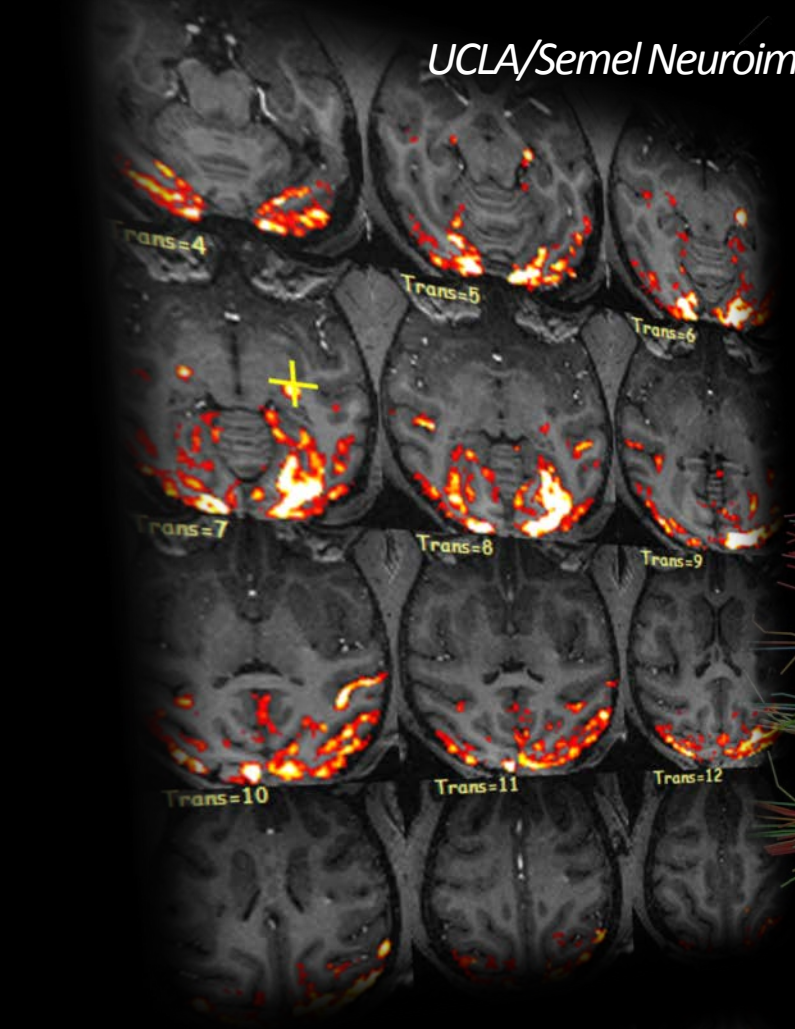
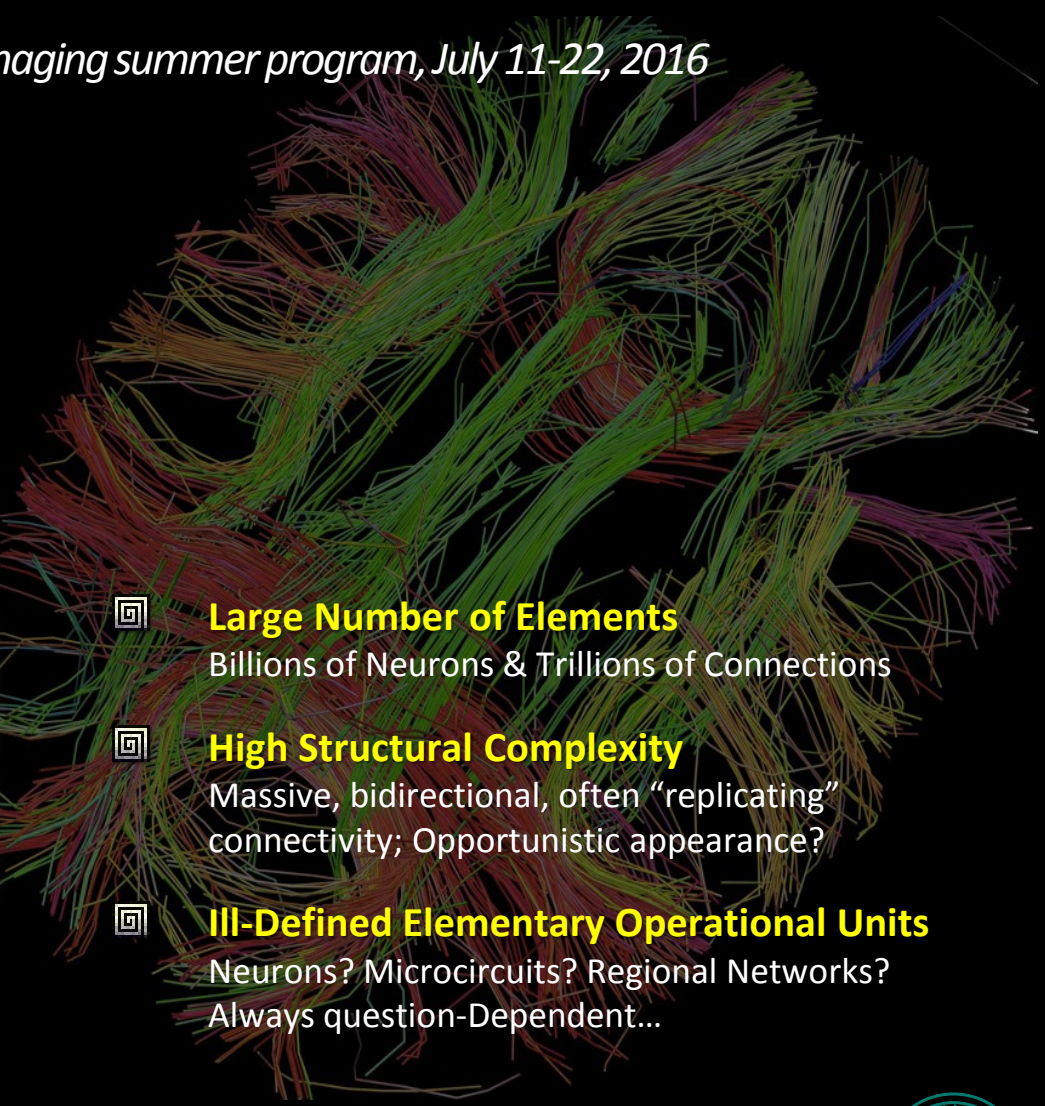
DES-fMRI: Direct Electrical Stimulation and fMRI

Mapping Monosynaptic Connectivity & Cortico-Thalamo-Cortical Loops

UCLA/Semel Neuroimaging summer program, July 11-22, 2016





- **Large Number of Elements**
  Billions of Neurons & Trillions of Connections
- **High Structural Complexity**
  Massive, bidirectional, often "replicating" connectivity; Opportunistic appearance?
- **Ill-Defined Elementary Operational Units**
  Neurons? Microcircuits? Regional Networks? Always question-Dependent…

Nikos K. Logothetis
Max Planck Institute for Biological Cybernetics

Connectivity: Histology, DTI, MEMRI, DES-fMRI & NET-fMRI

Traditional Fix Tissue-Requiring Histological Techniques

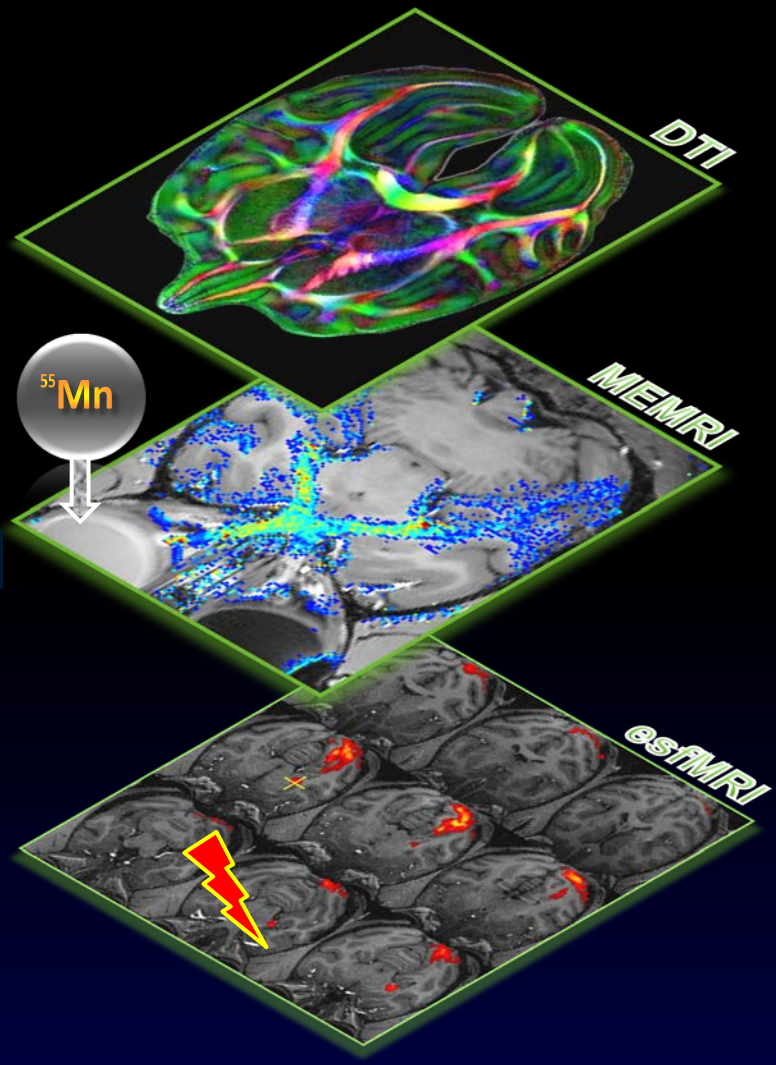
- **Degeneration Studies**
- **Conventional Tracers**

CT-HRP:	Horseradish peroxidase, conj. cholera toxin A/R
HRP:	Horseradish Peroxidase A/R
TAA-HRP:	HRP tritiated amino acids A/R
WGA:	Wheat germ agglutinin A/R
WGA-HRP	Anterograde tracing

- **Transneuronal Tracers**
  Herpes-Simplex Virus (HSV)
  Indocyanine green, carbocyanine fast Di-I Biotinylated dextran
- **Genetically Encoded Markers & Viral-Based Methods**
  Fluorescent proteins, transgenic constitutive & site-specific expression of markers for axonal connectivity

Non-Invasive or Minimally Invasive In vivo Connectivity with MRI Techniques

- **DTI & Effective Connectivity**
- **Paramagnetic Tracers - Mapping**
  Sensory Pathways
  [1] Diffuse ascending Systems (before/after learning)
  [2] Cortico-Subcortical Pathways
- **DES-fMRI (Direct Electrical Stimulation & fMRI**
- **NET-fMRI (Neural Event Triggered fMRI)**



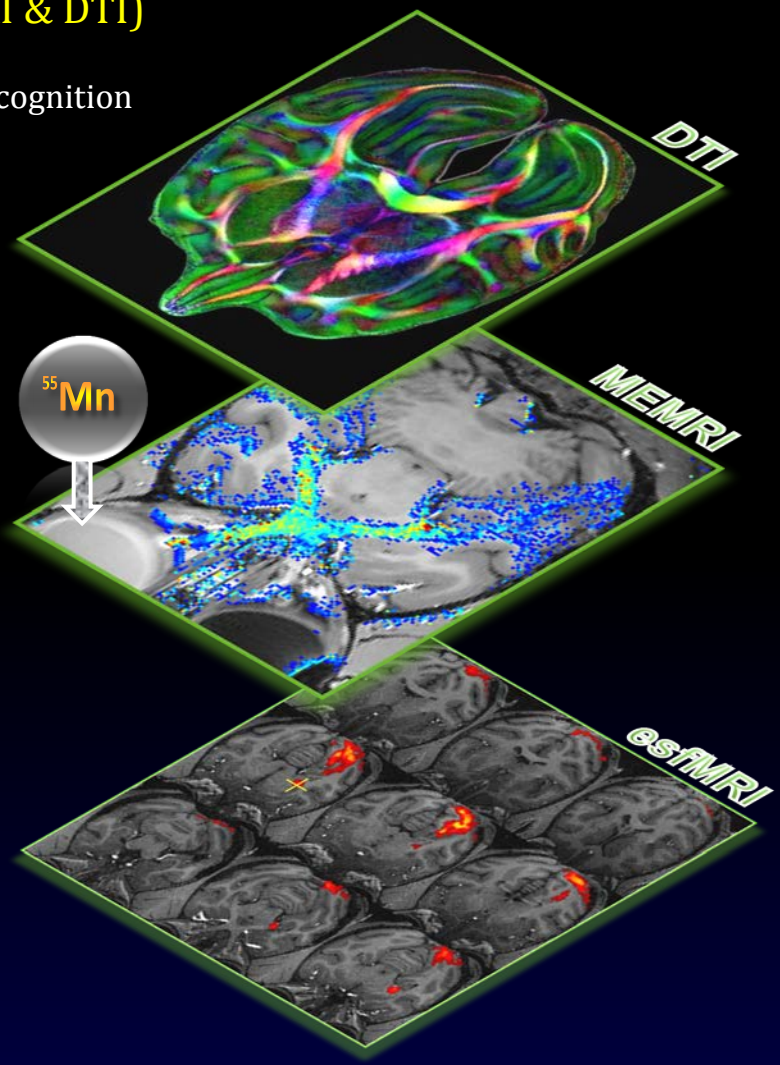
Saleem et al, Neuron, 2002; Murayama et al, MRI 2006; Canals et al, NeuroImage, 2008; [2] Eschenko et al, NeuroImage 2010; Eschenko et al, MRI 2009; Eschenko et al (submitted)

Potential Applications of DES-fMRI

- *In vivo* Connectivity (potentially combined w/ MEMRI & DTI)
  - Study of projective fields (*)
  - In search of "causalities" between neural activity and perception/cognition
  - Study of motor systems

- Network Plasticity
  - *Study of synaptic plasticity*
  - *Effect of local plasticity changes on global networks*
  - *Study of neuromodulatory systems*

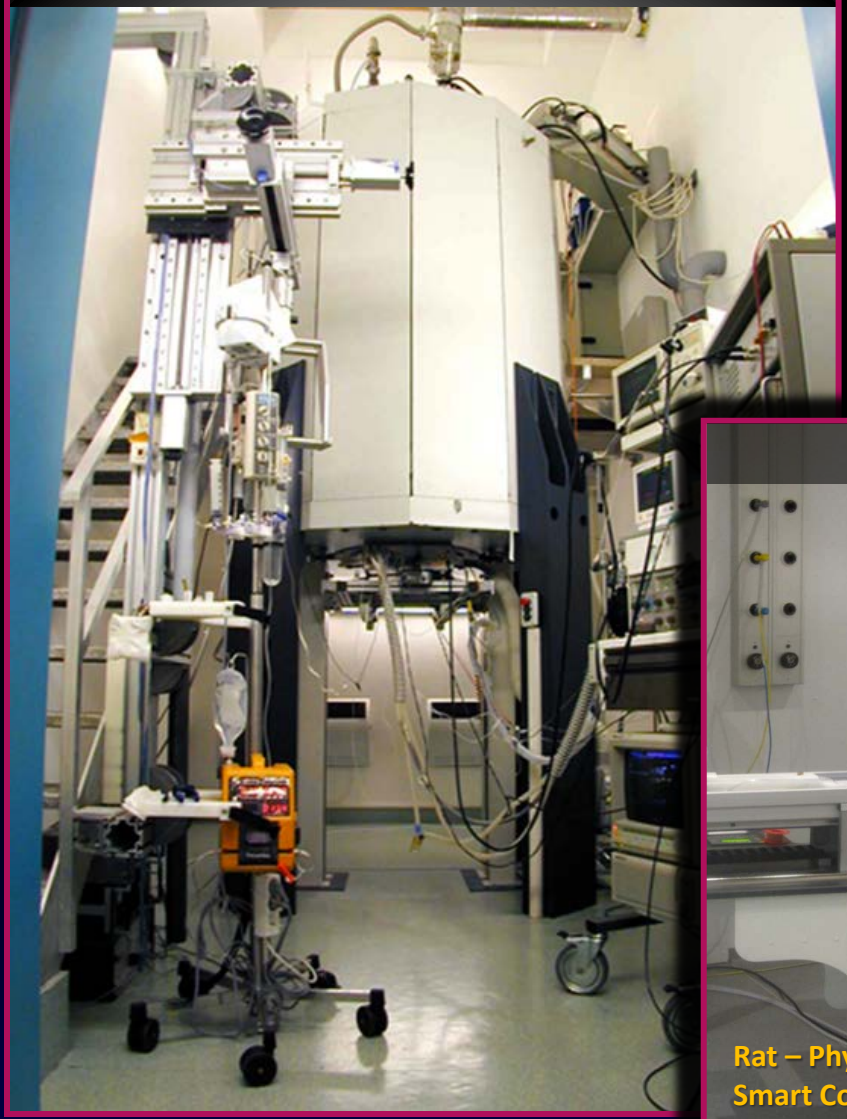
- Clinical Applications
  - *Identification of "eloquent" areas before surgical intervention*
  - *Insights into the mechanisms of electrotherapy*
  - *Design of neural prosthetic systems*



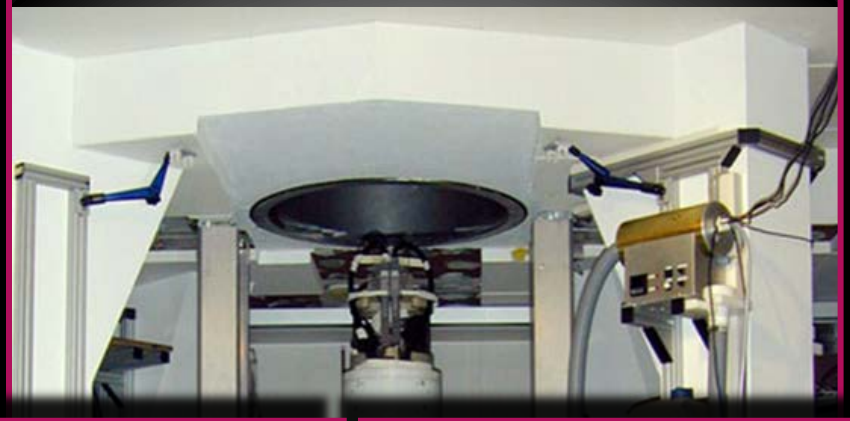
(*) E.g. see J.L. Hemmen & T. J. Sejnowski, 2006

MPIK Scanners for Combining fMRI with other Neuroscience-Techniques

4.7T/40cm - 50mT/m 180µs



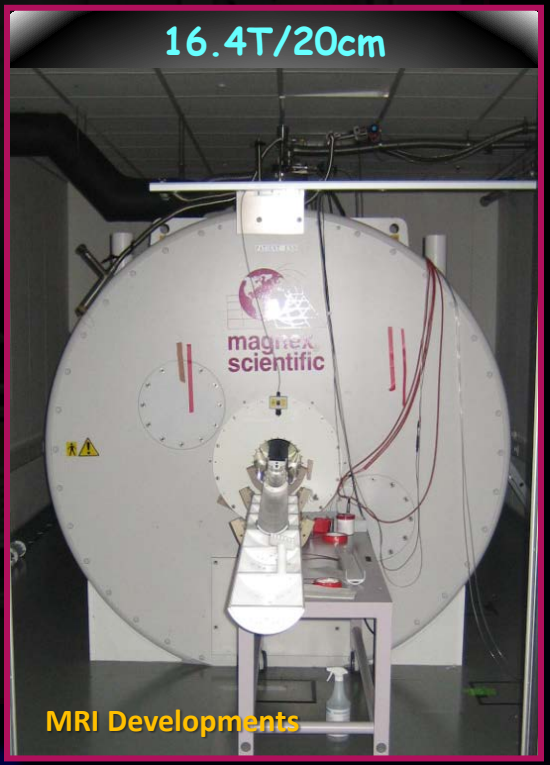
7T/60cm - 85mT/m 190µs



7T/30cm

Rat – Physiology/fMRI
Smart Contrast Agents
Microsampling-MS-fMRI

16.4T/20cm

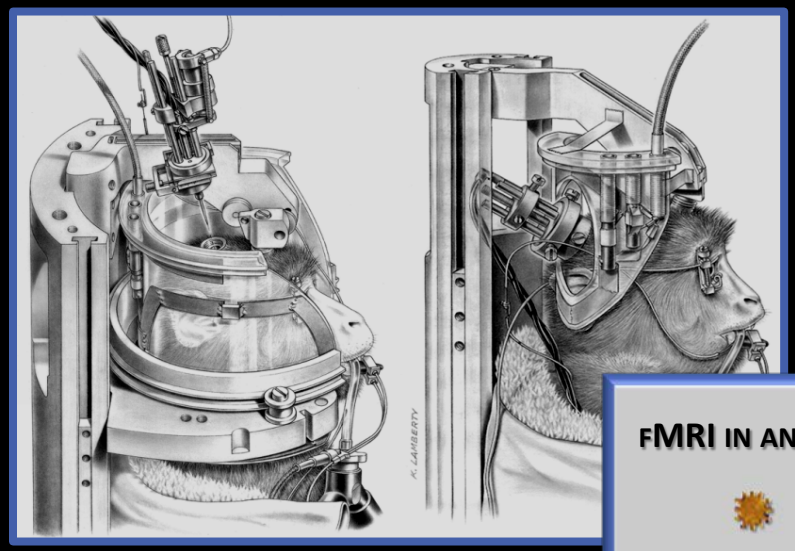


MRI Developments

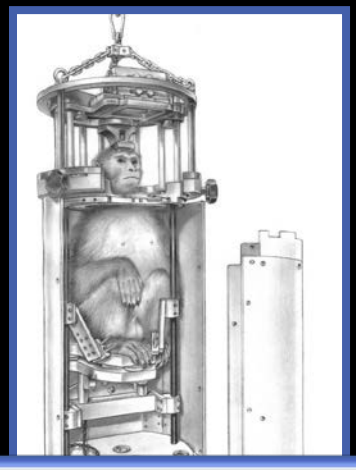
Bruker BioSpin Scanners

Electrophysiology, DES and fMRI in Anesthetized & Alert-Behaving Animals

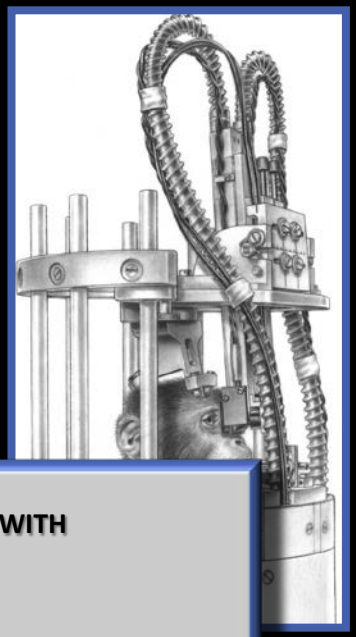
Coils, Sensors & Electrode-Holders



te-Chairs & Transport



navioral Monitoring

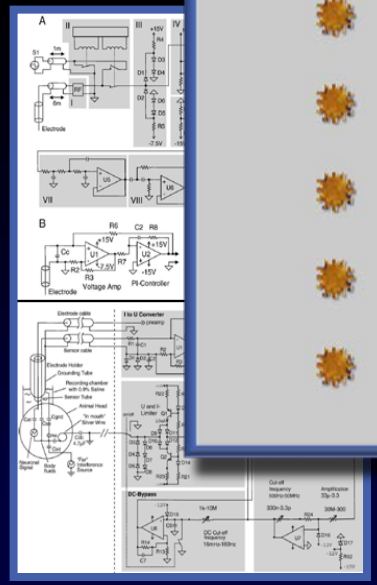


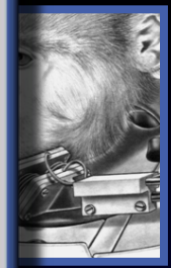
fMRI IN ANESTHETIZED AND ALERT ANIMALS, COMBINED WITH

- *Electrophysiology (ephysMRI)*
- *Neuropharmacology (phMRI)*
- *Capillary Microsampling (LC-MS/MS)*
- *Manganese Enhanced MRI (MEMRI)*
- *Direct Electrical Stimulation (DES)*
- *Neural-Event-Triggered Maps of Metabolic Changes*

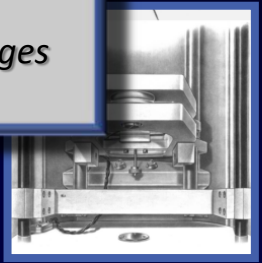
Electrodes & Interference-Sensors

Interference Compensation





ensors

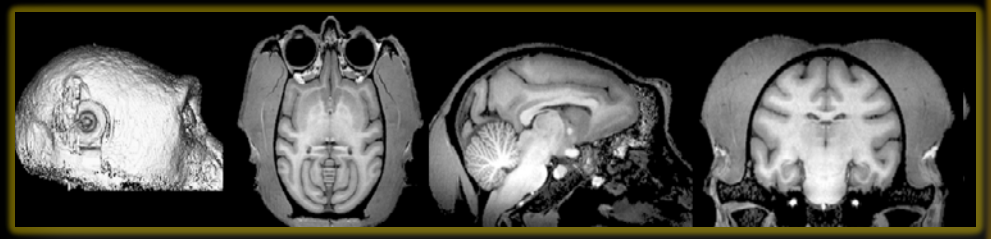


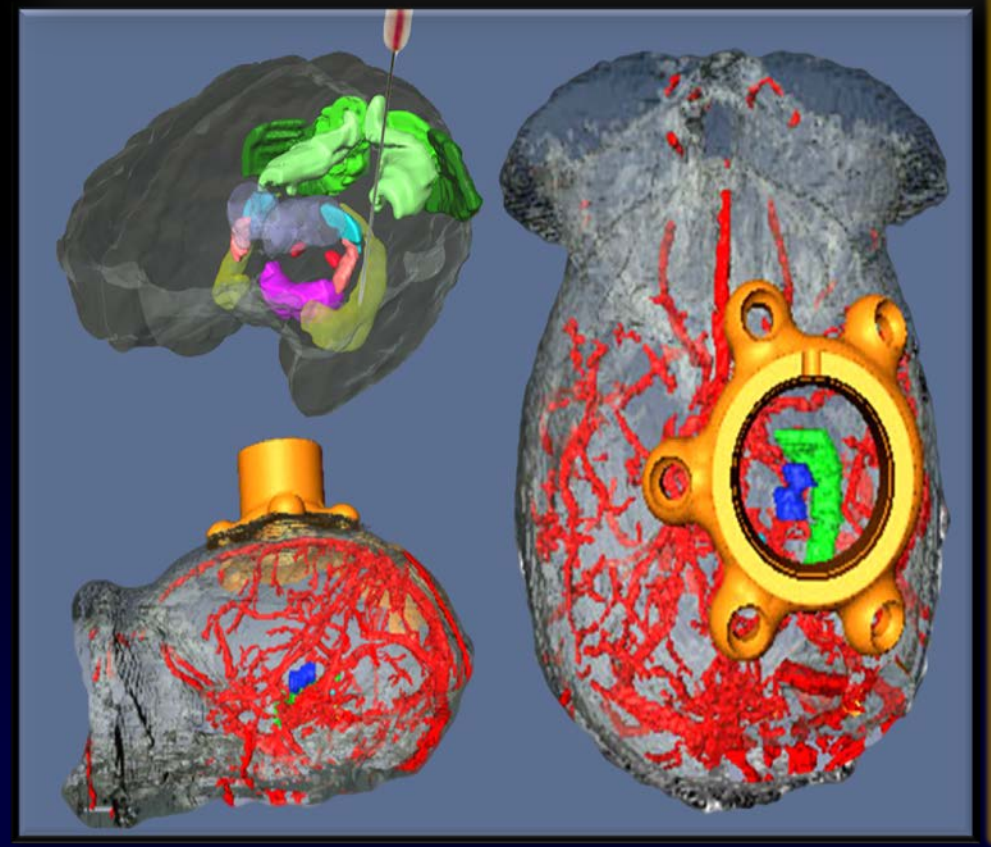
Goense, et al., 2008; Oeltermann et al. 2007a; Oeltermann et al. 2007b; Pfeuffer et al, 2007; Logothetis et al, Nature, 2001

Safe Targeting of Deep Brain-Structures

Angiography & 3D Site-Reconstruction

An attempt to reduce electrode-induced injury and infections
Localization verified w/ recordings

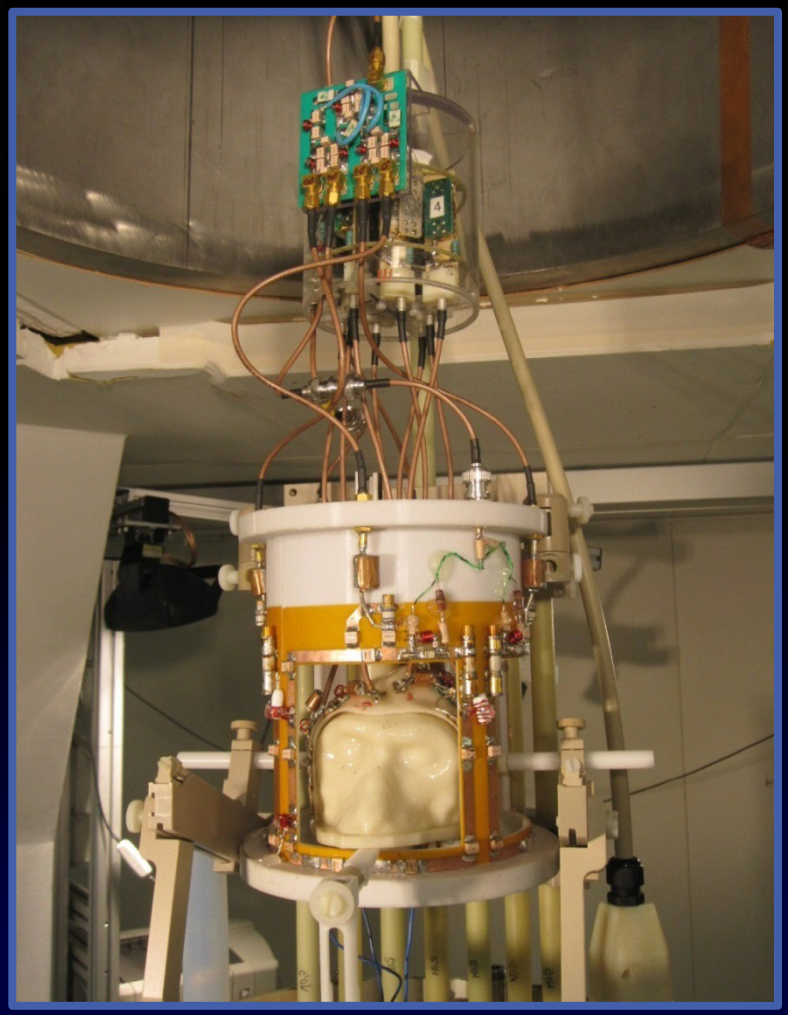




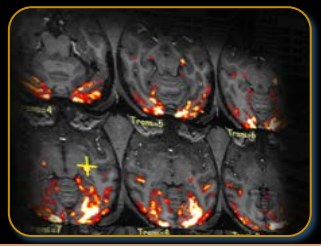
Parallel Imaging in the NHP

Phased RF-coil arrays;
Subject-Specificity w/ CAD-Reconstructed Heads

Voxel size .5x.5x1mm, Volume TR 500-250ms

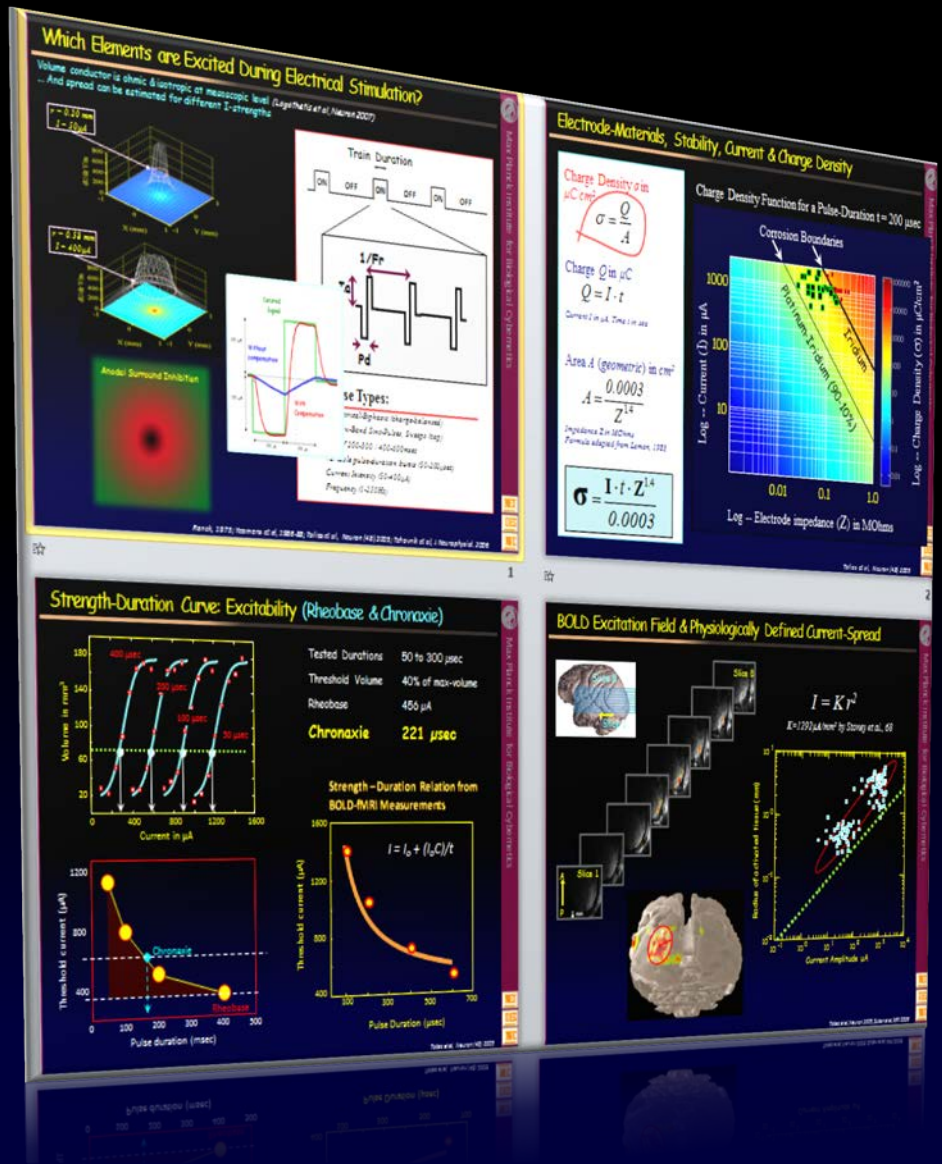


(Scheffler-Logothetis et al, Oeltermann-Logothetis, in Preparation), Goense, et al., 2008; Oeltermann et al. 2007a; Oeltermann et al. 2007b



DES-fMRI (Direct Electrical Stimulation & fMRI)

Connectivity of Structures Studied in Behavioral Experiments
Effects of Neuromodulation on Cortical Microcircuits
Network-Plasticity, E.G. Local-LTP-Induced Global Changes



DES-fMRI: Detailed Characterization

- ❑ Studies of Volume Conduction (isotropy/anisotropy)
- ❑ Selection of Electrode-Materials
- ❑ Current , Stability & Charge Density
- ❑ Electrophysiological & BOLD Estimation of Excitability
- ❑ Physiological Current-Spread & BOLD Excitation Fields

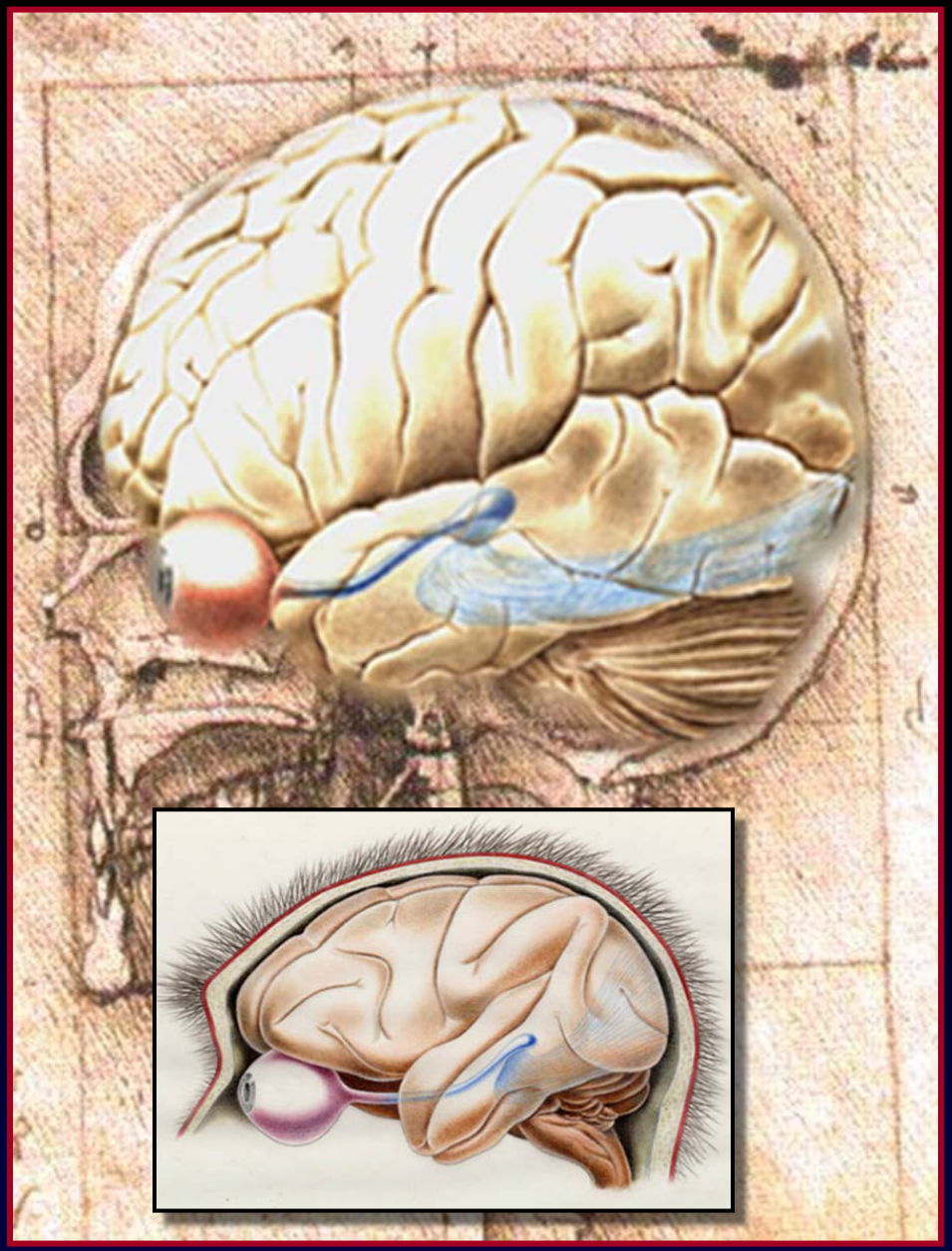
DES-fMRI: State-of-the-Art

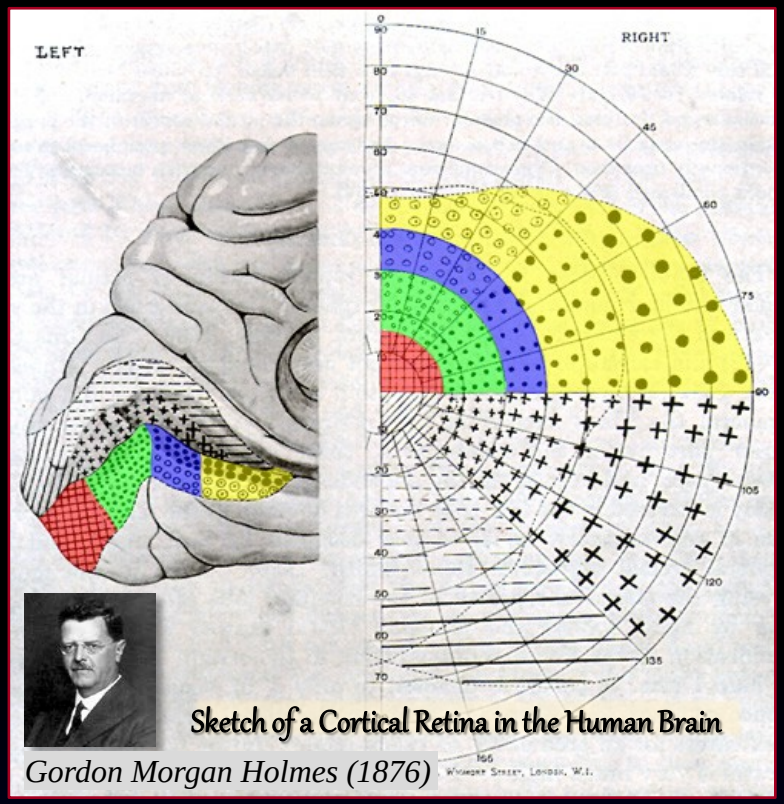
- ❑ Rheobase/Chronaxie excludes smooth-muscle excitation
- ❑ Overlap of Phys- and BOLD-Defined Current-Spread
- ❑ BOLD-fields ~2.5mm larger than neuronal-fields
- ❑ PBR reflect field potentials
- ❑ NBR reflect reduction of MUA

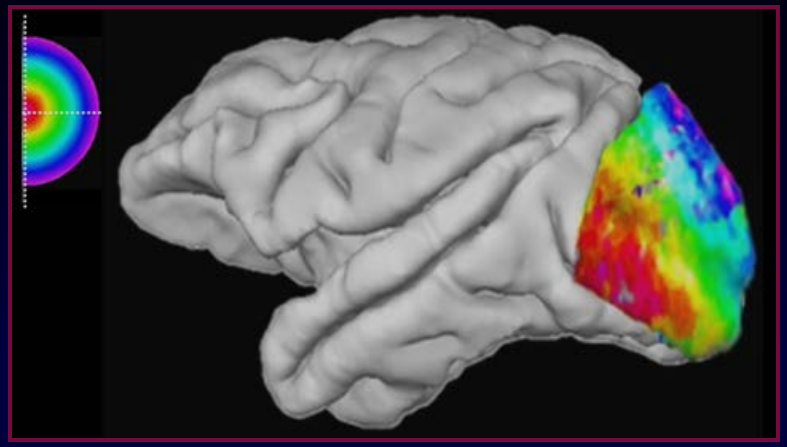
Layout of the Talk

- ❑ DES of Striate Cortex (V1)
- ❑ DES of Thalamic Nuclei (e.g. LGN & Pulvinar)
- ❑ DES & pharmacology in the Visual System
- ❑ DES & Lesion-Studies in the Visual System
- ❑ Optogenetic Stimulation of the LGN Konio-System
- ❑ DES of Hippocampus & LC

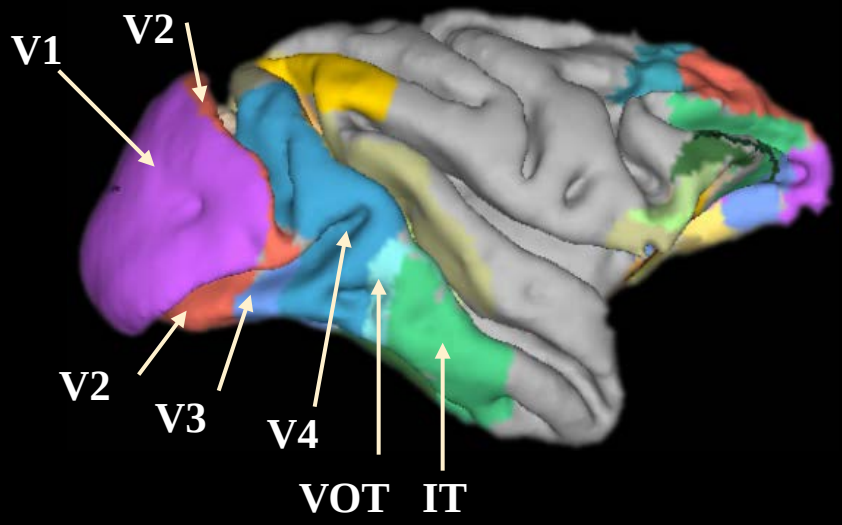
DES in Structures of the Visual System

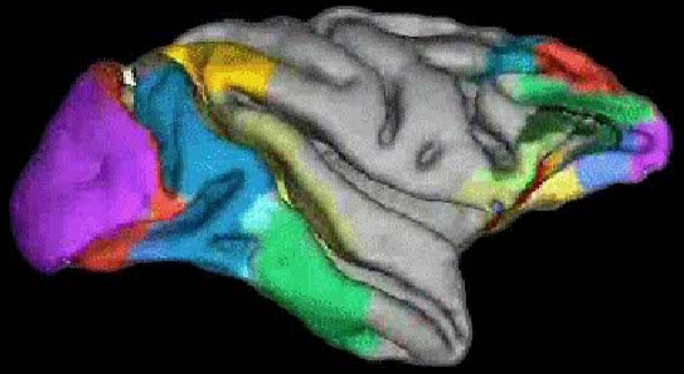




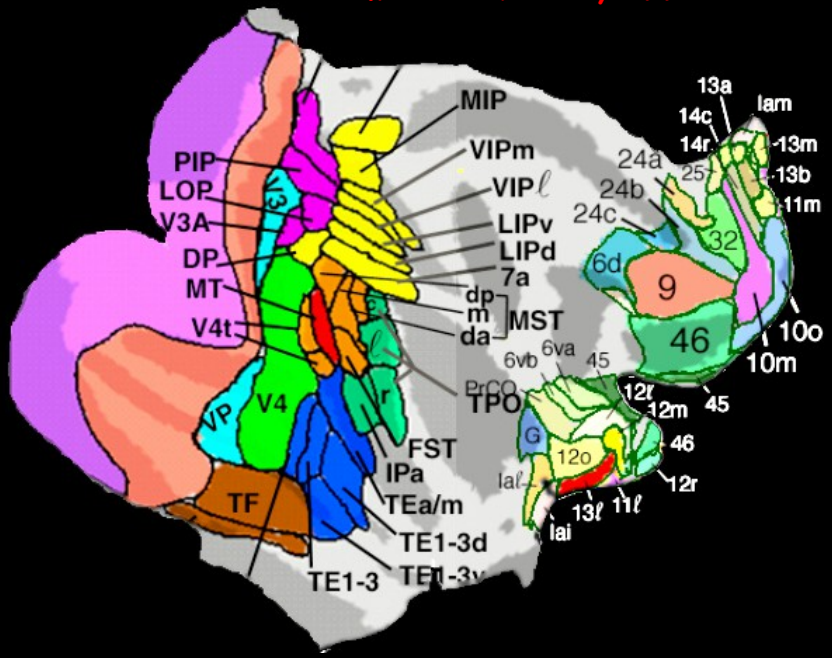


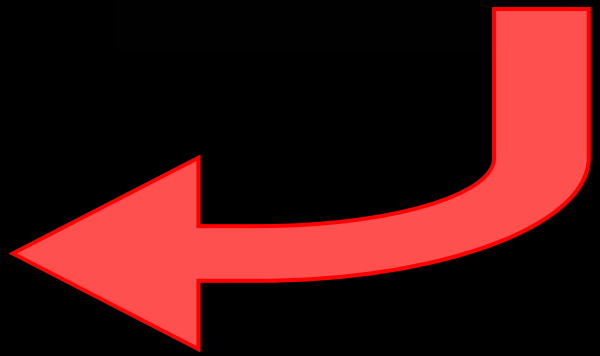
Visible & Hidden Visual Areas Beyond Striate Cortex





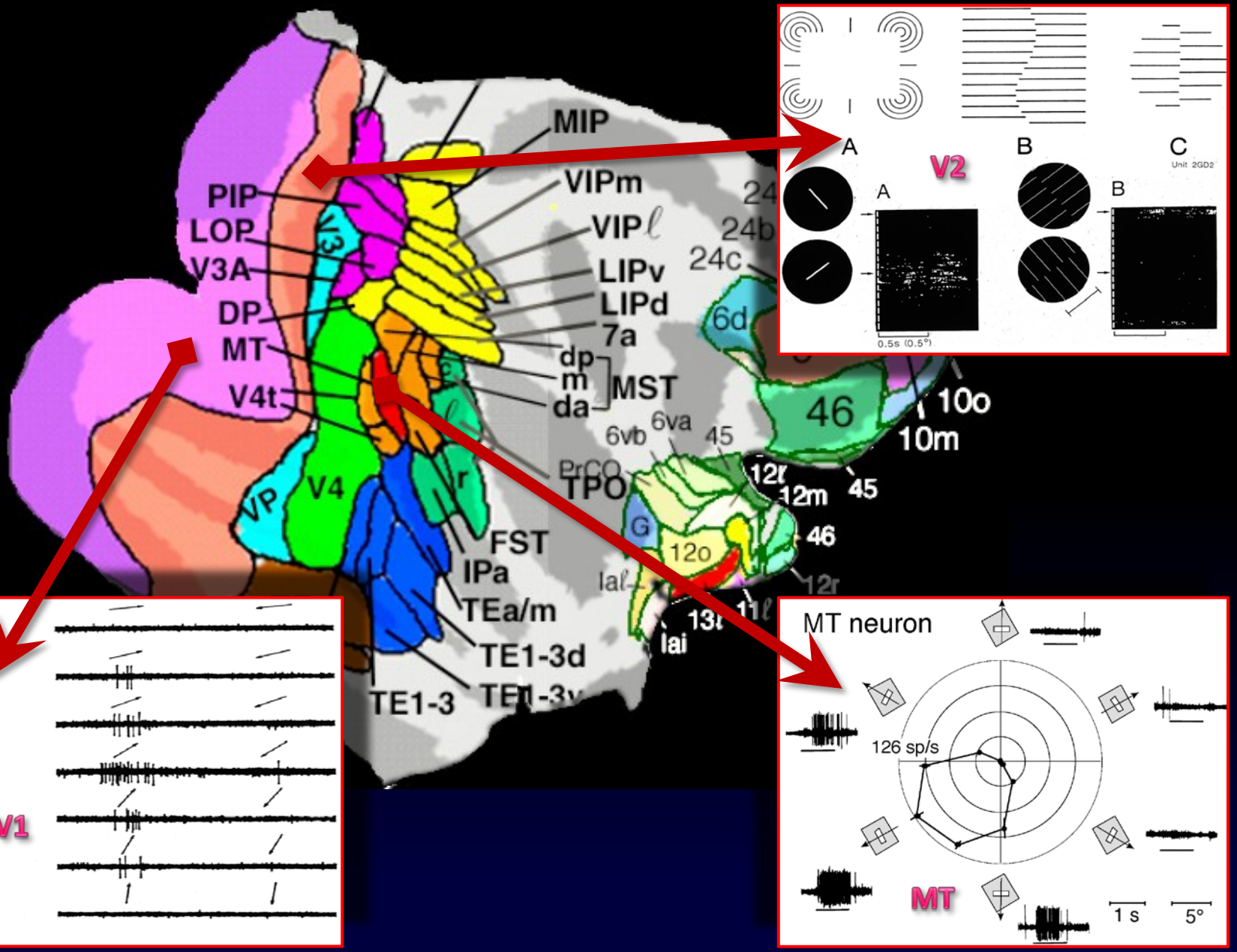
Lewis & Van Essen, 2000
Carmichael & Price, 1994



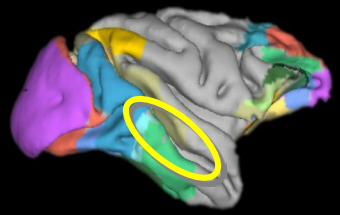


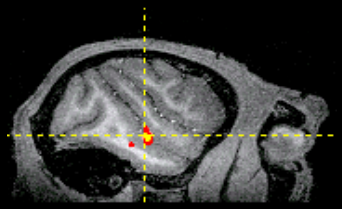
Visualization/Analysis: Caret & Surface-Based Atlases
Van Essen Lab, Washington University, St. Louis

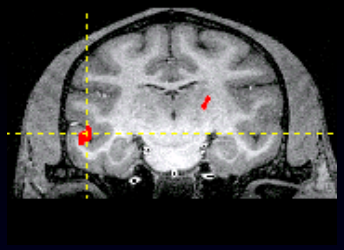
Neuronal Selectivity in areas V1, V2 & MT (V5)

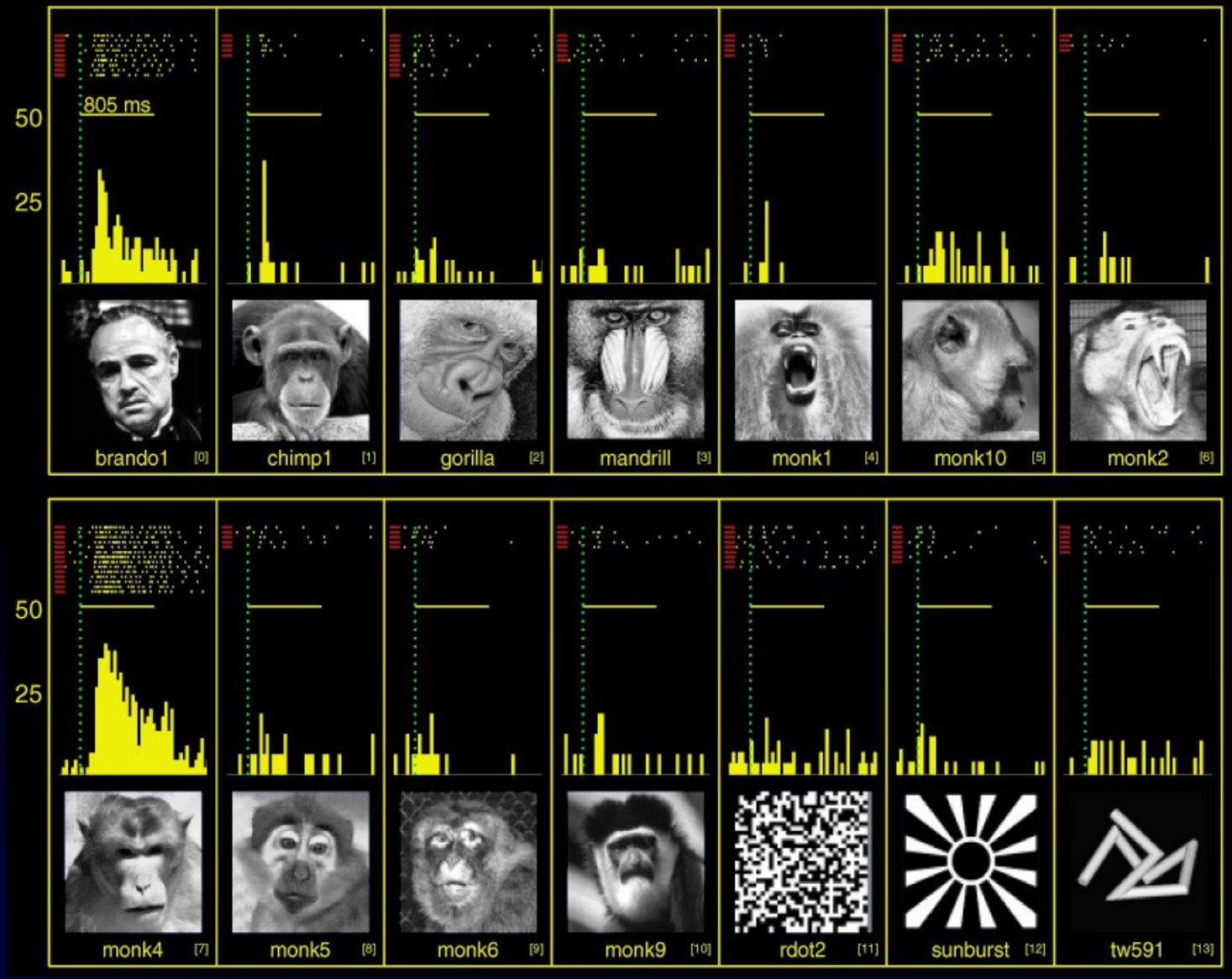


Neuronal Selectivity in areas in ITC (Top-14 out of 300)



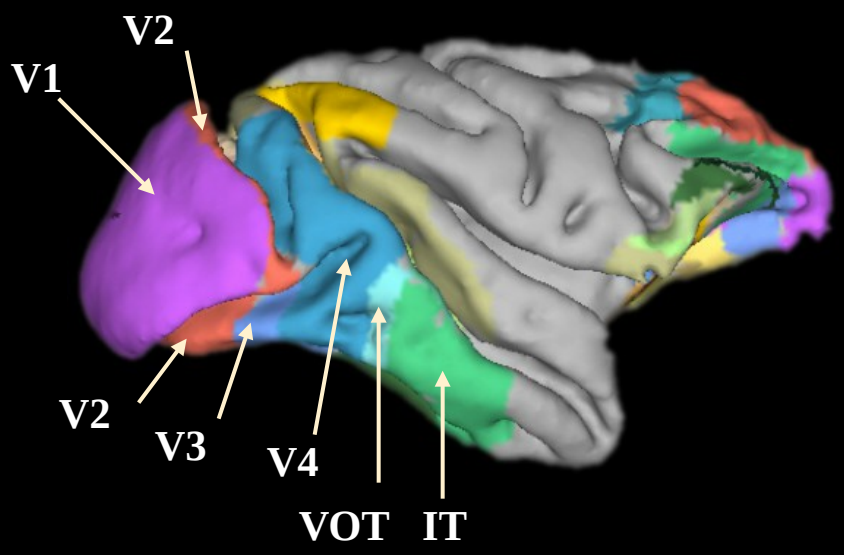


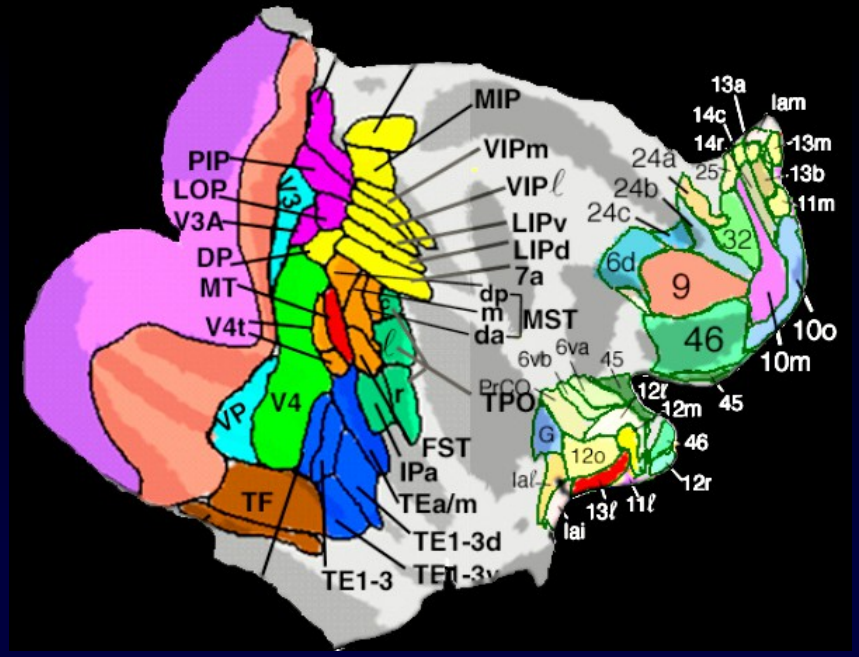


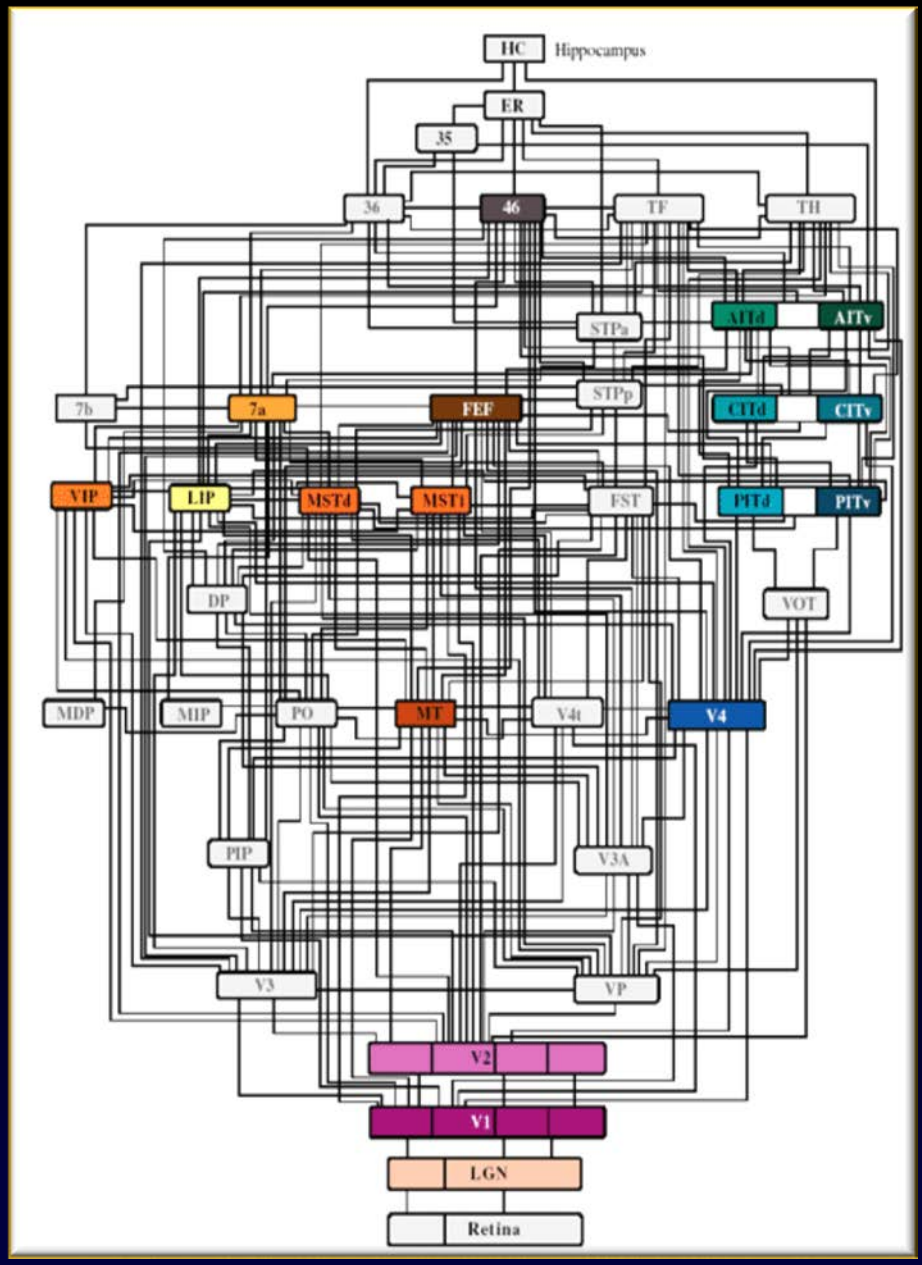


150 Spikes per Second

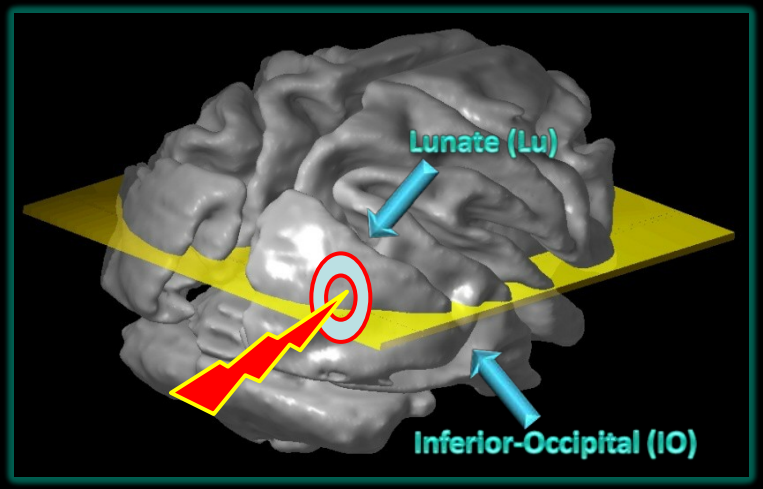
Hierarchical Processing in the Visual System

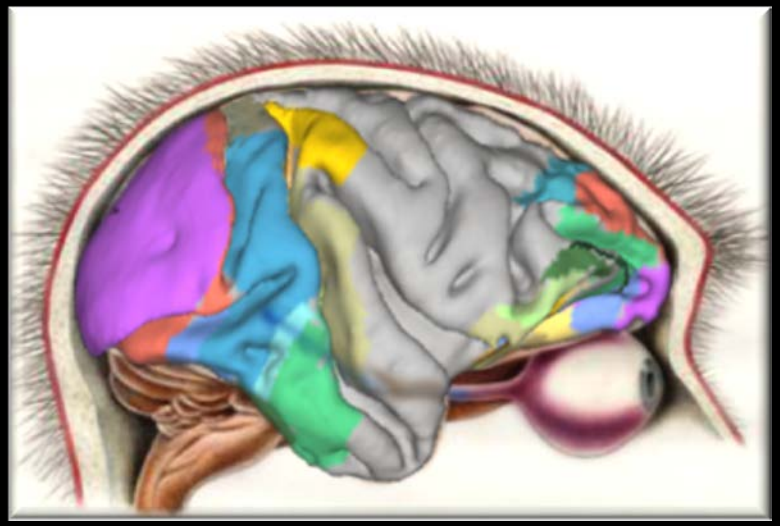


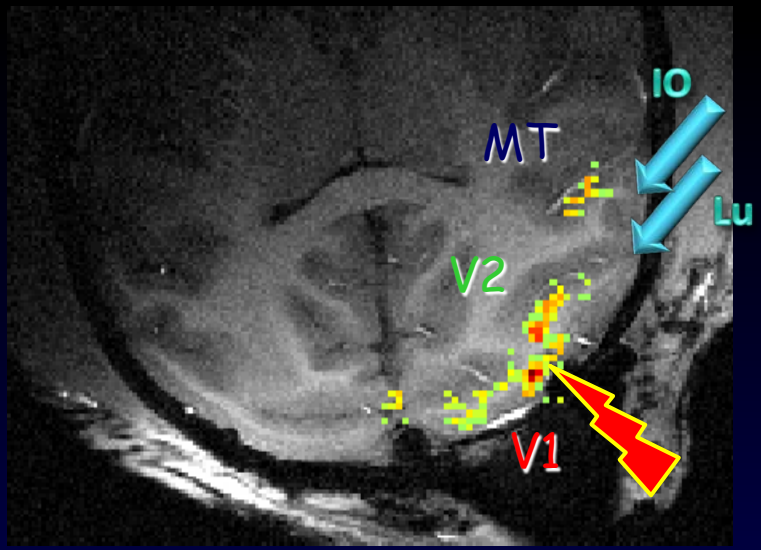


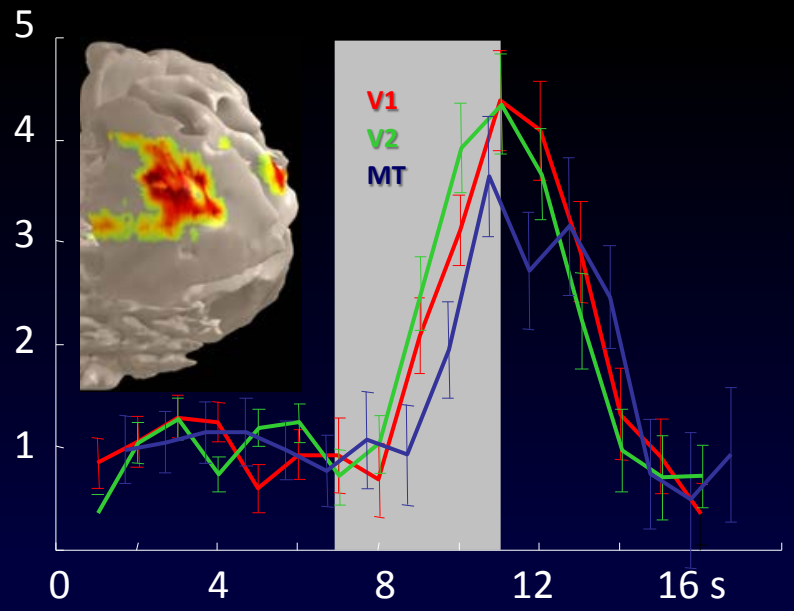


DES-fMRI – Activated Sites during DES of Primary Visual Cortex (V1)



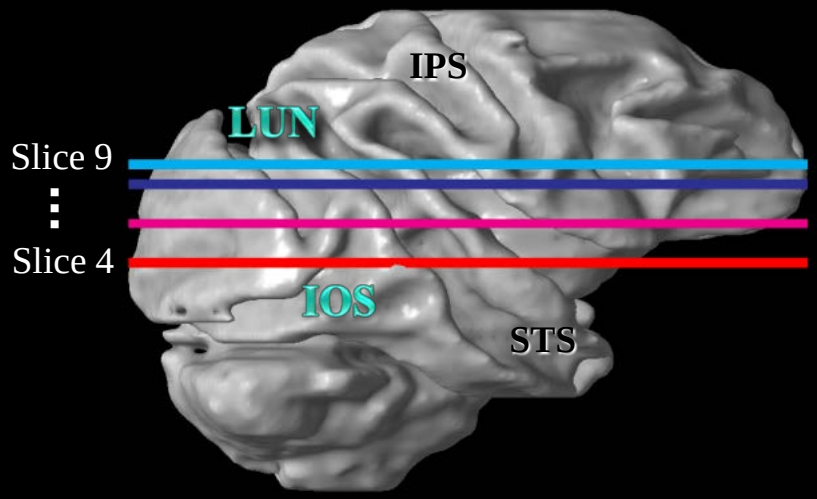


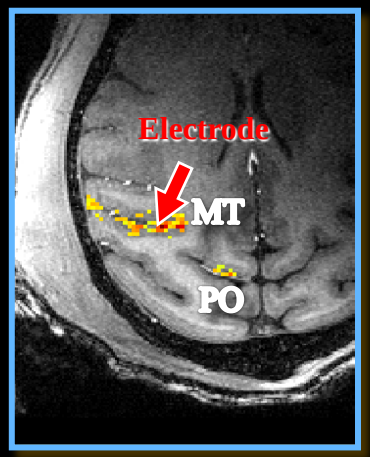


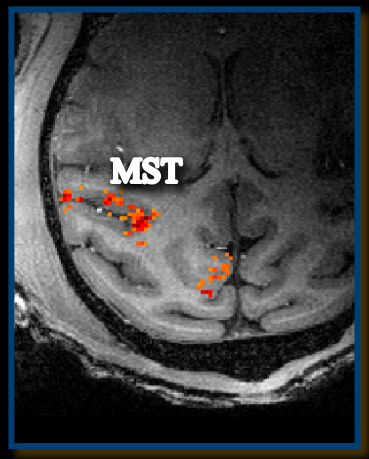


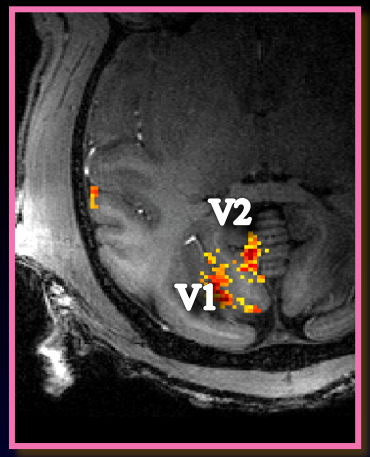
Tolias et al, Neuron 2005; Sultan et al, MRI 2006

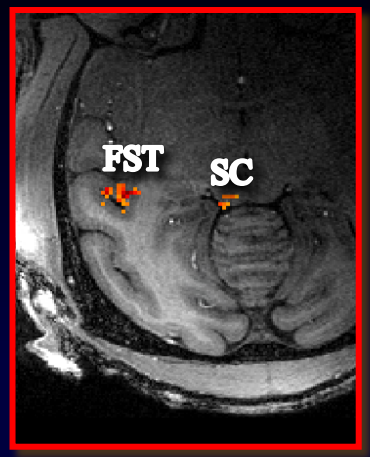
DES-fMRI – Activated Sites during DES of Association Visual Cortex (V5/MT)

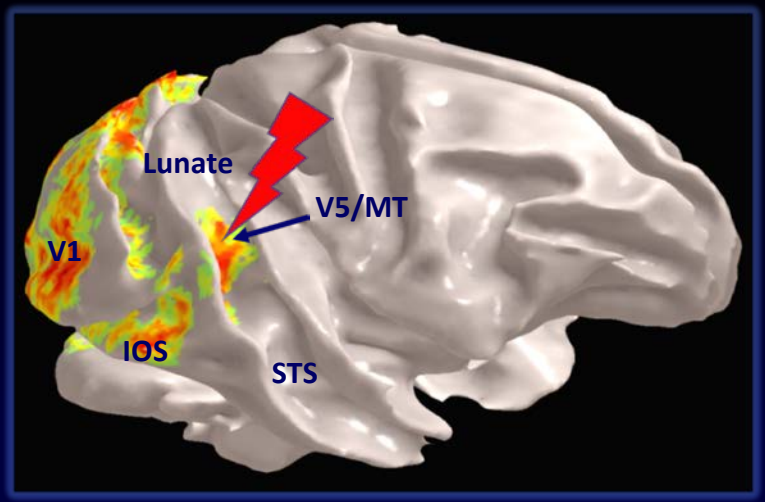








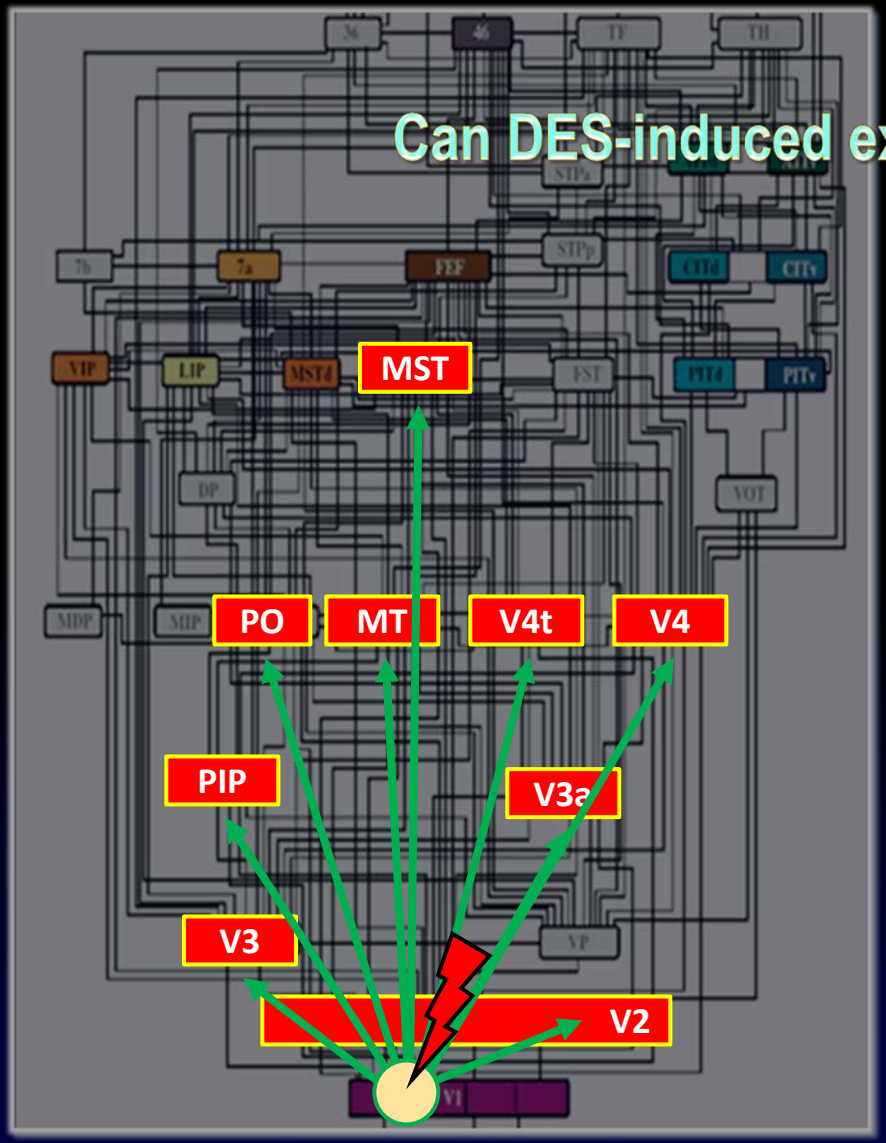




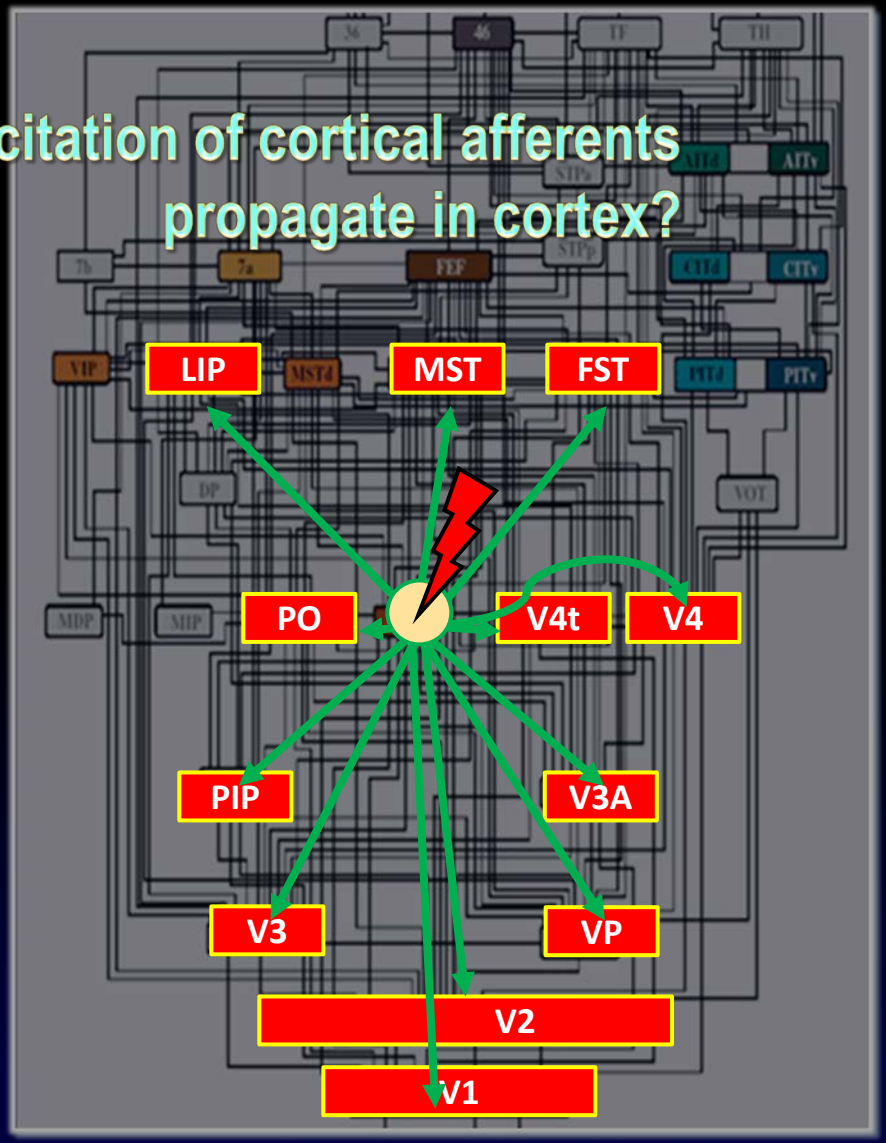
Sultan et al, MRI 2006, 2007

DES-fMRI Maps the Monosynaptic Targets of a Stimulated Area

V1 Stimulation



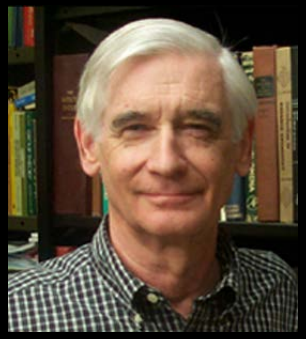
V5 (MT) Stimulation



Can DES-induced excitation of cortical afferents propagate in cortex?

Diagrams: Felleman, D.J.; Van Essen, D.C. Cer. Cortex 1991; Tolias et al 2005

What is Stimulated During DES (& DES-fMRI)



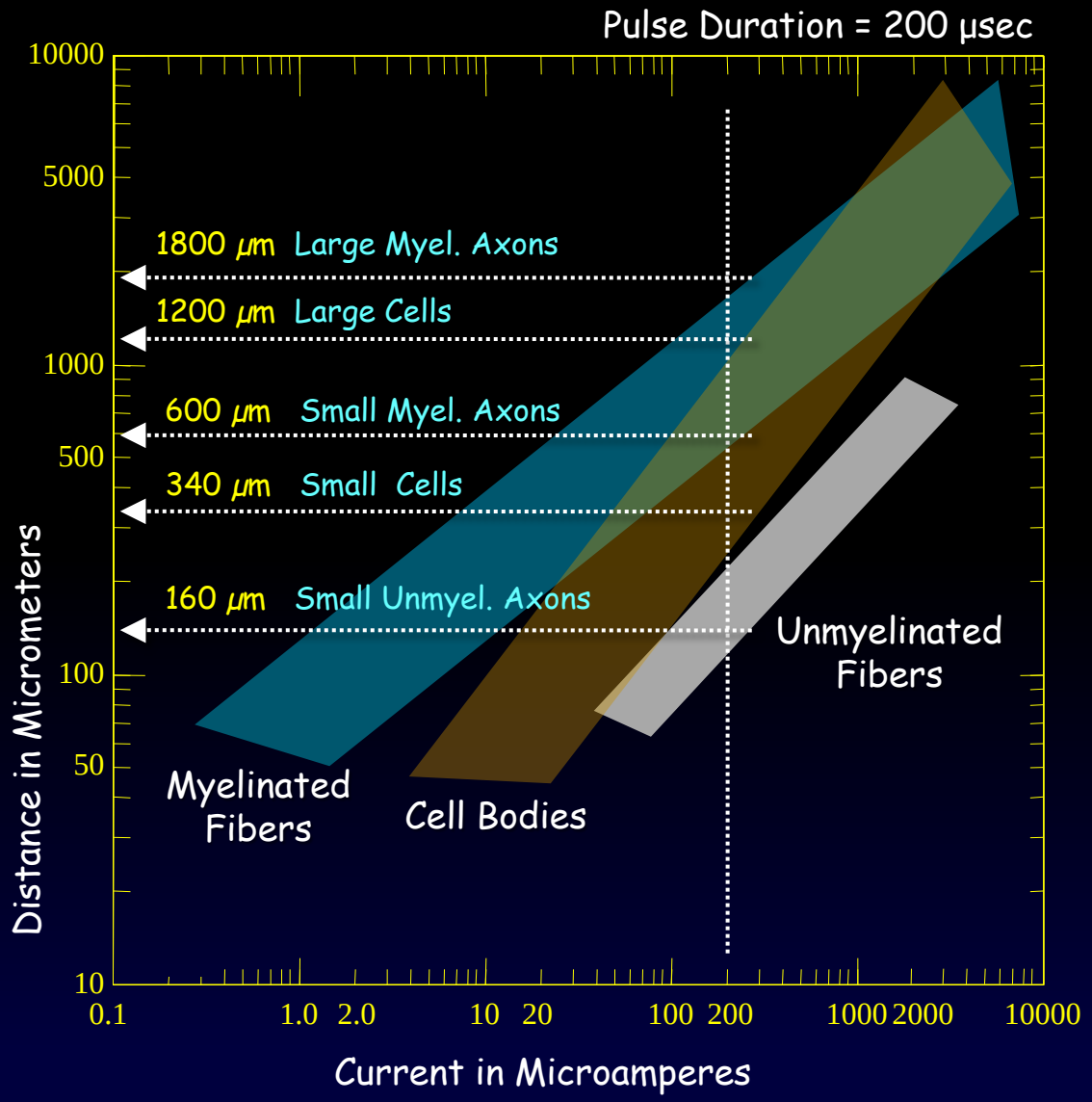
"…electrical stimulation of the lateral hypothalamus"

is a shorted version of the statement that

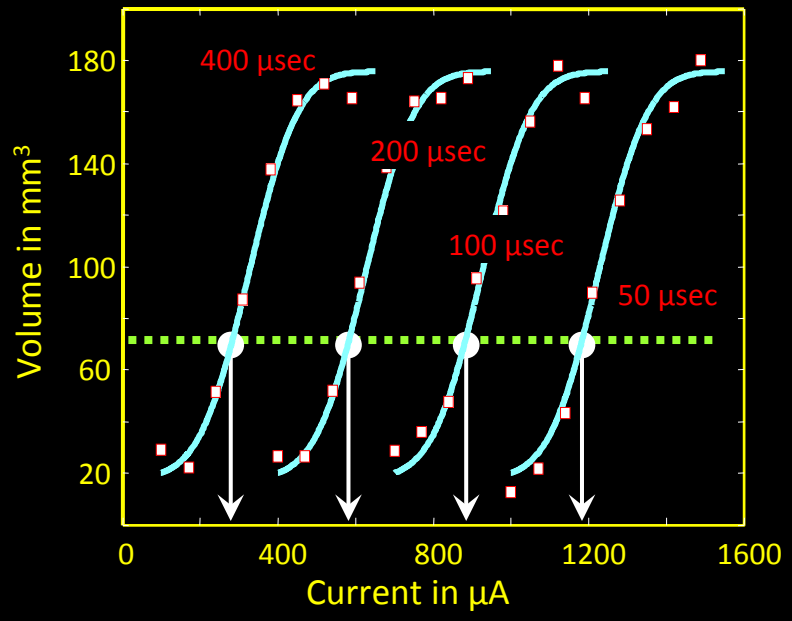
"there was a stimulating electrode in the lateral hypothalamus which affected an unknown number and unknown kinds of cells at unknown locations in the vicinity of the electrode…"

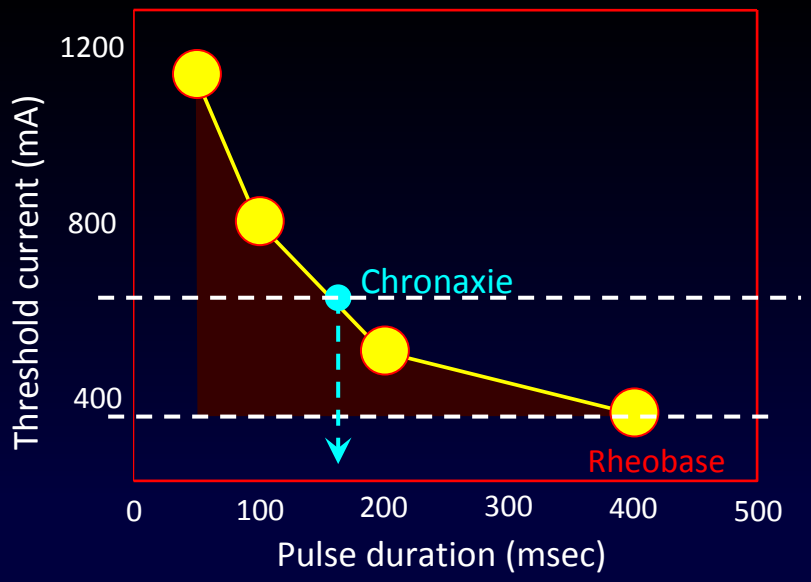
James B. Ranck Jr 1975

… About 40 percent of all DBS-treated patients experience a multitude of serious adverse events; They include psychiatric disorders, and other nervous system or cardiac disorders…



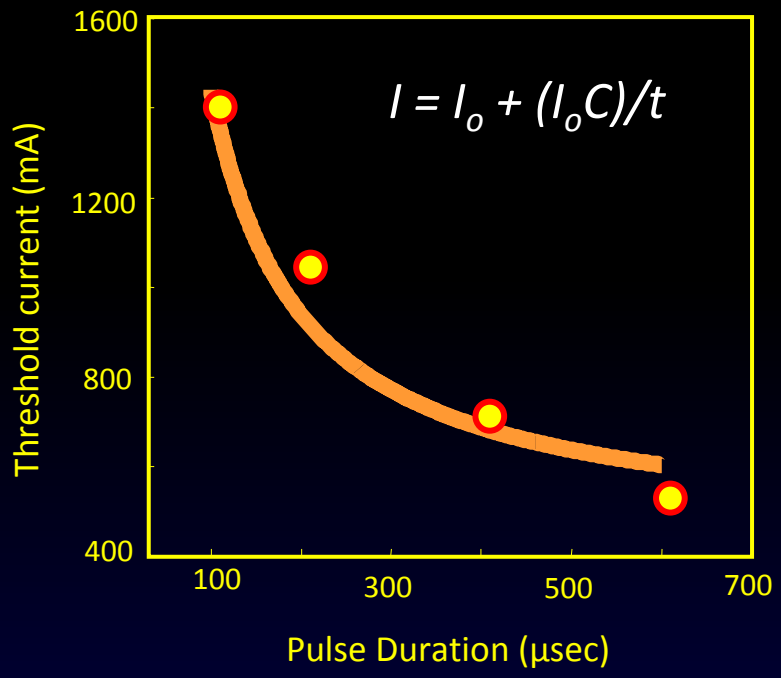
Source of fMRI-Activations: Neurons or Smooth-Muscles?





Strength – Duration Relation from BOLD-fMRI Measurements

Tested Durations	50 to 300 µsec
Threshold Volume	40% of max-volume

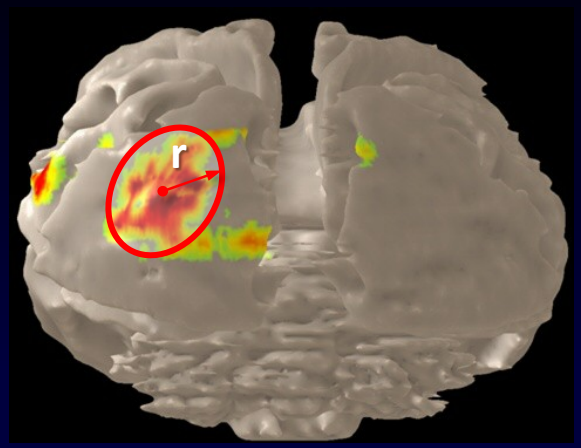


Rheobase 456 µA

Chronaxie 221 µsec (w/ Weiss-Method)

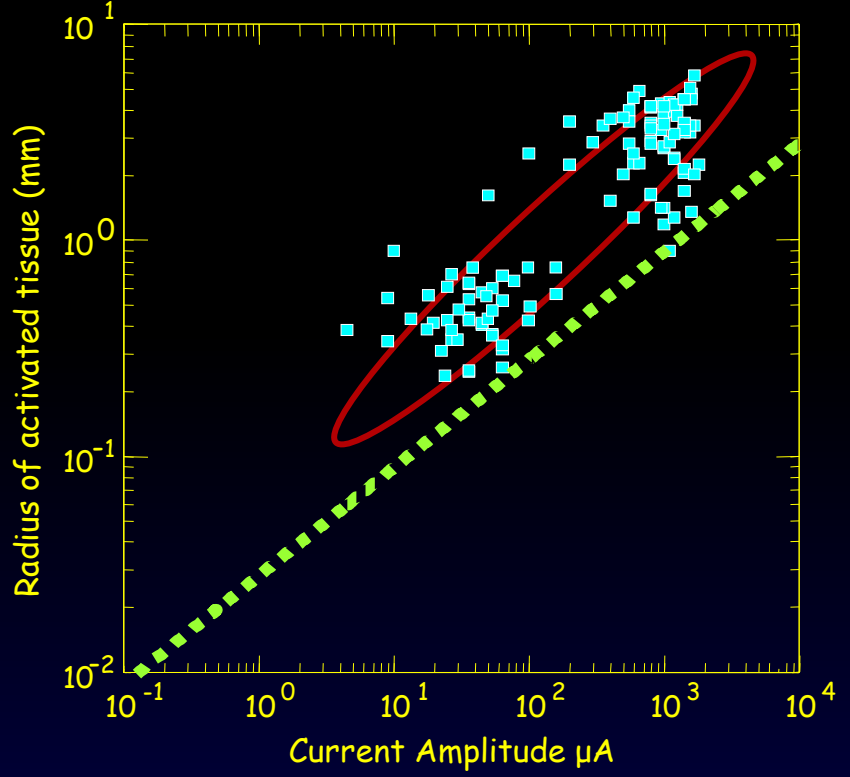
Tolias et al, Neuron (48) 2005

BOLD Excitation Field & Physiologically Defined Current-Spread



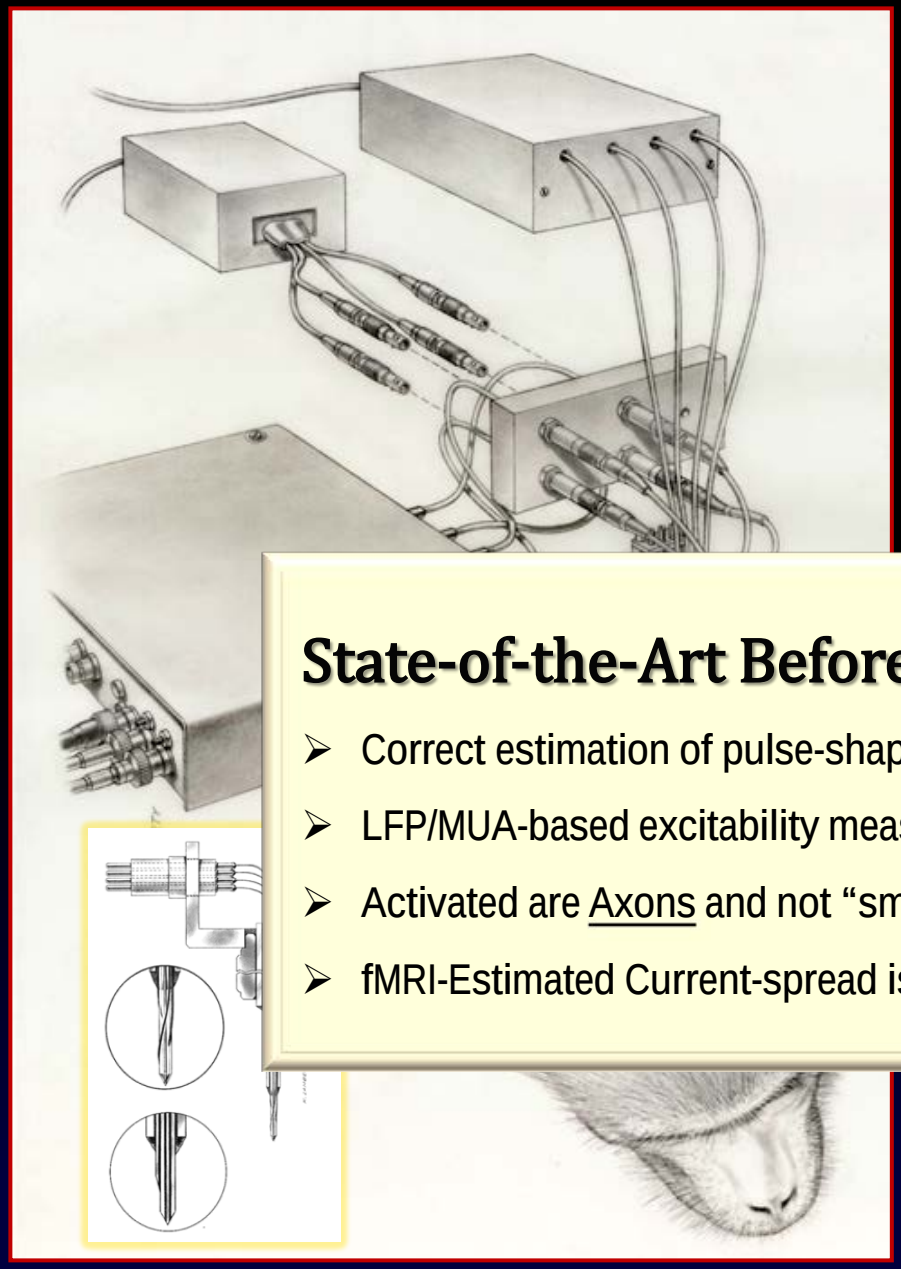
$$I = K r^2$$

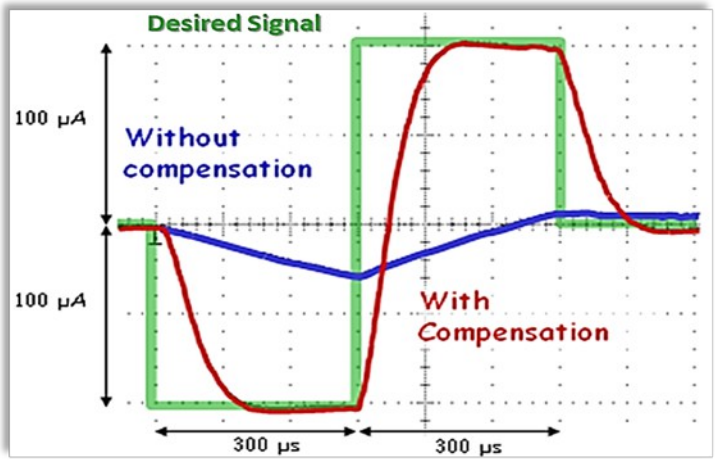
K=1292μA/mm² by Stoney et al., 68



Tolias et al, Neuron 2005; Sultan et al, MRI 2006

Custom-Made Current Sources & Optimization of Electric-Pulses





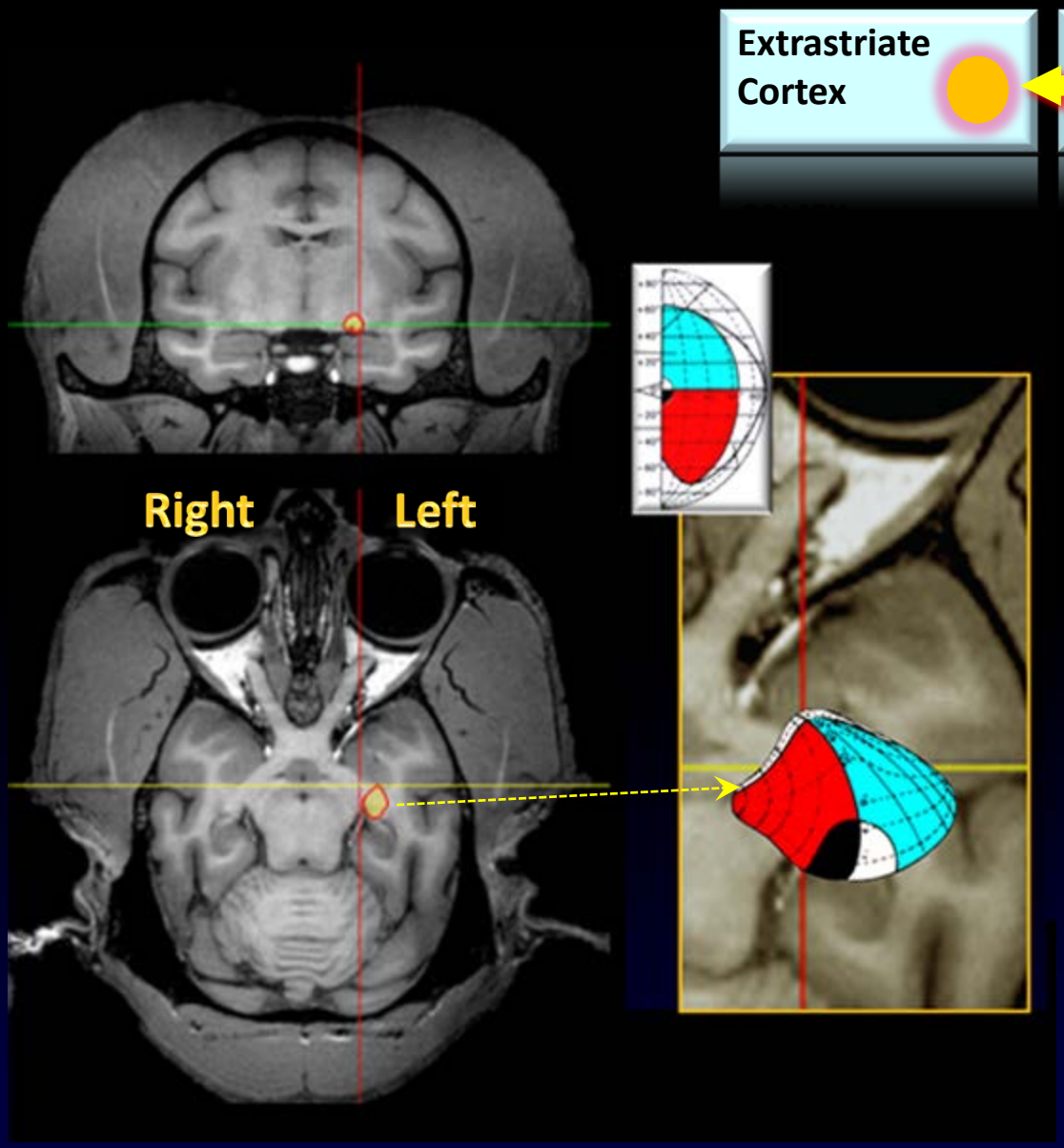
State-of-the-Art Before Starting DES-LGN

- Correct estimation of pulse-shape and strength
- LFP/MUA-based excitability measurements are similar to those obtained with fMRI
- Activated are Axons and not "smooth muscles" or other irrelevant elements
- fMRI-Estimated Current-spread is consistent with Field-Potential Recordings

Symmetrical-Biphasic (charge-balanced)
On/Off 200-300 / 400-600msec
Variable pulse-duration bursts (50-200µsec)
Current Intensity (50-400µA)
Frequency (1-250Hz)

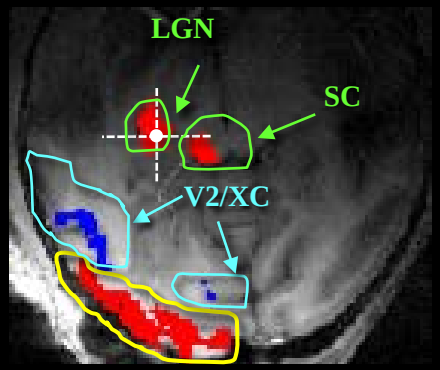
Goense, et al., 2008; Oeltermann et al. 2007a; Oeltermann et al. 2007b; Pfeuffer et al, 2007; Logothetis et al, Nature, 2001

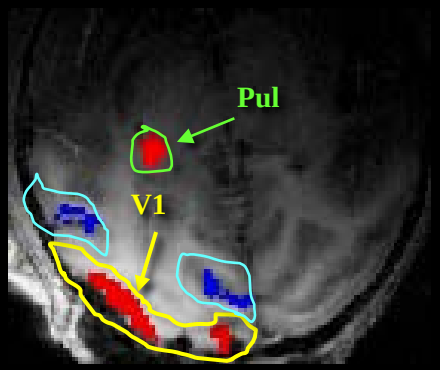
Retino-Geniculo-Cortical Pathway in the Monkey

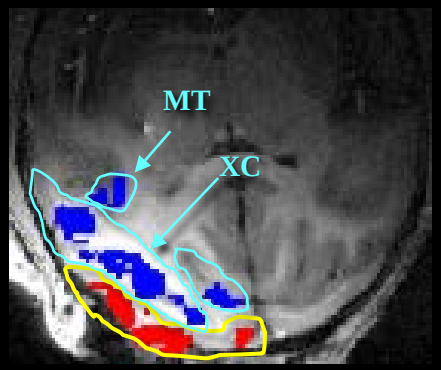


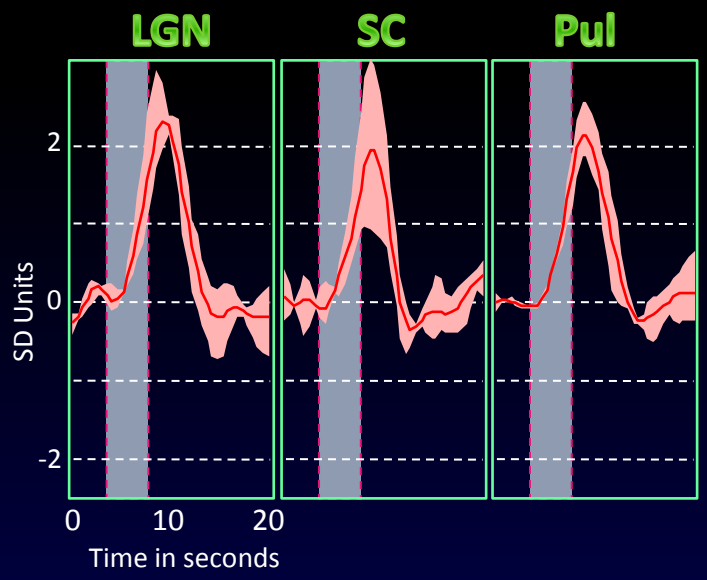
Inset adapted from Malpeli & Baker, J. Co 1975mp. Neur.

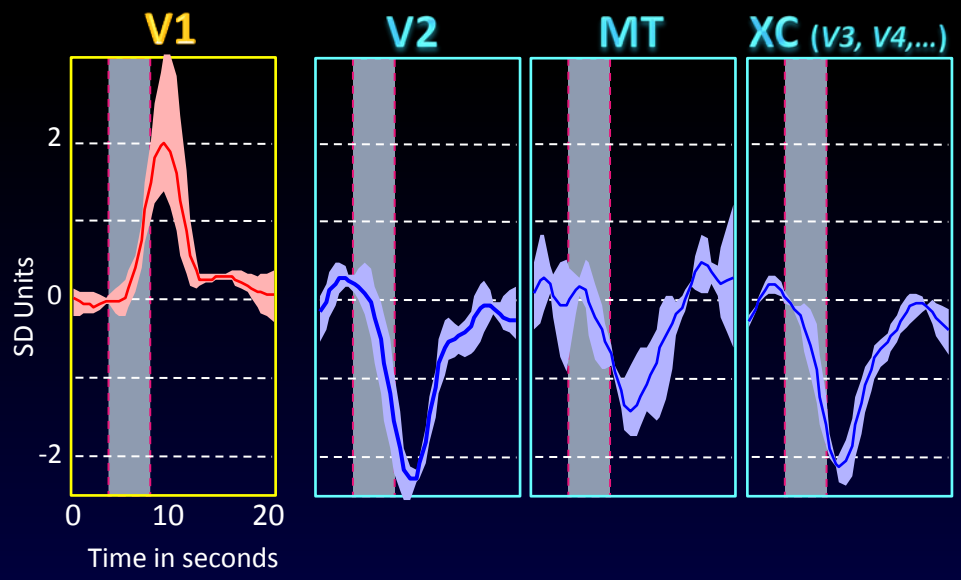
DES-fMRI of dLGN: Cortical Activation & Deactivation Patterns





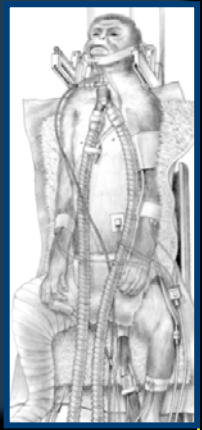




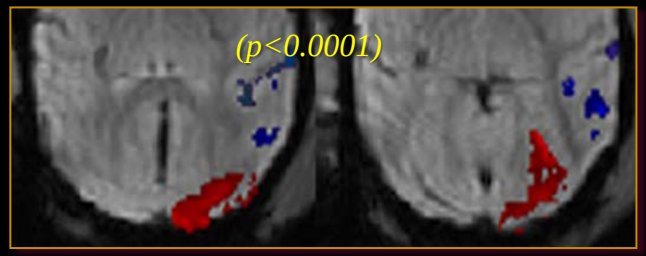


Logothetis et al. (Nat. Neuro. 2010)

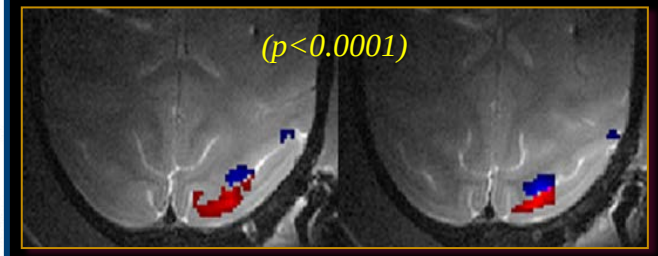
Extrastriate-Cortex Deactivation is Independent of Animal State

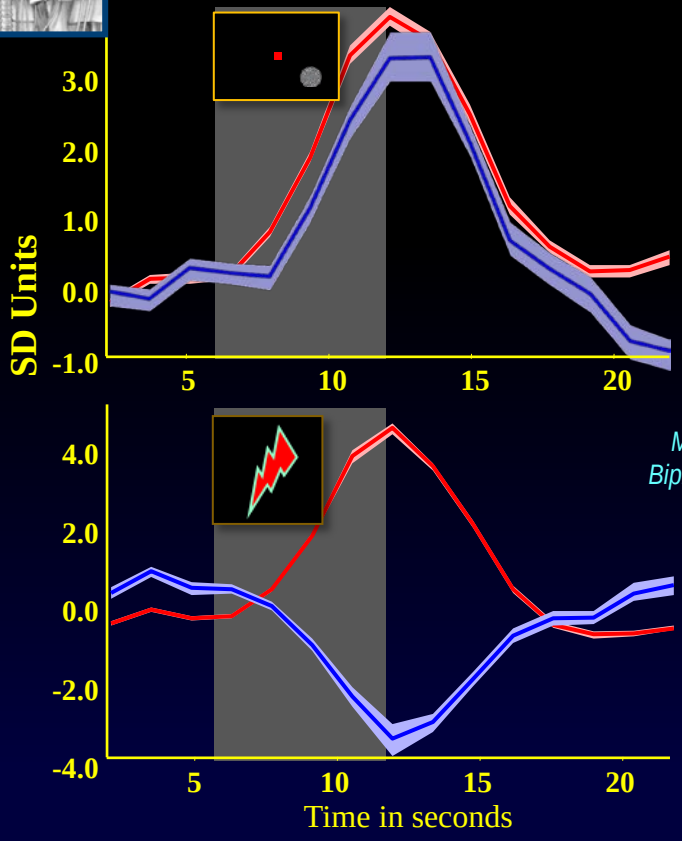


Opiate (Remifentanil) Anesthesia

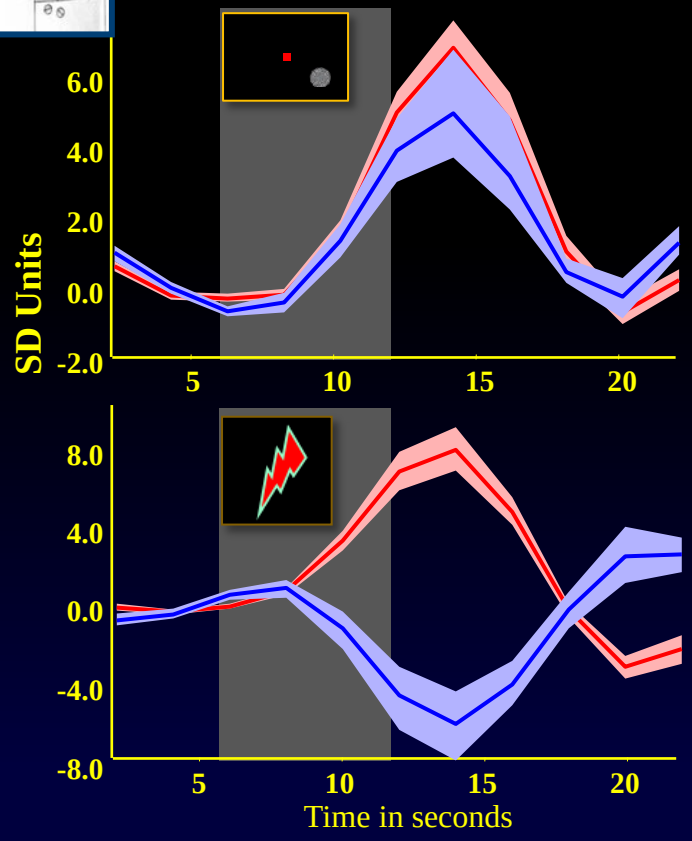


Awake Animal (Fixation Task)



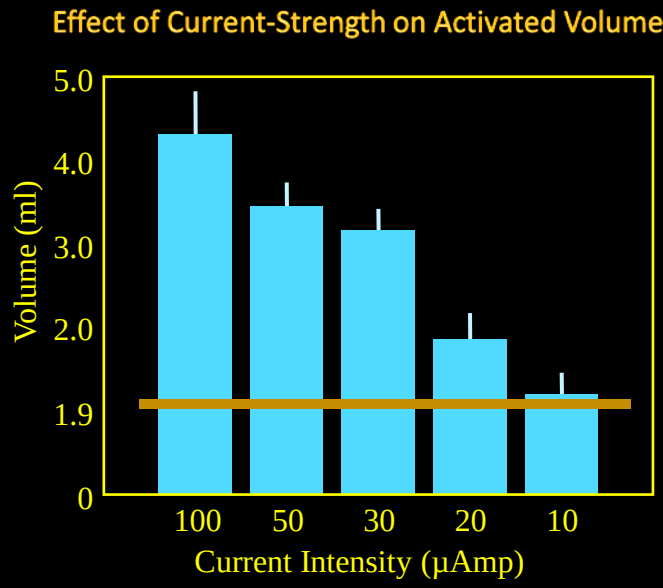


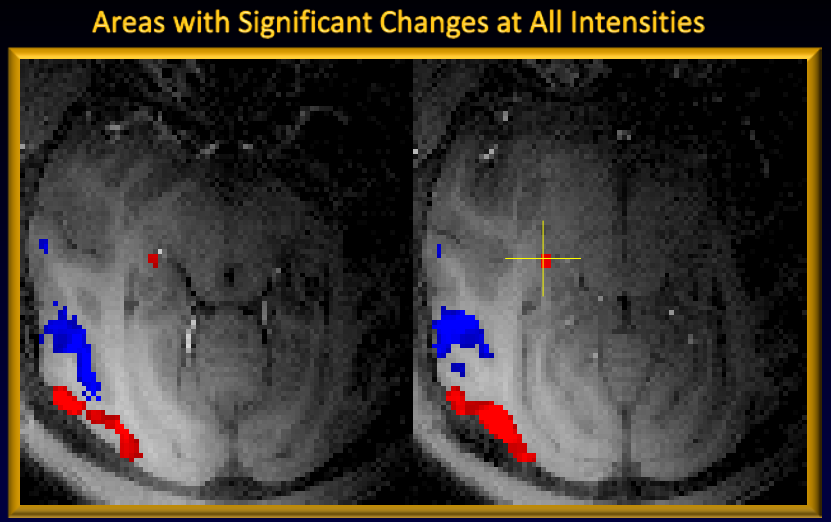
Monopolar Stimulation
Biphasic Pulses (200µsec)
Frequency 100Hz

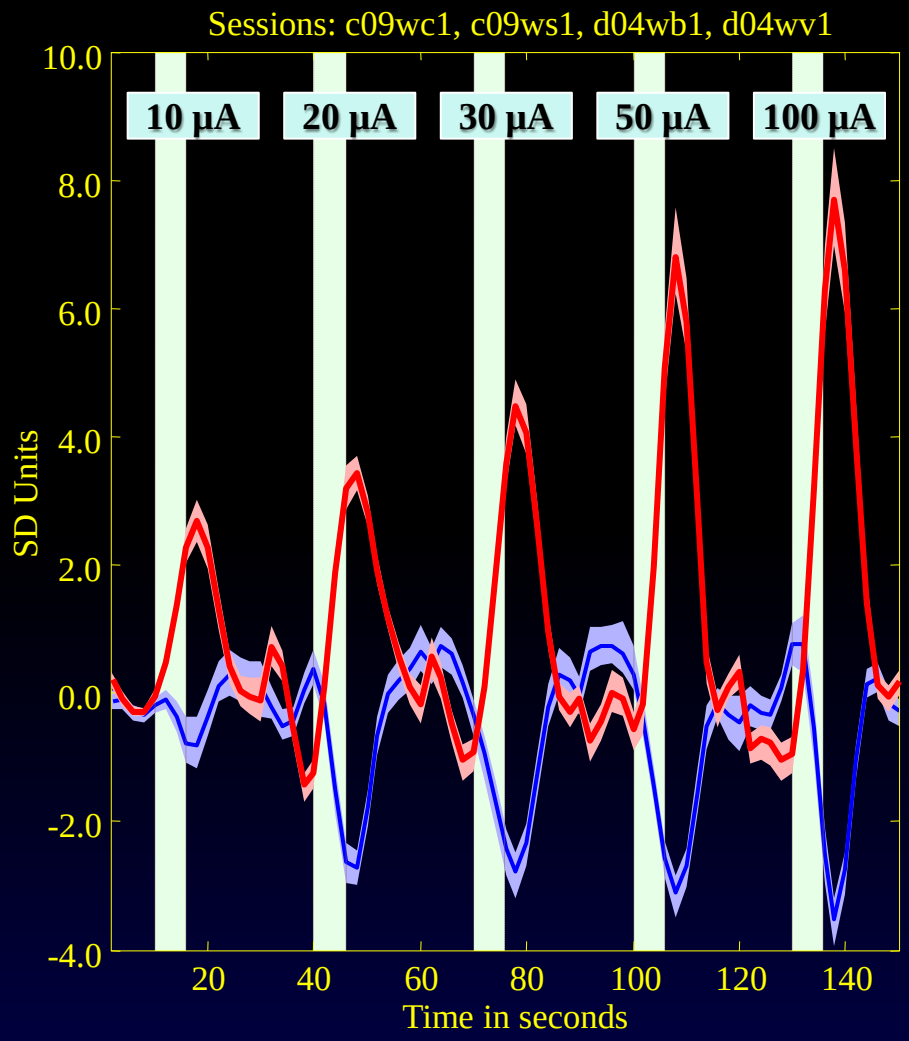


Goense, et al., 2008; Oeltermann et al. 2007a; Oeltermann et al. 2007b; Pfeuffer et al, 2007; Logothetis et al, Nature, 2001; Logothetis et al. (Nat. Neuro. 2010)

… and Independent of Current Intensity (10-450μA)



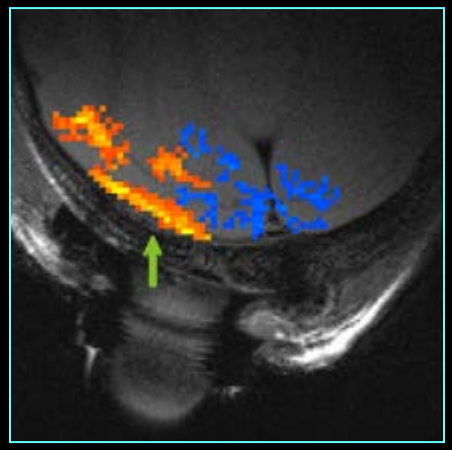




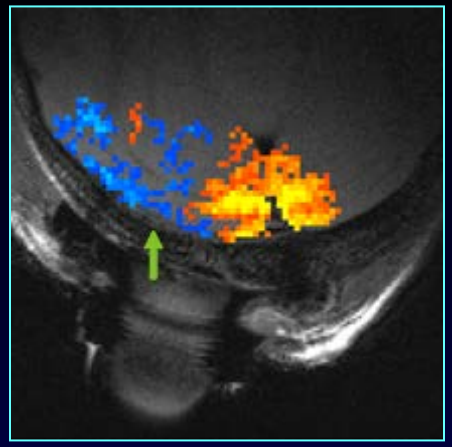
Logothetis et al. (Nat. Neuro. 2010)

Extrastriate-Cortex Deactivation is not related to sensory NBR

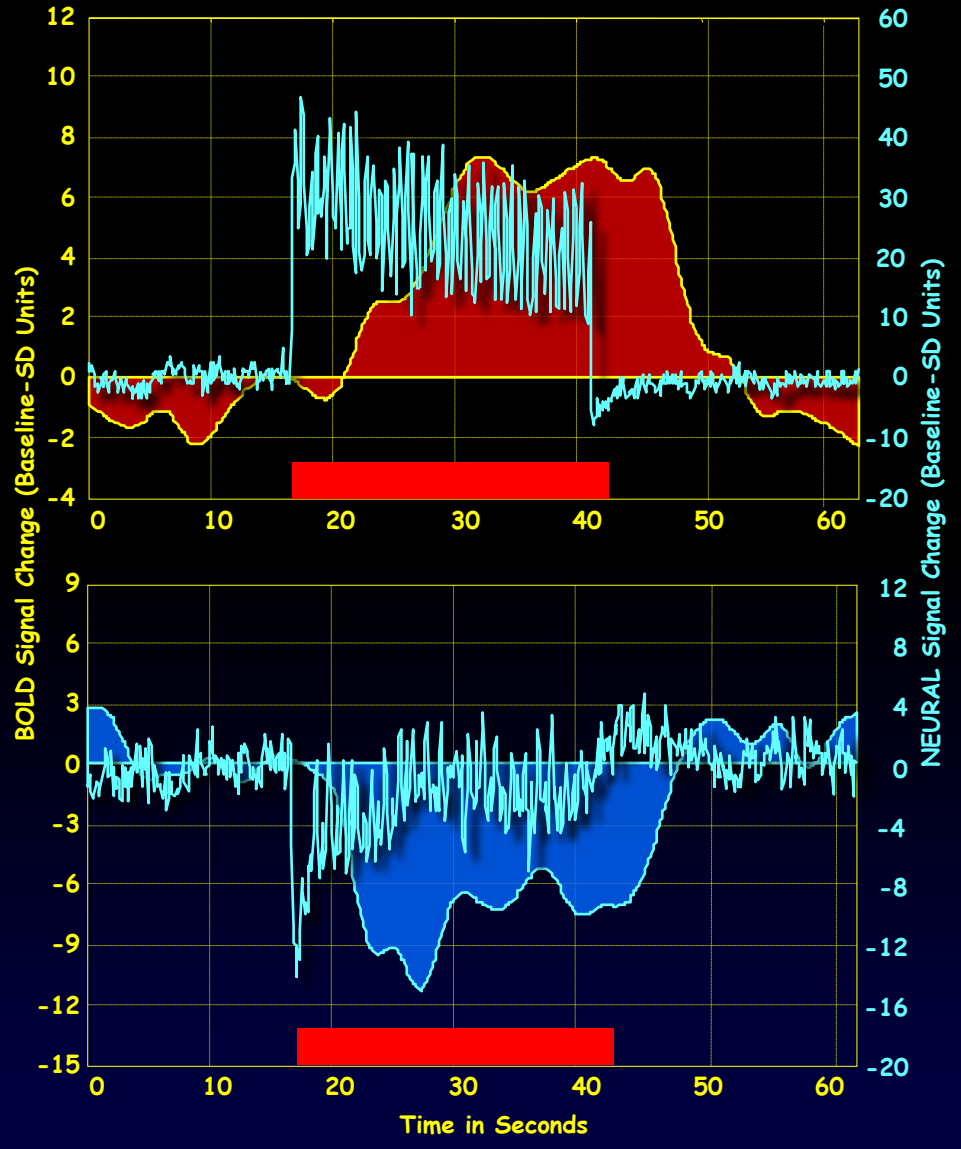
NBR is observed in brain regions that are not directly activated by sensory stimulation, and often occur together with PBR within a single cortical area…



3.5°-6.1°



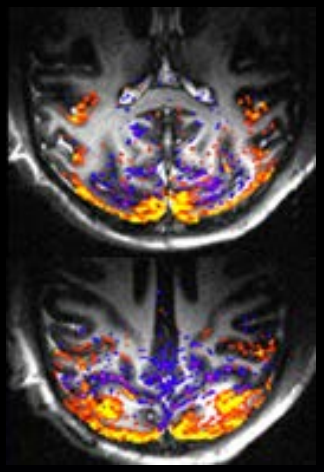
8.5°-14.7°

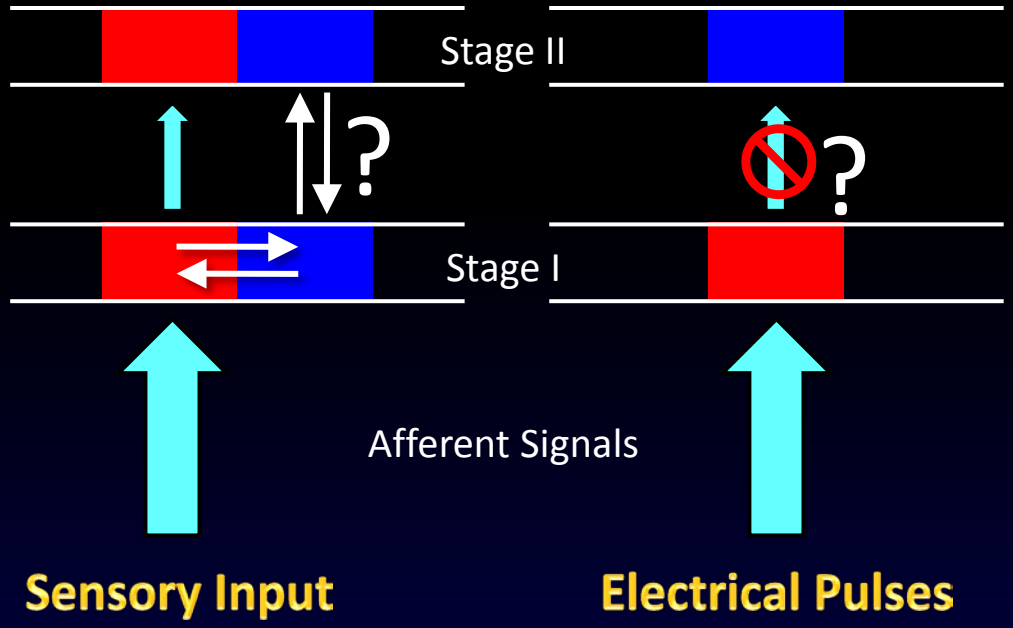


Shmuel et al. Nat Neuro 2006; Logothetis et al, Nature, 2001

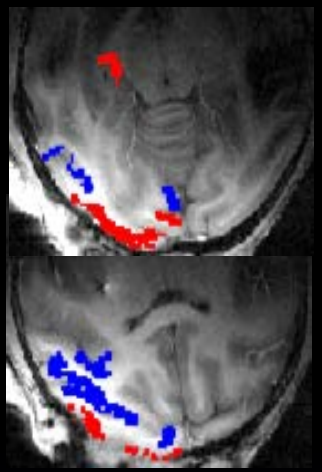
Tow Different Types of Cortical Negative BOLD Responses

Negative BOLD during sensory stimulation



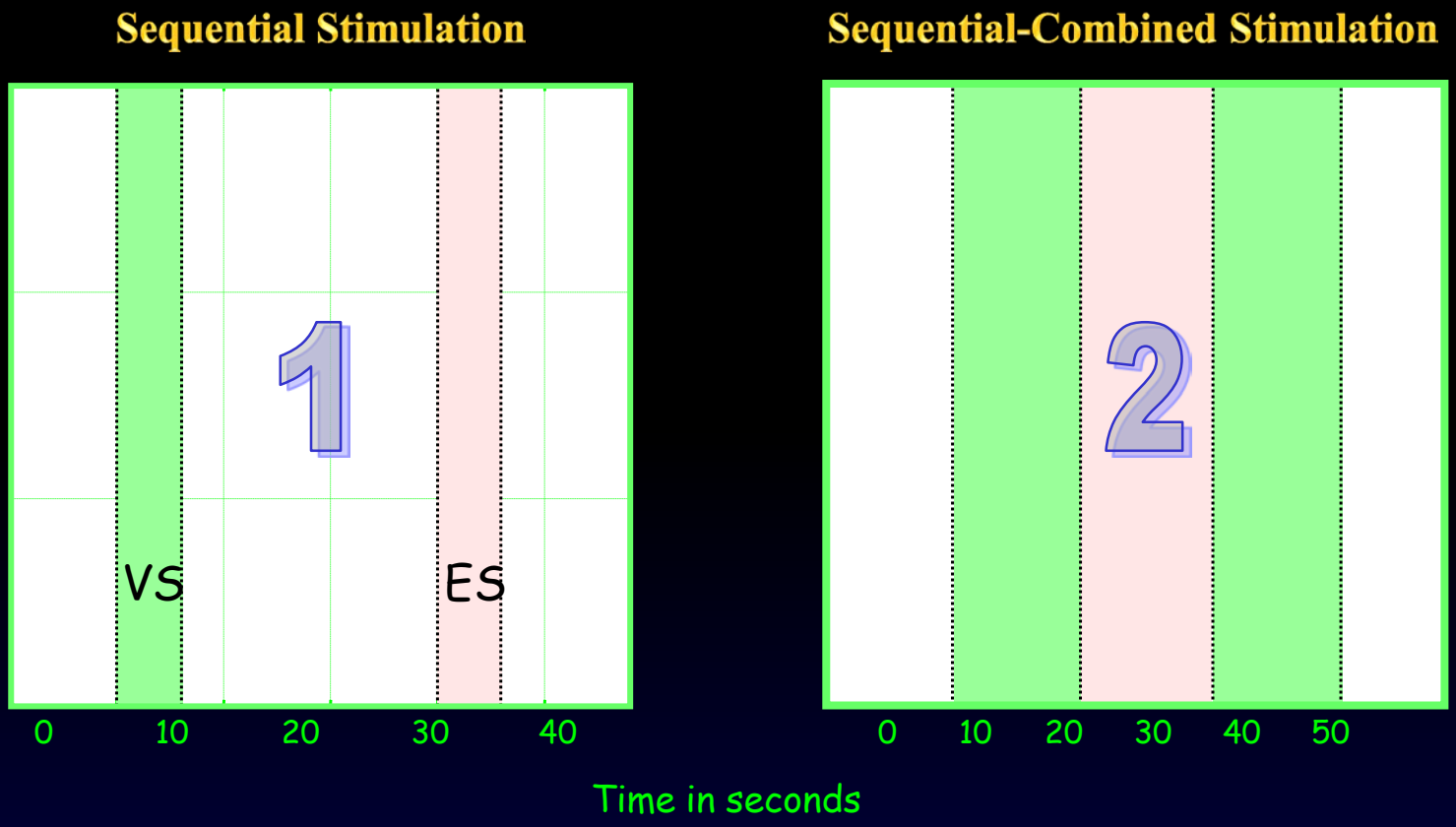


Negative BOLD during electrical stimulation



Logothetis 2002; Shmuel et al, Nat Neuroscience 2006

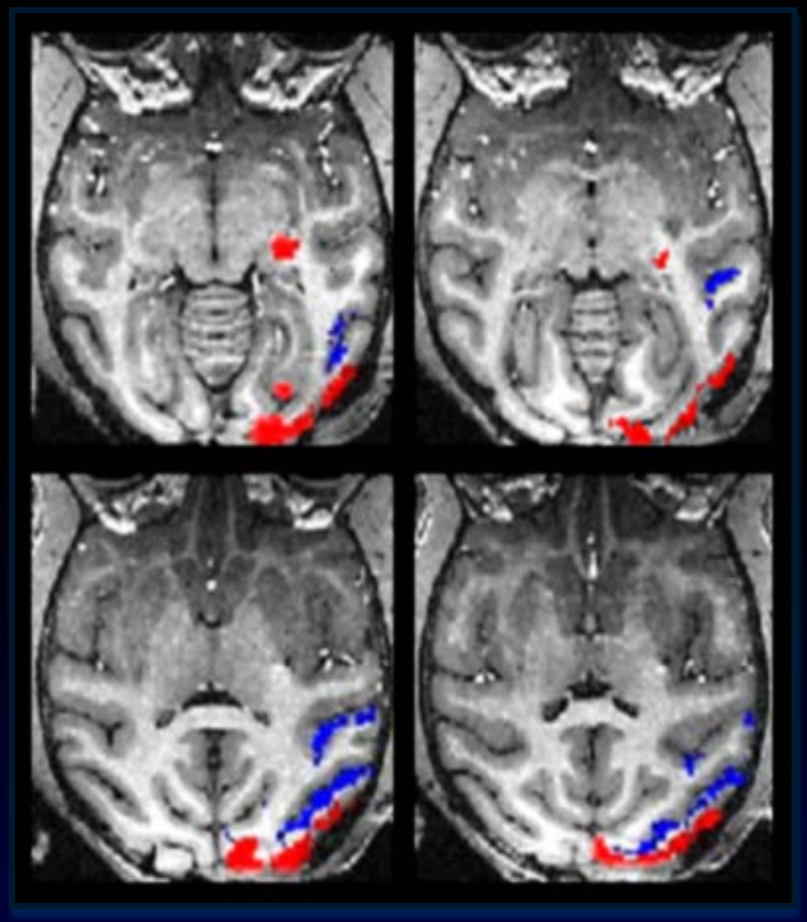
Mixed Event-Related Designs

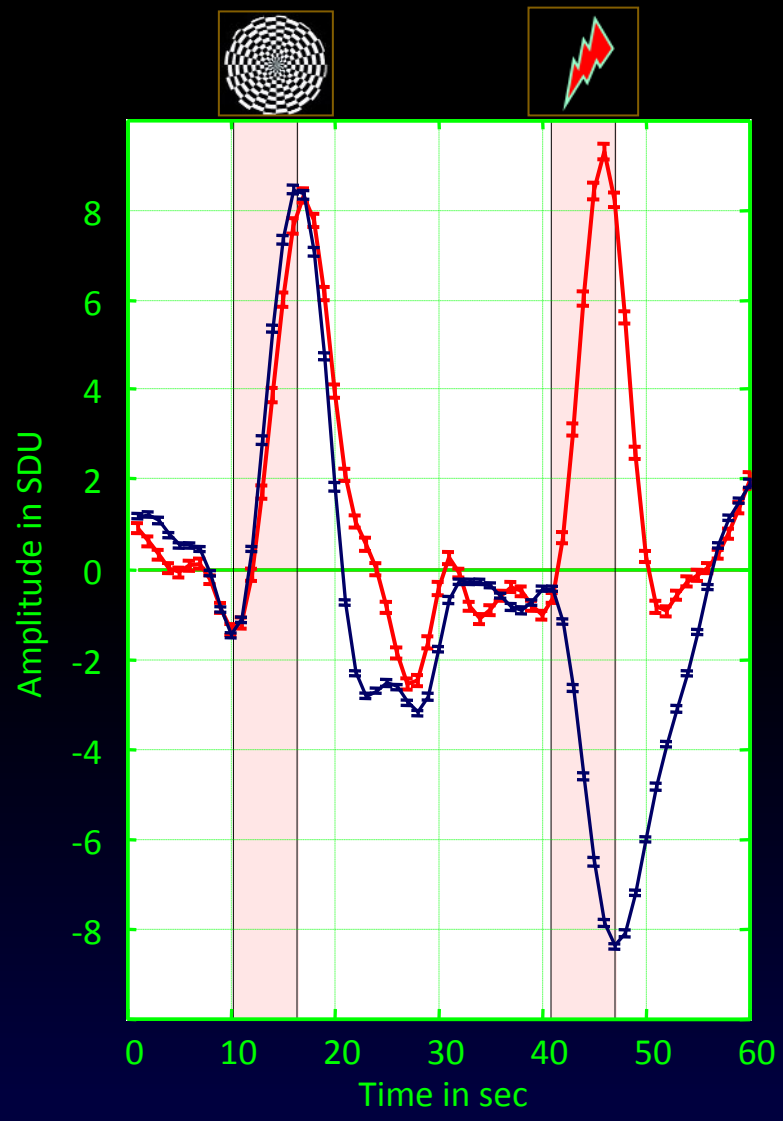


Logothetis et al. (Nat. Neuro. 2010)

Visual and Electrical (dLGN) Stimulation: Sequential Design

BOLD signal increases and decreases in striate and extrastriate cortex respectively

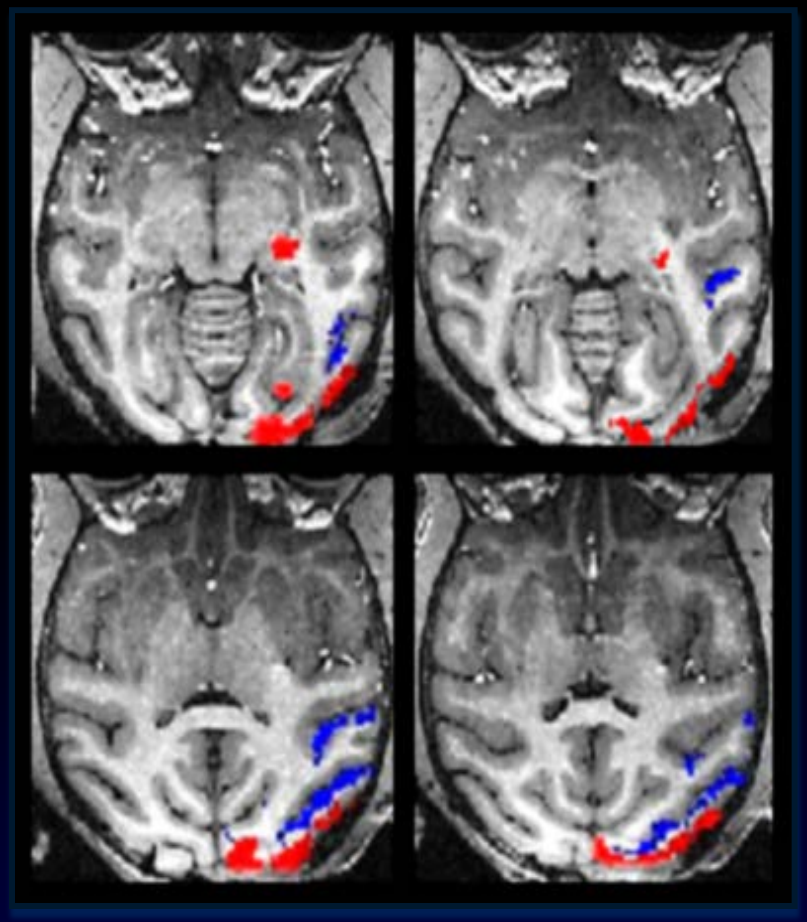


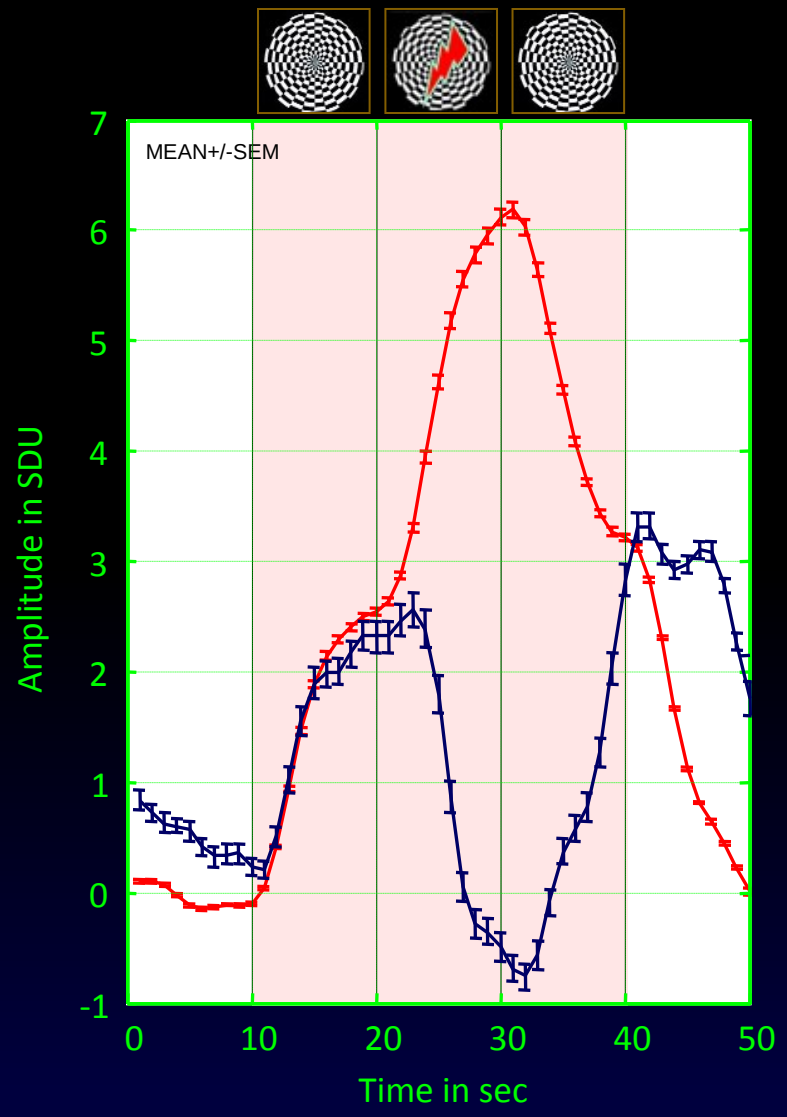


Logothetis et al. (Nat. Neuro. 2010)

Visual and Electrical (dLGN) Stimulation: Combined Design

BOLD signal increases and decreases in striate and extrastriate cortex respectively

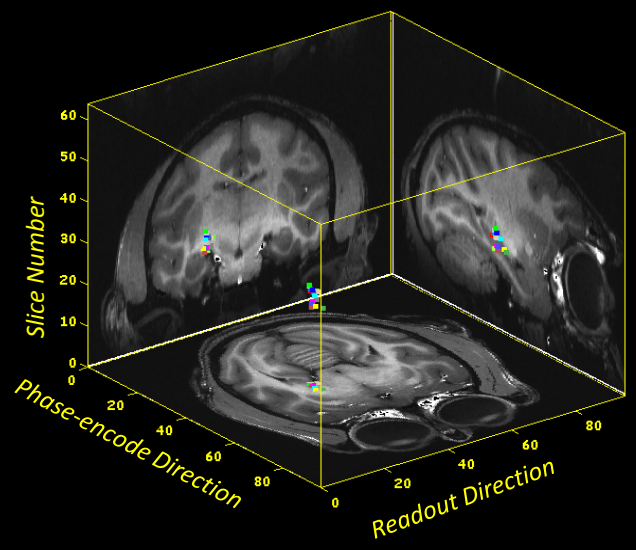


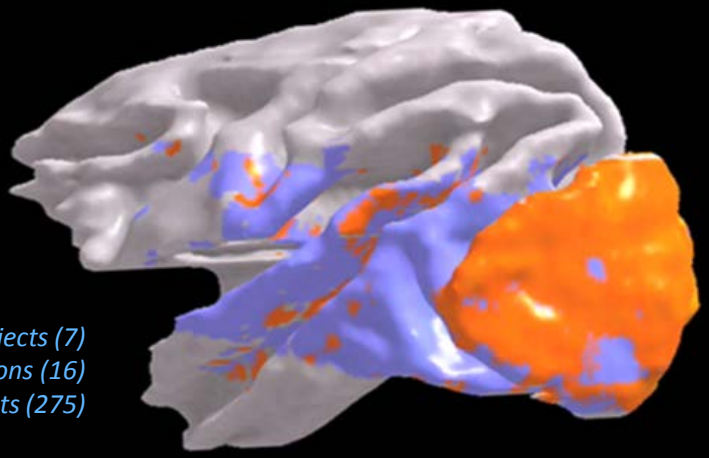


Logothetis et al. (Nat. Neuro. 2010)

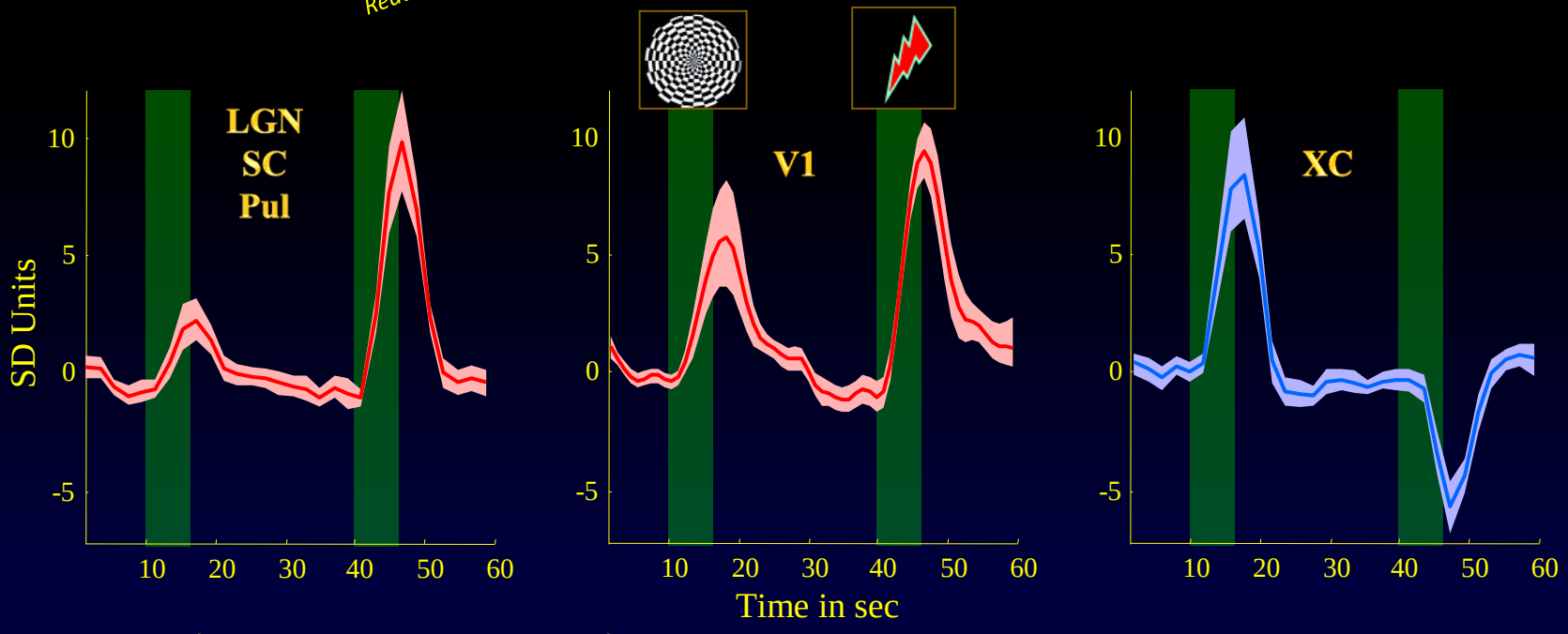
POPULATION DATA

fMRI of Electrical dLGN Stimulation (100-200Hz)





Subjects (7)
Sessions (16)
Experiments (275)

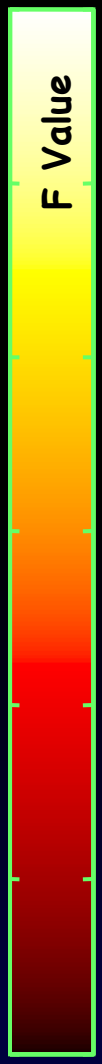


Logothetis et al. (Nat. Neuro. 2010)

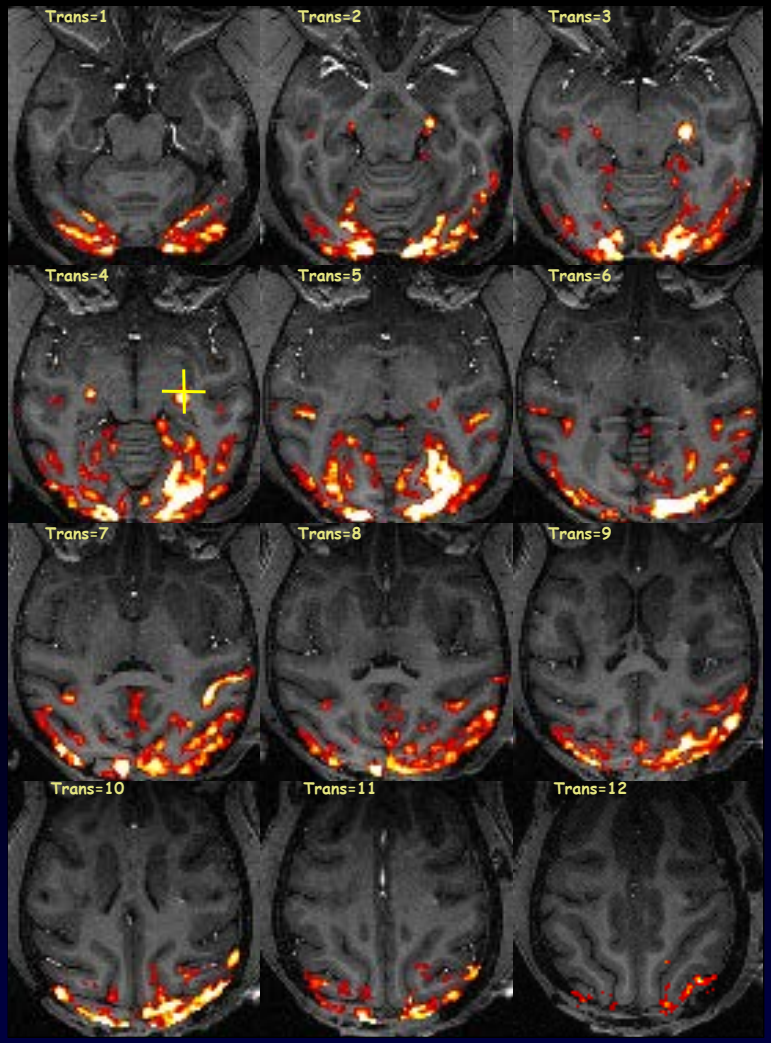
POPULATION DATA — Full-field Visual & Electrical Stimulation of dLGN

Subcortical and Cortical Sites with Significant Activity Modulation

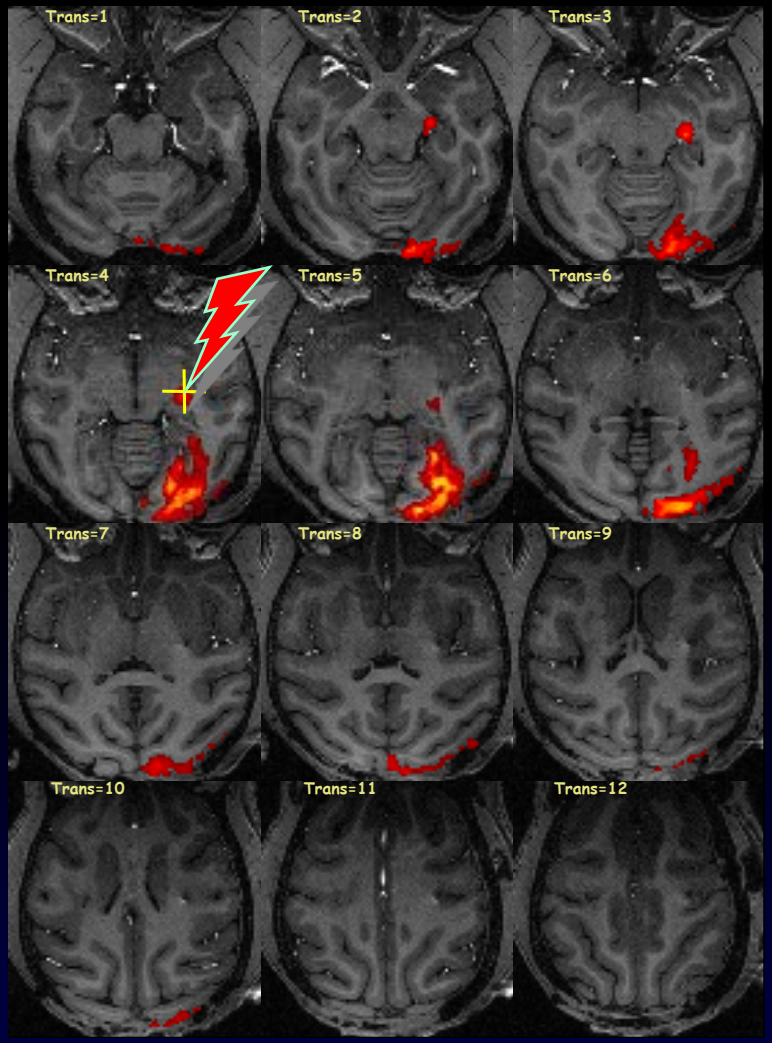
(Pd=200 µsec, Ia=250 µA, Fr=200 Hz)



Visual Stimulation

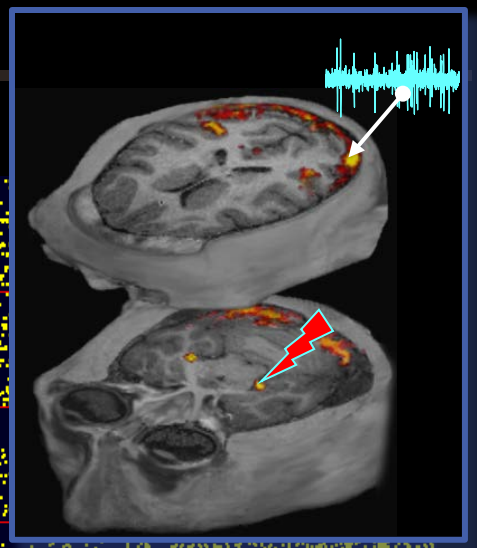


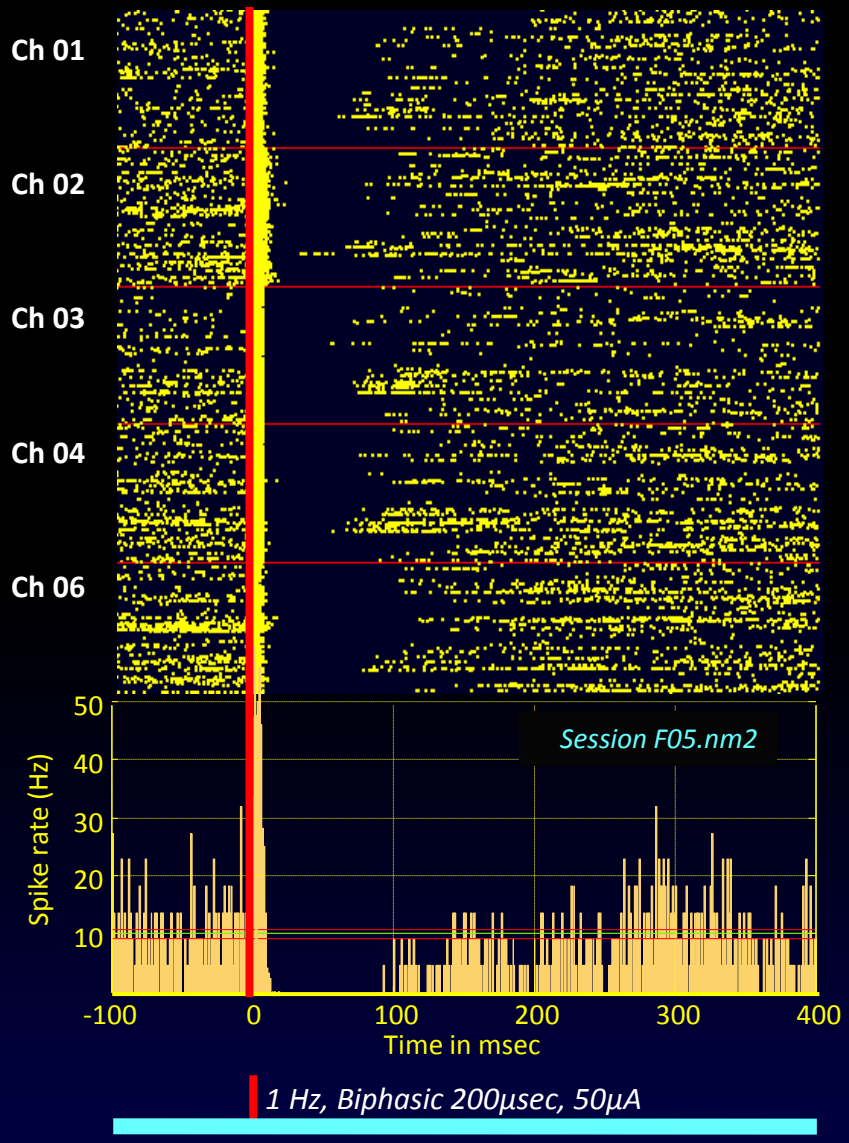
Electrical Stimulation



Logothetis et al Nat Neuroscience 2010, Logothetis et al, MRI 2012

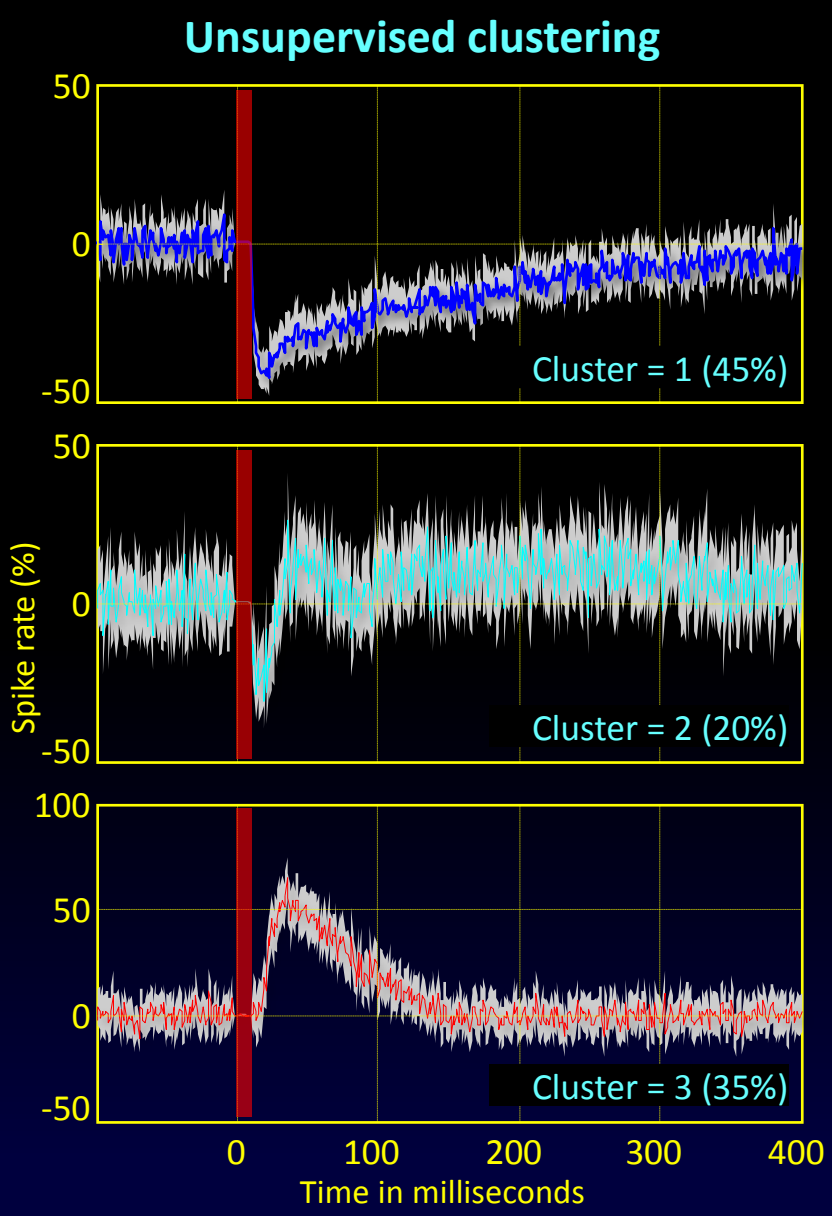
Cortical Responses to Single LGN Microstimulation Pulses

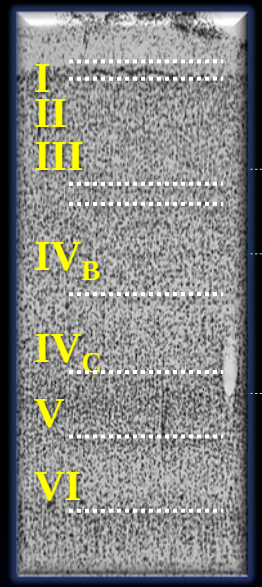


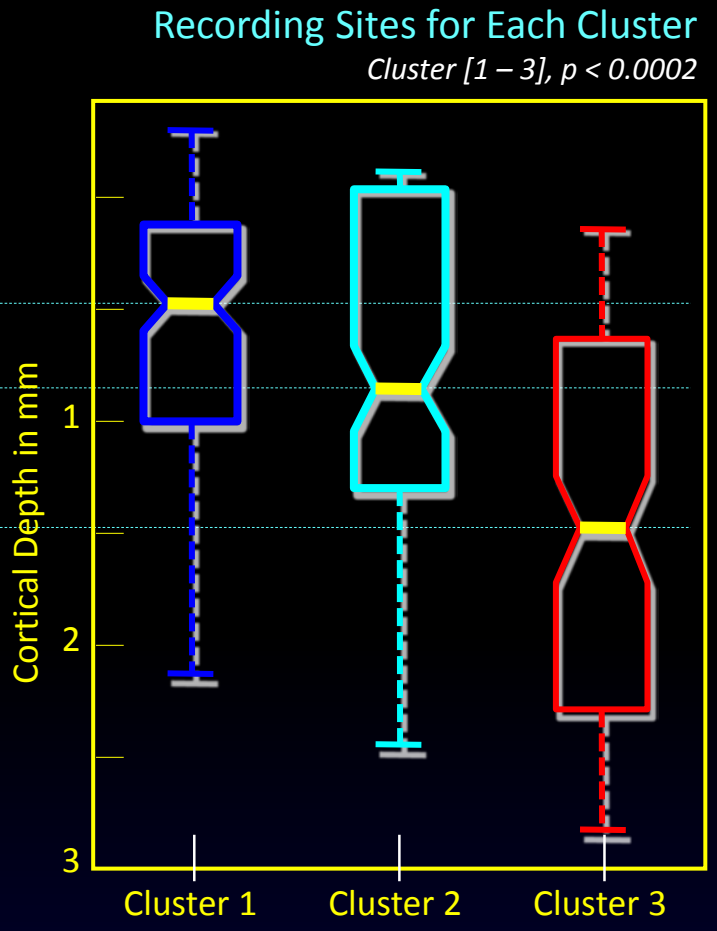


Logothetis et al. (Nat. Neuro. 2010)

Cortical Responses to Single LGN Microstimulation Pulses





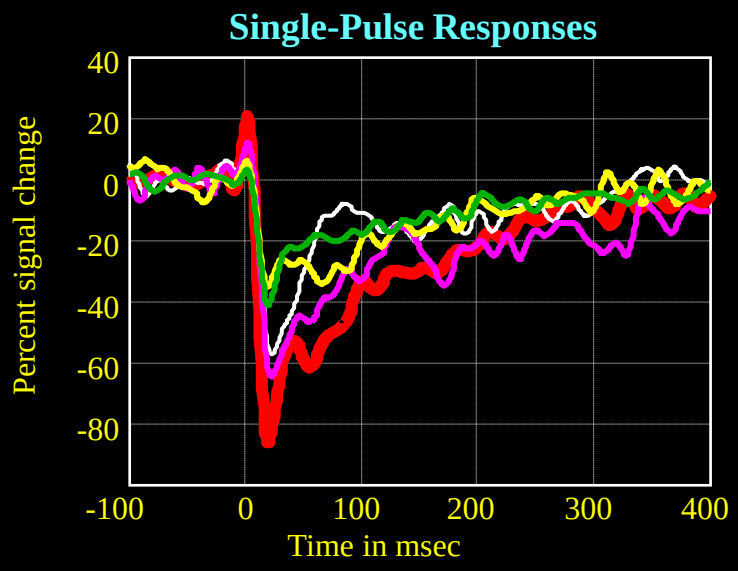


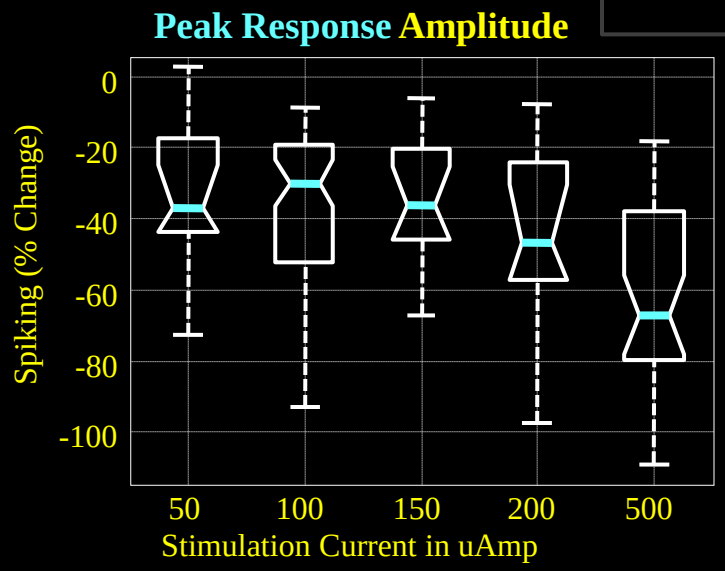
What is causing inhibition?

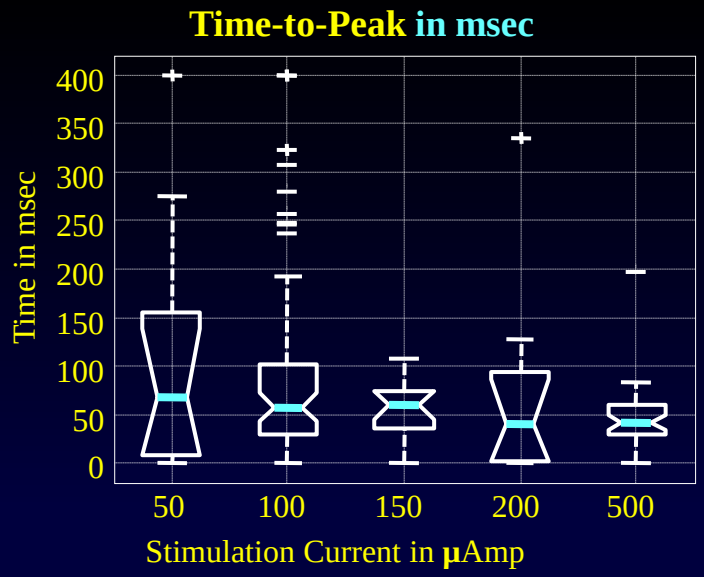
- Changes in Excitability?
- Synaptic Inhibition?

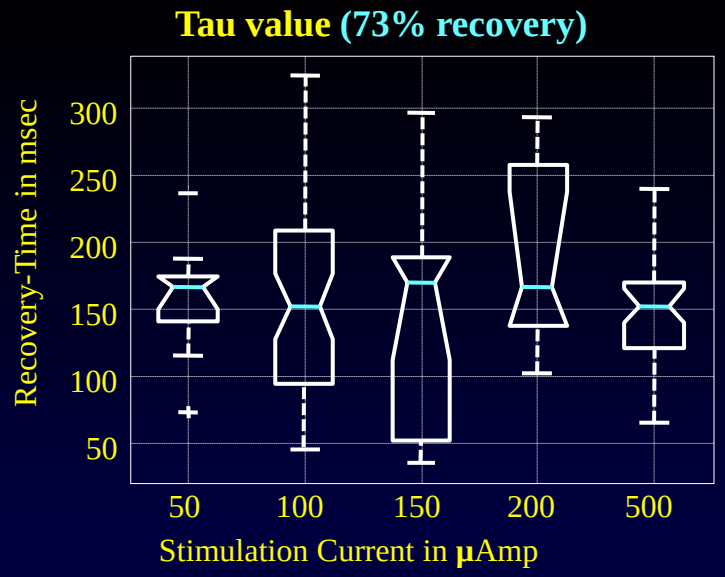
Logothetis et al. (Nat. Neuro. 2010)

DES-Responses for Different Current Strengths: Excitability Changes?









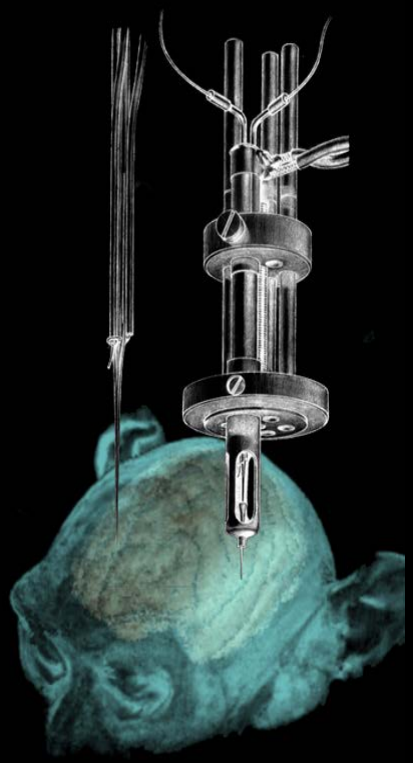
Logothetis et al. (Nat. Neuro. 2010)

DES-Responses after Blocking GABAergic Action: Synaptic Inhibition?

Blocking GABAergic action with 100 µM solution of bicuculline methiodide (BMI), injected into V1 (Rate: 1 µl/min for 10 min)

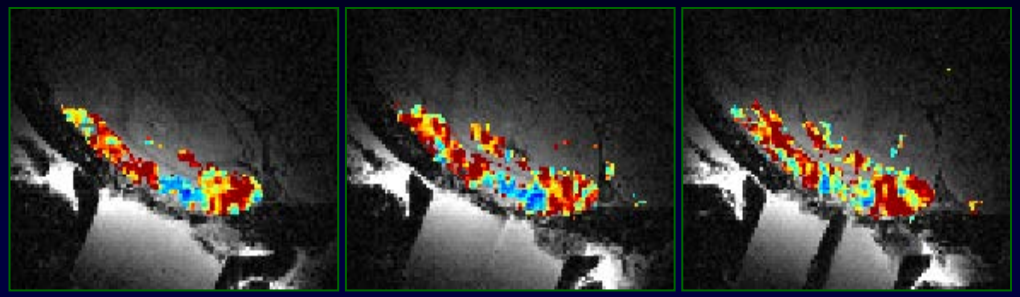
Injector

- Triple-barrel glass tube
- 3 Independent injection lines
- 3 HPLC pumps; Online selection
- High precision flow-meters
- Online pH adjustment
- Magnevist Dose-Optimization

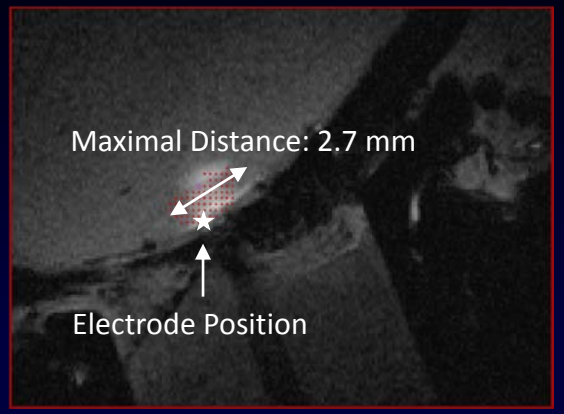


0.9 µl/min
in 20 min
total vol: 12.4 **µl**.

4.2 µl/min
in 10 min
total vol: 32 µl.



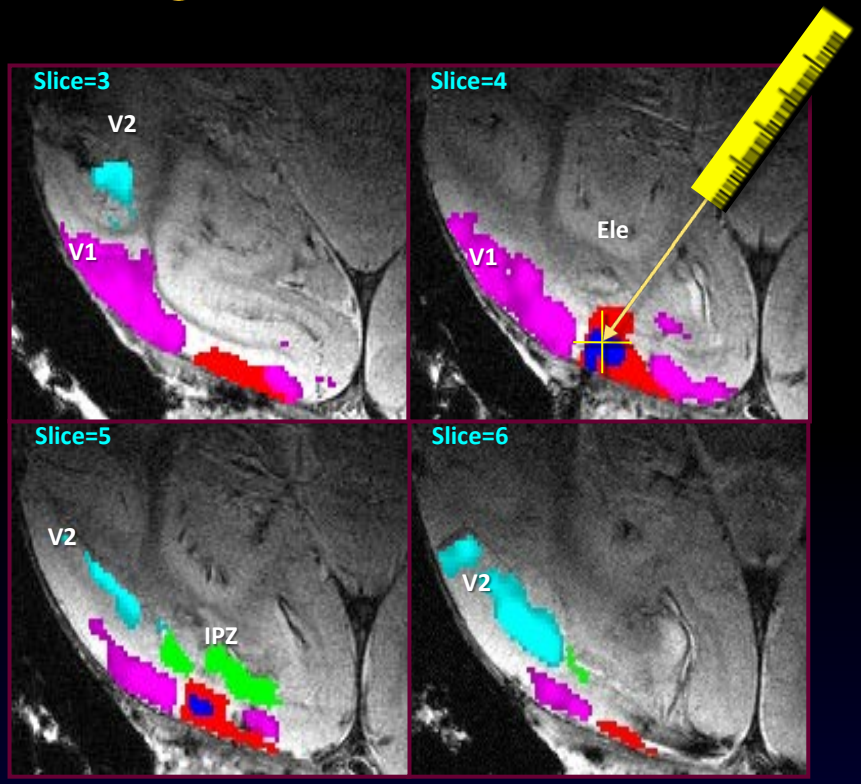
Example of Lidocaine Injection

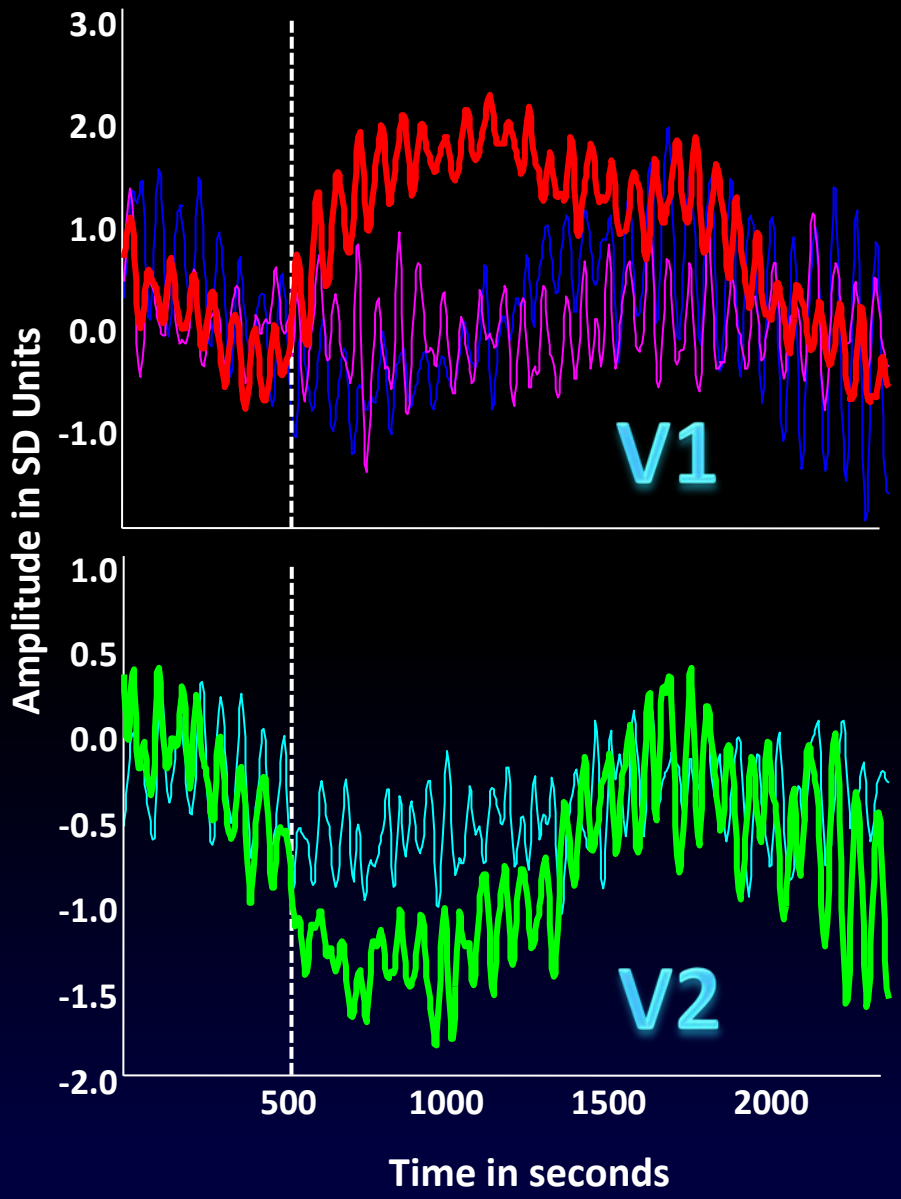


Rauch et al. , NeuroImage 2008; Rauch et al., PNAS 2008; Logothetis et al. (Nat. Neuro. 2010)

DES-Responses after Blocking GABAergic Action: Synaptic Inhibition?

Spatially filtered ICA Clusters in a Single Session





Logothetis et al. (Nat. Neuro. 2010)

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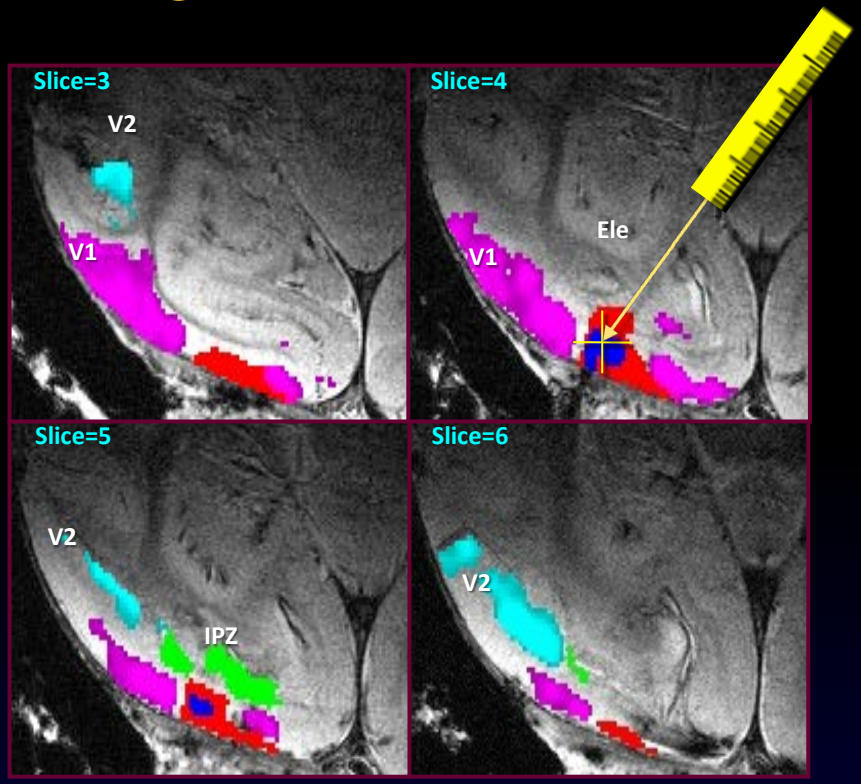
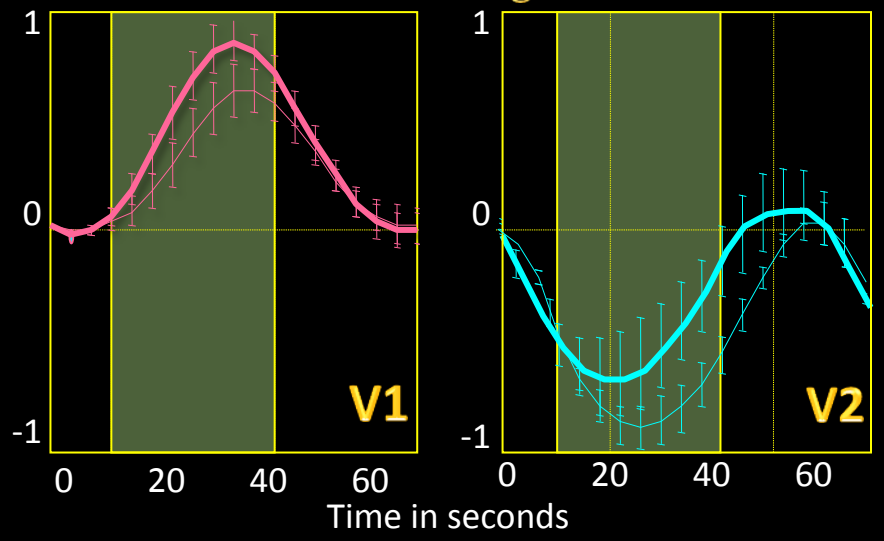
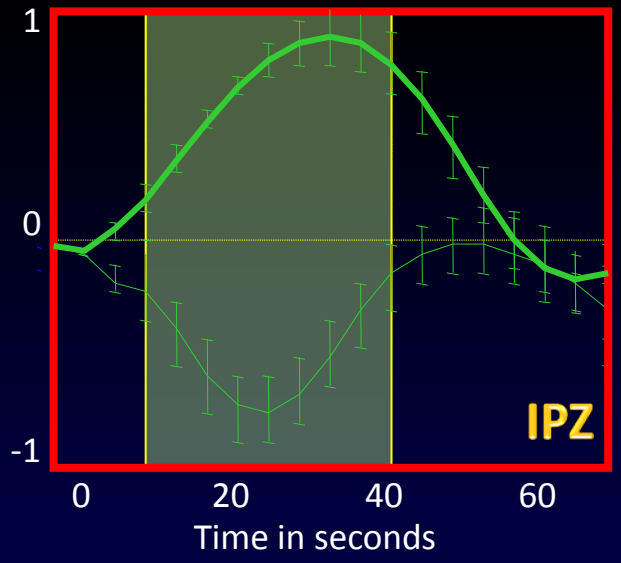


Unaffected Regions

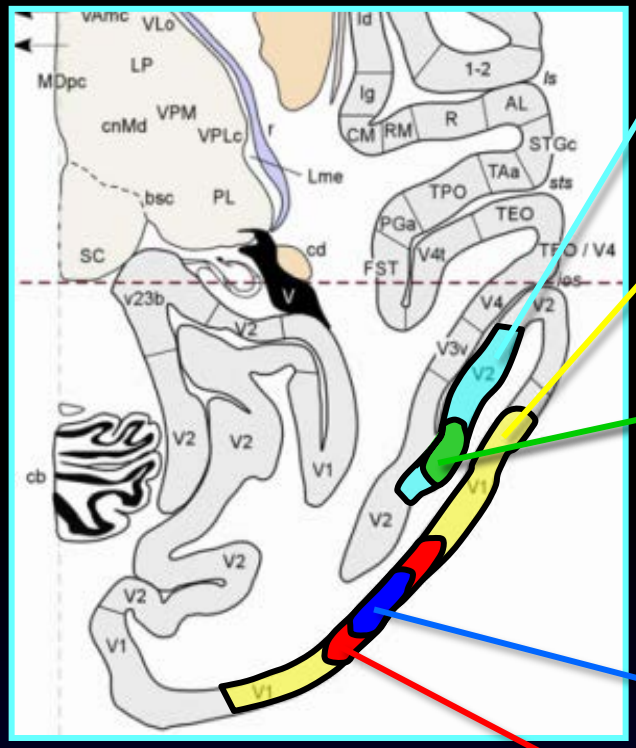


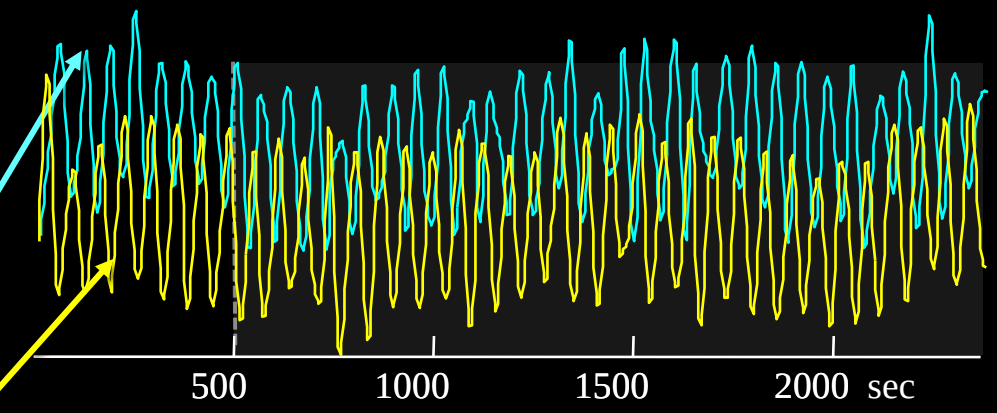


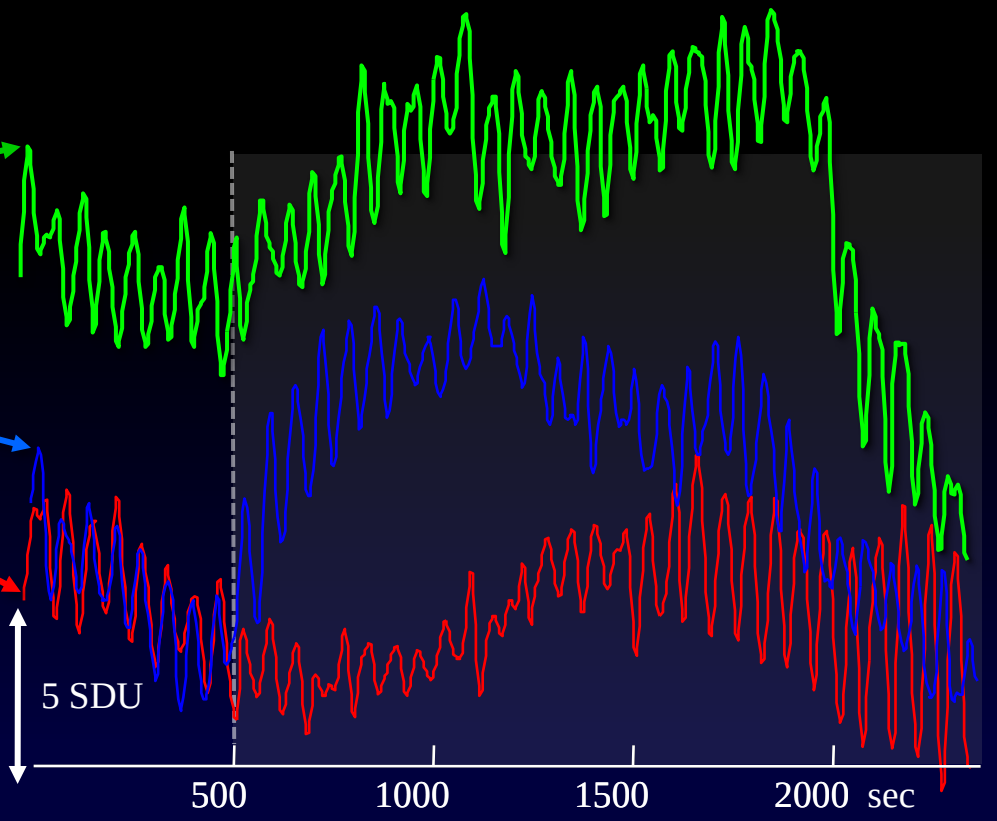
Logothetis et al. (Nat. Neuro. 2010)

POPULATION DATA

Effects of Injection of GABA-Antagonists on DES-fMRI

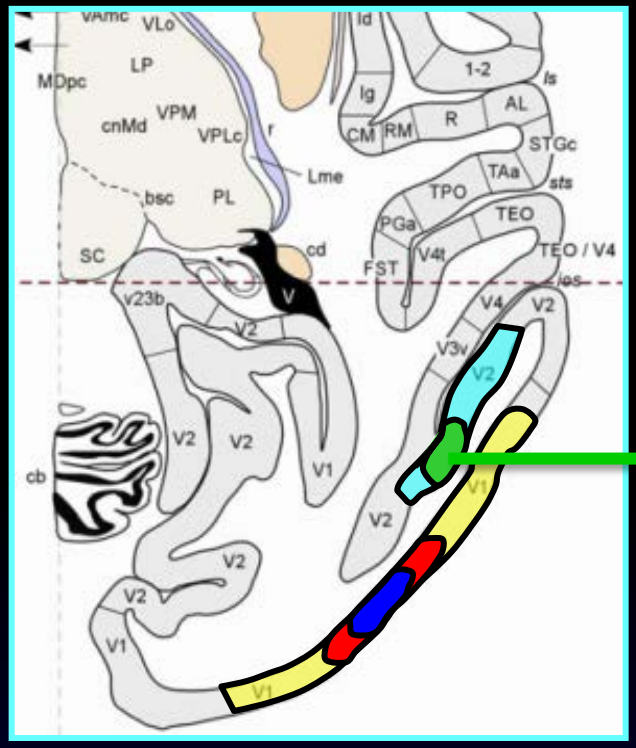


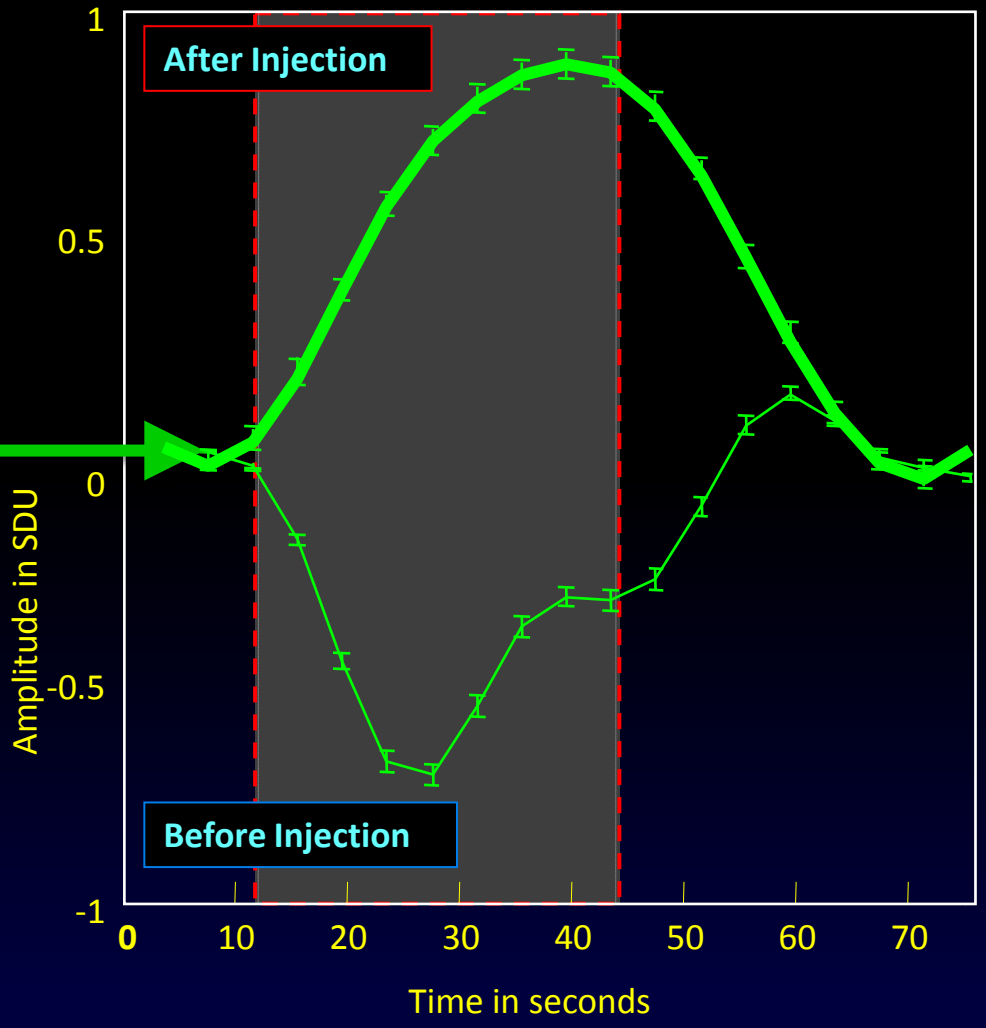




Logothetis et al. (Nat. Neuro. 2010)

Effects of Injection of GABA-Antagonists on DES-fMRI (Trial-Average)



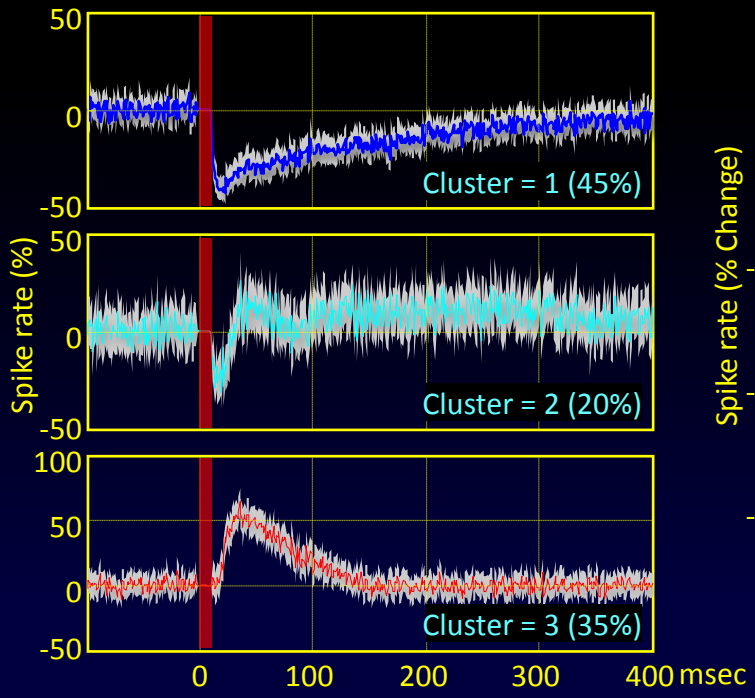


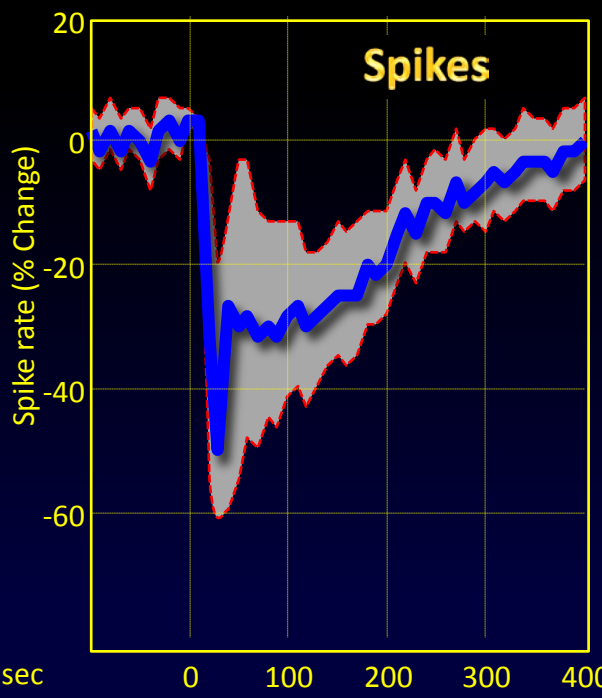
Logothetis et al. (Nat. Neuro. 2010)

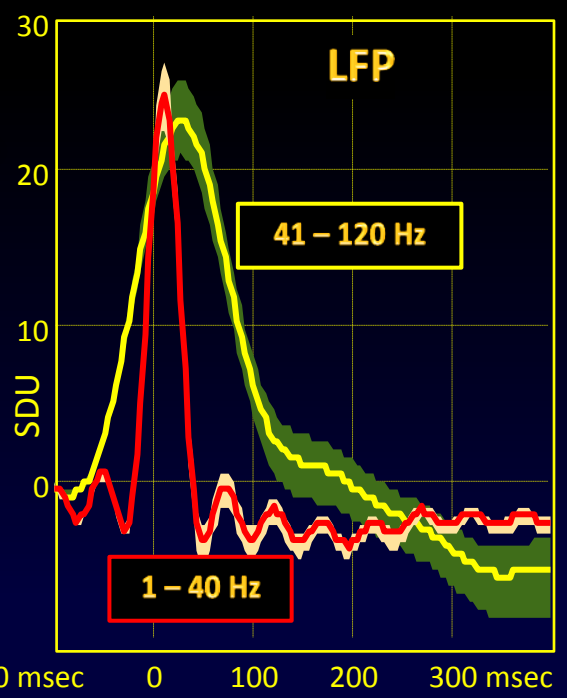
Interim Conclusions

DES-fMRI Overview of Physiology, Pharmacology & fMRI Results

- DES of V1-afferents **disrupts the propagation of signals from V1 to extrastriate areas**.. hence their **NBR**
- The findings are independent of animal-state and current-strength
- DES-induced Down Modulations are unrelated to the NBR observed during sensory stimulation
- Disruption of propagation is due to **synaptic inhibition** (rather than reduced excitability) likely due to the over-synchronized spatiotemporal profile of DES-elicited thalamic-input
- MUA **drops** in the supra- and briefly **increases** in the infra-granular cortical layers:



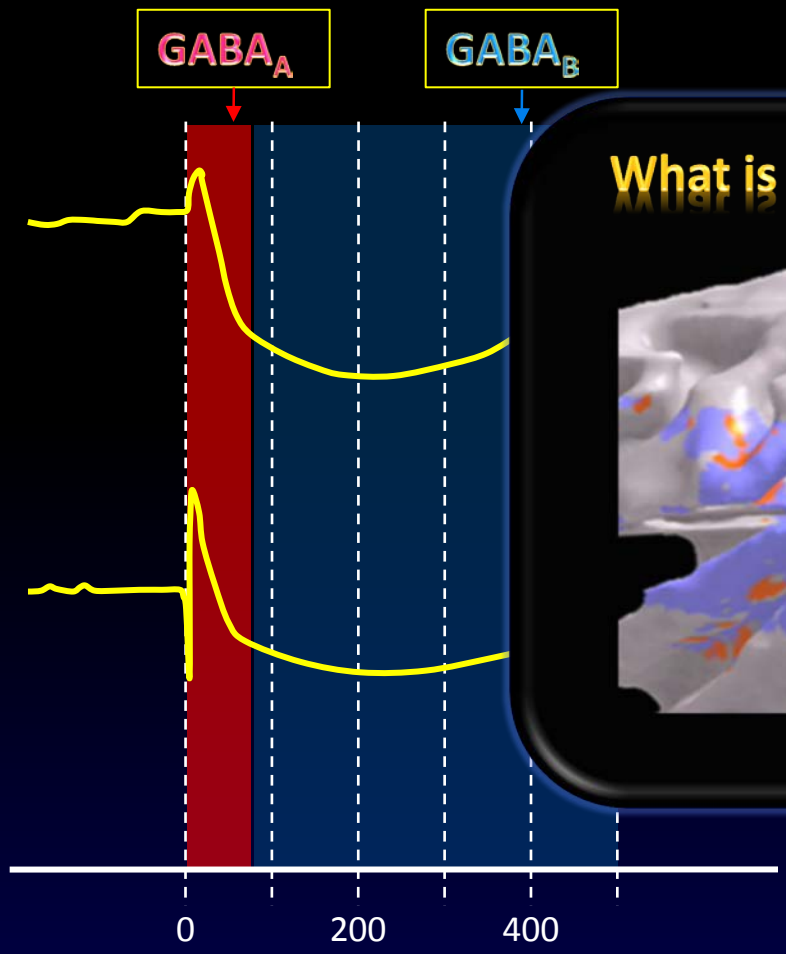




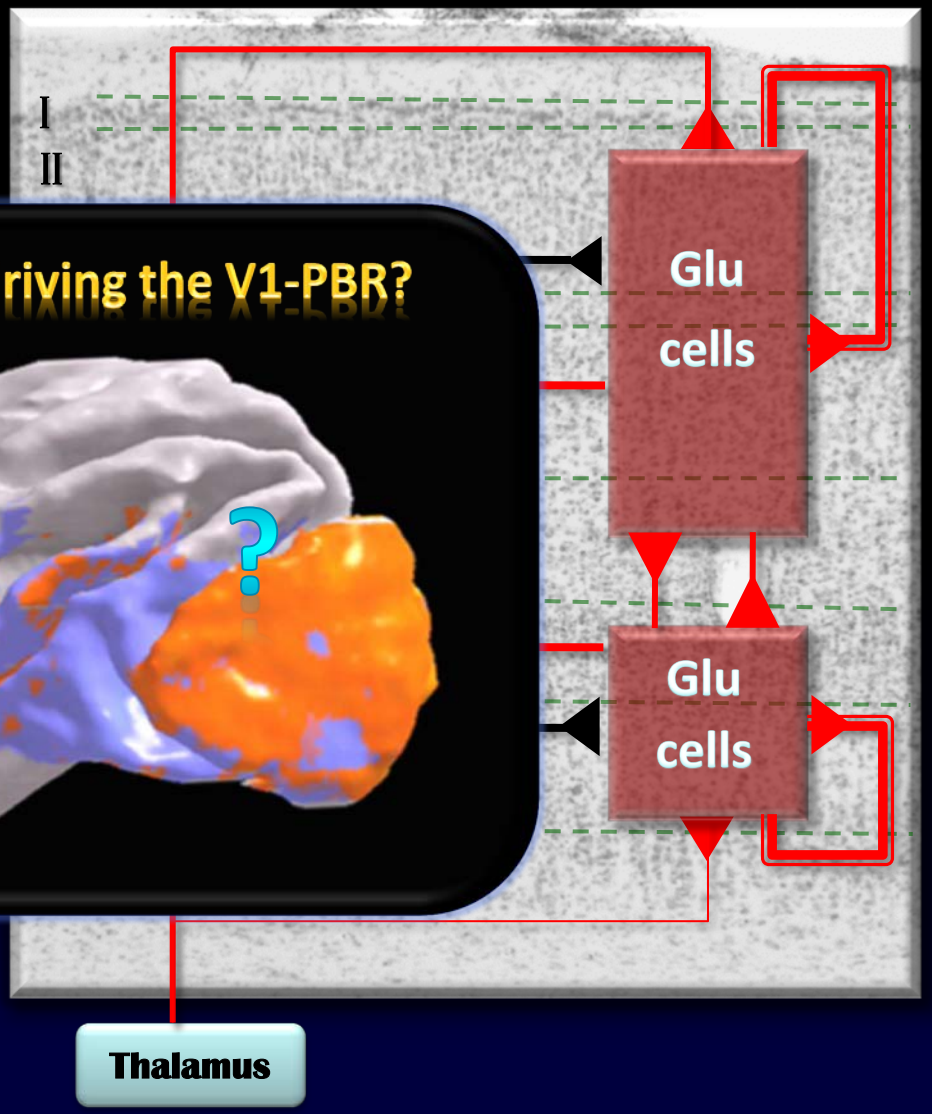
E-I Microcircuits?

Feedforward Inhibition Underlies the Shunting of Projection Neurons

Intracellular Recordings During Electrical Stimulation of Cortical Afferents



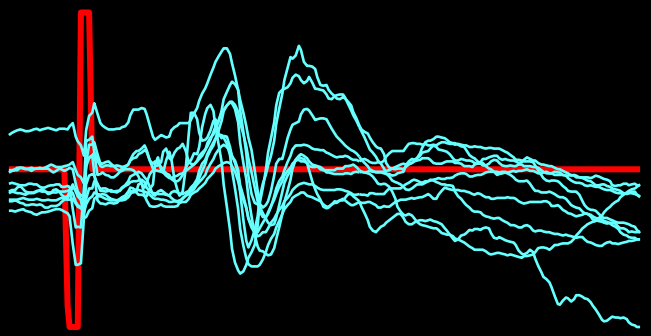
Excitation-Inhibition Networks

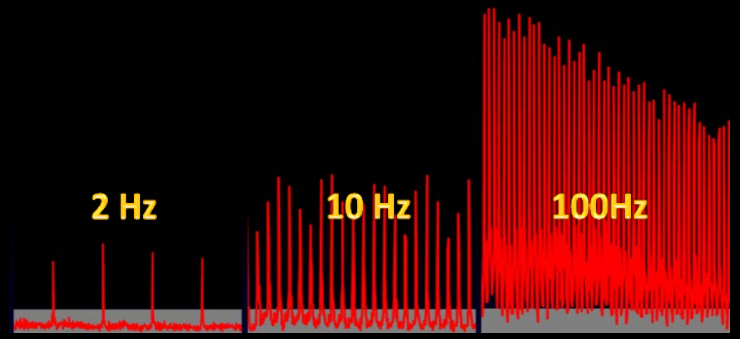


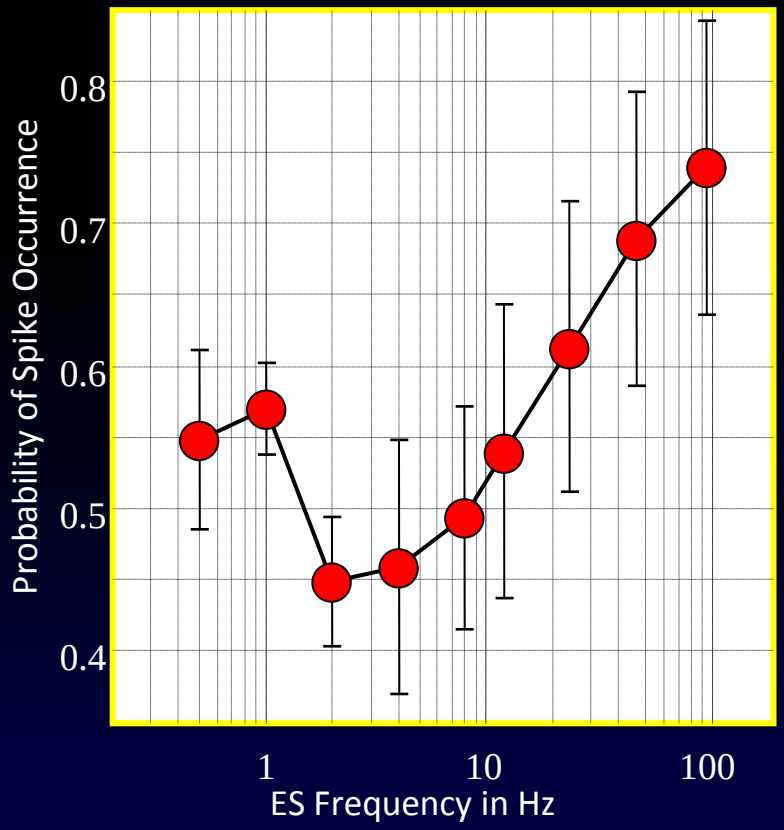
What is driving the V1-PBR?

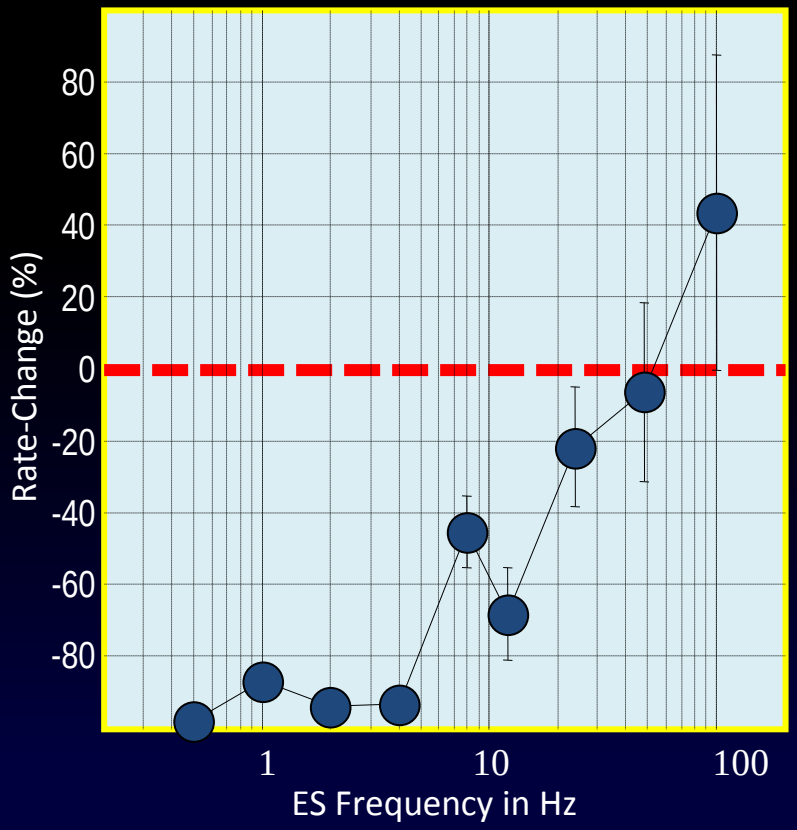
Plots & Drawing adapted from Douglas & Martin, J Physiol 1991; McCormick-Lab; Okun & Lampl, 2008

Neural-Activity Suppression is a Non-Monotonic Function of Frequency





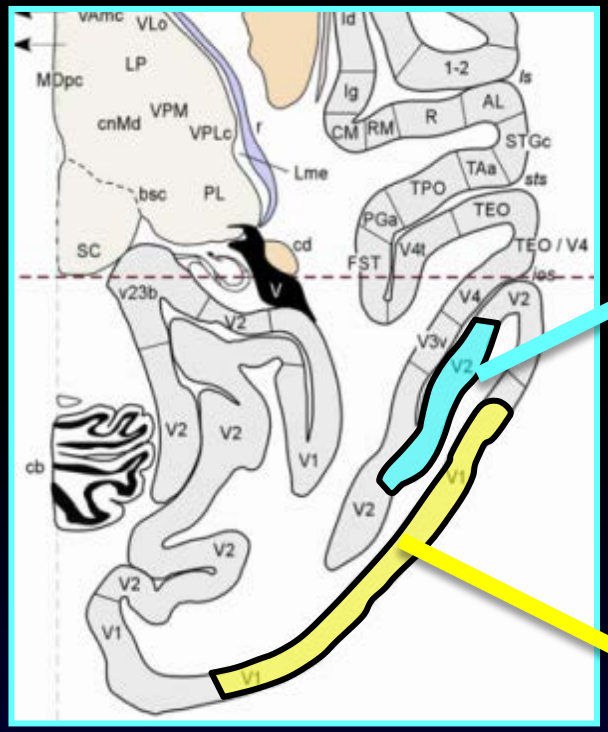


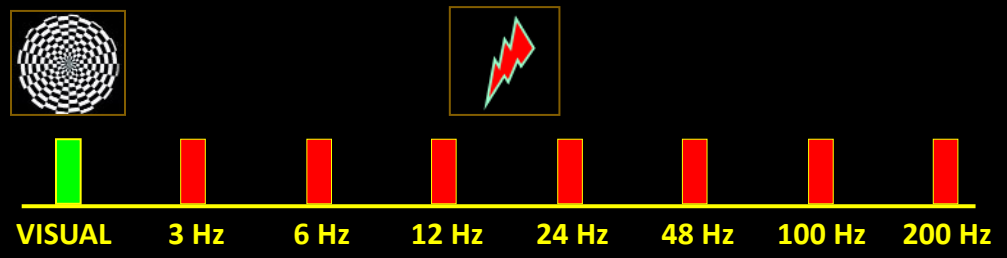


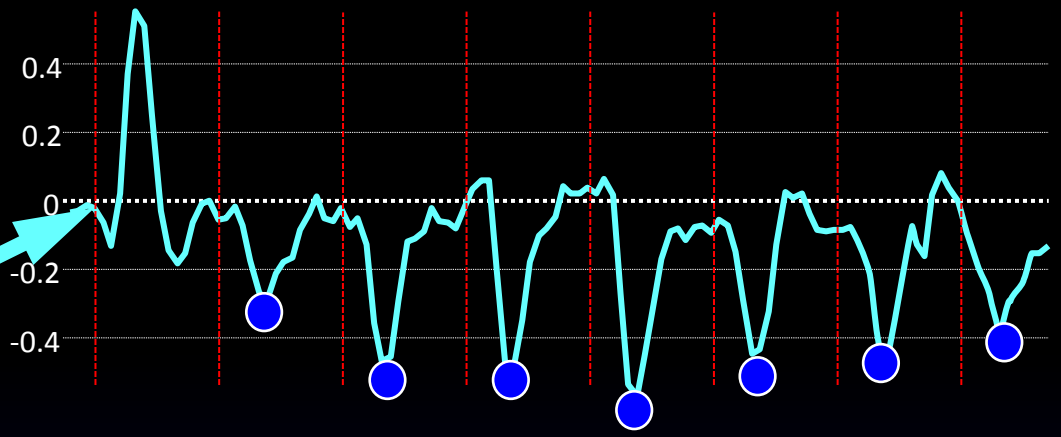
Logothetis et al. (Nat. Neuro. 2010)

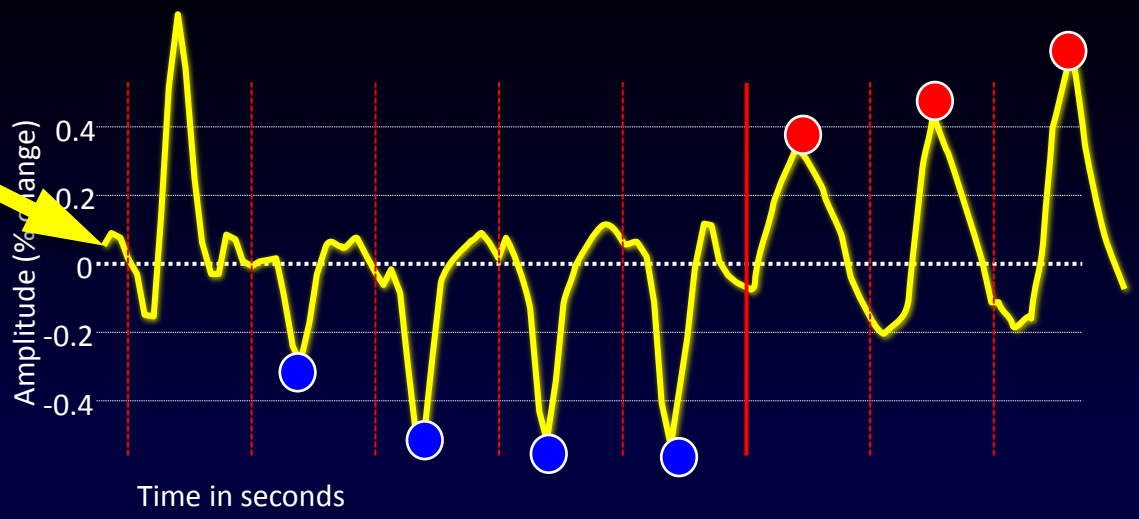
Neural-Activity Suppression is a Non-Monotonic Function of Frequency

. . . AND SO IS THE BOLD RESPONSE



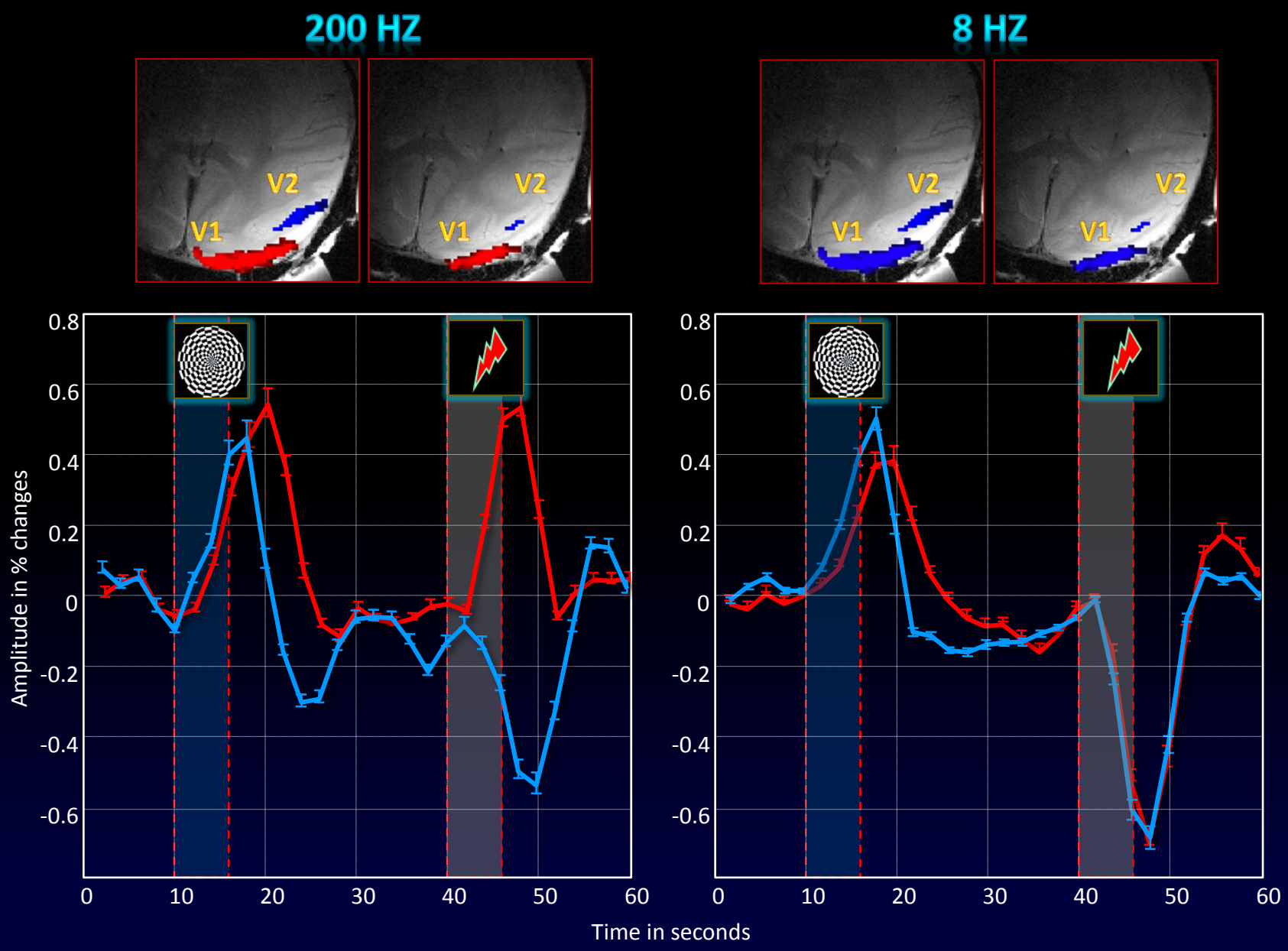






Logothetis et al. (Nat. Neuro. 2010)

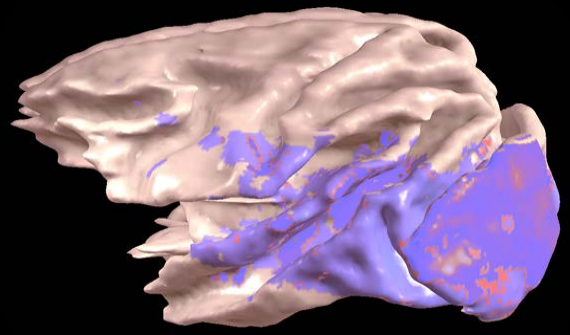
V1 & V2 BOLD Responses for HIGH and LOW Stimulation Frequencies



Logothetis et al. (Nat. Neuro. 2010)

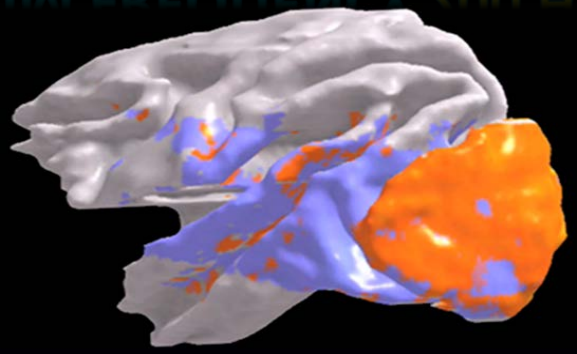
V1 & V2 BOLD Responses for HIGH and LOW Stimulation Frequencies

STIM FREQUENCY 8 HZ

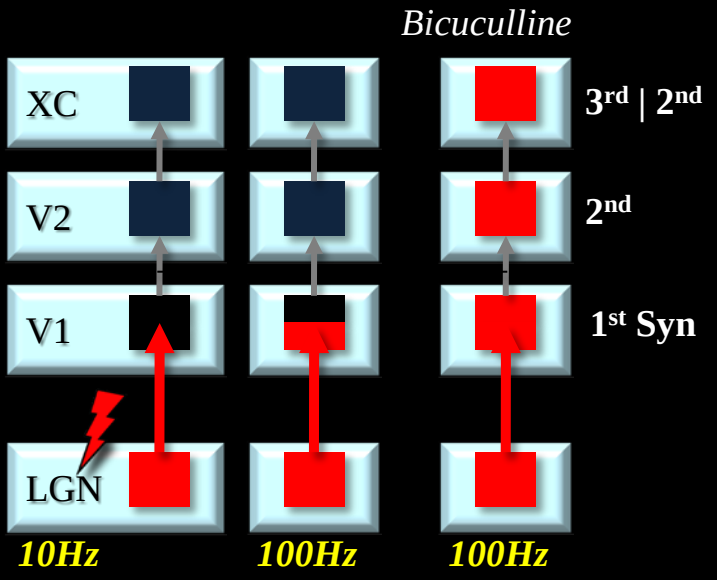


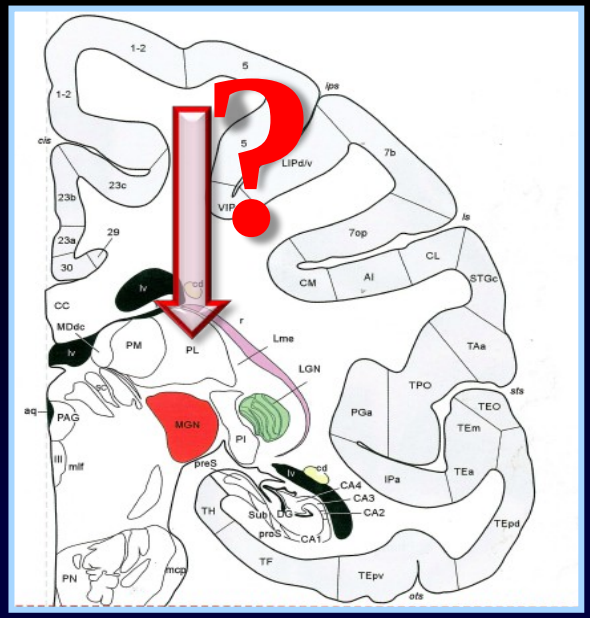
Cortical Output Shunted
Low Presynaptic Activity (NBR in V1)

STIM FREQUENCY 200 HZ



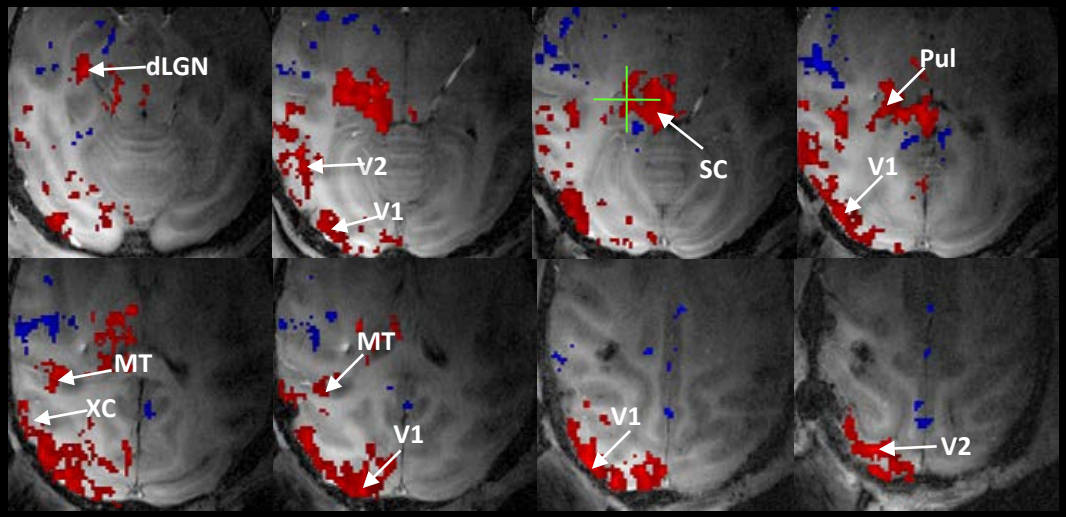
Cortical Output Shunted
High Presynaptic Activity (PBR in V1)

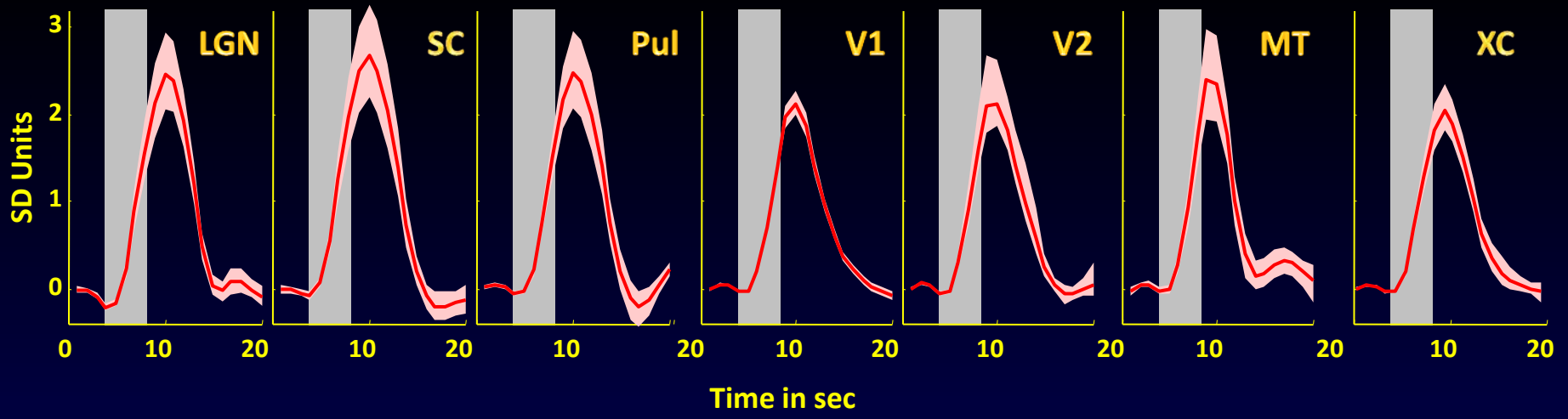




Logothetis et al. (Nat. Neuro. 2010)

Pulvinar Stimulation (Single Session)

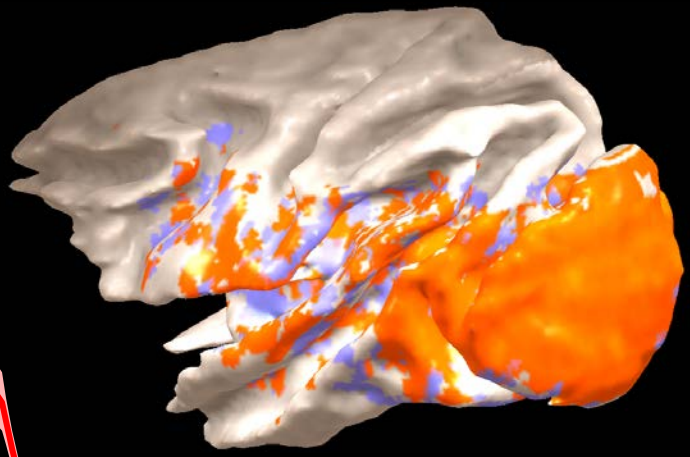


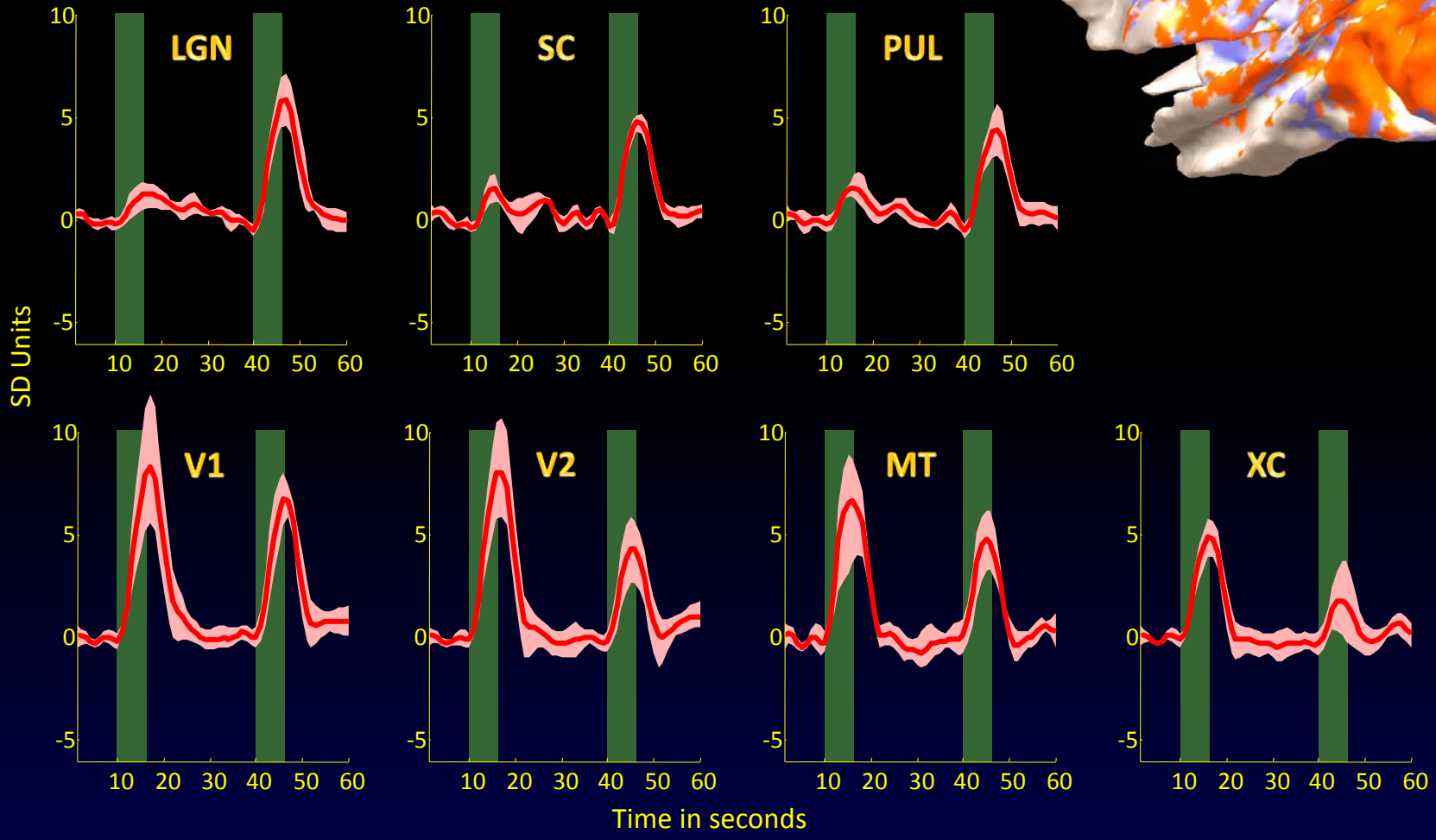


Logothetis et al. (Nat. Neuro. 2010)

POPULATION DATA Pulvinar Stimulation

Subjects = 6, Sessions = 11, Groups = 16, Experiments = 167

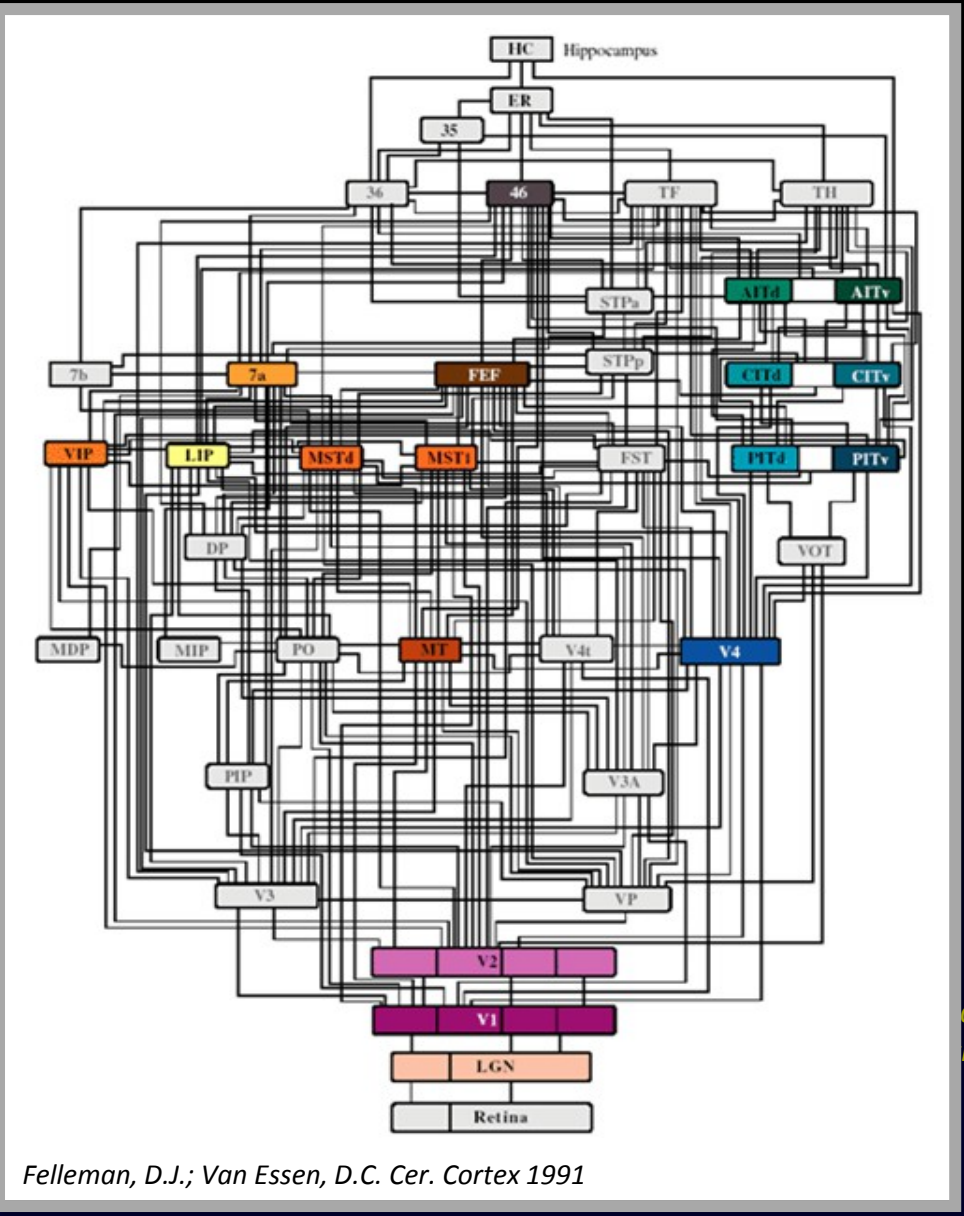




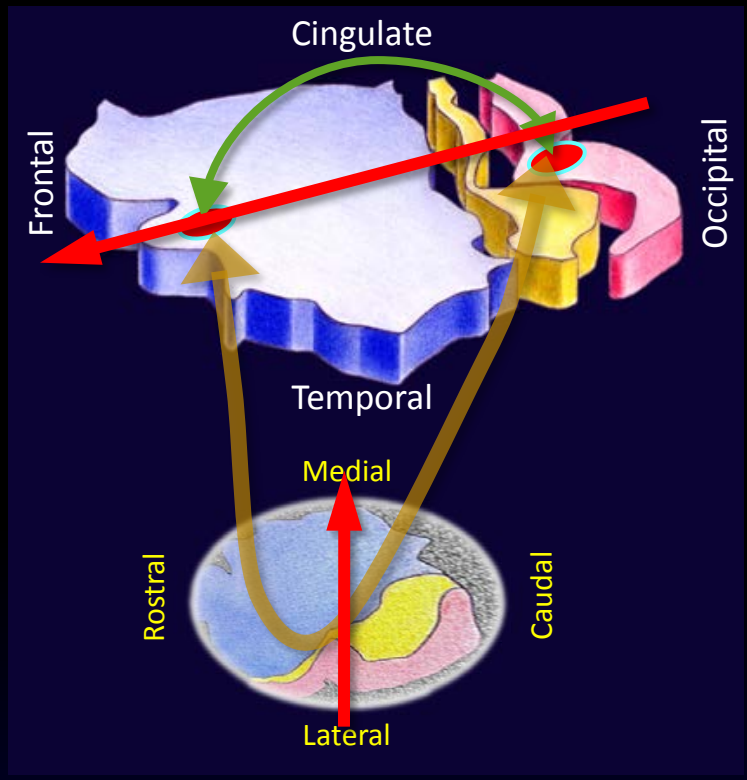
Logothetis et al. (Nat. Neuro. 2010)

Cortico-Thalamo-Cortical Connectivity

An alternative to the assumption "… once information reaches cortex, it stays within cortex …", is
"Information transfer is also on cortico-thalamo-cortical pathways involving higher order thalamic relays…", e.g. Guillery & Sherman, Neuron 2002



Felleman, D.J.; Van Essen, D.C. Cer. Cortex 1991



The Replication Principle

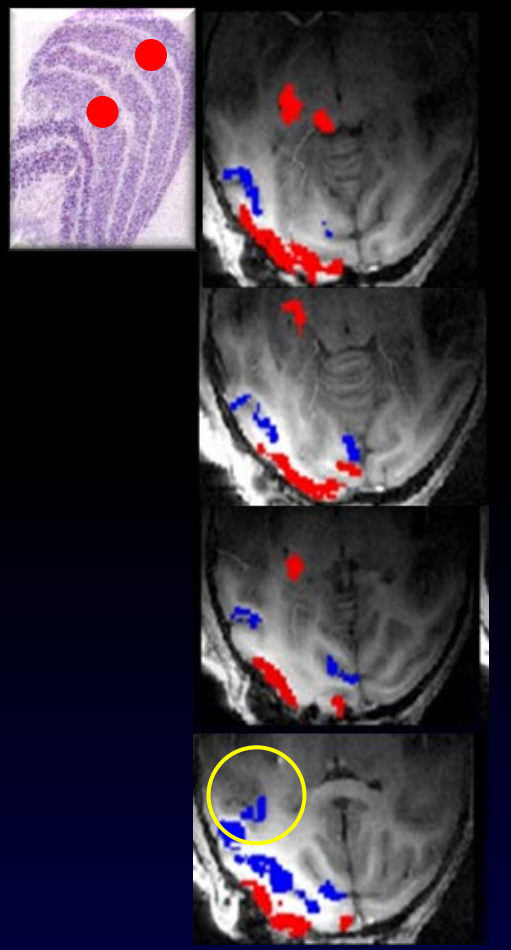
"… if two cortical areas communicate directly, they are likely to have overlapping thalamic fields; if not, their thalamic fields avoid each other. They are totally separate, or interdigitating!"
Stewart Shipp., 2003

Adapted from Sherman & Guillery, PNAS 1998, and Shipp Phil. Trans. Roy. Soc. 2003

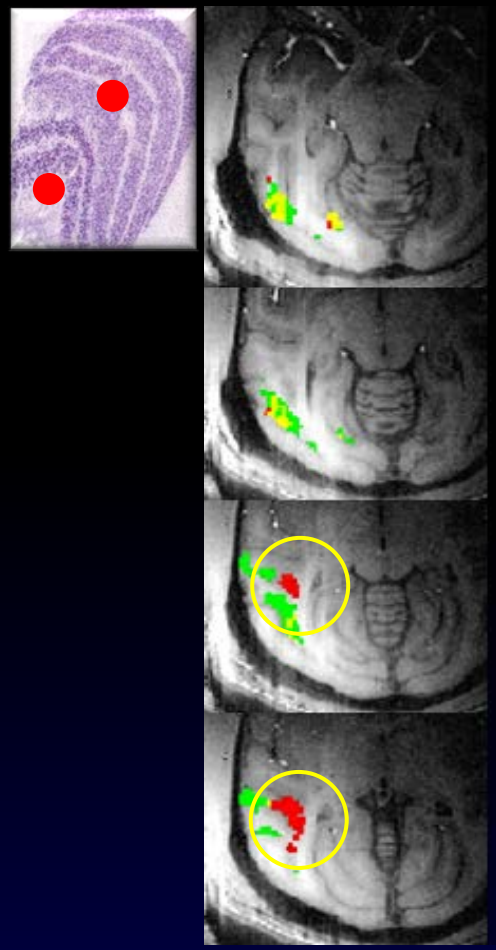
DES of Konio - Direct Thalamic Input to Extrastriate Cortex?

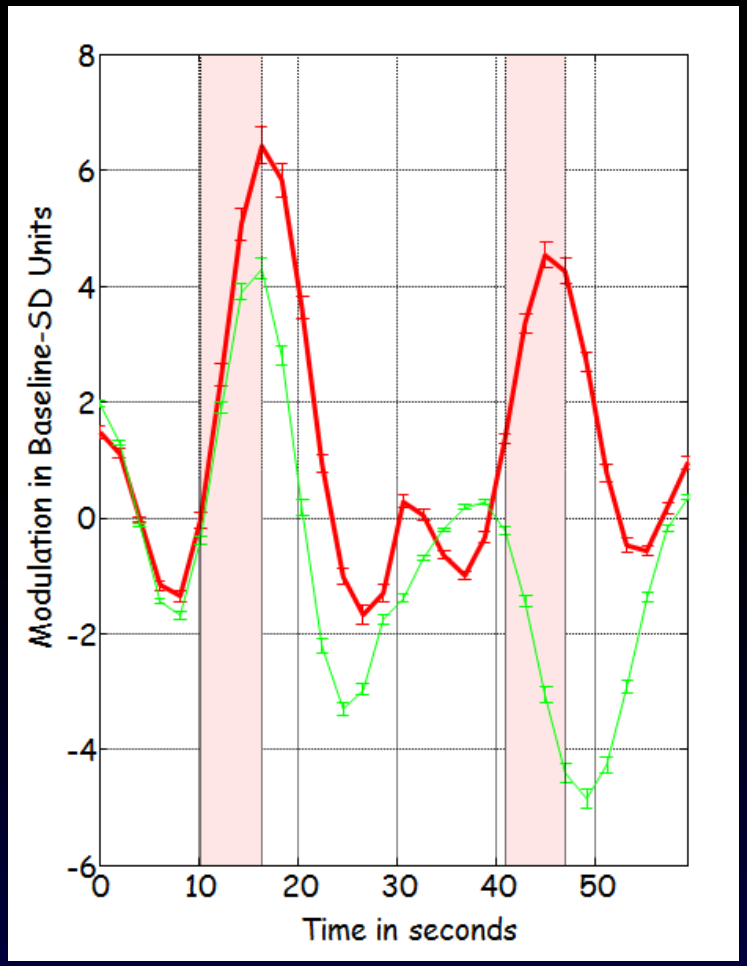
ES-Induced BOLD Responses in Area MT

Dominant Stimulation: Relay Cells



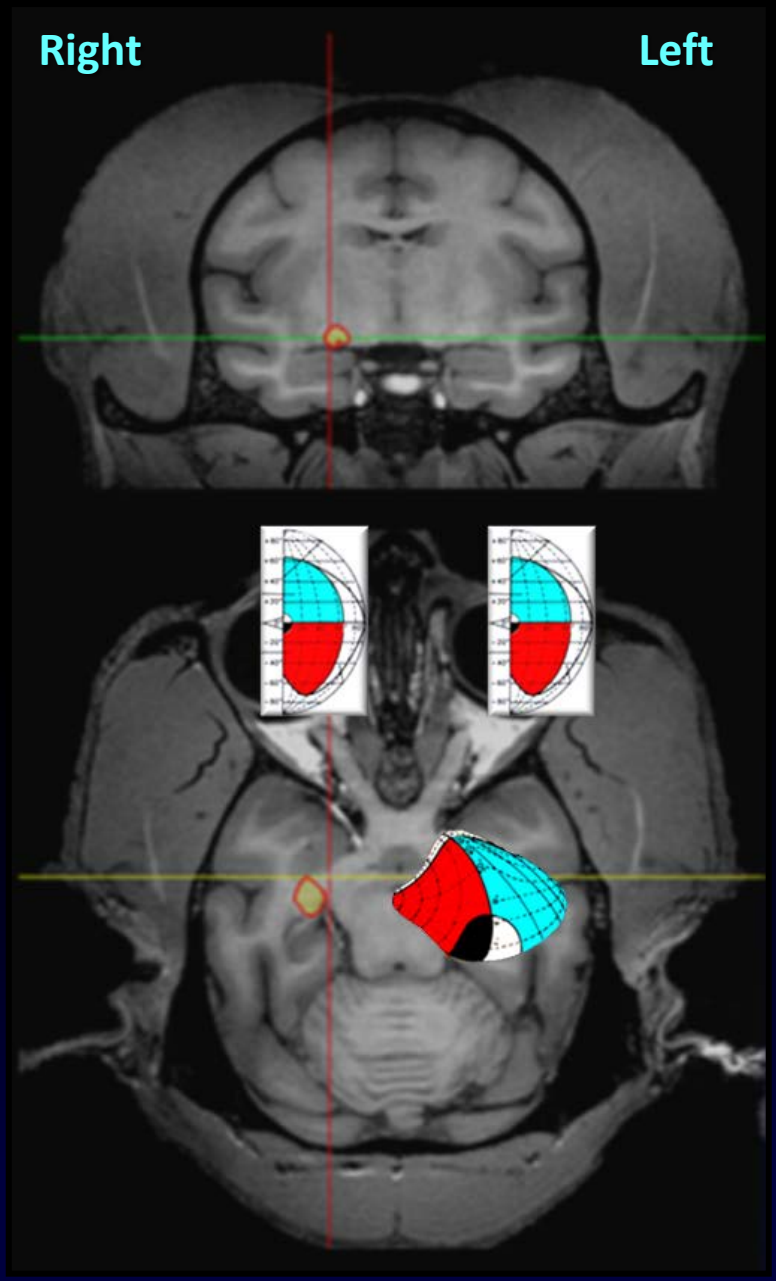
Dominant Stimulation: Koniocellular System (?)

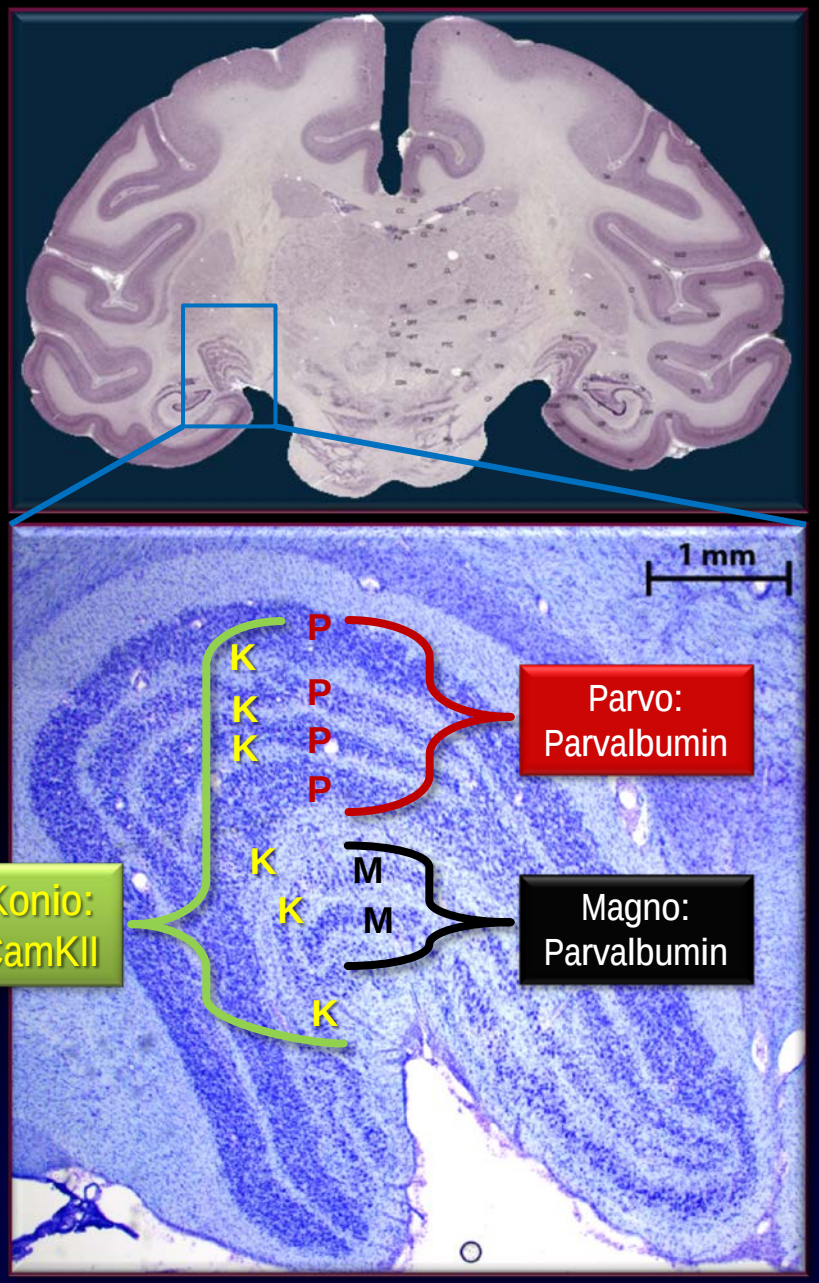




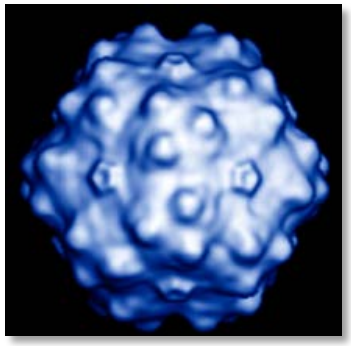
Logothetis et al. (Nat. Neuro. 2010)

Structure & Cell Types in the Lateral Geniculate Nucleus (LGN) of Monkeys





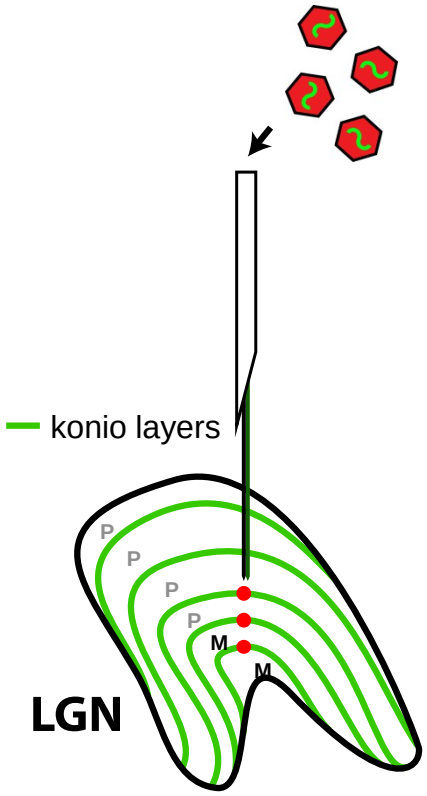
ChR2 Expression in the LGN Konio layers

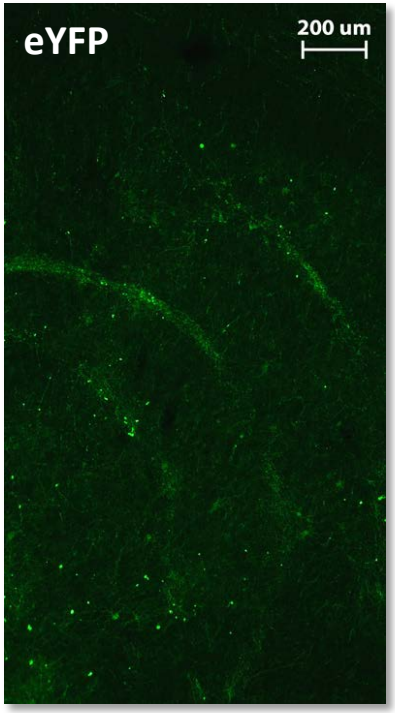


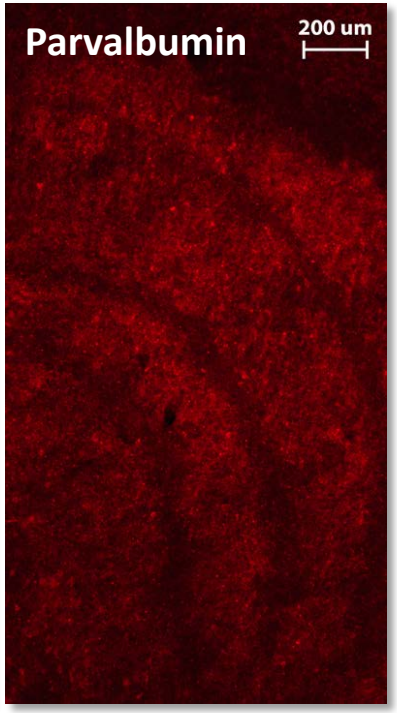
AAV5 Capsid

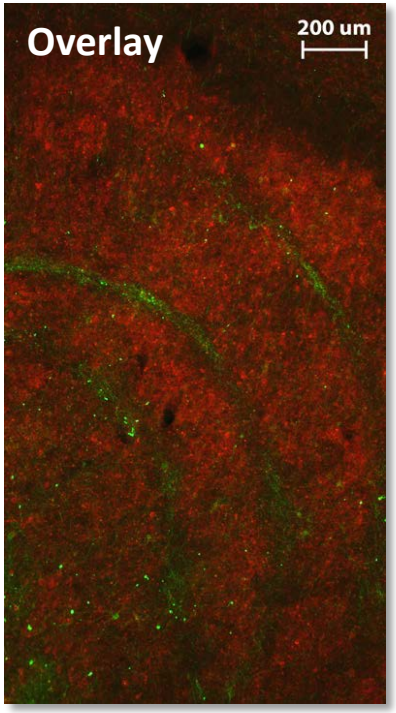
AAV-aCamKII-hCHR2-EYFP

4455bp

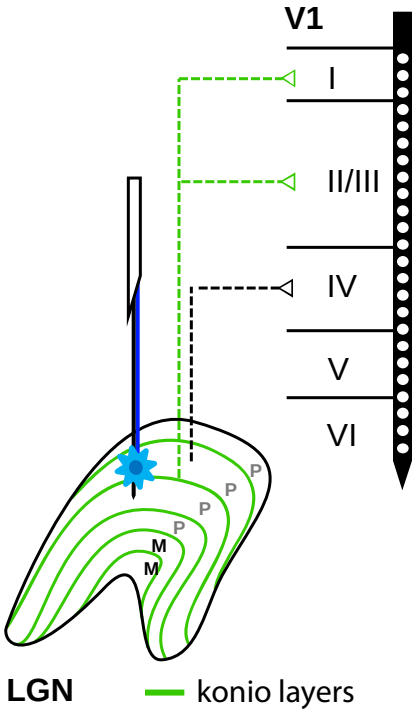


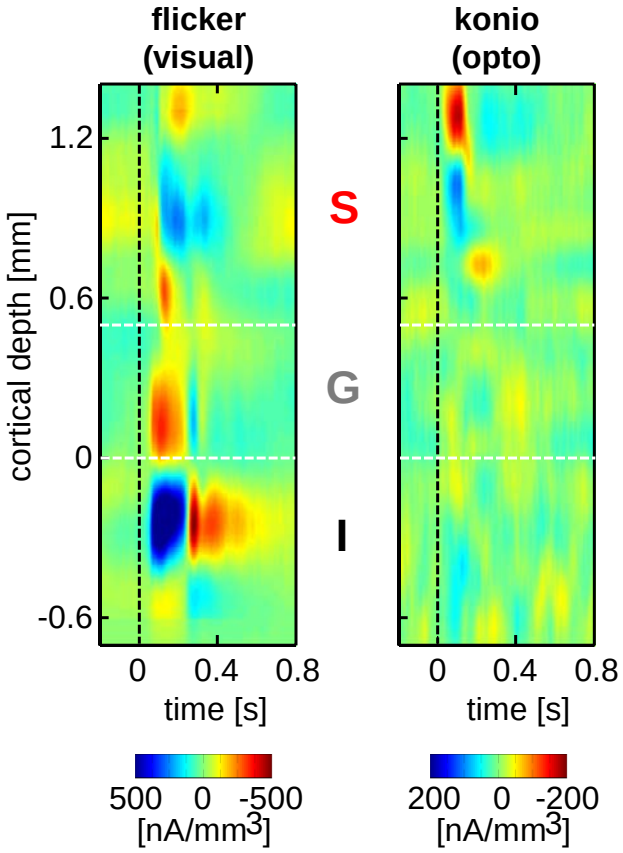


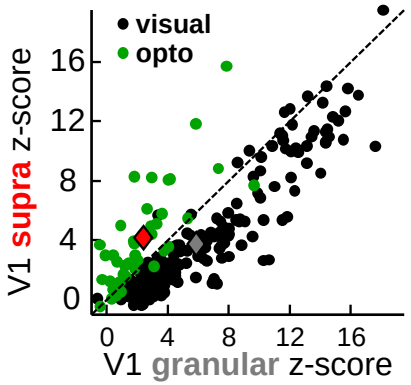


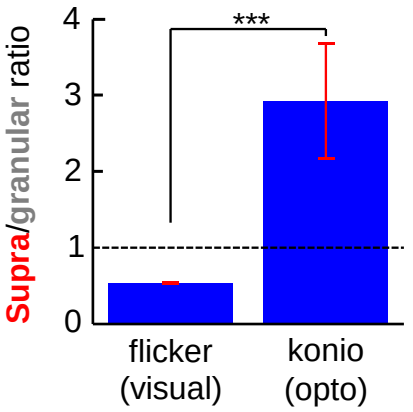


Result I: DOS of Konio Activates the Supra-Granular Layers of V1

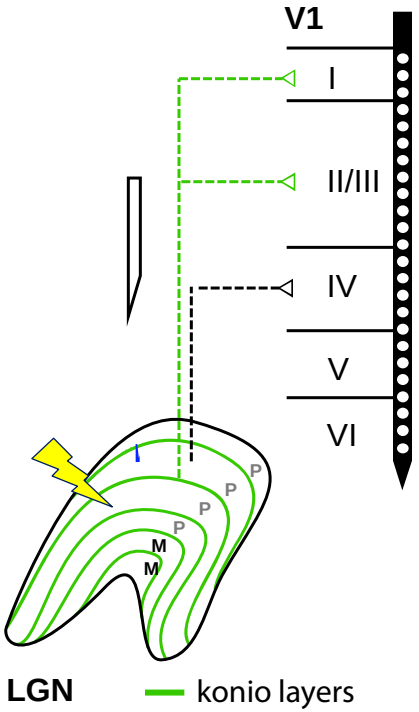


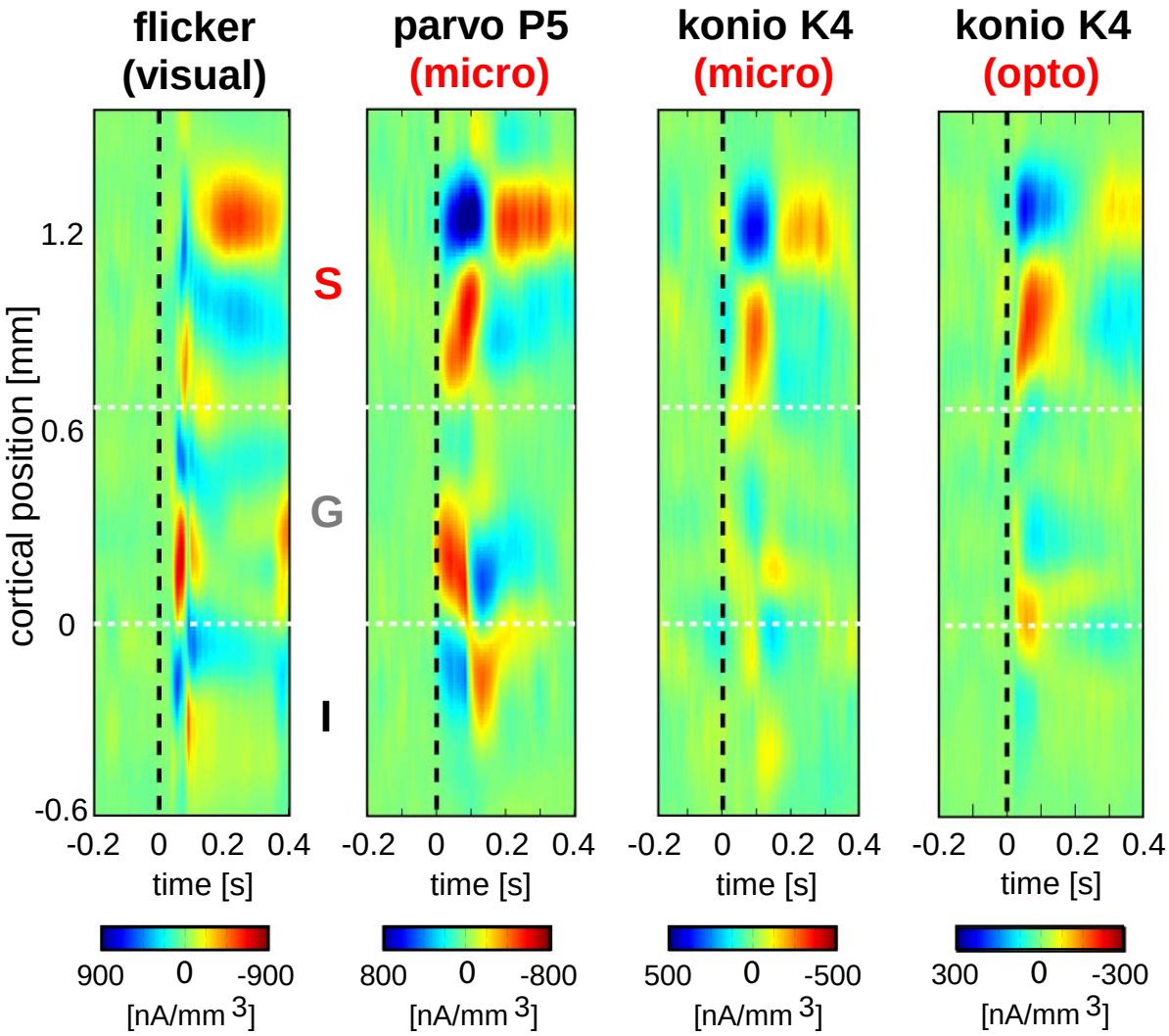




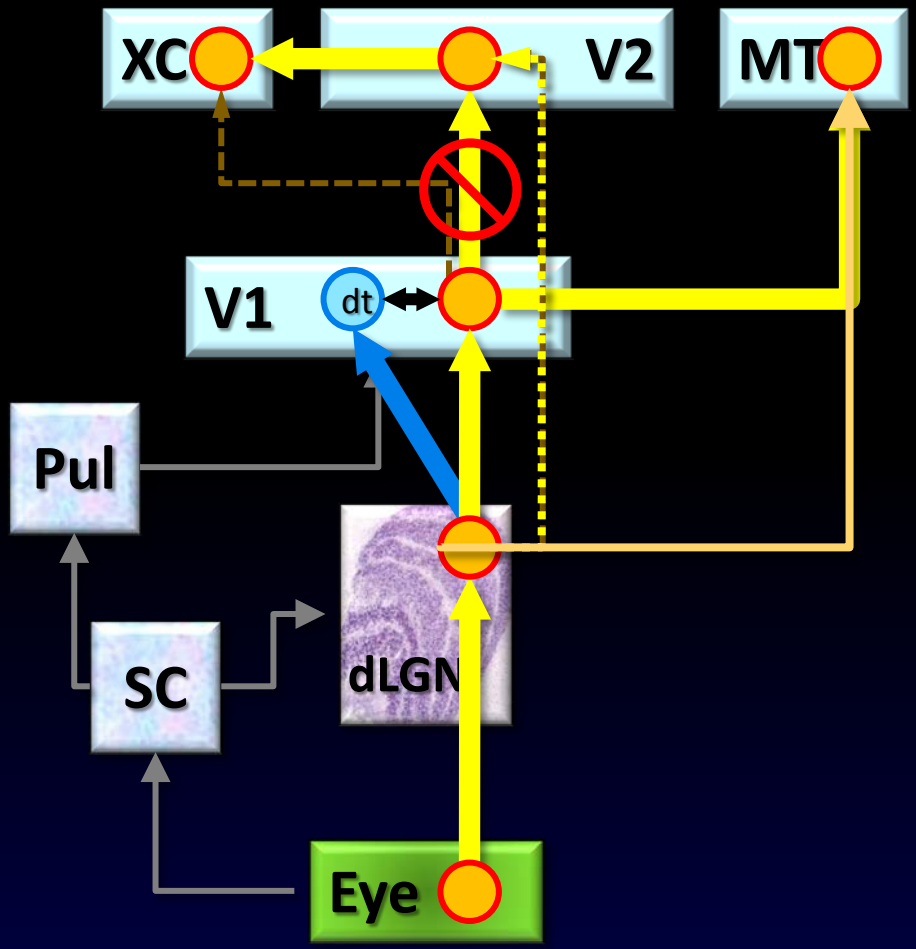


Result II: DES of Konio Activates the Supra-Granular Layers of V1 too; DES of Parvo Activates Granular Layers

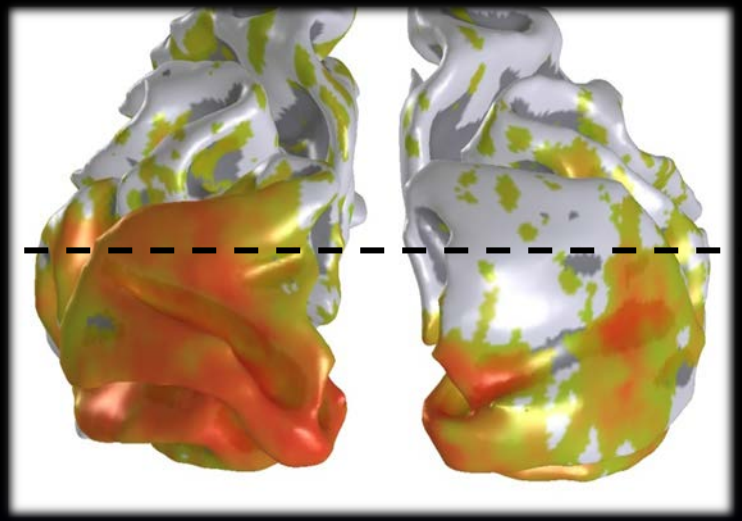


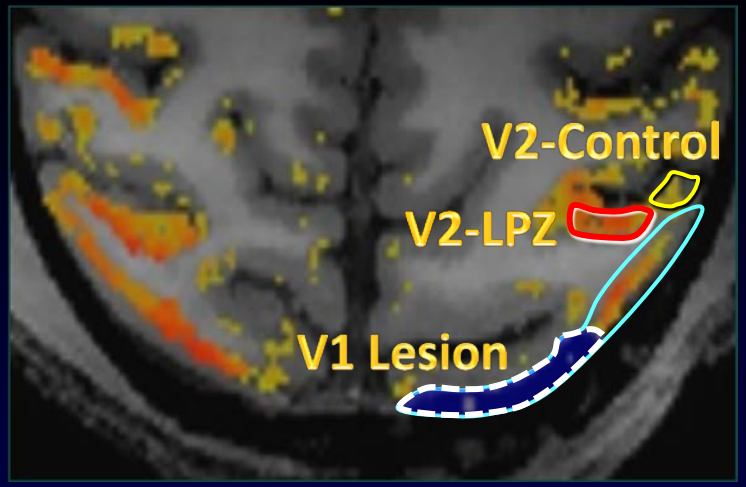


DES in Animals with V1 Lesions



dLGN: Electrical Stimulation in a V1-Lesioned Brain

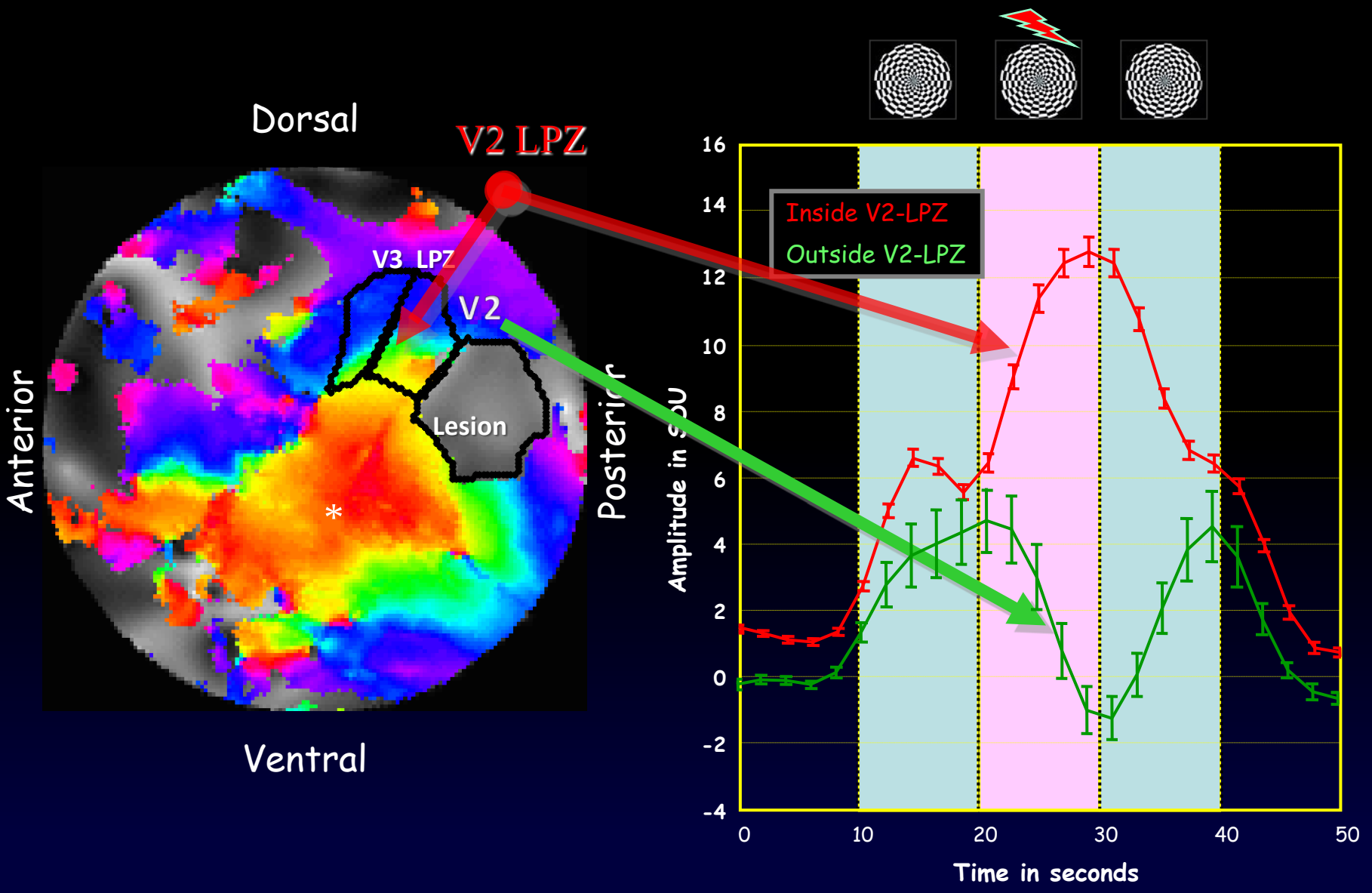




Schmid et al, PLoS One, 2009

Difference Between Intact Regions and Lesion-Projection-Zones

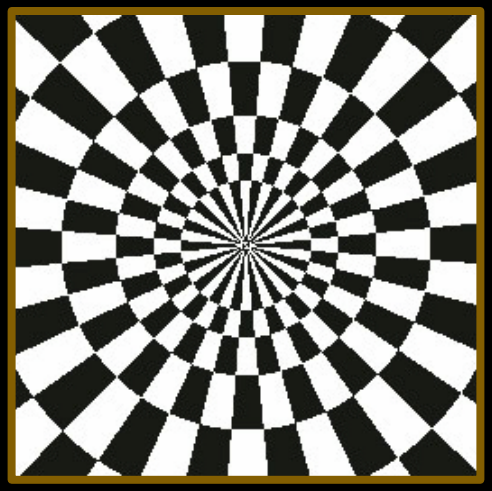
Time Courses of BOLD within and outside of the Lesion-Projection Zone (LPZ) of V2

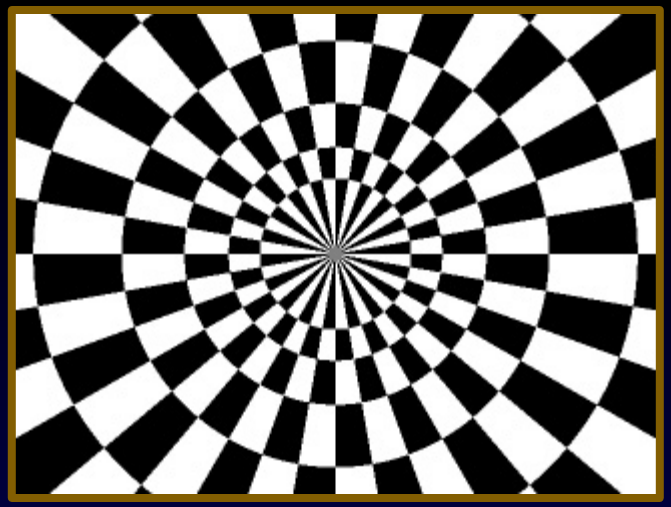


Schmid et al, PLoS One, 2009; Logothetis et al. (in review)

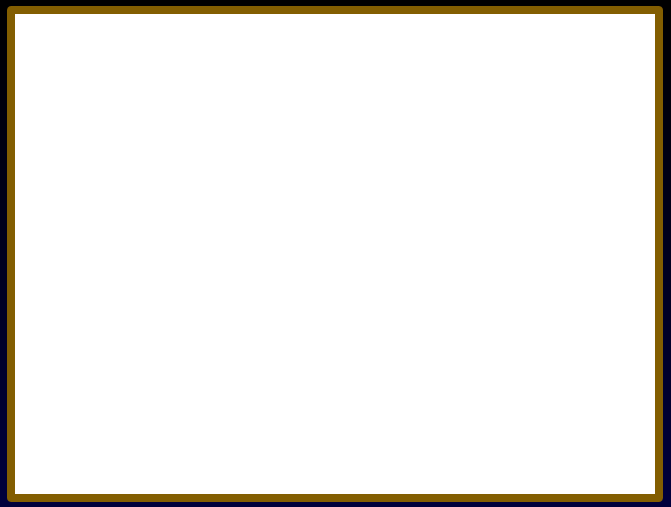
Visual Stimuli for the *Luminance-Flicker* Experiments

Rotating Pinwheel



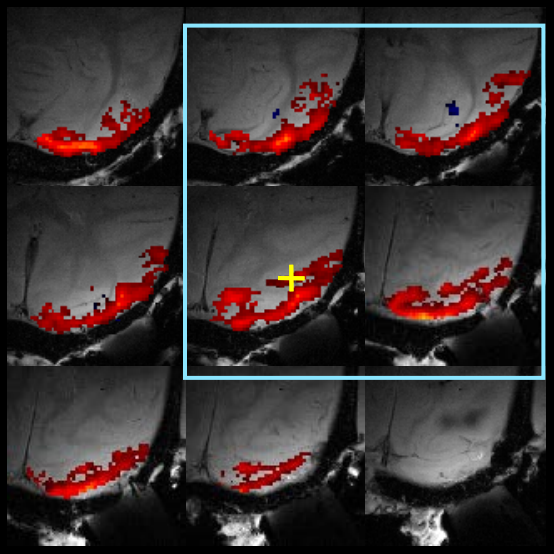


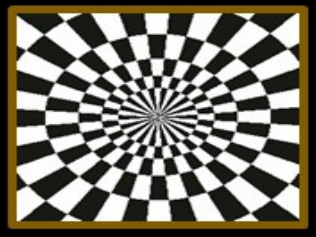
Counterphase Flicker



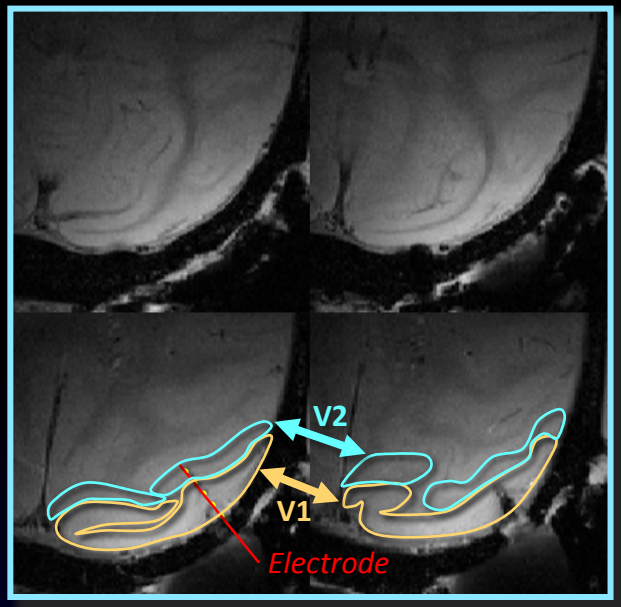
Whole-Field Luminance Flicker

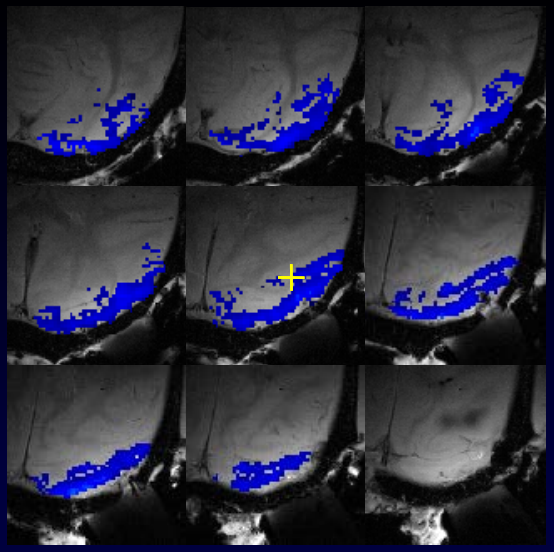
An DES-Analog: Unstructured Whole-Field Flicker ($p < 0.0001$)



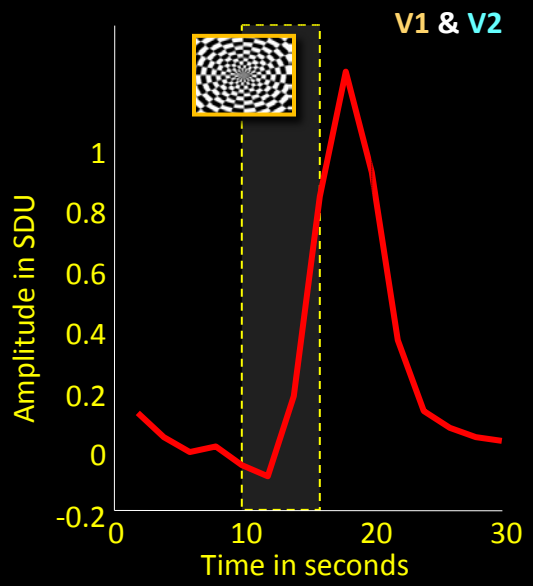


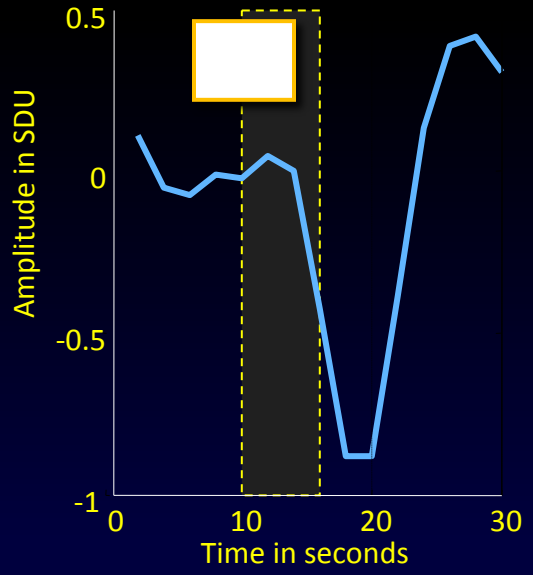
Rotating Pinwheel





Full-field Luminance Flicker

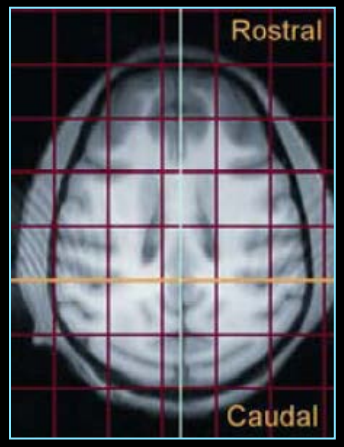


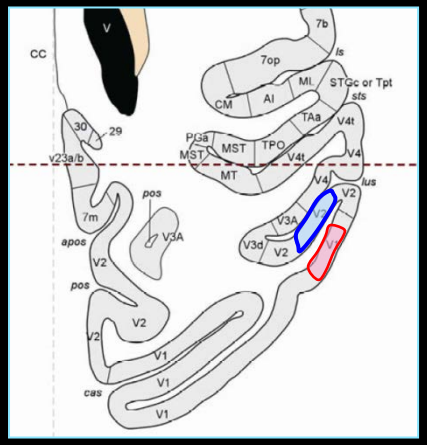


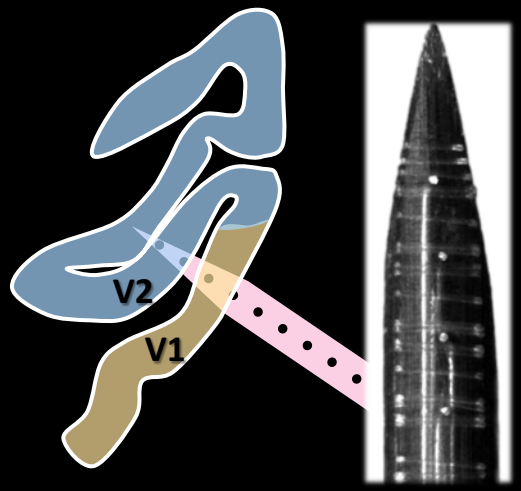
Murayama & Logothetis (in preparation)

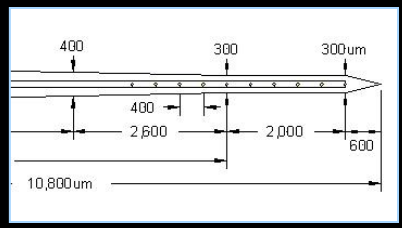
POPULATION DATA

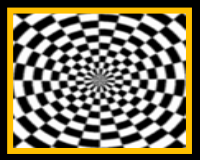
Average BOLD Responses for All Sessions (5 Monkeys)

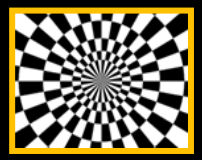


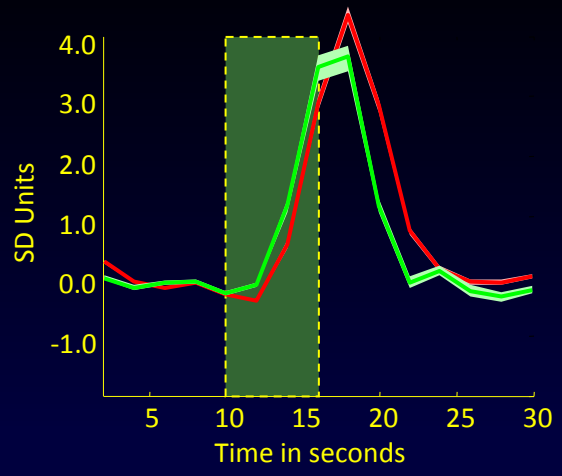


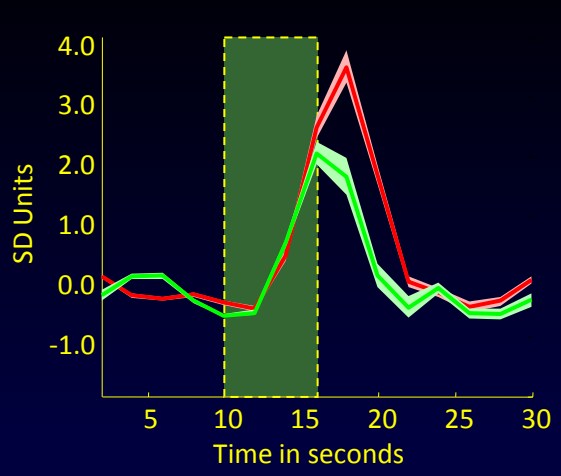


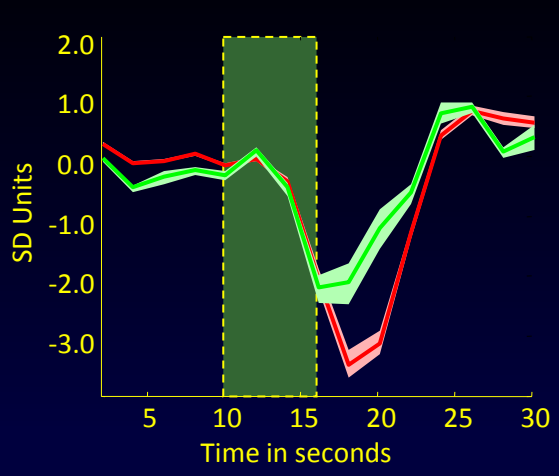










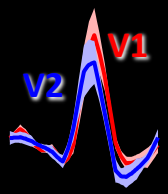


Murayama & Logothetis (in preparation)

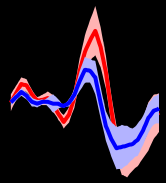
POPULATION DATA

Average Spike Rates for all Sessions for each Recording-Depth

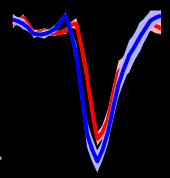
Rotating Pinwheel

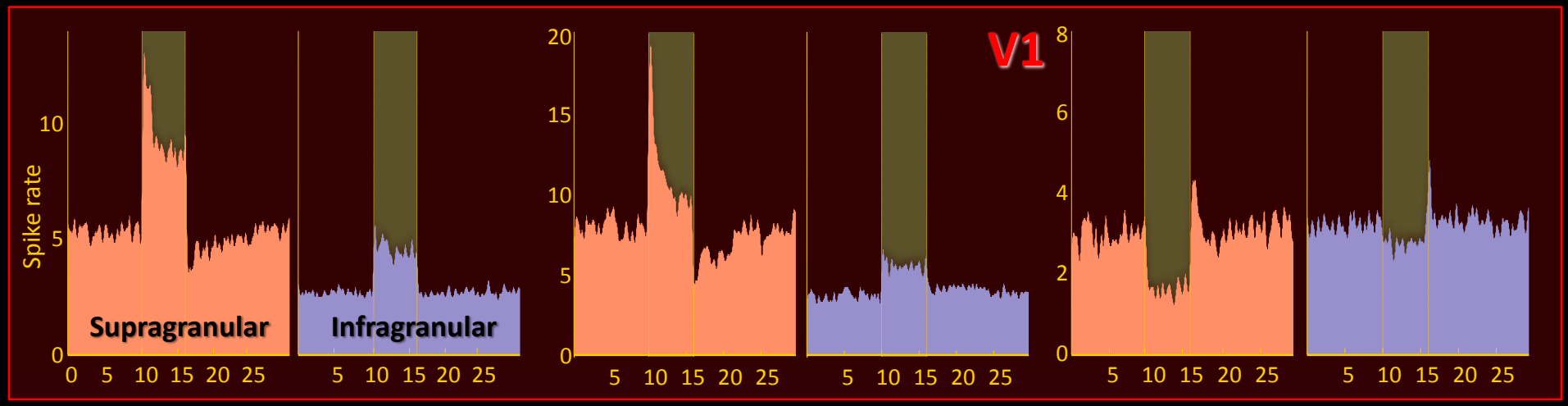


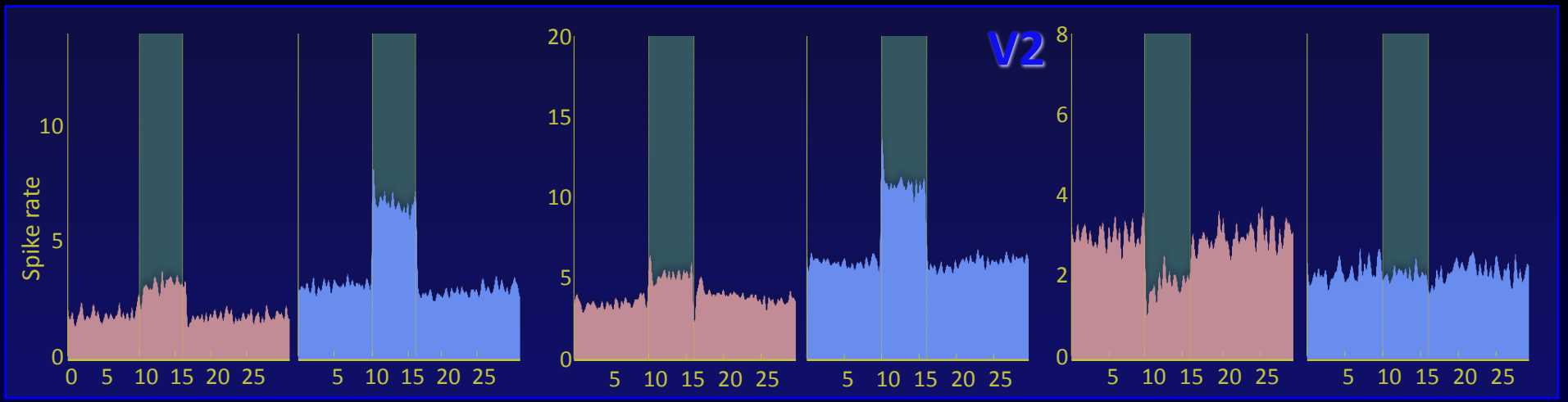
Counter phase Flicker



Full-field Flicker





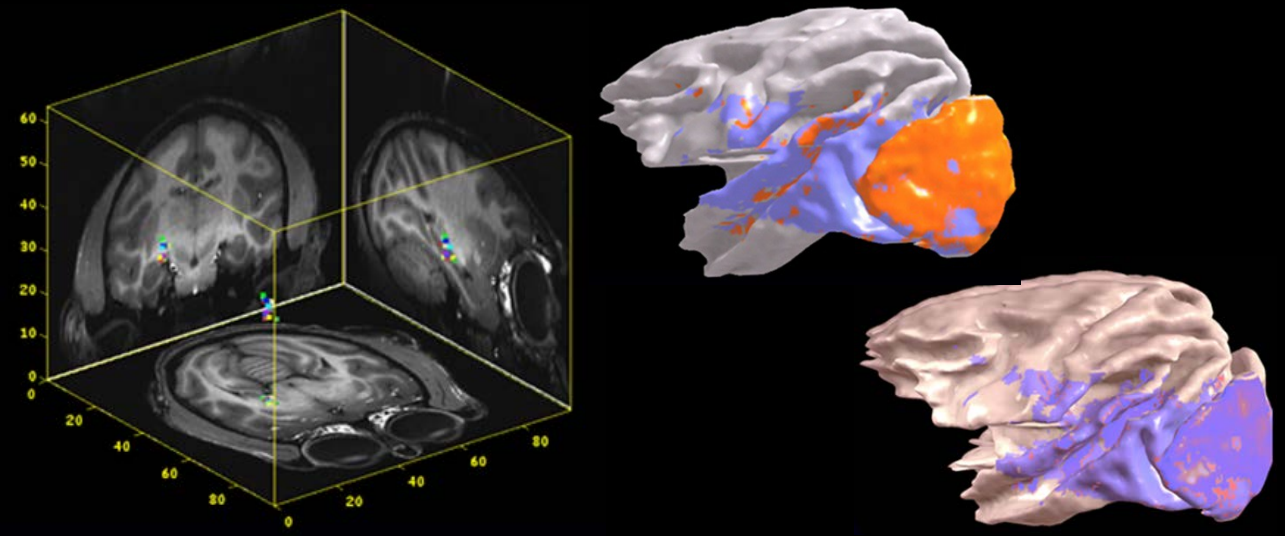


Time in sec

Murayama & Logothetis (in preparation)

CONCLUSIONS

DES-fMRI for the Study of Connectivity



- DES of afferents of a cortical area disrupts the propagation of signals from the projections neurons of the area to the rest of the brain, inducing Negative BOLD Responses (NBR)
- Disruption of propagation is due to strong synaptic-inhibition (rather than reduced excitability), that follows the over-synchronized spatiotemporal profile of ES-elicited thalamic-input
- The use of high-frequency DES increases pulse-efficiency & cortical synaptic activity, demarcating all monosynaptic targets of a stimulated brain-site
- Activation of polysynaptic targets likely reflects the antidromic stimulation of collaterals of infragranular projection neurons and the recruitment of replicating pathways *(e.g. activation of SC during LGN stimulation)*
- Behaviors induced by DES or TMS likely reflect cortico-subcortico-cortical pathways rather than direct cortico-cortical communication

DES-fMRI: Direct Electrical Stimulation and fMRI

Mapping Monosynaptic Connectivity & Cortico-Thalamo-Cortical Loops

Acknowledgments

Collaborators

Yusuke Murayama (Neuroscience)

Fahad Sultan (Neuroscience)

Mark Augath (Electrical & Bioengineering, MRI)

Andreas Tolias (Neuroscience)

Hellmut Merkle (Physics, RF Technology)

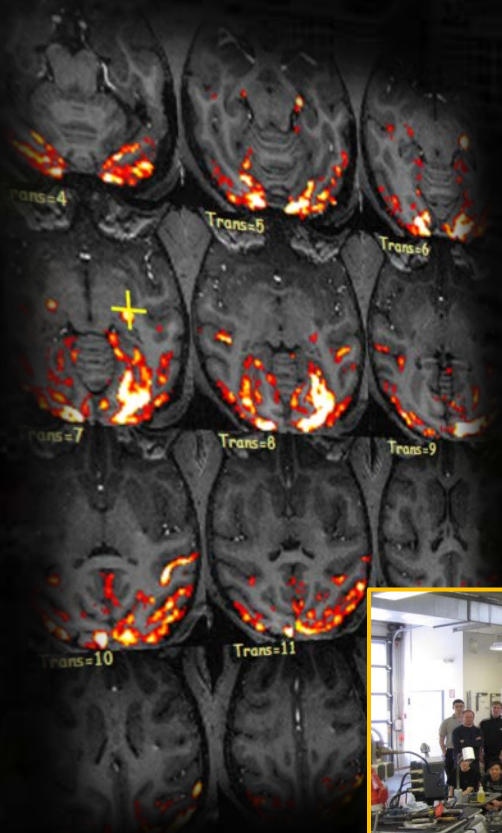
Axel Oeltermann (Physics, Electronics)

Thomas Steudel (Electrical Engineering, MRI)

Alexander Rauch (Neuroscience)

Santiago Canals (Neuroscience)

Jozien Goense (MRI, Biophysics)



MPI Infrastructure (Machine- & Electronic Shops)

Nikos K. Logothetis

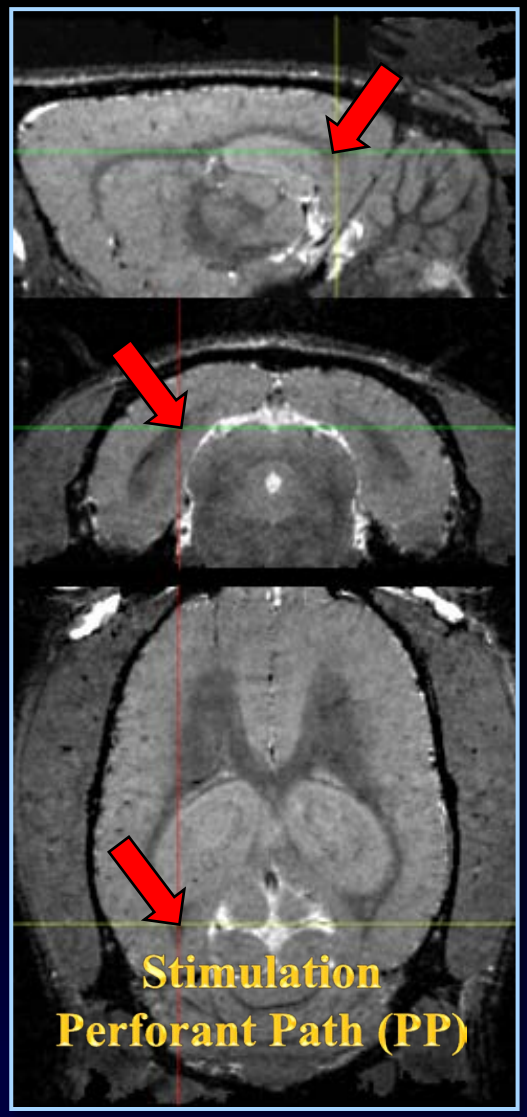
Max Planck Institute for Biological Cybernetics

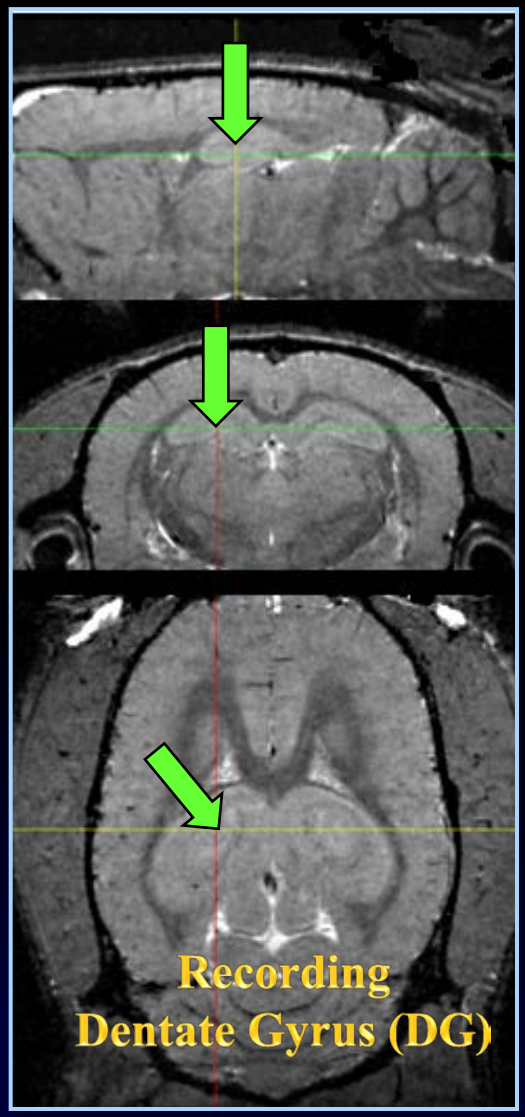
Basic Setup, Stimulation & Recording Sites

3D-FLASH @16T

Matrix: 256x140x256, FOV=25.6x14x25.6mm^3 (0.1mm Isotropic)

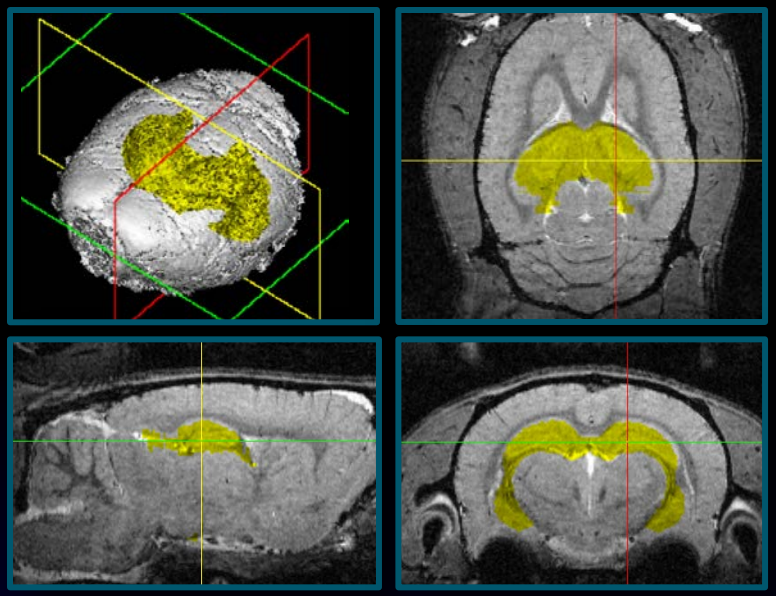
TE/TR=6/25ms, BW=60kHz,

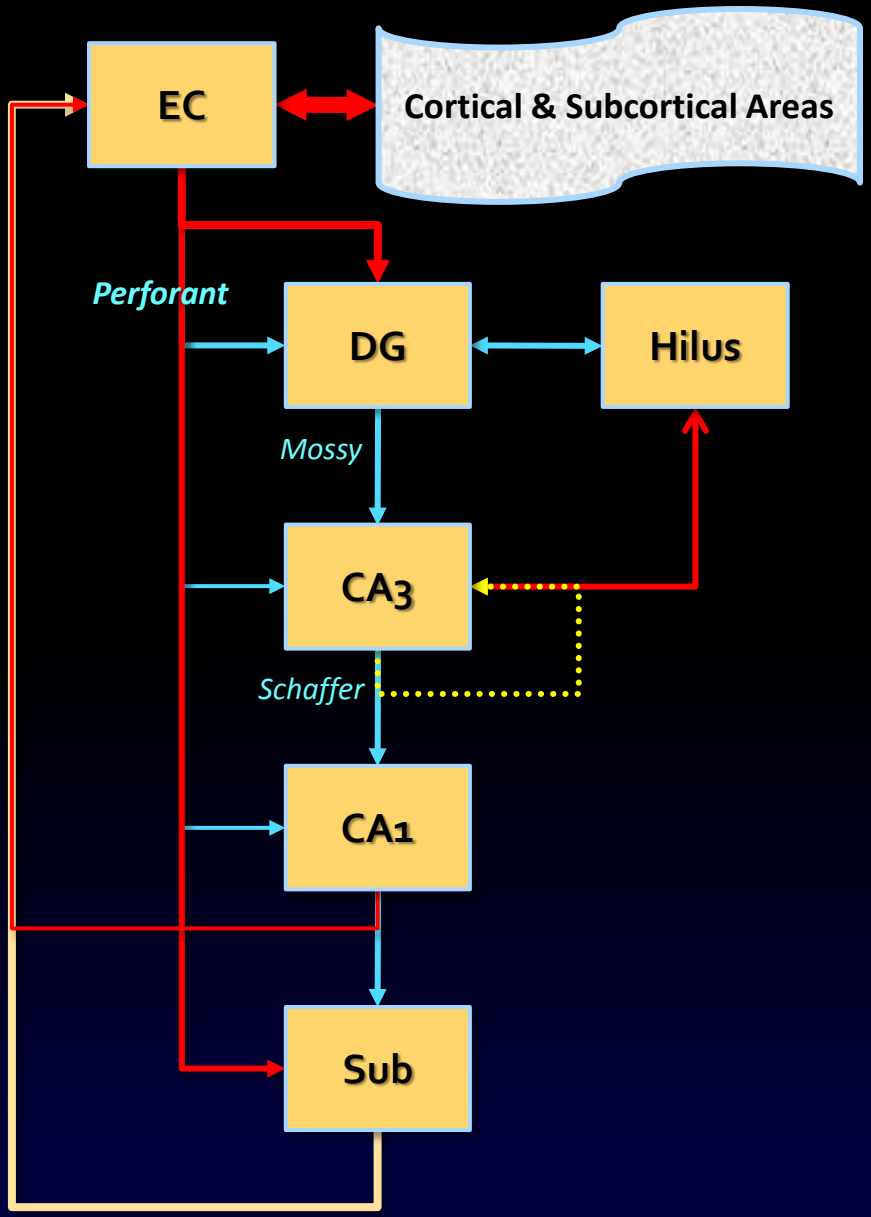




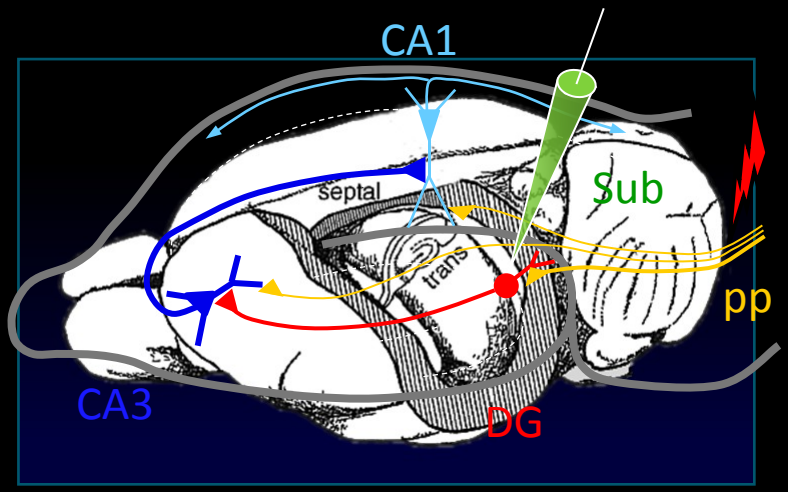
Logothetis, Pohman & Augath (in preparation)

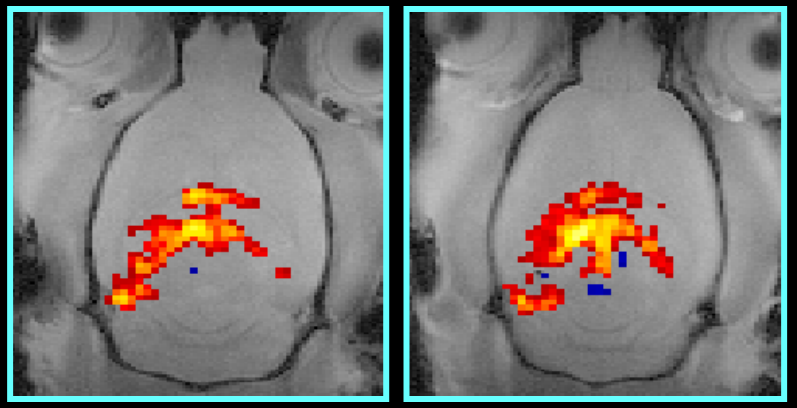
Hippocampus & fMRI of Long Term Potentiation (LTP)

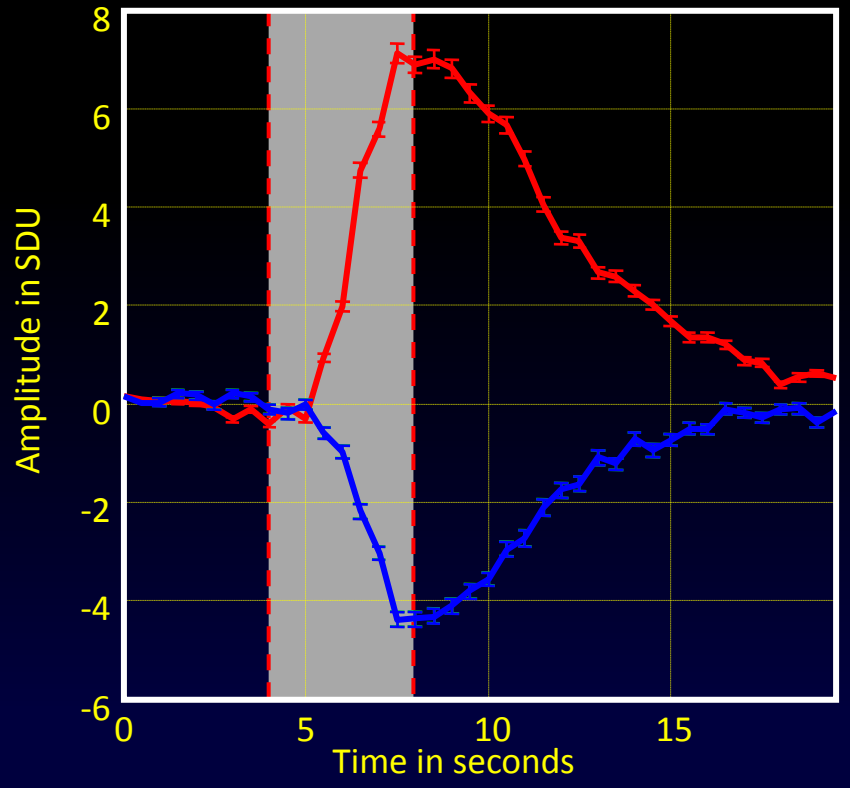




BOLD Responses in Hippocampal Subfields Following ES of Perforant Path

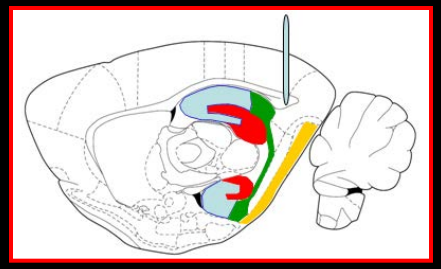


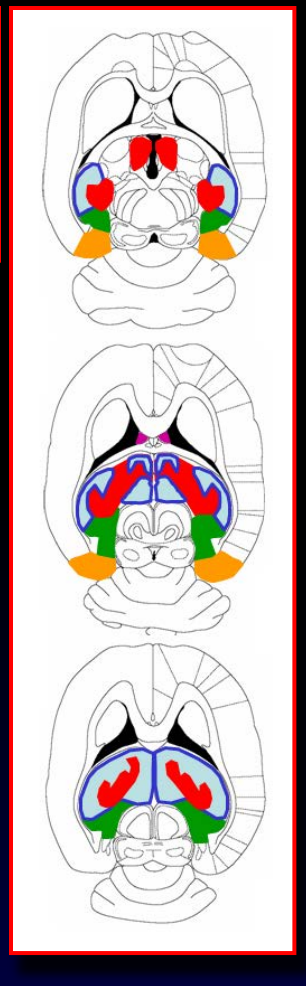




Canals et al, Mag Res Imaging (26), 2008; Canals et al, Cur. Biology, 2009

Stimulation of Perforant Path: Frequency-Dependent Activation of Hipp-Fields



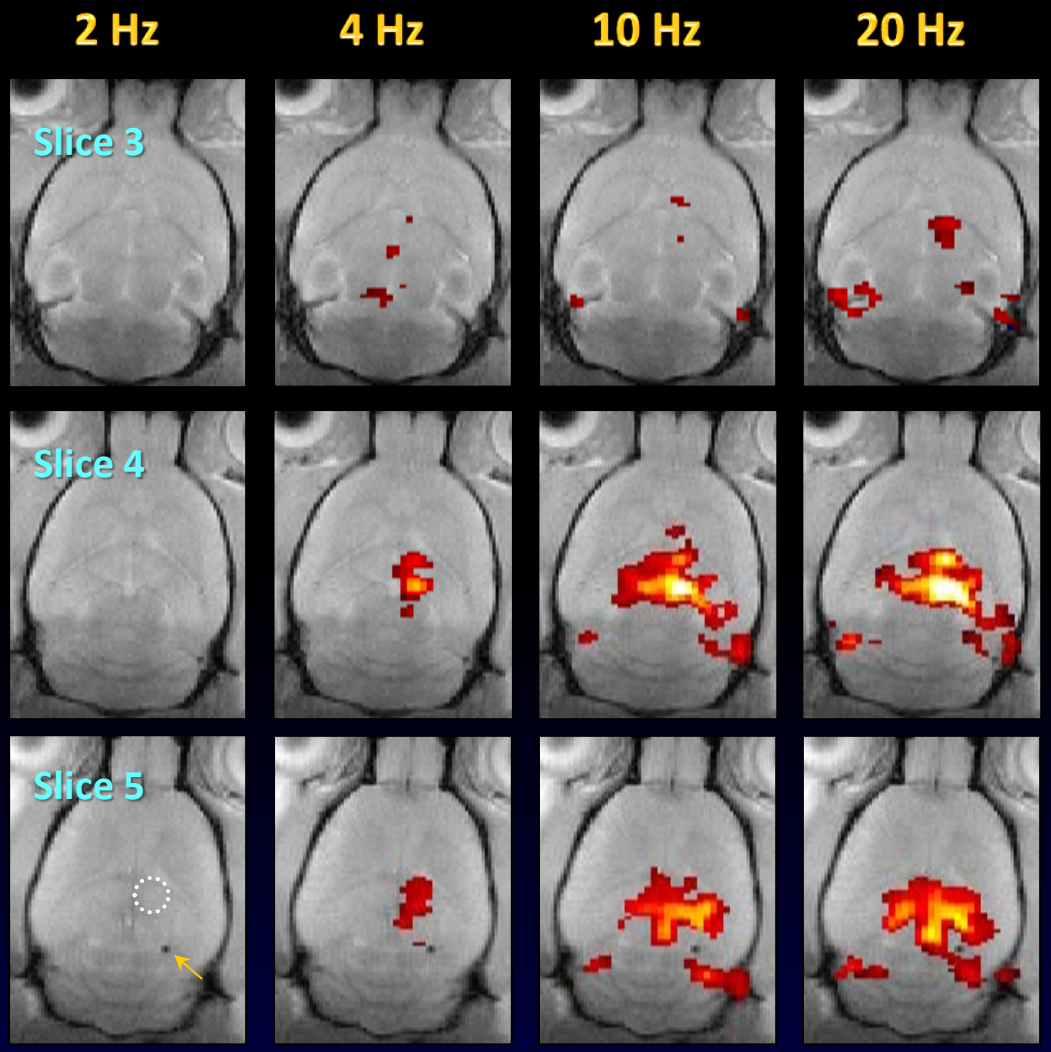


CA1-CA3

Sub

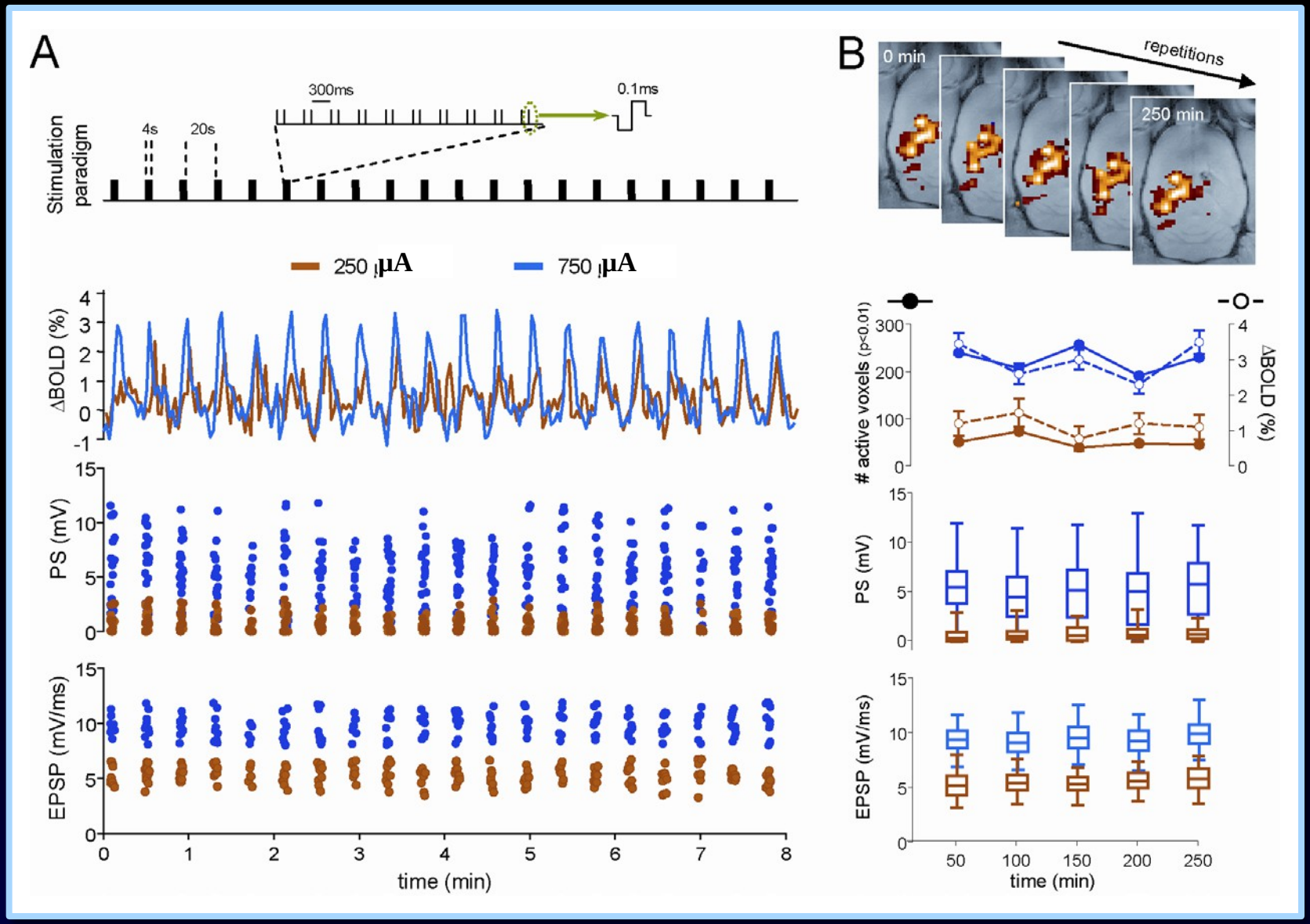
DG

EC



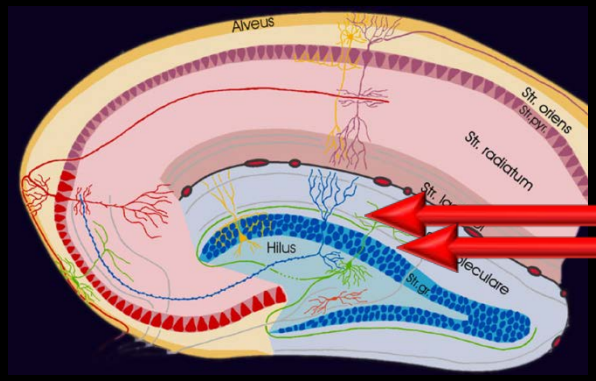
Canals et al, Mag Res Imaging (26), 2008; Canals et al, Cur. Biology, 2009

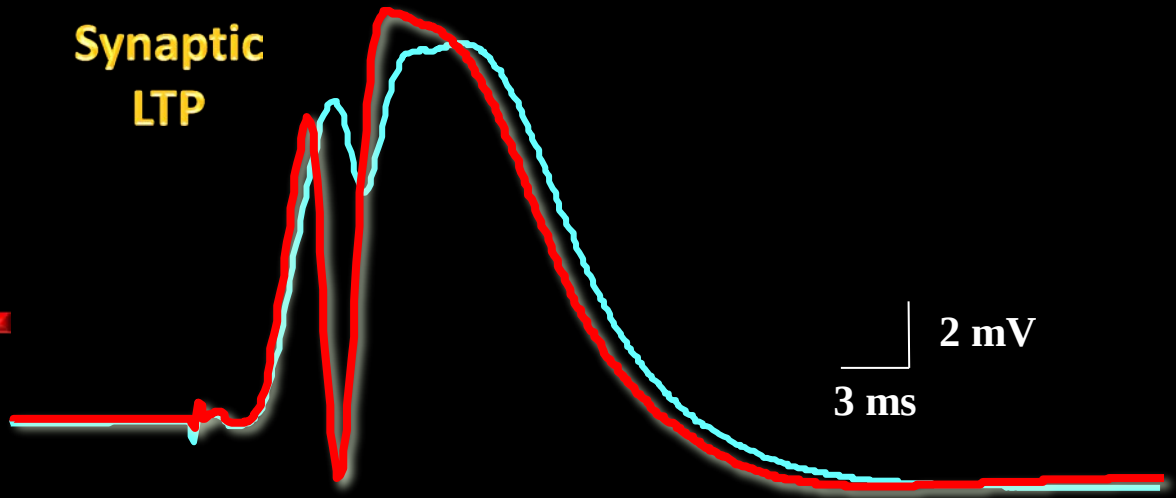
LTP-fMRI: Stimulation Protocol and Response-Stability

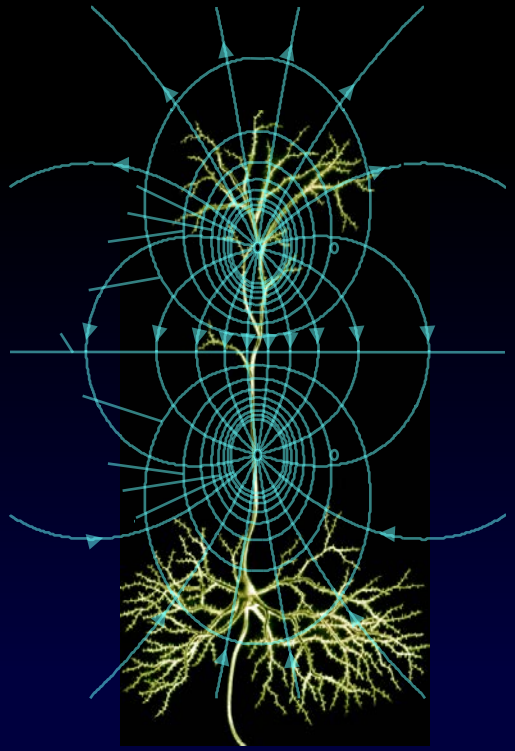


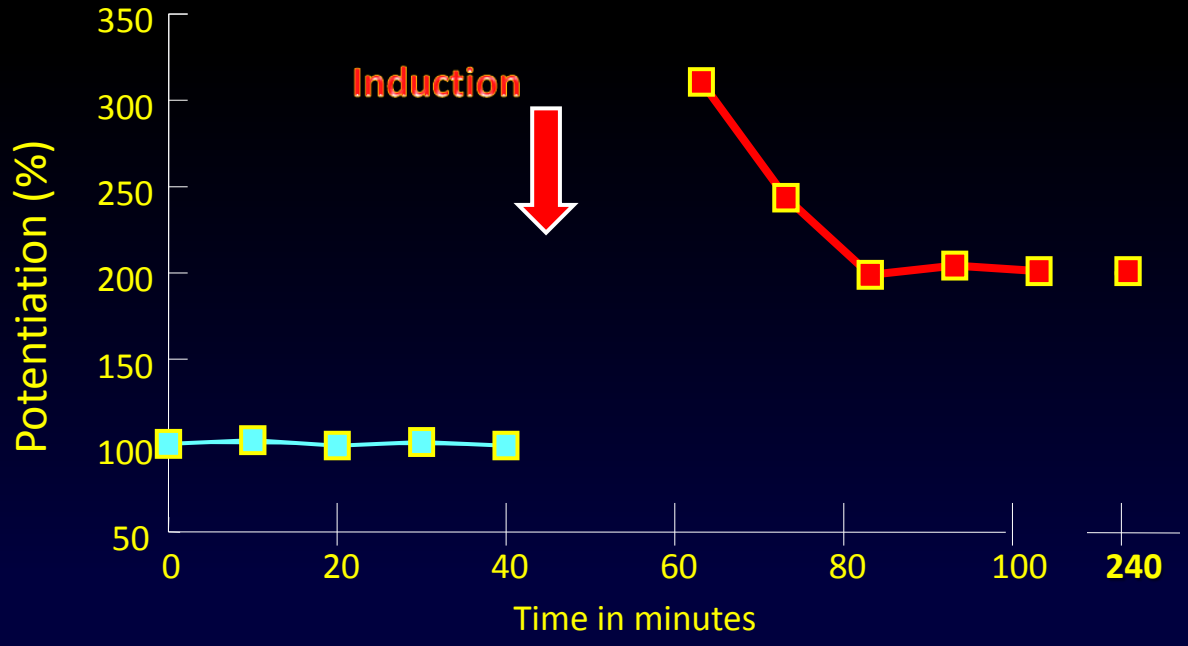
Canals et al, Mag Res Imaging (26), 2008; Canals et al, Cur. Biology, 2009

LTP-fMRI: Population spike – Time course & Amplitude Evolution



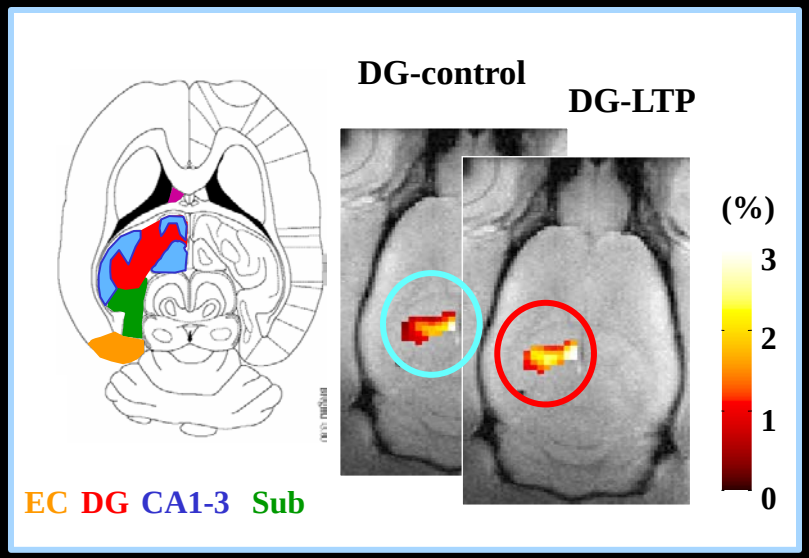


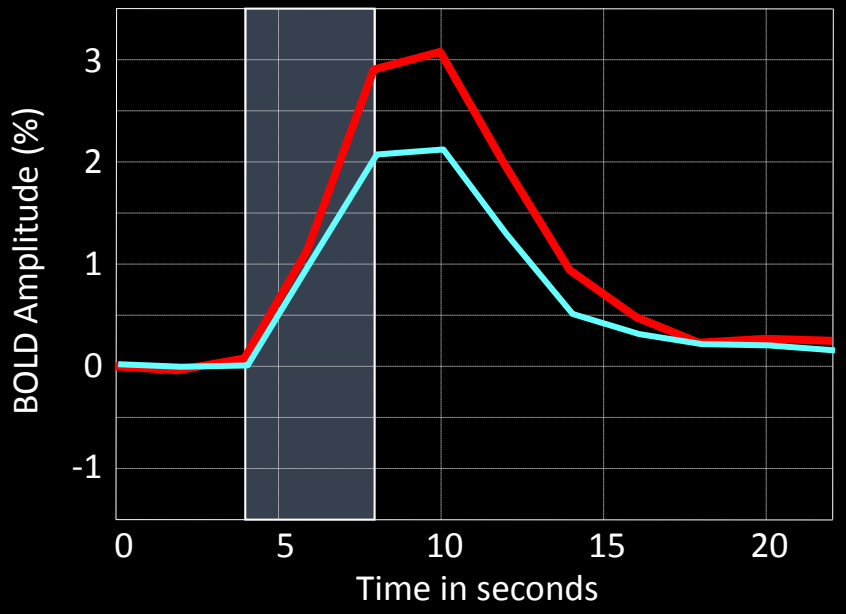


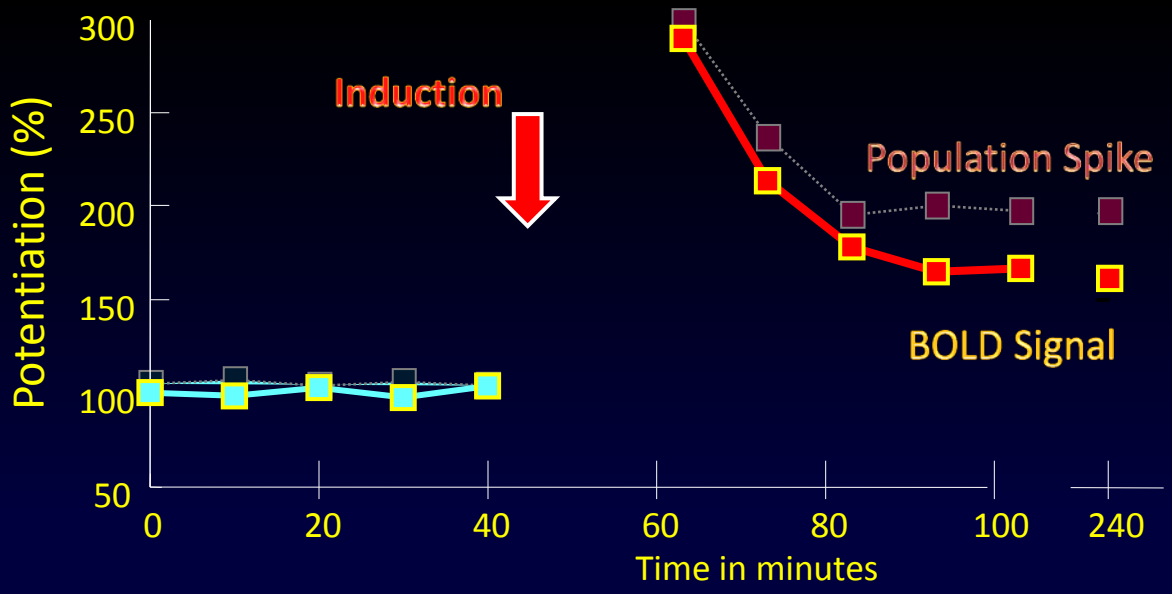


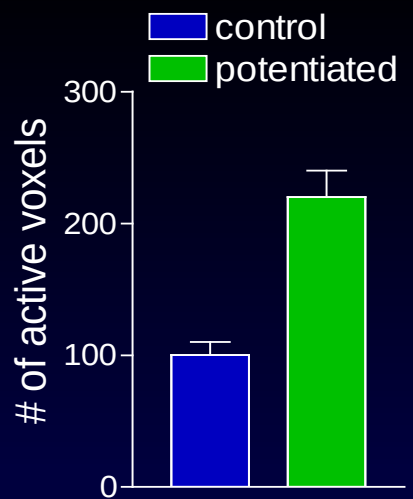
Canals et al, Cur. Biology, 2009

LTP-fMRI: BOLD Signal – Time course & Amplitude Evolution



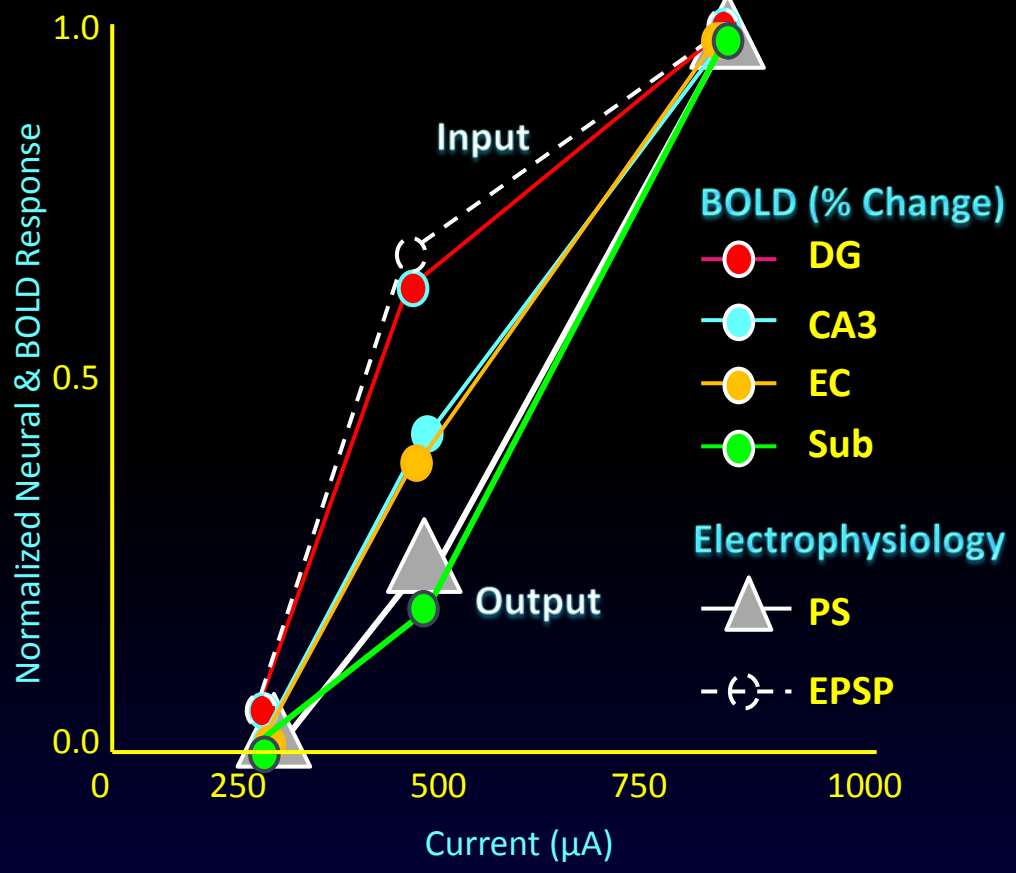




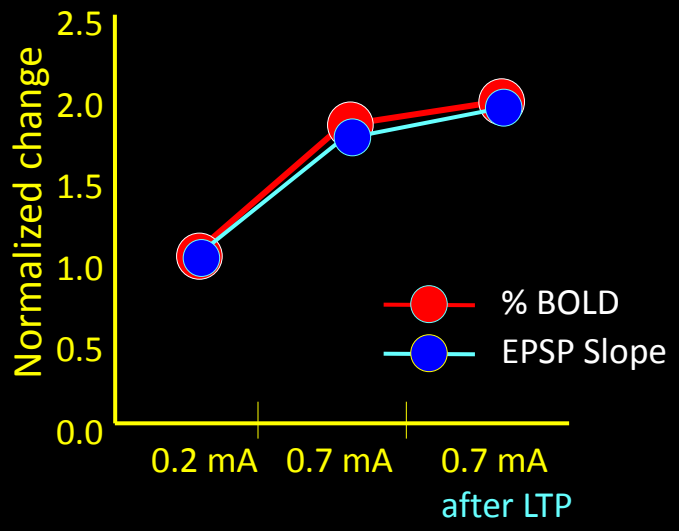


Canals et al, Cur. Biology, 2009

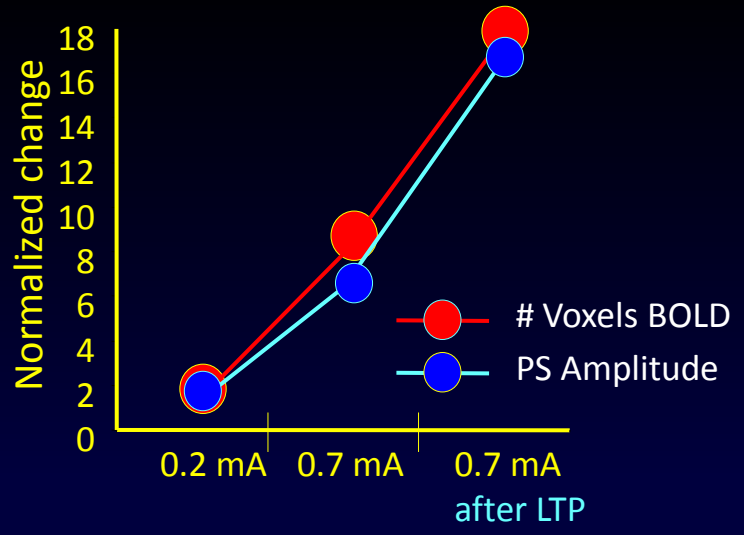
Neural & BOLD Responses in Hippocampus



BOLD Amplitude-Changes in DG correlate the EPSP

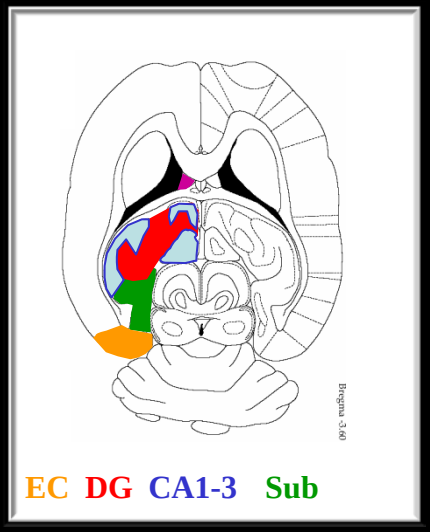


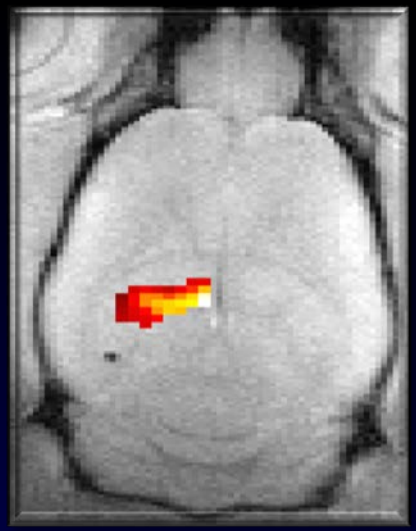
Activated volume correlates with PS

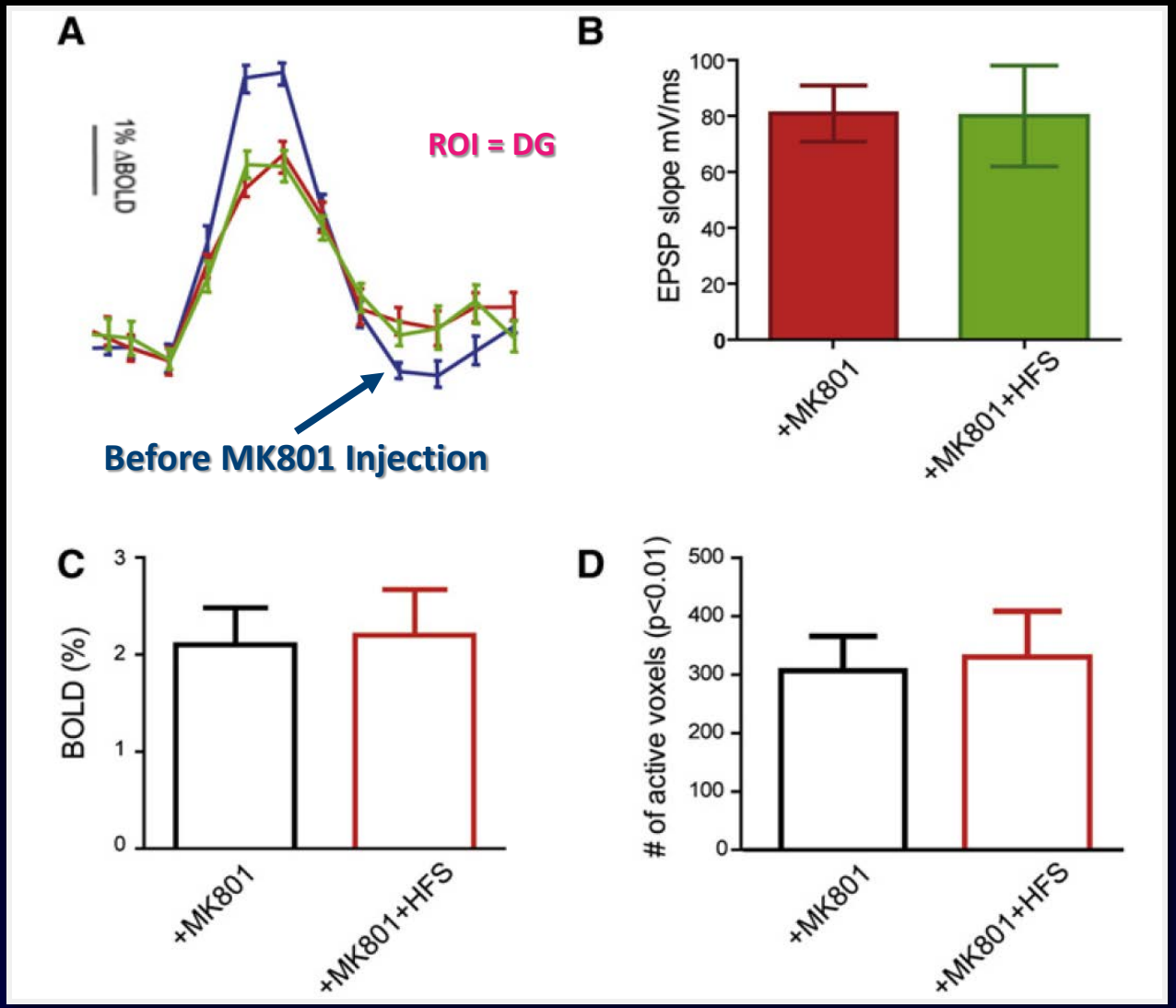


Eschenko et al (in progress), Canals et al, Mag Res Imaging (26), 2008; Canals et al, Cur. Biology, 2009

LTP-fMRI: NMDA-Channel Dependency of BOLD-Enhancement

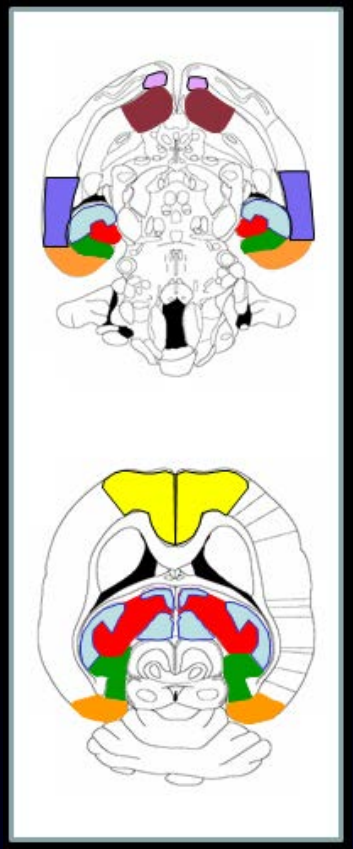


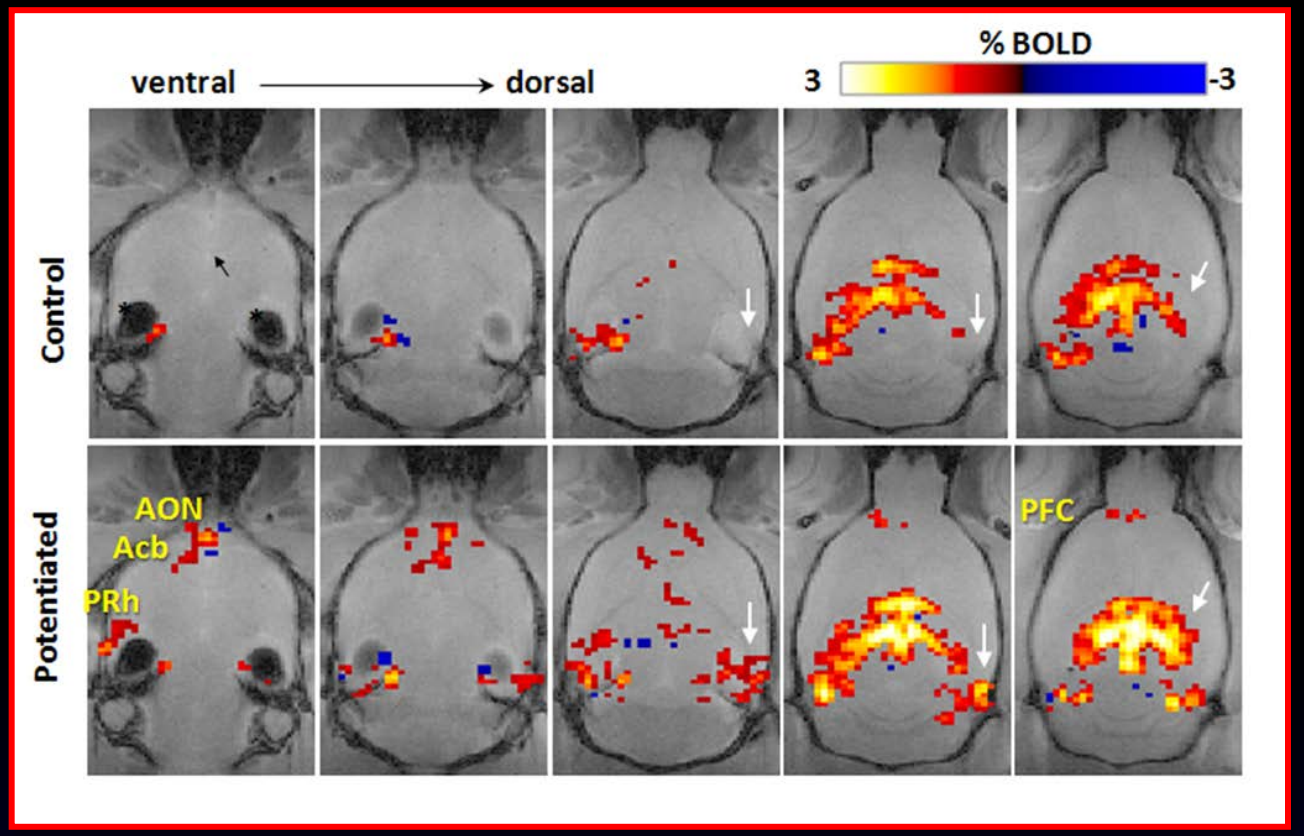




Canals et al, Cur. Biology, 2009

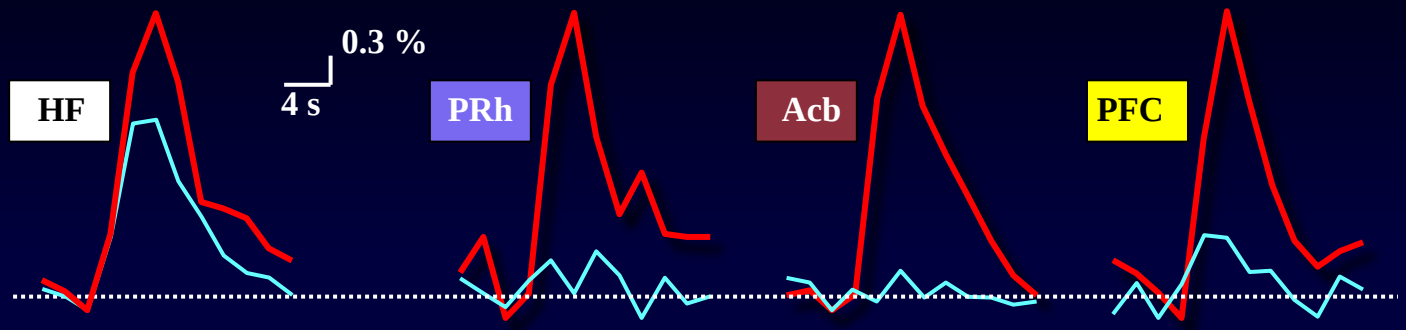
LTP-fMRI: Synaptic Plasticity & Effective Connectivity – Area Recruitment





DG
CA1-3
Sub
EC

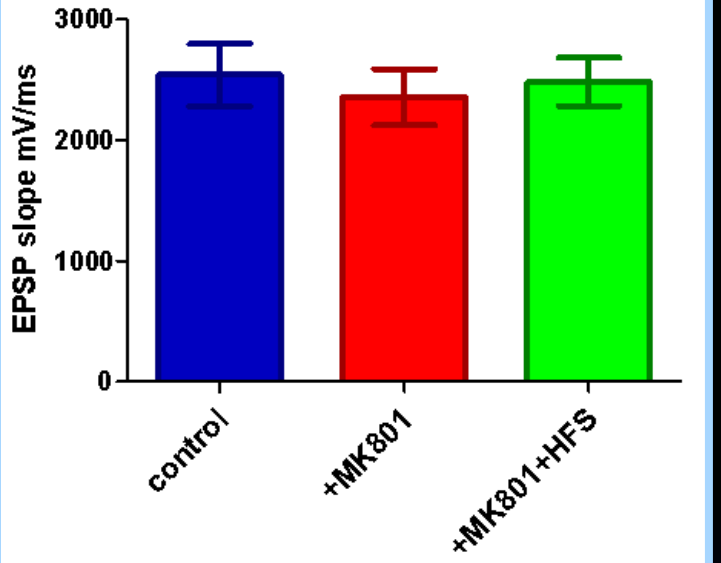
PFC
Acb
AON
PRh

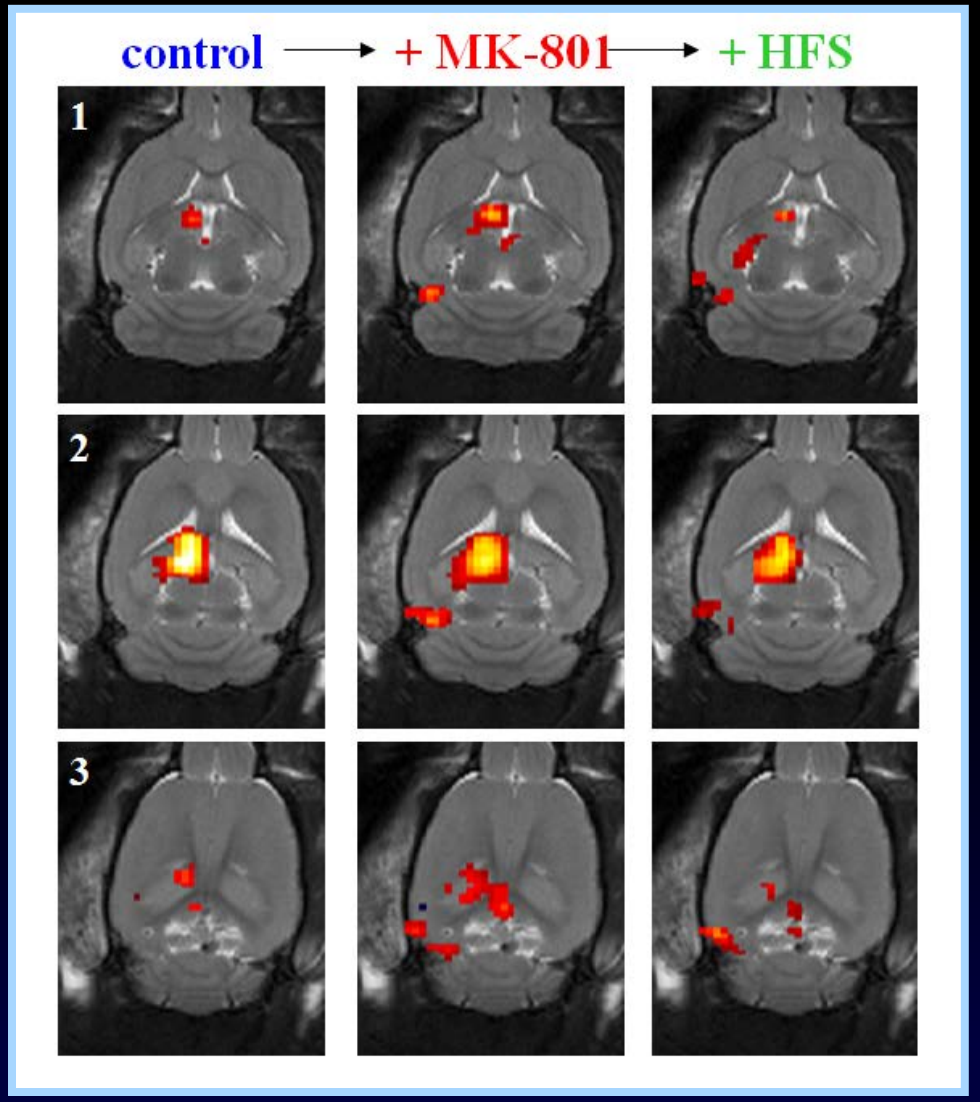


Canals et al, Cur. Biology, 2009

LTP-fMRI: Synaptic Plasticity & Effective Connectivity – NMDA Effects

Synaptic & Network Plasticity – NMDA Dependence

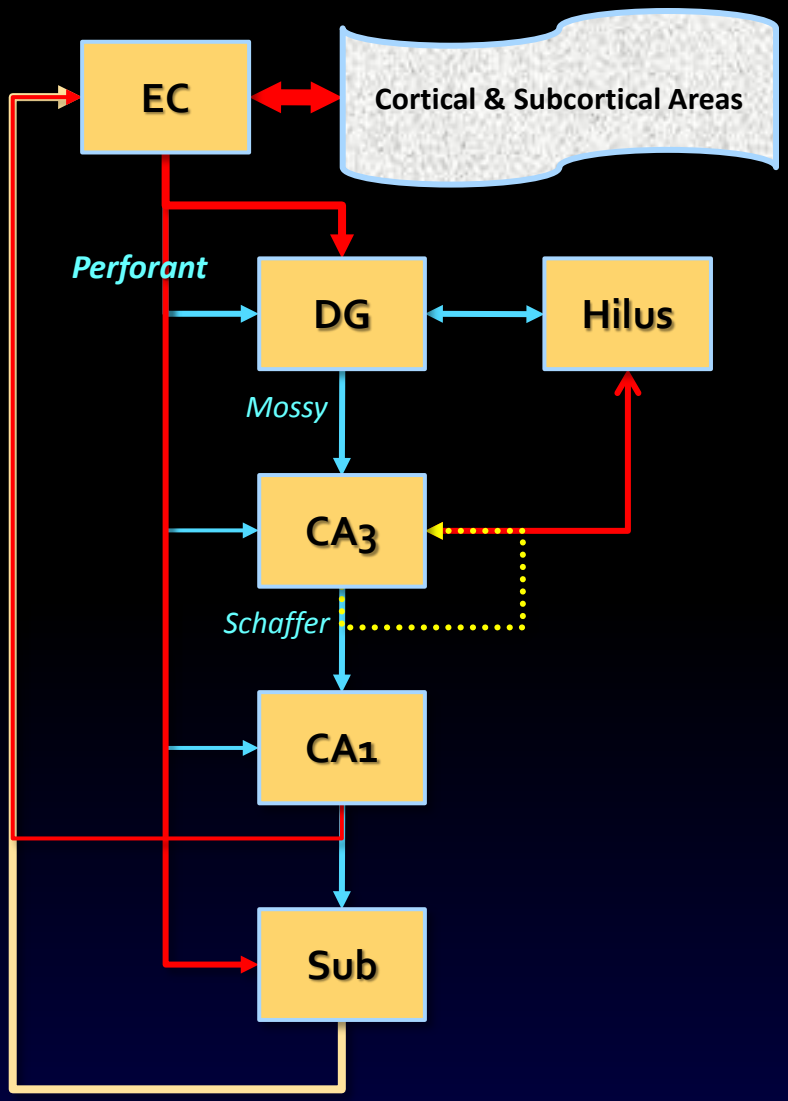




Canals et al, Cur. Biology, 2009

Stimulation: PP --- Recording: DG

- LTP induction changes the BOLD response of the target subfield of the hippocampus
- LTP-induction results in network-reorganization that includes increased interhemispheric communication, and recruitment of limbic and neocortical circuits
- The nature of the recruited structures points to an increased communication between associational, polysensory cortices with the cortical and subcortical limbic network subserving memory
- The number of targets of the hippocampal output greatly exceeds the number of extrahippocampal structures shown in the BOLD maps, suggesting that the functional consequences of synaptic potentiation do not uniformly affect the entire anatomically defined network



Canals et al, Cur. Biology, 2009