PHYSIOLOGICAL NOISE IN PHARMACOLOGICAL RS-FMRI

Najmeh Khalili-Mahani, PhD
najma@bic.mni.mcgill.ca

No conflict of interest to declare

Netherlands Organisation for Scientific Research
Physical Sciences

Outline and Learning Objective

- ❑ Physiological Noise
- ❑ Physiological Signals
- ❑ Correction Methods

- ❑ What can we learn from pharma RSfMRI?
- ❑ How and why is calibrated fMRI necessary?

Physiological "noise"

- Quasi-periodic variations in the BOLD signal due to
  - Respiration = 0.3 Hz
  - Cardiac = 1 Hz
- Typical EPI sampling rate 1-3 sec => Complex Aliasing
- Account for 10-40% of BOLD signal variations
- Can drown minute (5%) BOLD responses in fMRI (Birn, 2006; Dagli 1999)

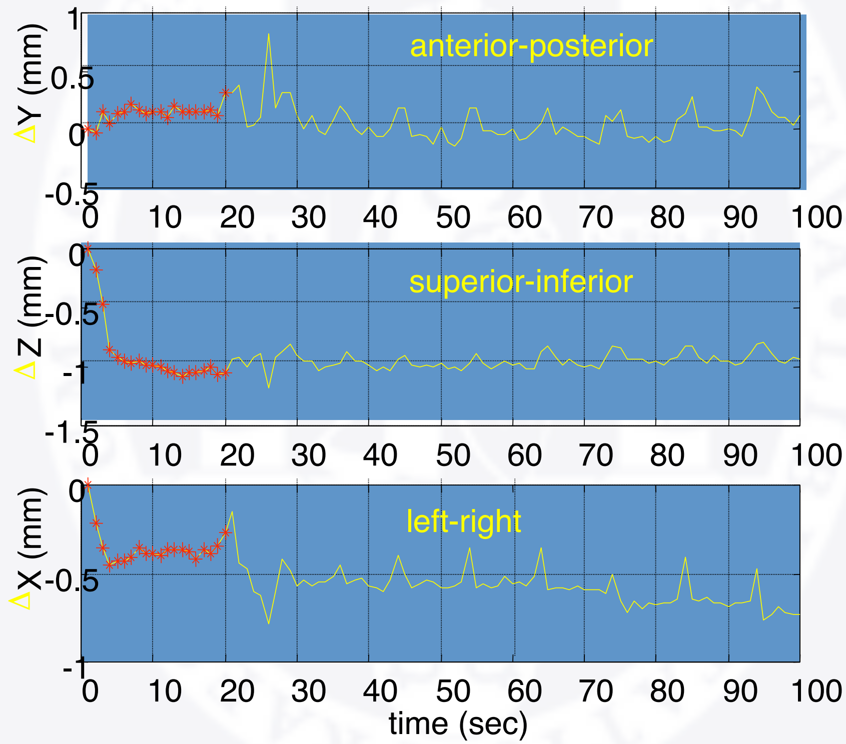
Pathways of Effect

- Motion related effects
- Intra-thoracic volume
- CBF autoregulation
- Cardiac pulsation
- ANS & CNS correlates of interoception & motor function

Pathways of Effect

- **Motion related effects**
- **Intra-thoracic volume**
- **CBF autoregulation**
- **Cardiac pulsation**
- **ANS & CNS correlates of interoception & motor function**

Breathing-related head movement detected using 3D orbital navigator echoes



Khalili-Mahani & Pike

Pathways of Effect

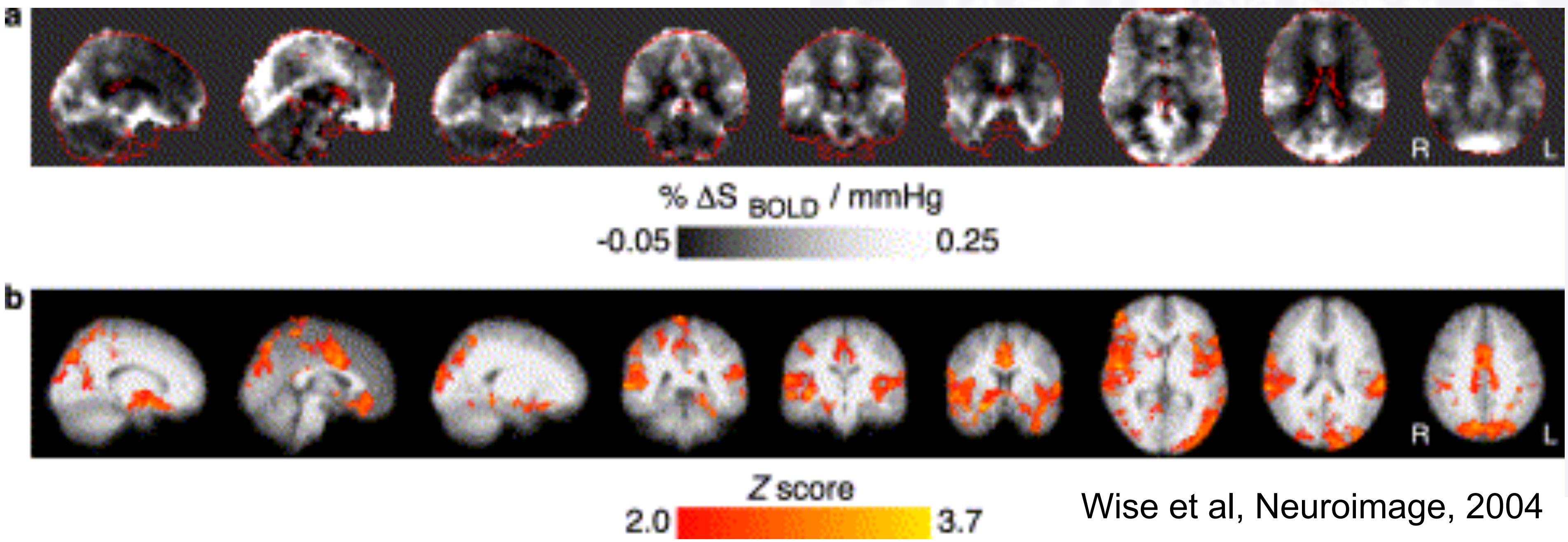
- Motion related effects
- Intra-thoracic volume
- CBF autoregulation
- Cardiac pulsation
- ANS & CNS correlates of interoception & motor function

- Magnetic susceptibility artifacts (Raj, 2001)
- Then why does changing the readout direction not change the topography of the effect? (Windischberger, 2002)

Pathways of Effect

- Motion related effects
- Intra-thoracic volume
- **CBF autoregulation**

- Change in perfusion pressure by intra-thoracic pressure
- Change in perfusion by arterial Co2 tension

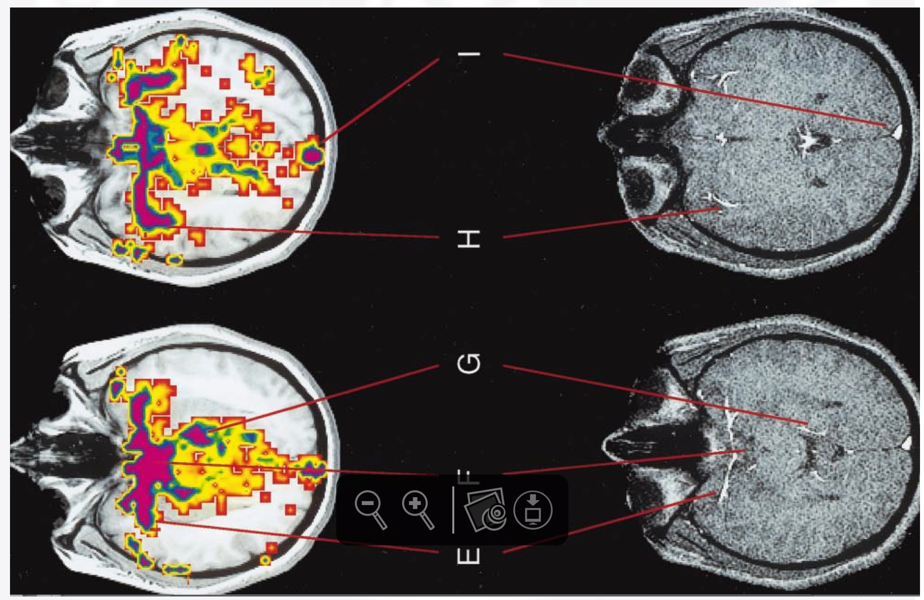


Wise et al, Neuroimage, 2004

Pathways of Effect

- Motion related effects
- Intra-thoracic volume
- CBF autoregulation
- Cardiac pulsation
  - inflow enhancement
  - dephasing
  - vessel-wall motion
  - **Effects are dominant around the cerebral arteries**

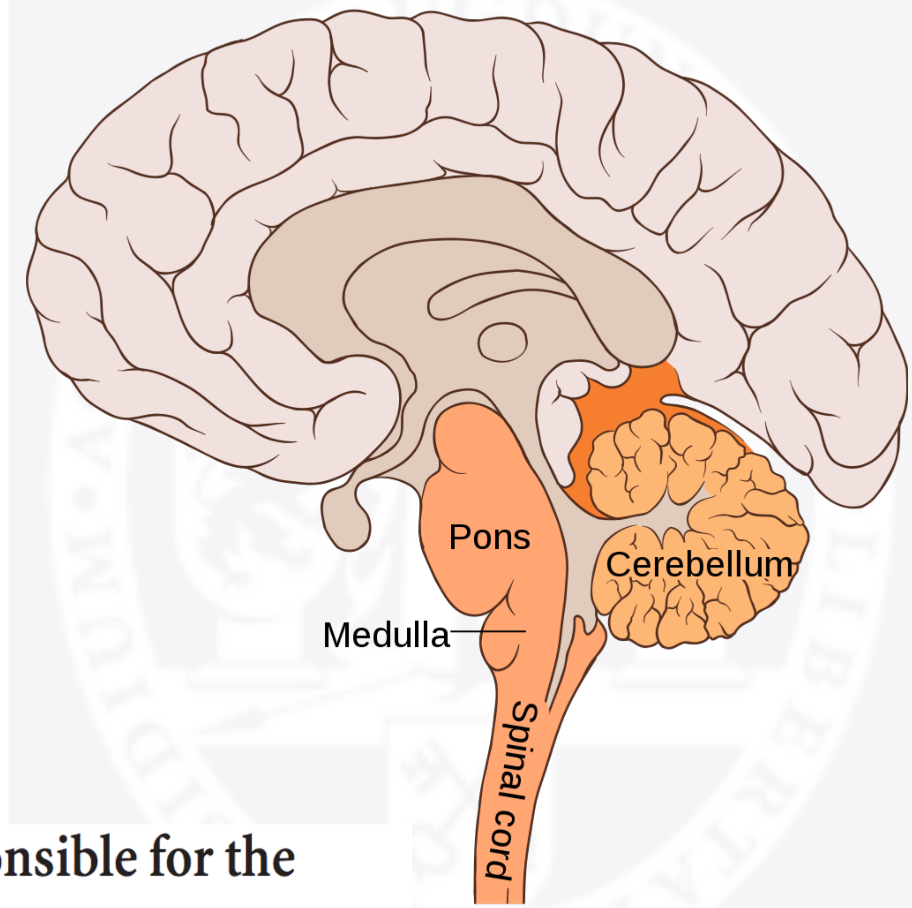
27% of all brain voxels affected by more than 4% of BOLD signal variations



Dagli, 1999

Pathways of Effect

- Motion related effects
- Intra-thoracic volume
- CBF autoregulation
- Cardiac pulsation
- ANS & CNS correlates of interoception & motor function



Opioids Depress Cortical Centers Responsible for the Volitional Control of Respiration

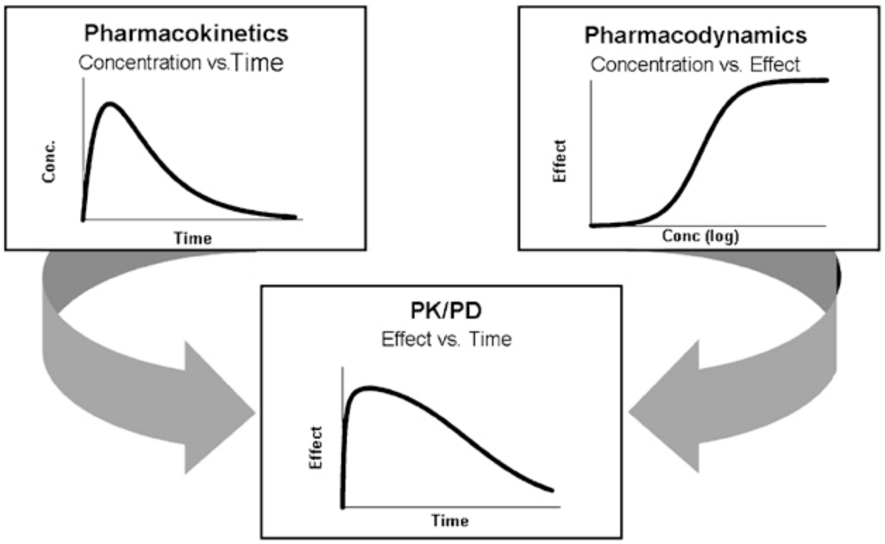
Kyle T. S. Pattinson,[1,2] Ricardo J. Governo,[2,3] Bradley J. MacIntosh,[2] Elizabeth C. Russell,[1,2] Douglas R. Corfield,[4] Irene Tracey,[1,2] and Richard G. Wise[2,5]

Everyone's noise

Pharmacologist's & Anesthetist's signal

Pharmacological Studies

- PK/PD modeling



TRANSFER FUNCTION

- Calibrated fMRI & ASL estimation follow the same principle

- Pharmacokinetic, PK
  - Plasma concentration of drug (morphine, Co2, O2, caffeine) in blood or tissue compartments /time

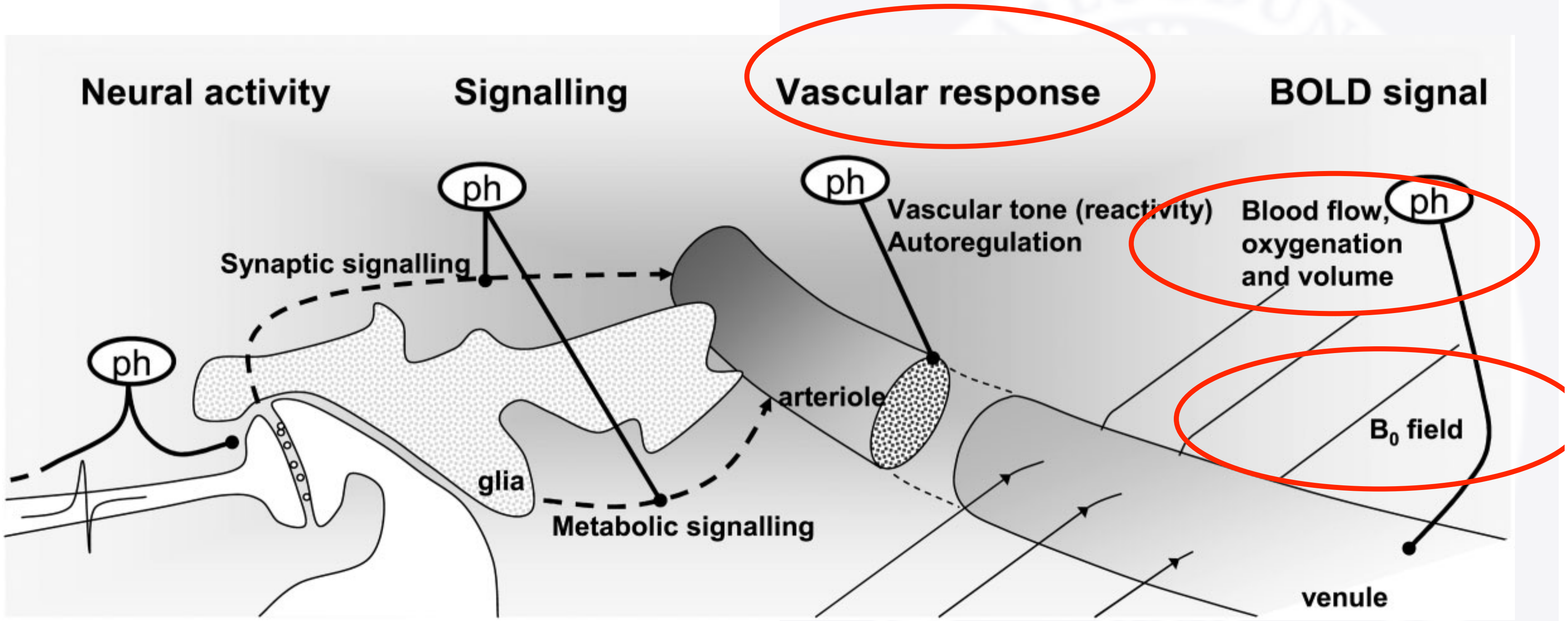
- Pharmacodynamic, PD
  - Response over time
    - Physiological change
    - Behavioral change
    - Therapeutic effects

CNS-Drug Action Pathways

- Direct drug effects on the brain
  - Cross the BBB
  - Target receptors
  - Neuromodulate

- Indirect
  - Peripheral afferents
  - Endocrine cascades
  - Autoregulation

Points of Interaction



Wise & Tracey, *JMRI,* 2006

Physiological ‘noise’ in Pharma

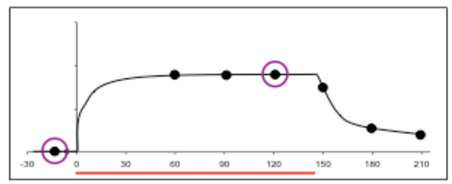
Can we remove it?

Should we remove it?

12 Healthy young men, 3 says, 7 RSfMRIs per person

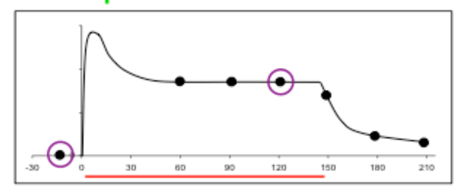
subject	S1,S2	S3,S4	S5,S6	S7S,S8	S9,S10	S11,S12
DAY1	A	A	P	P	M	M
DAY2	M	P	M	A	P	A
DAY3	P	M	A	M	A	P

Alcohol

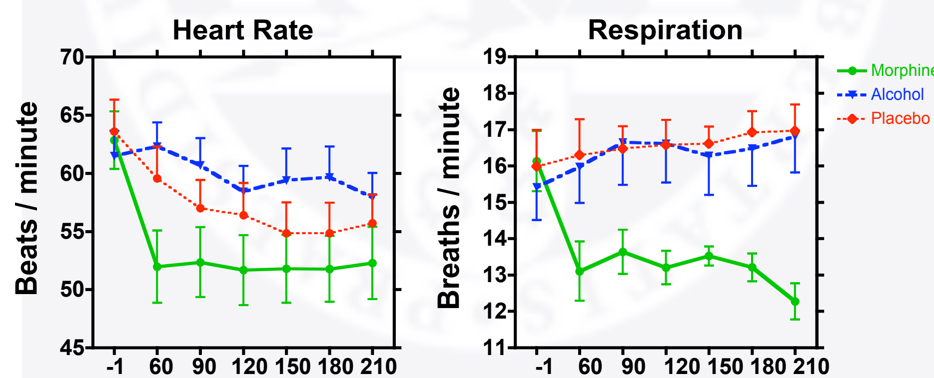


stable level of alcohol (0.6 g/L)
infusion rate ~ breath ethanol

Morphine



stable level of morphine (80 nmol/L)
bolus + continuous infusion



Objective of the Study

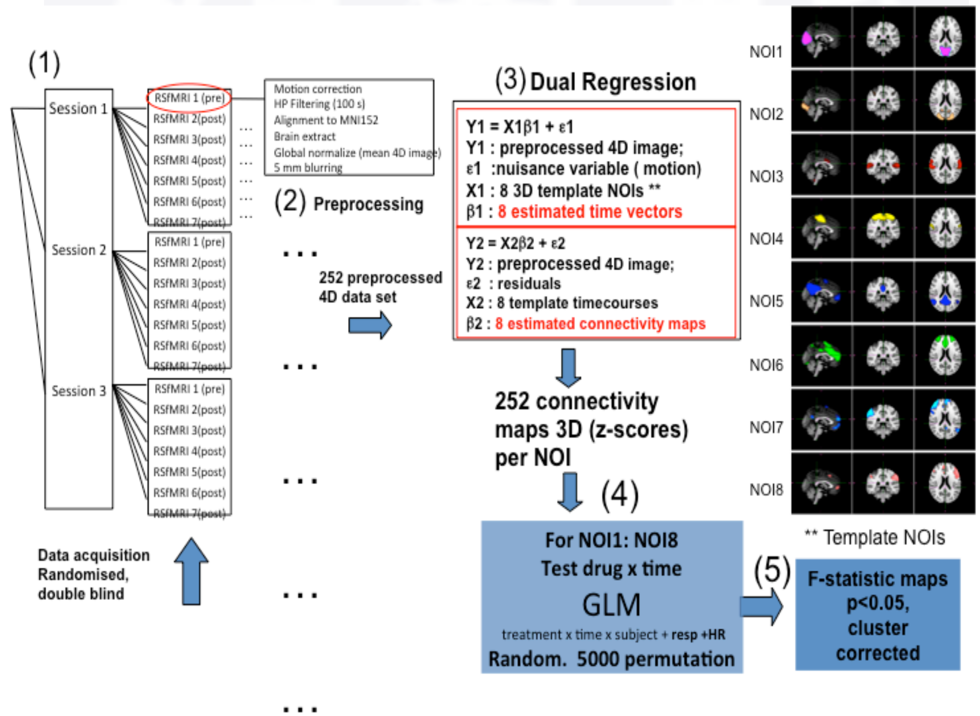
- Measure the correlated variance in the spontaneous BOLD signal

- Effects of correction on statistical outcome

All analysis are NOI-based dual regression

♦ Human Brain Mapping 33:1003–1018 (2012)

Effects of Morphine and Alcohol on Functional Brain Connectivity During "Resting State": A Placebo-Controlled Crossover Study in Healthy Young Men



Khalili-Mahani et al 2011

L U
M C

Respiration Correction Methods

CORRECTIVE PREPROCESSING
- RETROICOR — Glover et al, 2000
- RVHRCOR — Chang et al, 2009

CONNECTIVITY ESTIMATION
- RVcorr
- WM, CSF — Birn, 2012

GROUP STATISTICS
- Dominant respiration harmonic
- Avg Heart rate

ELSEVIER

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

The impact of "physiological correction" on functional connectivity analysis of pharmacological resting state fMRI

Najmeh Khalili-Mahani [a,b,c,*], Catie Chang [d], Matthias J. van Osch [c,e], Ilya M. Veer [a,b,c], Mark A. van Buchem [a,b,c], Albert Dahan [c,f], Christian F. Beckmann [g,h], Joop M.A. van Gerven [c,i,j], Serge A.R.B. Rombouts [a,b,c]

Respiration Correction Method 1

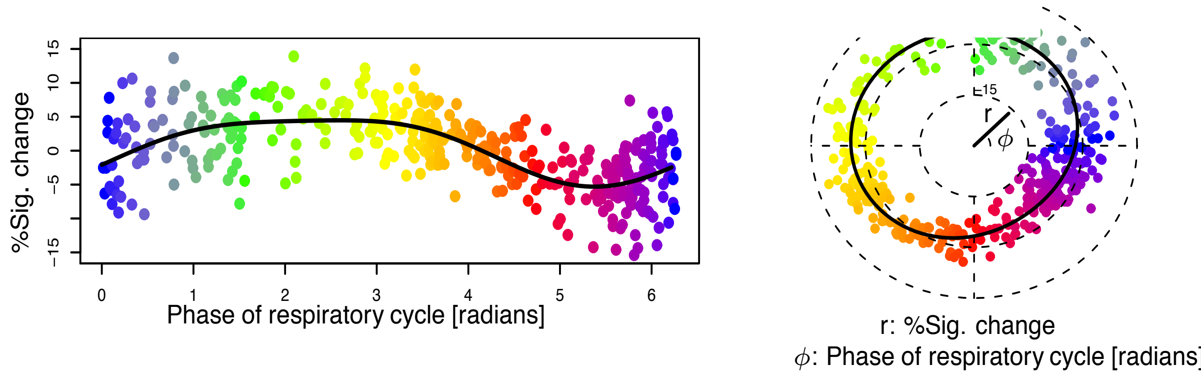
CORRECTION BEFORE ESTIMATING CONNECTIVITY

RETROICOR

RVHRCOR

Glover et al, 2000

Teichert, Grinband, Hirsch & Ferrera, Neuropsychologia, 2010



A priori model of phase

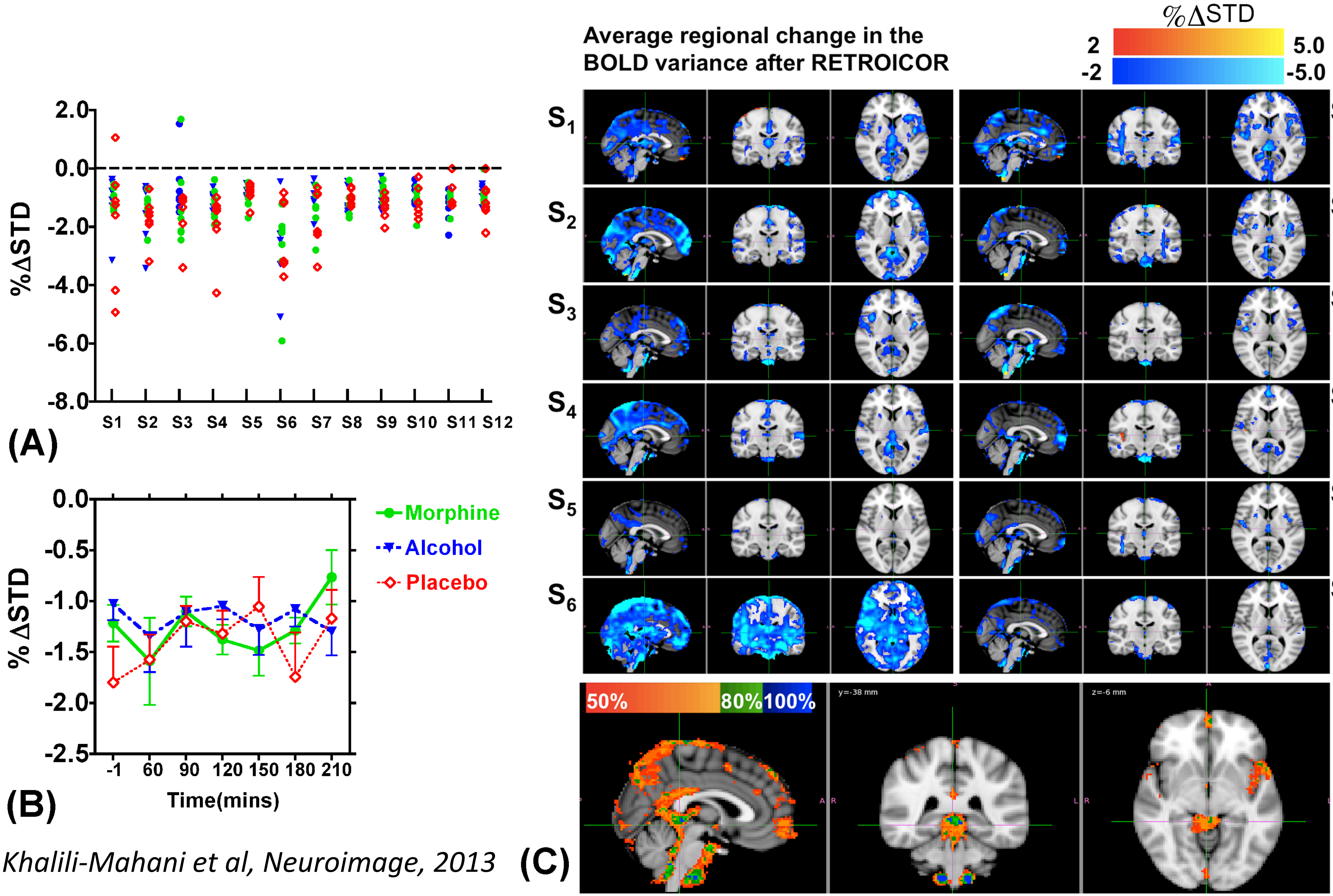
Models physiological noise as a **2nd order Fourier series**

$Noise(slice,t) = \Sigma_{m=1:2}\ a_{resp} Sin(m\ phase_{resp}(t)) + b_{resp} Cos(mphase_{resp}(t)) + a_{card} Sin(m\ phase_{card}(t)) + b_{card} Sin(m\ phase_{cardi}(t))$

$Phase_{card} = 2\pi\ (t\text{-}t1)/(t2\text{-}t1)$

$Phase_{resp}$ = function of depth of breathing)

RETROICOR: Reduces Variance



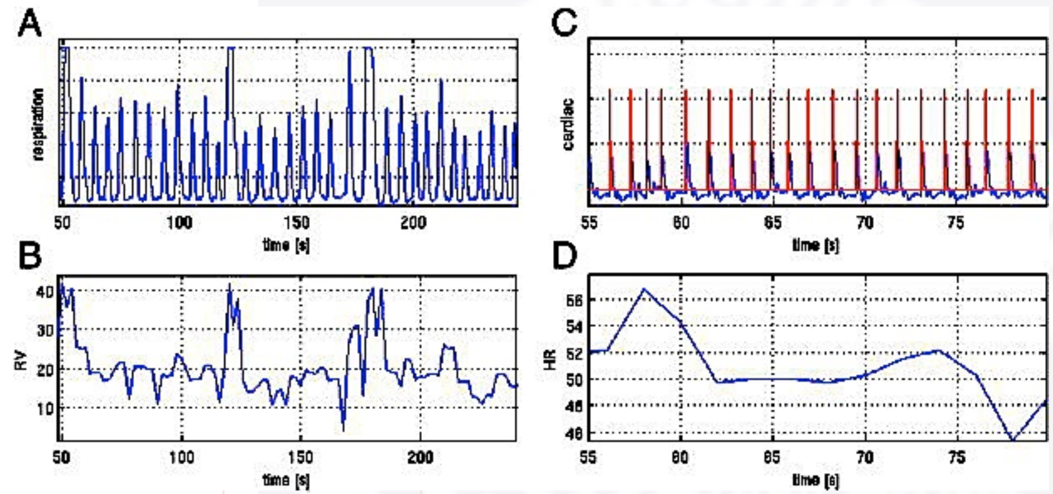
Khalili-Mahani et al, Neuroimage, 2013

Respiration Correction Method 2

CORRECTION BEFORE ESTIMATING CONNECTIVITY

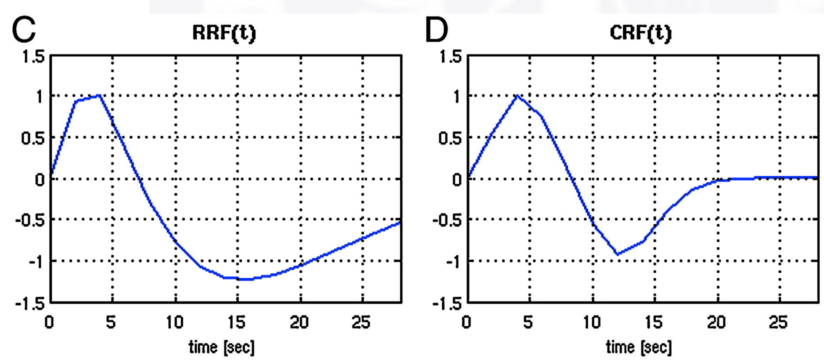
RVHRCOR

Chang et al, 2009

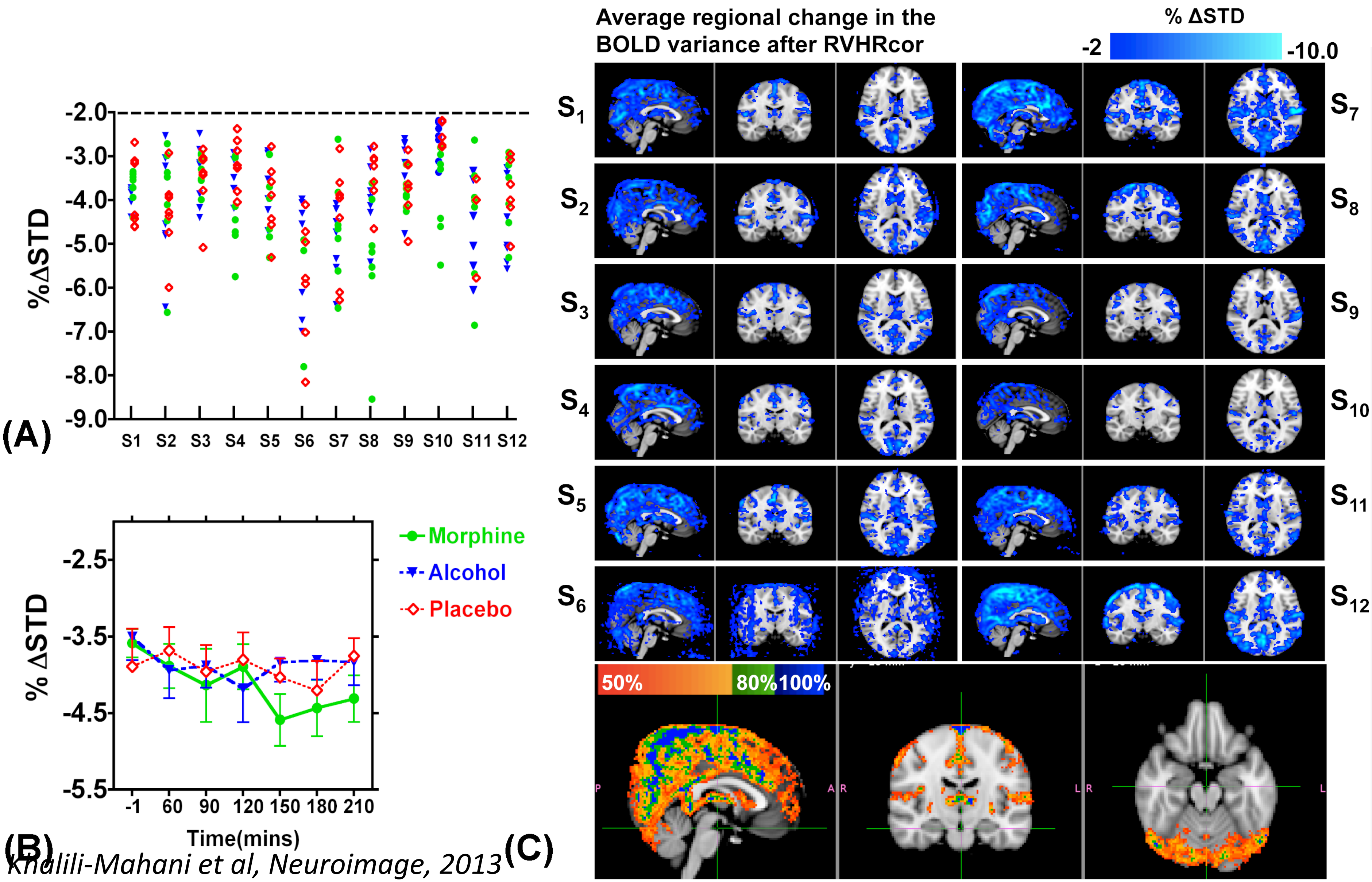


STD(resp) over 6sec window

Mean Δ(t)adjacent ECG triggers over 6 s



RVHRCOR: Reduces Variance

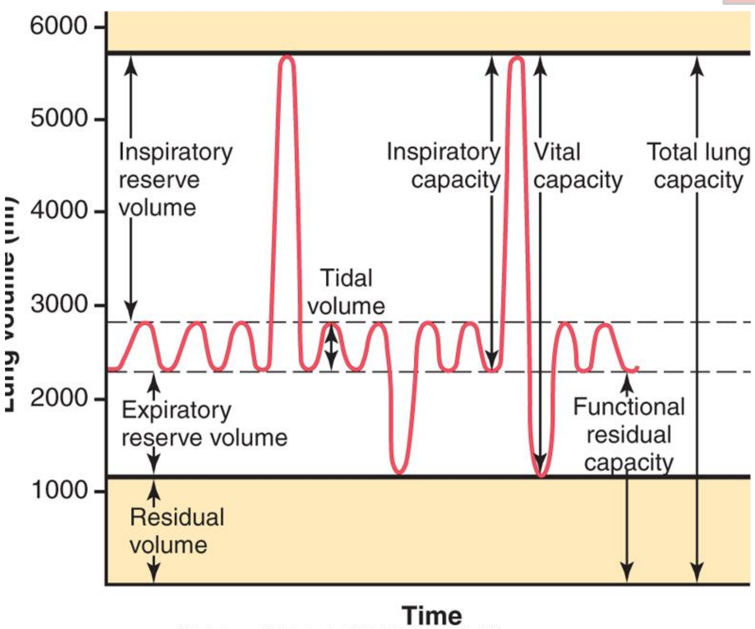


Khalili-Mahani et al, Neuroimage, 2013

Respiration Correction Method 3

CORRECTIVE REGRESSORS TO DUAL REGRESSION

RVcorr



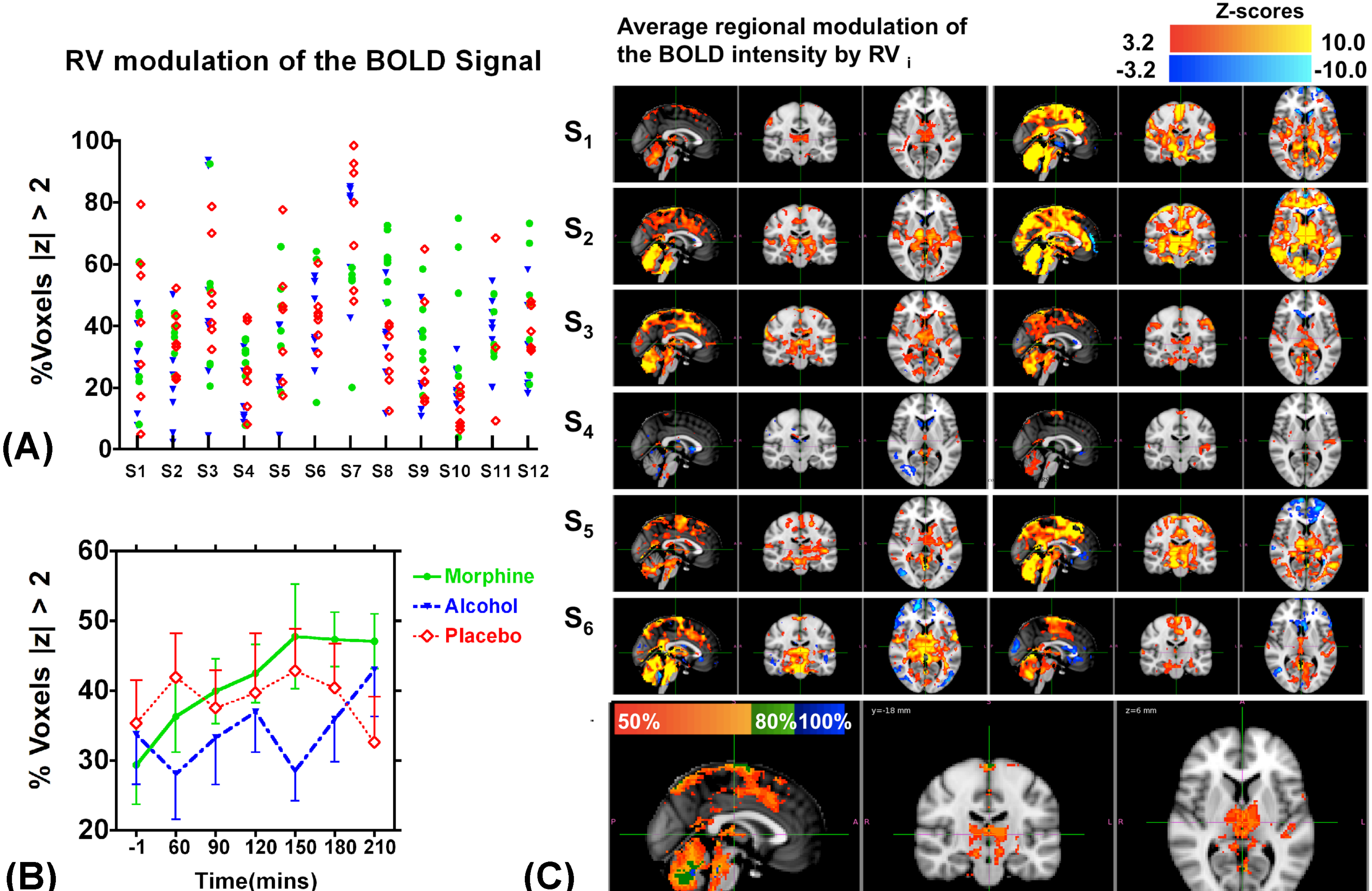
Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

The amount of air inhaled by each breath

- Take Δ min & max peaks of the respiratory waveform
- Divided by the the time between the peaks
- Smooth with a moving average filter that spanned 6 s.

(common to include derivatives & shifts)

Rvcorr: Reveals Correlated Noise



Khalili-Mahani et al, Neuroimage, 2013

Region Specific Residuals

APPLY CORRECTION to RAW data

APPLY REGRESSORS TO DUAL REGRESSION

RETROICOR

RVHRCOR

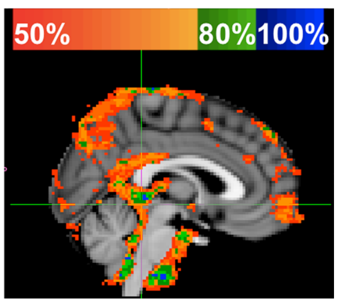
RV

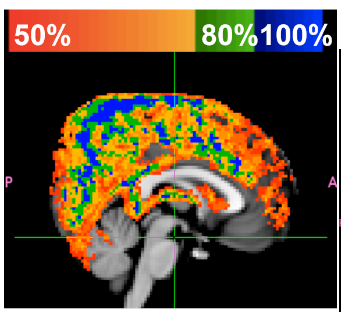
Glover et al, 2000

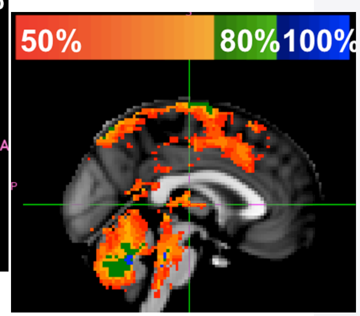
Chang et al, 2009

Birn 2008

Birn, 2012



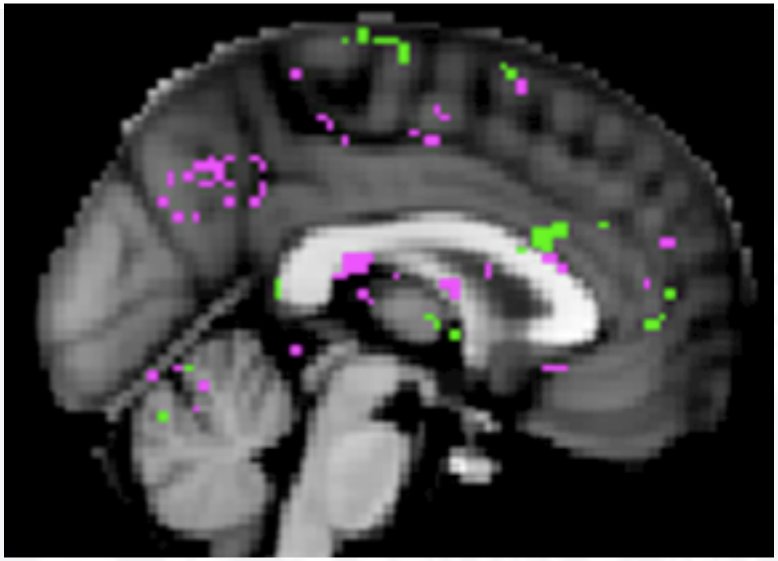




Birn et al, 2006: over 76% of variations in the posterior cingulate explained by respiration

Statistical Outcome Difference

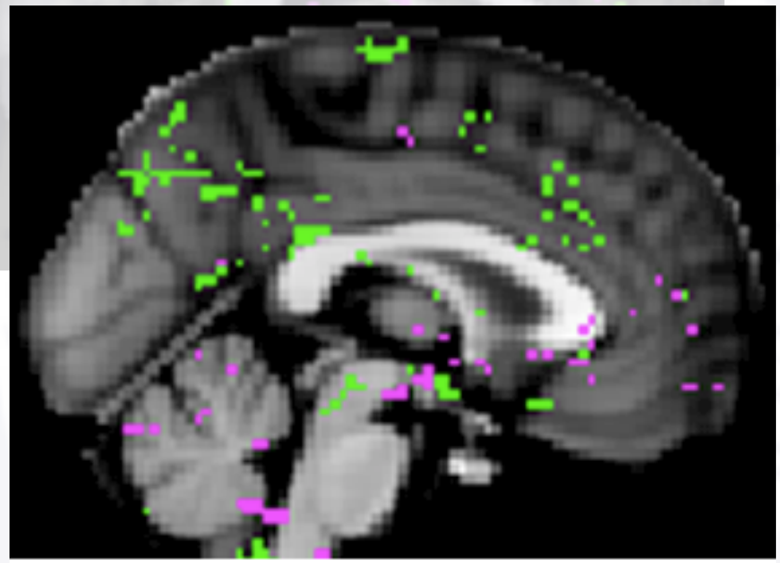
- **RETROICOR**
- Rvcorr
- RVHRCOR



Effects disappear with correction
Effects appear with correction

Statistical Outcome Difference

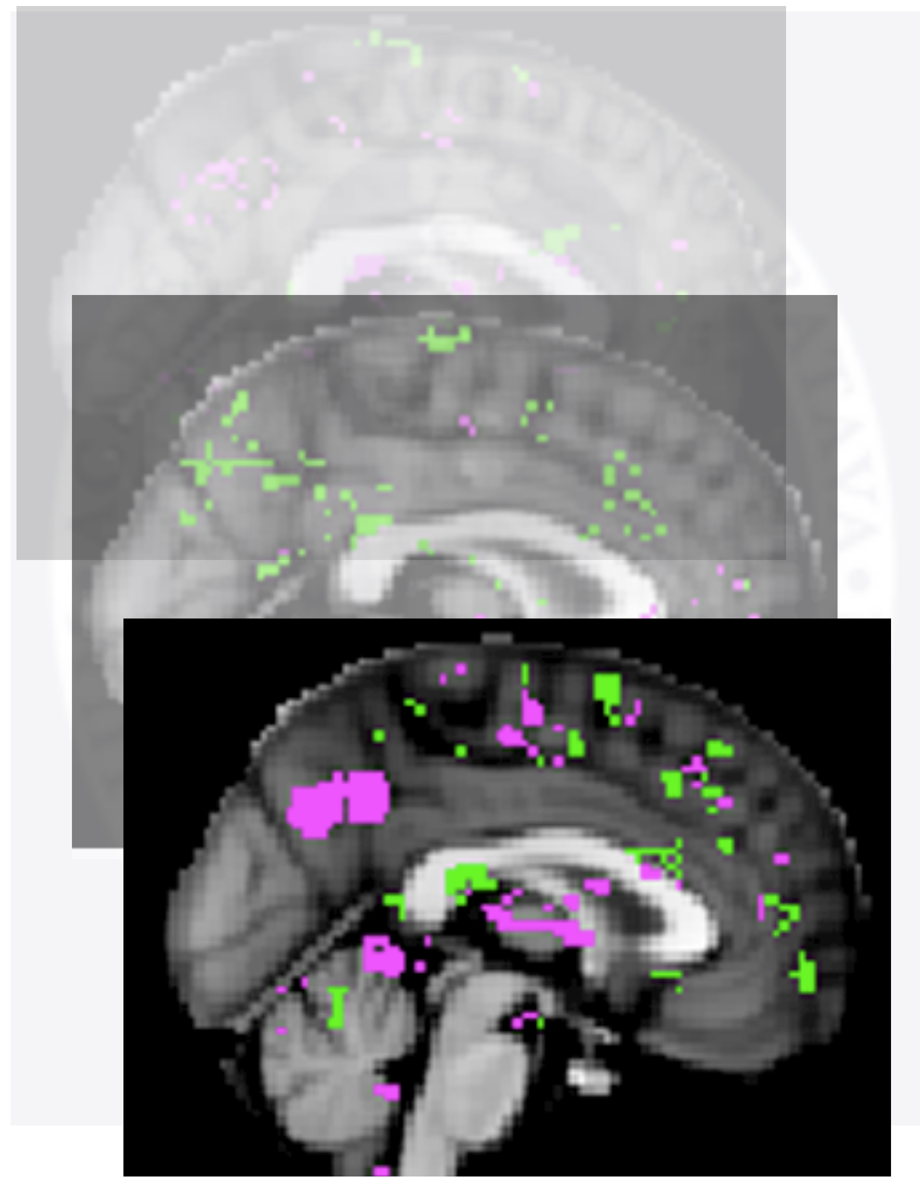
- ❑ RETROICOR
- ❑ Rvcorr
- ❑ RVHRCOR



Effects disappear with correction
Effects appear with correction

Statistical Outcome Difference

- RETROICOR
- Rvcorr
- RVHRCOR



Effects disappear with correction
Effects appear with correction

First Conclusion

- Does the physiological variable explain localized variance in BOLD signal? Yes

- Does noise correction change the statistical outcome of the test? Yes, for RVHRCOR that smoothes the respiration and cardiac pulses with an HRF

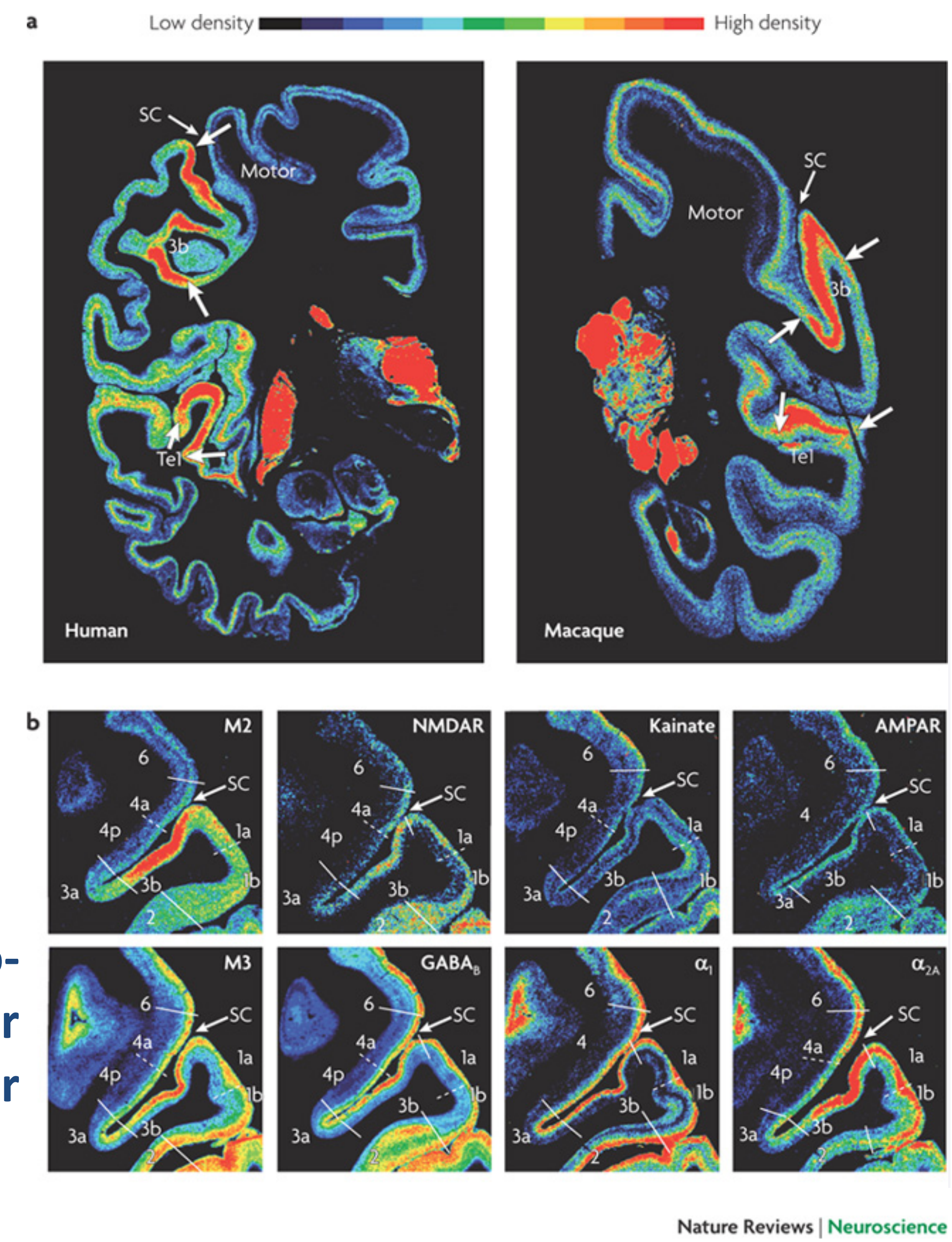
- Is the noise spurious and meaningless? Not really

- We need to separate the neuronal and the vascular components of the physiological effects?

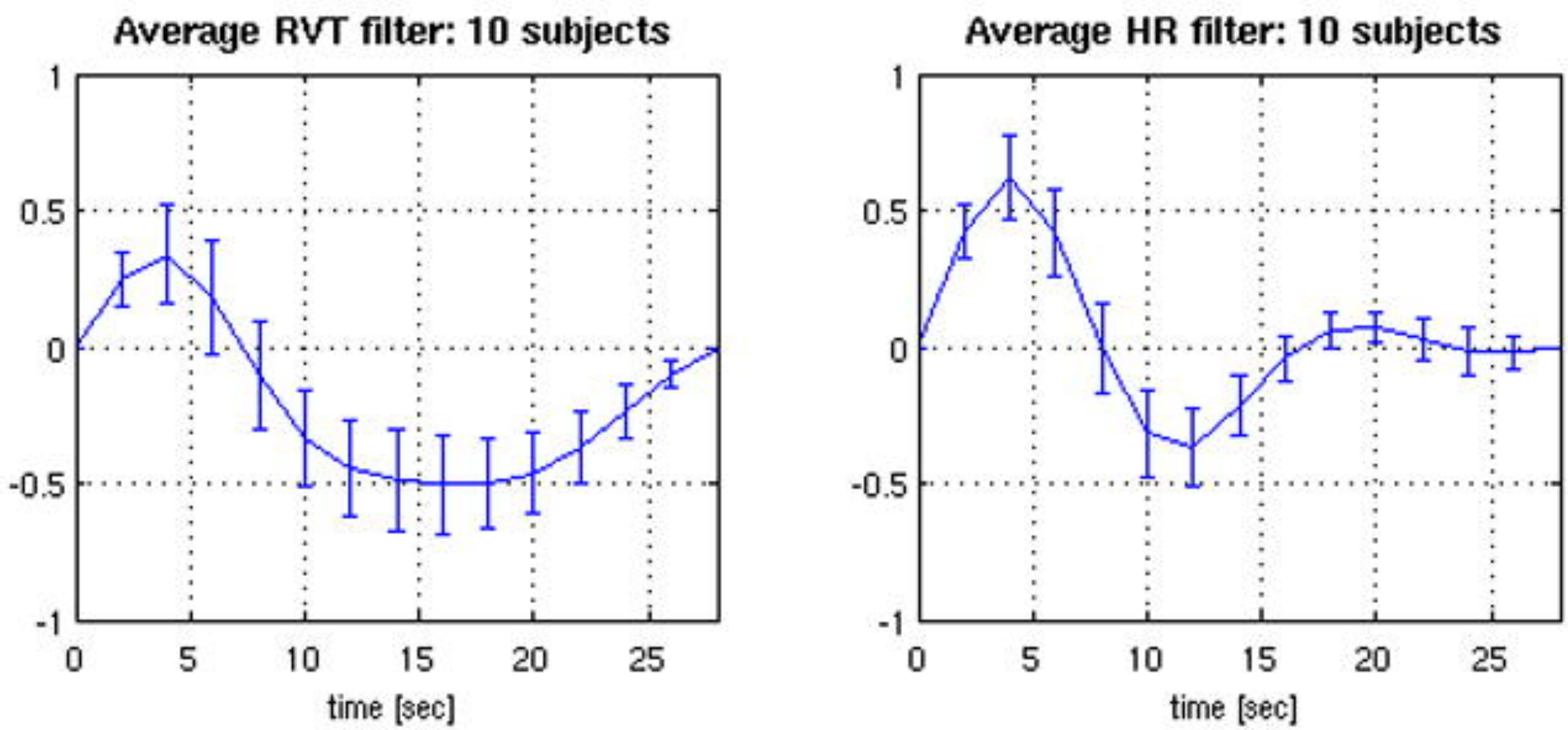
Why do we need calibrated fMRI?

To understand the regional heterogeneity of CBF, metabolism and oxygenation of a drugged brain

Quantitative in vitro receptor auto-radiography of the regional and laminar distribution of neurotransmitter receptors (Zilles & Amunt, 2010)

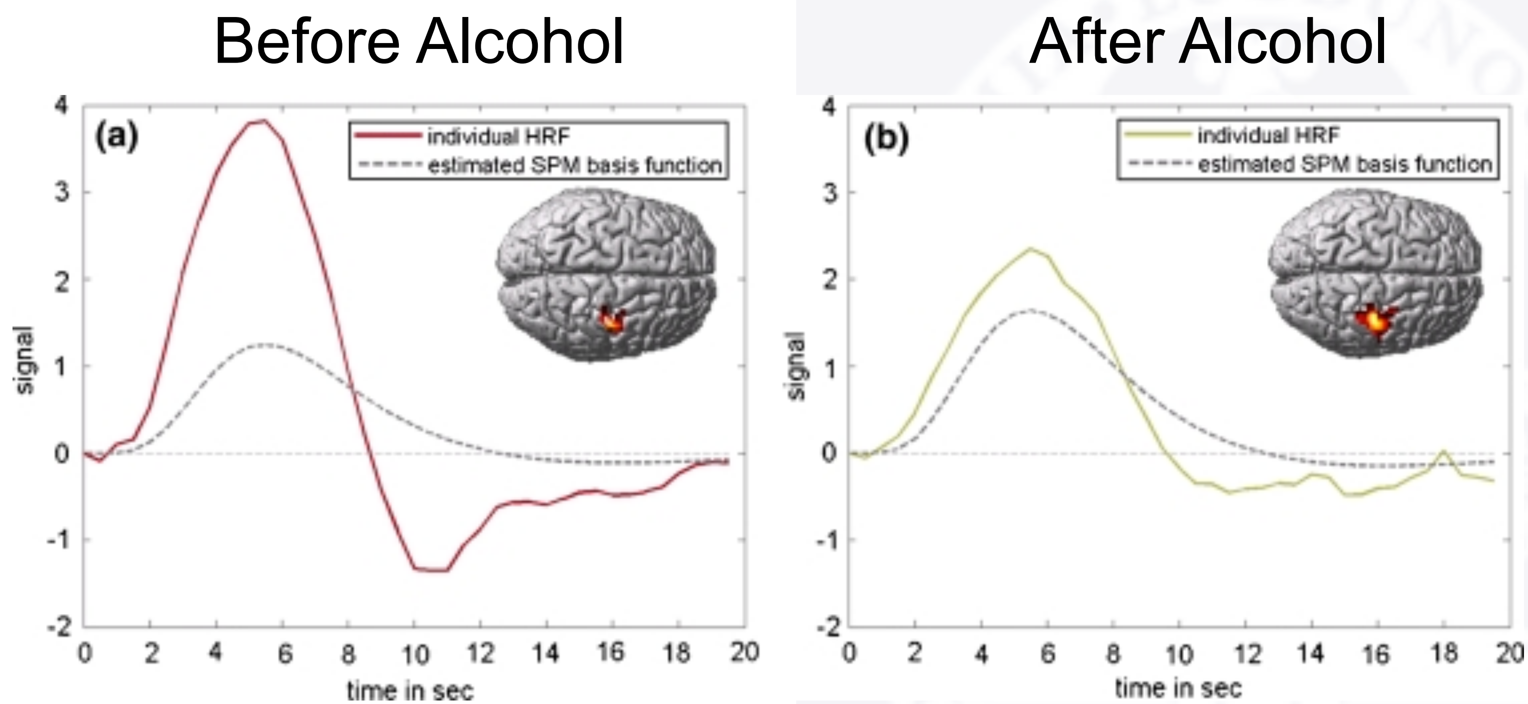


The Canonical HRF in RVHRCOR are not sufficient



"The estimation of an "impulse response function" does make the implicit assumption that the relationship between respiration changes and MRI signal changes is linear." ***Birn, Neuroimage 2009***

Drugs Upset the HRF Linearity

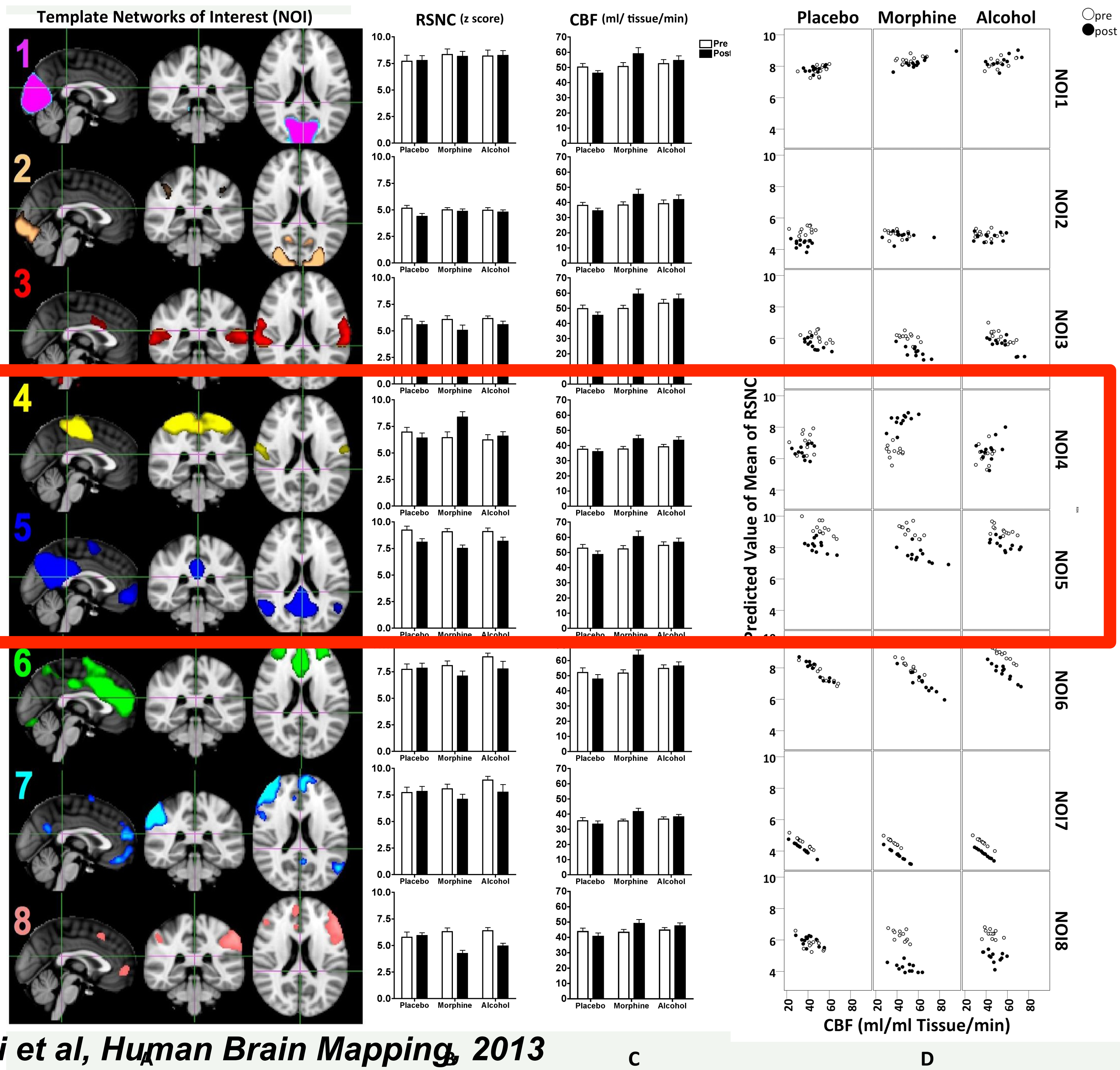


Flickering checkerboard test =>

- **Alcohol led to change in HRF shape (less undershoot)**
- **Variations in HRF were heterogeneous across different brain regions**

Luchmann et al 2010, Exp Brain res

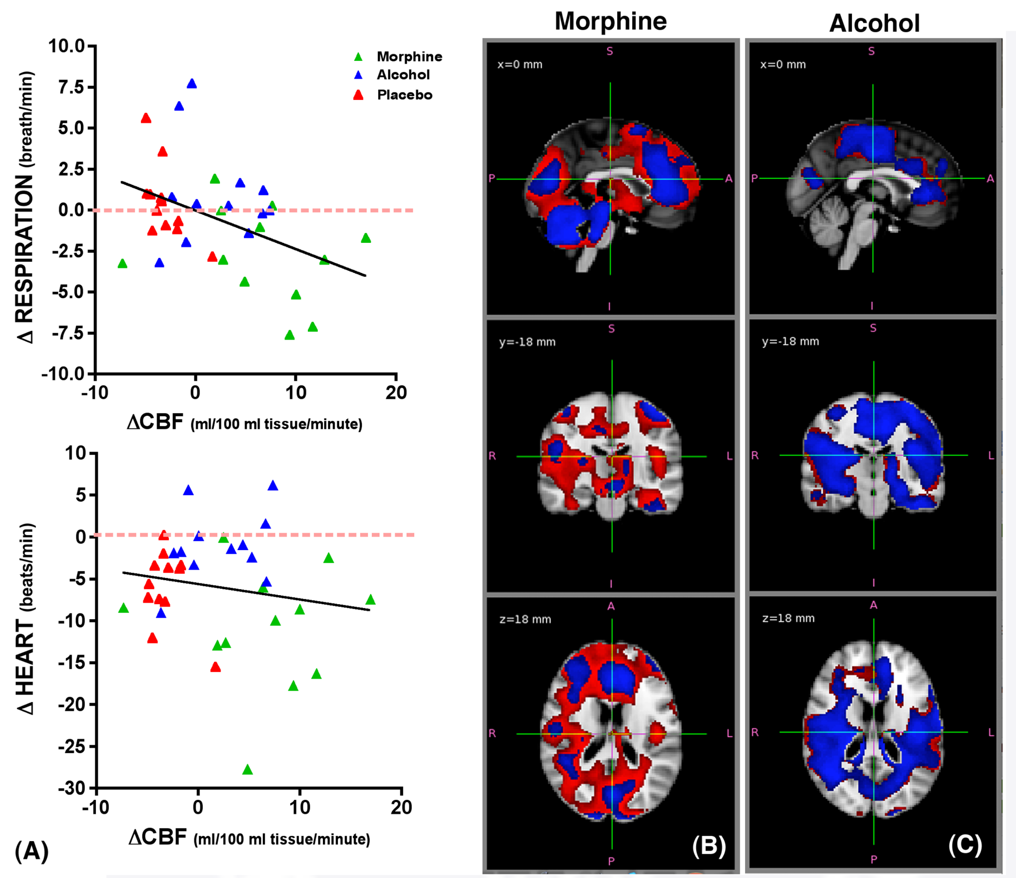
Heterogeneity of drug effects on CBF/RSN correlations



Khalili Mahani et al, Human Brain Mapping, 2013

Global and Regional Perfusion

- Drug-effect on respiration and on the brain share variance
- Respiration modulates cerebral perfusion



JCBFM Open

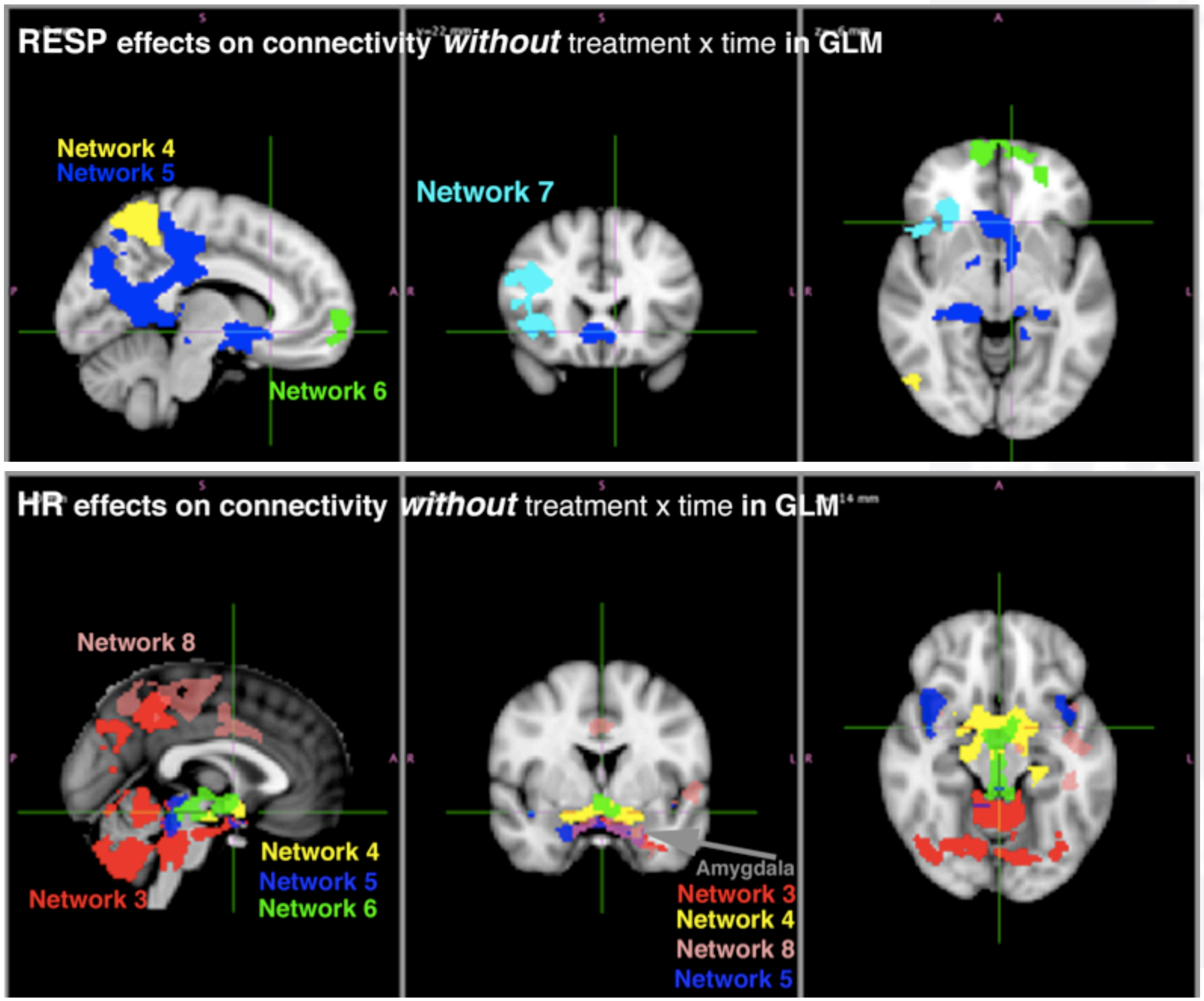
Journal of Cerebral Blood Flow & Metabolism (2011) 31, 1321–1333

www.jcbfm.com

Pseudocontinuous arterial spin labeling reveals dissociable effects of morphine and alcohol on regional cerebral blood flow

Najmeh Khalili-Mahani[1,2,3], Matthias JP van Osch[2,4], Evelinda Baerends[1,2,3], Roelof P Soeter[1,2,3], Marieke de Kam[5], Remco WM Zoethout[5,6], Albert Dahan[6], Mark A van Buchem[1,2], Joop MA van Gerven[5,7] and Serge ARB Rombouts[1,2,3]

Respiration Correction Method 4



APPLY CORRECTION IN THE HIGHEST LEVEL STATISTICAL MODELING

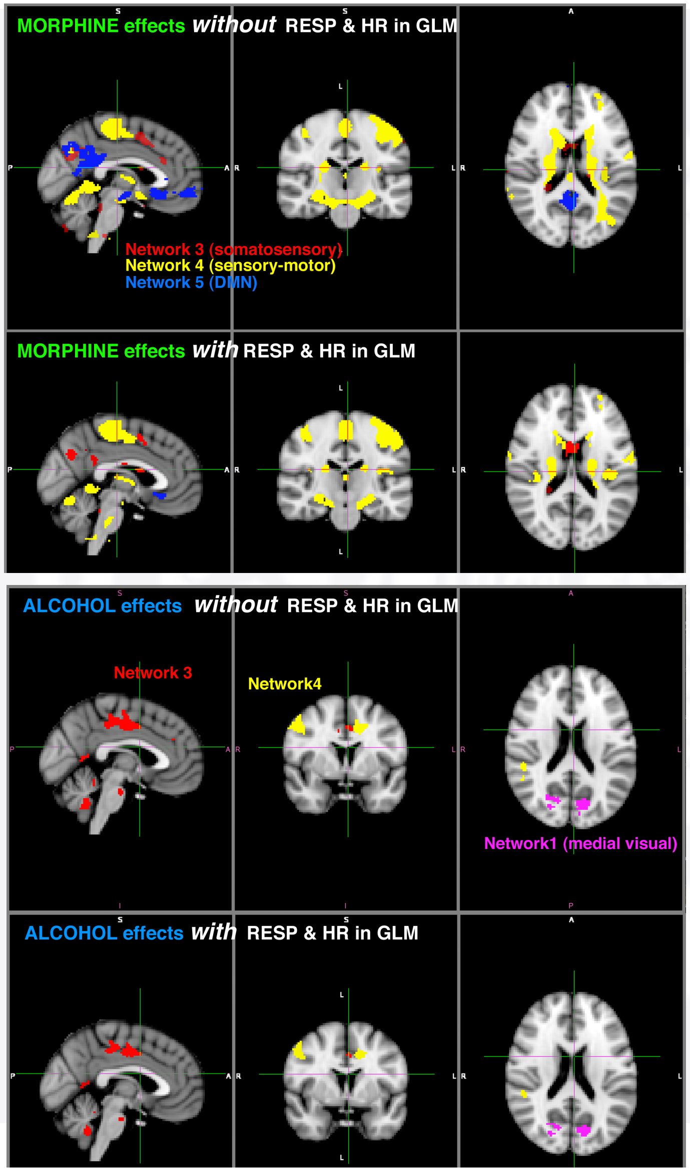
- Dominant respiration harmonic
- Avg Heart rate

Spectral analysis

Statistical Outcome Difference

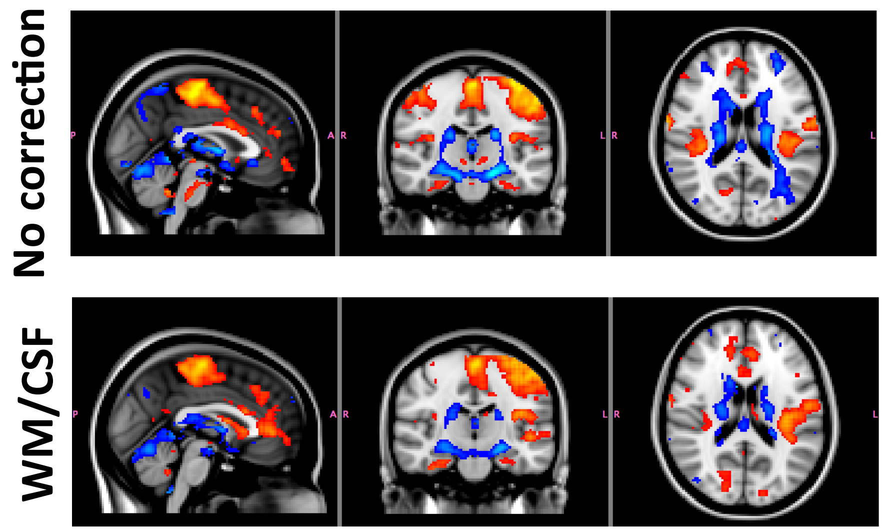
- Physiological rates are also pharmacodynamic endpoints

- Neuroimaging effects are significant only of the physiological rate has changed significantly

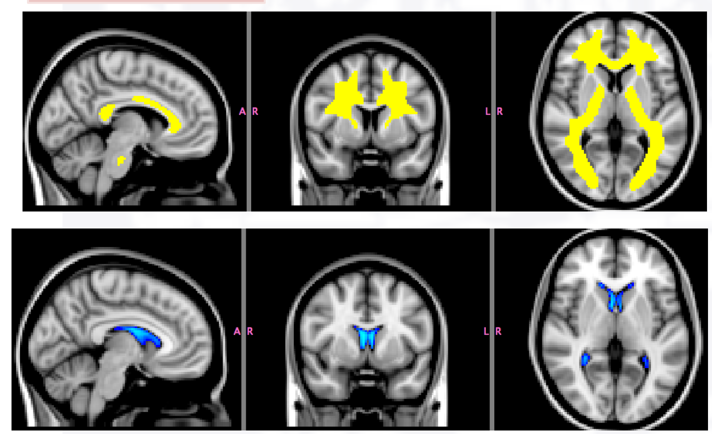


Respiration Correction Method 5

APPLY CORRECTIVE REGRESSORS TO DUAL REGRESSION



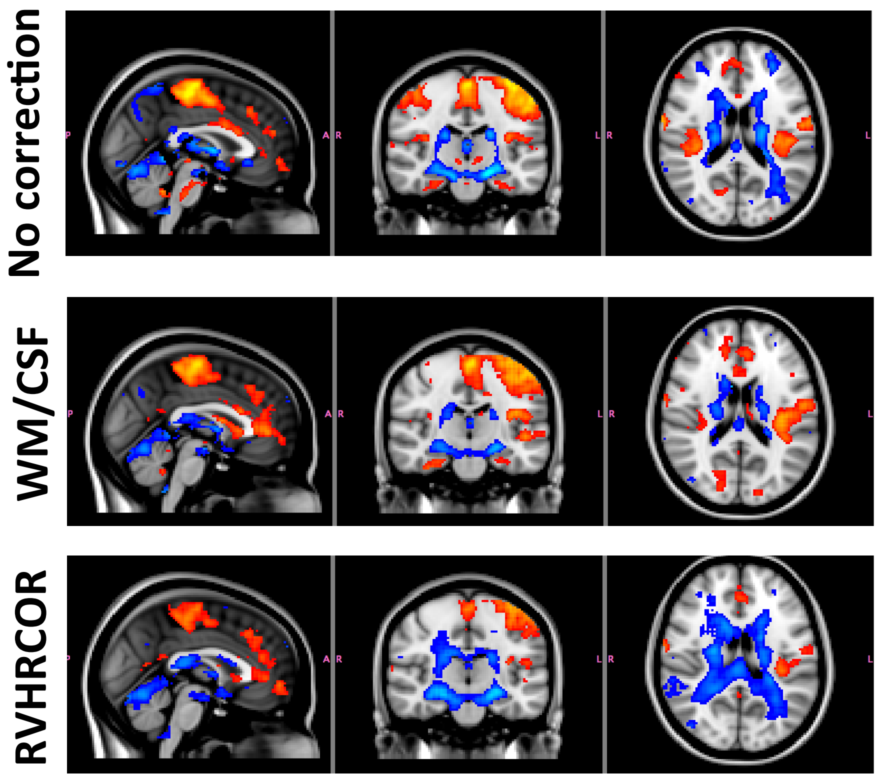
WM, CSF



Respiration Correction Method 5

APPLY CORRECTIVE REGRESSORS TO DUAL REGRESSION

WM, CSF



Second Conclusion

- Drug related change in physiological signals impacts global and regional hemodynamics

- Some brain regions are more sensitive to respiration-related changes in connectivity and flow

- Must we correct for noise or not?

Summary

	Easy to Use	Changes Outcome	Anatomical Residuals	Interpret
RETROICOR	NO	NO	NO	NO
RVHRCOR	NO	YES	YES	NO
RVcorr	NO	NO	YES	Maybe
WM/CSF	**YES**	**YES**	**YES**	**Maybe**
Heart rate	YES	NO	YES	YES
Resp rate	YES	YES	YES	YES

Recommendations

- Exploit noise, don’t eliminate it!
- Mind the flow (and the cerebrovascular architecture)!
- Avoid instrumentation hassles with poor man’s denoising (WM/CSF)
- PCC-seeding is contentious.

LUMC
Thijs van Osch
Albert Dahan
Mark van Buchem
Wouter Teeuwisse
Michele Huijbert

LIBC
Serge Rombouts
Ilya Veer
Mark de Rooij
Evelinda Baerends
Roelof Soeter

FMRIB
Christian Beckmann
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Matthew Webster
Steve Smith
David Cole

CHDR
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Linda Klumpers

Stanford University
Catie Chang

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