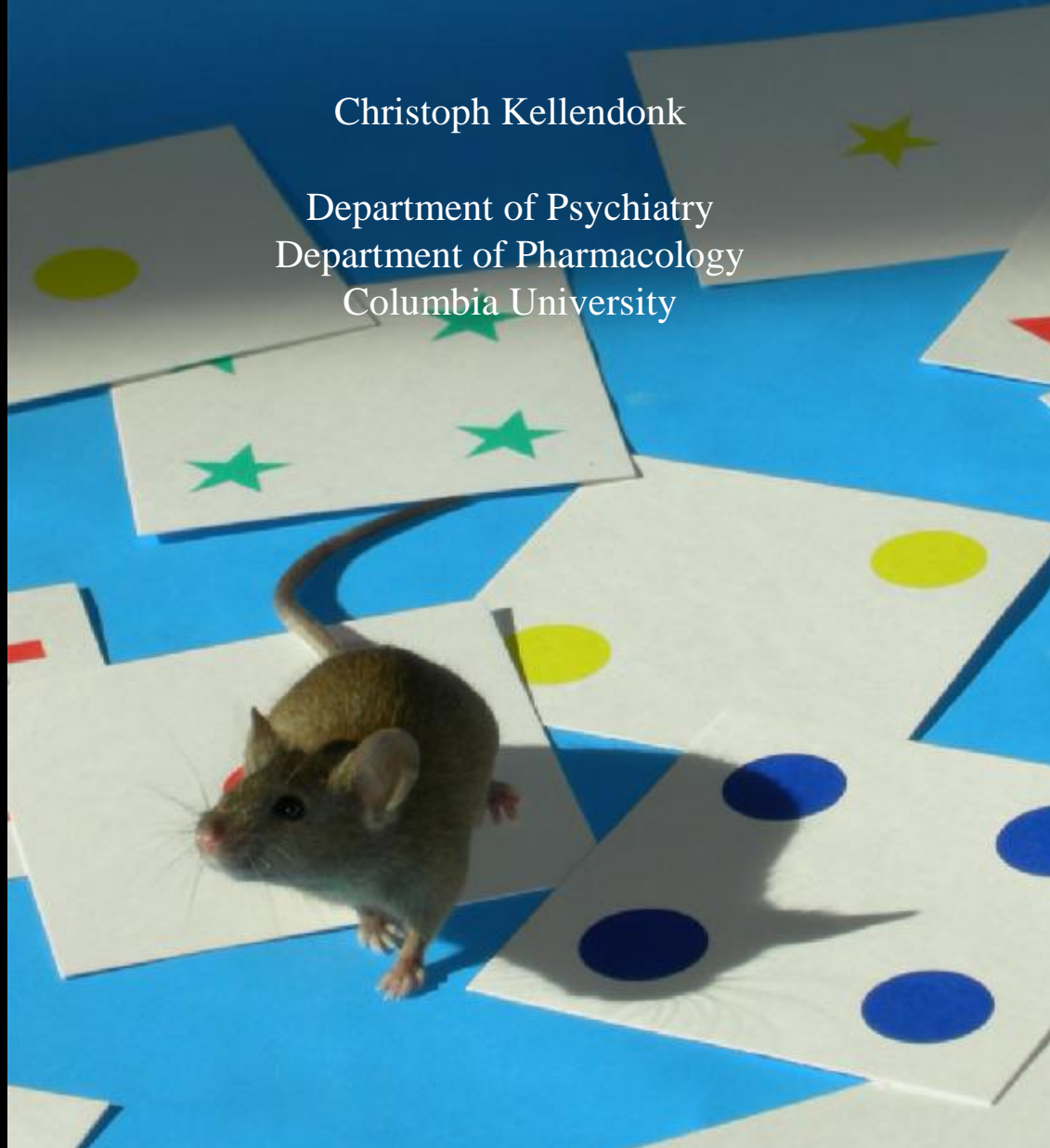


# Modeling endophenotypes for addiction and schizophrenia by D2 over-expression in mice

Christoph Kellendonk

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Columbia University



# Schizophrenia Is Characterized by a Genetic Predisposition to Develop Positive, Negative and Cognitive Symptoms

**The cognitive symptoms are of particular significance for schizophrenia**

- The degree of cognitive symptoms is more predictive for the long term prognosis of the disease than the degree of positive symptoms
- The cognitive symptoms are almost treatment resistant

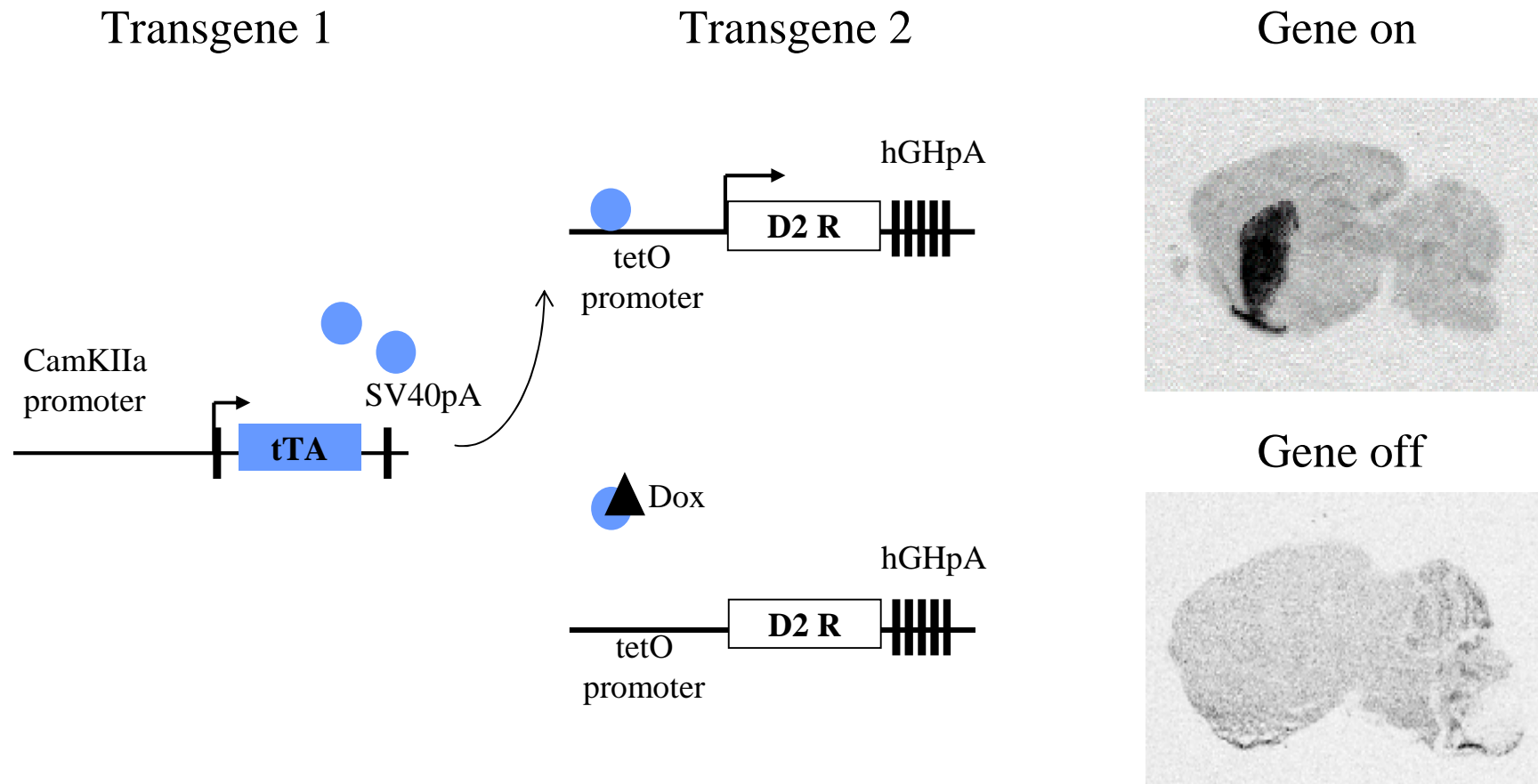
**Some of the cognitive symptoms can be modeled in mice**

- e.g. working memory is a reliable biological marker that can be modeled in mice because mice like people have a prefrontal cortex that is critical for working memory.

## **A Molecular Genetic Approach to Schizophrenia: The Dopamine D2 Receptor**

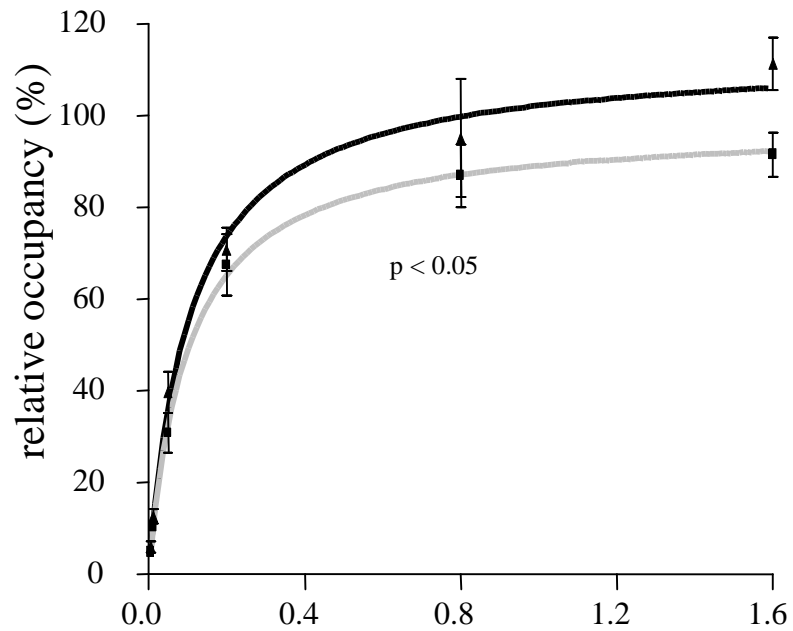
- 1) All effective antipsychotic drugs antagonize the D2 receptors
- 2) There is an increase in dopamine release in the striatum of patients with schizophrenia
- 3) There is an increased occupancy and density of D2 receptors in the striatum of patients with schizophrenia.
- 4) A polymorphism in the D2 receptor gene (C957T) is associated with schizophrenia.  
The C allele increases the stability of D2 receptor mRNA

# Overexpression of the D2 receptor in the Striatum

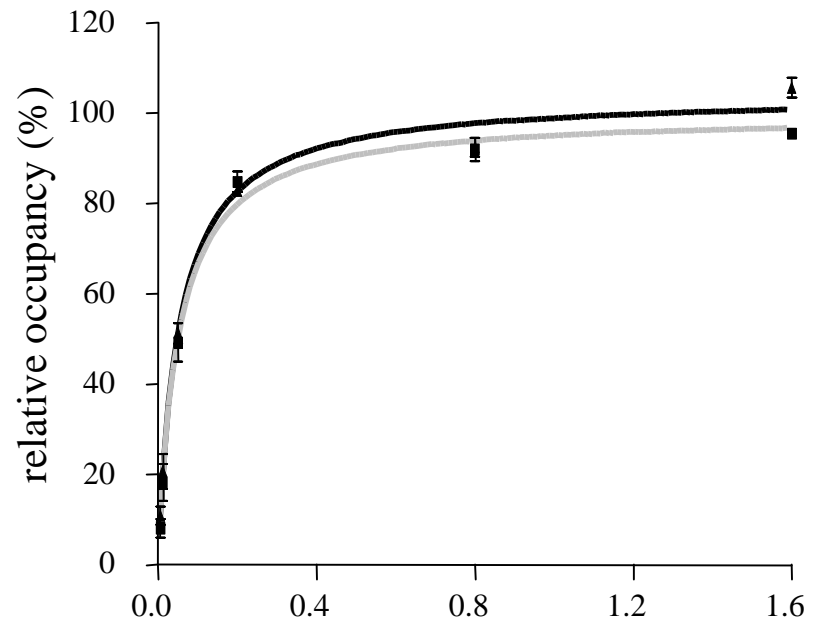


# 15% Increase in D2 Receptor Density

Gene on



Gene off



3H M-Spiperone (nM)

control  
D2R

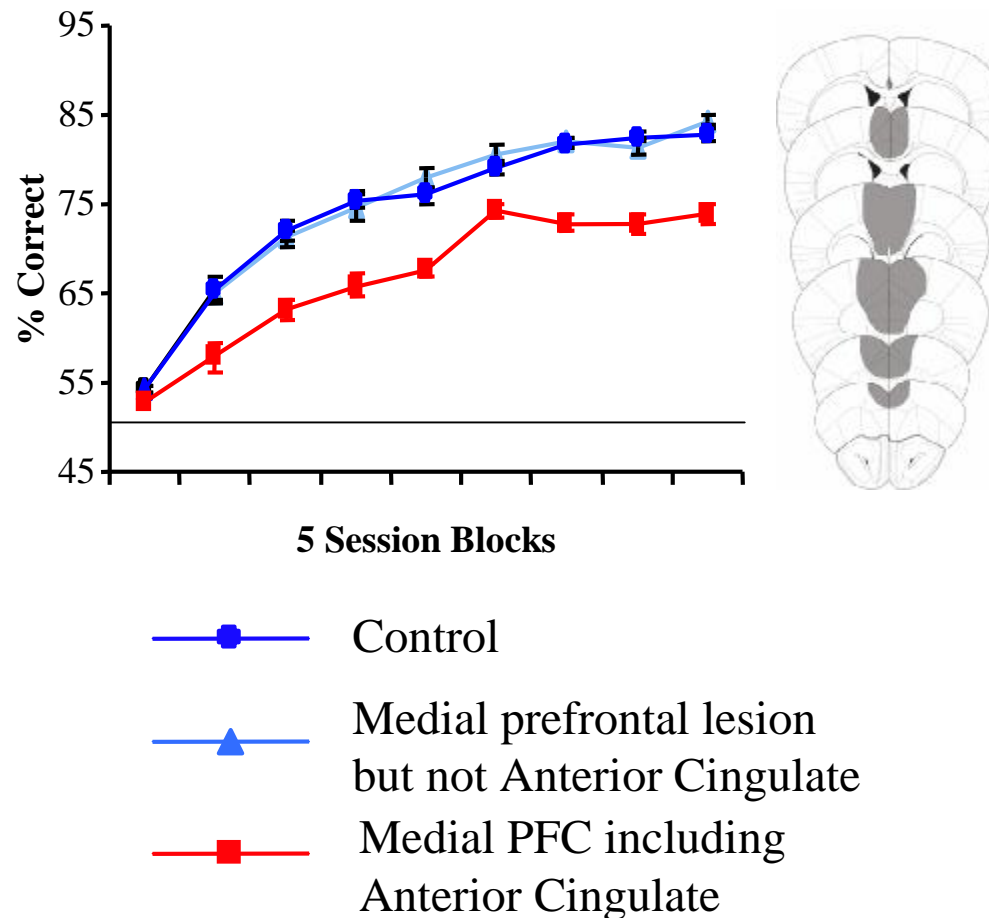
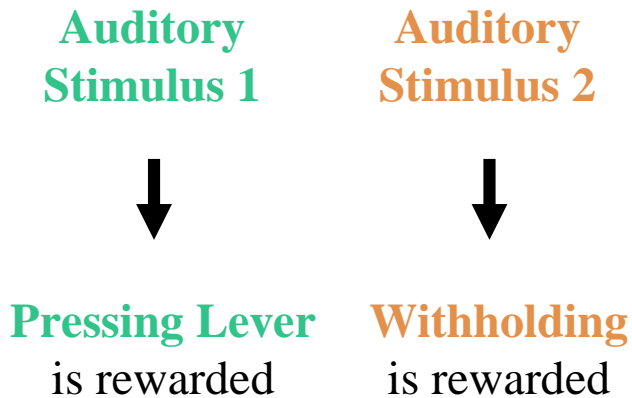
3H M-Spiperone (nM)

## **Overexpression of D2 Receptors in the Striatum leads to cognitive deficits that resemble some of the cognitive deficits of schizophrenia**

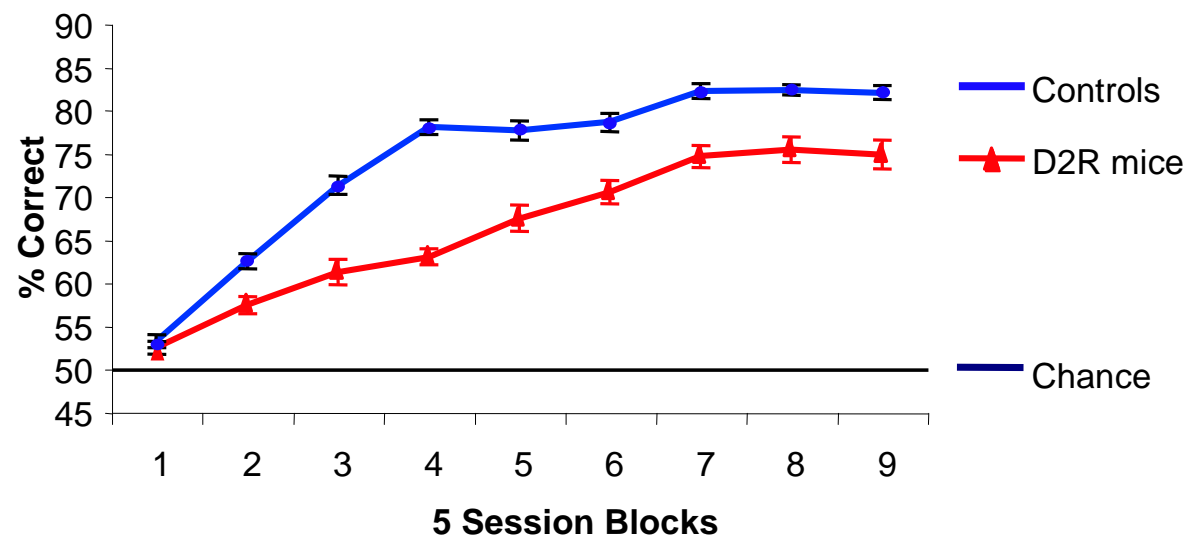
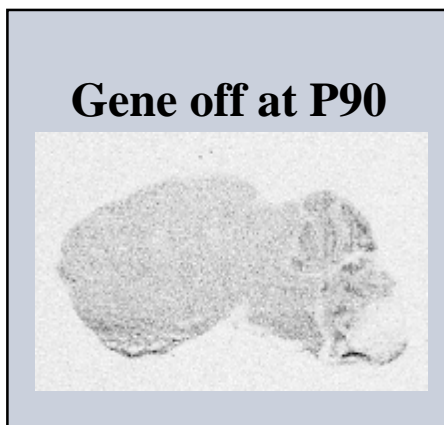
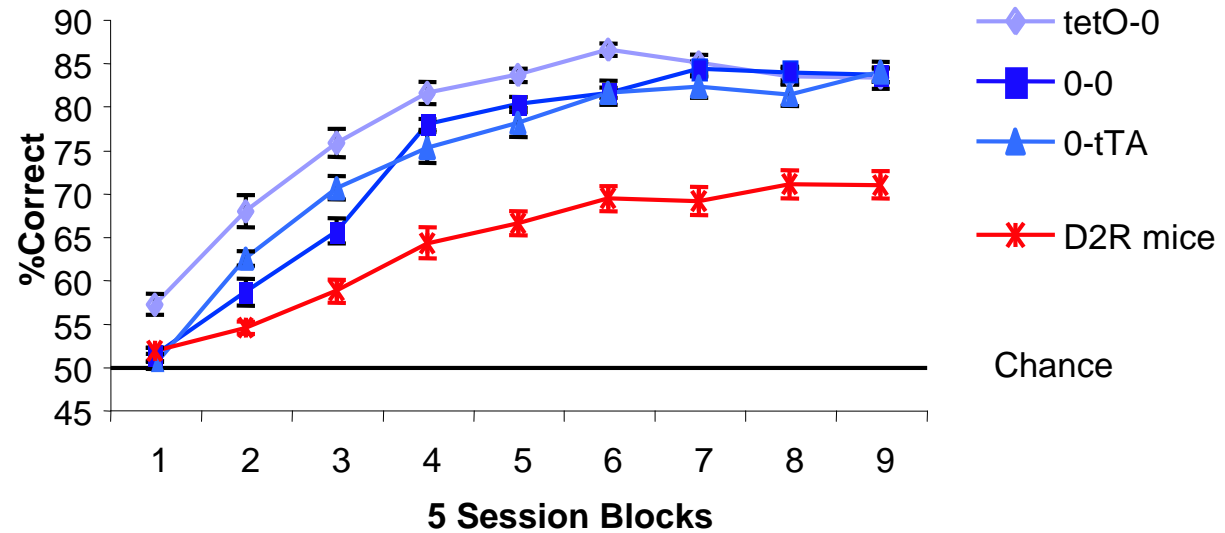
- Specific impairment in cognitive tasks that are dependent on the prefrontal cortex in mice
  - Two delayed non matched to sample working memory tasks (*Neuron* 2006 49:603)
  - Conditioned Associative Learning task (*PNAS* 2008 105:16027)

**D2 receptors in the striatum may be more important for the cognitive symptoms as it has generally been assumed**

# Acquisition of the Conditioned Associative Learning Task Requires the Medial Prefrontal Cortex in Mice



# Transient Over-expression of Striatal Dopamine D2 Receptors Leads to Deficits in Conditioned Associative Learning



## **Overexpression of D2 Receptors in the Striatum Causes Persistent Deficits in Prefrontal Cortex Functioning**

- Over-expression of D2 receptors in the striatum impacts dopamine levels, rates of dopamine turnover and activation of D1 receptors in the prefrontal cortex

**A hyperfunction of the subcortical dopamine system could induce a hypofunction of the prefrontal cortex**

- Developmental over-expression of D2 receptors in the striatum is sufficient for generating the deficit in the cognitive tasks

**Antipsychotic medication may be given too late to treat the cognitive symptoms**

## **The Severity of Cognitive and Negative Symptoms Correlate in Patients With Schizophrenia**

- Are the two causally related?
- Do D2 over-expressing mice show deficits similar to the negative symptoms?

# Modeling Negative Symptomatology in Mice

## Humans:

Social withdrawal  
Social isolation

Avolition,  
Motivational deficits

## Mice:

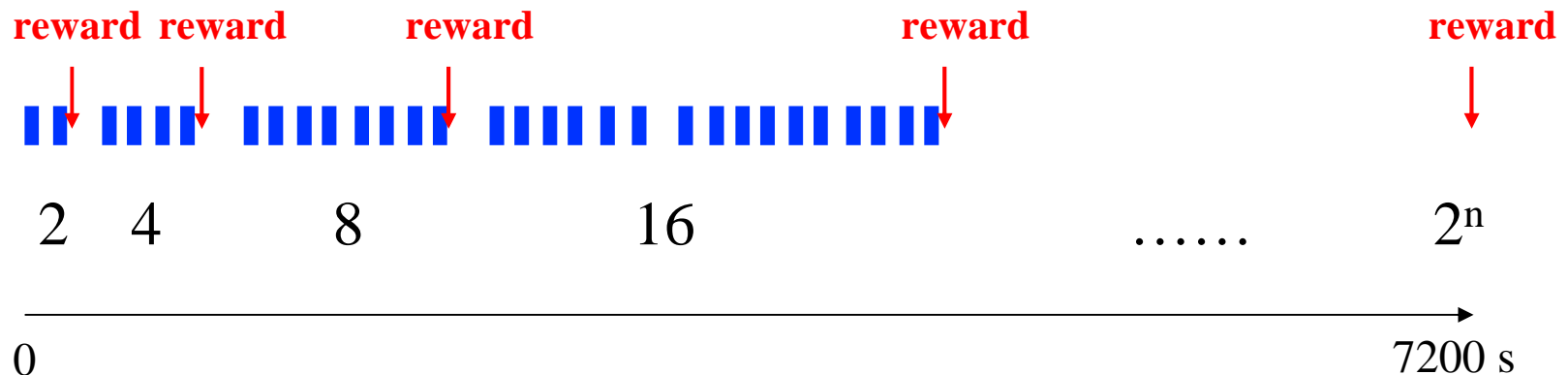
Social interaction

Motivation  
(e.g progressive ratio)

# Testing for Motivation: The Progressive Ratio Paradigm

How often does the animal press for a given reward ?  
(work related cost-benefit calculation)

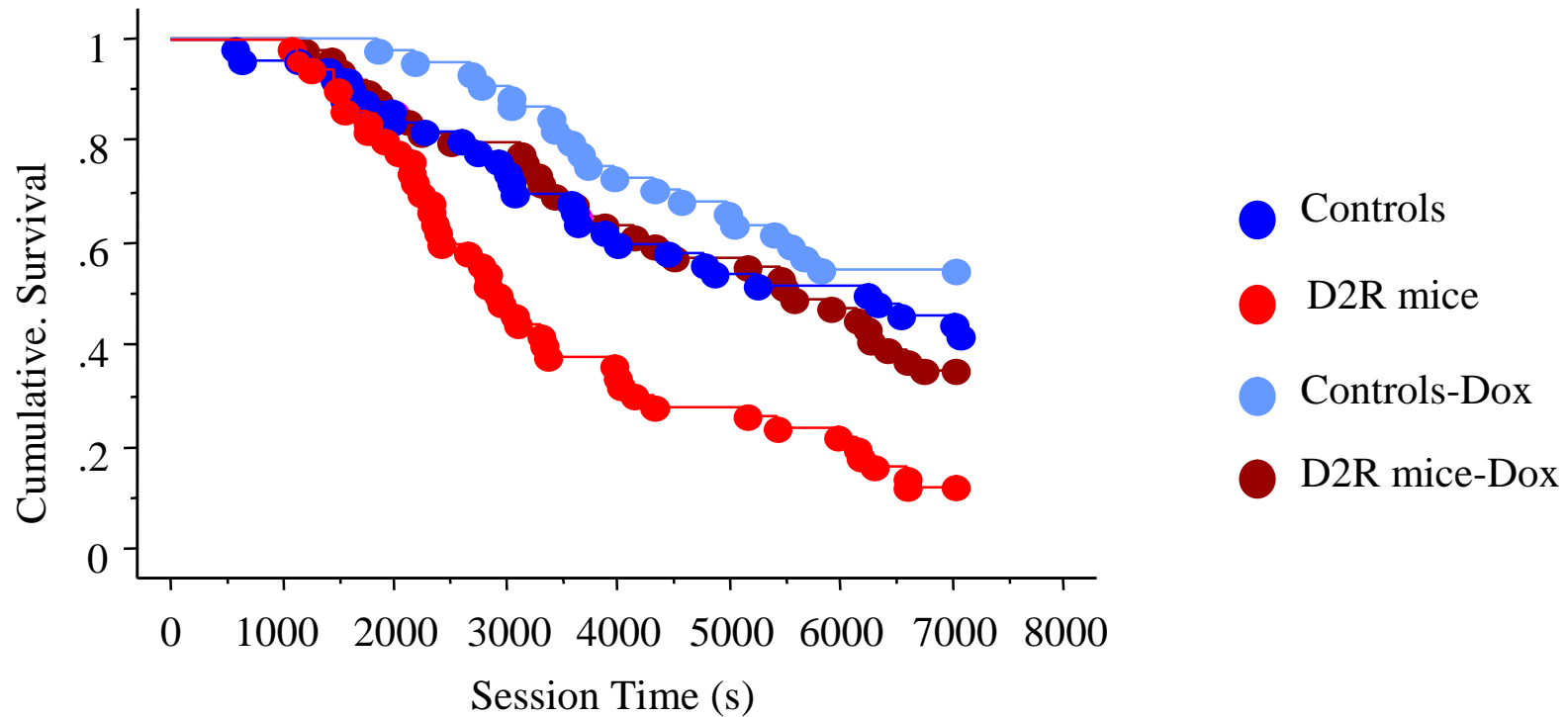
Each Trial:



■ Lever presses

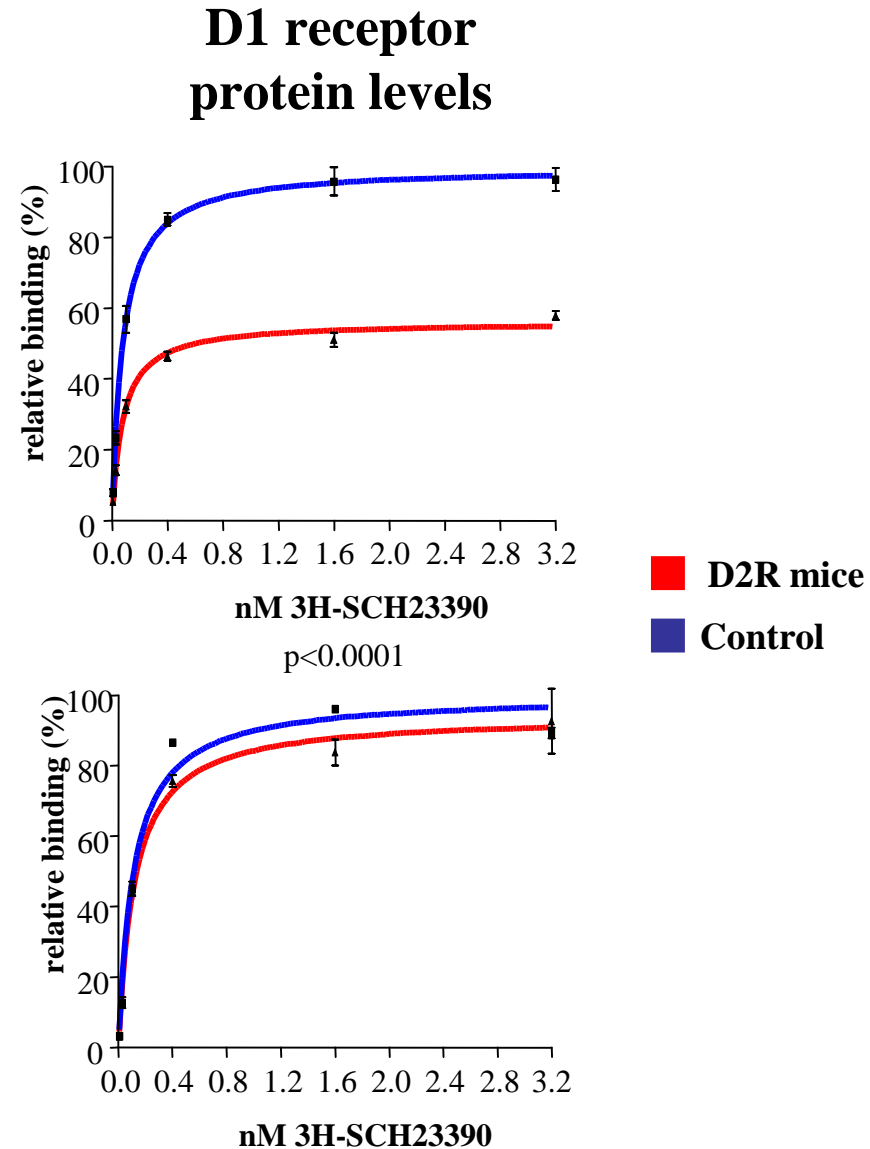
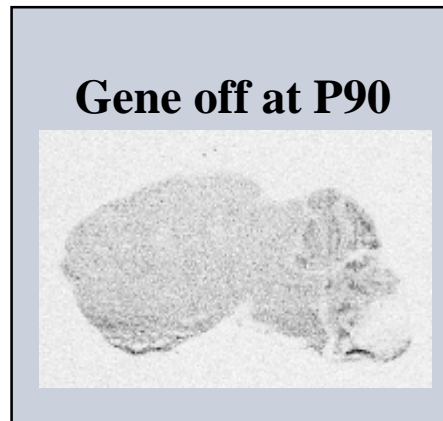
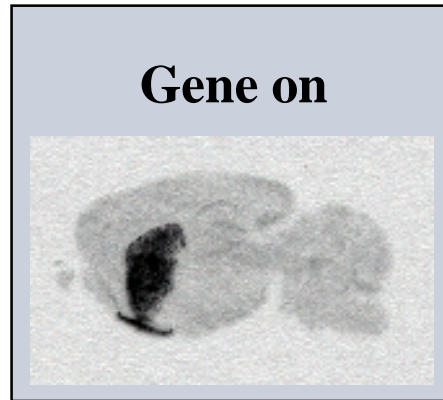
# D2 Transgenic Mice Work Less for Food in an Operant, Progressive Ratio, Schedule

Proportion of mice that is still working on the progressive ratio schedule

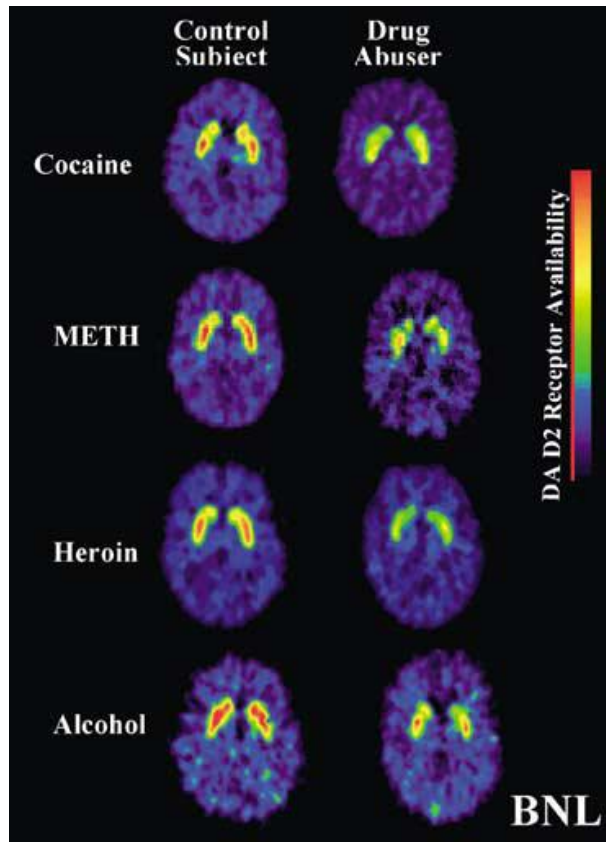


**This deficit is reversible!**

# Possible Underlying Mechanism 1: Striatal D1 Receptor Levels Are Decreased When D2 Receptors Are Upregulated



# High Comorbidity Between Schizophrenia and Drug Addiction: How do striatal D2 affect drug addiction?

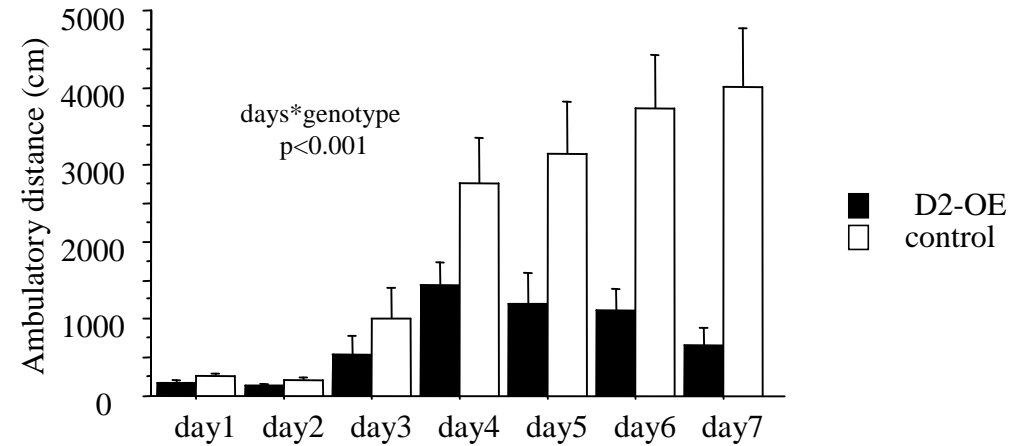
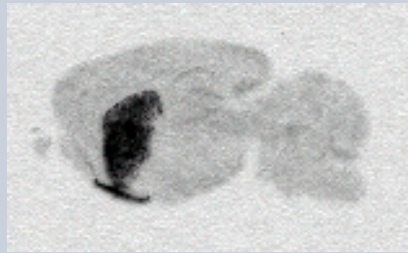


D2 receptor availability is decreased  
in the striatum of chronic drug abusers

Molecular Psychiatry (2004) 9, 557–569

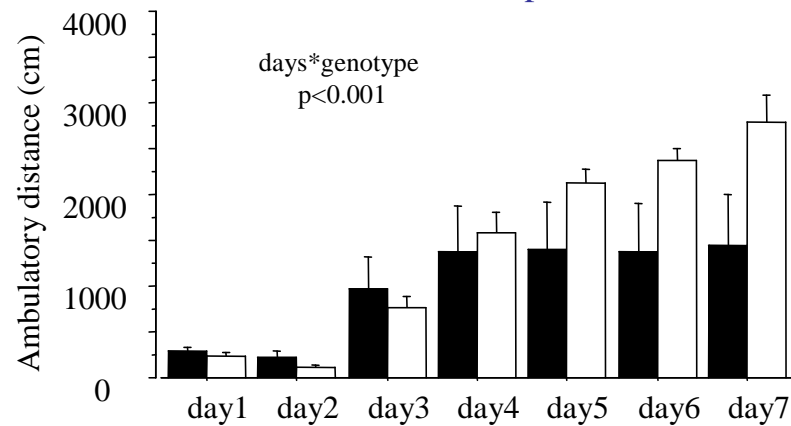
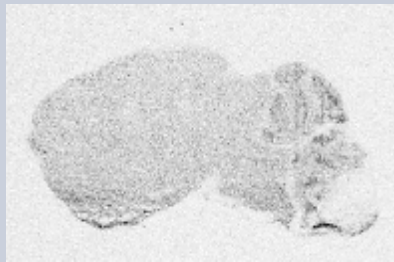
# Overexpression of D2 Receptors in the Striatum impairs Amphetamine Induced Behavioral Sensitization

Gene on



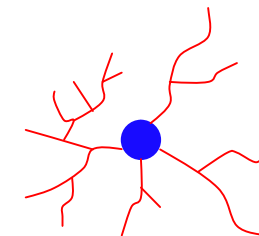
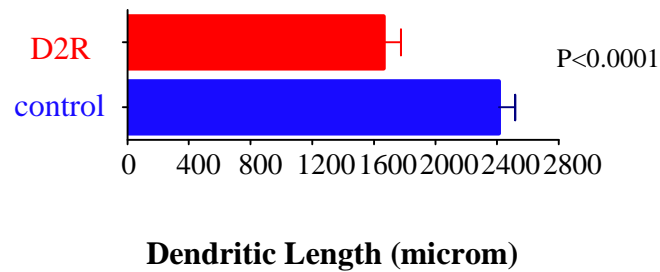
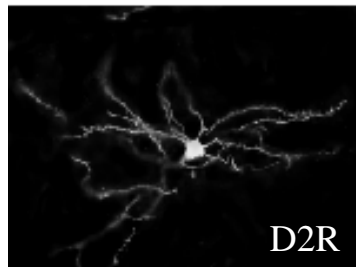
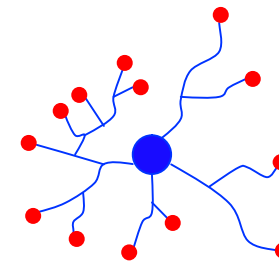
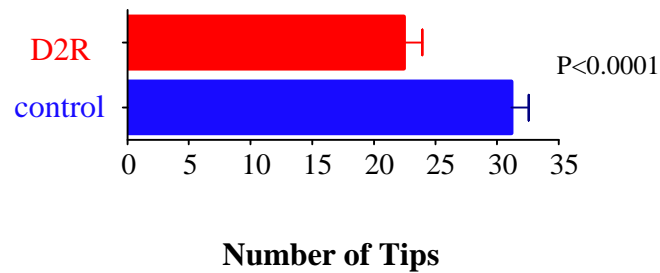
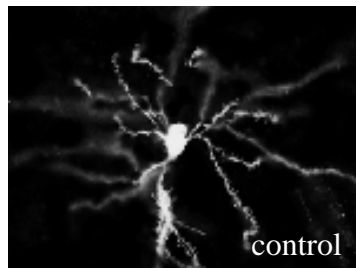
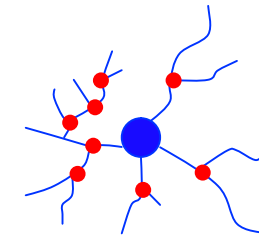
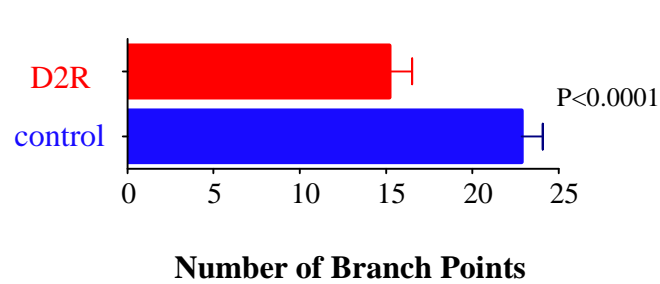
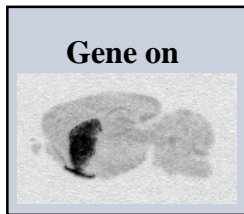
D-amphetamine

Gene off at P90



D-amphetamine

# Striatal D2 Receptor Upregulation Decreases Dendritic Complexity And Lengths of Medium Spiny Neurons in the Striatum



## Conclusion:

- 1) D2 overexpression in the striatum leads to persistent prefrontal dependent cognitive deficits
- 2) D2 overexpression in the striatum leads to persistent deficits in social interaction but reversible deficits in motivation

**In Mice Cognitive and Negative Impairments are affected by a common cause: Excess striatal D2 receptor activation**

- 3) D2 overexpression in the striatum leads to persistent deficits in amphetamine induced sensitization
- 4) Future studies will address whether D2 upregulation protects against addiction

**Eleanor Simpson**

Mary Elizabeth Bach

Lora Kahn

John Marshall

Tessa Hirschfeld-Stoler

Vanessa Winiger

Jonathan Polan

Gael Malleret

**Eric Kandel**

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Steve Fairhurst

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**Maxime Cazorla**

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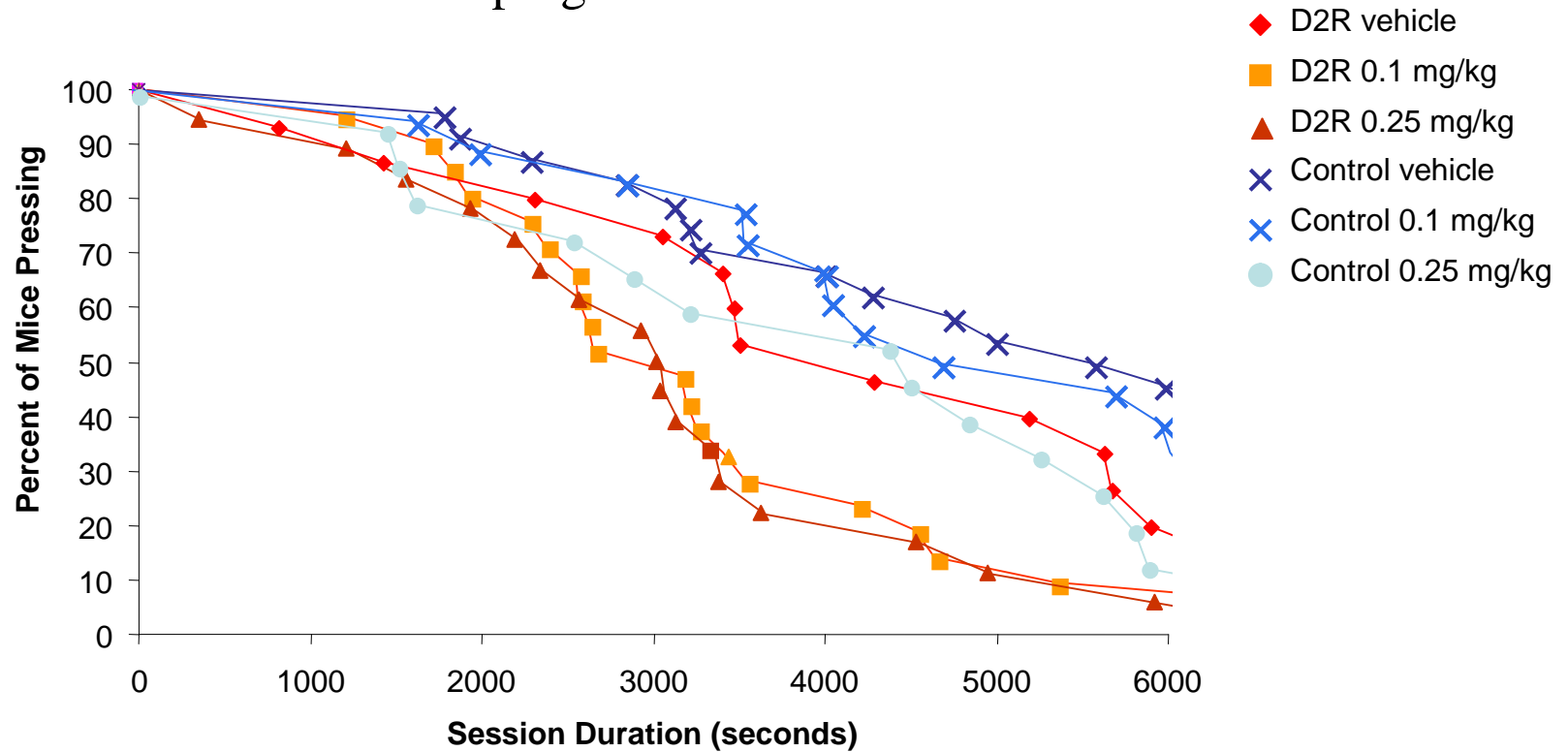
The Lieber Center

NARSAD

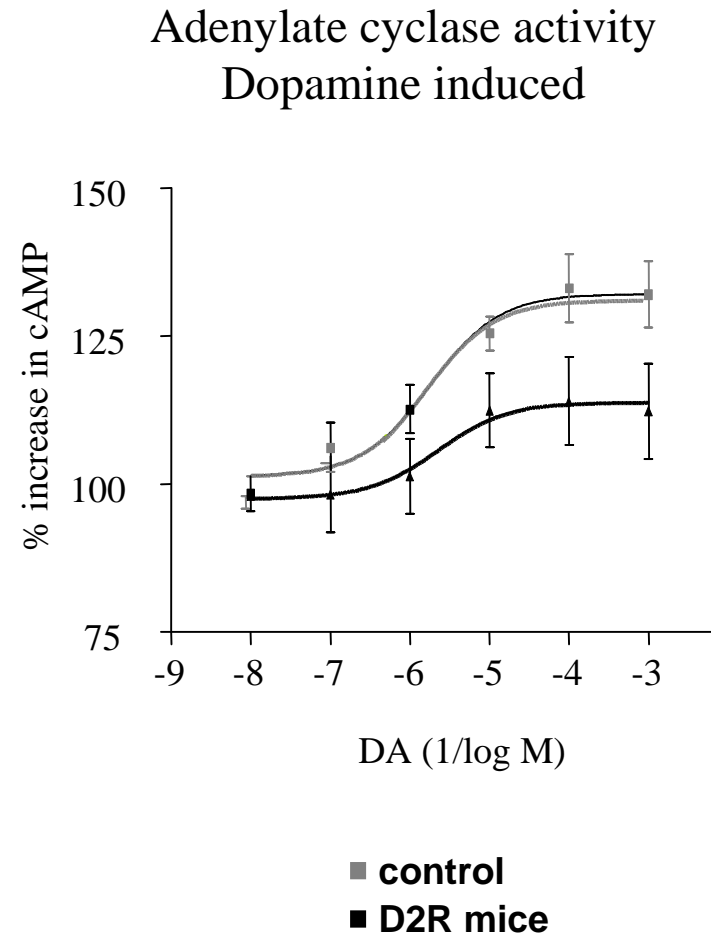
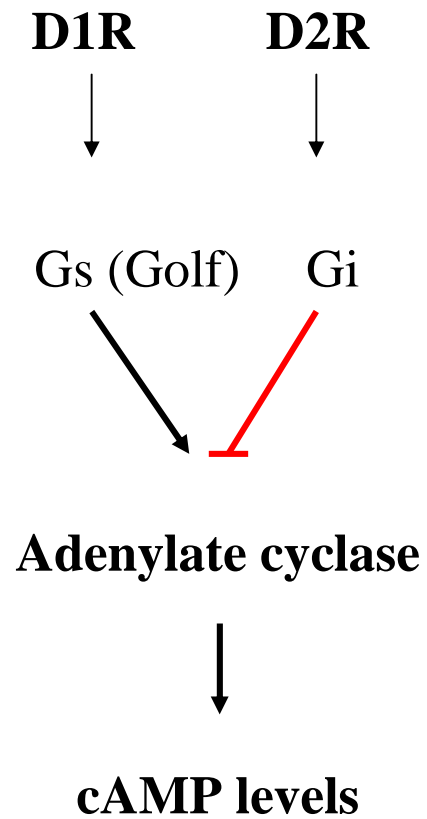
Deutsche Forschungsgemeinschaft

# Chronic Haloperidol Does Not Reverse Deficits in the Progressive Ratio Task

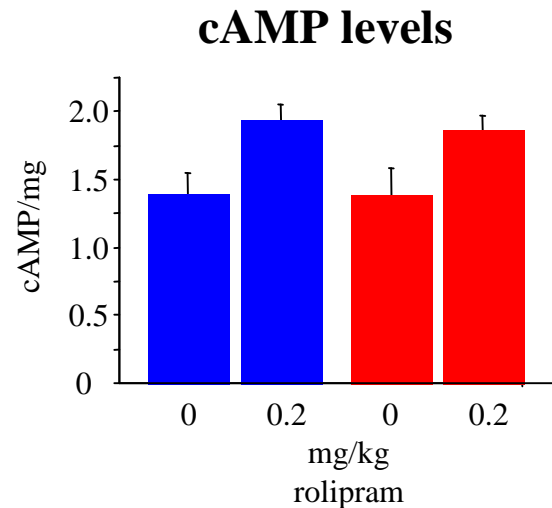
Proportion of mice that is still working on the progressive ratio schedule



# Overexpression of D2 Receptors in the Striatum Decreases Dopamine Stimulated $\gamma$ Adenylate Cyclase Activity

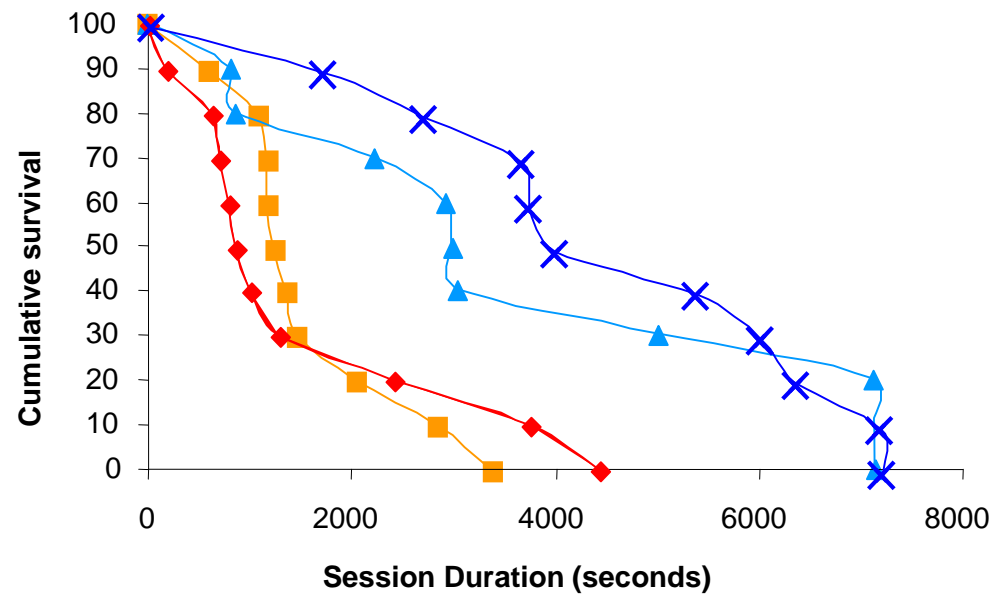


# Chronic Rolipram Does Not Reverse the Deficit in the Progressive Ratio Task



- Controls
- D2R mice

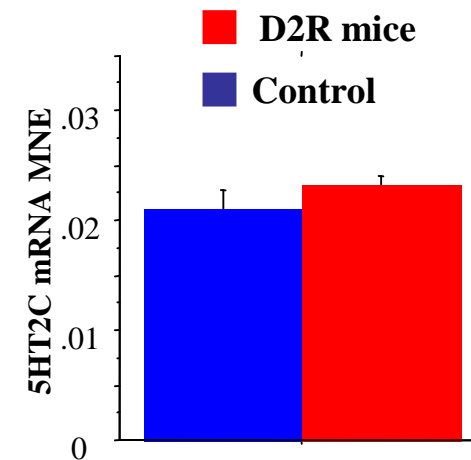
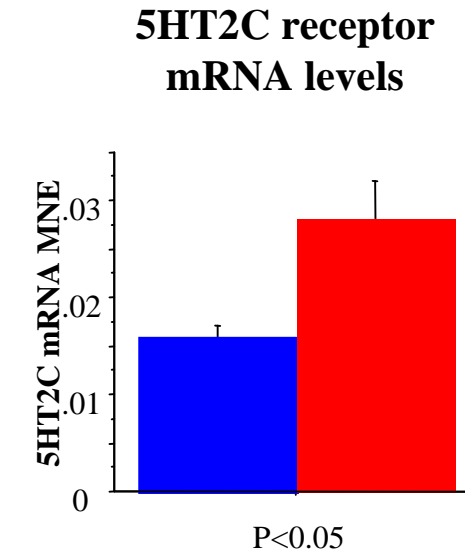
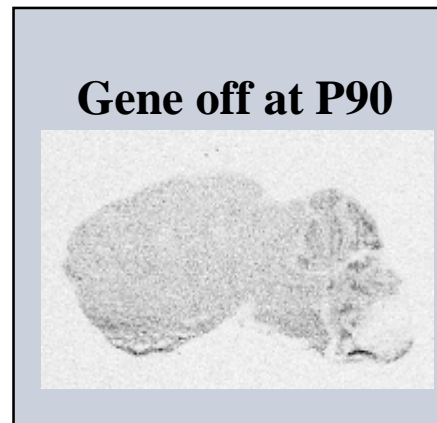
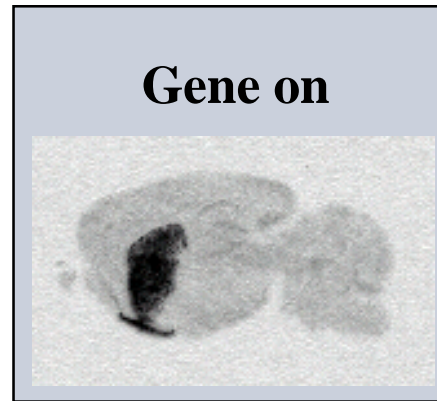
Proportion of mice that is still working on the progressive ratio schedule



- × Control Vehicle
- ▲ Control Rolipram
- ◆ D2R vehicle
- ◆ D2R rolipram

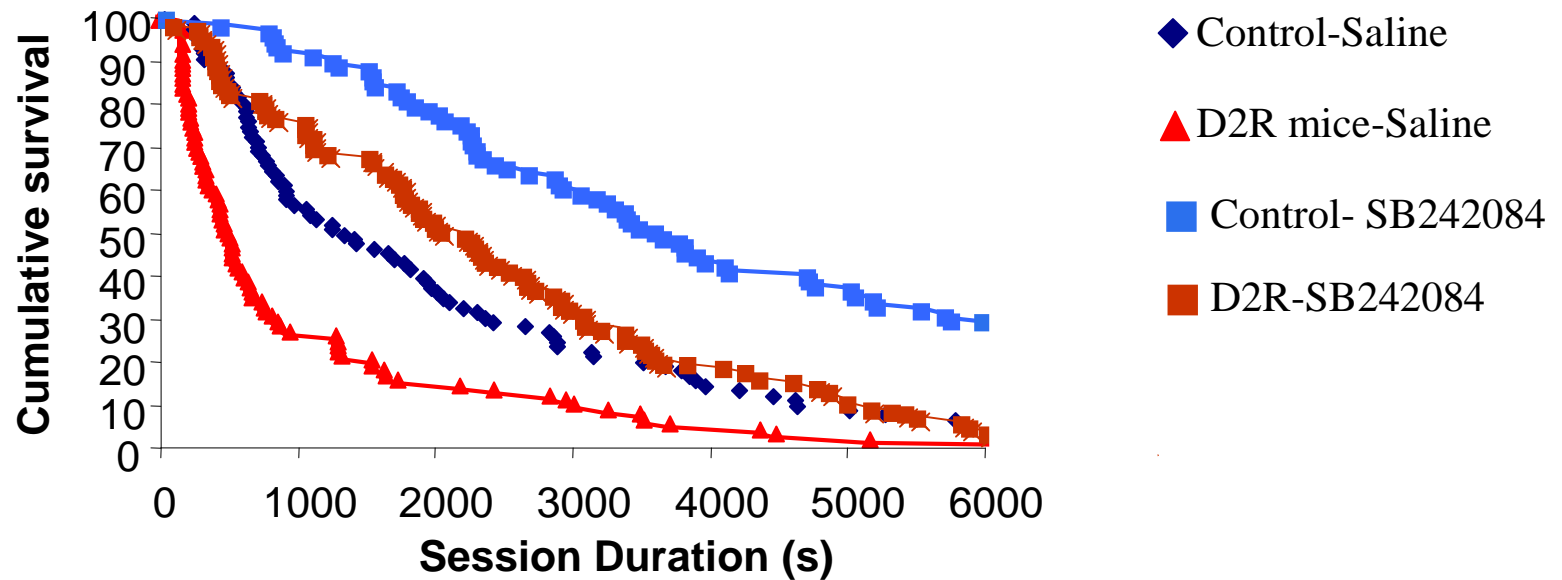
## Possible Underlying Mechanism 2: Increased Striatal D2 Receptors Affects Serotonin Signaling

	p-value	Fold
Serotonin transporter	0.64	1.02
5HT-1A Receptor	0.56	0.98
5HT-1A Receptor	0.63	0.98
5HT-1B Receptor	0.27	0.97
5HT-1D Receptor	0.93	1.00
5HT-1F Receptor	0.62	1.03
5HT-2B Receptor	0.26	0.94
<b>5HT-2C Receptor</b>	<b>0.02</b>	<b>1.38</b>
5HT-3A Receptor	0.18	1.02
5HT-3B Receptor	0.92	1.00
5HT-4 Receptor	0.10	0.94
5HT-5A Receptor	0.20	0.96
5HT-5B Receptor	0.32	0.97
5HT-6 Receptor	0.55	1.03
5HT-7 Receptor	<b>0.02</b>	<b>0.94</b>
5HT-2A Receptor	Not altered: quantitative PCR	



# Acute 5HT<sub>2C</sub> receptor Blockage Reverses Deficit In The Progressive Ratio Task

Proportion of mice that is still working on the progressive ratio schedule



## From Men to Mice and Mice to Men

- Upregulation of D2 receptors in the striatum leads to downregulation of D1 receptors in the striatum
- D1 receptors may be down-regulated in the associative striatum of patients with schizophrenia  
(Preliminary data: Anissa Abi-Dargham's laboratory)

## **General Conclusion:**

- 1) Mice can be used to study complex psychiatric disorders by focusing on specific endophenotypes of these disorders
- 2) This strategy is not restricted to schizophrenia but can be used for other neuro-developmental disorders such as ADHD or autism

# Schizophrenia Is Characterized by a Genetic Predisposition to Develop Positive, Negative and Cognitive Symptoms

- **Positive symptoms**

  - Disordered thought

  - Hallucinations

  - Delusions

  - (Difficult to model in mice)

- **Negative symptoms**

  - Social withdrawal

  - Blunted affect

  - Decreased motivation

- **Cognitive deficits**

  - Attentional deficits

  - Deficit in working memory and executive function

# **The Cognitive Symptoms Are of Particular Significance**

## **The Cognitive Symptoms Are of Particular Significance**

- The degree of cognitive symptoms is more predictive for the long term prognosis of the disease than the degree of positive symptoms
- The cognitive symptoms are almost treatment resistant

## **Some of the cognitive symptoms can be modeled in mice**

- e.g.: Working Memory is a reliable biological marker for a restricted component of schizophrenia that can be modeled in mice because mice like people have a prefrontal cortex that is critical for working memory.