Combining microstimulation and fMRI in an awake behaving monkey

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Monkey fMRI

- Apply fMRI to traditional neuroscience model → non-human primate visual system (Rhesus monkey)
- Bridge tool between human fMRI & past monkey work
- Subjects awake & behaving, not anesthetized
Why Monkey fMRI?

Three main reasons:

- Validate assumptions about human / animal correspondence → same tool, same experiment

- Complement other traditional modalities, guide to new areas of interest

- Platform for combining imaging with invasive techniques → explore interactions within a network, probe mechanisms of fMRI
Overview – What we did

- Developed method to **simultaneously microstimulate** specific brain regions while performing **fMRI**

- Microstimulation = focal injection of current to specific site to artificially induce output

- Stimulated site = **Frontal Eye Fields (FEF)**, node in eye-movement control network (target selection, movement planning), source of spatial attention?
Anatomical Location

Arcuate Sulcus

FEF Location: 2-6 mm below cortical surface, anterior bank of arcuate sulcus
Objectives of Study

Aim: Investigate functional effects of feedback connections originating in FEF by combining electrical stimulation & fMRI in awake, behaving monkeys

1) Is functionally defined in-vivo tract tracing possible?
2) Modulate visual representations throughout visual cortex by feedback from FEF?
Determine **connectivity** (and direction) between topographically separated regions in the brain, as a step to understanding functional relationships.

- Traditional histological method: inject radioactive tracer (ie. tritiated amino acid) or fluorescent dye, allow time for transport, examine brain $\rightarrow$ **very invasive** (ie. subject sacrificed)

- Diffusion-weighted MRI tractography $\rightarrow$ still awaiting validation
Background II – Frontal Eye Fields

- Primate visual system uses **discrete jumps** to ‘see’ (high-acuity fovea) → known as **saccades**
- Stimulating FEF (one in each hemisphere) induces saccades
- Thought to be site of **target selection** (has neurons that carry both visual & movement info)
Background III – Spatial Attention

- Typical visual scene carries more information that can be simultaneously processed by visual system

- Filter to identify behaviorally relevant information for further examination $\Rightarrow$ spotlight of attention

- Covert spatial attention known to modulate strength of visual representations & visual perception

- Source of this mechanism hotly debated
Background IV – Pre-motor Theory of Attention

- **Hypothesis**: Pre-motor theory of attention – structures involved in *saccade initiation* are (one of) the top-down source(s) for this modulation

- Previously shown that FEF *microstimulation modifies behavior* in spatial attention tasks & also produces spatial attention-like effects in *visual cortex* (V4)

- **Enhancement** occurs only when visual stimulus location corresponds to movement field of FEF site
Background V – A Visual Example

Visually driven neural activity

Site A | Site B

FEF (& other areas) | Rest of Brain

Visual Cortex

X
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Methodology Employed

- **Electrodes:**
  - In MR compatible manner, **25 \( \mu \text{m} \) diameter microwires chronically** implanted in anterior bank of Arcuate sulcus in two juvenile male rhesus monkeys
  - **Saccades consistently evoked** during MRI acquisition (now 20+ mo. after surgery)

- **functional MRI:**
  - Siemens Allegra 3T for GE-EPI \( T_2^* \) functional images (TE 24 ms / TR 4000 ms, 55 slices @ 1.25 mm\(^3\) voxels)
  - **MION-enhanced, awake monkey fMRI** (monkey sits in Sphinx position with head immobilized while performing passive fixation task \( \rightarrow \) liquid reward)
  - ISCAN IR camera used to monitor point of regard, administer behavioural reward
Experimental Setup
Anatomical Evidence: Electrodes in FEF

- Anterior bank of Arcuate sulcus, superior branch
- Anterior bank of Arcuate sulcus, inferior branch
- 7 T turbo spin-echo image at 0.3 x 0.3 x 1 mm³ resolution
- Slice caudal to Principal sulcus
Behavioral Evidence: Saccades Evoked in 3.0T Scanner

Eye position recorded at 120 Hz with infra-red camera

- **Electrical Stimulation**
  - Parameters:
    - 250 ms trains of bi-phasic square-waves @ 335 Hz
    - Currents to evoke saccades ranged from 47 ± 13 µA to 276 ± 58 µA across electrodes
    - fMRI experiments used SUB-THRESHOLD CURRENTS (~50%) → NO SACCADES
Experiment #1 – Electrical Stimulation without Visual Stimuli

4 Electrode Cycle / TR

p < 0.05, corrected
Experiment #1 – 4 Electrode Cycle / TR

- Claustrum
- Putamen
- S Colliculus

Huerta et al., 1987
Experiment #1 – 4 Electrode Cycle / TR

Lat IPS

V1

Δ% MR SIGNAL

Schall et al., 1995
Experiment #1 – Test - Retest
Same Contrast in Experiments Separated by 1 Month
Experiment #2 – Electrical Stimulation Effects on Visual Representations

4 Electrode Cycle / TR

p < 0.001 masked by p < 0.05, all uncorrected
Objective #2 – Modulation of Visual Information
Eye Position During Different Stimulation Epochs

- **Percent fixation**
  - Conditions: 1, 2, 3, 4
  - $n = 31$, $p = 0.664$

- **Saccades/min**
  - Conditions: 1, 2, 3, 4
  - $n = 31$, $p = 0.904$
So FEF is the Source of Spatial Attention, Right?

- Not necessarily…

- Stimulating FEF produces specific modulations throughout visual cortex and visual processing stream, similar to spatial attention

- Demonstrating same modulations during spatial attention task or ability to interfere with attention via stimulation \( \rightarrow \) next step

- FEF, other oculomotor node or some combination???
Conclusions

1) Is in-vivo tract tracing possible?  → YES
2) Modulate visual representations throughout visual cortex by feedback from FEF?  → YES

- We have proved a **causal** relationship between artificially increased output of the FEF and fMRI activity in anatomically connected regions
- This data supports the hypothesis that the FEF can modulate visual representations in occipital cortex, similar to covert spatial attention
- Repetition in 2\textsuperscript{nd} subject, specificity of stimulation (i.e. mismatch condition)  → in progress
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Questions?

Or contact lekstrom@mit.edu
fMRI Basics

- Visual Stimulus / Cognitive Task
- Neuronal Activation
- Metabolic Demands
  - $\Delta$ Cerebral Blood Flow
  - $\Delta$ Cerebral Blood Volume
  - $\Delta$ Cerebral Metabolic Rate for O$_2$
- Detectable MR Signal
Spatial Attention – An Example

Photo courtesy www.politicalcap.com
Experiment #1 – 4 Electrode Cycle / TR
Test - Retest
Experiment #1 – 4 Electrode Cycle / TR
Test - Retest
Stimulation Timing During fMRI

TR 1

1

133 ms

2

250 ms

ISI = 1 s

3

617 ms

TR 2

4

1000 ms
Experiment #3 – Retinotopic Specificity of Electrical Stimulation Effects

4 Electrode Cycle / TR

p < 0.001 uncorrected
Experiment #3 – Retinotopic Specificity

V1L V1R
Δ% MR Signal

V4v TEO
Δ% MR Signal

FST
Δ% MR Signal

Δ% MR Signal
Electrical Stimulation Effects on Visual Representations – Masking Explained
Connections with FEF

Huerta et al., 1987
Connections to FEF

Schall et al., 1995