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Applying Multivariate Analysis Approaches to 1H-MRS Data to Detect Neuronal Currents

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U.S. DEPARTMENT OF ENERGY

NNSA National Nuclear Security Administration

LDRD LABORATORY DIRECTED RESEARCH & DEVELOPMENT

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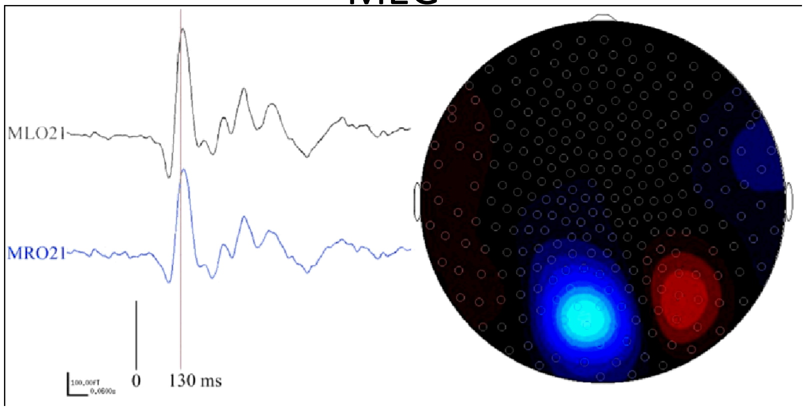
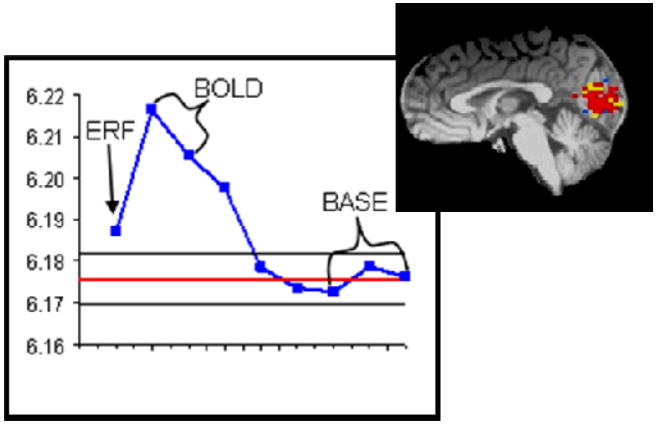
Motivation

- Problem
  - MEG and fMRI are not capable of directly measuring the neuronal response with high temporal and spatial resolution.
- Goal
  - Develop a neuronal current (NC) imaging technology by directly measuring neuronal responses with high temporal and spatial resolution.
    - Proton Magnetic Resonance Spectroscopy (1HMRS)
    - Multivariate analysis techniques
- Impact
  - Provides researchers with a revolutionary imaging tool to directly understand how the brain operates as the result of cognitive challenges.

MEG



fMRI



MR technologies measure local magnetic fields within the brain

$$\omega(r)=\gamma B(r)$$

The frequency of the MR signal is proportional to the magnetic field, where B consists of an ensemble of magnetic fields.

$$S(t,r)=K(t)e^{-i\omega(r)t}$$

MR signal at a point *r*. *K(t)* is an exponentially decaying signal.

$$S(t)=K(t)e^{-i\gamma\mu_B t}e^{-k\sigma_B^2 t}$$

$$\mu_B=Mean(p(B)) \qquad \sigma_B=Variance(p(B))$$

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FID – Free Induction Decay Signal. It decays approximately exponentially.

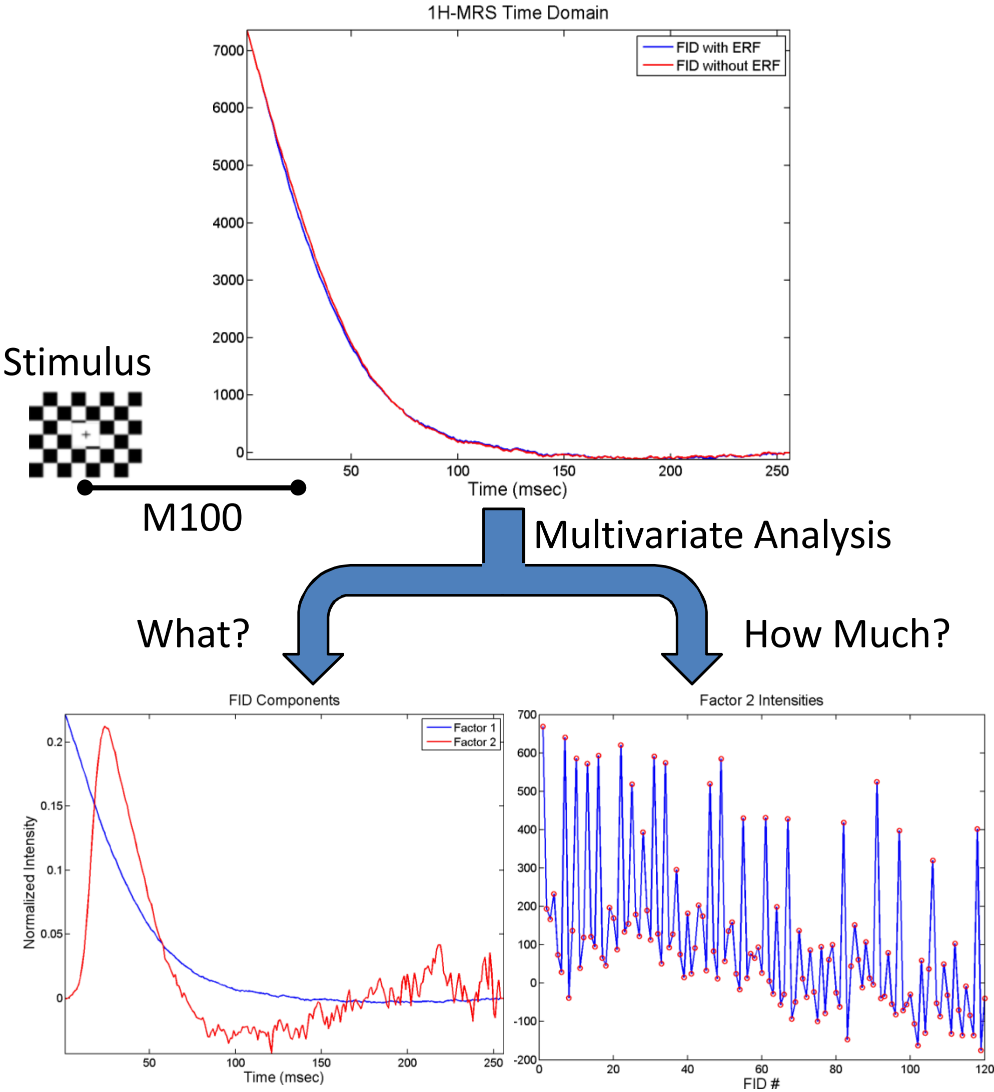
The neuronal current detection is based on the above equation modified to take into account the transient nature of the neuronal currents.

$$S(t)=K(t)e^{-i\int_0^t A_\phi f_{nc}(\tau)d\tau}\,e^{-\int_0^t A_M f_{nc}(\tau)d\tau}$$

$f_{nc}(\tau)$ is the neuronal current response

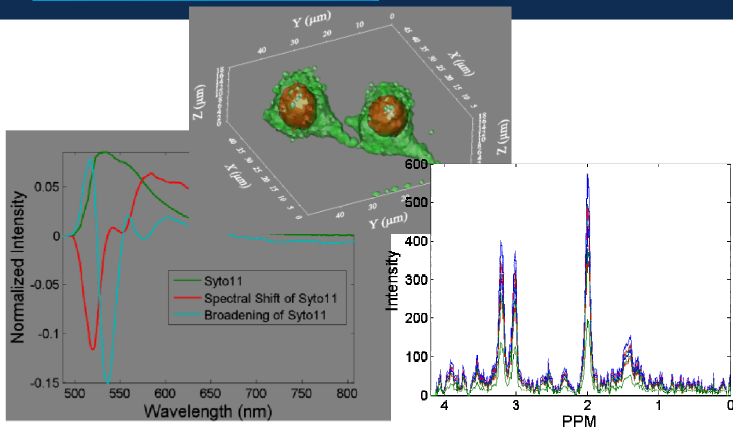
Our multivariate approach

Hypothesis: These NC event-related magnetic fields (ERFs) are the same fields that would be detected by MEG and will affect the 1H-MRS data in a manner that can be detected with our multivariate analysis methods.



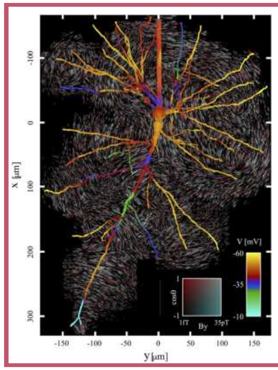
Striving to succeed where others have failed

- Current literature
  - **Theoretical and Computer Simulations** have shown the magnetic fields produced by some of brain's electrical activity should be large enough to be detectable.
    - Konn et al. MRM 2003
    - Bodurka et al. JMR 1999
    - Blagoev et al. Neuroimage 2007
  - **In-vitro** work has shown some success.
    - Bodurka et al. MRM 2002. (Petri dish experiments)
    - Park et al. Neuroreport 2004 (Snail Ganglia)
  - No **in-vivo** study has shown reliable detection.
    - Luo et al. MRM 2011 (other references for negative or non-reproducible results can be found here)
- Our vision to succeed
  - Use 1H-MRS time-domain data which has been proven to be successful in in-vitro literature.
  - Understand the signal, the noise and the artifacts present within the MR scanner and optimize the NC signal-to-noise.
  - Use multivariate data analysis approaches to quantitatively extract NC signal.



Imaging, Signal Processing, Multivariate Analysis,
Algorithm and Software Development

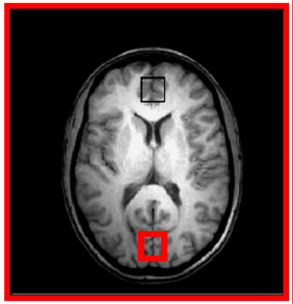
Magnetic Resonance Imaging, Physics, and Neuroscience



Programmatic and Research Goals

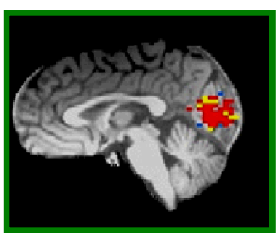
- Guide development of neuro-related detection equipment
- Better understanding of decision making processes
- Enhance Sandia's science basis for CS&T

Project roadmap



- **Year 1:** Detect neuronal current using single voxel 1HMRS in the **absence** of the Blood Oxygen Level Dependent (BOLD) response.
  - Optimize for 1HMRS noise and artifacts
  - Inter-trial intervals = **36 seconds**

- **Year 2:** Detect neuronal current using single voxel 1HMRS in the **presence** of BOLD response.
  - Improved SNR and controls to validate neuronal current signal
  - Inter-trial intervals = **1.5 seconds**



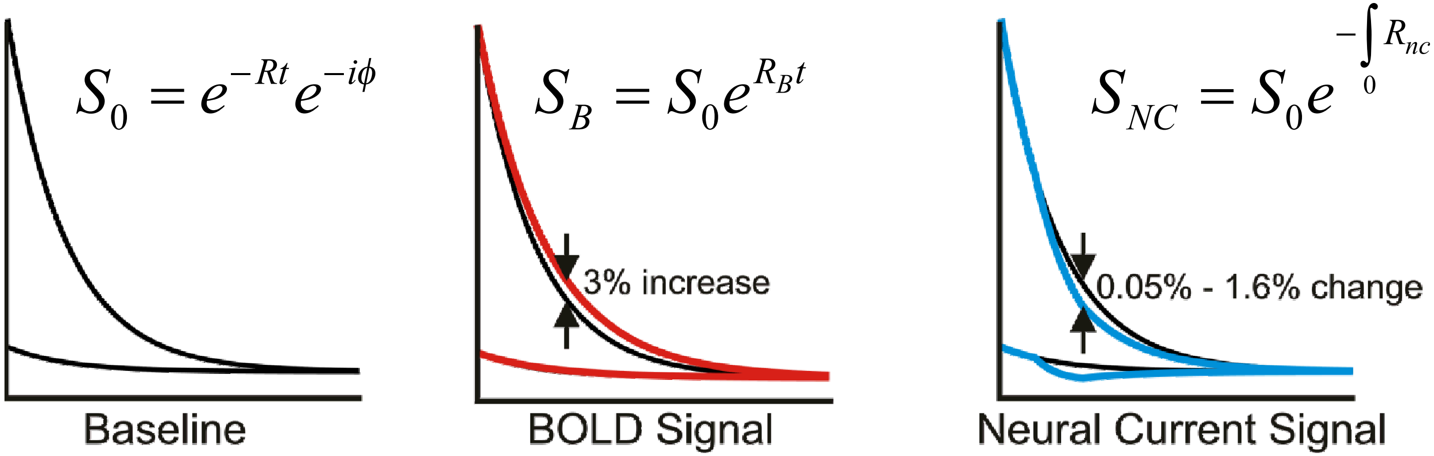
- **Year 3:** Neuronal current imaging using 1HMRSI
  - Optimize our multivariate analysis methods for 1HMRS imaging noise and artifacts
  - Inter-trial intervals = **1 second**

Understanding our signal

$$S_0 = e^{-Rt} e^{-i\phi}$$

$$S_B = S_0 e^{R_B t}$$

$$S_{NC} = S_0 e^{-\int_0^t R_{nc}(\tau)\,d\tau} e^{-i\int_0^t \omega_{nc}(\tau)\,d\tau}$$



On the order of a femto-Tesla.

<u>Generating realistic simulations will allow us to</u>:

1) Optimize our Instrument parameters for human subject studies
2) Optimize multivariate analysis algorithms
3) Optimize the design single voxel MRS NC studies

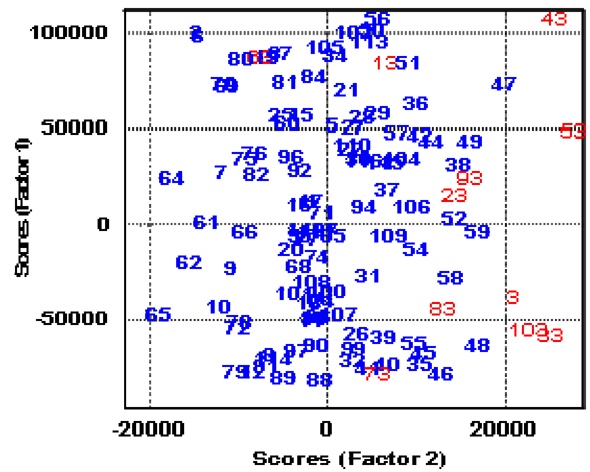
Blagoev et al., Modelling the magnetic signature of neuronal tissue. *Neuroimage*, 2007; **37:** 137-148.
Heller et al., Human Brain Mapping, 2009

Approaches to deal with instrument noise, artifacts and drift

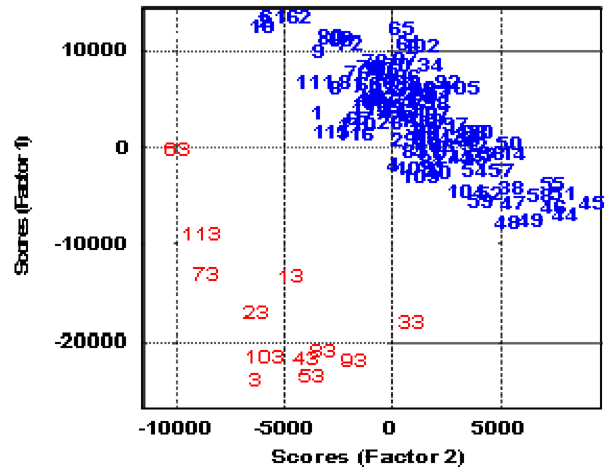
<u>Approach</u>: Apply NC simulations to real subject 1HMRS data and optimize pre-processing techniques to enhance signal detection

- Optimal pre-processing
  - Phase correct data using FID collected close in time
  - Frequency correction by padding FIDs
  - Truncate FIDs to 128
- Several background correction methodologies explored
  - Close in time FID background subtraction works best

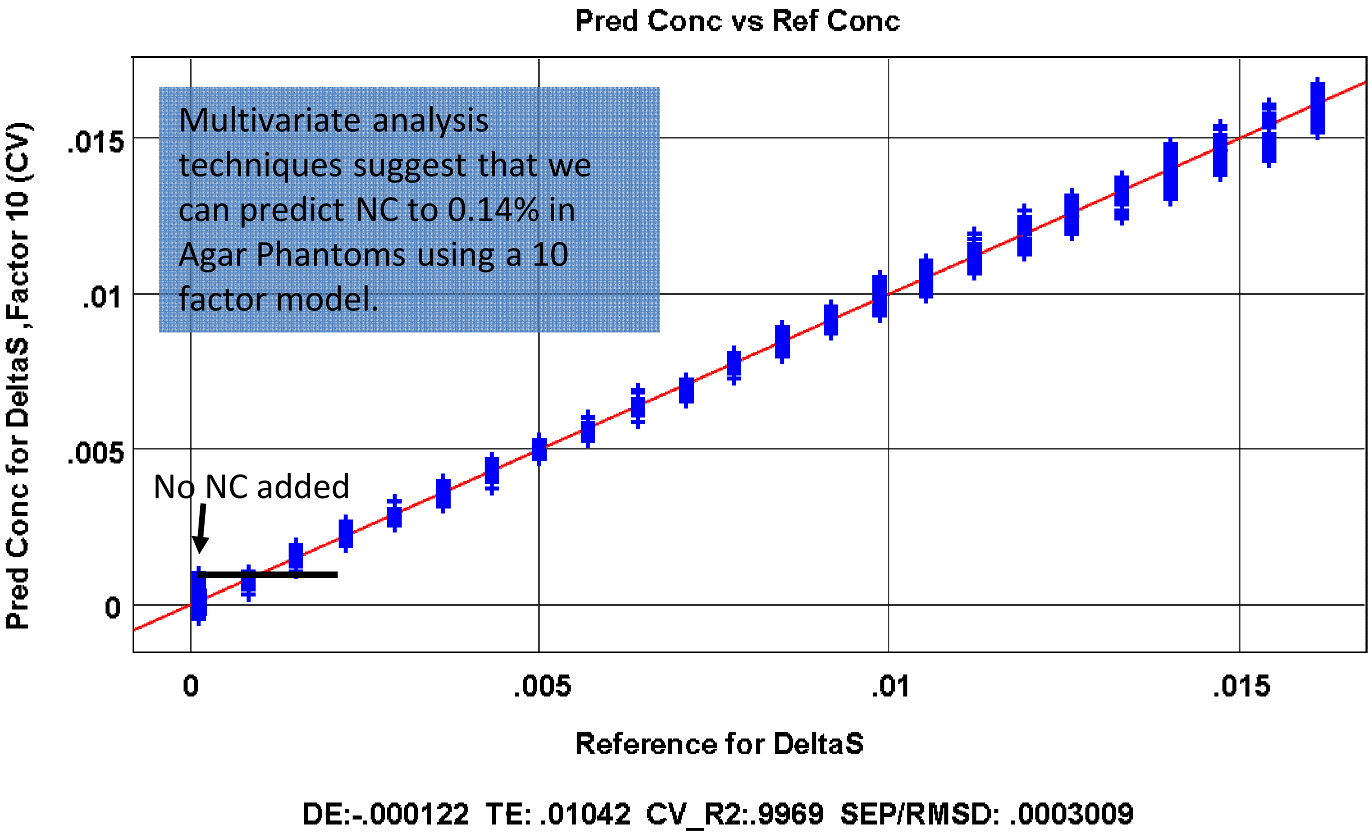
Before



After



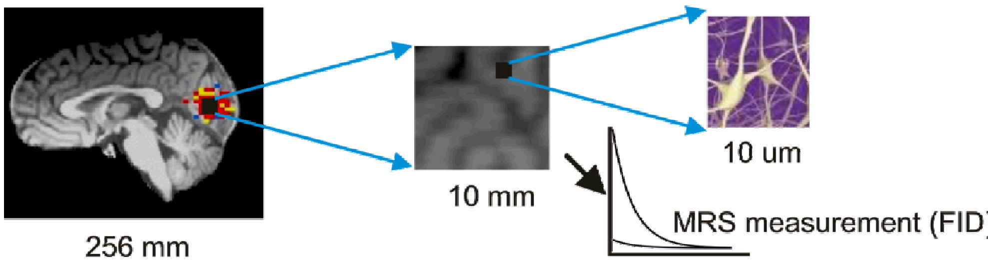
Understanding our detection limit using simulated data



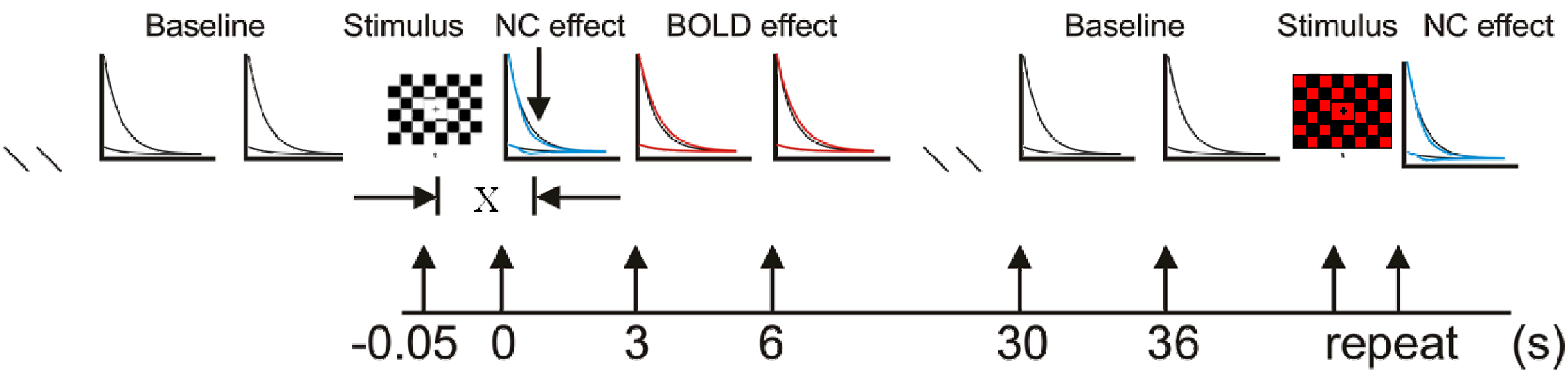
We used agar and human phantoms to characterize the Siemens MR Scanner to optimize the instrumental and experimental parameters to increase our signal-to-noise.

For example: voxel size, Te, TR, oversampling, etc.

Detection of neuronal current in the absence of the BOLD response.



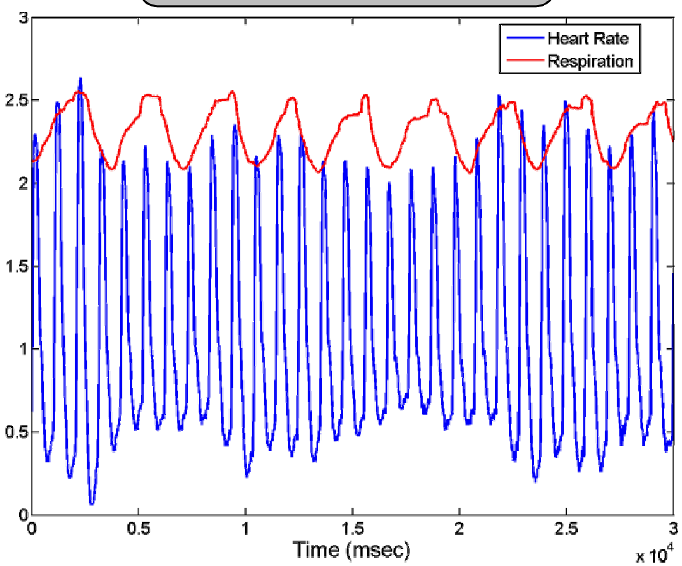
36 second inter-trial interval



Timing sequence for the 1H-MRS data collection

Continuous

Telemetry Data



Trigger

60 msec Delay

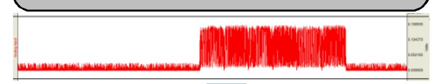
Projector

Software Delay

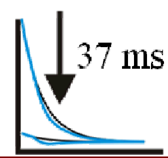
Stimulus

Diode

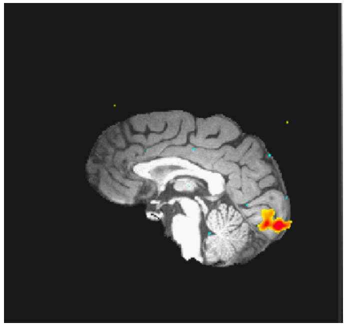
Photosensitive diode records stimulus timing



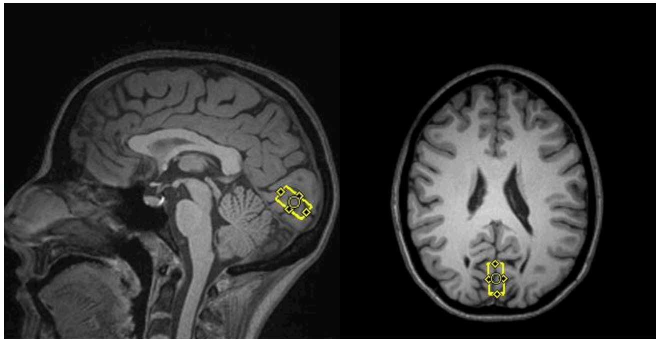
NC effect



Real-time optimized voxel placement for each subject



fMRI Analysis Map



MRS Voxel Placement

Experimental details

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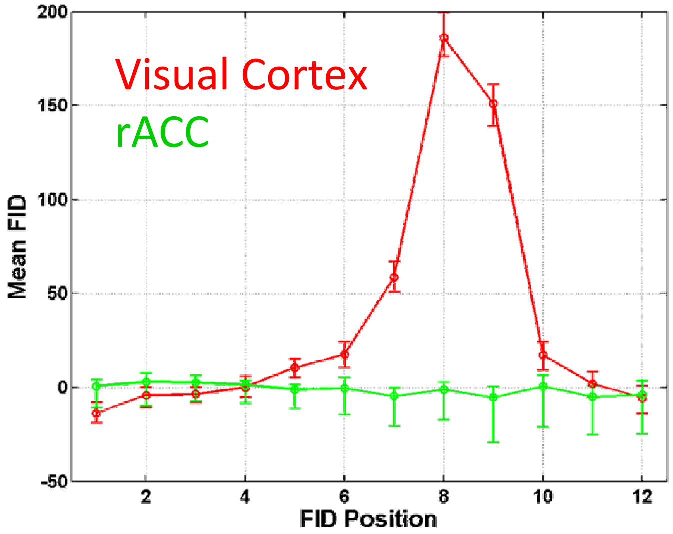
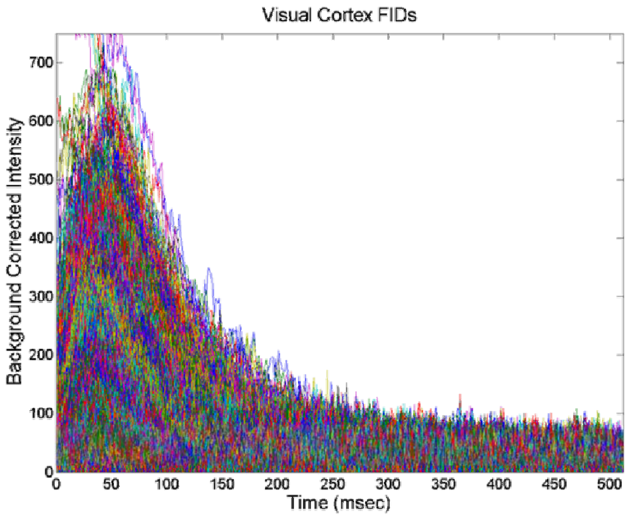
Mean Magnitude of FIDs



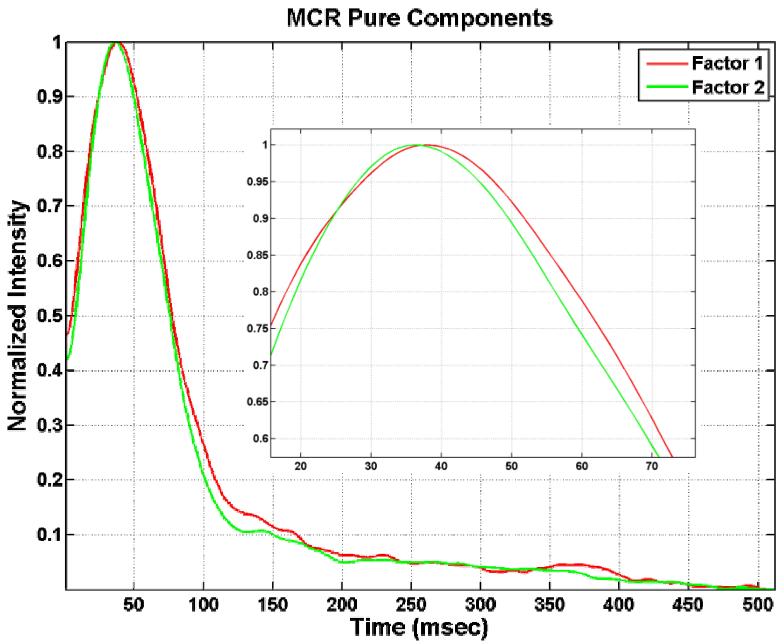
- In addition, conducted an additonal study as a control for current study
  - Moved 1HMRS voxel to the prefrontal gray matter away from the neuronal current (rACC)
  - 10 different subjects

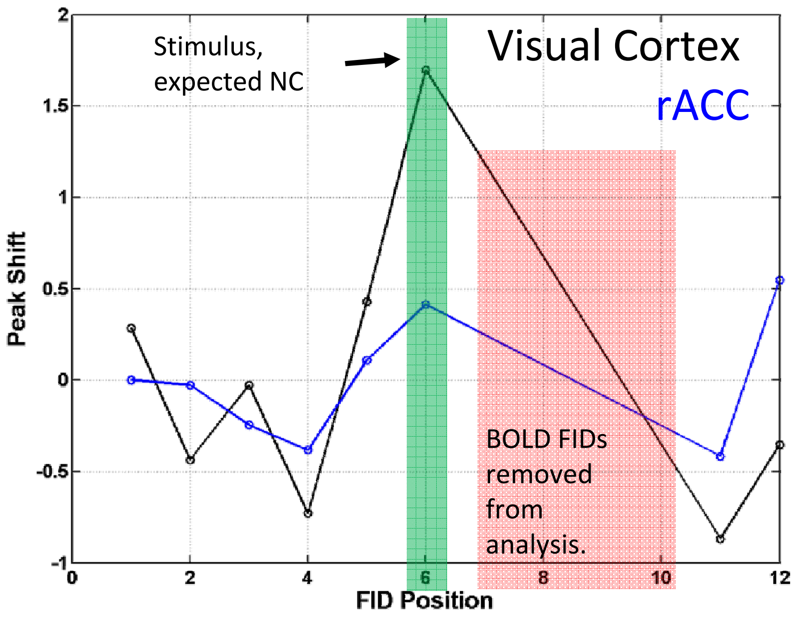
Positive indications of NC detection (our expectations)

- Visual cortex
  - Increased variance in NC FID data relative to baseline FID
  - The peak of the background corrected FID signal in gray matter is ~40 msec
    - Presence of the NC with a timed stimulus of 37 msec should shift peak to shorter times
- rACC
  - Lack of correlated signal response as a result of visual stimuli
    - No increase in variance
    - No shift in background corrected FID peak



Multivariate Curve Resolution (MCR) results





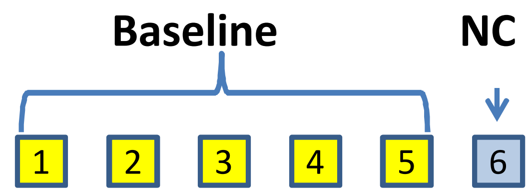
Using MCR we were able to detect a small shift (factor 2) in the FID difference peak location as a result of the stimulus. This result is consistent with our simulation expectations.

Using the MCR results we reconstructed a noise-free and artifact reduced dataset to determine the shift in the peak position.

These results are encouraging that we may be seeing a small shift due to the NC.

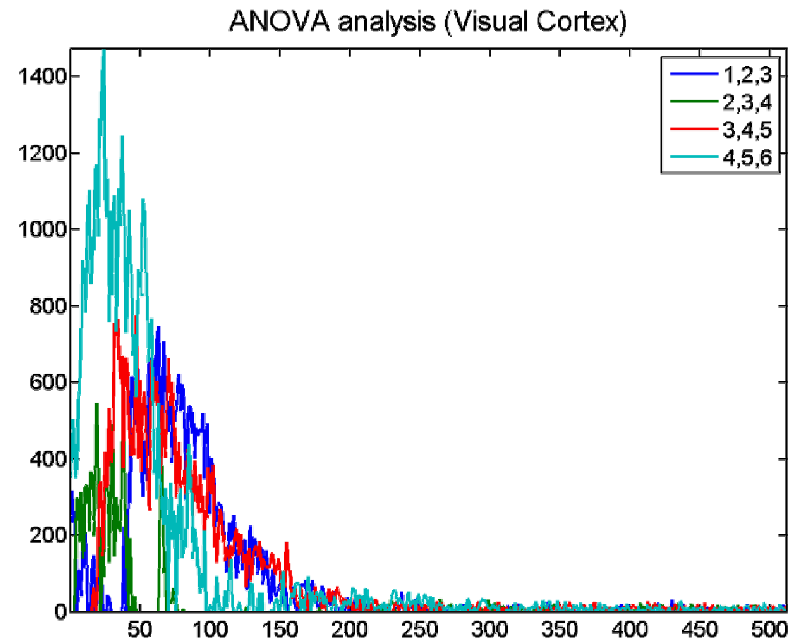
Separation of variances using paired difference FIDs

Idea: Use combinations of the first six FIDs for the ANOVA calculations across each time point of the FID.



$\sigma^2_{Stim} = \sigma^2_{Instr/phys/Stim} - \sigma^2_{Instr/Phys}$

$\sigma^2_{Stim} = \sigma^2_{6\text{-}5} - \sigma^2_{5\text{-}4}$



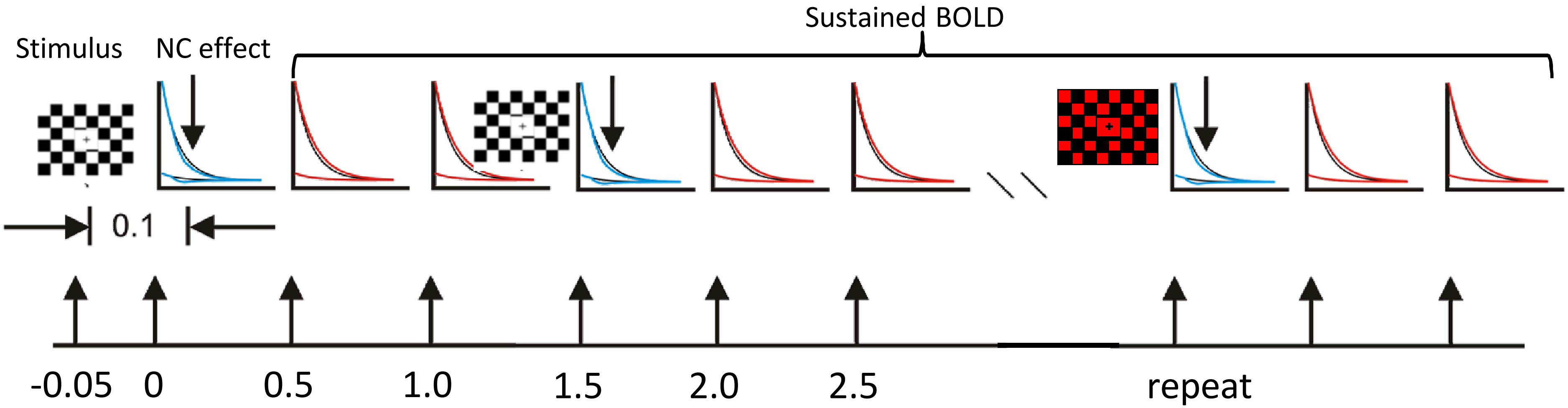
Shift is only observed in combination that contains the visual stimulus. The other combinations just show changes in difference FID magnitude.

The rACC did not show any noticeable trends.

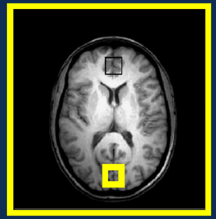
Summary from this first study

- Results are encouraging and consistent with what we would expect from NC signals.
- However, the results of these experiments may not be definitive.
  - We cannot definitively rule out other effects that may be causing changes in the FID.
    - Control experiment
      - Different locations in the brain
      - Different subjects
      - Different days
    - Although the difference FID shift was consistent with our experimental NC time location, further confirmation could be achieved with at least 2 NC timing locations in the FIDs.

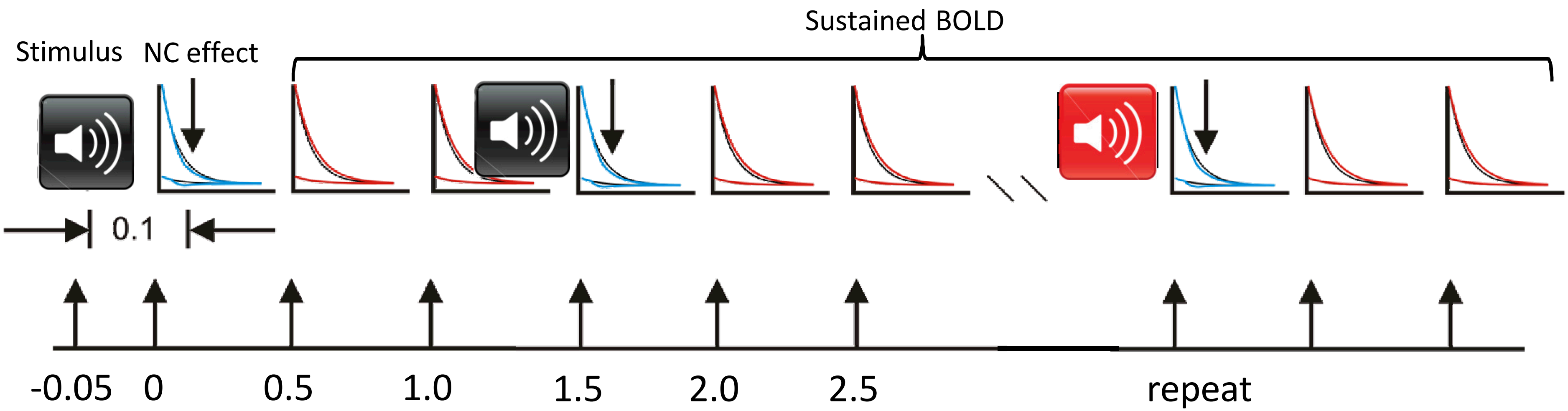
Detect neuronal current in the presence of BOLD response



- Frequent stimuli will significantly reduce startle response
- Increased SNR
  - Collecting more NC FID observations per run (164 vs. 8)
    - Allows for increased signal averaging in our multivariate algorithms
  - Visual "decision making" targets 33% of the time

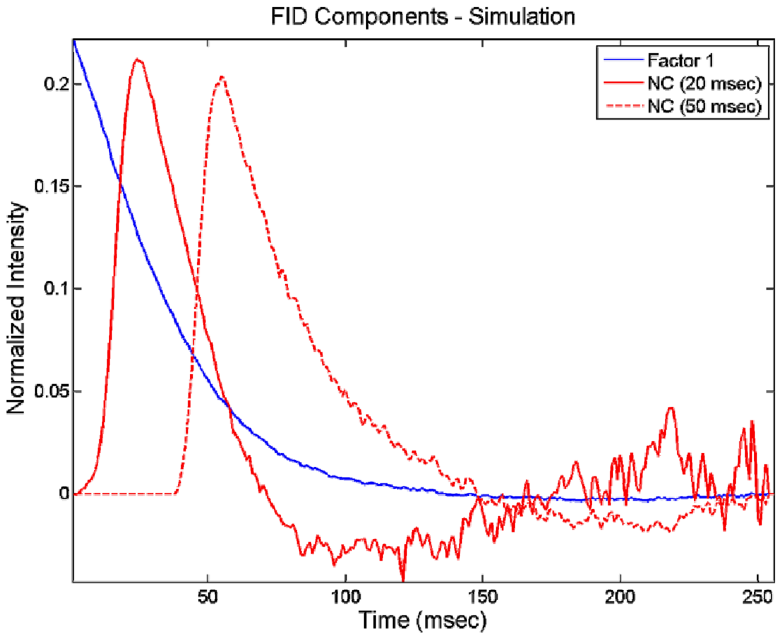


Detect neuronal current in the presence of BOLD response



- Improved validation of experimental results (built-in controls)
  - Same subject, same magnetic field
  - Same location in the brain (visual cortex), two stimuli (Visual, Auditory)
  - Stimulus timing of two different locations on FID (20 and 50 msec)
    - Peak shift must be consistent in the direction and amount of shift
  - Paired backgrounds to assess signals due to instrumental/physiological effects vs. NC effects

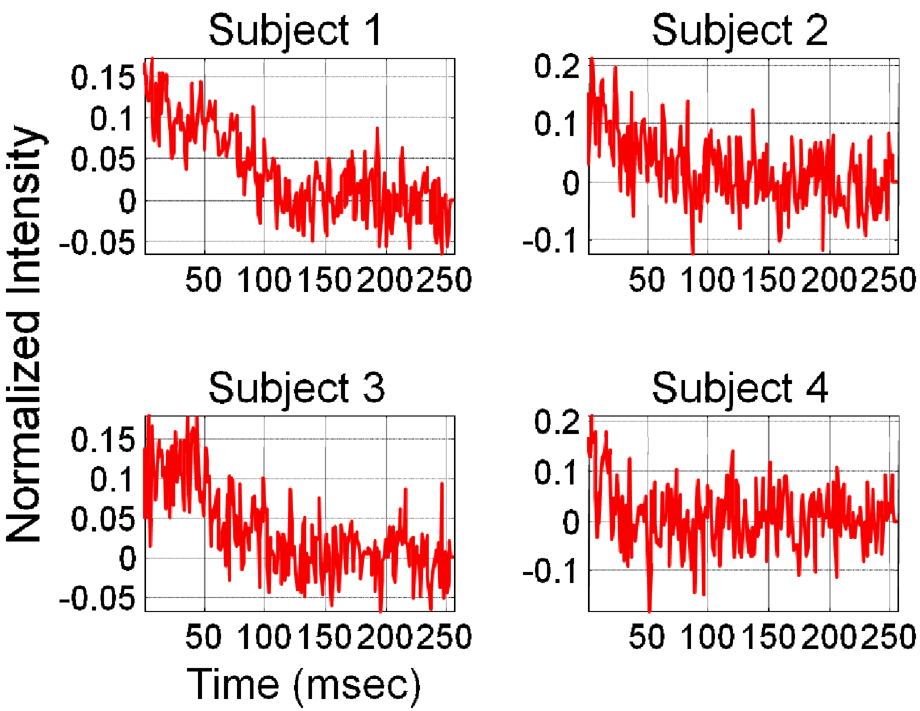
Confirmation of neuronal current detection in study 2



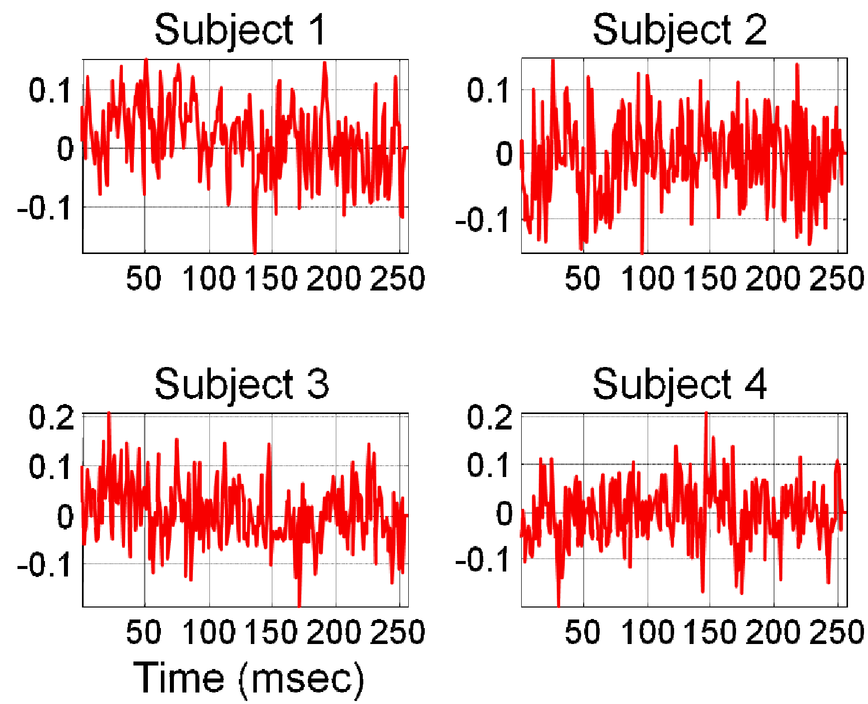
- We will be looking for two components that are associated with the expected NC stimulus timing
  - Location (20 vs. 50 msec)
  - Intensity (lower SNR for 50 msec)
- Compare results with auditory control
  - Positive auditory response would indicate signal may be due to motion (startle)
- Red target vs. black target
  - Intensity should be increased for the "decision-making" stimulus target

Preliminary analysis of first four subjects

Visual Stimulus



Auditory Stimulus



1st weight loadings from Partial Least Squares (PLS) analyses, which represents the spectral shape that is correlated with the stimulus.

Second study still in progress

- Finalized the re-collection of the final two subjects.
  - Our multivariate algorithms showed that the data from last two subjects were completely different than first four subjects.
    - System had higher noise due to problems with the RF synthesizer for these last two subjects. Therefore last two subjects were rerun after replacing synthesizer.
  - Depending on the results of the first six subjects, we may collect four additional subjects.

- We have barely scratched the surface of the analyses necessary to confirm our earlier observations.
  - Investigate different preprocessing methods to increase the SNR of the data.
  - Investigate different background correction methodologies.
  - Separate variances due to the various controls (stimulus timing, decision targets, etc.).
  - Analyze individual coil data as well as averaged data since coils nearest the NC signal may experience higher SNR for NC.

Summary and expectations

- Results from first study are encouraging.
- Encouraging initial results from the second NC confirmation experiment with improved study design.
  - Study still in progress.
- Upon the completion of the second study, we plan on publishing these results and submitting proposals for follow-on funding.

- This research, if successful, will revolutionize the way cognitive research is conducted by providing a tool to directly measure neuronal responses in the brain.
  - Understanding the interactions and correlations of groups of cells in the brain with high spatial and temporal resolution during cognitive tasks
    - For example, decision making processes