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

Michael A. Nader, Paul W. Czoty, Susan H. Nader, Robert Gould, Michelle Icenhower, Natallia Riddick and Jay R. Kaplan
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

Perception of Methylphenidate

- Pleasant
- Unpleasant
- Neutral

**Volkow et al. (1999)**

- $B_{max}/K_d$

- 3.8
- 3.6
- 3.4
- 3.2
- 3.0
- 2.8
- 2.6
- 2.4
- 2.2

**Nader et al. (2006)**

- Response Rate (responses/sec)

- Week 5

- $r = -0.86$

Baseline D2 DVR
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

Abstinence
- recovery of cocaine-induced changes
- long-term changes that influence relapse
Social Rank

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

1. Most Dominant
2. Most Subordinate
3. 
4.
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

Individually Housed

Socially Housed

Dominant

Subordinate

Environmental Variables, Brain Function and Cocaine Abuse

Subordinate
Vulnerable
↑ DA; ↓ D2 density
Stressed

Dominant
Protected
↓ DA; ↑ D2 density
Enriched
Female Cynomolgus Monkeys

**Individually housed**
- n=16

**Behavioral measures**
- Locomotor activity
- Impulsivity, novel object

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

**CSF**
- 5-HIAA, HVA, 5-HT

**Socially housed**
- n=4/ pen

**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

**Concentration (ng/ml)**

- **HVA**
  - $r^2=0.35$
  - $p=0.03$

- **5-HIAA**
  - $r^2=0.58$
  - $p=0.002$

**Latency to Touch (sec.)**
Modeling Addiction: Trait vs. State Variables

Vulnerability
• genetic or environmental factors mediating predisposition during early exposure

Maintenance
• behavioral & neurobiological consequences of repeated use

Abstinence
• recovery of cocaine-induced changes
• long-term changes that influence relapse
After 2-5 years of cocaine self-administration ...

After 2-5 years of cocaine self-administration ...

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)
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
Modeling Addiction: Trait vs. State Variables

**Vulnerability**
- genetic or environmental factors mediating predisposition during early exposure

**Maintenance**
- behavioral & neurobiological consequences of repeated use

**Abstinence**
- recovery of cocaine-induced changes
- long-term changes that influence relapse
Recovery of rank-related differences during abstinence from cocaine

CAUDATE

PUTAMEN

ANT CNG CTX
What’s next? Social reorganization: Can changes in the environment produce changes in D2 receptors and cocaine reinforcement?
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.
Basal cortisol levels do not predict eventual rank

Diurnal cortisol fluctuations prior to social housing

**Pen D**

<table>
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<th>Eventual rank</th>
<th>a.m.</th>
<th>p.m.</th>
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<tbody>
<tr>
<td>1</td>
<td>23.8 ± 2.2</td>
<td>14.8 ± 2.4</td>
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<tr>
<td>2</td>
<td>20.0 ± 1.2</td>
<td>11.7 ± 1.9</td>
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<td>3</td>
<td>22.2 ± 2.7</td>
<td>11.7 ± 3.0</td>
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<tr>
<td>4</td>
<td>20.4 ± 2.2</td>
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**Pen F**

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<td>20.4 ± 2.2</td>
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**Group data:**
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

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<th>Aggressive</th>
<th>Received</th>
<th>Submissive</th>
<th>Received</th>
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<td>Initiated</td>
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<tr>
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<td>1.3</td>
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<td>0.2</td>
<td>0.3</td>
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$n = 6 @ each rank$
D2 receptor availability in “reorganized” monkeys

*individual subject data*

[D18]FPC DVR

caudate

putamen

rank
Cocaine choice in “reorganized” monkeys

Individual subject data

% cocaine choice

Cocaine (mg/kg per injection)
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.


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.

# Acknowledgments

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<tr>
<th>Drake Morgan</th>
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