Processing Strategies for Real-Time Neurofeedback Using fMRI

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Cognitive Control

- Ability to regulate one's 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

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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 (CMRO₂).
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.

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

- Visual Attention Block Design
- Shift design by 4 seconds
- Raw data from fMRI pixel
- Shift design by 4 seconds
- Temporal filter (detrend)

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.

\[ Ax = b \]

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

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

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.
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 approach

t=1  t=2  t=3  t=M  t=N
**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)**

- **Choices for classification model:**
  - 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

- Choices for classification model:
  - 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

Imagination tasks:
Repetitive Motor & Spatial Navigation

Think about hitting a TENNIS ball to make the marker go UP

Image Reconstruction
fMRI Processing / Feedback GUI
Feedback Signal and Instructions
Controller GUI

fMRI Processing
(<0.5 seconds)

Projector computer

Synchronization of display with data acquisition
(negligible lag time)

MRI Scanner

Image reconstruction
(negligible lag time)

Continuous, real-time image transfer
(1-2 seconds)

Controller GUI fMRI Processing
(<0.5 seconds)

Transfer of controller commands and feedback data
(negligible lag time)

Continuous, real-time image transfer
(1-2 seconds)

Mirror

Headphones
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

\[ y = 1.12x - 0.14 \]
\[ R^2 = 0.83 \]
Time needed for Machine-Learning with PLS

A

B

4 training cycles

C

2 training cycles

D

1 training cycle
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.

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 oxygen 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 correct 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.
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

A: $R^2 = 0.75$

B: $R^2 = 0.82$

C: $R^2 = 0.71$

D: $R^2 = 0.35$

E: $R^2 = 0.25$
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:**

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

- \(\Box = \text{neutral video (30 sec)}\)
- \(\Box = \text{cocaine video (30 sec)}\)

[Graph showing predicted craving level over time for retrospective and prospective scenarios.]
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-suited for BOLD techniques (due to drift)
Distraction Paradigm

- 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

Cross-validated classification results
Distraction Paradigm: Prelim. Results

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

Same Healthy Control – t-score map
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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