
Fluctuations and Networks: Thinking and Breathing

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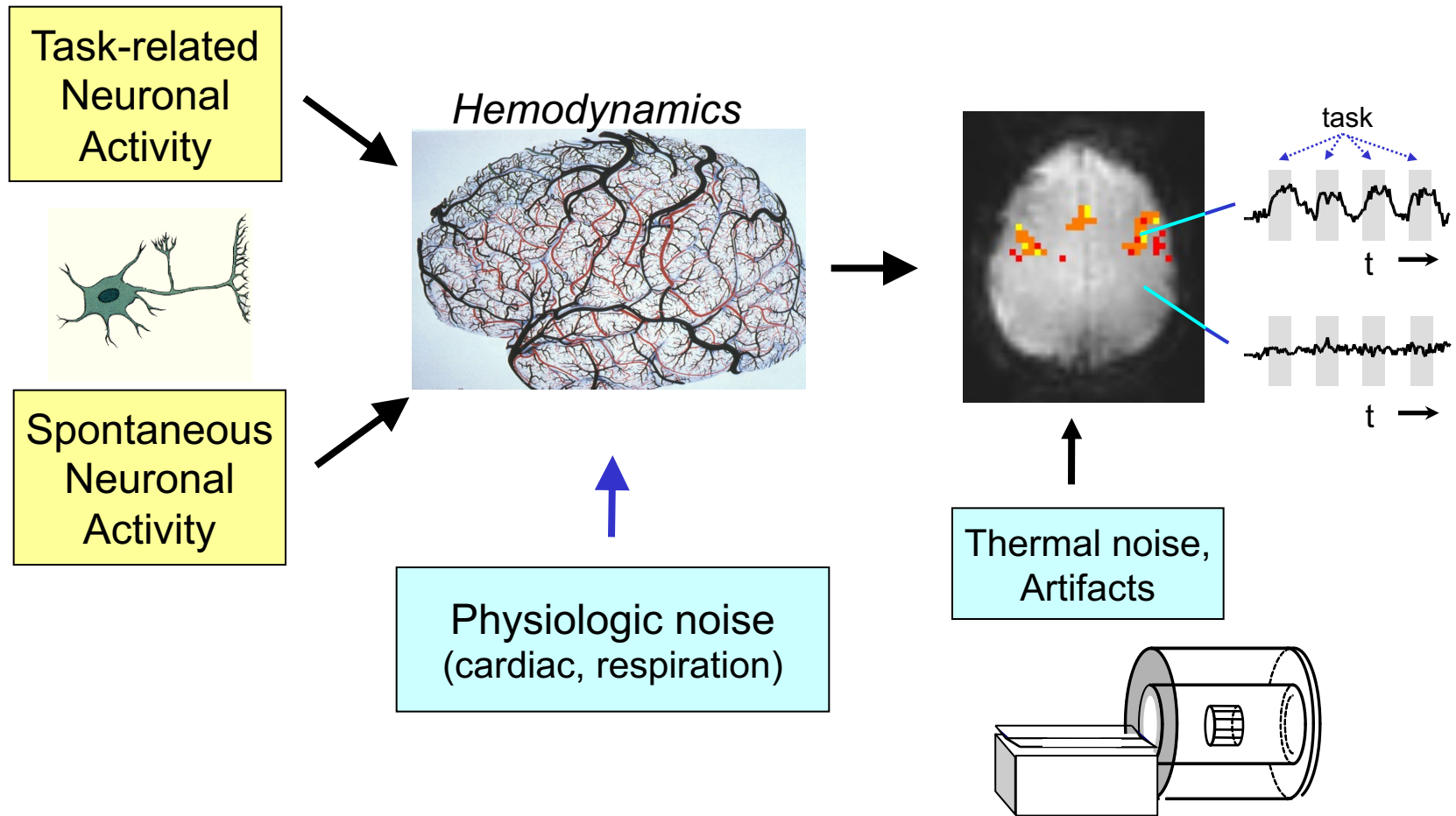
Overview

- “Functional connectivity”
 - Correlations in fMRI signal at rest
 - “Default Mode Network”
- Respiration changes in fMRI
- Respiration + Functional Connectivity
- Modeling respiration-induced fMRI changes



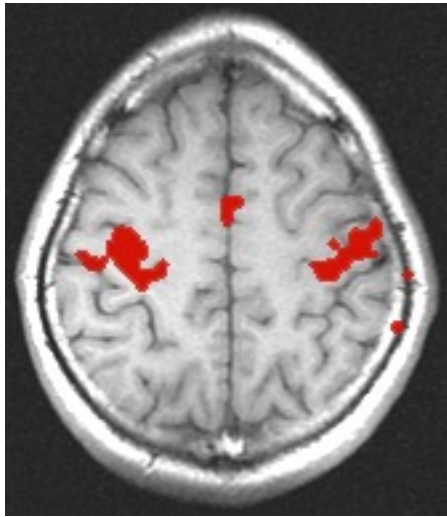
Rasmus Birn

The fMRI Signal

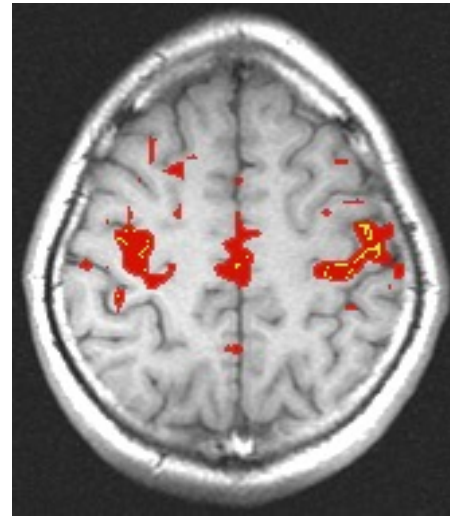


Resting-state functional connectivity

B. Biswal et al., MRM, 34:537 (1995)



Activation during
finger-tapping



Correlations with “seed voxel”
in motor cortex at rest

Further work:

M.J. Lowe, et al., NeuroImage 7(2), 1998.

D. Cordes, et al., AJNR 21(9), 2000.

⋮

“Default-Mode Network”

A default mode of brain function

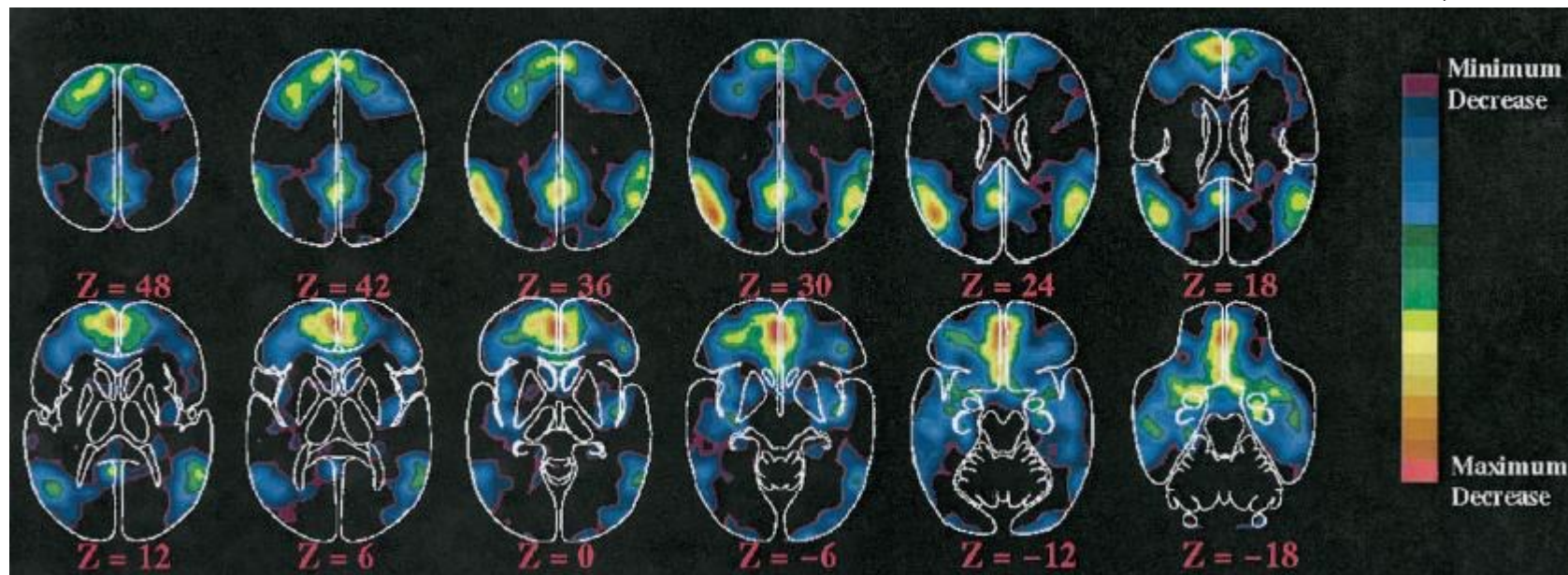
Marcus E. Raichle^{*†}, Ann Mary MacLeod^{*}, Abraham Z. Snyder^{*}, William J. Powers[‡], Debra A. Gusnard^{*§}, and Gordon L. Shulman[‡]

^{*}Mallinckrodt Institute of Radiology and Departments of [‡]Neurology and [§]Psychiatry, Washington University School of Medicine, St. Louis, MO 63110

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected on April 30, 1996.

Contributed by Marcus E. Raichle, October 26, 2000

PNAS 98, 2001



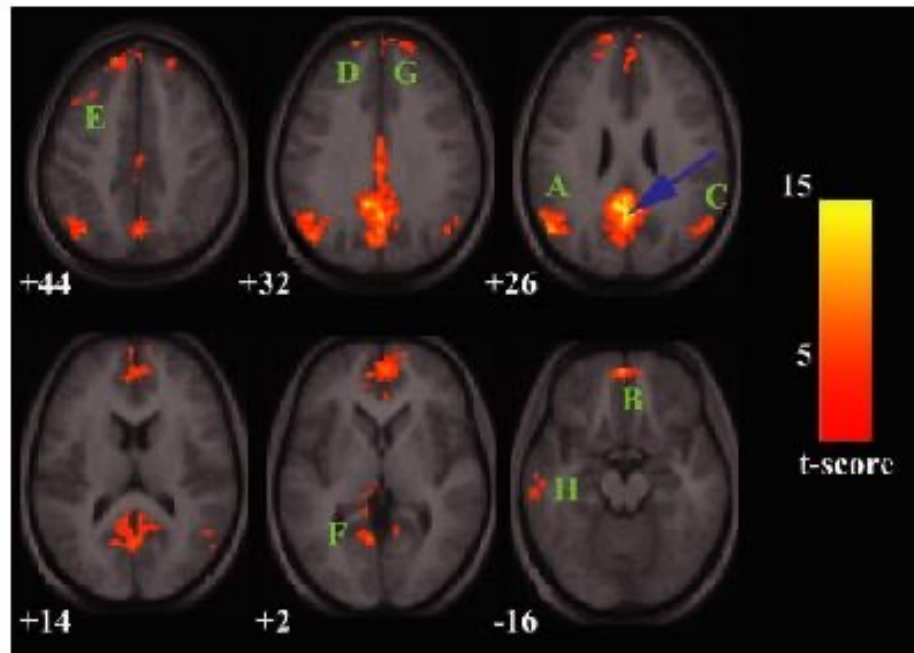
Resting-state functional connectivity

Functional connectivity in the resting brain: A network analysis of the default mode hypothesis

Michael D. Greicius^{*†‡}, Ben Krasnow^{*}, Allan L. Reiss^{*§¶}, and Vinod Menon^{*§¶}

Departments of ^{*}Psychiatry and Behavioral Sciences and [†]Neurology and Neurological Sciences, [§]Program in Neurosciences, and [¶]Stanford Brain Research Center, Stanford University School of Medicine, Stanford, CA 94305-5719

Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved November 12, 2002 (received for review August 21, 2002)



PNAS 100, 2003

Deactivations ↔ Resting correlations

- *Are there differences?*
 - Deactivation (blocked design)
 - Rest (functional connectivity)



Jason Diamond

- *Are deactivations related to the task, or to the brain “state”?*
 - Mixed blocked / event-related

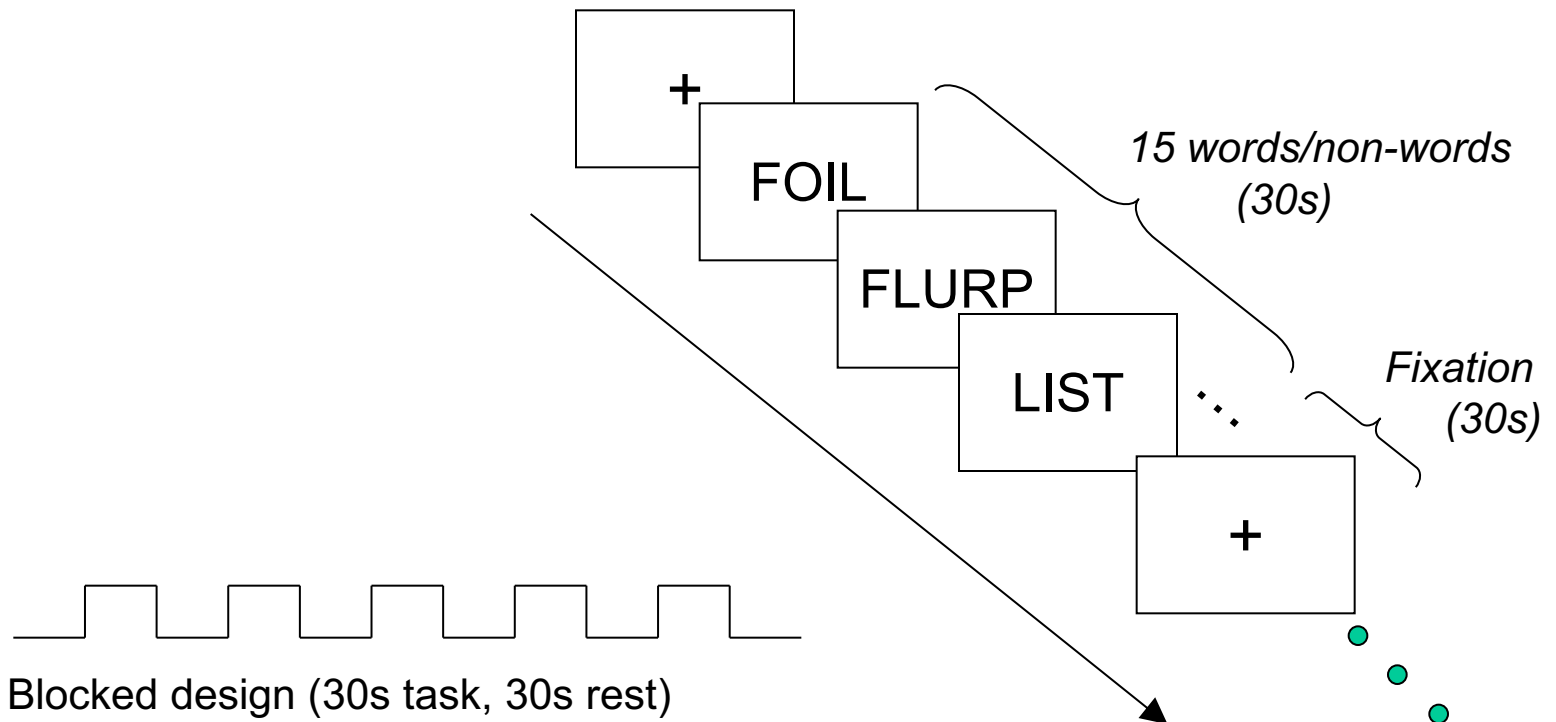
Methods

R.M. Birn, J.B. Diamond, M.A. Smith, P.A. Bandettini, NeuroImage 31, 2006

Task

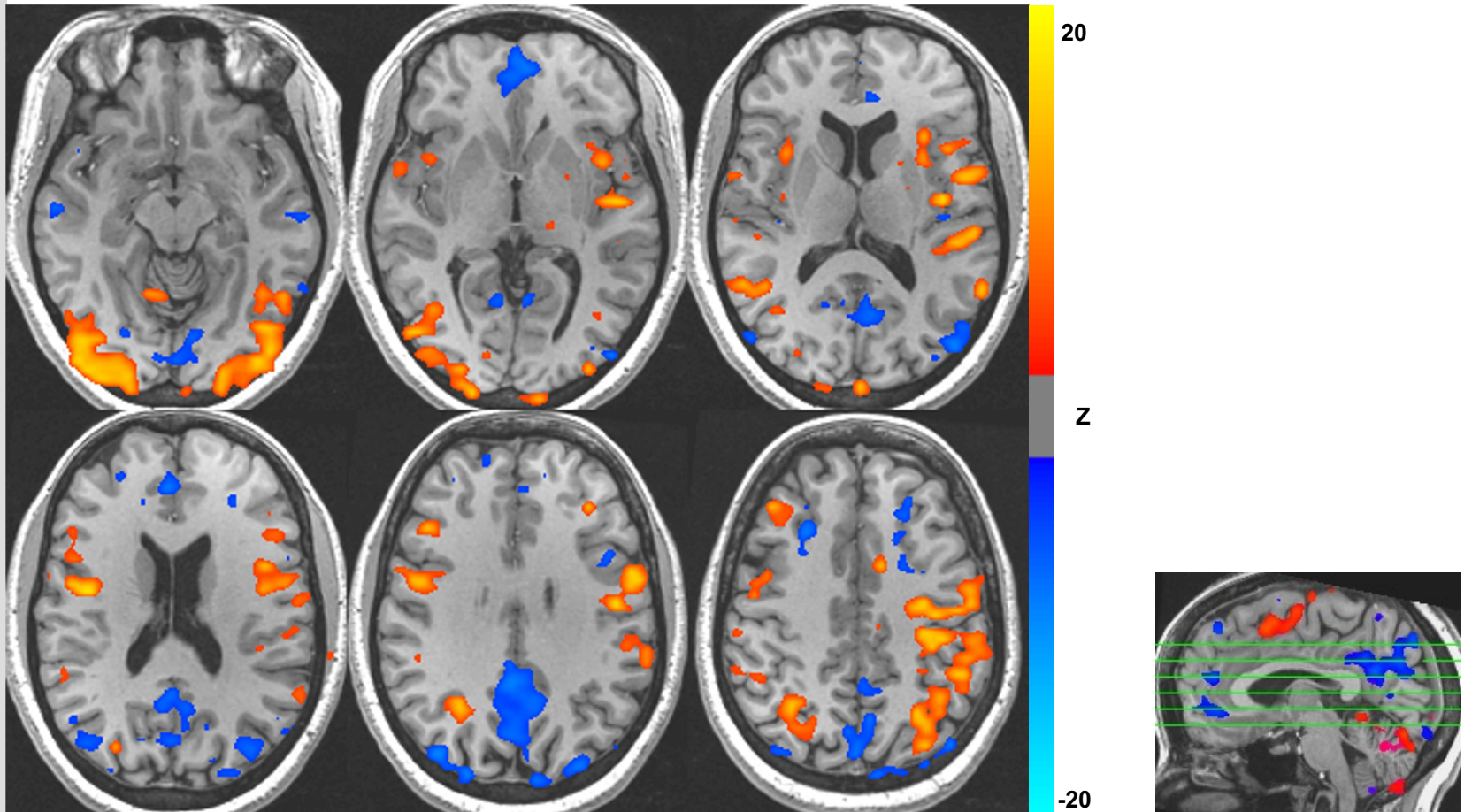
1. Rest (eyes-closed)

2. Lexical Decision: “word” or “non-word”?



Results – Lexical Task

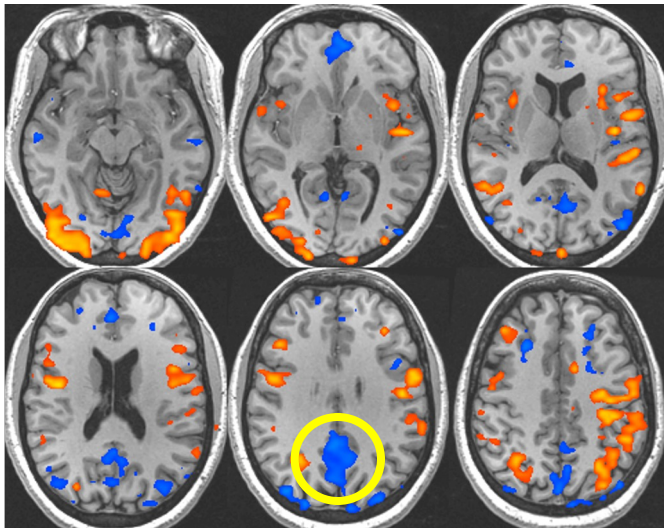
Activations and De-activations during lexical task



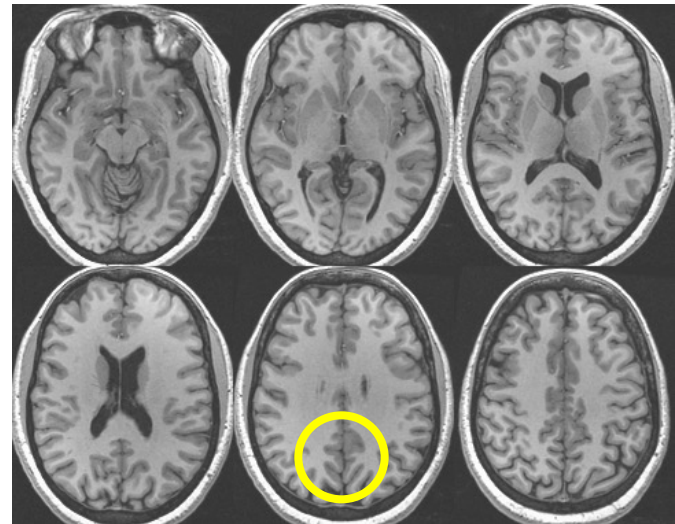
Methods

Functional Connectivity Analysis

- Filter (respiration (0.3Hz), cardiac (1 Hz))
- Define ROI (e.g. deactivations in posterior cingulate)
- Average time courses (at rest) in ROI
- Correlate average time course with all voxels

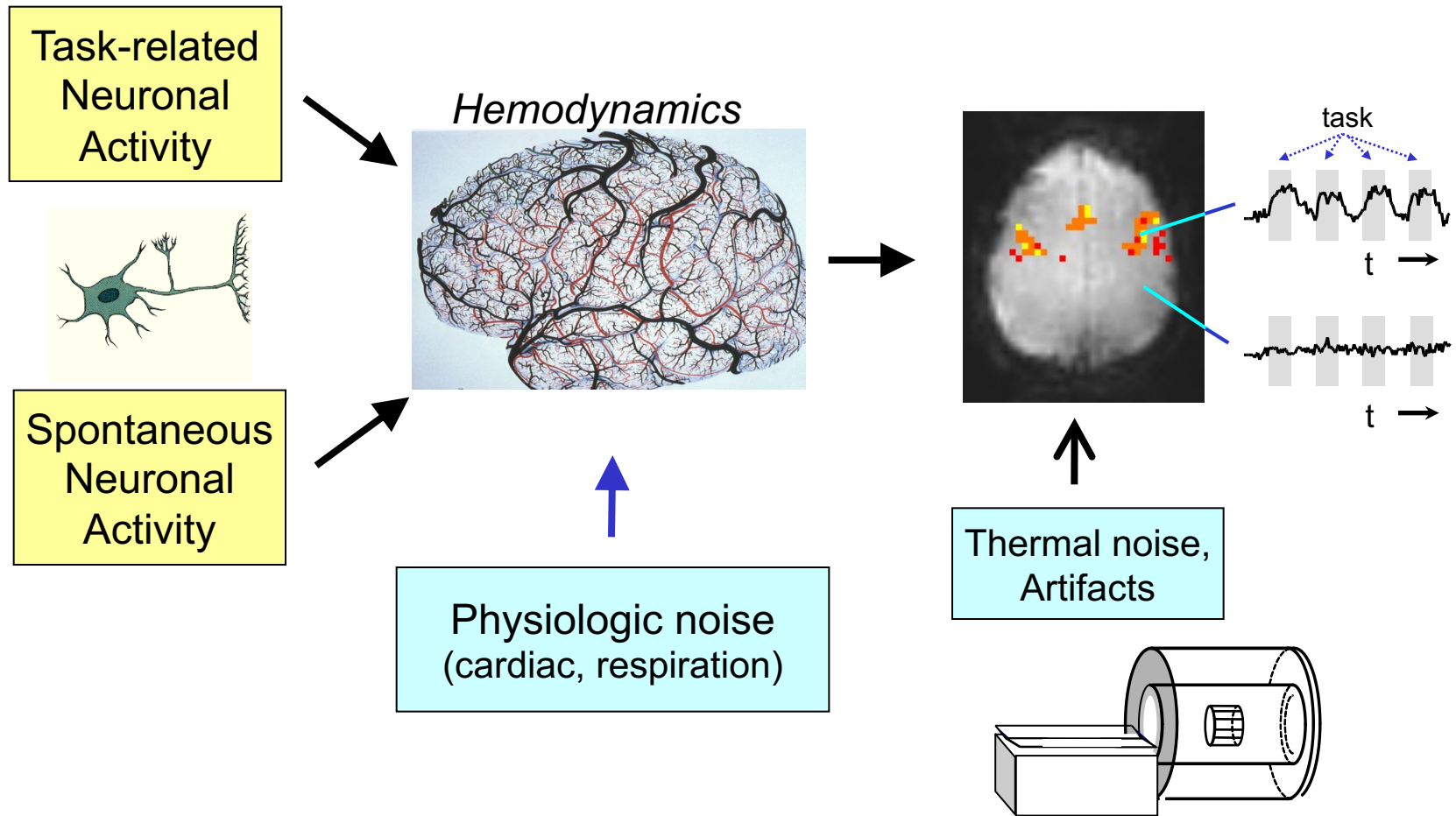


Lexical task



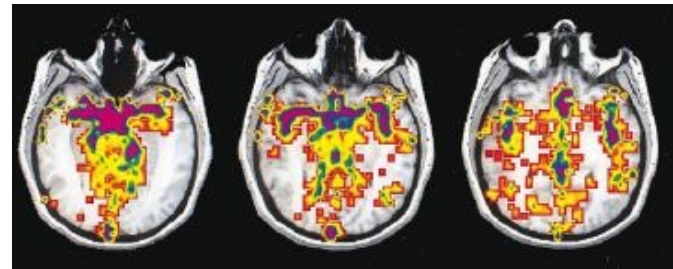
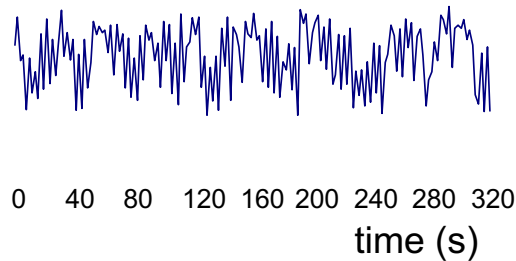
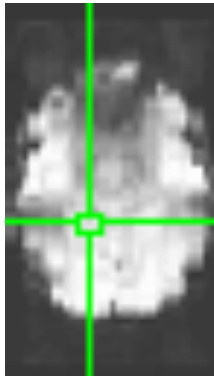
Rest

The fMRI Signal



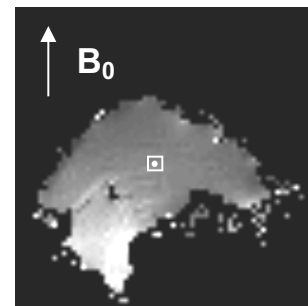
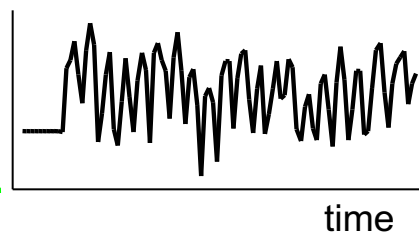
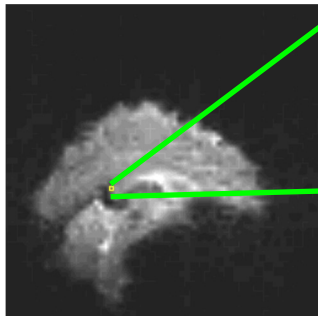
Physiological fluctuations

Cardiac



M.S. Dagli et al., NeuroImage 9, 1999

Respiration



Field Map

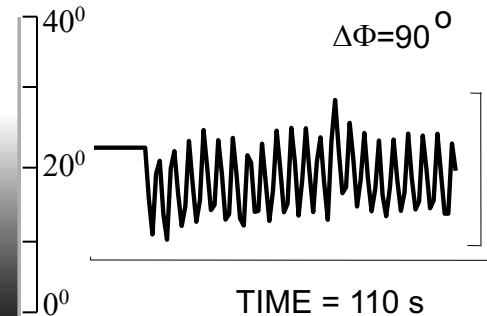
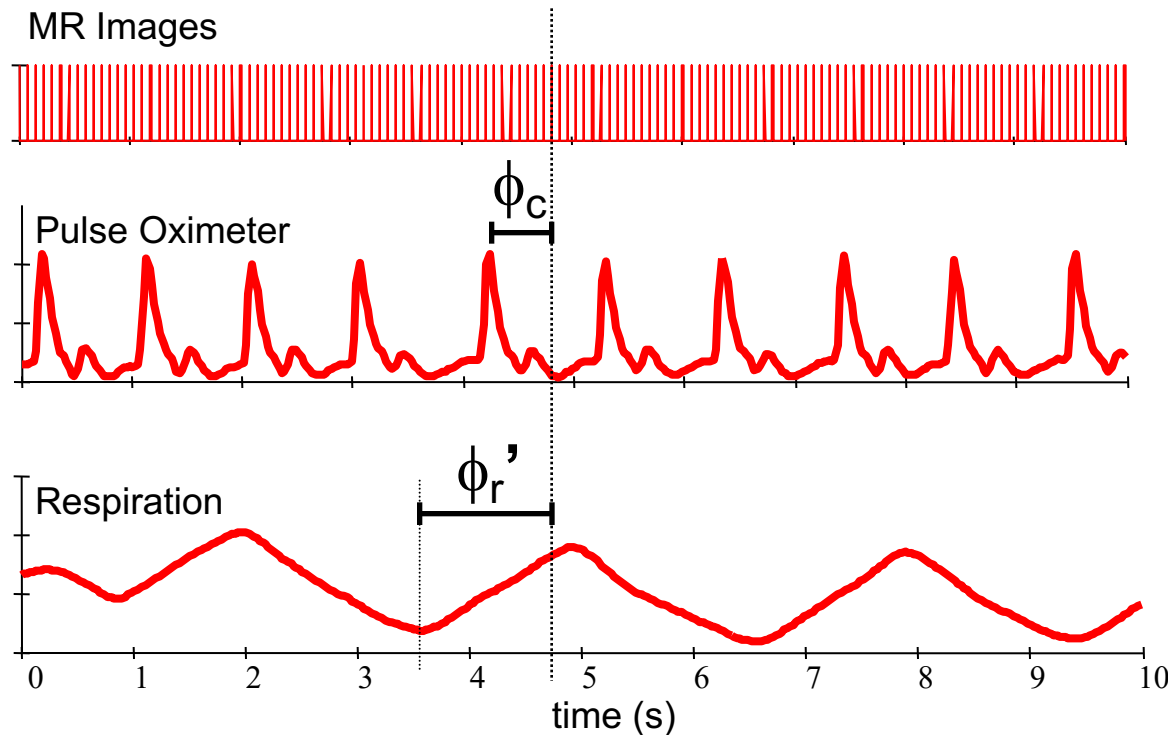


Figure courtesy of J. Bodurka

Correction of physiological noise

RETROICOR (G. Glover et al., *Magn. Reson. Med.* 44, 2000.)



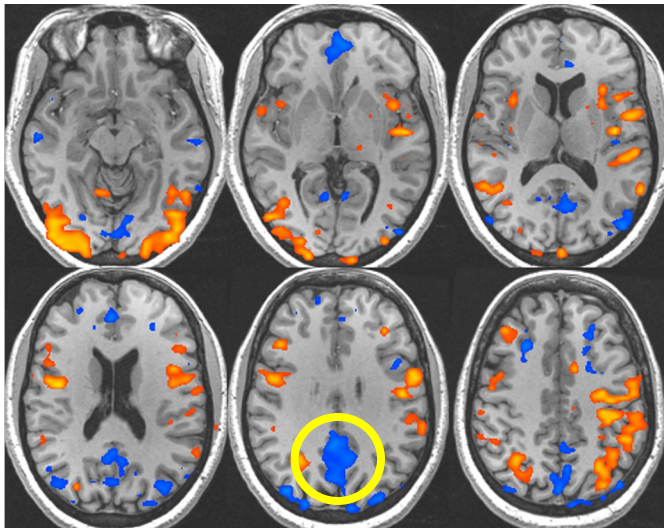
*Additional
Regressors:*

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

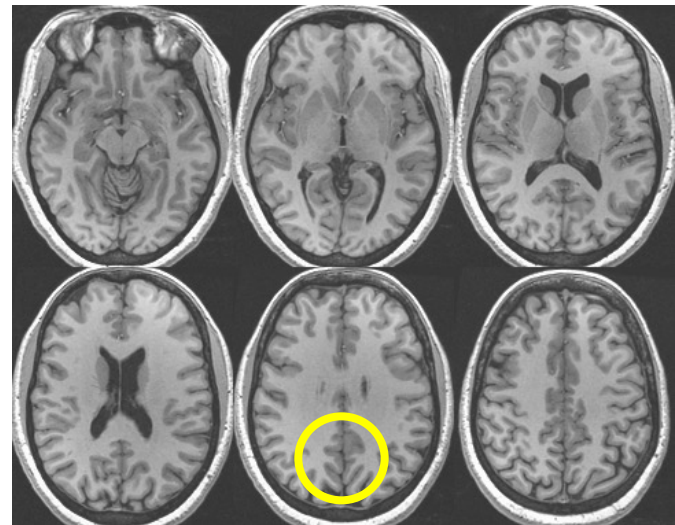
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- Filter (respiration (0.3Hz), cardiac (1 Hz))
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- Correlate average time course with all voxels



Lexical task

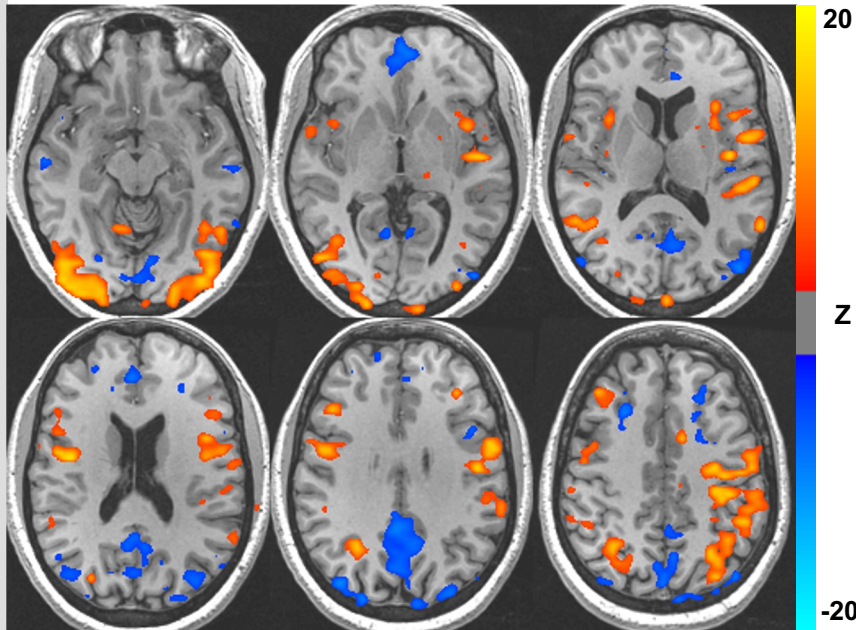


Rest

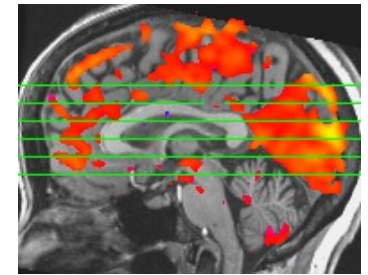
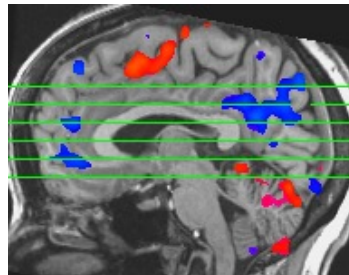
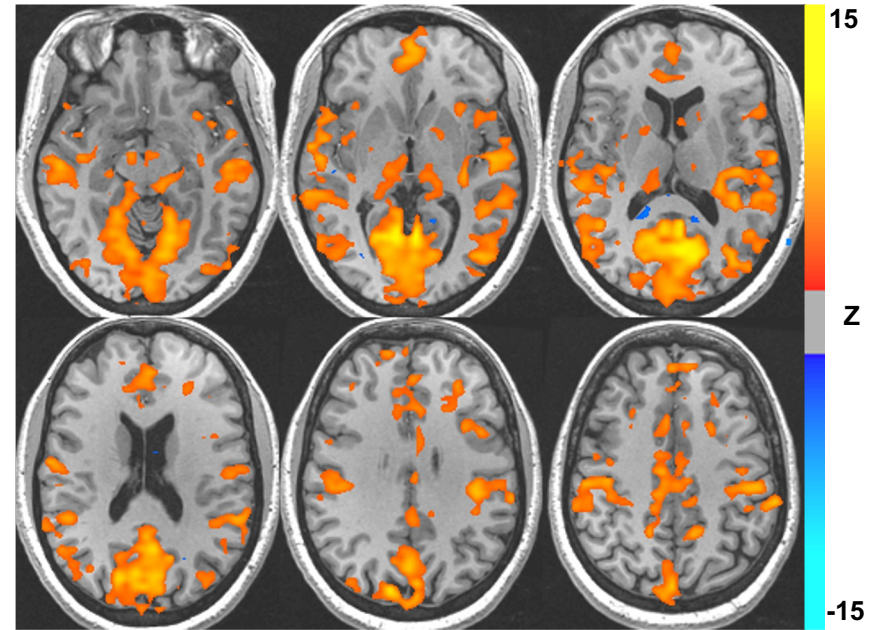
Functional Connectivity Analysis

1 subject

Activations during lexical task



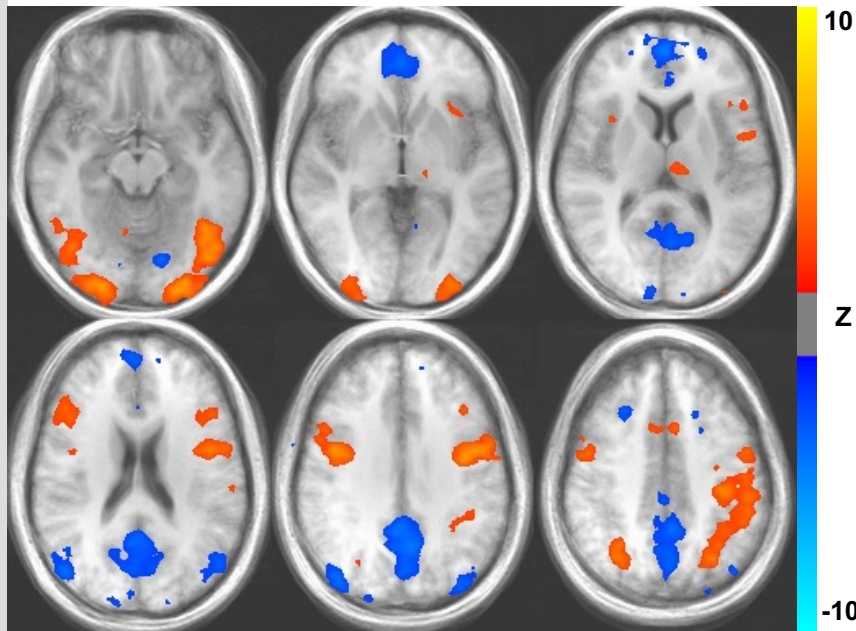
Correlation (of PC) at Rest



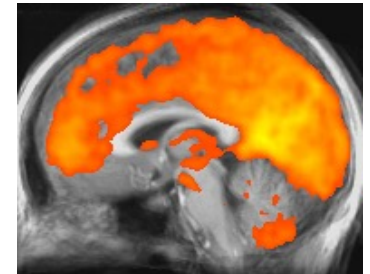
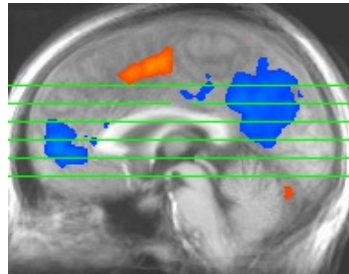
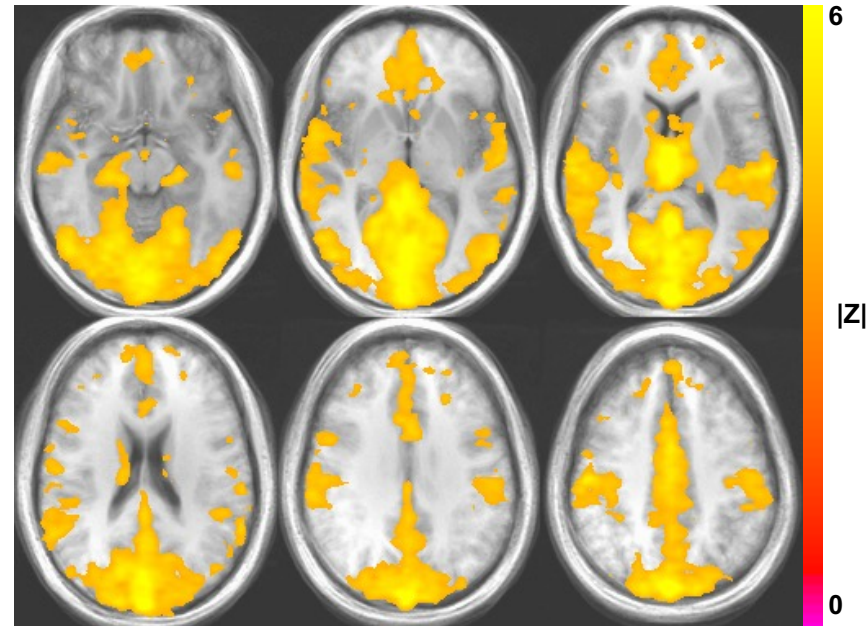
Functional Connectivity Analysis

Group (n=10)

Activations during lexical task



Correlation (of PC) at Rest

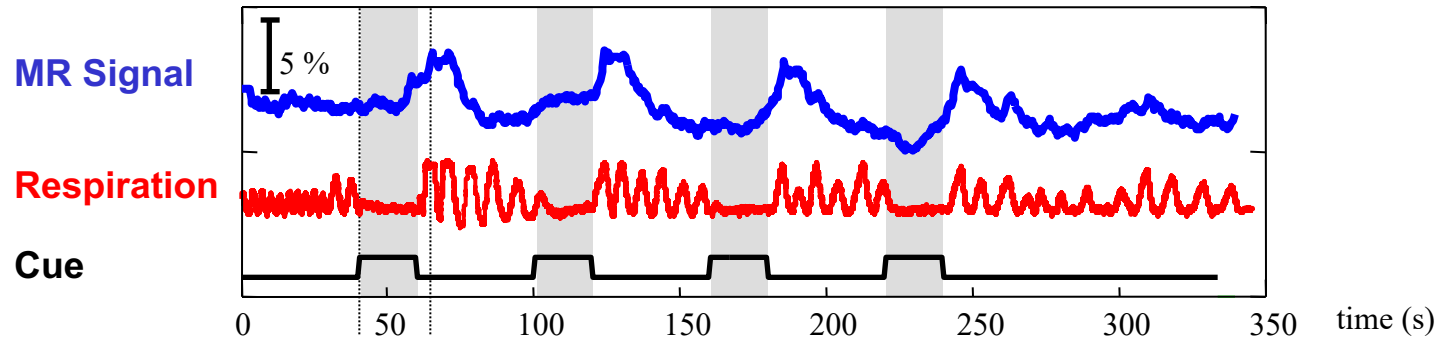


Overview

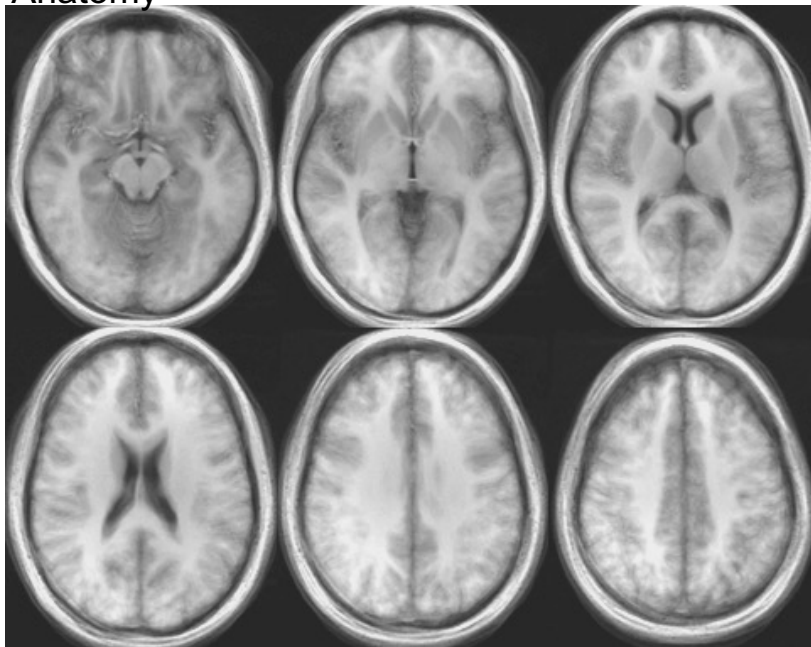
- “Functional connectivity”
 - Correlations in fMRI signal at rest
 - “Default Mode Network”
- **Respiration changes in fMRI**
- Respiration + Functional Connectivity
- Modeling respiration-induced fMRI changes

Breath-holding

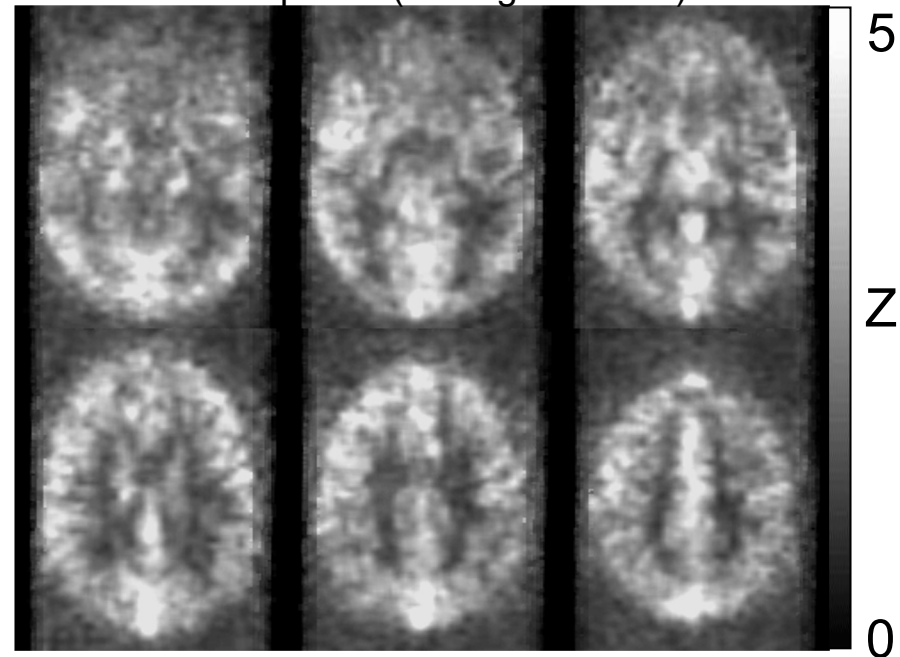
Group Maps (N = 7)



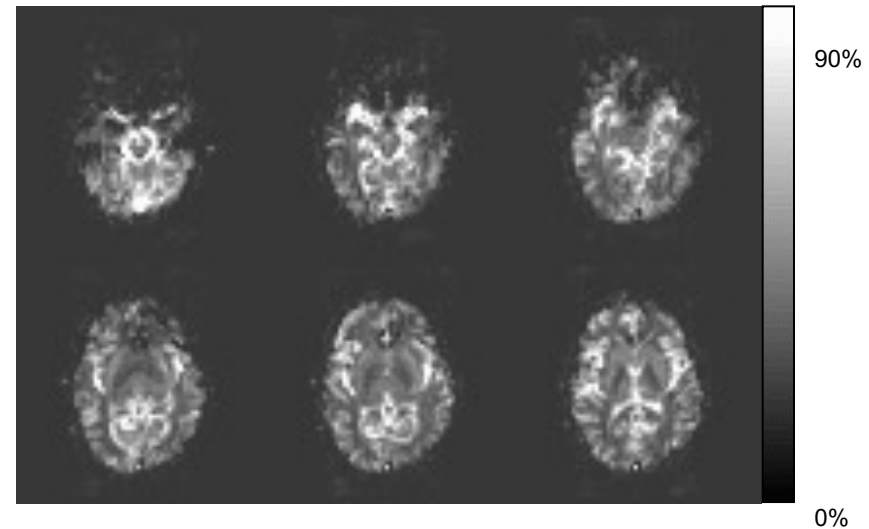
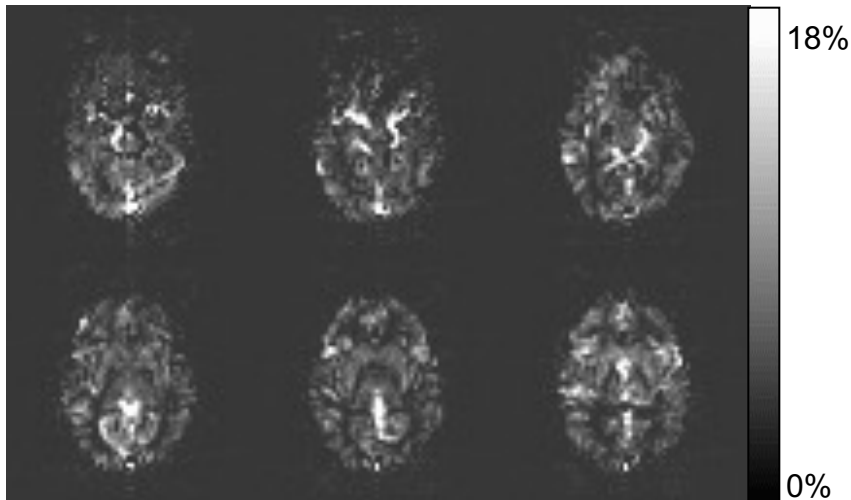
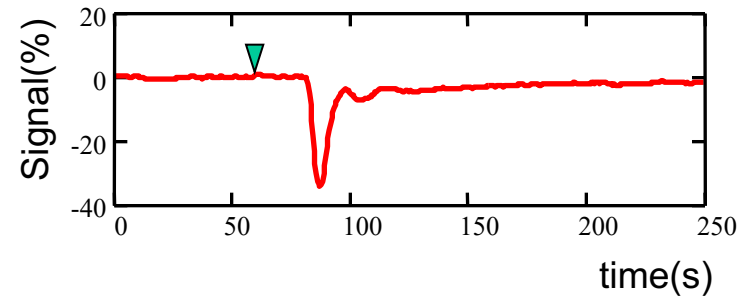
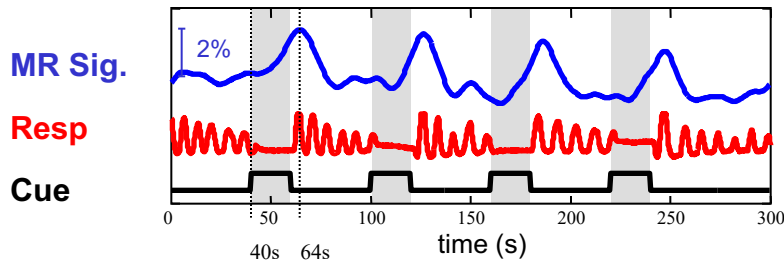
Anatomy



Breath-hold response (average Z-score)



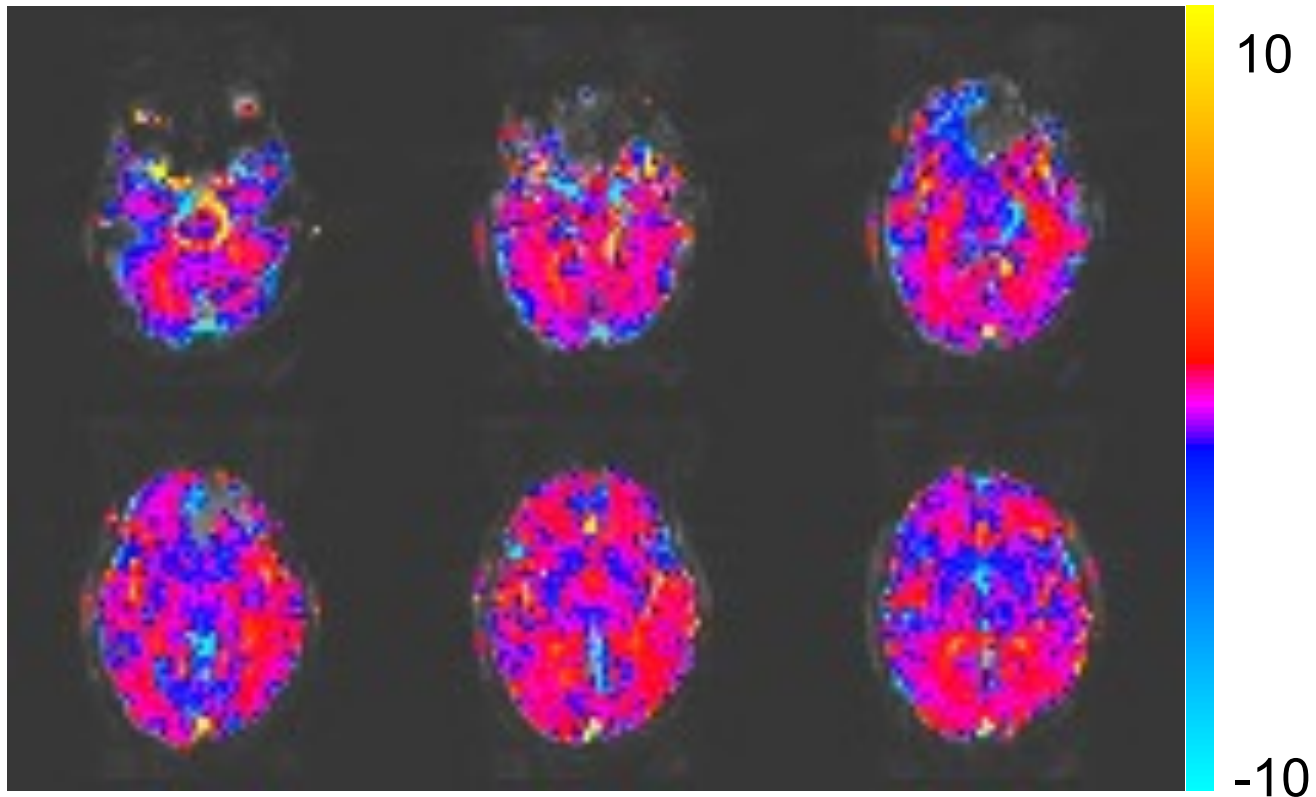
Breath-hold vs. bolus contrast (Gd-DTPA)



Breath-hold vs. bolus contrast (Gd-DTPA)

Relative difference: ΔS (Gd-DTPA) – ΔS (Breath-hold)

Arteries vs. *Veins* ?

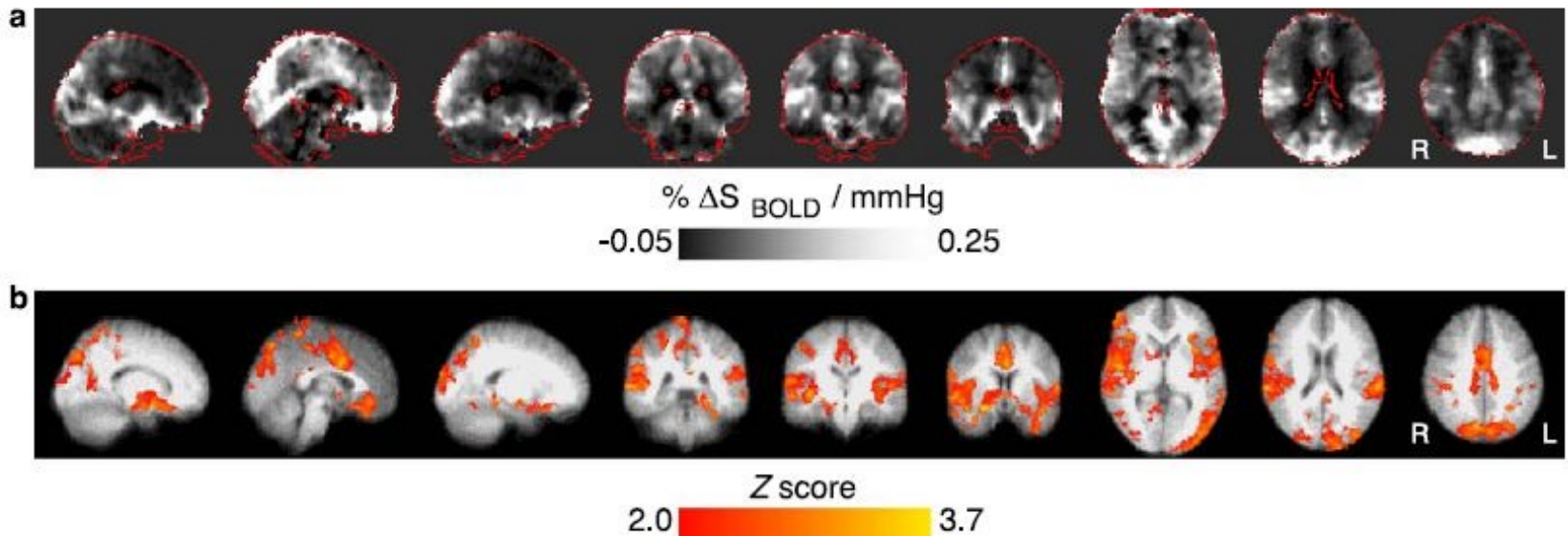


Resting fluctuations in respiration

Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal

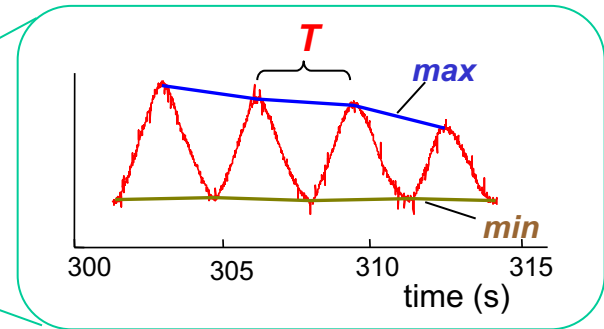
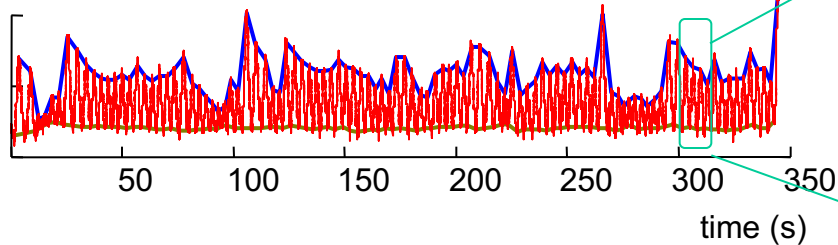
Richard G. Wise,^{a,b,*} Kojiro Ide,^{c,d} Marc J. Poulin,^{c,d} and Irene Tracey^{a,b}

NeuroImage 21, 2004

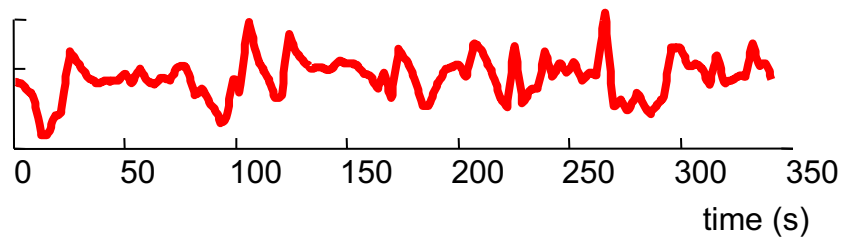


Estimating respiration volume changes

Respiration



Respiration Volume / Time (RVT)



$$\text{RVT} = \frac{\text{max} - \text{min}}{T}$$

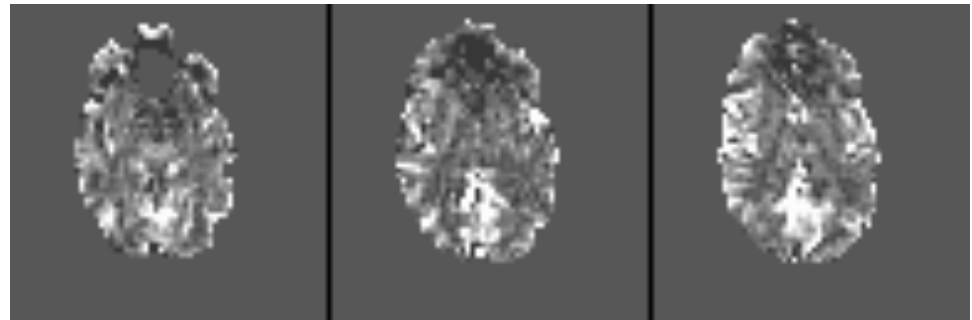
Resting fluctuations in respiration

Correlation of fMRI
time course with:

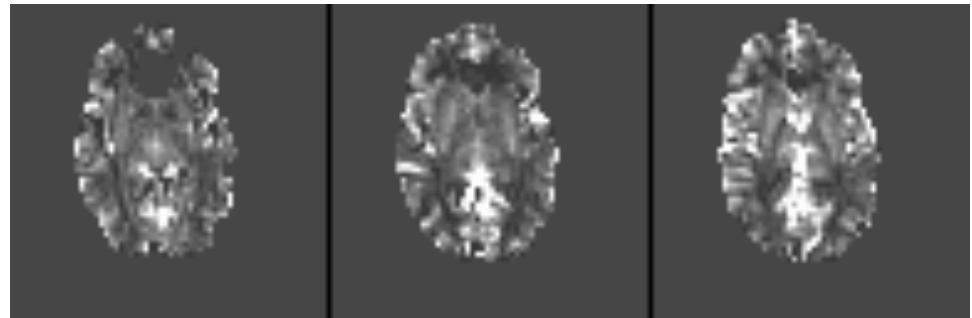
RVT



etCO2

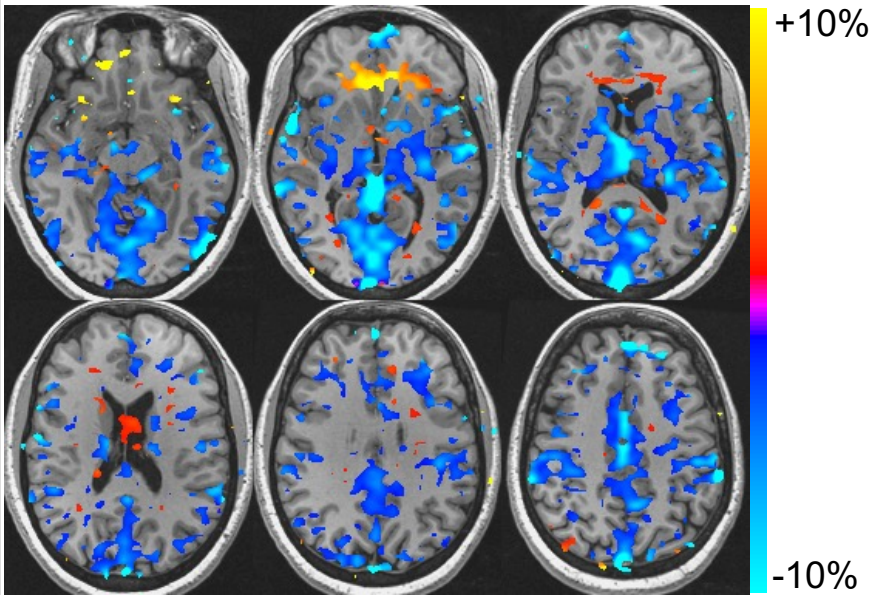


BH

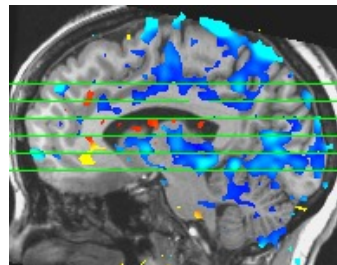


Resting fluctuations in respiration

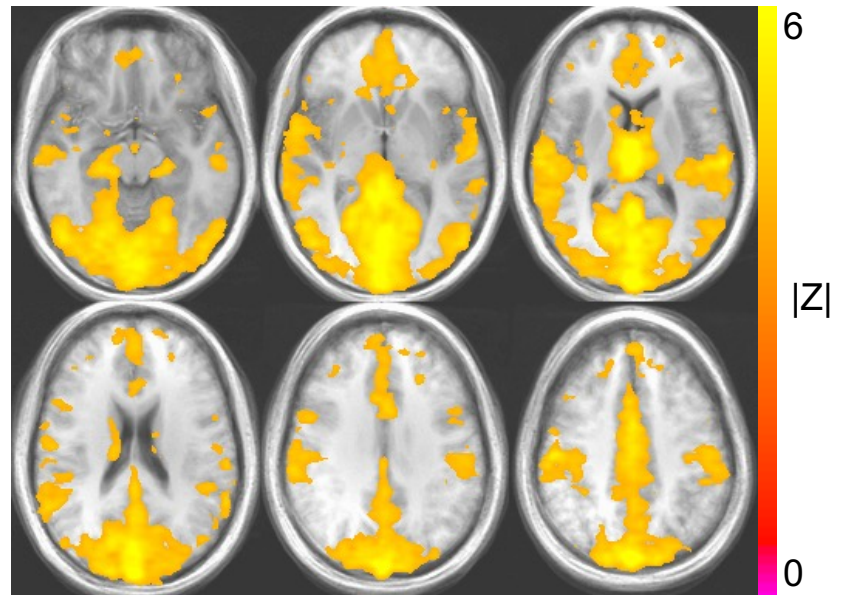
Amplitude of BOLD signal correlated w/ RVT



1 subject



Z-score of BOLD signal correlated w/ RVT

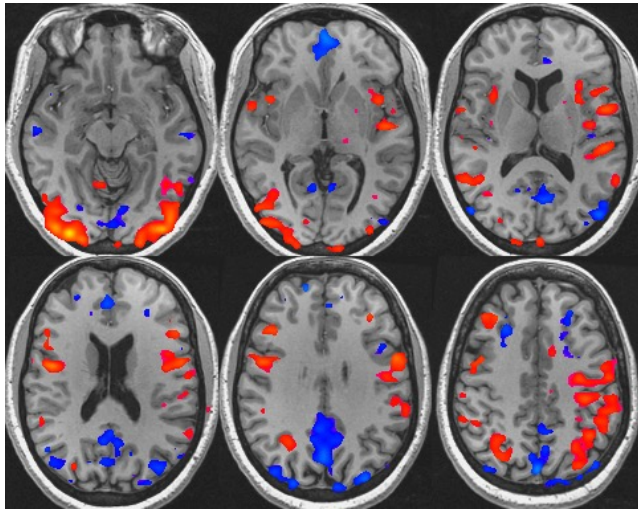


group (n=11)

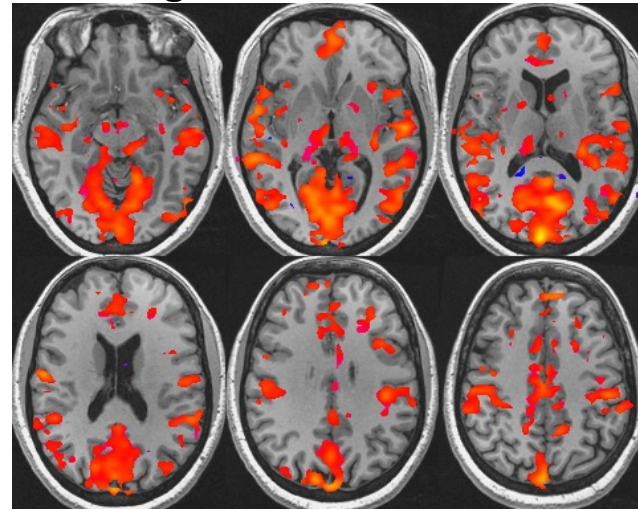
$RVT = \underline{R}espiration \underline{V}olume \underline{p}er \underline{T}ime$

Respiration changes co-localize

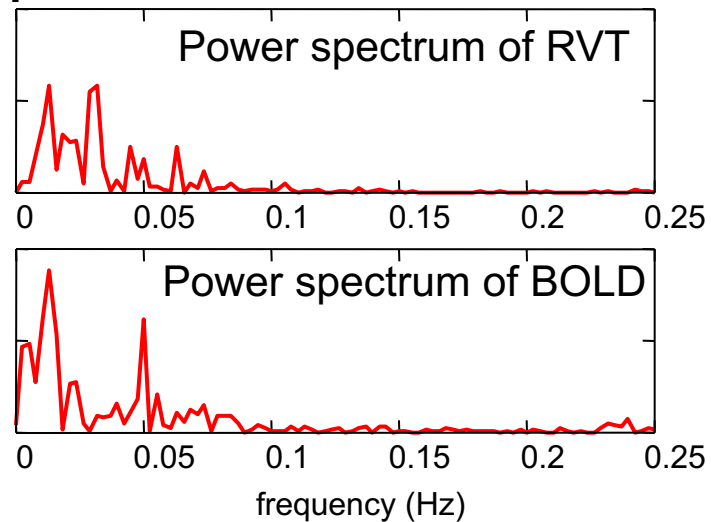
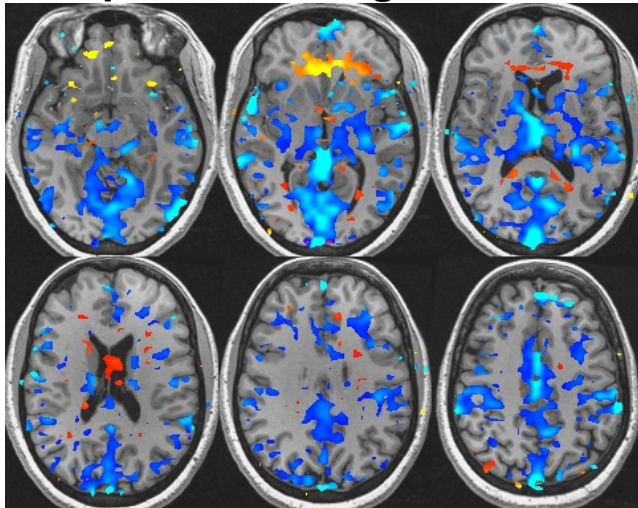
Deactivations



Resting-state corr. from seed ROI

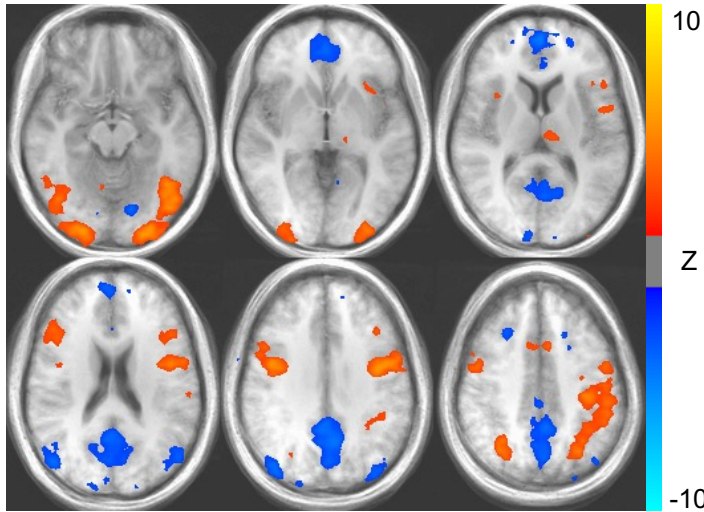


Respiration changes – corr. w/ RVT

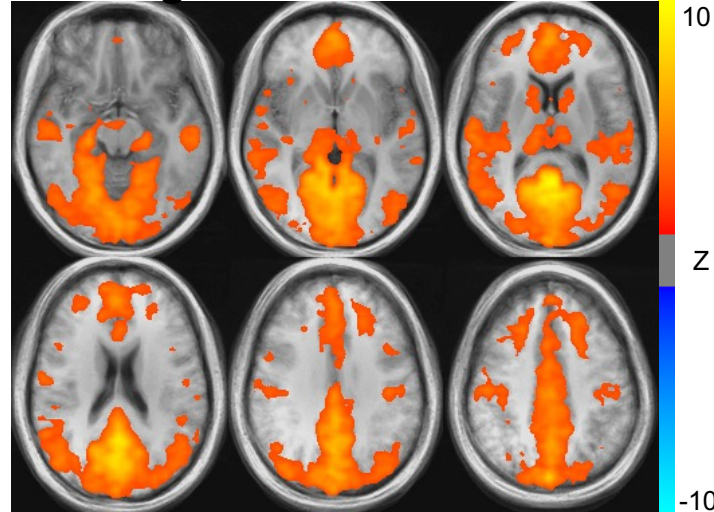


Respiration changes co-localize

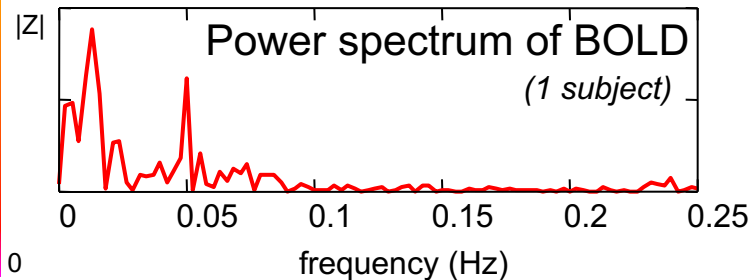
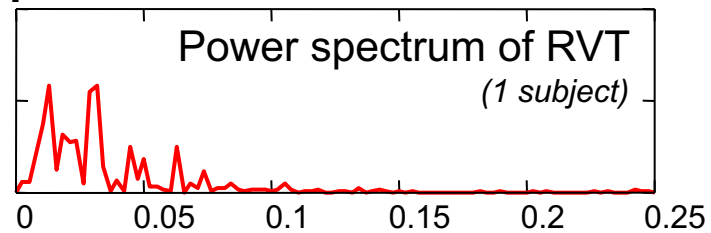
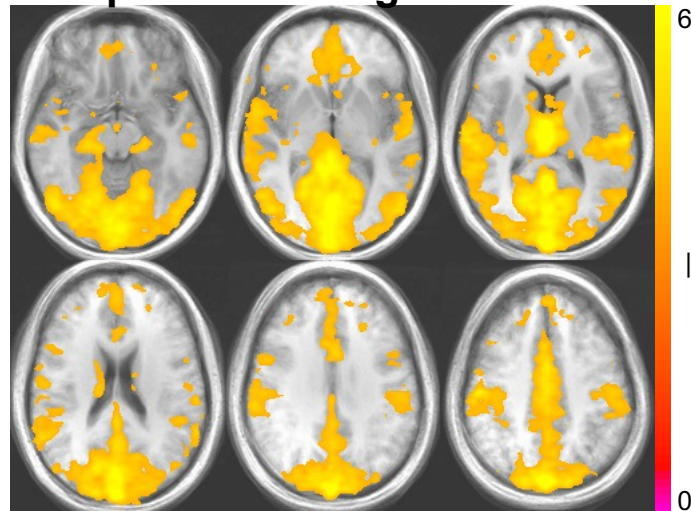
Deactivations



Resting-state corr. from seed ROI



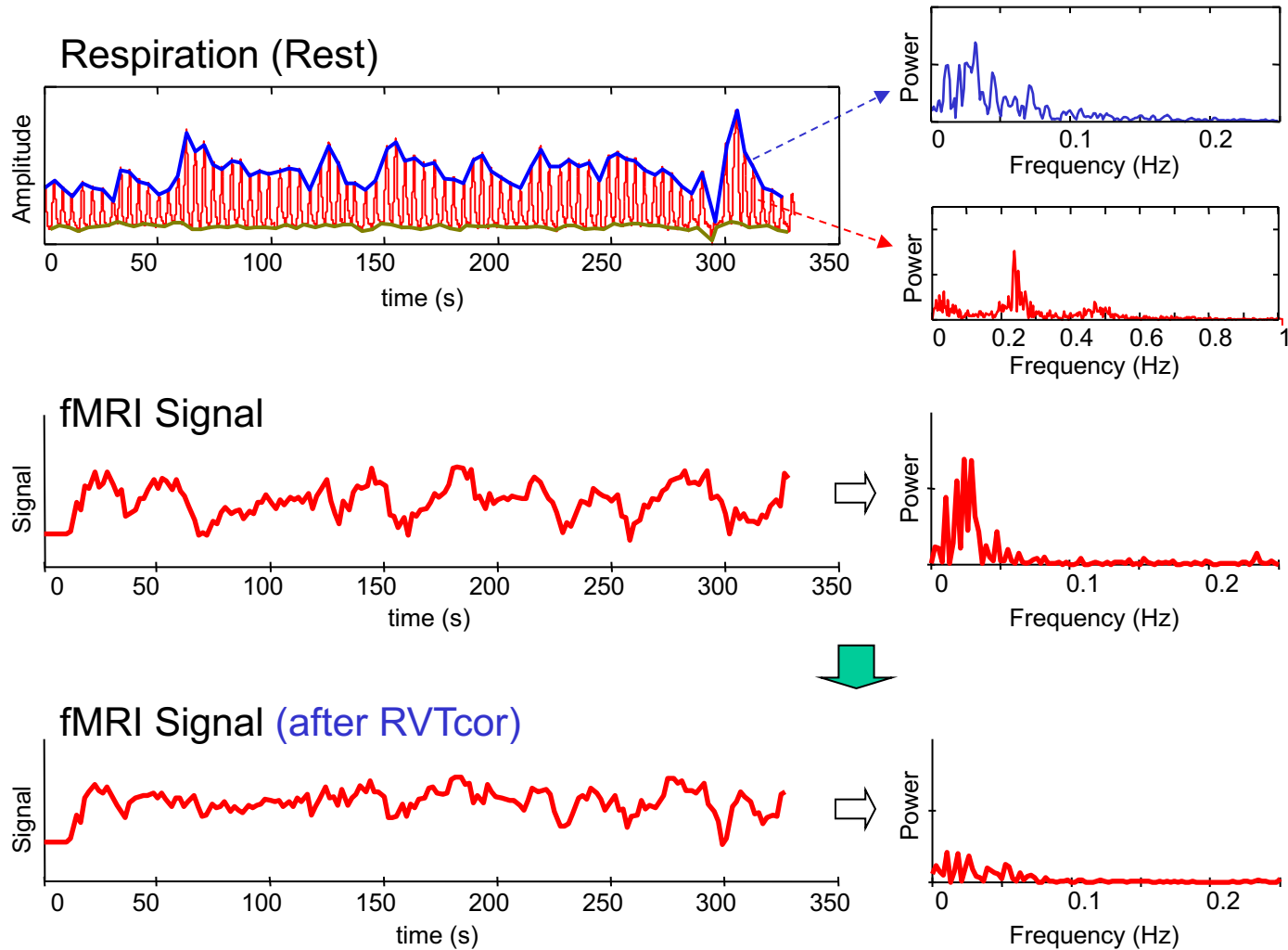
Respiration changes – corr. w/ RVT



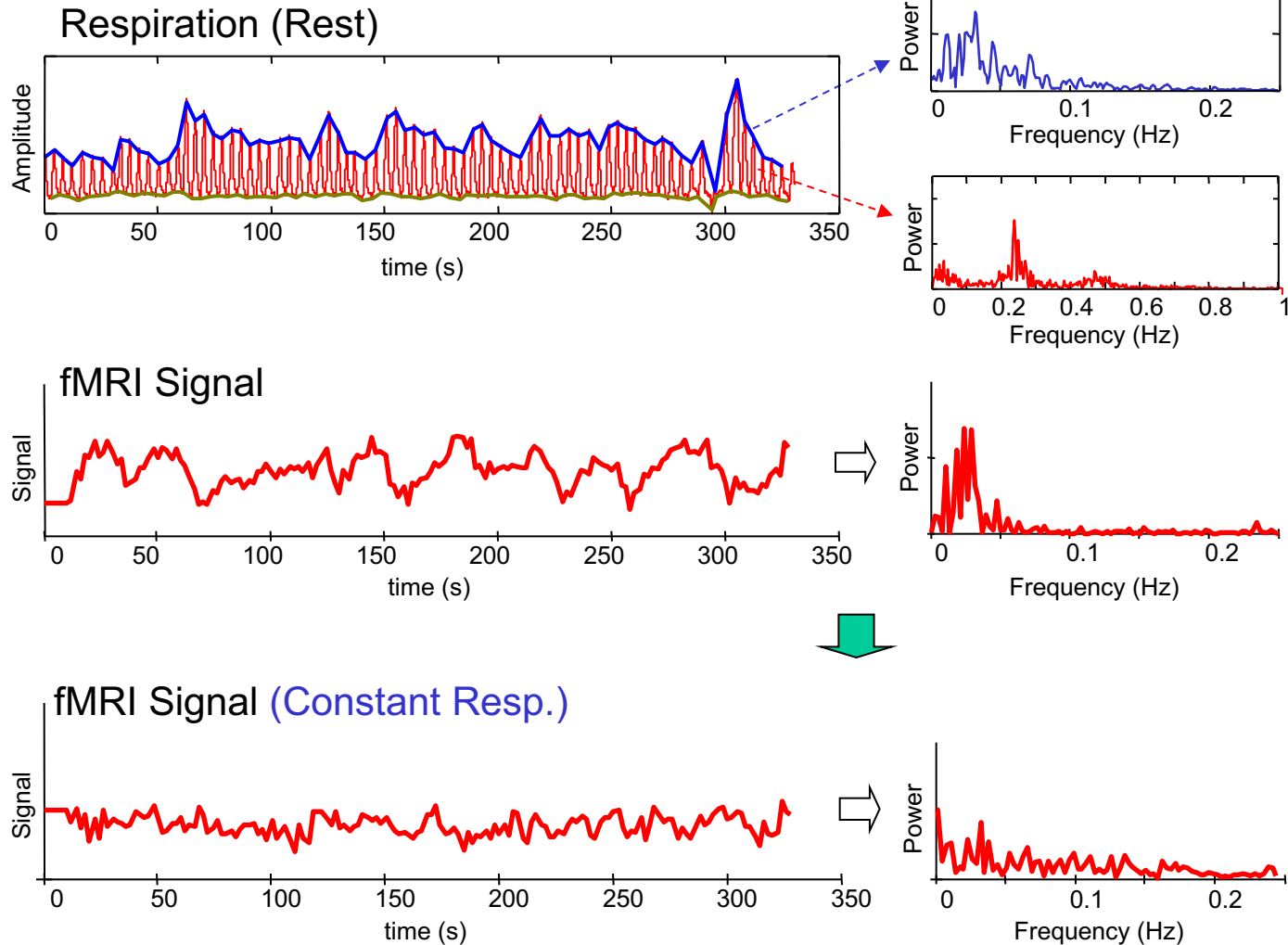
Correcting for changes in respiration

- Regress out RVT
- Keep respirations constant

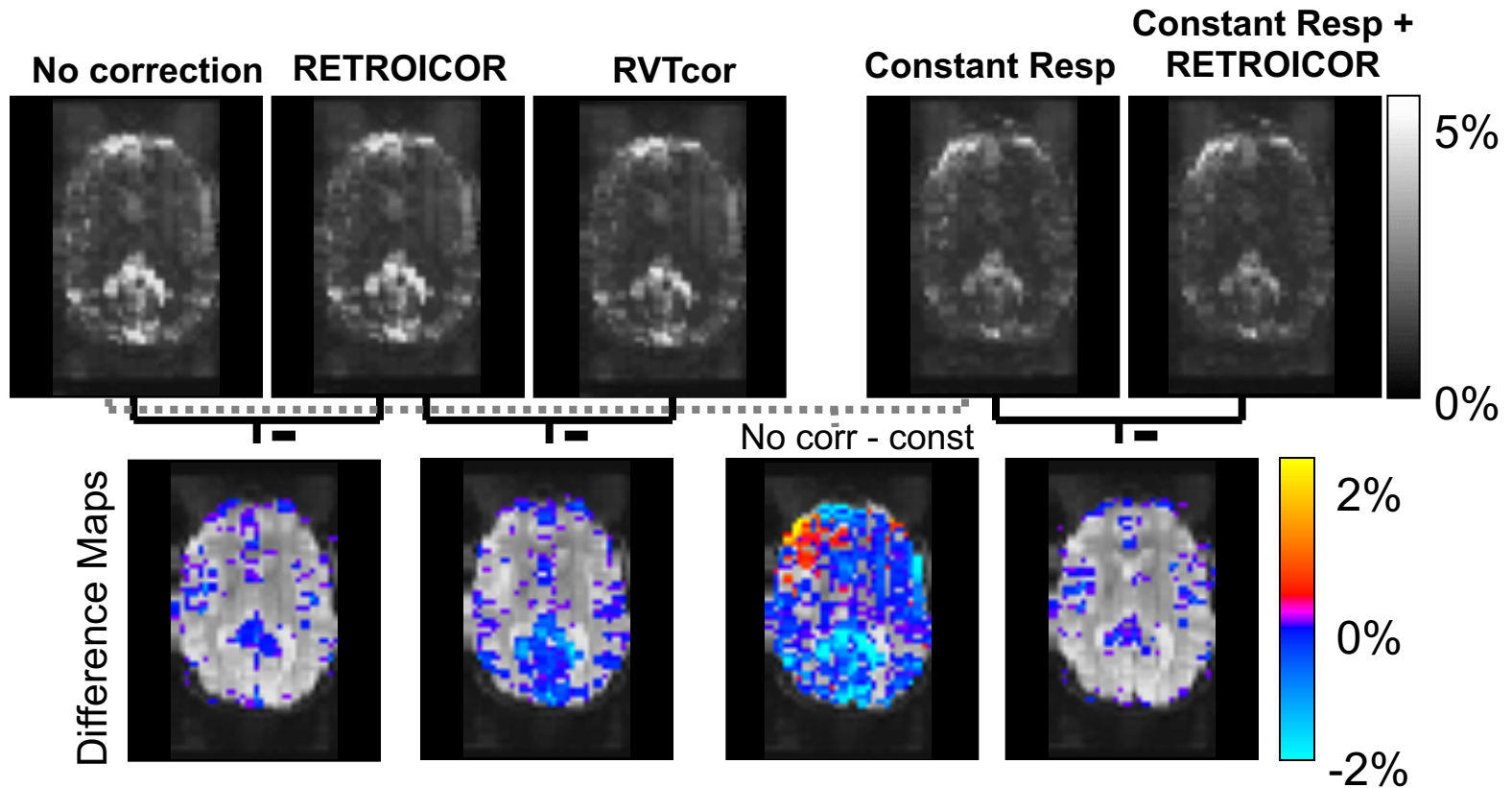
Regress out Cardiac, Respiration, RVT



Cue subject to keep breathing constant



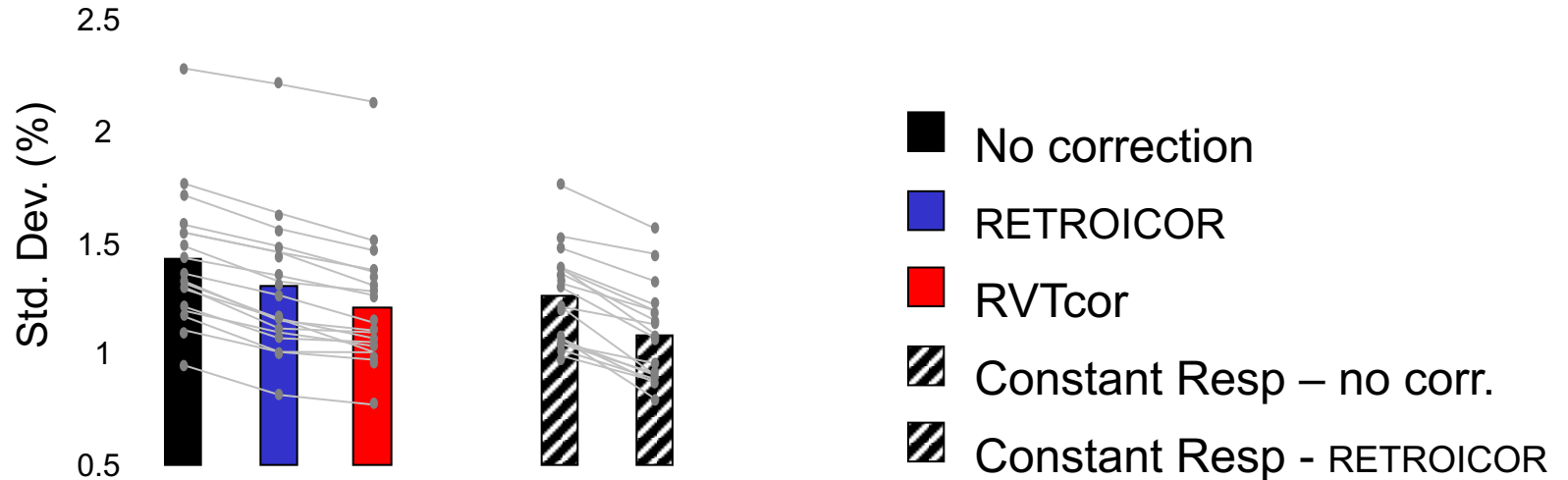
Standard Deviation over time



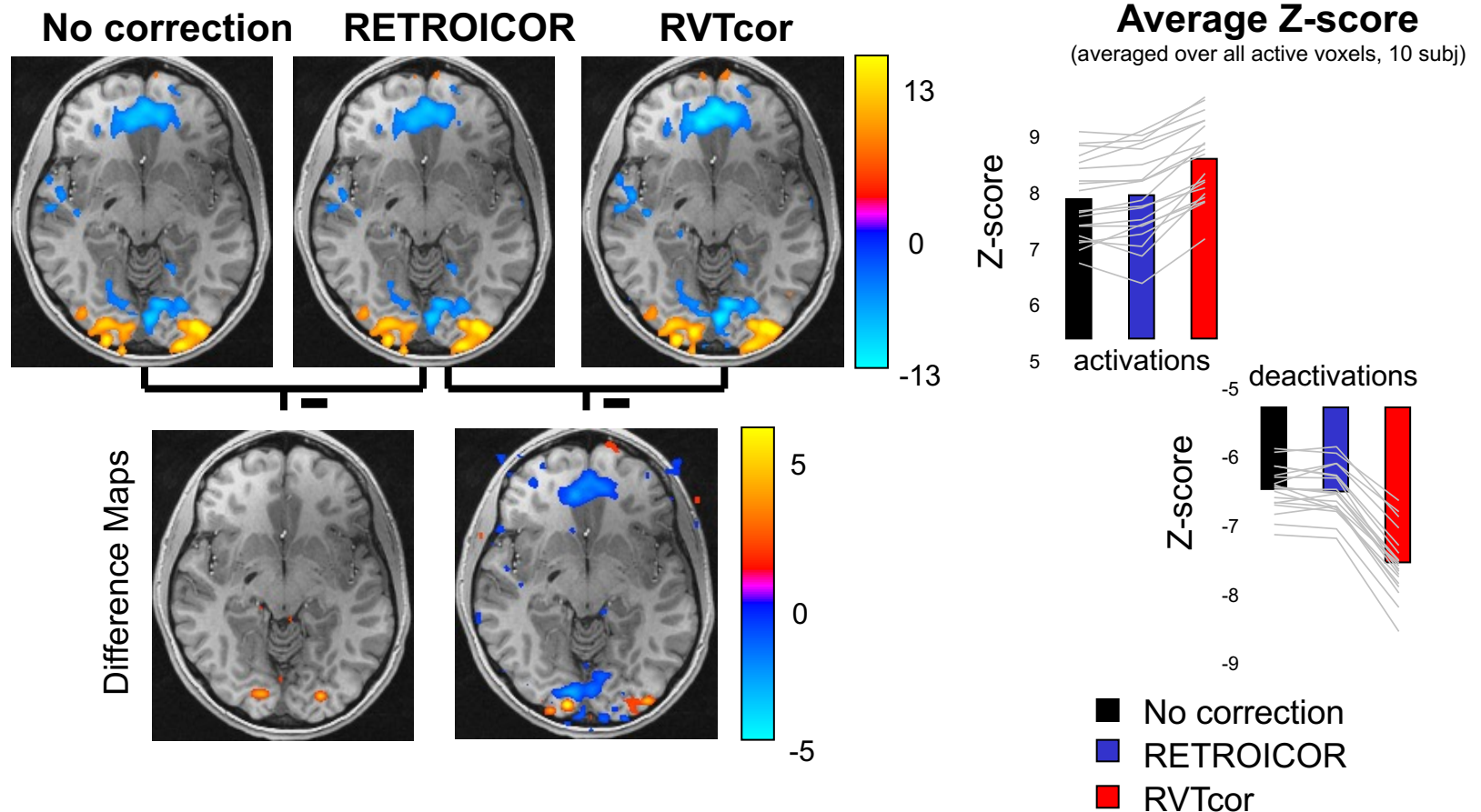
Standard Deviation over time

Average Std. Dev.

(averaged over all brain voxels, 10 subj)



Improving the detection of function



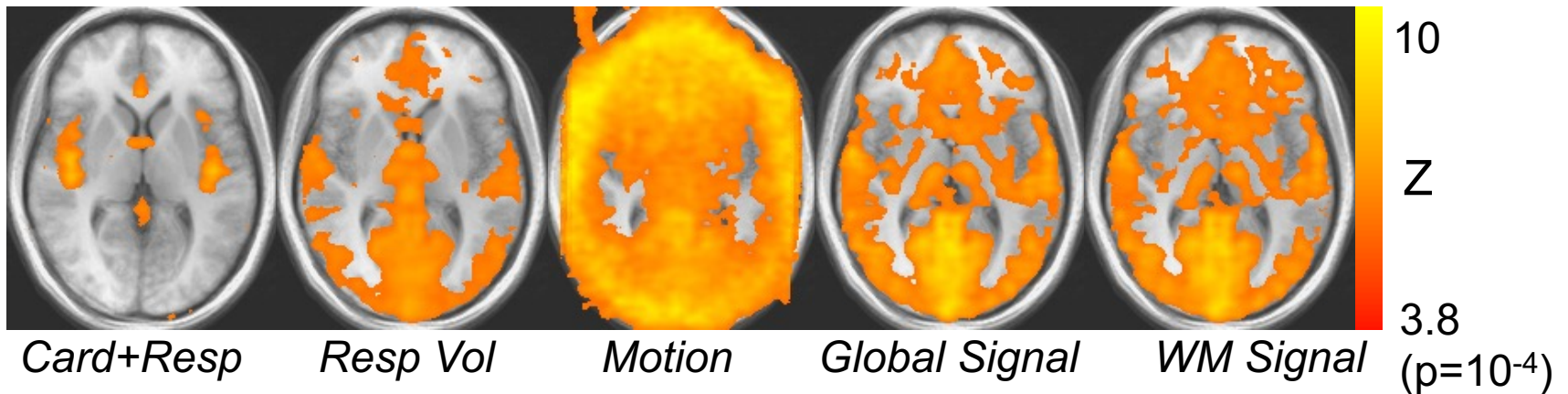
More Corrections?

- RETROICOR (cardiac, respiration)
- RVTcor (respiration volume / etCO₂)
- Motion parameters
- Global detrending
- White-matter detrending

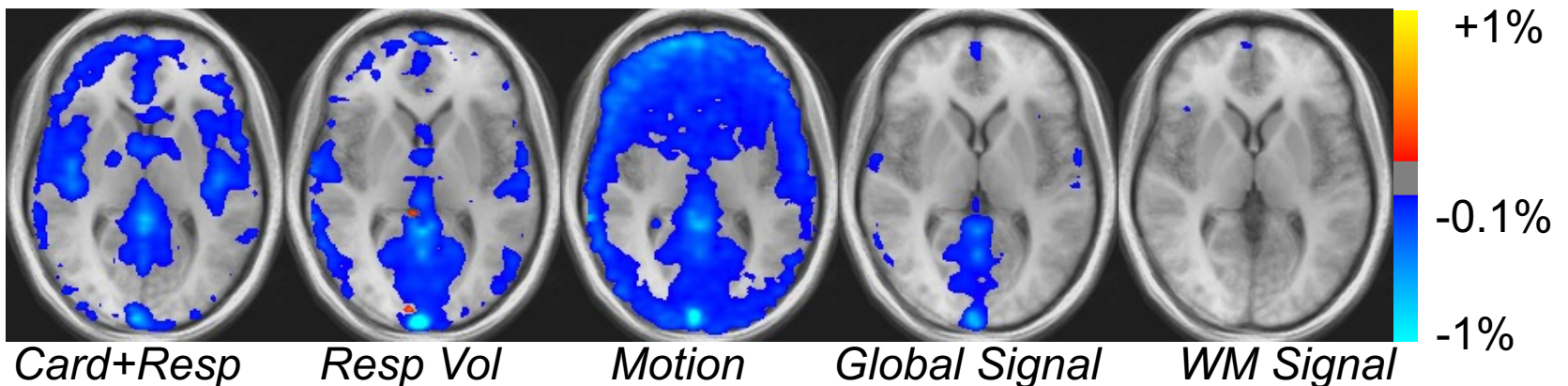
Multiple physiological corrections

Correlation with each regressor

(n = 10)



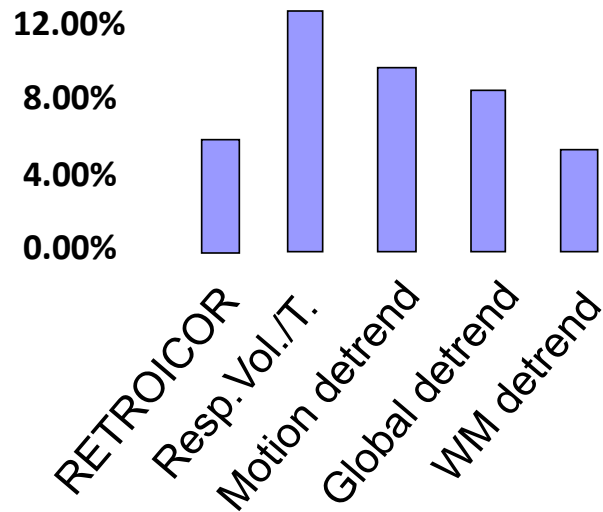
Differences in Std. Dev. when each regressor is removed



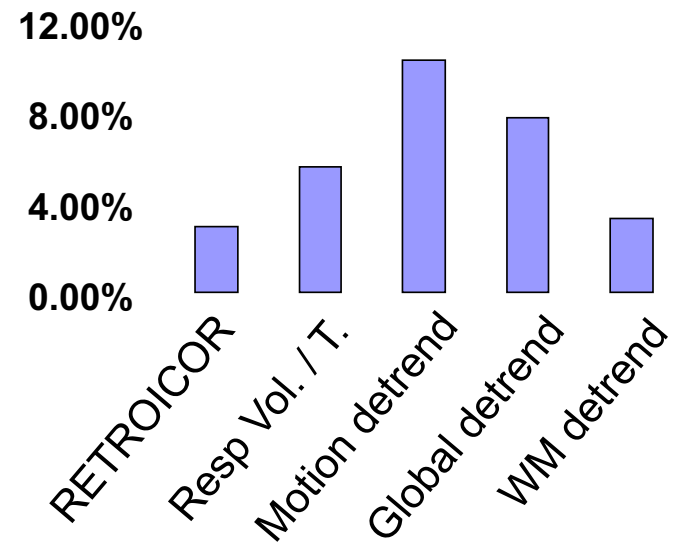
Relative contributions to noise

Averaged over Gray Matter (4 subjects)

*High Resolution
(1.7 x 1.7 x 4 mm, 80 time points)*

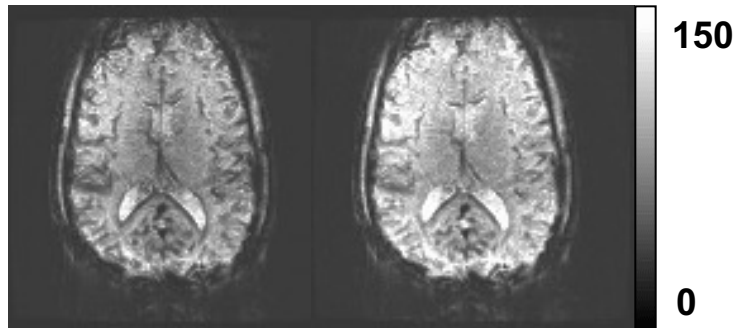


*Low Resolution
(7.5 x 7.5 x 5 mm, 700 time points)*



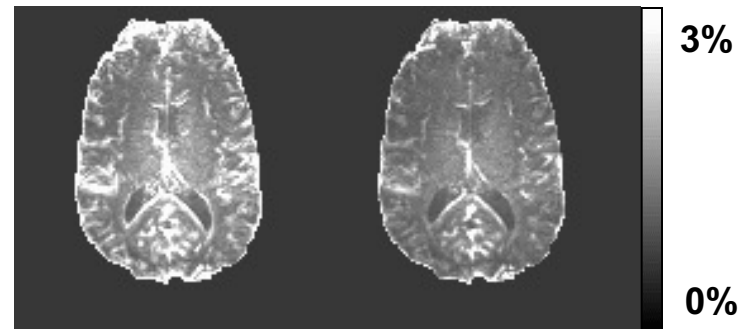
How much is the noise reduced?

TSNR

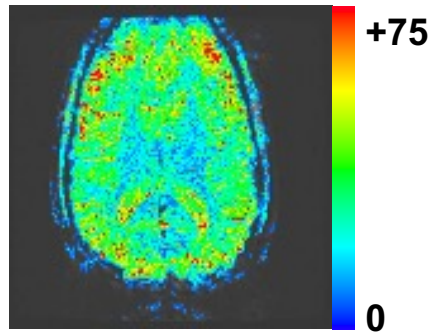


Before Correction After Correction

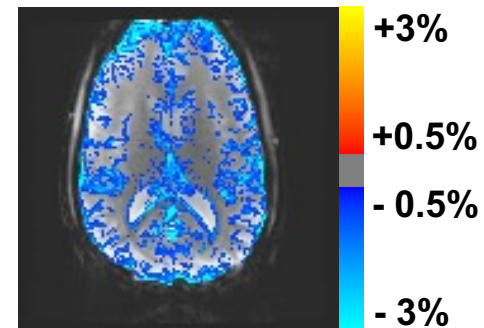
Std. Dev. over time



Before Correction After Correction



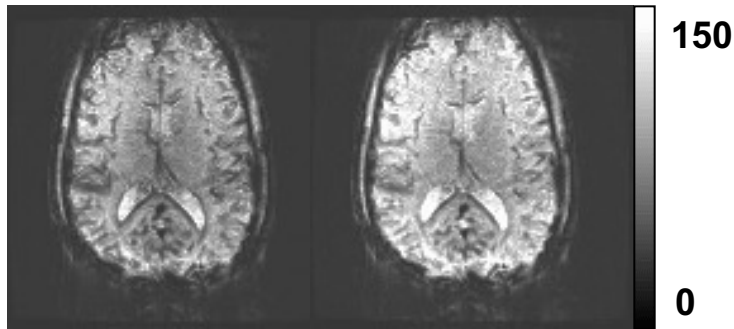
Difference



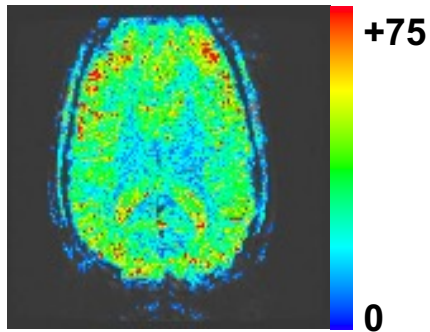
Difference

Improvement in temporal SNR (TSNR)

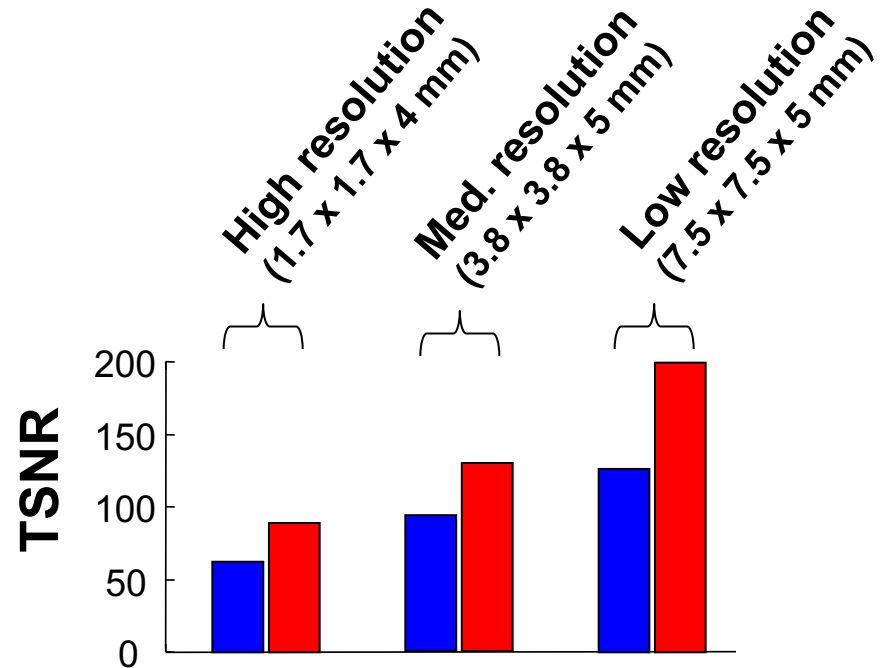
TSNR



Before Correction After Correction

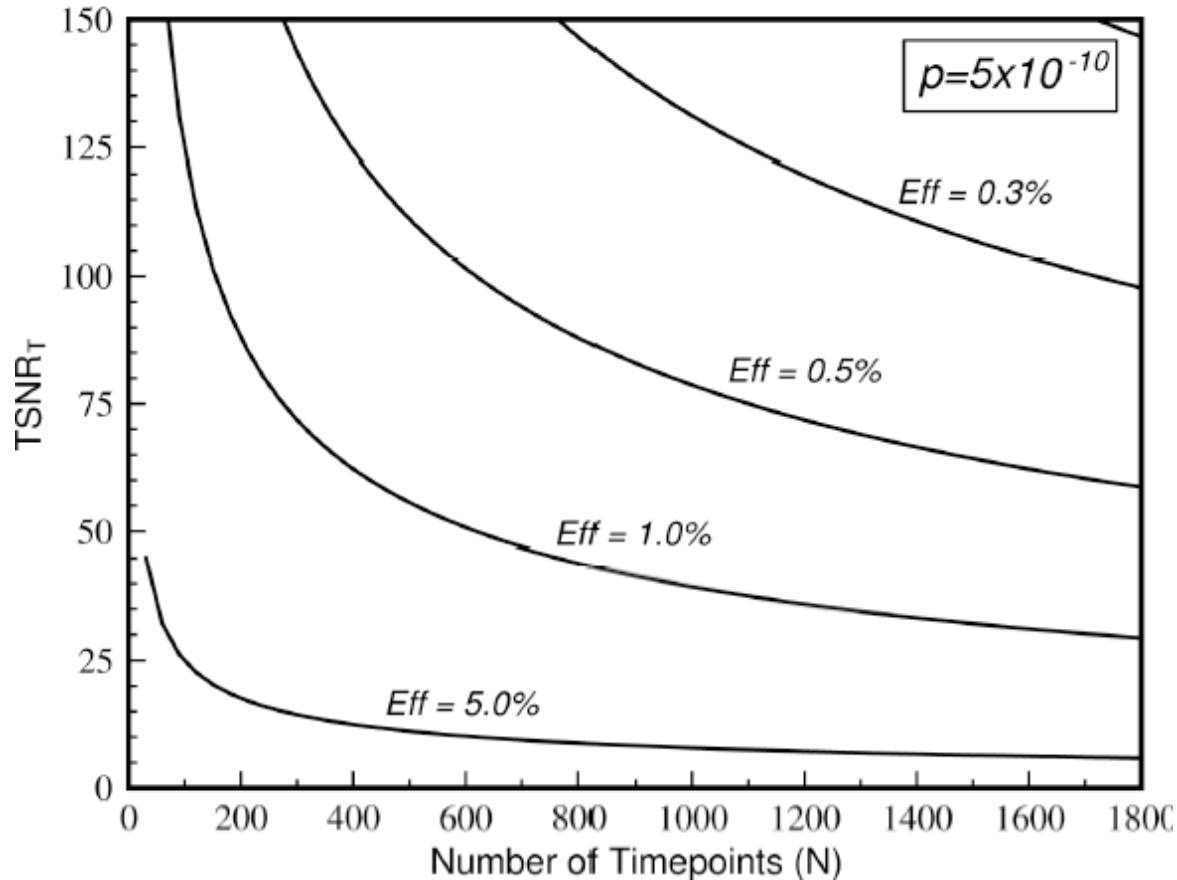


Difference



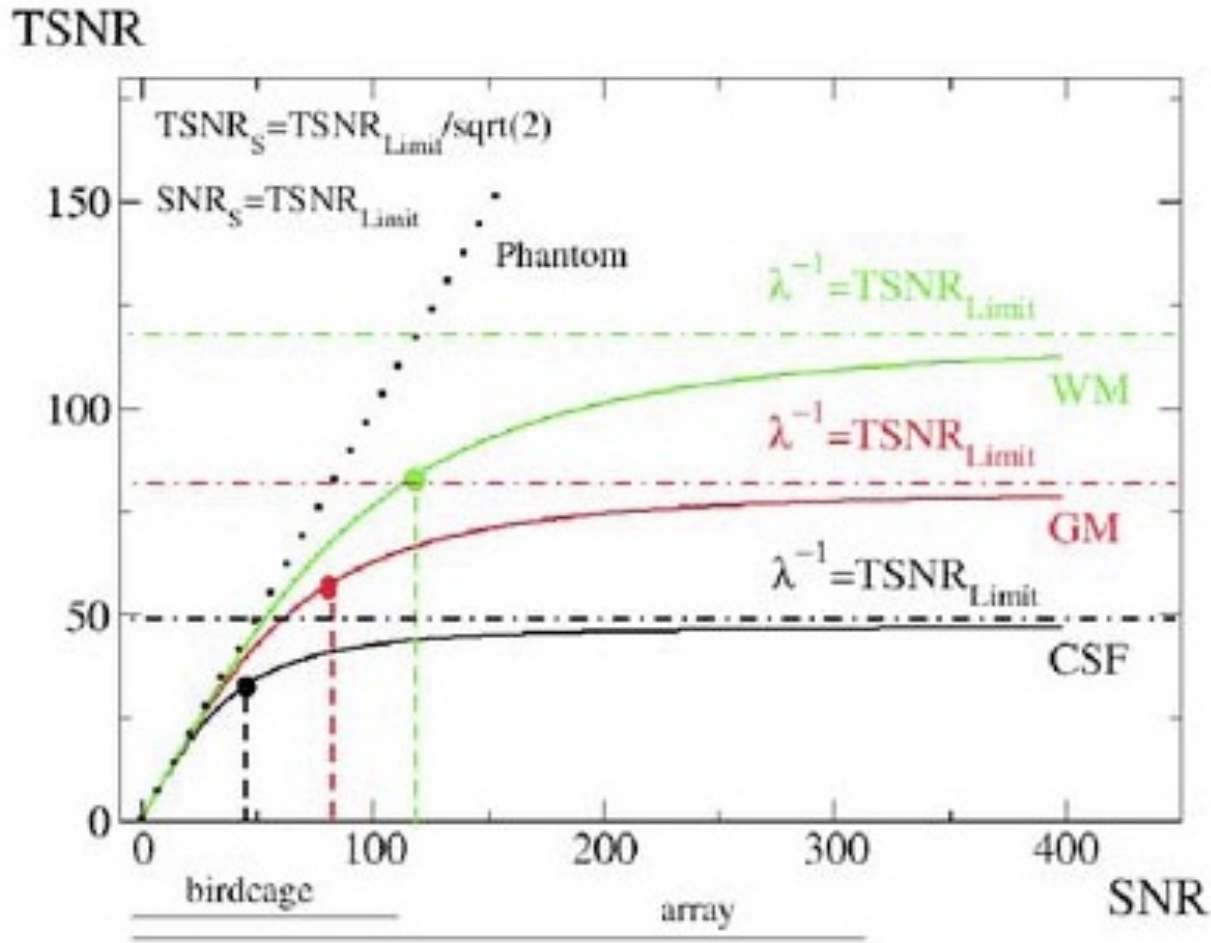
■ Before correction
■ After correction

How Improved TSNR Translates



Murphy K, Bodurka J, Bandettini P, "How long to scan: The relationship between temporal signal to noise ratio and necessary scan duration," *NeuroImage* (in press)

SNR vs TSNR



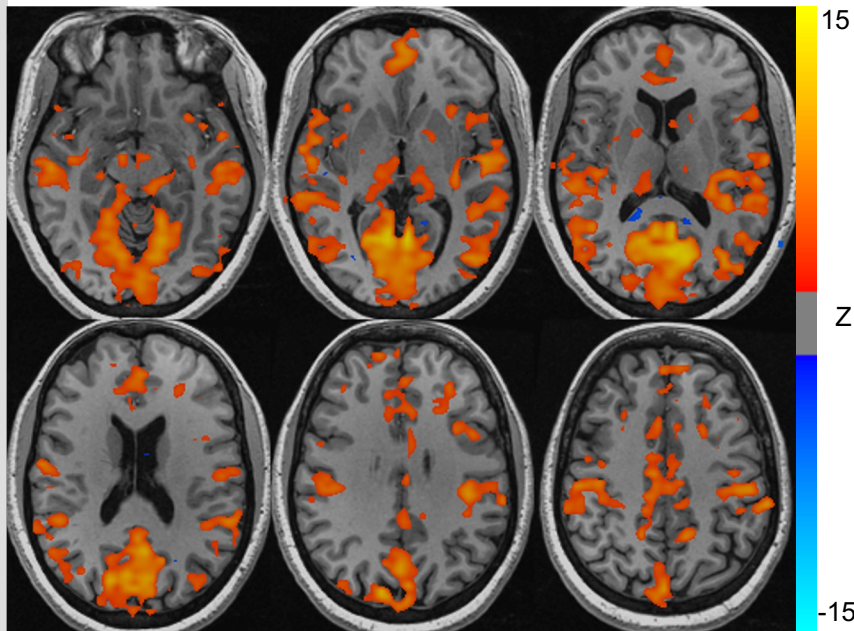
Bodurka J, Bandettini P, "Mapping the MRI voxel volume in which thermal noise matches physiological noise - implications for fMRI", NeuroImage (in press)

Resting-state correlations

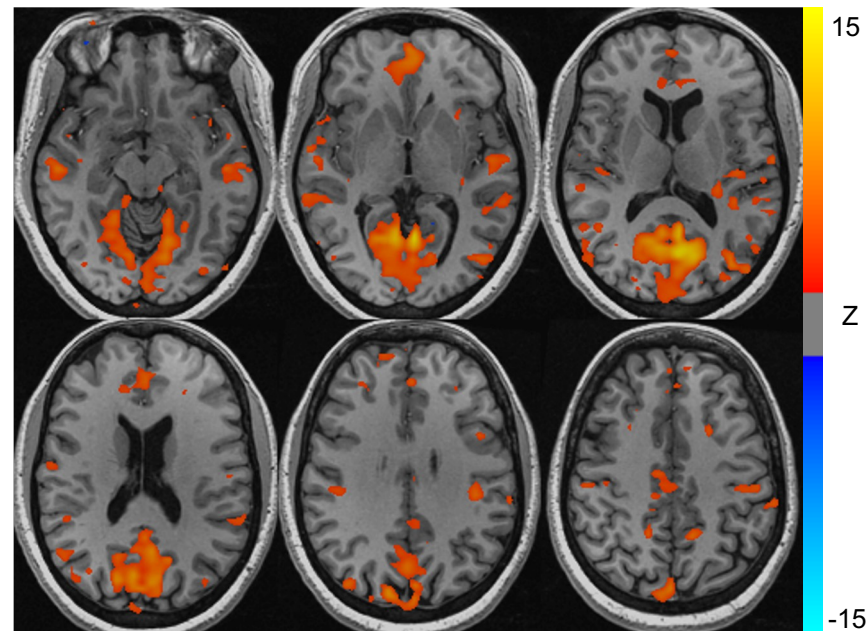
Areas correlated with posterior cingulate

1 subject

after RETROICOR



after RETROICOR + RVTcor

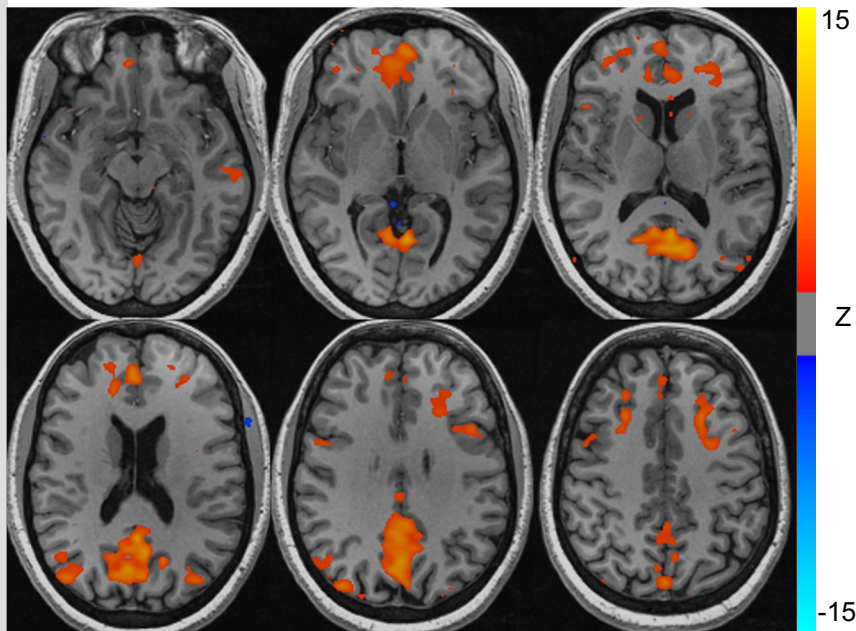


Resting-state correlations

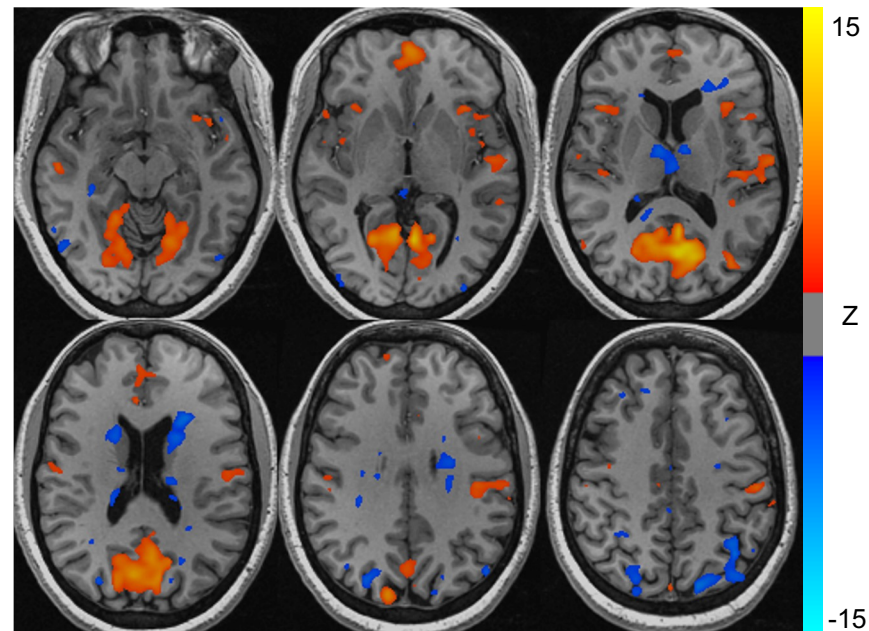
Areas correlated with posterior cingulate

1 subject

Constant Respirations



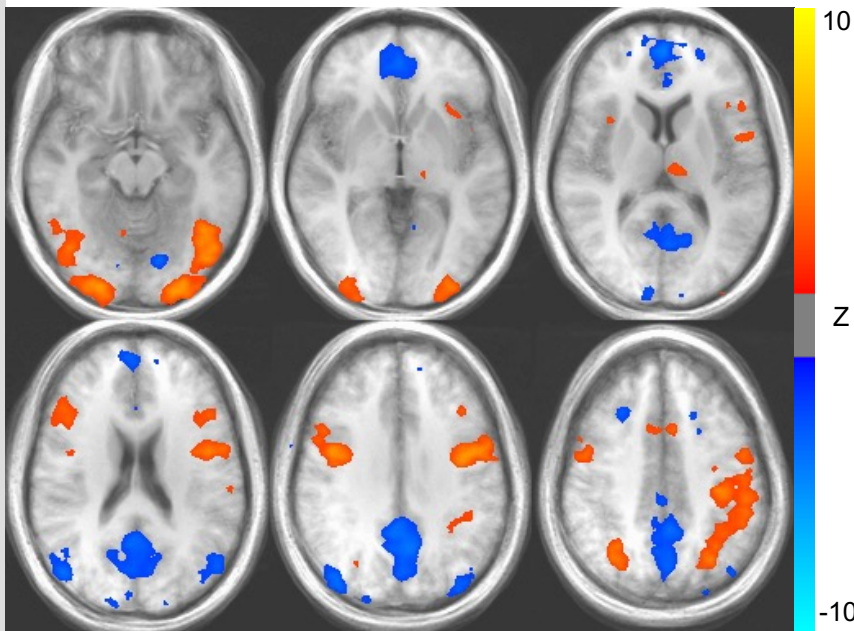
Remove global signal changes



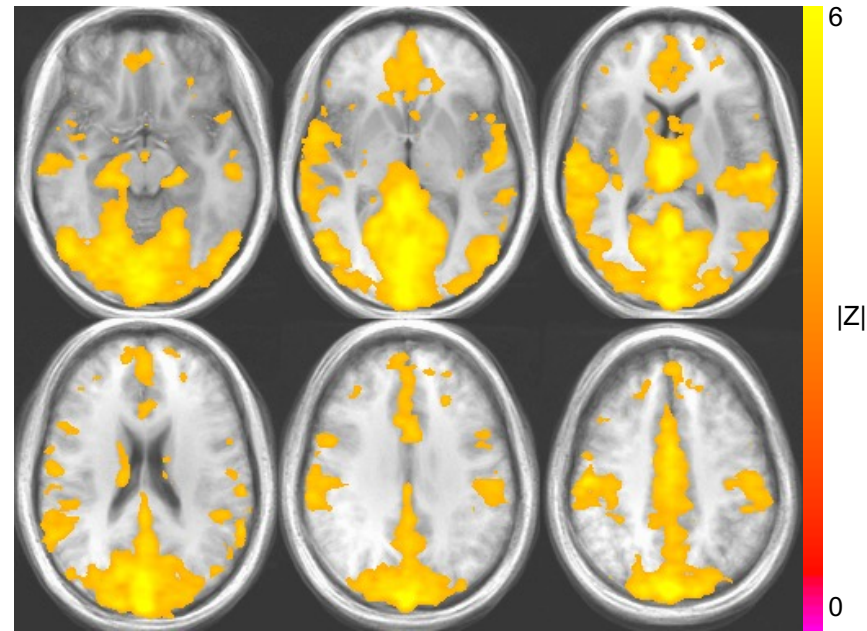
BOLD signal changes – *Group data*

Group data (n=10)

Lexical Task



Respiration changes

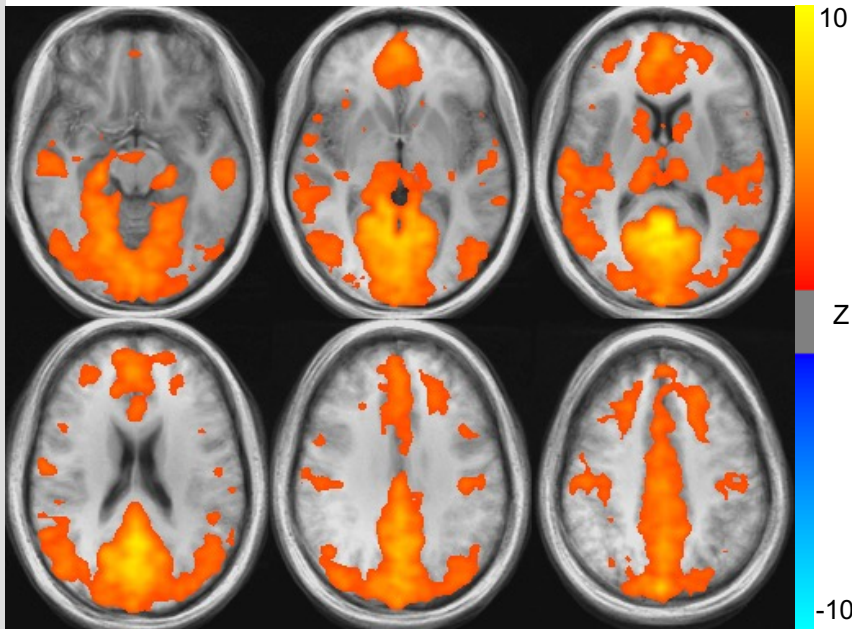


Resting-state correlations

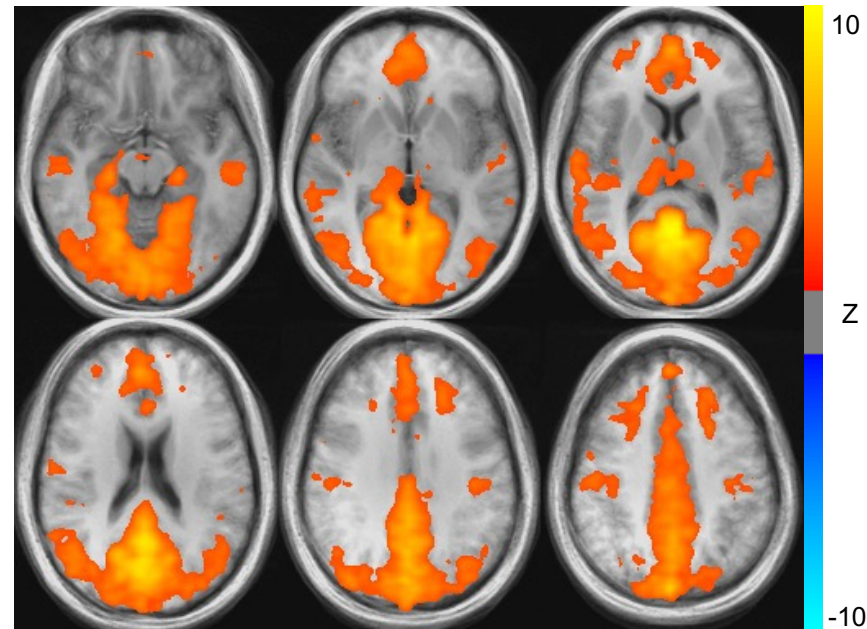
Areas correlated with posterior cingulate

Group data (n=10)

after RETROICOR



after RETROICOR + RVTcor

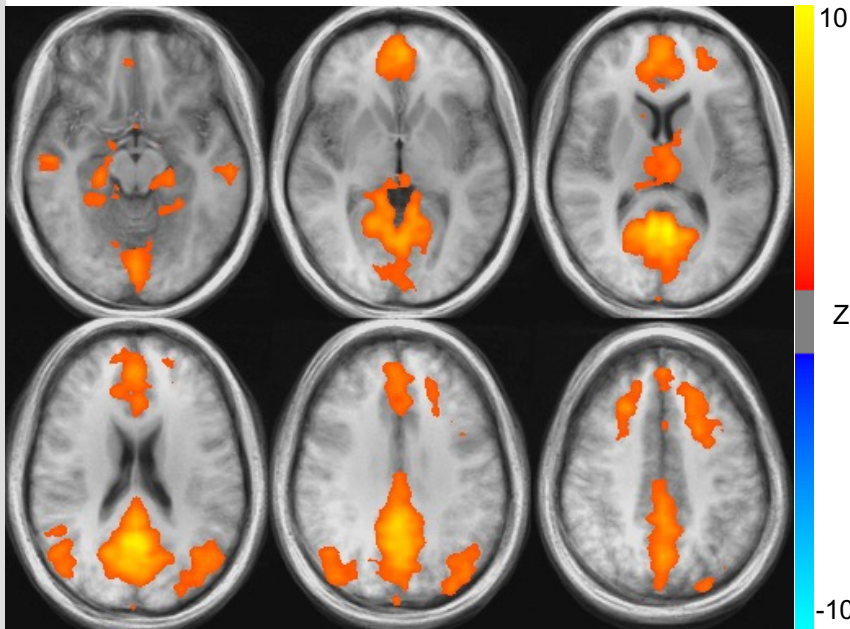


Resting-state correlations

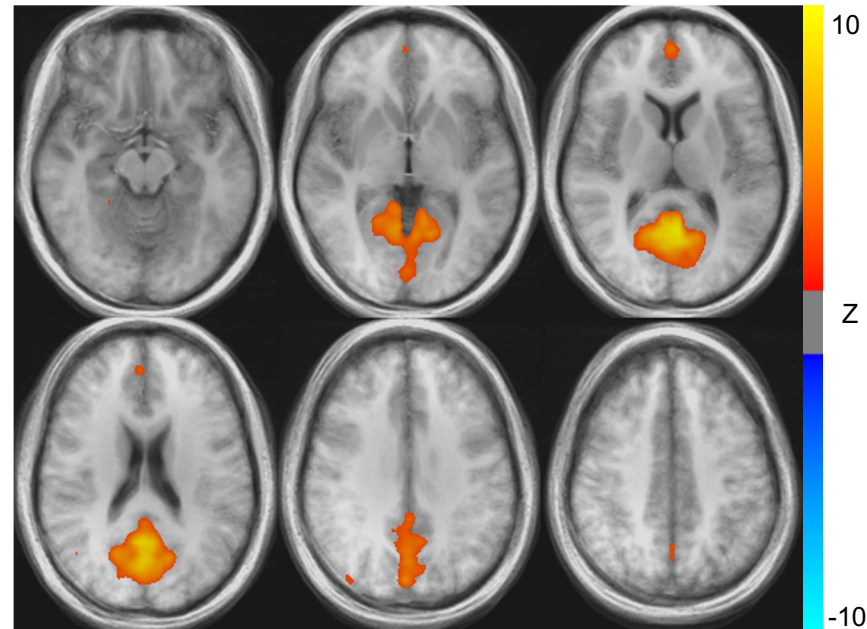
Areas correlated with posterior cingulate

Group data (n=10)

Constant Respirations



Remove global signal changes



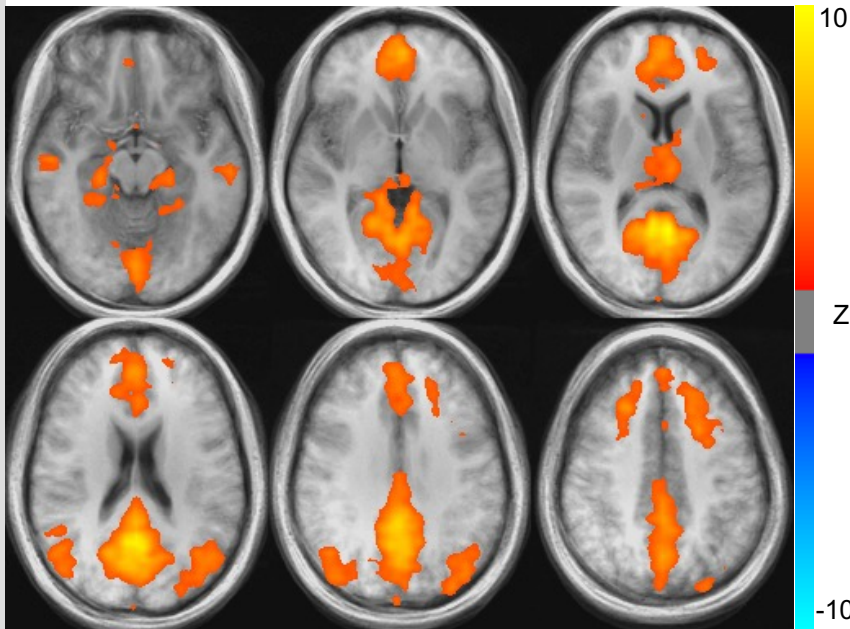
[Click here for unthresholded maps](#)

Resting-state correlations

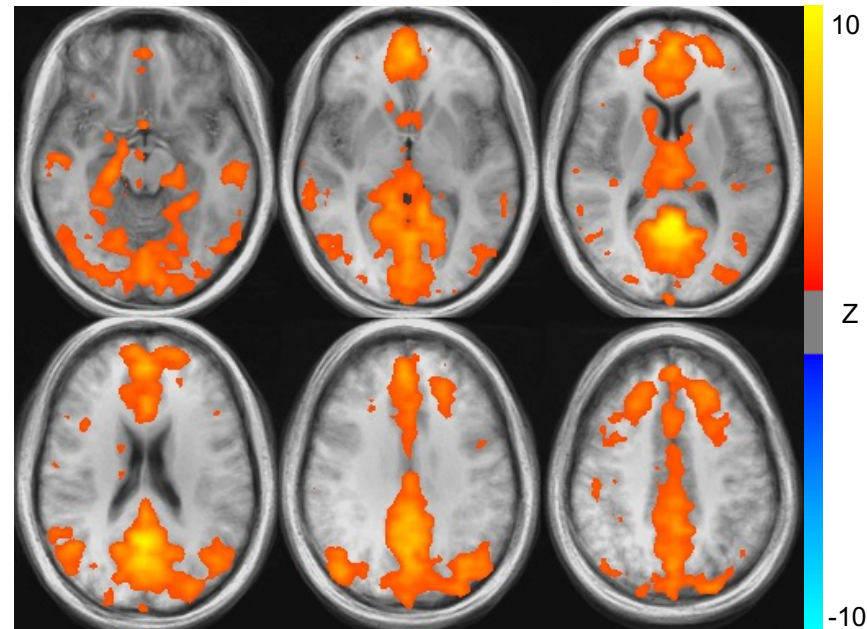
Areas correlated with posterior cingulate

Group data (n=10)

Constant Respirations



Cued Variable Respirations

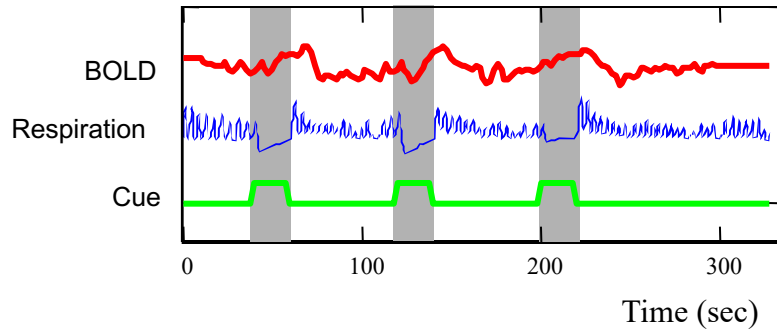


A closer look at respiration changes

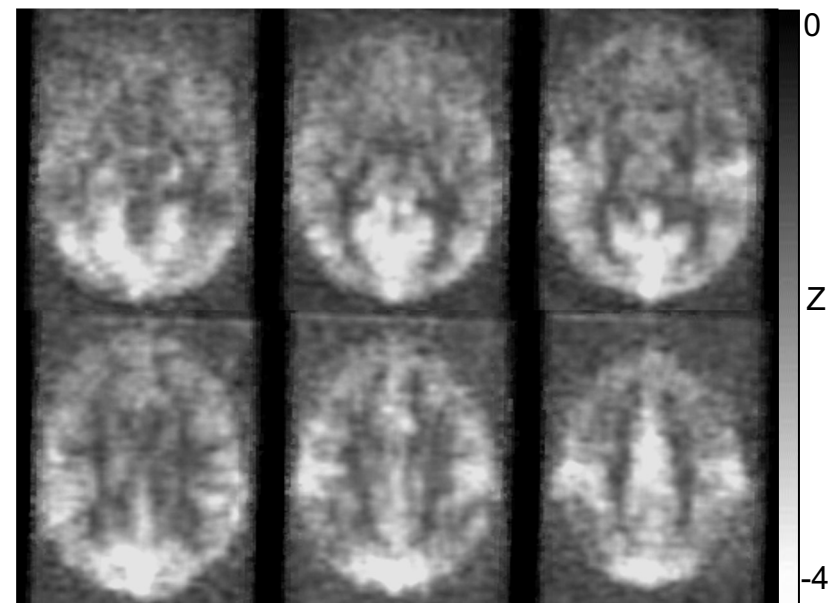
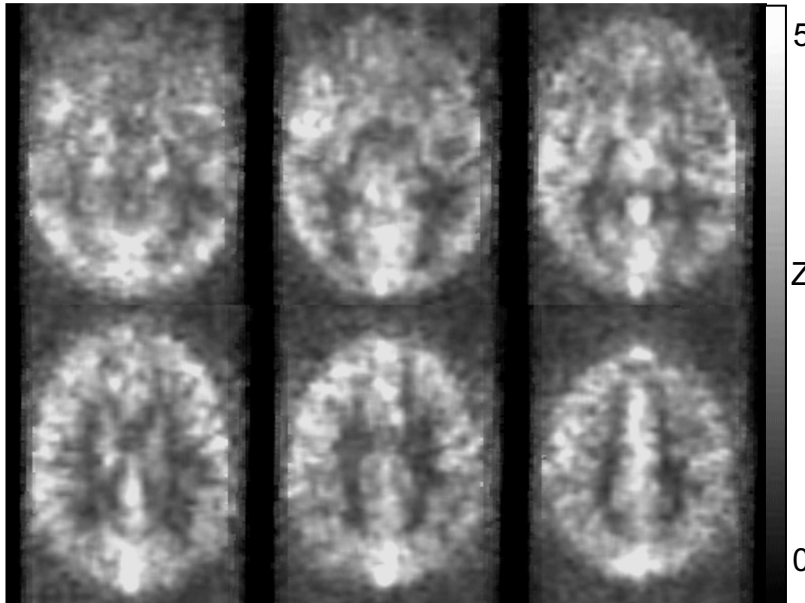
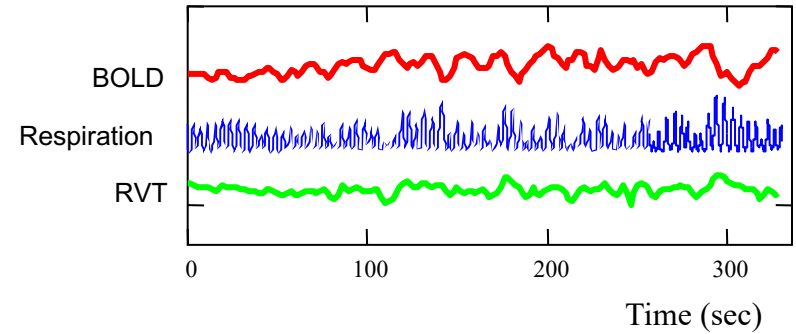
- Breath-hold vs. Resting variations in breathing
- The respiration “impulse response function”
 - *How do respiration changes really affect the BOLD signal? (shape, latency, ...)*
- Echo-time (TE) dependence

Respiration induced signal changes

Breath-holding



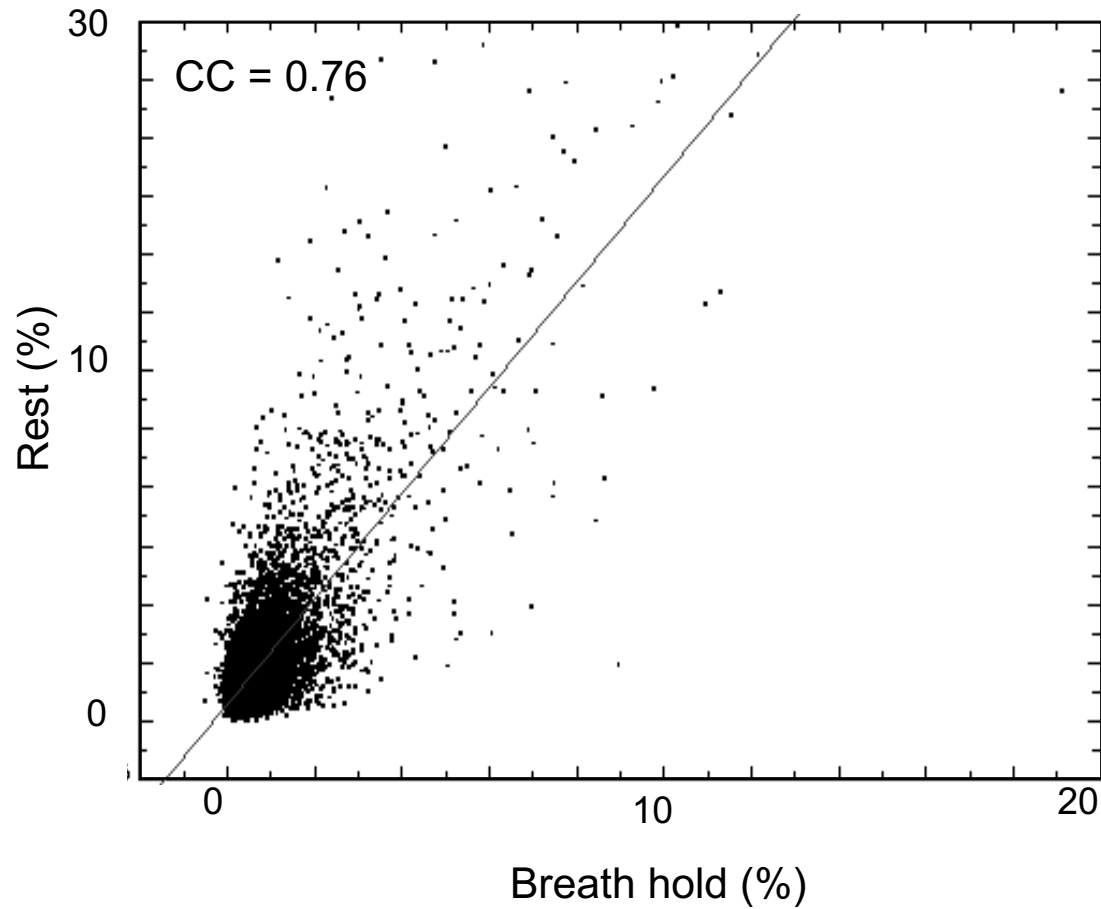
Rest



(N=7)

Resting changes in breathing vs. Breath-holding

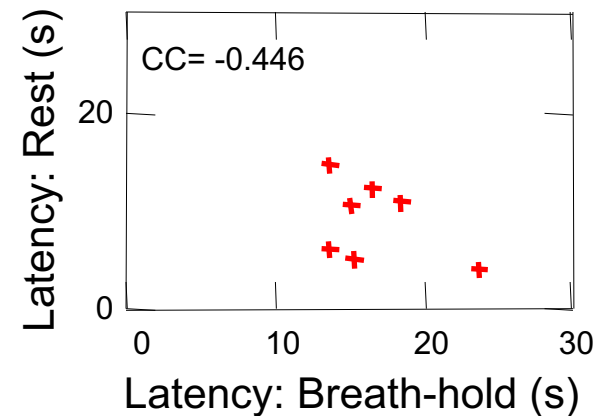
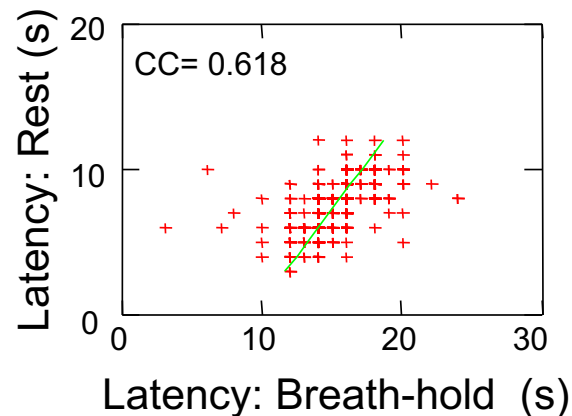
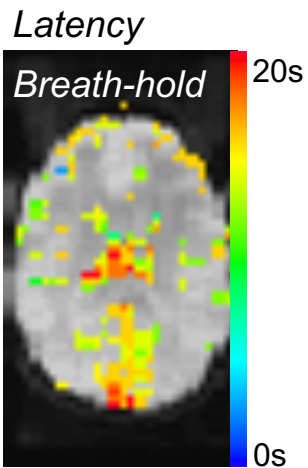
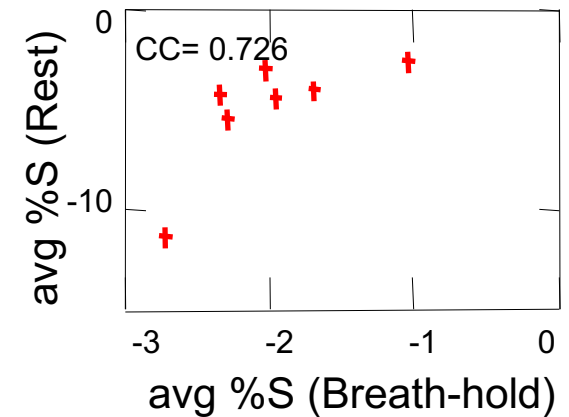
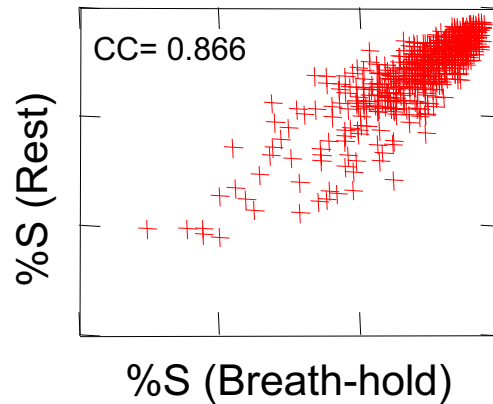
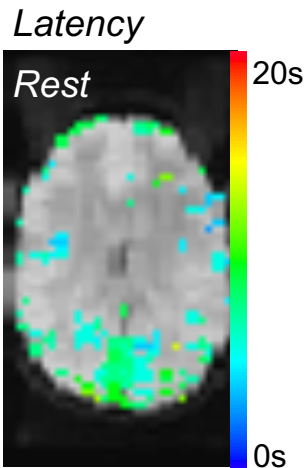
Correlation with Respiration Volume / Time (RVT)



Resting changes in breathing vs. Breath-holding

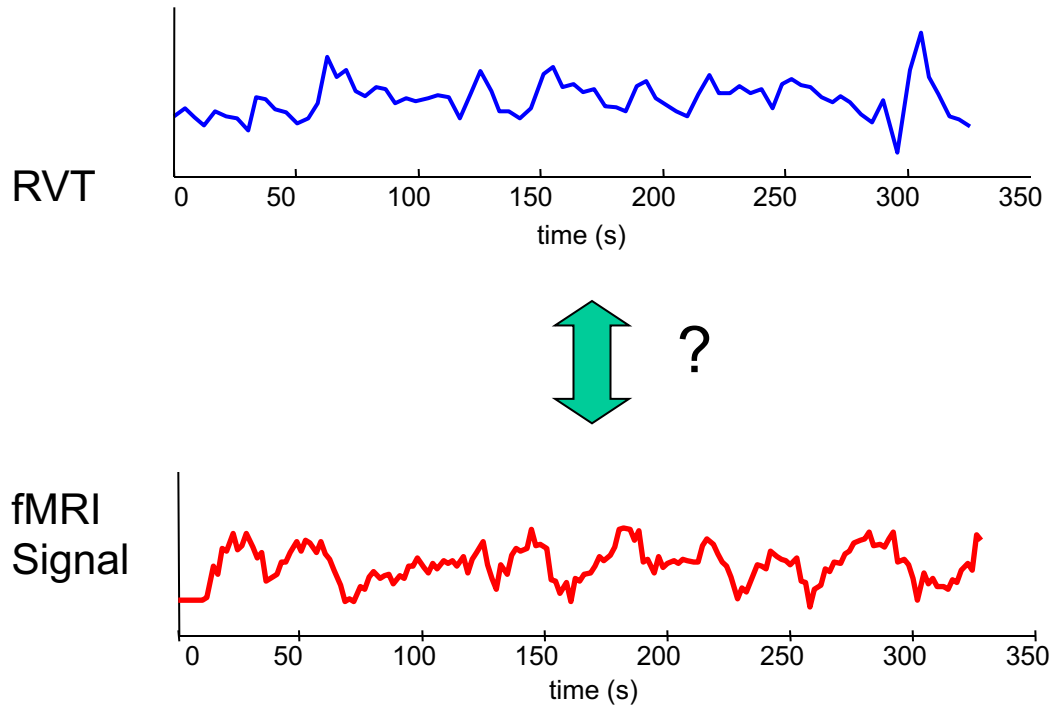
Rest vs. BH
within subject

Rest vs. BH
across subjects
(averaged over space)



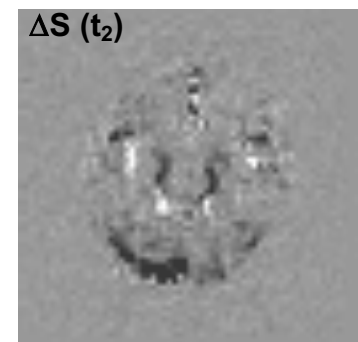
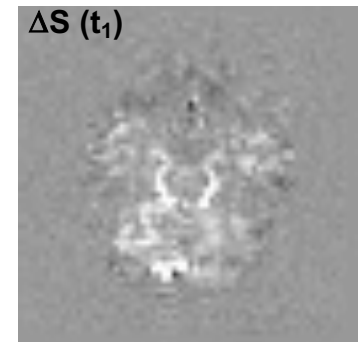
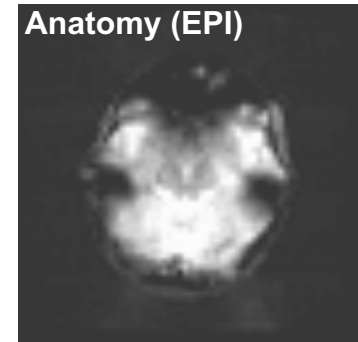
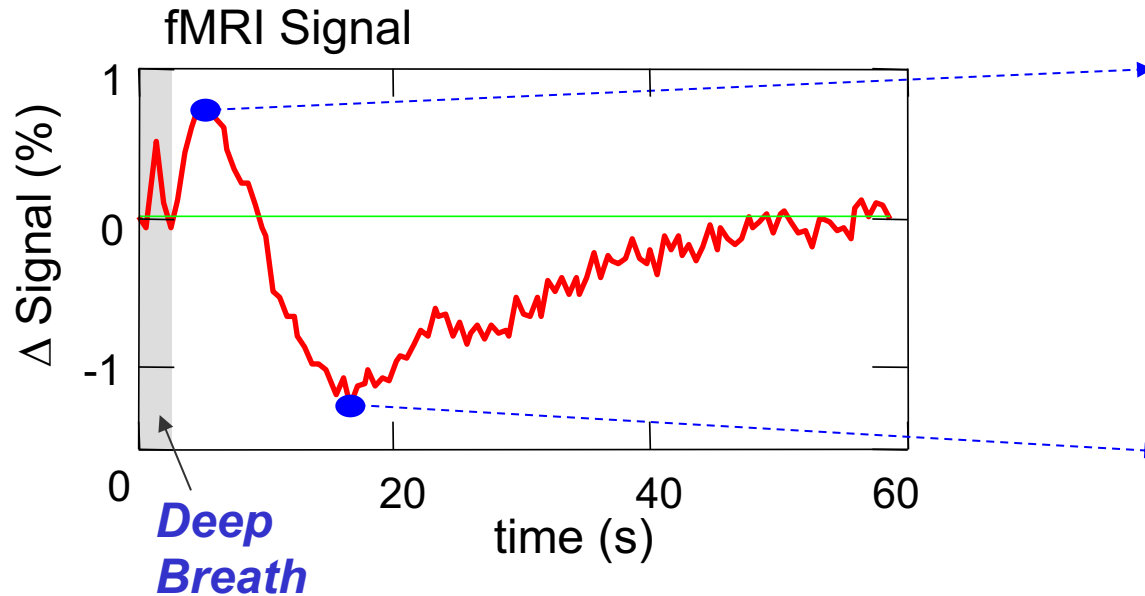
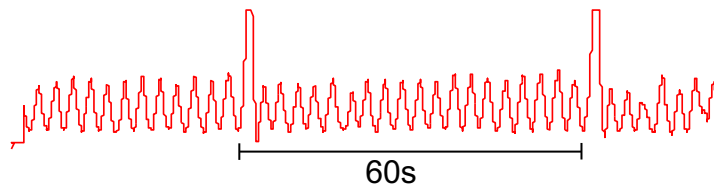
Respiration Changes vs. BOLD

How are the BOLD changes to respiration variations?

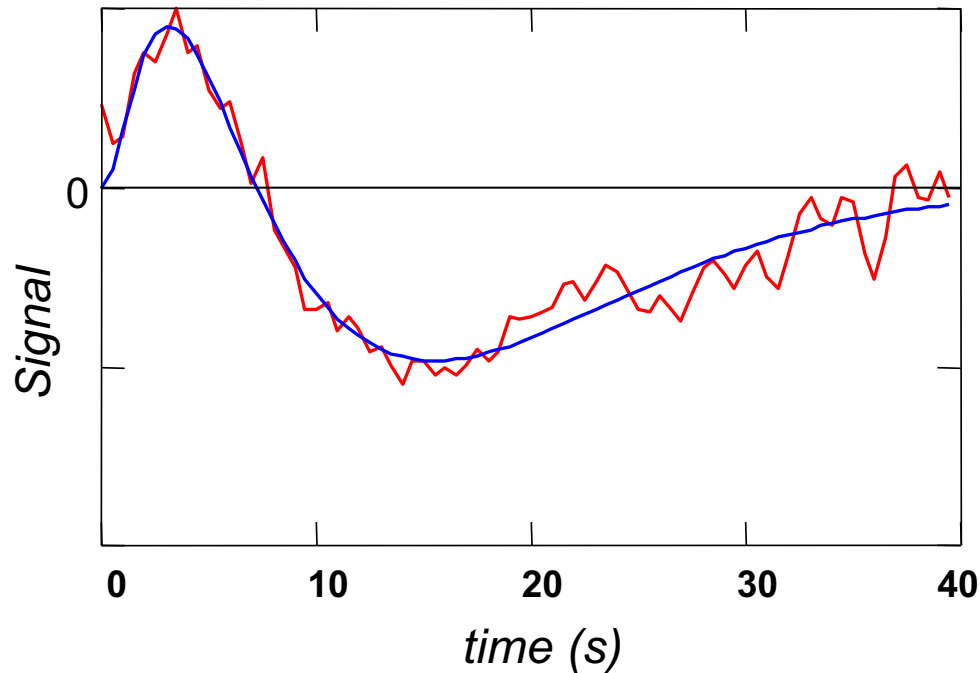


fMRI response to a single Deep Breath

Respiration



Respiration response function

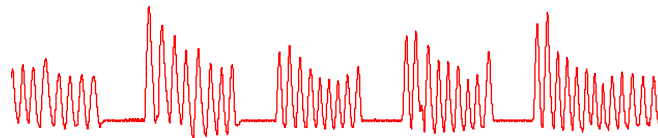


Average of 3 subjects

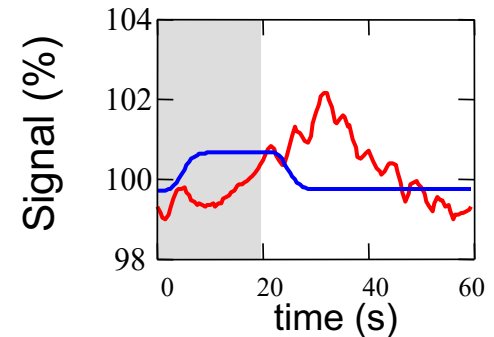
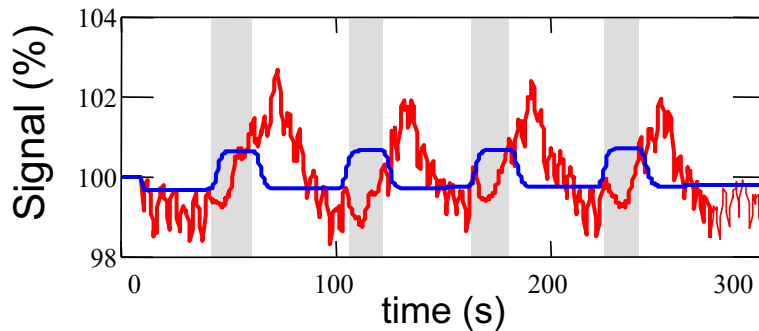
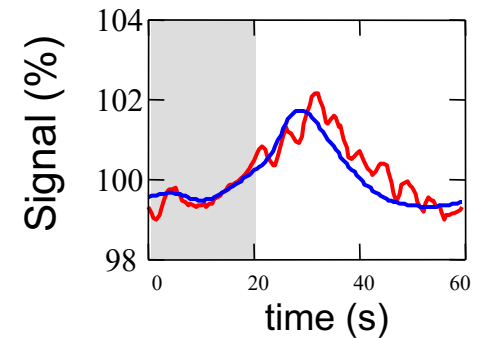
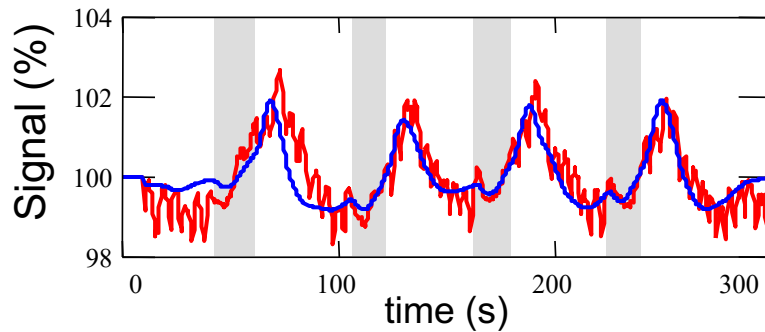
$$\text{RRF}(t) = 0.6 t^{2.1} e^{-1.6 t} - 0.0023 t^{3.54} e^{-4.25 t}$$

fMRI response to breathing modulations

Breath-holding

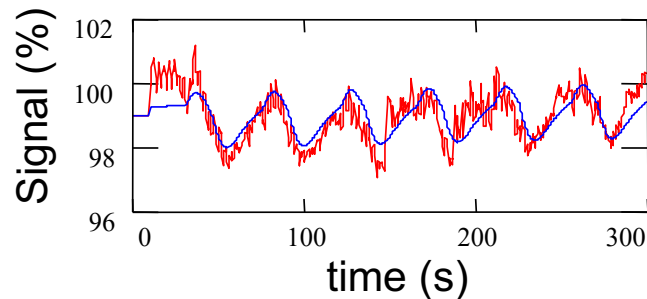
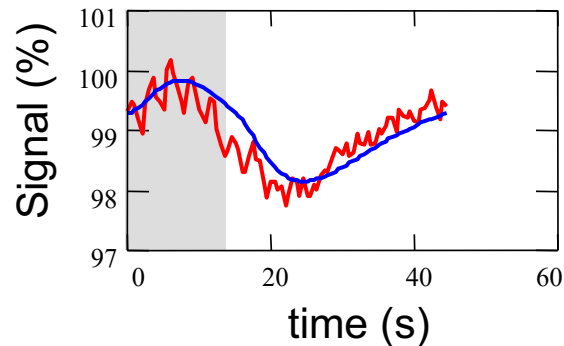
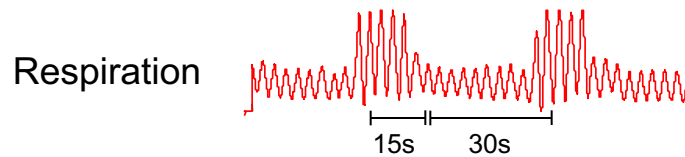


Respiration

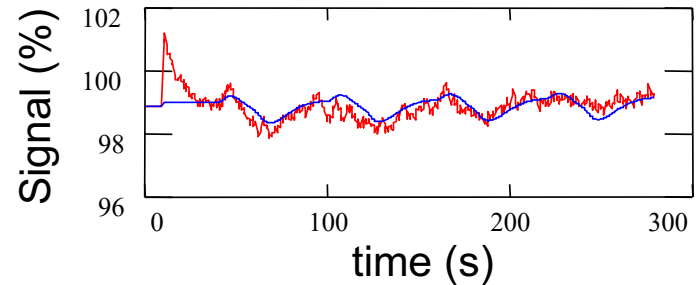
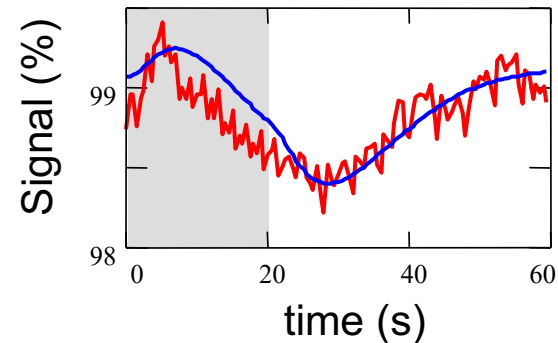
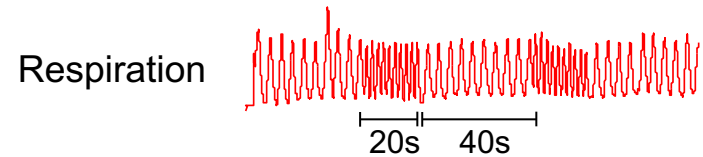


fMRI response to breathing modulations

Changes in Depth



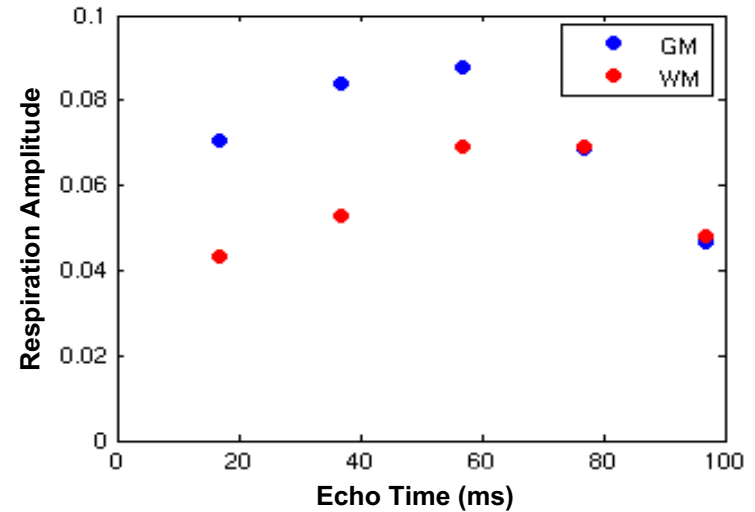
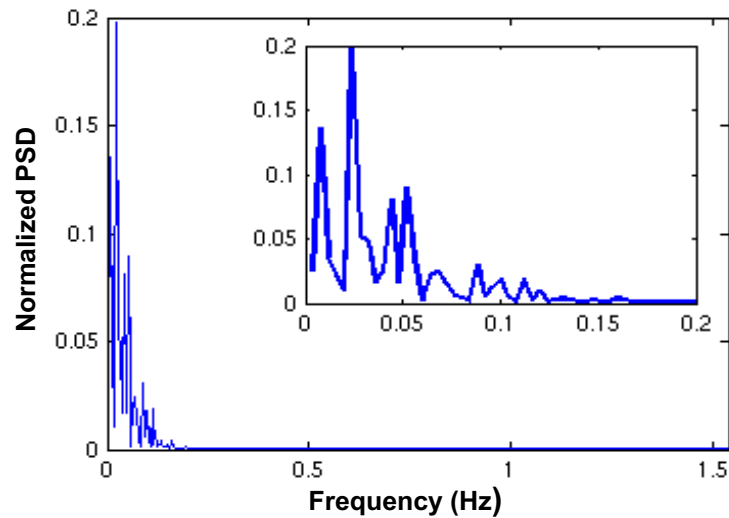
Changes in Rate



TE dependence of respiration changes

K. Murphy, R.M. Birn, P.A. Bandettini

The frequency profile of TE-dependent BOLD physiological fluctuations
ISMRM 2006



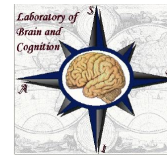
Future directions

- How do we best model respiration-induced BOLD signal changes?
 - New IRF from One Deep breath
- How are resting respiration changes different from cued respiration changes?
- Are these respiration and signal fluctuations related to changes in neuronal function?
 - EEG/fMRI, MEG
- Can we use resting respiration fluctuations for BOLD calibration?

Acknowledgements

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Rasmus Birn *
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Ziad S. Saad
Gang Chen



Unit on Cognitive Neurophysiology and Imaging

David A. Leopold

Research Services Branch

George Dold

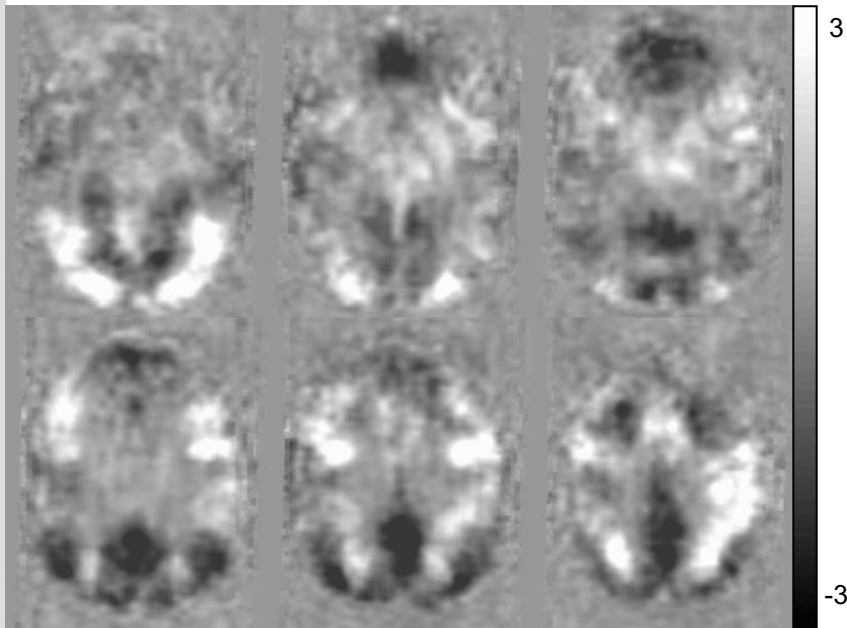


More...

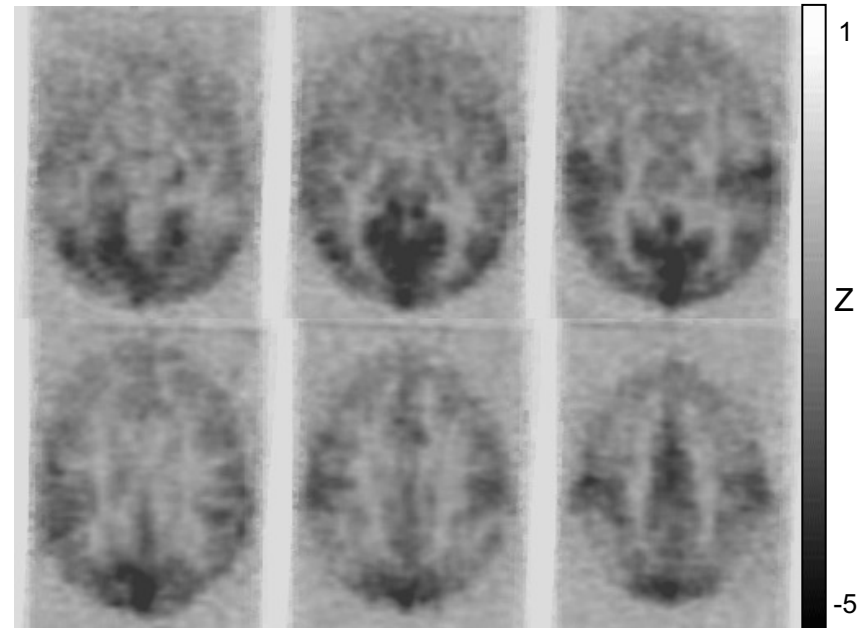
BOLD signal changes – *Group data*

Group data (n=10)

Lexical Task



Respiration changes

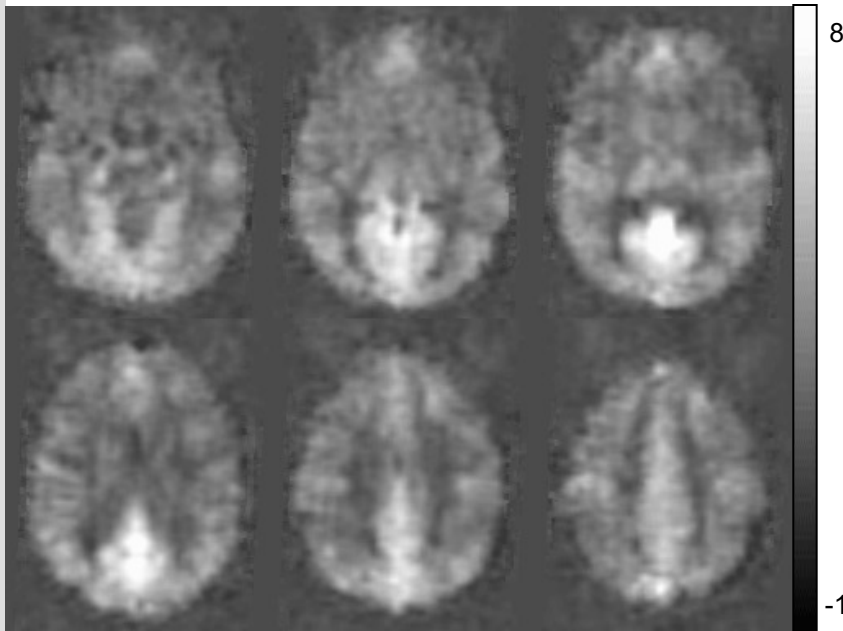


Resting-state correlations

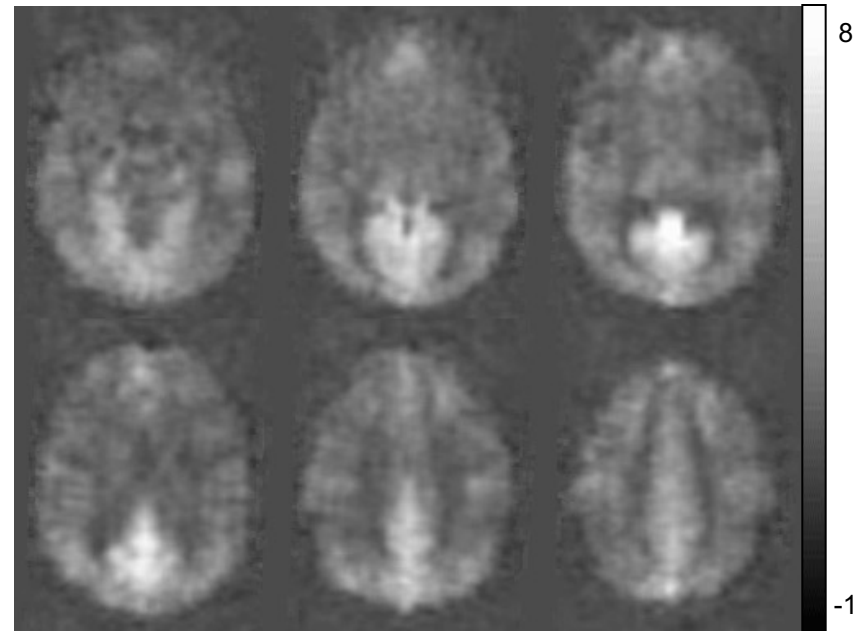
Areas correlated with posterior cingulate

Group data (n=10)

after RETROICOR



after RETROICOR + RVTcor

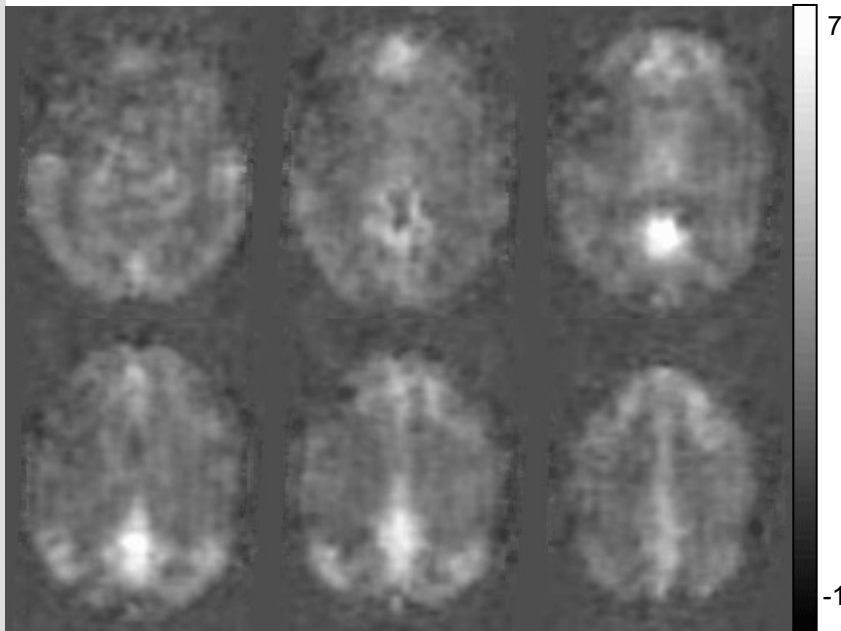


Resting-state correlations

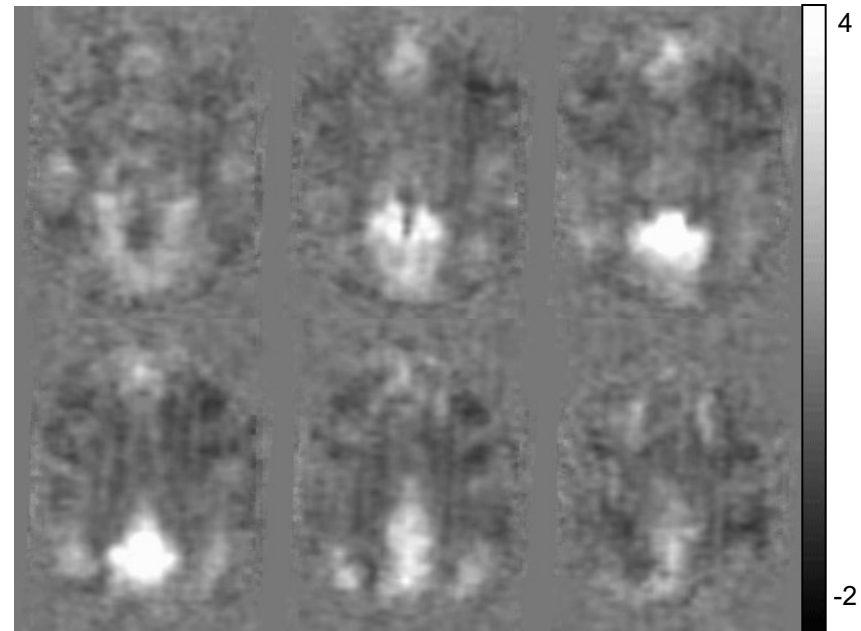
Areas correlated with posterior cingulate

Group data (n=10)

Constant Respirations



Remove global signal changes



Breath-hold changes

Breath-hold induced BOLD + Flow changes

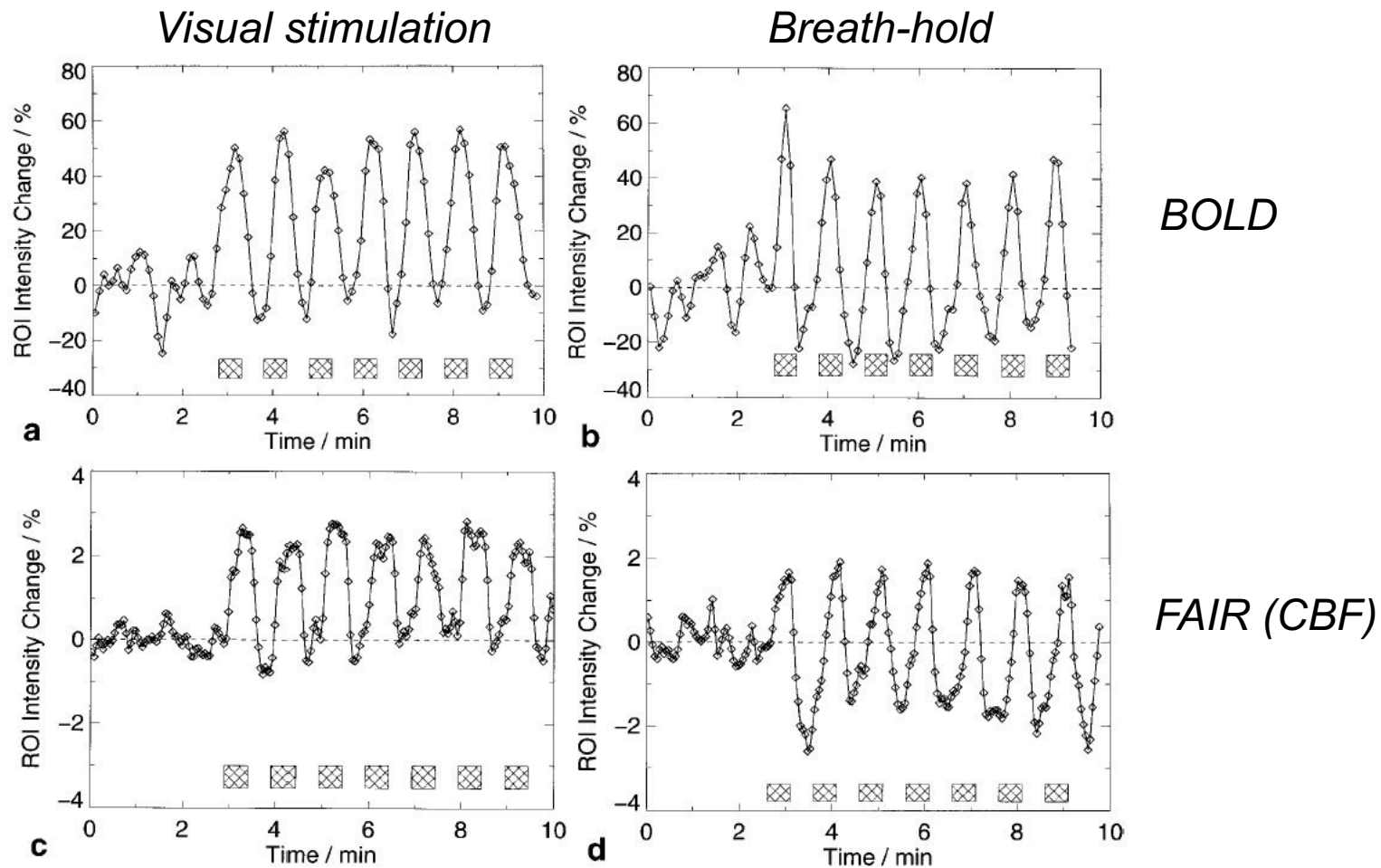
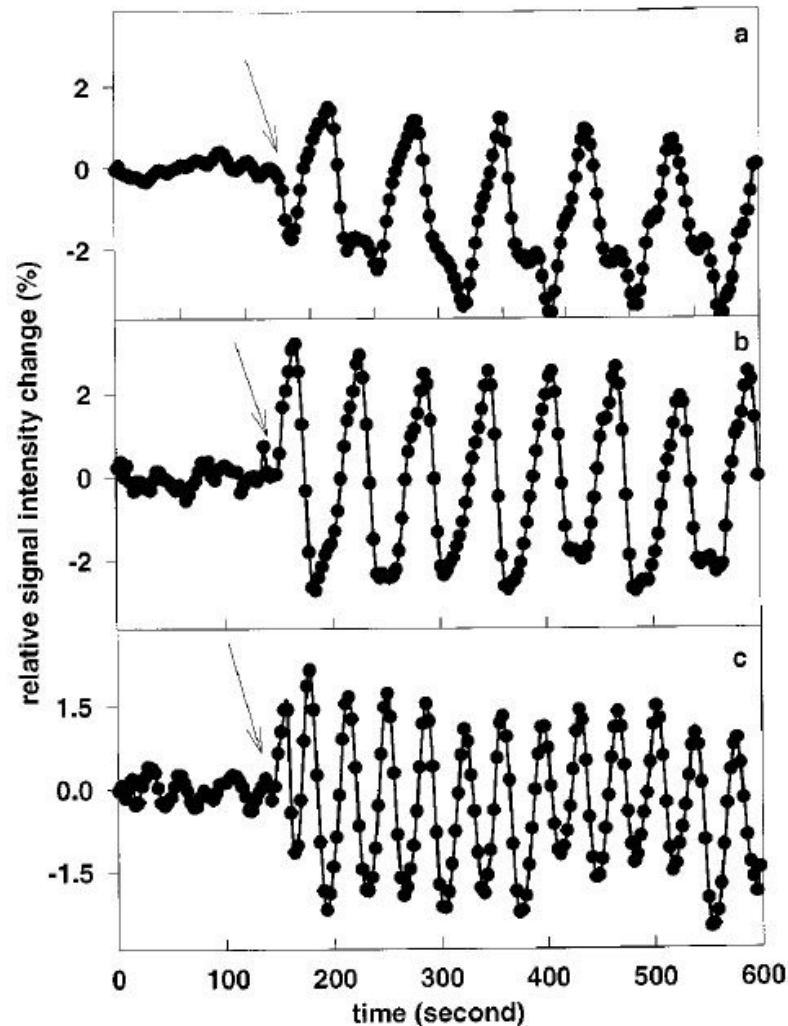


FIG. 2. Change in intensity of FAIR and BOLD signals during photic stimulation (a and c, respectively) and during breath holding (b and d, respectively). Time courses are of mean signal intensities in activated areas from the same subject as in Fig. 1.

Breath-hold induced BOLD changes

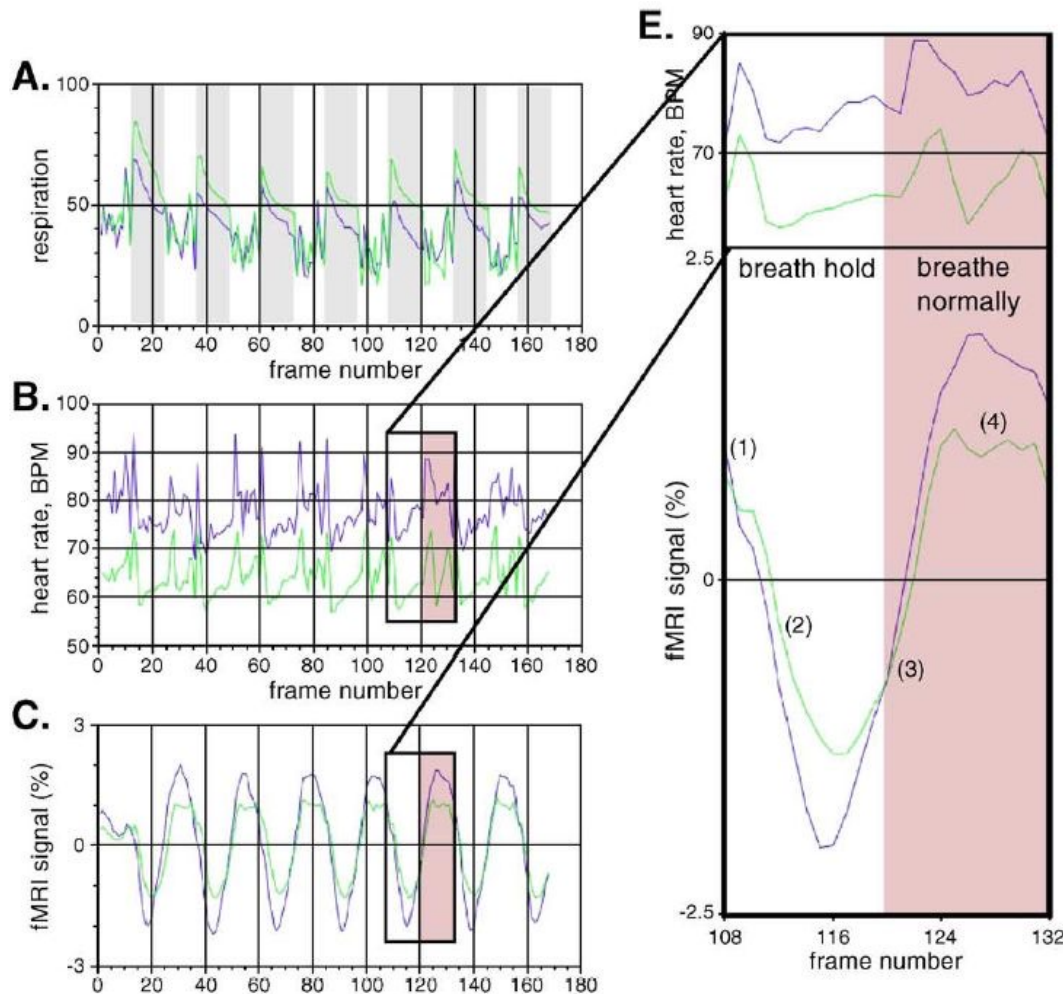


40s breath-hold
after *inspiration*

30s breath-hold
after *expiration*

18s breath-hold
after *expiration*

Breath-hold induced BOLD changes



1. Chest expansion →
↓ intrathoracic pressure
2. Baroreceptor regulation →
↓ Heart rate, ↓ CBF
3. ↑ CO₂ → ↑ CBF
4. Recovery of normal BF

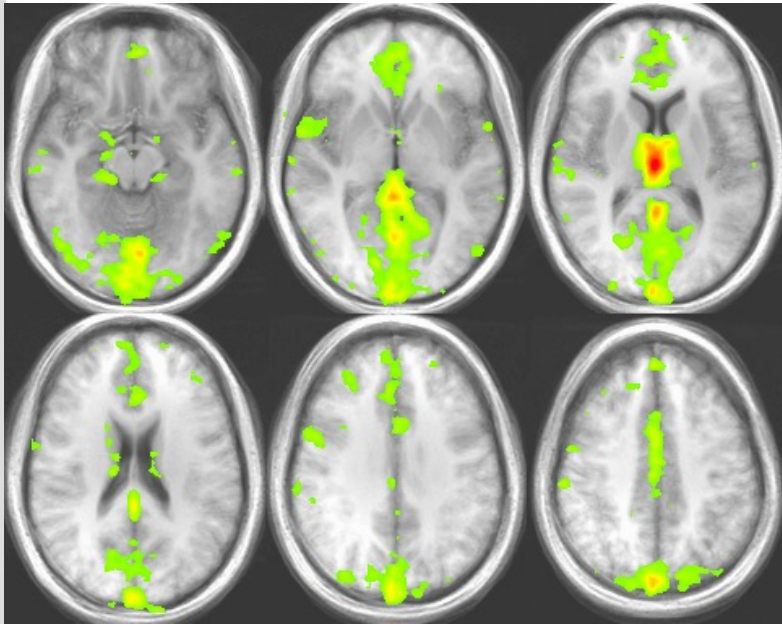
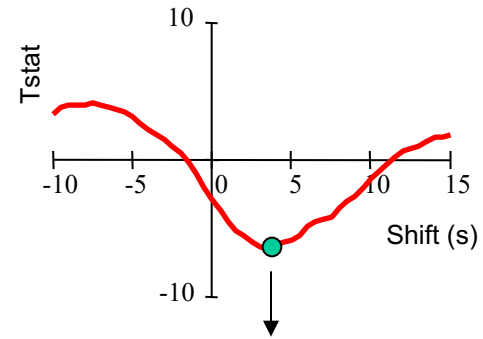
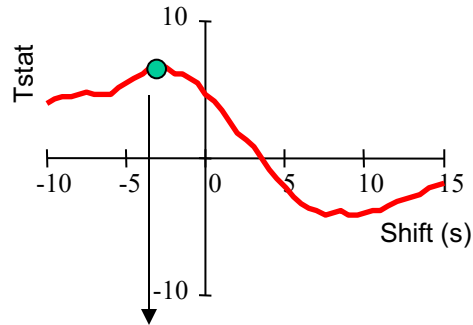
(1) chest expansion --> decreased intrathoracic pressure --> reduced vascular resistance --> increased inflow of blood to heart.

(2) autonomic regulation by baroreceptors --> reduced HR --> decreased blood flow to brain --> increased paramagnetic Hb --> reduced SI.

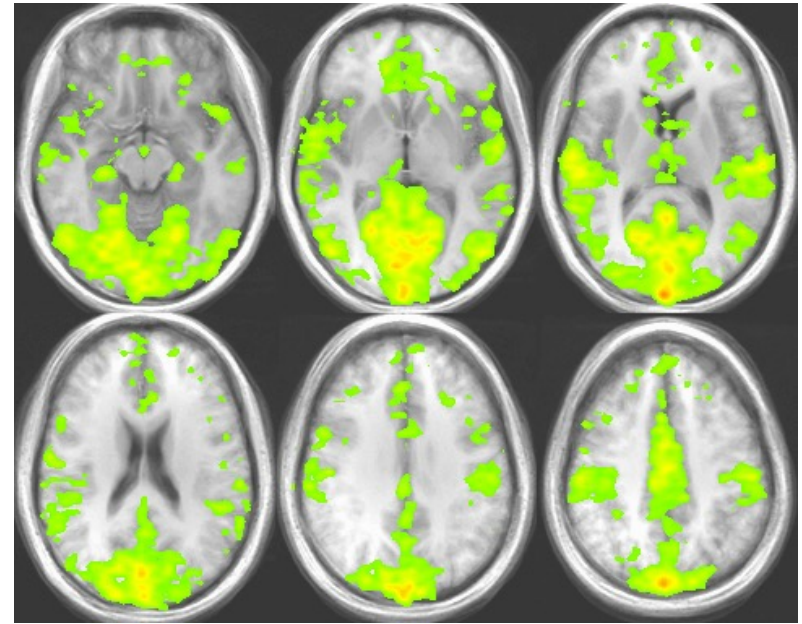
(3) Increase in CO₂ --> increased CBF in brain --> drop in paramagnetic Hb --> rise in oxyHb and SI.

(4) Recovery of normal blood flow --> reduced CO₂ --> vasoconstriction of arterials --> SI plateaus, return to normal rCBF, O₂, Hb levels.

Latency – RVT vs. BOLD



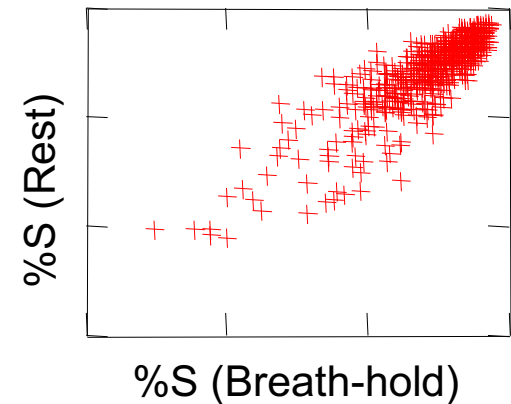
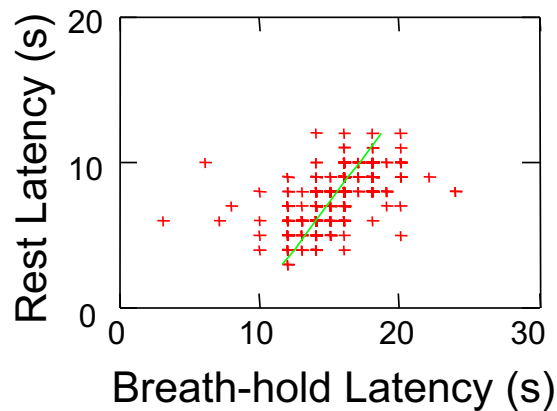
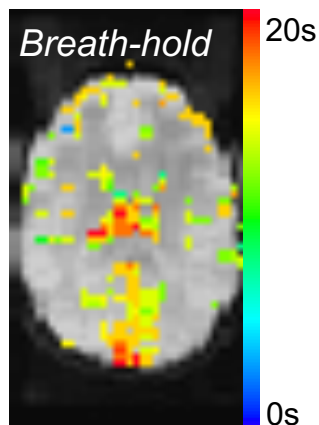
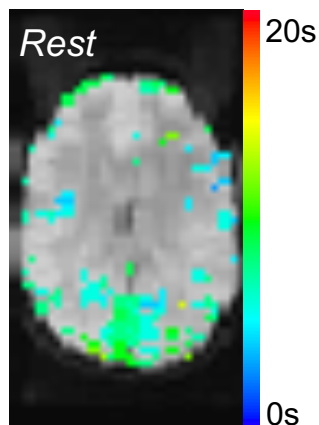
largest **positive** correlation (in each voxel)



largest **negative** correlation (in each voxel)

Resting changes in breathing vs. Breath-holding

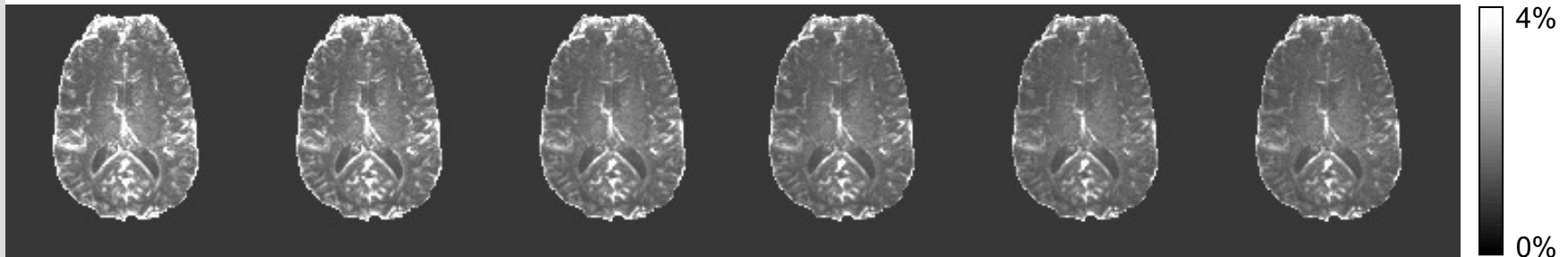
M.A. Smith, P.A. Bandettini, R.M. Birn, ISMRM 2006



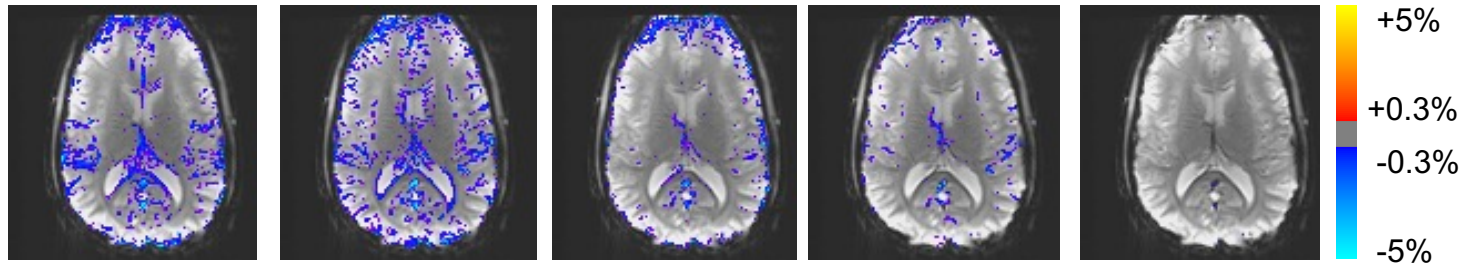
(each + represents one voxel signif. corr. With RVT)

Multiple Physiological Regressors

Standard Deviation Maps (1 subject)

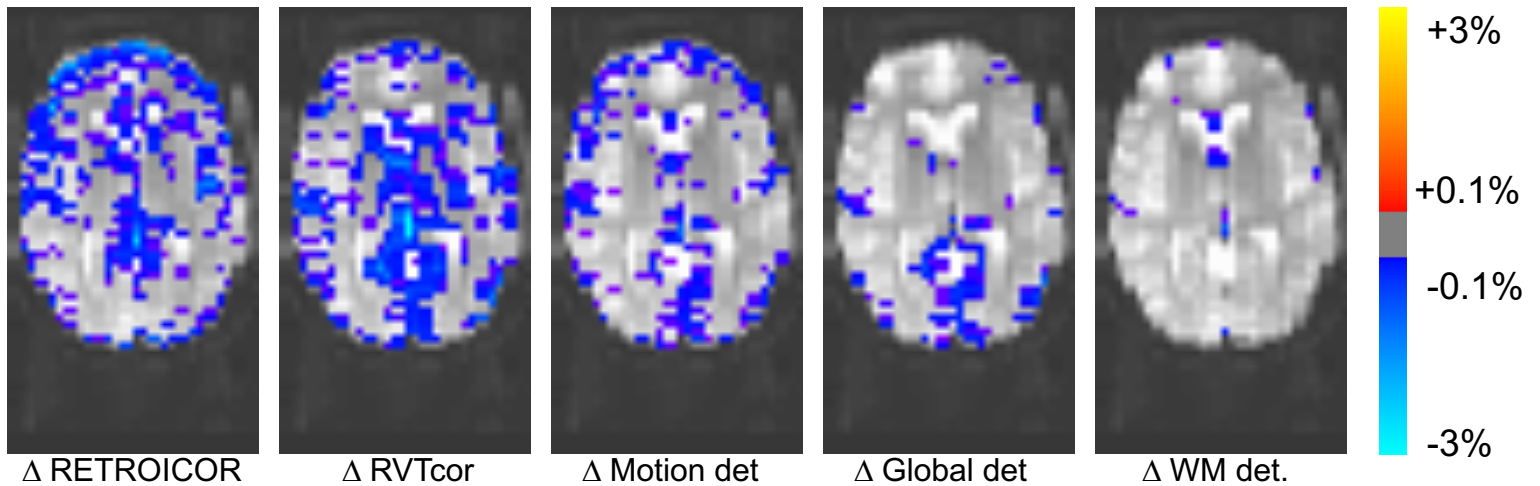
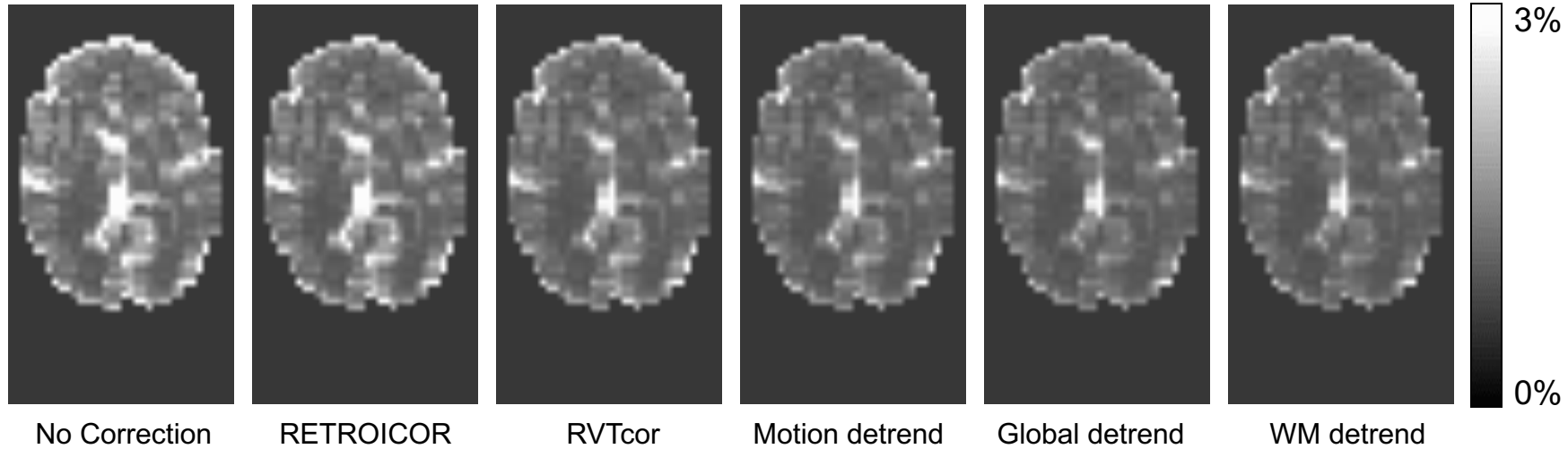


No Correction RETROICOR RVTcor Motion detrend Global detrend WM detrend

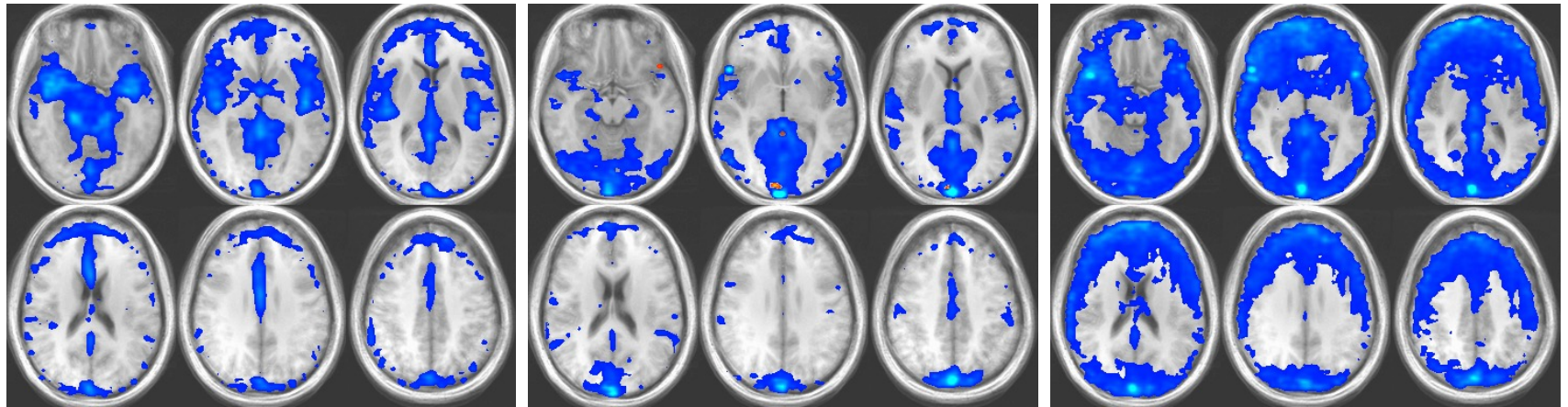


Δ RETROICOR Δ RVTcor Δ Motion det Δ Global det Δ WM det.

Standard Deviation Maps (1 subject)



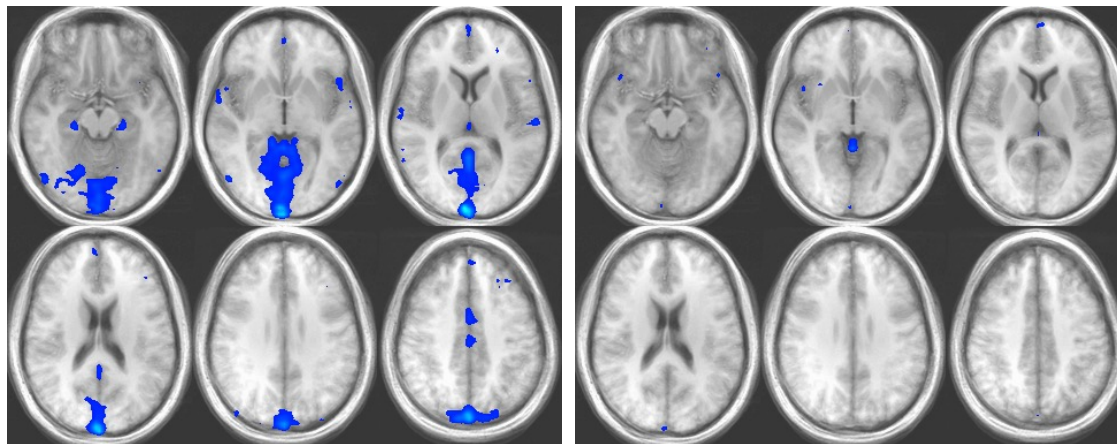
Change in StDev – Group data (n=10)



Δ RETROICOR

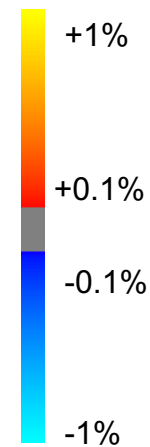
Δ RVTcor

Δ Motion detrend

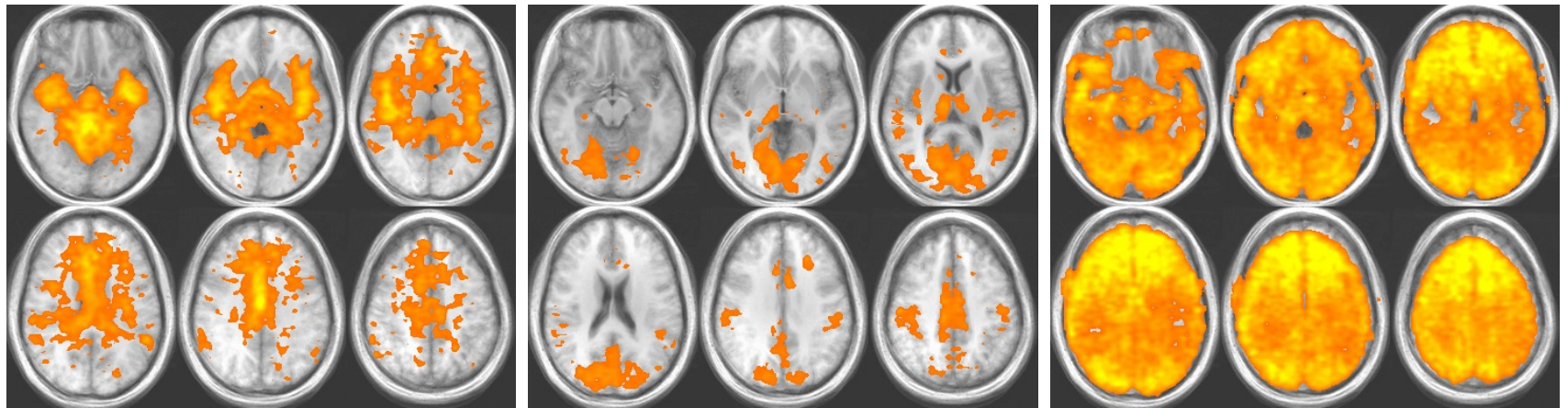


Δ Global detrend

Δ WM detrend



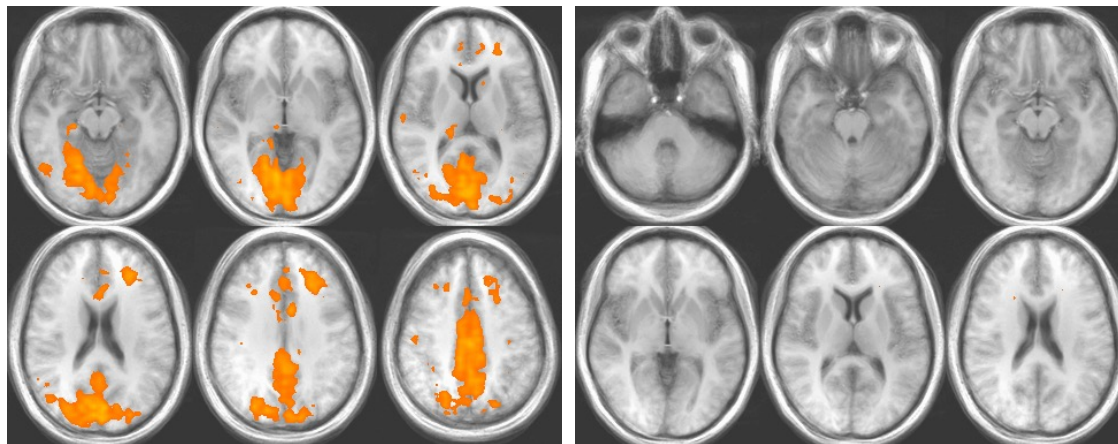
Change in TSNR – Group data (n=10)



Δ RETROICOR

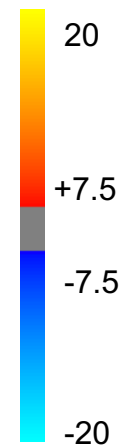
Δ RVTcor

Δ Motion detrend



Δ Global detrend

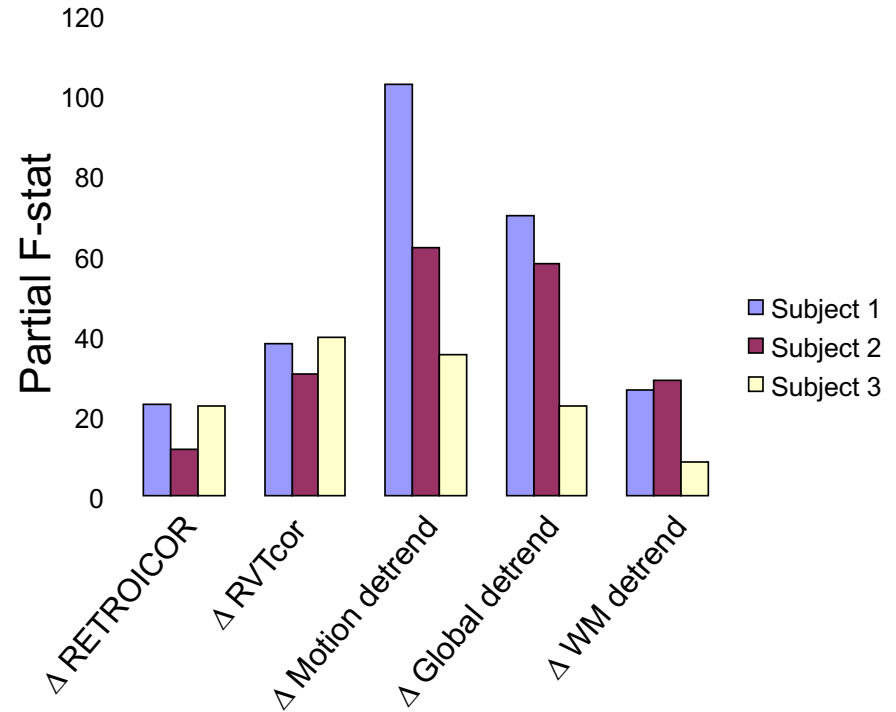
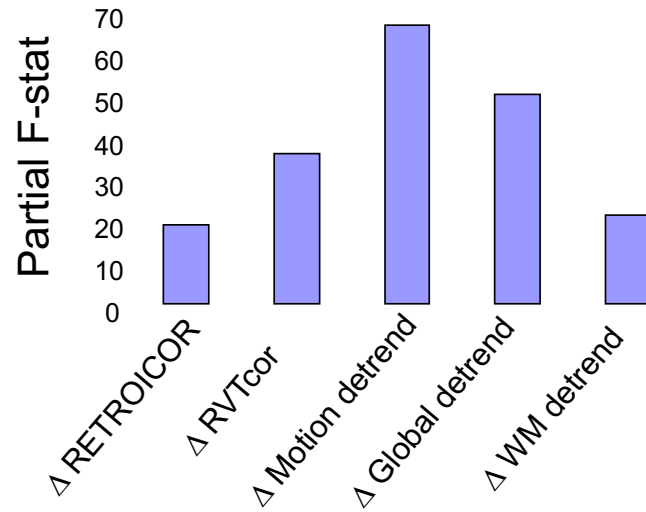
Δ WM detrend



Relative contributions to noise

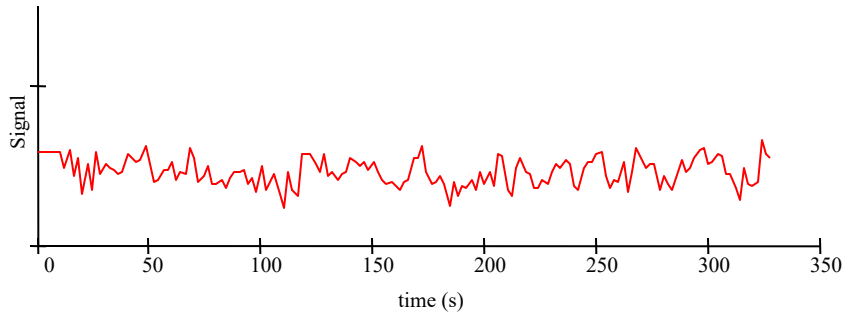
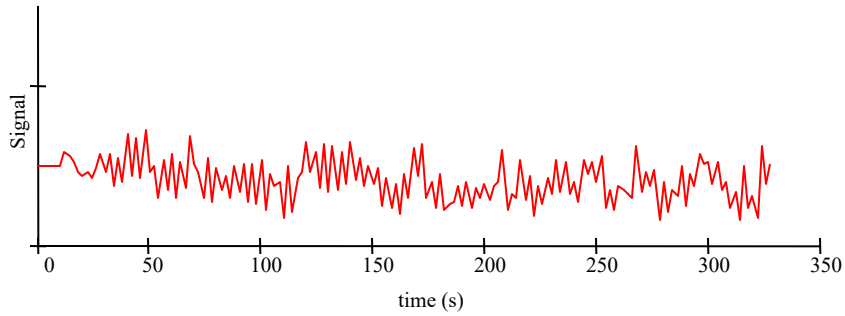
Averaged over Gray Matter

$$\left(\text{Partial F} = \frac{\text{SSE(R)} - \text{SSE(F)}}{\text{SSE(F)}} \frac{\text{dof(F)}}{\text{dof(R)-dof(F)}} \right)$$



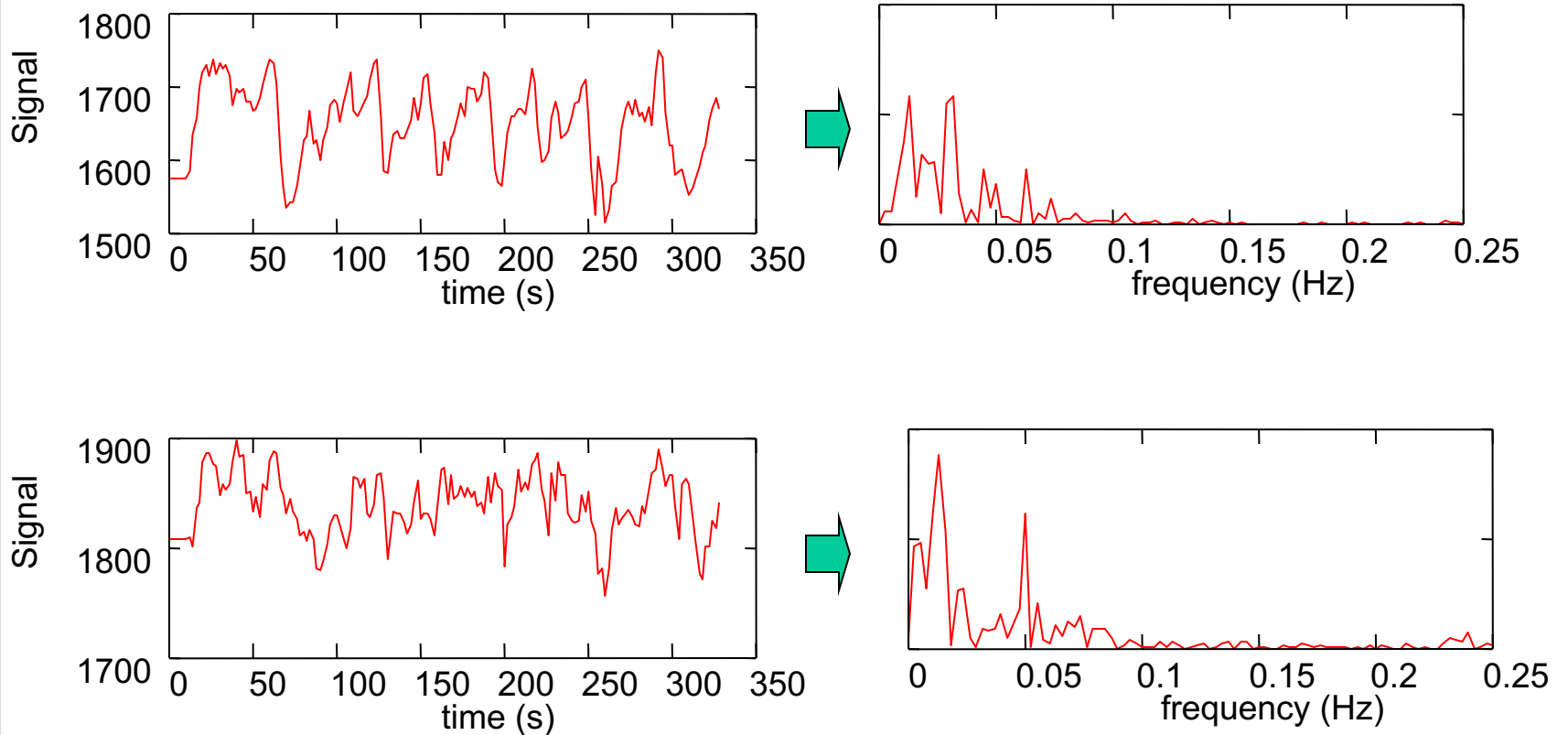
Example: regress out RVT

Regress out Card/Resp/RVT



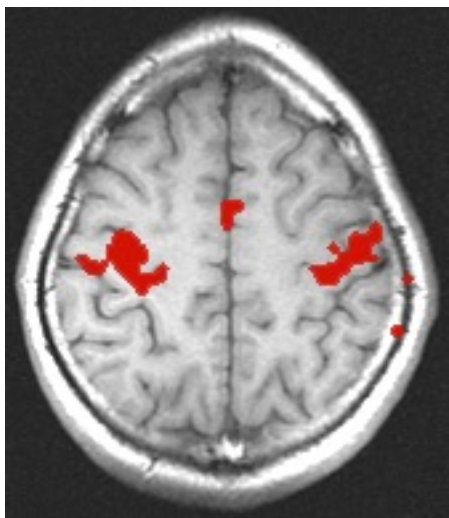
<END>

Sample time courses (& frequencies)

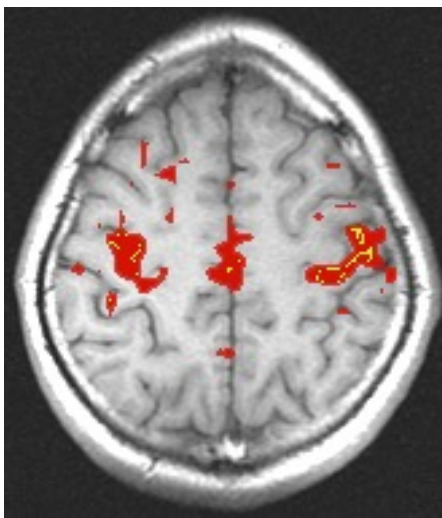


Resting-state functional connectivity

B. Biswal et al., MRM, 34:537 (1995)



Activation during
finger-tapping



Correlations with “seed voxel”
in motor cortex at rest

Further work:

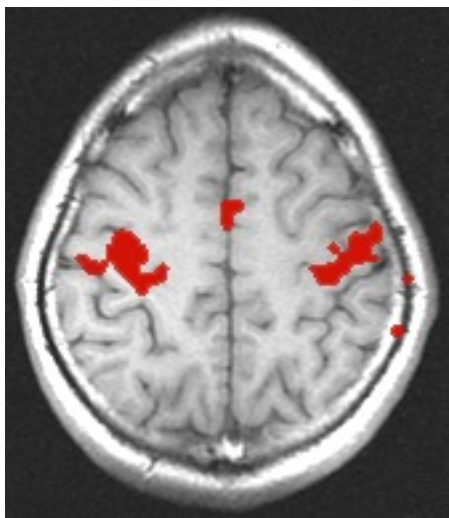
M.J. Lowe, et al., NeuroImage 7(2), 1998.

D. Cordes, et al., AJNR 21(9), 2000.

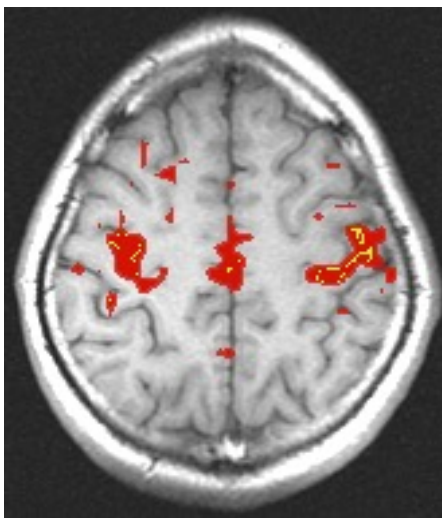
⋮

Resting-state functional connectivity

B. Biswal et al., MRM, 34:537 (1995)



Activation during
finger-tapping



Correlations with “seed voxel”
in motor cortex at rest

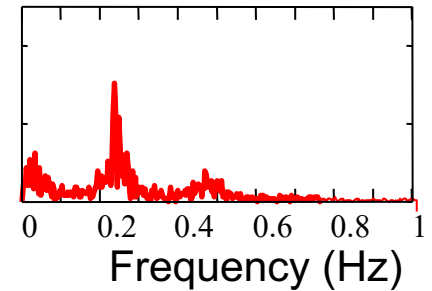
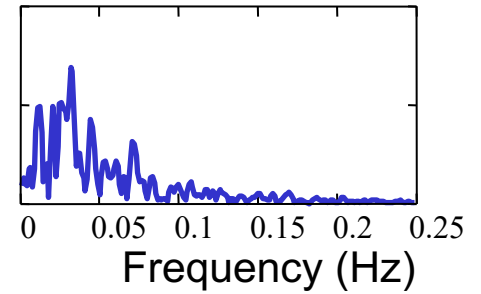
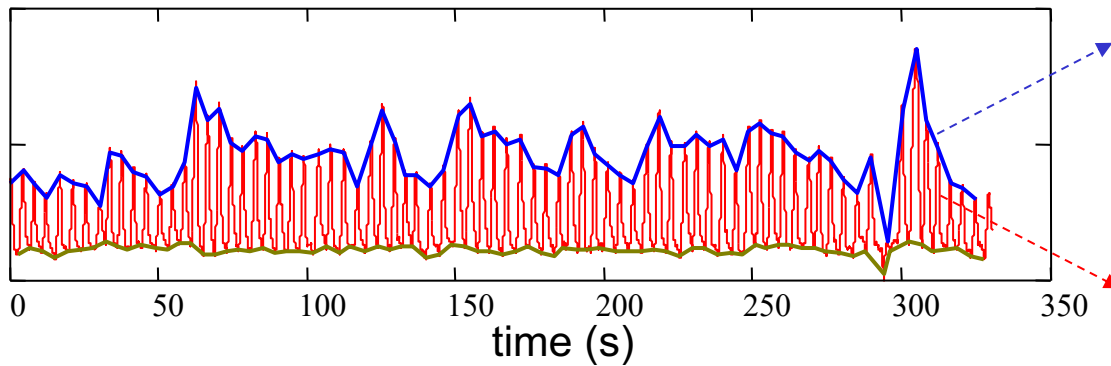
M.J. Lowe, et al., NeuroImage 7(2), 1998.

D. Cordes, et al., AJNR 21(9), 2000.

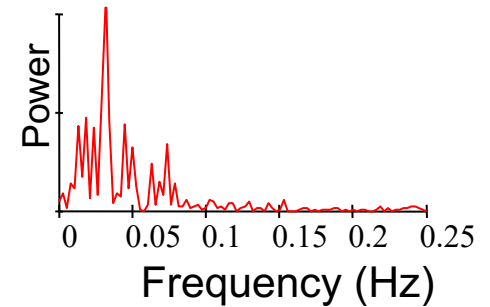
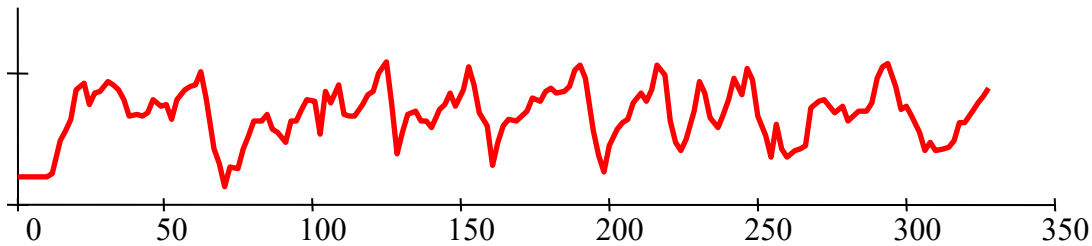
⋮

Resting fluctuations in respiration

Respiration



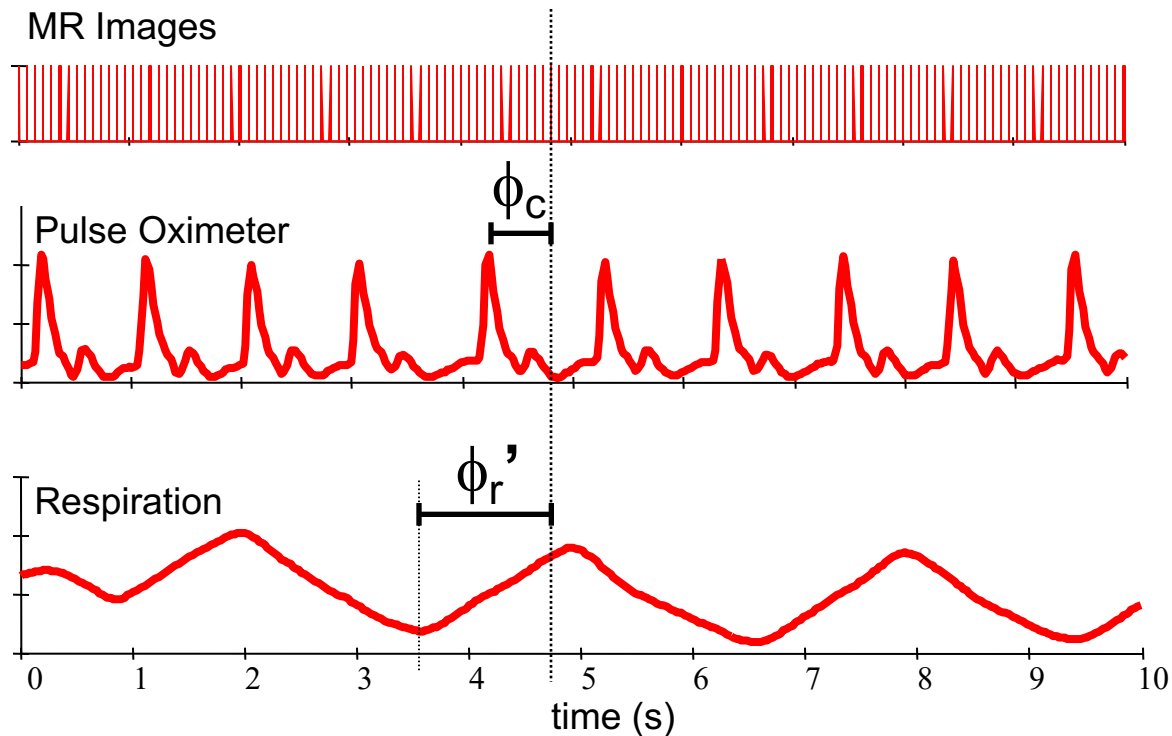
BOLD Signal



Methods

Analysis

1. Image Registration
2. RETROICOR



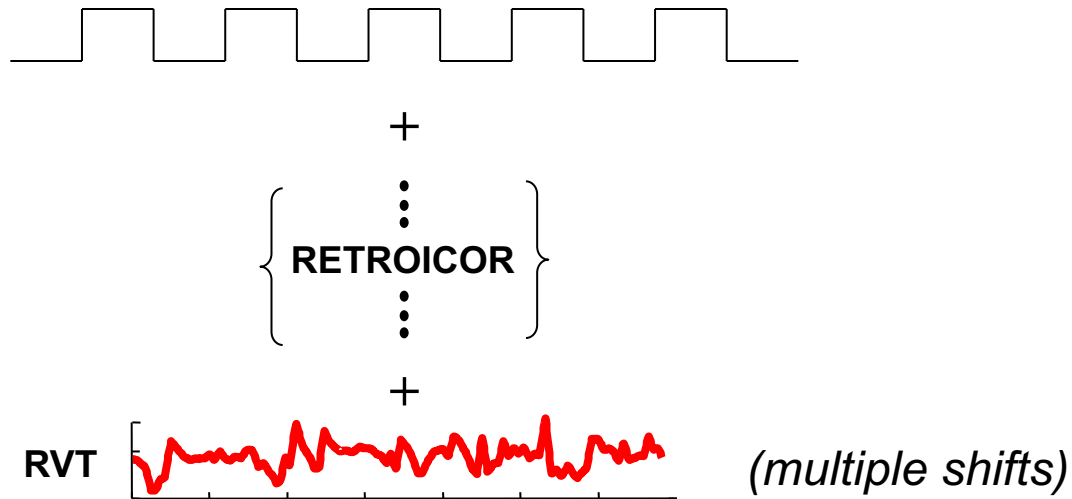
Additional Regressors:

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

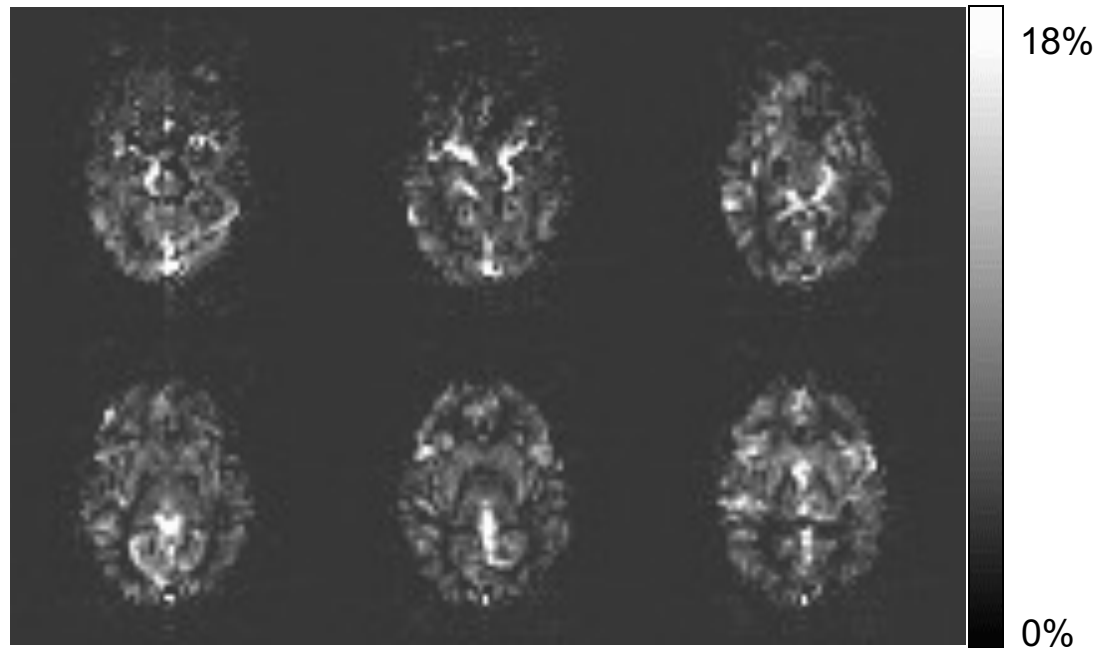
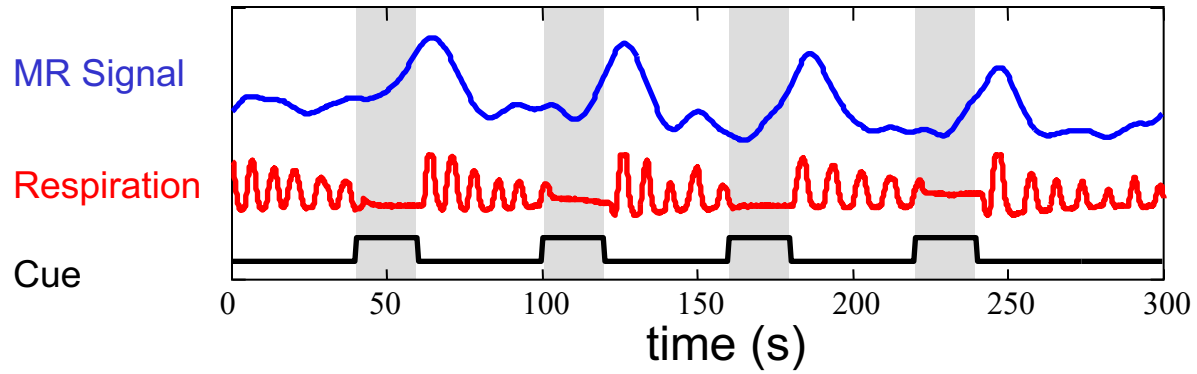
Methods

Analysis

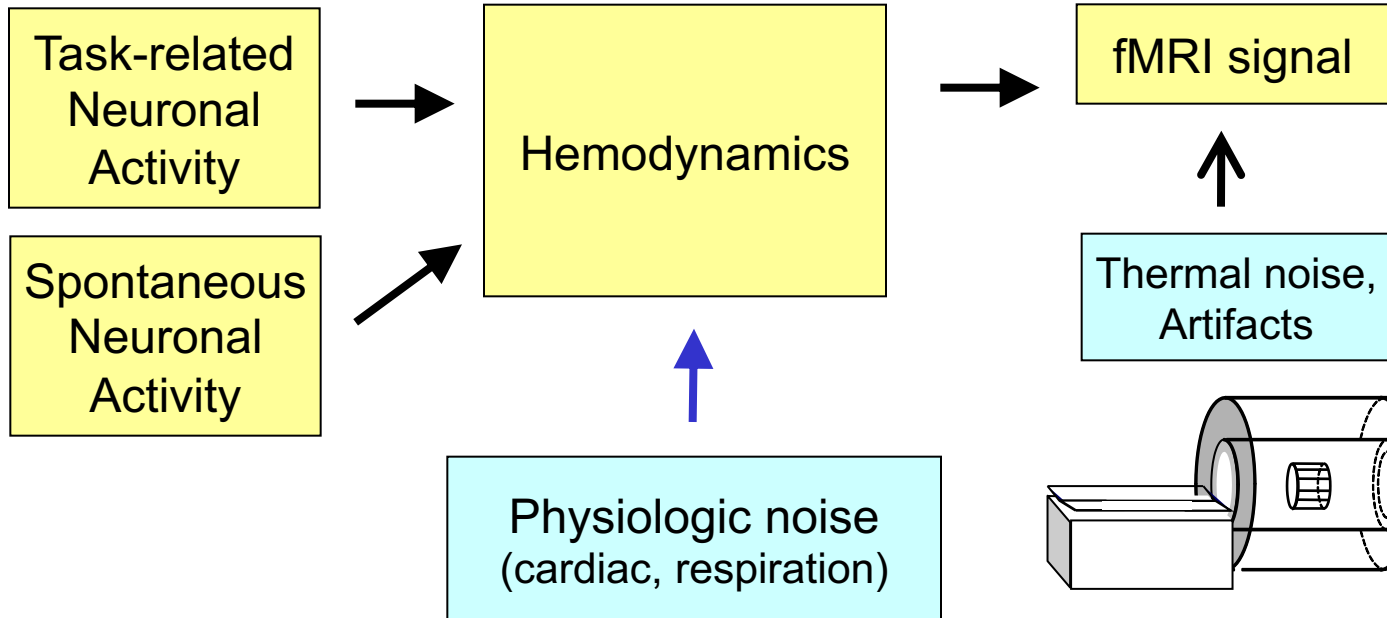
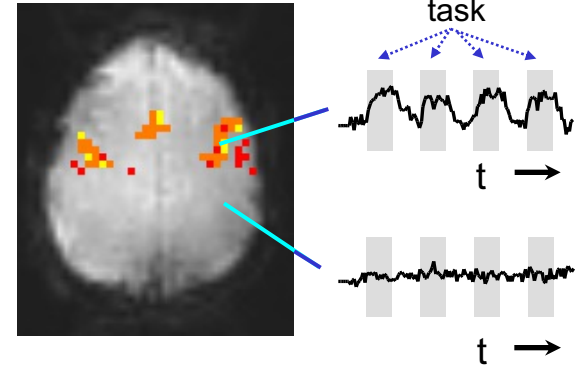
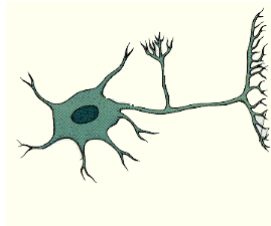
1. Image Registration
2. RETROICOR
3. RVTcor
4. Regression Analysis



Breath-holding



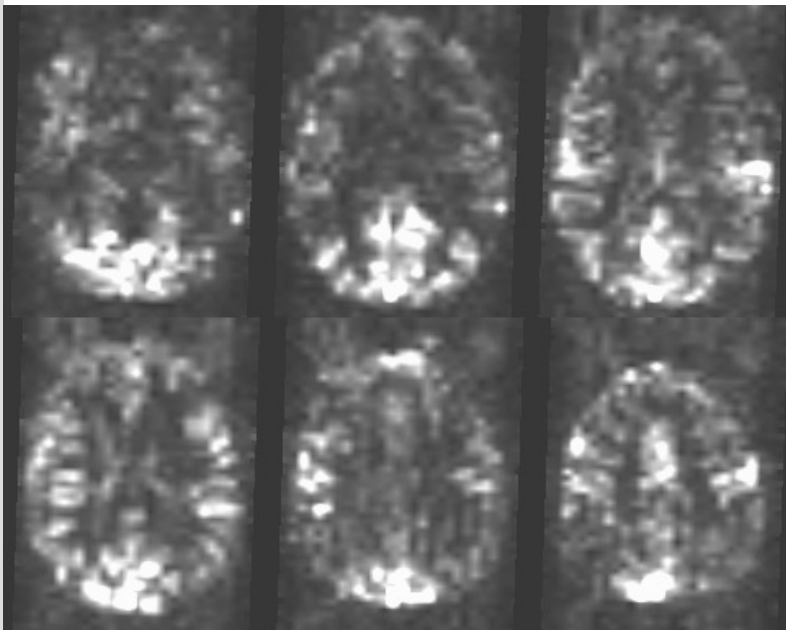
The fMRI Signal



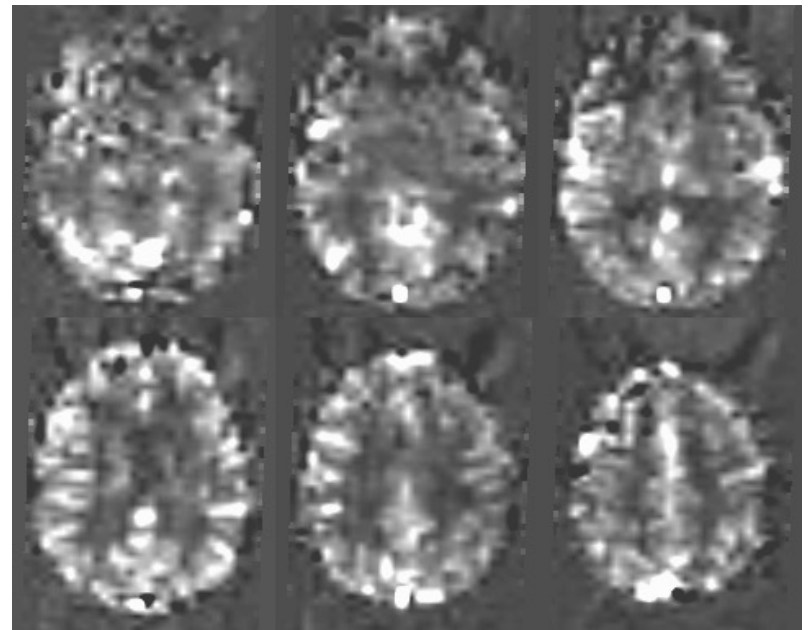
Resting changes in breathing vs. Breath-holding

Correlation with Respiration Volume / Time (RVT)

Rest



Breath-hold



General motivations for my research

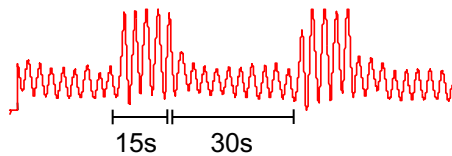
- Improve image quality
 - Motion correction
 - Optimal paradigm design
 - Reducing sources of noise (e.g. physiological noise)
- Improve interpretability of BOLD fMRI
 - How are BOLD changes related to neuronal activity?*
 - What does a certain % signal change really mean?*
 - Temporal dynamics
 - Comparison to other vascular measures (*CBF, CO₂, venogram, bolus contrast agent*)
 - Comparison of sequences with different contrast (*SE/ GE*)



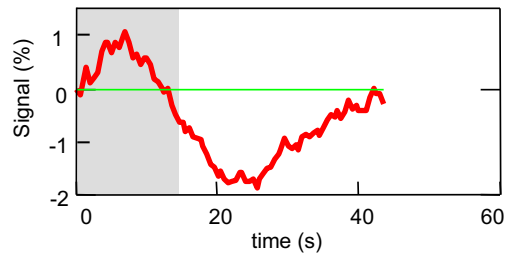
fMRI response to breathing modulations

Changes in Depth

Respiration

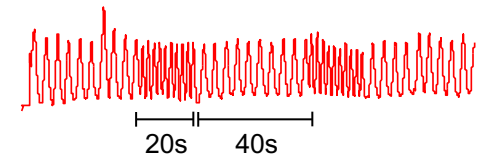


fMRI Signal

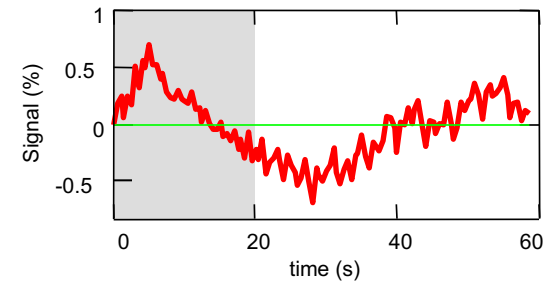


Changes in Rate

Respiration



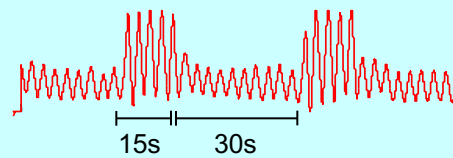
fMRI Signal



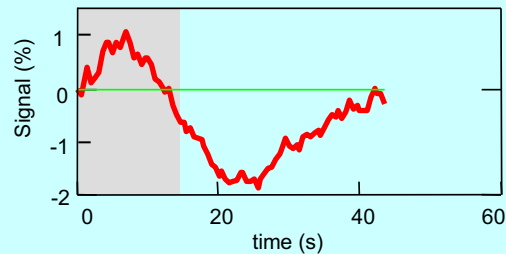
fMRI response to breathing modulations

Changes in Depth

Respiration

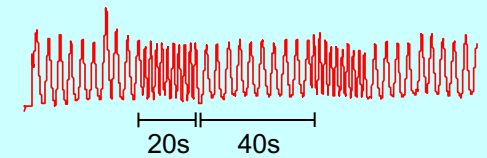


fMRI
Signal

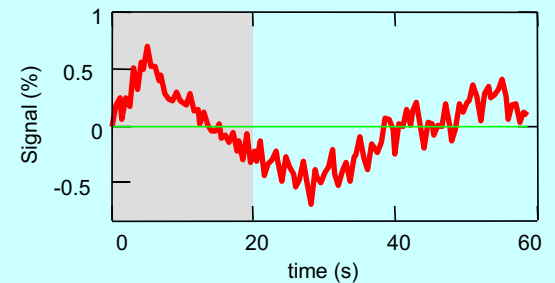


Changes in Rate

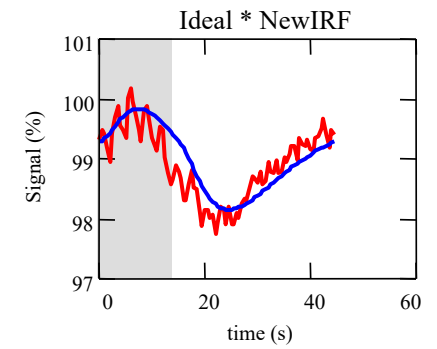
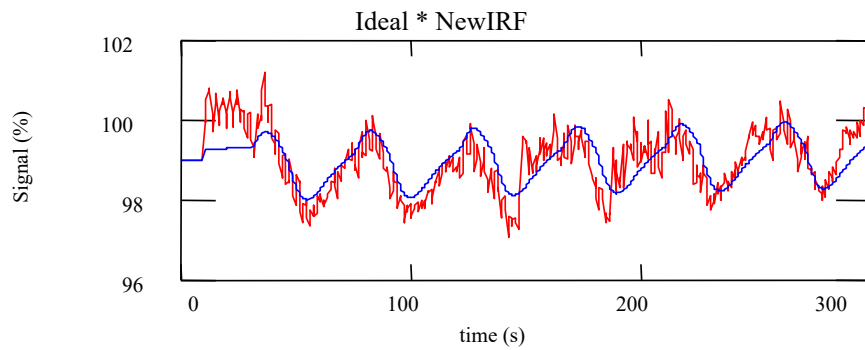
Respiration



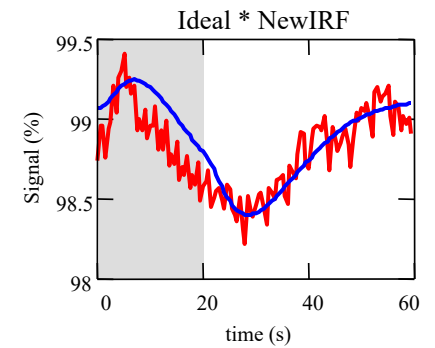
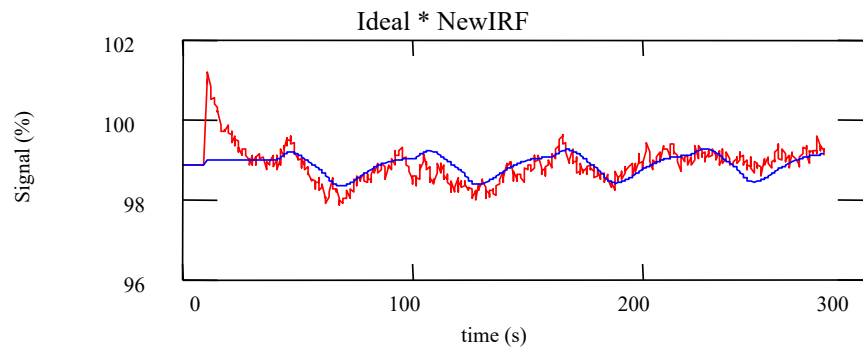
fMRI
Signal



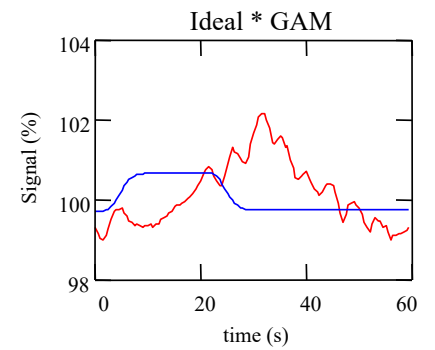
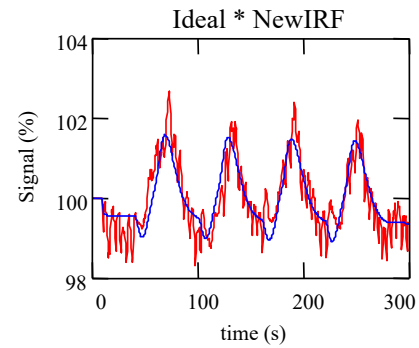
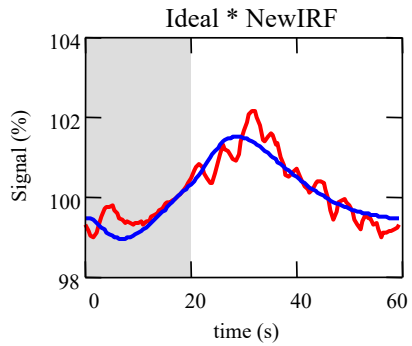
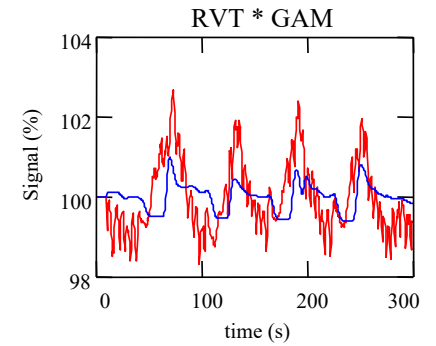
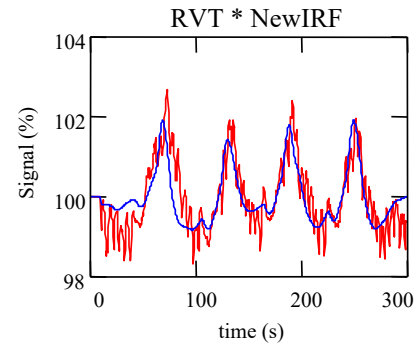
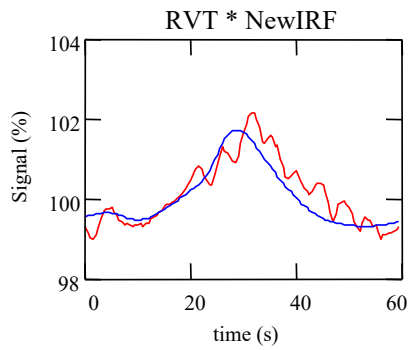
Depth



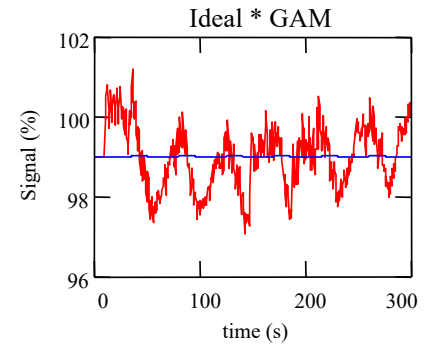
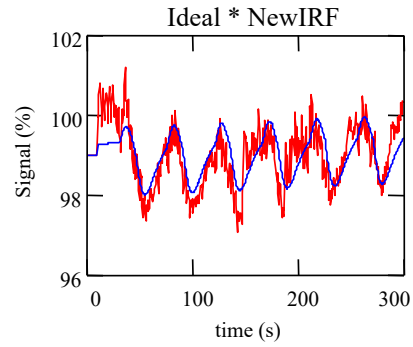
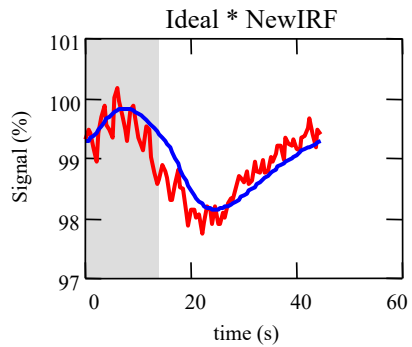
Rate



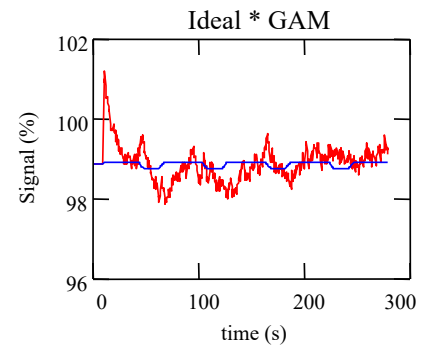
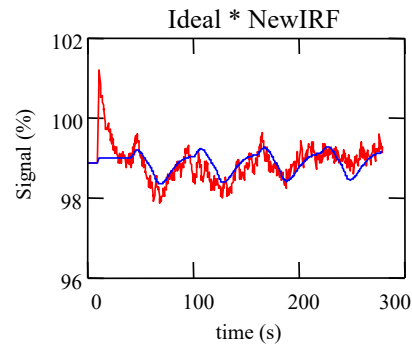
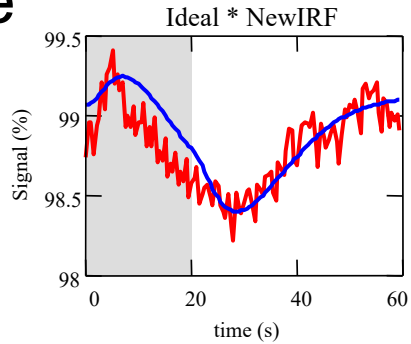
Breath-hold



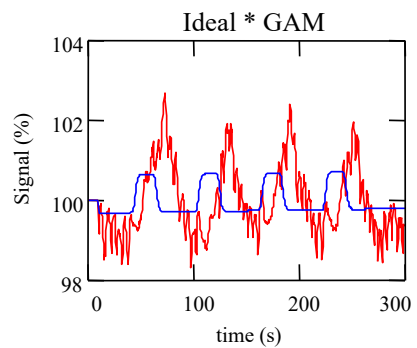
Depth



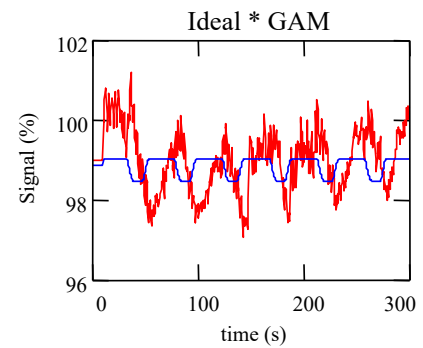
Rate



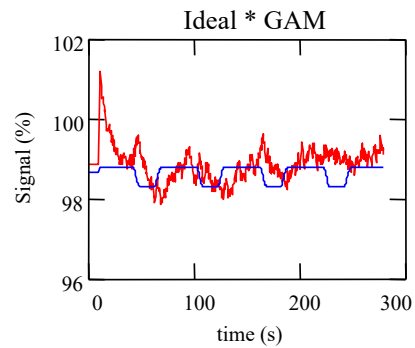
BH



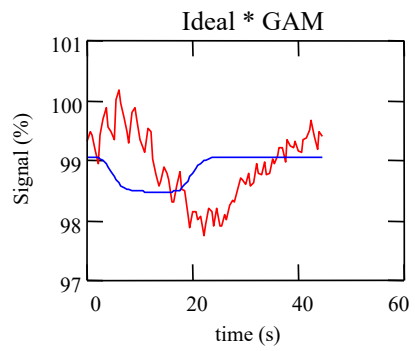
depth



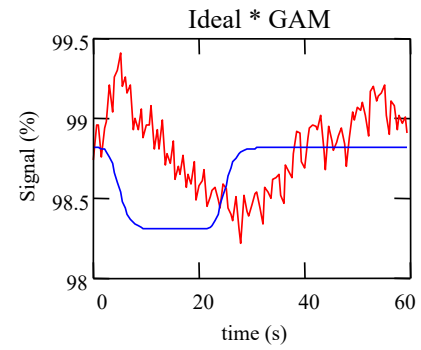
rate



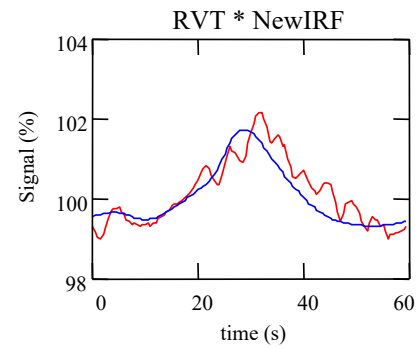
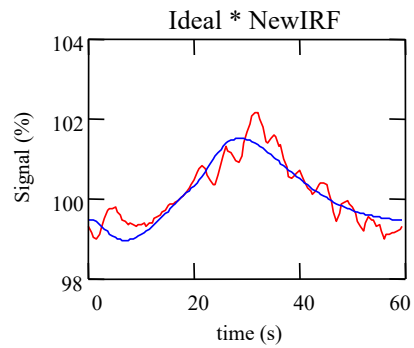
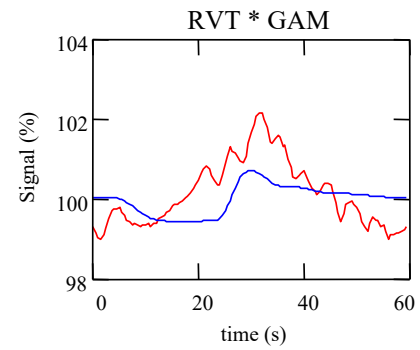
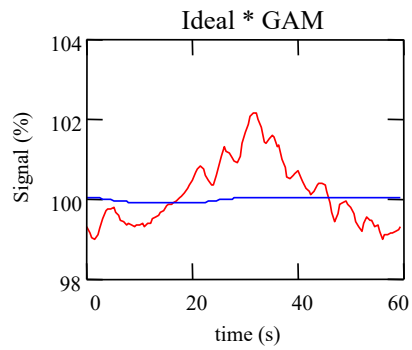
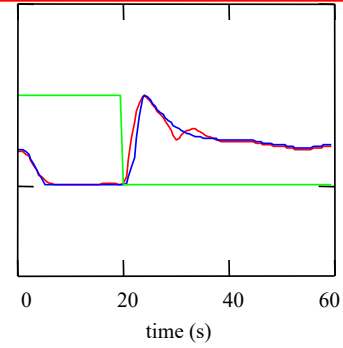
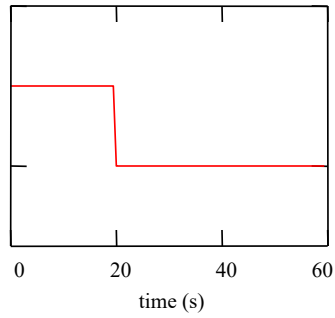
Depth



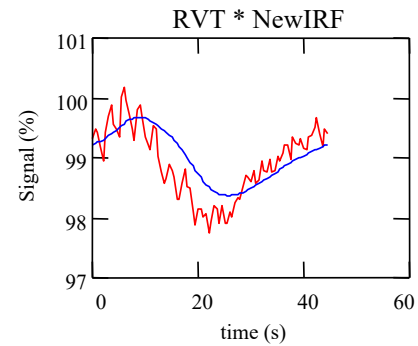
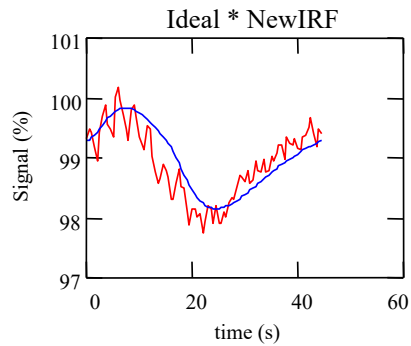
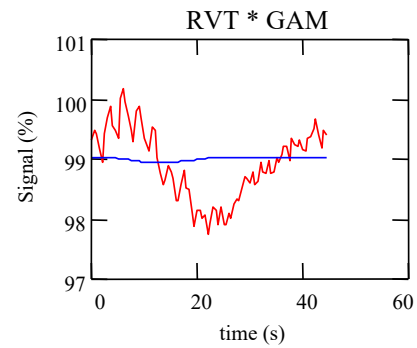
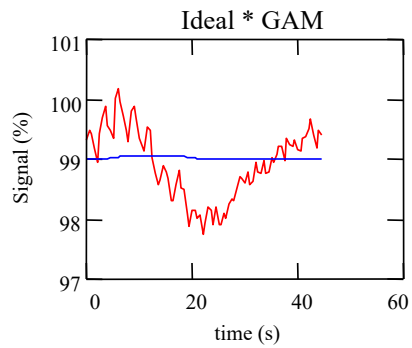
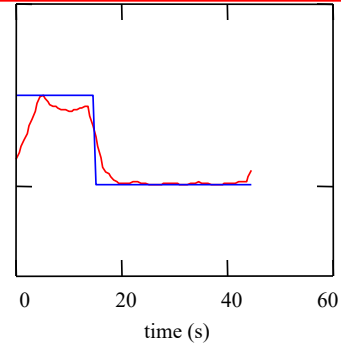
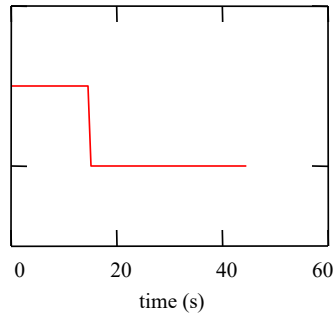
Rate



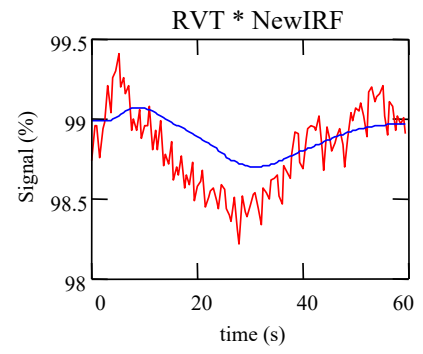
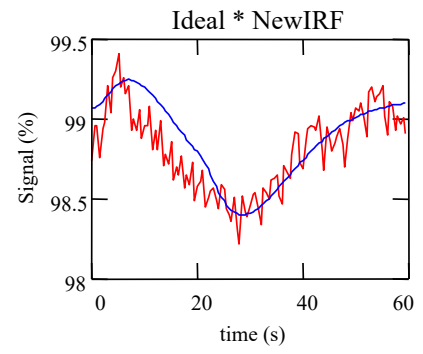
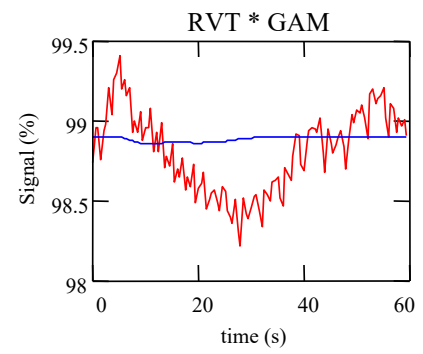
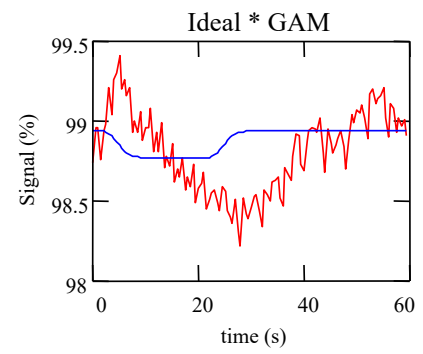
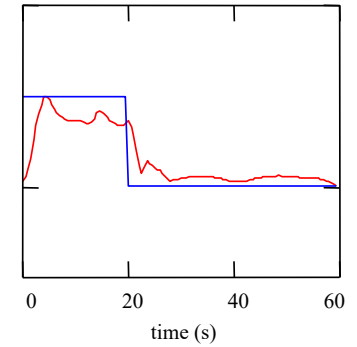
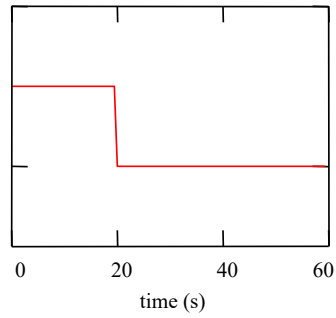
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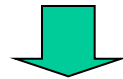
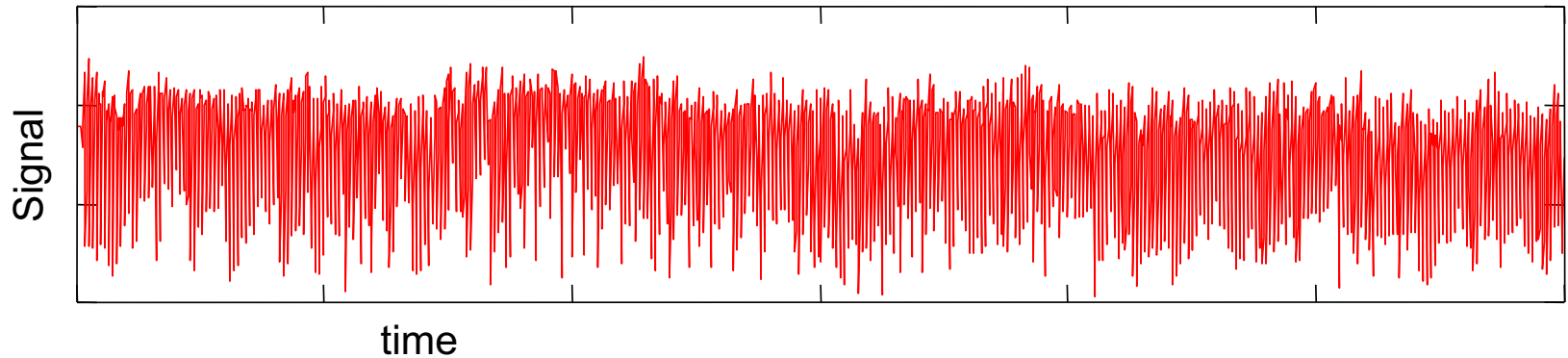
Depth



Rate



Correction of physiological noise



Reshuffle the data based on its cardiac or respiration phase

