NET-fMRI of Large- Scale Brain Networks:

Mapping Dynamic Connectivity During Epochs of Synaptic and System Consolidation

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

MAX PLANCK INSTITUTE FOR BIOLOGICAL CYBERNETICS

Nikos K. Logothetis

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Non-Adaptive Complex Systems: *Rayleigh–Bénard cells, cloud-streets, snow-flakes, sand-ripples…*



Adaptive Complex Systems: *Anthills, flocking, schooling, social organization, economics, genomes, CNS, …*

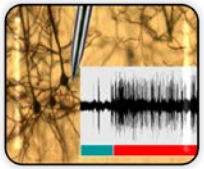
Brain – A Complex Dynamic System Par Excellence

86 Billion Neurons

6 Billion Neurons

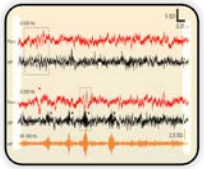
70 Million Neurons

- **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…



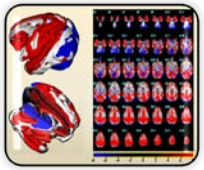
Microscopic Activity (various spike-types)

Neurons/Microcircuits (microns, msec), e.g. cortical E-I microcircuits



Mesoscopic Activity (mean extracellular field potentials)

Columns/Macrocolumns/Slabs [0.3-3mm, sec-fractions)
Covariant spiking, Neuropil activity, Integration over dendritic fields

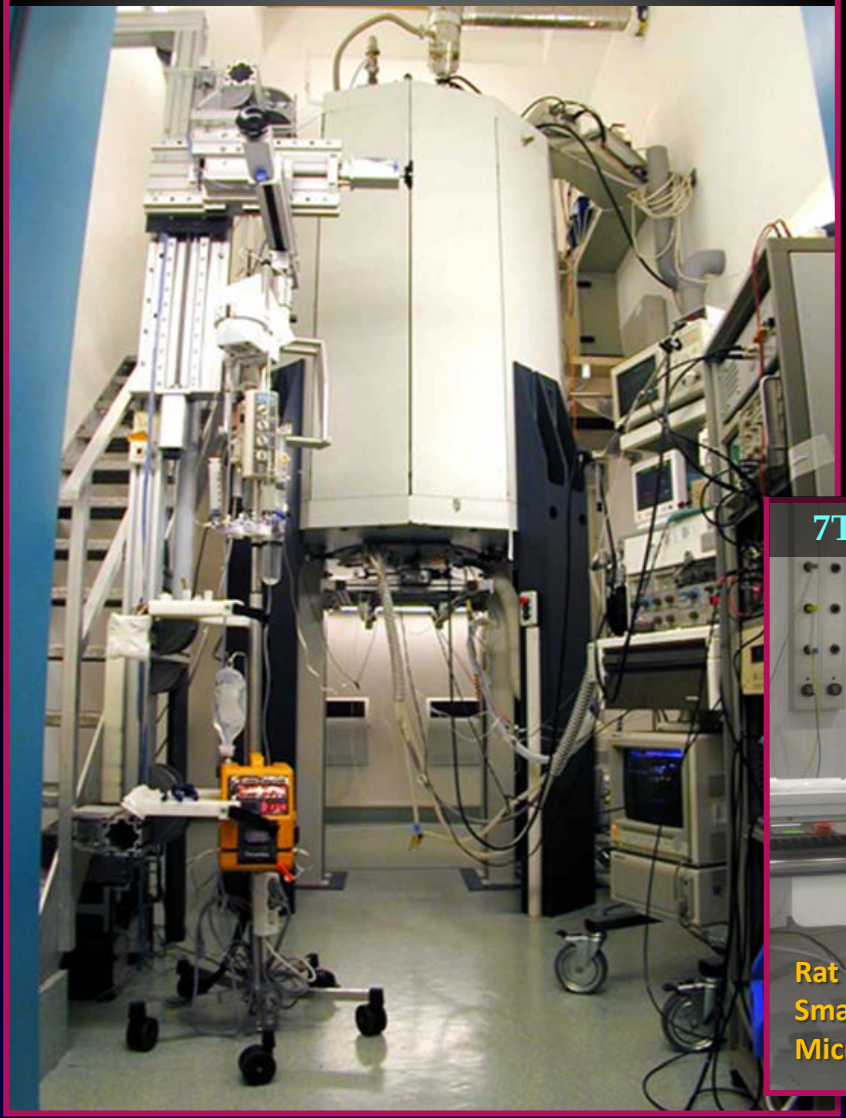


Macroscopic Activity (metabolic activity of networks)

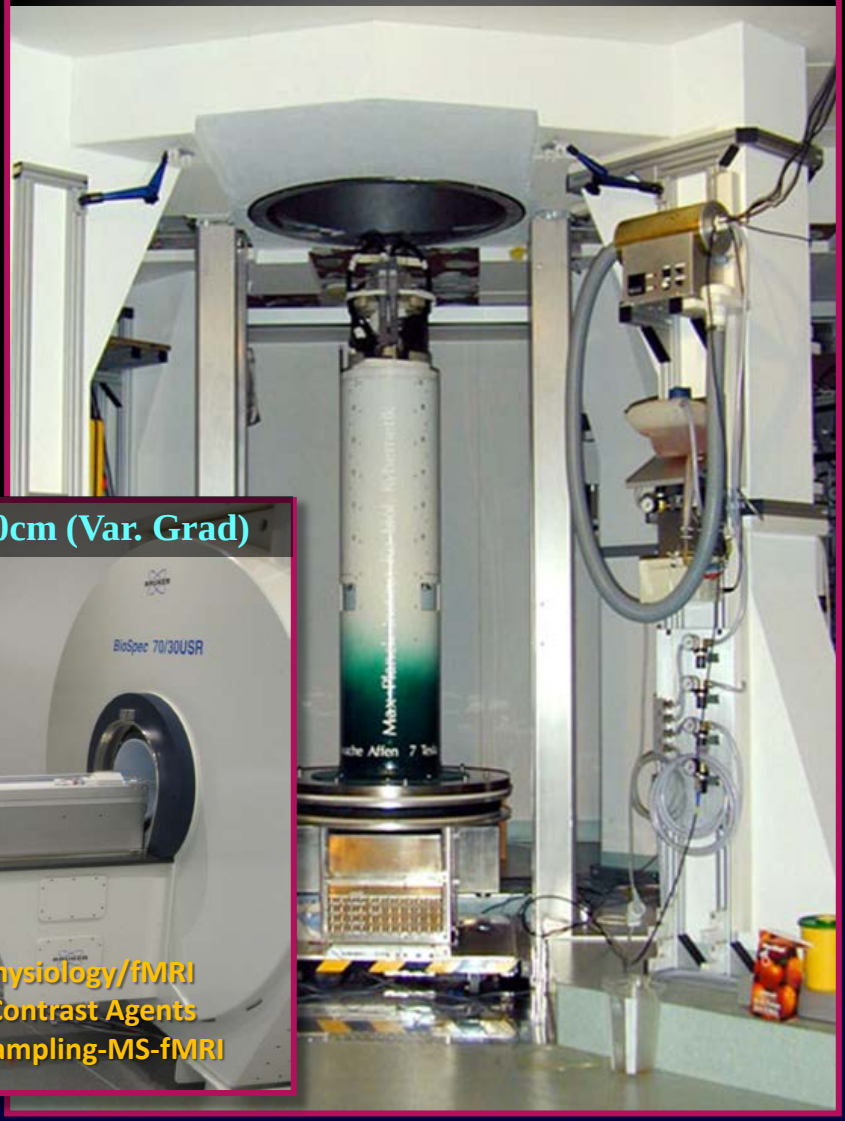
Anatomically defined ROIs/Fields/Areas (mm/cm, sec)
Interaction of multiple sensory structures within or between modalities
Neuromodulatory effects & non-synaptic volume transmission.

Multimodal Approach – Combining Micro (Phys)- and Macroscopic Scales (MRI)

4.7T/40cm - 50mT/m 180µs



7T/60cm - 85mT/m 190µs



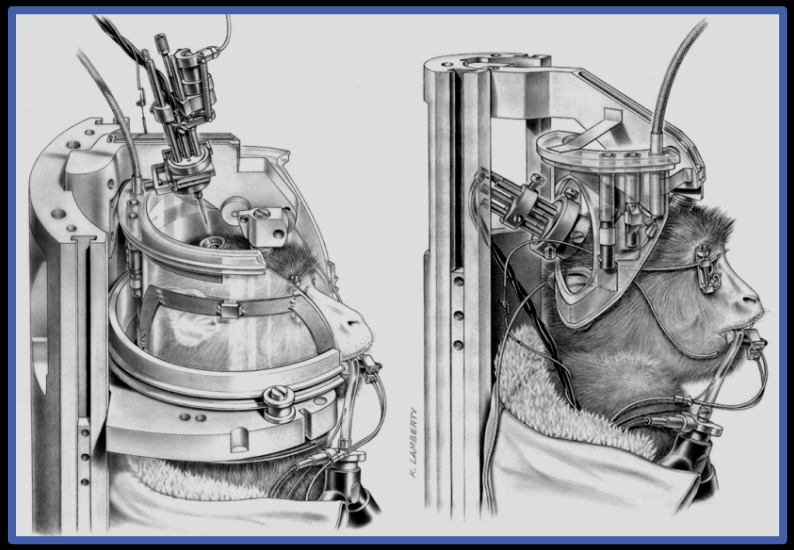
7T/30cm (Var. Grad)

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

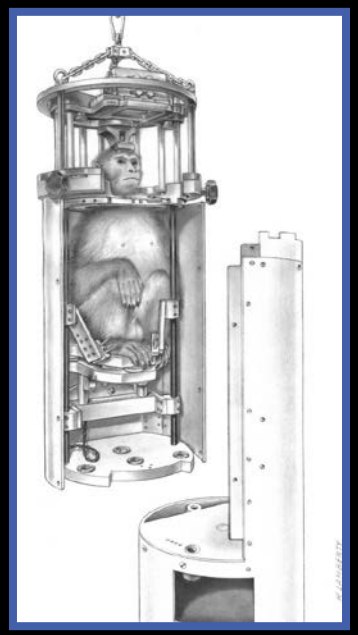
Bruker BioSpin Scanners

Multimodal Approach – Data Acquisition & Animal Training

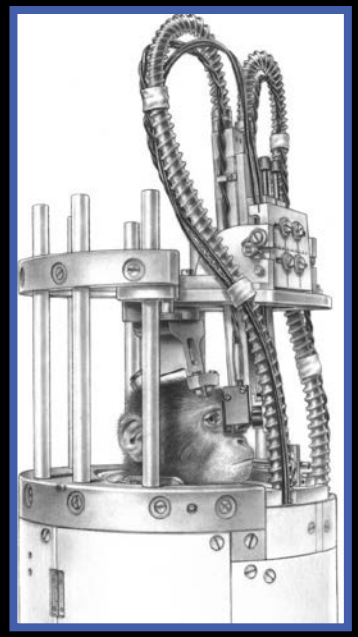
Coils, Sensors & Electrode-Holders



Primate-Chairs & Transport

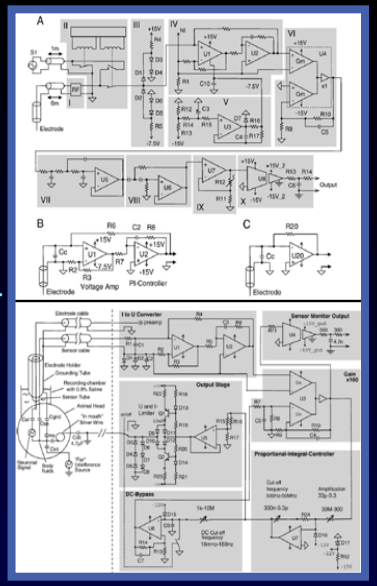


Behavioral Monitoring

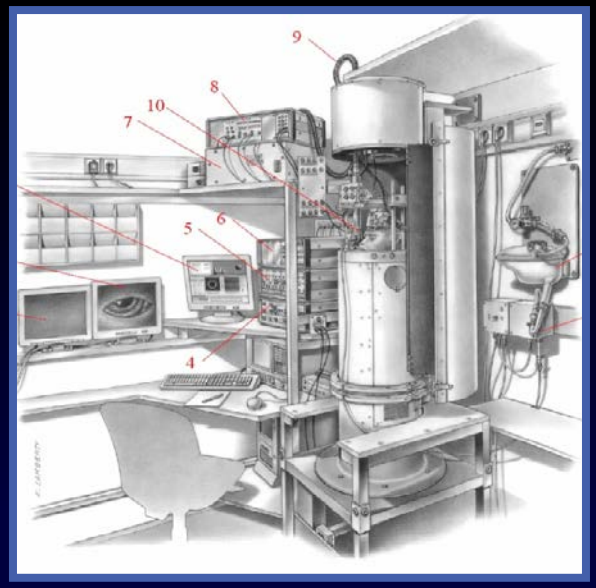


Electrodes & Interference-Sensors

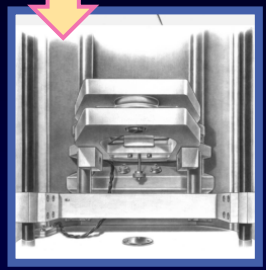
Interference Compensation



Mock Setups, Shaping & Training



Sensors

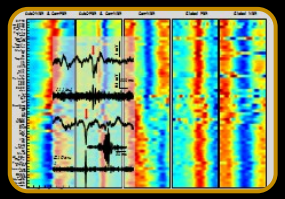


Goense, et al., 2008; Oeltermann et al. 2007a; Oeltermann et al. 2007b; Pfeuffer et al, 2007; Logothetis et al, Nature, 2001

Multimodal Approach – Recent, On-Going & Impending Applications

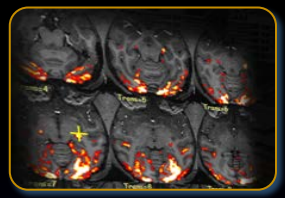
NET-fMRI (Neural-Event-Triggered fMRI)

Study of Effective Connectivity
by Detecting & Identifying Episodic Intrinsic Neural Events (INE)



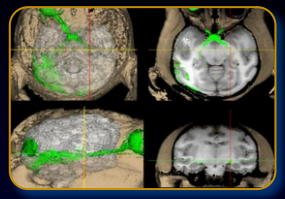
NET-fMRI (Neural-Event-Triggered fMRI)

Relation of Multi-Structure-Activity (MSA) Patterns to Episodic INE



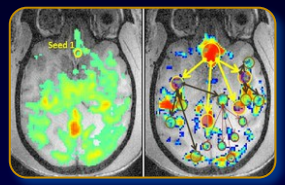
DES-fMRI (Direct Electrical Stimulation & fMRI)

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



MRI with Transynaptic Paramagnetic Tracers

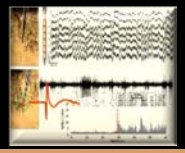
Structure-Function Relations by means of Manganese-Enhanced MRI &
di nuovo synthetized paramagnetic-tracers coupled
to *Ca++*, *Neurotransmitter & Neuromodulator* concentration-changes



Theoretical & Modeling Work

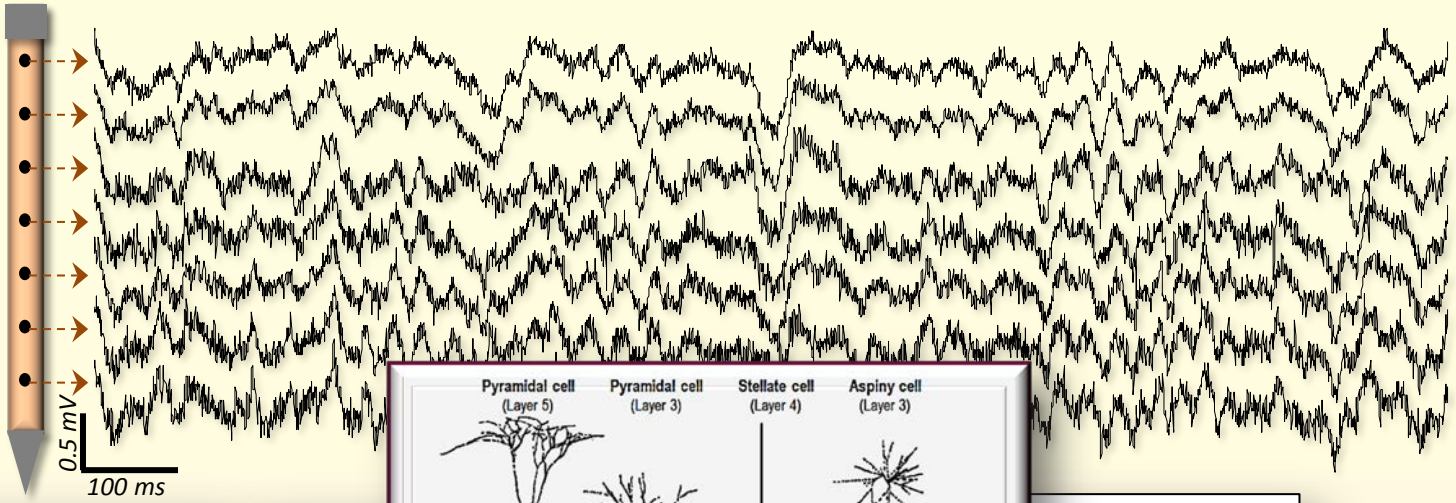
Data Statistical Learning methods
Data-Driven Graph-Theoretical Studies of Functional Connectivity
Application of Methods of Complex Dynamic Systems

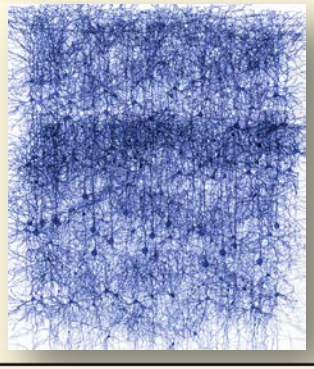
Logothetis et al, Nat Neuro 2010, Logothetis et al. Nature 2012, Saleem et al. Neuron 2002, Eshchenko et al, NeuroImage 2010, Besserve et al, JCN 2010, Angelovski et al. ACS Chem Neu 2014

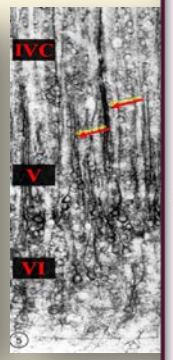


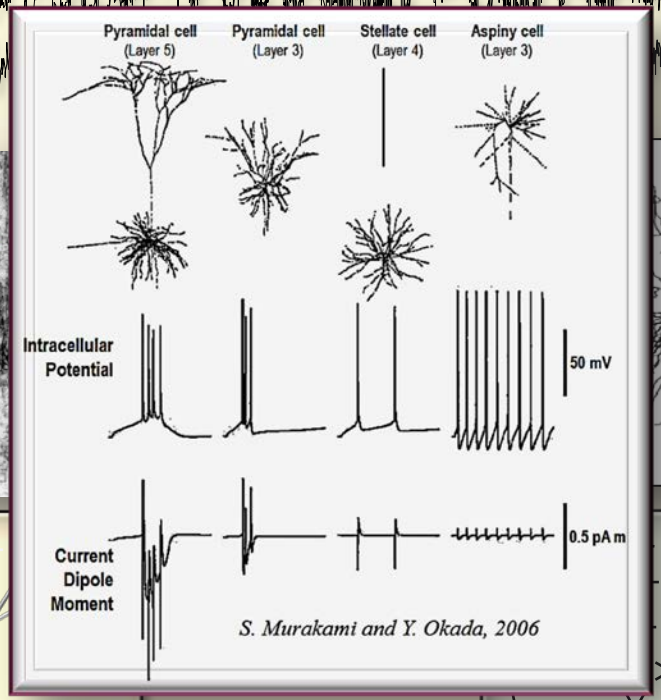
What are the "Neural Events" and What Signals are used to Detect them?

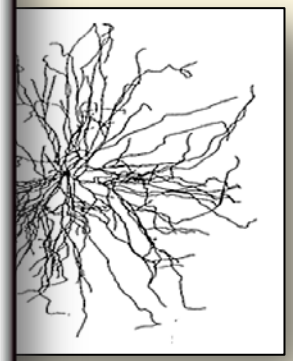
Volume conduction, Field-Generators & the mean Extracellular Field Potential

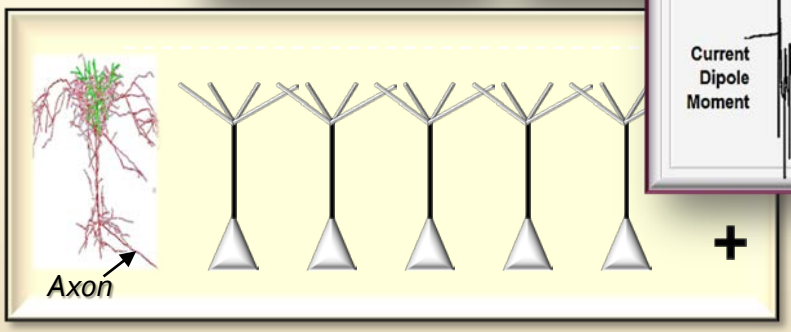


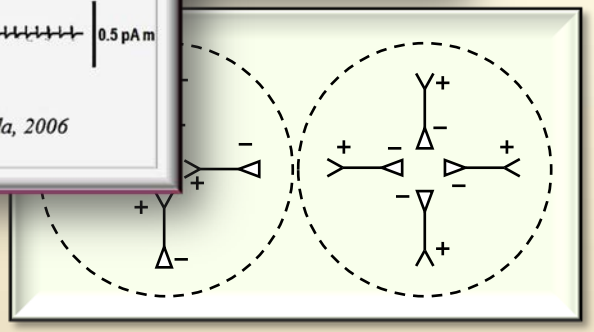










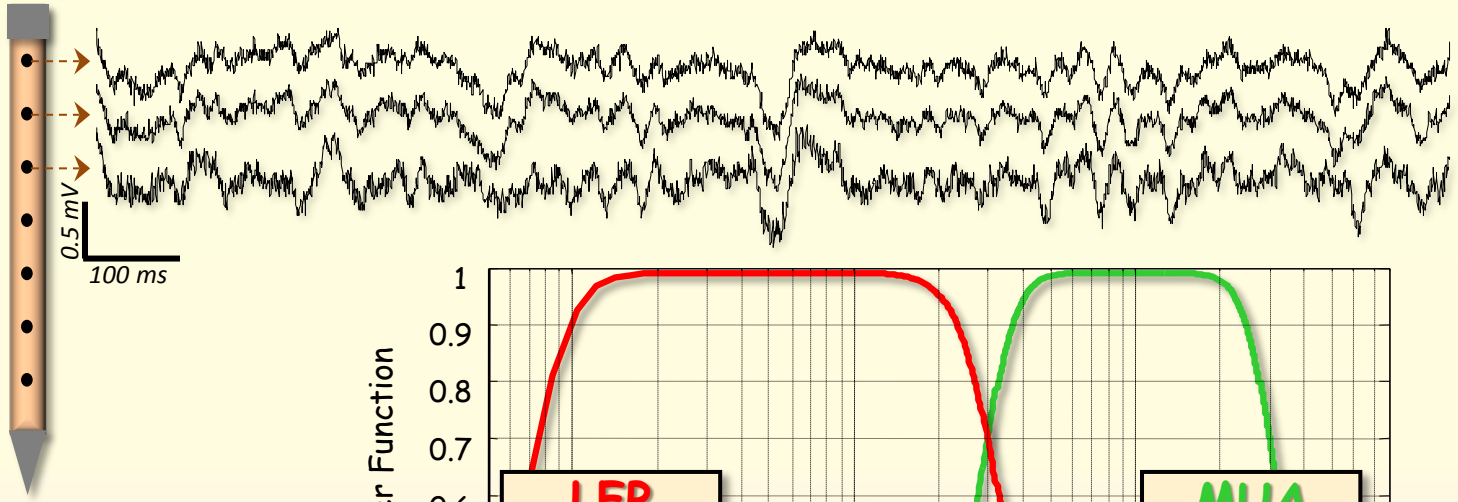


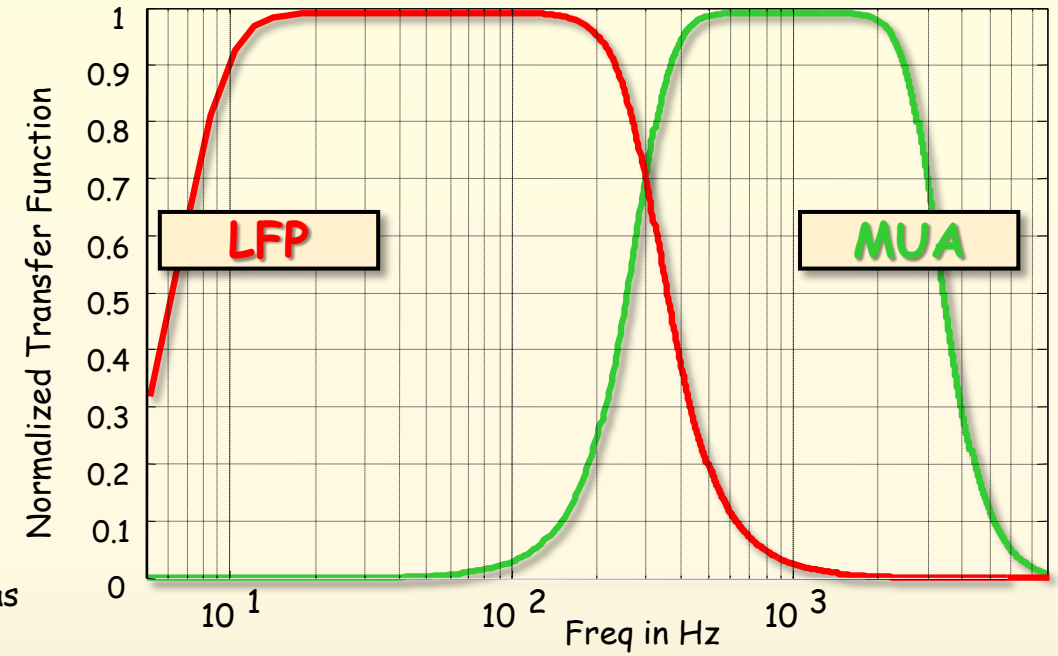
Open Field Generators (*large dipole-moments*)

Close Field Generators (*very small dipole-moments*)

Local Field Potentials (LFP) & Multiunit Activity (MUA)

Slow waveforms and high-frequency-signals reflecting activity of an area's projection neurons





LFP slow waveforms, including synaptic potentials, afterpotentials of somato-dendritic spikes, and voltage-gated membrane oscillations.

Reflect the input of a given cortical areas as well as its local intracortical processing, including the antagonistic activity of excitatory and inhibitory interneurons.

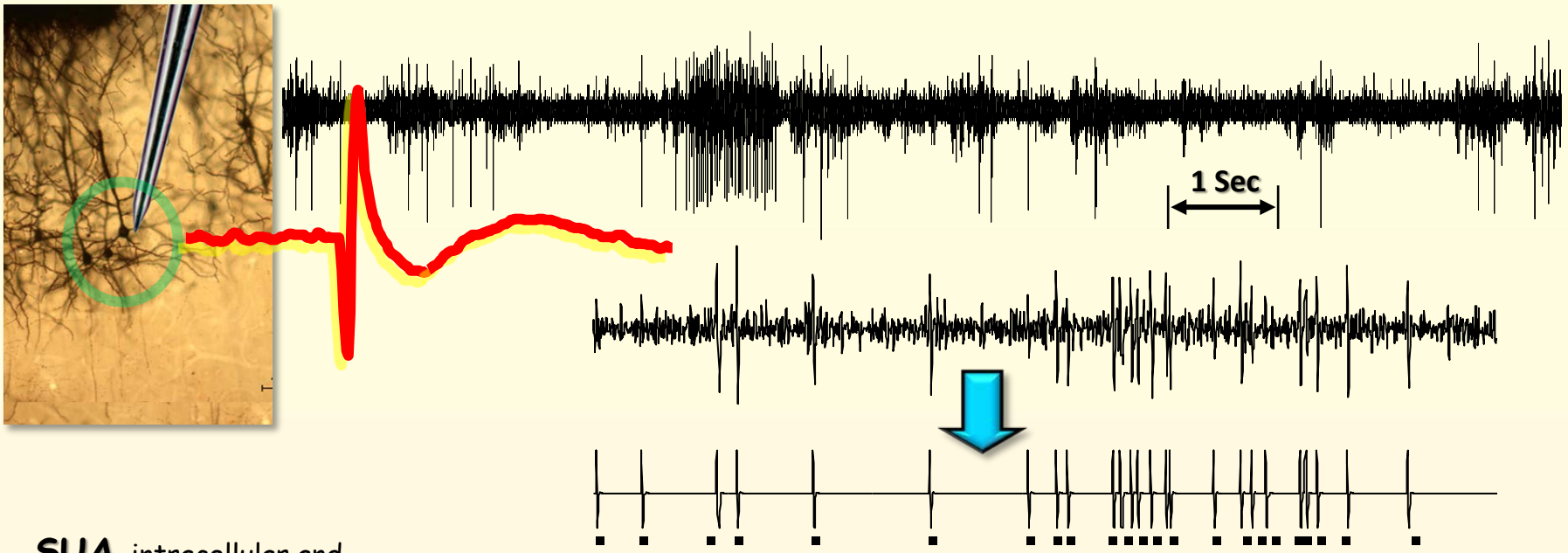
Single event duration: 10's msec
Spatial summation: Radius of 1-2mm

MUA Spiking of Neuronal Populations
Mainly activity of projection neurons forming the output of structure or area.

Single event duration: approx. 1 msec
Spatial summation: Radius of 100-200microns

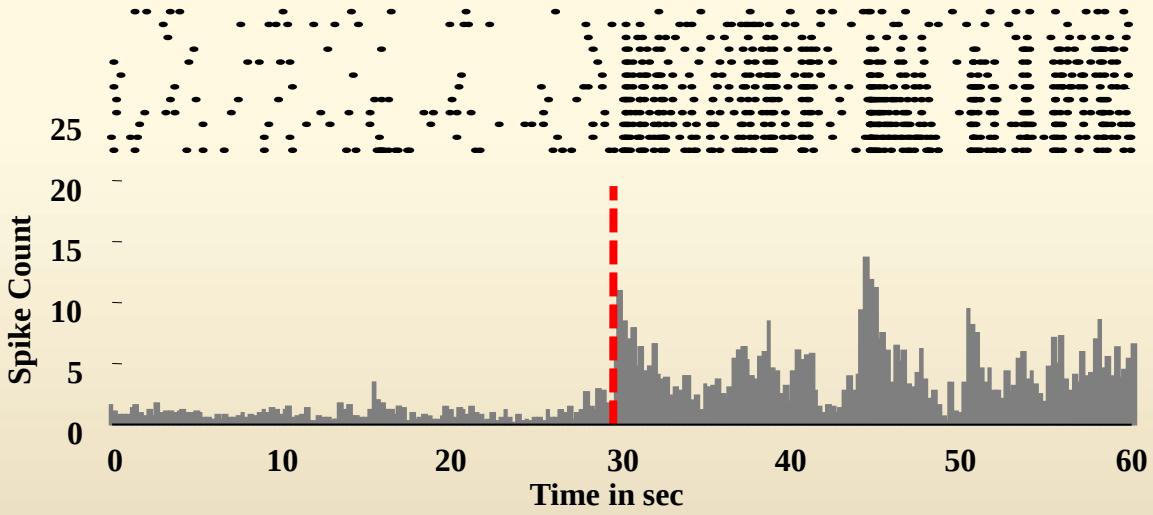
Single Unit Activity (SUA), Spike-Rates & PSTHs

Spike rates, peristimulus histograms, spike-field potentials, etc.



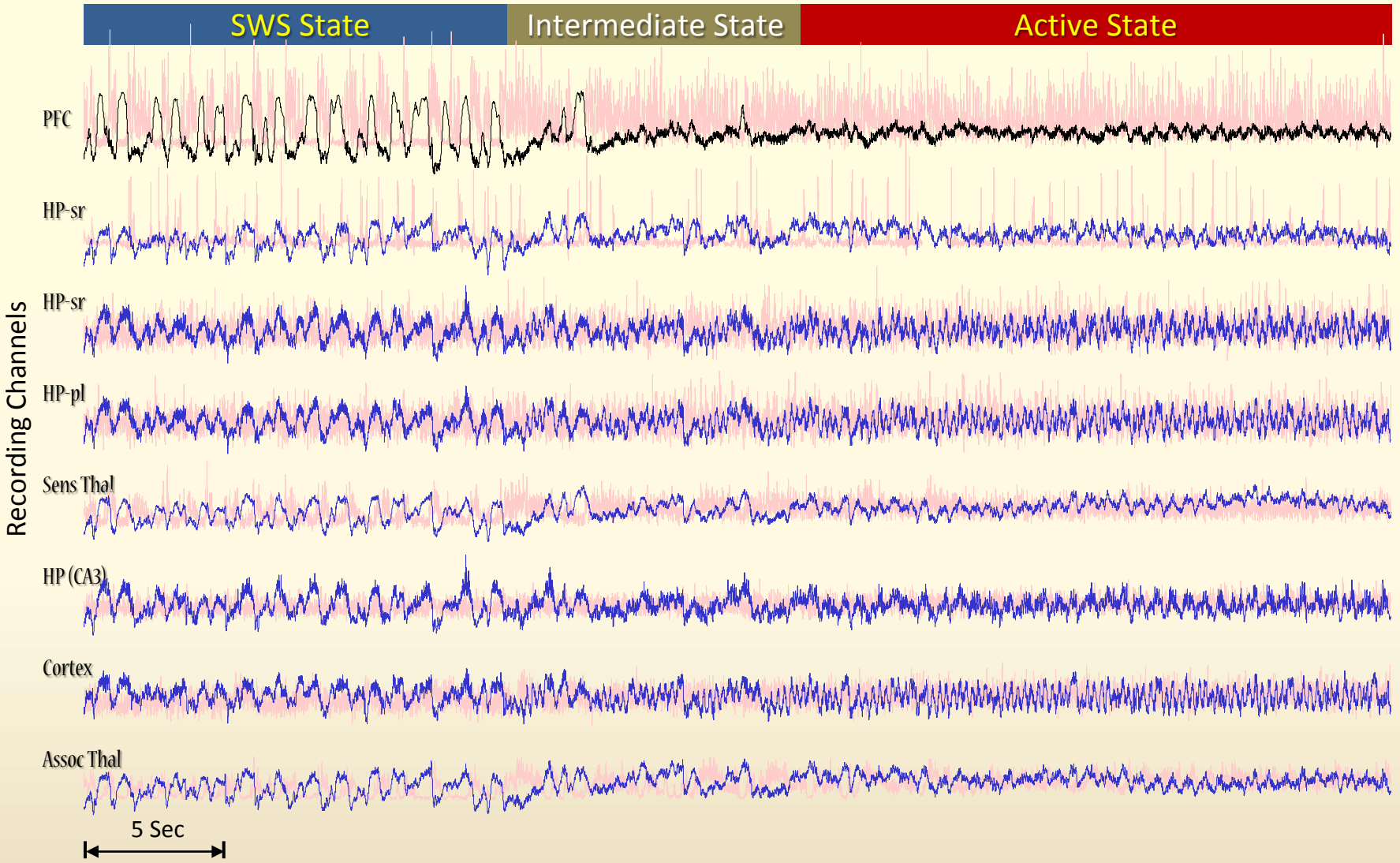
SUA intracellular and extracellular recordings of action potentials with cell-specificity, albeit with bias towards certain cell types and cell-size. Predominant methods in cellular and systems neuroscience

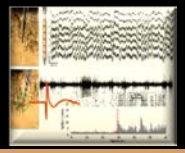
Single event duration: 1 msec
Spike-sorting permits concurrent measurements from different cells and cell-types



LFP-Profiles Reflecting Brain-States *(Signal-Changes of sec-Duration)*

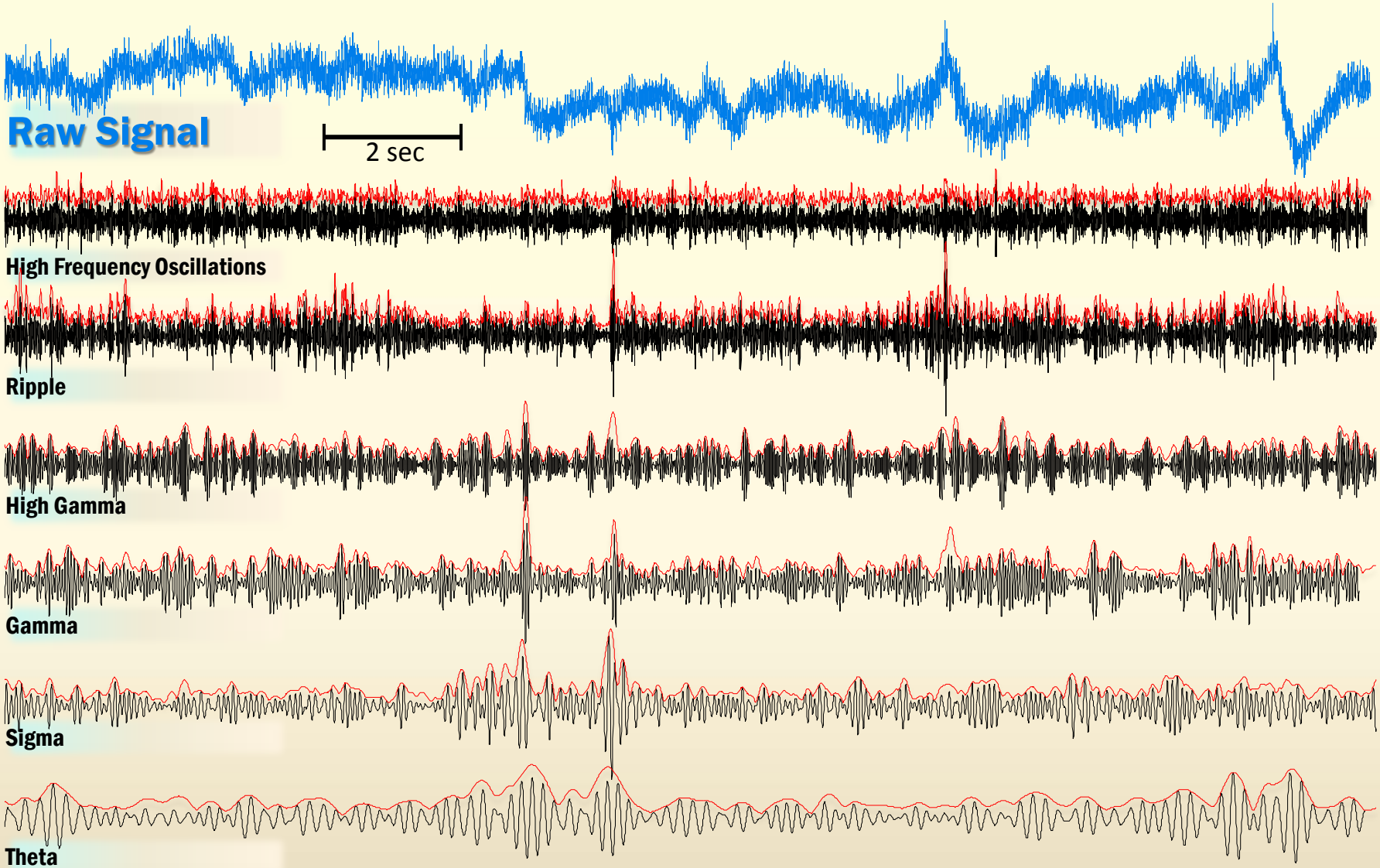
Up-Down States during Slow-Wave-Sleep (SWS) & Active Behavior





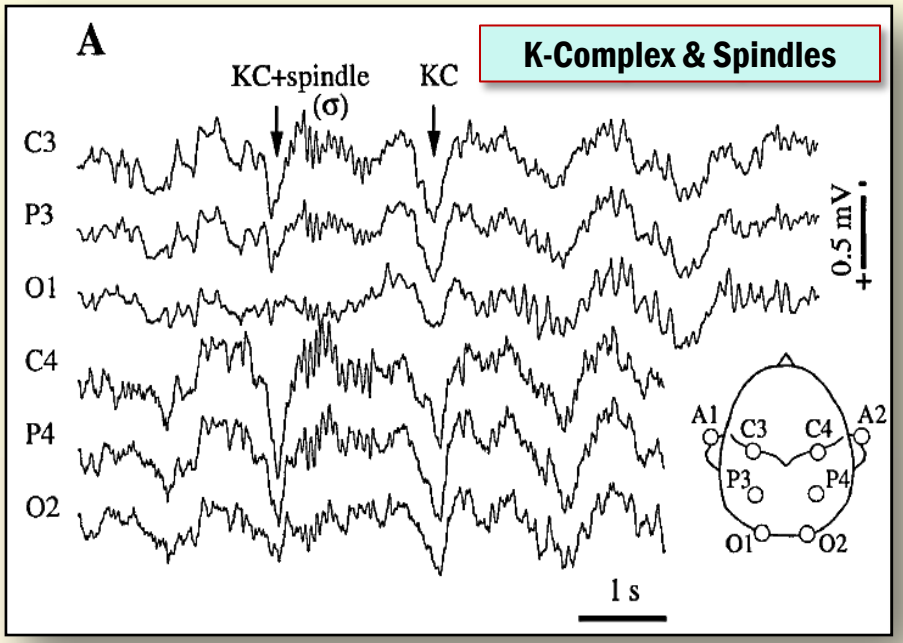
Band-Limited-Power (BLP) Signals

Band-Limited-Power (BLP) Signals used for Event Detection

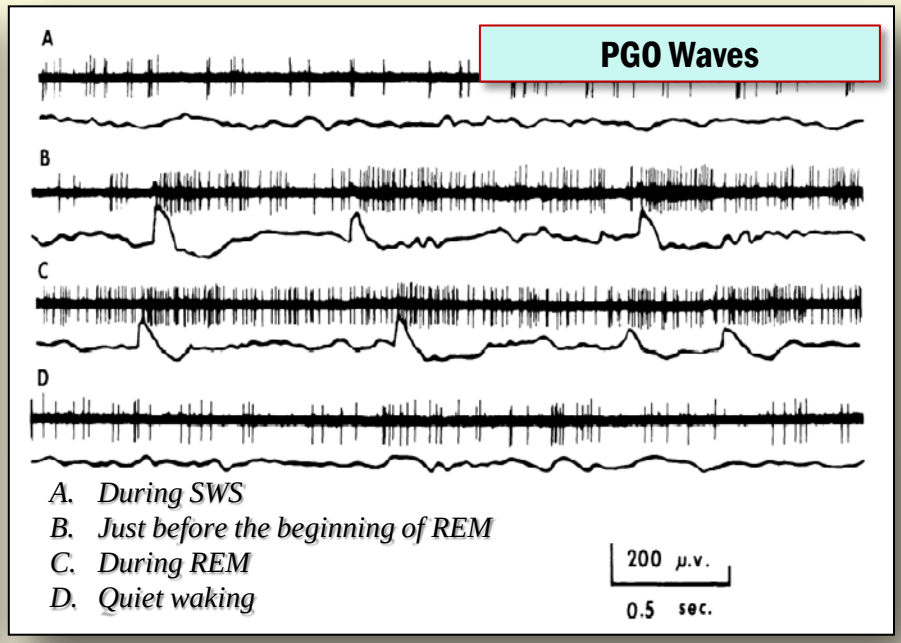


K-Complexes, PGO Waves & Sharp-Wave Ripple (SPW-R) Events

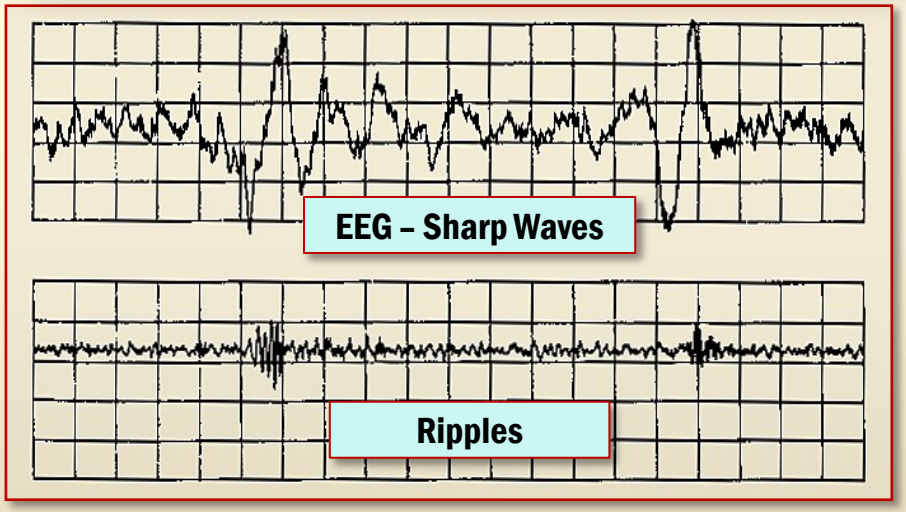
Well-studied Events Related to Cognition

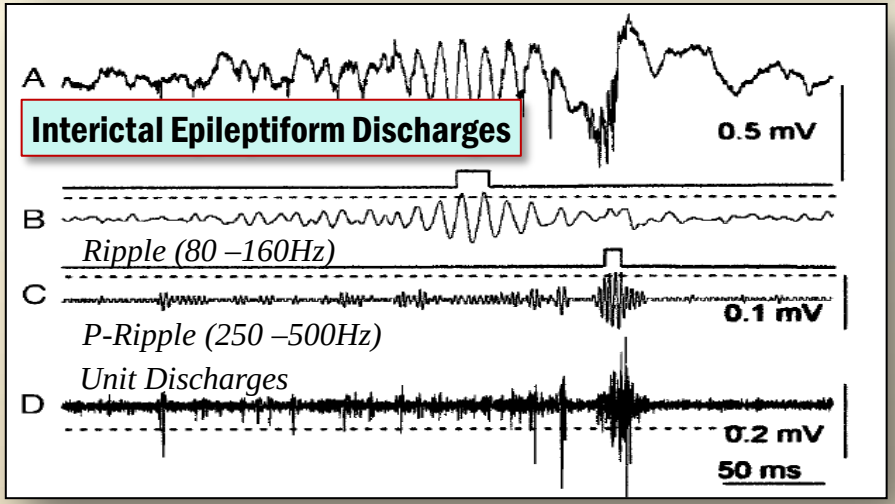


K-Complex & Spindles



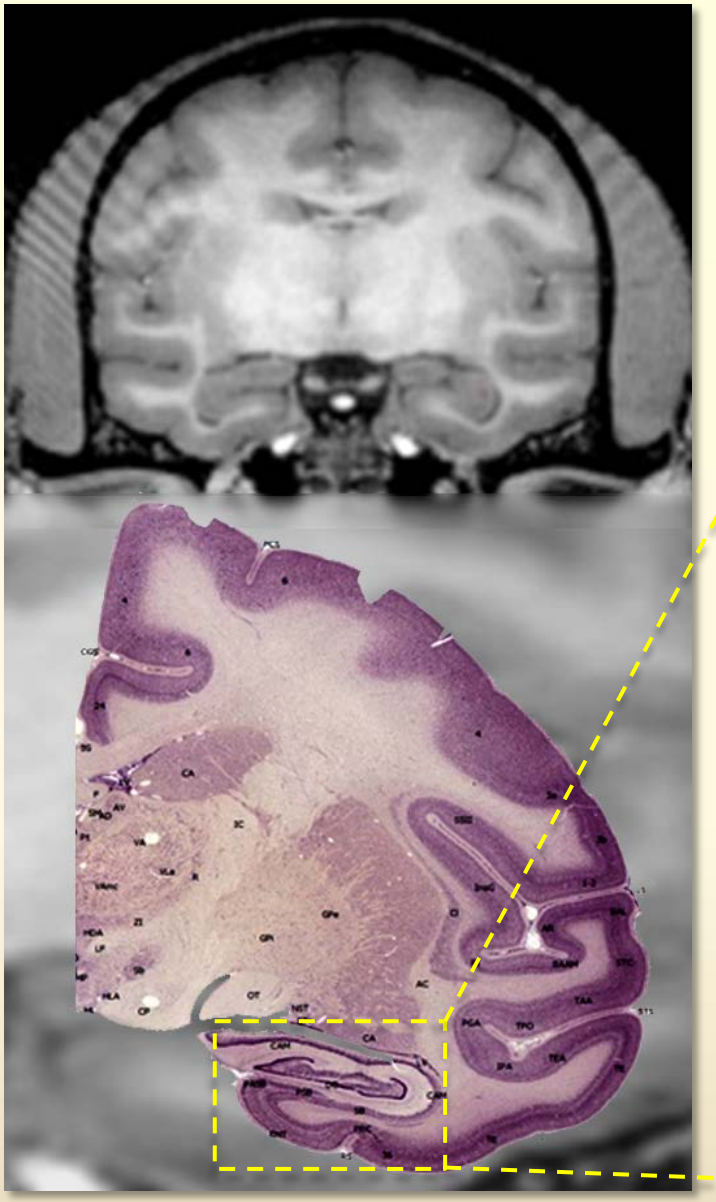
PGO Waves



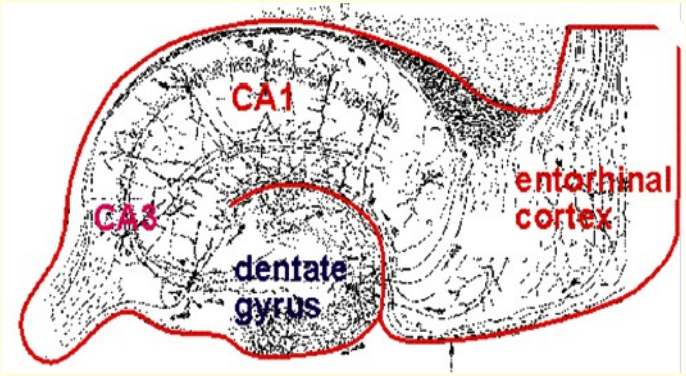


Hippocampal Pathways involved in the Generation of SPW-R

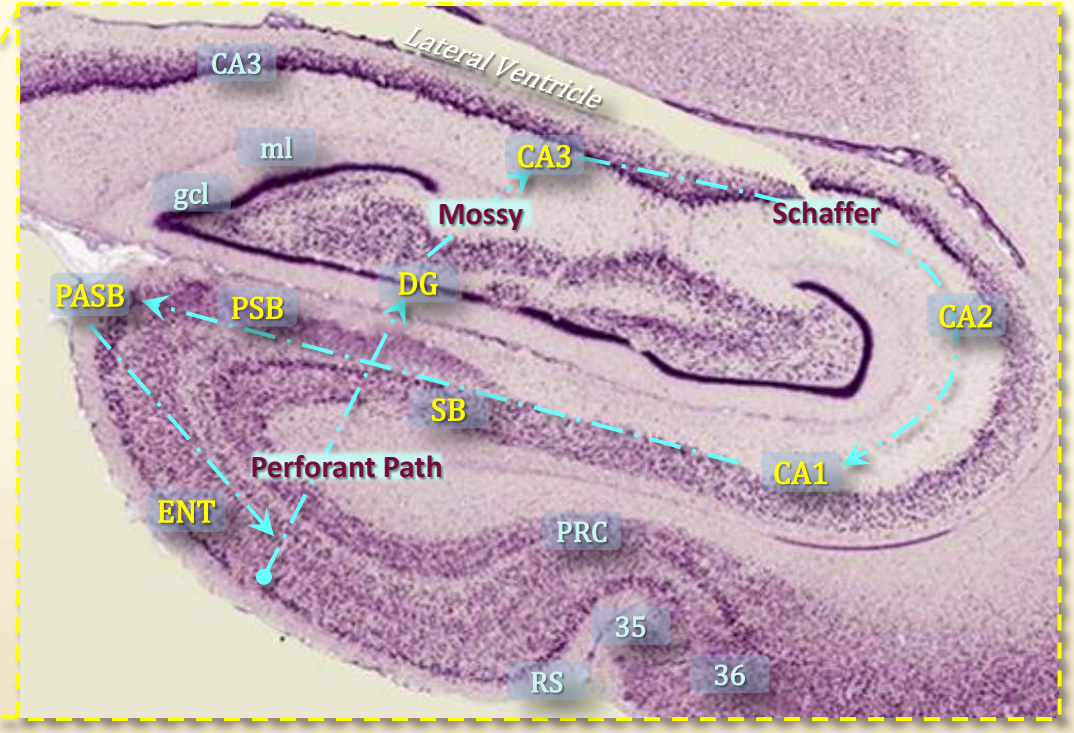
The Trisynaptic Circuit and Subicular Complex of Hippocampal Formation



In Primates

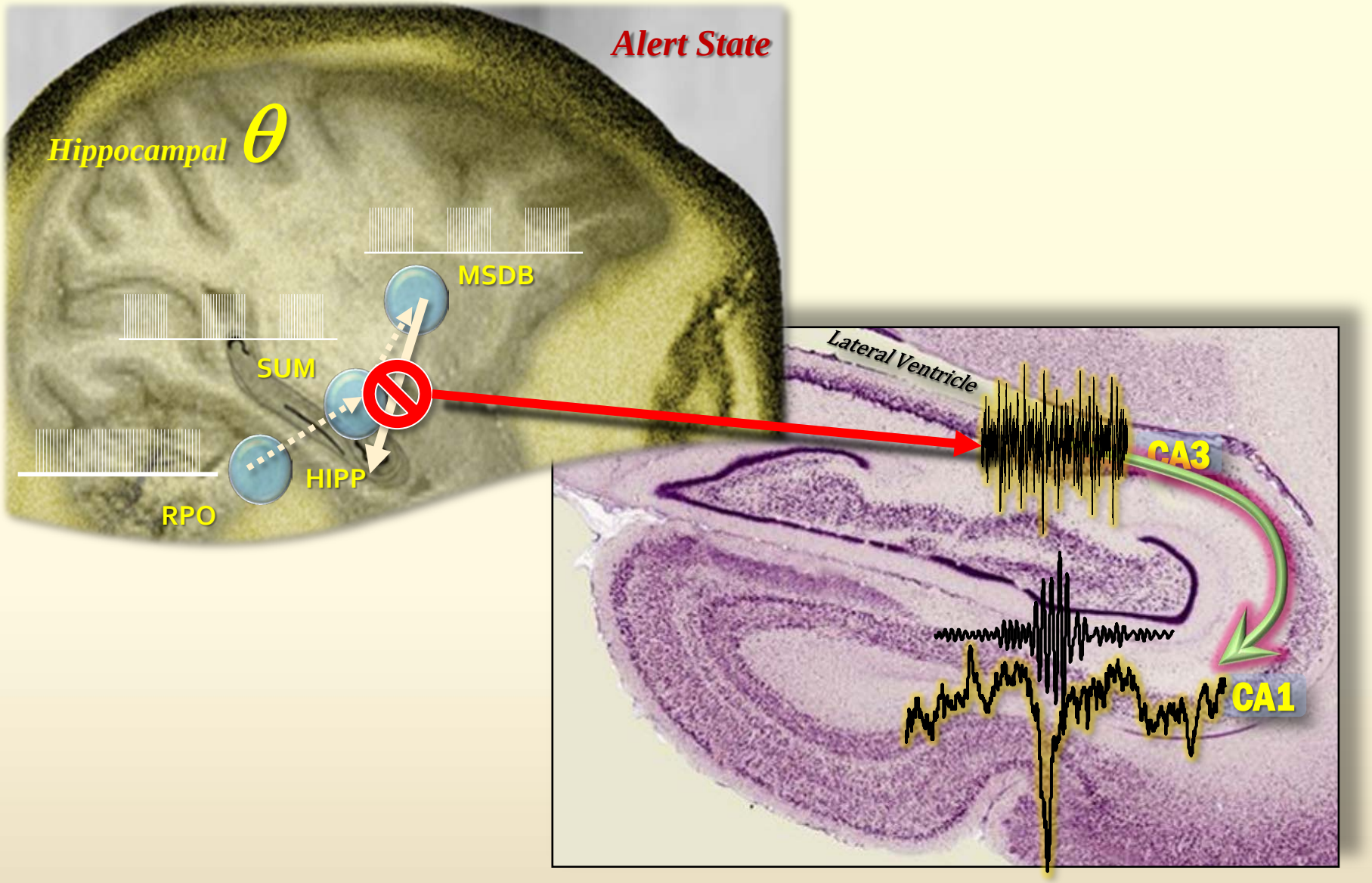


In Rats



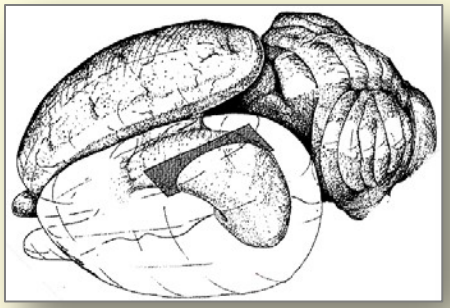
SPW-R Emergence Following Cessation of *Theta* - Oscillations

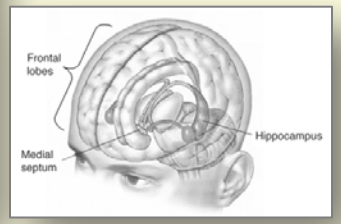
SPW-R is a "Release-Event" Following the Reduction of GABAergic/Cholinergic Activity of MS-DB



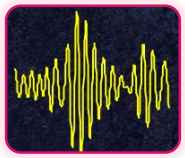
SPW-R in Rats & Humans - Role in Decision-Making & Memory?

Physiological Evidence from Rat & Human-Patient Studies

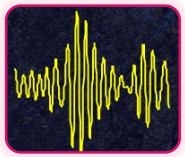




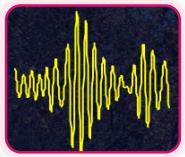
In Awake State: PW-Rs occur at path-choice points, when vicarious trial and error is reported, providing a mechanism for quickly recalling memories



In Deep Sleep: SPW-Rs coincide with the reactivation of neuronal ensembles, which were excited during awaking experience



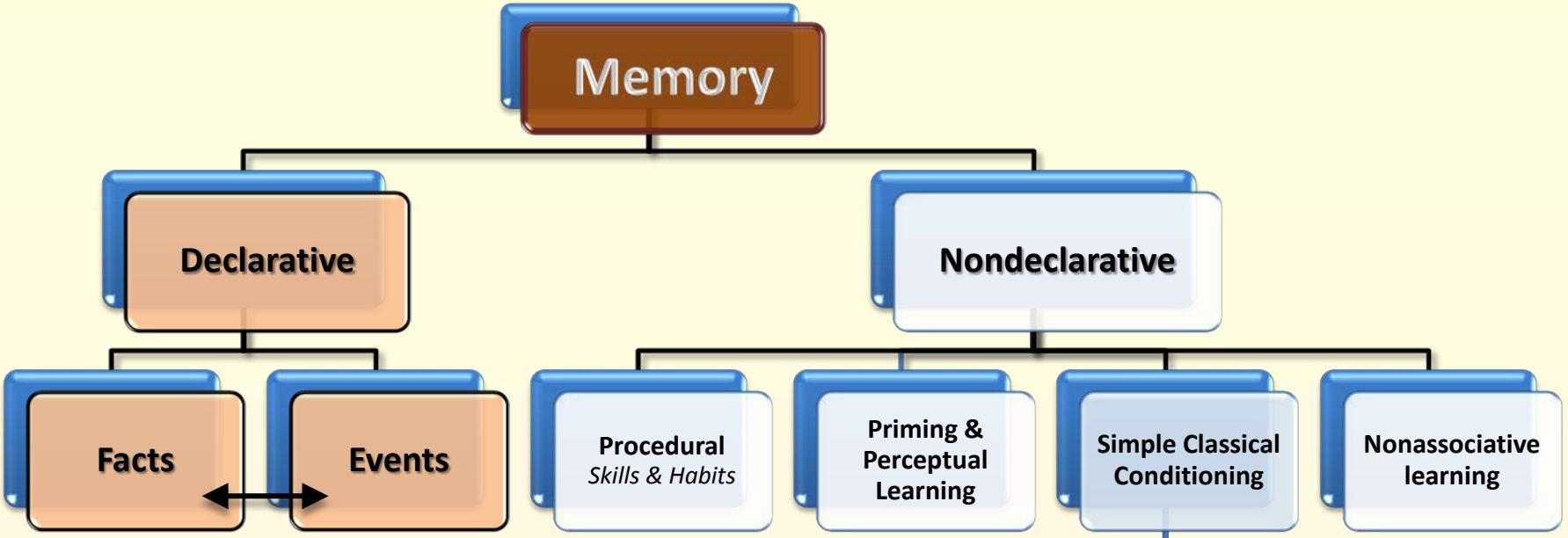
The number of ripples increases after learning, and
the increase predicts memory recall both in rats & in humans



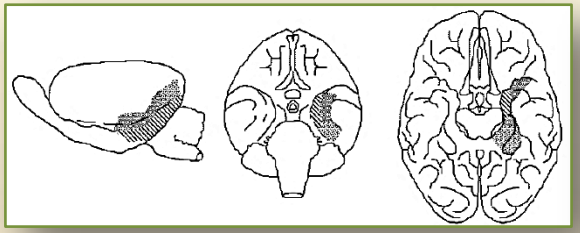
Elimination of ripples by electrical stimulation of Hippocampus during the post-learning *Slow-Wave-Sleep* interferes with memory consolidation

Learning & Memory Related Networks

Striking Sequences of Synergistic & Antagonistic Processes



Hippocampal formation; entorhinal, perirhinal & parahippocampal cortex, Burwell et al. 1996



Striatum

Neocortex

Amygdala

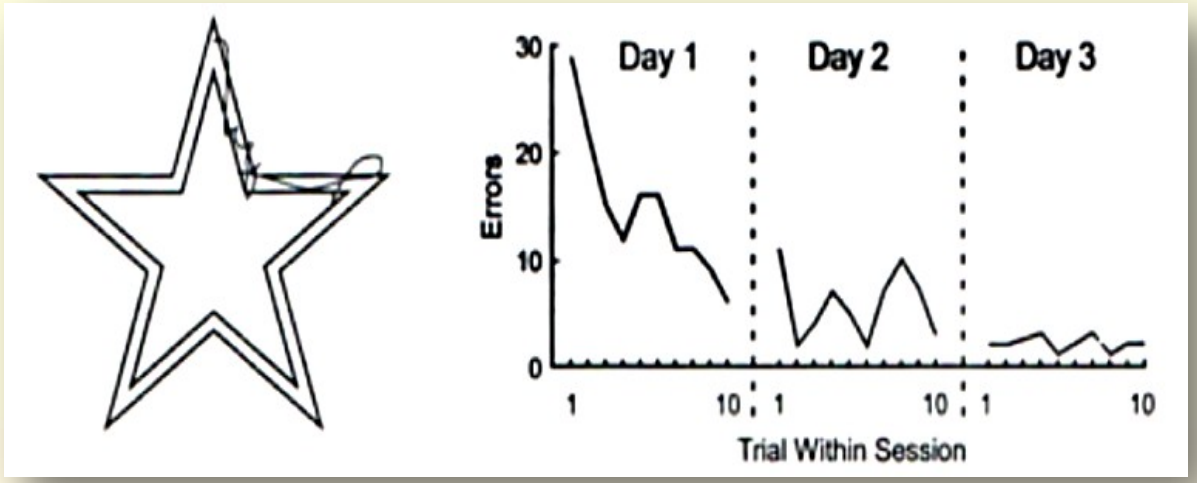
Cerebellum

Reflex Pathways

The Procedural & Declarative Memory Systems

Actions like Biking & Memorizing a Poem involve Fundamentally Different Memory Systems

Henry Molaison



Resection of Hippocampus

Leads to complete loss of declarative memory despite of the normally functioning systems underlying working- and procedural-memory

Hippocampal formation; entorhinal, perirhinal & parahippocampal cortex, Burwell et al. 1996

Striatum

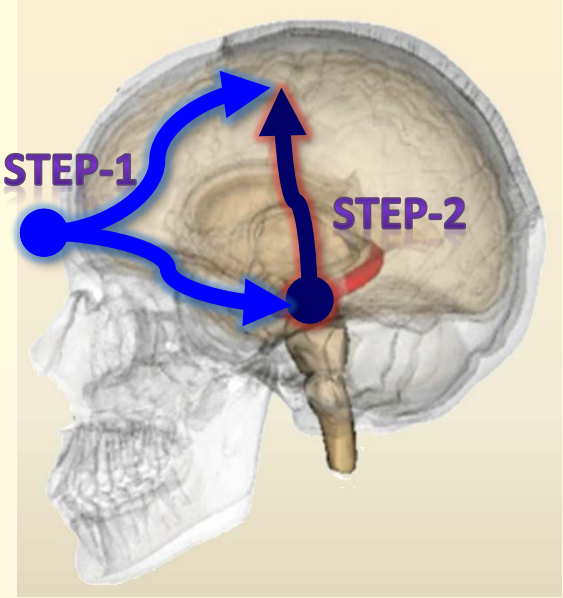
Neocortex

Amygdala

Cerebellum

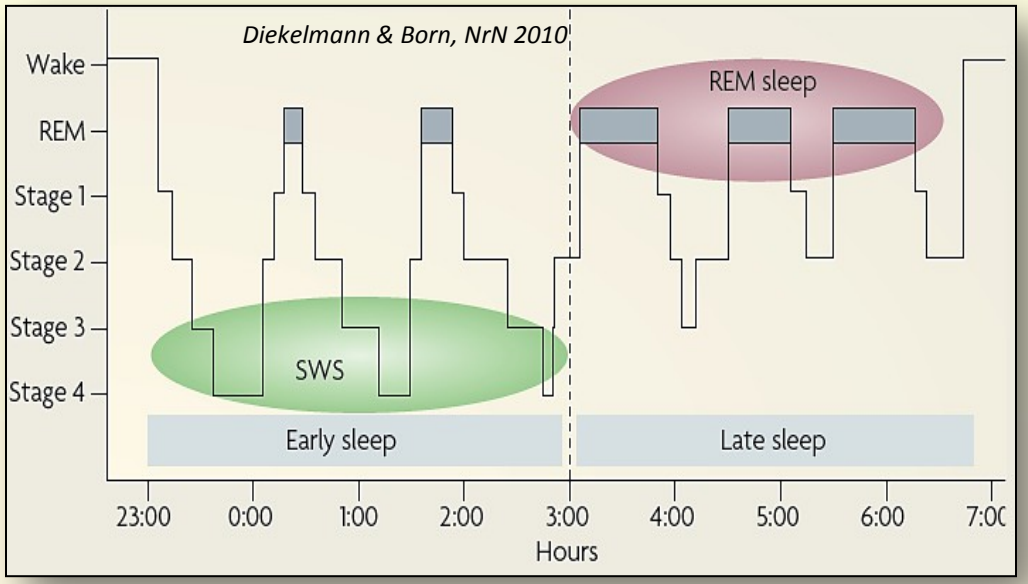
Consolidation of Memory – A Process Potentially Related to SPW-R

Consolidation of Declarative & Procedural Memory: **2-Systems, 2-Processes & 2-States**



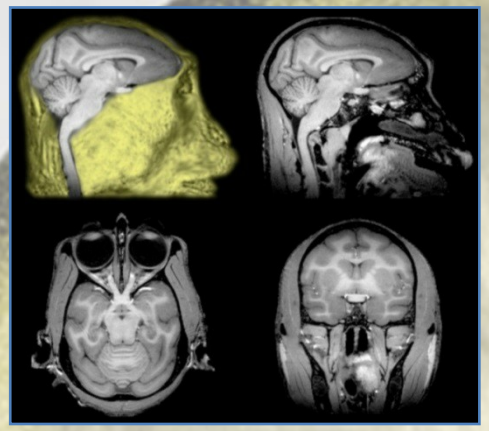
SPW-R

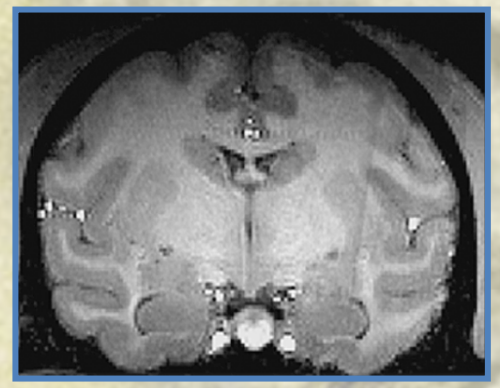
Hippocampo-Neocortical Interactions in the two-step Consolidation Process?

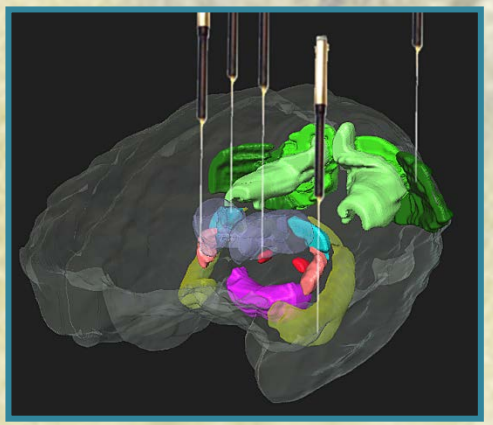


SWS (Declarative?)	REM (Procedural/Emotional ?)
Ripples, Spindles, Slow Osc.	**Theta, PGO Waves**
Low ACh	*High ACh*
Trans Serotonin Increase	*Low Serotonin*
Trans Noradrenaline Increase	*Low Noradrenaline*
Low Cortisol	*High Cortisol*
System consolidation	***Local Plasticity Change (LTP)***

SPW-R fMRI – Strategy & Questions







Initial Strategy

- Unsupervised electrophysiological detection & identification of the Neural Events (NE), starting w/ SPW-Rs that may be potential state-indicators of self-organized neuronal activity

- Description of fMRI-assessed patterns of **Multi-Structure-Activity (MSA)** that are robustly correlated to single-episodes or event–sequences

Currently: Over 70 Brain-Regions defined via MRI

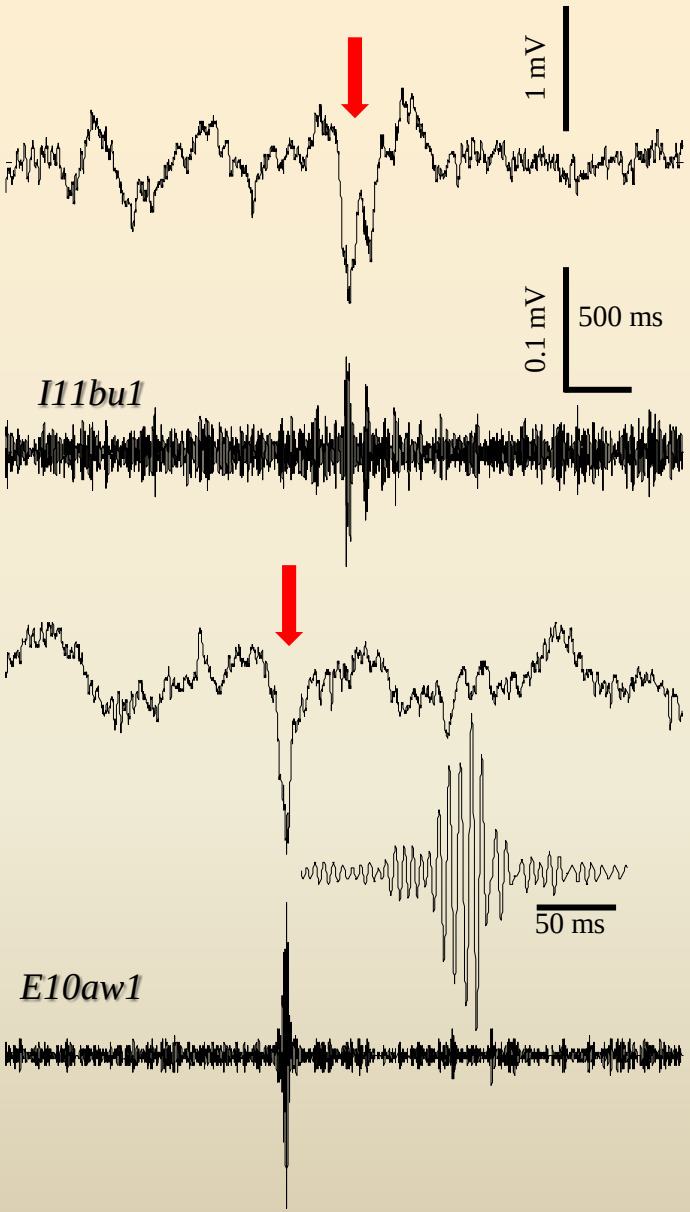
First Questions

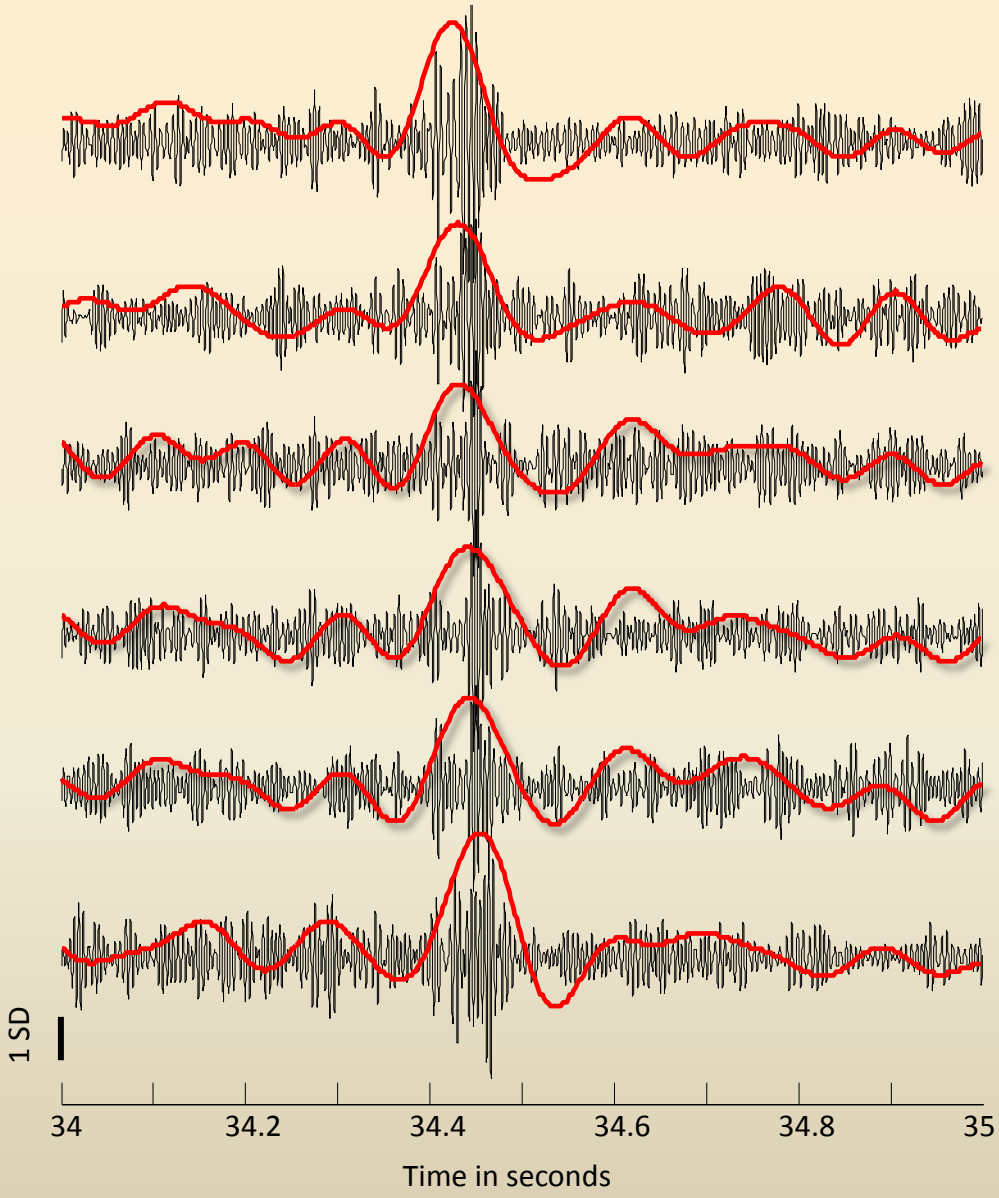
➔ Is there a Systematic NE-MSA Relationship?

➔ Neural Correlates of the NET-fMRI Up/Down-Modulations?

➔ Can MSA-Patterns Indicate the Occurrence of Neural Events?

SPW-R Examples in NHP (Temporal Profile & Synchronicity)





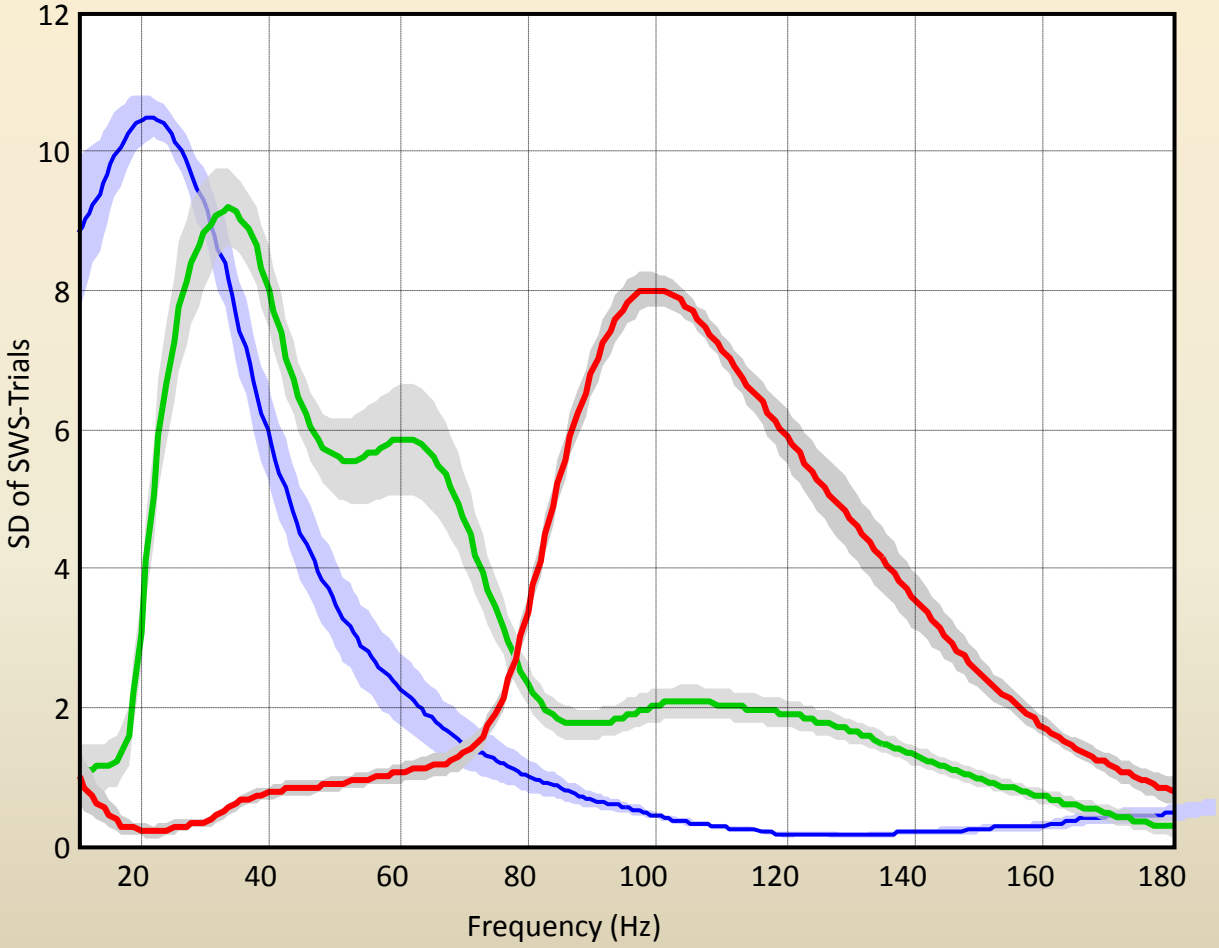
Logothetis et al. Nature 2012, Logothetis et al. Cur Op Neu 2015

Detecting & Identifying Frequency-Specific Events

Detection of Power-Changes in a Broad-Band Signal

↓

Unsupervised Clustering of Spectra

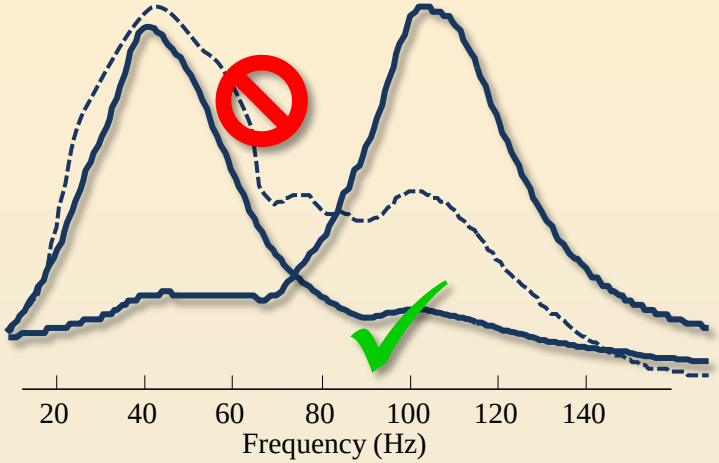


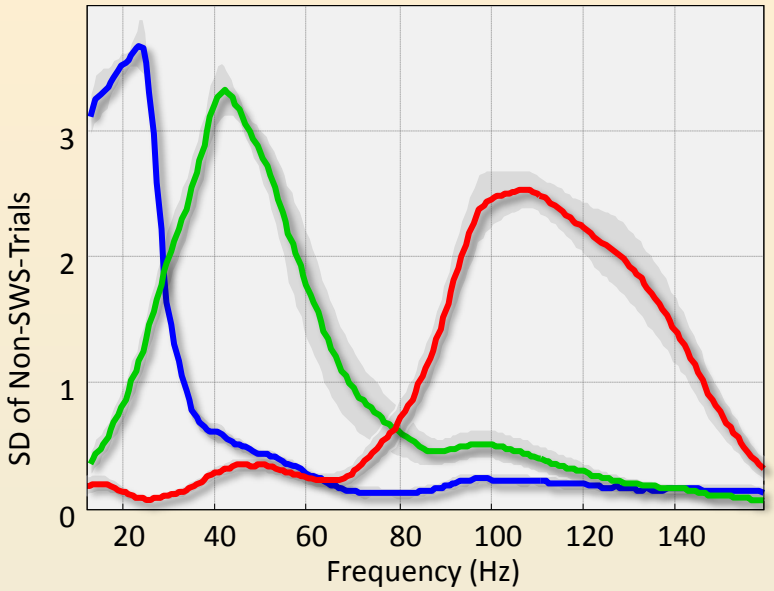
Algorithm: Non Negative Matrix Factorization (NNMF)

Logothetis et al. Nature 2012

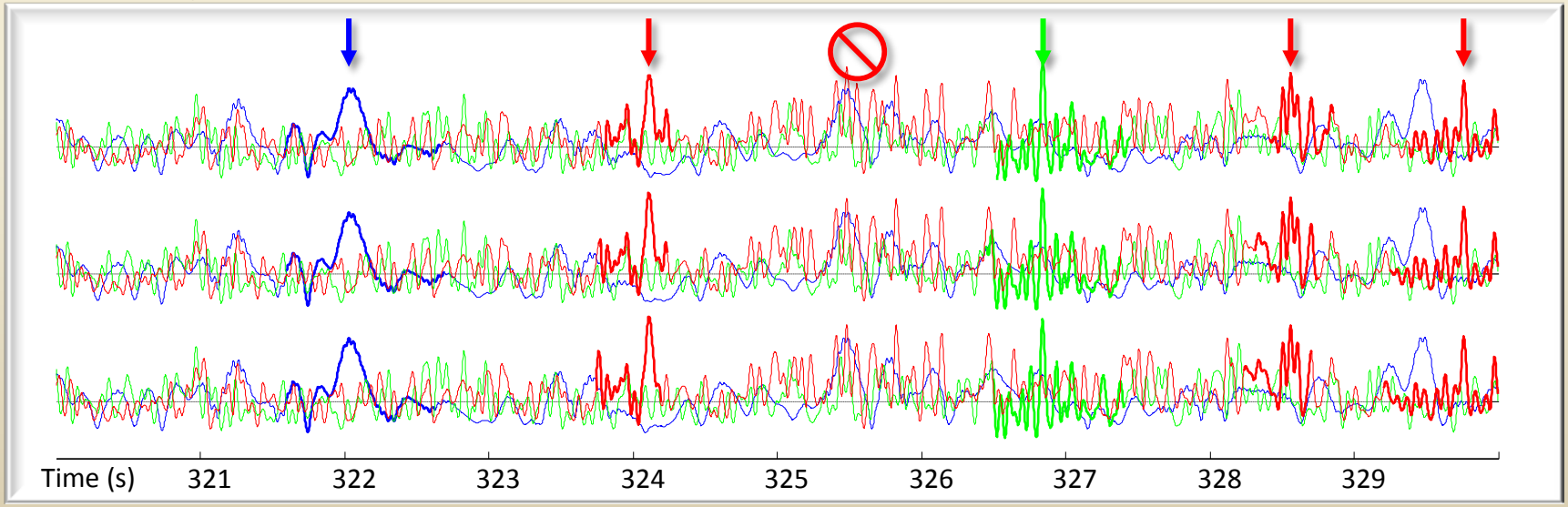
Selection of “Pure” Events by …

… Excluding Events w/ Broad (Overlapping) Power-Increases





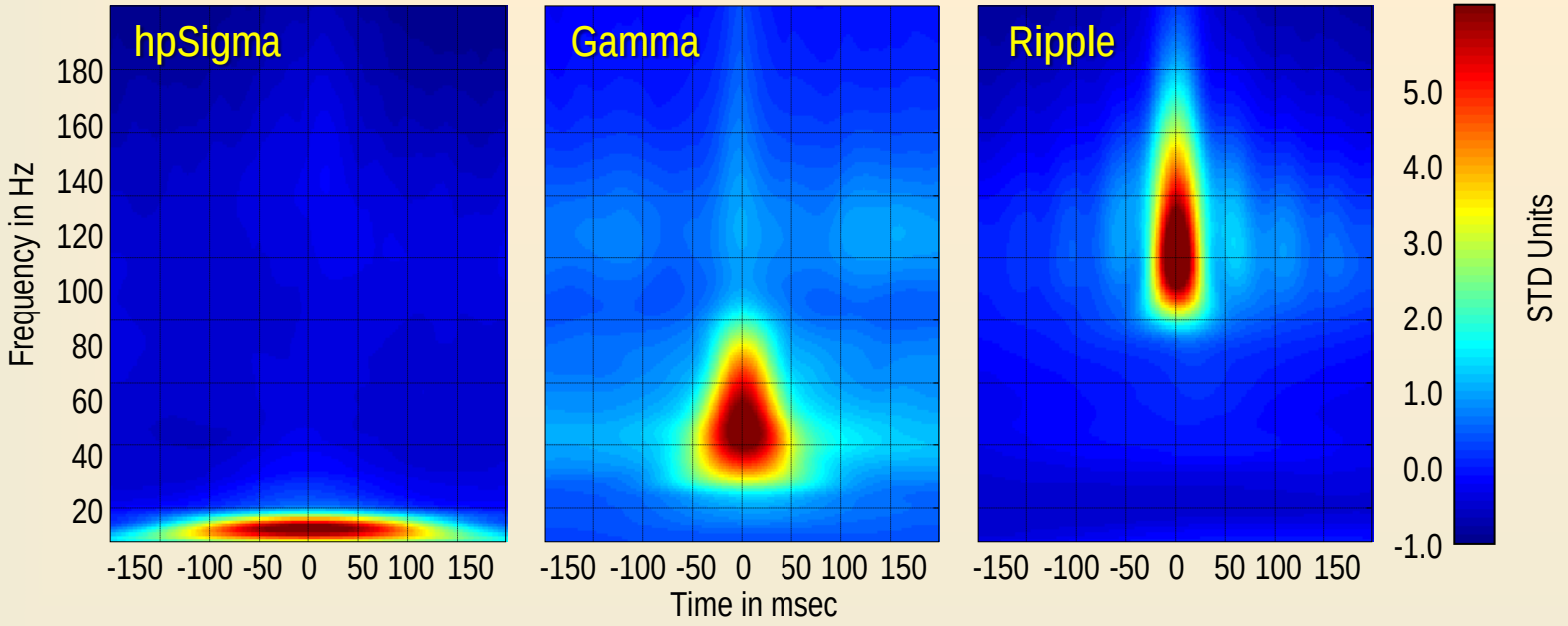
… Excluding Co-occurrences

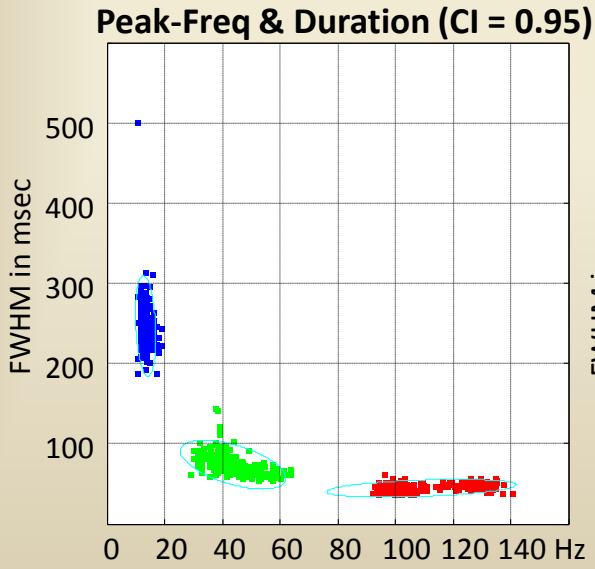


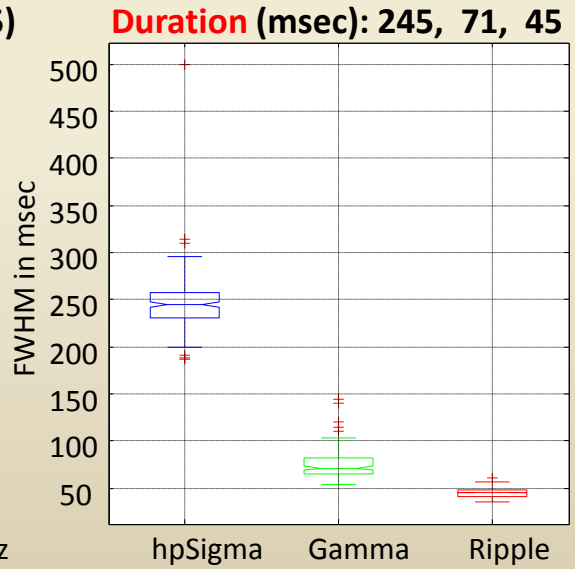
Logothetis et al. Nature 2012

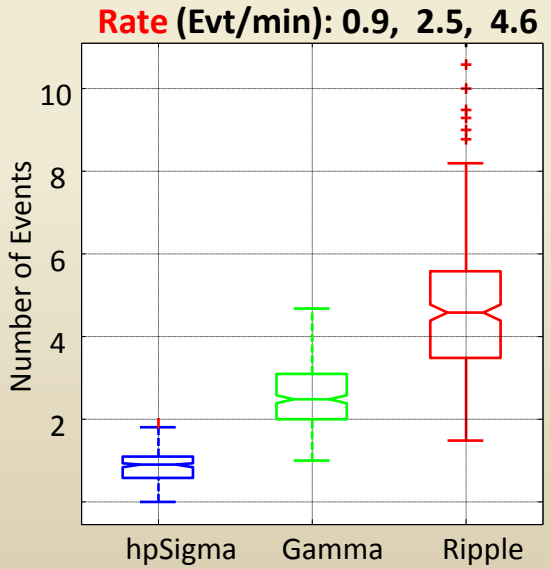
Population Data

Event-Types for NET-fMRI: hpSigma, Gamma & Ripples





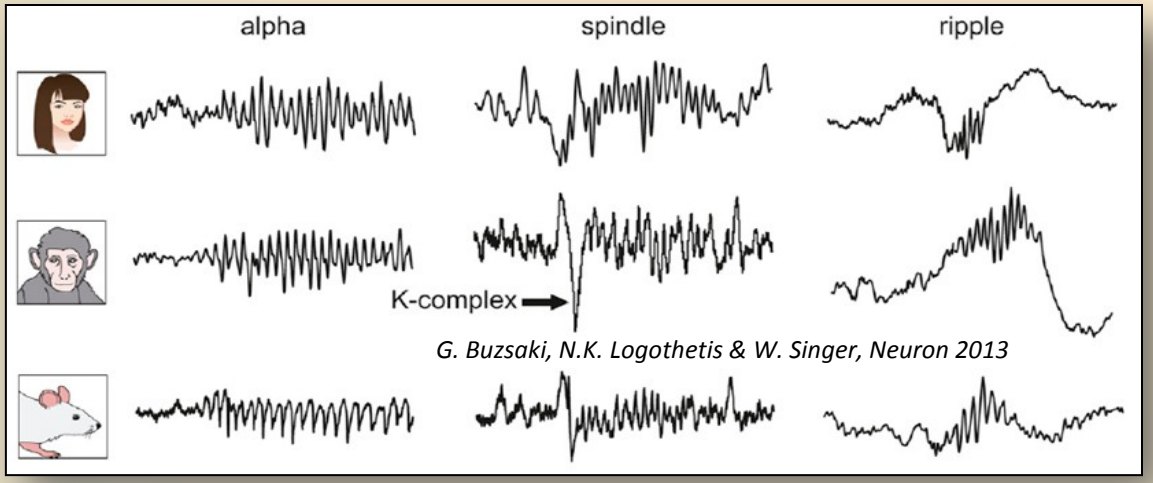


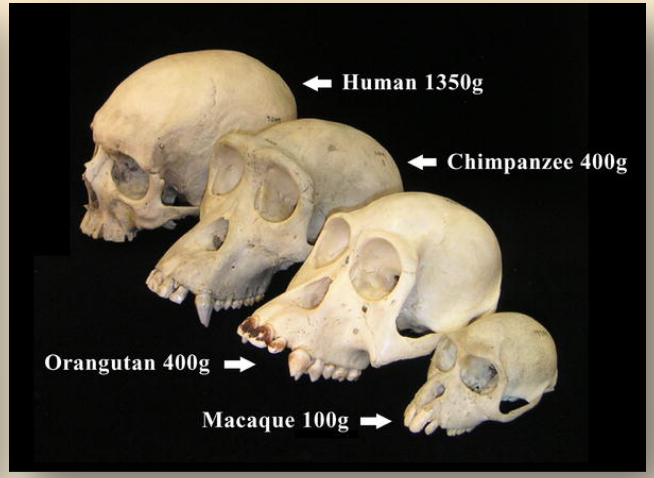


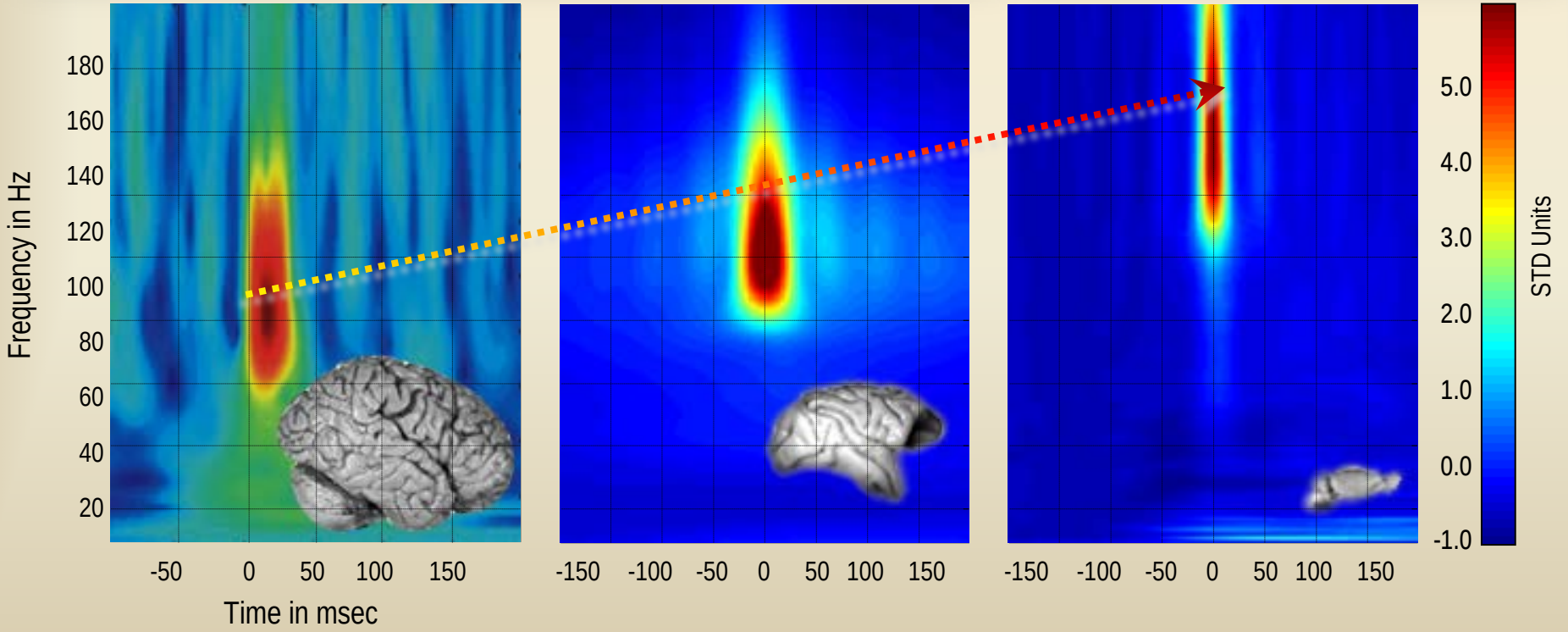
Logothetis et al. Nature 2012

Population Data

Event Shape & Spectra in Different Species



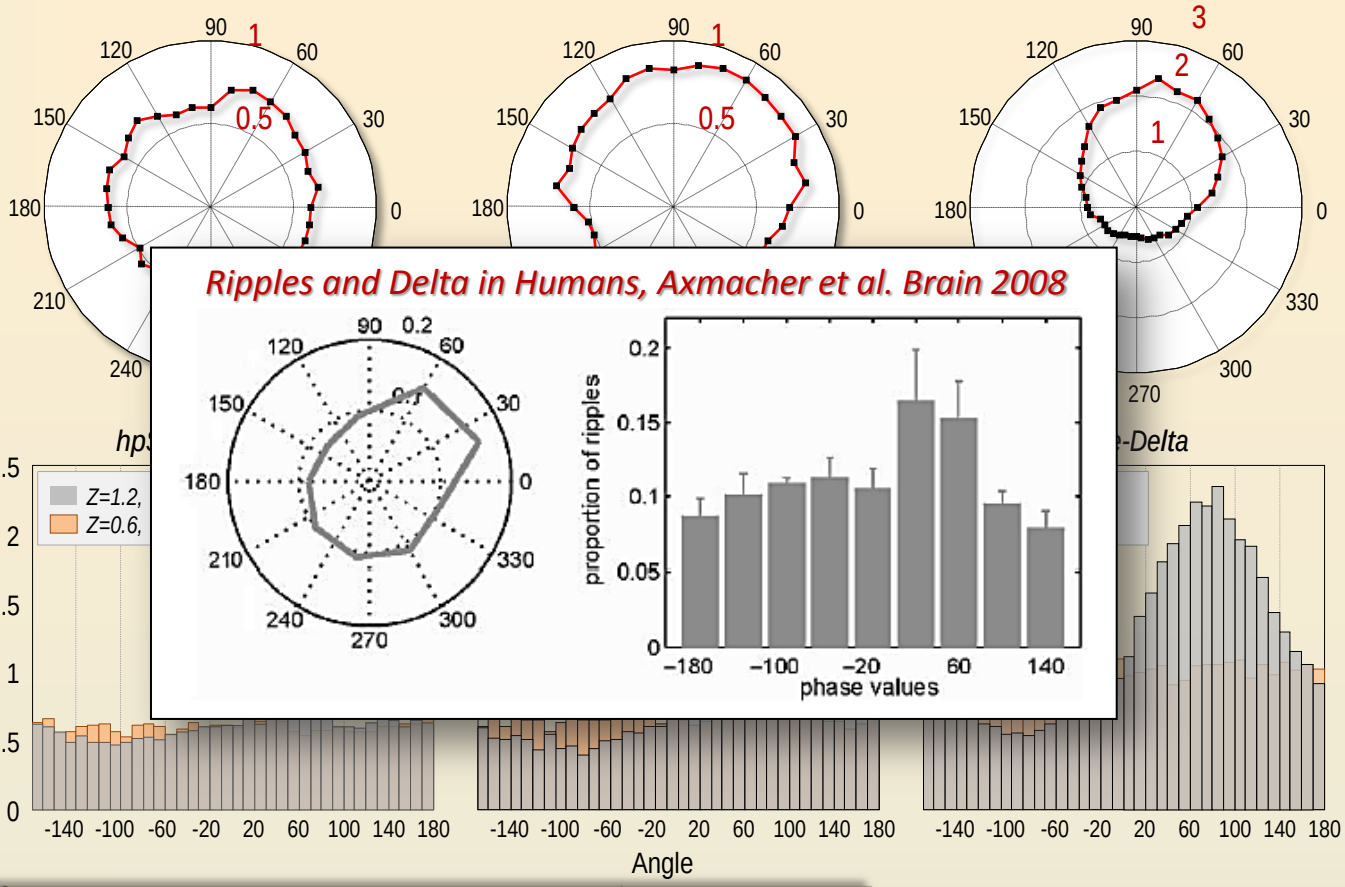


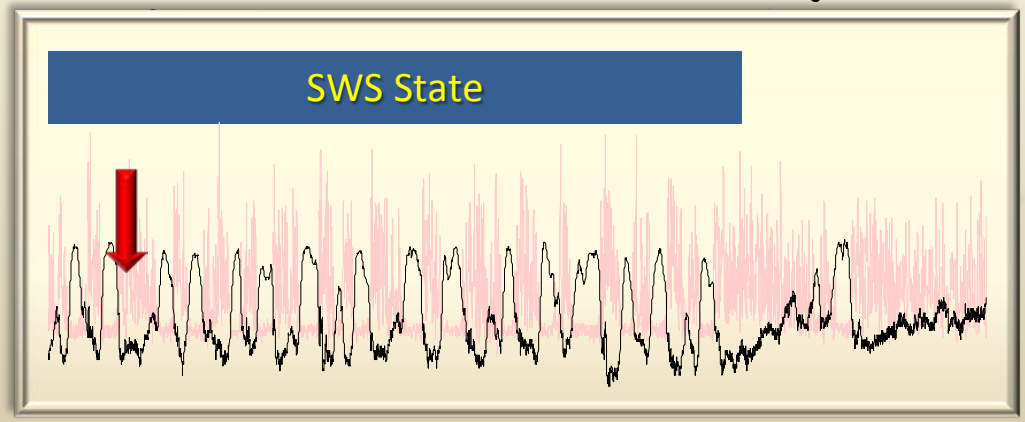


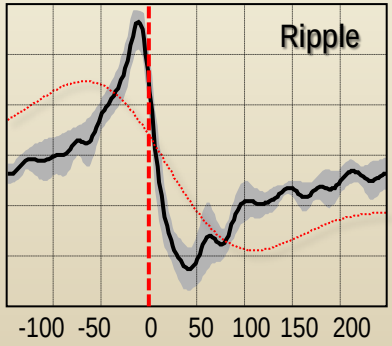
Monkey-Human-Ripples: Axmacher et al, Brain 2008; Logothetis et al. Nature 2012; Buzsaki-Logotheiis et al, 2013

Population Data

Hippocampal Ripple - Delta: Selective Cross-Frequency Coupling



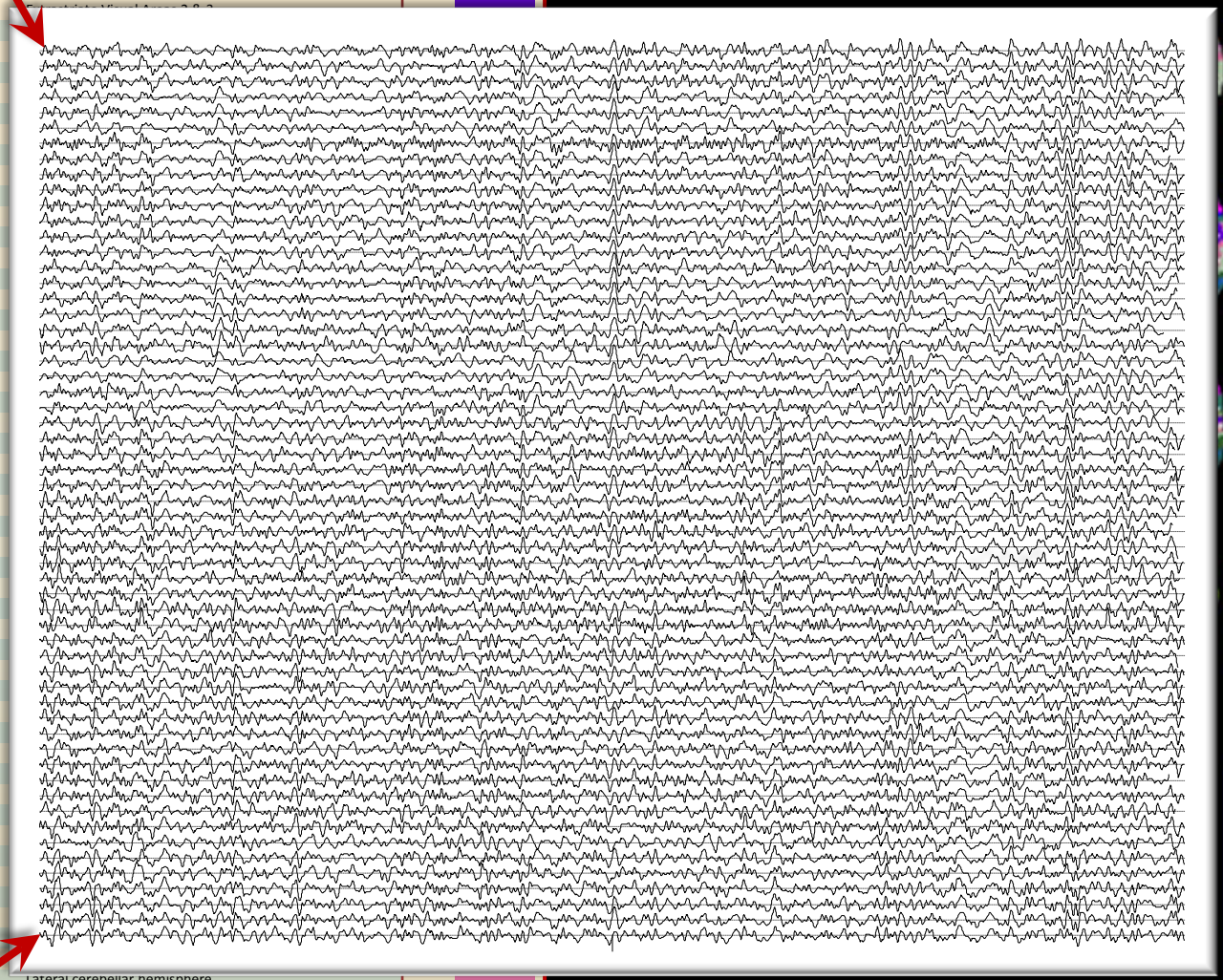




Logothetis et al. Nature 2012

Regions of Interest (ROI) & Multi-Structure-Activity (MSA)

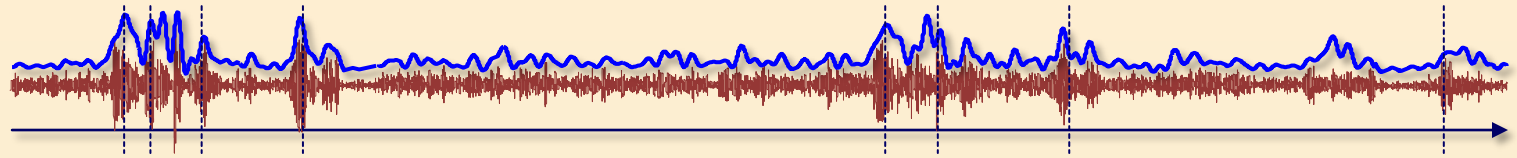
ParPrec	Parietal Precuneus
ParIntra	Intraparietal
ParLat	Parietal Lateral
TmpVis	Inferior Temporal Sulcus
TmpSTS	Superior Temporal Sulcus
TmpPol	Polar Temporal Cortex
TmpAu	Auditory Temporal
V5	Extrastriate Visual Area 5
V4	Extrastriate Visual Area 4
V2V3	
pV1	
pfV1	
fV1	
V1	
dlPFC	
medPFC	
orbPFC	
RetroSp	
PCC	
dACC	
ACC	
aIns	
Ins	
S2	
S1	
Motor	
Premotor	
Olf	
GP	
DS	
VS	
NBM	
PirFo	
Ent	
HP	
basalAmy	
Amy	
HTh	
MSDB	
BNST	
Pul	
LGN	
Tha	
VTA	
SN	
PAG	
InfCol	
SC	
LC CGn	
MesE	
ParabrachialN	
Raphe	
PontReg	
DCbN	
aICb	
pflCb	
LatHemCb	Lateral cerebellar hemisphere
IntHemCb	Intermediate cerebellar hemisphere
Vermis	Vermis



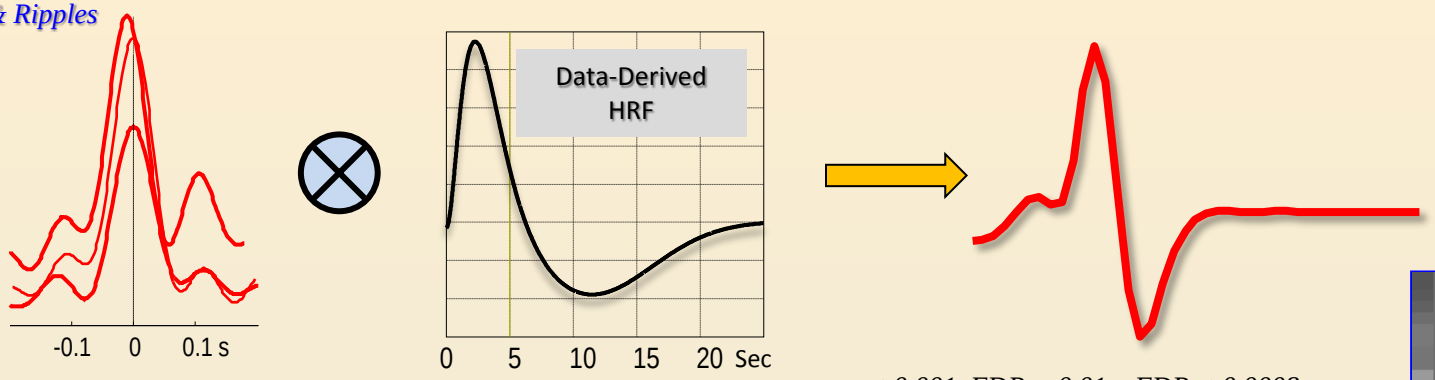
Saleem, K. S. and N. K. Logothetis (2012)

Events, Regressors, BOLD Responses & MAPS

Detection of *Sigma, Gamma & Ripples*

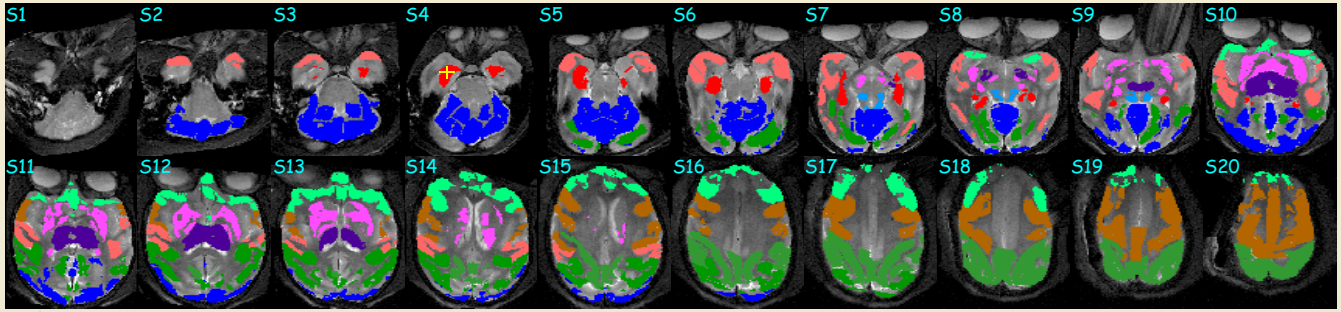


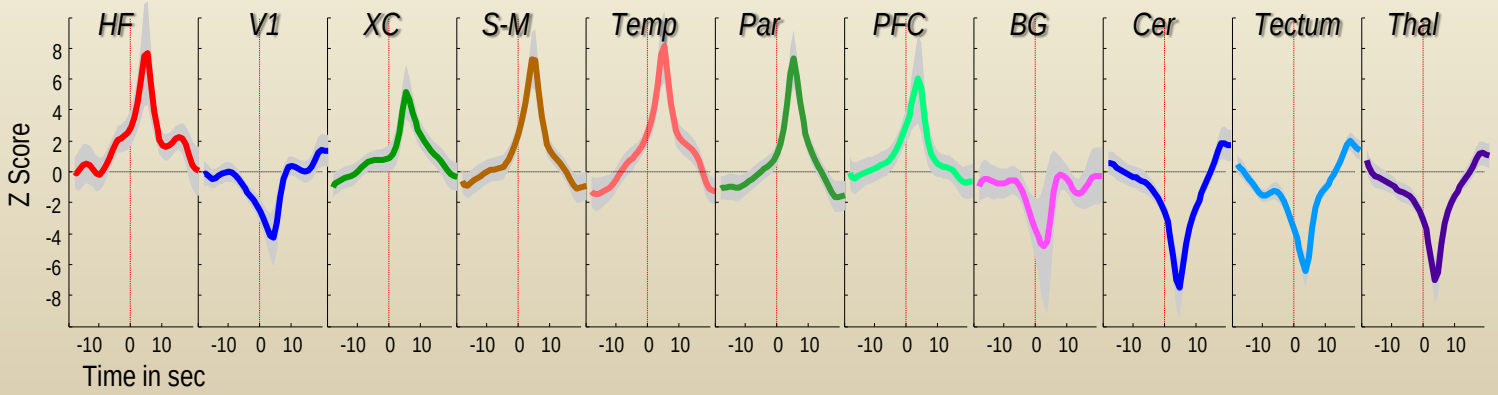
Regressors

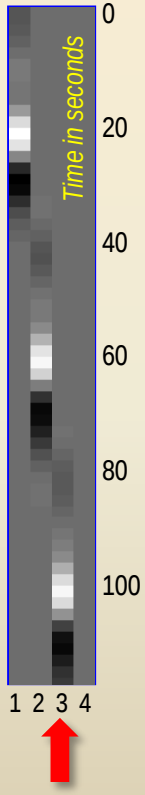


$p < 0.001$, $FDR = 0.01$, $pFDR < 0.0008$

GLM Maps & BOLD Responses



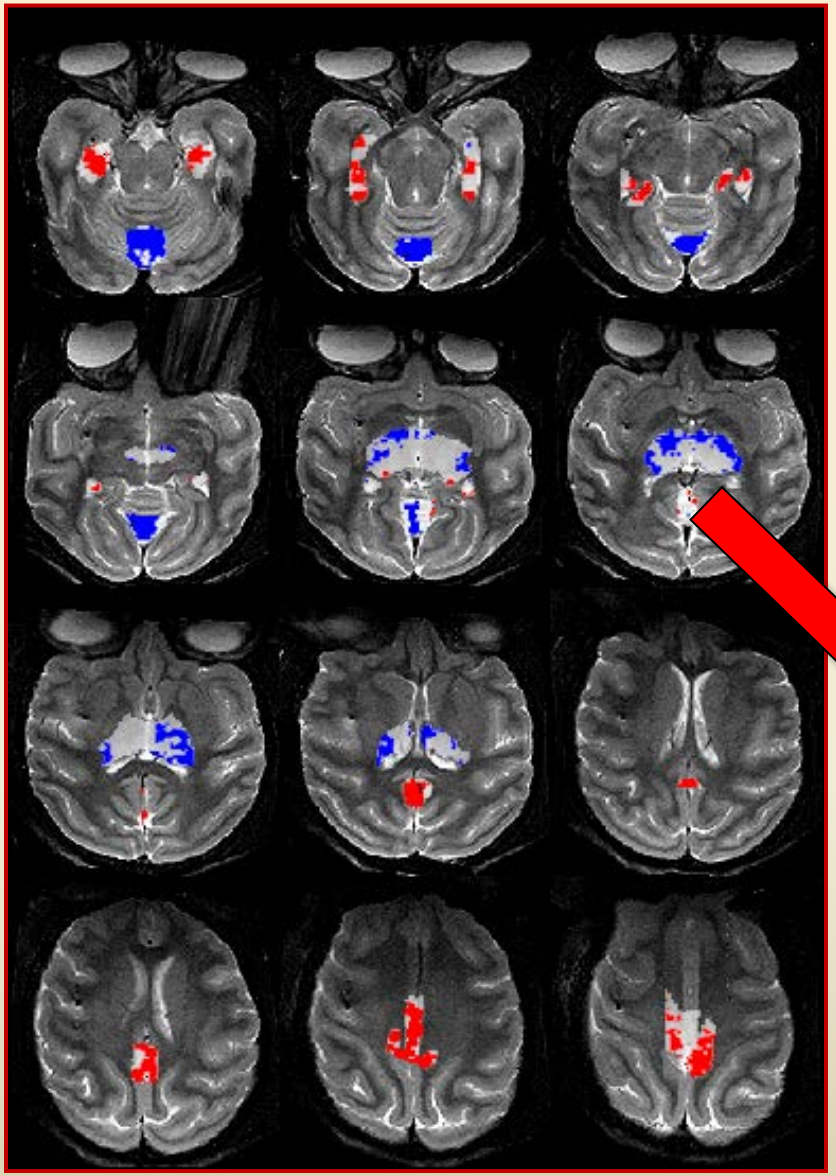


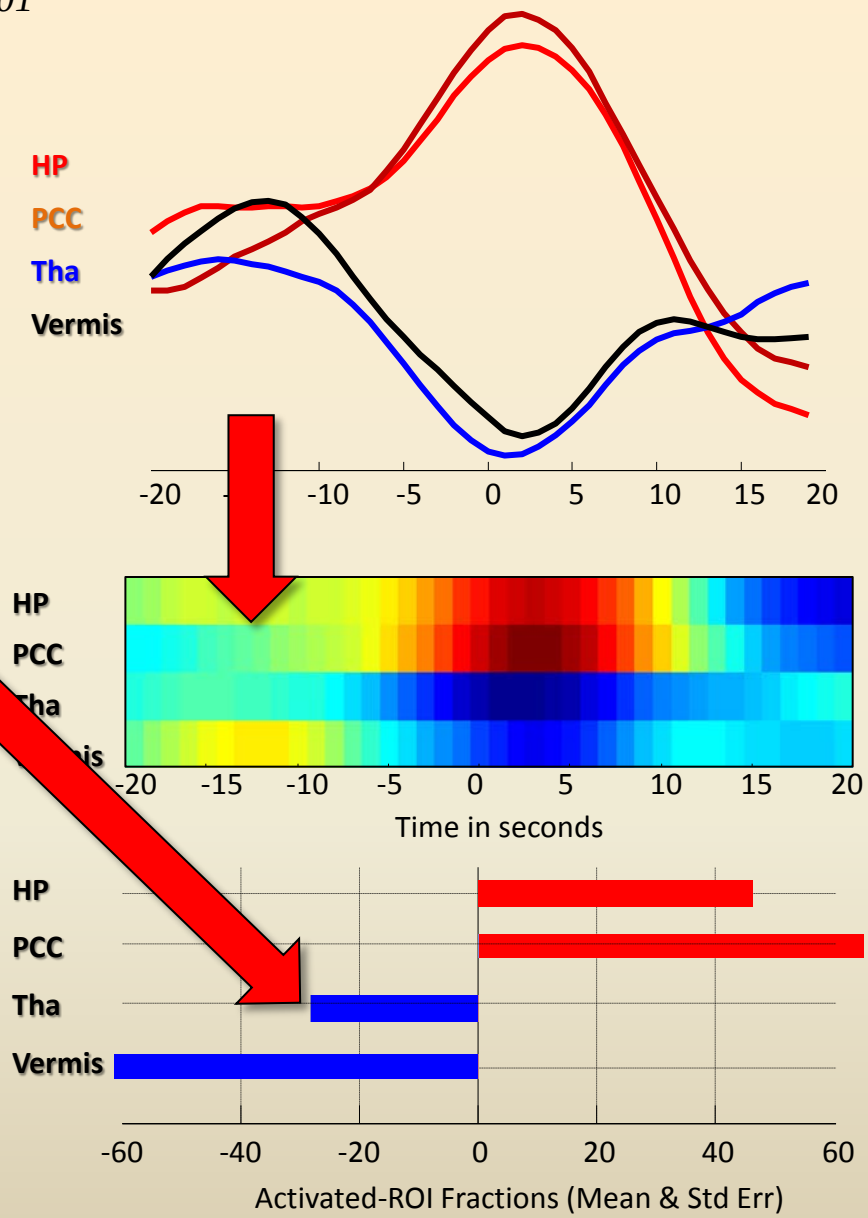


Logothetis et al. Nature 2012

Time Courses & Activation-Fractions of Regions of Interest (ROIs)

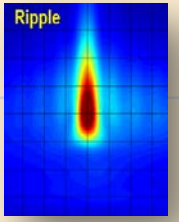
Selection of Slices (Monkey: i11bu1), p < 1e-5, FDR = 0.01





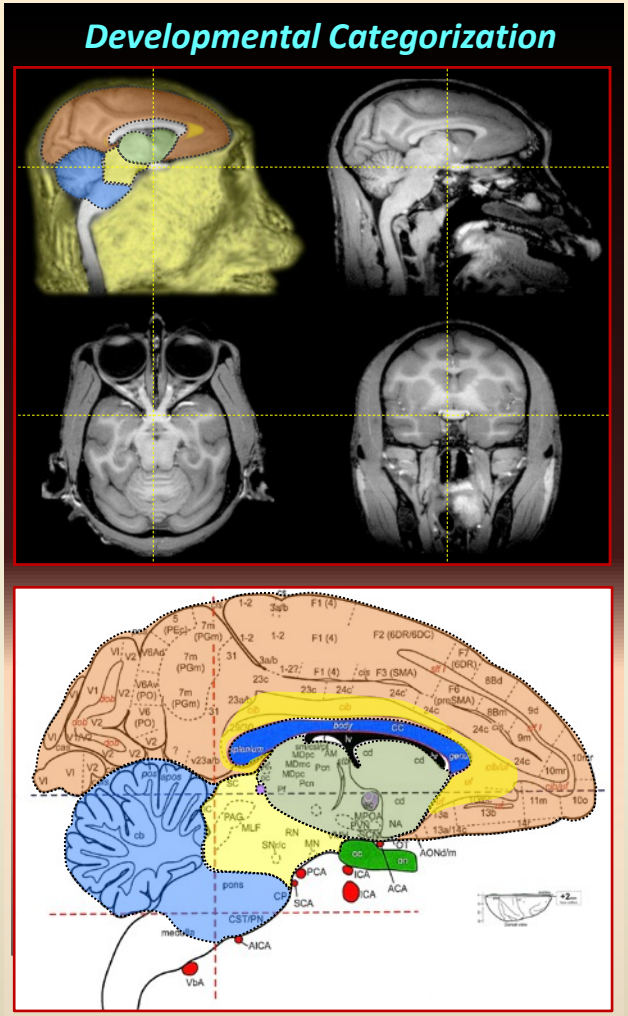
Logothetis et al. Nature 2012, Logothetis et al. Cur Op Neu 2015

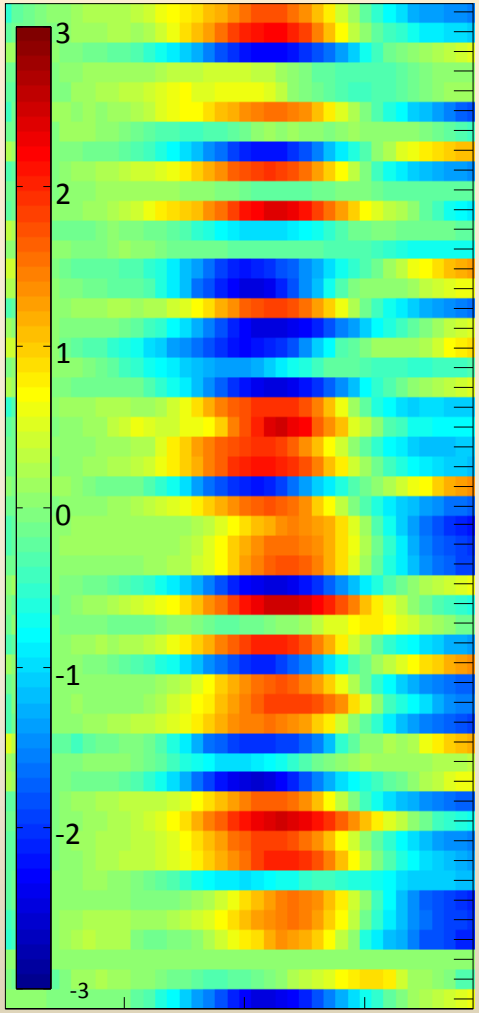
SPW-R Triggered & fMRI-Mapped Networks



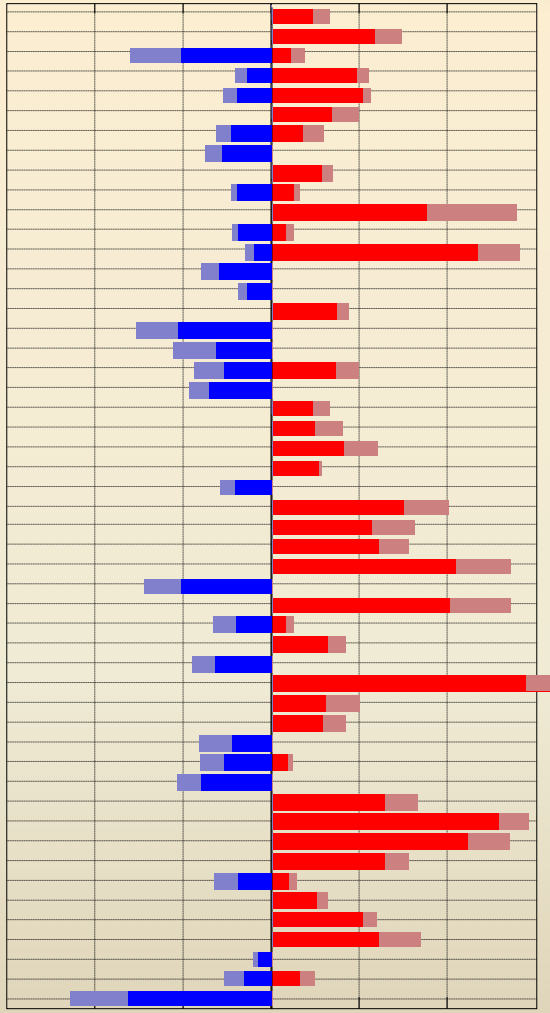
Selection of Slices (Monkey: i11bu1), p < 1e-5, FDR = 0.01

ROIs Sorted in Alphabetical Order





ACC
aIns
aICb
Amy
basalAmy
dACC
DB+MS
DCbN
dlPFC
DS
Ent
GP
HP
HTh
InfCol
Ins
IntHemCb
LC+CGn
LGN
LatHemCb
medPFC
Motor
Olf
orbPFC
PAG
PCC
ParIntra
ParLat
ParPrec
pflCb
PirFo
PontReg
Premotor
Raphe
RetroSp
S1
S2+
SC
SN
Tha
TmpAu
TmpPol
TmpSTS
TmpVis
V1
V2-V3
V4
V5
VS
VTA
Vermis



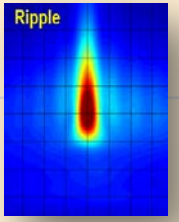
-8 -6 -4 -2 0 2 4 6 8
t-Score

-20 -10 0 10 20
Time in seconds

-60 -40 -20 0 20 40 60
Activated-ROI Fractions (Mean & Std Err)

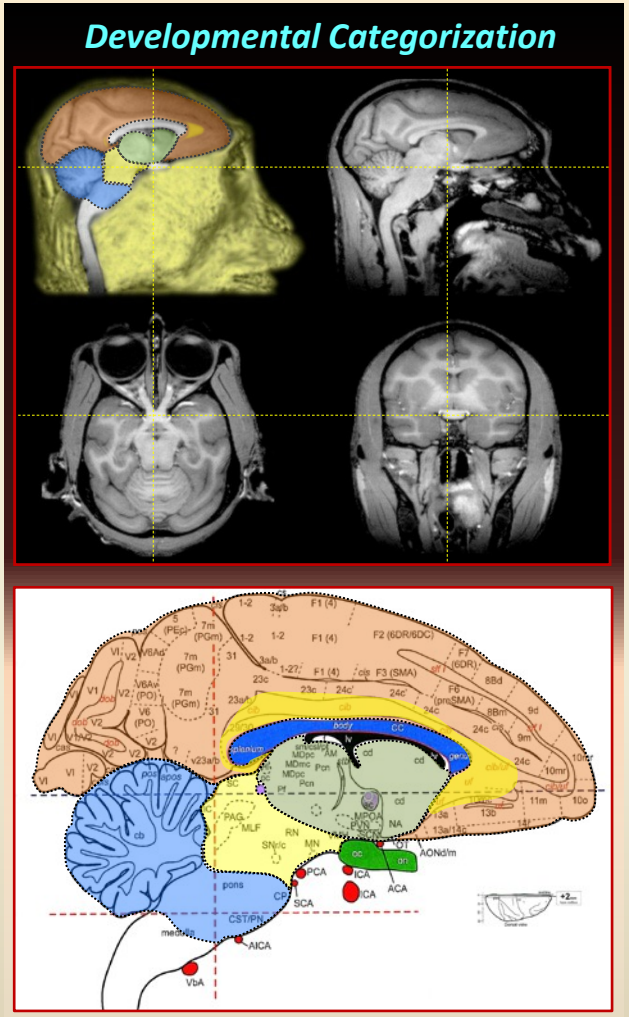
Logothetis et al. Nature 2012, Logothetis et al. Cur Op Neu 2015

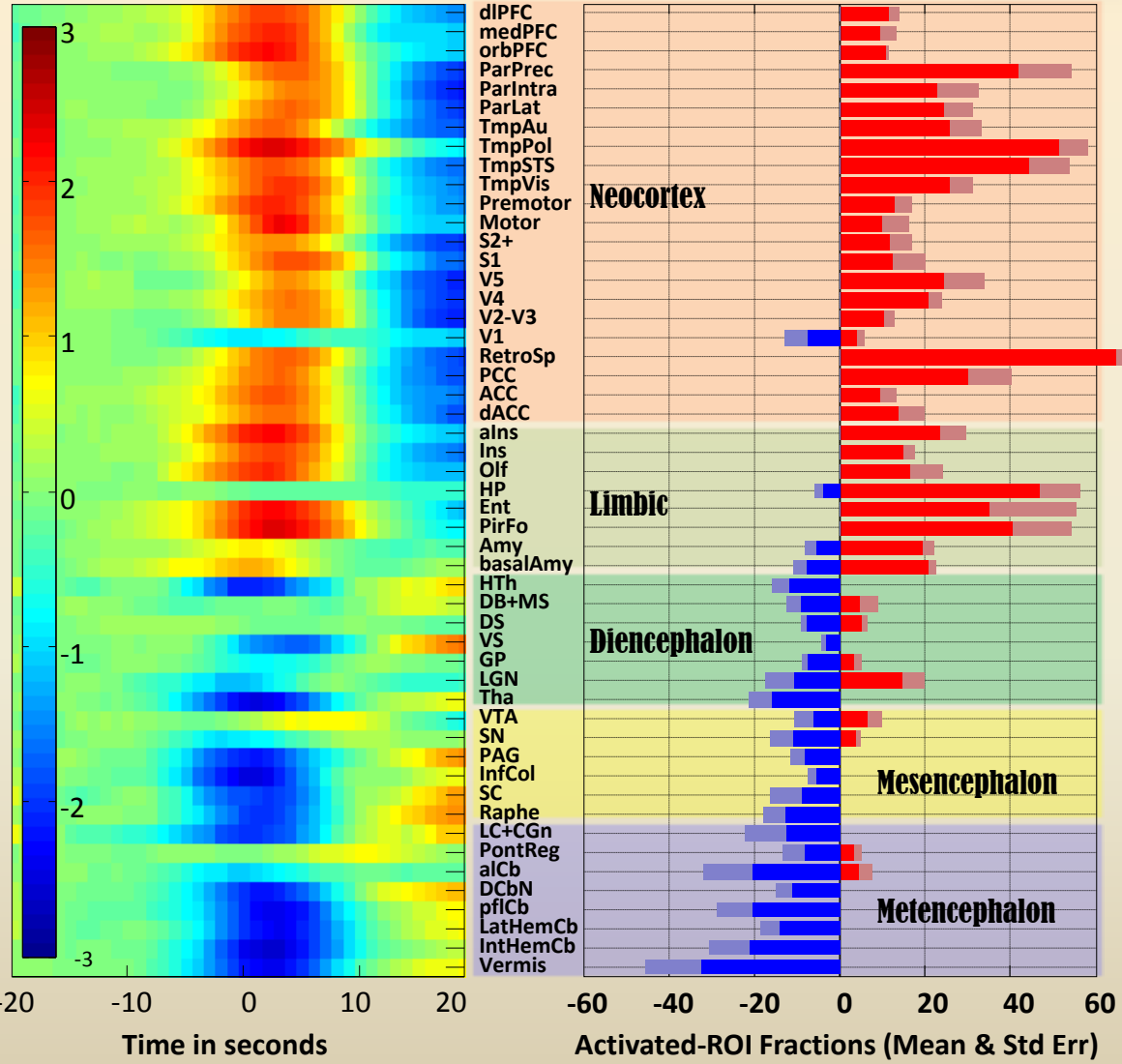
SPW-R Triggered & fMRI-Mapped Networks – Functional Interpretation



Selection of Slices (Monkey: i11bu1), p < 1e-5, FDR = 0.01

ROIs Sorted in the Order of Developmental Categorization

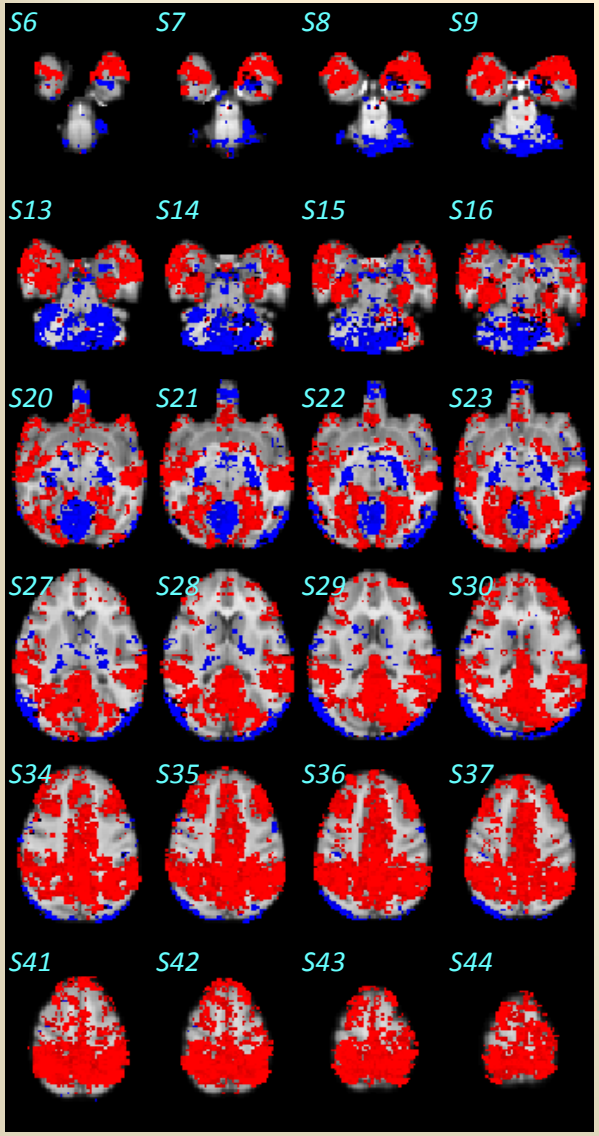


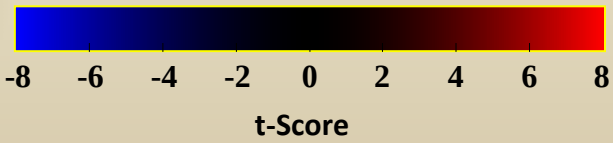


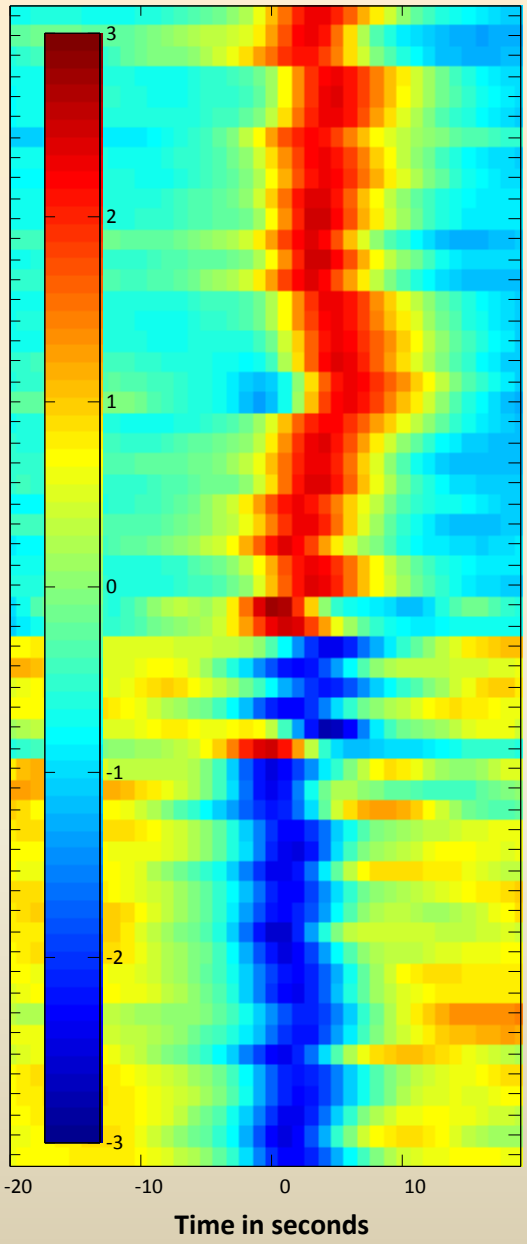
Logothetis et al. Nature 2012, Logothetis et al. Cur Op Neu 2015

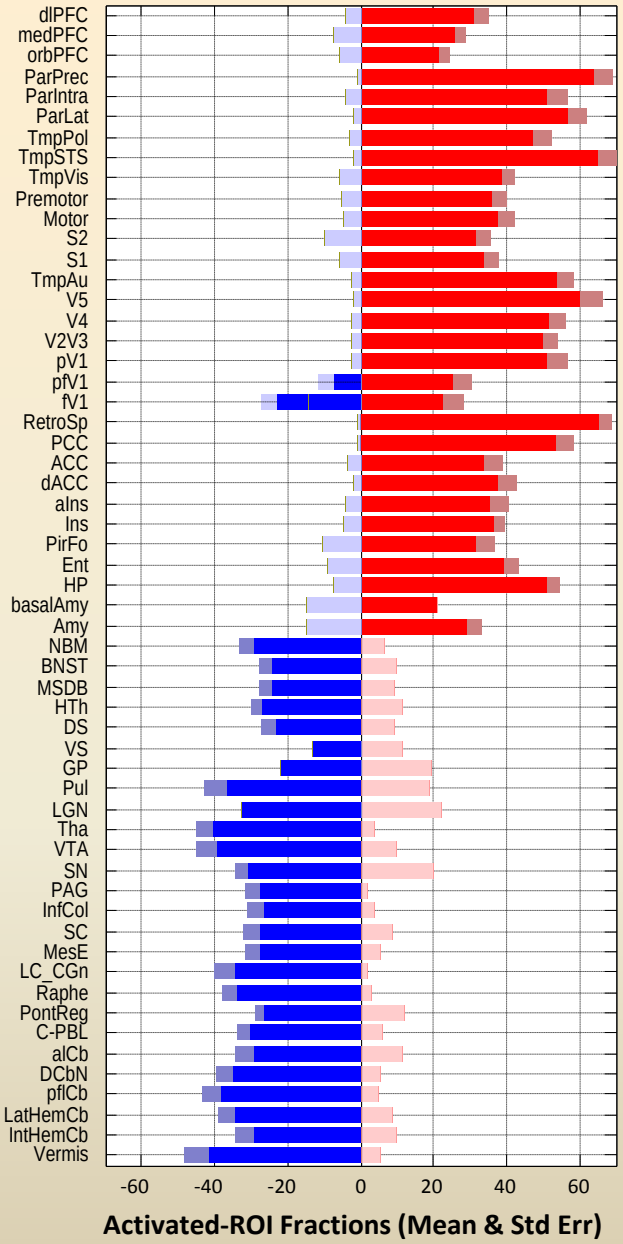
Population Data

Average Maps, BOLD Responses & Activation Fractions for 38 Sessions





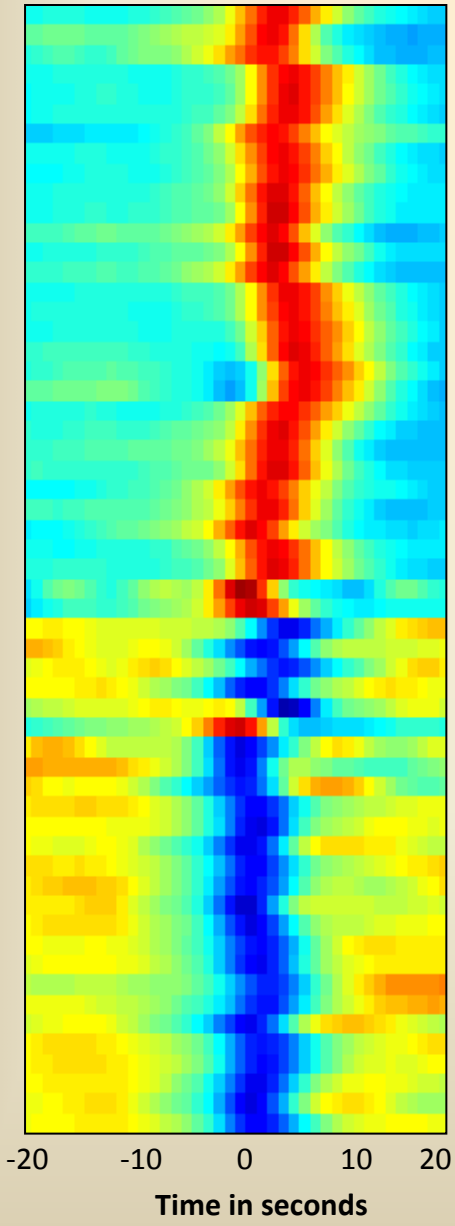


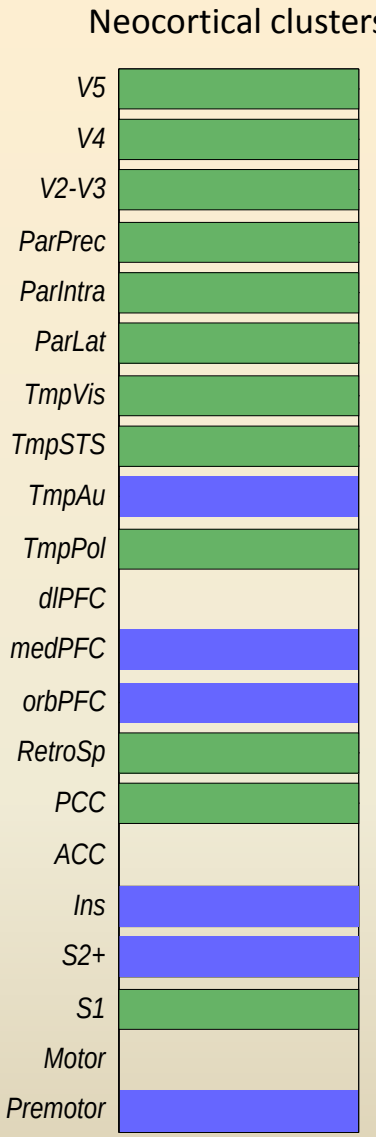


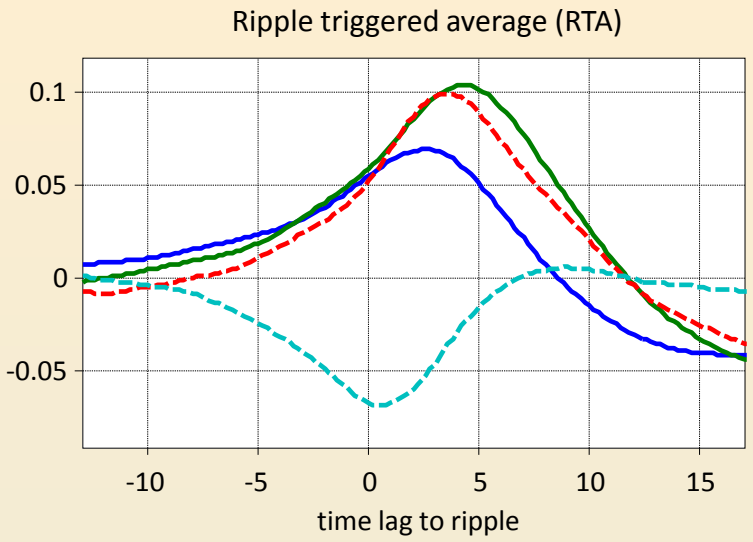
Logothetis et al. Nature 2012

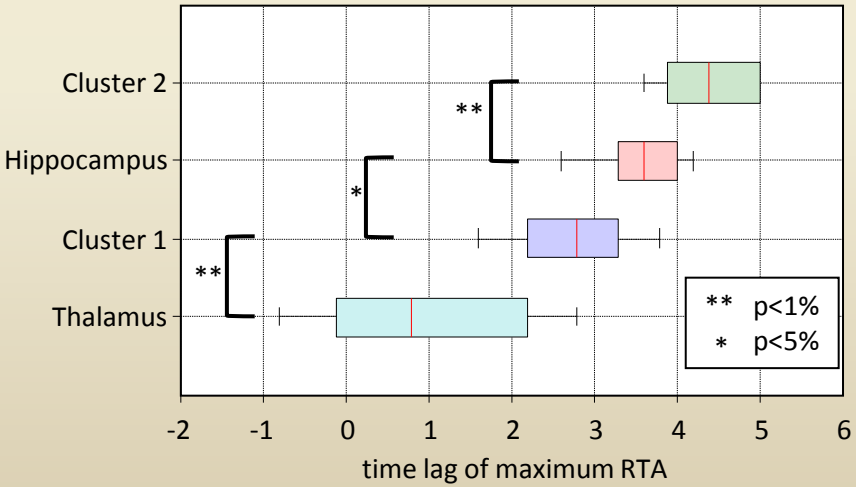
Population Data

Time lag Analysis of SPW-R Triggered Average Responses







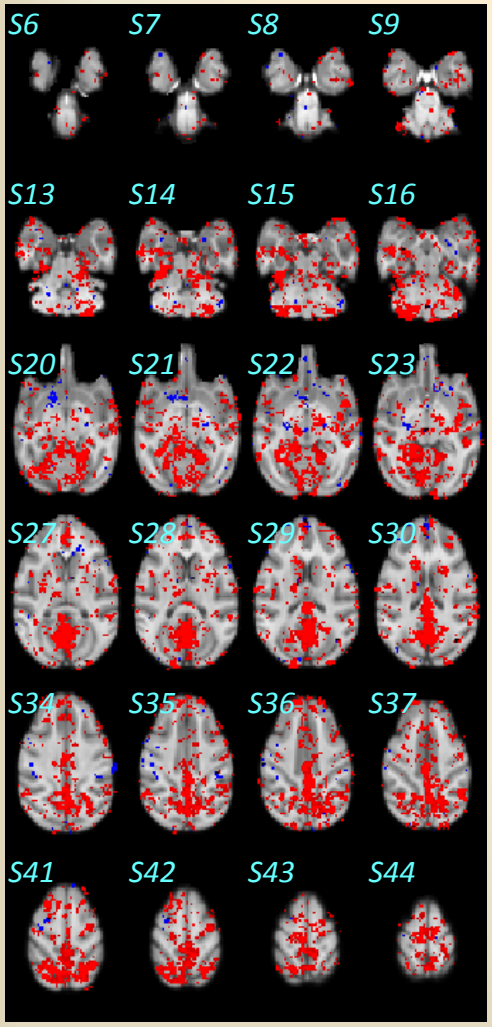


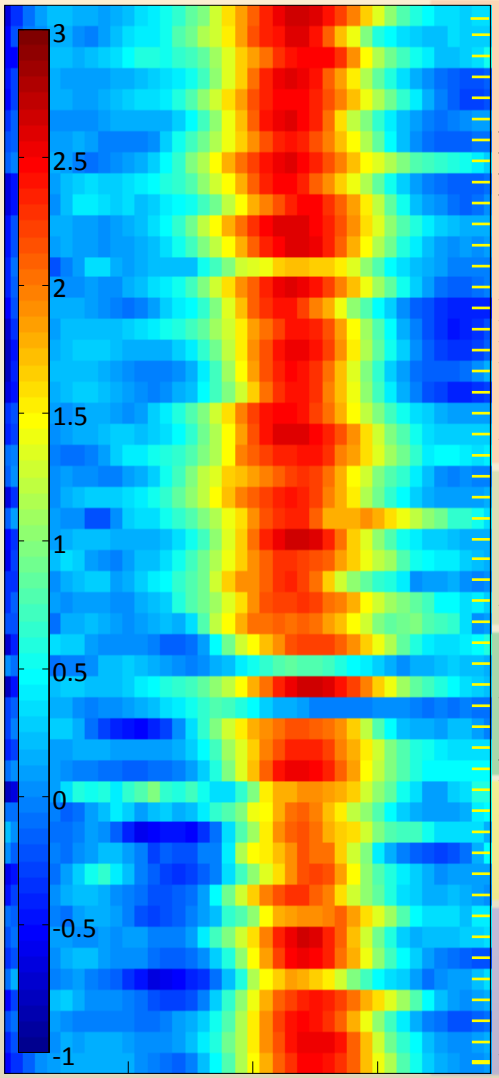
Logothetis et al. Nature 2012

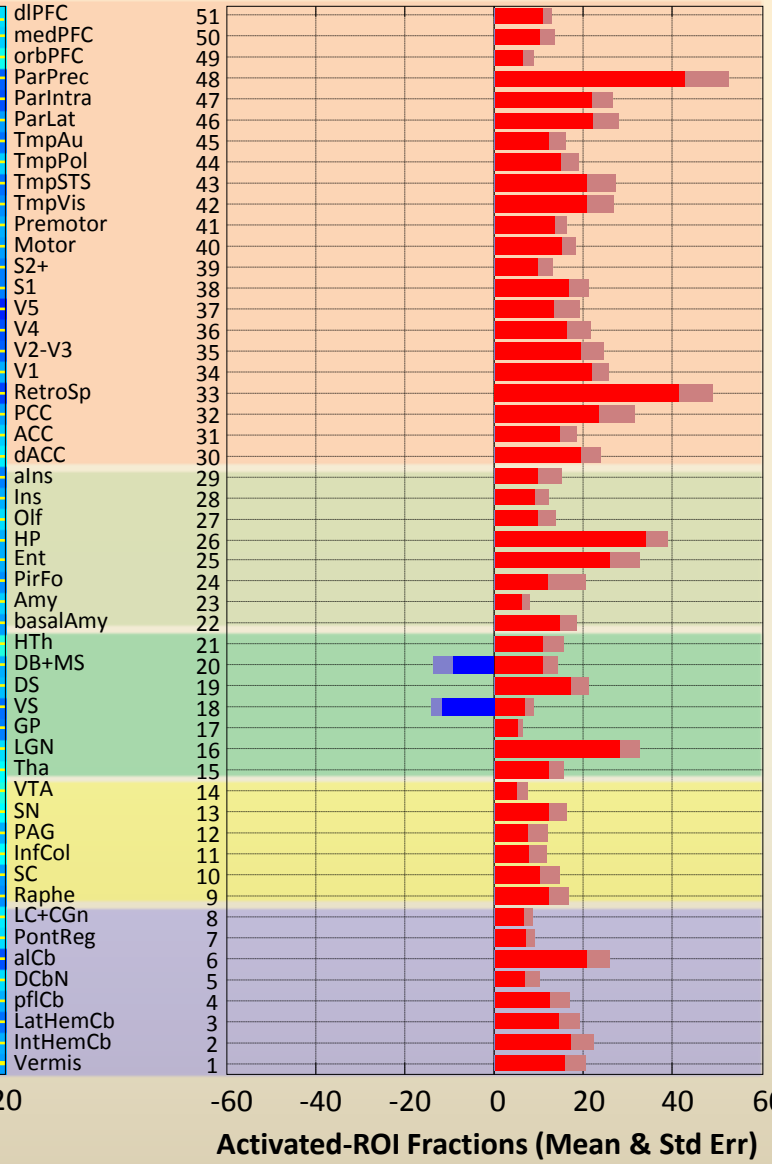
Population Data

NET-fMRI is Event-Specific – E.g. Gamma-fMRI

Hippocampal Gamma-Events Correlated with Global PBR



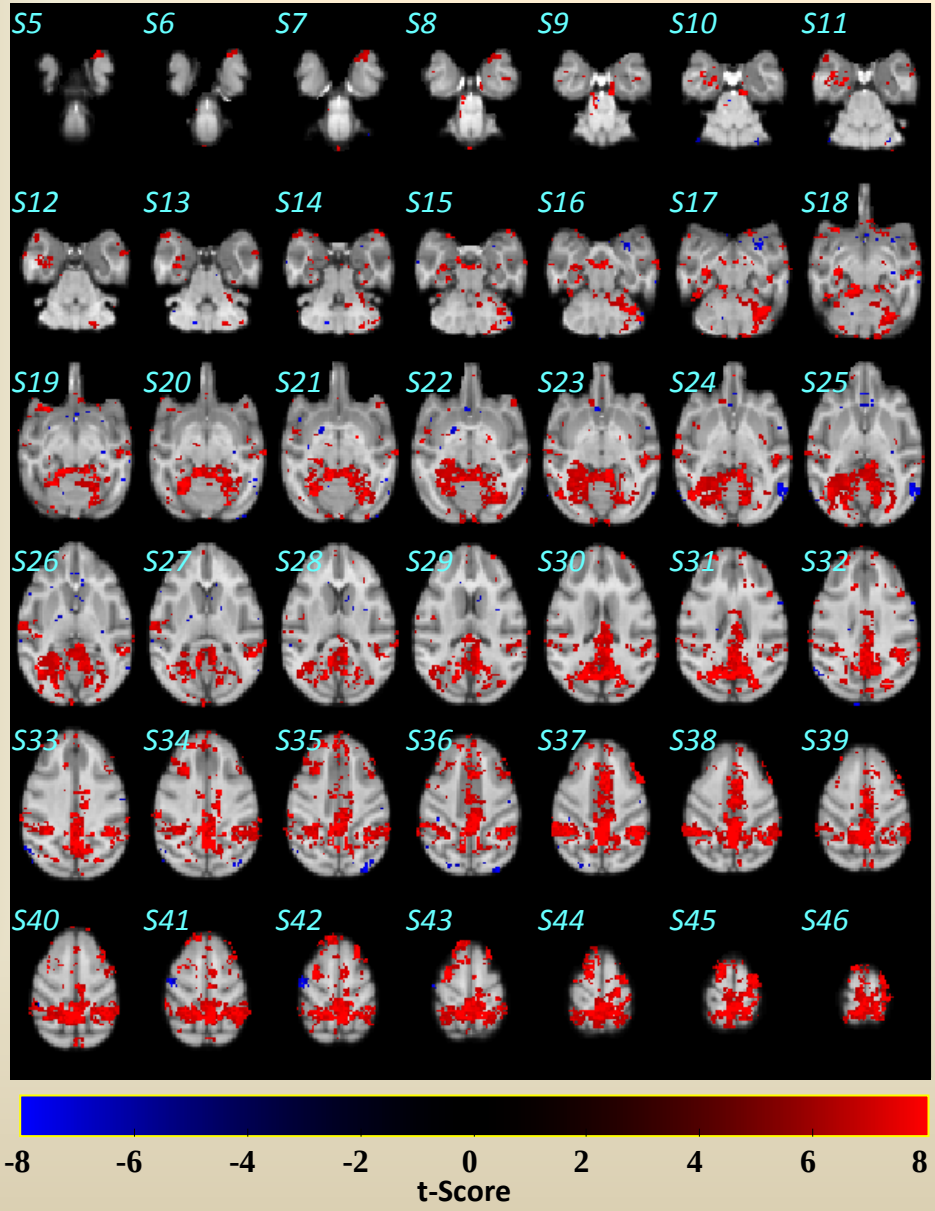


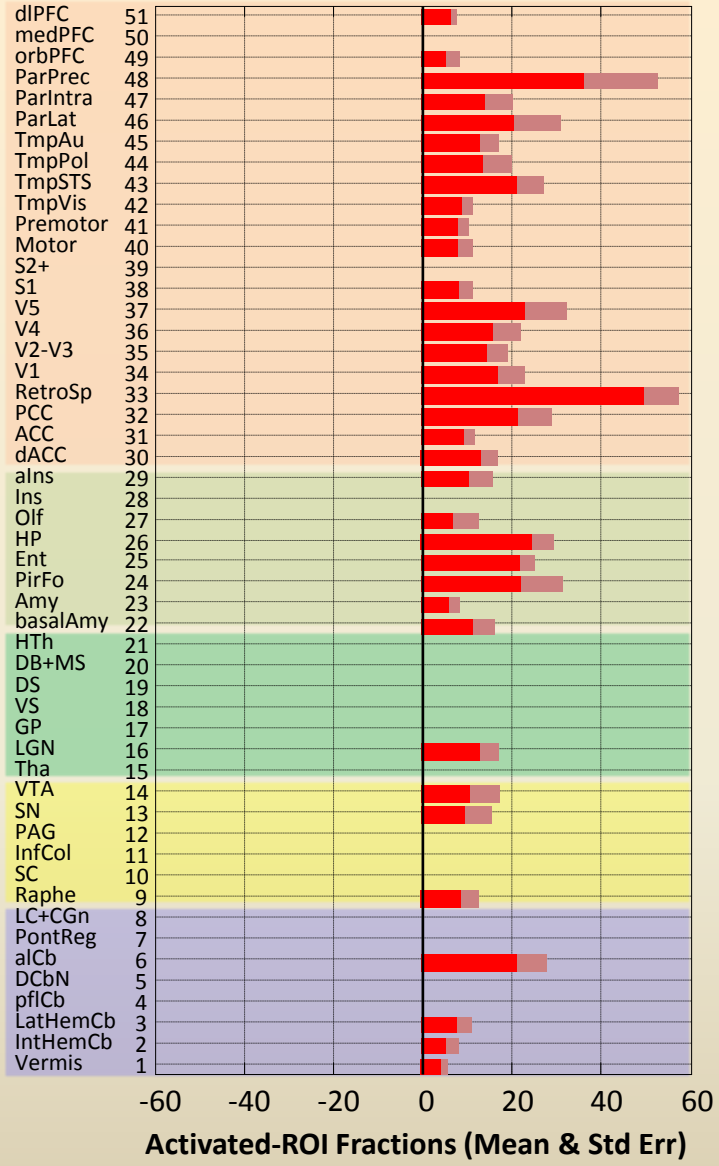


Gamma-Induced Maps, Time Courses & Fractions, Logothetis, Cur Op Neu, 2015

Population Data

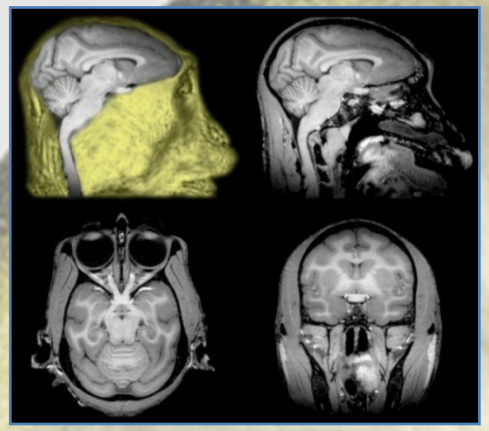
NET-fMRI is Anatomical-Structure-Specific – E.g. HFO(>90 Hz)-fMRI

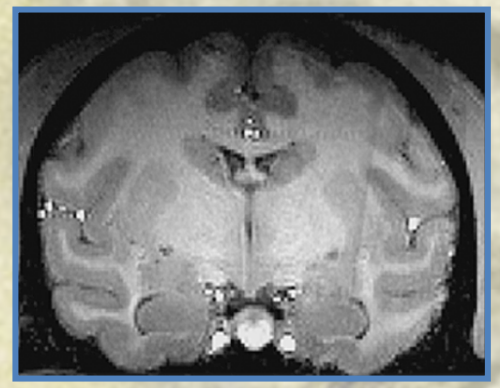


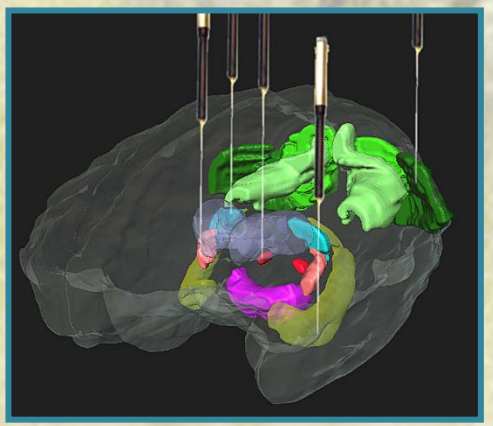


Work in Progress

SPW-R fMRI – Strategy & Questions







Initial Strategy

- Unsupervised electrophysiological detection & identification of the Neural Events (NE), starting w/ SPW-Rs that may be potential state-indicators of self-organized neuronal activity

- Description of fMRI-assessed patterns of **Multi-Structure-Activity (MSA)** that are robustly correlated to single-episodes or event–sequences

Currently: Over 70 Brain-Regions defined via MRI

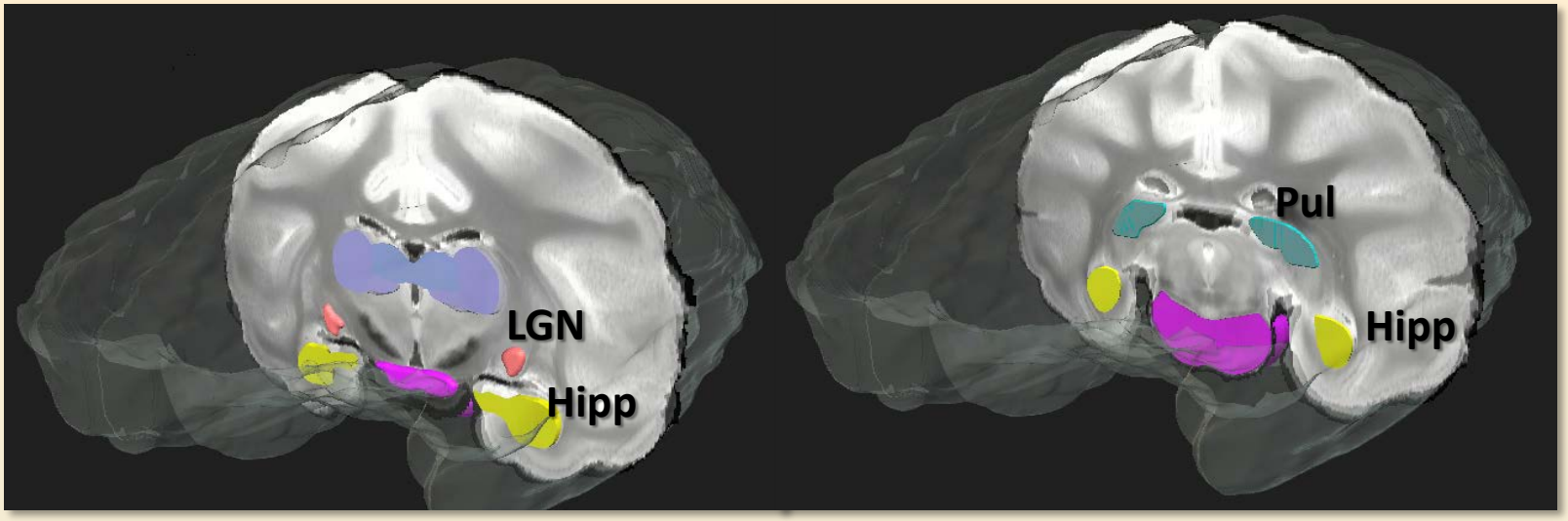
First Questions

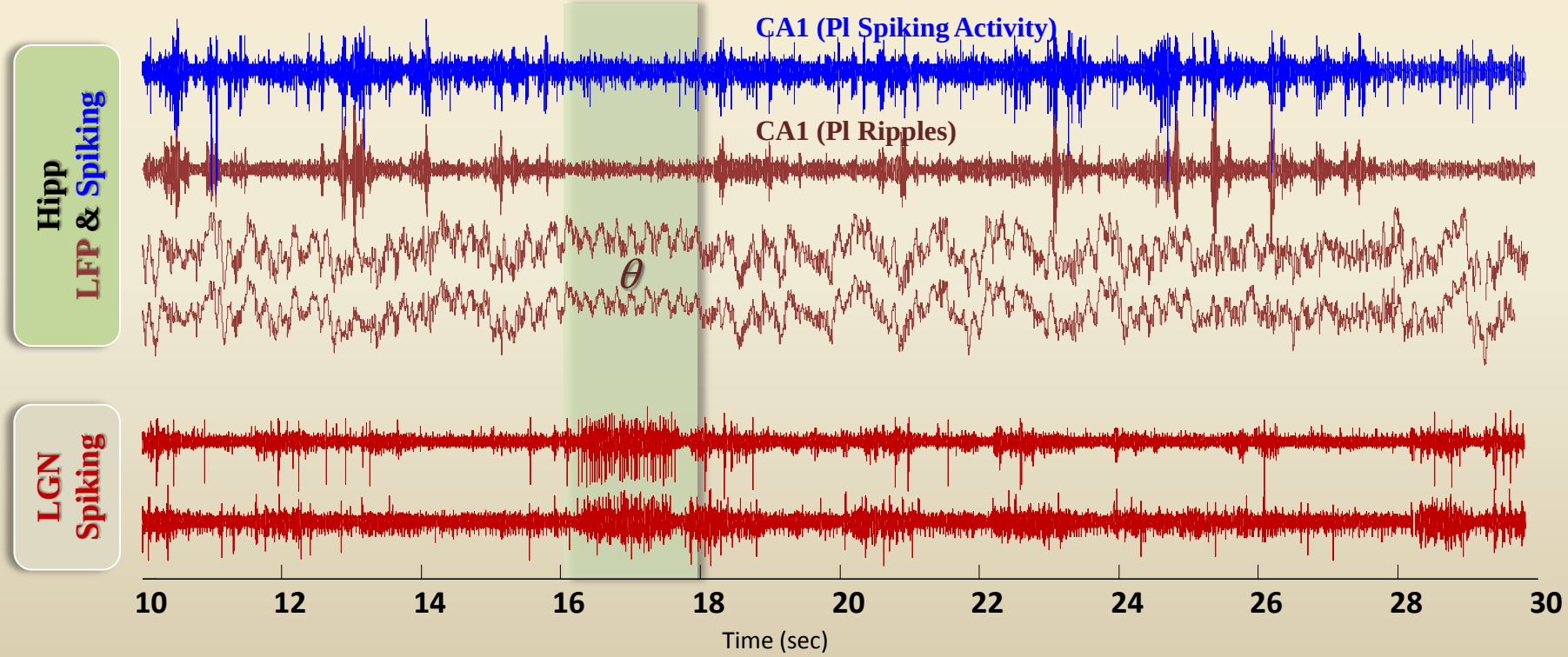
➔ Is there a Systematic NE-MSA Relationship?

➔ Neural Correlates of the NET-fMRI Up/Down-Modulations?

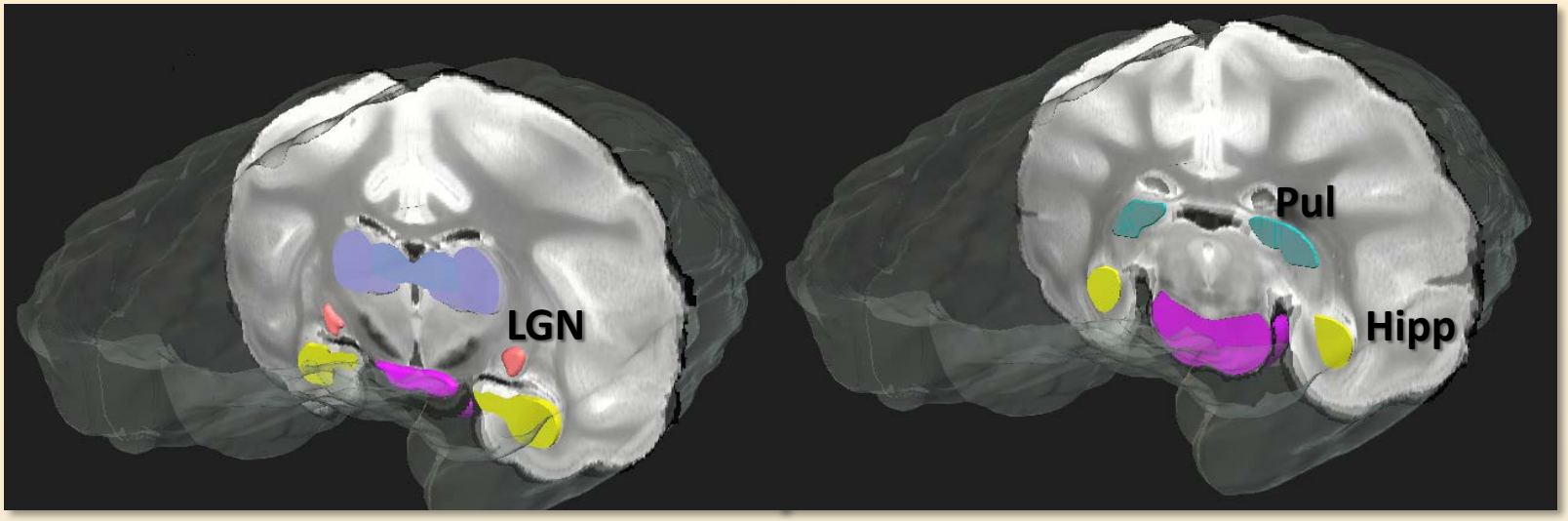
➔ Can MSA-Patterns Indicate the Occurrence of Neural Events?

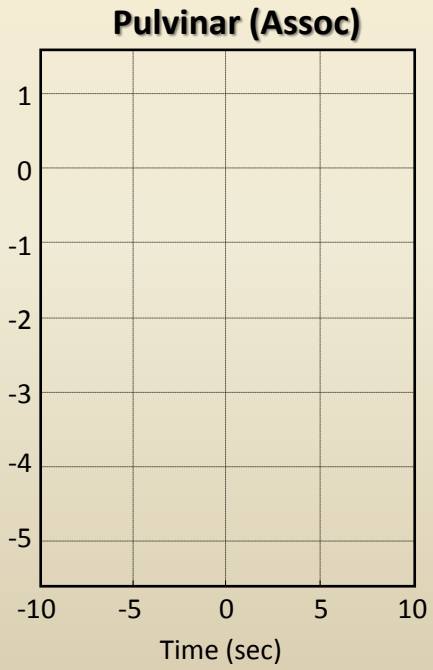
Hippocampus – Thalamus Interactions During SPW-R





Hippocampus – Thalamus Interactions During SPW-R





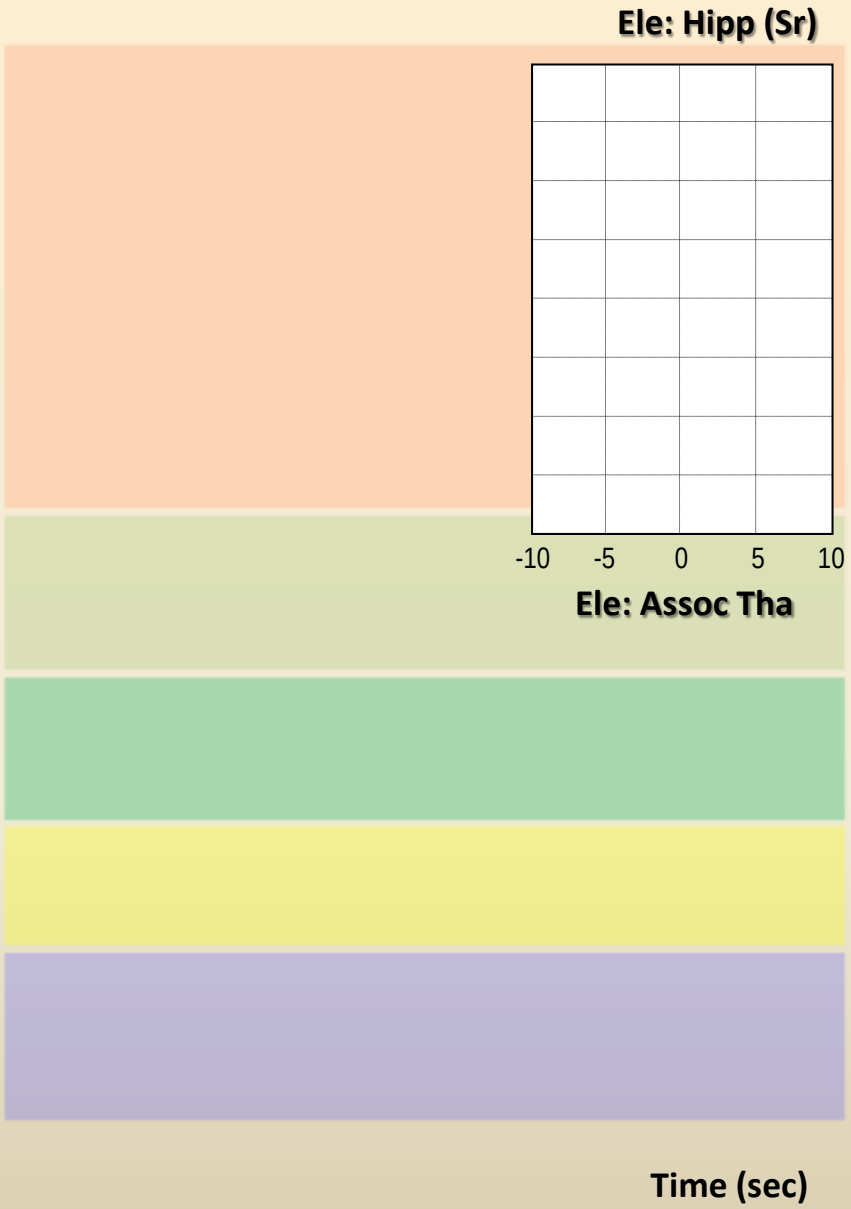
Z Score

Population Data

Two Characteristic MUA Response-Clusters in Thalamus

Population Data

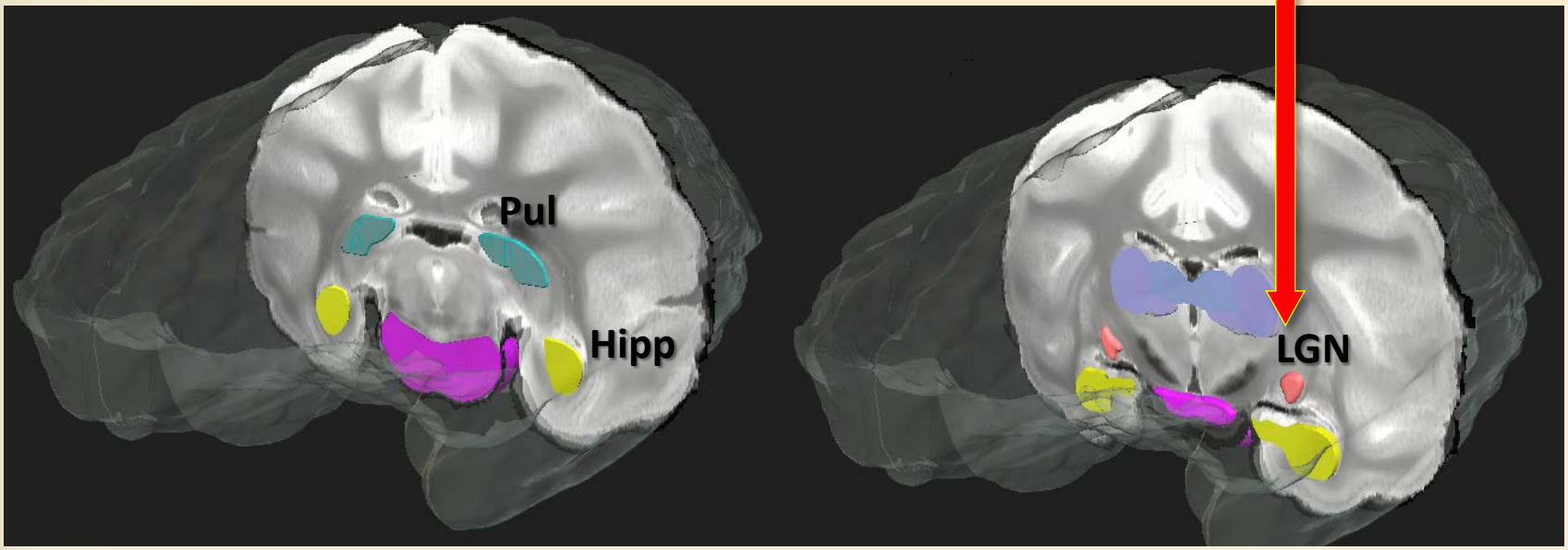
NET-BLP (like NET-fMRI) is Event-Specific – E.g. Gamma-BLP

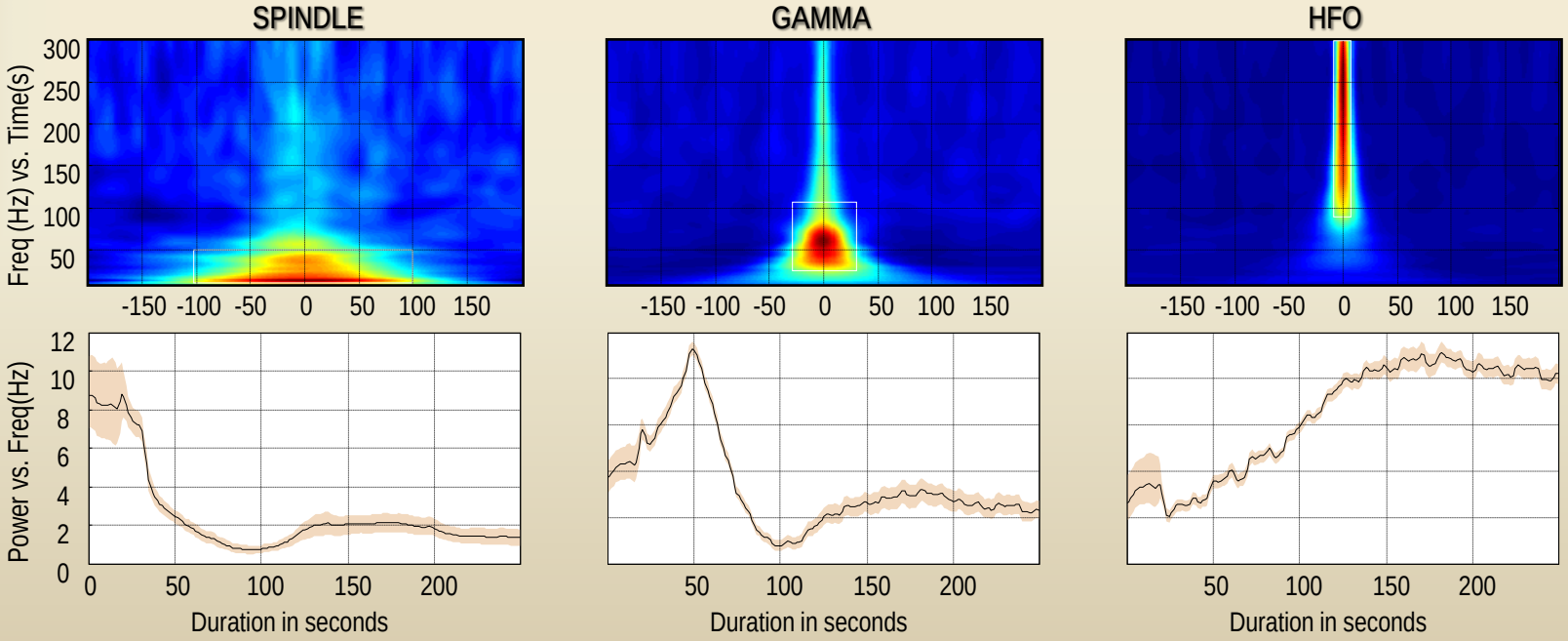


Logothetis et al. Nature 2012; Logothetis Cur Op Neu. 2015

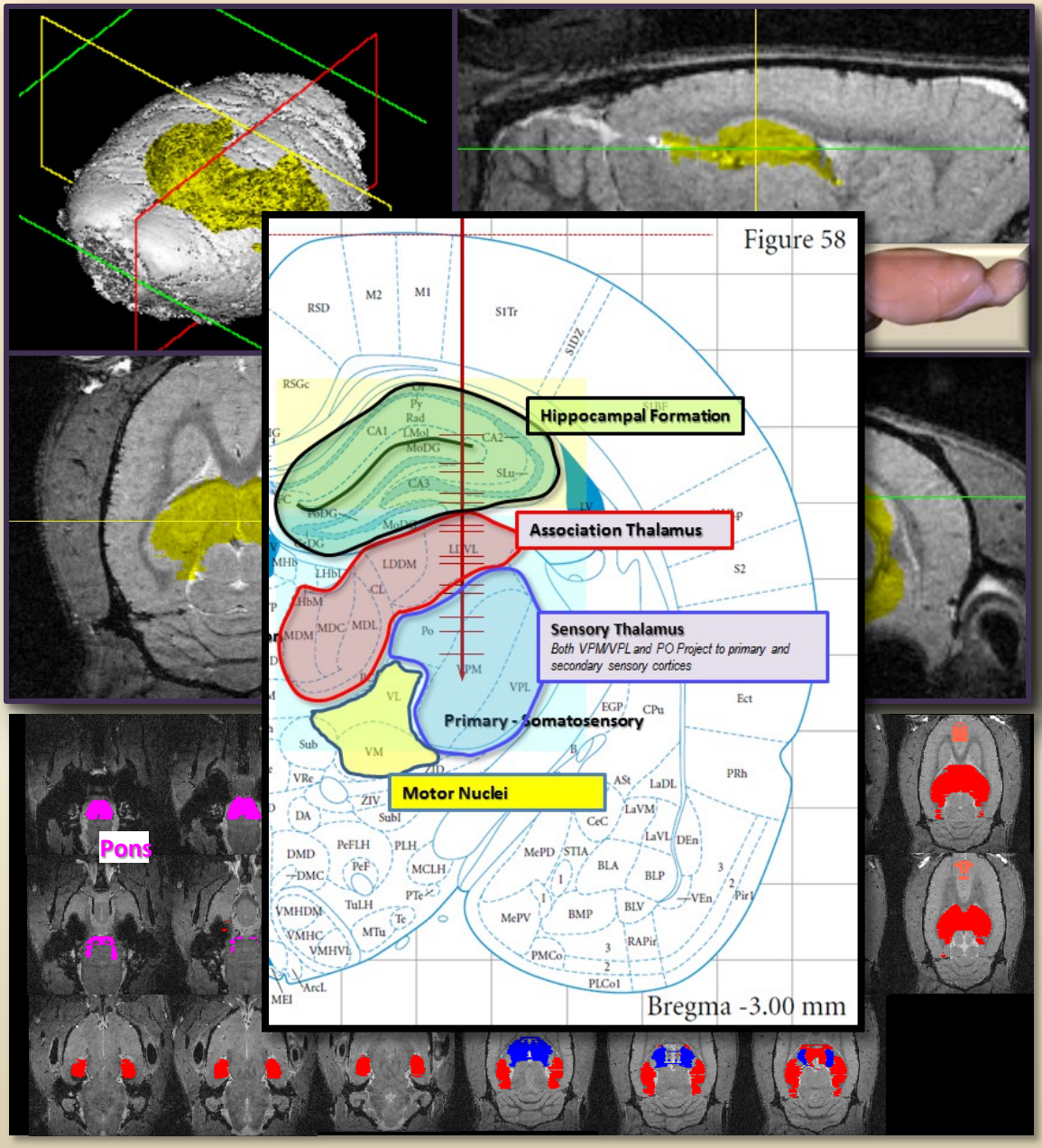
Population Data

NET-BLP (like NET-fMRI) is Anatomical Structure-Specific





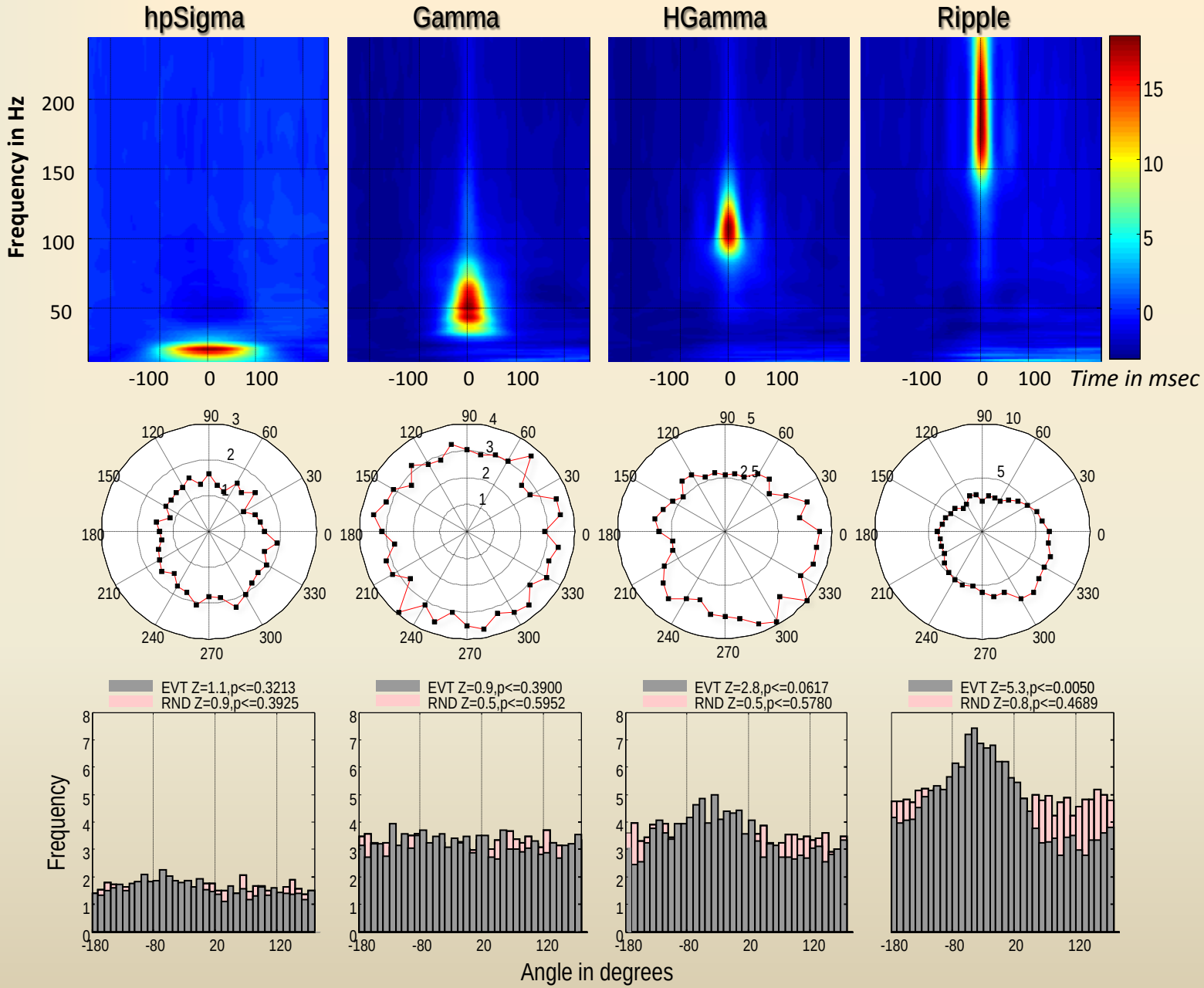
Neural-Event Triggered fMRI in Rats



Infralimbic-Prelimbic (PFC is mPFC + FrA)	PFC
Frontal_Association	
Orbitofronal_Cortex	
Parietal_Association_Cortex	
Temporal Association Cortex	
Secondary_Motor_Cortex	
Primary_Motor_Cortex	
Secondary_Somatosensory_Cortex	
Primary_Somatosensory_Cortex	
Secondary_Auditory_Cortices	
Primary_Auditory_Cortex	
Area_V2	
Visual_Cortex	
Retrosplenial_Cortex	
Cingulate	
Dysgranular_Granular_Insular_Cortex_Dorsal	
Agranular_Insular_Cortex	
Agranular_Posterior_Insular_Cortex	
Olfactory	
Entorhinal_Cortex	
Subiculum	HF
Ventral_Hippocampus	
Intermediate_Hippocampus	
Dorsal_Hippocampus	
Piriform_Cortex (part of rhinencephalon situated in telencephalon)	
Amygdala	
Zona_Inserta	
StriaTerminalis	
Diagonal_Band + Septum	
Hypothalamus (supramammilary receives RPO input/send MSDB)	
Globus_Pallidus	
Accumbens	
Ventromedial_Striatum	
Dorsolateral_Striatum	
Lateral_Thalamus	Thal
Median_Thalamus	
Anterior_Thalamus	
Ventral_Tegmental_Area	
SubNigra	
Periaqueductal_Gray	
Inferior_Colliculus	
Superior_Colliculus	
MesE	
LC+CGn+SubC	
Raphe	
Pontine_Region	Pons
Deep_cerebellar_nuclei	
Parafloculonodular	
Lateral_cerebellar_hemisphere	
Anterior_cerebellar_lobe	
Intermediate_cerebellar_hemisphere	
Vermis	

Population Data

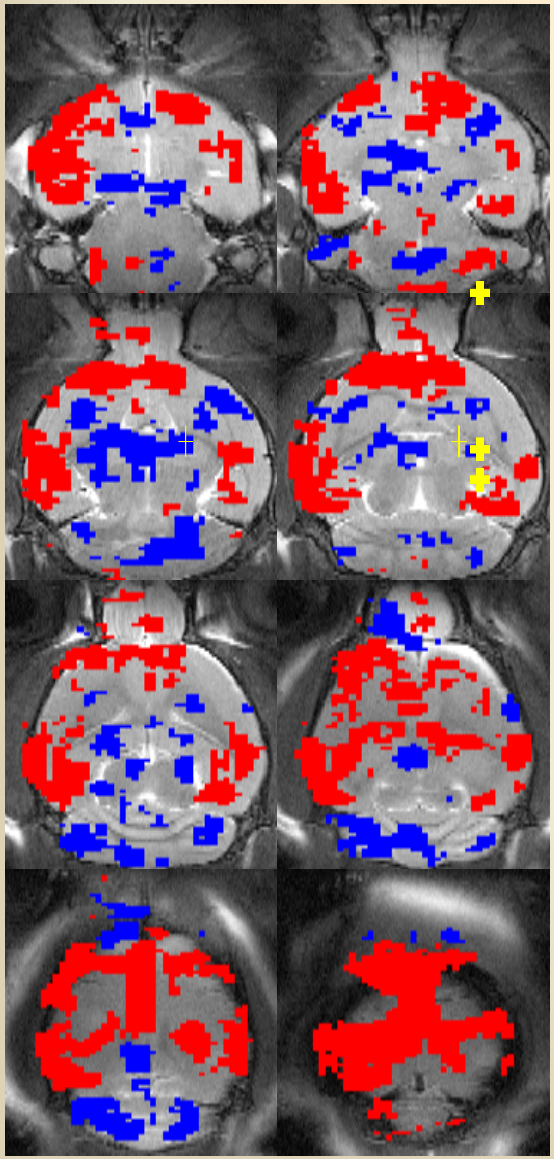
Rat SPW-R Time-Frequency Profiles

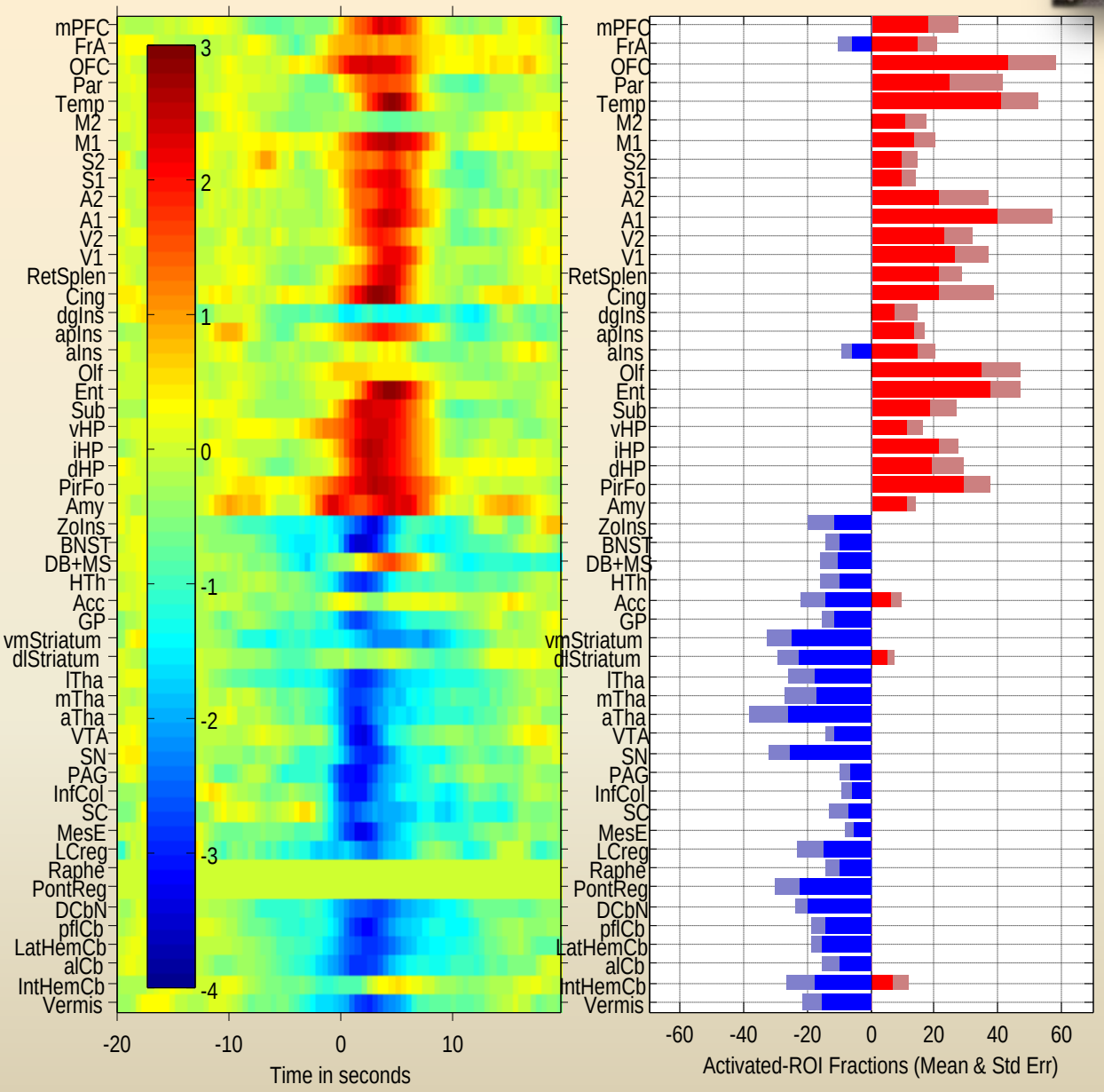


Work in progress; Logothetis et al (in prep)

Population Data

SPW-R-induced MSA in Rodents





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