Monkey Models of Cocaine Abuse: Sex, Drugs and the Environment

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Why Study Addiction?

Illegal drugs: $181 billion/year
Alcohol: $185 billion/year
Tobacco: $158 billion/year
Total: $524 billion/year

Twice the cost of any other brain disease!!

How should we attack the drug abuse problem?

By reducing the **supply** of drugs??

- source country control
- interdiction
- domestic enforcement
  - increase border patrols & searches
  - increase law enforcement
  - imprisonment of dealers

By reducing the **demand** for drugs??

- punishment
- treatment
- education

Research!
Is Treatment Too Expensive?

- Outpatient Treatment (cocaine): $2,722
- Methadone Maintenance (heroin): $3,500
- Residential Treatment (cocaine): $12,467
- Probation: $16,691
- Incarceration: $39,600
- Untreated Addiction: $43,200

Robert Wood Johnson (2001)
Individual Differences in Drug Effects

- **Clinical trials**: 40-50% positive responses. What’s different about them vs. the others in which the drug was not effective?
- **Drug history**: Prenatal drug exposure
- **Environmental context**: availability of alternative reinforcers; social context
- **Sex differences**: females sometimes respond similarly as males and sometimes not. Why?
“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
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.
Methods: i.v. cocaine self-administration
From Living Links, Yerkes Regional Primate Research Center, Emory University
Why use nonhuman primates?

1. similar to humans in neuroanatomy, neurophysiology
2. studies can last for years (*within-subjects designs*)
3. extensive behavioral repertoire and social structure
4. can be trained to perform complex tasks / behaviors
5. lack of confounds common to human studies:
   - polydrug use
   - self-reports
   - monkeys always show up!
Research Subjects

*Macaca mulatta*
Rhesus macaque

*Macaca fascicularis*
Cynomolgus macaque
Research Strategies

Behavioral Pharmacology of Cocaine Abuse Using Drug Self-Administration, Drug Discrimination and Cognition Paradigms

- Effects of D3 compounds (e.g., PG 619)
- Effects of “top-down” treatments (buspirone, varenicline)

Behavioral Pharmacology of Cocaine Abuse Using PET Imaging of the Dopamine D2 Receptor

- Effects of social rank in male and female monkeys
- Effects of prenatal drug exposure on DA receptor function in adults
Tyrosine → DOPA → DA

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

Bennett et al. (1995)
<table>
<thead>
<tr>
<th>Dopamine Receptors</th>
<th>D1-like</th>
<th>cAMP</th>
<th>D1</th>
<th>Caudate-Putamen</th>
<th>Nucleus Accumbens</th>
<th>Olfactory Tubercles</th>
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<td>D5</td>
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<td>D2-like</td>
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<td>Nucleus accumbens</td>
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<td>Olfactory Tubercles</td>
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<td></td>
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<td></td>
<td>Frontal cortex</td>
<td></td>
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<td></td>
<td>D4</td>
<td></td>
<td></td>
<td></td>
<td>Brainstem</td>
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PET Imaging Protocol

Tyrosine → DOPA → DA

Receptor

<table>
<thead>
<tr>
<th>Receptor</th>
<th>$K_i$ [nM]</th>
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<tbody>
<tr>
<td>$D_1$</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>$D_2$</td>
<td>0.95 ±</td>
</tr>
<tr>
<td>$D_3$</td>
<td>5.46 ±</td>
</tr>
<tr>
<td>$D_4$</td>
<td>144 ±</td>
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Postsynaptic Neuron

$[^{18}F]FCP$ → $[^{18}F]FCT$
Tissue-time activity curve

Distribution Volume Ratio is the ratio of binding in the basal ganglia to the cerebellum.

Higher the number, more radioligand is bound.
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 predisposition or environmental factors
- Host: baseline D2 levels, hormone levels
- Agent: pharmacological history
- Context: social variables

Maintenance

Behavioral & neurobiological consequences of repeated use
- increasing cost of cocaine
- alternative reinforcers
- stressors and enrichers

Abstinence

Recovery of cocaine-induced changes
- reinstatement
- treatment
D2 receptor availability & sensitivity to stimulants

Does D2 DVR predict rate of cocaine self-administration?


**Significant correlation between D2 DVR and response rate**

Week 5

![PET scan](image)

Baseline D2 DVR vs. Response Rate (responses/sec)

- **r = -0.86**
Social Housing: a model of chronic stress & enrichment

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

- **Most Dominant**
  - > greater access to resources
  - > groomed more by others

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

- **Most Subordinate**
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
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)

D2 receptor levels are state variables for social rank.

Environmental Variables, Brain Function and Cocaine Abuse

- Subordinate
- Vulnerable
  - $\uparrow$ DA; $\downarrow$ D2 density
- Stressed

- Dominant
- Protected
  - $\downarrow$ DA; $\uparrow$ D2 density
- Enriched
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)
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).
Menstrual cycle influences D2 receptor availability

D2 receptor availability was significantly lower during follicular (F) versus luteal (L) phase

Czoty et al., Neuropsychopharmacology (2008)
D2 receptor availability increased in dominant females

Nader et al., 2012

D2 DVRs from [18F]FCP PET Studies

<table>
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<th>Rank</th>
<th>Indiv</th>
<th>Social</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.18</td>
<td>3.78</td>
<td>+ 21%</td>
</tr>
<tr>
<td>2</td>
<td>2.92</td>
<td>3.36</td>
<td>+ 17%</td>
</tr>
<tr>
<td>3</td>
<td>2.94</td>
<td>3.16</td>
<td>+ 9%</td>
</tr>
<tr>
<td>4</td>
<td>2.78</td>
<td>2.93</td>
<td>+ 5%</td>
</tr>
</tbody>
</table>
D2 receptor availability increased in dominant females

Nader et al., 2012
### Male monkeys
- D2 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 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) and unpublished work
Harassment, Mortality, and Survival in Group Living Male and Female 30 Monkeys

From Jay Kaplan
What’s next with females?

What is relationship between D2-like receptors and cocaine SA?

![Graph showing the relationship between Baseline D2 DVR and Response Rate (responses/sec). The correlation coefficient, r, is -0.86.](image)

**Graph Details:**
- **Baseline D2 DVR:** 2.0, 2.2, 2.4, 2.6, 2.8, 3.0
- **Response Rate:** 0.00, 0.05, 0.10, 0.15, 0.20
- **Correlation Coefficient:** $r = -0.86$
What’s next with females?

What is relationship between D2-like receptors and cocaine SA?
What about chronic cocaine exposure?

D2-like receptors, as assessed with PET imaging.

D₃ receptors, as assessed with novel pharmacological tools.

*These studies have only been conducted in males, to date.*
Changes in $D_2$ DVR as a consequence of cocaine self-administration

Cocaine-Induced Changes in D2/D3 Receptor Availability

Baseline | 6 months | 12 months

Staley and Mash (1996); Nader et al. (2002, 2006)
D₂/D₃ Mediated Unconditioned Behaviors

Collins et al., 2007

Number of Yawns vs. Dose (mg/kg; s.c.)

- Yawning
- Hypothermia
- D₂, D₃

Graph showing the relationship between dose and number of yawns, with a peak at around 0.3 mg/kg s.c.
No Differences in Unconditioned Behaviors Elicited by Quinpirole (i.v.) in Cocaine-Experienced and Cocaine-Naïve Monkeys

Blaylock et al., 2011
D₃ Partial Agonist PG 619 Elicits “Agonist Effect” After Cocaine Exposure

Blaylock et al., 2011
D₃ Partial Agonist PG 619 Elicits “Agonist Effect” After Cocaine Exposure

Blaylock et al., 2011
Effects of PG 619 on Cocaine-Induced Reinstatement:

Blaylock et al., 2011
D2 binding potential during cocaine abstinence

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

12 yrs old – present: WFUSM
Currently monkeys are about 17-18 years old
Prenatal Cocaine Exposure and D2-like Receptor Function

PET imaging of D2 receptors

- **Controls (n=7)**
- **Prenatal Cocaine (n=10)**

<table>
<thead>
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<th>Regions of Interest</th>
<th>Average FCP DVR</th>
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<tbody>
<tr>
<td>Cd</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>Pt</td>
<td>3.2 ± 0.3</td>
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**Quinpirole-induced yawning**

- **C**
  - **GROUP COMPARISON**
  - **13 years following prenatal cocaine exposure**

![Graph showing number of yawns vs. quinpirole dose](image)
Prenatal Cocaine Exposure and D2-like Receptor Function

PET imaging of D2 receptors

Controls (n=7)
Prenatal Cocaine (n=10)

Average FCP DVR

Regions of Interest

Hamilton et al. (2010)

$r^2 = 0.79$
p < 0.001
Acquisition of Cocaine Self-Administration

AUC *p < 0.05
Animal Models of Impulsivity

• Children exposed to cocaine *in utero* exhibited poor impulse control

• High impulsivity is a predictor for greater likelihood to self-administer drugs of abuse in animal and human studies

Bendersky and Lewis, 1998; Savage et al., 2005; Perry et al., 2005; Dalley et al., 2007; Alessi et al., 2003
Delay Discounting
Delay Discounting

0 – 300-sec
Determining Indifference Points

Prenatally Cocaine Exposed

R-1568

IP = 49.7

% Choice Larger Reinforcer

Delay Associated with Larger Reinforcer (sec)

Control

R-1564

IP = 99.9

% Choice Larger Reinforcer

Delay Associated with Larger Reinforcer (sec)
Food-Food Choice

Less impulsive

More impulsive

Hamilton et al. (2011)
Delay Discounting
Delay Discounting

0 – 300-sec
0-sec delay

Brutcher et al. (in preparation)
Cocaine-Food Choice

![Bar chart showing the indifference point (sec) for Control and Cocaine in utero groups.](chart.png)
Interactions Between Social Behavior and Cocaine

Saline → Individually Housed → Cocaine Self-Admin

Tx → Individually Housed → Cocaine Self-Admin

Saline → Socially Housed → Cocaine Self-Admin

Tx → Socially Housed → Cocaine Self-Admin
Medications for cocaine dependence: dopaminergic strategies

1. agonist
2. partial agonist
3. antagonist

intrinsic efficacy

FULL
- dopamine
- quinpirole

(-) NPA

apomorphine

terguride

ariepilpazole

eticlopride

NONE
CHRONIC ARIPIPRAZOLE DIFFERENTIALLY AFFECTS COCAINE CHOICE ACCORDING TO SOCIAL RANK

Effects of 5 days of treatment with 0.03 mg/kg ARI on cocaine choice in 2 dominant (top row) and two subordinate monkeys (bottom row). Overall, ARI at some dose decreased cocaine choice in 3 of 4 dominant monkeys tested to date. Of 5 subordinates tested to date, ARI increased cocaine choice in three monkeys and had no effect in 2 monkeys.
Caudate and Putamen

[18F]FCP DVR

Chronic Aripiprazole and D2R availability

0.03 mg/kg per day

pre post pre post

Czoty and Nader (under review)
Summary

• D2 receptor availability is inversely related to rates of cocaine self-administration.

• Males < follicular females < luteal females.
Summary

• D2 receptor availability increased as a result of becoming dominant and this protected male monkeys from cocaine reinforcement.

• Sub Male < Sub Fem < Dom Male < Dom Fem
Summary

• Chronic cocaine exposure robustly decreases D2 receptor availability and may increase DAT.

• Pharmacotherapy should increase D2 receptor levels in males and (perhaps) decrease D2 levels in females.
Implications

1. There is always evidence for individual differences in drug effects. We typically attribute this variability to a lack of “robust” treatment effect, but these data are relevant to symptomatology of addiction.

2. Animal models have the power to associate etiology with clinically relevant outcome.

3. Drug history, social context, sex of the individual are all critical factors in delineating treatment strategies.
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