Processing Strategies for Real-Time Neurofeedback Using fMRI

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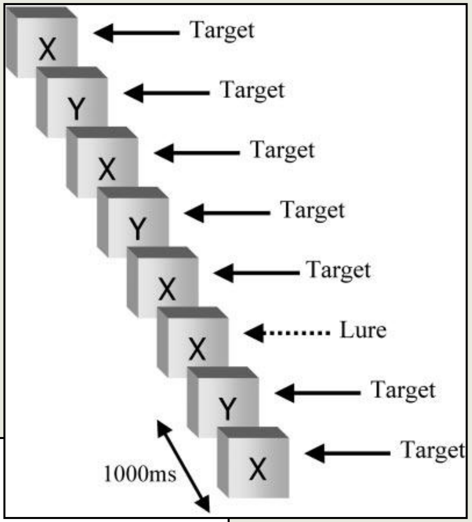
Cognitive Control

- Ability to regulate ones thoughts, feelings, and actions.
- Varies substantially between individuals.
- Often the target of clinical research.
- Deficits in cognitive control are linked to:
  ADHD, substance abuse, depression, Parkinson's, aging, …

Measurement of Cognitive Control Deficit Using fMRI

- Functional MRI (fMRI) tasks have recently been developed to quantify cognitive control in the context of disorders.
- For example, the GO-NOGO task



Brief Communication

Cingulate Hypoactivity in Cocaine Users During a GO–NOGO Task as Revealed by Event-Related Functional Magnetic Resonance Imaging

Jacqueline N. Kaufman,[1] Thomas J. Ross,[1] Elliot A. Stein,[1] and Hugh Garavan[1,2]
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Real-time fMRI for Therapeutics

- However, mere quantification is insufficient for therapeutics.
- Real-time fMRI:
  - Inform patients about ***ongoing*** brain activity while in the scanner.
  - Reward patients in real-time (e.g. by scoring points) as they
    - Increase (frontal) cognitive control circuitry
    - Decrease (limbic) impulse circuitry
    - Etc.

Real-time fMRI: Special challenges for data processing

- What do conventional task-based fMRI analyses provide?...
  - A picture of brain activity over time? *No.*
  - A picture of task-correlated brain activity over time? *No.*
  - A spatial map of an individual's brain regions participating in a task throughout a 10-minute scan? *Usually Not.*
  - A spatial map of brain regions participating in a task throughout 10-minute scans, averaged over a cohort of subjects. ***Yes!***

Real-time fMRI: Special challenges for data processing

- Key differences between real-time and conventional fMRI:
  - Moment-to-moment measurement: repetition time (TR) ≈ 2 seconds.
  - No statistical time (or group) averaging.
  - Temporal filtering must be prospective.
  - Need to perform analyses on the fly.
  - Requires particularly robust/reliable measurements.

What is BOLD? (empirically)

- *BOLD: "Blood Oxygen Level Dependent"*
- ***Empirically***, when local neuronal activity increases, MRI signal increases slightly (1-4%).
- Thus, MRI can be used to probe brain activity!!!
- … but why does the NMR signal increase?

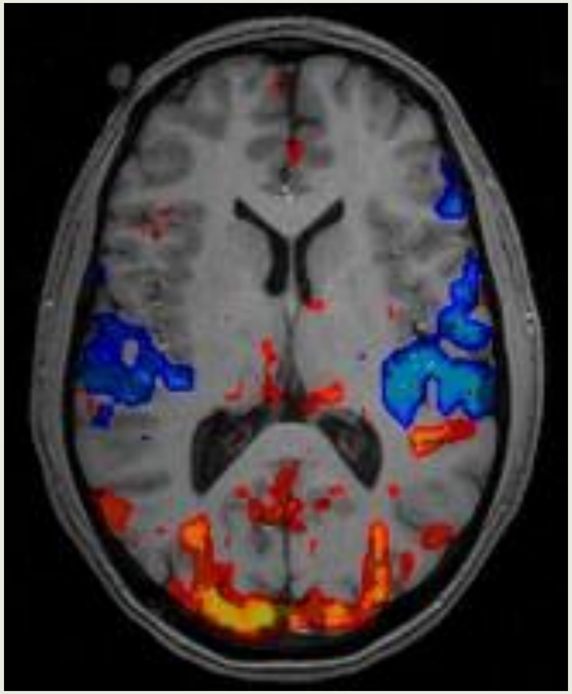


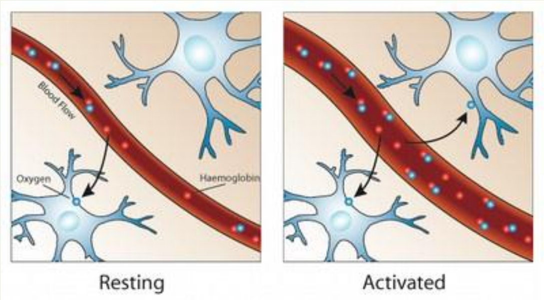
Image from web: "What is Functional Magnetic Resonance Imaging (fMRI)?" By Hannah Devlin. psychcentral.com

What causes BOLD?

- Hemoglobin (Hb) is diamagnetic when oxygenated, but paramagnetic when deoxygenated. Deoxyhemoglobin in blood vessels induces microscopic field distortions.

- Increased blood oxygenation…
  → slightly reduces the microscopic inhomogeneous fields…
  → slightly increases the local T2* of the tissue…
  → slightly increases the local MR signal

- But why does blood oxygenation increase with neuronal activity?



- Physiologic phenomenon:
  Increased neuronal activity leads to increased local cerebral blood flow (CBF), which over-compensates for the increased local cerebral metabolic rate of oxygen ($CMRO_2$).

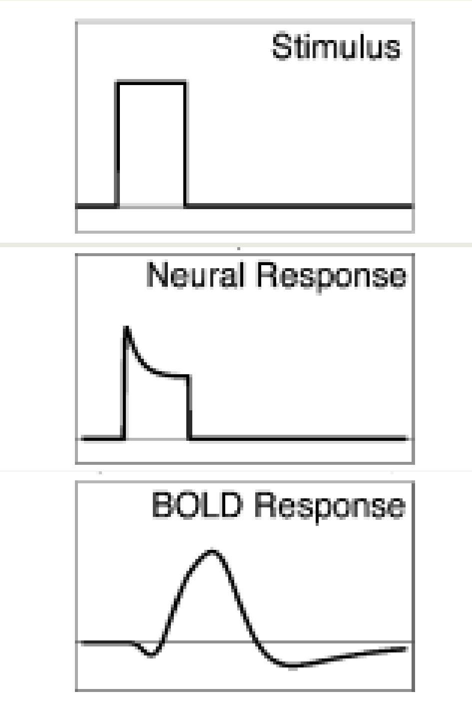
BOLD: An Indirect Measure of Brain Activity

- BOLD Signal does not directly measure neuronal activity, and is therefore susceptible to changes in:
  - Cerebral Blood Flow (CBF)
  - Cerebral Metabolic Rate of Oxygen ($CMRO_2$)
  - Cerebral Blood Volume (CBV)

- The collective signal change due to these effects is known as the 'Hemodynamic Response'

Hemodynamic Delay

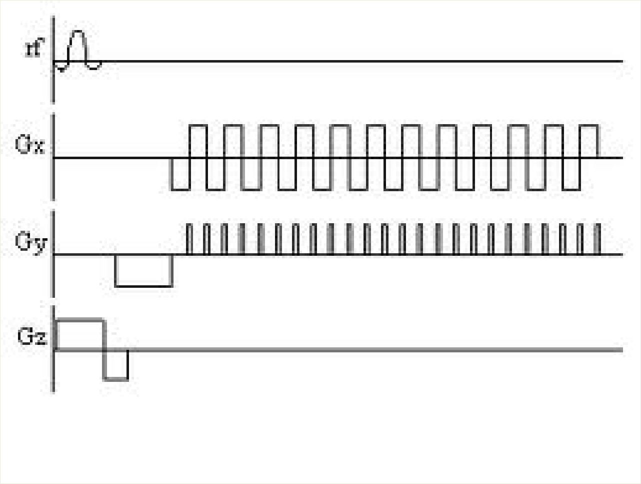
- (Unfortunately) there is a somewhat variable physiologic delay (typically 4-6 seconds) between neuronal activity and the peak of the resulting hemodynamic response.



R.B. Buxton et al. / NeuroImage 23 (2004) S220–S233

BOLD Acquisition

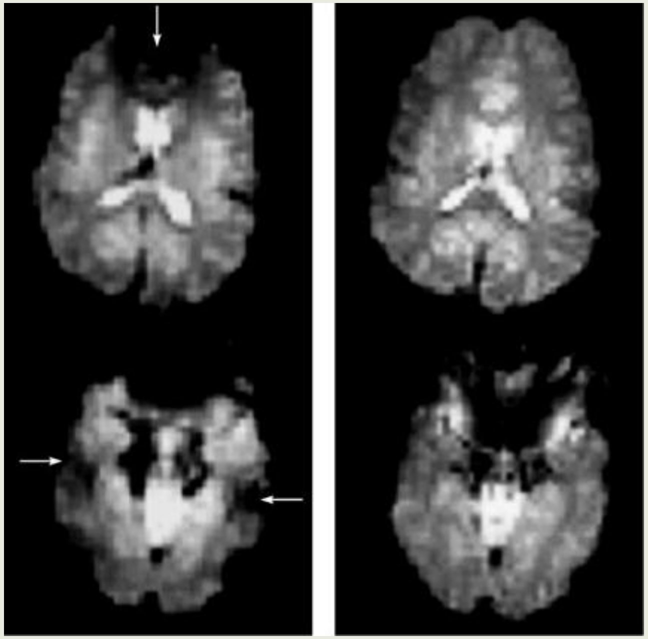
- Typical BOLD Acquisition
  - Multi-slice 2D Echo-Planar Imaging,
    TR ≈ 1-3 seconds
    TE ≈ 20-40 milliseconds
    Resolution ≈ 3x3 mm in-plane, 5 mm thickness
  - Also used: Spiral, 3D SSFP

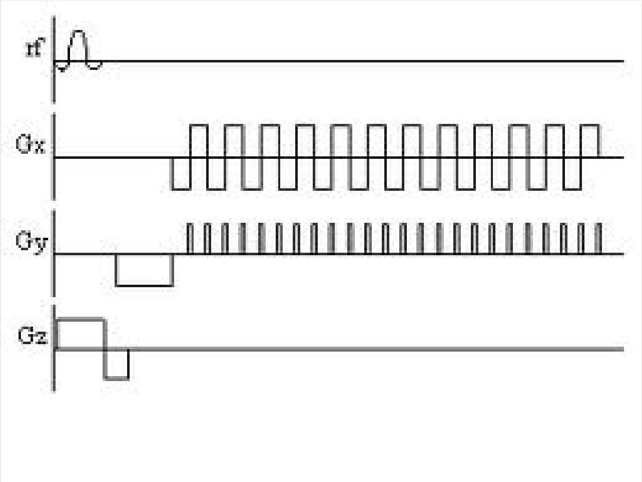


- Key Requirements:
  - Sensitive to changes in T2*
  - High temporal resolution.
  - Good brain coverage

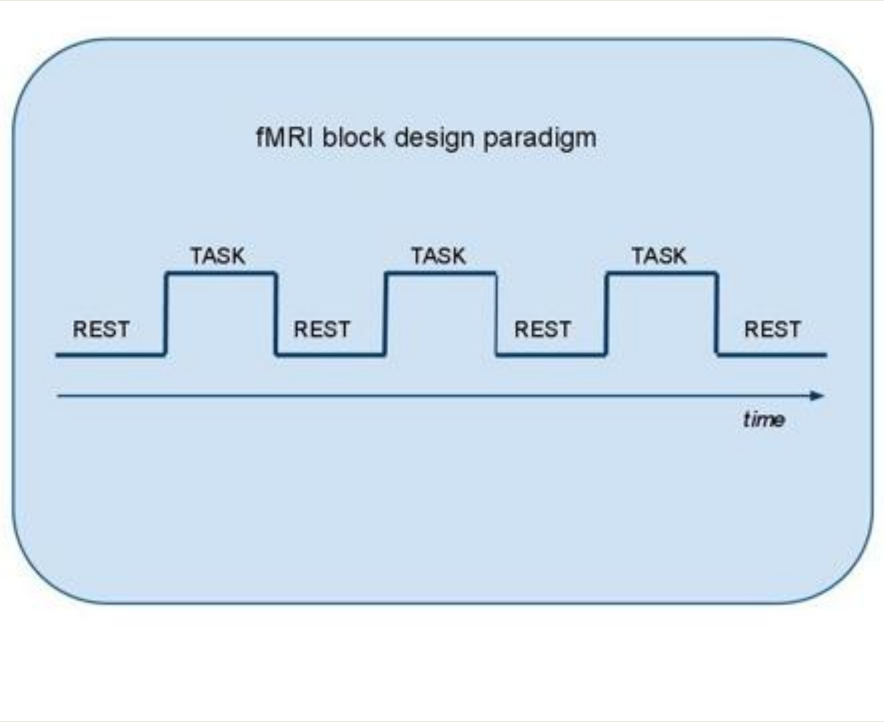
BOLD Acquisition: Low-res, Susceptibility Artifacts

- EPI and related techniques can suffer from geometric distortions and signal loss due to susceptibility-induced inhomogeneous fields.





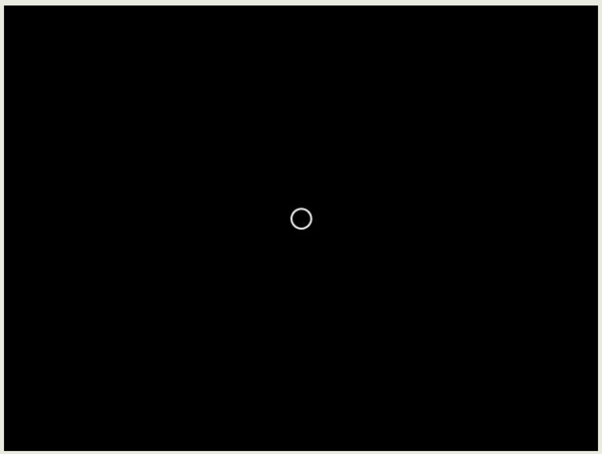
Block Design



- Most basic fMRI experiment: block design.
- Subject alternates between performing a cognitive task and resting.

Example: Visual Attention Block Design

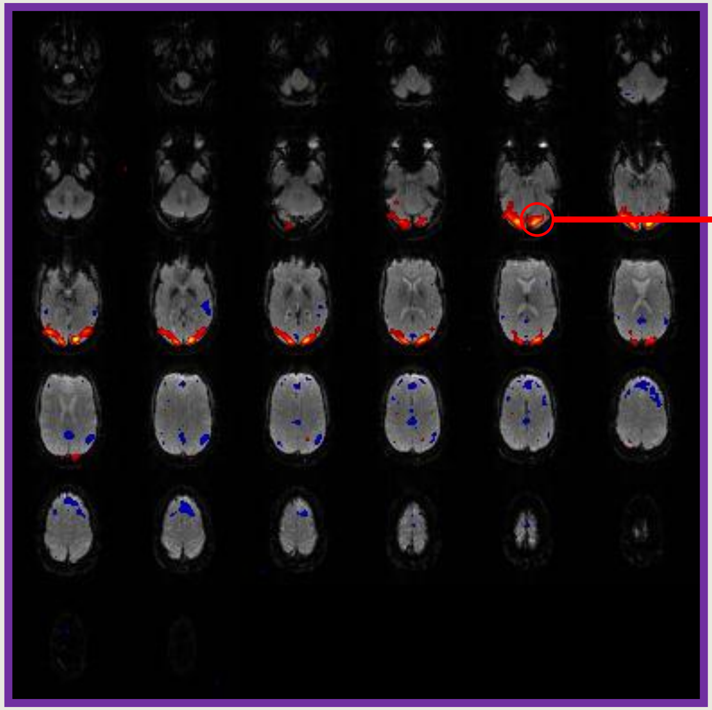
Alternating Visual Stimuli

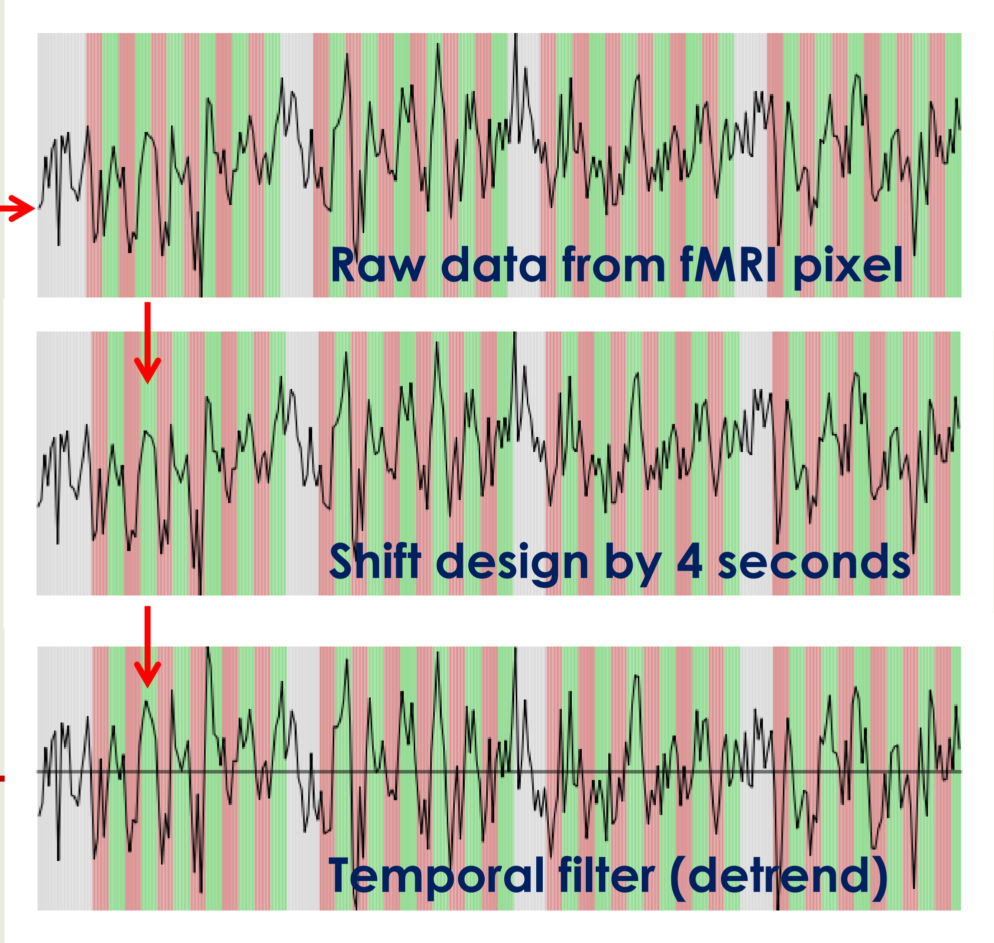


10 seconds
"Think about
playing basketball"

10 seconds
"Focus on the
painting"

Example:
Visual Attention Block Design





Difference of means
t-test: t>10
p < 0.0001

fMRI: Conventional Processing

- Within-scan motion correction (alignment)
- Registration with prior scans or to standard template
- Spatial Smoothing
- Temporal Filter
  - Low-pass: remove noise, physiologic processes
  - High-pass: remove low-frequency drift (detrend)
- Statistical test at each image pixel or within *a priori* region of interest: can the variation in the fMRI time series be explained (in part) by the experimental design function?

fMRI: Conventional Processing 'General Linear Model'

Statistical test to see how significantly the design explains the BOLD signal.

The test is performed at every pixel throughout the brain, and the results are displayed in a parametric map.

$$\mathbf{Ax = b}$$

Predictor variables are:

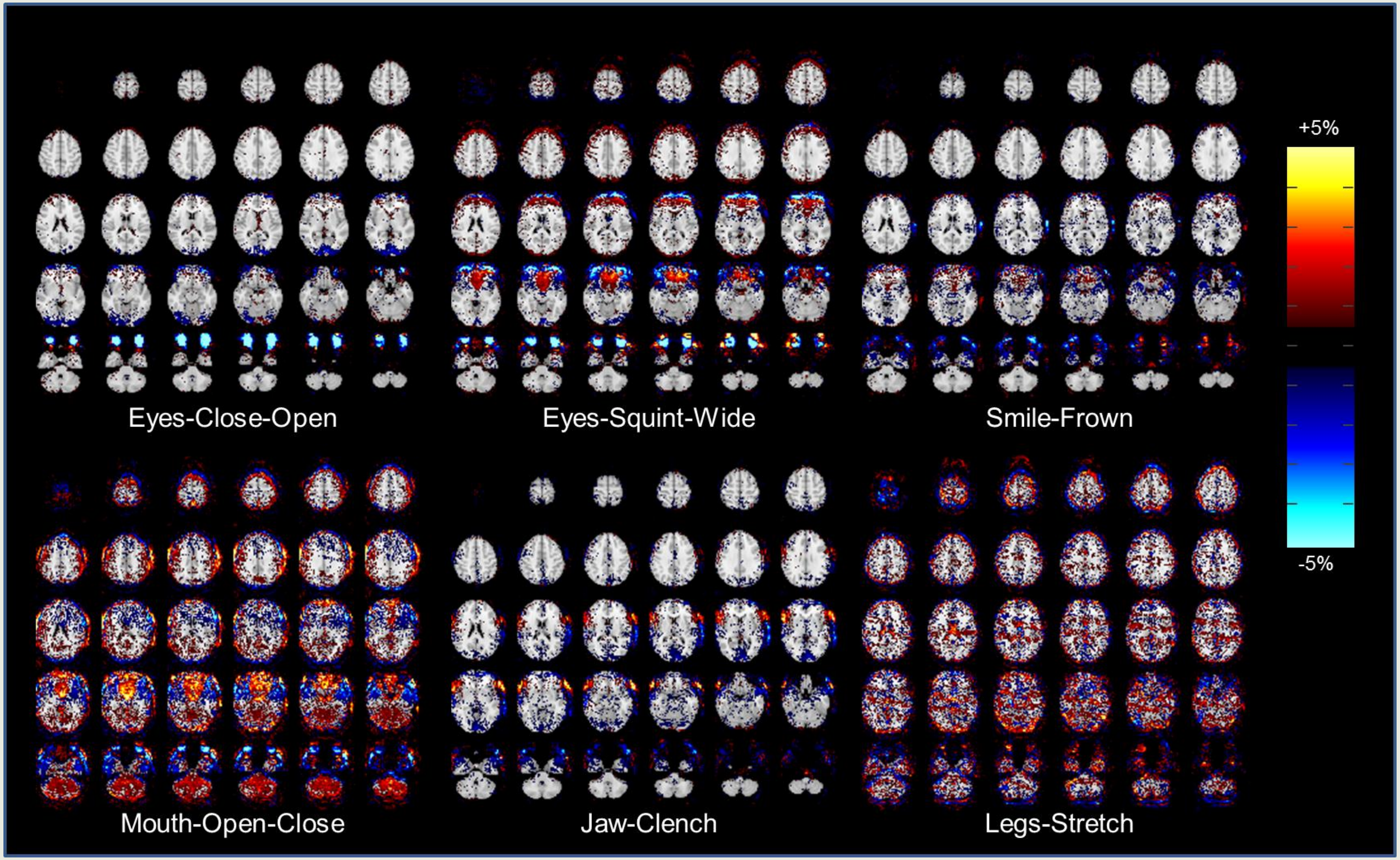
- Task design function convolved with hemodynamic response kernels
- Other control variables – eye tracking, motion tracking, etc.

Dependent variable is the raw fMRI time series at each pixel, after temporal filtering.

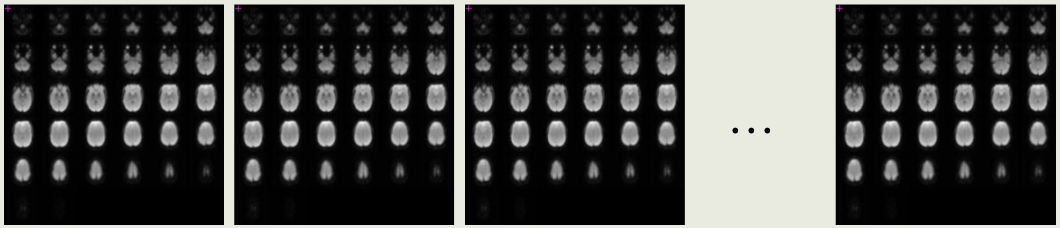
fMRI Technical Challenges

Technical Challenge in fMRI	Typical Remedy
Thermal noise	Spatial smoothing, scanning at higher field strength (3T, 7T), low-pass temporal filter, increase scan time, average results over multiple subjects
Low-frequency Drift (BOLD drift)	High-pass filter during pre-processing. Places limitations on task design (e.g., tasks periods should not last more than 1 minute).
Subject motion	Head restraint, registration/realignment, use of motion parameters as covariates in statistical analyses.

Subject motion...



How to adapt fMRI for Real-time?



Need to make a measurement specific to a single frame.

Strategies for Providing Feedback

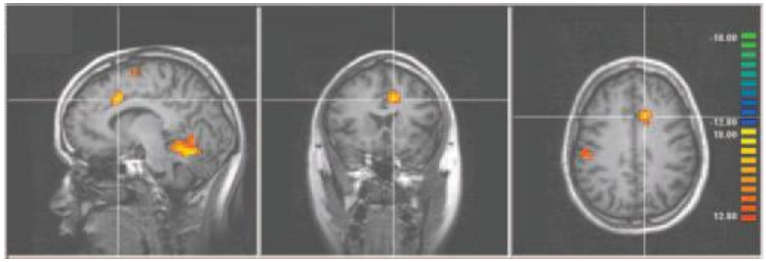
METHOD 1: Regional BOLD Feedback

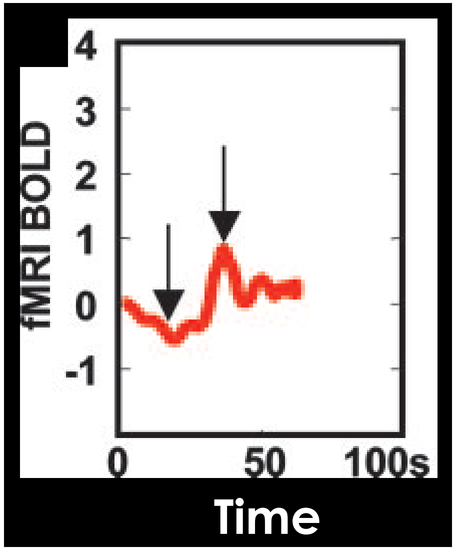
- Region of Interest (ROI) selected according to target application.
- BOLD signal fluctuations are shown to the subject during the scan.
- Subject attempts to control the feedback using his/her thoughts.

Cons:

- Noisy: physiologic variation and drift in BOLD signal.
- Requires ROI selection
- May not be well understood where activation should take place.

rACC - Rostral anterior cingulate cortex





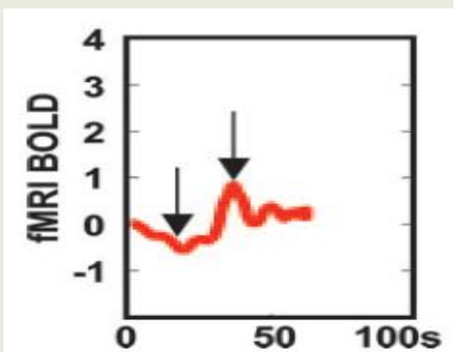
deCharms et al. Proc Natl Acad Sci U S A. 2005 Dec 20;102(51):18626-31.

Application to Chronic Pain: deCharms 2005 PNAS

Control over brain activation and pain learned by using real-time functional MRI

R. Christopher deCharms[†‡], Fumiko Maeda[§¶], Gary H. Glover[‖], David Ludlow[††], John M. Pauly[‡‡], Deepak Soneji[††], John D. E. Gabrieli[§,§§], and Sean C. Mackey[††]

- Chronic pain patients learned to control activation in the rostral anterior cingulate cortex, and reported a reduction in ongoing pain.
- Feedback consisted of the BOLD signal in the ROI as a scrolling line graph.



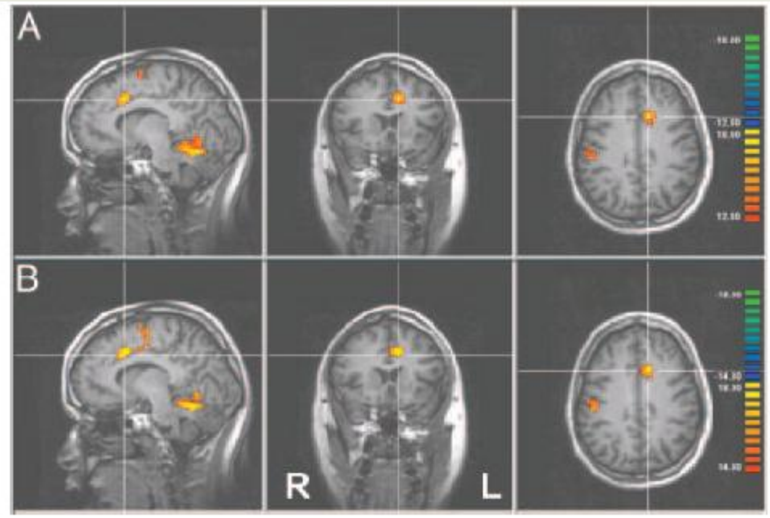


Fig. 2. Volumetric analysis of the spatial pattern of learned control over activation. (*A*) Change in activation comparing the last training session to the first training session showing activation in rACC, the targeted brain region. Seven total clusters were observed at this threshold level ($t > 12.80$, top of scale $t = 18.00$; for coordinates, see Table 1, which is published as supporting information on the PNAS web site). (*B*) Repeat of the same analysis comparing the posttest session (performed after the last training session) to the initial training session, showing similar results. Data are presented as thresholded, Bonferroni-corrected *t*-maps superimposed on high-resolution T1 data. The crosshairs indicate the three planes of section displayed and the group mean of the target ROI *y* and *z* coordinates used for rACC rtfMRI-based training (*x* coordinate for training ROI was midline). Color designates the *t* value, using a general linear model comparing different time periods convolved with a canonical hemodynamic response function. All data are experimental group averages after normalization to Talairach–Tournoux coordinates.

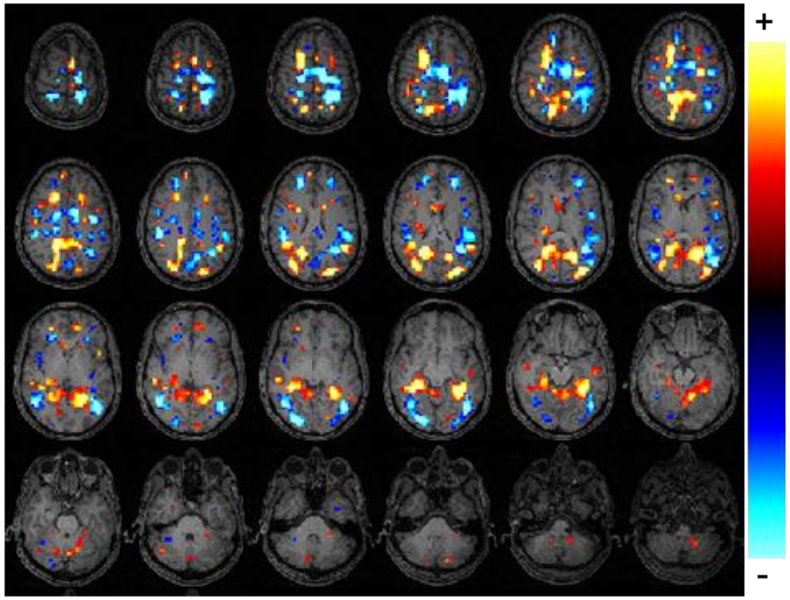
Strategies for Providing Feedback

METHOD 1: Regional BOLD Feedback

METHOD 2: Whole Brain-State Feedback

•Whole brain classifier developed on the basis of training portion of the scan.

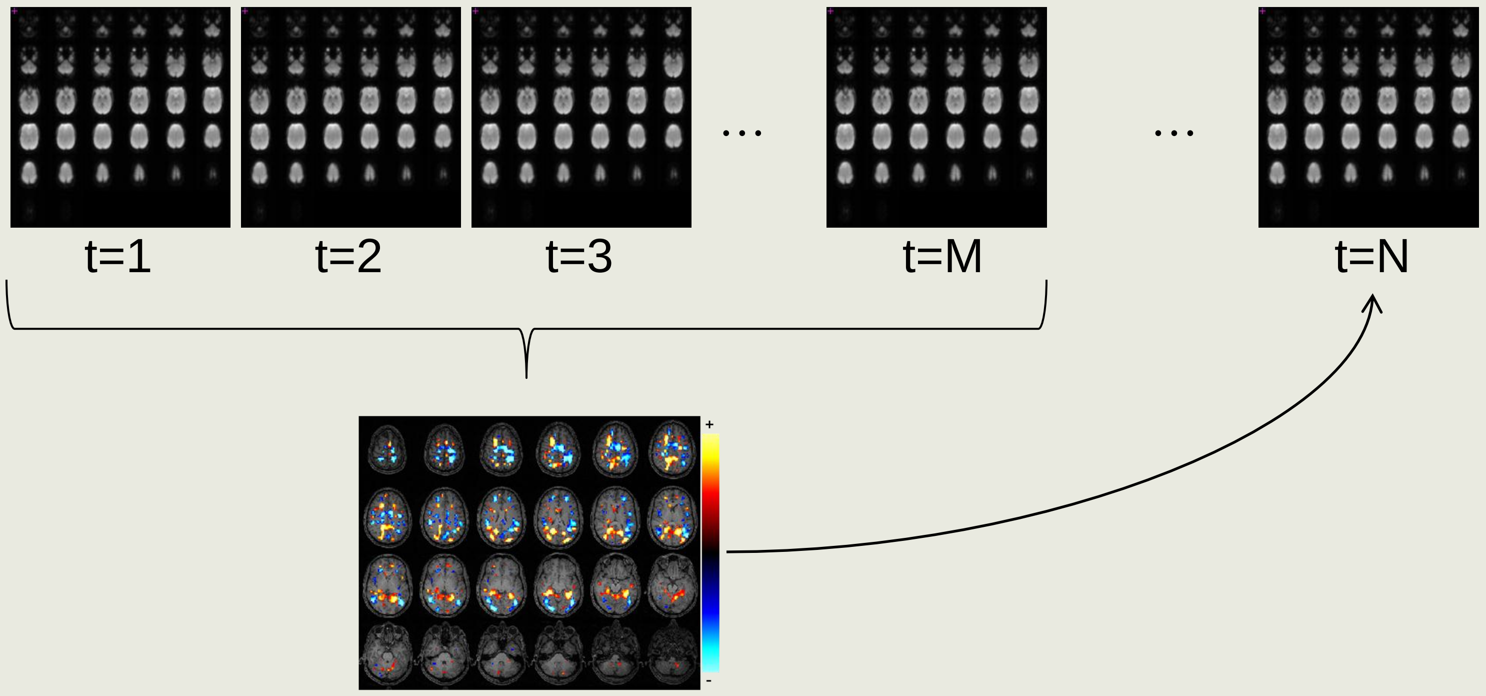
• Many pixels throughout the brain contribute to the feedback signal.



Whole brain classifier map for Tennis / Room-to-Room task.

LaConte et al. Real-time fMRI using brain state classification. Hum Brain Mapp. 2007 Oct;28(10):1033-44.

Whole-brain classifier approach



Strategies for Providing Feedback

METHOD 1: Regional BOLD Feedback

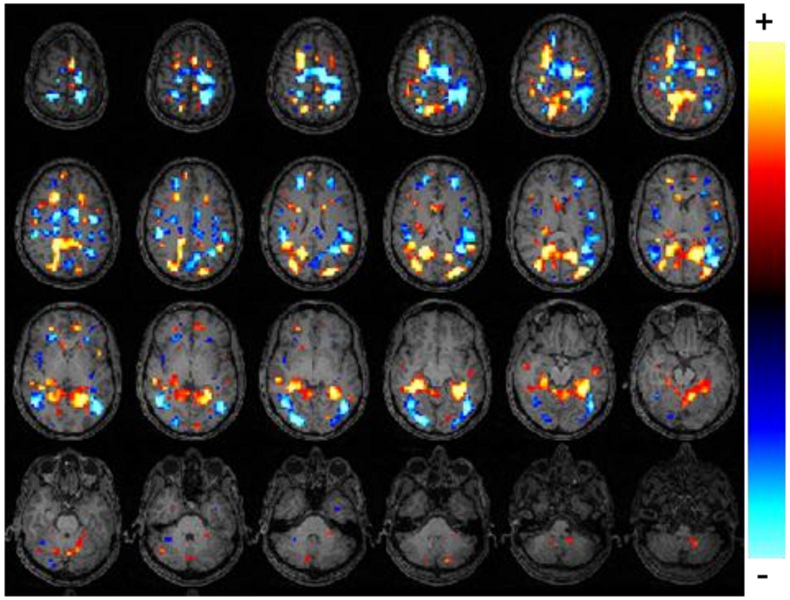
METHOD 2: Whole Brain-State Feedback

Pros:

- No ROI selection required.
- Automatically customized classifier for each particular patient / application.
- Automatic removal of irrelevant physiologic and cognitive processes.

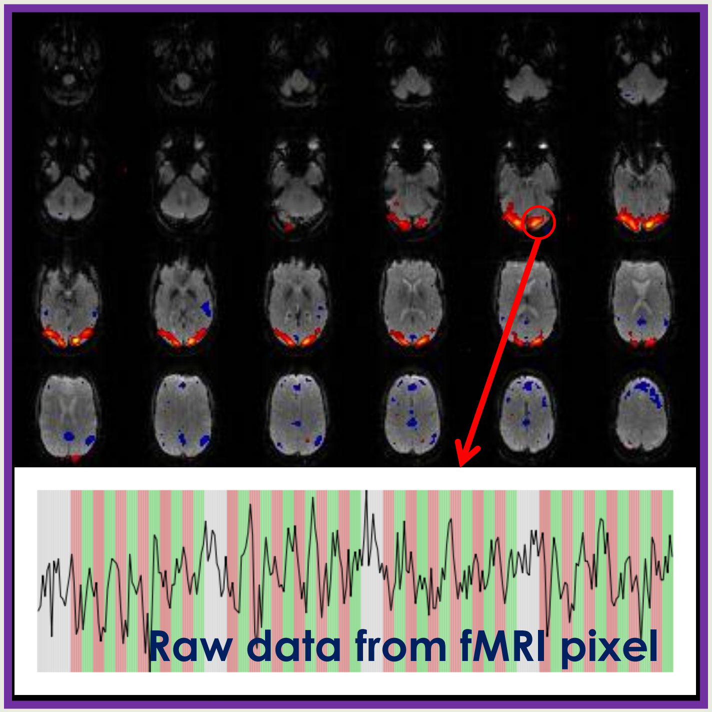
Cons:

- No spatial information in feedback
- Requires training period
- Susceptible to movement



Whole brain classifier map for Tennis / Room-to-Room task.

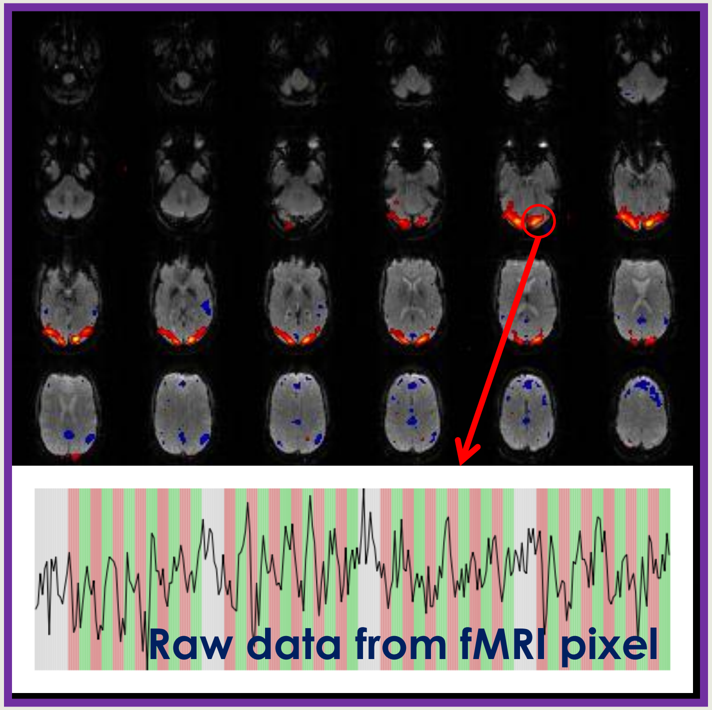
Whole-brain classification: Highly under-determined system



- Each pixel is a predictor variable (~ 40,000 predictors)
- Design function is dependent variable
- Each time point gives an equation (every 2 seconds)
- **Model needs to be computed in real time (within a few seconds)**

- <u>Choices for classification model:</u>
  - Support vector machine (SVM)
  - Principal component regression (PC-R)
  - Partial Least-Square Regression (PLS-R)
  - Ridge regression, and other techniques

Whole-brain classification: Highly under-determined system

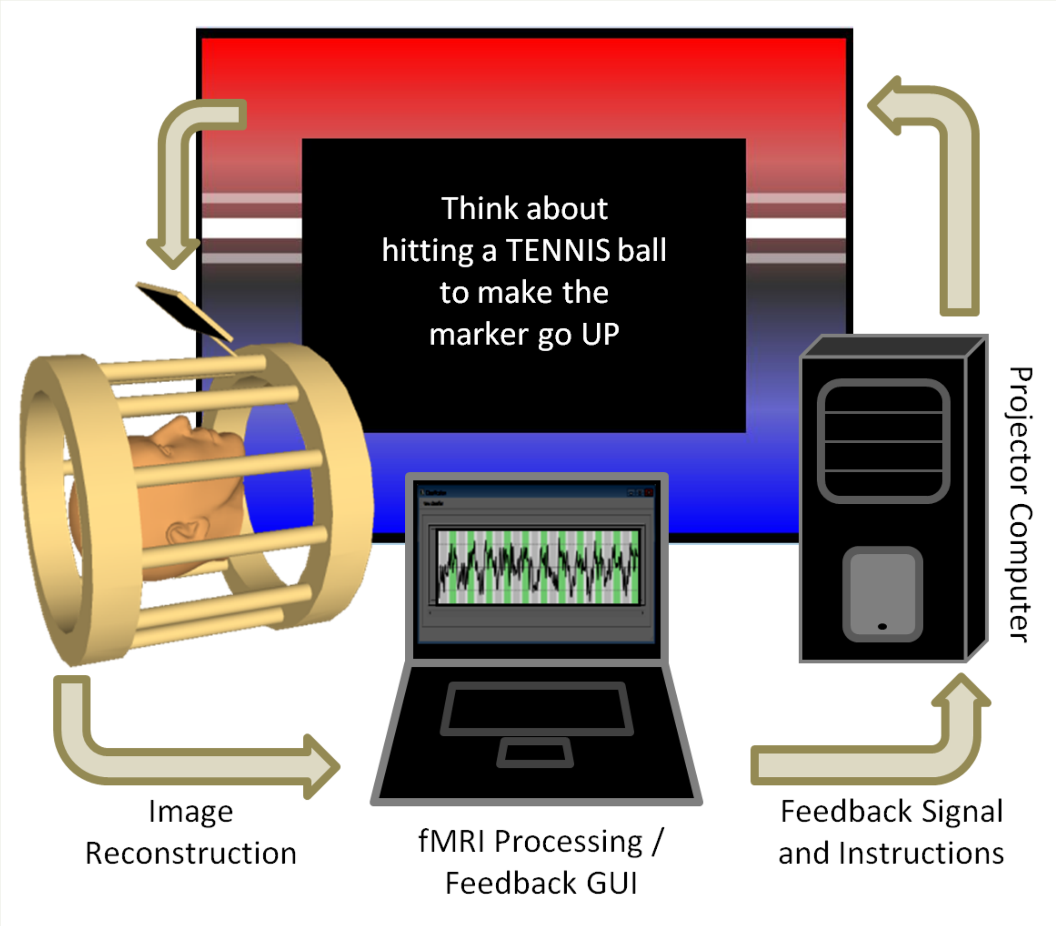


- <u>Choices for classification model:</u>
  - Support vector machine (SVM)
  - Principal component regression (PC-R)
  - Partial Least-Square Regression (PLS-R)
  - Ridge regression, and other techniques

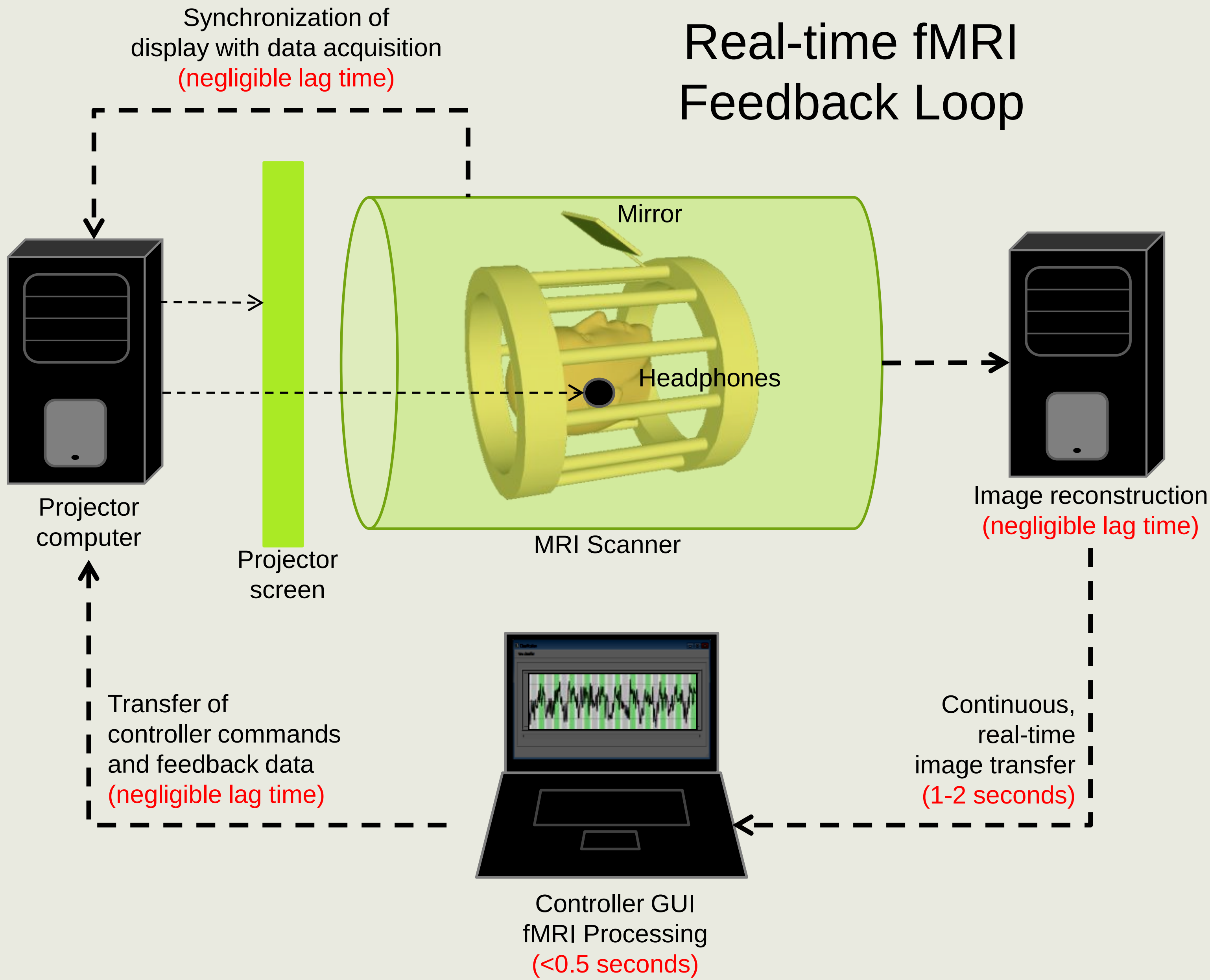
- Tried SVM, PC-R, and PLS-R
  - Produced very similar results
  - However, PLS-R was the clear choice because it is by far the least computationally demanding – (Important for real-time applications.)

Real-time Results

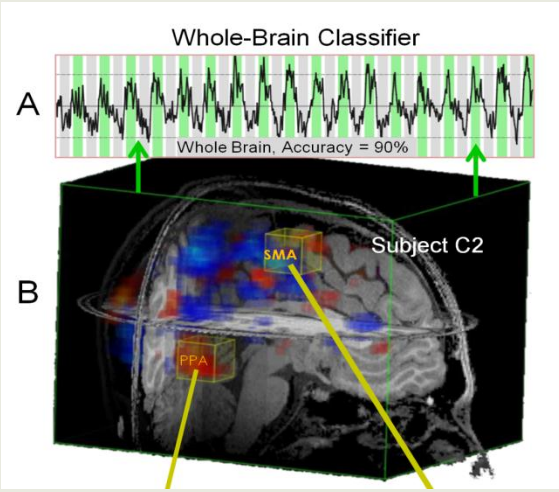
<u>Imagination tasks</u>:
Repetitive Motor
& Spatial Navigation

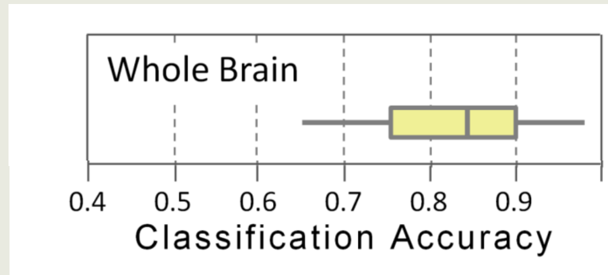


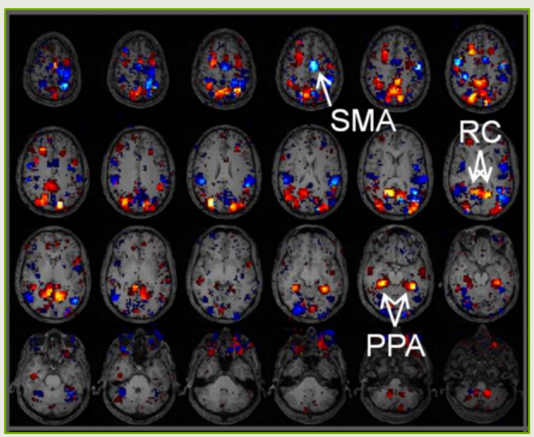
Real-time fMRI Feedback Loop



Real-time Results



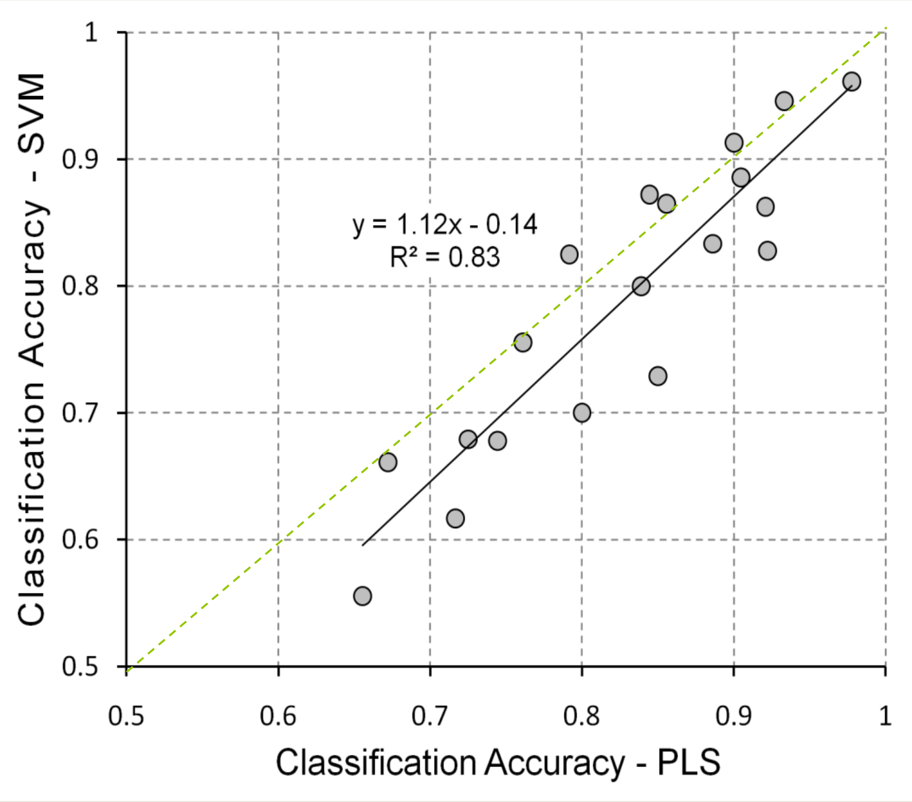




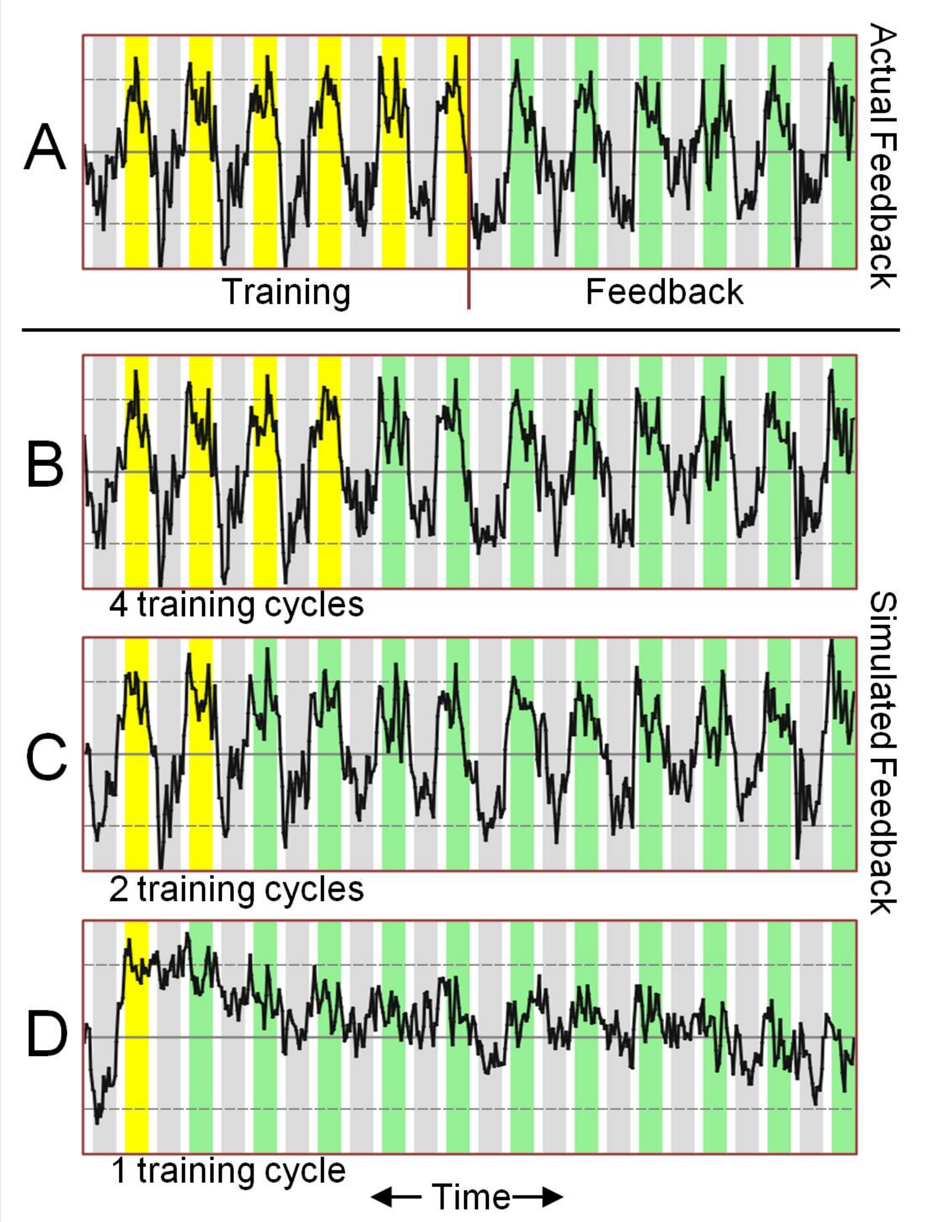
19 of 19 subjects were able to control the feedback cursor using only of their thoughts.

Feedback was provided on the basis of the whole-brain (PLS) classifier.

Real-time Results: SVM vs. PLS



PLS outperforms default SVM



Time needed for Machine-Learning with PLS

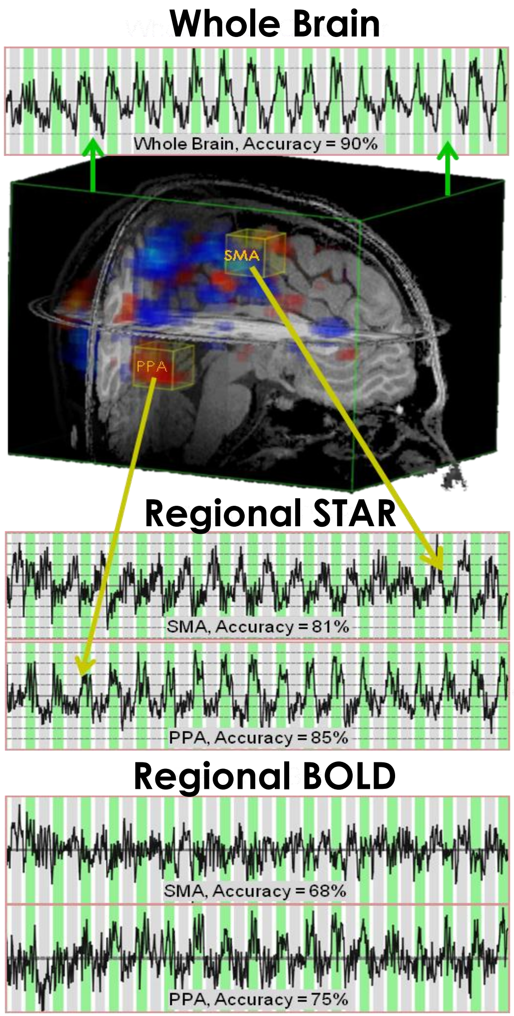
…

Strategies for Providing Feedback

METHOD 1: Regional BOLD Feedback
METHOD 2: Whole Brain State Feedback
METHOD 3: Spatio-temporally resolved activity in real time (STAR).

Idea:

- (Local) classifier is obtained at each spatial location (neighborhood of each pixel).
- Principal component analysis is used to remove noise.
- Robustness of whole-brain approach is combined with regional specificity.



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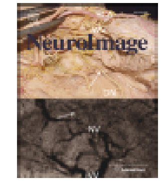

Spatio-temporal activity in real time (STAR): Optimization of regional fMRI feedback

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ABSTRACT

The use of real-time feedback has expanded fMRI from a brain probe to include potential brain interventions with significant therapeutic promise. However, whereas time-averaged blood oxygenation level-dependent (BOLD) signal measurement is usually sufficient for probing a brain state, the real-time (frame-to-frame) BOLD signal is noisy, compromising feedback accuracy. We have developed a new real-time processing technique (STAR) that combines noise-reduction properties of multi-voxel (e.g., whole-brain) techniques with the regional specificity critical for therapeutics. Nineteen subjects were given real-time feedback in a cognitive control task (imagining repetitive motor activity vs. spatial navigation), and were all able to control a visual feedback cursor based on whole-brain neural activity. The STAR technique was evaluated, retrospectively, for five a priori regions of interest in these data, and was shown to provide significantly better (frame-by-frame) classification accuracy than a regional BOLD technique. In addition to regional feedback signals, the output of the STAR technique includes spatio-temporal activity maps (movies) providing insight into brain dynamics. The STAR approach offers an appealing optimization for real-time fMRI applications requiring an anatomically-localized feedback signal.

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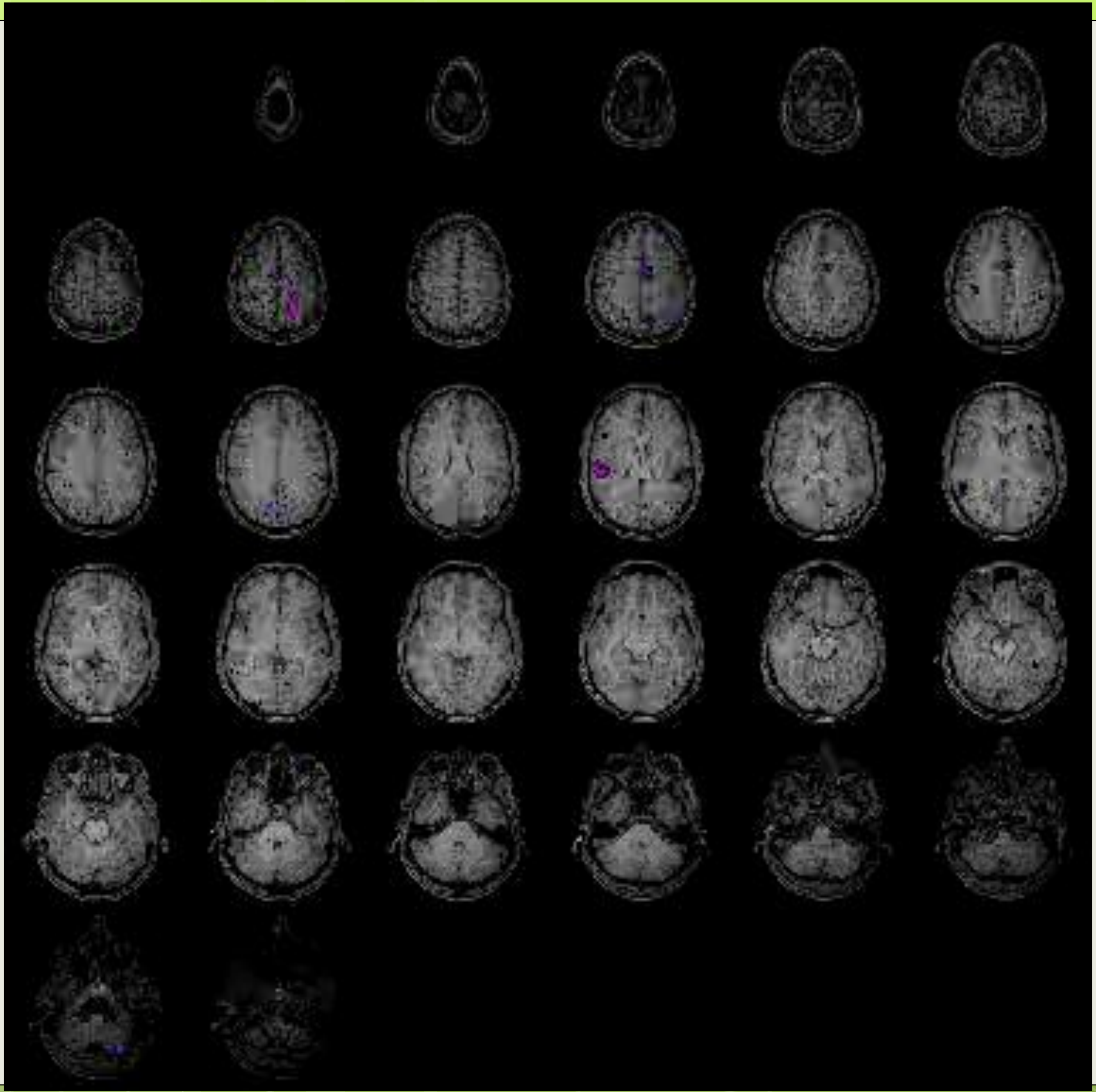
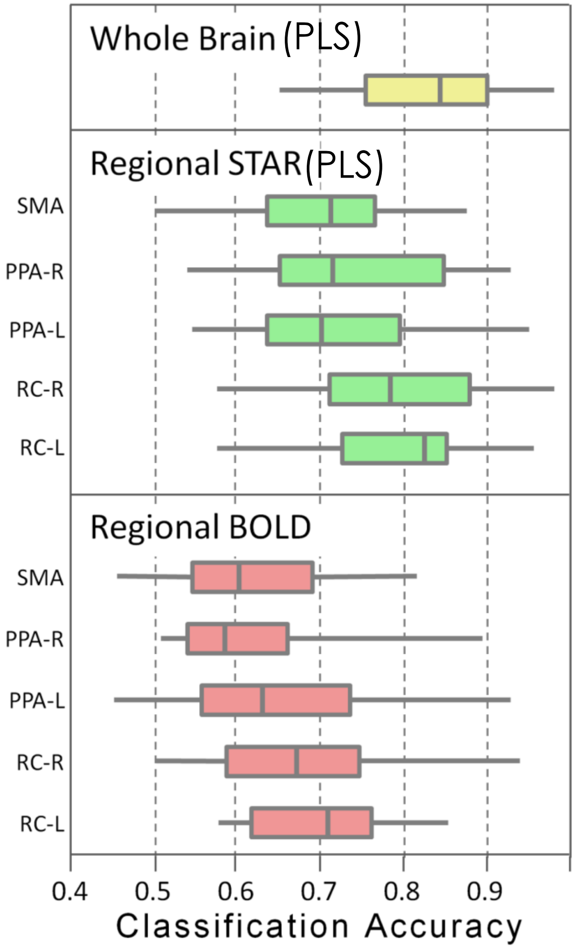
Introduction

Helping individuals to control their brain function through biofeedback has long-standing appeal. Brain biofeedback began by utilizing EEG (electroencephalogram, e.g., cortical rhythms, slow or evoked cortical potentials, etc.) Wolpaw et al. (2002) which features good temporal sensitivity, but has relatively poor spatial resolution

Although these demonstrations are encouraging, the regional BOLD technique presents significant unresolved challenges. A primary limitation of BOLD signal is its susceptibility, not only to drift (Yan et al., 2009), but also to physiologic noise, including non-cognitive processes such as motion and respiration as well as cognitive processes that are unrelated to the task(s) of interest. In conventional fMRI, such effects pose less of a problem, as they are averaged out over a typical 10- to 15-minute scan



STAR Method: Results



Study Protocol

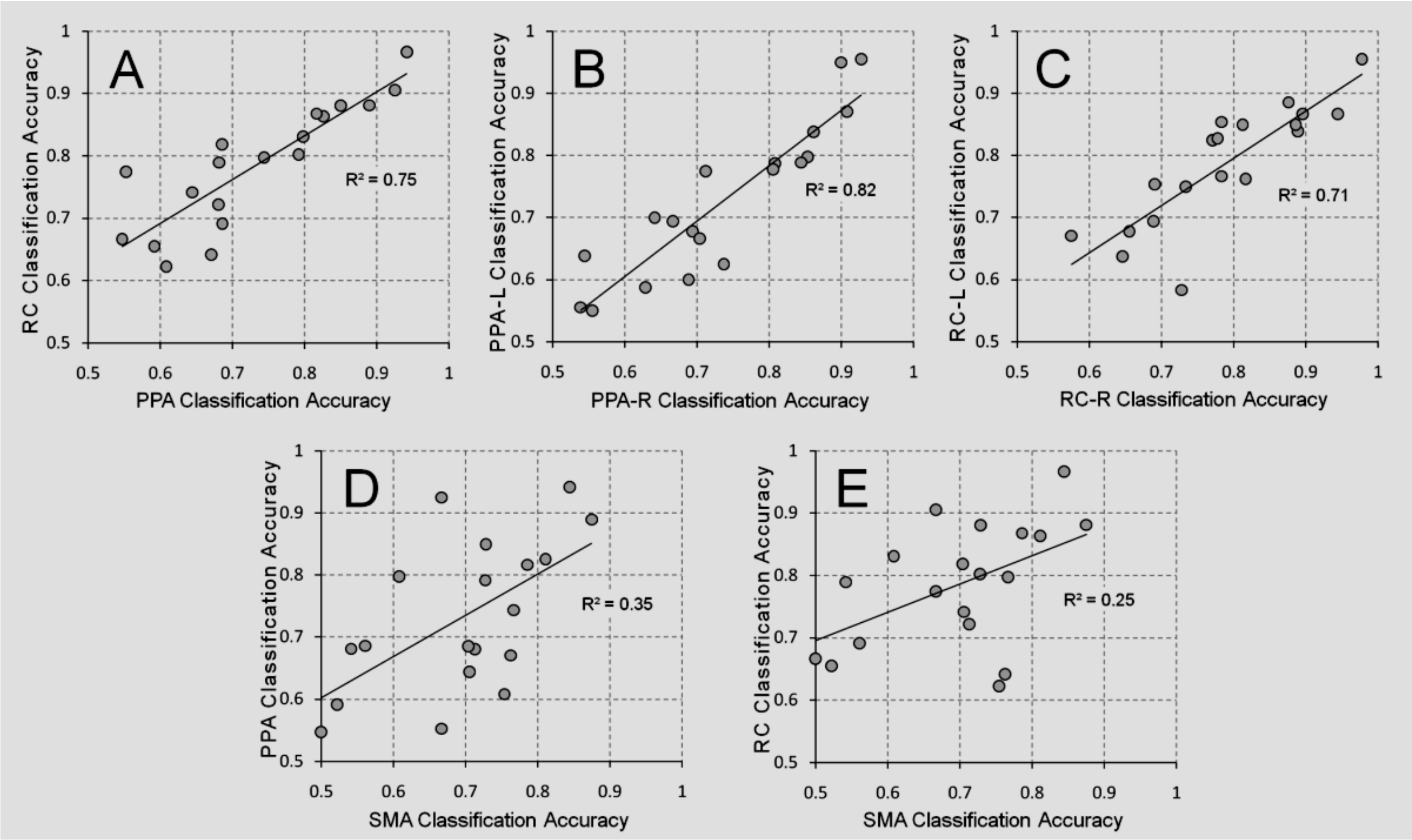
- 19 Subjects were scanned, 13 controls, 6 cocaine patients

- Classifier training period (~5 minutes) followed by a feedback period (8-24 minutes).

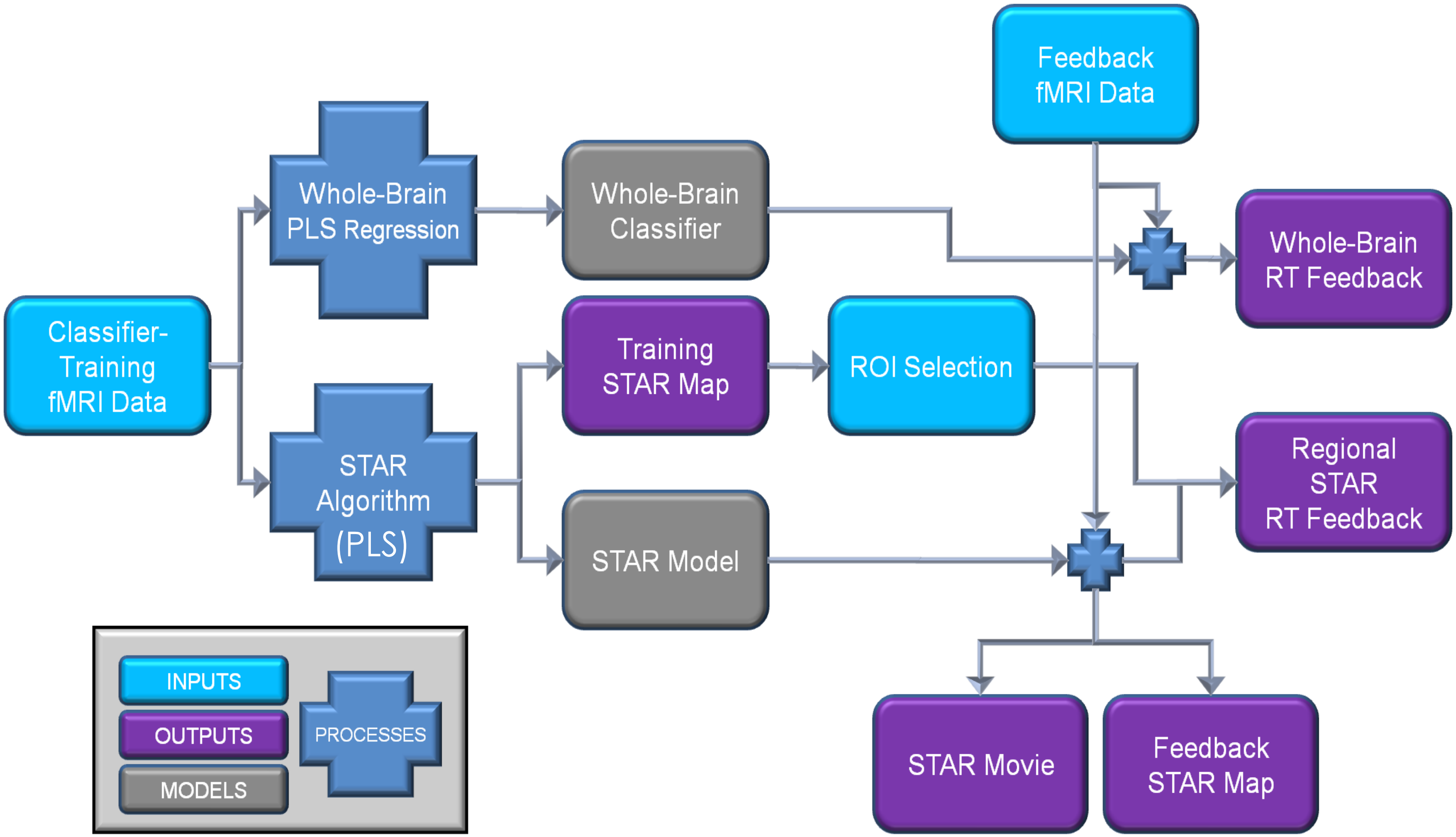
- Subjects were instructed to alternate between two sets of thoughts:
  (1) Repeatedly hitting a tennis ball to an imaginary partner (30 seconds)
  (2) Navigating from room to room in a familiar building (30 seconds)

STAR Method: Results

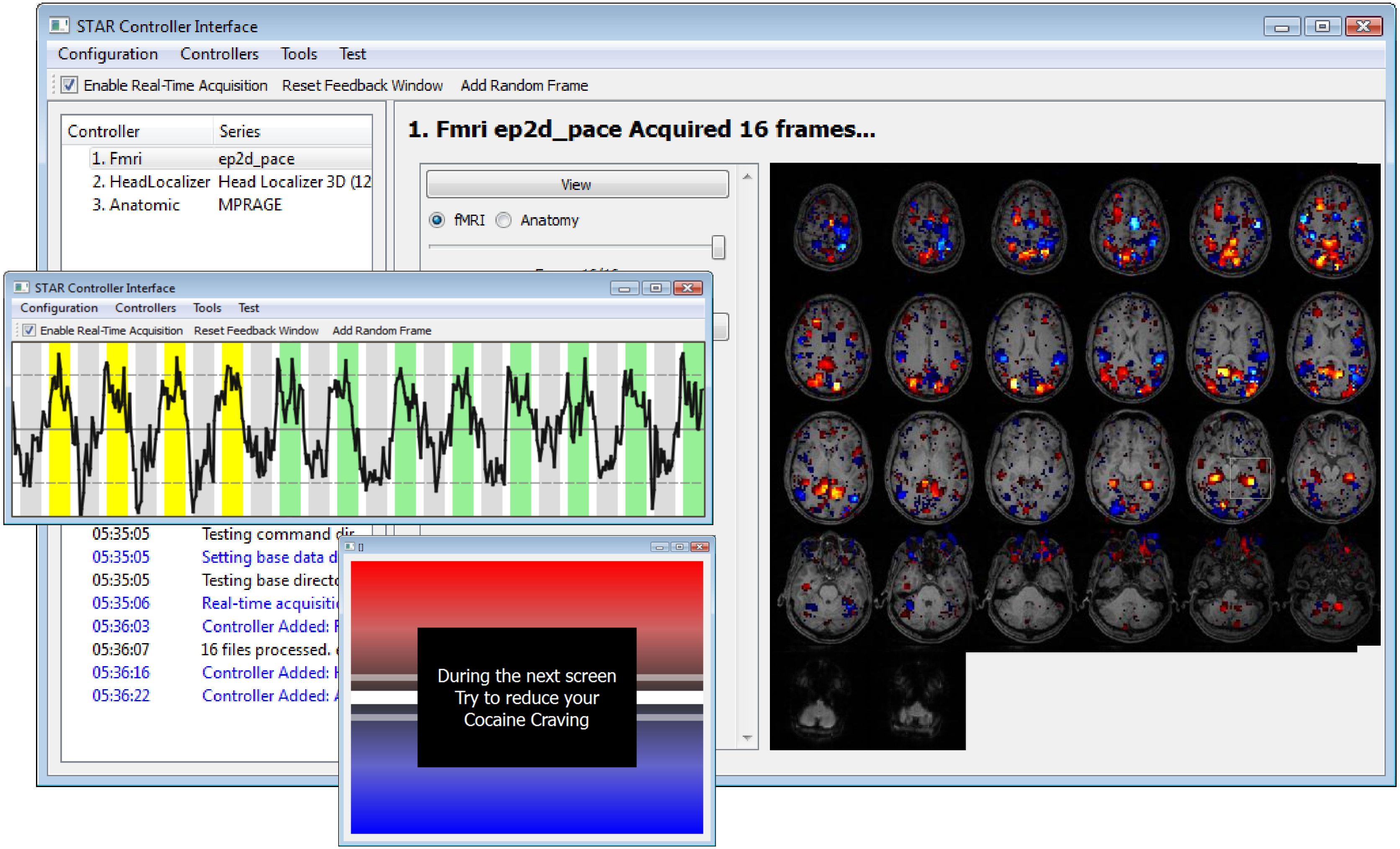
Evidence for Regional Specificity in STAR



STAR: Processing Pipeline



User Interface

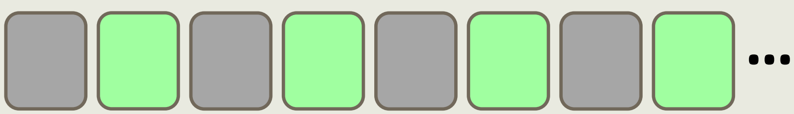


Target Application: Treatment of Craving and Addiction

- (Anna Rose Childress): Real-time fMRI pattern training for treatment of craving and addiction.
- Goal: To determine whether substance abuse patients can use rtfMRI feedback technology to control patterns in their own motivational circuitry, with associated reductions in drug craving.

Cocaine Application: Initial Experiments

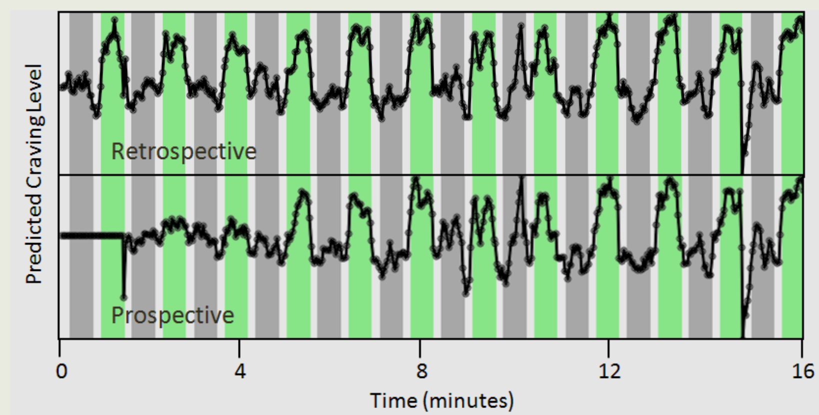
- Previously acquired fMRI datasets from cocaine-addicted subjects were retrospectively analyzed for feasibility of whole-brain real-time classification.
- **Block design**:



= neutral video (30 sec)

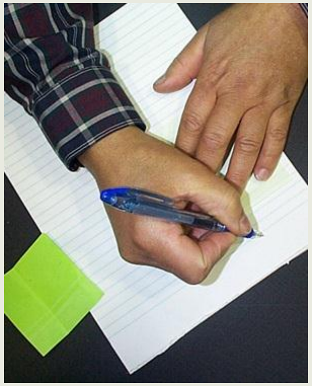
= cocaine video (30 sec)

- **Results**: Whole-brain classifier was able to quickly distinguish between cocaine and neutral videos
- Training duration was 3-5 minutes for all subjects.



Cocaine Application: Initial Experiments

- We soon realized that direct tracking of the 'craving' state is problematic.
- Although classifier could distinguish between cocaine and neutral videos, we were probably *not* tracking 'craving', but other processes triggered by the videos.
- Issue: when craving goes on, it does not go off easily -- could persist for many minutes.
- Therefore, not well-suitable for BOLD techniques (due to drift)



Distraction Paradigm

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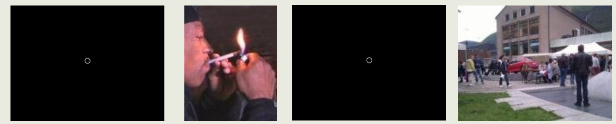
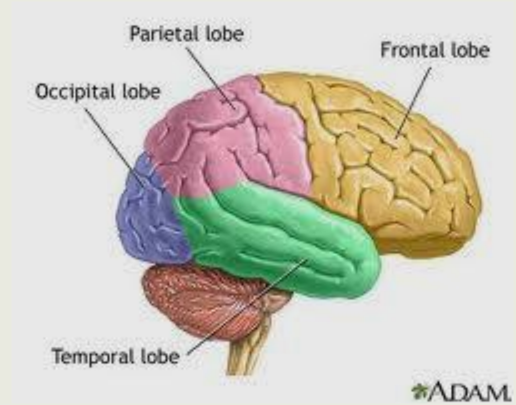


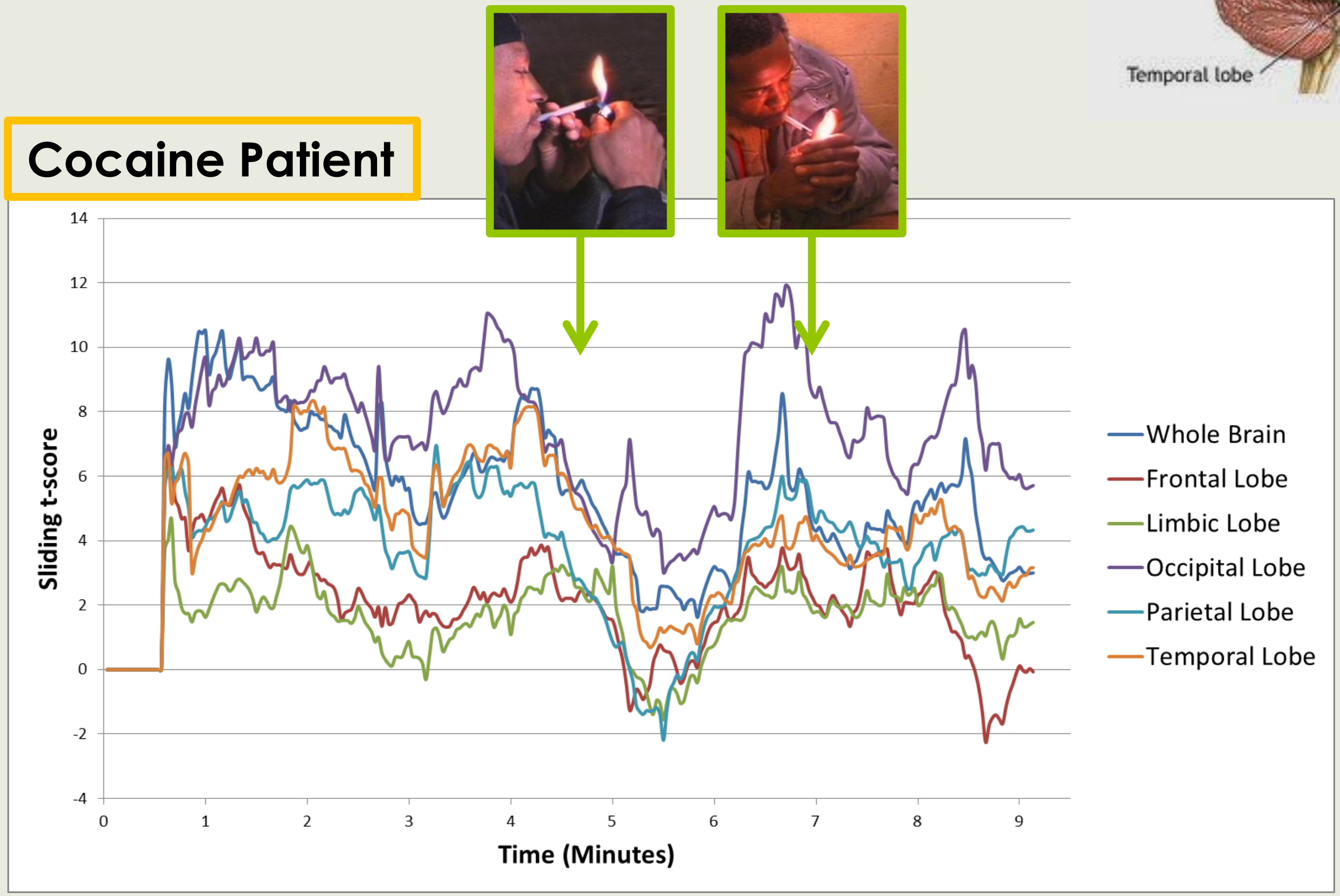
…

- Six seconds on each stimulus.
- Instructions: When you see the place pictures, imagine yourself in that place, interacting with the people, etc.
- More than just a visual stimulus paradigm.
- Cognitive control task: stay focused on the pictures as they appear
- Blank screens provides contrast (brain is resting)
- ‘Craving’ is measured in terms of a breakdown in cognitive control after the distraction image appears.

Distraction Paradigm: Prelim. Results

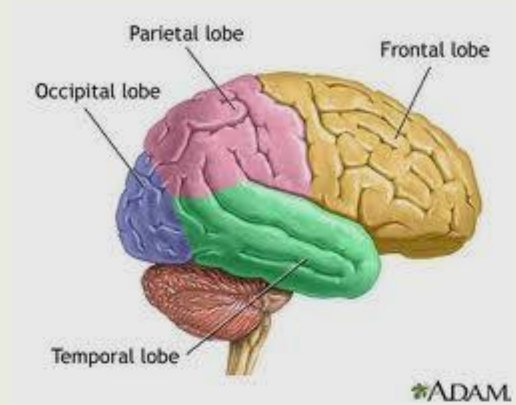


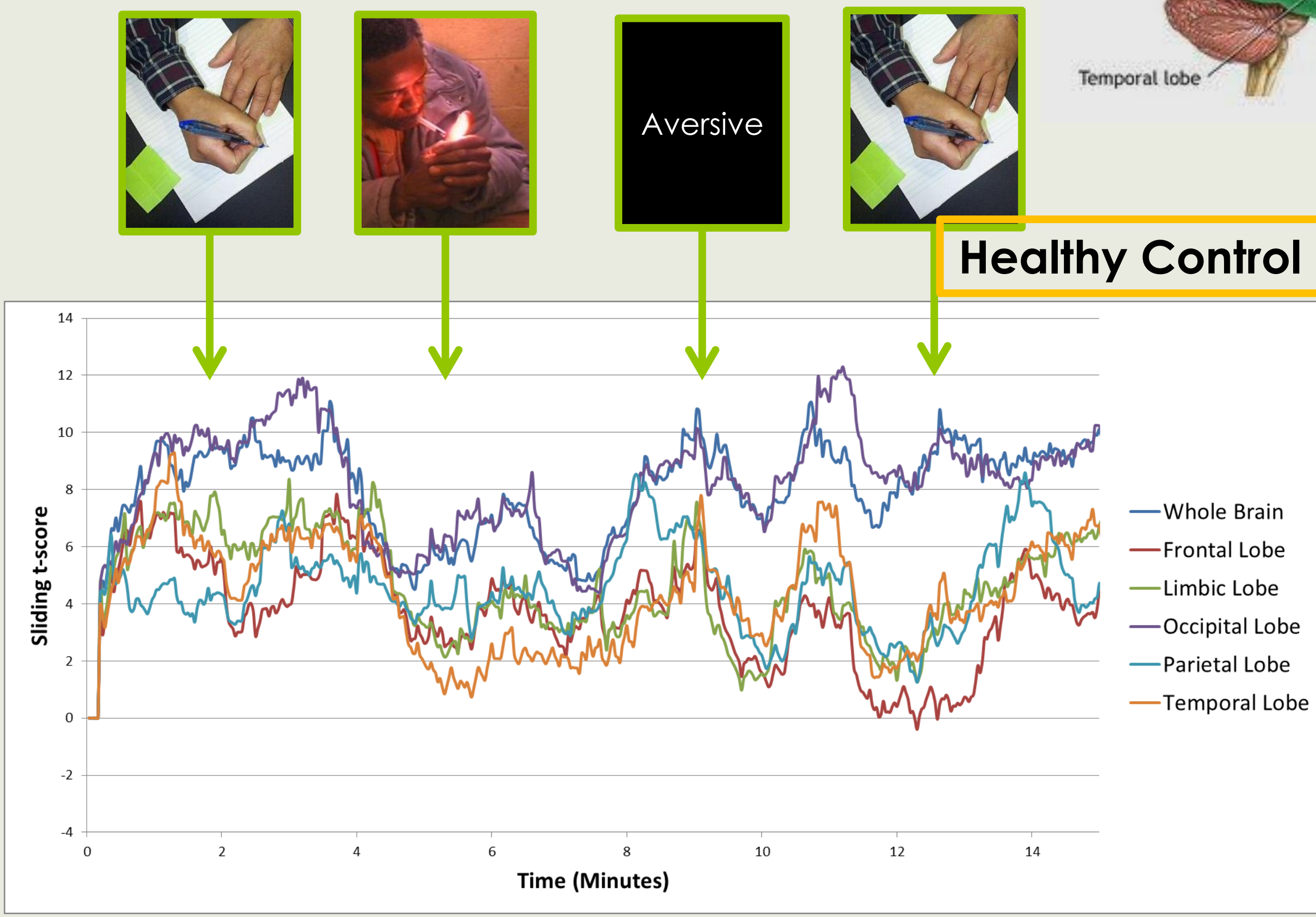
Cocaine Patient



Cross-validated classification results

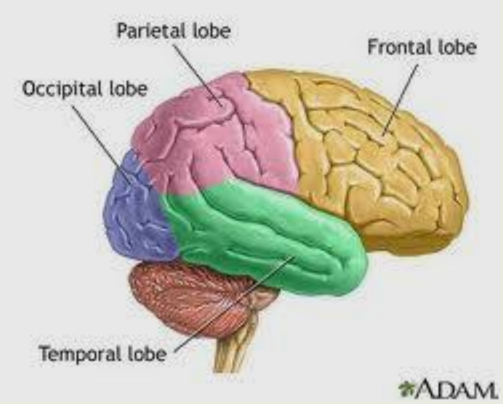
Distraction Paradigm: Prelim. Results





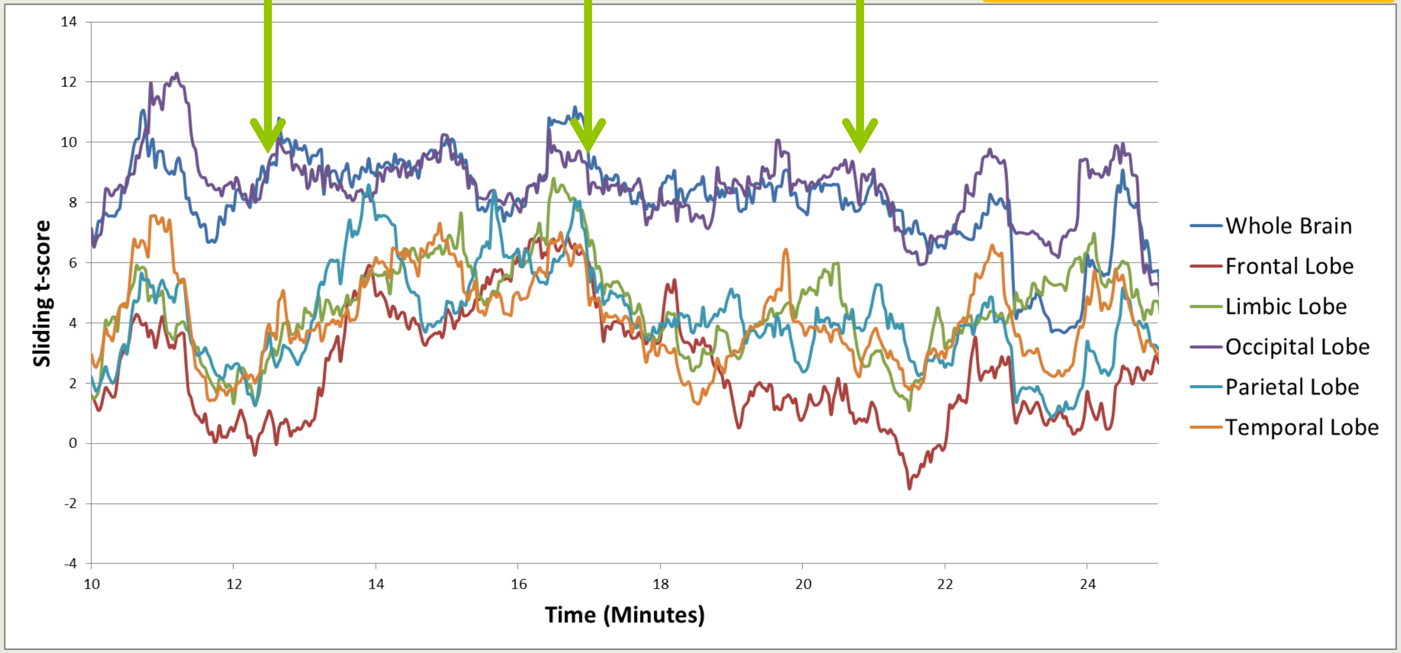
Cross-validated classification results

Distraction Paradigm: Prelim. Results



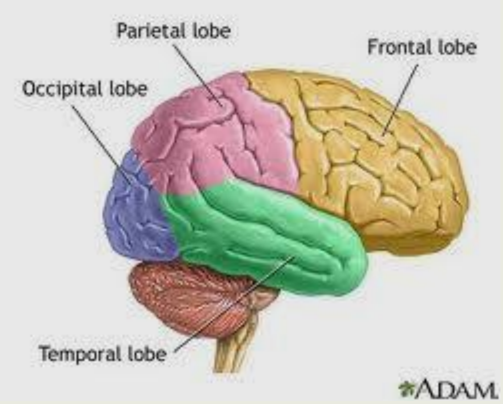
Aversive

Healthy Control

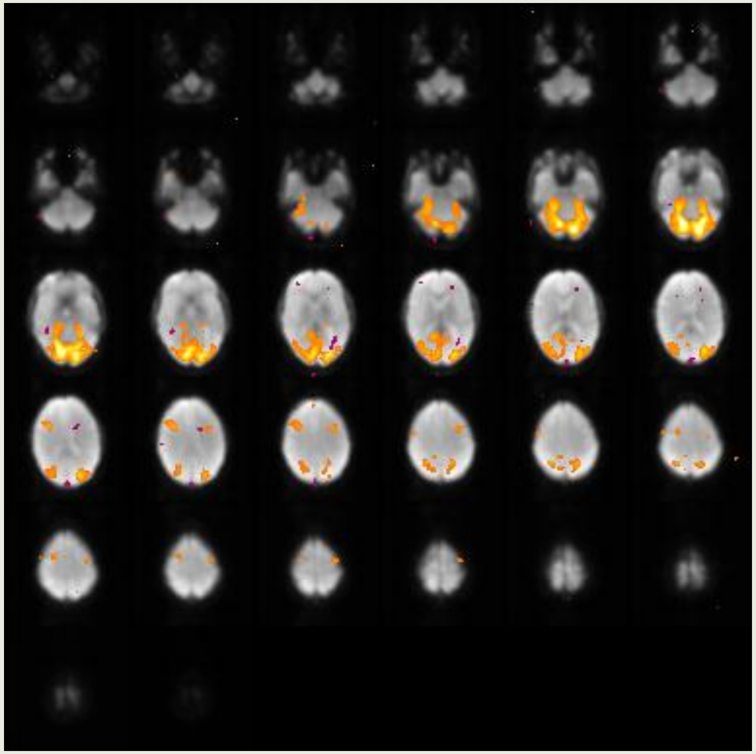


Cross-validated classification results

Distraction Paradigm: Prelim. Results



Same Healthy Control – t-score map



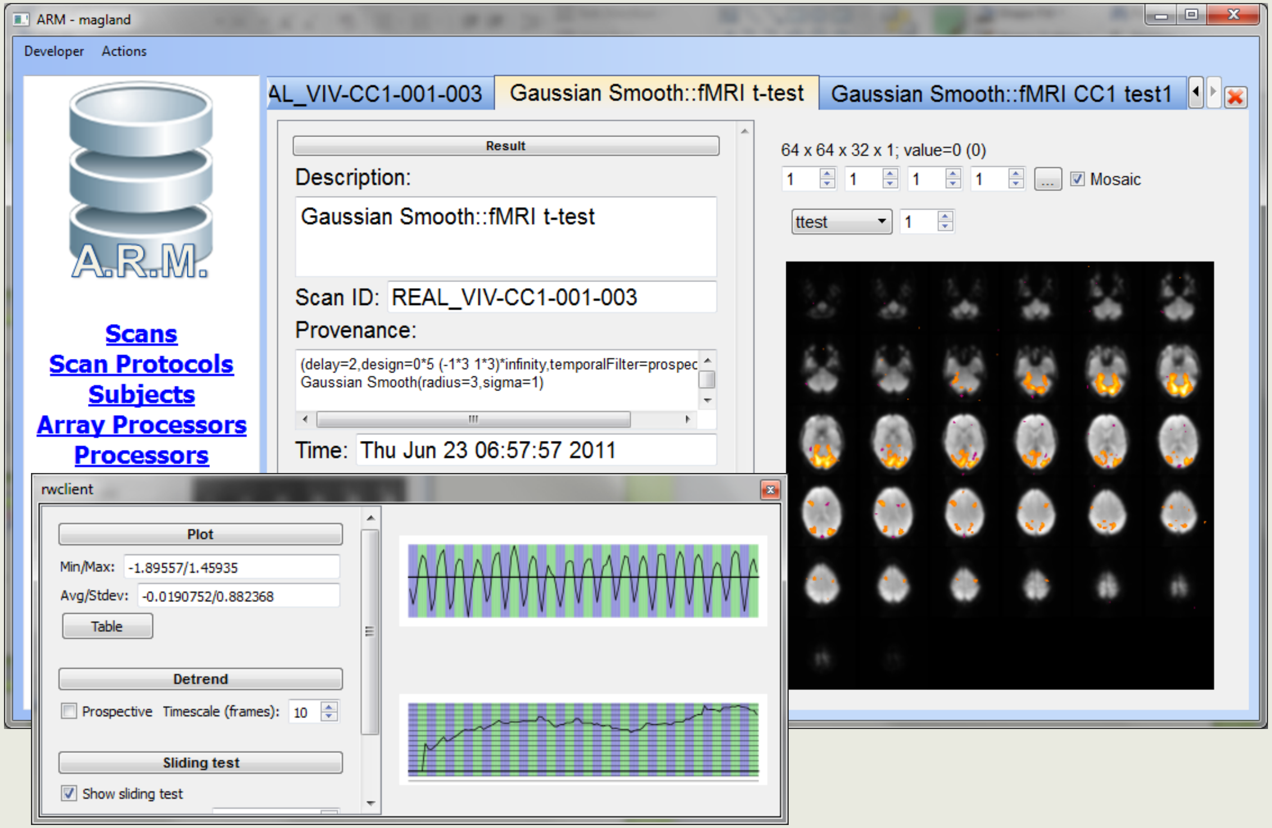
- Spatial parametric map does not provide as much information as multi-voxel/classifier approaches.

Summary

- Real-time fMRI requires special data processing considerations
- Classifier-based approaches can be used to provide robust real-time fMRI feedback.
- We have explored a paradigm for quantifying cognitive control (under preliminary testing).
- In the presence of distractions, this paradigm could be used to quantify and/or treat various cognitive disorders.

Working to make data available for collaborative exploration

Cloud-based
software for
fMRI data exploration



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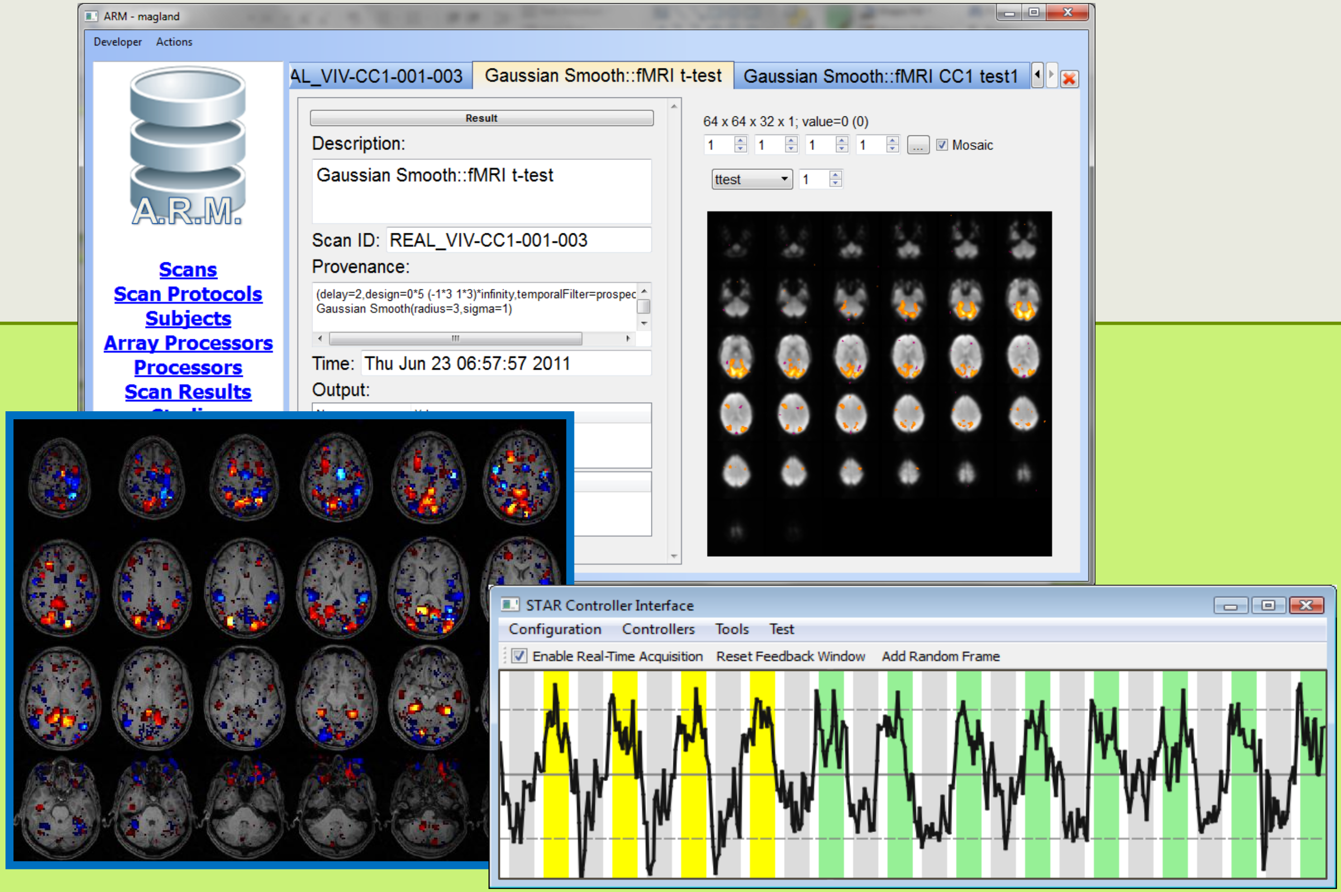
P50-DA12756

P60-DA005186

Thank you!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Developer
Actions
A.R.M.
Scans
Scan Protocols
Subjects
Array Processors
Processors
Scan Results
AL_VIV-CC1-001-003
Gaussian Smooth::fMRI t-test
Gaussian Smooth::fMRI CC1 test1
Result
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Time: Thu Jun 23 06:57:57 2011
Output:
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Mosaic
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STAR Controller Interface
Configuration
Controllers
Tools
Test
Enable Real-Time Acquisition
Reset Feedback Window
Add Random Frame