



University of
Zurich ^{UZH}

ETH zürich



Translational
Neuromodeling
Unit

Noise Models and Correction for fMRI

- an Introduction to the PhysIO Toolbox

Matthias Müller-Schrader

Nov 19th, 2019

Generous slide courtesy

Lars Kasper

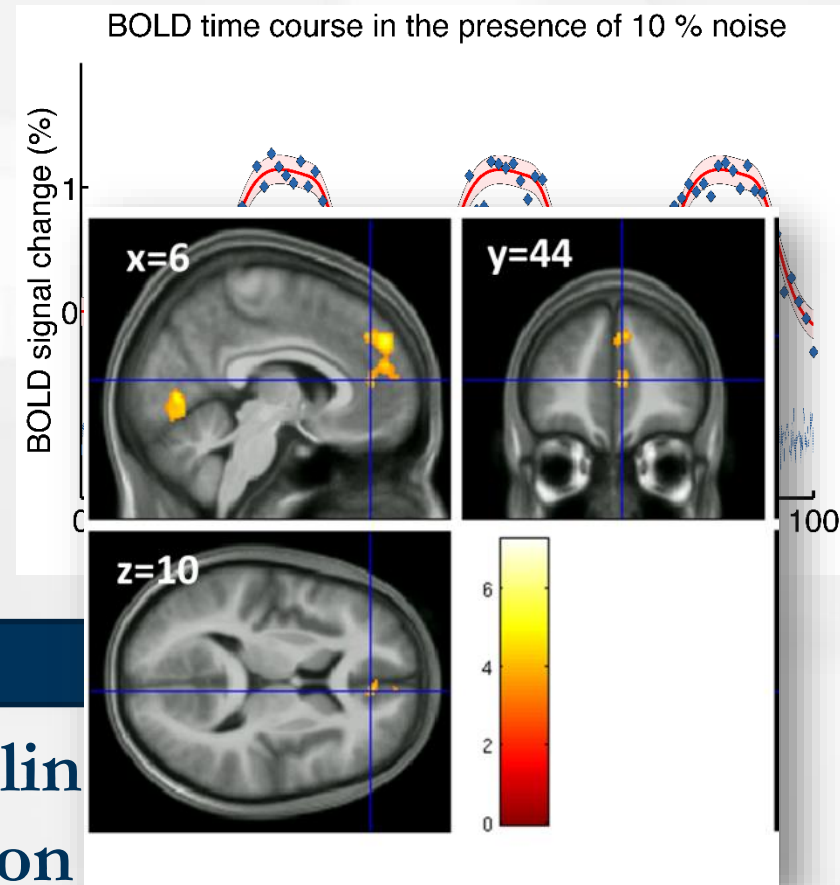
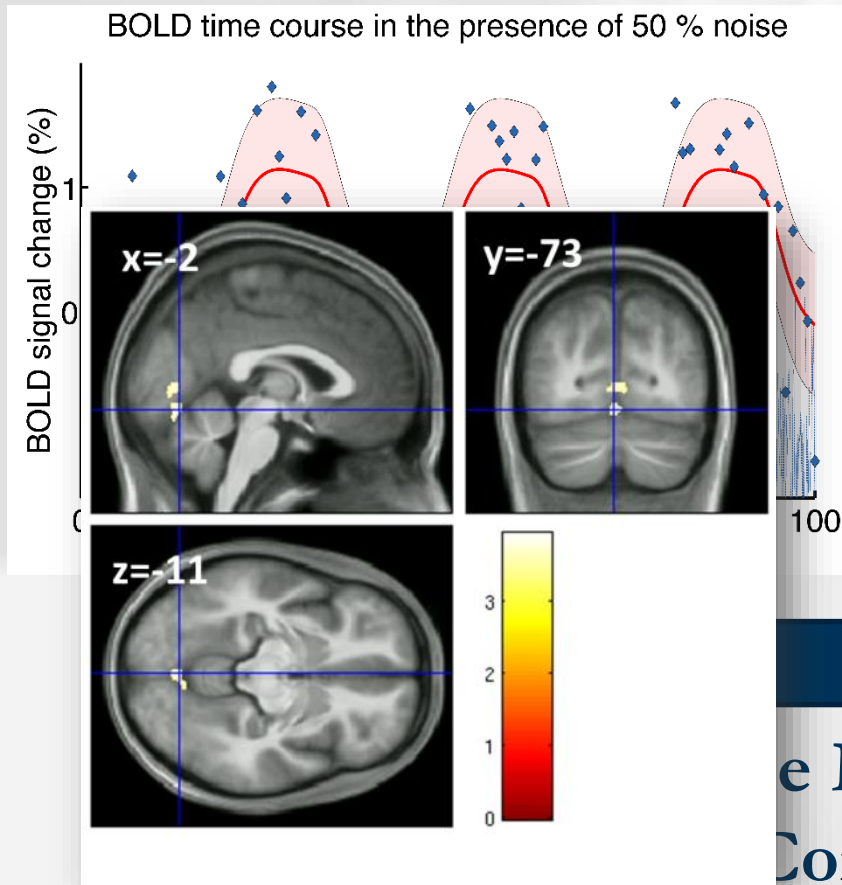


The Goal of Noise Correction

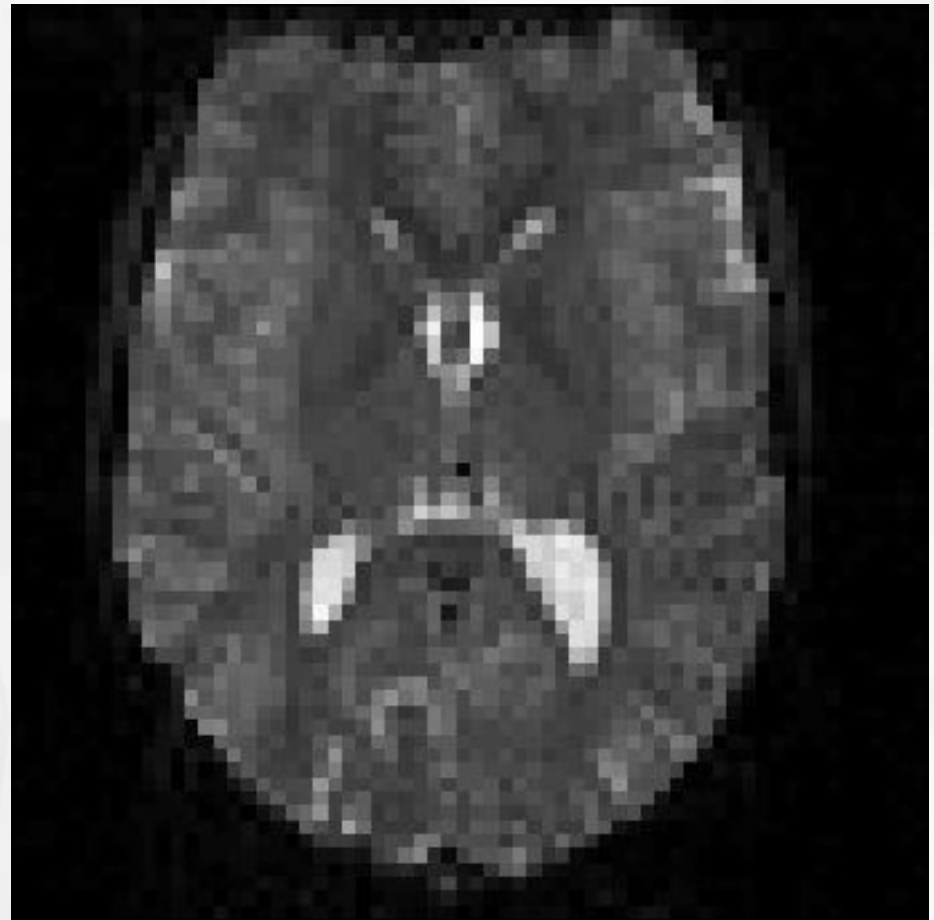
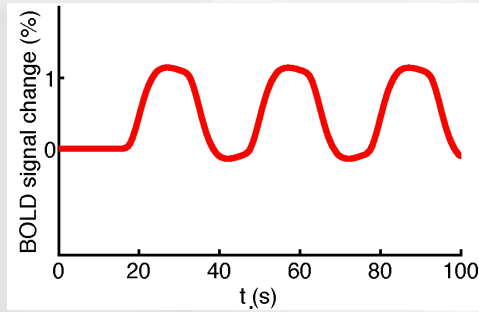


Before

After



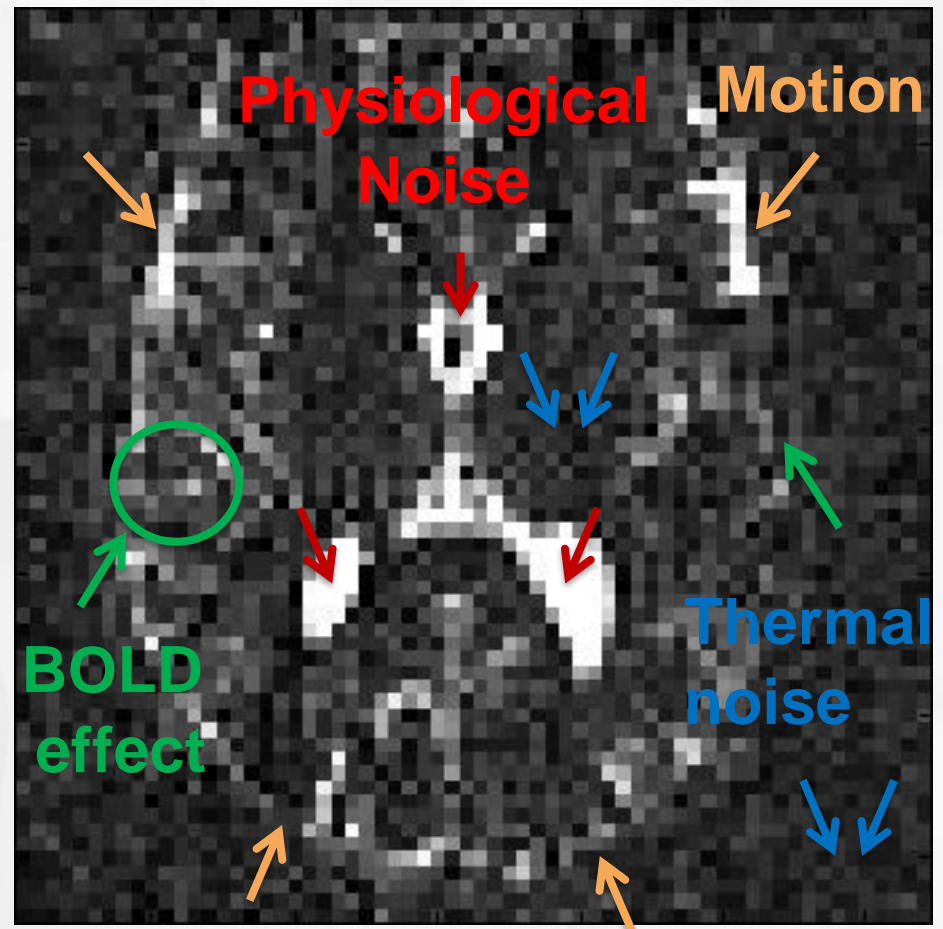
Reminder: fMRI Data is noisy...



fMRI Data is noisy...



- Interest in fluctuations only: Subtract the mean



Previously...



- How we ended 6 weeks ago (after preprocessing)
- After smoothing... still some fluctuation



Recap: Imaging pathway



- See blackboard.

- Noise: «Fluctuations we are not interested in.»
 - Often random
- Sources of noise
 - MR-System
 - Heating of gradient coils
 - Noise in amplifiers
 - Spikes in coils
 - Subject in the Scanner
 - Motion
 - Physiological noise
 - Cardiac cycle
 - Breathing cycle
 - **Not the BOLD-signal**

- Why denoising?
- Pathways of physiological noise
 - Recap: MR image encoding
 - Cardiac effects
 - Respiratory effects
- Noise correction approaches
 - Method Preprocessing vs modeling
 - Input fMRI data vs. peripheral measure
- Effects of noise correction
- Limitations

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fMRI = Acquiring Movies

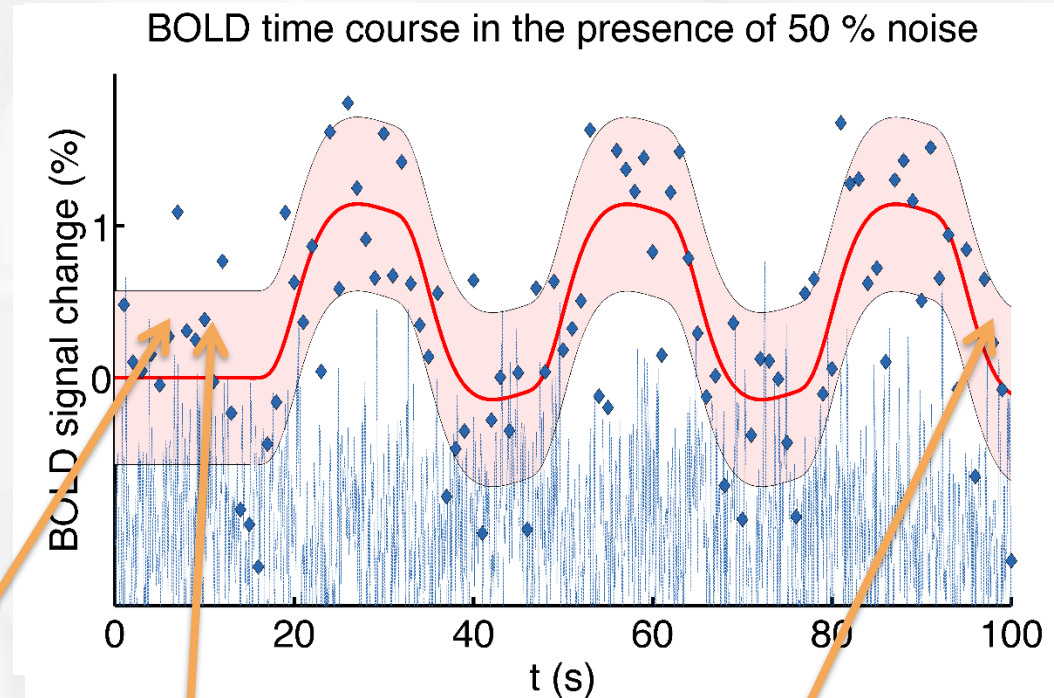


- The Localized Time-series is the Fundamental Information Unit of fMRI

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

Noise: All other fluctuations

- Run/Session: Time Series of Images



scan 1



...



scan N

time

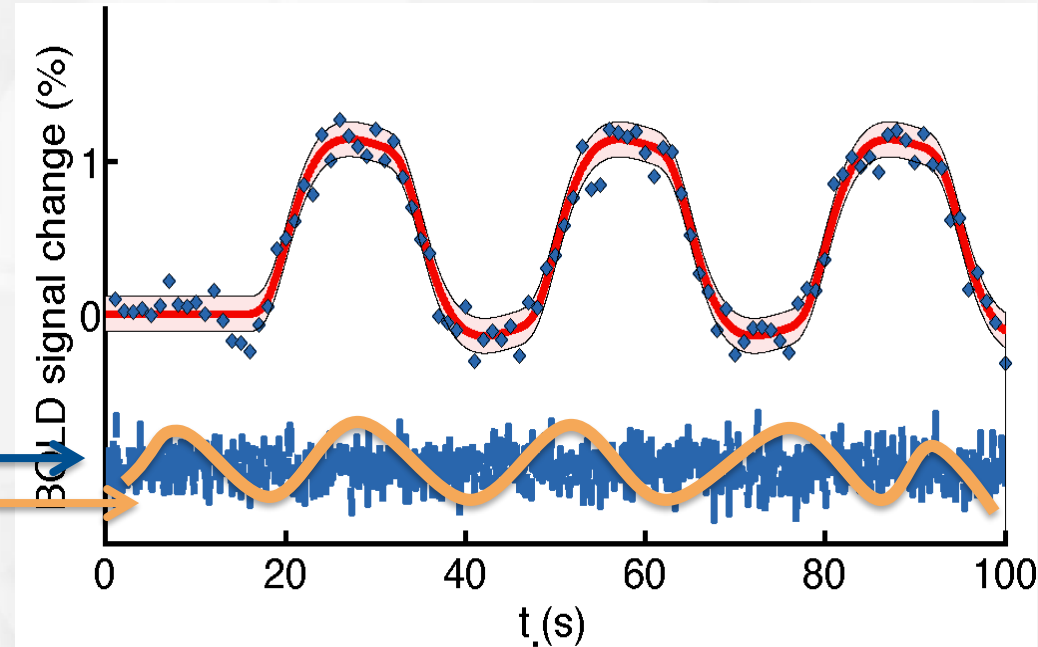
Noise Categories



- 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

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

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

False positives in resting state fmri

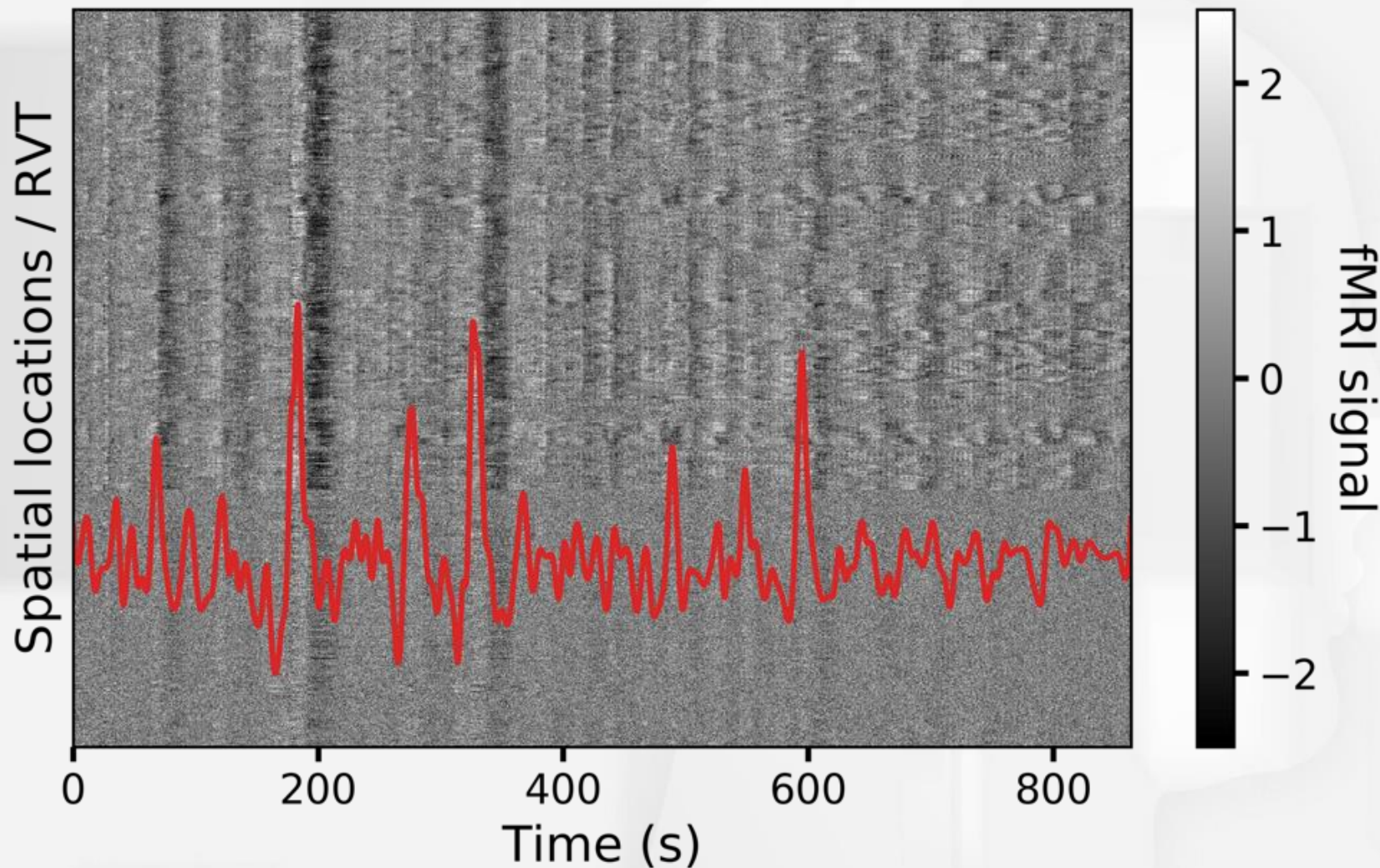
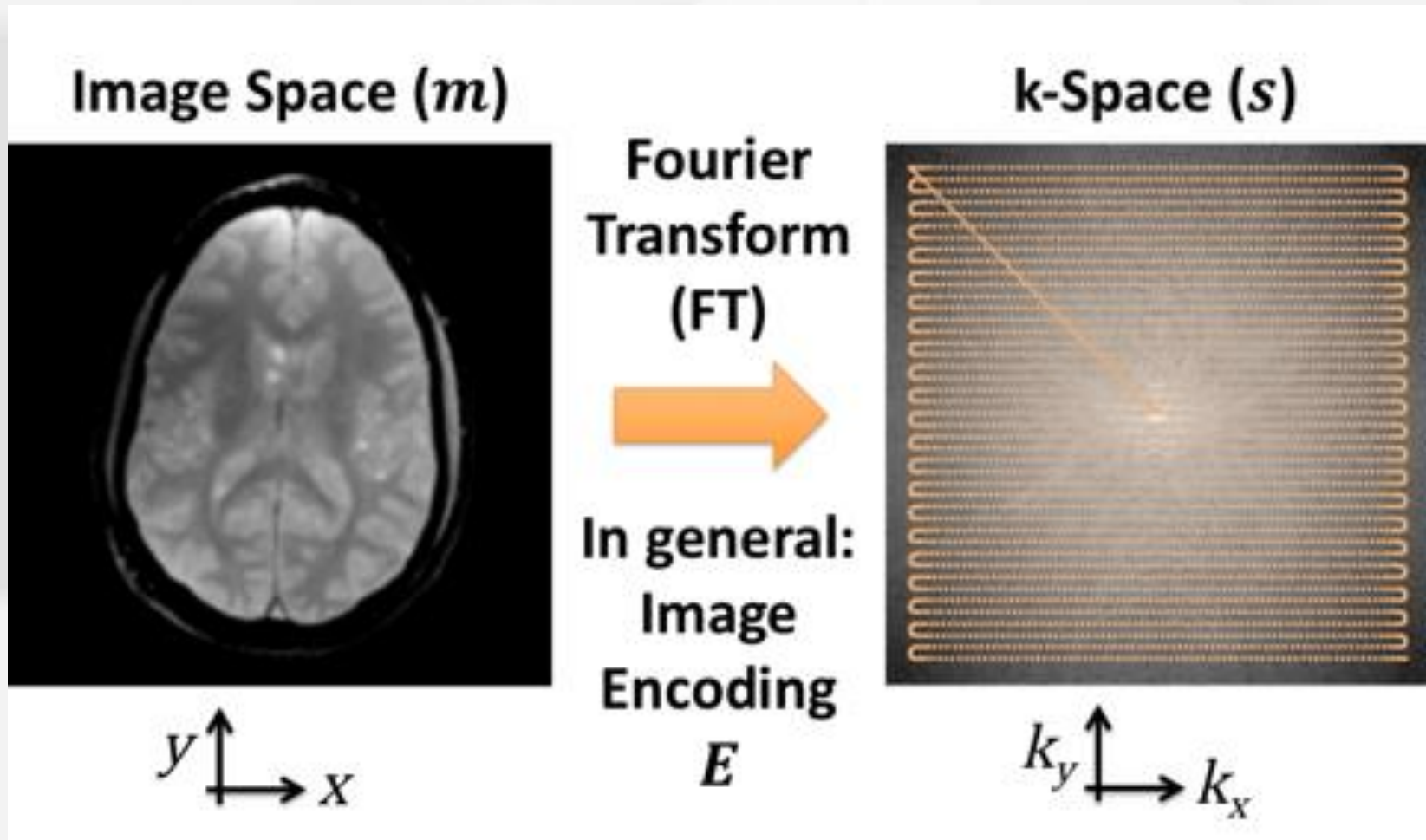
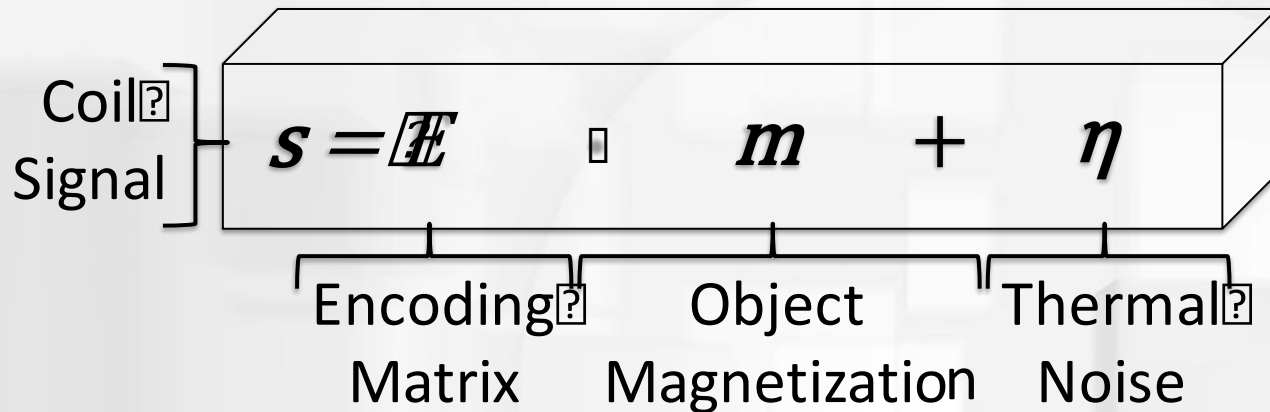


Image from Sam Harrison

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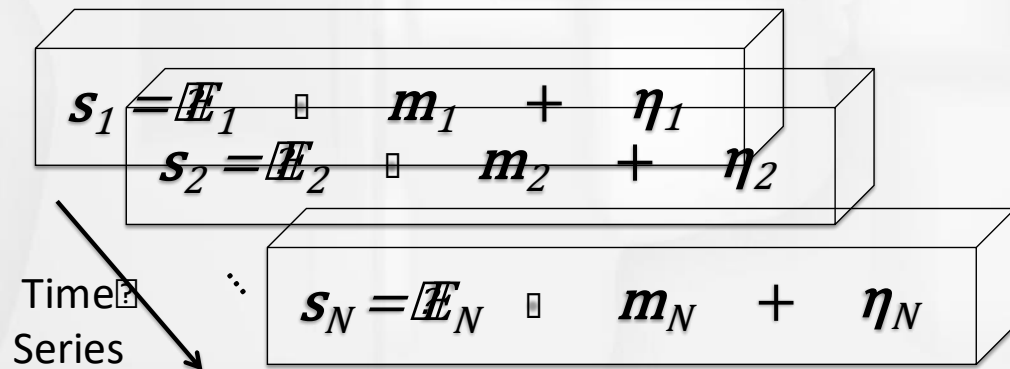
Recap: MR Image Encoding



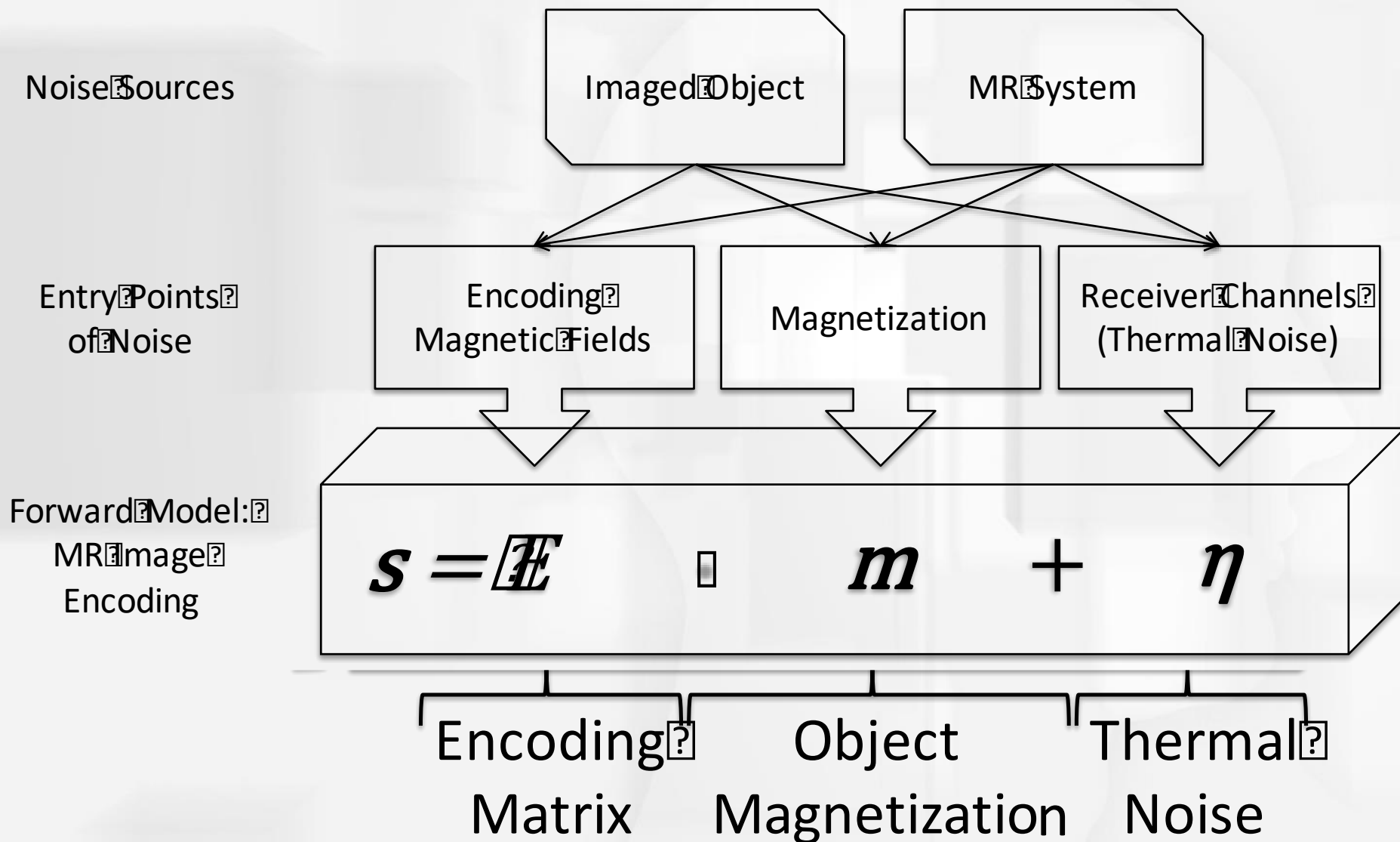


- Image reconstruction is also a *huge* GLM, $\sim 10^5$ - 10^6 rows
 - 3 mm slice, 8 chan: $64^2 \cdot 8 = 512k$
 - 1 mm slice, 32 ch: $256^2 \cdot 32 = 2M$
- Any change between volumes in encoding matrix (field), object magnetization and thermally induces image noise

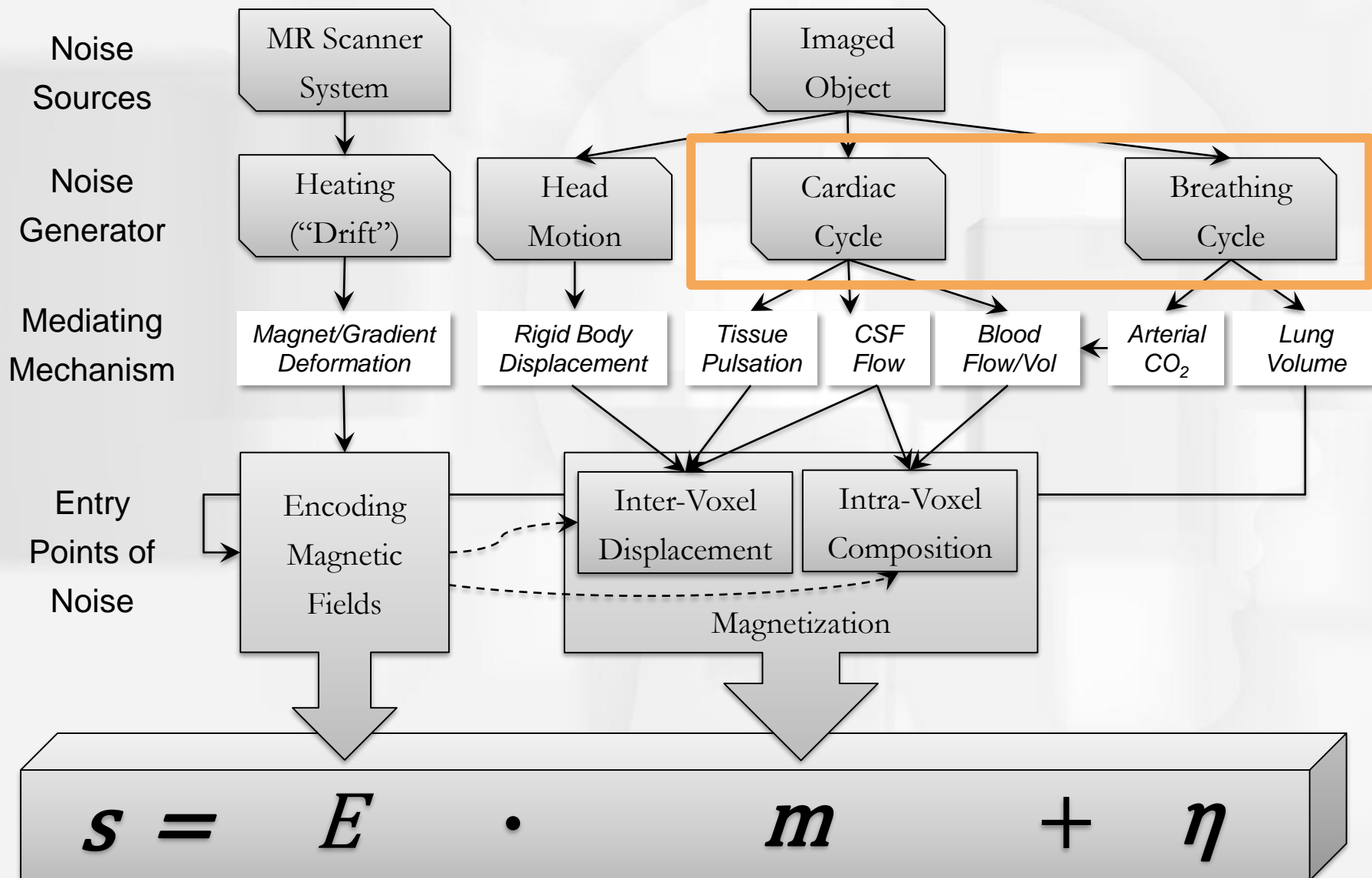
$$\hat{m} = (E^H E)^{-1} E^H s$$



What fluctuates?



Structured Noise in MRI



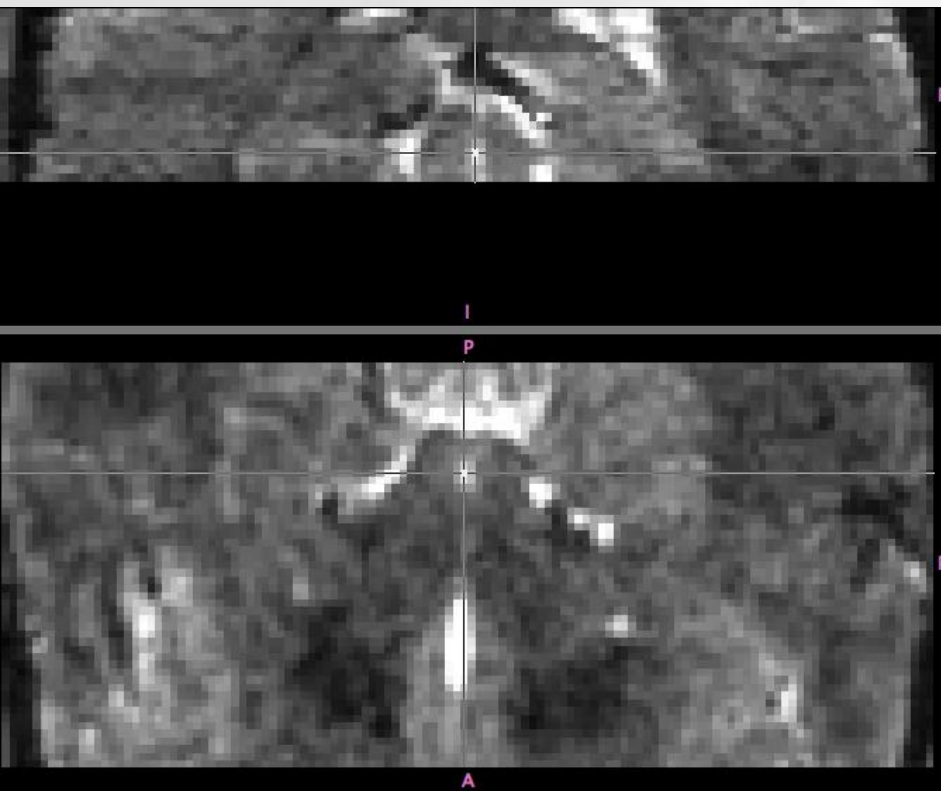
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- CSF pulsation:
 - Systole:
 - Blood pumped into brain, vessel volume increases: pulsatile vessels
 - CSF pushed down: pulsatile CSF
 - Diastole:
 - Vessel volume decreases
 - CSF flows back into “void” brain volume

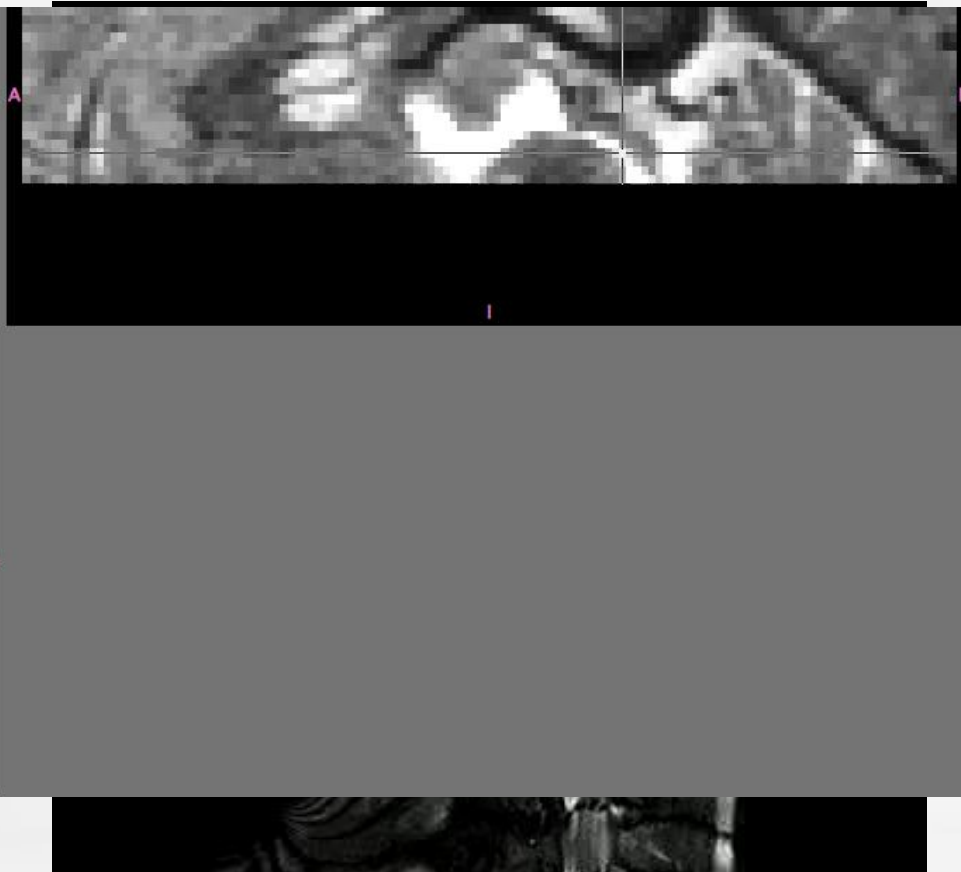
A Cardiac Cycle in the Brain

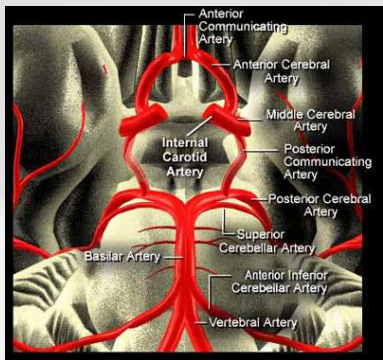
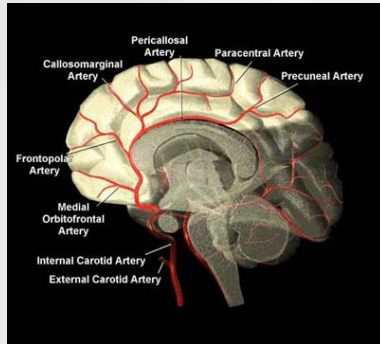
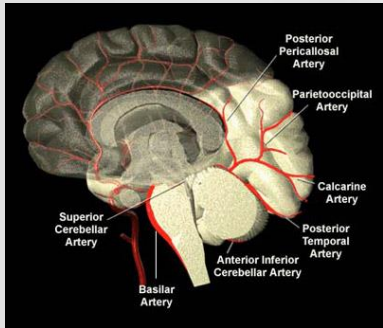


Triggered High-Resolution fMRI

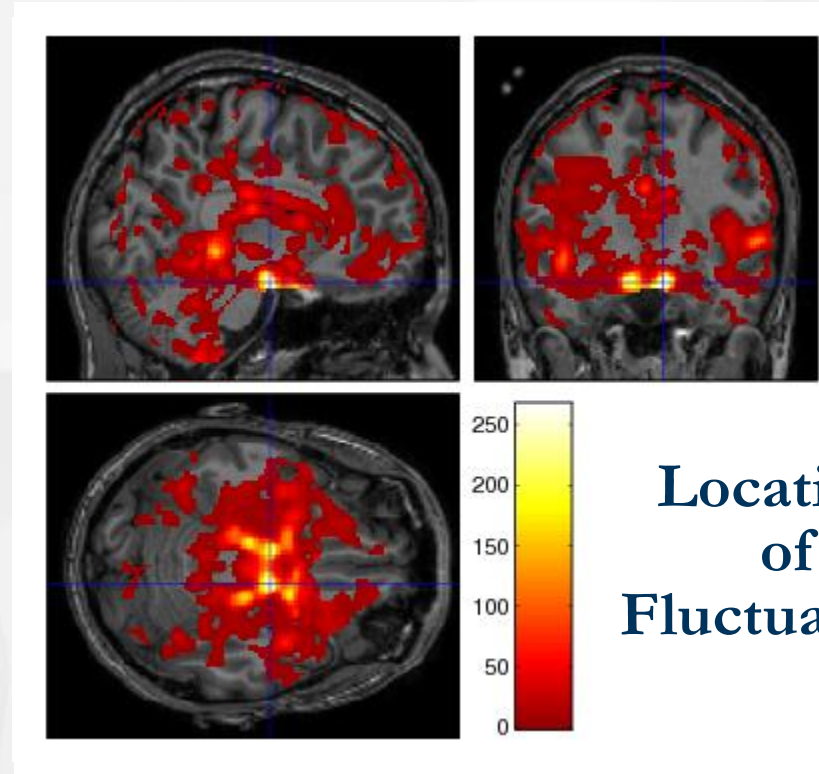


A Cardiac Cycle in the Brain

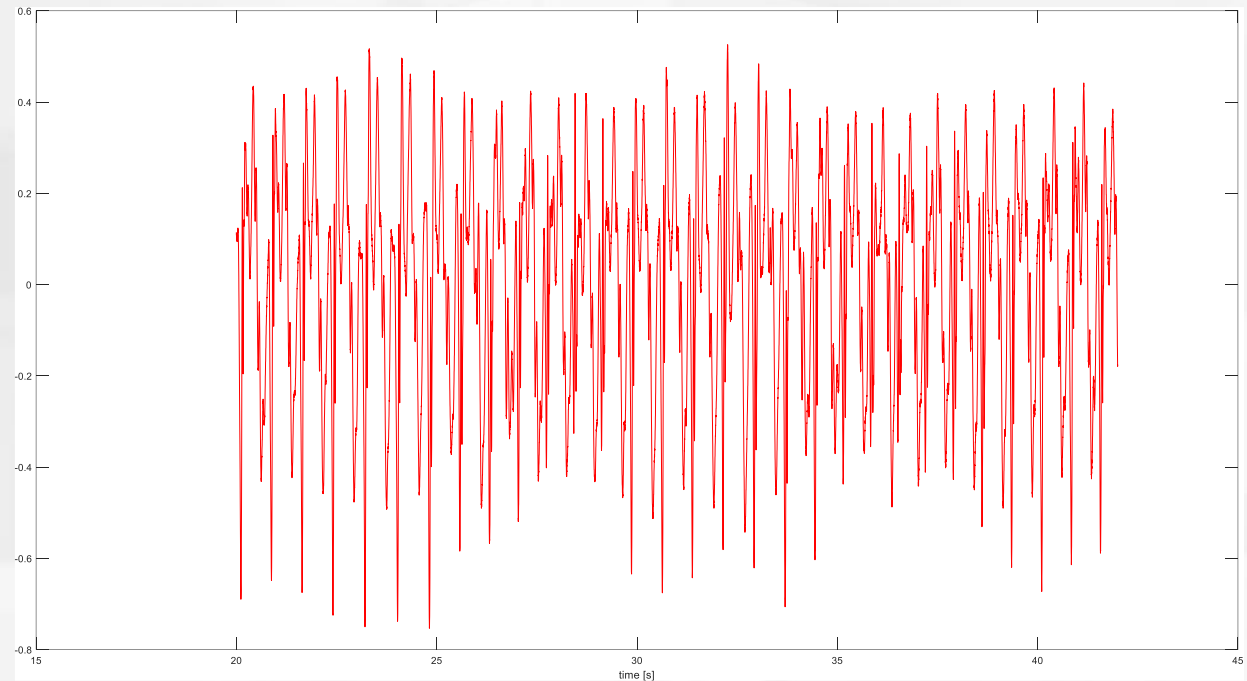




Vessel Anatomy

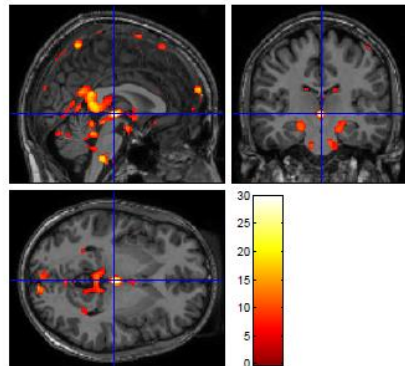
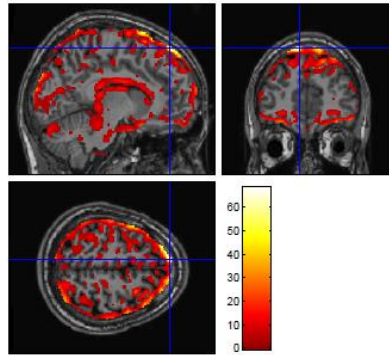
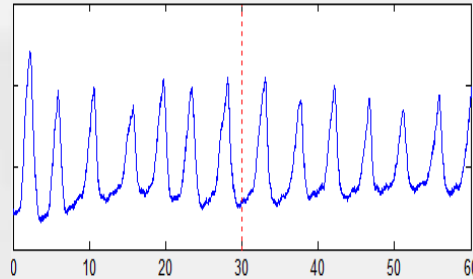


- (almost) periodic



- But:
 - Fluctuations in BOLD-level due to heart-rate variability (HRV)

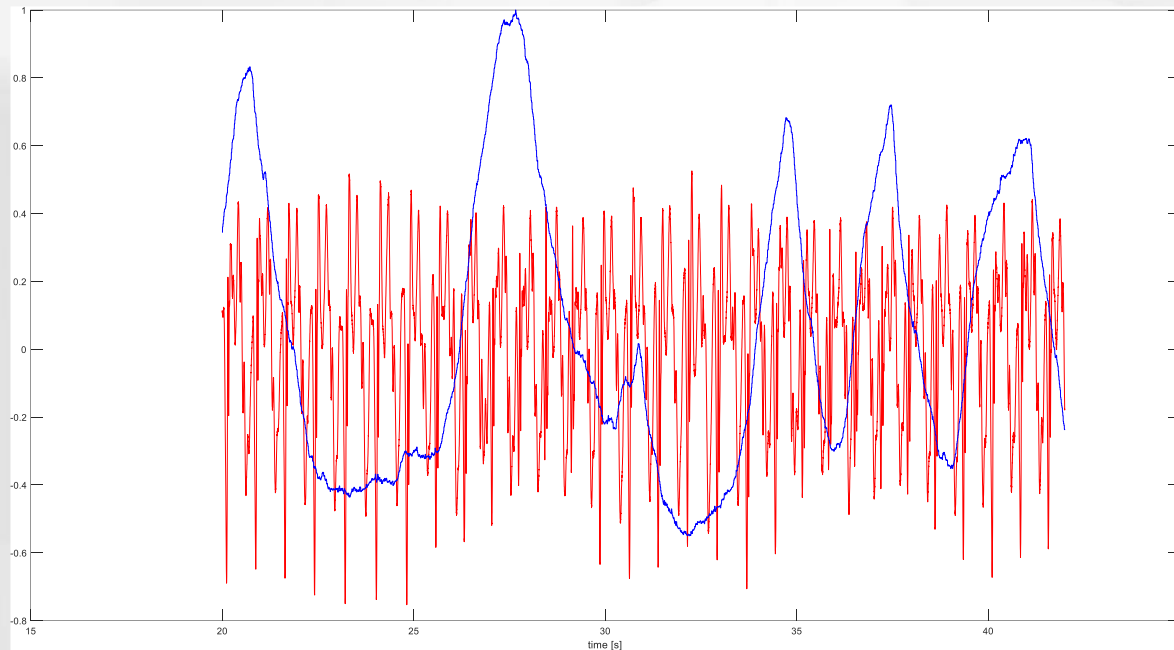
Respiratory effects



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

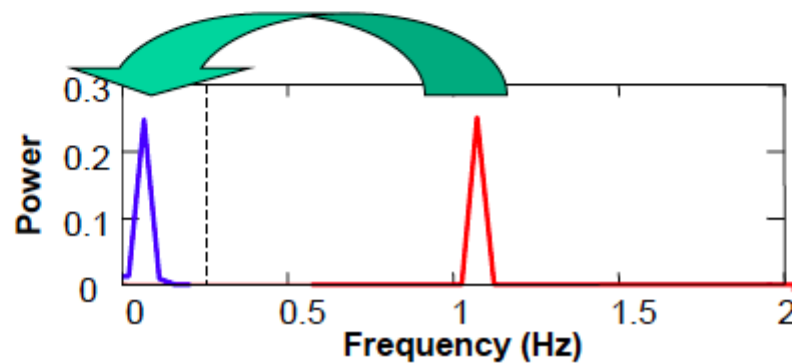
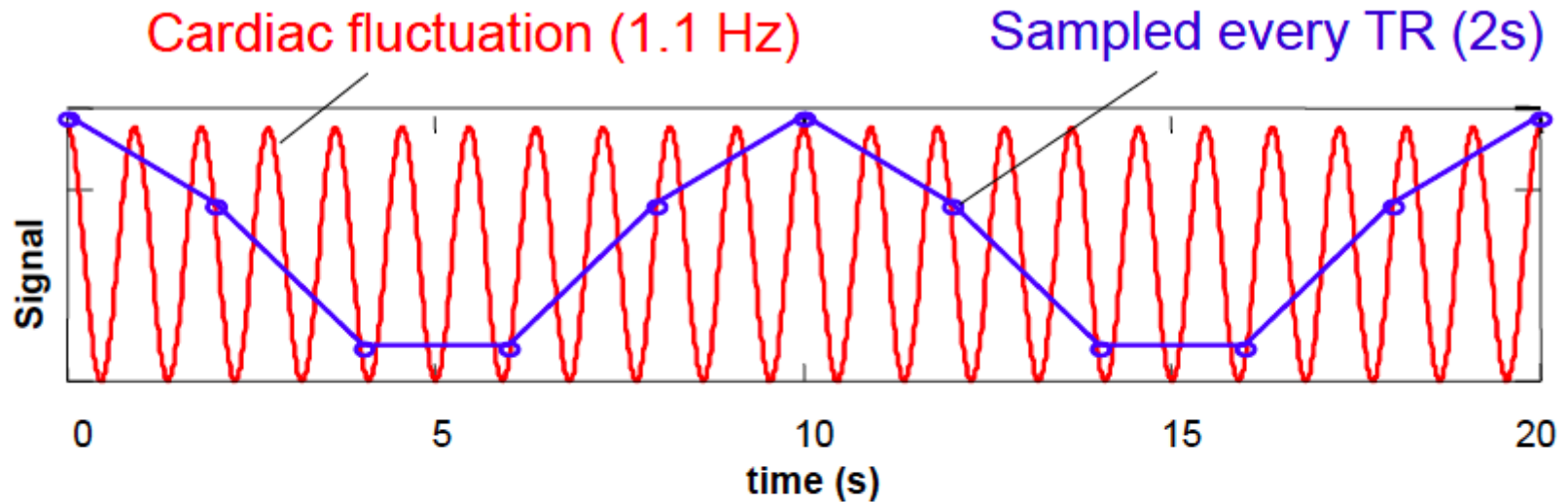
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Why not just filtering?



- Cycles are (almost) periodic
- Problem: Aliasing
 - Could filter frequencies
 - 0.2-0.4 Hz respiration
 - 0.8 – 1.2 Hz heart beat (main)

Aliasing of Physiology



Courtesy: R. Birn, HBM 2015



- 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)



- 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

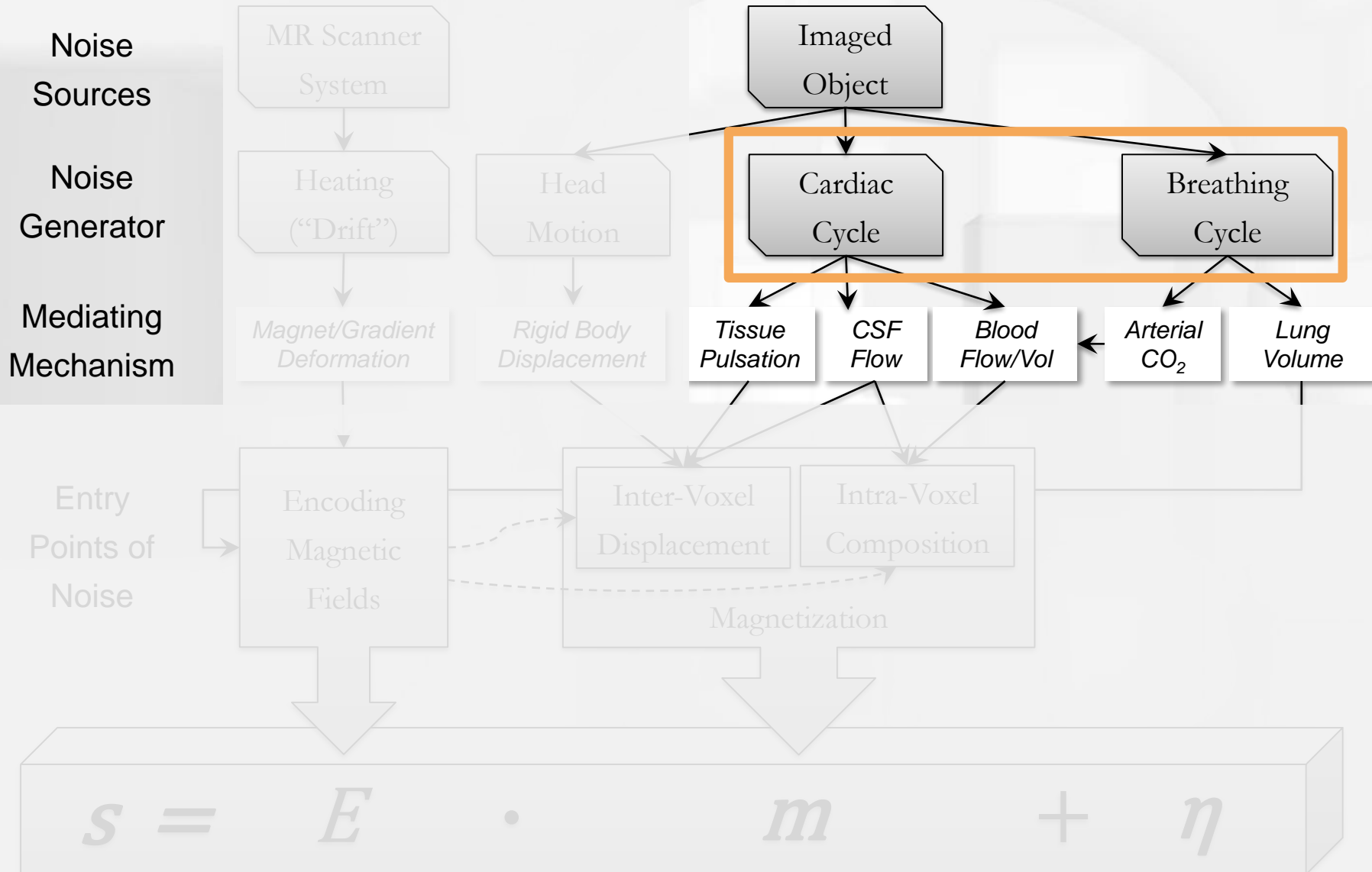
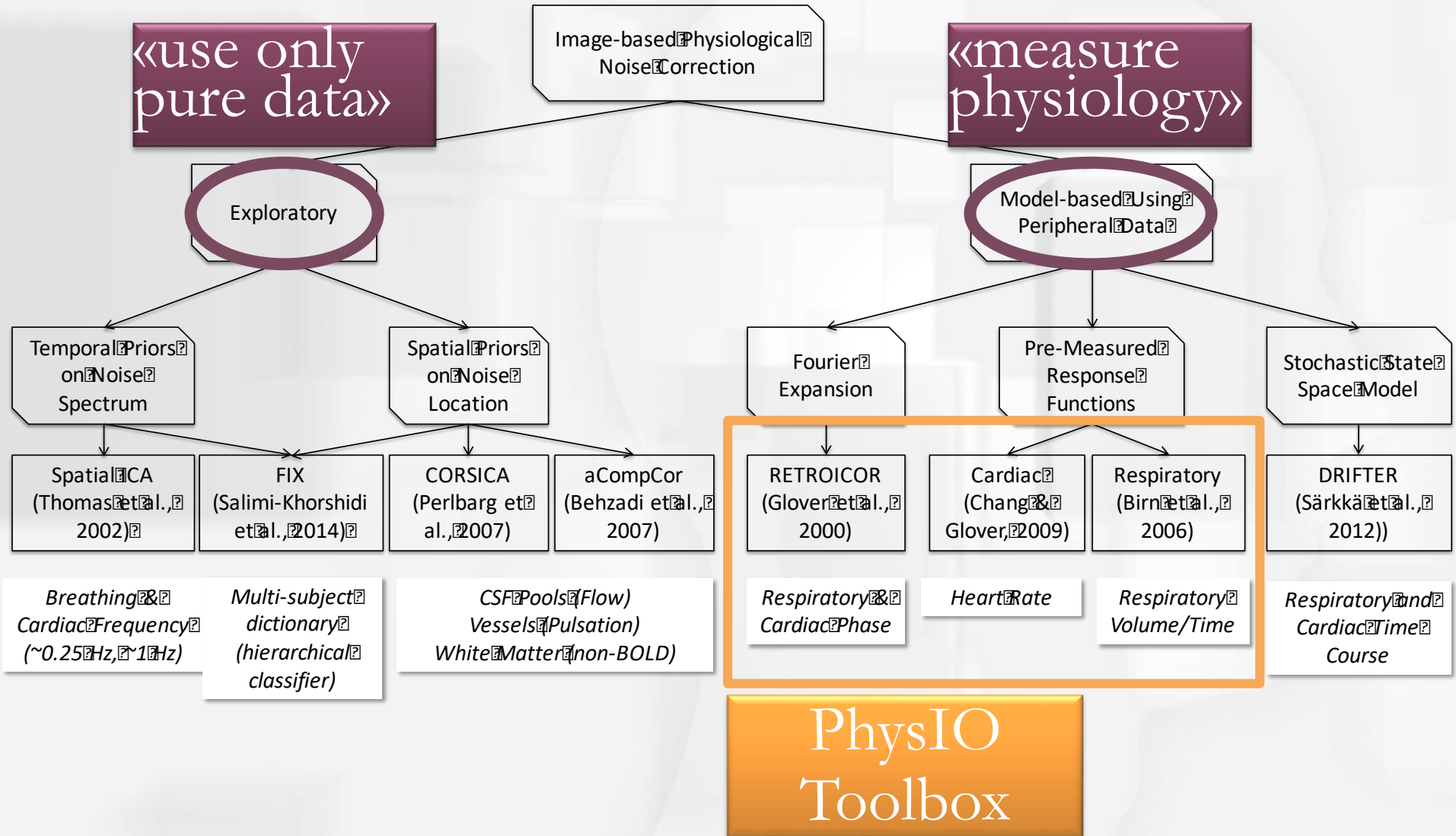


Image-based Noise Correction





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

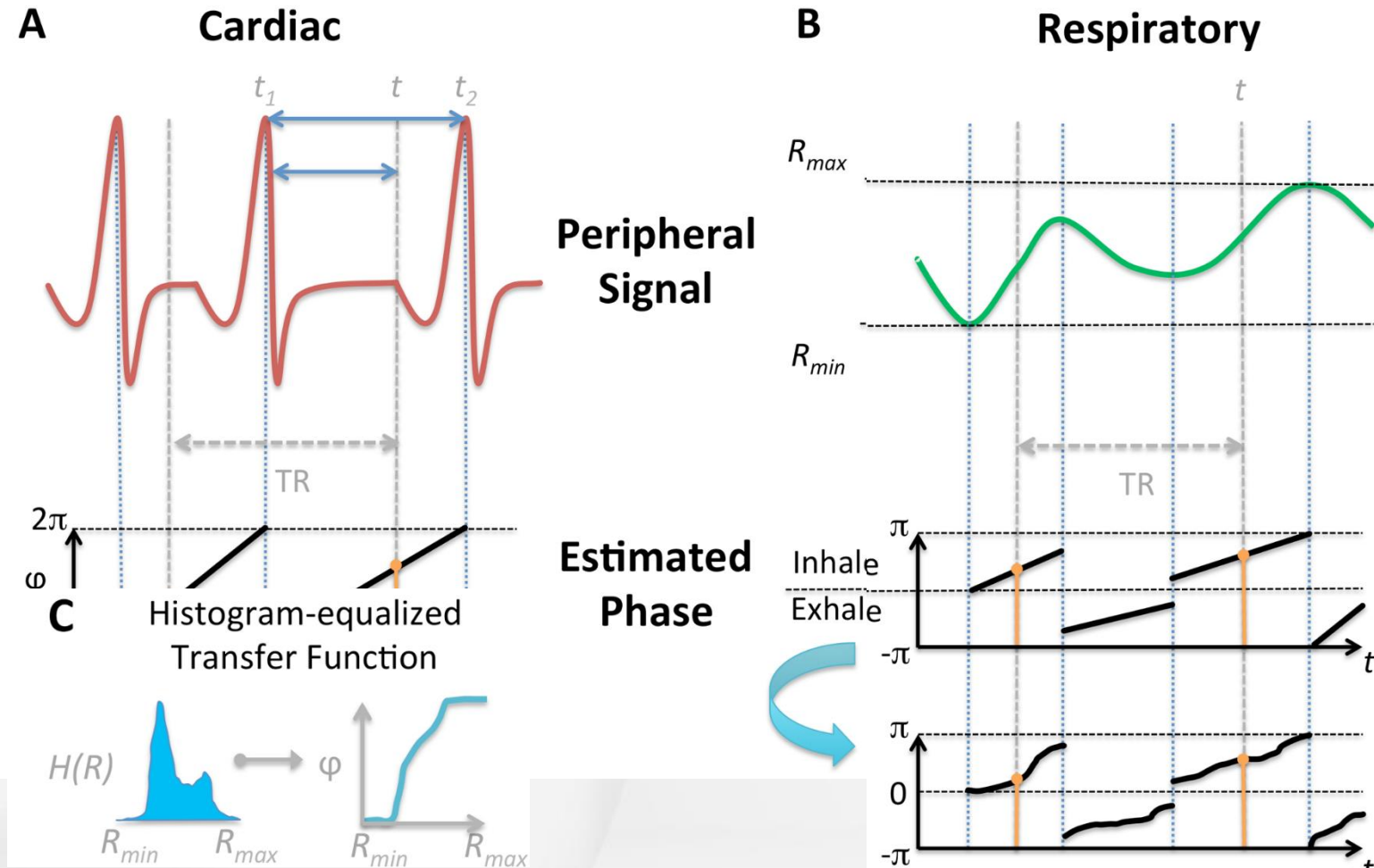
Noise Modeling



RETROspective Image CORrection

Cardiac Response Function φ_C

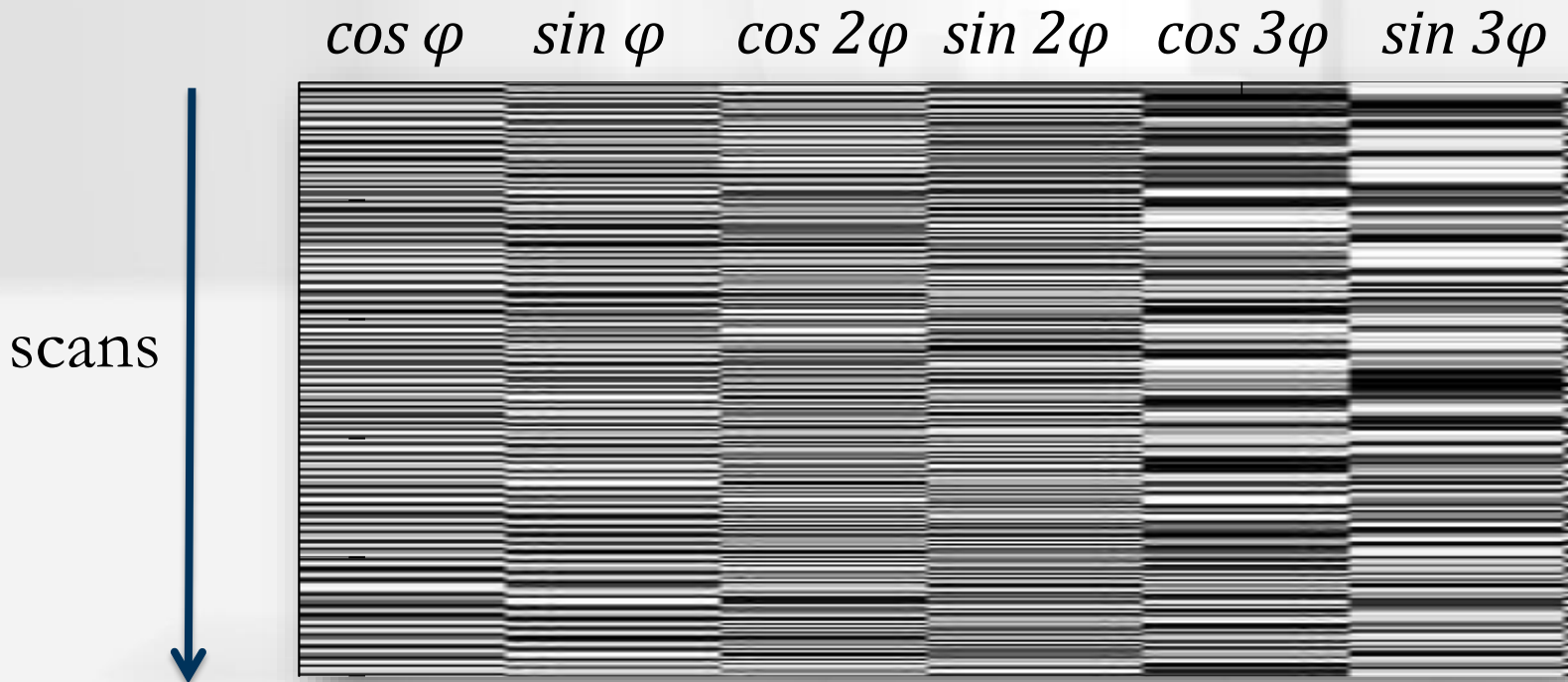
Respiratory Response Function φ_r



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



RETROspective
Image CORrection

Cardiac Response
Function

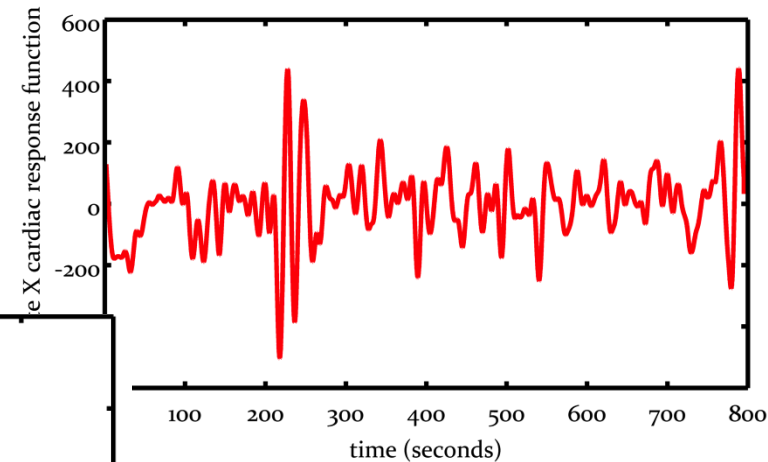
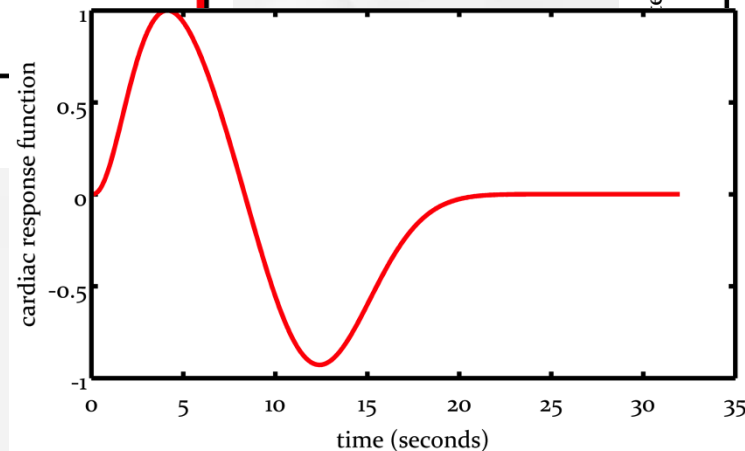
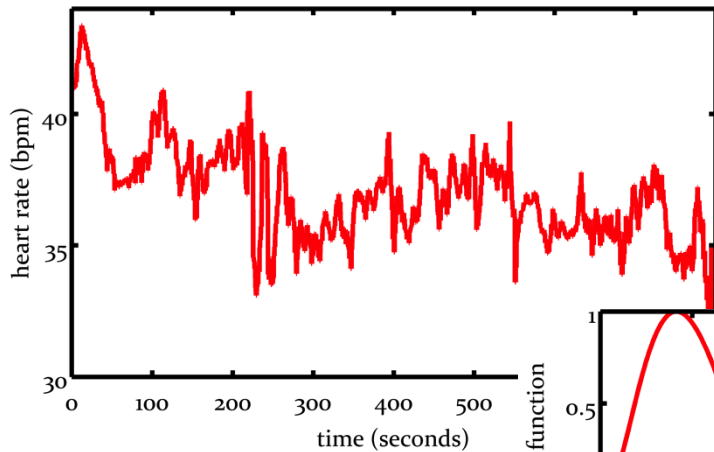
Respiratory
Response Function

- Heart Rate

- Heart Rate Variability
Response Regressor

- convolved with

CRF



Noise Modeling



RETROspective
Image CORrection

Cardiac Response
Function

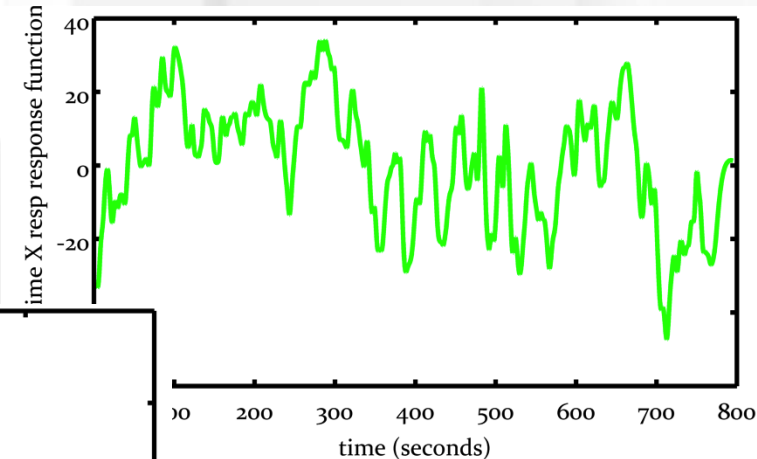
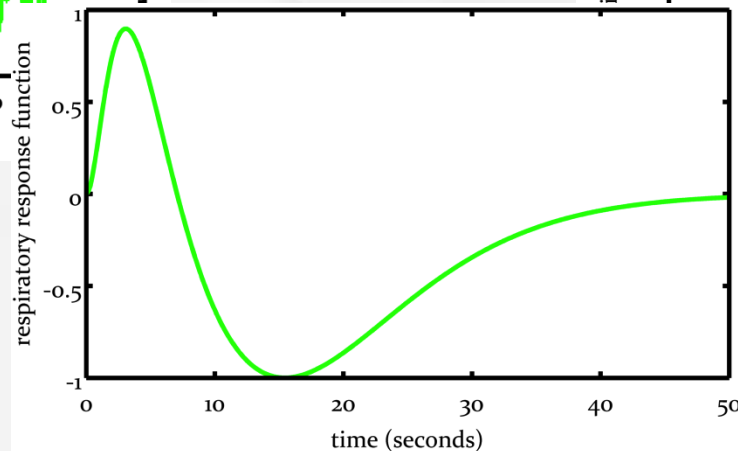
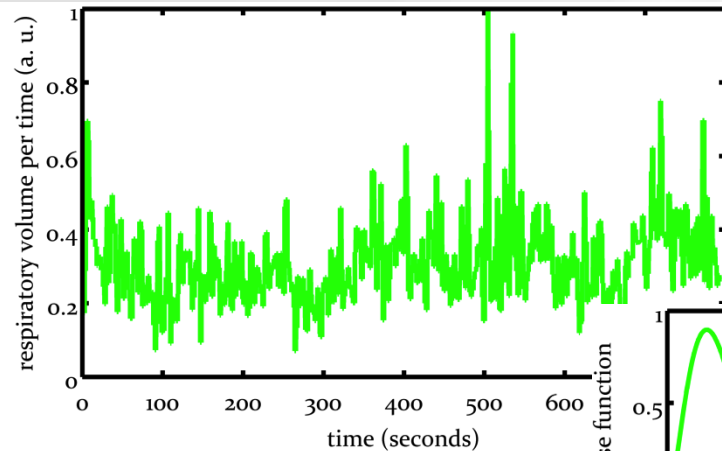
Respiratory
Response Function

■ Respiratory
Volume per Time

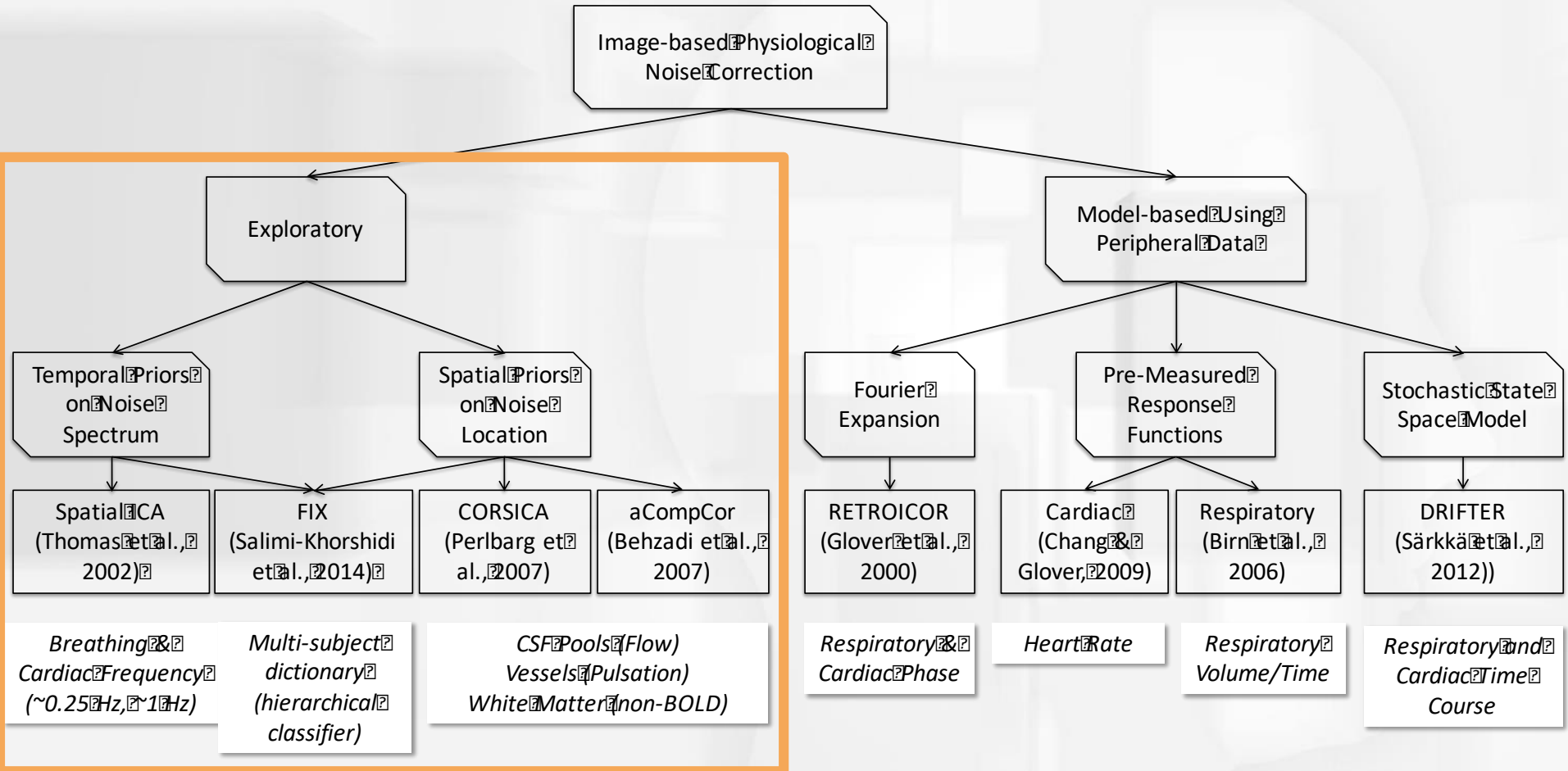
■ convolved with

■ Respiratory Volume
per Time Regressor

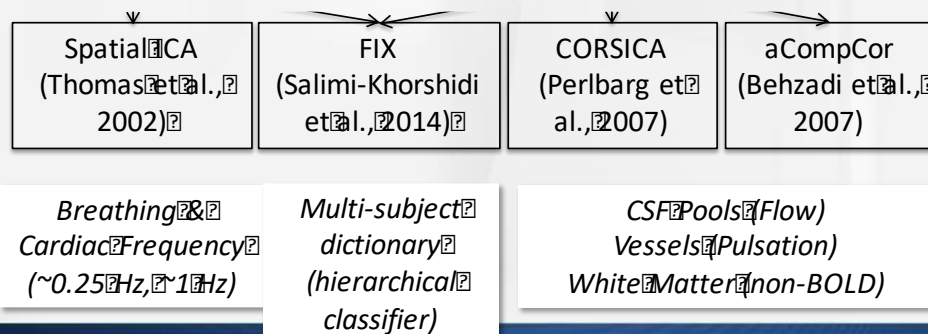
RRF



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 previous talk (resting state analysis) for more details



- 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

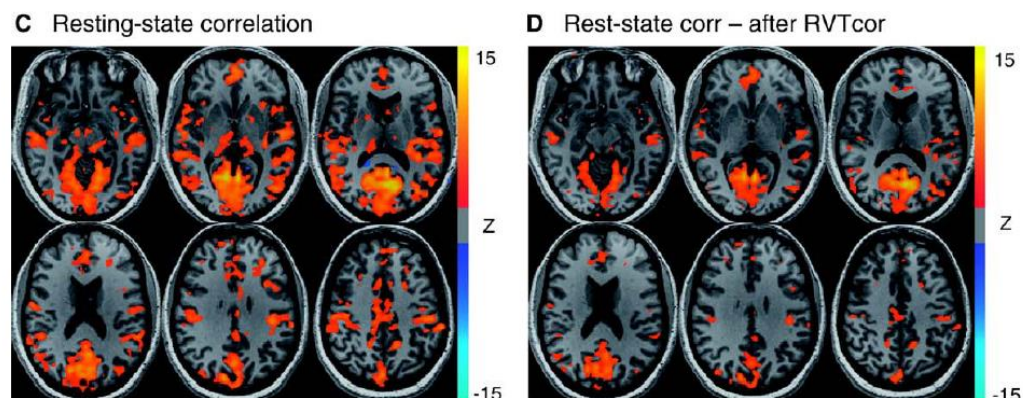
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When? – Literature Evidence



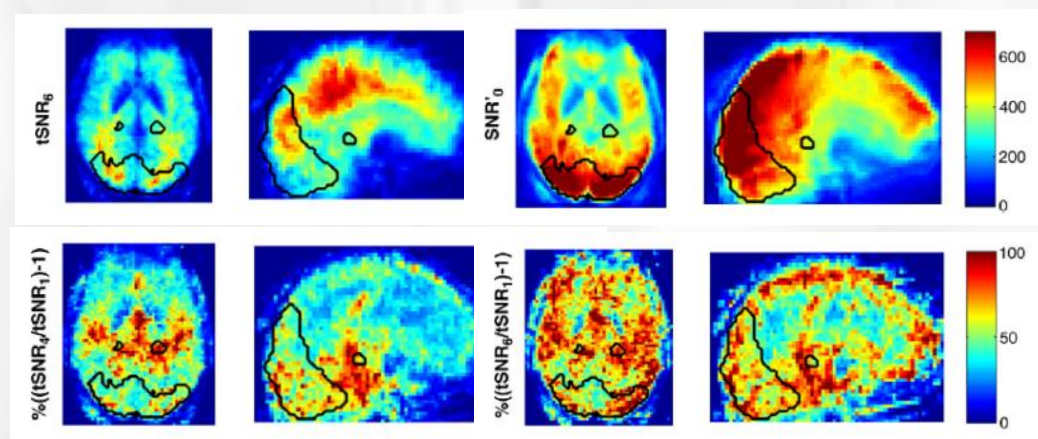
■ Resting-state:

- 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)

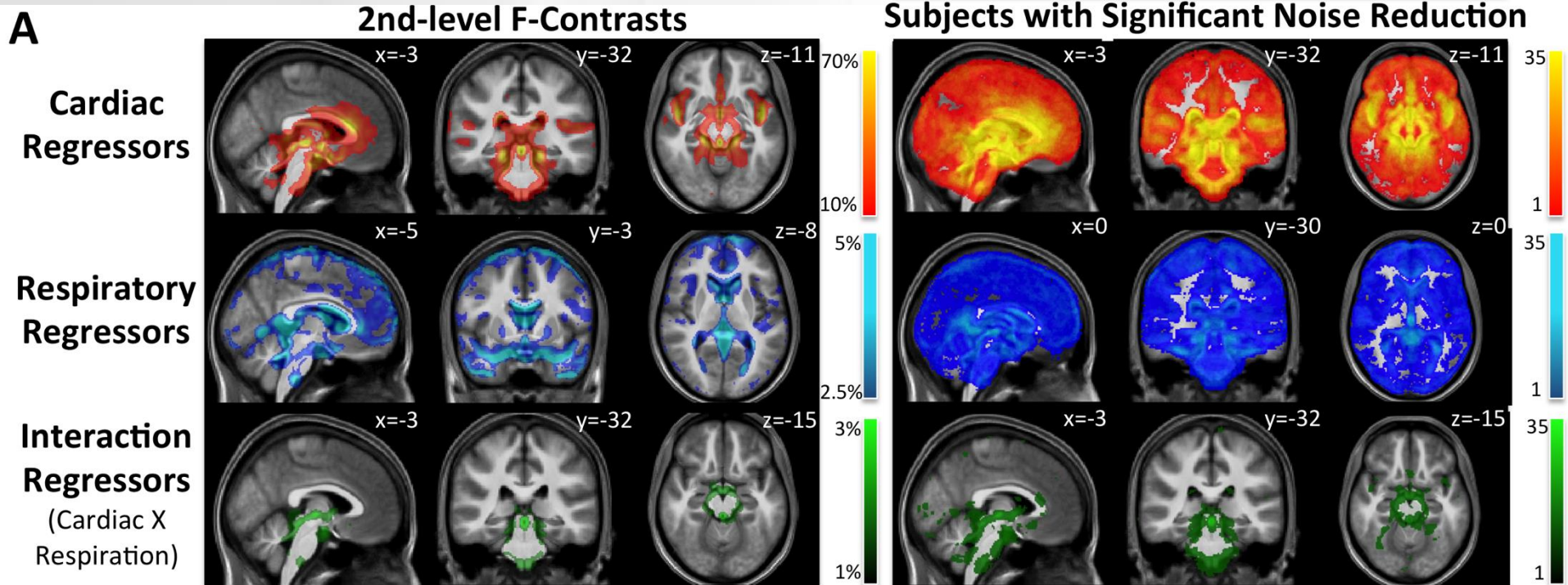
volatility of advice (changing intentions of adviser through incentive structure)

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

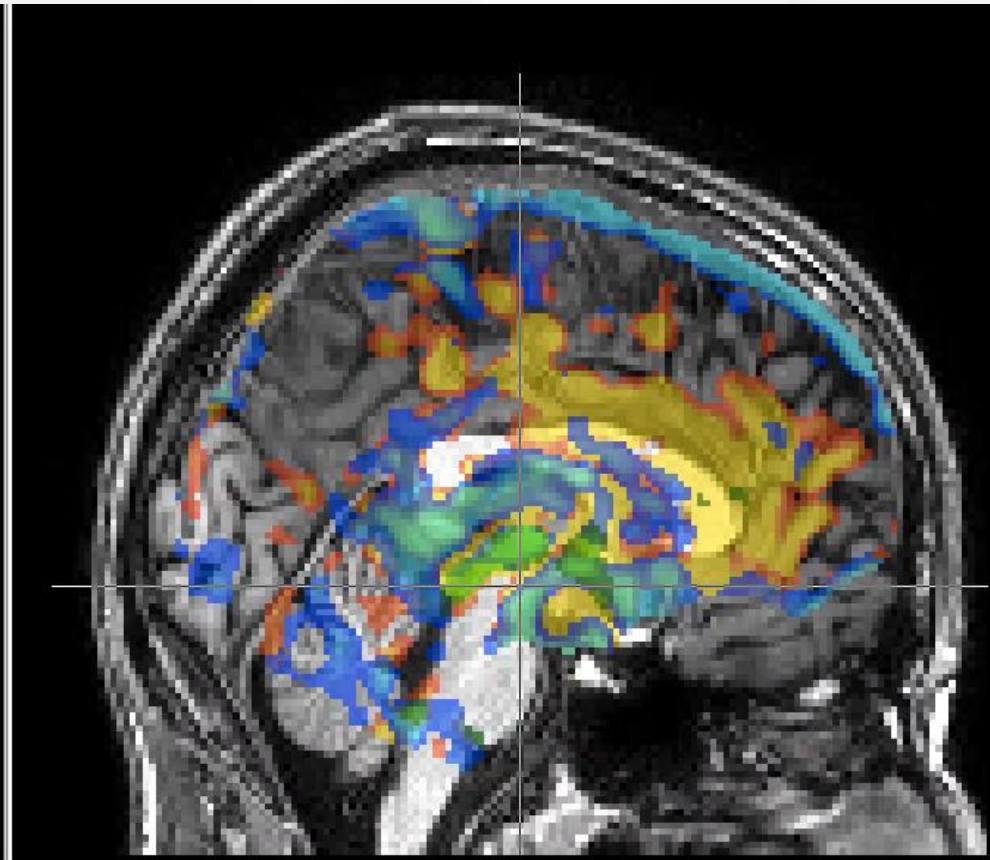
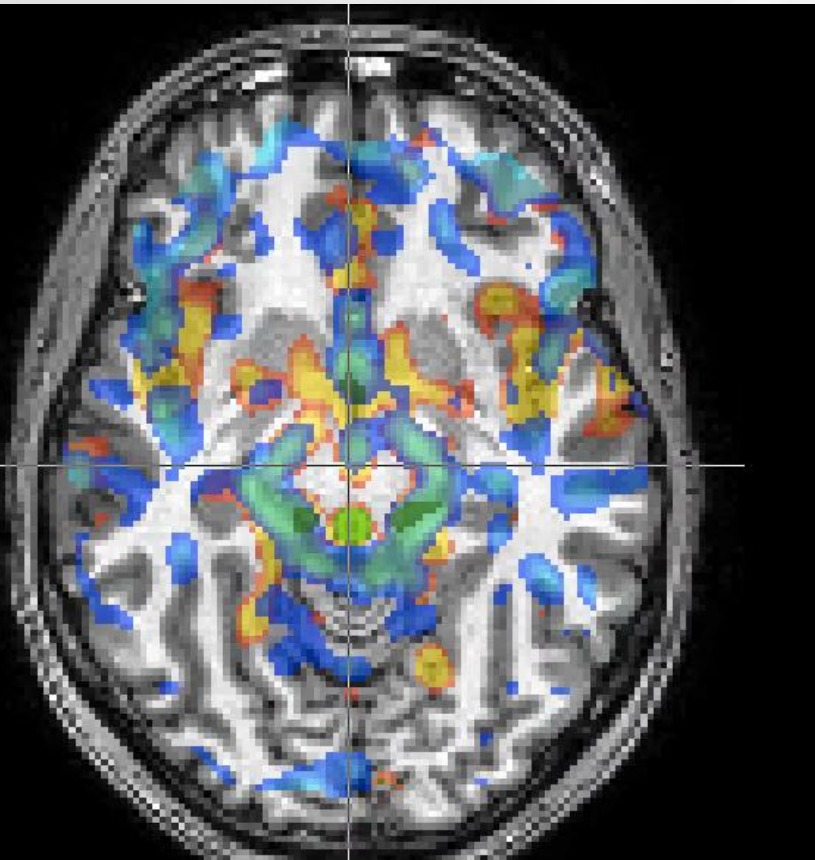
fMRI design: Philips Achieva 3T
TR/TE 2500/36ms, 2 x 2 x 3 mm³

Diaconescu et al, 2014, PLoS Comp. Biol.

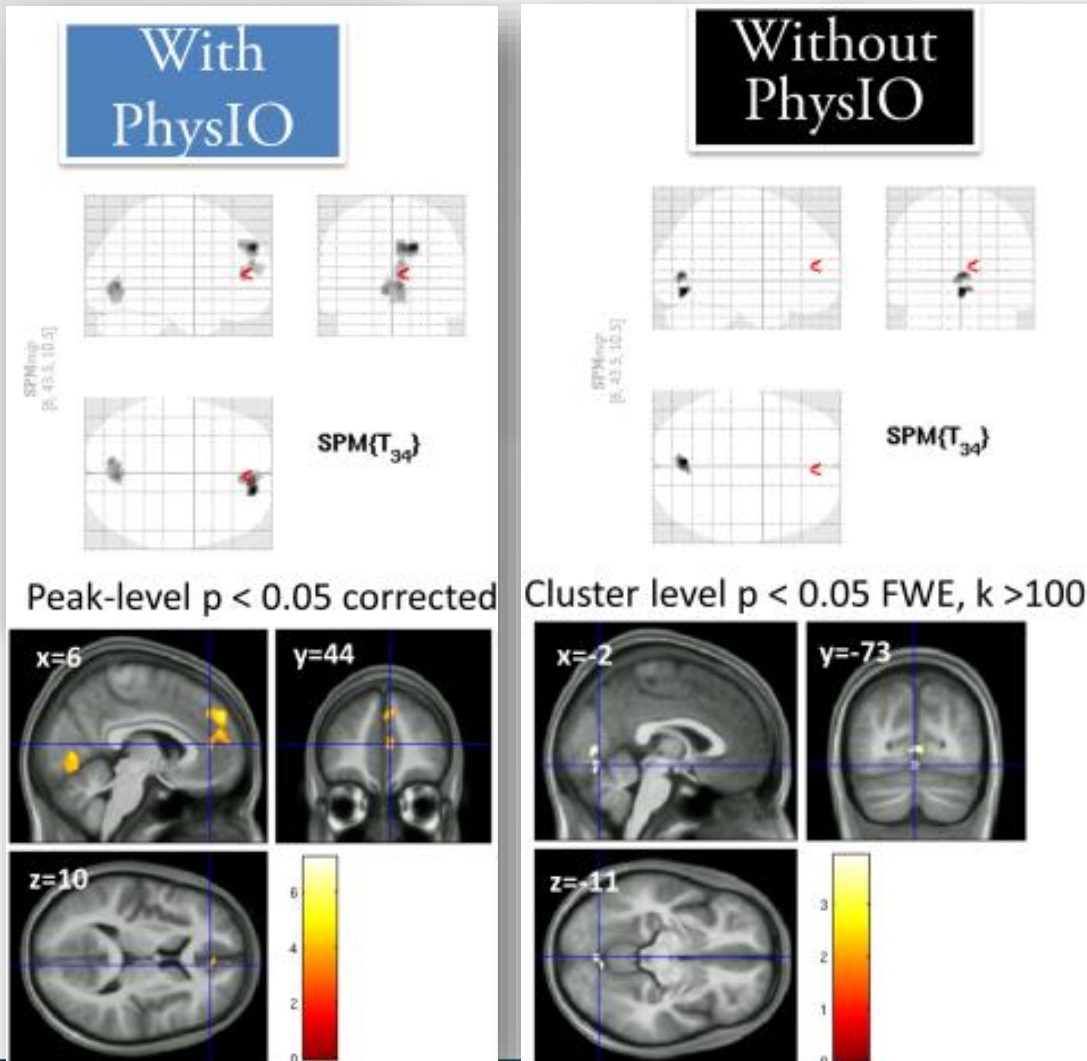
- Andreea Diaconescu (TNU): Social Learning Experiment 2012-2014, (N=35)
- F-contrast: Where does physiological noise model explain significant variance?



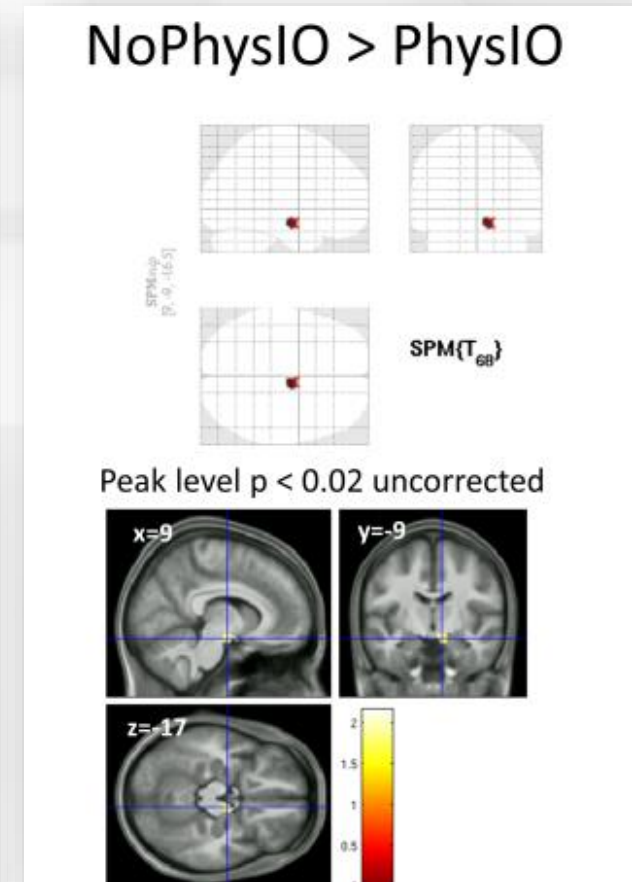
- cardiac (red), respiratory (blue), cardXresp (green)



Higher Sensitivity



False Positives



2nd level t-contrast
Social Prediction Error

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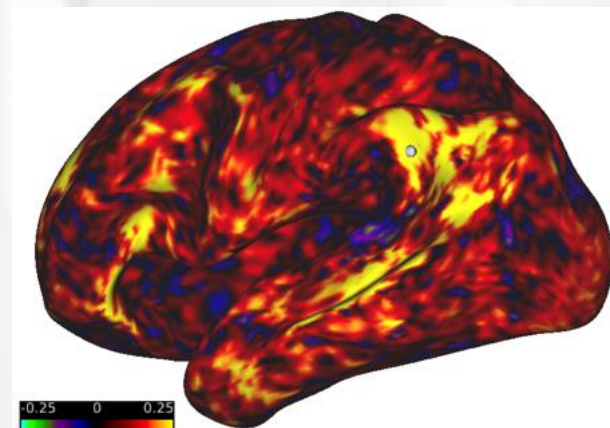
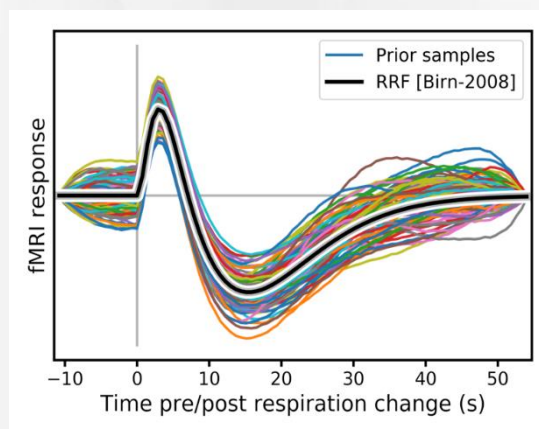
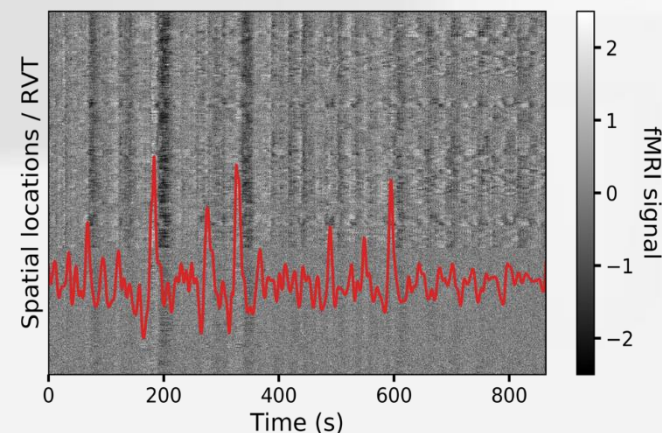


- Degrees of freedom, sensitivity reduced by too many ineffective regressors
 - F-test informative
- Intrinsic correlations of functional areas of interoception and peripheral physiology
 - E.g. Amygdala, Insula, ACC
 - Controversial reading:
[fMRI of the Amygdala: All In Vein? – Neuroskeptic](#)
 -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



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

- “Subject-specific physiological noise removal with deep Bayesian inference”
 - Semester / Master thesis
 - Start early next year
 - harrison@biomed.ee.ethz.ch



Thank you for your attention

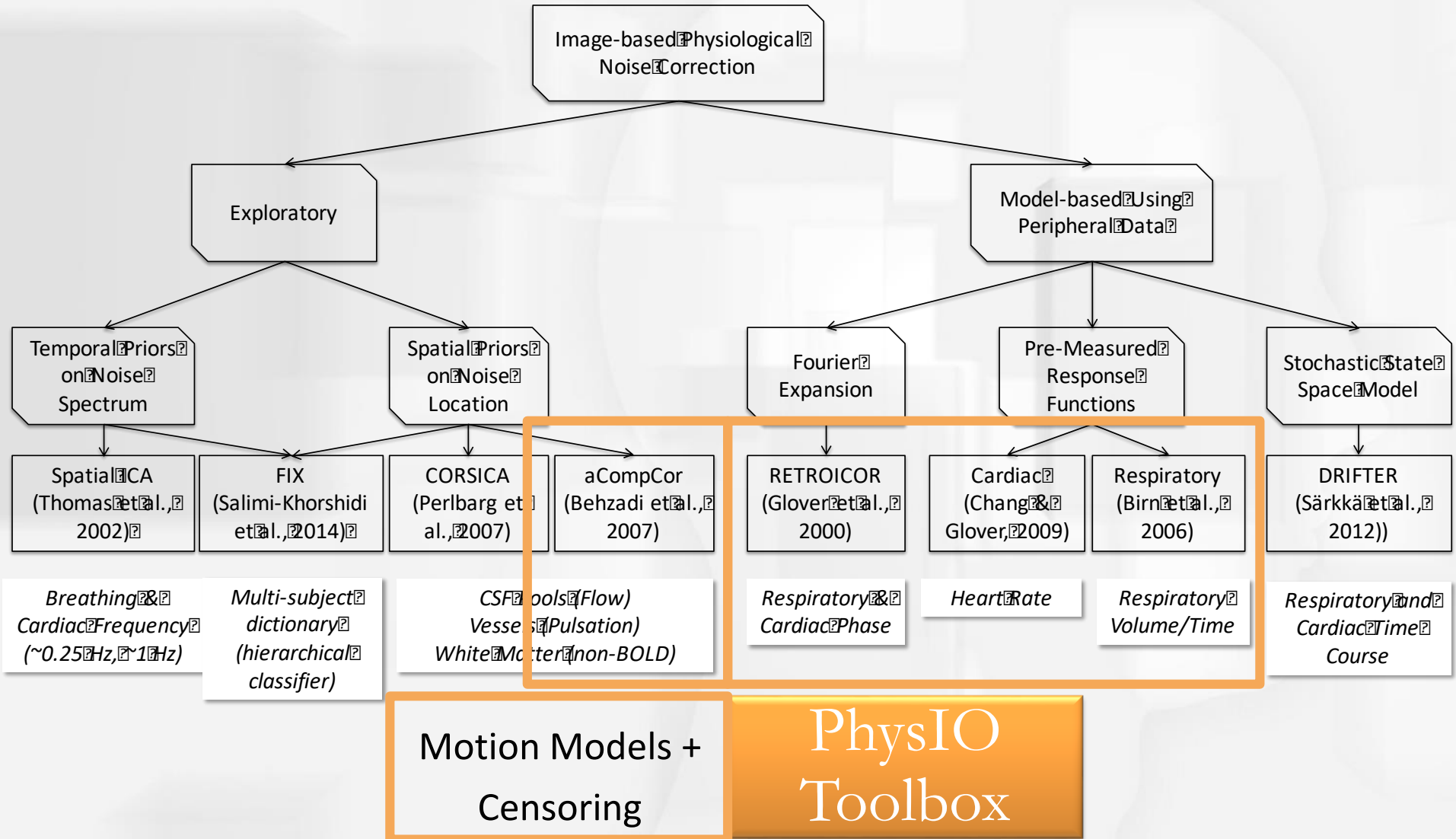


- ... and
 - TNU
 - Lars Kasper



- **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://www.tnu.ethz.ch/en/software/tapas.html>
 - <https://www.tnu.ethz.ch/en/software/tapas/data.html>



- Download as zip:

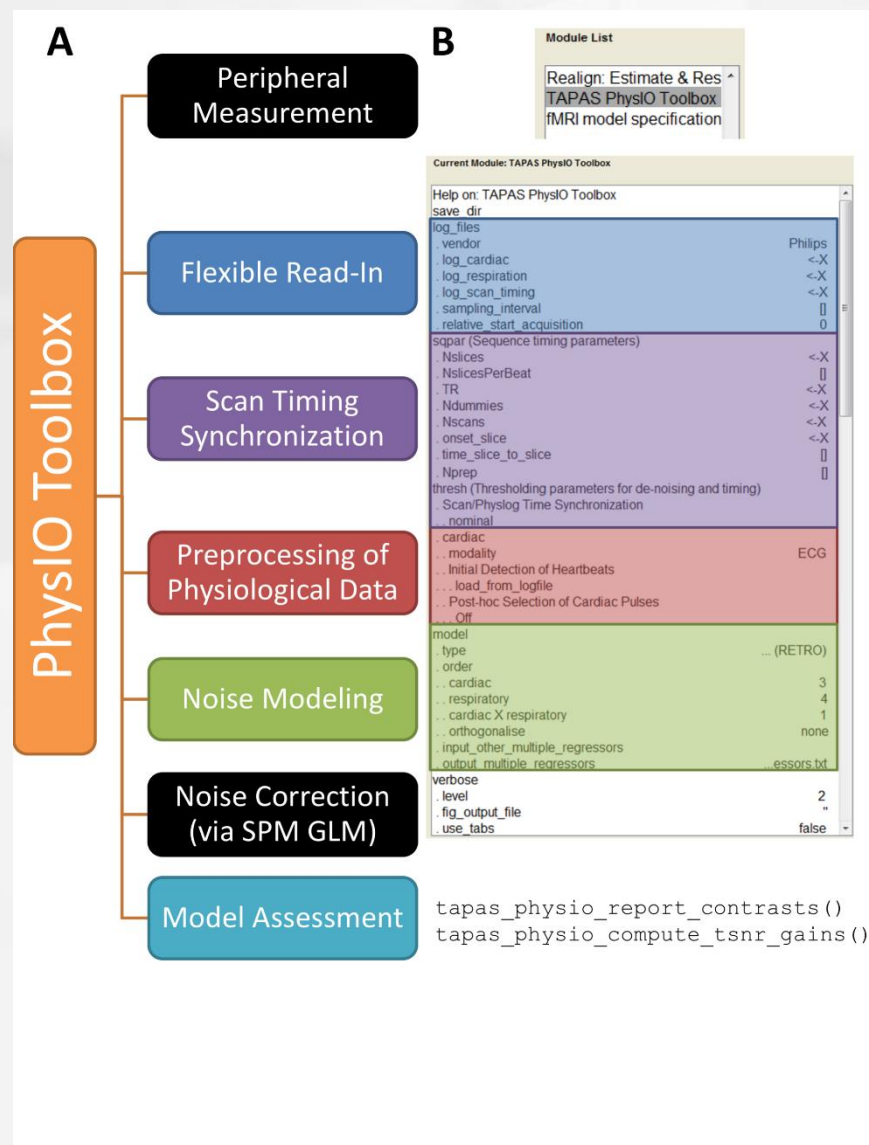
<https://translationalneuromodeling.github.io/tapas/#download>

- Git/SVN:

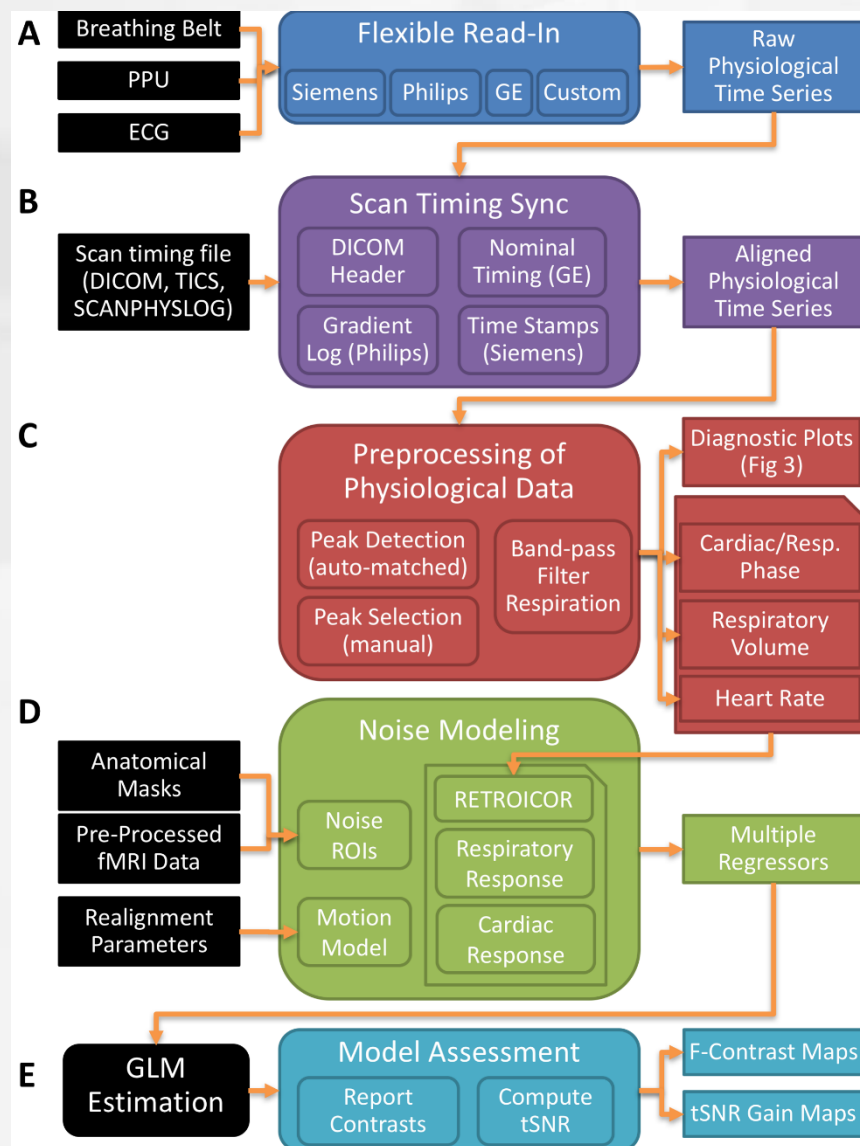
<https://github.com/translationalneuromodeling/tapas.git>

- Run `tapas/tapas_init.m` (adds `tapas` folder to path)
- Run `tapas_physio_init.m` (for SPM integration)

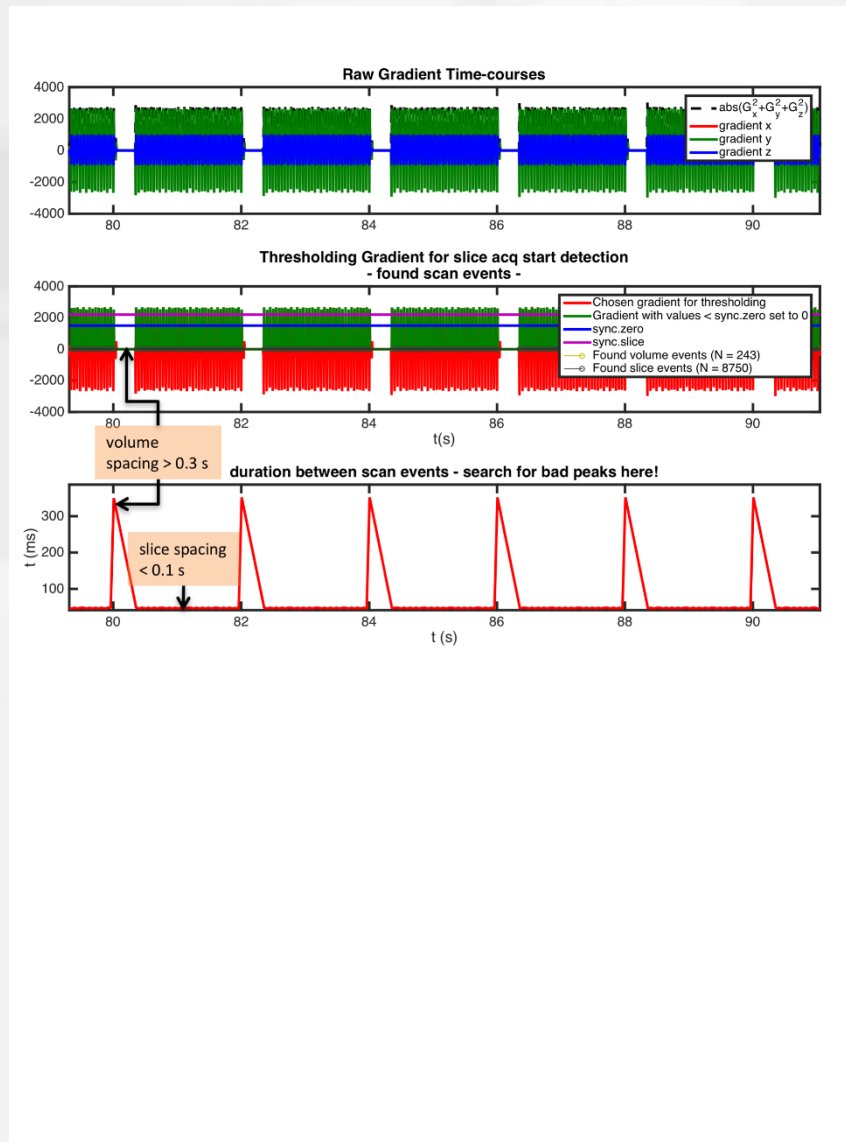
Workflow of the PhysIO Toolbox



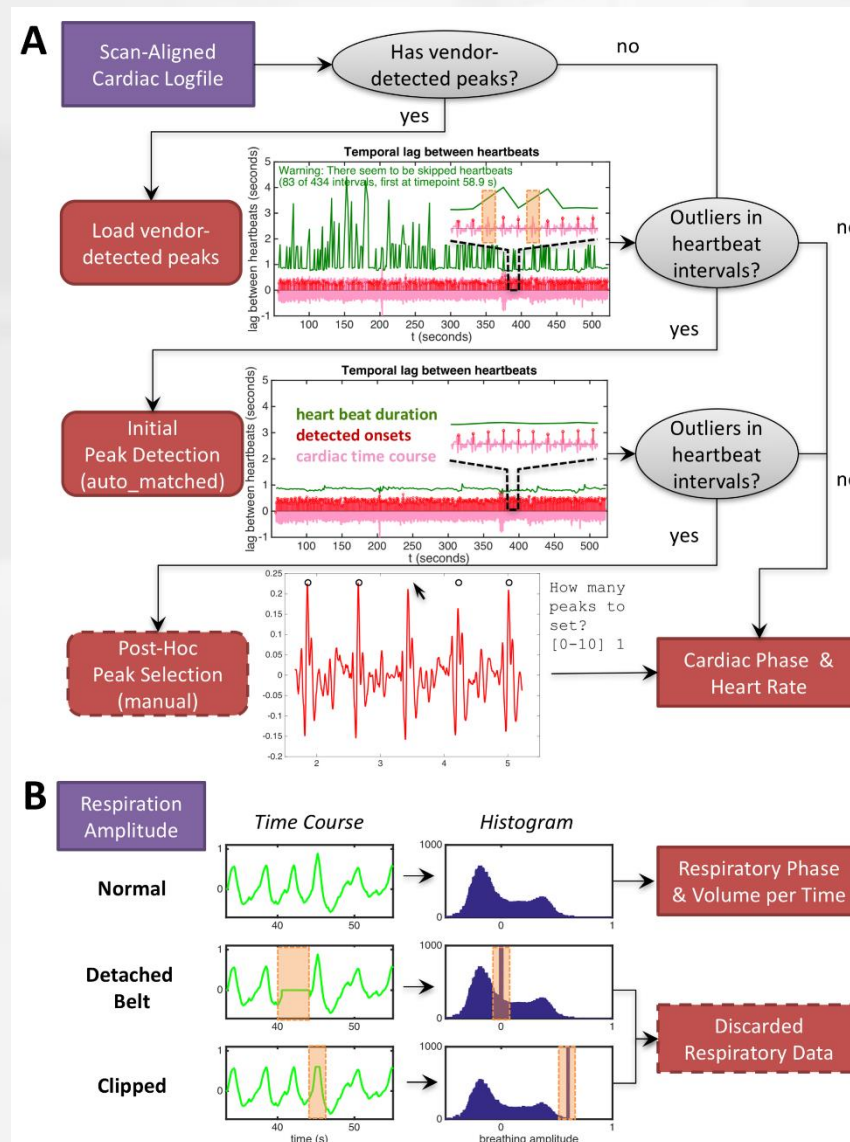
Flowchart of Noise Correction



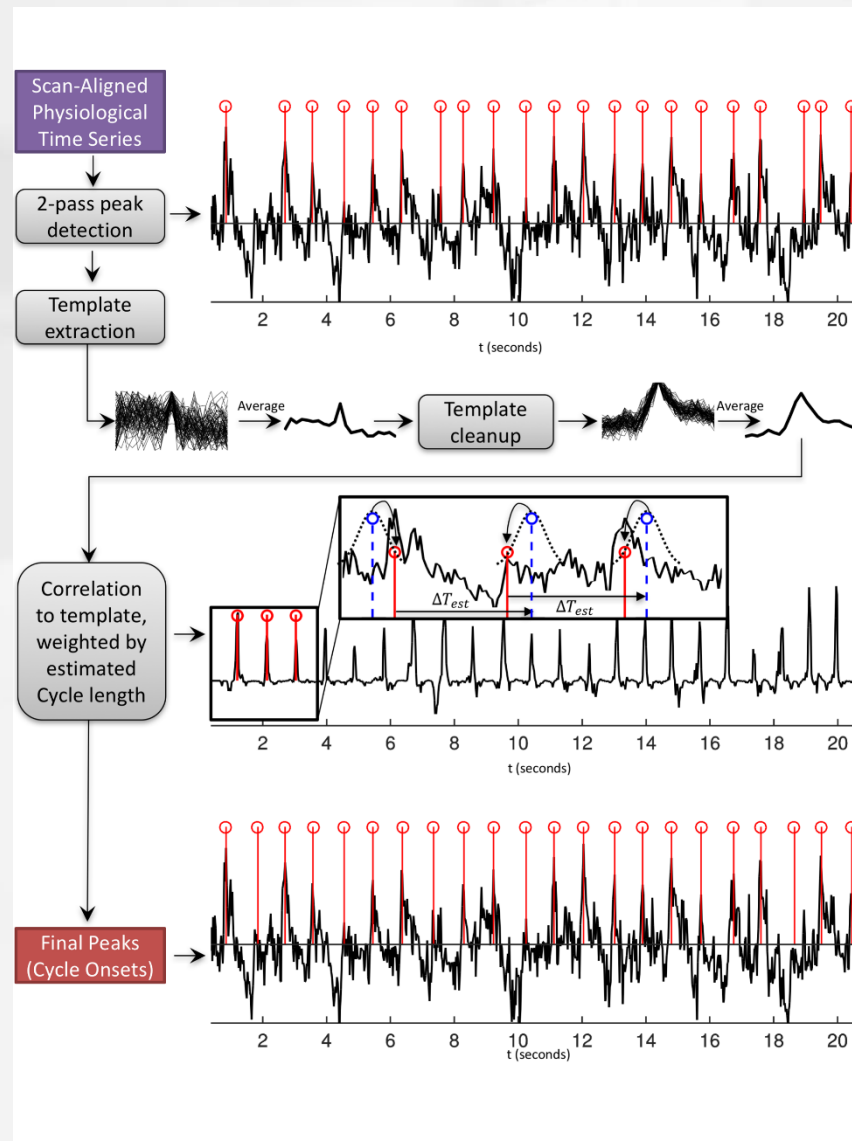
Scan Sync with Philips Gradients



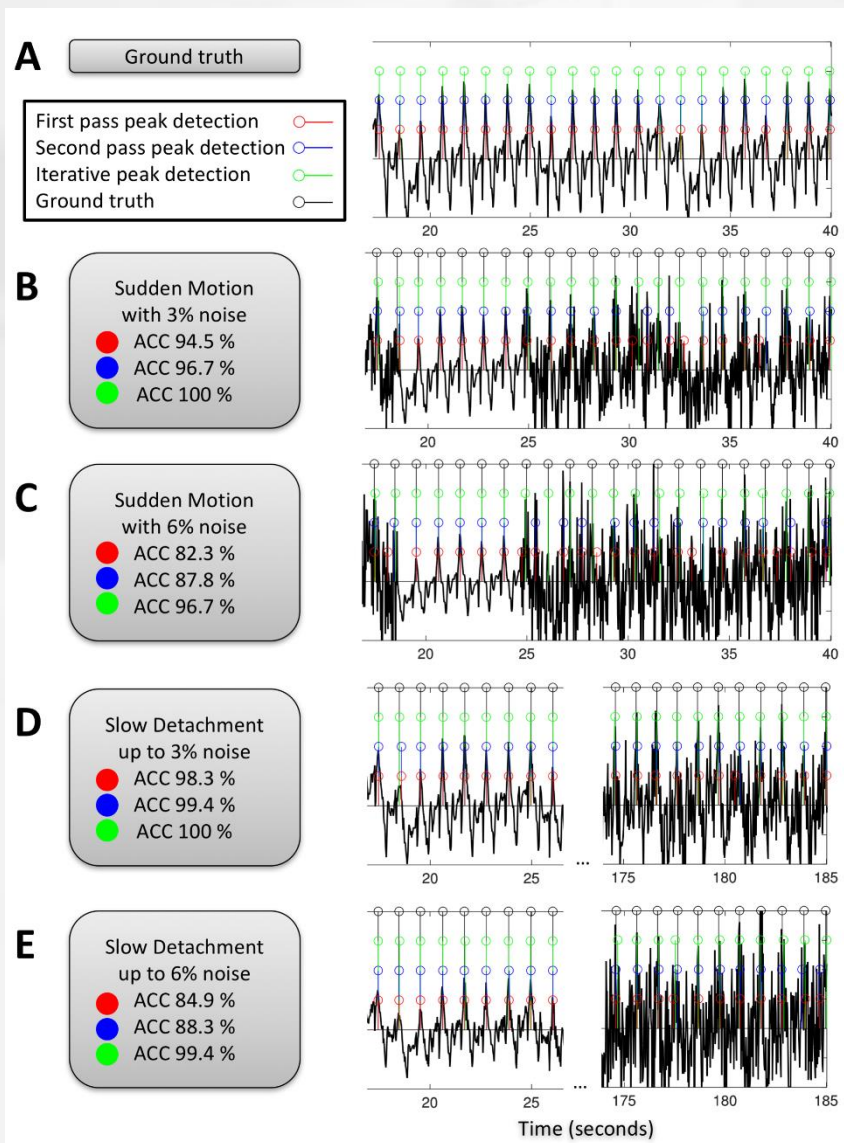
Data Preprocessing Overview



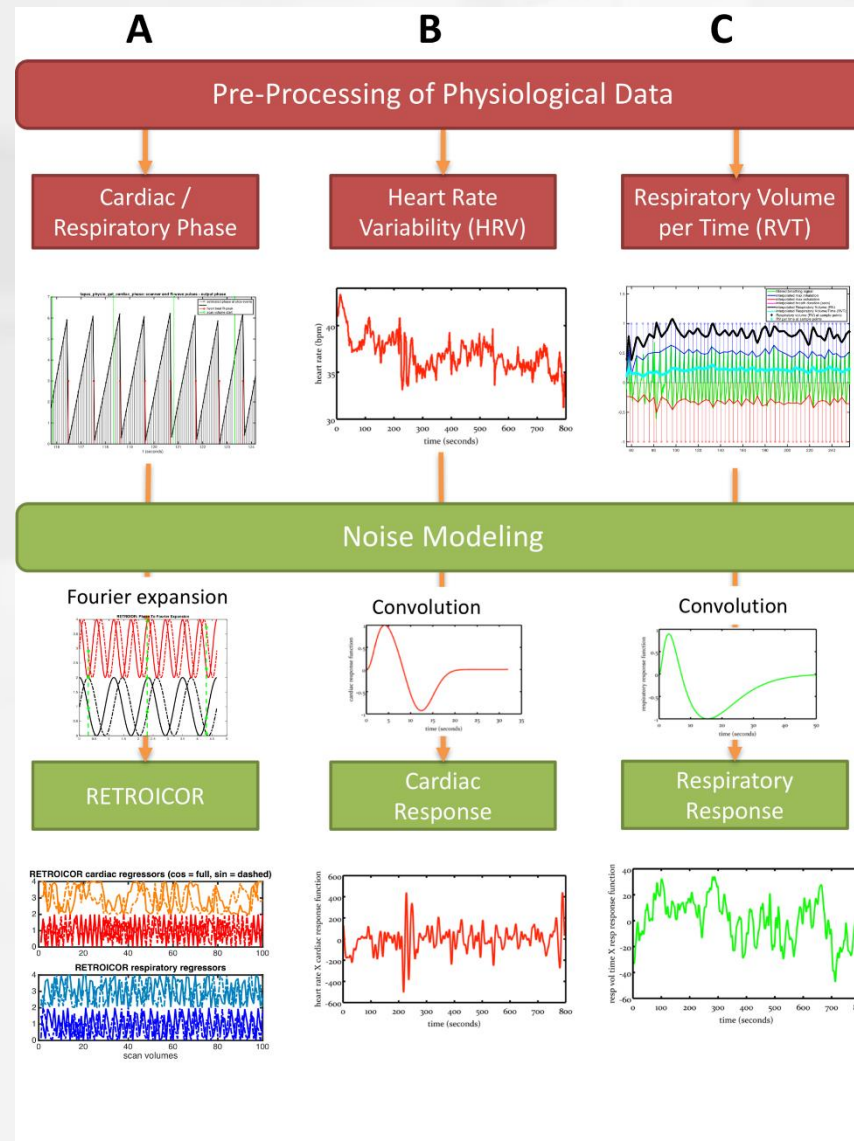
Preprocessing: Peak Detection

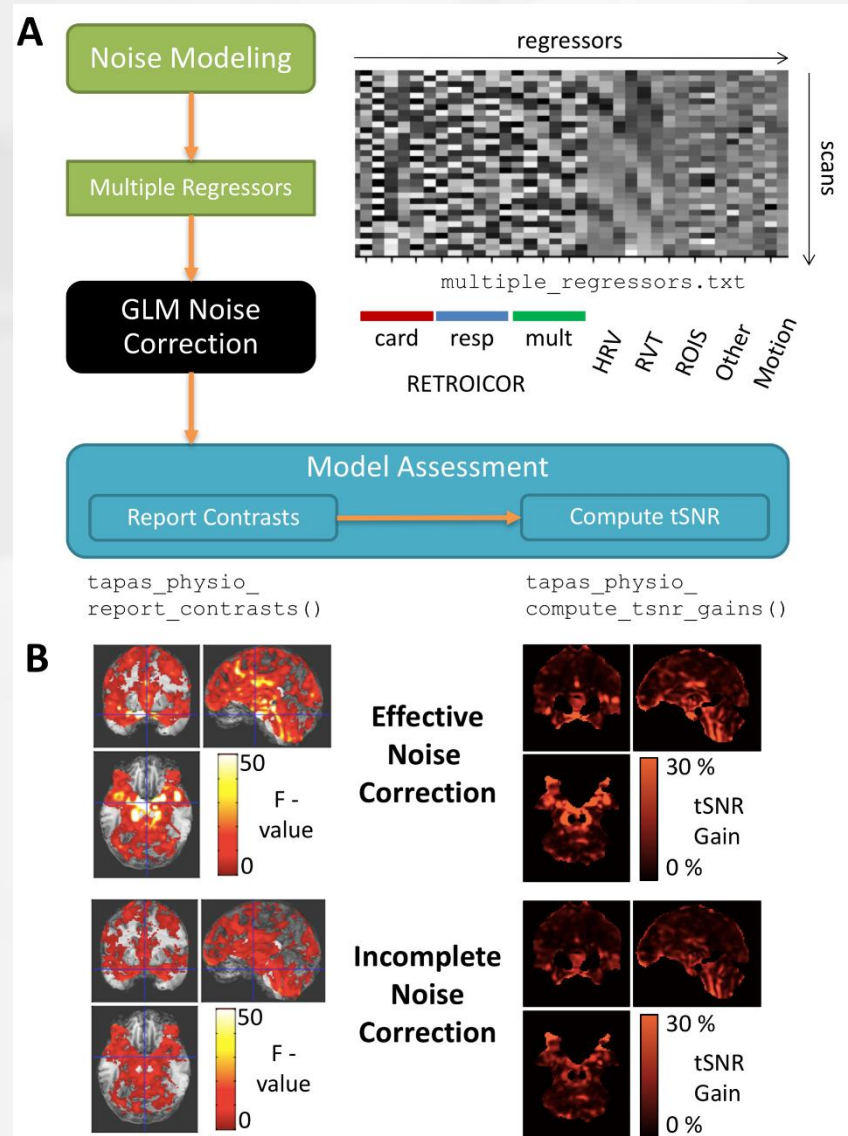


Peak Detection: Robustness



Noise Modeling

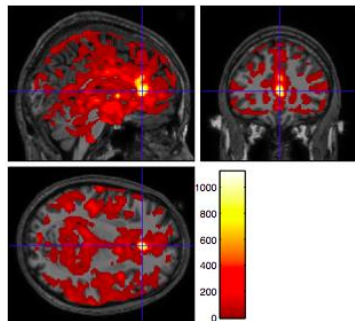
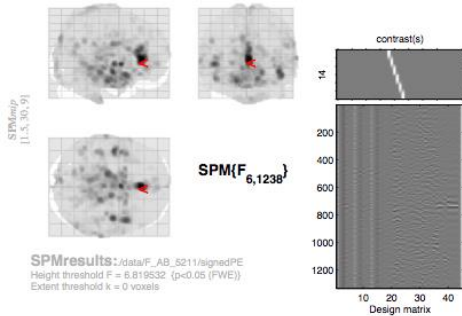




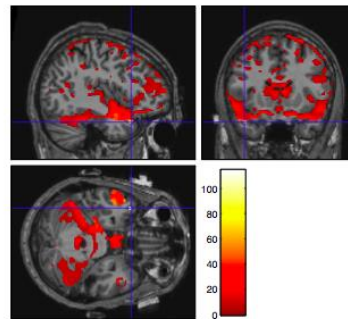
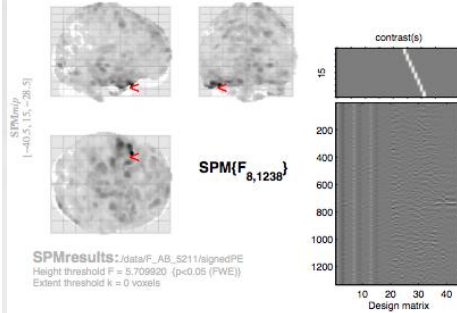
Model Check: SPM F-contrasts



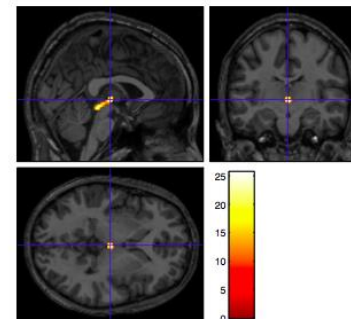
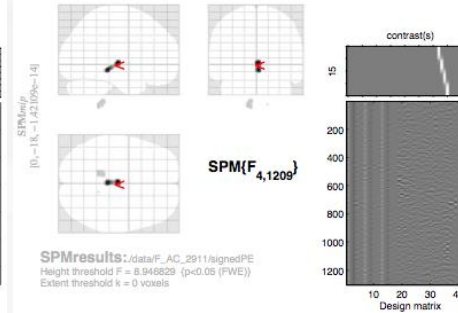
Cardiac regressors



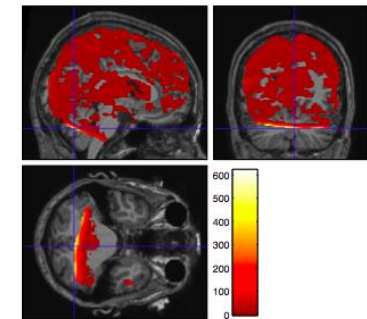
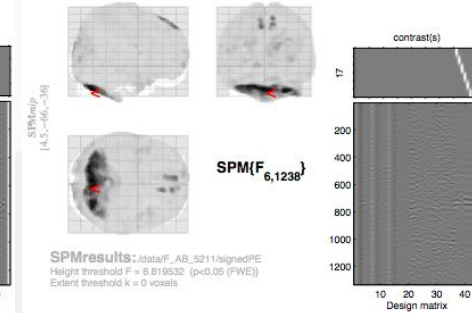
Respiratory regressors



Cardiac x Respiratory



Movement regressors

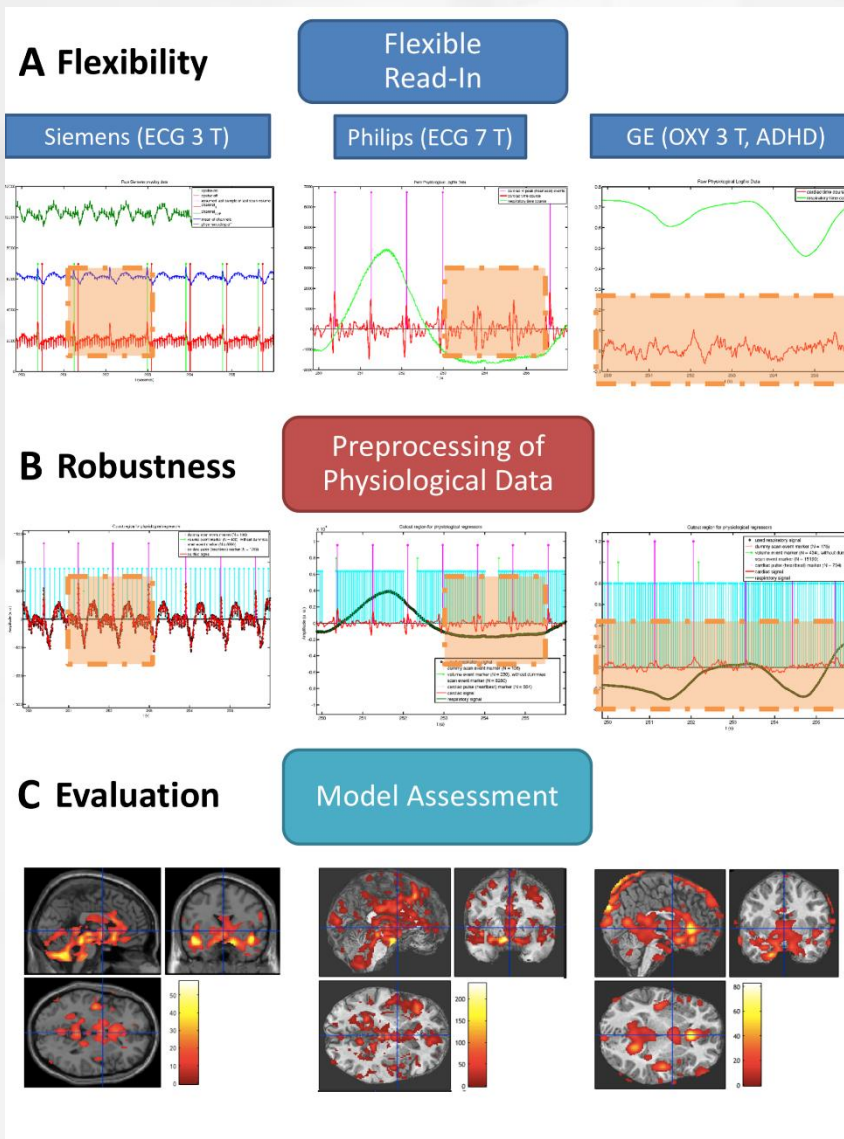


Finally:

Check Influence of Physiological Noise (Correction) on Data

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

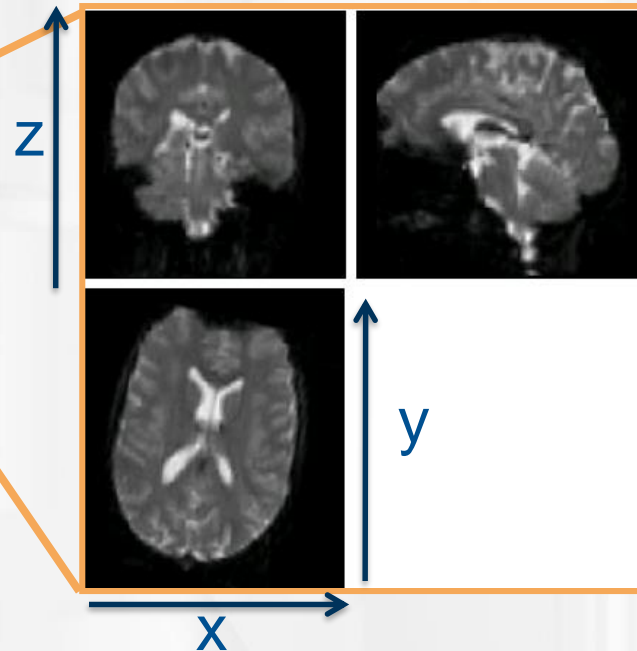
Flexibility: Scanner vendors





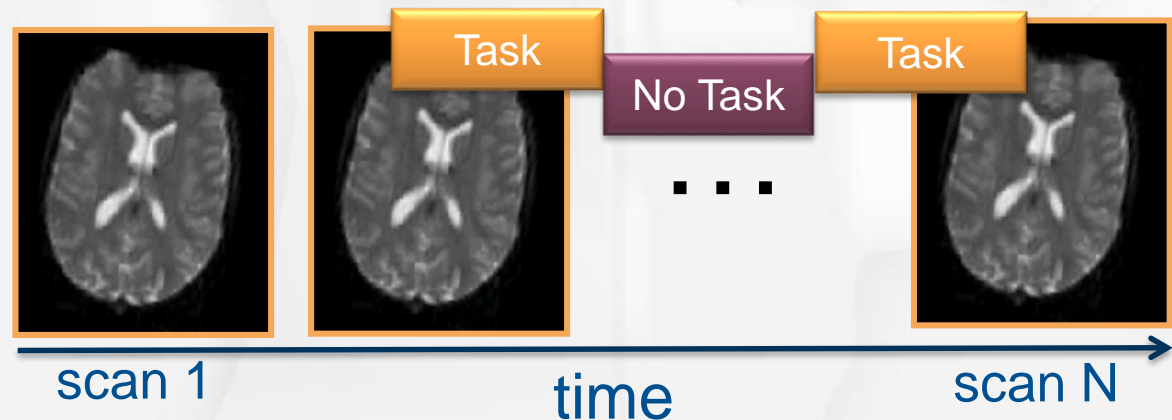
- **Birn**, Rasmus M., Jason B. Diamond, Monica A. Smith, and Peter A. Bandettini. 2006. “Separating Respiratory-variation-related Fluctuations from Neuronal-activity-related Fluctuations in fMRI.” *NeuroImage* 31 (4) (July 15): 1536–1548. doi:10.1016/j.neuroimage.2006.02.048.
- **Glover**, G H, T Q 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., 2016. The PhysIO Toolbox for Modeling Physiological Noise in fMRI Data. *Journal of Neuroscience Methods* *accepted*. 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



- Old version of an batch. OR: `physio = tapas_physio_new()`;

```
-----  
% Job saved on 25-Mar-2018 11:50:11 by cfg_util (rev $Rev: 6942 $)  
% cfg_basicio BasicIO - Unknown  
% spm_SPM - SPM12 (7219)  
-----  
matlabbatch(1).spm.tools.physio.save_dir = {'/*/Results01/Sub01'};  
matlabbatch(1).spm.tools.physio.log_files.vendor = 'Philips';  
matlabbatch(1).spm.tools.physio.log_files.cardiac = {'/*/Results01/Sub01/physlog/physlog_run01.log'};  
matlabbatch(1).spm.tools.physio.log_files.respiration = {'/*/Results01/Sub01/physlog/physlog_run01.log'};  
matlabbatch(1).spm.tools.physio.log_files.scan_timing = {''};  
matlabbatch(1).spm.tools.physio.log_files.sampling_interval = [];  
matlabbatch(1).spm.tools.physio.log_files.relative_start_acquisition = 0;  
matlabbatch(1).spm.tools.physio.log_files.align_scan = 'last';  
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matlabbatch(1).spm.tools.physio.scan_timing.sqpar.Ndummies = 1;  
matlabbatch(1).spm.tools.physio.scan_timing.sqpar.Nscans = 145;  
matlabbatch(1).spm.tools.physio.scan_timing.sqpar.onset_slice = 16;  
matlabbatch(1).spm.tools.physio.scan_timing.sqpar.time_slice_to_slice = [];  
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matlabbatch(1).spm.tools.physio.scan_timing.sync.gradient_log.grad_direction = 'z';  
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matlabbatch(1).spm.tools.physio.preproc.cardiac.initial_cpulse_select.auto_matched.min = 0.4;  
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matlabbatch(1).spm.tools.physio.preproc.cardiac.posthoc_cpulse_select.off = struct([]);  
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matlabbatch(1).spm.tools.physio.model.output_physio = 'physio_run01.mat';  
matlabbatch(1).spm.tools.physio.model.orthogonalise = 'none';  
matlabbatch(1).spm.tools.physio.model.censor_unreliable_recording_intervals = false;  
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matlabbatch(1).spm.tools.physio.model.retroicor.yes.order.r = 4;  
matlabbatch(1).spm.tools.physio.model.retroicor.yes.order.cr = 1;  
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matlabbatch(1).spm.tools.physio.model.movement.yes.file_realignment_parameters = {'/*/Results01/Sub01/scandata/rp_afmri01.txt'};  
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matlabbatch(1).spm.tools.physio.model.movement.yes.censoring_threshold = 1;  
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matlabbatch(1).spm.tools.physio.verbose.level = 2;  
matlabbatch(1).spm.tools.physio.verbose.fig_output_file = 'physio.fig';  
matlabbatch(1).spm.tools.physio.verbose.use_tabs = false;
```