Resting state fMRI

- Introduction: The default mode network
- Resting state fMRI
- Physiological basis
- Other networks and their relation to EEG
- Our Application: Resting state networks in the severely injured brain
- Outlook

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Weill Cornell Medical College, Sackler Institute Summer School, 2009

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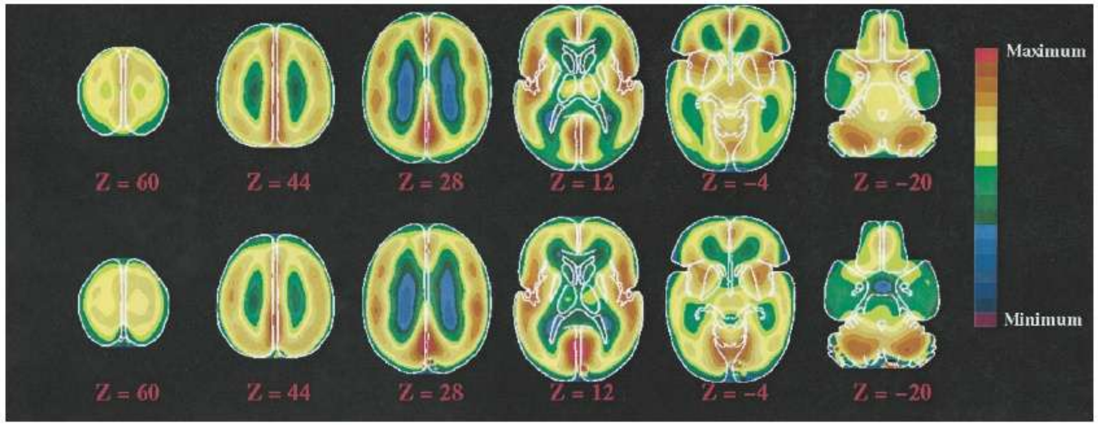
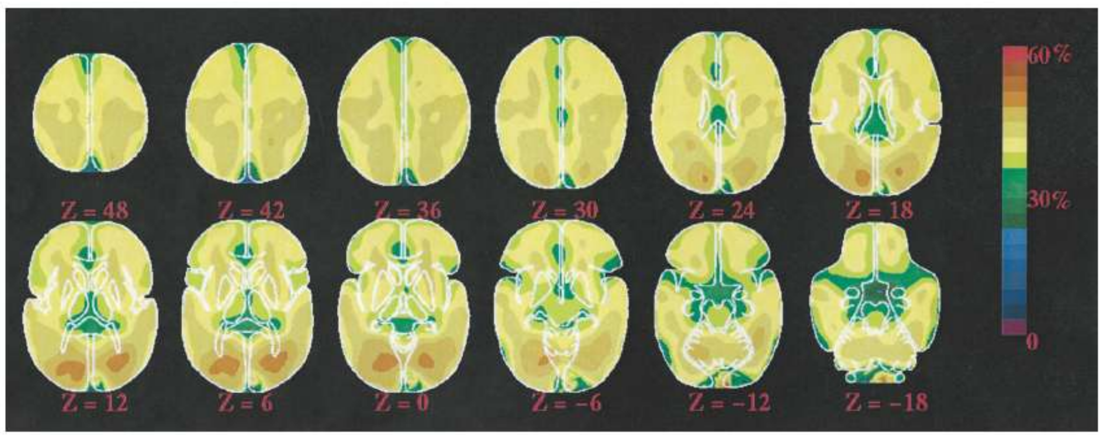
(Raichle et al. 2001): Brain activity does not vary unpredictably if left unconstrained but brain oxygen extraction fraction defines a “baseline state”

Blood flow

Oxygen consumption



OEF = ratio of oxygen used by the brain to oxygen delivered by flowing blood



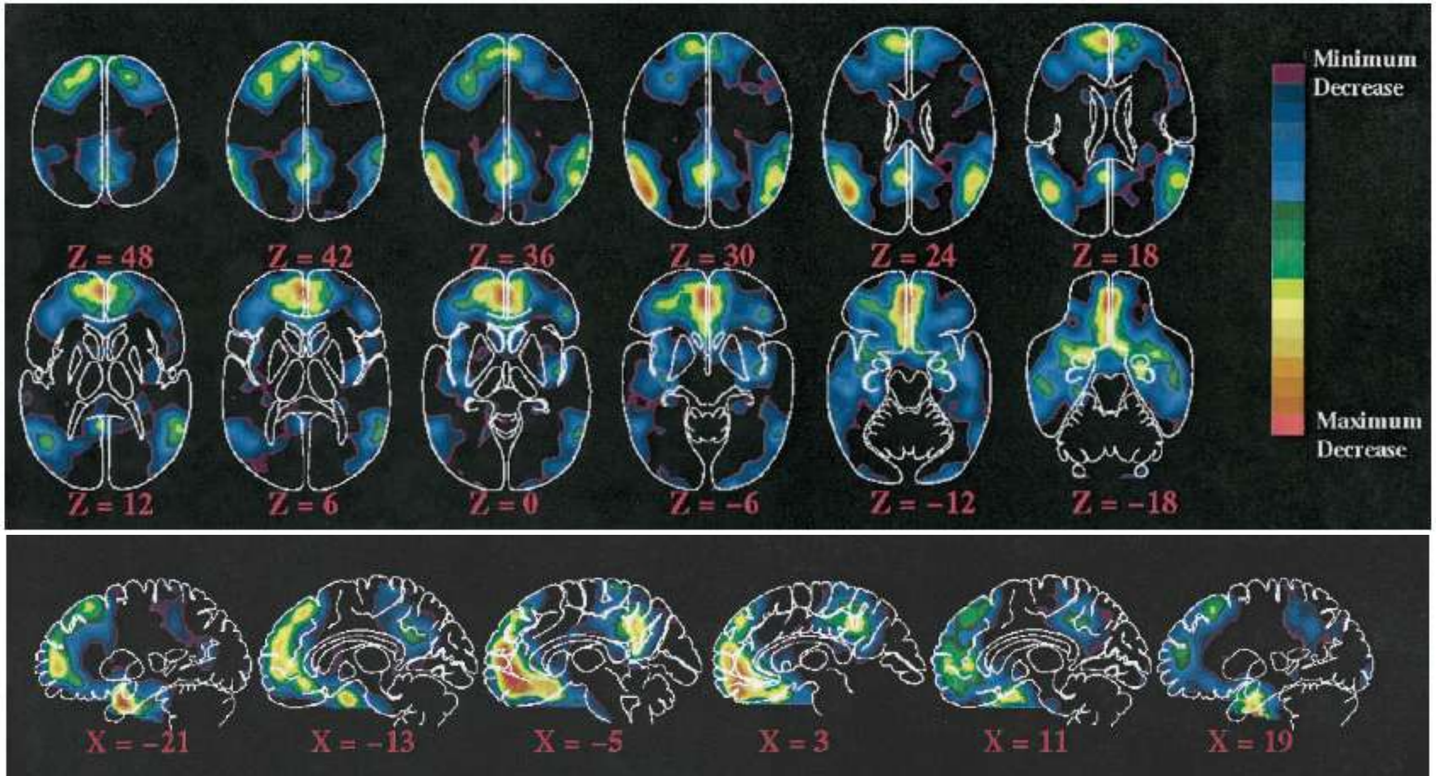
Baseline state

Quantitative maps of blood flow (Upper) and oxygen consumption (Lower) in the subjects from group I while they rested quietly but awake with their eyes closed. The quantitative hemisphere mean values for these images are presented in Table 1. Note the large variation in blood flow and oxygen consumption across regions of the brain. These vary most widely between gray and white matter. Despite this variation, blood flow and oxygen consumption are closely matched, as also reflected in the image of the oxygen extraction fraction

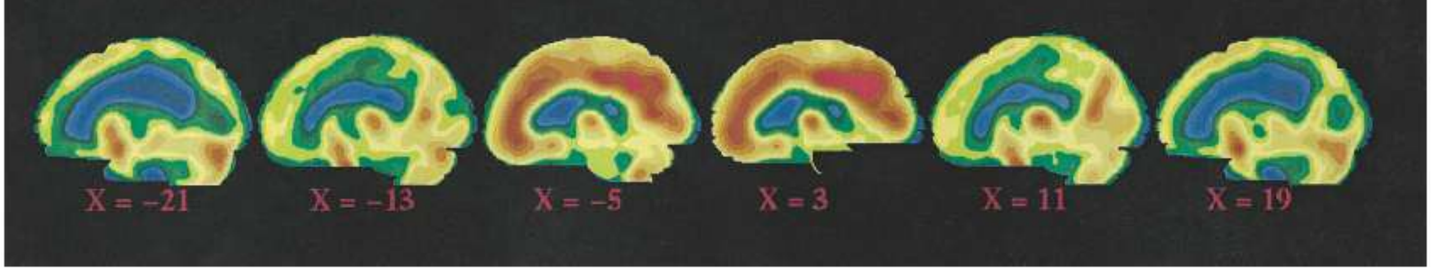
Maps of the fraction of oxygen extracted by the brain from arterial blood (oxygen extraction fraction or OEF expressed as a percentage of the available oxygen delivered to the brain). The data come from 19 normal adults (group I, Table 1) resting quietly but awake with their eyes closed. The data were obtained with PET. ***Despite an almost 4-fold difference in blood flow and oxygen consumption between gray and white matter, the OEF is relatively uniform, emphasizing the close matching of blood flow and oxygen consumption in the resting, awake brain****. Areas of increased OEF can be seen in the occipital regions bilaterally*

PET: Increases of OEF (deactivation) during specific goal directed behaviors or attention demanding tasks suggest the existence of an organized, baseline default mode of brain function

Increase of OEF / Decrease of activity



Blood flow



Regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks. These data represent a metaanalysis of nine functional brain imaging studies performed with PET and analyzed by Shulman and colleagues. In each of the studies included, the subjects processed a particular visual image in the task state and viewed it passively in the control state. One hundred thirty-two individuals contributed to the data in these images. These decreases appear to be largely task independent.

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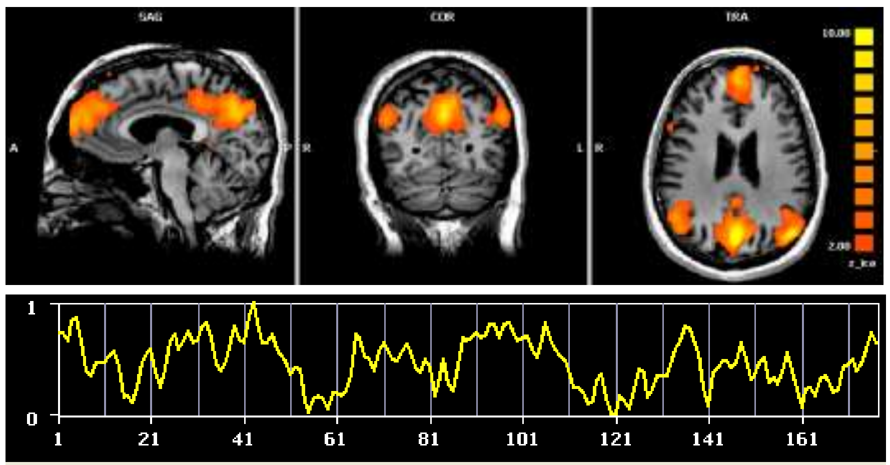
The default mode network and fMRI

Default mode network shows up in resting fMRI as areas with temporally correlated baseline activity, 0.01 Hz < frequency < 0.08 Hz

Two approaches: PCA/ICA and ROI



Greicius et al. 2003: First fMRI resting-state connectivity analysis of the default mode

Recent review: Fox & Raichle 2007

ICA

*The problem of the ICA decomposition of fMRI **time series** X can be formulated as the estimation of both matrices of the right side of*

$X=AC$

*under the constraint that the **processes** Ci are spatially independent. No a priori assumption is made about the **mixing matrix** A. The amount of statistical dependence within a fixed number of spatial components can be quantified by their mutual information. Thus, the ICA decomposition of X can be defined (up to a permutation of the components and a multiplicative constant) as a linear transformation*

$C=WX$

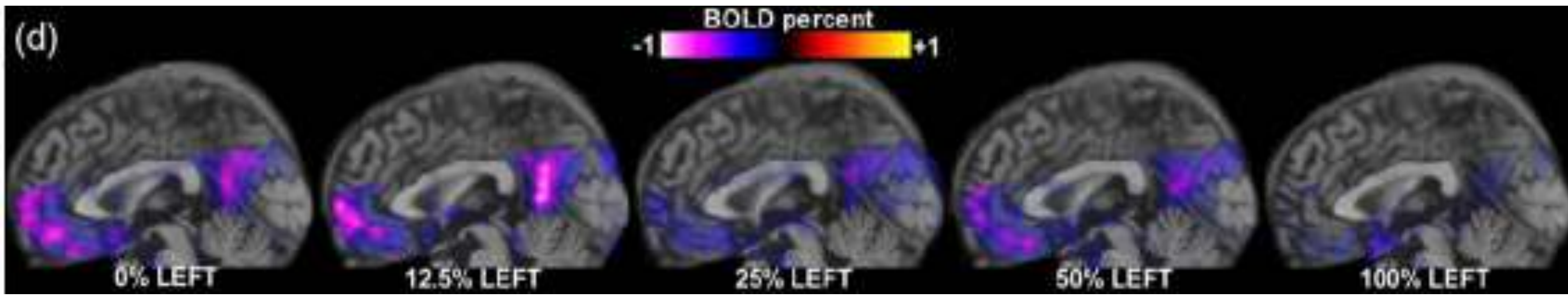
*where the **unmixing** matrix W minimizes the mutual information of the target components Ci. Matrix A can be computed as the pseudoinverse of W.*

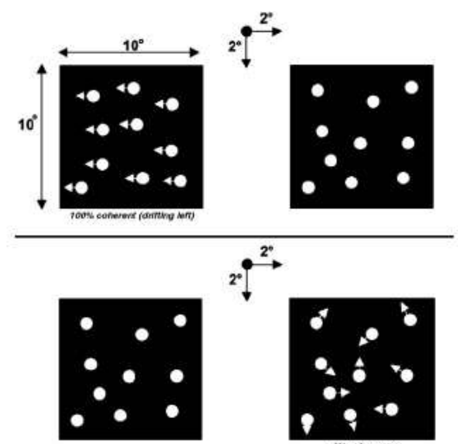
ICA used in Brainvoyager

*The spatial decomposition of the data is performed using "**FastICA"**, a fixed-point ICA algorithm. The FastICA algorithm minimizes the mutual information of the components using a robust approximation of the negentropy as a contrast function and a fast, iterative algorithm for its maximization.*

Example for the appearance of the default mode network as negative activation in fMRI with a visual stimulation paradigm (Singh et al., 2008):

*"… we demonstrate that this network is **transiently suppressed** in an event-related fashion, reflecting a **true negative activation** compared to baseline… Deactivation across the network varied in an inverse linear relationship with motion coherency, demonstrating that the **strongest suppression occurs for the most error-prone tasks**. .. We also show that the magnitude of task related activation of the individual sub-components of the default-mode network are strongly correlated, indicating a **highly integrated system**."*

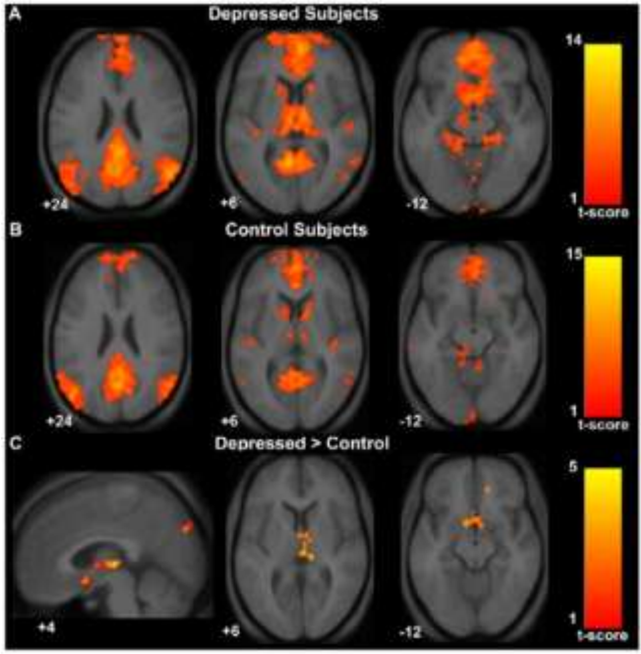




Clinical applications

AD (Greicius et al. 2004): Decrease
AD (Rombouts et al. 2007): Decrease
AD (Sorg et al. 2007): Decrease
AD (Wang et al. 2007): Decrease + increase

Depression (Greicius et al. 2007): Increase



Schizophrenia (Liu et al. 2008): Network disruptions

ADHD (Wang et al., 2007): Altered “small world network” structure
ADHD (Zhu et al. 2008): Thalamus involvement

The aging brain (Andrews-Hanna et al., 2007): Disruption of large-scale brain systems
The aging brain (Wu et al., 2007): Disruption of (motor) network

Epilepsy (Waites et al., 2006): Disruption
Epilepsy (Laufs et al., 2007): Decrease + increase

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I. Birn et al. 2006 / 2008:

•The BOLD fMRI signal in certain brain regions is significantly correlated with small variations in end-tidal CO_2 (Wise et al., 2004).

•*Variability* in respiration can affect the fMRI time series changing the arterial level of $CO_{2,}$ a vasodilator; frequency of 0.03 Hz overlaps with resting activity (<0.08 Hz).

•The regions within the default mode network overlap with many of the regions that are strongly affected by respiration.

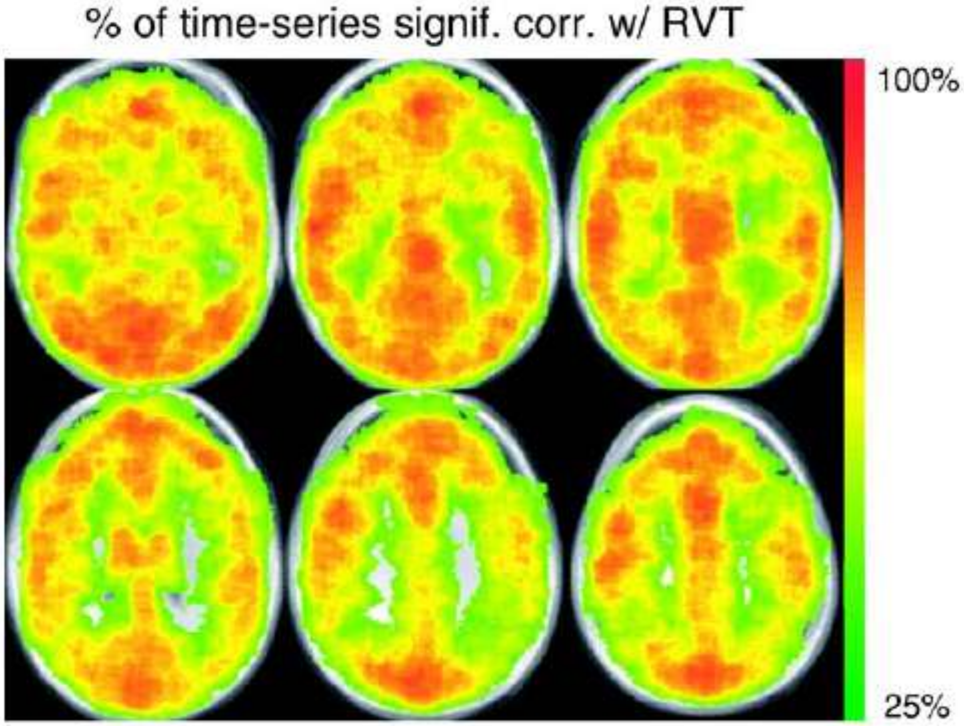


Fig. 2. Location of respiration changes: map showing for each voxel the percentage of time series (out of a total of 16 runs from 10 subjects) where the fMRI signal during rest was significantly (CC > 0.4, $P < 10^{-6}$ uncorrected) correlated with the respiration volume per time (RVT) changes. Signal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

•Global fMRI signal changes during rest were significantly correlated with changes in respiration volume per time.

• When global signal changes were regressed out, or when subjects were cued to maintain a constant breathing rate and depth, regions correlated with the posterior cingulate included primarily the regions of the default mode network.

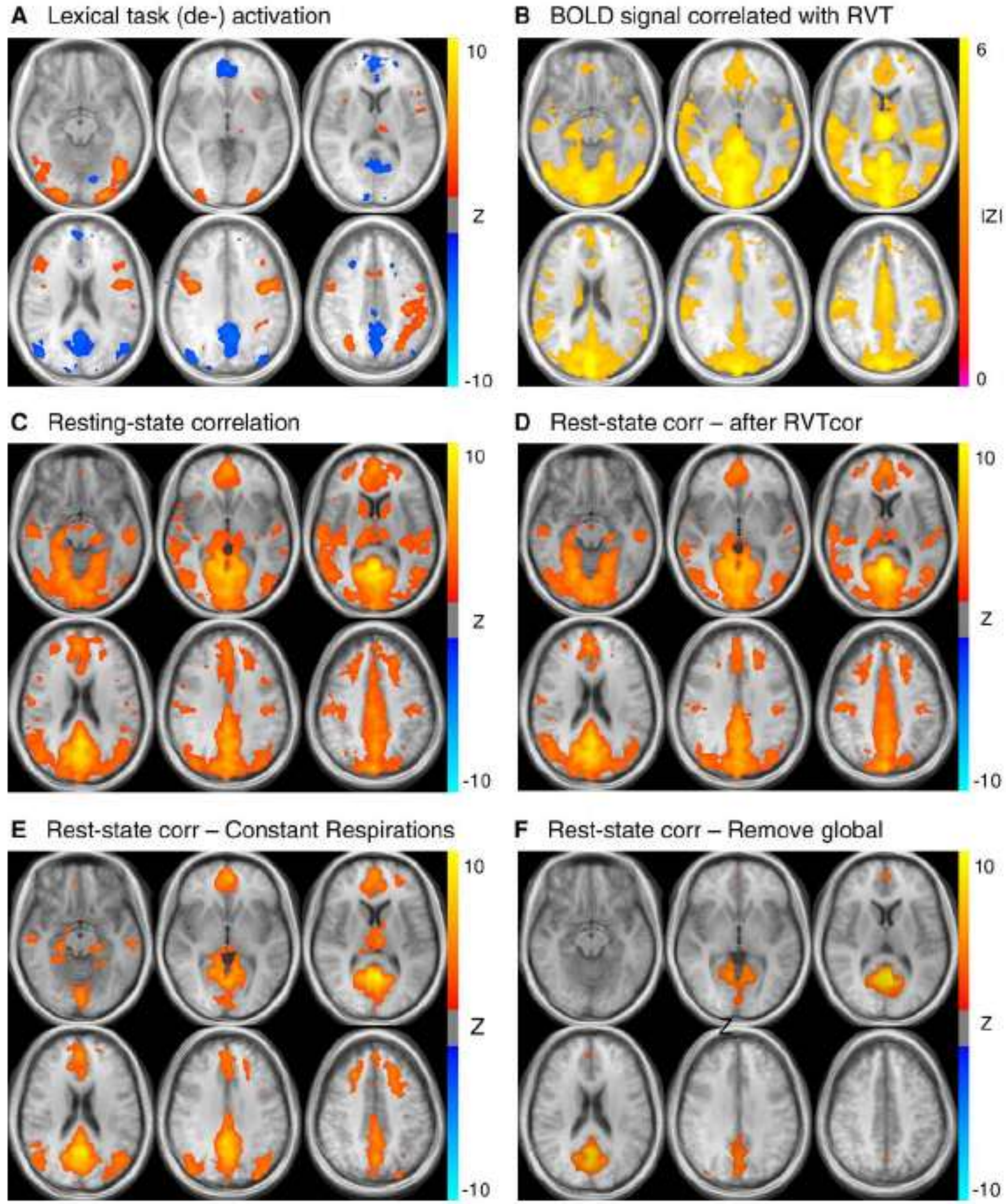


Fig. 7. Group maps: (A) activations and deactivations from a lexical task. (B) fMRI signal correlated with respiration volume per time (RVT) changes. (C–F) Functional connectivity map obtained by correlating the average resting signal, before or after correction, from areas in the posterior cingulate that were deactivated in the lexical task. (C) Without any physiological correction. (D) After removing signal changes correlated with respiration volume per time (RVTcor). (E) When subjects were asked to breathe at a constant rate and depth. (F) After global signal changes (averaged over the whole brain) were regressed out.

•Respiration changes were significantly correlated with fMRI signal changes, particularly in highly vascular regions, such as gray matter and large vessels. This correlation was predominantly negative, with fMRI signal increases resulting from decreases in respiration depth.

•Regressing out variations in the respiration volume per time, as derived from a respiration belt, resulted in only a small reduction of correlated regions outside the default mode network.

The similarity between the fMRI signal changes correlated with respiration volume changes and the default mode network is striking.

Alternative explanations:

1. *May reflect a direct or indirect involvement of the default mode network in the control of respirations.*

2. *Regions comprising the default mode network have a denser vascular supply which therefore also leads to larger respiration-induced flow changes.*

3. *These regions have such a large blood volume and baseline metabolism that the "default mode network" might simply reflect those regions where BOLD fMRI is most sensitive to any tiny change in blood oxygenation because of the large blood volume.*

It is unclear, how well ICA can differentiate fMRI signal changes related to variations in respiration from BOLD signal changes induced by activity of the default mode network since these two effects occur in similar regions and at similar frequencies.

II. Razavi et al. 2008:

- Phase analysis in one single slice in white matter/gray matter/CSF/vessels/background

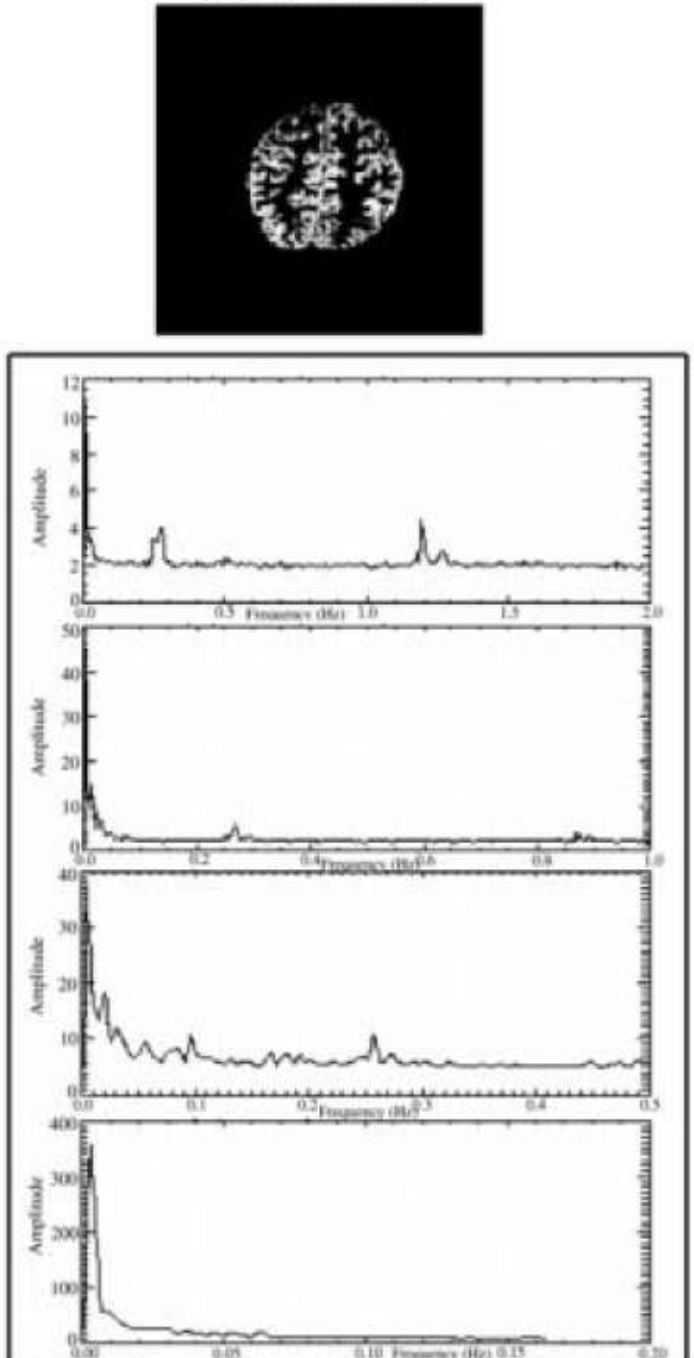
- LFF in fMRI signal of cerebral blood vessels and CSF were synchronous and preceded those of gray and white matter

- Varying sampling rates (TR): Power spectra of cardiac data showed only one peak at the cardiac frequency, while the resampled cardiac signal aliased below 0.1 Hz. Equivalent for respiration data.

- Power spectra of head-motion parameters showed one peak below 0.01 Hz

- **The primary physiologic source of native LFF in fMRI signal is (arterial) vasomotion.**

GRAY MATTER



TR=0.25 — 0…2 Hz

TR=0.5 — 0…1 Hz

TR=1 — 0…0.5 Hz

TR=3 — 0…0.2 Hz

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The default network is not unique in showing restingstate activity, but is unique in its response to cognitive tasks.

Biswal et al. 1995: Correlations in low-frequency fMRI signal fluctuations between the left and right motor cortices even when subjects were not explicitly performing a motor task.

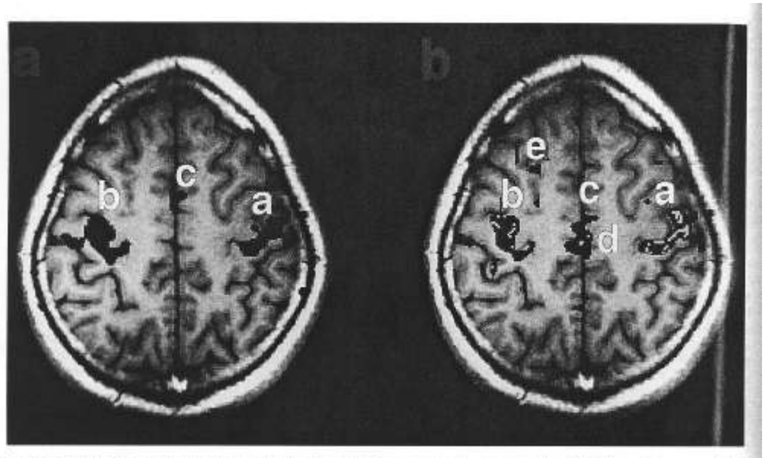
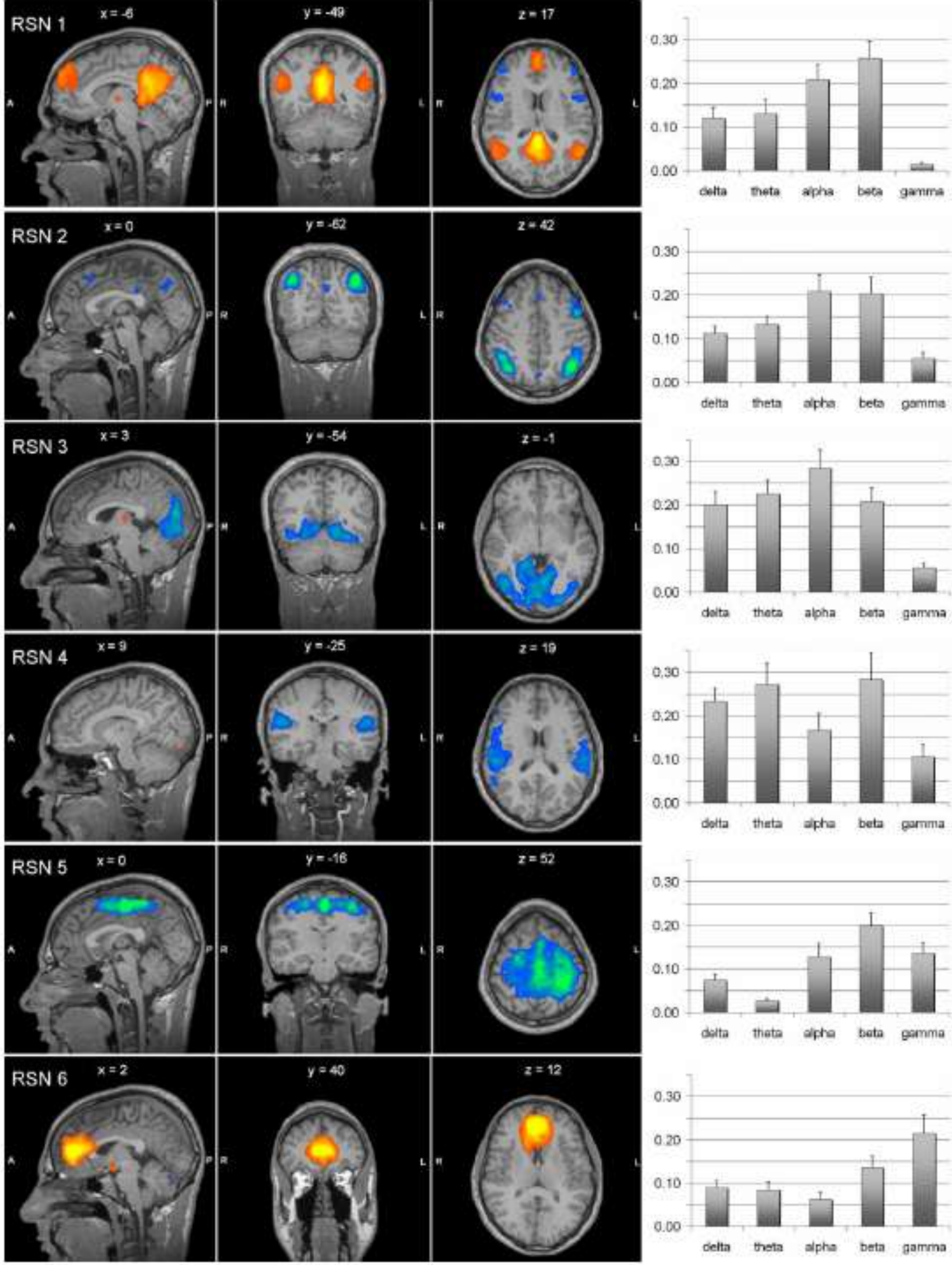


FIG. 3. (Left) FMRI task-activation response to bilateral left and right finger movement, superimposed on a GRASS anatomic image. (Right) Fluctuation response using the methods of this paper. See text for assignment of labeled regions. Red is positive correlation, and yellow is negative.



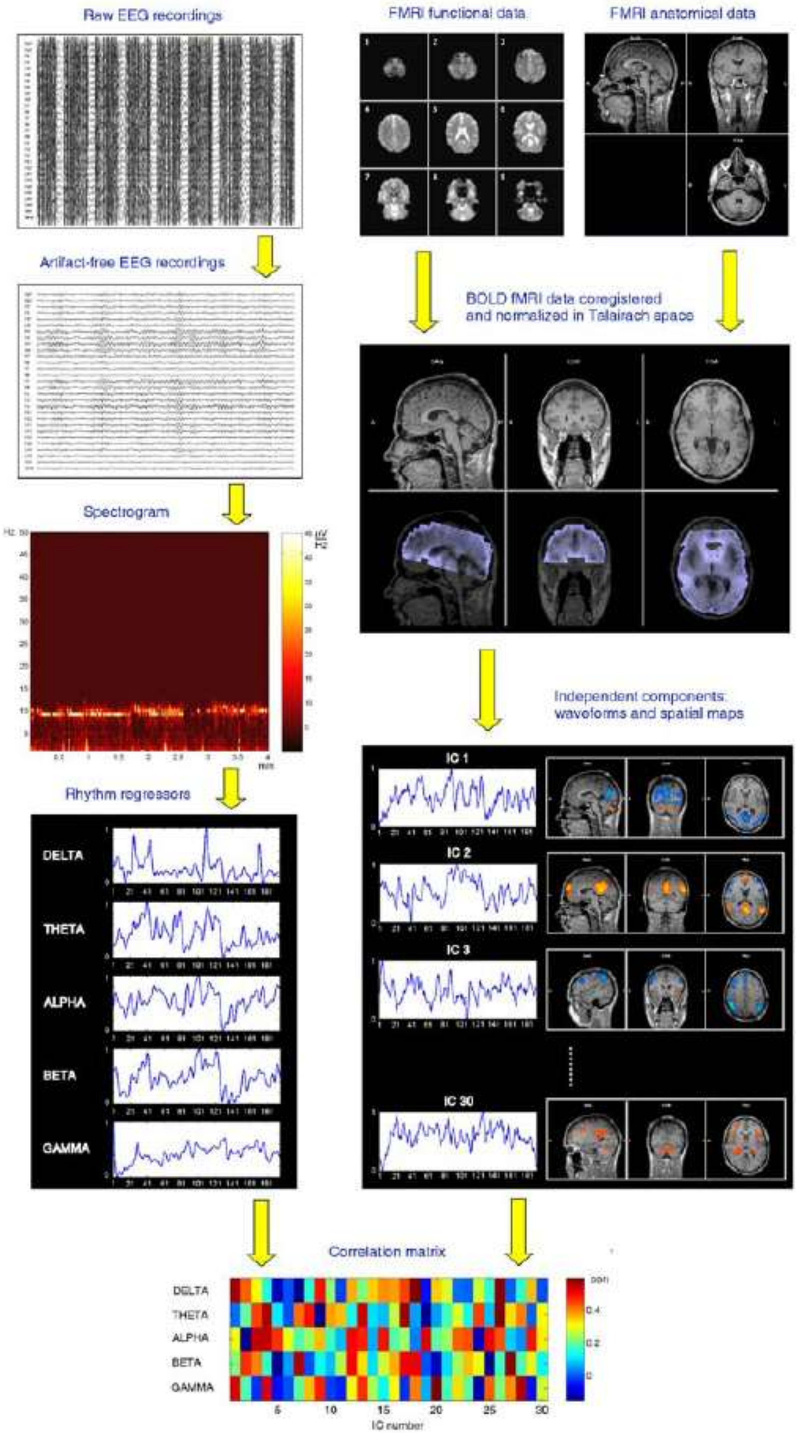
Mantini et al. (2007):

Bar plots of the average correlations between the brain oscillatory activity in the delta, theta, alpha, beta, and gamma bands, and the RSN time courses, selcted from 15 subjects

RSN 1: default mode network, including the posterior cingulate and precuneus, medial prefrontal cortex, dorsal lateral prefrontal cortex and inferior parietal cortex.
RSN 2: dorsal attention network, including the intraparietal sulci, areas at the intersection of precentral and superior frontal sulcus, ventral precentral, and middle frontal gyrus.
RSN 3: visual processing network, including the retinotopic occipital cortex and the temporal-occipital regions.
RSN 4: auditory-phonological network, the superior temporal cortices.
RSN 5: sensory-motor network, including the precentral, postcentral, and medial frontal gyri, the primary sensory-motor cortices, and the supplementary motor area.
RSN 6: self-referential network, including the medial-ventral prefrontal cortex, the pregenual anterior cingulate, the hypothalamus, and the cerebellum.

Damoiseaux et al. 2006 found 10 distinct patterns,
De Luca et al. 2006 found 5 patterns,
Esposito et al. 2005 found 6 patterns,

I found 6 patterns



EEG bands are correlated; analysis of simultaneous EEG/fMRI data requires methods that consider the whole frequency spectrum rather than single frequency bands.

The power spectrum was calculated by using a fast Fourier transform.
The spectrum was averaged in epochs of 1,200 ms, corresponding to the volume TR, and over all EEG channels. The resulting spectrogram was divided into five subbands, corresponding to delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–50 Hz) rhythms.

Further results:

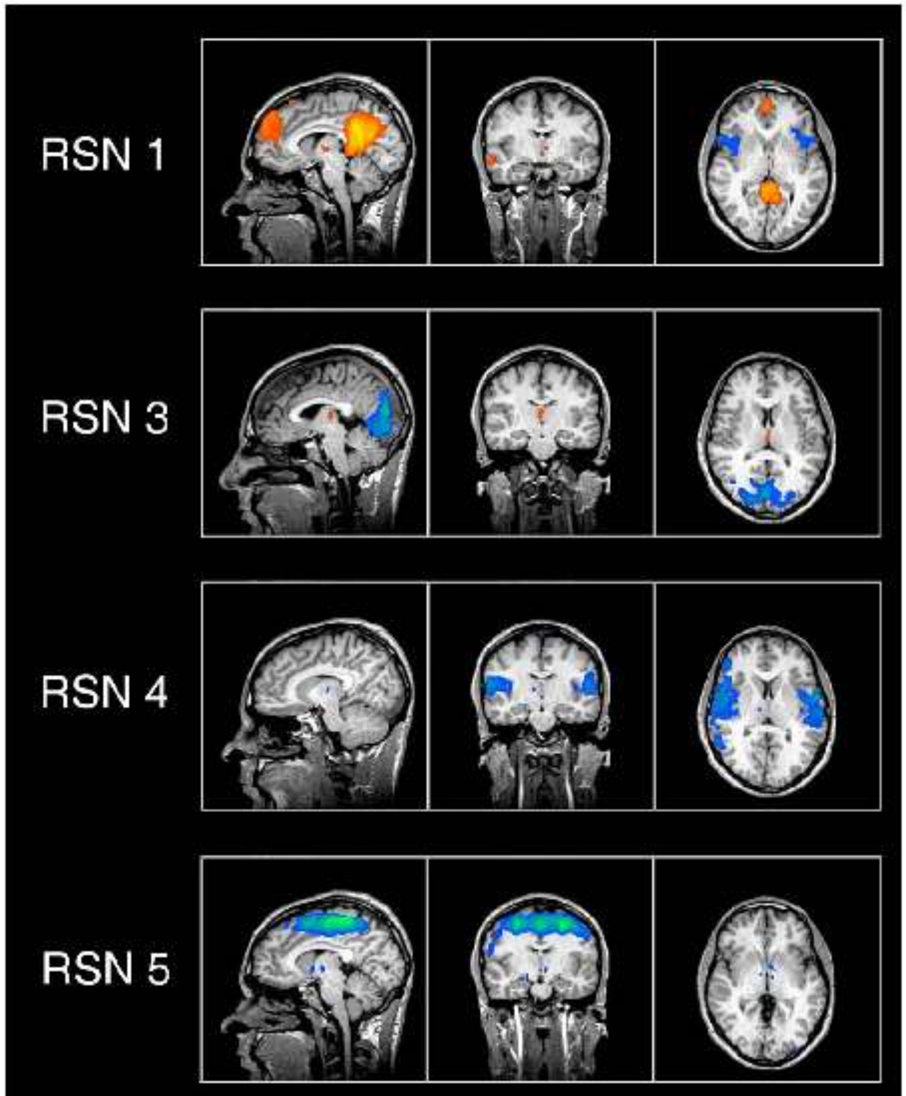
• Rhythm power fluctuations of different bands are positively cross-correlated, suggesting that neuronal signals are dynamically coupled in different frequency bands (as published by others before)

• The six replicable functional brain networks are similar to those obtained by other research groups using ICA

• They correspond to main functional networks reported before

• They are similar to the maps obtained with the previous EEG/fMRI studies. In particular, RSNs 1 --- 4 have been associated with different EEG rhythms before

Thalamo-cortical connectivity for RSNs 1, 3, 4, and 5, showing the participation of the thalamus in the modulation of resting cerebral fluctuations



Important limitation: Analysis is based on the correlation between BOLD signal and EEG power time courses, independent of their amplitude.

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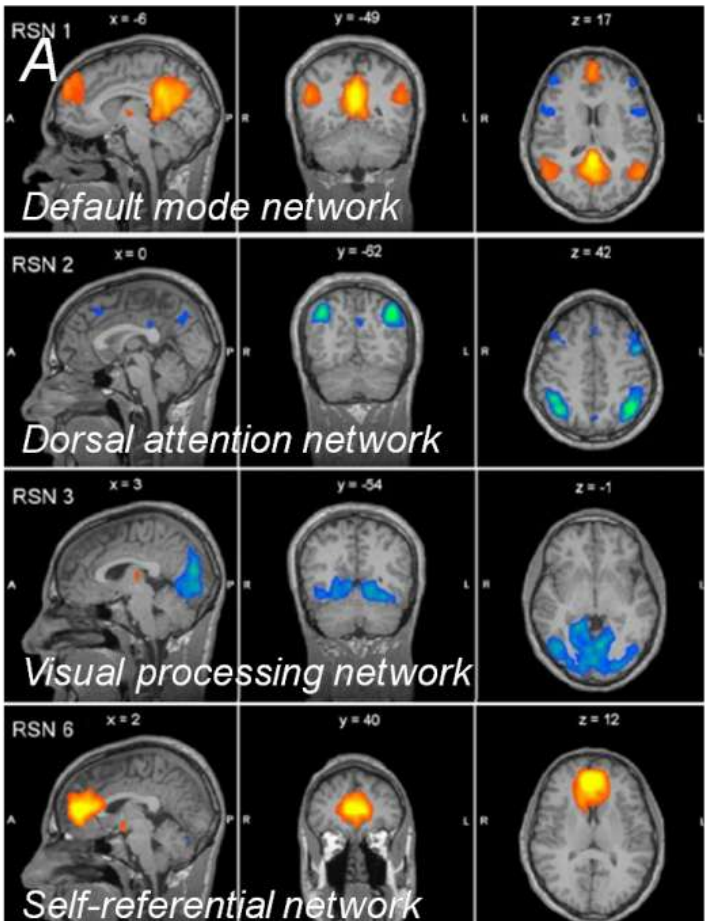
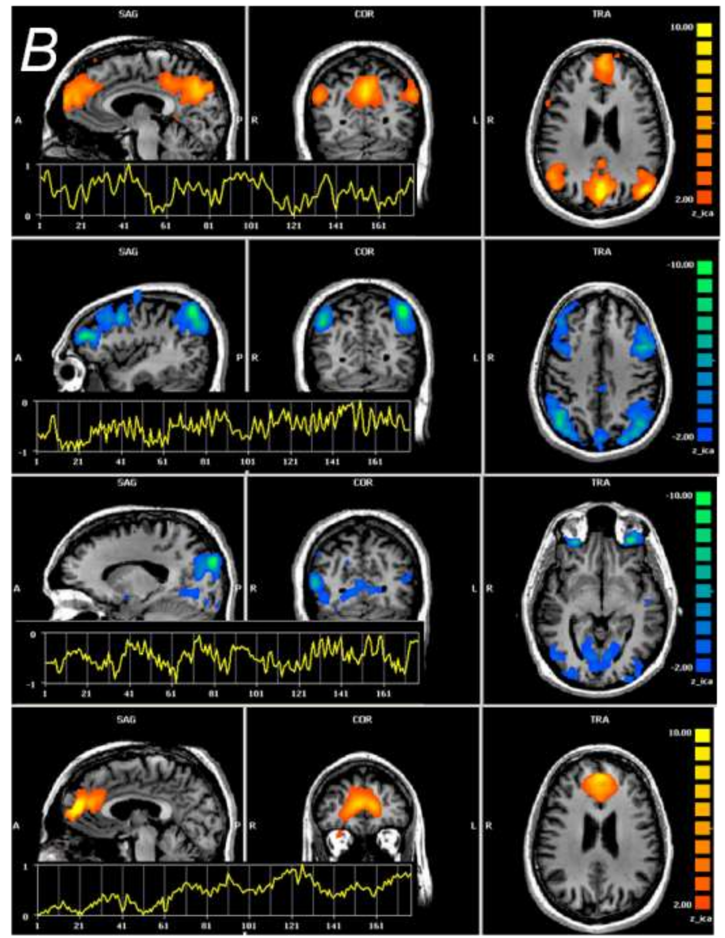
Collaboration with Nicholas D. Schiff, MD

H.U. Voss, B. J. Beattie, J.P. Dyke, N.D. Schiff, Two case studies of resting state network MRI in subjects with severe brain injuries following vascular occlusions, Society for Neuroscience (2008); H.U. Voss and N.D. Schiff, MRI of neuronal network structure, function, and plasticity, Progress in Brain Research 175, 483-496 (2009); H.U. Voss, L.A. Heier & N.D. Schiff, Multimodal imaging of recovery of functional networks associated with reversal of paradoxical herniation after cranioplasty, Clinical Imaging 35 (4), 253-258 (2011).

fMRI validation on 9 normal subjects:
We could identify the default mode (RSN 1), visual processing (RSN 3), auditory-phonological (RSN 4), and self-referential (RSN 6) networks.
The dorsal attention (RSN 2) and sensory-motor networks (RSN 5) could not reliably be identified in all subjects.

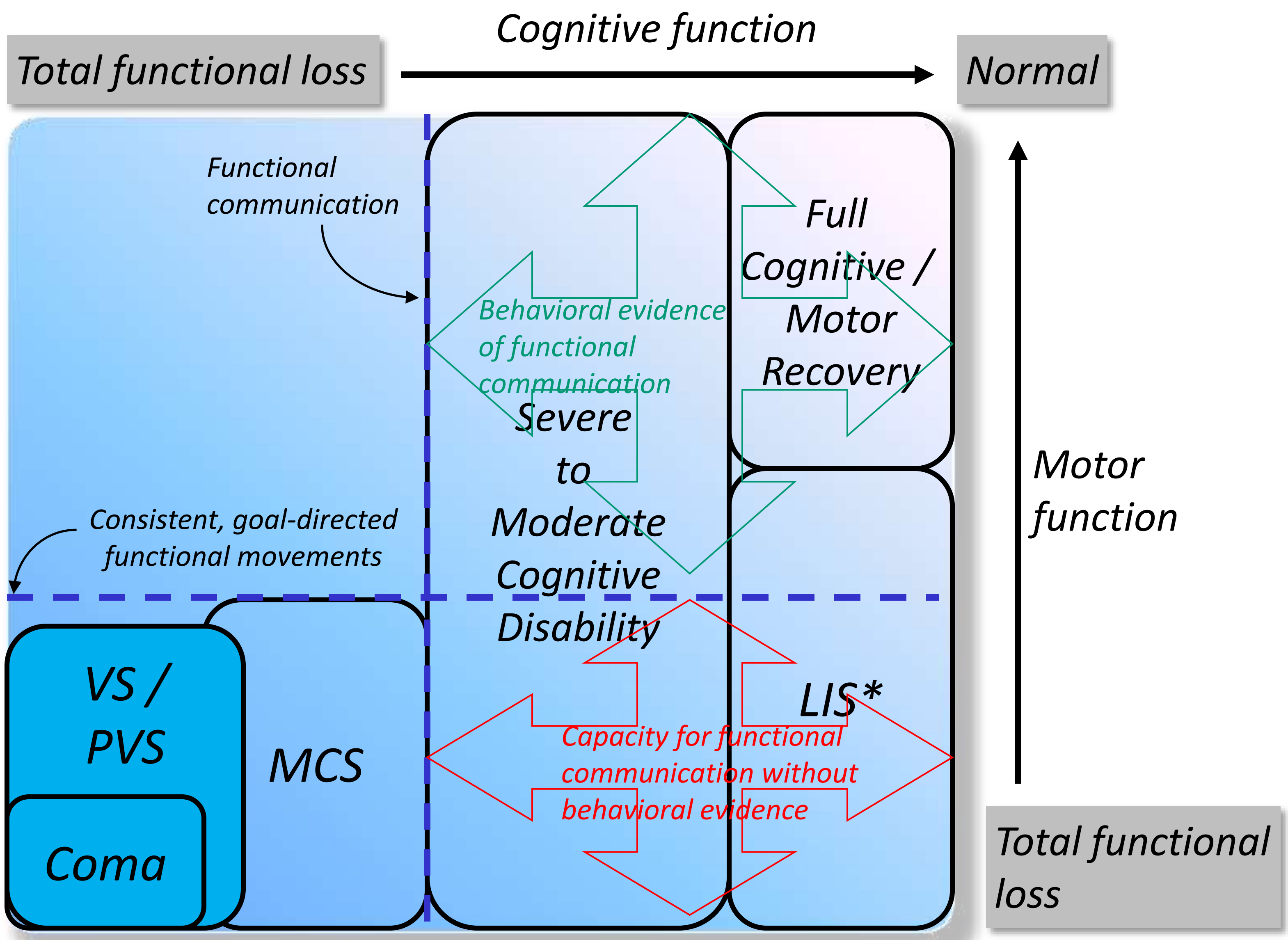


Mantini et al. 2007



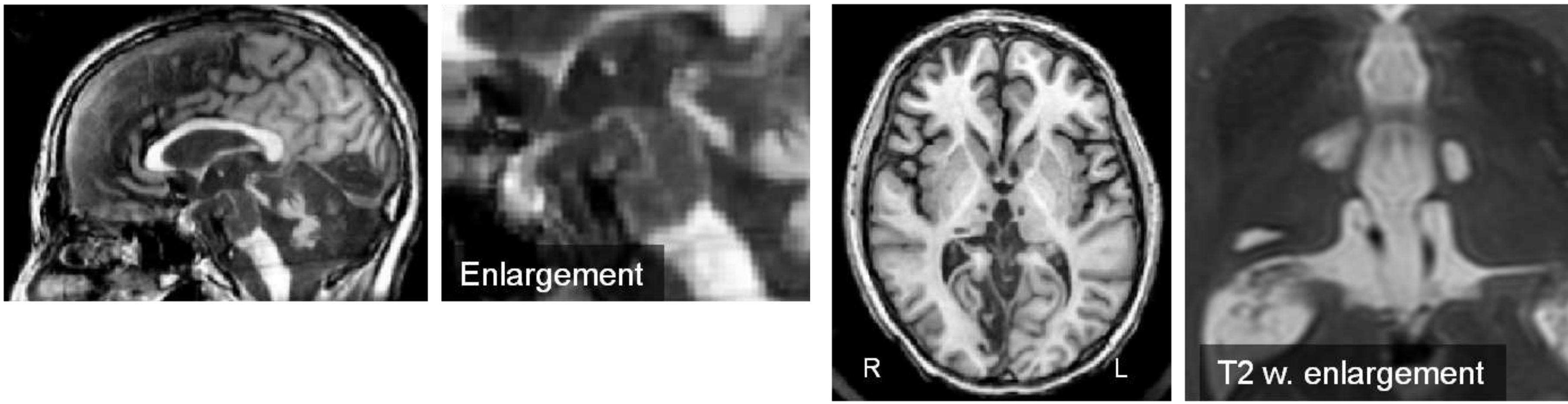
our data on one subject

Disorders of consciousness

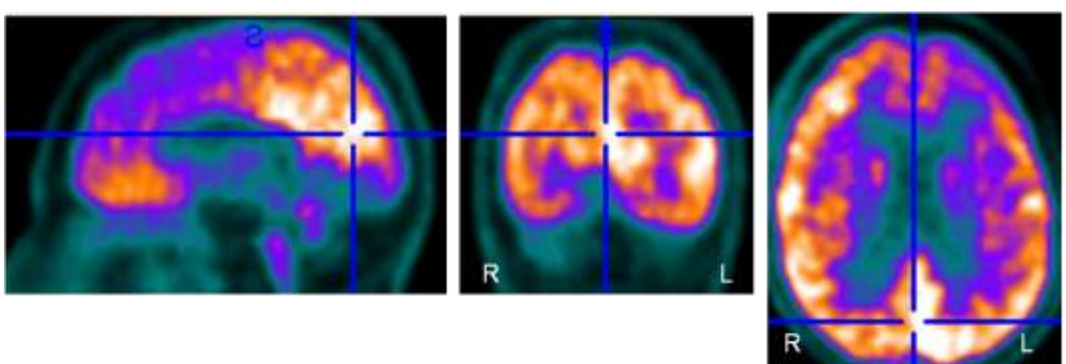


Modified from Schiff, ND, The Neurology of Impaired Consciousness, Cognitive Neurosciences III, MIT Press

Patient 1 (f, 24) suffered multi-focal brain lesions in the brainstem and thalamus secondary to basilar artery thrombosis and infarction of the ventral pons and tegmental midbrain 18 m prior to MRI. Behavior: Only vertical left eye movement, command following. Lesions can be seen in the anterior intralaminar nuclei and in the right LGN:

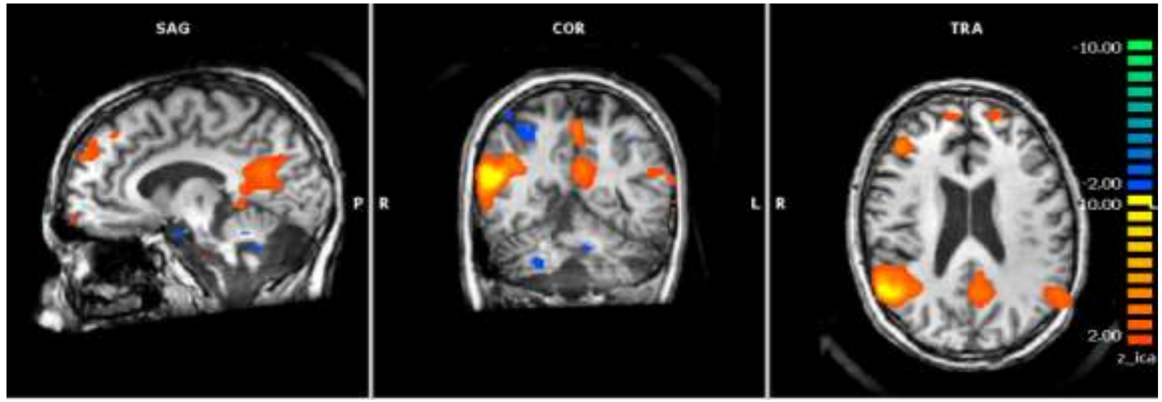


PET: Metabolic rates showed left frontotemporal downregulation which is traceable to the central thalamic lesion, and loss of calcarine metabolism on the right, ipsilateral to the LGN infarct:

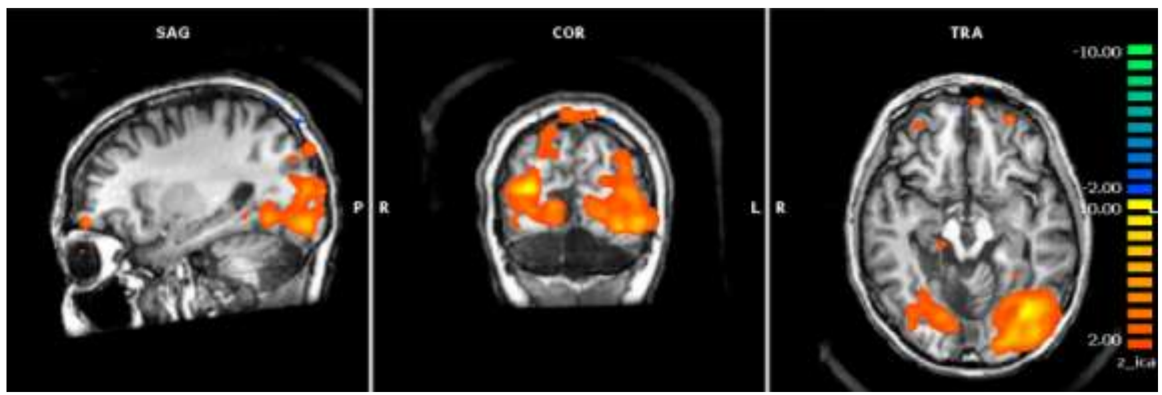


Resting state: We could identify RSN 1, 3, and 4. The parietal regions of RSN 1 (default) appeared stronger, by means of both volume and connectivity, on the right side. The RSN 3 (visual) cluster is smaller on the right side, but has a comparable connectivity.

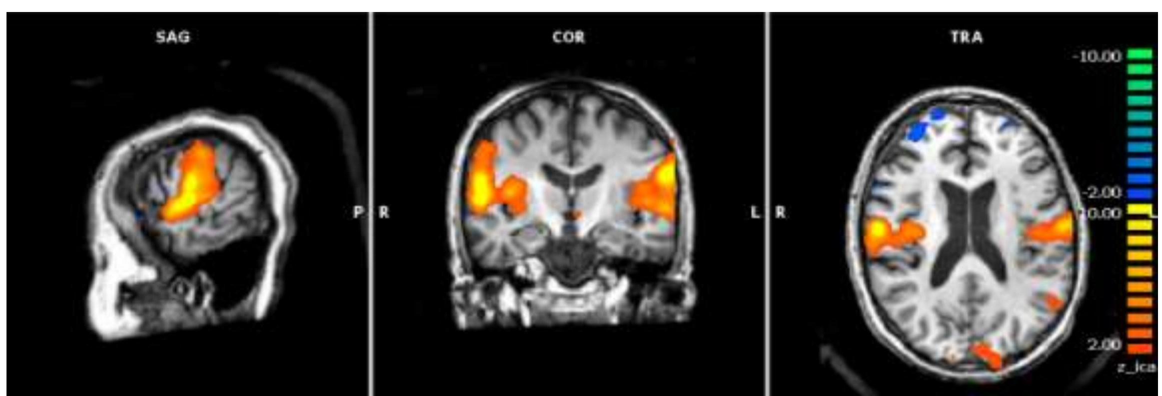
RSN1
default mode



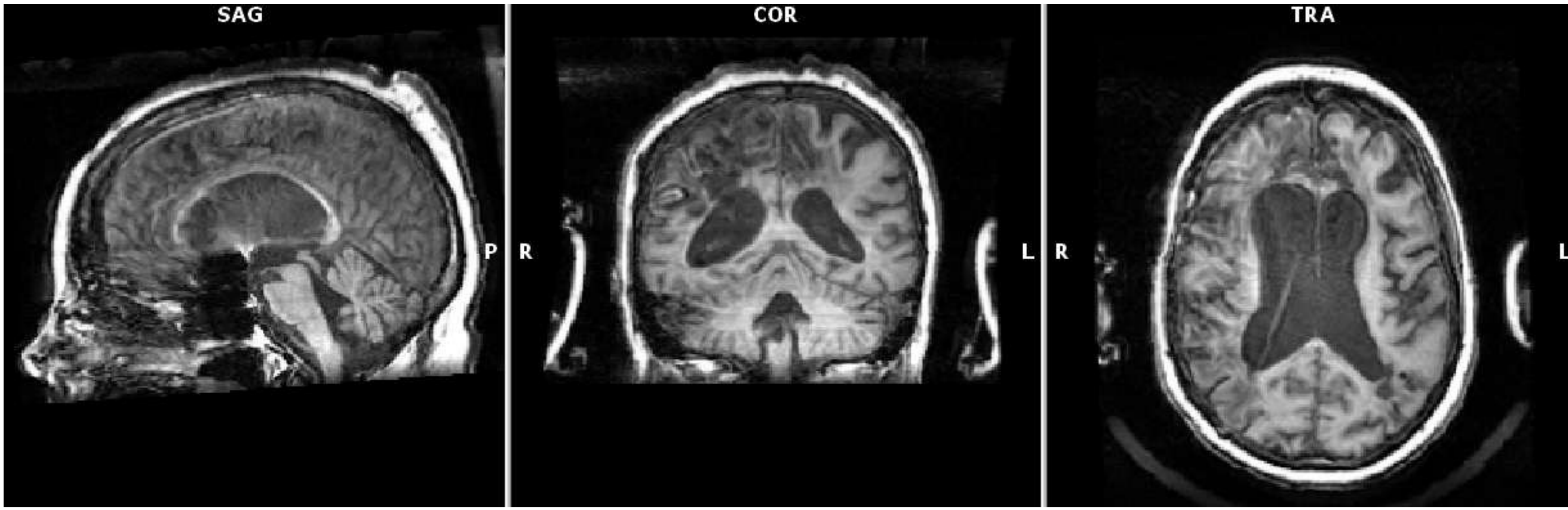
RSN3
visual



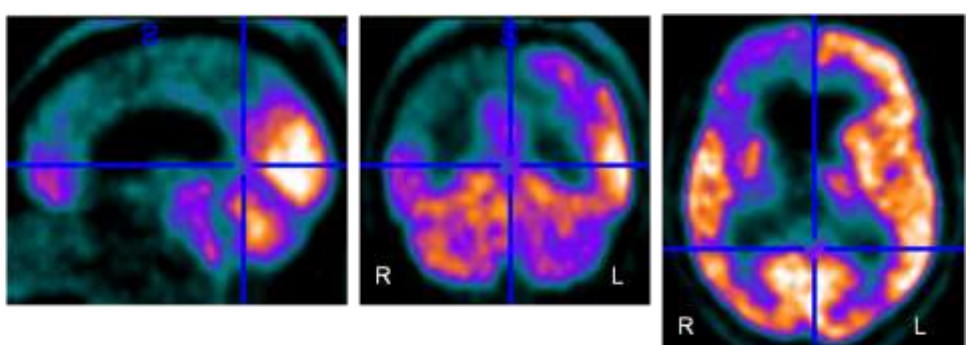
RSN4
auditory-phonological



Patient 2 (f, 56) suffered multi-focal injuries bilaterally within the anterior and middle cerebral artery distributions following severe cerebral vasospasm induced by anterior communicating artery rupture 32 m prior to MRI. Behavior: Inconsistent command following with eye blink, thumb movement, some spoken sentences, some gestures, non-verbal yes/no answers.



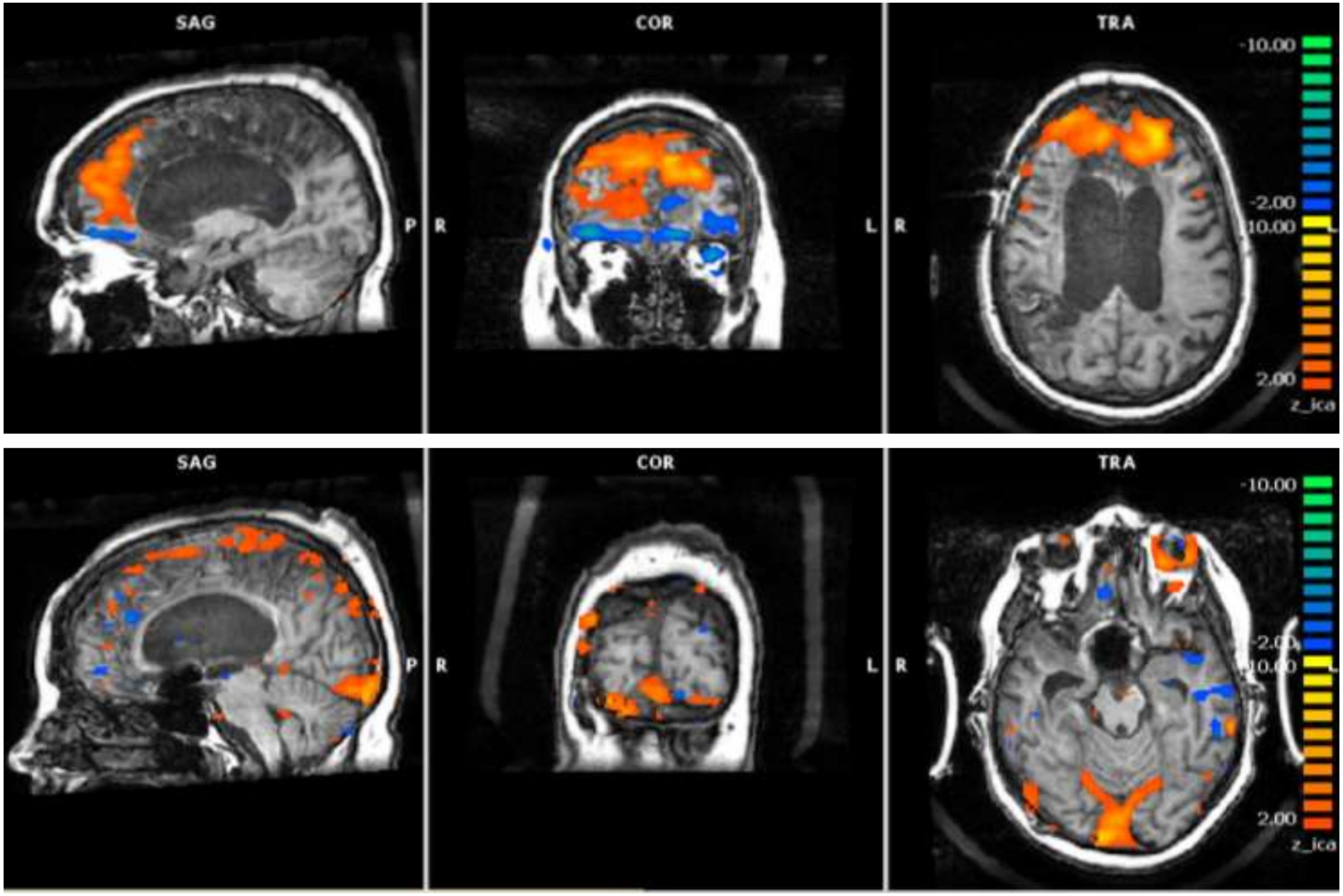
PET: We observed a particularly low metabolism in the corresponding regions, and extensive loss of midline cortical regions.



Resting state: We could identify the anterior part of RSN 1, and RSN 3, 5, and 6. The posterior areas of RSN 1 were missing, and also the other RSN's appeared to be weak. These results are discordant with the clinical exam.

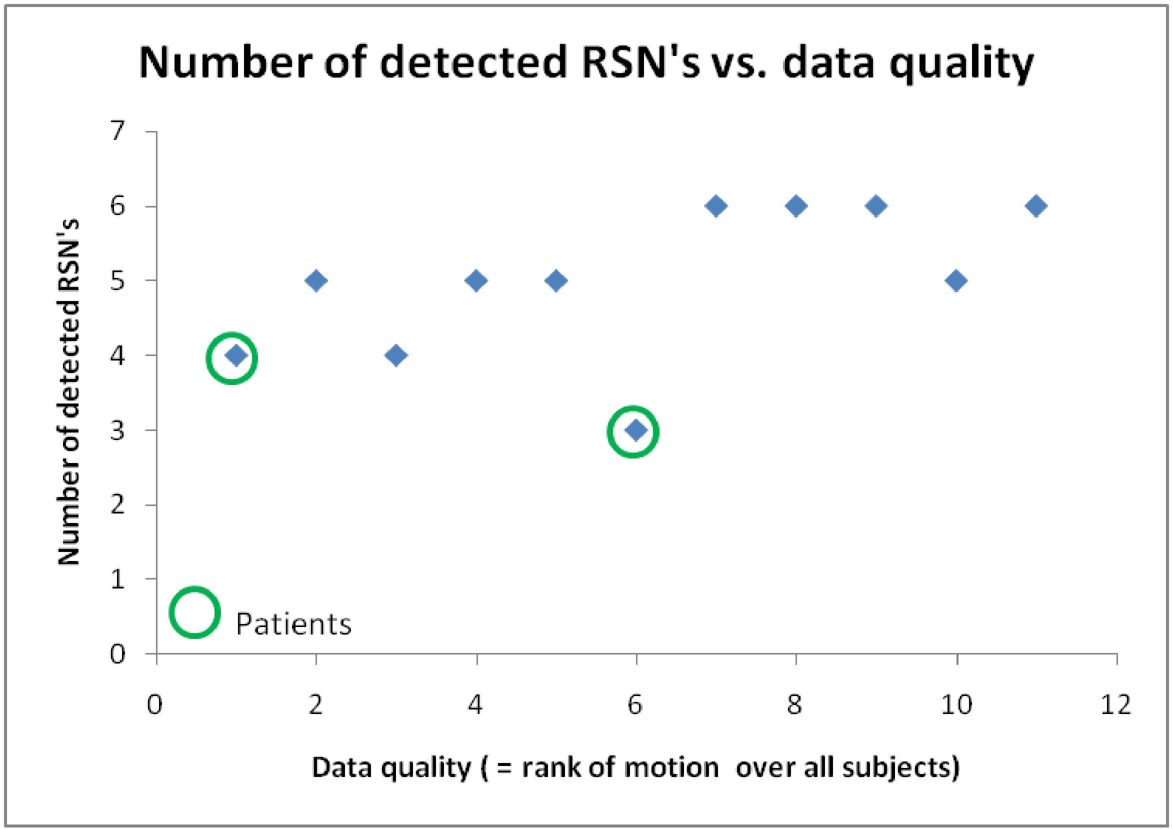
RSN1
default mode

RSN3
visual



Discussion

• Not all RSNs could be found in all normal control subjects.
• Table: unambiguously identified networks, x, incomplete networks, (x), and uncertain networks, ?.
• Findings in resting state fMRI data were apparently influenced by head motion. Roughly, the stronger the head motion, the fewer networks were detected by ICA. This makes it difficult to decide if a resting state network does not show up because of motion or its non- or sub-threshold existence.



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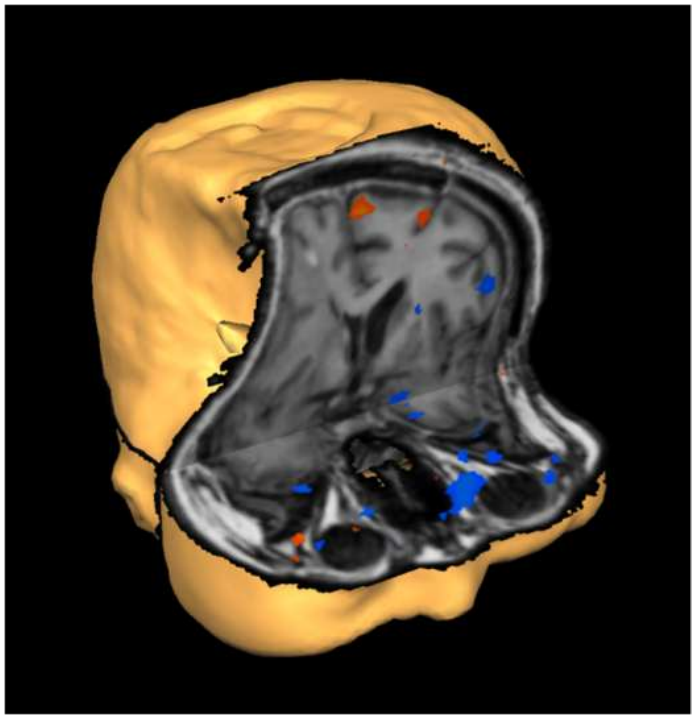

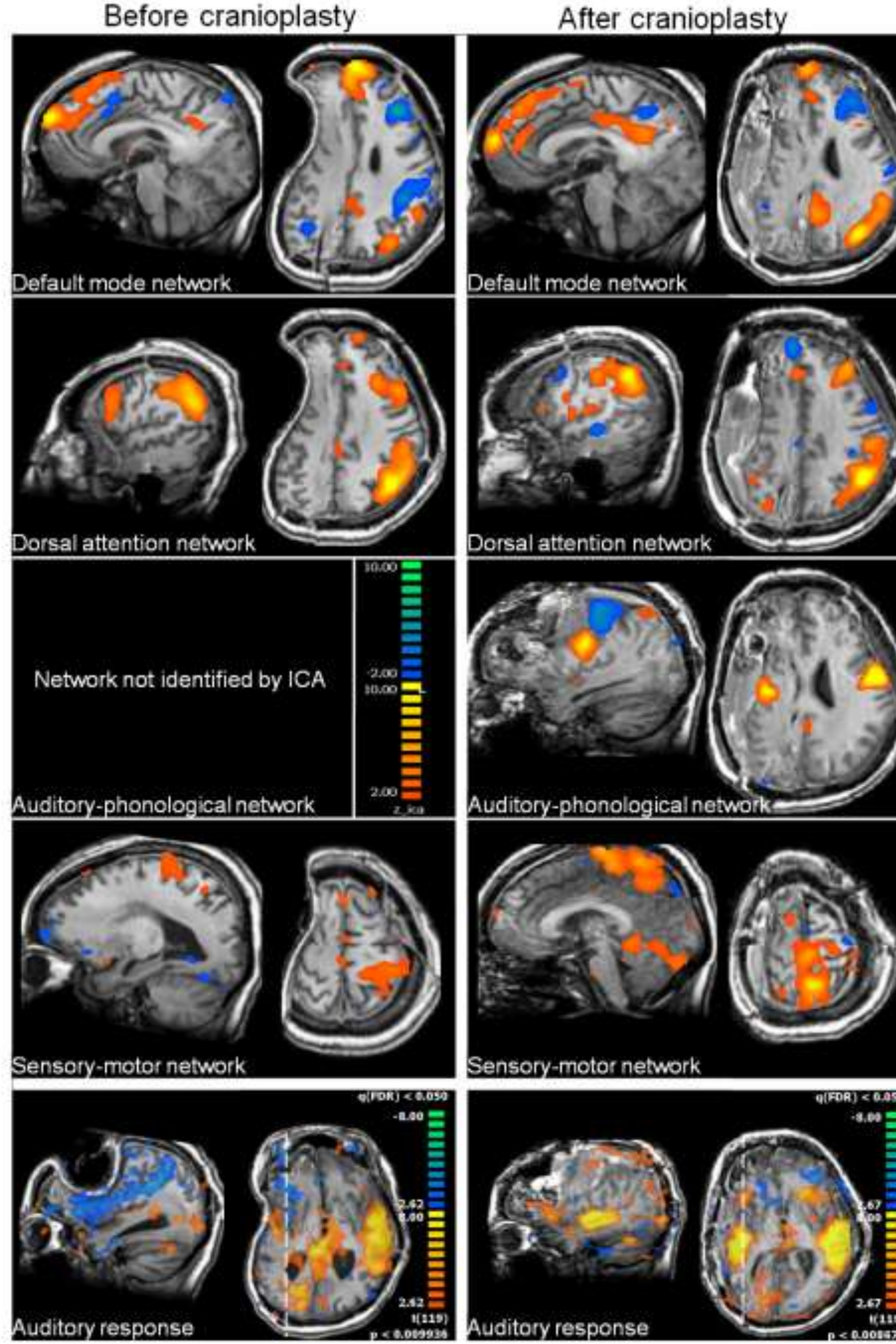

auditory network restored
default mode network +40%
dorsal attention network -2%
sensory-motor network +46%

Conclusions

• Resting state fMRI could become a promising tool to understand neurovascular connectivity in the brain but needs more validation against alternatives, and a better understanding of the role of neuronal vs. vascular factors on the signal

• In the application of severe brain injury **a confounding factor is motion** of the subject – does a resting state network not show up because of motion or its non-existence?