# Addiction Therapy-2014

**Chicago, USA**

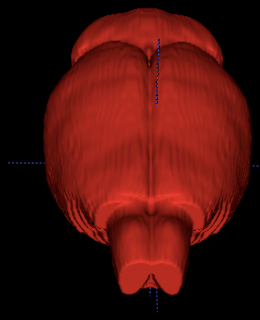
**August 4 - 6, 2014**



**Marcelo Febo**

UF | UNIVERSITY of FLORIDA

# Brain Reward Functional Connectivity During Resting State in Animal Models




Marcelo Febo, Ph.D.

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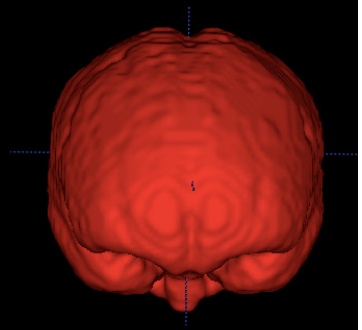
Translational Research Imaging Laboratory

McKnight Brain Institute, University of Florida, Gainesville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## Cocaine

| | Health Care | Overall |
|---|---|---|
| Tobacco | $96 billion | $193 billion |
| Alcohol | $30 billion | $235 billion |
| Illicit Drugs | $11 billion | $193 billion |

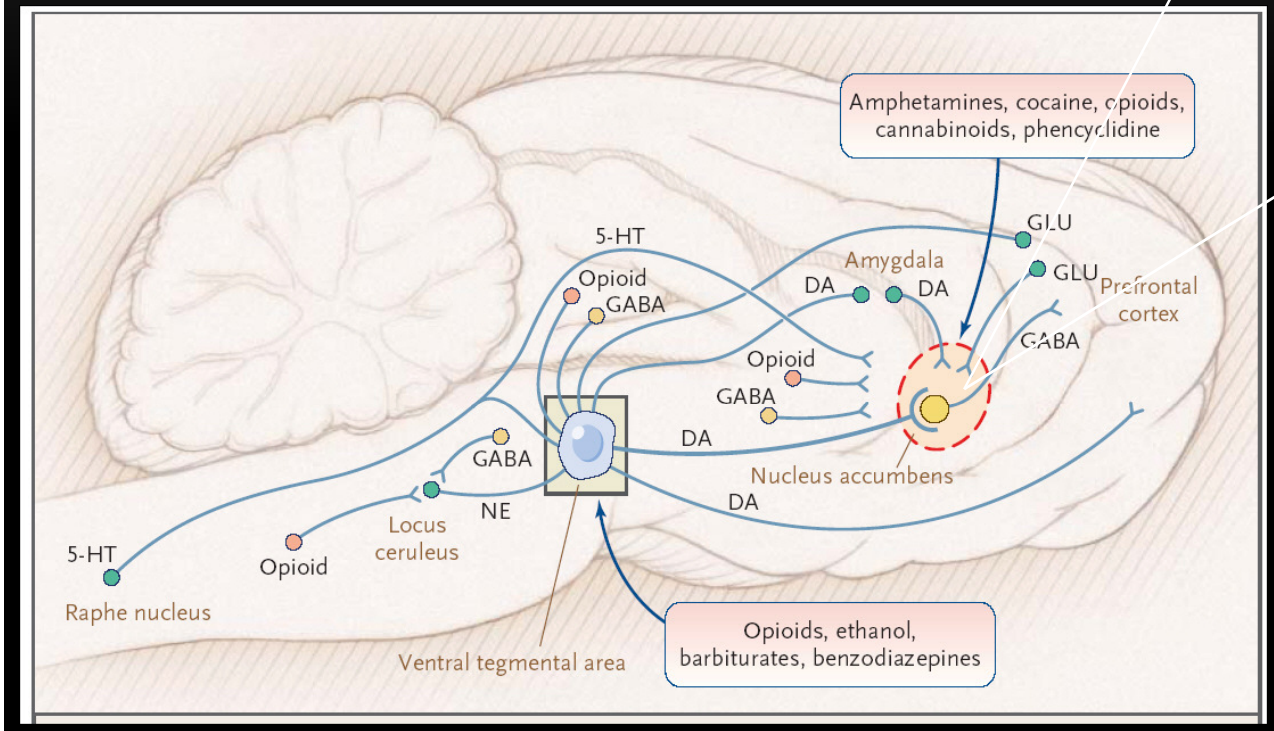
drugabuse.gov

## Nicotine

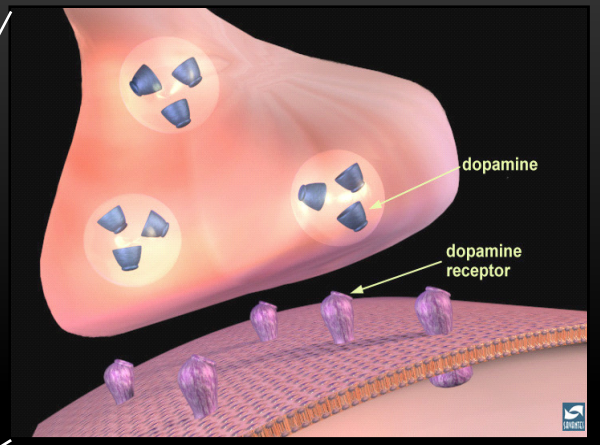
## Bath Salts

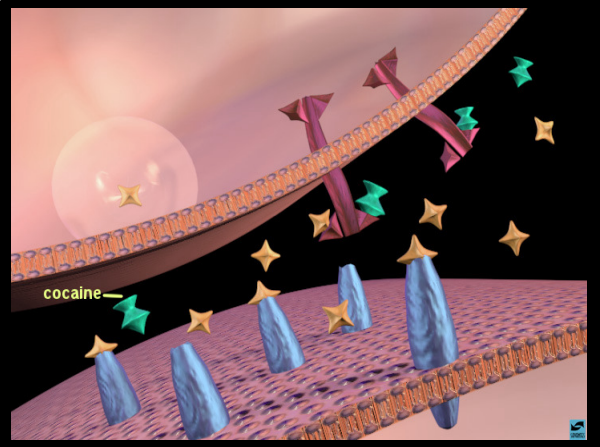
# Neural circuitry affected by drugs of abuse

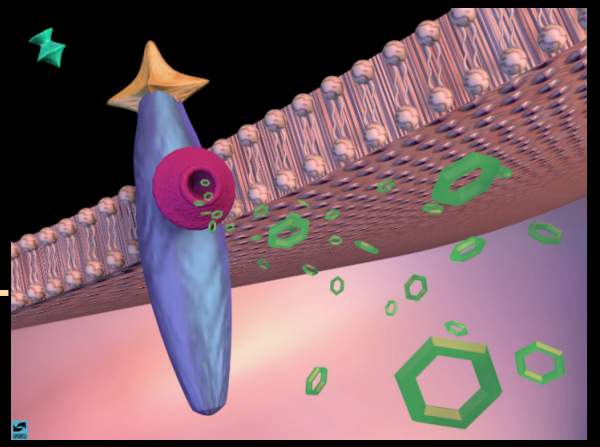
**Capturing signatures of *in vivo* functional changes**




Camí and Farré (2003) *New England J Medicine* 349: 975.



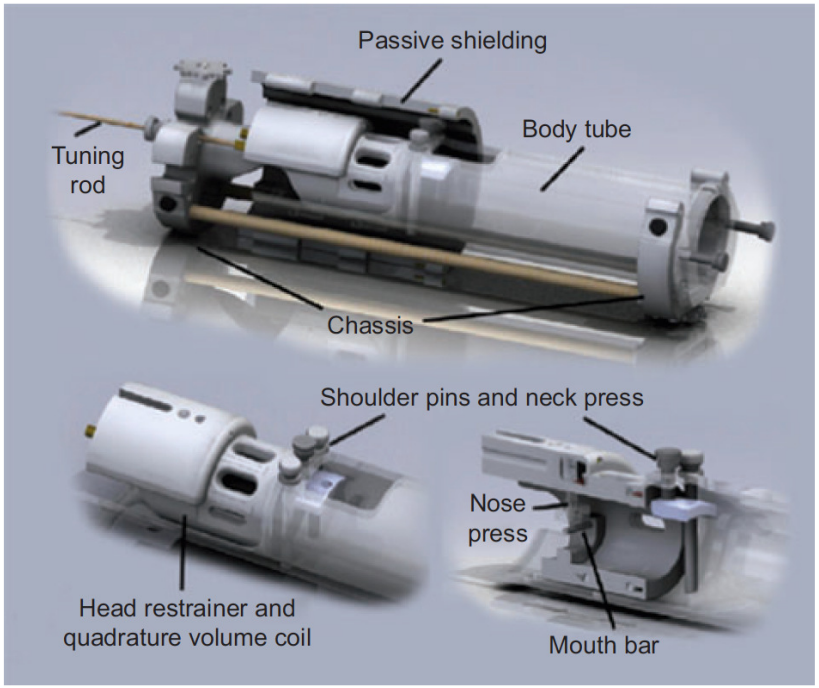



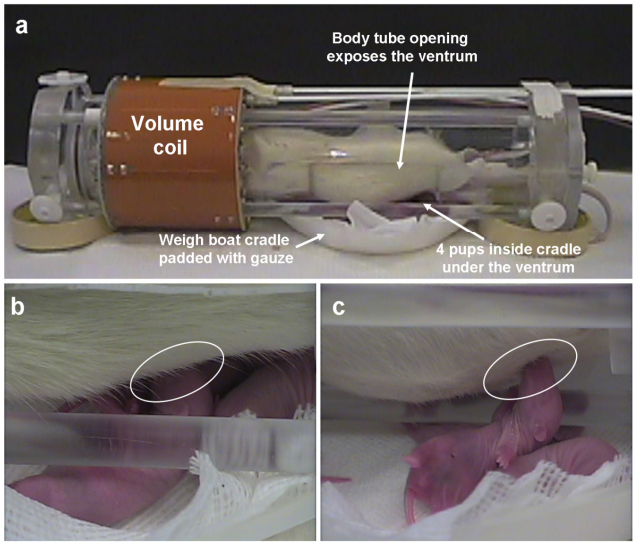



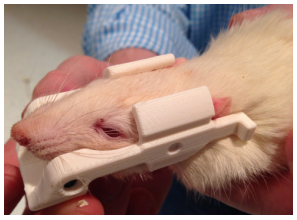
NIDA, drugabuse.gov web

# Functional magnetic resonance imaging in awake animals

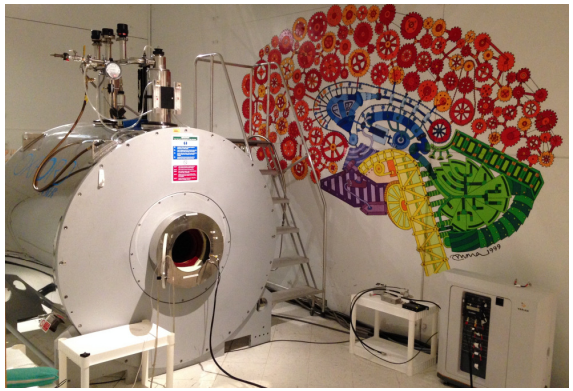
Craig F. Ferris[1,*], Brain Smerkers[2],
Praveen Kulkarni[1], Martha Caffrey[1], Onur Afacan[1],
Steven Toddes[3], Tara Stolberg[1] and Marcelo Febo[4]

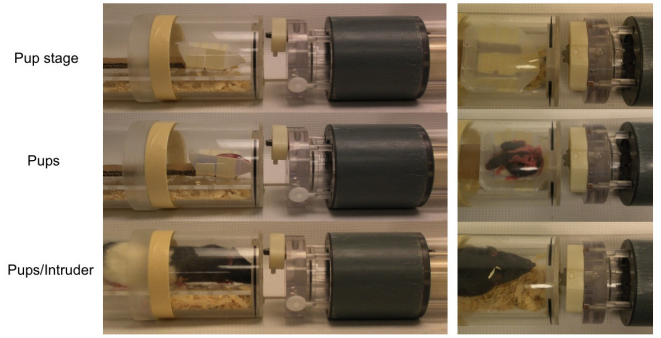


Animal Imaging Research, LLC

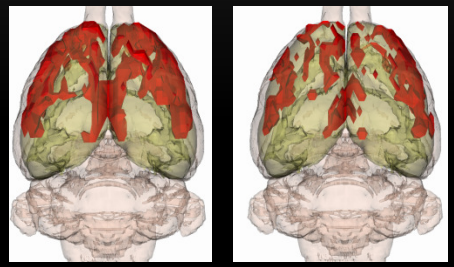




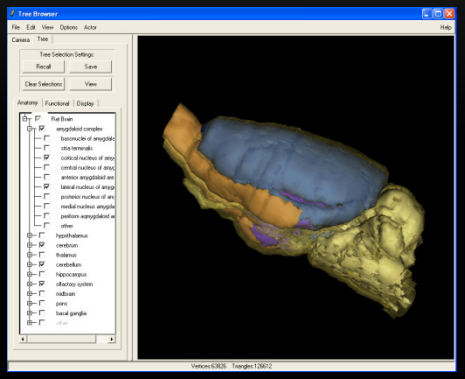
# MIVA

## Medical Image Visualization and Analysis

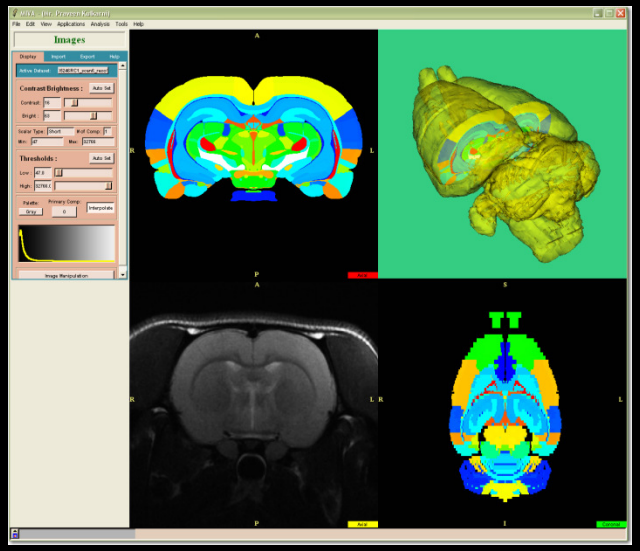
### Visualization



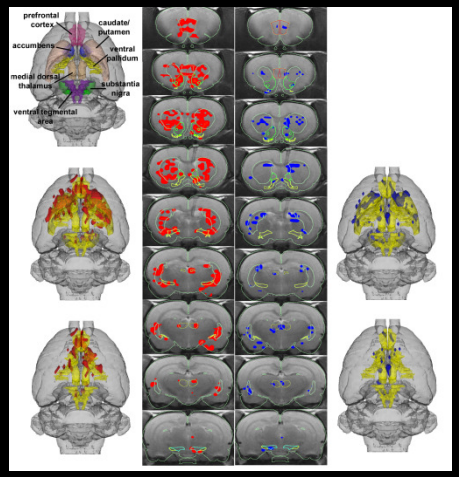
### Atlas



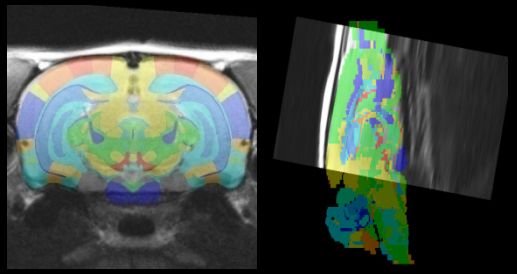
### GUI



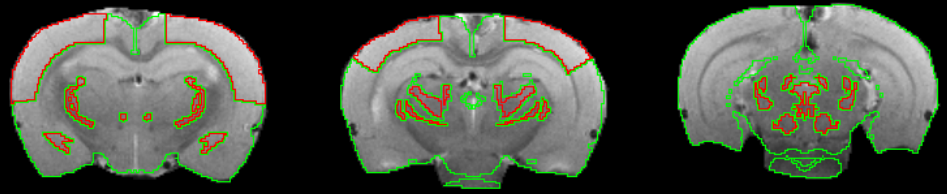
### Statistical Maps

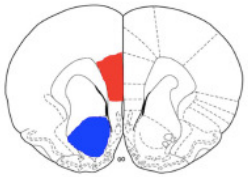


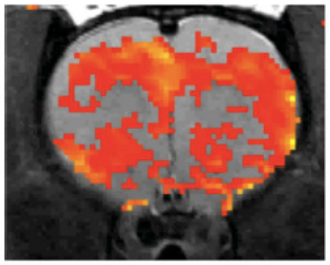

### Registration

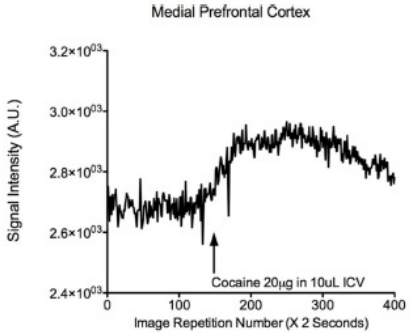


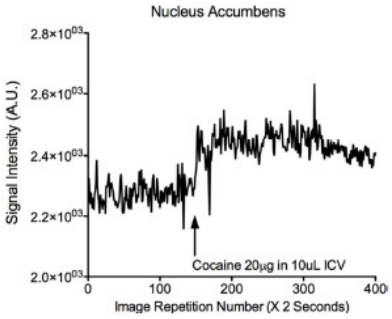
### Segmentation

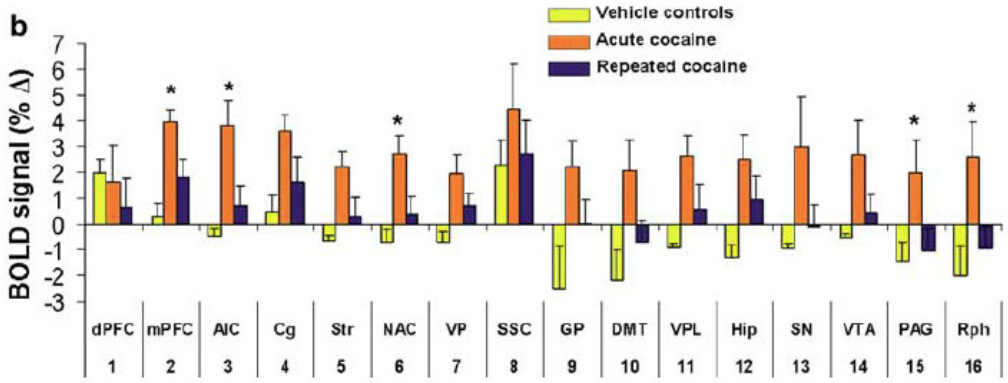




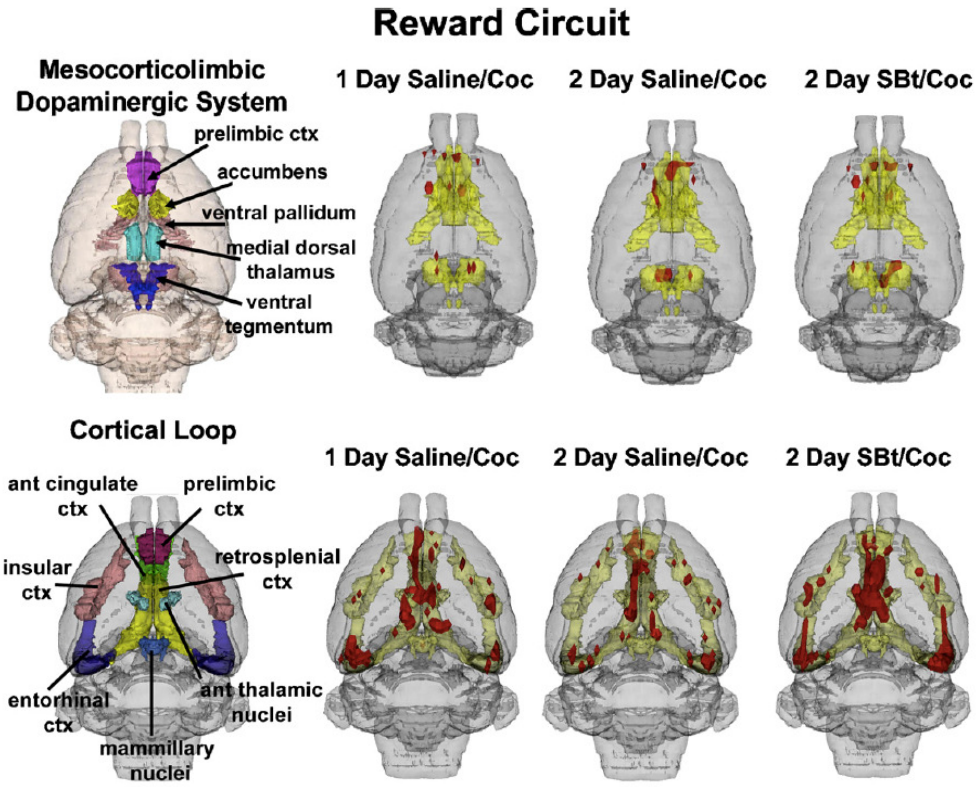





M. Febo et al. / Neuroscience Letters 465 (2009) 267–271

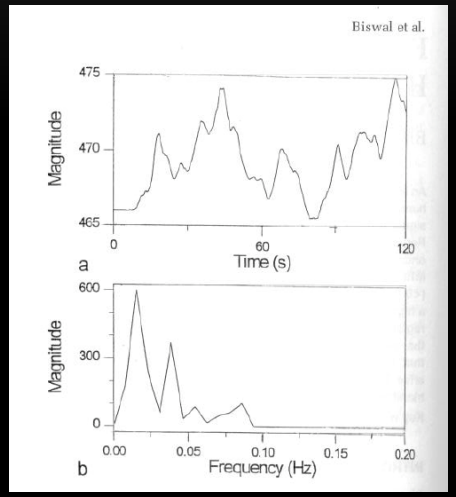


# INVESTIGATING NEURAL CIRCUITRY LEVEL CHANGES FOLLOWING CHRONIC DRUG ABUSE WHICH CONTRIBUTE TO ADDICTION

- Addiction and drug abuse severity might occur as a result of network level changes in the brain and not restricted to one or a few brain regions. The coordinated physiological interactions across multiple sites is perhaps decoupled or skewed from normalcy.
  - A systems level approach needs to complement reductionist approaches.
- Investigate the neural circuitry directly activated/deactivated by drugs of abuse, drug associative sensory cues, and changes in function and structure following chronic administration.
- A growing number of MRI experiments are now examining synchronous changes in BOLD across multiple brain regions. The brain during rest appears to continuously oscillate at a very low frequency (below 0.1Hz).
- Cocaine, heroin, alcohol had all been shown to be associated with a reduction in, or at least an altered, resting state BOLD activation.

## Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

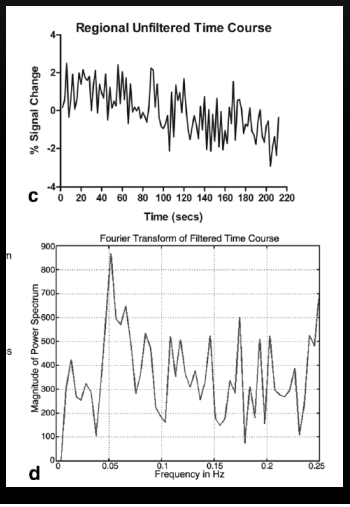
Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde

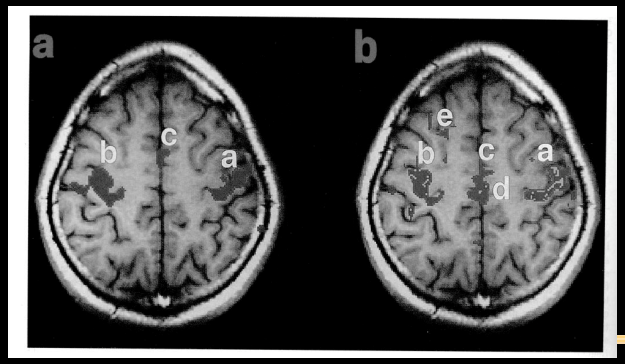


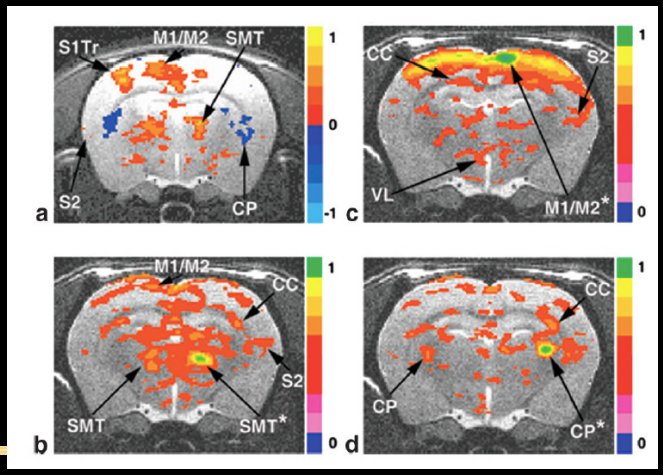

Magnetic Resonance in Medicine 59:1021–1029 (2008)

## Resting-State Functional Connectivity of the Rat Brain

Christopher P. Pawela,[1] Bharat B. Biswal,[2] Younghoon R. Cho,[3] Dennis S. Kao,[3] Rupeng Li,[1] Seth R. Jones,[3] Marie L. Schulte,[4] Hani S. Matloub,[3] Anthony G. Hudetz,[4] and James S. Hyde[1]*



# Resting State Activity in the Brain

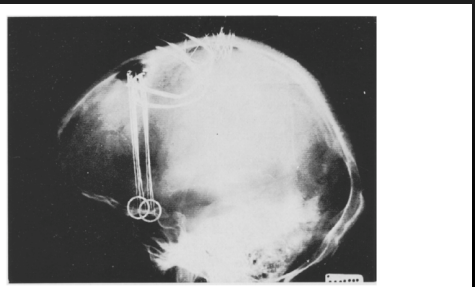
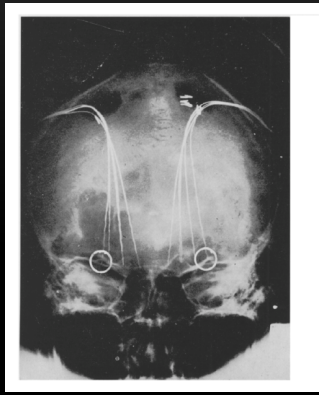
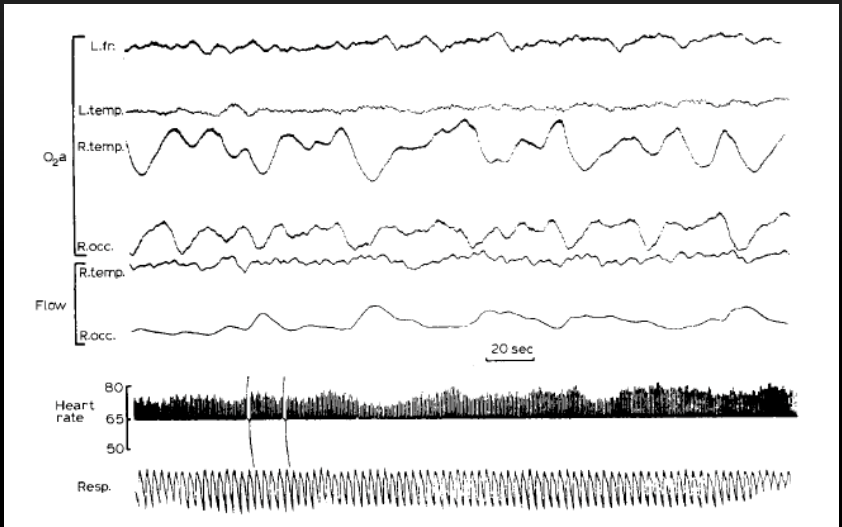


Fig. 1. Posterior/anterior and lateral x-ray photographs showing implanted electrodes in a psychiatric patient. The thermistors are circled.

*Brain Research*, 3 (1966) 174–191






"A striking feature of the recordings of brain oxygen availability in man is their fluctuating nature."

"The fluctuations are irregularly rhythmical changes in amplitude, occurring at a frequency of about 6 waves per min. They were seen, to a greater or less extent, at almost all electrodes. The fluctuations at different electrodes appeared to be independent of each other, even when the electrodes were only a few millimetres apart, and they also occurred at different frequencies. Their frequency range and their independence from region to region show that these fluctuations are not directly due to changes in respiration or cardiac pulsations or output."

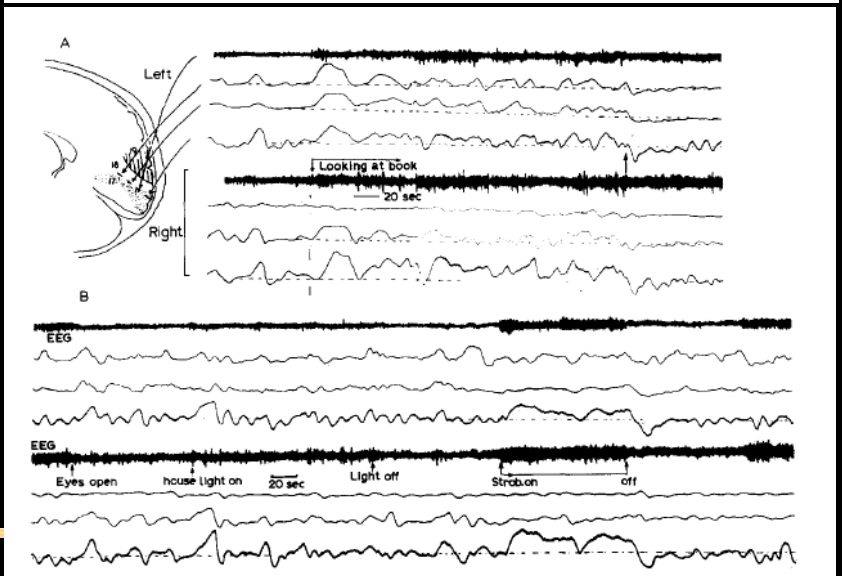


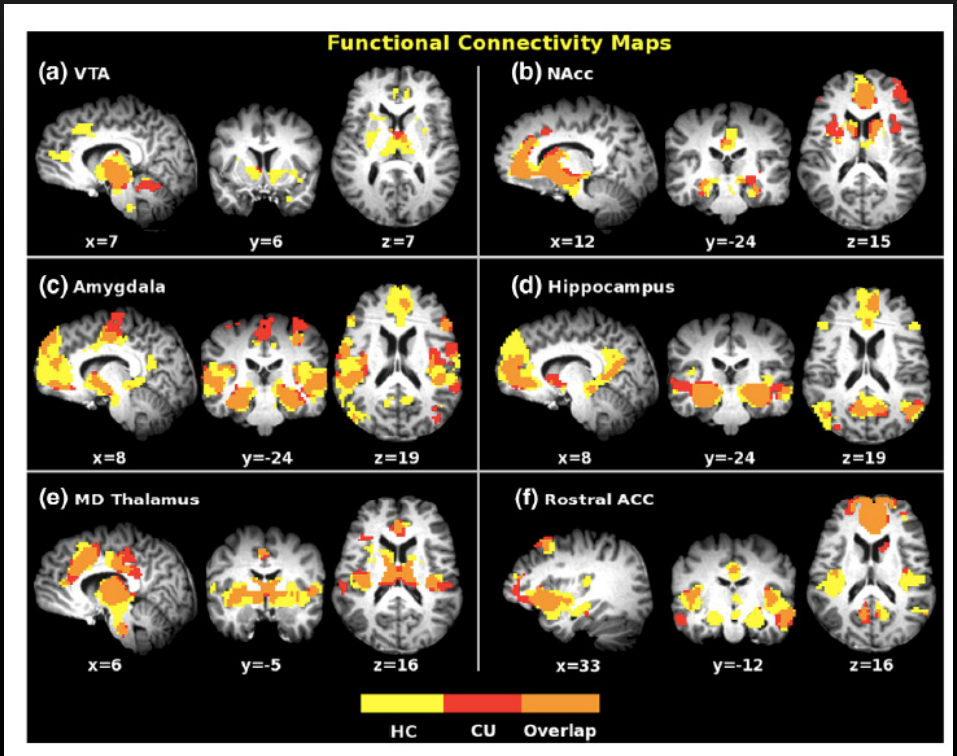

Fig. 10. Change of $O_2a$ during visual stimulation. Electrodes in this patient were in area 18 and bordering area 17 (see inset). (A) Record shows that 5 out of 6 channels showed changes of $O_2a$ with reading. (B) Eyes opening and house lights on produced only transitory changes at a few electrodes. At two electrodes (Ch. 4 and Ch. 8) stroboscopic illumination produced a marked and sustained increase of $O_2a$. The EEG recorded from electrodes near to those showing $O_2a$ changes showed large flicker-evoked responses (Ch. 1 and 5).

Cooper et al BRES 1966

Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity

Hong Gu, Betty Jo Salmeron, Thomas J. Ross, Xiujuan Geng, Wang Zhan, Elliot A. Stein *, Yihong Yang *

*Neuroimaging Research Branch, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA*




**SEED REGIONS:**

1) Mesolimbic (NAc, VTA)
Responding to rewarding stimuli

2) Amygdala, Hippocampus
Memory functions, especially related to learning cue and context associations

3) Mediodorsal thalamus
An intermediary node linking midbrain and prefrontal cortex, and a key component of thalamo**–cortico–basal** ganglia circuits implicated in aberrant habit learning disorders

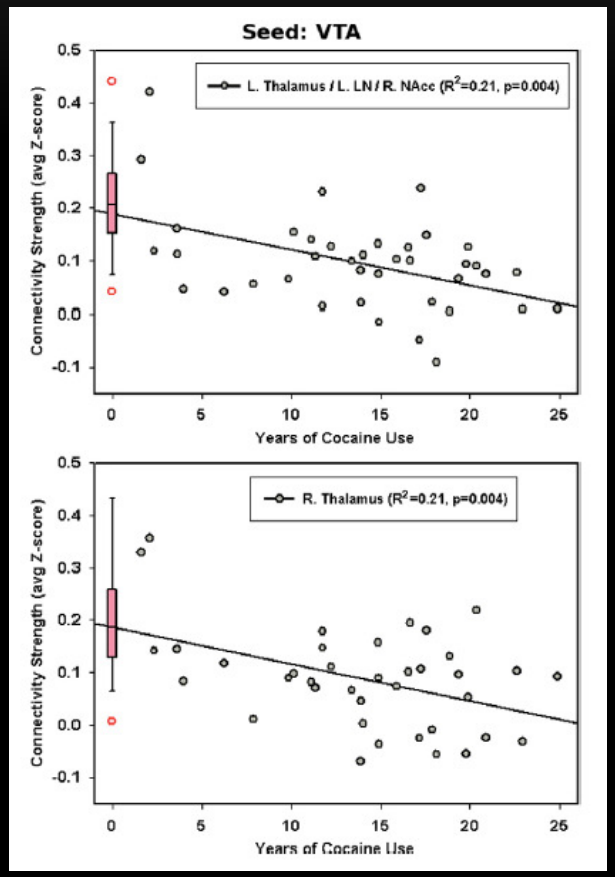
4) Prefrontal/orbitofrontal cortex (PFC/OFC) and anterior cingulate cortex (ACC)
Involved in emotional regulation, cognition and executive function, especially inhibitory control processes

Cocaine dependent subjects show reduced functional 'connectivity' with regions of the mesocorticolimbic system.

The MCL networks include VTA, NAc, amygdala, thalamus, prefrontal cortex and hippocampus

Gu et al NeuroImage 2011

# REDUCED RESTING STATE 'CONNECTIVITY' WITH CHRONIC COCAINE USE




Gu et al NeuroImage 2011

Similar network level changes are reported across the recent literature:

Wang et al PLoS One 2013 Heroin dependence

Park et al JNS 2010 Alcohol dependence

Motzkin et al HBM 2014 Substance dependence

McHugh et al Frontiers in Psychiatry 2014 in association with relapse risk

McHugh et al Am J Drug & Alc Abuse 2013 in association with impulsivity

Li et al MRM 2000 as a consequence of cocaine administration

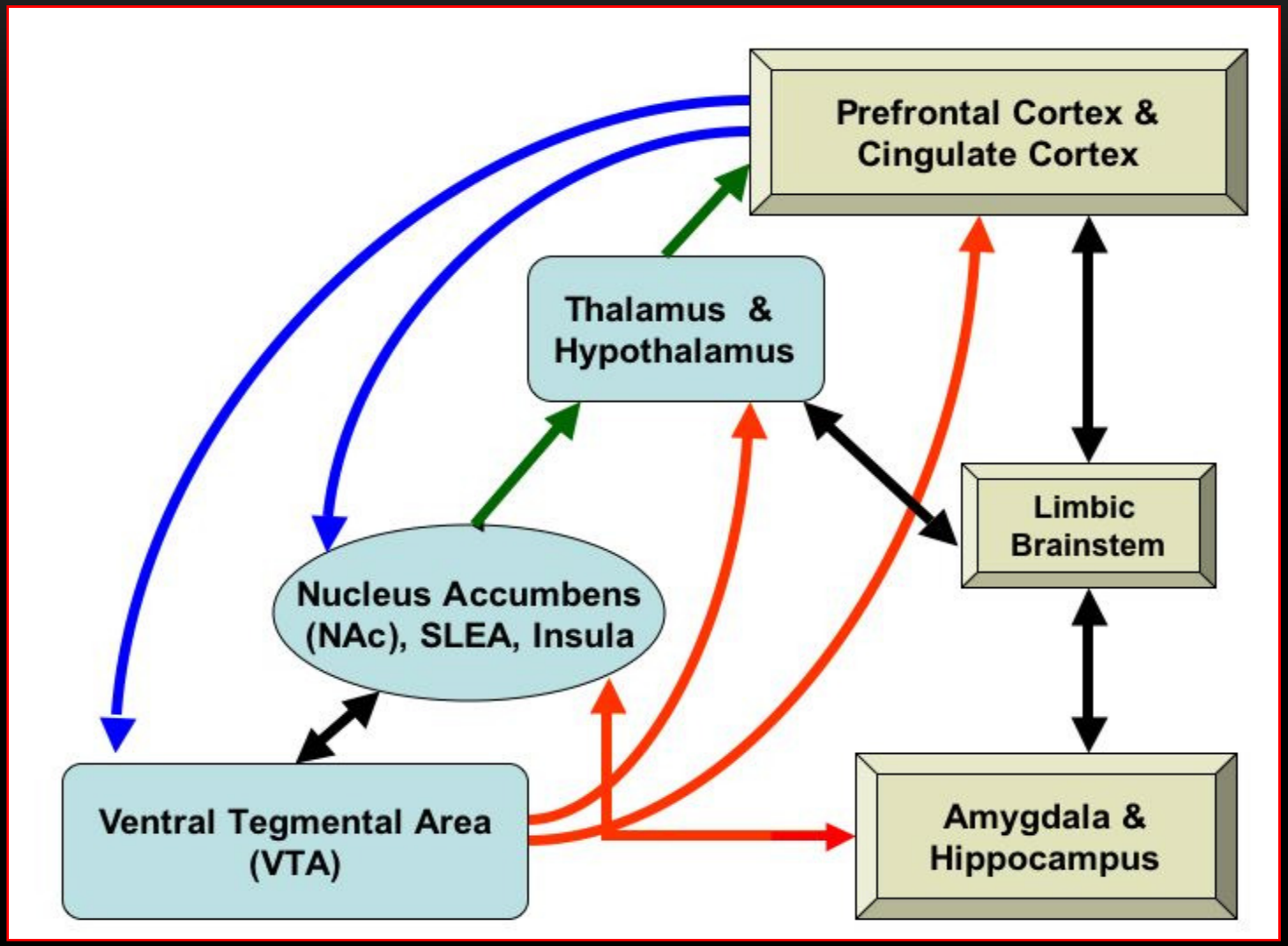
Kelly et al Bio Psychiatry 2011 reductions in interhemispheric connectivity in cocaine addicts

Cisler et al Psychiatry Res 2013, Altered rsFC in similar networks

# EFFECT OF DOPAMINERGIC AGENT ON RESTING STATE FUNCTIONAL CONNECTIVITY IN AN ANIMAL MODEL

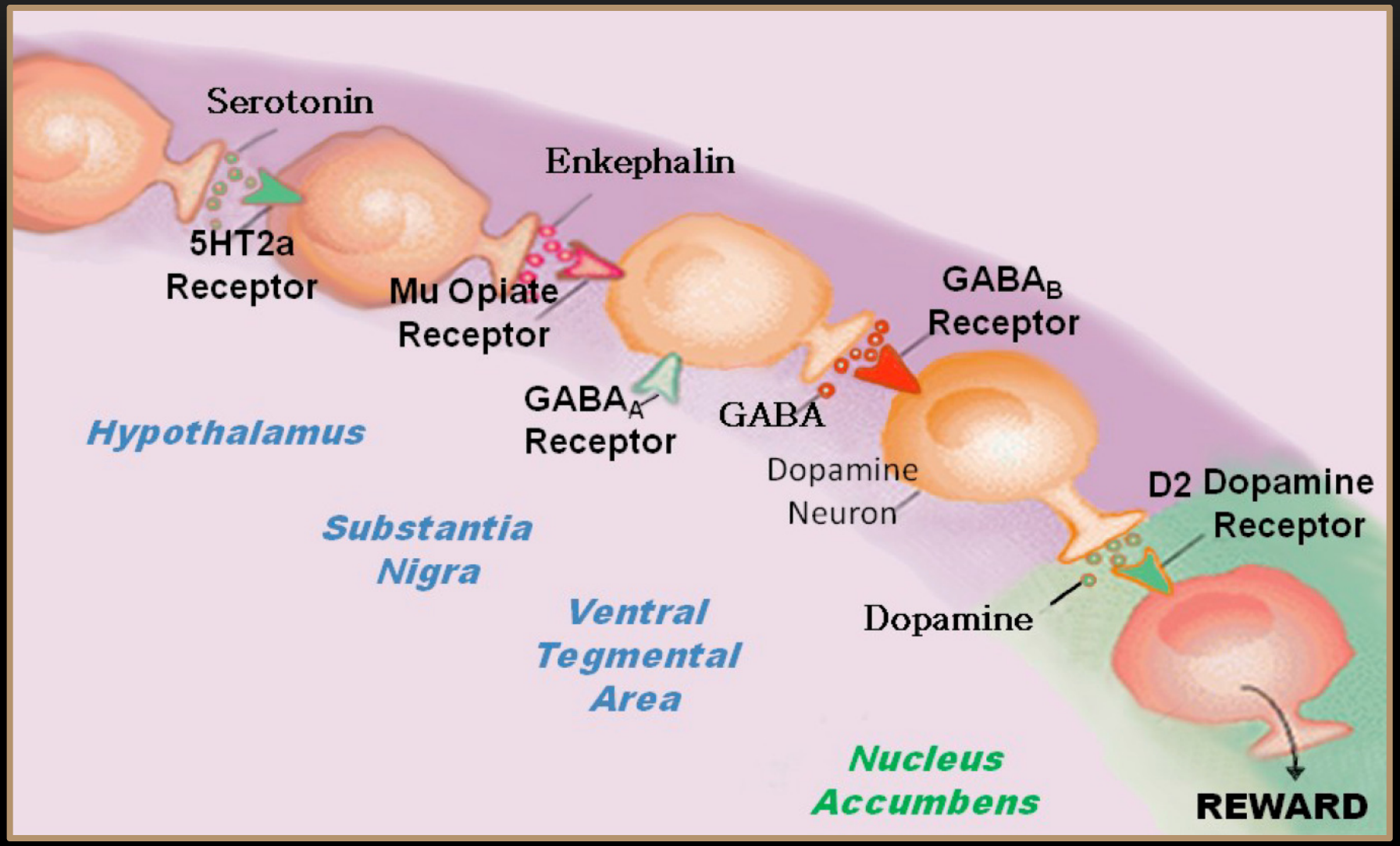
- Oral syringe-dosed delivery of KB220Z, a nutriceutical consisting of various supplements along with enzymatic inhibitors and neurotransmitter precursors targeting biochemical events regulating dopamine levels in the brain.
- Syringe-dosed animals may reflect lingual or buccal absorption of part of the dose, involving rapid absorption through the capillaries of the mouth. In contrast, the entire dose in the gavage-dosed animals would have been subjected to first-pass hepatic metabolism; therefore, more of the dose would have been exposed to first-pass metabolism before being distributed throughout the body. (Matsui et al., 1999 Drug Metab Disp; Atcha et al., 2010 J AALAS).
- Measure 'seed'-based resting state functional connectivity within regions of the reward system of the rat brain.
- It was predicted that by enhancing dopaminergic activity, there would be an enhancement of rsFC compared to vehicle controls.

# BRAIN REWARD CIRCUITRY




Courtesy of Dr. Ken Blum

# BRAIN REWARD CASCADE



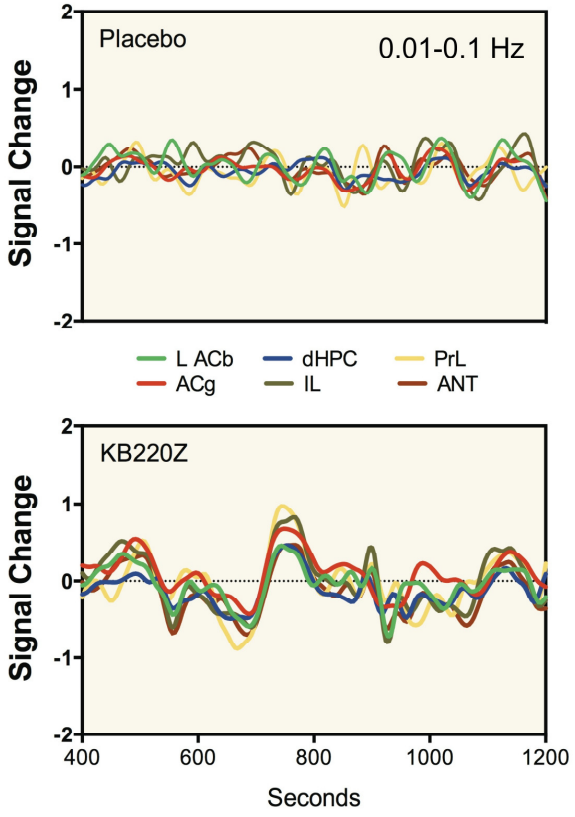

Courtesy of Dr. Ken Blum

A

## fMRI Setup in Rat

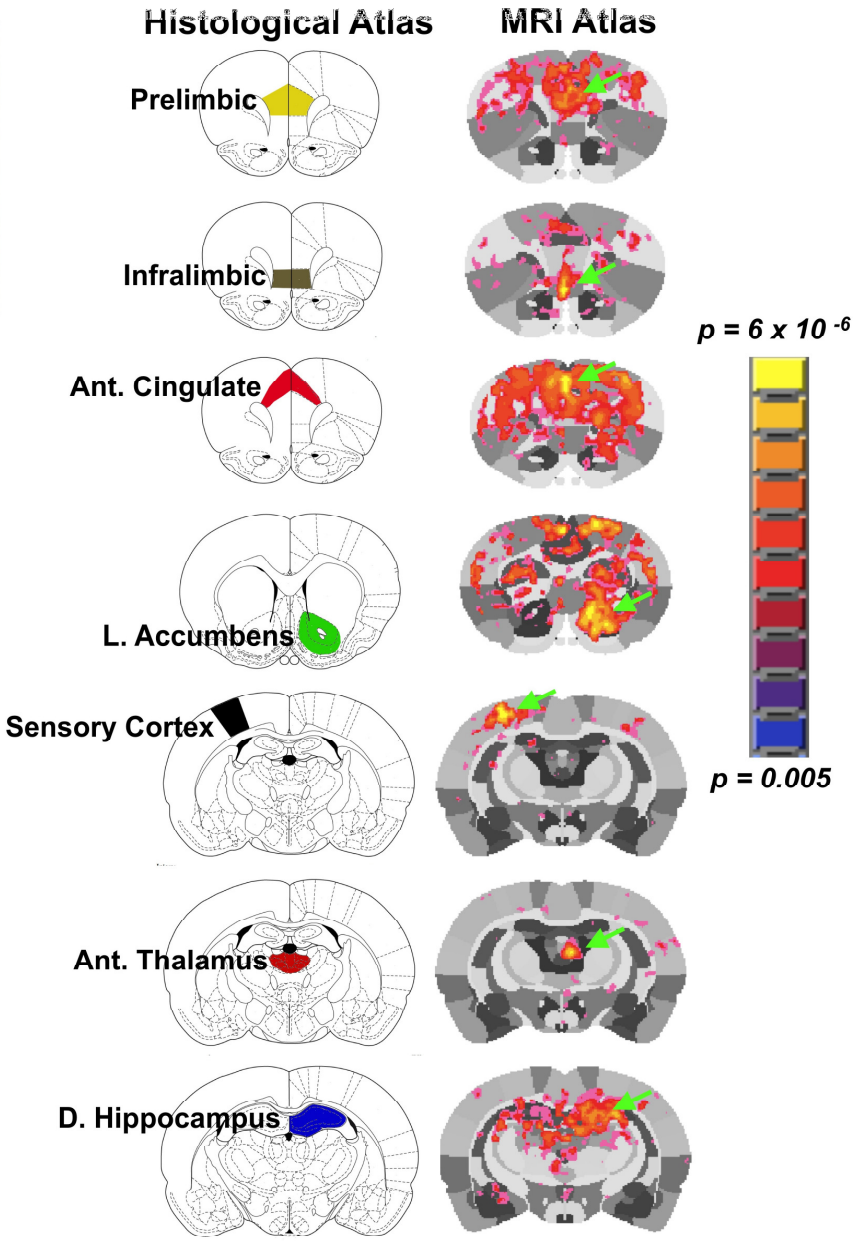

B

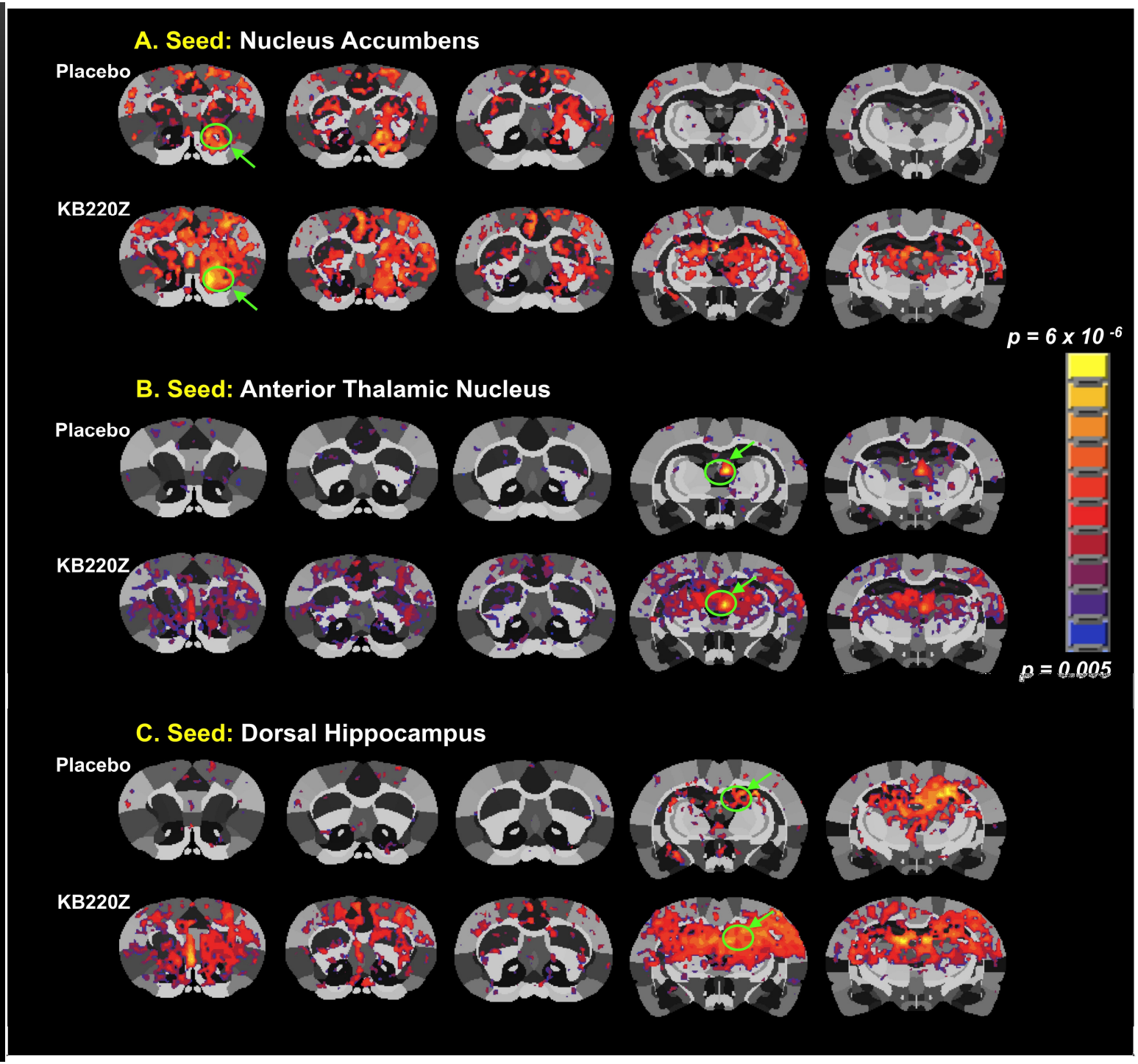
## Spontaneous Fluctuations in BOLD Signal

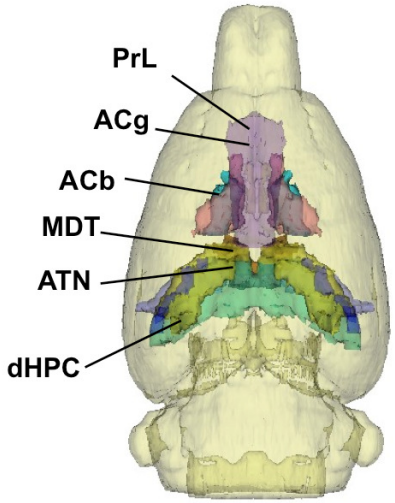


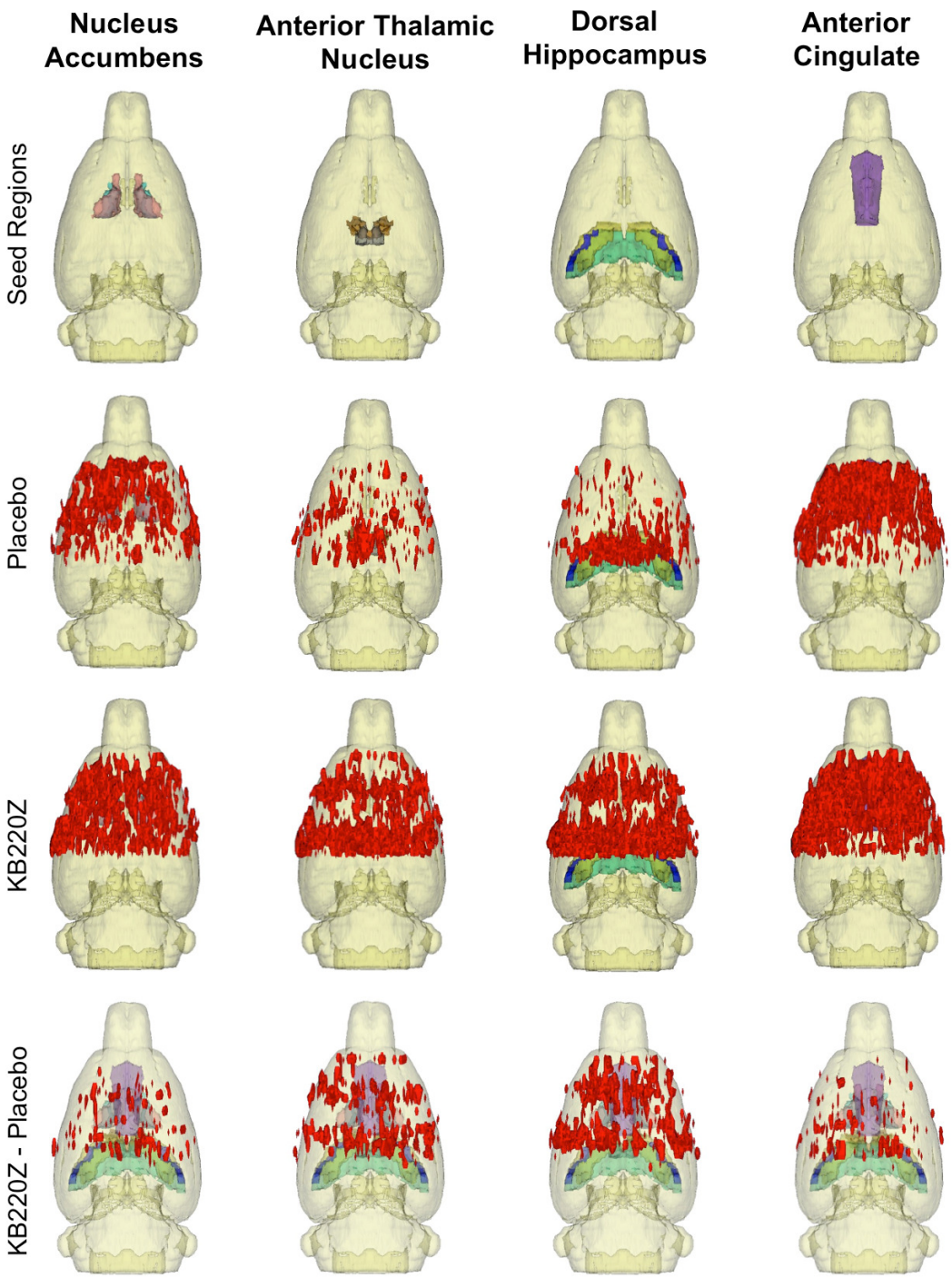

C

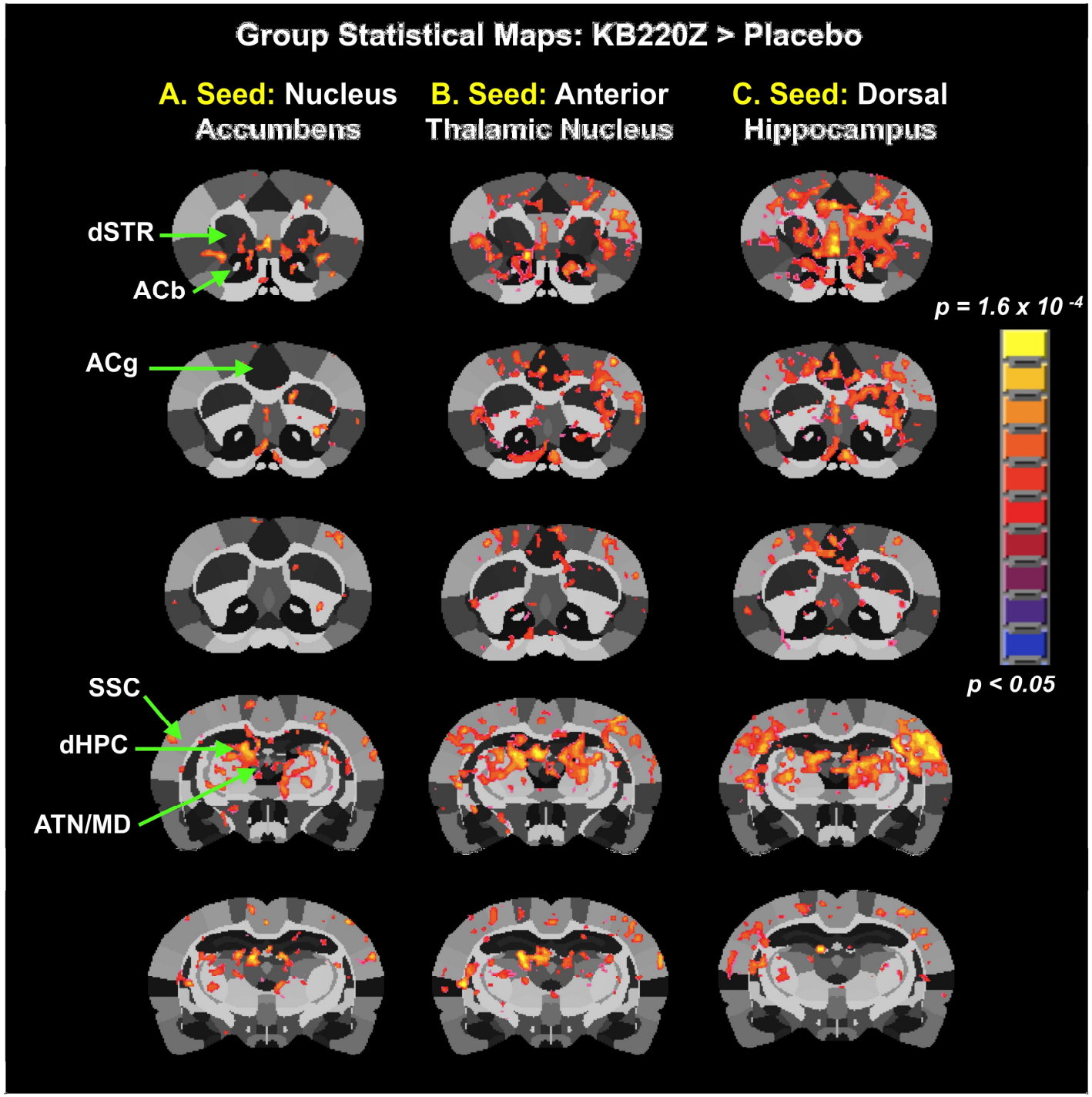
## Seed Regions

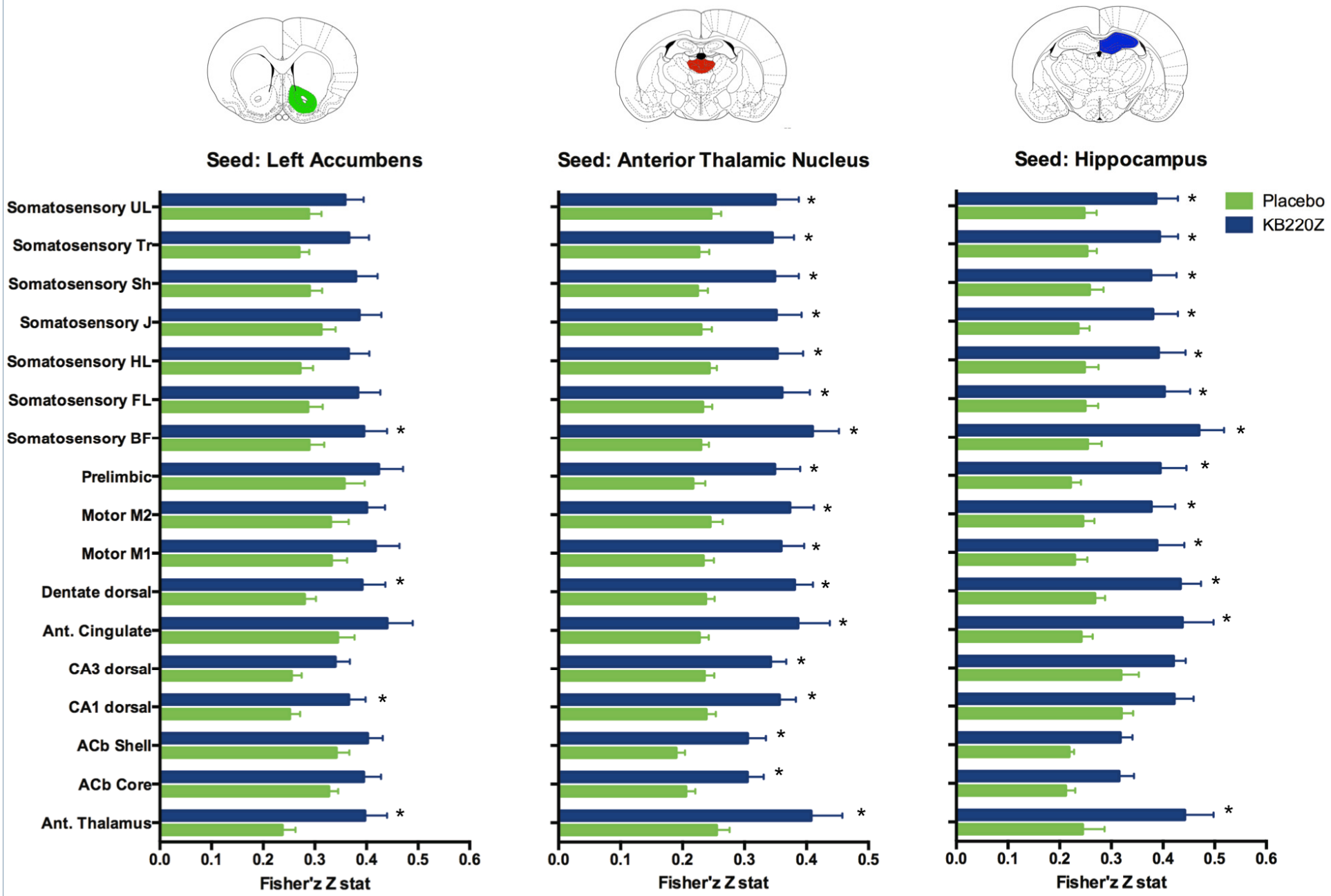


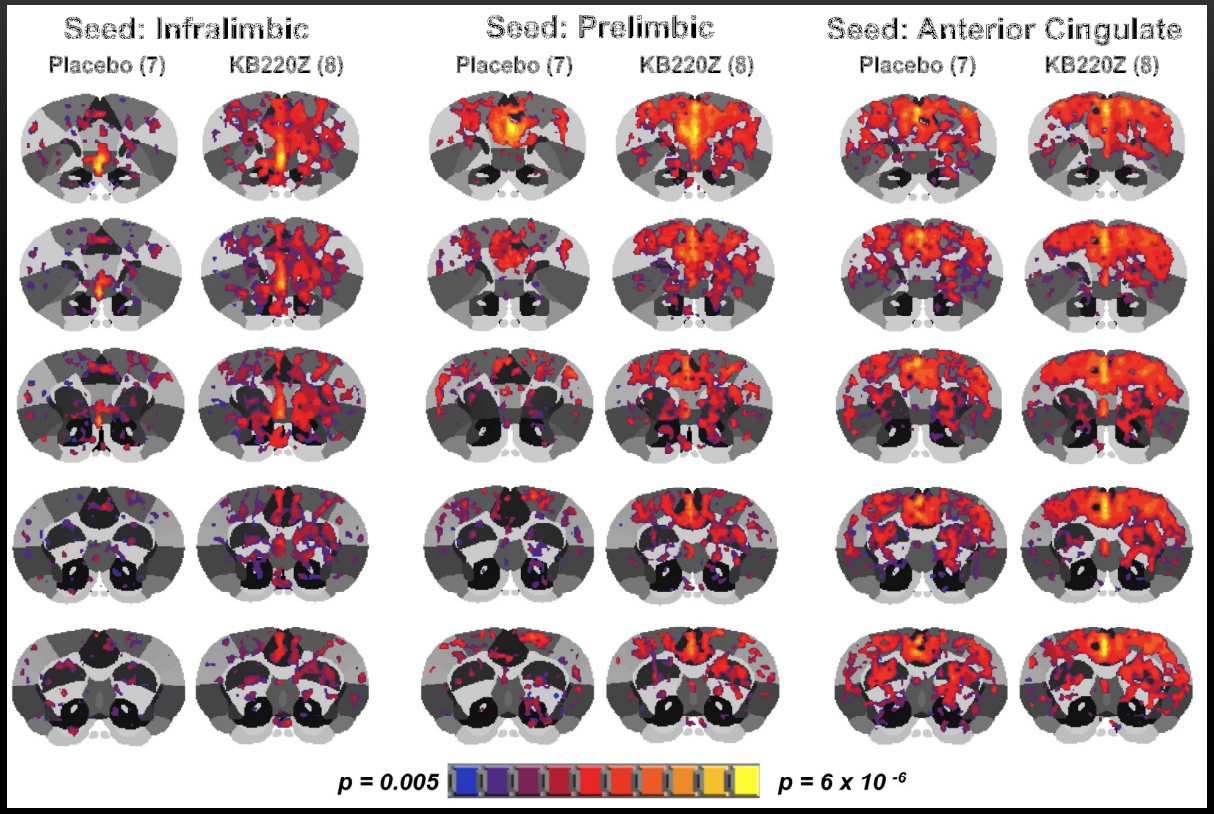

A. Seed: Nucleus Accumbens
Placebo
KB220Z
p = 6 x 10 -6
B. Seed: Anterior Thalamic Nucleus
Placebo
KB220Z
p = 0.005
C. Seed: Dorsal Hippocampus
Placebo
KB220Z

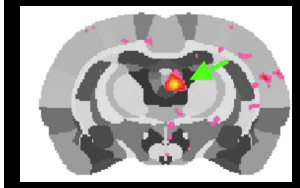

PrL
ACg
ACb
MDT
ATN
dHPC

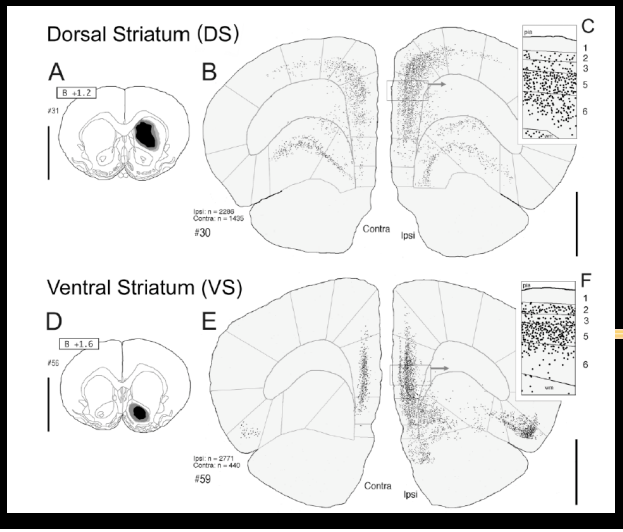

Nucleus Accumbens
Anterior Thalamic Nucleus
Dorsal Hippocampus
Anterior Cingulate
Seed Regions
Placebo
KB220Z
KB220Z - Placebo

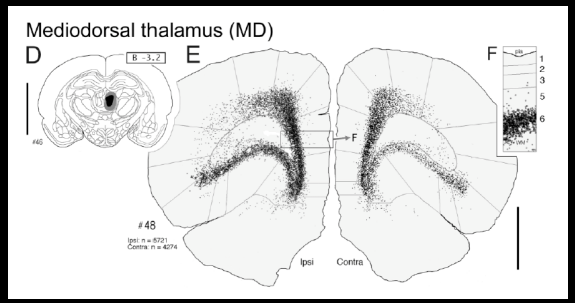

Group Statistical Maps: KB220Z > Placebo
A. Seed: Nucleus Accumbens
B. Seed: Anterior Thalamic Nucleus
C. Seed: Dorsal Hippocampus
dSTR
ACb
ACg
SSC
dHPC
ATN/MD
p = 1.6 x 10 -4
p < 0.05


Seed: Left Accumbens
Seed: Anterior Thalamic Nucleus
Seed: Hippocampus
Placebo
KB220Z
Somatosensory UL
Somatosensory Tr
Somatosensory Sh
Somatosensory J
Somatosensory HL
Somatosensory FL
Somatosensory BF
Prelimbic
Motor M2
Motor M1
Dentate dorsal
Ant. Cingulate
CA3 dorsal
CA1 dorsal
ACb Shell
ACb Core
Ant. Thalamus
0.0 0.1 0.2 0.3 0.4 0.5 0.6
Fisher'z Z stat
0.0 0.1 0.2 0.3 0.4 0.5
Fisher'z Z stat
0.0 0.1 0.2 0.3 0.4 0.5 0.6
Fisher'z Z stat

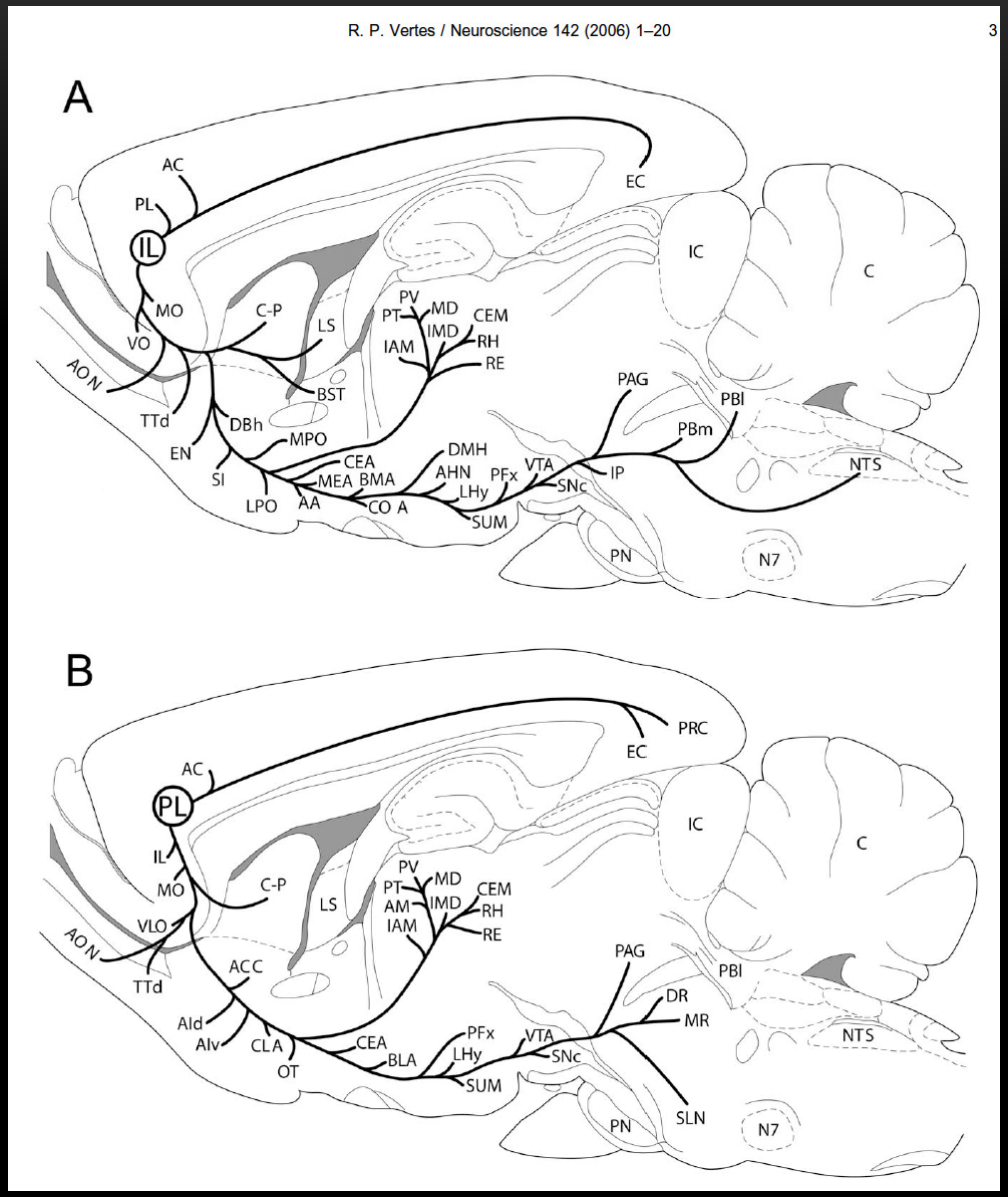





Gabbott et al J Comp Neurol 2005




Vertes, Neuroscience 2006

# SUMMARY

- The present study illustrates the modulatory actions of a putative DA agonist (KB220Z) upon rsFC in association to a key region of the reward system, the NAc. *We find that KB220Z increased connectivity between this central striatal reward structure and areas of the brain that are critical for cognitive processing, the dorsal hippocampus and anterior thalamus.*
- Moreover, there is evidence of recruitment of additional brain structures such as hippocampus, anterior thalamus, and somatosensory regions indicating inclusion of *these regions in the putative neural network*.
- The discovery that KB220Z increases functional connectivity has enormous implications for treatment of psychiatric conditions like RDS. *Re-establishment of baseline connectivity, prior to drug use and addiction, could be a strategy that may be targeted through the diagnostic use of resting state functional MRI and may be supplemented by administration of KB220Z*.

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