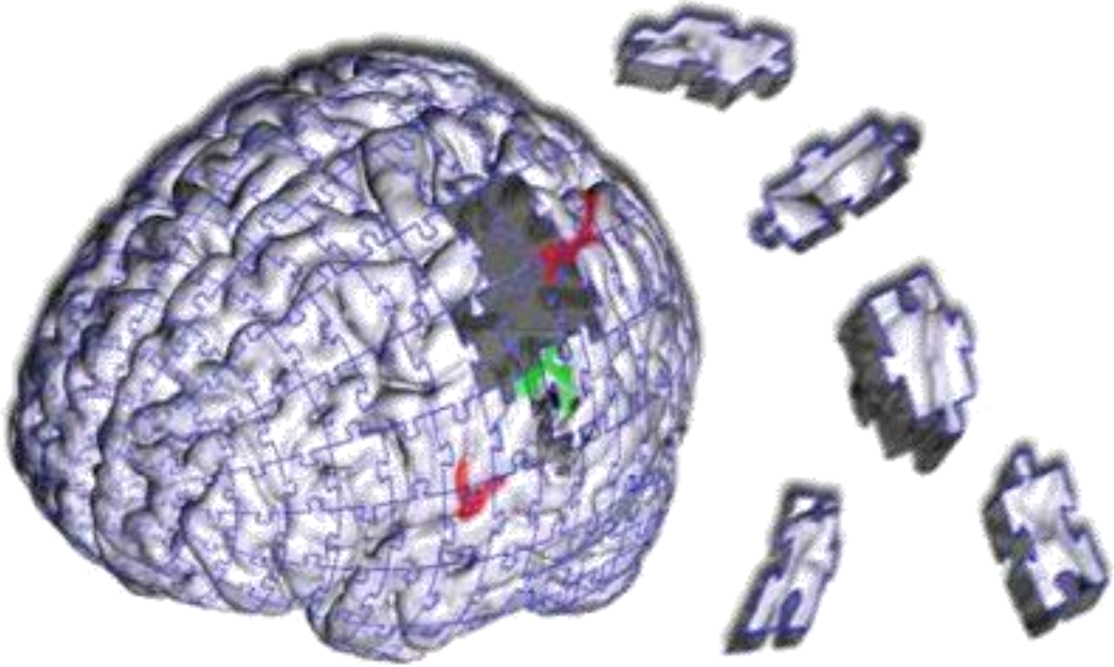
Controlling spontaneous brain activity - a paradox?

Institut für Systemische Neurowissenschaften

SPM Kurs 2016



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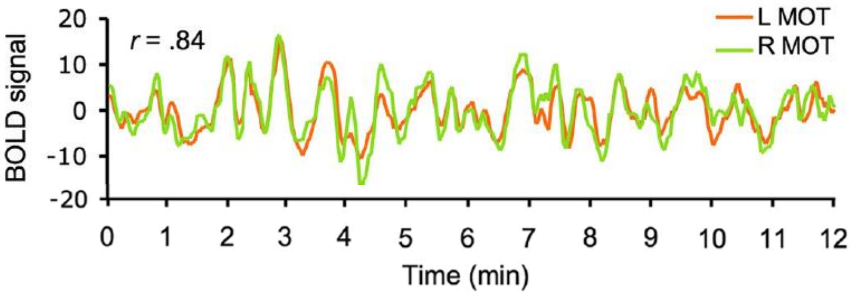
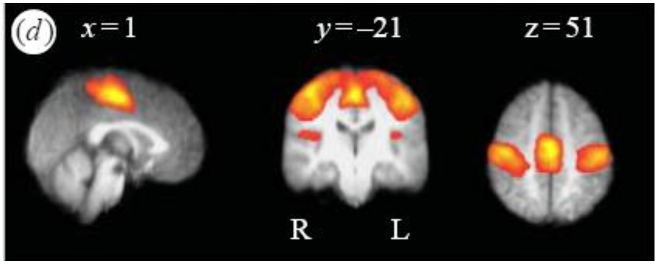
und Forschung

Resting State Brain Activity

I. **What is it (phenomenology)?**
II. When should we consider RS experiments?
III. How do we do it?
IV. Caveats (technical)
V. When resting state experiments (part II)?
VI. Caveats (biological)

Resting state brain activity
correlations despite task absence





sensory
motor

left: Van Dijk et al. Journal of neurophysiology 2010; *right*: Beckmann et al. Phil Trans Roy Soc London 2005

Biswal, B. B.: Resting State Fmri: A Personal History, Neuroimage, *62 (2012), 938-44*.

Biswal, B.; Yetkin, F. Z.; Haughton, V. M.; Hyde, J. S.: Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI, Magn Reson Med, *34 (1995), 537-41*.

Resting state brain activity

(fMRI, functional connectivity)

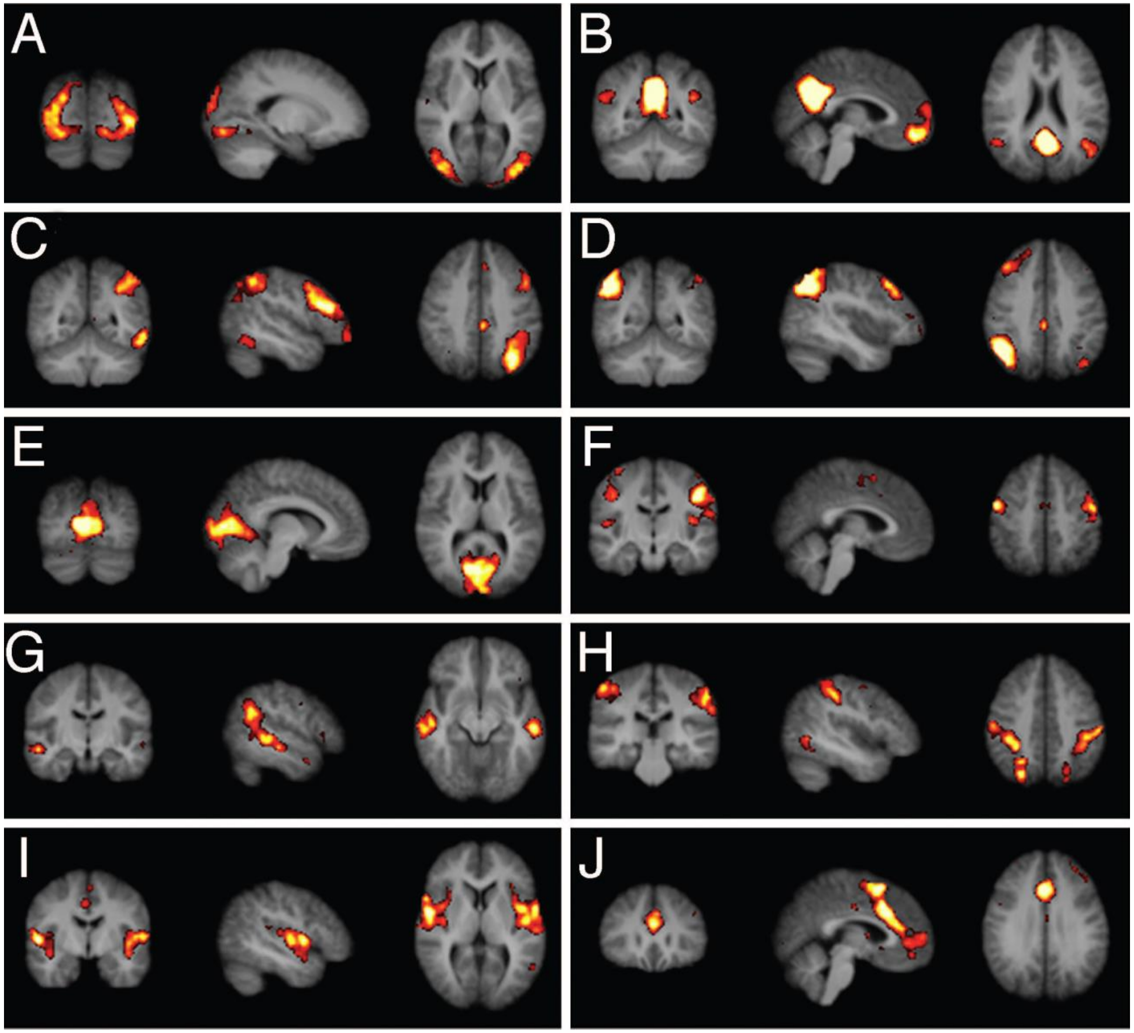
lateral visual

memory (left)

medial visual

ventral stream (visual)

auditory



default mode

memory (right)

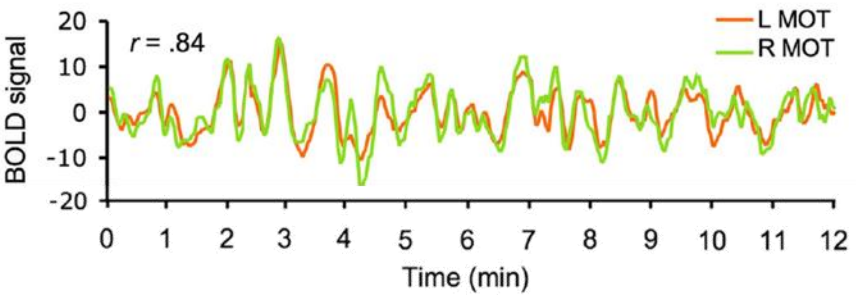
sensory-motor

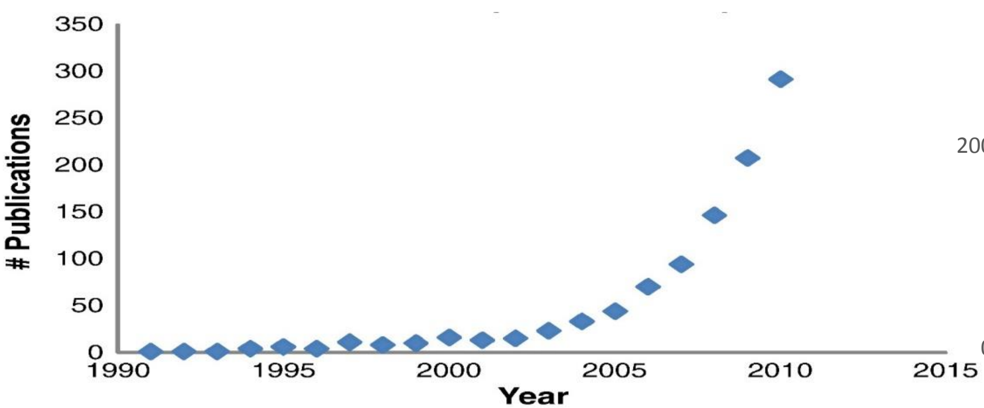
executive control

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103, 13848-13853.

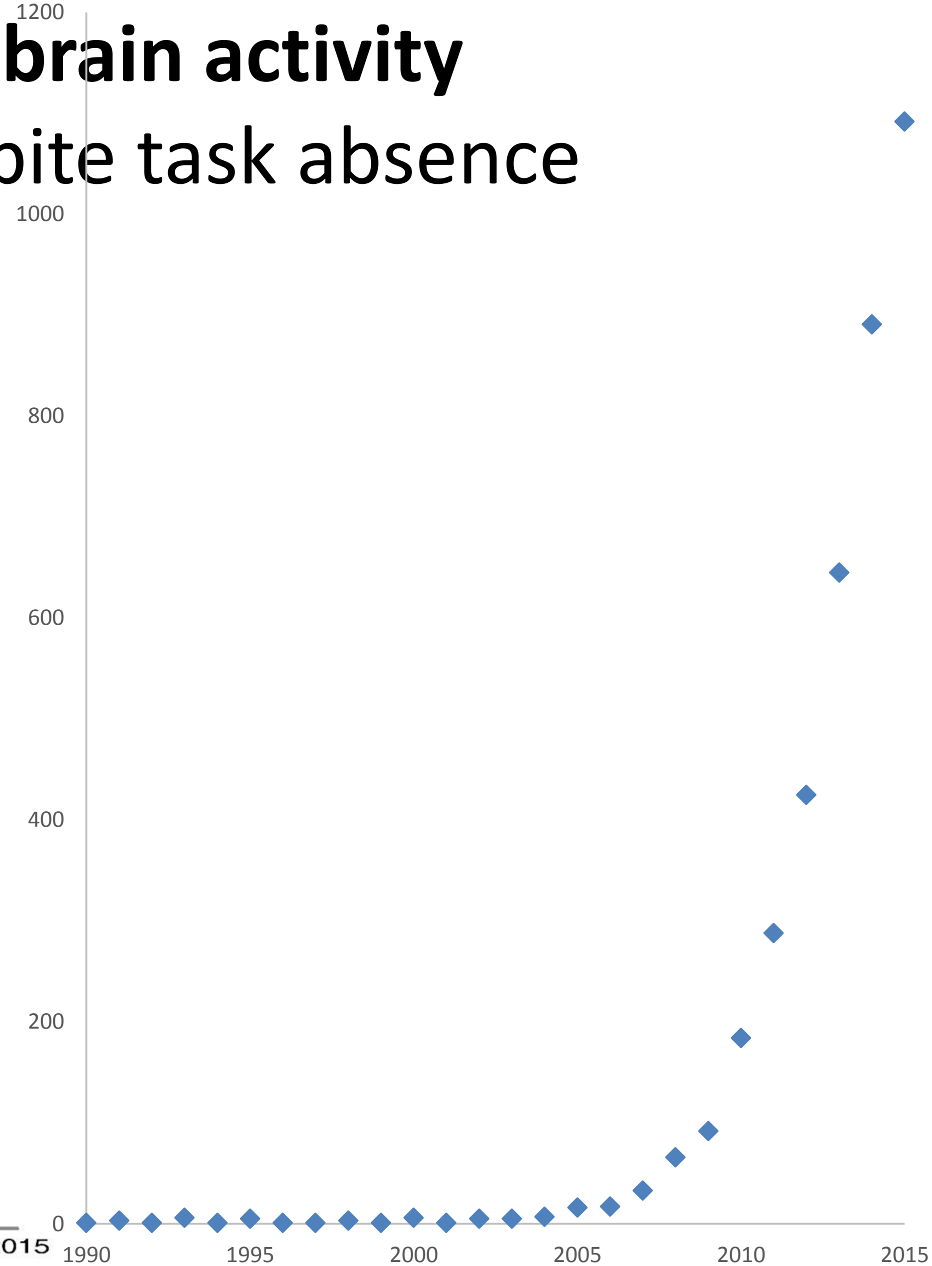
Resting state brain activity

correlations despite task absence



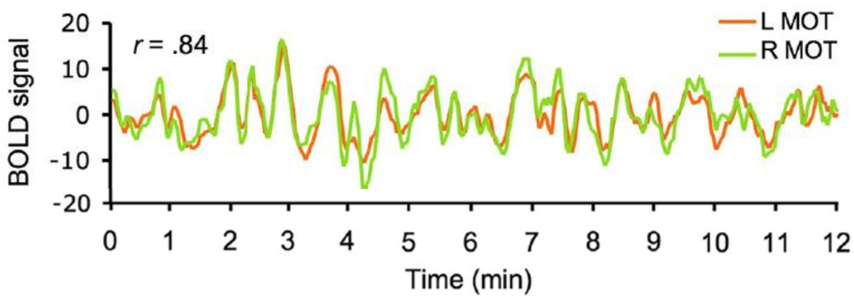


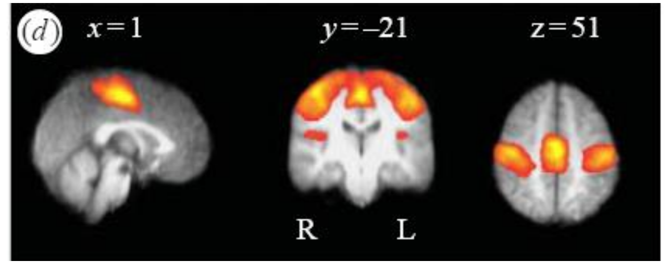
Number of publications per year on resting-state functional connectivity.



resting state functional connectivity (PubMed, 21.09.2016)

Resting state brain activity
correlations despite task absence





sensory
motor

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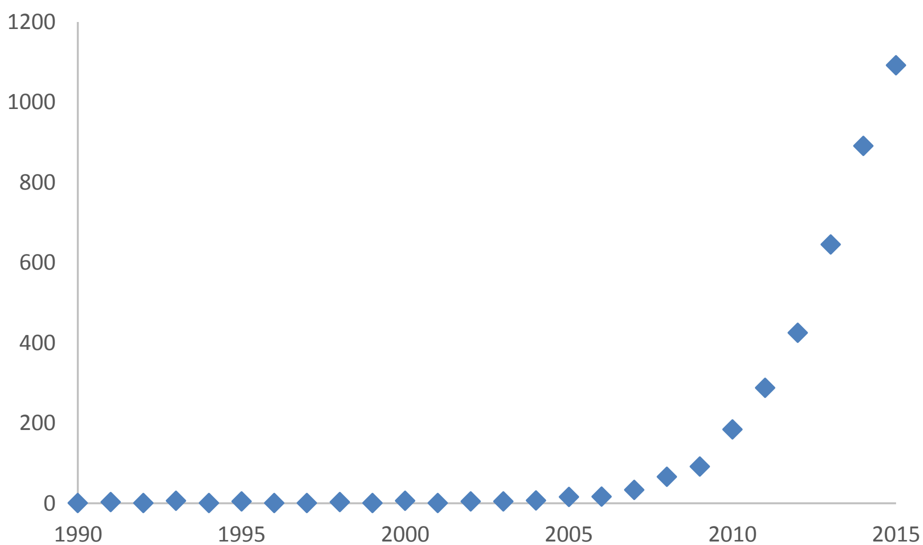

resting state functional connectivity (PubMed, 21.09.2016)

…established

Biswal et al. Magn Reson Med 1995

…en vogue

~900 PubMed citations past year

…unknown

what is the biological origin?

Buckner and Vincent, 2007; Greicius et al., 2003; Gusnard et al., 2001, Shmuel et al. 2008, 2002

…uncontrolled

eyes closed rest, no task

4 – 12 min (Van Dijk et al. J Neurophys 2010)

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Three scenarios

I. subjects cannot engage in a paradigm
II. spontaneously occurring phenomena are of interest
III. network comparison between healthy and patient groups

Three more scenarios

I. subjects cannot engage in a paradigm
II. spontaneously occurring phenomena are of interest
III. Network comparison between healthy and patient groups

IV. Let's just do it, the subject is in the scanner anyway.
V. It only lasts for an additional 10 min.
VI. We can worry about the science later (student).

scenario I

I. **subjects cannot engage in a paradigm**

- Sleep

  e.g. Dang-Vu et al. Proc Natl Acad Sci U S A 2008
- Coma

  e.g. Owen et al. Prog Brain Res 2009
- epileptic seizure

  e.g. Tyvaert, Hawco et al. Brain 2008
- studies of infants

  e.g. Ment, Hirtz et al. Lancet Neurol 2009
- studies of (untrained) animals

  e.g. Vincent, Patel et al. Nature 2007

scenario II

II. spontaneously occurring (EEG) phenomena of interest

- epileptic spikes

  e.g. Gotman et al. J Magn Reson Imaging 2006; Laufs et al. Curr Opin Neurol 2007, 2012
- sleep spindles, vertex sharp waves, K-complexes

  e.g. Schabus et al. PNAS 2007; Stern et al. Clin Neurophys 2011; Jahnke et al. Neuroimage 2012
- resting EEG oscillations

  e.g. Laufs Hum Brain Mapp 2008

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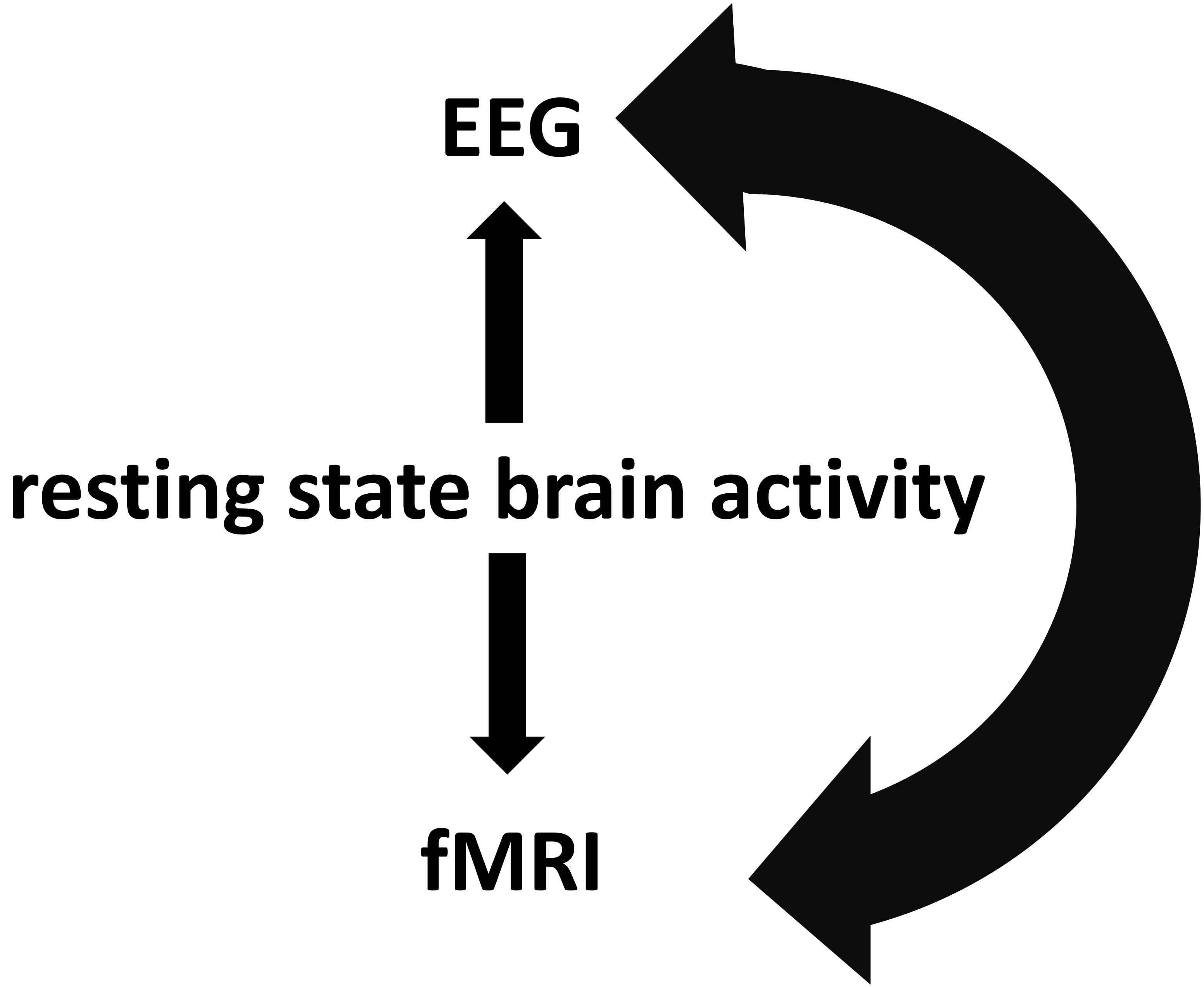
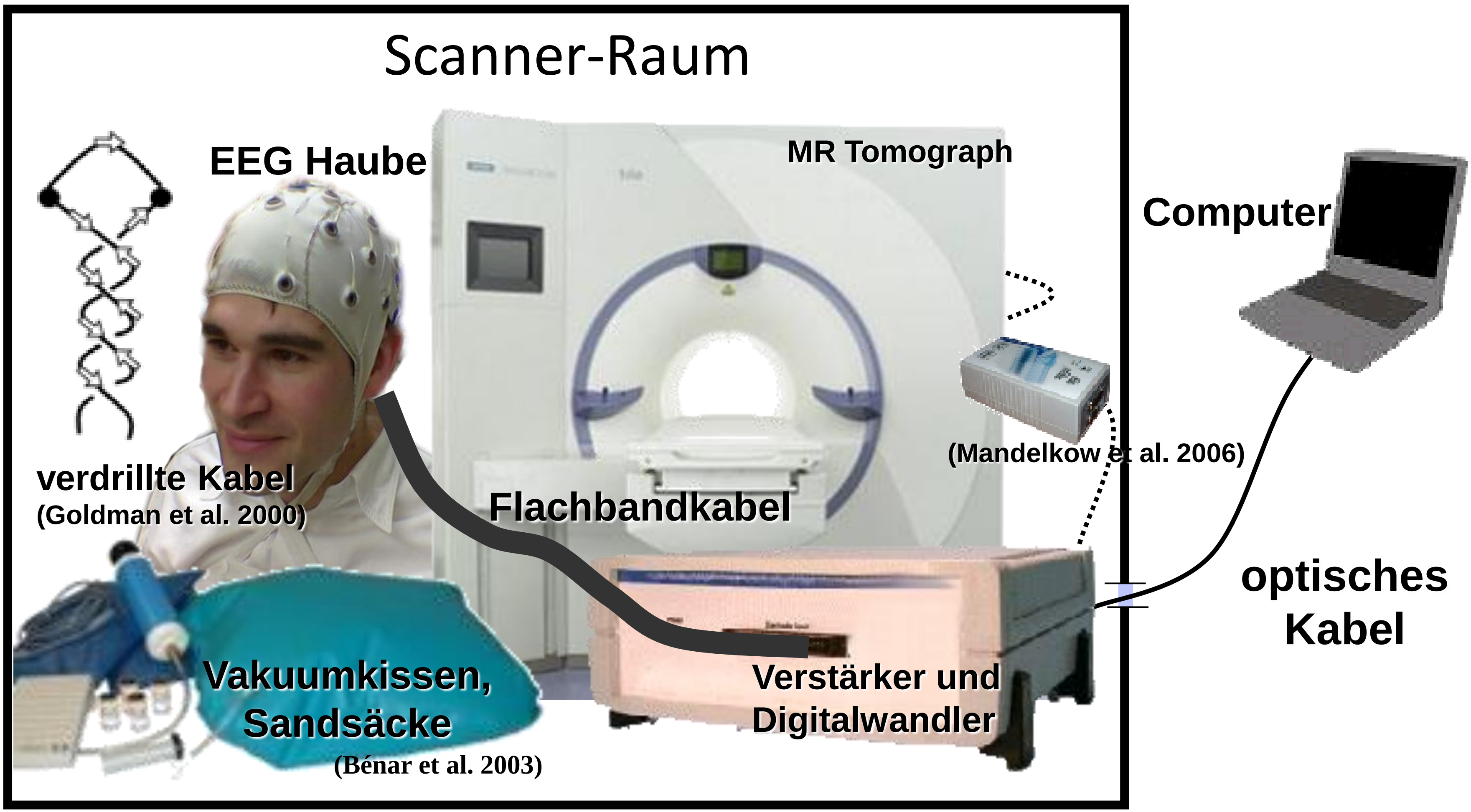
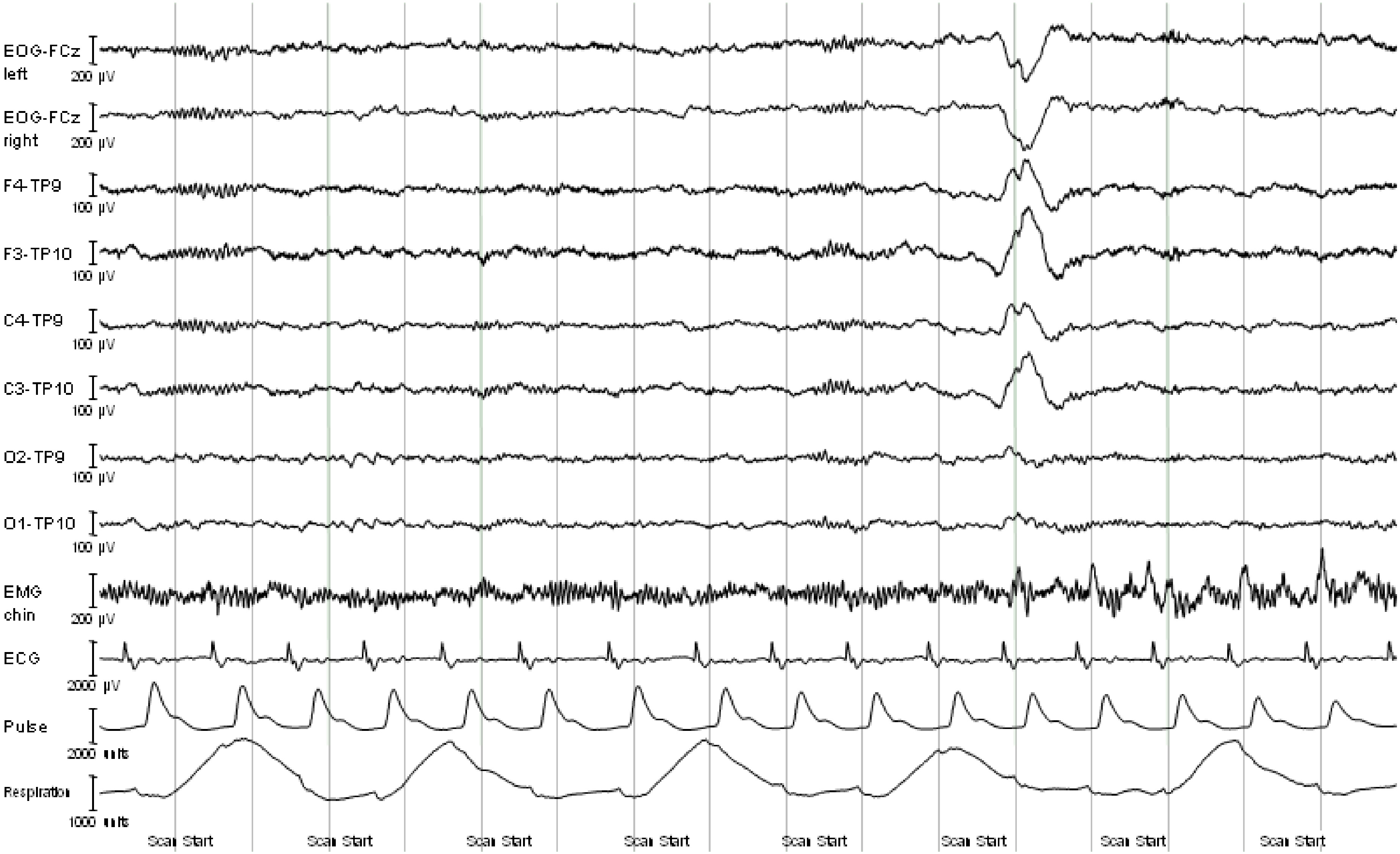

EEG
resting state brain activity
fMRI

Simultane Aufzeichnung von EEG/fMRT

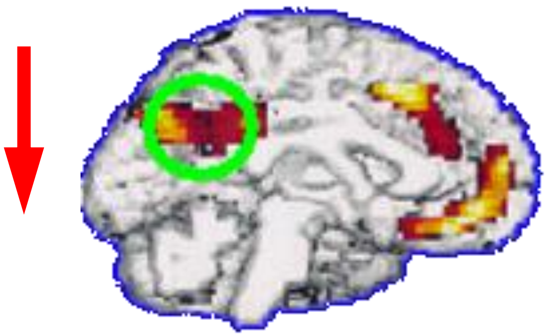


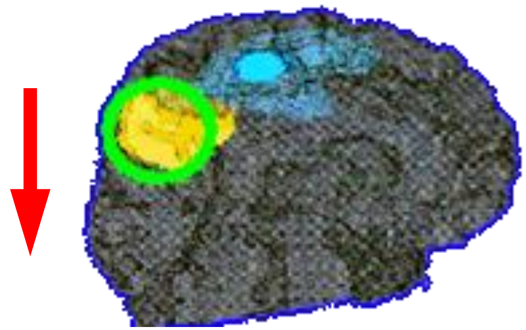
polysomnography-fMRI



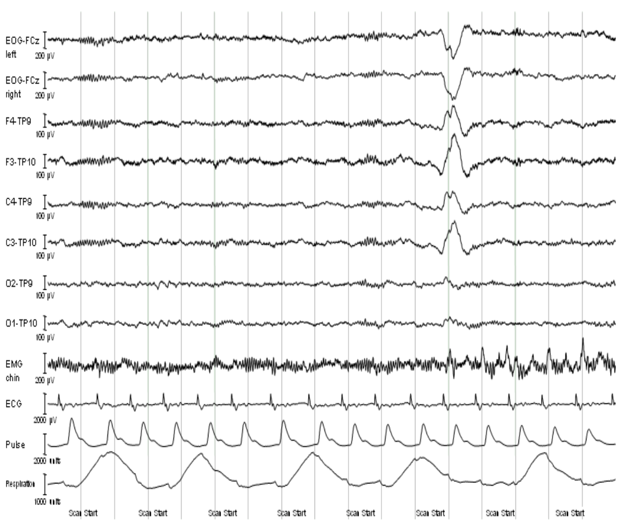
(Jahnke et al. 2012)

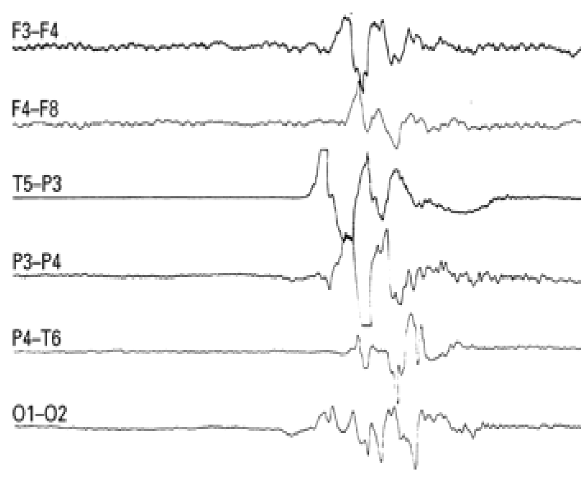
I. subjects cannot engage in a paradigm: **sleep, coma, seizure**

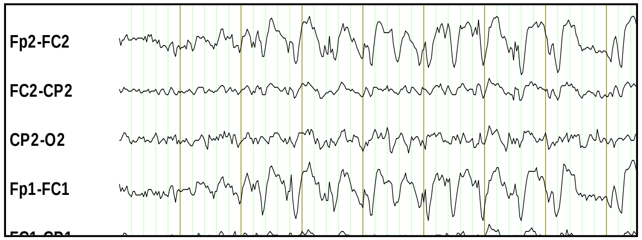




sleep vs. awake | **coma vs. awake** | **seizure vs. no seizure**

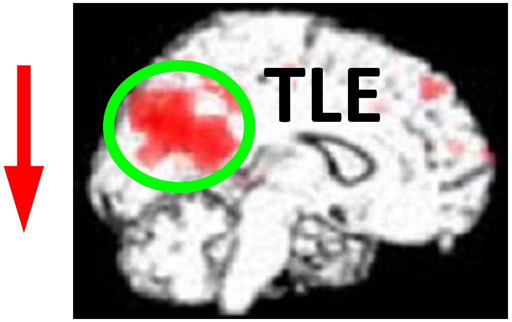


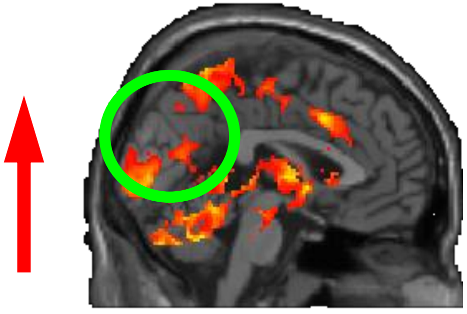


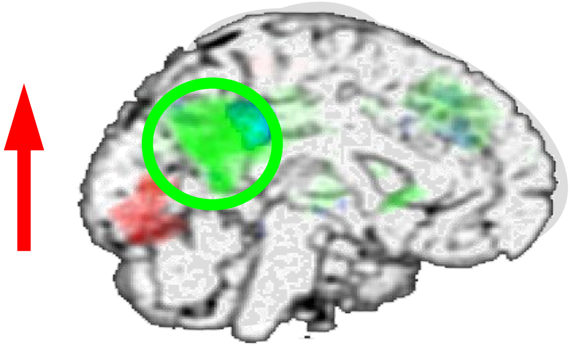


II. spontaneously occurring (EEG) phenomena of interest

epileptic spikes, K-complexes, beta oscillations



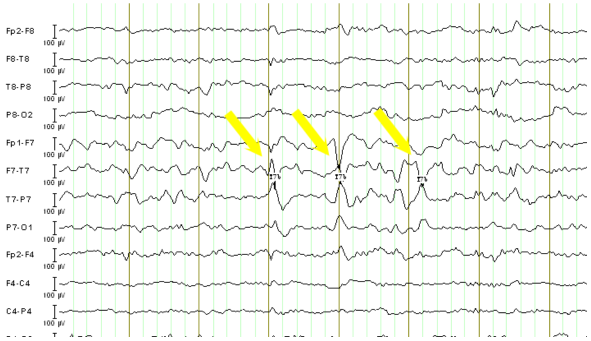


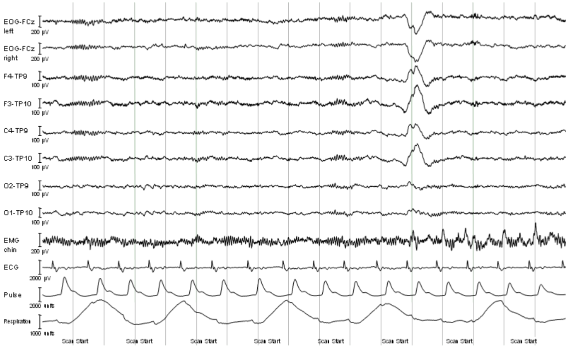


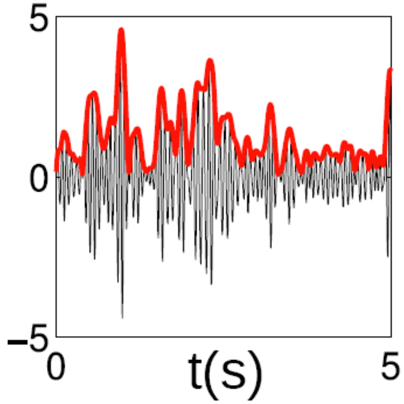
temporal lobe spikes vs. background

K-complexes vs. N2 background

17-23 Hz beta oscillations







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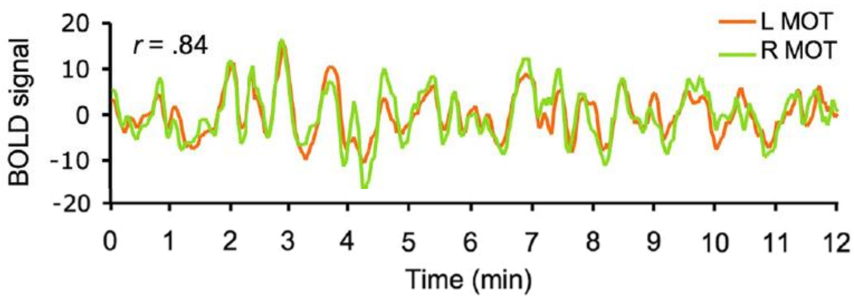
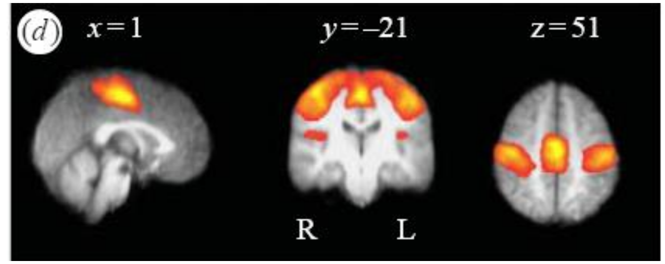
If you do not have EEG…?

Data driven approaches

I. seed correlation (functional connectivity)
II. ICA
III. graph analysis

Resting state brain activity
seed correlation (functional connectivity)





sensory
motor

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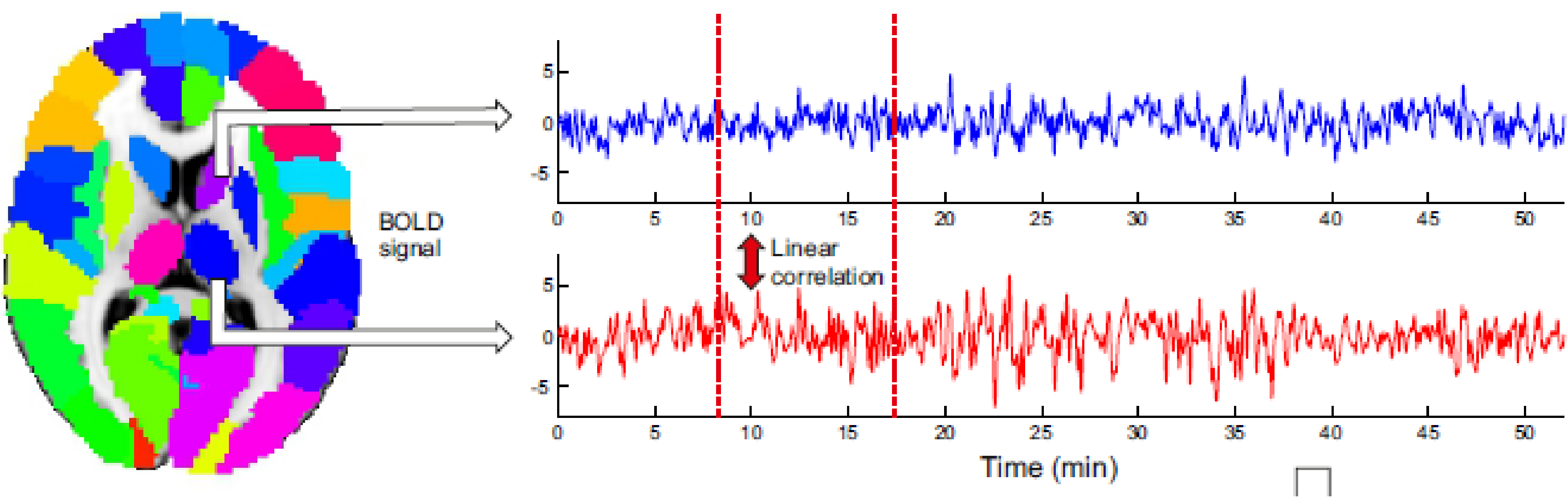

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respiratory noise

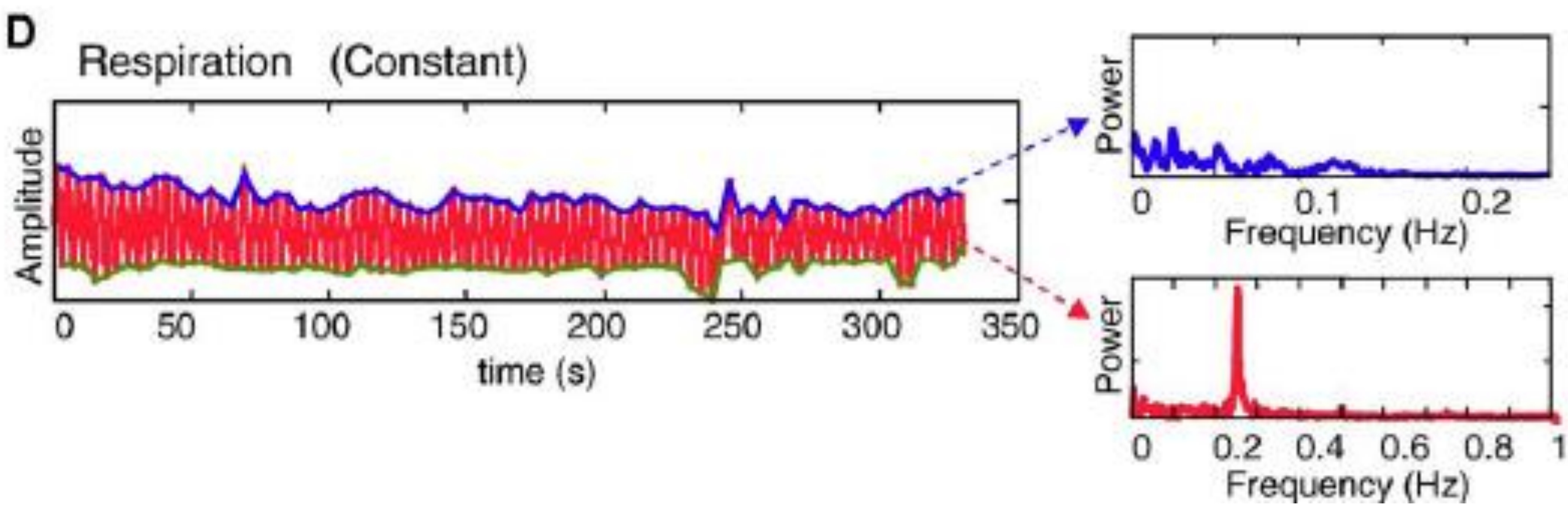
ELSEVIER

NeuroImage

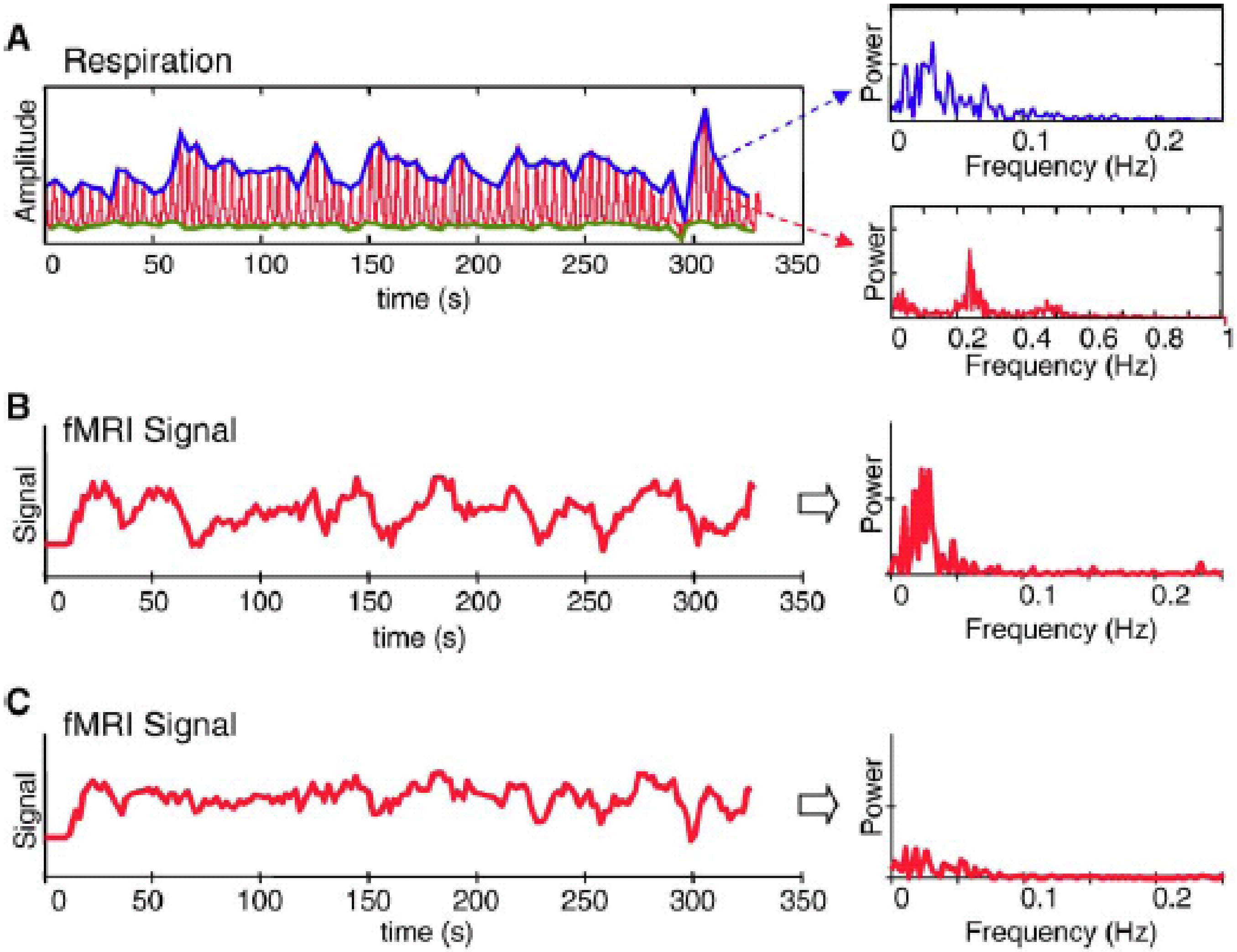
www.elsevier.com/locate/ynimg
NeuroImage 31 (2006) 1536 – 1548

Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI

Rasmus M. Birn,* Jason B. Diamond, Monica A. Smith, and Peter A. Bandettini



respiratory noise

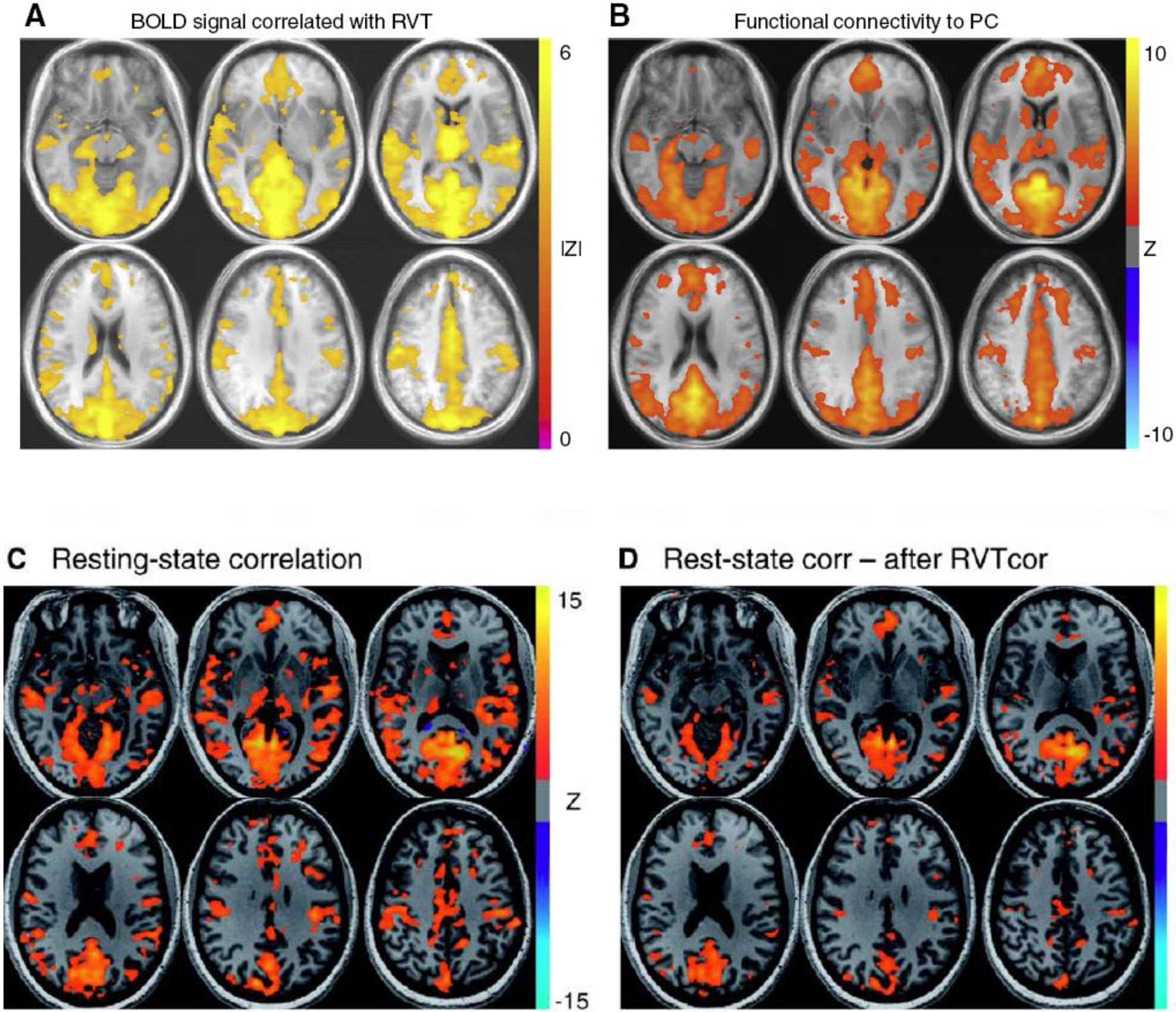


respiration and envelope

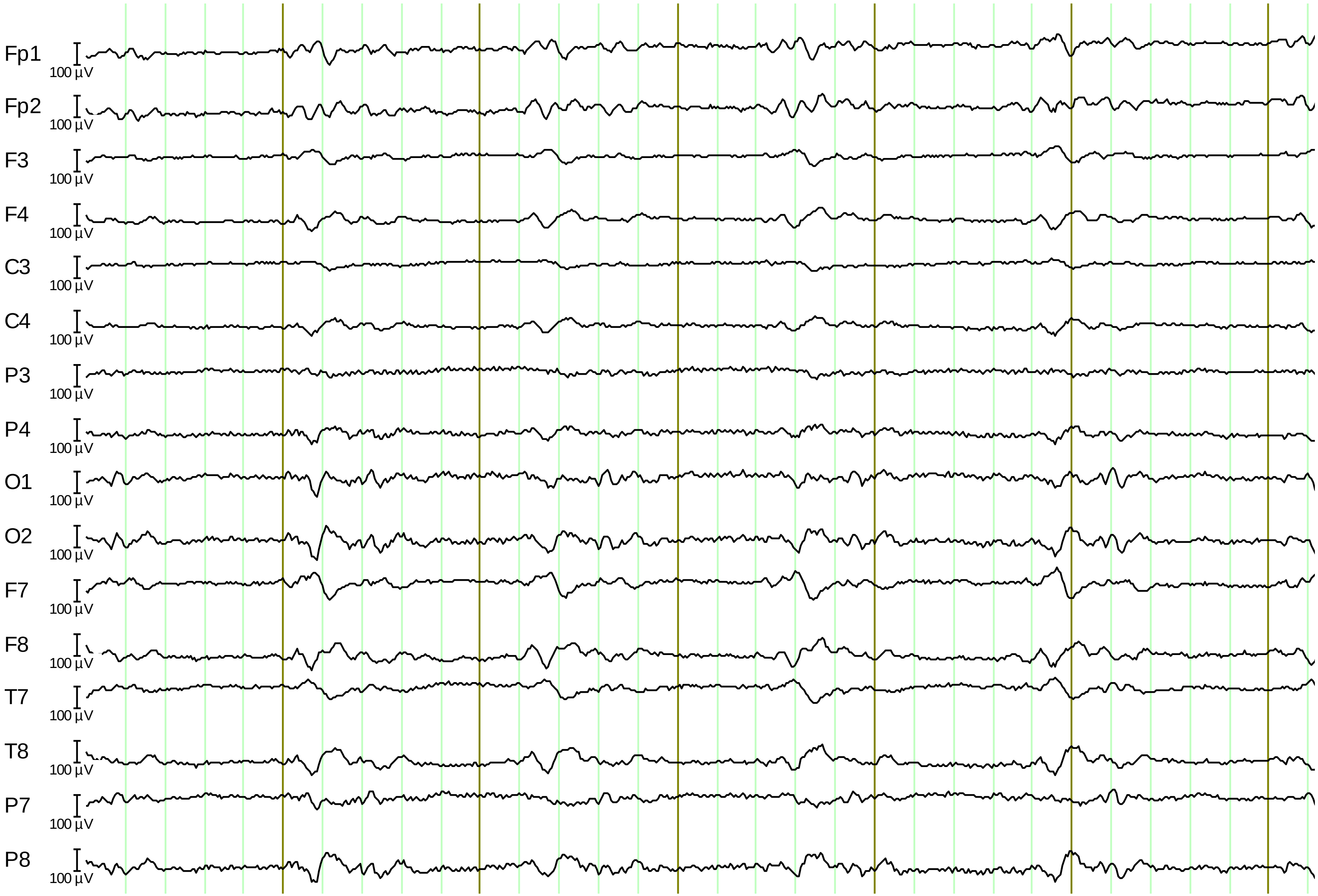
fMRI signal from 1 voxel

after RVT regression

Birn et al. 2006


A
BOLD signal correlated with RVT
6
|Z|
0
B
Functional connectivity to PC
10
Z
-10
C
Resting-state correlation
15
Z
-15
D
Rest-state corr – after RVTcor
15
Z
-15

Cardiac noise

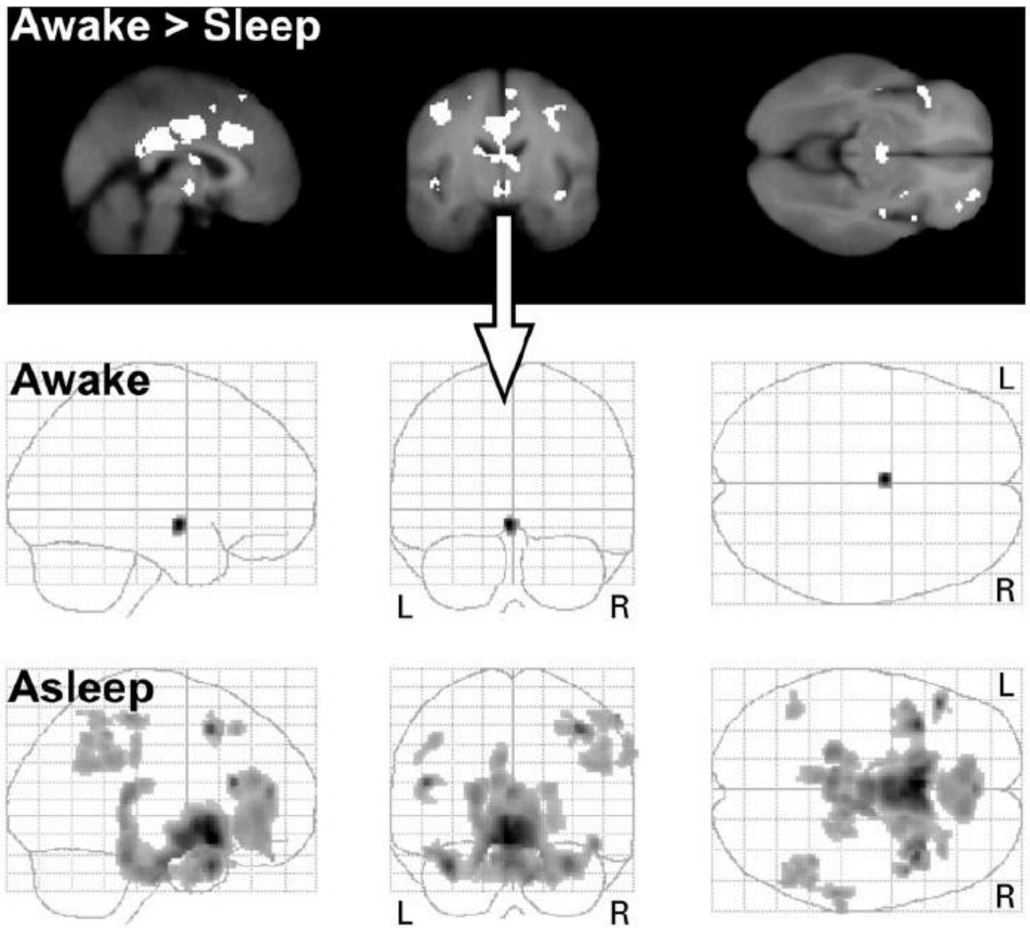


Cardiac noise

doi:10.1093/brain/awh686

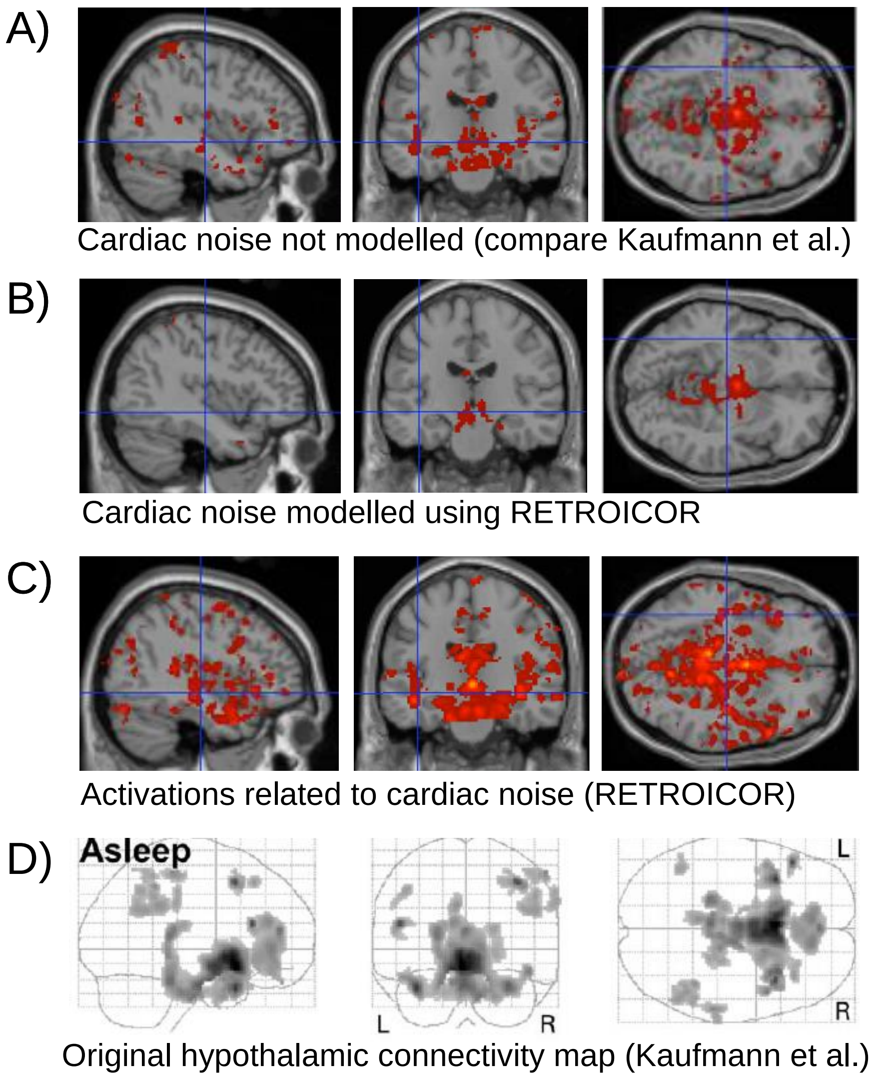
Brain (2006), **129**, 655–667

Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study



Cardiac noise

Maps of functional connectivity and cardiac noise



Kaufmann et al. 2006, Laufs et al. 2007

contributions to the BOLD signal unrelated to neuronal activity

1. Scanner drift
2. Subject motion
3. Circulation
4. Respiration

contributions to the BOLD signal unrelated to neuronal activity

1. Scanner drift
2. Subject motion
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4. Respiration

=> „false positive“ correlations in the BOLD signal

excursion: the „global“ signal

„global“ signal = average fMRI time course

excursion: the „global“ signal

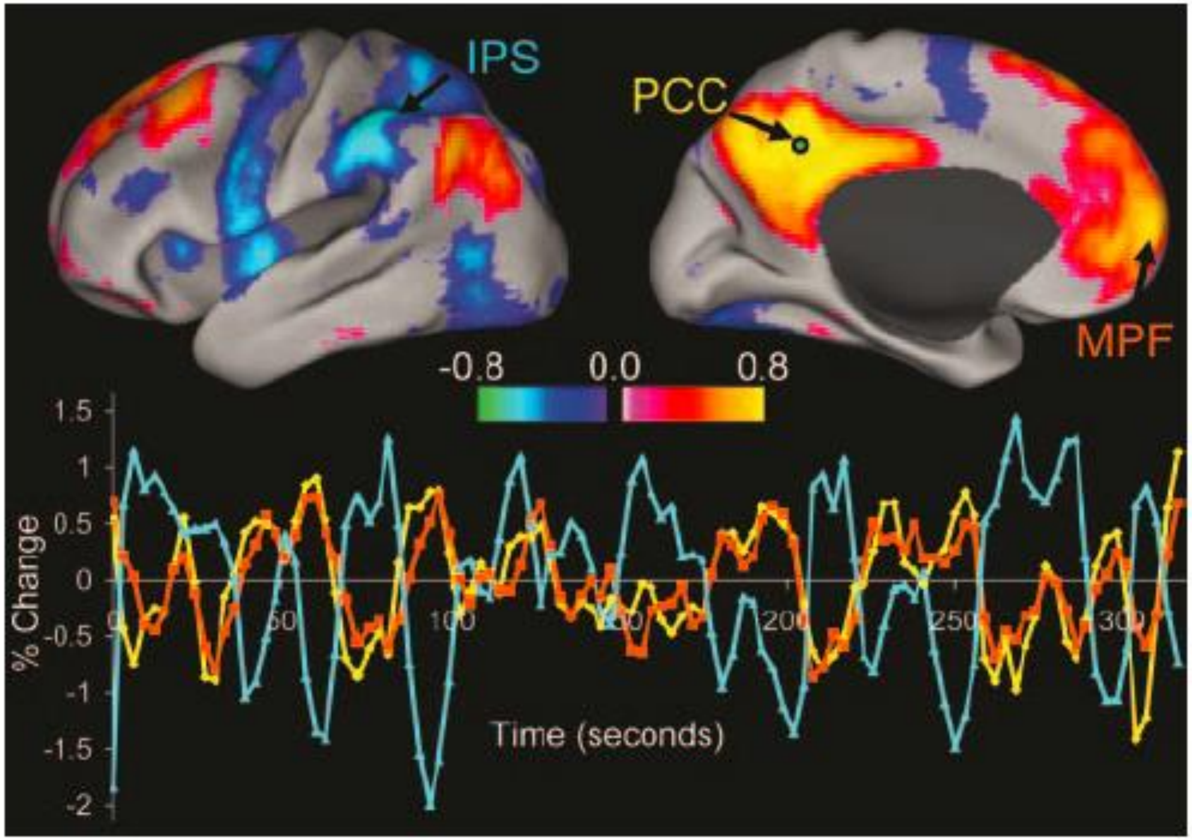

Fig. 1. Intrinsic correlations between a seed region in the PCC and all other voxels in the brain for a single subject during resting fixation. The spatial distribution of correlation coefficients shows both correlations (positive values) and anticorrelations (negative values), thresholded at $R = 0.3$. The time course for a single run is shown for the seed region (PCC, yellow), a region positively correlated with this seed region in the MPF (orange), and a region negatively correlated with the seed region in the IPS (blue).

Fox, M. D., A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. Van Essen and M. E. Raichle (2005). "The human brain is intrinsically organized into dynamic, anticorrelated functional networks." Proc Natl Acad Sci U S A **102(27): 9673-9678.**

anticorrelated networks

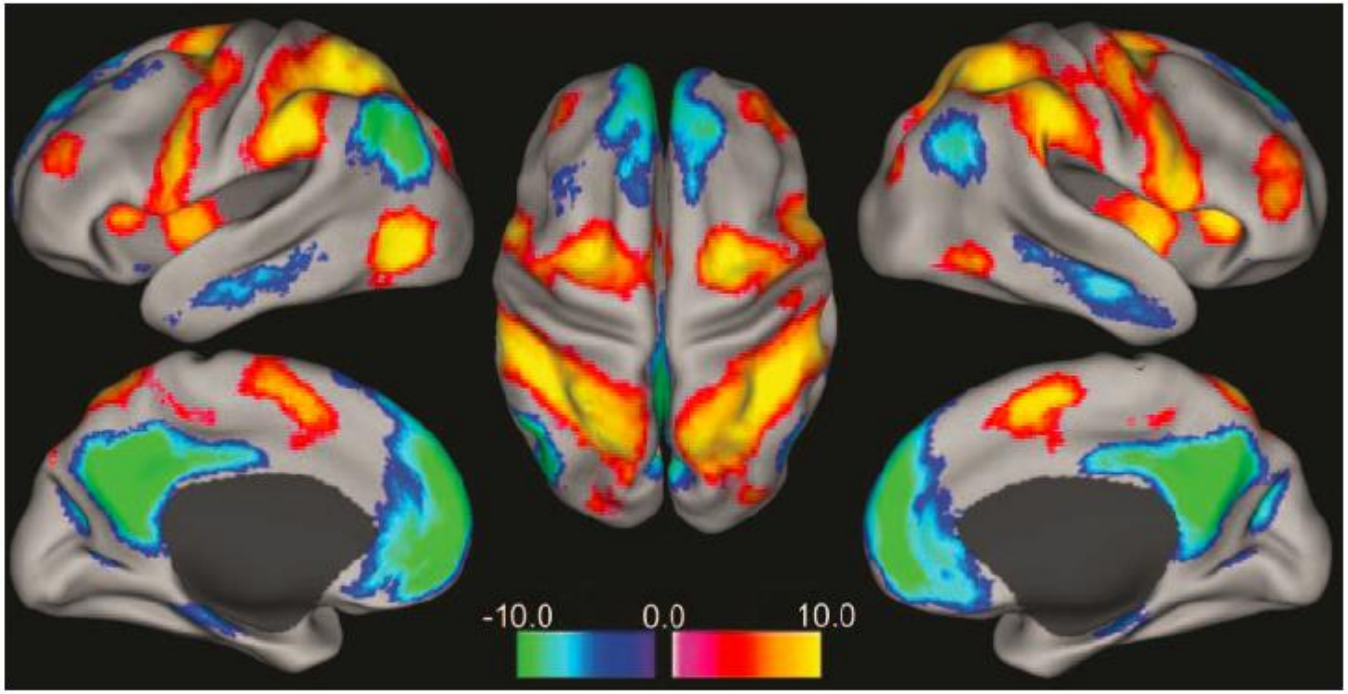

Fig. 3. Intrinsically defined anticorrelated processing networks in the brain. Positive nodes are significantly correlated with seed regions involved in focused attention and working memory (task-positive seeds) and significantly anticorrelated with seed regions routinely deactivated during attention demanding cognitive tasks (task-negative seeds). Negative nodes are significantly correlated with task-negative seed regions and significantly anticorrelated with task-positive seed regions. (*Left*) Lateral and medial views of left hemisphere. (*Center*) Dorsal view. (*Right*) Lateral and medial views of right hemisphere.

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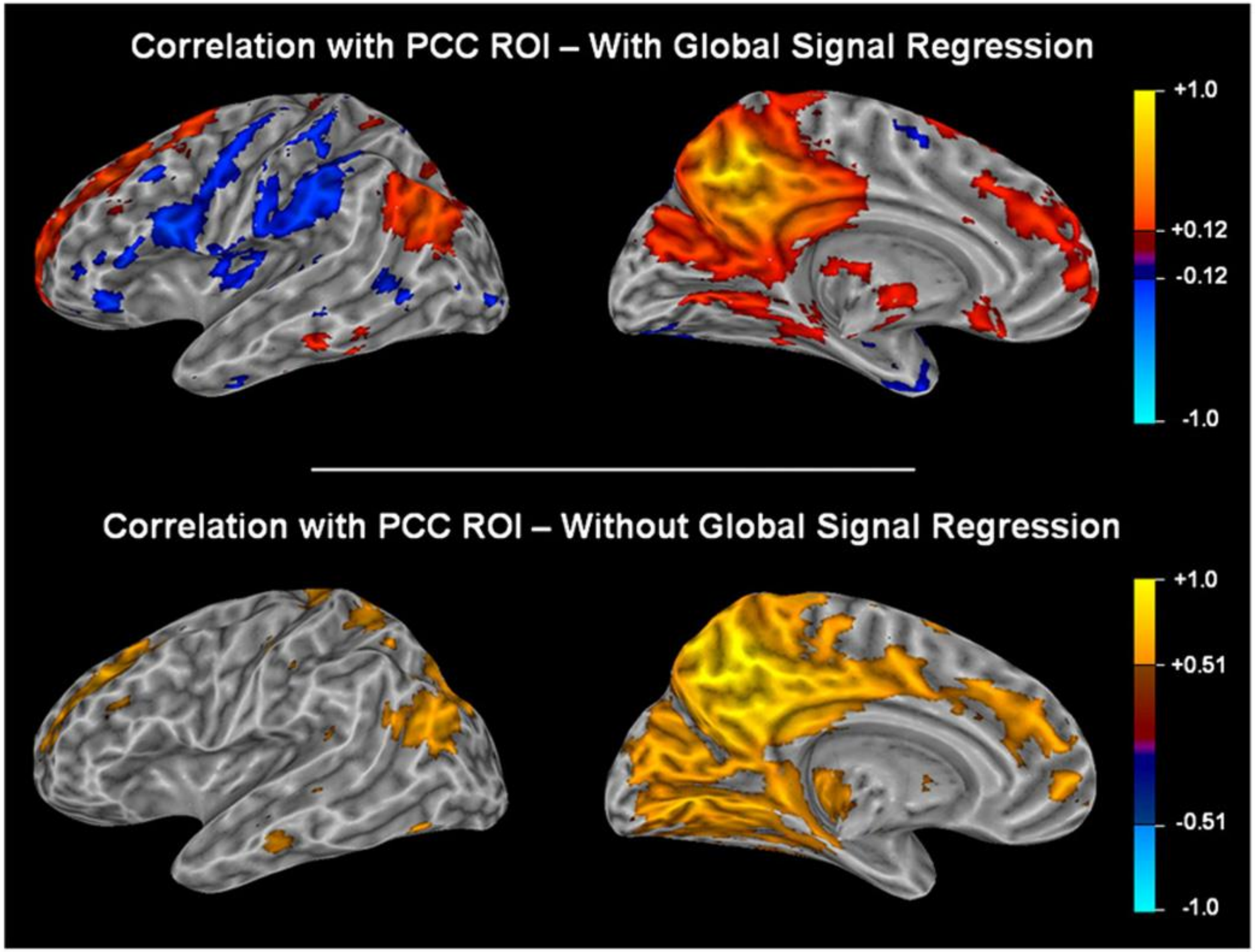
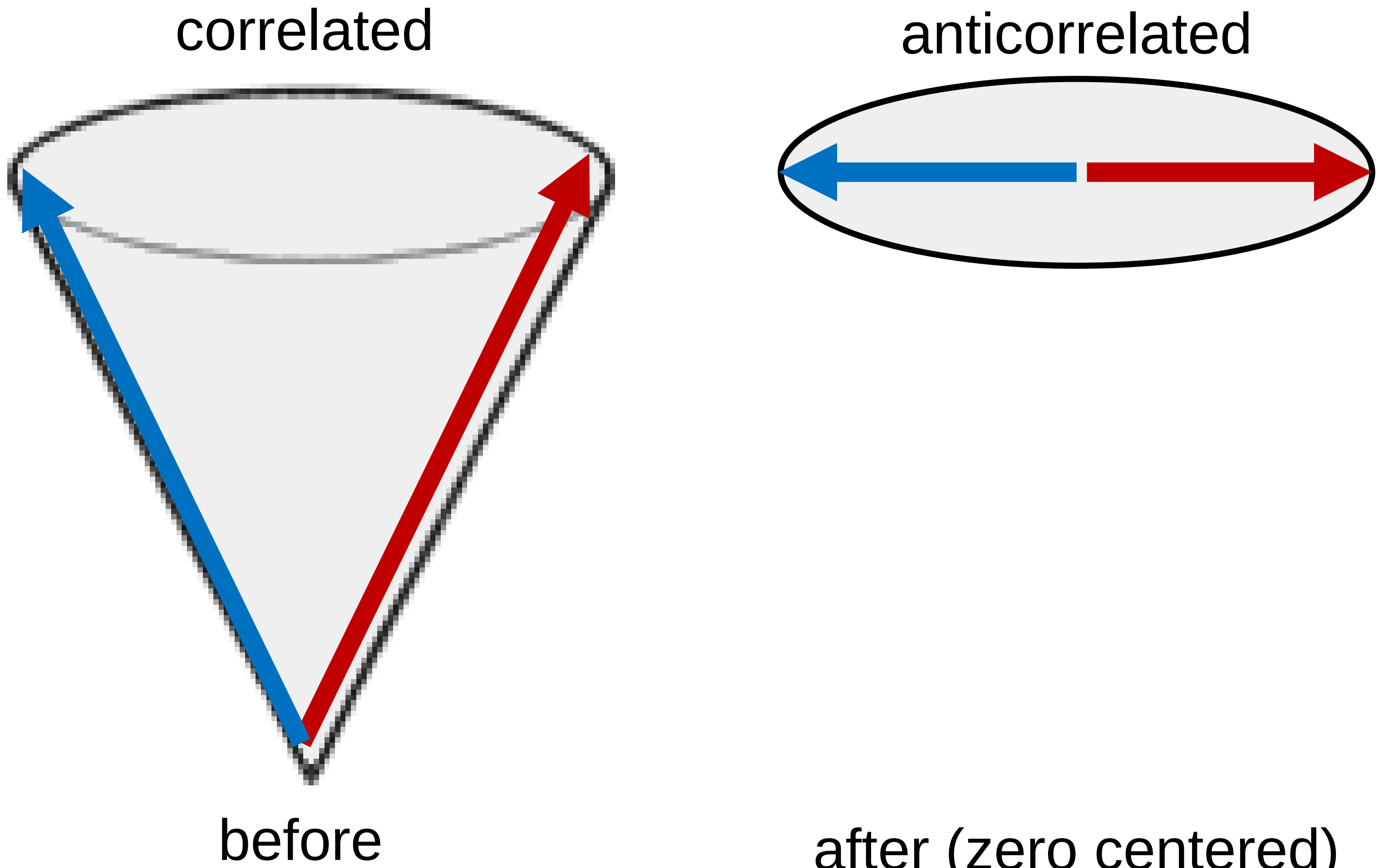
anticorrelated networks?!



Murphy, K., R. M. Birn, D. A. Handwerker, T. B. Jones and P. A. Bandettini (2009). "The impact of global signal regression on resting state correlations: are anti-correlated networks introduced?" Neuroimage **44(3): 893-905.**

anticorrelated networks

removal of „global“ signal introduces anticorrelations



„global“ signal regression

other noise on the topic:

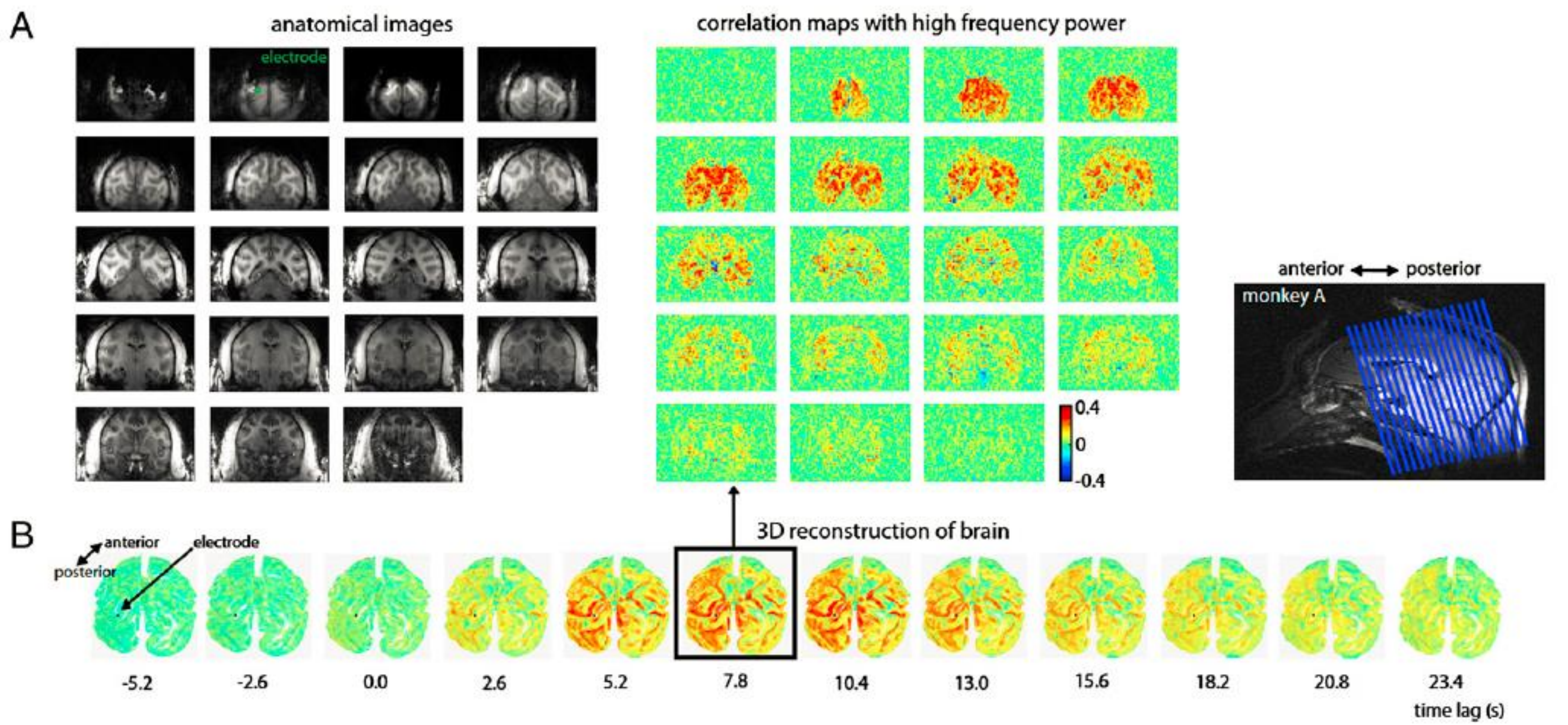


Fig. 3. Spatial extent of the correlation between the neural signal in V1 and spontaneous fMRI fluctuations. (*A*) Correlation maps from one run, obtained at a temporal lag of 7.8 s, are shown for 19 coronal slices in monkey A. The image at the top left corner is from the most posterior slice. The position of the electrode is shown in green on slice 2. Correlation maps from monkeys V and S are shown in Figs. S2 and S3. (*B*) Correlation maps from the same run as a function of temporal lag are shown on an inflated 3D reconstruction of the monkey's brain. The position of the electrode is shown as a black dot. The temporal coupling between the two signals, as well as the large spatial extent of the correlations, are clearly visible.

[…] This coupling was, however, dependent on the monkey's behavioral state, being stronger and anticipatory when the animals' eyes were closed.

Scholvinck, M. L., A. Maier, F. Q. Ye, J. H. Duyn and D. A. Leopold (2010). "Neural basis of global resting-state fMRI activity." <u>Proceedings of the National Academy of Sciences of the United States of America **107(22): 10238-10243.**</u>

„global“ signal regression

other noise on the topic:

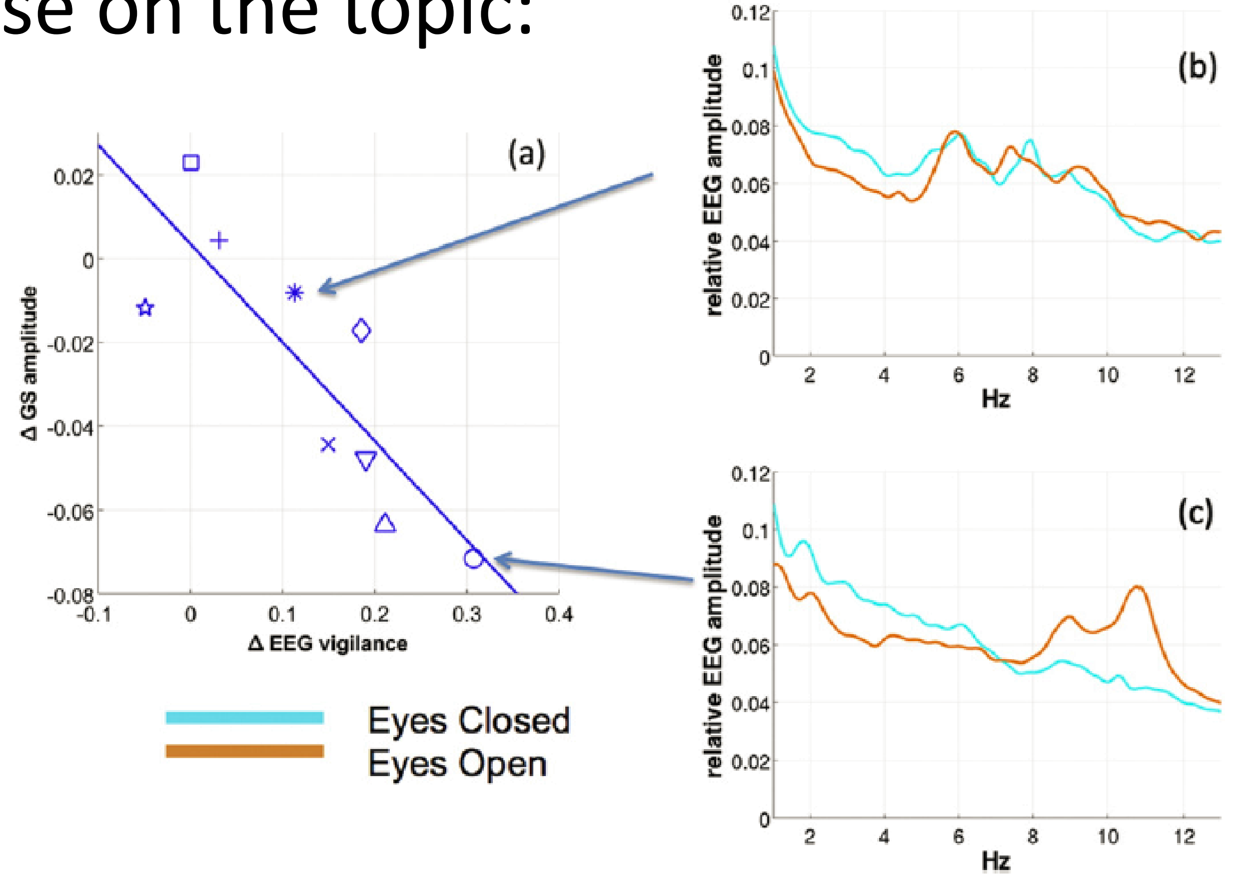


Fig. 2. The EEG spectra for two representative subjects are shown in panels b and c, alongside the plot (panel a) of changes in global signal amplitude versus EEG vigilance previously presented in Fig. 1a. The EO and EC states are indicated by the brown and cyan lines, respectively. When there is relatively little difference between the EO and EC spectra (panel b), there are minimal changes in both the global signal amplitude and EEG vigilance. When there is a pronounced shift to higher frequencies in the EO spectrum (panel c), there is a sizeable decrease in the global signal amplitude accompanied by a substantial increase in vigilance.

Wong, C. W., P. N. DeYoung and T. T. Liu (2016). "Differences in the resting-state fMRI global signal amplitude between the eyes open and eyes closed states are related to changes in EEG vigilance." Neuroimage **124(Pt A): 24-31.**

Wong, C. W., V. Olafsson, O. Tal and T. T. Liu (2013). "The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures." Neuroimage **83: 983-990.**

„global“ signal regression

other noise on the topic:

Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37, 90-101.

Carbonell, F., Bellec, P., Shmuel, A., 2011. Global and system-specific resting-state fMRI fluctuations are uncorrelated: principal component analysis reveals anti-correlated networks. Brain Connect 1, 496-510.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102, 9673-9678.

Fox, M.D., Zhang, D., Snyder, A.Z., Raichle, M.E., 2009. The global signal and observed anticorrelated resting state brain networks. J Neurophysiol 101, 3270-3283.

Fransson, P., 2005. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26, 15-29.

Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., Martin, A., 2013. The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. Front Hum Neurosci 7, 356.

He, H., Liu, T.T., 2012. A geometric view of global signal confounds in resting-state functional MRI. Neuroimage 59, 2339-2348.

Jo, H.J., Saad, Z.S., Simmons, W.K., Milbury, L.A., Cox, R.W., 2010. Mapping sources of correlation in resting state FMRI, with artifact detection and removal. Neuroimage 52, 571-582.

Keller, C.J., Bickel, S., Honey, C.J., Groppe, D.M., Entz, L., Craddock, R.C., Lado, F.A., Kelly, C., Milham, M., Mehta, A.D., 2013. Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. J Neurosci 33, 6333-6342.

Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44, 893-905.

Saad, Z., Reynolds, R.C., Jo, H.J., Gotts, S.J., Chen, G., Martin, A., Cox, R., 2013. Correcting Brain-Wide Correlation Differences in Resting-State FMRI. Brain Connect.

Saad, Z.S., Gotts, S.J., Murphy, K., Chen, G., Jo, H.J., Martin, A., Cox, R.W., 2012. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect 2, 25-32.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., Wolf, D.H., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage 64, 240-256.

Scholvinck, M.L., Maier, A., Ye, F.Q., Duyn, J.H., Leopold, D.A., 2010. Neural basis of global resting-state fMRI activity. Proc Natl Acad Sci U S A 107, 10238-10243.

Wong, C.W., Olafsson, V., Tal, O., Liu, T.T., 2013. The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures. Neuroimage.

Yan, C.G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R.C., Di Martino, A., Li, Q., Zuo, X.N., Castellanos, F.X., Milham, M.P., 2013a. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage 76, 183-201.

Yan, C.G., Craddock, R.C., Zuo, X.N., Zang, Y.F., Milham, M.P., 2013b. Standardizing the intrinsic brain: towards robust measurement of inter-individual variation in 1000 functional connectomes. Neuroimage 80, 246-262.

excursion: the „global“ signal

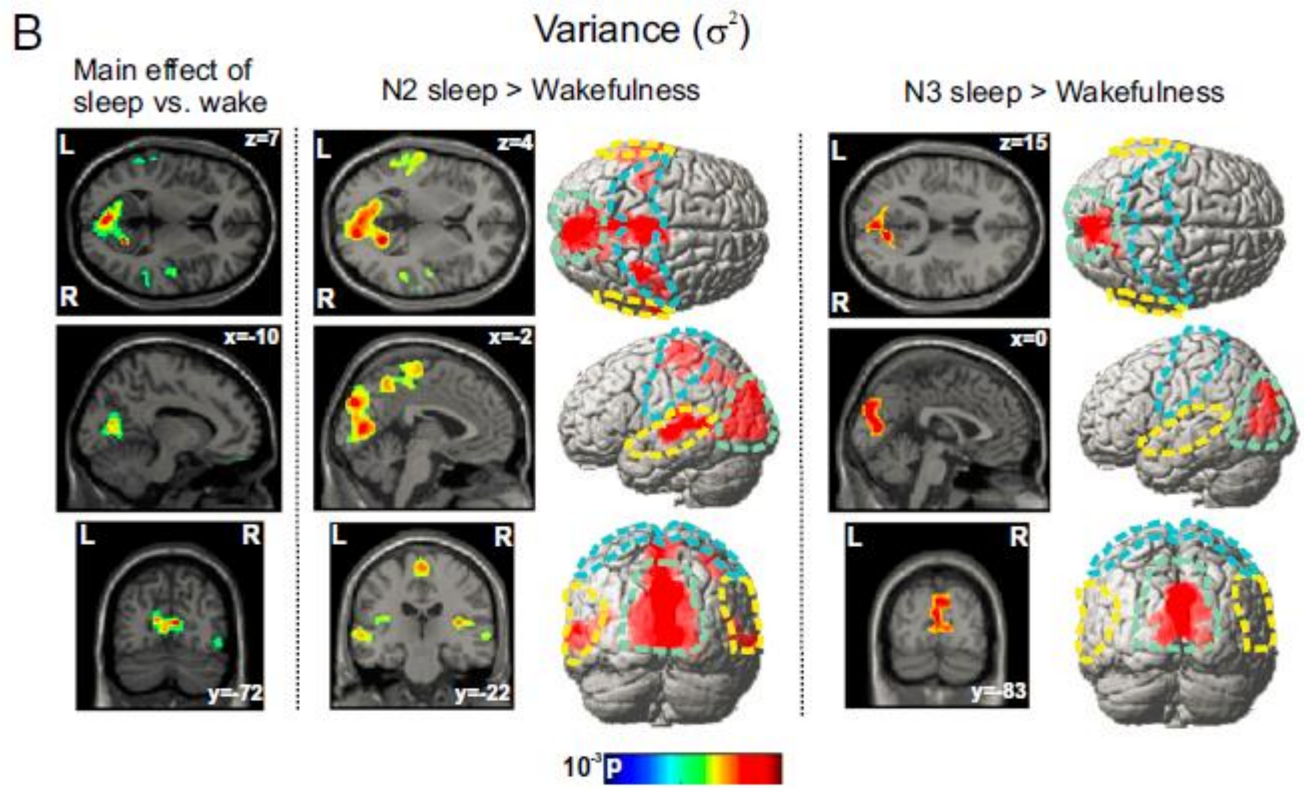
„global“ signal = average fMRI time course

this implies that BOLD signal covaries across voxels!

excursion: the „global“ signal

„global“ signal = average fMRI time course

this implies that BOLD signal covaries across voxels – but:



Large regional effects might drive global signal.

Tagliazucchi, E., F. von Wegner, A. Morzelewski, V. Brodbeck, K. Jahnke and H. Laufs (2013). "Breakdown of long-range temporal dependence in default mode and attention networks during deep sleep." Proc Natl Acad Sci U S A **110(38): 15419-15424.**

excursion: the „global“ signal

suggestion:

- regress out physiological noise but
  [especially motion, respiration]
- do not regress out physiological signal (e.g. sleep)

solution

know your enemy!

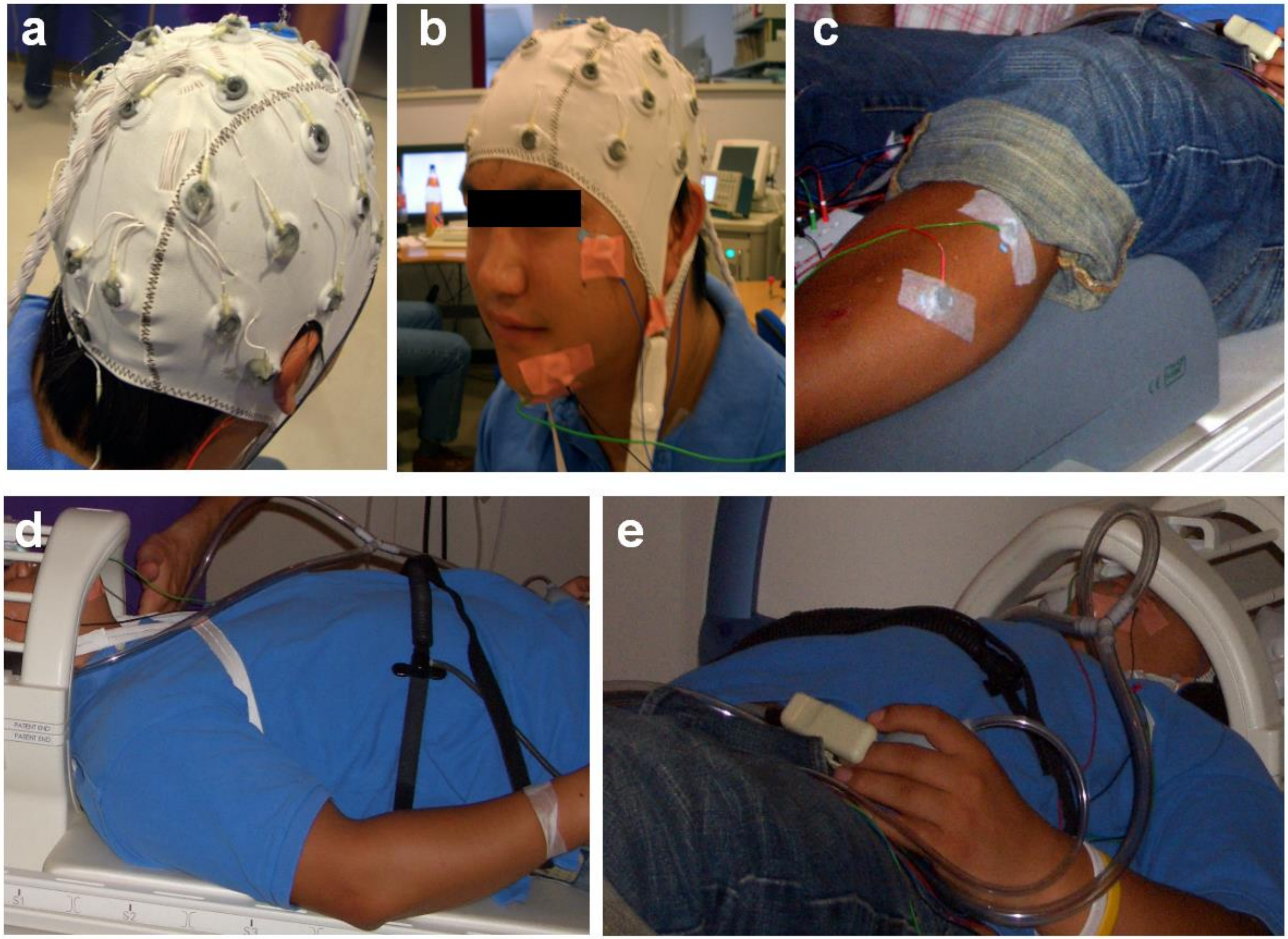
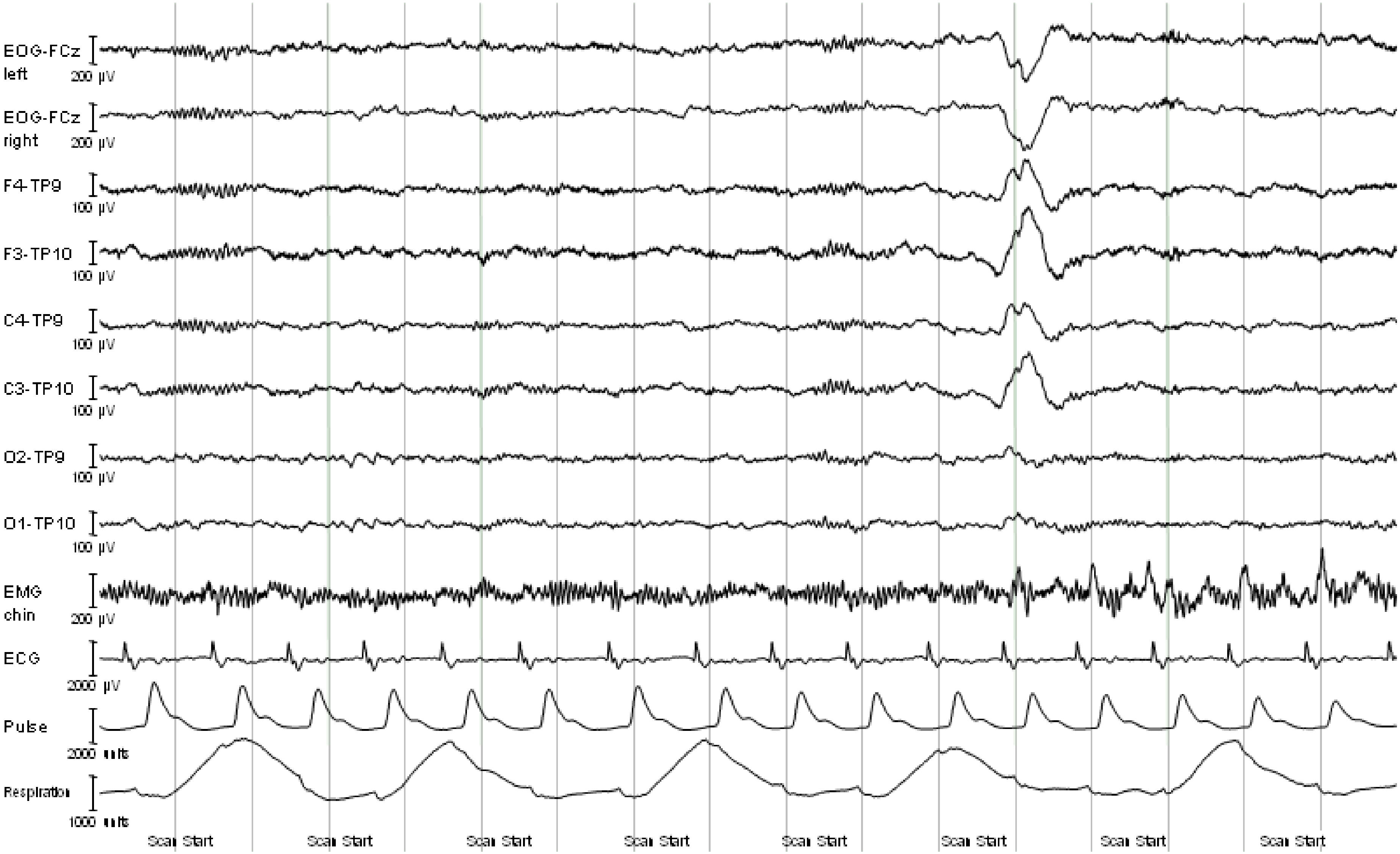


Figure 1: a: EEG cap; **b:** EOG and M. mentalis EMG electrodes; **c:** M. tibialis EMG electrodes; **d:** respiration belt; **e:** pulse oximetry

polysomnography-fMRI



(Jahnke et al. 2012)

Magnetic Resonance in Medicine 44:162–167 (2000)

Image-Based Method for Retrospective Correction of Physiological Effects in fMRI: RETROICOR

Gary H. Glover,[1*] Tie-Qiang Li,[1] and David Ress[2]

$$y_\delta(t) = \sum_{m=1}^{M} a_m^c \cos(m\varphi_c) + b_m^c \sin(m\varphi_c) + a_m^r \cos(m\varphi_r) + b_m^r \sin(m\varphi_r) \quad [1]$$

$$\varphi_c(t) = 2\pi(t - t_1)/(t_2 - t_1) \quad [2]$$

$$\varphi_r(t) = \pi \frac{\sum_{b=1}^{\mathrm{rnd}[R(t)/R_{\max}]} H(b)}{\sum_{b=1}^{100} H(b)} \operatorname{sgn}(dR/dt) \quad [3]$$

$$a_m^x = \sum_{n=1}^{N} [y(t_n) - \bar{y}] \cos(m\varphi_x(t_n)) / \sum_{n=1}^{N} \cos^2(m\varphi_x(t_n))$$

$$b_m^x = \sum_{n=1}^{N} [y(t_n) - \bar{y}] \sin(m\varphi_x(t_n)) / \sum_{n=1}^{N} \sin^2(m\varphi_x(t_n)) \quad [4]$$

If you do not have EEG…?

Data driven approaches

I. seed correlation
II. **ICA**
III. graph analysis

Resting state networks - ICA

(fMRI, functional connectivity via ICA)

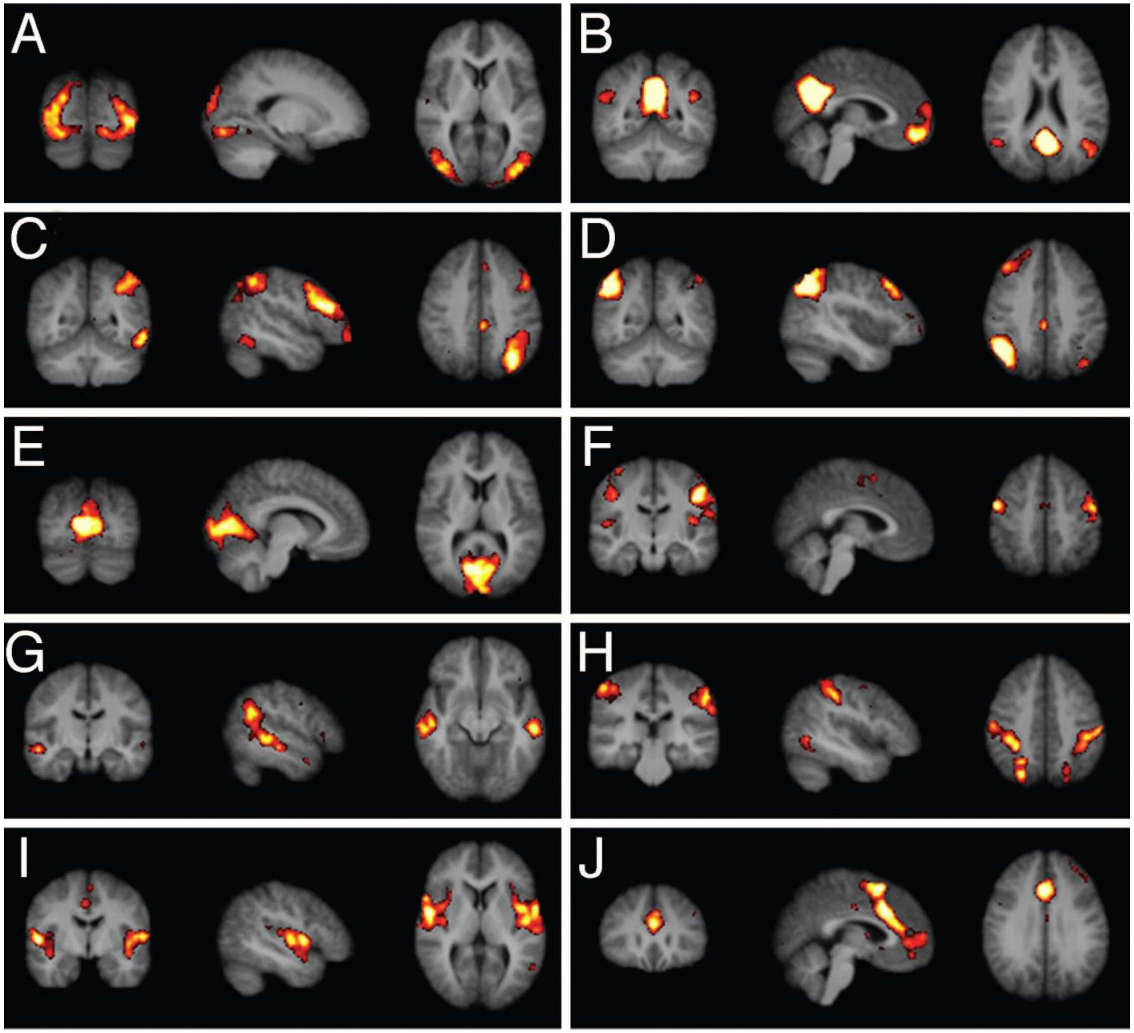
lateral visual

memory (left)

medial visual

ventral stream (visual)

auditory



default mode

memory (right)

sensory-motor

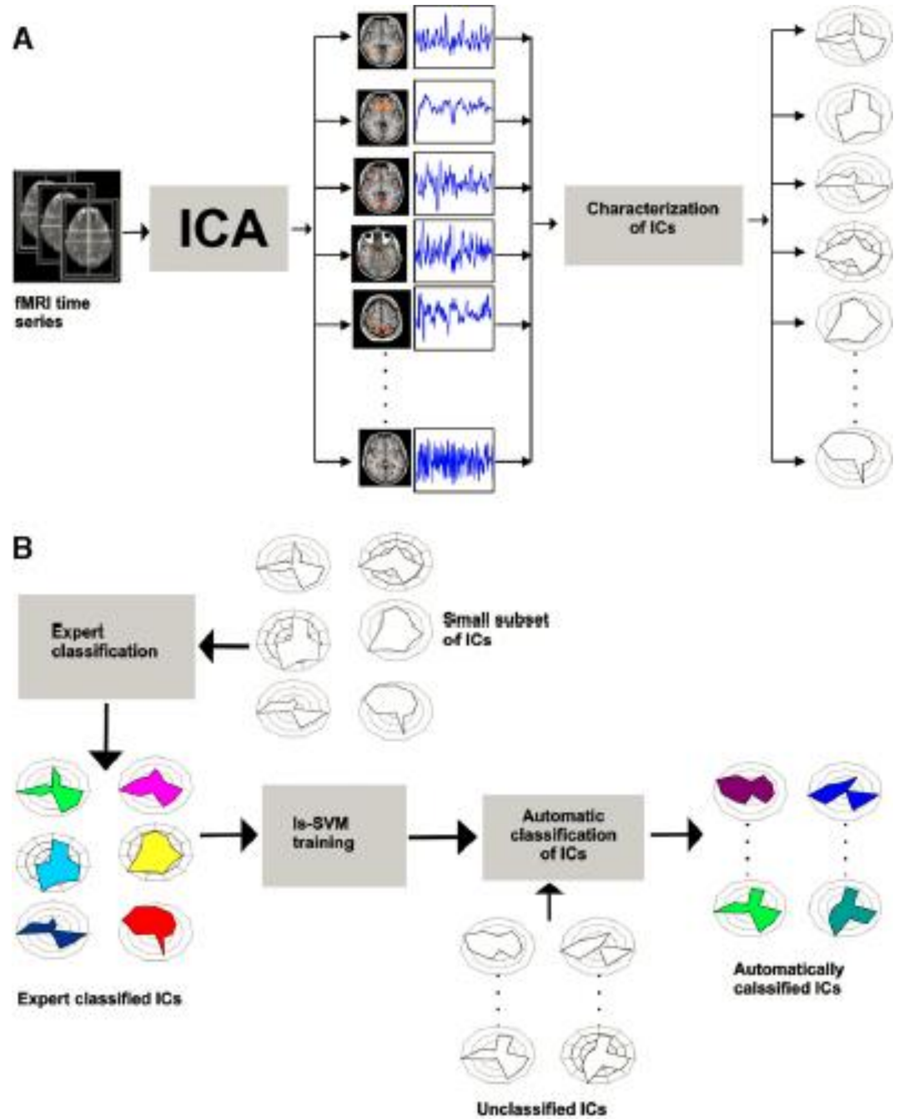
executive control

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103, 13848-13853.

What about physio noise?

Resting state networks – ICA

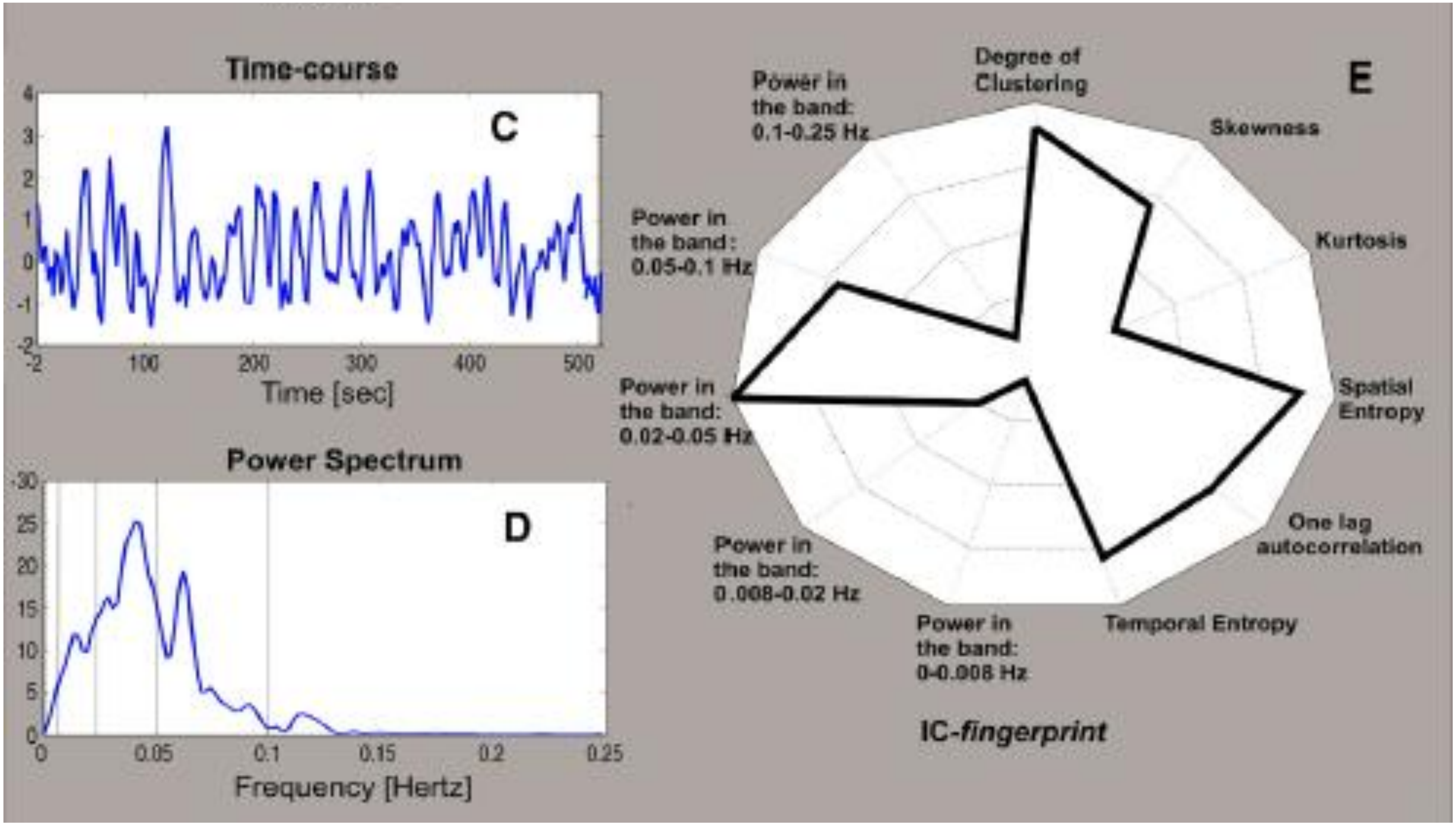
(classifier to detect non-noise components)



De Martino, F., Gentile, F., Esposito, F., Balsi, M., Di Salle, F., Goebel, R., Formisano, E., 2007. Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. Neuroimage 34, 177-194.

Resting state networks - ICA

(classifier to detect non-noise components)



De Martino, F., Gentile, F., Esposito, F., Balsi, M., Di Salle, F., Goebel, R., Formisano, E., 2007. Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. Neuroimage 34, 177-194.

If you do not have EEG…?

Data driven approaches

I. seed correlation
II. ICA
III. **graph analysis**

Graph analysis of functional connectivity networks

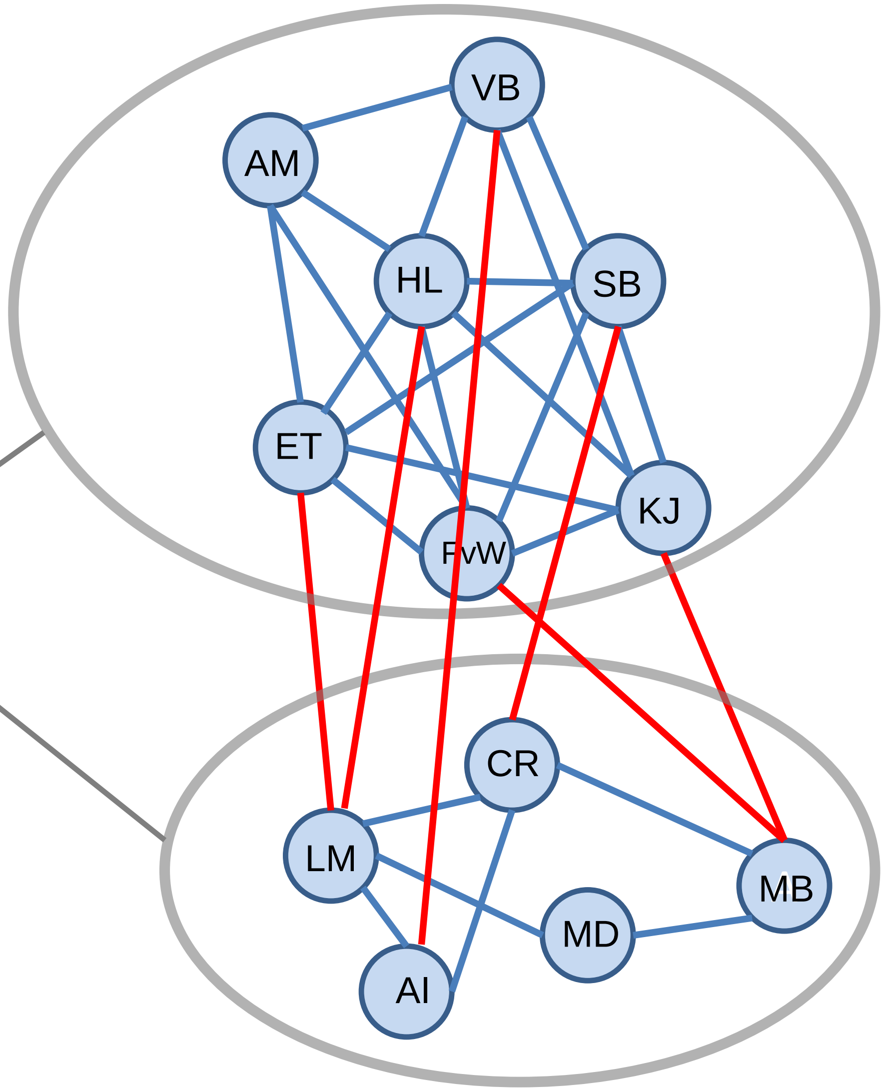
- Graphs are simply a representation of **objects** and the **connections** between them

The language of interactions

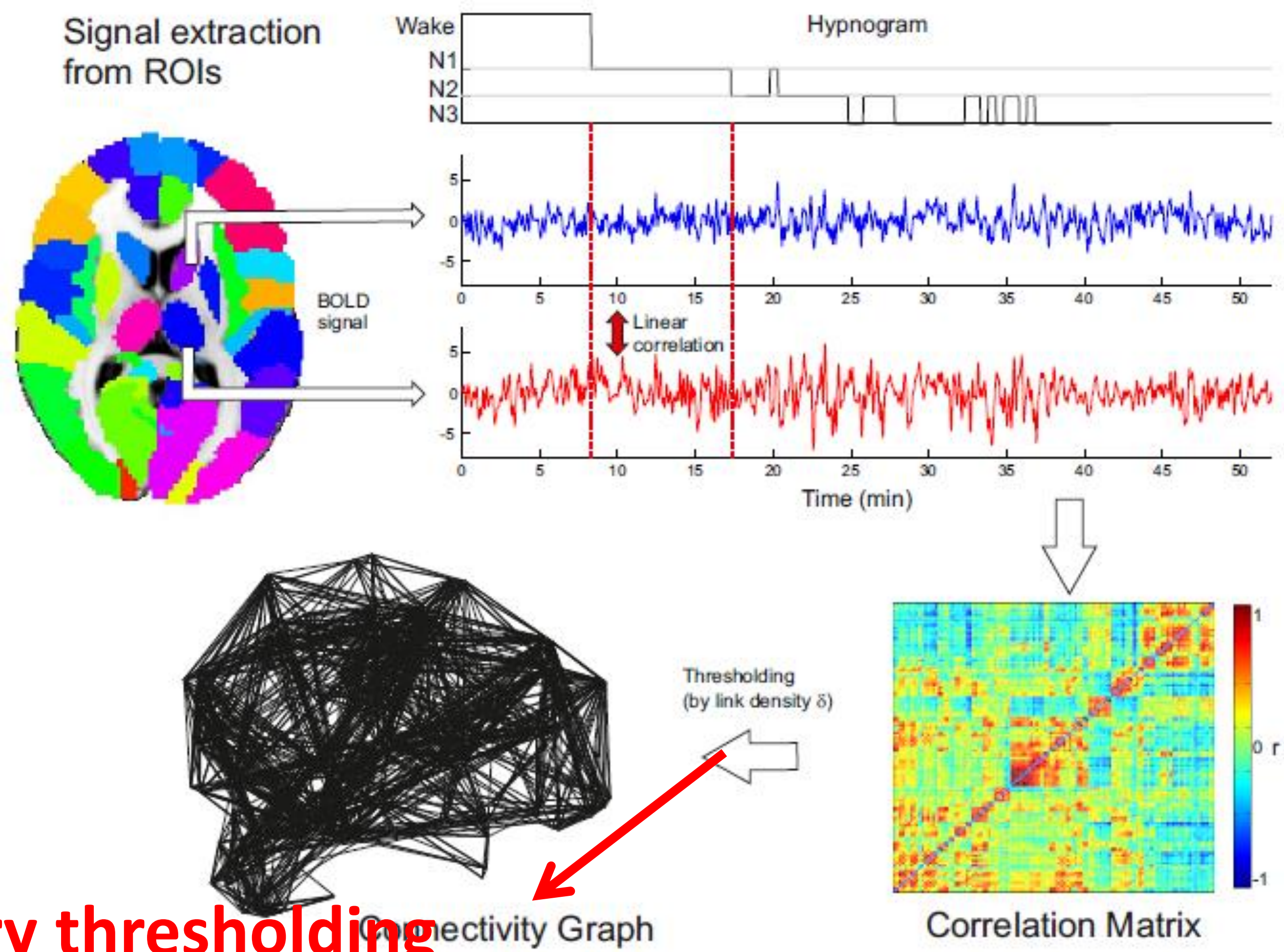
A graph is a group of **nodes** *(persons, brain regions, soccer players, actors, etc)* and a group of **edges** representing relationships *(love, hate, neuronal coordination, movie co-starring,etc)*

Separated (but interacting) social groups

More interactions gradually destroys the identity of separed modules



From BOLD time series to graphs

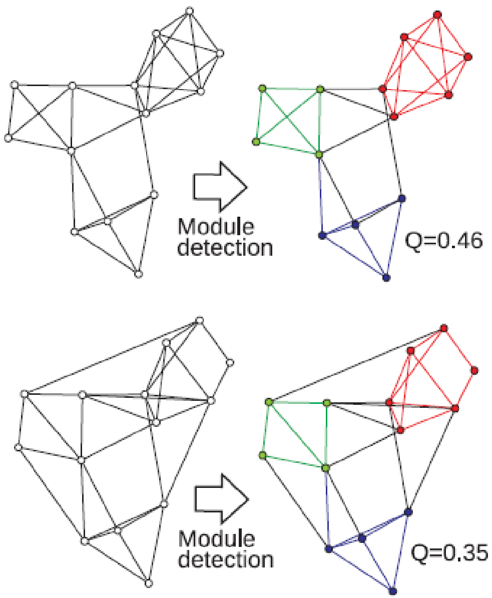


Arbitrary thresholding of functional connectivity

What to study in a graph?

(see *Bullmore and Sporns , Nat Rev Neurosci 2009* for a review)

- Average path length (L) : mean distance between each pair of nodes
- Clustering coefficient (C) : number of triangles in the network
- Modularity (Q) : How well can the network be separated into subsets of nodes which interact more strongly between them than with the rest of the network?



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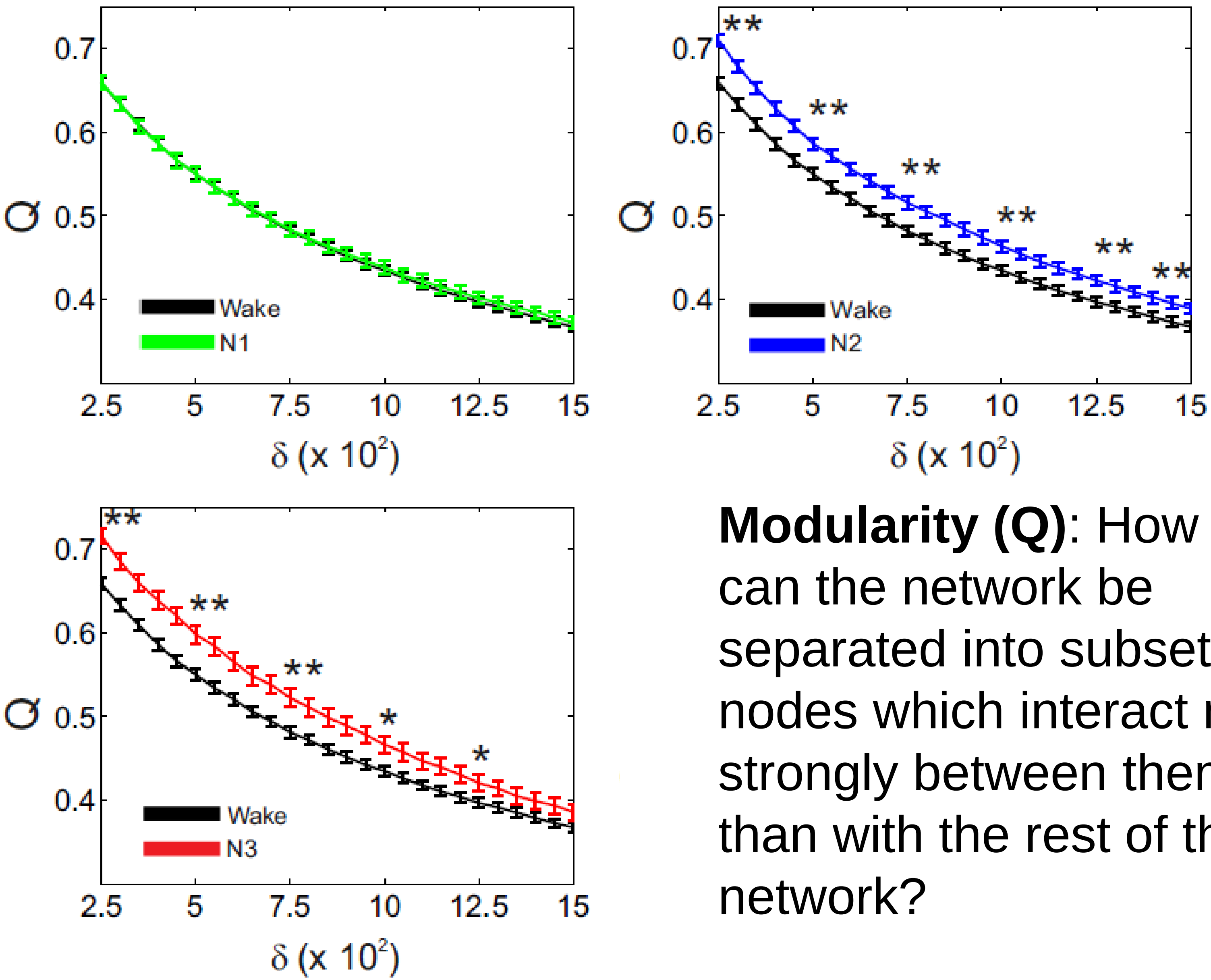
- Clustering coefficient (C) : number of triangles in the network
- Modularity (Q) : How well can the network be separated into subsets of nodes which interact more strongly between them than with the rest of the network?
- Degree: what is the number of connections each node has?
- Betweeness: what is the number of shortest paths going through each node?

Modularity increase in N2 & N3



Modularity (Q): How well can the network be separated into subsets of nodes which interact more strongly between them than with the rest of the network?

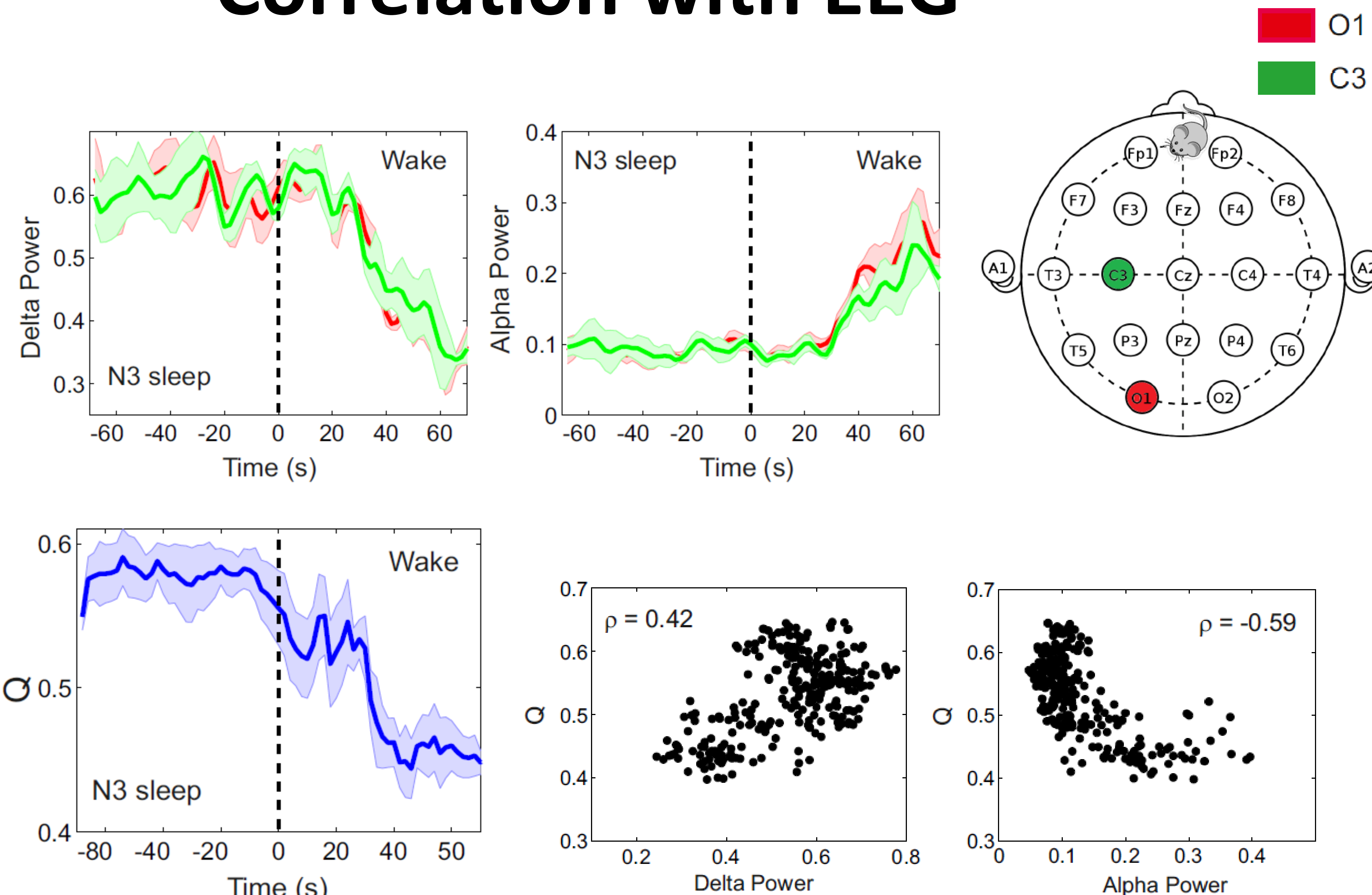
(tieferer) Schlaf ↓

Modularität ↑

reduziertes Bewußtsein ↓

Modularität ↑

Correlation with EEG



monotonous relationship

biological excursion

- Increased segregation during deeper sleep might underlie reduced consciousness
- EEG delta waves during sleep reflect increased modularity (segregation)

Resting State Brain Activity

I. What is it (phenomenology)?
II. When should we consider RS experiments?
III. How do we do it?
IV. Caveats (technical)
V. When resting state experiments (part II)?
VI. Caveats (biological)

Can resting state functional connectivity serve as a biomarker?

scenario III

III. Network comparison between healthy and patient groups

- Identification of biomarkers
  e.g. Greicius Curr Opin Neurol 2008
- Study subclinical disease stages/covert behavioural changes
  e.g. Laufs Hum Brain Mapp 2008

Resting-state functional connectivity in neuropsychiatric disorders

Michael Greicius

Stanford University School of Medicine, Neurology and Neurological Sciences, Stanford, California, USA

Correspondence to Michael Greicius, MD, MPH, Stanford University School of Medicine, Neurology and Neurological Sciences, 300 Pasteur Drive, Rooom A343, Stanford, CA 94305-5235, USA
E-mail: greicius@stanford.edu

Current Opinion in Neurology 2008, 21:424–430

Purpose of review

This review considers recent advances in the application of resting-state functional magnetic resonance imaging to the study of neuropsychiatric disorders.

Recent findings

Resting-state functional magnetic resonance imaging is a relatively novel technique that has several potential advantages over task-activation functional magnetic resonance imaging in terms of its clinical applicability. A number of research groups have begun to investigate the use of resting-state functional magnetic resonance imaging in a variety of neuropsychiatric disorders including Alzheimer's disease, depression, and schizophrenia. Although preliminary results have been fairly consistent in some disorders (for example, Alzheimer's disease) they have been less reproducible in others (schizophrenia). Resting-state connectivity has been shown to correlate with behavioral performance and emotional measures. It's potential as a biomarker of disease and an early objective marker of treatment response is genuine but still to be realized.

Summary

Resting-state functional magnetic resonance imaging has made some strides in the clinical realm but significant advances are required before it can be used in a meaningful way at the single-patient level.

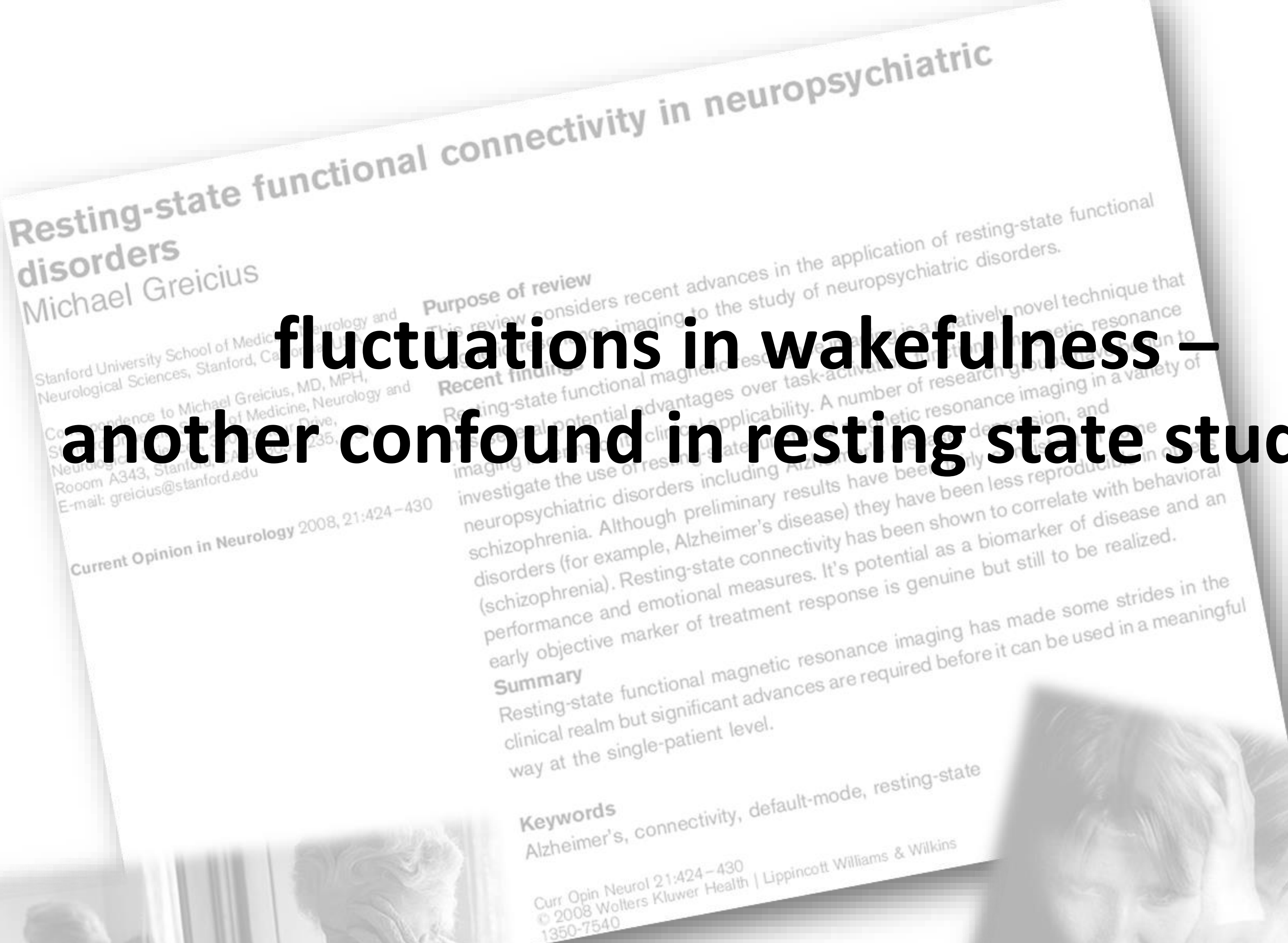
Keywords

Alzheimer's, connectivity, default-mode, resting-state

Curr Opin Neurol 21:424–430

1350-7540

fluctuations in wakefulness – another confound in resting state studies?



Resting-state functional connectivity in neuropsychiatric disorders

Michael Greicius

Current Opinion in Neurology 2008, 21:424–430

Purpose of review

This review considers recent advances in the application of resting-state functional ... imaging to the study of neuropsychiatric disorders.

Recent findings

Resting-state functional magnetic resonance ... relatively novel technique that ... advantages over task-activation ... applicability. A number of research groups ... magnetic resonance imaging in a variety of ... investigate the use of resting-state ... neuropsychiatric disorders including ... schizophrenia. Although preliminary results have been ... less reproducible in other disorders (for example, Alzheimer's disease) they have been shown to correlate with behavioral (schizophrenia). Resting-state connectivity has been shown to correlate with behavioral performance and emotional measures. It's potential as a biomarker of disease and an early objective marker of treatment response is genuine but still to be realized.

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Resting-state functional magnetic resonance imaging has made some strides in the clinical realm but significant advances are required before it can be used in a meaningful way at the single-patient level.

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Curr Opin Neurol 21:424–430
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1350-7540

wakefulness fluctuations – a potential confound in resting state studies?

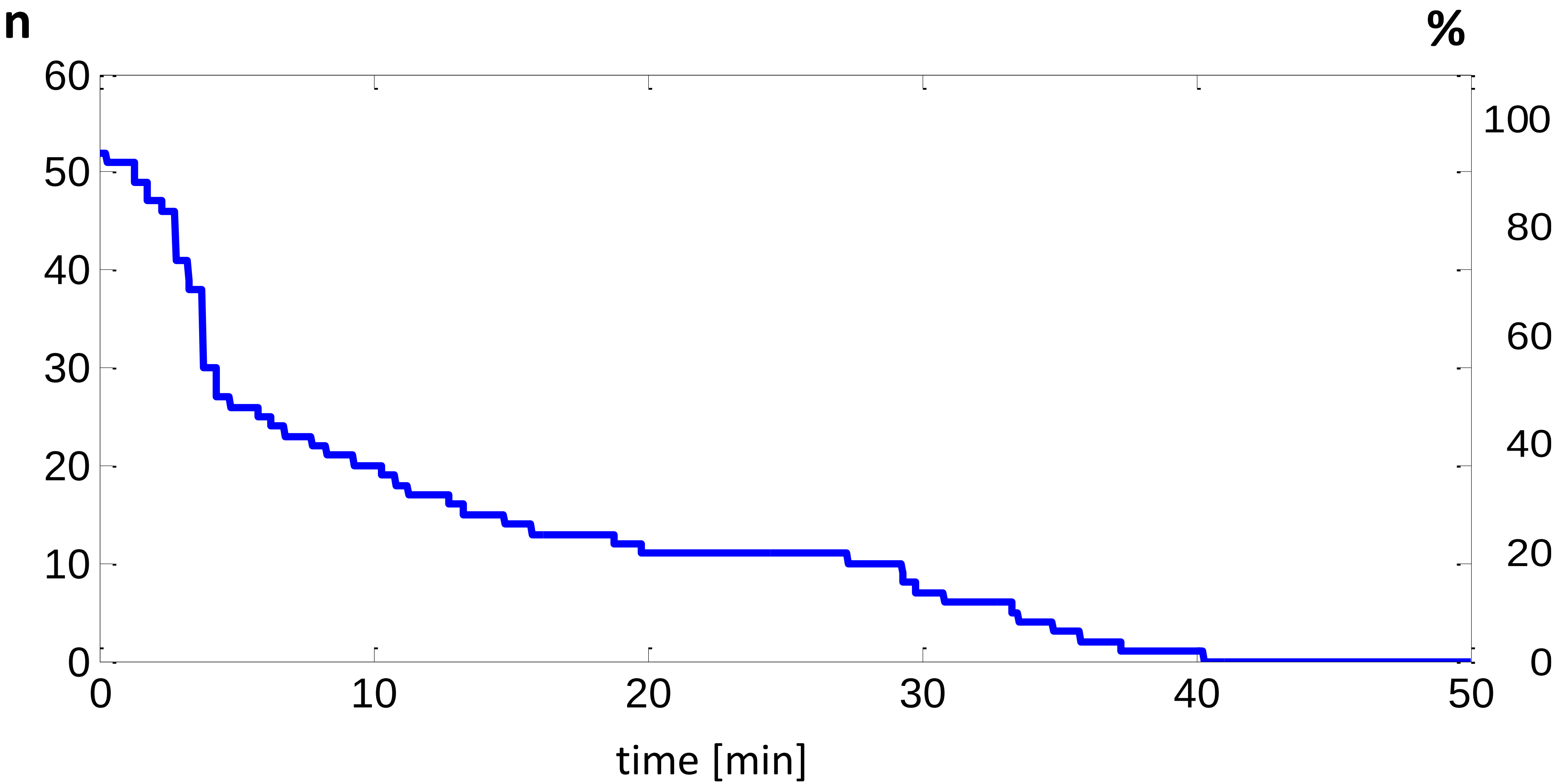
Prevalence of insomnia in neurological diseases.

Neurologic disease	Study	Number of patients	Prevalence
Neurologic disease in general	Taylor et al.[5]	772	7.3%
Multiple sclerosis	Bamer et al.[84]	1067	Men 31% Women 37%
Parkinson's disease	Gjerstadt et al.[37]	231	54–60%
Dementia : Alzheimer disease	Deschenes et al.		25–35%
Stroke	Leppavuori et al.[53]	277	56.7% 37,6% fulfilled DSM-IV criteria
Traumatic brain injury	Quellet and Morin[64]	552	50.2% 29.4% fulfilled DSM-IV criteria
Epilepsy	De Weerd et al.[69]	486	38.6% (partial epilepsy)
	Khatami et al.	100	34–58%
Headache	Kelman and Rains[75]	1283	53–61%

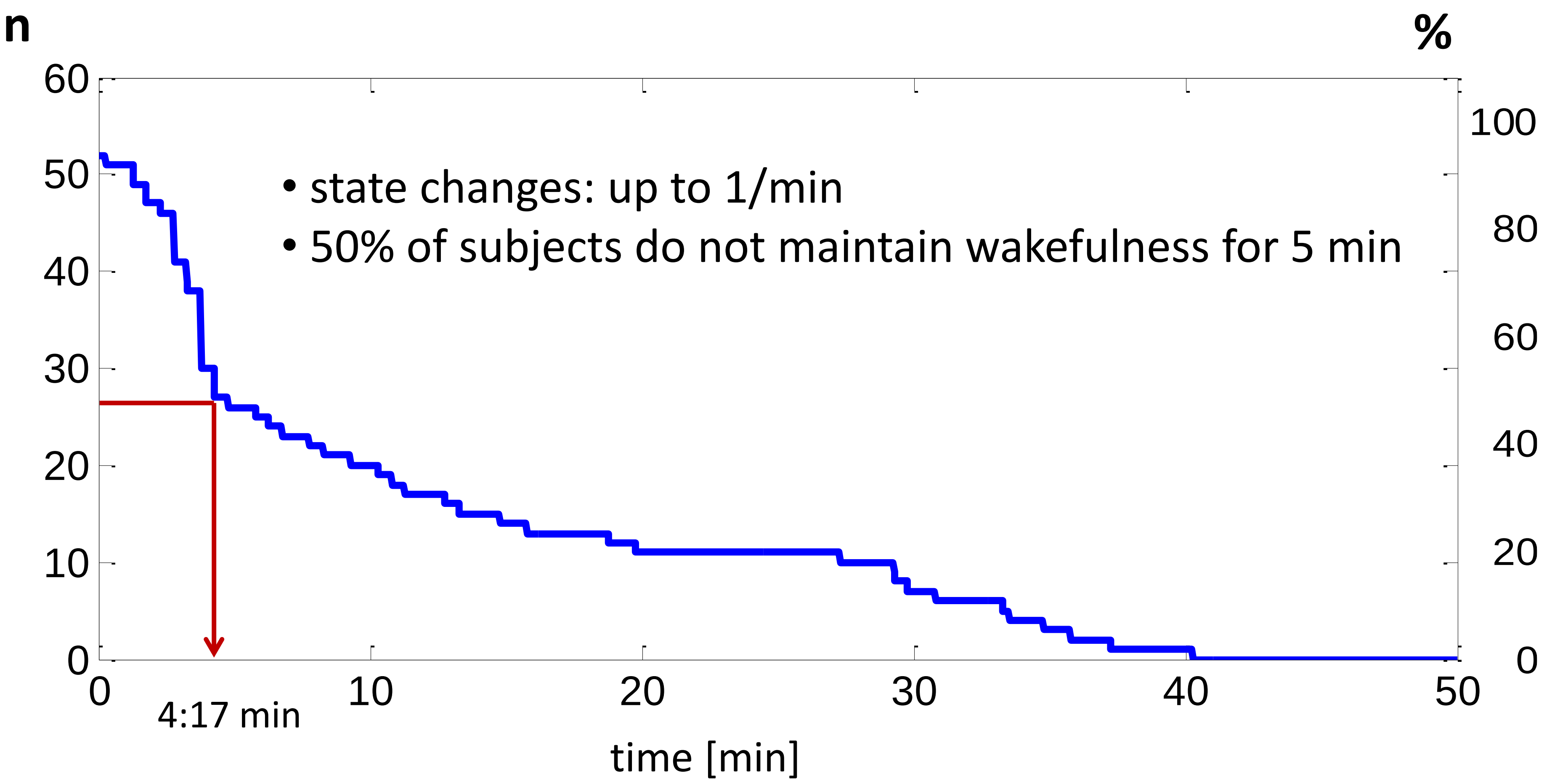
Mayer, G. et al. Sleep med. reviews 2011. Insomnia in central neurologic diseases--occurrence & management.
Sateia, M.J. et al. Seminars in clinical neuropsychiatry 2000. Sleep in neuropsychiatric disorders.
Ford, D.E., Kamerow, D.B., JAMA 1989. Epidemiologic study of sleep disturbances and psychiatric disorders […].

The subject at rest

subjects steadily awake over time



subjects steadily awake over time

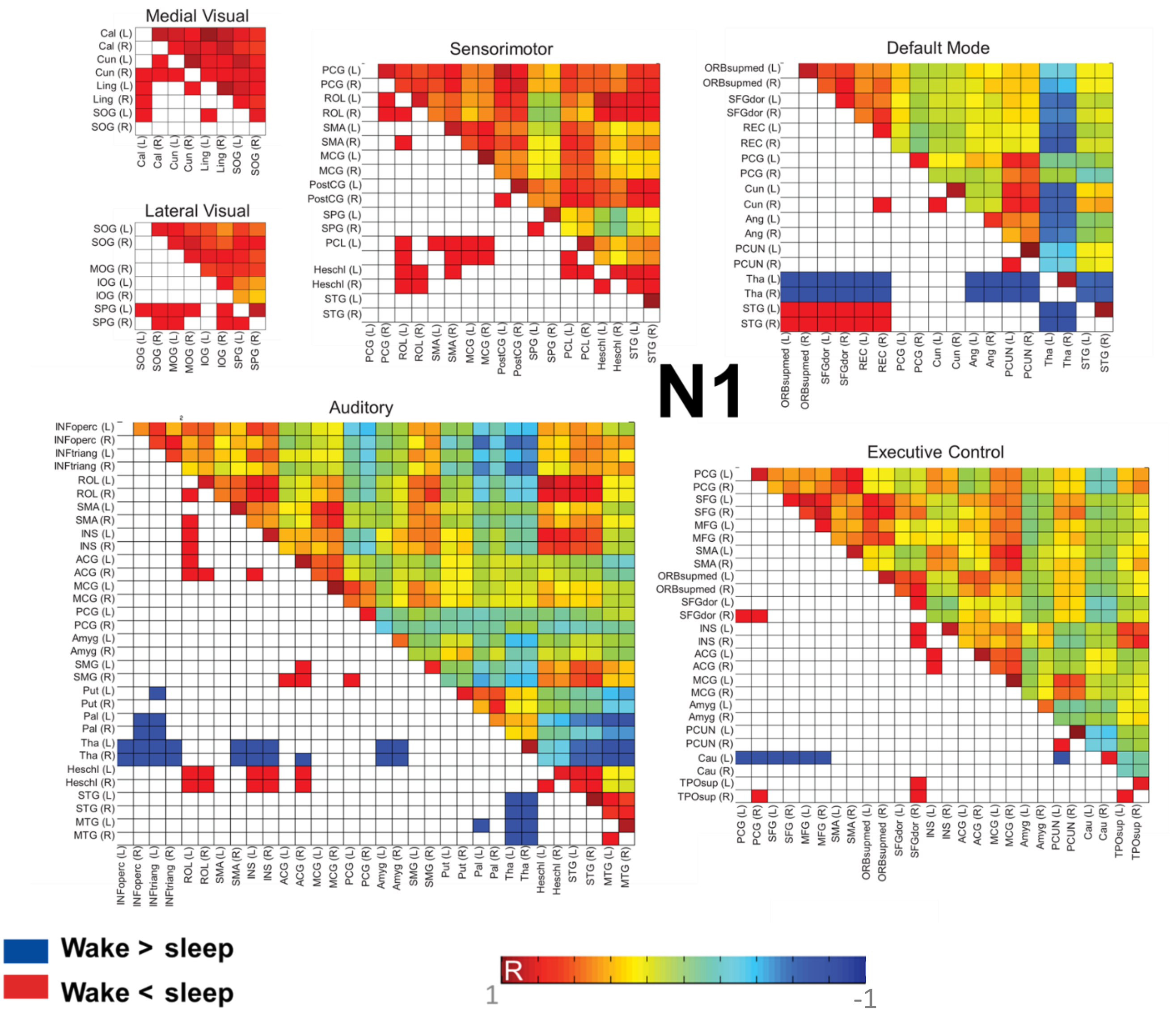


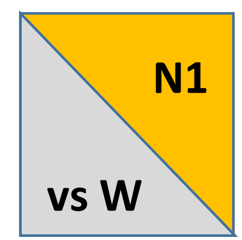
…so what?

- Do I need to bother (see next slides)?
- Is this a general effect?

Changes in functional connectivity – N1

thalamus disconnects

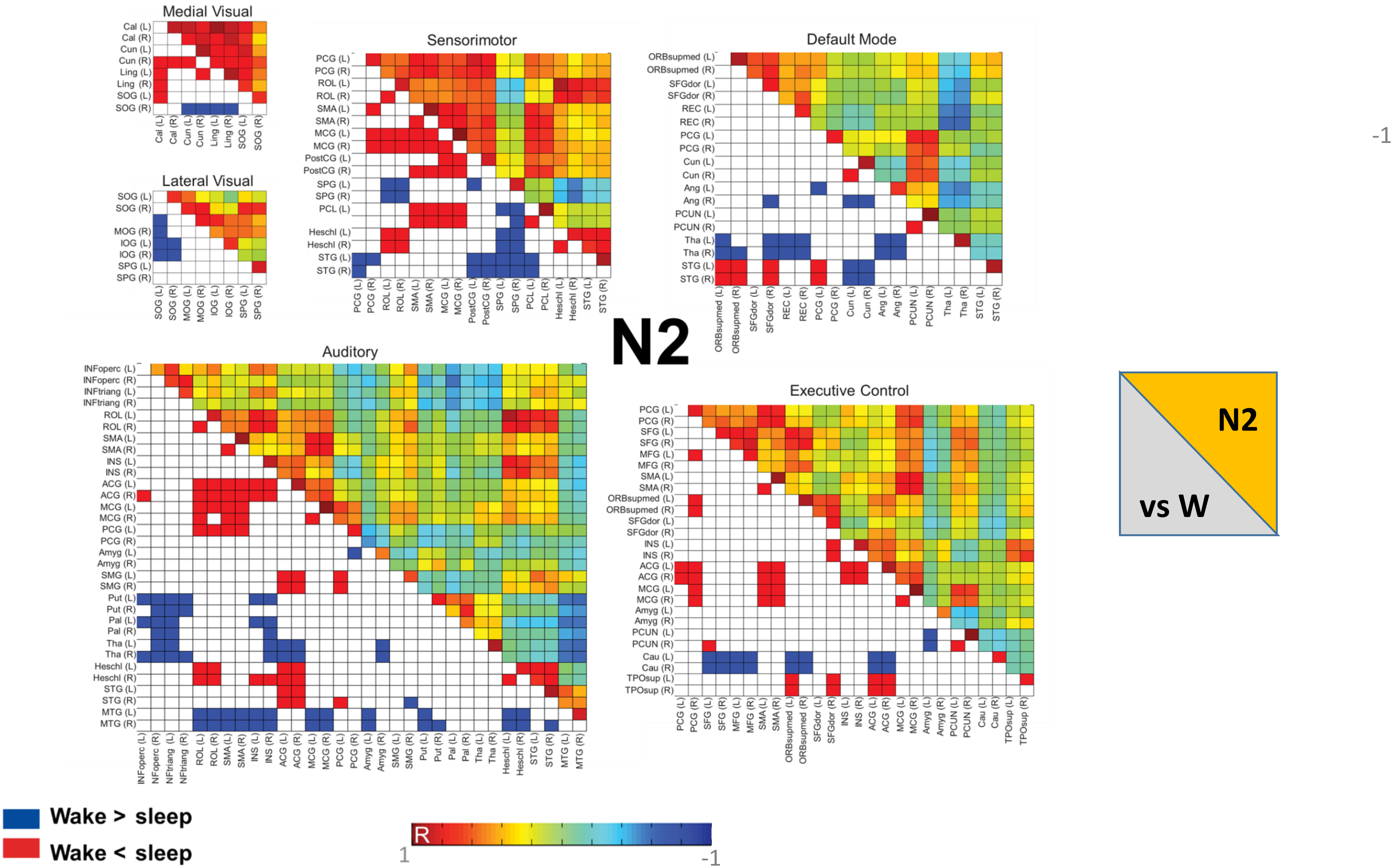




Tagliazucchi, E. & Laufs, H. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. *Neuron (2014)*.

Changes in functional connectivity – N2

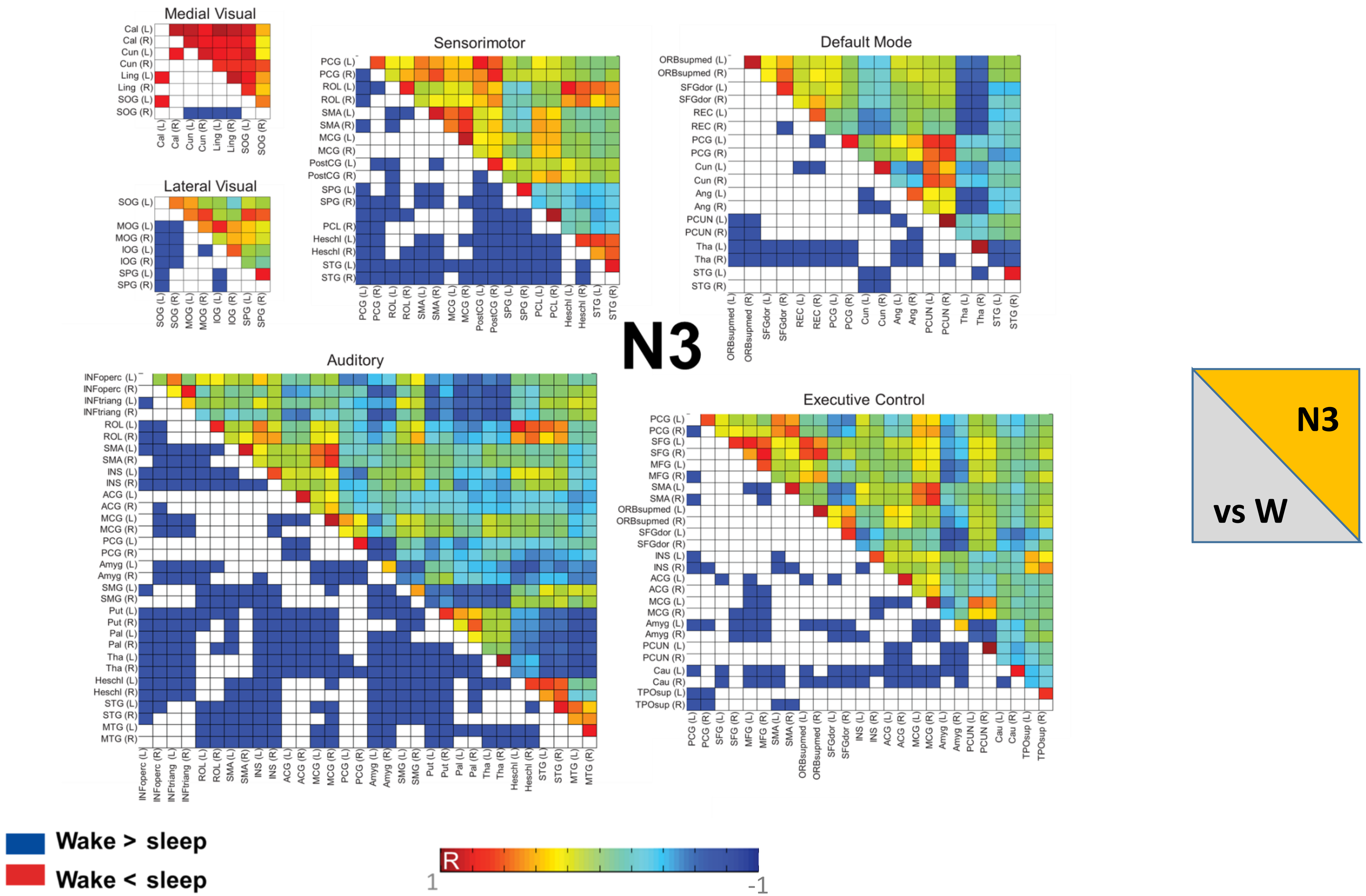
...and on...



Tagliazucchi, E. & Laufs, H. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. *Neuron (2014).*

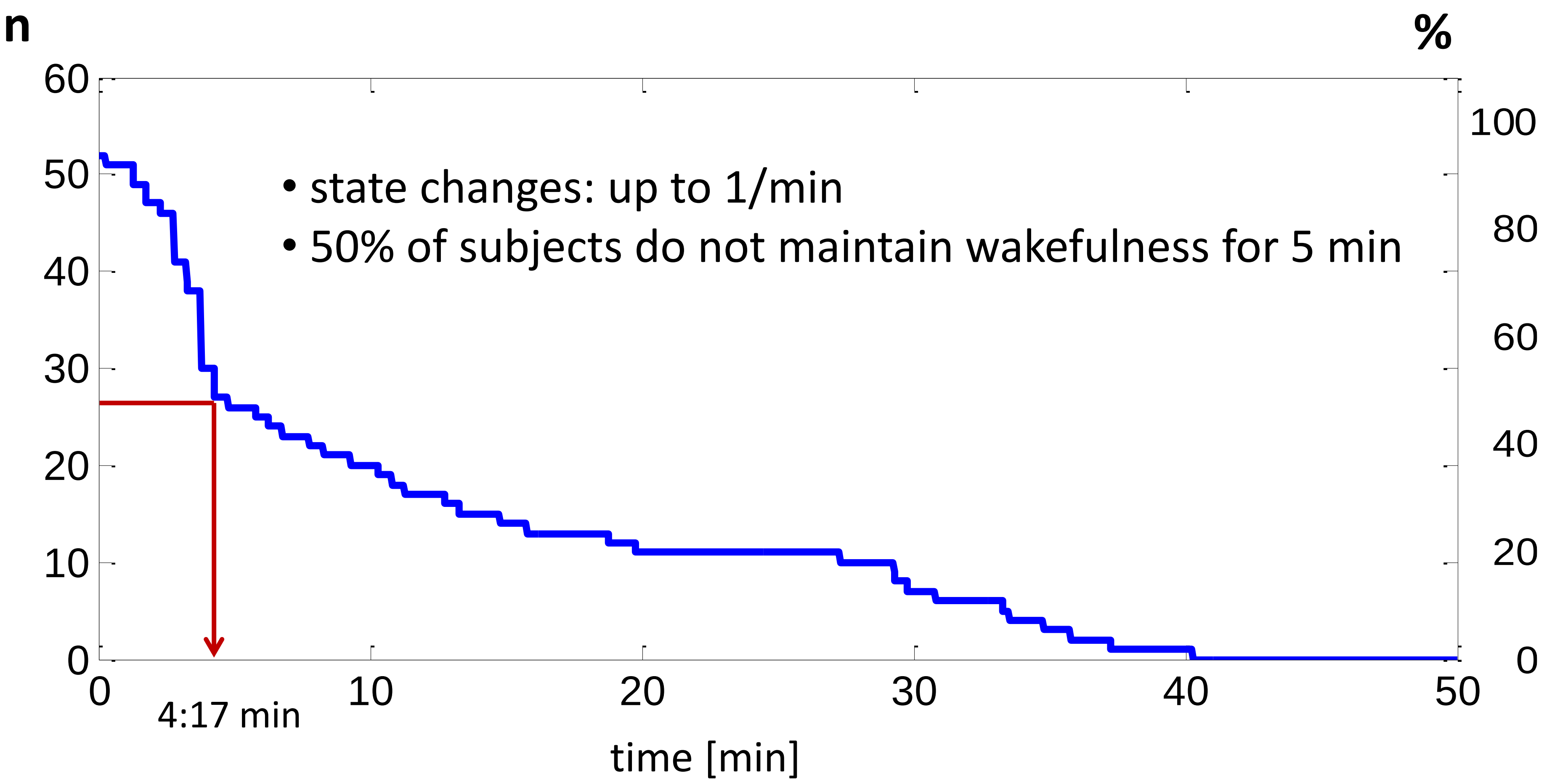
Changes in functional connectivity – N3

“global“ disconnection



Tagliazucchi, E. & Laufs, H. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. *Neuron (2014).*

subjects steadily awake over time



generalizable?

Chinese

76 young adults (18-26 yrs)
EPI, 33 slices, 225 images, TR = 2 s
7.5 min resting state fMRI

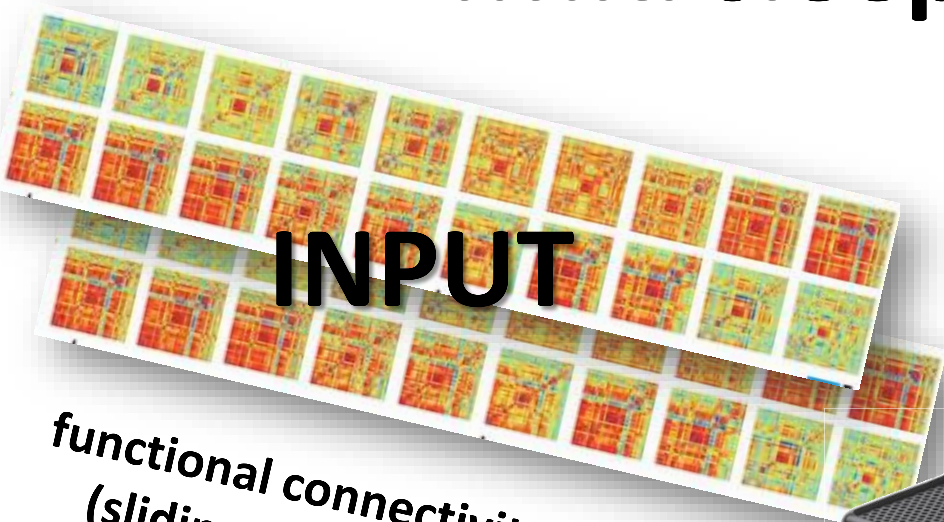
German

55 young adults (23 +-3 yrs)
EPI, 32 slices, 1500 images, TR = 2.08 s
52 min resting state fMRI

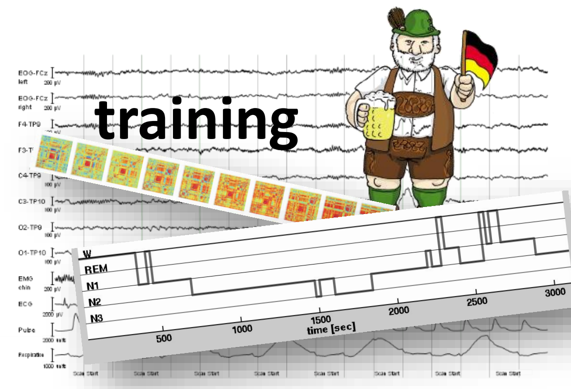
No EEG! Vigilance?

http://www.nitrc.org/frs/?group_id=296
Biswal et al. "Toward discovery science of human brain function." PNAS 2010

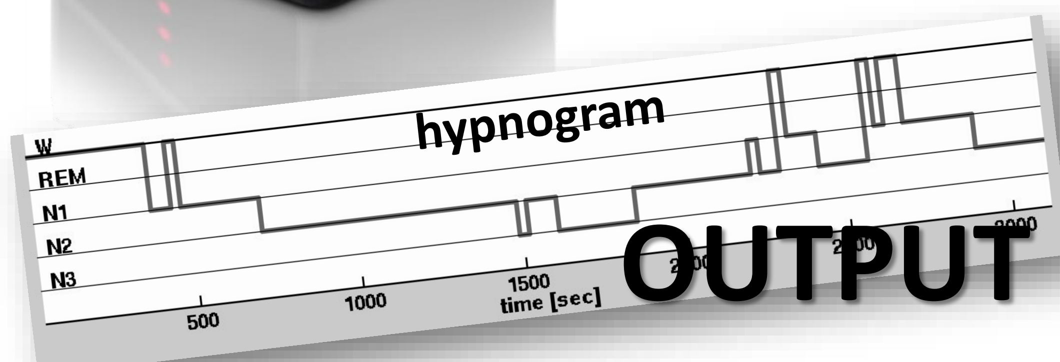
fMRI sleep classification



functional connectivity matrices
(sliding window, 60 images)



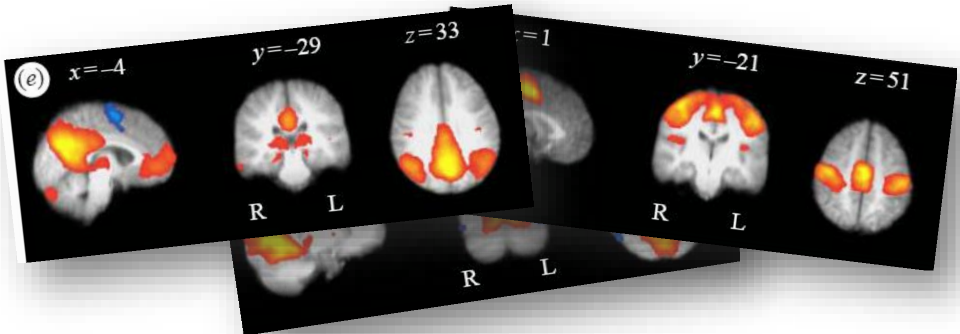
sleep staging based
on RS correlations !

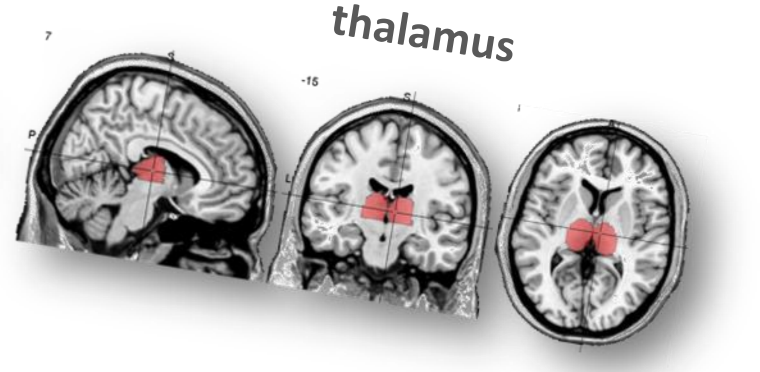


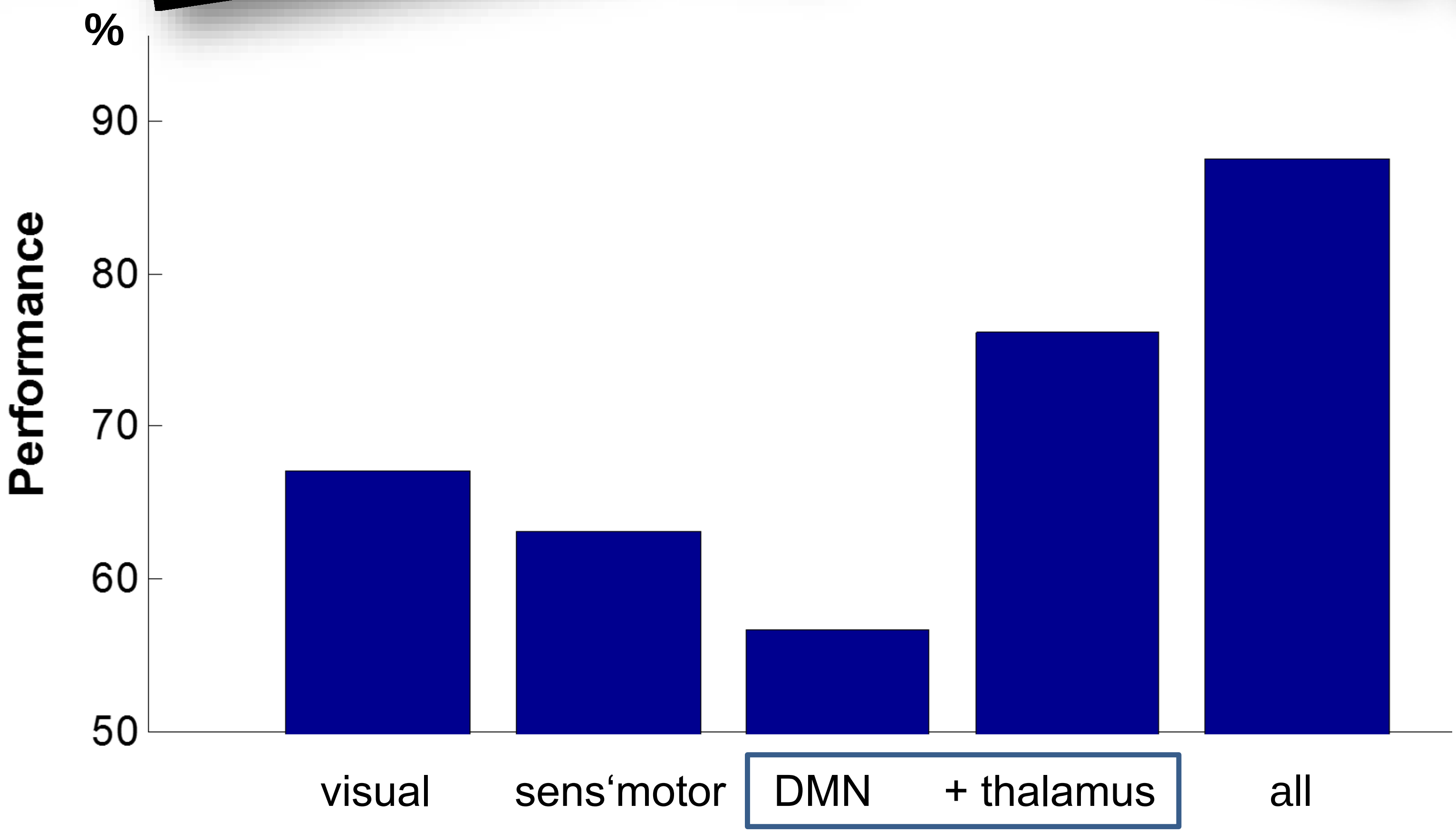
Tagliazucchi et al. Neuroimage 2012

classifier performance

as a function of input regions w.r.t. manual scoring (AASM 2007)







biological excursion

- RSN configuration is sleep stage specific
- DMN + [subcortical] thalamus -> outperforms cortical

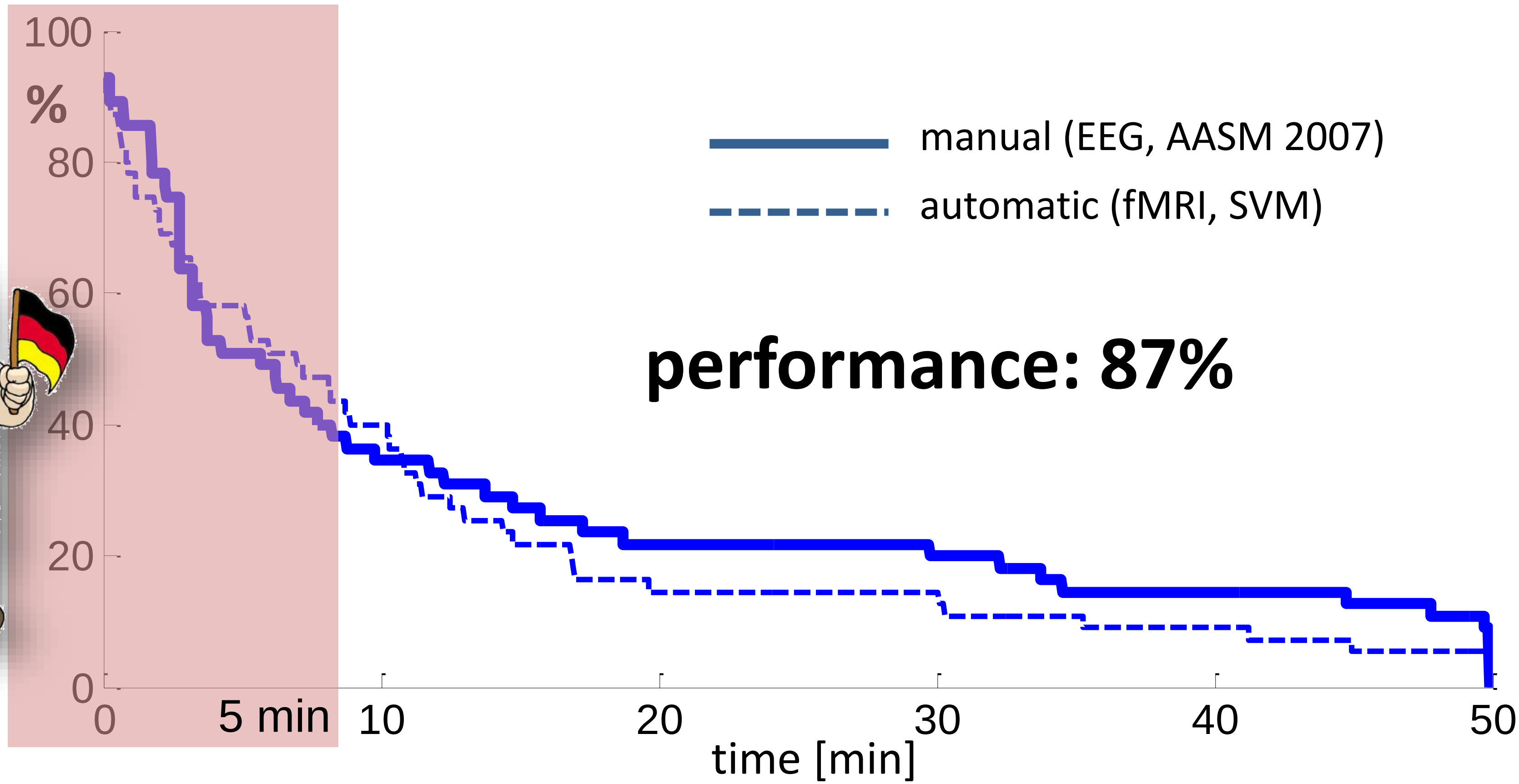
a tribute to the creator of SPM

- RSN configuration is sleep stage specific
- DMN + [subcortical] thalamus -> outperforms cortical

Friston 1996:

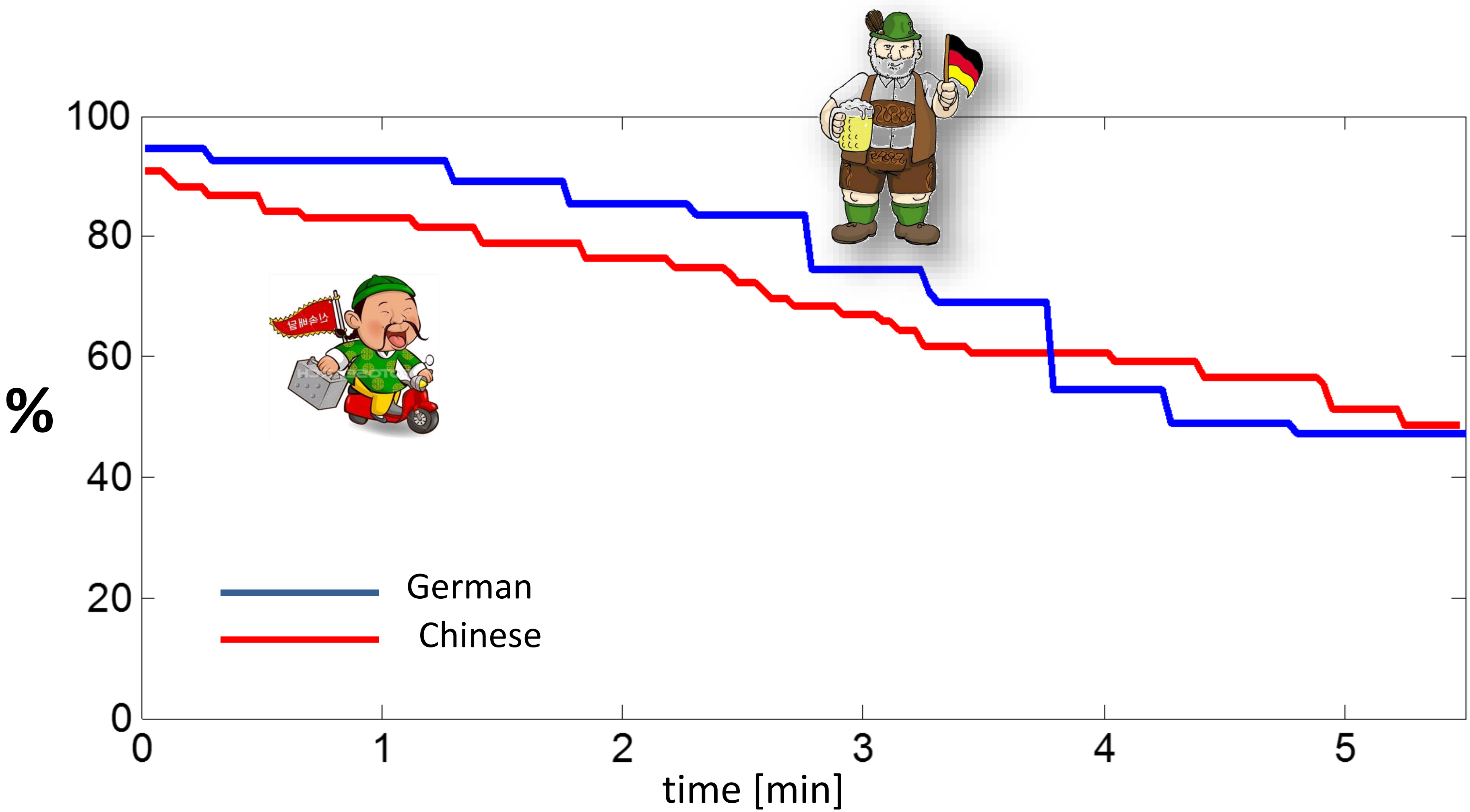
cortical resting state activity influenced by thalamus

classifier trained on fMRI data



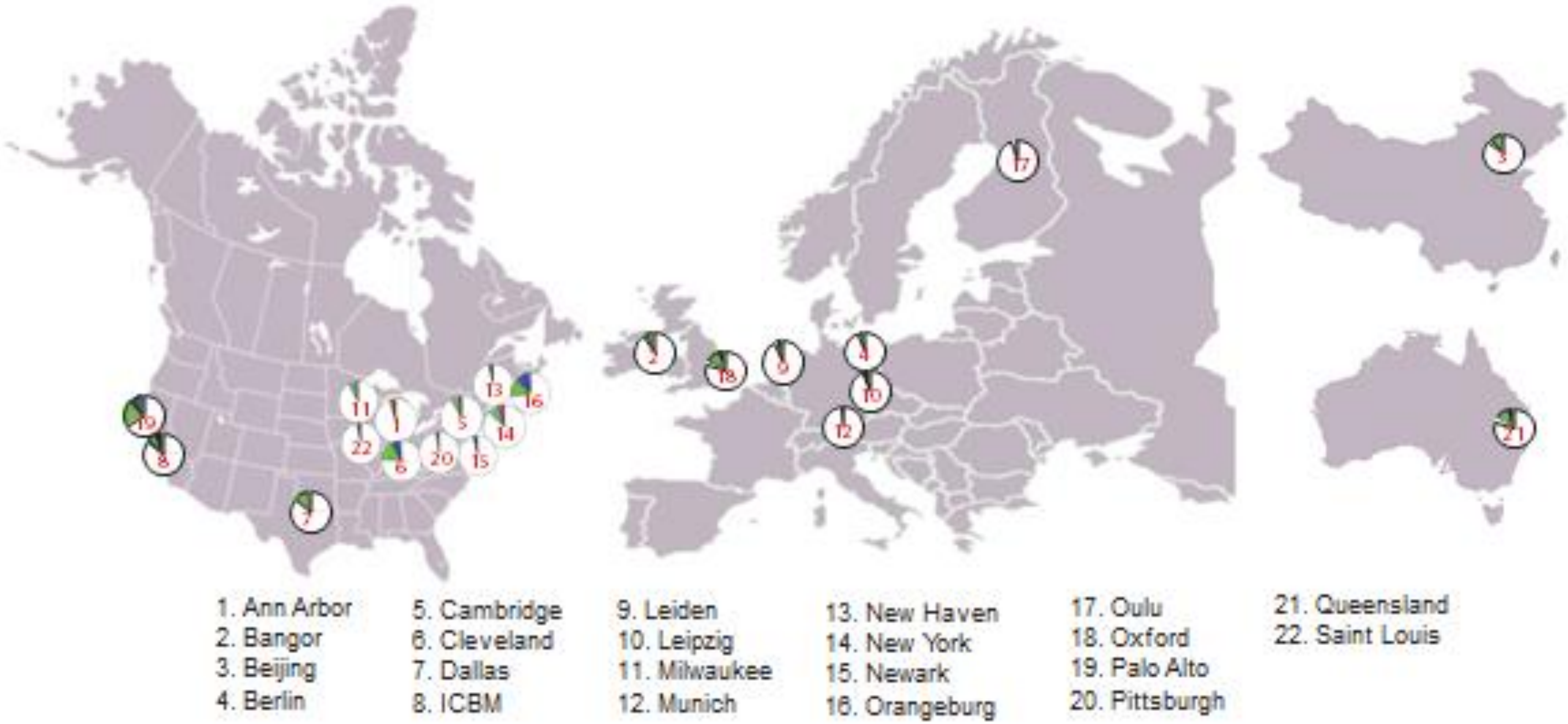
Tagliazucchi et al. Neuroimage 2012

not steadily awake over time



Tagliazucchi et al. Neuroimage 2012

1000 Functional Connectome Project, n=1147



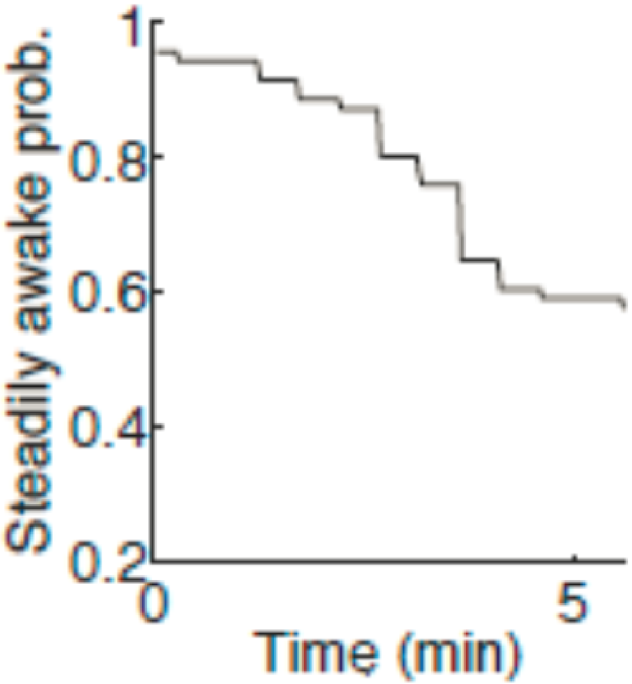
http://fcon 1000.projects.nitrc.org
Milham MP (2012) Open neuroscience solutions for the connectome-wide association era. Neuron 73:214-218.

Frankfurt vs. Connectomes Project

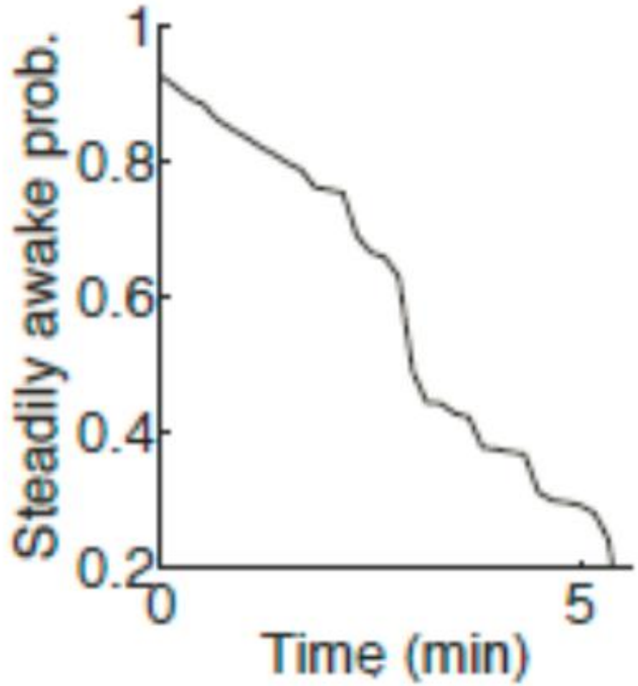
Kaplan Meier

n_F=71 (EEG+AASM), n_C=1147 (fMRI+SVM)

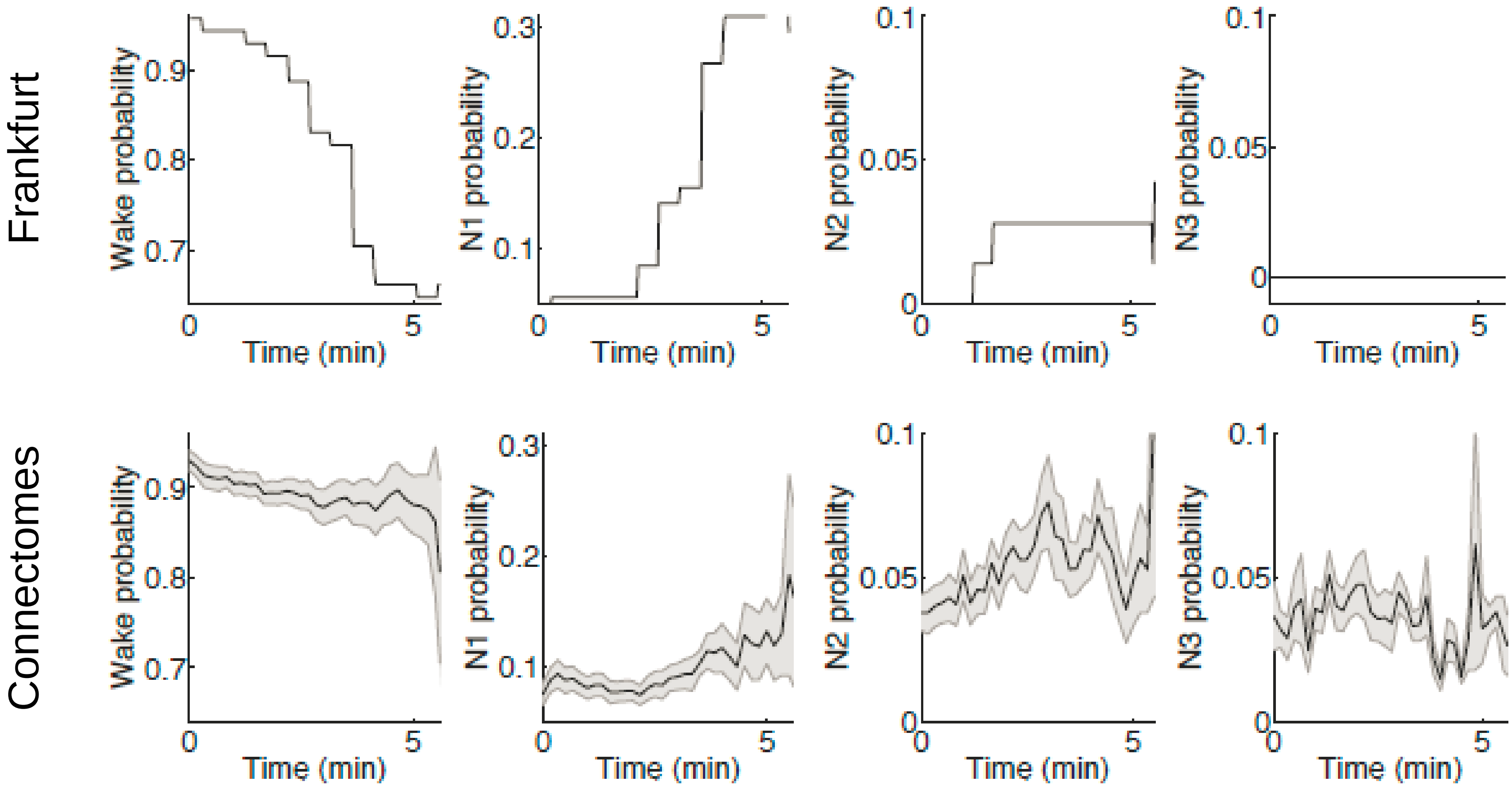
Frankfurt



Connectomes



Frankfurt vs. Connectomes Project
state probabilites
n_F=71 (EEG+AASM), n_C=1147 (fMRI+SVM)



Tagliazucchi, Laufs Neuron 2014

biological excursion

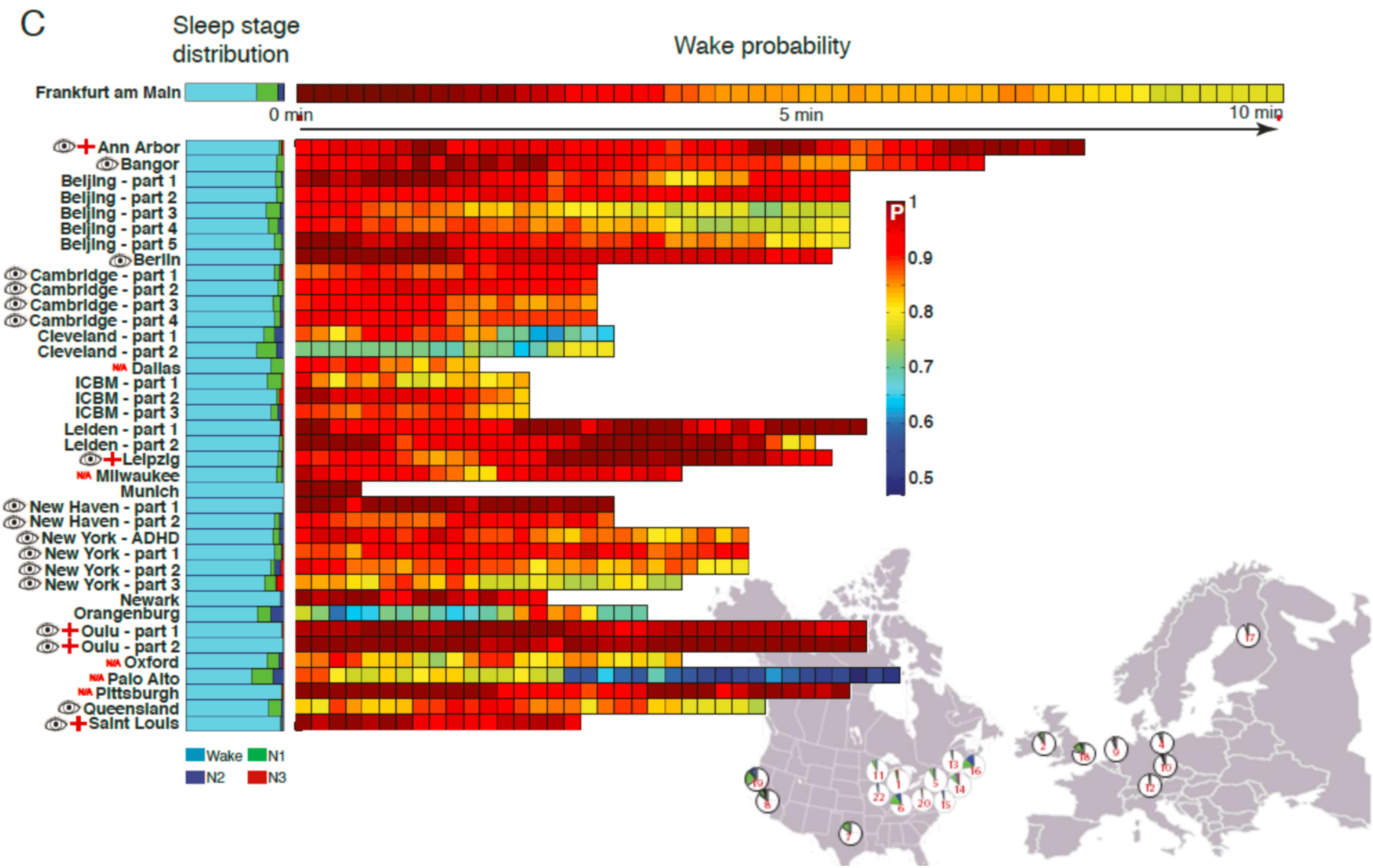
- ICN configuration is sleep stage specific
- differences are significant
- differences are biological in nature
- no „regression“ as such possible
- but: „pattern recognition“

Was tun?!

-> Know your enemy!

Frankfurt vs. Connectome Project

n_F=71 (EEG+AASM), n_C=1147 (fMRI+SVM)



Implication

- expect 50% of subjects not to be steadily awake
  for >5 min - unless proven otherwise
- vigilance changes affect resting state functional connectivity

Tagliazucchi, Laufs Neuron 2014

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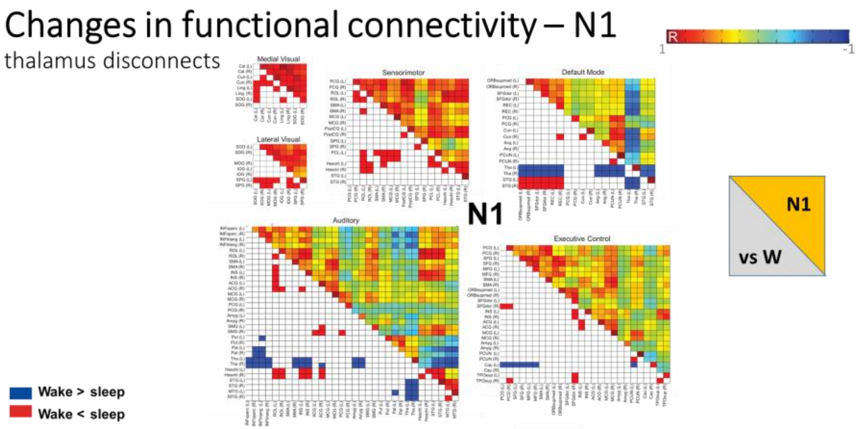

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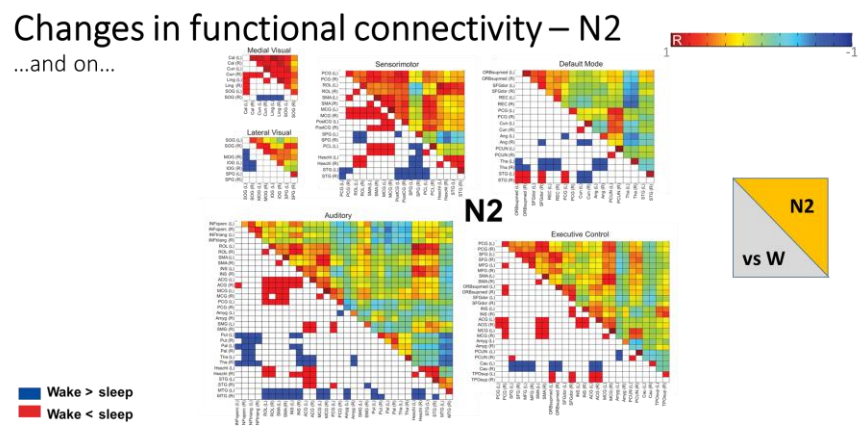


Tagliazucchi, E. & Laufs, H. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. *Neuron (2014).*

Problem

- false positives/negatives due to mixing of states

Tagliazucchi, Laufs Neuron 2014

Solution I

- record simultaneous EEG (polysomnography during fMRI)
- sleep score EEG
- analyse “pure states” separately

…can’t we do without EEG?

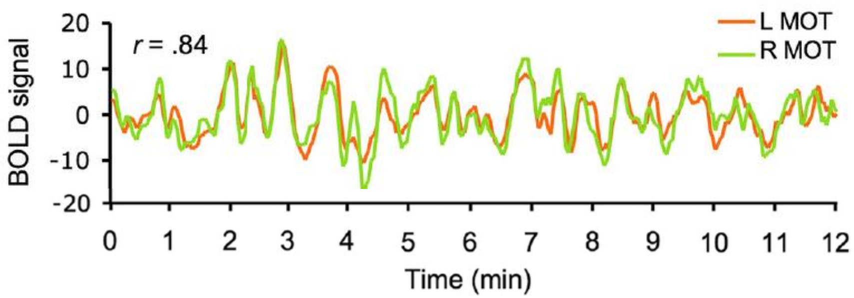
Yes, we can!

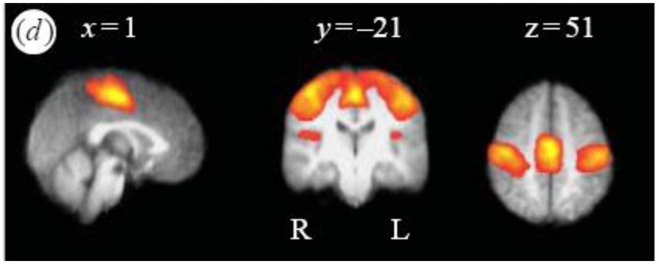
Controlling spontaneous brain activity - a paradox?

Controlling spontaneous brain activity - a paradox?

1. Scanner drift
2. Subject motion
3. Circulation
4. Respiration
5. Wakefulness
6. Non-stationarity

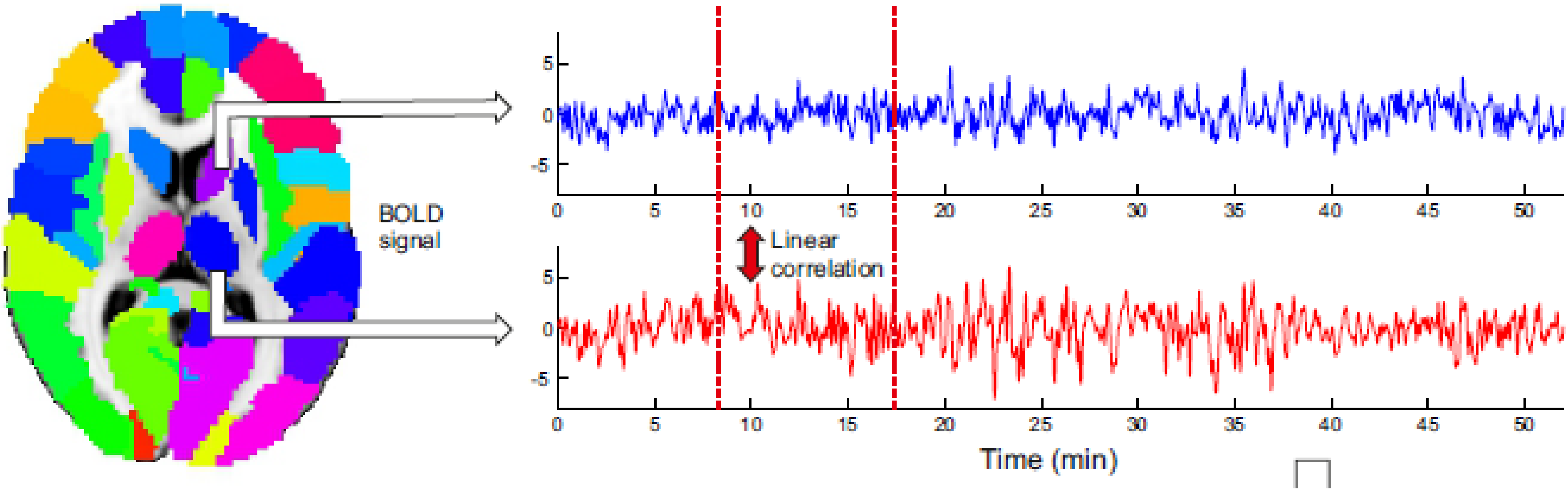
Static functional connectivity
seed correlation (functional connectivity)



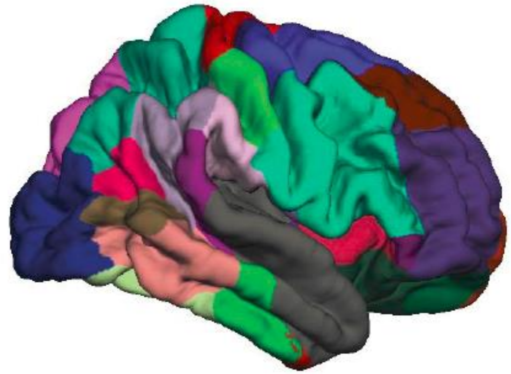


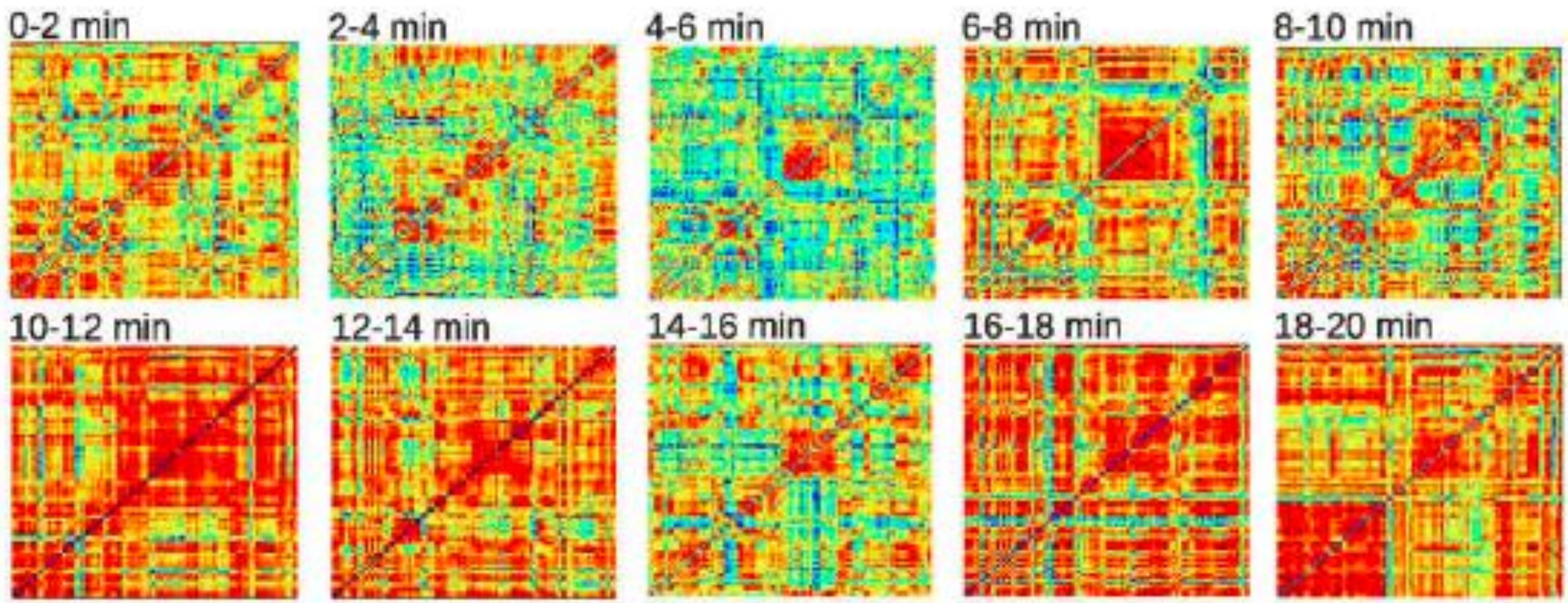
sensory
motor

left: Van Dijk et al. Journal of neurophysiology 2010; *right*: Beckmann et al. Phil Trans Roy Soc London 2005



Non-stationarity





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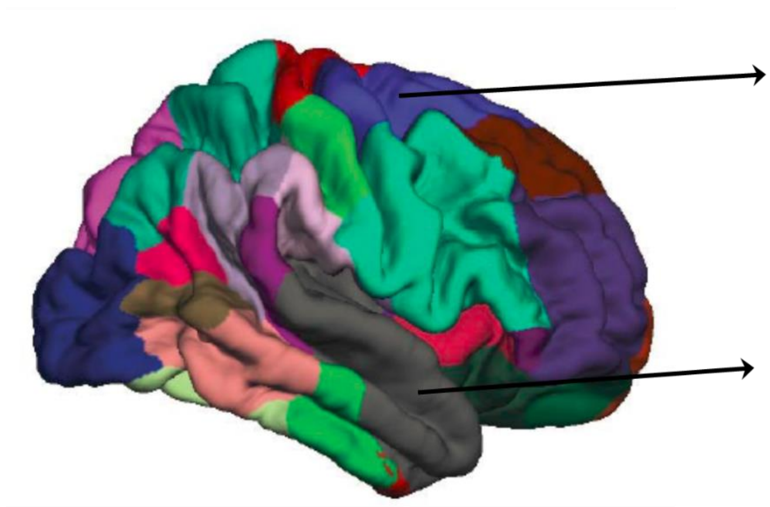
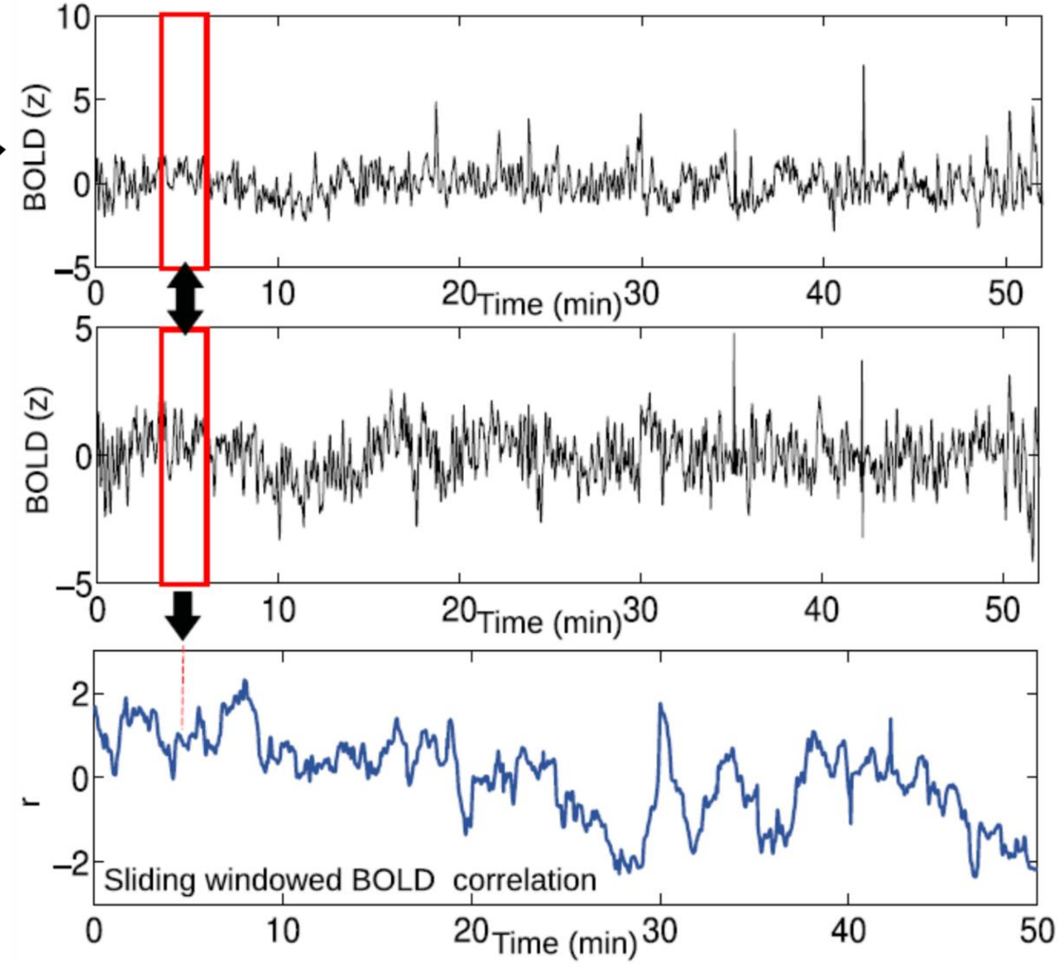
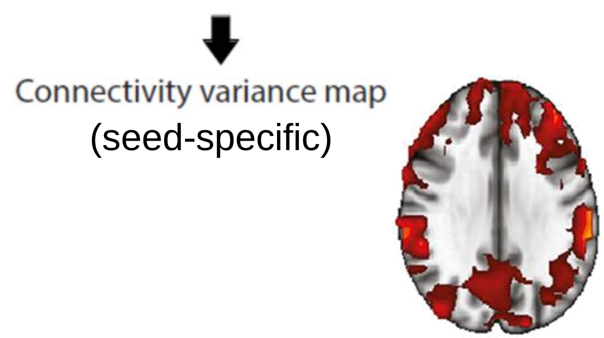
Non-stationarity







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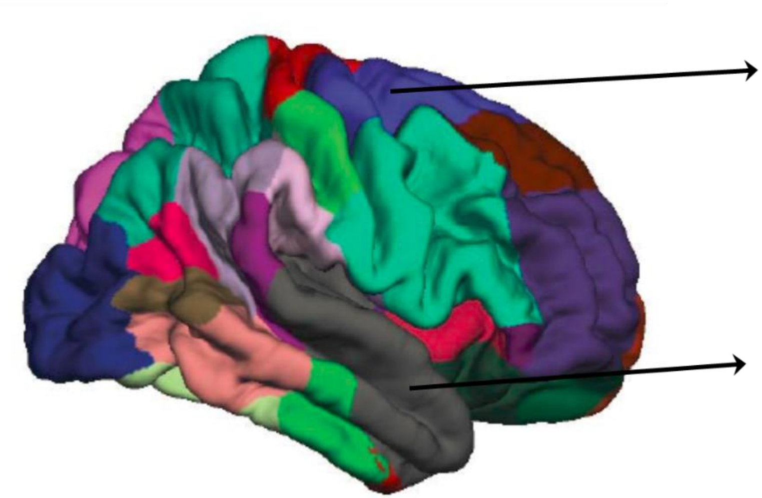
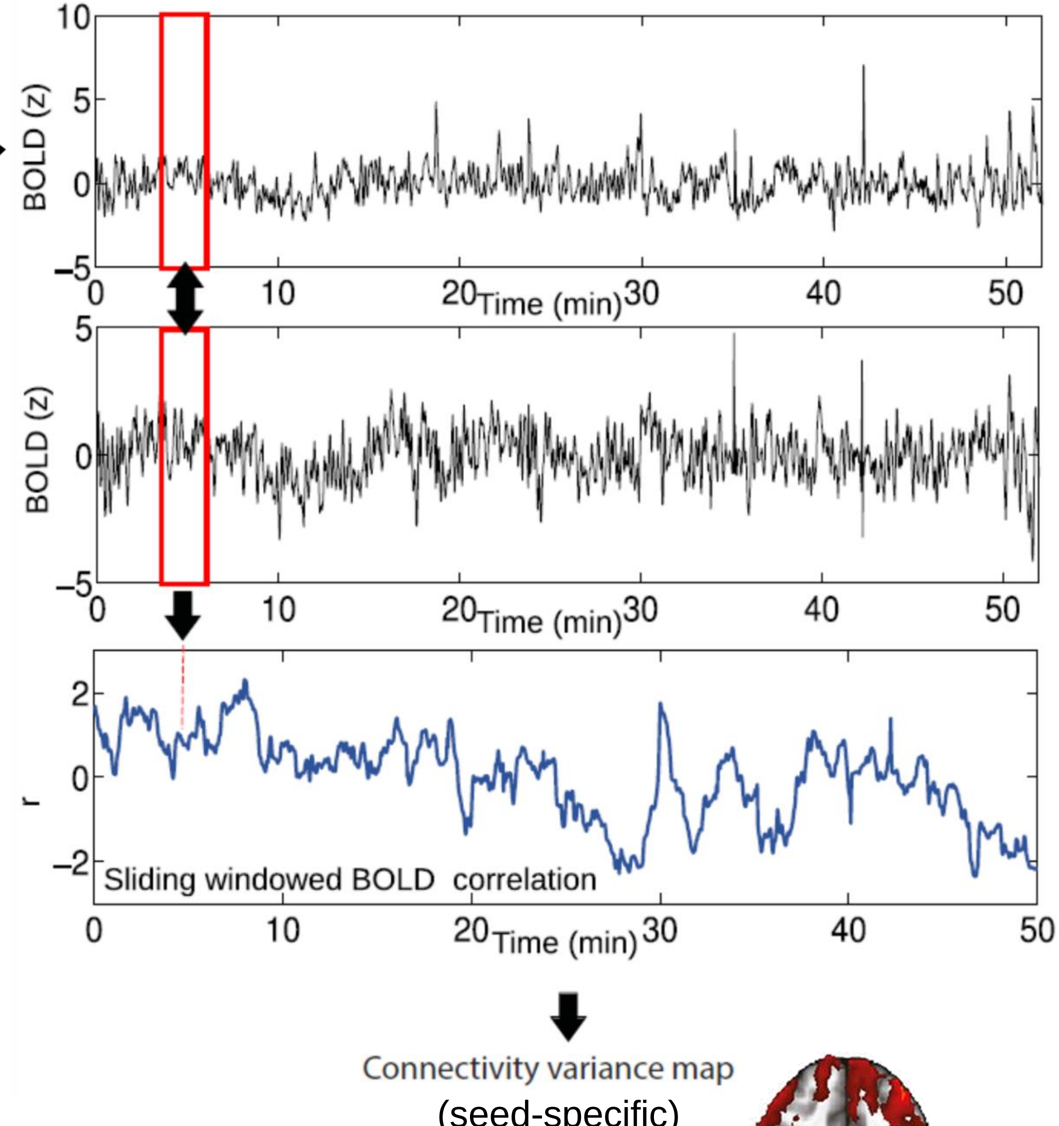
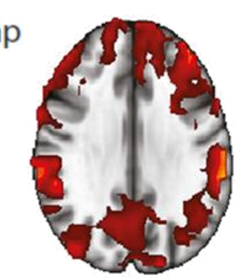
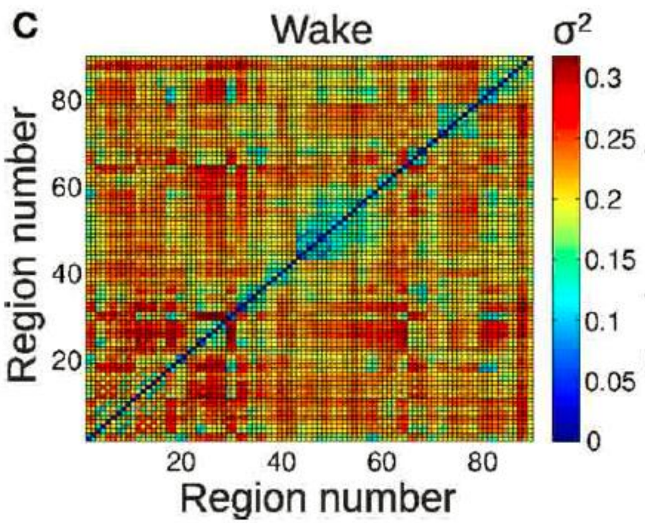
Non-stationarity







Standard deviation with Thalamus as ROI



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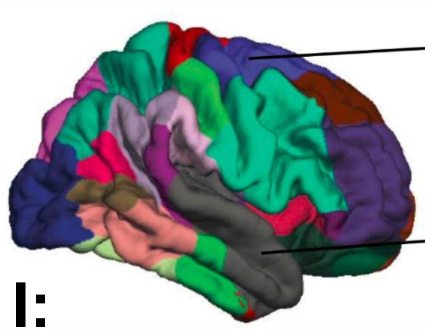
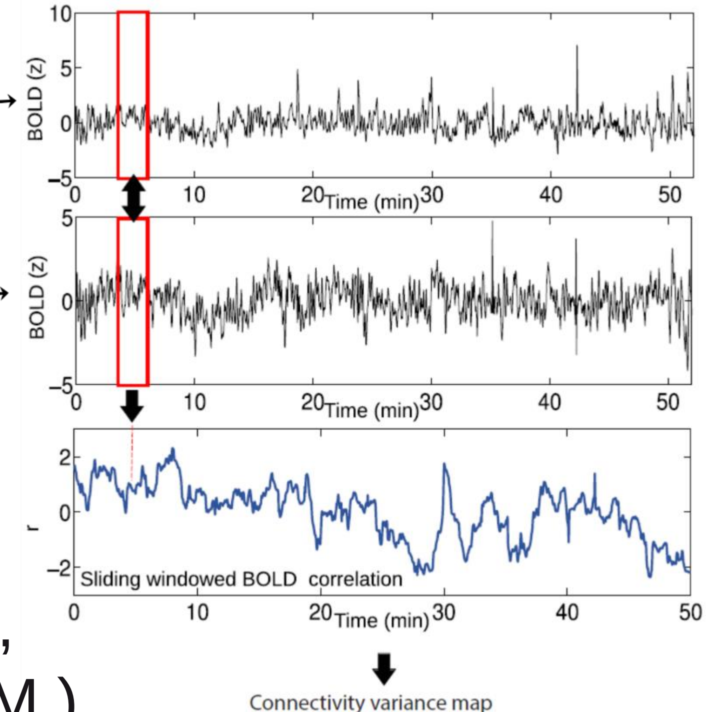
Dynamic functional connectivity





example recipe I:
fMRI data

- realign, normalize (atlas space), smooth (8 mm^3 Gaussian FWHM,)
- regress out:
  cardiac-, respiratory (RETROICOR, Glover et al. 2000), motion-induced noise (Friston 1996)
- bandpass filter fMRI (0.01-0.1 Hz, 6^{th} order Butterworth)

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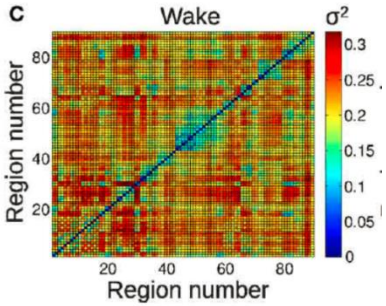
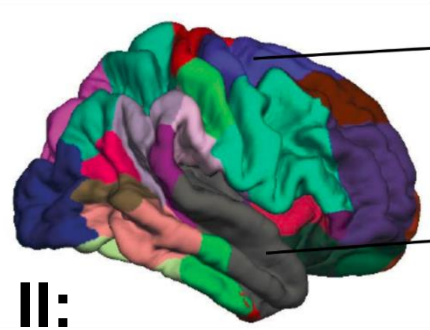
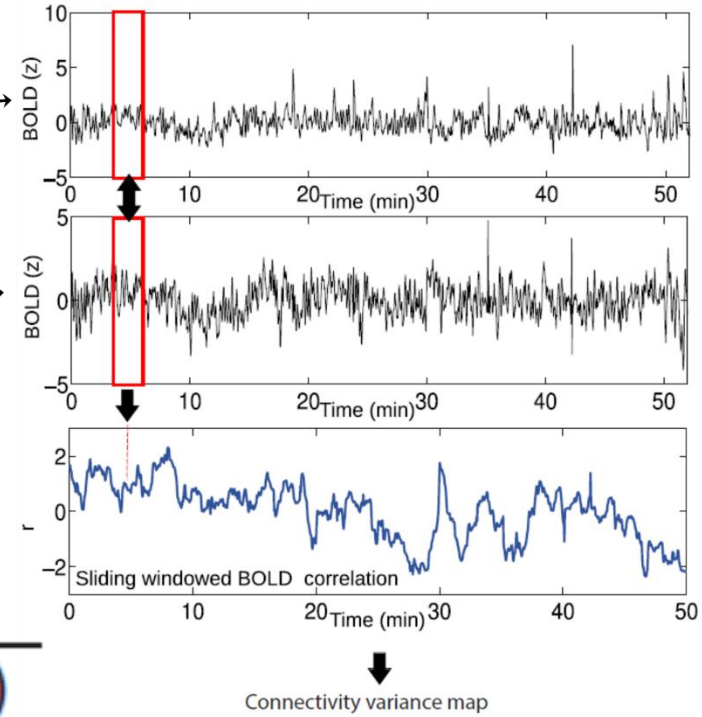
Dynamic functional connectivity







example recipe II:
sliding window analysis
(correlation)

$$C_{ij}(t) = \frac{(x_j(t : t+k) - \langle x_j(t : t+k) \rangle))}{\sigma\,(x_i(t : t+k))\,\sigma\left(x_j(t : t+k)\right)}$$

- window length of ≈ 2 min (60 volumes = 60 data points) compromise between "reliable" connectivity (Van Dijk, 2010) and expected fluctuations/length of experiment
- (spatial) average BOLD signal for each AAL region
- MATLAB vector syntax; $x_{i/j}(n{:}m)$ represents the part of the time series x (of the region indexed i or j) ranging from data point n to data point m. $C_{ij}(t)$ is the linear correlation between x_i and x_j during a window of length k starting from t (e.g. k = 60 data points ~ 2 min window).

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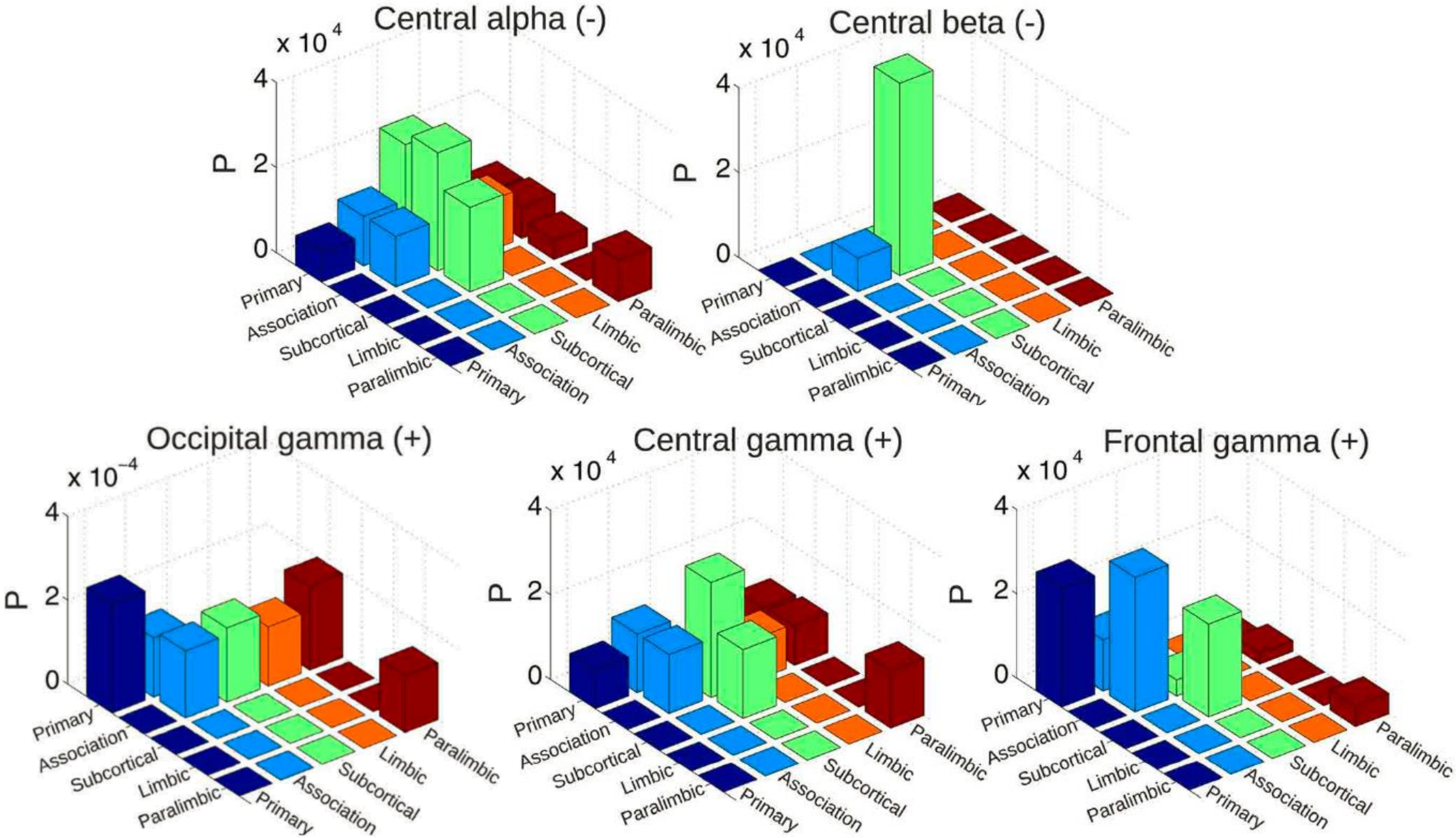
Dynamic functional connectivity



Probability of finding connections between different systems (sensory, association, subcortical, limbic, and paralimbic) which correlate either positively or negatively with spontaneous EEG power fluctuations (normalized by the total number of possible connections between each pair of systems). Results are for the group of awake subjects.

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Controlling spontaneous brain activity

not a paradox - but a necessity

Conclusion I

- **add control to your resting state data**

Conclusion II

- **add control to your resting state data**