Social Behavior of Nonhuman Primates: Effects on Brain Dopamine Systems and on Cocaine Reinforcement

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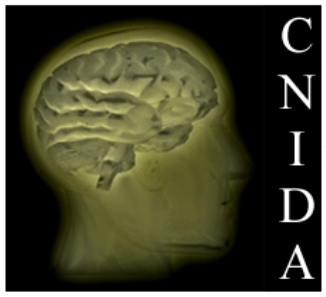

Center for the Neurobiological Investigation of Drug Abuse

OUTLINE

1. Factors that predict social rank in male and female cynomolgus monkeys

   Body weight, locomotor activity, hormone levels, receptor availability

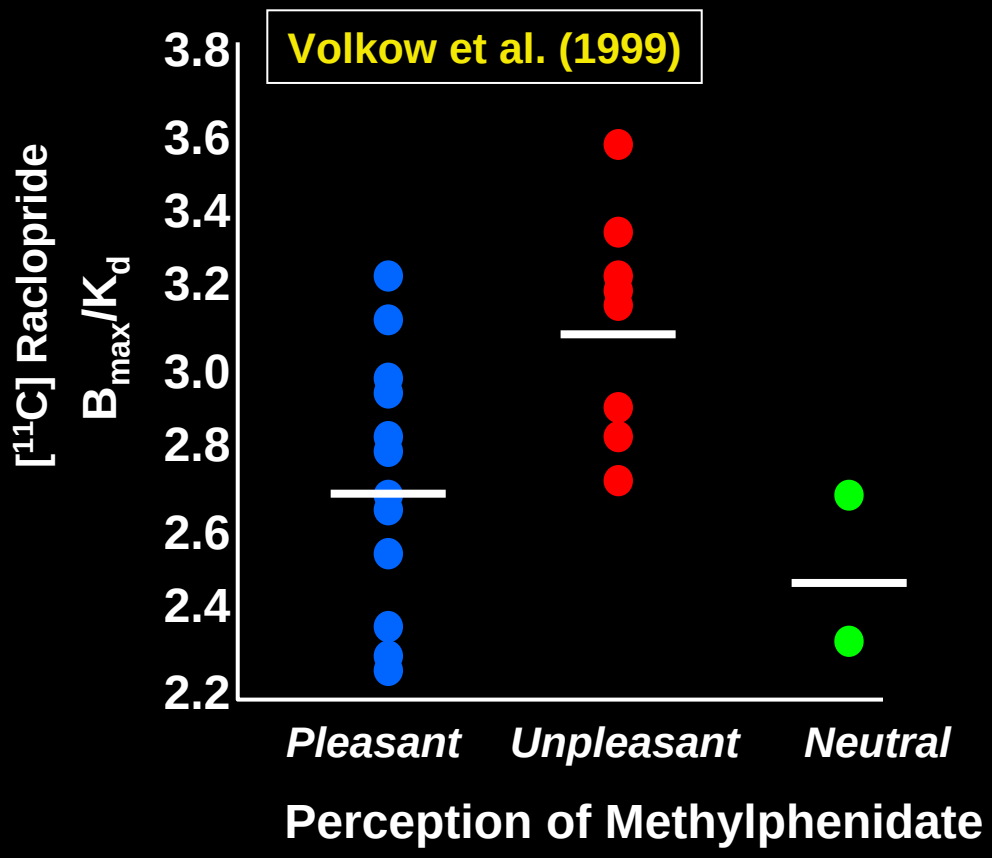
2. Variables that change as a consequence of social group formation

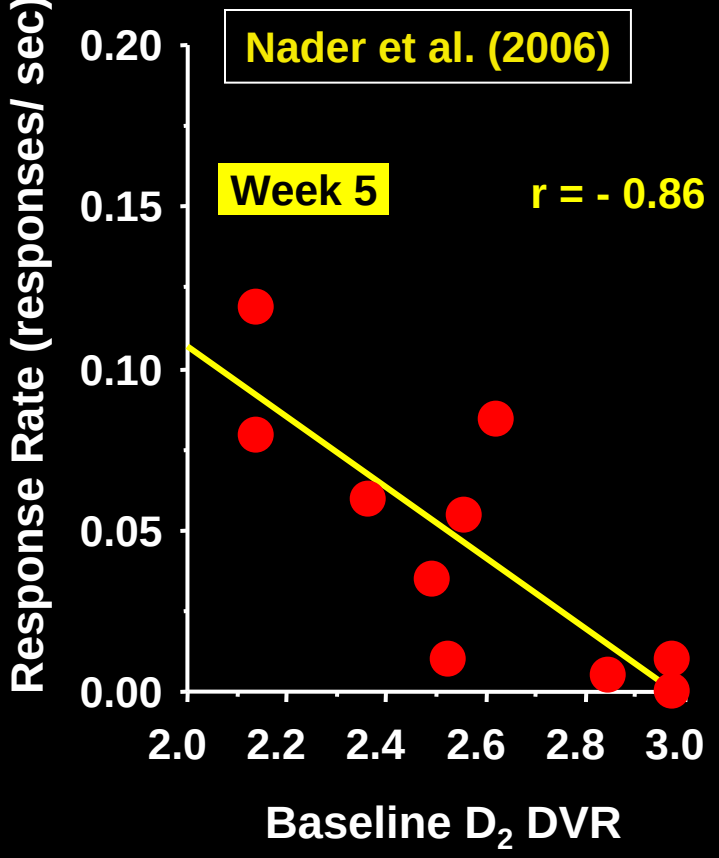
   Dopamine D2 receptor availability, cocaine self-administration

3. Variables that are affected by abstinence and social re-organization

   Dopamine D2 receptor availability, cocaine self-administration

Inverse Relationship between D2 Availability and Reinforcement





Types of Animal Models

I. Predictive

- Does not resemble the disease in terms of etiology or symptomatology, but is predictive of clinical outcome.

II. Isomorphic

- Resembles the disease in terms of symptoms and predictive outcome, but is artificially produced in the lab.

III. Homologous

- Resembles the disease in terms of etiology, symptomatology, and predictive outcome.

Genetic vs. Environmental Modulation

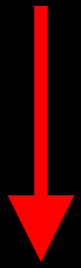
Trait Variable - a distinguishable characteristic of one's personal nature.

State Variable - a distinguishable characteristic attributable to environmental circumstances.

Modeling Addiction: Trait vs. State Variables

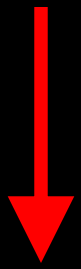
Vulnerability

- genetic or environmental factors mediating predisposition during early exposure



Maintenance

- behavioral & neurobiological consequences of repeated use



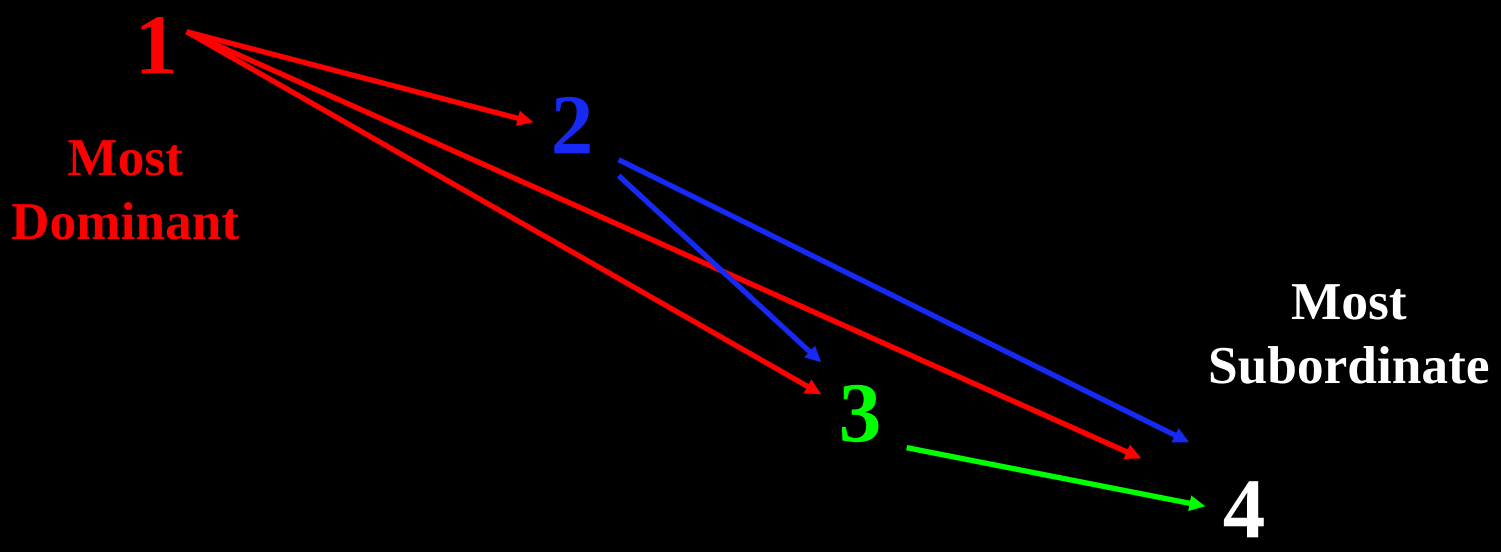
- recovery of cocaine-induced changes

Abstinence

- long-term changes that influence relapse

Social Rank

Based on the outcomes of agonistic encounters (i.e. fights)



Vulnerability to Cocaine Use

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

Individually-housed (n=20)

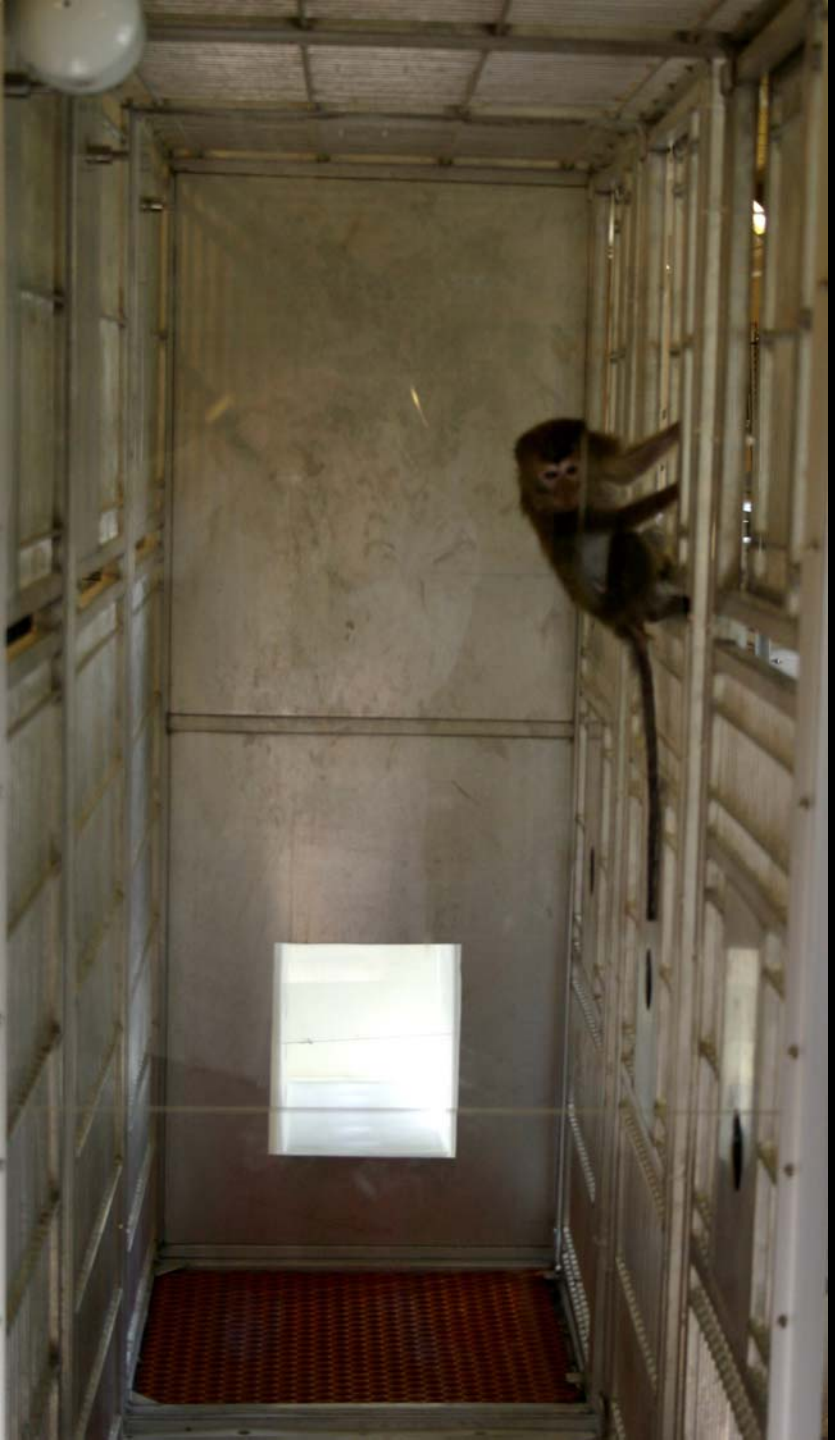
PET imaging
Hormonal profiles
Locomotor reactivity

Socially-housed (n=4/group)

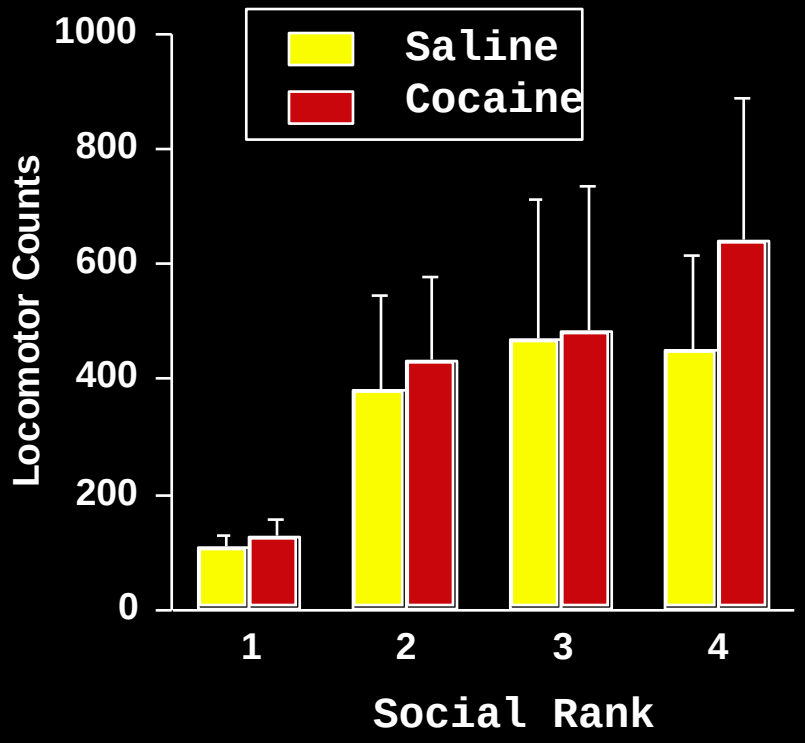
PET imaging
Hormonal profiles
Social behavior

Cocaine self-administration

PET imaging



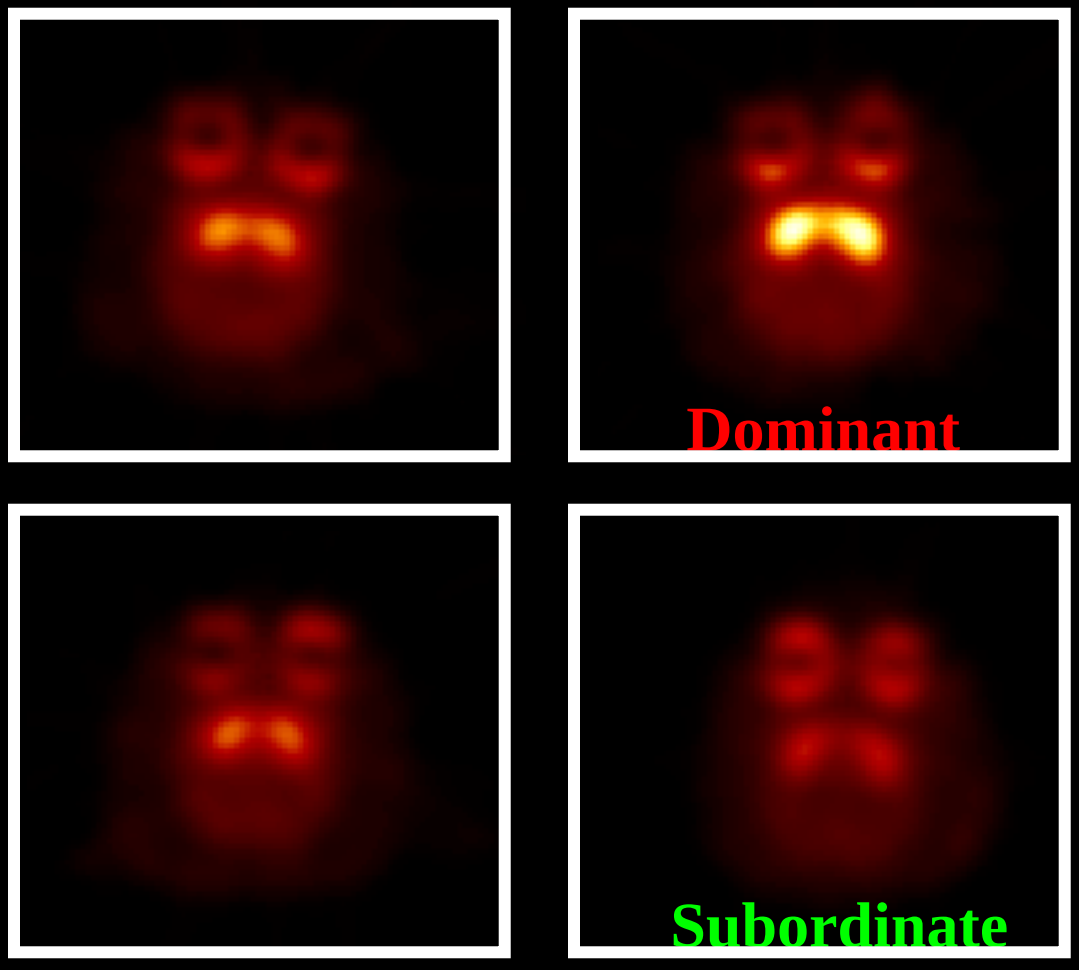
Locomotor Reactivity



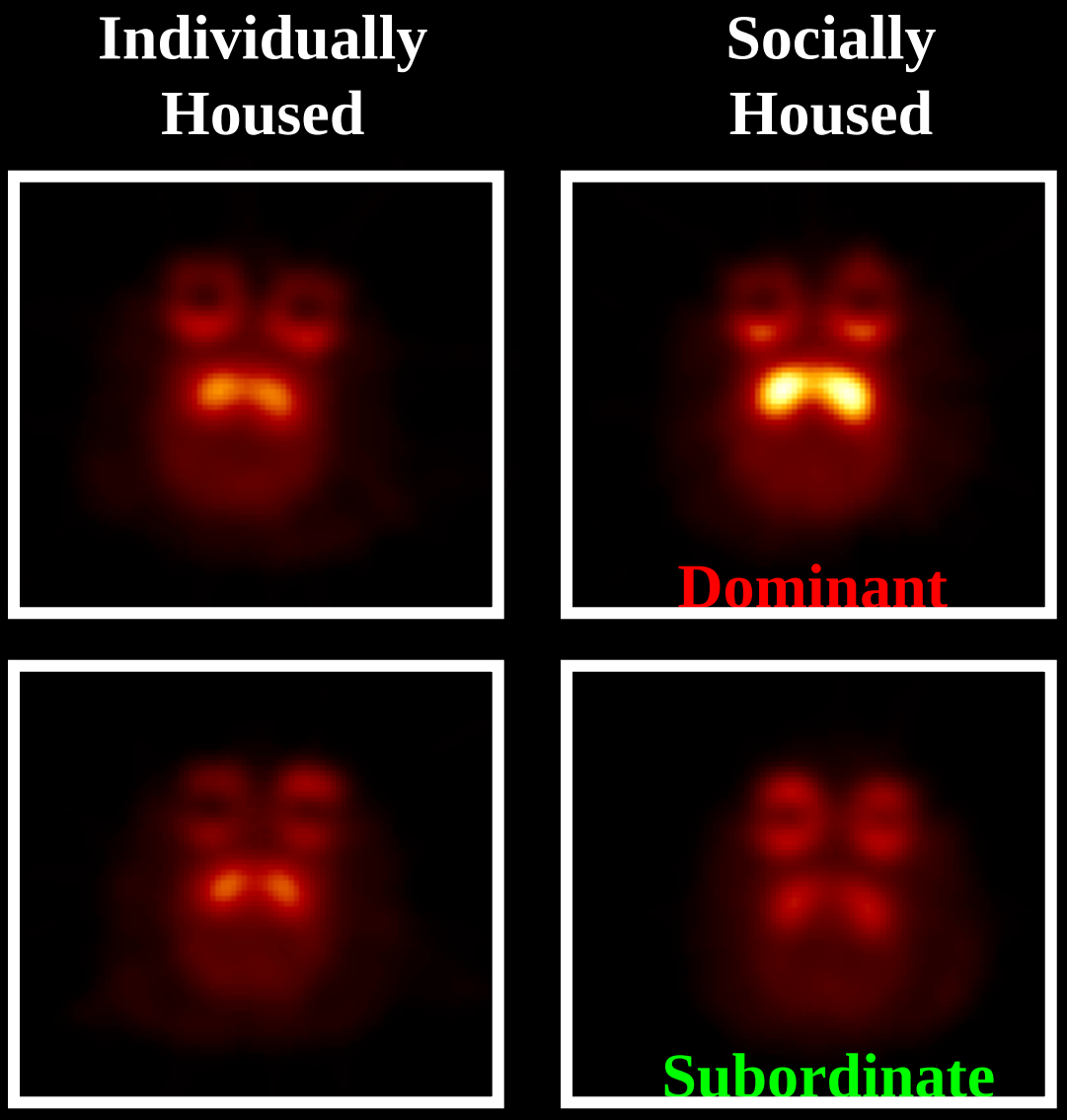
Morgan et al. (2000) *Am J Primatol* 52: 115-131

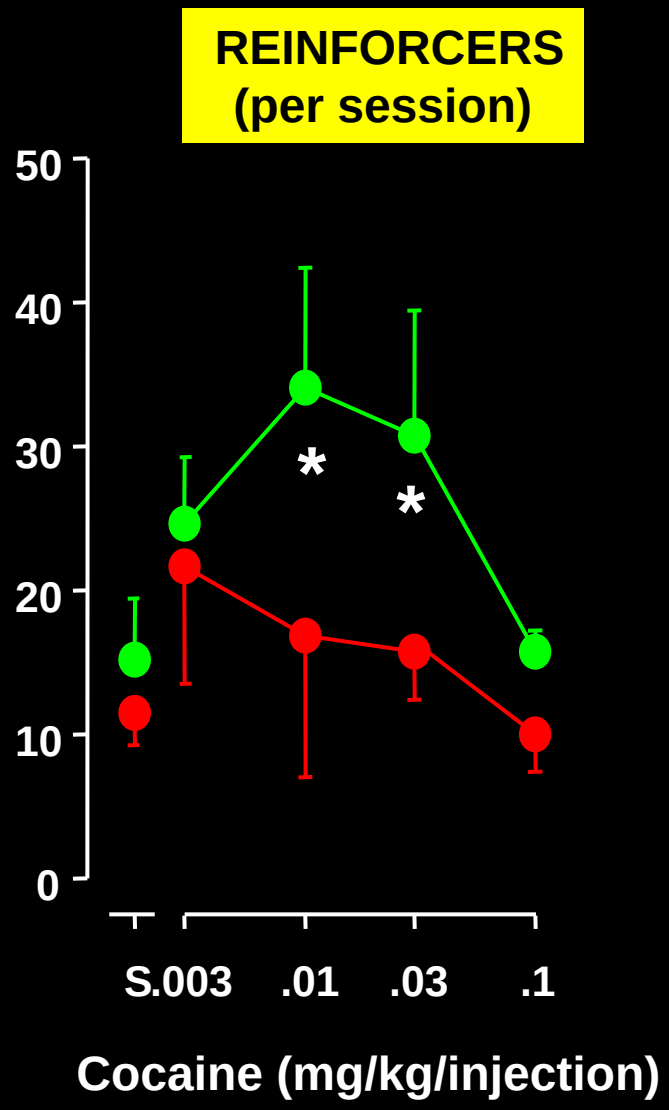
Individually Housed

Socially Housed



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





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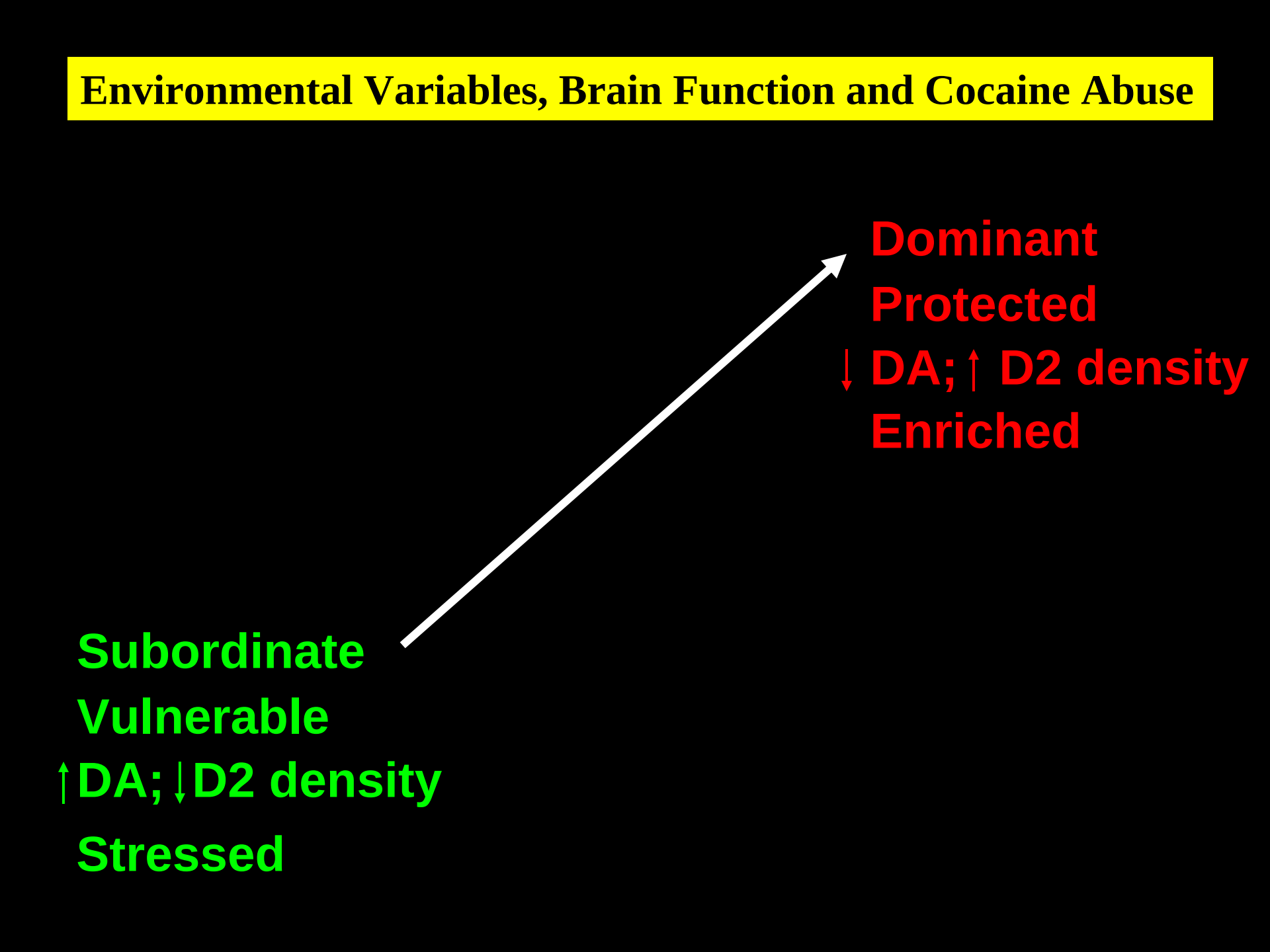
Environmental Variables, Brain Function and Cocaine Abuse



Female Cynomolgus Monkeys

Individually housed

n = 16

Socially housed

n = 4 / pen

Behavioral measures

- Locomotor activity
- Impulsivity, novel object

PET

- [^{18}F]FCP
- [^{18}F]FCT
- [^{11}C]DASB

CSF

- 5-HIAA, HVA, 5-HT

Behavioral measures

- Social behavior
- 5-HT drugs

PET

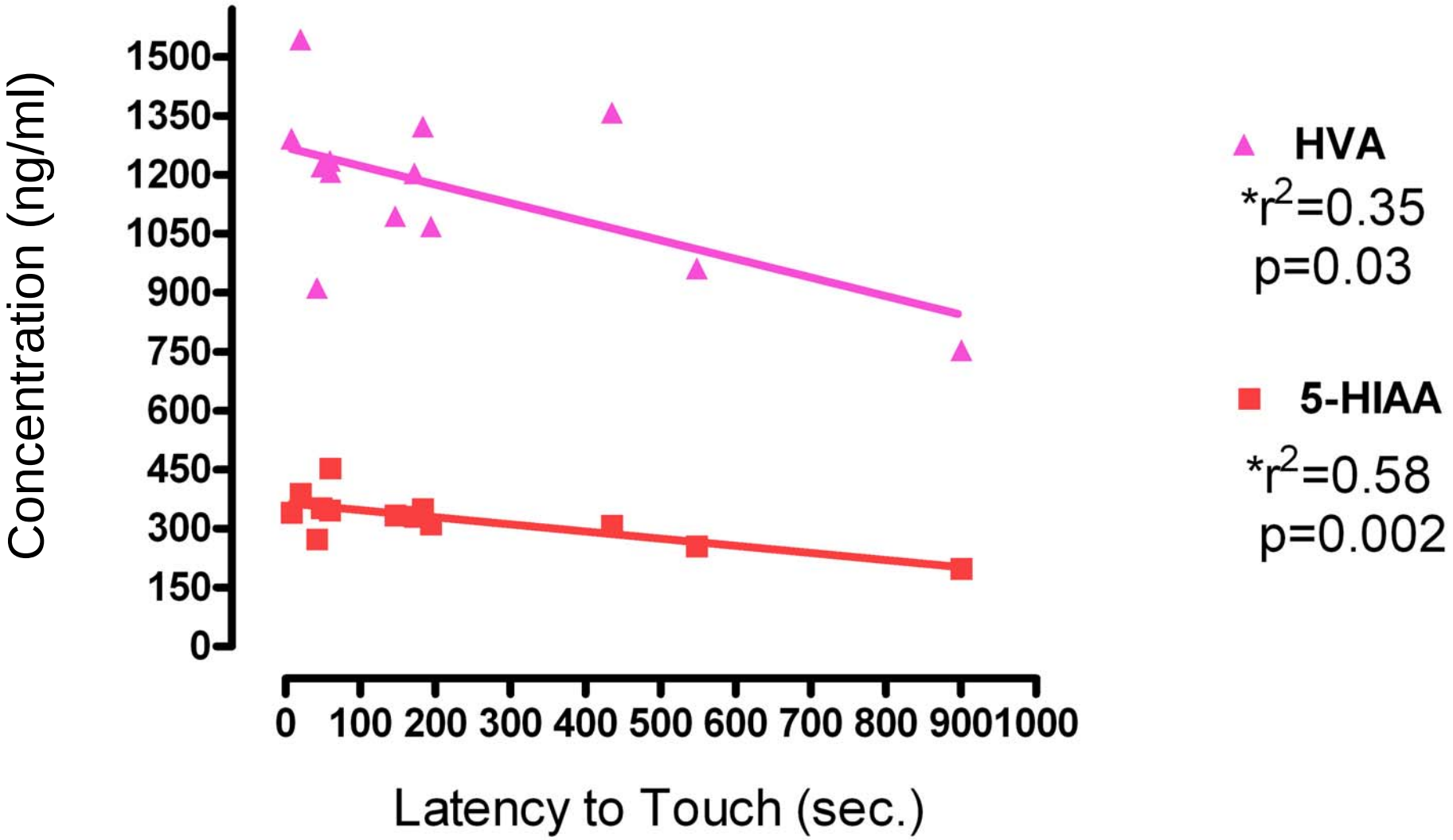
- [^{18}F]FCP
- [^{18}F]FCT
- [^{11}C]DASB

CSF

- 5-HIAA, HVA, 5-HT

Cocaine self-administration

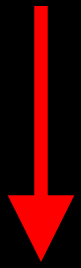
Impulsivity and CSF Metabolite Levels



Modeling Addiction: Trait vs. State Variables

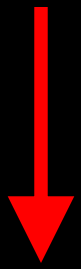
Vulnerability

- genetic or environmental factors mediating predisposition during early exposure



Maintenance

- behavioral & neurobiological consequences of repeated use

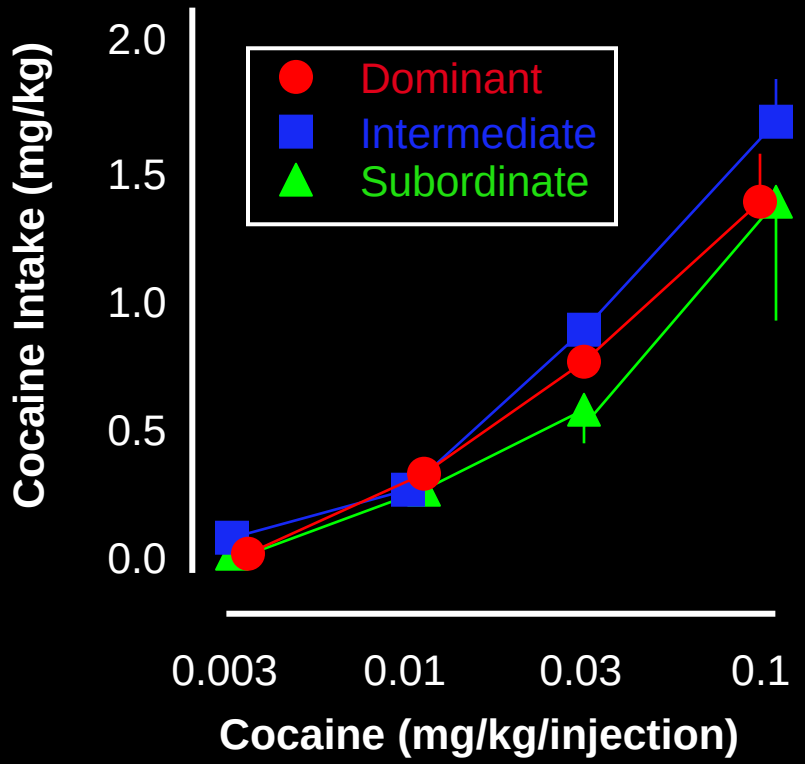


- recovery of cocaine-induced changes

Abstinence

- long-term changes that influence relapse

After 2-5 years of cocaine self-administration …



Czoty et al. (2004) *Psychopharmacology* 174: 381-388

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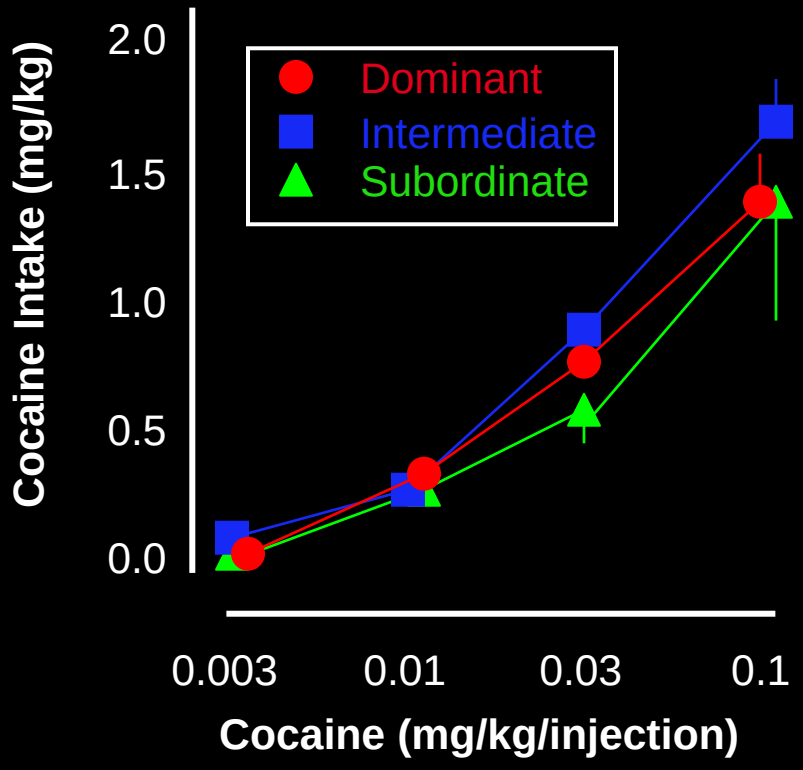
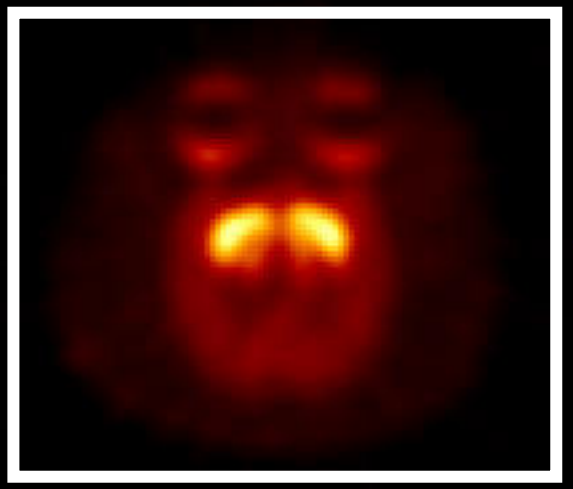
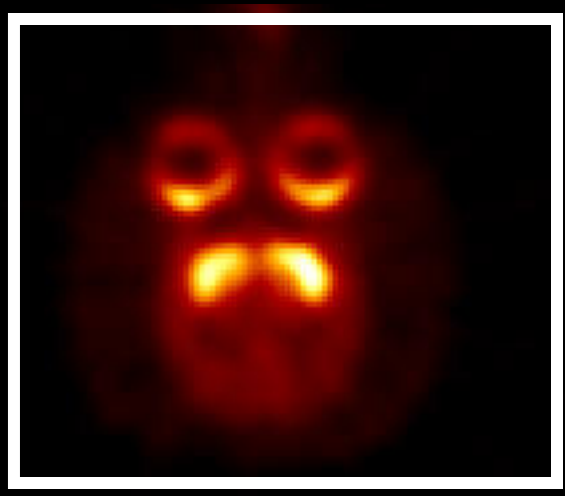


dominant



subordinate



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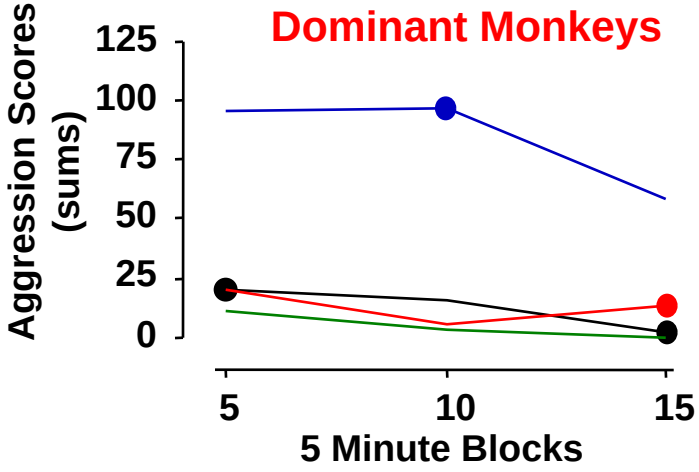
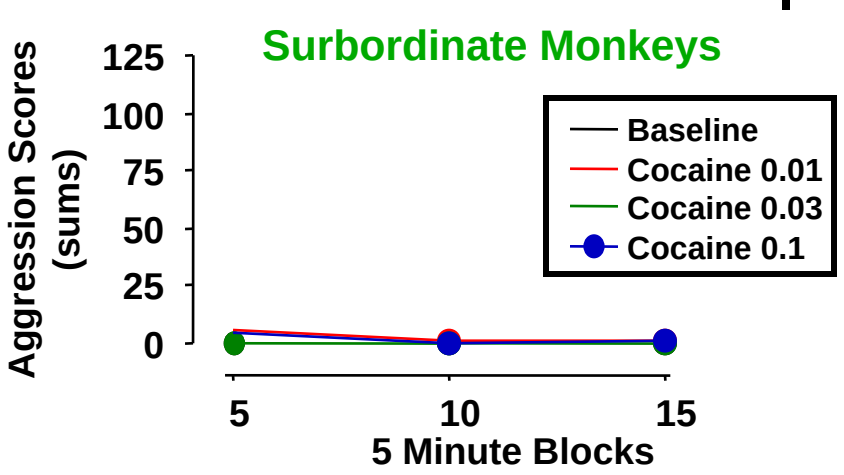
Interactions of cocaine reinforcement with social behavior

Methods

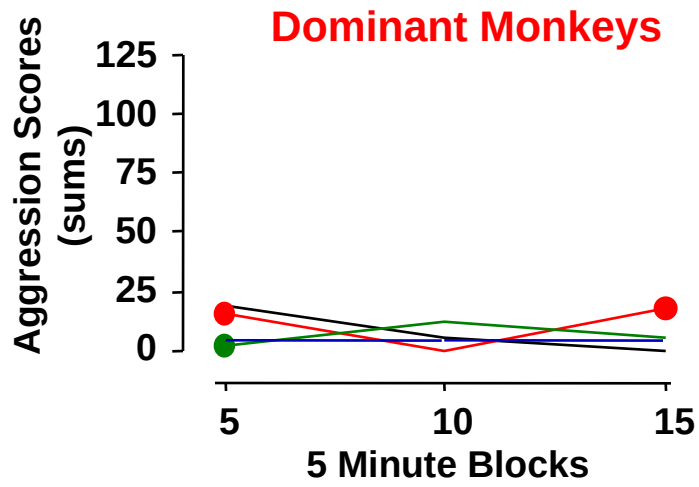
- **Cocaine (saline, 0.03-0.3 mg/kg/inj) dose-response curve determined.** ***Only one monkey per social group self-administered cocaine (Mon-Fri).***
- **Dependent variables:**
  (a) response rates as a function of dose
  (b) social behavior (aggression, affiliation)

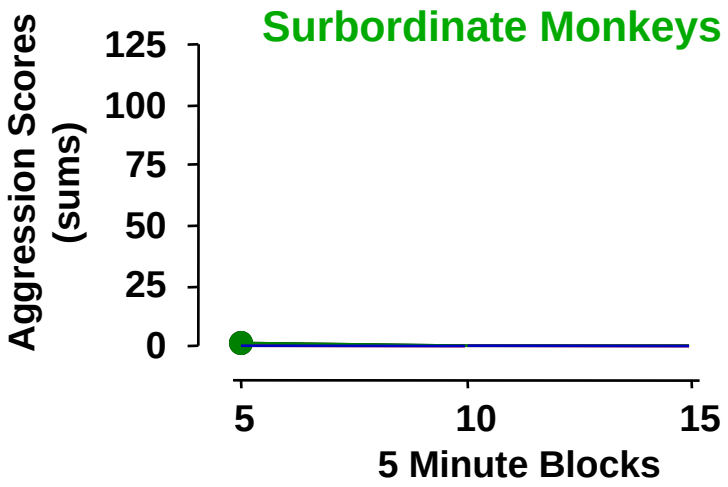
Dominant Monkeys Self-Administering





Surbordinate Monkeys Self-Administering





Issues Related to Decision Making in Cocaine Abusers

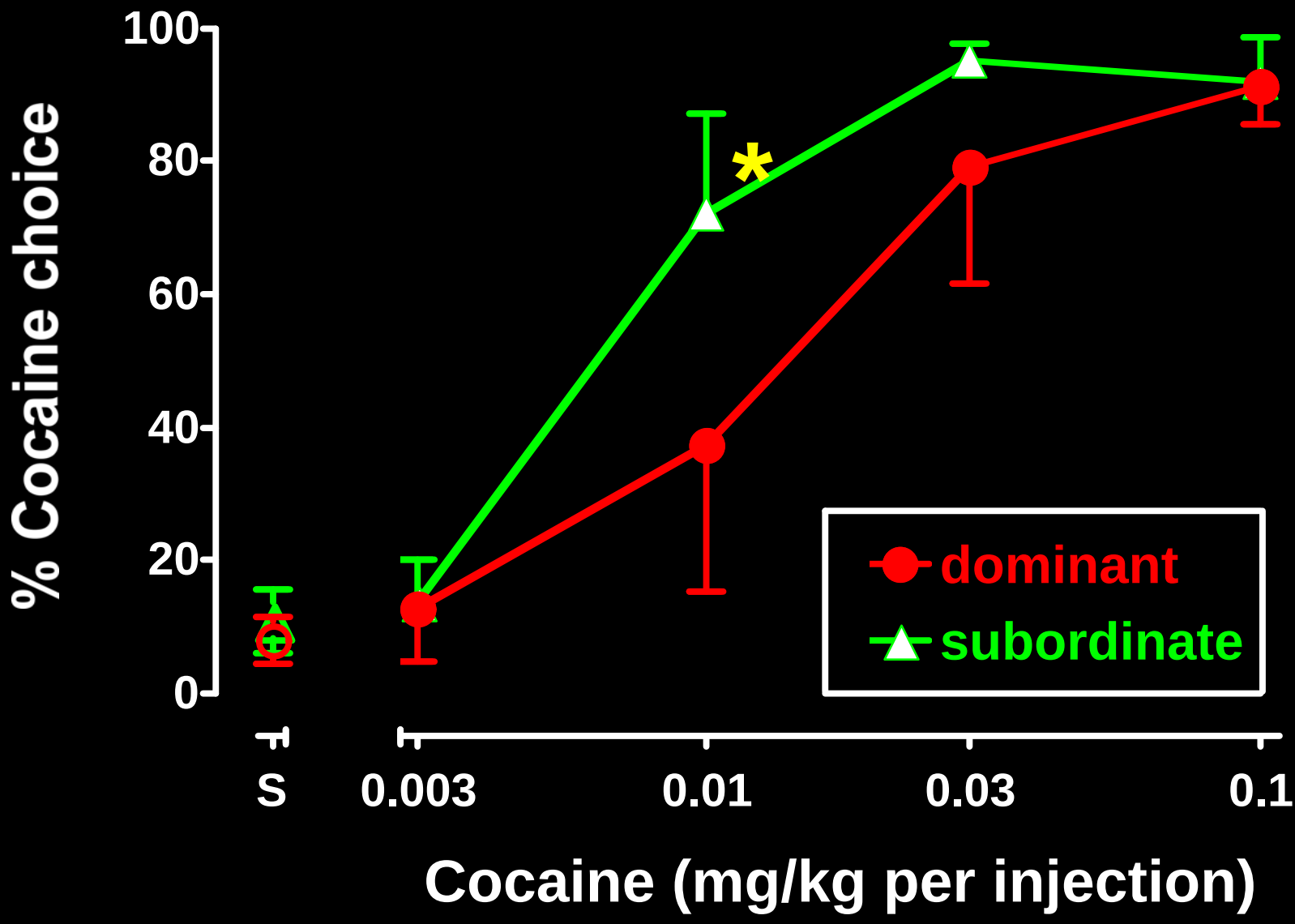
Cocaine abusers:

- **make poor decisions**
- **are highly impulsive**
- **over-value cocaine relative to other reinforcing activities**

Single-lever self-administration procedures do not take into account the aspect of *choice*

Solution: *concurrent (simultaneous) availability of cocaine and another reinforcer*

Cocaine choice in socially housed monkeys



Czoty et al. (2005) *JPET* 312: 96-102

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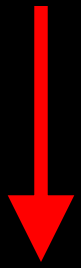

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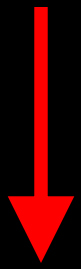
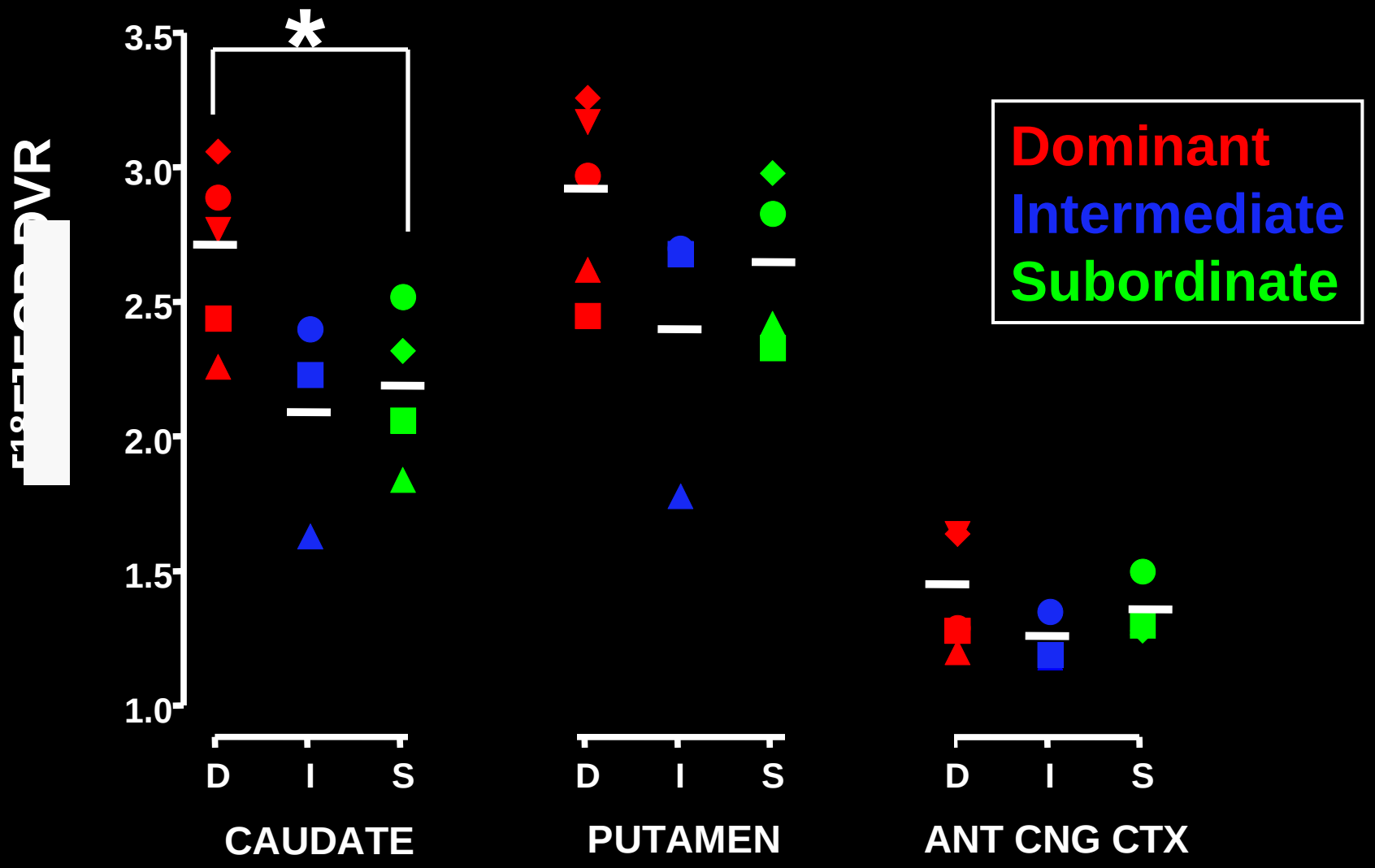


Abstinence

- recovery of cocaine-induced changes
- long-term changes that influence relapse

Recovery of rank-related differences during abstinence from cocaine



What's next? Social reorganization:

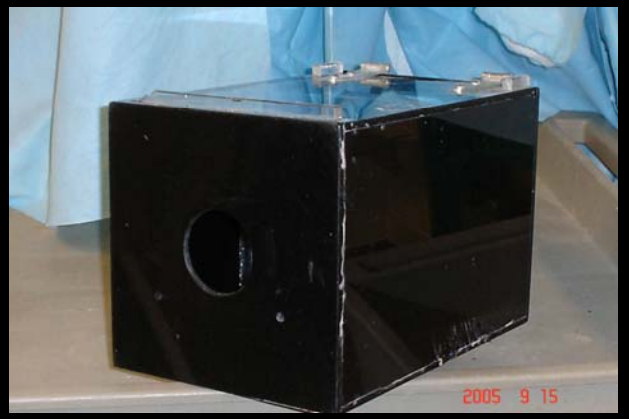
Can changes in the environment produce changes in D2 receptors and cocaine reinforcement?

4 Dominant	4 Subordinate	4 Intermediate
4 Intermediate	2 Intermediate 2 Naive	4 Naïve

Social Reorganization

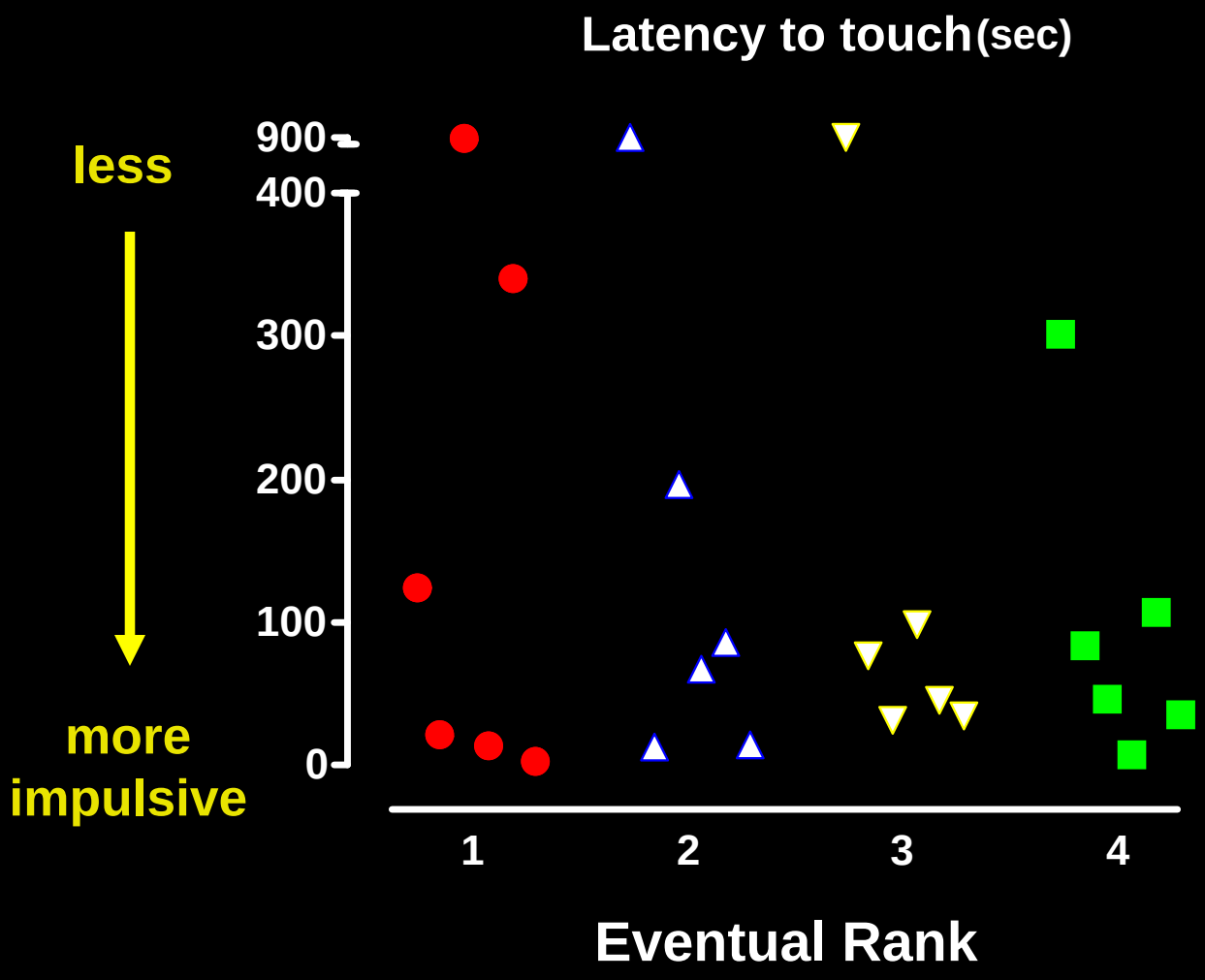
What are some of the predictors of social rank?

Measures of “impulsivity”
Cortisol levels

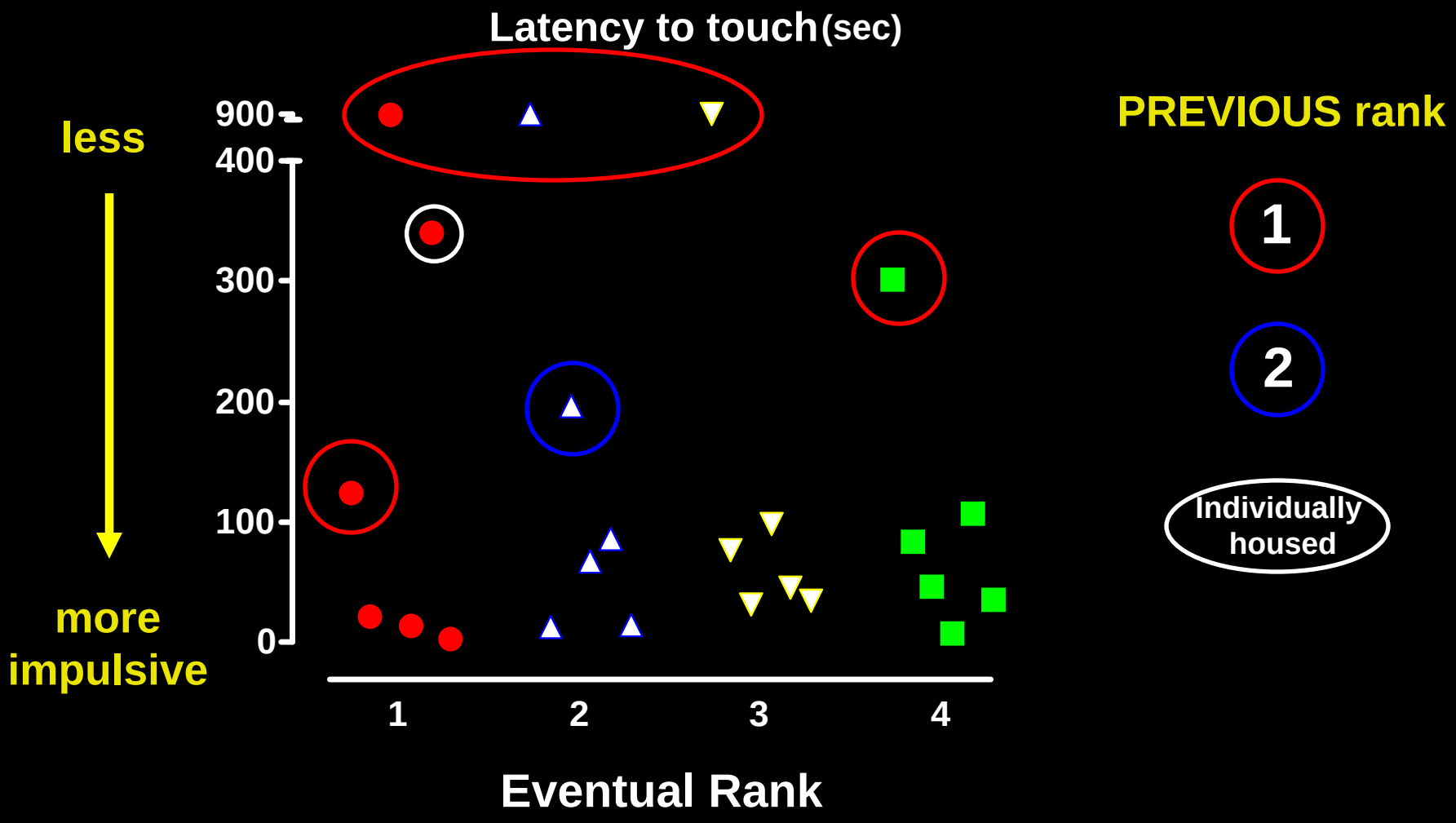


What are some of the consequences of the new social rank?

Cortisol levels
Social behavior
PET imaging
Cocaine self-administration

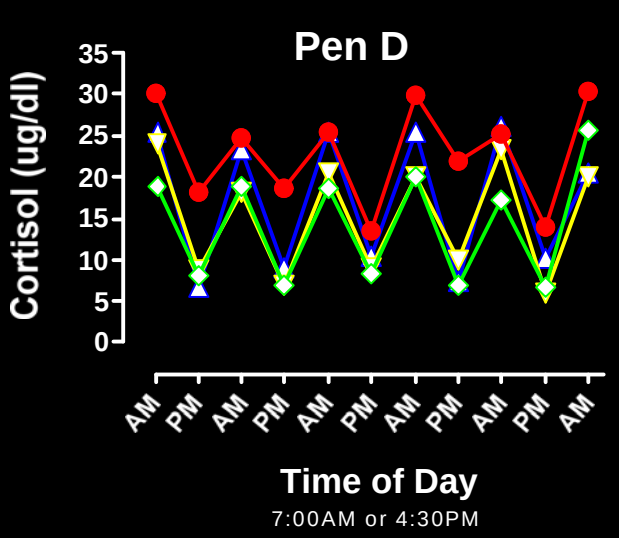


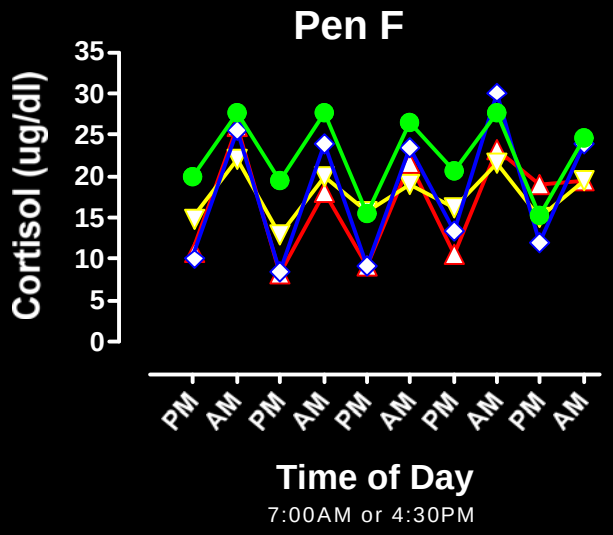
“Impulsivity” did not predict eventual social rank



“Impulsivity” did not predict eventual social rank, but was related to previous social rank.

Diurnal cortisol fluctuations prior to social housing





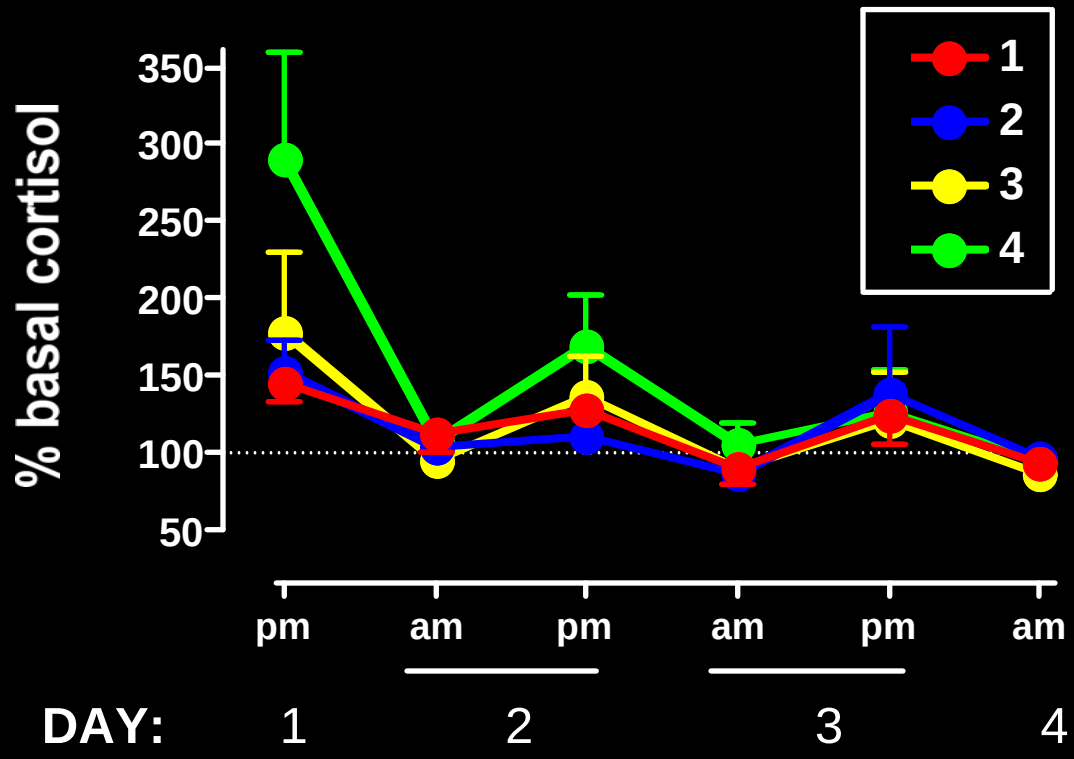
Group data:

Eventual rank	a.m.	p.m.
1	23.8 ± 2.2	14.8 ± 2.4
2	20.0 ± 1.2	11.7 ± 1.9
3	22.2 ± 2.7	11.7 ± 3.0
4	20.4 ± 2.2	10.6 ± 2.4

Basal cortisol levels do not predict eventual rank

Cortisol levels during initial social housing

Monkeys were individually housed overnight, group housed during the day.



n = 6 @ each rank

Social reorganization- determining hierarchy

Average Actions/hour

Aggressive

Initiated: Rank	Received: 1	2	3	4
1	----	1.3	1.3	5.5
2	0.3	----	3.7	5.3
3	0.2	0.3	----	13.0
4	0.2	0.2	0.3	----

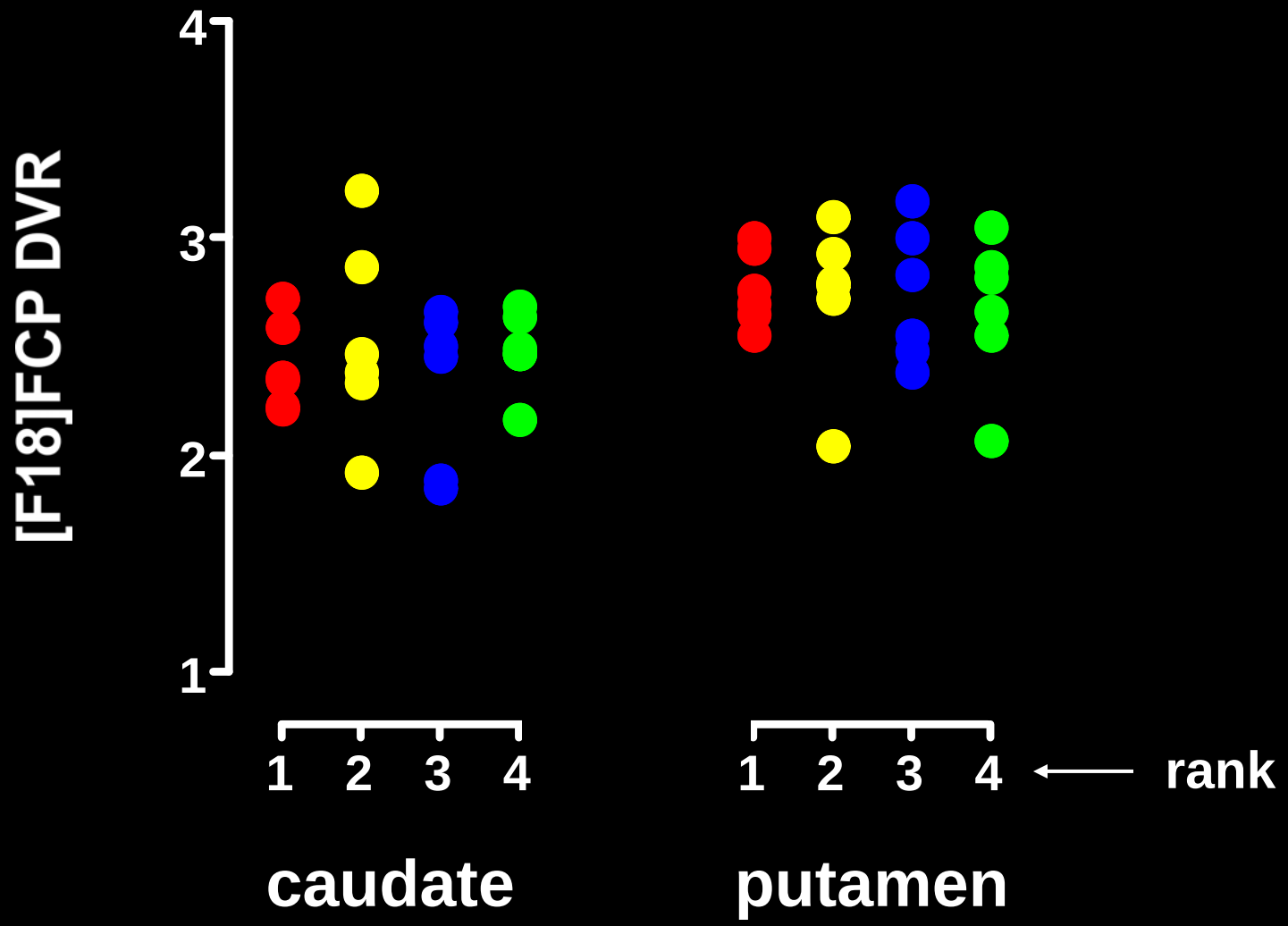
Submissive

Initiated: Rank	Received: 1	2	3	4
1	----	0.1	0.0	0.0
2	4.9	----	0.1	0.0
3	10.6	3.9	----	0.2
4	14.7	9.2	19.8	----

n = 6 @ each rank

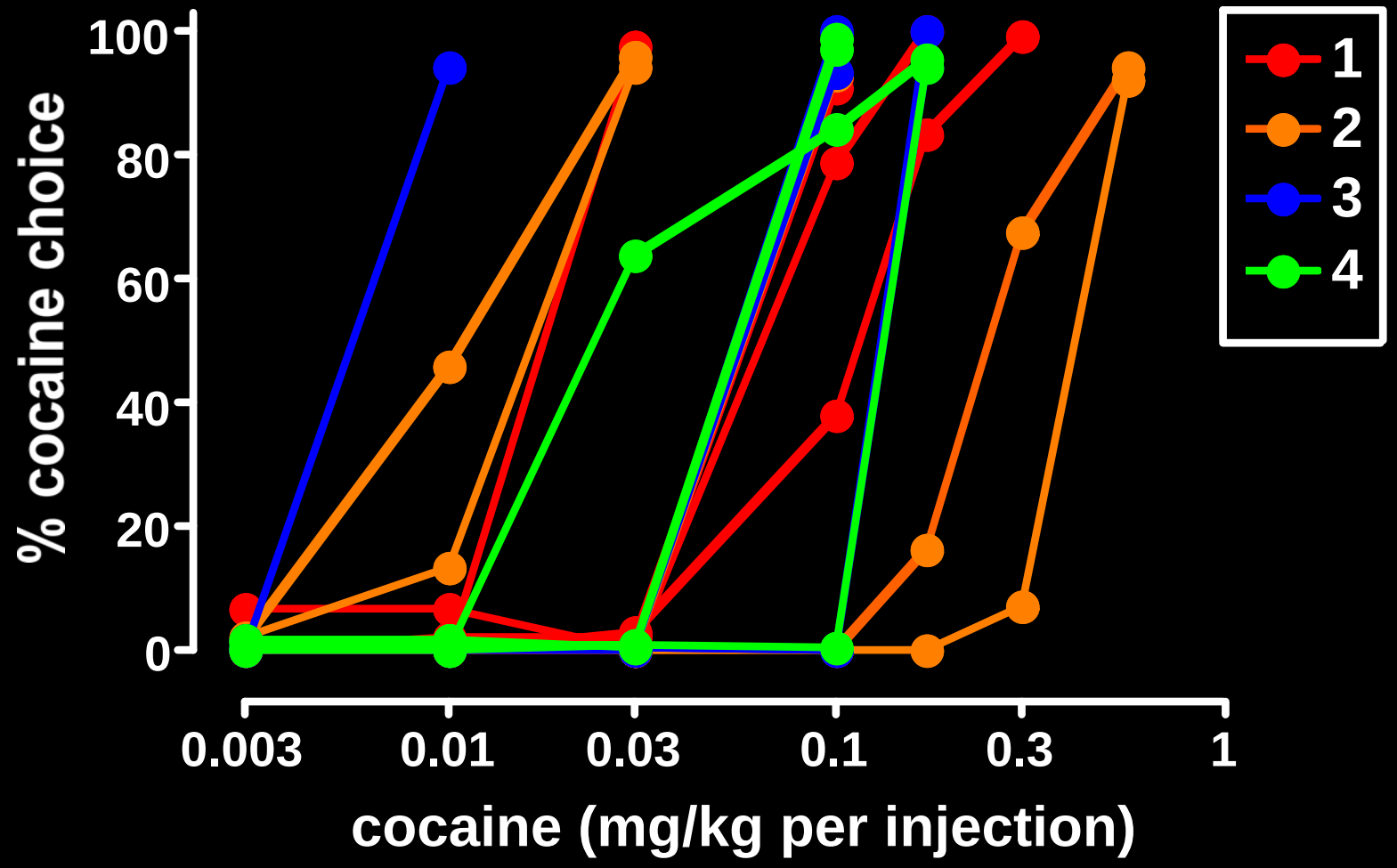
D2 receptor availability in “reorganized” monkeys

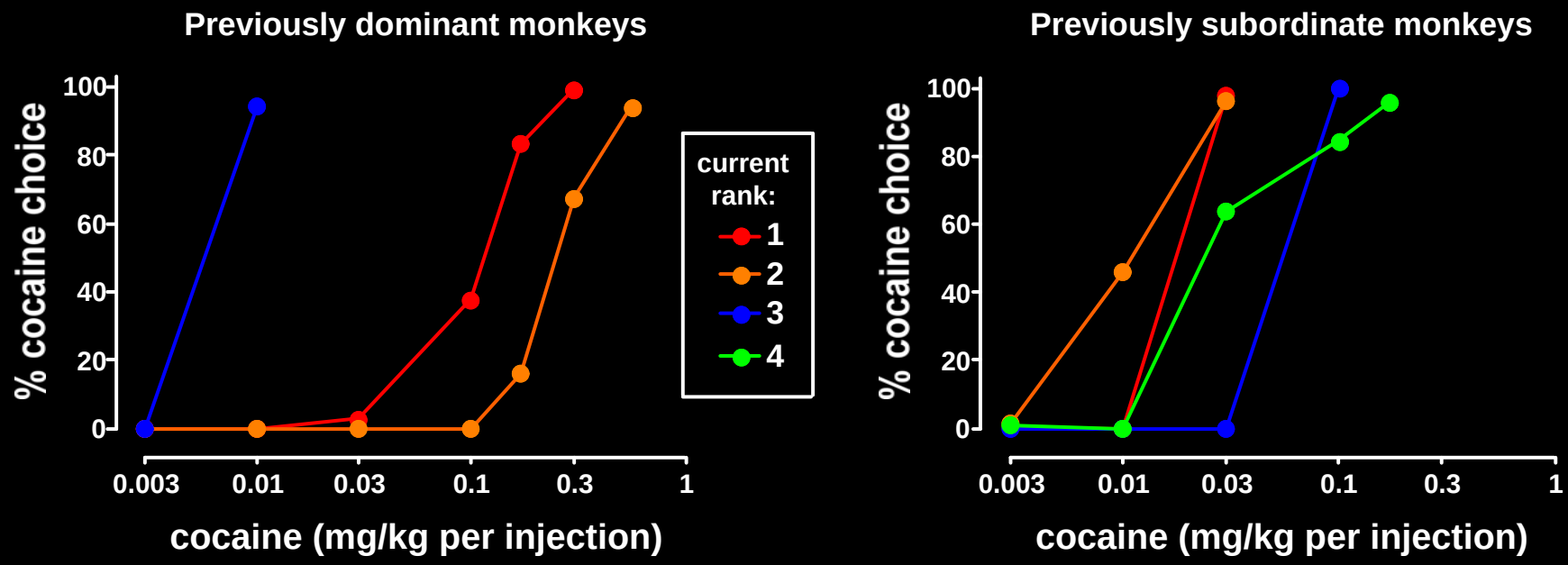
individual subject data



Cocaine choice in “reorganized” monkeys

individual subject data





Influence of environmental variables on the brain and behavior persists, but may be influenced by social housing and/or drug history.

SUMMARY

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

- **the neurobiological basis of vulnerability to addictive effects of drugs. D2 receptors and social rank; CSF and impulsivity.**
- **the influence of environmental variables on brain function and behavior. Social rank and drug choice.**
- **neurobiological changes produced by long-term drug use, abstinence and reorganization. An interaction between previous social rank and current conditions on D2 receptors and cocaine reinforcement .**

SUMMARY

The environment exerts profound effects on brain function that can impact clinical outcomes.

O'Brien and Anthony (2005): education has an inverse relationship with risk of becoming cocaine dependent.

Butzin et al. (2005): work release programs for inmates resulted in greater abstinence rates and higher rates of employment after leaving the program.

Daniel et al. (2006): exercise reduces desire to smoke cigarettes and reduces withdrawal symptoms.

Winkelman (2003): percussion instruments (drums) during treatment. Music reduces stress, is reinforcing, enhances awareness and alleviates isolation.

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DA 17763