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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevalence (%)</th>
<th>Treatment Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>55.6</td>
<td>Campral, Revia</td>
</tr>
<tr>
<td>Marijuana</td>
<td>35.6</td>
<td>None</td>
</tr>
<tr>
<td>Narcotics</td>
<td>4.8</td>
<td>Methadone, Suboxone</td>
</tr>
<tr>
<td>Cigarettes (past 30 days)</td>
<td>10.5</td>
<td>NRT, Chantix, Welbutrin</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>6.7</td>
<td>None</td>
</tr>
<tr>
<td>MDMA (Ecstasy)</td>
<td>2.7</td>
<td>None</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2.3</td>
<td>None</td>
</tr>
<tr>
<td>Ritalin</td>
<td>1.2</td>
<td>None</td>
</tr>
</tbody>
</table>

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?

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

- **M. mulatta** (Rhesus monkey)
  - phylogenetic, neuroanatomical, neurohormonal similarity
  - within-subjects designs
  - longitudinal studies
  - social hierarchies
  - complex behaviors
  - females: ~ 28 day menstrual cycle

- **M. fascicularis** (Cynomolgus monkey)

From Living Links, Yerkes National Primate Research Center, Emory University
Premise: Individual Differences Are a Hallmark of SUD

- Similar cocaine histories
- Similar current patterns of self-administration
Monoamine reuptake blocker
DAT: 173 nM
SERT: 302 nM
NET: 404 nM

Bennett et al. (1995)
PET Imaging Protocol

- Tyrosine
  - DOPA
  - DA
- Postsynaptic Neuron
  - D2
  - D1
- DAT
- [18F]FCP
- [18F]FCT
- [11C]Raclopride
- [18F]FDG
- [11C]PHNO
- [11C]DASB
- [11C]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

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

Data from Anthony et al. (1994); cf: O’Brien (2011)
D2/D3 Receptor Availability and Sensitivity to Stimulants

<table>
<thead>
<tr>
<th>Perception of Methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleasant</td>
</tr>
<tr>
<td>2.2</td>
</tr>
<tr>
<td>2.8</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>3.2</td>
</tr>
<tr>
<td>3.4</td>
</tr>
</tbody>
</table>

Does D2/D3R Predict Rates of Cocaine SA?

**PET scan**

![PET scan image](image)

**Response Rate** (responses/sec)

<table>
<thead>
<tr>
<th>Baseline D2 DVR</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>0.15</td>
</tr>
<tr>
<td>2.2</td>
<td>0.10</td>
</tr>
<tr>
<td>2.4</td>
<td>0.05</td>
</tr>
<tr>
<td>2.6</td>
<td>0.00</td>
</tr>
<tr>
<td>2.8</td>
<td>0.00</td>
</tr>
<tr>
<td>3.0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Week 5**

$r = -0.86$

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

Social Housing: a model of chronic stress & enrichment

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

Most Dominant

1. > greater access to resources
   > groomed more by others

Subordinates:

3. > receive more aggression
   > spend more time alone
   > are groomed less often

4. Most Subordinate

Cynomolgus macaques
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

Individually Housed

Socially Housed

Dominant + 22%

Subordinate - 1%

Environmental Variables, Brain Function and Cocaine Abuse

Subordinate
Stressed
Vulnerable
↑DA; ↓D2 density

Dominant
Enriched
Protected
↓ 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 (± 0.17)
Pt: 2.95 (± 0.10)

“… 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 < follicular females < luteal females.
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

Volkow et al., PNAS 2011
Cocaine and DA D2/D3 receptor distribution

Drug-naïve

Cocaine history

Nader et al. (2006)
Individual Differences in Recovery

Nader et al. (2006)
Cocaine Decreases 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 and in females.
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
Cocaine-Food Choice Paradigm

Antagonist
Stress

Agonist
Enrichment

% Cocaine Choice

Cocaine (mg/kg per injection)
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

Cocaine (mg/kg per injection)

% Cocaine Reinforcers

Cocaine (mg/kg per injection)

Baseline

Intruder

Dom  Sub

Gould et al. (2017)
Individual Differences in Outcome Measures

LARGE CAGE

% Cocaine Choice

C-7425

Baseline
Enrichment Pen

Cocaine (mg/kg per injection)

Homecage Condition
Individual Differences in Outcome Measures

**LARGE CAGE**

**PAIR-HOUS ED WITH FEMALE**

<table>
<thead>
<tr>
<th>Cocaine (mg/kg per injection)</th>
<th>% Cocaine Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fd 0.003 0.01 0.03 0.1</td>
<td></td>
</tr>
<tr>
<td>0% Cocaine Choice C-7425</td>
<td></td>
</tr>
</tbody>
</table>

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<th>Cocaine (mg/kg per injection)</th>
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<td></td>
</tr>
</tbody>
</table>
Medications for cocaine dependence: dopaminergic strategies

1. agonist
   - dopamine
   - quinpirole
   - (-) NPA

2. partial agonist
   - apomorphine
   - terguride
   - aripiprazole
   - buspirone

3. antagonist

intrinsic efficacy

FULL

NONE
D₃/₄ receptors: Buspirone

MALES

Dominant (n=6)

Subordinate (n=7)

Czoty & Nader (2015) Neuropsychopharmacology
D$_{3/4}$ receptors: Buspirone

**MALES**

- Dominant
  - (n=6)

**FEMALES**

- Dominant
  - (n=4)

- Subordinate
  - (n=7)

- Subordinate
  - (n=2)

*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

Dominant (n=4)

NPA-HIGH efficacy

ARI-LOW efficacy

Subordinate (n=5)

Czoty & Nader (2012) JPET
D2-like receptor drugs – female monkeys

**HIGH efficacy**

NPA

**Dominant**

(n=4)

**LOW efficacy**

ARIPIPRAZOLE

(n=4)

(n=2)  

(n=1)

% Cocaine choice

Cocaine (mg/kg per injection)

% Cocaine choice

Cocaine (mg/kg per injection)
### DA Compounds on Cocaine Choice

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOM</td>
<td>SUB</td>
<td>DOM</td>
</tr>
<tr>
<td><strong>Buspirone</strong></td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>NPA</strong></td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

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
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

NIDAIRP
Intramural Research Program
Baltimore, MD
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

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Lindsey Hamilton
Natallia Riddick
Robert Gould
Robert Brutcher
Sarah Kromrey
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