Contribution of Systemic Vascular Effects on White Matter BOLD fMRI Signal

#193

Advanced MRI

PS Özbay, C Chang, D Picchioni, H Mandelkow, TM Moehlman, MG Chappel-farley, P van Gelderen, JA de Zwart, and JH Duyn

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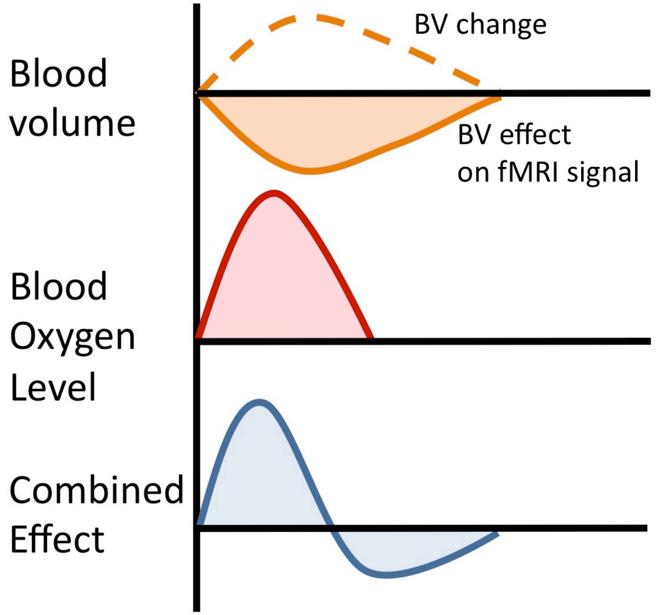
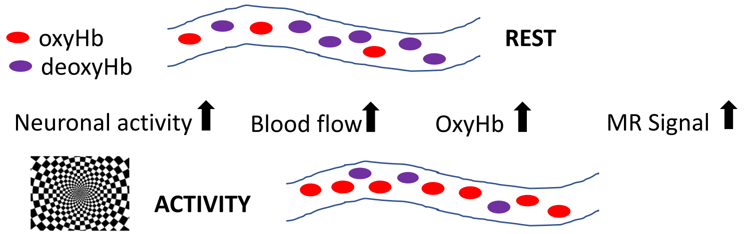
BOLD fMRI

- Typical BOLD fMRI response to a brief, local (neuro) vascular dilatory event results from the combination of a (**negative**) cerebral blood volume and a (**positive**) blood oxygenation effect.
- As the signal results from primarily local blood flow response to changes in neural activity, it is mostly localized to gray matter or to nearby downstream venous vasculature (Turner 2002, Logothetis & Wandell 2004).





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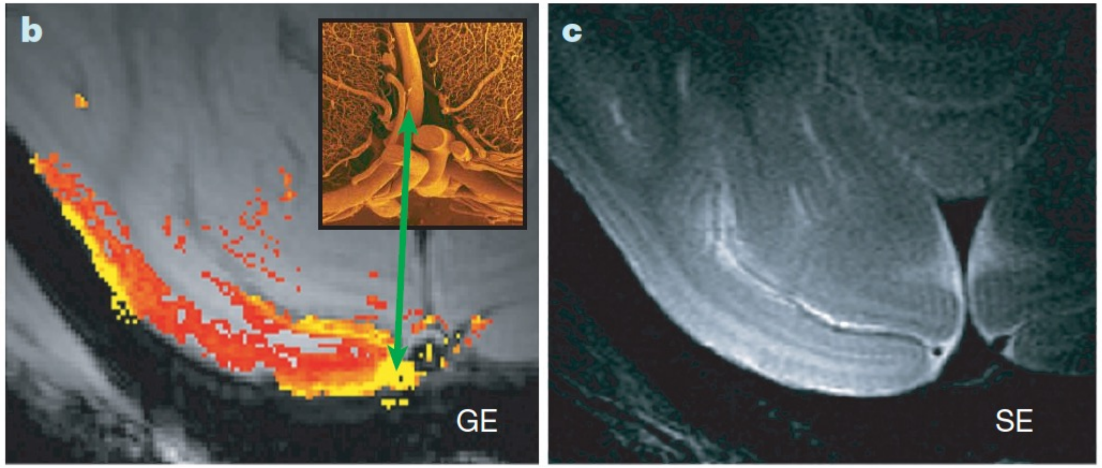

(left) For the functional image red indicates low and yellow indicates high. In-plane resolution 0.3x0.3 mm^2; slice thickness 2 mm. Green arrow shows scanning electron microscopy image of an area of pia vessel. (right) Anatomical scan, SE-EPI.

Logothetis 2008, Nature Reviews

BOLD fMRI – white matter

- Extensive lesion and anatomic studies have implicated the functional significance of white matter in neurological and psychiatric diseases.
- Recent studies have **also** reported the detection of BOLD fMRI signal in WM.
- *A tool to non-invasively investigate the functional dynamics of WM, which could substantially broaden current approaches to study brain connectivity, and may provide considerable insight into WM diseases, such as multiple sclerosis.*

frontiers in NEUROSCIENCE
REVIEW ARTICLE
published: 08 August 2014
doi: 10.3389/fnins.2014.00239

Does functional MRI detect activation in white matter? A review of emerging evidence, issues, and future directions

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[3] Applied Sciences, Simon Fraser University, Burnaby, BC, Canada
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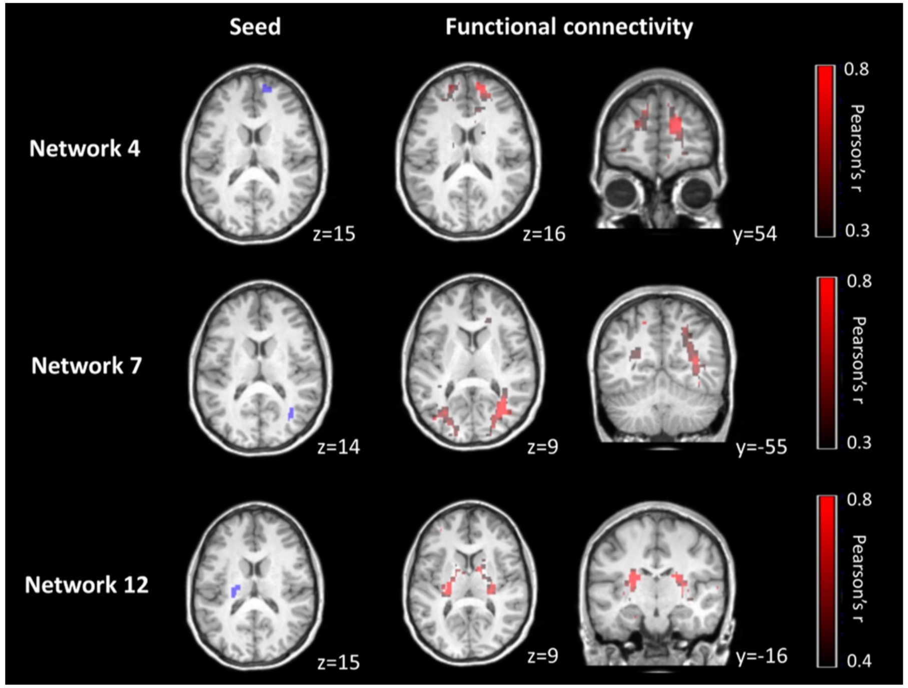
6394 • The Journal of Neuroscience, July 5, 2017 • 37(27):6394–6407

Systems/Circuits

Evidence for Functional Networks within the Human Brain's White Matter

Michael Peer,[1,2] Mor Nitzan,[3,4,5] Atira S. Bick,[2] Netta Levin,[2] and Shahar Arzy[1,2]
[1]Computational Neuropsychiatry Laboratory, Department of Medical Neurosciences, Hadassah Hebrew University Medical School, Jerusalem 91120, Israel, [2]Department of Neurology, Hadassah Hebrew University Medical Center, Jerusalem 91120, Israel, [3]Racah Institute of Physics, The Hebrew University of Jerusalem, Jerusalem 90401, Israel, [4]Department of Microbiology and Molecular Genetics, Institute for Medical Research Israel-Canada, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel, and [5]School of Computer Science, The Hebrew University of Jerusalem, Jerusalem 90401, Israel

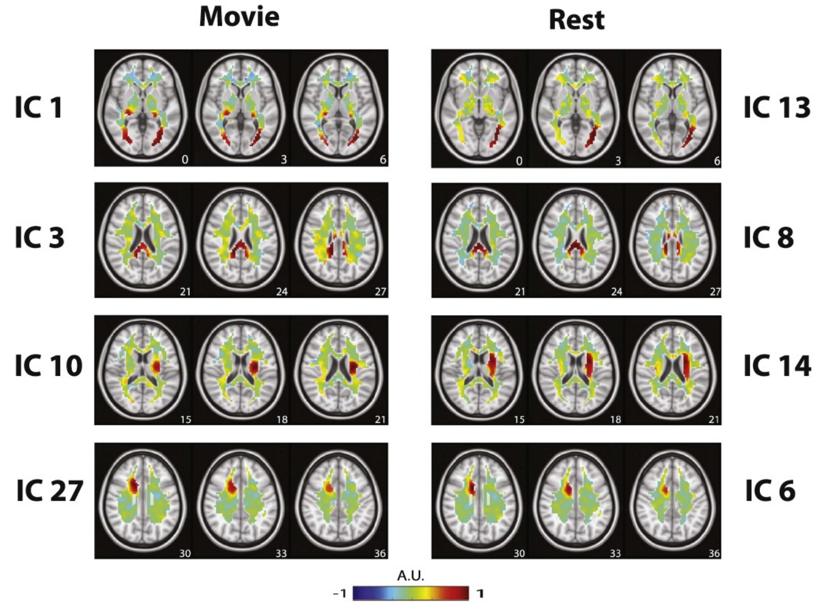


Seed-based analysis in a small group (n=5) identifies the functional networks. Seeds are marked in blue and correlated voxels in red.

NeuroImage 146 (2017) 1128–1141
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/neuroimage

Mapping white-matter functional organization at rest and during naturalistic visual perception

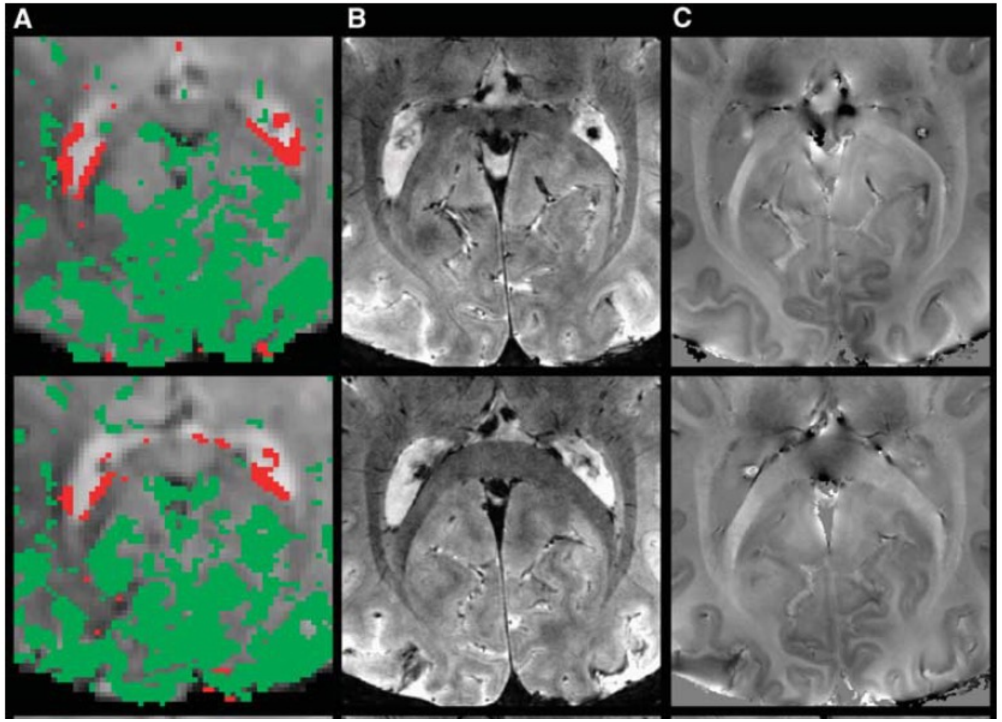
Lauren Marussich[a], Kun-Han Lu[b], Haiguang Wen[b], Zhongming Liu[a,b,c,*]
[a] Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN, USA
[b] School of Electrical and Computer Engineering, Purdue University, West Lafayette, IN, USA
[c] Purdue Institute for Integrative Neuroscience, Purdue University, West Lafayette, IN, USA



Four example pairs of **independent components** obtained from resting-state (right) and task-state (left) are shown.

"WM-fMRI signals are functionally relevant, and hence report, at least in part, neural activity in the WM."

Negative BOLD-fMRI signals in large cerebral veins
M Bianciardi *et al*

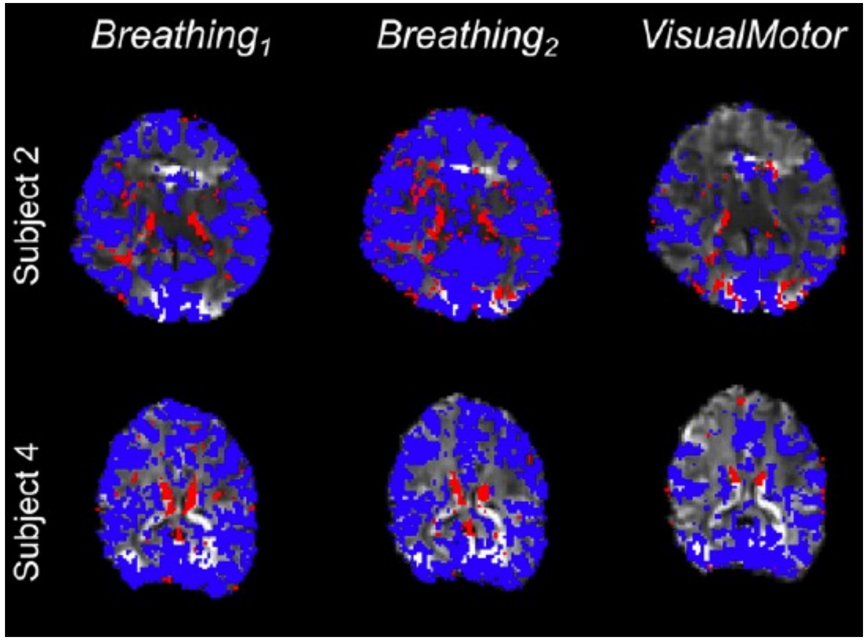


(A) the spatial distribution (red/green) of fMRI signals **anti-correlating** and **positively correlating** with the seed time series in the visual cortex; (B) magnitude and (C) phase images (TE=28.5 ms).

NeuroImage 87 (2014) 287–296
Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

Early anti-correlated BOLD signal changes of physiologic origin

Molly G. Bright [a,b,*], Marta Bianciardi [a,c], Jacco A. de Zwart [a], Kevin Murphy [b], Jeff H. Duyn [a]



Significantly **correlated** (blue) and **anti-correlated** (red) voxels in the Breathing and VisualMotor data.

Background & motivation

- WM signals are generally small.
- Their occurrence is sporadic.
- Low synaptic and vascular densities, plus the low metabolic demands of axonal signaling in WM.
- Hence, their origin is poorly understood.

"Yet, activation of the white matter has been rarely reported in the neuroimaging literature, and a reasonable investigator may doubt the presence of a BOLD signal in white matter altogether." *Logothetis & Wandell, 2004.*

- One particular concern is that a portion of WM signal may result from variations in systemic physiology.

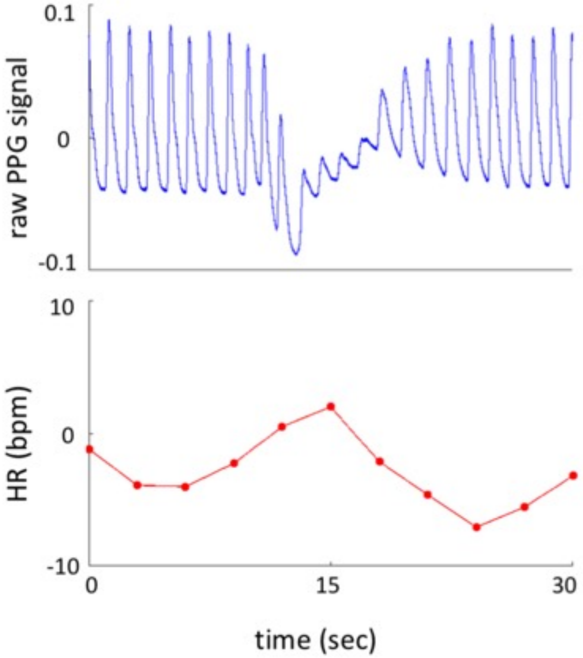
- Peripherally measured data from the fingertip with photoplethysmography (PPG) or near-infrared spectroscopy (NIRS).

Background & motivation

To investigate a potential contribution of systemic physiology to those reported BOLD fMRI signals in WM, with used pulse-oximetry signals, as measured from finger-tip **photo-plethysmography (PPG)**, **with EEG and fMRI** signals co-recorded during an **over-night sleep study**.

Finger-tip PPG device

The change in volume caused by the pressure pulse is detected by illuminating the skin with the light and then measuring the amount of light either transmitted or reflected to a photodiode.



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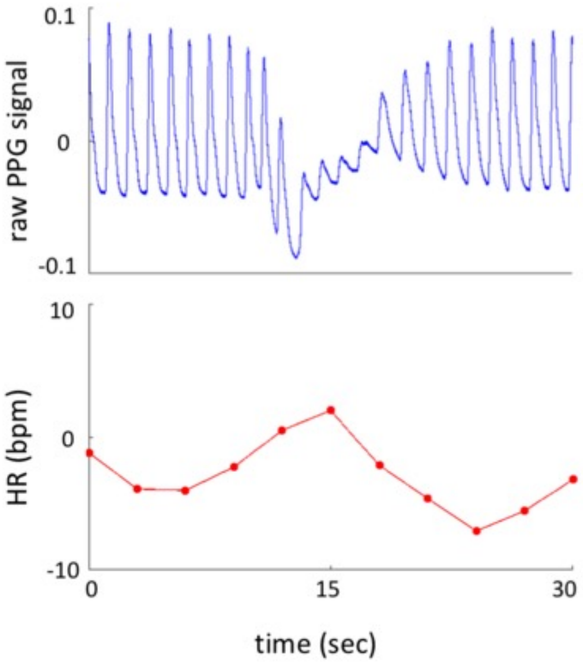
To investigate a potential contribution of systemic physiology to those reported BOLD fMRI signals in WM, with used pulse-oximetry signals, as measured from finger-tip **photo-plethysmography (PPG)**, **with EEG and fMRI** signals co-recorded during an **over-night sleep study**.

Finger-tip PPG device

The transducer recording the PPG signal was placed on the finger-tip. It predominantly measures total hemoglobin content in the vasculature of the skin; thus, the amplitude of the PPG (PPG-AMP) signal reflects blood volume and its pulsatile variations with the cardiac cycle (Shelley, 2007).



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Advanced MRI

RS-fMRI & peripheral data

NeuroImage 76 (2013) 202–215

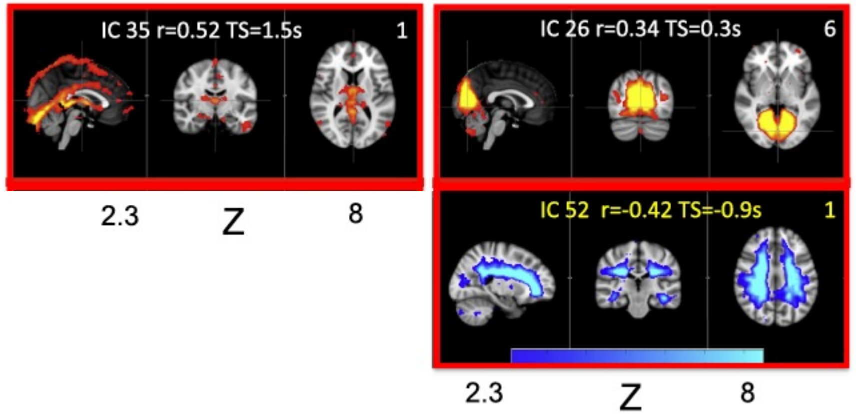
Contents lists available at SciVerse ScienceDirect

NeuroImage

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

Evaluating the effects of systemic low frequency oscillations measured in the periphery on the independent component analysis results of resting state networks

Yunjie Tong [a,b,*], Lia M. Hocke [a,c], Lisa D. Nickerson [a,b], Stephanie C. Licata [a,b], Kimberly P. Lindsey [a,b], Blaise deB. Frederick [a,b]



Components that show high positive correlations & highest negative correlation with the peripheral data (fNIRS), n=6.

◆ Human Brain Mapping 31:311–325 (2010) ◆

Correction For Pulse Height Variability Reduces Physiological Noise in Functional MRI When Studying Spontaneous Brain Activity

Petra J. van Houdt,[1,2*] Pauly P.W. Ossenblok,[3] Paul A.J.M. Boon,[1] Frans S.S. Leijten,[4] Demetrios N. Velis,[5] Cornelis J. Stam,[6] and Jan C. de Munck[2]

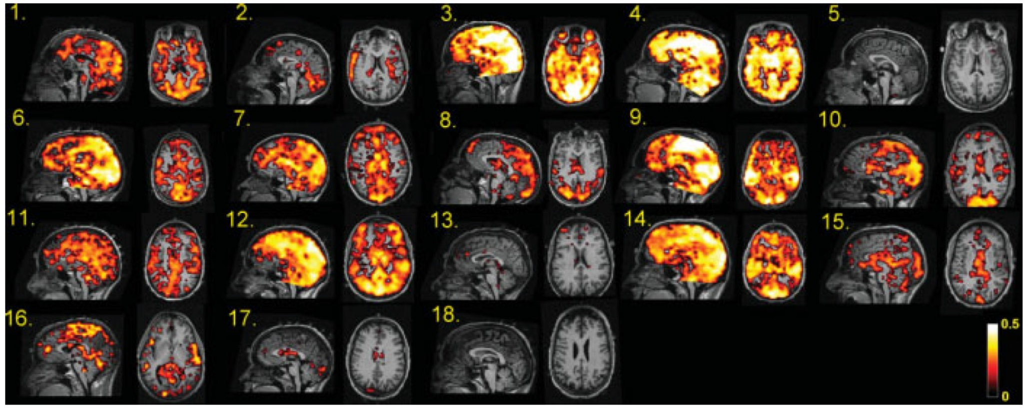
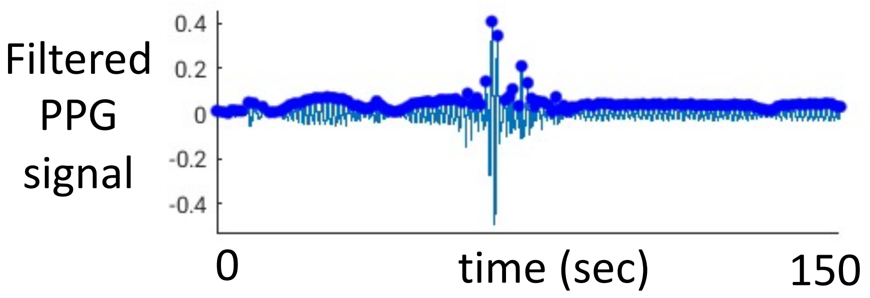


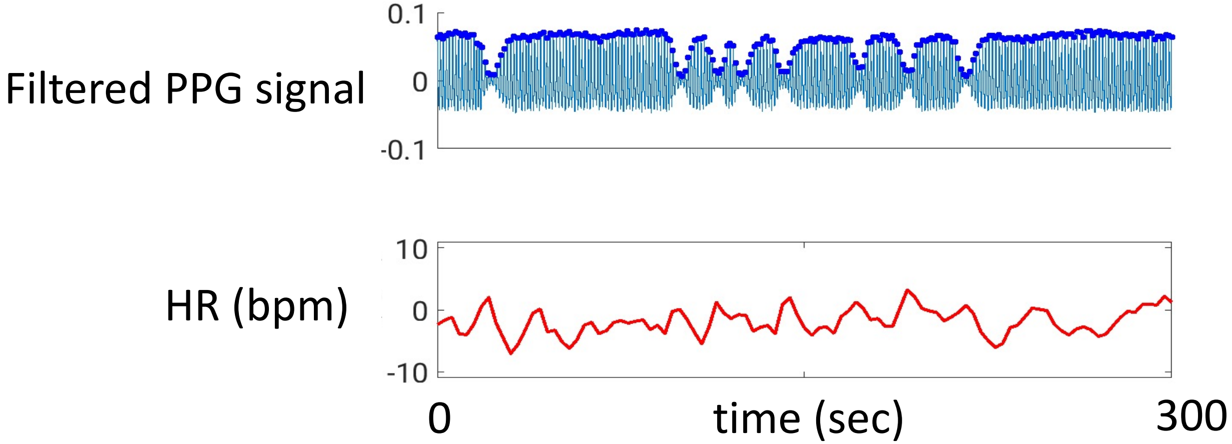
Figure 3.
Statistical maps representing the significant BOLD changes which correlate with the variations in pulse height (VIPH) for all subjects (mid sagittal and axial views) at an FDR <1%. The statistical maps of Subject 1 till 5 represent the correlation patterns of the patients with epilepsy, whereas the statistical maps of Subject 6 till 18 represent the activated voxels of the healthy volunteers.

Sleep data

Corresponding data among fMRI scans which had

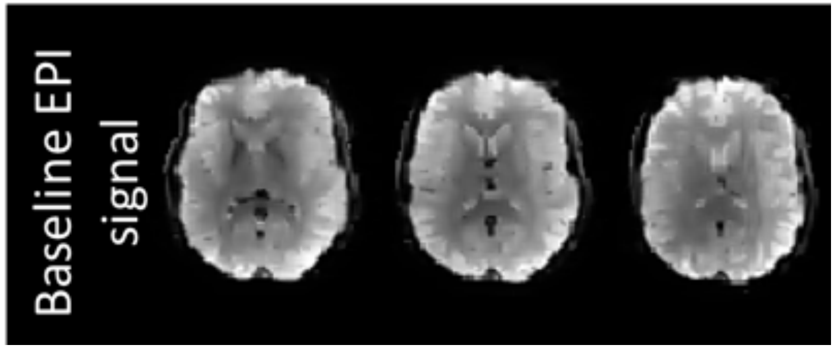
1) **least amount of motion**
2) **cleanest PPG data**
3) **isolated amplitude drops in PPG signal**
4) **segment of NREM sleep** (EEG based sleep scoring)
[light sleep]





Sleep data

fMRI data summary
TR=3s, TE=36ms, in-plane res=2.5 mm,
slice thickness=2 mm, slice gap=0.5 mm,
Grappa=2, 3T



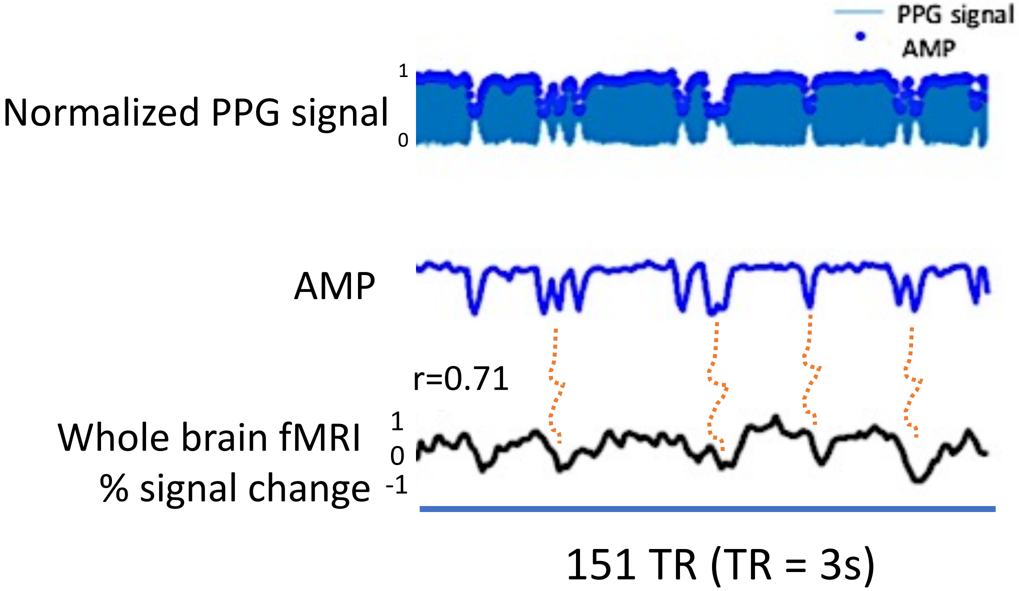
fMRI processing (AFNI)

Motion coregistration (six-parameter rigid body correction) (*3dvolreg*)

Correction of residual motion (*3dDetrend*)

Low-order polynomial regression up to 3rd order

Slice timing correction (*3dTshift*)



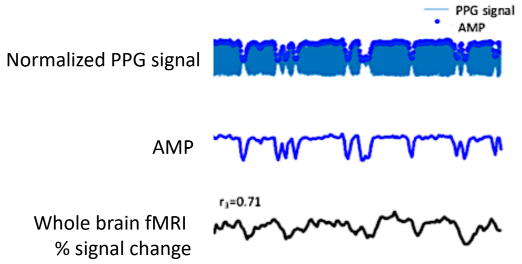
PPG signal

Bandpass-filtering raw PPG data

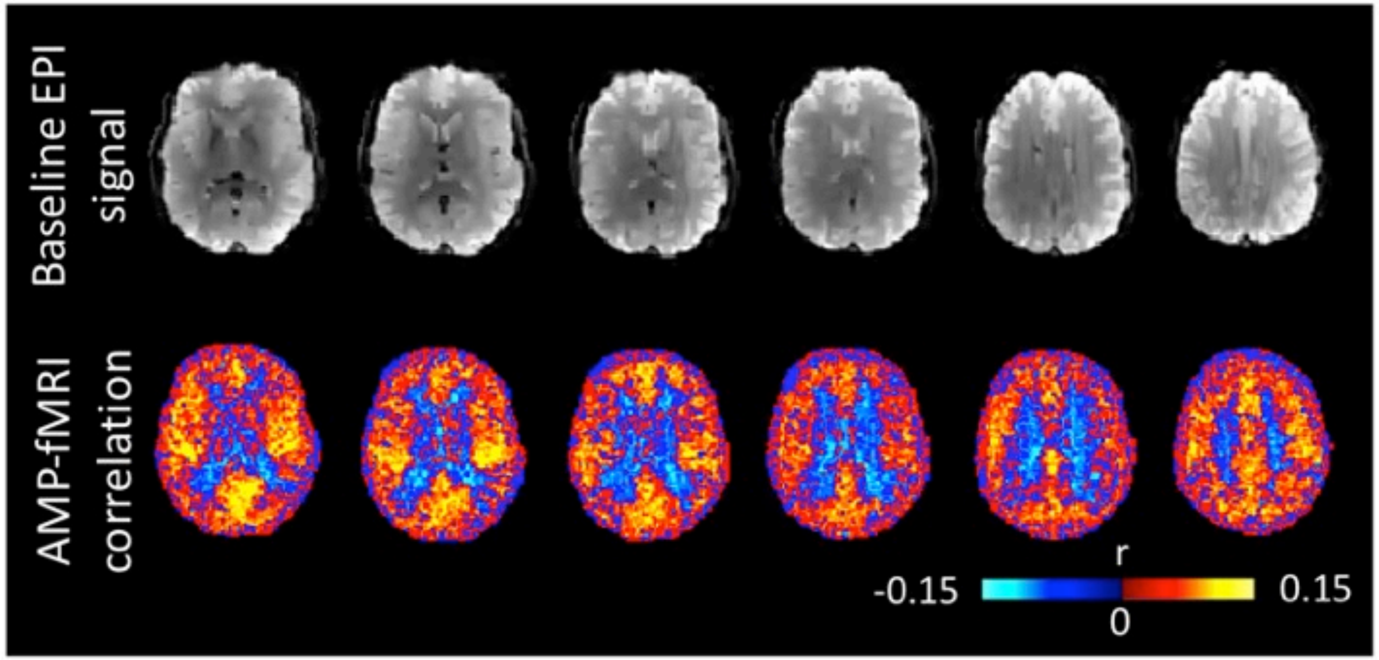
Peak detection

AMP: amplitude of PPG signal

PPG AMP – fMRI correlations



Voxel-wise correlation maps (N=8)



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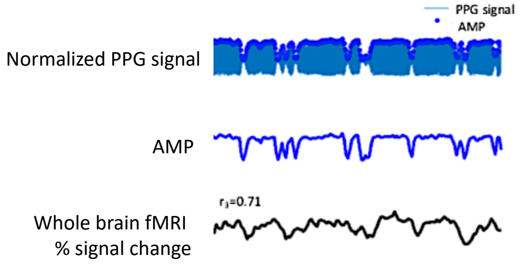
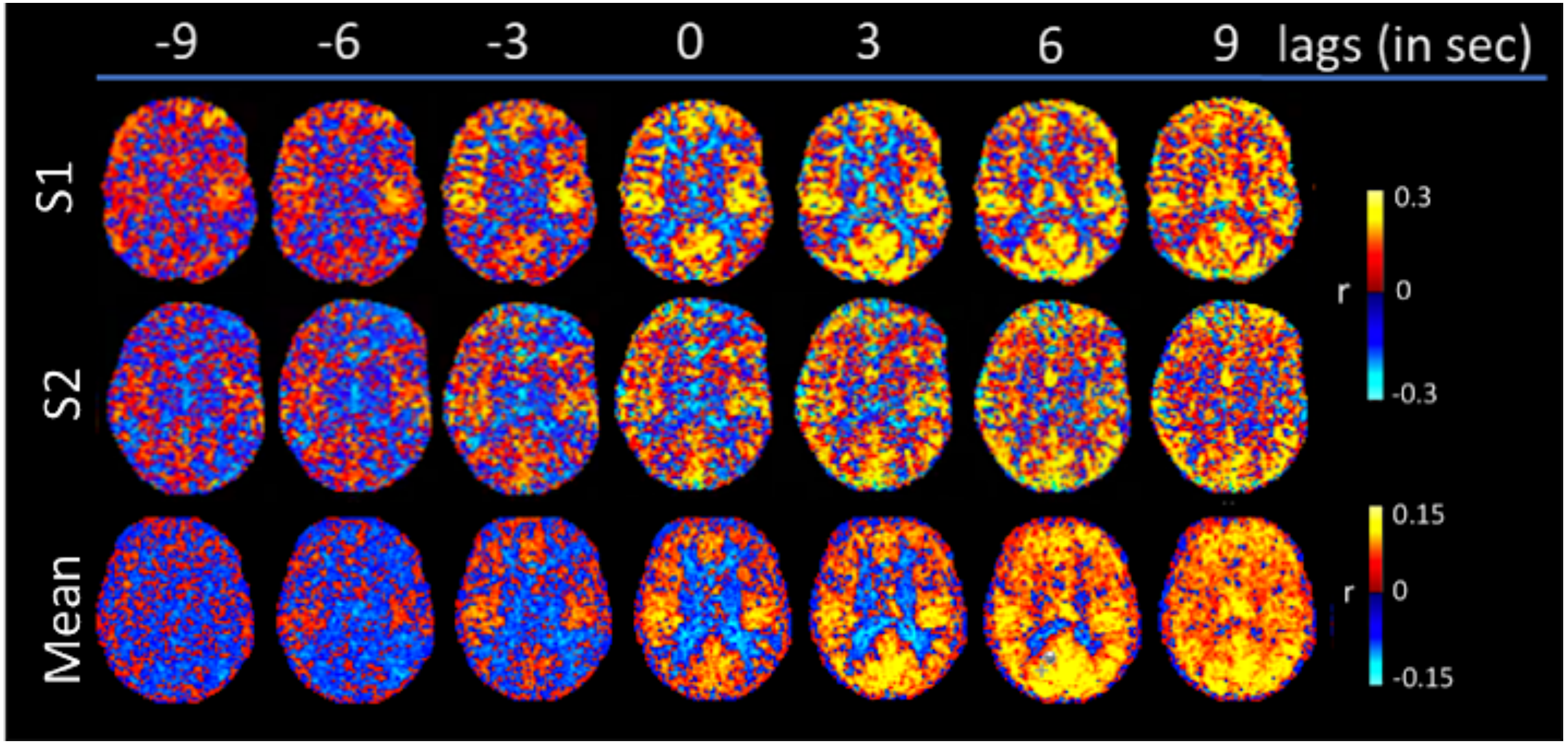
Advanced MRI

Lag-dependent PPG AMP – fMRI correlations





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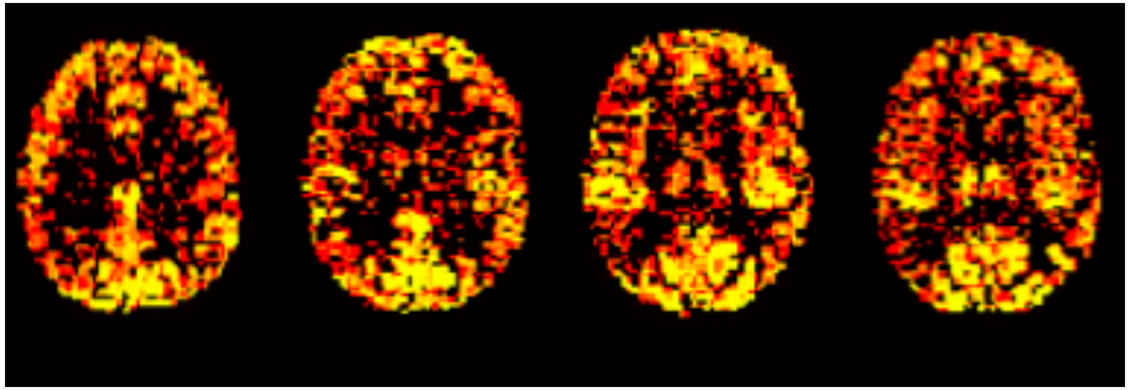
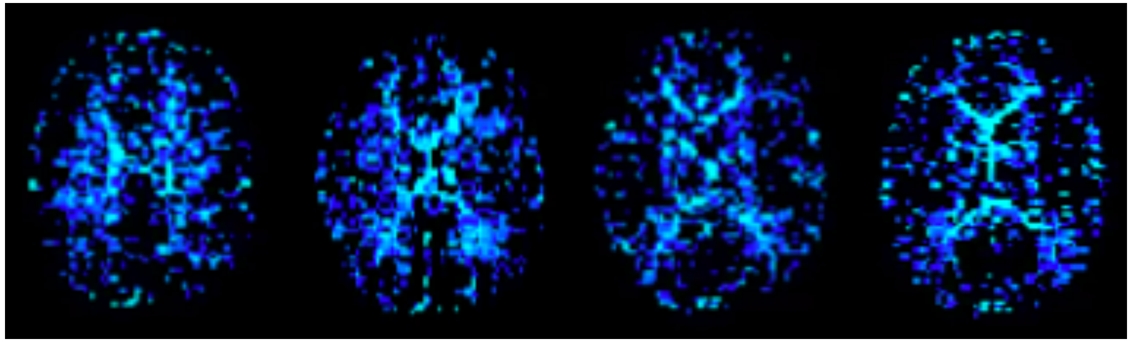
ROI-based correlations

Correlation (corr) maps between each voxel and the PPG amplitude across a lag range of -9 to 9 sec (-3 to 3 TR)

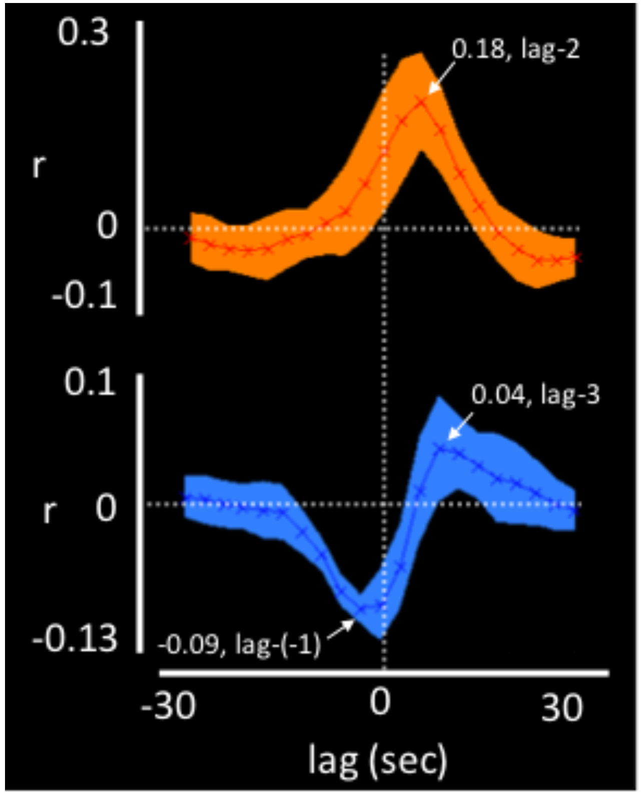
Max corr map
r >= 0.1



Min corr map
r <= -0.1



Group average (n=8) lag-dependent correlations, based on GM and WM ROIs.

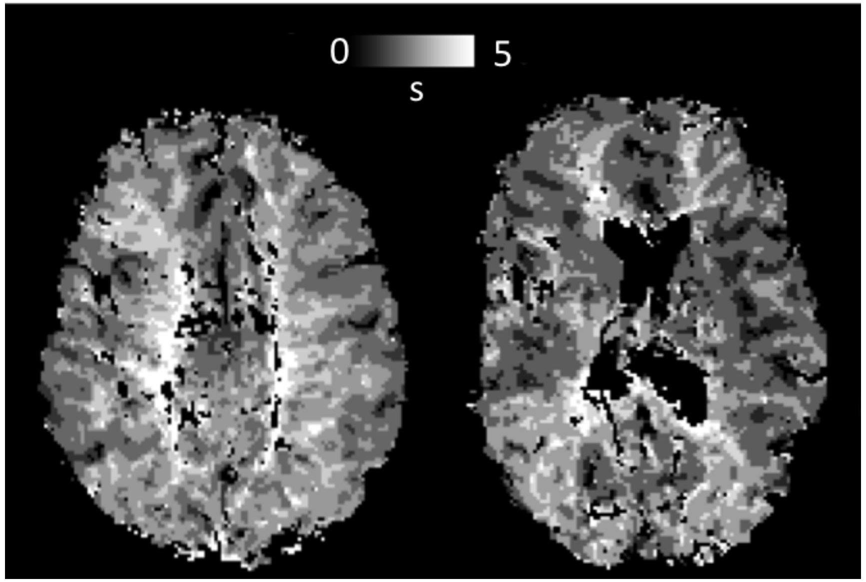


Transit time

Our results can be supported further with the results of an earlier study (van Gelderen et al. 2008), where the range of transit times were estimated in healthy subjects based on Gd-DTPA bolus-tracking experiments.

PPG AMP & fMRI correlation

Bolus arrival of Gd-DTPA injection

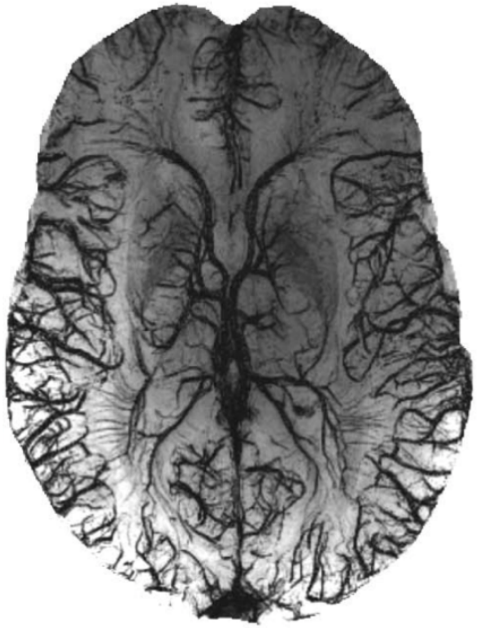


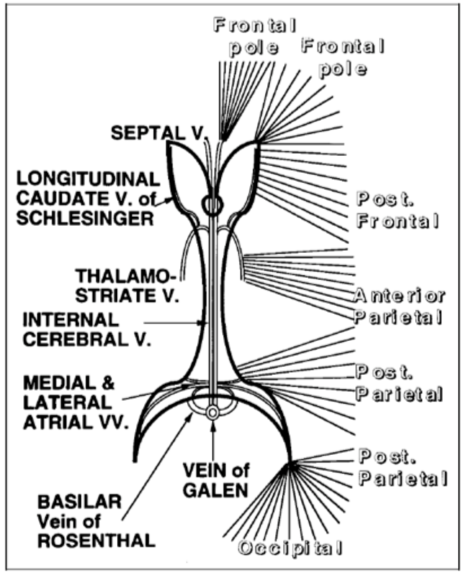
(different subject data)

Resemblance of correlation pattern in WM with distribution of deep veins


*SWI, mIP, 3T


PPG AMP & fMRI correlation


*SWI, mIP, 7T



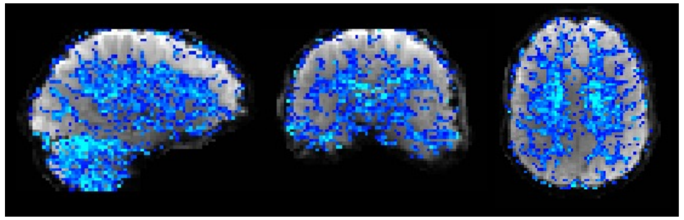
Deep Venous System (Lee, Pennington, and Kenney 1996).

*Monti et al., IEEE TRANSACTIONS ON MEDICAL IMAGING, VOL. 36, NO. 5, 2017

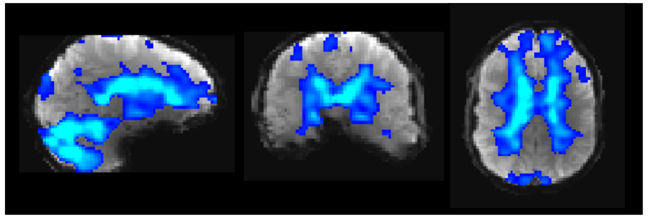
ICA – WM component

- The PPG drops are interpreted as systemic **vasoconstrictive events**, possibly related to intermittent increases in **sympathetic tone related to fluctuations in arousal state**, which supports previous work that recorded the peripheral signals with functional near-infrared spectroscopy (fNIRS).

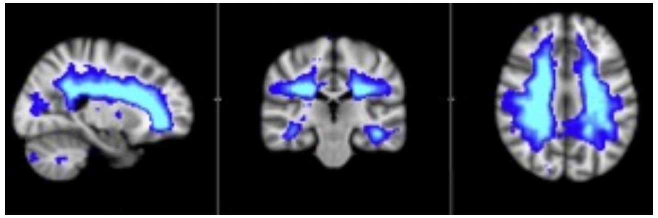
PPG-AMP & fMRI, r<-0.05



PPG-AMP & fMRI (ICA)
r = -0.64



fNIRS & fMRI (ICA)
r = -0.42



Tong et al., NIMG 2013

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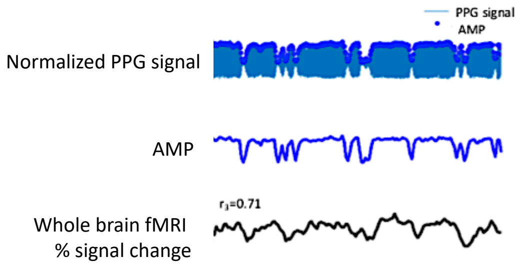
Advanced MRI

PPG drops & WM/GM anti-correlation



PPG AMP & fMRI correlation

- Transit times in WM might be substantially longer due to differences in **vascular architecture**.

Blood oxygenation (BO) changes in WM are slower than in GM by several seconds.

Blood volume (BV) changes may occur more rapidly, as they do not depend on vascular transit but rather more closely follow upstream pressure changes, which could be driven by **vasoconstriction**.

Contribution of Systemic Vascular Effects on White Matter BOLD fMRI Signal

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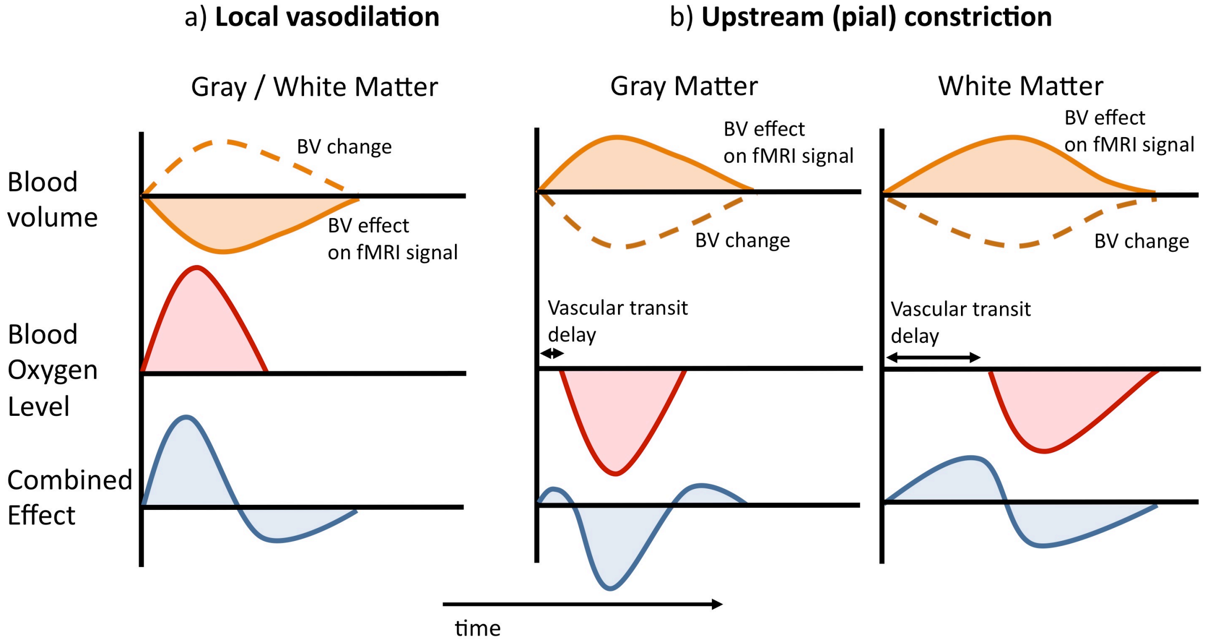
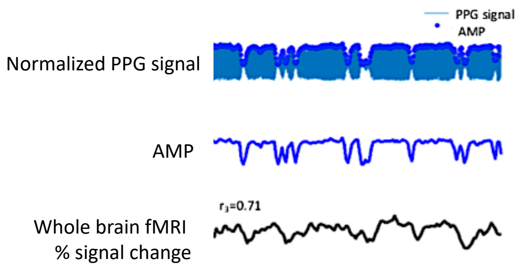
Proposed balloon model



We would expect to observe a positive BOLD contrast in response to a **local vasodilation**.

However, a physiologically originated effect such as **vasoconstriction**, which has been observed as PPG AMP drops in our data, could lead to anti-correlations in WM and GM.



PPG AMP & fMRI correlation

Contribution of Systemic Vascular Effects on White Matter BOLD fMRI Signal

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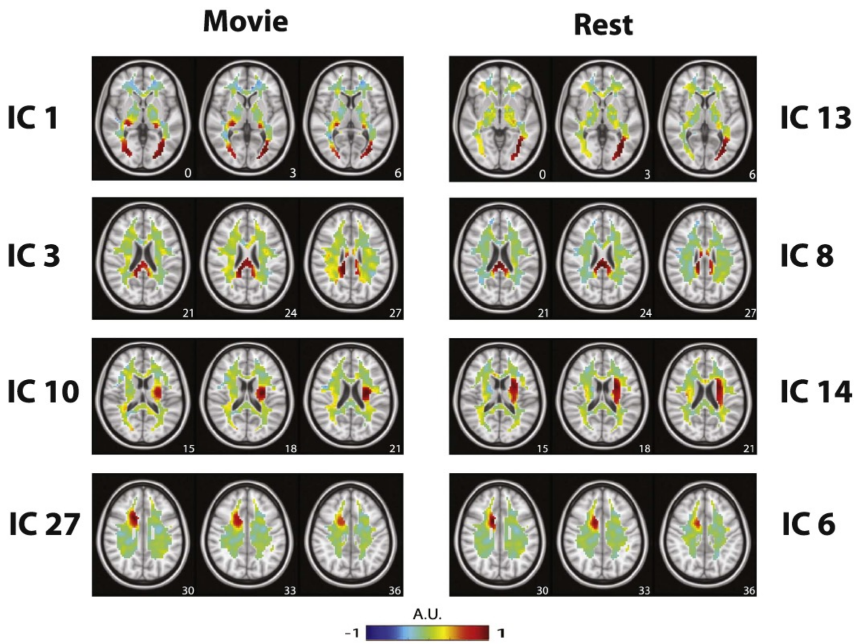
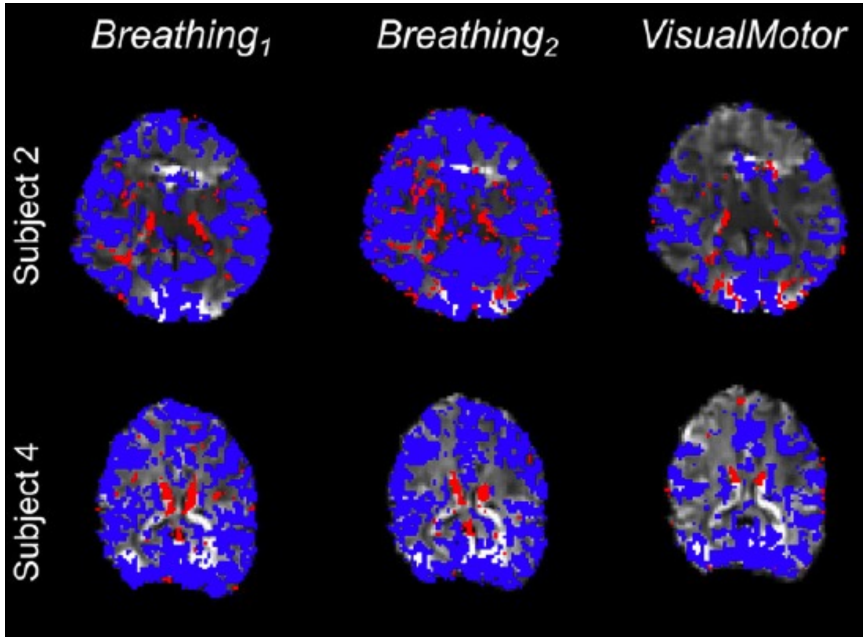
- Mismatch between BO and BV in WM:
  - **Time-lag maps & proposed balloon model & bolus tracking**

- A similar mechanism may explain **previous findings** of fMRI signals around WM & large draining veins & ventricles.





The hypocapnic CDB challenge: vasoconstriction

Contribution of Systemic Vascular Effects on White Matter BOLD fMRI Signal

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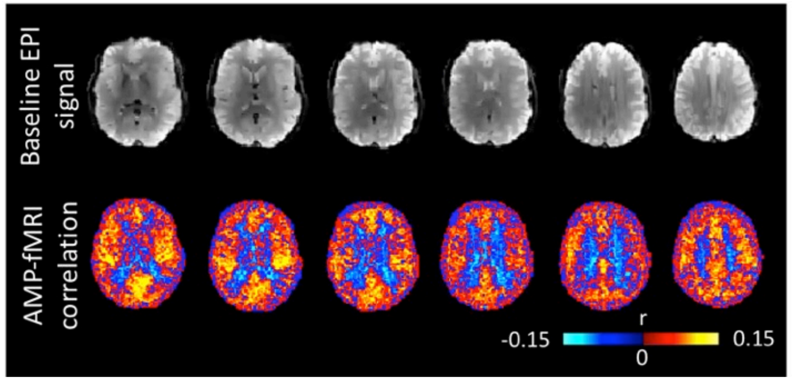
Advanced MRI

Conclusion – Part 1

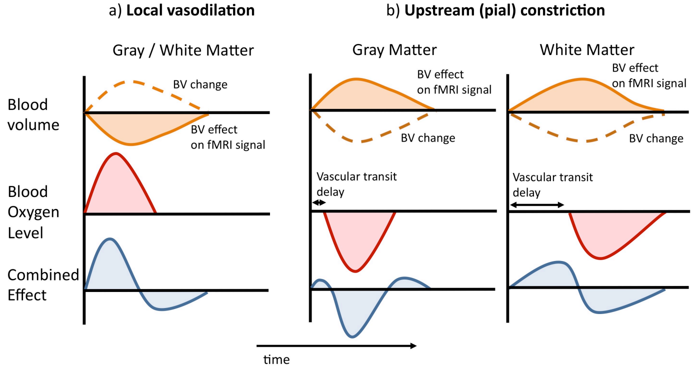


- We characterized the spatiotemporal pattern of fMRI activity in WM in response to changes in **peripheral vascular tone**.

- Our results suggest that the temporal dynamics of signal characteristics in WM often observed in the fMRI literature can be explained by a **temporal mismatch between blood volume and blood oxygenation effects** [proposed balloon model].

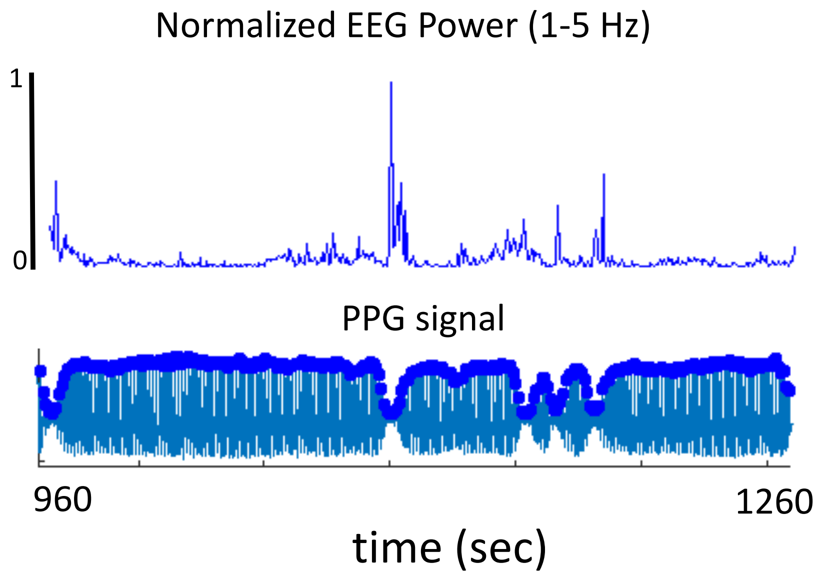
- These results highlight the possible contribution of systemic vasoconstriction events to fMRI signal in WM.

- Care should be taken while interpreting white matter BOLD fMRI signals in functional (connectivity) studies.



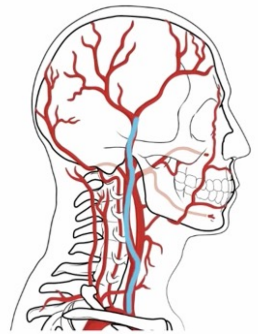
Conclusion – Part 2

- Intermittent PPG-AMP drops are interpreted as systemic **vasoconstrictive** events, related to correlations between **EEG measures of arousal and PPG-AMP drops** (Ackner et al., 1957).



- Our findings suggest a contribution to the fMRI signal from the extrinsic sympathetic innervation of the pial vasculature and is expected to be important for a range of conditions that activate the sympathetic pathway.

- Due to the close integration of brain stem systems that regulate sympathetic nervous activity and intracortical neuronal activity, separation of these two sources of fMRI activity is challenging and will require further research to establish a comprehensive model of the relationship between **fMRI, EEG, and peripheral measures**.



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Jacco A de Zwart
Peter van Gelderen
Thomas Moehlman
Miranda Chappel-Farley
…

Advanced MRI Section / LFMI / NINDS / NIH

Thanks !

DELETED SCENES

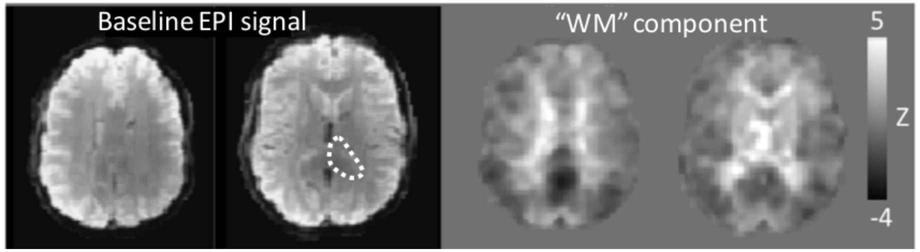
Summary of data

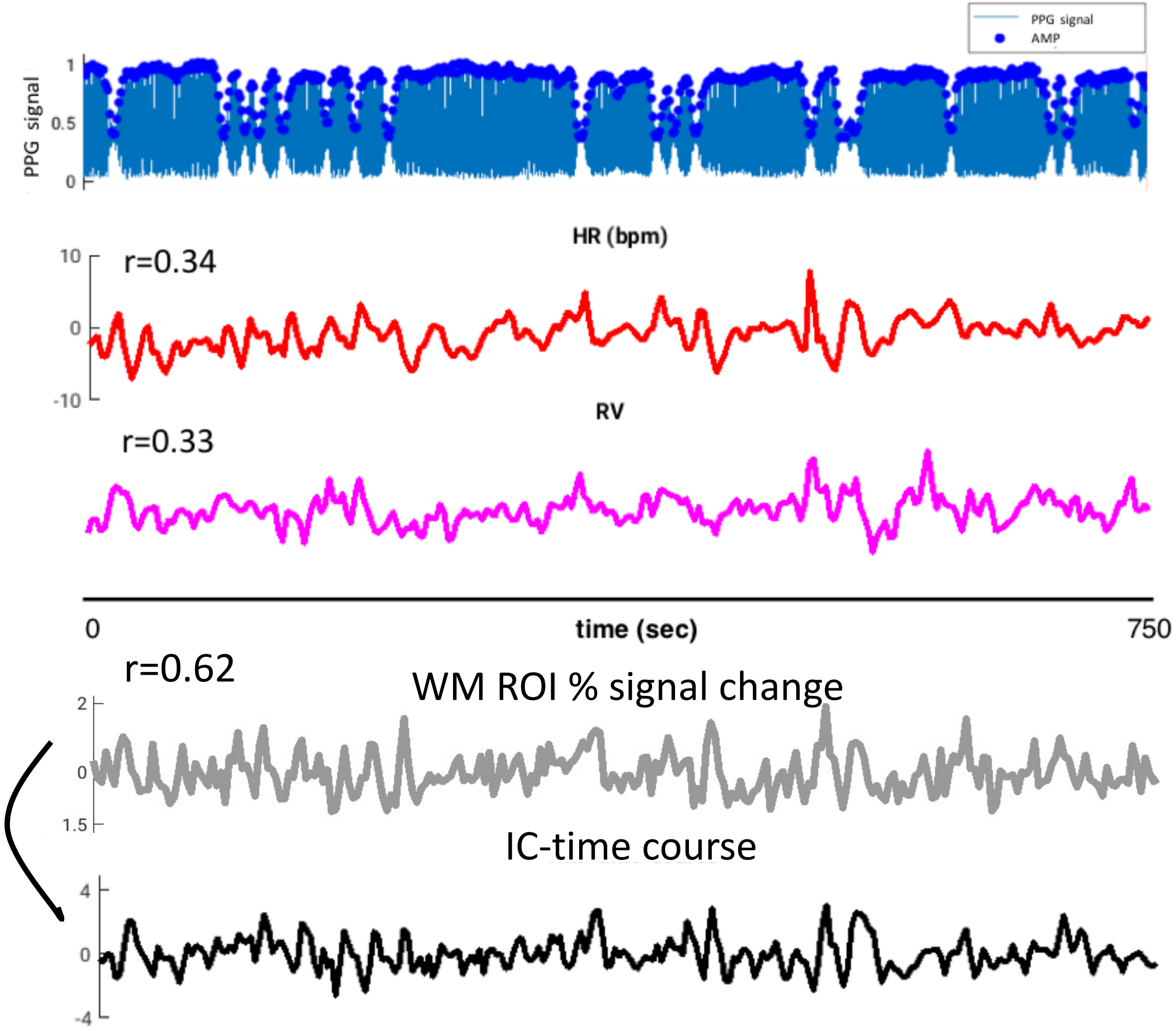
We found PPG-AMP dips, with strong correlation with fMRI signal, **primarily during light sleep**.

Subject	Length of segment selected for correlation analysis (TR)	Distribution of sleep stages within segments (%)			
		W	S1	S2	S3/S4
S1	151	9	4.5	82	4.5
S2	151	6	11	83	-
S3	151	-	-	100	-
S4	151	15	10	70	5
S5	111	-	100	-	-
S6	151	-	67	33	-
S7	101	21	-	79	-
S8	151	-	6	94	-

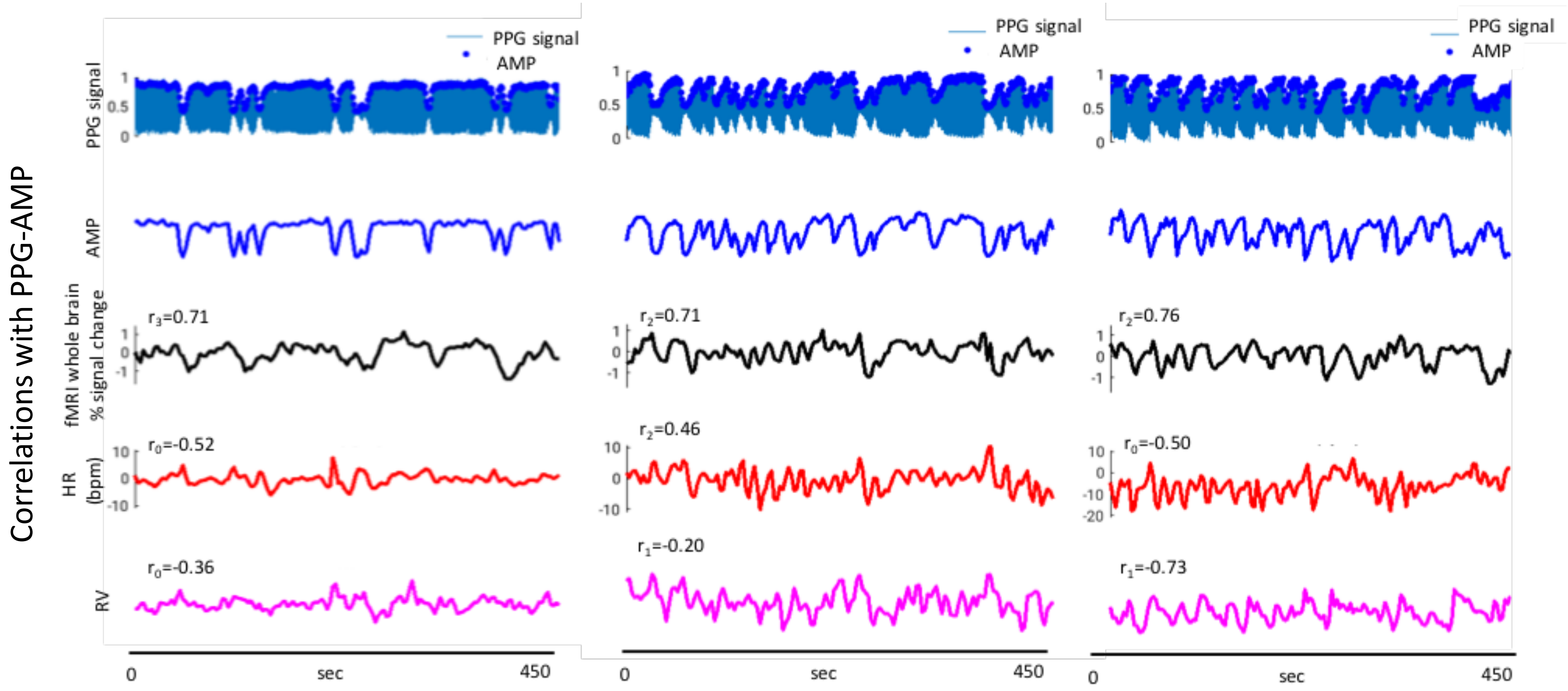
PPG AMP – fMRI correlations

ROI-based correlations





Physio – fMRI correlations

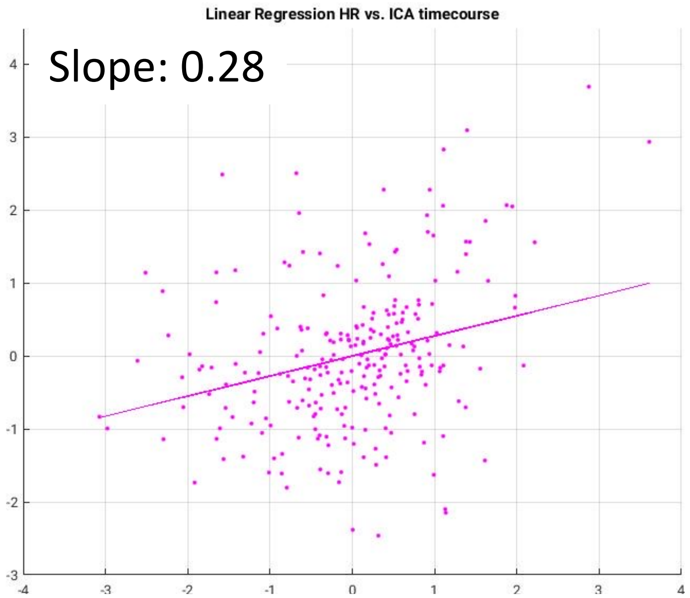


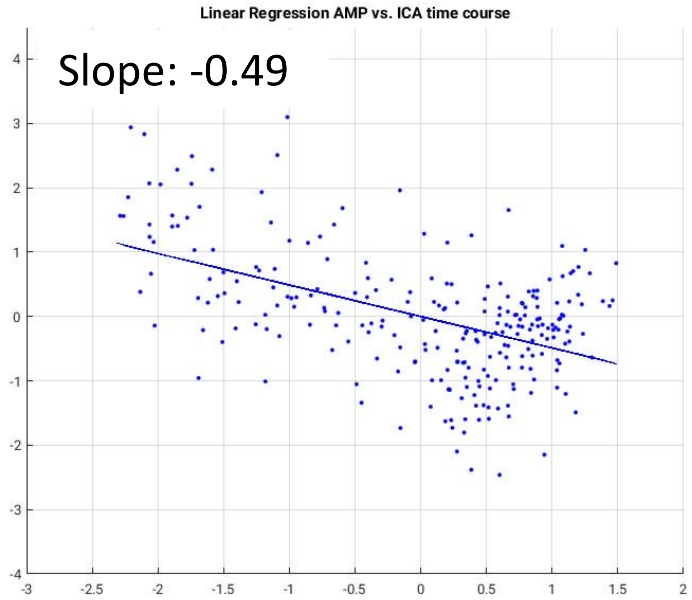
Subject average correlation of PPG-AMP, HR and RV with fMRI signal were 0.54 ± 0.19 (lag=2TRs), 0.34 ± 0.15 (0 lag), and -0.36 ± 0.22 (lag=3TRs), respectively. Subject average peak-to-peak BOLD signal changes were 2.17% ± 0.39%.

Multi-regression with HR and PPG-AMP

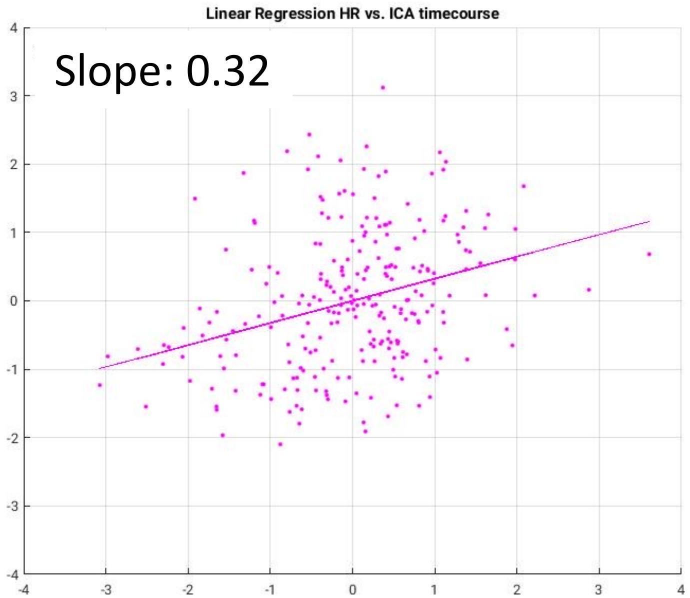
A) wm component time course and B) gm (visual) component time course

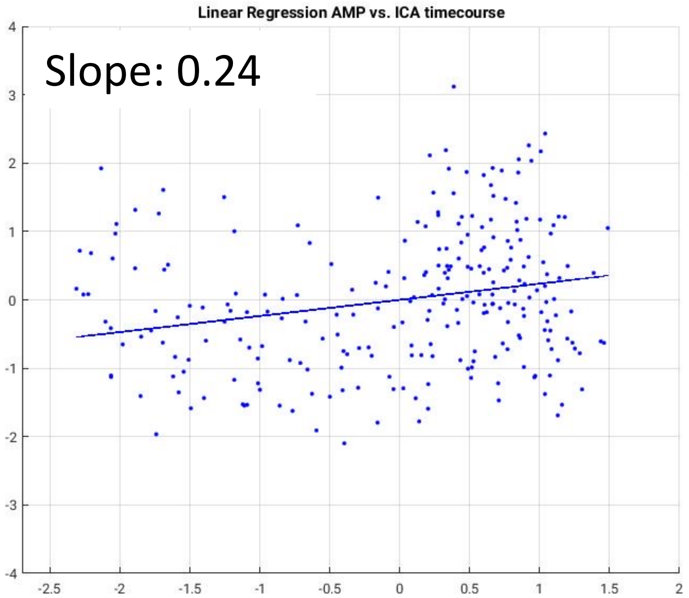
WM
time course





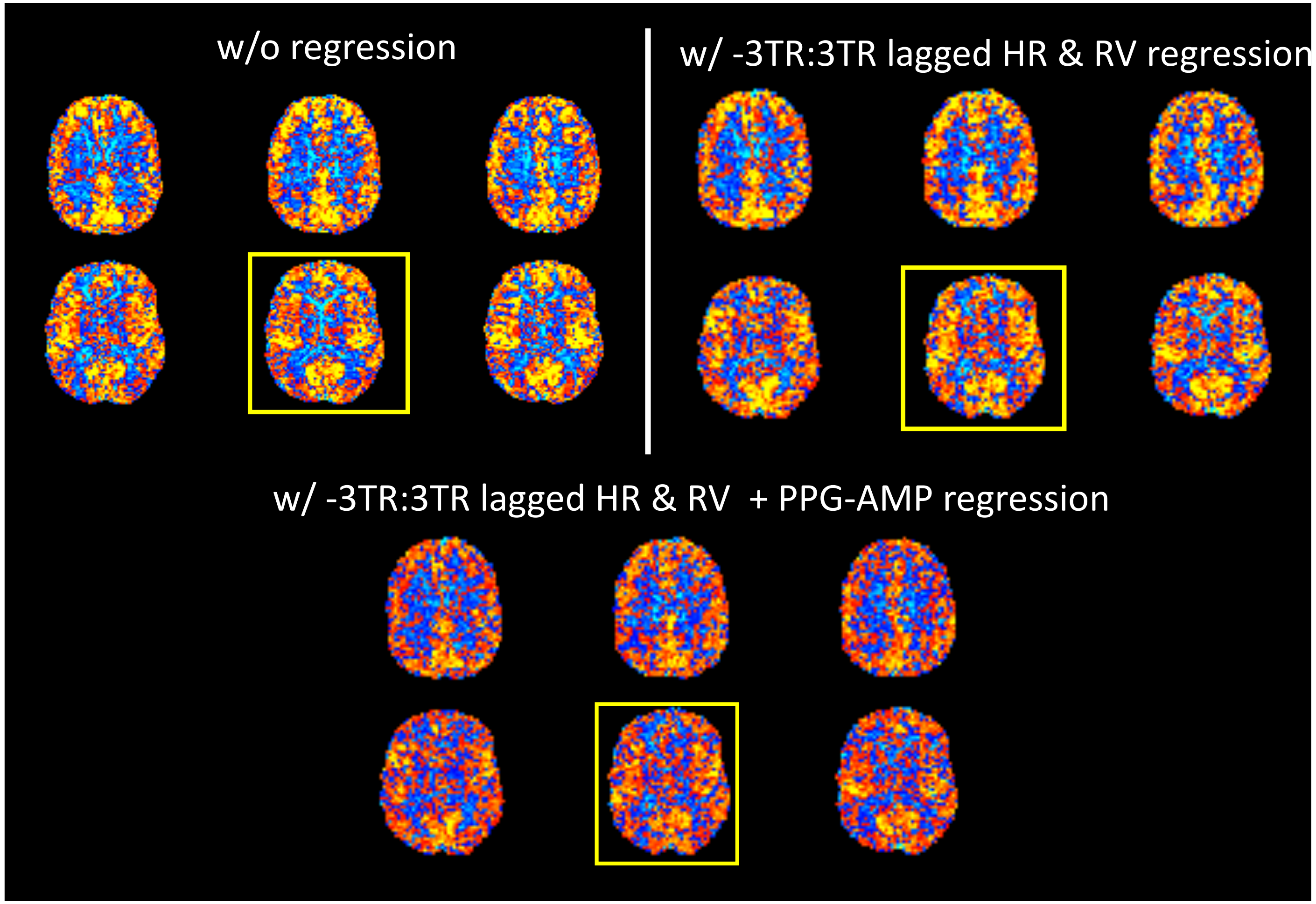
GM
time course



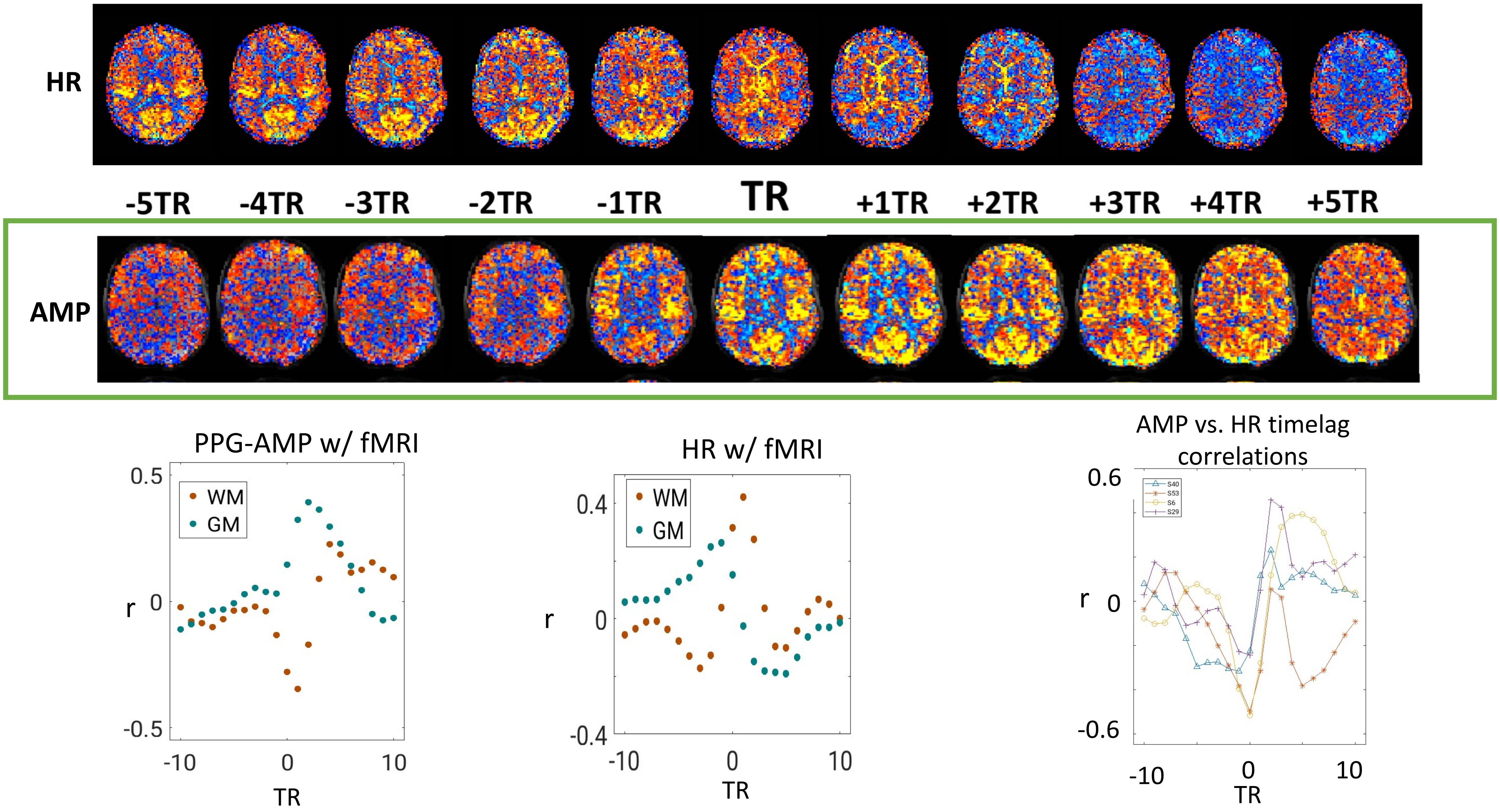


HR/RV and PPG-AMP as regressors

PPG-AMP & fMRI correlation maps

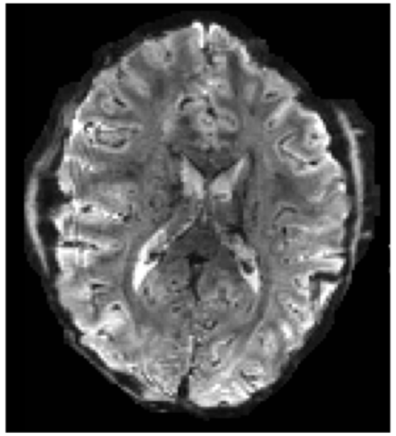


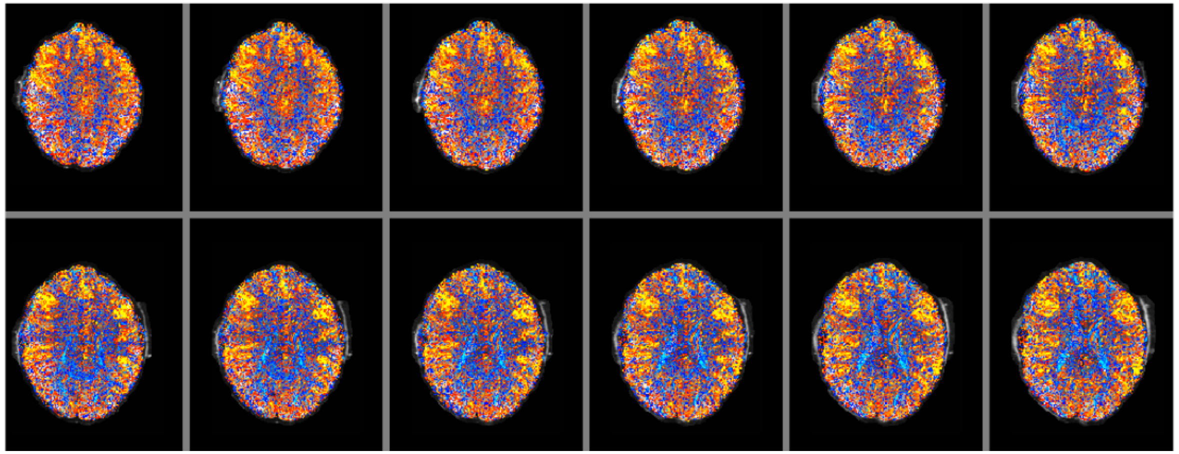
HR and PPG-AMP relations



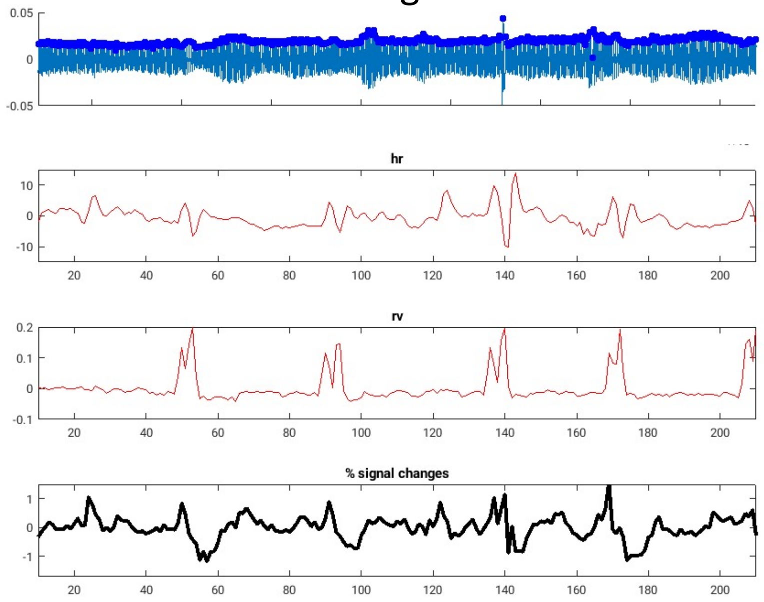
7T, TR=2s, TE=33ms, 32 slices
Cued deep breathing, PPG-AMP & fMRI correlation maps
0-lag

EPI slice





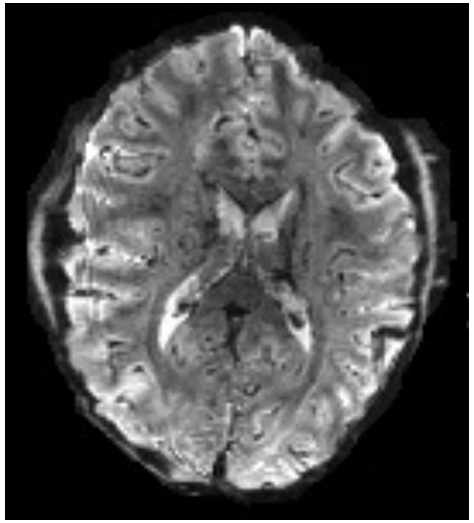
PPG signal

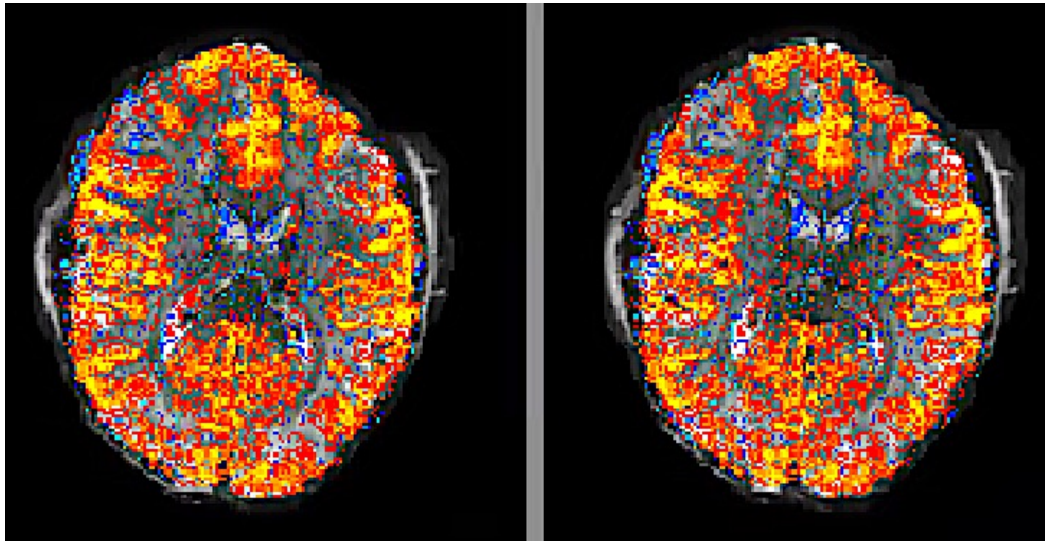


TR

Experiment 1, cont'
Cued deep breathing, voxel-vise correlation maps with mean global signal

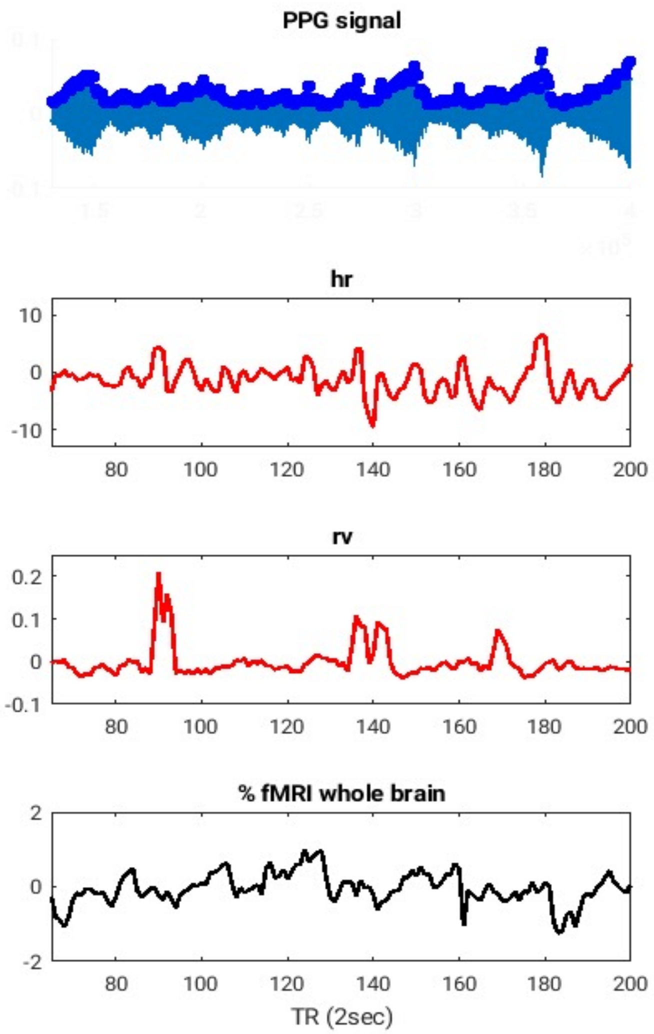
EPI slice



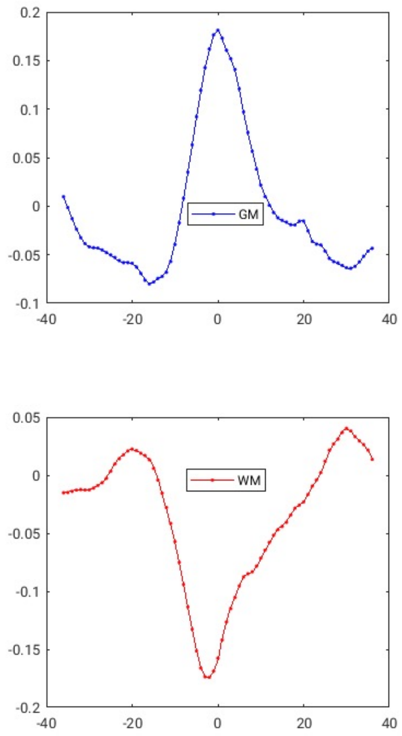


Experiment 2

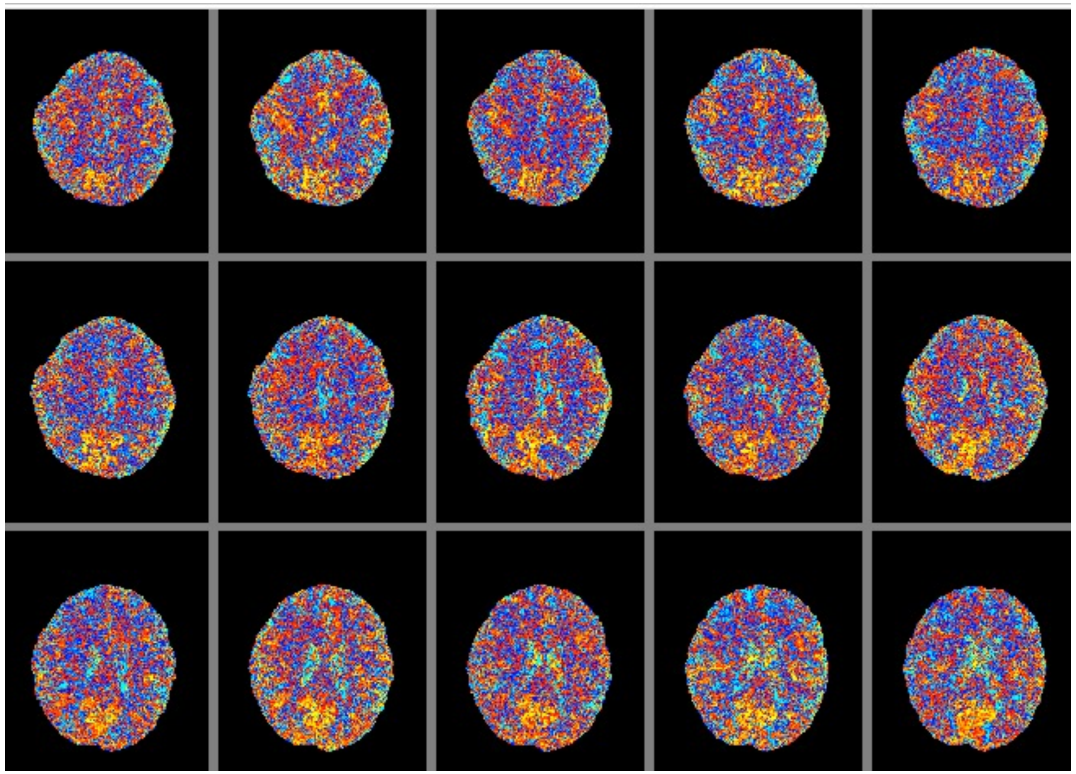
PART 1: more related to deep breathing (RV)



Lags in sec

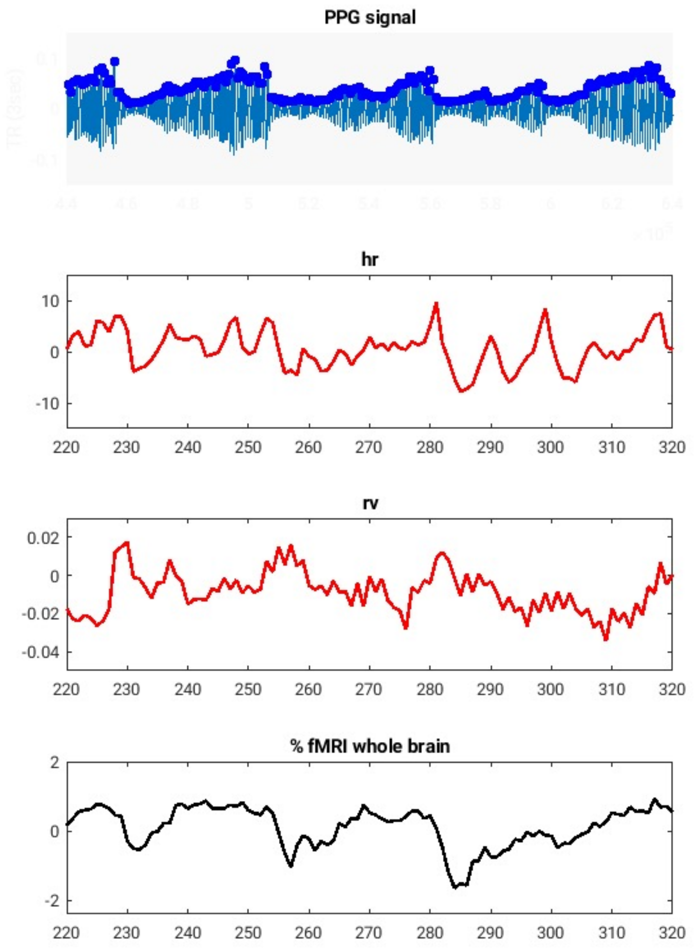


PPG & fMRI

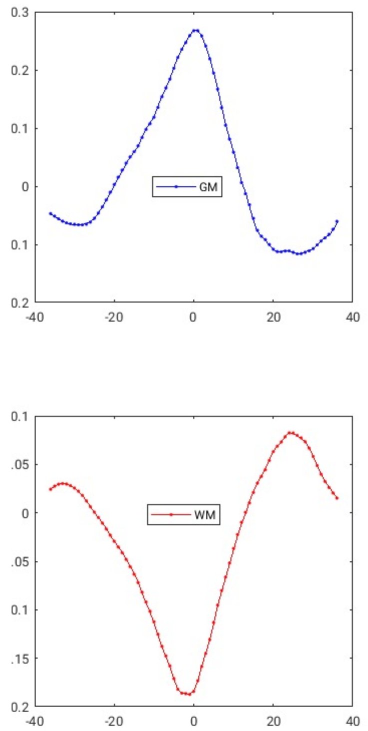


Experiment 2

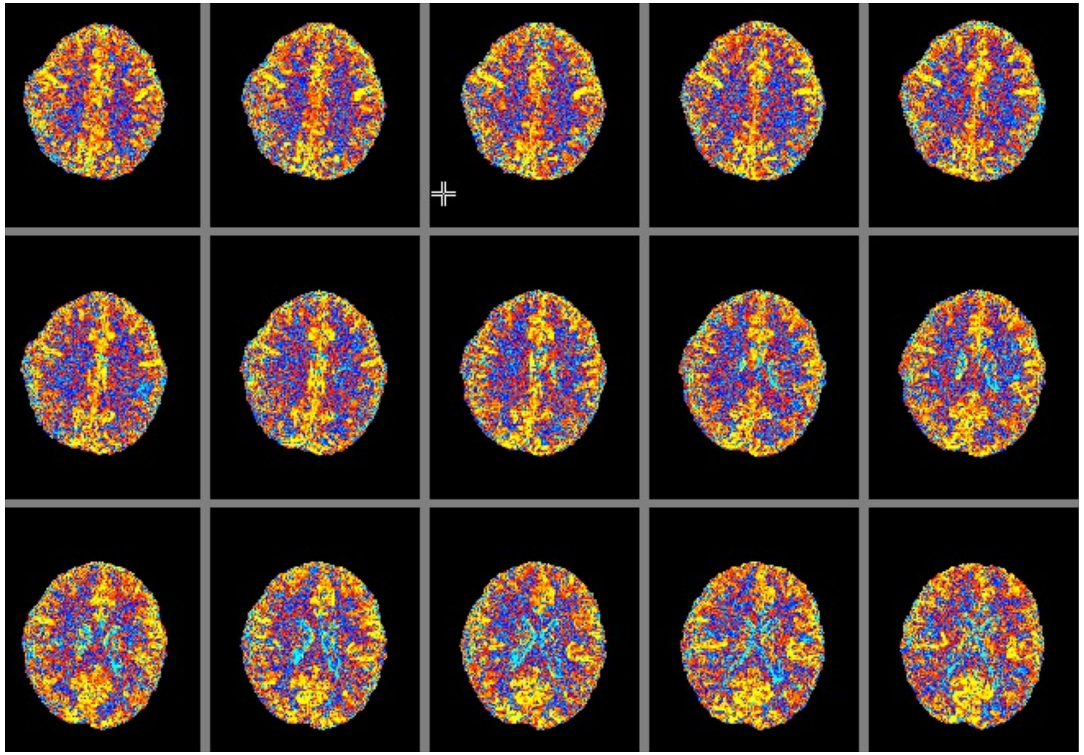
PART 2: more related to light sleep (PPG)



Lags in sec



PPG & fMRI



On-going work - EEG

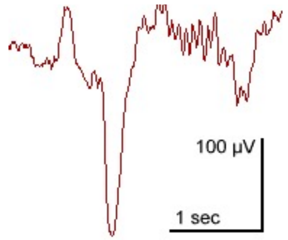
Previous studies have found those dips to be associated with K-complexes (Kcs), which are signs of arousal.

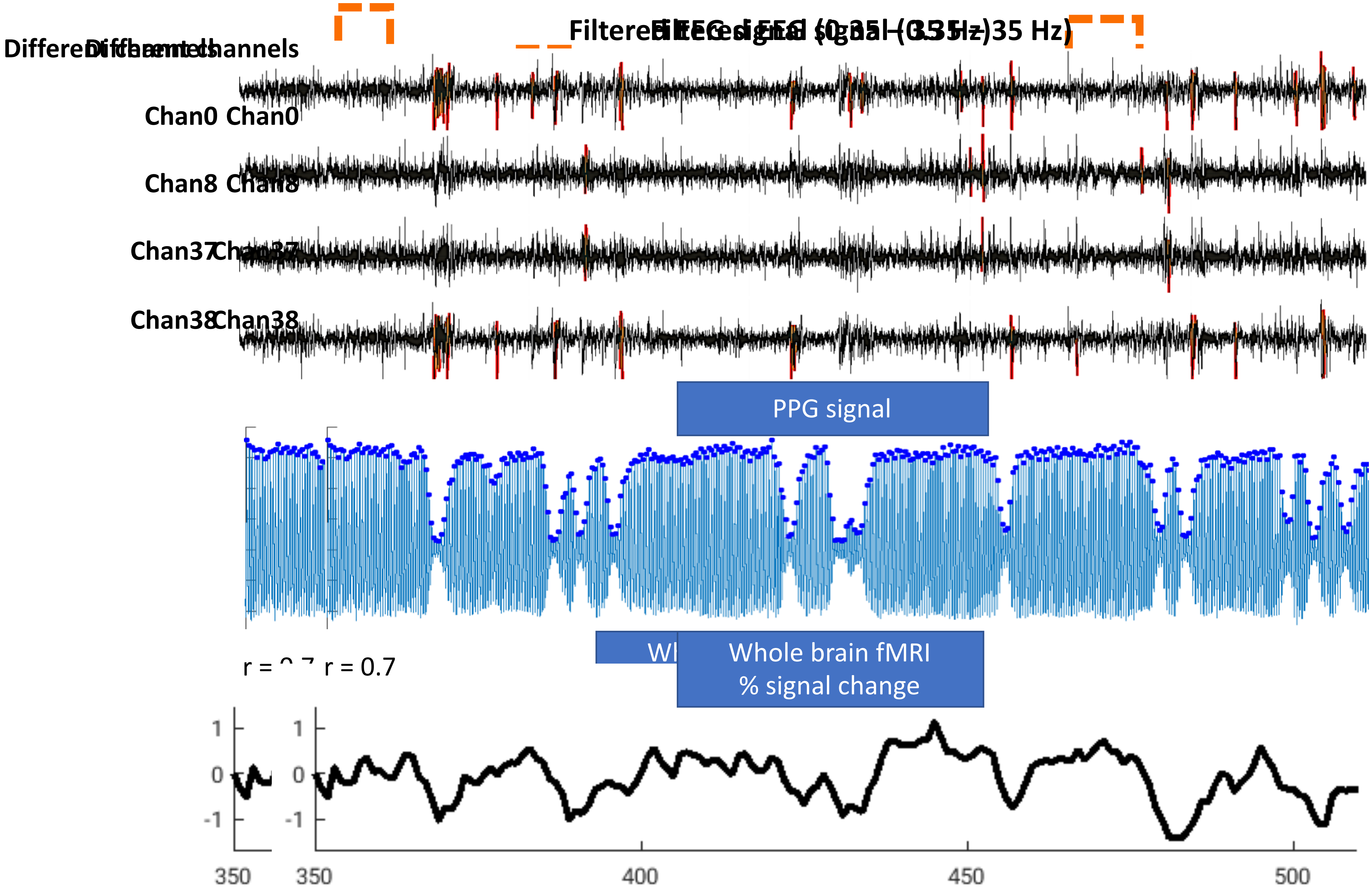
Monstad et al. 1999, Kcs relation with blood pressure (BP) during NREM, spontaneous Kcs predominantly occurred during drop in BP.

Catcheside et al. 2002, Acoustic induced arousal during NREM, PPG is more sensitive as a marker of autonomic (subcortical) arousal.

Czisch et al. 2004, BOLD signal decrease during NREM sleep, increased number of Kcs upon acoustic stimulation.

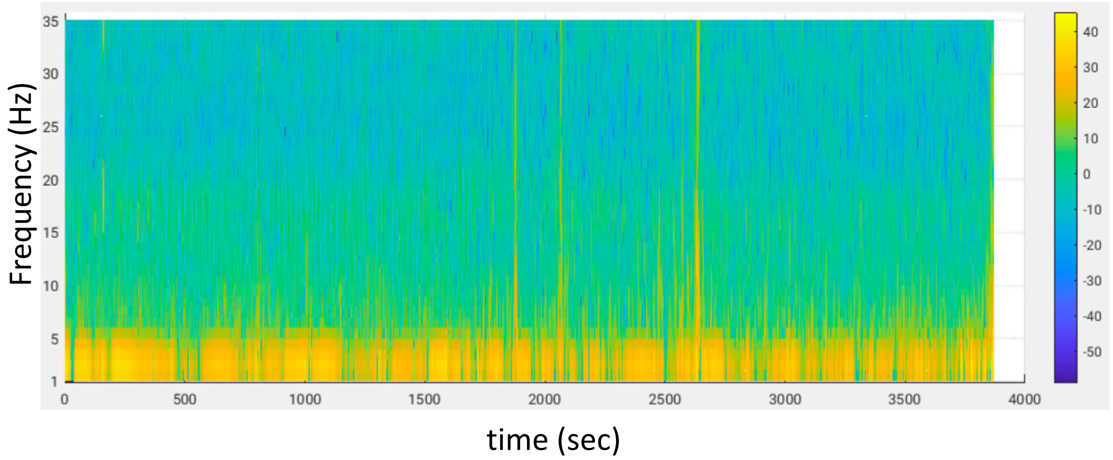
A K-complex is an EEG waveform that occurs primarily during stage 2 of NREM sleep.





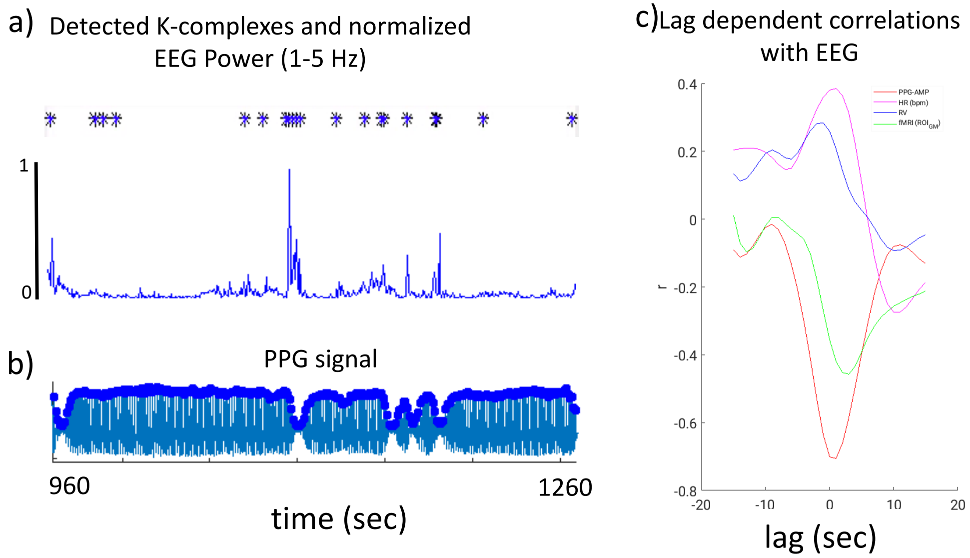
Different channels
Chan0
Chan8
Chan37
Chan38
PPG signal
Whole brain fMRI
% signal change
r = 0.7
1
0
-1
350
400
450
500

Power spectral density of EEG



Exemplary power spectral density showing ~1hr of EEG data (channel Fp1) from one subject. Yellow color represents high power, while green/blue less power per frequency.

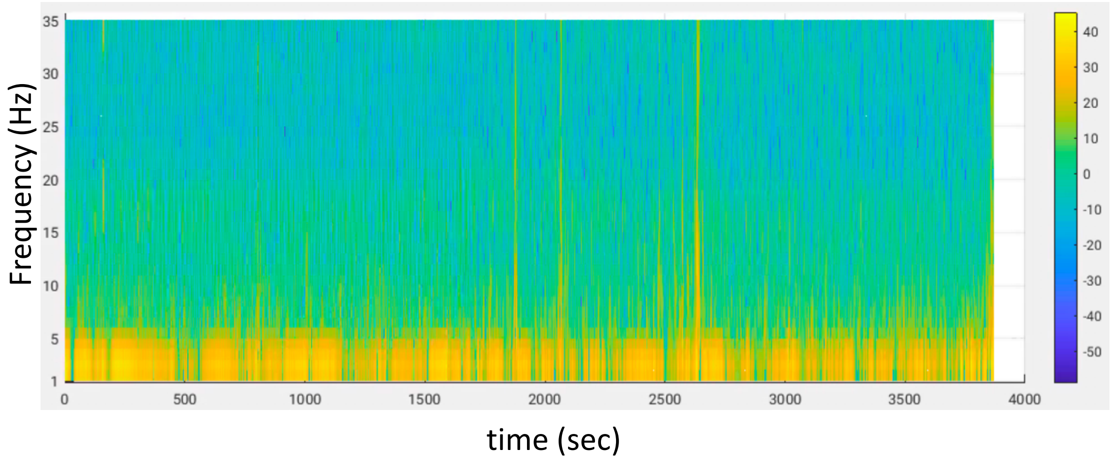
From the spectrum, we could see the highest power segments correspond to delta frequency range, 1-5 Hz, in which K-complexes are known to occur predominantly (Forget et al., 2011).



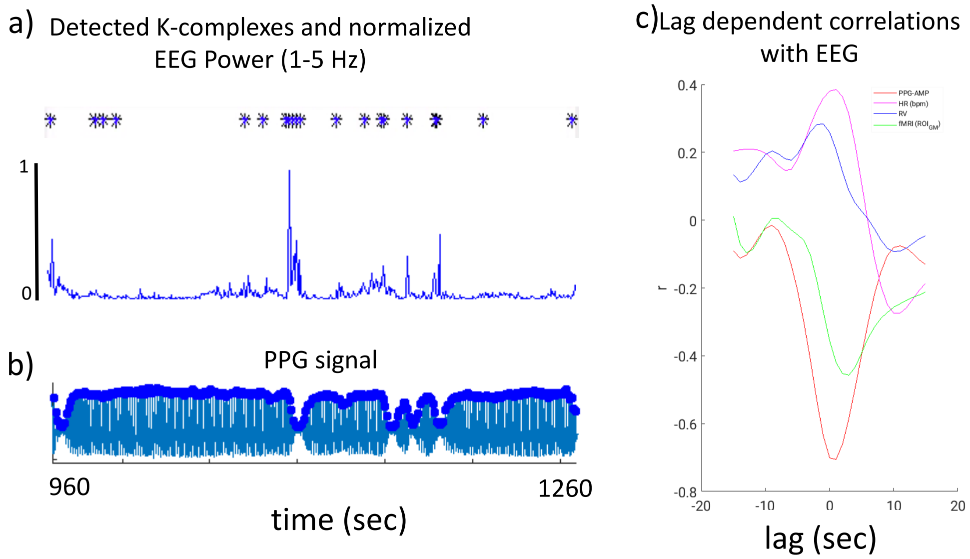
Segment of N2 selected from data shown above. (a) Detected K-complexes combined from all channels (blue stars, top), normalized EEG power (1-5Hz) (bottom), (b) corresponding PPG signal, (c) EEG power correlations with PPG-AMP, HR, RV and fMRI (ROI: primary visual area) signals.

[More will be discussed during SFN, San Diego !]

Power spectral density of EEG



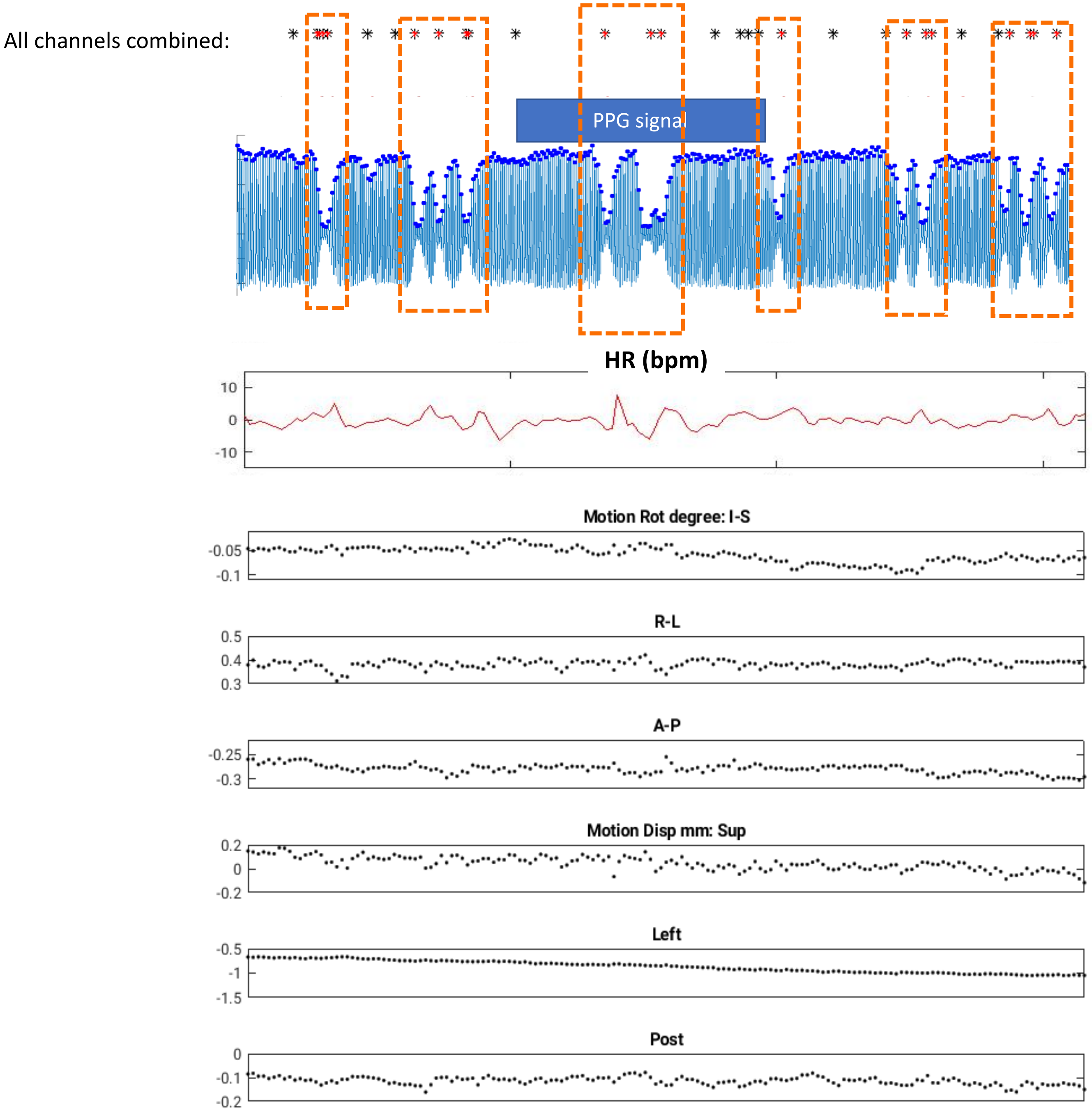
Exemplary power spectral density showing ~1hr of EEG data (channel Fp1) from one subject. Yellow color represents high power, while green/blue less power per frequency.



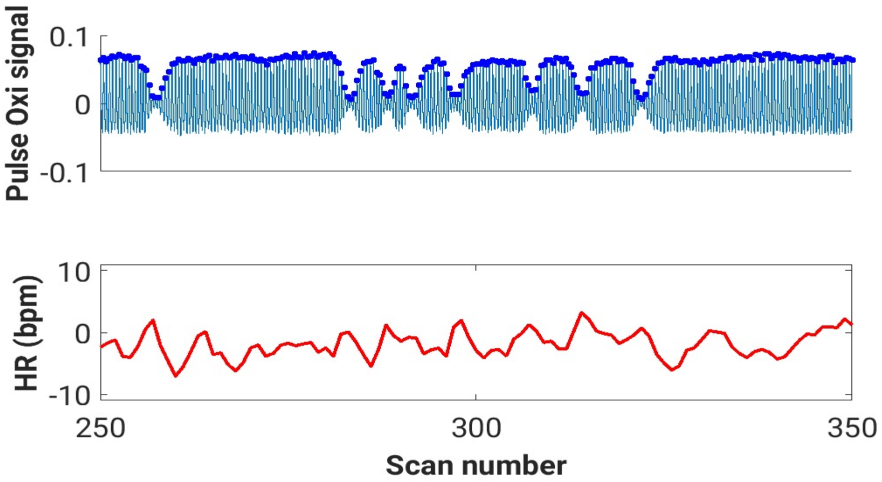
- During time segments of NREM N2 sleep, on average, we observed **a high co-occurrence (>80%) of the PPG-AMP drops with K-complexes in the EEG data.**

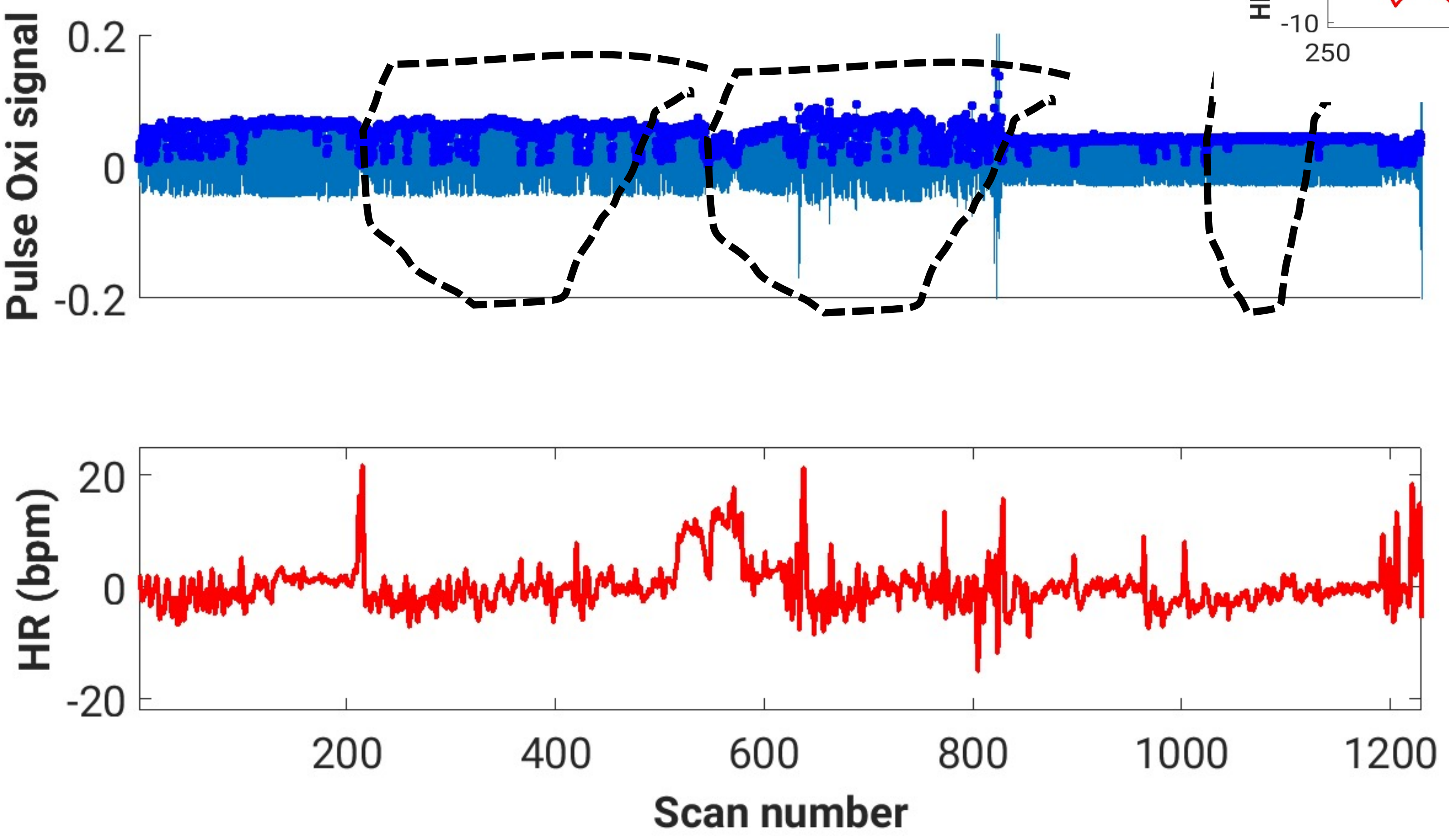
- Furthermore, **we found substantial correlation (r, ranging from -0.2 to -0.7 between subjects) between EEG and peripheral vascular tone,** consistent with previous studies that linked it to sympathetic activation (Ackner and Pampiglione, 1957)(Catcheside et al., 2002) of the super cervical ganglion, followed by changes in the fMRI signal.

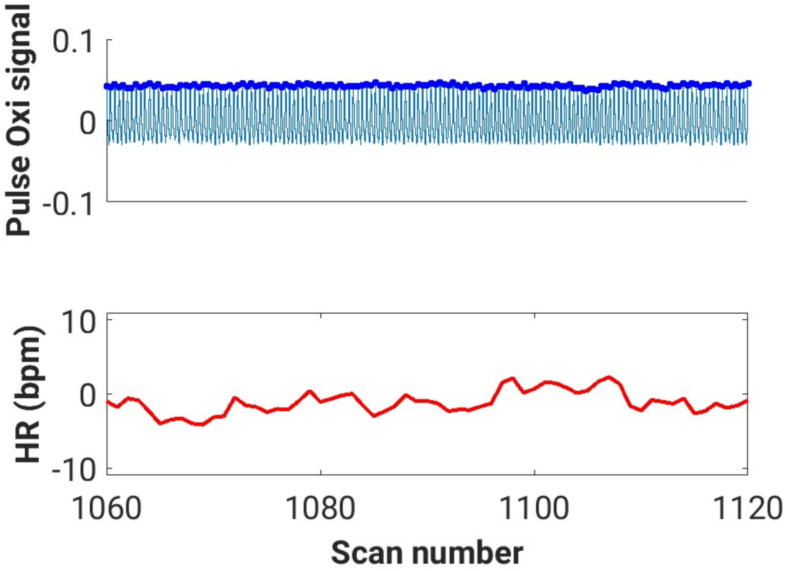
HR & Motion


All channels combined:
PPG signal
HR (bpm)
10
0
-10
Motion Rot degree: I-S
-0.05
-0.1
R-L
0.5
0.4
0.3
A-P
-0.25
-0.3
Motion Disp mm: Sup
0.2
0
-0.2
Left
-0.5
-1
-1.5
Post
0
-0.1
-0.2

Sleep data


Pulse Oxi signal
0.1
0
-0.1
HR (bpm)
10
0
-10
250
300
350
Scan number


Pulse Oxi signal
0.2
0
-0.2
HR (bpm)
20
0
-20
200
400
600
800
1000
1200
Scan number


Pulse Oxi signal
0.1
0
-0.1
HR (bpm)
10
0
-10
1060
1080
1100
1120
Scan number

Background (in house)

NeuroImage 87 (2014) 287–296

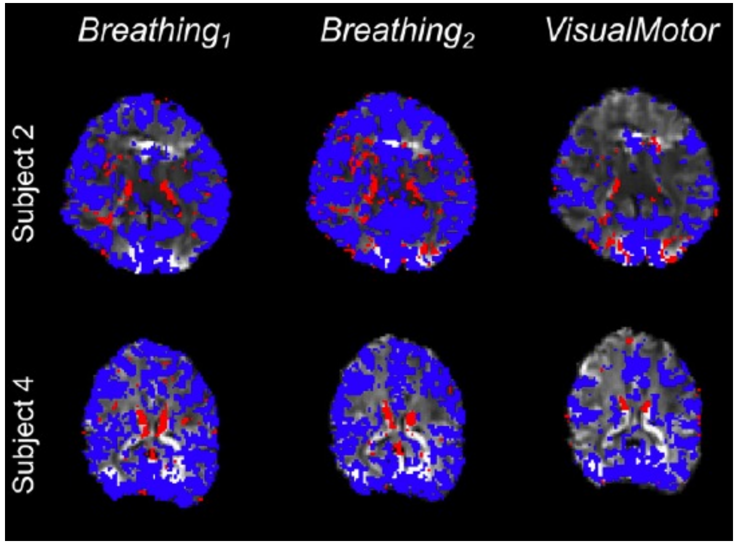
Contents lists available at ScienceDirect

NeuroImage

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

Early anti-correlated BOLD signal changes of physiologic origin

Molly G. Bright [a,b,*], Marta Bianciardi [a,c], Jacco A. de Zwart [a], Kevin Murphy [b], Jeff H. Duyn [a]



Significantly correlated (blue) and anti-correlated (red) voxels in the Breathing and VisualMotor data.

.. identified anti-correlated BOLD signal changes in response to respiratory challenges in voxels primarily located near edges of CSF stores.

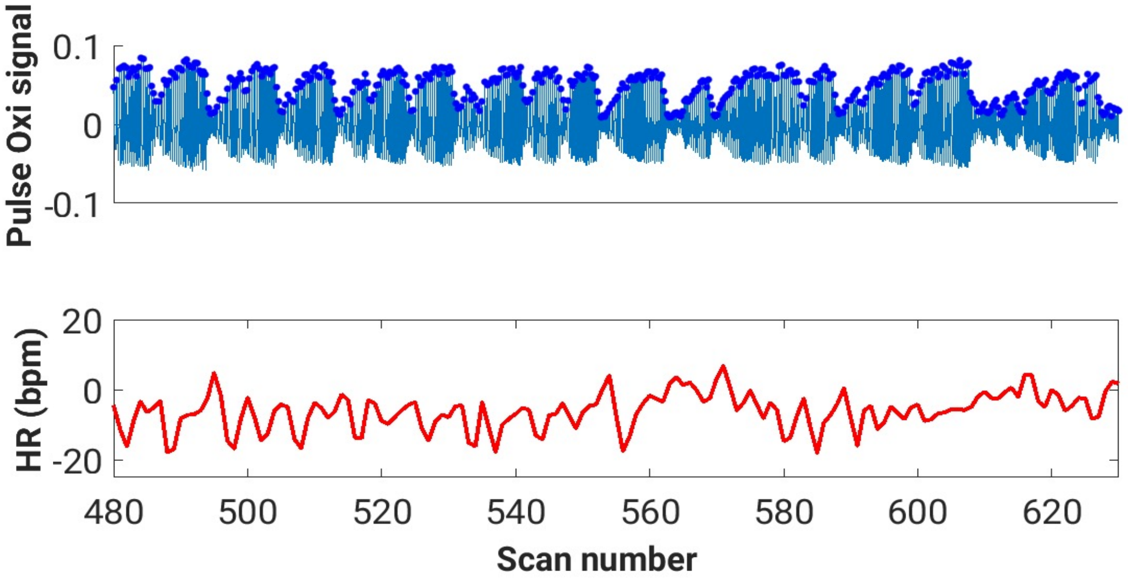
These signal changes occur earlier than the response across most of GM voxels.

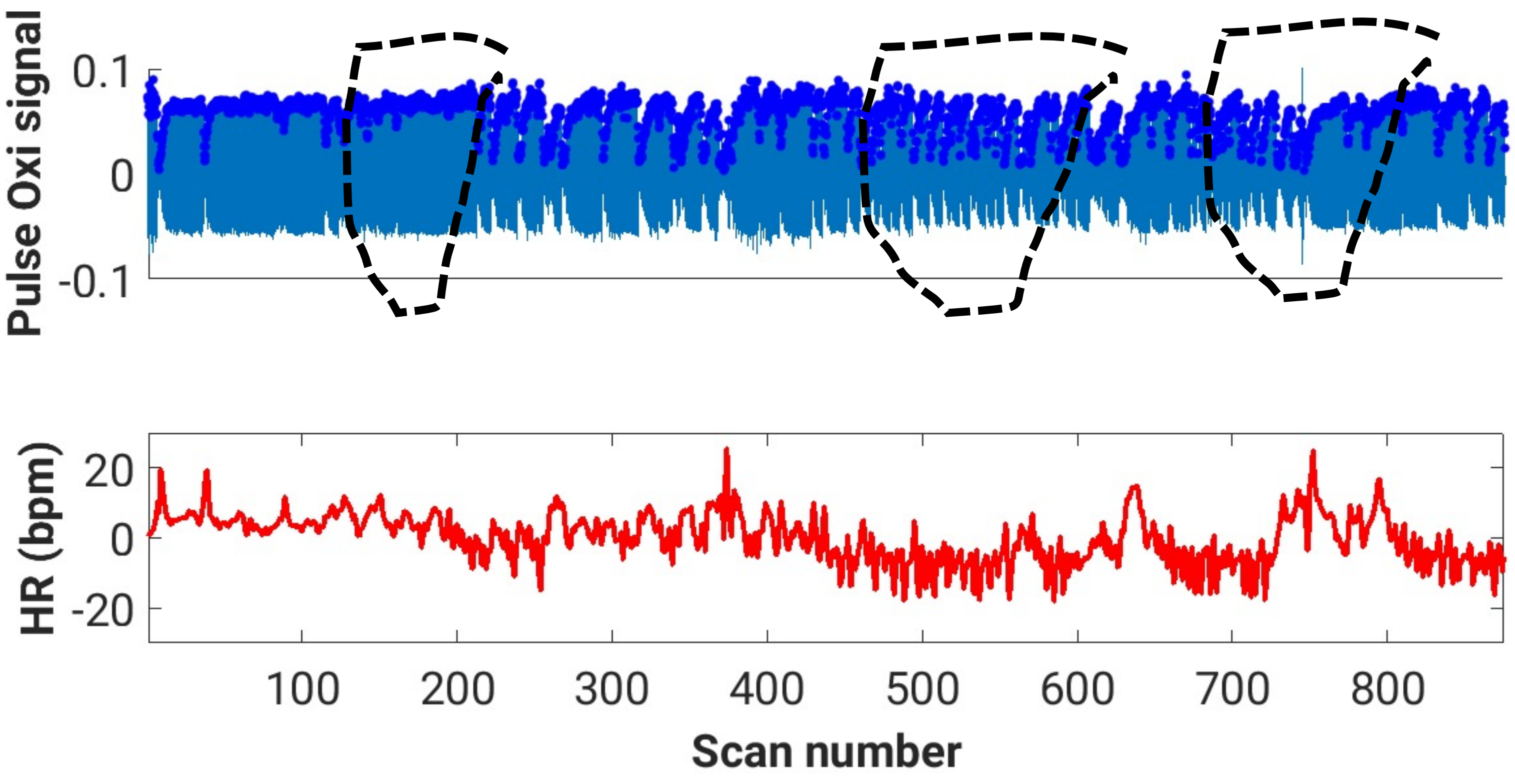
*.. these signal changes can be attributed primarily to changes in S0 associated with **increases in intracranial CSF volume** during widespread changes in cerebral perfusion.*

Sleep data

Subject 3

TR=3s, TE=36ms, in-plane res=2.5 mm, slice thickness=2 mm, slice gap=0.5 mm), Grappa = 2, 3 T





- Extensive lesion and anatomic studies have implicated the functional significance of white matter in neurological and **psychiatric diseases**.

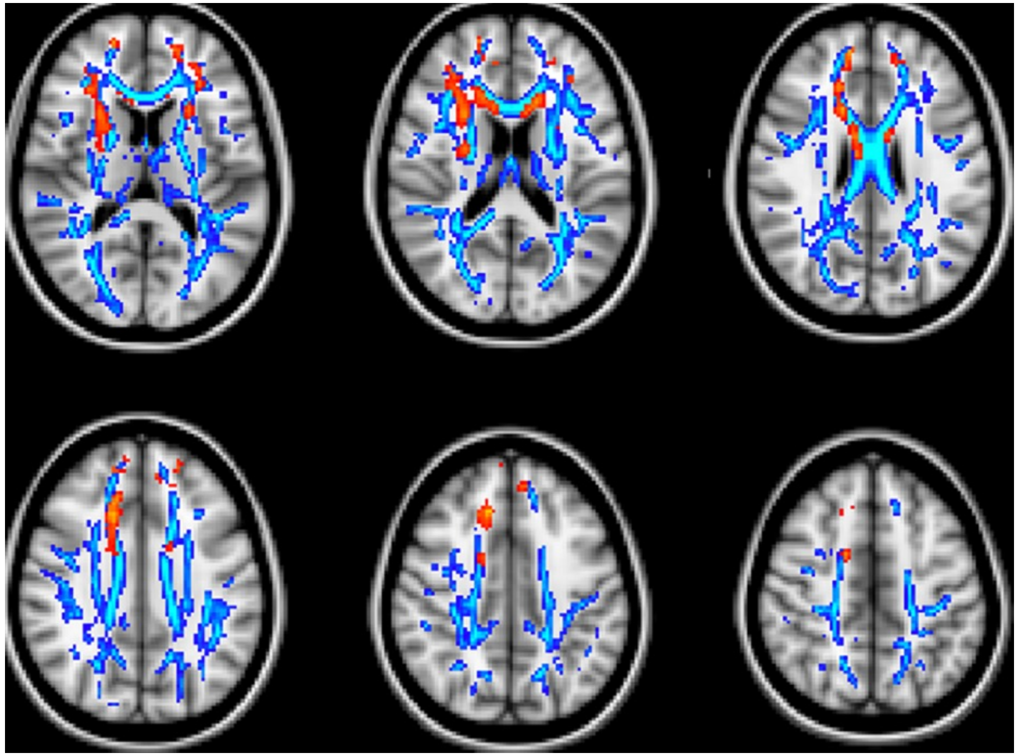
Brain Imaging and Behavior (2015) 9:868–877
DOI 10.1007/s11682-014-9349-1

ORIGINAL RESEARCH

White matter abnormalities of microstructure and physiological noise in schizophrenia

Hu Cheng · Sharlene D. Newman · Jerillyn S. Kent · Amanda Bolbecker · Mallory J. Klaunig · Brian F. O'Donnell · Aina Puce · William P. Hetrick

- Decrease in fractional anisotropy (FA): an indicator of white matter integrity.
- Regions of significant **FA reduction** for schizophrenia (blue-light blue, track-based spatial significance analysis, $p<0.05$ to $p<0.01$)
- Voxels that are significantly different between patient and control from the **temporal-SNR analysis** (red-yellow, $p<0.001$ uncorrected to $p<0.05$ FEW corrected).



Background

Original Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
2017, Vol. 37(2) 564–576

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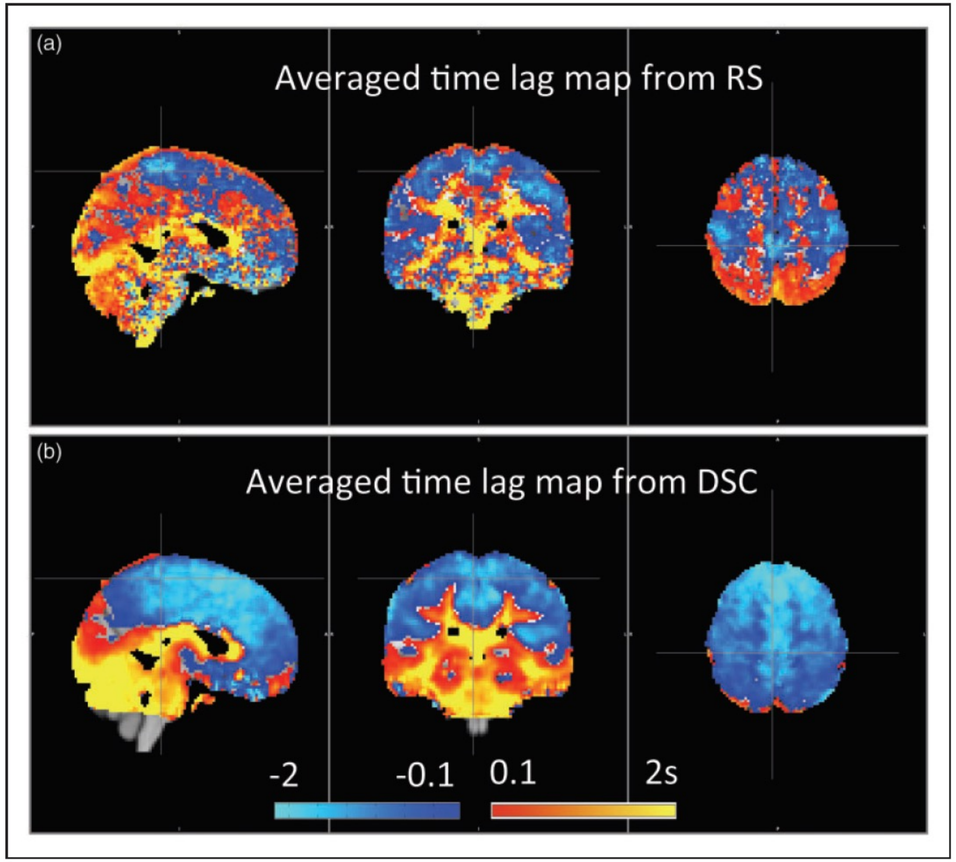
DOI: 10.1177/0271678X16631755
jcbfm.sagepub.com
SAGE

Perfusion information extracted from resting state functional magnetic resonance imaging

Yunjie Tong[1,2], Kimberly P Lindsey[1,2], Lia M Hocke[1,3], Gordana Vitaliano[1,2], Dionyssios Mintzopoulos[1,2] and Blaise deB Frederick[1,2]



The first 10 ICs that show high positive correlations with the peripheral data.

The IC pattern with the highest negative correlation with the peripheral data is also shown in the last panel.

Background

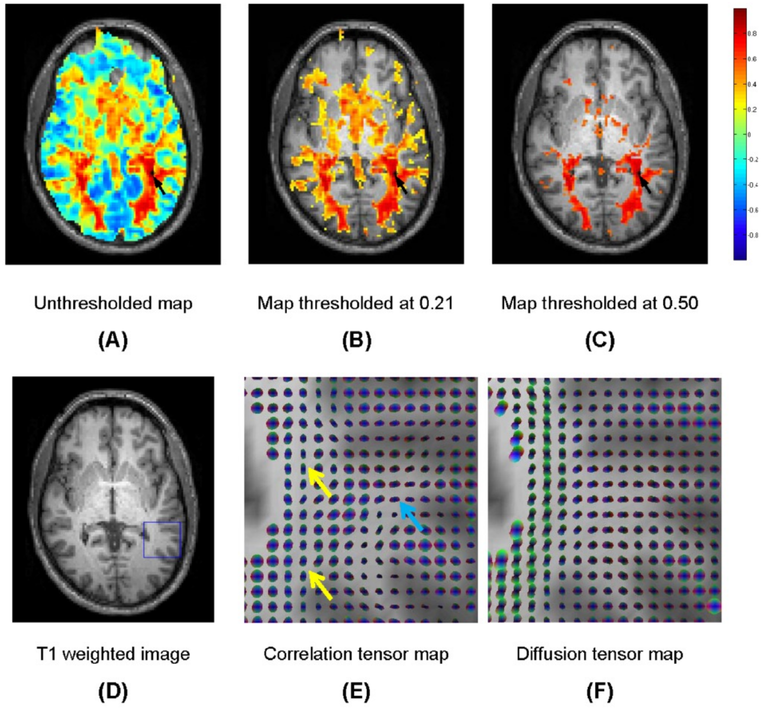
OPEN ACCESS Freely available online PLOS | ONE

Spatio-Temporal Correlation Tensors Reveal Functional Structure in Human Brain

Zhaohua Ding[1,2,3,4,5]*, Allen T. Newton[1,6], Ran Xu[1,2], Adam W. Anderson[1,2,3], Victoria L. Morgan[1,2,3], John C. Gore[1,2,3,5,7,8]

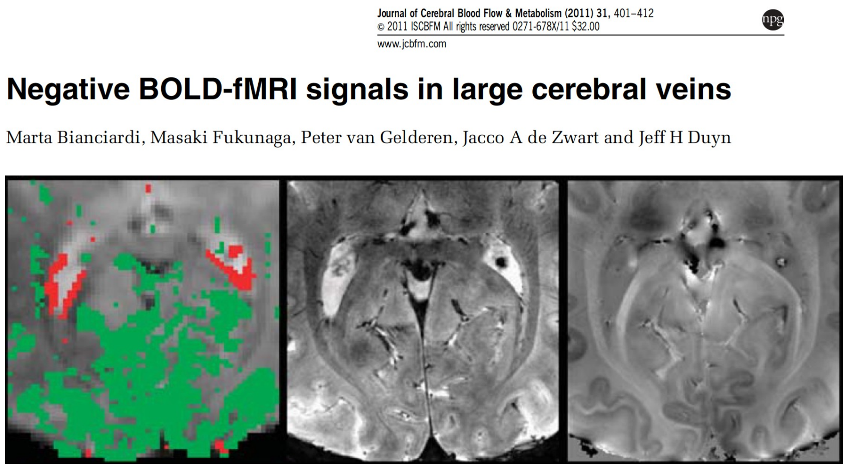
.. appropriate analysis of resting state acquisitions may reveal MRI signal variations within WM that reflect neural electrical activity and the propagation of information.

In WM, evidence of anisotropy would be consistent with our hypothesis and could form the basis of a new way to integrate directly the structure and function of neural networks in the human brain.



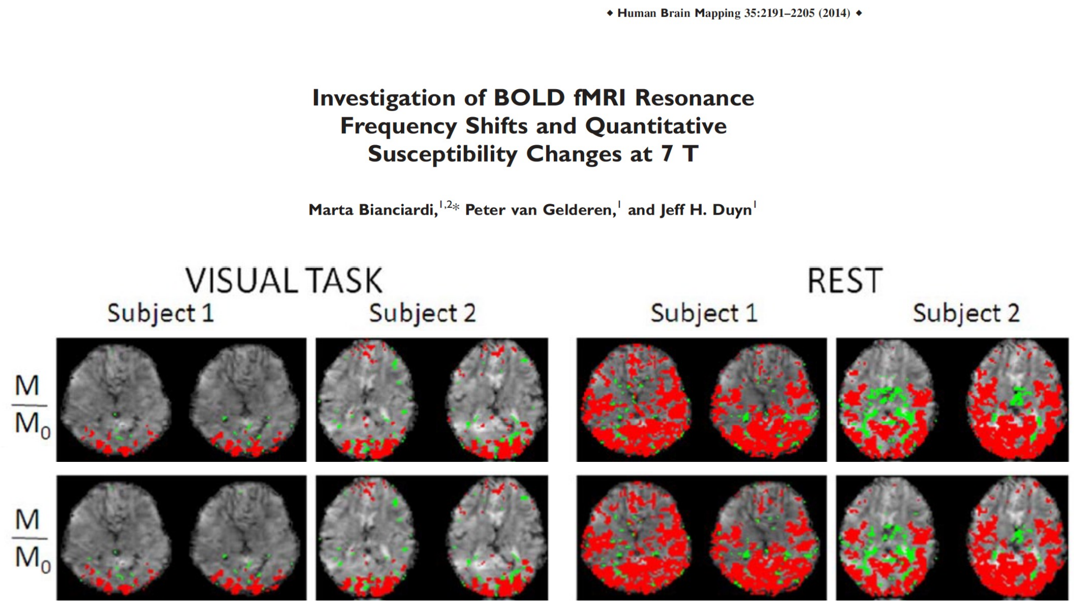
Maps of temporal correlations of BOLD signals to a seed in the left optic radiation.

Background



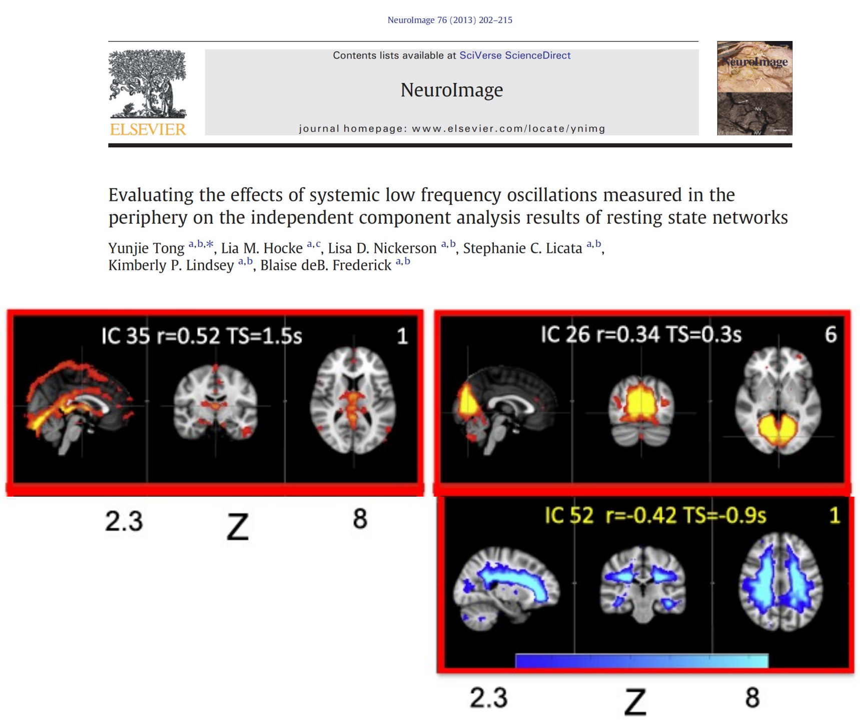
(left) the spatial distribution (red/green) of fMRI signals anti-correlating and positively correlating with the seed time series in the visual cortex; (middle) magnitude and (right) phase images (TE=28.5 ms).

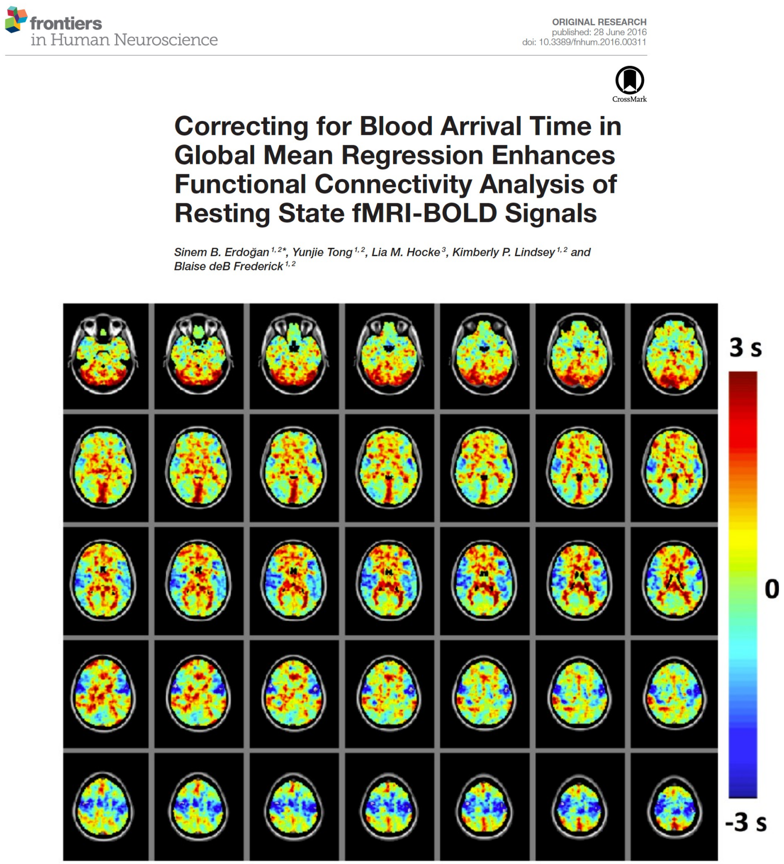
*.. negative BOLD signals were consistent with increases in **local blood volume**.*



BOLD fMRI (Magnitude) activity maps during visual task and at rest for two subjects (red/green: positive/negative activity): (top) without and (bottom) with physiological noise correction.

Background





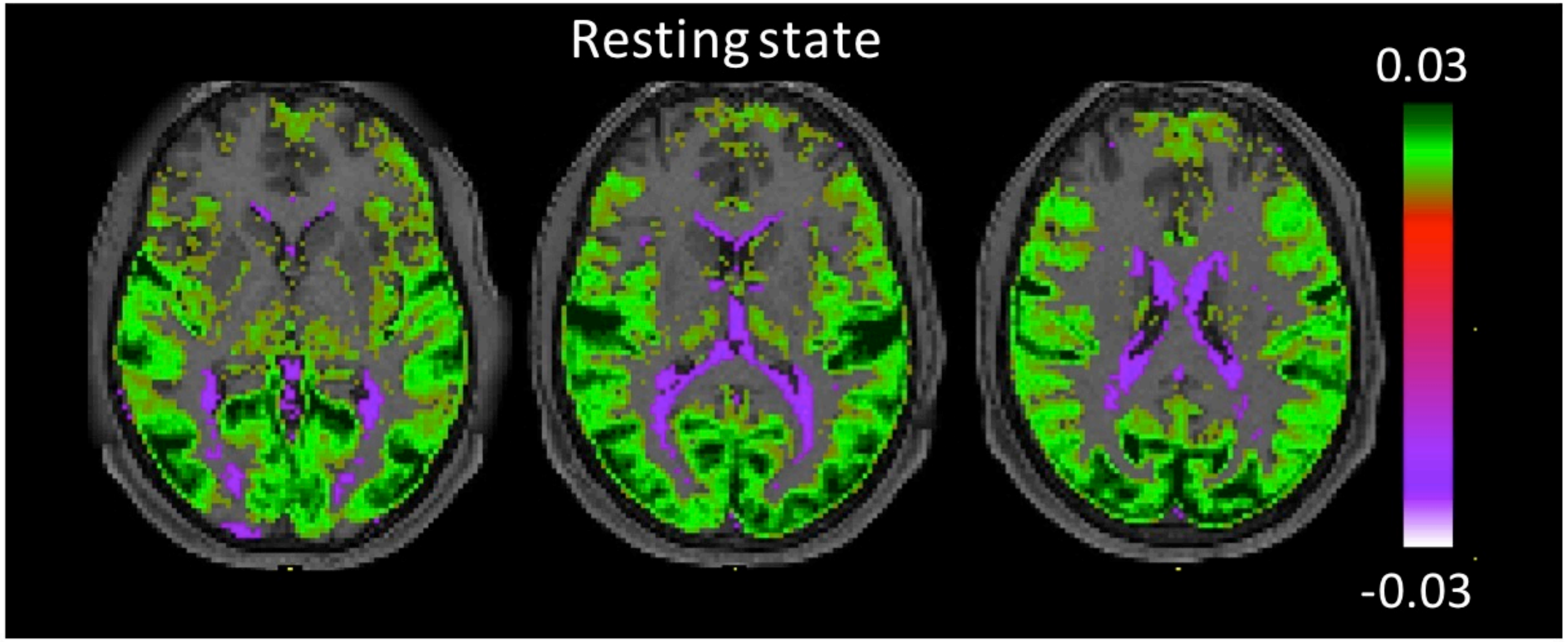
.. ICs that show high positive correlations & highest negative correlation with the peripheral data.

Common areas: deep-WM & ventricles & large veins

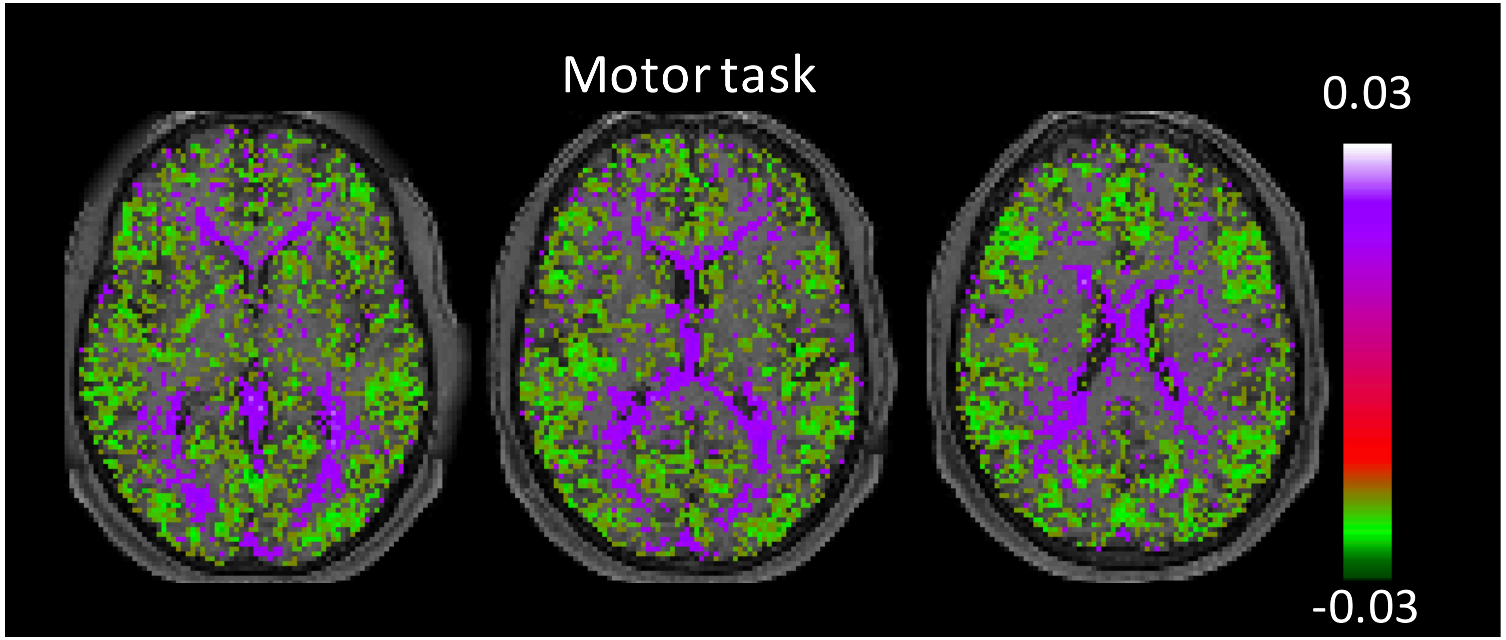
Time delay map indicates the relative arrival time of global signal to each voxel.

Maps represent the group (#) average of the voxel-specific delays in arrival time of the global signal.

Human connectome data *(1200 subject release), similar correlation patterns observed with PPG amplitude, average results shown for ~600 subjects, correlation lag 3.5 s.*



Human connectome data *(1200 subject release), similar correlation patterns observed with PPG amplitude, average results shown for ~600 subjects, correlation lag 3.5 s.*



Sleep data

Corresponding data among fMRI scans which had

1) **least amount of motion**
2) **cleanest PPG data**
3) **isolated amplitude drops in PPG signal**
4) **segment of NREM sleep**

[light sleep]

Resting state and sleep

~30% of connectome data scored as sleep