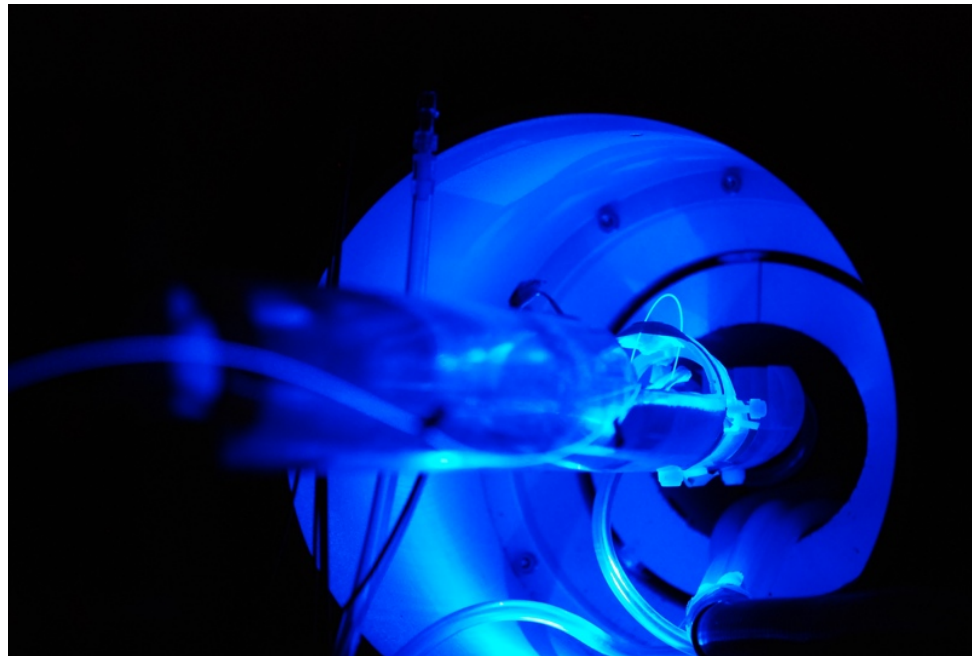University of California, Los Angeles

Optogenetic fMRI: Genetically Targeted Brain Circuit Analysis and Debugging
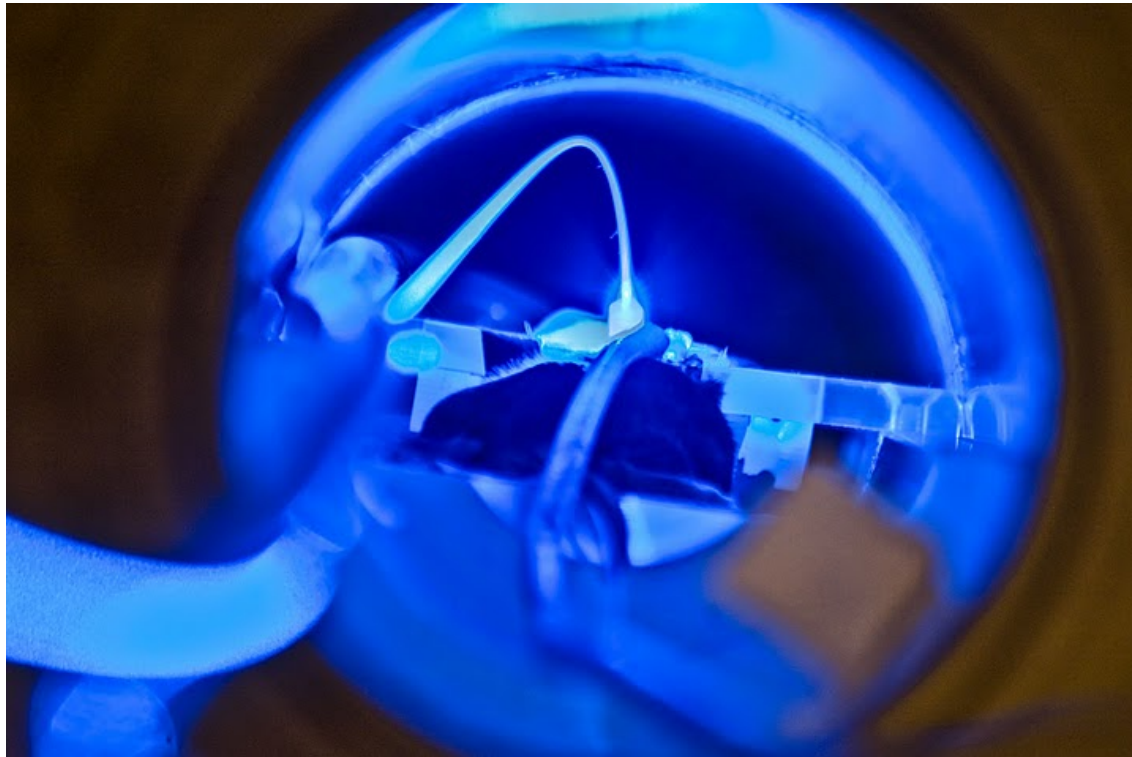
Jin Hyung Lee

July 26, 2011

DEPARTMENT OF ELECTRICAL ENGINEERING,
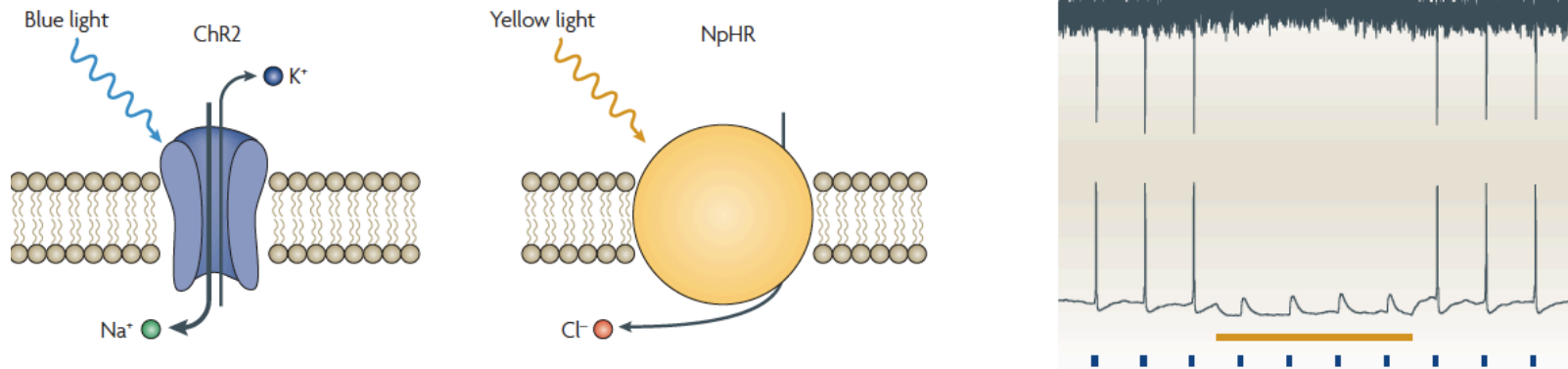PSYCHIATRY, RADIOLOGY, BIOMEDICAL ENGINEERING, AND NEUROSCIENCE

Optogenetic fMRI (ofMRI)

Stimulate **specific cell types** with **temporal precision**.
Monitor **causal**, **in vivo**, and **brain-wide** activity responses.

Lee et al., Nature 2010

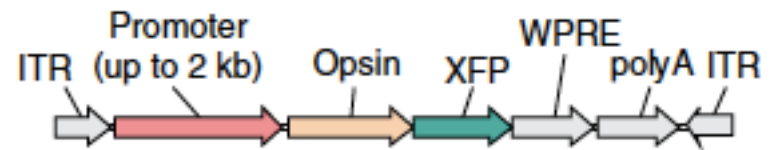# Optogenetics Enables Cell-Type Specific, Temporally-Precise Stimulation

- Selectively express **light sensitive rhodopsins (ChR2, NpHR)** in **genetically targeted cells**.

- Optical stimulation **activates (ChR2, blue light)** or **silences (NpHR, yellow light)** genetically targeted neurons.

Boyden et al., Nature Neurosci. 2005
Zhang et al., Nature Methods 2006

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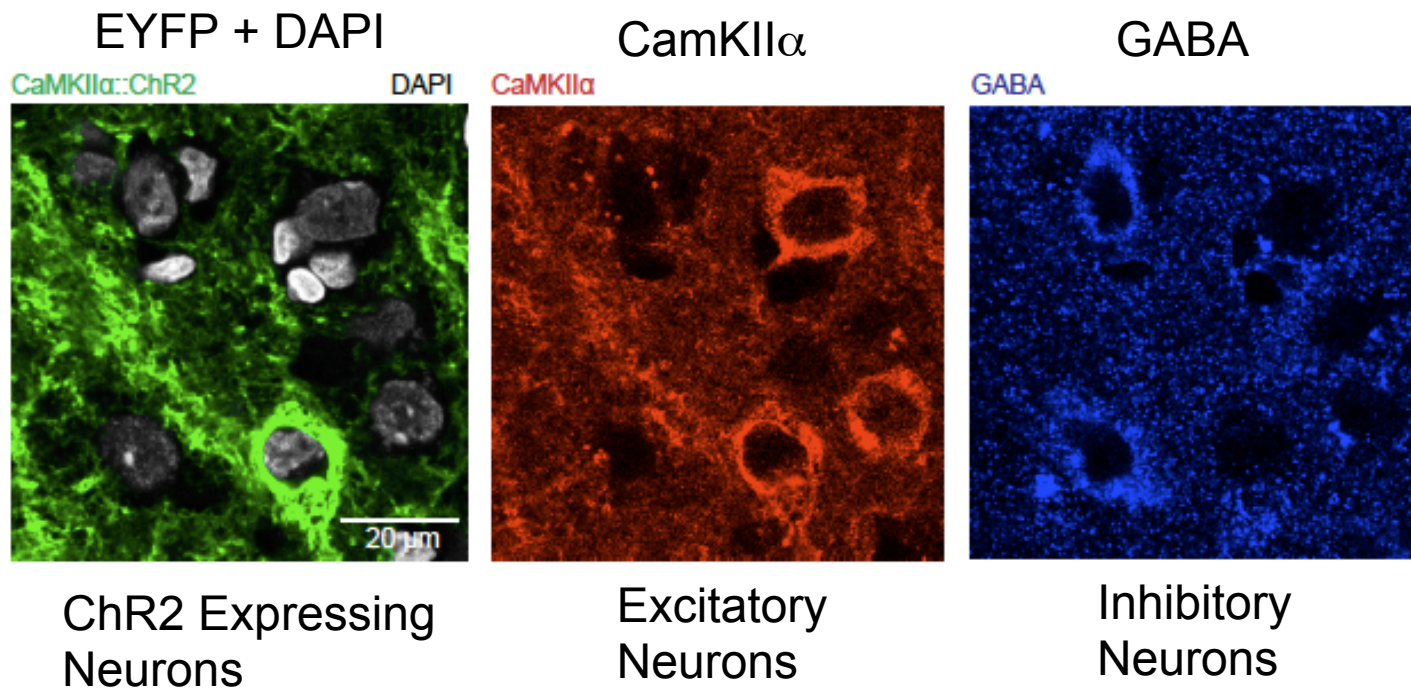
Cell Type Specific Expression of ChR2, NpHR

- Viral Expression Systems
  - Lentivirus
  - **<u>Adeno-Associated Virus (AAV)</u>**
- In Utero Electroporation
- Transgenic Mice
  - ChR2 under Thy-1 promoter
- Cre-driver transgenic mouse lines
  - Cre-dependent AAV Vector

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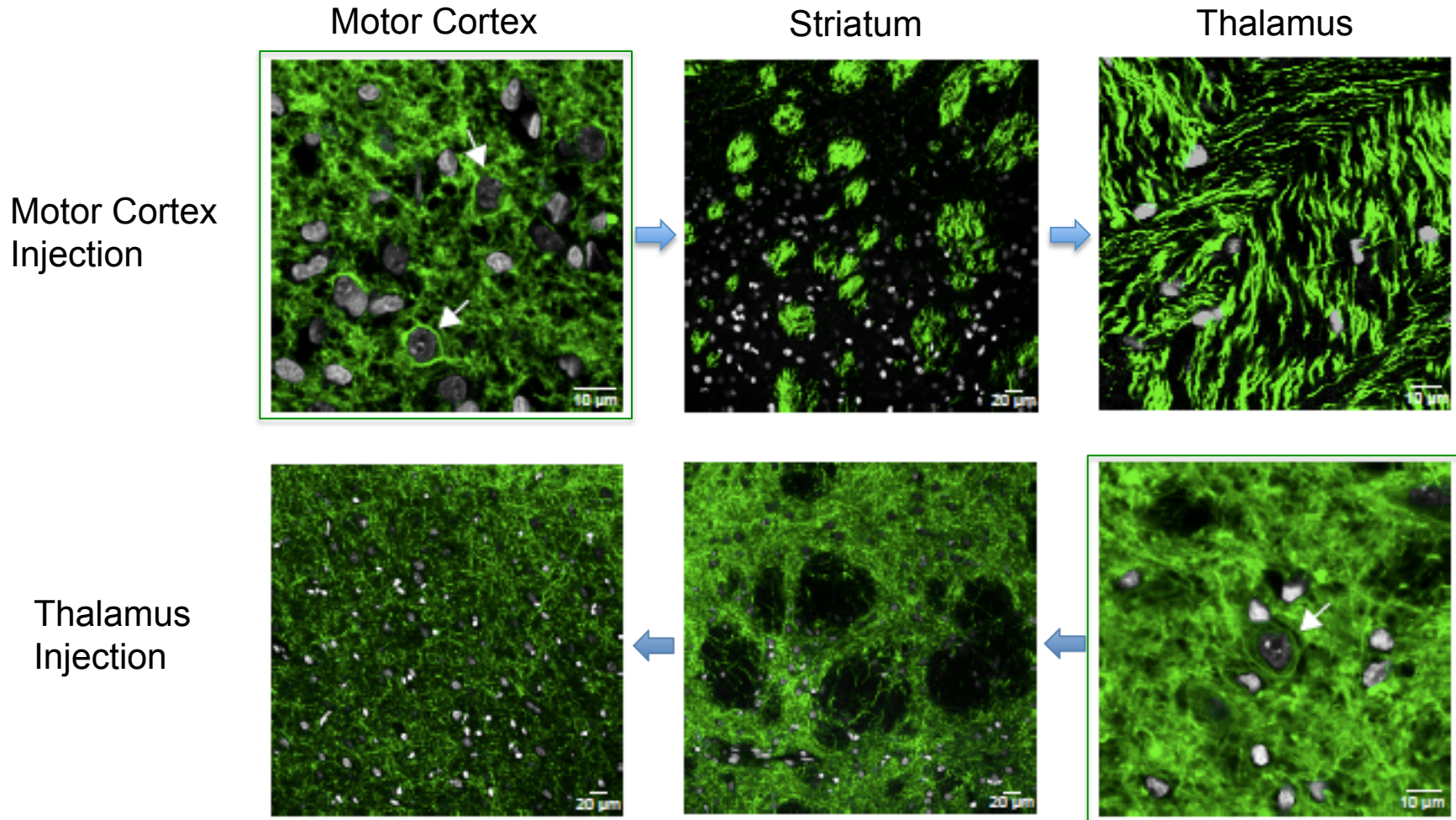# Targeting Excitatory Neurons
w/ Viral Injections

Virus: AAV5-CaMKIIα::ChR2-EYFP   **Specificity:** 99 %, **Sensitivity:** 89 %

EYFP + DAPI   CamKIIα   GABA

ChR2 Expressing   Excitatory   Inhibitory
Neurons   Neurons   Neurons

Lee et al., Nature 2010

Virus Infection is Limited to Neurons with Cell Body at Injection Site

Motor Cortex Injection
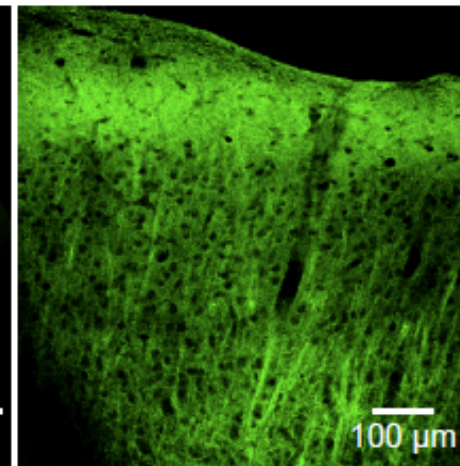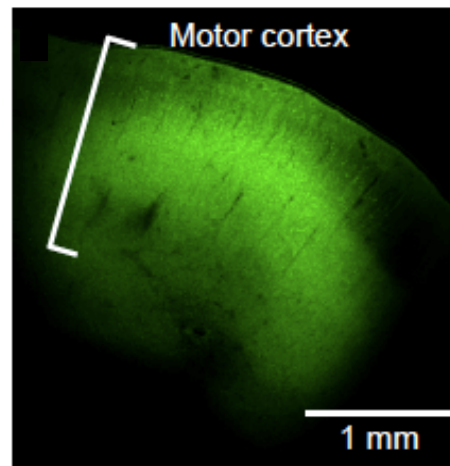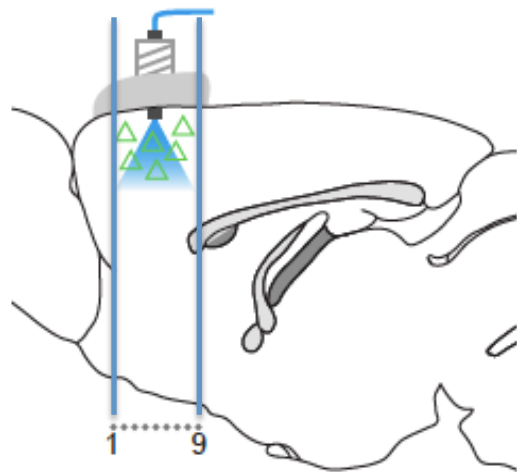
Thalamus Injection

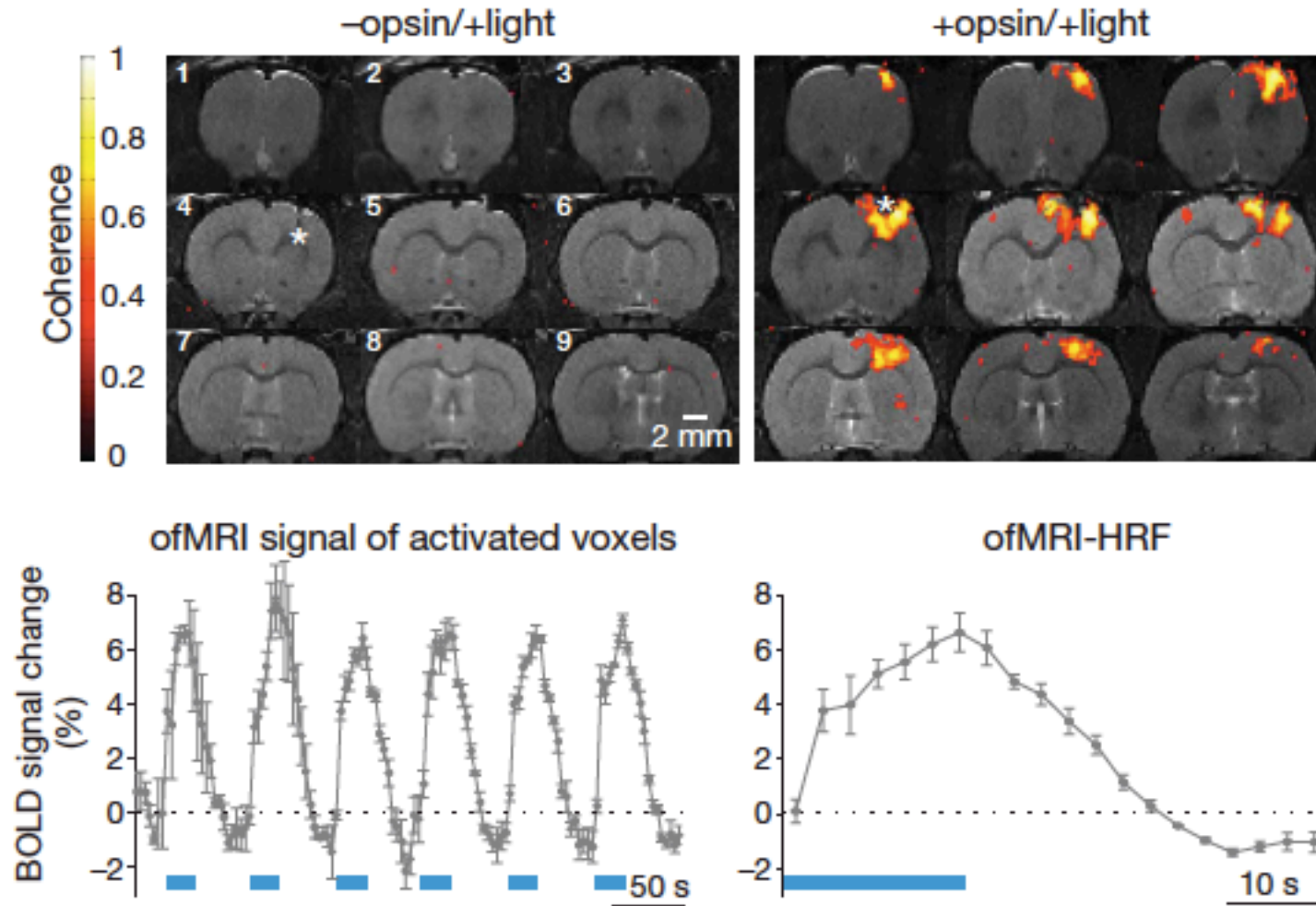**Virus:** AAV5-CaMKIIα::ChR2-EYFP

Lee et al., Nature 2010

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Excitatory Neurons in Motor Cortex are Triggered with Blue Light
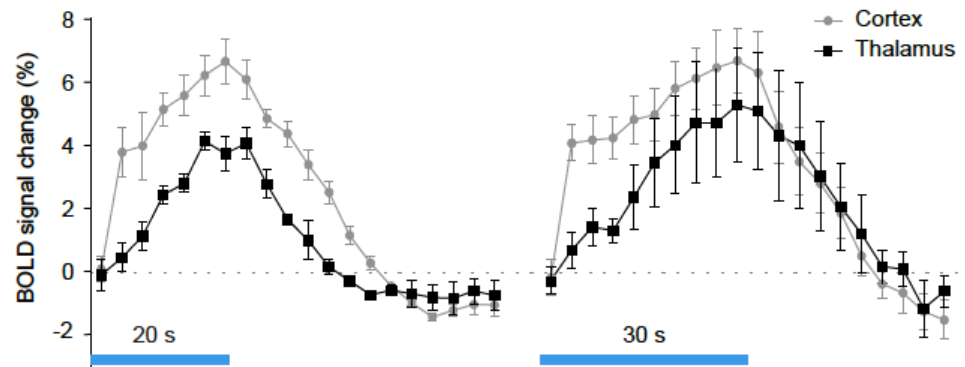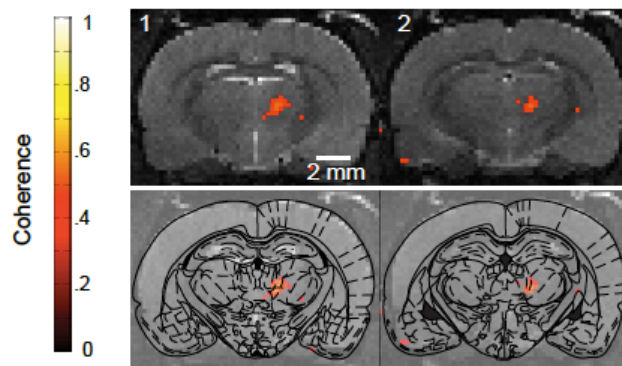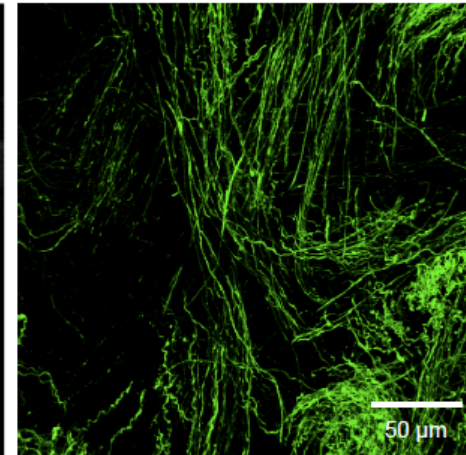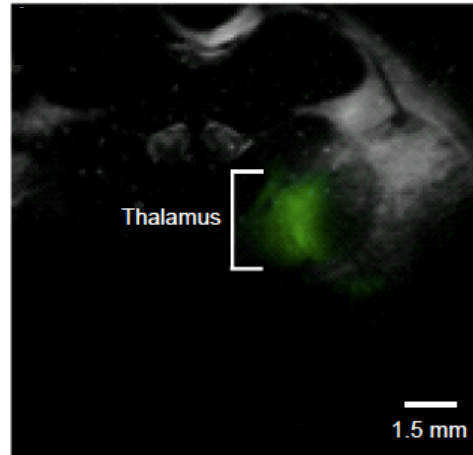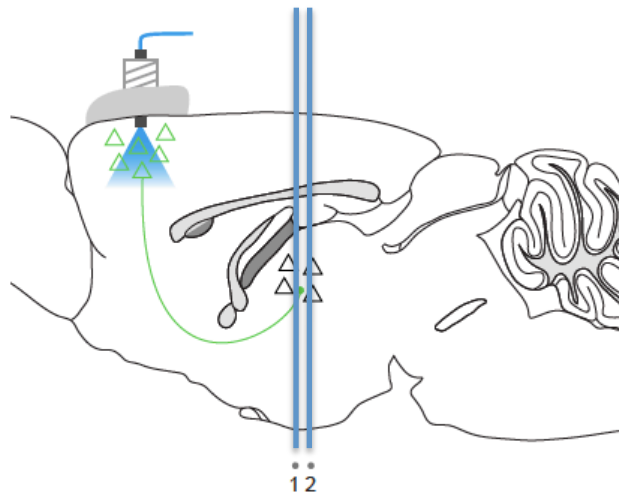
AAV5-CaMKIIα::ChR2-EYFP

Lee et al., Nature 2010

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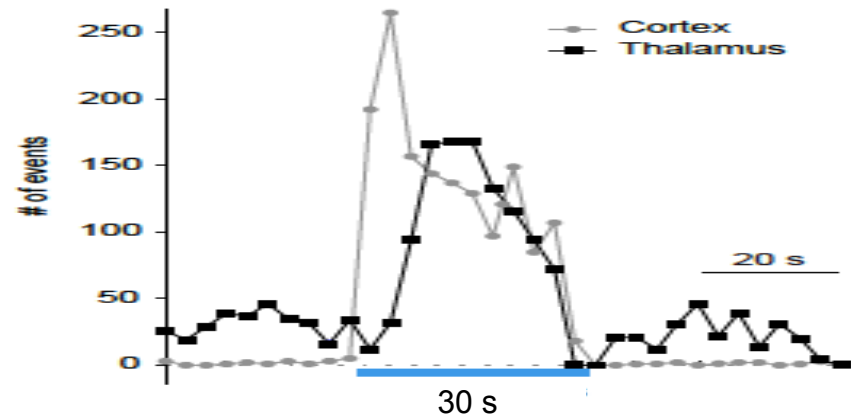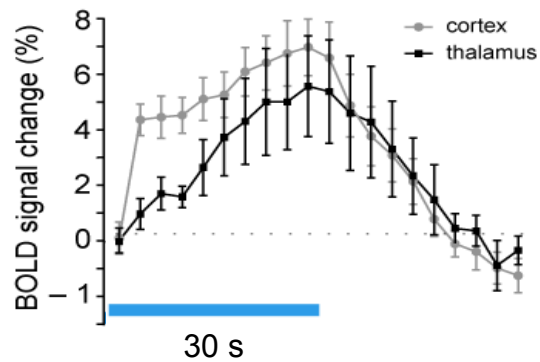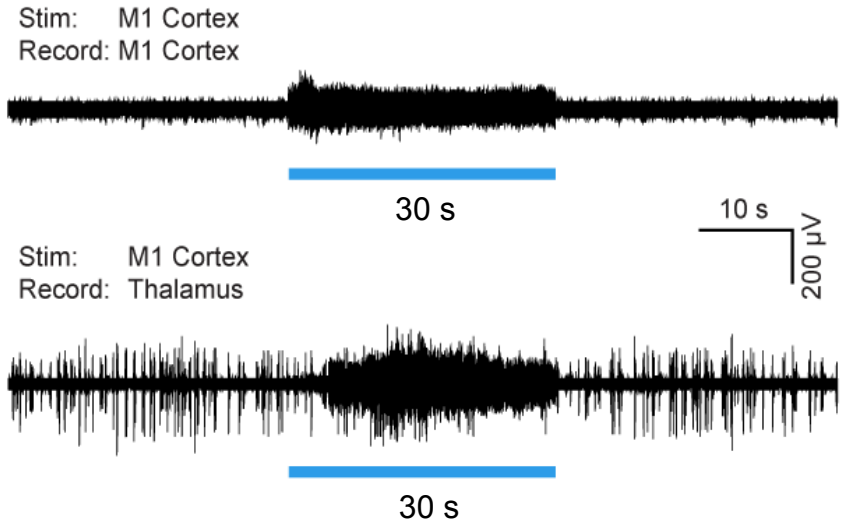# ofMRI: Excitatory Neuron Triggering Leads to Robust BOLD signal with Classical Dynamics
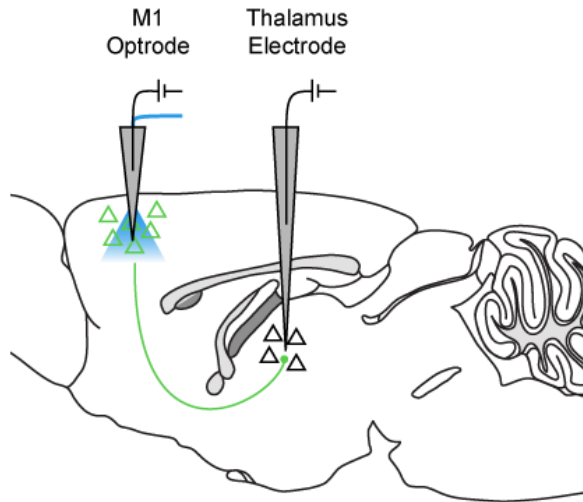

Lee et al., Nature 2010

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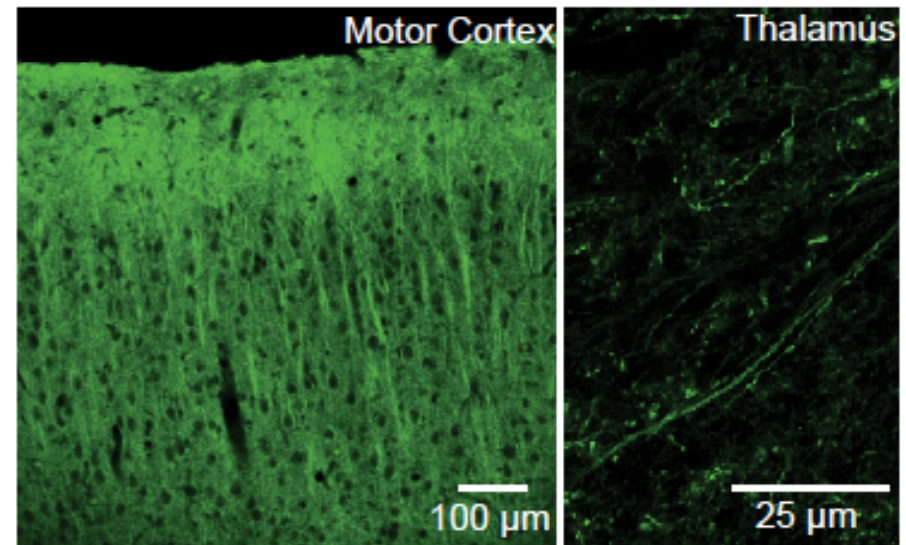# ofMRI Triggers Distal BOLD Response with Distinct Temporal Dynamics
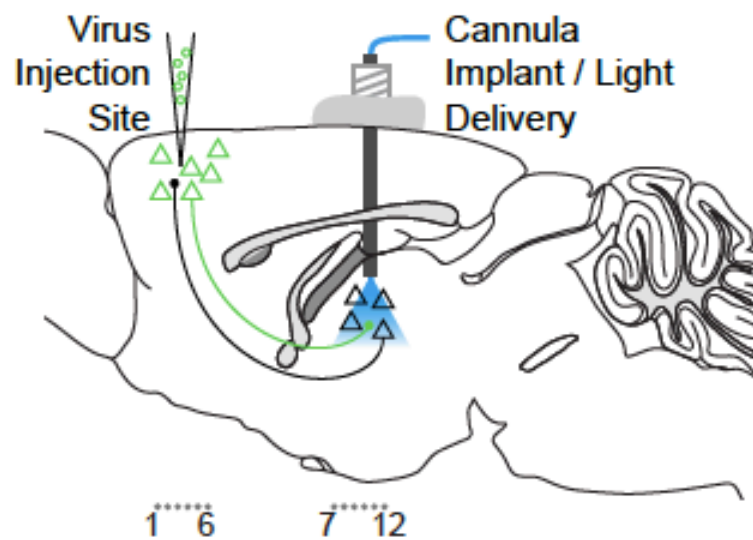

Lee et al., Nature 2010

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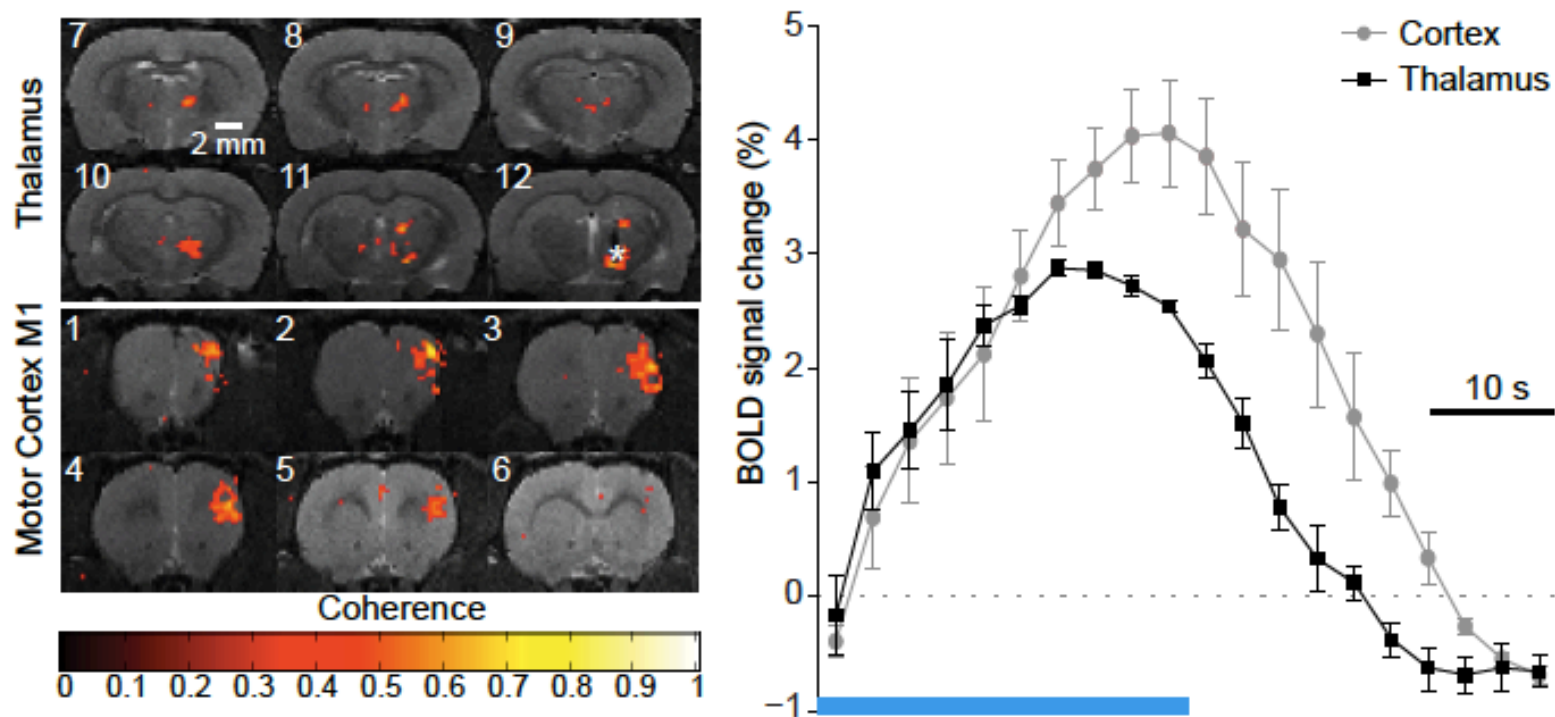# ofMRI HRF shows Close Correlation with Electrophysiology

Lee et al., Nature 2010

Injection in Motor Cortex, Stimulation of Axonal Fibers in Thalamus
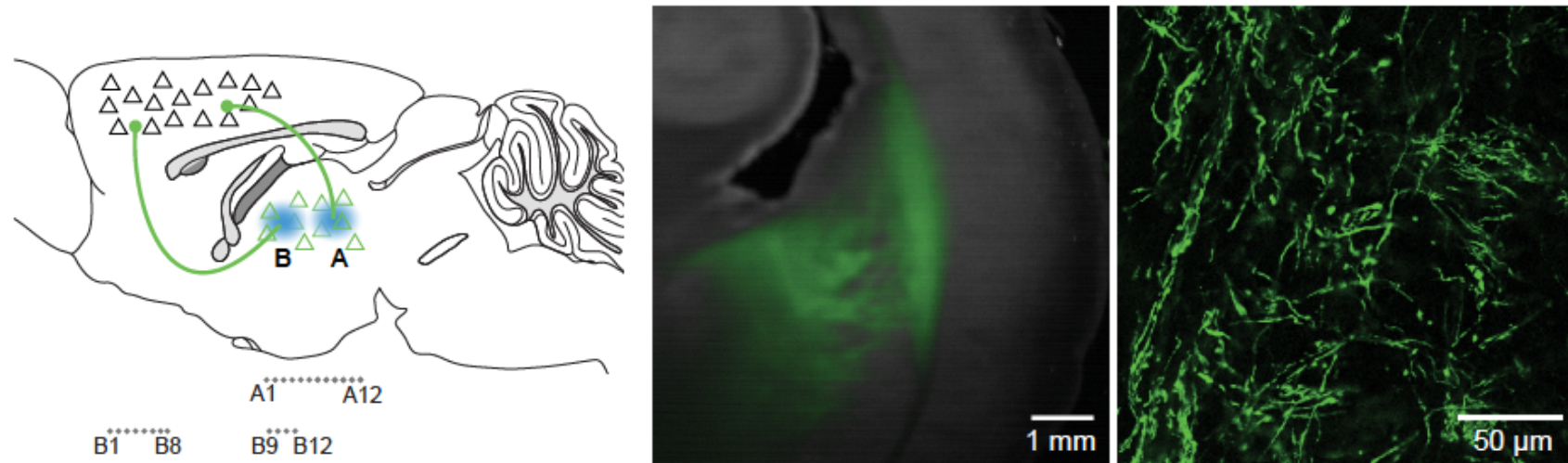

Lee et al., Nature 2010

Stimulation of Axonal Fibers Projecting from Motor Cortex To Thalamus Yields Robust Local and Distal BOLD

Lee et al., Nature 2010

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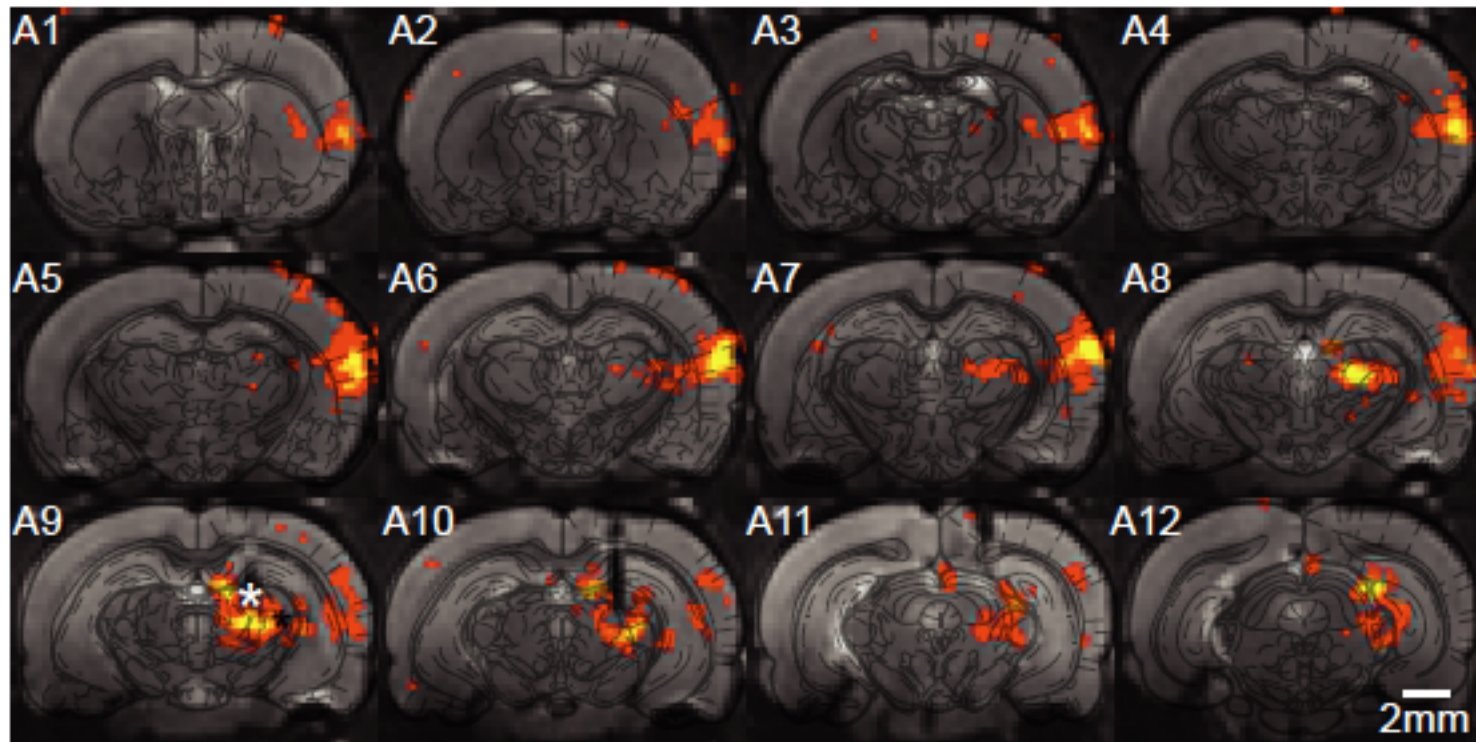
Thalamo-Cortical Circuit

Stimulation of Excitatory Neurons in Thalamus

- **A:** Unilateral Thalamo-Sensory Cortex Connection
- **B:** Bilateral Thalamo-Motor Cortex Connection

Lee et al., Nature 2010

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Posterior Thalamic Nuclei Stimulation
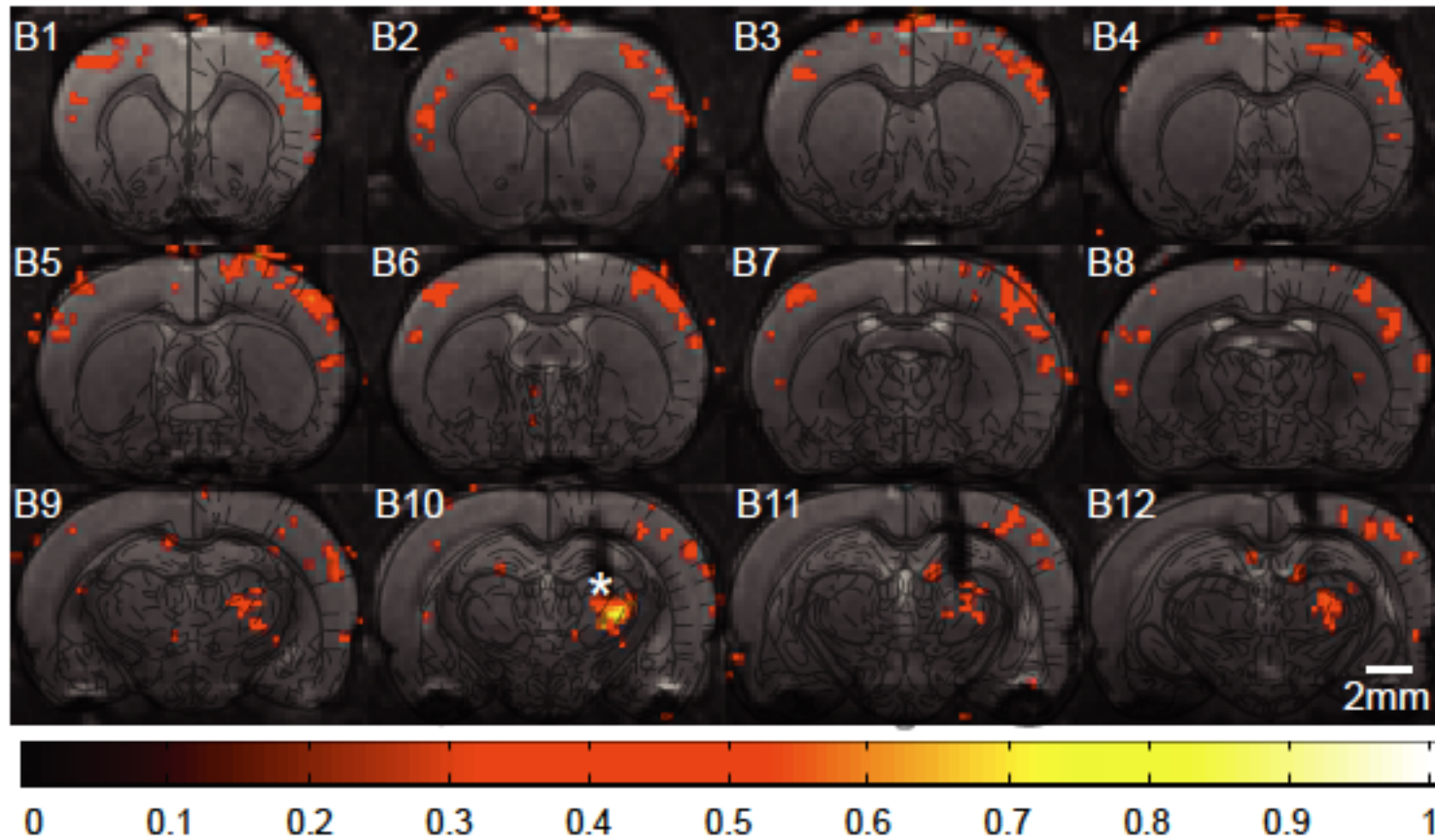
Unilateral Sensory Cortex Activity

In slice experiment: Cruikshank et al., Neuron 2010

Lee et al., Nature 2010

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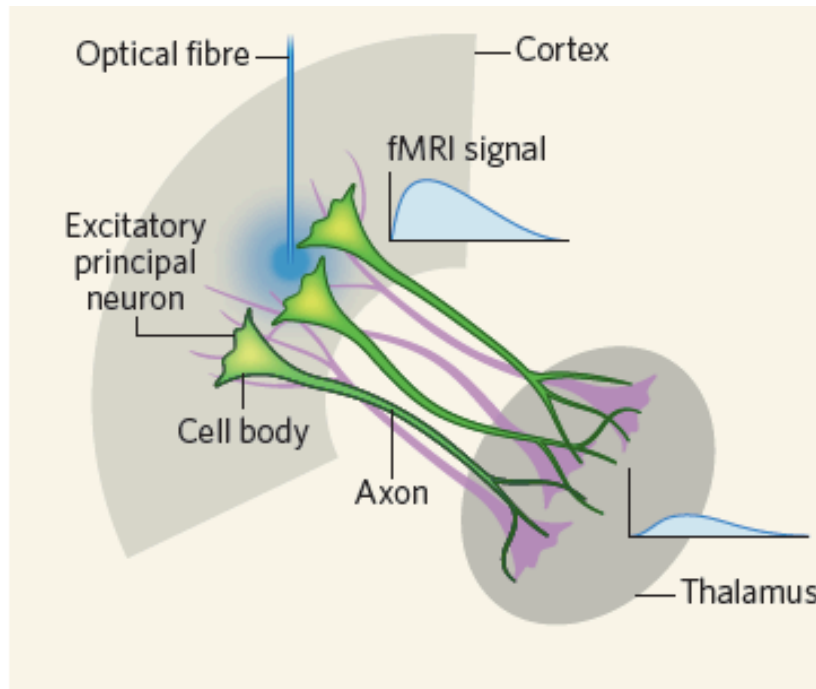# Anterior Thalamic Nuclei Stimulation

Bilateral Motor Cortex Activity

Lee et al., Nature 2010
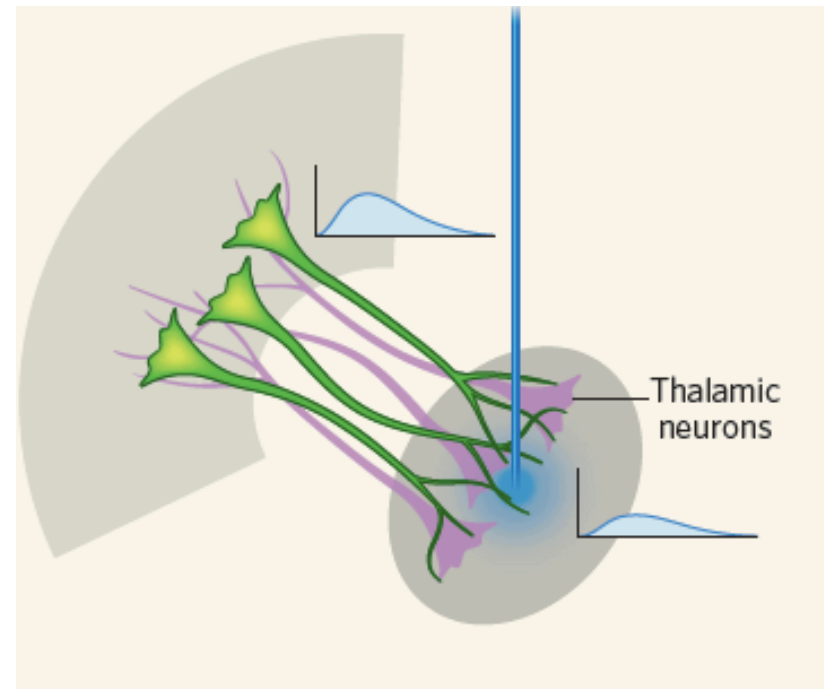
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In Vivo Brain Circuit Analysis and Debugging with ofMRI

Cell Body Location, Genetic identity

Cell Body Location, Genetic identity, Axonal Projection Target
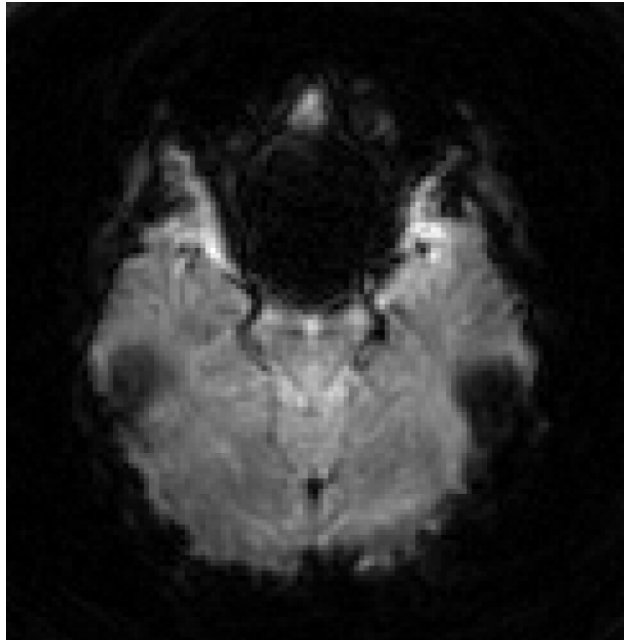

Leopold, Nature News and Views 2010
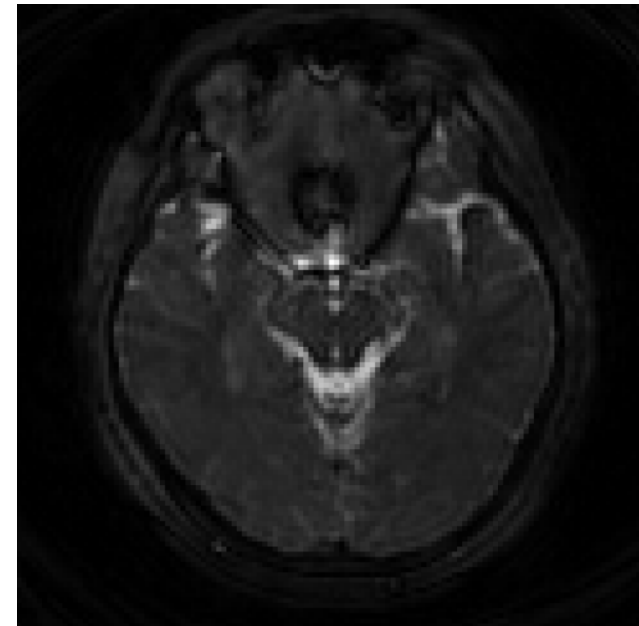
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BOLD fMRI Limitations

- **<u>Ambiguity of Signal Source</u>**

  – Sensory stimulation: complicated activation pathway, difficult to tell which element triggered the signal.

  – Resting State: correlation, non-causal

  – Solution: **<u>Optogenetic fMRI</u>**

- **<u>Image Quality</u>**

  – Large Distortions and Signal Dropout

  – Low spatial resolution

  – Solution: **<u>Passband b-SSFP fMRI</u>**

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BOLD vs. Passband b-SSFP fMRI
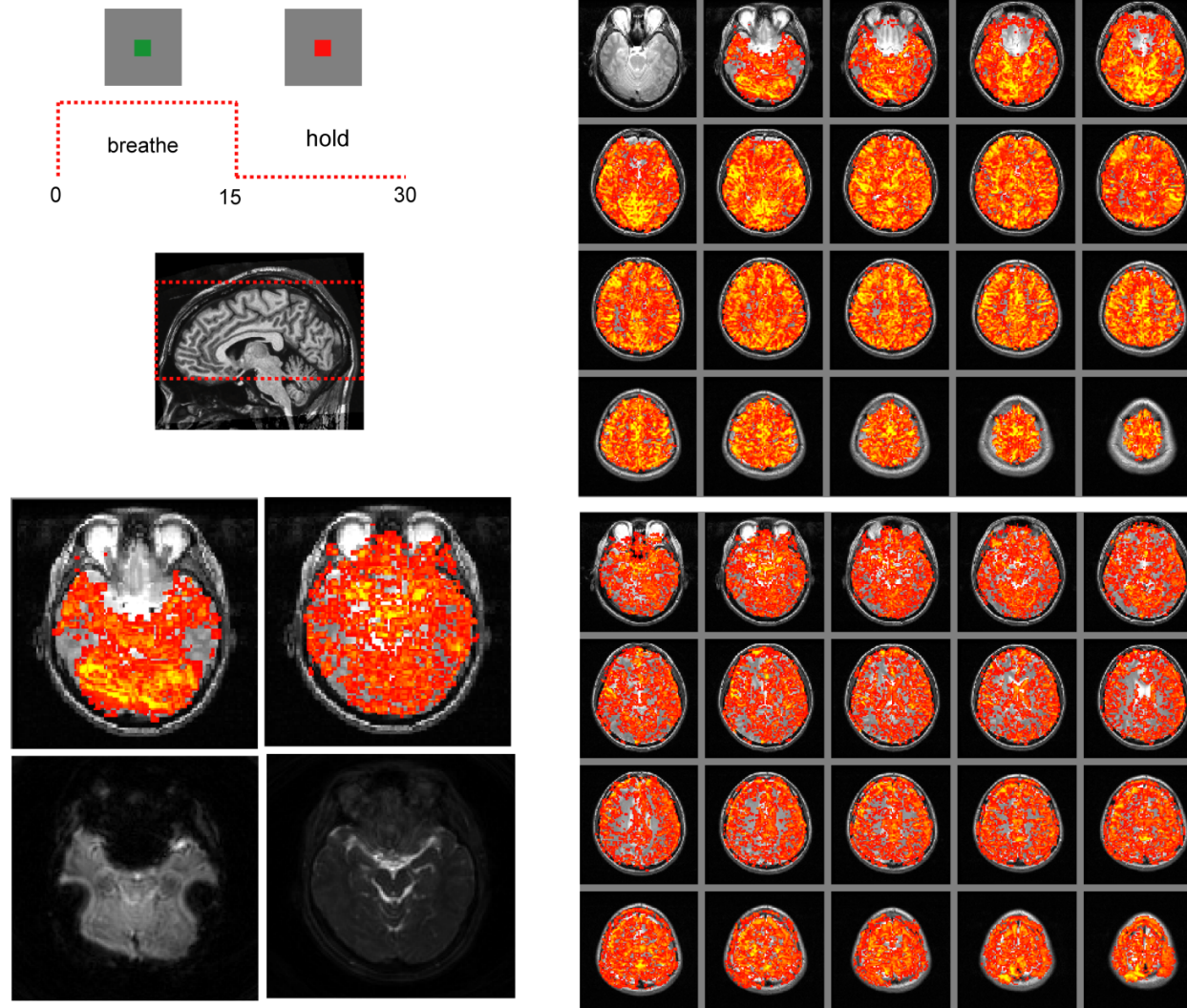
Conventional BOLD

Passband b-SSFP

- reduced distortion and signal dropout
- better voxel definition (effectively higher resolution)
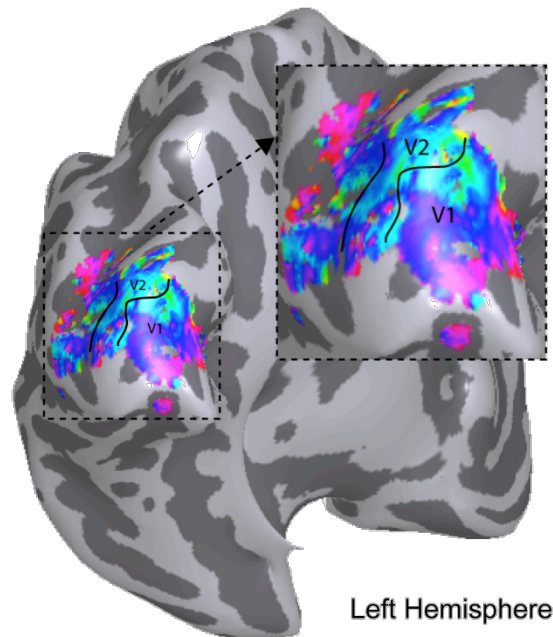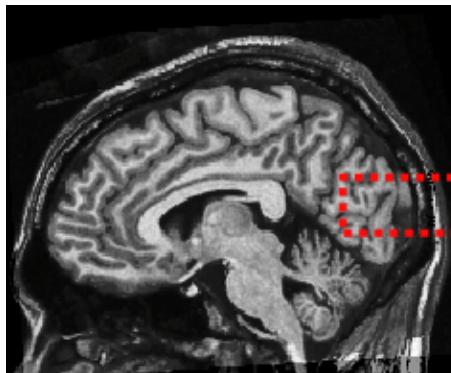
Lee et al., MRM 2008
Lee, Int. J. of Imaging Systems Technology 2010
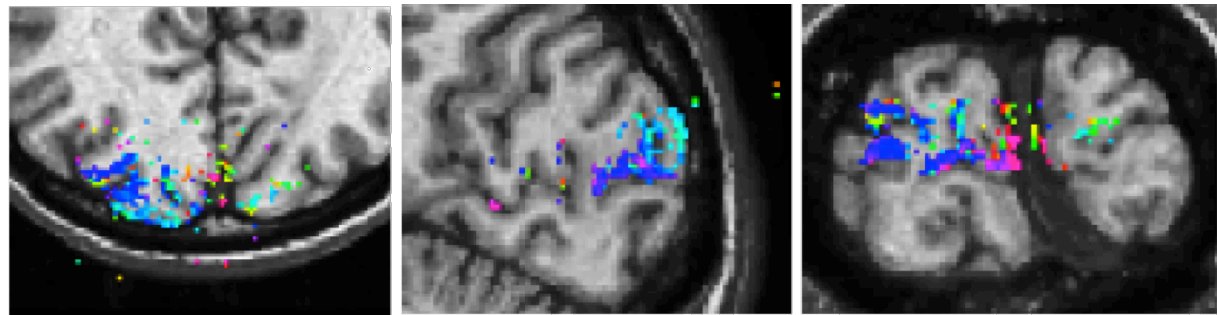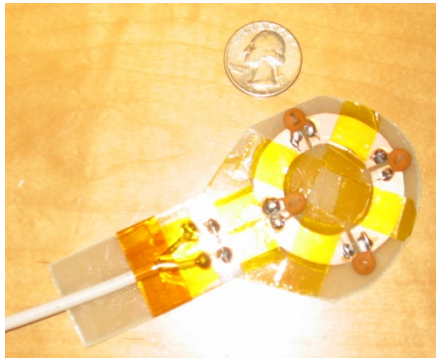
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Distortion-Free Full Brain Coverage
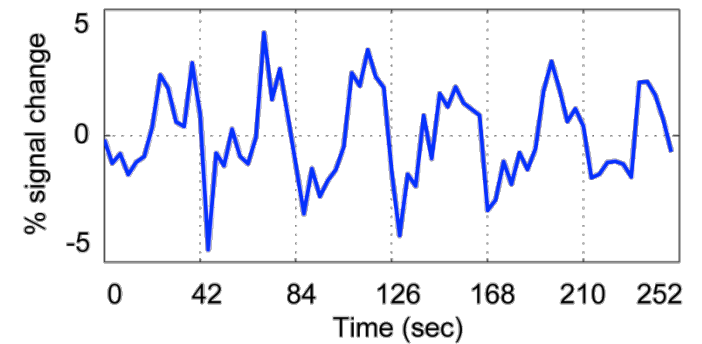

breathe · hold

0 · 15 · 30
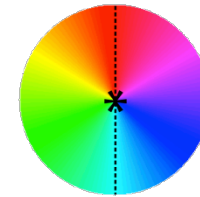
Lee et al.,
MRM 2008

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Isotropic 1 mm Visual Field Map

Left Visual Field

Right Visual Field

Left Hemisphere
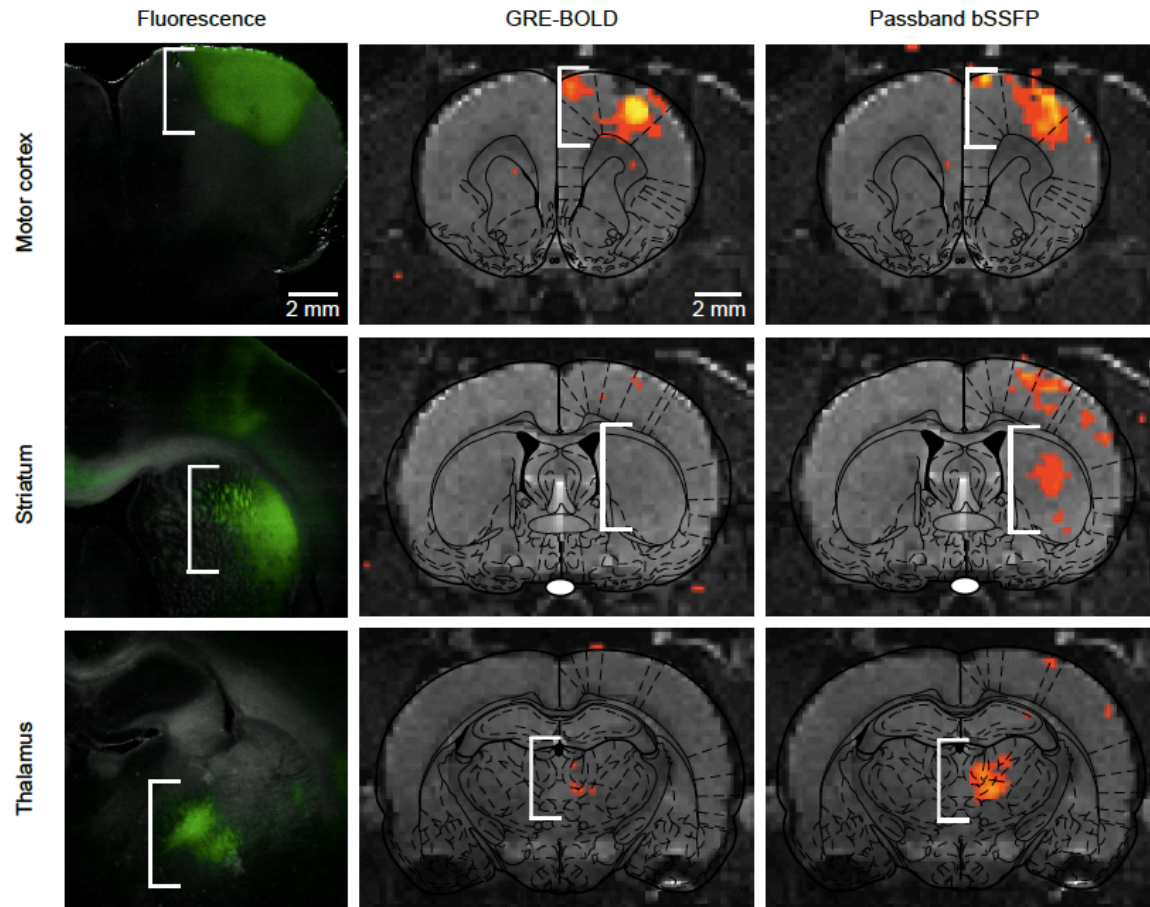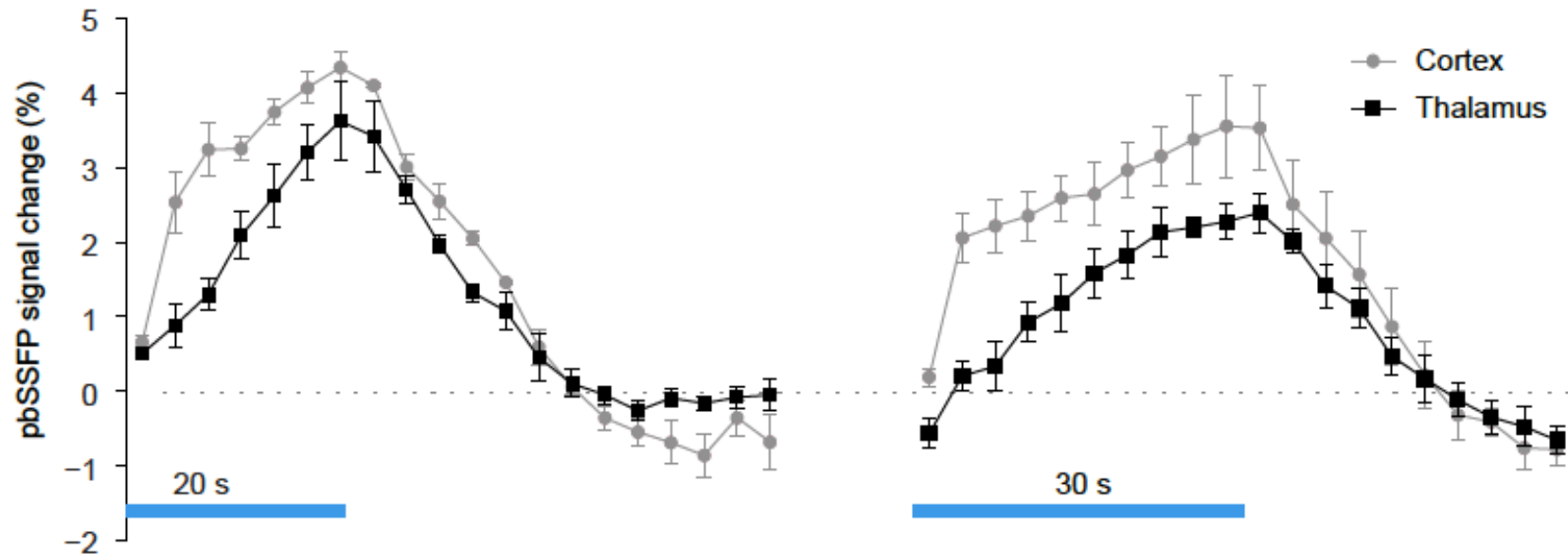
Lee et al., MRM 2008

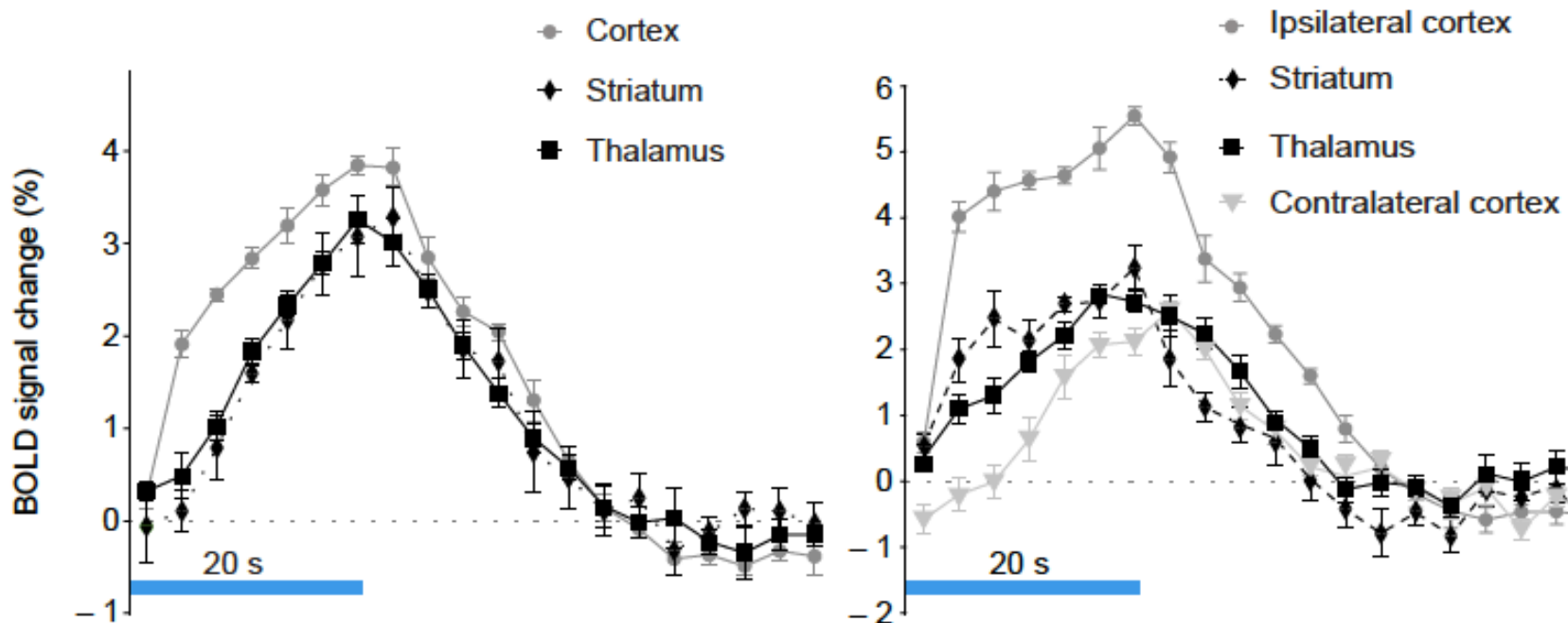# Passband bSSFP ofMRI allows more Accurate Monitoring of Global Activity

Lee et al., MRM 2008
Lee et al., Nature 2010

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HRF of Passband bSSFP ofMRI is Similar to Conventional BOLD

Lee et al., MRM 2008
Lee et al., Nature 2010

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bSSFP ofMRI allows Accurate Measurement in Individual Animals

Lee et al., MRM 2008
Lee et al., Nature 2010

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Conclusion

- **Optogenetic fMRI (ofMRI)** provides a platform to visualize the brain circuit's <u>causal network response</u> from elements specified by *<u>genetic identity</u>*, <u>cell body location, and axonal projection target</u>. – Systematic **<u>Brain Circuit Analysis and Debugging</u>**!

- Improved **Passband b-SSFP fMRI** images are critical.
  - Small brain of rodents
  - Small target neural populations of interest

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http://www.ee.ucla.edu/~jhlgroup/index.html

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