BASQUE CENTER ON COGNITION, BRAIN AND LANGUAGE

Vancouver, June 25 2017

2017 OHBM VANCOUVER June 25-29, 2017

Educational Course
Advanced methods for cleaning up fMRI time series

Overview of noise and denoising methods in BOLD fMRI

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San Sebastian - Donostia, Spain
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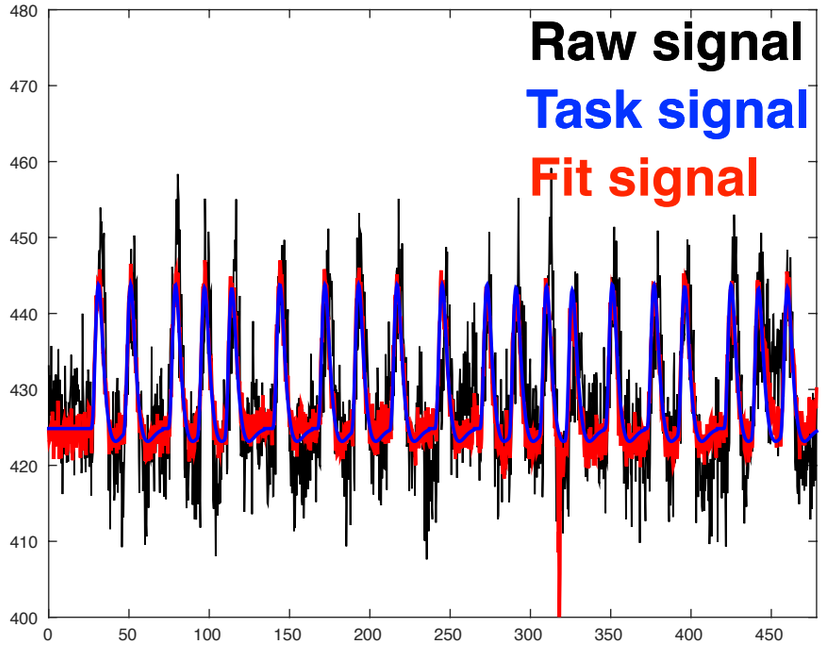
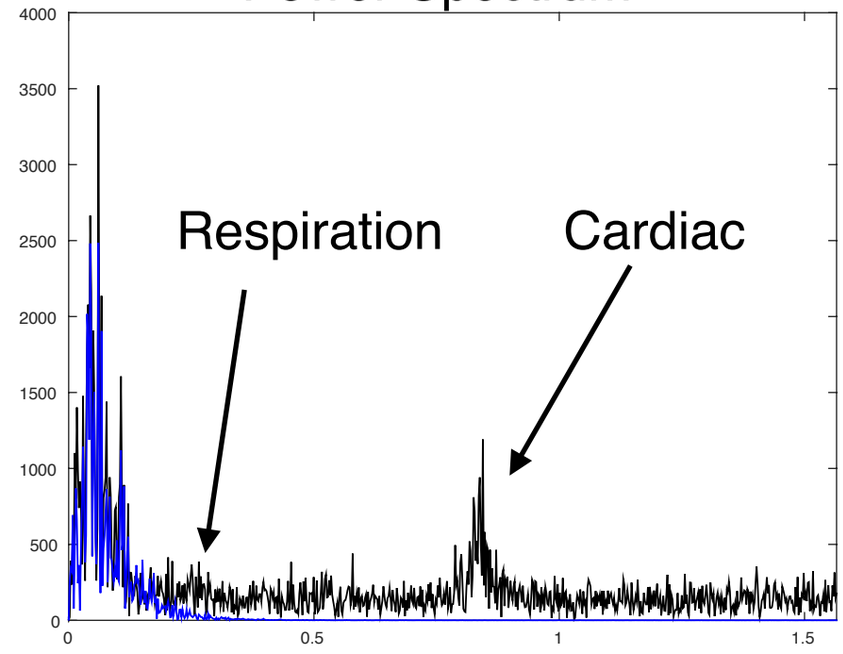
Basics of BOLD fMRI (data analysis)

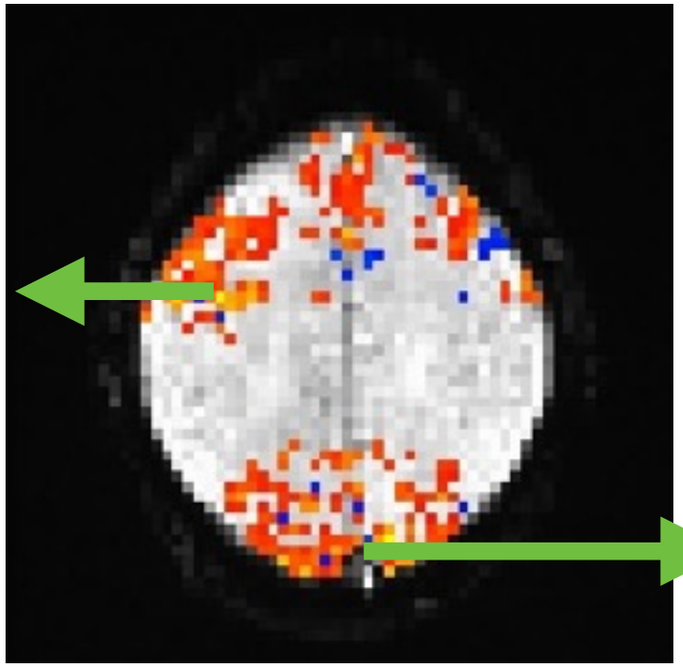
Introduction: Task-based fMRI



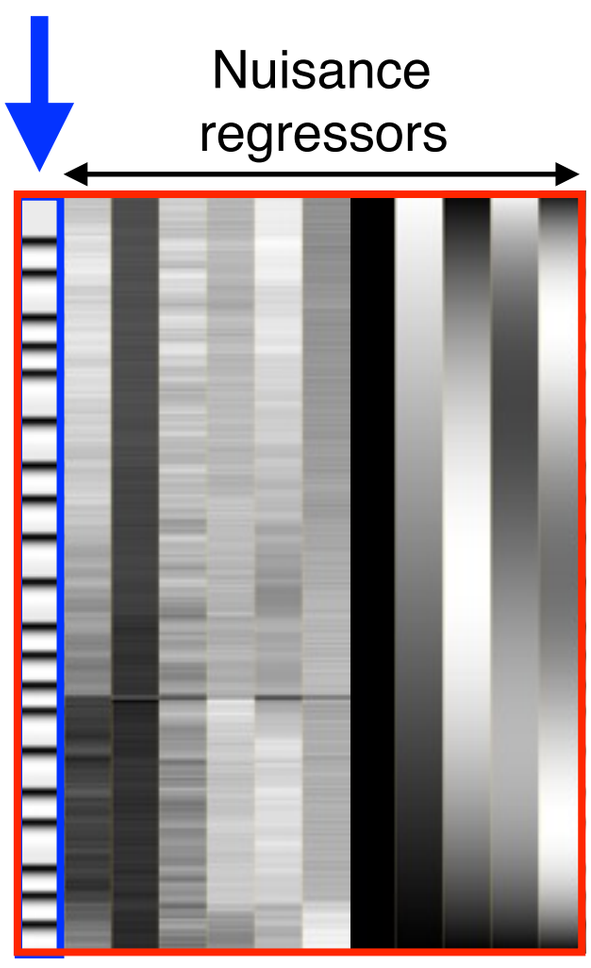
TR: 319 m

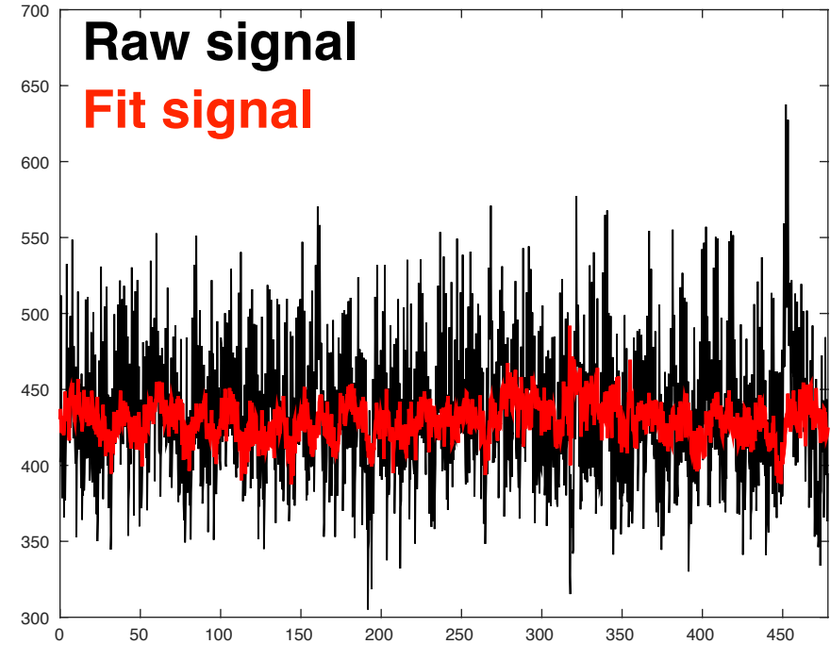
$F_{nyquist}$: 1.56 Hz

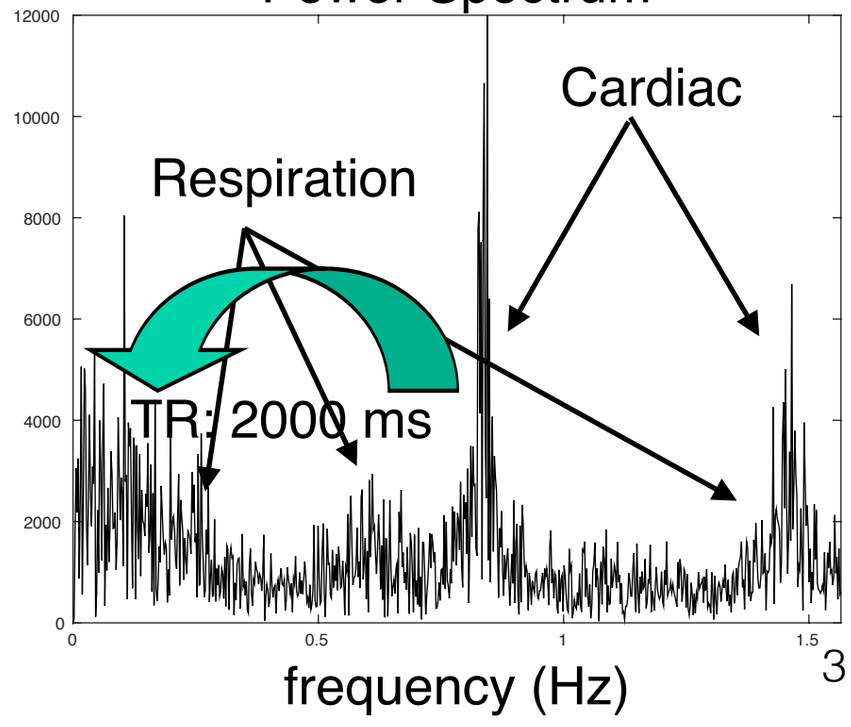




Nuisance regressors

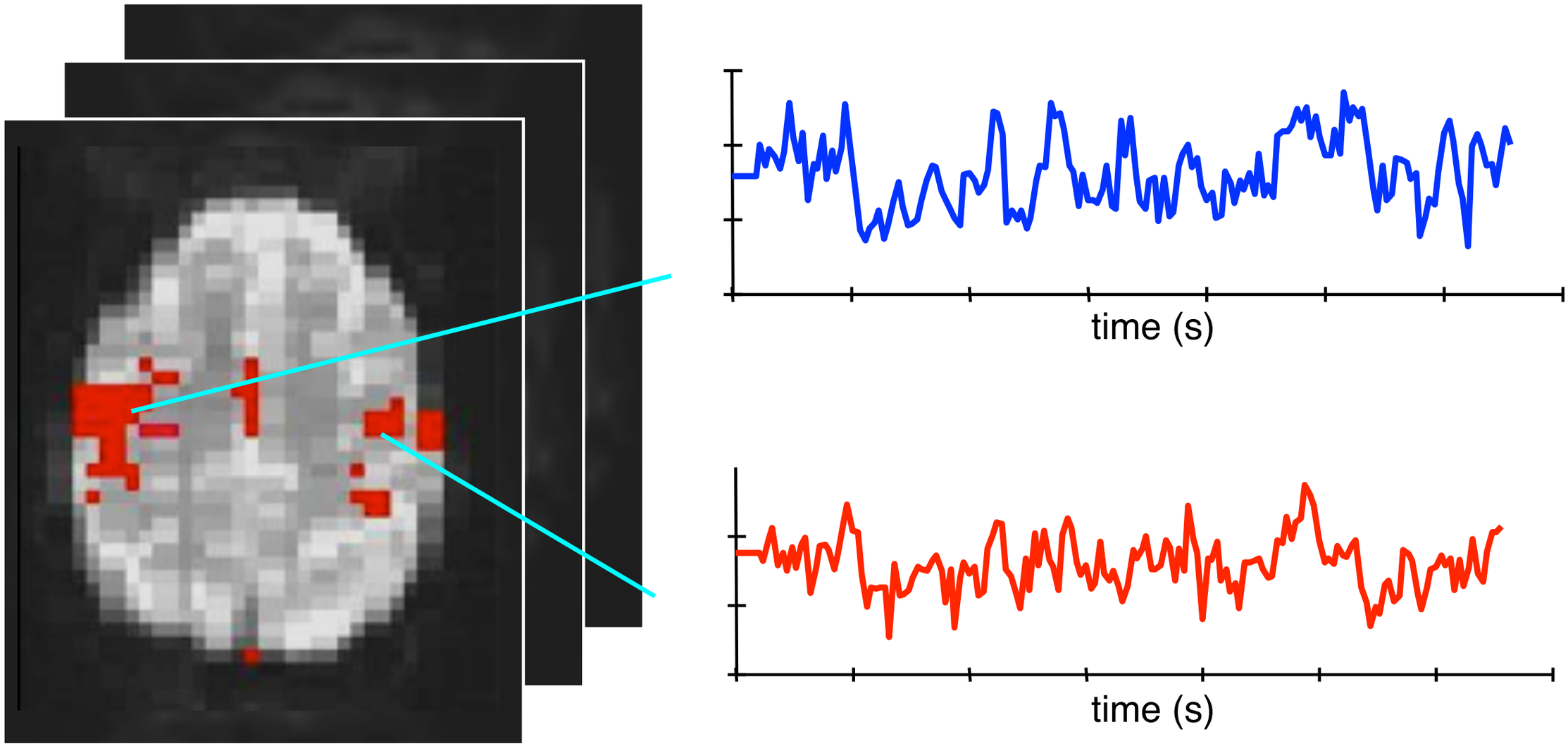






Introduction: Resting-state fMRI

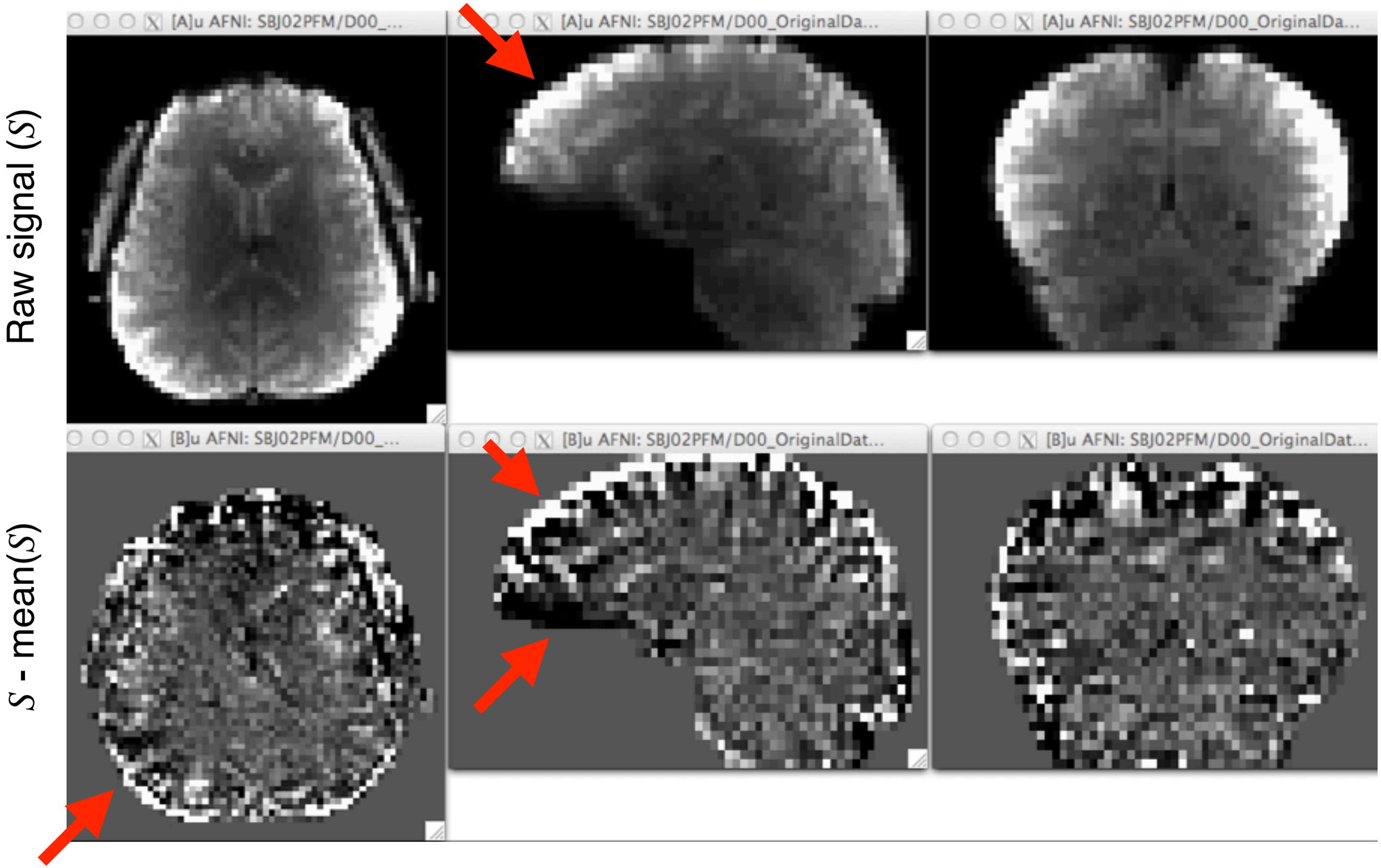
- In resting-state fMRI, the reference signal is usually the time series of a voxel or region of interest.



Slide courtesy of Rasmus Birn (University of Wisconsin-Madison)

Sources of the BOLD fMRI signal

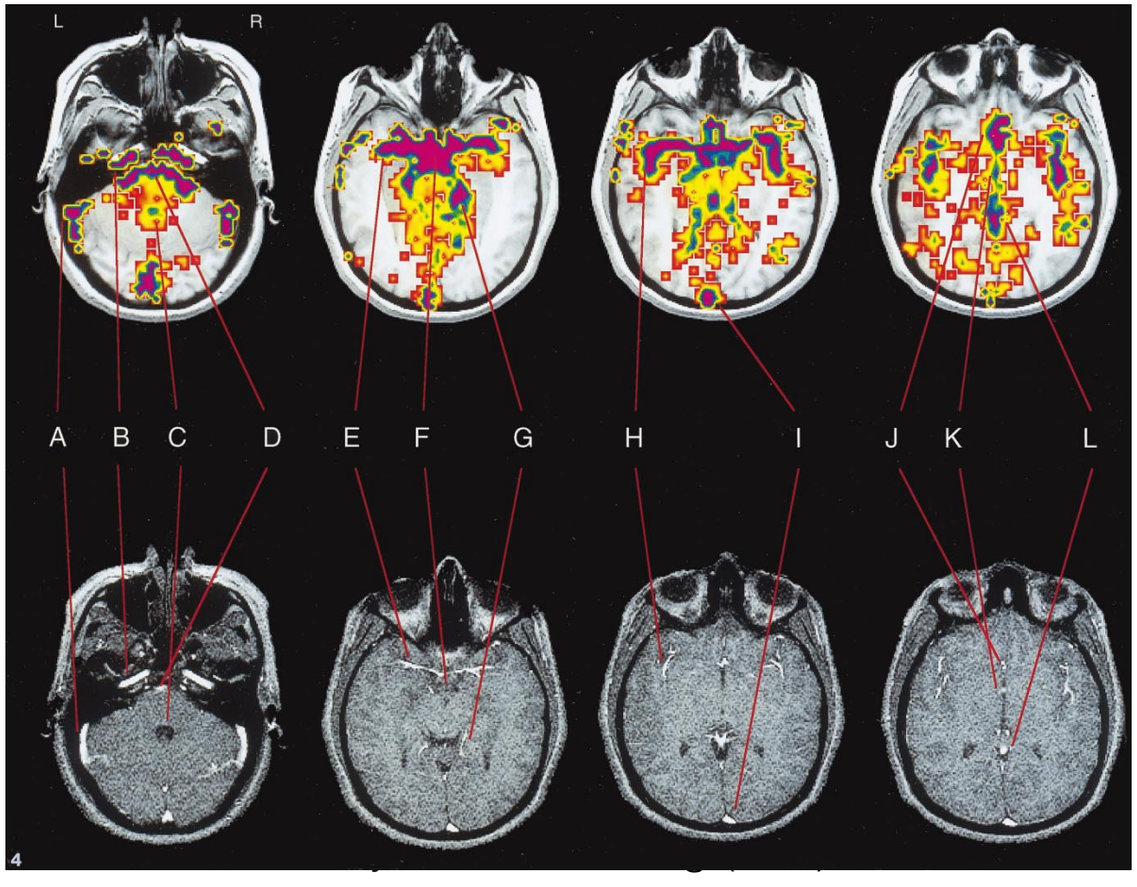
Sources of the fMRI signal: Motion-related fluctuations

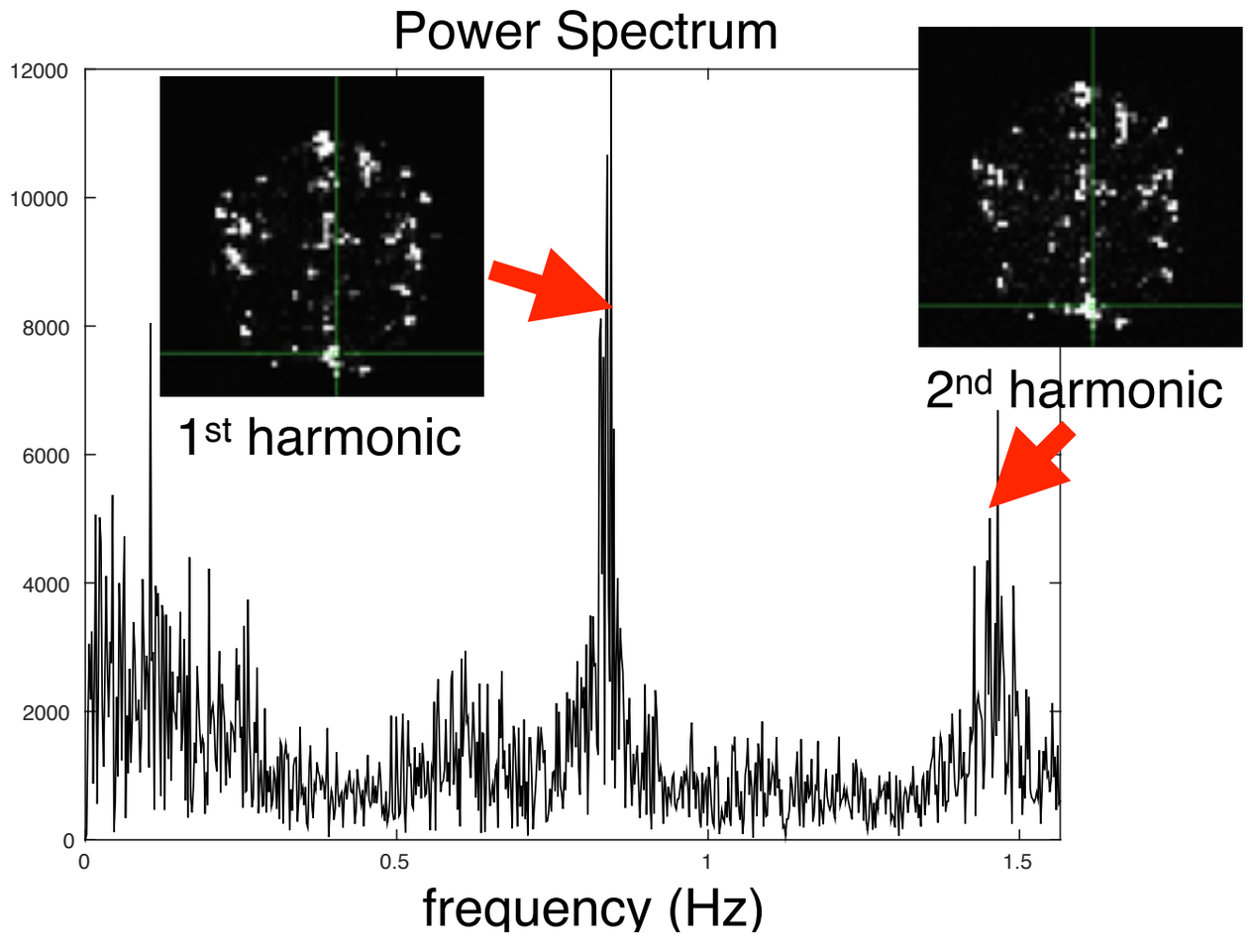


Video courtesy of Javier Gonzalez Castillo (NIH)

Cardiac Noise

- Cardiac pulsability generates small movements in brain tissue as well as inflow effects in and around vessels. It is often localized in tissue regions close to:
  - Large arteries and draining veins (e.g. sagittal sinus or circle of Willis)
  - Edges of the brain, lateral ventricals and sulci.
- Heart rate is usually 50-70 beats/min: Main frequency around 0.8-1.2 Hz.



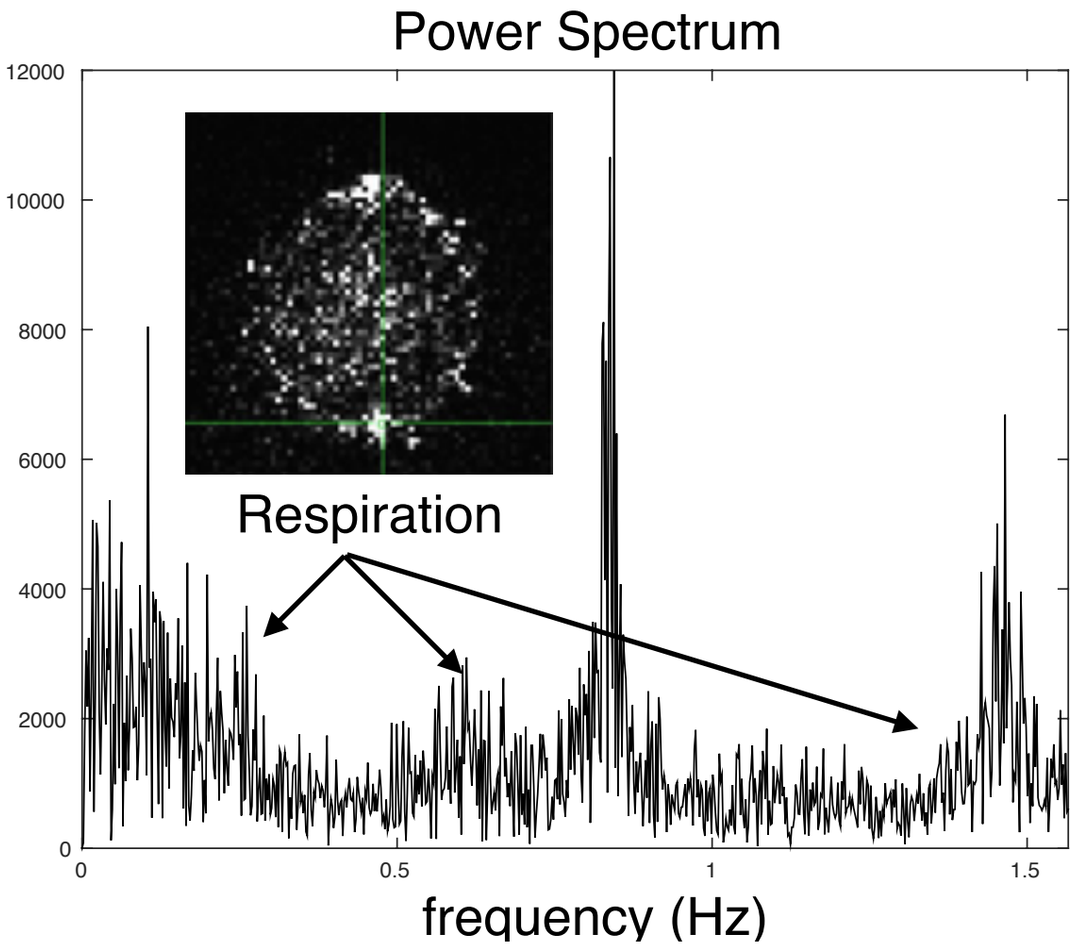


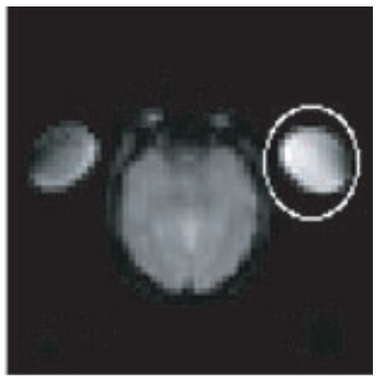
Dagli et al. (1999). Localization of cardic-induce signal change in fMRI. Neuroimage 9:407-415

Bhattacharyya and Lowe (2004). Cardiac-induced physiological noise in tissue is a direct observation of cardiac-induced fluctuations. Magn Reson Imaging 22(4):9-13.

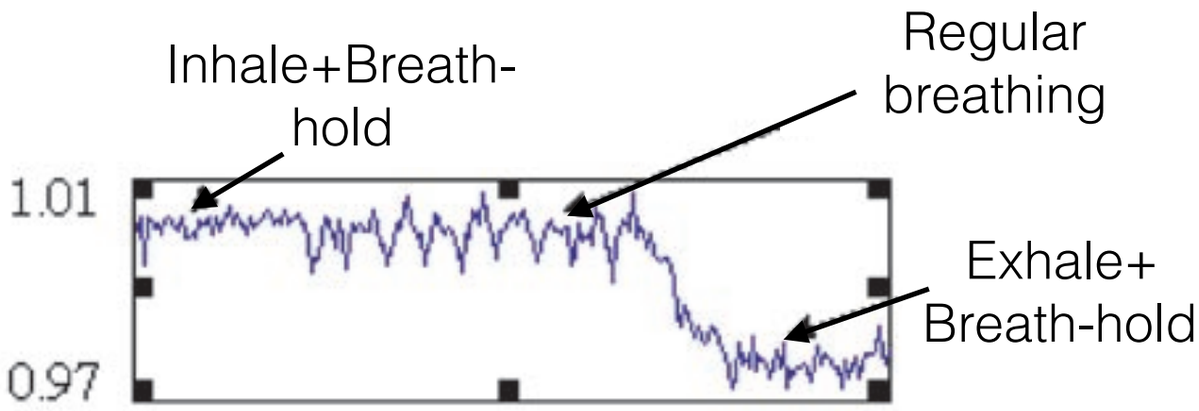
Respiratory Noise

- Thoracic movements during breathing result in respiratory-dependent changes in the magnetic field in the head volume that produce a phase shift in the image, resulting in more spatially global effects.
- Breathing rate is usually 15-25 cycles/min: Main frequency around 0.25-0.4 Hz.
- Small changes of the head also introduce spin history artefacts. Closely related to head movement artefacts and also cardiac pulsability.





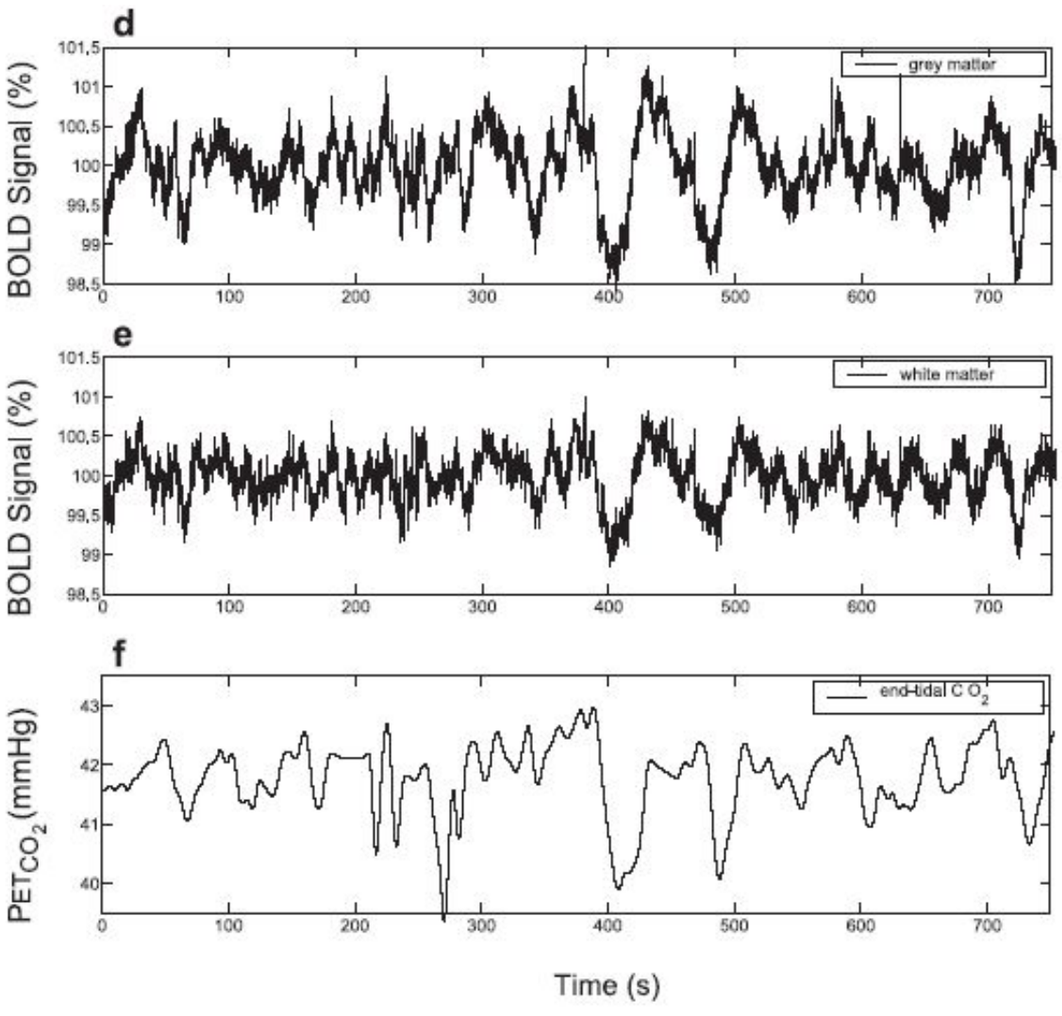
2 bottles of copper sulfate attached to the head coil

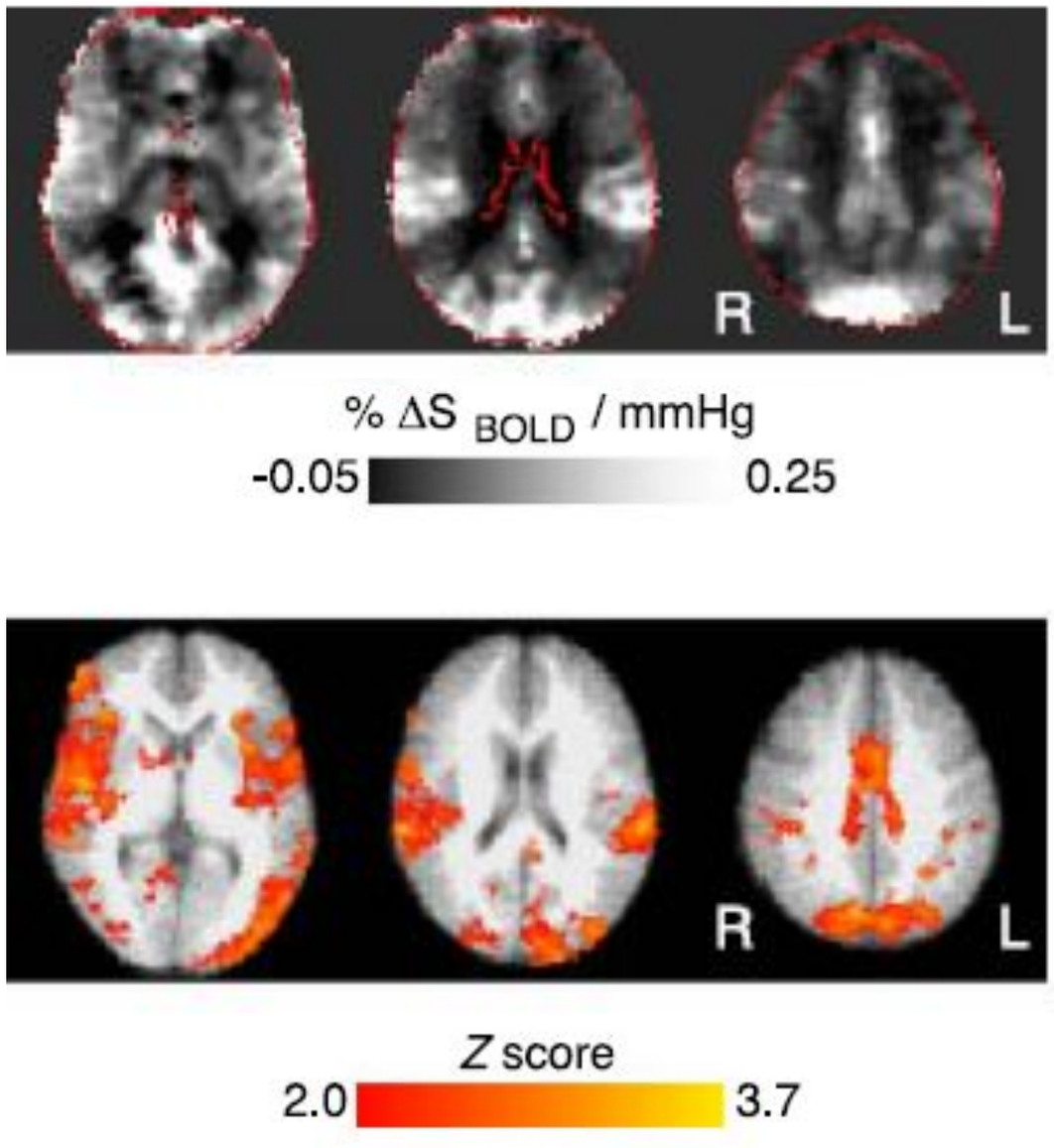


Raj et al (2001). Respiratory effects in human functional magnetic resonance imaging due to bulk susceptibility changes. Phys. Med. Biol. 46:3331-3340

Low frequency physiological fluctuations (below 0.1 Hz)

- Variations in respiratory rate affect the fMRI signal by changing the oxygenation level and arterial level of CO_2, which is a potent cerebral vasodilator.





Wise et al. (2004). Resting fluctuation in arterial carbon dioxide induce significant low frequency fluctuations in BOLD signal. Neuroimage 21(4):1652-1664.

Sources of the fMRI signal: Draining veins

- Gradient-Echo (GE) Echo-Planar Imaging (EPI) typically used for BOLD fMRI has stronger contribution from macrovessels, mainly located in pial surface.
- BOLD contamination from macrovessels (large arteries, draining veins) are a serious impediment for high-resolution localization of neuronal activity in fMRI.

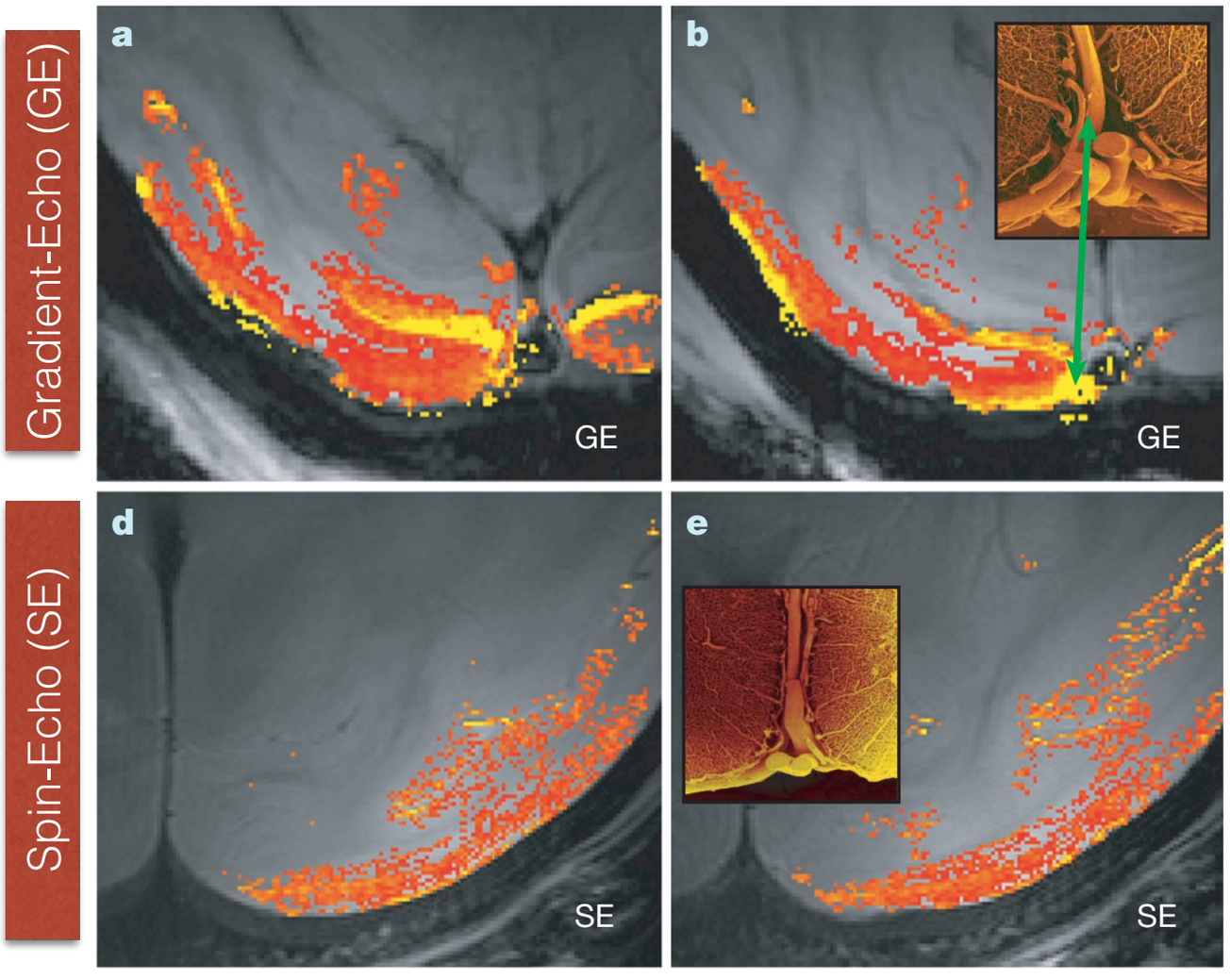
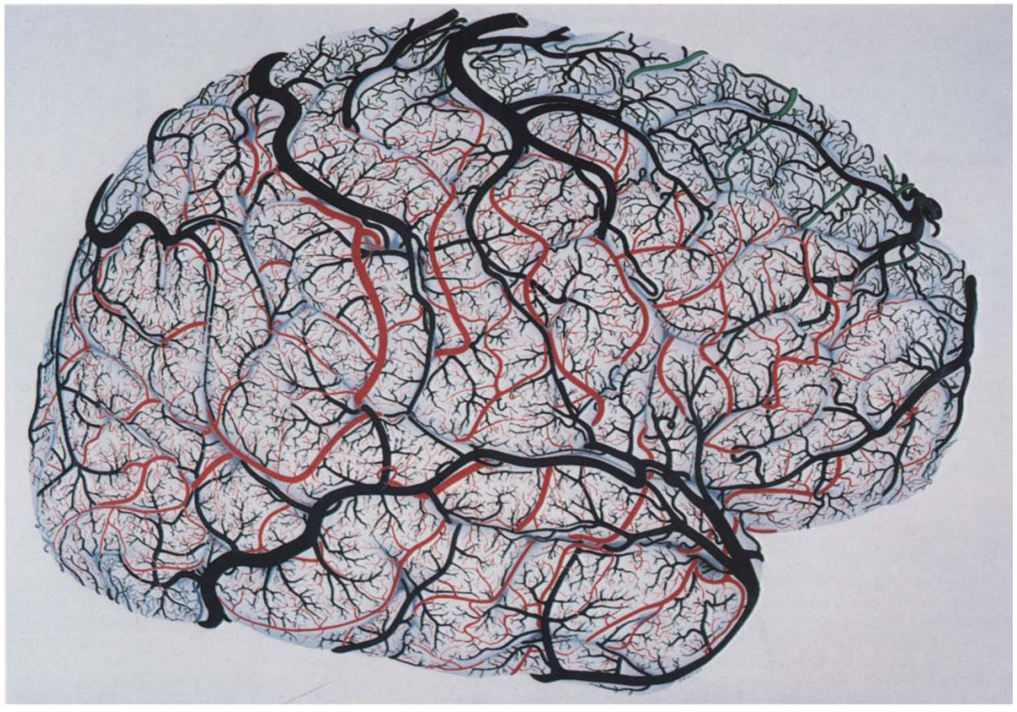


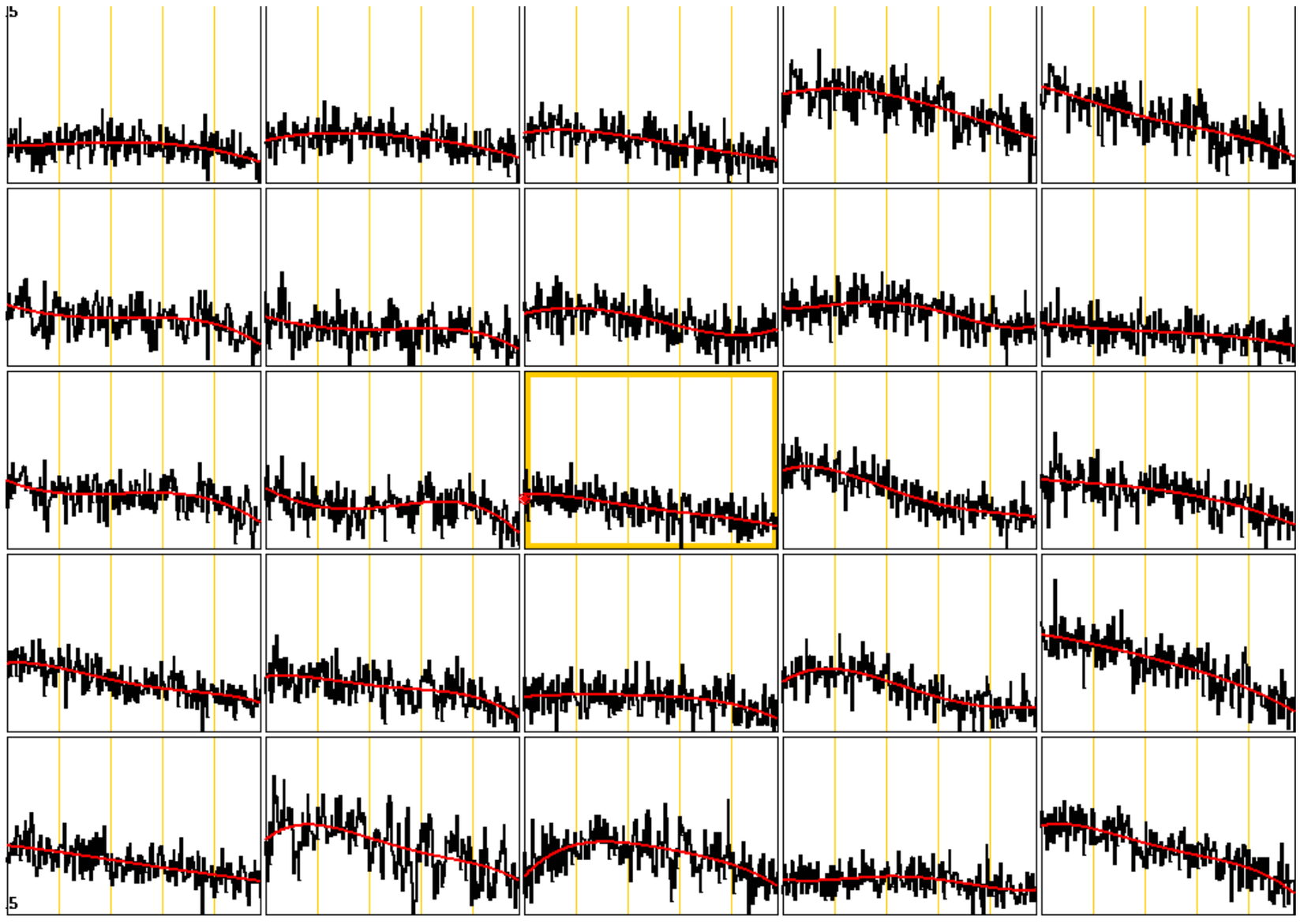
Figure adapted from Logothetis (2008) What we can do and what we cannot do with fMRI. Nature 453:869-878



Drawing of the cortical pial vessels. Right hemisphere. Tributaries of the middle cerebral artery (RED), the anterior cerebral artery (GREEN), and the posterior cerebral artery (BLUE), and veins (BLACK). Taken from Duvernoy et al. (1981) Cortical Blood Vessels of the Human Brain. Brain Res. Bulletin 7:519-579

Sources of the fMRI signal: Low frequency drifts

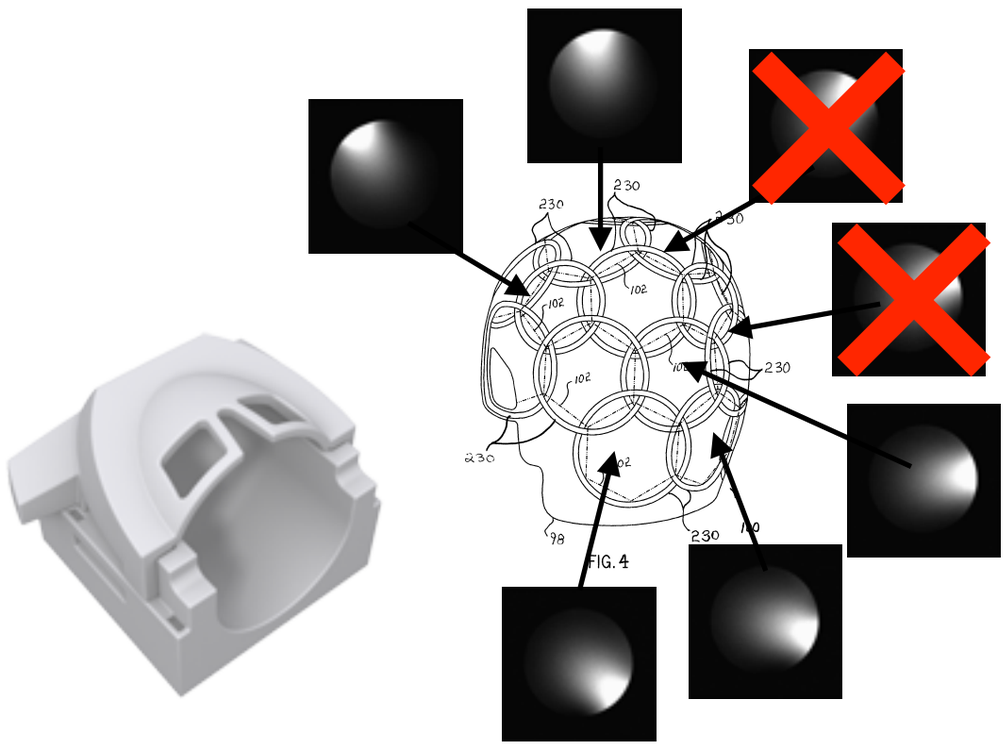
- Low frequency fluctuations in the signal (< 0.01 Hz) related to very slow head displacements, scanner-related drifts (e.g. heating), etc.
- Different for each voxel (even neighbouring voxels)



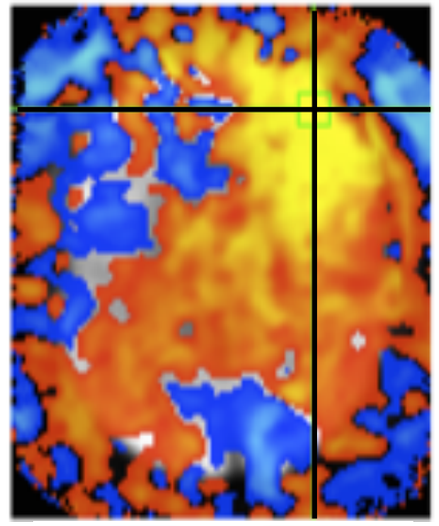
Figures courtesy of Javier Gonzalez Castillo (NIH)

Sources of the fMRI signal: Hardware-related instabilities

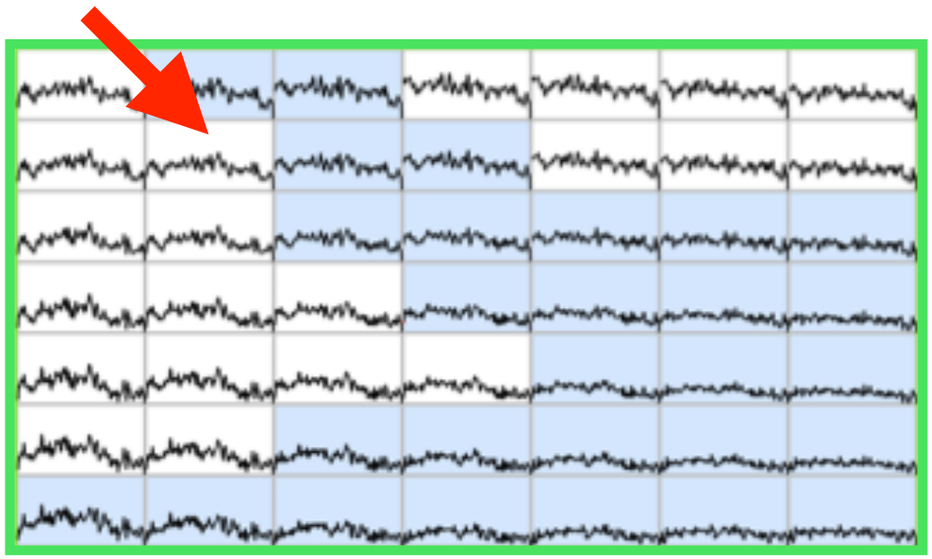
- Nowadays, most MRI scanners use multichannel receiver coils for data acquisition

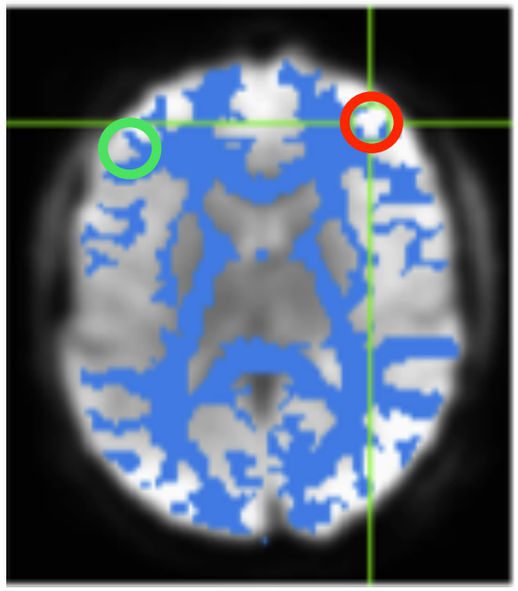


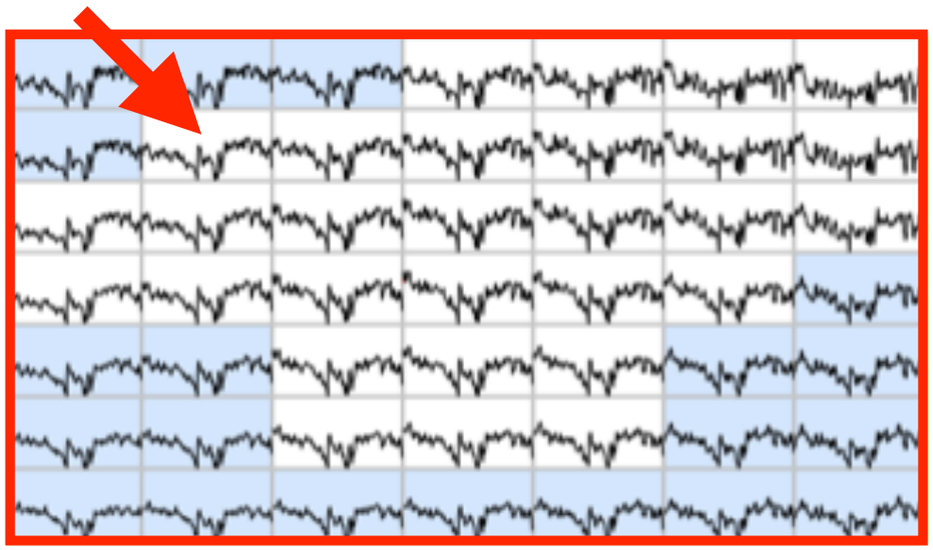
Functional Connectivity Map (@InstaCorr)



Malfunction of multichannel head coil





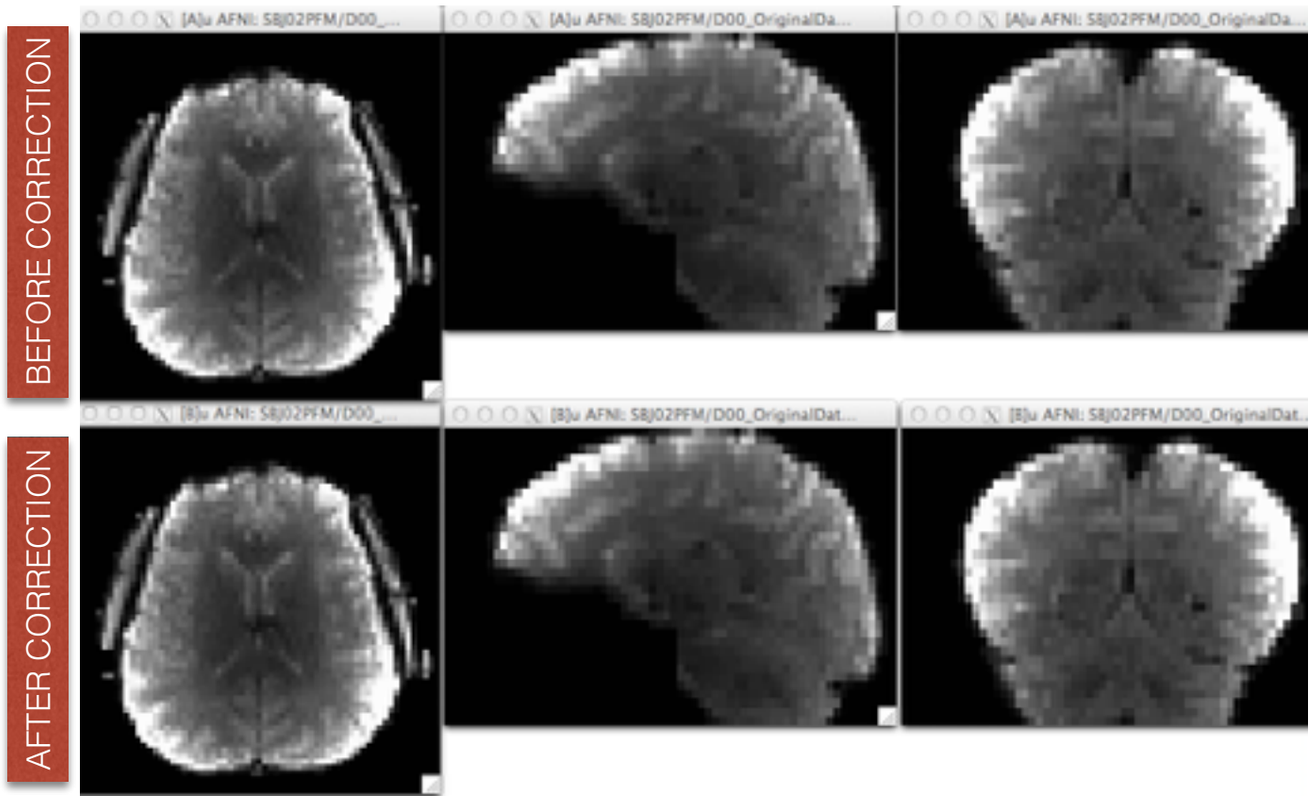


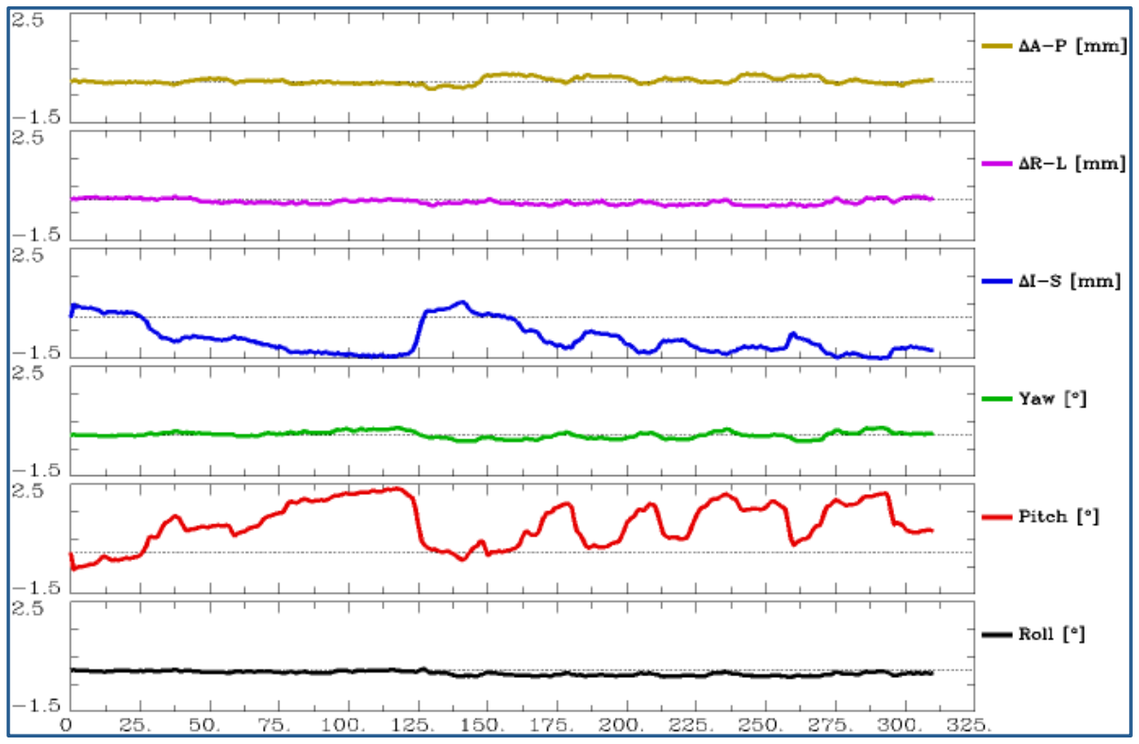
Figures courtesy of Javier Gonzalez Castillo and Vinai Roopchansingh (NIH)

Methods for denoising the BOLD fMRI signal

Compensation of motion effects: Volumetric realignment

- Translation ($\Delta x, \Delta y, \Delta z$) and rotation (yaw, pitch roll) to reference image





- Realignment does not fully compensate for motion-related signal changes. It cannot correct the data as if motion had never occurred.
- Slice-wise motion correction approaches are becoming increasingly effective for compensating within-volume motion , e.g. SLOMOCO (Beall and Lowe, 2014), using EEG-cap as motion sensor (Zotev et al., 2012),
- Prospective motion correction (e.g. navigators or optical tracking systems) are also very effective ways of compensating motion occurring faster than the TR.

Compensation of motion effects: Volumetric realignment

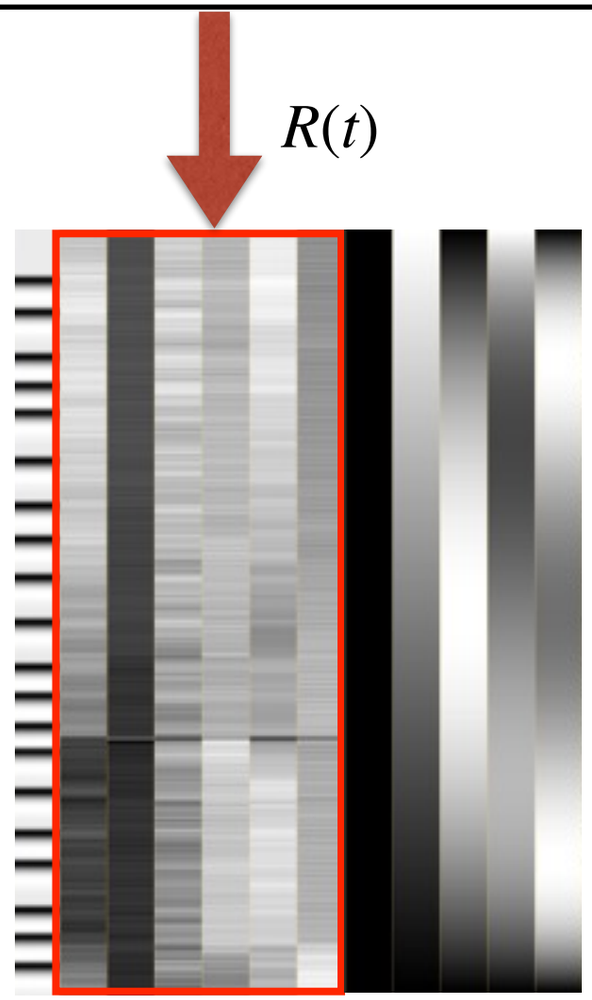
Realignment parameters: $R(t) = \{\Delta x, \Delta y, \Delta z,$ yaw, pitch roll$\}$	6 regressors
+ the temporal derivatives: $R(t\text{-}1)$	12 regressors
+ the corresponding squares, i.e. $R^2(t)$ and $R^2(t\text{-}1)$	24 regressors
+ the second temporal derivative: $R(t\text{-}2)$ and $R^2(t\text{-}2)$	36 regressors

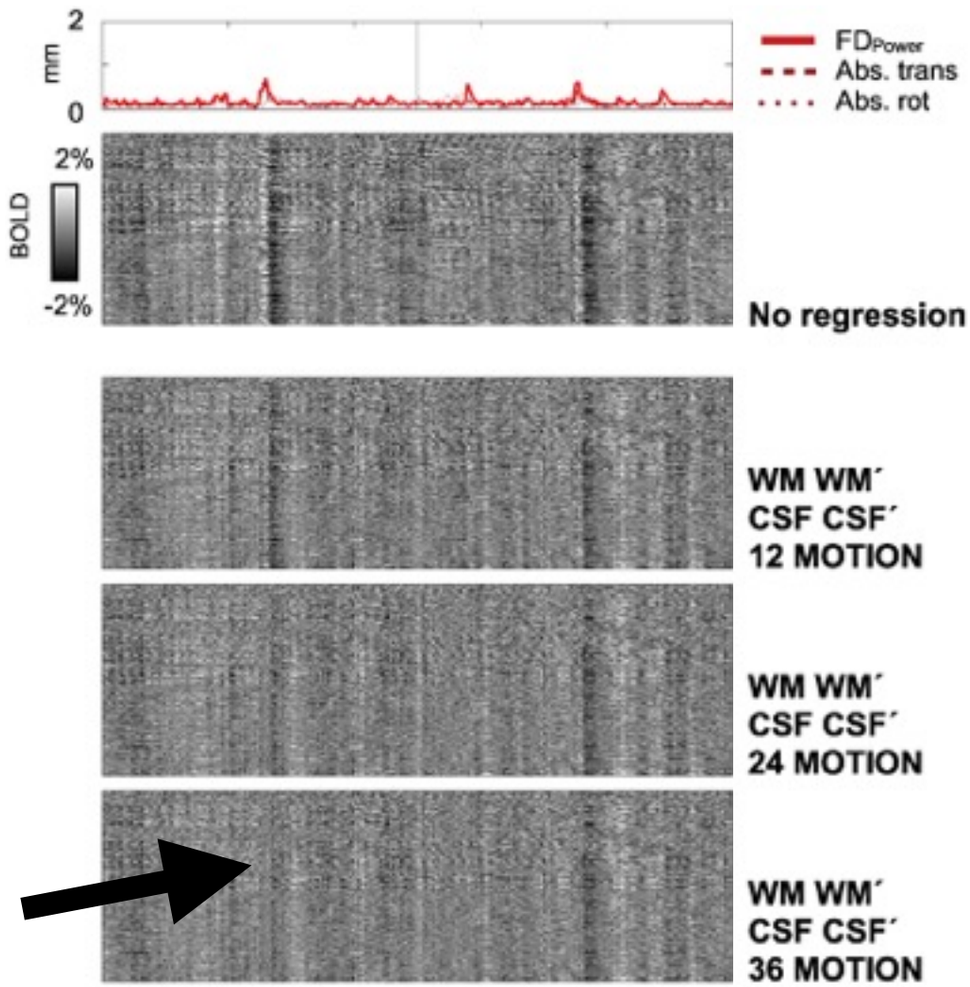
+
+
+

More nuisance regressors

More loss of degrees of freedom

Less statistical confidence

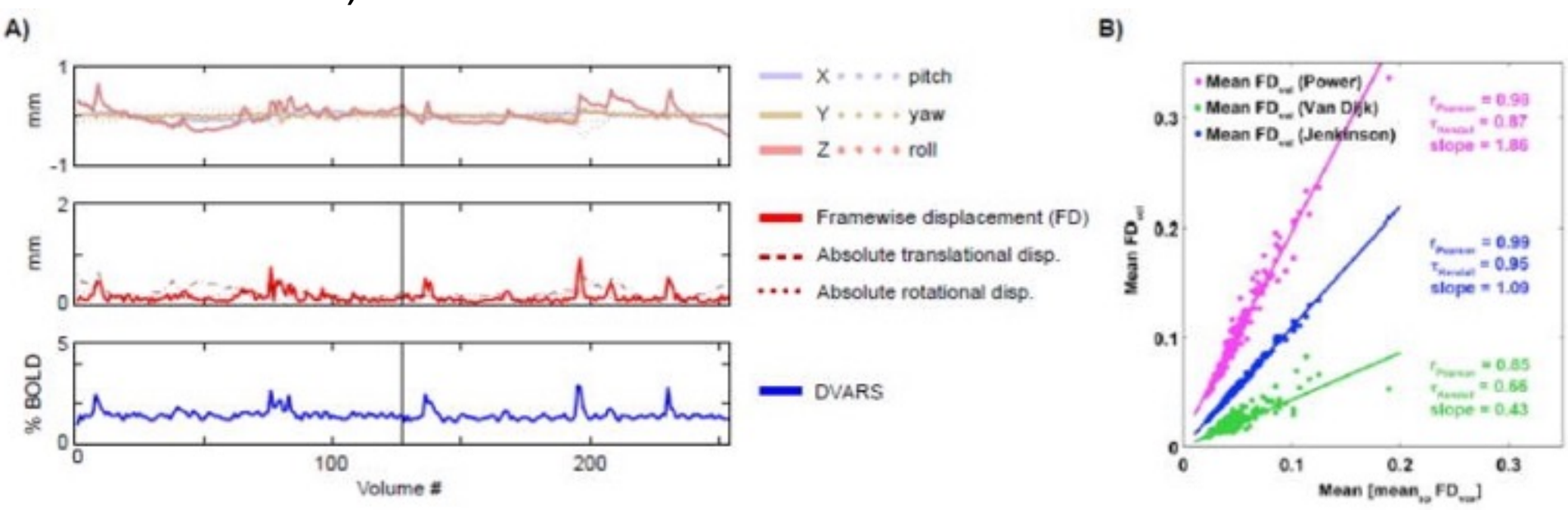




In this session do not miss Jonathan Power's talk to know how to create grayplots, and Molly Bright's talk to know more about critical questions for performing nuisance regression

Censoring and data interpolation

- **Censoring:** Time points with large artefacts (e.g. excessive motion, hardware instabilities, etc.) are first identified and then zeroed, excluded from further analysis or interpolated with new data (e.g. linear or splines interpolation).
- Time points are identified in time courses computed from:
  - Realignment parameters: Multiple definitions of **Framewise displacement** (FD)
  - **DVARS**: Root-mean square value of the differentiated fMRI signal
  - Percentage of voxels with spike-like pattern at each time point (e.g. 3dDespike function in AFNI)

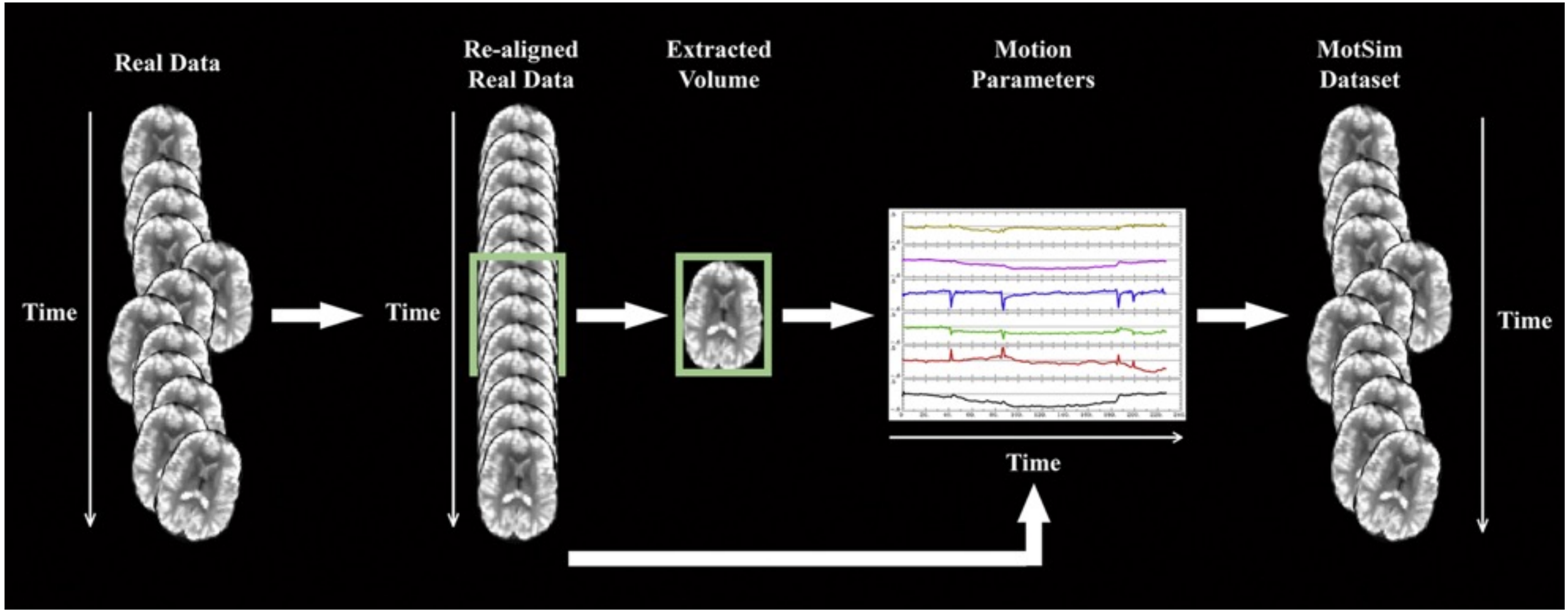


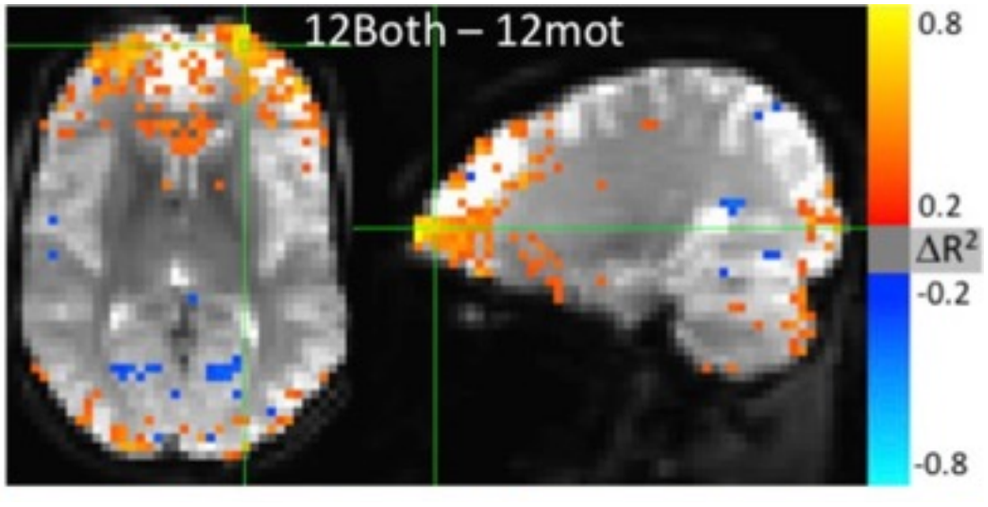
It is important to report methods used for censoring (criteria, threshold) and interpolation as well as the number of censored scans per subject or groups, and whether data was interpolated, zeroed, or nulled for subsequent analyses.

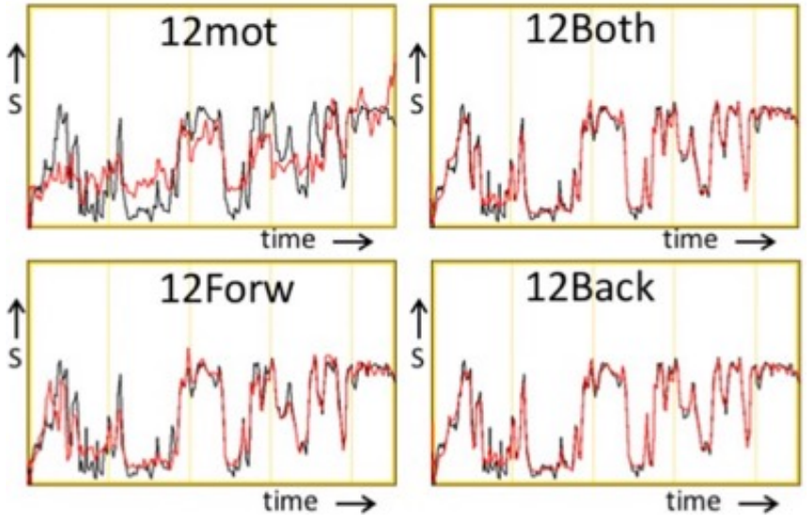
Power et al. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. Neuroimage 105:536-551.

Motion Simulation (MotSim)

- Nuisance regression uses the principal components from a dataset that simulates motion (MotSim) and its realignment (MotSimReg)



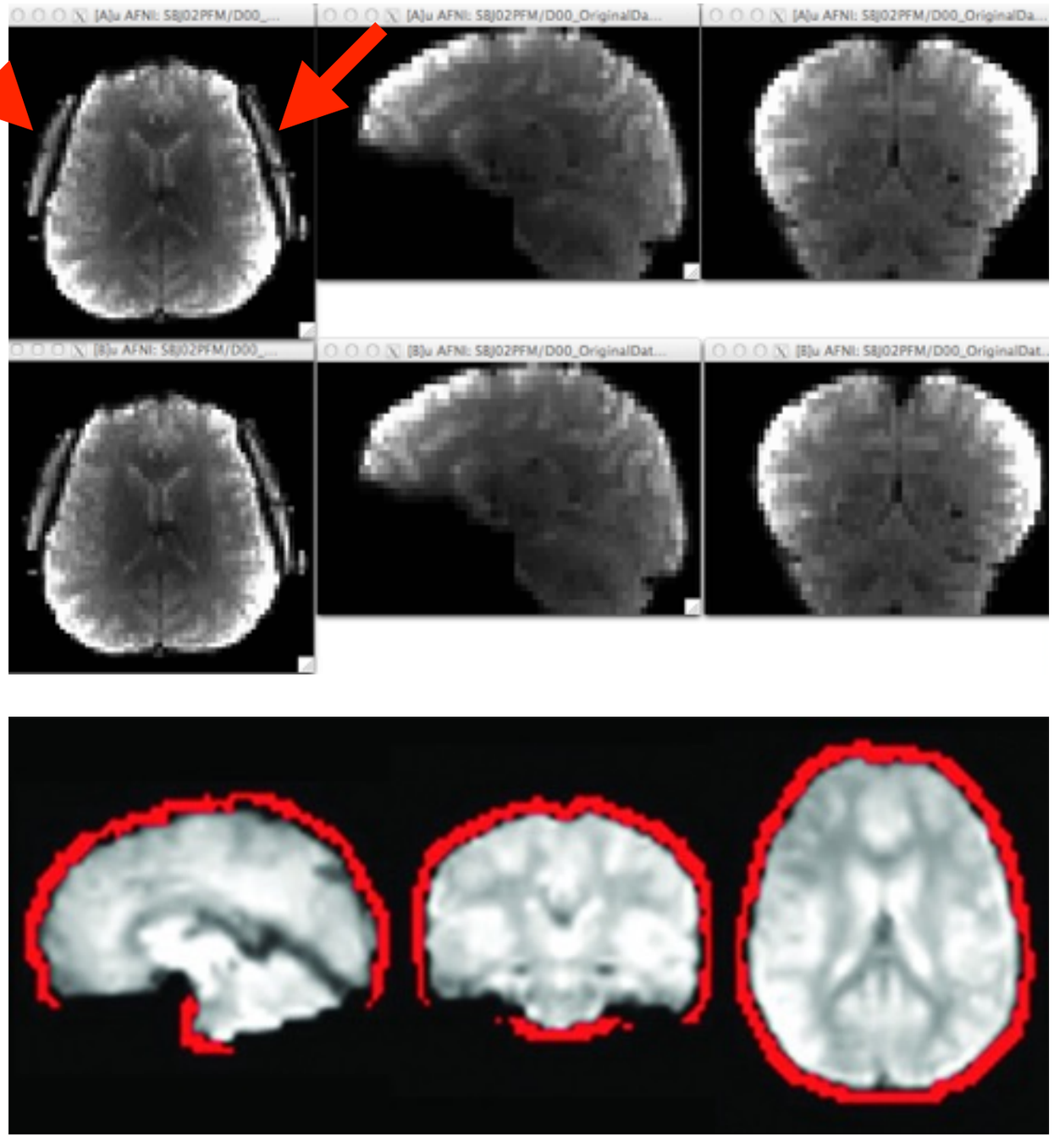


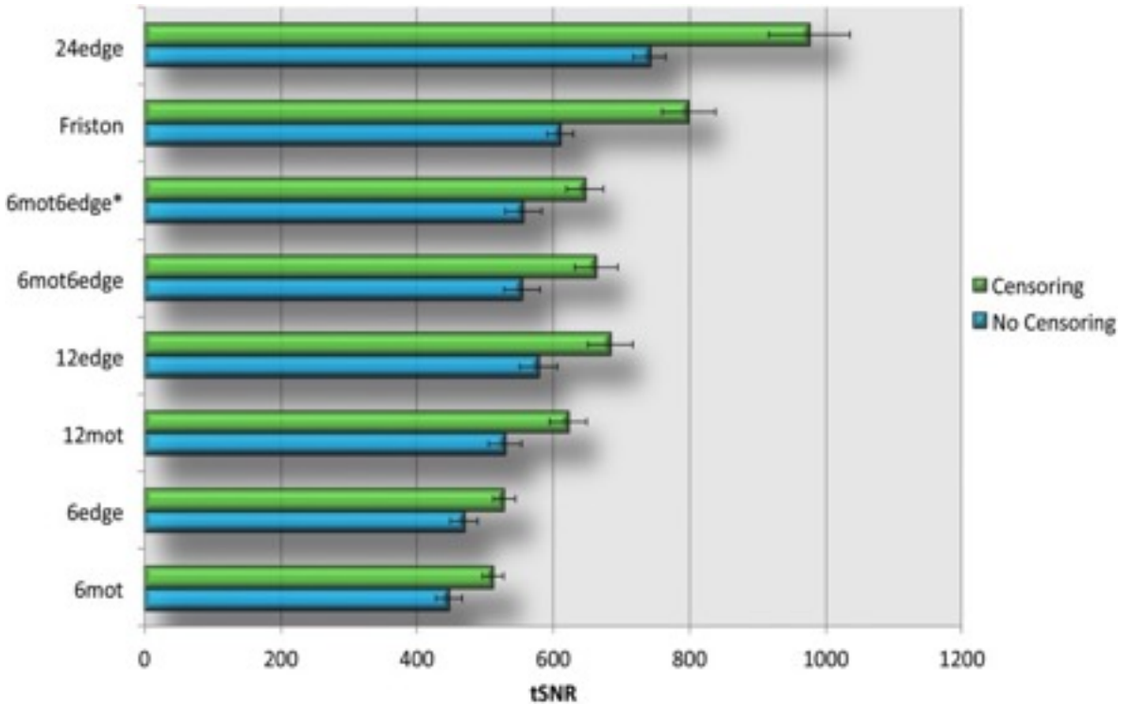


Patriat et al., (2017). An improved model of motion-related signal changes in fMRI. Neuroimage 144(Part A): 74-82

Edge Brain Voxels

- Principal components with largest variance from voxels at the edges of the brain





- Intersection of functional and anatomical edge brain mask to avoid inclusion of voxels in areas with signal drop-outs.

Patriat et al., (2015). Using edge voxel information to improve motion regression for rs-fMRI connectivity studies. Brain Connect. 5(9): 582-596.

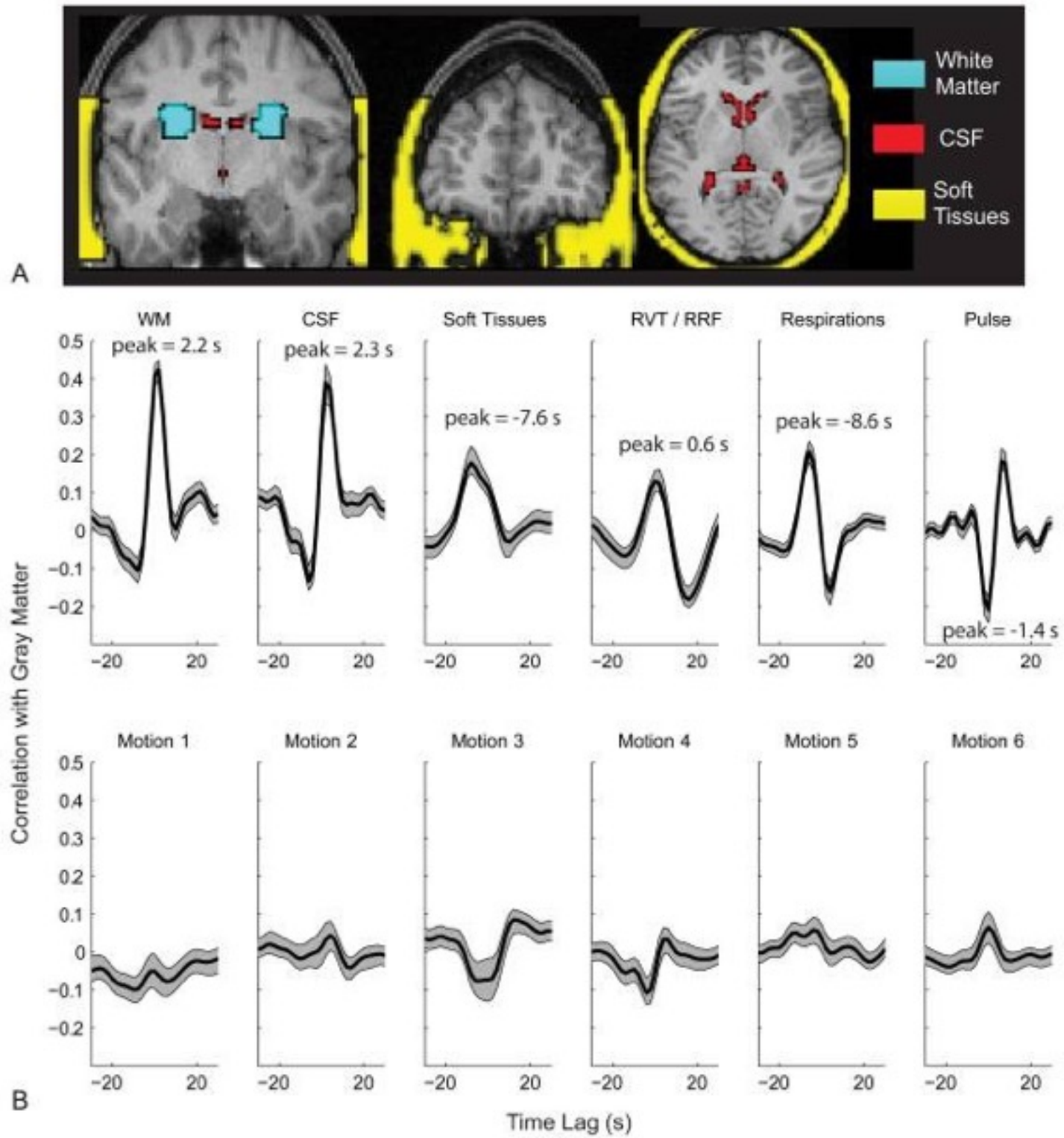
Phase-shifted Soft Tissue Regression (PSTCor)

- Account for motion-related effects and additional noise and artefactual fluctuations (e.g. physiological noise)

- Compute correlation with time-shifted time series from:
  - white matter ROIs,
  - CSF from lateral ventricles
  - soft tissues (i.e. face, skull)
  - physiological signals

  plus realignment parameters

- Optimal time-shifts are chosen for maximum cross-correlation with average GM signal.

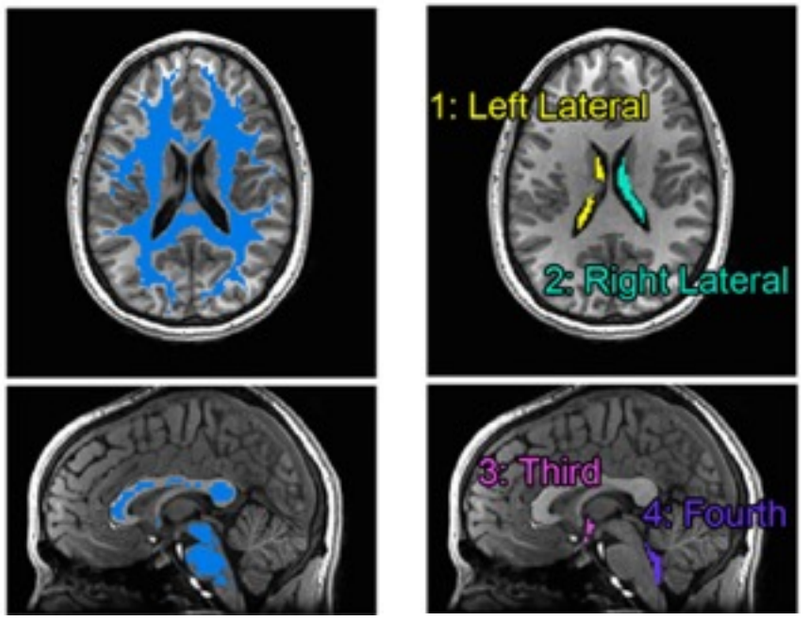


Anderson et al. (2011). Network Anticorrelations, Global Regression, and Phase-shifted Soft Tissue Correction (PSTCor). Human Brain Mapping 32(6): 919–934.

Component Based Noise Correction Method (CompCor)

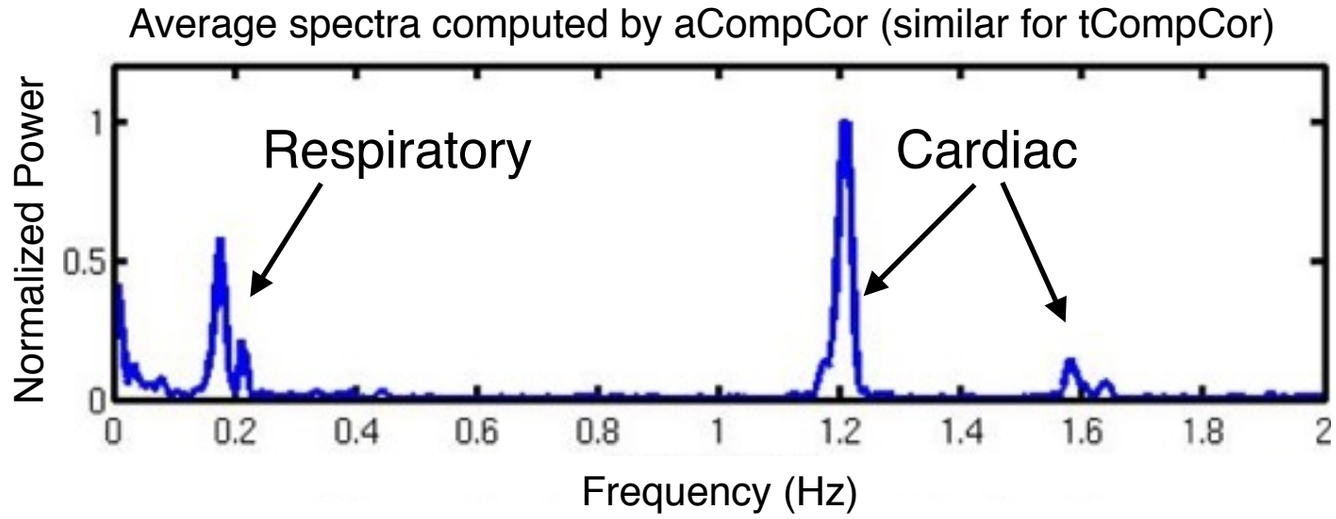
- Principal Components (PCs) explaining the highest variance from voxels within eroded WM and ventricles CSF anatomical masks (aCompCor), voxels with largest temporal standard-deviation (tCompCor), or combination of both.
- It is able to account for physiological fluctuations without the need of external recordings.

Tissue masks for aCompCor



White matter eroded (WMe)

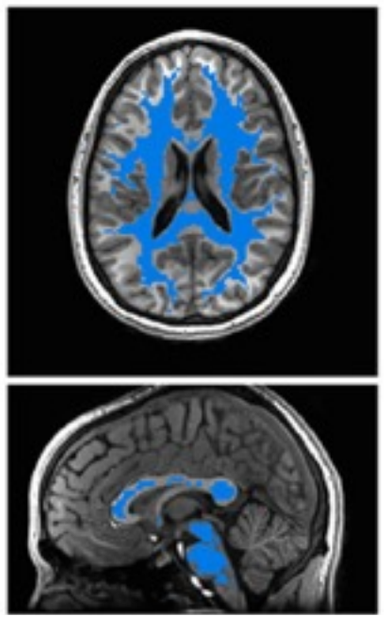
Large Ventricles eroded (LVe_{1-4})



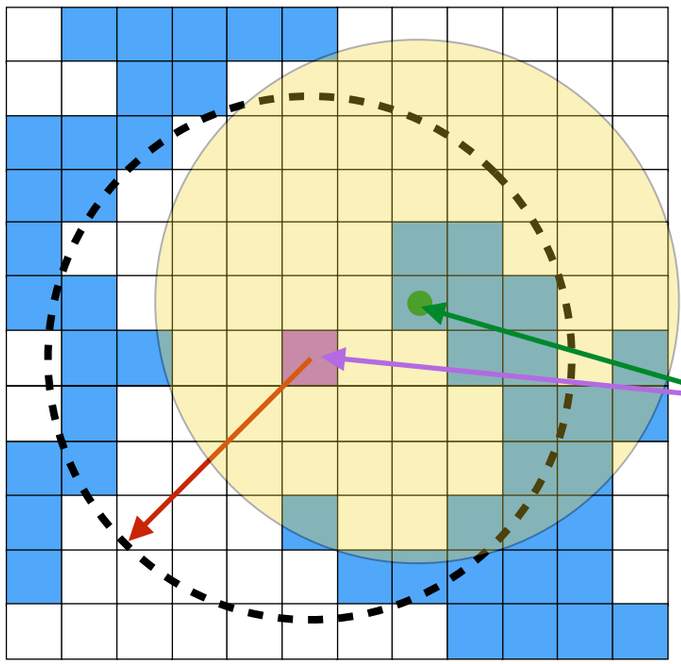
- Determining the optimal number of PCs is an open question (e.g. fixed number vs. % of variance)

Behzadi et al., (2007). A Component Based Noise Correction Method (CompCor) for BOLD and Perfusion Based fMRI. Neuroimage 37(1): 90-101.

Anatomy-based Correlation Correction (ANATICOR)



White matter eroded (WMe)

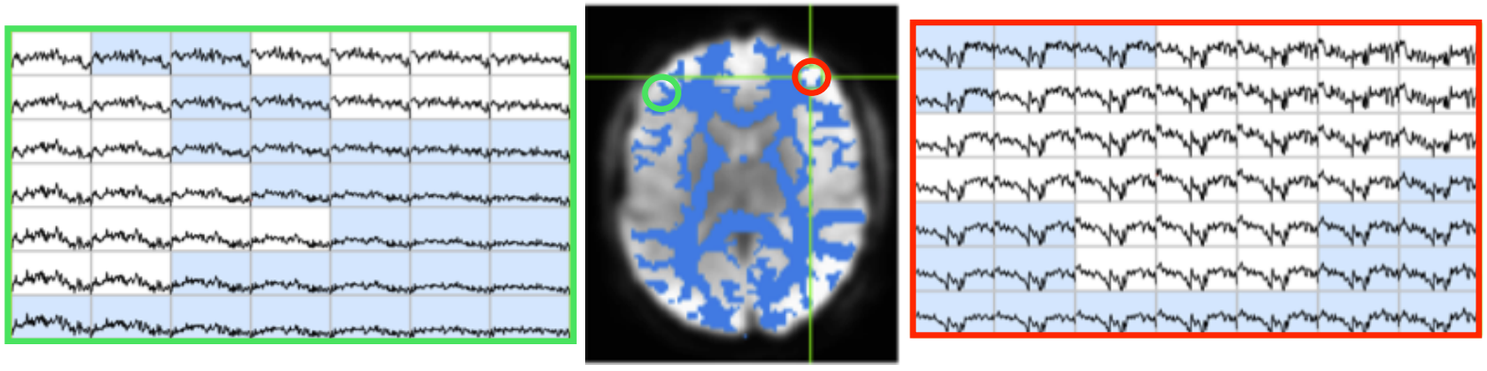


Average signal over WMe voxels inside 20 mm radius

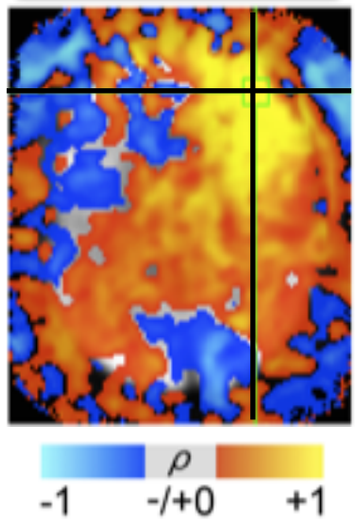
Voxel-dependent nuisance regressors

Figure adapted from Box Cox (AFNI)

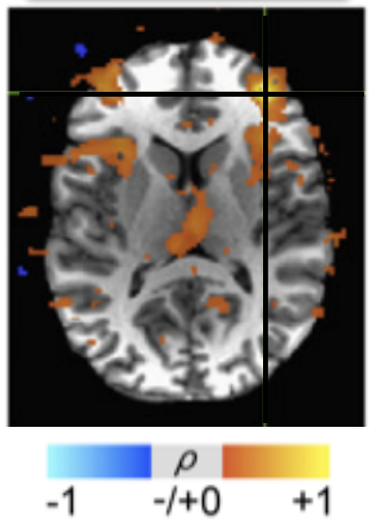
LOCALIZED HARDWARE INSTABILITIES



BEFORE ANATICOR



AFTER ANATICOR



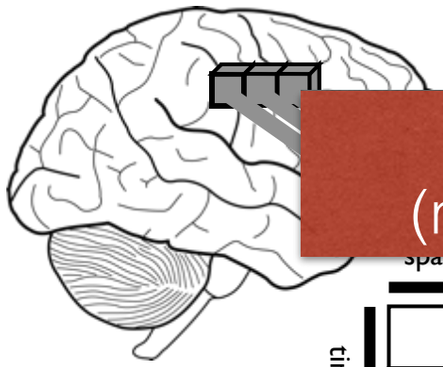
Jo et al., (2010). Mapping Sources of Correlation in Resting State FMRI, with Artifact Detection and Removal. Neuroimage 52(2): 571–582.

Independent Component Analysis (ICA) based Denoising

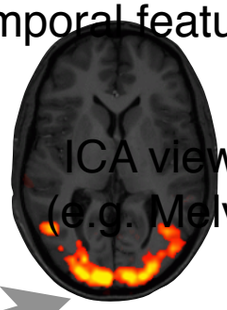
fMRI dataset

Your favourite ICA algorithm (e.g. GIFT, MELODIC)

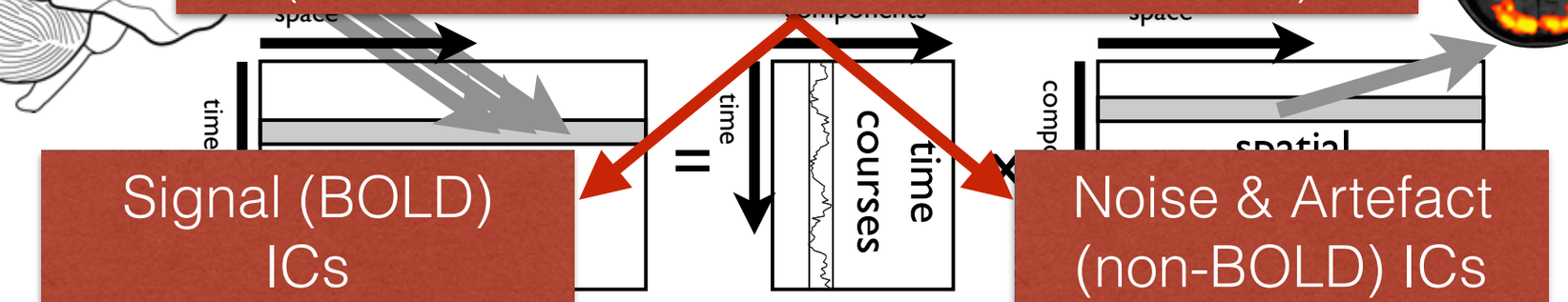
Computation of spatial and temporal features for each IC



Your favourite ICA classification
(manual, semi-automated or automated)



ICA viewer very useful
(e.g. Melview, FSLeyes)



Signal (BOLD) ICs

Noise & Artefact (non-BOLD) ICs

Data is represented as a 2D matrix and decomposed into factor matrices (or modes)

Nuisance Regression

Non-Aggressive

Aggressive

***FSL Documentation**: http://fsl.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf*

Denoised fMRI dataset

Denoised fMRI dataset

Independent Component Analysis (ICA) based denoising

- **Manual Labelling:** GOLD standard IF AND ONLY IF done by experts, time consuming, difficult reproducibility within and across raters.

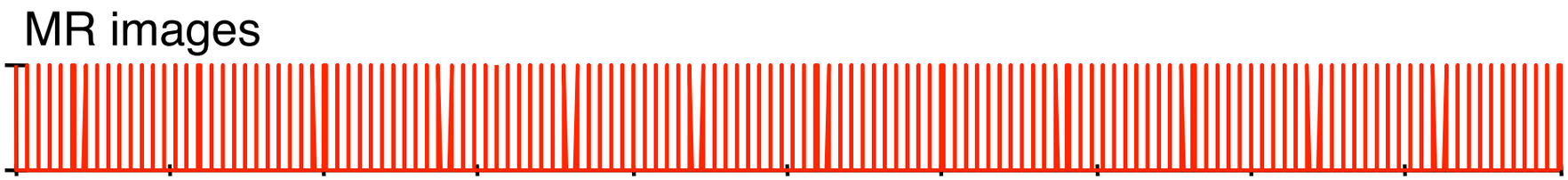
Griffanti et al. (in press). Hand classification of fMRI ICA noise components. Neuroimage

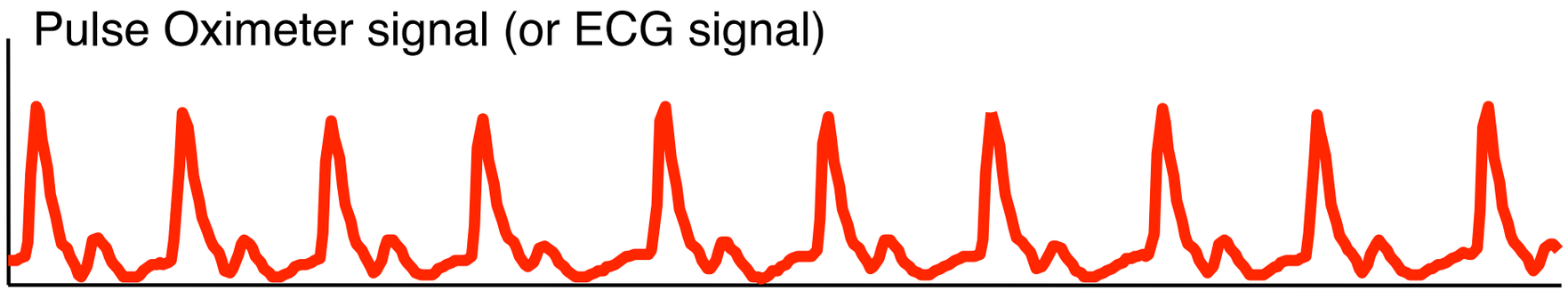
Kelly et al., (2010). Visual inspection of independent components: Defining a procedure for artefact removal from fMRI data. J Neurosci Methods 189(2): 233–245.

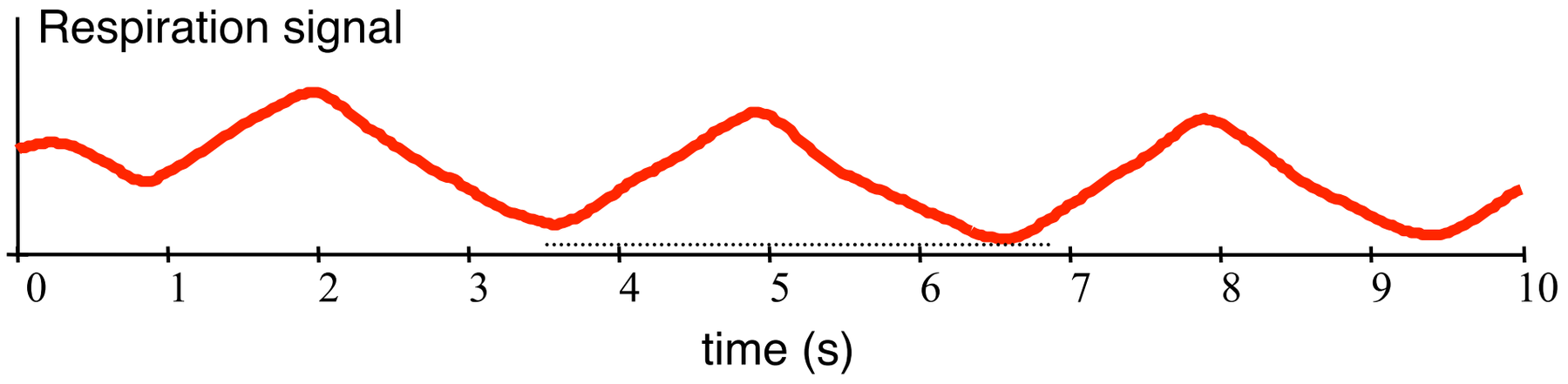
- **Automated or Semi-automated classification:** Distinguish between signal-related (BOLD), and noise- or artefact-related (non-BOLD) components.
  - **Algorithms:** Support Vector Machines, Linear Discriminant Analysis, Decision Trees, Naïve Bayes, (Sparse) logistic regression, K-Nearest Neighbourhood, Random Forests, etc, or ensemble of classifiers.
  - **Spatial features**: spatial frequency, entropy and smoothness, fraction of IC map within GM, CSF, WM, edges of the brain, etc.
  - **Temporal features**: power fraction above a certain frequency, correlation with realignment parameters, spectral distribution, autoregressive properties, etc.

Check out Ludovica Griffanti's talk on this session for more ICA-based denoising

Denoising physiological noise with external recordings

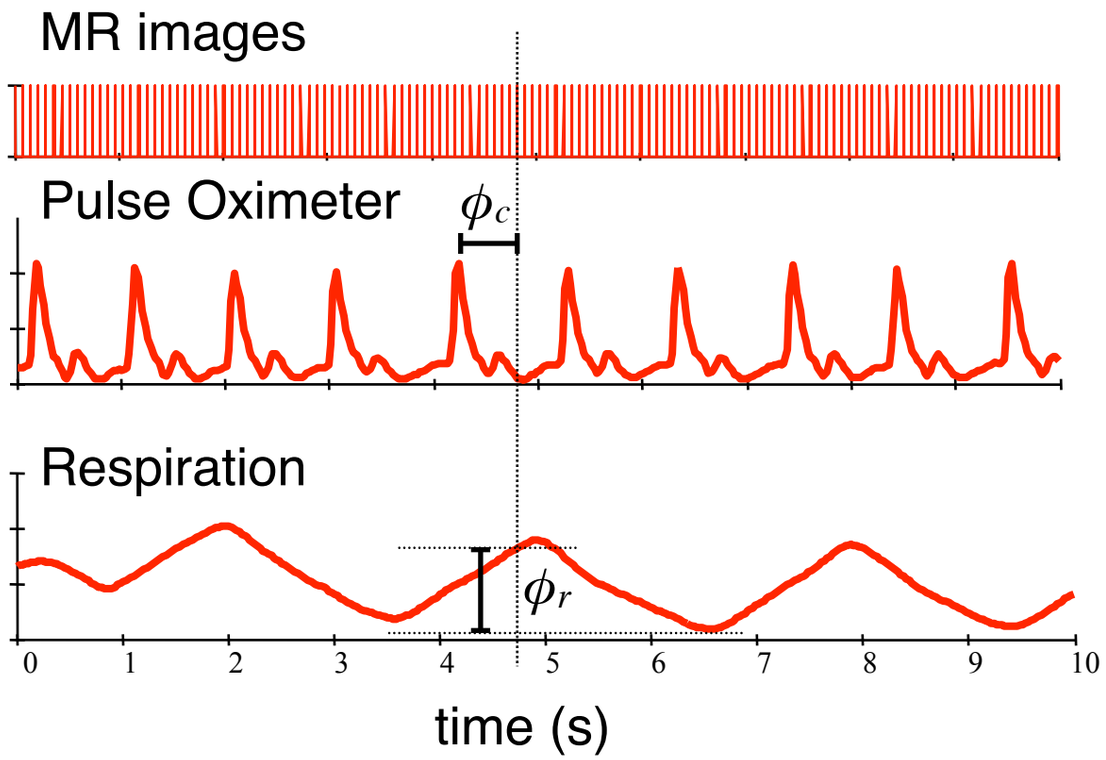


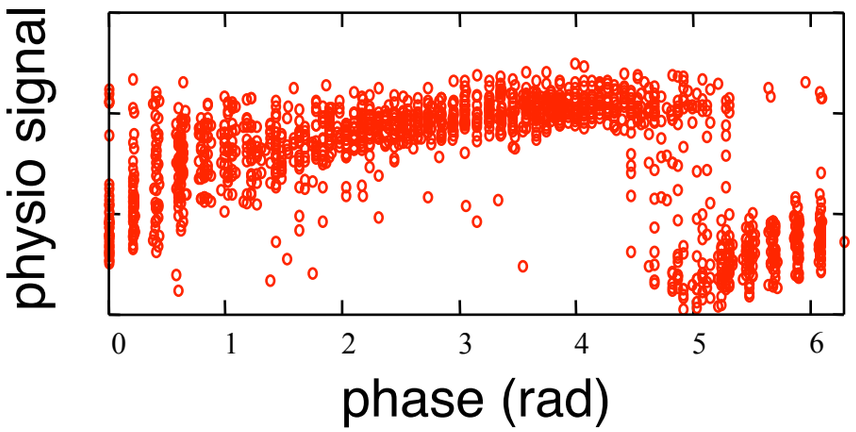




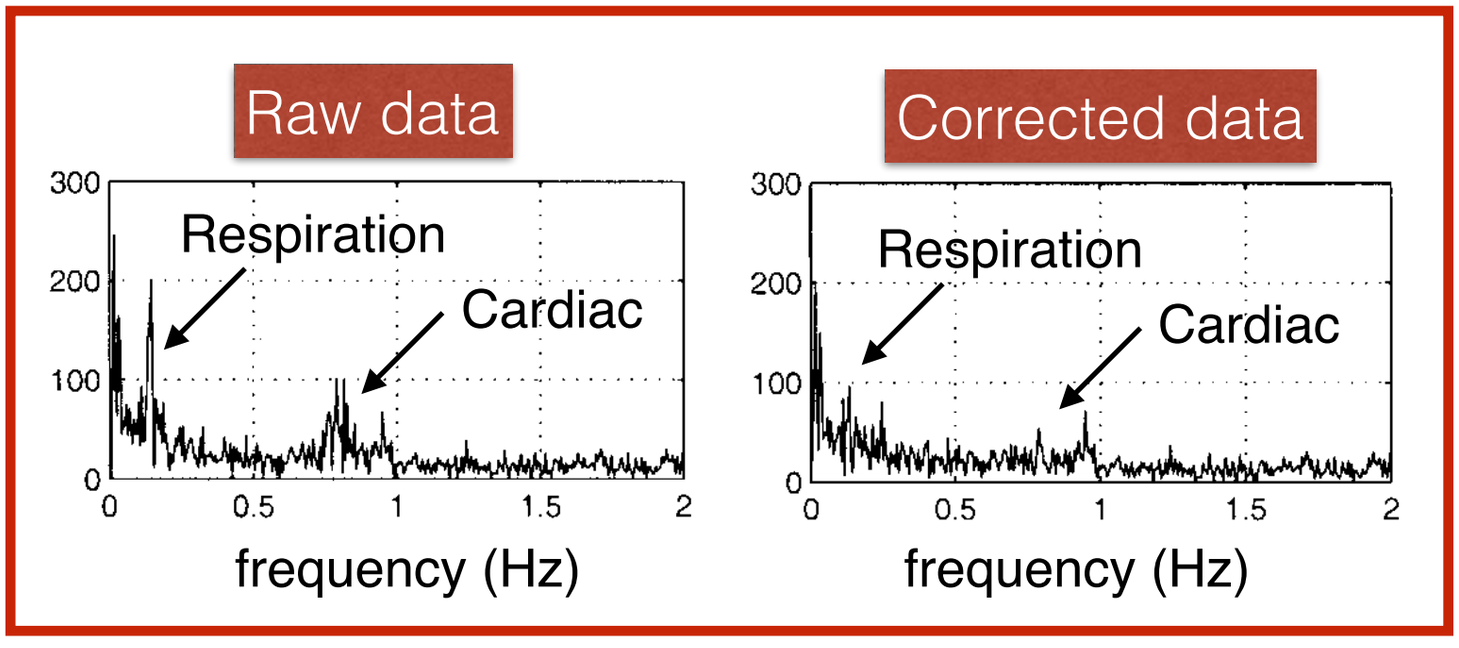
RETROICOR

Figures courtesy of Rasmus Birn (University of Wisconsin-Madison)





$$\left\{\begin{array}{c}\cos(\phi_r)\\ \sin(\phi_r)\\ \cos(2\phi_r)\\ \sin(2\phi_r)\\ \cos(\phi_c)\\ \sin(\phi_c)\\ \cos(2\phi_c)\\ \sin(2\phi_c)\end{array}\right\}$$

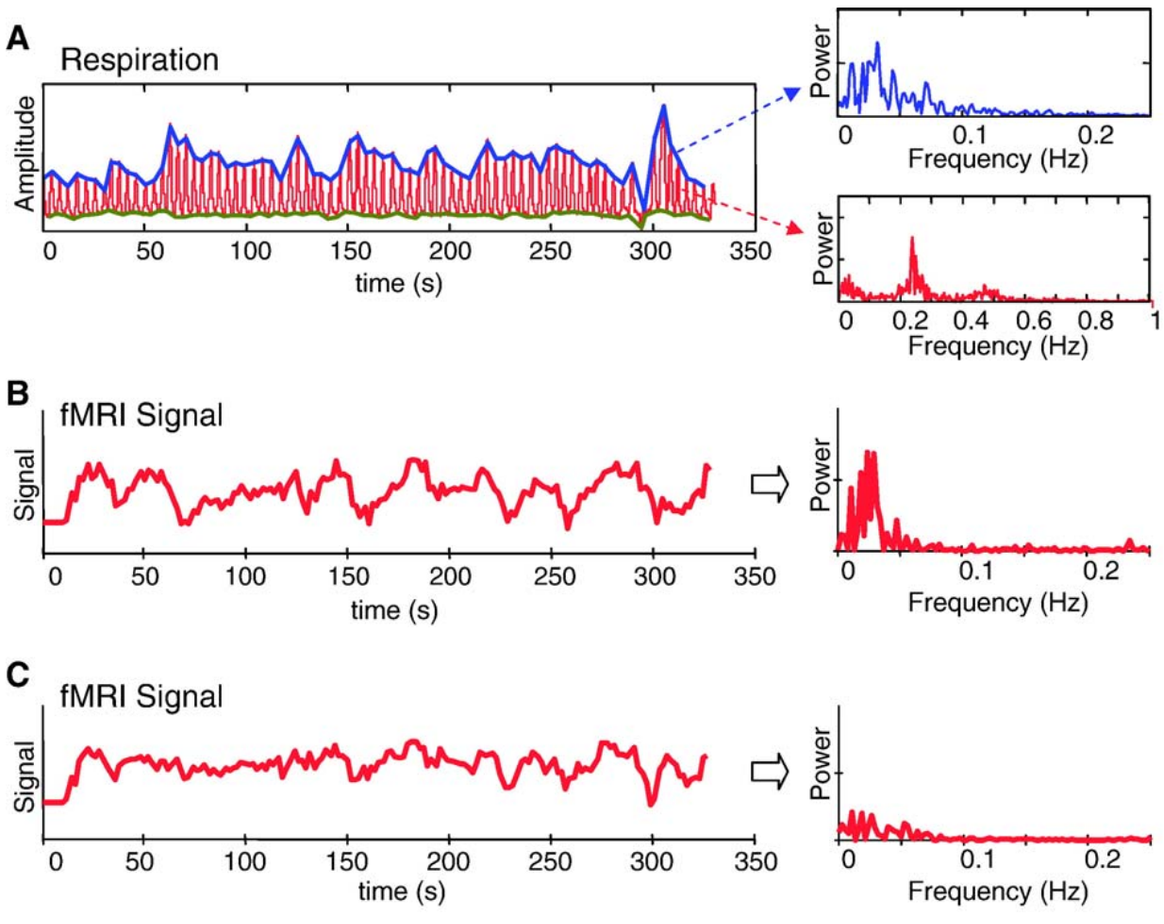


Glover et al., (2000). Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magn Reson Med. 44(1):162-167

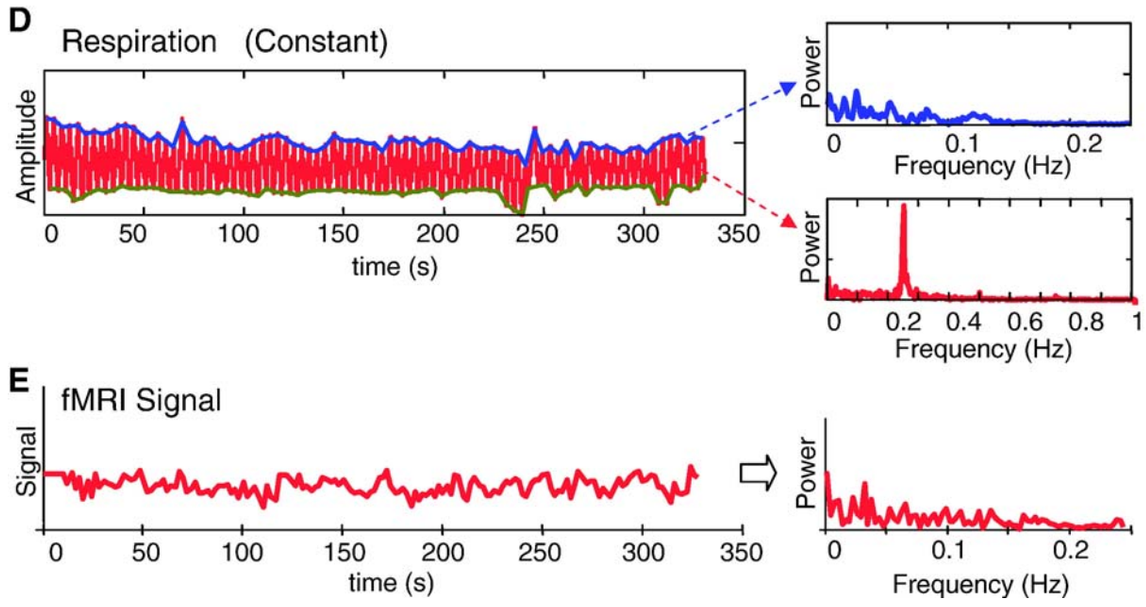
Low frequency fluctuations in respiratory volume (RVT)

- Variations in respiratory rate can be reduced by regressing out changes in respiratory volume (RVT) that are assumed to correlate with fluctuations in arterial CO_2 concentrations.

Regular Breathing



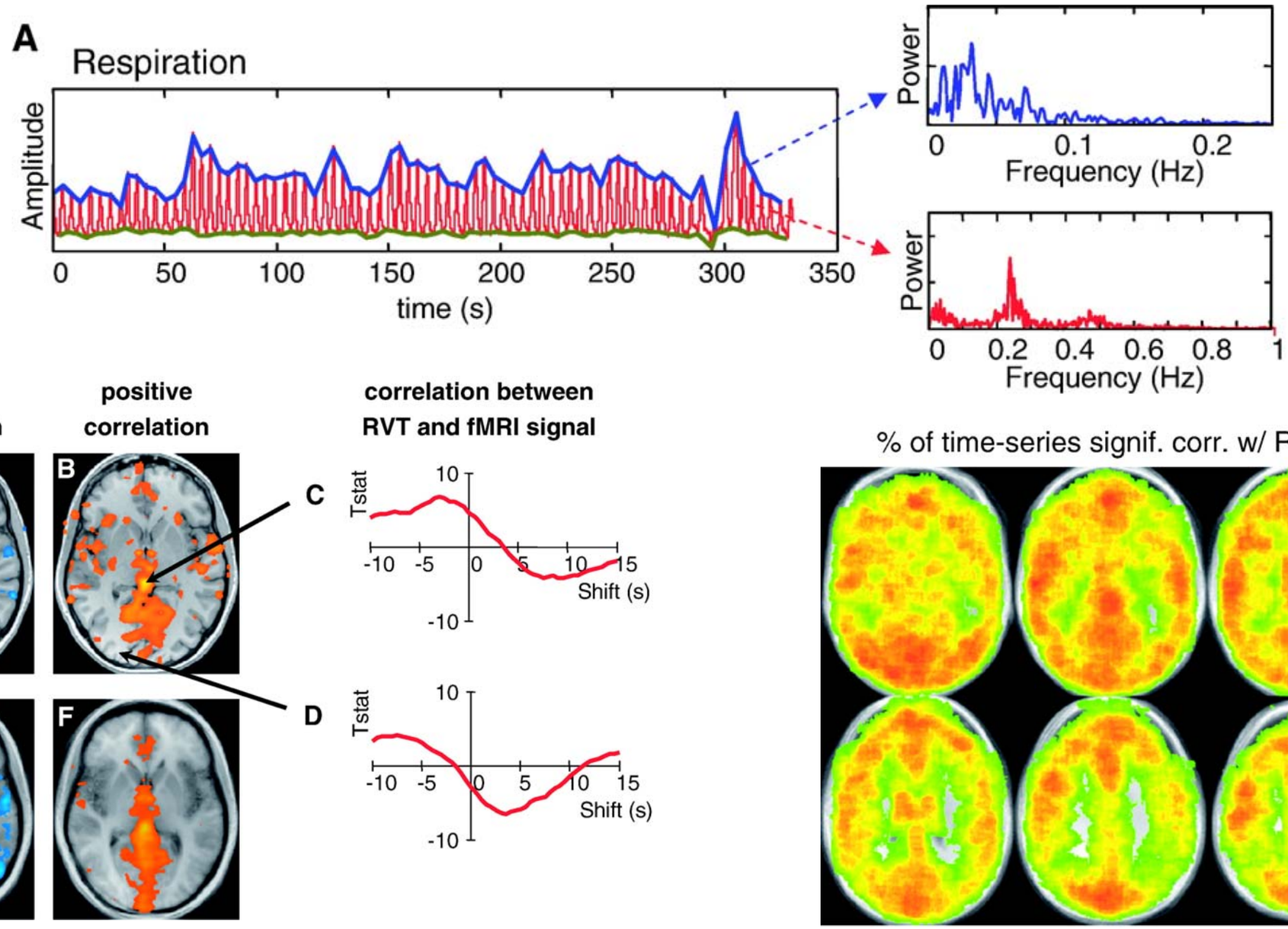
Constant Breathing



Birn et al. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31(4):1536–1548.

Low frequency fluctuations in respiratory volume (RVT)

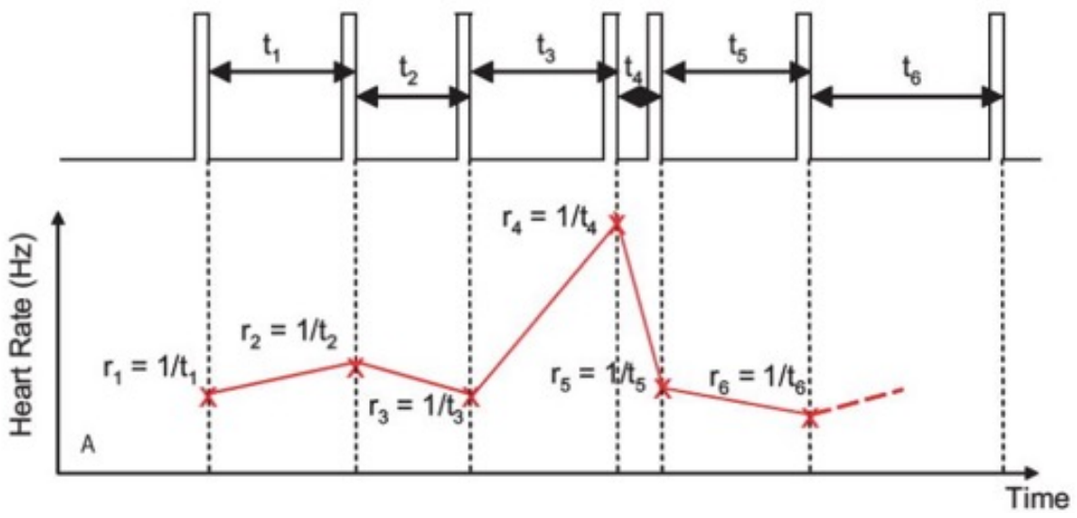
- The Respiratory Volume Time (RVT) is correlated with the average GM (or global) time series at multiple lags, and usually the two lagged RVT with maximum positive and negative correlation are used as nuisance regressors.

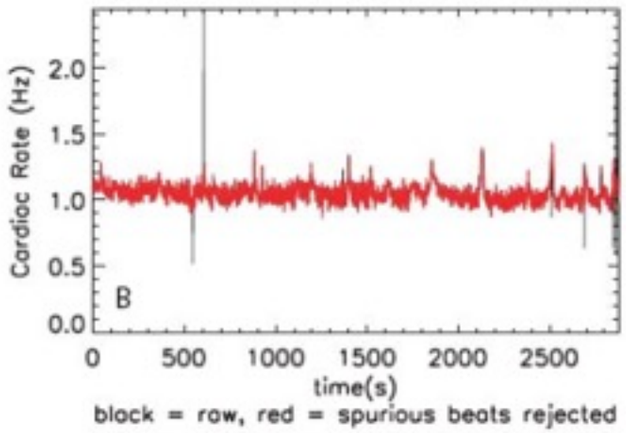


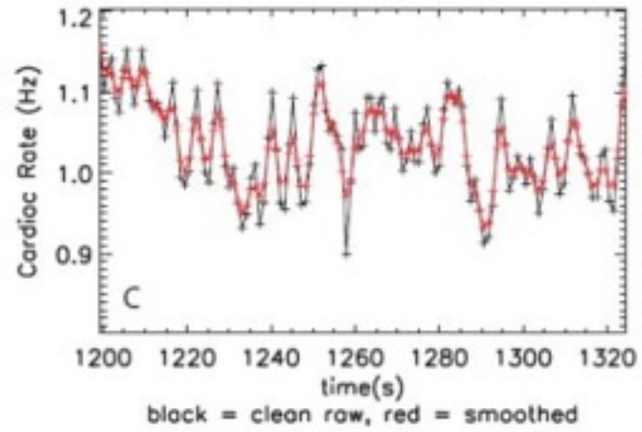
Birn et al. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31(4):1536–1548.

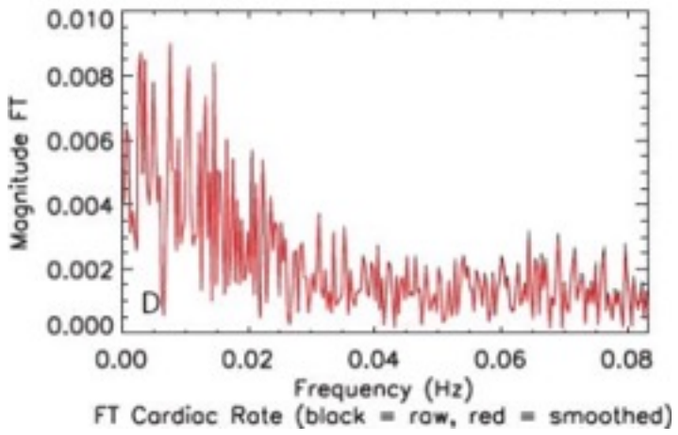
Low frequency fluctuations in cardiac rate (CR)

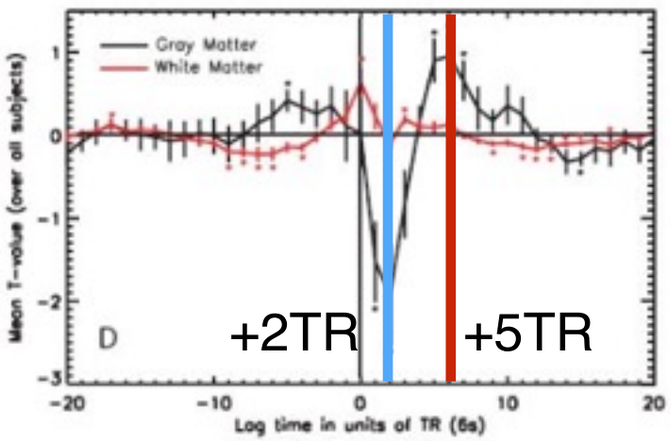
- Similar for variations in cardiac rate

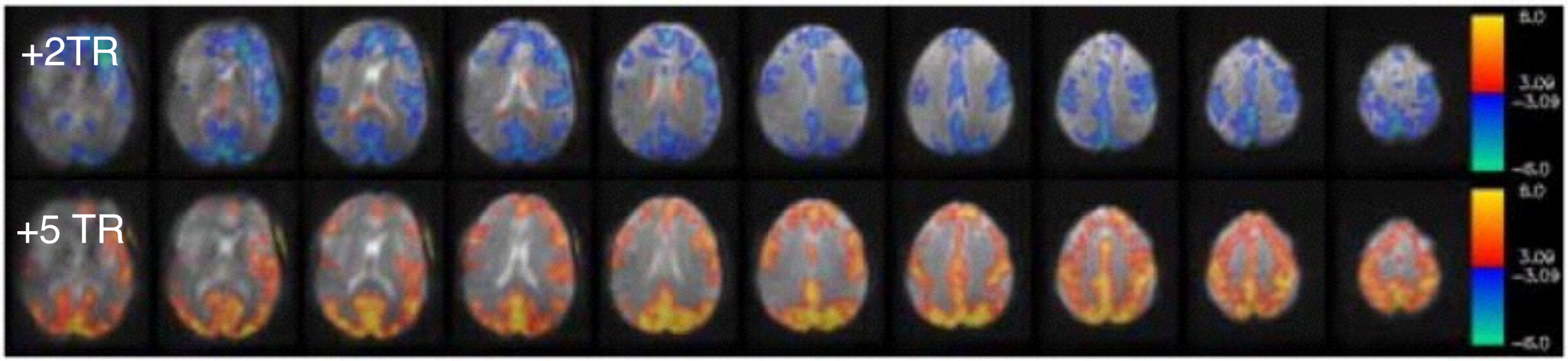








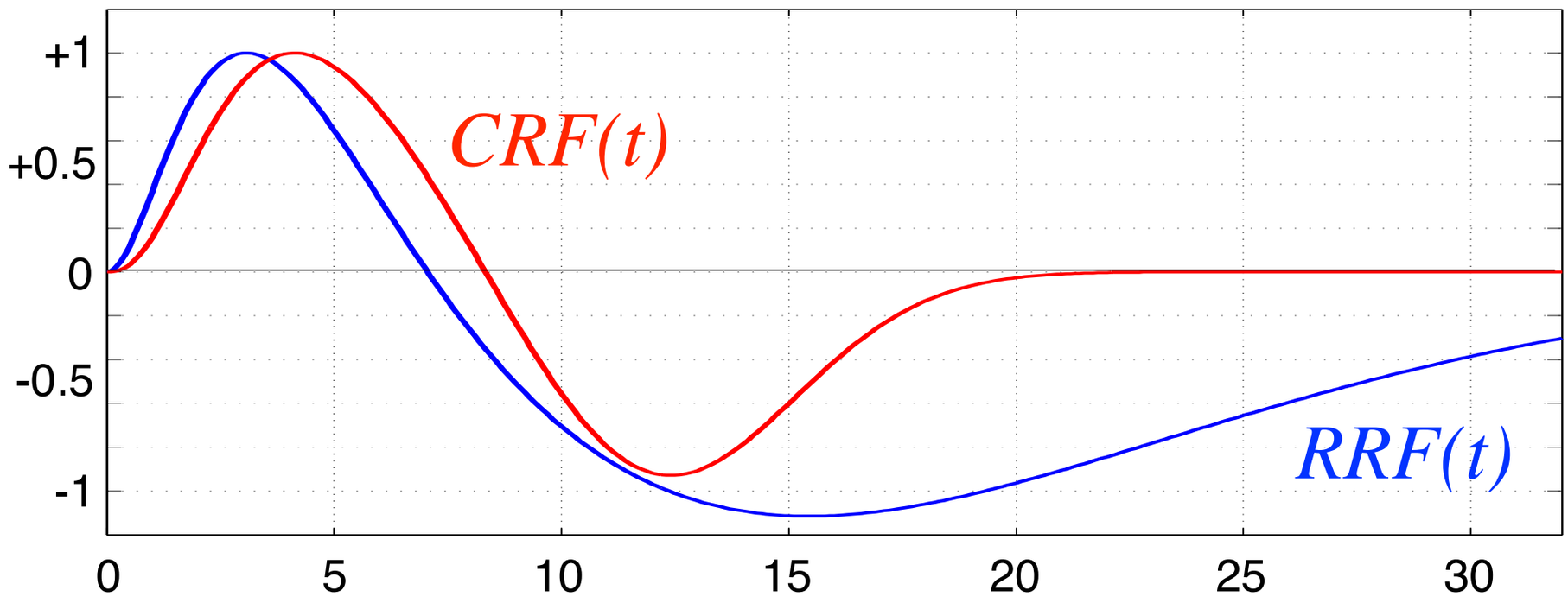




Shmueli et al. (2007). Low frequency fluctuations in the cardiac rate as a source of variance in the resting state fMRI BOLD signal. Neuroimage 38(2):306-320.

Respiration and Cardiac Response Functions (RRF & CRF)

- Instead of fitting 2 lags of the respiratory volume (RV) and cardiac rate (CR) time series, deconvolve their responses from the fMRI signal.



$$RRF(t) = 0.6t^{2.1}e^{-t/1.6} - 0.0023t^{3.54}e^{-t/4.25}$$

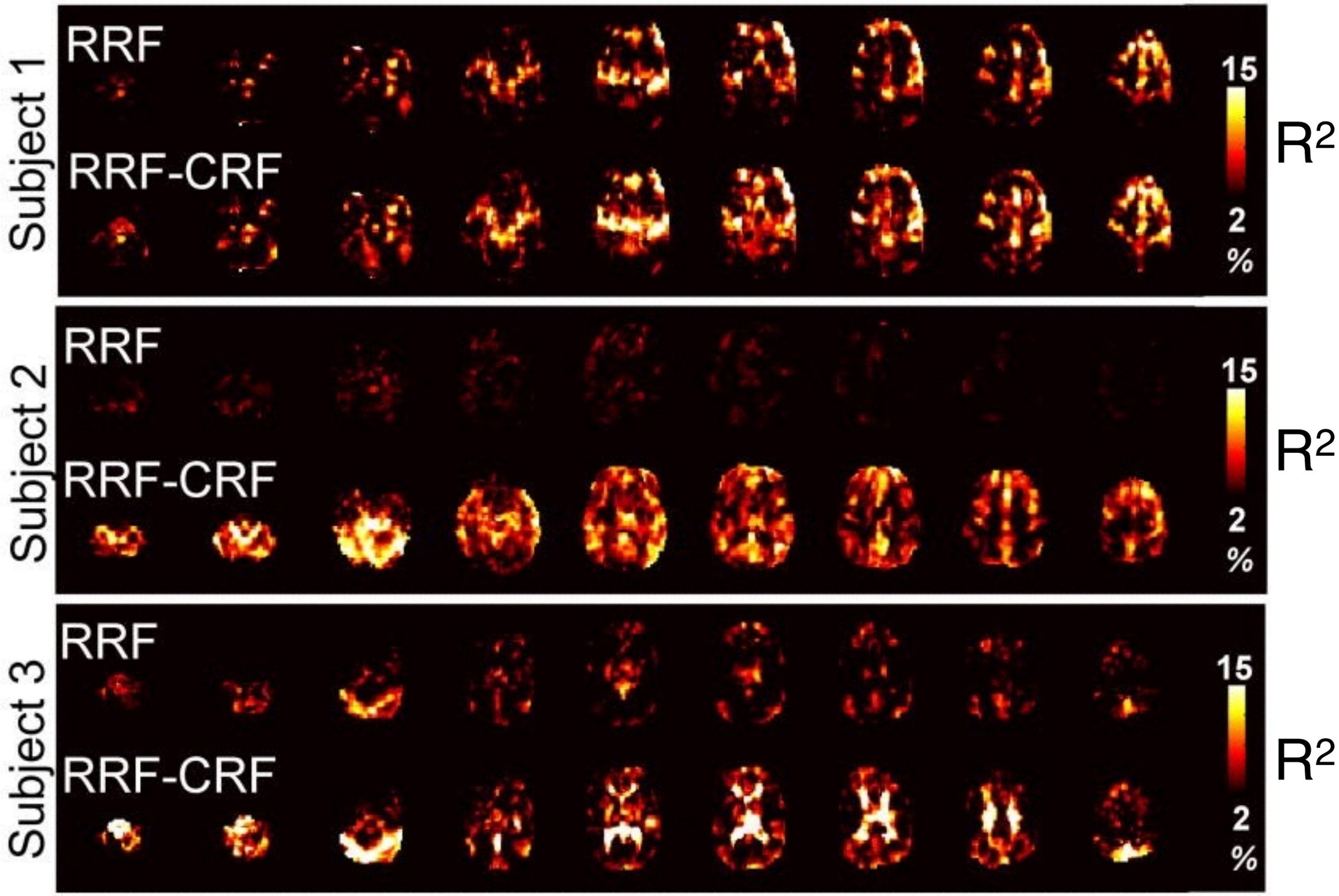
RRF(t) was initially estimated as the average response to brief breath-holding events

$$CRF(t) = 0.6t^{2.7}e^{-t/1.6} - \frac{16}{\sqrt{18\pi}}e^{-(t-12)^2/18}$$

Birn et al. (2008). The Respiration Response Function: The temporal dynamics of fMRI signal fluctuations related to changes in respiration. Neuroimage 40(2):644-654.

Chang et al. (2009). Influence of heart rate on the BOLD signal: The cardiac response function. Neuroimage 44(3):857-869.

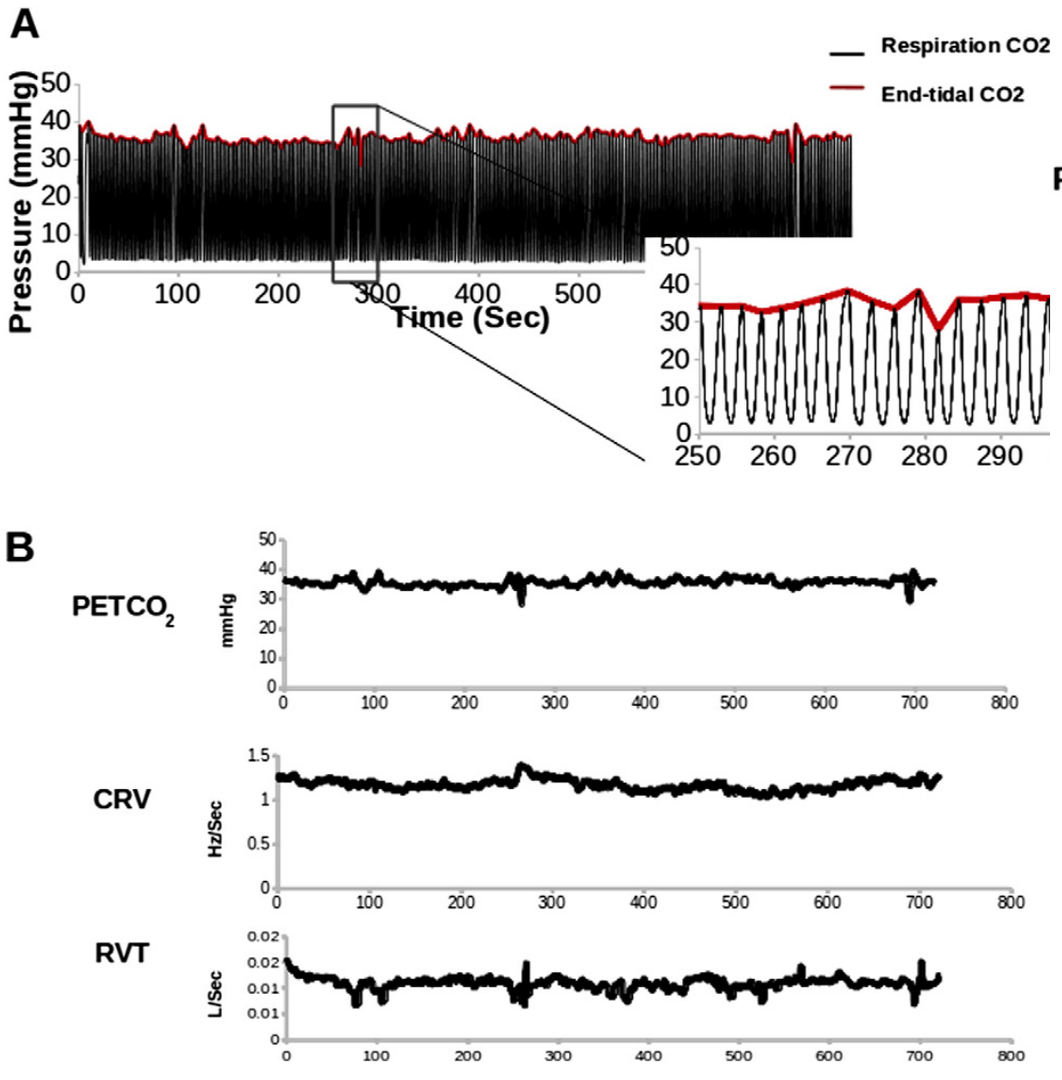
RVHRCOR: RVT(*)RRF and CR(*)CRF

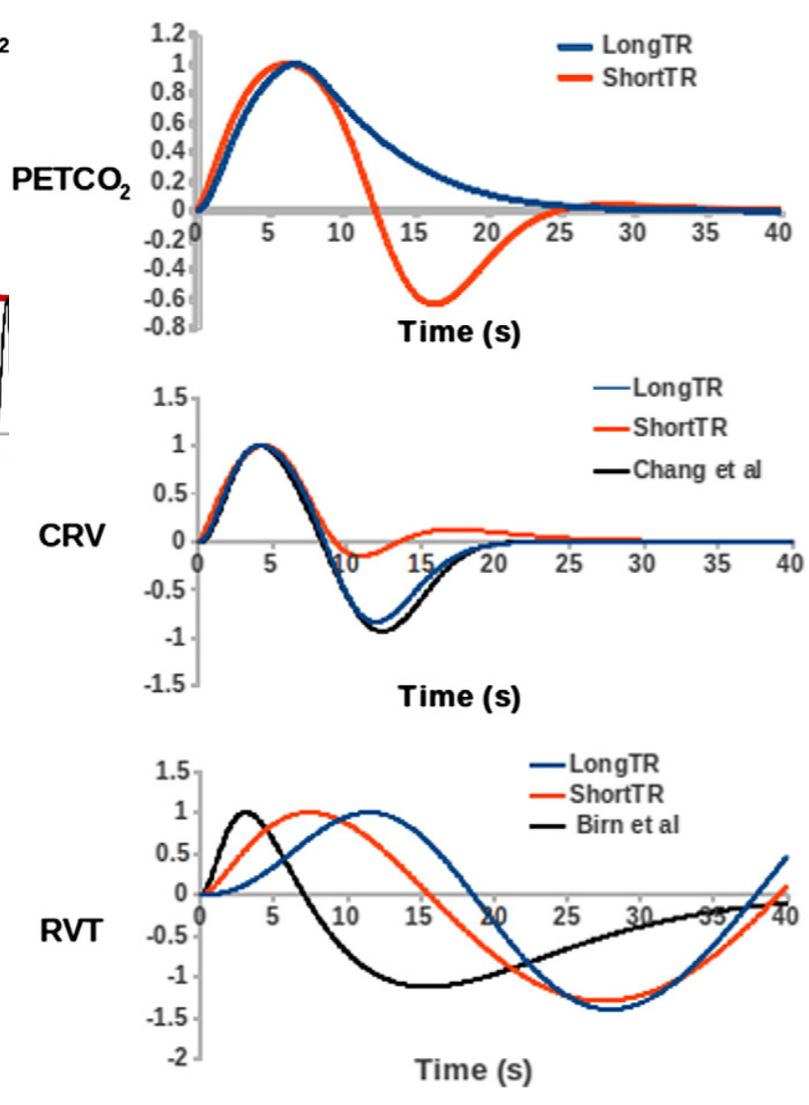


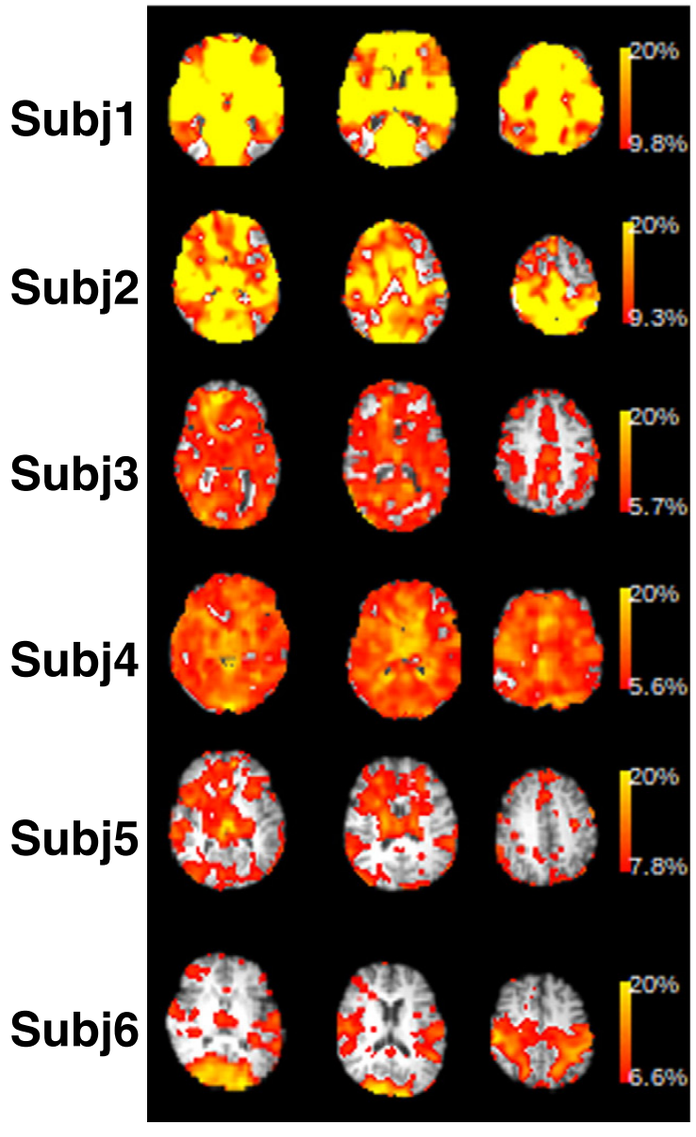
Chang et al. (2009). Influence of heart rate on the BOLD signal: The cardiac response function. Neuroimage 44(3):857-869.

Modelling End-tidal CO_2 fluctuations

- End-tidal CO_2 ($PetCO_2$) measurements can also be recorded during fMRI experiments via a nasal cannula or face mask.
- The $PetCO_2$ response function can be estimated in similar fashion to the cardiac and respiratory response functions



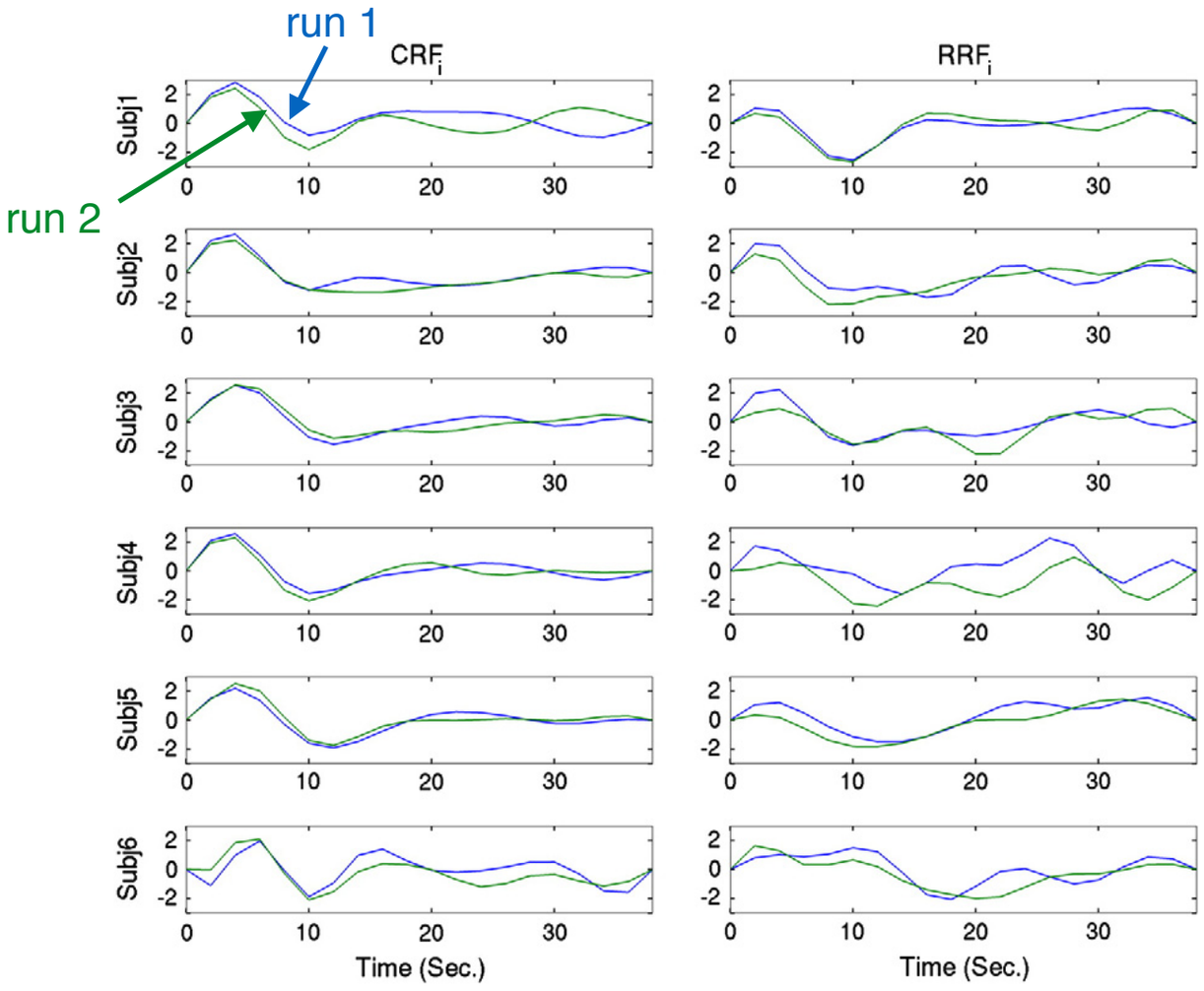


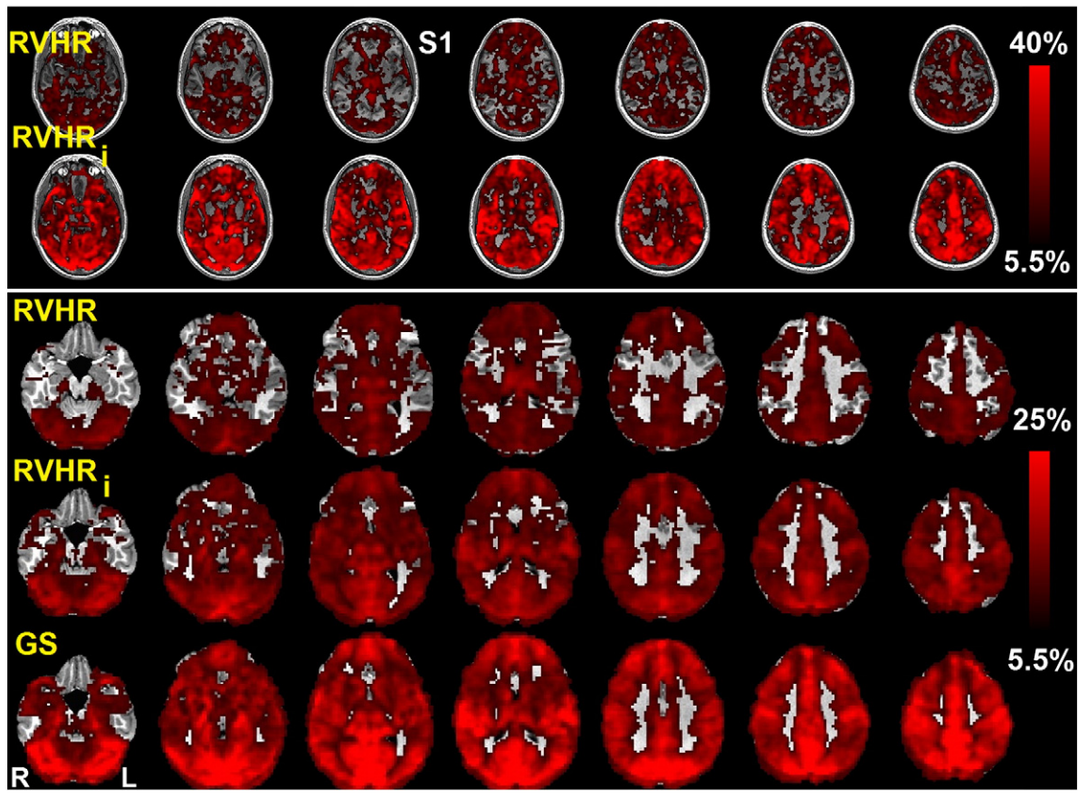


Golestani et al. (2015). Mapping the end-tidal CO2 response function in the resting state BOLD fMRI signal: Spatial specificity, test-retest reliability and effect of fMRI sampling rate. Neuroimage 104:266-277.

Subject-specific physiological response functions

- The RRF and CRF were computed as the average physiological responses across subjects; yet, employing these responses, however, does not warrant for intra-subject variations in physiological response, particularly for clinical cases.
- Derive the RRF and CRF from the global or average GM signal since we are in the physiological noise regime (thermal noise is averaged across voxels).

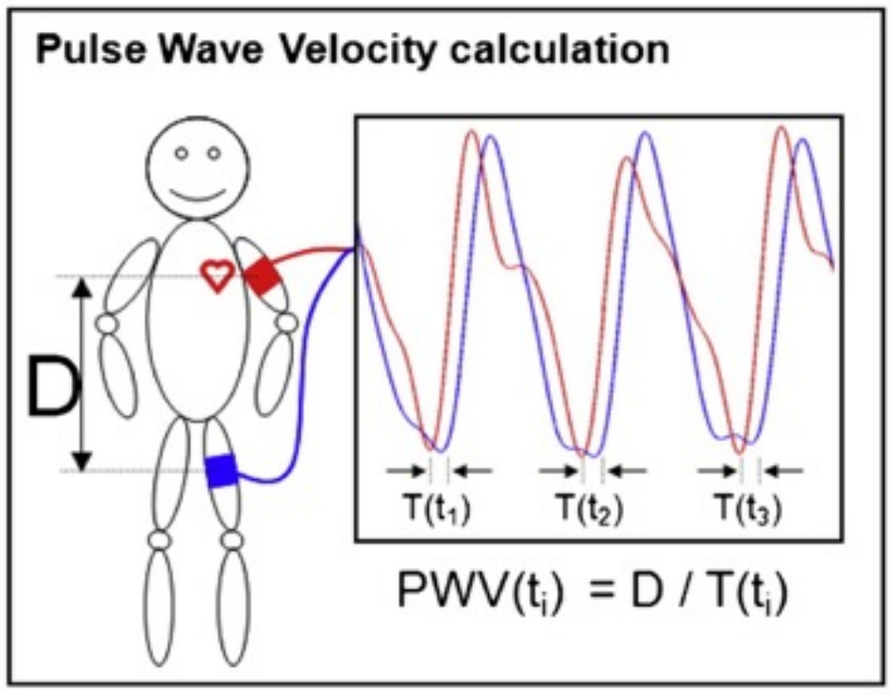


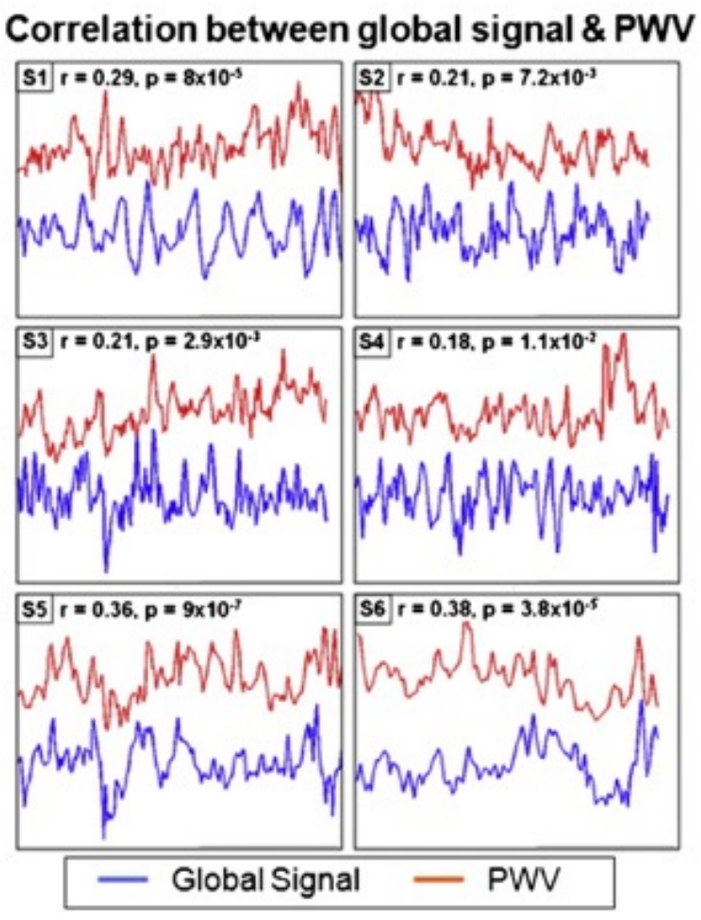


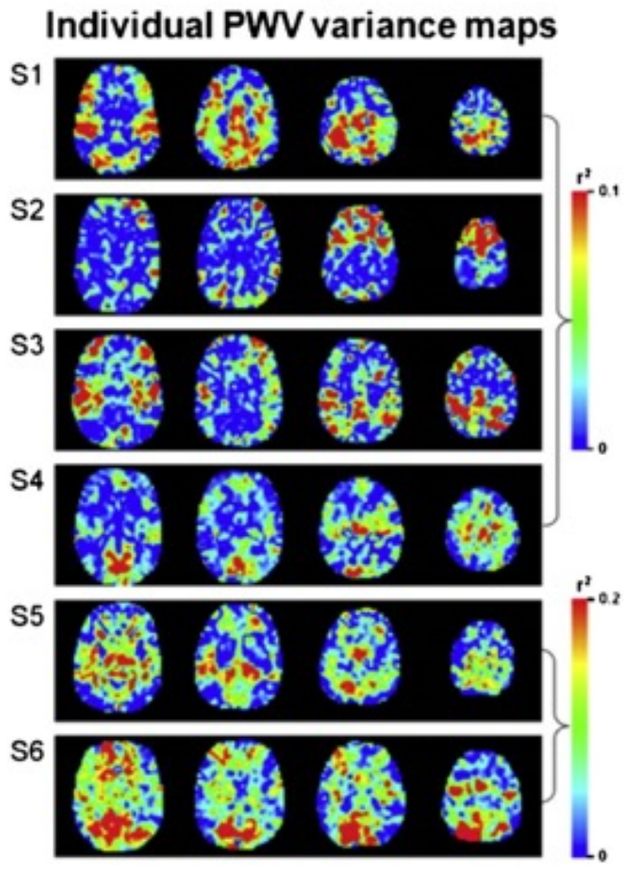
Falahpour et al. (2013). Subject specific BOLD fMRI respiratory and cardiac response functions obtained from global signal. Neuroimage 72:252-264.

Accounting for continuous blood pressure recordings

- Changes in blood pressure can also be monitored with MR-compatible continuous blood pressure devices in order to minimise intrinsic fluctuations related to cerebral autoregulation.
- Continuous blood pressure traces have been observed to strongly correlate with the global signal.





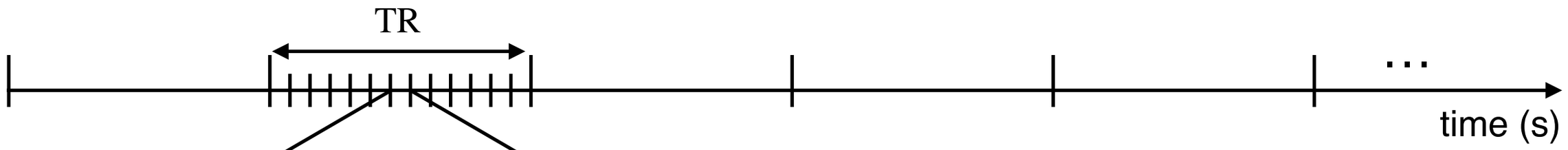


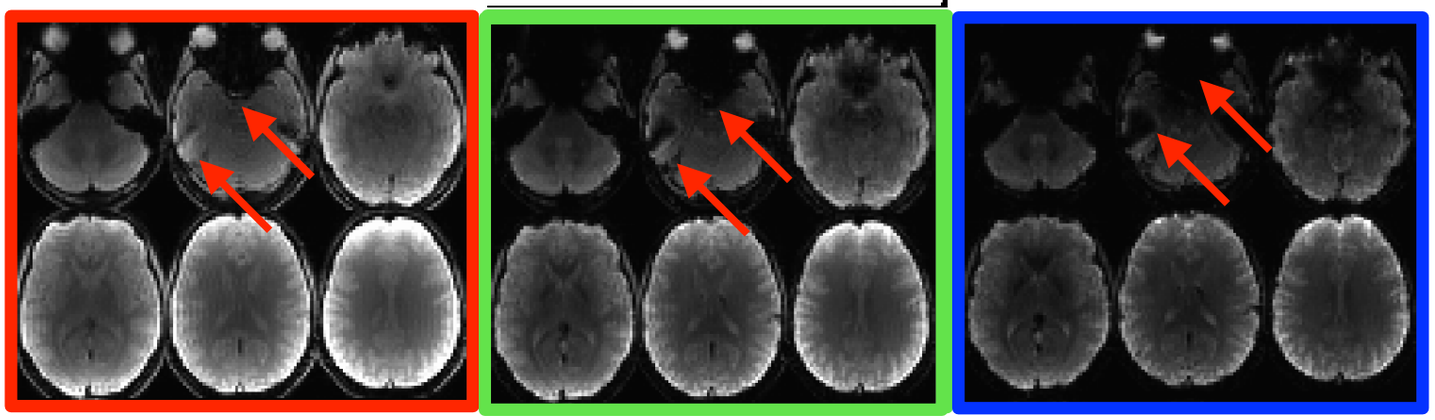
Murphy et al. (2011). The association between pulse wave velocity, as a marker of sympathetic tone, and resting state BOLD signals. Proceedings of 19th Annual Meeting ISMRM, p. 3561

Whittaker et al. (2016). Beat-to-beat blood pressure fluctuations are present in time-frequency dynamics of resting-state fMRI. Proceedings of 24th Annual Meeting ISMRM, p. 0309

Multi-echo FMRI

Multi-echo fMRI (your advanced fMRI acquisition)

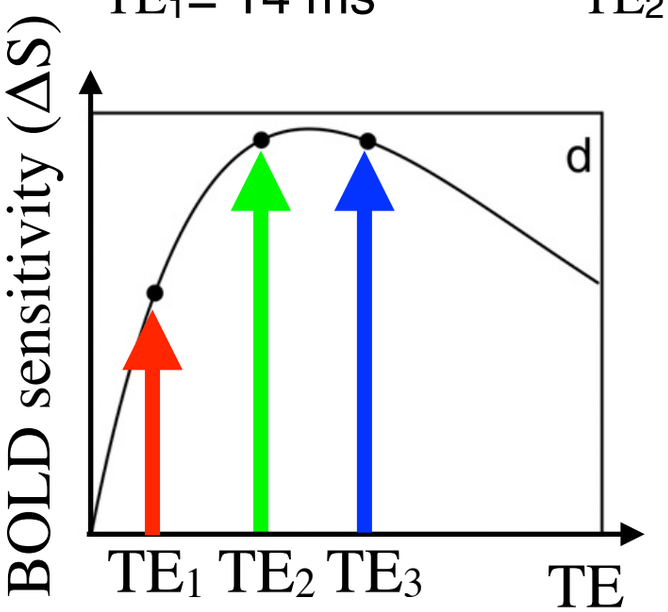


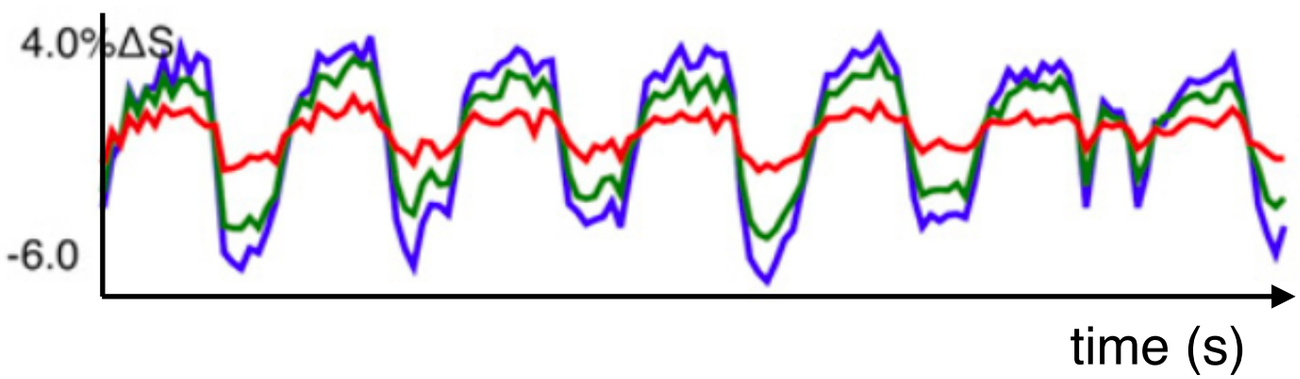


TE_1= 14 ms TE_2 = 29 ms TE_3 = 44 ms

- No SAR cost, as there are not additional excitation pulses
- ~~Slight increase in TR to acquire additional echoes~~
- ~~Slight decrease in spatial resolution to ensure last echo has signal~~

Not big limitations nowadays with SMS acquisitions





Slide courtesy of Javier Gonzalez Castillo (NIH)

Multi-echo FMRI: Optimal combination to maximize CNR

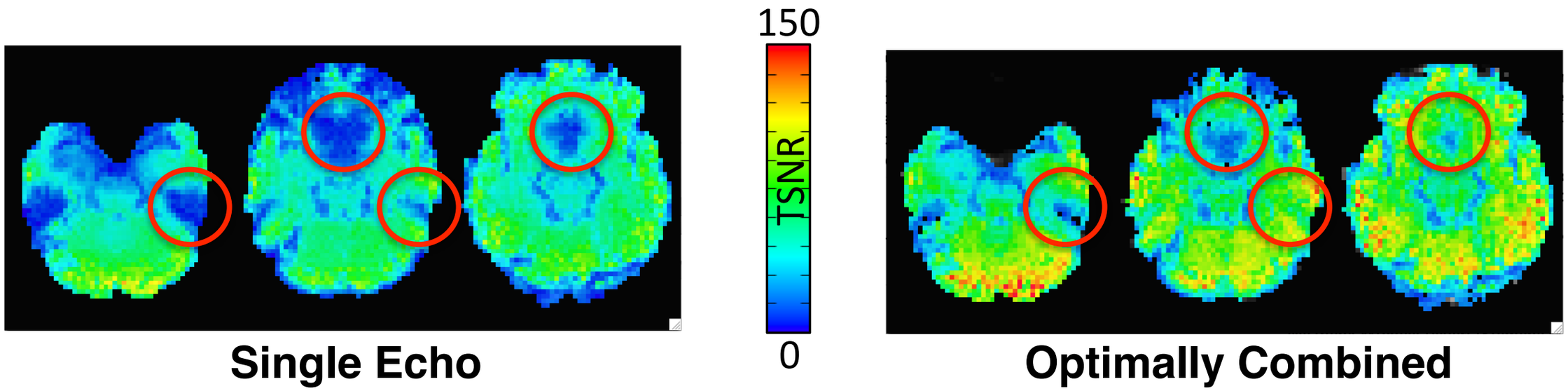
- We have N_e pseudo-concurrent signals, why not simply combine them to reduce the uncorrelated noise present in each individual signal?

Optimally weighted summation

$$\hat{S}(x,t) = \sum_{n=1}^{N} S(x,t,TE_n) \cdot w_x(TE_n)$$

$$w_x(TE_n) = \frac{TE_n e^{-TE_n/T^*_{2,x}}}{\sum_{n=1}^{N} TE_n e^{-TE_n/T^*_{2,x}}}$$

- Optimizes contrast-to-noise ratio (CNR) with respect to single-echo signal.
- Helps to recovers signal in regions with large signal drop-outs at standard single-echo acquisitions (i.e. inferior temporal, temporal pole, orbitofrontal).

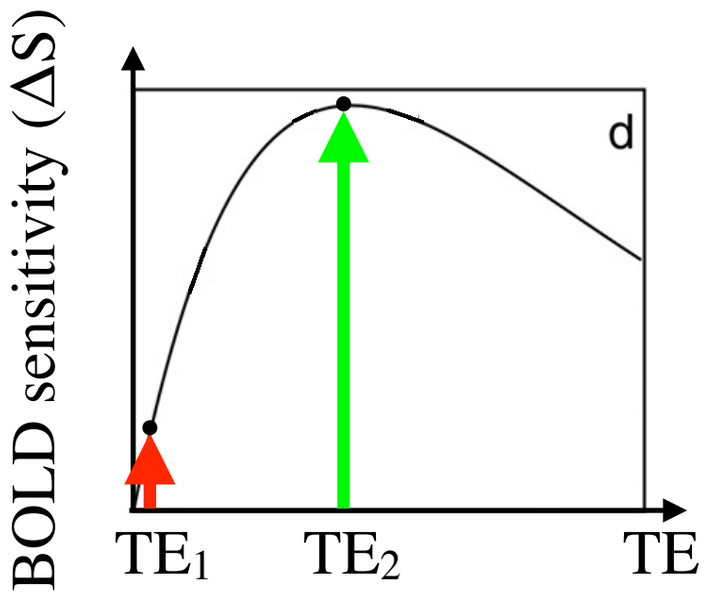


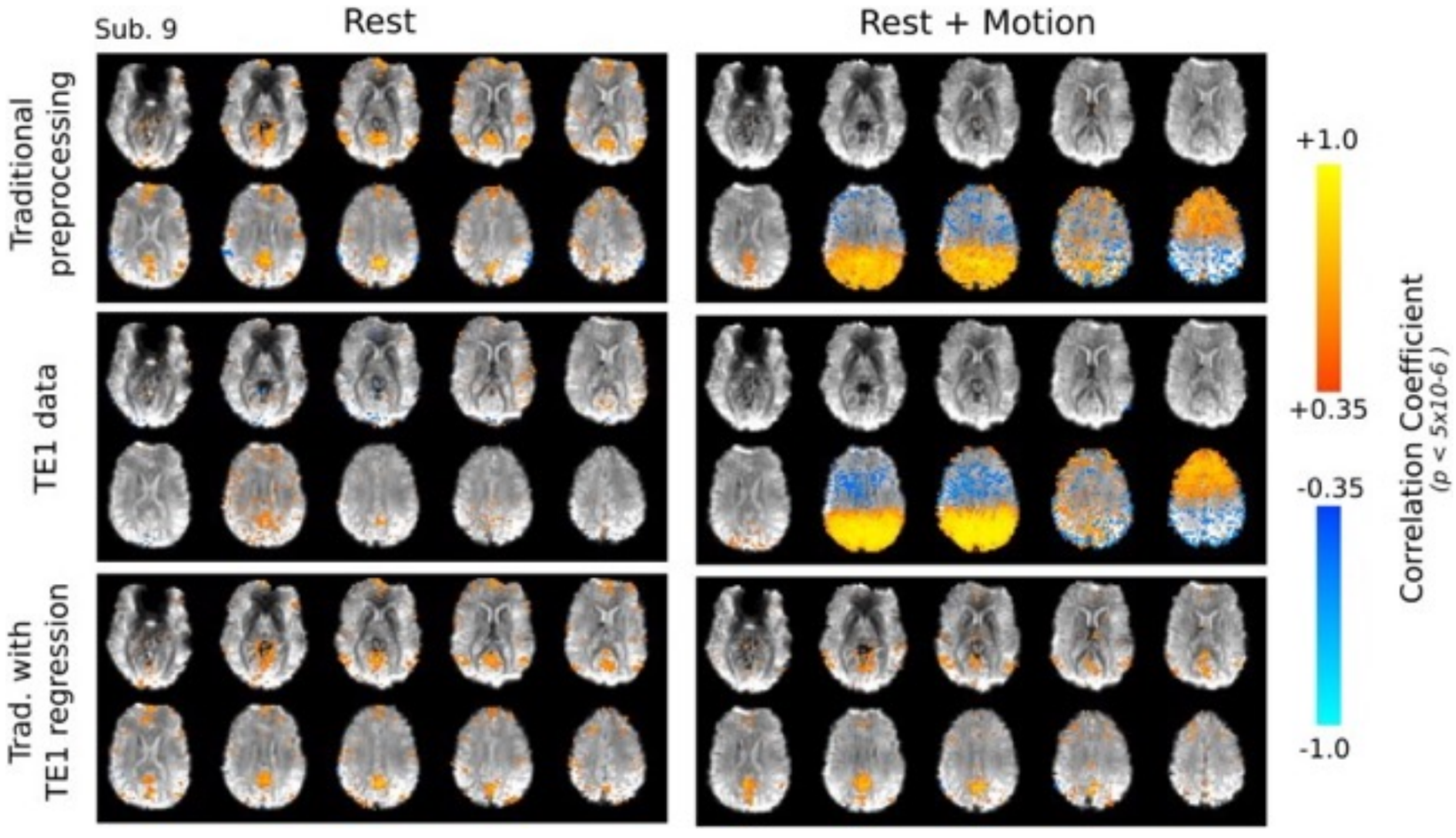
Posse et al. (1999). Enhancement of BOLD-contrast sensitivity by single-shot multi-echo functional MR imaging. Magn Reson Med 42(1):87-97

Slide courtesy of Javier Gonzalez Castillo (NIH)

Denoising with Multi-echo FMRI: Dual-echo approaches

- Acquisition of 2 echoes (TE_1 and TE_2) with short TE_1 for minimal T2*-weighting and high sensitivity to fluctuations in the net magnetization S_0 (i.e. capturing motion-related signal changes, inflow effects and respiratory-related fluctuations)
- Short TE_1 signal is used as nuisance regressor for the optimal TE_2 (≈ T2*) signal.
- Shorter TE_1 achievable with spirals (≈ 3 ms) than with EPI trajectories (≈ 10 ms)



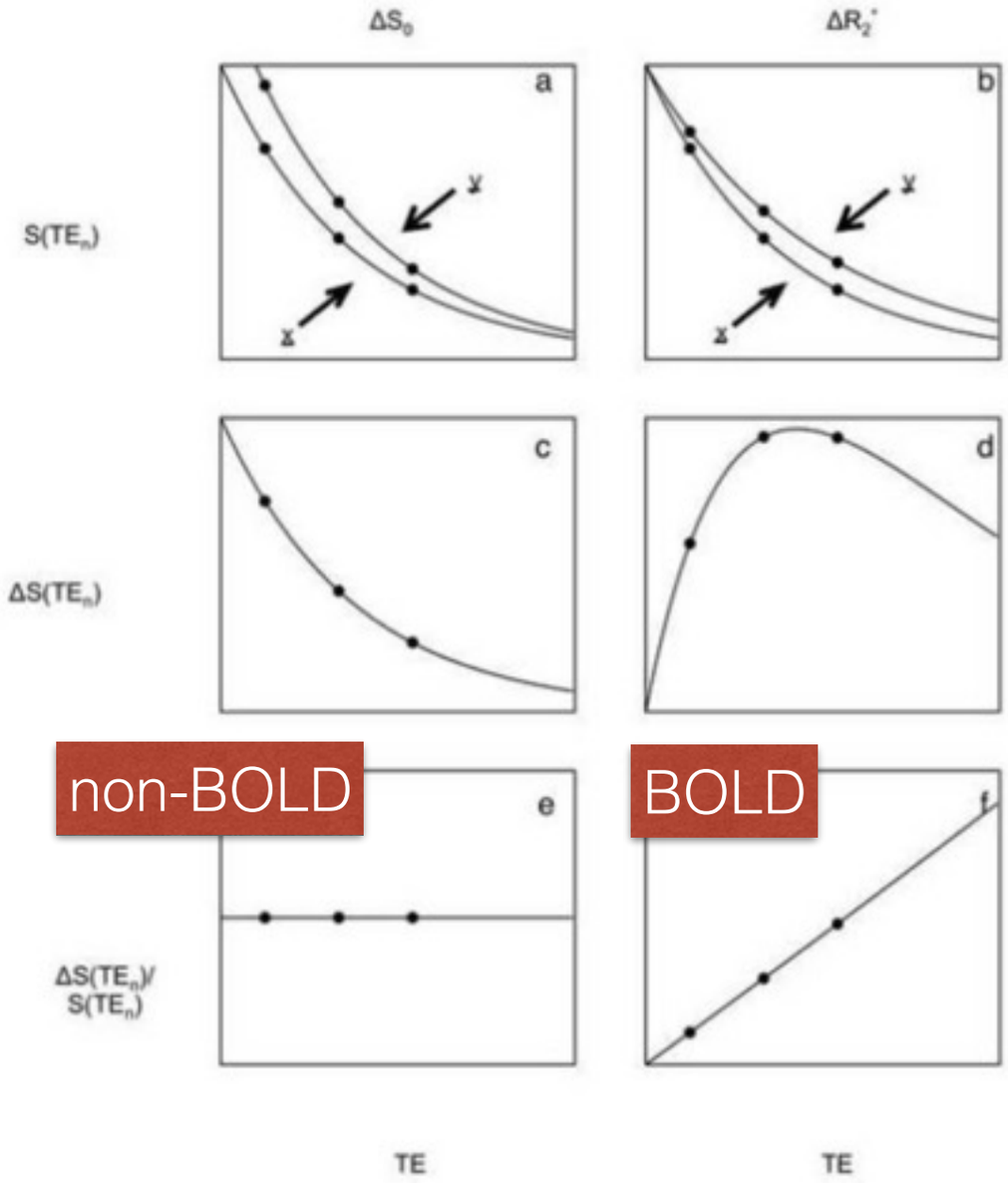


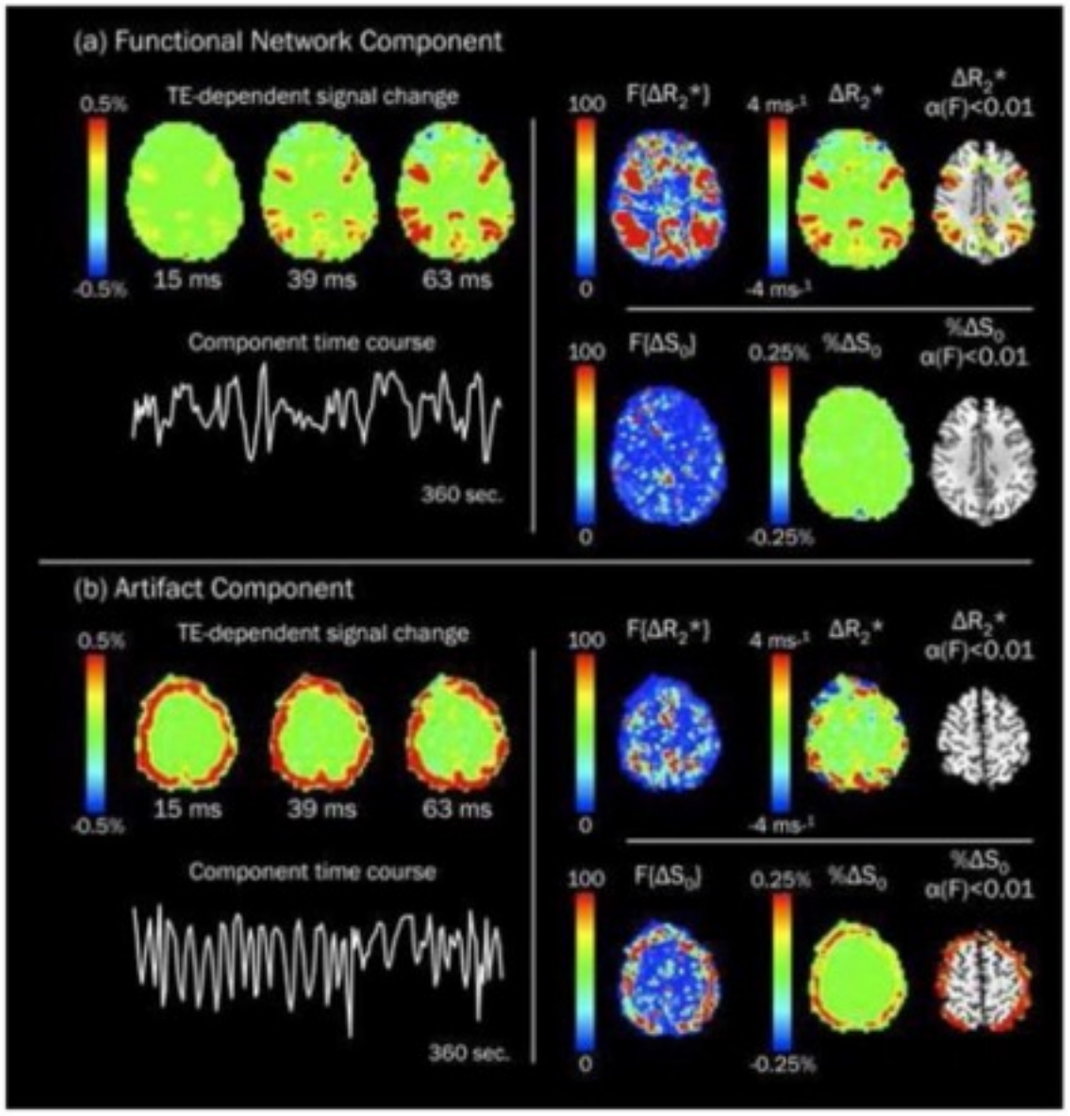
Buur et al. (2009). A dual echo approach to removing motion artefacts in fMRI time series. NMR Biomed. 22:551–560.

Bright & Murphy (2013). Removing motion and physiological artefacts from intrinsic BOLD fluctuations using short echo data. Neuroimage 64(6):526-537

Denoising with Multi-echo FMRI: ME-ICA

- BOLD and non-BOLD independent components are classified according to the TE-dependence of the ICA spatial maps.





Kundu et al. (2012). Differentiating BOLD and Non-BOLD Signals in fMRI Time Series Using Multi-Echo EPI. Neuroimage 60(3): 1759–1770.

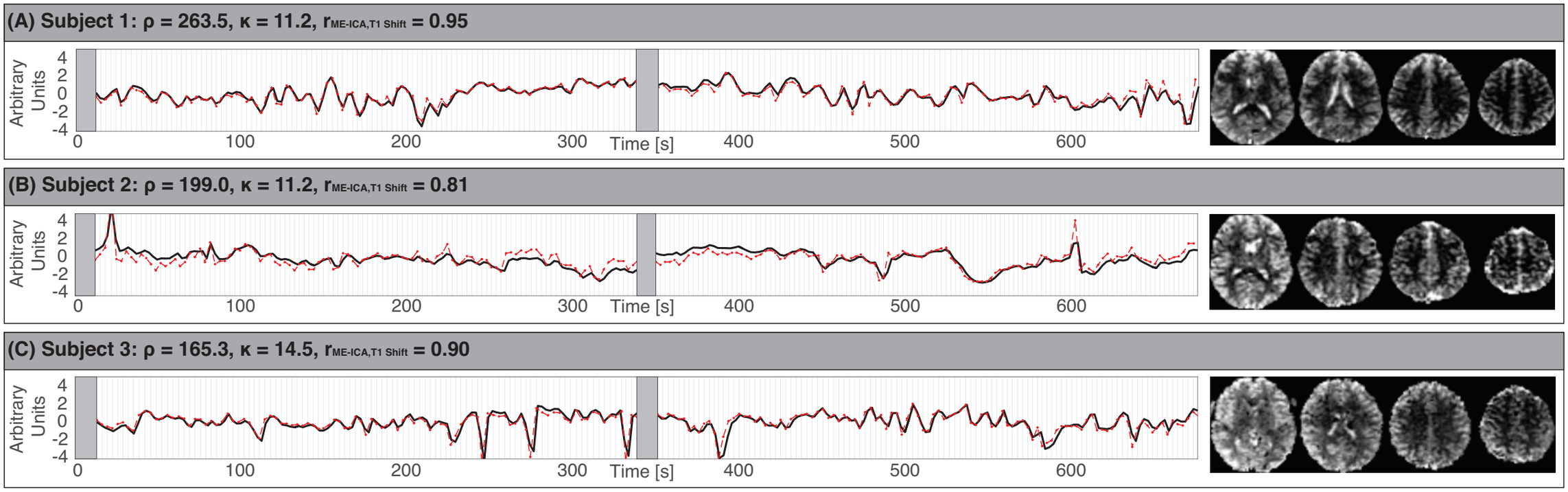
Check out Prantik Kundu's talk on this session for more denoising with ME-fMRI

Non-constant TR: Denoising with Multi-echo FMRI

- Non-constant TR: Cardiac gating to freeze pulsation-brain movement (e.g. fMRI studies of brainstem, amygdala, hippocampus, thalamus), TR is triggered by the subject's response, variable sparse fMRI sampling, etc.

- Non-constant TR introduces **a strong T1-related fluctuation in the fMRI signal** that can be effectively removed by Dual-echo or ME-ICA approaches

T1-weighted ICs selected by ME-ICA

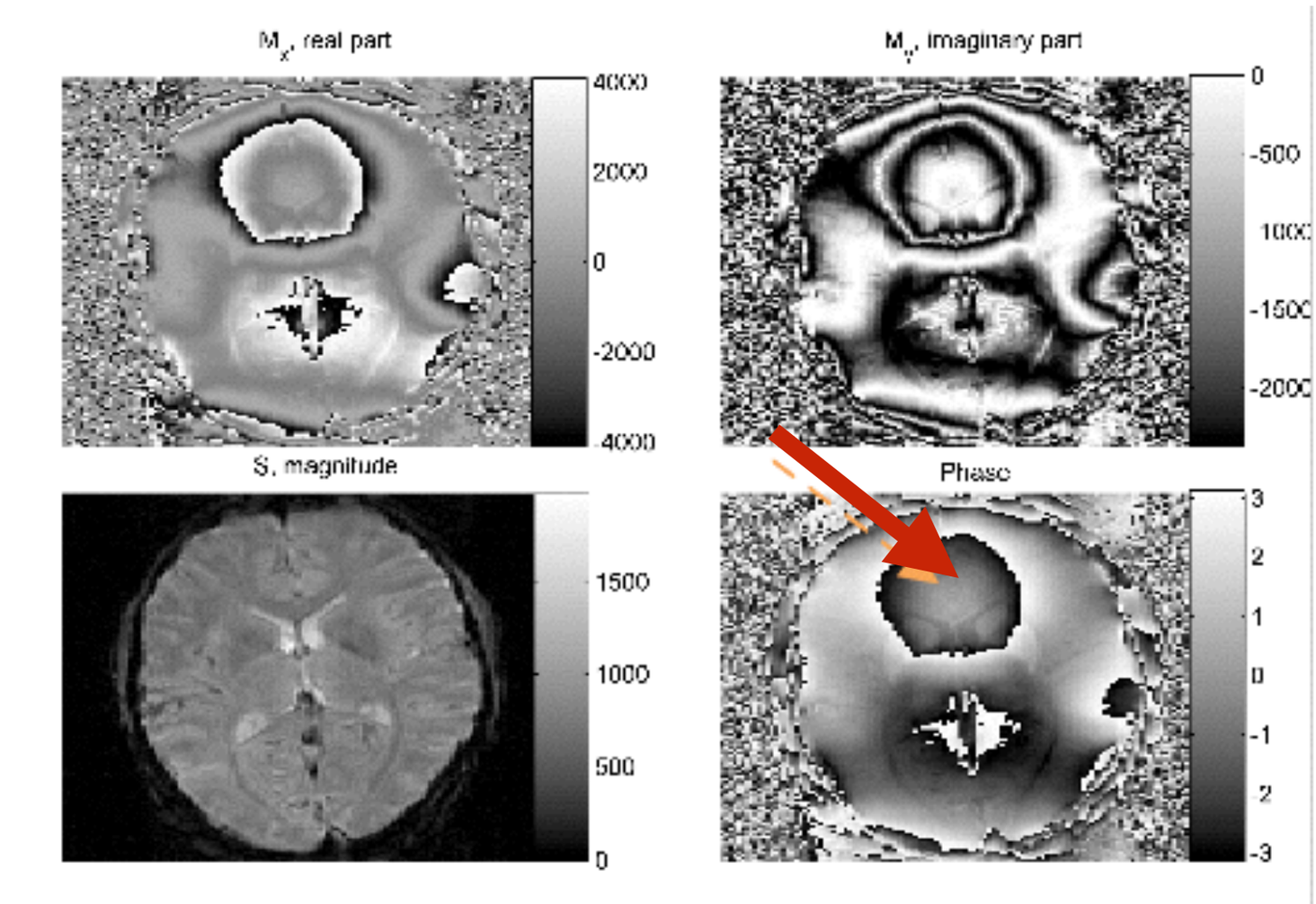


IC maps look like T1-maps

Gonzalez-Castillo et al., (2016). Evaluation of multi-echo ICA denoising for task based fMRI studies: Block designs, rapid event-related designs, and cardiac-gated fMRI.. Neuroimage 141:452-468.

Phased-based methods

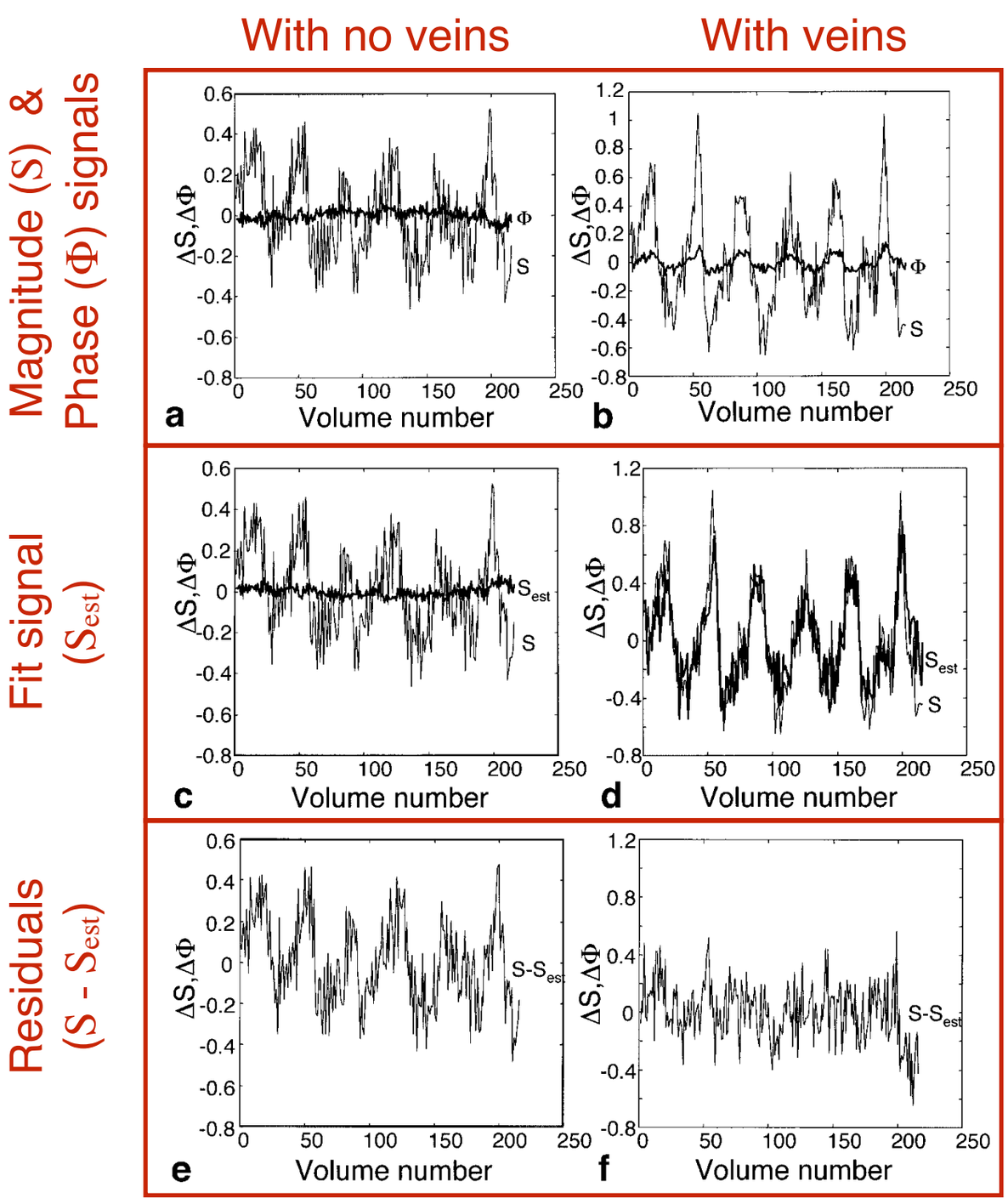
- MRI is inherently a complex signal with its real and imaginary part, or equivalently its magnitude and phase signal.
- Typically, the magnitude signal is only used in fMRI data analysis;
- The phase signal contains relevant information about magnetic field variations, e.g. differences in susceptibility in regions near air and tissue boundaries.



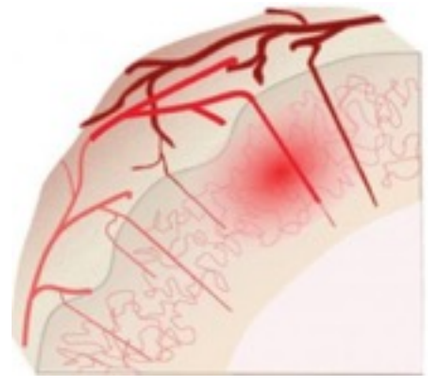
Hagberg and Tuzzi (2014) Phase variations in fMRI time series analysis: Friend or Foe?

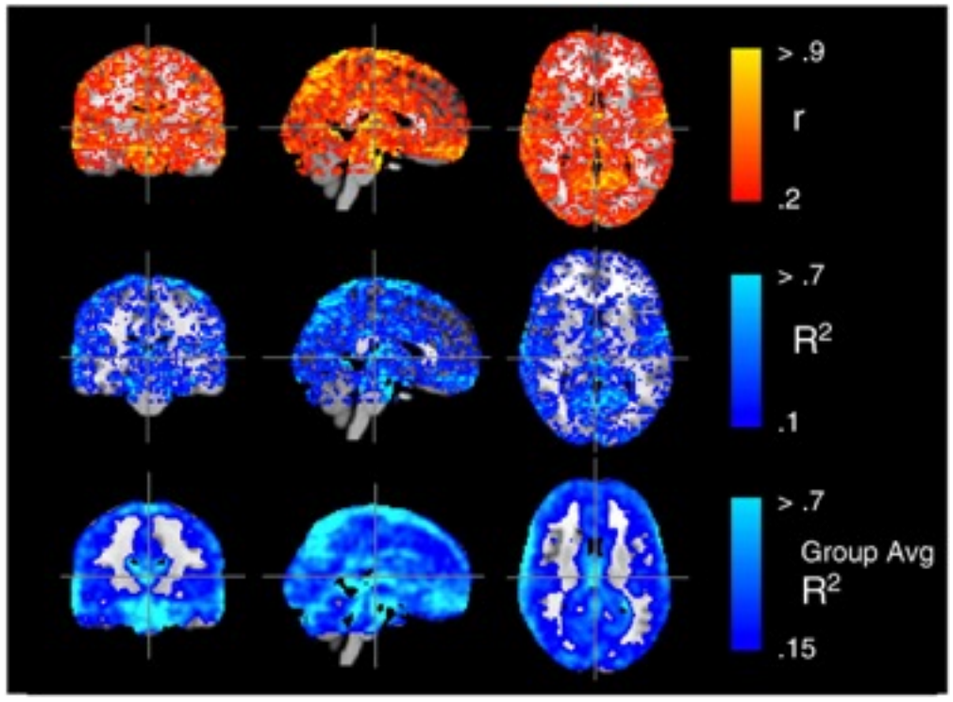
Phased-based regression for venous signal suppression

- The phase signal can be also used as nuisance regressor to remove the effect of large vessels and draining veins in Gradient Echo fMRI.



- Quasi-random orientation of vessels in capillary bed results in incoherent phase signal changes.





Menon (2002) Postacquisition suppression of large-vessel BOLD signals in high-resolution fMRI. Magn Reson Med. 47:1-9

Curtis et al. (2014). Phase based venous suppression in resting-state BOLD GE-fMRI. Neuroimage 100:51-59.

Take home message

- **fMRI is very noisy.** The BOLD effect due to neuronal activity is only 2-5% of the mean amplitude and the signal is corrupted by multiple noise components.

- **Denoising is critical for both task and resting state fMRI.** Numerous techniques are available for denoising the BOLD fMRI signal.

- Motion-related signal changes and physiological noise fluctuations are usually the main targets for denoising.

- Phase-based and multi-echo fMRI can help to improve cleaning the signal, but require extra attention at the time of data acquisition.

- There is no 'best' method for preprocessing and denoising, but there are incorrect methods.

ALWAYS LOOK AT THE DATA!!
(BEFORE AND AFTER PREPROCESSING)

References

NeuroImage (xxxx) xxxx–xxxx

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/neuroimage

Methods for cleaning the BOLD fMRI signal

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ARTICLE INFO

Keywords:
BOLD fMRI
Denoising methods
Motion artifacts
Physiological noise
Multi-echo
Phase-based methods

More than 300 references

ABSTRACT

Blood oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) has rapidly become a popular technique for the investigation of brain function in healthy individuals, patients as well as in animal studies. However, the BOLD signal arises from a complex mixture of neuronal, metabolic and vascular processes, being therefore an indirect measure of neuronal activity, which is further severely corrupted by multiple non-neuronal fluctuations of instrumental, physiological or subject-specific origin. This review aims to provide a comprehensive summary of existing methods for cleaning the BOLD fMRI signal. The description is given from a methodological point of view, focusing on the operation of the different techniques in addition to pointing out the advantages and limitations in their application. Since motion-related and physiological noise fluctuations are two of the main noise components of the signal, techniques targeting their removal are primarily addressed, including both data-driven approaches and using external recordings. Data-driven approaches, which are less specific in the assumed model and can simultaneously reduce multiple noise fluctuations, are mainly based on data decomposition techniques such as principal and independent component analysis. Importantly, the usefulness of strategies that benefit from the information available in the phase component of the signal, or in multiple signal echoes is also highlighted. The use of global signal regression for denoising is also addressed. Finally, practical recommendations regarding the optimization of the preprocessing pipeline for the purpose of denoising and future venues of research are indicated. Through the review, we summarize the importance of signal denoising as an essential step in the analysis pipeline of task-based and resting state fMRI studies.