

Functional Magnetic Resonance Imaging

**Bridging the Science Between Animal
and Human Research**

Craig Ferris, Ph.D. Director

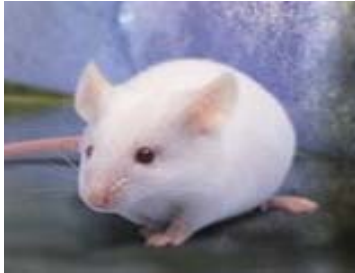
Center for Comparative Neuroimaging

Department of Psychiatry

University of Massachusetts Medical School

Center For Comparative Neuroimaging

mouse



rat



marmoset



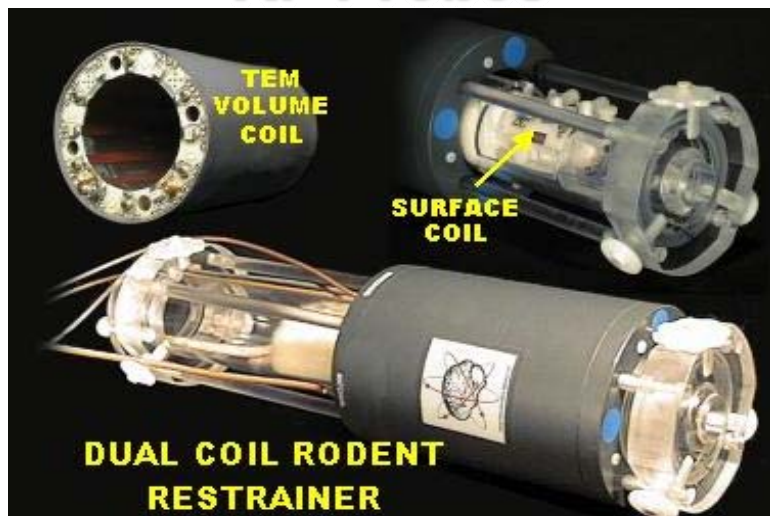
rhesus



University Massachusetts
Medical School

Magnetic Resonance Spectrometer (4.7 T)

RF Probes



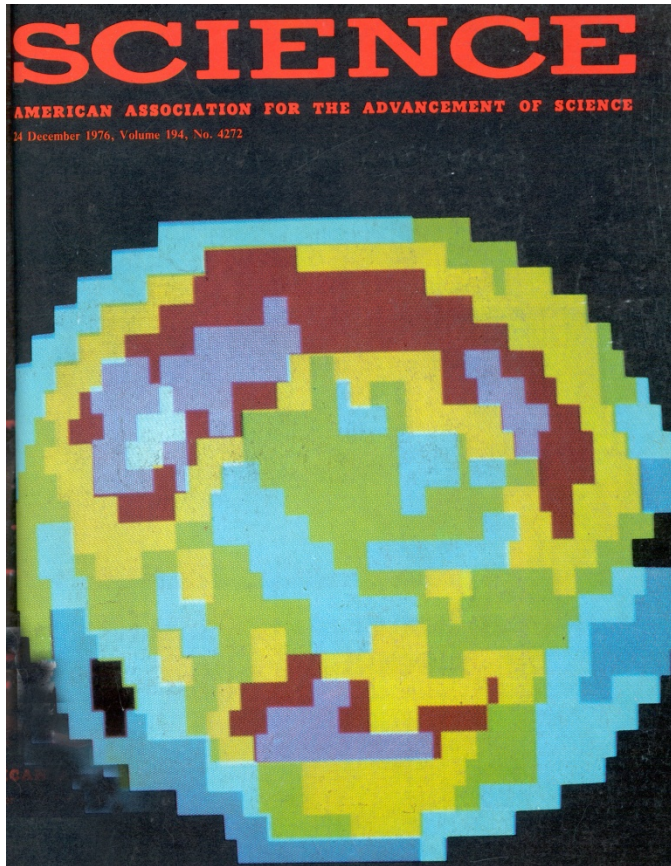
Passive Shielding



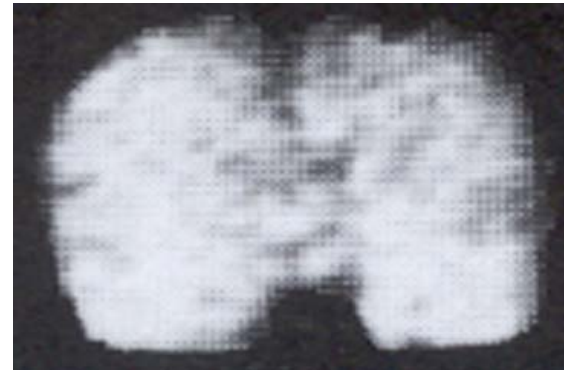
Computer Console



Magnetic Resonance Imaging “Then & Now”



Damadian et al., Science
194:1431, '76

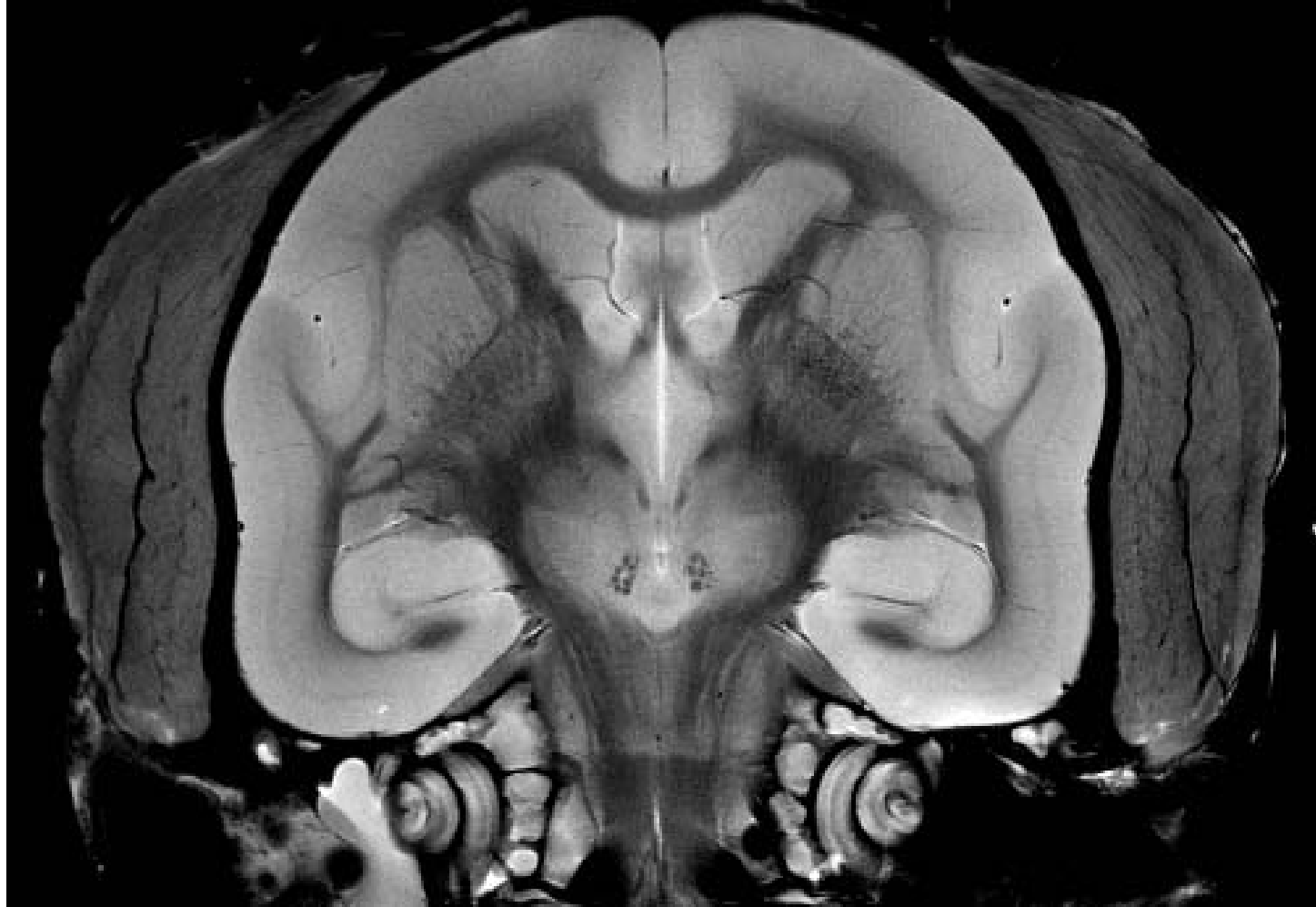


Kramer et al., Neuroradiology
21:239 '81 - Lauterbur

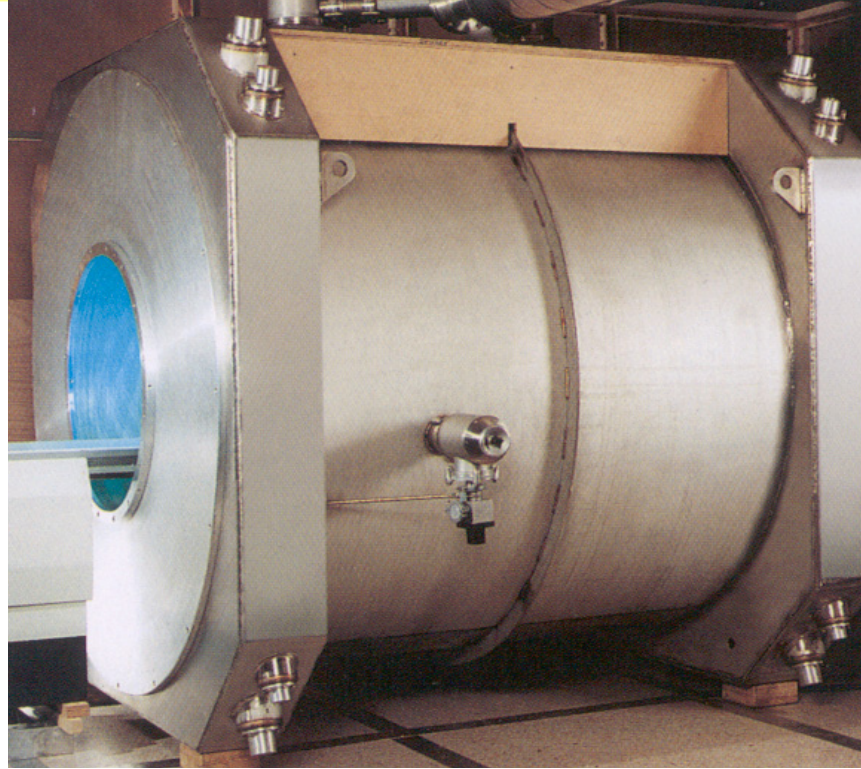


CCNI, 9.4T

High Resolution Magnetic Resonance Image Of Marmoset Monkey Brain



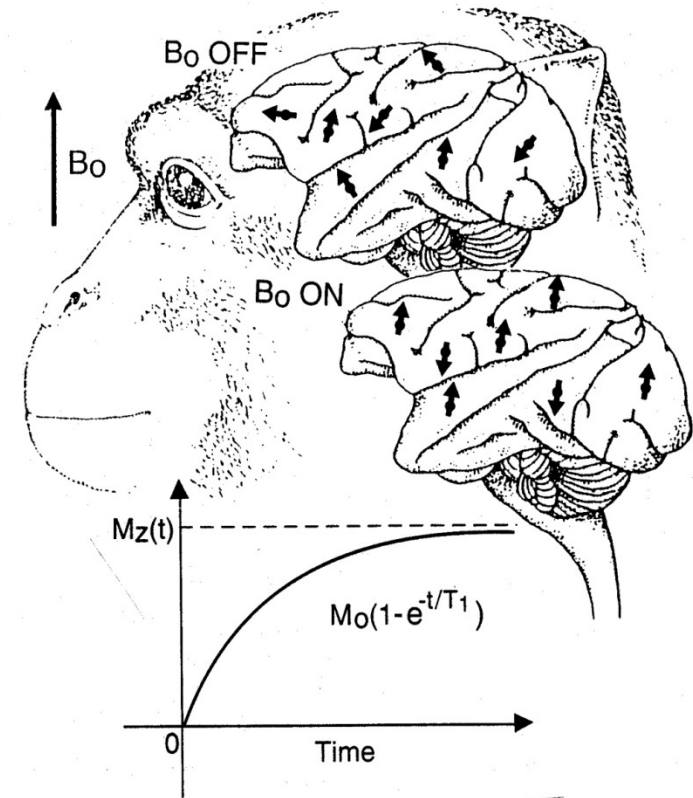
Superconducting Magnets



- **Generate External Magnetic Field - B_0**
- **Field Strength Between 1.5 – 11.7 Tesla (T)**
- **Operate Near Absolute Zero Temperature**

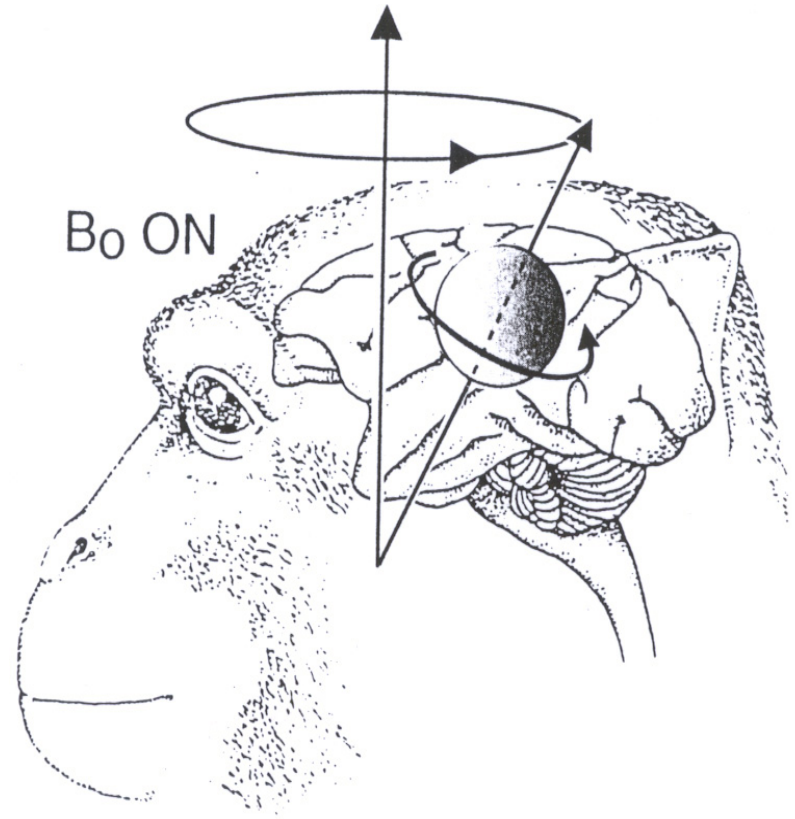
Manipulating Hydrogen Atoms

- MRI is non-invasive and uses the protons from mobile hydrogen in water and fat to generate signals
- The hydrogen nucleus spins creating a local magnetic field causing the charged nucleus to act like little magnets aligning in B_0 .
- Over time (2-3 sec) protons come to equilibrium or net magnetization M_0



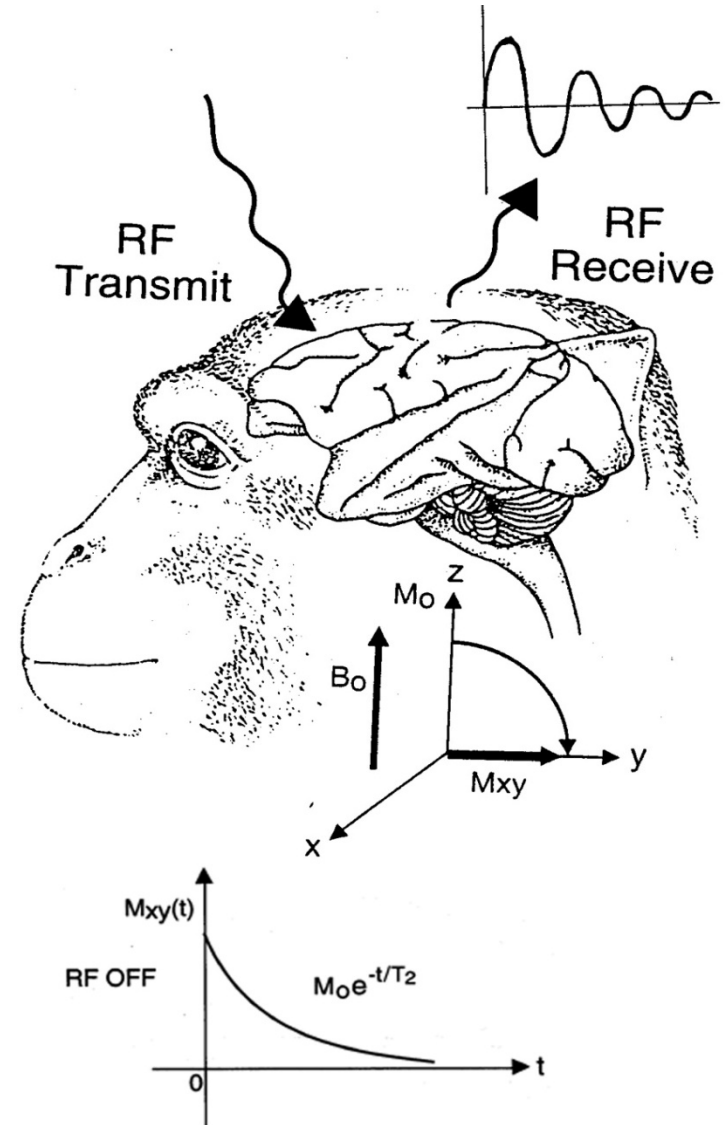
Hydrogen Protons “Wobble”

- Not only does the nucleus of the hydrogen atom spin like a top but it also precesses or “wobbles.”
- The precessional frequency is defined by the Larmor Equation $\omega = \gamma B_0$
 $\gamma = 42.6 \text{ MHz/T}$ for hydrogen
- When the field strength increases so does the precessional frequency



Flipping Hydrogen Protons To Get MR Signal

- An RF pulse with the same precessional frequency can “flip” the proton into the transverse plane
- Protons precess around the transverse plane giving off an oscillating signal
- Protons are initially in phase but rapidly dephase and signal decays in 20 to 30 msec.
- The time constant that defines the rate of decay is T_2



What can a neuroscientist learn about the brain using a magnet?

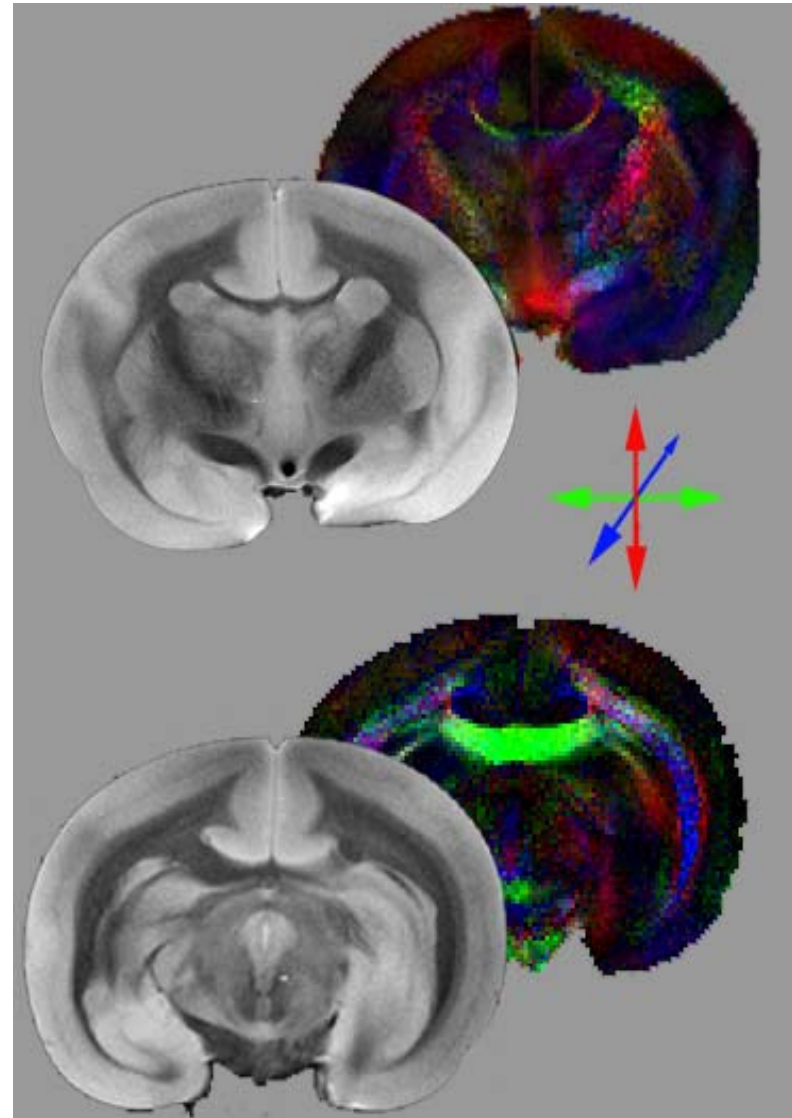
- Spectroscopy
- Quantitative Anatomy
- Tract Tracing with Manganese Chloride
- Angiography
- Diffusion Weighted Tensor Imaging
- Diffusion/Perfusion Imaging
- Function Imaging
 - CBF – cerebral blood flow
 - CBV – cerebral blood volume
 - BOLD imaging**

Diffusion Weighted Tensor Imaging

Applications

- brain myelination and development
- neurodegeneration

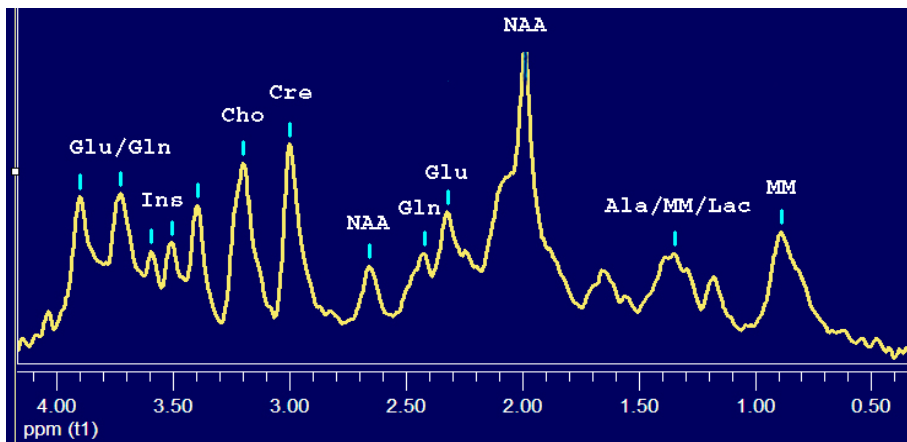
DT maps of marmoset



MR Spectroscopy Quantifying Brain Chemistry

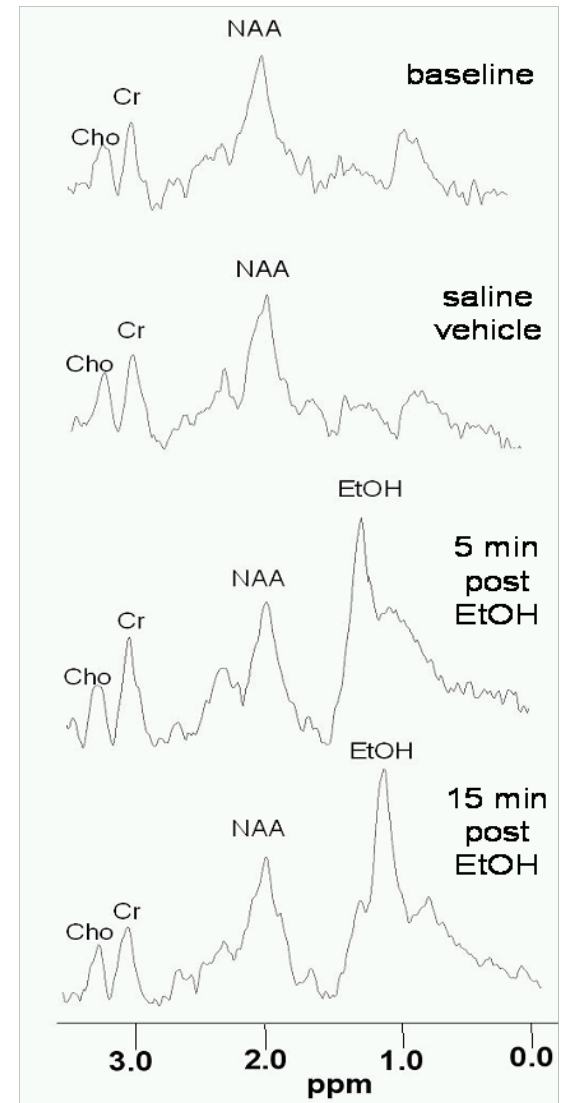
Applications

- phenotyping transgenic mice
- developmental biology
- neurotoxicology



unpublished data, CCNI 4.7T

Brain EtOH Levels



Tract Tracing with Manganese Chloride

Application

- tracing functional neural circuits

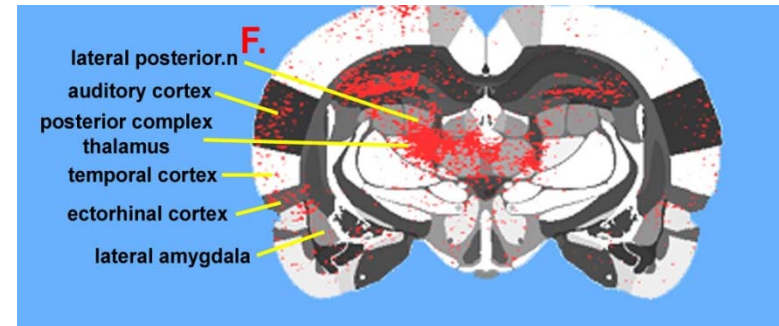
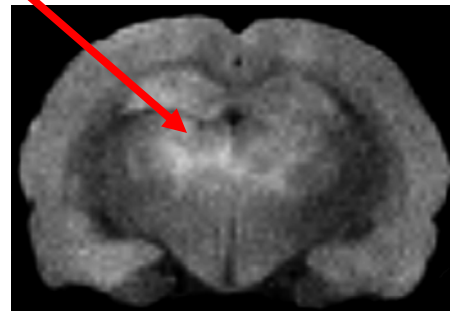
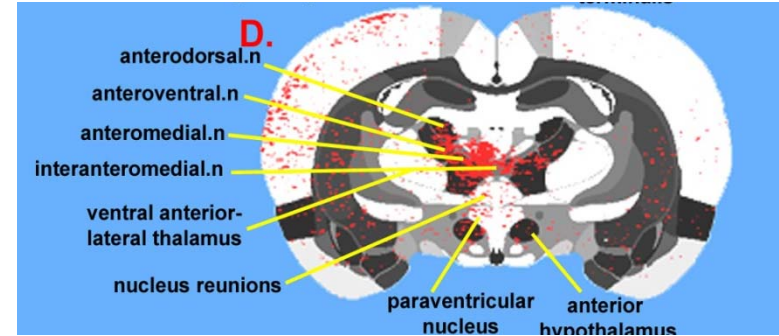
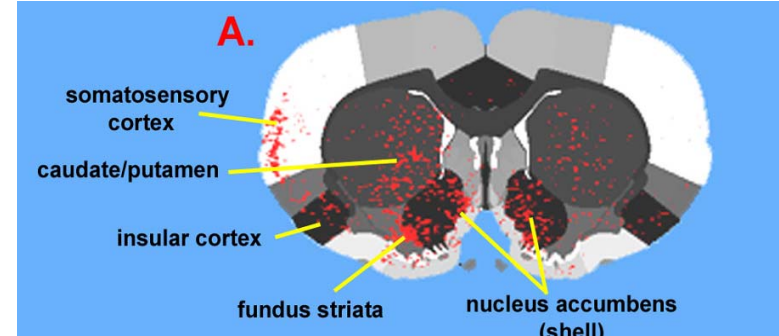
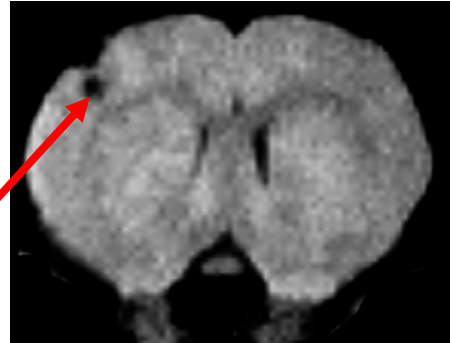
MnCl₂
injection site

Mn²⁺ accumulation
8 hr after injection

Absence Status Seizure

T1-weighted contrast

in-plane resolution 50 μm²



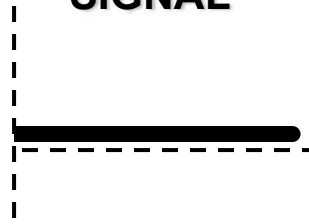
Functional Imaging Using BOLD

BOLD Signal
Blood Oxygen Level Dependent

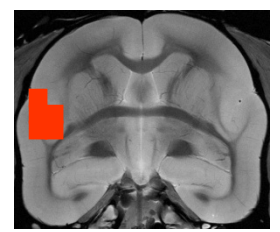
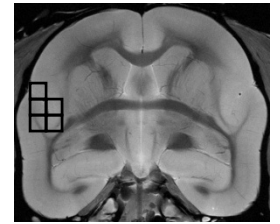
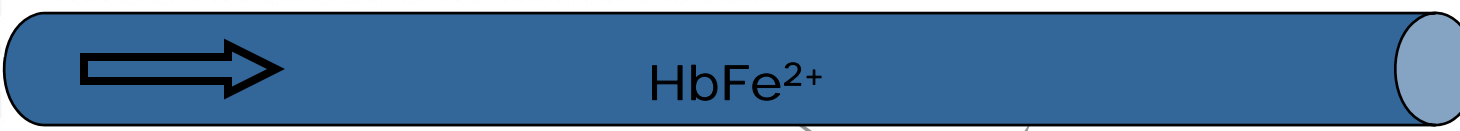
Basal condition



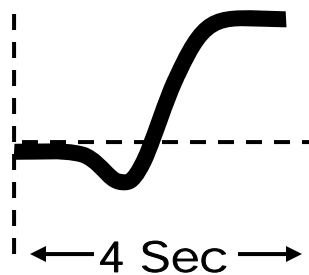
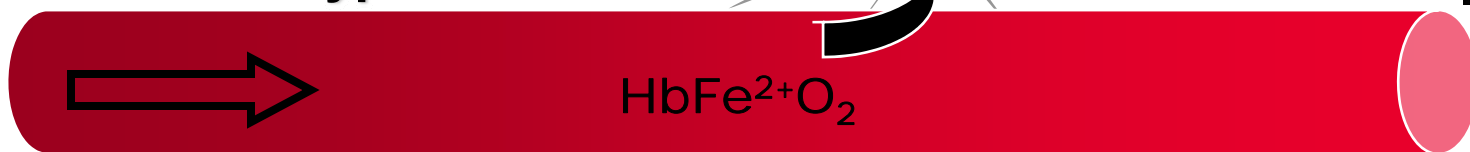
Δ BOLD SIGNAL



Initial increase in metabolism



Reactive hyperemia



BOLD Imaging and Psychiatry: A Critical Tool for Studying Brain Function

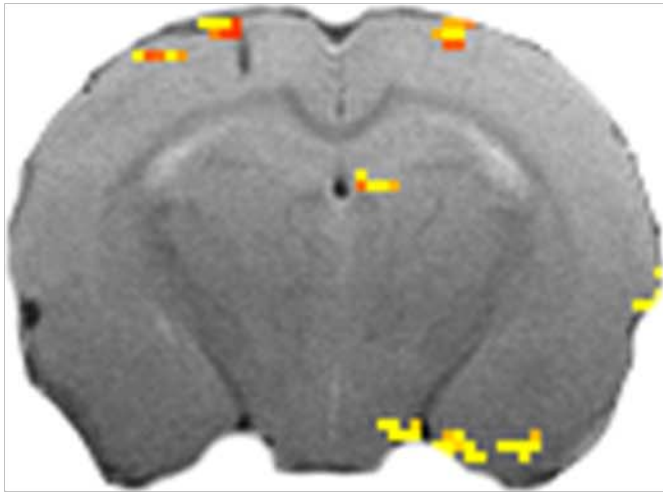
- Since Ogawa's original publication there have been close to 1,800 publications on BOLD imaging.
- Only around 300 have used animals – why?

They don't sit still.

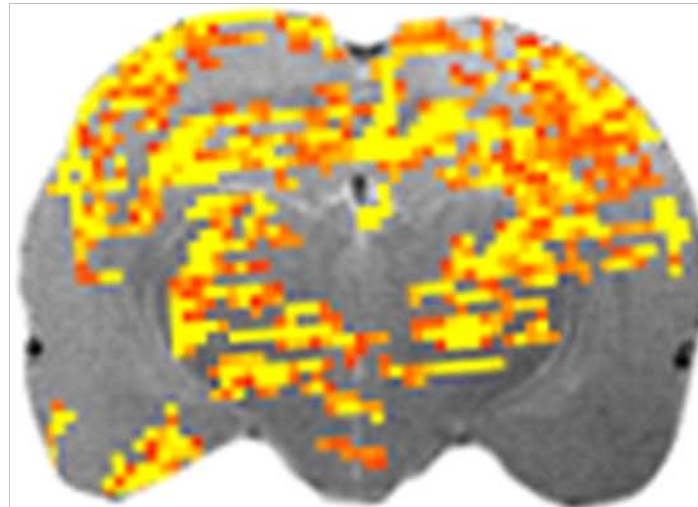
Why Conscious Animals?

- BOLD Signal is depressed with anesthesia

**Anesthetized
Absence Seizure**



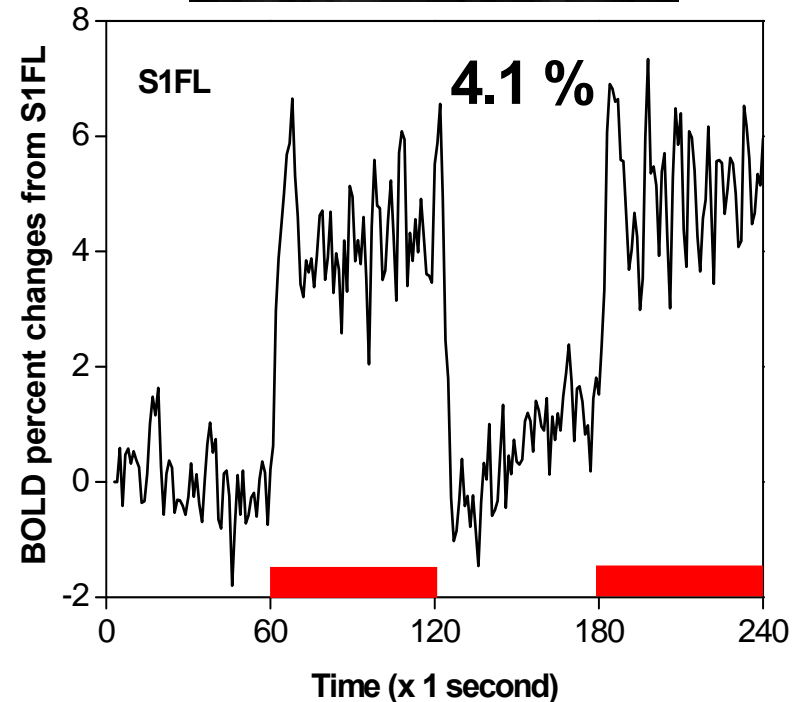
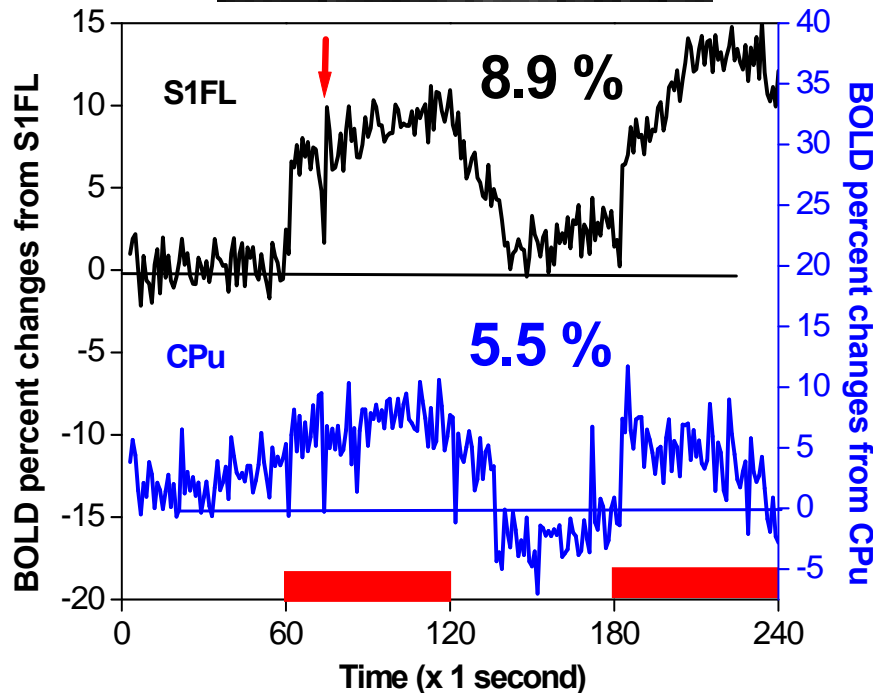
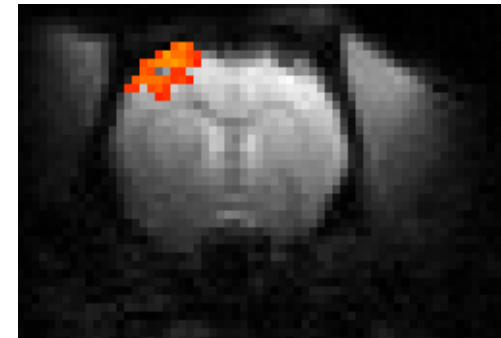
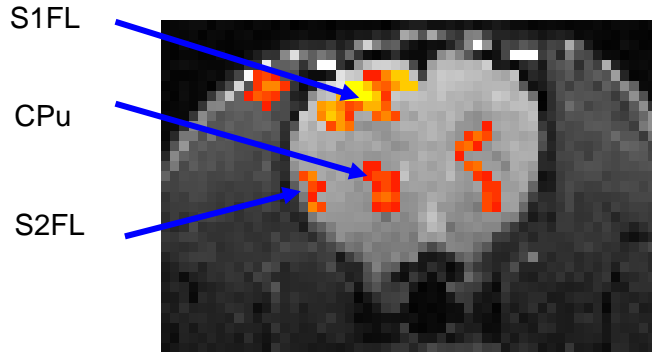
**Awake
Absence Seizure**



BOLD Signal Changes In Awake vs Anesthetized Rats

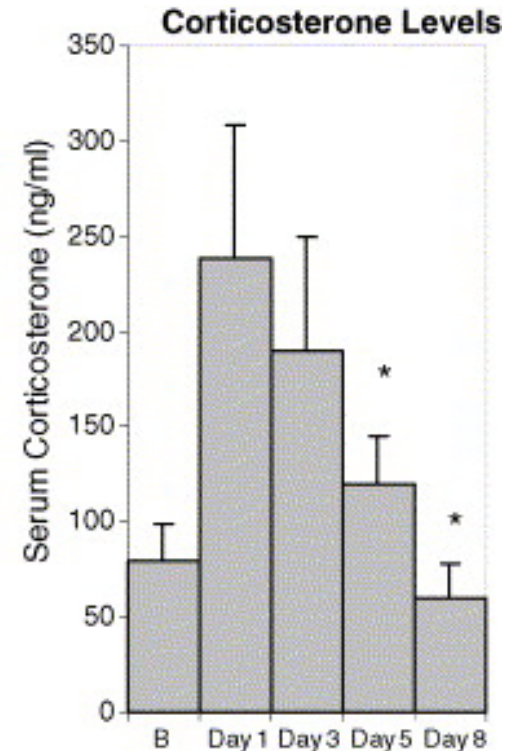
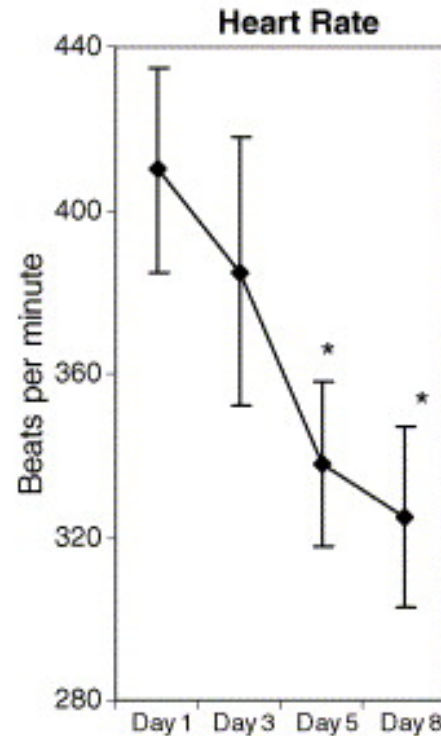
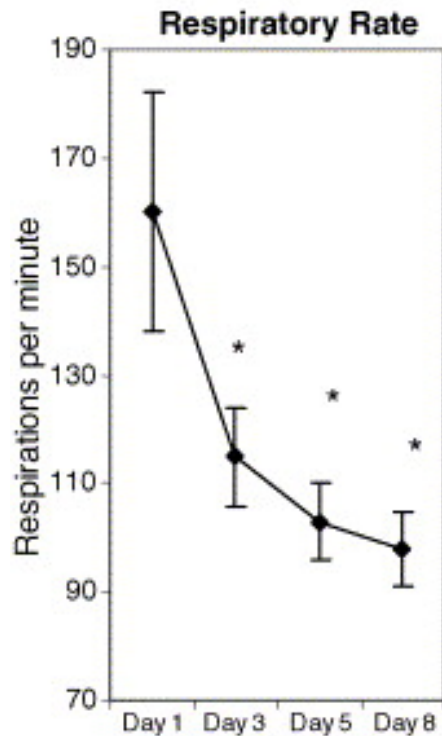
Awake

Anesthetized (α -chloralose)



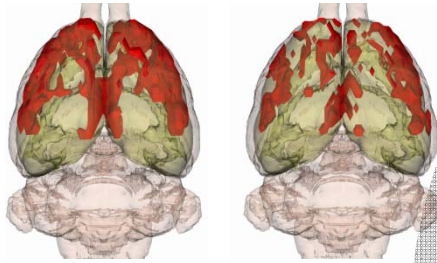
Getting Started: Acclimating Animals to the Imaging Protocol

Physiology and Stress Hormone

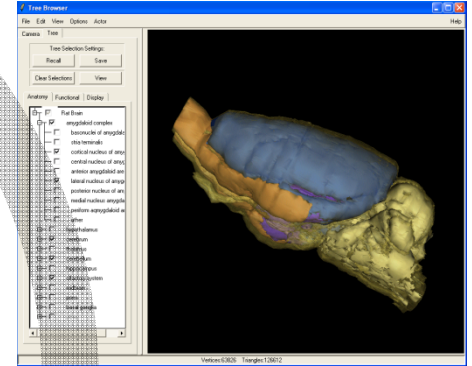


Three Dimensional Segmented Rat Atlas

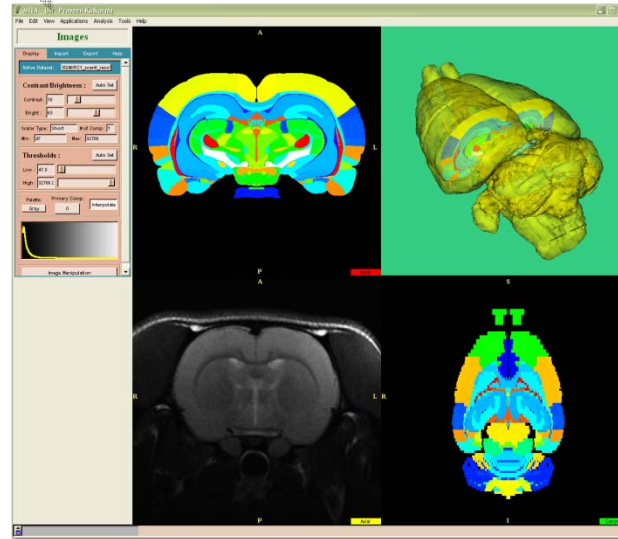
3D Visualization



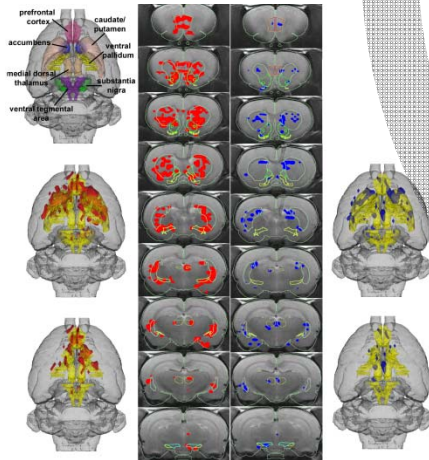
Atlas



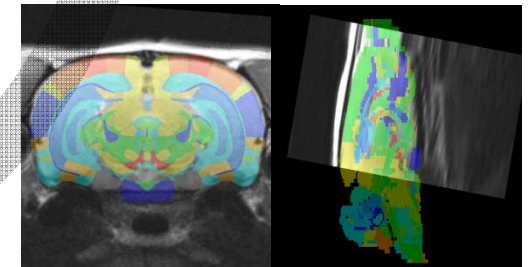
GUI



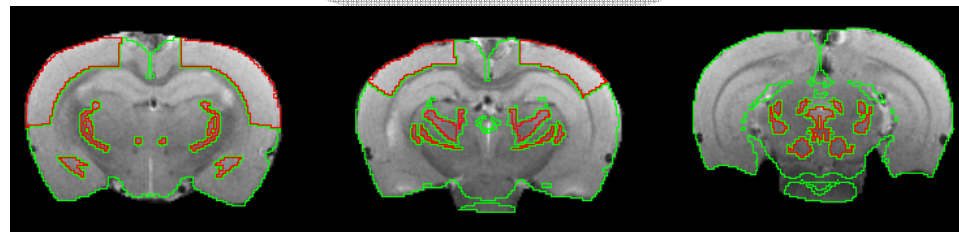
Activation Maps



Registration
"Group Statistics"



Segmentation



Stimulation Paradigms

“How do you talk to an animal in a magnet?”

- **Odors**
- **Visual Images**
- **Tactile Stimulation**
- **Drug Challenges**
- **Complex Environmental Cues**

“vivarium”

Applications In Neuroscience

- Imaging emotional states, e.g. sexual arousal, hunger, fear, etc.
- Developmental studies on neurological disorders, e.g. stroke, seizure, dementia, etc.
- Drugs and brain function, e.g. cocaine, MDMA, anxiolytics, neuroleptics, etc.
- Learning and memory

PRESENT AREAS OF RESEARCH

- **Maternal Behavior**
- **Stress**
- **Drugs of Abuse**
 - **MDMA “ecstasy”**
 - **Cocaine**
 - **Nicotine**
- **Aggression**
- **Fear and Anxiety**
- **Drug Discovery**

MOTHER/INFANT BONDING

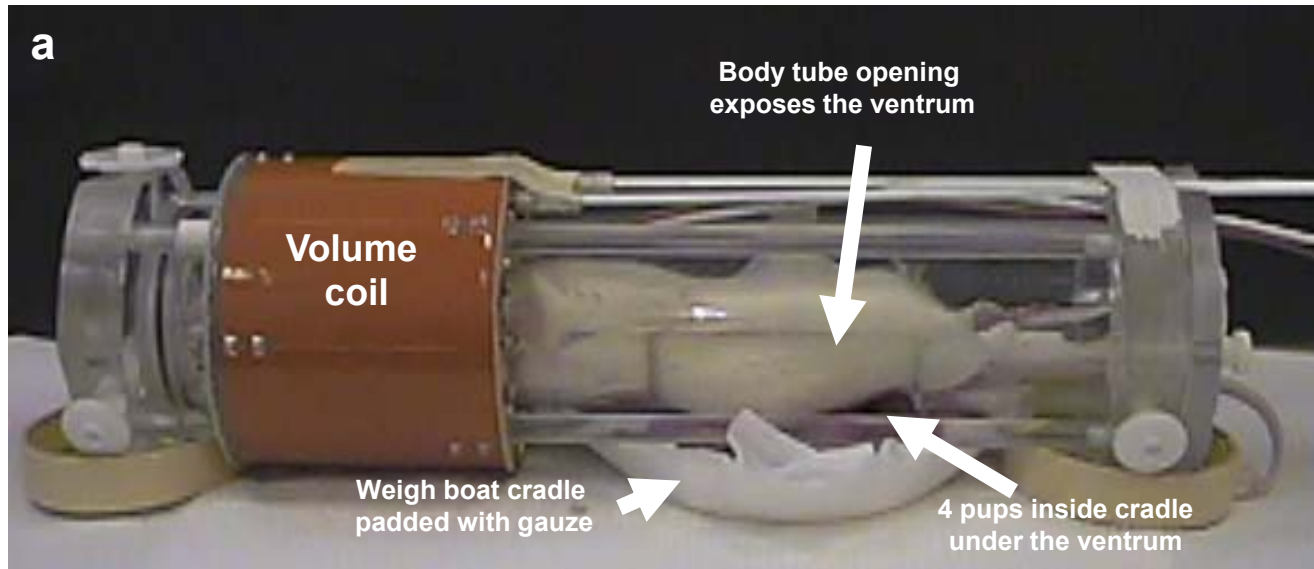


Courtesy of Steve Suomi

Early maternal care is critical for the psychosocial development of infants.

With the evolution of mammals, nursing has helped strengthen the mother/infant bond and extend the period of parental investment in young.

Can We Image the Nursing Brain?



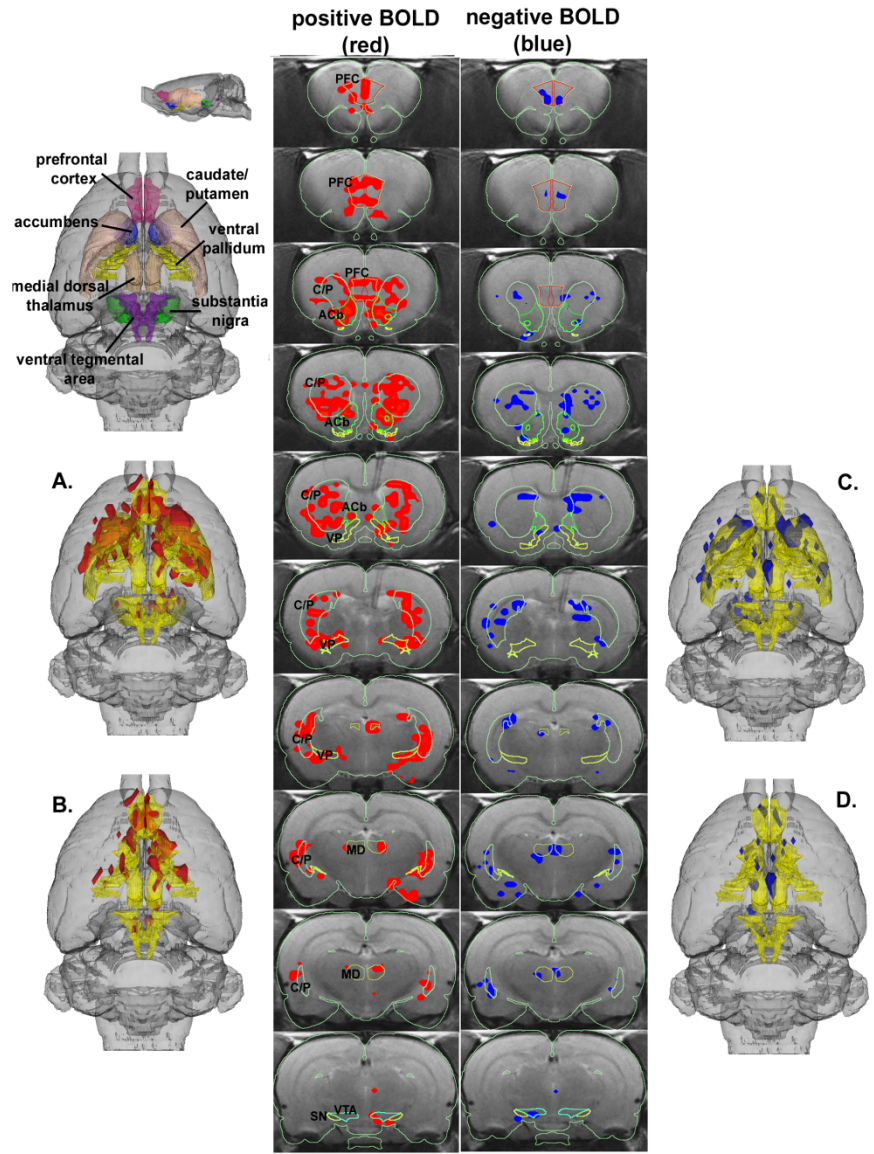
Yes ...

Interestingly, the Brain Activity Suggests Suckling is a Rewarding Experience

- Mesocorticolimbic dopaminergic pathways are activated.
- Previous studies show suckling has many of the properties of addictive drugs. Suckling motivates bar pressing for pups and conditioned place preference.

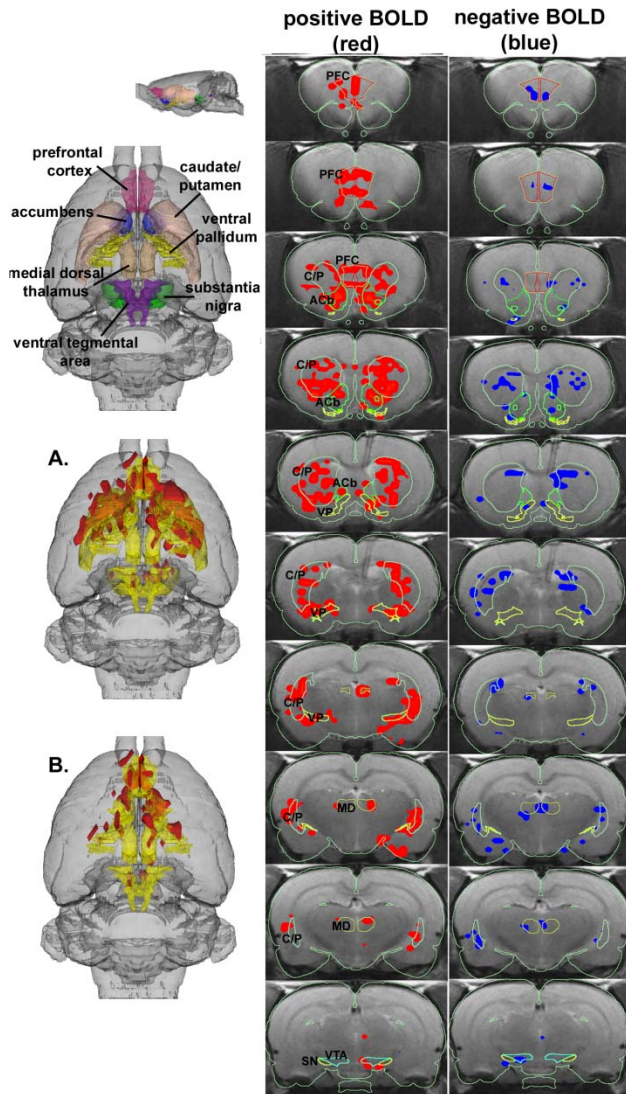
(Fleming, Spear, and Morrell labs)

Pup Stimulation in Lactating Dams

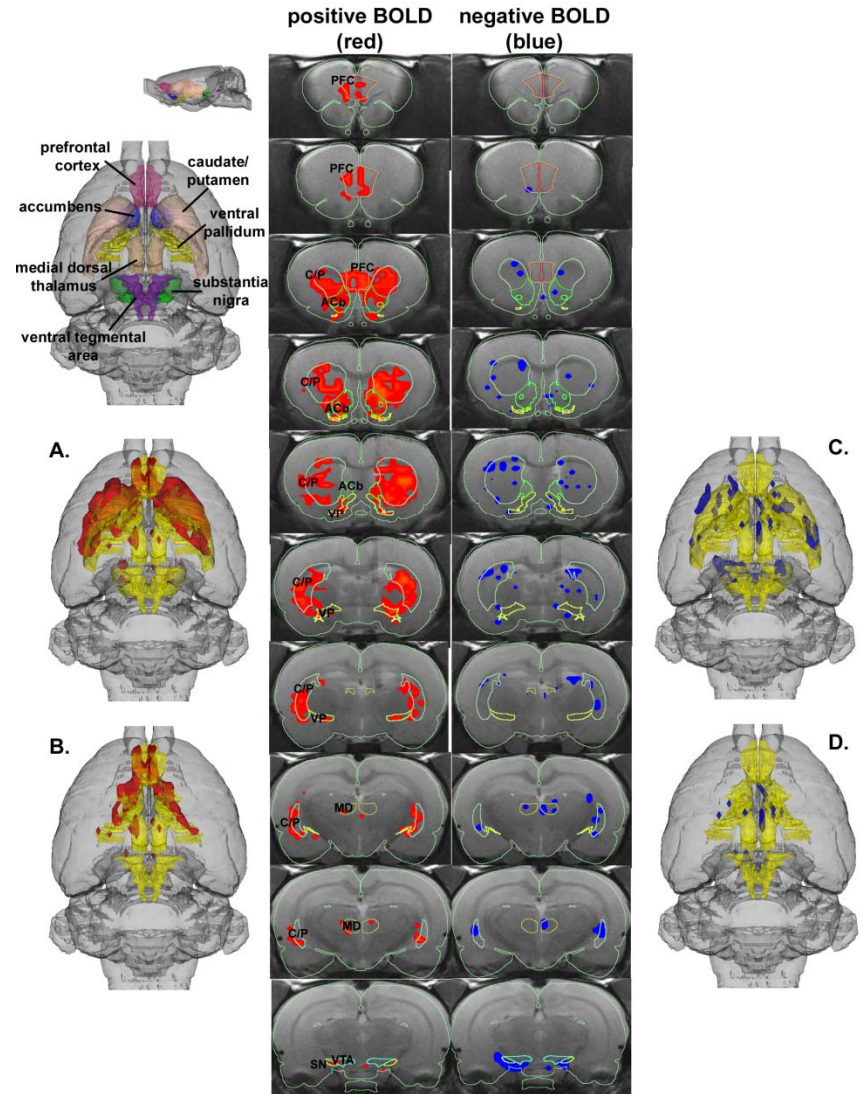


Is motherhood more rewarding than cocaine?

Pup Stimulation in Lactating Dams

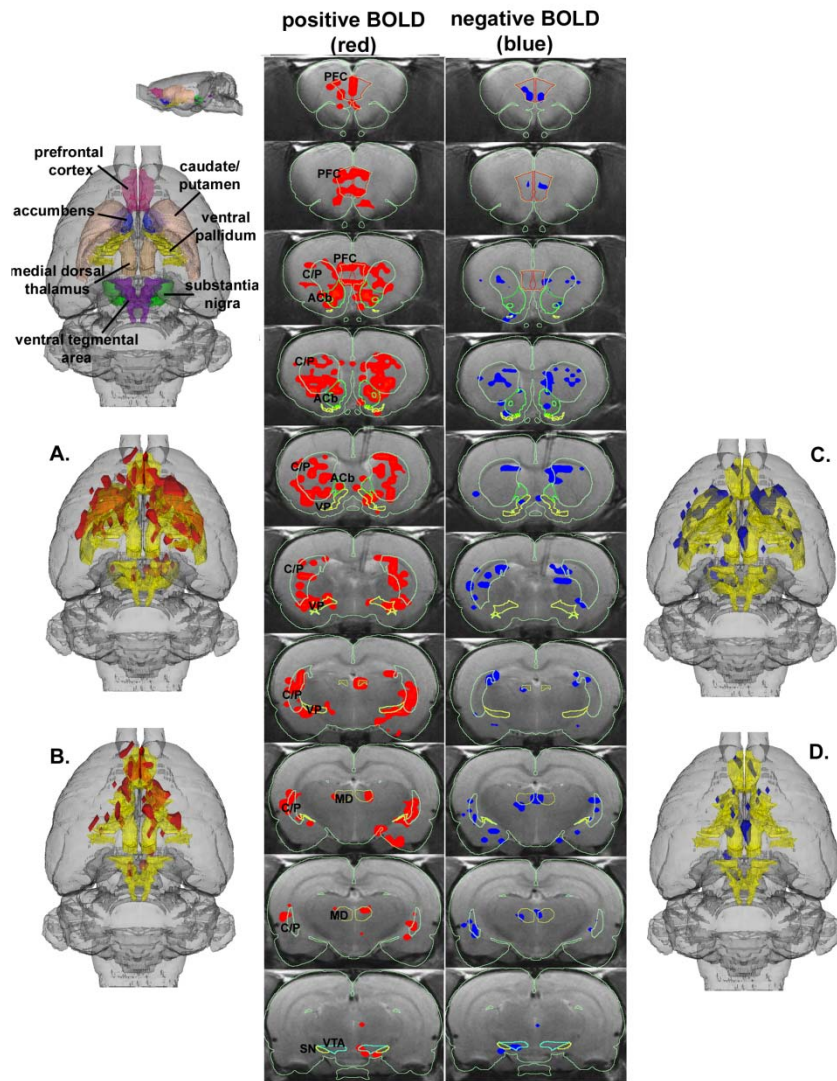


Cocaine Stimulation in Virgin Female

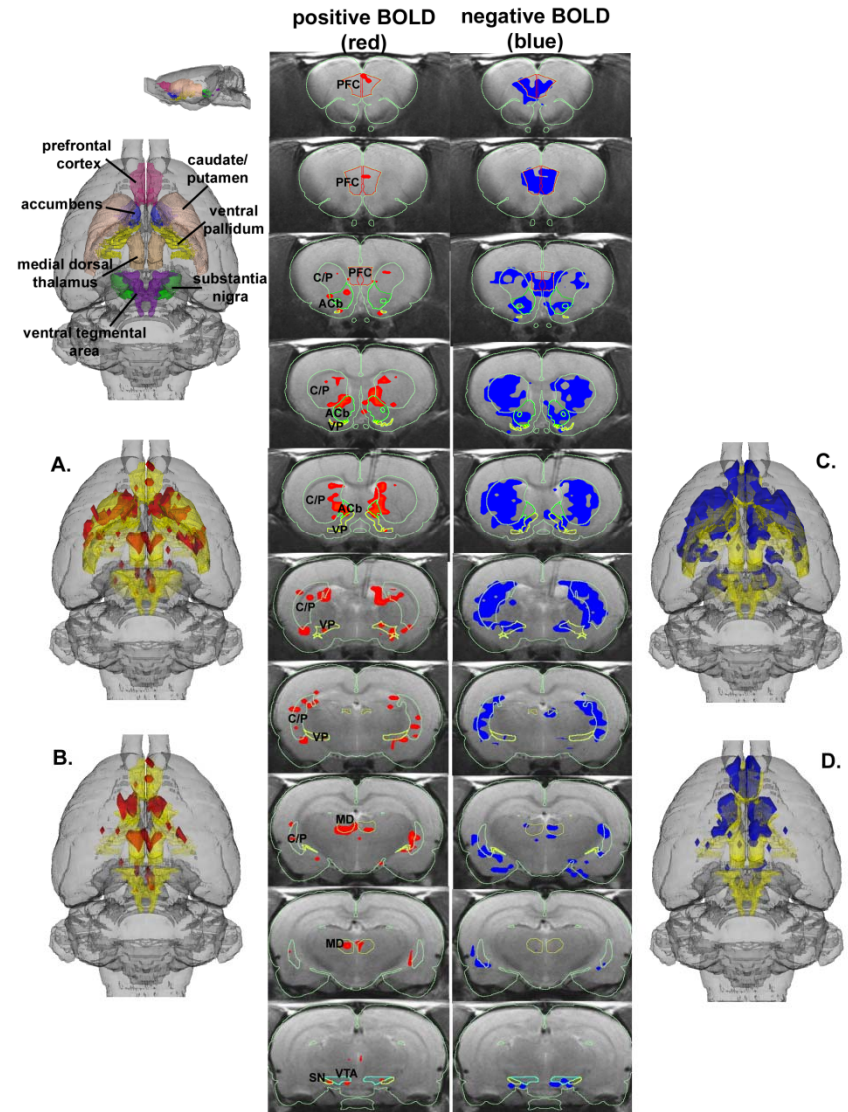


... it would seem so.

Pup Stimulation in Lactating Dams



Cocaine Stimulation in Lactating Dams



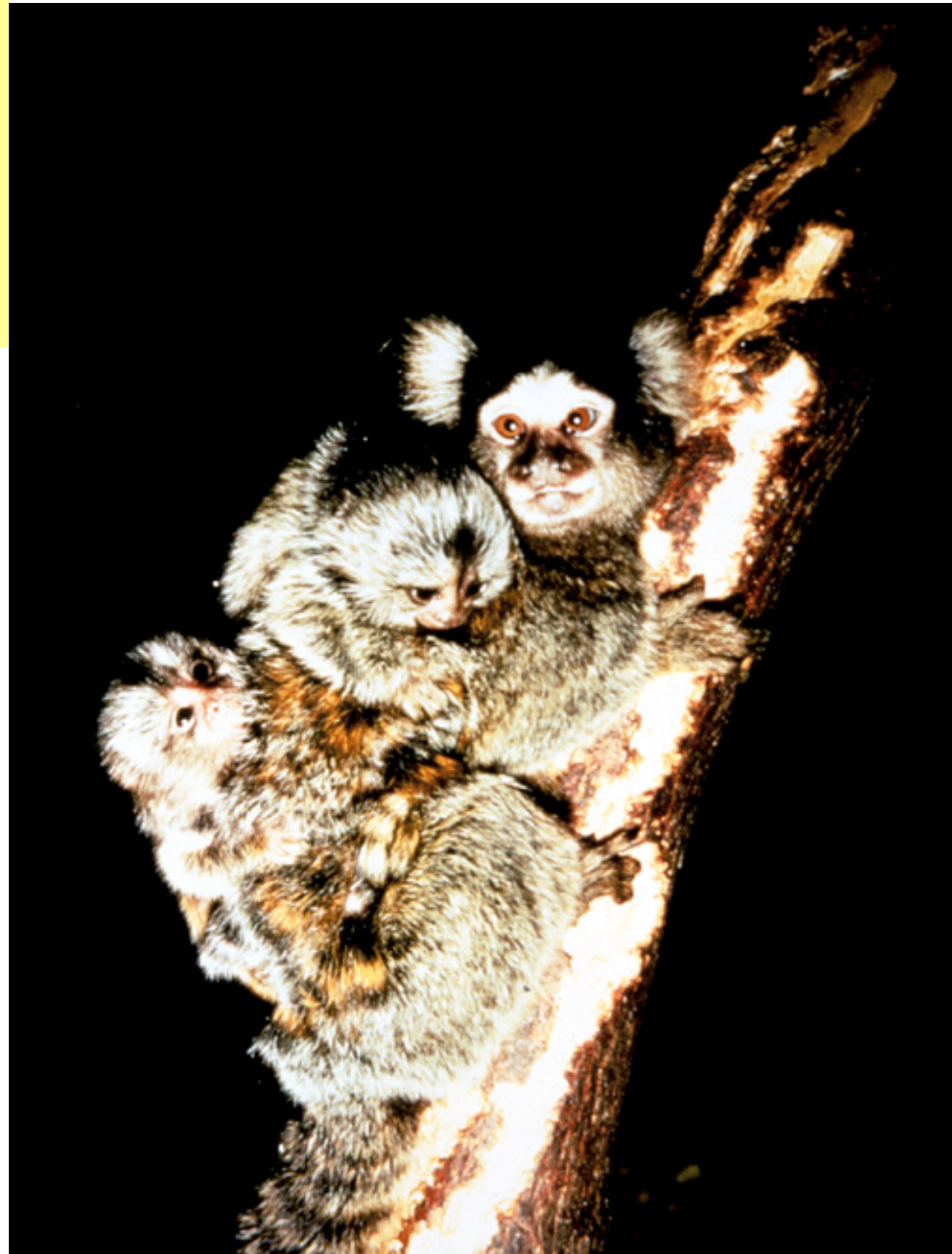
MARMOSET FAMILIES

“MOM, DAD, & THE KIDS”

- **MONOGAMOUS**
- **TWINS**
- **AFFILIATION**
- **DEVELOPMENT**
- **SMALL SIZE**

Primatologists and collaborators:

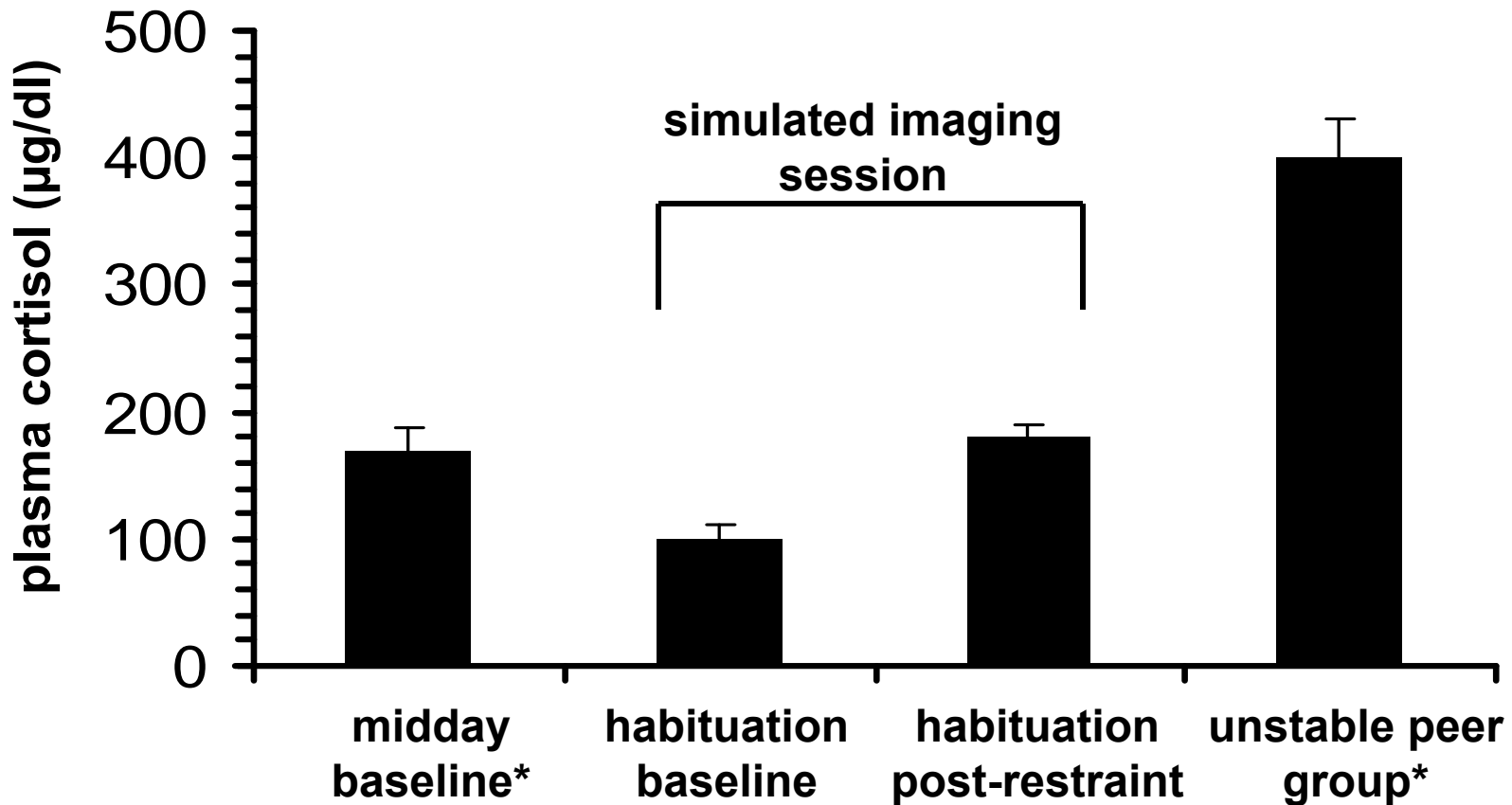
- Charles Snowdon
- Toni Zeigler
- Nancy Shultz-Darken
- Melinda Novak



Courtesy of Nancy Shultz-Darken

Habituating Marmosets to the Stress of Restraint and Imaging

Stress-Induced Changes in Plasma Cortisol



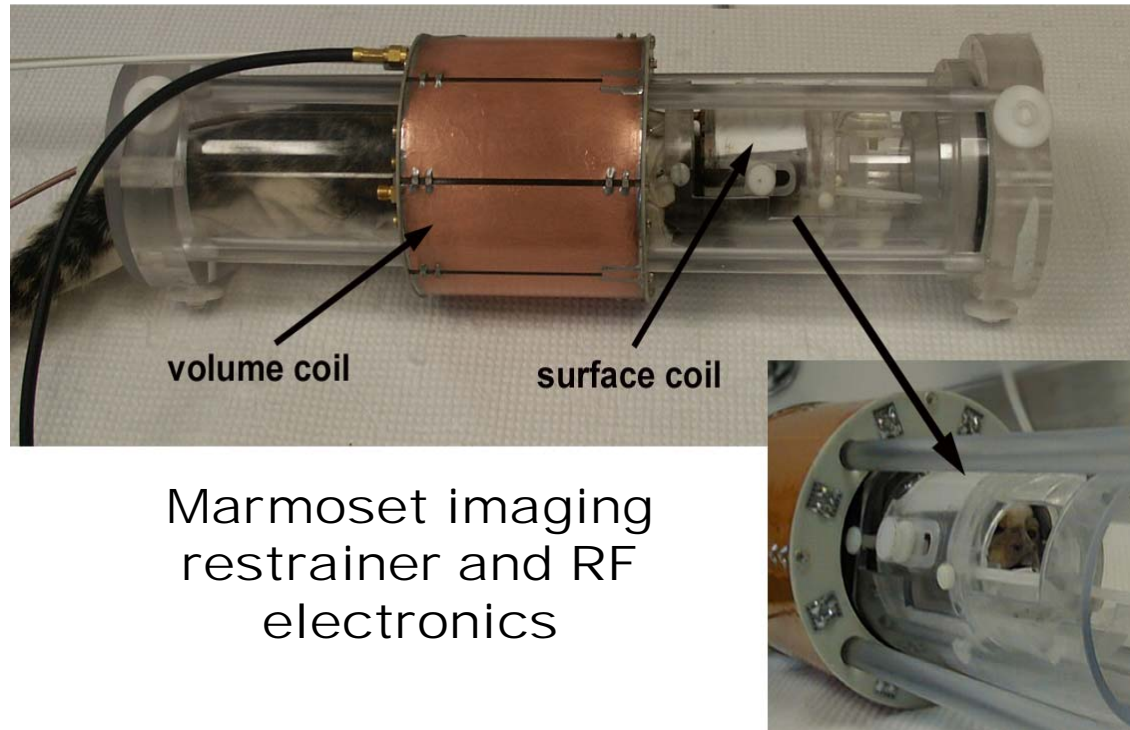
*Wisconsin Marmoset Colony

Choice of Anesthetic

- **sodium pentobarbital**
- **chloral hydrate**
- **propofol**
- **isoflurane**
- **medetomidine/atipamezole**
(Domitor/Antiseden)

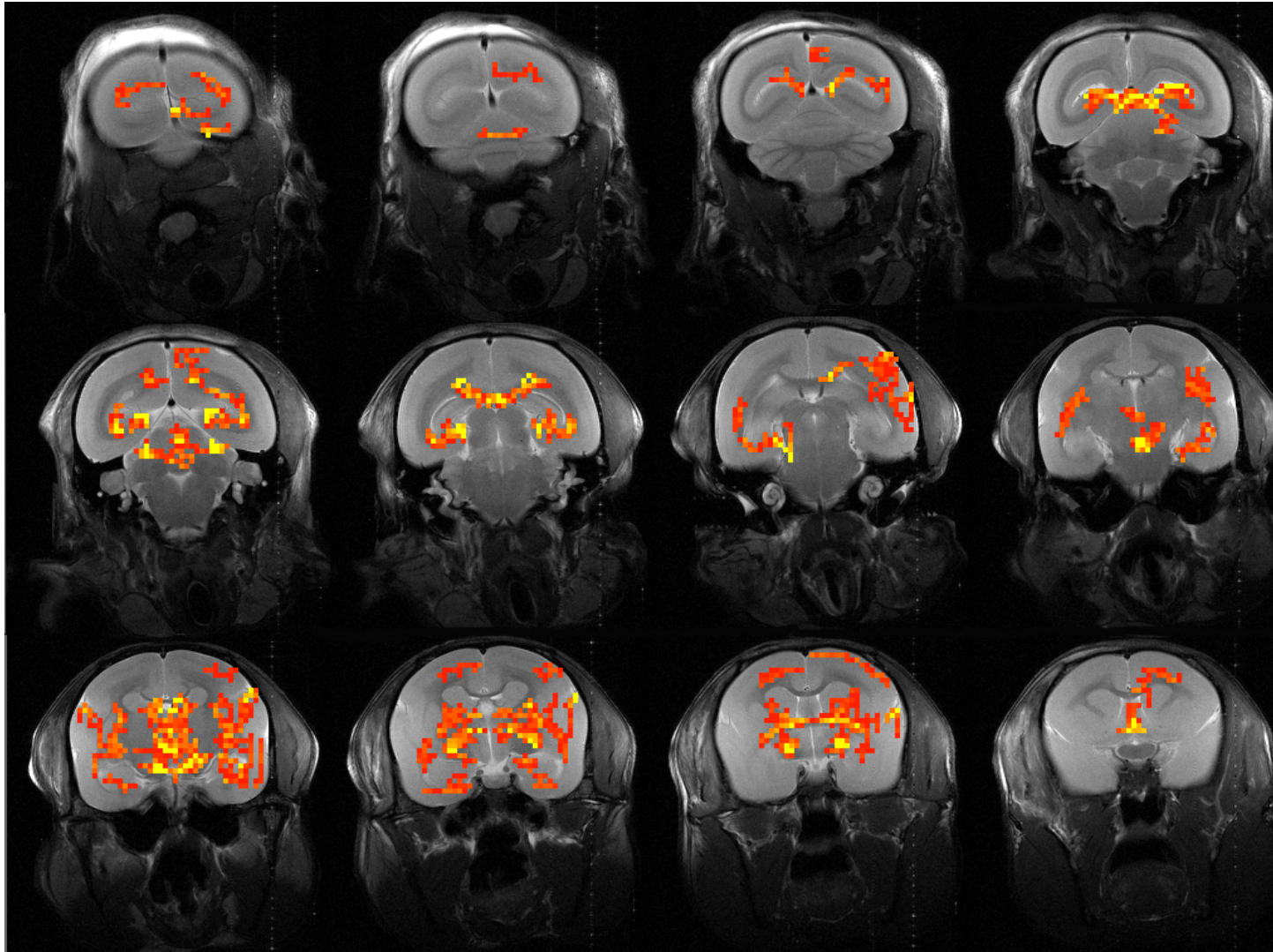


Brain Activity and Recreational MDMA “Ecstasy”

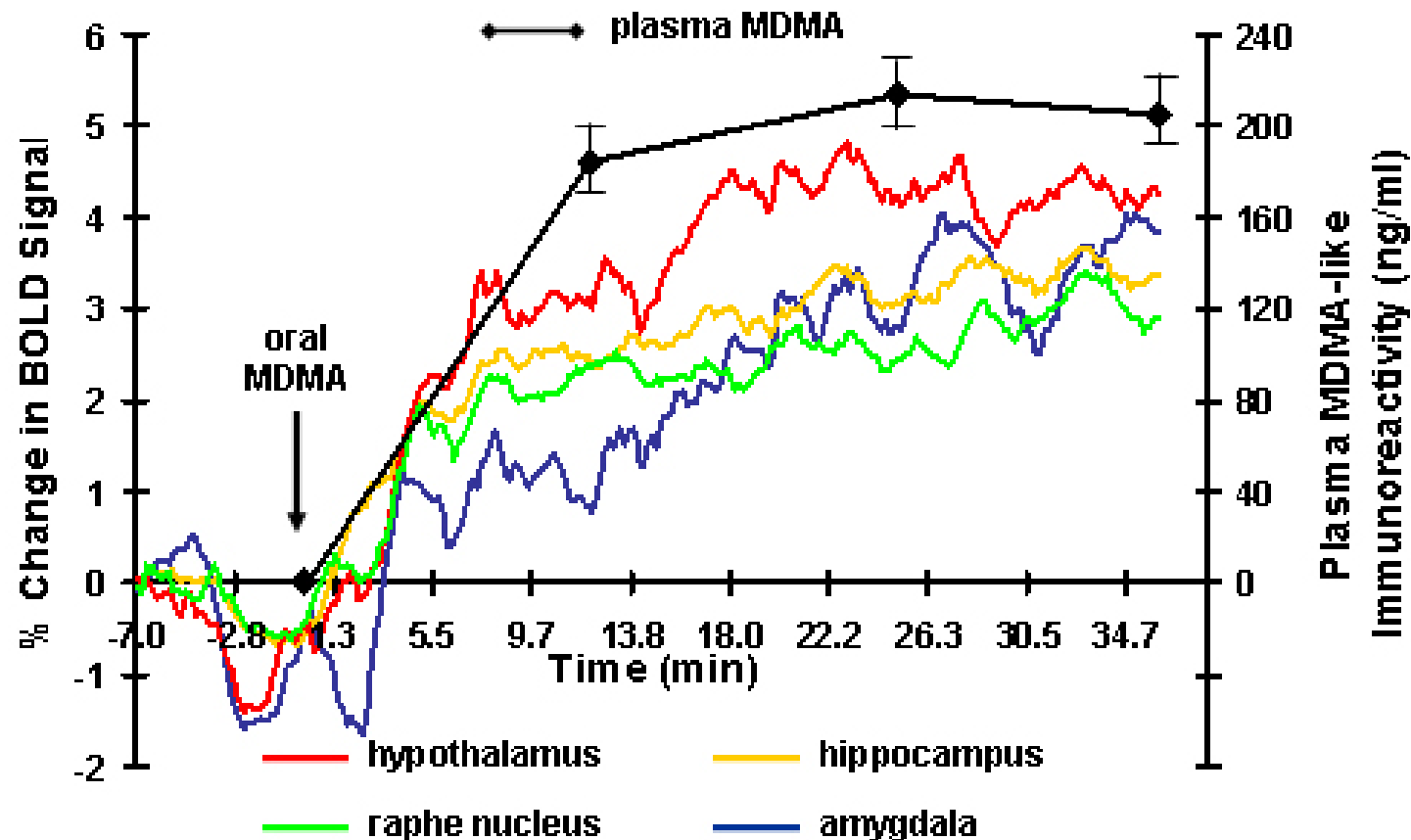


To date, no one has done fMRI studies on humans or monkeys to observe changes in brain activity following oral MDMA.

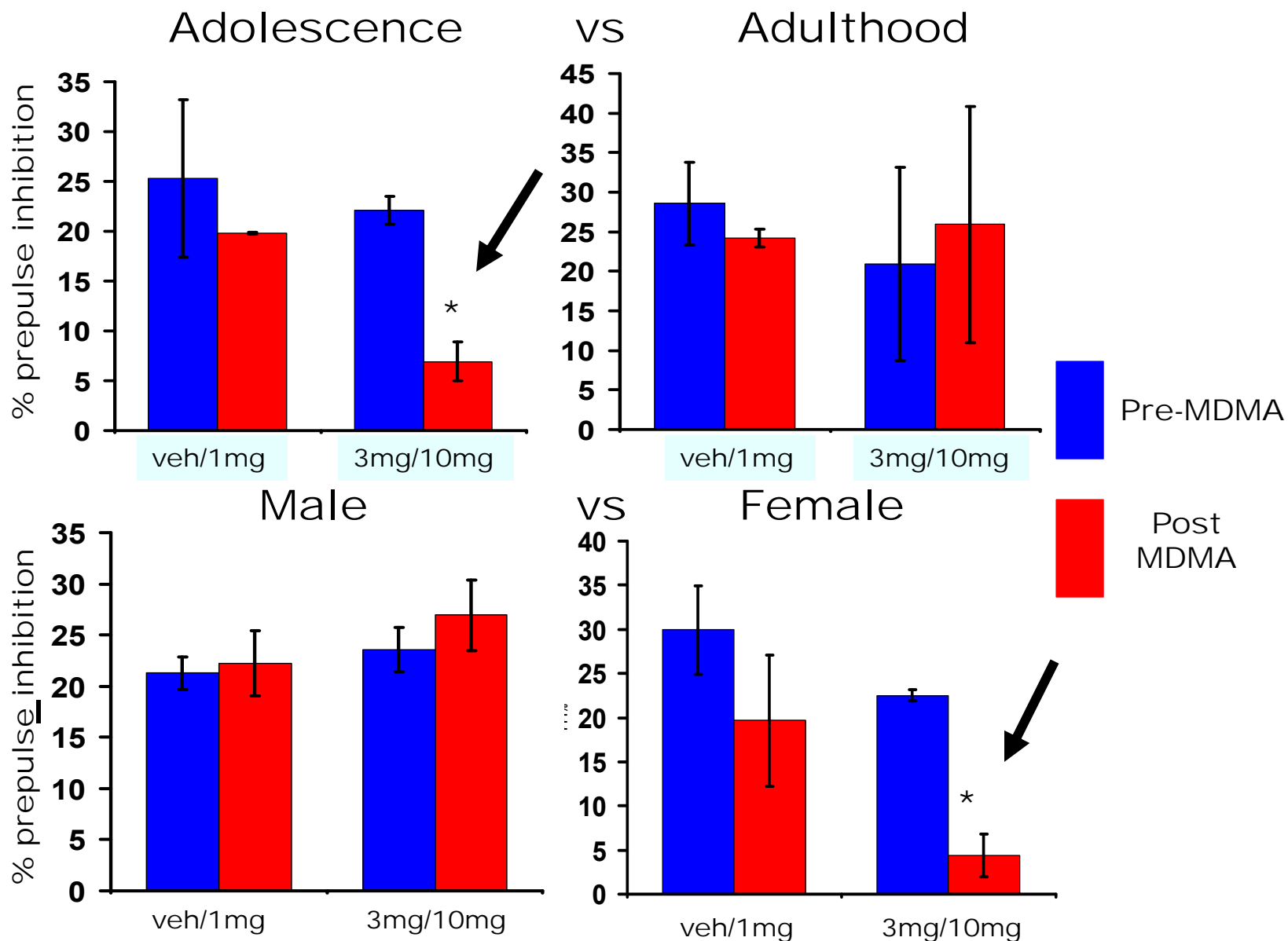
Brain Activation Following Oral MDMA (1mg/kg)



Activation of Limbic Circuitry Following Oral MDMA



Adolescent females are most vulnerable to the MDMA



A Special Thanks to...

Tara Messenger

Praveen Kulkarni

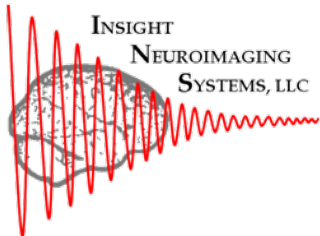
Marcelo Febo

Josie Harder

Mathew Brevard

SUPPORT

National Institute of Mental Health
National Institute on Drug Abuse
&
Insight Neuroimaging Systems (INSL)* Booth #1610
&
Azevan Pharmaceuticals**



*Disclosure: Craig Ferris has a financial interest in INSL, the bioengineering company that produces the RF electronics and holders for animal imaging.



**Disclosure: Craig Ferris has a financial interest in Azevan, the pharmaceutical company developing drugs for the treatment of psychiatric disorders.

Animal Imaging Has Its Limits



Thank You