

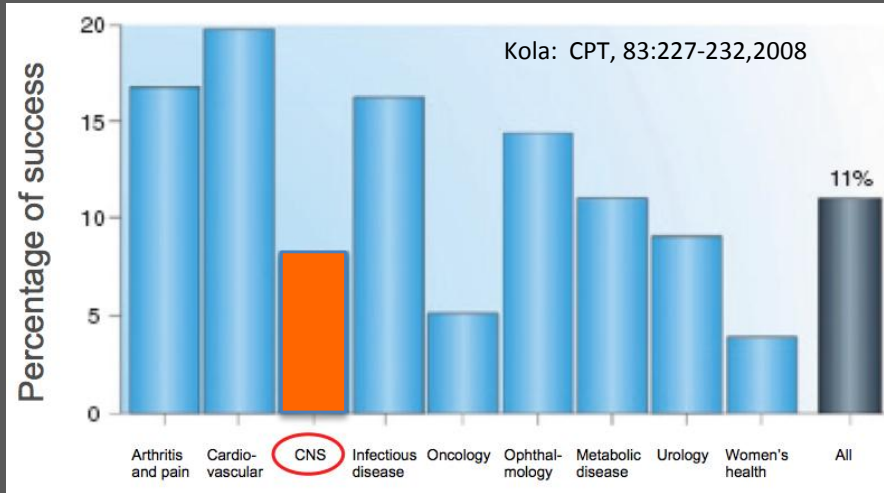
Imaging in Analgesic Drug Development (iADD)

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Center for Pain and the Brain
Harvard Medical School

Pain and the Six Conundrums

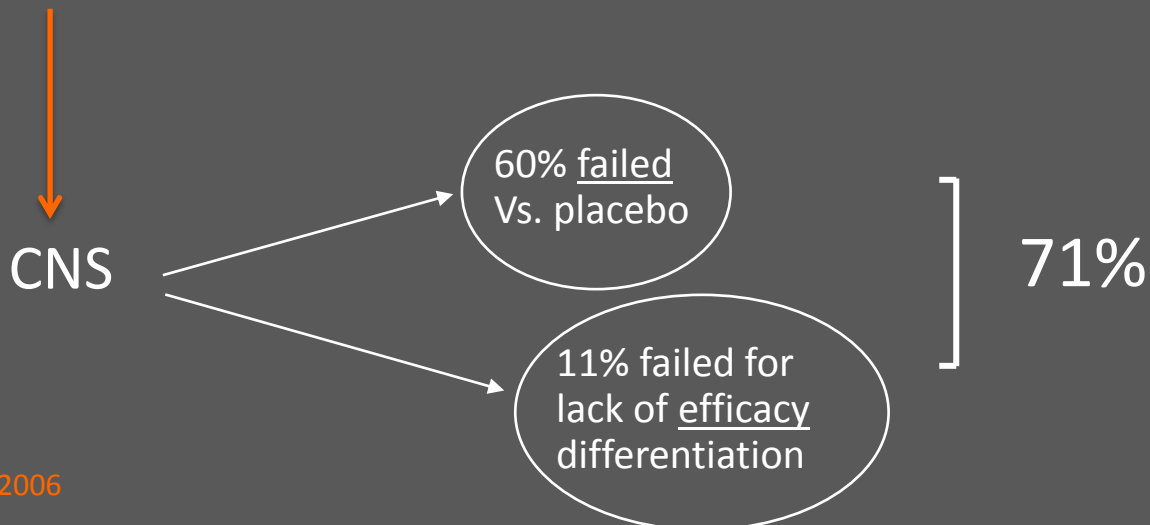
- Societal Conundrum – an epidemic
- Subjective Measure Conundrum – not objective
- Preventive Conundrum – e.g., postsurgical pain
- Therapeutic Conundrum – 30% efficacy
- Translational Conundrum – no good models
- Drug Development Conundrum – failure rate

Drug Development Conundrum

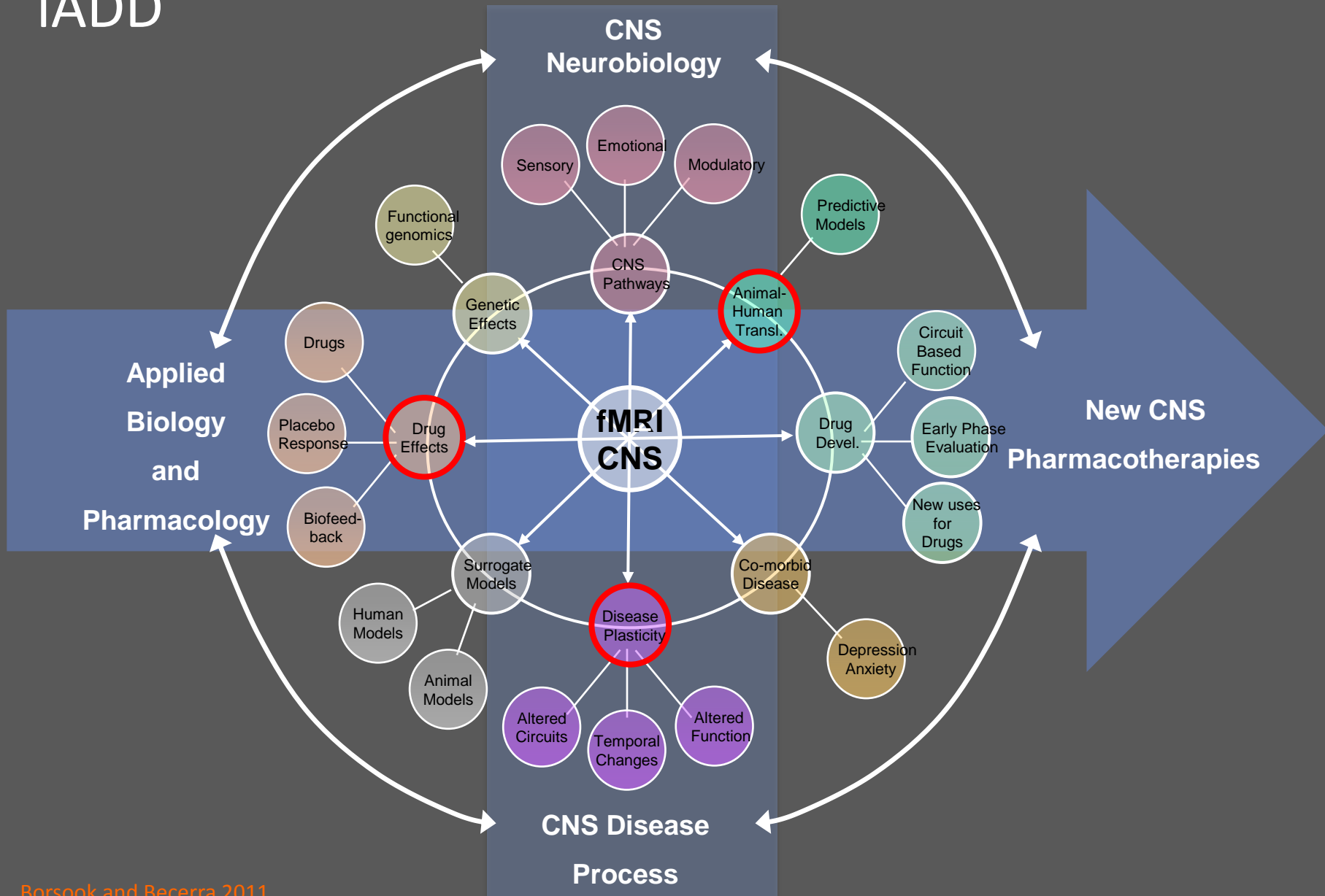


CNS has traditionally lacked tools for early pharmacologic read-outs

Borsook et al., 2011a; 2011b



Elias et al., 2006

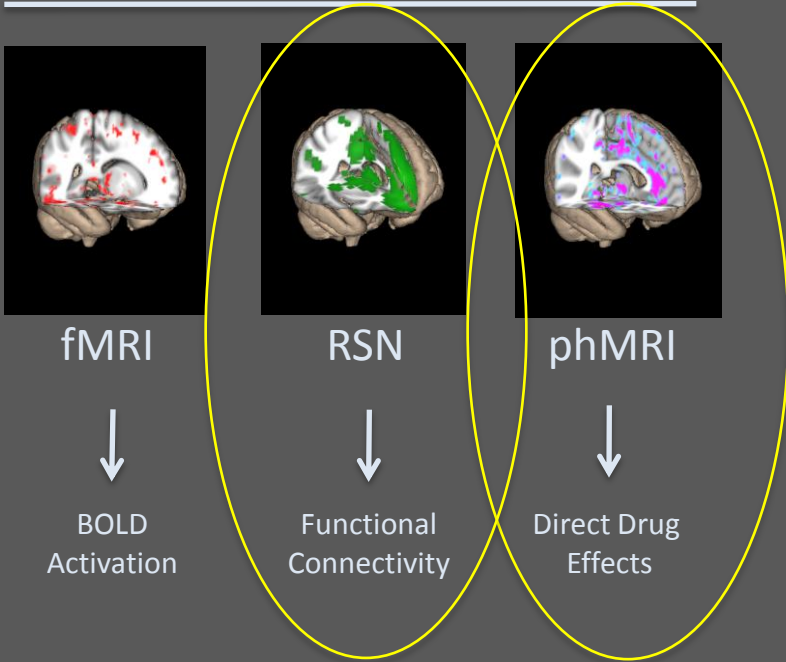


iADD in CNS Drug Evaluation

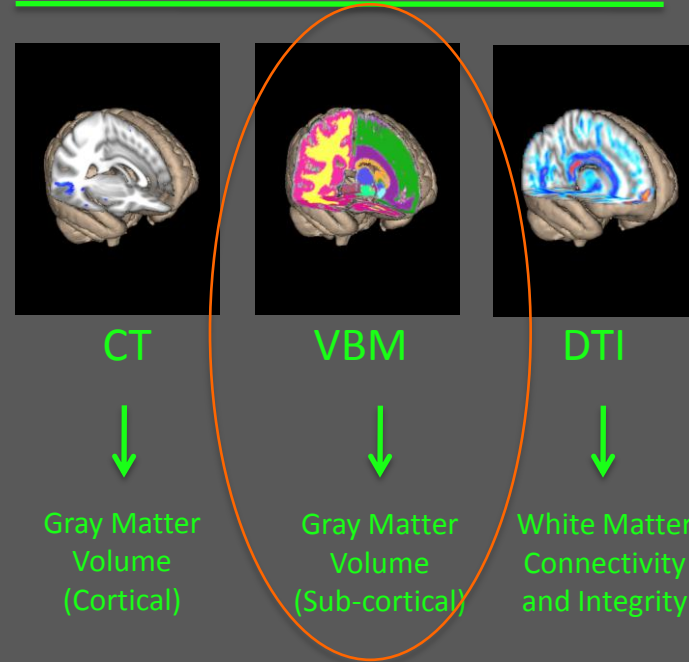
- **Define Disease States**
- **Defining Drug Effects**
 - Opioids - Acute Effects
 - Opioids - Chronic Effects
- **Choosing Analgesics**
 - Buprenorphine/Aprepitant
- **phMRI, PET and Drug Evaluation**
 - PETability
 - Drug Dissection
- **Enhancing Animal-Human Translational**
 - Drugs
 - Pain
 - Disease

Defining Disease States

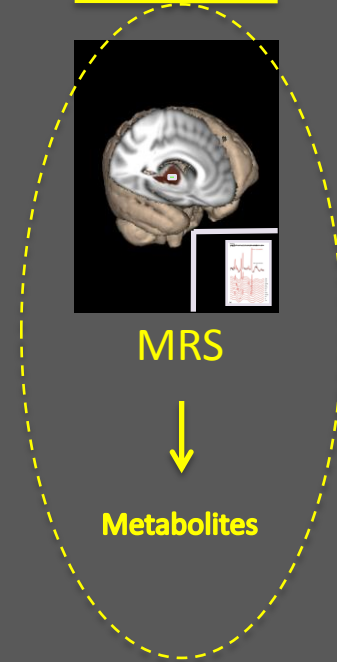
Functional



Anatomical

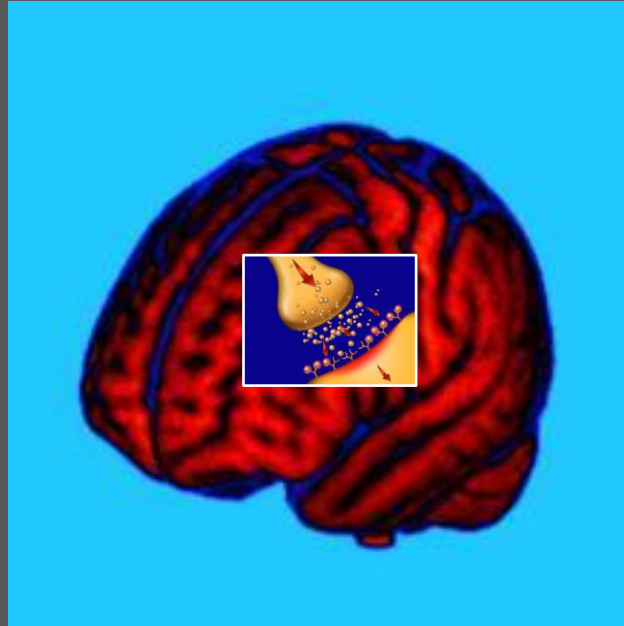


Chemical



Objective Measures of Disease State or Drug Effect

Defining Drug Effects



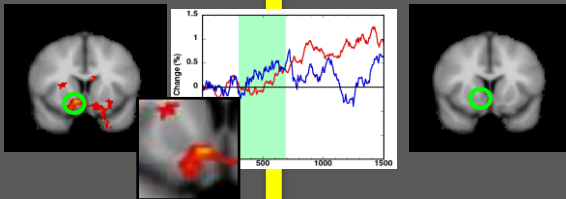
How well can imaging measure CNS drug effects?

Morphine

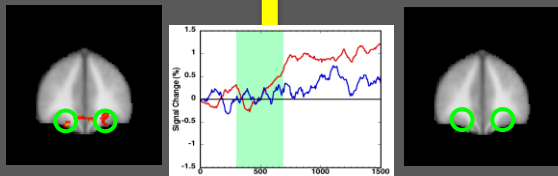


Reward Circuitry

Nucleus Accumbens



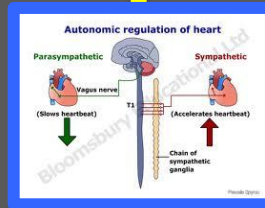
Orbitofrontal Cortex



Morphine

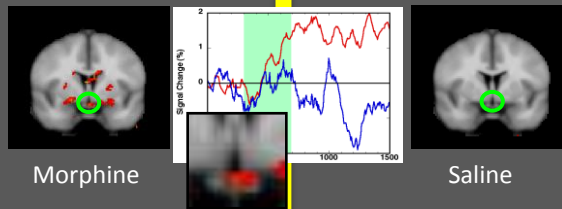
Saline

— Morphine
— Saline



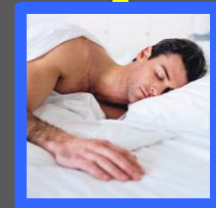
Autonomic Circuitry

Hypothalamus



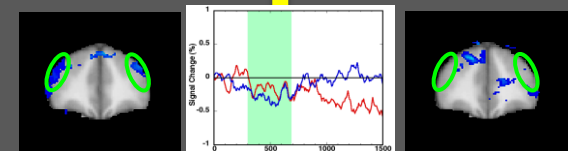
Morphine

Saline

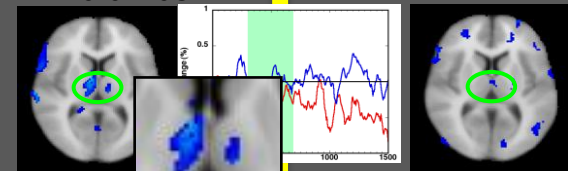


Sedative Circuitry

Cortical Regions (LPFC)



Thalamus

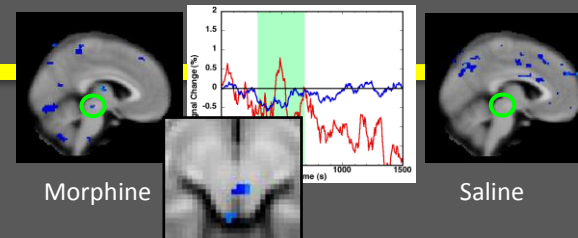


Morphine

Saline

Analgesic Circuitry

Periaqueductal Gray

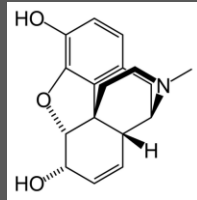


Morphine

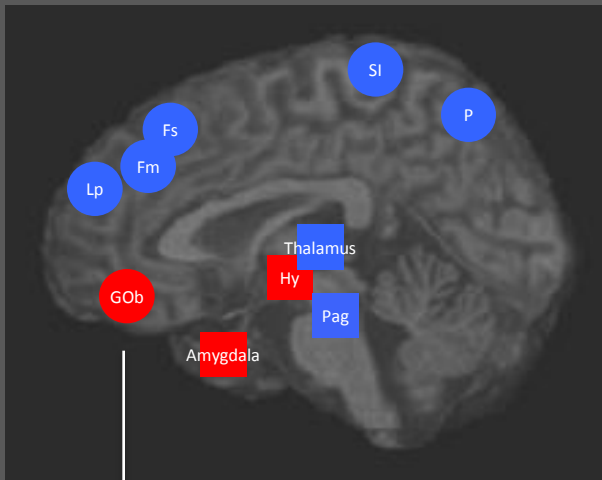
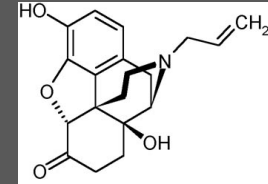
Saline

Morphine (agonist) vs. Naloxone (antagonist)

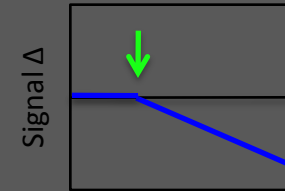
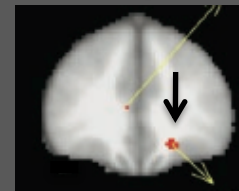
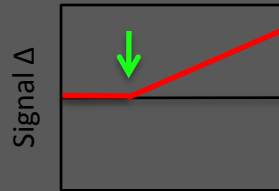
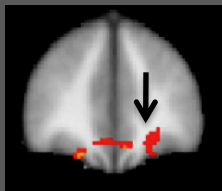
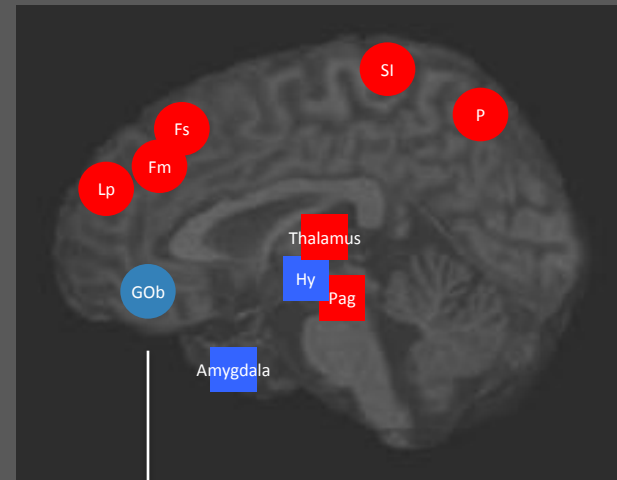
Morphine



Naloxone



○ Cortical
 □ Sub Cortical

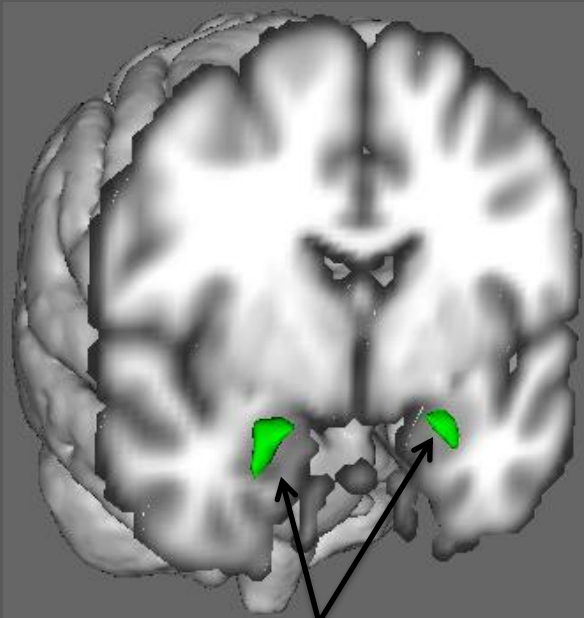


Becerra et al., 2006

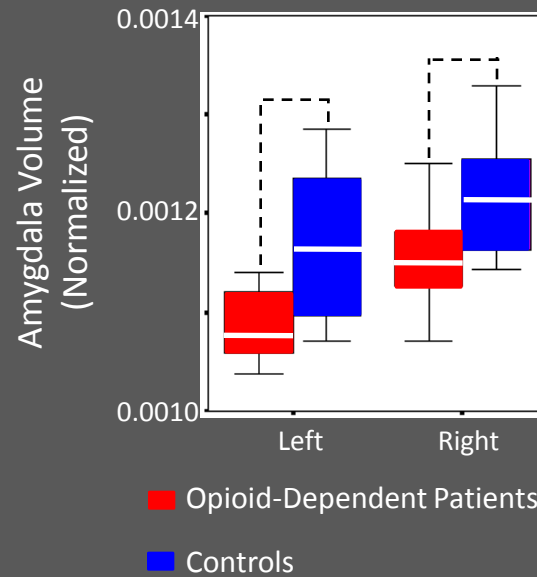
Borras et al., 2004

Borsook et al., 2010

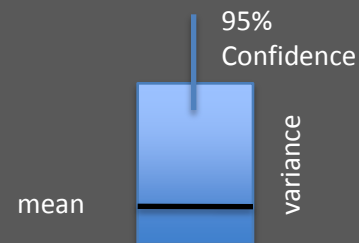
Predicting Chronic Drug Effects



Amygdala

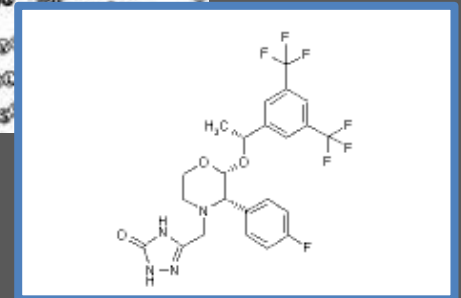
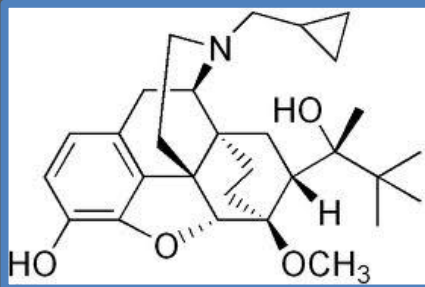
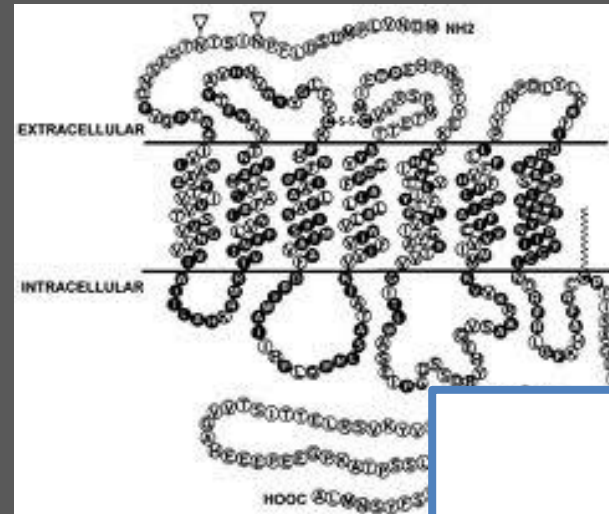
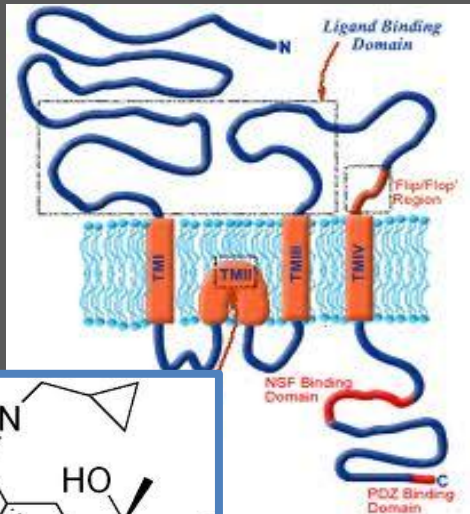


* $p < 0.05$



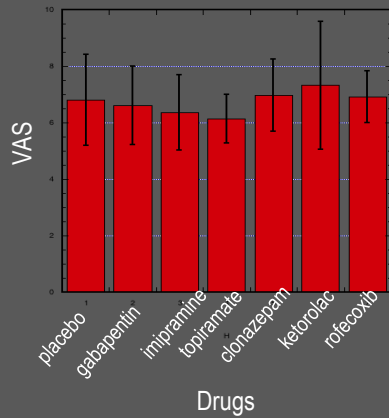
Upadhyay et al., 2010

Choosing Effective Analgesics

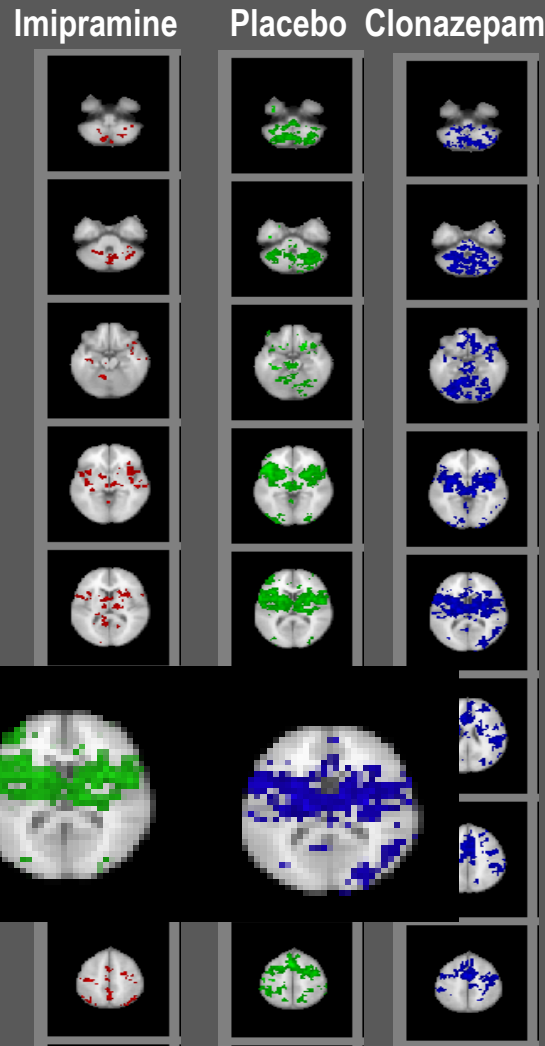


Predicting Good Drugs

Subjective Ratings

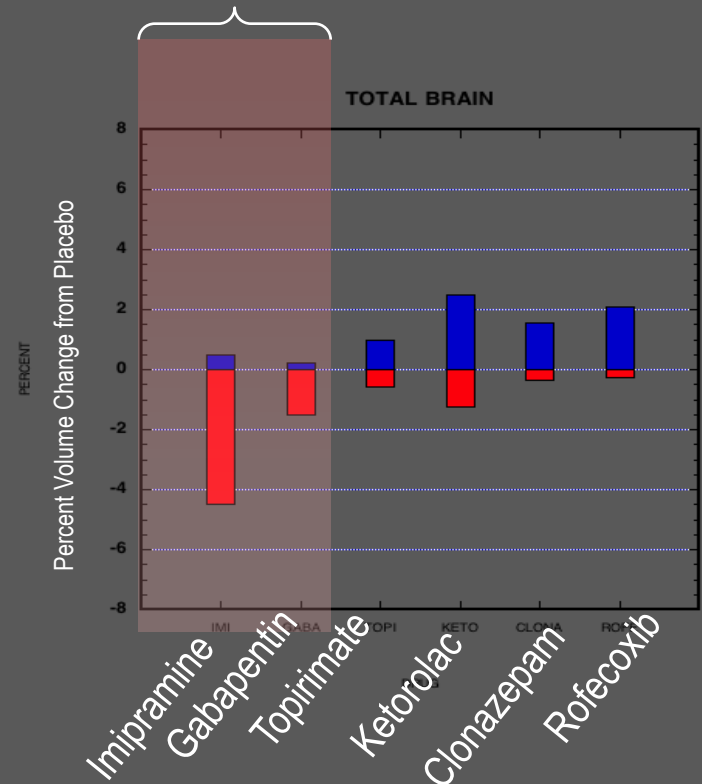


fMRI Response

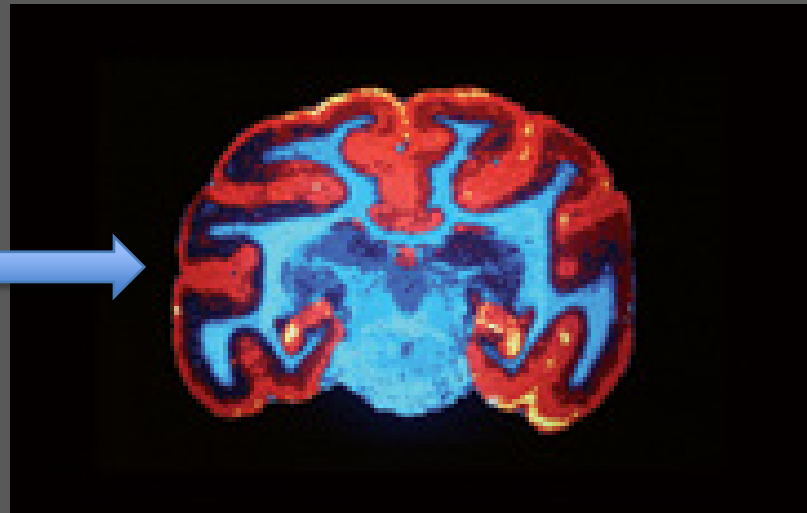
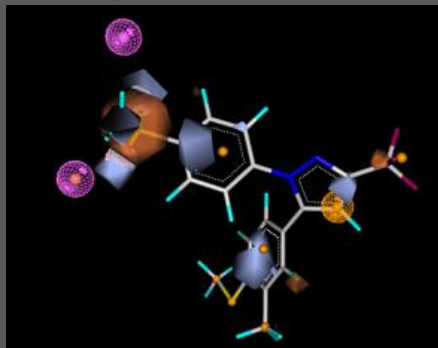


Quantitative Analysis

Good
Drugs

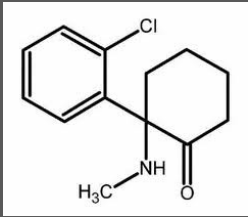


phMRI, PET and Drug Evaluation



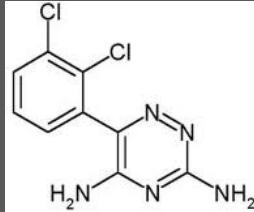
Can we use functional imaging for CNS Receptor Activation?
CNS Dosing?
Drug Receptor Binding does not equal drug efficacy!

iADD and Chronic Pain



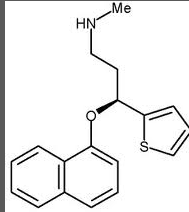
Ketamine

Borsook et al., 2007



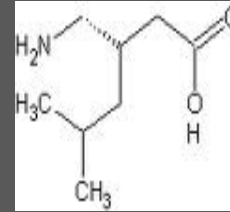
Lamotrigine

Scrivani et al., 2009



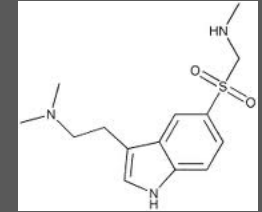
Duloxetine

Borsook et al., Im sub.



Pregabalin

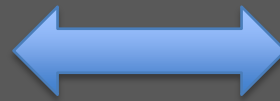
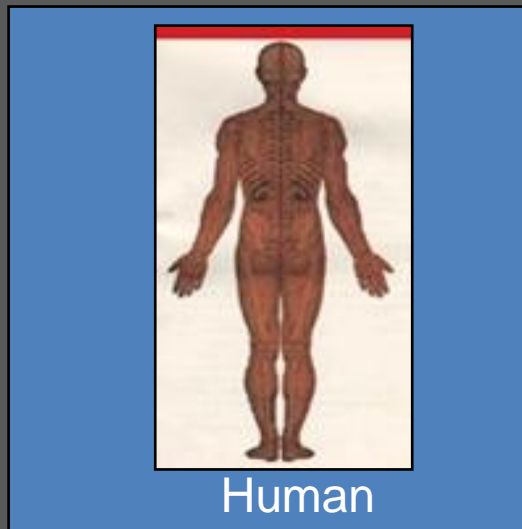
Becerra et al., Im sub.



Migraine Rx

Borsook et al., Im sub.

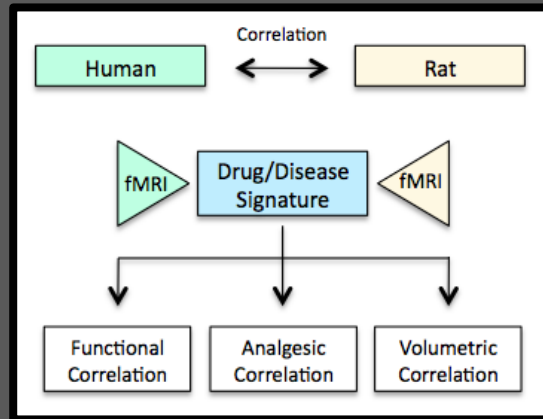
Enhancing Animal-Human Translational Processing



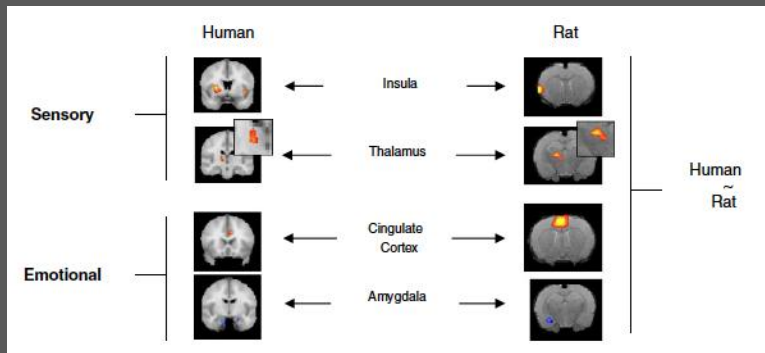
A language of translation?

Borsook and Becerra 2010

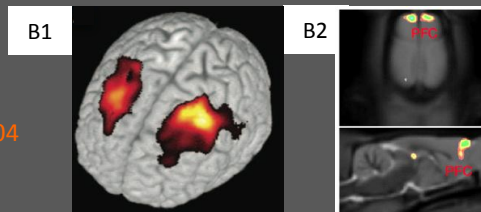
Human-Animal Parallels



A. Functional Correlations



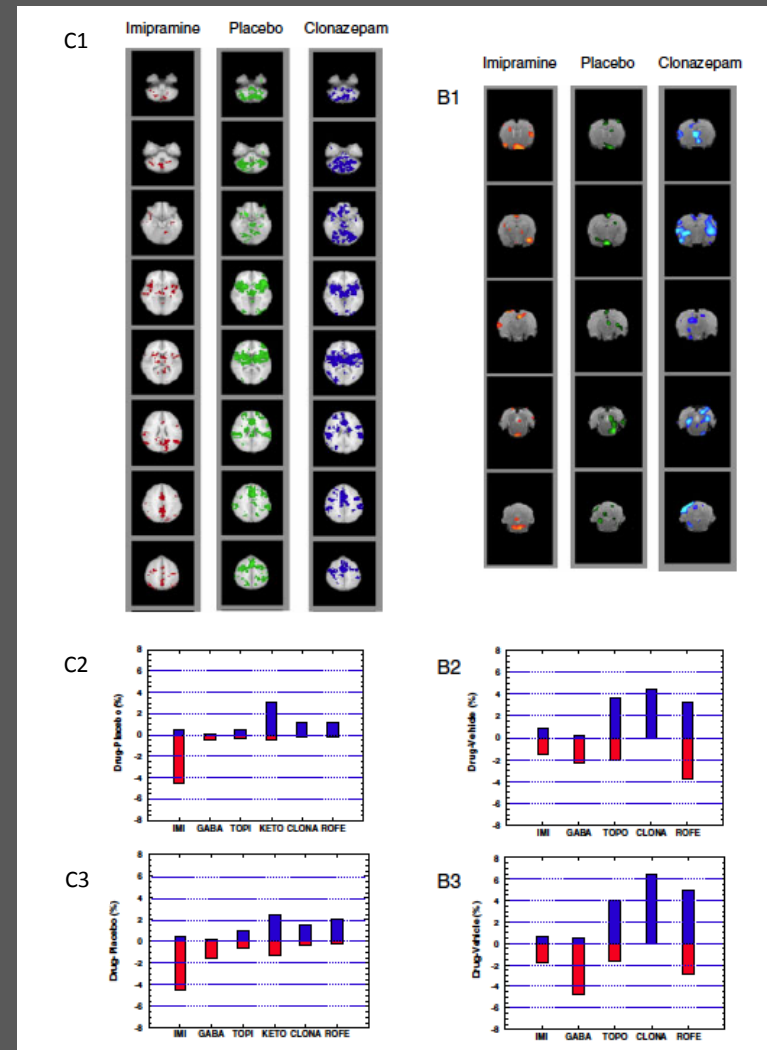
B. Morphometric Correlations



Apkarian et al., 2004

Seminowicz et al., 2009

C. Analgesic Correlations



Borsook and Becerra, 2011

iADD – The Potential in Clinical Trials

- Decreasing the Risk (\$)
- Enhancing the Opportunity (# Molecules)
- Evaluating Systems Targets (CNS diseases are Complex)
- Target-Systems Integration (PET/fMRI)
- Rx Domains (Symptoms vs. Disease Modification)
- Responders vs. Non-Responders
- Decreasing the Variance
- CNS Dosing
- Putting it into Action – fNIH/European

~~Pain~~

and

Zero Clinical Conundrums