Pain and Addiction:
Can we actually see the relationships?

Jon-Kar Zubieta, M.D., Ph.D.

Phil Jenkins Professor of Psychiatry

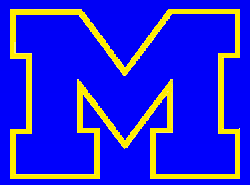
Associate Professor

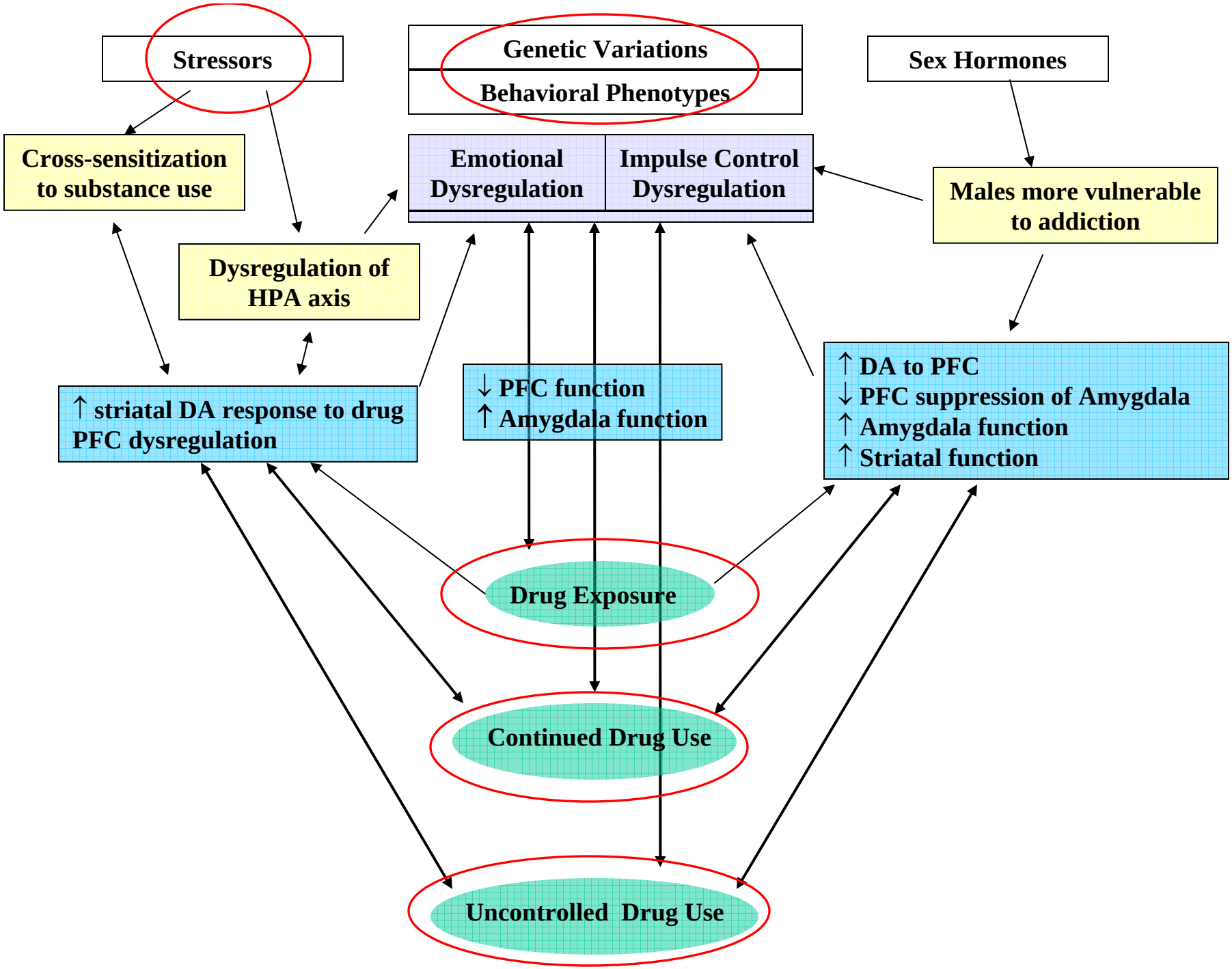
Departments of Psychiatry, Radiology, and Neurosciences Program

Associate Research Professor

Molecular and Behavioral Neuroscience Institute

The University of Michigan




Stressors
Genetic Variations
Behavioral Phenotypes
Sex Hormones
Cross-sensitization to substance use
Emotional Dysregulation
Impulse Control Dysregulation
Males more vulnerable to addiction
Dysregulation of HPA axis
↑ striatal DA response to drug
PFC dysregulation
↓ PFC function
↑ Amygdala function
↑ DA to PFC
↓ PFC suppression of Amygdala
↑ Amygdala function
↑ Striatal function
Drug Exposure
Continued Drug Use
Uncontrolled Drug Use

MAO-A

promoter polymorphism

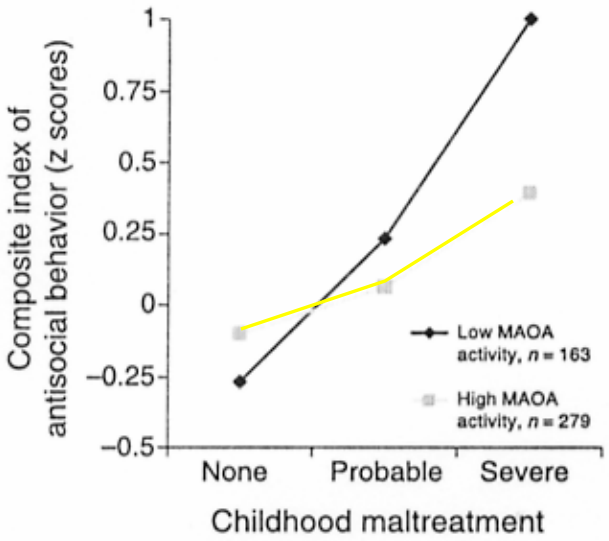
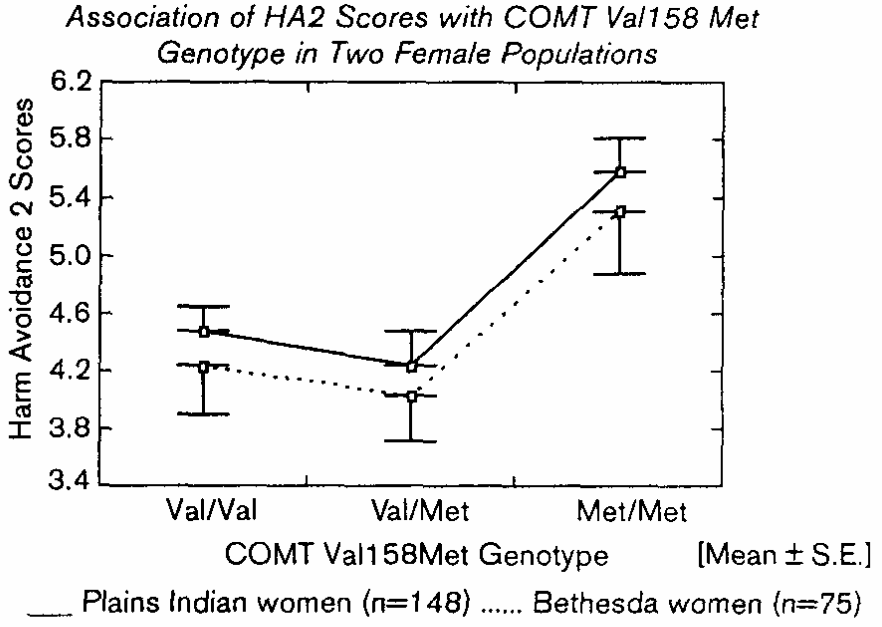


Fig. 1. Means on the composite index of antisocial behavior as a function of *MAOA* activity and a childhood history of maltreatment (27). *MAOA* activity is the gene expression level associated with allelic variants of the functional promoter polymorphism, grouped into low and high activity; childhood maltreatment is grouped into 3 categories of increasing severity. The antisocial behavior composite is standardized (z score) to a M = 0 and SD = 1; group differences are interpretable in SD unit differences (d).

Caspi et al., 2002

COMT

val158met polymorphism



Mean Tridimensional Personality Questionnaire HA2 scores (± standard error) by catechol-*O*-methyltransferase (COMT) Val158Met genotype for Bethesda women ($n = 75$, $P = 0.087$) and Plains Indian women ($n = 148$, $P = 0.031$).

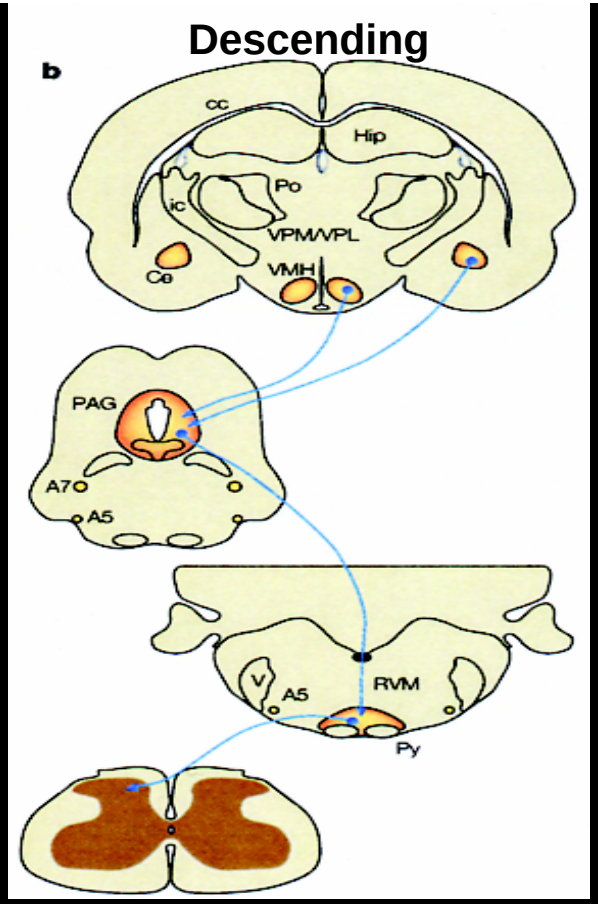
Enoch et al., 2003

Behavioral Risk Factors for Opiate Analgesic Requirements in Chronic Pain

- Previous or concurrent history of substance abuse
- Elements related to the ***characteristics of pain*** report:
  - Preoccupation with physical symptoms
  - Subjective lack of treatment efficacy
  - Higher levels of pain and higher variability of pain over time
- Elements related to ***emotional functioning*** during chronic pain:
  - Depression symptoms
  - Anxiety
  - Psychosocial distress
  - **"Pain Catastrophizing"** "a negative mental set brought to bear during actual or anticipated painful experience (Sullivan et al., 2004, Pavlin et al 2005)

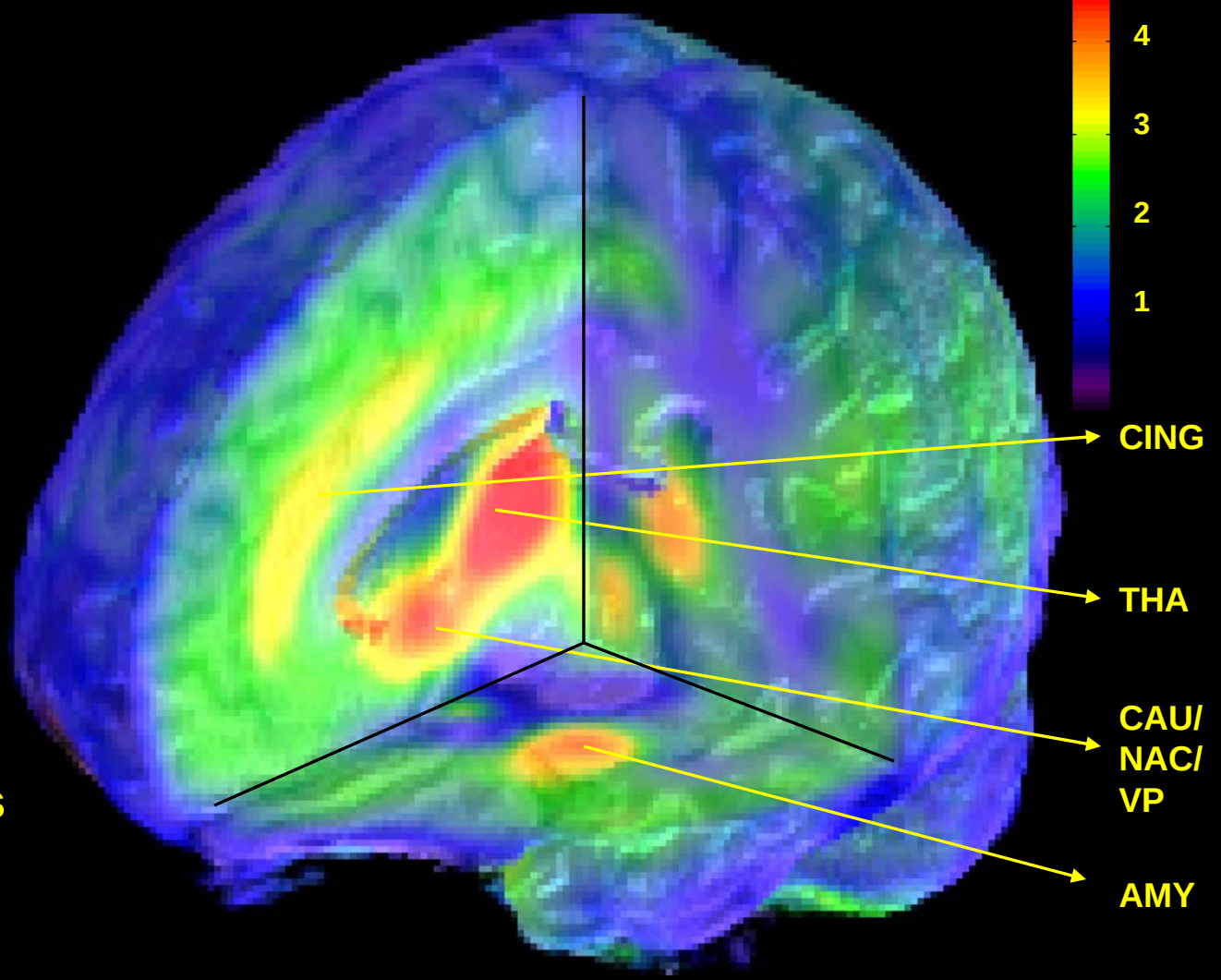
Behavioral Risk Factors for Opiate Analgesic Requirements in Chronic Pain: Neurobiological Mechanisms?

- **Higher levels of pain-associated disability, more negative emotional states:**
  - **Associated with lower levels of morphine analgesia (Burns and Bruehl 2005; Fillingim et al., 2005; Wasan et al., 2005)**
  - **Lower endogenous opioid system tone (as evidenced by challenges with the non-selctive opioid receptor antagonist naloxone) (Bruehl et al., 2004)**
- **Role of opiate-induced hyperalgesia ?**



CNS Inhibitory Controls

Mu Opioid Receptor-Mediated Neurotransmission



Distributed in pain regions but also "affective / motivational circuits" - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.

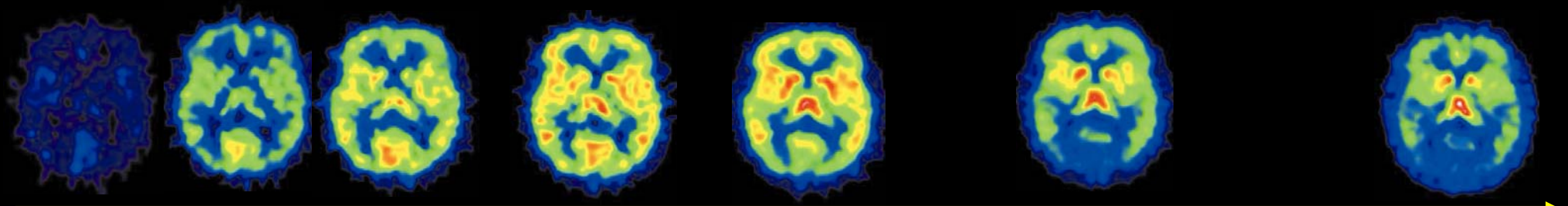
μ-Opioid Receptor Quantification with PET

Tracer Transport

(rCBF x Tracer Extraction)

Incorporation to

Specific Binding Sites

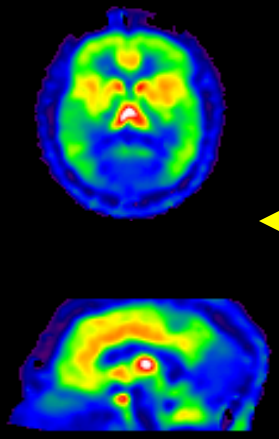


1 min **2 min** **3 min** **5 min** **10 min** **30 min** **70 min**

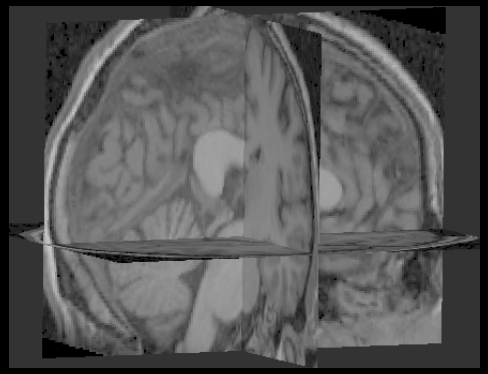
Data Analysis

Generation of Parametric Maps

e.g., Logan Plots (K_1, DVR)



Coregistration with Anatomical MRI

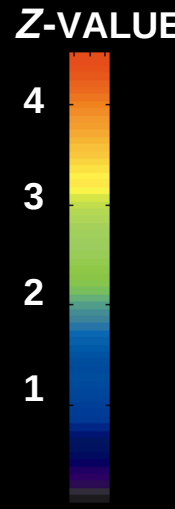


Non-Linear Anatomical Standardization

(ICBM Coordinates)

STATISTICAL PARAMETRIC MAPS OF SIGNIFICANCE

(SPM'99)



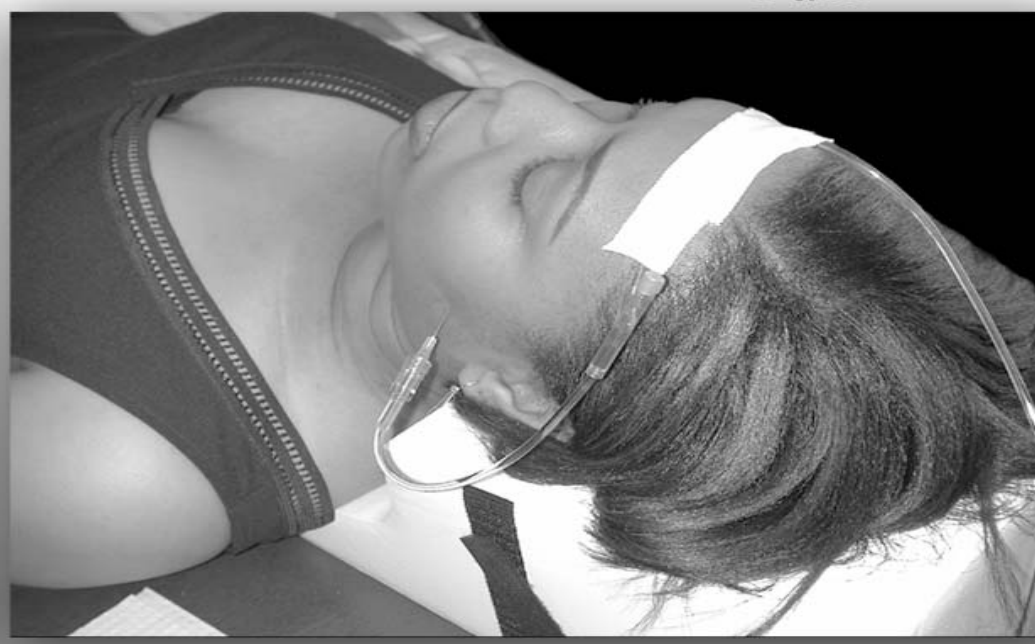
Mu Opioid Neurotransmission

- **Experimental evidence (animal models and humans) and transgenic models implicate them in:**
  - **Endogenous opioid analgesia and effects of opiate analgesics**
  - **Stress responses and stress-induced analgesia**
  - **Regulation of affiliative behavior and responses to novelty**
  - **Regulation of amygdala and nucleus accumbens-mediated responses to salient stimuli, including drugs of abuse**
  - **Thought to mediate placebo effects during expectation of analgesia**

- **Direction of modulation is typically suppressive of the relevant response (e.g., pain, stress, anxiety, …)**
- **Typically activated by stimuli that threatens the homeostasis of the organism (e.g., unpredictable stress, sustained, more rostral pain…)**

Saline-Control

Pain



Randomization

Saline-Control
0.9% Infusion-grade Saline

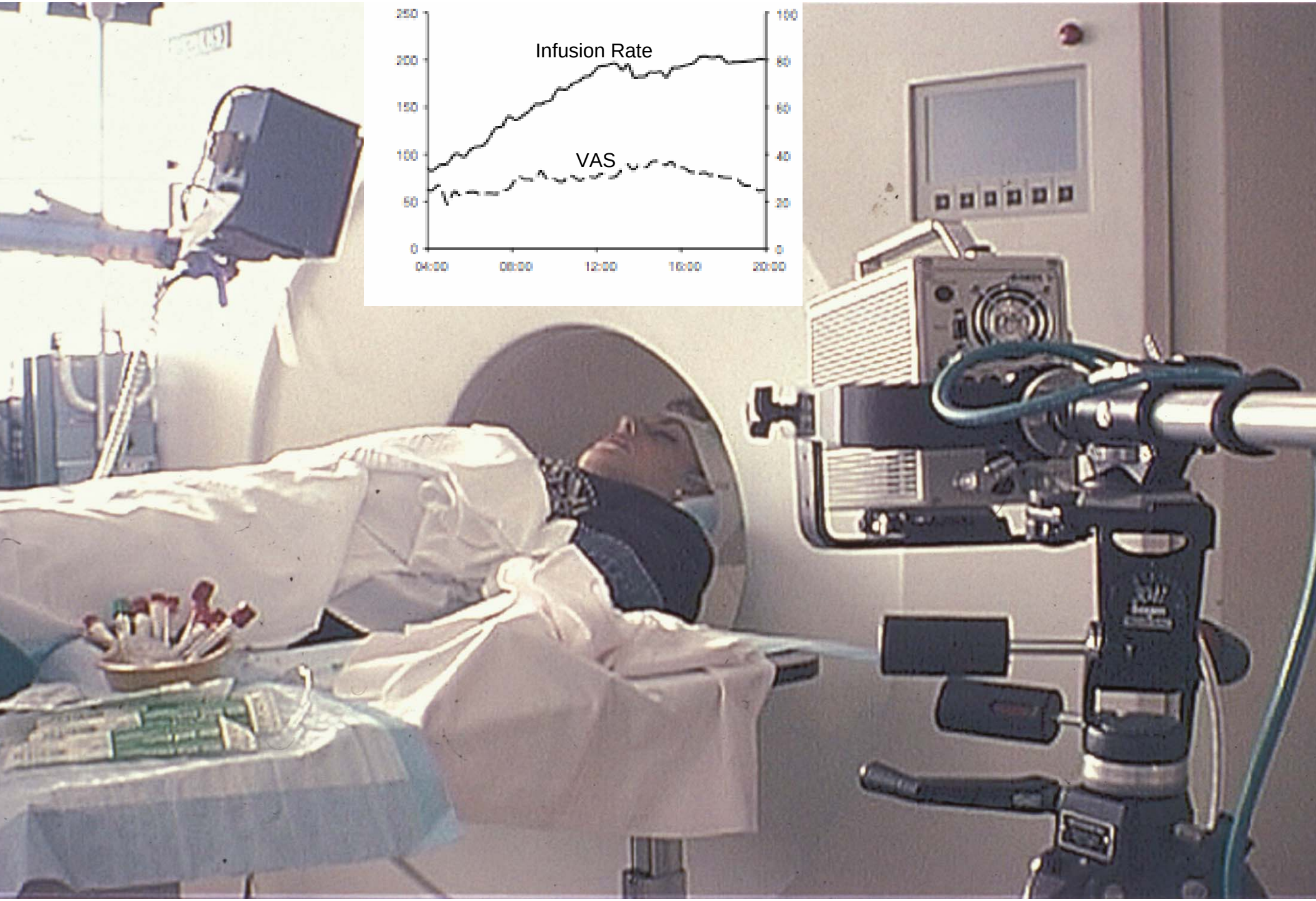
Washout

Pain
5% Infusion-grade Saline

Pain
5% Infusion-grade Saline

Washout

Saline-Control
0.9% Infusion-grade Saline

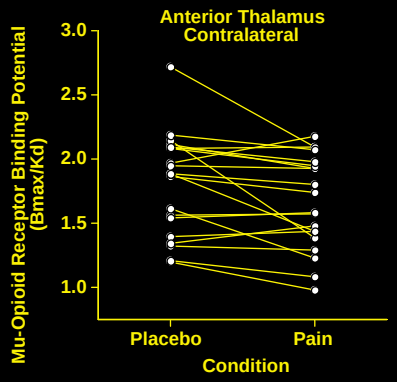

Infusion Rate
VAS
250
200
150
100
50
0
100
80
60
40
20
0
04:00
08:00
12:00
16:00
20:00

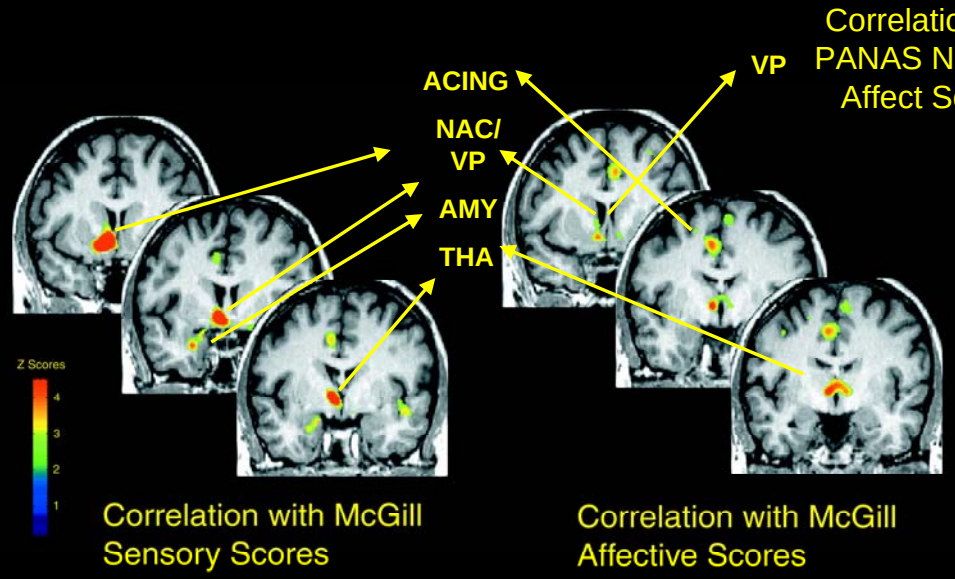
Previous Results

μ-Opioid System Suppression of Sensory and Affective Qualities of Pain

(Zubieta et al., Science 293:311, 2001)

Note the interindividual variations in binding and release

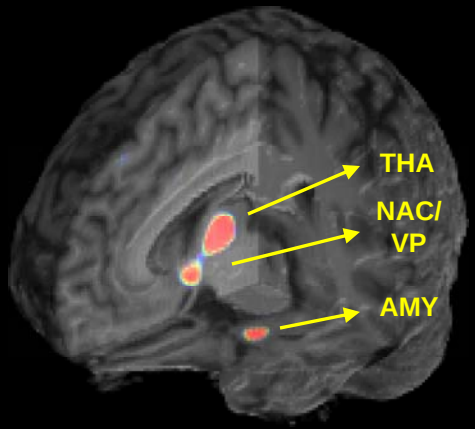




Correlation with PANAS Negative Affect Scores

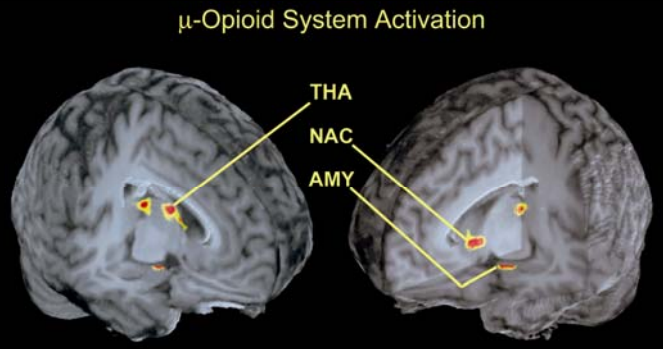
μ-Opioid Receptor Mediated Antinociception Differs in Men and Women

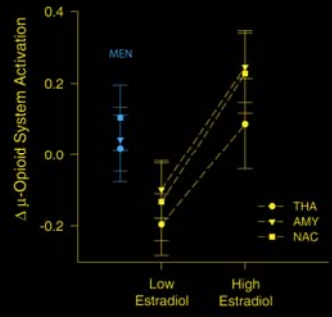
(Zubieta et al., J Neuroscience 22:5100, 2002)



Sex Differences: Regulation by Estradiol

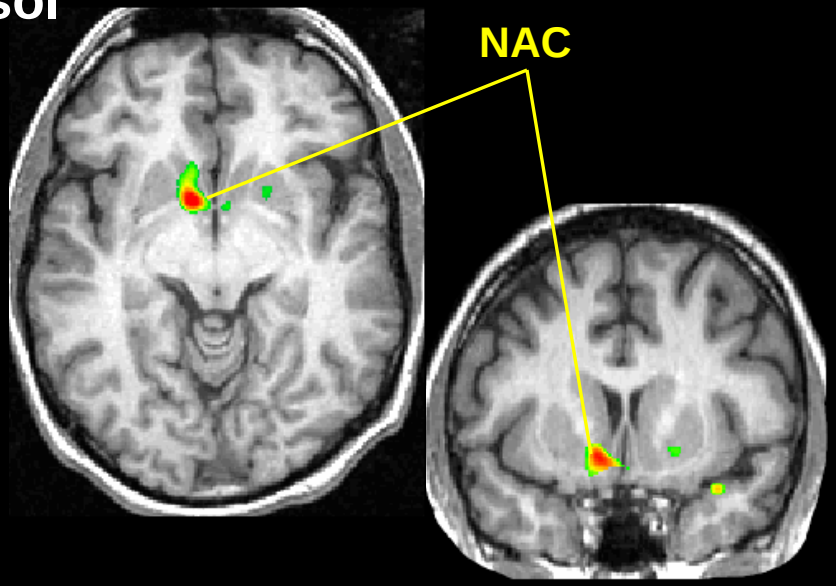
(Smith et al., J Neuroscience 26:5777-5785, 2006)



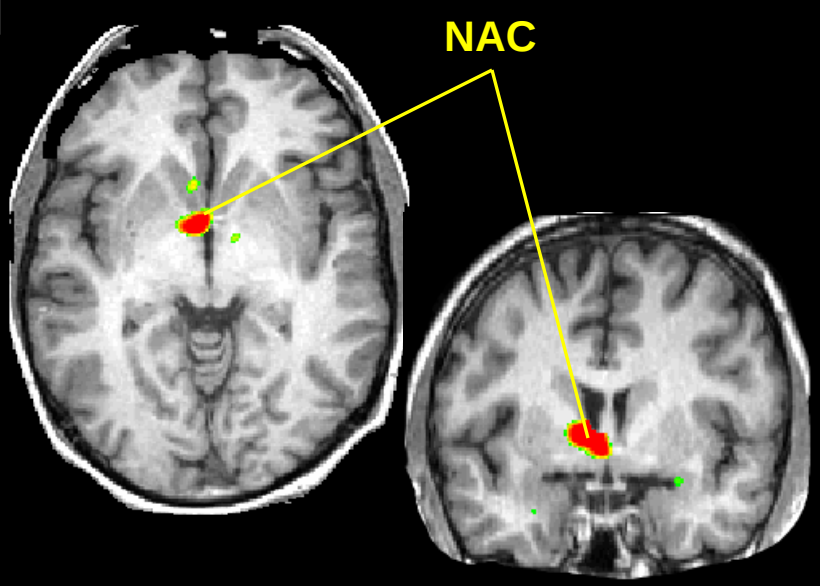


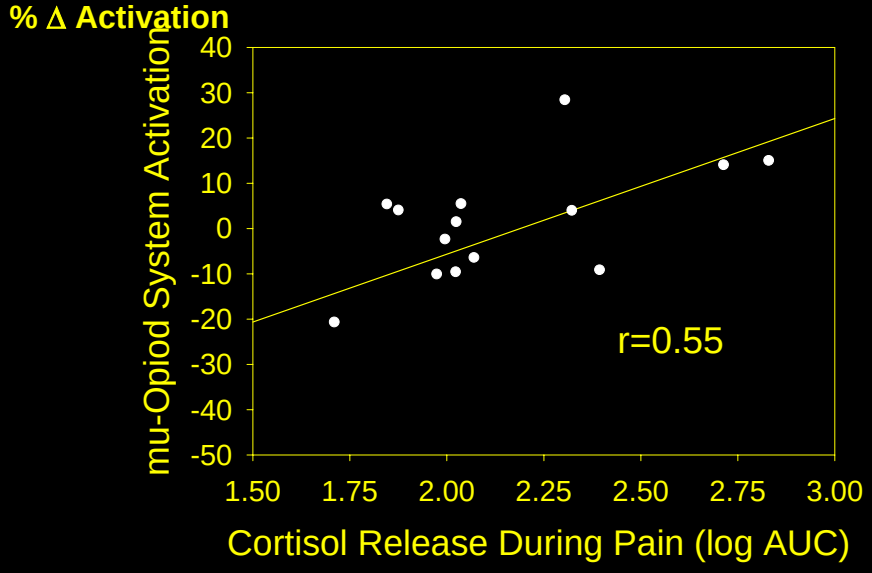
Parallel HPA and μ-Opioid System Activation

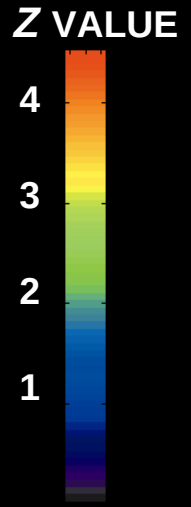
Cortisol

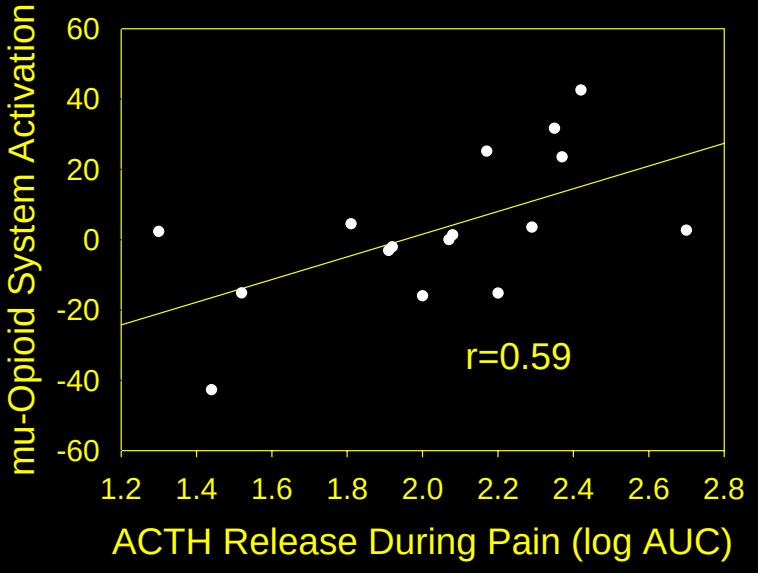


ACTH







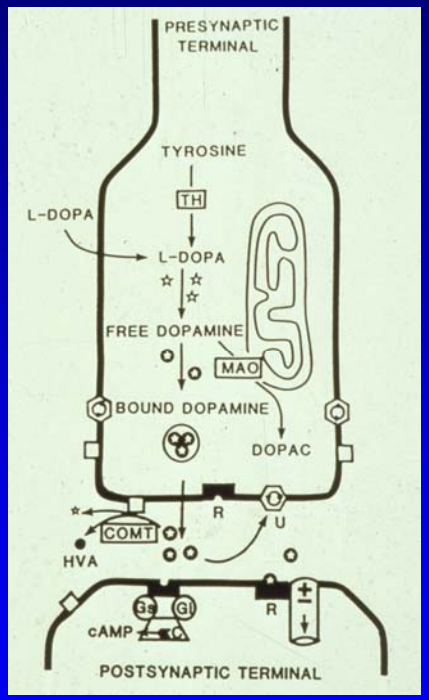


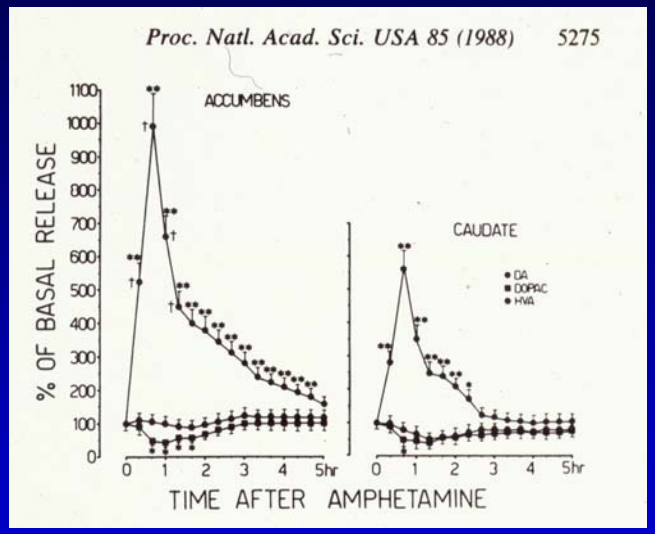
Heitzeg et al., 2003

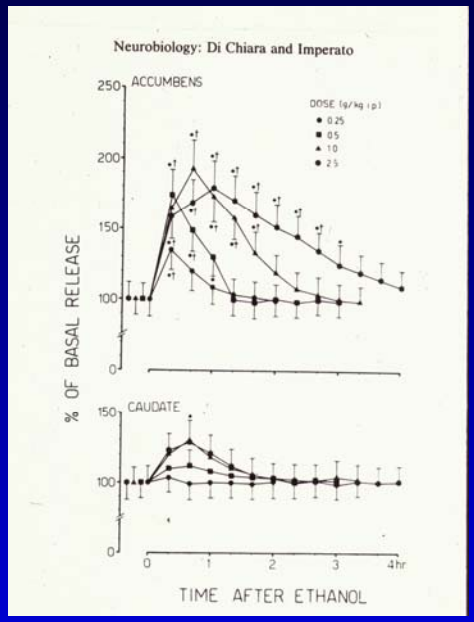
μ-Opioid System Suppression of Sensory and Affective Qualities of a Pain Stressor

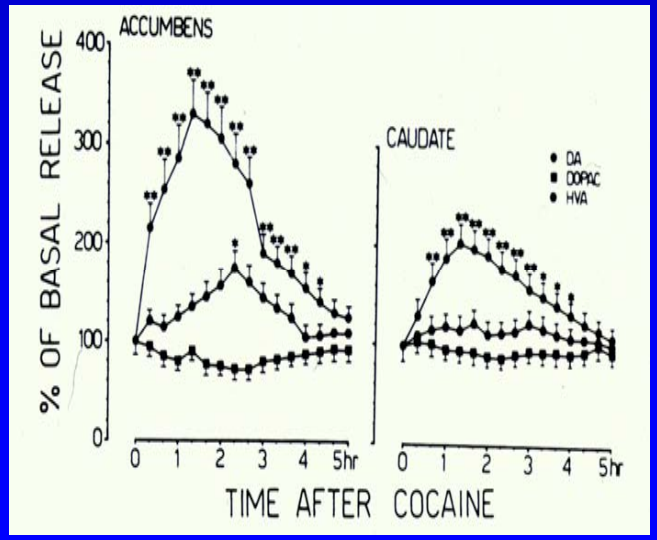
- During sustained painful stress, μ-opioid neurotransmission is activated to suppress responses
- This activation takes place in numerous regions (anterior cingulate, prefrontal cortex, insula, thalamus, ventral basal ganglia, amygdala, PAG)
- Some of these regions are involved in the perception and regulation of sensory aspects of pain (i.e., intensity and localization -thalamus, PAG-)
- …But also in the regulation of stimulus salience and cognitive-emotional integration -anterior cingulate, insula, nucleus accumbens, ventral pallidum, amygdala-)

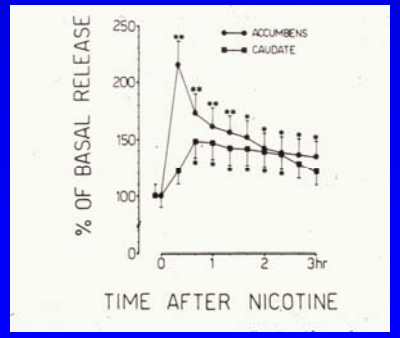
Effects of Drugs of Abuse on DA Neurotransmission

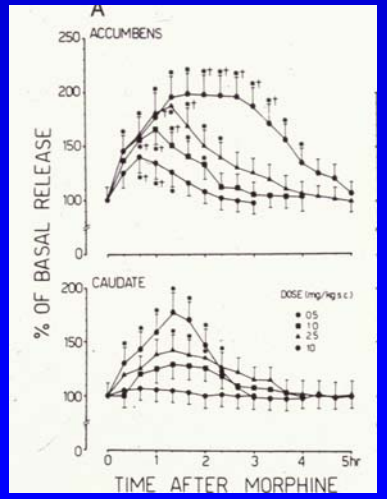


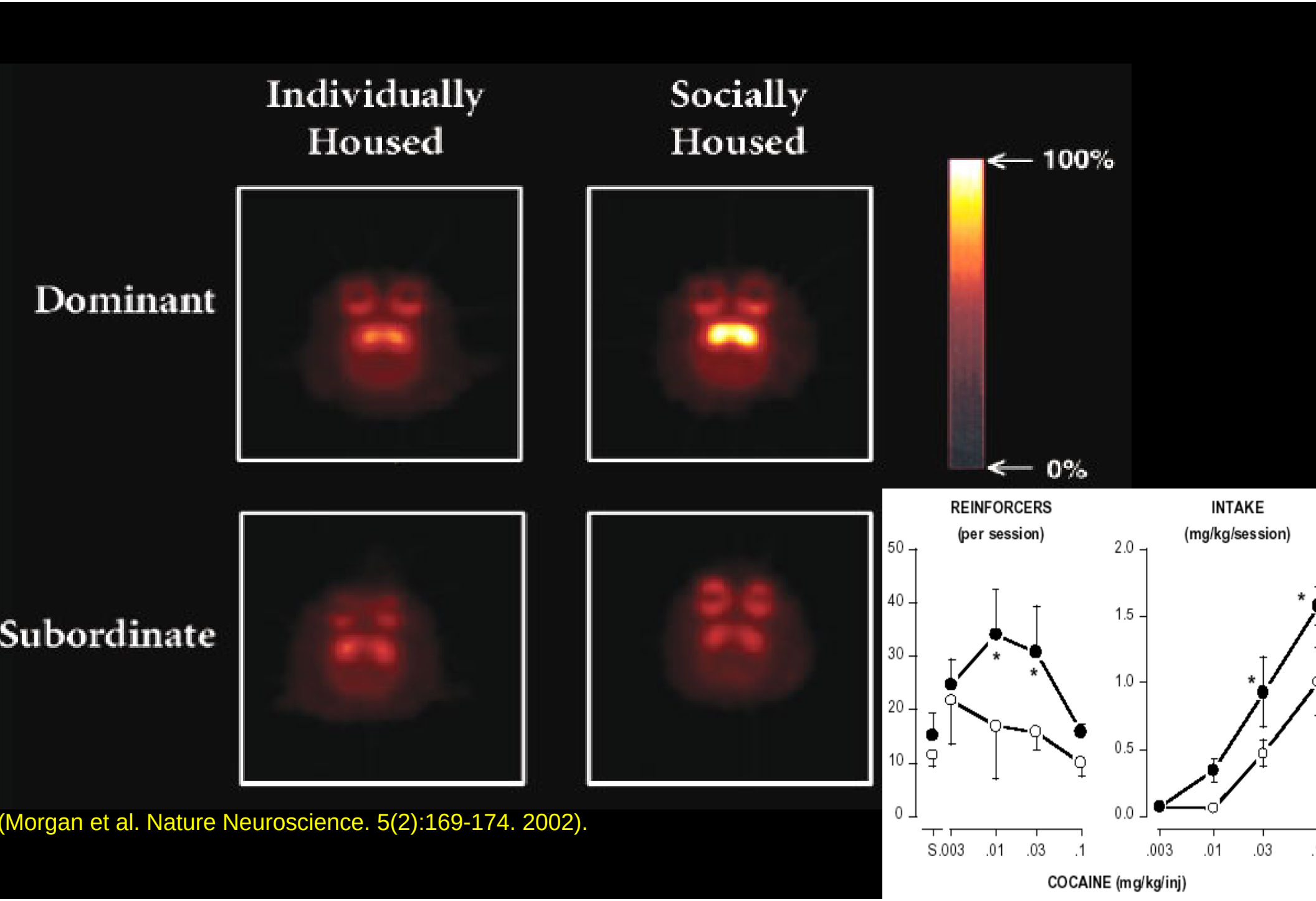












(Morgan et al. Nature Neuroscience. 5(2):169-174. 2002).

Basal Ganglia Dopamine and Pain

- In animal models, results equivocal depending on pain model (phasic, acute, or more sustained).
- Typically implicate D2 and not D1 receptors in the nigrostriatal pathway.
- Mesolimbic DA activated by more prolonged pain, not acute pain (pain as a stressor ?).
- Animal model data suggest an antinociceptive effect of dopamine in the ventral basal ganglia (blocked by D2 antagonists).
- In humans, however, D2 antagonists have been used in the treatment of chronic pain with success in RCT's. Interspecies differences?

Basal Ganglia Dopamine and Pain

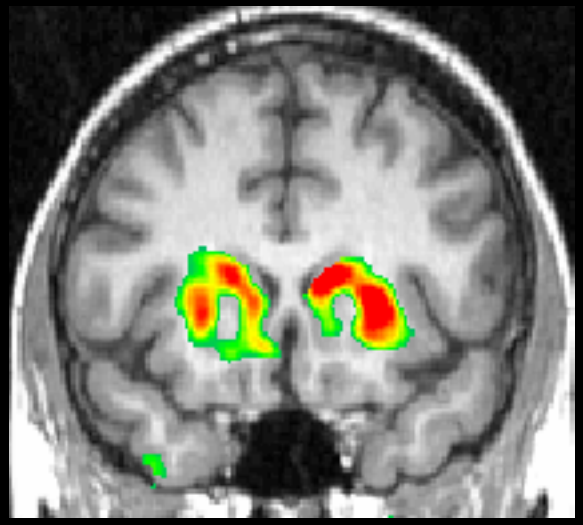
- DA D2 receptor concentrations in humans ([^{11}C]raclopride and PET) in putamen inversely correlated with cutaneous pain thresholds in healthy subjects and in atypical facial pain (Hagelberg et al., 2002, Pertovaara et al., 2004; Martikainen et al., 2005).

- Reduced [^{18}F]FDOPA uptake in idiopathic mouth burning syndrome, not in atypical facial pain (Jaaskelainen et al., 2001)

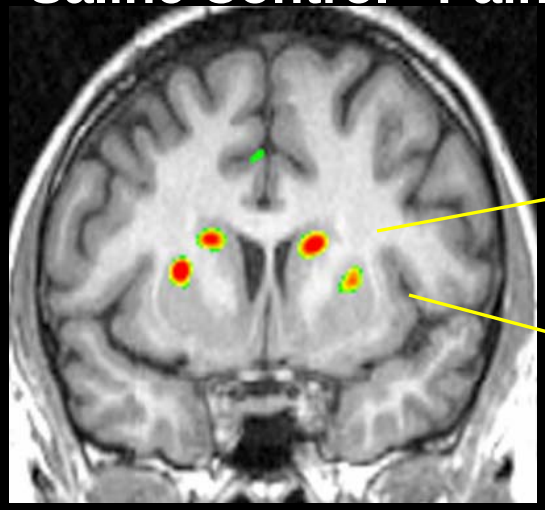
- Increases in putamen D2, but not D1 ([^{11}C]NNC-756) receptor concentrations in idiopathic mouth burning syndrome and atypical facial pain (Hagelberg et al., 2003)

Activation of DA D2 Neurotransmission During Sustained Pain: Healthy Controls

Overall Response: Baseline - Pain



Saline Control - Pain

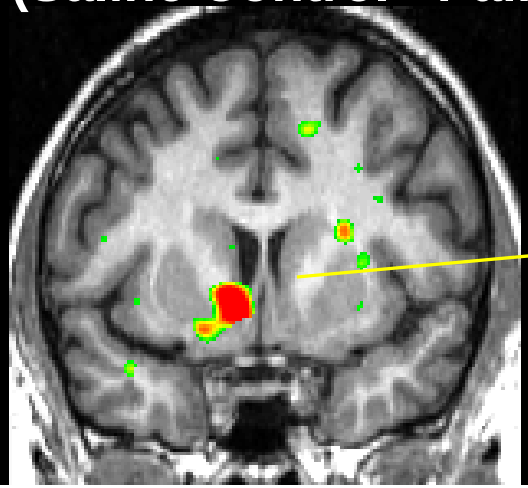


Correlations

- MPQ Sensory, r = 0.67
- VAS Intensity, r = 0.72

- MPQ Sensory, r = 0.76
- VAS Intensity, r = 0.79

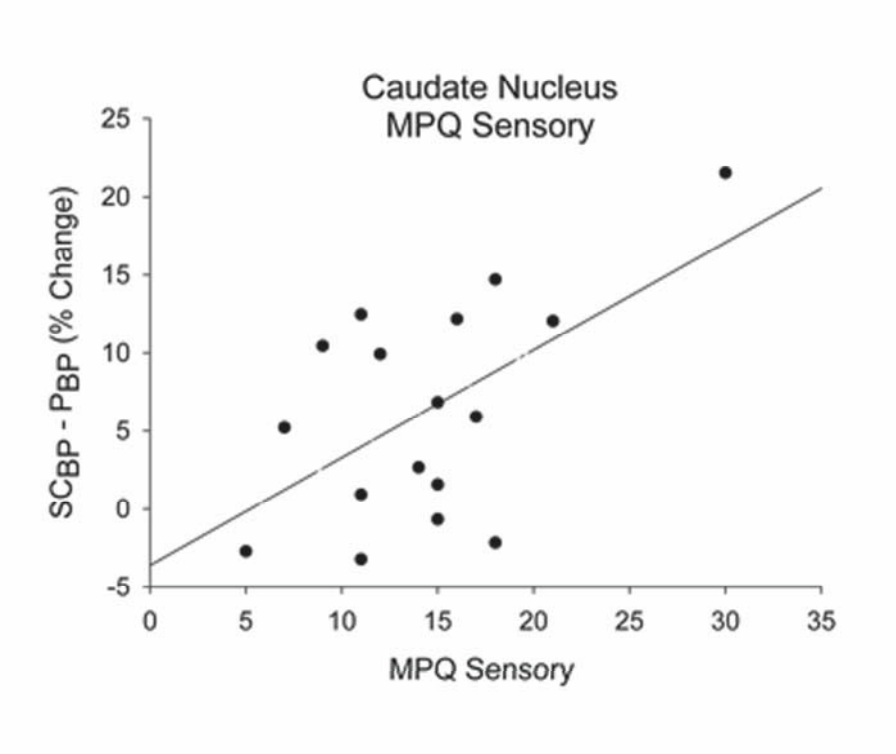
(Baseline - Pain) - (Saline Control - Pain)

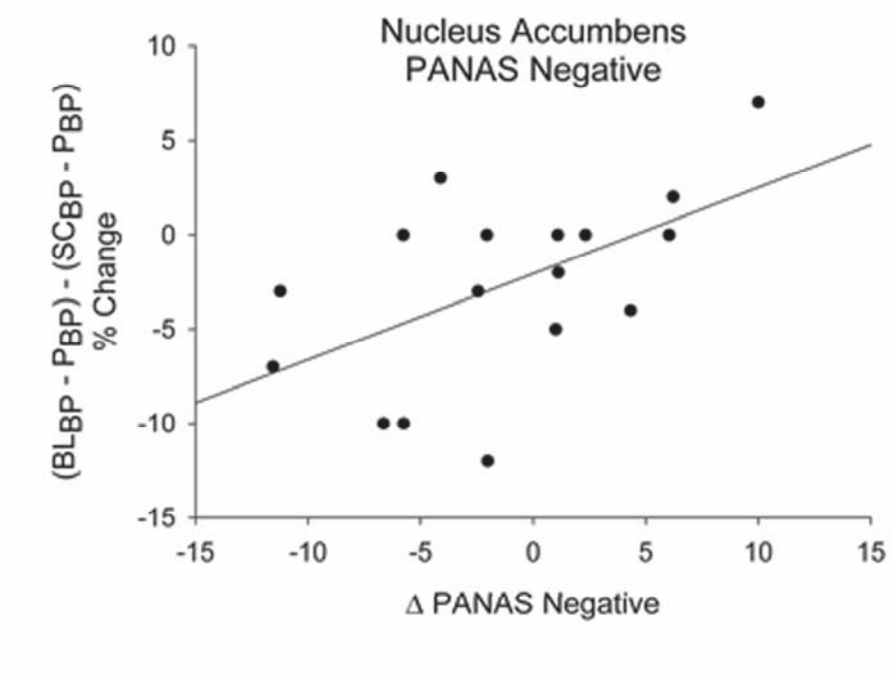


- PANAS negative, r = 0.53
- PANAS fear, r = 0.45

(Scott et al., J Neuroscience 26:10789-10795, 2006)

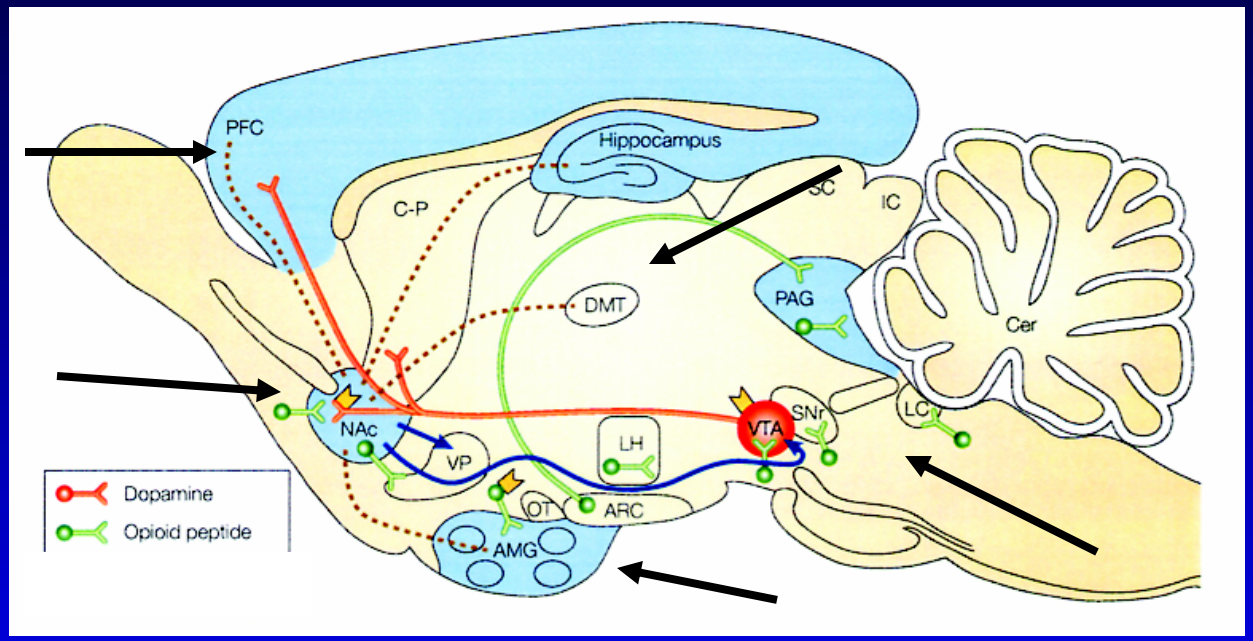
Activation of DA D2 Neurotransmission During Sustained Pain: Healthy Controls

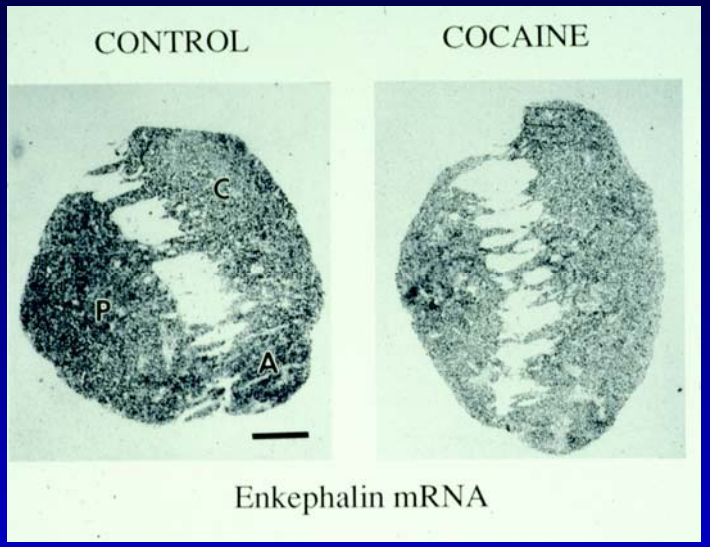


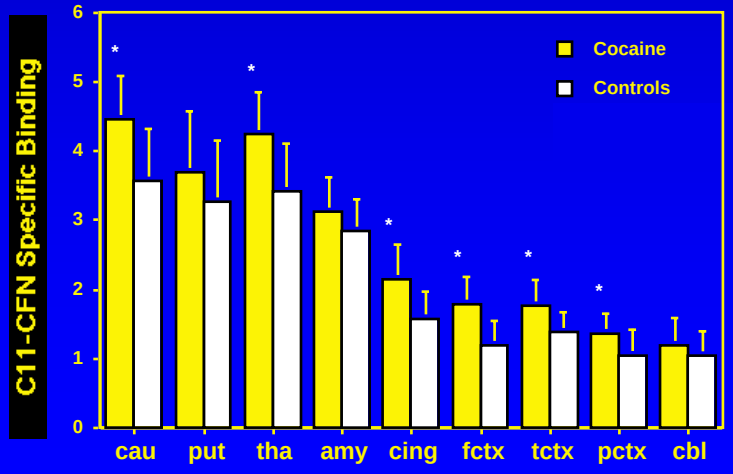


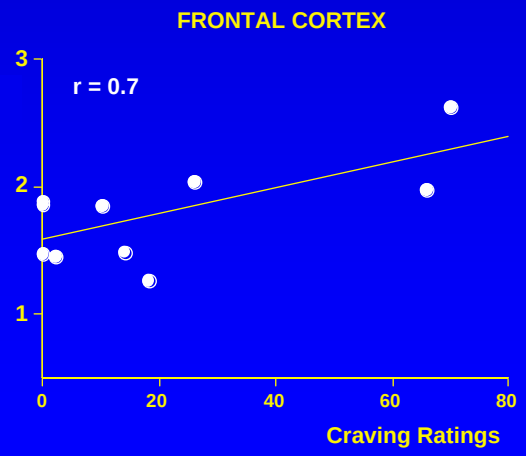
(Scott et al., J Neuroscience 26:10789-10795, 2006)

Monoamine- Opioid Interactions









Zubieta et al., Nature Medicine, 1996

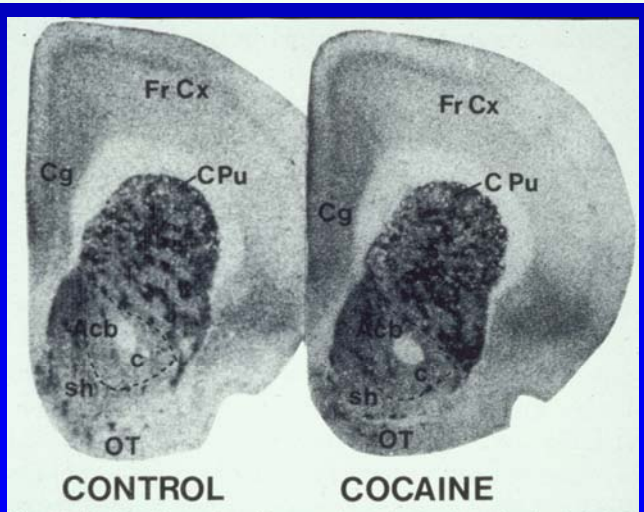
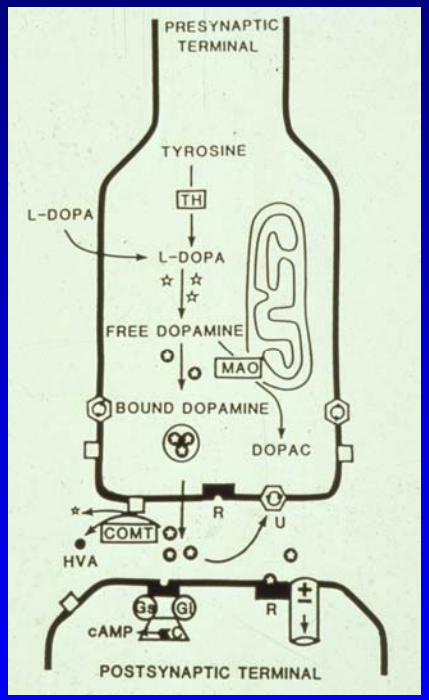


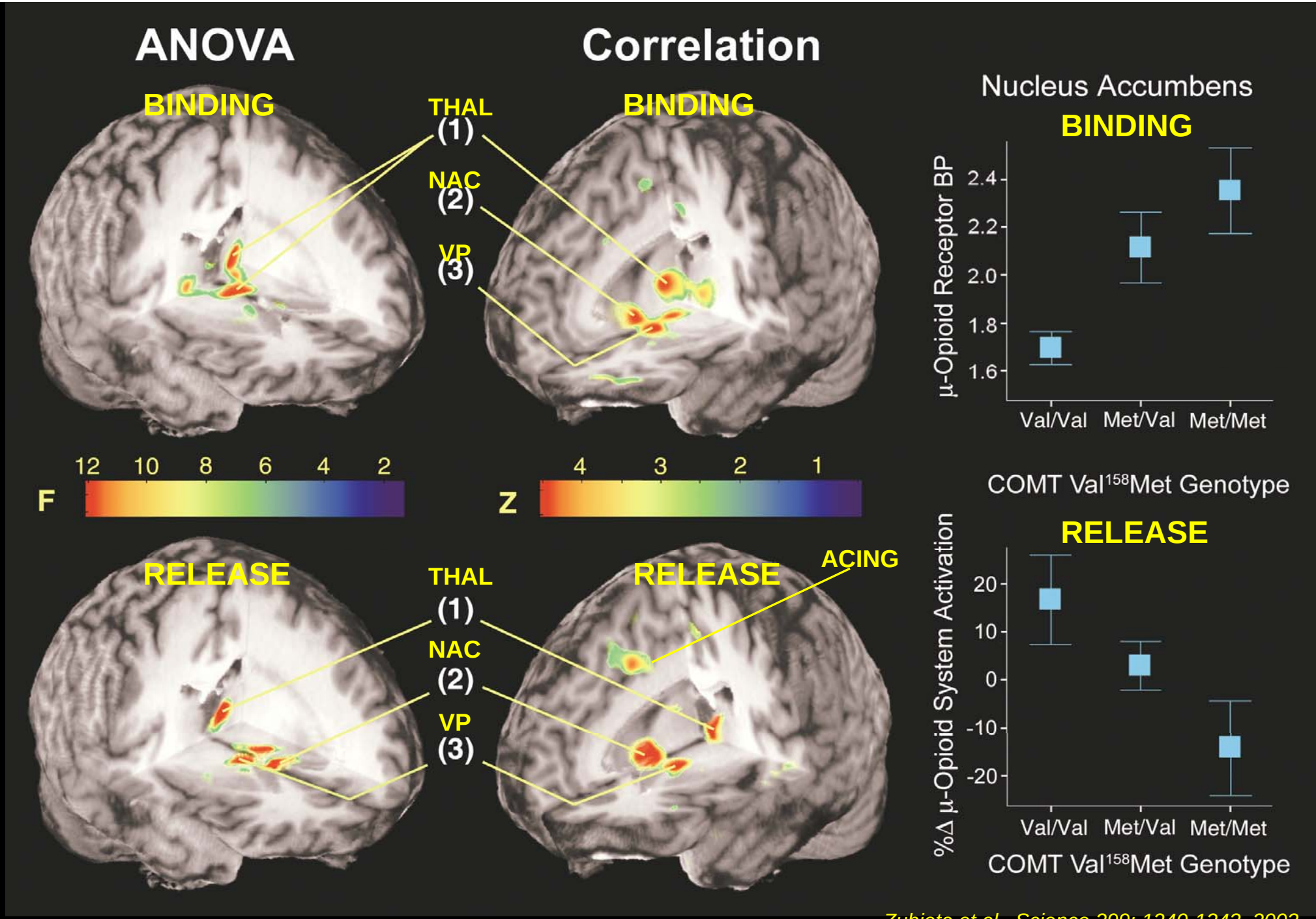
Fig. 1. Autoradiographs of coronal sections of rat brains labelled with [^{3}H]DAMGO from a saline-treated control rat (left) and a cocaine-treated (30 mg/kg/day) rat (right). Cocaine treatment resulted in increased binding in the caudate putamen, nucleus accumbens, and cingulate cortex. Acb = nucleus accumbens; c = core region of the nucleus accumbens; Cg = cingulate cortex; CPu = caudate putamen; FrCx = frontal cortex; OT = olfactory tubercle; sh = shell region of the nucleus accumbens.

COMT *Val*^{158}*Met* Polymorphism: Hypothesized Effects



- Reduction in enkephalin mRNA
- Increase in μ-opioid receptor binding
- PFCTX, striatopallidal pathway
- Models: psychostimulant administration, D2 agonists
- *Met*^{158}*met COMT alleles ?*

- Increase in enkephalin mRNA
- Reduction in μ-opioid receptor binding
- Models: 6OHDA, D2 antagonists
- *Val*^{158}*val COMT alleles ?*



Zubieta et al., Science 299: 1240-1243, 2003

Psychophysiological responses: Correlations with COMT activity

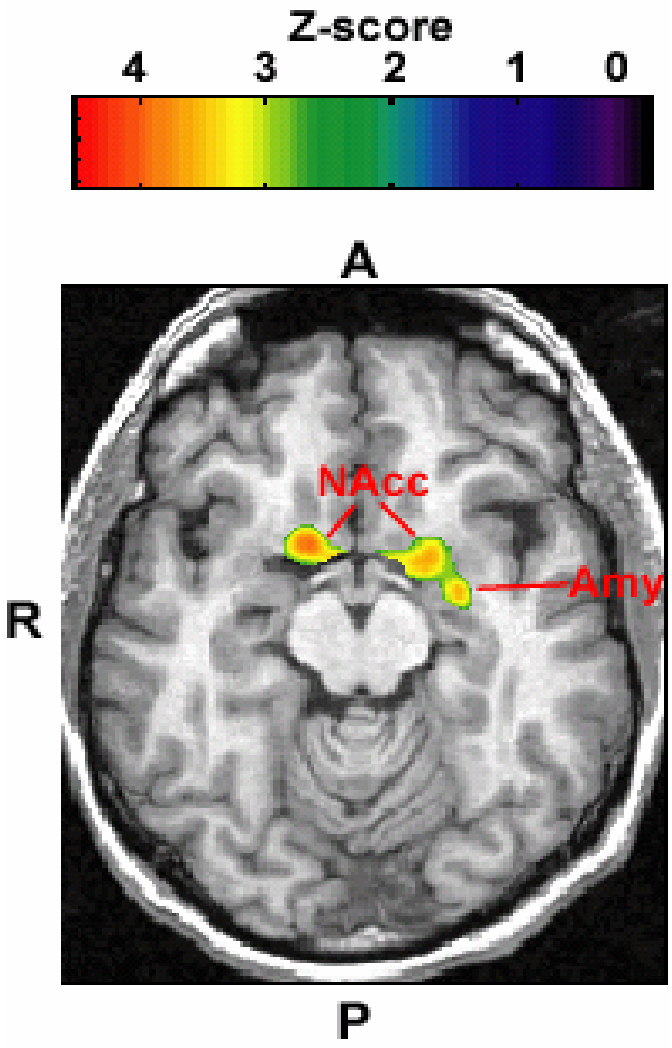
COMT Enzyme Activity Genotype	High *Val/Val* (n = 3)	Intermediate *Met/Val* (n =22)	Low *Met/Met* (n =4)	r
Age	24.7 ± 2.5	24.5 ± 2.1	24.0 ± 3.3	
Education (years)	17.3 ± 1.5	17.5 ± 2.3	17.8 ± 3.2	
Acute Pain (15 sec) VAS Intensity	50.0 ± 35.0	47.4 ± 28.0	47.5 ± 8.7	0.04
Sustained Pain (0-20 min) VAS	34.2 ± 6.6	37.3 ± 8.8	39.5 ± 7.3	- 0.15
Average Infusion rate (µl/min)				
0-10 min	72.3 ± 78.2	80.4 ± 54.9	45.3 ± 23.9	0.29
10-20 min	188.4 ± 60.6	149.7 ± 56.7	130.1 ± 67.7	0.36 *
Rating - Stimulus Ratio				
MPQ Sensory	11.1 ± 5.9	16.2 ± 8.6	25.9 ± 19.4	- 0.29
MPQ Affective	0.3 ± 0.5	2.6 ± 2.9	5.1 ± 7.2	- 0.32 †
MPQ Total	17.8 ± 11.5	25.6 ± 14.0	42.9 ± 37.8	- 0.24
PANAS Negative Affect (Pain)	2.1 ± 3.6	7.5 ± 8.5	16.0 ± 19.2	- 0.37 *

Zubieta et al., Science 299: 1240-1243, 2003

Dysregulation of Opioid Mechanisms in Chronic Pain

- **Opioid receptor concentrations reduced in rheumatoid arthritis and trigeminal neuralgia in humans ([^{11}C]diphrenorphine and PET), reversed after 3 to 12 weeks of pain relief** (Jones et al., 1994, 1999).
- **Similar results in post-stroke pain and one case of pontine infarction** (Willoch et al., 1999, 2004)
- **Secondary to activation of endogenous opioid neurotransmission, receptor downregulation or both?**
- **Relationship with clinical pain report ?**

Dysregulation of Opioid Mechanisms in Chronic Pain: Fibromyalgia



- N = 11 women diagnosed with fibromyalgia
- N = 11 matched controls
- fMRI with thumb pressure
- PET with [^{11}C]carfentanil

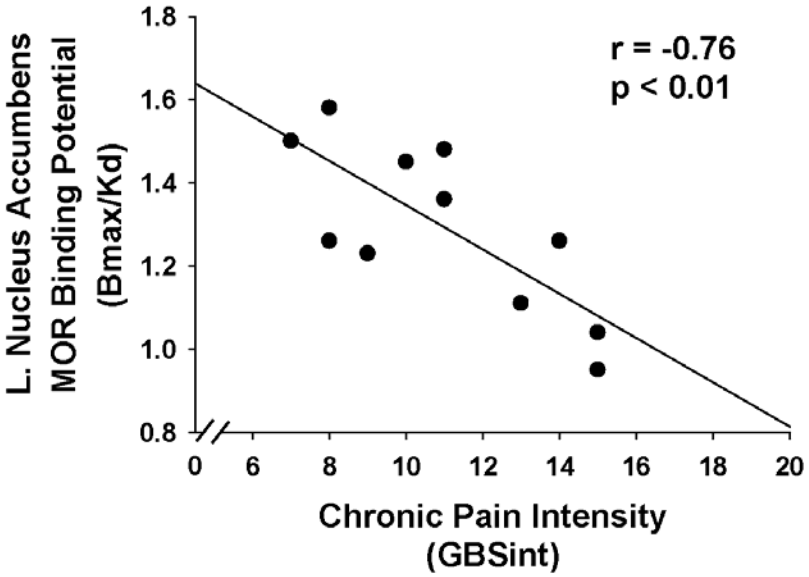
	L NAC	R NAC	L AMY
size mm^3	82	208	257
Z	3.8	4.4	3.6
p-value	<0.0005	< 0.0005	<0.0005
%Δ BP	25±13	21±15	23±17

Harris et al., under review

Dysregulation of Opioid Mechanisms in Chronic Pain: Fibromyalgia

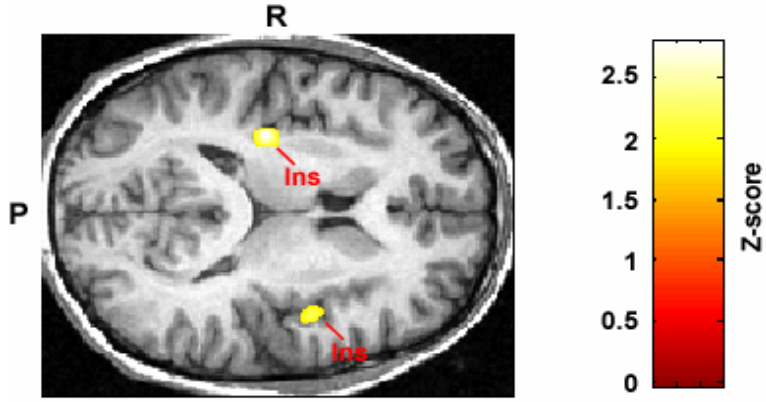
A

Relationship with Clinical Pain



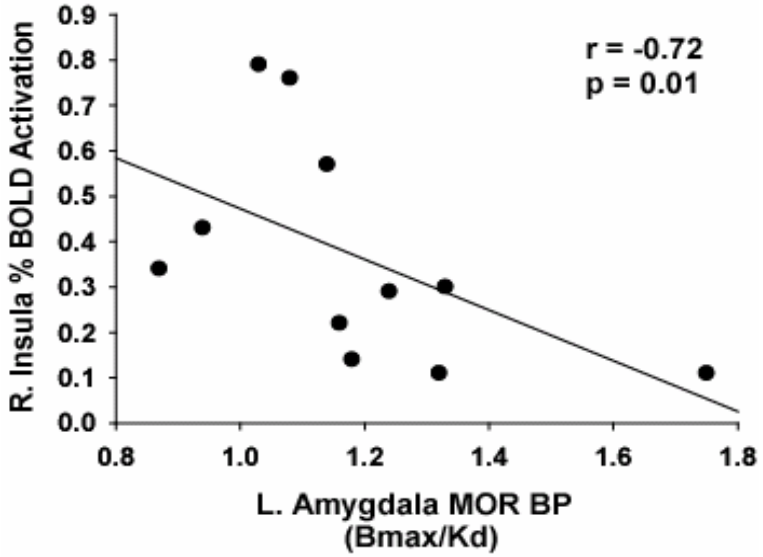
B

BOLD -fMRI Response to 2kg/cm² pressure



C

Correlation AMY μ-ORs and INS BOLD response



Harris et al., under review

Conclusions

- **Two neurochemical systems centrally implicated in the effects of opiates and drugs of abuse, the endogenous opioid/μ-opioid receptor and the dopaminergic/D2 receptor, are also involved in responses to sustained pain in humans.**
  - **Think of pain as a physical and emotional stressor**
- **Substantial interindividual variability is observed in the function of these systems at the level of pain report and affective responses to pain.**
  - **Subject to genetic and gonadal steroid influences**
- **Evidence of DA D2 and μ-opioid system dysregulation in various forms of chronic pain.**
  - **Reducing initial risk for opiate abuse in chronic pain patients ?**
  - **Effect of individual variability in chronic pain samples ?**
  - **Implications for opiate and other drug abuse risk not explored.**

The Team …

RADIOCHEMISTRY
Michael A. **Kilbourn**, PhD

RADIOTRACER KINETIC MODELING
Robert A. **Koeppe**, PhD

REPRODUCTIVE ENDOCRINOLOGY
Yolanda R. **Smith**, MD, MS

NEUROENDOCRINOLOGY
Elizabeth A. **Young**, MD

fMRI
Douglas **Noll**, PhD
Luis **Hernandez**, PhD

STATISTICAL MODELS
Thomas **Nichols**, PhD

WARPING METHODS
Charles R. **Meyer**, PhD

GENOTYPING
David **Goldman**, MD
Margit **Burmeister**, PhD

PAIN MODELS
Christian S. **Stohler**, DDS, PhD

PROGRAMMING
Heng **Wong**, PhD

NURSING
Kathie **Singer**, RN
Virginia M. **Weinberg**, RN, MS

JUNIOR FACULTY
Mary M. **Heitzeg**, PhD
Scott **Langenecker,** PhD
Carol **Persad**, PhD
Richard **Harris**, PhD

POST-DOCTORAL FELLOWS
Alison **Berent-Spillson**, PhD
David **Hsu**, PhD
Tal **Shafir**, PhD
Brian **Mickey**, MD
(Research Track Resident)
Yunhai **Qiu**, MD, PhD

GRADUATE STUDENTS
Tiffany M. **Love**
David J. **Scott**
Catherine **Evans**

RESEARCH ASSOCIATES
Christine **Egnatuk**, BS
Wendy **Yau**, BS

… and the technologists of the PET Center and fMRI Laboratory

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