THE UNIVERSITY OF NEW MEXICO ◆ HEALTH SCIENCES CENTER
SCHOOL OF MEDICINE

Real-Time Functional MRI

Stefan Posse, PhD

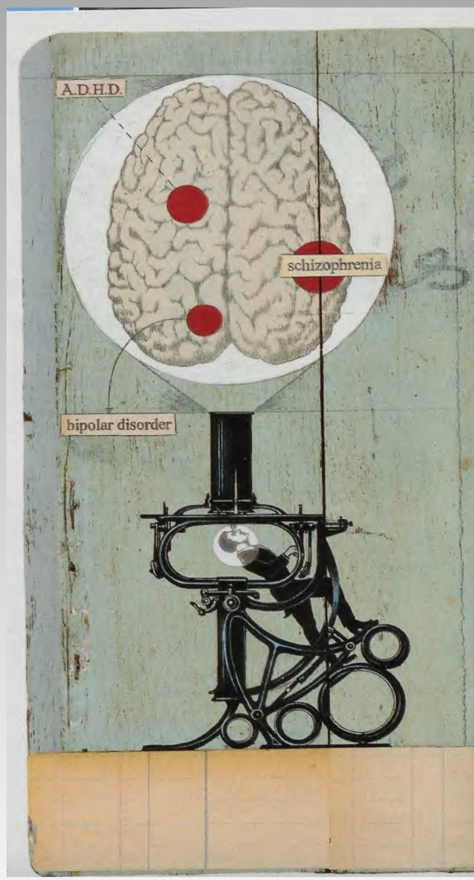
Depts. of Neurology and Electrical & Computer Engineering,
and Physics and Astronomy
Univ. of New Mexico, Albuquerque, New Mexico, USA

The Expanding Role of MR based Functional Neuroimaging

- Neuroscience Research
  - Spatial-temporal brain organization
  - Characterization of individuality (creativity, intelligence,…)
  - Neurofeedback
- Clinical Applications
  - Alteration of functional networks in neurological and psychiatric disease
  - Presurgical mapping of brain function (brain tumor, epilepsy,…)
- Other Applications:
  - Mind reading (lie detection)
  - Neuro-Economics, Neuro-Marketing, Neuro-Law
  - Brain-controlled computer games
  - …

- Brain scan can read your mind (BBC 2007)
- The fMRI Brain Scan: A Better Lie Detector? (Times Magazine 2009)
- Can brain scans tell us who makes a good chief executive? (BBC 2010)
- Brain scans may someday detect autism (CNN 2011)

Brain Scans…



The Therapeutic Mind Scan
(SPECT, fMRI, MRS)
NYT, Feb. 20, 2005

"Your car keys are under the sofa, and you crave marshmallows with peanut butter."

Adapted from
www.CartoonStock.com

BRAIN
COMPUTER
INTERFACES

Outline

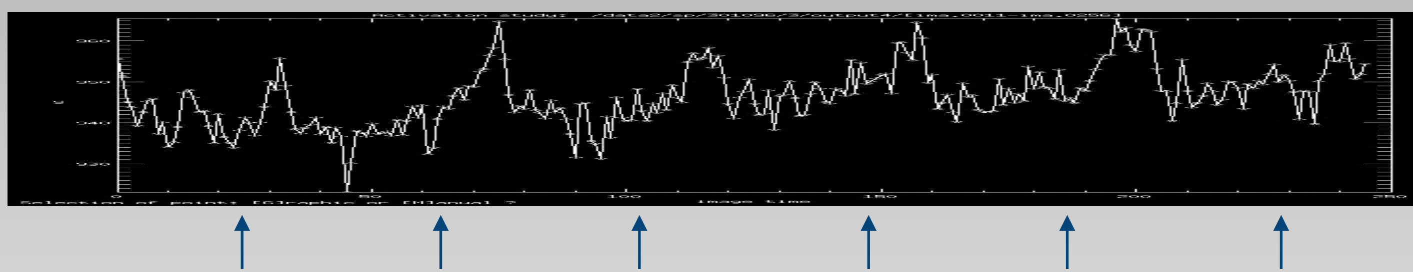
- Background and historical perspective
- Data Acquisition and Analysis Methods
- Neuroscience Applications
- Clinical Applications
- Works-in-Progress
- A practical example

Definitions of Real-Time fMRI

- Finish data analysis shortly after the scan is finished (near real-time fMRI)
  - See the activation patterns emerge as the scan progresses (initial definition of real-time)
    - Capture changes in activation over short periods of time (single blocks or single trials)
      - Single trial: *Non-averaged* response to single light flash, movement or thought process
      - Can fMRI even capture neuronal activity?

The Dawn of Real-Time fMRI in the mid-90s

- The realization of single trial sensitivity in fMRI, initially shown by Bob Savoy



Visual cortex response to single 50 ms light flashes

- Computational power: Cardiac imaging requires online image reconstruction
- Advances in statistics: Cumulative correlation analysis (Cox et al 1995)

Real-Time fMRI: Motivation

- Monitor data quality and scan success (in patients that are hard to recruit or before surgery)
- Monitor changes in attention and subject performance (in uncooperative patients)
- Optimize paradigm and scan parameters
- Neuro-feedback to control localized brain activation for therapeutic use (motor learning, control of cognition,…)
- Watch your own brain activation!

✓ Rapid results – time and cost saving

Real-Time fMRI: Challenges

- Computational power
- Statistical power
  - Group average vs. single individual
    - Within subject averaging vs. single trial
- Sensitivity to transients
  - Head movement, swallowing, eye movement,…
  - Physiological signal fluctuation (cardiac, respiratory)
  - Resting state signal fluctuation
  - “Extraneous thoughts”
- Human - machine interface
  - Information overload and observer bias
  - ➢ Team effort
  - ➢ Automated interpretation (e.g. classification) desirable

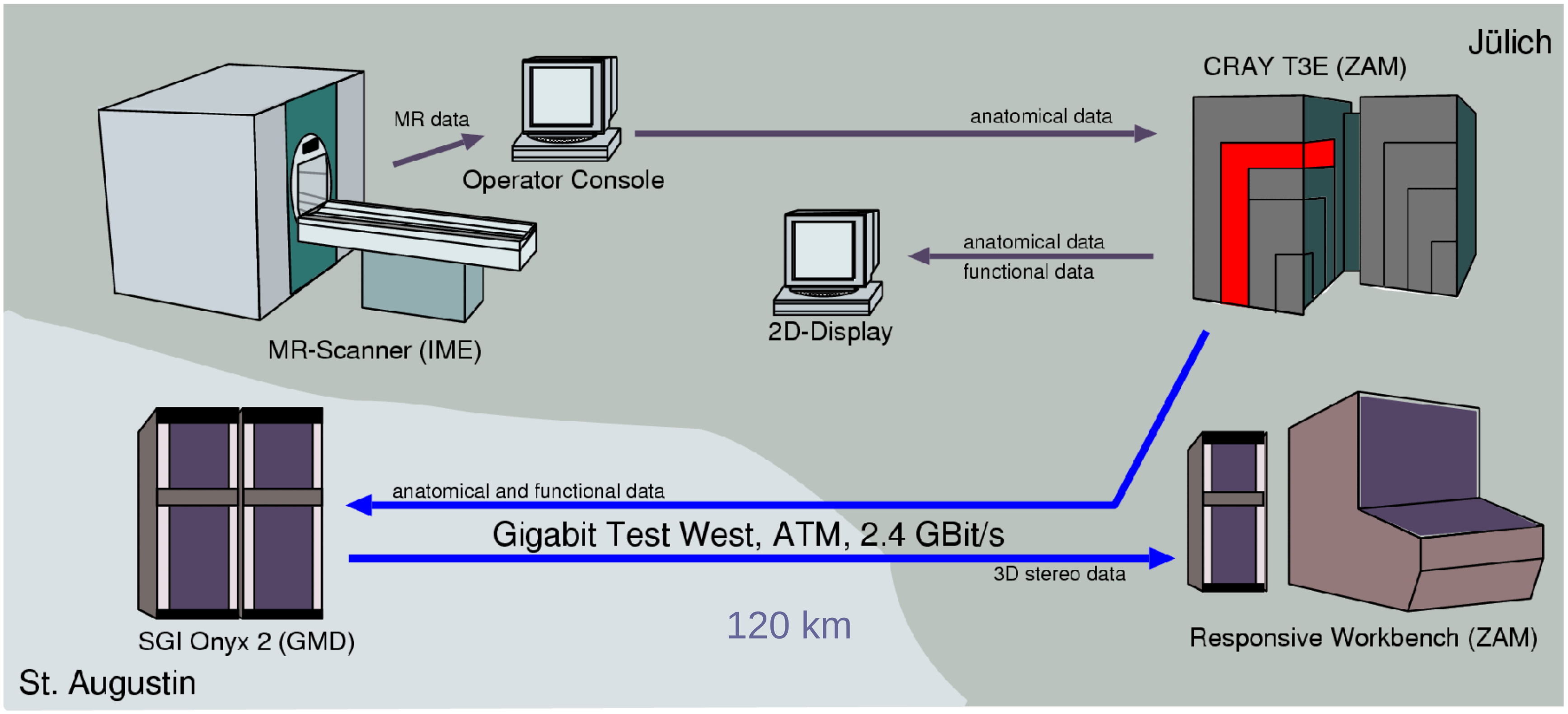
Method Development – The Early Years

- 1995. *Cox et al.*: Cumulative correlation analysis
- 1997. *Goddard et al.*: Parallelized on-line analysis
- 1998. *Cohen et al.*: Real-time artifact detection
- 1999. *Voyvodic*: Real-time paradigm control, physiology, behavior and statistics
- 2000. *Gembris et al*.: Sliding window correlation analysis and reference vector optimization

Method Development – More Recent Developments

- 2001. *Smyser et al.:* Multiple linear regression
- 2003. *Bagariano et al.*: Real-time general linear model
- 2003. *Esposito et al.*: Real-time independent component analysis
- 2007. *LaConte et al*.: Brain state classification
- 2008. *Lee et al*: Atlas based fMRI in real-time

Real-Time fMRI for Telemedicine using Distributed Computing



Eickermann et al., IEEE Concurrency 2000

Intra-operative real-time fMRI

Gering and Weber, JMRI 1998

Neuroscience and Clinical Applications

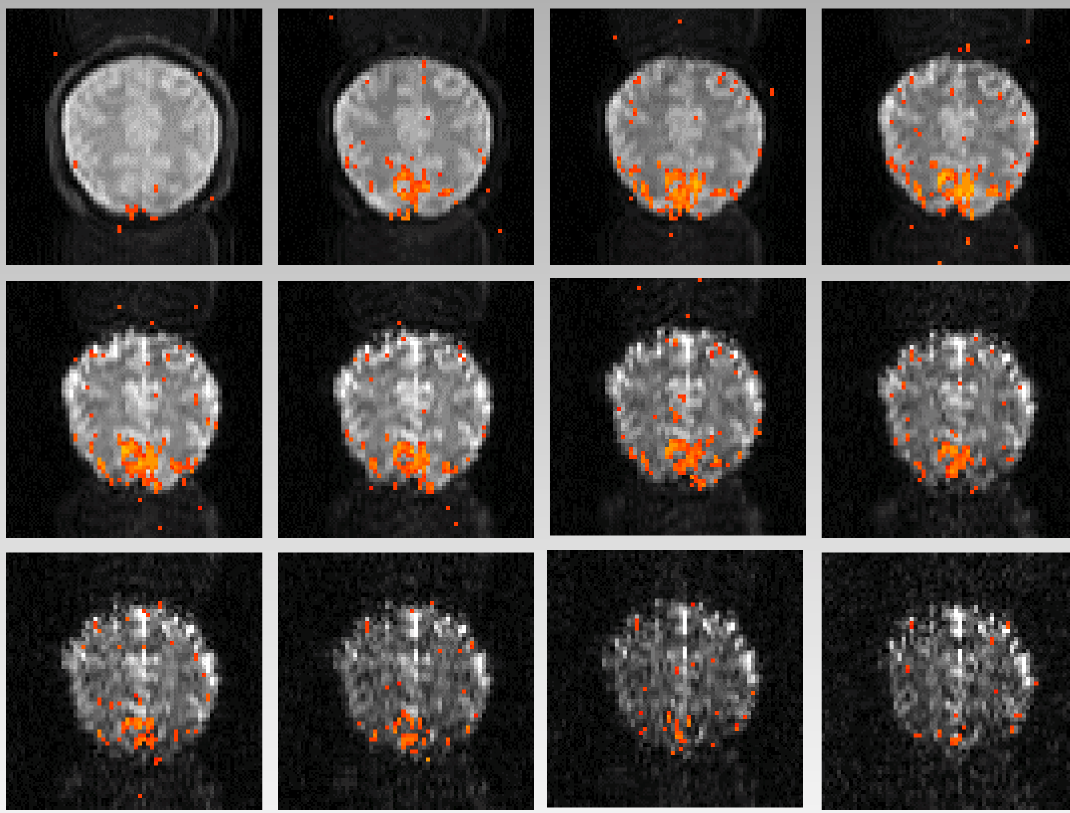
- 2001. *Posse et al:* Single trials in real-time
- 2002. *Yoo and Jolesz*: fMRI neurofeedback
- 2003. *Posse et al*.: Mood induction using feedback
- 2003. *Weiskopf et al.*: Physiological self-regulation
- 2004. *DeCharms et al*.: Learned regulation of brain activation
- 2005. *DeCharms et al*. (PNAS): Modulation of pain perception in chronic pain patients
- 2007 *Caria et al.*: Regulation of anterior insular cortex
- 2009. *Lee et al.*: Brain-machine interface
- 2011 Shibata et al. (Science): Perceptual learning neurofeedback

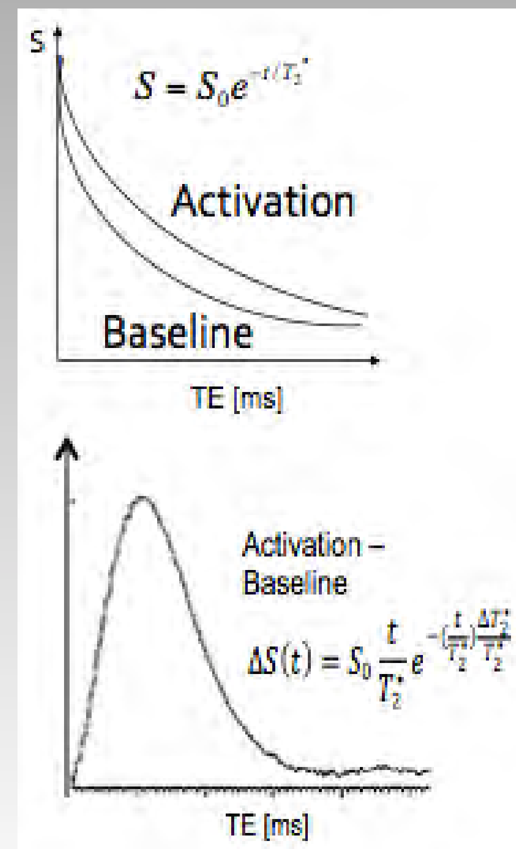
Real-Time fMRI Software Tools

- All major MR manufacturers have basic real-time fMRI analysis tools integrated in their scanners
- Turbo-BrainVoyager (Brain Innovations)
- AFNI with plug-in (NIH)
- TurboFIRE (UNM)
- Custom designed packages for specific applications (Omneuron, La Conte,…)

TE-Dependence of BOLD Contrast using Multi-Echo EPI

1.5 T, TE: 12-213 ms (20 msec/image)





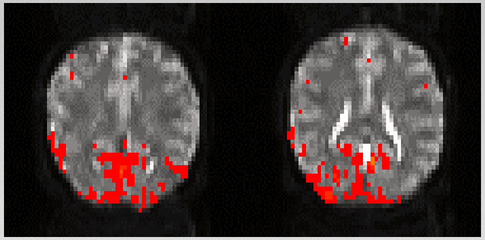
Posse et al., MRiM 1999

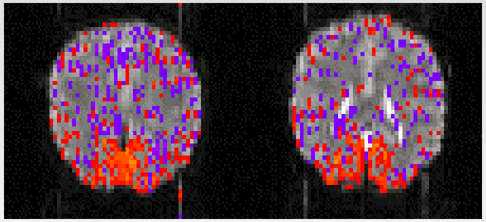
Optimization of BOLD Contrast

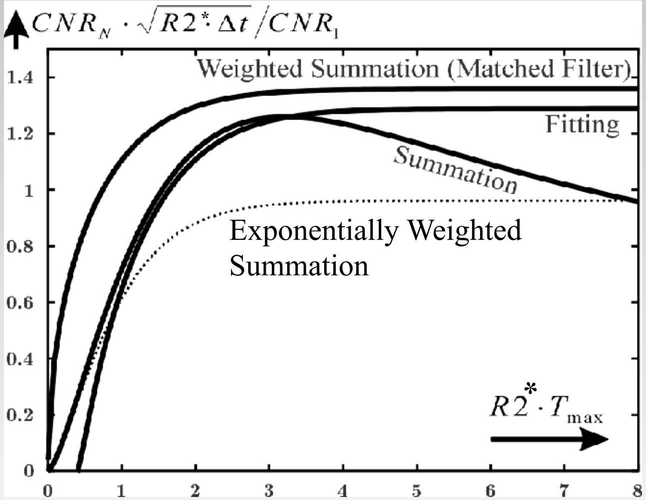
- Multi-echo averaging maximize BOLD sensitivity
  - Linear
  - Weighted by expected BOLD contrast
  - Average activation maps at different TEs or individual images

Weighted
12-echo
average

EPI

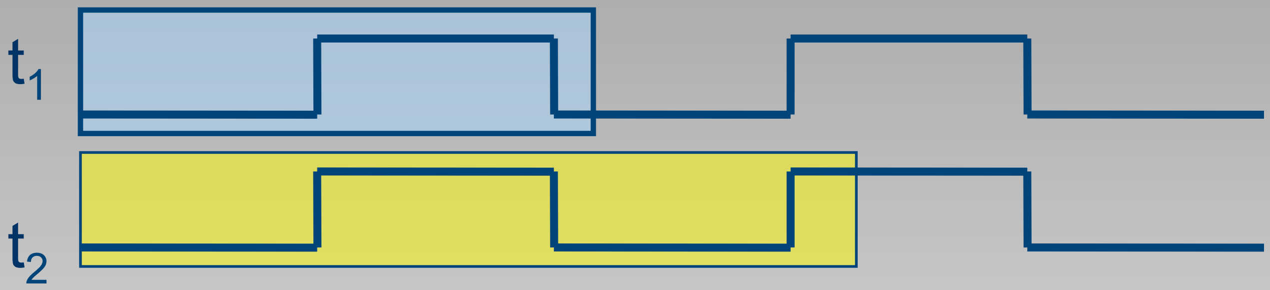




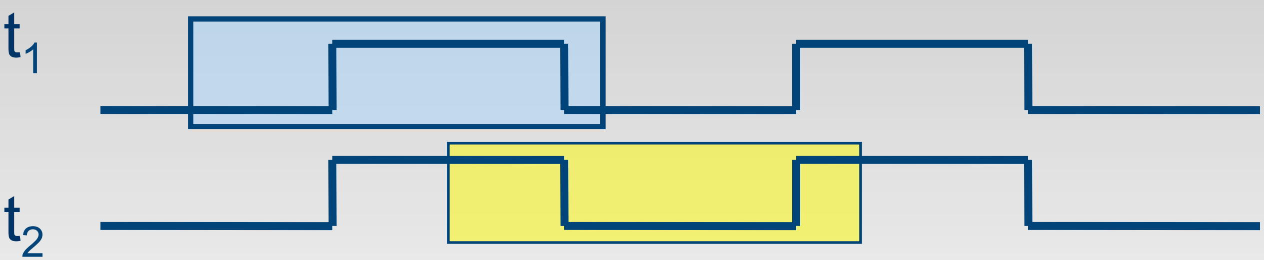


Posse et al., MRiM 1999

Statistical Analysis: Cumulative vs. Sliding Window

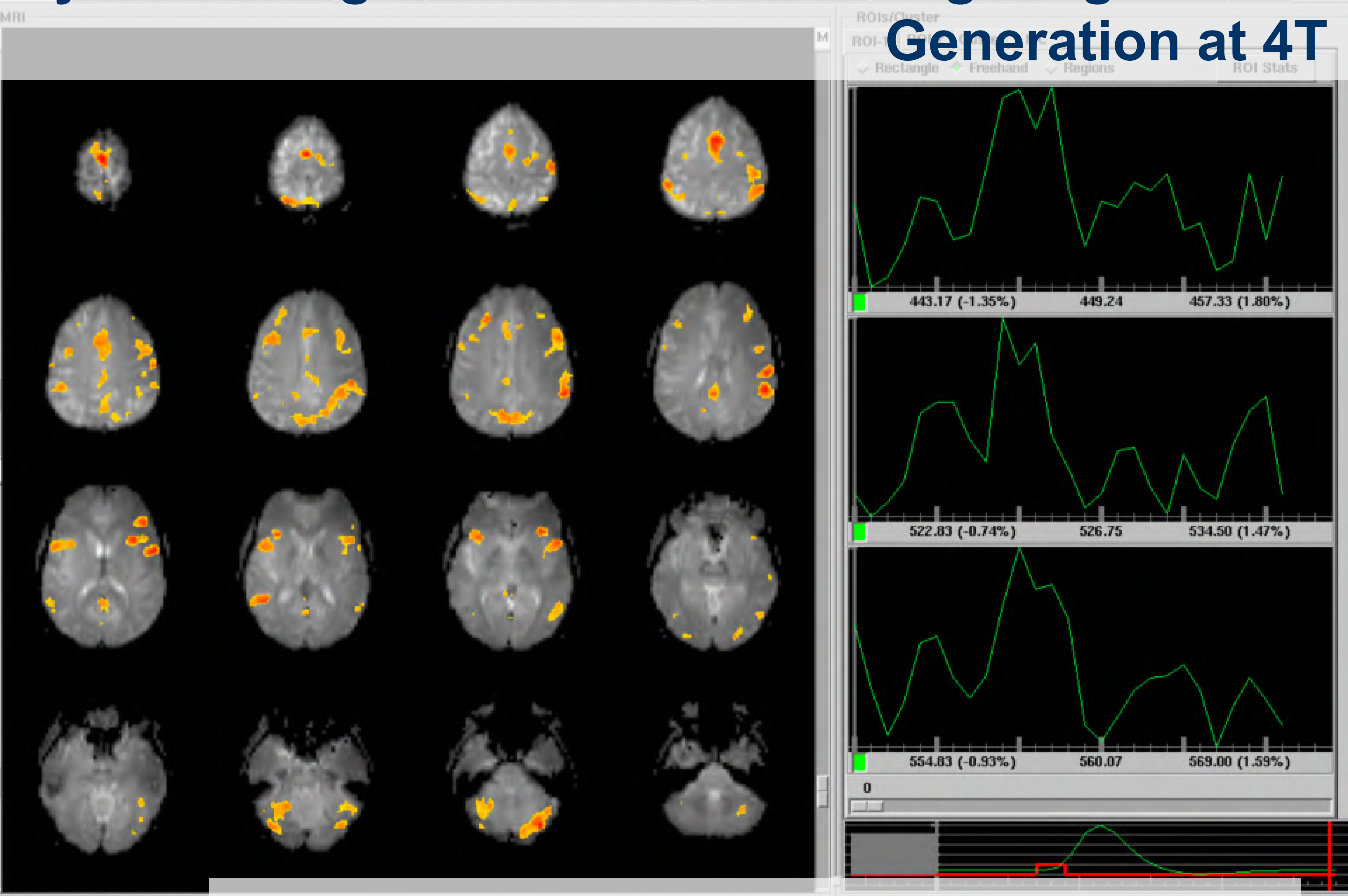


Decreasing sensitivity to functional signal changes as scan progresses (Cox et al., MRM 2005)



Constant sensitivity to functional signal changes during entire scan, but sensitive to transients (e.g. movement) (Gembris et al MRM 2000)

Dynamic Cognitive Networks during Single Word Generation at 4T



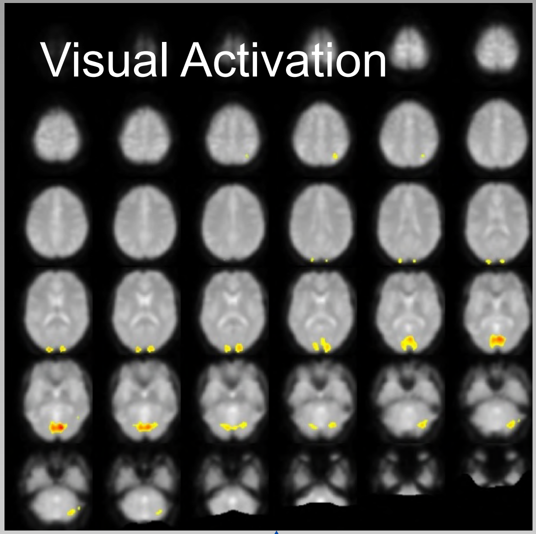
Posse and Mayer, Abstr. Soc. Neuroscience, 2004

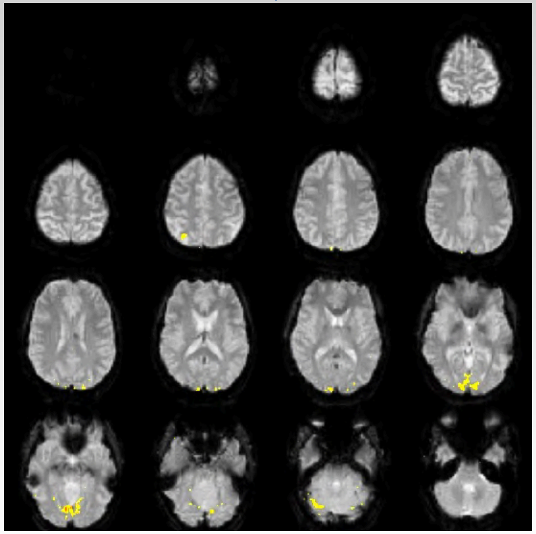
Real-Time Spatial Normalization in Reference to Talairach Atlas

1. *Conventional approach*

   Map individual brain into atlas space

   Disadvantages: resampling is computationally intensive, spatial smoothing is required

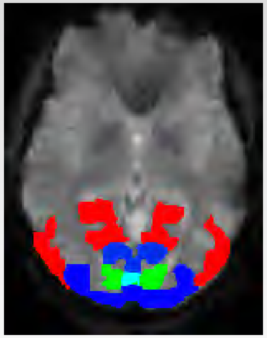




2. *Inverse lookup table approach*

   Map Talairach Atlas into individual brain using lookup table

   Advantages: fast, preserves original images

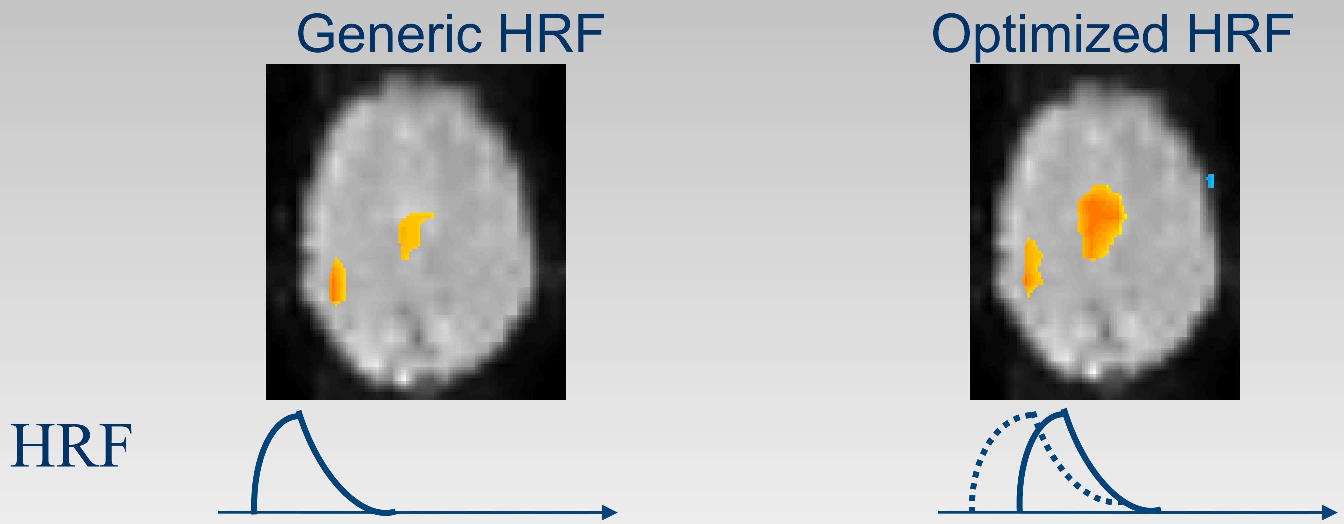


Gao and Posse, Abstr. HBM 2003

Reference Vector Optimization Enhances Functional Sensitivity

Hemodynamic Response Function varies with brain region, trial repetition and baseline CBF!

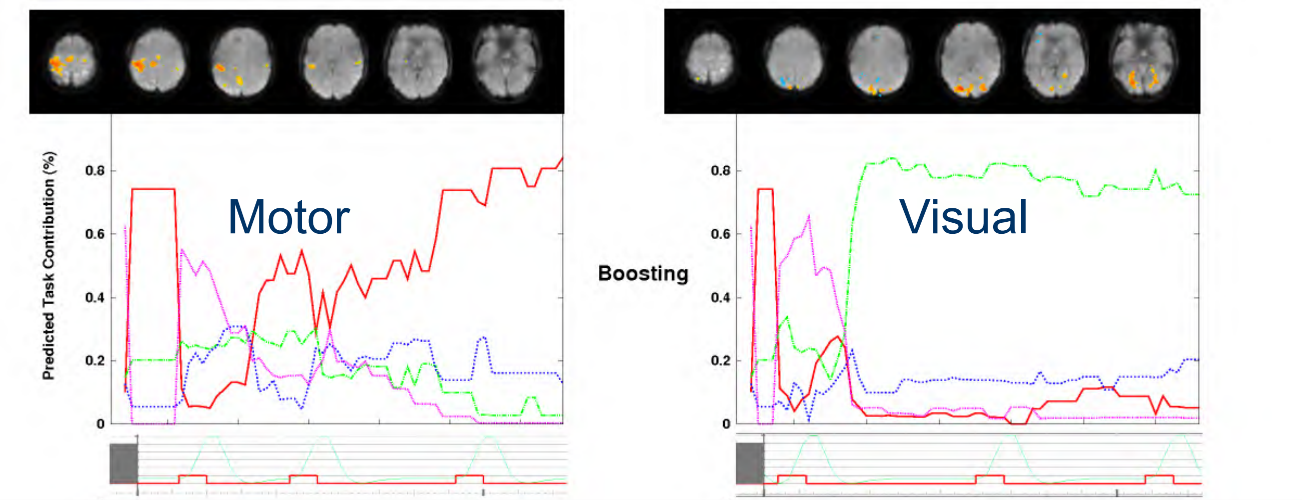
Single Finger Tap, Multi-Echo EPI, 8 TEs: 30 - 158 ms , TR: 1 s



Gembris et al. MRiM 1999

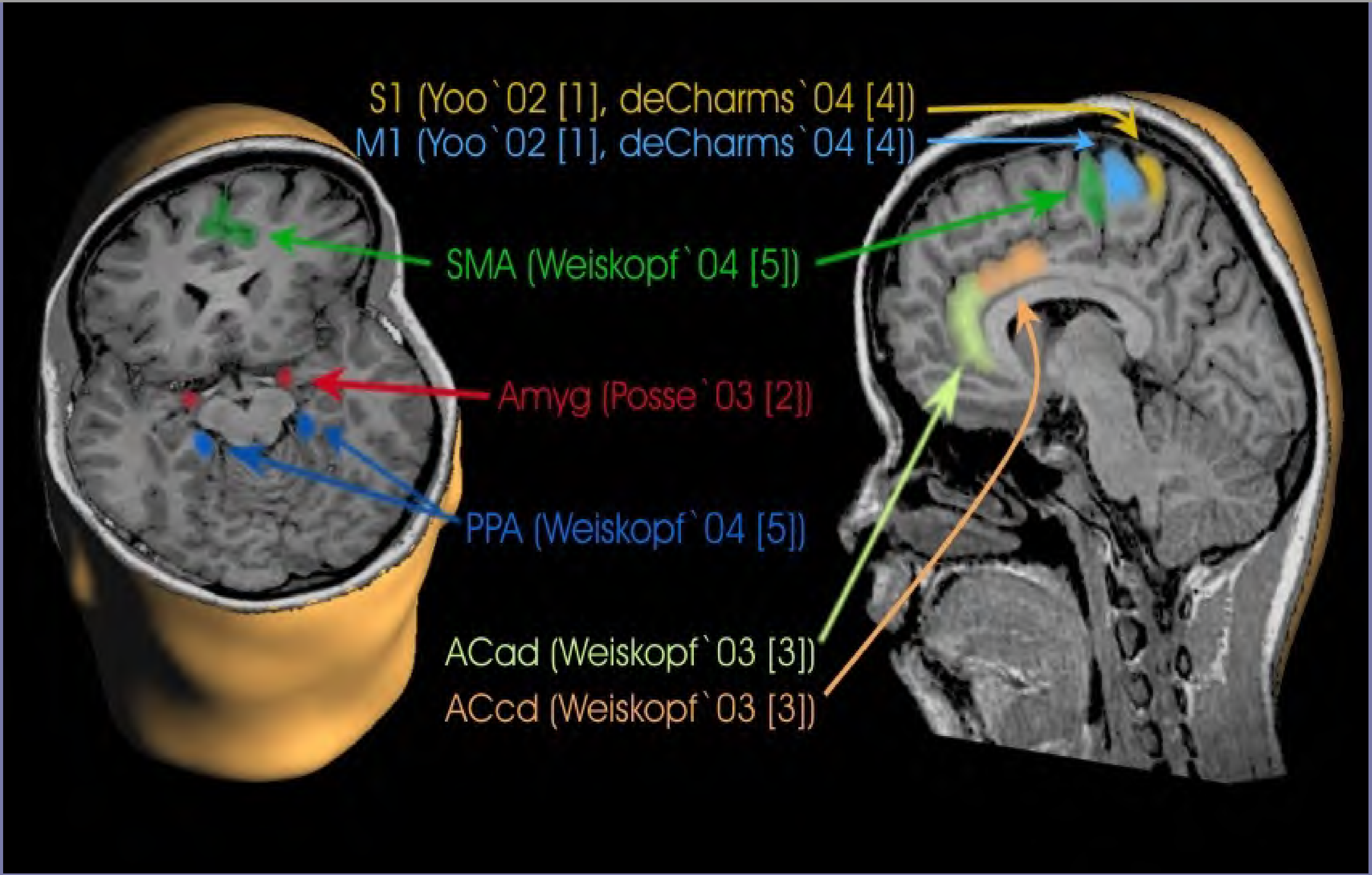
Pattern Classification in Real-Time

- Neurofeedback interface (Yoo et al., Neuroreport 2004)
- Brain state classification (LaConte et al. Human Brain Mapping 2007, Neuroimage 2011)
- Dynamic multi-class predictions using spatially aggregated classifiers (Martinez-Ramon et al. Neuroimage 2006, Zheng et al. Magn Reson Imag, in press)



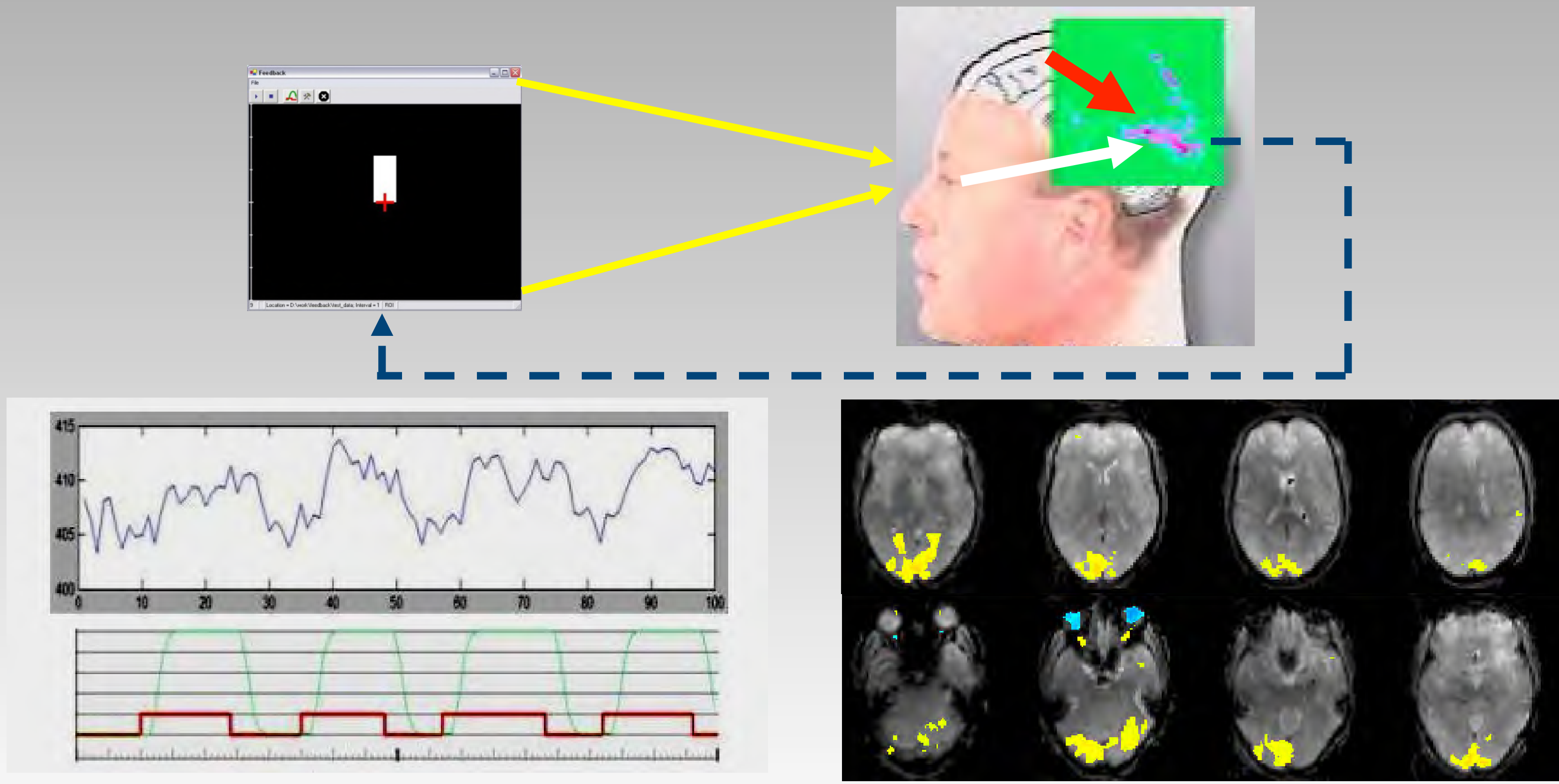
Neuroscience Applications

Modulation of Brain Activity with Real-Time Neurofeedback



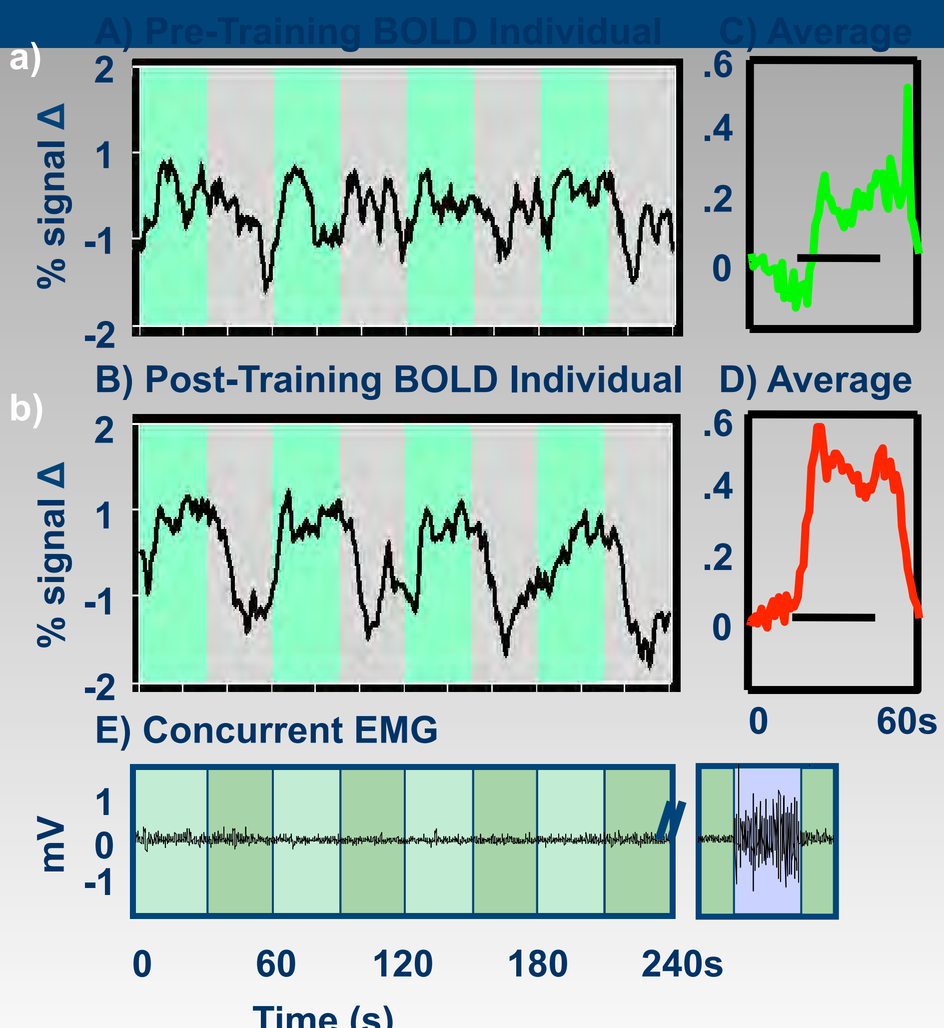
Neurofeedback to Up- and Down-regulate Activation in Visual Cortex

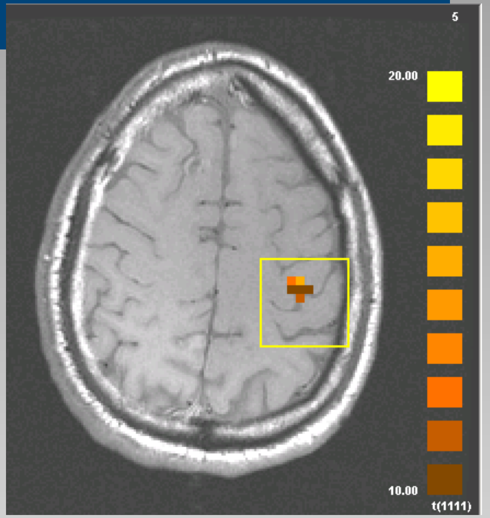
Graded visual attention (top-down process)

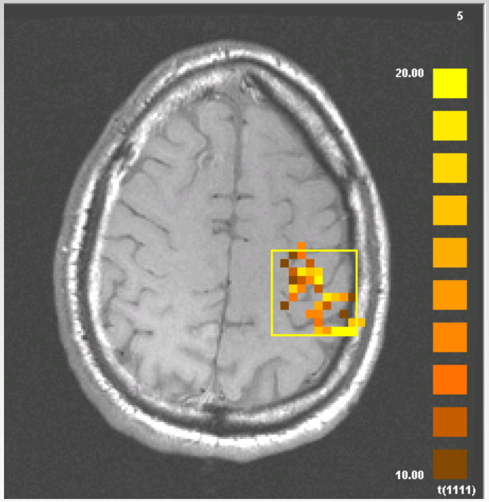


Posse et al, Abstr. HBM 2005

Learned regulation of brain activation – Motor Imagery

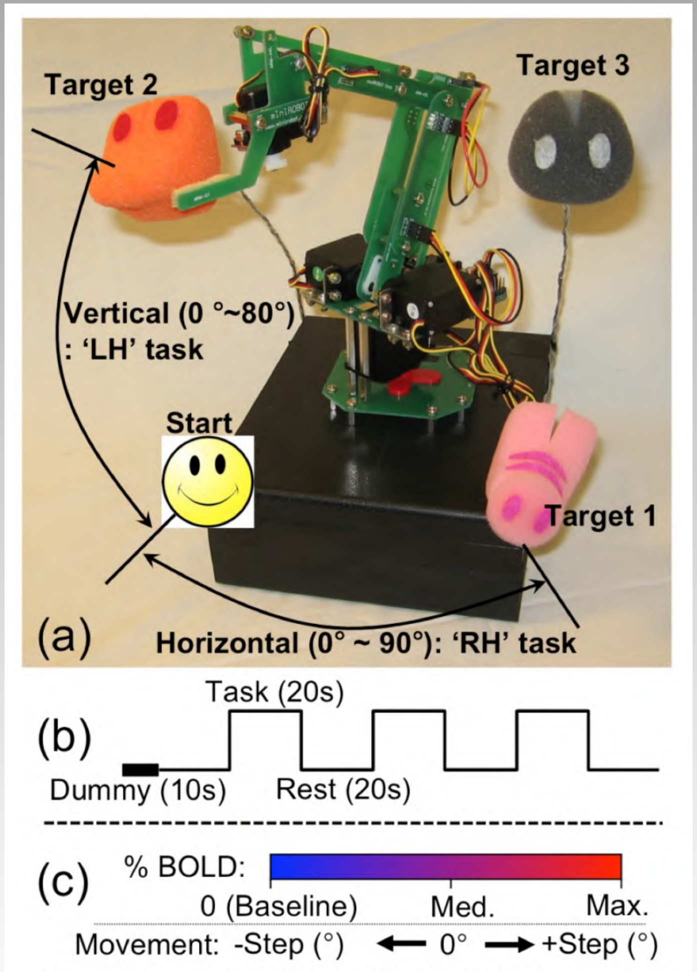


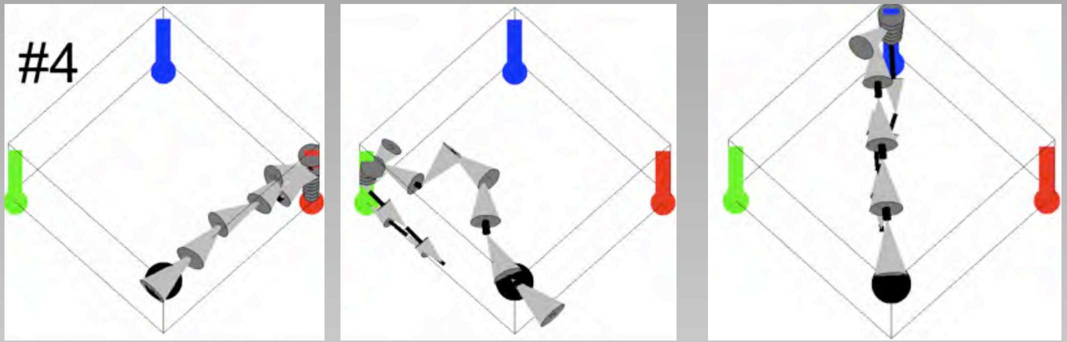




DeCharms et al Neuroimage 2004

Brain-Machine-Interface: Thought-Controlled Robotic Arm (Motor Imagery)



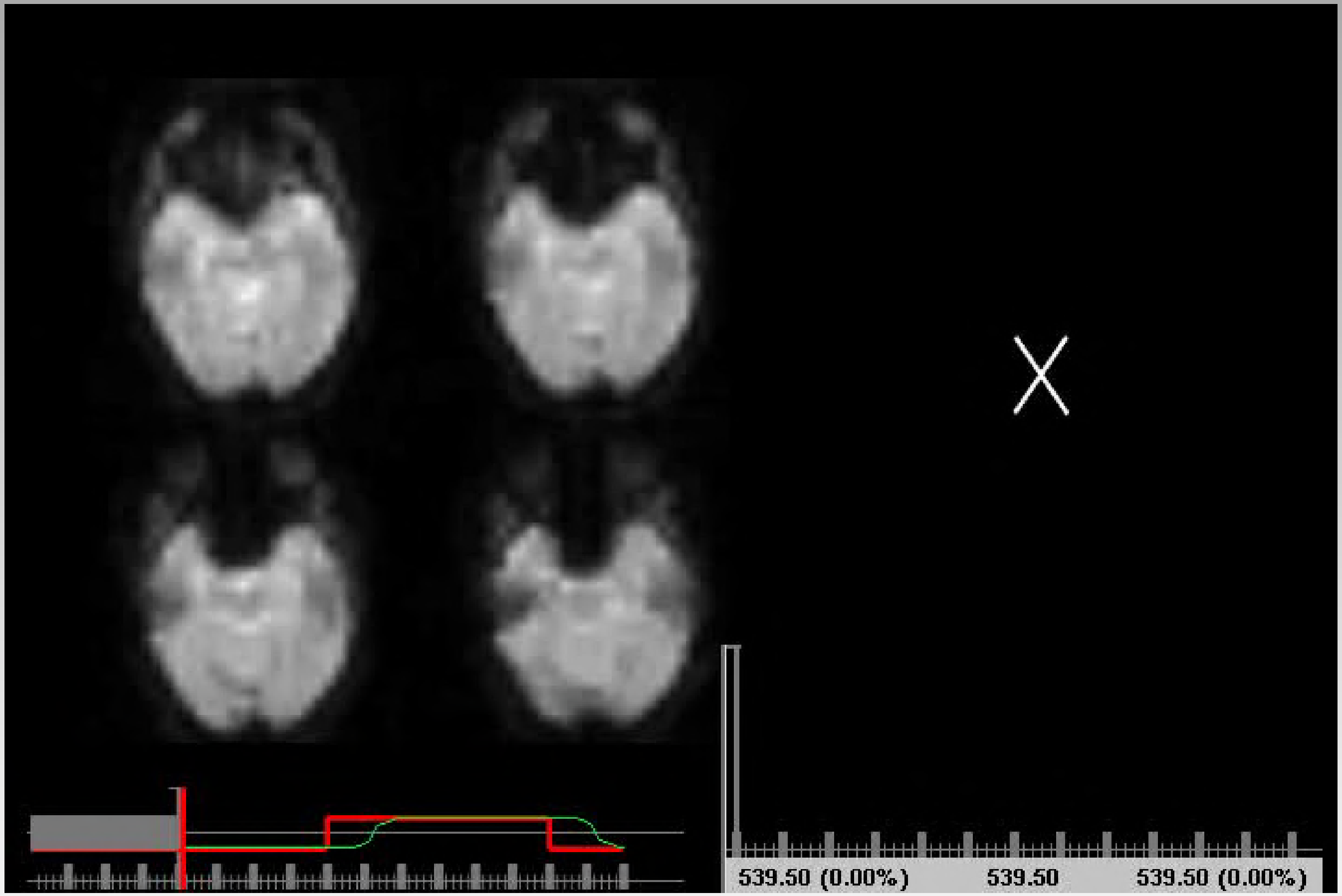


Examples of successful trajectories

- Over 50% success rates from one experienced subject
- At least one successful trial (25%) for two fMRI-naïve subjects

Lee et al. Neurosci. Letters 2009

Neural Correlates of Emotions during Mood Induction in Single Trials

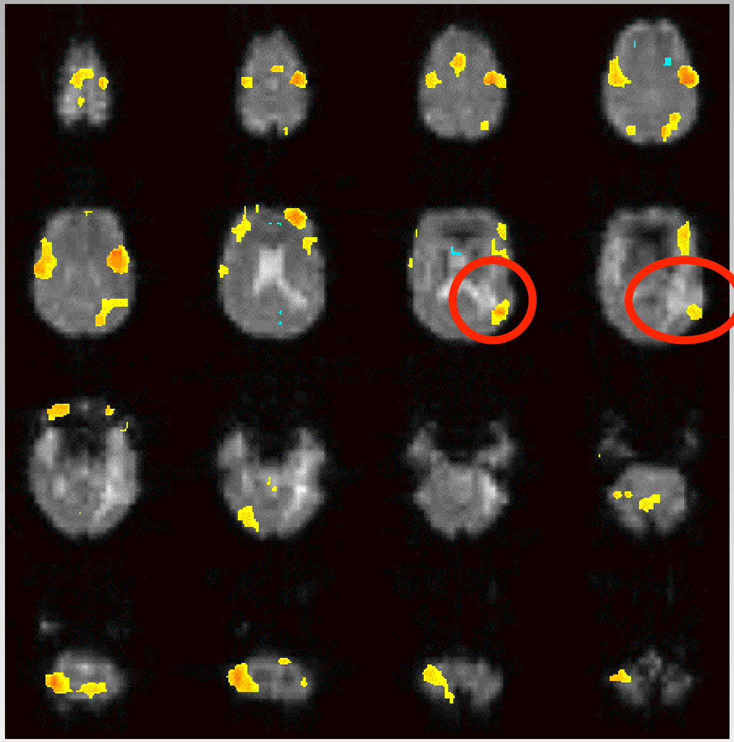


Posse et al., Neuroimage 2003

Clinical Applications

Motor Localization and Language Lateralization

- Presurgical localization of motor cortex (Moeller et al, Eur Radiol. 2005, Feigl et al. Eur J Surg Oncol. 2008) and language areas (Fernandez et al, Neuroimage 2001, Schwindack Br J Neurosurg. 2005)



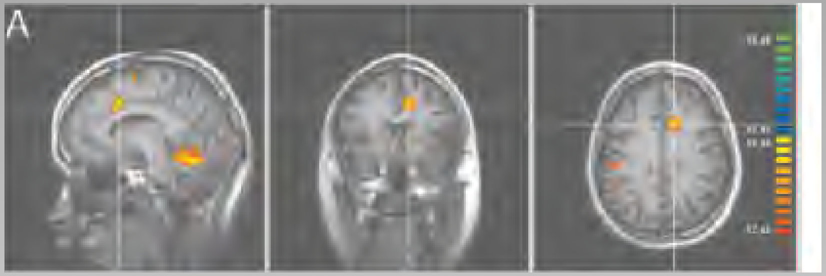
- *Example:* Language lateralization in patient with high grade glioma (1 min).
- Potential to replace WADA test

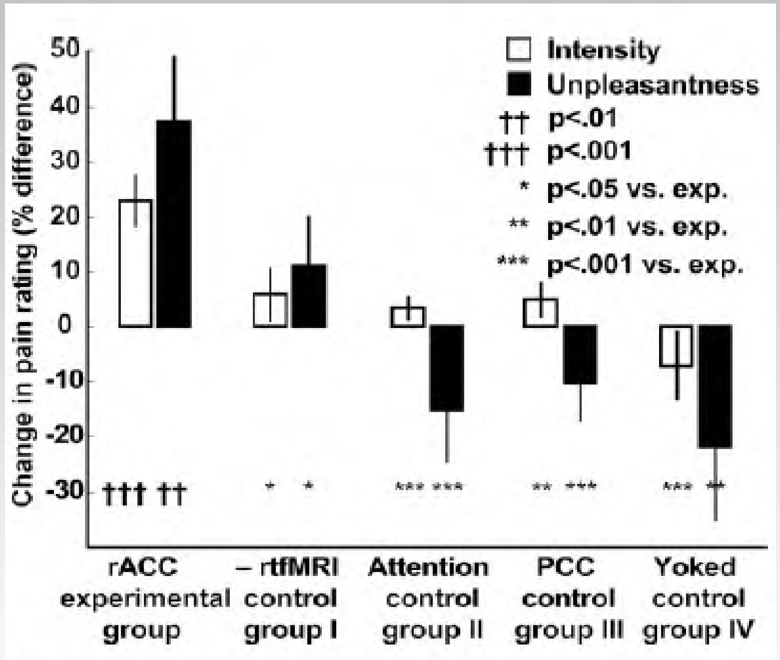
Clinical and Preclinical Studies

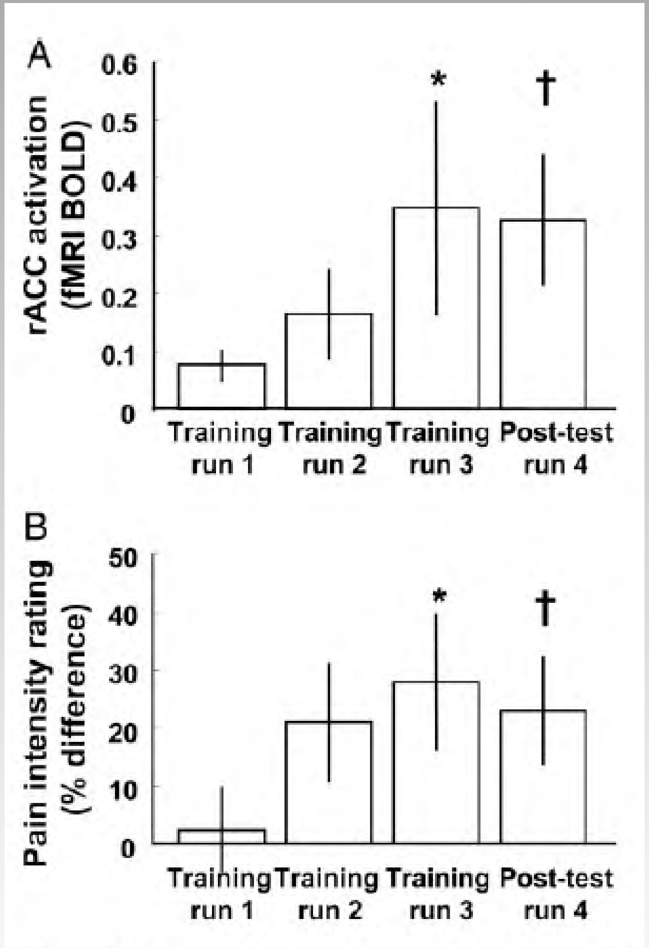
- Intra-operative real-time fMRI (Gering and Weber, J Magn Reson Imaging. 1998)
- Presurgical evaluation of paediatric epilepsy (Kesavadas et al., Pediatr Radiol. 2007)
- Brain development in children (Almli et al. at Washington U., Shaw et al. at U. Washington,…)

- Neuropharmacological studies in animals (Lu et al. Magn Reson Imaging. 2008)

Control over Brain Activation and Pain learned by using real-time fMRI



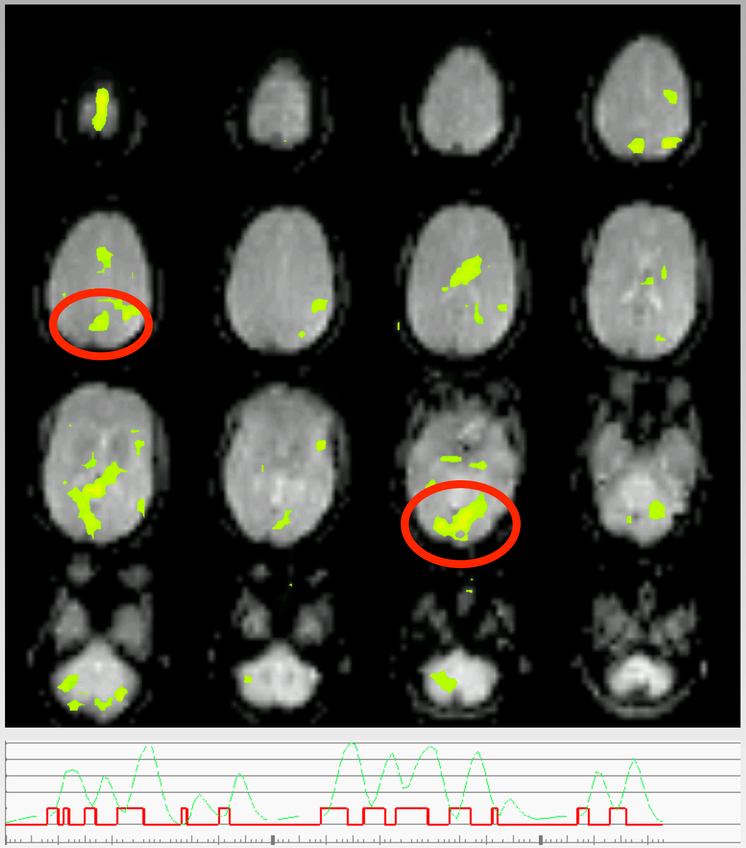




DeCharms et al. PNAS 2005

Neural Correlates of Visual Hallucinations in Schizophrenia

- Characterize spontaneous changes in brain activity in Schizophrenia, which may appear as noise in conventional fMRI
- Online generation of reference vector based on subject responses
- Challenge: Multi-Tasking



Gao et al., Abstr. HBM 2004

Works-in-Progress

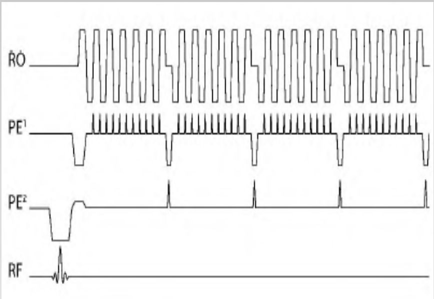
Ultra-High-Speed Real-Time fMRI

- Echo-Volumar Imaging (EVI)
  - Detection of negative dip (Lindquist et al 2008)
  - Delineation of physiological noise (Witzel et al 2011)
- Inverse Imaging (InI)
  - Regional hemodynamic onset delay (Lin et al 2006-2010),
  - Improved modeling of the hemodynamic response using time domain filter (Lin et al 2011)
- Ultrafast k-space trajectories
  - Undersampled projection imaging (Grotz et al 2009)
  - 3D rosette trajectories (Zahneisen et al 2011)
- Multi-Band and Multiplexed EPI
  - Improved sensitivity for detecting resting state networks (Moeller et al 2010, Feinberg et al 2011)

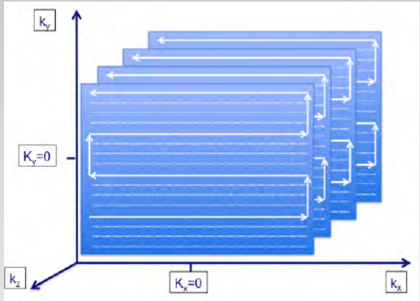
Sensitivity Enhancement using Multi-Slab EVI at 3 Tesla (Posse et al. Neuroimage 2012)

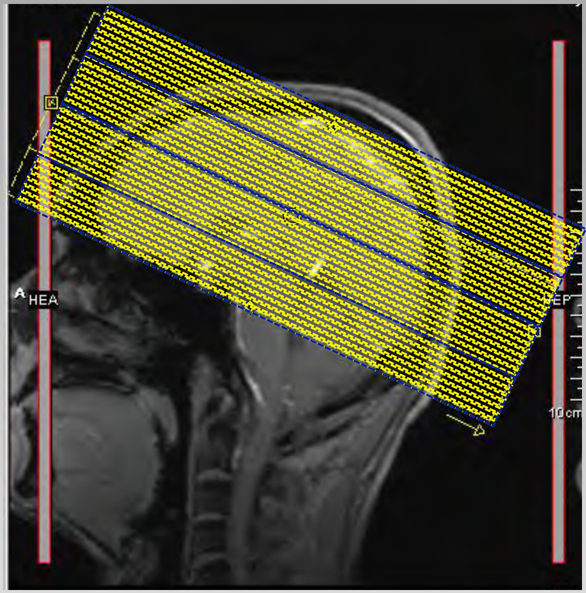
- Sequential multiple-slab excitation with 3D encoding and parallel imaging within slabs reduce geometrical distortion and blurring

Pulse sequence



K-space trajectory





12 channel head coil

- In-plane reconstruction of magnitude and phase images with 4xGRAPPA on scanner (up to 250 slices/s)
- Through-plane reconstruction and real-time fMRI analysis on external workstation using TurboFIRE

Rea-Time EVI Reconstruction

Trio with 12 Channel Array

Raw Data

2D Recon-struction with GRAPPA

DICOM Images

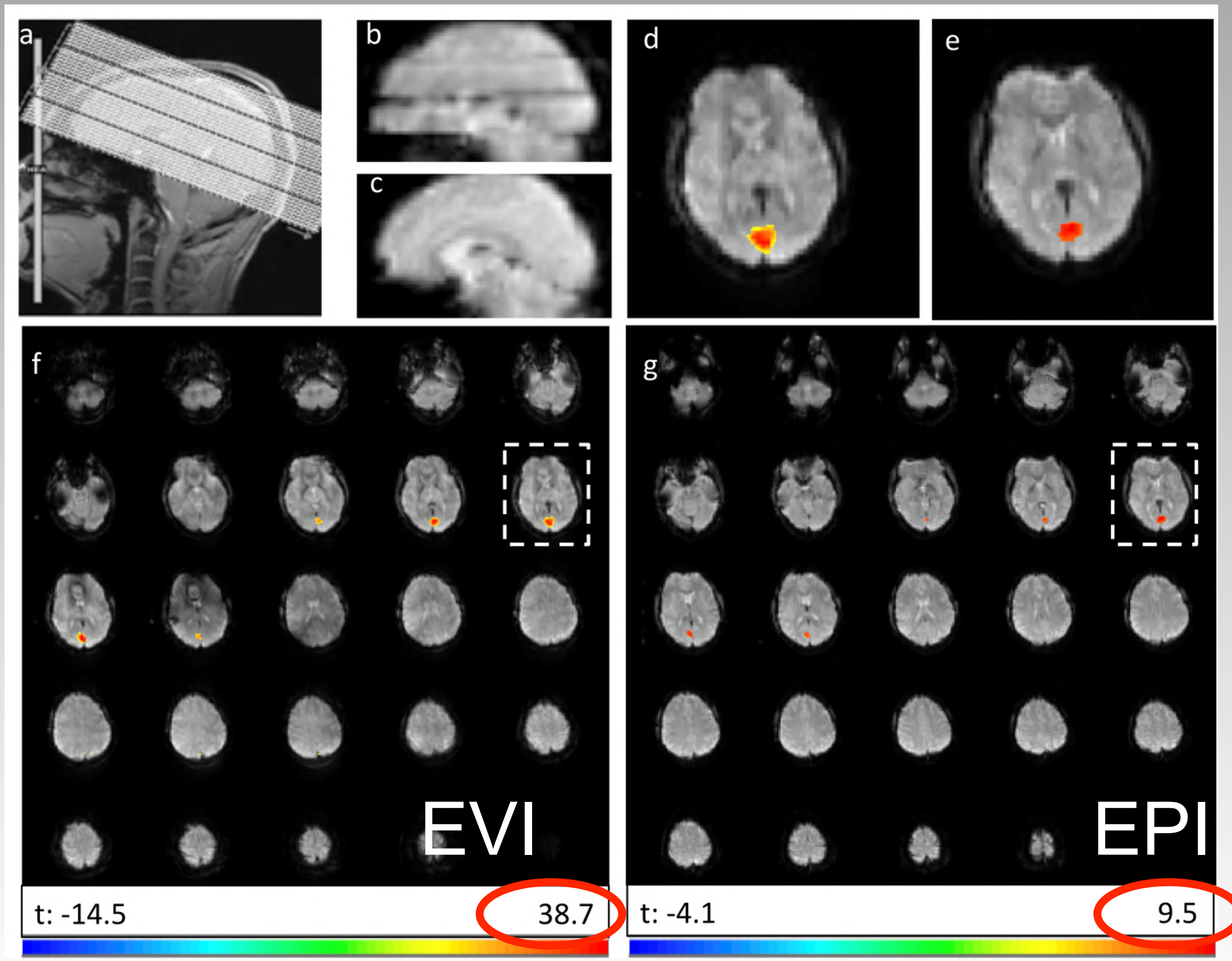
TCP/IP via scanner host

Magn.+Phase

LINUX Workstation
with
TurboFIRE Real-time fMRI Software

Real-time transfer of up to 250 slices/s (Magnitude and Phase)

Comparison of 4-slab EVI (TR: 286 ms) and EPI (TR: 2 s)

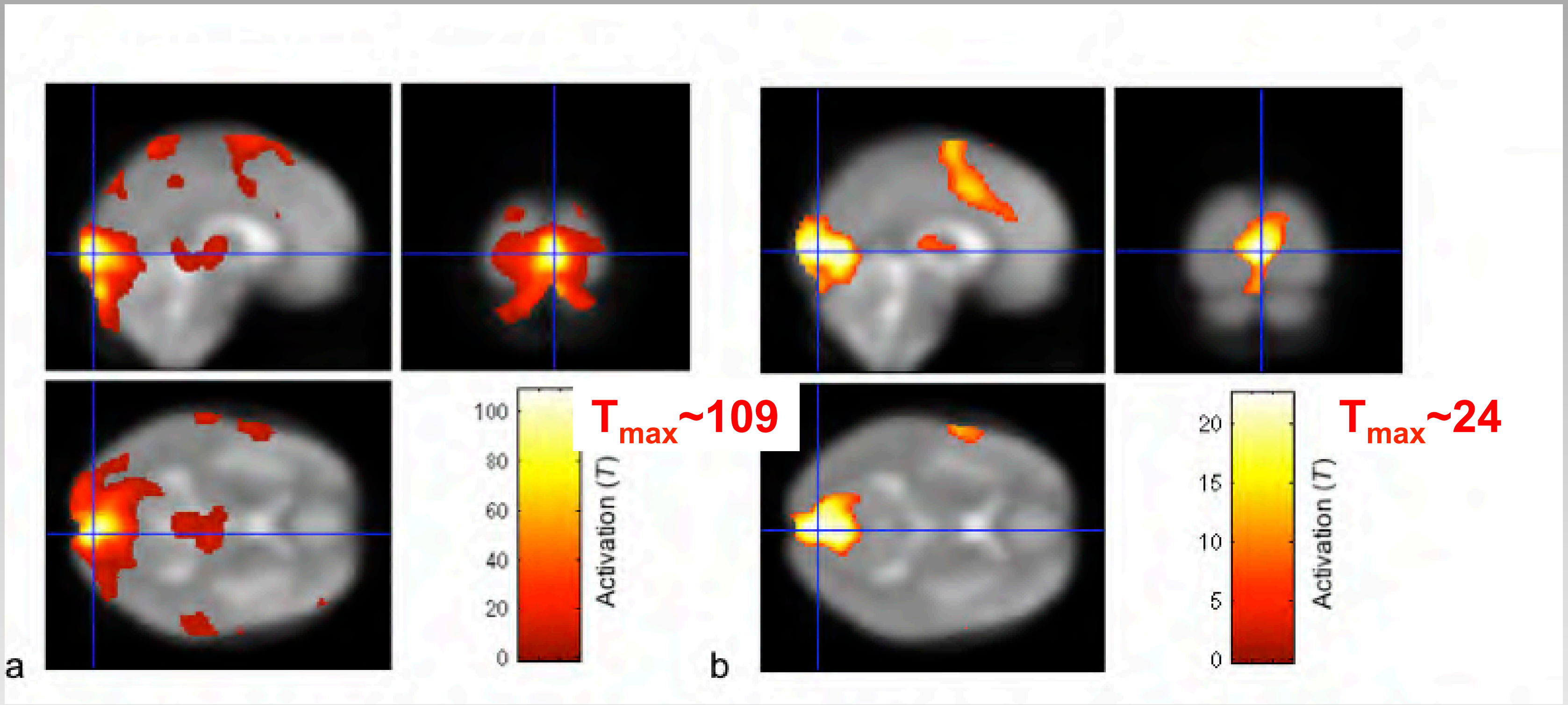


TE: 29 ms

Voxel:
4x4x4 mm3

BOLD Sensitivity Comparison: EVI vs. EPI

Block design : Finger Tapping + Visual Stimulation



TR: 286 ms

TR: 2 s

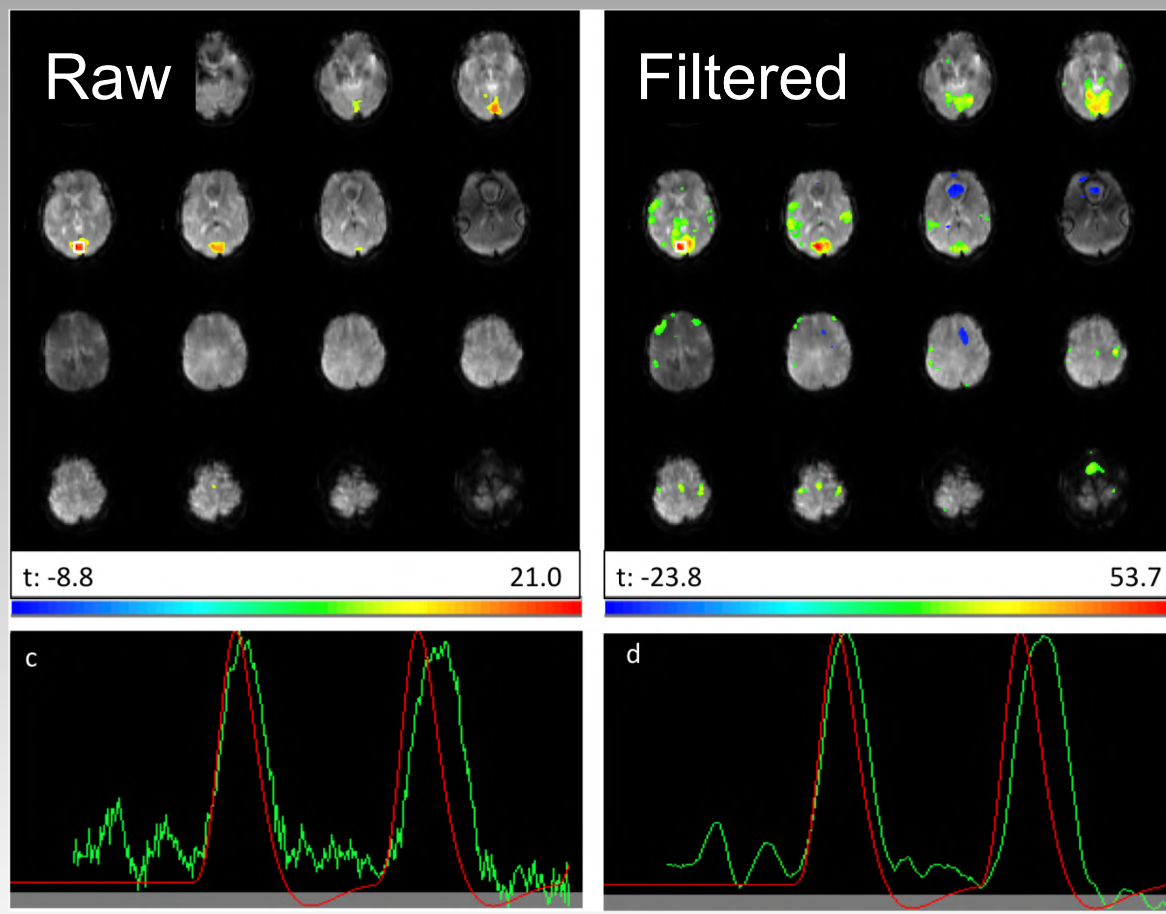
SPM8: concatenated scans, autoregressive modeling - AR(3), p<0.05, corrected

Sensitivity Enhancement using Time Domain Moving Average Filter

2-slab EVI

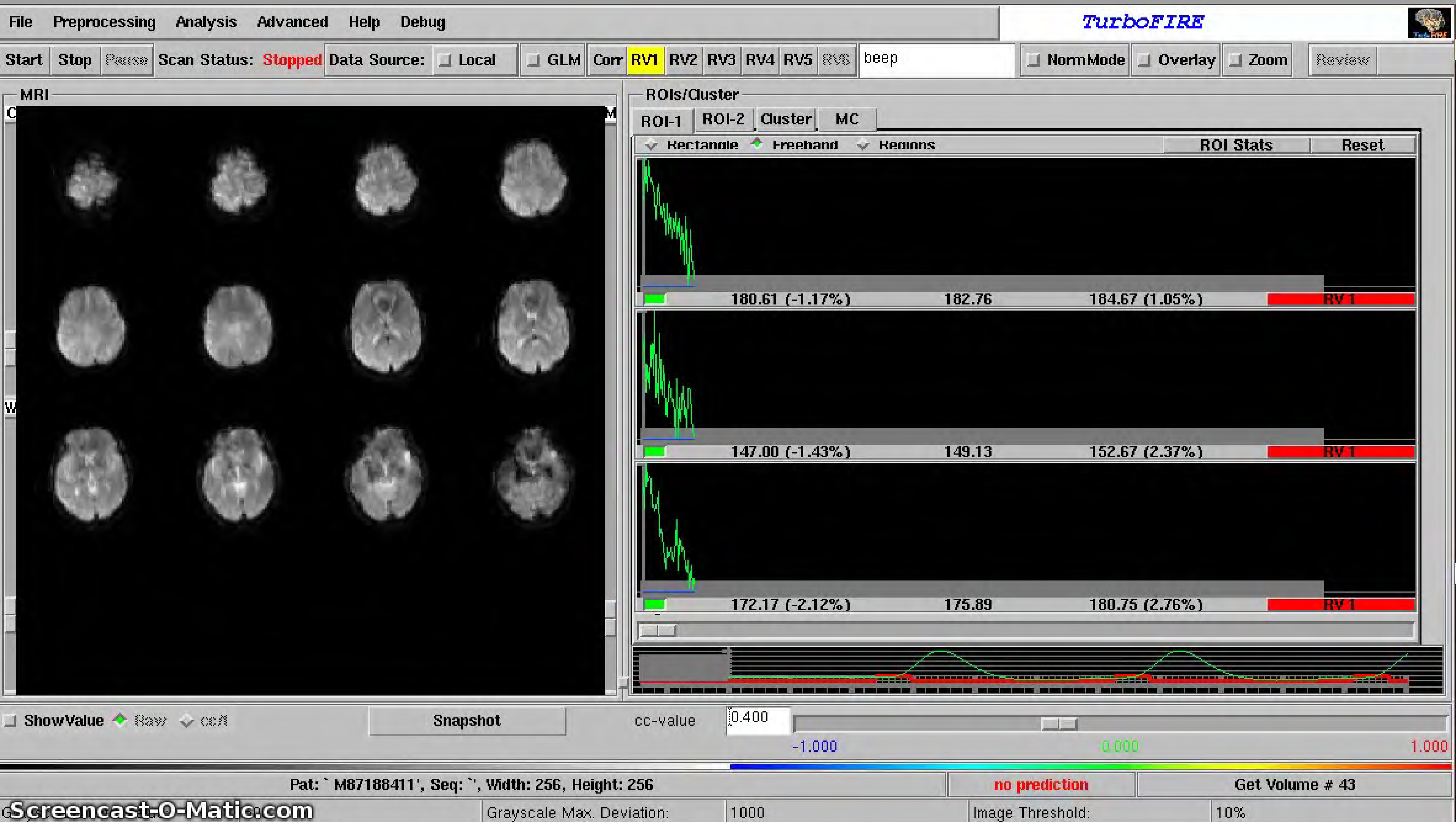
TR: 136 ms

TE: 29 ms



- Filter width: 2 s (optimal choice based on Lin et al 2011)

Real-time fMRI @ TR: 136 ms



BOLD Sensitivity: EVI4, EVI4 with Time Domain Moving Average Filter and EPI

T-Scores

	VISUAL						MOTOR					
	EVI4		EVI4-MA		EPI		EVI4		EVI4-MA		EPI	
	mean	max	mean	max	mean	max	mean	max	mean	max	mean	max
Least Squares Mean Estimate	**15.3**	**37.4**	**23.1**	**49.8**	**7.8**	**10.3**	**9.6**	**20.6**	**13.9**	**27.6**	**5.8**	**9.2**
Standard Error	**0.9**	**1.9**	**0.9**	**1.9**	**0.9**	**1.9**	**1.8**	**4.1**	**1.8**	**4.1**	**1.8**	**4.1**

Spatial Extent

	VISUAL			MOTOR		
	EVI4 [voxels]	EVI4-MA [voxels]	EPI [voxels]	EVI4 [voxels]	EVI4-MA [voxels]	EPI [voxels]
Least Squares Mean Estimate	**820.0**	**1104.0**	**639.0**	431.0	**582.0**	343.0
Standard Error	**164.0**	**164.0**	**164.0**	63.0	**63.0**	63.0

BOLD Amplitude

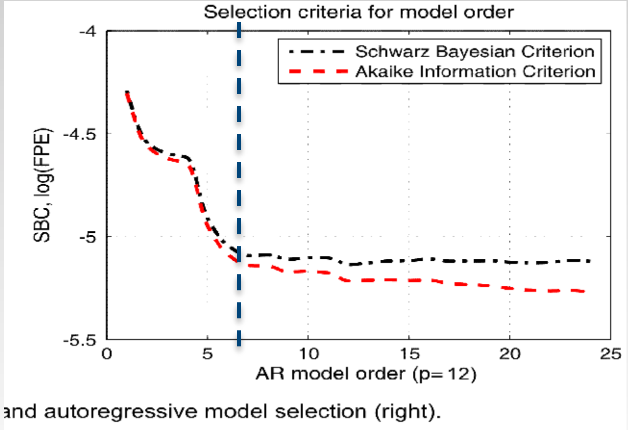
	VISUAL						MOTOR					
	EVI4		EVI4-MA		EPI		EVI4		EVI4-MA		EPI	
	mean	max	mean	max	mean	max	mean	max	mean	max	mean	max
Least Squares Mean Estimate	**4.3%**	**12.5%**	2.9%	10.5%	**2.7%**	9.7%	**3.7%**	**8.5%**	**2.2%**	**6.9%**	**1.6%**	5.1%
Standard Error	**0.3%**	**1.2%**	0.3%	1.2%	**0.3%**	1.2%	**0.1%**	**1.5%**	**0.1%**	**1.5%**	**0.1%**	1.5%

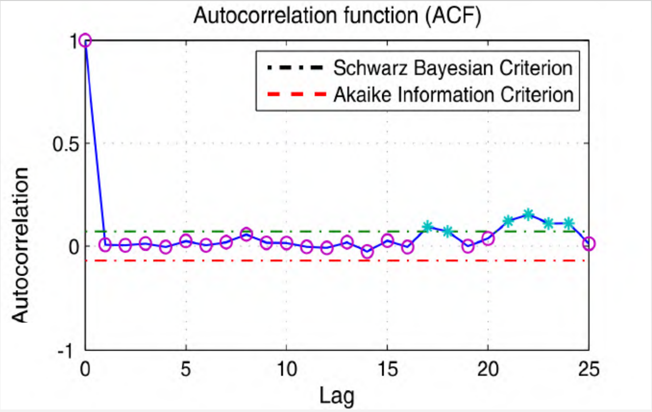
Temporal Correlations and Higher Order Autoregressive Modeling

- Different sources of correlation at different time scales: cardiac, respiratory, resting state (may vary regionally)

- FSL: Reduction of t-score with prewhitening:
  - EVI4: up to 61 %
  - EVI2: up to 42 % (!?)

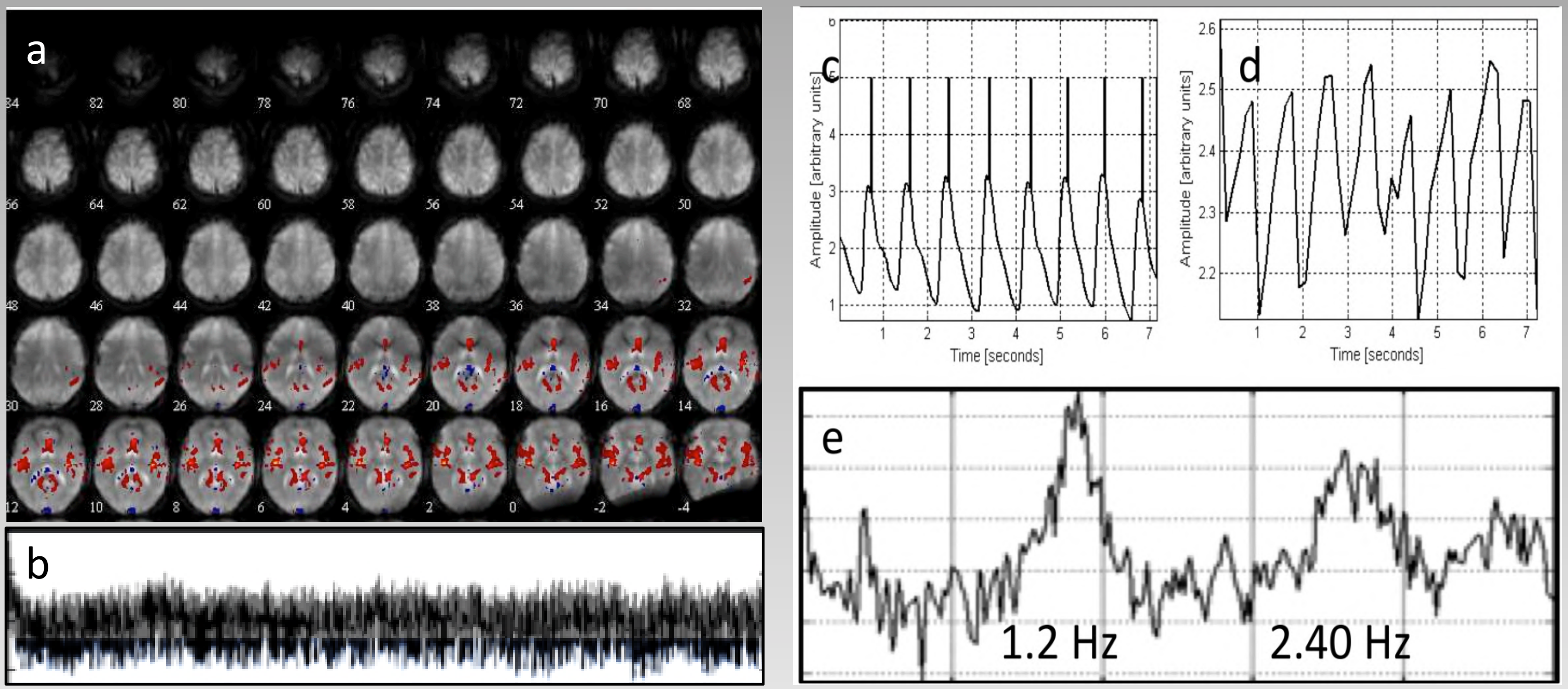
- Autoregressive modeling of EVI4 data in visual cortex





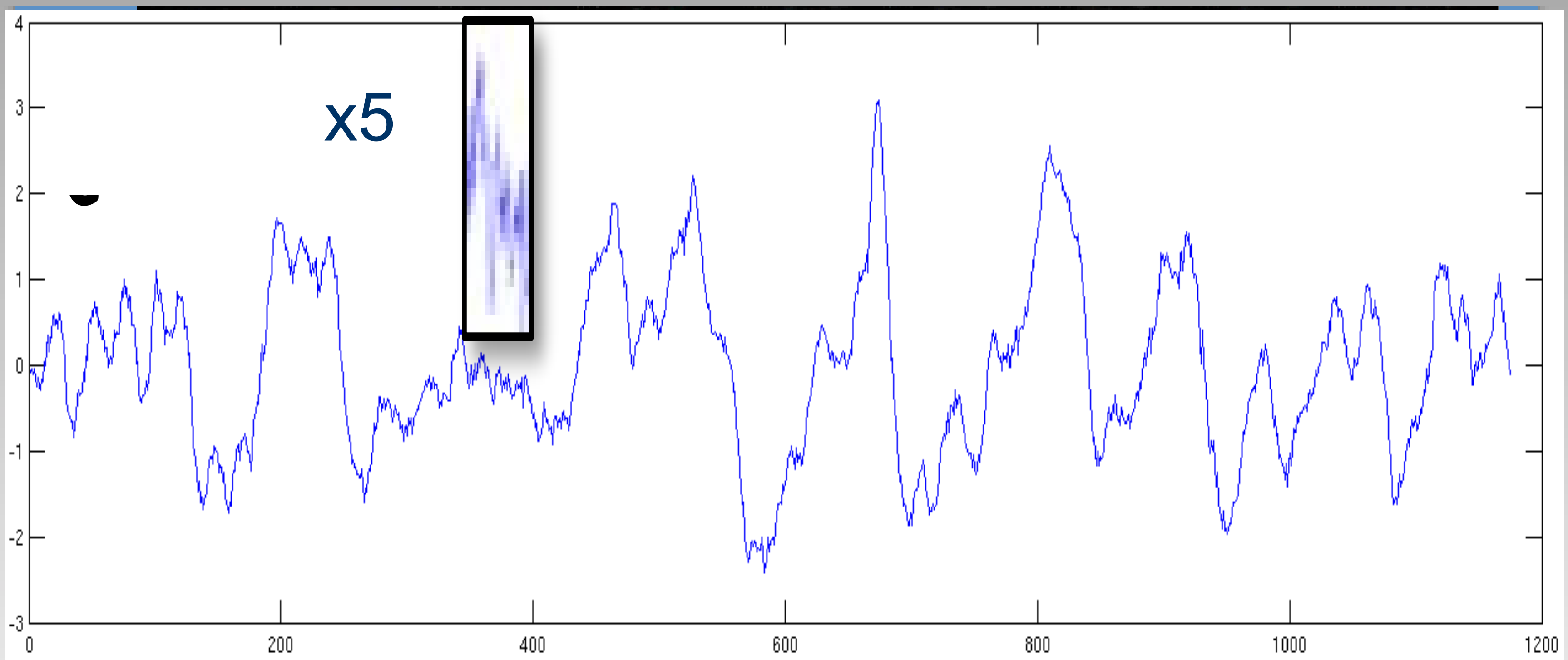
Mutihac et al ESMRMB 2011

Physiological Signal Fluctuation at TR: 135 ms



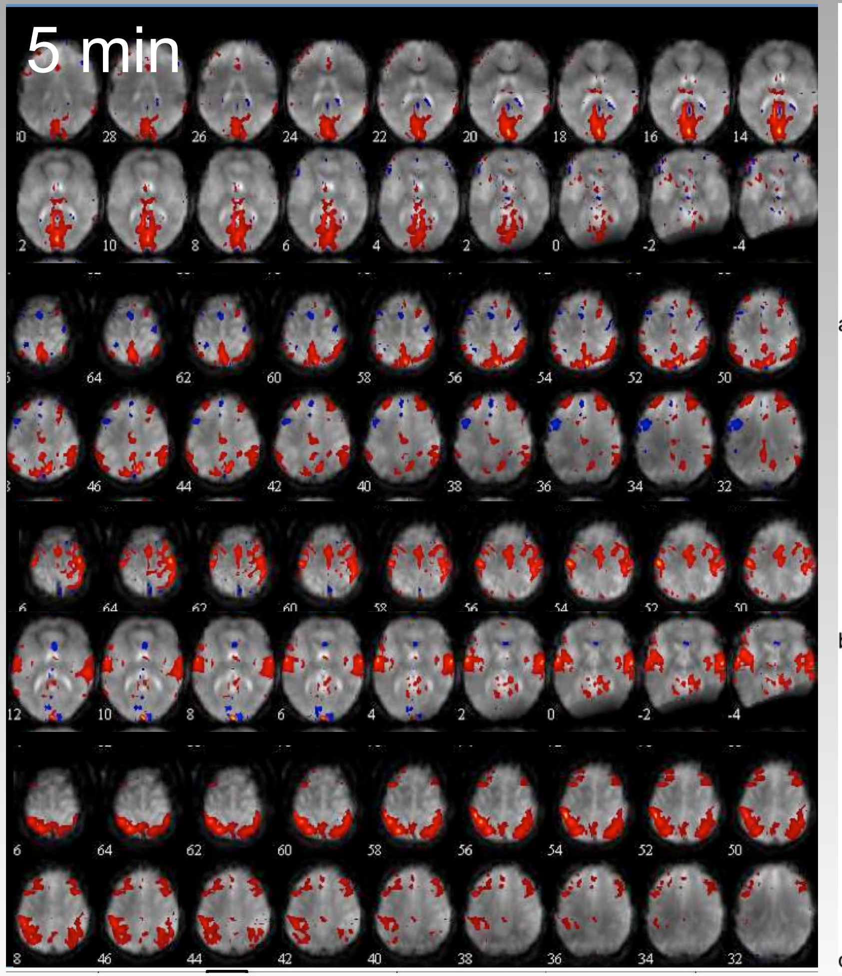
(a) ICA map of cardiac related signal fluctuations in brain stem and insular cortex and (b) corresponding ICA time (c) peripheral pulse (d) zoomed ICA time course and (e) power spectrum

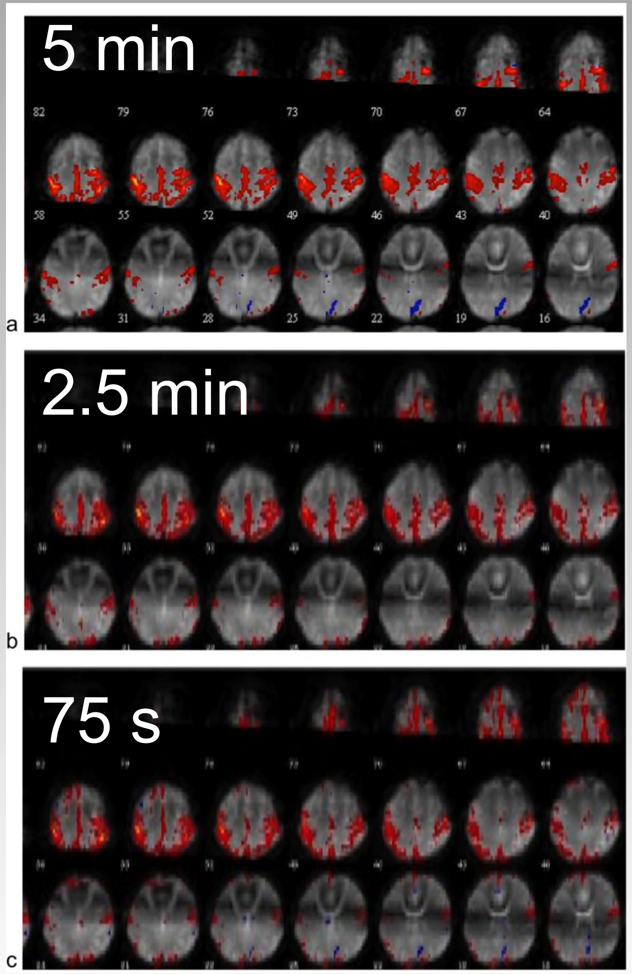
ICA Time Course well above Thermal Noise Level Identifies Resting State Networks



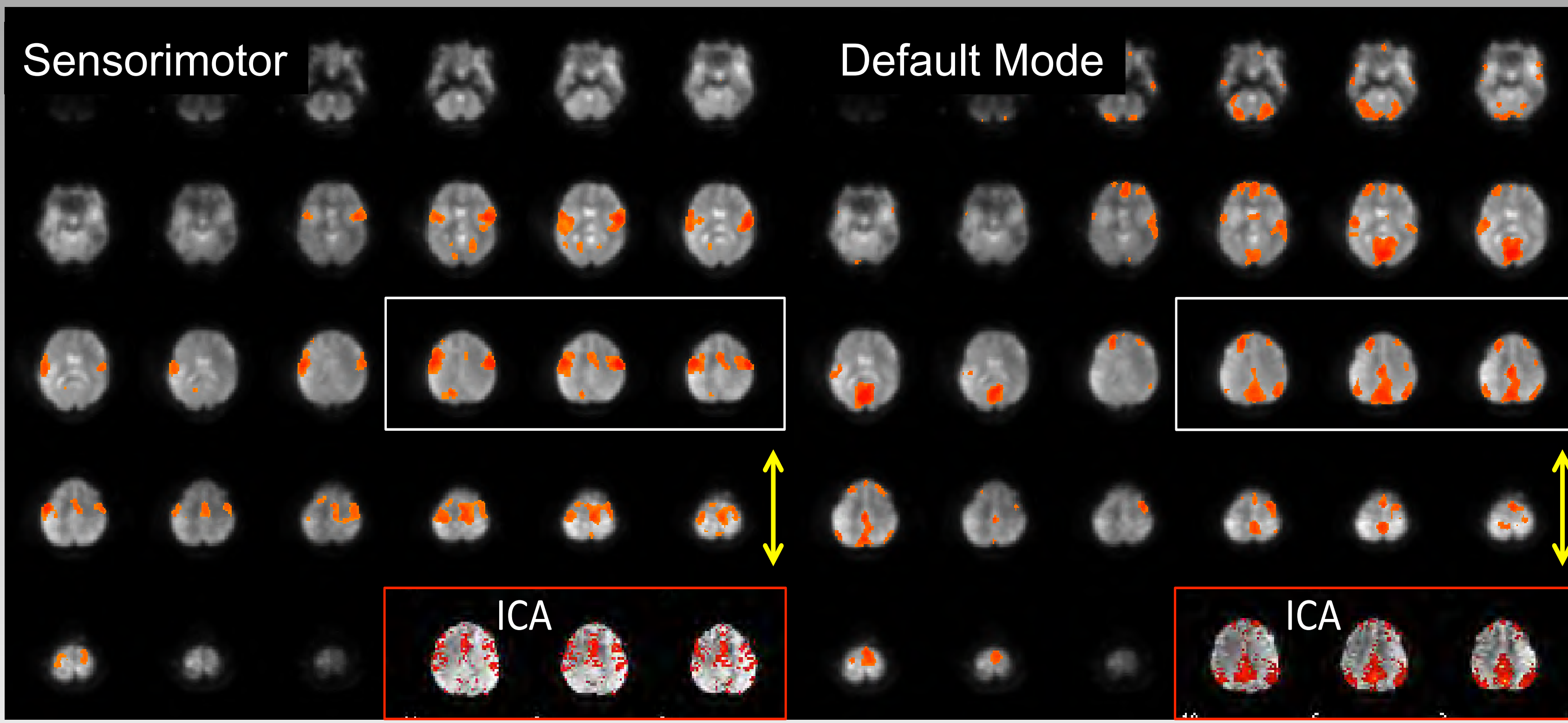
Default Mode Network

Detection of Resting State Networks in Short Scan Times





Real-Time Seed-Based Correlation Analysis



- 70 s scan time (Default Mode Network appear in ~20 s)
- Spatial Gaussian filter: isotropic 8 mm, temporal moving average filter: 6s, 2^{nd} order detrending

Real-Time fMRI at Ultra-High Field

- “Physiological noise” may become useful information to unravel non-task-related and subconscious thought processes
- Parallel imaging will drive temporal resolution (Wiesinger et al MRM 2004)
  - Echo-Volumar-Imaging (Witzel ISMRM 2008)
  - Inverse Imaging (Lin et al MRM 2006)
  - Superresolution Imaging (Otazo et al. Neuroimage, 2009)
- Will BOLD still be the method of choice? Consider flow sensitive methods, such as ASL that are less sensitive to magnetic field inhomogeneity.

Challenges and Opportunities (I)

- Need to tightly control/monitor all aspects of the experiment to avoid unexplained activation – any measured signal change has a source!!
- How to display and analyze the wealth of information?
  - Multiple display monitors
  - Automated interpretation of rapidly changing activation patterns using data driven analysis and machine learning
  - fMRI is not the only source of information → multi-modal integration and classification

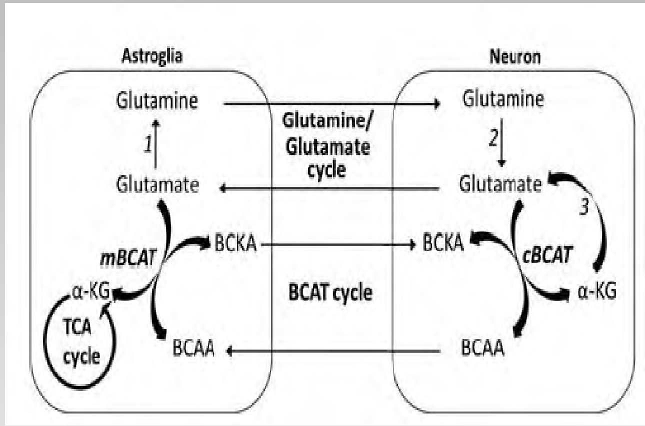
Challenges and Opportunities (II)

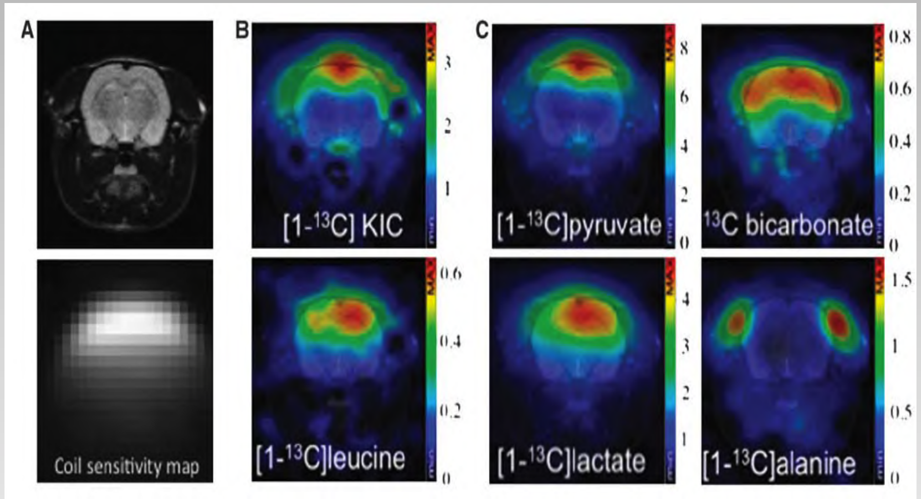
- Ease of operation is key – none of the existing tools come anywhere close
- It would be nice to robustly correct moderate to large head movement in children and uncooperative subjects (currently not feasible)
- Interactive neuro-psychological and neuro-psychiatric interview (Ethical issues!)

- Emerging real-time imaging methods: Optical imaging, photoacoustic imaging,…

Real-time Imaging of Brain Metabolism using Hyperpolarized Contrast Agents

- Chemical shift imaging of rat brain branched chain amino acid transaminase (BCAT) activity in vivo.





Butt SA, et al. J Cereb Blood Flow Metab 2012

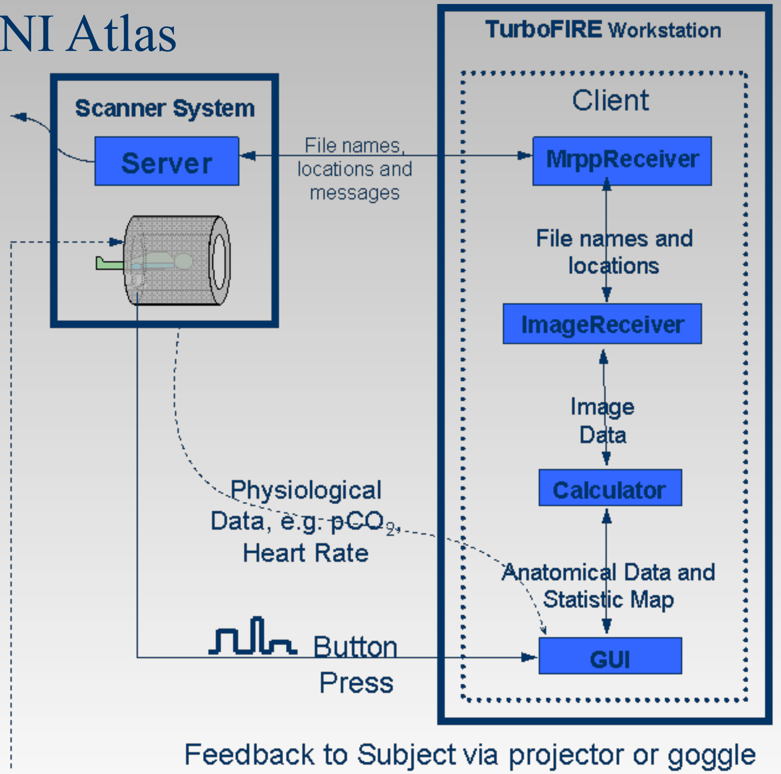
Up to 10,000 fold signal enhancement!

A Practical Example: Real-Time fMRI using TurboFIRE

Preprocessing
- Multi-echo EPI: T_2^*-LM fit or weighted echo average based on T_2^*-value
- 3D motion correction
- Spatial normalization in reference to MNI Atlas

Statistical Modeling
- Block and event related design
- "Sliding-Window" correlation analysis
    - •6 simultaneous reference vectors
    - •Reference Vector Optimization
- Simultaneously: General Linear Model
- Real-time reference vector generation
- Seed-based correlation analysis

Quantification
- Integrated Talairach Daemon database
- ROI and cluster analysis
- Spatially aggregated pattern classifier



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Elena Ackley

Thank you for your attention!

Any Questions, Suggestion or Inspirations?

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3D Visualization of Brain Activation