Nonhuman Primate Models of Drug Addiction

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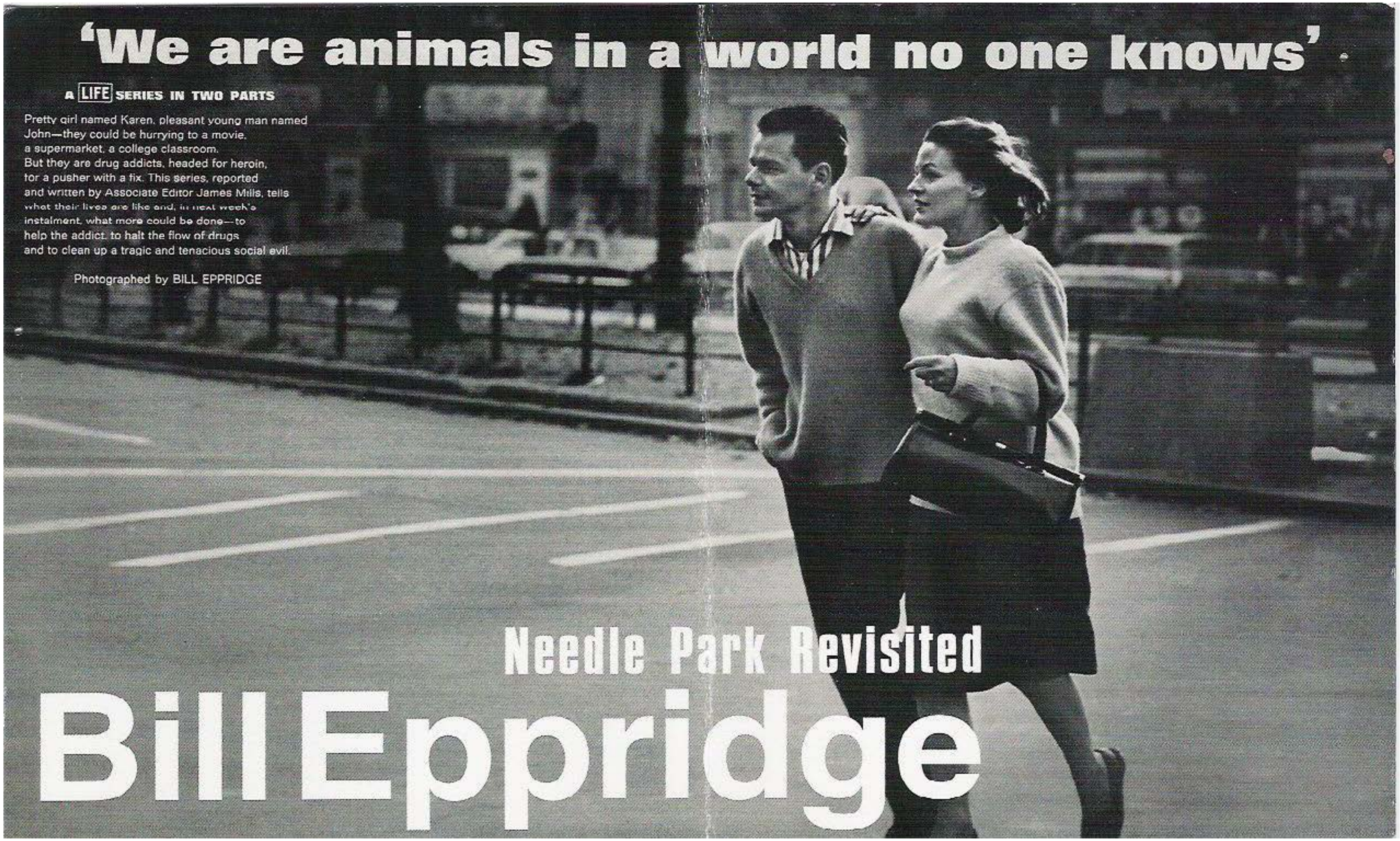
"Any disease - including drug addiction - depends for its spread on the three necessities: a susceptible individual, an infecting substance and an environment where the two can meet." James Mills, LIFE magazine, March 5, 1965



Cost to Society - $720 Billion/year

2016 Monitoring the Future Study
Prevalence of Past Year Drug Use – 12th Graders

		Treatment Medications
Alcohol	55.6	Campral, Revia
Marijuana	35.6	**None**
Narcotics	4.8	Methadone, Suboxone
Cigarettes (past 30 days)	10.5	NRT, Chantix, Welbutrin
Amphetamines	**6.7**	**None**
MDMA (Ecstasy)	**2.7**	**None**
Cocaine	**2.3**	**None**
Ritalin	**1.2**	**None**

Over 47 million used an illicit or non-prescribed drug

What We Study in Animal Models

Vulnerability

Genetic
Environmental

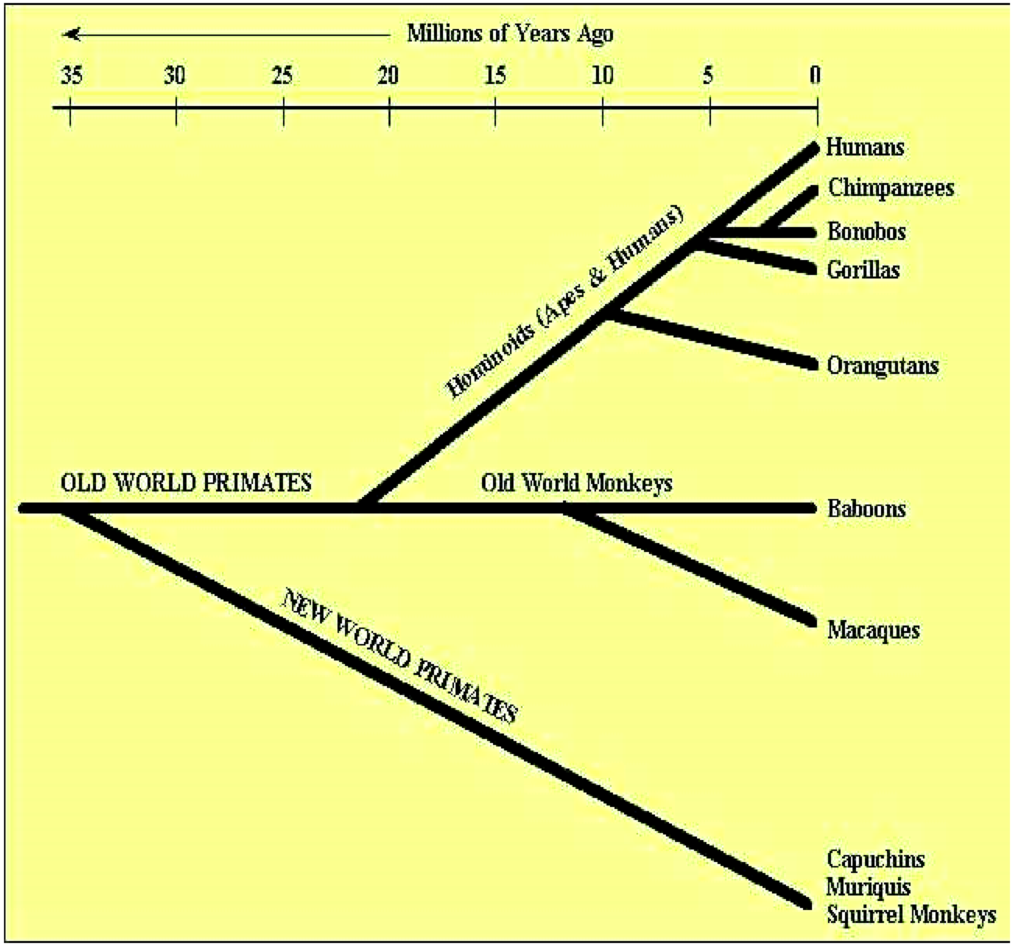
Maintenance

Co-morbidity
Alternative
Reinforcers

Treatment

Behavioral
Drug Tx

Why Use Nonhuman Primates?



M. mulatta
Rhesus monkey

M. fascicularis
Cynomolgus monkey

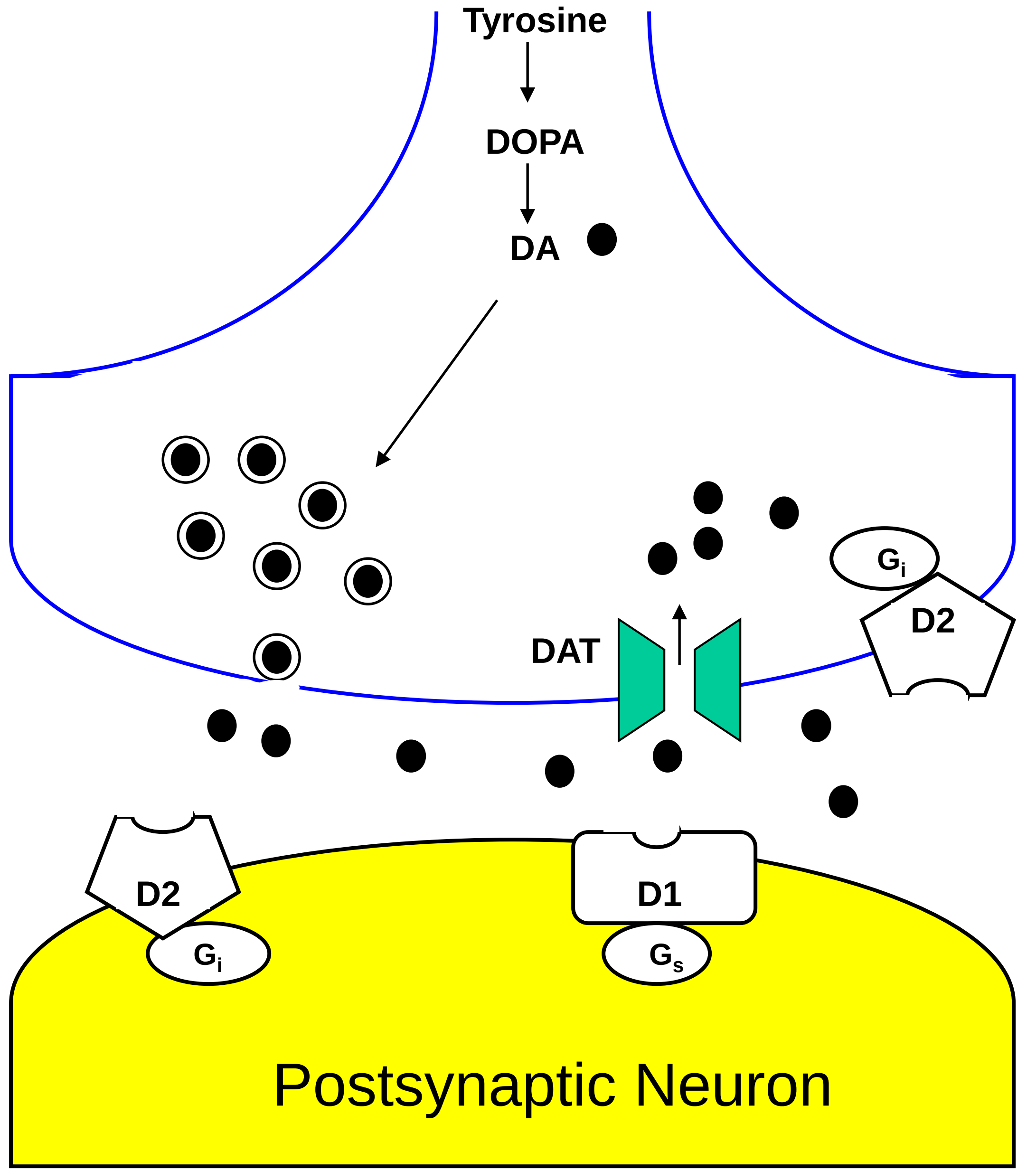
- phylogenetic, neuroanatomical neurohormonal similarity
- within-subjects designs
- longitudinal studies
- social hierarchies
- complex behaviors
- females: ~ 28 day menstrual cycle

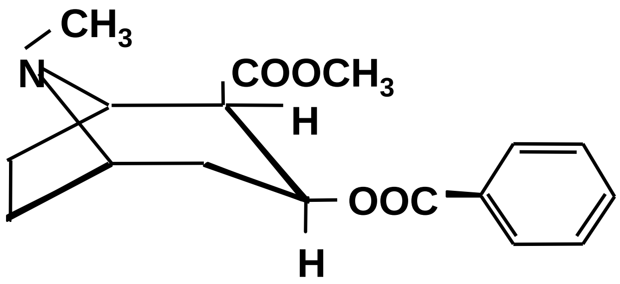
From Living Links, Yerkes National Primate Research Center, Emory University

Premise: Individual Differences Are a Hallmark of SUD

History
Env. Context
Sex
Social variables

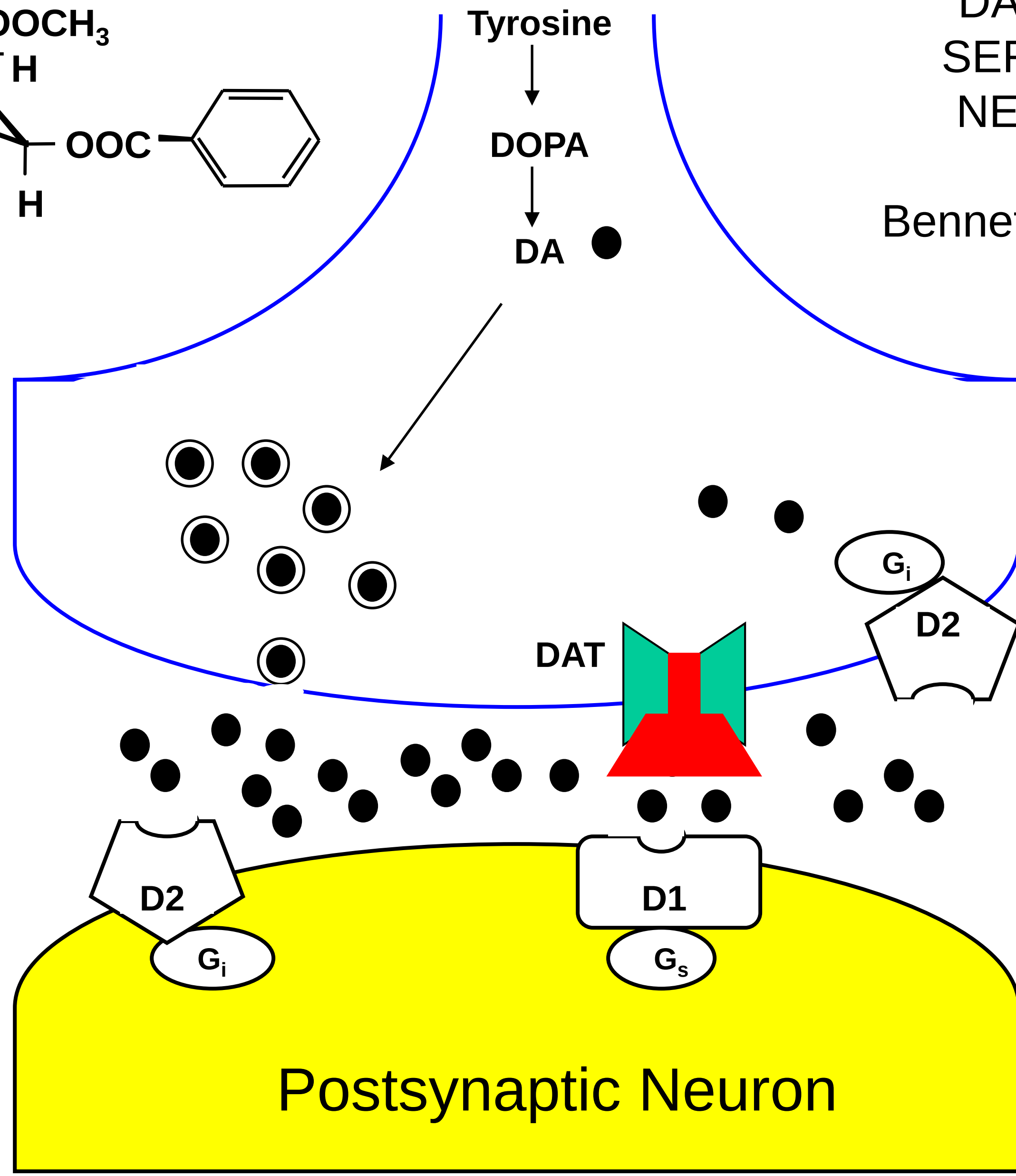
- **Similar cocaine histories**
- **Similar current patterns of self-administration**


Tyrosine
DOPA
DA
DAT
G$_i$
D2
D2
G$_i$
D1
G$_s$
Postsynaptic Neuron

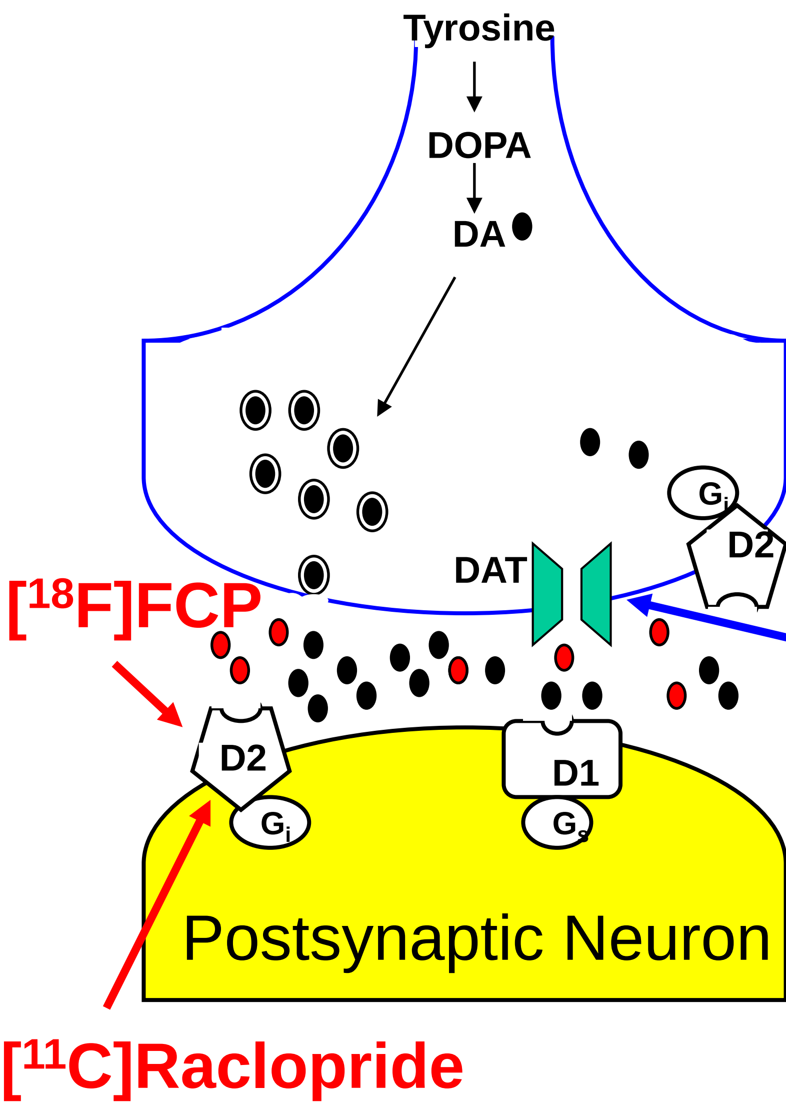


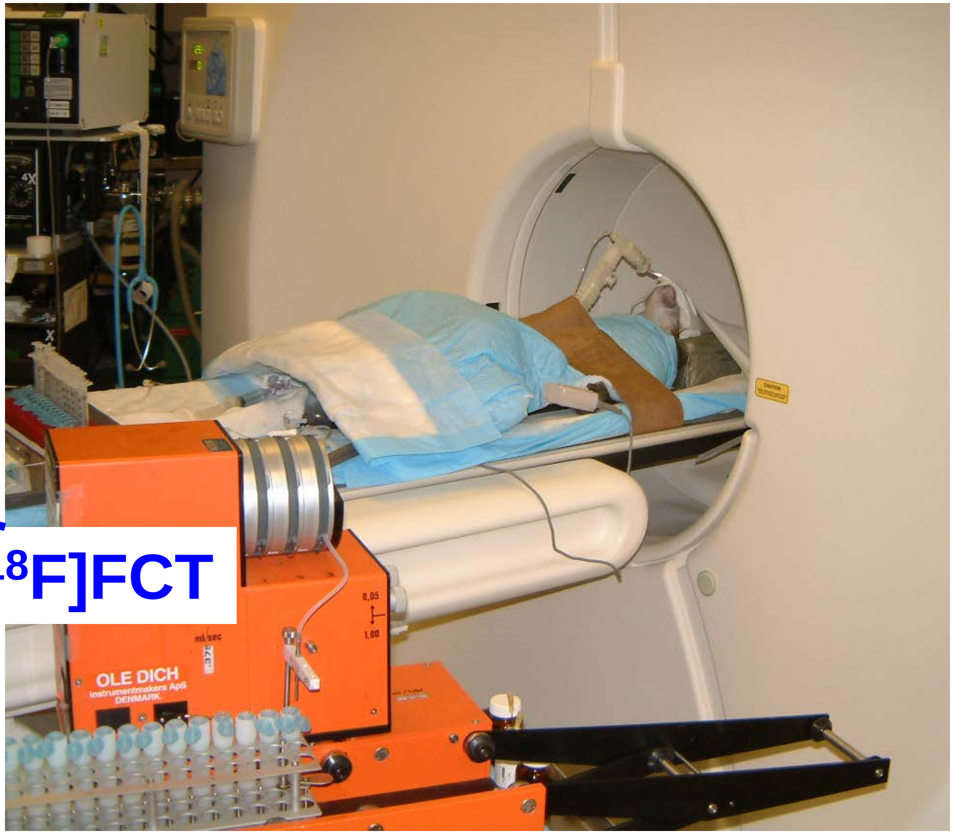
Monoamine reuptake blocker
DAT: 173 nM
SERT: 302 nM
NET: 404 nM

Bennett *et al.* (1995)



PET Imaging Protocol





[^{18}F]FDG [^{11}C]DASB

[^{11}C]PHNO [^{11}C]Nicotine

Outline

Vulnerability

Baseline D2-like receptors
- **Individually housed males**
- **Socially housed males and females**

Maintenance

D2-like receptor changes
- **Long-term consequences of cocaine exposure**

Abstinence

Treatment
- **Personalized medicine approach**
- **Non-pharmacological interventions**

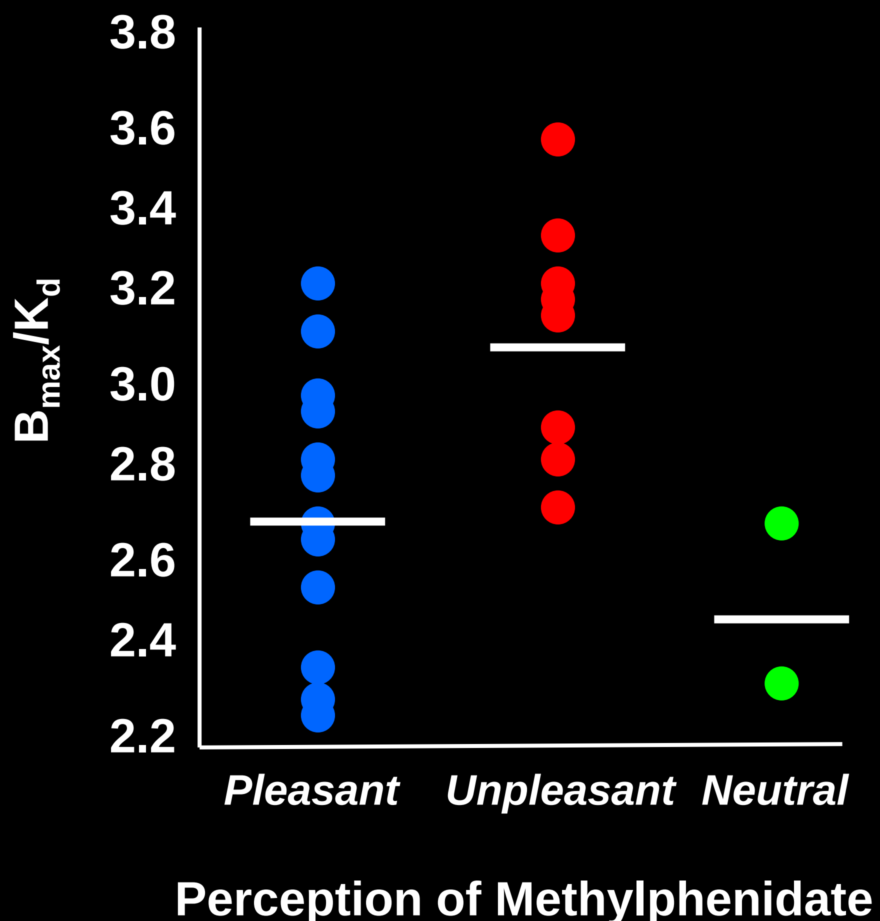
Vulnerability

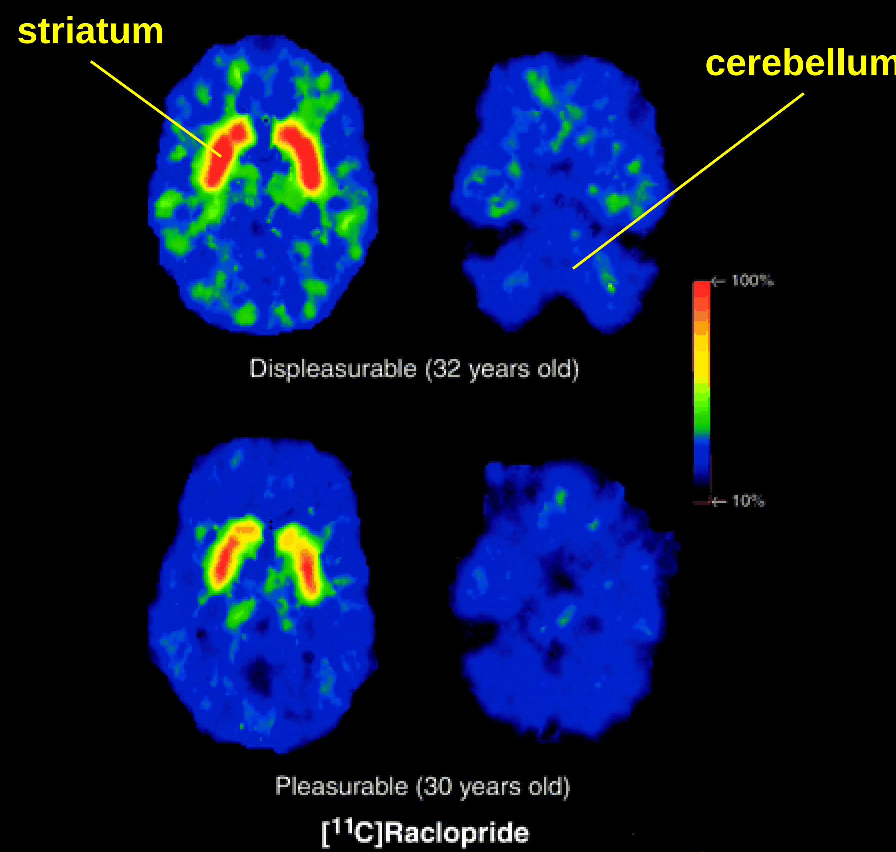
Table 24–2 Dependence among Users 1990–1992

AGENT	EVER USED* %	ADDICTION %	RISK OF ADDICTION %
Tobacco	75.6	24.1	31.9
Alcohol	91.5	14.1	15.4
Illicit drugs	51.0	7.5	14.7
Cannabis	46.3	4.2	9.1
Cocaine	16.2	2.7	16.7
Stimulants	15.3	1.7	11.2
Anxiolytics	12.7	1.2	9.2
Analgesics	9.7	0.7	7.5
Psychedelics	10.6	0.5	4.9
Heroin	1.5	0.4	23.1
Inhalants	6.8	0.3	3.7

Data from Anthony et al. (1994); cf: O'Brien (2011)

D2/D3 Receptor Availability and Sensitivity to Stimulants

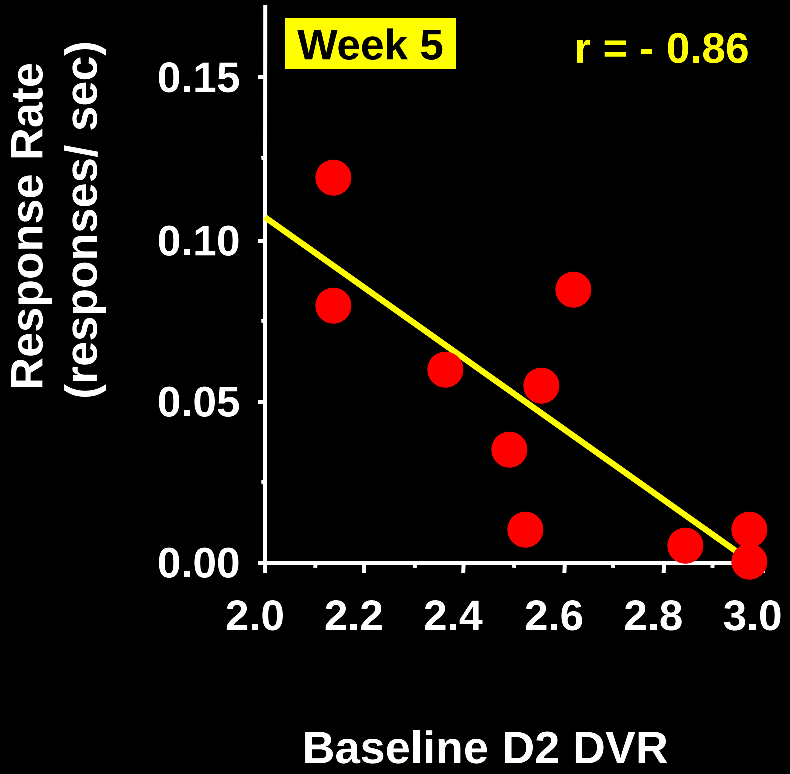




Volkow et al. (1999) *Am J Psychiatry* 156: 1440-43

Does D2/D3R Predict Rates of Cocaine SA?

PET scan



Significant correlation between D2 DVR and response rate

Nader et al. (2006) *Nature Neuroscience* 9: 1050-1056.

Social Housing: a model of chronic stress & enrichment

Cynomolgus macaques

Social rank based on outcomes of agonistic encounters (i.e. fights)

Most Dominant 1

2

3

4 Most Subordinate

Dominants:
> greater access to resources
> groomed more by others

Subordinates:
> receive more aggression
> spend more time alone
> are groomed less often

Vulnerability to Cocaine Use

What are some of the neurobiological, neuroendocrine and behavioral predictors and consequences of cocaine use?

Individually-housed (n=20)

PET imaging

Hormonal profiles

Locomotor reactivity

Socially-housed (n=4/group)

PET imaging

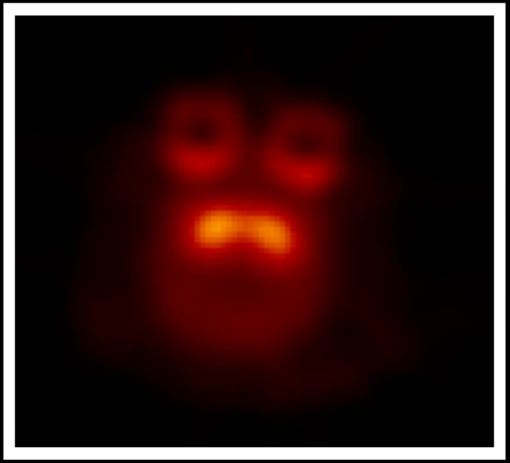
Hormonal profiles

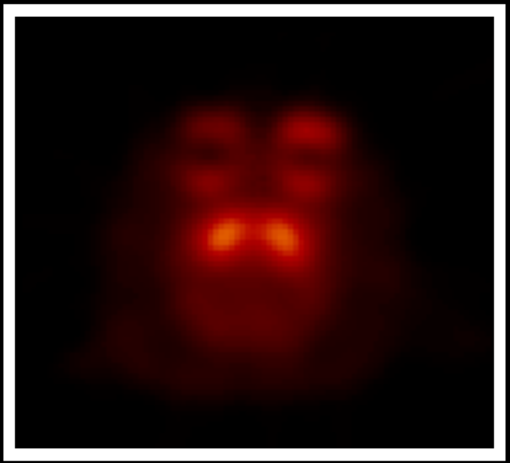
Social behavior

Cocaine self-administration

PET imaging

Individually Housed





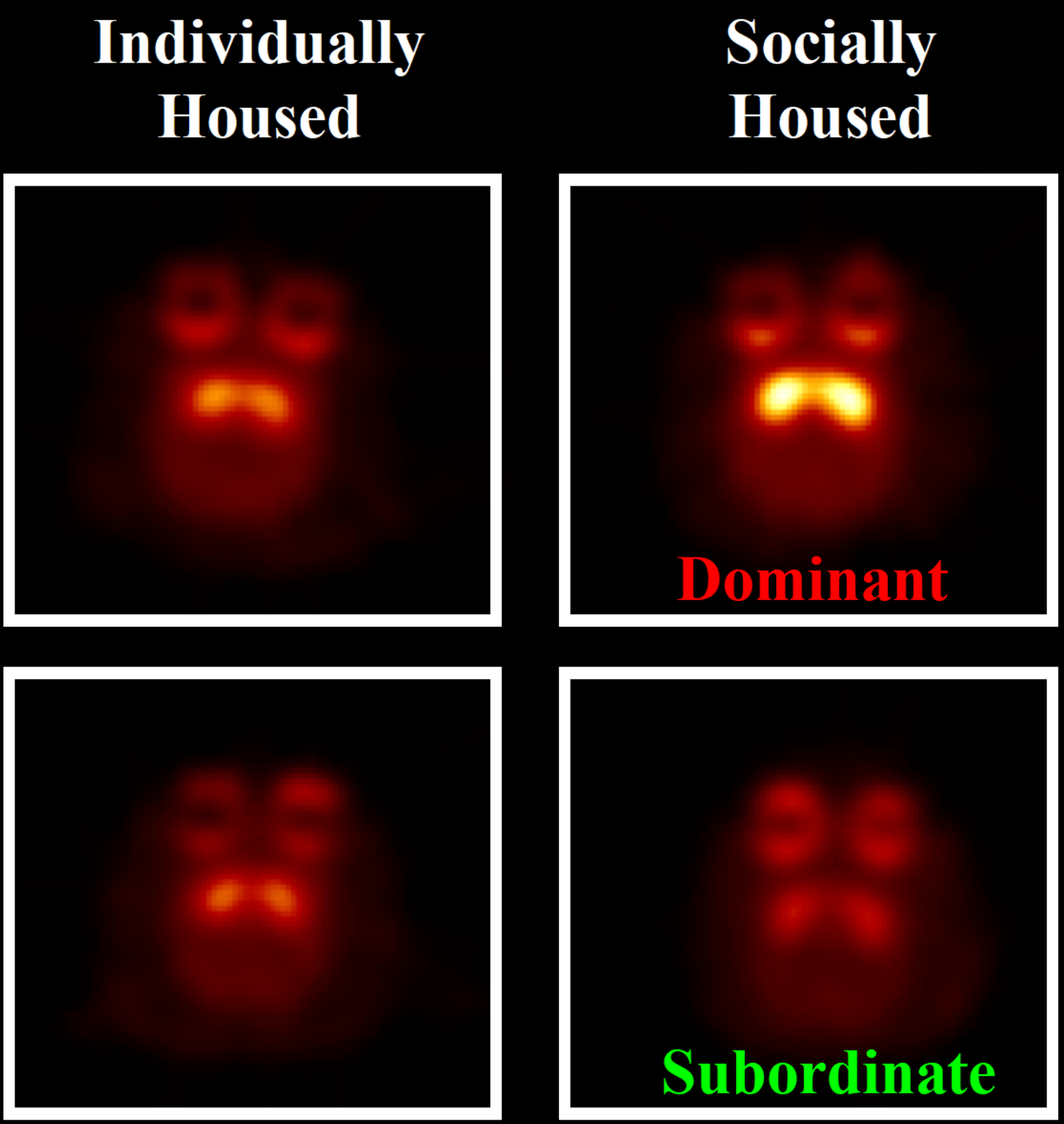
D2 receptor levels are not trait variables for social rank

Eventual dominant monkey
2.51 ± .12 (n=5)

Eventual subordinate monkey
2.49 ± .04 (n=5)

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

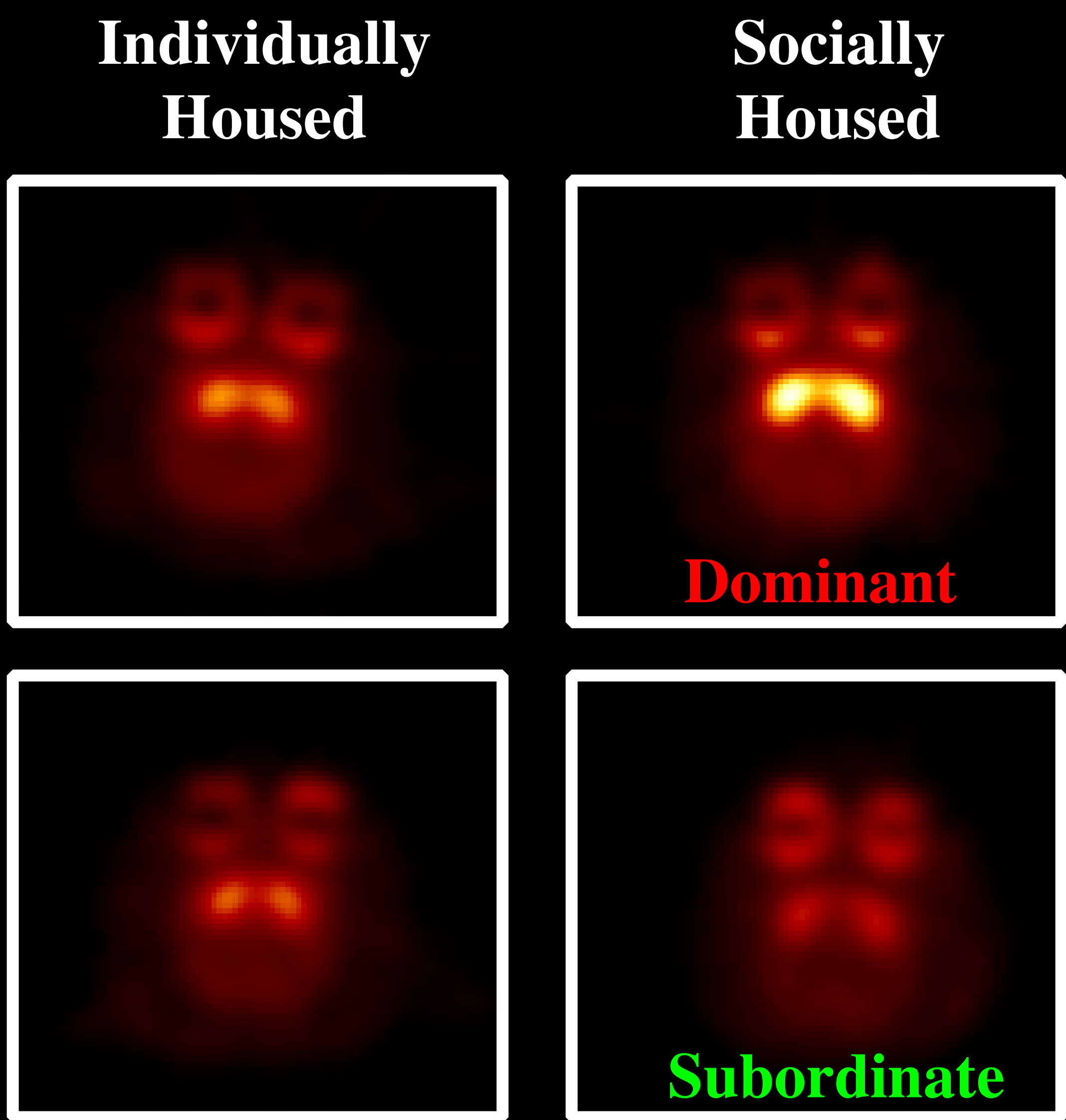
D2 receptor levels are state variables for social rank

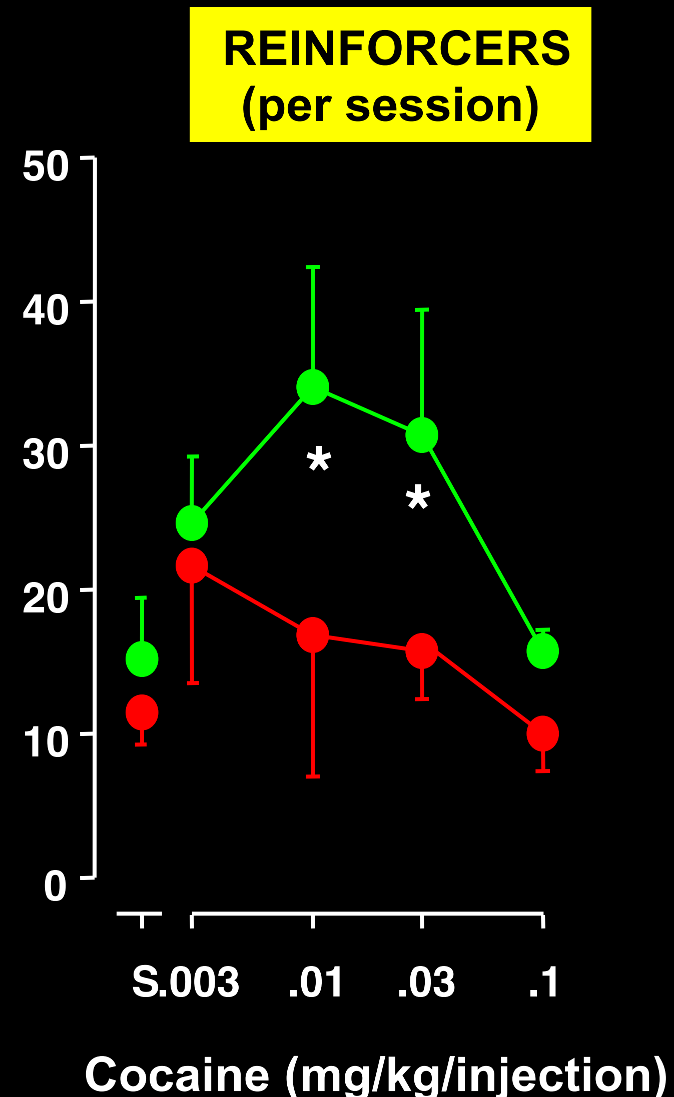


+ 22%

- 1%

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





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

Environmental Variables, Brain Function and Cocaine Abuse

Dominant

Enriched

Protected

↓ DA; ↑ D2 density

Subordinate

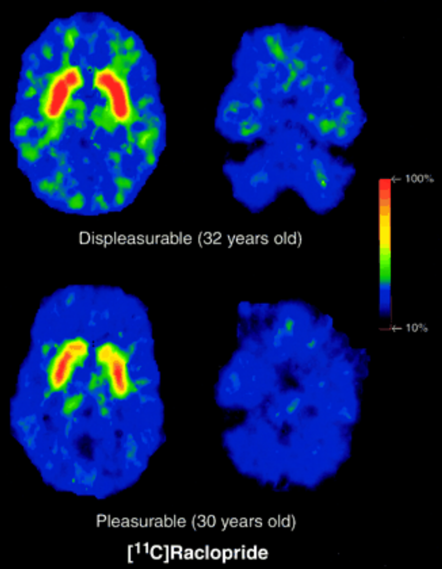
Stressed

Vulnerable

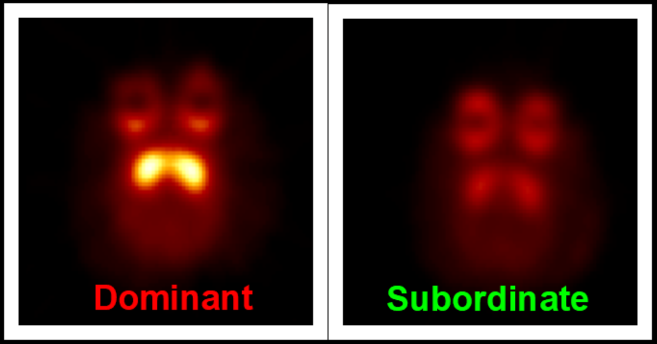
↑DA; ↓D2 density

Sex Differences?

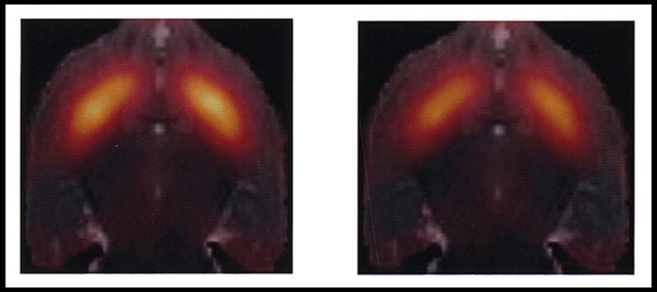
Females who start using cocaine are 3-4 times more likely to become cocaine dependent within 24 months of cocaine onset, as compared to male recent-onset users (O' Brien and Anthony, 2005).



humans: Volkow et al. (1999)

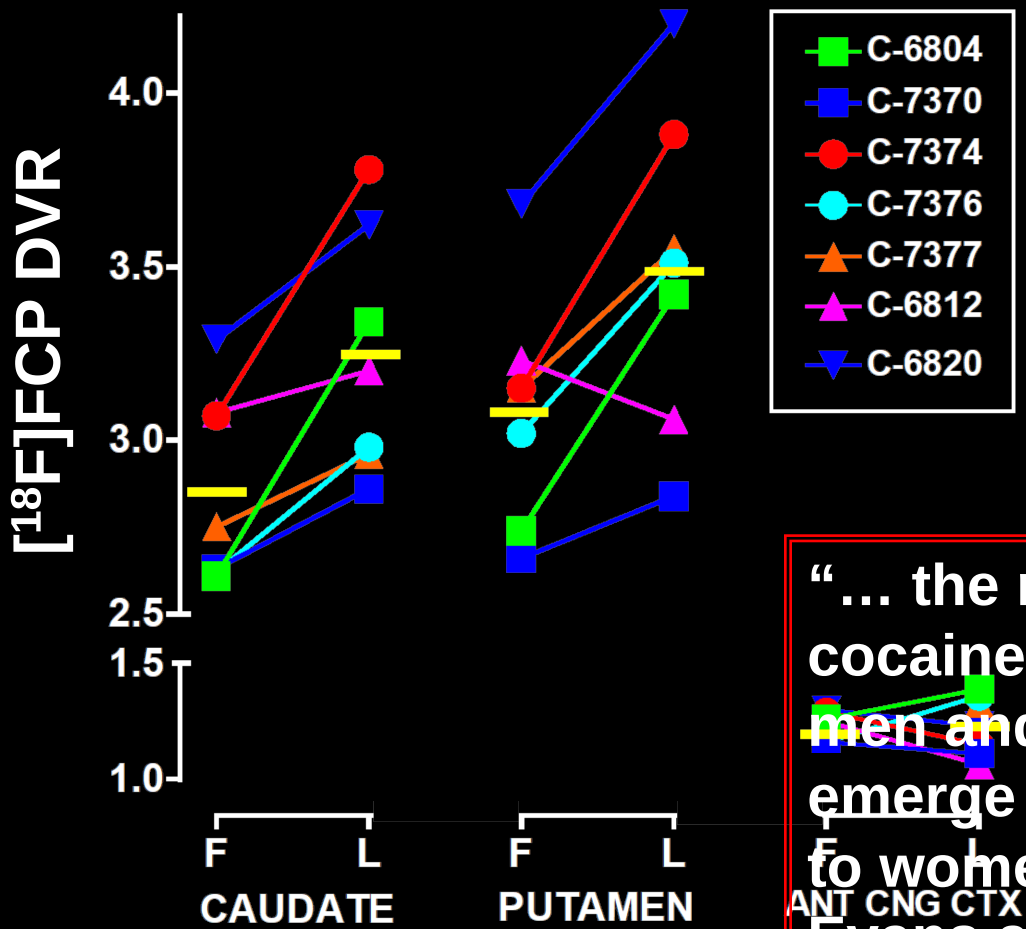


monkeys: Morgan et al. (2002)



rats: Dalley et al. (2007)

Menstrual cycle influences D2 receptor availability

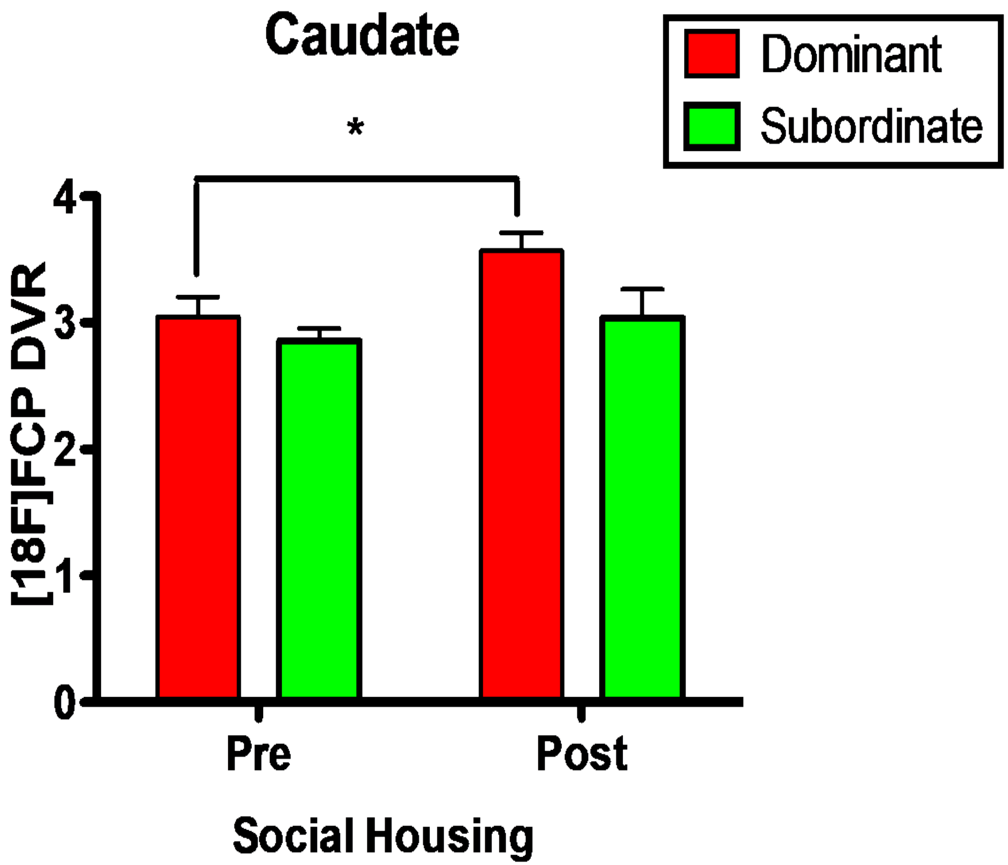


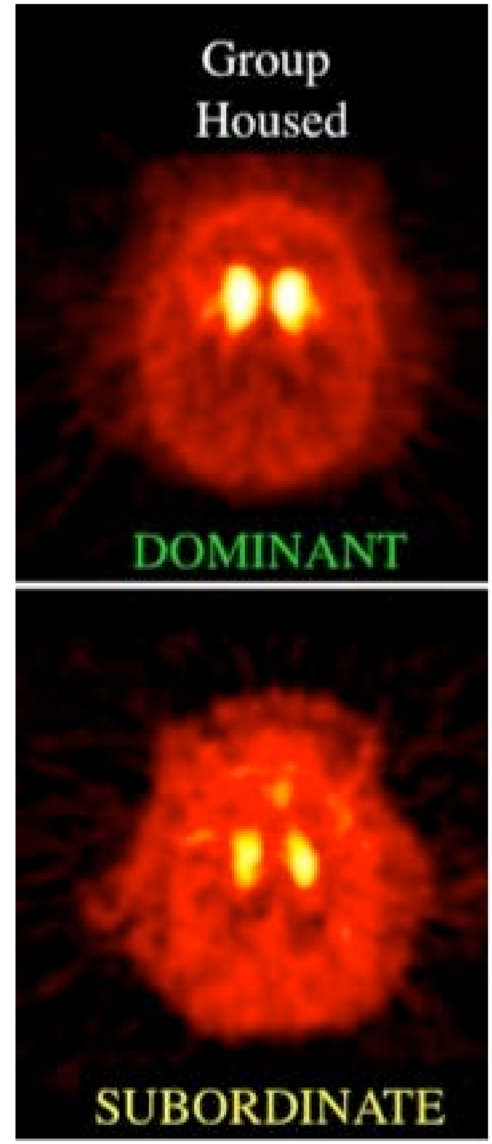
Males:
Cd: 2.54 (± .17)
Pt: 2.95 (± .10)

"… the response to smoked cocaine … differences between men and women generally only emerge when men are compared to women in the luteal phase"
Evans and Foltin (2010)

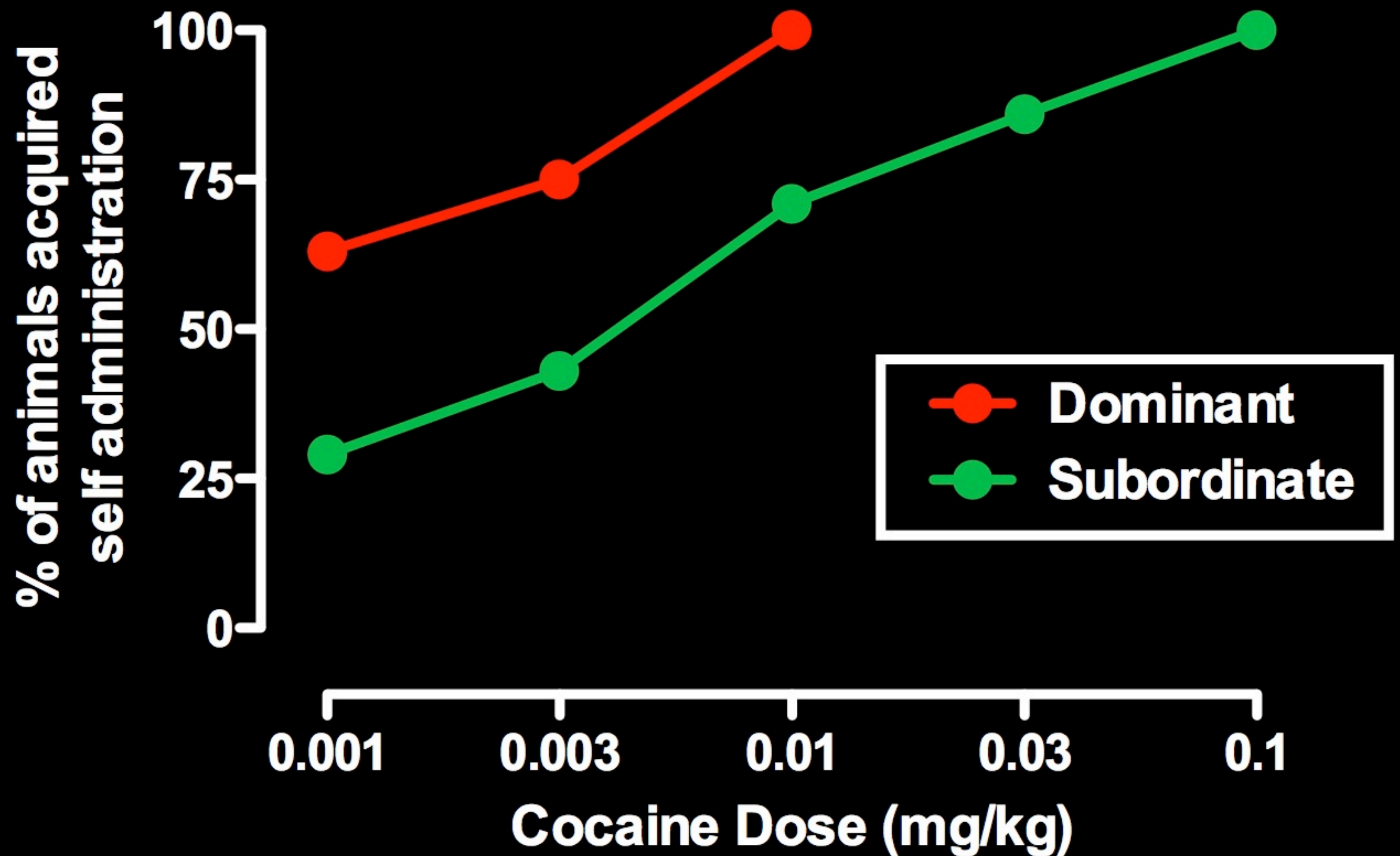
Czoty et al., Neuropsychopharmacology (2008)

D2 receptor availability increased in dominant females





Nader et al. (2012)



Nader et al. (2012)

Females Are Different From Males !

Male monkeys

- D2/D3 receptor availability greater in dominants
- initial cocaine SA greater in subordinates
- CSF HVA, 5-HIAA : dom = sub
- basal cortisol: dom > sub
- ACTH challenge: sub > dom
- testosterone: dom > sub

Female monkeys

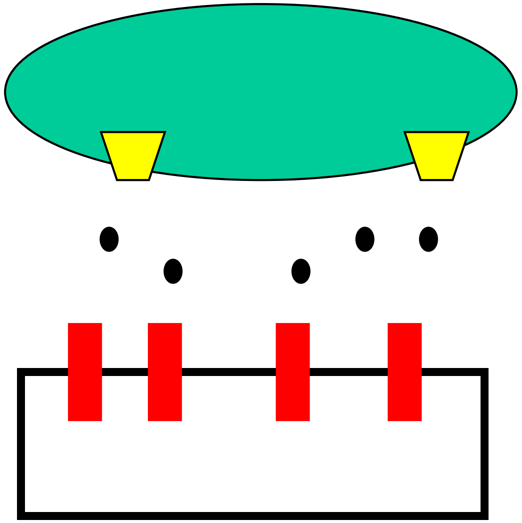
- D2/D3 receptor availability greater in dominants
- acquisition of cocaine SA greater in dominants
- CSF HVA: sub > dom;
- CSF 5-HIAA: sub > dom
- basal cortisol: dom = sub
- ACTH challenge: dom = sub
- E and PG: dom = sub
- DAT availability: dom > sub
- SERT availability: dom = sub

Morgan et al. (2002); Czoty et al. (2009); Riddick et al. (2009); Nader et al. (2012)

Interim Summary

- D2/D3 receptor availability is related to rates of cocaine self-administration
- In males, the relationship is negative; in females it appears to be positive
- Males $\leq$ follicular females < luteal females

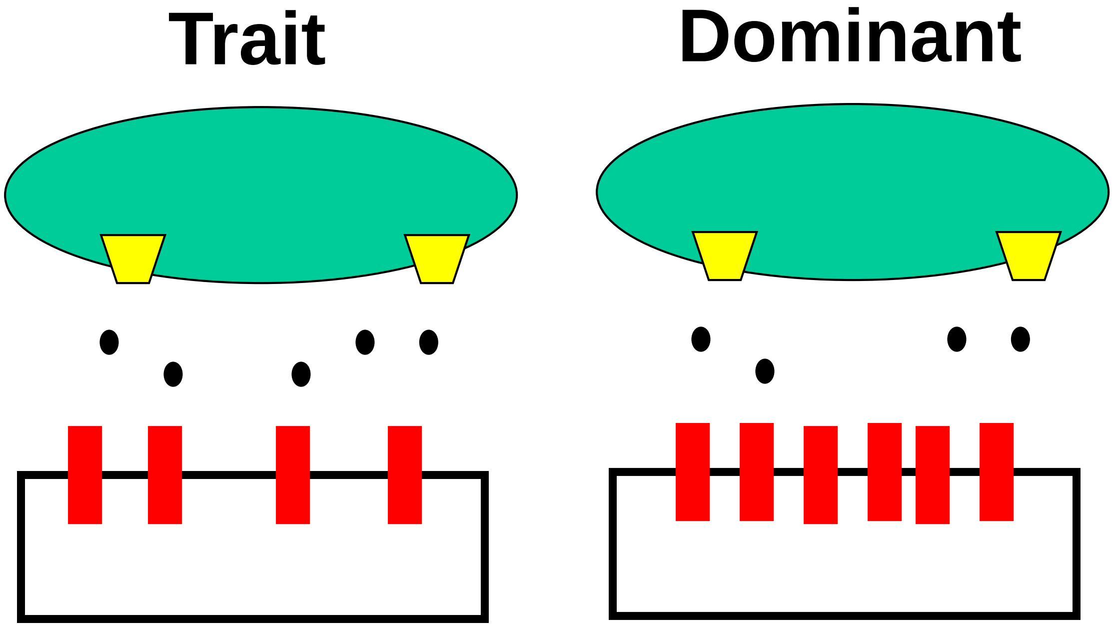
Trait



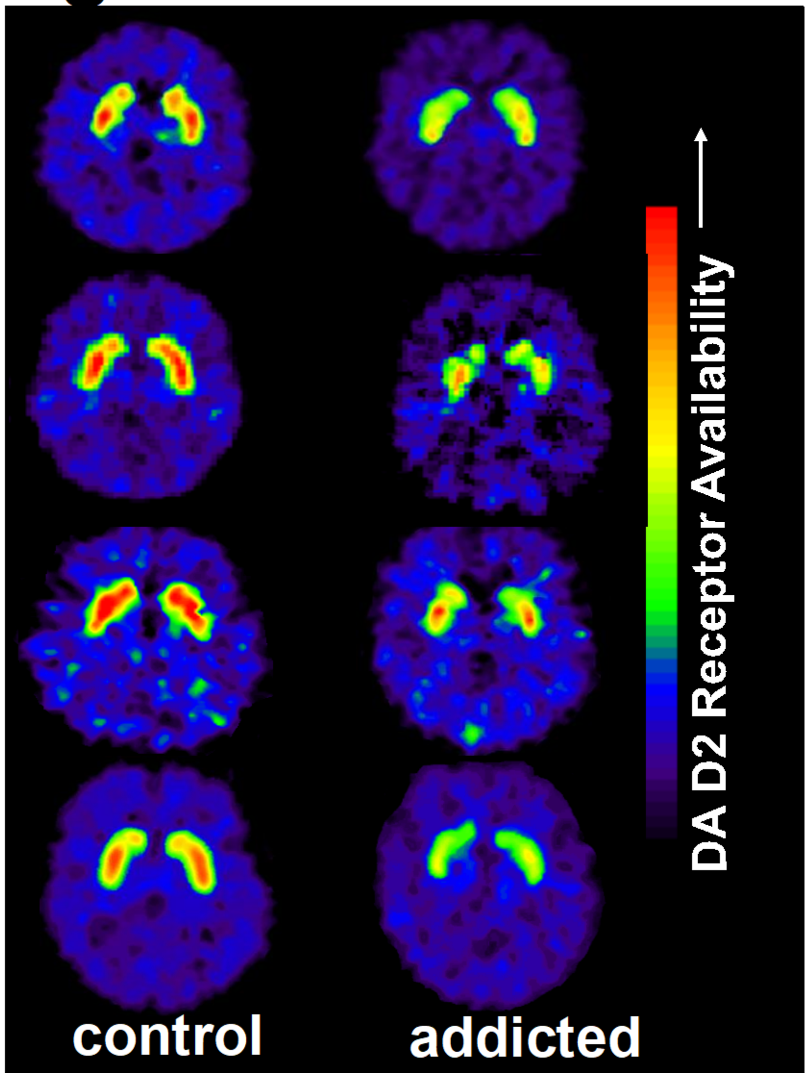
Interim Summary

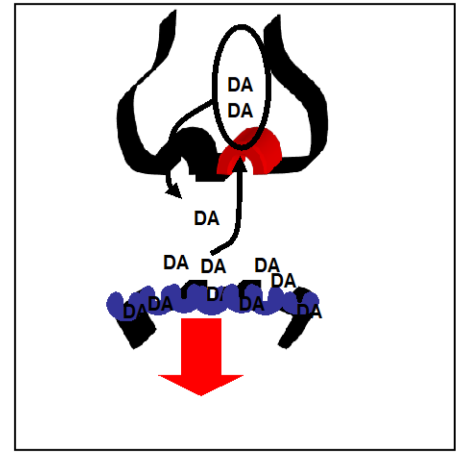
- D2/D3 receptor availability increased as a result of becoming dominant; this protected males, but not females, from cocaine reinforcement.

- Sub Male < Sub Fem < Dom Male < Dom Fem

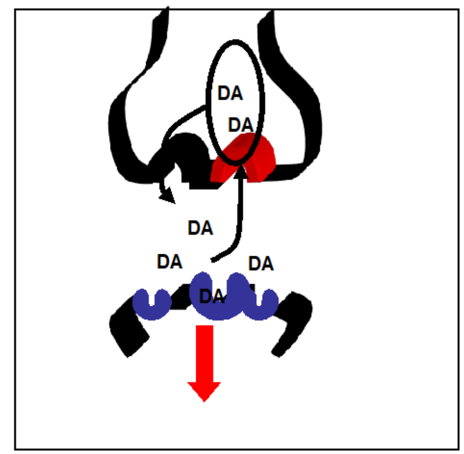


Decreased Levels of DA D2 Receptors in Drug Addicted Individuals





Non-Drug Abuser



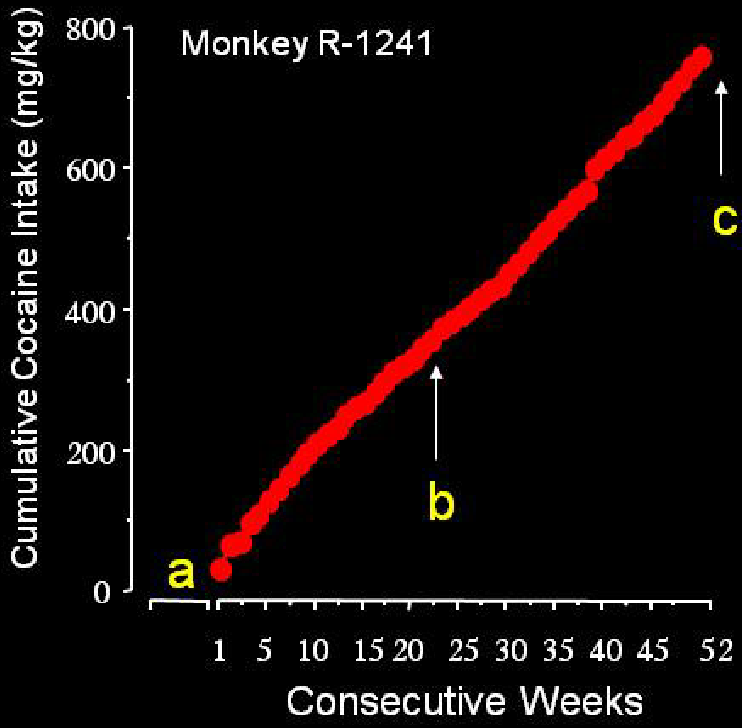
Drug Abuser

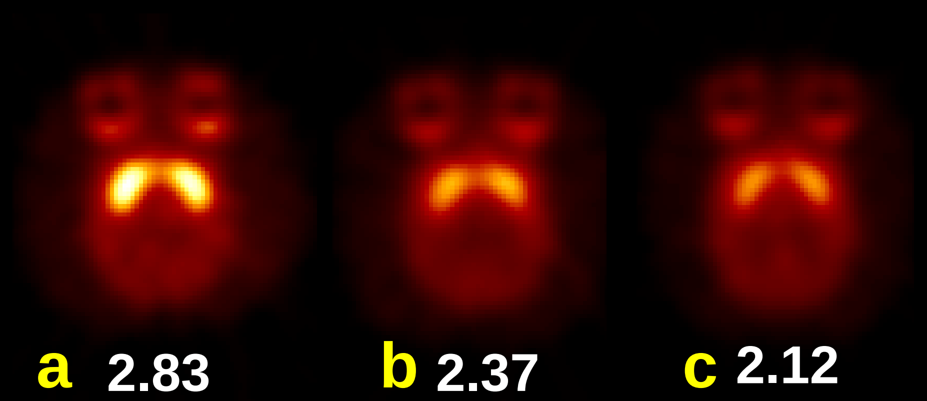
Volkow et al., PNAS 2011

Slide from Nora Volkow

Cocaine and DA D2/D3 receptor distribution

Drug-naïve → **Cocaine history**

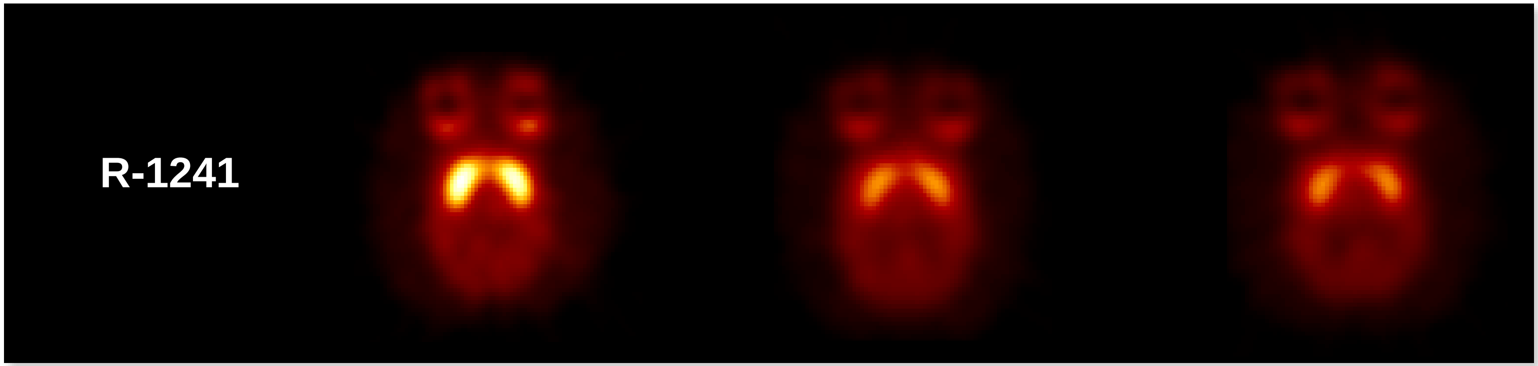




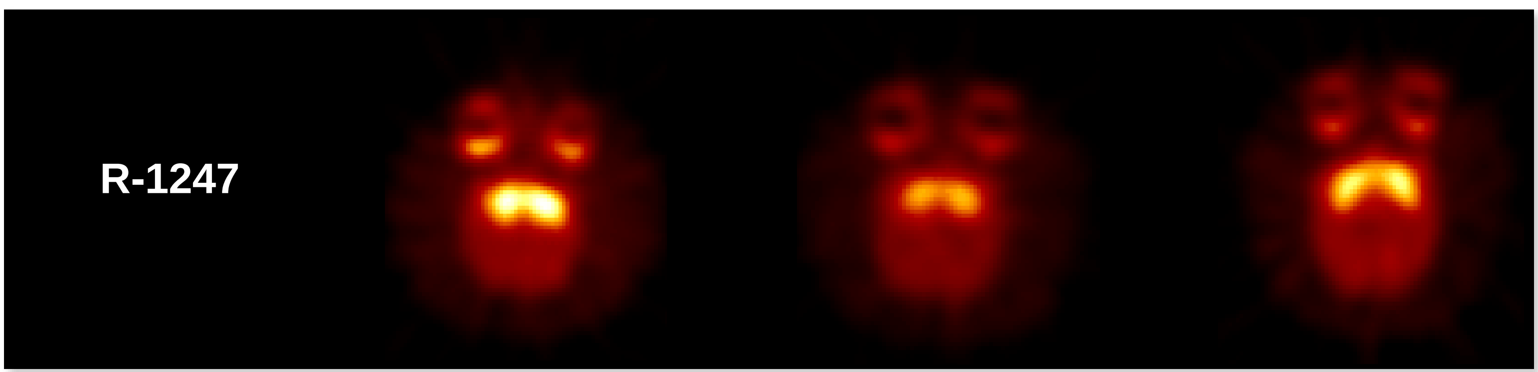
Nader et al. (2006)

Individual Differences in Recovery

1 year



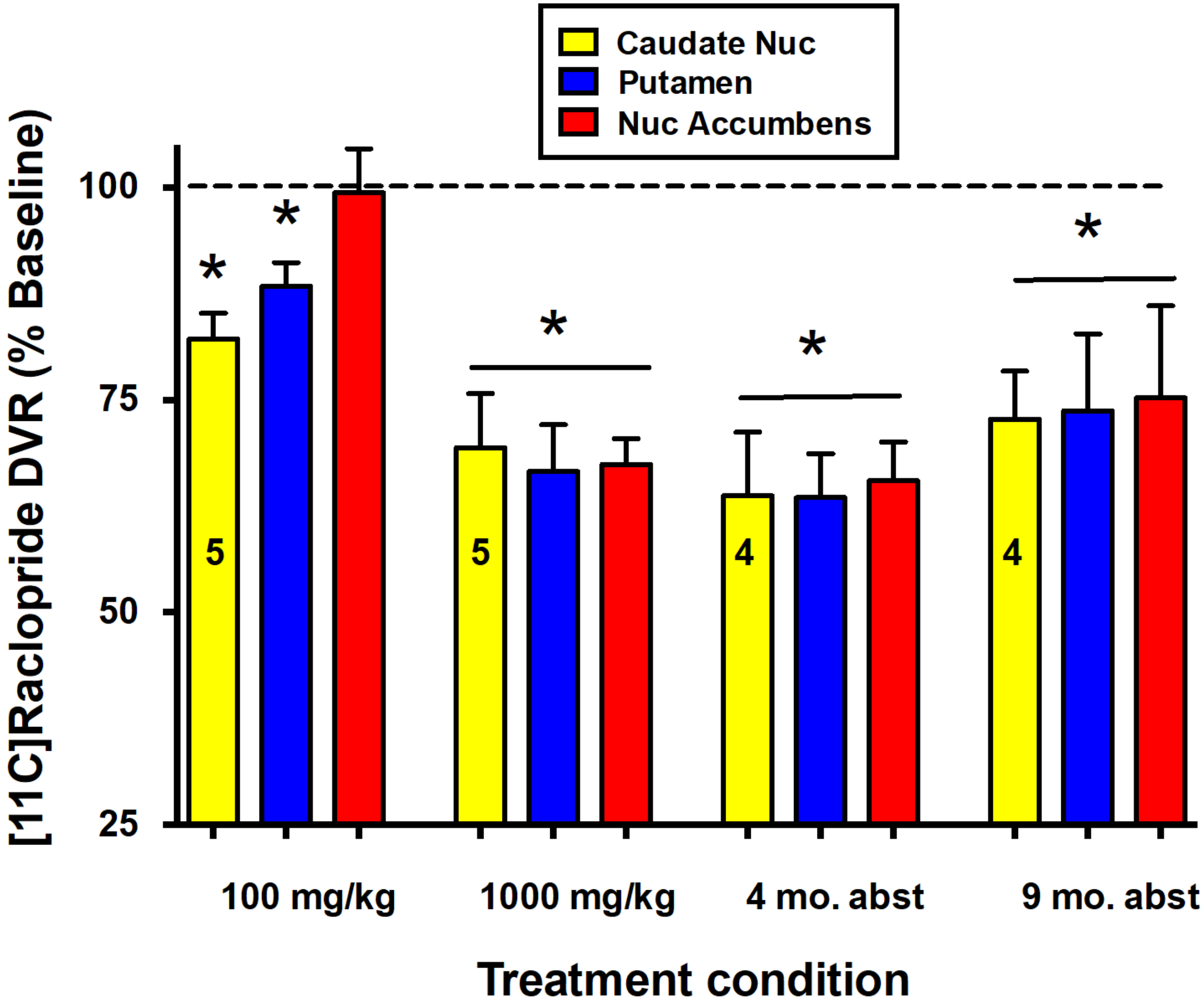
Baseline **1 year SA** **Abstinence**



3 months

Nader et al. (2006)

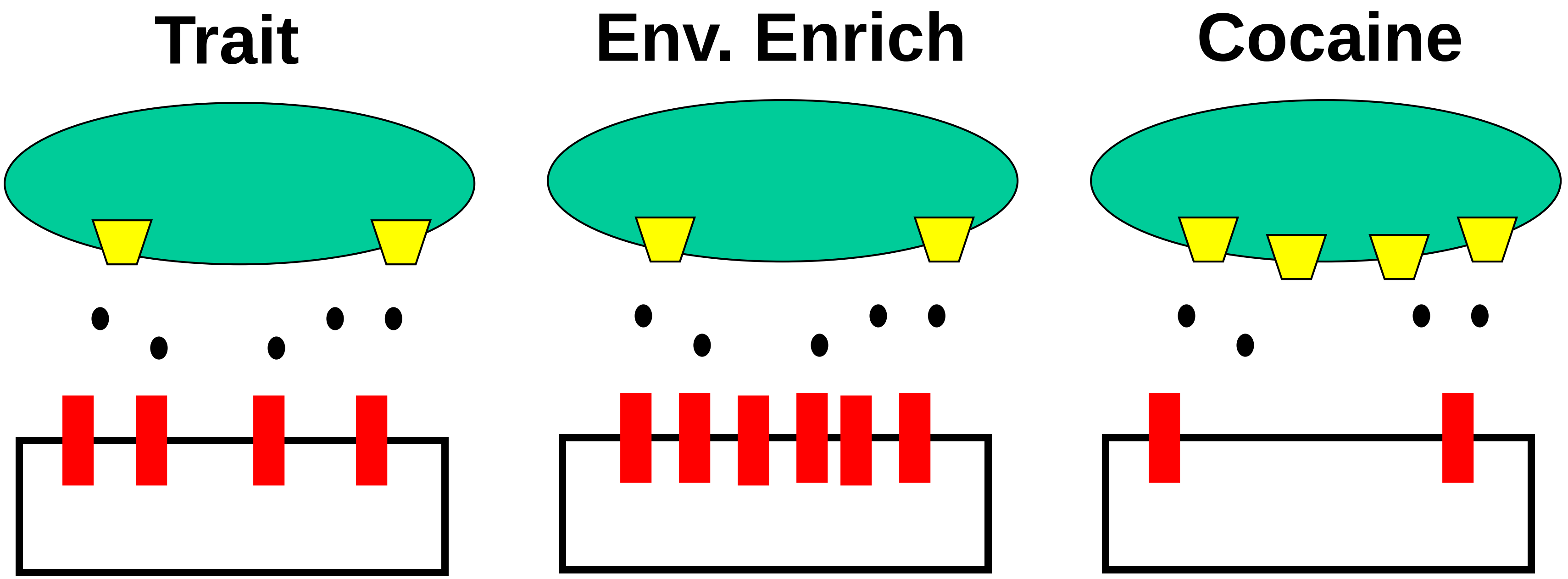
Cocaine Deceases D2/D3R Availability in Female Monkeys



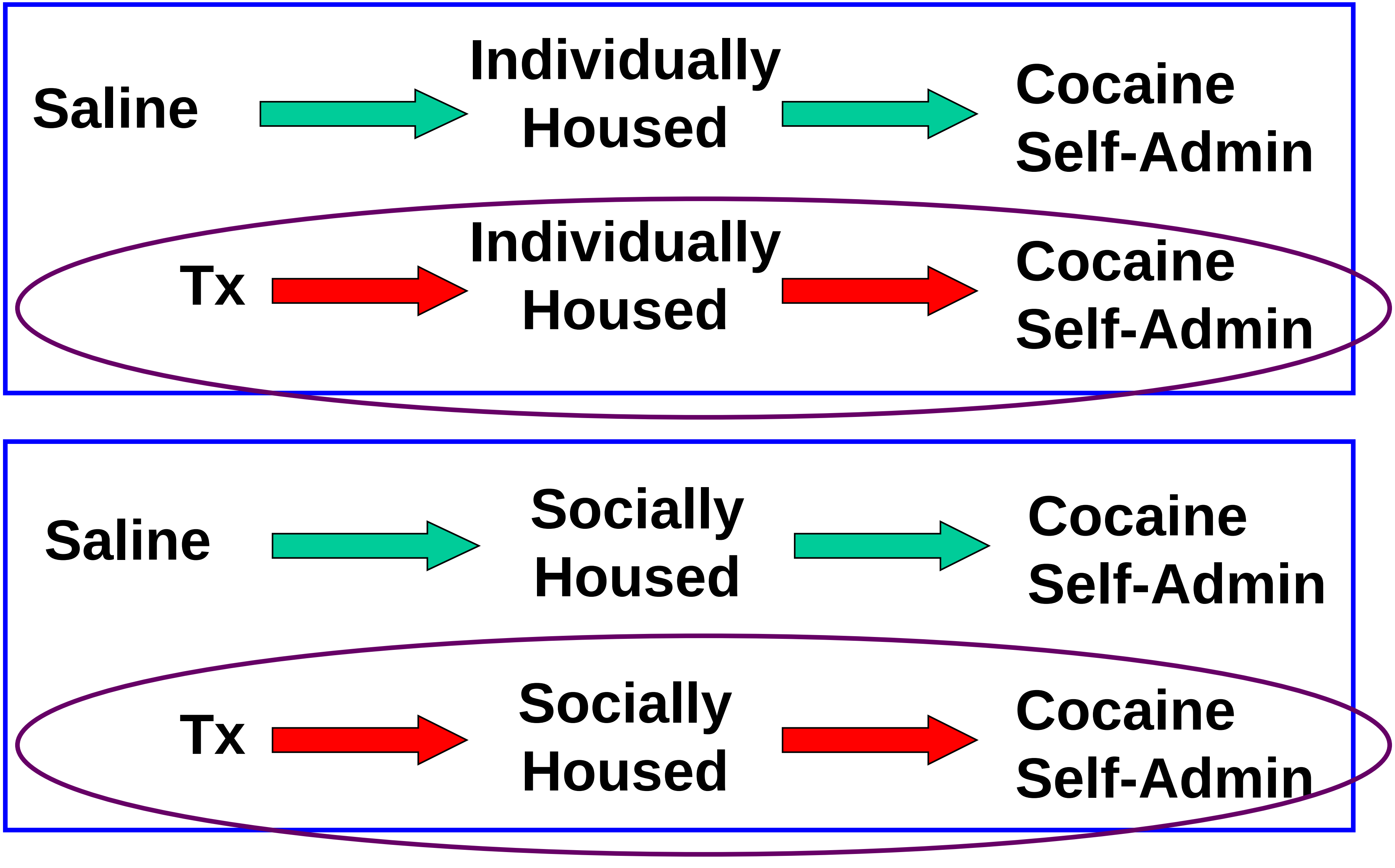
Inerim Summary

- **Chronic cocaine exposure robustly decreases D2/D3 receptor availability.**

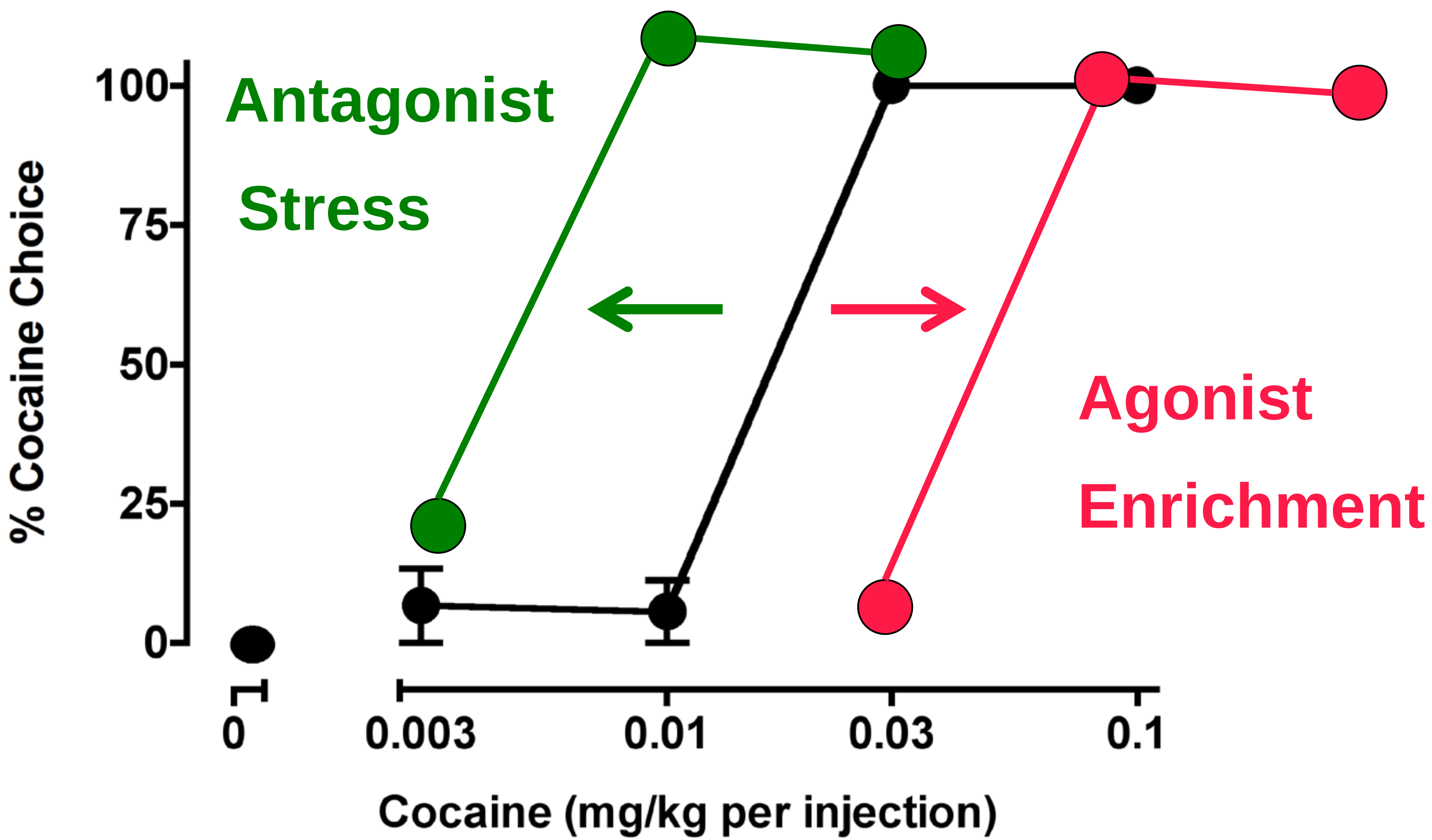
- **Pharmacotherapy should increase D2/D3 receptor levels in males <u>and</u> in females.**



Interactions Between Social Behavior and Cocaine

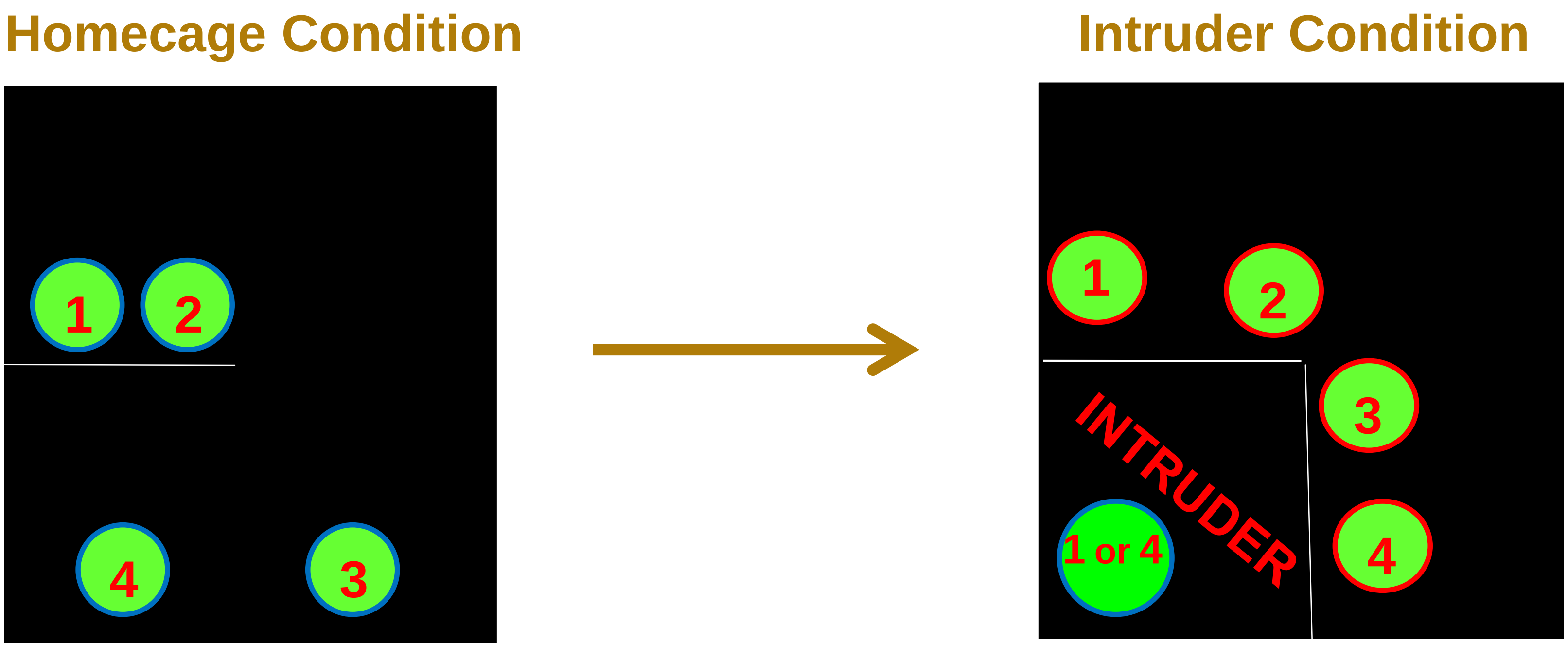


Cocaine-Food Choice Paradigm



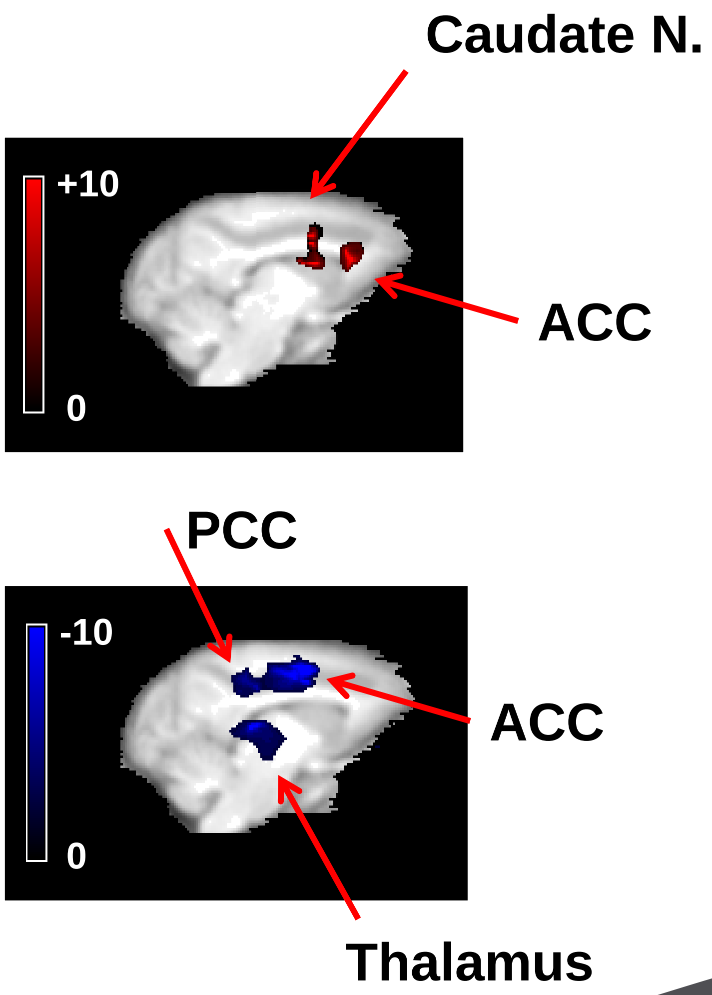
Methods: Intruder Condition (acute social encounter)

- Male cynomolgus macaques (#1 and #4 ranked monkeys)
- Similar age and drug histories
- 45 (FDG) or 30 (SA) minute exposure as intruder



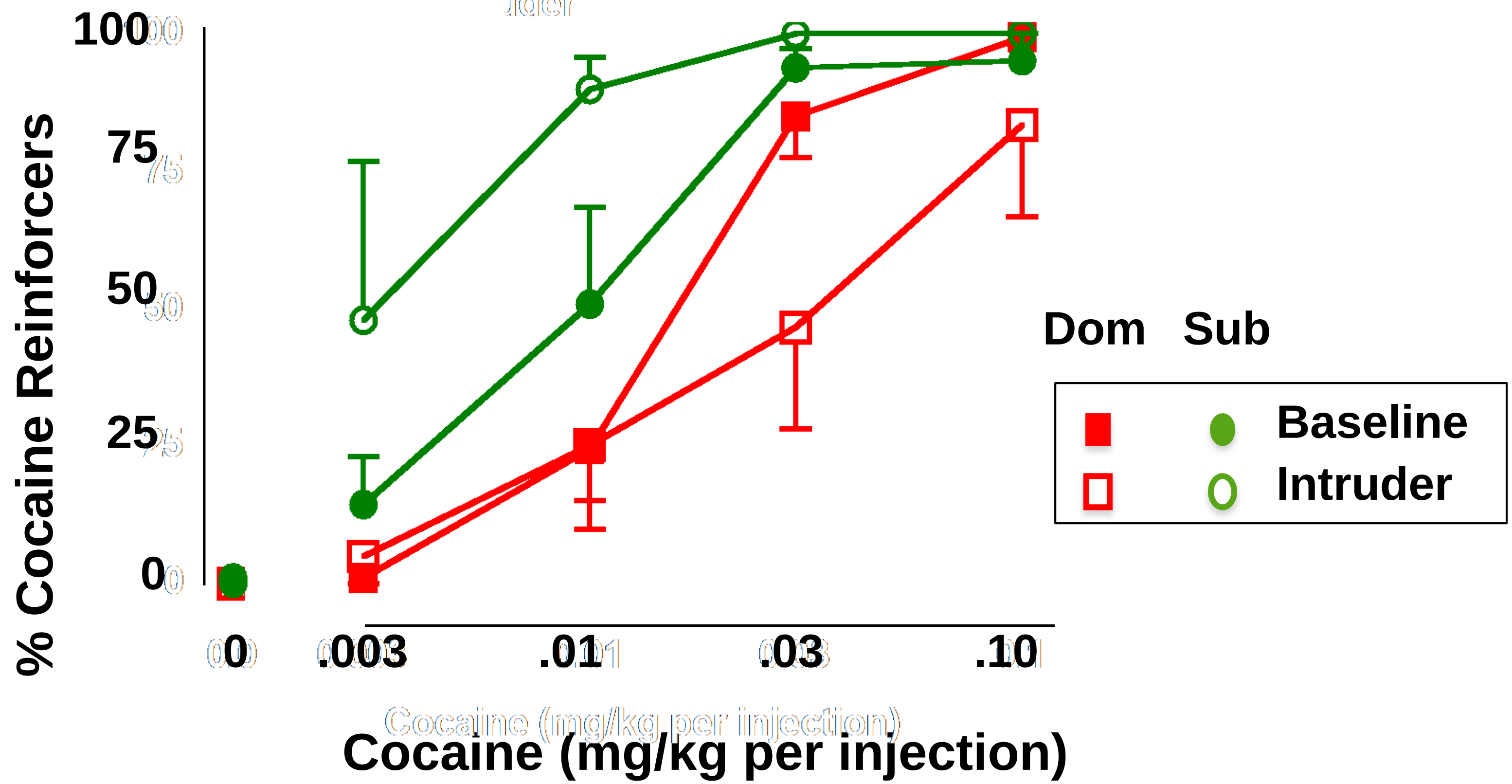
Similar to rodent resident-intruder model (Miczek and colleagues 2004, 2005)

Different Responses to Acute Social Conditions



Gould et al. (2017)

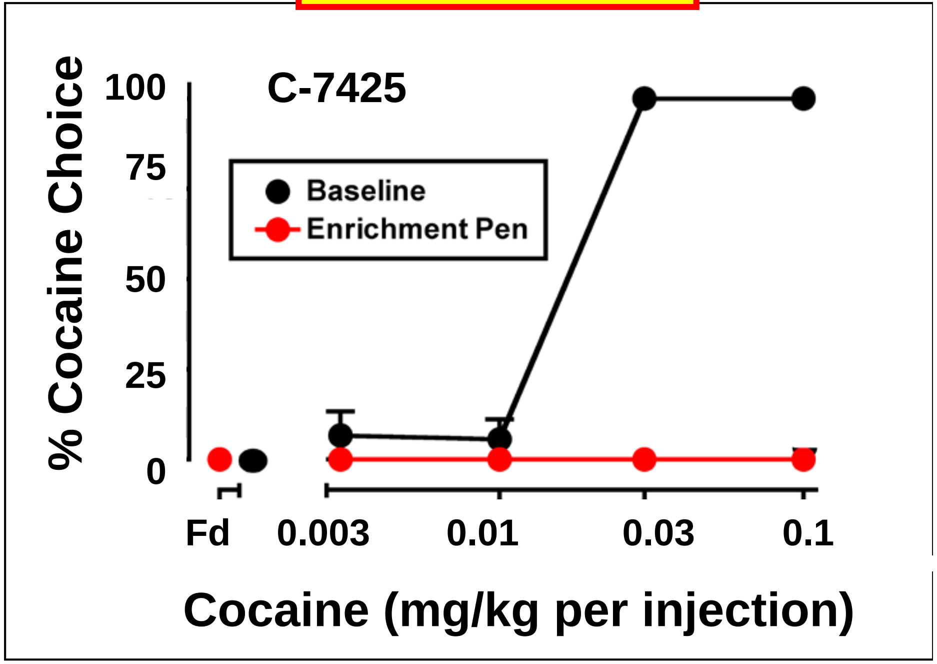
Different Responses to Acute Social Conditions



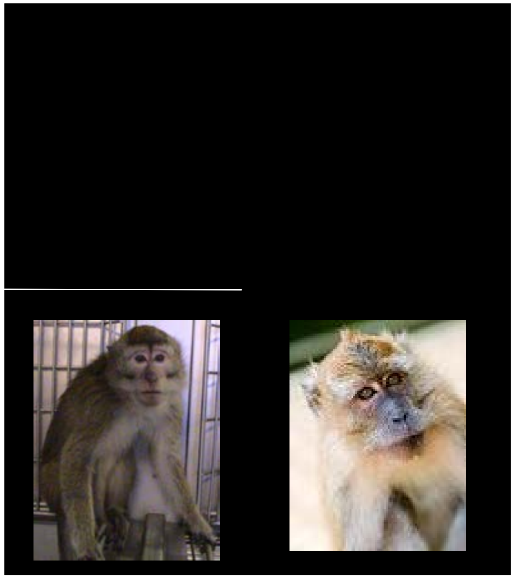
Gould et al. (2017)

Individual Differences in Outcome Measures

LARGE CAGE



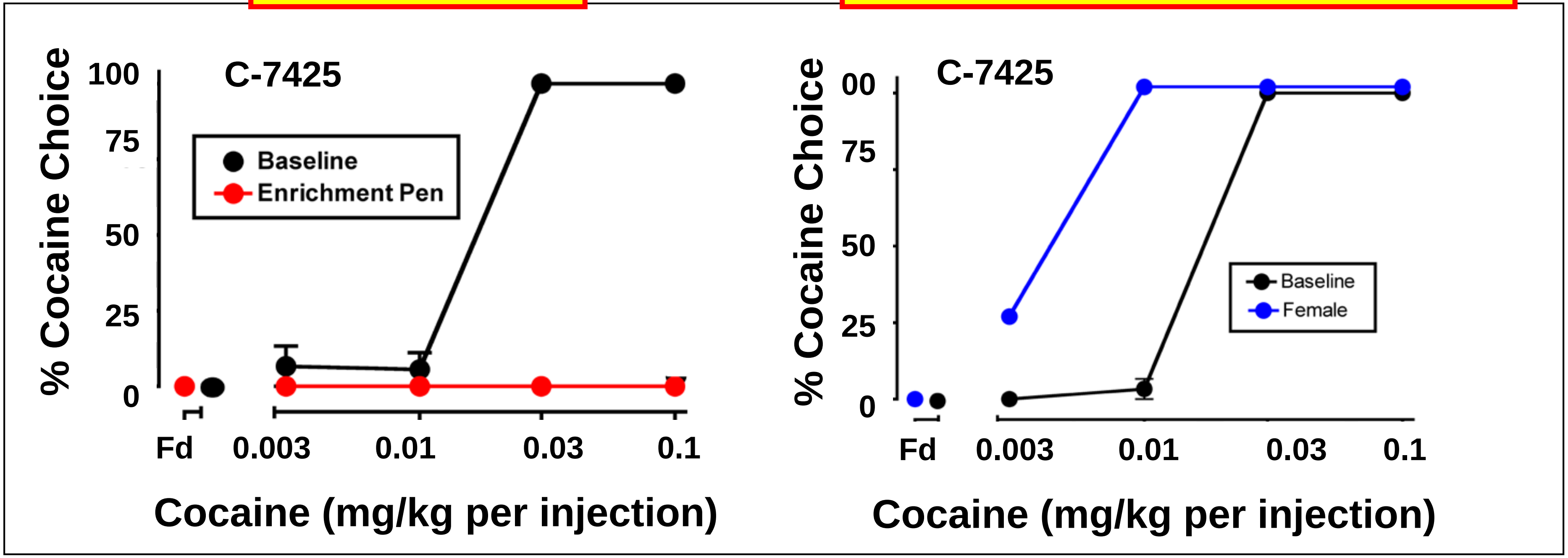
Homecage Condition



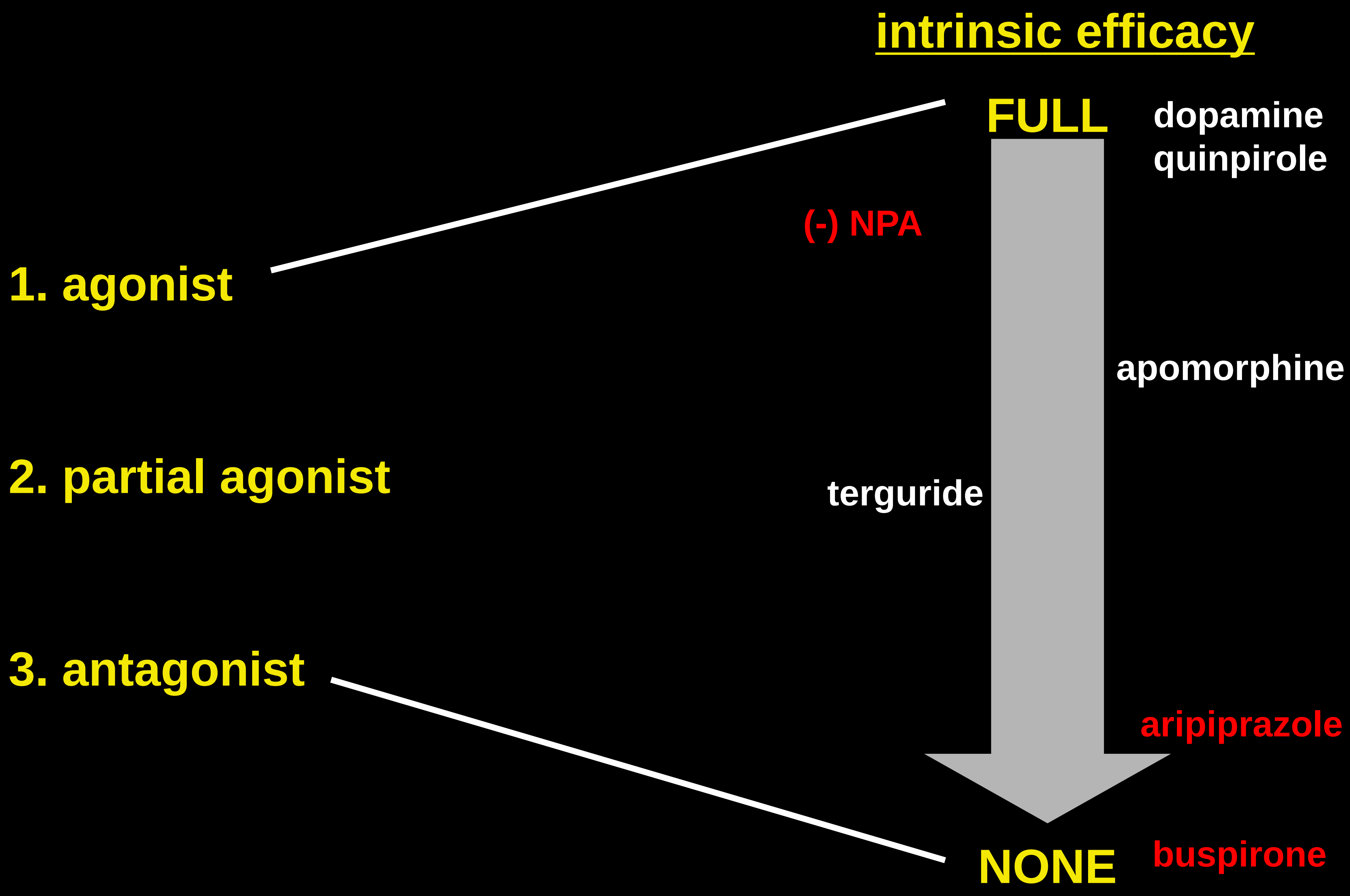
Individual Differences in Outcome Measures

LARGE CAGE

PAIR-HOUSED WITH FEMALE



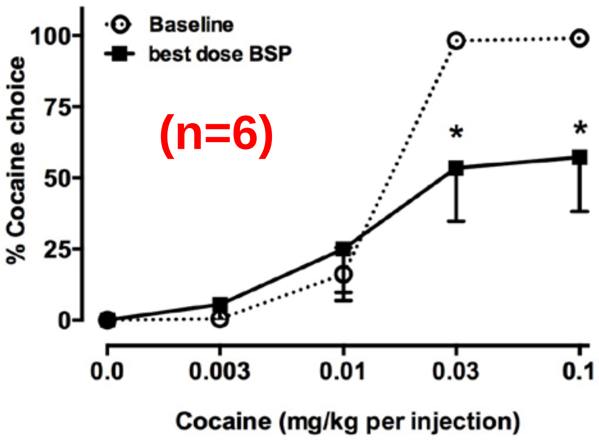
Medications for cocaine dependence: dopaminergic strategies



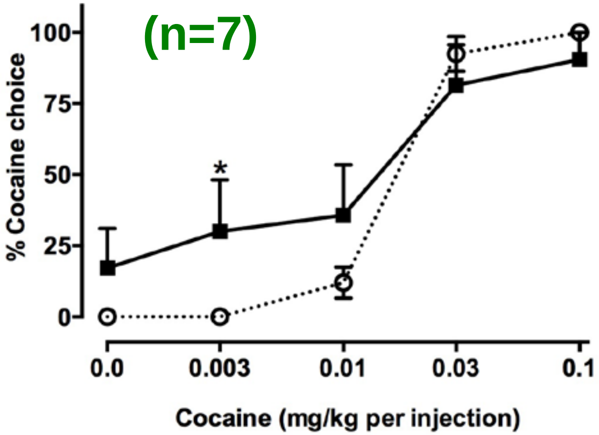
$D_{3/4}$ receptors: Buspirone

MALES

Dominant



Subordinate

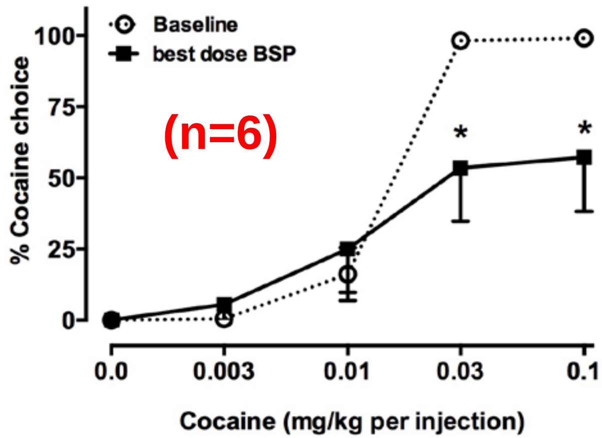


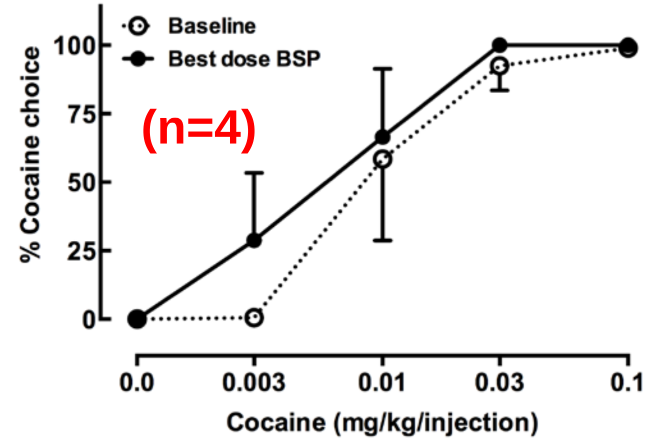
Czoty & Nader (2015) Neuropsychopharmacology

$D_{3/4}$ receptors: Buspirone

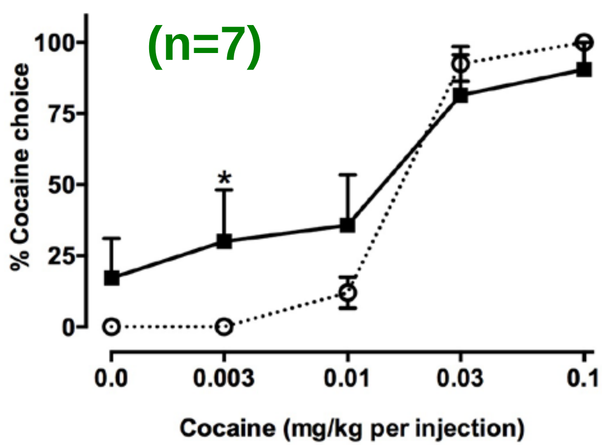
MALES | **FEMALES**

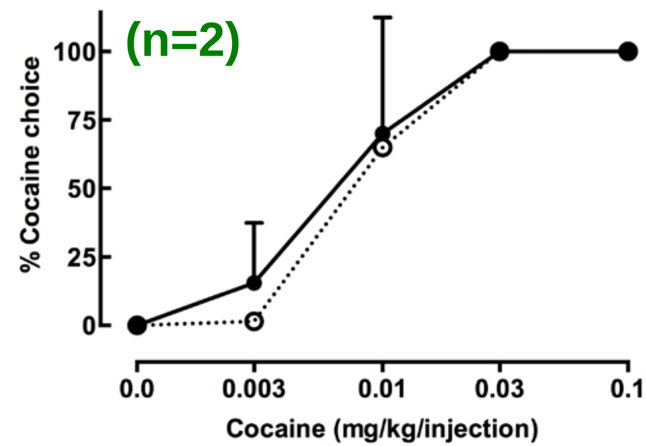
Dominant





Subordinate



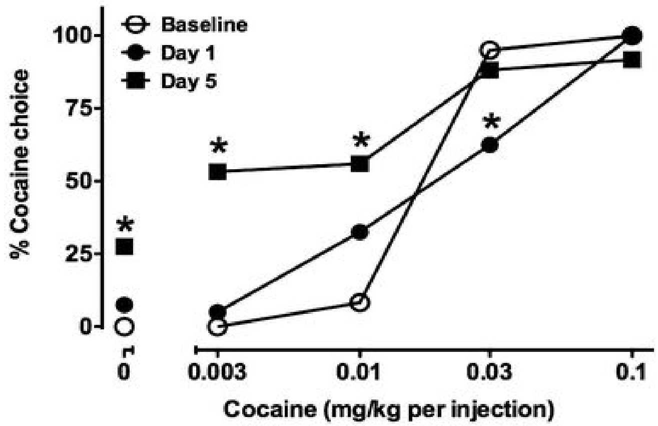


Czoty & Nader (2015) Neuropsychopharmacology

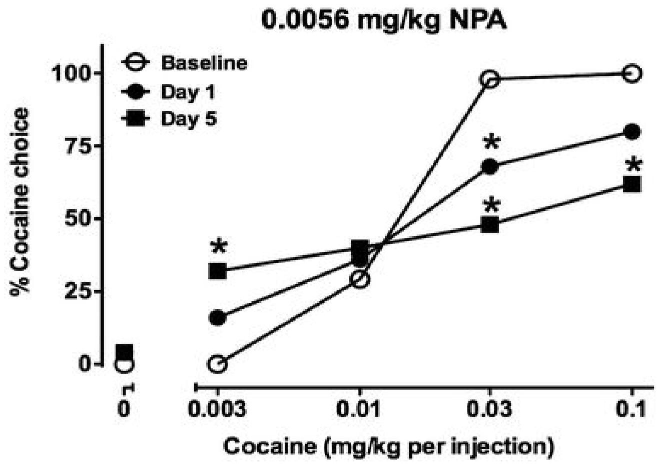
D2-like receptor drugs – male monkeys

NPA-HIGH efficacy

Dominant (n=4)



Subordinate (n=5)



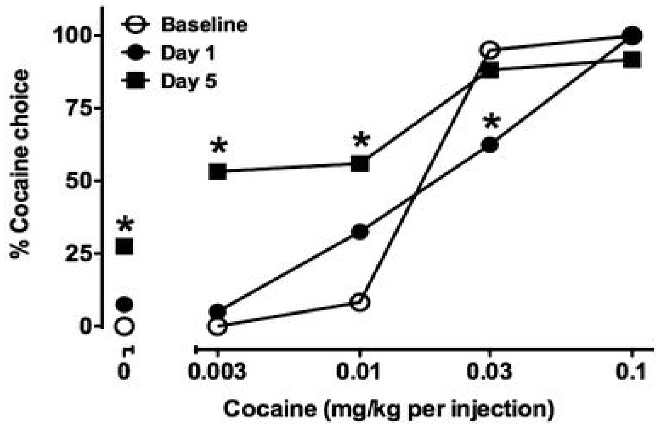
Czoty & Nader (2012) JPET

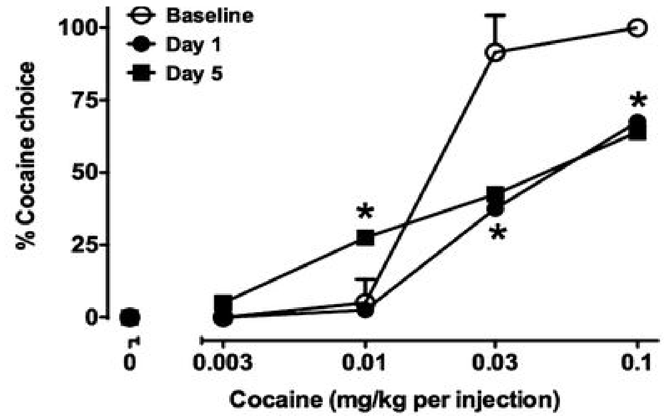
D2-like receptor drugs – male monkeys

NPA-HIGH efficacy

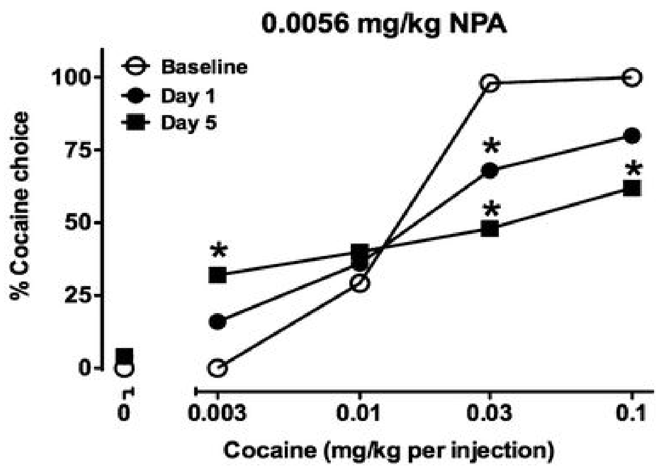
ARI-LOW efficacy

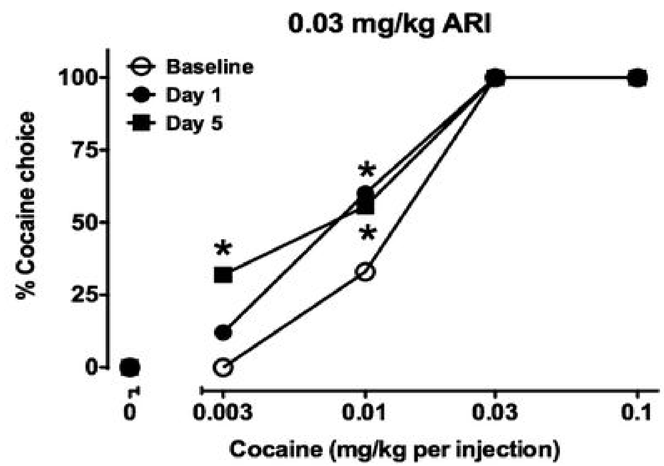
Dominant (n=4)





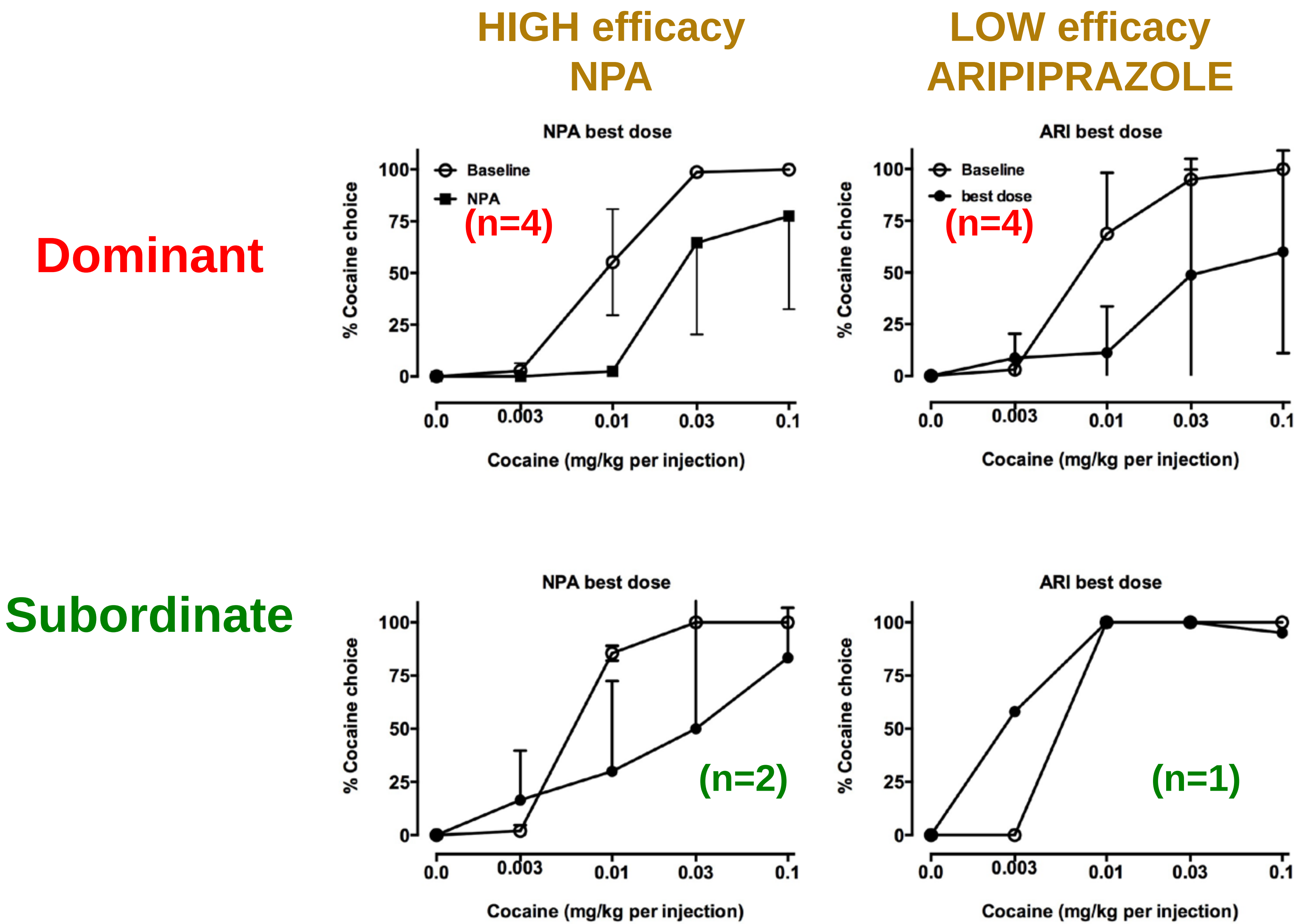
Subordinate (n=5)





Czoty & Nader (2012) JPET

D2-like receptor drugs – female monkeys



DA Compounds on Cocaine Choice

	Males		Females	
	DOM	SUB	DOM	SUB
Buspirone	↓	↑	↑	↑
Aripiprazole	↓	↑	↓	—
NPA	↑	↓	↓	↓

1. Every drug shows rank-related differences in males
2. Sex differences observed in dominant monkeys
3. No drug is effective in all groups

What About Opioids and Nonhuman Primate Models?

Neonatal Abstinence Syndrome

- Brain Development
- Behavioral Consequences

Evaluating Novel Treatments

- Within-Subjects designs
- Physical Dependence

Prenatal Cocaine Exposure

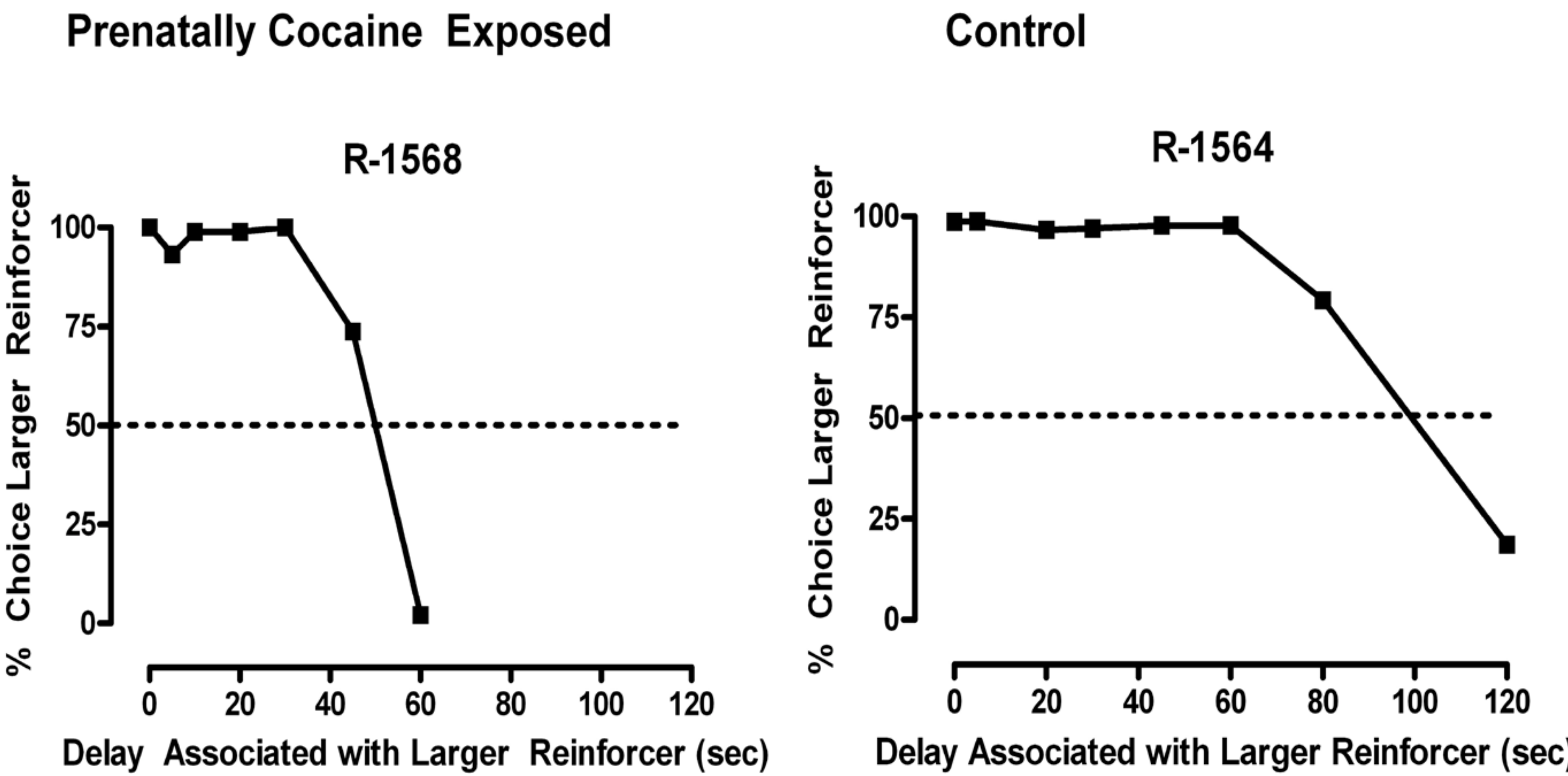
20 adult rhesus monkeys
- 10 prenatally cocaine exposed (6 ♂, 4 ♀)
- 10 prenatally saline exposed (5 ♂, 5 ♀)

Mean gestational dose: 2200 mg/kg cocaine

Birth – 11 yrs old: National Center for Toxicological Research, Arkansas

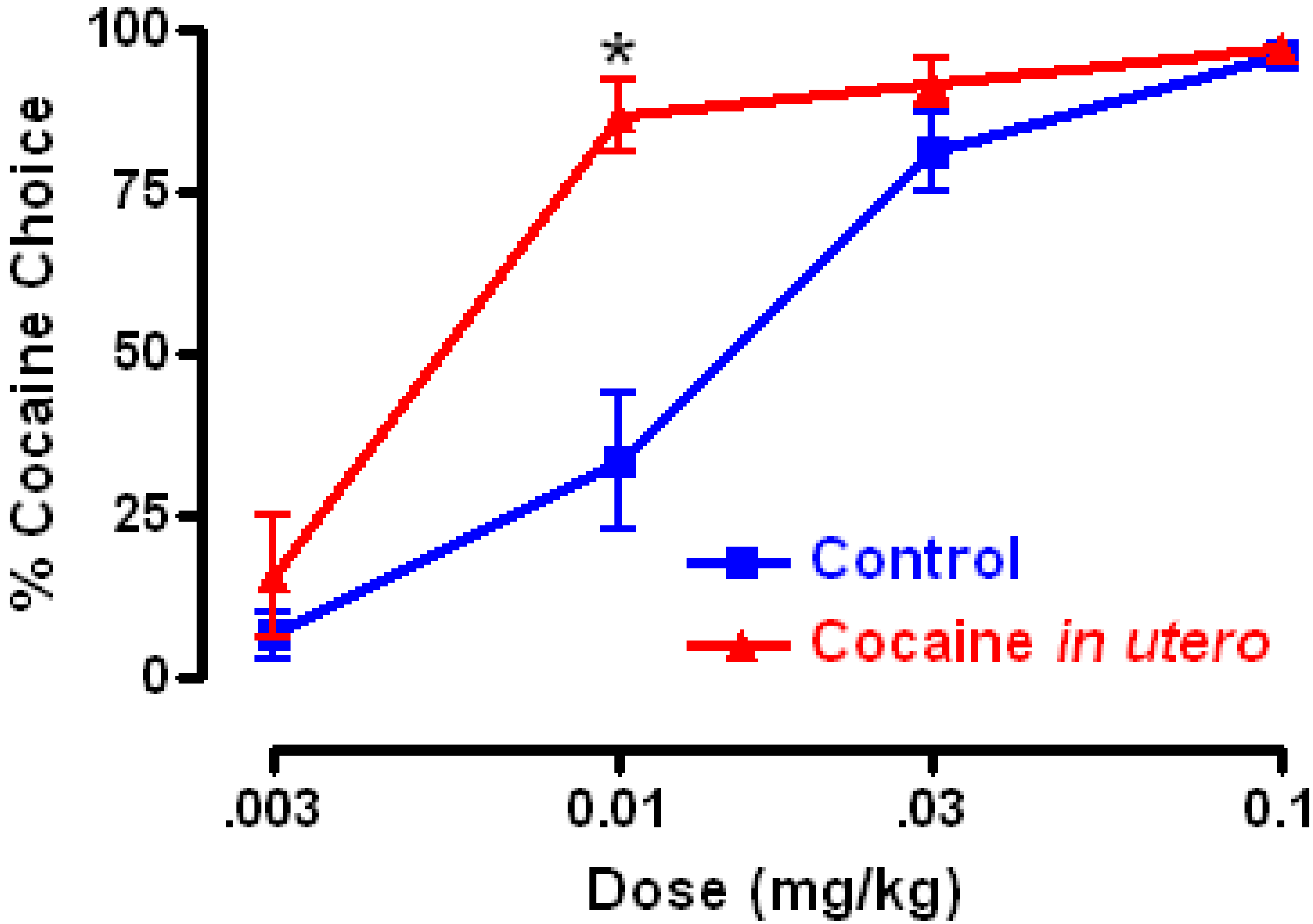
~ 26 week gestation

Prenatal Cocaine Exposure and Impulsivity



Hamilton et al. (2011)

Prenatal Cocaine Exposure and Vulnerability



Brutcher et al. (in preparation)

Opioids and Nonhuman Primate Models

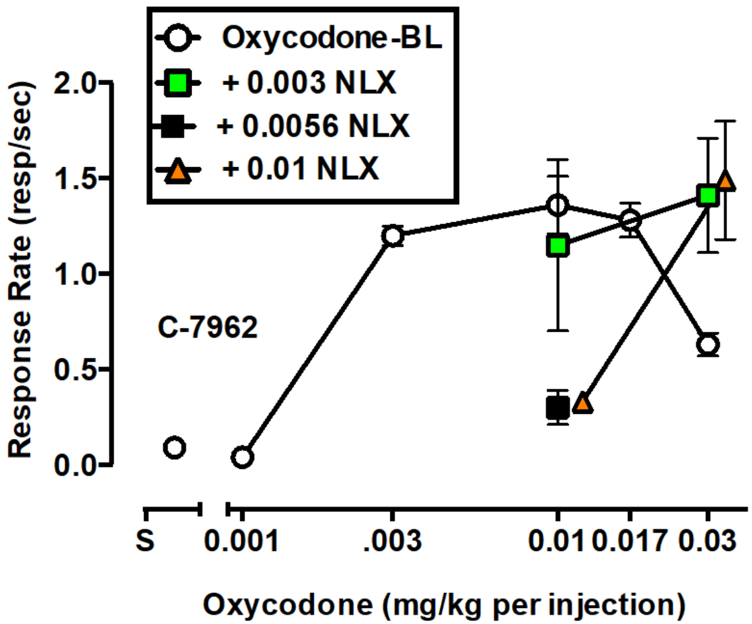
Neonatal Abstinence Syndrome

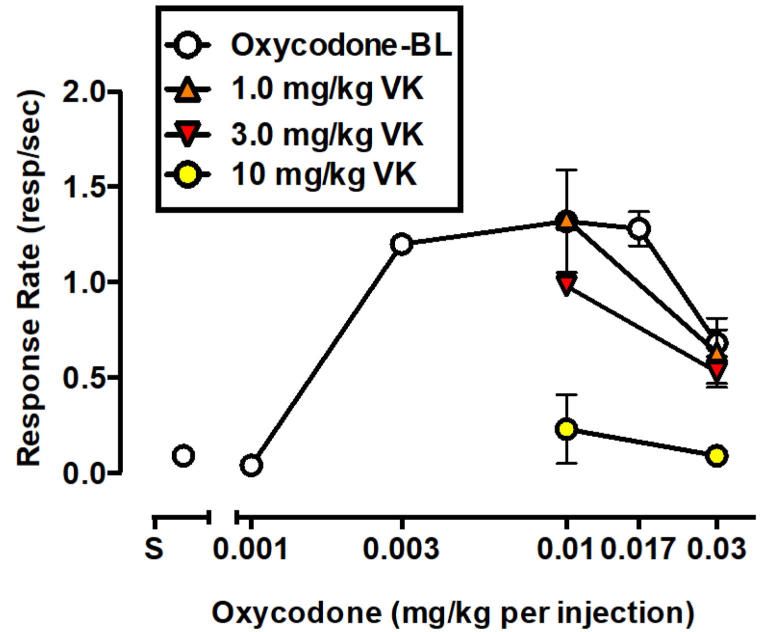
- **Brain Development – MRI and PET**
- **Behavioral Consequences – Cognition, Vulnerability**

Evaluating Novel Treatments

- **Within-Subjects designs**
- **Physical Dependence**

Effects of a Dopamine D3R Antagonist on Oxycodone Self-Administration





Dr. Amy Newman

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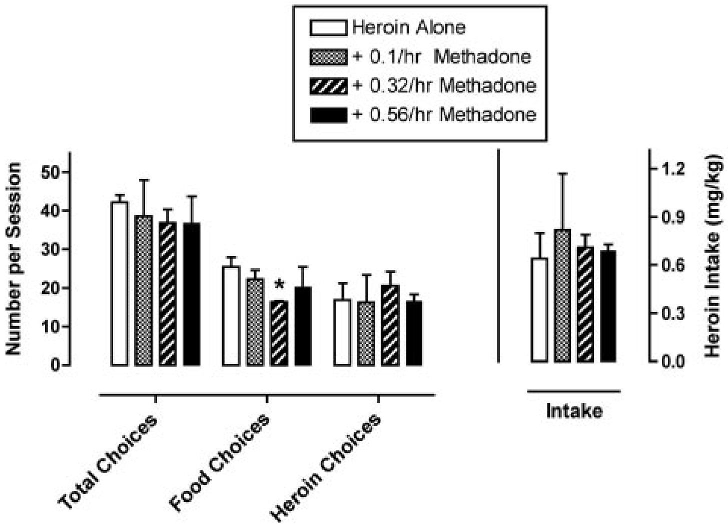
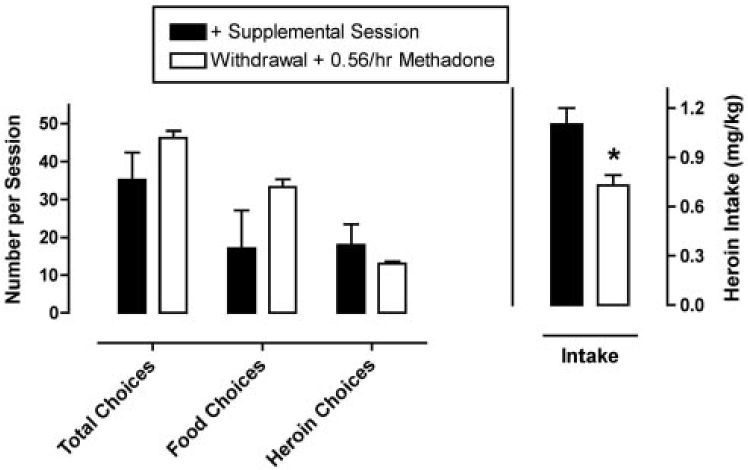
Importance of Physical Dependence in Evaluating Treatments for Opioid Use Disorder

Not Physically Dependent



Physically Dependent



Negus (2006)

Summary & Conclusions

The combination of nonhuman primate social behavior, models of drug abuse, behavioral pharmacology and noninvasive brain imaging techniques has provided important evidence regarding:

1. **Social stress and enrichment similarly impact brain D2/D3 receptors in male and female monkeys. However, the consequences with respect to cocaine reinforcement may be different.**

2. **While symptomology may appear similar, the interactions between genes, environment, chronic drug history can lead to "apparent" equivocal treatment outcomes.**

3. **Understanding the biological basis for individual differences may lead to more effective, sex-specific treatments for substance use disorders.**

Past Lab Members


Drake Morgan


Lindsey Hamilton

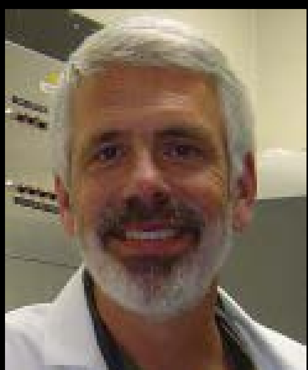

Natallia Riddick


Robert Gould


Robert Brutcher


Sarah Kromrey

Acknowledgments



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