INSTITUT JACQUES MONOD

Animal Models in Psychiatry

Troubles du comportement : mémoire, schizophrénie

Lydia Danglot

Télécharger le cours sur http://lydia.danglot.free.fr

Master de Biothérapies Tissulaires, Cellulaires et Géniques
Module « Modèles Animaux »
Faculté de Médecine de Créteil - Université Paris 12
17 Novembre 2014

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Life Science & Imaging

Novembre 2, 2009

- Thème de recherche
- Publications
- Enseignement
- Liens favoris
- CONTACT

French English

Enseignement

Cours

- Master2 de Neurosciences - UE Synapse et synaptogenèse (code UE : MBIP5019) - Université Pierre et Marie Curie (Paris 6): Planning ***Neuritogenèse et polarité neuronale.***
- Master2 de Neurosciences - UE Communication Cellulaire (code UE : MBIP5003) - Université Pierre et Marie Curie (Paris 6): ***Les protéines SNARE et l'exocytose*** : classification des SNAREs, voie de recyclage des VS, comment mesurer l'exocytose, comment mesurer le recyclage, les protéines régulant l'assemblage des SNARE (Munc18, munc13, Syt, complexine), souris KO Syb2, souris mocha,...
- Master2 de Génétique - Université Paris Diderot (Paris 7), UE Neurobiologie cellulaire et développementale. ***Développement de l'hippocampe et synaptogenèse:*** Neuroanatomie générale, présentation du SNC, présentation du télencéphale et de l'hippocampe, développement de l'hippocampe, migration des neurones excitateurs et inhibiteurs, modèle des neurones dissociés d'hippocampe en culture, polarité neuronale, formation des synapses.
- Ecole doctorale Frontières du Vivant (Universités Paris V, VI, VII) Club Neurobiologie & Optique: ***Diversité et usage des protéines fluorescentes en Neurosciences.***

MANUEL de cours

Master2- Paris 6 Neuritogenèse et polarité neuronale.
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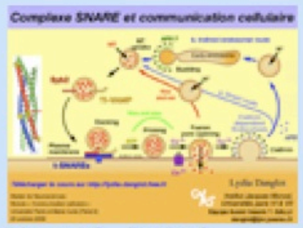

Master2- Paris 6 Complexe SNARE et communication cellulaire.
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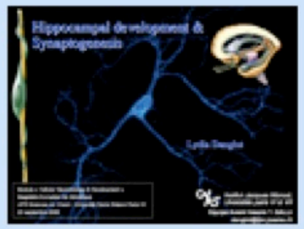

Master2- Paris 7 Développement de l'hippocampe et synaptogenèse
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Psychosis

Definition

• from the Greek "psyche", for mind/soul, and "-osis", for abnormal condition) - **abnormal condition of the mind**,

and is a generic psychiatric term for a **mental state** often described as involving a **"loss of contact with reality"**.

Age onset: 20–28 years for males 26–32 years for females.

Causes

Symptoms of psychosis can be induced by external stimuli or by central nervous system diseases :

* brain tumors or damage
* exposure to some traumatic event (violent death, etc.) or severe psychosocial stress
* sleep deprivation
* drug abuse amphetamines, cocaine, marijuana, alcohol[8] among others

* schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder
* bipolar disorder (manic depression), severe clinical depression
* some focal epileptic disorders especially if the temporal lobe is affected

Signs and symptoms

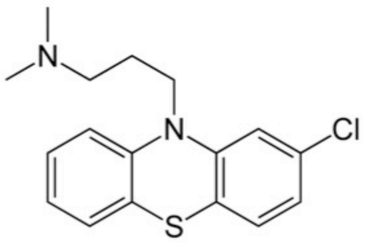
• People with psychosis may have one or more of the following:

  • hallucinations: sensory perception in the absence of external stimuli. (such as lights, colors, tastes, and smells, hearing voices, having complex tactile sensations)

  • delusional beliefs, some of which are paranoid in nature

  • a thought disorder disturbance to conscious thought, disconnection and disorganization of the semantic content of speech and writing.

Neuroleptics and antipsychotics



Definition

Neuroleptic (used by french doctors) or antipsychotics (anglo-saxon doctors) is a tranquilizing psychiatric medication primarily used to manage psychosis, and might be used for schizophrenia, bipolar disorder and delusional disorder.

Nomenclature

Antipsychotics are broadly divided into two groups :

- the typical or first-generation antipsychotics: discovered in the 1950s.
- atypical or second-generation antipsychotics: most of them have been developed more recently.

Action

Both generations of medication tend to block receptors in the brain's dopamine pathways, but antipsychotic drugs can also encompass a wide range of receptor targets (serotin particularly 5HT2A, C and 5HT1A receptors).

Side effects

Antipsychotics are associated with a range of side effects. Extrapyramidal reactions include acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, intense dreams or nightmares, and hyperprolactinaemia.

The aim is now to reduce these side effects by developing new and more specific molecules.

First generation antipsychotics :

Butyrophenones

* Haloperidol (Haldol, Serenace)
* Droperidol (Droleptan)

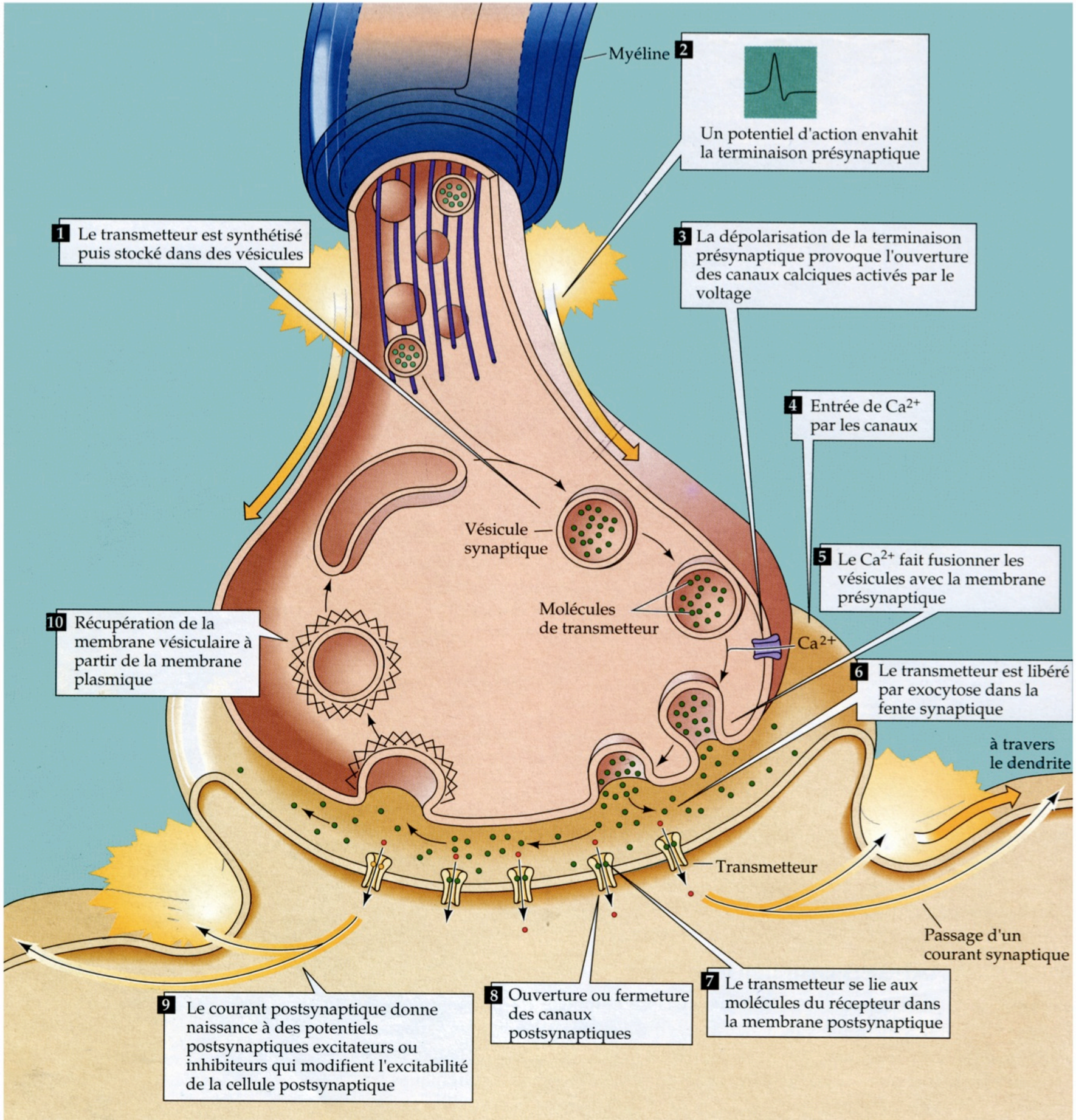
Phenothiazines

* Chlorpromazine (Thorazine, Largactil)

Second generation antipsychotics

* Clozapine (Clozaril) -
* Amisulpride (Solian) - Selective dopamine antagonist.

L'exocytose synaptique



D' après Neurosciences,
à la découverte du cerveau
M. F. Bear

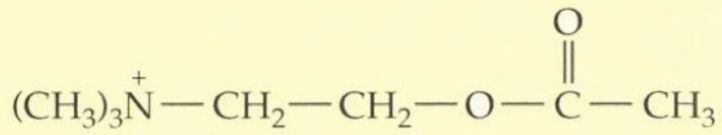
TABLEAU
Propriétés de quelques-uns des principaux neurotransmetteurs

Neurotransmetteur	*Effet*[a] *Postsynaptique*	*Précurseur(s)*	*Étape limitante de la biosynthèse*	*Mécanisme d'élimination*	*Type de vésicule*
ACh	Excitateur	Choline + acétyl CoA	CAT	AChEase	Petite, claire
Glutamate	Excitateur	Glutamine	Glutaminase	Transporteurs	Petite, claire
GABA	Inhibiteur	Glutamate	GAD	Transporteurs	Petite, claire
Glycine	Inhibiteur	Sérine	Phosphosérine	Transporteurs	Petite, claire
Catécholamines (adrénaline, noradrénaline, dopamine)	Excitateur	Tyrosine	Tyrosine hydroxylase	Transporteurs, MAO, COMT	Petite centre dense ou grande, irrégulière centre dense
Sérotonine (5-HT)	Excitateur	Tryptophane	Tryptophane hydroxylase	Transporteurs, MAO	Grande, centre dense
Histamine	Excitateur	Histidine	Histidine décarboxylase	Transporteurs	Grande, centre dense
ATP	Excitateur	ADP	Phosphorylation oxydative mitochondriale ; glycolyse	Hydrolyse en AMP et adénosine	Petite, claire
Neuropeptides	Excitateur et inhibiteur	Acides aminés (synthèse protéique)	Synthèse et transport	Protéases	Grande, centre dense

[a] On a indiqué l'effet postsynaptique le plus commun ; rappelons que le même neurotransmetteur peut provoquer, au niveau postsynaptique, soit une excitation, soit une inhibition, selon la nature du canal ionique affecté à la liaison du transmetteur (voir Chapitres 5 et 7).

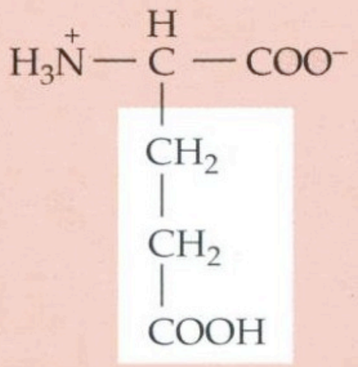
NEUROTRANSMETTEURS À PETITE MOLÉCULE

Acétylcholine

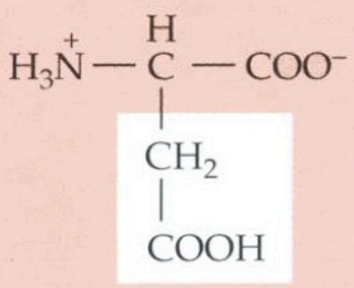


ACIDES AMINÉS

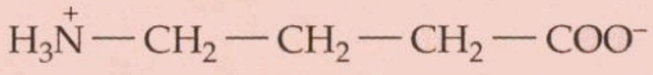
Glutamate



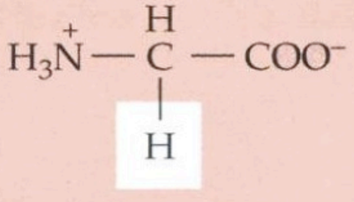
Aspartate

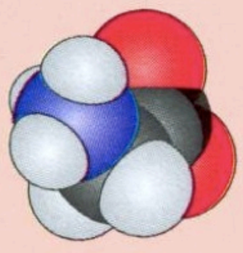


GABA



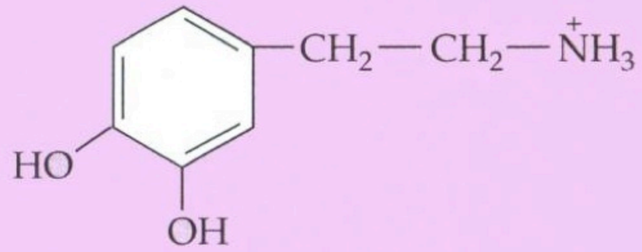
Glycine



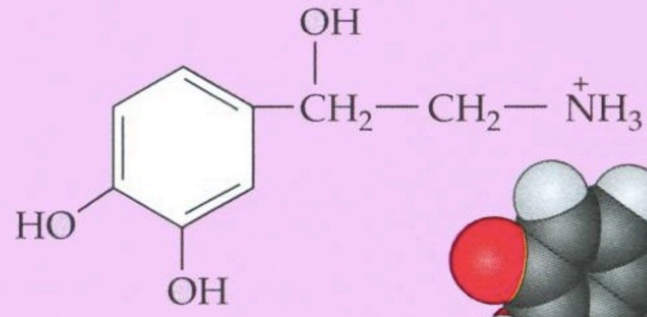


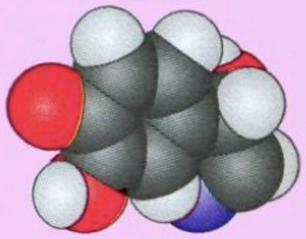
CATÉCHOLAMINES

Dopamine

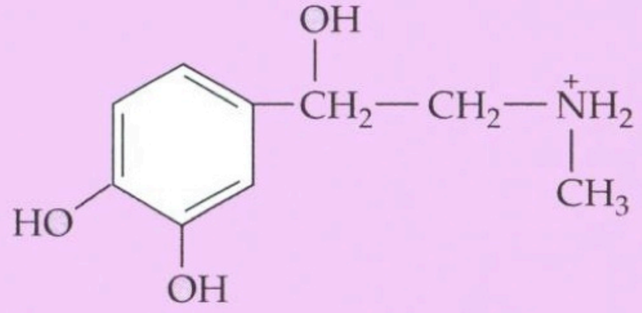


Noradrénaline



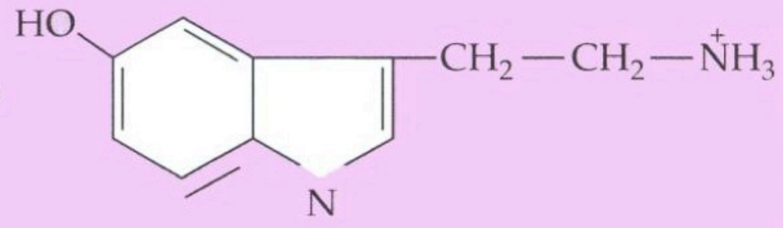


Adrénaline



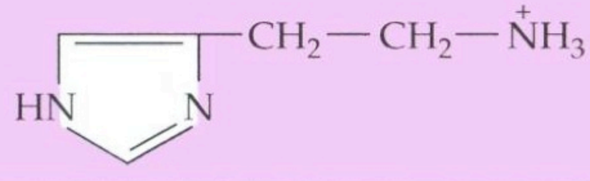
INDOLAMINE

Sérotonine (5-HT)



IMIDAZOLAMINE

Histamine

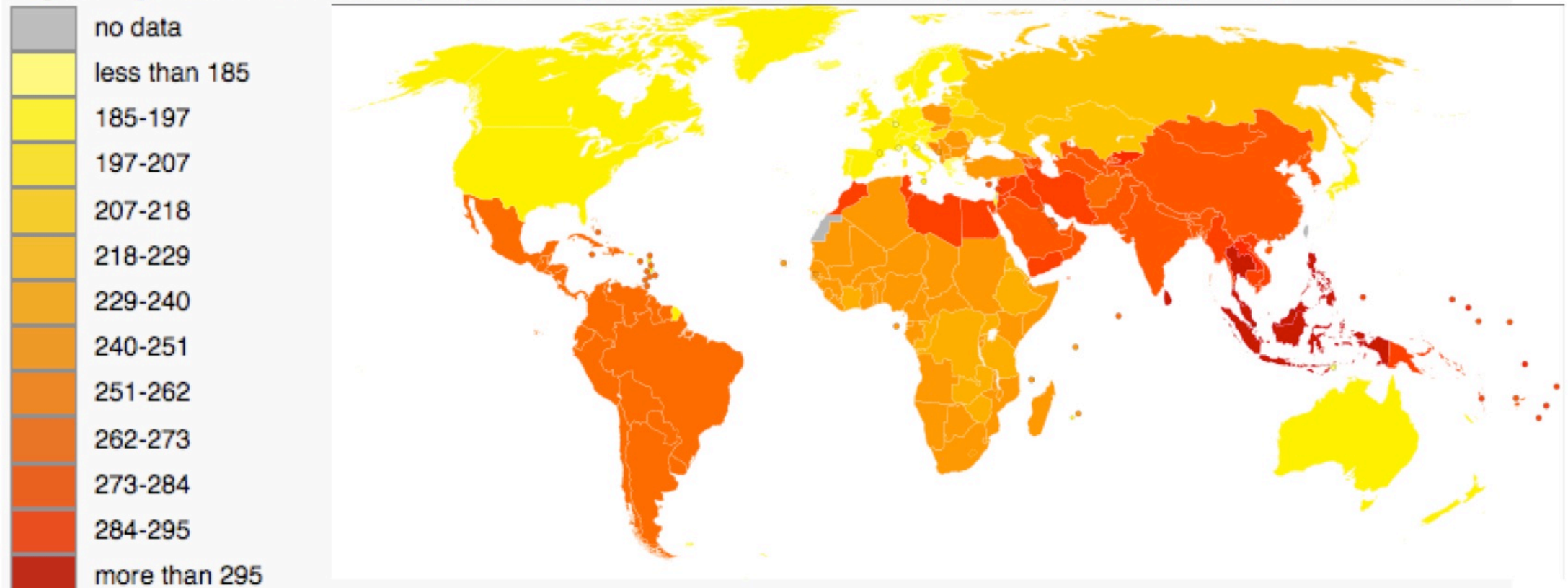


Schizophrenia

Epidemiology

- Schizophrenia occurs equally in males and females,
- Age onset: 20–28 years for males 26–32 years for females.
- Lifetime prevalence (= proportion of individuals expected to experience the disease at any time in their lives): 1%.

In a 1999 study of 14 countries, active psychosis was ranked the third-most-disabling condition after quadriplegia and dementia and ahead of paraplegia and blindness.



Schizophrenia

« Positive symptoms »:

(Excess of normal function)

- **Delusions**
- **auditory hallucinations**
- **thought disorder**
- **speech disorder**

« Negative symptoms »:

(reduction of normal functions)

- **flat or blunted affect and emotion**
- **poverty of speech (alogia)**
- **inability to experience pleasure (anhedonia)**
- **lack of desire to form relationships (asociality)**
- **lack of motivation (avolition)**
- **attention deficit**

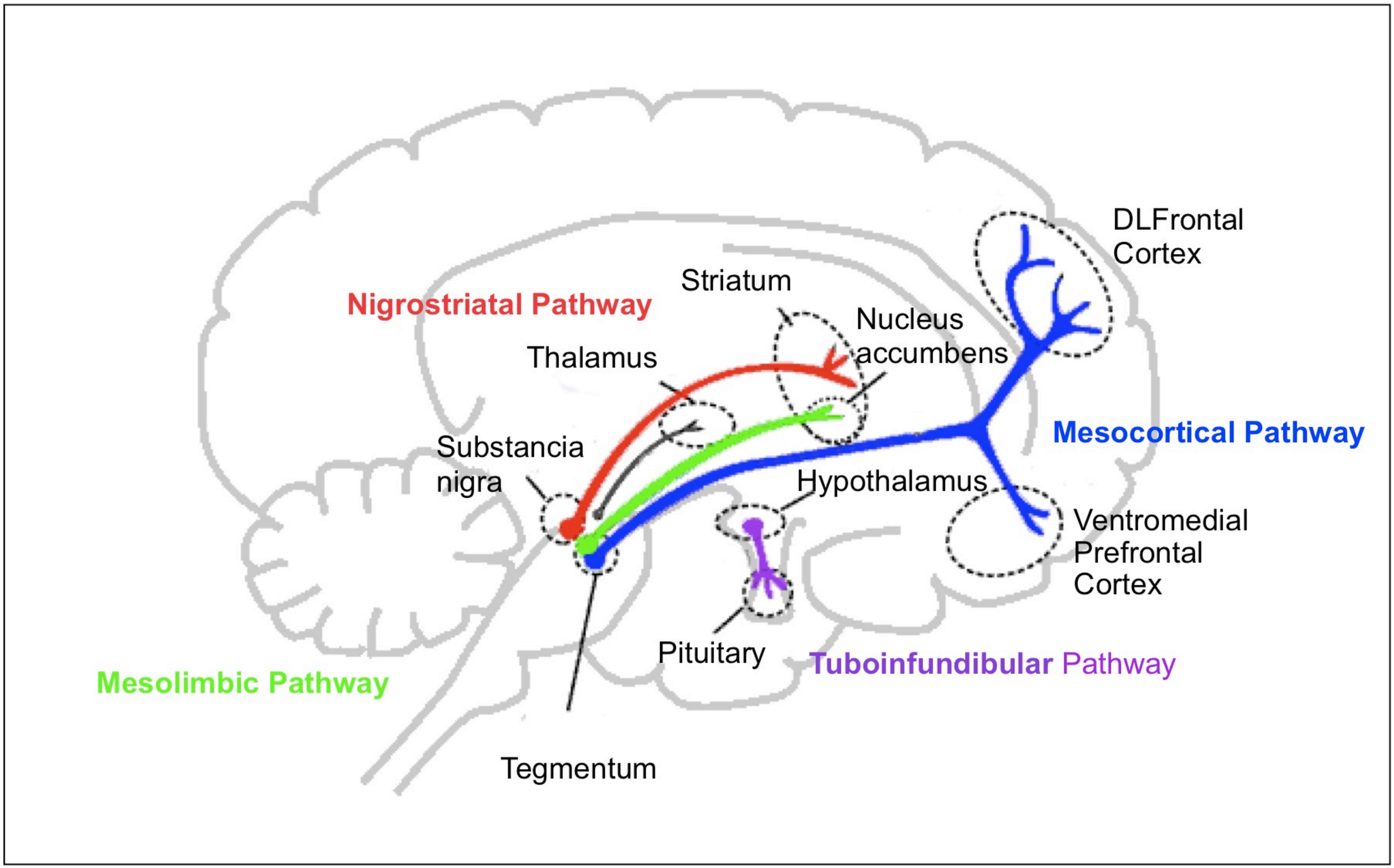
« Cognitive symptoms »:

- **thought disorder**
- **speech disorder** (« word salad »)
- **attention deficit**

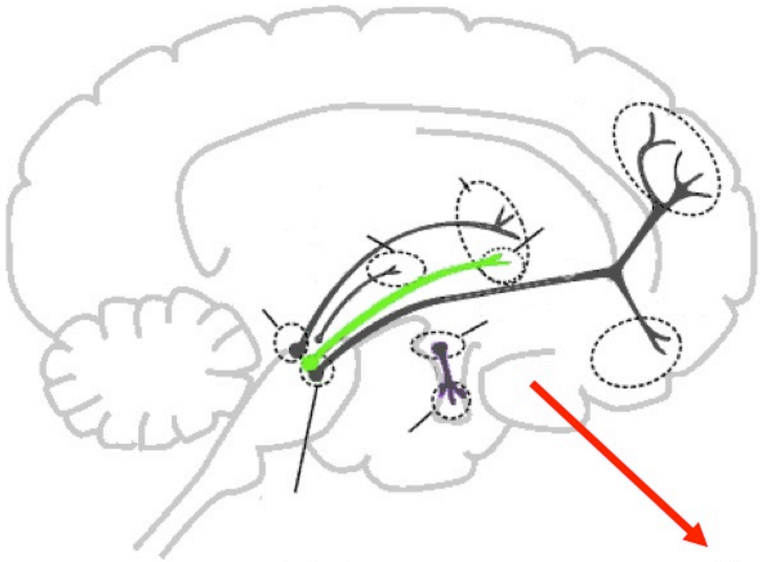
« Affective symptoms »:

-lack of responsiveness or motivation.
-paranoia, and social isolation

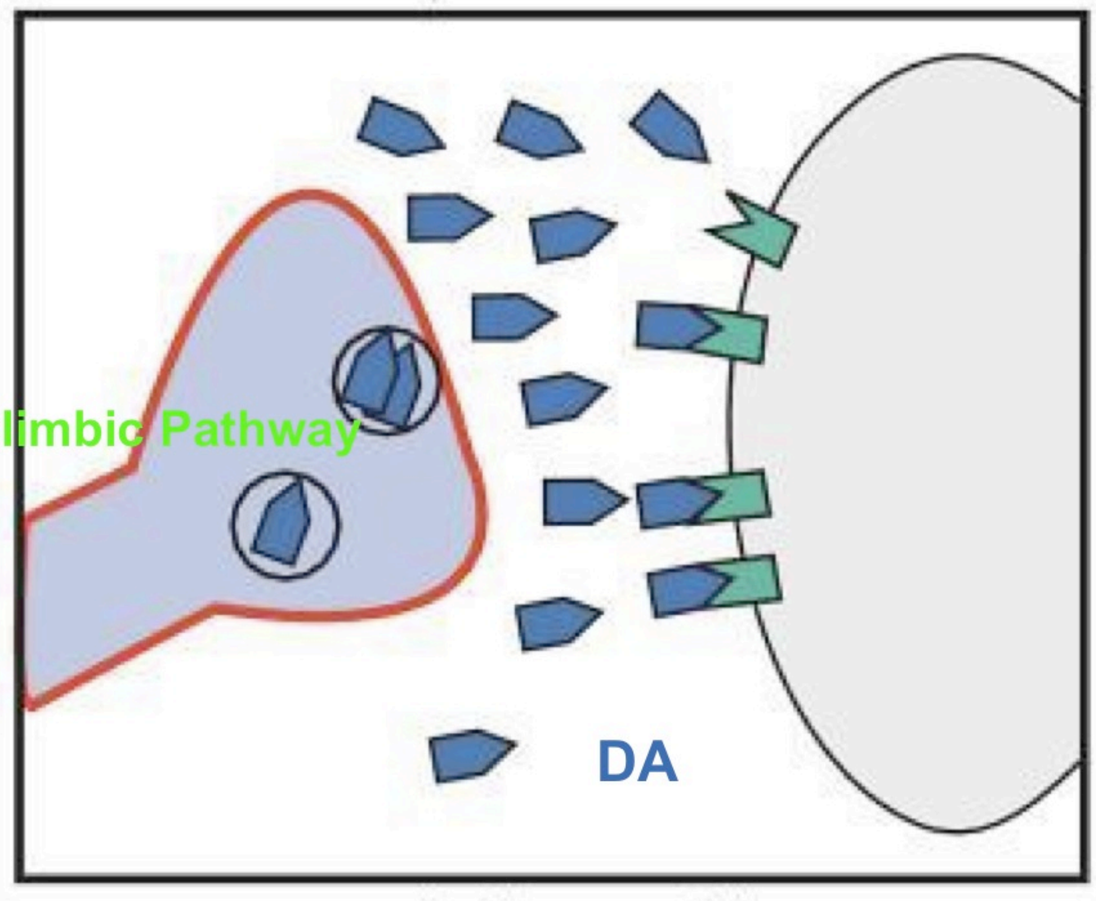
Dopamine Pathways in the human brain



The Mesolimbic Dopamine hypothesis of positive symptoms of schizophrenia



Hyperactivity of DA neurons of the mesolimbic pathway

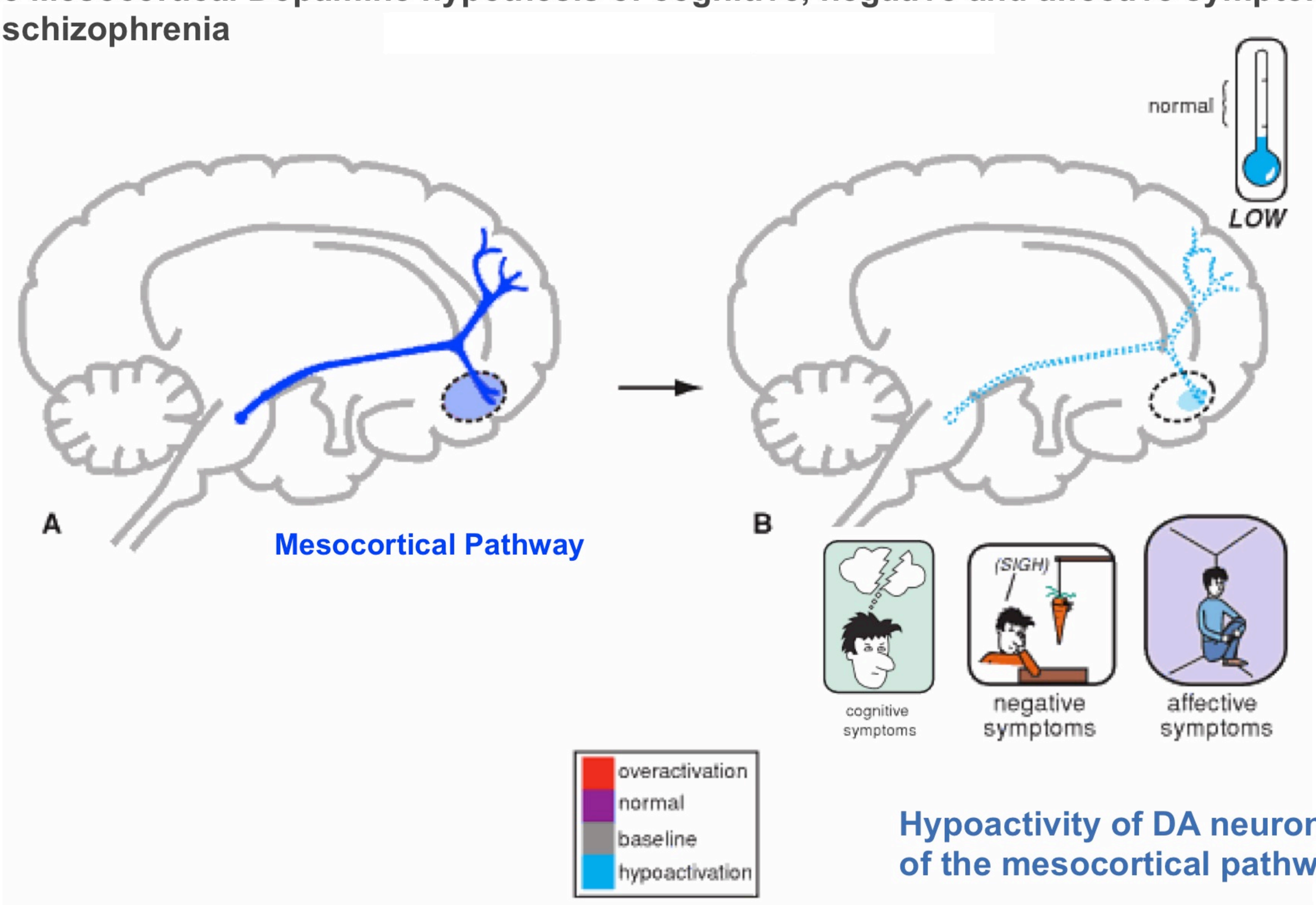


mesolimbic overactivity =
positive symptoms of schizophrenia

positive symptoms

Adapted from Essential Psychopharmacology, Stephen Stahl, Flammarion.

The Mesocortical Dopamine hypothesis of cognitive, negative and affective symptoms of schizophrenia



Hypoactivity of DA neurons of the mesocortical pathway

Adapted from Essential Psychopharmacology, Stephen Stahl, Flammarion.

Psychiatry and Animal Models

I- Introduction (definition, validity, specificity of the psychiatry)

- ✓ Modèles Animaux et Psychiatrie
  Verdoux et Bourgeois, Monographies de l'ANPP, 1991, vol 5.

- ✓ Psychiatric Genetics: search for phenotypes
  Leboyer *et al.* TINS 21-3, 1998, 102-5.

II - From Genetic to Psychiatry:

- ✓ Invalidation of the dopamine transporter (DAT)

III - From Clinic to Mouse:

- ✓ Behavioural lateralization

- ✓ Anxiety

IV - Conclusions

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Animal Models

Définition:

« **Compromis** expérimental dans lequel un système expérimental **simple** est utilisé pour représenter un système beaucoup plus complexe et moins immédiatement accessible : l'animal pour représenter le patient, la coupe tissulaire pour le cerveau, … ».

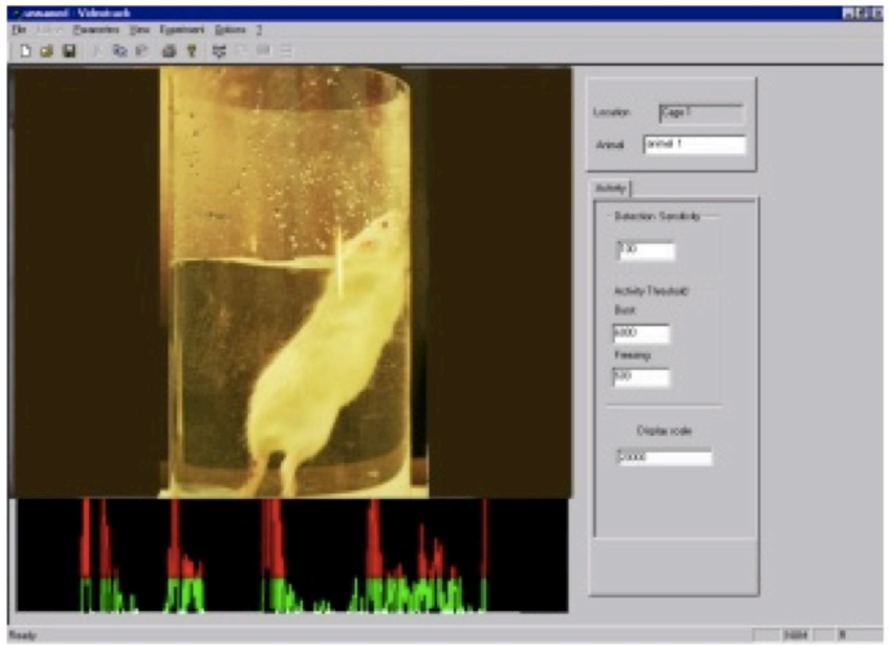
(Verdoux et Bourgeois, 1991)

Categorizations according to the required goal :		Validity :
Models		
Homologue	Etiological identity	construct
Isomorphic	Phenomenological identity	face
Predictive	Drugs screening	predictive

Animal Models in Psychiatry ?

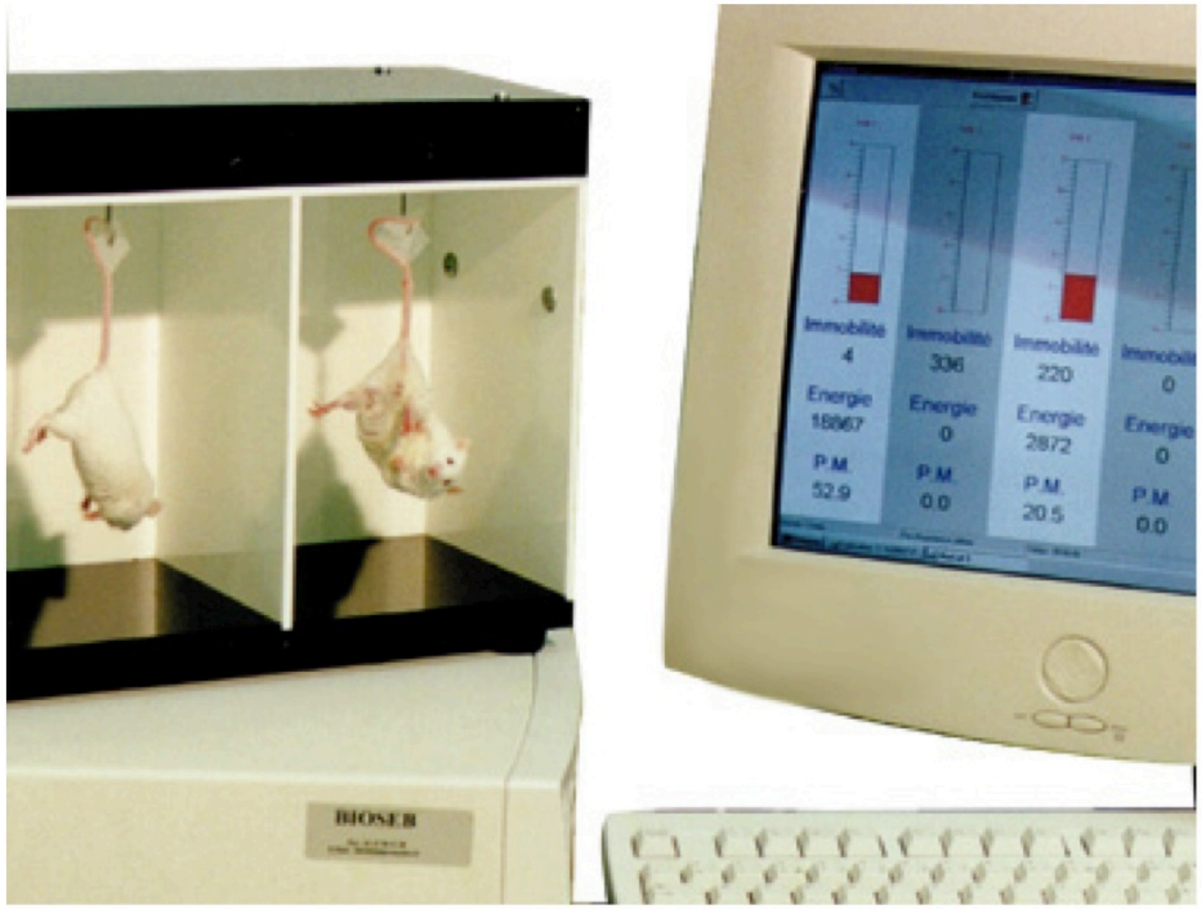
… < 1990
Predictive Models

Porsolt Swim Test PST



Antidepressants:
- ✓ Inactivity ↘
- ✓ Swimming
- ✓ Climbing ↗

Tail Suspension Test TST



Antidepressants:

- ✓ Immobility ↘

Psychiatry and Animal Models

1990 …
From the pharmacology to the neuropsychiatry genetic
From predictive models to etiological models

1) Genetic

Genome sequencing, molecular genetic,
random and targeted mutagenesis, etc…

2) Psychiatry

Animal Models of which Psychiatric Disorders (Schizophrenia, Autism, TOC,…) ?

The Psychiatric Disorders

➢ Lack of specific marker

Nosography: classification criteria: reliable standard diagnostic

=> High inter-rater reliability, but what genetic validity?

Leboyer *et al.* TINS, 1998

New Phenotypic Approaches

In affected individuals

"candidate symptom approach"

Compounds of the phenotype
with high **«genetic validity»**

- intra-familial resemblance
- identify homogeneous clinical forms
- increase the familial risk
- mode of genetic transmission
- join to candidate genes

In non-affected subjects

" endophenotypes "

Biological/cognitive/
electrophysiological markers of
underlying genetic vulnerability

- more frequent in related
- independent of the state
- stable
- mode of genetic transmission
- join to candidate genes

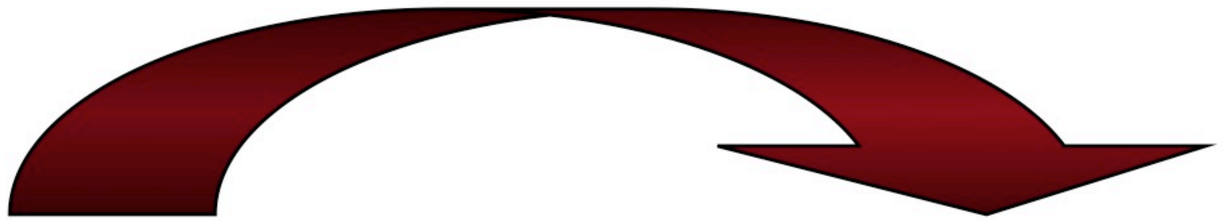
Examples :
Deficit of lateralization
Deficient sensorimotor gating…

- ✓ **Trans-nosographical**
- ✓ **Available to animal modeling**

Leboyer *et al.* TINS, 1998

Genetic Analysis of Complex Traits

Genetic-driven approach
(« reverse genetics »)

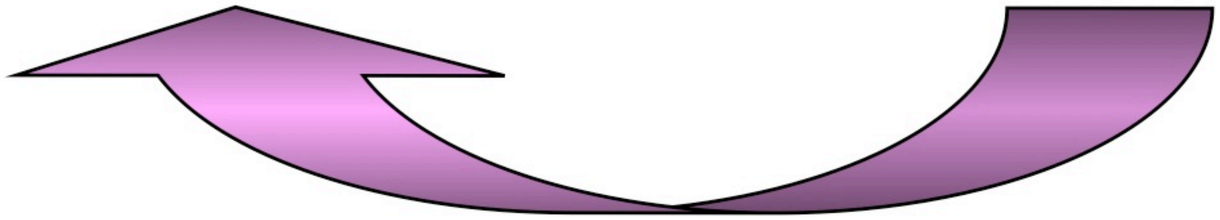


DAT

GENE

PHENOTYPE

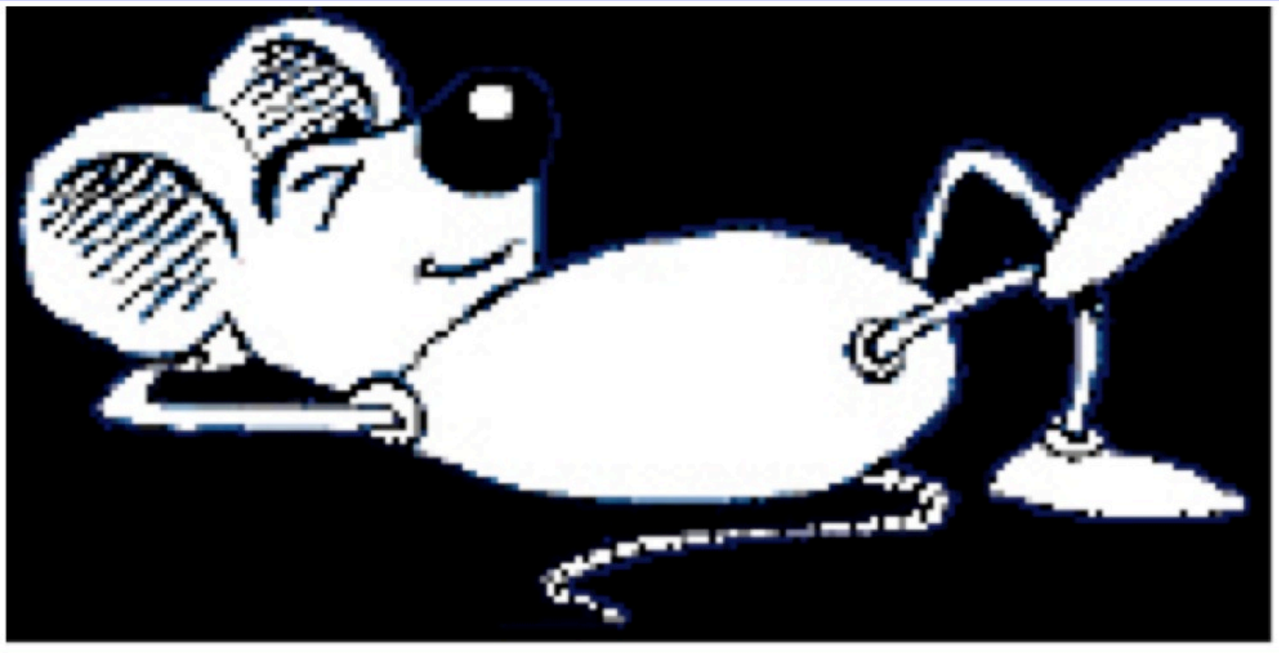
Lateralization
Anxiety



Phenotype-driven approach
(« forward genetics »)

Mouse Model

Limited behavioural repertoire



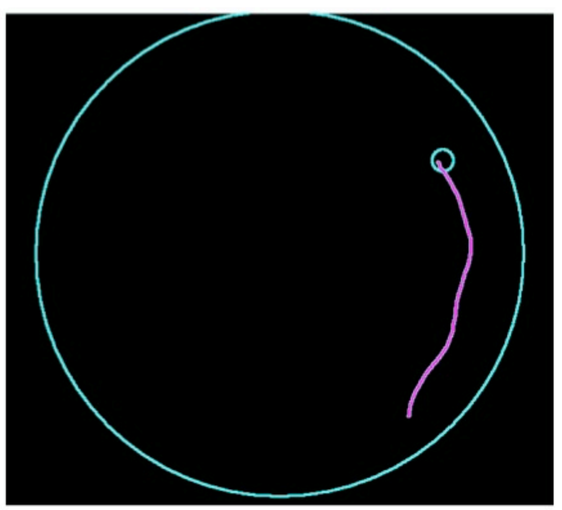
locomotor Activity

Activity

Exploratory behaviour
Social interactions

Anxiety
Dependence / addiction
Learning / memory
...

Food intake, body weight...



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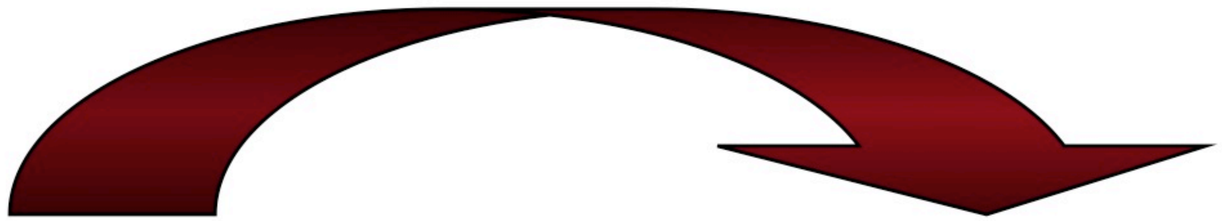


DAT

GENE

PHENOTYPE

Phenotype-driven approach
(« forward genetics »)

Psychiatry and Animal Models

I- Introduction (definition, validity, specificity of the psychiatry)

II - From Genetic to Psychiatry :

- ✓ Invalidation of the dopamine transporter (DAT)
  - DAT-/- and toxicomania
  - DAT-/- and ADHD
  - DAT-/- and genetic background
  - DAT-/- and plasticity

III - From Clinic to Mouse :

- ✓ Behavioural lateralization
- ✓ Anxiety

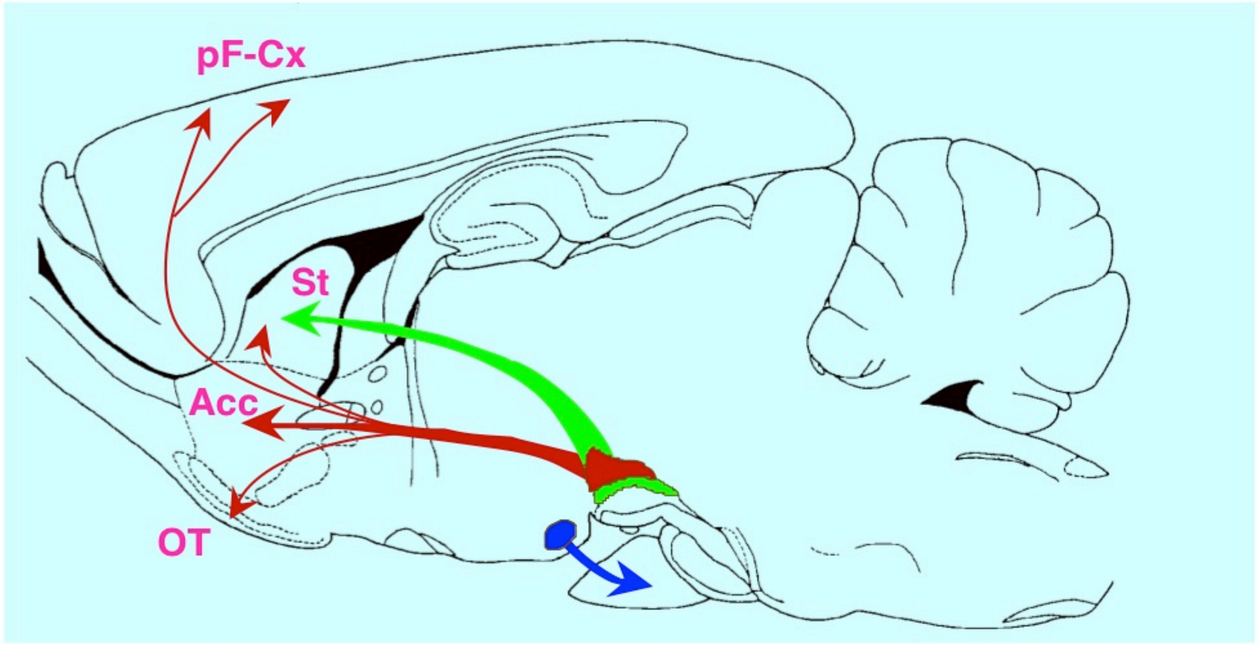
IV - Conclusions

Dopamine and Psychiatric Pathologies

✓ **Addiction**

- Morphine
- Cocaine
- Nicotine
- THC
- Alcohol

DA ↑



A9 : nigrostriatale A10 : mésocorticolimbique A12 : tubéro-infundibulaire

pF-Cx : cortex préfrontal ; St : striatum ; Acc : noyau accumbens ; OT : tubercules olfactifs

✓ **Schizophrenia**

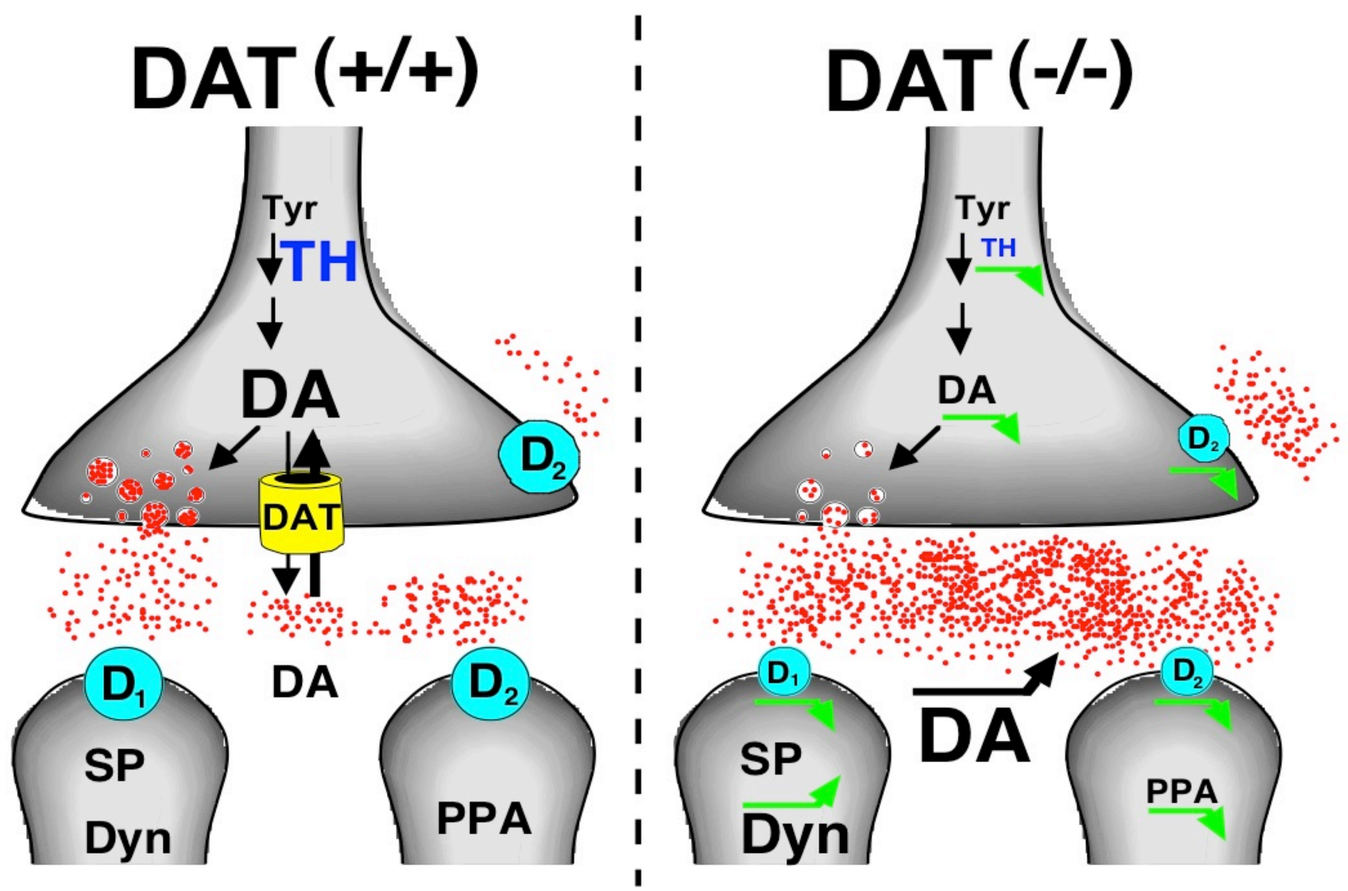
- Neuroleptics : antagonists of DA receptors
- Agonists of DA receptors : psychomimetic

✓ **Attention Deficit and Hyperactivity Disorder: ADHD**

- Agonists of DA receptors

Mutant Mice for the Dopamine Transporter (DAT): Hyperdopaminergic Mice

DAT = plays a critical role in calibrating the duration and intensity of DA neurotransmission



DA: dopamine; D1, D2: Dopamine D1 and D2 receptors; DAT: DA transporter; Dyn: dynorphin; SP: substance P; TH: tyrosine hydroxylase; tyr: tyrosine; PPA: pre-proenkephalin A (Giros, 1996).

(Giros *et al.* 1996)

Mutants Mice for the Dopamine Transporter (DAT)

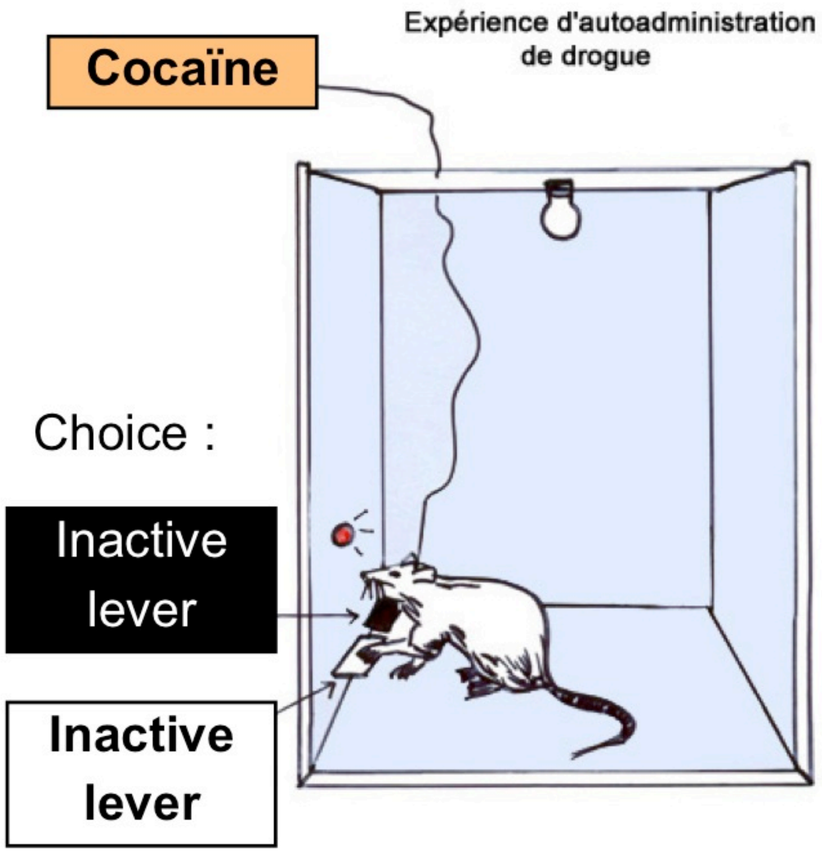
and Toxicomania?

DAT: target of the cocaine

Models of drug-habit in mouse:

- ✓ Self-administration
- ✓ Conditioned place preference
- ✓ Sensitization

lf-administration of Cocaine



article

Cocaine self-administration in dopamine-transporter knockout mice

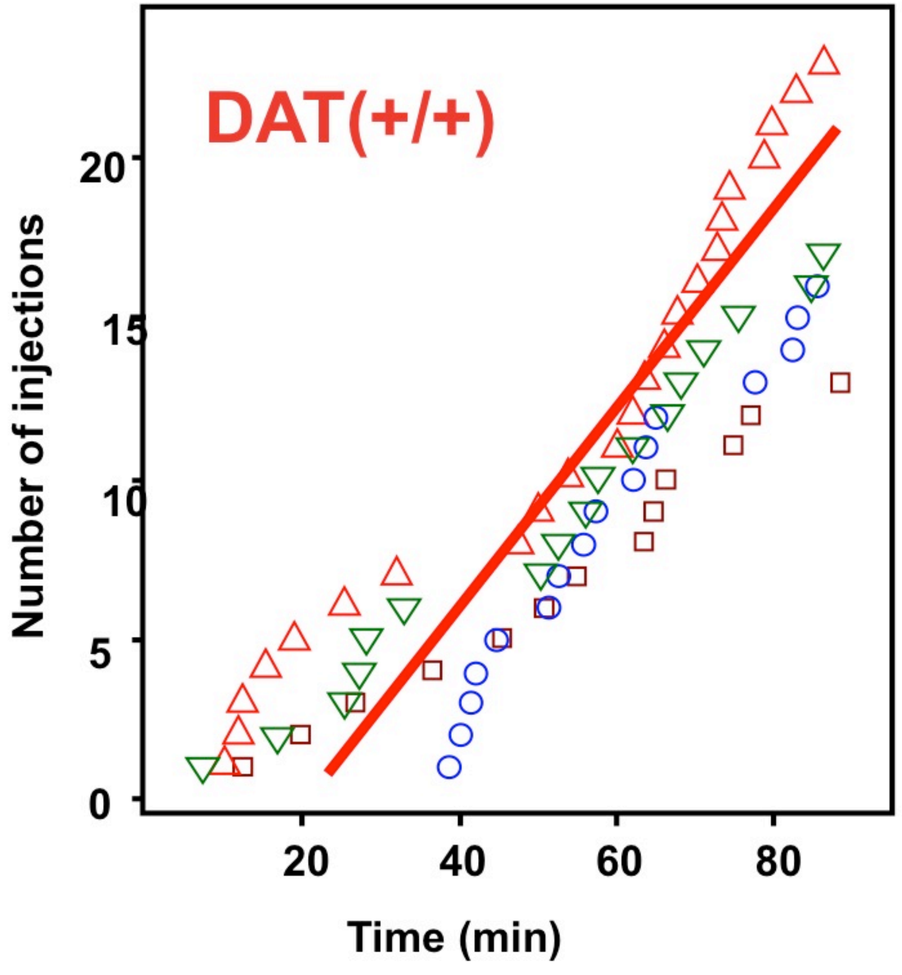
Beatriz A. Rocha[1], Fabio Fumagalli[2], Raul R. Gainetdinov[2], Sara R. Jones[2], Robert Ator[1], Bruno Giros[2,3], Gary W. Miller[2] and Marc G. Caron[2]

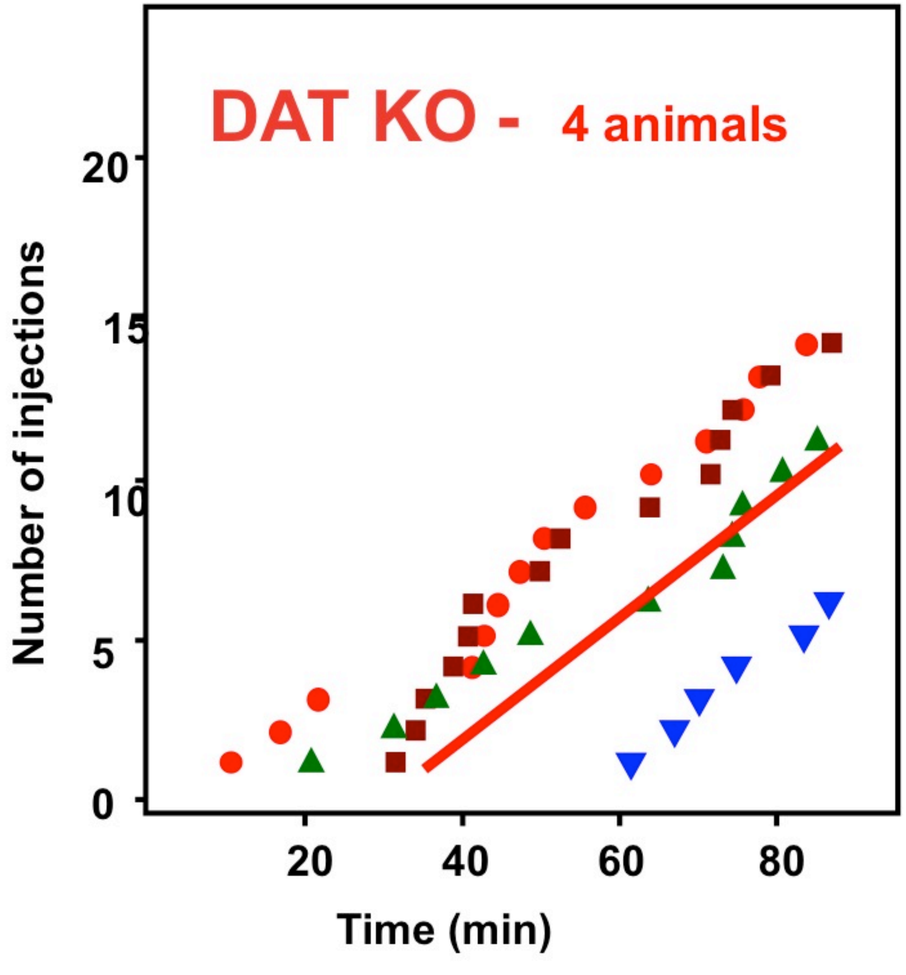
Table 1. Sessions required to meet food shaping or cocaine self-administration acquisition criteria in two-lever operant box

	Food	Cocaine
Wild type	5.7 ± 0.6	5.1 ± 0.4
DAT$^{-/-}$	5.0 ± 0.7	10.8 ± 0.6[1]

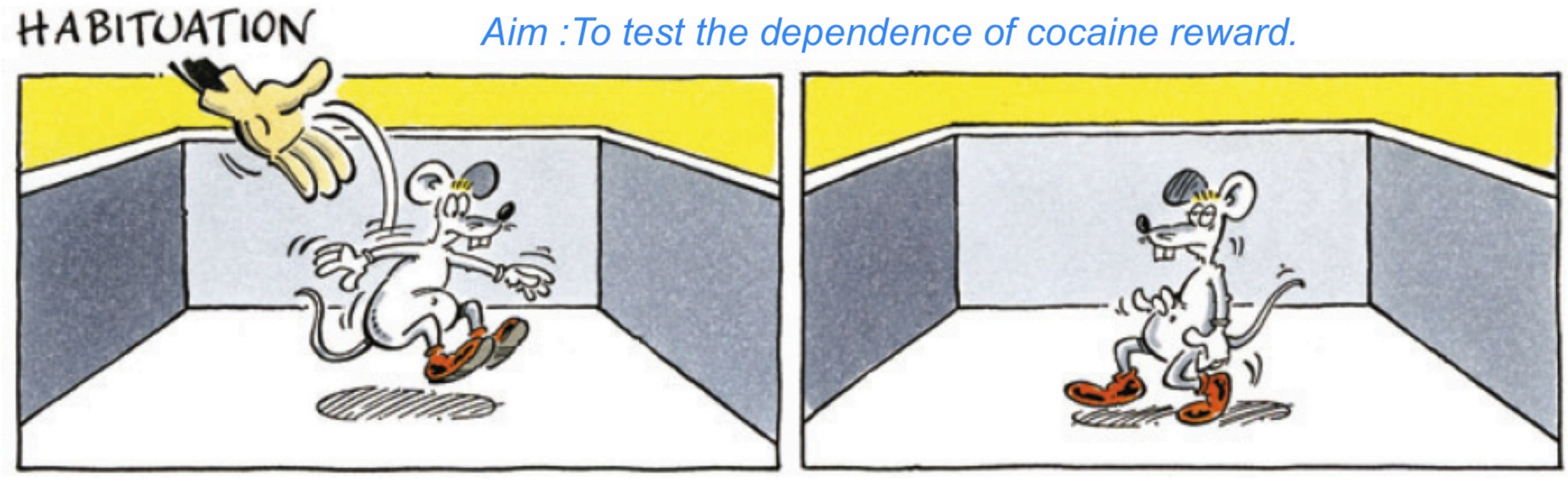
DAT KO mice required more sessions to meet self-administration than WT.
DAT blockade facilitates cocaine-taking behavior

Nevertheless, once cocaine self-administration is acquired, DAT–/– mice consistently and dose-dependently self-administered cocaine.





Conditioned Place Preference (Injection of cocaine)



Aim :To test the dependence of cocaine reward.

Adapted from C. Sanchis-Segura & R.Spanagel, Addiction Biology, 11 , 2–38.

Conditioned Place Preference (Injection of cocaine)

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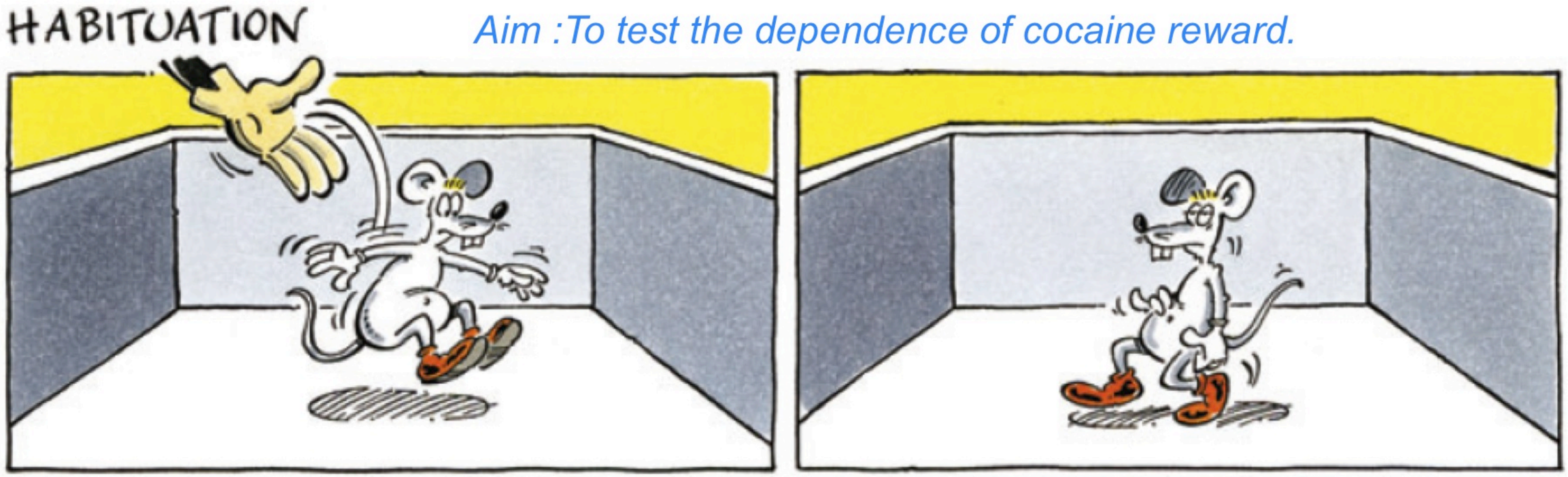
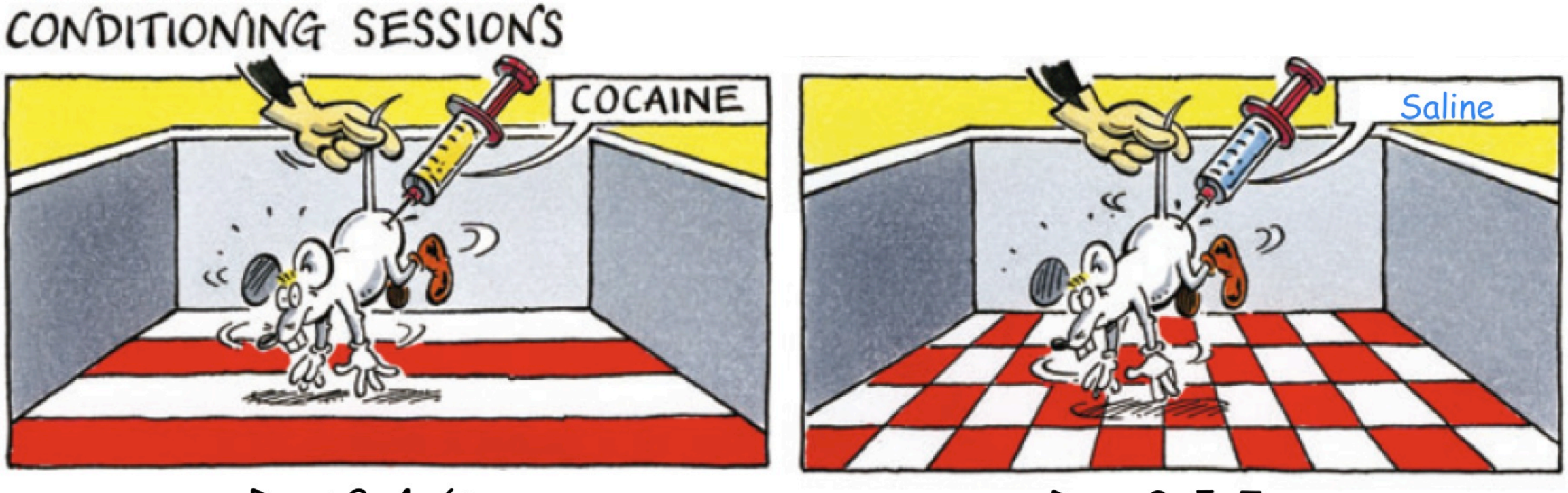


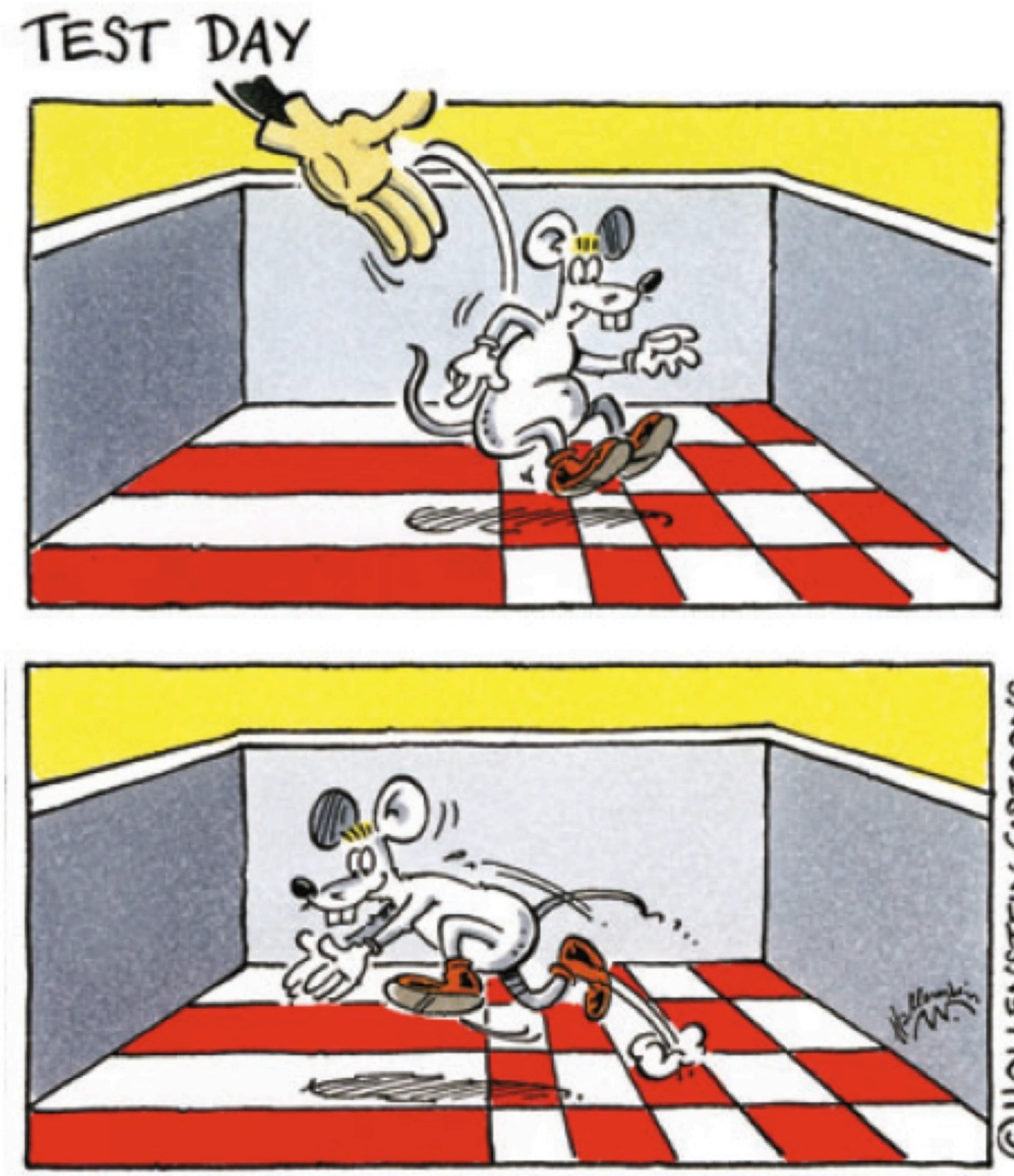


- Days 2, 4, 6:
drug injection

- Days 3, 5, 7:
Saline injection

Adapted from C. Sanchis-Segura & R.Spanagel, Addiction Biology, 11 , 2–38.

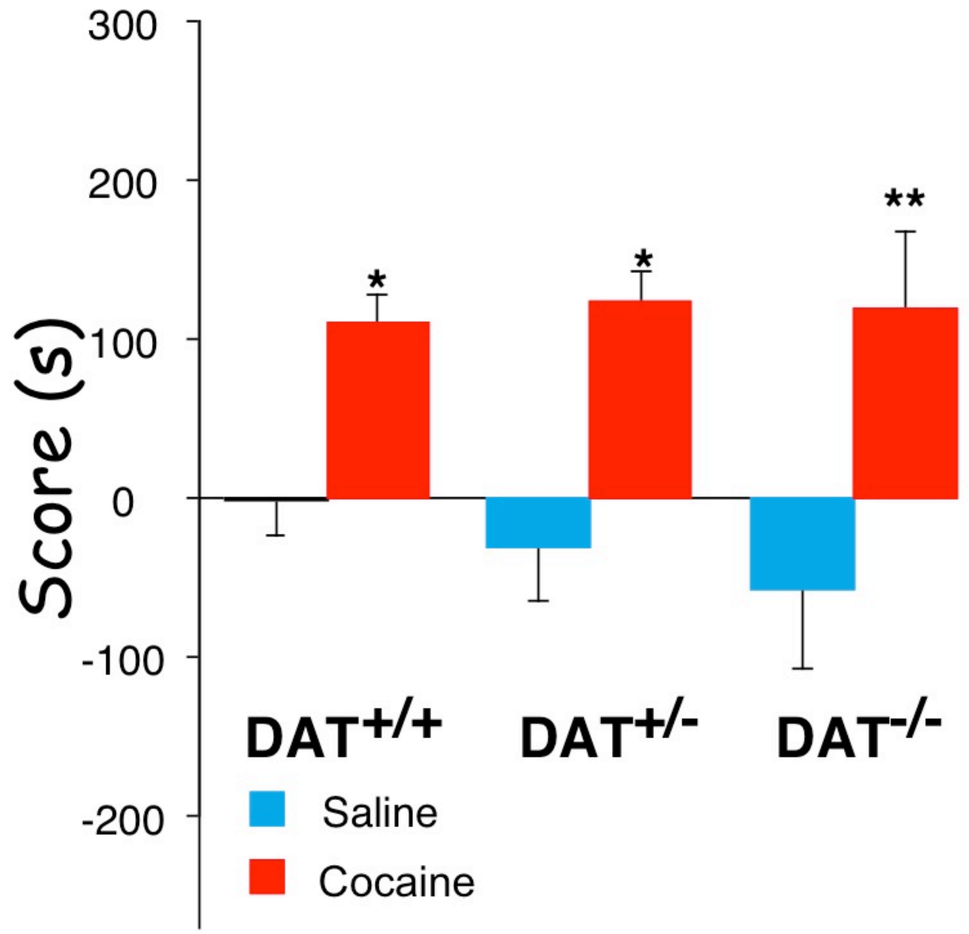
Conditioned Place Preference



Adapted from C. Sanchis-Segura & R.Spanagel, Addiction Biology, 11 , 2–38.

Aim :To test the dopamine-transporter dependence of cocaine reward.

Which preference for wild type and DAT KO mice ?



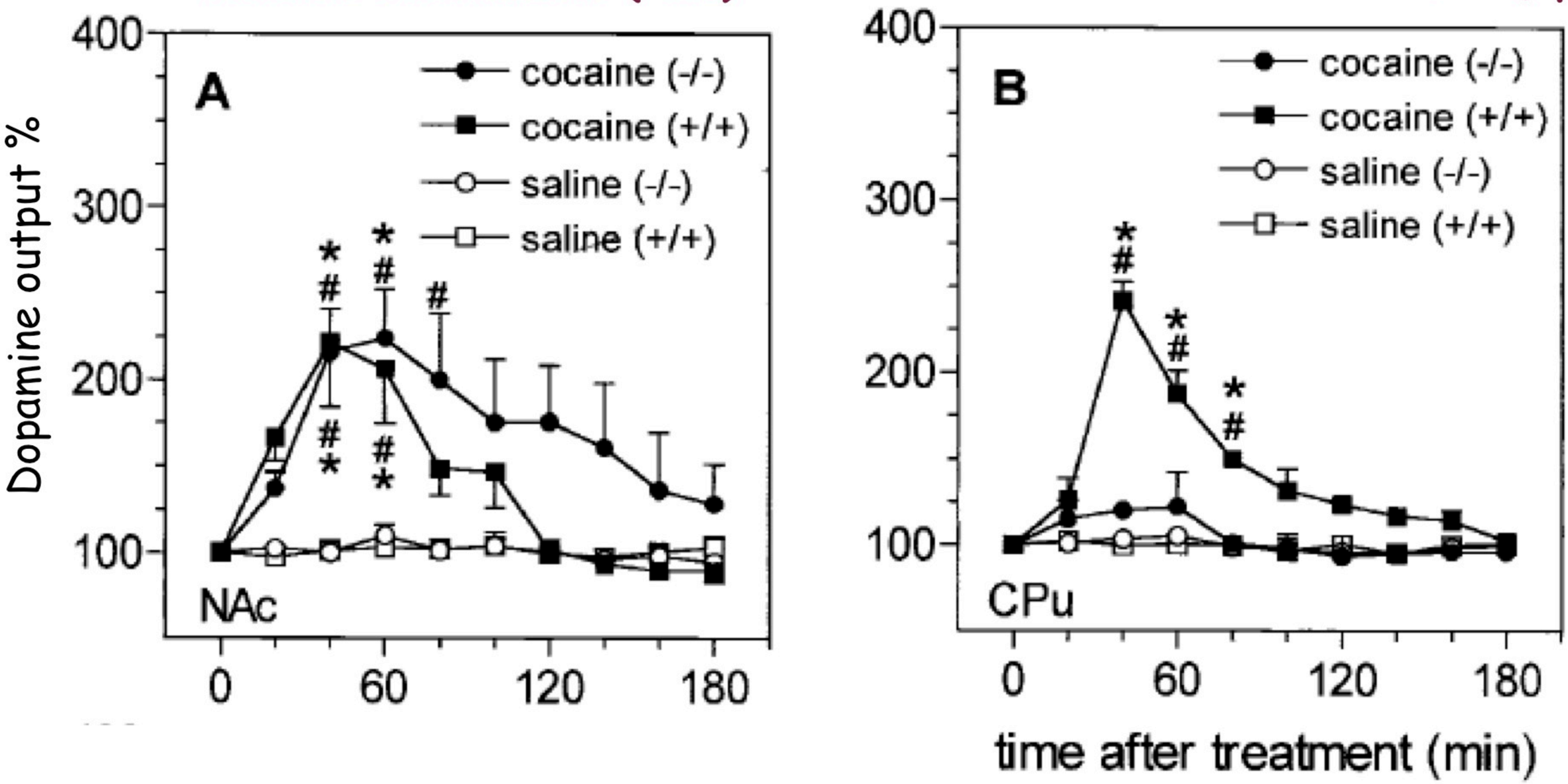
Sora *et al.* 1998

DAT knockout mice still establish cocaine-conditioned place preferences.

Measure of the Extracellular Dopamine by *in vivo* Microdialysis

Nucleus Accumbens (Nac)

Caudate Putamen (Cpu)



Cocaine (20mg/kg,i.p.) increase extracellular DA in the NAc of both DAT-KO but not in Cpu.

In the DAT-KO mice, the NET expressed by NE terminals of the Nac could, because of the absence of DAT, act as an alternative site for DA clearance from the extracellular compartment.

Carboni *et al.* 2001

Mutants Mice for the Dopamine Transporter (DAT)

and Toxicomania?

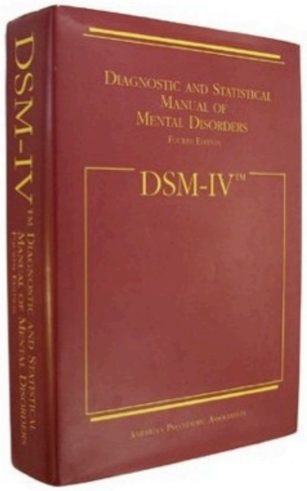
Conclusions

- ✓ Role of the dopamine in the rewarding effects of the cocaine
- ✓ Specific role of the Nucleus accumbens
- ✓ Model to study molecular compensatory mechanisms

Mutants Mice for the Dopamine Transporter (DAT)

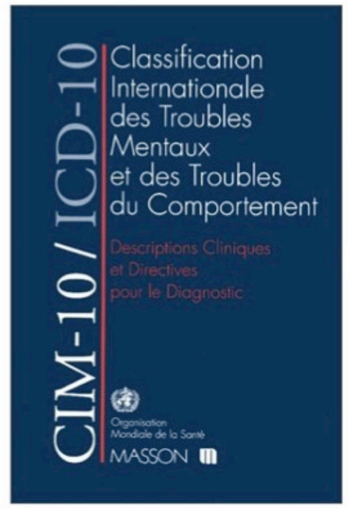
and ADHD (Attention Deficit and Hyperactivity Disorder)?

Attention-deficit hyperactivity disorder (ADHD)



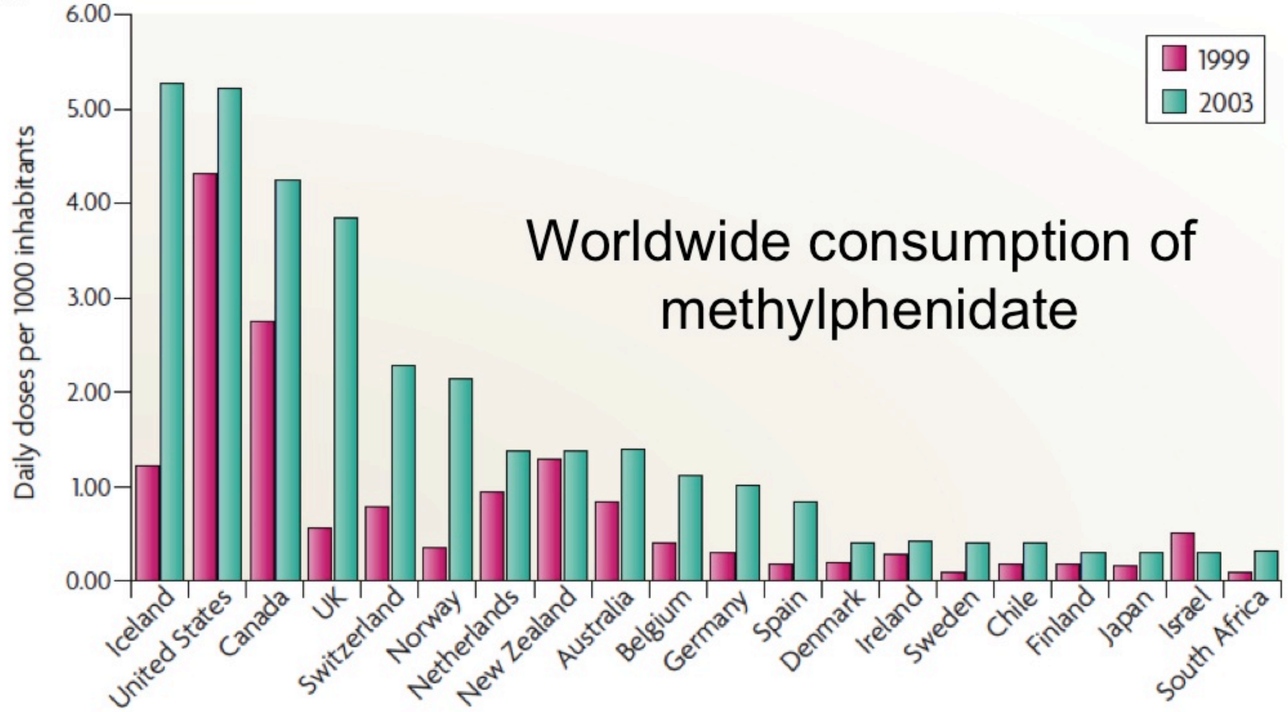
- one of the most common childhood psychiatric disorders in the world.

Diagnosis described in the DSM IV (US) or in CIM-10 (Europe)
(Diagnostic and Statistical Manual of Mental Disorders, 4th Edition).
- symptoms are : inattention, hyperactivity and impulsiveness.
- first diagnosed : when they reach school age (75% are male).
- most common treatment : stimulants methylphenidate and amphetamine.



Prevalence:
- South American :11.8% of school-age children
- european countries :(4.6%).
- US vary from 2% to 8%
- UK vary from 0.5% to 26%

Genetic factors (Genome-wide association studies): only weak associations found
- the dopamine transporter (DAT)
- dopamine receptor (DRD4)
- serotonin transporter (SERT)



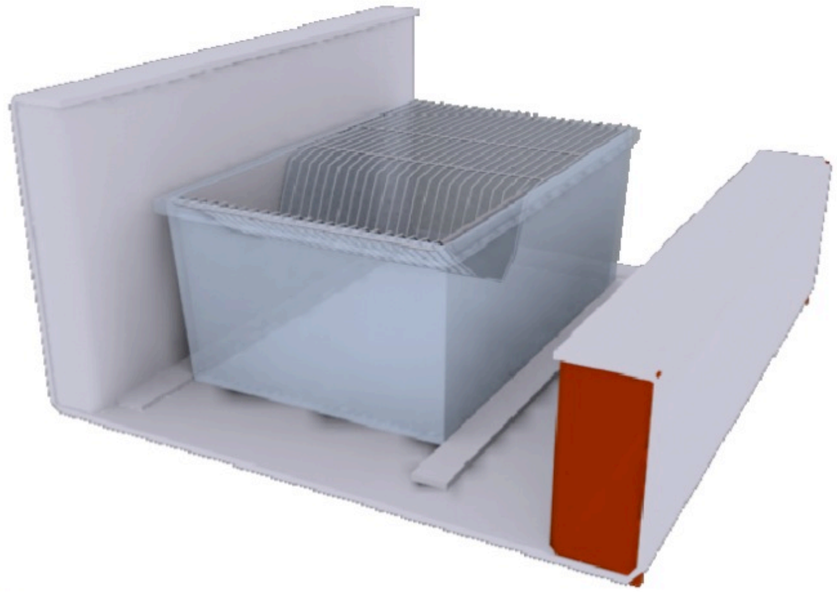
Dopamine theory : dysfunctions in the dopamine neurotransmitter system interfere with attention and motivation.

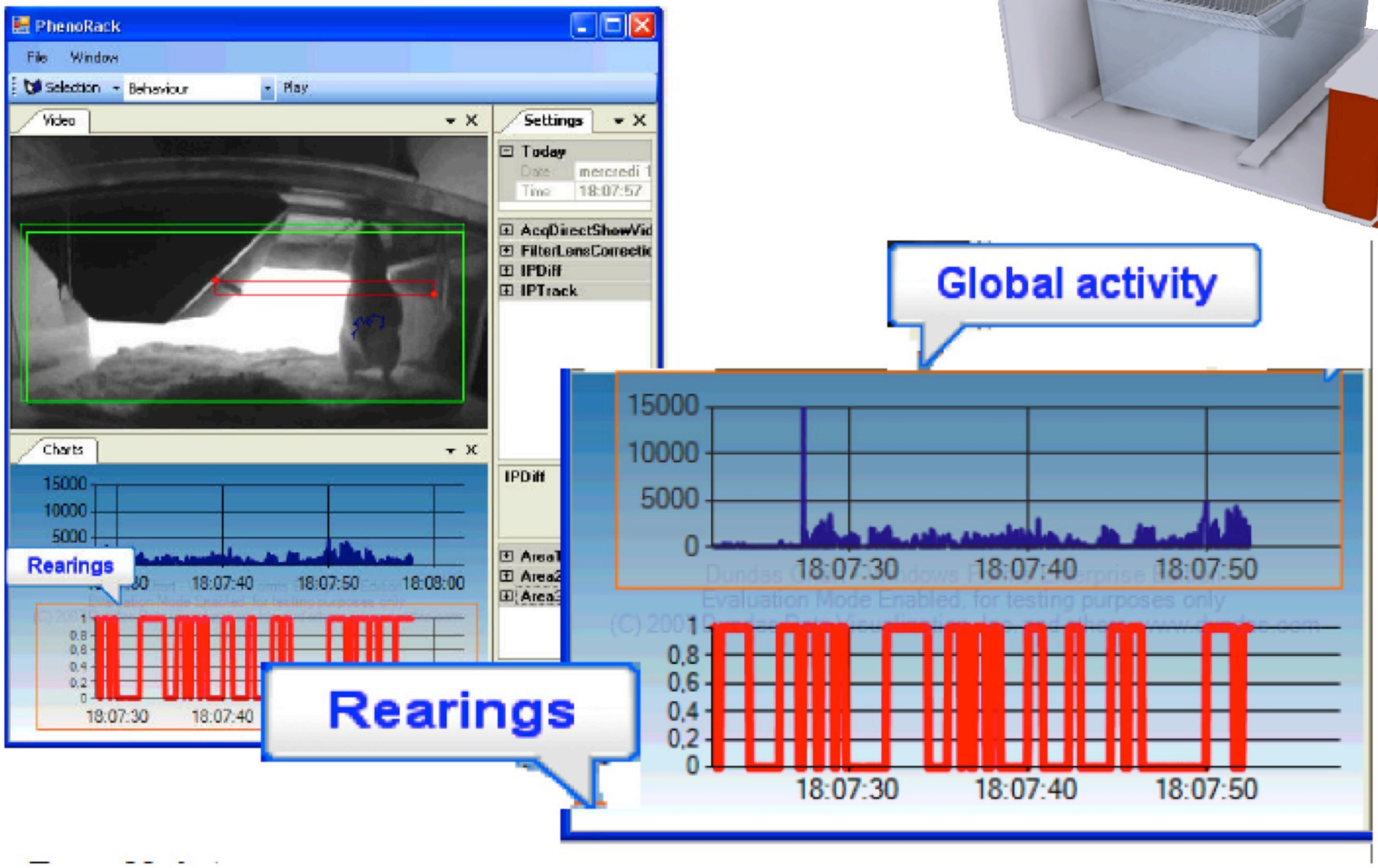
Most common reatment: stimulants methylphenidate and amphetamine:
they bind preferentially to DAT to prevent dopamine reuptake.

From *Ilina Singh (2008)* NATURE REVIEWS | **neuroscience** volume 9 | december 2008 | 957

Phenorack (lomotor activity)

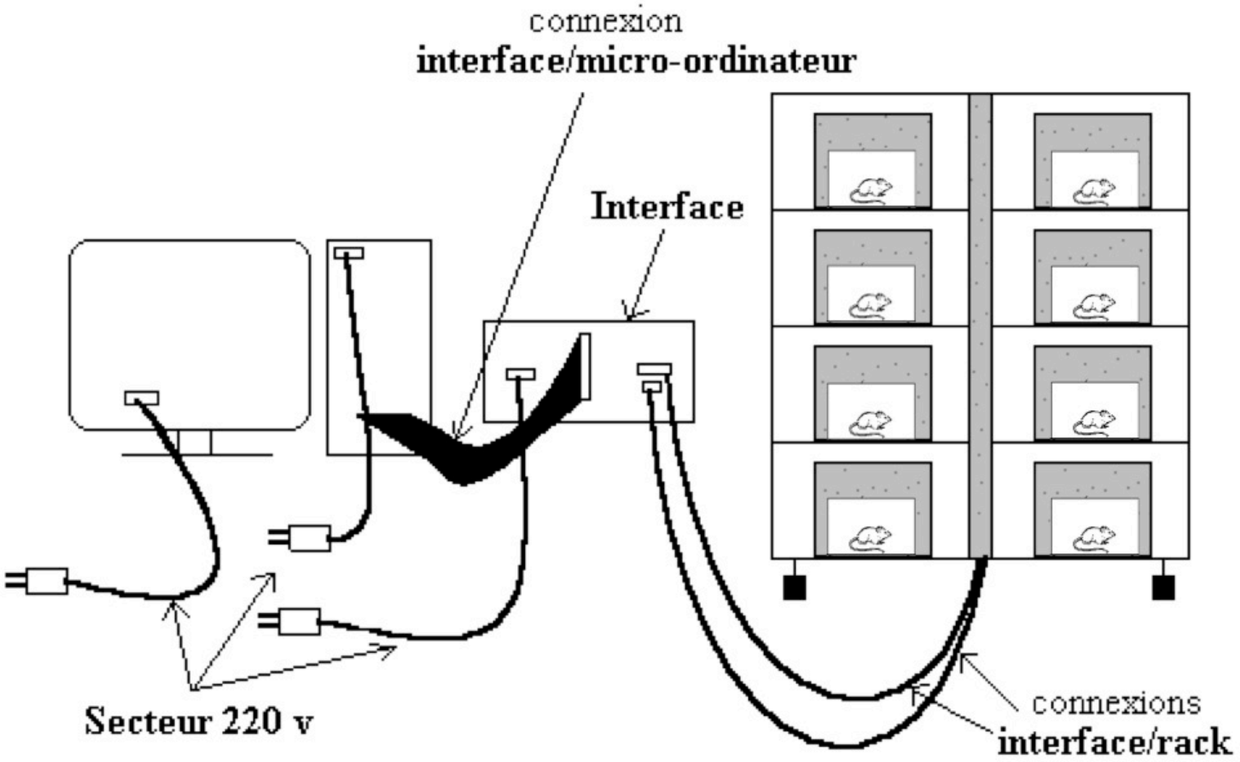
The system automatically calculates various parameters :
Locomotion : Distance travelled, speeds & duration of movement.
Behaviors : Rearing, Drinking, Eating,
Freezing, Burst and medium movements

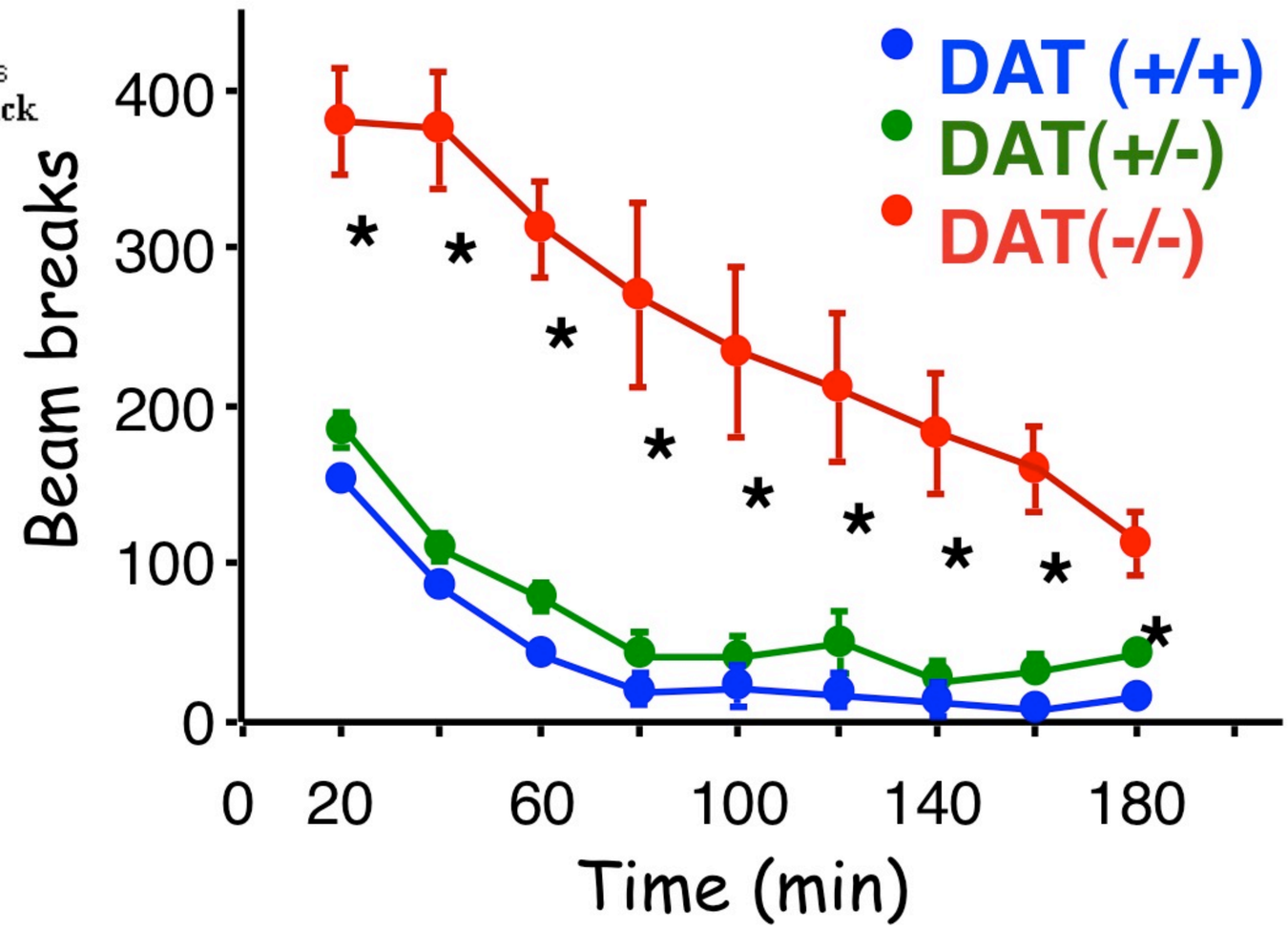




From *Viewpoint Technology (http://www.vplsi.com/)*

Spontaneous locomotor Activity in DAT-/- Mice





Giros *et al.* 1996

Mutants Mice for the Dopamine Transporter (DAT)
Constitutive Hyperdopaminiergia
and
Locomotor Hyperactivity

DA transporter (DAT) knockout (KO) mice lack the gene encoding the plasma membrane transporter that regulates spatial and temporal DA signaling at the synapse.

Due to loss of the DAT, these mutants exhibit :

- a persistent 5-fold increase in extracellular DA levels
- locomotor hyperactivity,
- and impaired learning and memory

DAT-KO mice display decreased hippocampal theta oscillations frequencies. These oscillations control the timing of activity across neuronal populations in hippocampus, prefrontal cortex, and amygdala and coordinate gamma oscillatory activity. Altered HTO's observed in DAT-KO mice are not corrected via treatment with haloperidol.

→ **DAT-/- Mice = Animal Model of ADHD?**

Gainetdinov *et al.* 1999

Mutants Mice for the Dopamine Transporter (DAT)
Constitutive Hyperdopaminiergia
and
Locomotor Hyperactivity

Conclusions

- ✓ Hyperactivity : locomotion, rearing, stereotypic activities,…
- ✓ Novelty driven
- ✓ No habituation; no adaptation
- ✓ «Calming» effects of psychostimulants (methylphenidate, amphetamine, cocaine)
- ✓ Role of the serotoninergic transmission

→ **DAT-/- Mice = Animal Model of ADHD?**

Gainetdinov *et al.* 1999

Mutants Mice for the Dopamine Transporter (DAT)

and Genetic Background?

DAT-/- Mice and Genetic Background

Backcross C57BL/6 (B6)

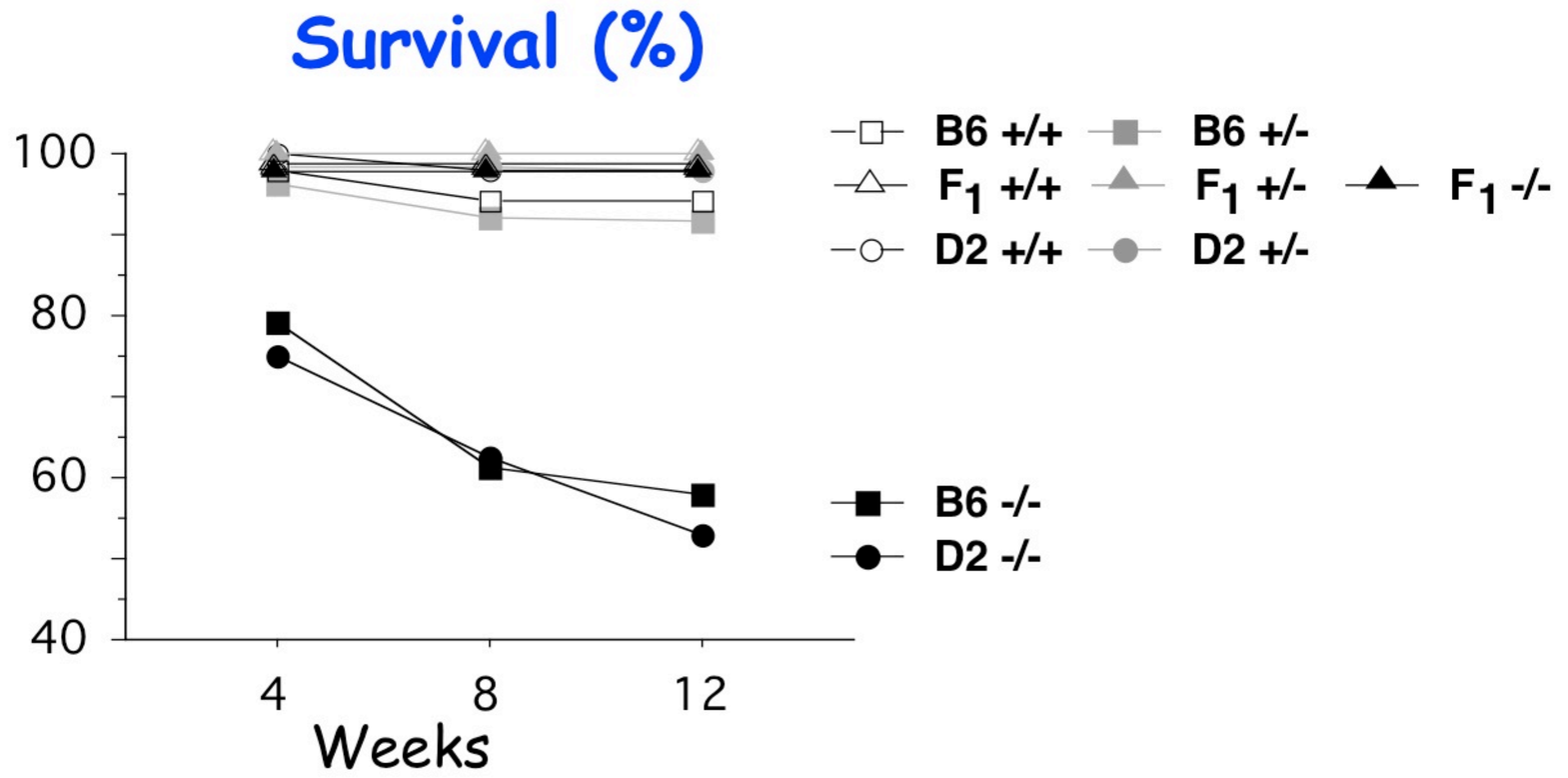
Backcross DBA/2 (D2)

B6 — WT, KO, HT

WT, KO, HT — D2

$B6xD2F_1$ (F_1)
WT ; HT ; KO

Effect of Genetic Background



(Morice *et al.* 2004)

Mutants Mice for the Dopamine Transporter (DAT)

and Genetic Background?

Conclusions

- Effects of the genetic background on the DAT mutation expression

  - Physiological variables
    - Survival,
    - Body weight development,
    - Ability to lactate

  - Behavioural variables
    - Maternal behaviour,
    - Spontaneous locomotor activity,
    - Responses to acute or chronic injections of drugs

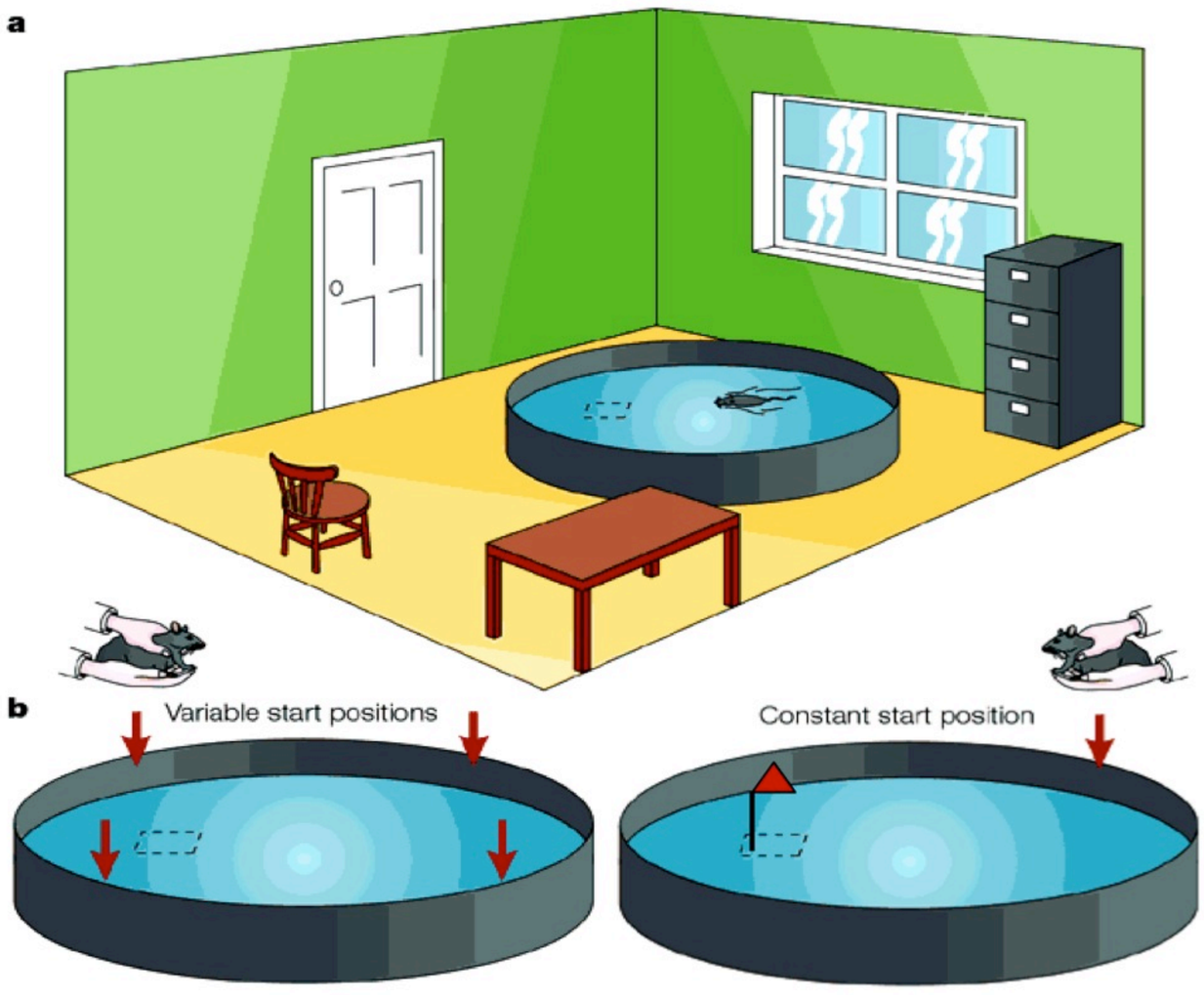
↳ Identification of modifier genes

Mutants Mice for the Dopamine Transporter (DAT)

and Plasticity?

- ✓ Behavioural
- ✓ Synaptic

Morris Water Maze



SPATIAL VERSION
Platform: fixed position

CUED VERSION
Platform: variable position

ACQUISITION TRIALS

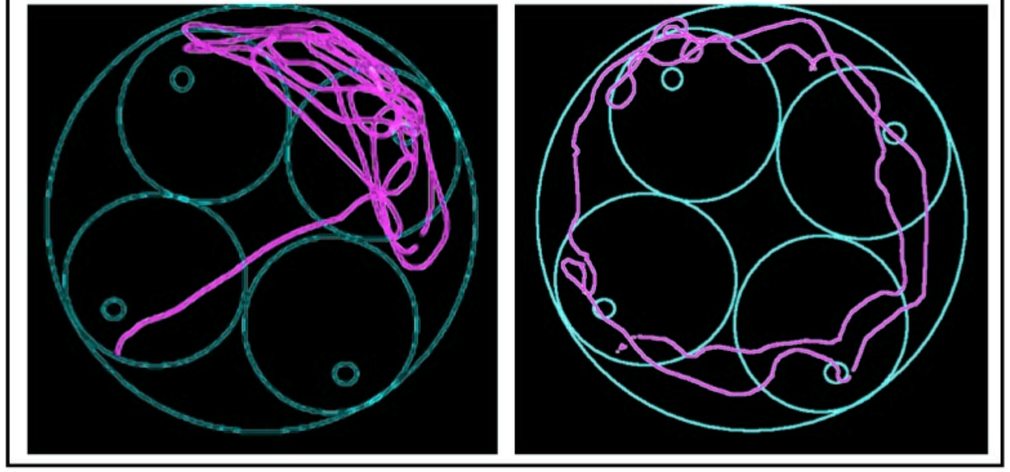
Duration of test: 90 sec
Variables:

- **Inactivity** (s)
- **Swim speed** (cm/min)
- **Latency** (s)
- **Distance** travelled (cm)
- **Successful trials** (proportion)

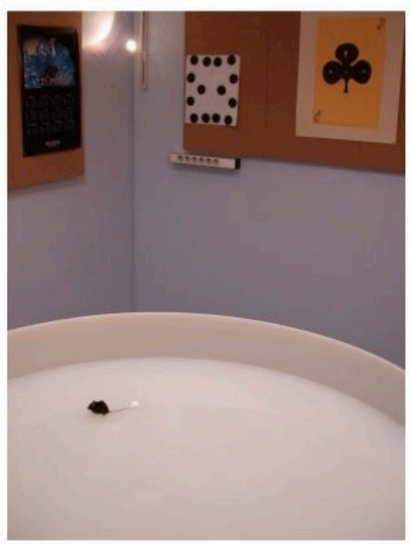
PROBE TRIAL

Duration of test: 60 sec
Variables:

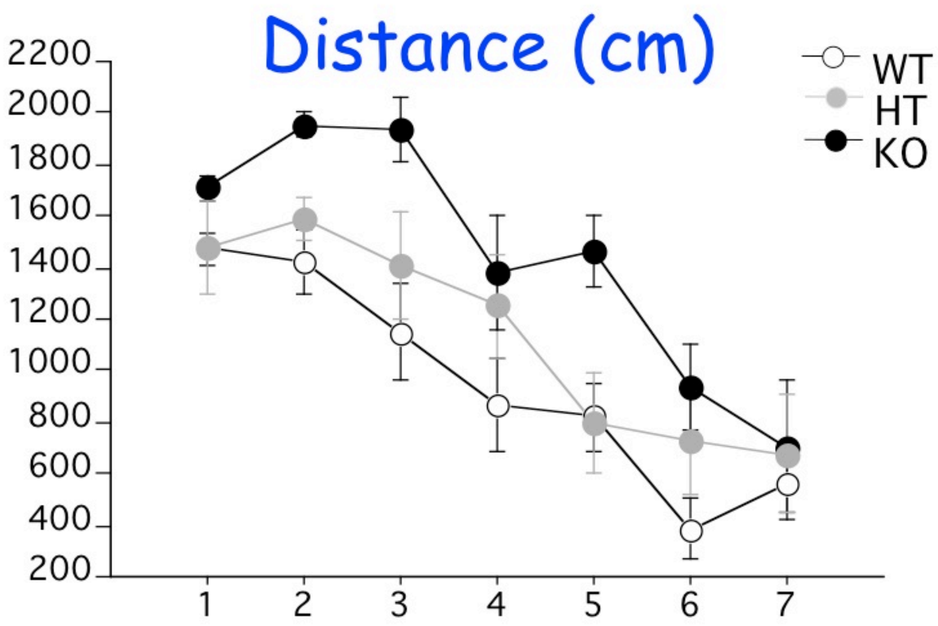
- **Distance travelled (%)** per quadrant
- **Number of annulus crossings**



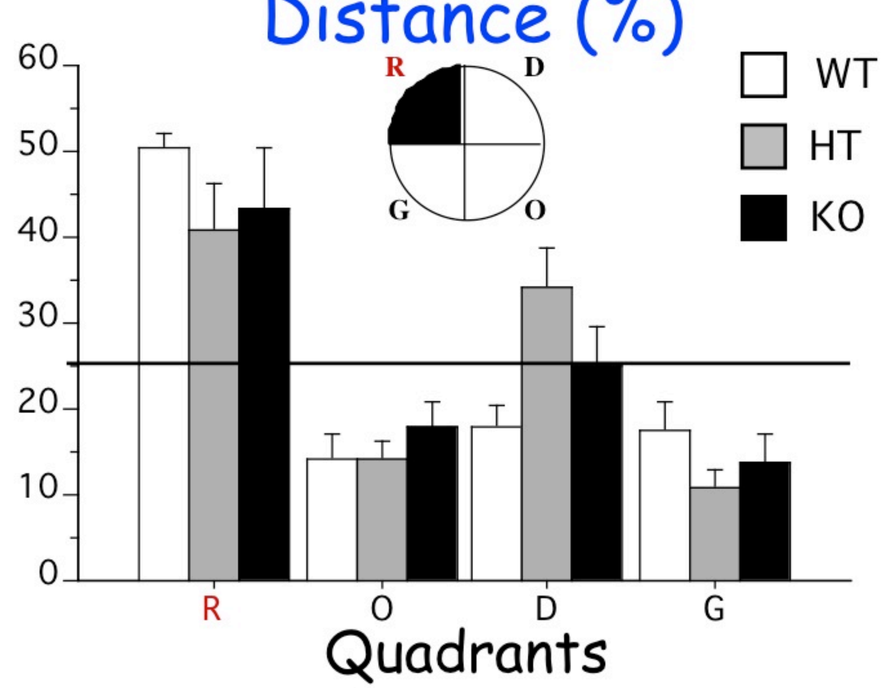
Spatial Learning and Memory

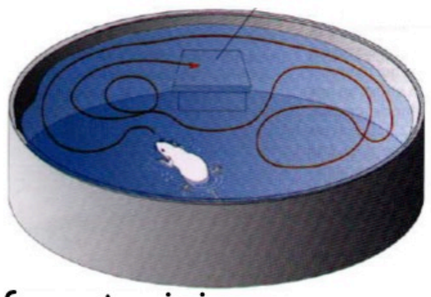


Acquisition trials

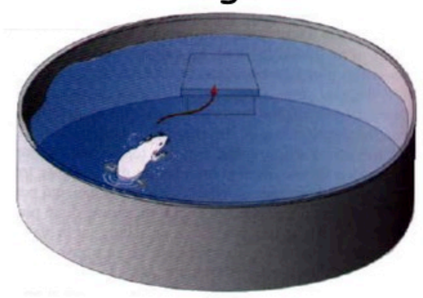


Probe trial



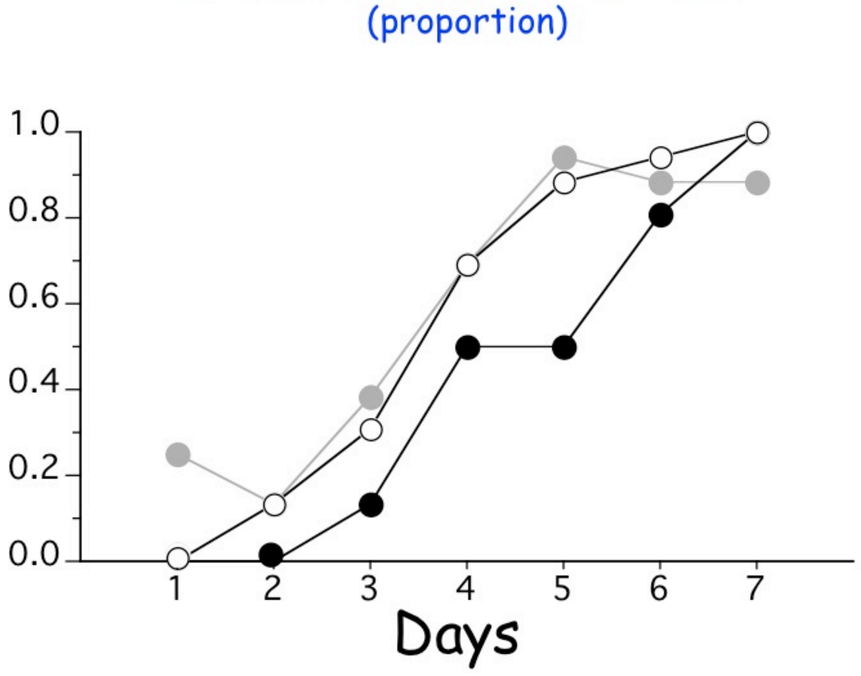


Before training

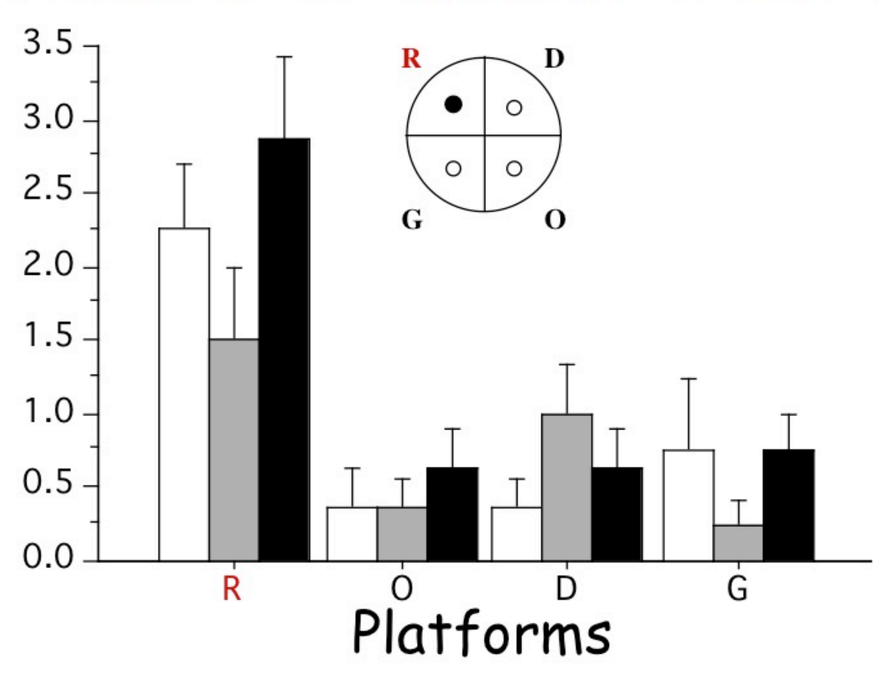


After training

Successfull trials



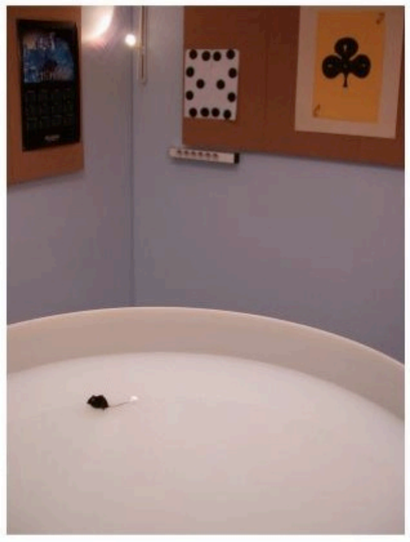
Number of annulus crossings



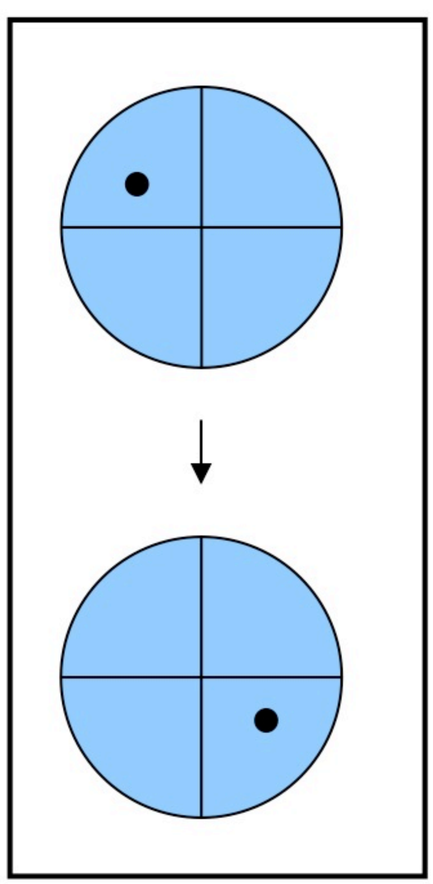
(Morice *et al.* 2007)

Spatial learning still occurred but is delayed

Spatial Reversal Learning

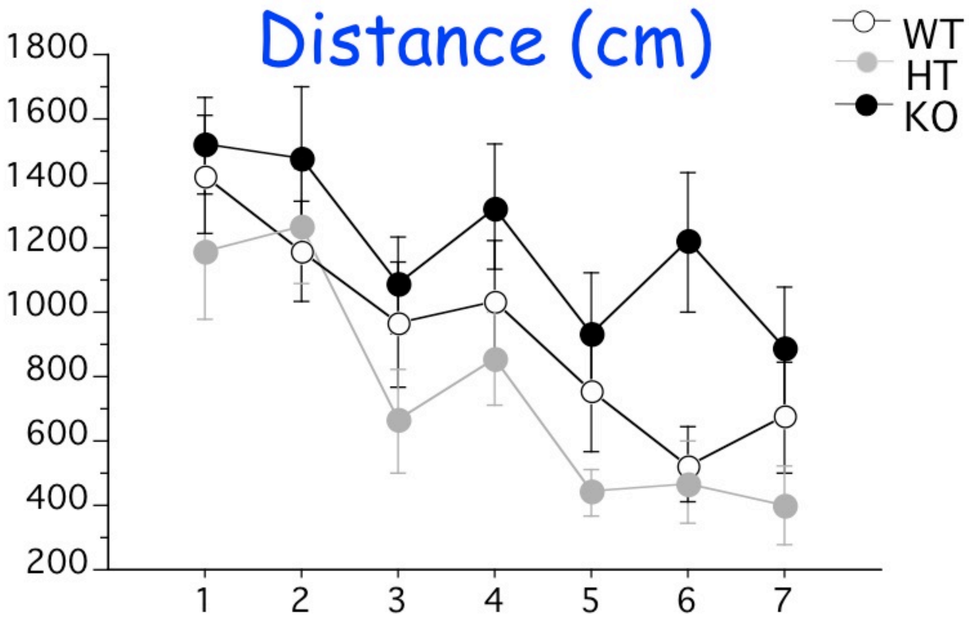


Change of the platform position

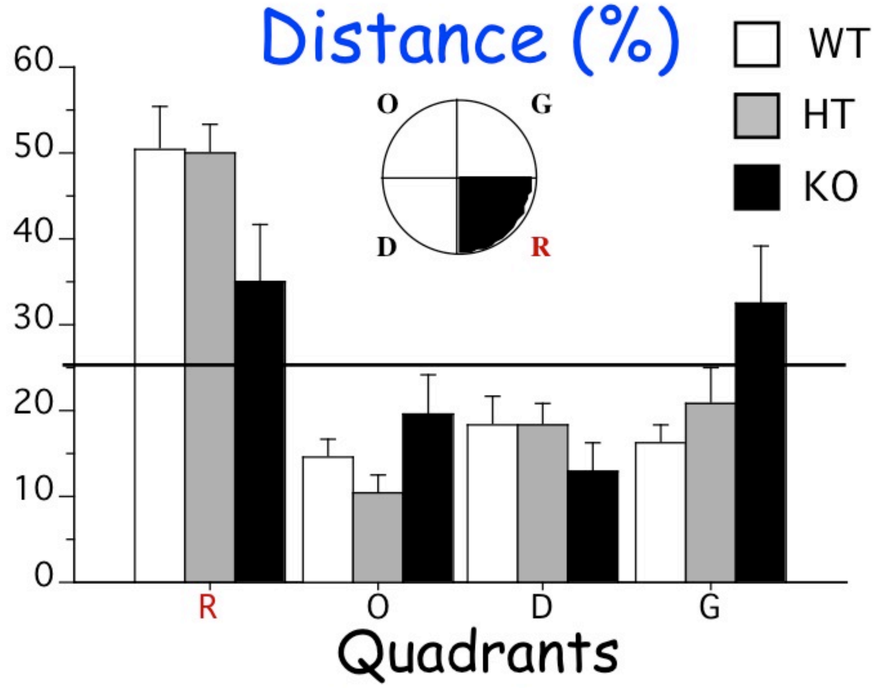


(Morice *et al.* 2007)

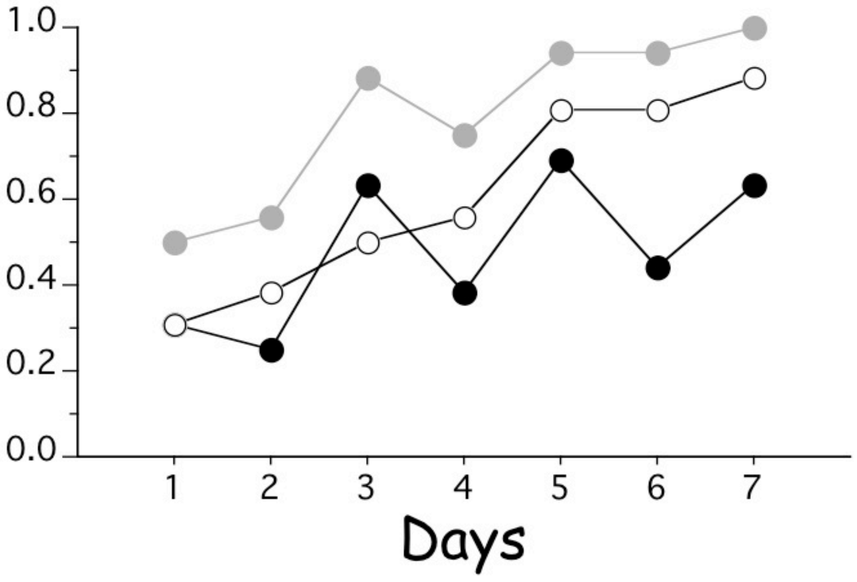
Acquisition trials



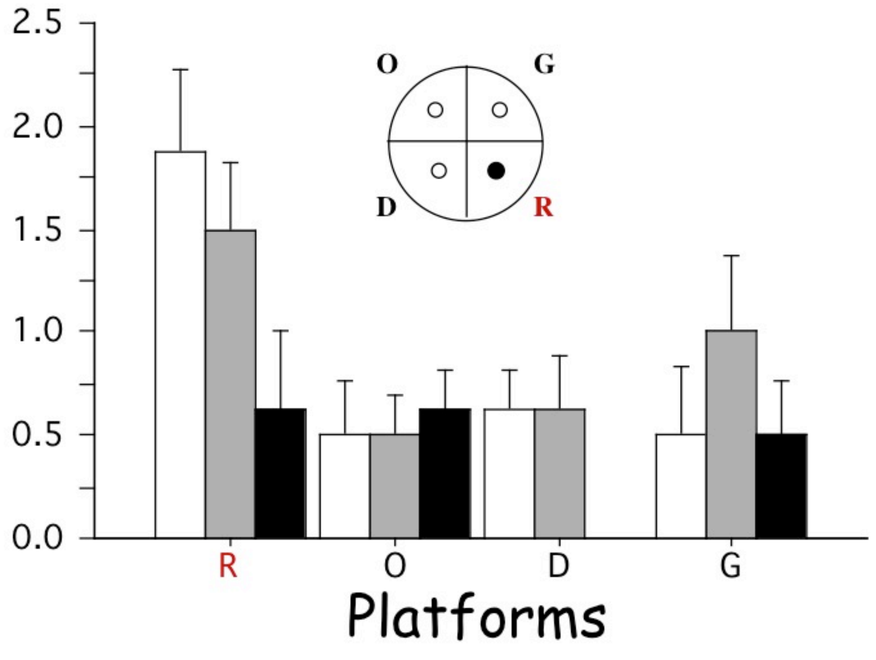
Probe trial



Successfull trials

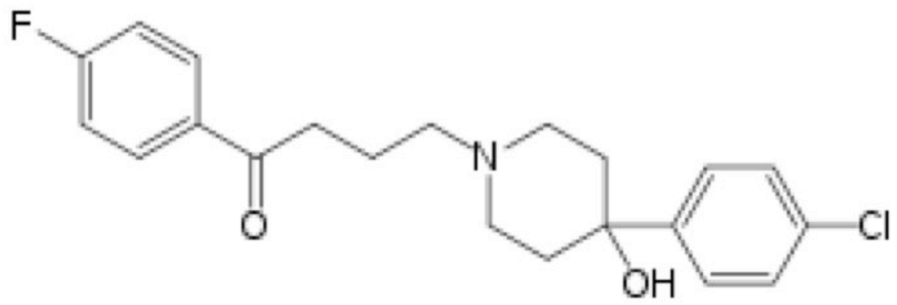


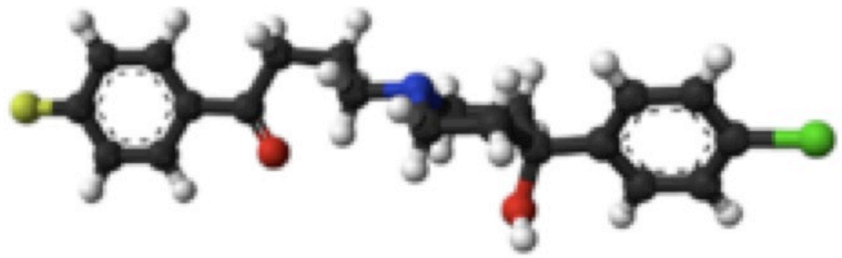
Number of annulus crossings



Reversal learning is disrupted : loss of flexibility

Haloperidol

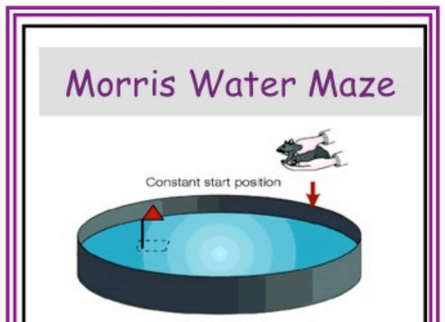




Haloperidol is a typical antipsychotic.
It is in the butyrophenone class of antipsychotic medications.
Due to its strong central antidopaminergic action, it is classified as a highly potent neuroleptic.
Haloperidol possesses a strong activity against delusions and hallucinations, most likely due to an effective dopaminergic receptor blockage in the mesocortex and the limbic system of the brain.
It blocks the dopaminergic action in the nigrostriatal pathways, which is the probable reason for the high frequency of extrapyramidal-motoric side-effects (dystonias, akathisia, pseudoparkinsonism).
Haloperidol also has sedative properties and displays a strong action against psychomotor agitation due to a specific action in the limbic system. It therefore is an effective treatment for mania and states of agitation.

From *Wikipedia Encyclopedia (http://en.wikipedia.org/wiki/Haloperidol)*

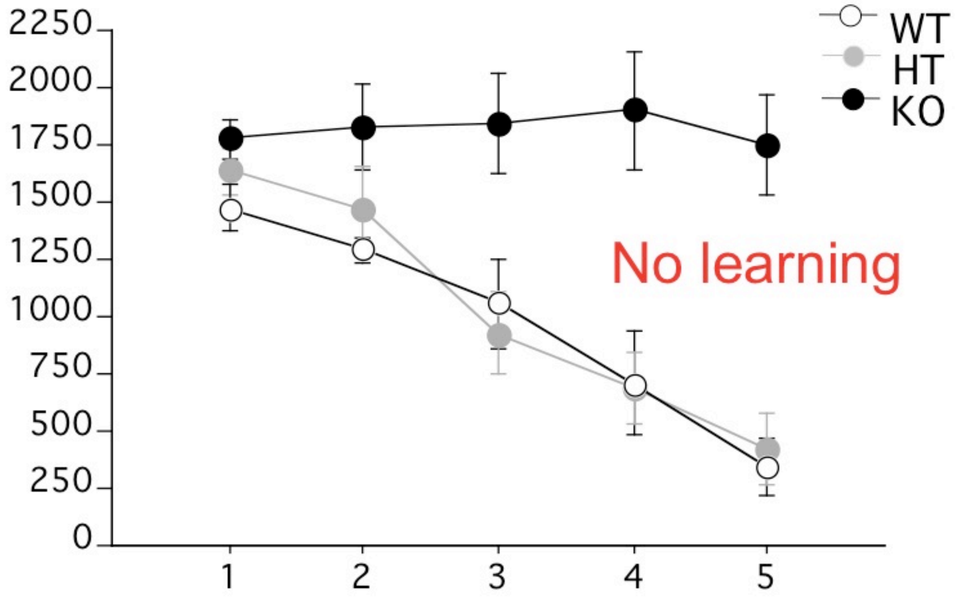
Cued Learning



(Morice *et al.* 2007)

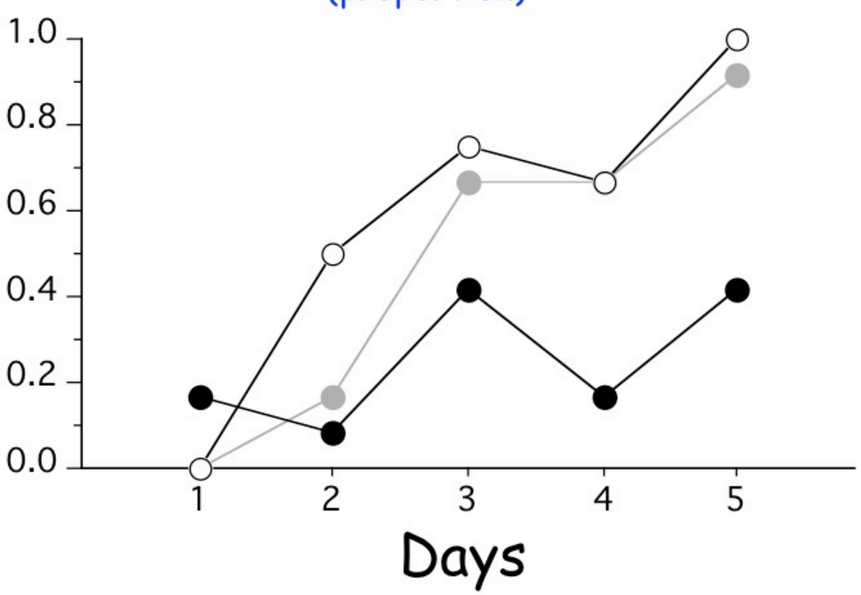
Spontaneous

Distance (cm)



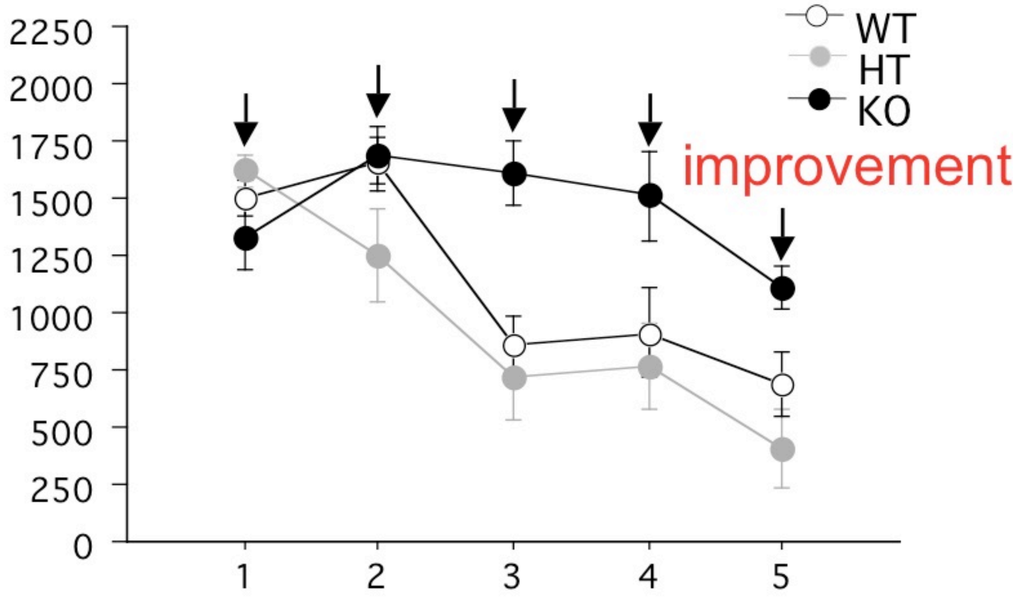
Successfull trials

(proportion)



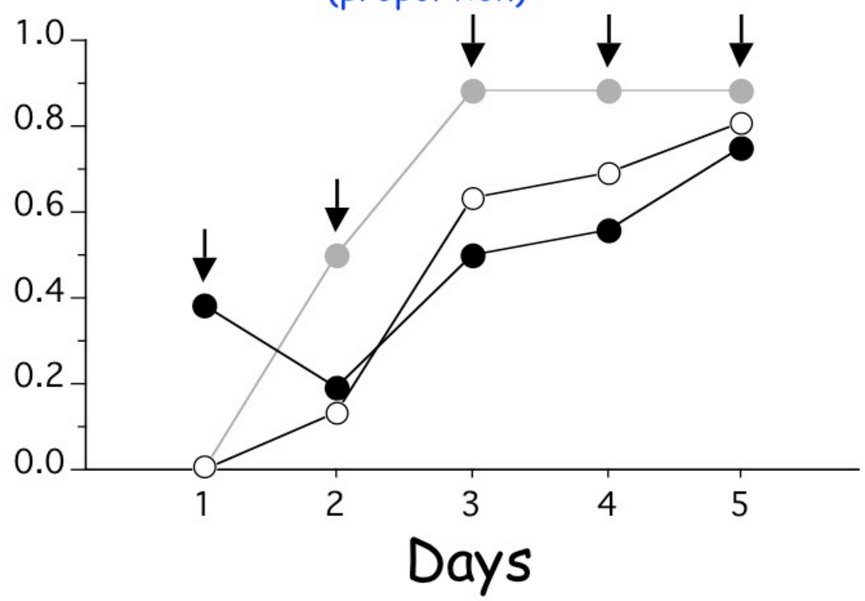
Haloperidol

Distance (cm)



Successfull trials

(proportion)



Haloperidol improves the performances of DAT-KO mice in the cued version.

DAT-/- Mice and Cognitive Functions

Morris Water Maze

- Delayed spatial learning and normal spatial memory
- Deficit in the reversal learning
- Deficit in the cued version → Reversible by haloperidol

Other tests

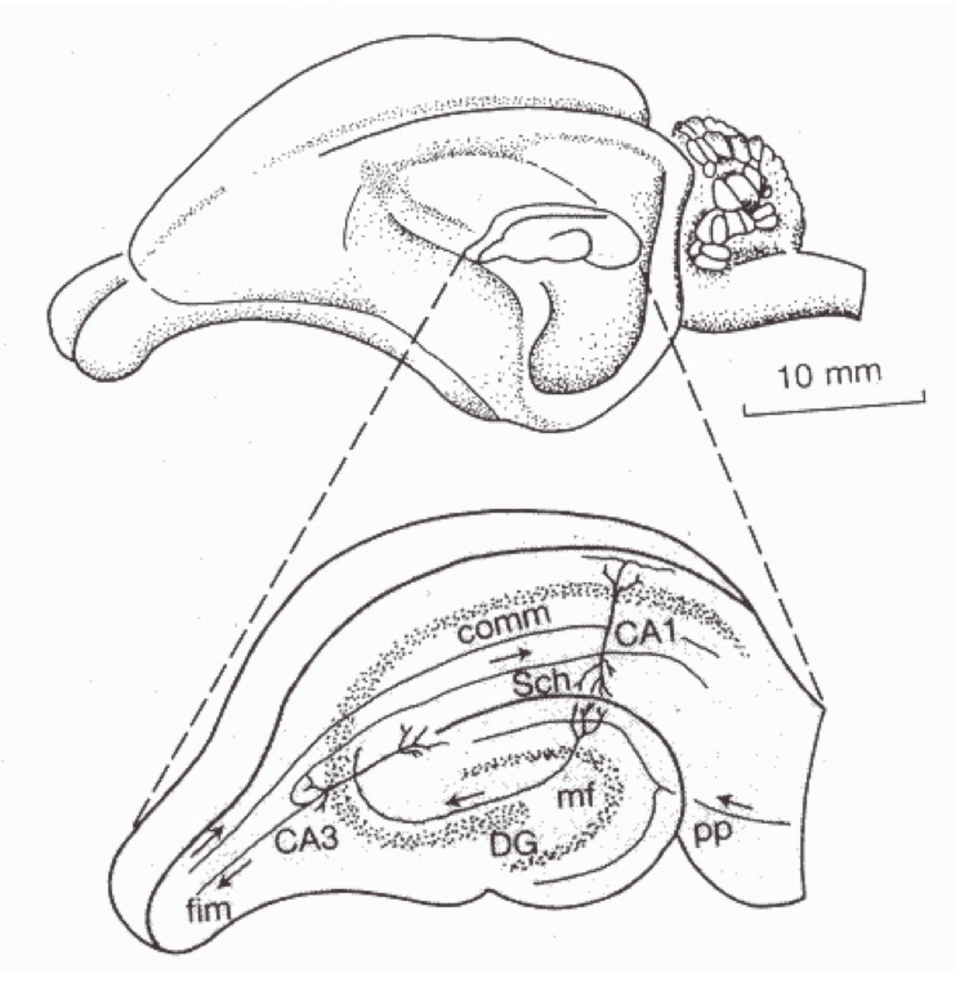
- Radial maze: ↗ perseverative errors (Gainetdinov, 1999)
- Open field: ↗ repeated motor sequences, non focal (Ralph, 2001)
- Social interactions: limited behavioural repertoire (Rodriguiz, 2003)

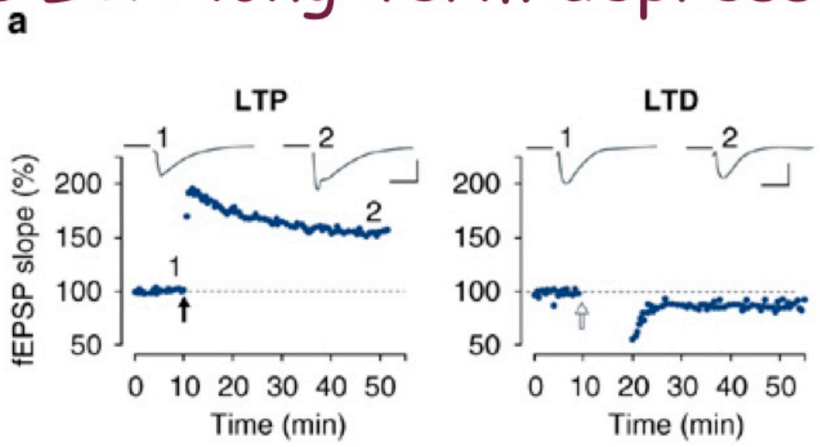
Hyperdopaminergia:
⇢ Loss of Behavioural Flexibility

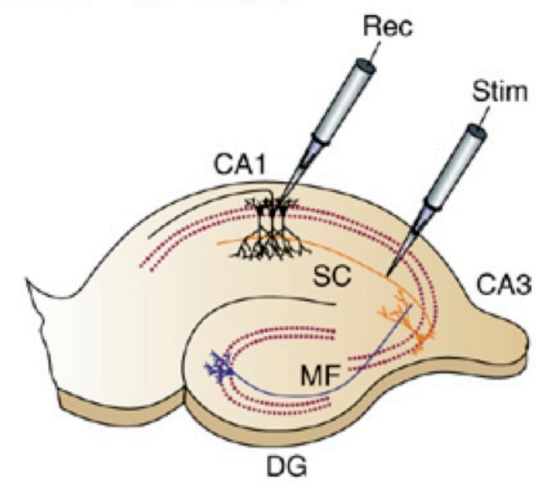
Synaptic Plasticity: a Cellular Model of Memory?

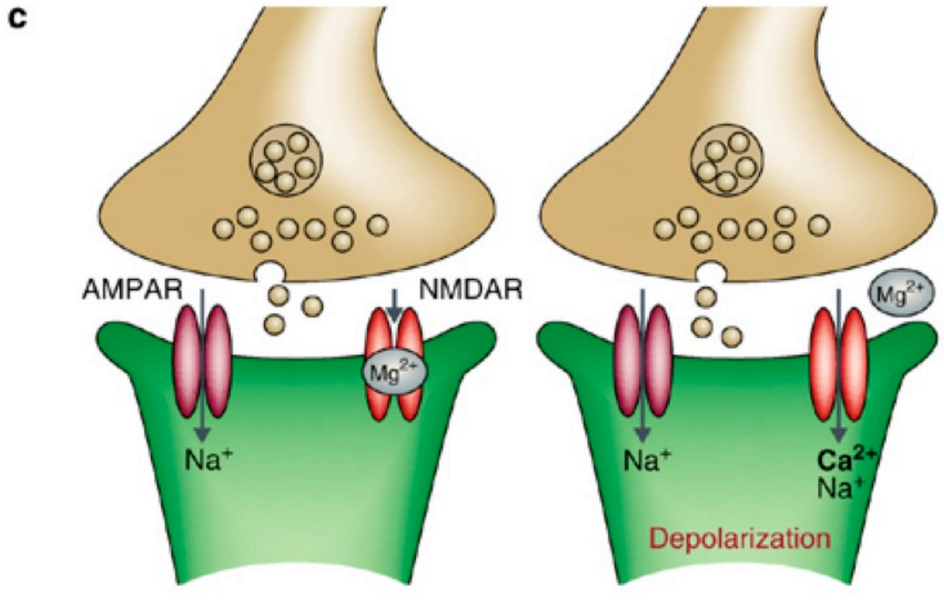
- Memory formation might be due to a persistent increase in synaptic strength, called long-term potentiation or LTP.

- The opposite mechanism of the LTP: long-term depression or LTD.

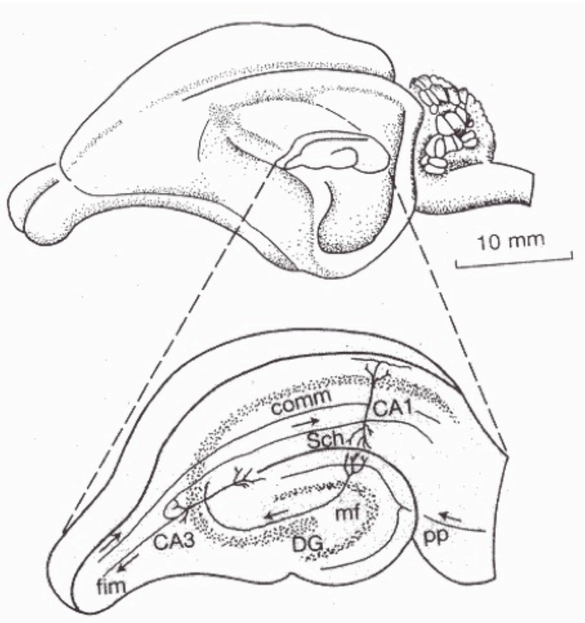


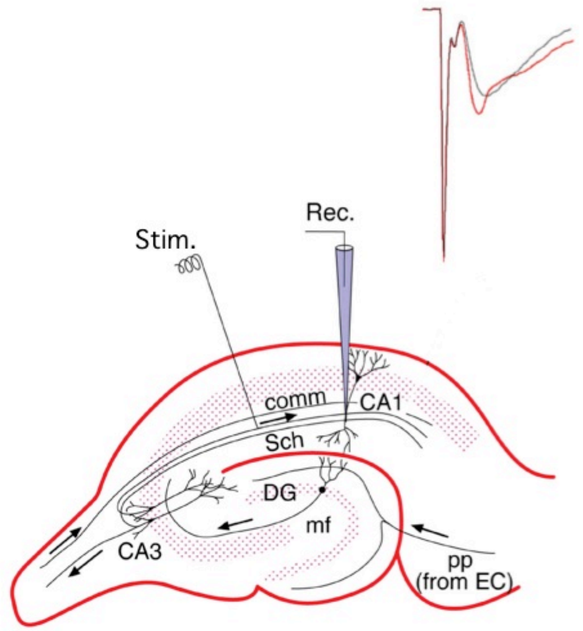


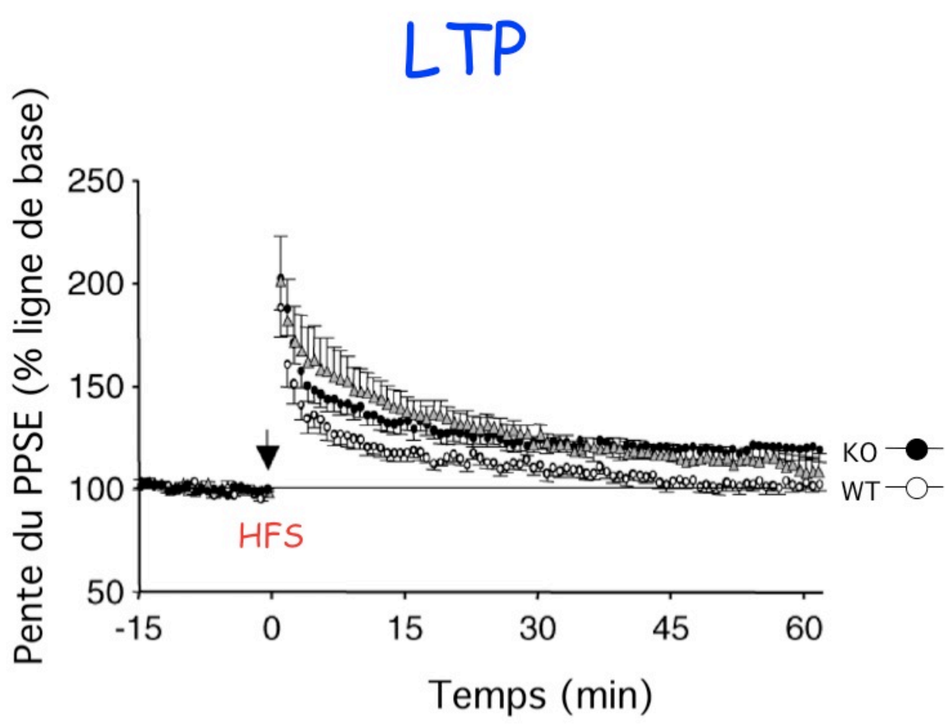




Long-Term Potentiation: LTP





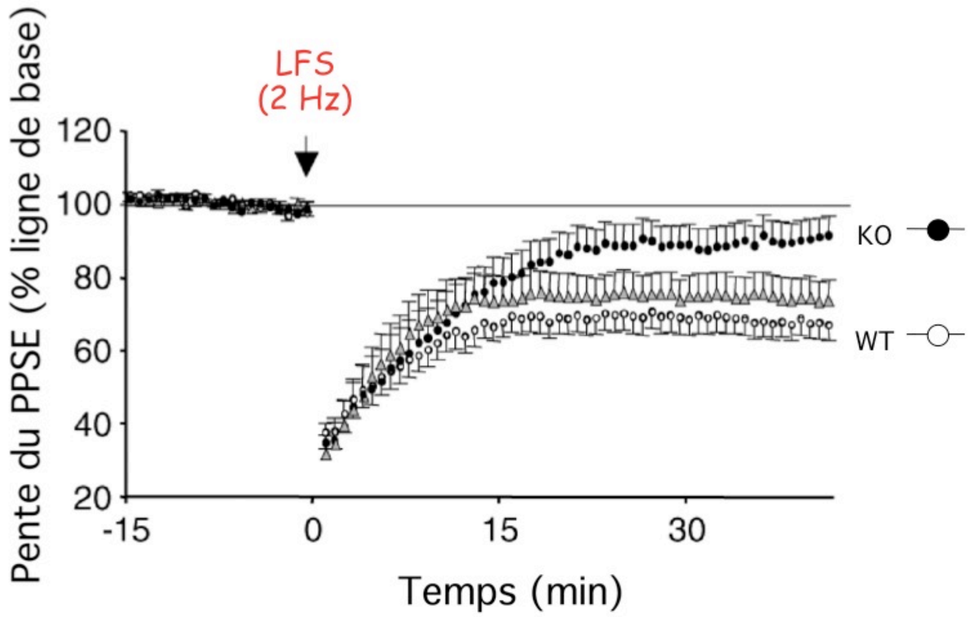


➡ Enhanced LTP in DAT-/- mice

(Morice *et al.* 2007)

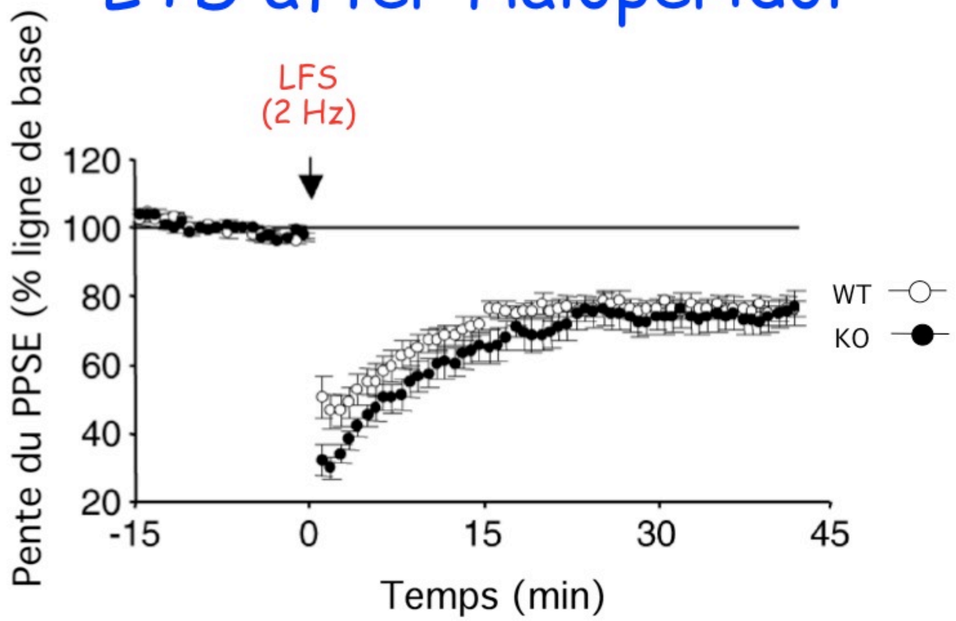
Long-Term Depression: LTD

LTD



➡ LTD Deficit in DAT-/- mice

LTD after Haloperidol



➡ Haloperidol fully restores LTD

(Morice *et al.* 2007)

Mutants Mice for the Dopamine Transporter (DAT)

and Plasticity?

Conclusions

Hyperdopaminergia

Behavioural flexibility

Synaptic Plasticity

?

Mental rigidity, perseveration and
Inability to adapt behaviours to context
Schizophrenia, ADHD,…

DAT-/- Mice
General Conclusion

➢ **Neurobiology:** Interaction DA / other systems...

➢ **Clinical psychiatry:** Potentials endophenotypes

➢ **Genetic:** Complex traits

Multigenic, genetic heterogeneity

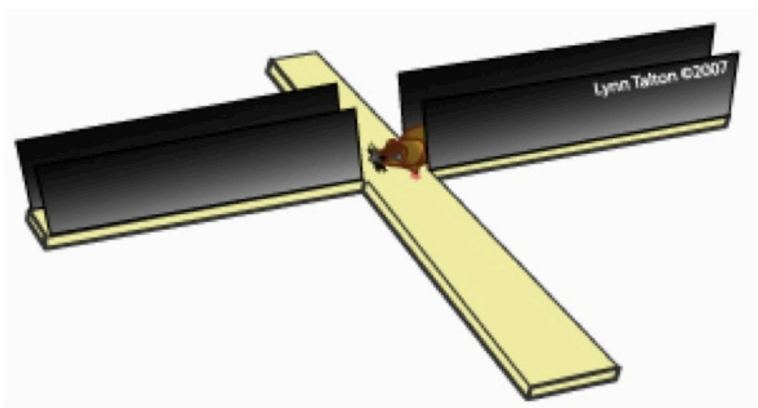
Epistatic effect

Forced swim

Since some mutations cause a deficit in swimming ability, the forced swim test can be used to demonstrate normal swimming and floating ability.
The test is most frequently used to examine the "learned helplessness" response common in animal models of depression.

Tail suspension

The subject is suspended by the tail for a set interval the percentage of time the subject spends still versus moving is examined for evidence of the "learned helplessness" response common in models of depression.

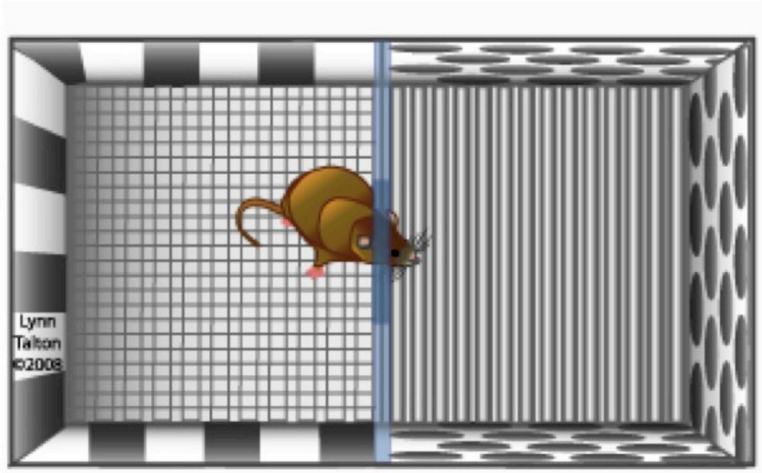


Elevated Plus Maze

This test is used to assess anxiety. The basic measure is the animal's preference for dark, enclosed places over bright, exposed places.

Procedure

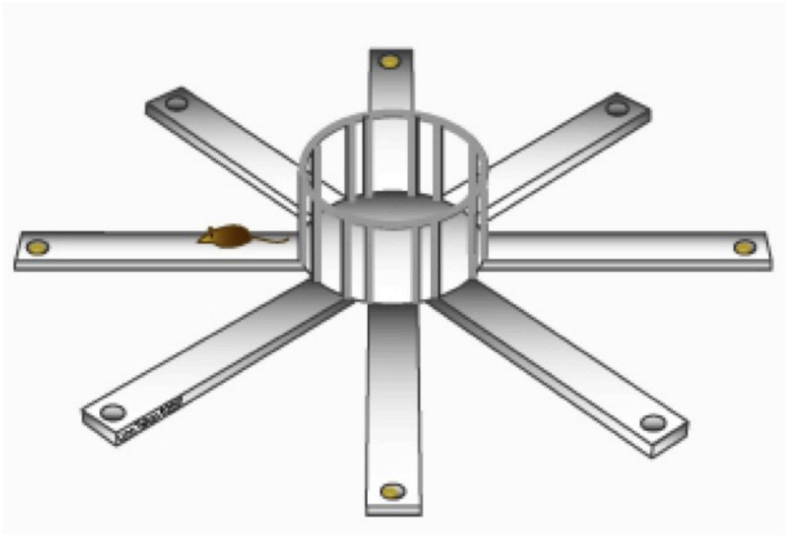
The animal is placed in the center of the apparatus and observed for a set time. Measurements compare the include total time spent in the open and closed arms (and central platform) as well as entries into the open and closed arms.



Conditioned Place Preference

In a Conditioned Place Preference experiment, subjects are returned to an apparatus were they can freely move between a compartment in which they were conditioned with drug-related cues, and a compartment with neutral cues. If the conditioning was successful for positive, reinforcing drug states, they should spend more time in the compartment with drug-related cues.

From http://btc.bol.ucla.edu/lightdark.htm

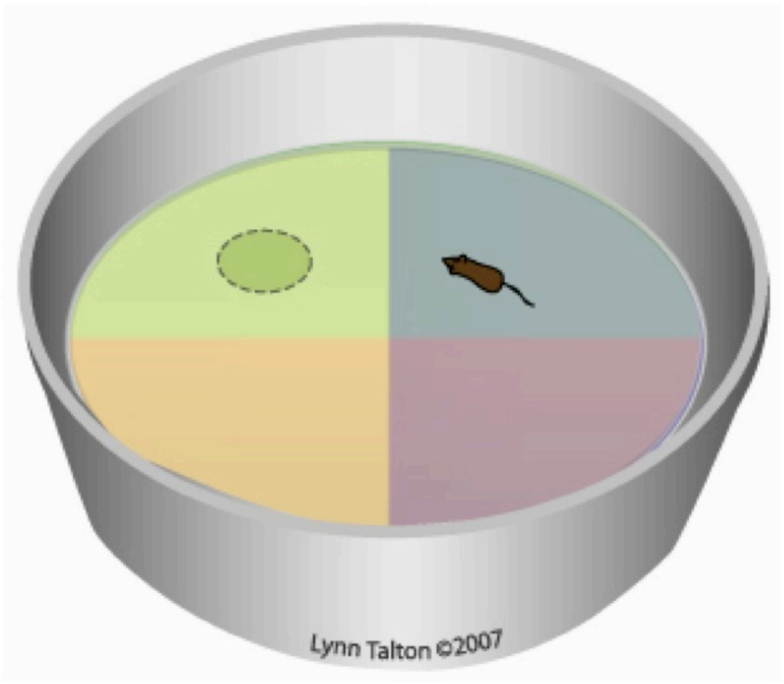


Radial Arm Maze Task

This task is used primarily to measure spatial learning and memory. Some versions of the task can be used to examine concurrently both working and reference memory. Like the water maze, this task is sensitive to hippocampal function. The task is designed to mimic natural foraging behaviors.

Procedure

Subjects are placed in the center of an eight-arm radial maze. Four randomly chosen arms are baited with food pellets in opaque containers. The subject is given the opportunity to visit all the arms and collect all the available food pellets. After a rentention delay, the subject is returned to the maze. In win-stay conditions, the same four arms are baited, and the number of correct choices the subject makes in collecting the pellets is recorded. In win-shift conditions, the four arms NOT baited in the earlier trial are now baited, and the number of correct arm choices is recorded. Each day, a new set of four arms is chosen randomly.



Morris Water Maze Task

The Morris Water Maze is the most popular task in behavioral neuroscience. In its most basic form, the water maze assesses spatial learning and memory. Performance in the Morris Water Maze is acutely sensitive to manipulations of the hippocampus.

Procedure

Subjects are placed in a circular pool of warm, opaque water in a random start location. An escape platform is hidden just under the surface of the water. During training trials, latency to find the platform location is recorded. During probe trials, the platform is removed, and the percentage of time spent in the quadrant that normally contains the platform is compared to the time spent in other quadrants.

Psychiatry and Animals Models

I- Introduction (definition, validity, specificity of the psychiatry)

II - From Genetic to Psychiatry:

- ✓ Invalidation of the dopamine transporter (DAT)

III - From Clinic to Mouse:

- ✓ Behavioural lateralization
- ✓ Anxiety

IV - Conclusions

Genetic Analysis of Complex Traits

Genetic-driven approach
(« reverse genetics »)

GENE

QTLs
DNA ships…

PHENOTYPE

Lateralization
Anxiety

Phenotype-driven approach
(« forward genetics »)

Lateralization and Psychiatry
Schizophrenia, Dyslexia, manic-depressive disorder, Autism...

- Consensus: lateralization defects:
  - Behavioural / Cognitive
  - Neuro-anatomical
  - Neuro-physiological / Biochemical...
- Debate:
  1/ Nature of the defect:
  - Lateralization: Right vs. Left
  - Atypic, mixed,
  - Ambiguous...

  2/ Role of the lateralization in the l'etiology:
  - Origin or epiphenomenon?

Lateralization and Psychiatry

1- Clinical studies:

- Endophenotype: characterization of populations (affected and non-affected…)

2 - Studies in Mouse:

- Research of phenotypic markers:
  - Behavioural lateralization
  - Inter-hemispheric asymmetry
    - Molecular
    - Cerebellar functional imaging

- Identification of genetic factors :
  - QTL mapping (strains: RI, RC, F_2…)
  - Identification of candidate genes

Lateralization and Psychiatry

- ***Schizophrenic patients:*** anomalies in behaviour but also neuroanatomical asymmetry

- 19 studies on schizophrenia (Sommer et al. 2001):

  Non-right handedness was higher in schzophrenia patients

  - ***Handedness*** is an attribute of humans defined by their unequal distribution of fine motor skill between the left and right hands.
  - ***Right-handed:*** An individual who is more dexterous with the right hand is called right-handed,
  - ***Left-handed :*** more skilled with the left is said to be left-handed.
  - ***Ambidextrous:*** A minority of people are equally skilled with both hands, and are termed ambidextrous.

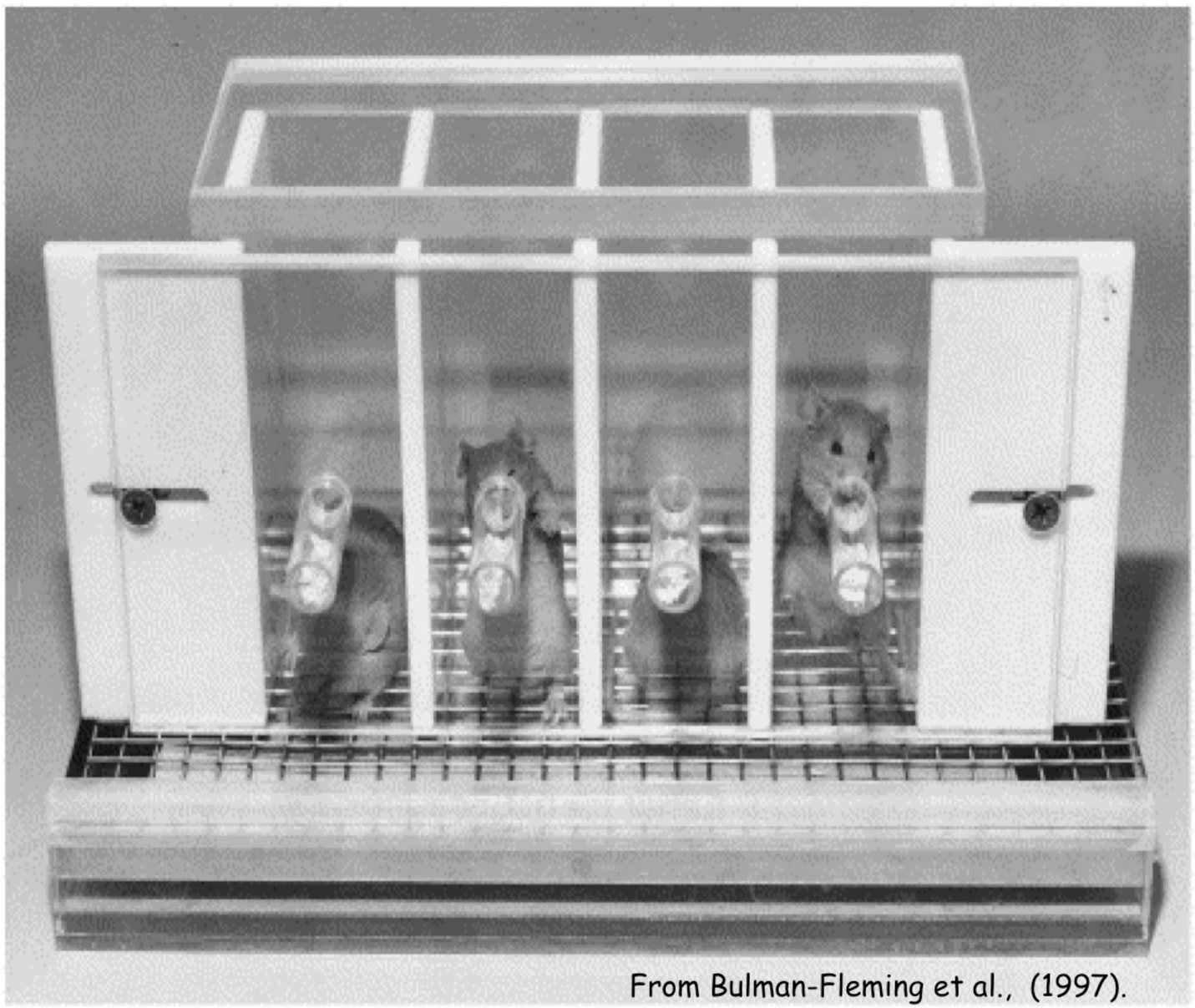
- In vivo imaging: **loss of the right-left asymmetry** of the DA synthesis capacity and of the DAT binding in the caudate nucleus **in schizophrenic patients** (Hietala et al. 1999, 1995, Laakso et al. 2000).
- Haloperidol-induced downregulation of DA synthesis is greater in the leftthan in the right striatum (Grunder et al., 2003).

➡ ***Support the hypothesis of a link between cerebral lateralization and schizophrenia***

Positive schizophrenia symptoms (hallucinations, delirium,…) are attributed to hyperdopaminergia,

Hypothesis : hyperdopaminergia could be associated with a reduced functional brain asymmetry.

Paw Preference Test (Collins)



From Bulman-Fleming et al., (1997).

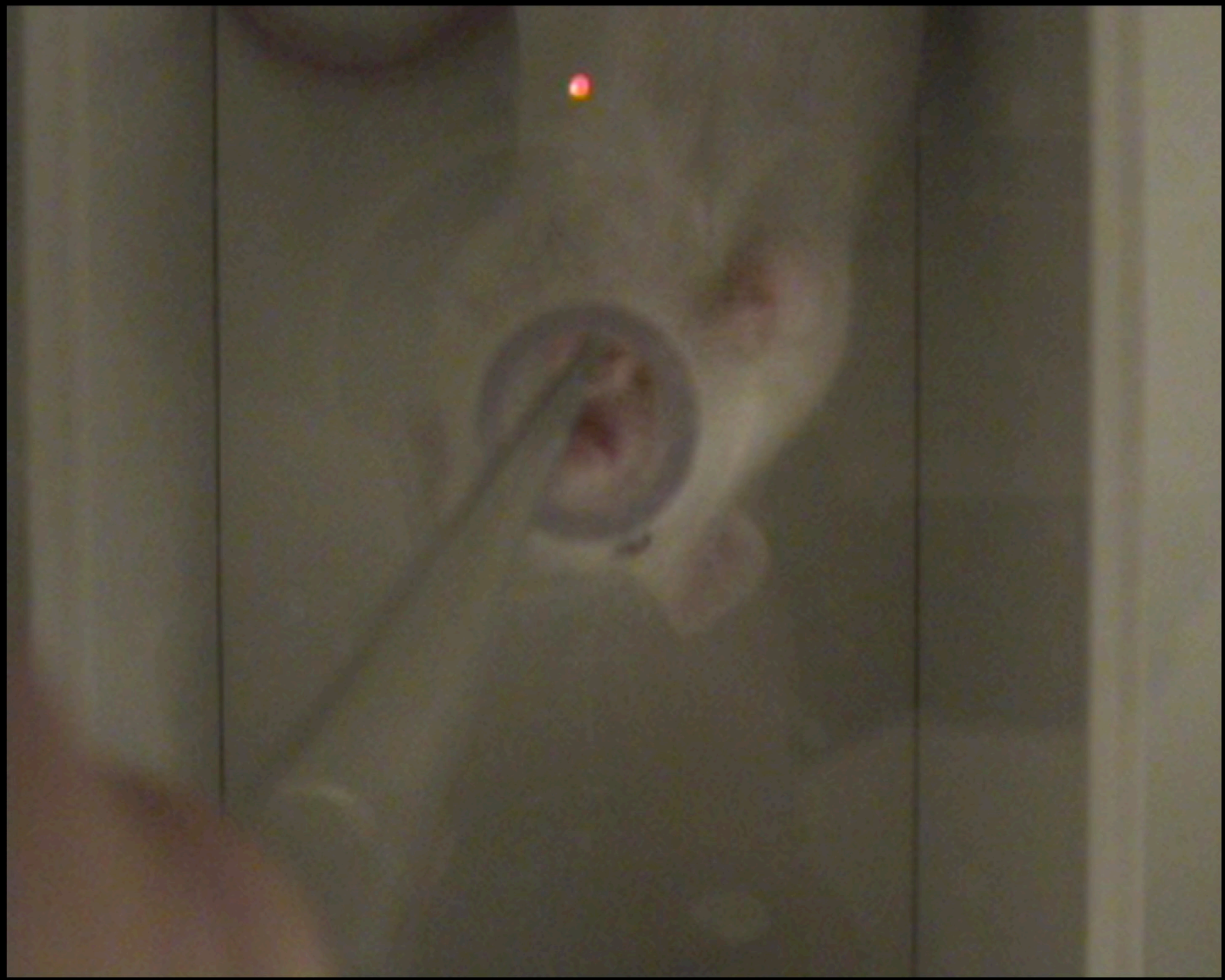
Variables :

- **Direction** of lateralization: number of right paw entries

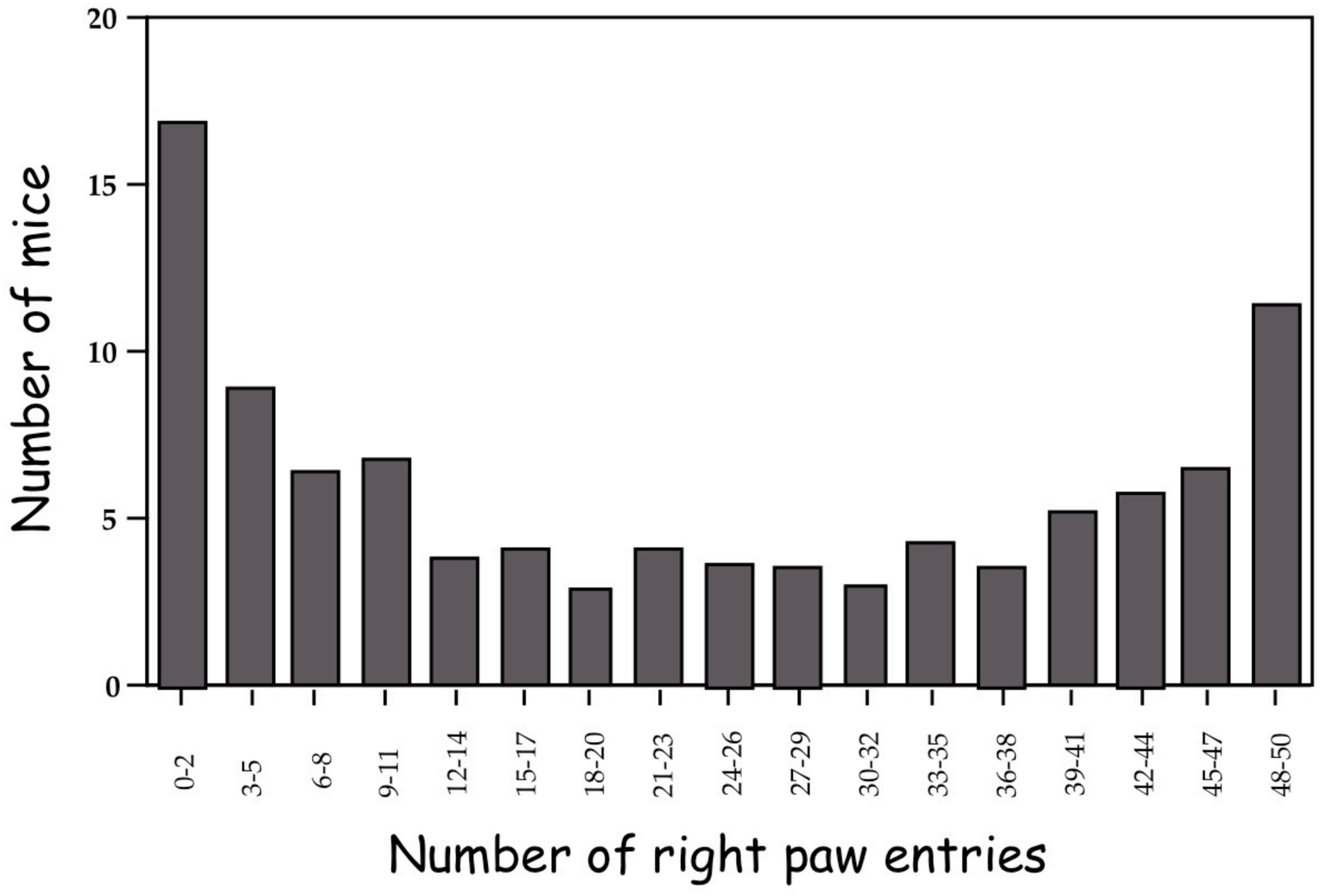
- **Degree** of lateralization: |R-L|

- 3 classes :
  - High: **H** (|R-L| ≥ 46)
  - Low: **L** (|R-L| ≤ 30)
  - Medium: **M** (32 ≤ |R-L| ≤ 44)

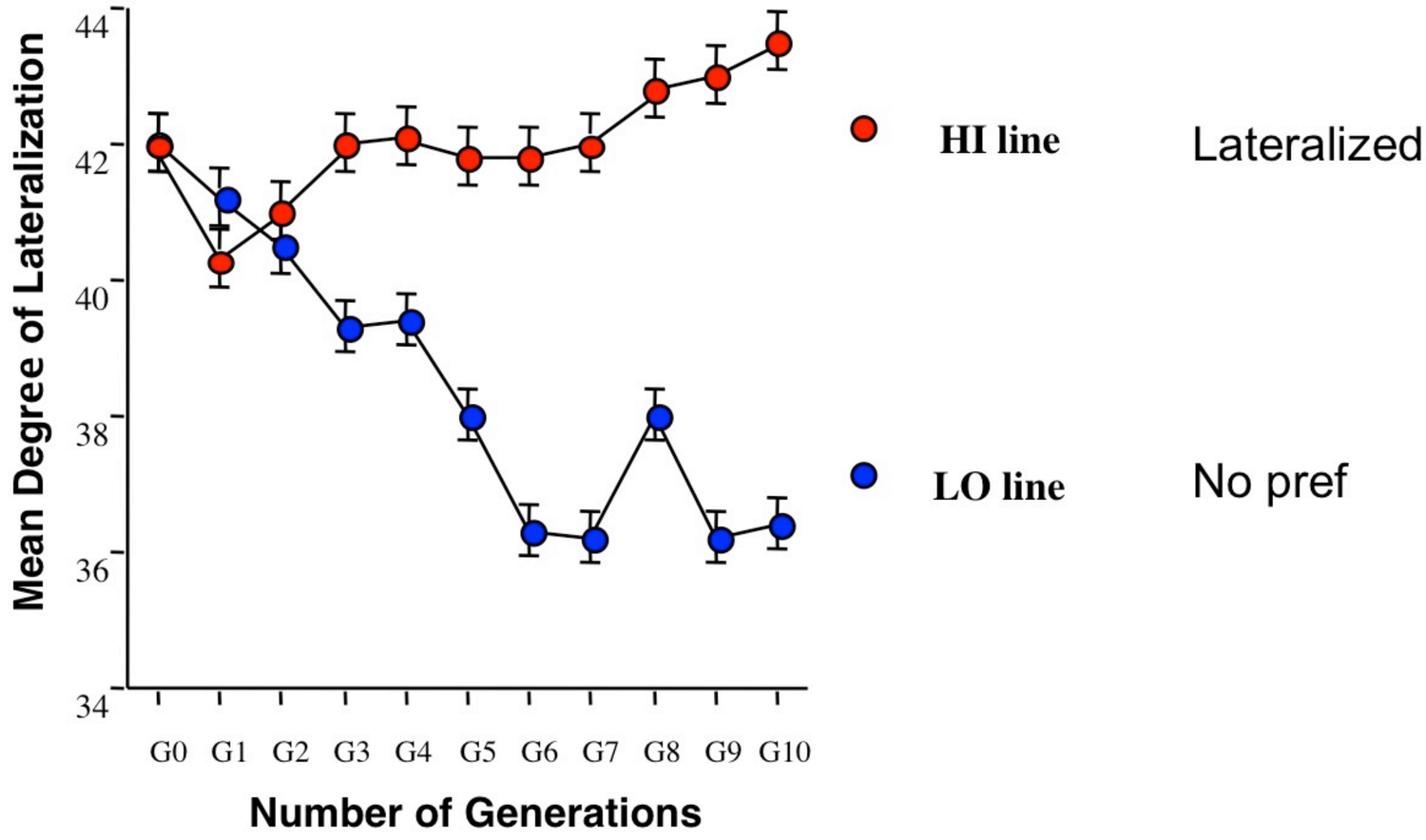
- Mice were deprived of food for 24h.
- 50 consecutive reaches for food.



Direction of Lateralization



Bidirectional Selection for the Degree of Lateralization

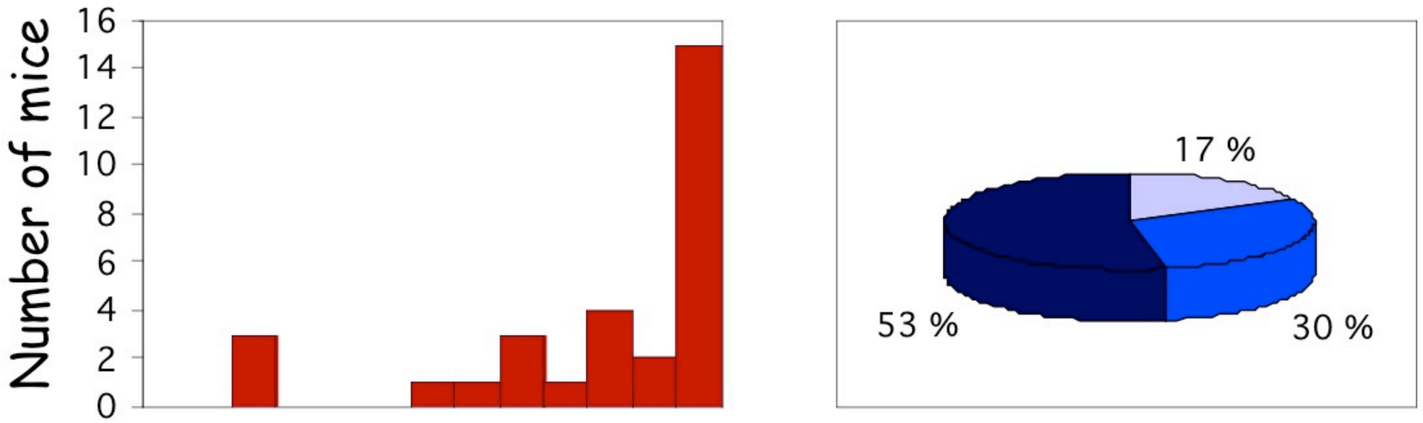


Collins, 1985

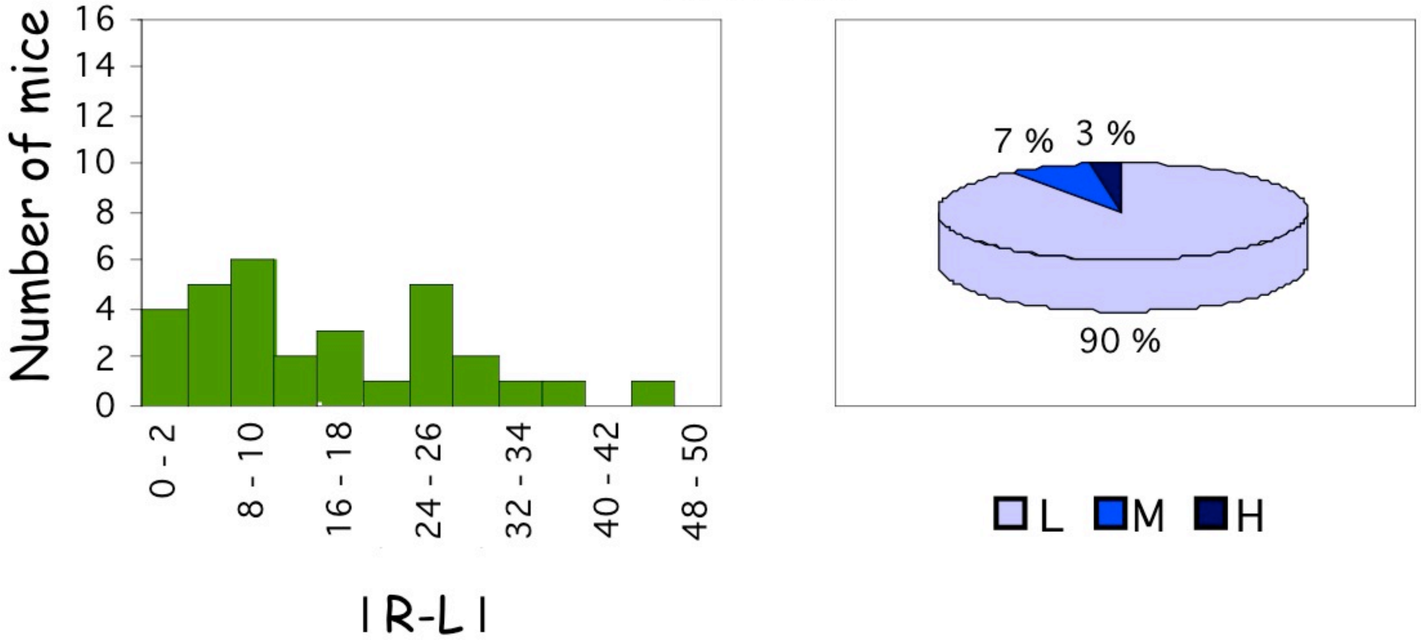
Wild Inbred Stains

Degree of lateralization

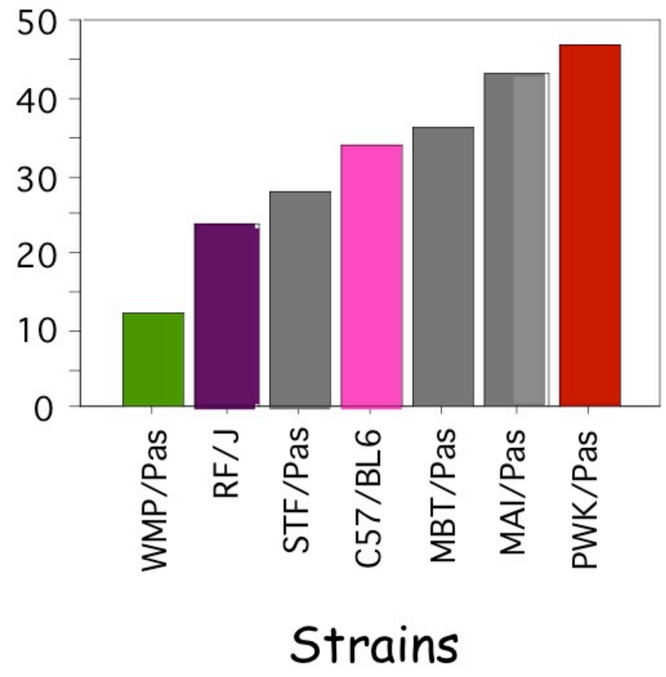
PWK/Pas



WMP/Pas

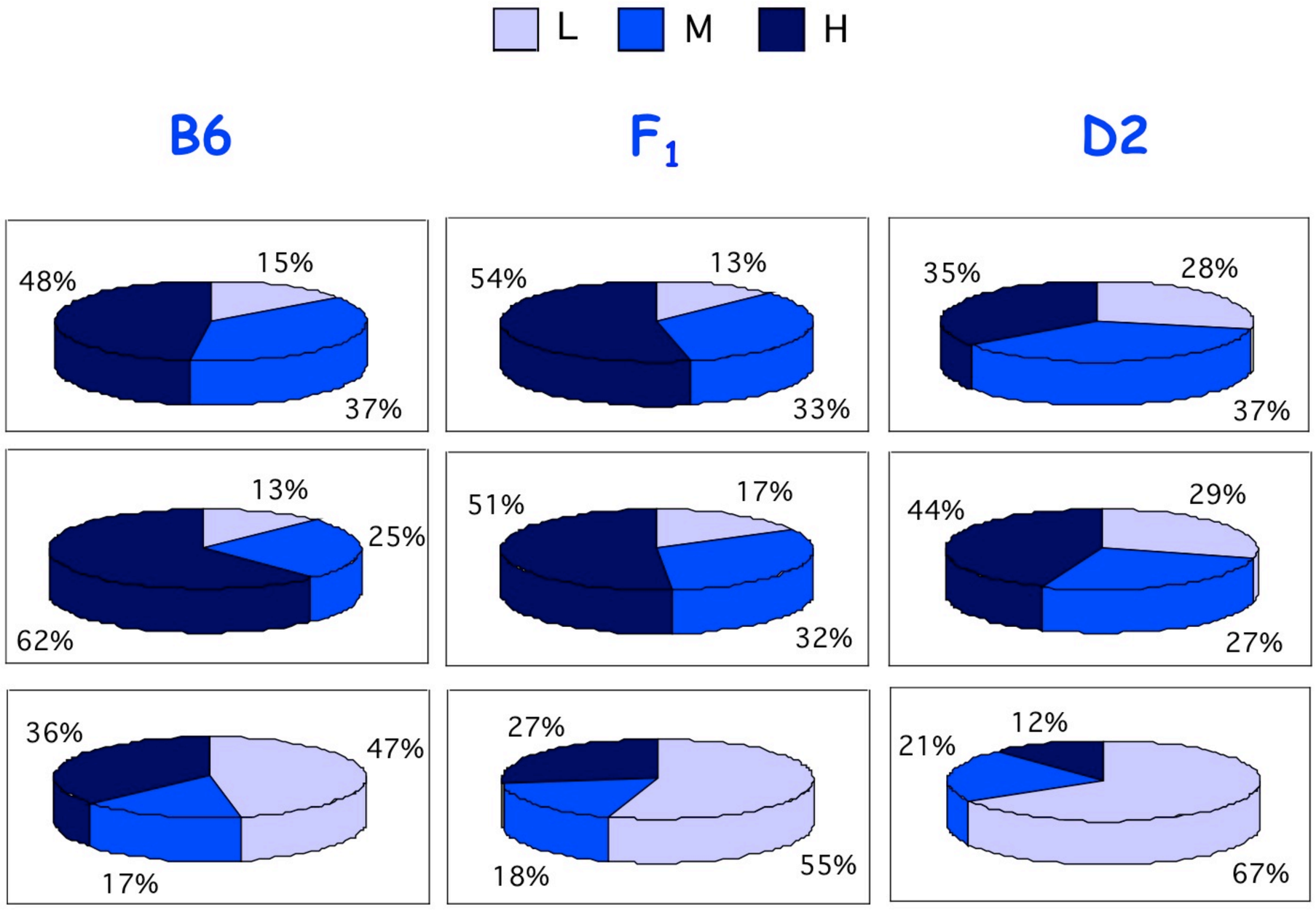


Median IR-LI



Morice *et al.* en prép

DAT-/- Mice



➡ ***Whatever the genetic background, hyperdopaminergia impairs the degree of lateralization without affecting the direction.***

Morice *et al.* 2005

Lateralization

Conclusions

- Analysis of QTLs for the | D-G | → identification of genes
- Dopaminergic hyperactivity : ↘ of the degree of lateralization
- Degree of lateralization: phenotype of interest in the genetic analysis

In mice

↳ Research of anatomical, biochemical markers of behavioural lateralization

↳ To test the hypothesis of a functional link between lateralization defect and cognitive deficit

In human being

↳ Potentials candidates as genetic factors of susceptibility in psychiatric disorders

Anxiety

Subjective manifestations :

- A heightened sense of awareness to a deep fear of impending disaster and death

Objective manifestations :

- Racing heart
- Avoidance behavior and signs of restlessness
- Heightened responsiveness
- Palpitations
- Tremor
- Sweating
- Increased blood pressure
- Dry mouth
- Desire to run or escape

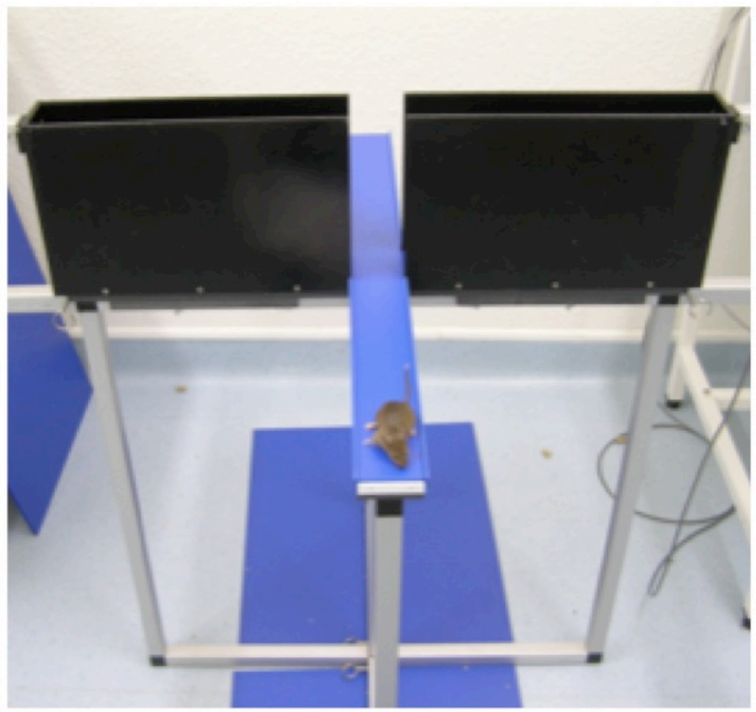
Anxiety disorders: panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, social phobia, specific phobias, generalized anxiety disorder

Behavioral Anxiety-Like Tests for Mice

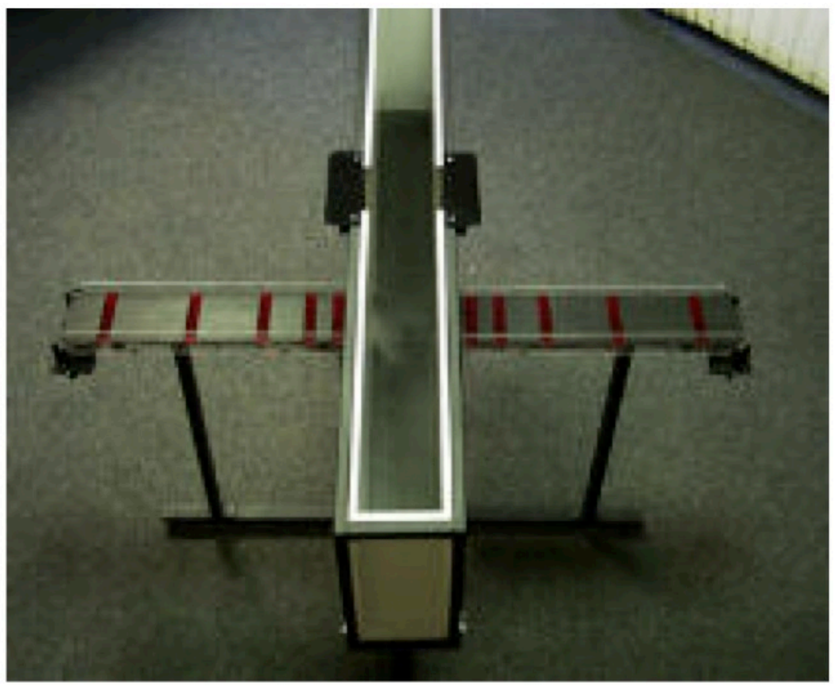
- ✓ Unconditioned
  - Elevated plus-maze / O-maze
  - Open field activity
  - Dark-light box

- ✓ Conditioned
  - Fear conditioning

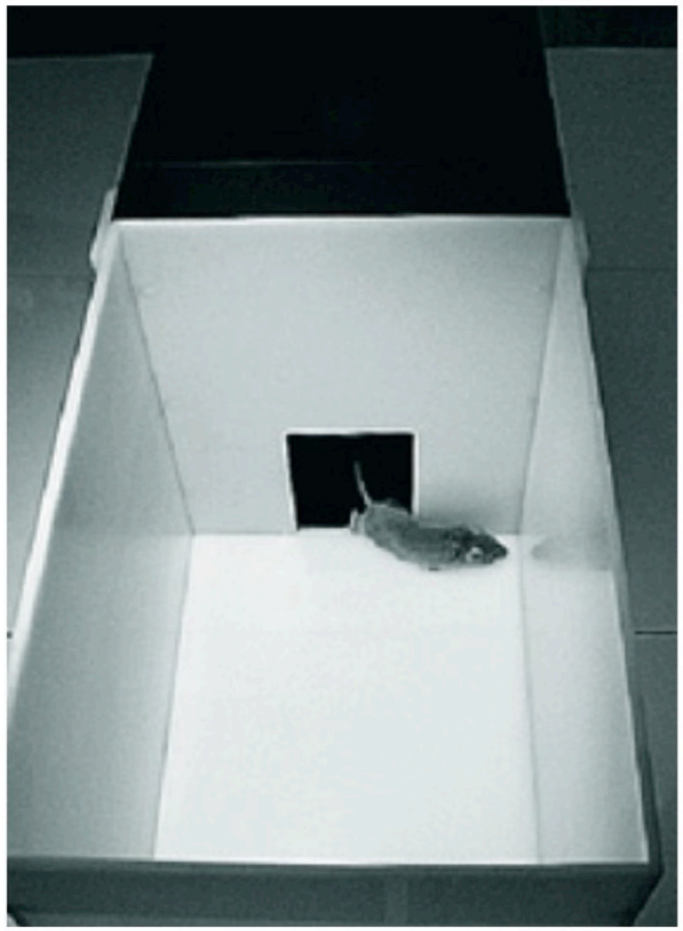
Elevated Plus-Maze

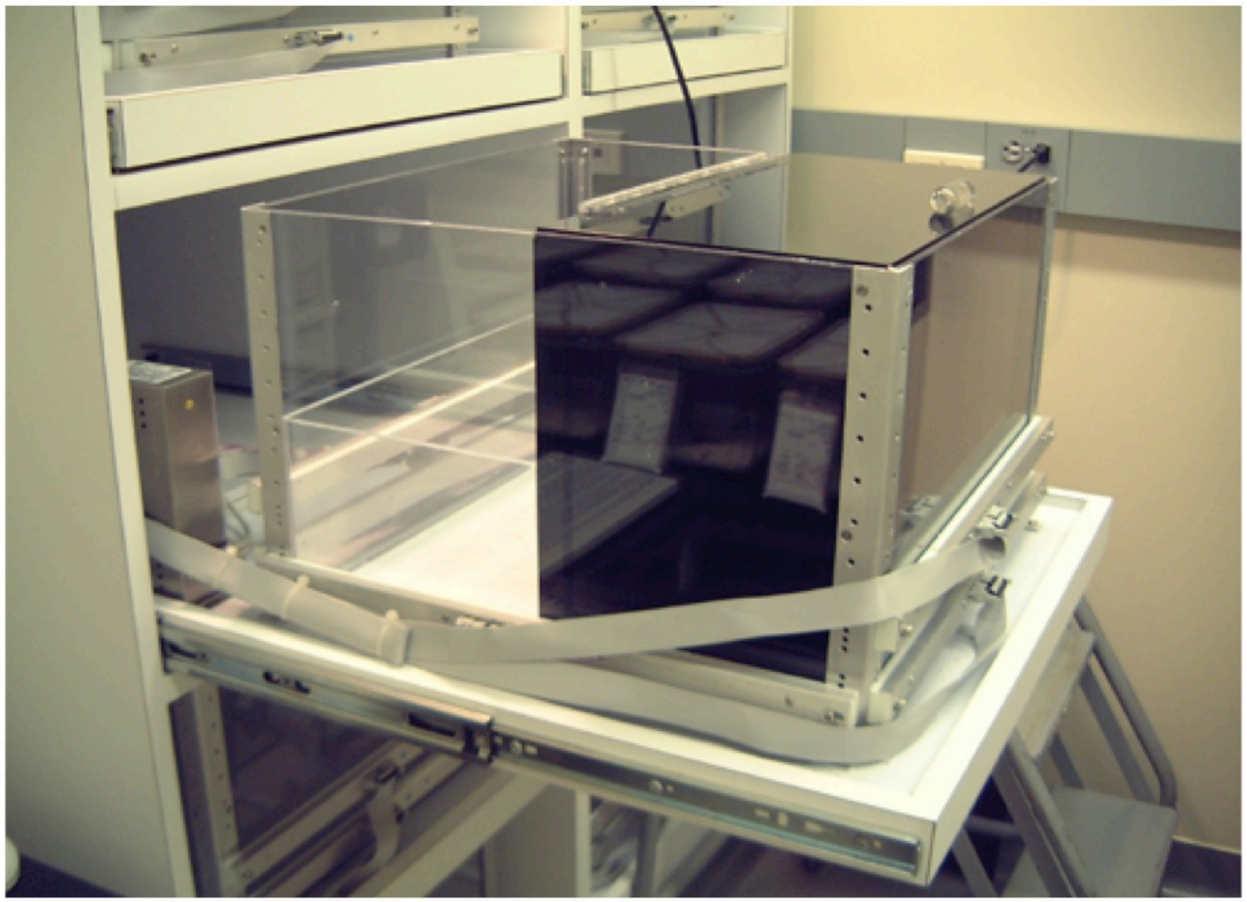


O-Maze

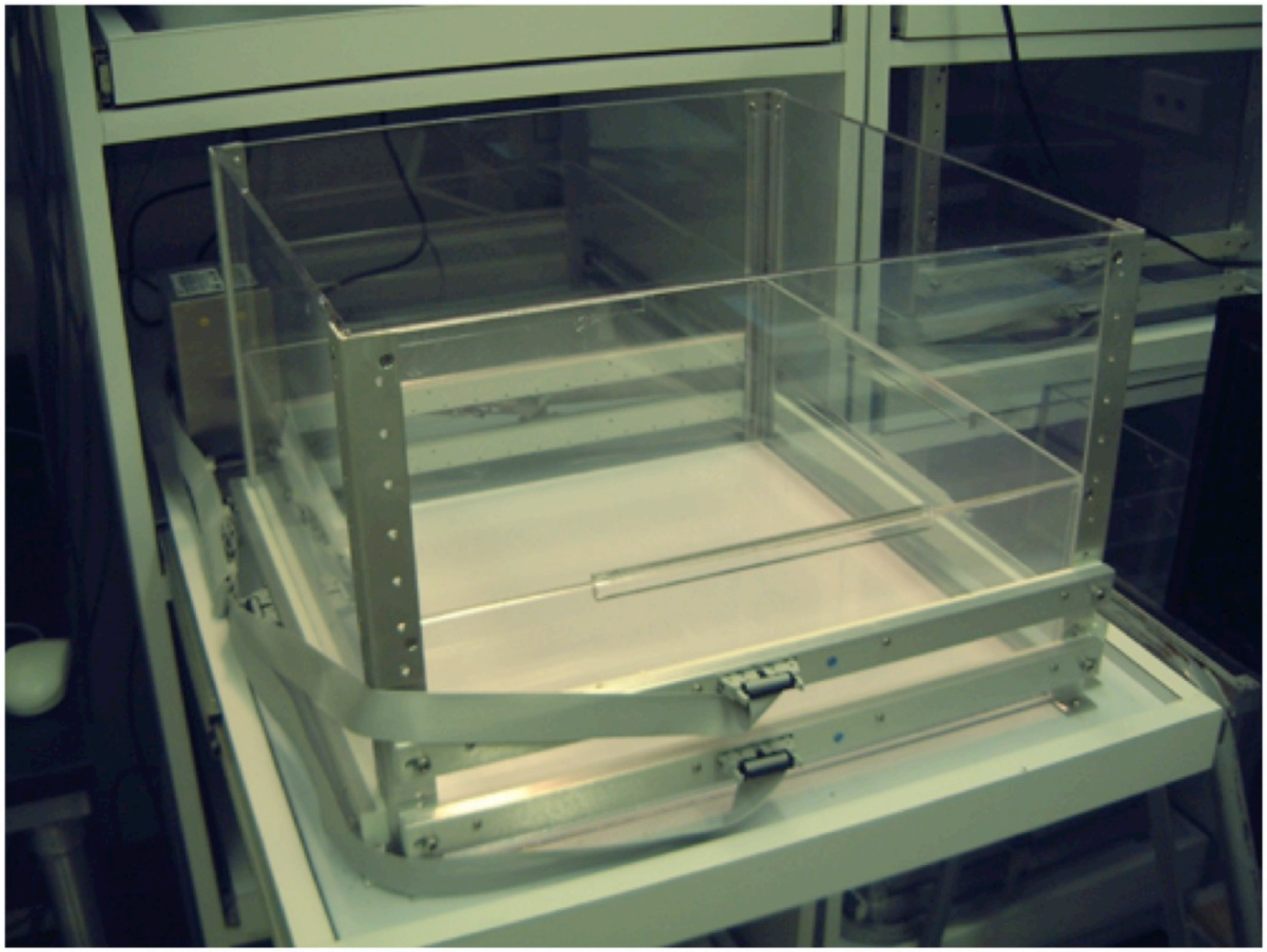


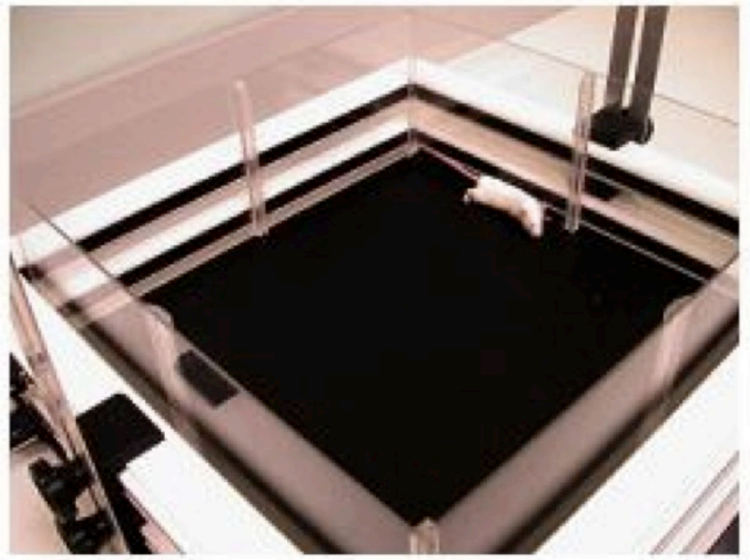
Light-Dark Box Test

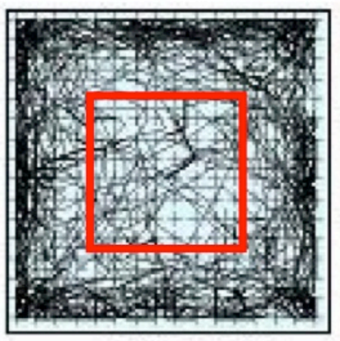




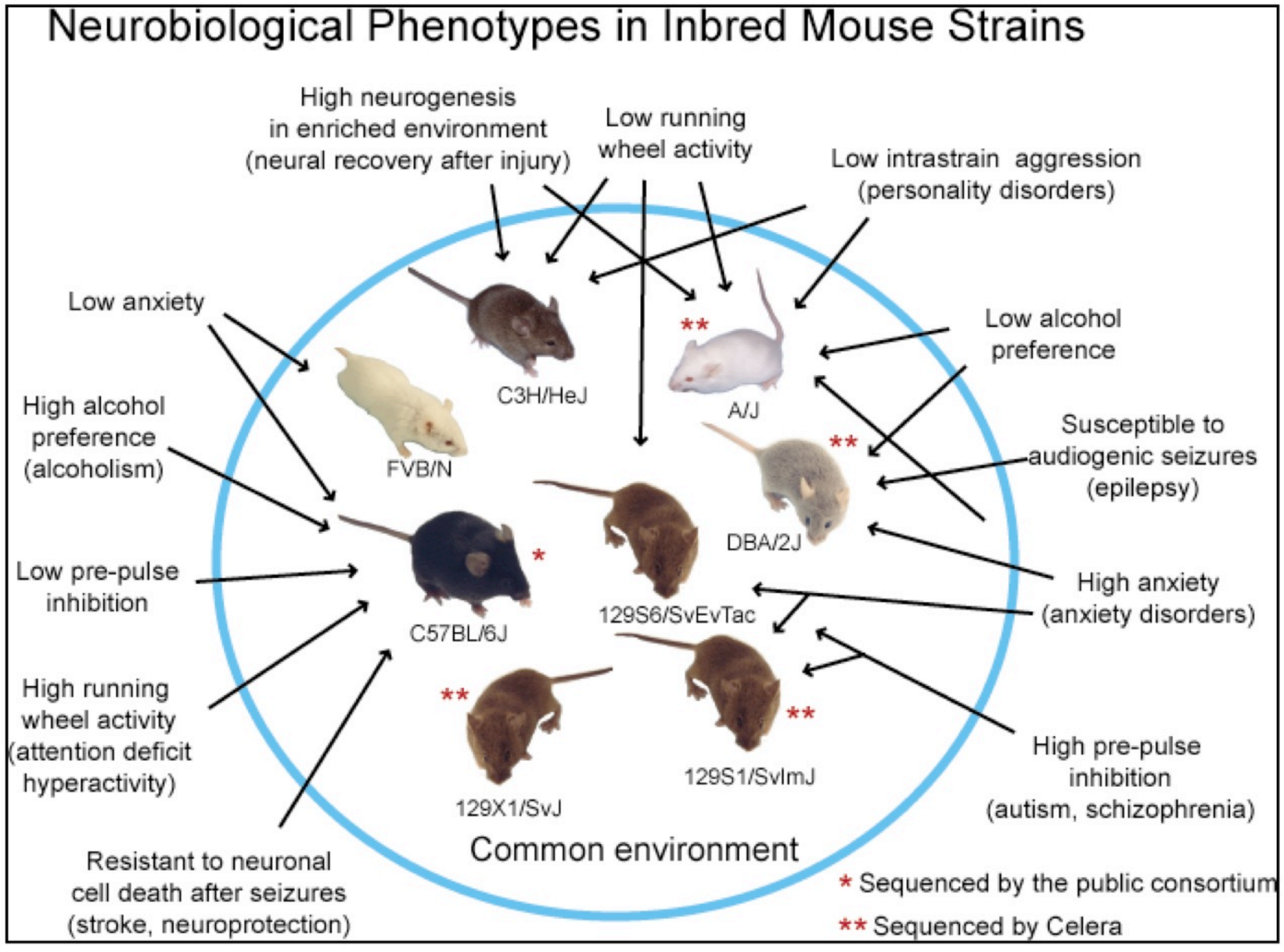
Open-Field Test







Inbred Mouse Strains for Behavior and Brain Dissections

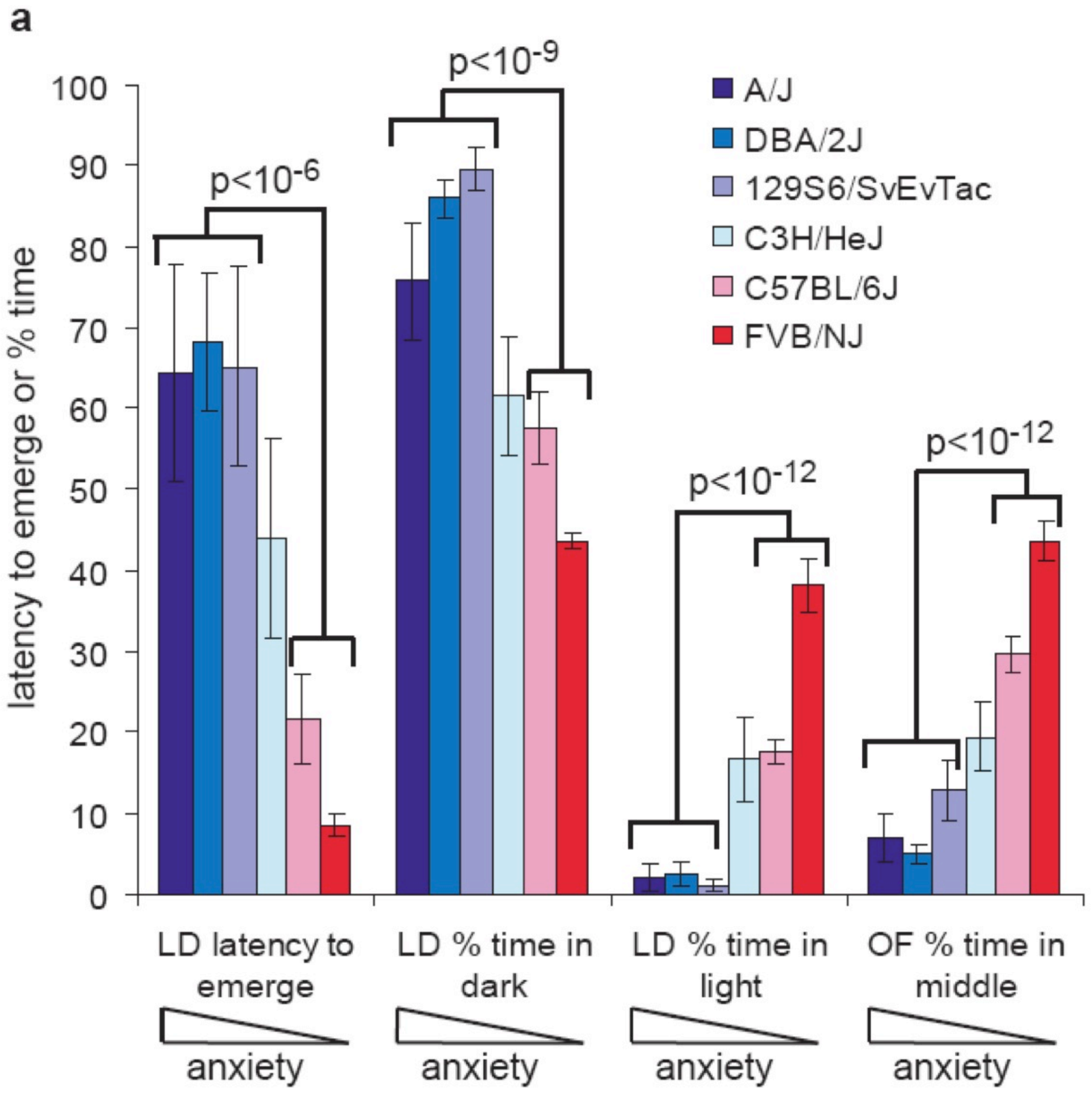


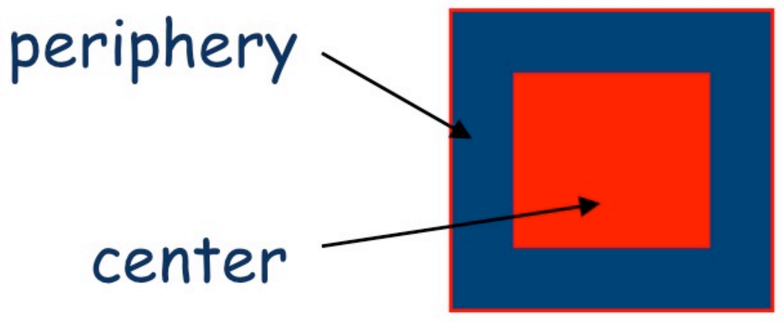
- A/J
- C3H/HeJ
- C57BL/6J
- DBA/2J
- FVB/NJ
- 129S6/SvEvTac

- Male mice, 8 weeks old
- 15/strain for dissections
- 10/strain for behaviors

Hovatta *et al.* 2005

Results from Behavioral Testing





Hovatta *et al.* 2005

Dissected Brain Regions

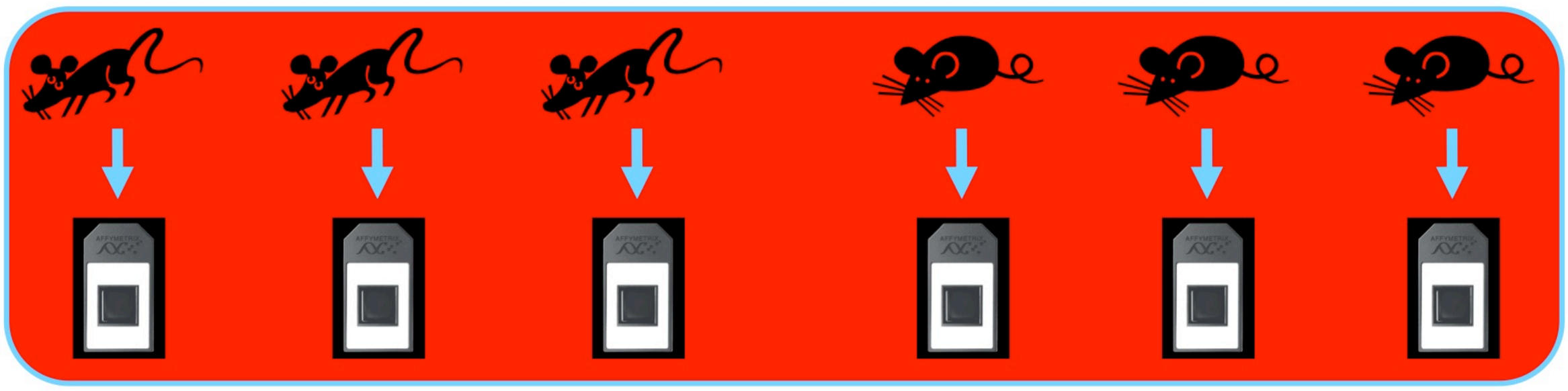
- Amygdala
- BNST (Bed nucleus stria terminalis)
- Cingulate cortex
- Hippocampus
- Hypothalamus
- PAG (Periaqueductal grey)
- Pituitary gland

Hovatta *et al.* 2005

Chipping

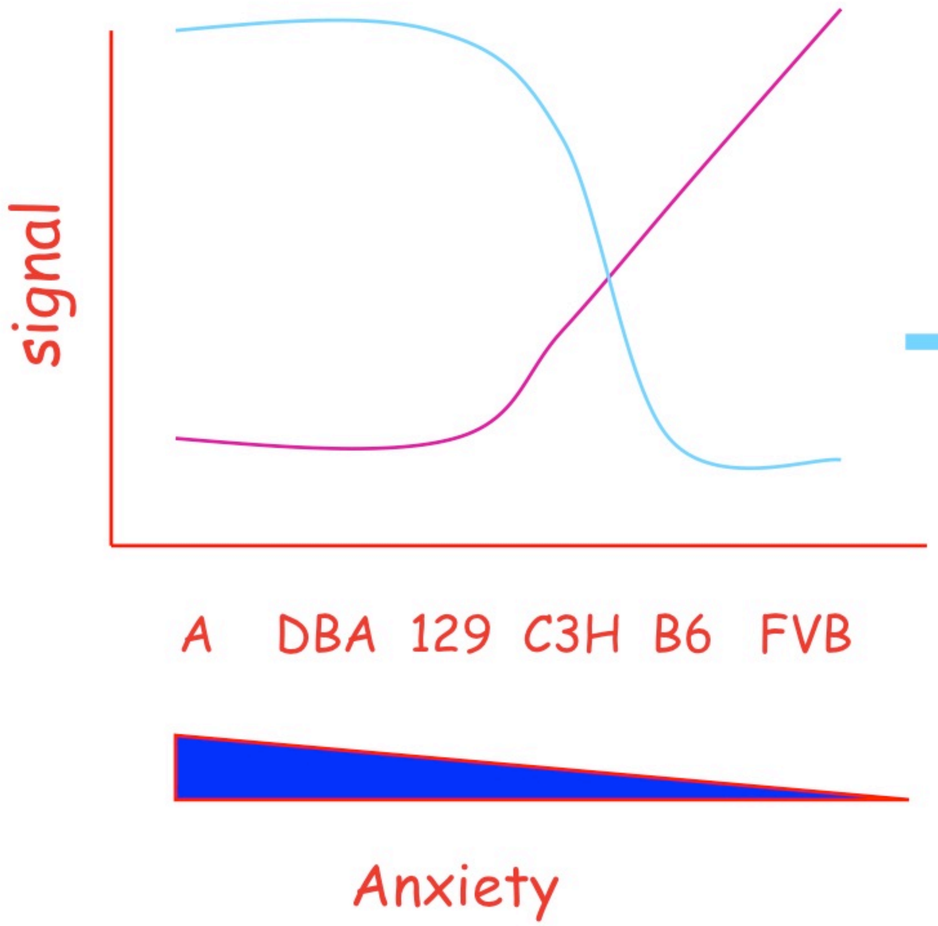
MG_U74Av2 arrays from Affymetrix
6 mouse strains, 7 brain regions, 2 replicates

84 chips



Hovatta *et al.* 2005

Differentially Expressed Genes in Anxious vs. Non-Anxious Mice



FVB/NJ
C57BL/6J ---

DBA/2J
A/J +++

Results:
1- Statistical differences

2- Correlation analysis

17 candidate genes

Hovatta *et al.* 2005

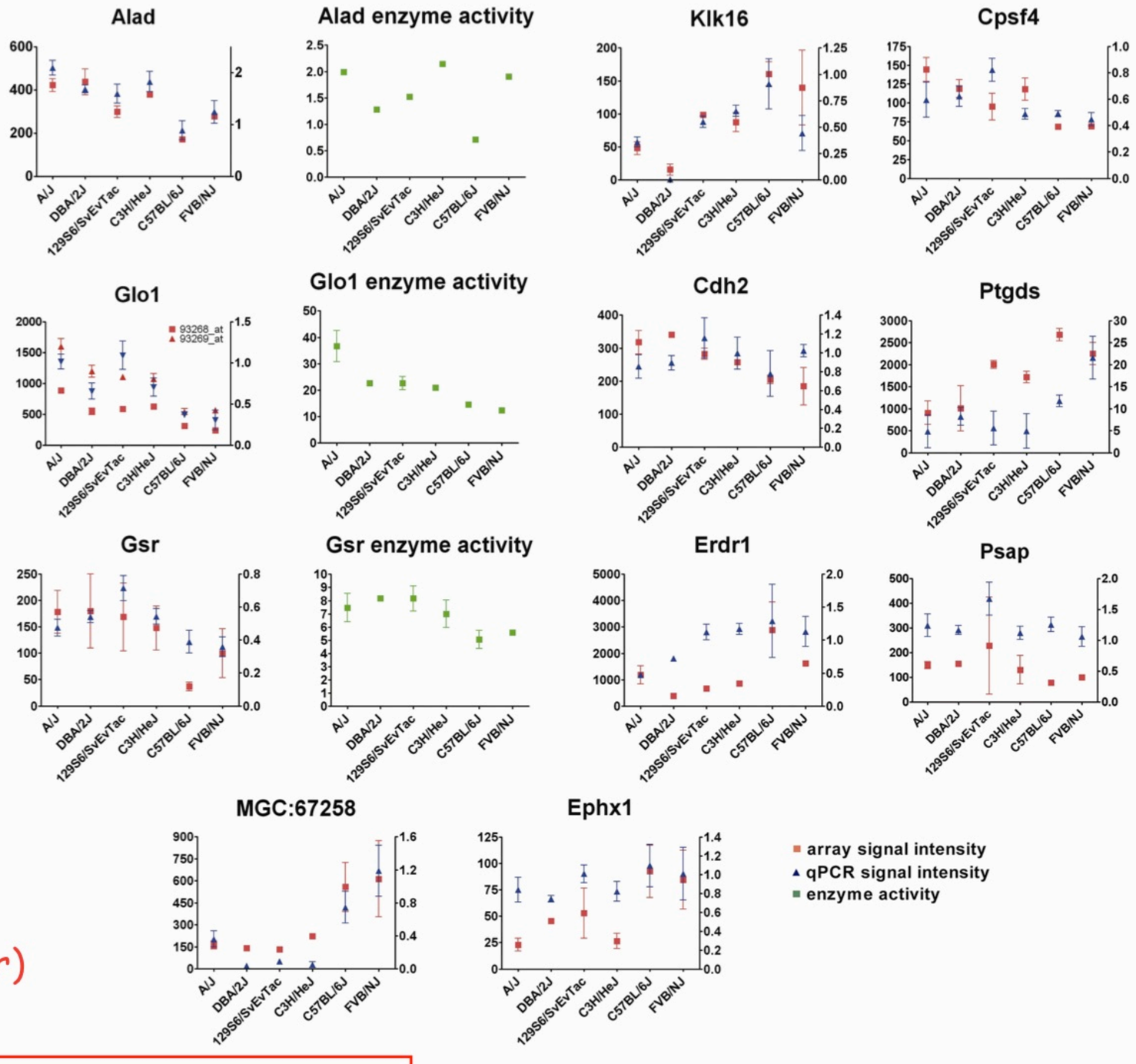
Confirmation by qPCR and Enzyme Activity

Glyoxalase 1

Glutathione reductase 1

GSH
(antioxydant majeur)

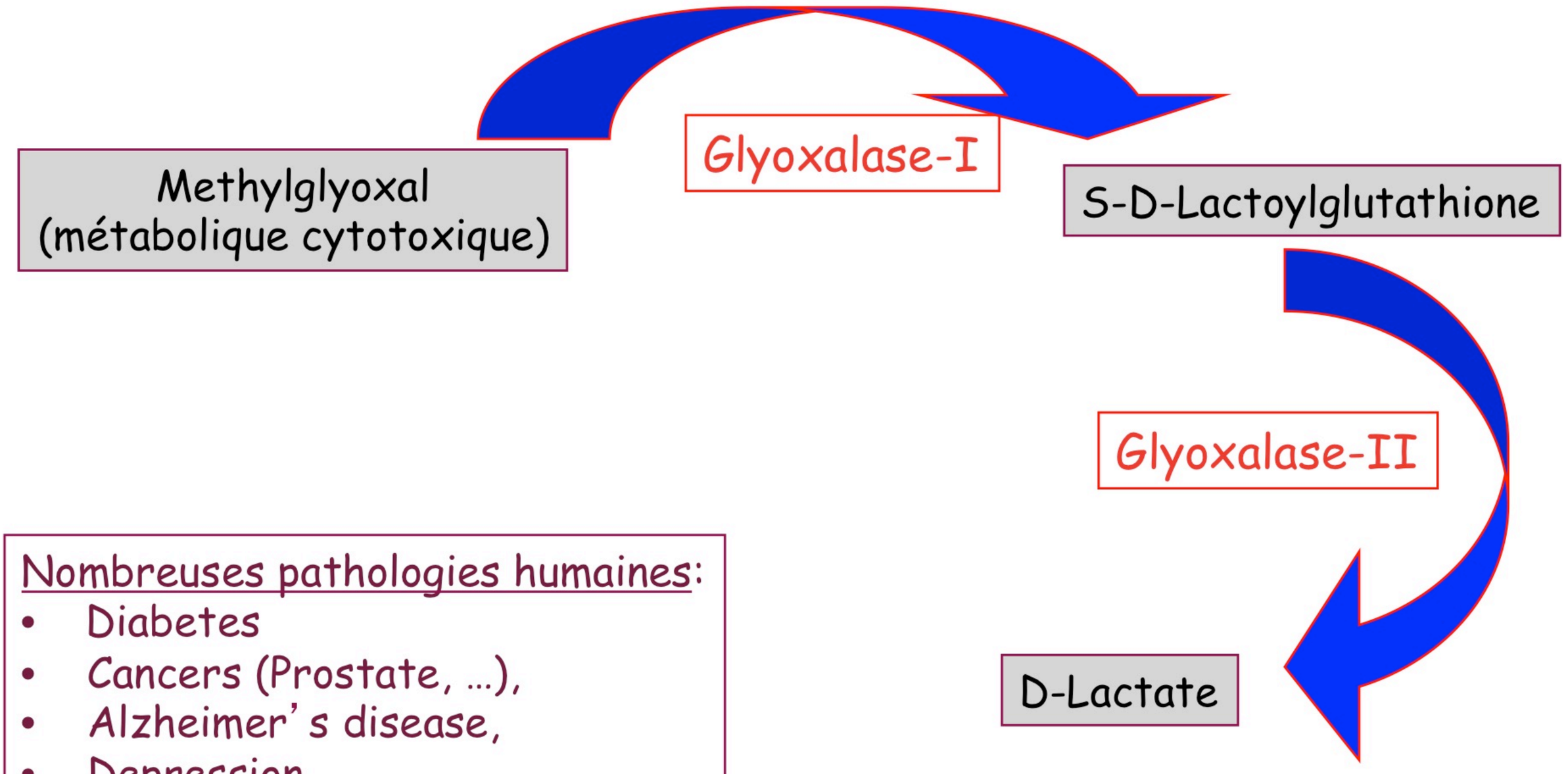
Detoxification methylglyoxal



Hovatta *et al.* 2005

The glyoxalase system

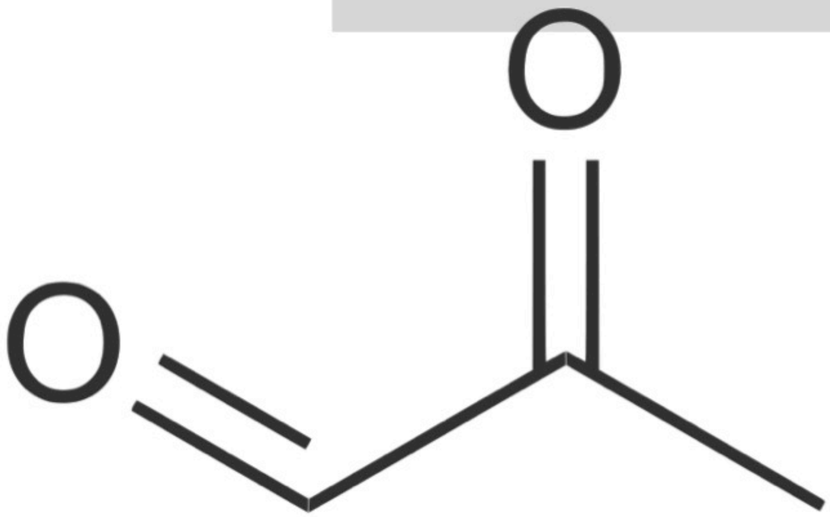
Cycle de détoxification des α-ketoaldehydes
↘ Formation d' AGEs (advanced glycation end products)



Nombreuses pathologies humaines:

- Diabetes
- Cancers (Prostate, …),
- Alzheimer's disease,
- Depression,
- Neurodegenerative diseases, …

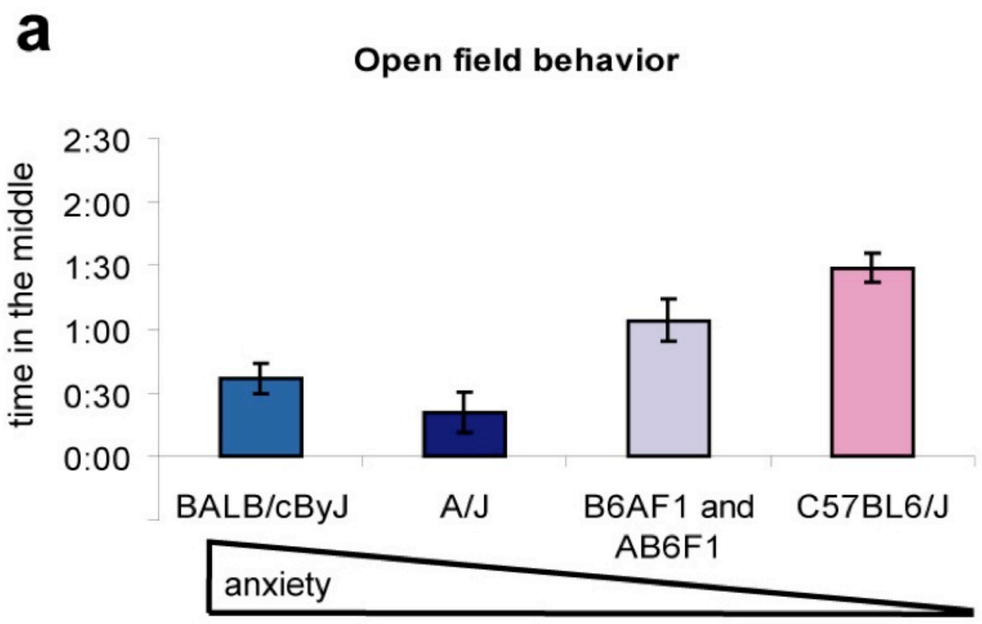
The glyoxalase system

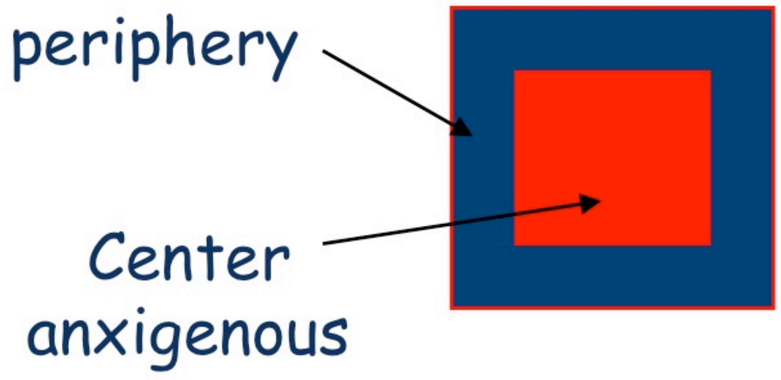


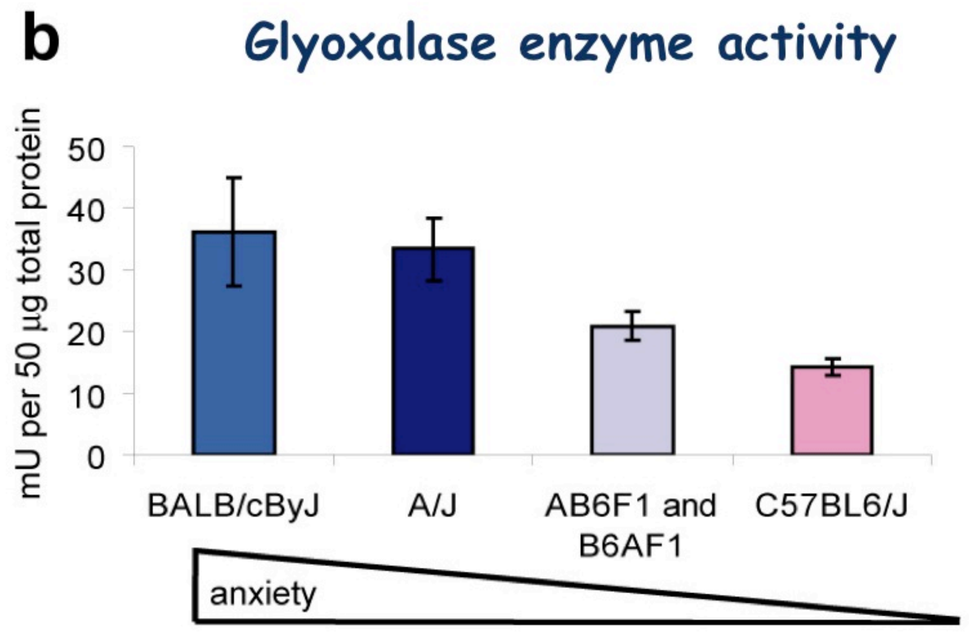
Methylglyoxal, also called pyruvaldehyde or 2-oxo-propanal (CH3-CO-CH=O or C3H4O2) is the aldehyde form of pyruvic acid. It has two carbonyl groups, so it is a dicarbonyl compound. Methylglyoxal is both an aldehyde and a ketone.

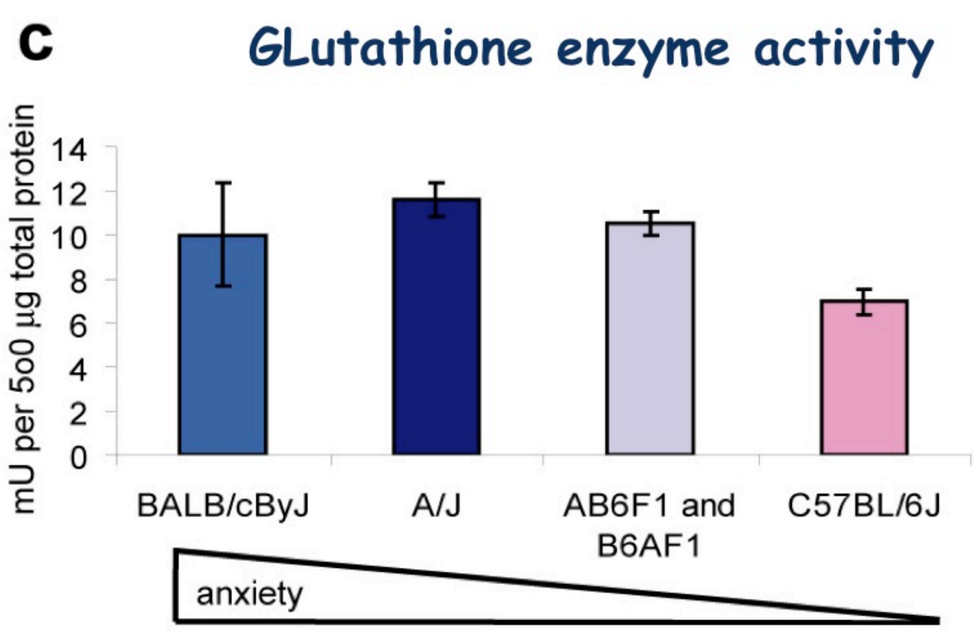
In organisms, methylglyoxal is formed as a side-product of several metabolic pathways.[1] It may form from 3-amino acetone, which is an intermediate of threonine catabolism, as well as through lipid peroxidation. However, the most important source is glycolysis. Here, methylglyoxal arises from non enzymatic phosphate elimination from glyceraldehyde phosphate en dihydroxyacetone phosphate, two intermediates of glycolysis. Since methylglyoxal is highly cytotoxic the body developed several detoxification mechanisms. One of these is the glyoxalase system. Methylglyoxal reacts with glutathione forming a hemithioacetal. This is converted into S-D-lactoyl-glutathione by glyoxalase I,[2] and then further metabolised into D-lactate by glyoxalase II.[3]

Behavior and Enzyme Activity of A x BL6 F_1 Animals







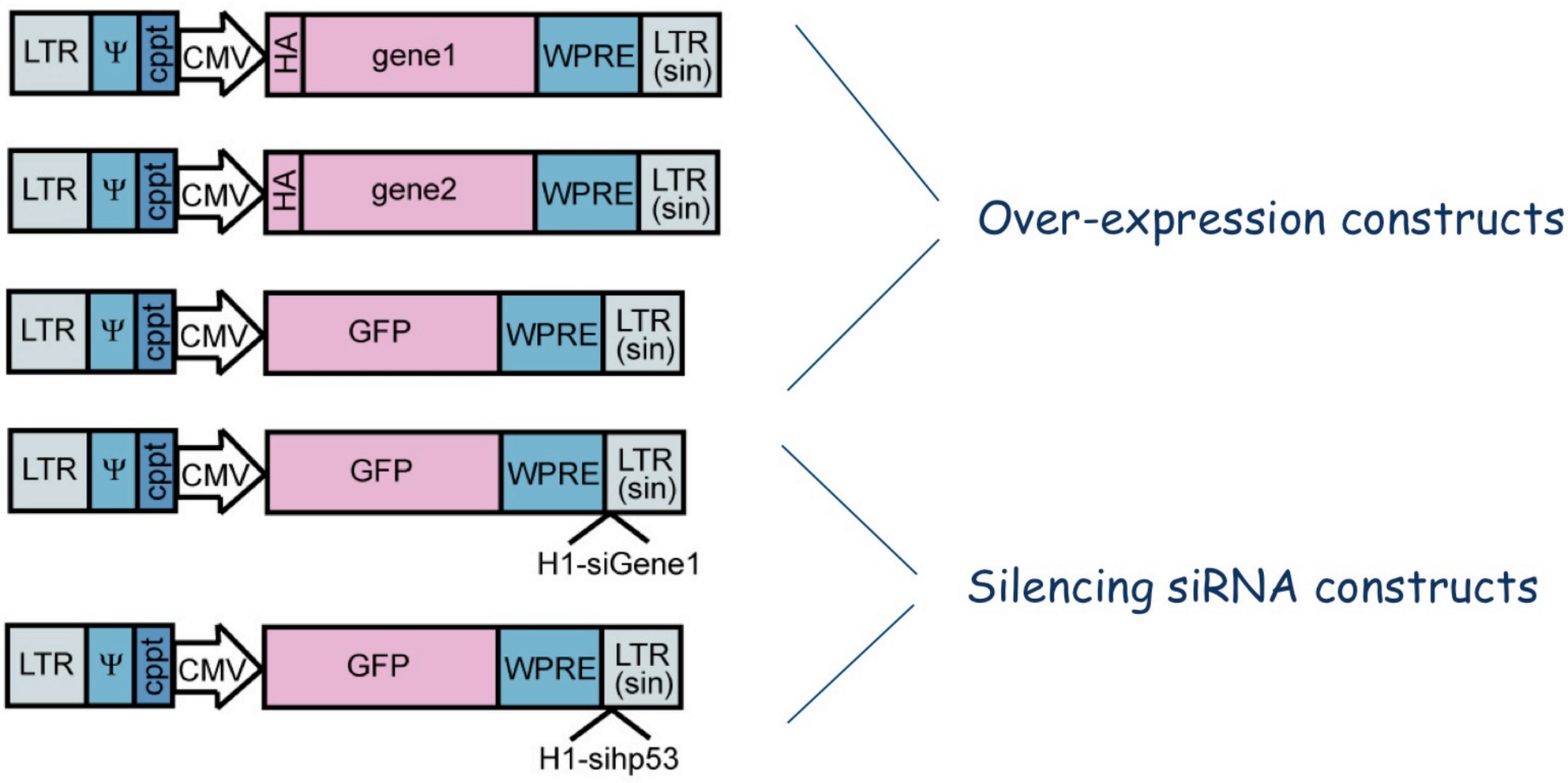


Hovatta *et al.* 2005

Construction of Animals Models to Study the Function of Glo1 and Gsr *in vivo*

Lentivirus mediated gene transfer

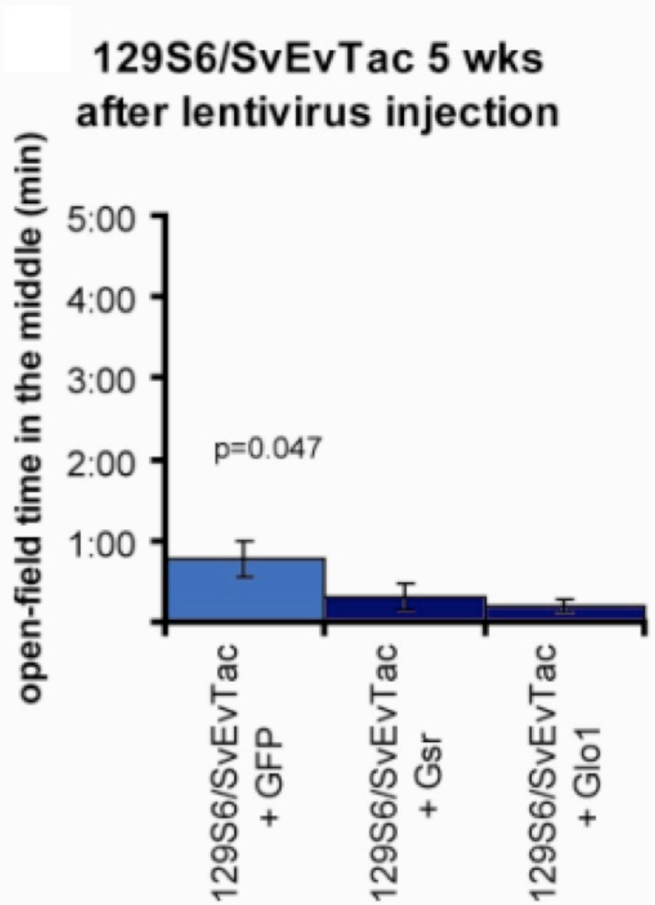
d

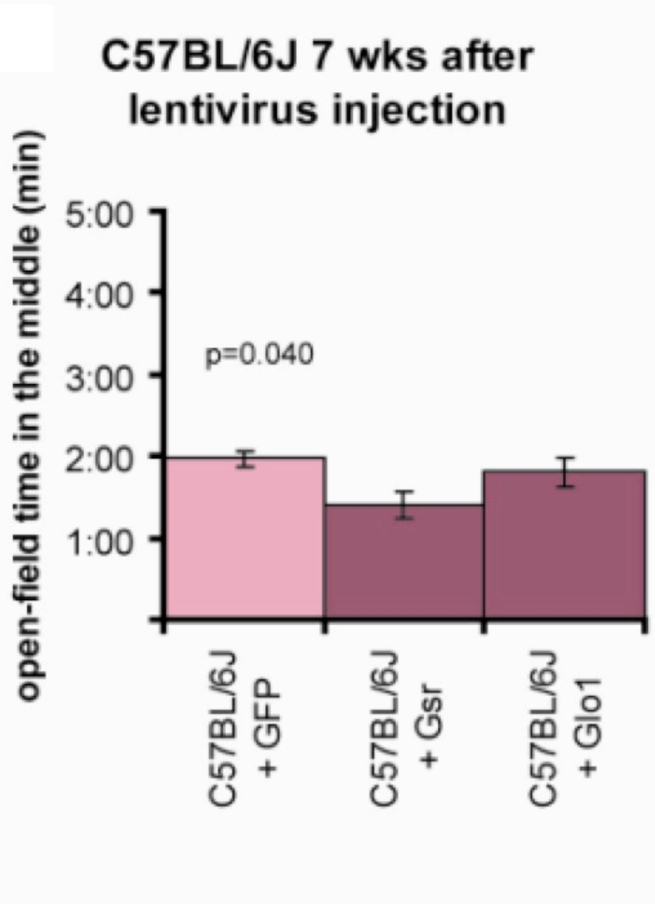


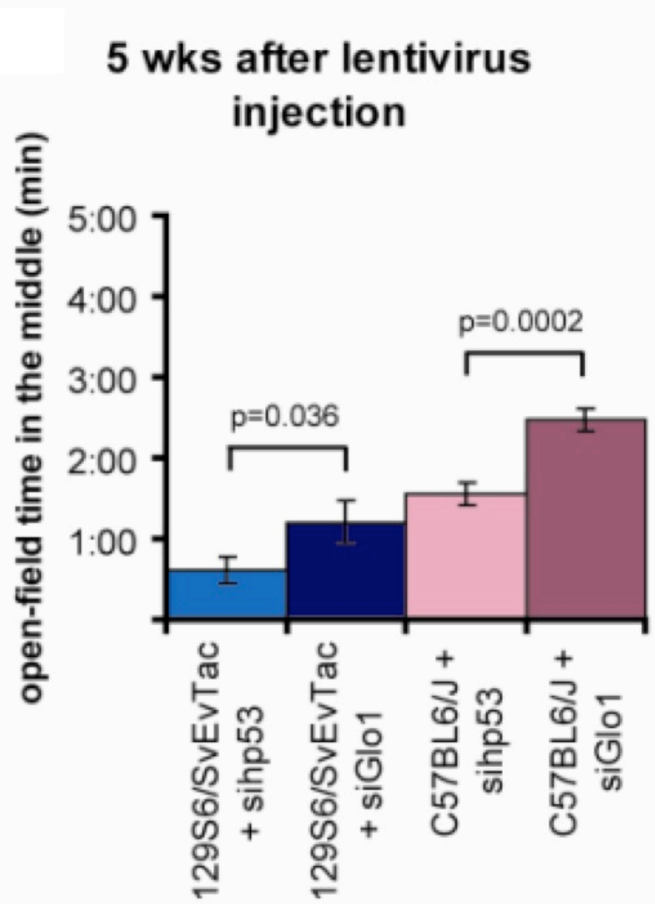
- Animals: 10 129S6/SvEvTac and 10 C57BL/6J per construct
- Inject 1 ml bilaterally into the cingulate cortex using a stereotaxic frame
- Behavioral testing 5 and 7 weeks after injections

Hovatta *et al.* 2005

Open-Field Behavior of Lentivirus Injected C57BL6/J and 129 Mice







Over-expression of Glo1

129 anxiety ↑

BL6 —

Over-expression of Gsr

129 anxiety ↑

BL6 ↑

Silencing of Glo1

129 anxiety ↓

BL6 ↓

Hovatta *et al.* 2005

Anxiety

Conclusions

- How to model complex diseases, such as anxiety, in animal

- Identification of genes and molecular pathways

- Validation of a model for the development of therapeutic drugs

- Identification of regulatory elements in human

General Conclusion

Animals models and psychiatric disorders

- Genetic analysis of complex traits
  → Definition of the phenotype
→ Complementarity of the reverse and forward genetic approaches

- Tool immediately available for pharmacological studies and the screening of new molecules acting on the CNS

- Animal models can answer questions raised by clinical studies in human

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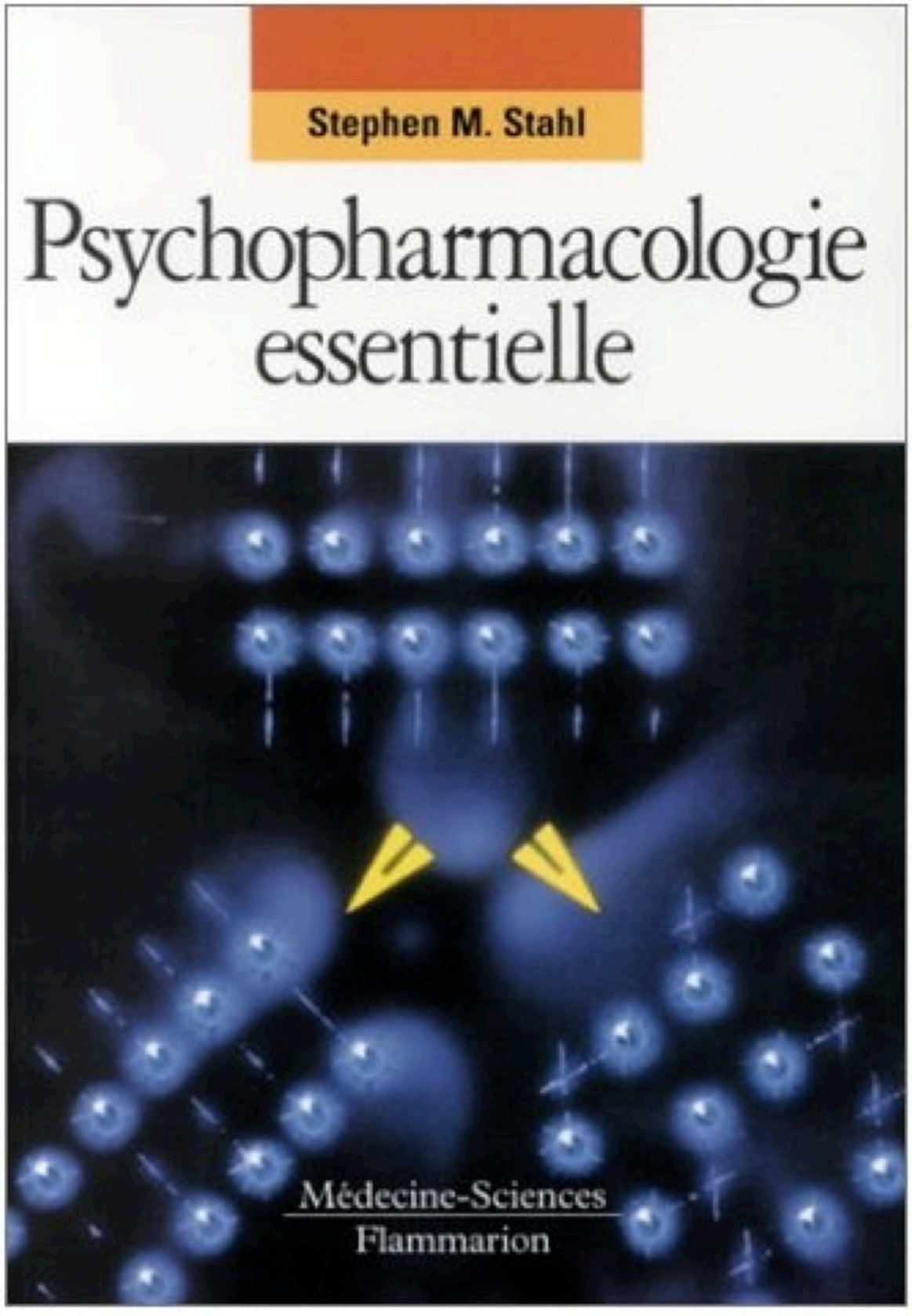

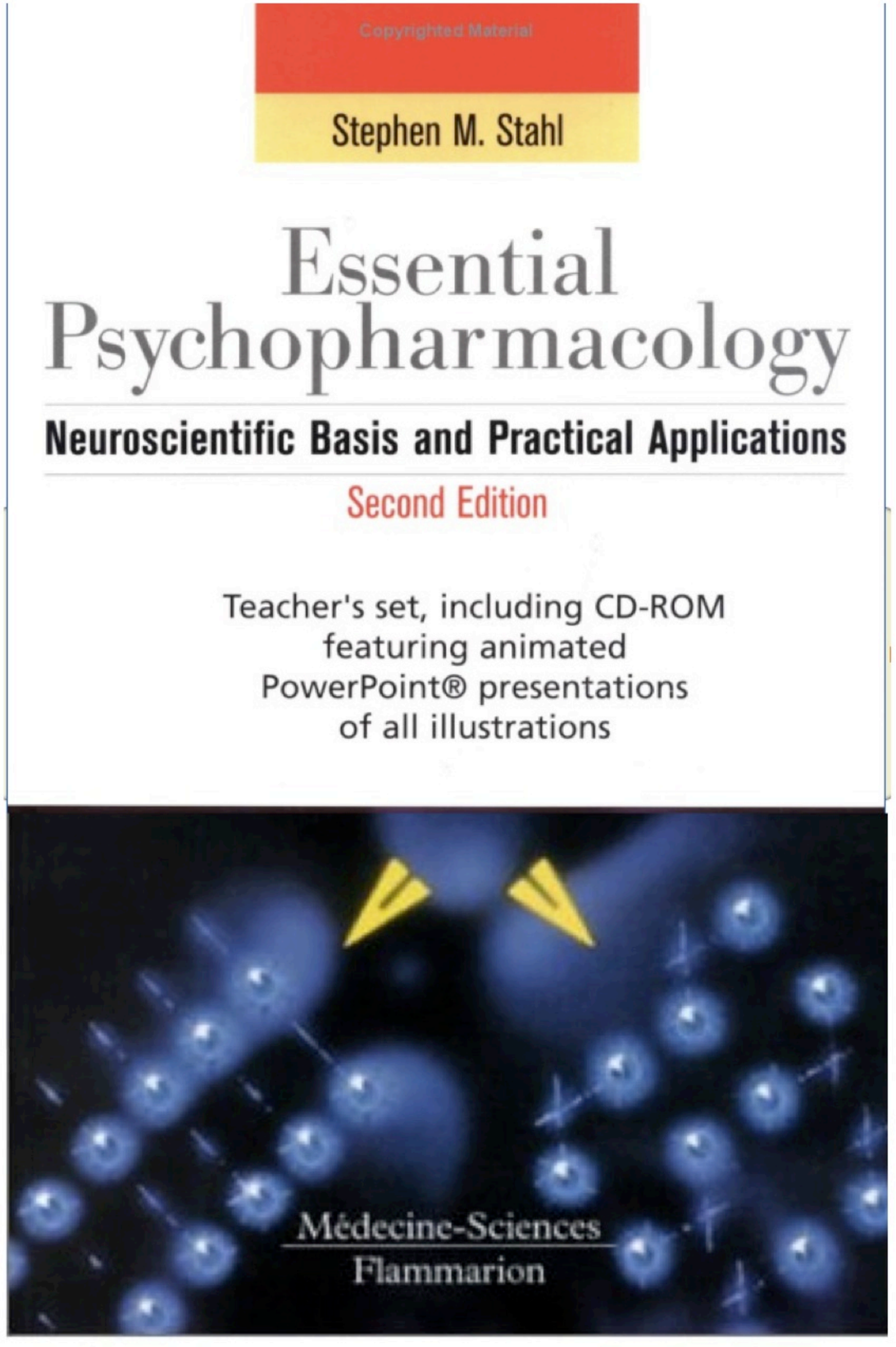

Adapted from Essential Psychopharmacology, Stephen Stahl, Flammarion.