Midbrain Modulation of Motivation

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Nice place Sydney, but the weather is much the same as Boston.
Orienting Movements

Mesencephalic “midbrain” dopamine systems and...

- Sensorimotor and pre-attentive processing
Appetitive and Addictive Behaviors
At Least Two Things That I’m Still, Really Good At!

Mesencephalic “midbrain” dopamine systems and...
- Sensorimotor and pre-attentive processing
- Incentive-motivation (eating, drinking, sex, & drugs)
Terminal Modulation

Mesencephalic “midbrain” dopamine systems and...

- Sensorimotor and pre-attentive processing
- Incentive-motivation (eating, drinking, sex, & drugs)
- Limbic interactions in emotive-motor integration
Mesencephalic “midbrain” dopamine systems and...

- Sensorimotor and pre-attentive processing
- Incentive-motivation (eating, drinking, sex, & drugs)
- Limbic interactions in emotive-motor integration
- Excitatory afferent modulation and synaptic plasticity
The Nucleus Accumbens and Incentive Learning

Natural or Drug-Related Rewards

Primary Incentives
Rewards (good or bad) Drive Dopamine Neurons

Natural or Drug-Related Rewards

Primary Incentives

DA

Nucleus Accumbens Dopamine Functions

Motivation Craving

behavioural switching reward prediction amplifier
In turn, the Accumbens mediates goal-directed behaviours and acquisition of rewards.

- **Natural or Drug-Related Rewards**
  - DA
  - Nucleus Accumbens dopamine functions
    - Behavioural switching
    - Reward prediction
    - Amplifier

- **Consummatory Behaviours**
  - Goal Oriented Approach

- **Primary Incentives**
  - Motivation Craving

- **Preparatory Behaviours**
And the Neural System is Capable of Incentive Learning
Where to Begin?

Mesencephalic “midbrain” dopamine systems and...

- Sensorimotor and pre-attentive processing
- Incentive-motivation (eating, drinking, sex, & drugs)
- Limbic interactions in emotive-motor integration
- Excitatory afferent modulation and synaptic plasticity
Fixed Potential Amperometry: Afferent Modulation, Receptor Mechanisms and Synaptic Plasticity in Dopamine Systems
### Extent of Drug Abuse Problem – USA #1

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Addicted</th>
<th>Per 1000</th>
<th>Per Population</th>
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<tbody>
<tr>
<td>United States</td>
<td>15.0</td>
<td></td>
<td>3.9 million</td>
</tr>
<tr>
<td>Australia</td>
<td>14.0</td>
<td></td>
<td>280 thousand</td>
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<tr>
<td>Canada</td>
<td>7.0</td>
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<td>196 thousand</td>
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<td>Switzerland</td>
<td>6.7</td>
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<td>50 thousand</td>
</tr>
<tr>
<td>France</td>
<td>2.6</td>
<td></td>
<td>150 thousand</td>
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<tr>
<td>United Kingdom</td>
<td>2.6</td>
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<td>150 thousand</td>
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#### Psychostimulant and Opiate Drugs of Abuse

- Cocaine
- Amphetamine
- Ecstasy
- Methamphetamine
- Heroin
- Codeine

*Source: U.S. Office of National Drug Control Policy 2000*
Intravenous Drug Self-Administration Setup

Electrometer and Drug Infusion Pump ==> Isolation Chamber ==> Operant Chamber ==> Subject electrode implanted and jugular catheterised
Intravenous Drug Self-Administration (IVSA)

**FR-2 drug reinforcement:**
(0.25 mg/kg i.v. injection of amphetamine)

**Conditioned stimulus:**
(5-sec light flash and 30-sec light “off” period) paired with each injection (drug self- and yoked-groups) or saline (vehicle yoked-group)
Changes in Accumbens Dopamine on:
IVSA TEST DAY 7

Graph showing the change in DA oxidation current (nA) over time (Min) for Amphetamine Self-Administration and Yoked Saline.
Changes in Accumbens Dopamine on:

IVSA TEST DAY 7

CONDITIONED TEST DAY 9

Amphetamine Self-Administration

Yoked Saline

Conditioned Stimulus
NO DRUG

Change in DA Oxidation Current (nA)

Drug infusions per 10 min

Time (Min)
48 Hour Amphetamine “Binge” – Saline Control
48 Hour Amphetamine “Binge” – Yoked Drug Control

Change in DA Oxidation Currents (nA)

Time of Day (0 - 2400 hr)

Lights Off in Colony

Lights Off in Colony

Infusions per Hour

Yoked Amphetamine

Yoked Saline
48 Hour Amphetamine “Binge” – Self-Administration

[Graph showing the change in DA oxidation currents (nA) over time of day (0-2400 hours). The graph compares self-administration of amphetamine, yoked amphetamine, and yoked saline. Key time points and changes are highlighted.]
Examine a **Snapshot** of Drug Abstinence
Abstinence and Amphetamine Challenge

Change in DA Oxidation Currents (nA)

Time into Abstinence (Hrs)

Drug Abstinence + Challenge Injections

rat #1

rat #3

rat #2

rat #4

Challenge Injections
Dopamine Model of Drug Self-Administration

1. Binge
Dopamine Model of Drug Self-Administration

1. Binge  2. Crash
Dopamine Model of Drug Self-Administration

1. Binge  
2. Crash  
3. Burn (Relapse)
CONCLUSIONS:
A Model of Psychostimulant Abuse - Binging

'Binge'
maintenance of dopamine levels above a reward 'threshold'

Short term: binge-abstinence cycles correspond to activation
CONCLUSIONS:
A Model of Psychostimulant Abuse - Abstinence

'Binge'
maintenance of dopamine levels above a reward 'threshold'

'crash'

Abstinence
short-term decrease in dopamine levels leading to further drug-taking behaviour

Short term: binge-abstinence cycles correspond to activation, depletion
CONCLUSIONS:
A Model of Psychostimulant Abuse – Short Term

'Start
maintenance of dopamine levels above a reward 'threshold''

'Abstinence'
short-term decrease in dopamine levels leading to further drug-taking behaviour

Short term: binge-abstinence cycles correspond to activation, depletion, and recovery of mesolimbic dopamine neuronal systems.
CONCLUSIONS: Model of Psychostimulant Abuse – Long Term

'Start term': binge-abstinence cycles correspond to activation, depletion, and recovery of mesolimbic dopamine neuronal systems.

Long-term: associative learning of drug-related cues and their conditional activating effects on dopamine systems may lead to recidivism.
"Well," said Pooh, "what I like best..."
...and then he had to stop and think.

Because although Eating Honey was a very good thing to do, there was a moment just before you began to eat it which was better than when you were...

The House at Pooh Corner
A.A. Milne, 1928
"Well," said Pooh, "what I like best..."
...and then he had to stop and think.

Because although Eating Honey was a very good thing to do, there was a moment just before you began to eat it which was better than when you were...

but he didn't know what it was called!!

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"Well," said Pooh, "what I like best..." ...and then he had to stop and think.

Because although Eating Honey was a very good thing to do, there was a moment just before you began to eat it which was better than when you were...

but he didn't know what it was called!!

It's called conditioned dopamine release in the Nucleus Accumbens.

The House at Pooh Corner
A.A. Milne, 1928
In Vivo Electrochemical Analysis of Afferent Circuitry:

I. Modulating Dopamine Cell Burst Firing and Release

II. Involved in Deep Brain Stimulation for Parkinson's Disease

III. Mediating Synaptic Plasticity in Dopamine Neurons
Basic Requirements For Studies:

1. Well-equipped lab
2. Enthusiastic students
3. Reasonably lucid supervisor
Adrian Allen (grad) and Alex Falcon (grad)
Joleen Stockton (tech), Tony Miller (grad) and Jenny Dawson (grad)
A few reasons why I came back to the US.
I. Analysis of Afferent Circuitry Modulating Dopamine Cell Burst Firing and Release

Prefrontal Cortex
Subthalamic Nucleus
Pedunculopontine Nucleus
Superior Colliculus
Dopamine responses comply with basic assumptions of formal learning theory

Pascale Waelti¹, Anthony Dickinson² & Wolfram Schultz¹

1 Institute of Physiology and Programme in Neuroscience, University of Fribourg, CH-1700 Fribourg, Switzerland
2 Department of Experimental Psychology, University of Cambridge, Cambridge CB2 3EB, UK

1. Dopamine neurons (>90%) burst fire to presentation of a salient stimuli.
2. Burst firing elicits >4x more dopamine release and thus may encode learning of 'natural' and drug-related rewards.
3. Dopamine neurons can also be conditioned by predictive stimuli repeatedly paired with a primary reward.
4. Dopamine neurons also exhibit prediction error learning by decreasing their activity when primary reward is omitted.
5. Thus, dopamine neuronal responses comply with formal learning theory.

Midbrain Dopamine Cell Burst Firing to Unexpected Rewards - Stimulus Time-Locked Response

Midbrain Dopamine Cell Burst Firing can be Conditioned -
Shift in Dopamine Cell Response

Wolfram Schultz, The Reward Signal of Midbrain
Dopamine Neurons, News Physiol. Sci., 14:249, 1999
Dopamine Cell Burst Firing in the Absence of a Reward – Stimulus Prediction Error Learning in Neurons

Origin of Dopamine Cell Burst Firing: Mono-synaptic

Dopamine Tsunami

Spontaneous Single Spikes (5-10/second)

Spontaneous DA Cell Burst (4-6/200 ms)

PFC-Elicited DA Cell Burst (4-6/200 ms)

Tong et al., J Neural Transm, 103, 889, 1996; Schultz, J Neurophys, 80, 1, 1998
Origin of Dopamine Cell Burst Firing: Mono-synaptic

Tong et al., J Neural Transm, 103, 889, 1996; Schultz, J Neurophys, 80, 1, 1998
Origin of Dopamine Cell Burst Firing: Di-synaptic

Dopamine Tsunami

Spontaneous Single Spikes (5-10/second)

Spontaneous DA Cell Burst (4-6/200 ms)

150 ms

PFC-Elicited DA Cell Burst (4-6/200 ms)

Tong et al., J Neural Transm, 103, 889, 1996; Schultz, J Neurophys, 80, 1, 1998
Origin of Dopamine Cell Burst Firing: Tri-synaptic

Dopamine Tsunami

Spontaneous Single Spikes (5-10/second)

Spontaneous DA Cell Burst (4-6/200 ms)

PFC-Elicited DA Cell Burst (4-6/200 ms)

Tong et al., J Neural Transm, 103, 889, 1996; Schultz, J Neurophys, 80, 1, 1998
Prefrontal Cortex Stimulated Dopamine Release in Striatum: Electrochemical Recording Setup
Prefrontal Cortex Stimulated Dopamine Release in Striatum: Impulse Dependency and Electrode Selectivity
Prefrontal Cortex Stimulated Dopamine Release in Striatum: Blockade of All Cortical and Sub-cortical Inputs to the SN

- Dopamine recording electrode
- Electrometer
- Infusion cannulae for lidocaine or AChR and GluR antagonists
- 10K samples per second
- Dopamine release
- Post-drug infusion
- Time
- PFC
- Striatum
- STN
- SN
- Dopamine
- Glutamate
- Acetylcholine
- PPT

Diagram showing neural pathways and stimulation electrodes.
Prefrontal Cortex Stimulated Dopamine Release in Striatum: Blockade of Cortical to PPT Inputs to the SN
Prefrontal Cortex Stimulated Dopamine Release in Striatum:
Blockade of Cortical to STN Inputs to the SN
Prefrontal Cortex Stimulated Dopamine Release in Striatum: Blockade of Cortical to STN and PPT Inputs to the SN
STN and PPT Stimulated Dopamine Release in Striatum: 
Electrochemical Recording Setup
STN Stimulated Dopamine Release in Striatum:
Blockade of STN to PPT Inputs to the SN
PPT Stimulated Dopamine Release in Striatum: Blockade of PPT to STN Inputs to the SN
Prefrontal Cortex Stimulated Dopamine Release in Striatum: Mono-synaptic and Di-synaptic Contributions
Subthalamus Stimulated Dopamine Release in Striatum:
Mono-synaptic and Di-synaptic Contributions
Pedunculopontine Stimulated Dopamine Release in Striatum: Mono-synaptic and Di-synaptic Contributions
A New Enlightening Means of Modulation
Superior Colliculus to Substantia Nigra

Nature Neuroscience
2003 Sep; 6(9):974-980

A direct projection from superior colliculus to substantia nigra for detecting salient visual events

Eliane Comoli, Veronique Coizet, Justin Boyes, J Paul Bolam, Newton S Canteras, Rachel H Quirk, Paul G Overton & Peter Redgrave

Midbrain dopaminergic neurons respond to unexpected and biologically salient events, but little is known about the sensory systems underlying this response. Here we describe, in the rat, a direct projection from a primary visual structure, the midbrain superior colliculus (SC, to the substantia nigra pars compacta (SNc) where direct synaptic contacts are made with both dopaminergic and non-dopaminergic neurons. Complementary electrophysiological data reveal that short-latency visual responses in the SNc are abolished by ipsilateral lesions of the SC and increased by local collicular stimulation. These results show that the tectonigral projection is ideally located to relay short-latency visual information to dopamine-containing regions of the ventral midbrain. We conclude that it is within this afferent sensory circuitry that the critical perceptual discriminations that identify stimuli as both unpredicted and biologically salient are made.
My *Enlightened* Colleague

Prof. Peter Redgrave
Anterograde and Retrograde Tract Tracing Reveals the Tectonigral Projection

(a) Anterograde tracer biotinylated dextran amine shows ventral projecting tectonigral fibers directed to TH-positive cells (purple) in the SNC.

(b) Tectonigral fibers with numerous boutons coursing rostrally between TH-positive cells (purple) in SNC.

(c) Tectonigral boutons in close association with SNC cells.

(d) Tectonigral boutons in close association with VTA cells.

Abb. in colliculus: SGS, stratum griseum superficiale; SO, stratum opticum; SGI, stratum griseum intermediale; SAI, stratum album intermediale; Substantia nigra: SNC, pars compacta; SNr, pars reticulata. Scale bars: 0.5 mm (a), 30 μm (b), 5 μm (c and d)
Light-Evoked Neuronal Activity in SC and SNc Neurons

Superior Colliculus

Dopamine Neurons

Baseline    Light Flash (Time=0)    Light Flash + Bicuculline    Light Flash
Light-Evoked Dopamine Release in Striatum
Electrochemical Recording and Drug Infusion Setup
Light-Evoked Dopamine Release in Striatum: GABA-A-r Antagonism in SC Required
Light-Evoked Dopamine Release in Striatum: Potentiation by Dopamine Re-uptake Blockade

A. Light Pulses Pre-DA Uptake Blockade
B. No Light Pre-DA Uptake Blockade
C. Light Pulses Post-DA Uptake Blockade
D. No Light Post-DA Uptake Blockade

Graphs show the change in dopamine oxidation current over time with light pulses and no light, with and without dopamine re-uptake blockade.
Light-Evoked Dopamine Release (ECHEM) versus Light-Evoked Dopamine Cell Activity (EPHYS)
A New *Enlightening* Means of Modulation
Visually-Evoked Dopamine Transmission

**Science**

How Visual Stimuli Activate Dopaminergic Neurons at Short-latency

Eleanor Dommett, Véronique Coizet, Charles D. Blaha, John Martindale, Véronique Lefebvre, Natalie Walton, John E.W. Mayhew, Paul G. Overton and Peter Redgrave

Dopamine (DA) neurons respond to unexpected, biologically salient events, including those associated with reward, but what information is specifically conveyed to forebrain target structures remains uncertain.

Chemical disinhibition of the superior colliculus enabled a predictable light stimulus to evoke short latency DA cell burst firing and terminal release in the absence of reward.

This suggests that as the *primary source* of visual input to DA neurons, the limited processing capabilities of the superior colliculus constrains the visual information content of burst firing (phasic) DA responses.
II. Analysis of Afferent Circuitry Involved in Deep Brain Stimulation for Parkinson's Disease

Subthalamic Nucleus
Striatal Dopamine Efflux
STN Glutamate Efflux
DBS Collaborators
Emad Eskandar, Ramin Amirnovin, Dennis Meredith, and Kendall Lee
Deep Brain Stimulation (DBS)
More or Less?
Subthalamic DBS \textit{In Vivo}

Less
Tyrosine Hydroxylase Immunoreactivity Shows Dopaminergic Axons Dorsal to the STN
Dopamine Recordings in Monkey
Multi-Carbon Fiber Composite Electrode
Glutamate Sensor
Glutamate-Oxidase Enzyme Electrode

- Enzymatic glutamate biosensor (Platinum-Iridium electrode)
- Sensing Cavity Dimensions: 0.18 mm diameter; ~1.0 mm length
- Sensitivity: >3nA/10μM glutamate (300 pA/μM)
- Ascorbate Sensitivity: <0.5nA/250μM (2 pA/μM)
- Response: 90% response time <4s, linear 0-100μM in buffer solution
Dopamine and Glutamate Recordings
Carbon Fiber and Enzymatic Electrode

Electrometer
A/D Converter
10K samples/sec

Glutamate Recording Electrode
Dopamine Recording Electrode

15 pulses of stimulation
time (msec)

Striatum
STN
SNC

dopamine

DBS electrode

Dopamine and Glutamate Efflux
Selectivity of the Response to Dopamine
Re-uptake Transporter Inhibition

Subthalamic Nucleus Stimulation

Change in Dopamine Oxidation Current (pA)

Time (sec)

A
- Control
- Dopamine Re-uptake Blockade
- Nomifensine

B
- Control
- Norepinephrine + Serotonin Re-uptake Blockade
- Desipramine + Fluoxetine
Intensity-Dependent Response to STN Stimulation

RAT CAUDATE
(15 pulses at 50 Hz)

A

Change in Dopamine Oxidation Current (pA)

Time (1 sec/tic mark)

B

Stimulation Intensity (µAmps)
Intensity-Dependent Dopamine Response to STN Stimulation

MONKEY CAUDATE

A

DA current (nA)

50 µA 100 µA 300 µA 500 µA 700 µA 900 µA 1100 µA

B

Peak DA current (nA)

20 pulses of 200 Hz stimulation over a range of current intensities (50-1100 µA)
Frequency-Dependent Response to STN Stimulation

RAT CAUDATE
(15 pulses at 300 µA)

A

Change in Dopamine Oxidation Current (pA)

Time (0.5 sec/tic mark)

5 Hz
10 Hz
17 Hz
25 Hz
37 Hz
50 Hz
75 Hz
100 Hz
200 Hz
300 Hz

B

Stimulation Frequency (Hz)

0
100
200
300

0
100
200

0
Frequency-Dependent Response to STN Stimulation

MONKEY CAUDATE

A

DA current (nA)

50 Hz

100 Hz

300 Hz

400 Hz

800 Hz

B

Peak DA current (nA)

50

100

300

400

800

Frequency (Hz)

10 sec pulse duration; 500 µA amplitude; 25-1000 Hz frequency
Time-Dependent Response to STN and MFB Stimulation

RAT CAUDATE (1000 pulses at 50 Hz)

Change in Dopamine Oxidation Current (pA) During STN Stimulation

Change in Dopamine Oxidation Current (pA) During Stimulation Dorsomedial to the STN

Dorsomedial to STN Stimulation

STN Stimulation

0 2 4 6 8 10 12
Time (sec)

0 50 100 150 200
Change in Dopamine Oxidation Current (pA) During STN Stimulation

0 100 200 300 400
Change in Dopamine Oxidation Current (pA) During Stimulation Dorsomedial to the STN
Time-Dependent Dopamine Response to STN Stimulation

MONKEY CAUDATE

Dorsal STN Stimulation

Ventral STN Stimulation

Change in Dopamine Oxidation Current (nAmps)

Time (sec)
Intensity-Dependent Glutamate Response to STN Stimulation

10 sec pulse duration; 100-3000 µA amplitude; 100 Hz frequency
Frequency-Dependent Glutamate Response to STN Stimulation

A. 10 sec pulse duration; 500 µA amplitude; 25-1000 Hz frequency

B. RAT SUBTHALAMIC NUCLEUS

Change in [Glutamate] (µM)

10 sec pulse duration; 500 µA amplitude; 25-1000 Hz frequency
Time-Dependent Glutamate Response to STN Stimulation

RAT SUBTHALAMIC NUCLEUS

\[ y = 80.142 \ln(x) - 160.35 \]

\[ R^2 = 0.938 \]
Amperometric Recordings During DBS in PD Patients
Dual Stimulating and Amperometric Probe for Parkinsons
Dual Stimulating and Amperometric Recordings in PD Patients
III. Analysis of Afferent Circuitry Mediating Synaptic Plasticity in Dopamine Neurons

Ionotropic Glutamate Receptors
Metabotropic Glutamate Receptors
Muscarinic Acetylcholine Receptors
Dopamine Autoreceptors
Synaptic Plasticity: Long-Term Depression

Electrode to measure induction of LTD in response to tetanising stimulation of Schaeffer collateral inputs to CA1 pyramidal cells.

Entorhinal cortical inputs to the hippocampus (new memories for consolidation and storage).
First Demonstration of Long-Term Depression in Dopamine Cells: Brain Slices

Tetanizing train of 10 pulses at 100 Hz applied 3 times at 1 min intervals

In Vitro Midbrain Slice Preparation

Jones et al., & Thomas et al., J Neurosci, 20, 5575 and 5581, 2000
Ionotropic and Metabotropic Glutamate Antagonists: No effect on LTD expression

Jones et al., & Thomas et al., J Neurosci, 20, 5575 and 5581, 2000
Dopamine Agonists (Amphetamine or Cocaine): LTD expression blocked

Jones et al., & Thomas et al., J Neurosci, 20, 5575 and 5581, 2000
Functional Consequences of Long-Term Depression in Dopamine Cells on Terminal Release: Pre-TET Responses
LTD in Dopamine Cells and Dopamine Terminal Release:
Tetanizing Stimulus Applied to Prefrontal Cortex
LTD in Dopamine Cells and Dopamine Terminal Release: Post-Tetanization Responses – LTD Present
LTD in Dopamine Cells and Dopamine Terminal Release: Repeat Experiment - Pre-TET Responses
LTD in Dopamine Cells and Dopamine Terminal Release:
Intra-SN Infusion of Receptor Selective Drugs
LTD in Dopamine Cells and Dopamine Terminal Release: Tetanizing Stimulus Applied in Presence of Drug
LTD in Dopamine Cells and Dopamine Terminal Release:
Post-Tetanization Responses – LTD Present or Absent?
Cortex Stimulated Dopamine Release in Striatum: Pre-Tetanization Response
Cortex Stimulated Dopamine Release in Striatum:
Intra-SN Infusion of mGluR Antagonist

Change in Dopamine Oxidation Current (pA)

Pre-TET

5 min post-MCPG (mGluR)

Time (sec)
Cortex Stimulated Dopamine Release in Striatum:
Tetanization in Presence of mGluR Antagonist
Cortex Stimulated Dopamine Release in Striatum:
LTD PRESENT

Change in Dopamine Oxidation Current (pA)

Pre-TET
0 hr TET applied
5 min post-MCPG (mGluR)

Post-TET (long-term depression PRESENT)
0.5 hr
1.0 hr
1.5 hr

Time (sec)
Cortex Stimulated Dopamine Release in Striatum: Pre-Tetanization Response
Cortex Stimulated Dopamine Release in Striatum: Intra-SN Infusion of Indirect DAR Agonist
Cortex Stimulated Dopamine Release in Striatum: Tetanization in Presence of Indirect DAR Agonist
Cortex Stimulated Dopamine Release in Striatum:

LTD ABSENT
### LTD in Dopamine Cells and LTD of Dopamine Release: Comparative Findings

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<tr>
<td>Saline</td>
<td>PRESENT</td>
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<td>PRESENT</td>
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<tr>
<td>iGluR (-)</td>
<td>PRESENT</td>
<td>iGluR (-)</td>
<td>PRESENT</td>
</tr>
<tr>
<td>mGluR (-)</td>
<td>PRESENT</td>
<td>mGluR (-)</td>
<td>PRESENT</td>
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<tr>
<td>DAR (+)</td>
<td>ABSENT</td>
<td>DAR (+)</td>
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<tr>
<td>DA₂R (+)</td>
<td>ABSENT</td>
<td>DA₂R (+)</td>
<td>ABSENT</td>
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<tr>
<td>mAChR (-)</td>
<td>untested</td>
<td>mAChR (-)</td>
<td>ABSENT</td>
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How do drugs of abuse modify neural circuitry and thereby lead to addictive behavior? As for many forms of experience-dependent plasticity, modifications in glutamatergic synaptic transmission have been suggested to be particularly important. Evidence of such changes in response to in vivo administration of drugs of abuse is lacking, however. Here we show that a single in vivo exposure to cocaine induces long-term potentiation of AMPA (\(\alpha\)-amino-3-hydroxy-5-methyl-isoxazole propionic acid) receptor-mediated currents at excitatory synapses onto dopamine cells in the ventral tegmental area. Potentiation is still observed 5 but not 10 days after cocaine exposure and is blocked when an NMDA (N-methyl-D-aspartate) receptor antagonist is administered with cocaine. Furthermore, long-term depression is enhanced by in vivo cocaine exposure. These results show that a prominent form of synaptic plasticity can be elicited by a single in vivo exposure to cocaine and therefore may be involved in the early stages of the development of drug addiction.
Receptor Model of Cortical and Mesopontine Modulation of Midbrain Dopamine Cell Activity and Forebrain Transmission

**RECEPTOR SUBTYPES**

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<th>PPT &amp; LDT</th>
<th>SN &amp; VTA</th>
<th>Striatum &amp; NAc</th>
<th>MCtx &amp; PFCtx</th>
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<tr>
<td>nAChR</td>
<td>mAChR</td>
<td>iGluR</td>
<td>GABA-A</td>
</tr>
<tr>
<td>nAChR</td>
<td>mAChR</td>
<td>mGluR</td>
<td>GABA-B</td>
</tr>
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**Receptors increasing DA activity:**
1. $+^n_{17}$ and $+^m_{13}$ on DA Cells - **fast**
2. $+^n_{19}$ on Glu Terminals - **fast**
3. $+^n_{16}$ on GABA Cells - **fast**
4. $+^m_{5}$ on DA Cells - **slow**
5. $+^m_{7}$ and $-^m_{7}$ on GABA Terms - **slow**

**Receptors reducing DA activity:**
1. $+^n_{26}$ and $+^m_{1}$ on GABA Cells - **fast**
2. $+^n_{16}$ and $-^m_{16}$ on DA Cells - **fast**
3. $+^n_{12}$ on Glu Terminals - **fast**
4. $+^m_{18}$ on ACh Terminals - **fast**
5. $-^m_{7}$ on ACh/Glu Terminals - **slow**