Investigations in Resting State Connectivity

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Overview

- Introduction
- Functional connectivity explorations
  - Dynamic change (motor fatigue)
  - Neurological change (Asperger's Disorder, depression)
  - Consciousness change (Anesthesia)
- Model-free connectivity detection
  - Principal component analysis (PCA)
  - Independent component analysis (ICA)
  - Self-organizing maps (SOMs)
- Practical considerations
  - Time duration and sampling
  - Physiological noise removal
  - Nuisance covariates

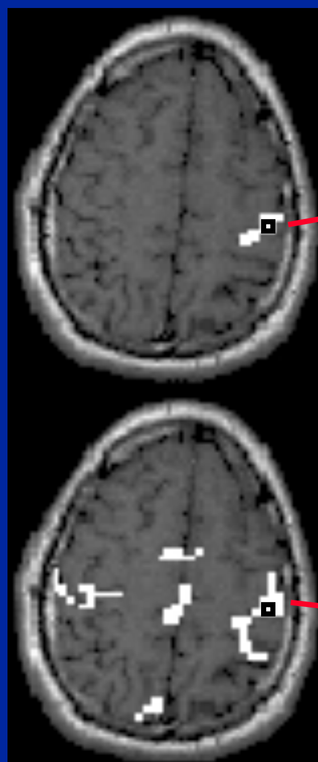
Functional connectivity

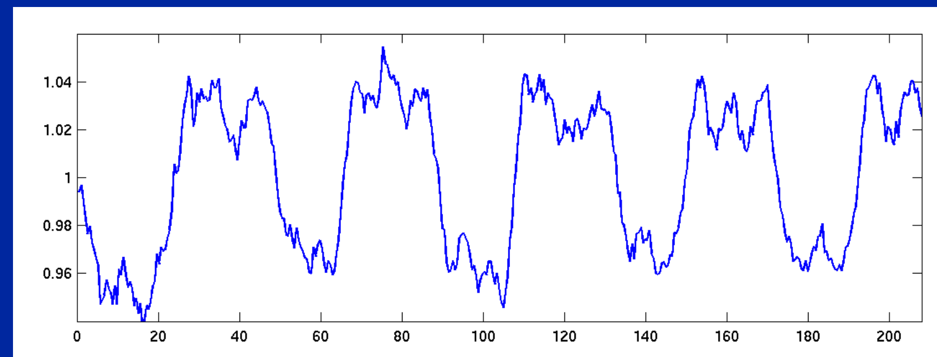
- Temporal correlations of low frequency (<0.08 Hz) fluctuations exist in the brain, even at "rest"
  - Biswal et al. *Magn Reson Med* **34**:537 (1995)
- Connectivity of functionally related areas
  - Motor, visual, auditory
  - Language
  - "Default mode" network

Functional connectivity

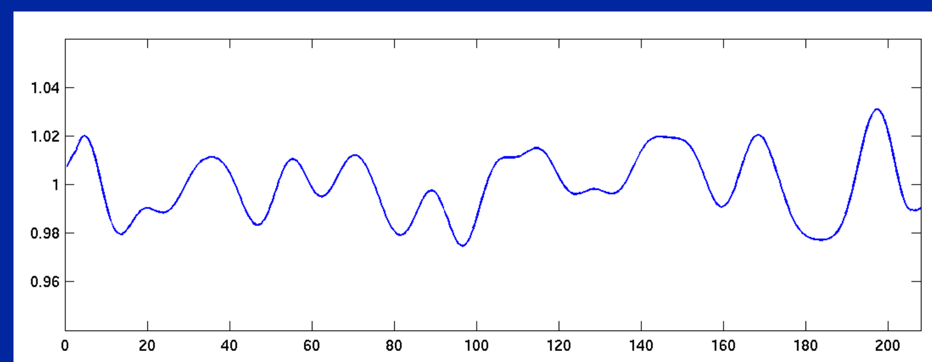
Task

Rest



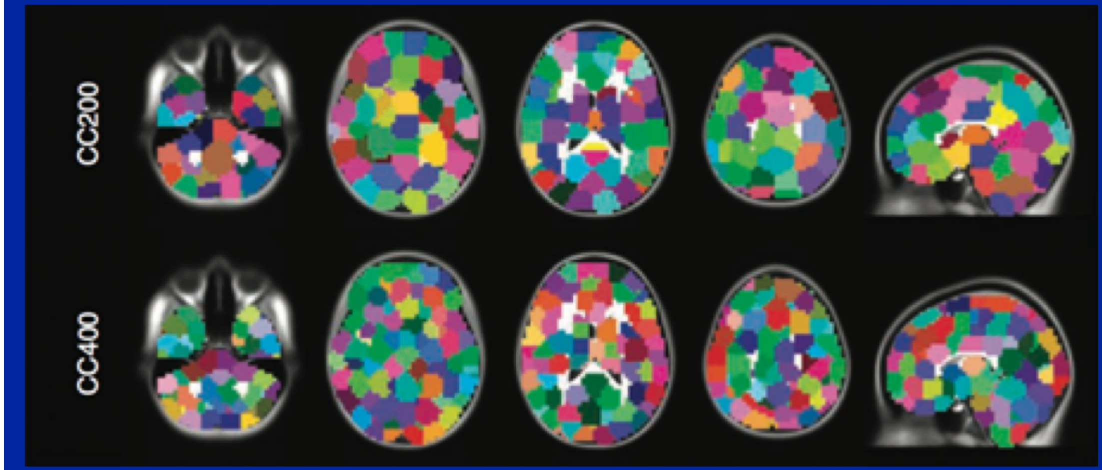


Motor activation, smoothed by 8 pts

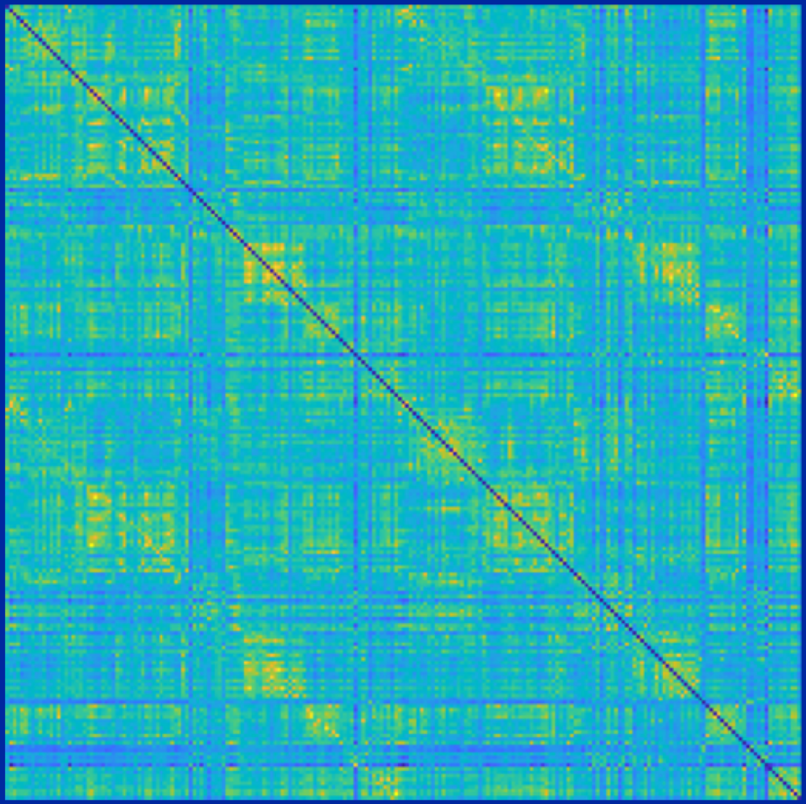


Low-frequency reference waveform

Connectomes



Parcellate

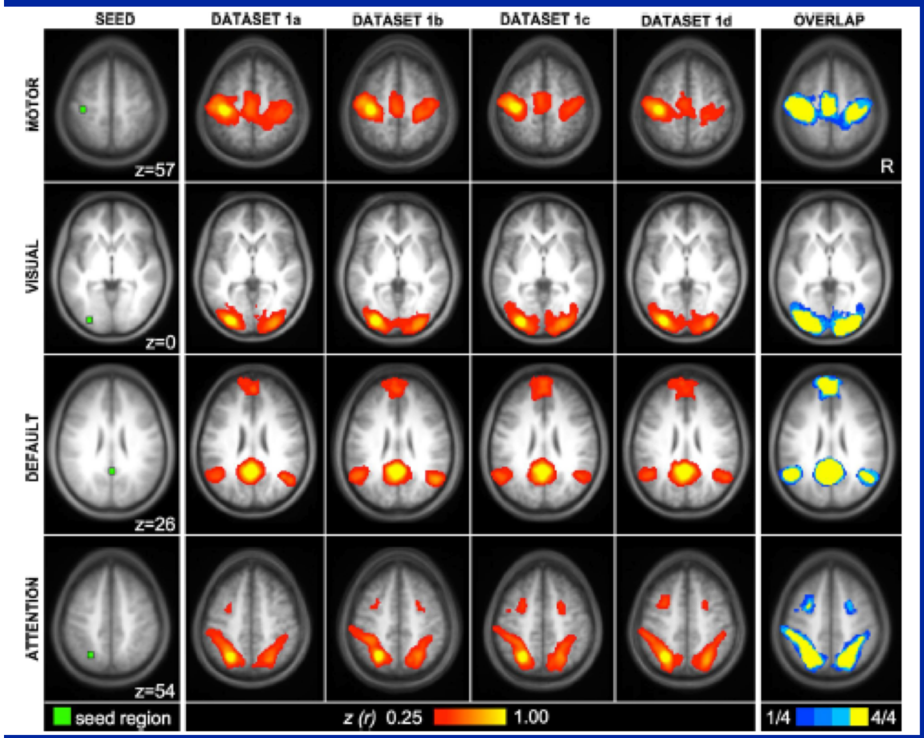


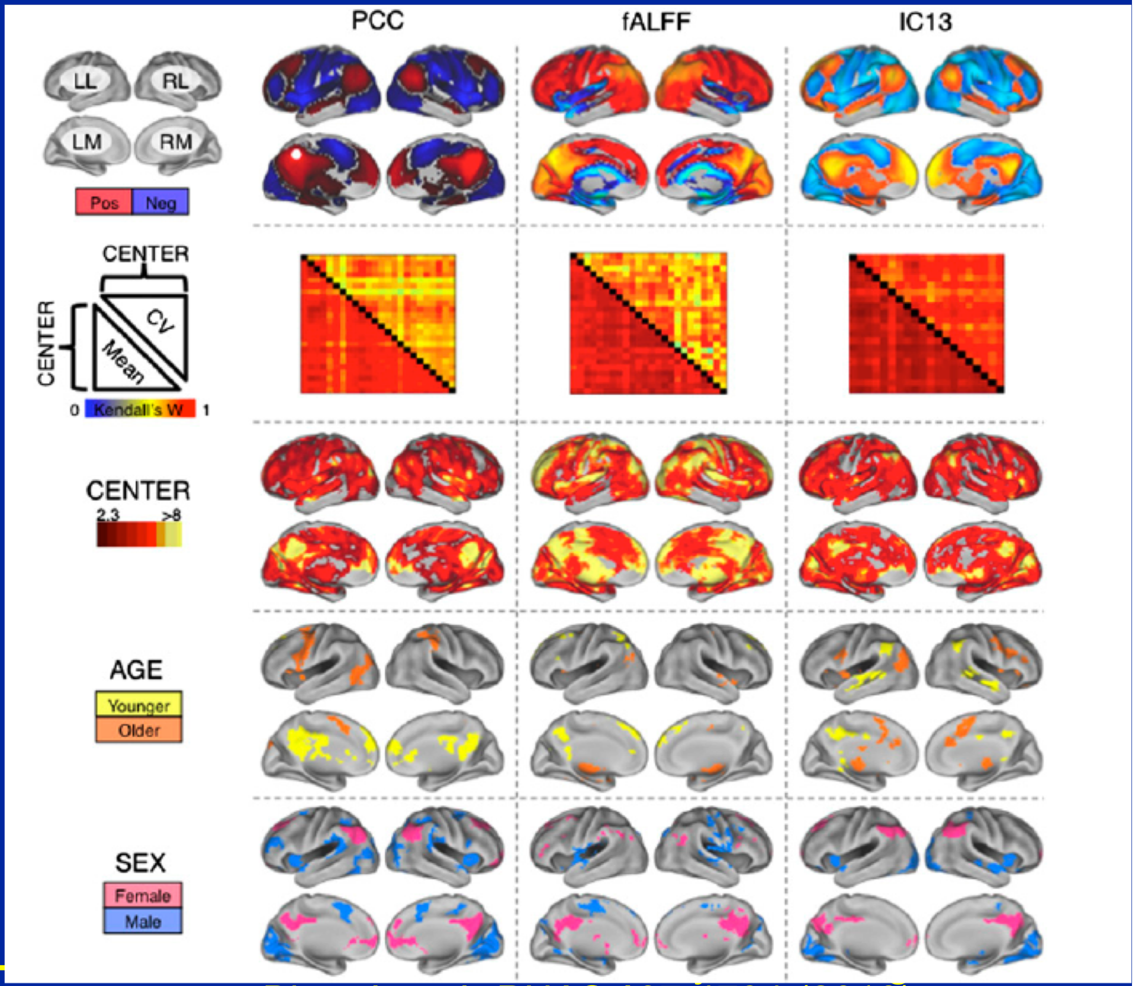
Whole-Brain connectivity

Reproducibility

N = 12 x 4

N > 1000 (!!)





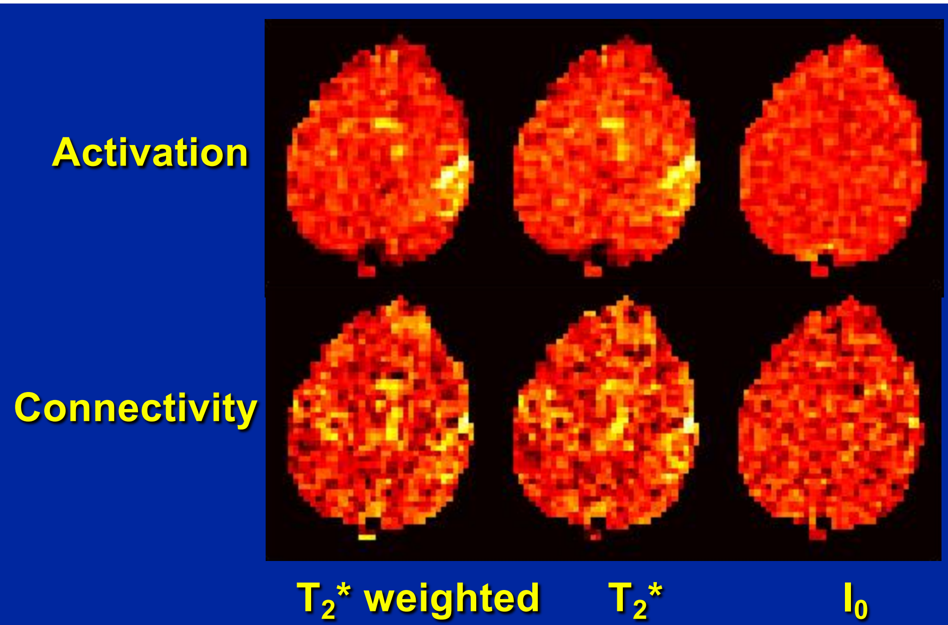
Van Dijk et al. *J Neurophysiol* **103**:297 (2010)

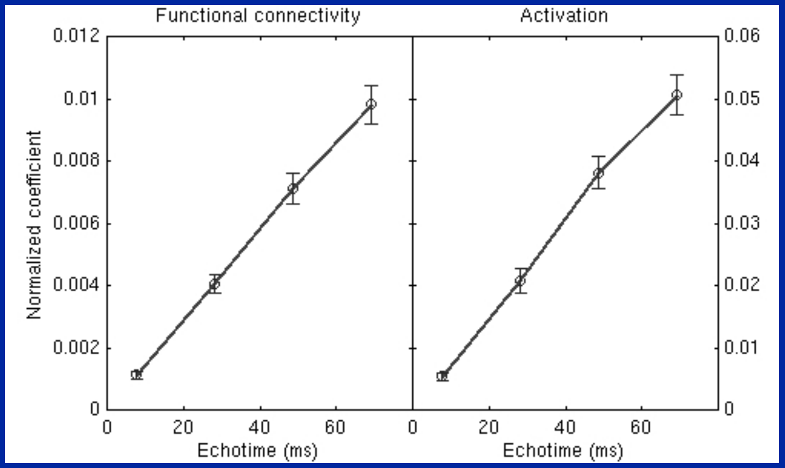
Biswal et al. *PNAS* **107**:4734 (2010)

Peltier

Characterization

- Activation and functional connectivity maps formed using multi-echo sequence
- Comparison shows similar T_2^* dependence
- Both activation and connectivity signal change are linear with echo time (TE)
- Low frequency functional connectivity has same echo time characteristics as “regular” activation





Peltier & Noll, *NeuroImage,* **16**:985 (2002)

➡ Functional connectivity seems to arise from BOLD-related origins

Motivation

- Can characterize changes in brain state
- Disruption may indicate pathology
  - Alzheimer's Disease
  - Multiple sclerosis
- Functional connectivity explorations
  - Dynamic change
    - Effect of motor fatigue
  - Neurological change
    - Effect of Asperger's Disorder, Depression
  - Consciousness change
    - Effect of anesthesia

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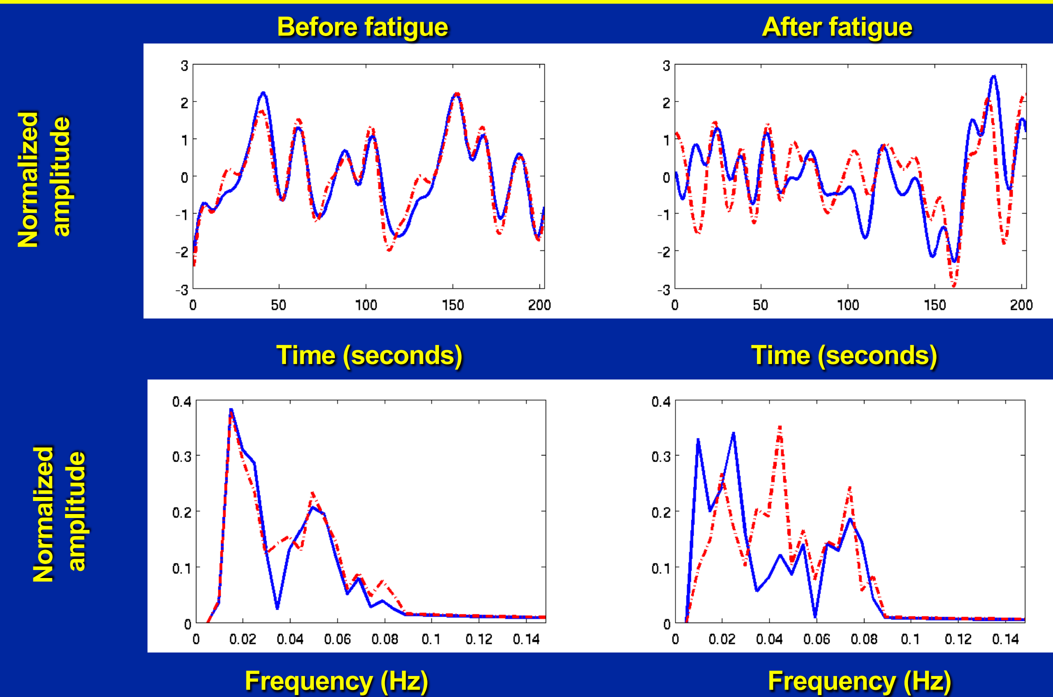
Motor fatigue

- Muscle fatigue effects activity of primary motor cortices
- Not known whether disruptive effect lasts beyond the fatiguing task
- Examined fatiguing unilateral motor task on the bilateral motor network

Methods

- 10 right-handed subjects (males, age = 32.8 ± 8.4 years)
- 3 T Siemens Trio scanner using an EPI sequence, TR/TE/FA/FOV = 750 ms/35 ms/50° /22 cm, with 10 oblique slices (parallel to AC-PC), with in-plane resolution of 3.44 mm^2
- Resting state data were acquired (subjects lying still, with fixation cross being presented), total scan time of 200 s, one scan acquired before and after a fatigue task
- Repetitive handgrips at 50% maximal voluntary contraction (MVC) level by gripping a bottle-like device, connected to a pressure transducer to measure handgrip force
- Fatigue task lasted 20 minutes, with 120 total contractions performed by each subject

Results



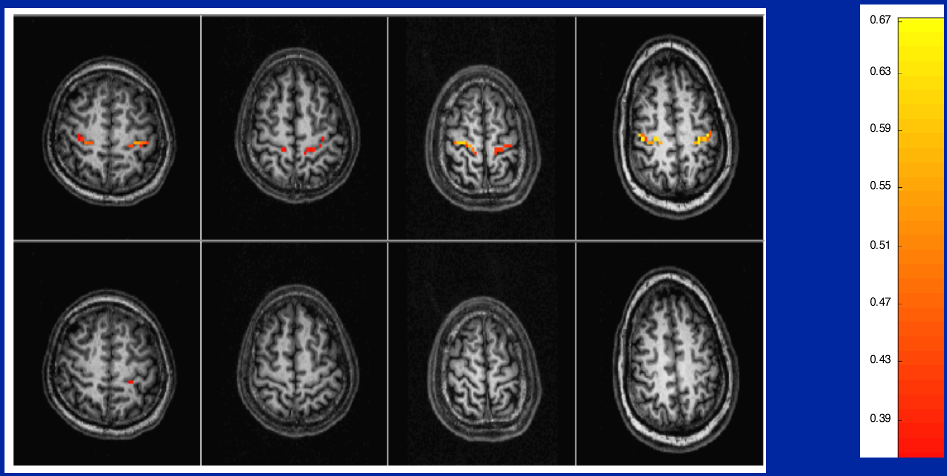
Average time courses (top) and their corresponding power spectra (bottom) for the left (blue, solid) and right (red, dashed) motor cortices for a typical subject, before and after fatigue.

- The time courses and their corresponding frequency content are more dissimilar after the fatigue task, with the left and right motor cortices' time courses having a correlation of 0.95 before and 0.64 after the fatigue task.

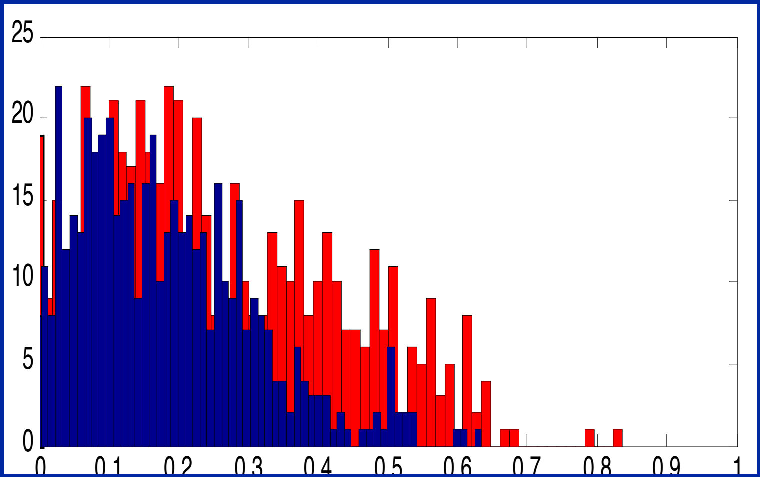
Results

Before fatigue task

After fatigue task



Interhemispheric correlation for motor cortex voxels in four of the eight subjects before and after the fatigue task.



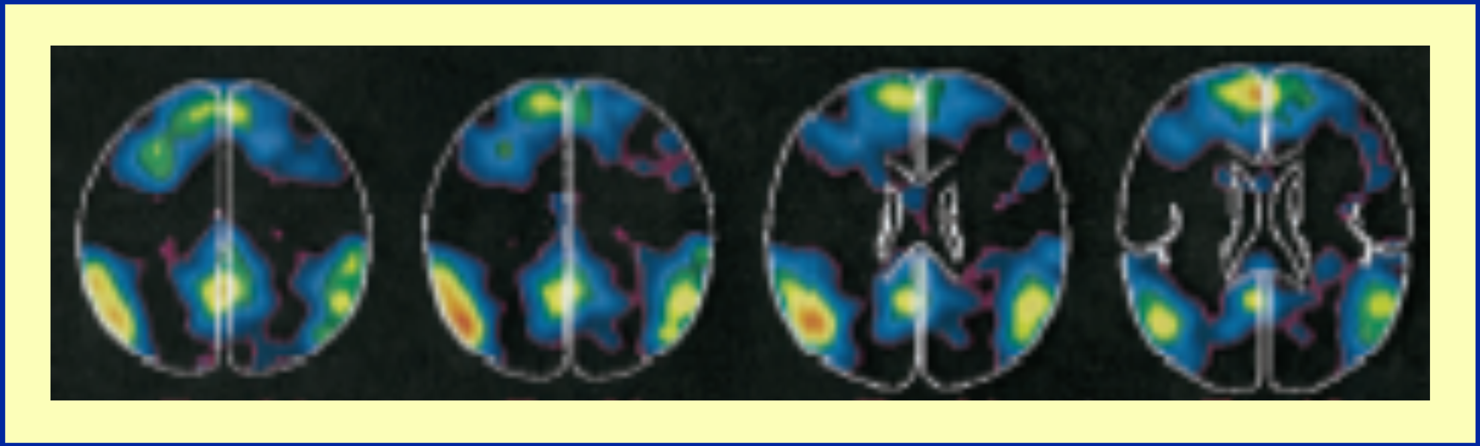
Histogram of the mean interhemispheric correlation values over all subjects before (red) and after (blue) fatigue.

- Interhemispheric correlation in both cortices decreases after the fatigue task.
- Across all subjects, there was a 72% reduction in the number of significant mean correlations ($p < 0.05$) from before fatigue.

Peltier et al., *Brain Research,* **1057**:11 (2005)

Asperger's Disorder

- Previous study* identified resting-state "default mode" network including PCC, thought to be associated with internal focus, social awareness   * Grecius et al.(2003) PNAS 100:253



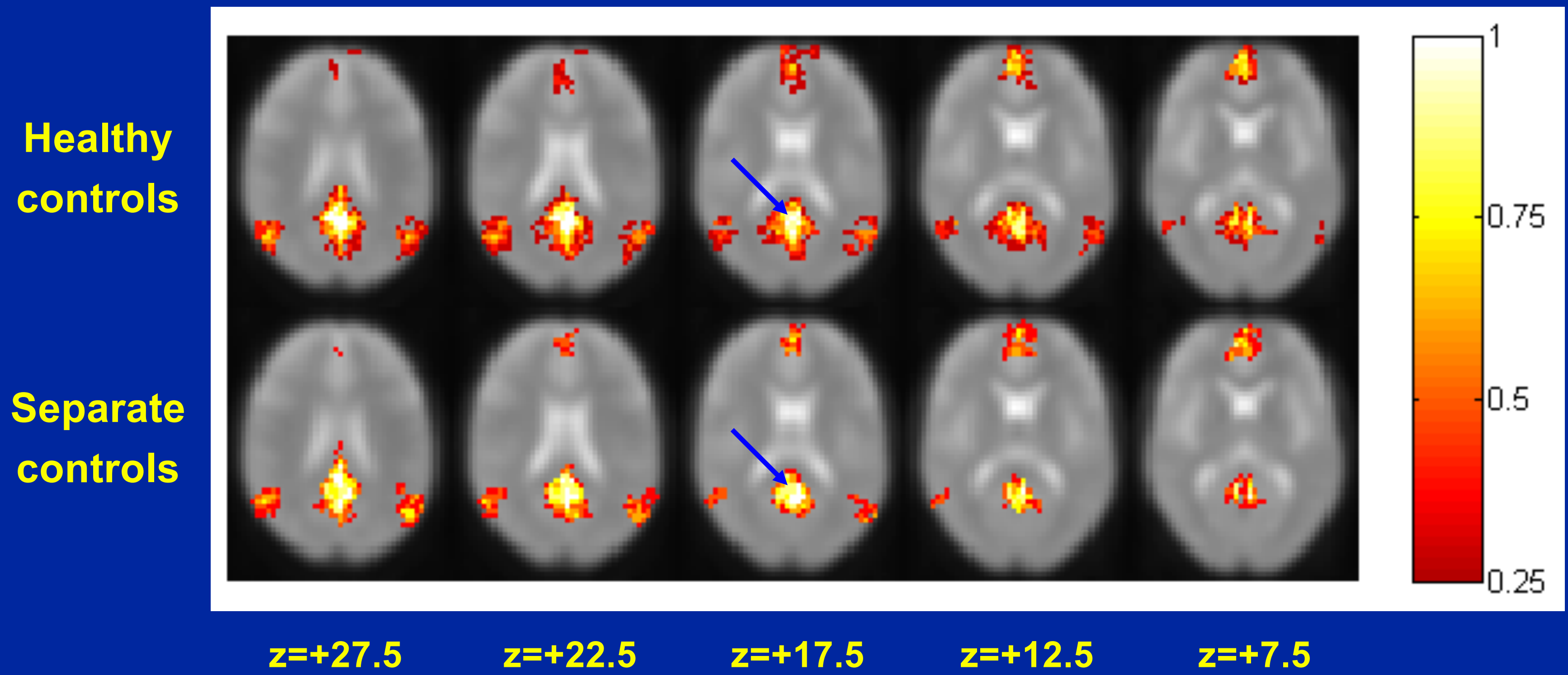
Raichle et al,. (2001) PNAS 98:676

- Subjects with Asperger's Disorder have deficits in social interaction

Experimental Design

- This work examined this network in adults with Asperger's Disorder and control subjects
- EPI acquisition on 3.0 T Siemens Trio:
  - TR/TE/FA/FOV = 750ms/35ms/50/22cm
  - Ten 5mm thick slices, in-plane resolution 3.44x3.44 mm
- Resting-state data acquired while subjects were lying still (eyes open, with visual fixation cross), with 280 volumes collected
- Eight subjects with AD, ten age-matched controls, eight separate controls as reference group

Connectivity results

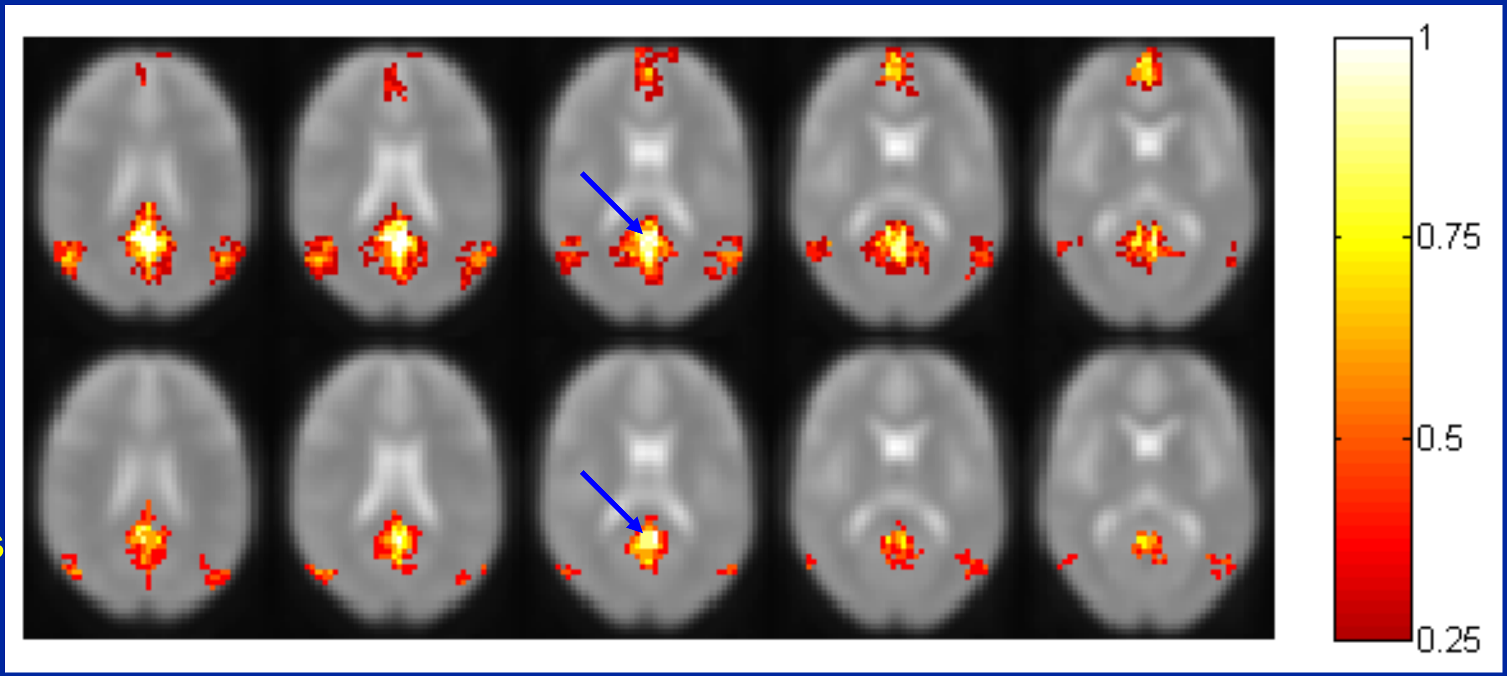


- Functional connectivity results for each group using a seed in the posterior cingulate (indicated by arrow). The average map is thresholded at 0.25 coincidence and >5 connecting voxels for viewing purposes.

Connectivity results

Healthy controls

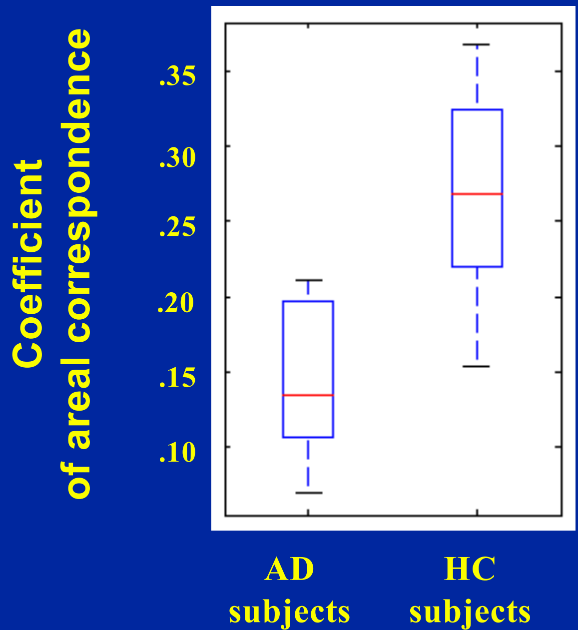
Subjects with Asperger's Disorder



z=+27.5 z=+22.5 z=+17.5 z=+12.5 z=+7.5

- Functional connectivity results for each group using a seed in the posterior cingulate (indicated by arrow). The average map is thresholded at 0.25 coincidence and >5 connecting voxels for viewing purposes.

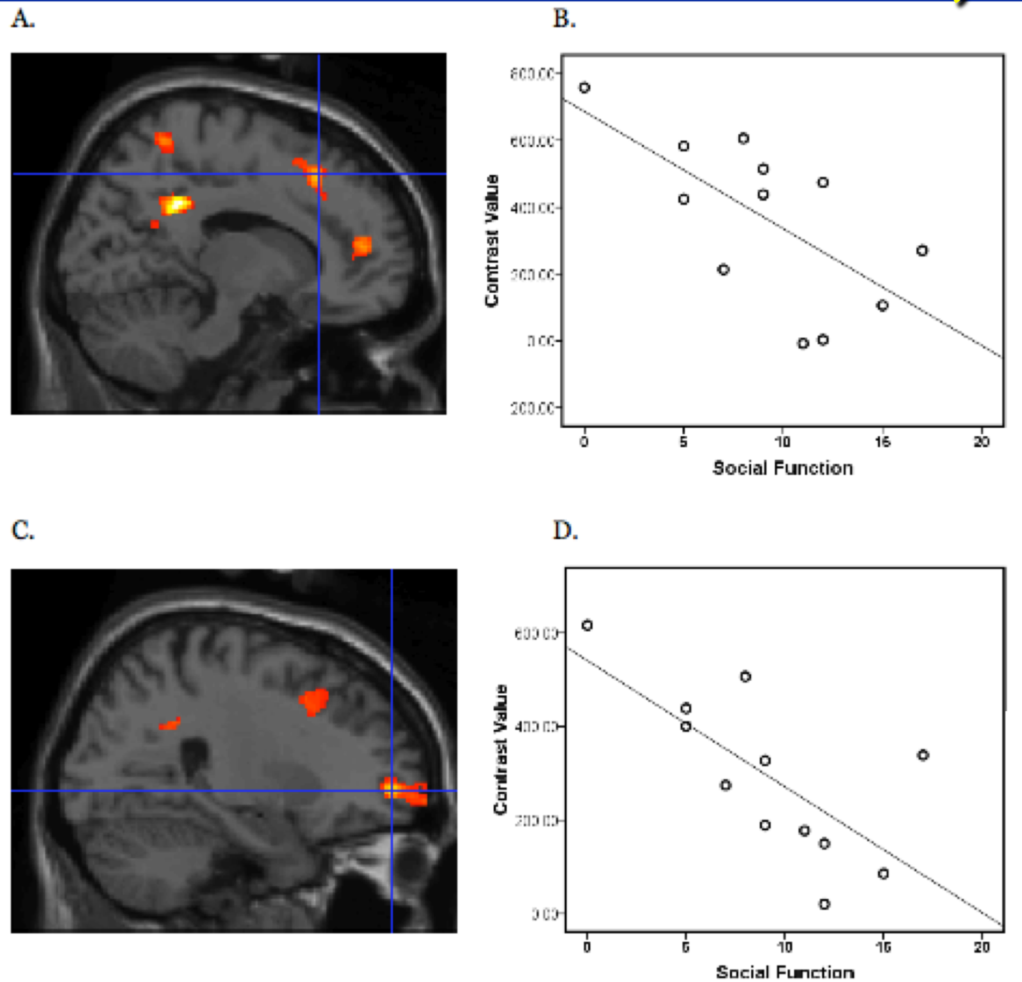
Connectivity results



#	AD	#	Controls
1	0.13	1	0.16
2	0.07	2	0.22
3	0.20	3	0.26
4	0.09	4	0.28
5	0.14	5	0.24
6	0.13	6	0.37
7	0.21	7	0.15
8	0.20	8	0.32
		9	0.32
		10	0.34
Mean (Std)	0.15(±0.05)		0.27(±0.07)

- T-test of group values revealed a significant difference ($p < 0.0015$) between the two groups.
- The separate control group connectivity map was used as a reference map
- With the current data, a threshold of 0.22 classifies Asperger's subjects with 100% accuracy, and control subjects with 80% accuracy.

Autism, continued



Recent work has related behavioral measures of social deficits in subjects with autism to resting state functional connectivity.

Figure 4. Within the ASD group, social functioning based on the ADI-R measure of total reciprocal social interaction (current), was negatively correlated with functional connectivity with two areas of the superior frontal gyrus, $t(10)=3.02$, p = .006, xyz coordinates 14 26 48 (A) and $t(10)=3.37$, p = .004, xyz coordinates 26 54 -2 (C). A higher score in the ADI-R measure indicates worse social function. For Figure 4A and 4C, the threshold was set at p = .05 with a minimum cluster size of 50 voxels. To illustrate this association, contrast values were extracted from a 4 mm sphere around the peak activation and plotted with the ADI-R measure of social function, Pearson r = -.66, P = .019 for xyz coordinates 14 26 48 (B) and Pearson r= -.707 P = .008 and for xyz coordinates 26 54 -2 (D). Although other areas correlated with social function, analyses focused on areas of the default network where group differences were found.

Monk et al., *Neuroimage* **47**:764-772 (2009).

Summary

- Functional connectivity patterns associated with the PCC differentiated between controls and adults with Asperger's Disorder

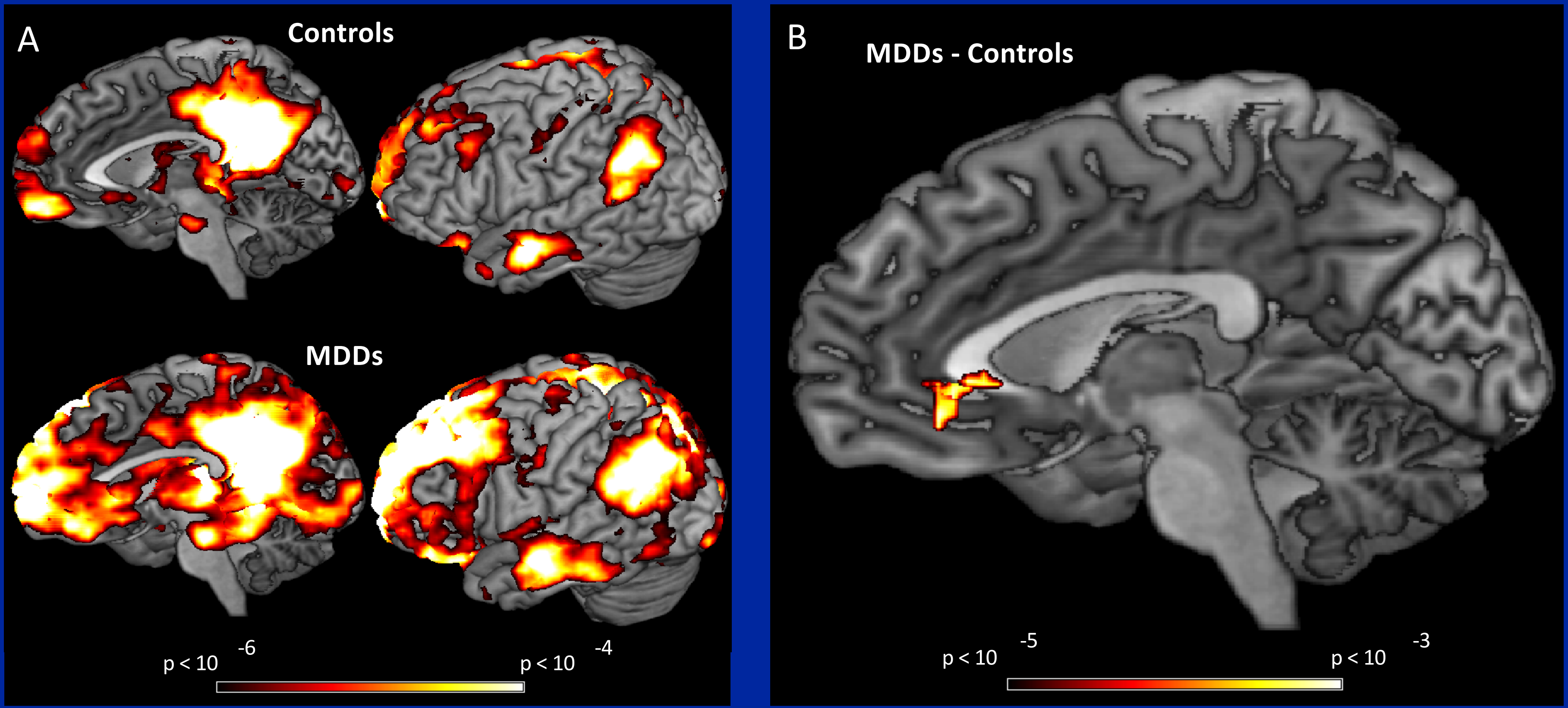
- Functional connectivity thus may serve as a potential biomarker of Asperger's Disorder

Disorders: depression

- Rumination may be a crucial psychological process tied to depression

- Resting-state might aid in studying rumination, as being engaged in a task may interfere with ruminative process
  - 15 healthy controls and 15 subjects with major depressive disorder
  - 3 T, reverse spiral, TR/TE/FA/FOV = 2000 ms/35 ms/90°/22 cm, 40 slices, 3 mm thickness, in-plane resolution of 3.44 mm^2
  - Resting-state scans before and after valenced memory task were concatenated

Depression



- Subjects with major depressive disorder show hyperconnectivity in subgenual cingulate compared to healthy controls

Berman et al., *Soc. Cogn. Affect. Neurosci.* **6**:548 (2011)

Anesthesia

- The mechanism of anesthesia, a (reversible) state of profound CNS suppression, is not completely understood
- Anesthesia is not a uniform entity, with different end-points of interest, including ablation of motor responses, memory function, and consciousness
  - Veselis. *Consc Cogn* **10**:230 (2001)
- Recent studies underline a necessity to address global disconnecting effects, besides the regional suppressive effects of anesthetic agents on isolated brain structures
  - White & Alkire. *Neuroimage* **19**:402 (2003)

Objective

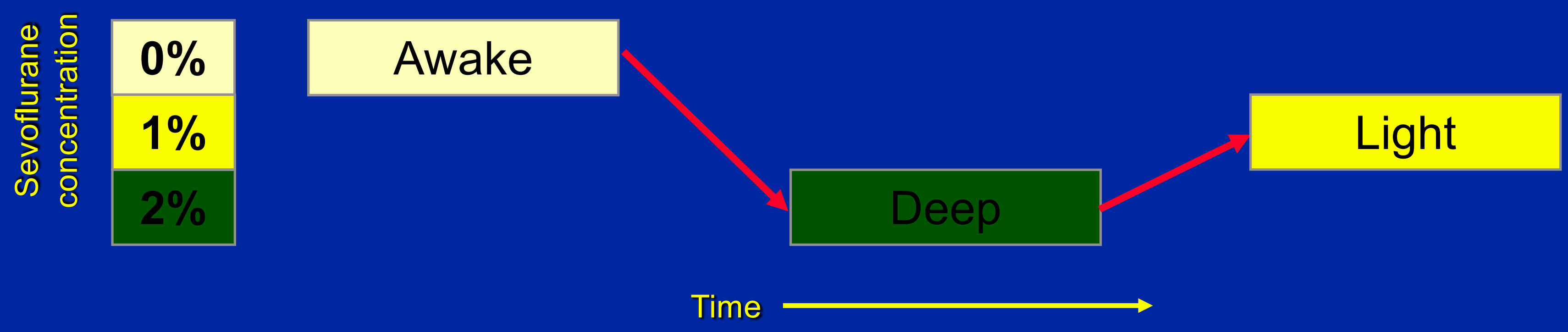
- By employing gradations of anesthetic influence, we explored the effect of anesthesia on fMRI resting-state functional connectivity of the motor network

- Examined suppression and disconnection effects

Methods

Anesthesia

- 6 right-handed, male volunteers were studied under three successive conditions: while breathing 0, 2.0 and 1.0% end-tidal sevoflurane (Awake, Deep, Light state, respectively).
- Sevoflurane concentration was held constant for 15 min to allow for equilibration at each level, after which scans were obtained.



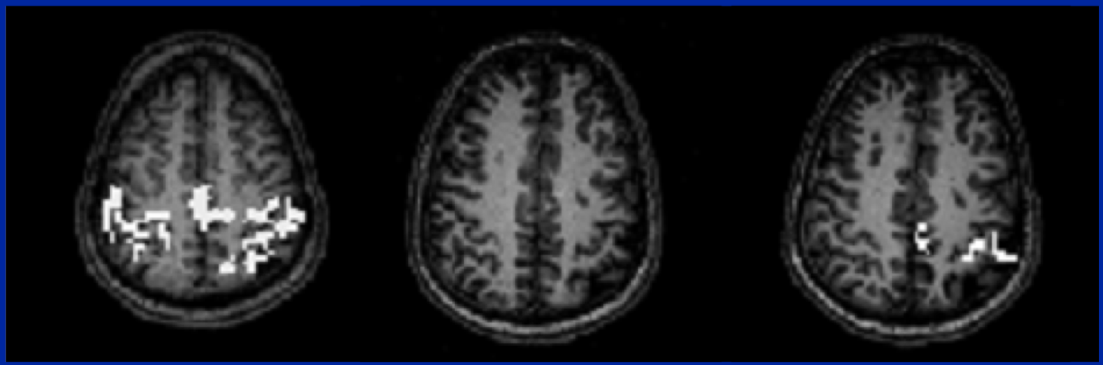
Acquisition

- EPI pulse sequence was used on a 3 T Siemens Trio scanner, TR/TE/FA/FOV = 750 ms/35 ms/50° /22 cm. Ten 5 mm thick axial slices were acquired in each TR, with in-plane resolution of 3.44 mm x 3.44 mm. In each condition, 280 images were collected.
- Data were acquired while volunteers were lying still, with eyes closed.
- Simultaneous acquisition of the cardiac rhythm was done using a pulse oximeter.

Analysis

- Formed functional connectivity maps
  - Data low-pass filtered (< 0.08 Hz)
  - Seed ROI (4 voxel block) in primary motor cortex
  - ROI timecourses detrended, averaged to form reference waveform
  - Correlated low frequency reference waveform with all other low-pass filtered data
- Maps for three slices covering bilateral motor cortex were used for analysis

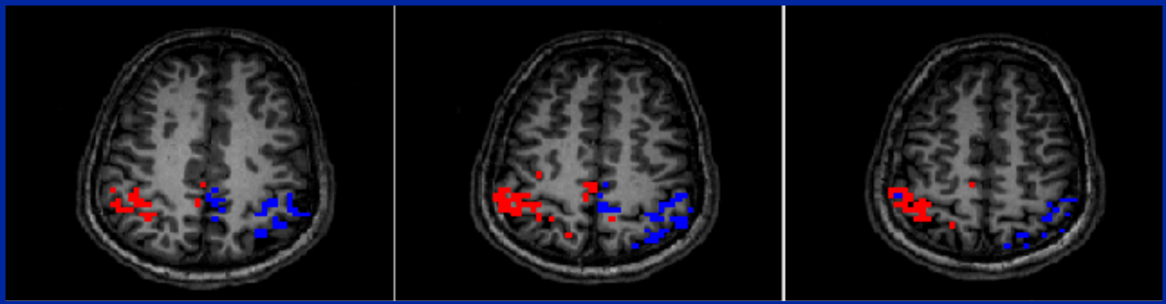
Results - suppression



- Significant voxels (r > 0.65) were reduced by 78% for light anesthesia, 98% for deep anesthesia
- Significant decrease from Awake to Deep ($p < 10^{-8}$), significant increase from Deep to Light ($p < 0.0085$)

Results - disconnection

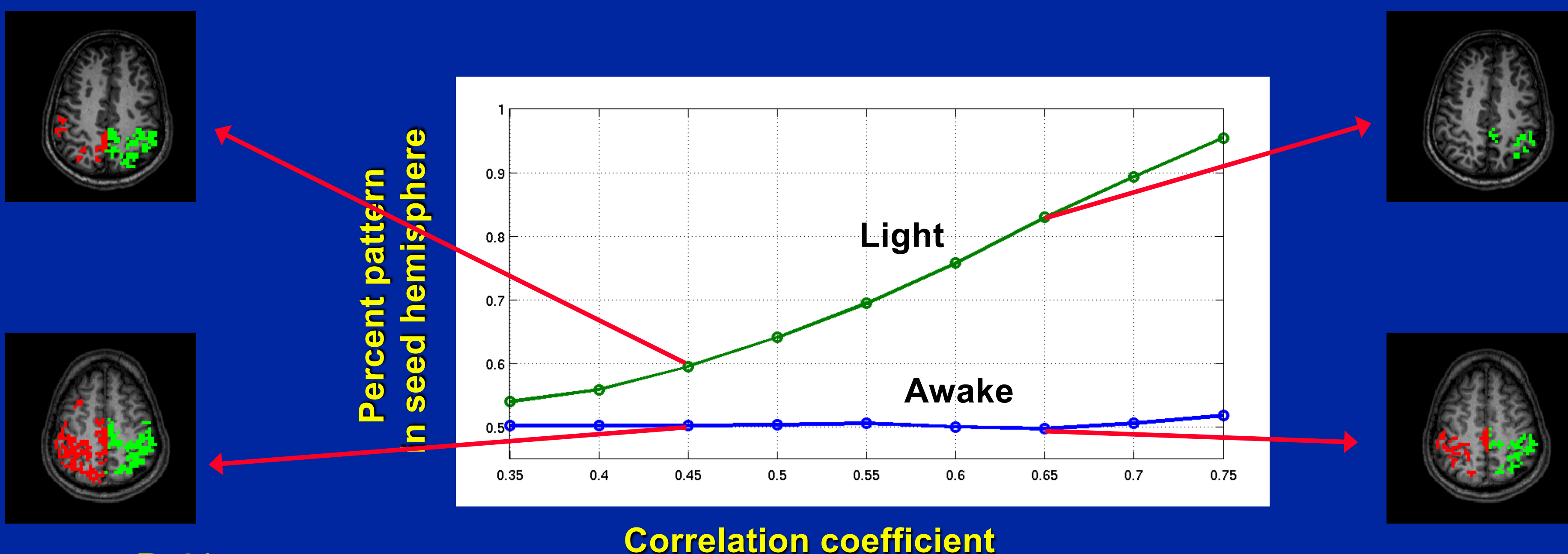
- Laterality in Light state investigated further using right and left motor seeds
- Resultant functional connectivity maps show stronger response in hemisphere of seed



Unilateral results

- Significance threshold adjusted to investigate laterality dependence on threshold

- Awake maps consistently bilateral, while Light maps have increasing unilaterality with increasing significance threshold



Summary

- Sevoflurane anesthesia significantly reduces synchronized, functionally related activations throughout the hemispheres

- Additionally, in comparing the awake state to that of light anesthesia, we observe a shift from bilateral to unilateral functional connectivity in the motor network

- This has implications for how anesthetic concentrations affect cortical activity, and for characterizing functional connectivity in brain networks

Peltier et al., *NeuroReport,* **16**:285 (2005)

- For further examples, please see:

  “Biophysical modulations of functional connectivity”,
  Peltier & Shah, *Brain Connectivity*, 1(4):267-77 (2011)

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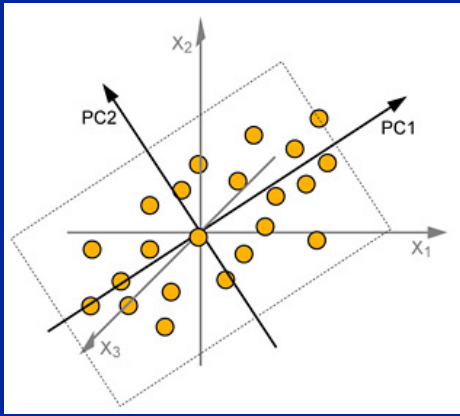
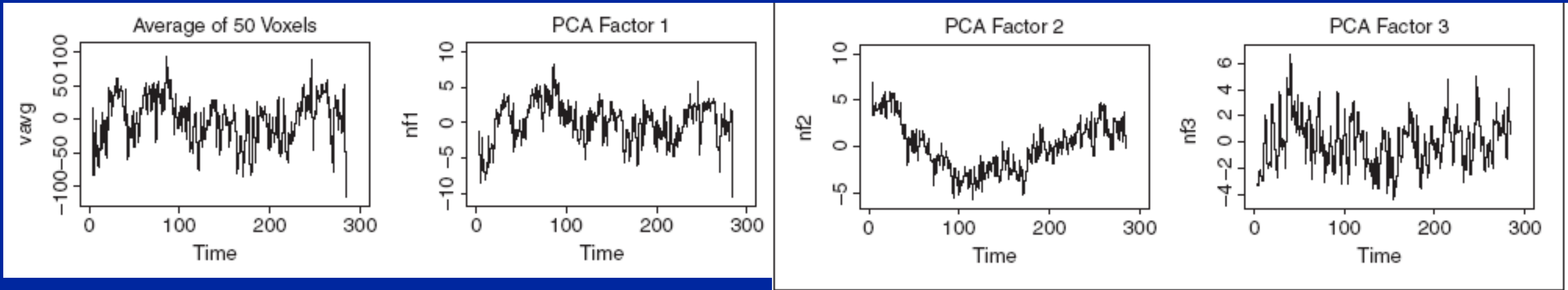
Connectivity detection

- Challenge to detect and quantify low-frequency spatio-temporal patterns in fMRI data
- Primary method: "seed clusters“ - pixel timecourses are correlated with ROI reference waveform to form functional connectivity maps
- Drawbacks: user-biased, and not easily applicable in cases where pre-supposed ROIs are not known
- Alternative: data-driven methods

Principal component analysis (PCA)

- Perform singular value decomposition (SVD) to find eigenvalues, eigenvectors, eigenimages
- Find components that explain maximal variation in the data
- Each component is orthogonal to the others





Rowe & Hoffman, Engineering in Medicine and Biology Magazine, IEEE, 25:2, p. 60-64 ,March-April 2006

Fig. 2. Graph of the average of 50 voxels in an ROI together with the first three eigenvectors of the PCA of the same 50 voxels.

Independent component analysis

- Solve source separation problem:

$$x = As$$

x - the observed data

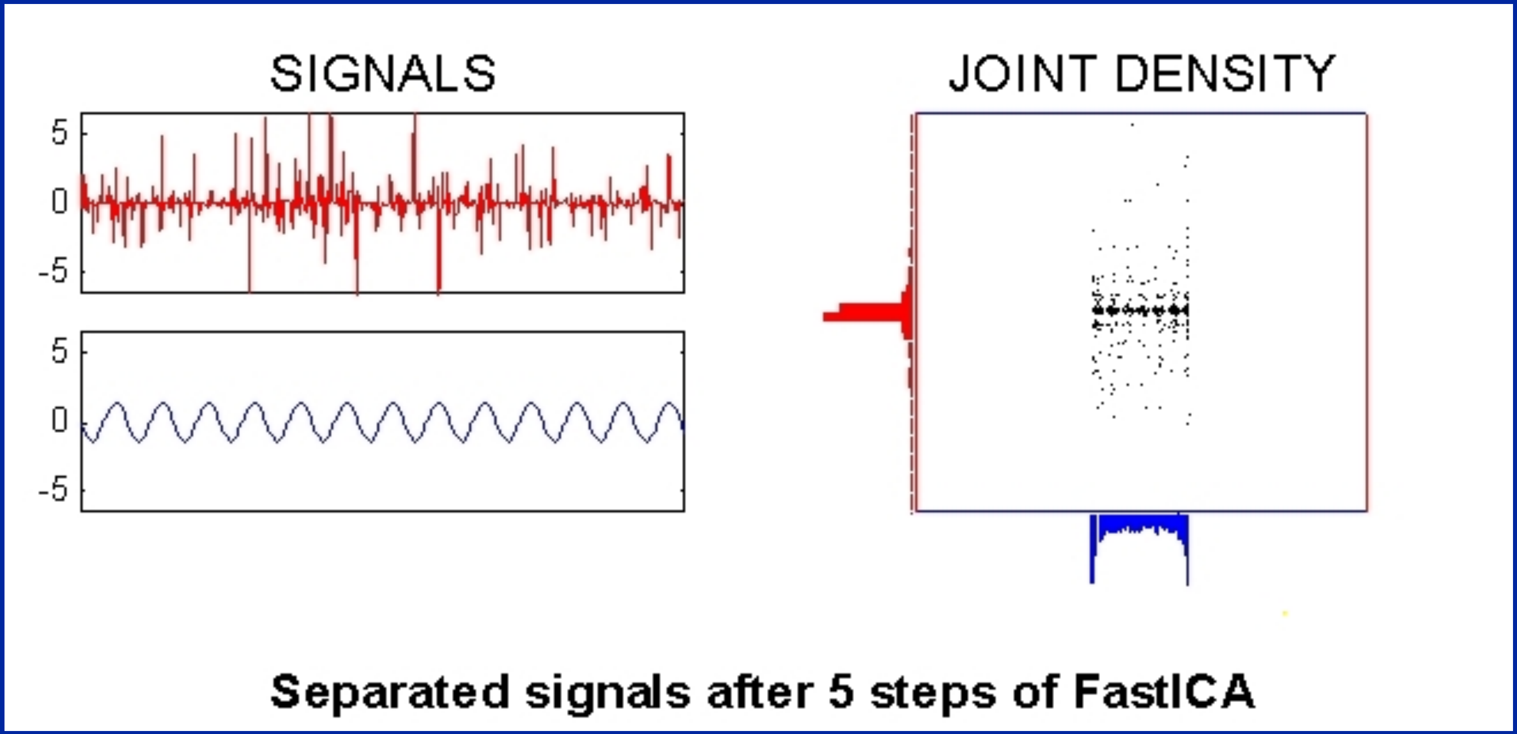
A - the unknown mixing matrix

s - the unknown source signals

- Whiten data, then isolate independent signals by maxmizing non-normality of marginal densities

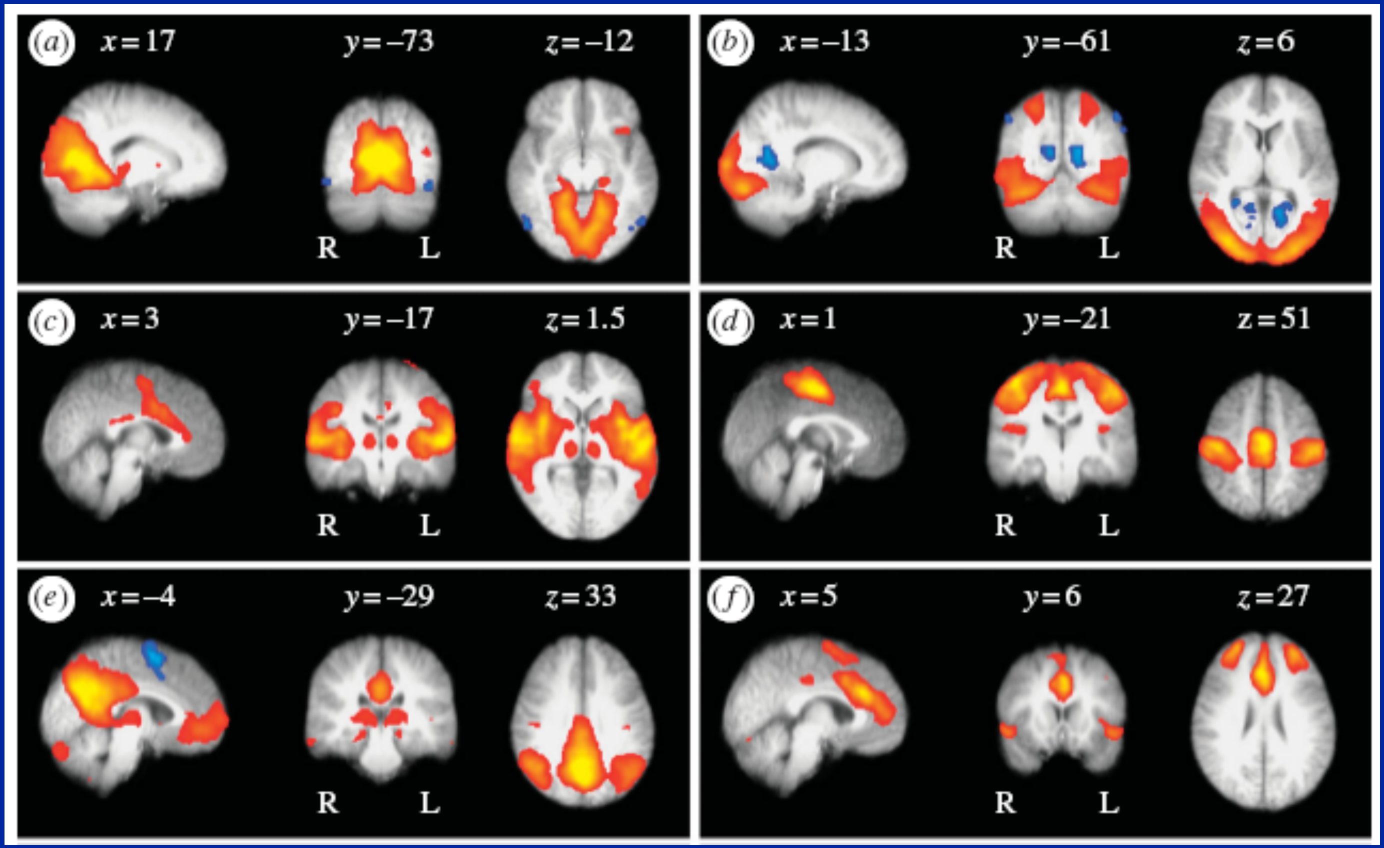
- ICA limitations:
  - Cannot determine sign of signals
  - Cannot determine order of signals

ICA



Example from http://www.cis.hut.fi/projects/ica/icademo/

ICA: Example



Beckmann, Phil. Trans. R. Soc. B (2005) 360, 1001–1013

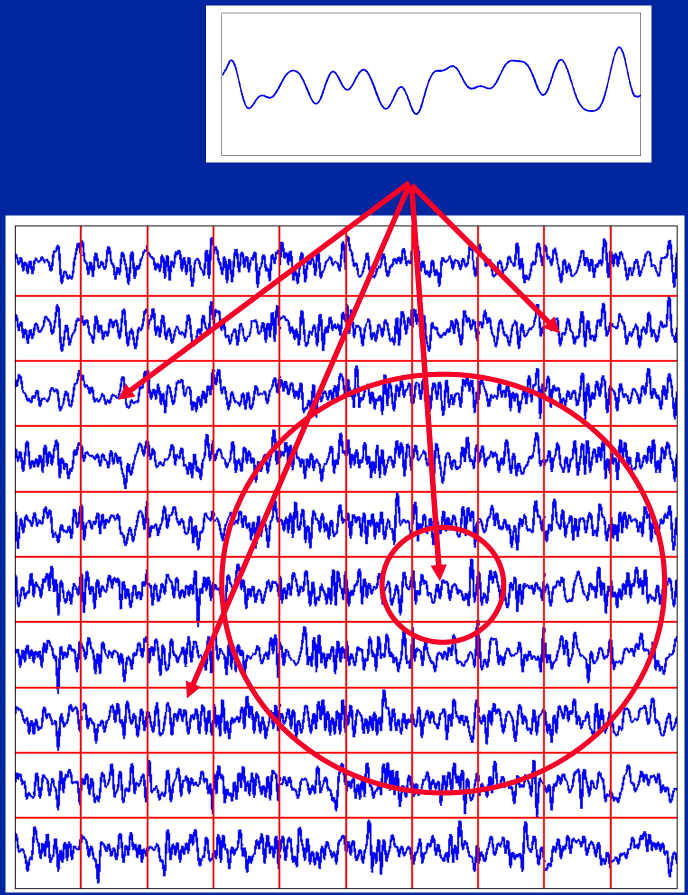
SOM algorithm

Closest exemplar $\|\mathbf{x}-\mathbf{m}_c\| = \min_i (\|\mathbf{x}-\mathbf{m}_i\|)$ $i=1,..,N$

Iterative updating $\mathbf{m}_i(t+1) = \mathbf{m}_i(t) + h_{ci}(t)*[\mathbf{x}-\mathbf{m}_i(t)]$

Neighborhood function $h_{ci}(t) = \alpha(t)*\exp(-\|r_i - r_c\|^2/(2*\sigma^2(t)))$

Voxel timecourse



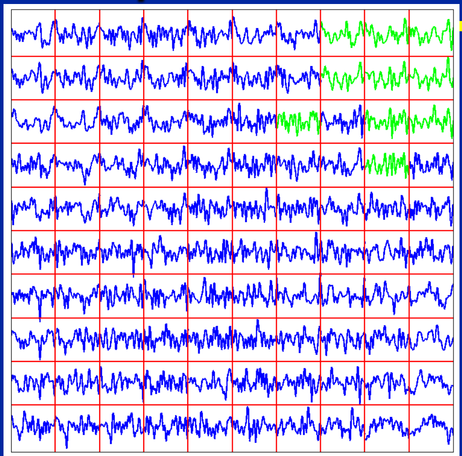
Exemplar matrix

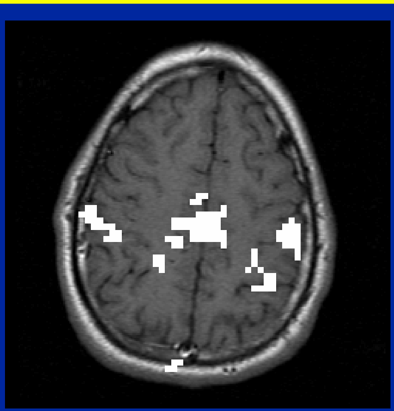
x	voxel timecourse being considered
m	exemplar timecourse
c	label of the closest exemplar
t	iteration number
$\alpha(t)$	learning rate
N	total number of exemplars
r_n	coordinate of the nth exemplar
σ	controls the width of the Gaussian kernel

- Results in topologically-ordered exemplar matrix

Clustering

Exemplar matrix

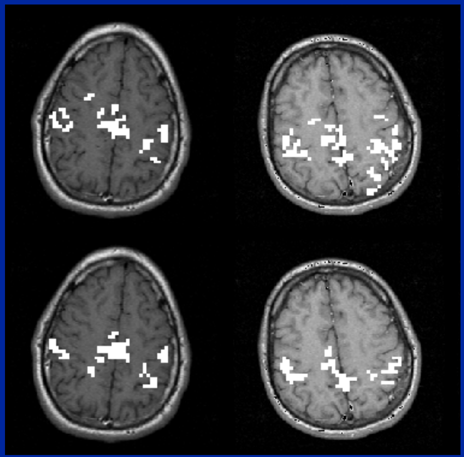




Supercluster pattern

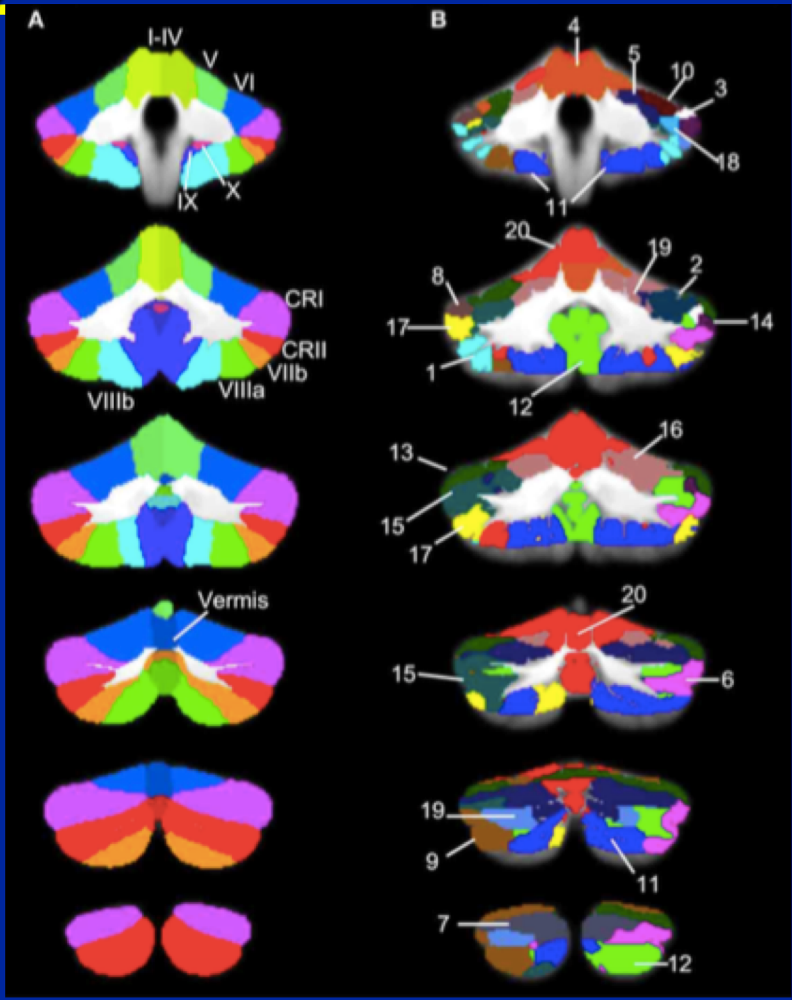
Resting state seed correlation

Resting state SOM analysis



Peltier, Polk, & Noll, *Human Brain Mapping,* **20**:220 (2003)

Anatomical parcellation **SOM parcellation**



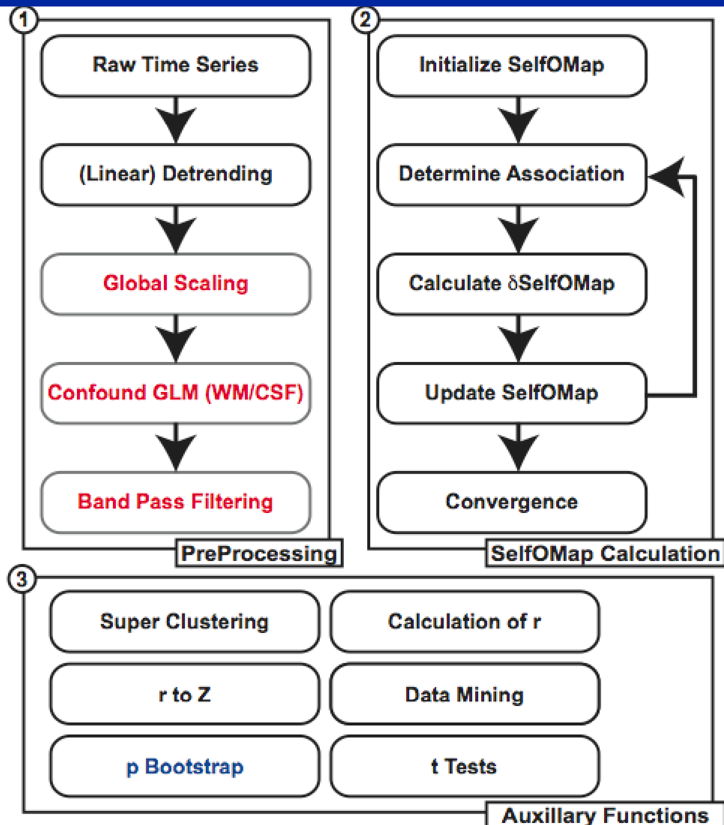
Bernard, et al. *Front in Neuroanatomy,* **6**:31 (2012)

Model-free resources

- PCA
  - MATLAB: princomp, svd
- ICA
  - FASTICA toolbox for MATLAB
    - http://research.ics.aalto.fi/ica/fastica/
  - MELODIC ICA in FSL
    - http://www.fmrib.ox.ac.uk/fsl/

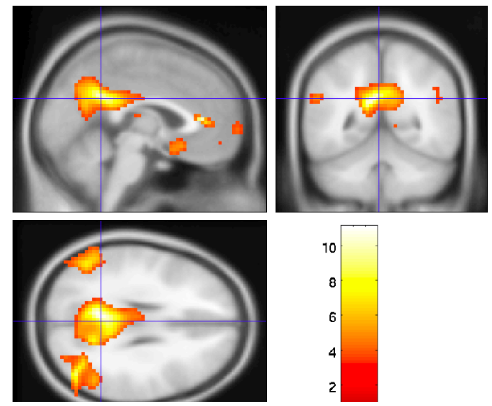
Self Organizing Map Toolbox

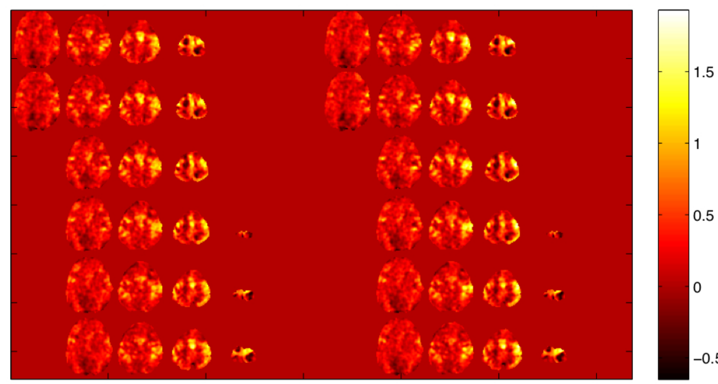
MATLAB toolbox available from: robert.c.welsh@utah.edu



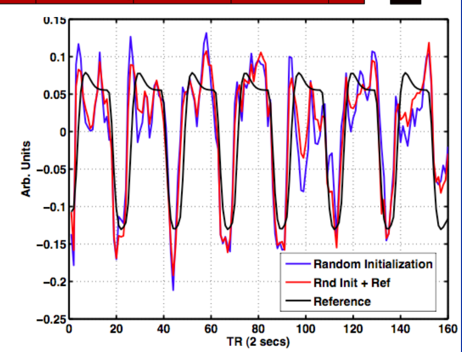
$$\sigma_l = \sigma_0 e^{-k/\tau_\sigma}$$
$$\alpha_k = \alpha_0 e^{-k/\tau_\alpha}$$
$$\vec{v}_i \rightarrow \vec{v}_i + \alpha_k \sum_{j \in i} \vec{u}_j$$
$$|\vec{u}_i| = 1 \quad |\vec{v}_i| = 1$$

Default Network





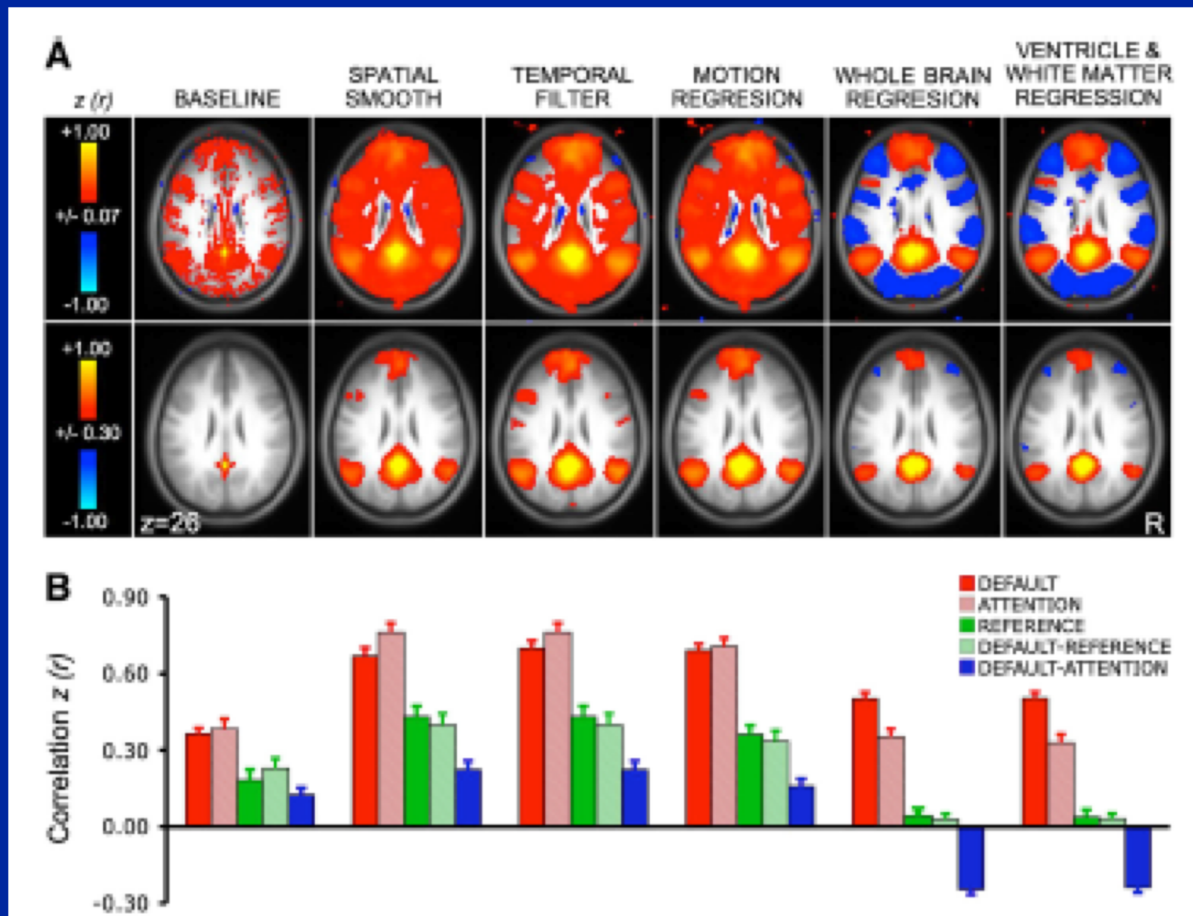
Motor Activation



Practical considerations

- Resting-state networks are affected by condition, preceding tasks
  - Consider order of experiments in study
- Resting-state networks are relatively robust over voxel size selection, duration of scans (5-6 minutes or longer)
  - Optimize for normal fMRI considerations
  - Be aware of loss of degrees of freedom in single subject analysis
- Nuisance covariates are important to consider (residual head motion, physiological waveforms, etc)

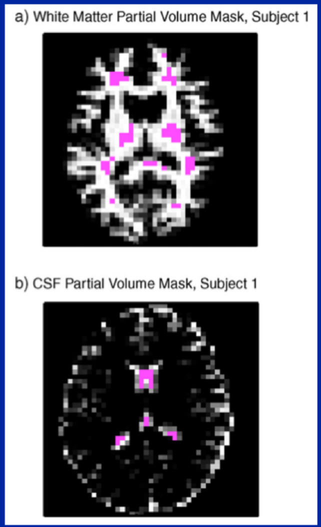
Preprocessing steps

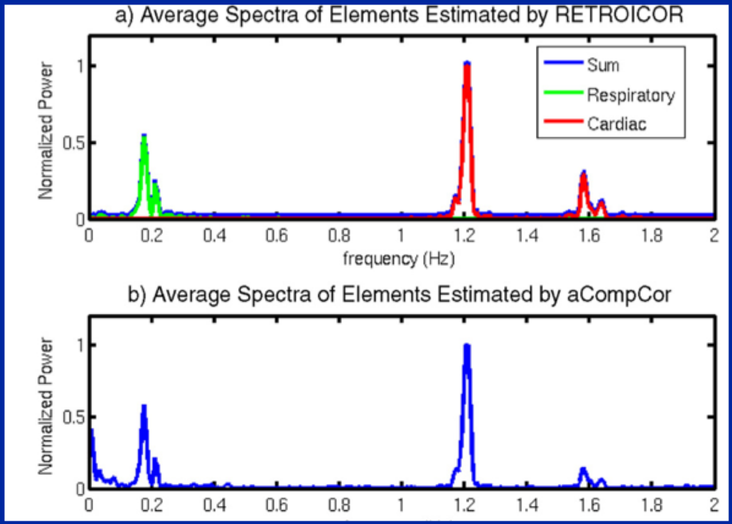


Van Dijk et al. *J Neurophysiol* **103**:297 (2010)

Physiological noise

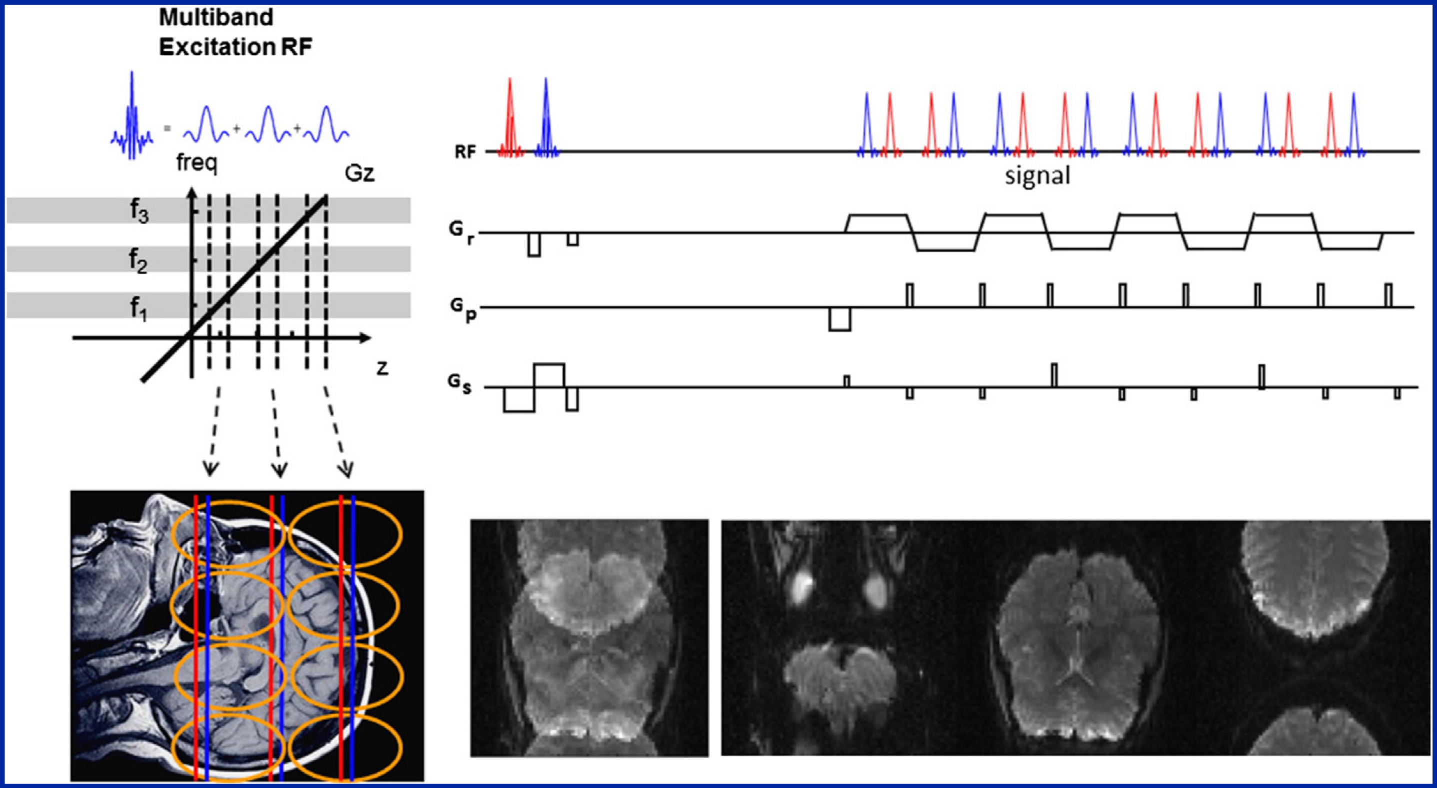
- Physiological noise can alias into band of interest
  - –Acquire physiological rhythms (respiration, cardiac) for use as nuisance covariates (e.g. RETROICOR)
  - –Can also generate estimate of physiological waveforms from data itself (e.g. CompCor)
  - –Faster acquisition can also help with this





Behzadi, et al.
NeuroImage, **37**:90 (2007)

Multiband imaging



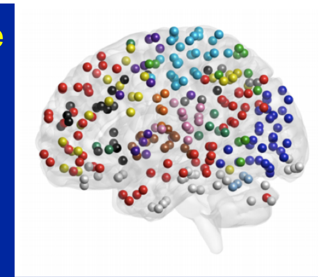
Chen, et al.
NeuroImage **104**:452 (2015)

-Modified acquisition combined with multiple coils leads to imaging speedup factor

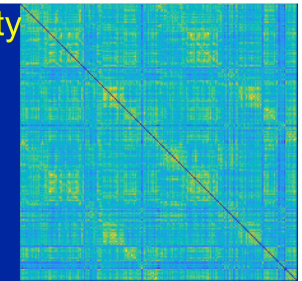
-Offers whole brain imaging in sub-second acquisitions (useful for dynamic connectivity)

Prediction examples

Parcellate



Connectivity matrix

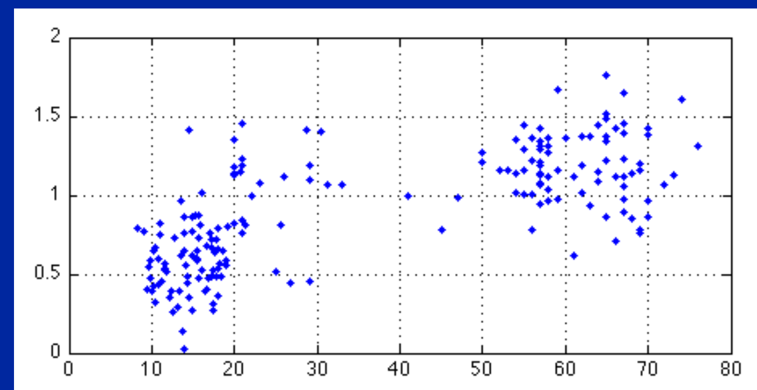


Can use resting-state connectivity maps with labels (e.g. age, behavior) for prediction

Prediction of brain maturity

- rsfMRI connectivity maps, 160 ROIs
- n=188 control subjects
- Achieved 92% prediction accuracy for young vs. old using SVM
- Support vector regression resulted in predicted brain age that tracked well with chronological age

Peltier et al., *ISMRM 2013*



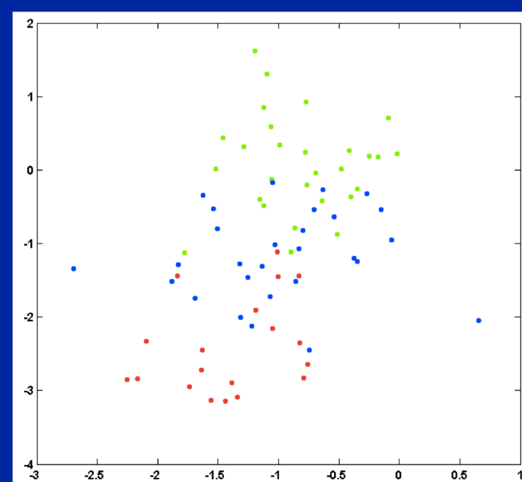
Chronological age vs predicted brain maturity

Prediction of composite memory scores

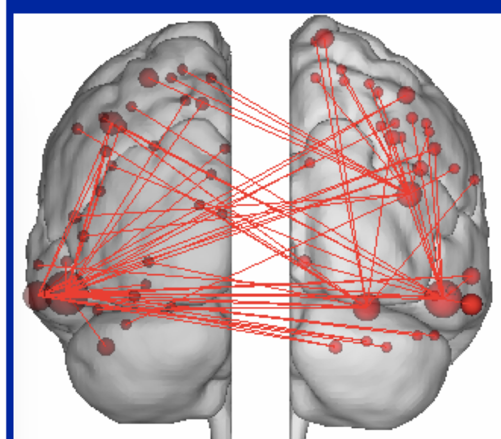
- rsfMRI connectivity maps, 272 ROIs
- n=28 control, 29 MCI, 28 AD subjects
- Significant positive relationship was found (r=0.35, p=.001) using Connectome Predictive Modeling
- Nodes with highest degree of connection were found in regions related to memory processing

Peltier et al., *ISMRM 2019*

Actual composite memory scores



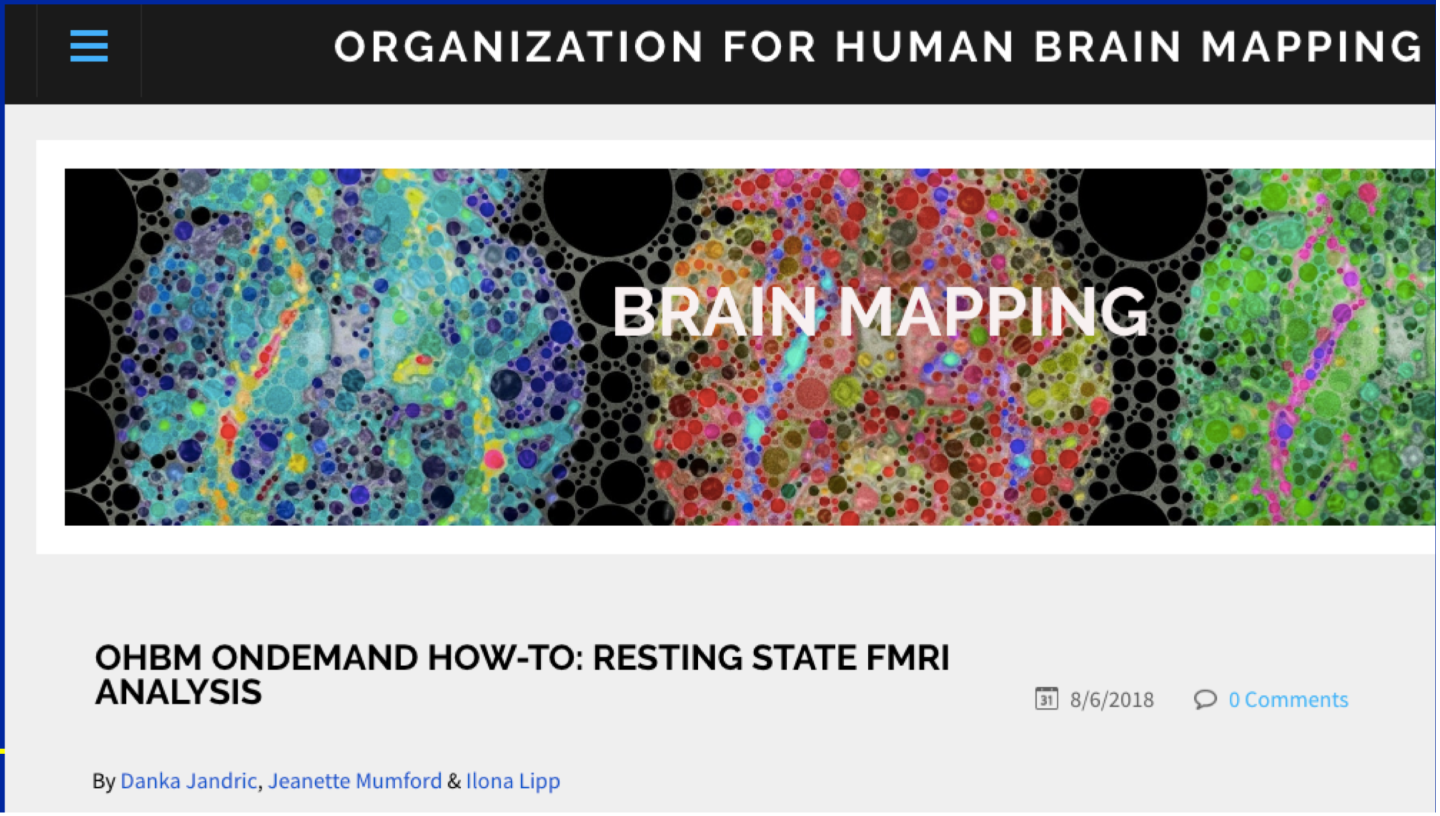
Predicted brain scores



Significant nodes

Resource: www.ohbmbrainmappingblog.com

Recent OHBM blog (8/6/2018) has comprehensive resting-state analysis overview, with links to numerous talks and papers



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