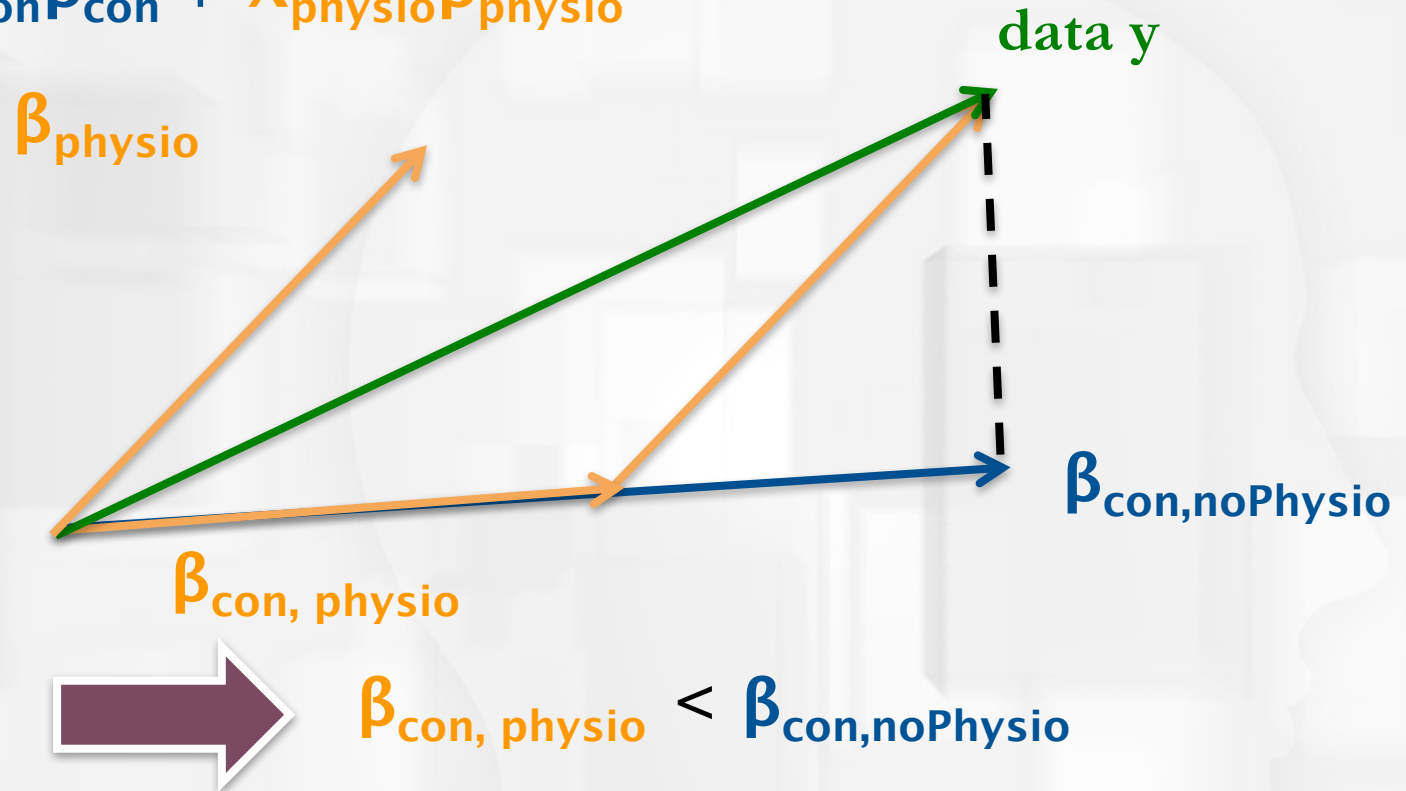
Significant Clusters



Noise modeling impact on task?



$$y = X_{\text{con}}\beta_{\text{con}} + X_{\text{physio}}\beta_{\text{physio}}$$



- Phys noise correction can change parameter estimates for regressors of interest (correlation!)
- Thereby change distribution of $\beta \Rightarrow$ Mean? Variance?

Group Effect: Correlated Regressors

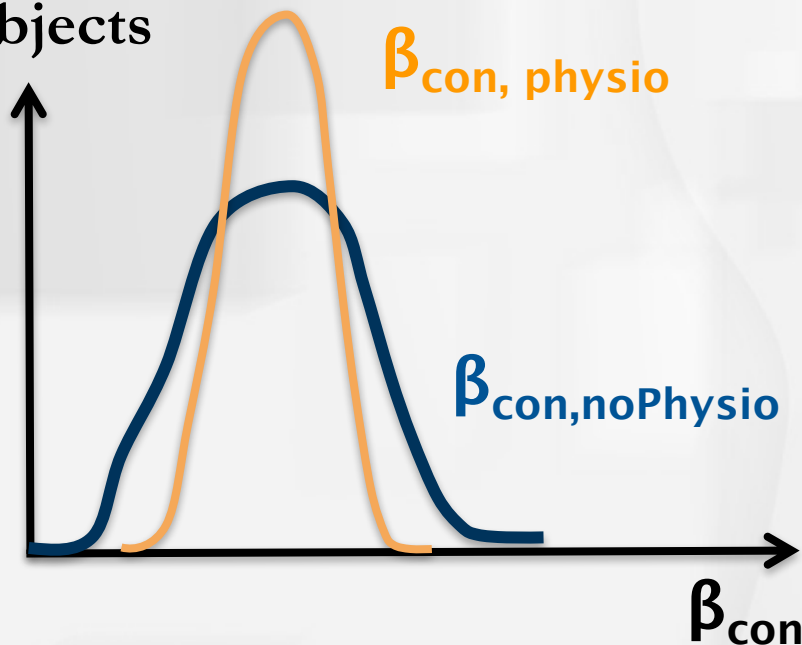


- Two mechanisms imaginable

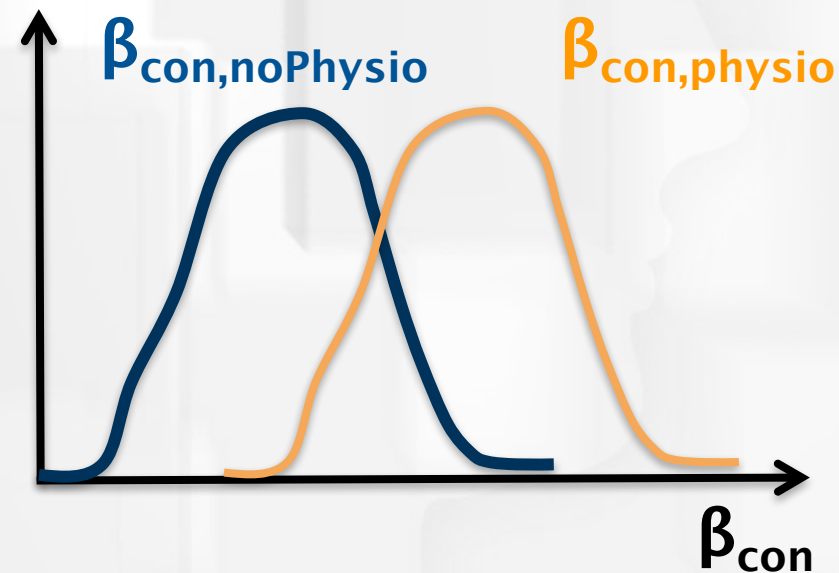
Reduced inter-subject
variance

Increased inter-subject
mean estimates

frequency of
subjects



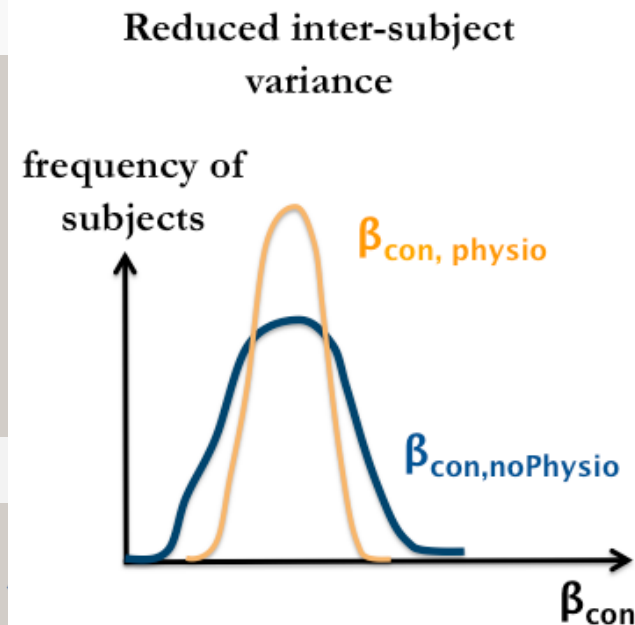
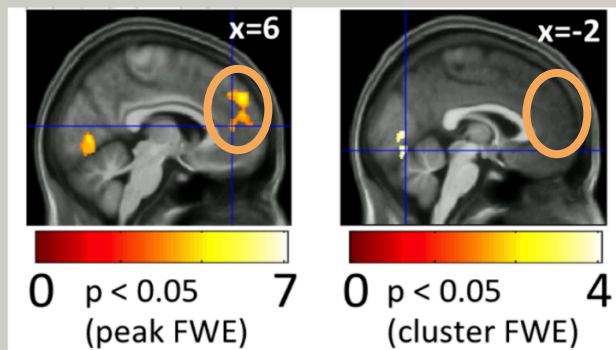
frequency of
subjects



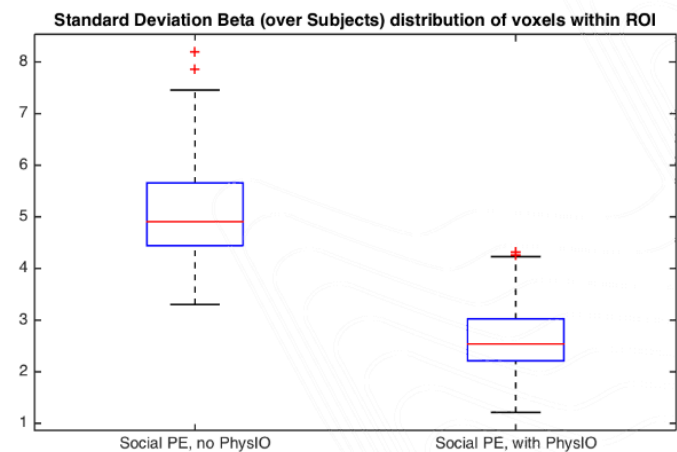
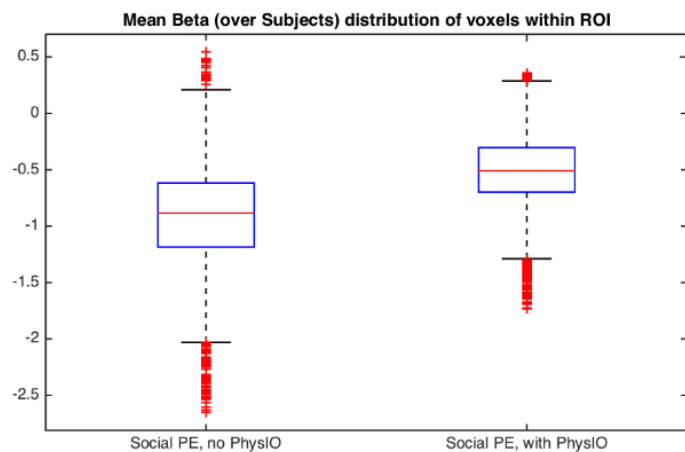
The Corrective Mechanism



Social Pred. Error



Mean





- MRI Time Series Recap and Noise Sources
 - Why de-noising? Structured Noise; Noise Pathways
- Noise Correction Approaches
 - Method: Modeling VS Preprocessing
 - Target: Motion, Cardiac/Breathing Cycle
 - Input: fMRI Data VS Peripheral Measures
- Prospects for Improving Group Statistics
- **Limitations**
 - Degrees of Freedom; Task-related “noise”; Interoception



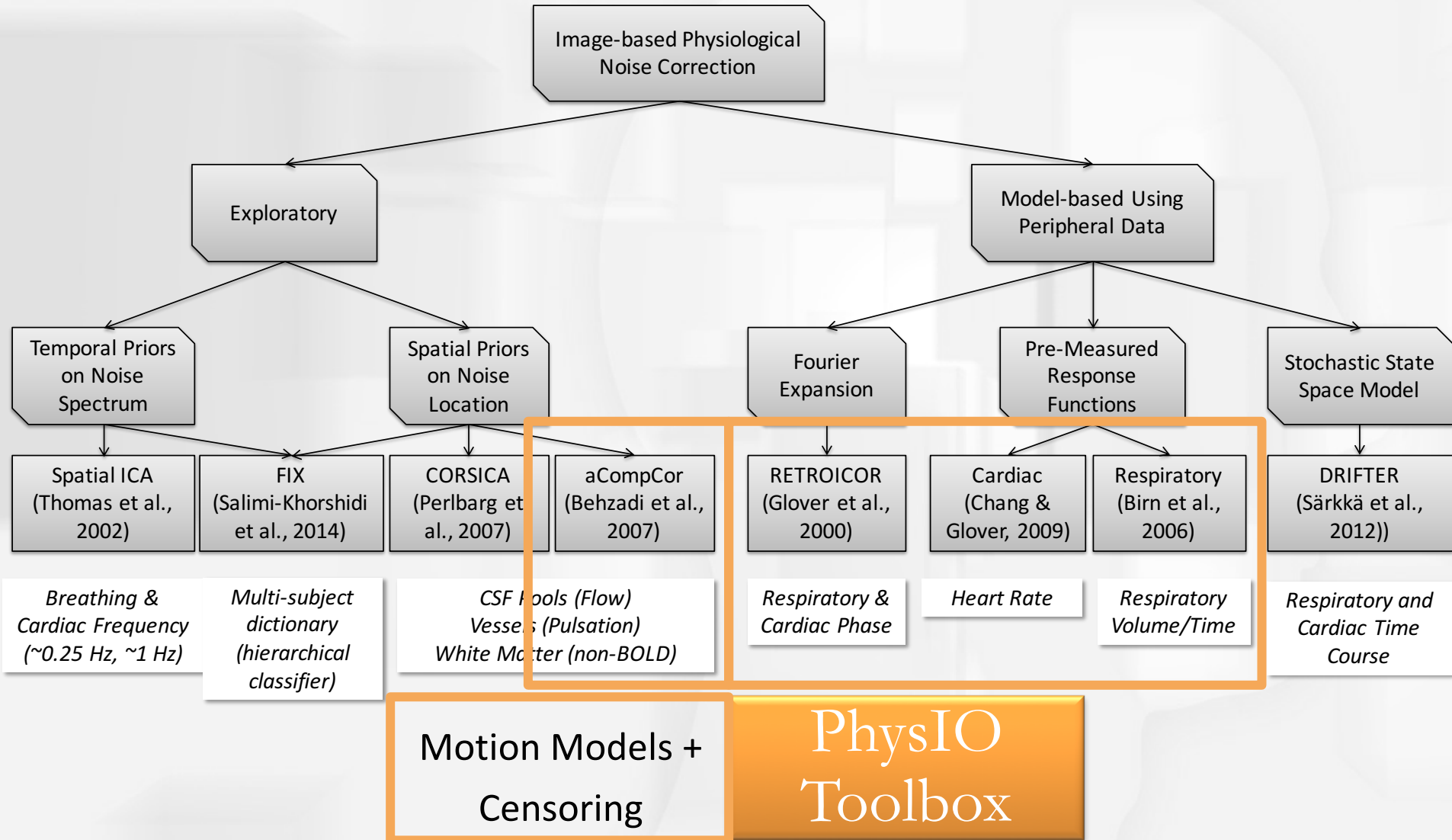
- Degrees of freedom, sensitivity reduced by too many ineffective regressors
 - F-test informative
- Intrinsic correlations of functional areas of interoception and peripheral physiology
 - E.g. Amygdala, Insula, ACC
 - Controversial reading:
[fMRI of the Amygdala: All In Vein? – Neuroskeptic](#)
 - Alternative: Masking, Pure anatomical priors removing CSF, angiography (vessels)



- MRI Time Series and Physiological Noise
- Model-based Correction
- Noise Modeling Prospects: Group FX
- The PhysIO Toolbox
- Structured noise through cardiac/resp cycle (70%)
- Within the GLM, Nuisance regressors from Fourier expansion, response functions
- Increase group sensitivity (lower inter-subject variability), fewer false positives
- Correction in SPM/Matlab in practice => **NOW!**

- **Demo: The PhysIO Toolbox for Physiological Noise Correction in fMRI**
 - Features and Workflow
 - Image-based physiological noise correction in the GLM
 - RETROICOR, HRV, RVT
 - Noise-ROIs
 - Practical Demo (SPM Batch)
 - Estimating different Models
 - Understanding the Preprocessing Plots
 - Automatic Model Assessment, Diagnostics on Contrast

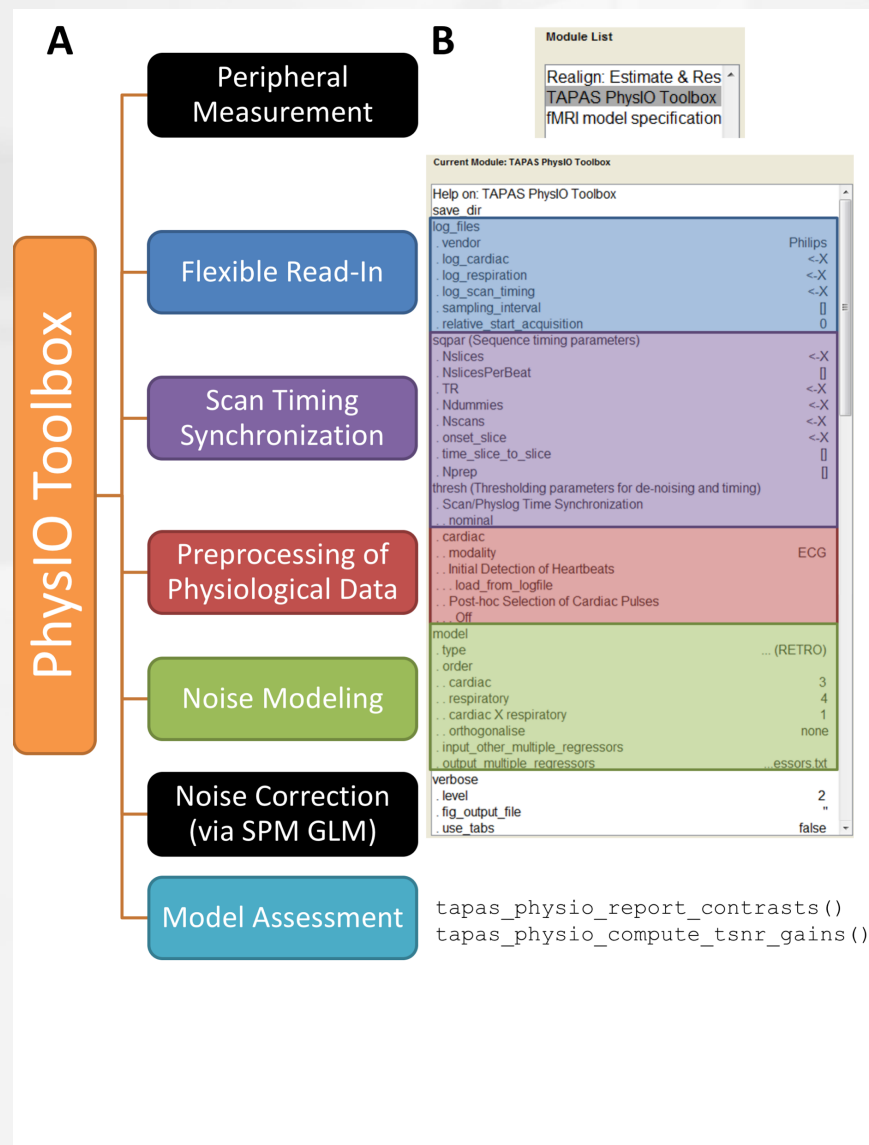
Image-based Noise Correction



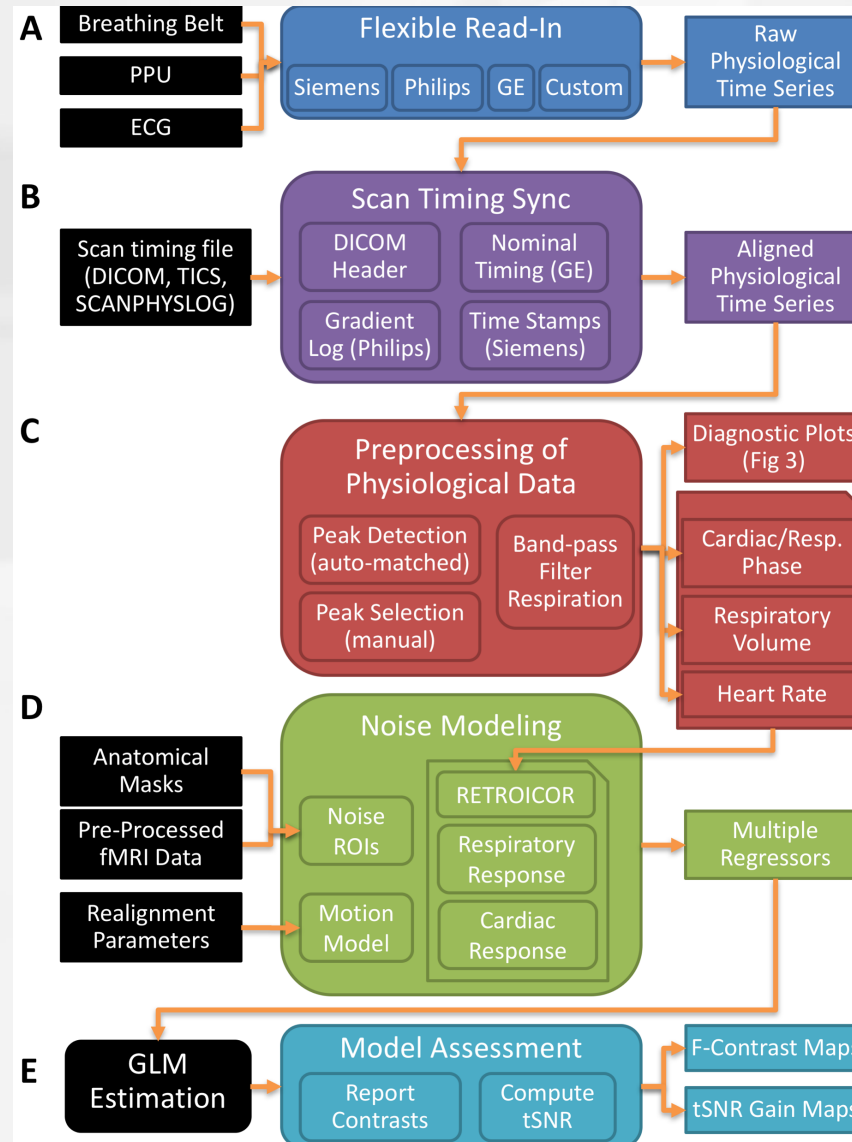


- Developed at the Translational Neuromodeling Unit (TNU) since 2008
 - Lead programmer: Lars Kasper (TNU)
 - Contributors: Jakob Heinzle (TNU), Steffen Bollmann (KiSpi Zurich)
- Part of the TNU «TAPAS» software suite
- Used at the TNU, in Zurich and beyond by ~50 researchers
 - Iglesias 2013, Neuron; Kasper 2014, NeuroImage; Bollmann 2014, PhDThesis; Sulzer 2013, NeuroImage; Hauser 2014, NeuroImage; Grueschow 2015, Neuron
- Download & Example Data:
 - <https://translationalneuromodeling.org/tapas>
 - <https://www.tnu.ethz.ch/en/software/tapas/data.html>

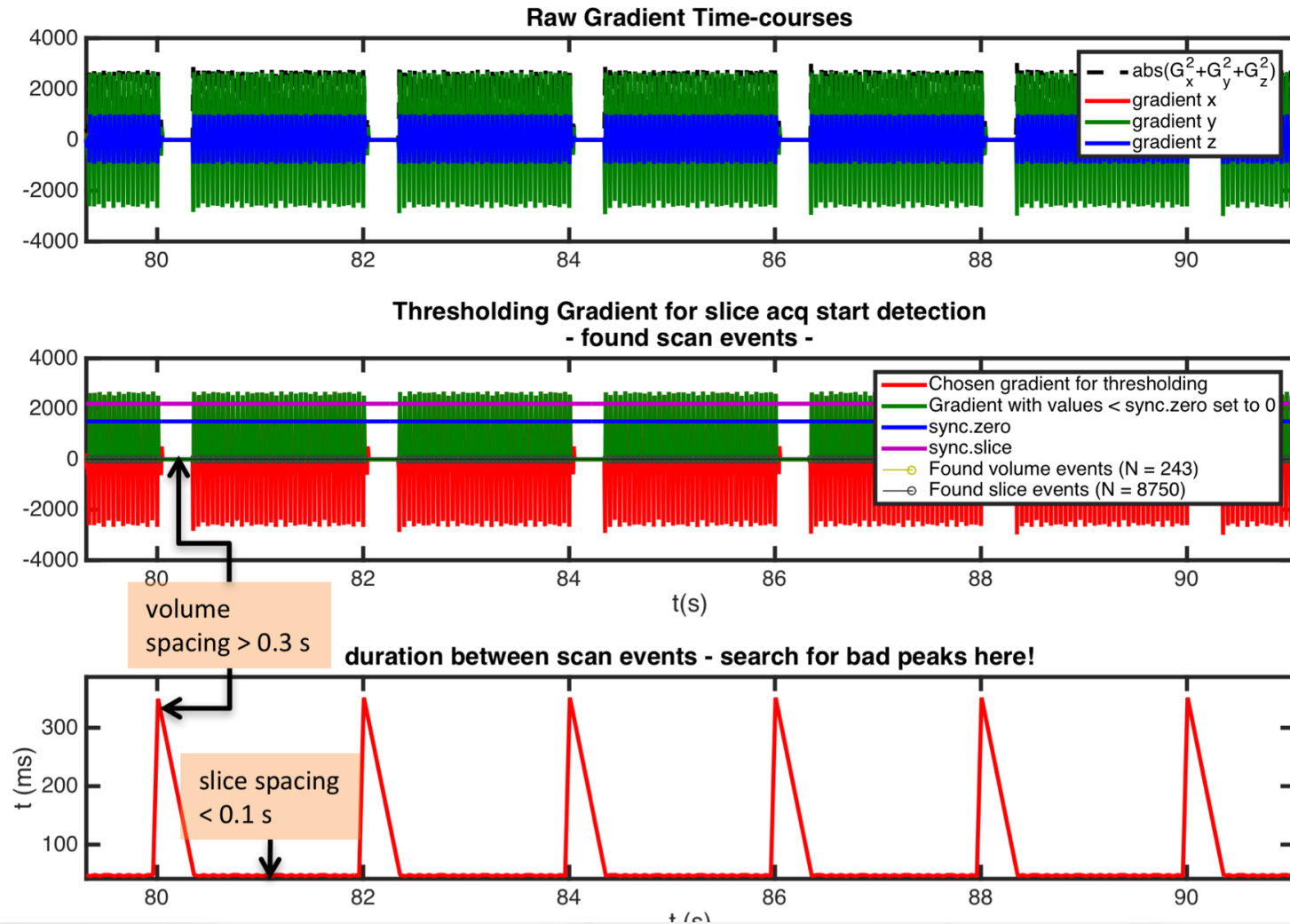
Workflow of the PhysIO Toolbox



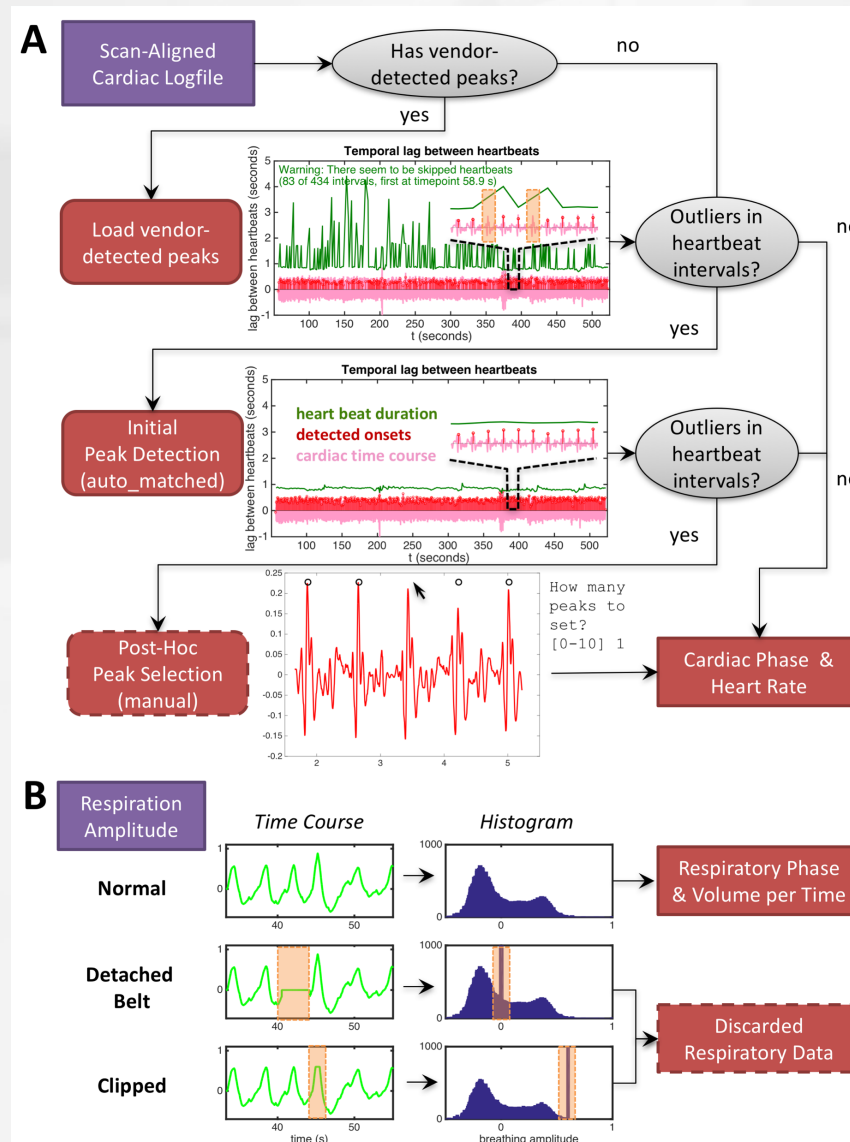
Flowchart of Noise Correction



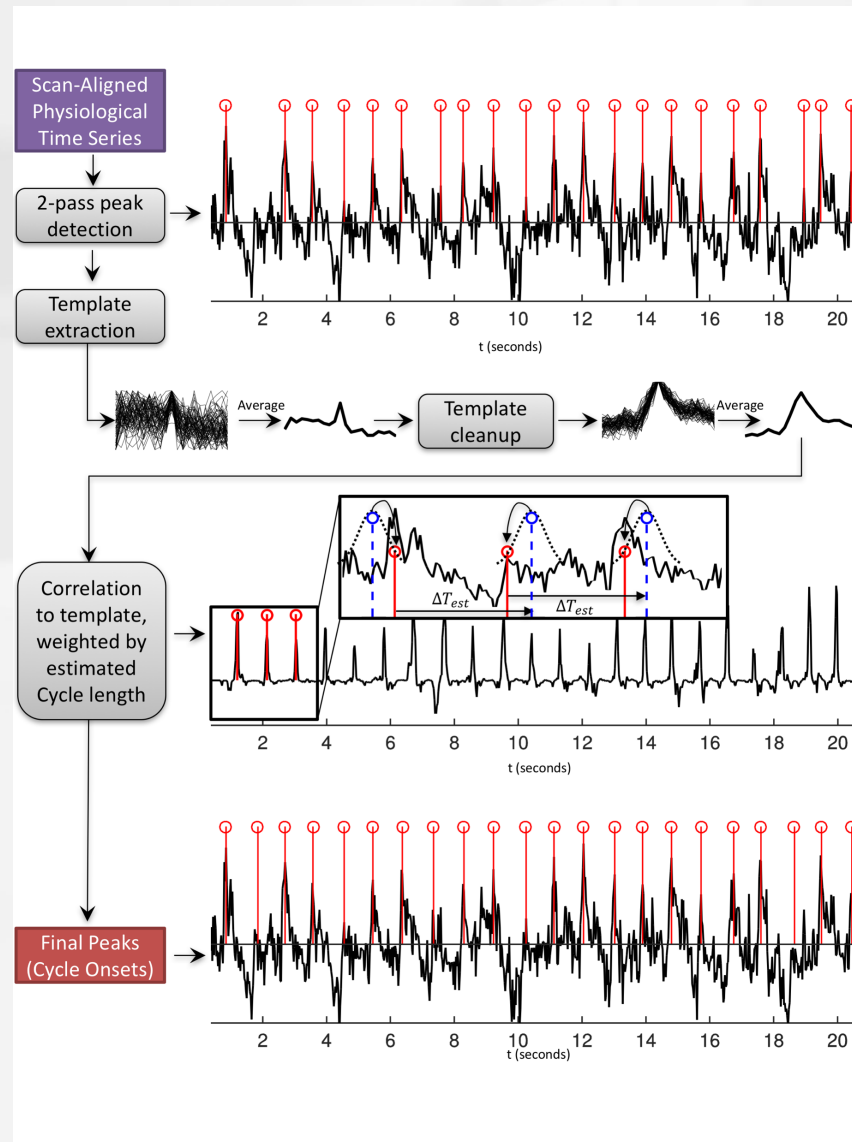
Scan Sync with Philips Gradients



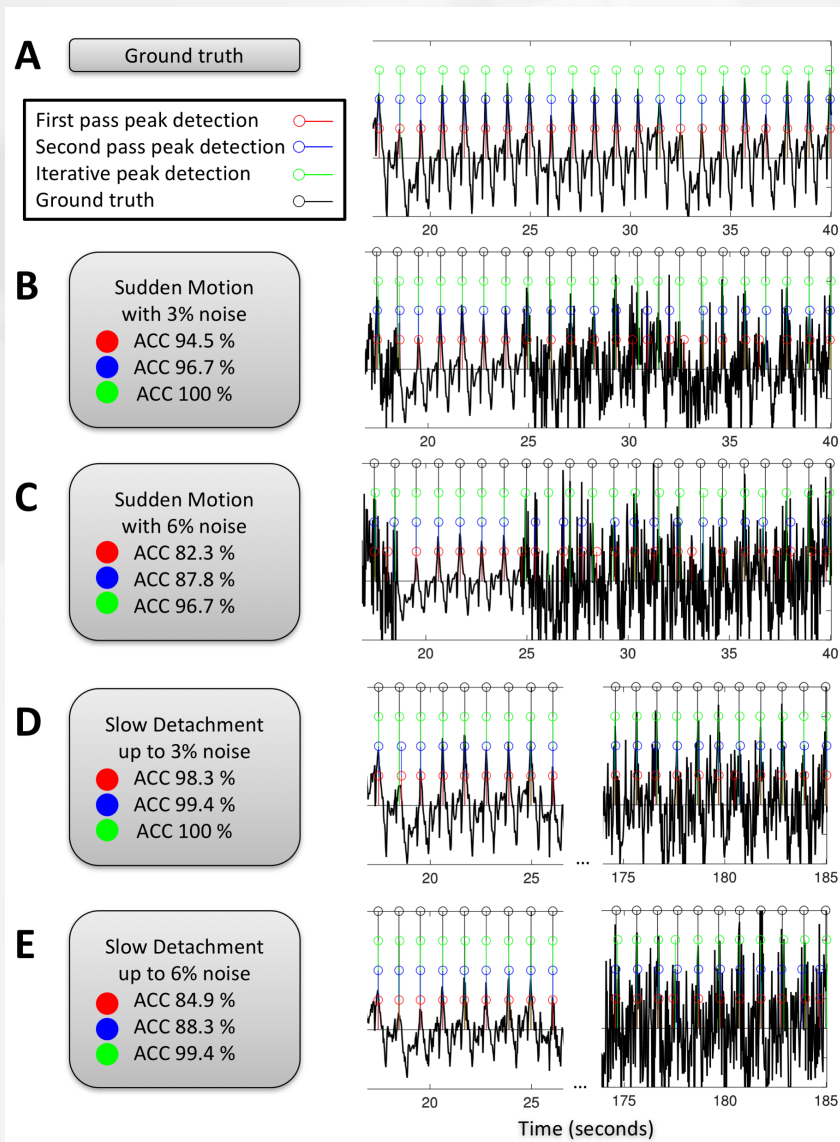
Data Preprocessing Overview



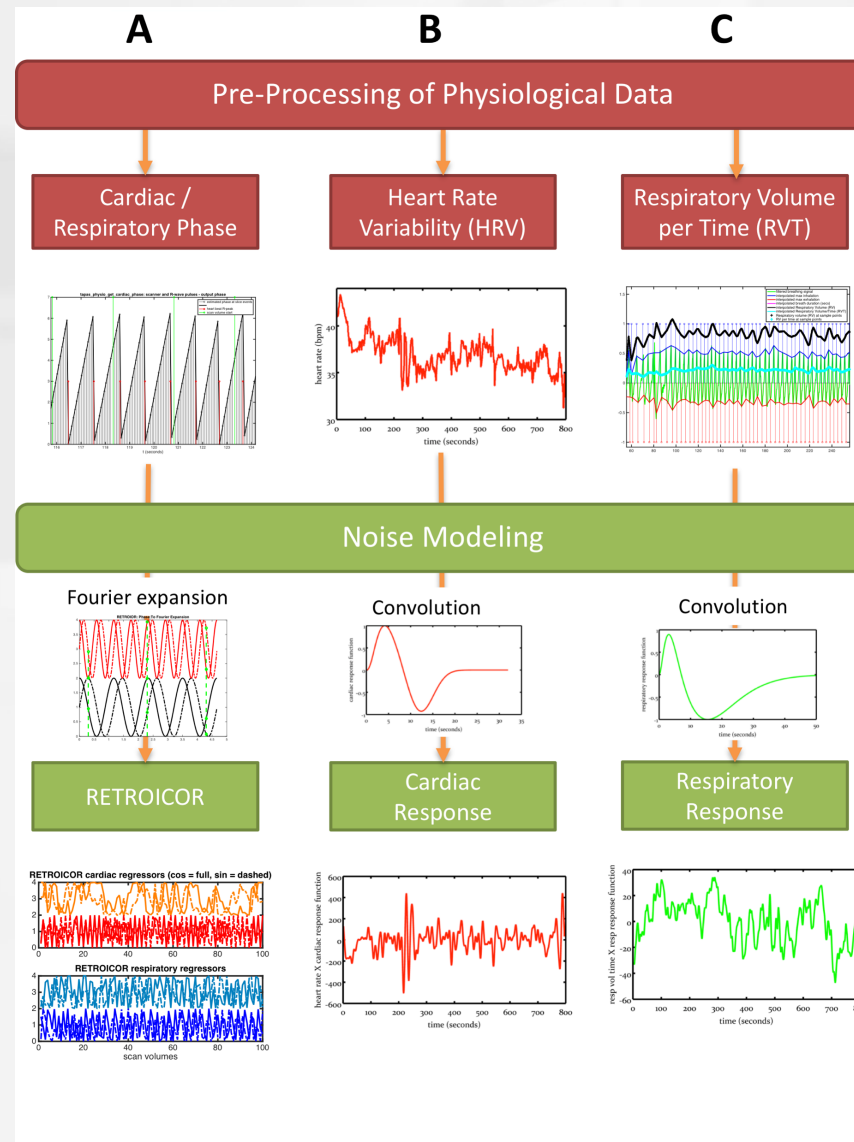
Preprocessing: Peak Detection

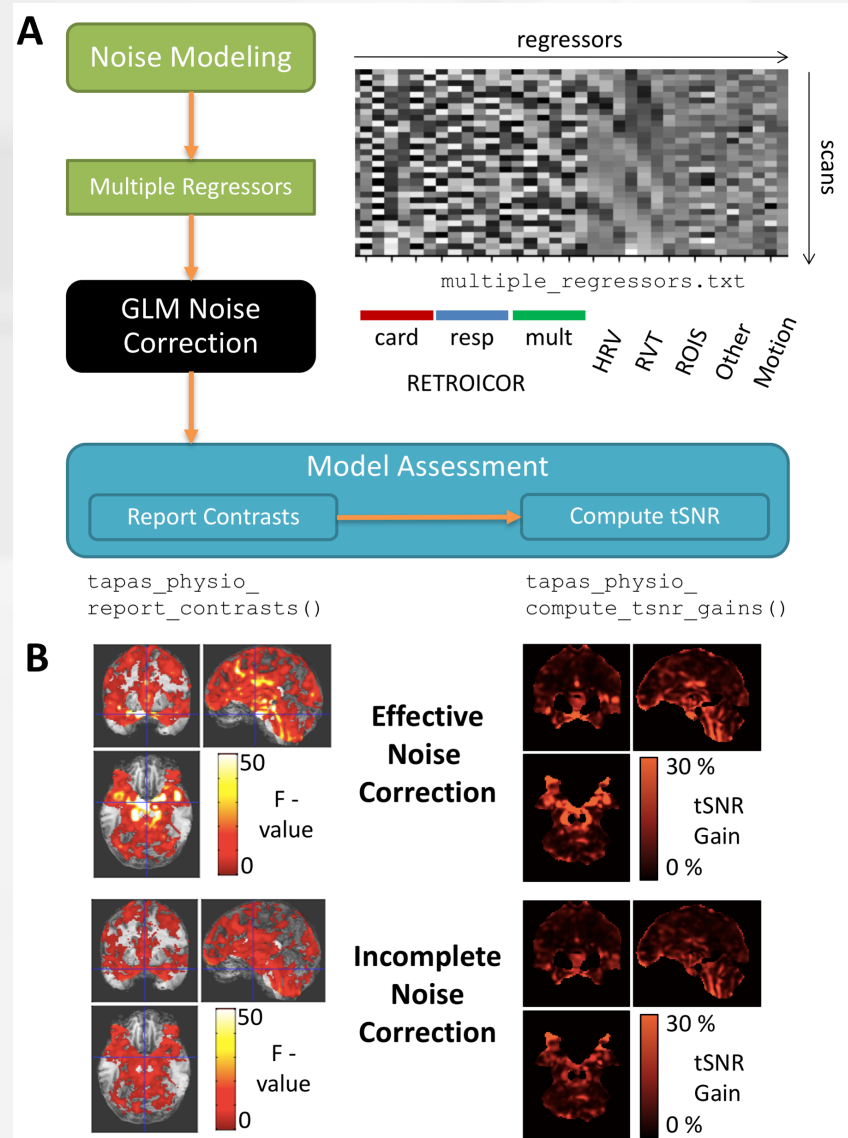


Peak Detection: Robustness



Noise Modeling

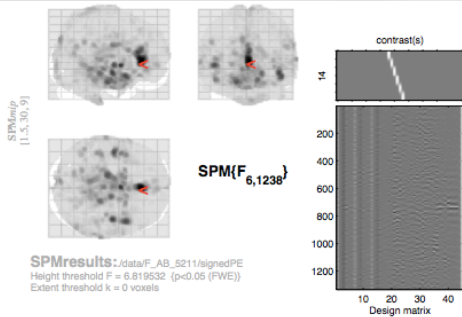




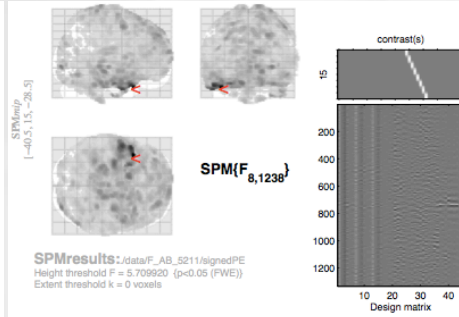
Model Check: SPM F-contrasts



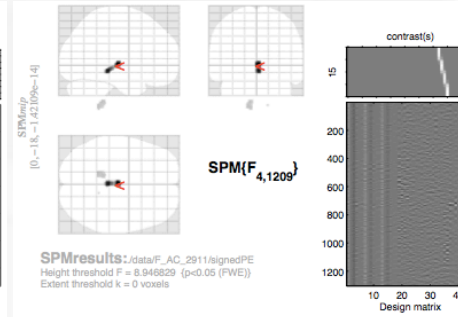
Cardiac regressors



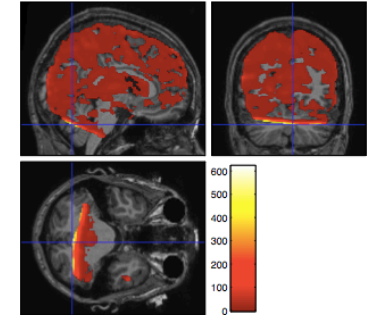
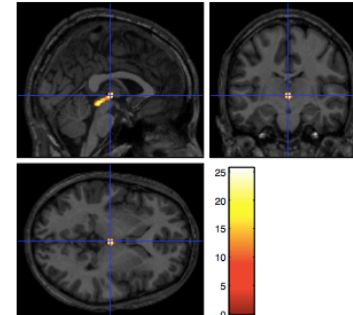
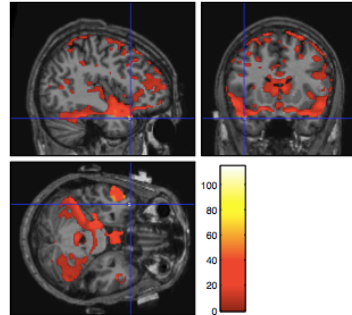
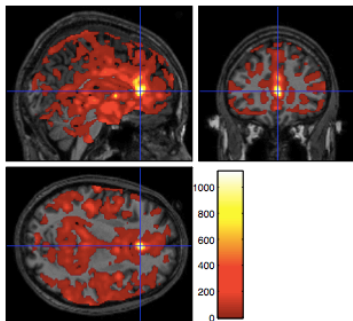
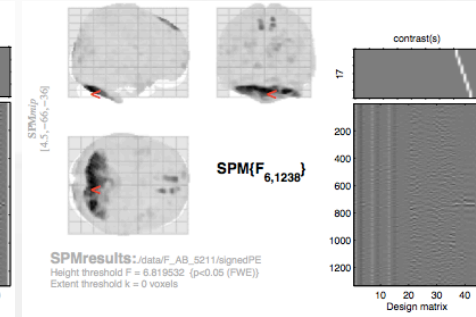
Respiratory regressors



Cardiac x Respiratory



Movement regressors



Finally:

Check Influence of Physiological Noise (Correction) on Data

- SPM
- F-contrast on 1st and second level

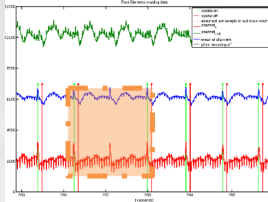
Flexibility: Scanner vendors



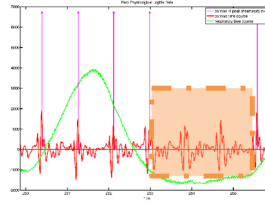
A Flexibility

Flexible
Read-In

Siemens (ECG 3 T)



Philips (ECG 7 T)

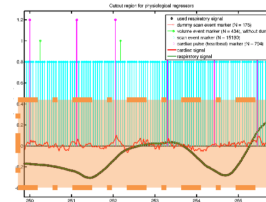
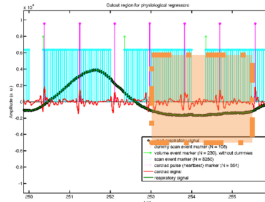
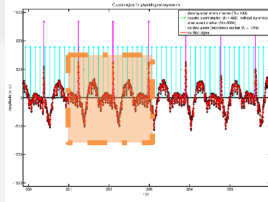


GE (OXY 3 T, ADHD)



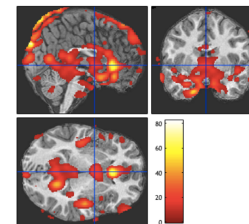
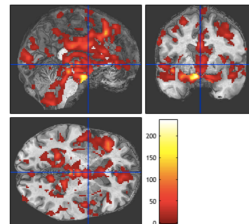
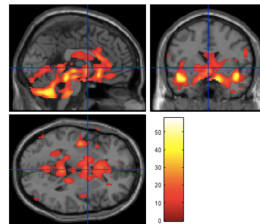
B Robustness

Preprocessing of
Physiological Data



C Evaluation

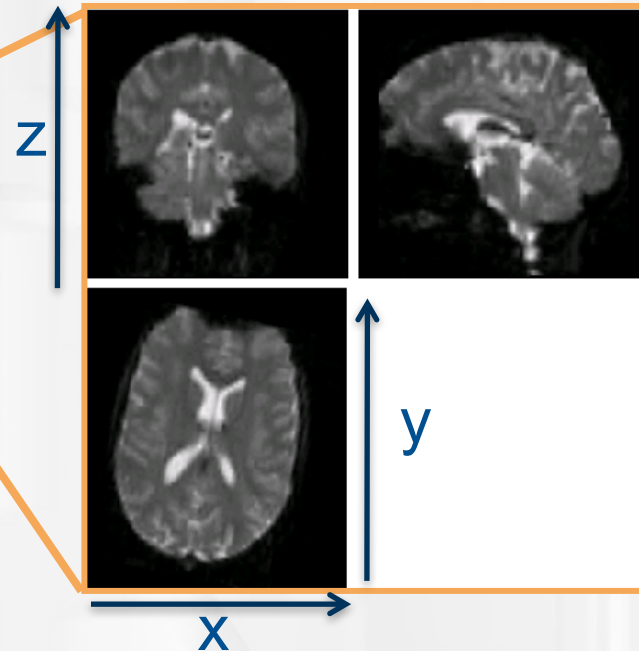
Model Assessment





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- **Glover**, G H, T Q Li, and D Ress. 2000. “Image-based Method for Retrospective Correction of Physiological Motion Effects in fMRI: RETROICOR.” *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine* 44 (1) (July): 162–7.
- **Harvey**, Ann K., Kyle T.S. Pattinson, Jonathan C.W. Brooks, Stephen D. Mayhew, Mark Jenkinson, and Richard G. Wise. 2008. “Brainstem Functional Magnetic Resonance Imaging: Disentangling Signal from Physiological Noise.” *Journal of Magnetic Resonance Imaging* 28 (6): 1337–1344. doi:10.1002/jmri.21623.
- **Hutton**, C., O. Josephs, J. Stadler, E. Featherstone, A. Reid, O. Speck, J. Bernarding, and N. Weiskopf. 2011. “The Impact of Physiological Noise Correction on fMRI at 7 T.” *NeuroImage* 57 (1) (July 1): 101–112. doi:10.1016/j.neuroimage.2011.04.018.
- **Josephs**, O., Howseman, A.M., Friston, K., Turner, R., 1997. “Physiological noise modelling for multi-slice EPI fMRI using SPM.” *Proceedings of the 5th Annual Meeting of ISMRM, Vancouver, Canada*, p. 1682
- **Kasper**, L., Bollmann, S., Diaconescu, A.O., Hutton, C., Heinzle, J., Iglesias, S., Hauser, T.U., Sebold, M., Manjaly, Z.-M., Pruessmann, K.P., Stephan, K.E., 2017. The PhysIO Toolbox for Modeling Physiological Noise in fMRI Data. *Journal of Neuroscience Methods* 276, 56–72. doi:10.1016/j.jneumeth.2016.10.019

fMRI = Acquiring Movies



- ...of three-dimensional Blood Oxygen-Level Dependent (BOLD) contrast images

- Run/Session: Time Series of Images

