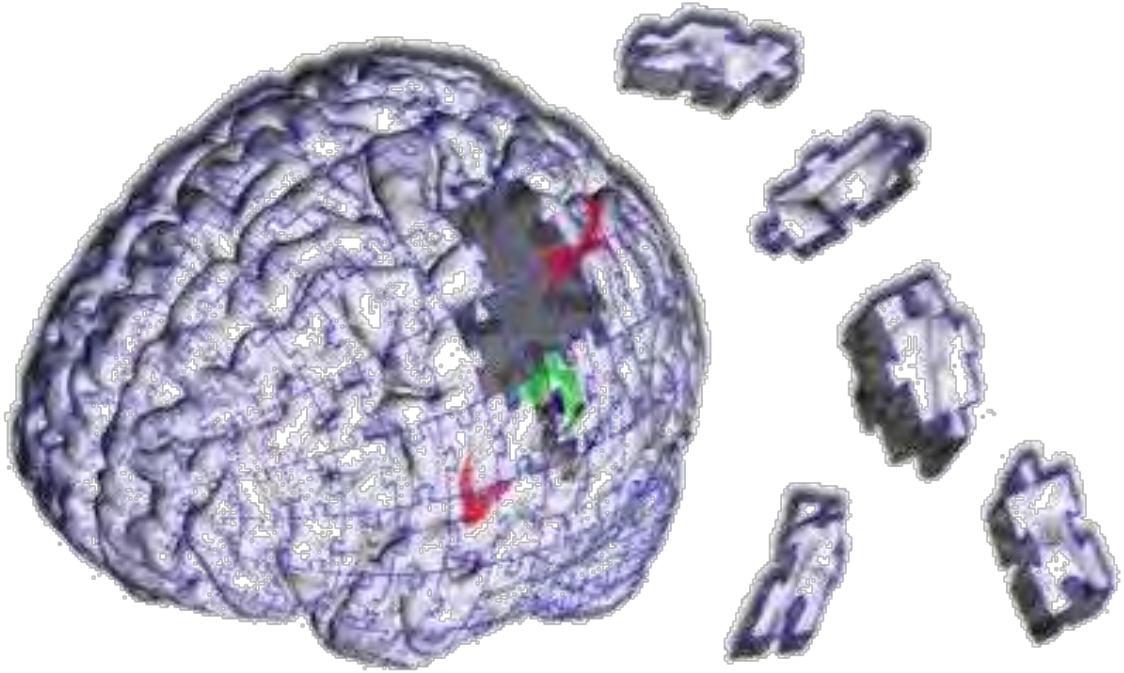
Controlling spontaneous brain activity - a paradox?

Institut für Systemische Neurowissenschaften

13.09.2012



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NeFF
Neuronale Koordination
Forschungsschwerpunkt Frankfurt

Bundesministerium
für Bildung
und Forschung

BIC
Brain Imaging Center
Frankfurt am Main

Structure

I. background
II. When resting state experiments (part I)?
III. Caveats (part I)
IV. When resting state experiments (part II)?
V. Caveats (part II)

Structure

I. background
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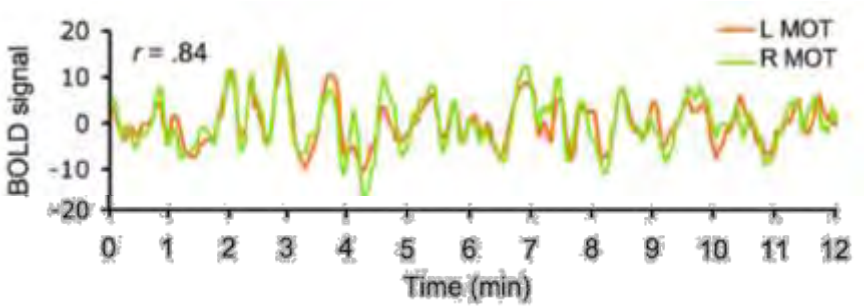
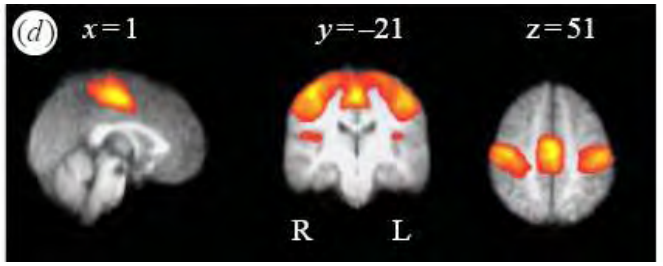
Resting state brain activity
correlations despite task absence





sensory
motor

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

Resting state brain activity

(fMRI, functional connectivity)

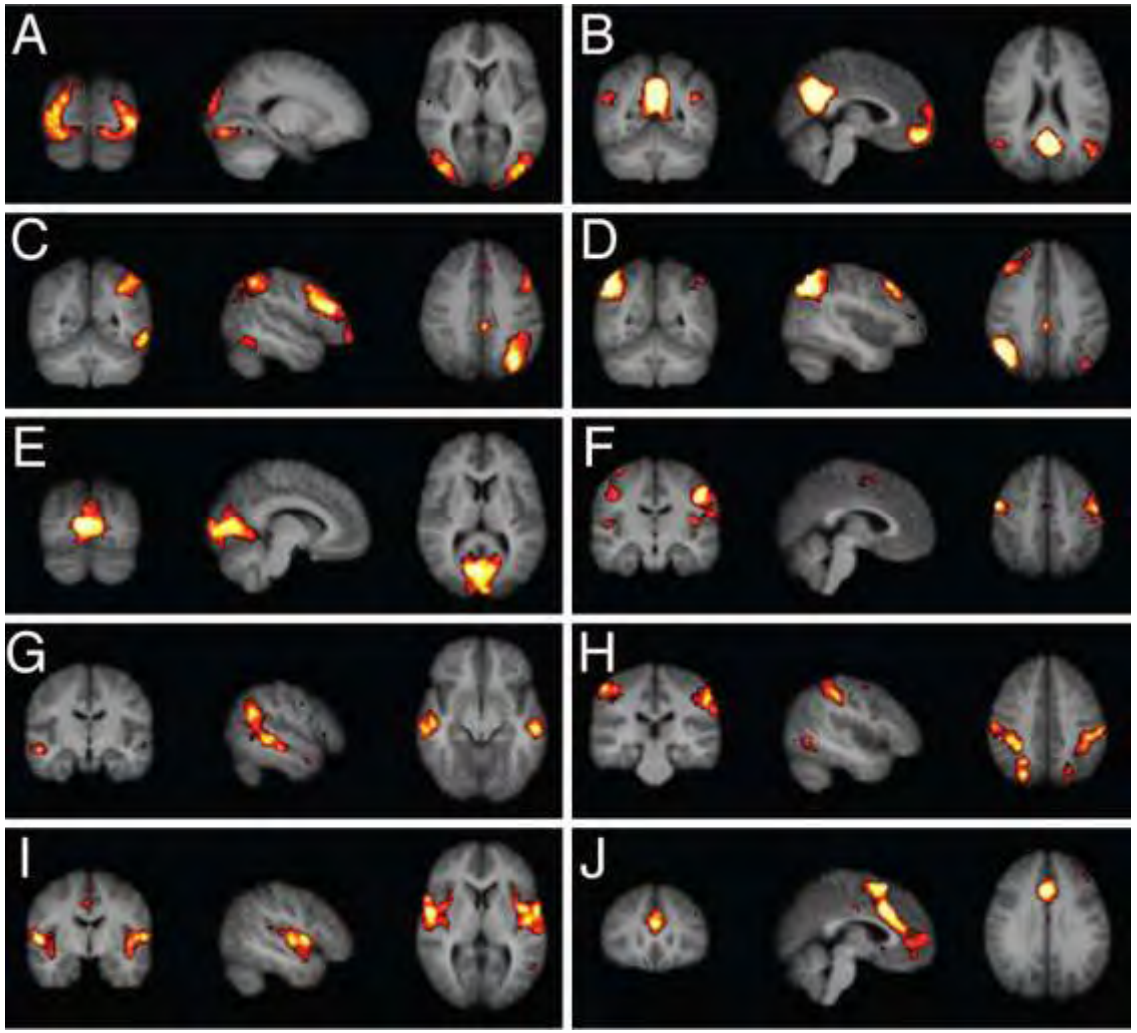
lateral visual

memory (left)

medial visual

ventral stream (visual)

auditory



default mode

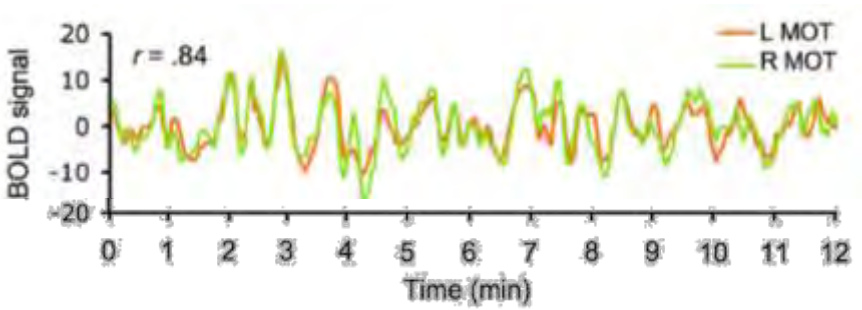
memory (right)

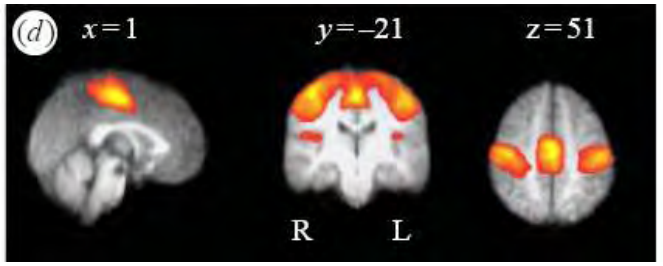
sensory-motor

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





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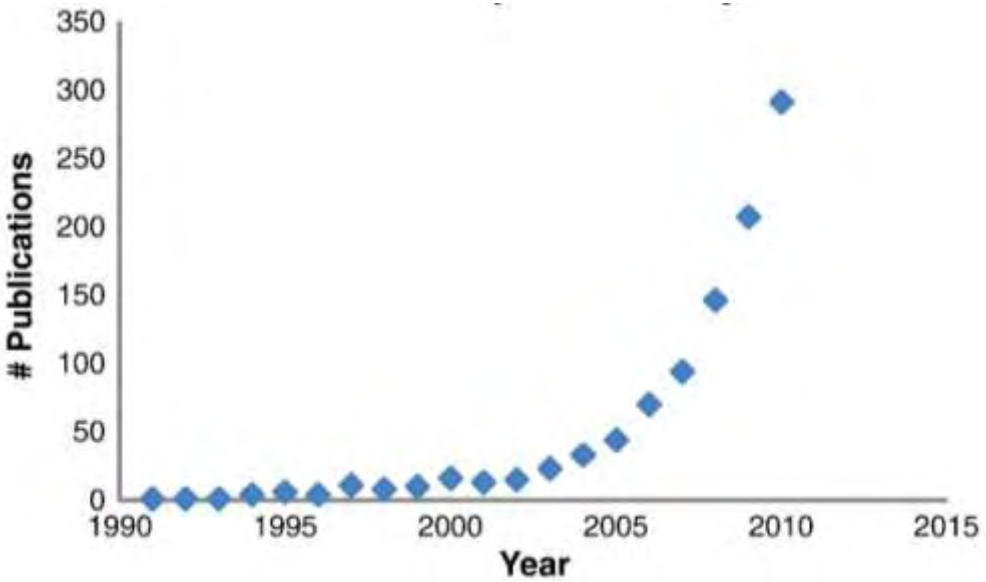
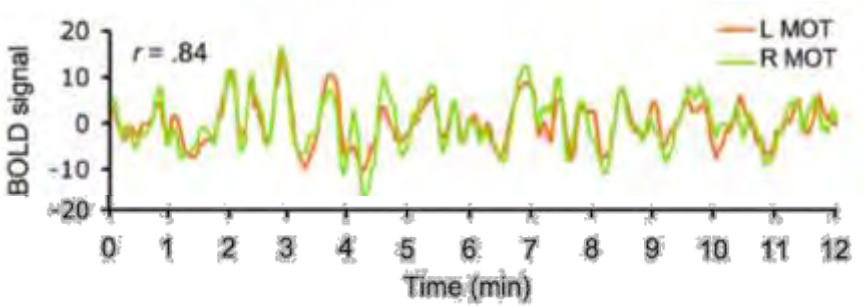
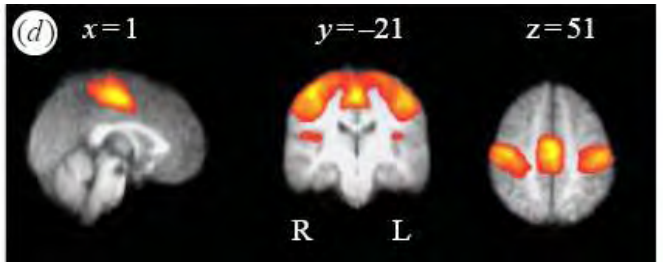


Number of publications per year on resting-state functional connectivity. Birn, R.M Neuroimage 2012

Resting state brain activity
correlations despite task absence





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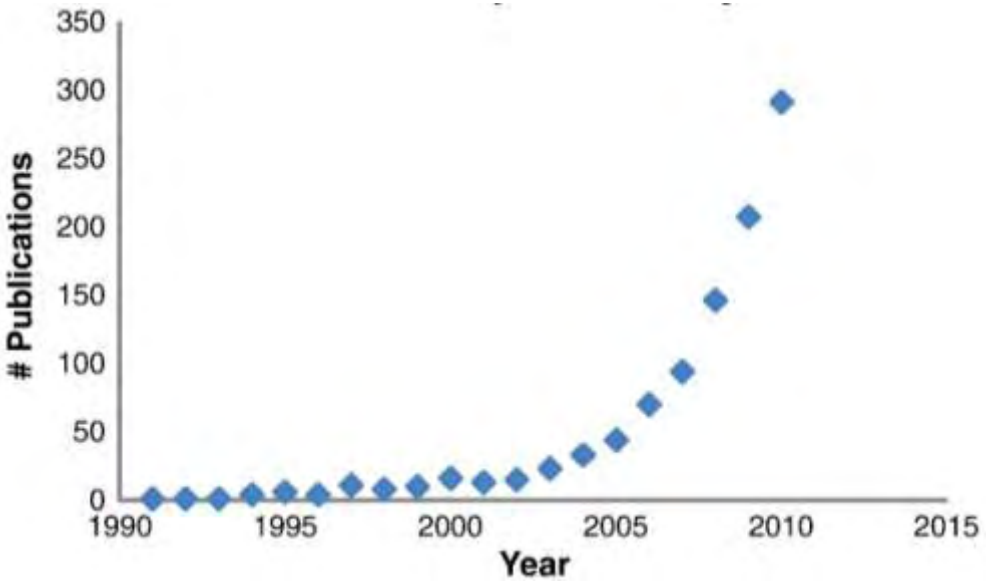


Number of publications per year on resting-state functional connectivity. Birn, R.M Neuroimage 2012

…established

Biswal et al. Magn Reson Med 1995

…en vogue

~300 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)

Structure

I. background
II. **When resting state experiments (part I)?**
III. Caveats (part I)
IV. When resting state experiments (part II)?
V. Caveats (part II)

Three scenarios

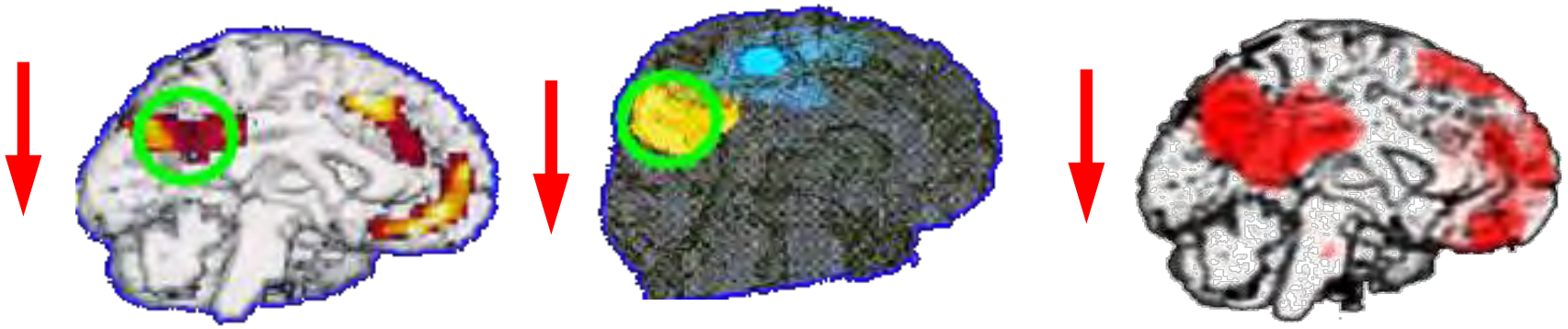
I. subjects cannot engage in a paradigm
II. spontaneously occurring phenomena are of interest
III. Network comparison between healthy and patient groups

scenario I

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

- Sleep
  e.g. Dang-Vuet 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

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



?

?

?

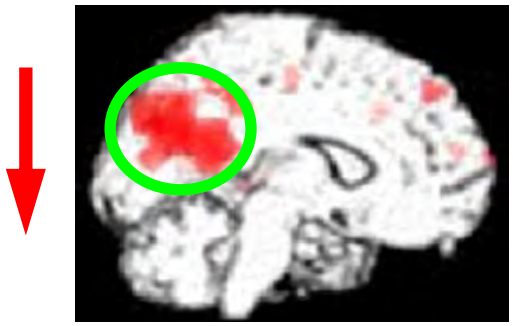
scenario II

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
- sleep spindles, vertex sharp waves, K-complexes
  e.g. Schabus et al. Proc Natl Acad Sci U S A 2007; Laufs et al. Brain 2007; Jahnke et al. Neuroimage 2012
- resting EEG oscillations
  e.g. Laufs Hum Brain Mapp 2008

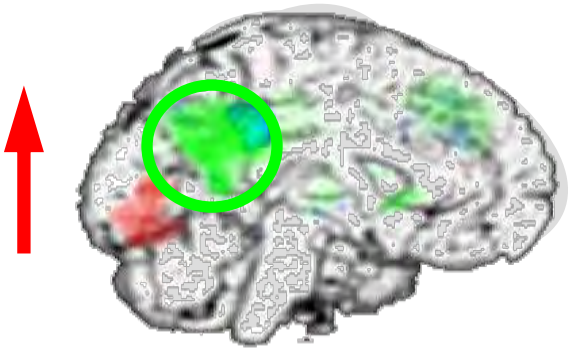
II. spontaneously occurring (EEG) phenomena of interest

epileptic spikes, K-complexes, beta oscillations



?

?

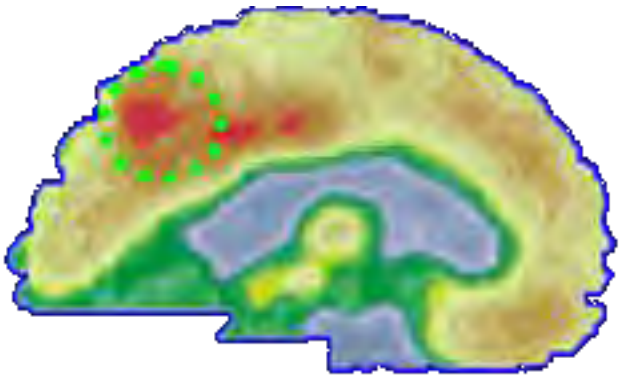


?

quiz

K-complexes vs. N2 background

temporal lobe spikes vs. background



coma vs. awake

sleep vs. awake

seizure vs. no seizure

17-23 Hz beta oscillations

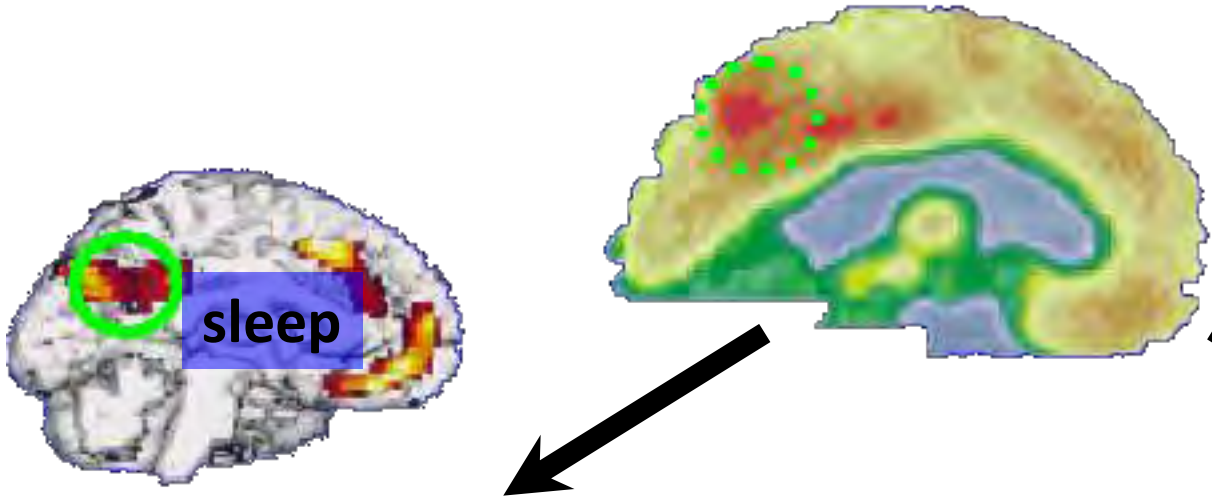
Wie mach ich’s?

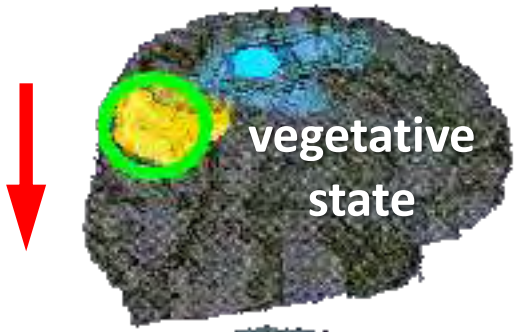
Was bedeutet’s?

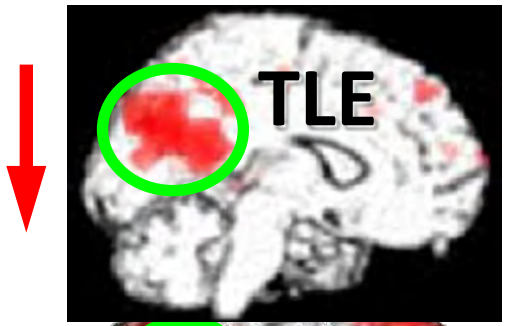
Wie mach ich’s?

Was bedeutet’s?

states of reduced consciousness ⟷ **rest** (default mode) ⟷ perception and action







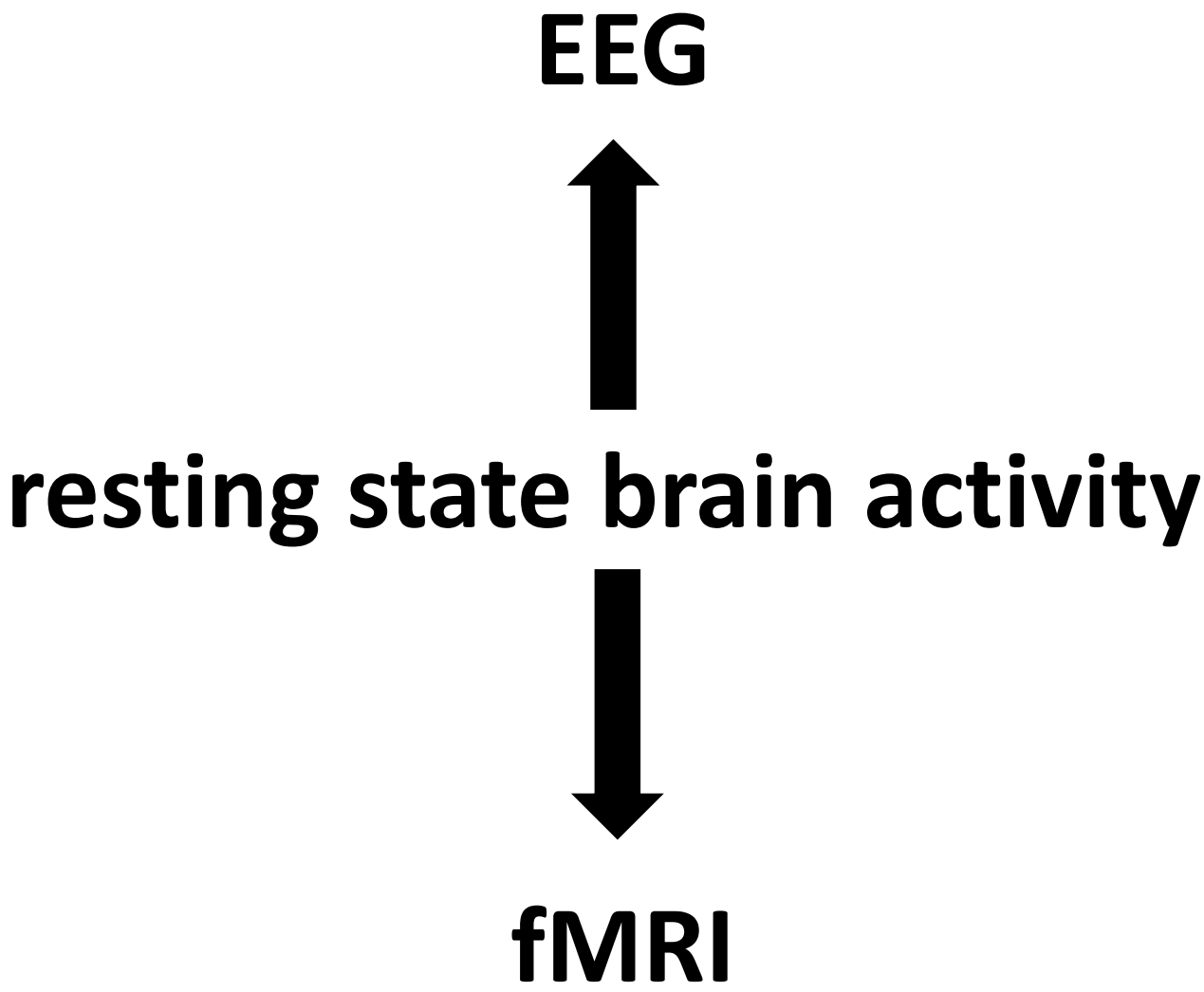
Laureys et al. 2004

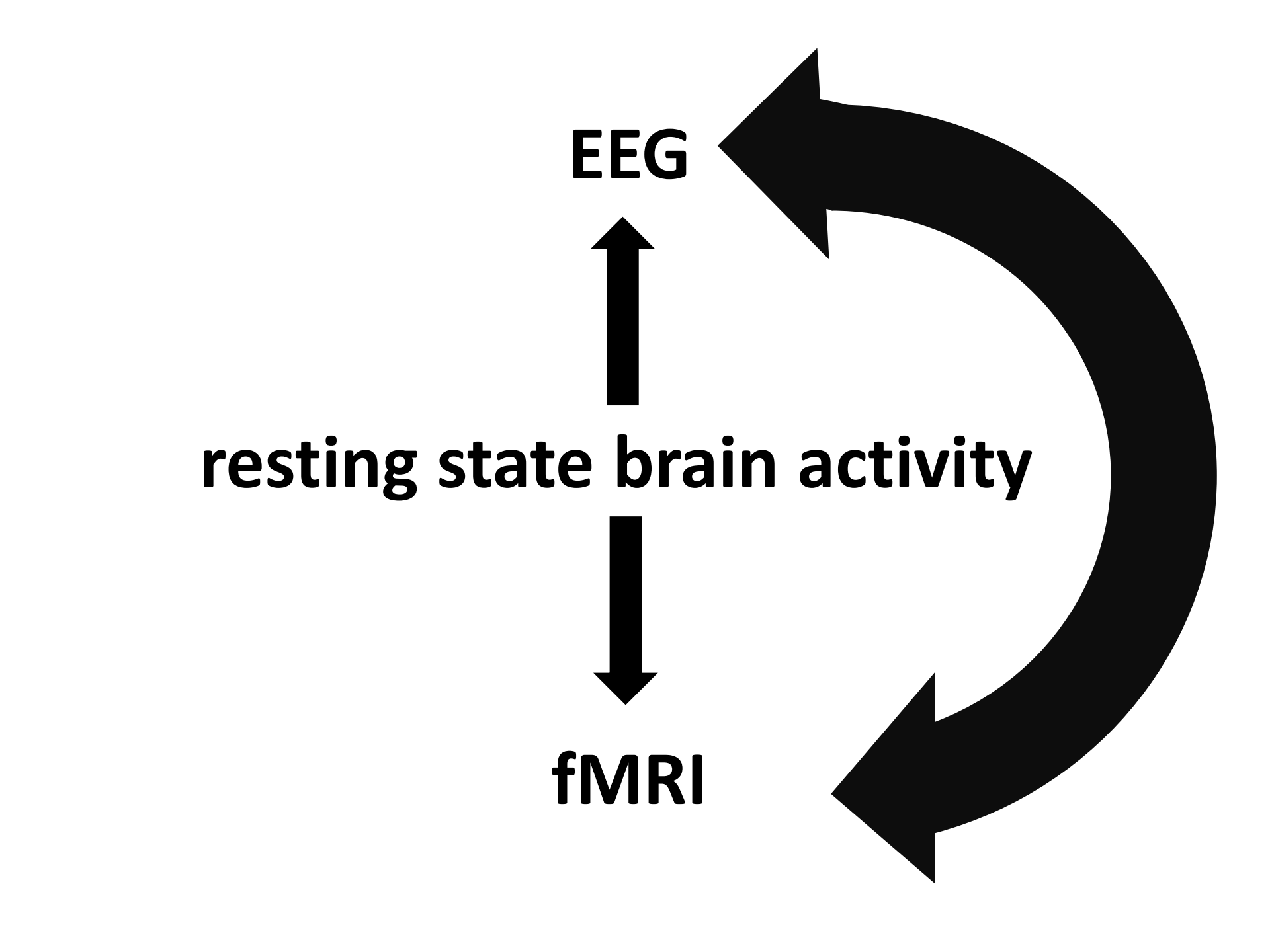
Laufs et al. 2006, 2007

Gusnard and Raichle 2001

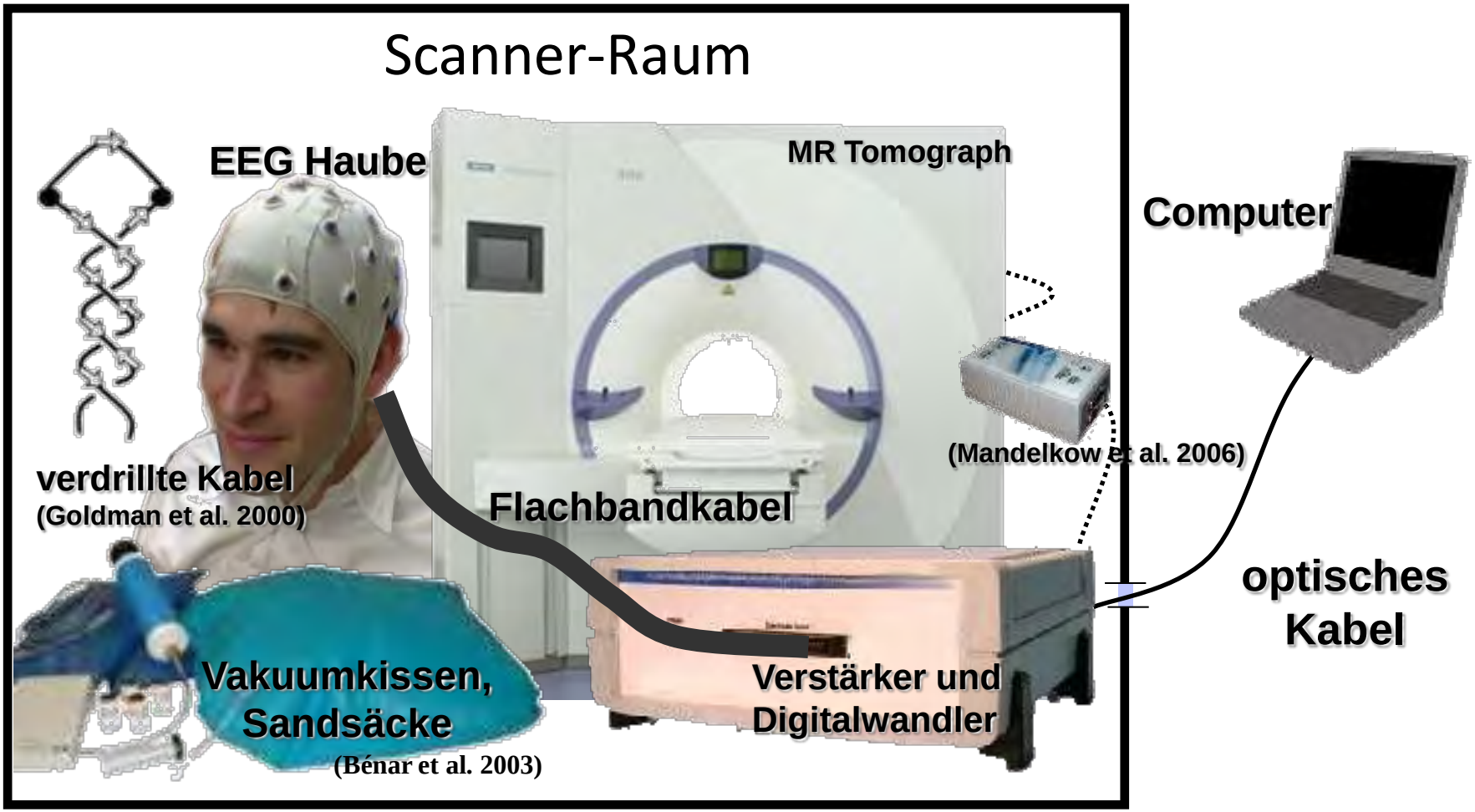
Wie mach ich’s?

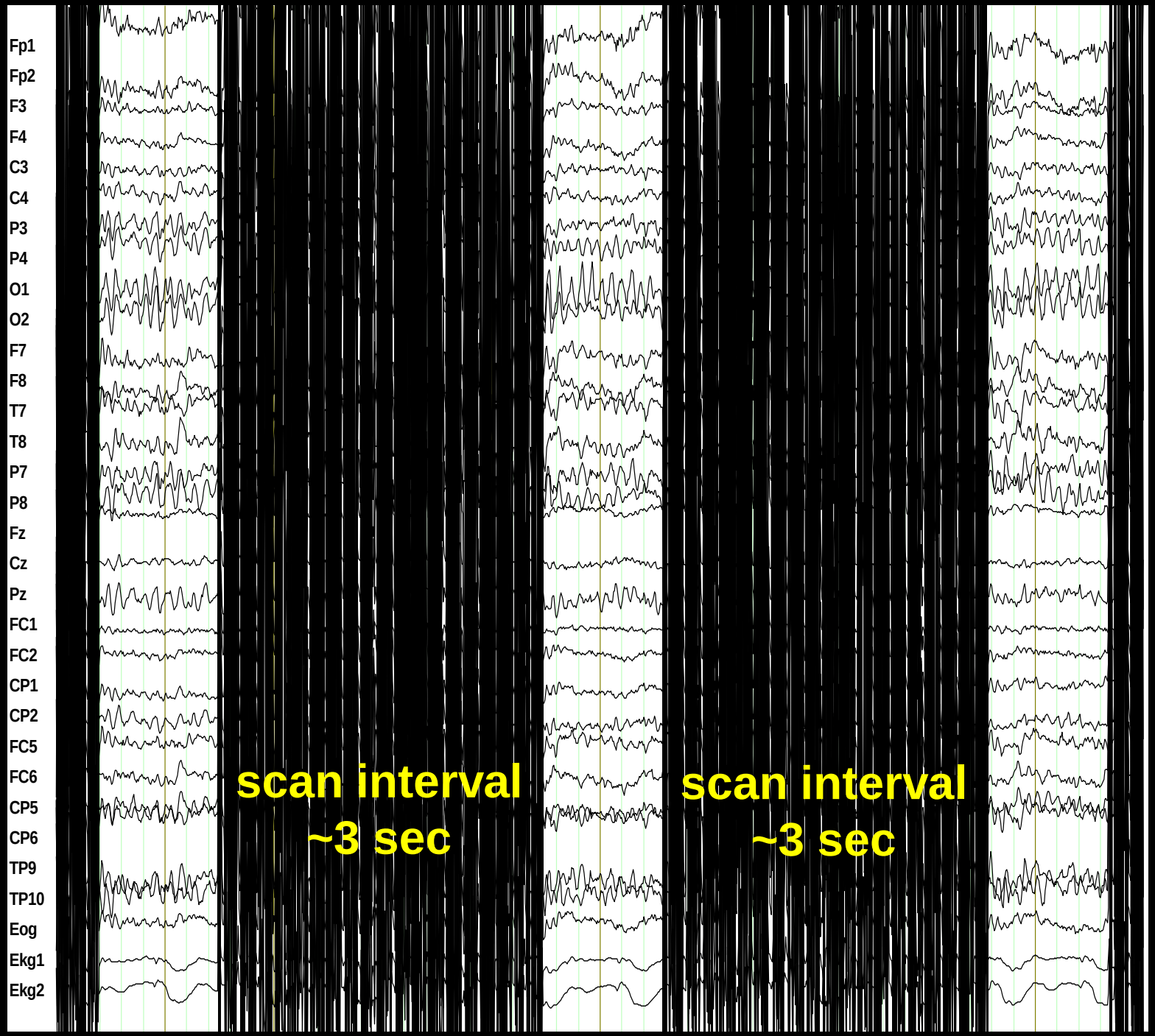
Was bedeutet’s?


EEG
resting state brain activity
fMRI


EEG
resting state brain activity
fMRI

Simultane Aufzeichnung von EEG/fMRT




Fp1
Fp2
F3
F4
C3
C4
P3
P4
O1
O2
F7
F8
T7
T8
P7
P8
Fz
Cz
Pz
FC1
FC2
CP1
CP2
FC5
FC6
CP5
CP6
TP9
TP10
Eog
Ekg1
Ekg2
scan interval
~3 sec
scan interval
~3 sec


Fp1
Fp2
F3
F4
C3
C4
P3
P4
O1
O2
F7
F8
T7
T8
P7
P8
Fz
Cz
Pz
FC1
FC2
CP1
CP2
FC5
FC6
CP5
CP6
TP9
TP10
Eog
Ekg1
Ekg2


Fp1
Fp2
F3
F4
C3
C4
P3
P4
O1
O2
F7
F8
T7
T8
P7
P8
Fz
Cz
Pz
FC1
FC2
CP1
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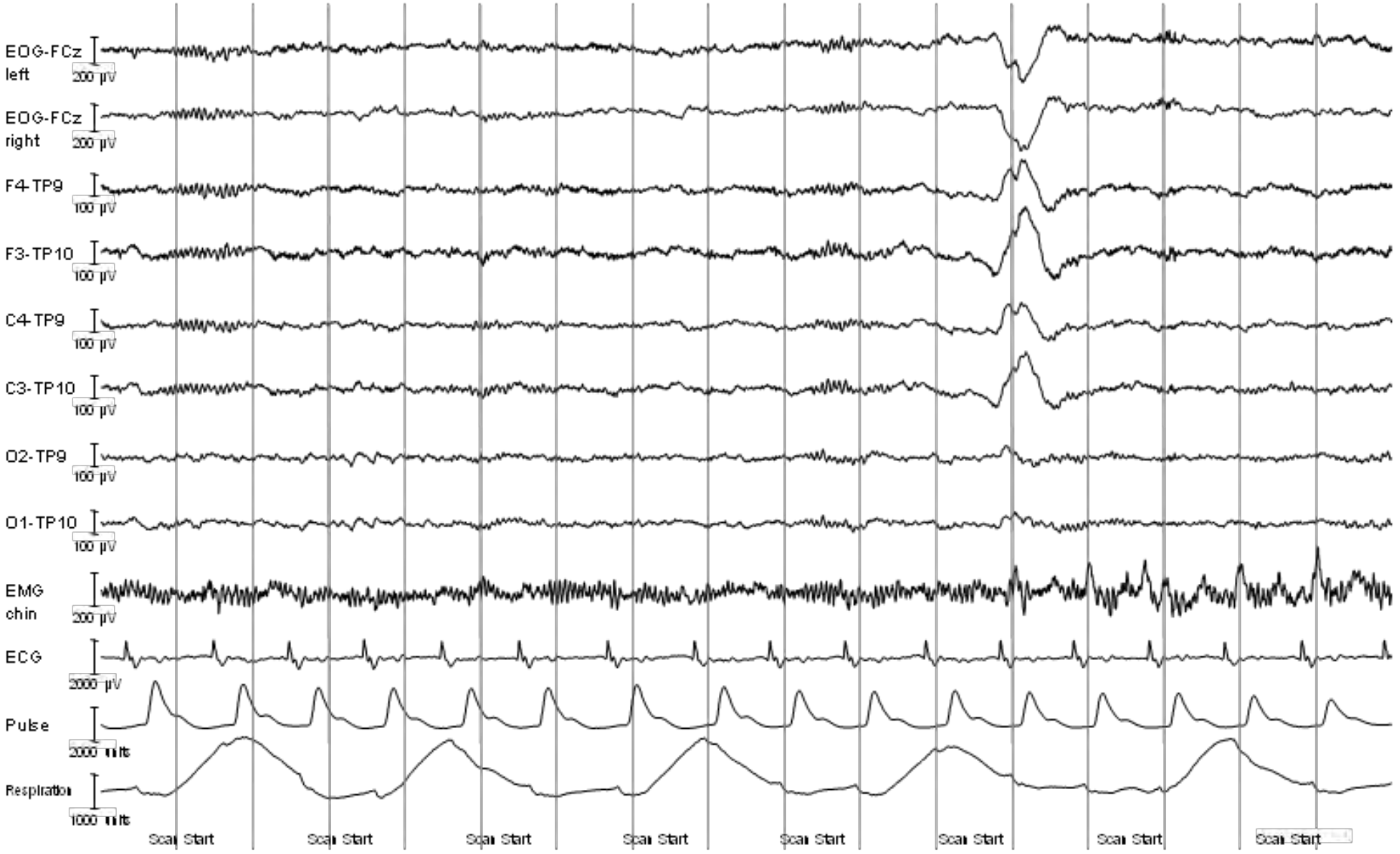
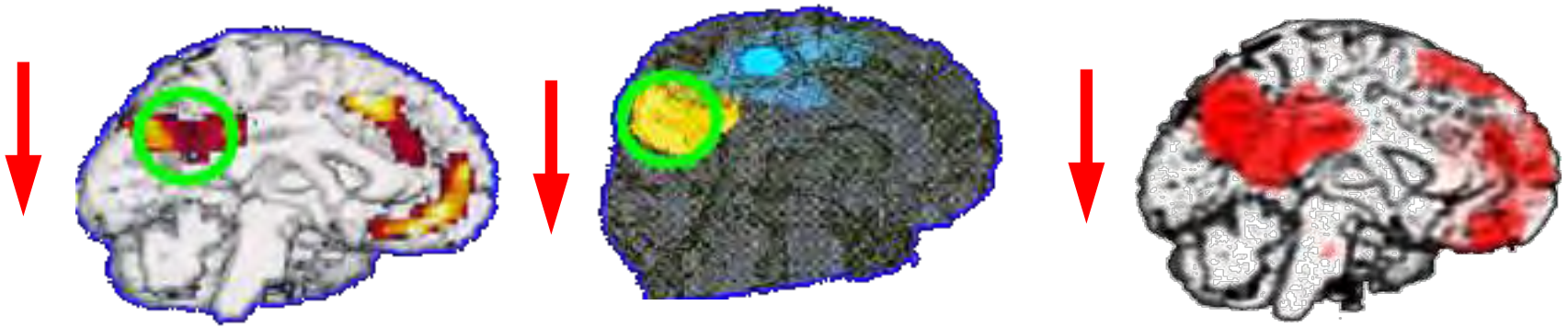
FC5
FC6
CP5
CP6
TP9
TP10
Eog
Ekg1
Ekg2

polysomnography-fMRI

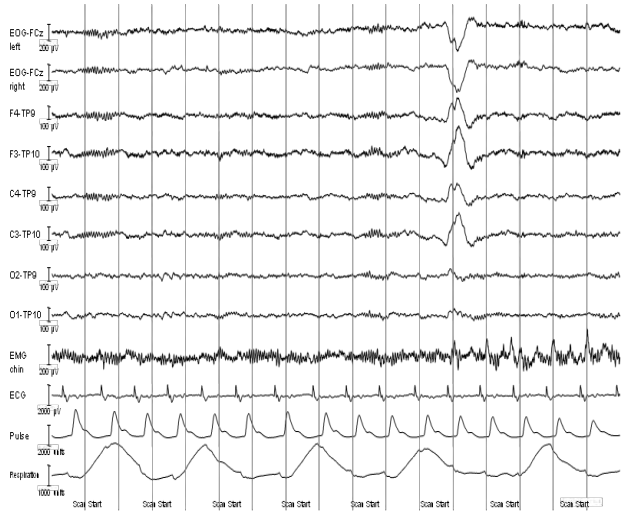


(Jahnke et al. 2012)

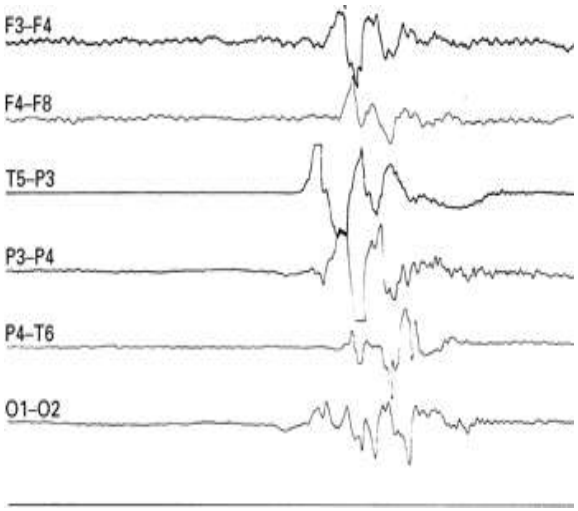
I. subjects cannot engage in a paradigm: **sleep, coma, seizure**



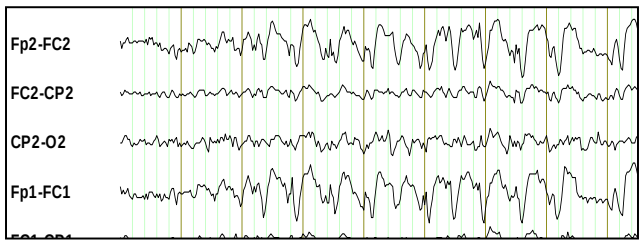
sleep vs. awake



coma vs. awake

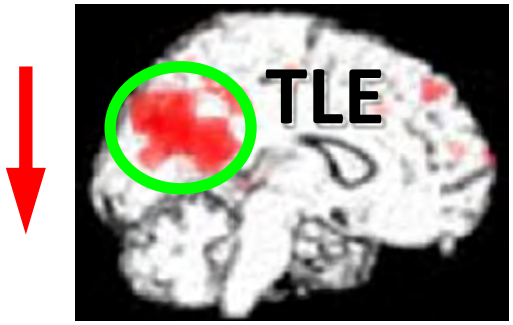


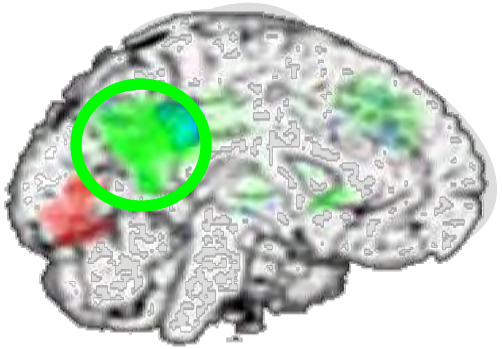
seizure vs. no seizure



II. spontaneously occurring (EEG) phenomena of interest

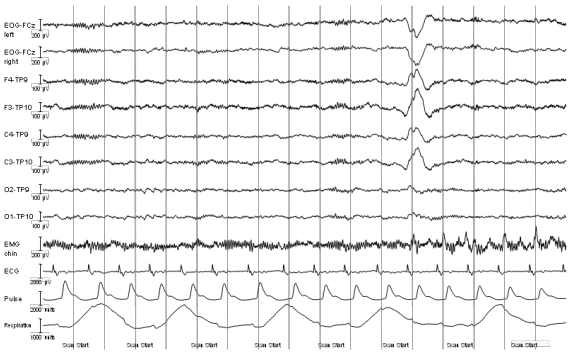
epileptic spikes, K-complexes, beta oscillations



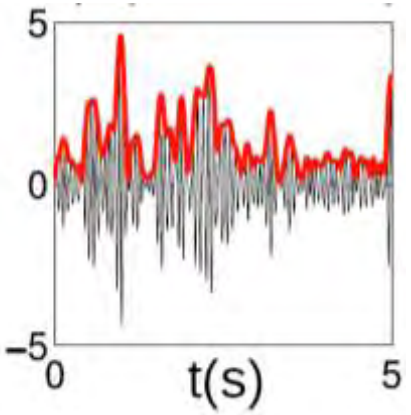


temporal lobe spikes vs. background

K-complexes vs. N2 background



17-23 Hz beta oscillations



Structure

I. background
II. When resting state experiments (part I)?
III. Caveats (part I)
IV. When resting state experiments (part II)?
V. Caveats (part II)

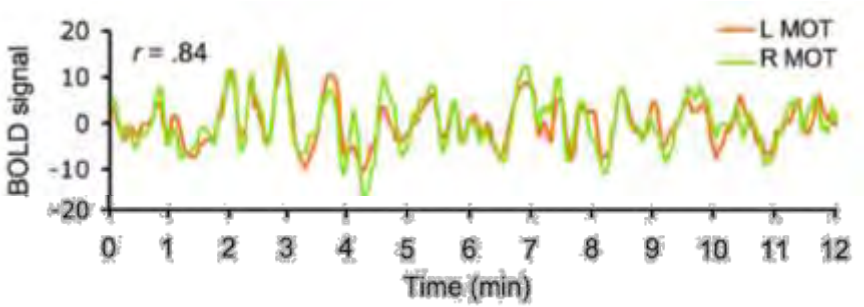
If you do not have EEG…?

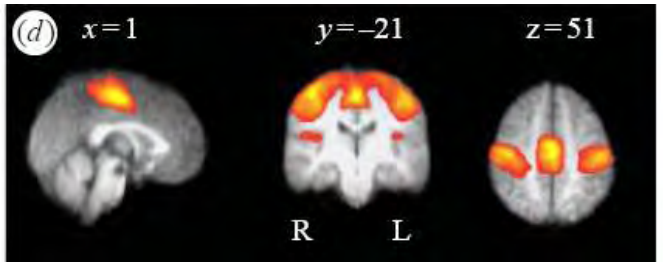
If you do not have EEG…?

Data driven approaches

I. **functional connectivity**
II. **ICA**

Resting state brain activity
functional connectivity





sensory
motor

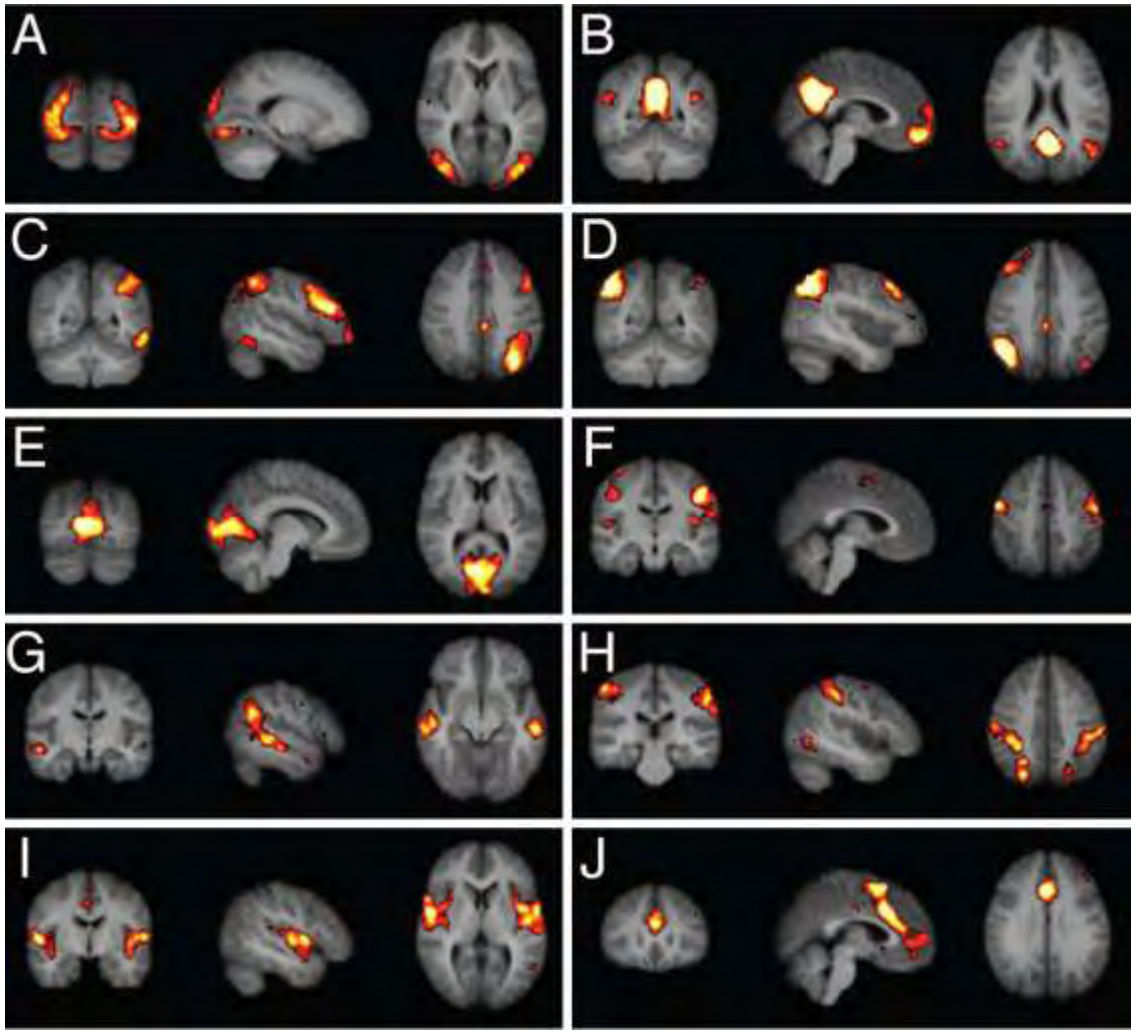
left: Van Dijk et al. Journal of neurophysiology 2010; *right*: Beckmann et al. Phil Trans Roy Soc London 2005

Resting state brain activity

(fMRI, functional connectivity via ICA)

lateral visual

default mode



memory (left)

memory (right)

medial visual

sensory-motor

ventral stream (visual)

auditory

executive control

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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

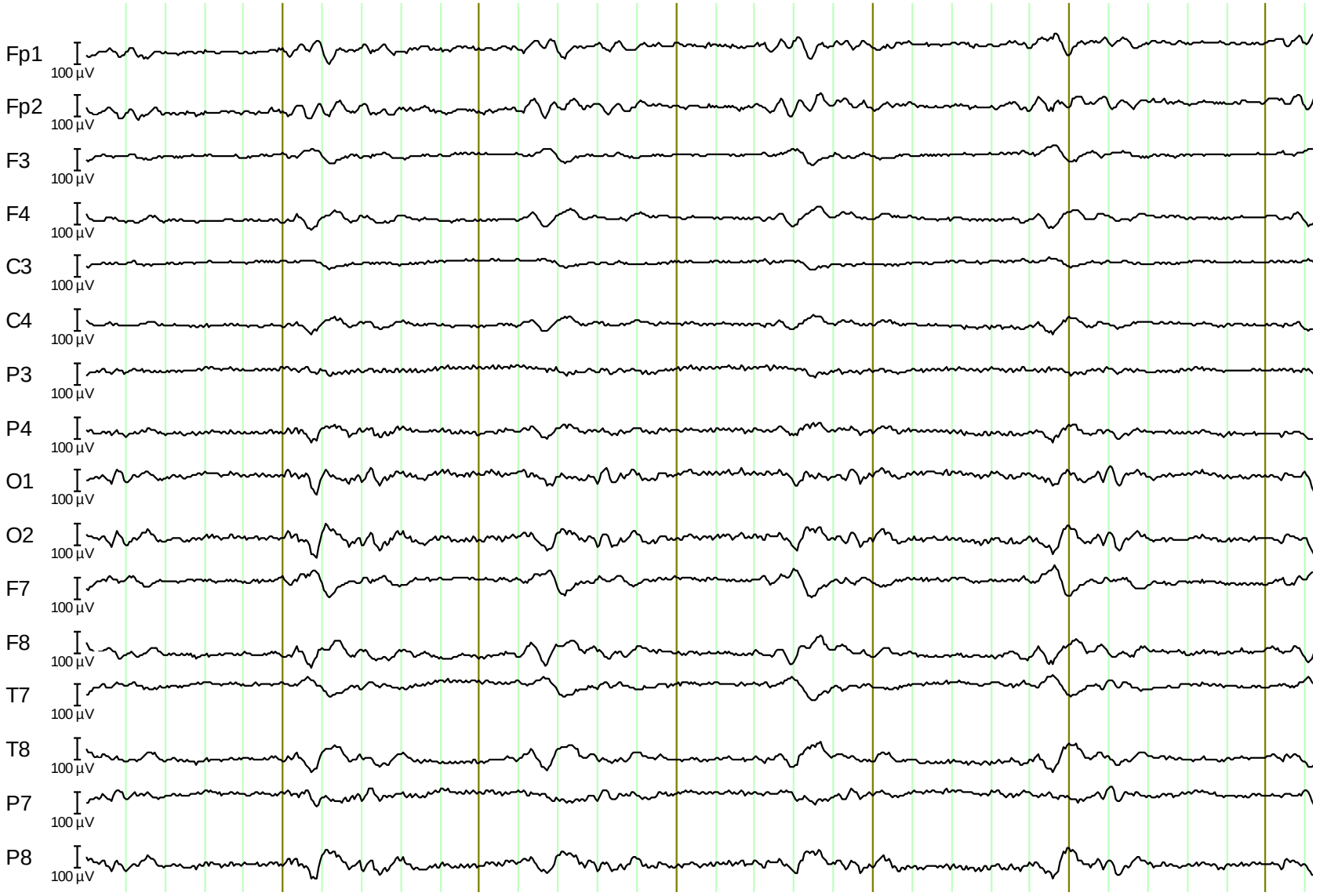
1. Scanner drift
2. Subject motion
3. Circulation
4. Respiration

=> „false positive“ correlations in the BOLD signal

the brain at rest

...credit?!

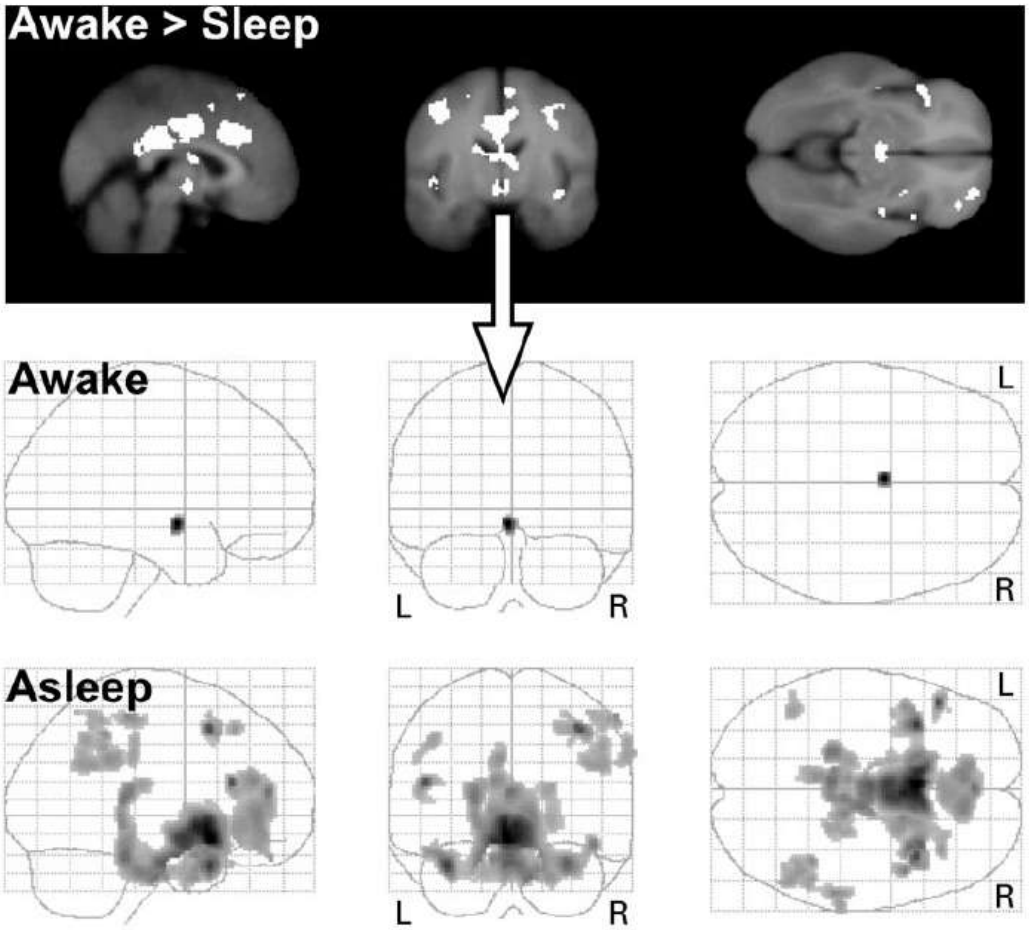
Cardiac noise



Cardiac noise

doi:10.1093/brain/awh686 *Brain* (2006), **129**, 655–667

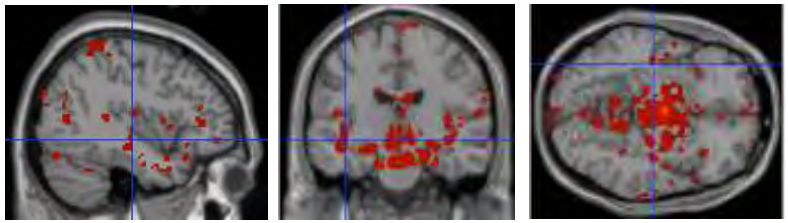
Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study



Cardiac noise

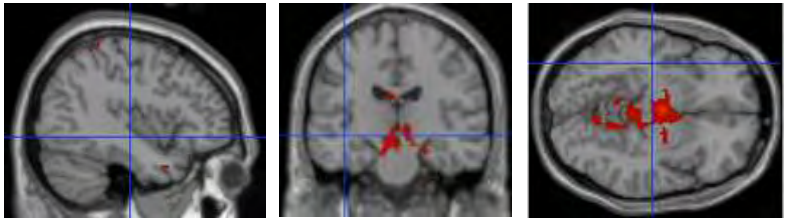
Maps of functional connectivity and cardiac noise

A)



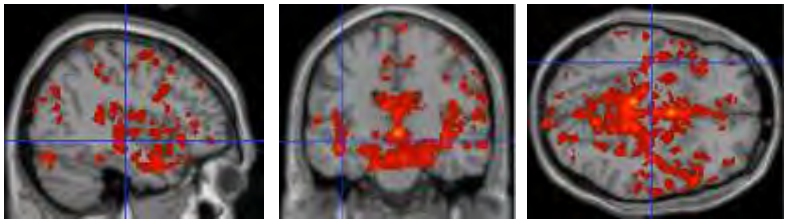
Cardiac noise not modelled (compare Kaufmann et al.)

B)



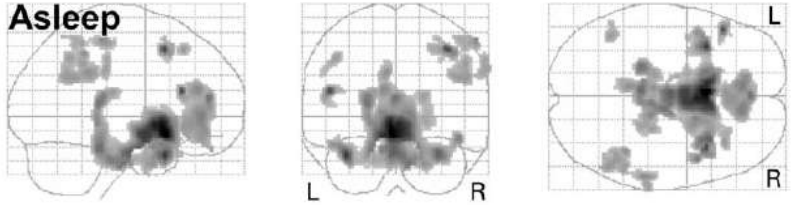
Cardiac noise modelled using RETROICOR

C)



Activations related to cardiac noise (RETROICOR)

D)



Original hypothalamic connectivity map (Kaufmann et al.)

Kaufmann et al. 2006, Laufs et al. 2007

take a deep breath

...credit?!

respiratory noise

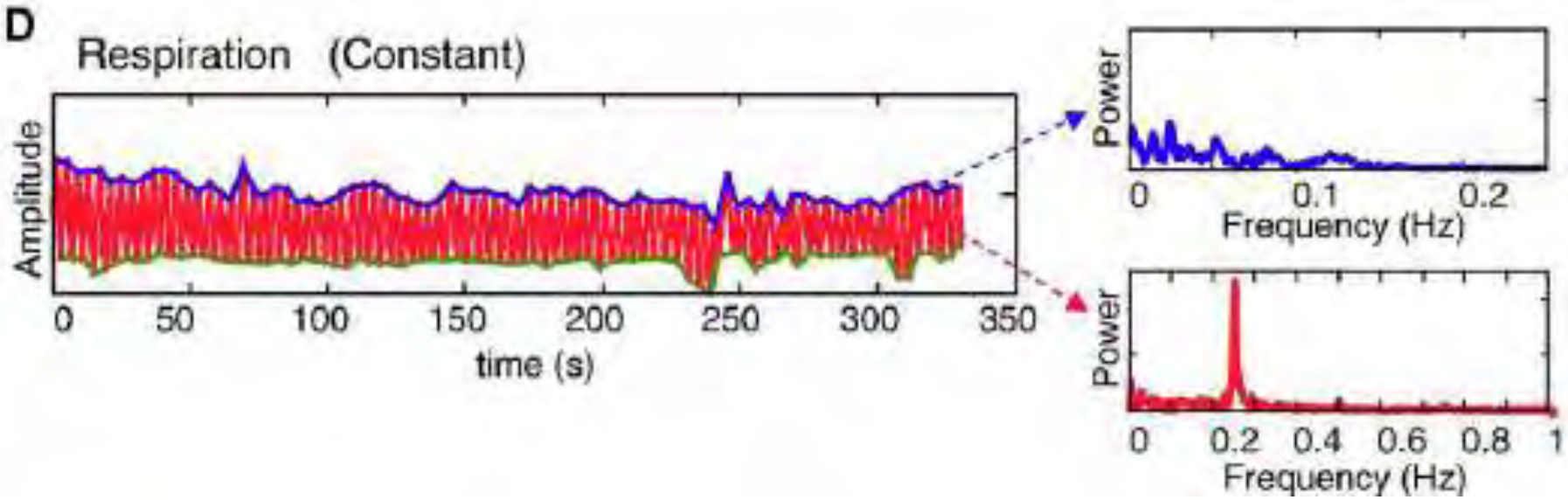
ELSEVIER

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



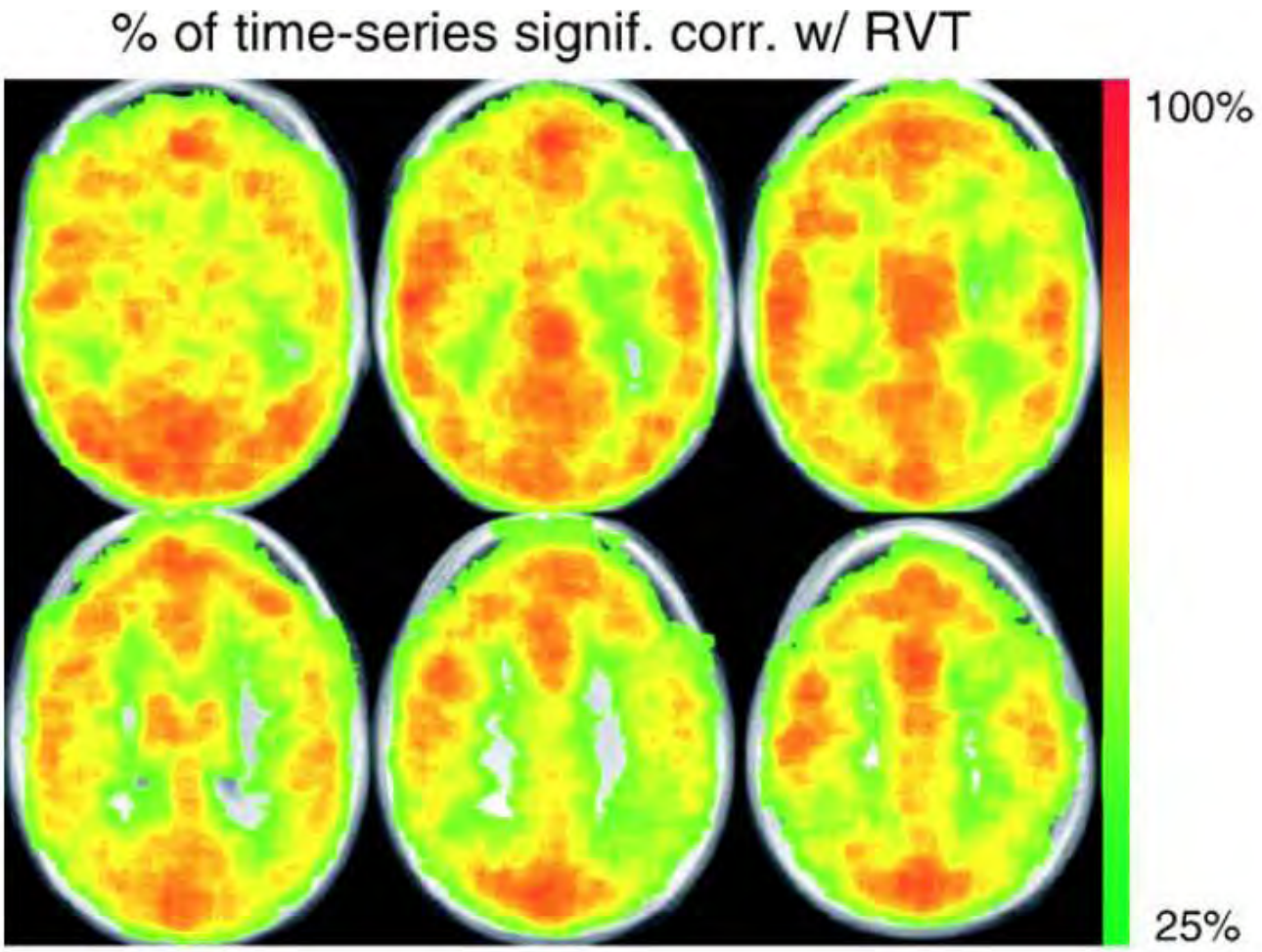


Fig. 2. Location of respiration changes: map showing for each voxel the percentage of time series (out of a total of 16 runs from 10 subjects) where the fMRI signal during rest was significantly (CC > 0.4, $P < 10^{-6}$ uncorrected) correlated with the respiration volume per time (RVT) changes. Signal changes are largest in gray matter and near large blood vessels.

Birn et al. 2006

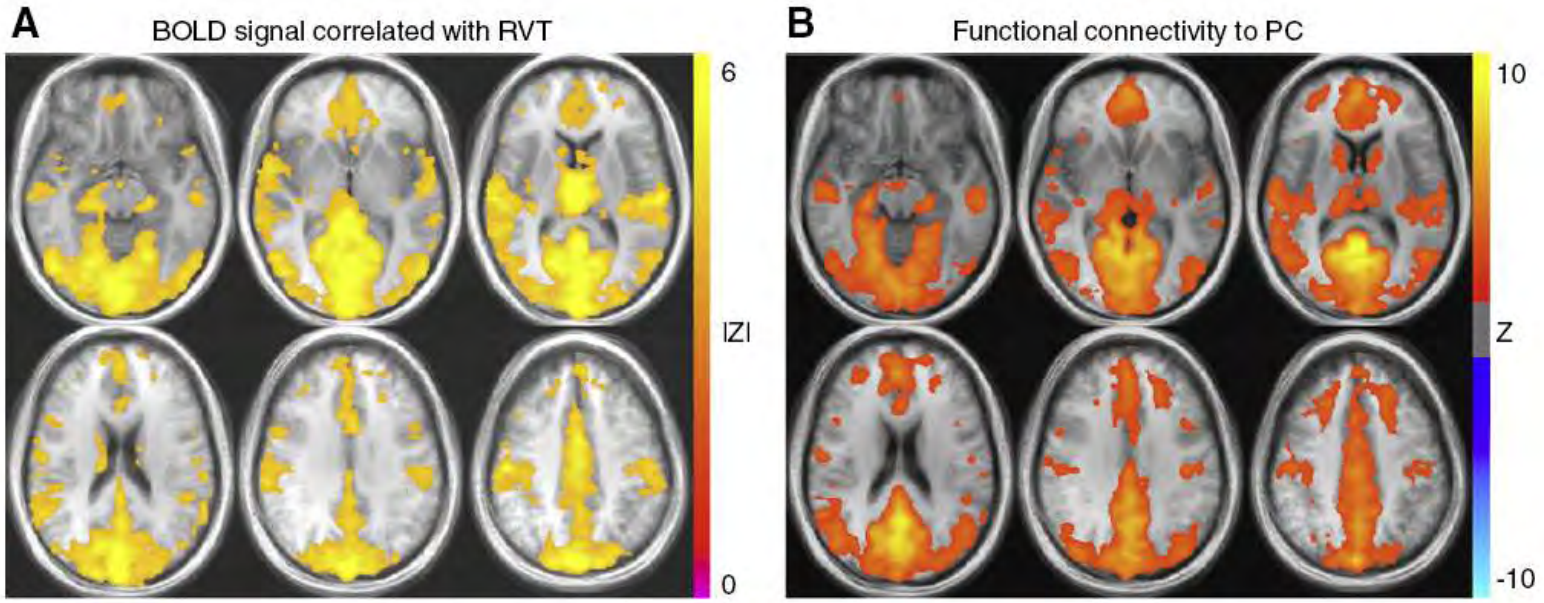
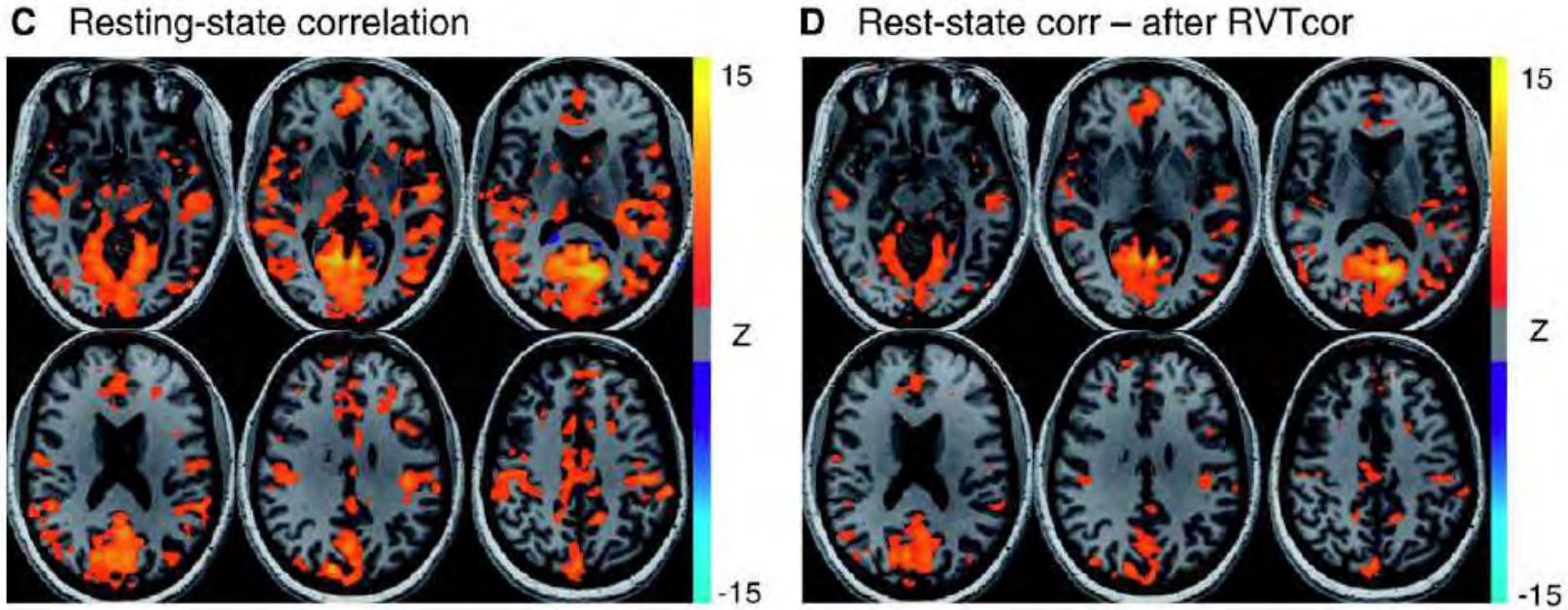
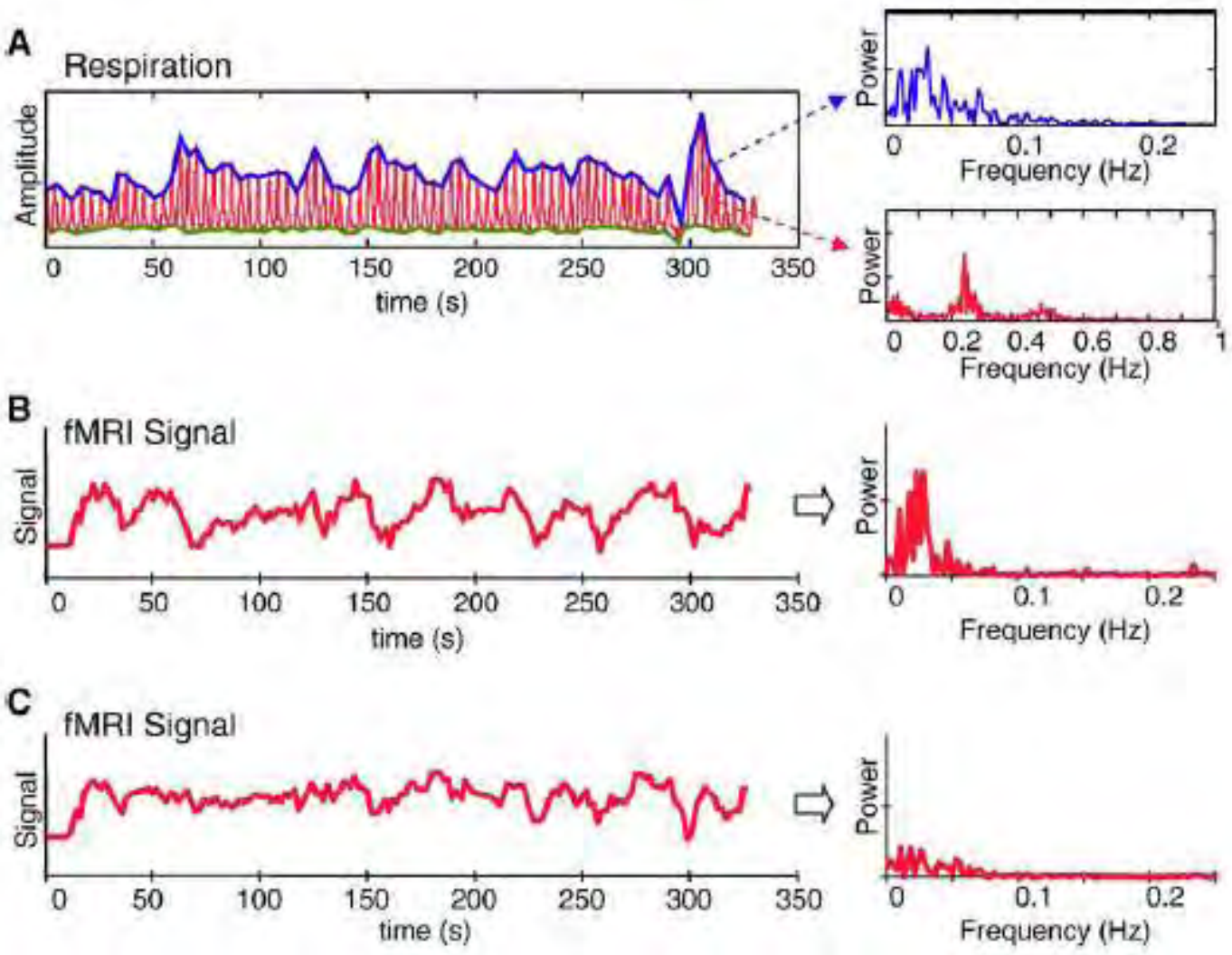


Fig. 2. A) fMRI signal correlated with respiration volume per time (RVT) changes, B) functional connectivity with a seed region in the posterior cingulate from a group of 10 subjects. Adapted from Birn et al., 2006.



respiratory noise



respiration and envelope

fMRI signal from 1 voxel

after RVT regression

Birn et al. 2006

solution

know your enemy!

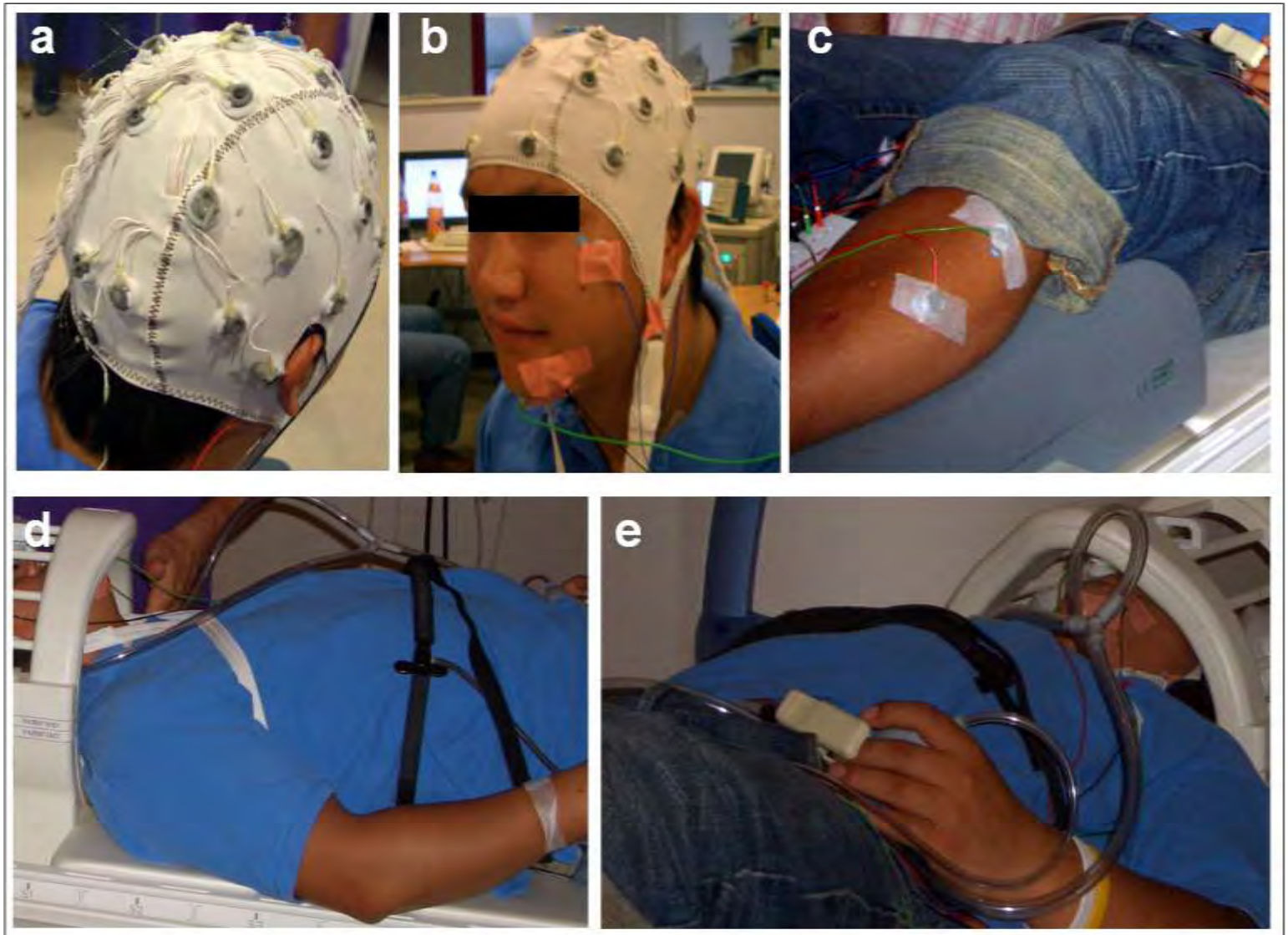


Figure 1: a: EEG cap; **b:** EOG and M. mentalis EMG electrodes; **c:** M. tibialis EMG electrodes; **d:** respiration belt; **e:** pulse oximetry

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

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

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

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

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

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

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

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

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

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

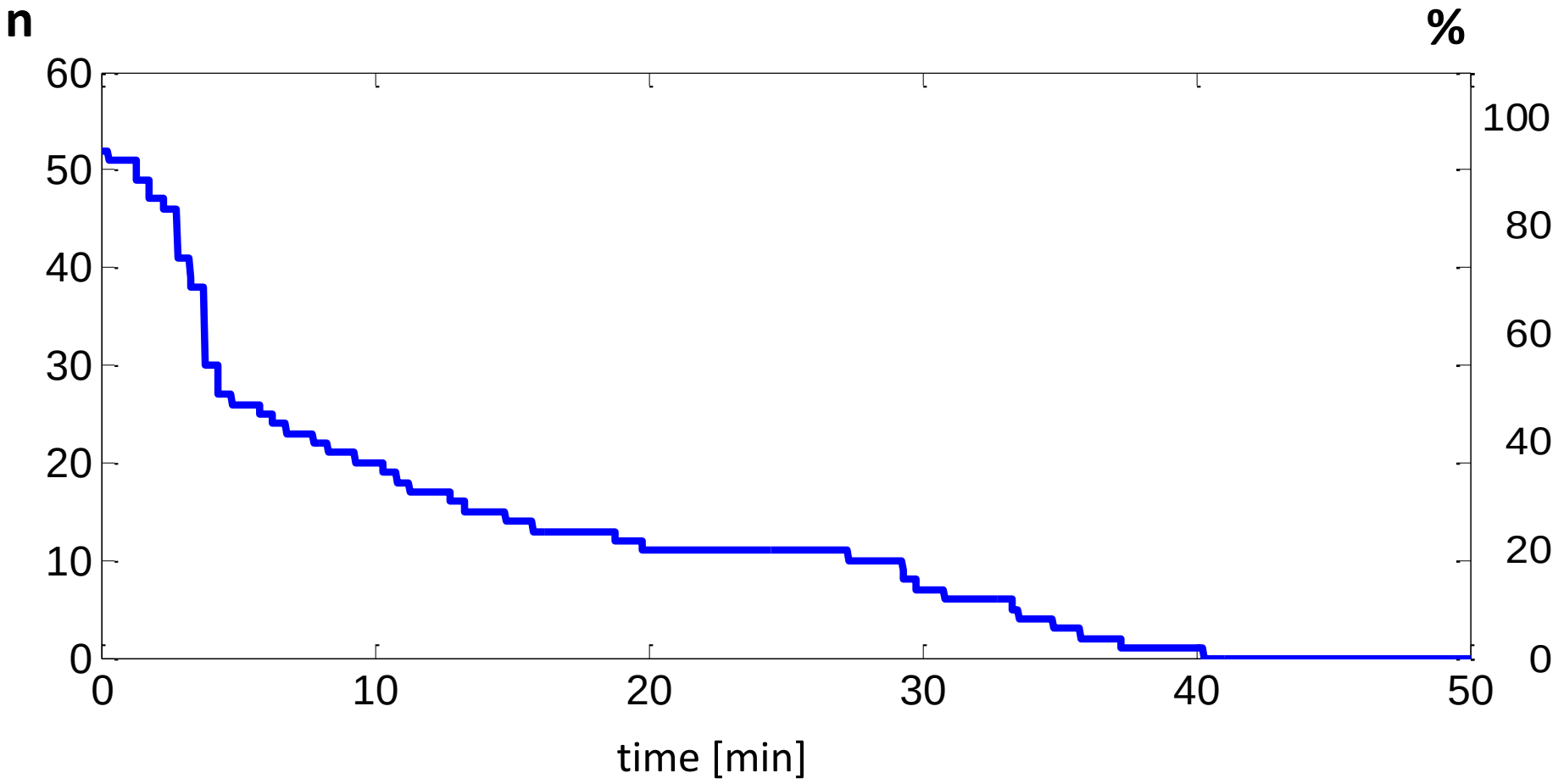
Controlling spontaneous brain activity - a paradox?

Controlling spontaneous brain activity

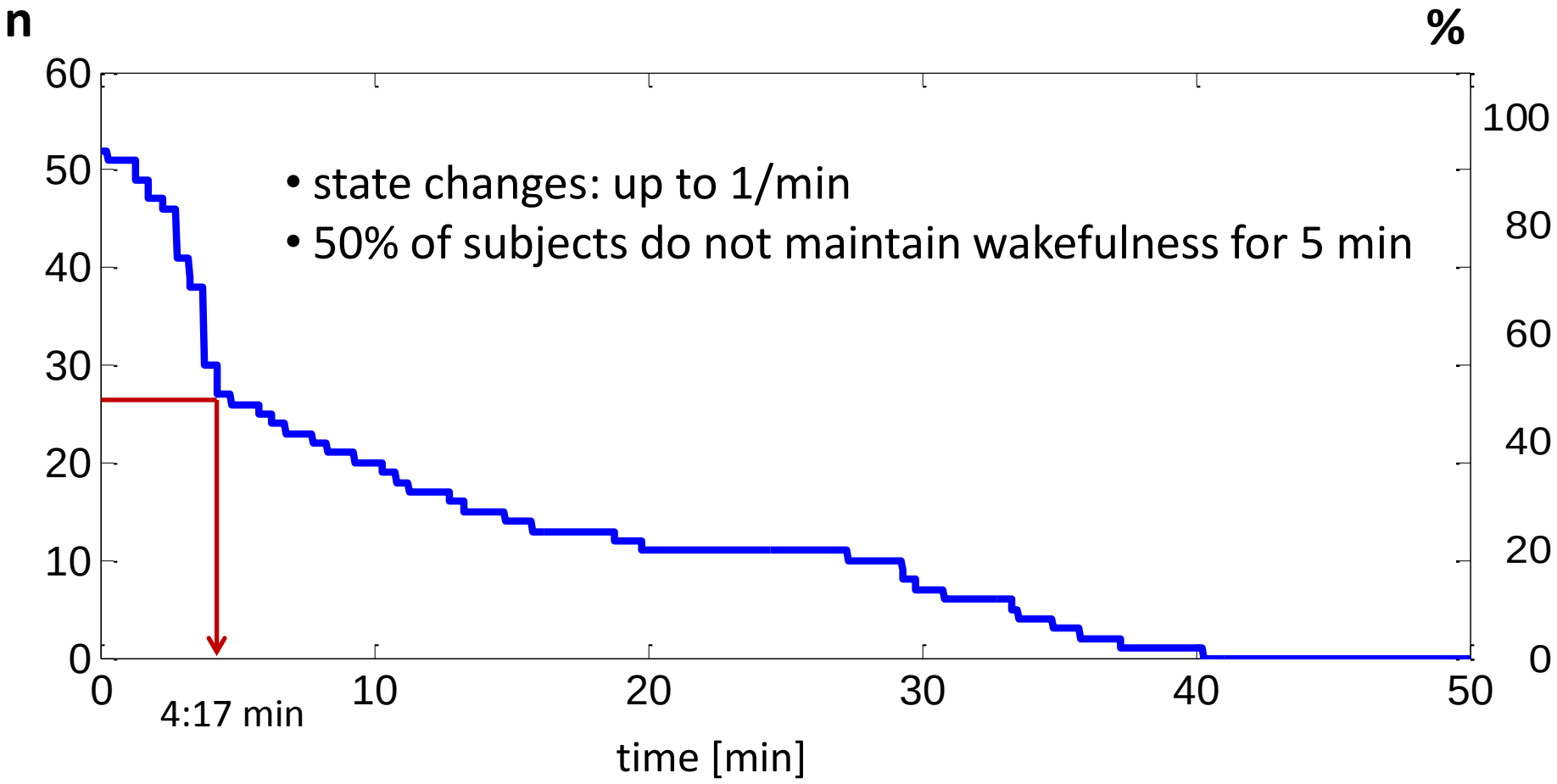
not a paradox - but a necessity

The subject at rest

subjects steadily awake over time



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

http://www.nitrc.org/frs/?group_id=296

Biswal et al. "Toward discovery science of human brain function." PNAS 2010

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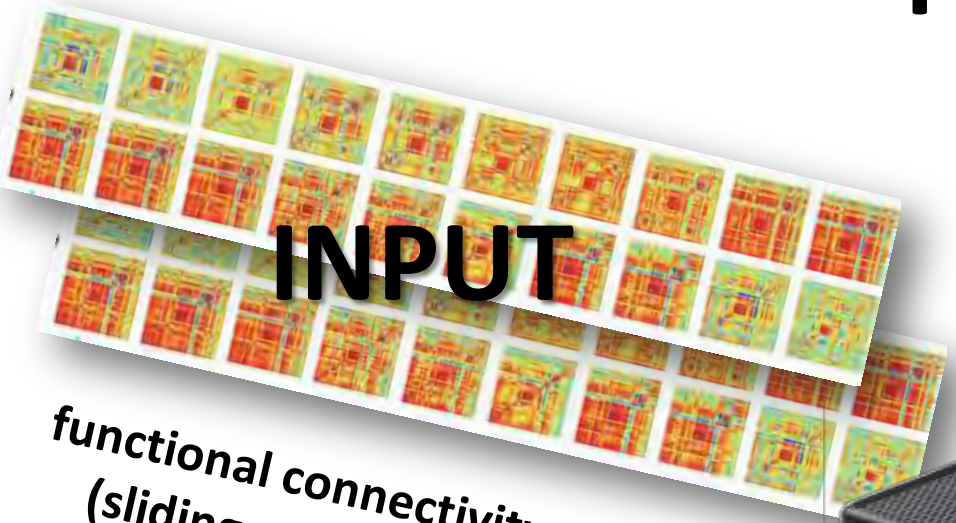
No EEG! Vigilance?

http://www.nitrc.org/frs/?group_id=296

Biswal et al. "Toward discovery science of human brain function." PNAS 2010

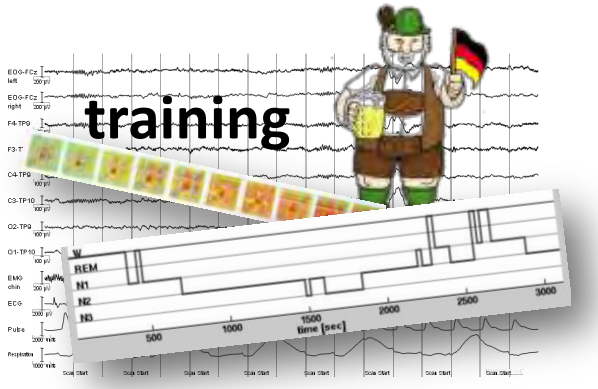
fMRI sleep classification

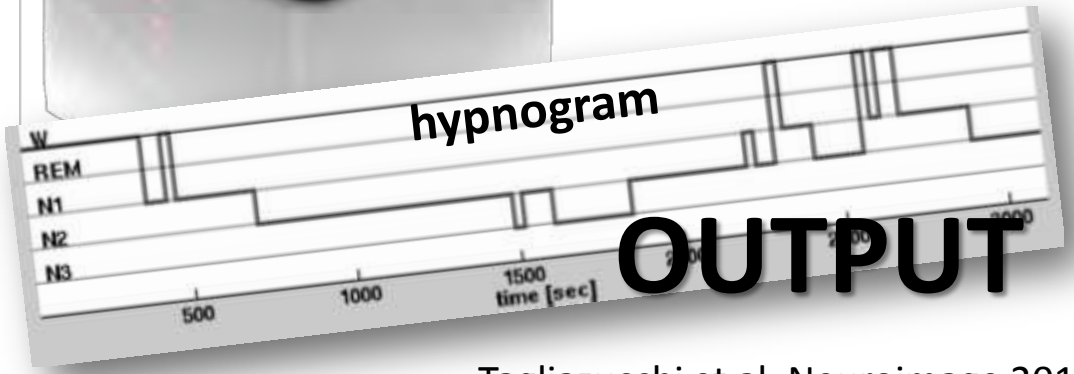


functional connectivity matrices
(sliding window, 60 images)

sleep staging based
on RS correlations

!

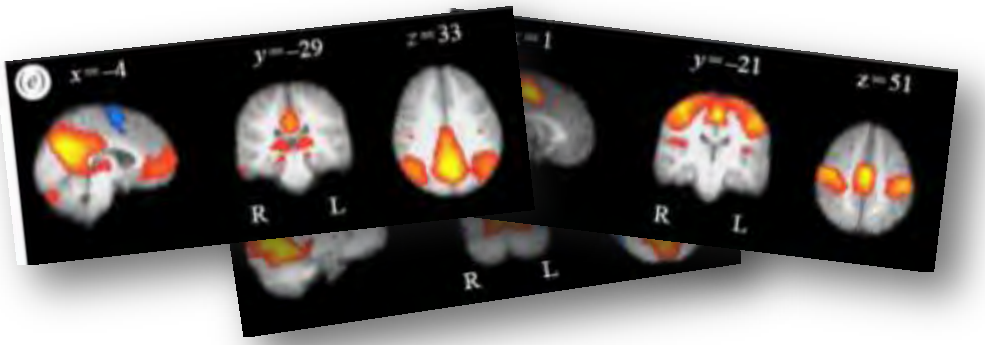


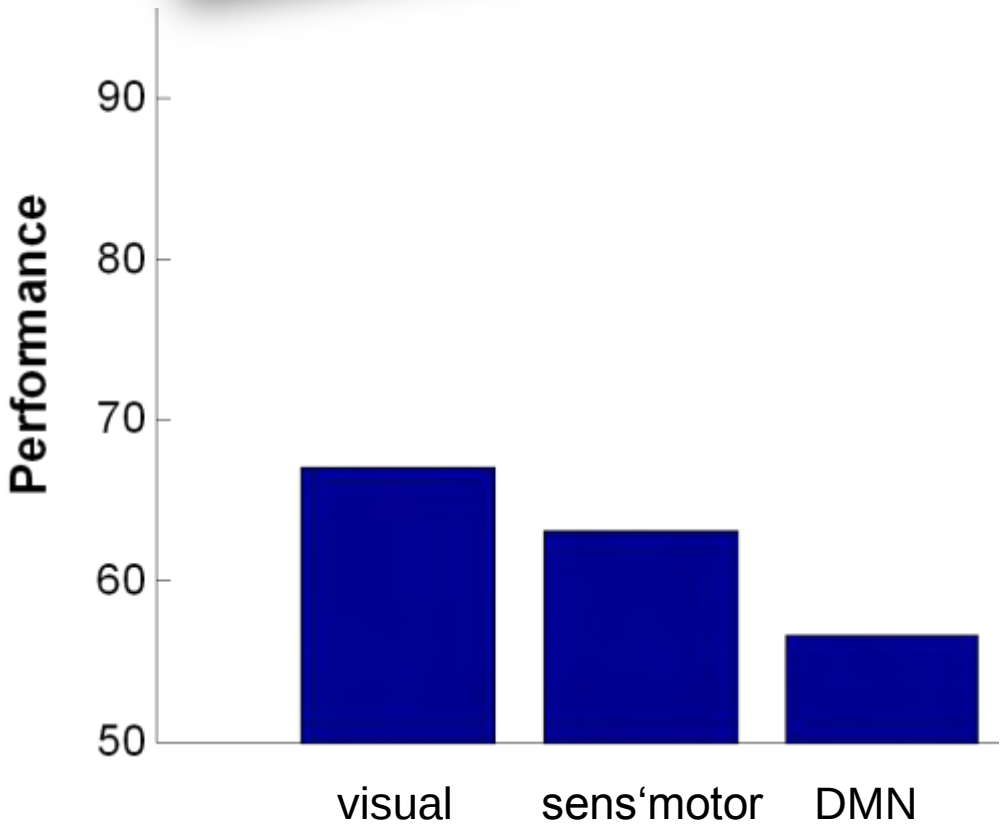


Tagliazucchi et al. Neuroimage 2012

classifier performance

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





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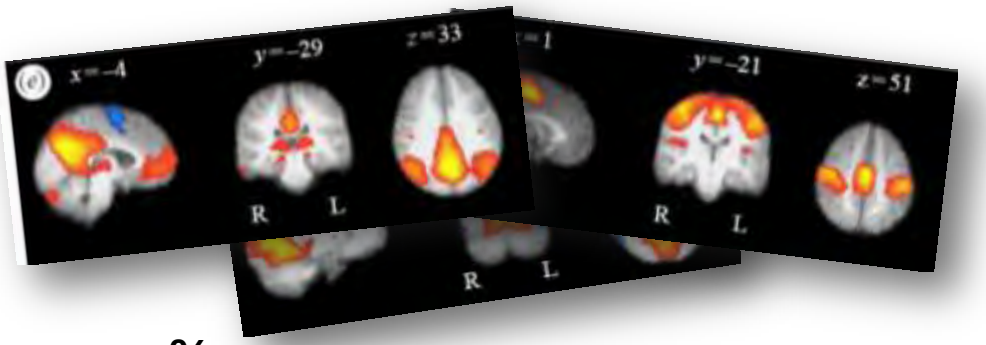

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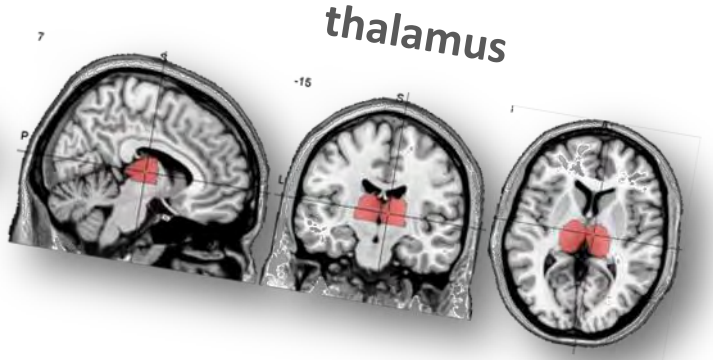

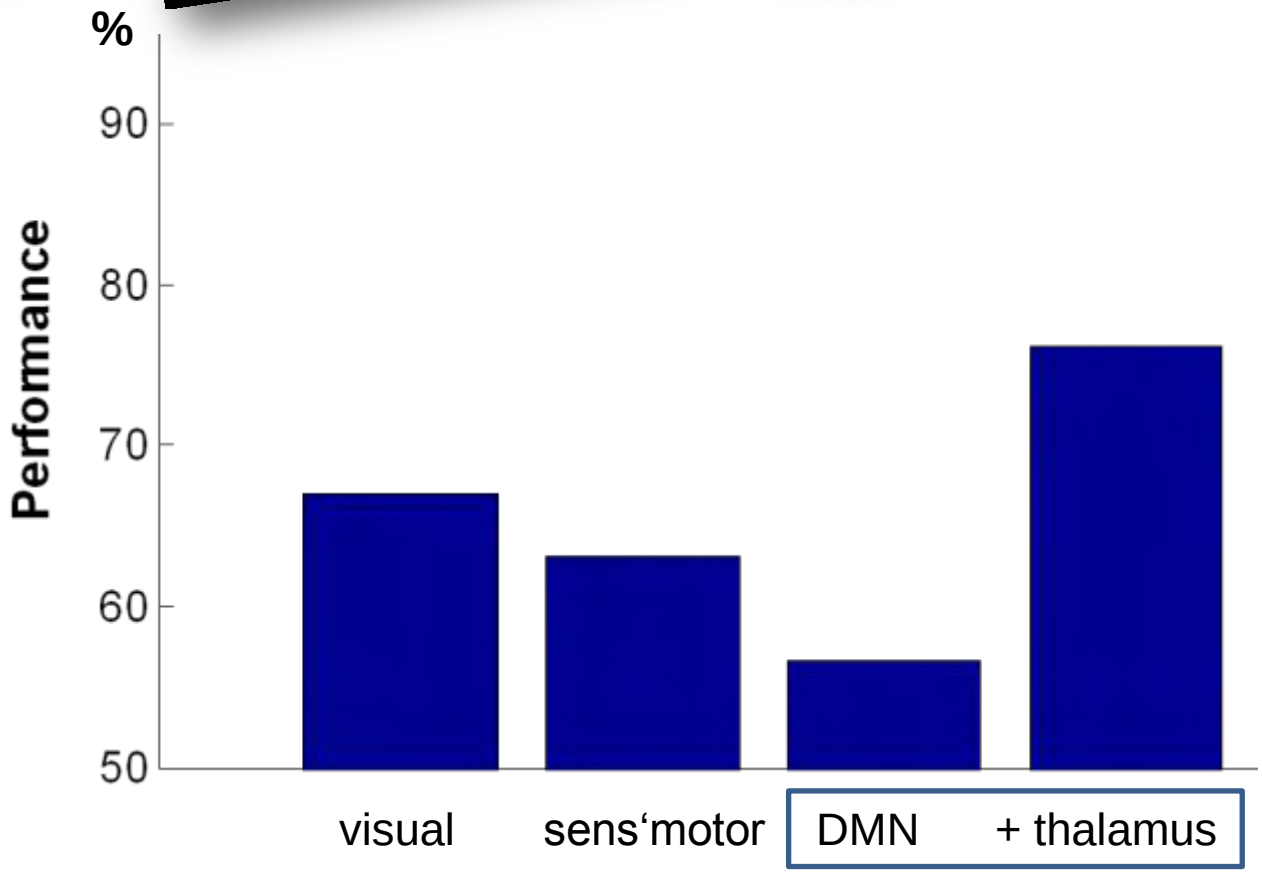

classifier performance

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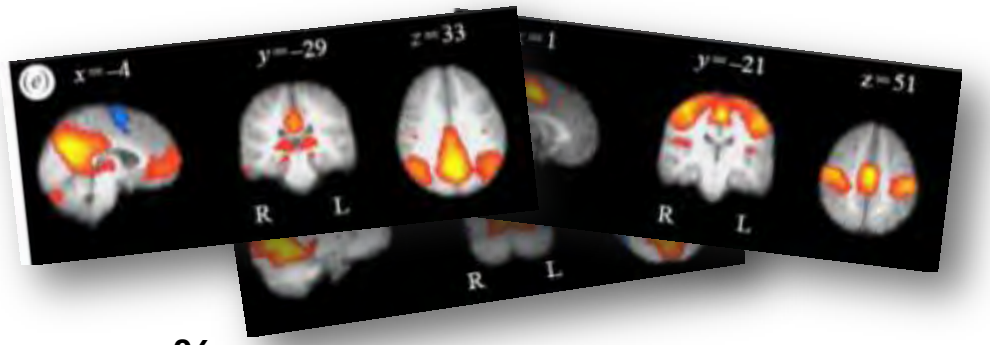

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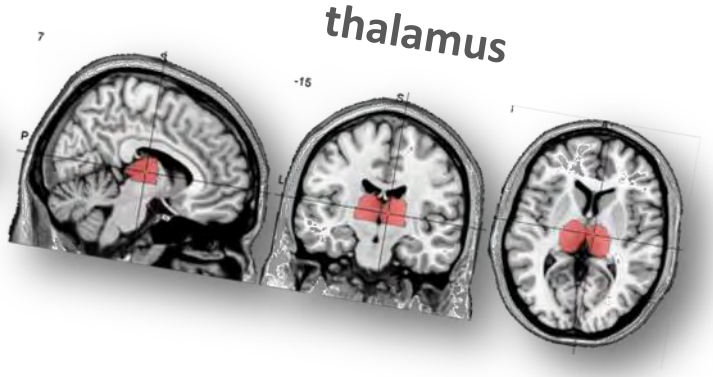
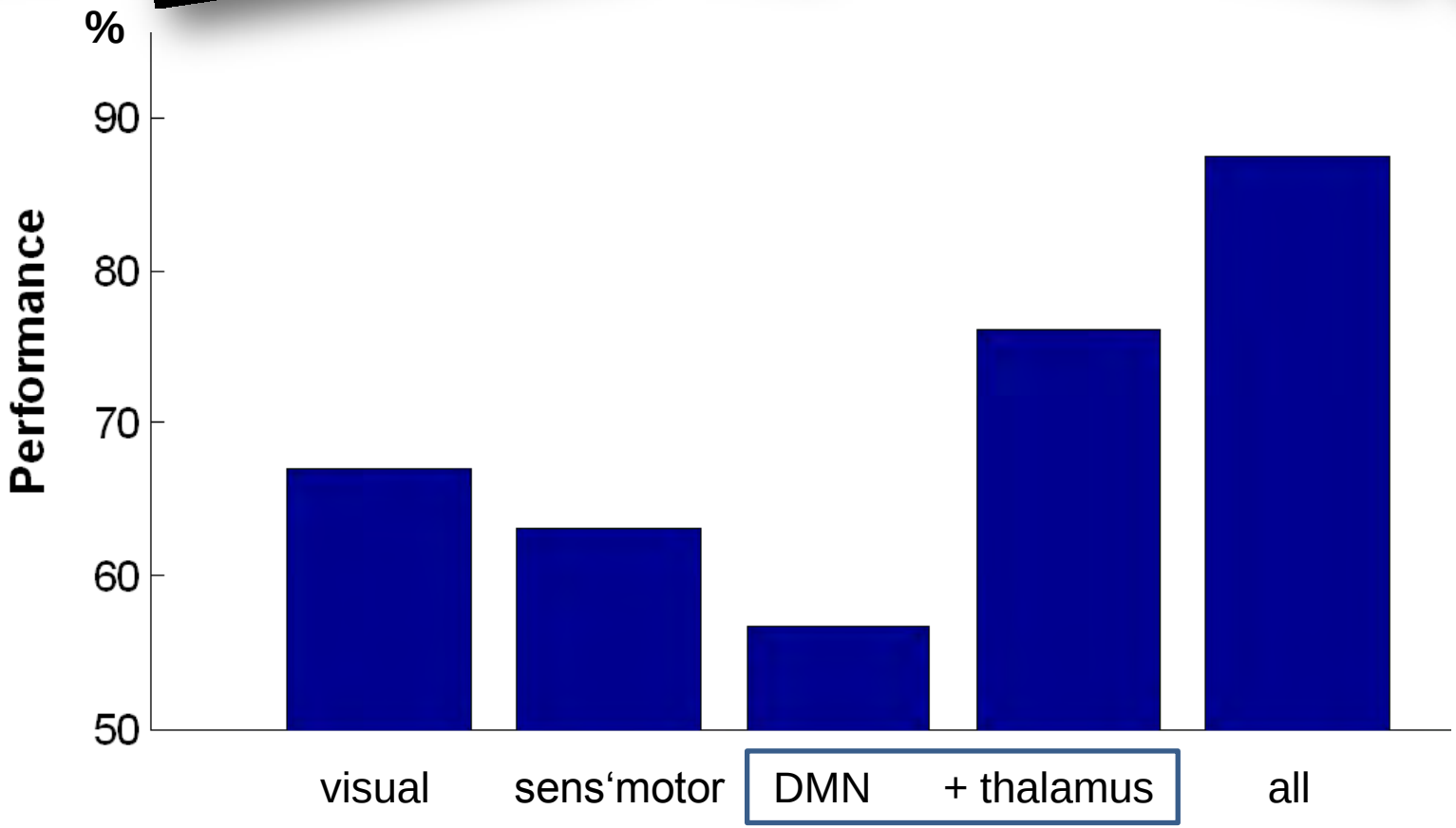




interim summary II

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

interim summary III

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

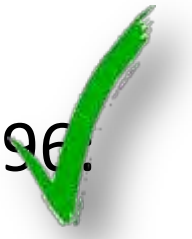
Hypothesis I. Friston 1996:

cortical resting state activity influenced by thalamus

interim summary III

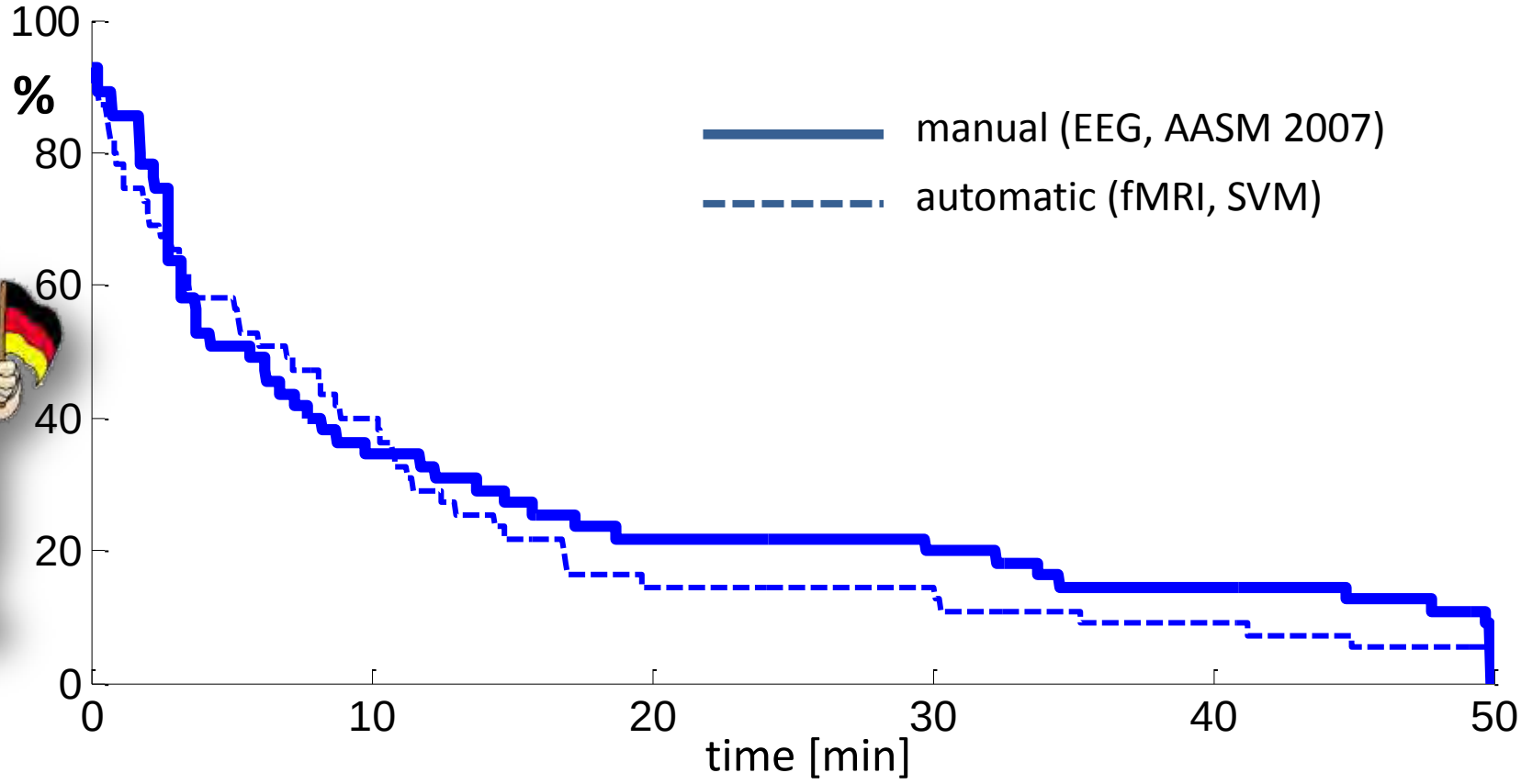
- RSN configuration is sleep stage specific
- DMN + [subcortical] thalamus -> outperforms cortical

Hypothesis I. Friston 1996:



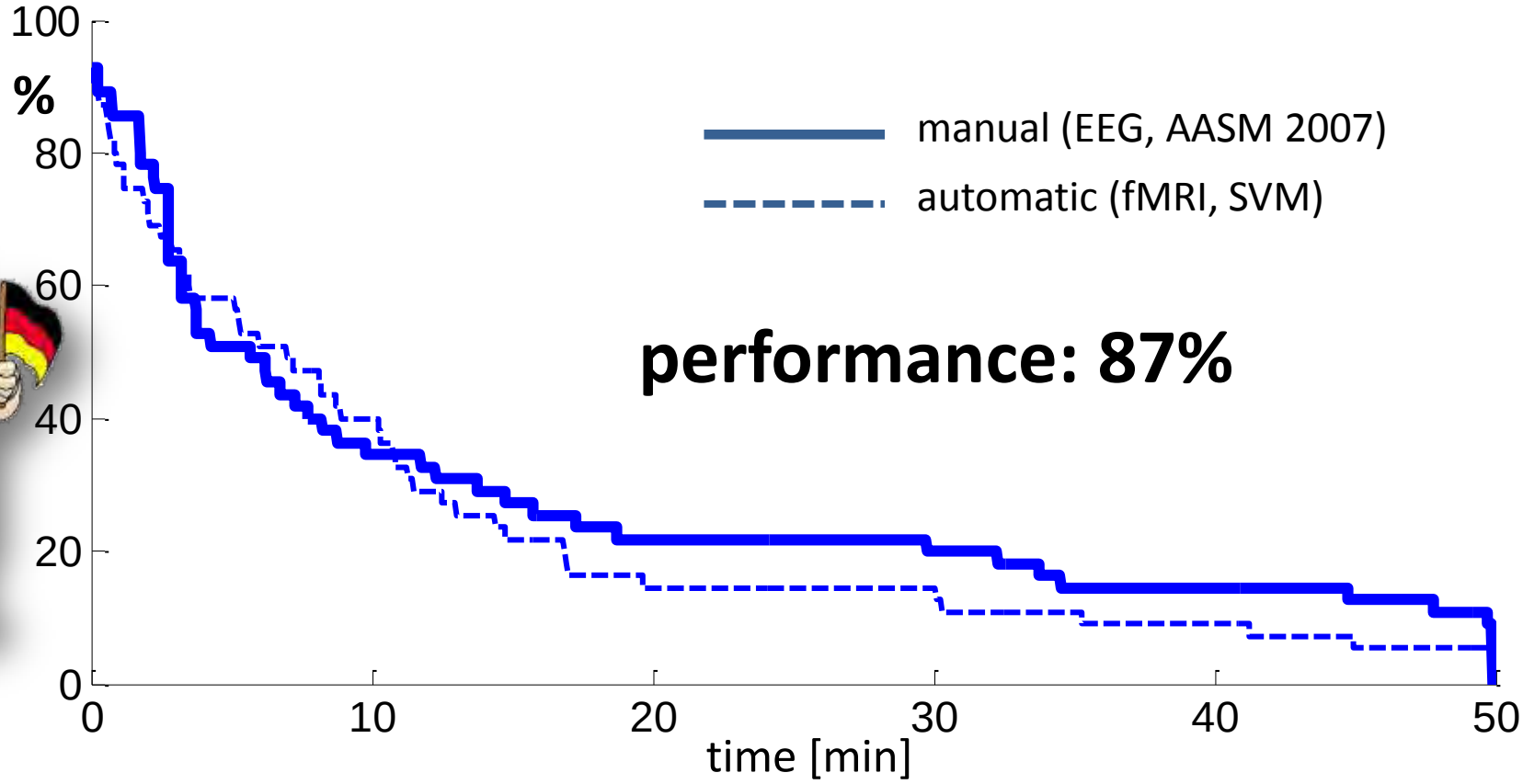
cortical resting state activity influenced by thalamus

classifier trained on fMRI data



Tagliazucchi et al. Neuroimage 2012

classifier trained on fMRI data



Tagliazucchi et al. Neuroimage 2012

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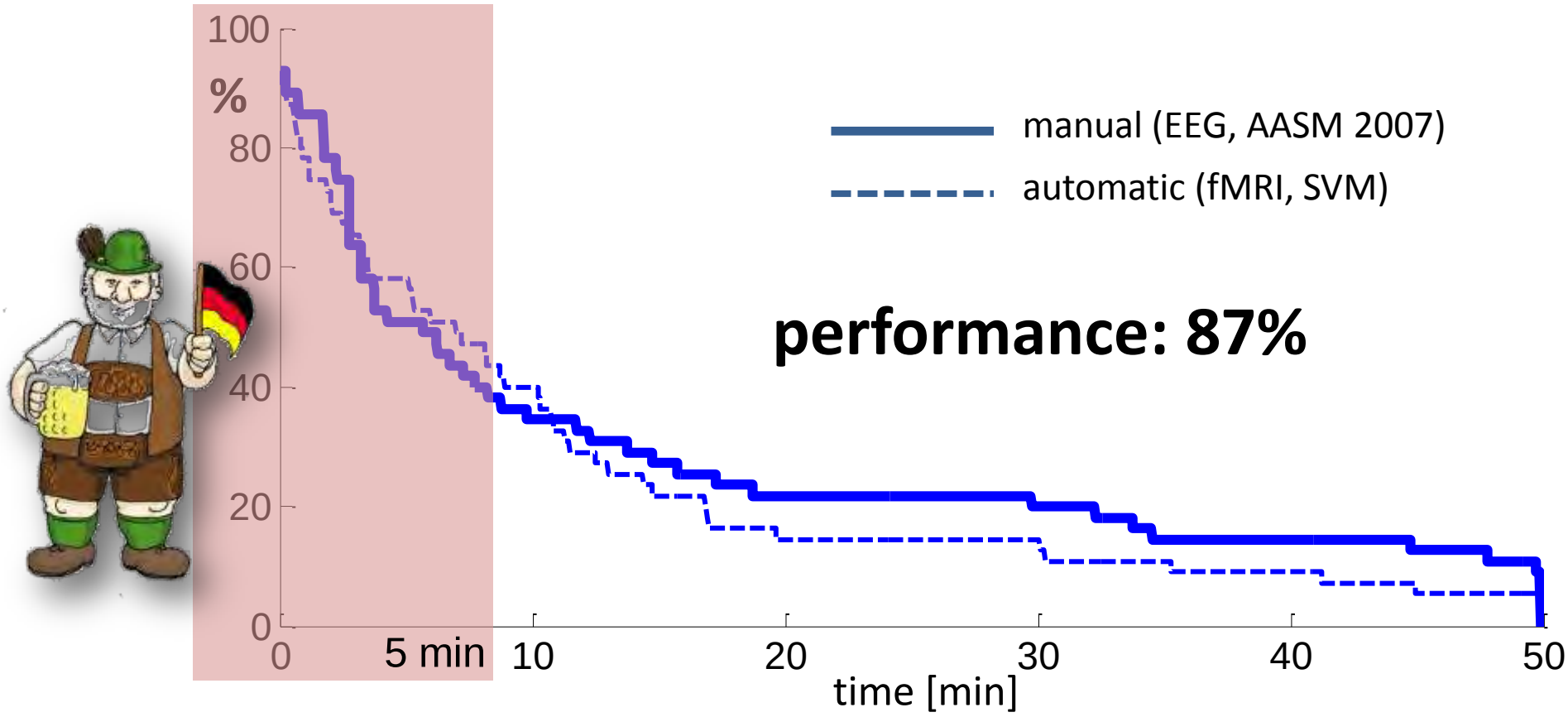

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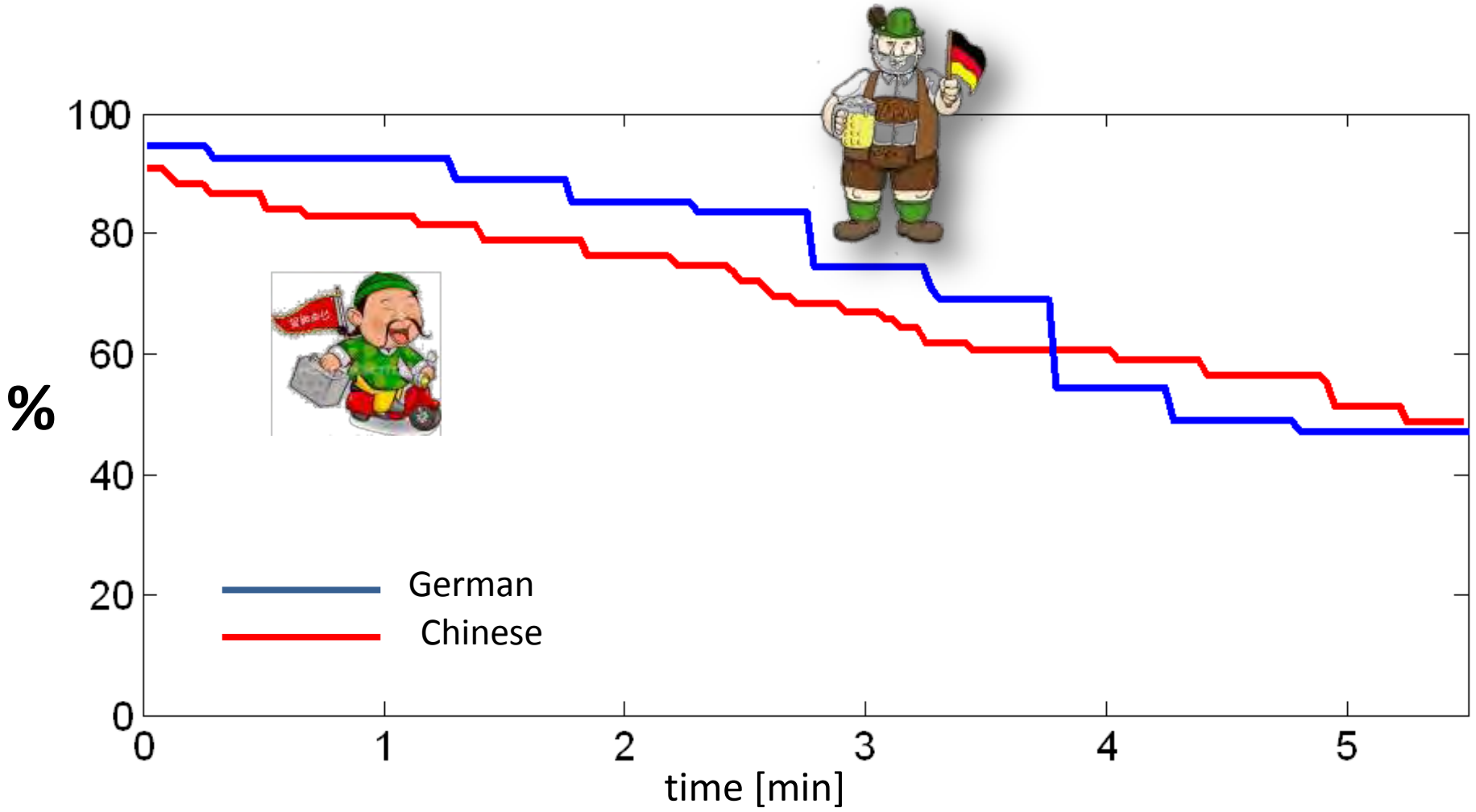
not steadily awake over time



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Implications

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

Implications

- expect 50% of subjects not to be steadily awake for >5 min - unless proven otherwise
- vigilance changes affect resting state functional connectivity
- **can resting state functional connectivity serve as a biomarker?**

Structure

I. background
II. When resting state experiments (part I)?
III. Caveats (part I)
IV. When resting state experiments (part II)?
V. Caveats (part II)

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

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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

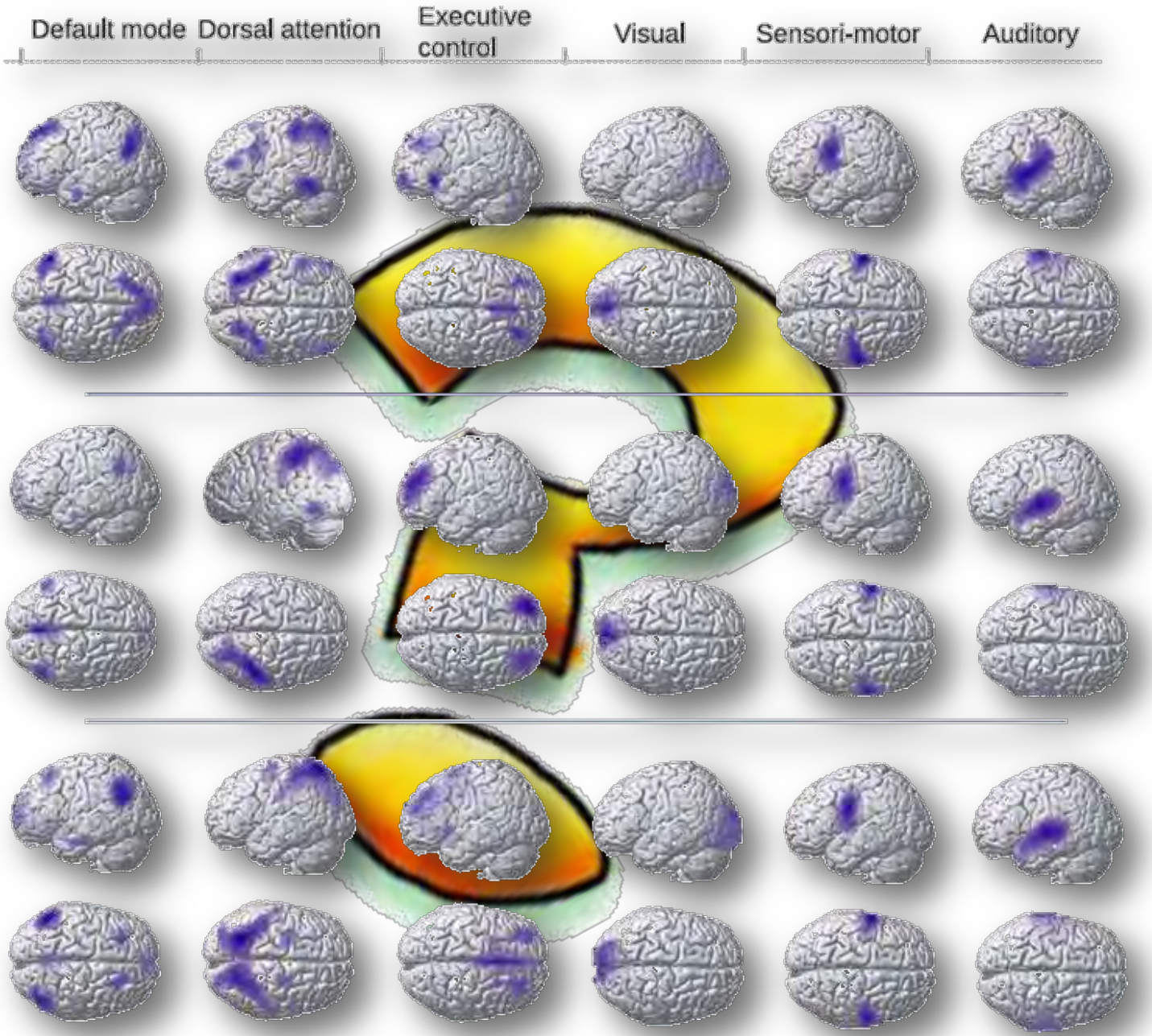
Quiz (for experts)

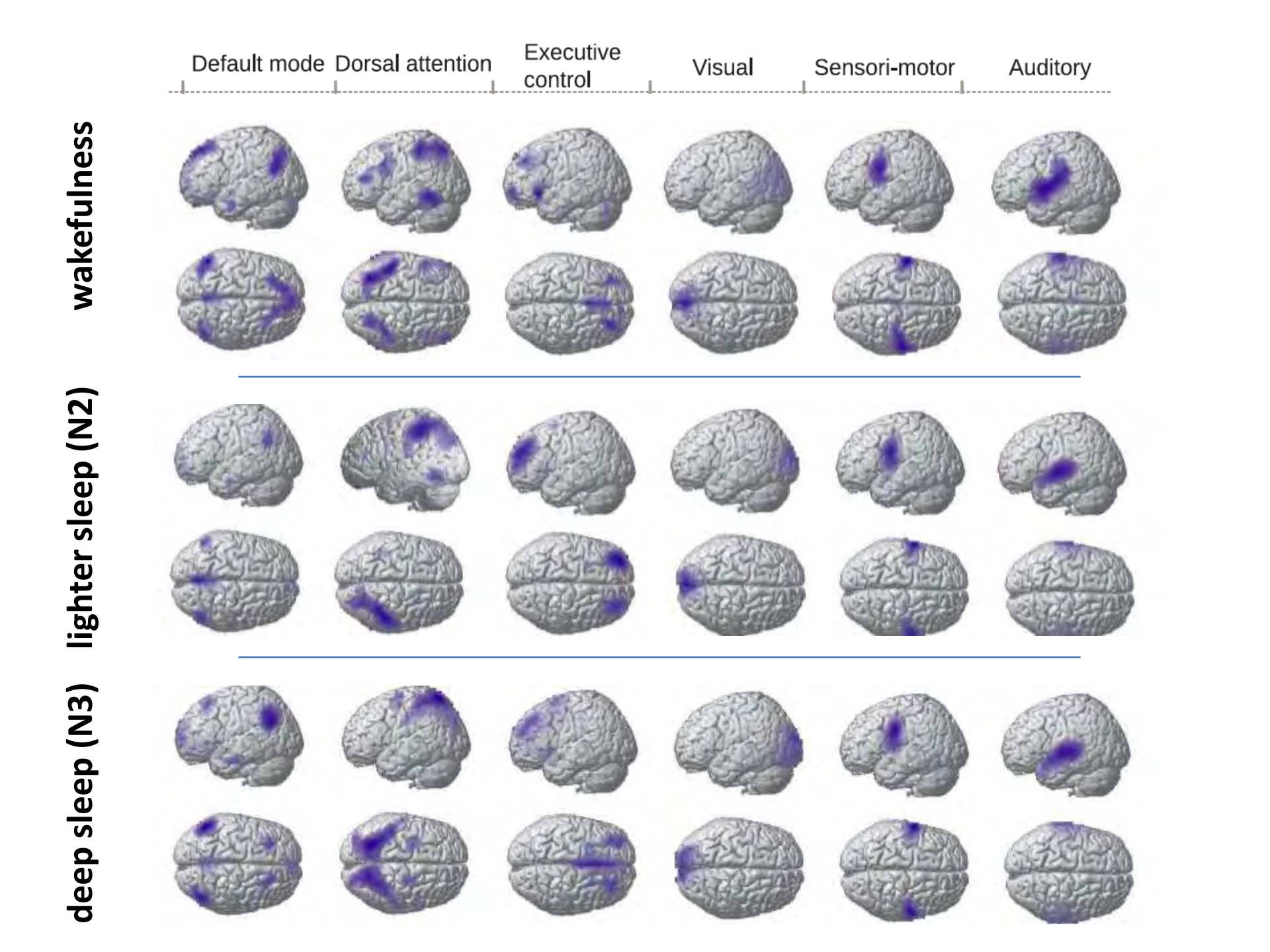
biomarker of which condition?

I.

II.

III.




Default mode
Dorsal attention
Executive control
Visual
Sensori-motor
Auditory
wakefulness
lighter sleep (N2)
deep sleep (N3)

vigilance 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 […].

vigilance fluctuations – another confound in resting state studies!

Conclusion I

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

Conclusion II

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

http://user.uni-frankfurt.de/~laufs/spm_talk.pdf/

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und Forschung