Anatomical and Functional Magnetic Resonance Imaging in Small Animal Models

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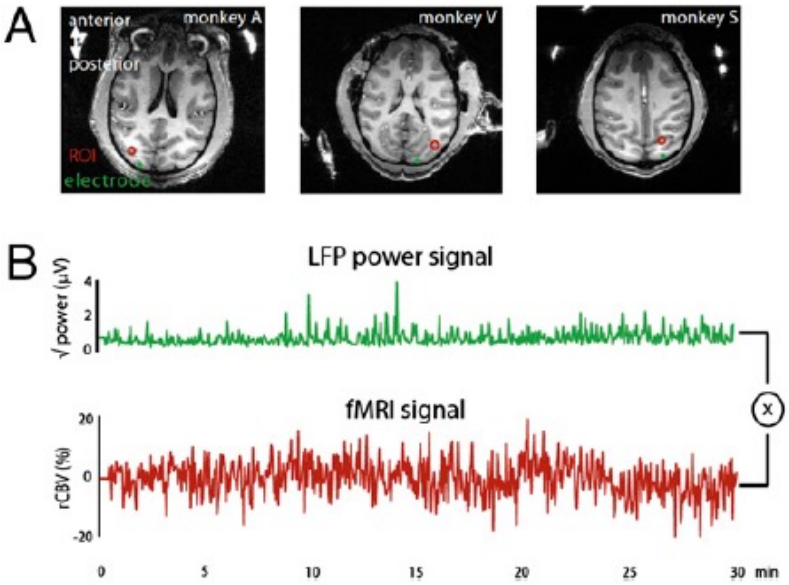
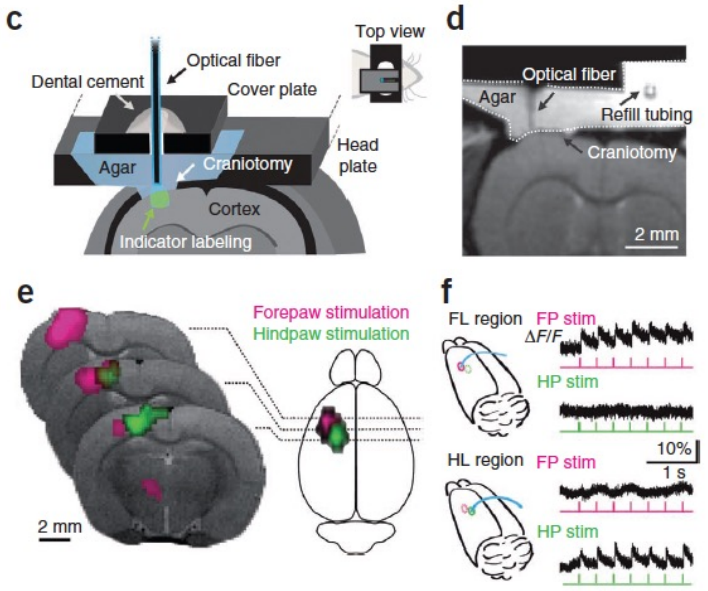
Advantages of Animal Models

- Comprehensive, multi-modal investigations
  - fMRI + Electrophysiology
  - fMRI + Optical Imaging
  - Pharmacological Manipulations
  - Genetics, etc.

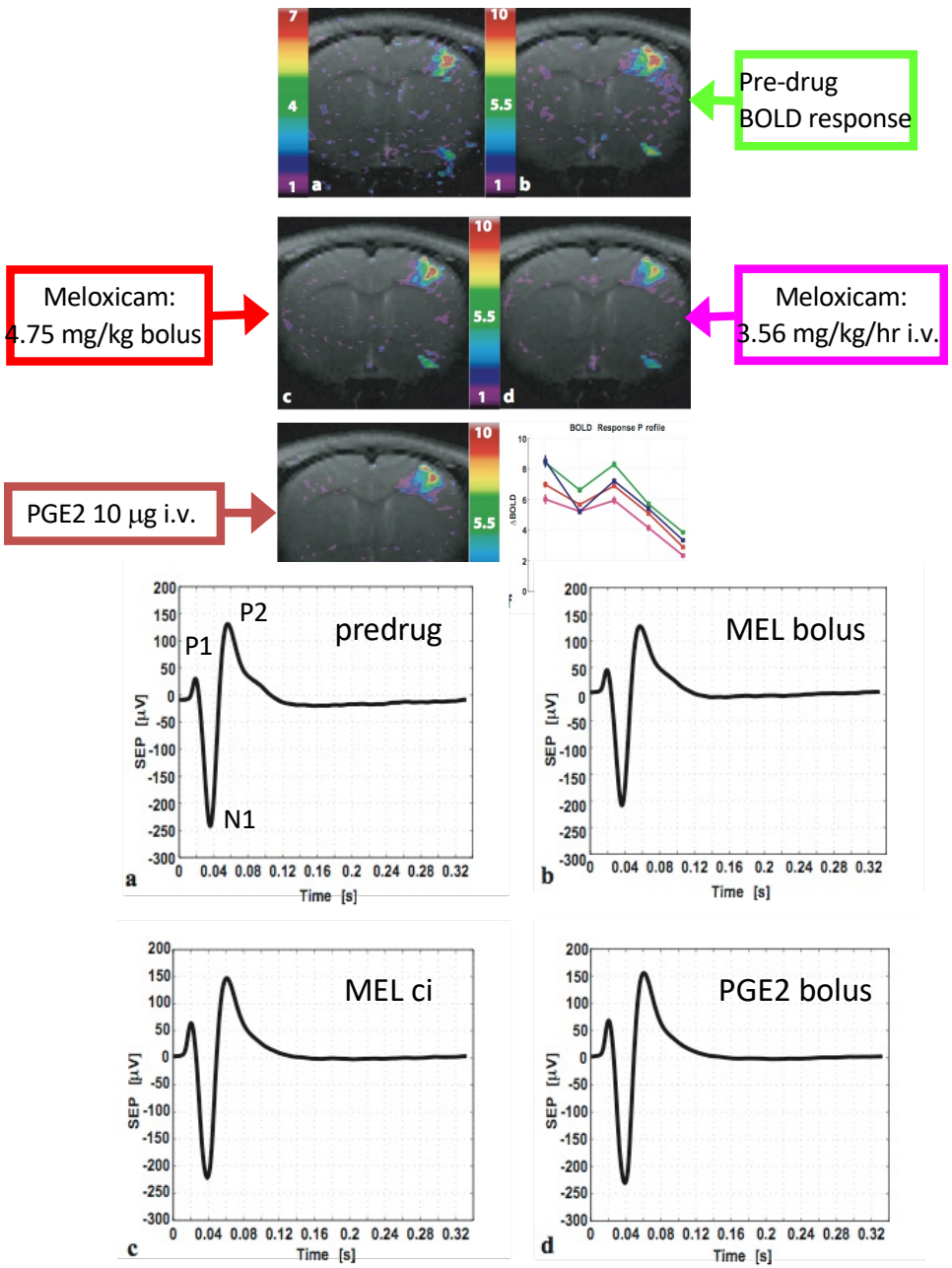


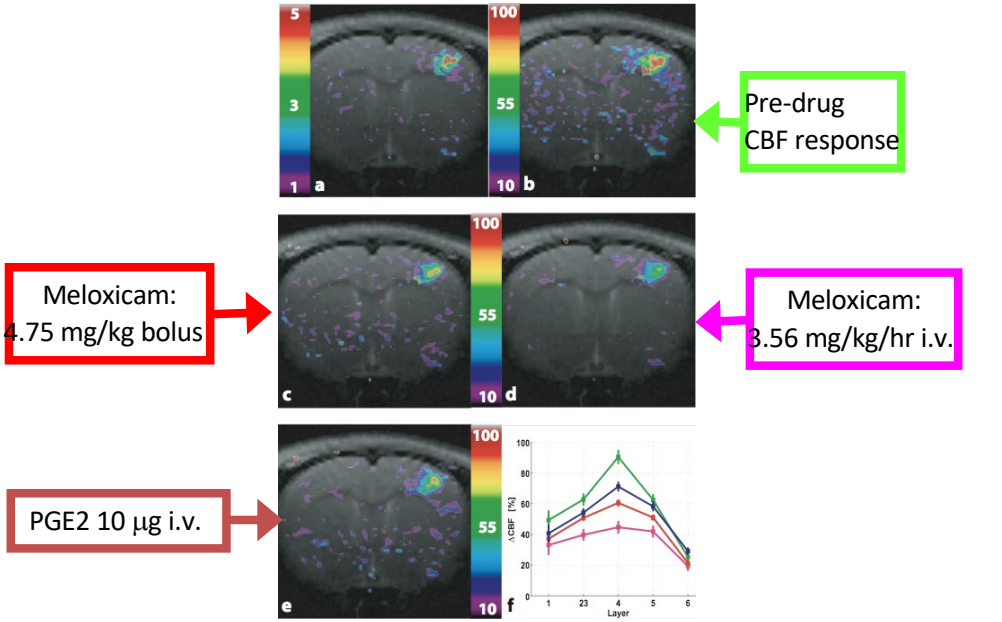
Schölvinck et al. Proc Natl Acad Sci USA. 2010;107(22):10238-43

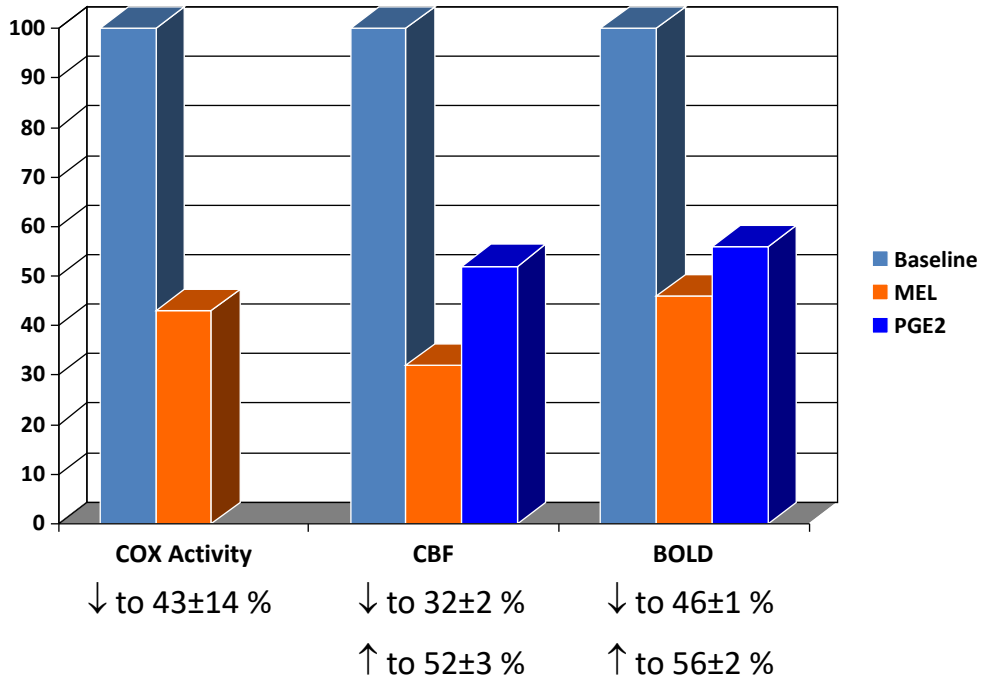


Schultz et al. Nat Methods. 2012;9(6):597-602

Pharmacological Inhibition of COX-2 Uncouples Hemodynamics from Neural Activity



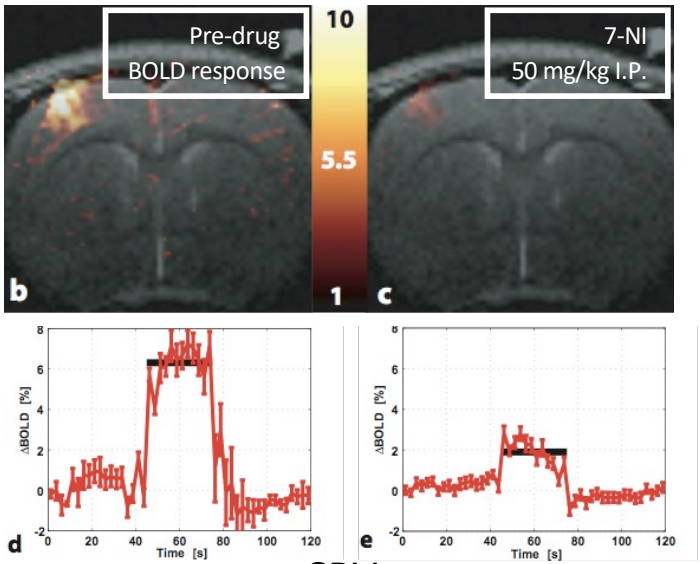




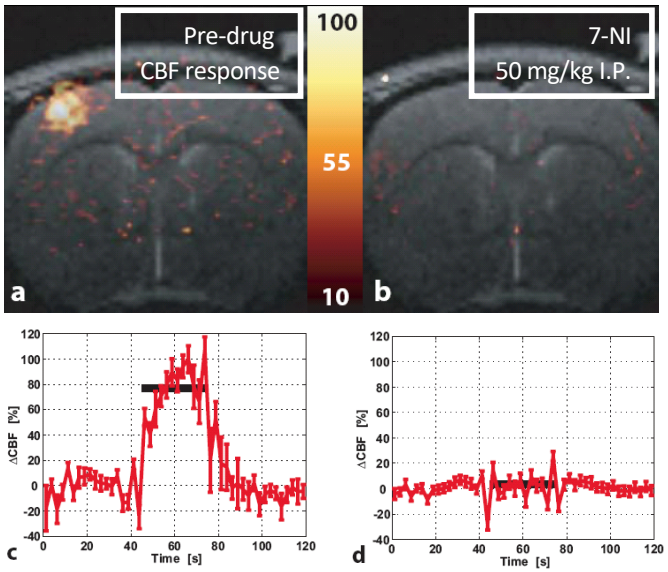
Stefanovic et al, Neuroimage 2006,32(1): 23-32

Pharmacological Inhibition of Nitric Oxide Uncouples BOLD from CBF

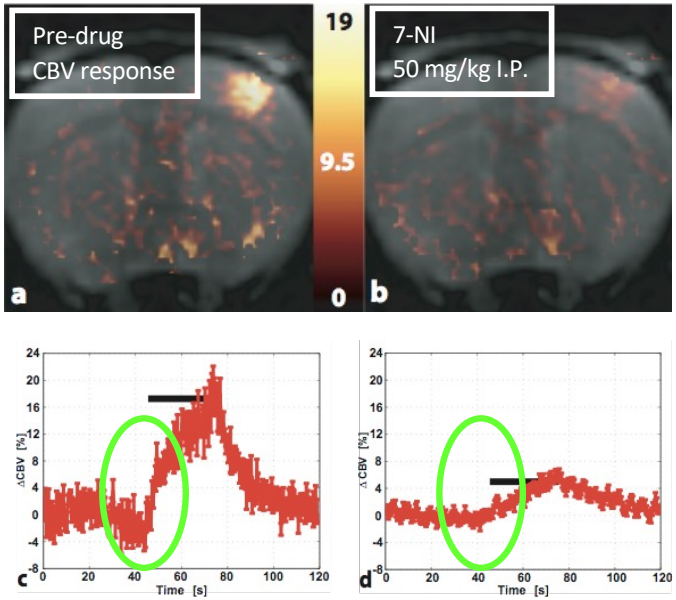
BOLD

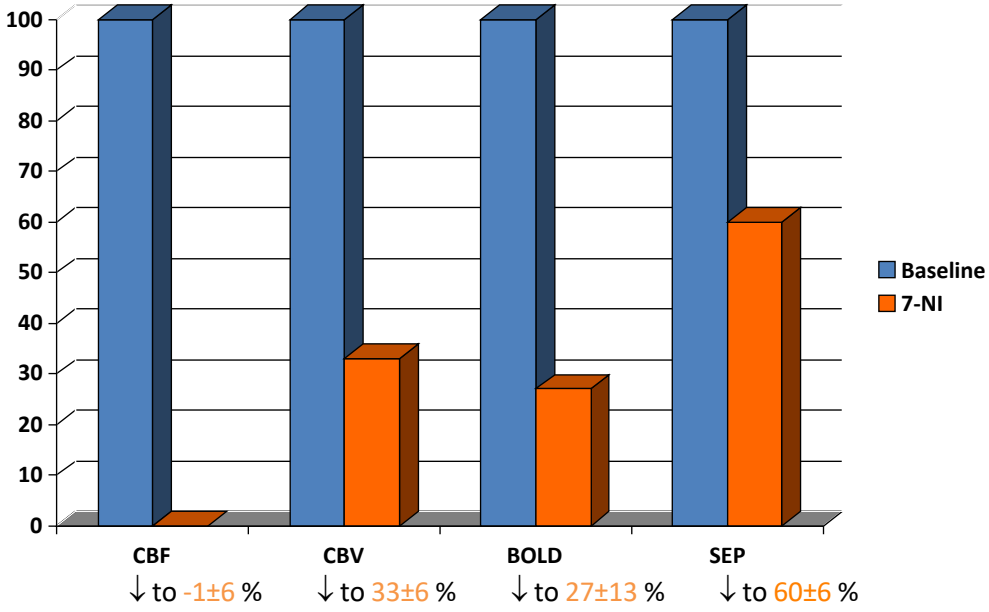


CBF



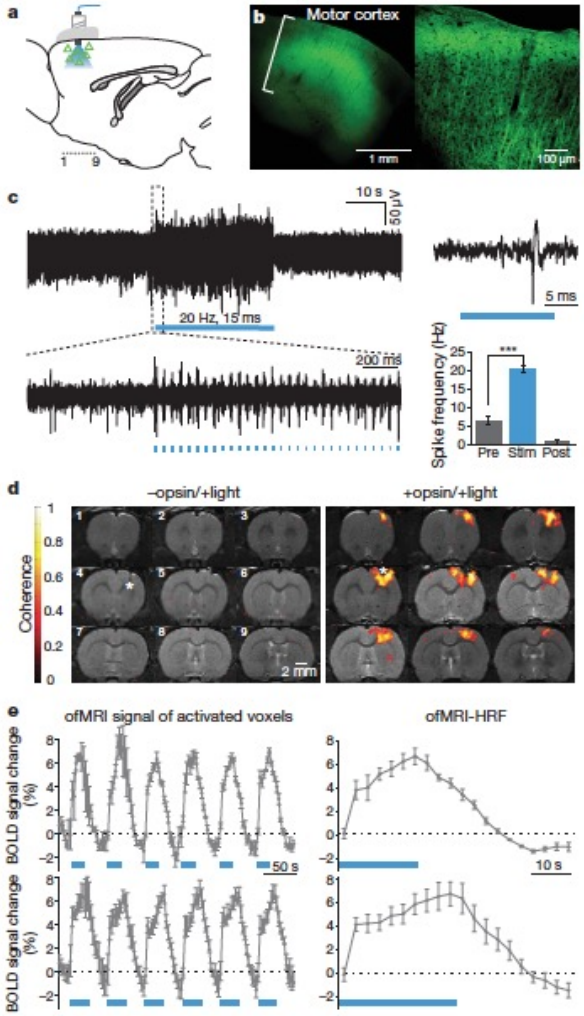
CBV



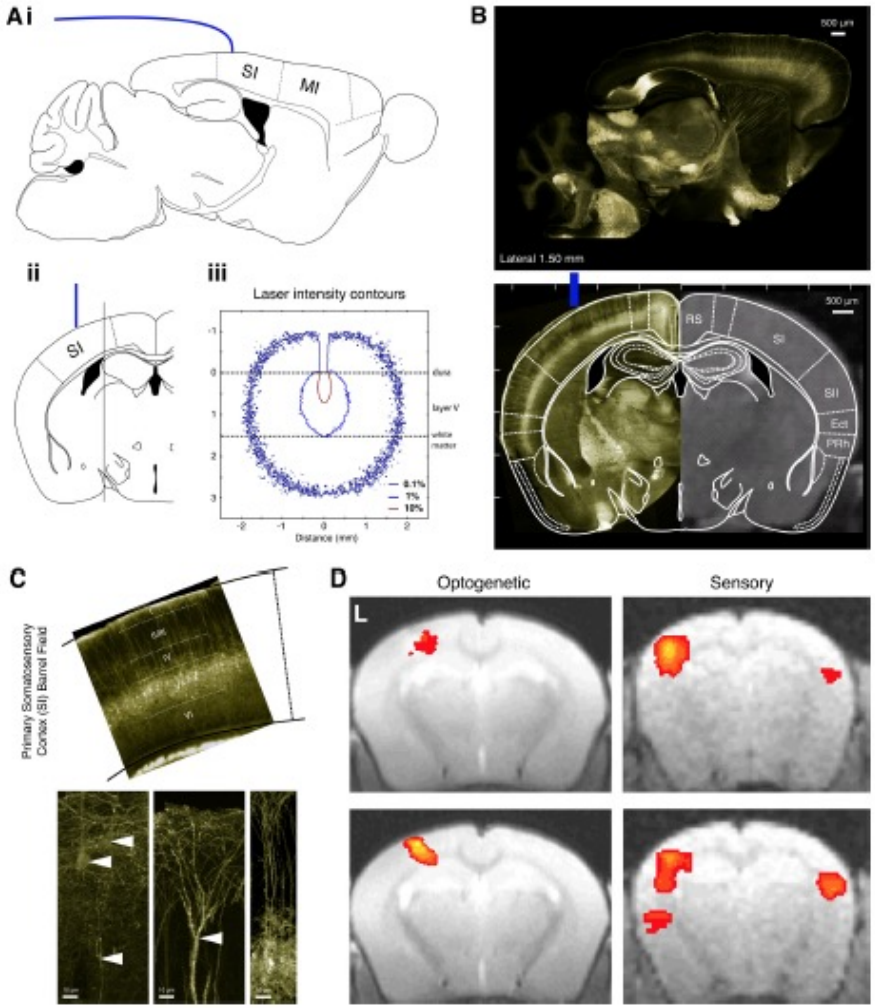


Stefanovic et al. J Cereb Blood Flow Metab. 2007;27(4):741-54.

Genetic Manipulations: Optogenetics



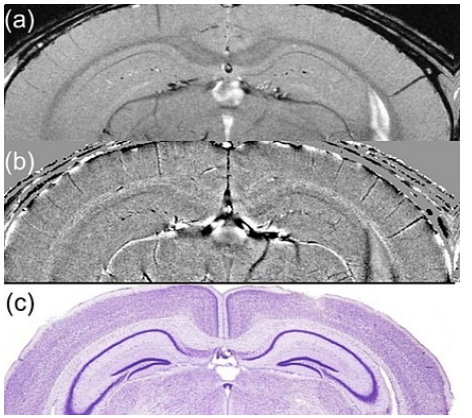
Lee et al. Nature. 2010 Jun 10;465(7299):788-92



Kahn et al., J Neurosci. 2011 Oct 19;31(42

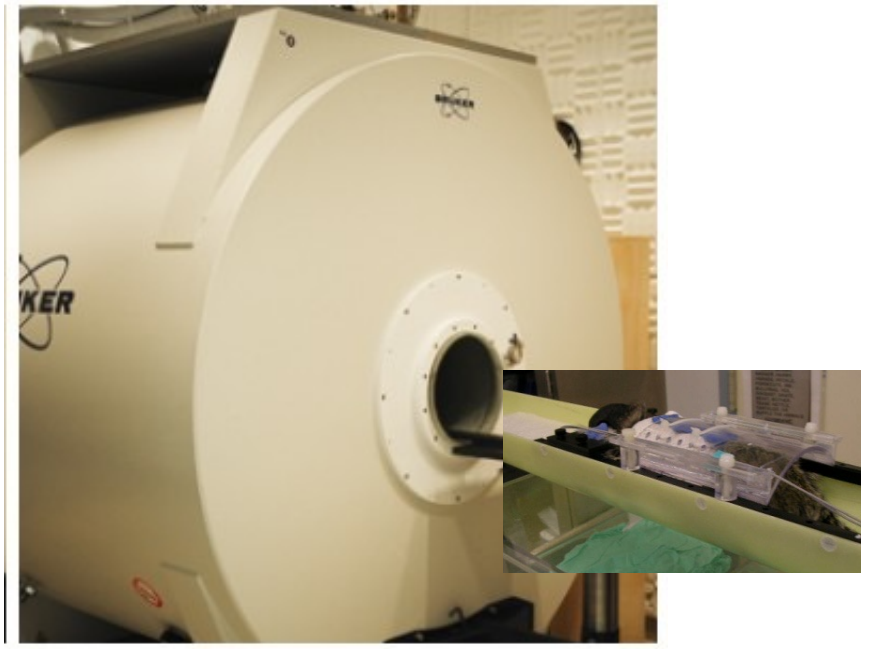
Advantages of Animal Models

- Technical
  - Ultra-High Field Magnets
    - up to 21T vertical
    - up to 17.6T horizontal
  - Stronger Gradients
    - Up to 1000 mT/m in 12 cm ID
  - Small FOV due to smaller brain size
    - Improved spatial resolution
    - Improved SNR with specialized RF coils

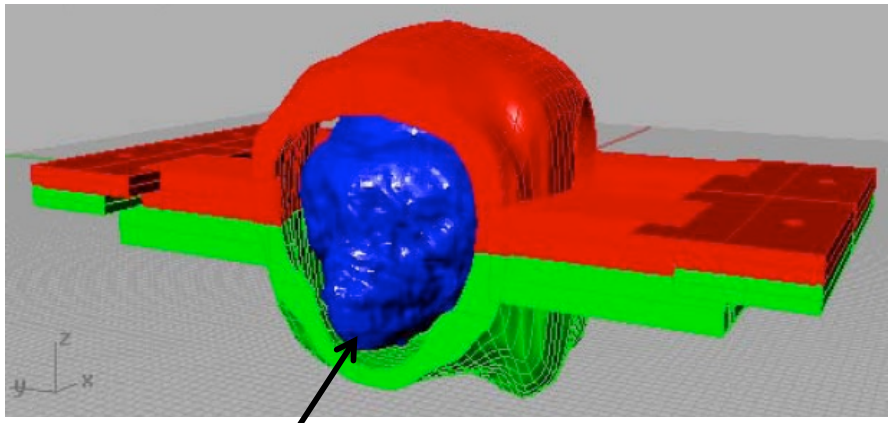


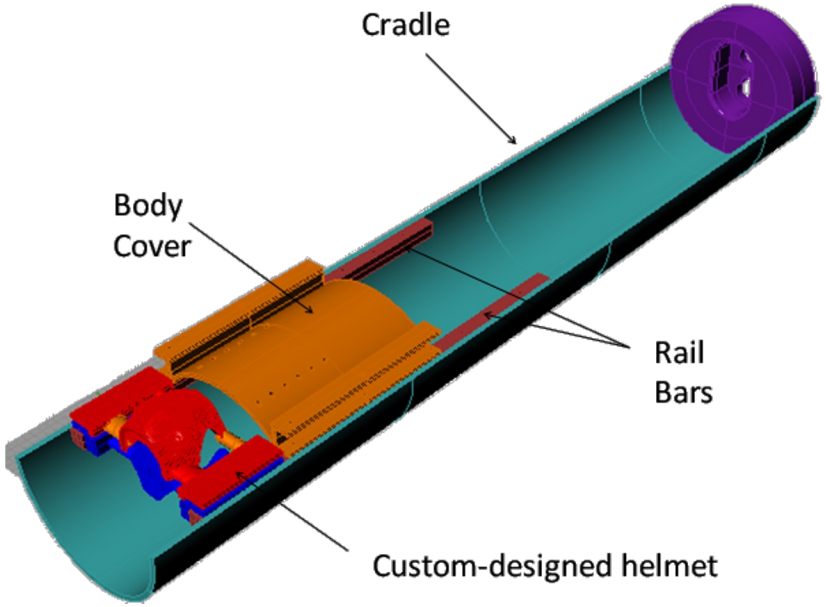
How to Do MRI/fMRI in Small Animals

- Two types of setup
  - Anesthetized Animals
    - Isoflurane (anatomic studies)
    - Chloralose (functional studies)
    - Propofol + Fentanyl (functional studies)
  - Awake
    - Anatomical or functional Studies
- Extensive Physiological Monitoring
  - Temperature
  - Blood Pressure and Heart Rate
  - Pulse oximetry
  - $ETCO_2$



Anatomical and Functional MRI in Conscious, Awake Marmosets

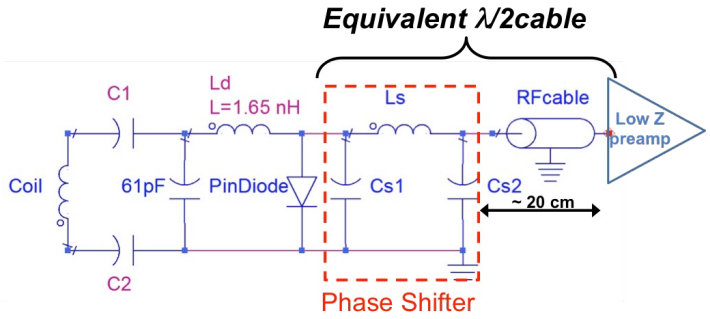




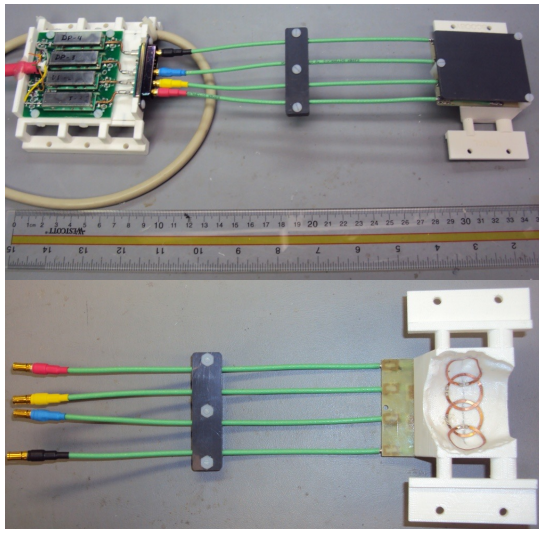
Individual
Helmet

State-of-the-Art Neuroimaging Techniques

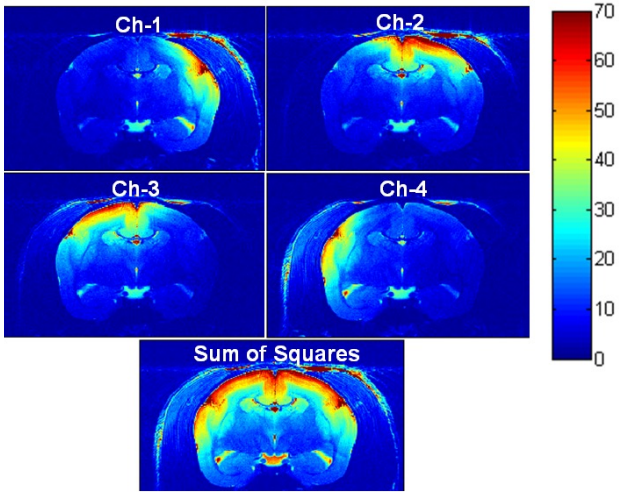
- Embedded RF receiver arrays



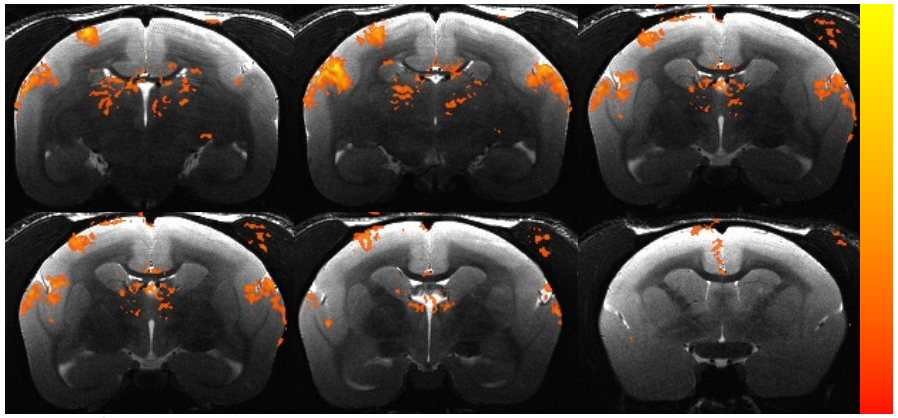
Circuit Diagram



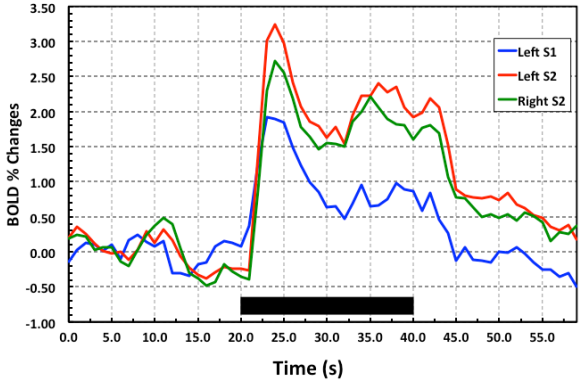
Embedded helmet array and preamps



In vivo SNR Maps

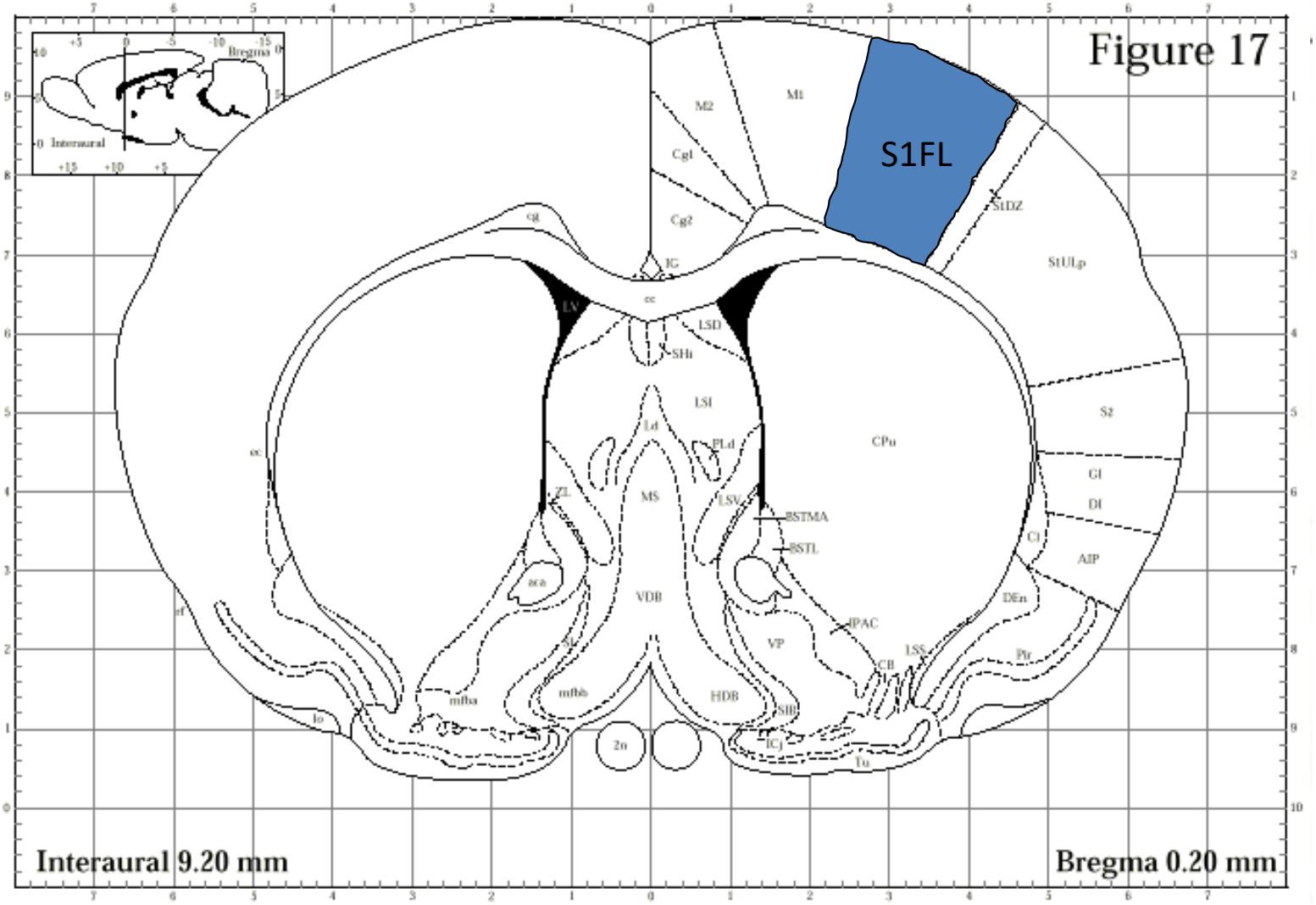


fMRI in Conscious, Awake Marmosets
250 x 250 x 1000 µm³



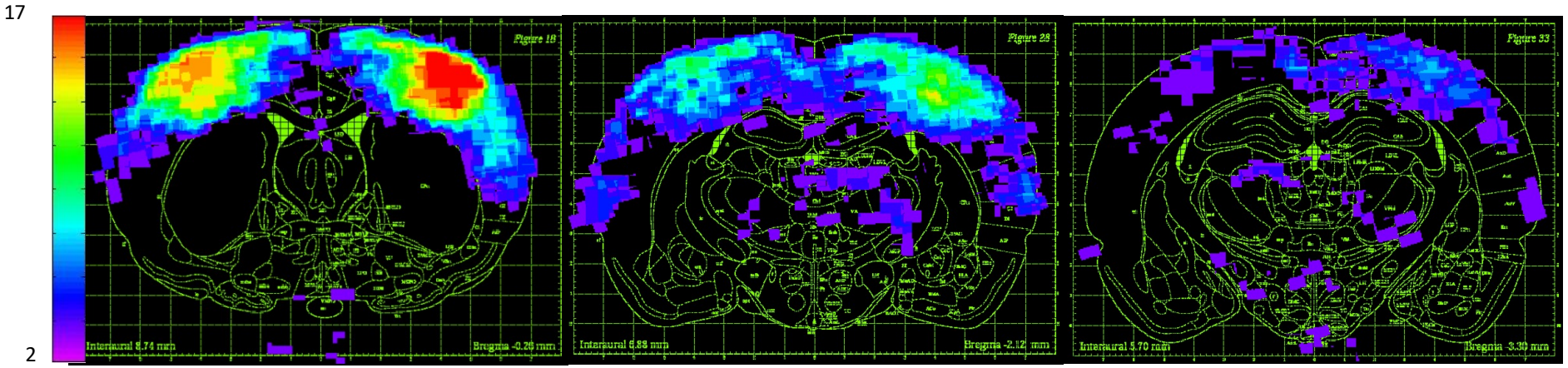
Daniel Papoti, Cecil Yen, Julie Mackel, Hellmut Merkle, Afonso Silva, in preparation

How to Stimulate Animals: Somatosensory Stimulation in Rat

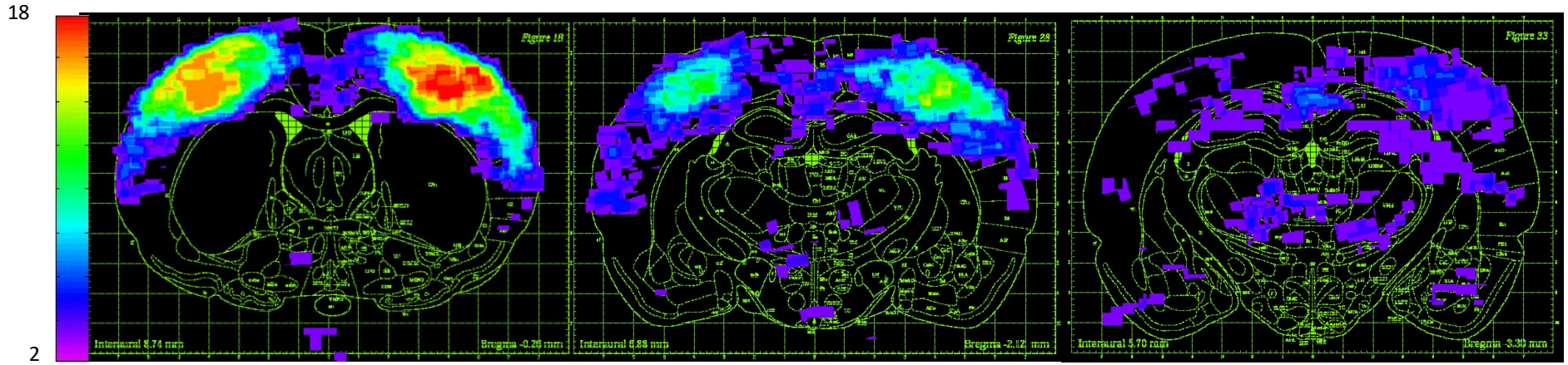


Atlas: "The Rat Brain in Stereotaxic Coordinates", Paxinos & Watson, 1998

Reproducibility: BOLD and CBV Incidence Maps at 11.7T



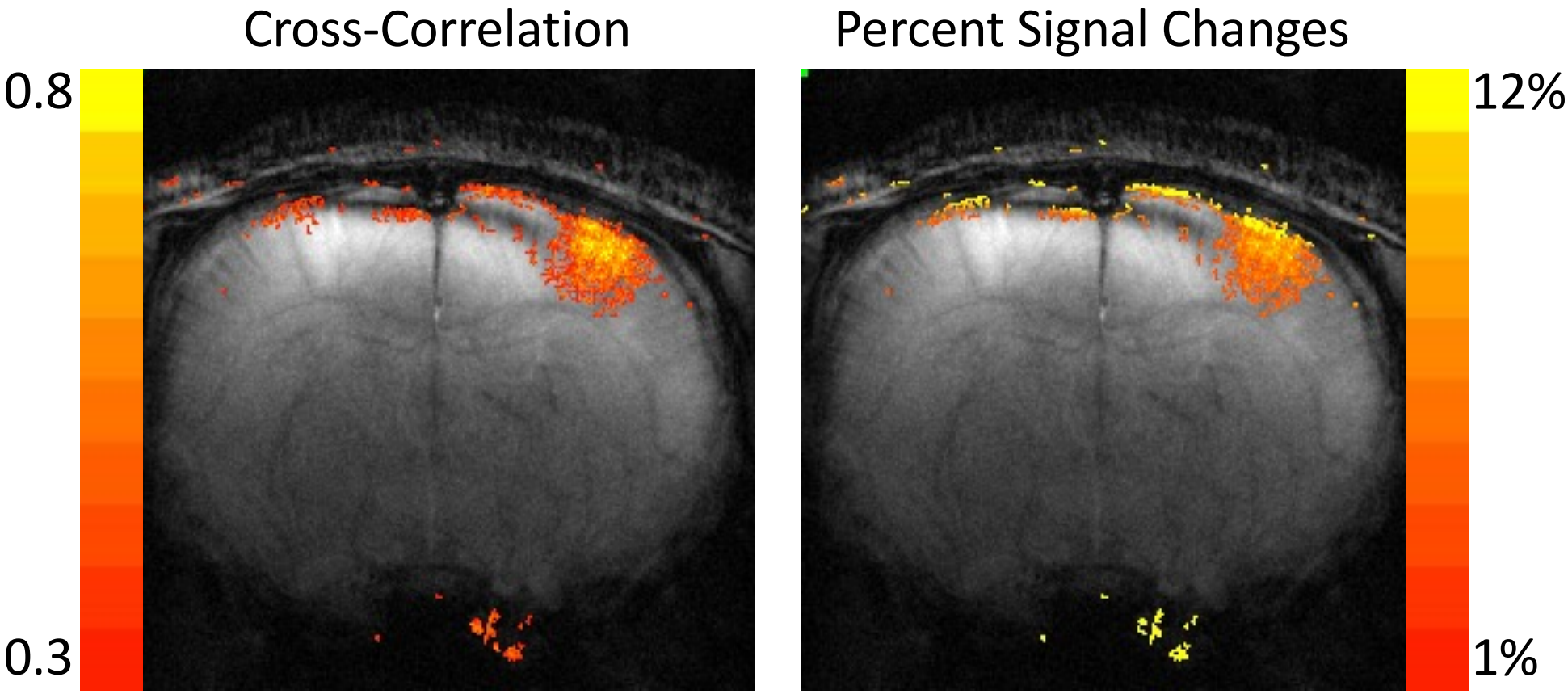
BOLD



CBV

Keilholz et al, MRM 55:316–324 (2006)

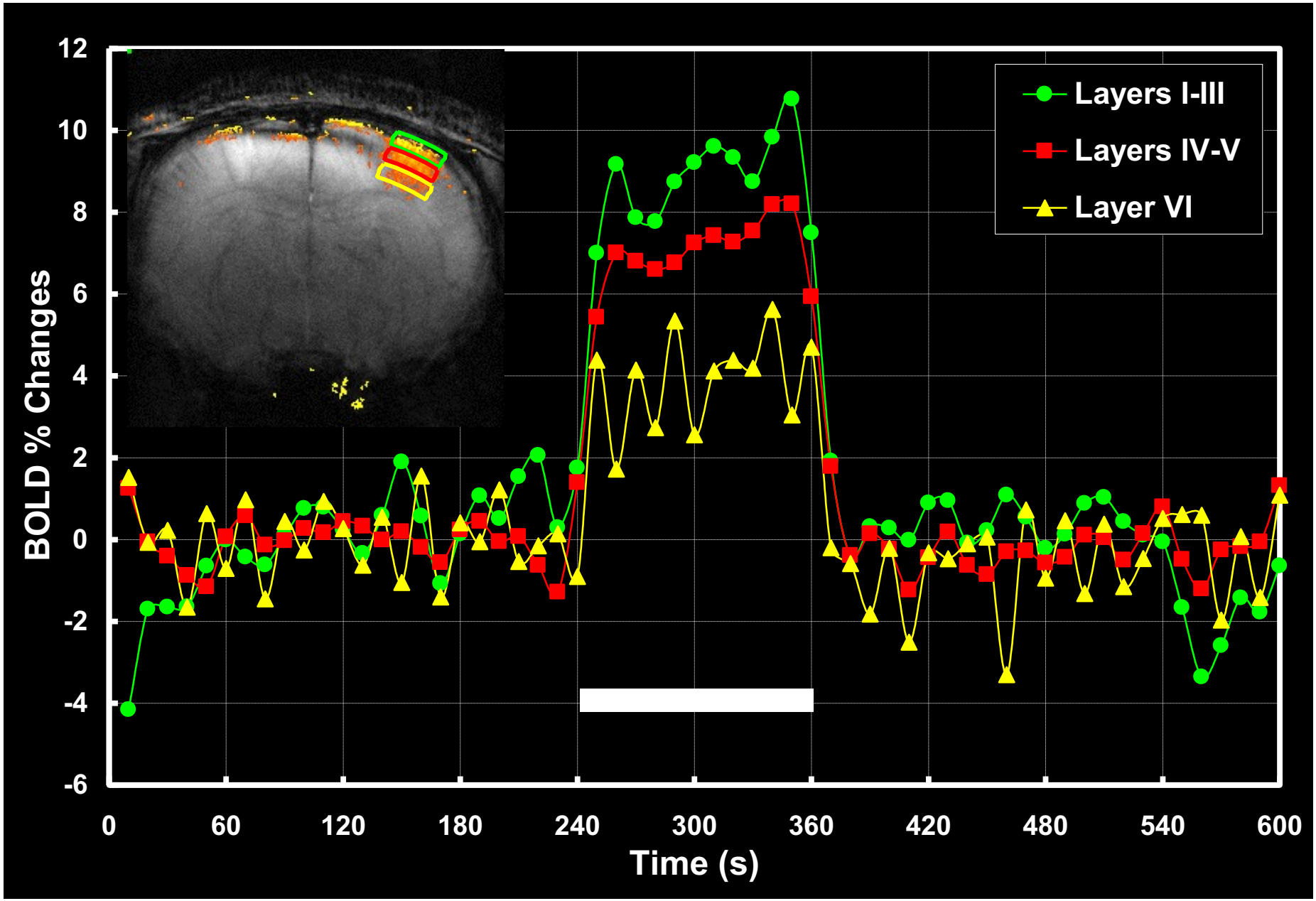
Spatial Resolution: BOLD Functional Maps



11.7T Gradient-Echo, 50 x 50 x 2000 μm^3

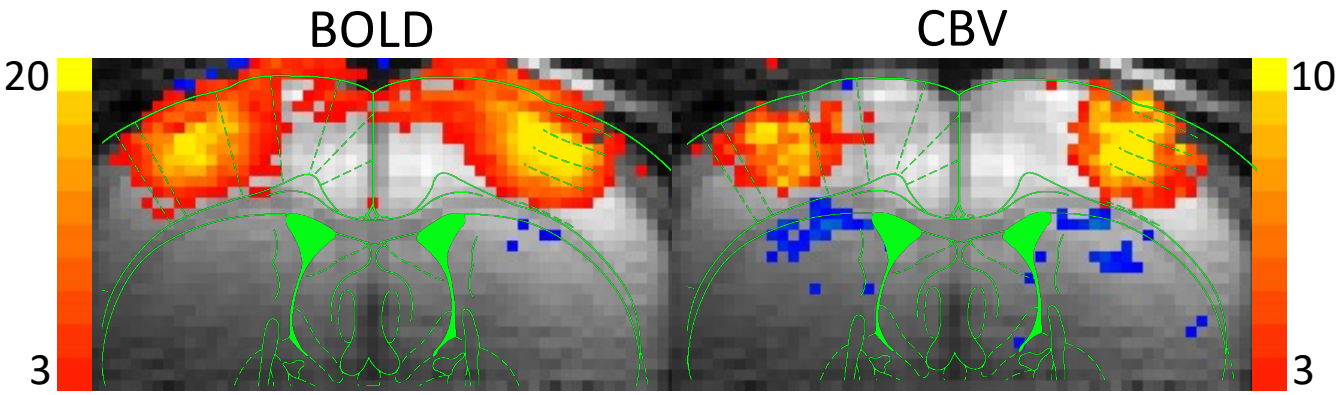
Silva and Koretsky PNAS 99: 15182-15187 (2002)

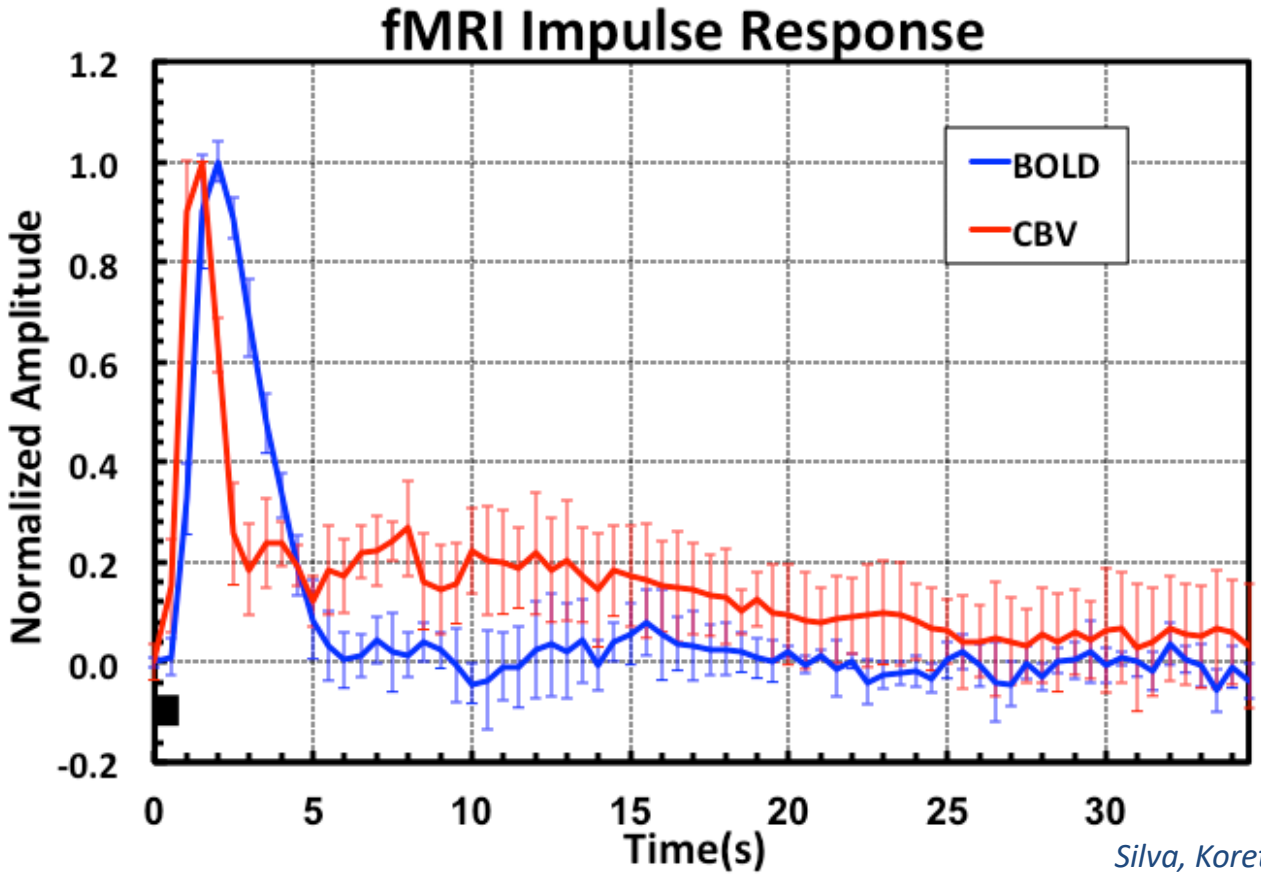
Laminar Specificity of BOLD Signal Changes



Silva and Koretsky PNAS 99: 15182-15187 (2002)

BOLD and CBV Impulse Responses

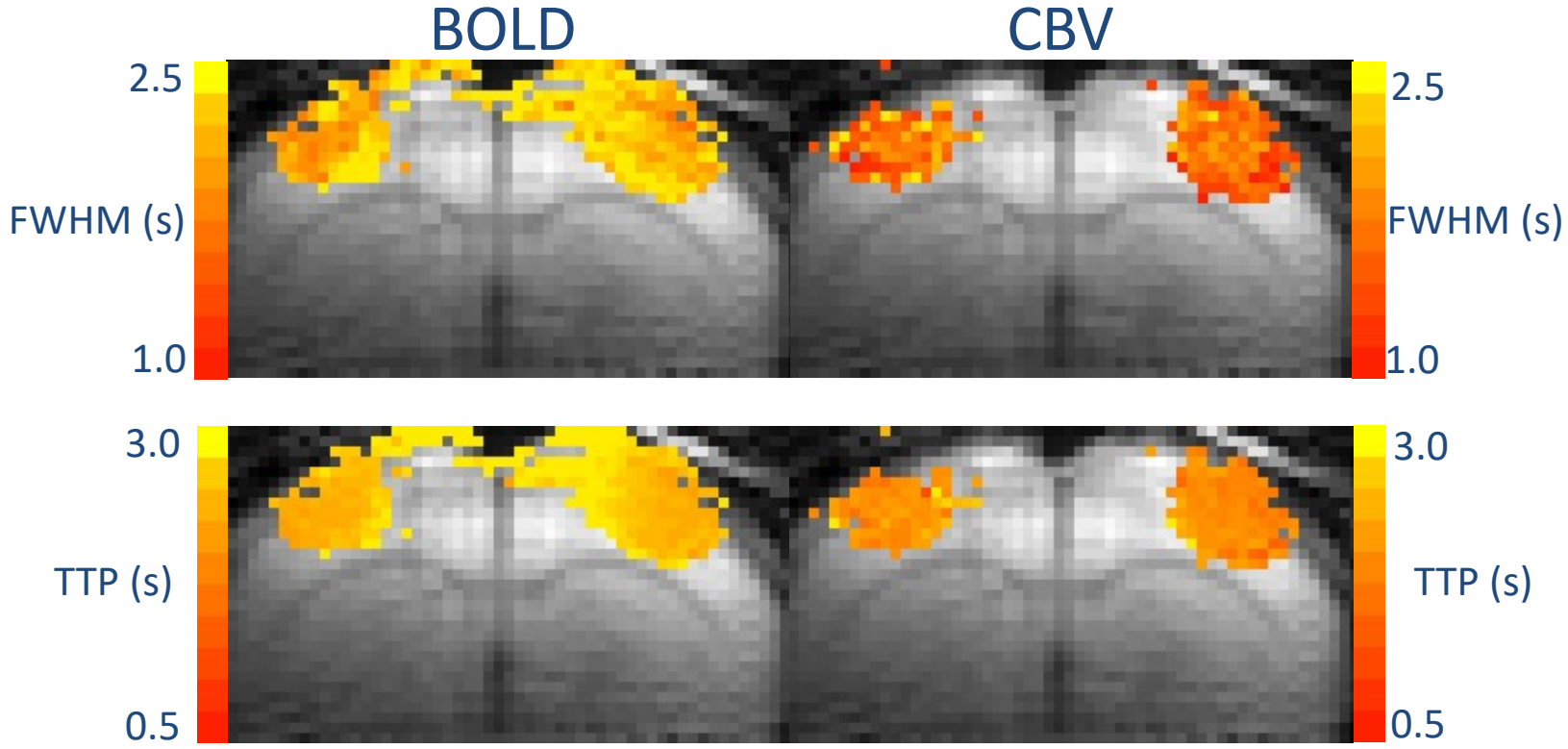




- α-chloralose anesthetized rat
- Electrical stimulation of the forepaw
- Stimulation parameters optimized by laser-Doppler flowmetry:
  - 2.0 mA; 3 Hz; 0.3 ms

Silva, Koretsky, Duyn, Magn Reson Med 57:1110-8, 2007

Parametric Maps: Time-to-Peak (TTP) & Full-Width at Half-Maximum (FWHM)

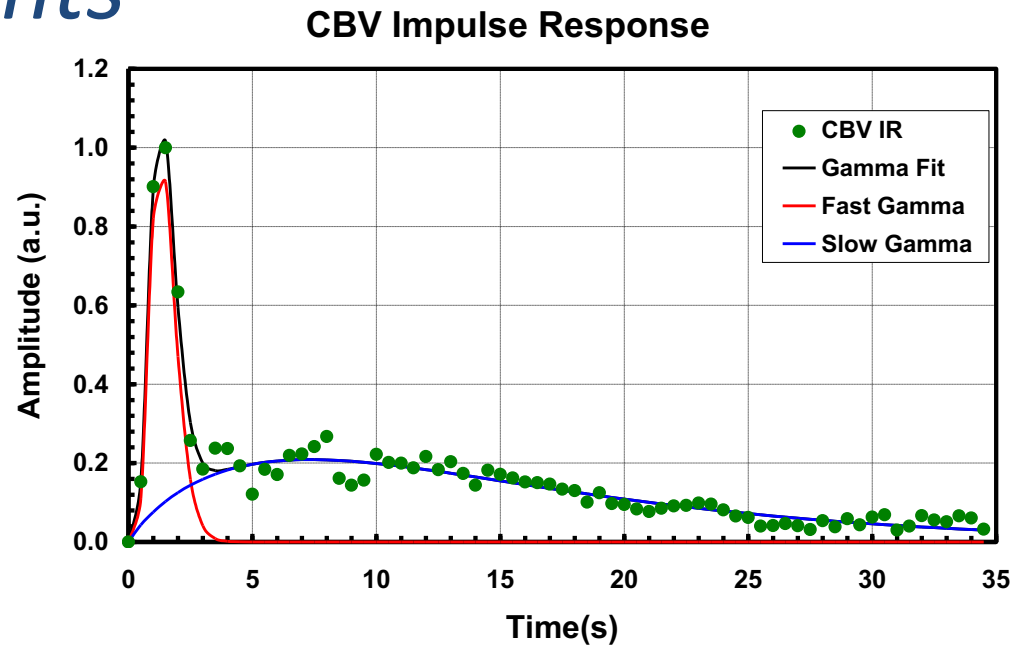


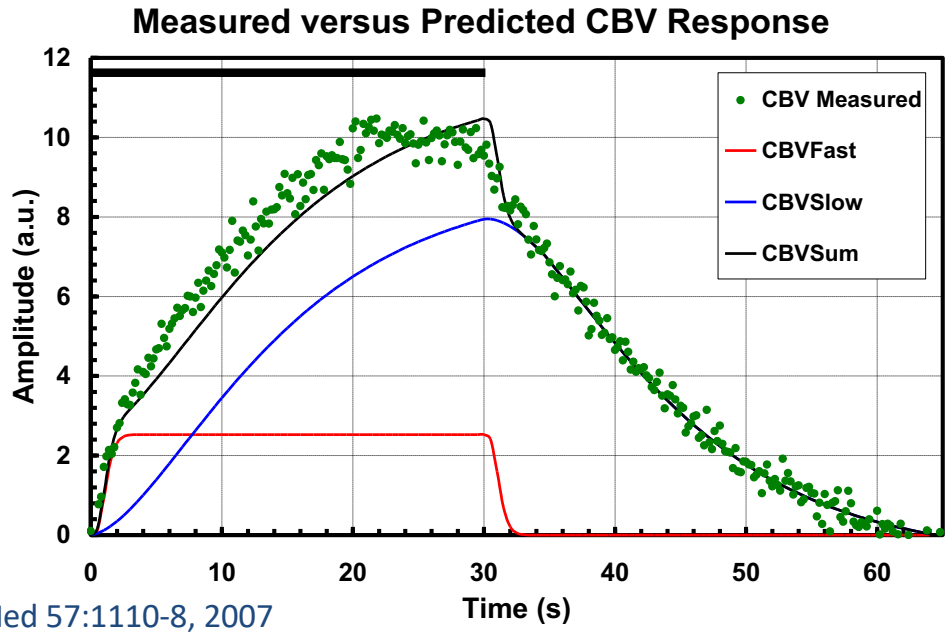
BOLD		CBV		ΔOnset (s)
TTP (s)	FWHM (s)	TTP (s)	FWHM (s)	
2.18 ± 0.14	1.92 ± 0.22	1.65 ± 0.15	1.37 ± 0.11	0.44 ± 0.24

Compare to TTP = 4.51 ± 0.52 s and FWHM = 4.04 ± 0.42 s in humans (*de Zwart et al, Neuroimage 24:667-677 (2005)*)

Silva, Koretsky, Duyn, Magn Reson Med 57:1110-8, 2007

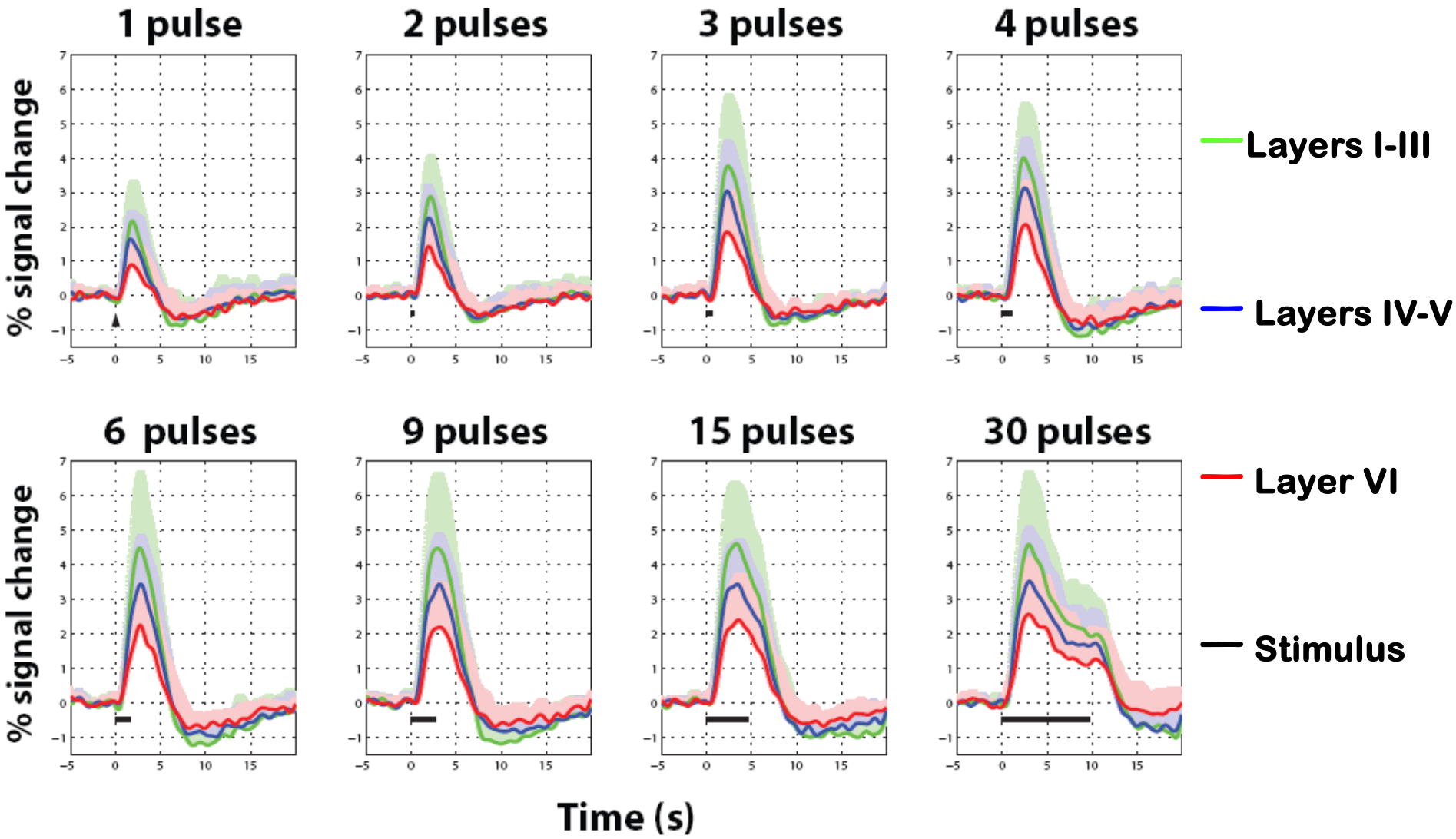
CBV Impulse Response Has Fast and Slow Components





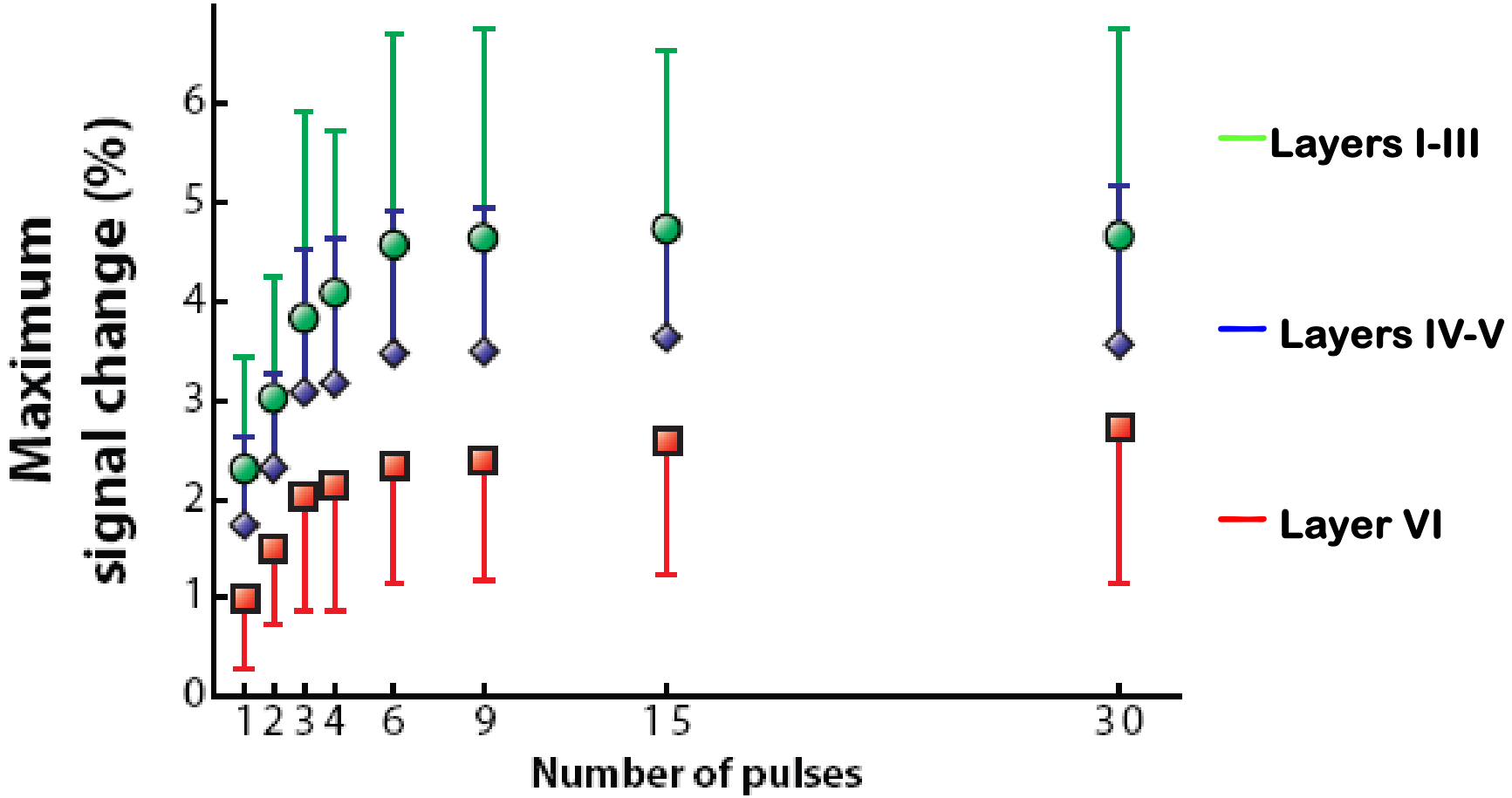
Silva, Koretsky, Duyn, Magn Reson Med 57:1110-8, 2007

Variation of HDR with Stimulus Duration



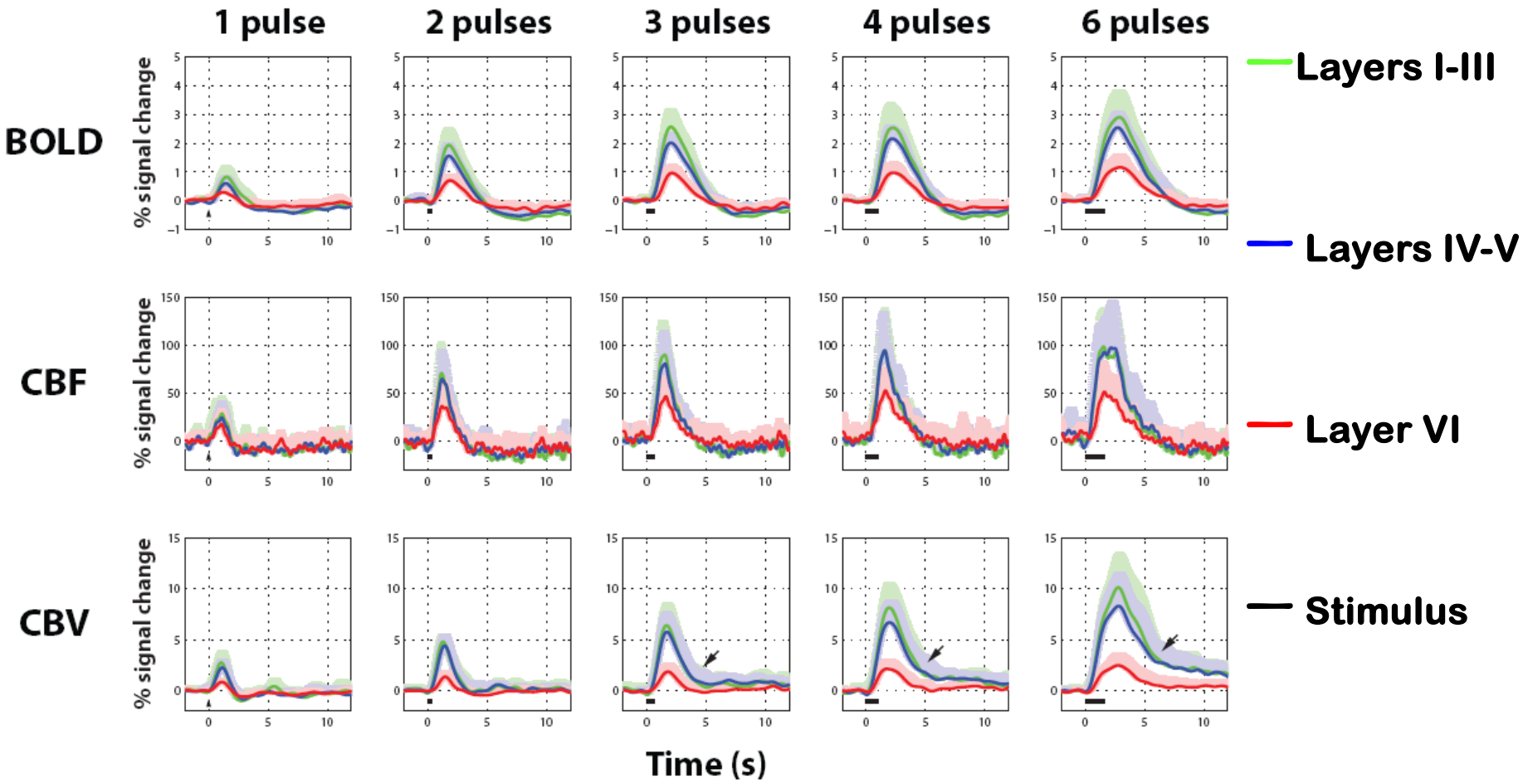
Hirano, Stefanovic and Silva J Neurosci. 31(4):1440-7 2011

Variation of the Peak Intensity with Stimulus Duration



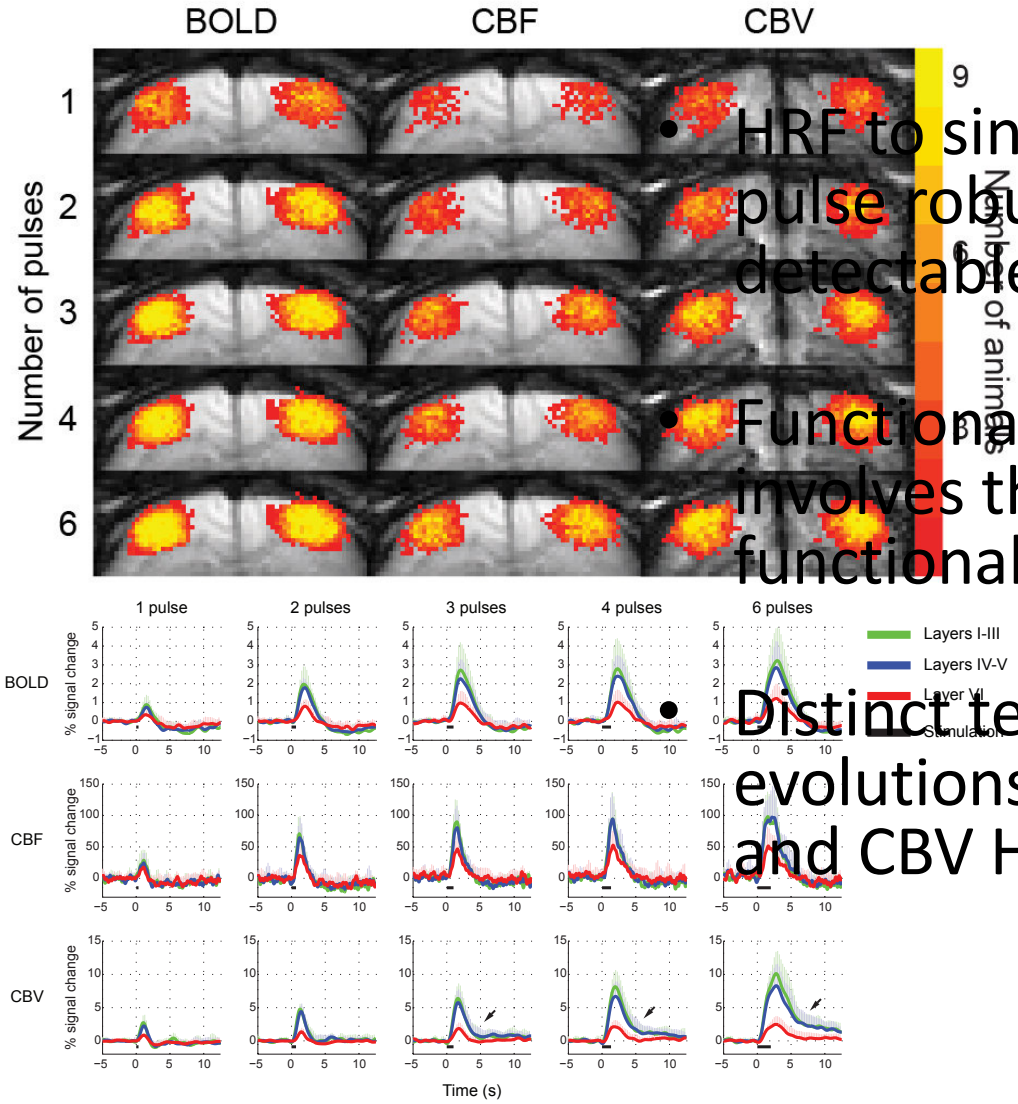
Hirano, Stefanovic and Silva J Neurosci. 31(4):1440-7 2011

BOLD, CBF and CBV Have Distinct Temporal Characteristics



Hirano, Stefanovic and Silva J Neurosci. 31(4):1440-7 2011

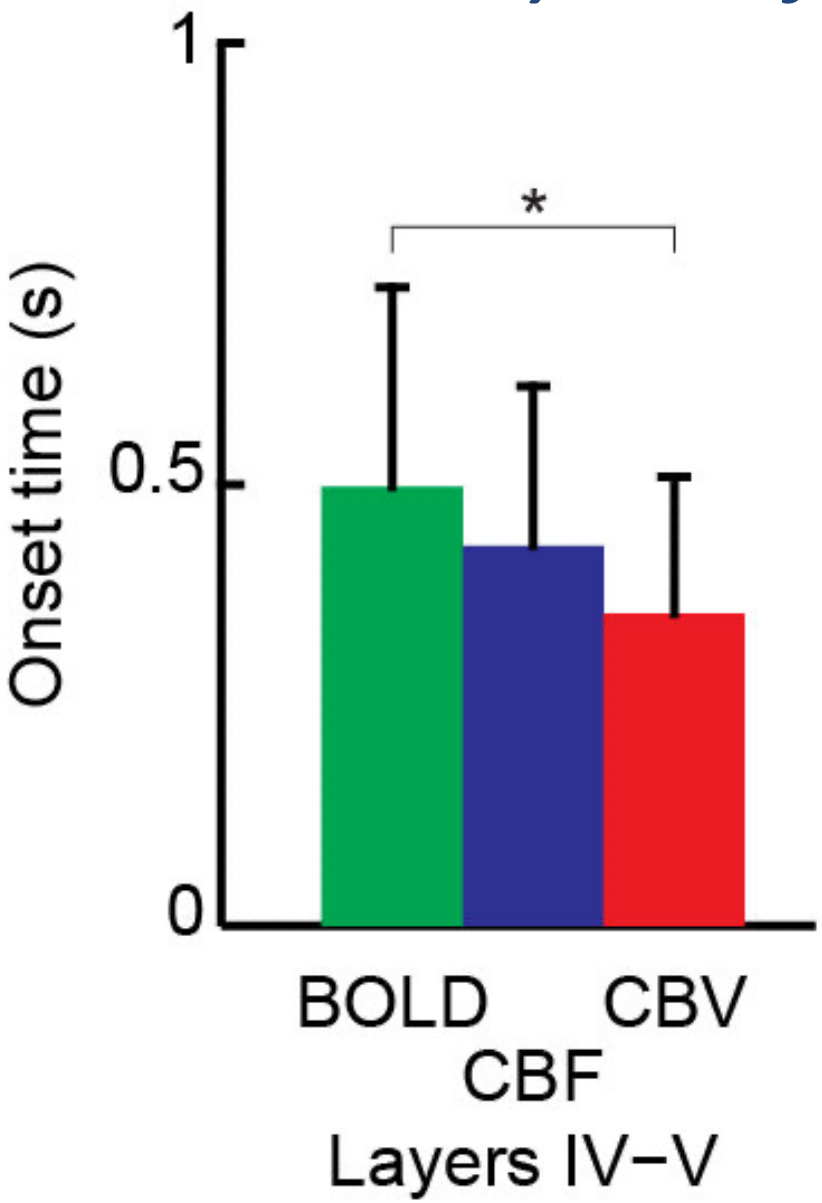
Robust fMRI Responses to Ultrashort Stimuli

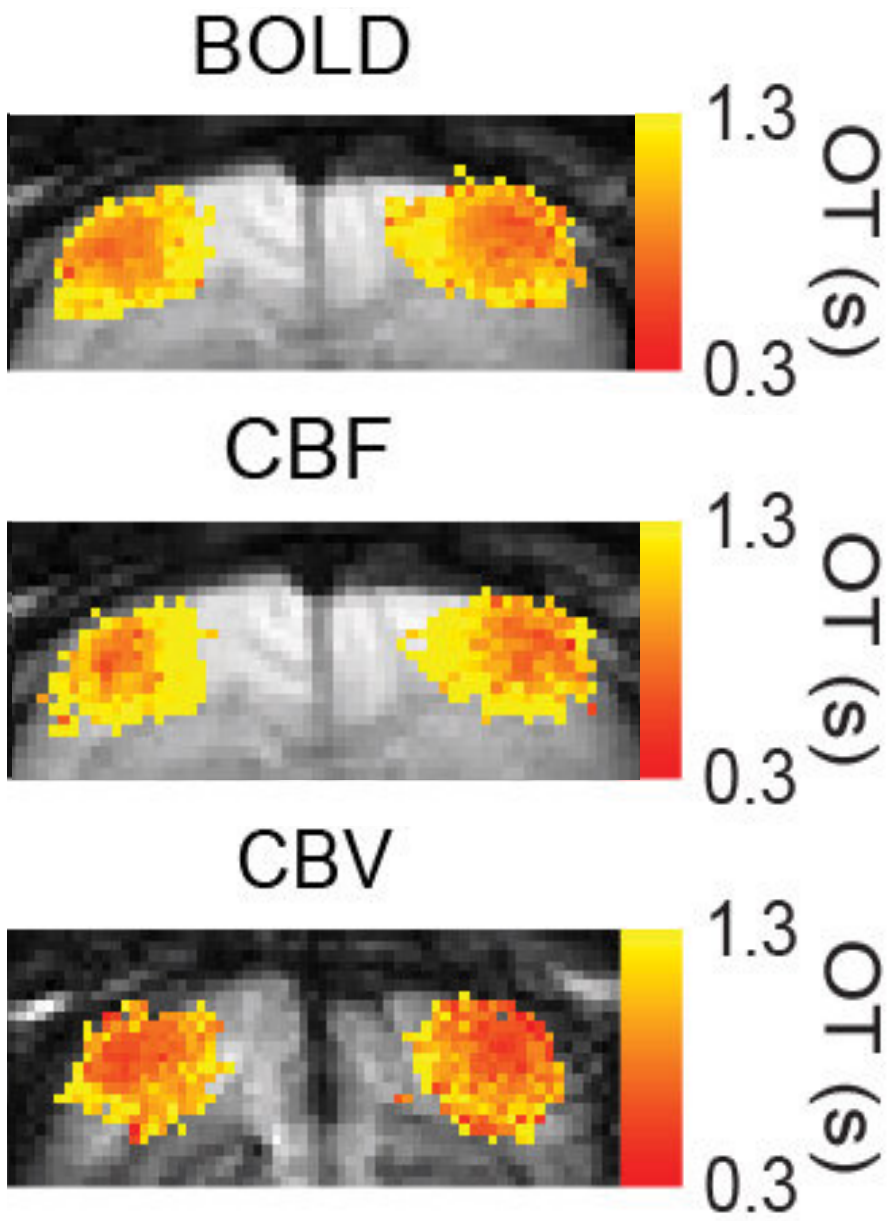


- HRF to single 300µs pulse robustly detectable
- Functional Hyperemia involves the entire functional cortical depth
- Distinct temporal evolutions of BOLD, CBF and CBV HRF

Hirano, Stefanovic and Silva J Neurosci. 31(4):1440-7 2011

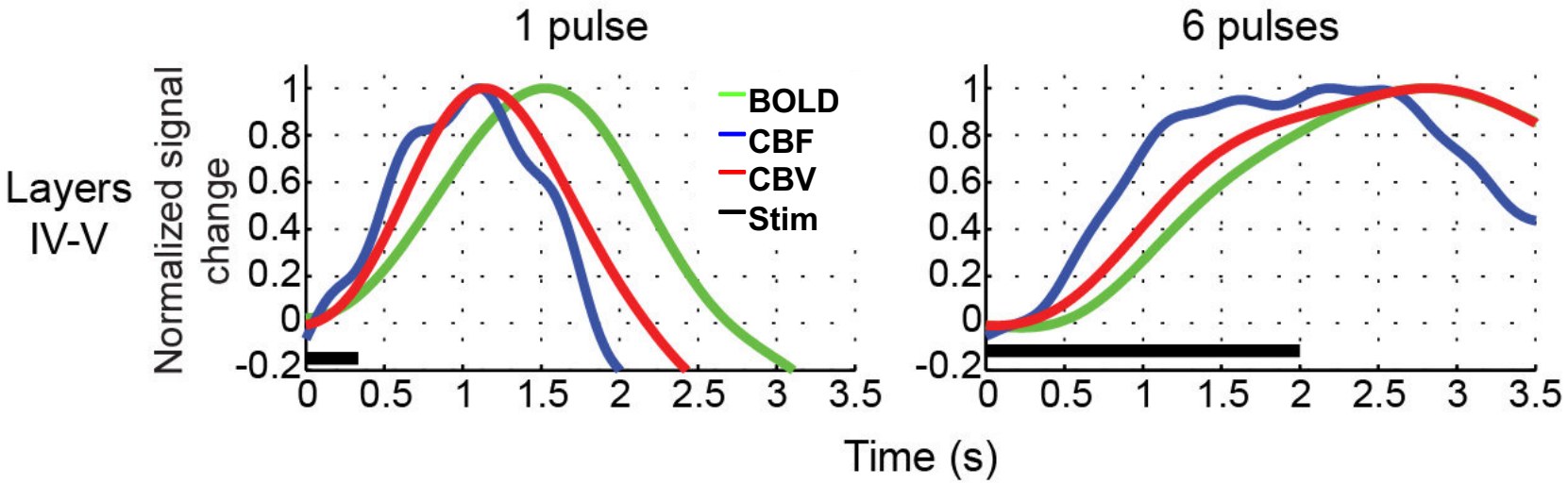
Remarkably Fast fMRI Onset Times





Hirano, Stefanovic and Silva J Neurosci. 31(4):1440-7 2011

Distinct Temporal Evolution of CBV HRF



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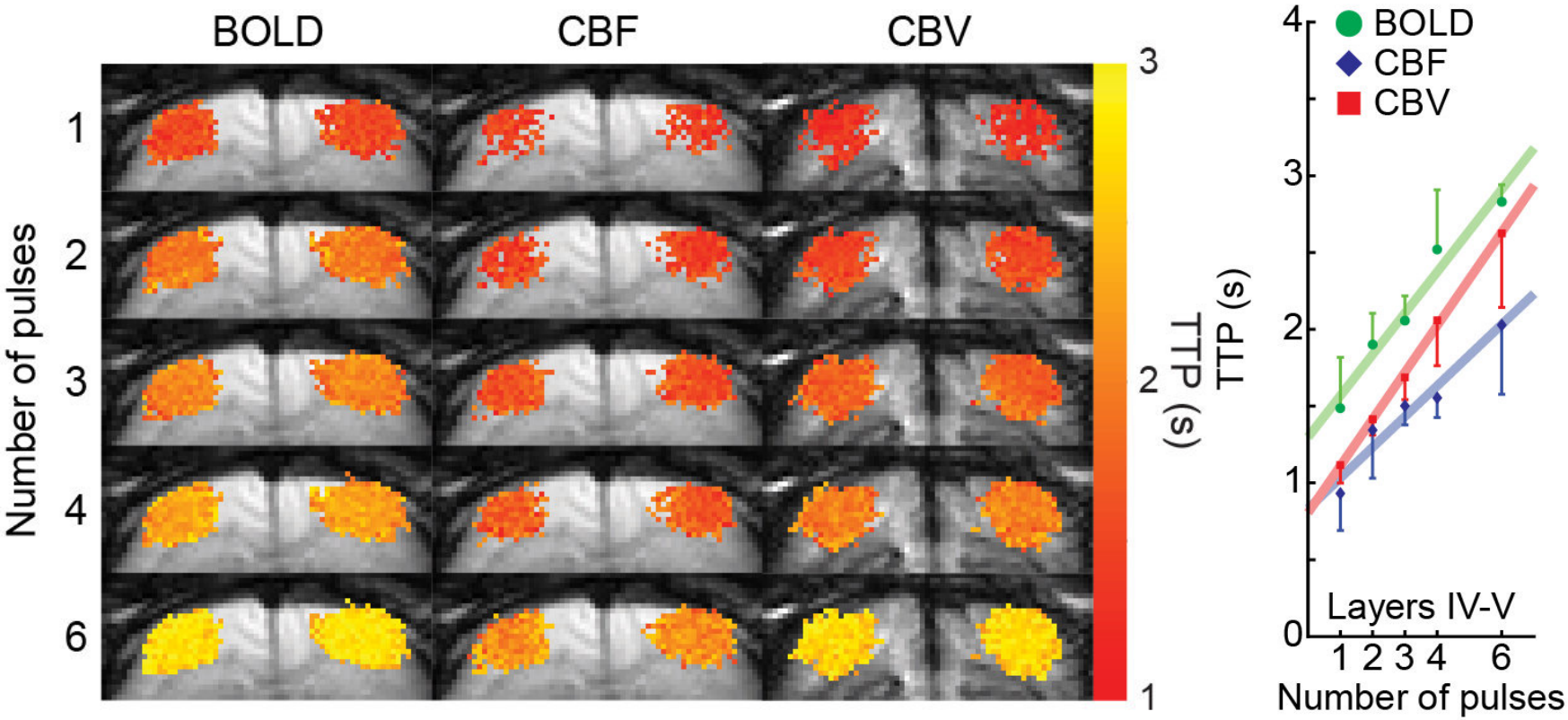
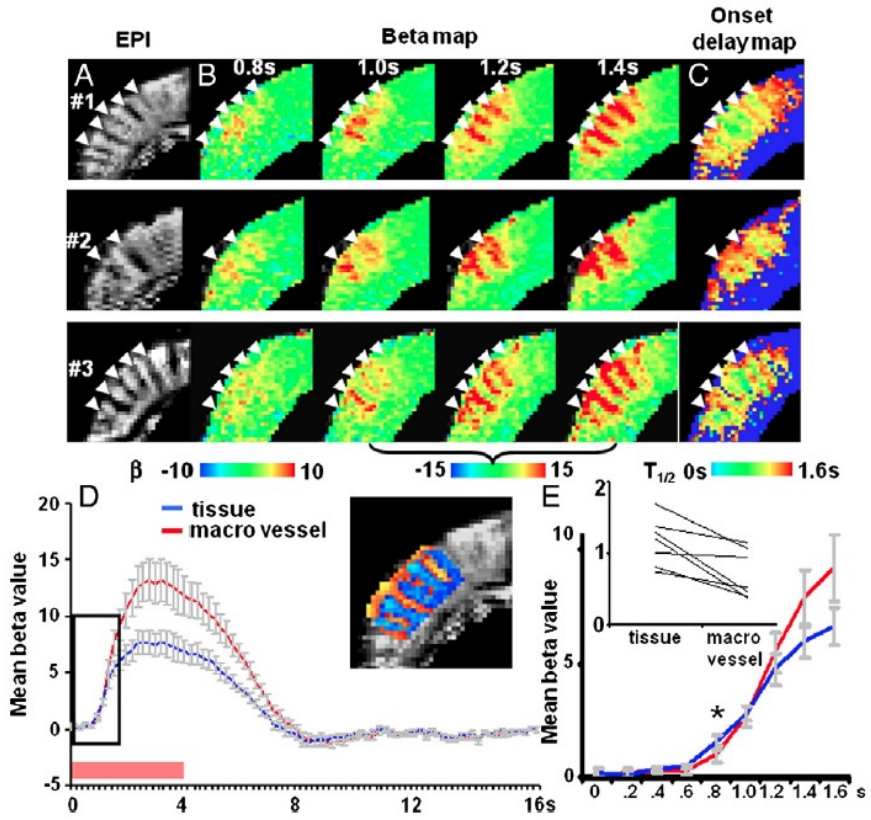
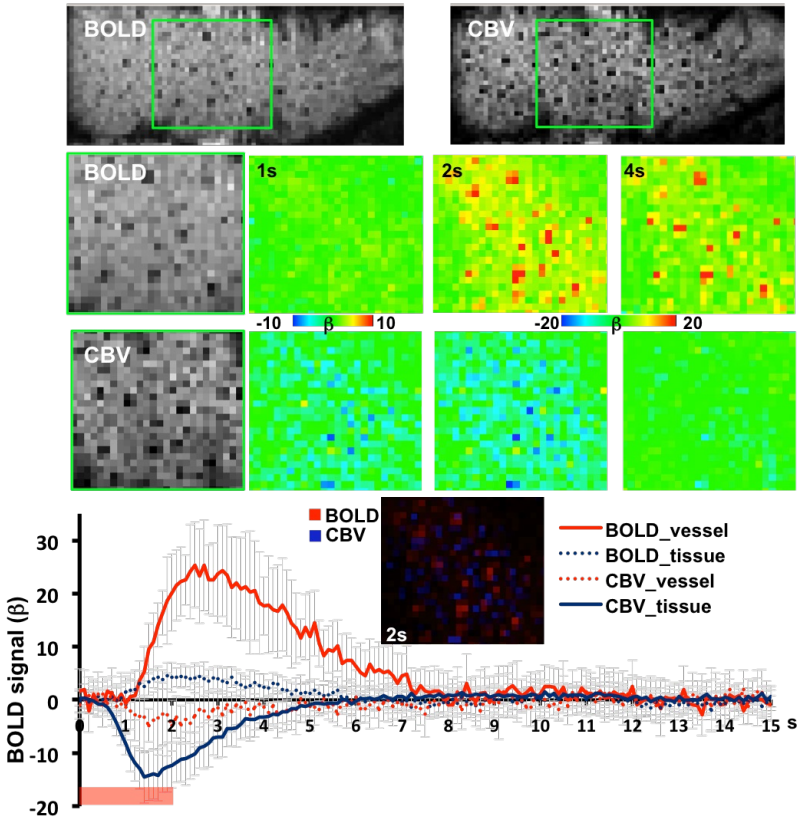
Distinct Temporal Evolution of CBV HRF



Hirano, Stefanovic and Silva J Neurosci. 31(4):1440-7 2011

High Resolution fMRI Shows Early Activation of Capillary Network

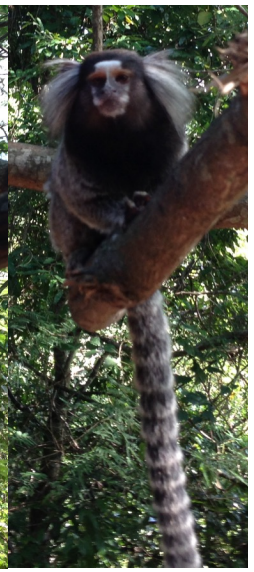




X. Yu et. al, Neuroimage 59(2):1451-60 2012

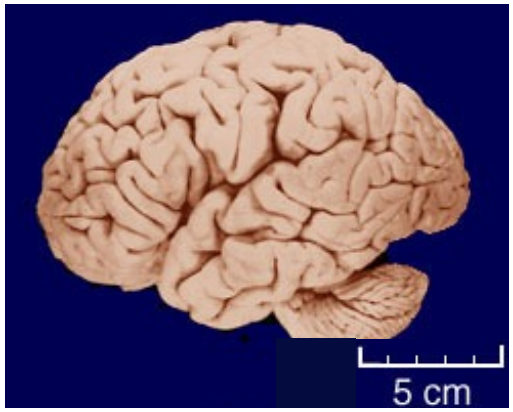
Marmoset (Callithryx Jacchus)

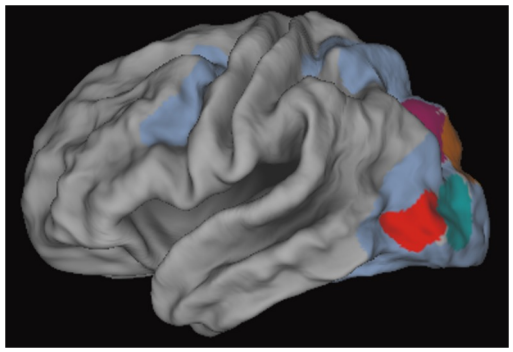
- Adult weight: 300-500 grams
- Life span: 12+ years
- Age at maturity: 18 months
- Age at 1st reproduction: 17-20 months
- Gestation: 144 days
- Number of offspring: 2+; every 6 months

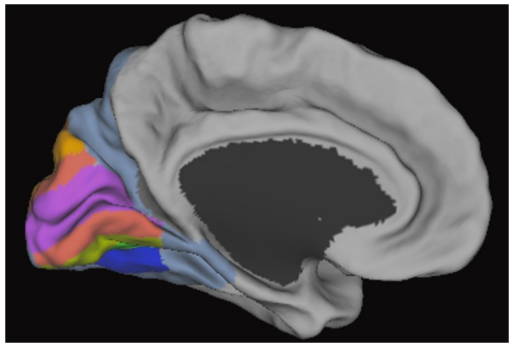


Marmosets Retain the Primate Anatomical and Functional Brain Organization

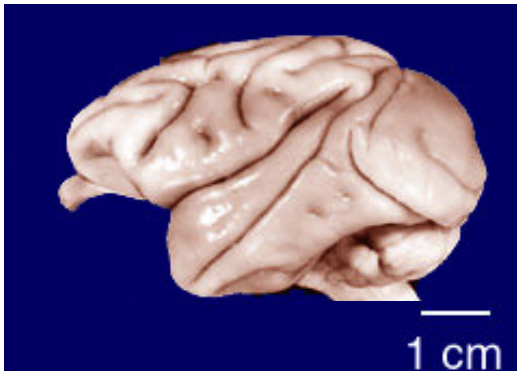
Human

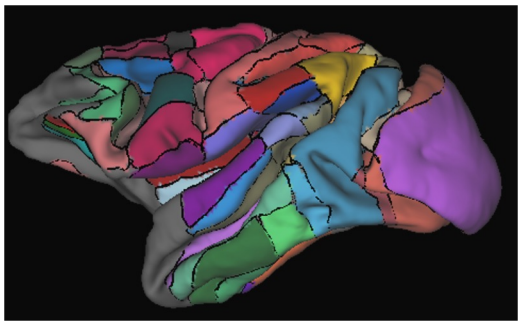




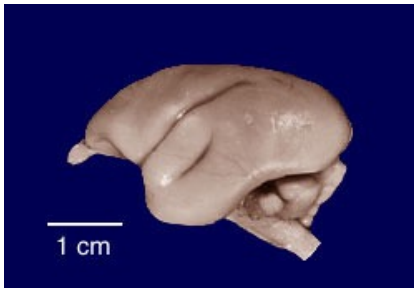


Macaque

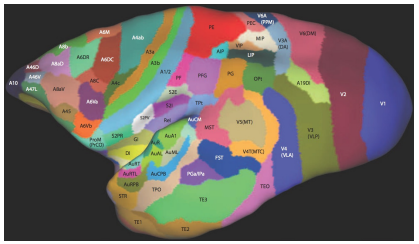




Marmoset



http://www.brainmuseum.org/

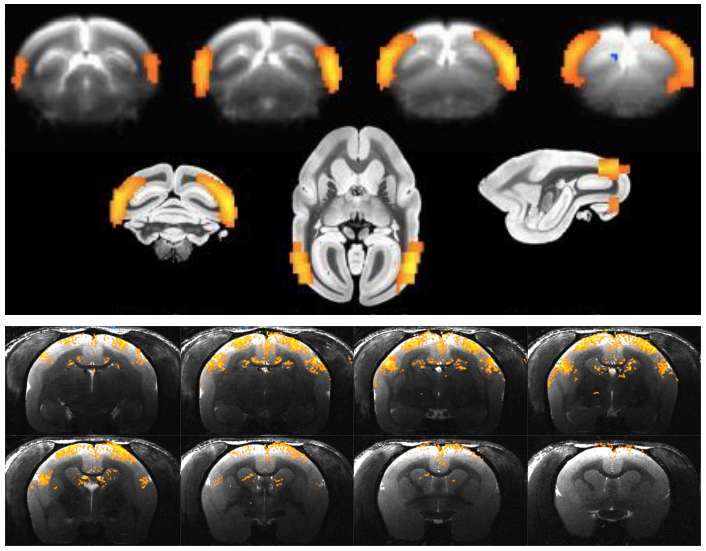


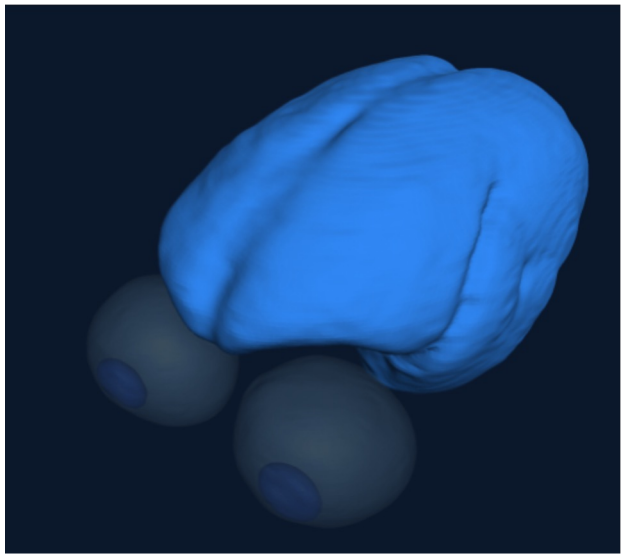
G. Paxinos et al. The Marmoset Brain in Stereotaxic Coordinates, 2011

Web caret, Washington University St. Louis, MO, USA

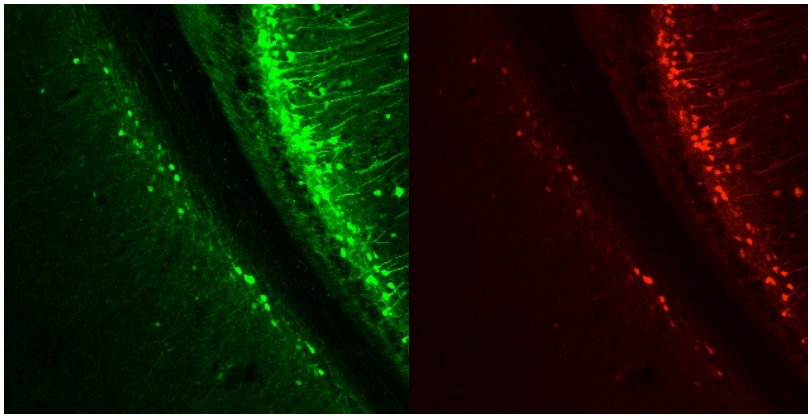
Marmosets are Lissencephalic

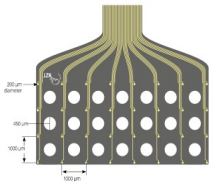
fMRI



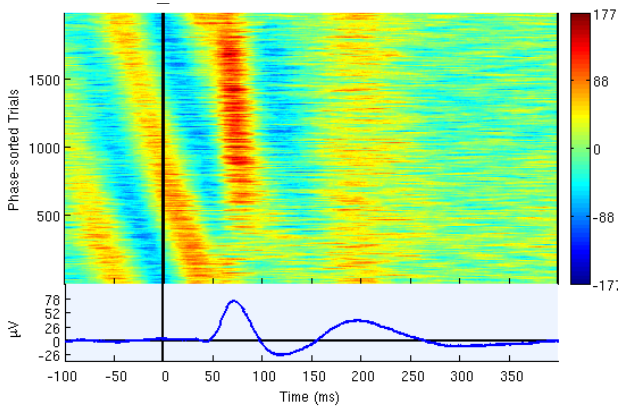


Optical Imaging

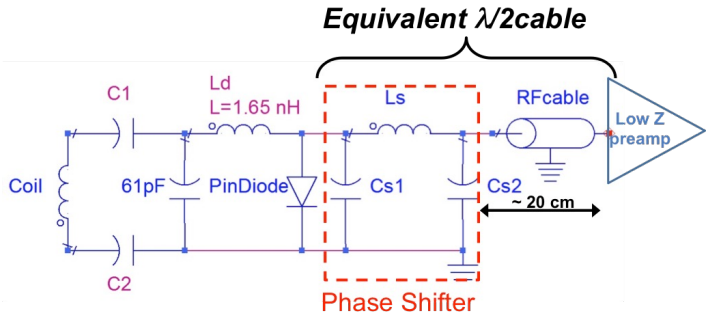




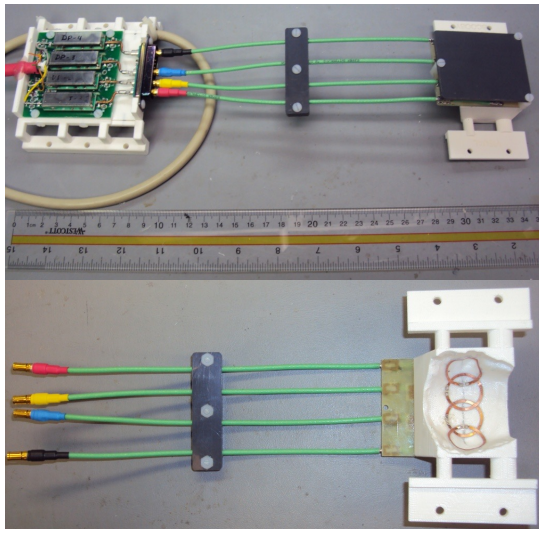
Electrophysiology



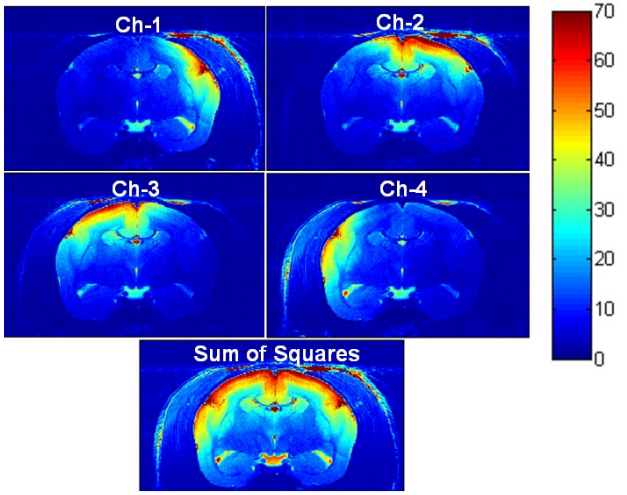
In-Helmet Embedded RF Coil Arrays



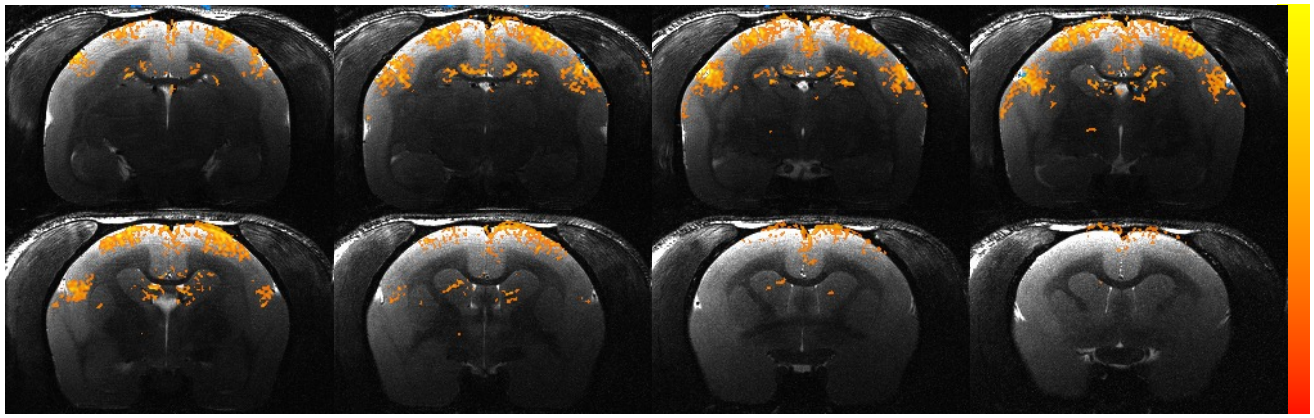
Circuit Diagram



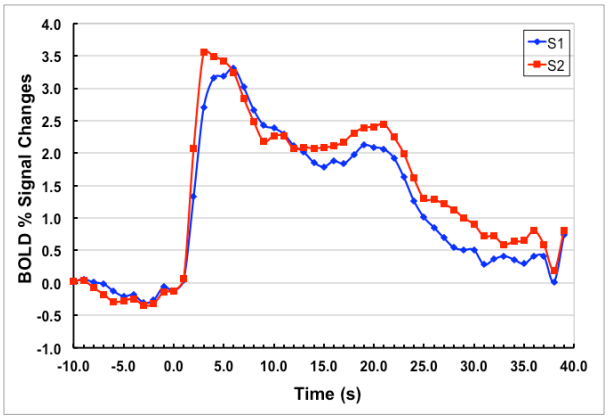
Embedded helmet array and preamps



In vivo SNR Maps

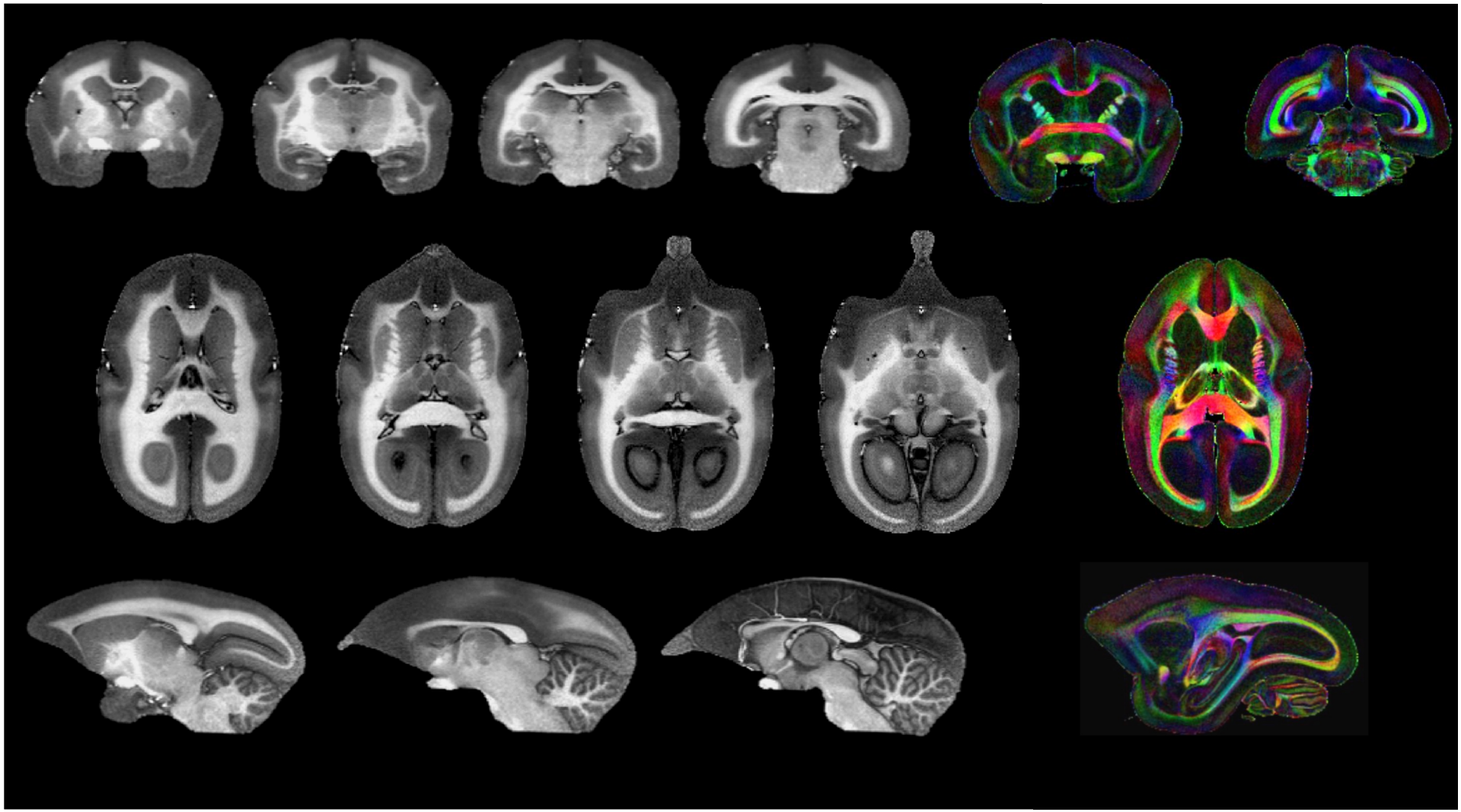


fMRI in Conscious, Awake Marmosets
250 x 250 x 1000 µm³



D. Papoti, C.C. Yen, J. Mackel, H.Merkle, A. Silva, NMR in Biomed., 2013

Anatomical MRI of the Marmoset Brain

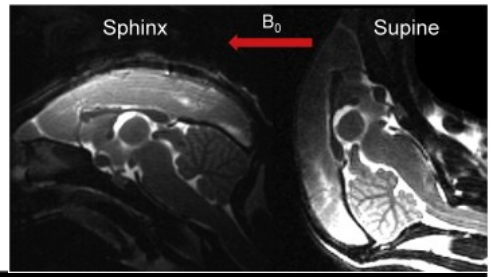


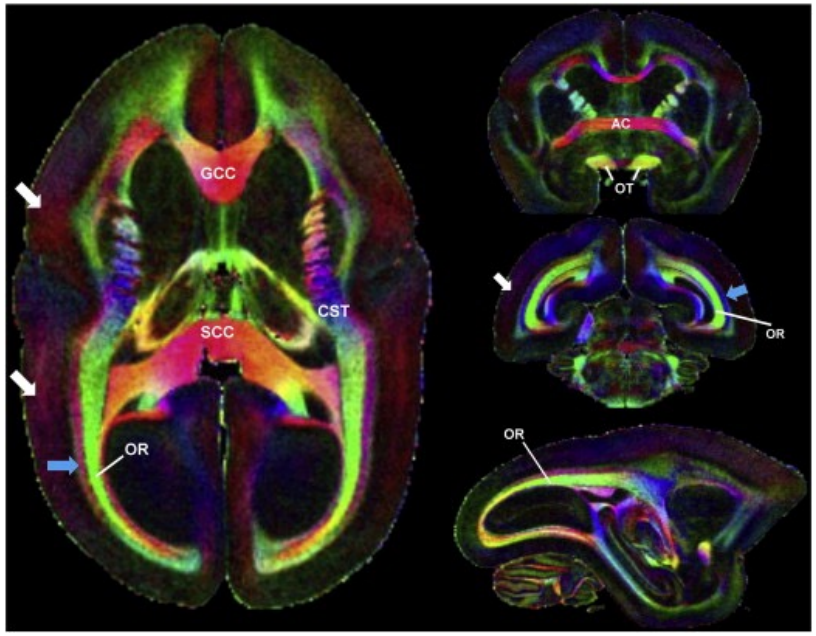
in vivo T1w-MPRAGE 150 µm^3

ex vivo DTI 150 µm^3

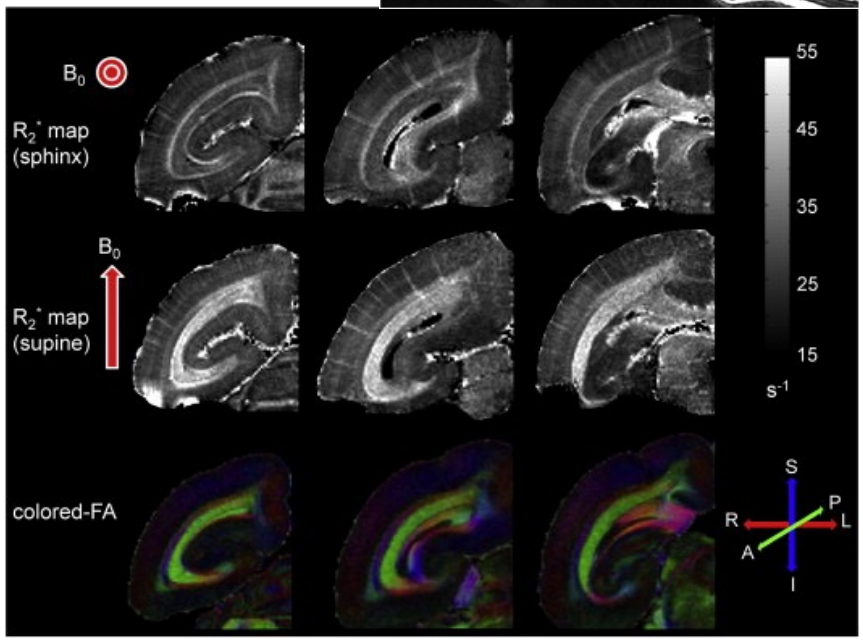
State-of-the-Art Neuroimaging Techniques

- High Resolution Anatomical MRI





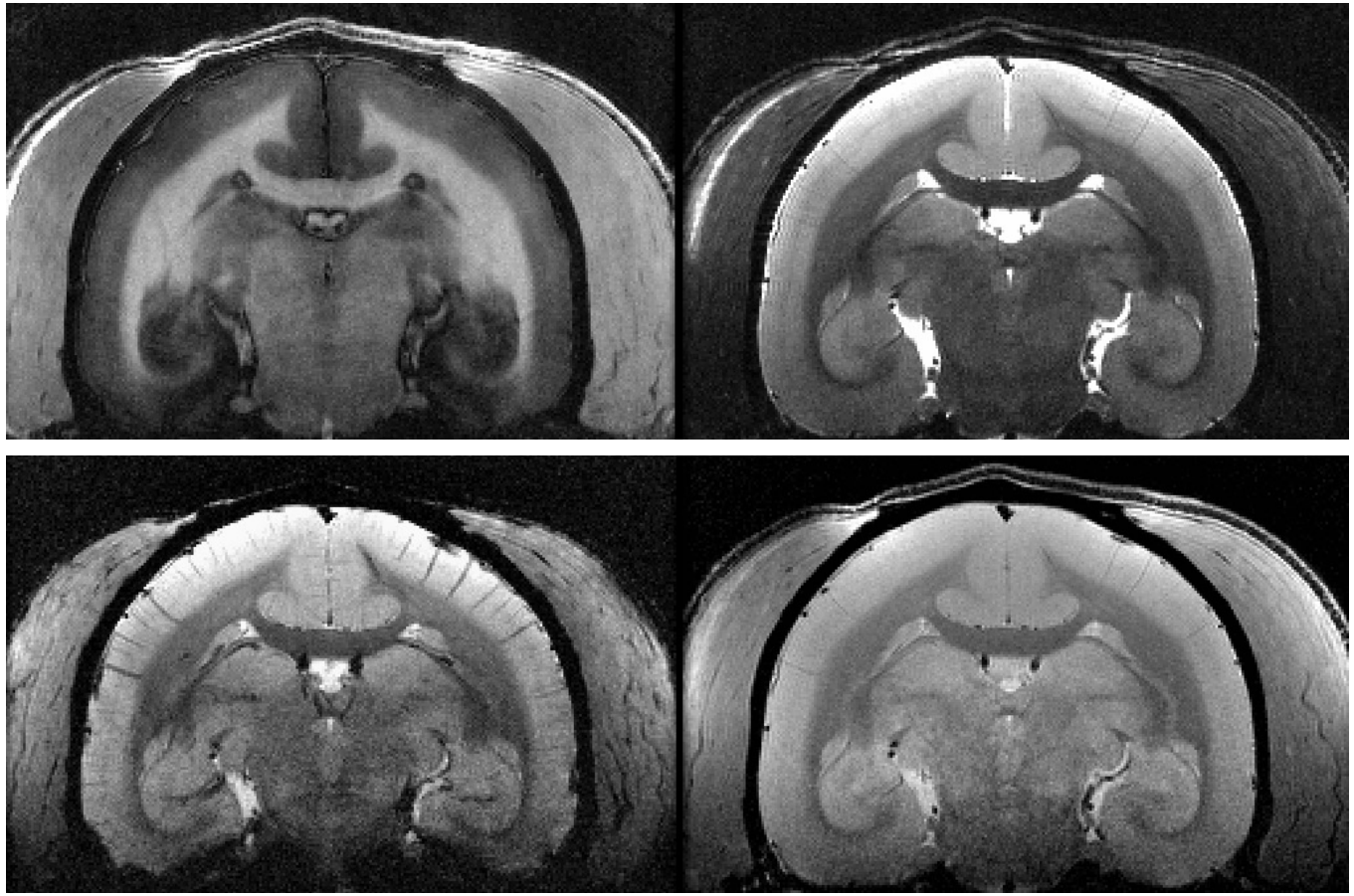
Architecture of white matter fibers
150 x 150 x 150 µm^3



In vivo quantification of T_2^* anisotropy
150 x 150 x 600 µm^3

Sati et. al, Neuroimage. 2012 59(2):979-85

Anatomical "Clinical" MRI Protocol for Scanning Marmoset Brain

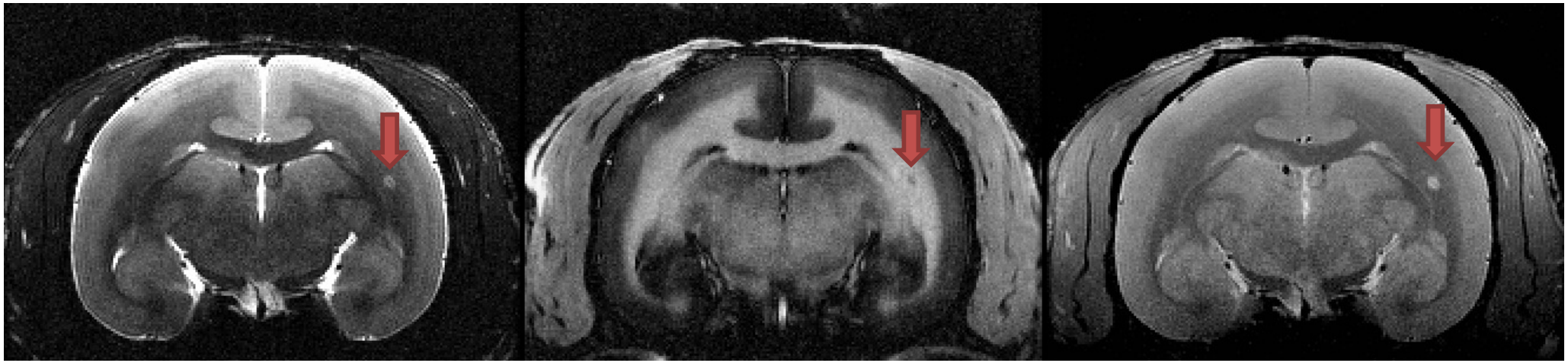


- Voxel size= 125 µm × 125 µm × 600 µm
- Whole brain coverage (54 coronal slices)
- Total acquisition time ≈1h 20min

Joseph Guy, Pascal Sati, Steve Jacobson and Danny Reich

Speeded-Up, Three Contrast for Detecting Brain Lesions in Marmoset Model of Experimental Autoimmune Encephalomyelitis (EAE)

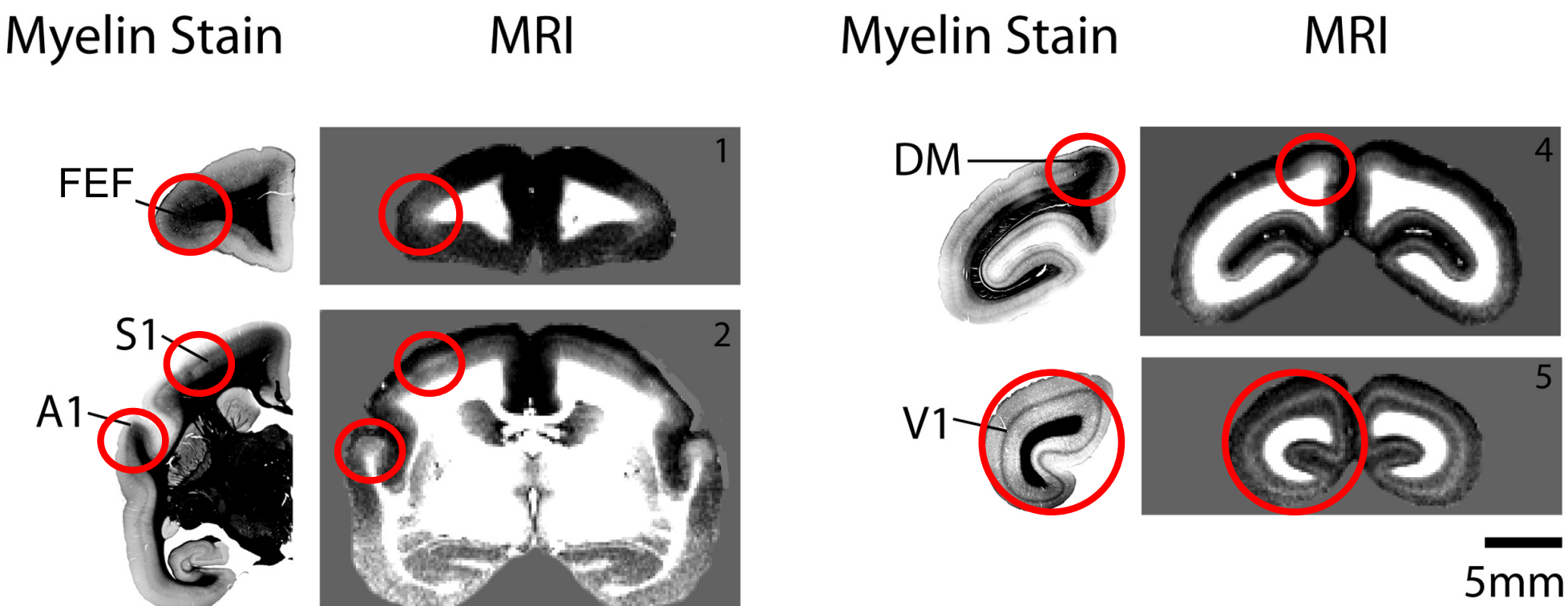
T_2 T_1 PD



- Voxel size= 150 µm × 150 µm × 600 µm
- Whole brain coverage (54 coronal slices)
- Total acquisition time ≈ 35 min

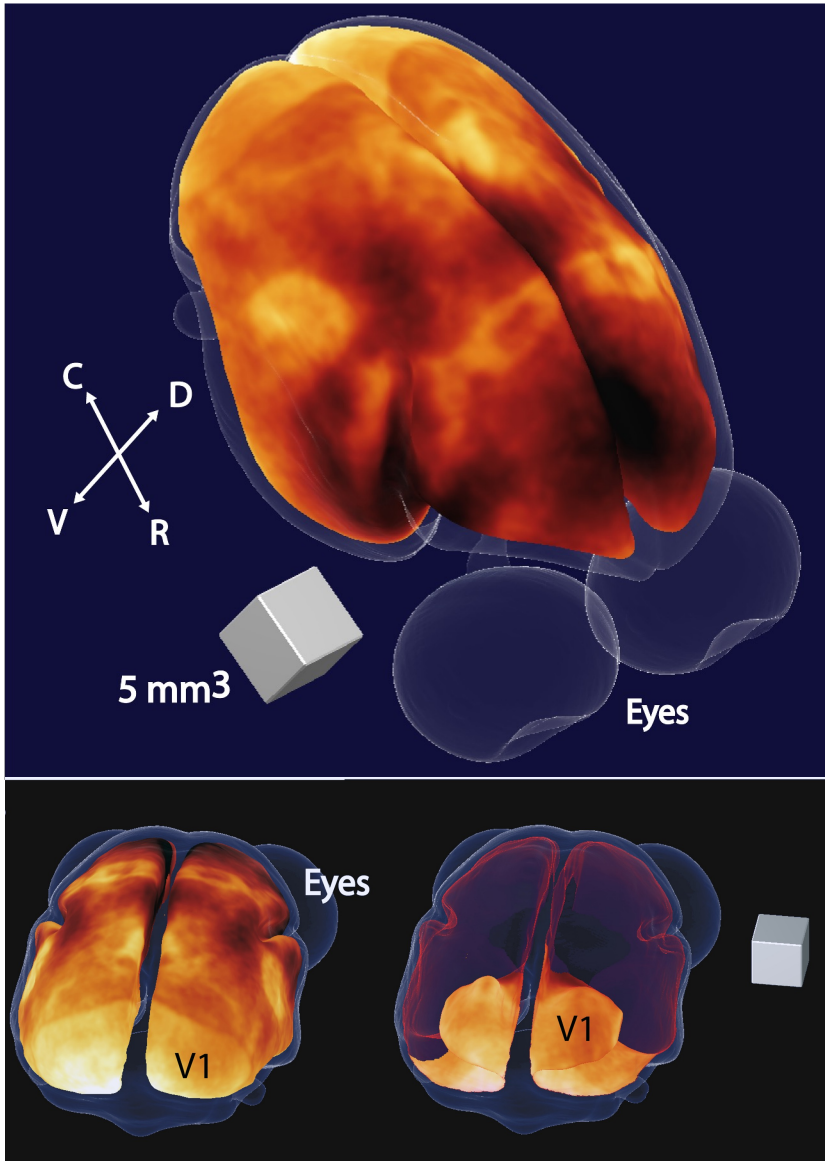
Joseph Guy, Pascal Sati, Steve Jacobson and Danny Reich

T_1-Weighted MRI Reveals Cortical Myeloarchitecture



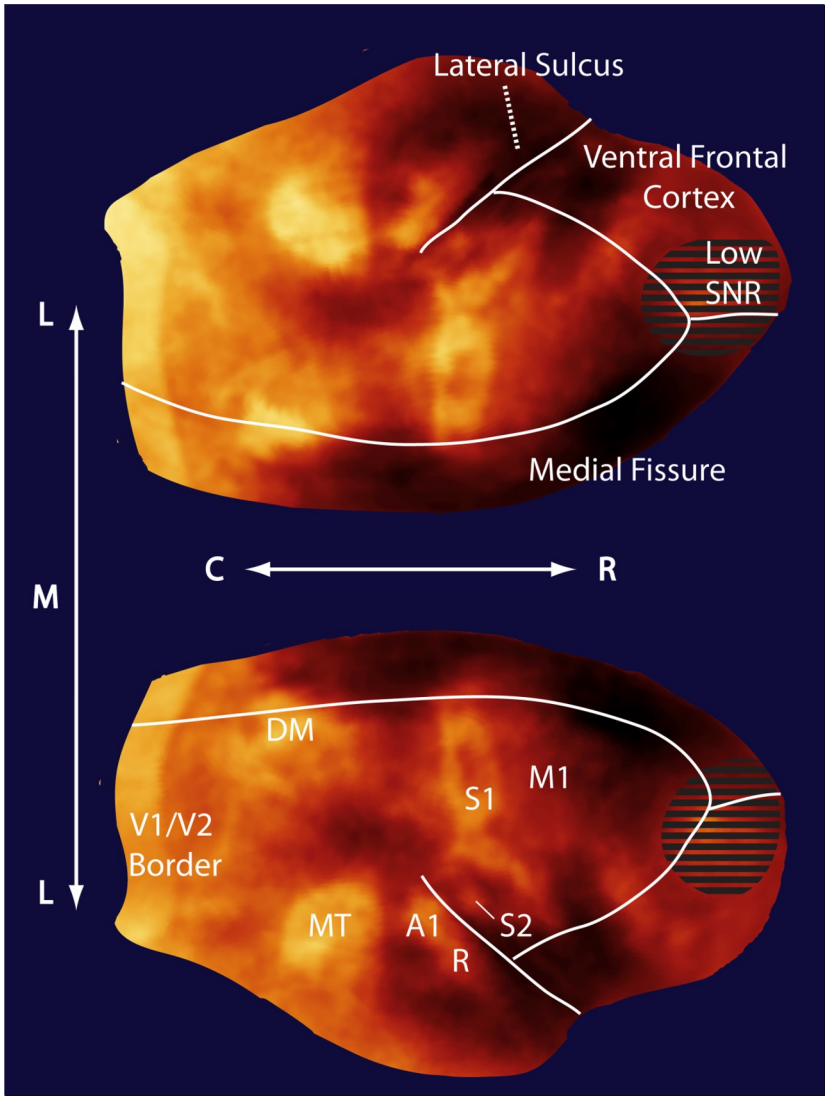
Bock et al., J Neurosci Methods. 2009;185(1):15-22

Cortical Myeloarchitecture Map



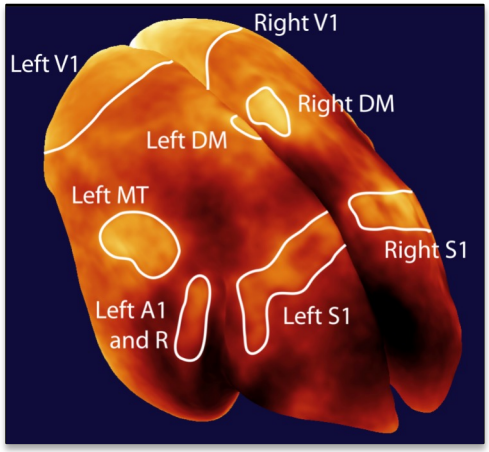
Voxel size 150 µm^3

Flattened View



Bock et al., *J Neurosci Methods. 2009 185(1):15-22*

Reproducible and Quantitative Myeloarchitecture

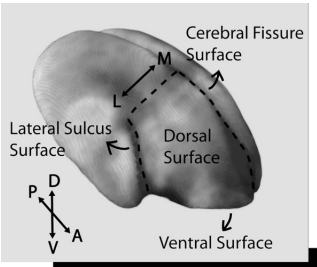


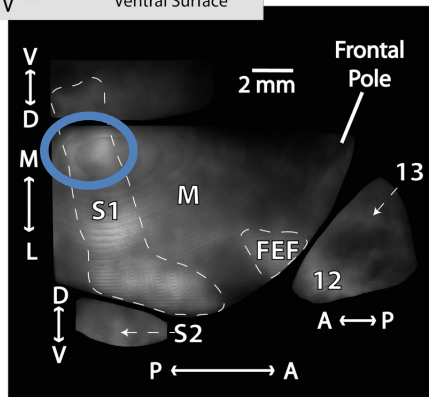
Region	Surface Area (mm^2)		Surface Area (%)
	Left	Right	
Cortex	1005 ± 21	1007 ± 34	100
V1	219 ± 12	222 ± 3	22
S1	28 ± 4	30 ± 4	3
MT	17 ± 3	19 ± 2	2
A1 and R	11 ± 3	11 ± 3	1
DM	8 ± 1	7 ± 1	1

- Agrees well with histological measures of areas:
  - V1: 200-205 mm^2: *Fritsches and Rosa 1996 JCN 372:264-82; Missler, Wolff 1993 JCN 333:53-67*
  - MT: 14 mm^2: *Pessoa et al. 1992 Exp. Brain Res. 2: 459–462.*
  - DM: *no well defined borders.*
- More than ¼ of the marmoset cortex dedicated to processing of visual information

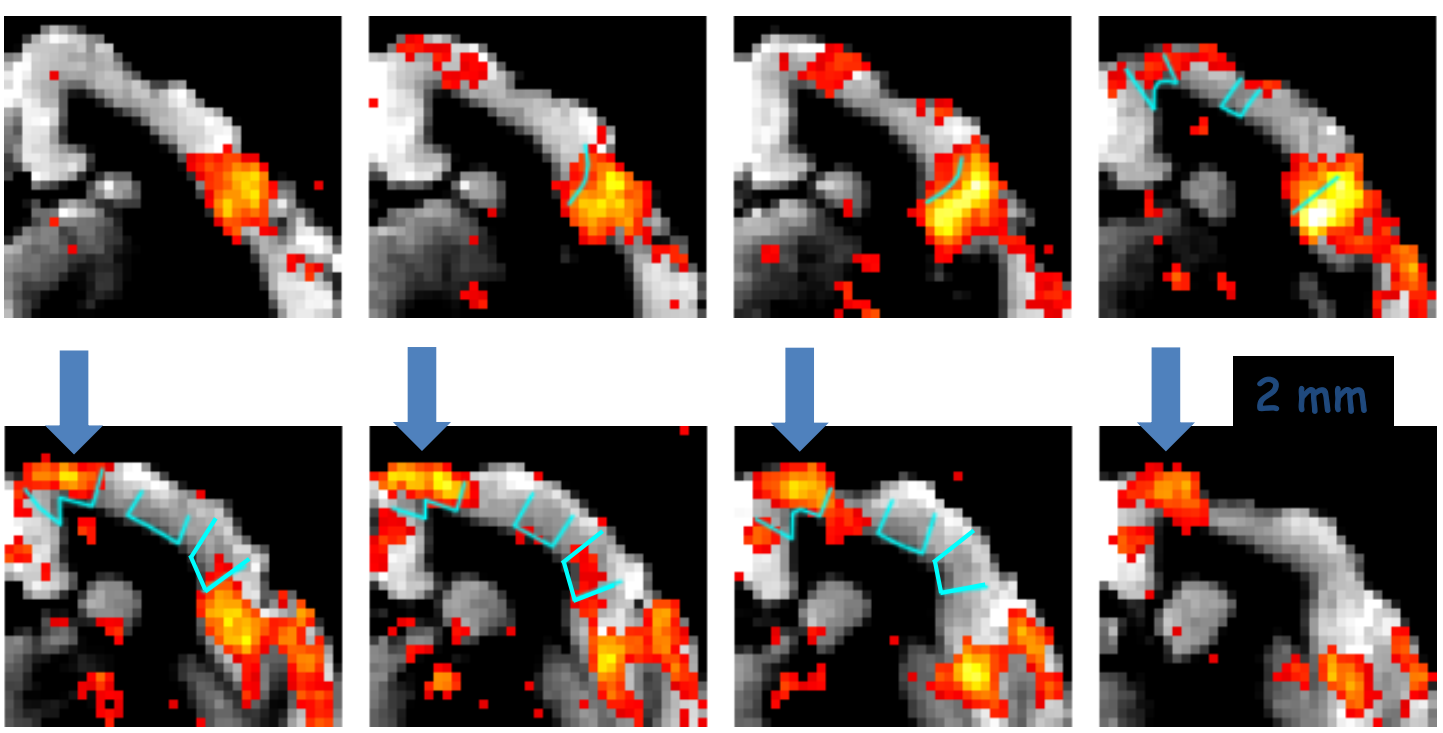
Bock *Ann N Y Acad Sci. 2011 1225 Suppl 1:E171-81*

fMRI Activation Regions Map Well onto Myeloarchitectonic Maps





Leg Stimulation: 1.5 mA, 0.3ms, 50 Hz



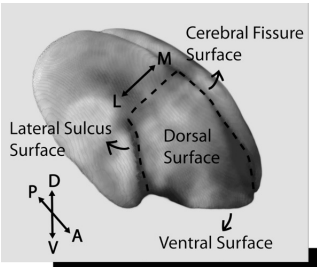
0.60

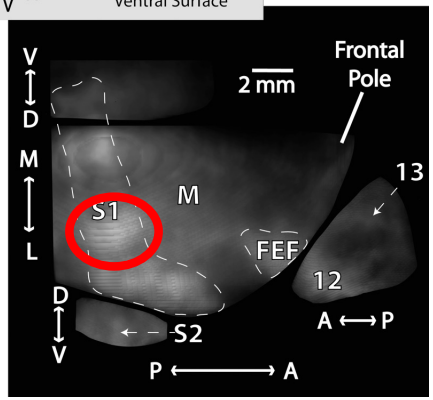
Correlation Coefficient

0.20

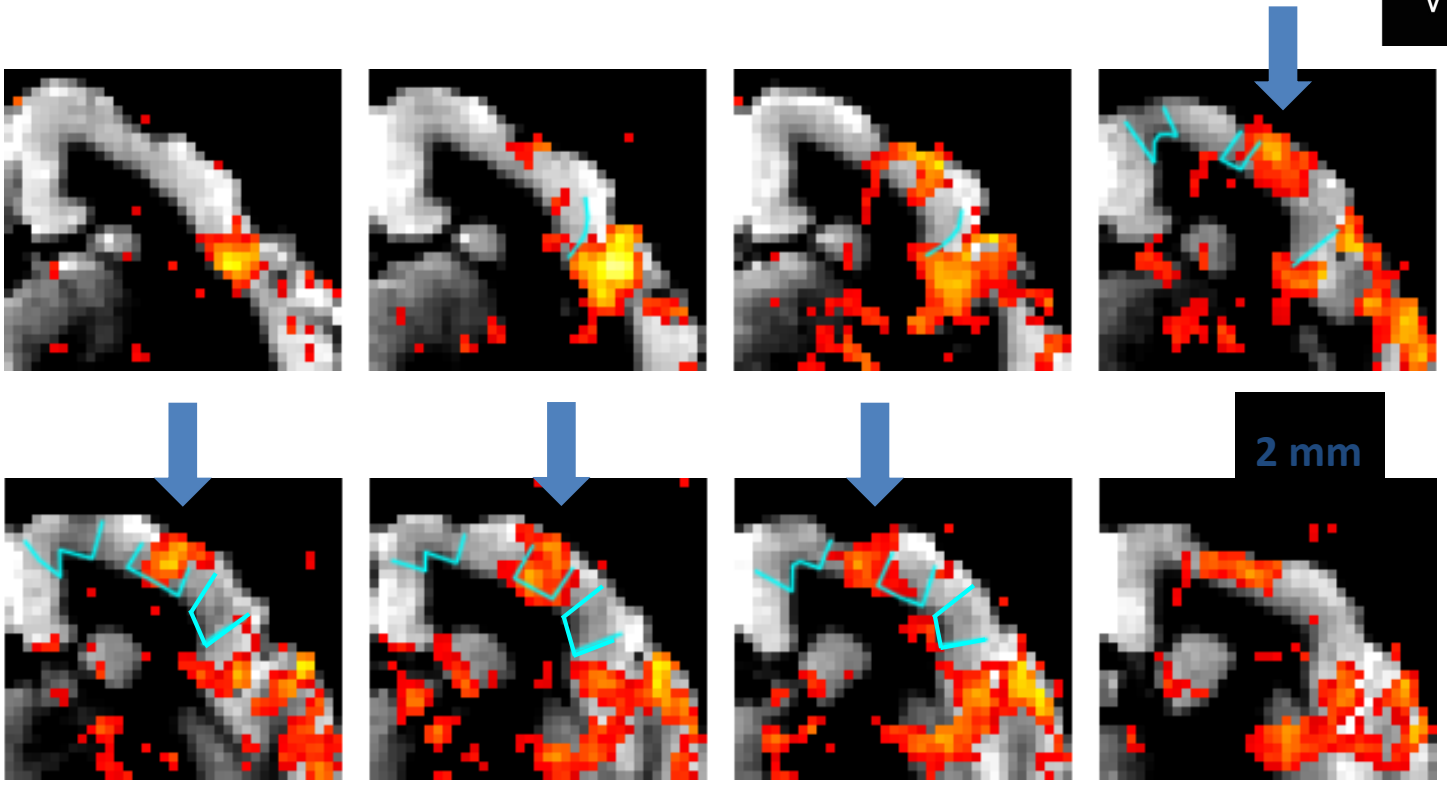
Liu et al . Neuroimage. 2013 78:186-95.

fMRI Activation Regions Map Well onto Myeloarchitectonic Maps





Forearm/Wrist Stimulation: 1.5 mA, 0.3ms, 50 Hz



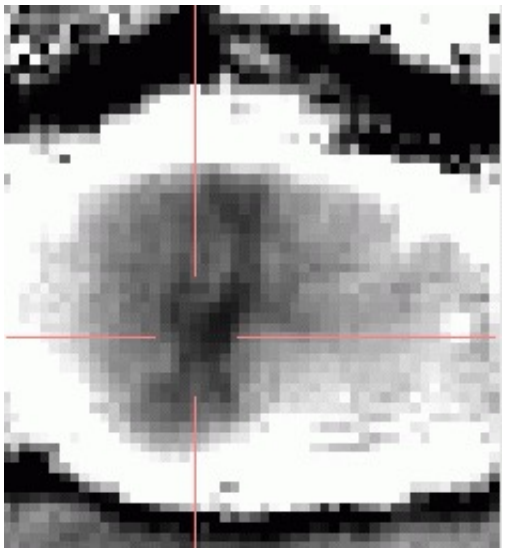
0.60

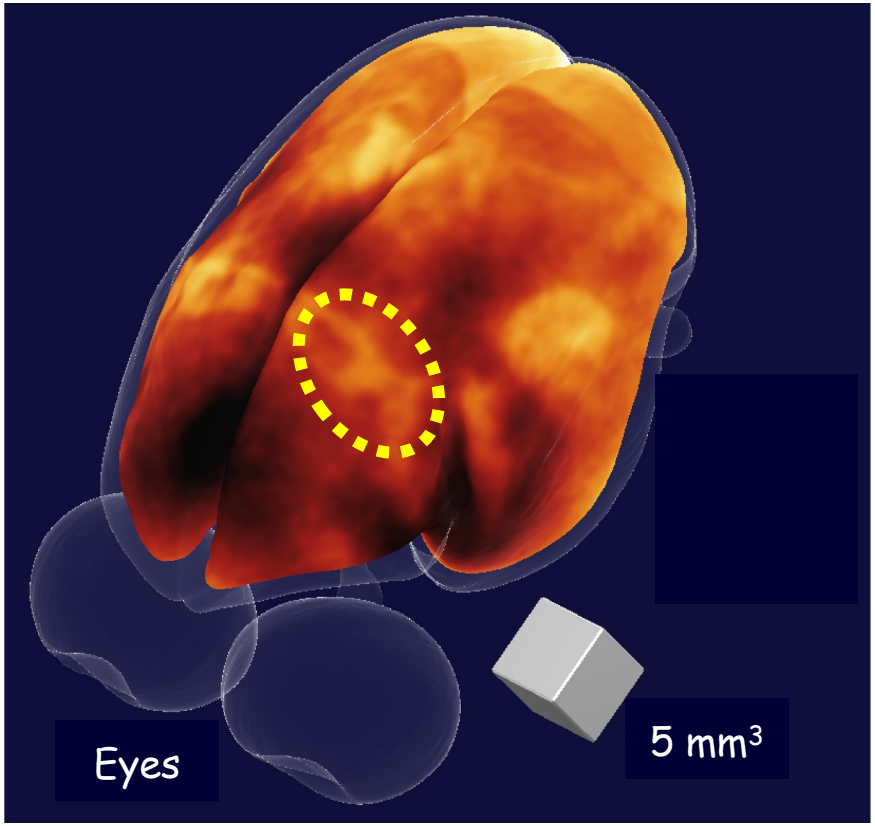
Correlation Coefficient

0.20

Liu et al . Neuroimage. 2013 78:186-95.

fMRI Response Overlaid on Myeloarchitecture

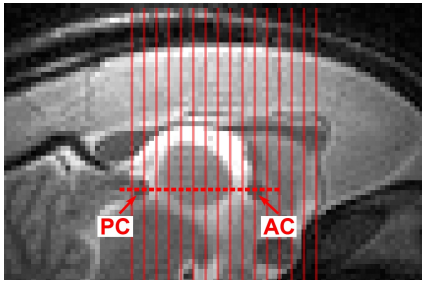


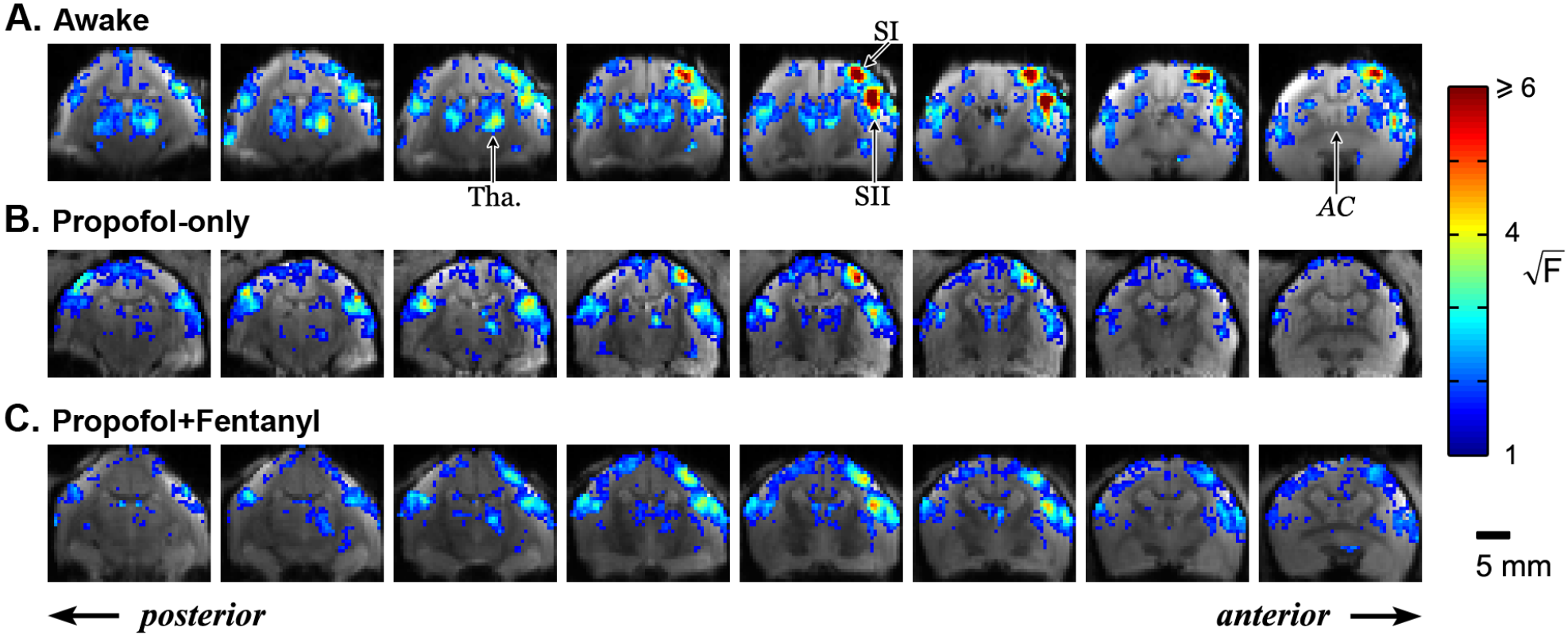


Liu et al . Neuroimage. 2013 78:186-95.

More Widespread Spatial Extent of Functional Regions in Awake Marmosets

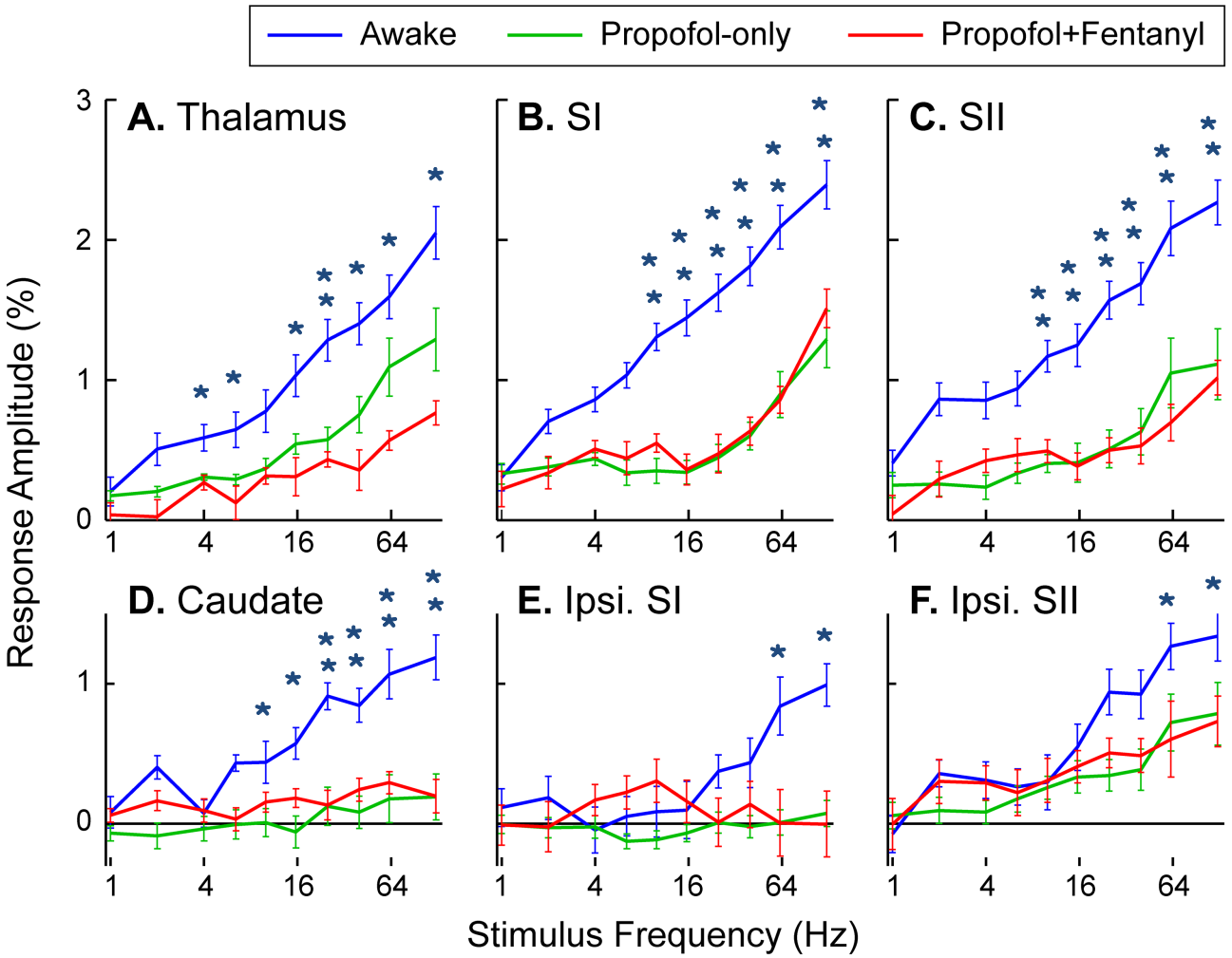
Responses throughout the somatosensory pathway significantly enhanced when compared to anesthetized subjects





Liu et al . Neuroimage. 2013 78:186-95.

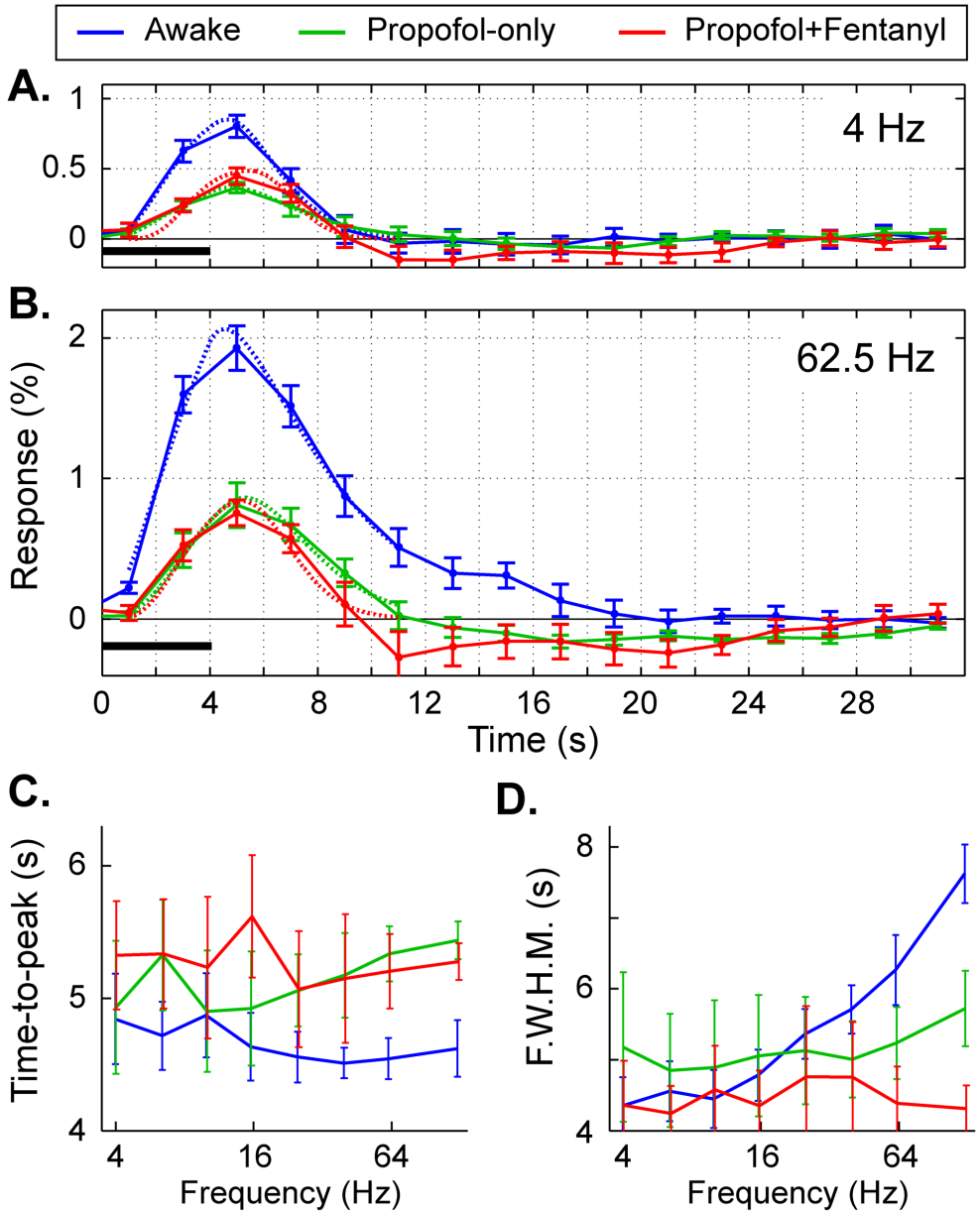
Amplitude of BOLD HRF Significantly Enhanced at High Stimulus Frequencies in Awake Monkeys



Liu et al . Neuroimage. 2013 78:186-95.

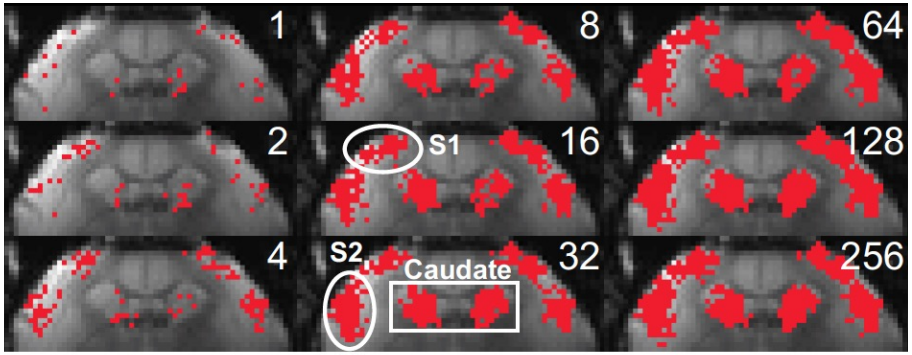
BOLD HRF in Awake Marmosets Has Faster Times-to-Peak

TTP shorter by ~0.5 s

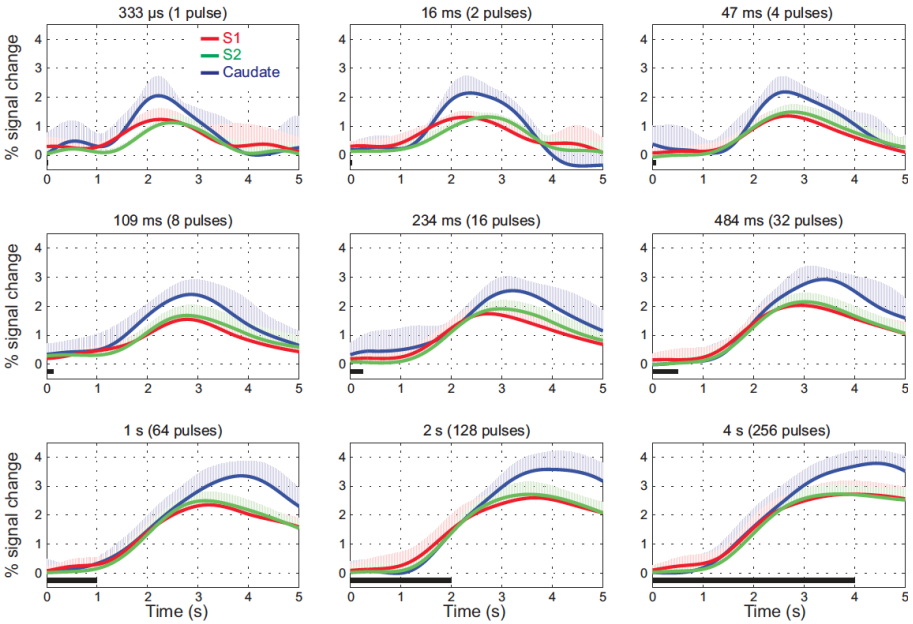


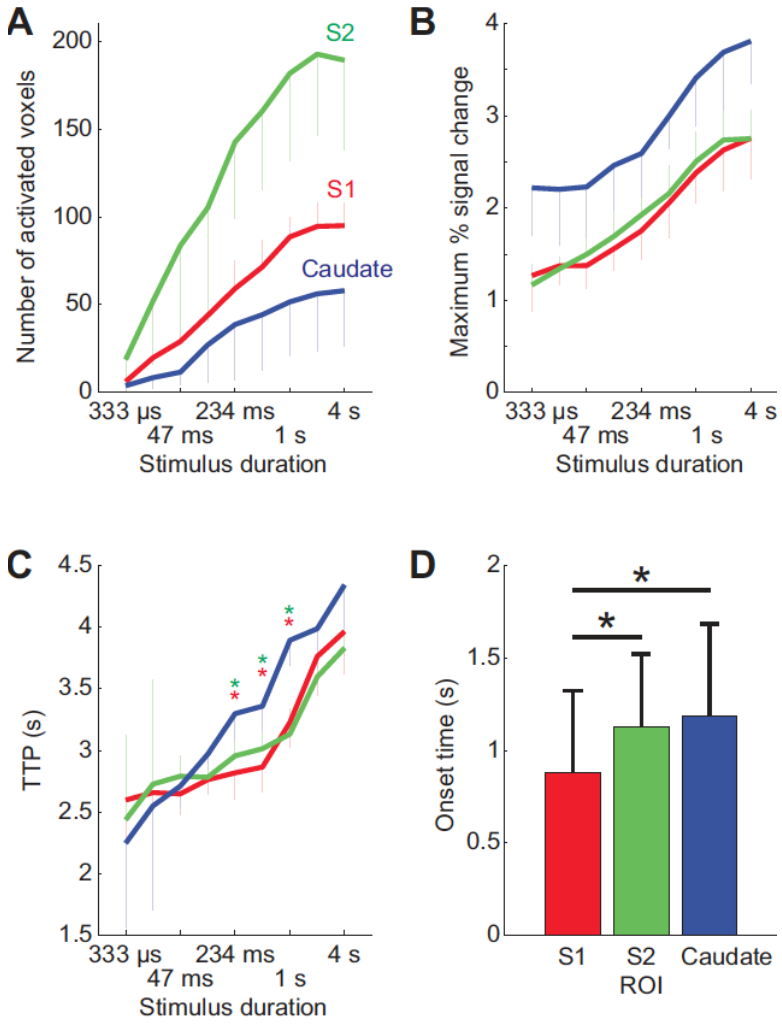
Liu et al . Neuroimage. 2013 78:186-95.

Robust Activation of S1, S2 and Caudate



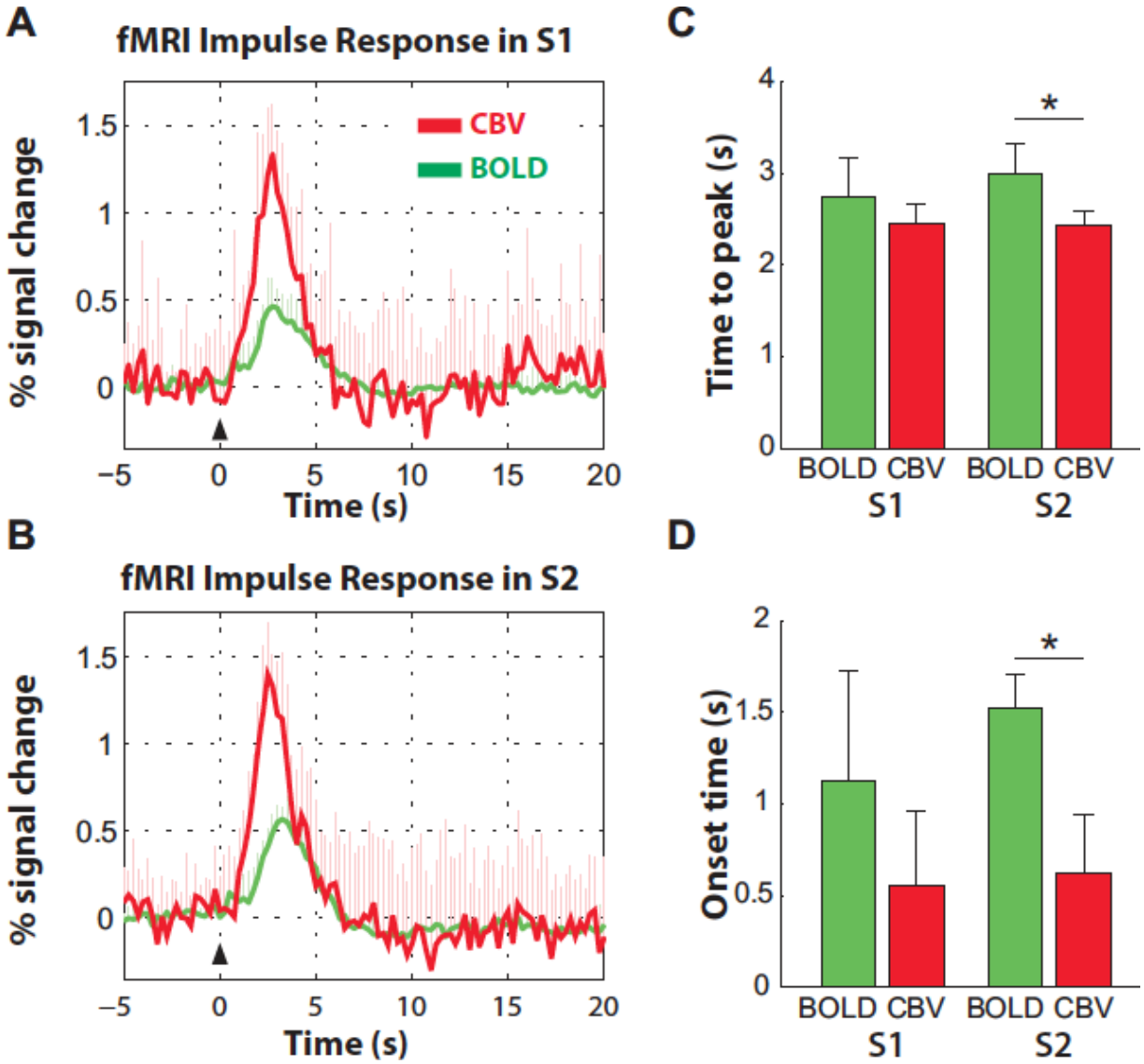
# of pulses @ f = 64 Hz





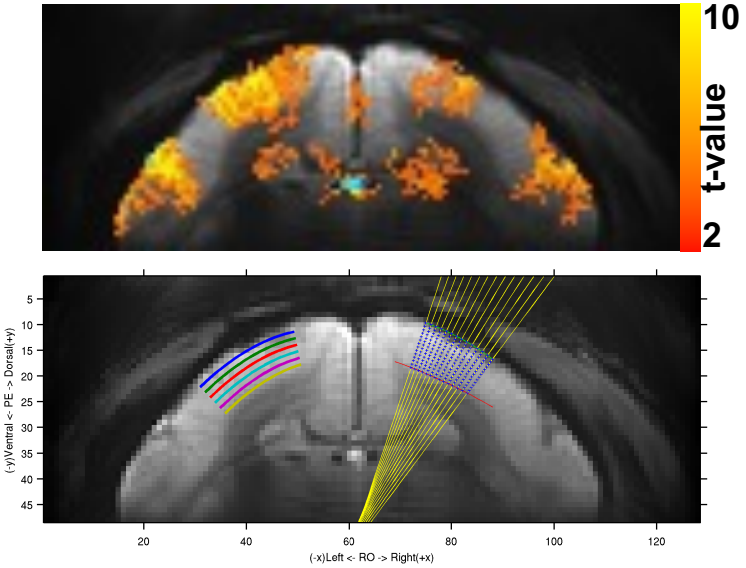
Yoshiyuki Hirano, in preparation

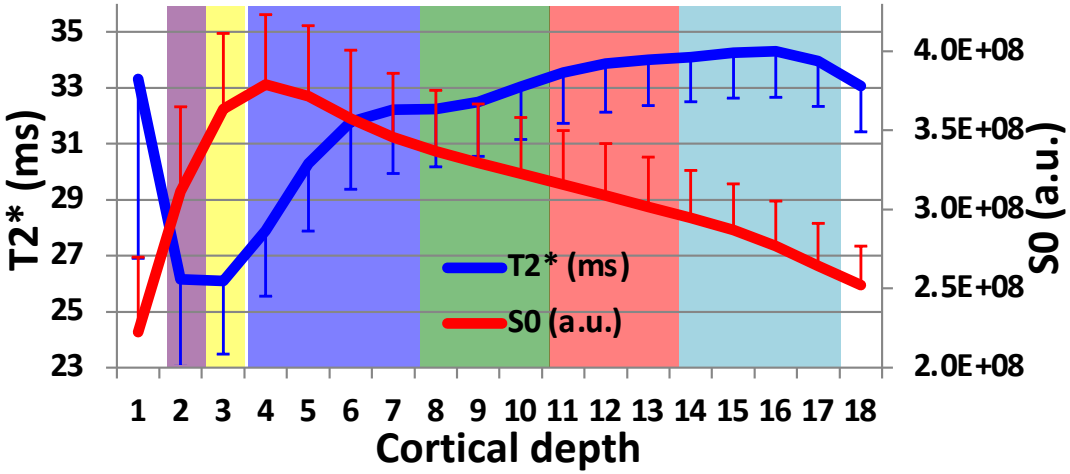
CBV Response Has Shorter Onset Times

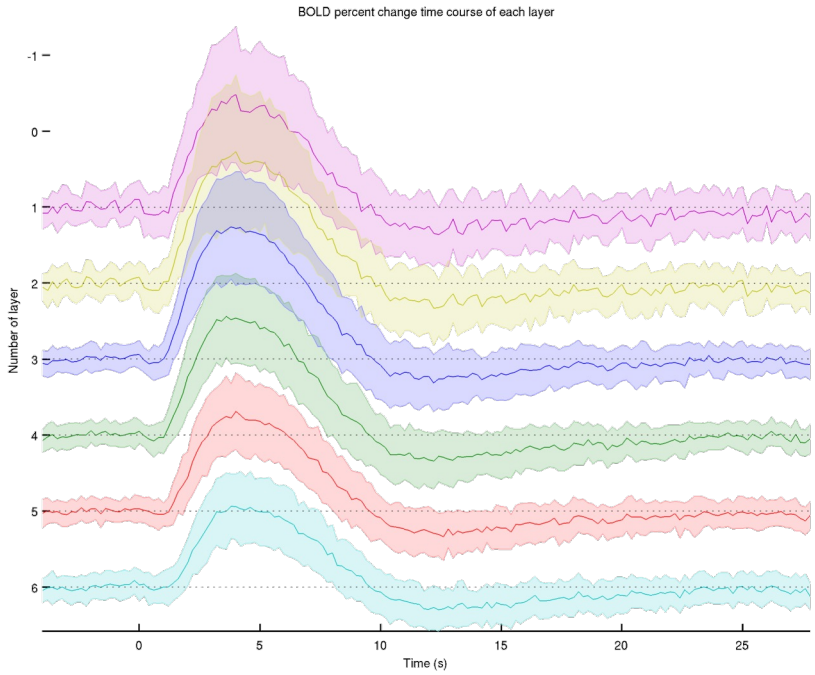


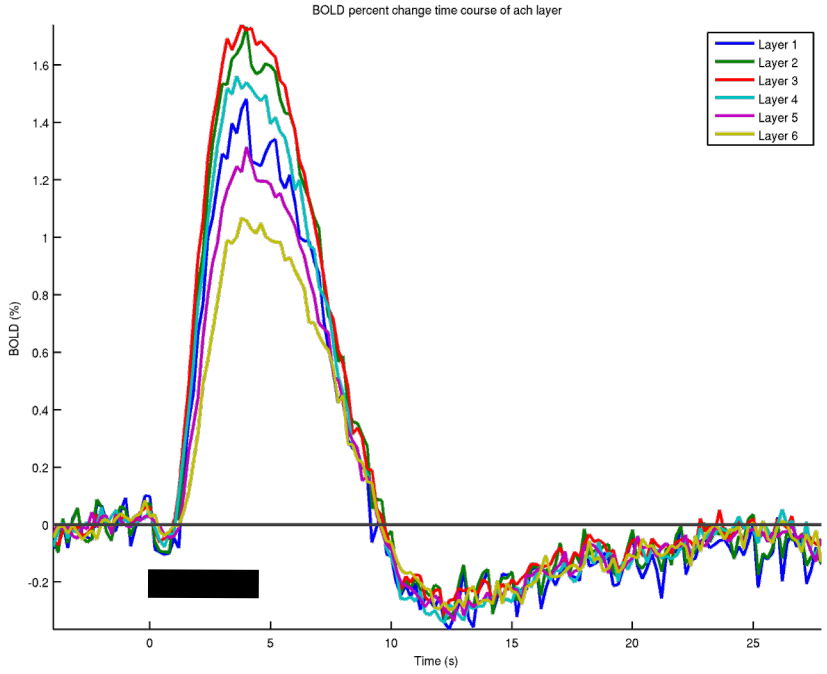
Yoshiyuki Hirano, in preparation

Hand Representation in Somatosensory Cortex



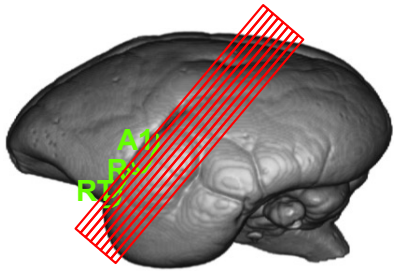


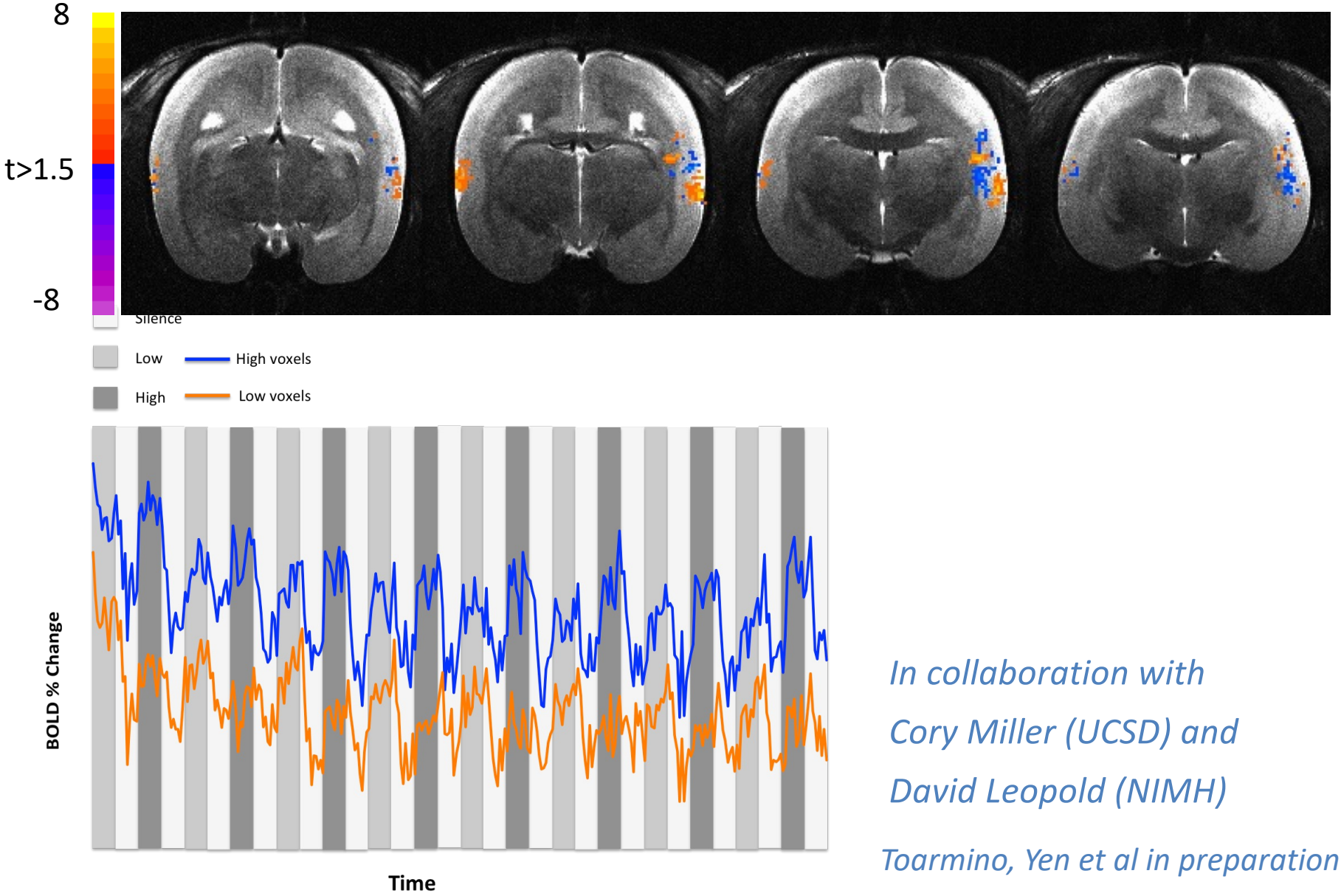




Cecil Yen, in preparation

Tonotopic Mapping in Marmoset Auditory Cortex





In collaboration with

Cory Miller (UCSD) and

David Leopold (NIMH)

Toarmino, Yen et al in preparation

Resting State Networks In Conscious Marmosets

High Order Visual Cortex
V3, V4, A19, A19DI

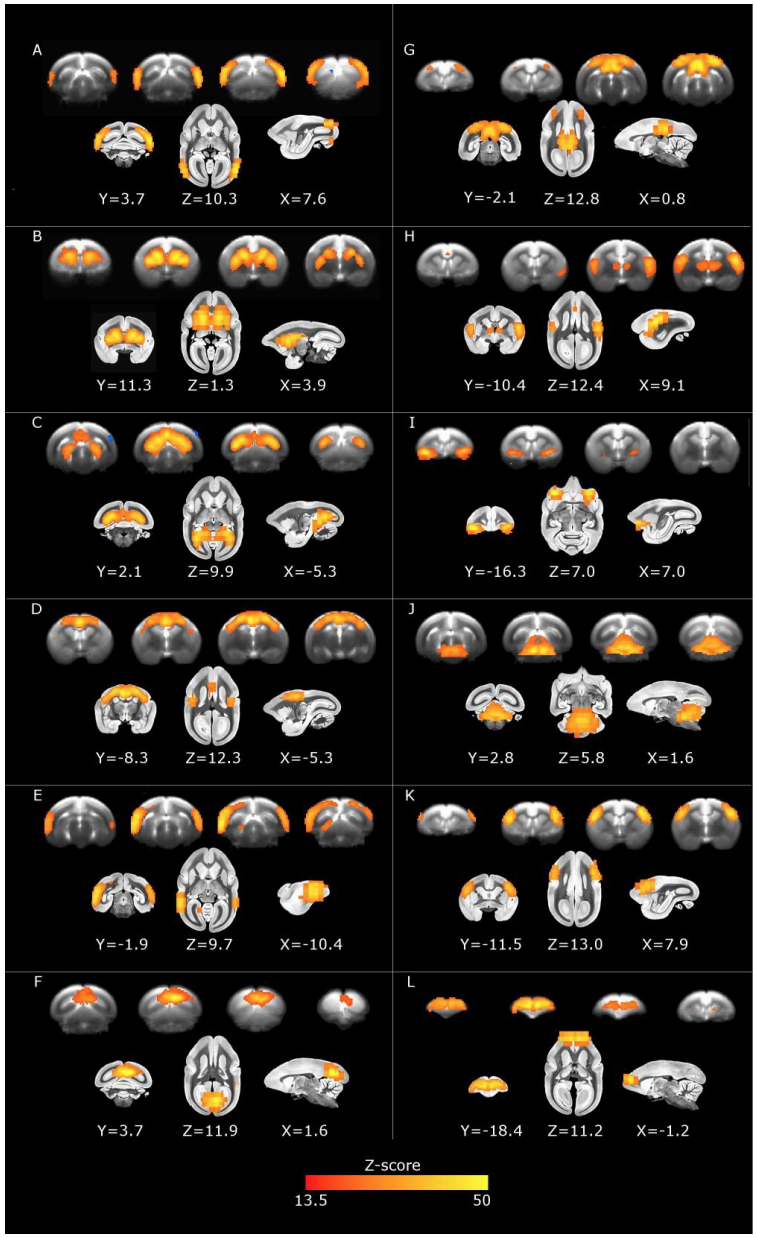
Basal Ganglia

Primary Visual Cortex

Dorsomedial
Somatomotor

High Order Visual Cortex
V4, V5, V6, FST, TE3

High Order Visual Cortex
V2, A19M, V6(DM)



Default Mode Network

Salience

Orbitofrontal Cortex

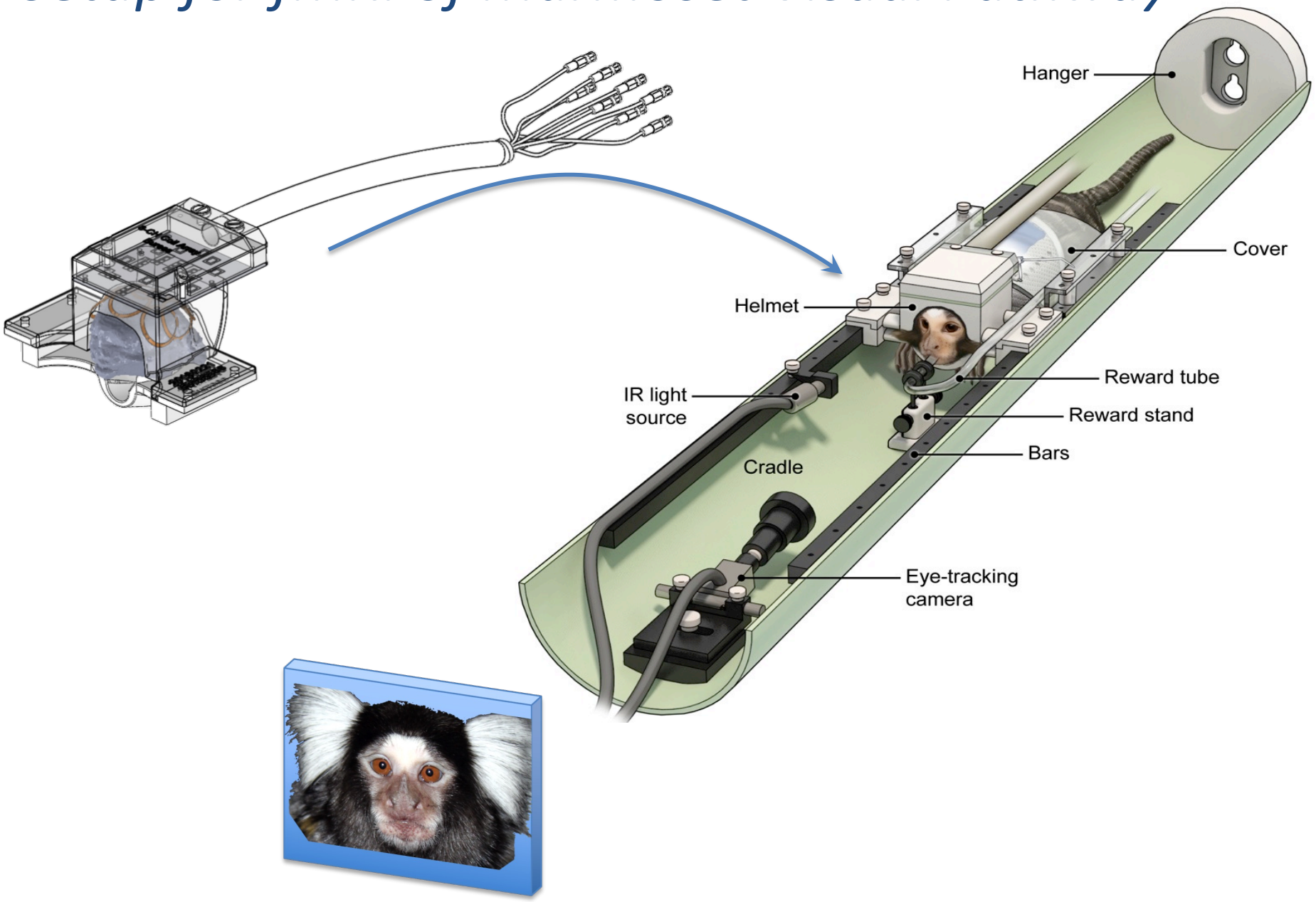
Cerebellum

Ventrolateral
Somatomotor

Frontal Pole

Belcher J Neurosci. 2013 33(42):16796 –16804

Setup for fMRI of Marmoset Visual Pathway

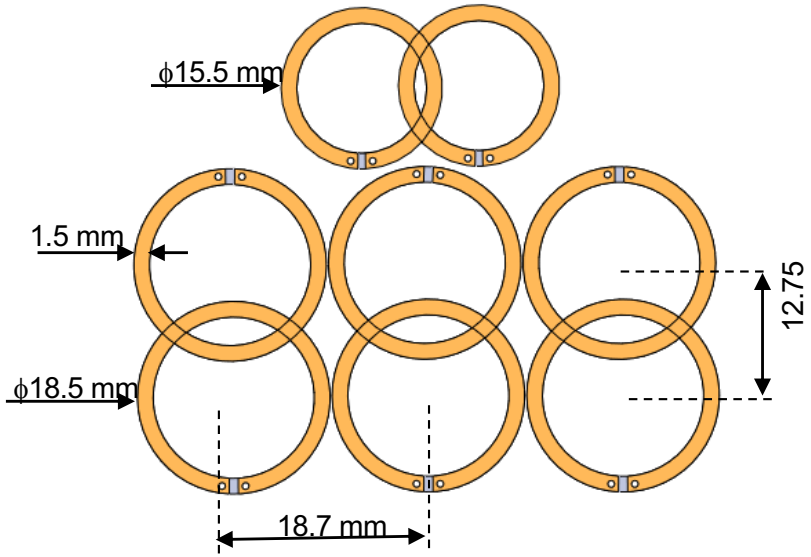


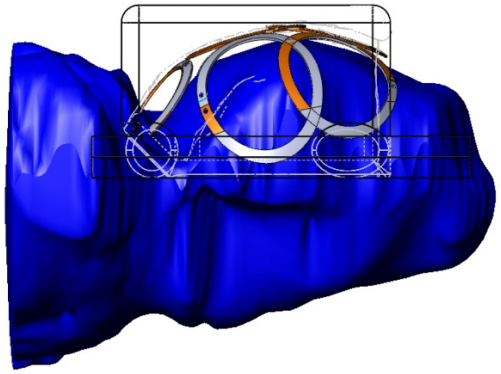
In collaboration with David Leopold (NIMH)

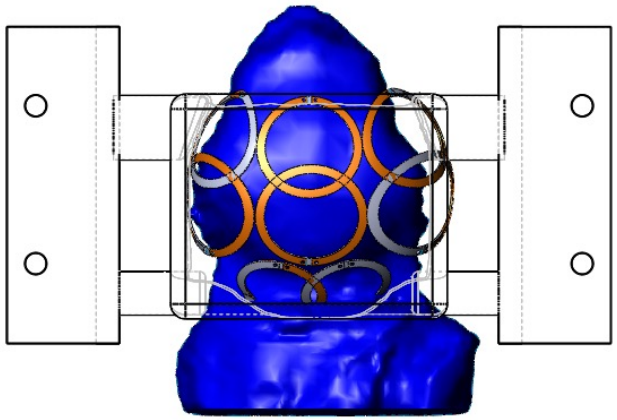
Hung, Yen et al in preparation

8 – Channel embedded array for visual fMRI

Coil layout

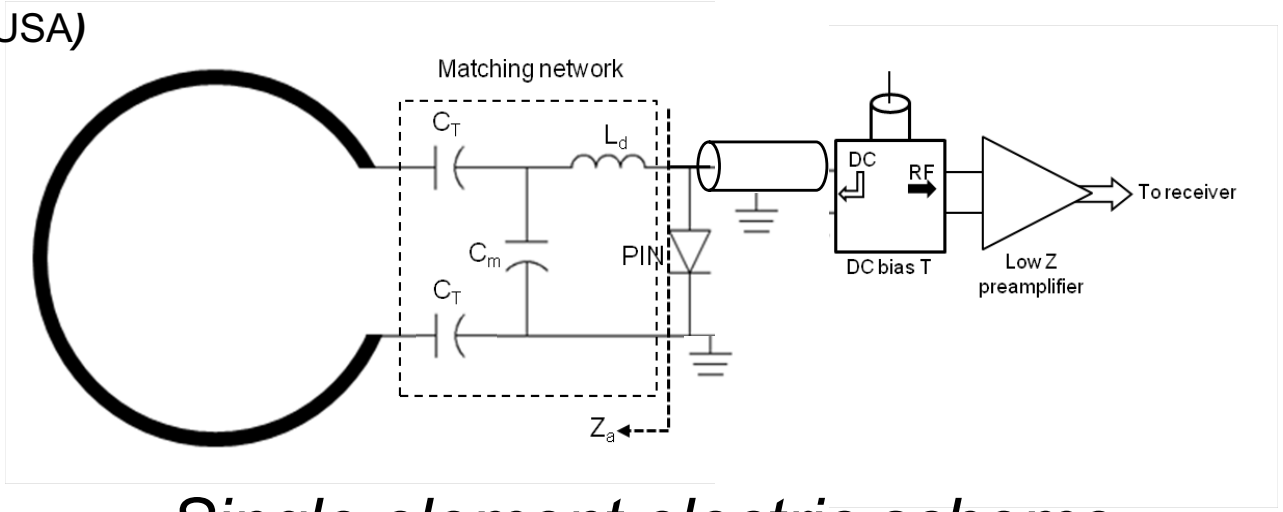






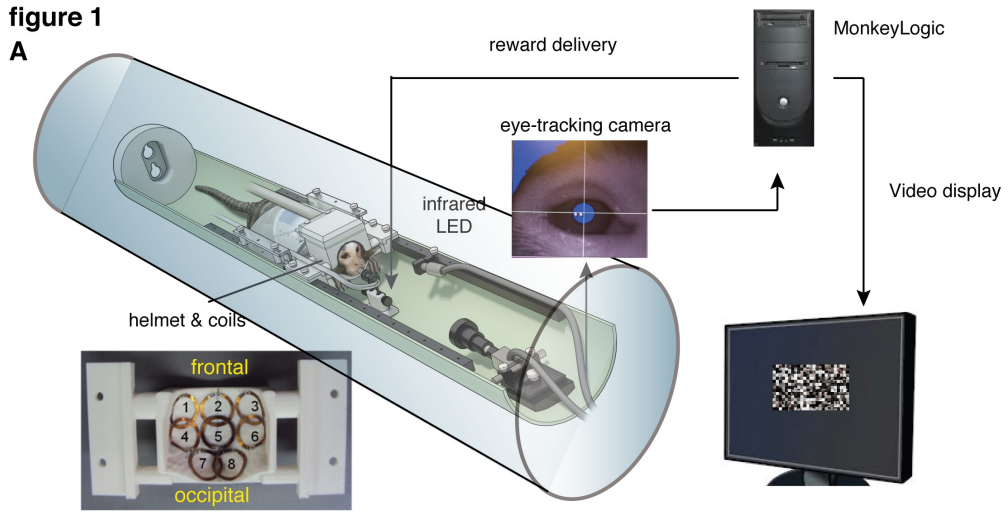
CuFlon (Polyflon Inc., Norwalk, CT, USA***)***

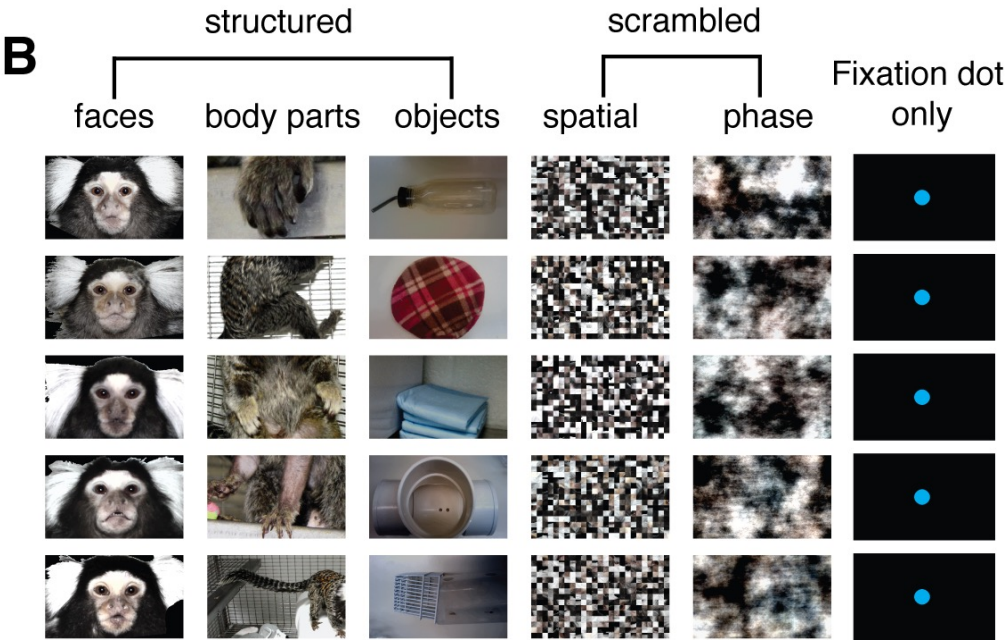
- *2oz/ft² of copper deposited*
- *0.25 mm thick PTFE dieletric*

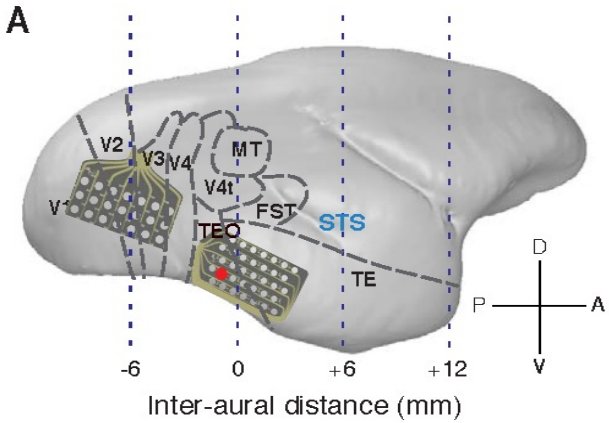


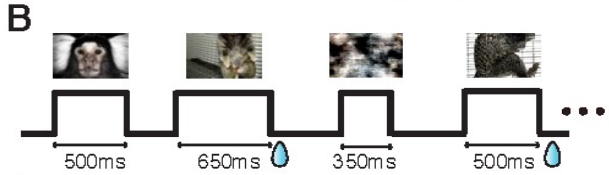
Single element electric scheme

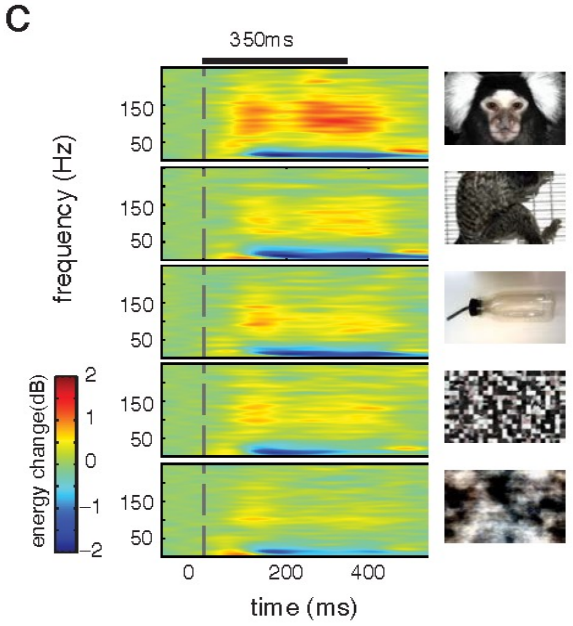
fMRI/ECoG during visual stimulation







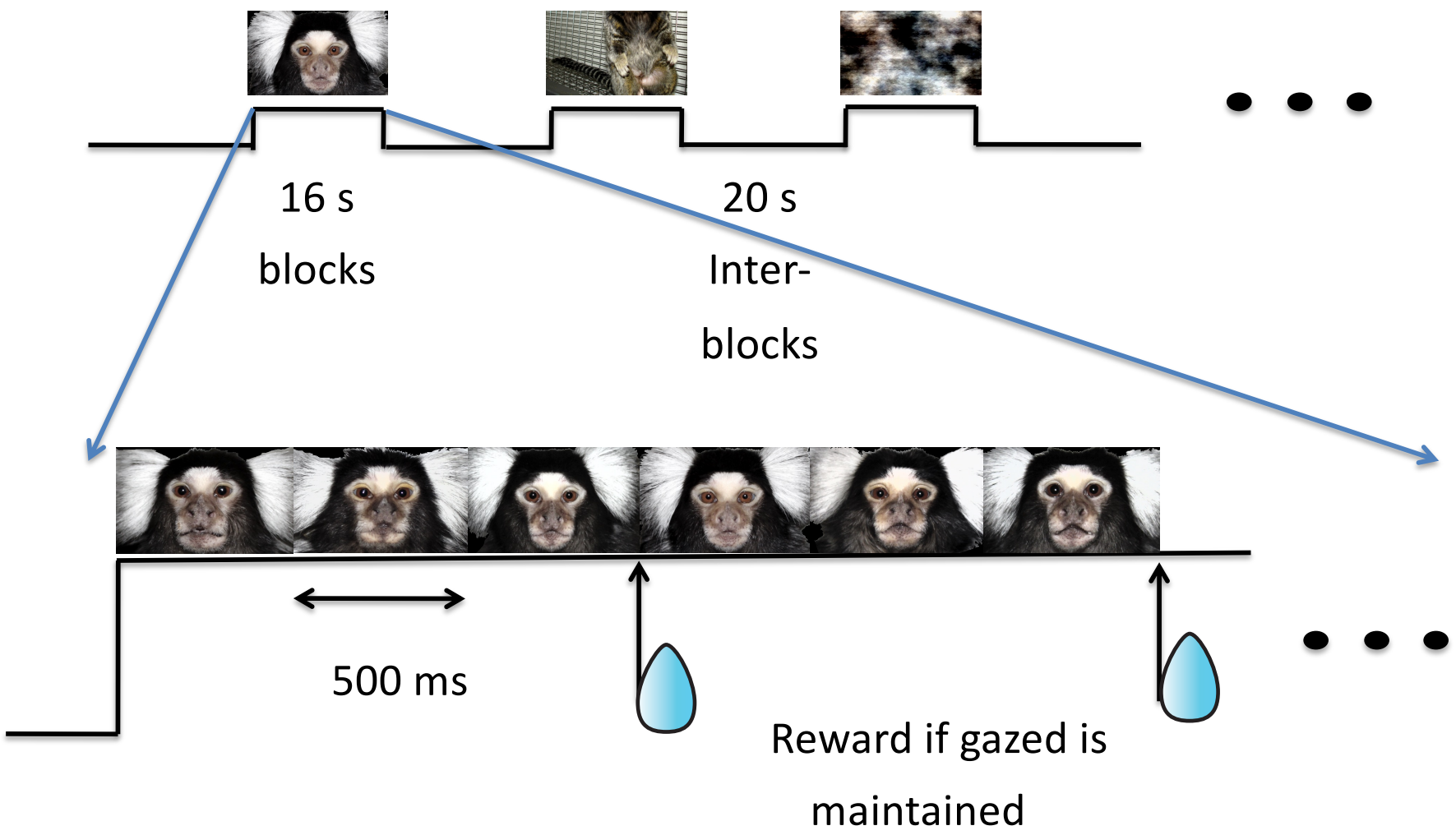




C.-C. Hung et al Neuroimage in press 2015

C.-C. Hung et al J Neurosci 2015 35(3):1160-72.

Experimental paradigm for fMRI of Visual System

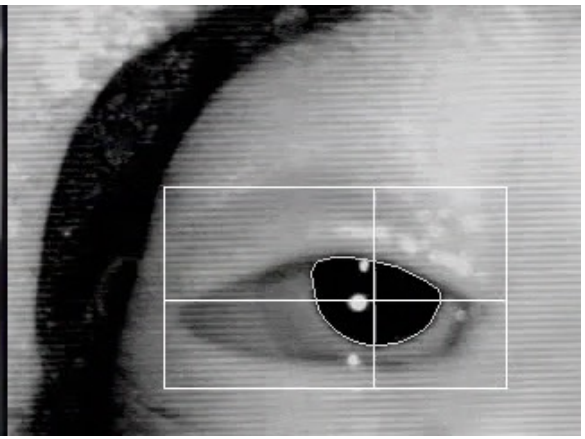


C.-C. Hung et al J Neurosci 2015 35(3):1160-72.

Typical behavior of awake marmoset to a stimulus block

Positive reinforcement

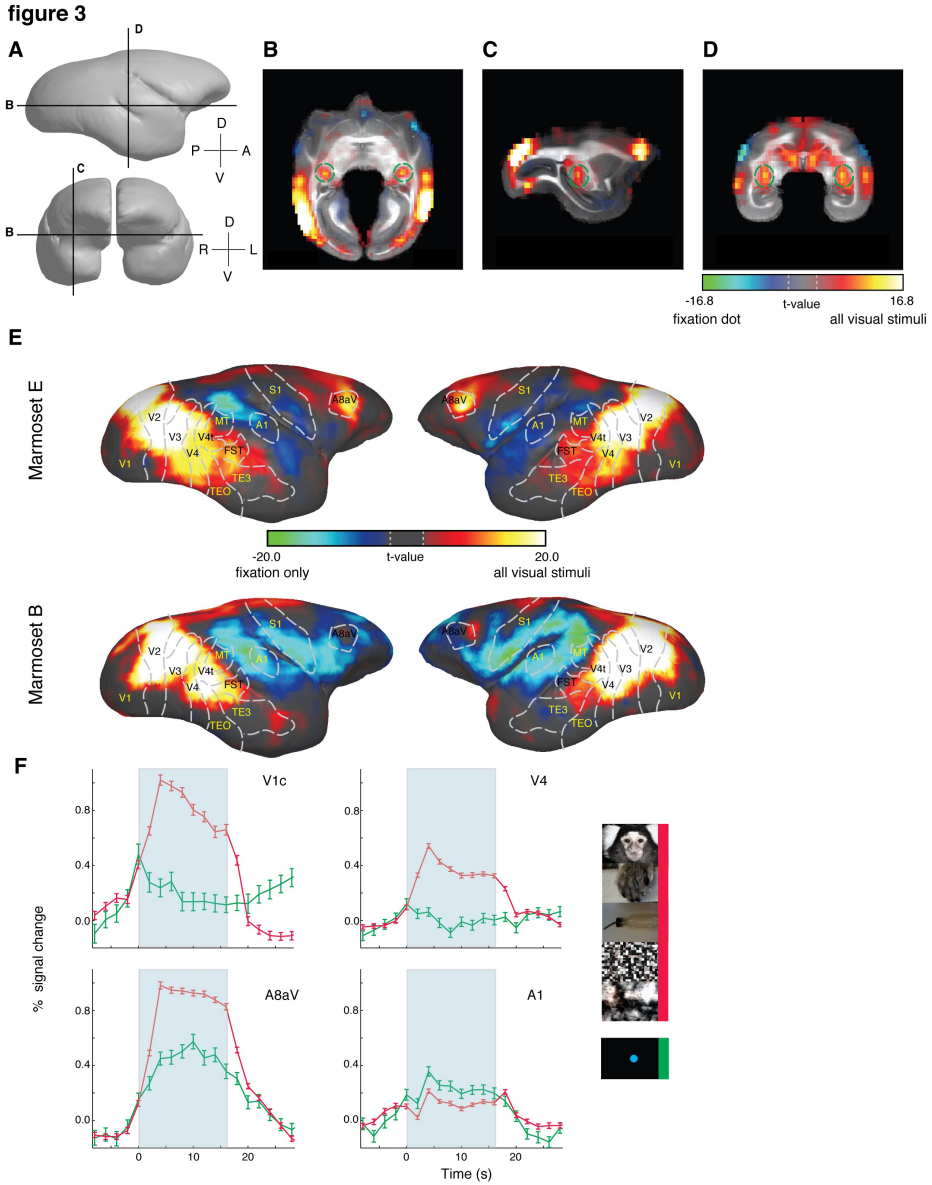
Infra-red eye-tracking

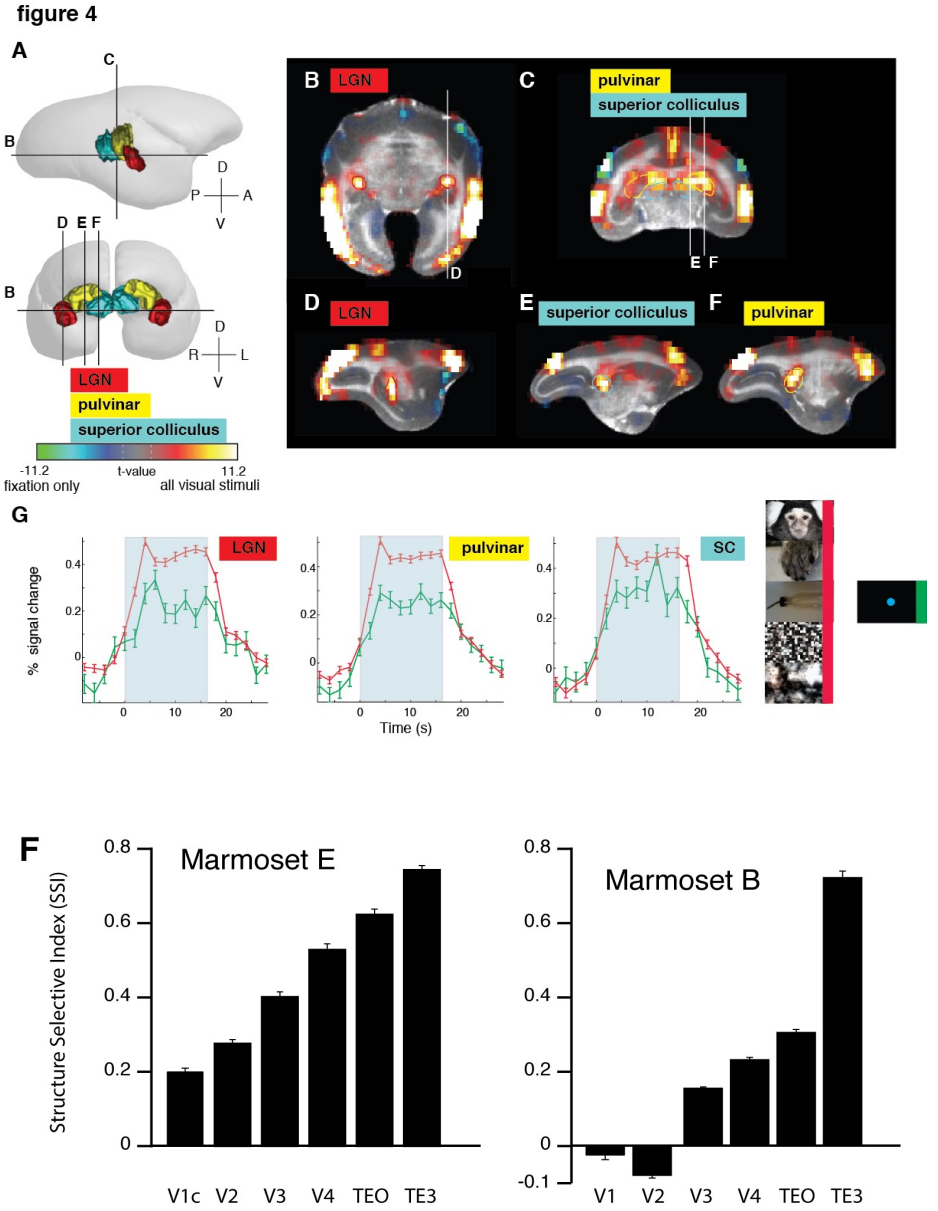


Visual Stimulus

C.-C. Hung et al J Neurosci. 2014 in press

Visual responses in cortical and sub-cortical areas





C.-C. Hung et al J Neurosci 2015 35(3):1160-72.

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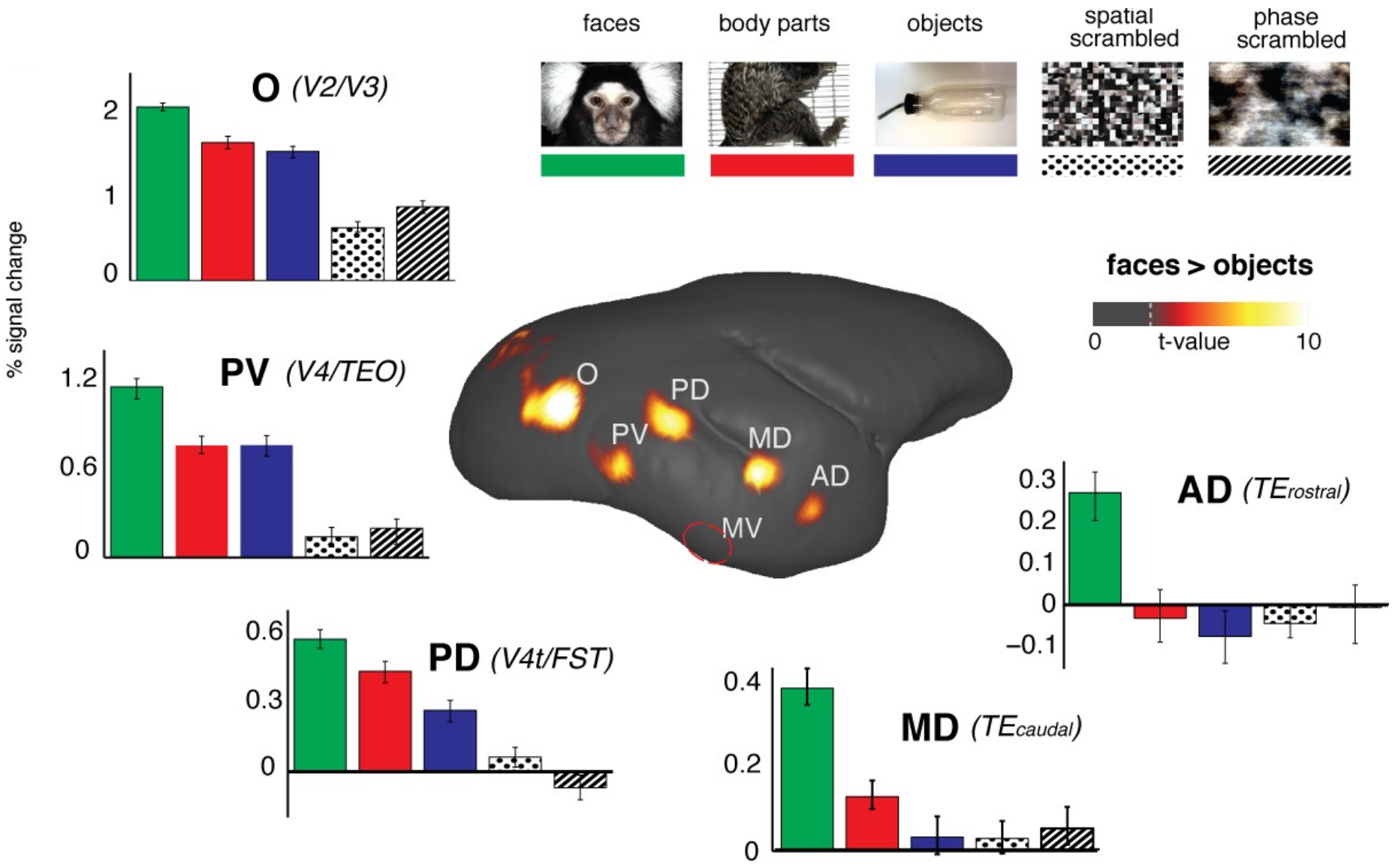
Face-selective patches along ventral visual pathway



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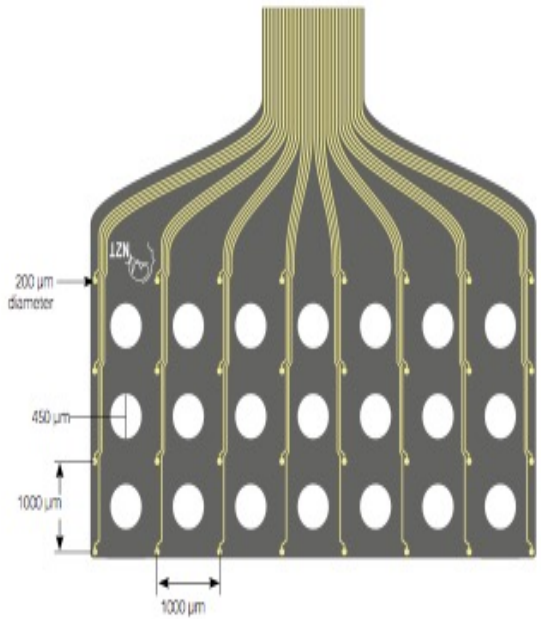
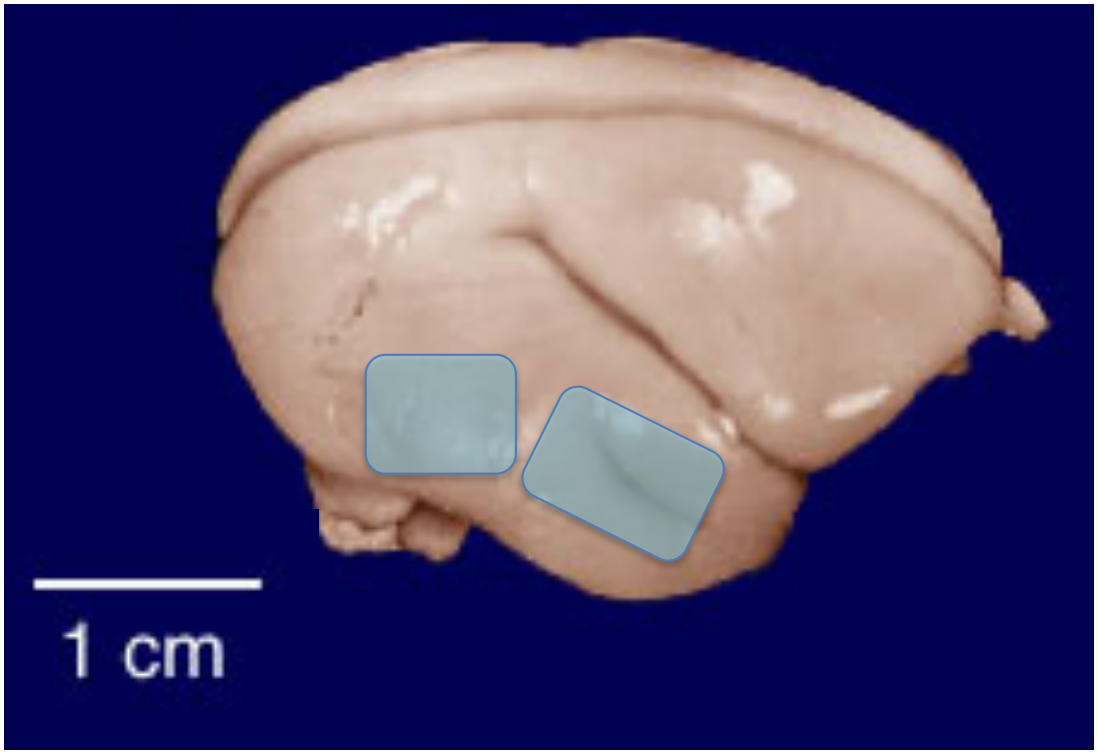
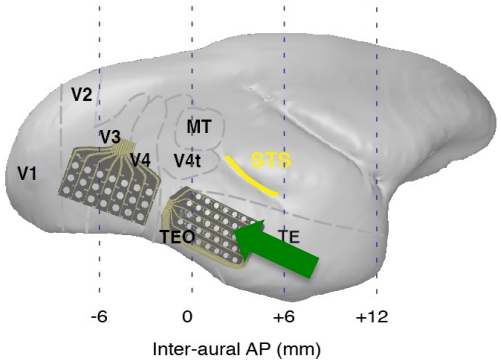
Electrocorticography (ECoG)

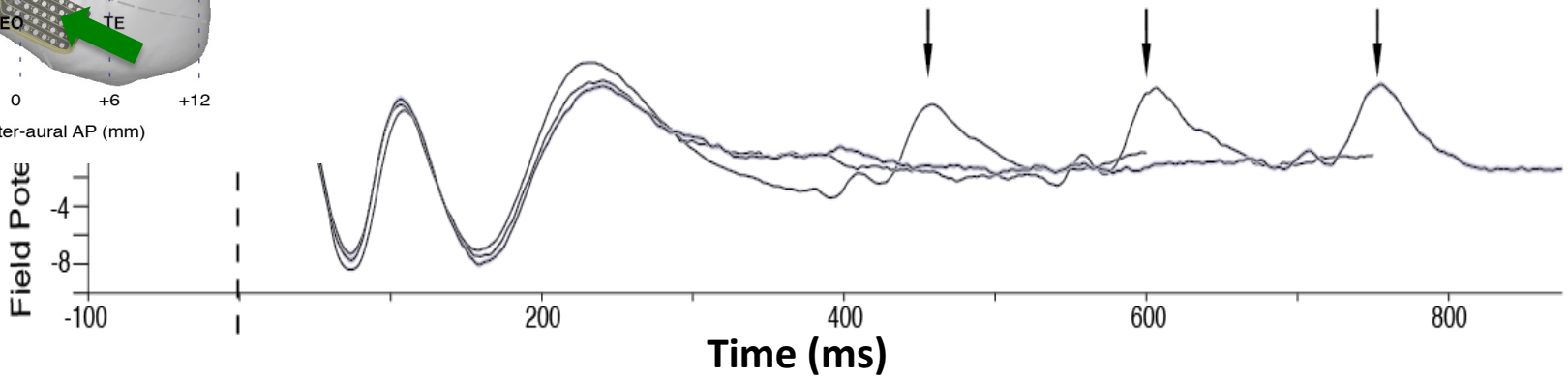
- High density, multi-channel electrode arrays
- Implanted on surface of brain underneath dura
- Record LFPs, good spatial resolution
  - on the order of electrode separation. e.g. 1 mm)

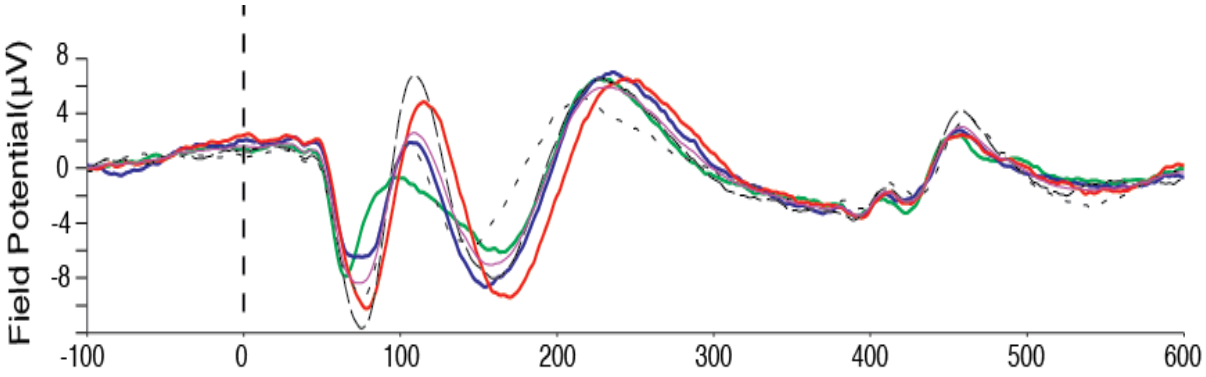




ECoG measures event-related potentials







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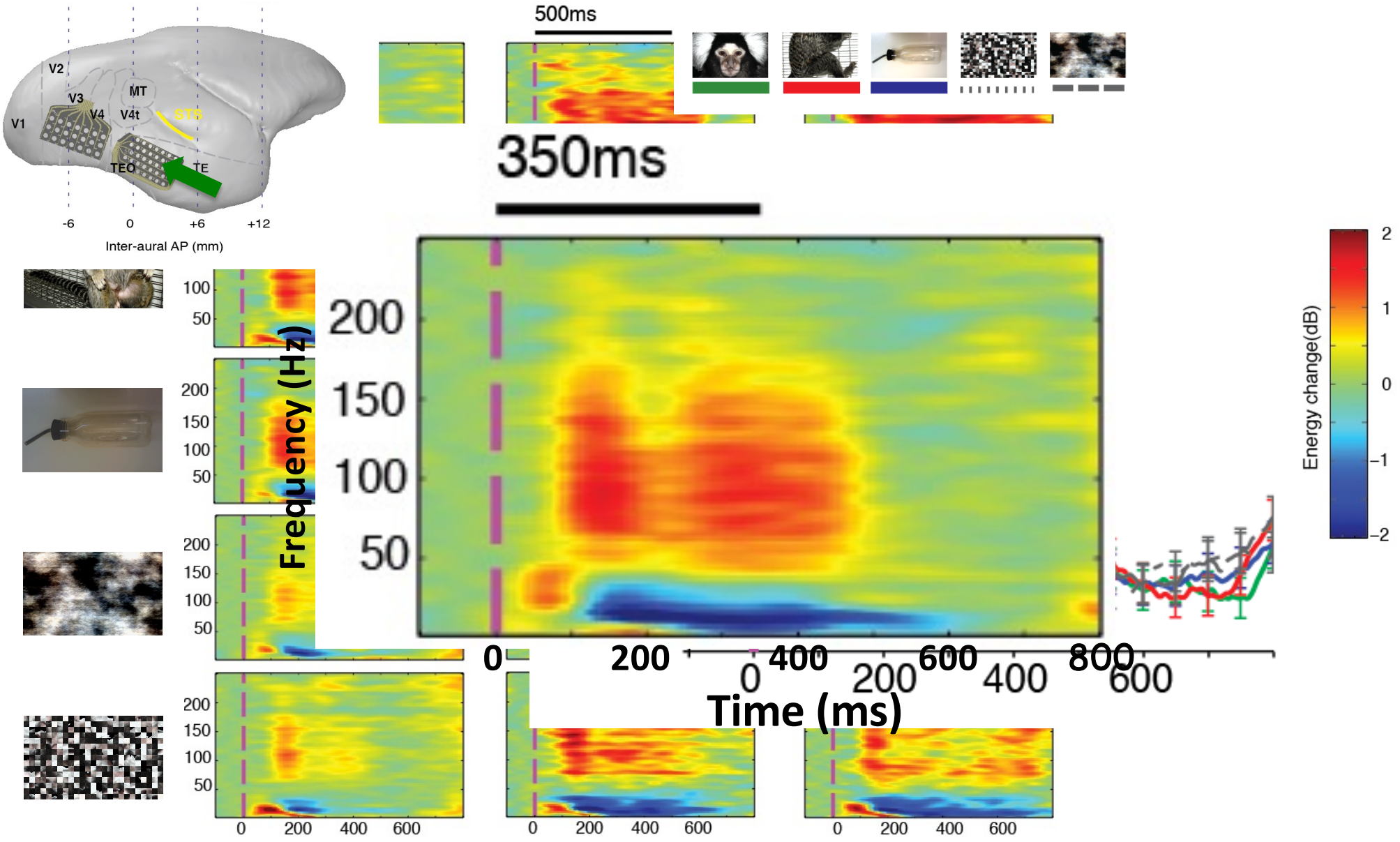
Time-frequency Analysis (An example site)



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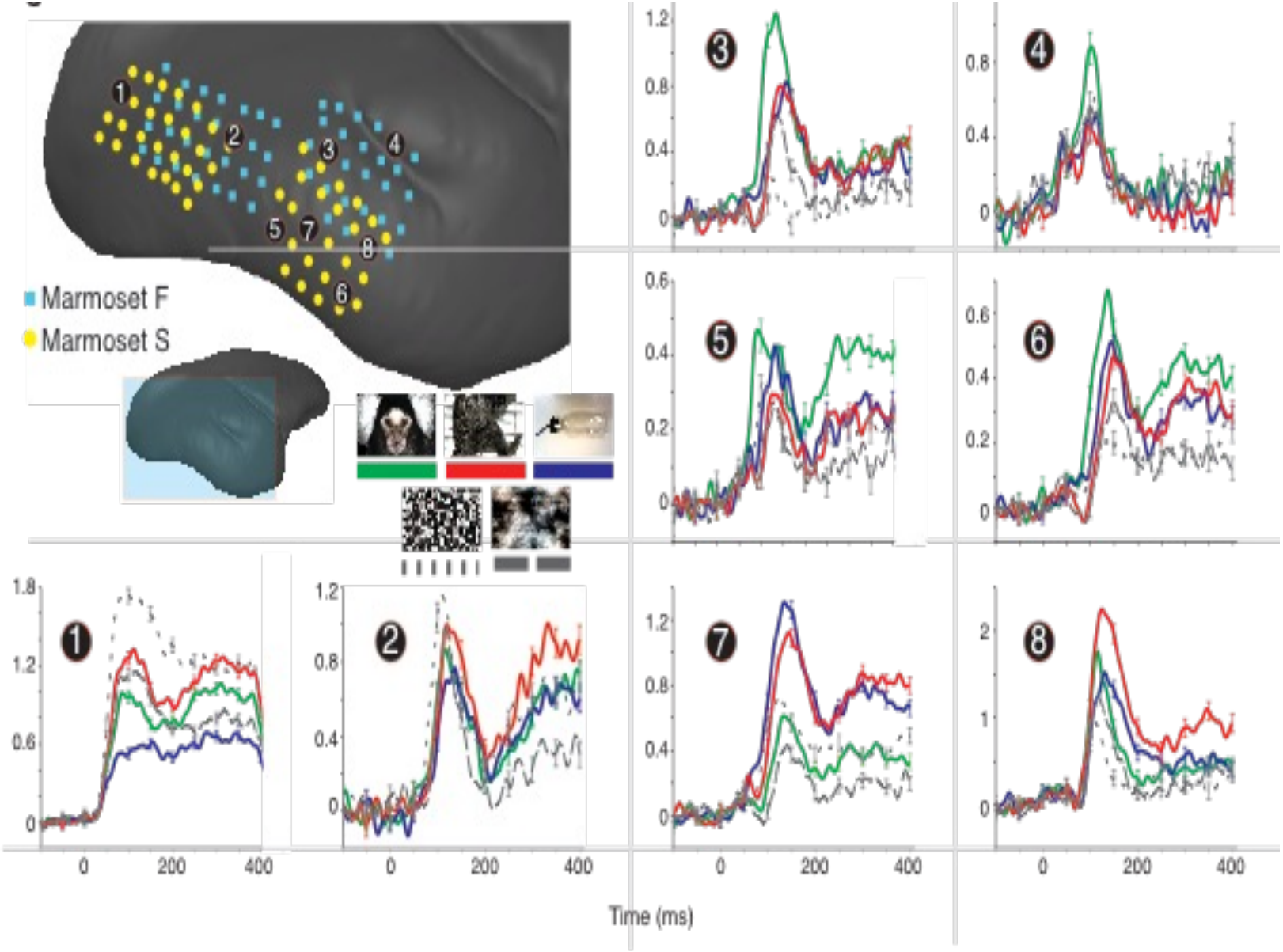
Spatial layout of the high-gamma responses



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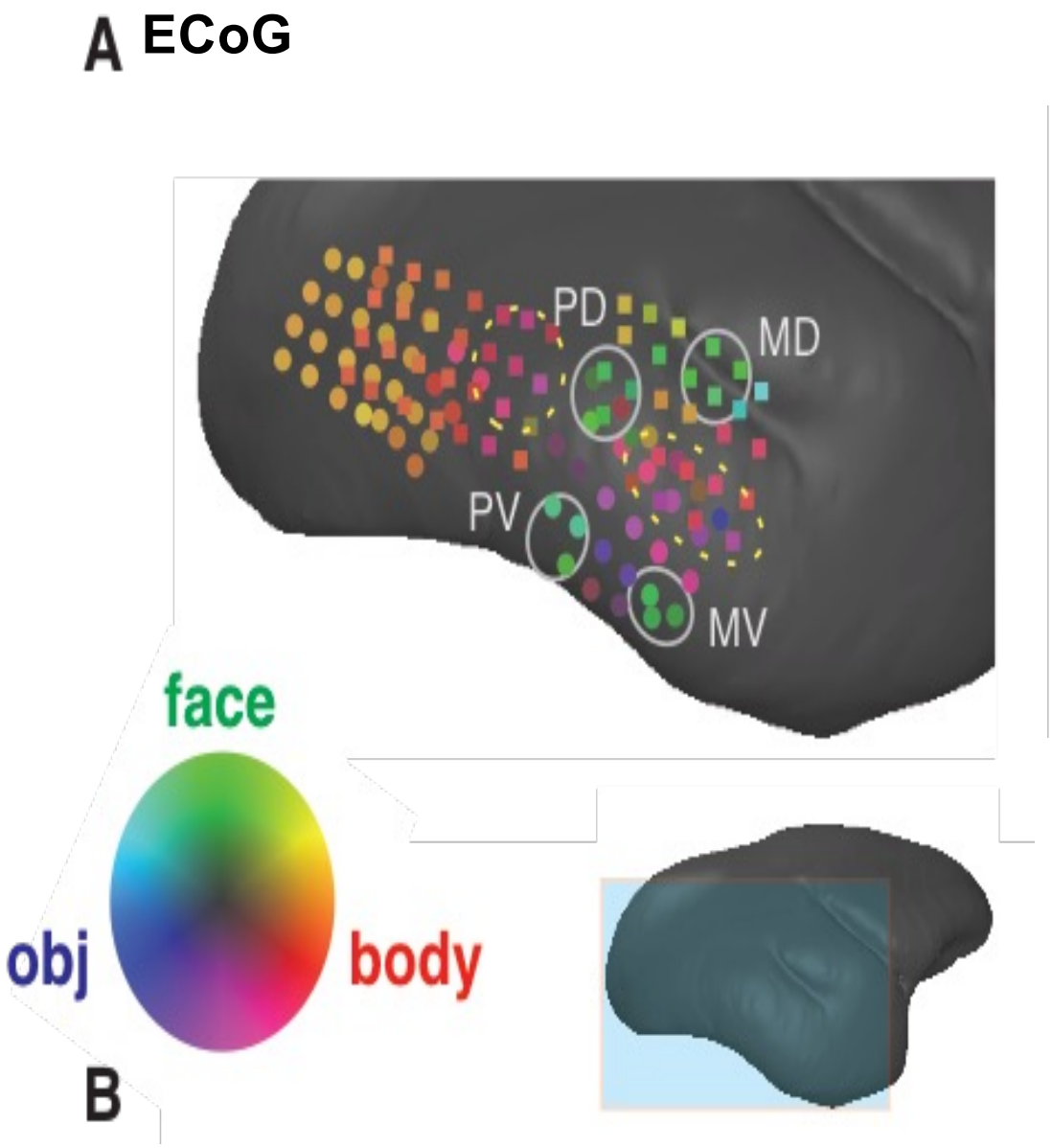
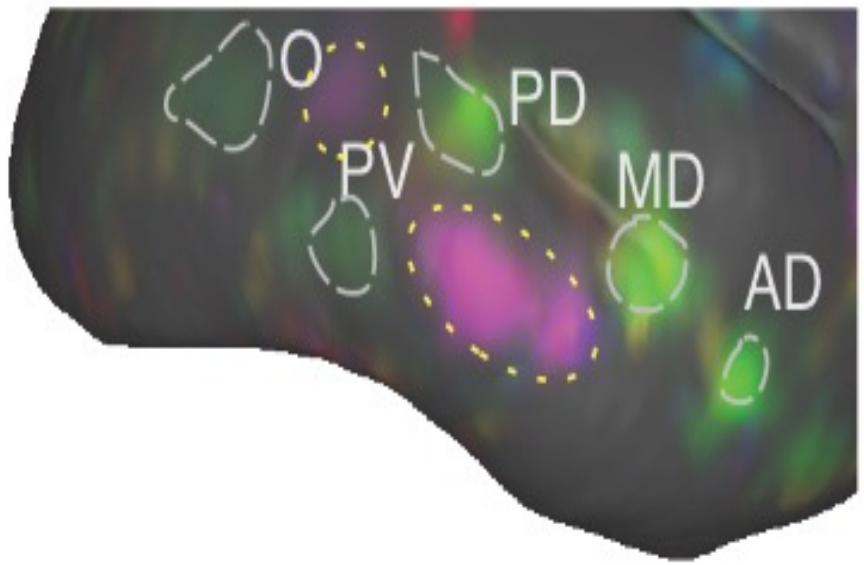
Good spatial correspondence between fMRI and ECoG in marmoset extrastriate visual pathway





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Conclusions

- Advantages of Animal Models
  - Allow comprehensive, multi-modal investigations
  - Can be Performed in State of the Art MRI Systems
  - High SNR, Spatial and Temporal Resolution

- Challenges
  - Use of *anesthesia* is a major confound for fMRI studies
  - Training of animals to perform specialized tasks can be quite challenging

Cerebral Microcirculation Unit

main.html

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  - *Lisa Zhang*
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  - *Calvin Kersbergen*
- Postdoctoral Fellows
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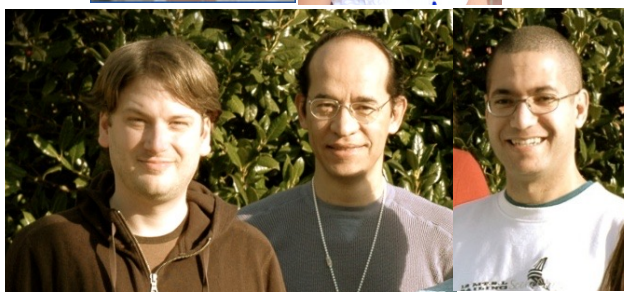

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Thank You!