université PARIS-SACLAY | FACULTÉ DE PHARMACIE

Animal models of anxiety-depression : use for pharmacology

M1

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Abbreviations

NSF : novelty suppressed feeding
FST : Forced swim test
CORT model : mouse model of anxiety-depression based on chronic administration of corticosterone
CMS : Chronic mild stress
AHN : Adult hippocampal neurogenesis

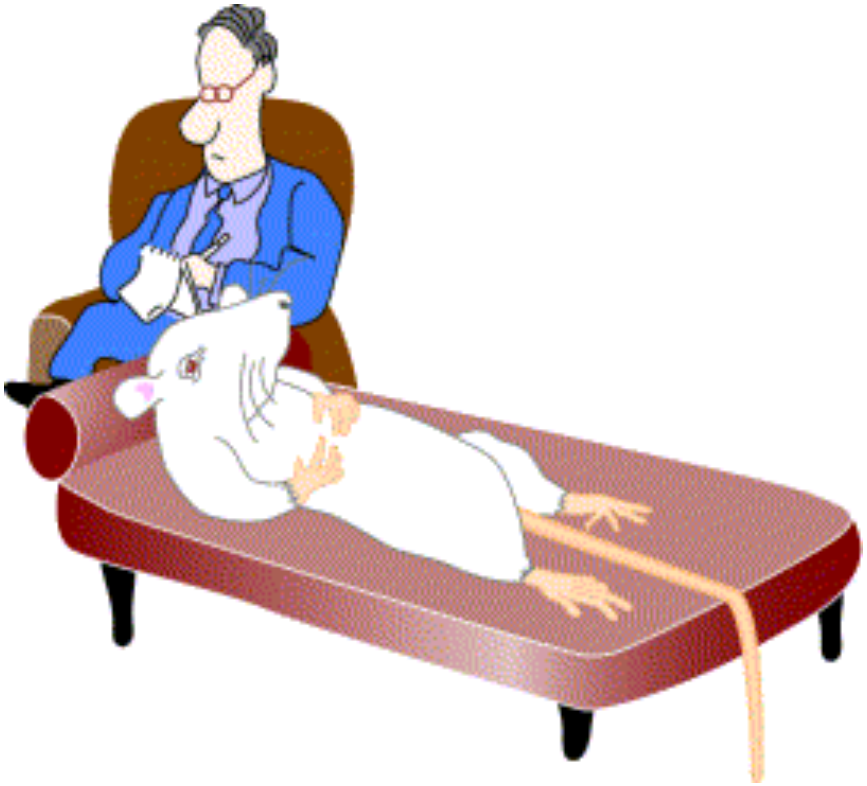
To model anxiety / depression in animals ?

Creative validity : Same symptoms as the human disease : in psychiatry : what seems depression for animals ?

Predictive validity : The Treatment's answer of the model should be similar to the ones observed in the human illness

Theoretical validity : Involvement of the same mechanisms between the model and the human pathology.

I- Creative and predictive validities

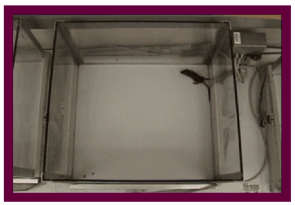


- **Social interactions**
- **Learning**
- **Curious:**
  - Exploration behavior
- **Fearful**
  - afraid of big empty spaces
  - afraid of heights

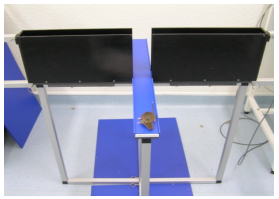
I- Creative and predictive validities
Behavioural tests

Anxiolytic activity | **Mixed activity** | **Antidepressive activity**

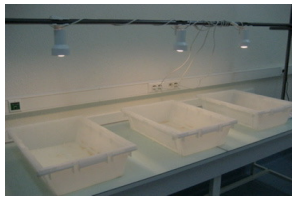
Elevated plus maze



Open Field



Novelty Suppressed Feeding

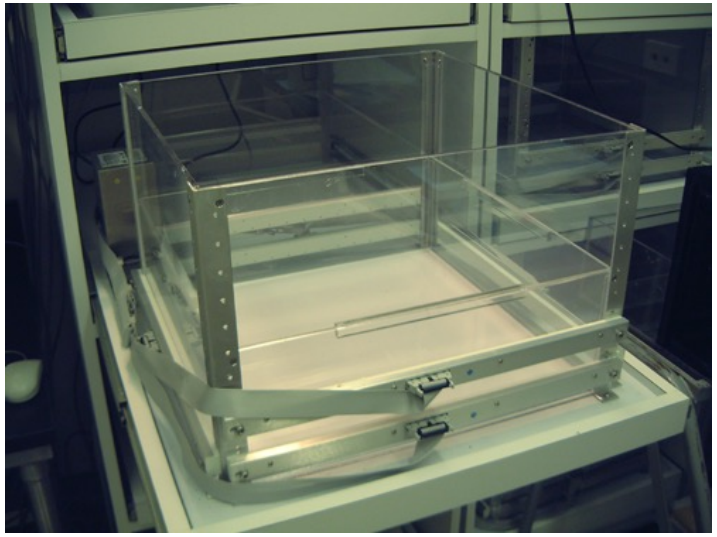


Forced swim test

predictivity

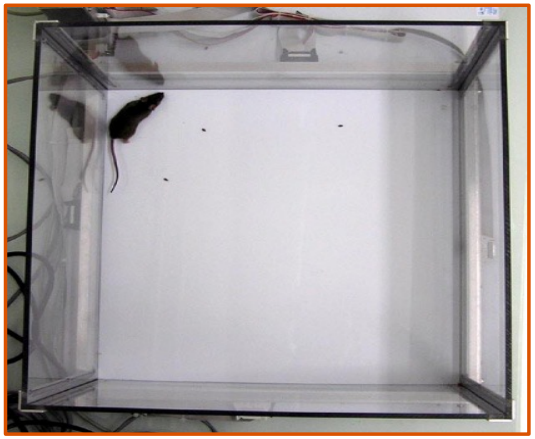
I- Creative and predictive validities

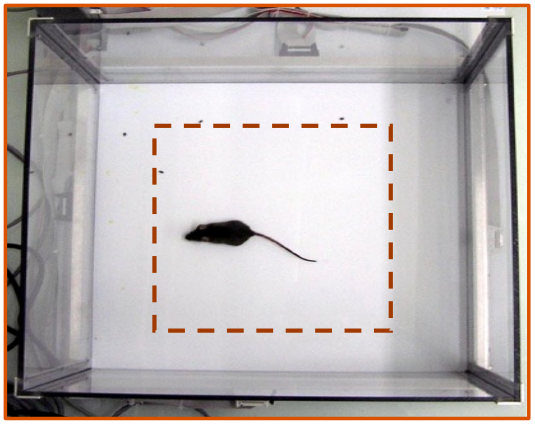
Predictive test of anxiolytic activity : the openfield test

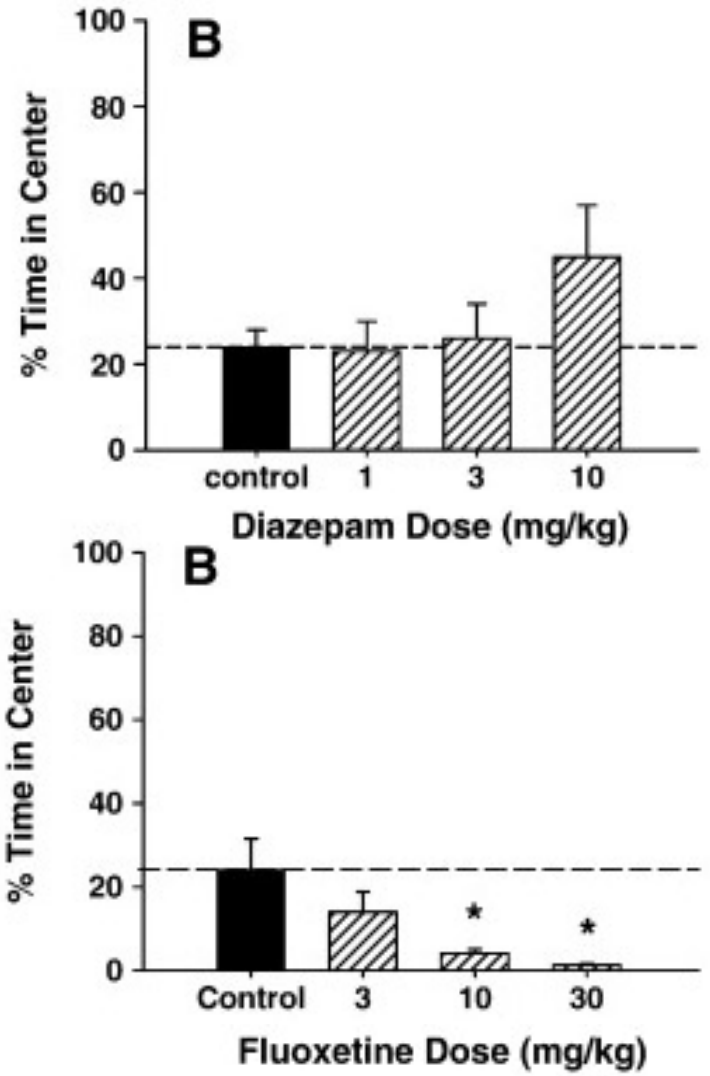


I- Creative and predictive validities

Openfield test : results

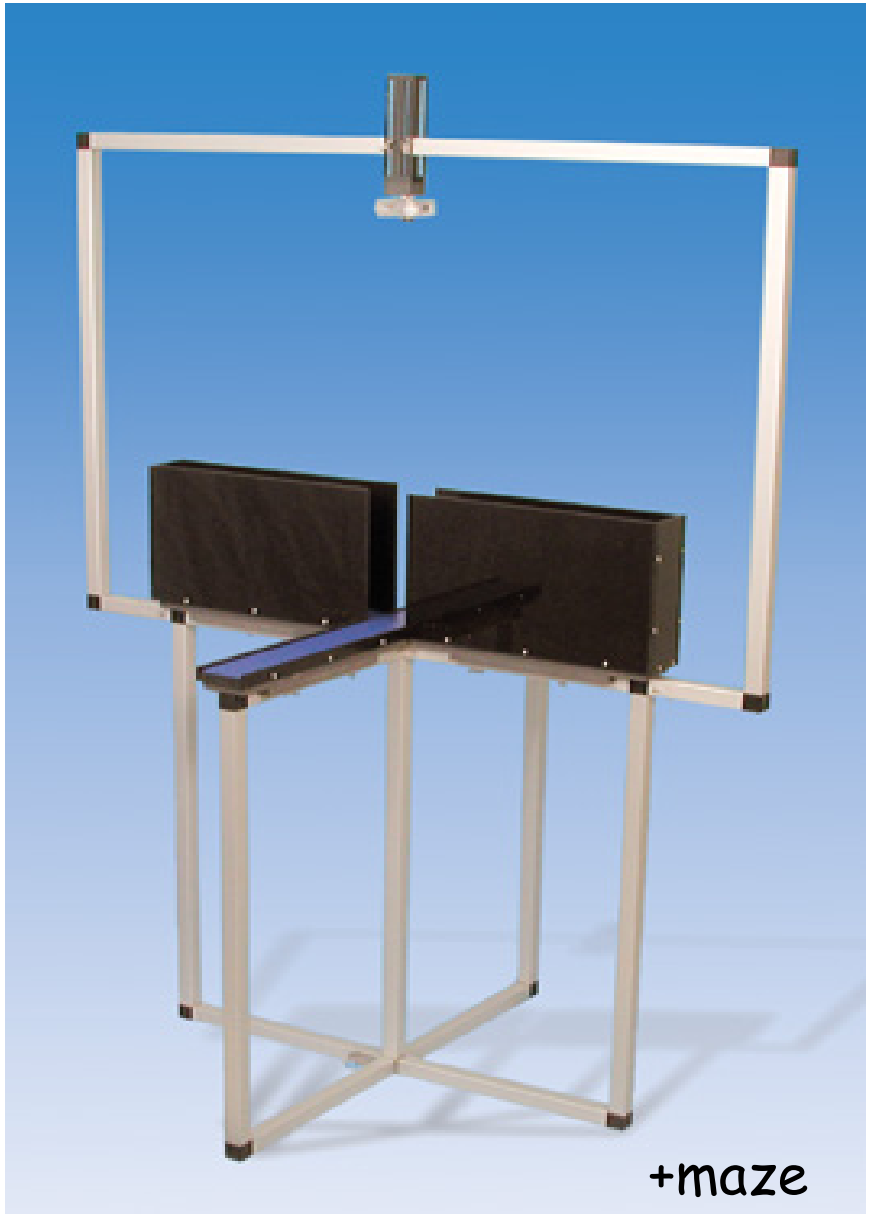






Adapted from Birkett et al., 2011

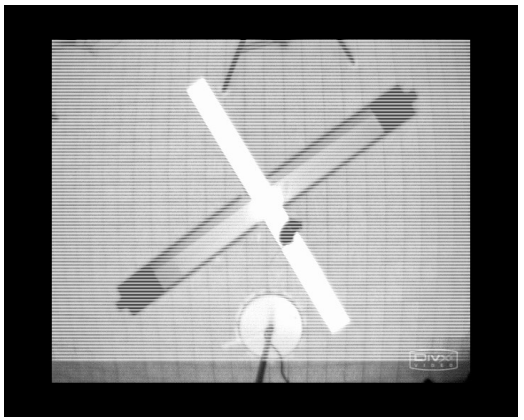
Predictive Tests of anxiolytic activity :
Elevated mazes

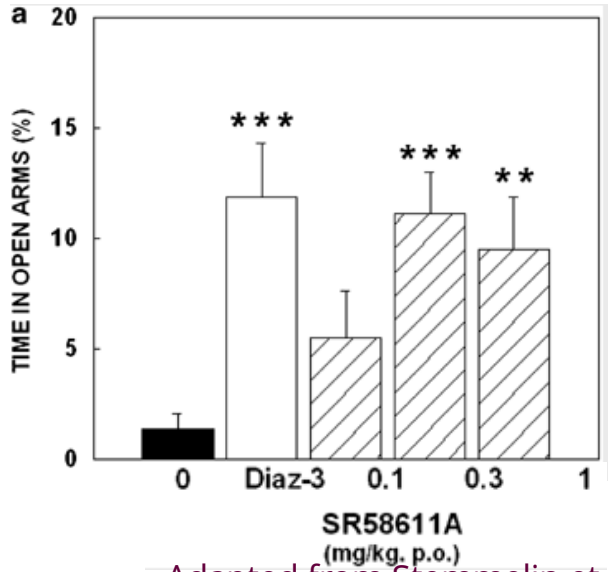


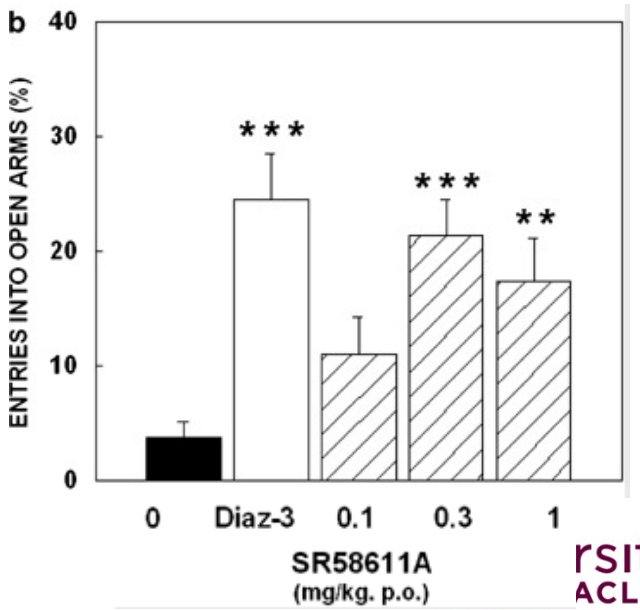
The Elevated Plus Maze

Anxio/depressive mouse

Anxio/depressive mouse treated Chronically with an antidepressant







Adapted from Stemmelin et al., 2008

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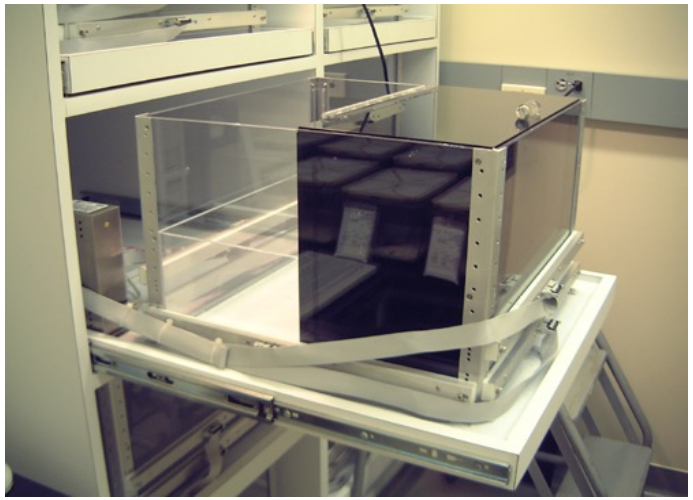
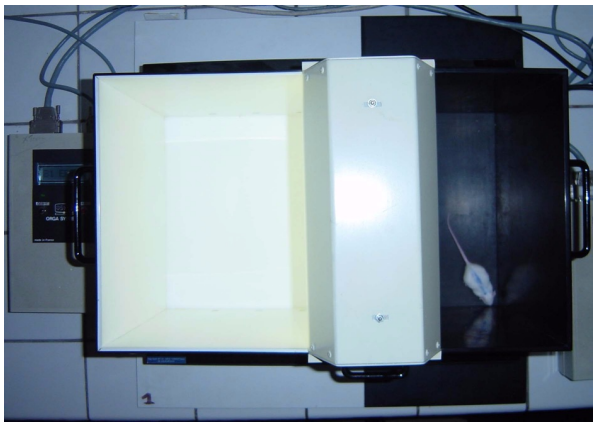
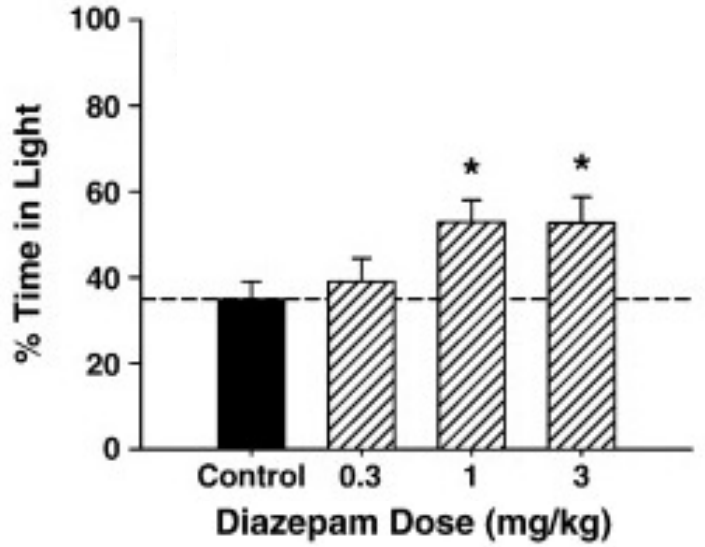
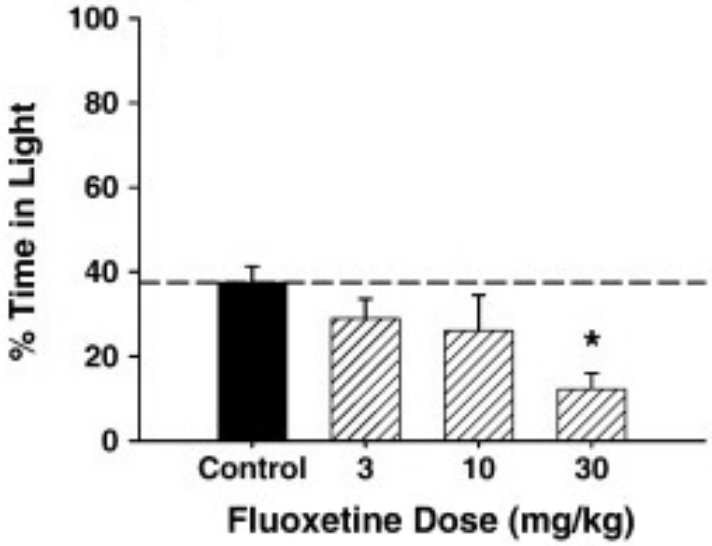
Predictive Tests of anxiolytic activity : The Light-Dark Case Test (Crawley et al 1981)



The Light-Dark Case Test







Adapted from Birkett et al., 2011

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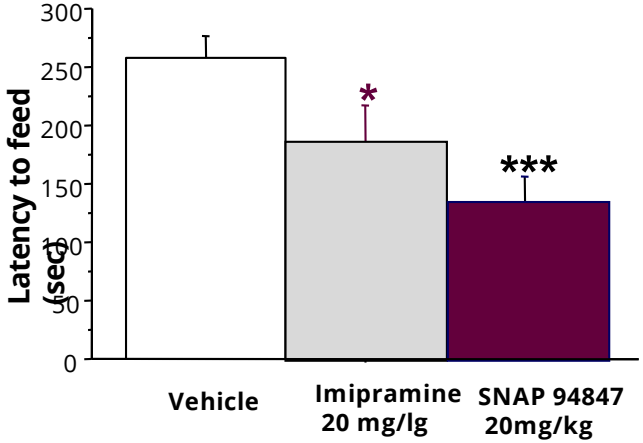
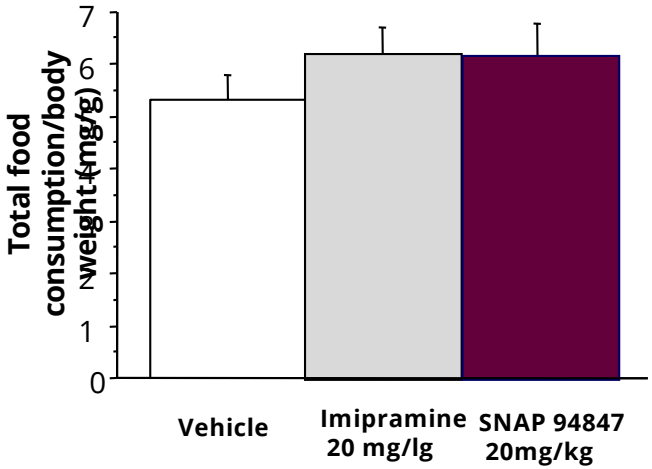
Predictive Tests of anxiolytic /antidepressive activity:
Le Novelty Suppressed Feeding (Santarelli et al., 2003)





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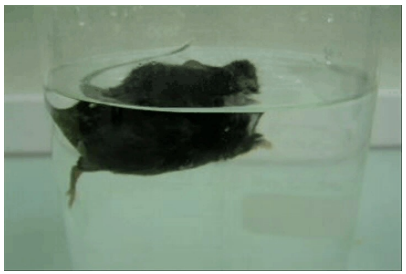
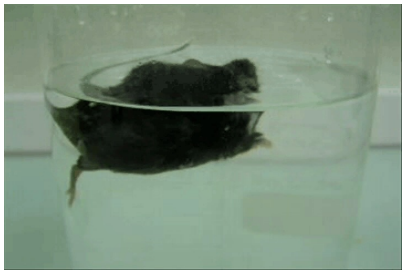
Predictive Tests of antidepressive activity:

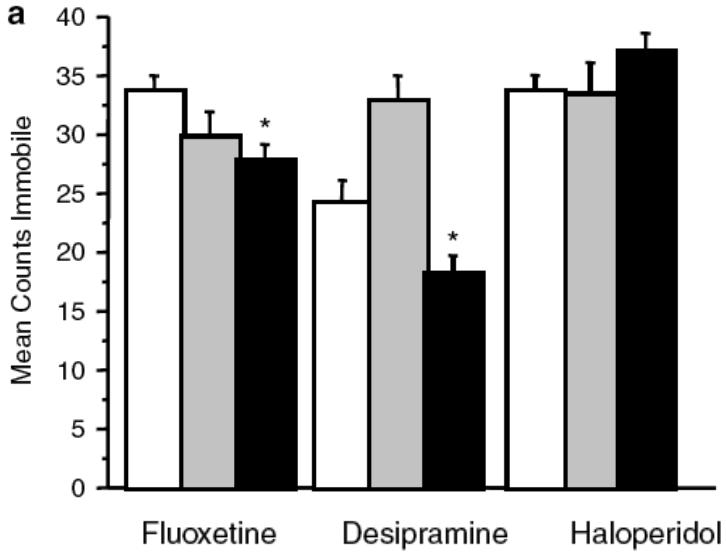
Forced Swim Test (Porsolt Test) (Porsolt et al., 1997)



Porsolt et al., 1977

Forced Swim Test: results

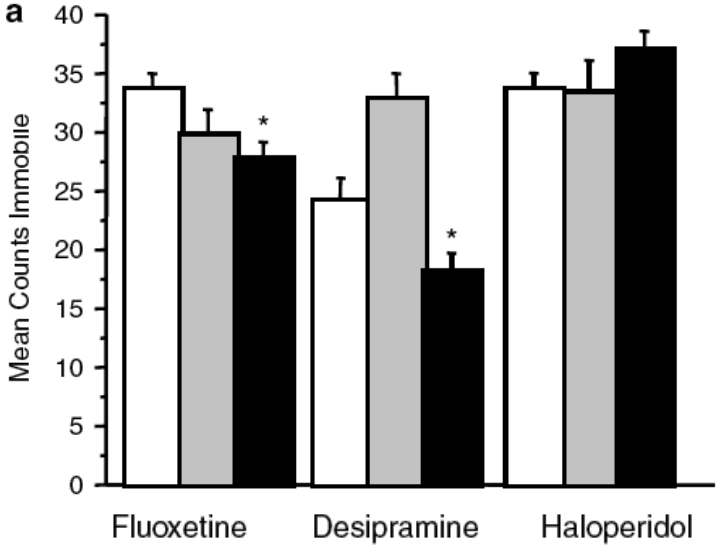


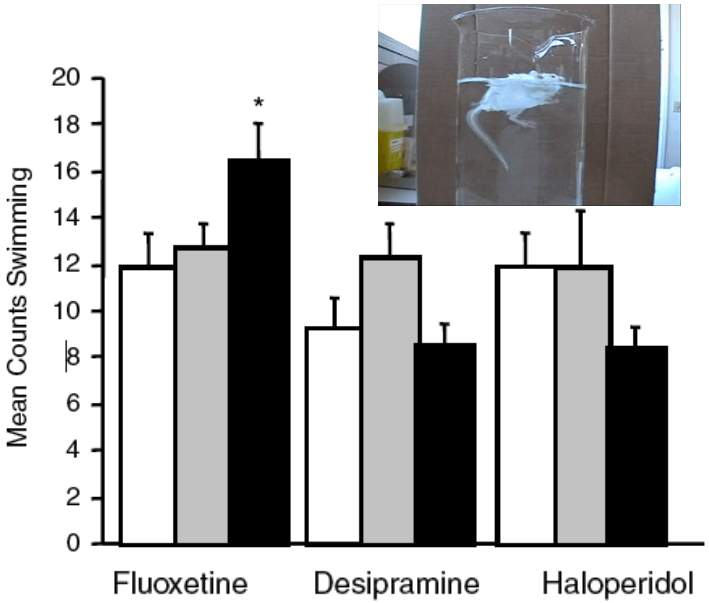


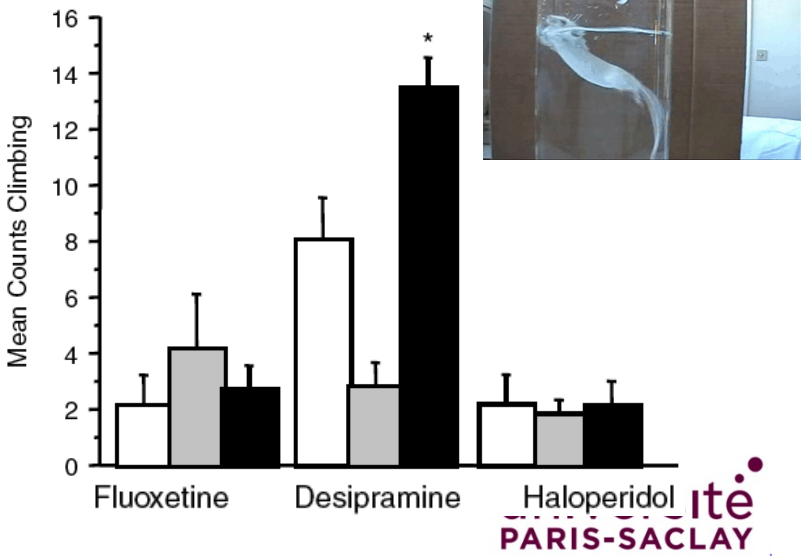
Adapted from Dulawa et al., 2004

Forced Swim Test: results

Adapted from Dulawa et al., 2004)







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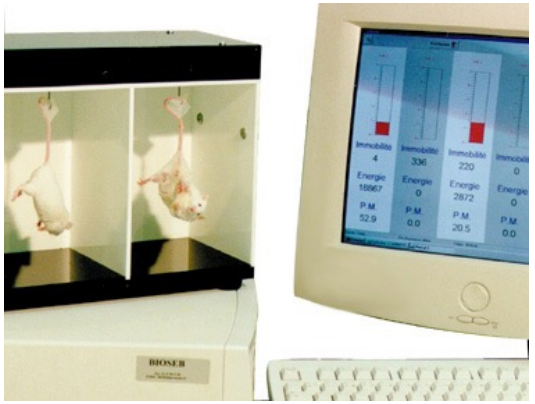
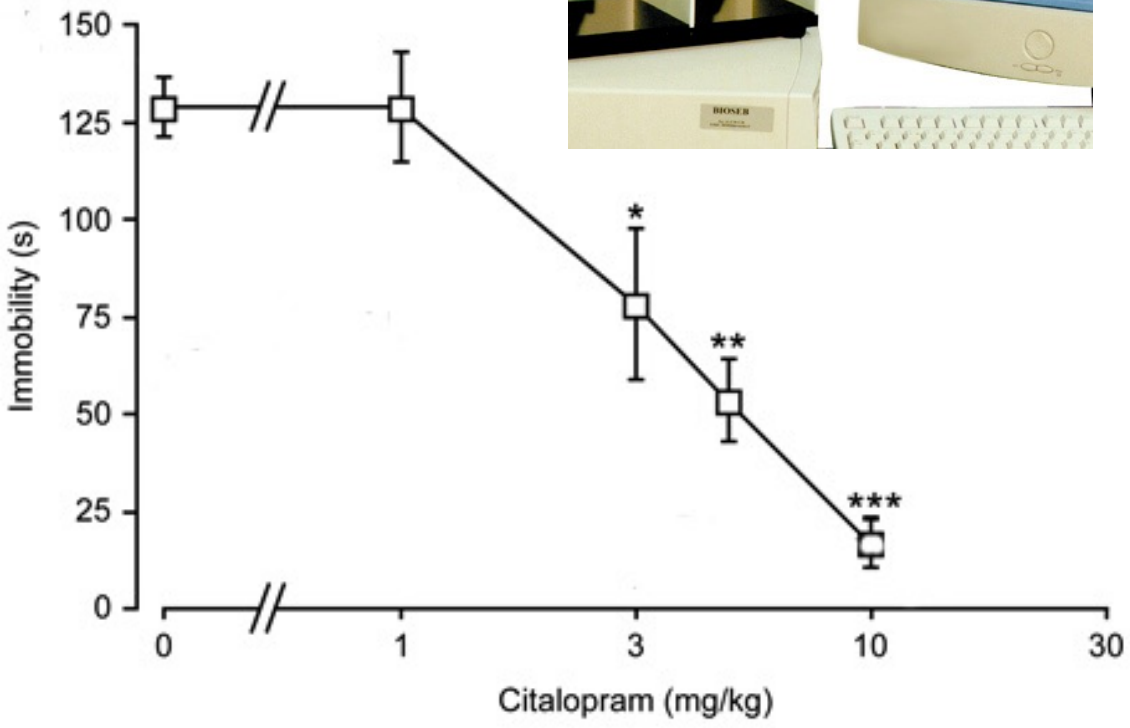
Predictive Tests of antidepressive activity:
Tail Suspension Test (Steru et al., 1985)



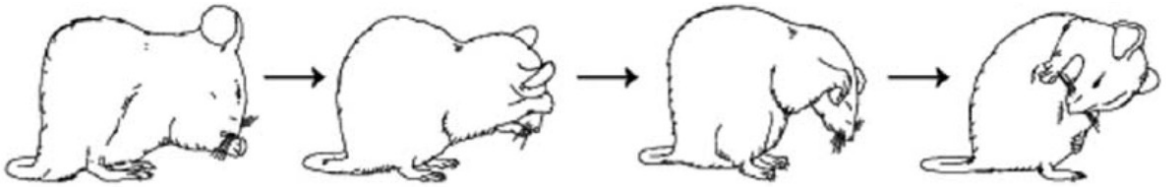


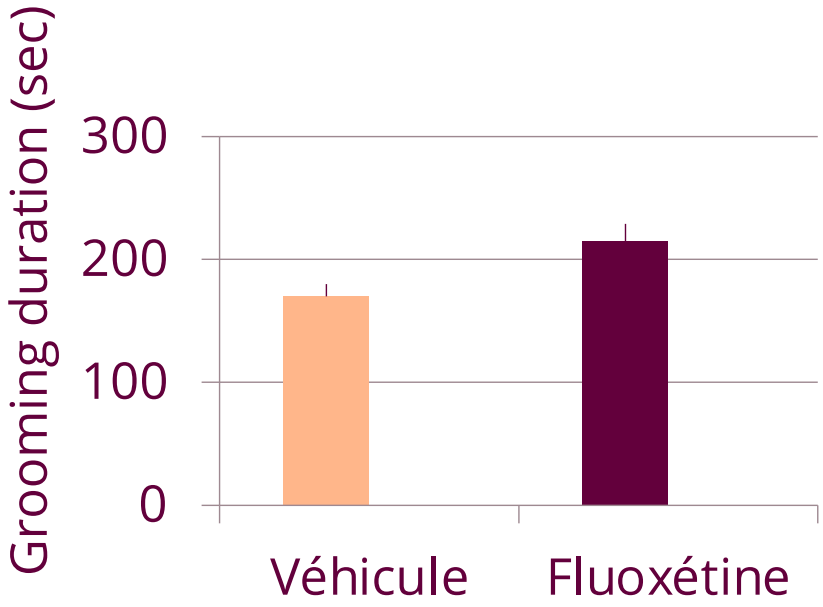
(Adapted from Sarkisyan et al., 2004)

Predictive Tests of antidepressive activity:

Splash Test: measure of the grooming activity

(David et al., 2009)





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To perform a screening protocol

- To choose the specie
- To choose the test
  - *Targeted screening vs. non-targeted screening*
  - Animal number
- To choose the reference (positive/negative control)
- Control group
- Way of administration
- Doses
- Acute vs. chronic administration

DSM V and Major depressive episodes

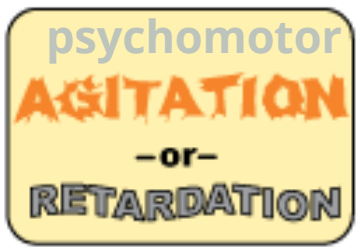
depressed mood

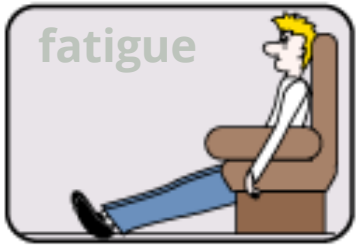
apathy/ loss of interest

one of these required

weight/ appetite changes

sleep disturbances





worthlessness

executive dysfunction

suicidal ideation

Four or more of these required

Stahl's Essential Psychopharmacology, 3rd edition, 2008

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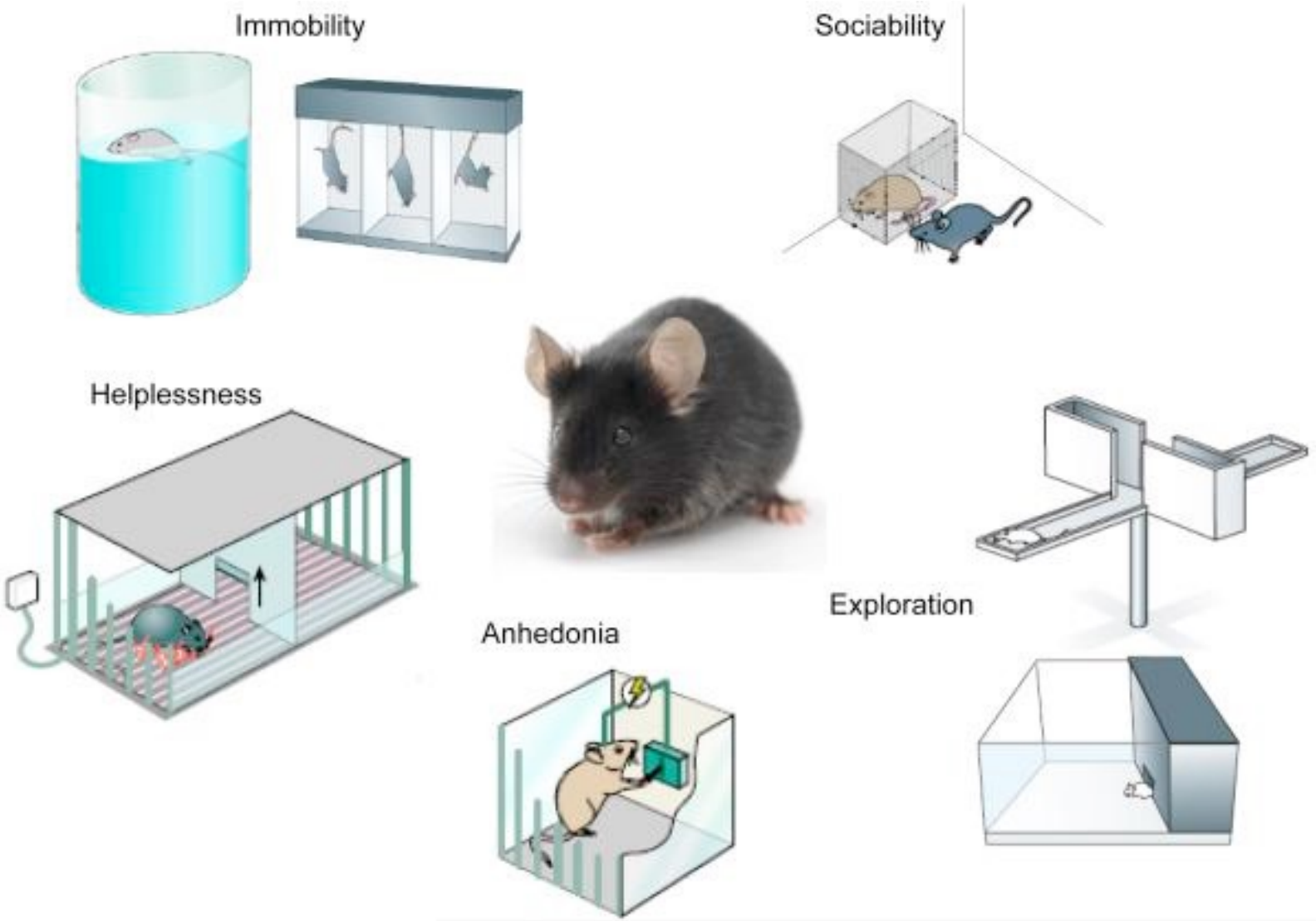
Endophenotype in the depression models

- Anhedonia
- Behavioral despair
- Changes in the feeding/the weight
- Neuroanatomical
- Endocrine changes
- Sleep alterations
- Anxious behavior

Etiological models of the depression



(D'après Krishnan et Nesler

The Unpredictible Chronic Stress

Start

3rd week

6th week

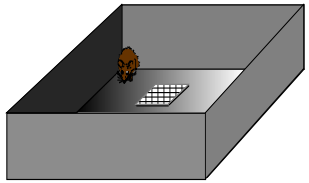
Treatment

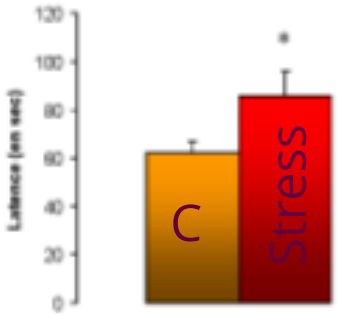
Unpredictible Chronique Stress

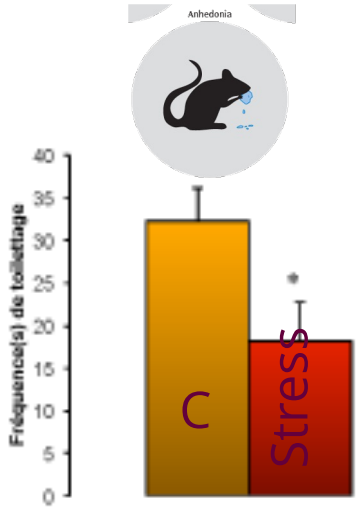
	Sun.	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.
Water Deprivation	1600 →	0800					
Continuous Illumination	1600 →	0800			1700 →	1000	
Cage Tilt		1100-1700					
Paired Housing	→	0800		1800 →	1400	1000	→
Damp Bedding					1700 →	1000	
Empty Water Bottle		0800-0900					
Strobe Light	1100-1600			1300-1500			
White Noise						1000-1300	
Sucrose Preference Test				1200-1300			

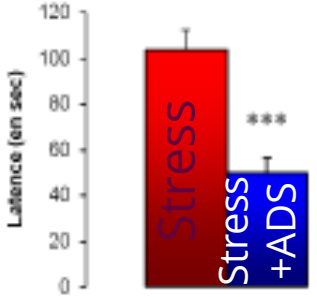
Adapted from Belzung, 2007

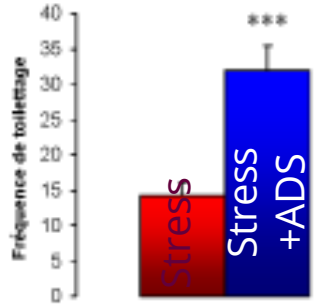
Chronic Mild Stress





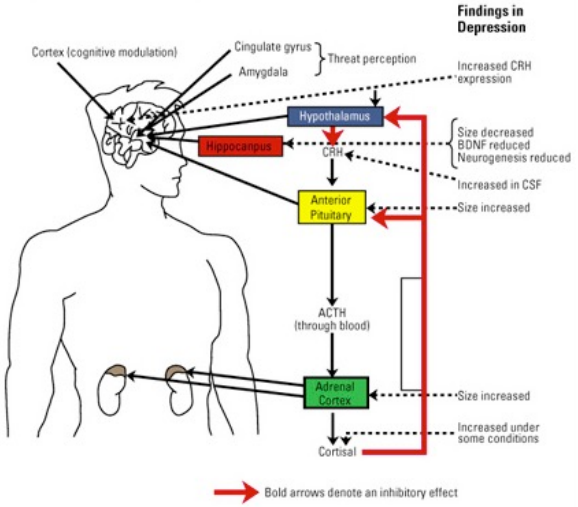






Belzung, 2007

Animal modelization of the depression

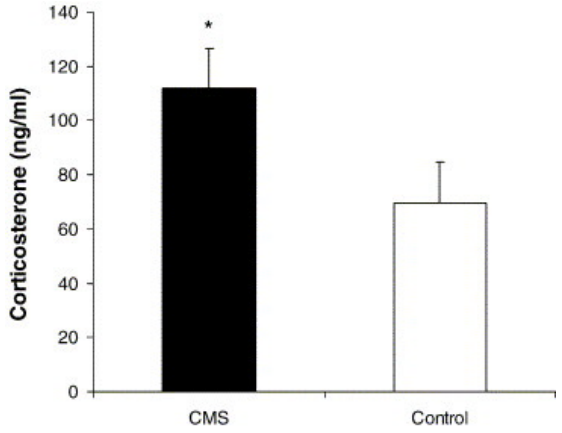


Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med.* 2008;358:55-68.

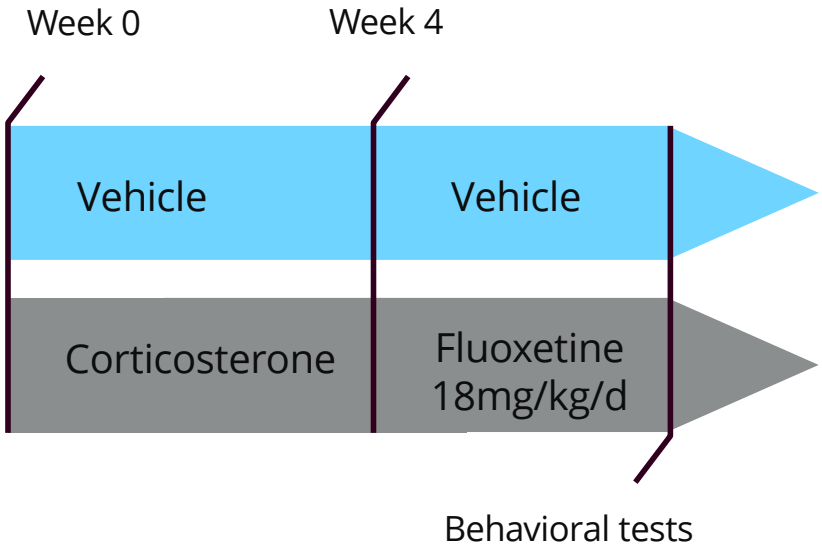
Carroll BJ, Cassidy F, Naftolowitz D, et al. Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand Suppl.* 2007;(433):90-103.

CRH=corticotropin-releasing hormone; BDNF=brain-derived neurotrophic factor; CSF=cerebrospinal fluid; ACTH=adrenocorticotropic hormone.

Belmaker RH. *CNS Spectr.* Vol 13, No 8. 2008.



CORT model: “anxio-depressive”



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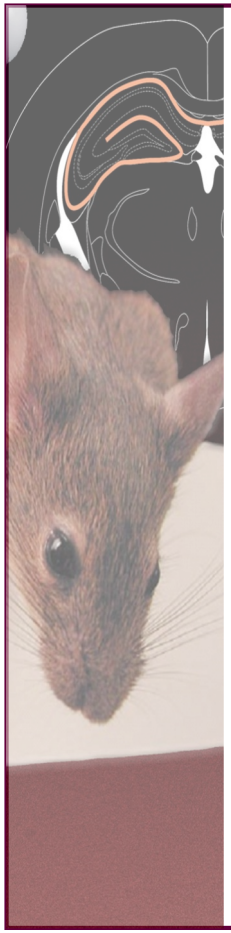
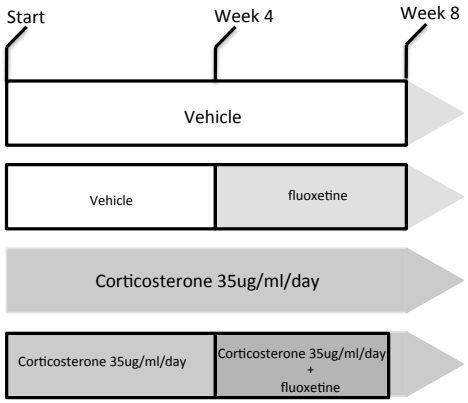
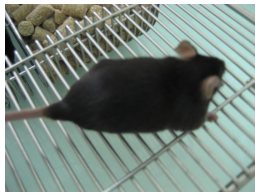
The CORT model

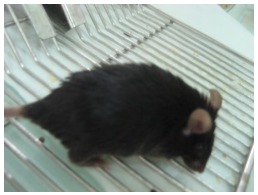


CORT model

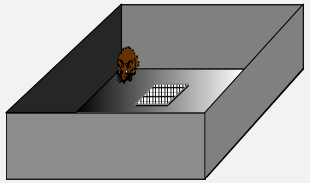


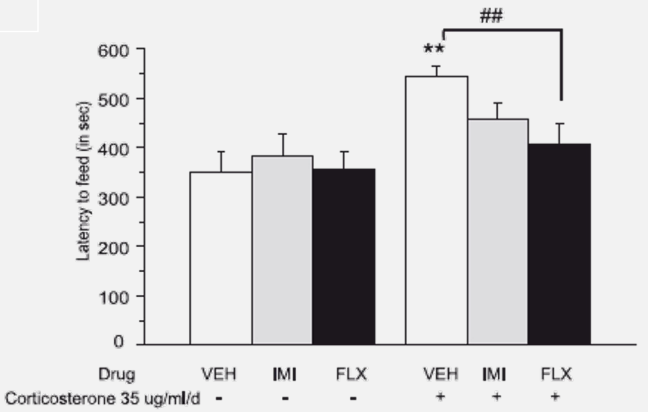


Control animal



Corticosterone–treated animal





Neuron

David, D. J., B. A. Samuels, et al. (2009). "Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression." Neuron 62(4): 479-493.

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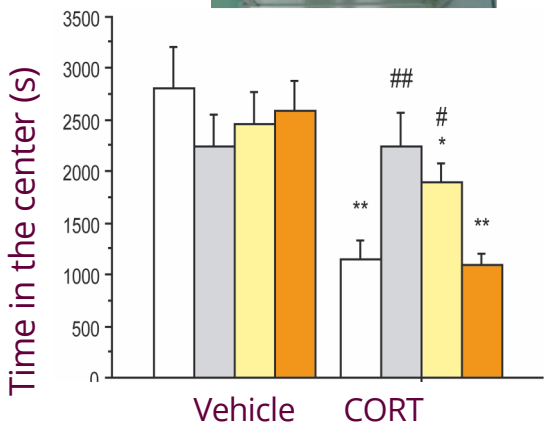
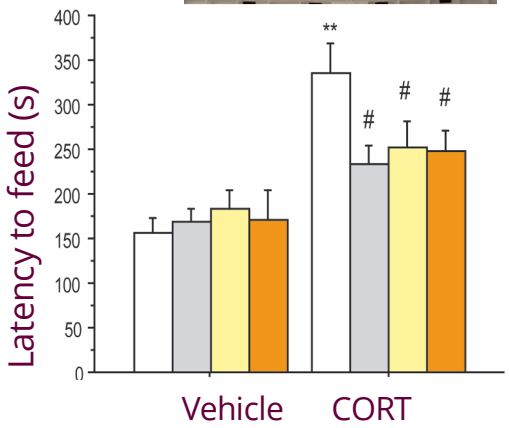
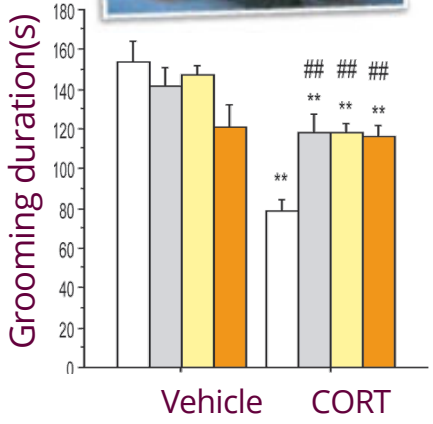
CORT model: results

Anxiety — Depression

Open field | NSF | Splash test







Vehicle | Fluoxetine 18 mg/kg/d | Agomelatine 10 mg/kg/d | Agomelatine 40 mg/kg/d

David et al (2009) Neuron; Rainer et al (2011) Int J Neuro

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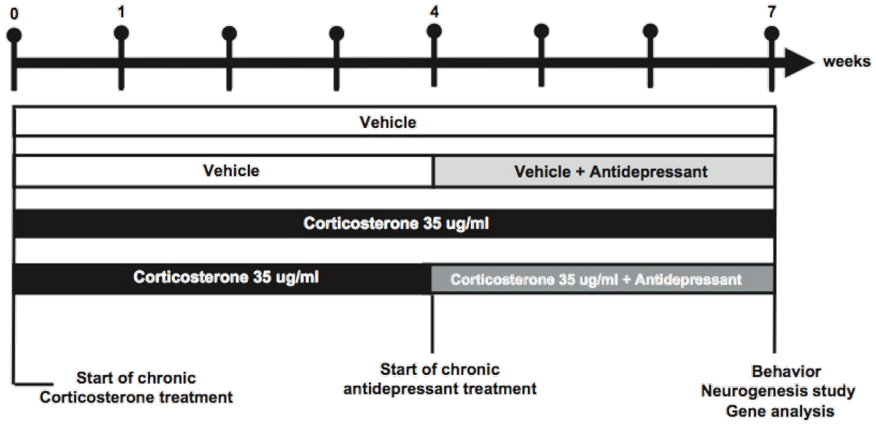
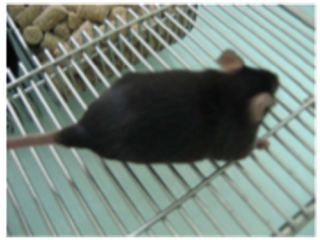
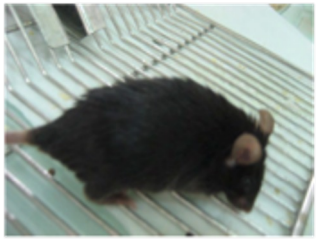
The CORT model



Vehicle-treated animal



Corticosterone-treated animal



Drugs	Pharmacological target	Phenotype	Neurogenic effects
Fluoxetine	Serotonin reuptake inhibitors	Reversed anxiogenic/depressive-like phenotype No effect on the flattened circadian rhythm induced by chronic corticosterone	Reversed the decrease in cell proliferation induced by chronic corticosterone Increased all steps of adult hippocampal neurogenesis For all neurogenic parameters in the hippocampus: effects more pronounced in corticosterone-treated mice
Imipramine	Tricyclics	Reversed anxiogenic/depressive-like phenotype	Not tested
Reboxetine	Norepinephrin reuptake inhibitors	Reversed anxiogenic/depressive-like phenotype	Not tested
Agomelatine	MT1/MT2 agonist and 5-HT2 C antagonist	Reversed anxiogenic/depressive-like phenotype Reversed the flattened circadian rhythm induced by chronic corticosterone	Reversed the decrease in cell proliferation induced by chronic corticosterone Reversed (ventral effects for maturation)

[1]David et al., 2009; Rainer et al., 2011; [2]Mendez-David et al., 2013

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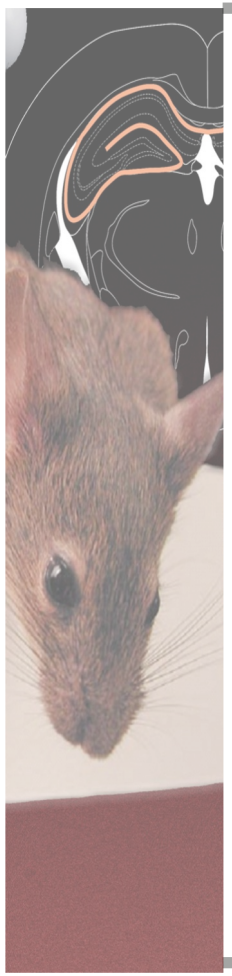
Animal Modelization of Anxiety and Depression



	Modèle CORT
Creative validity	++
Theoretical validity	+++
Predictive validity	+++
Reproducibility	+++

Neuron

David, D. J., B. A. Samuels, et al. (2009). "Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression." Neuron 62(4): 479-493.

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From clinic to pre-clinic

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

Patient Name _____ Today's Date _____

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

1. DEPRESSED MOOD
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0 = Absent
1 = Sadness, etc.
2 = Occasional weeping
3 = Frequent weeping
4 = Extreme symptoms

2. FEELINGS OF GUILT
0 = Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt
3 = Present illness is a punishment; delusions of guilt
4 = Hallucinations of guilt

3. SUICIDE
0 = Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead
3 = Suicidal ideas or gestures
4 = Attempts at suicide

4. INSOMNIA - Initial
(Difficulty in falling asleep)
0 = Absent
1 = Occasional
2 = Frequent

5. INSOMNIA - Middle
(Complains of being restless and disturbed during the night. Waking during the night.)
0 = Absent
1 = Occasional
2 = Frequent

6. INSOMNIA - Delayed
(Waking in early hours of the morning and unable to fall asleep again)
0 = Absent
1 = Occasional
2 = Frequent

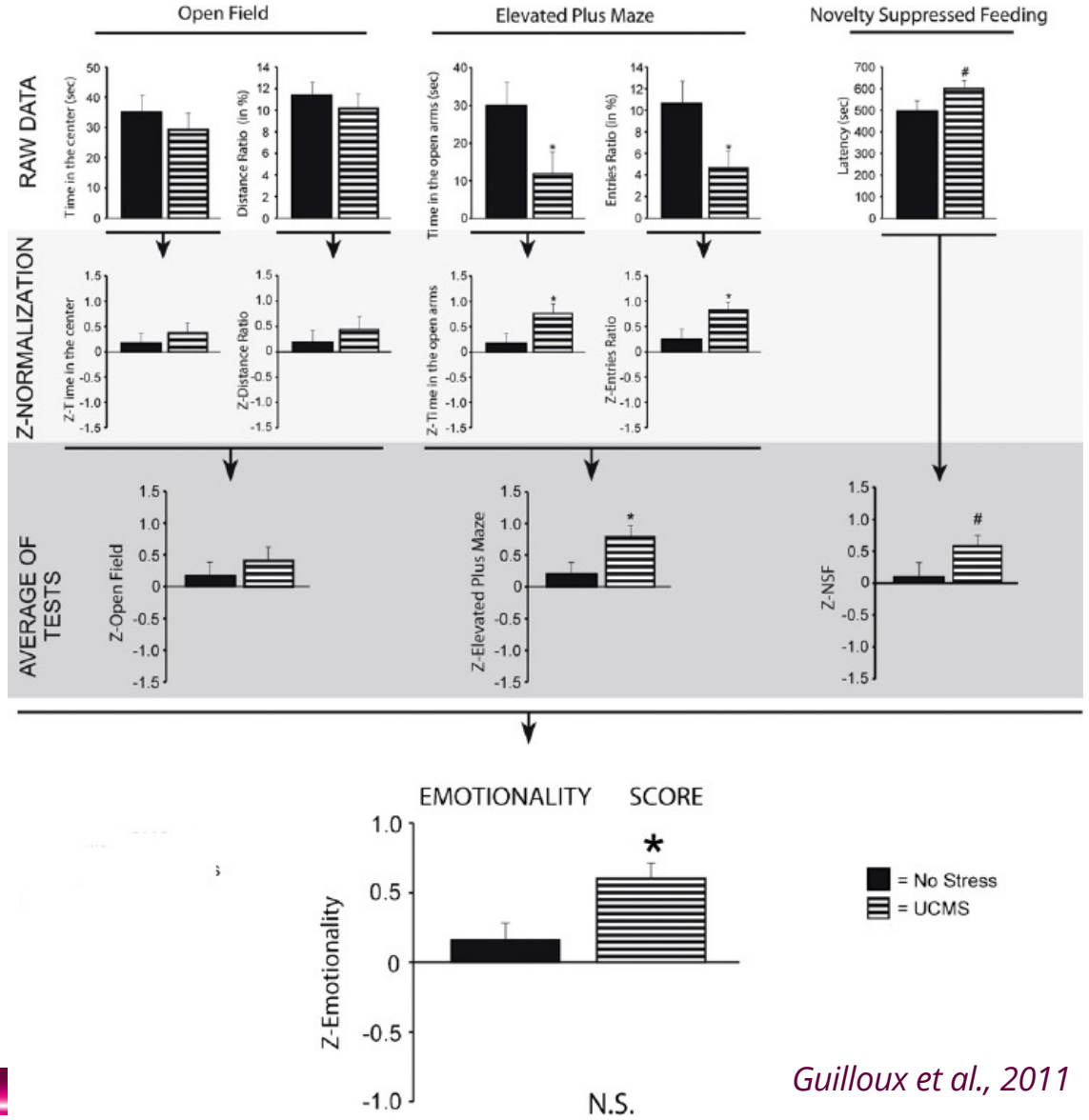
7. WORK AND INTERESTS
0 = No difficulty
1 = Feelings of incapacity, listlessness, indecision and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

8. RETARDATION
(Slowness of thought, speech, and activity; apathy; stupor.)
0 = Absent
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

9. AGITATION
(Restlessness associated with anxiety.)
0 = Absent
1 = Occasional
2 = Frequent

10. ANXIETY - PSYCHIC
0 = No difficulty
1 = Tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude
4 = Fears

TOTAL ITEMS 1 TO 17: _____
0 - 7 = Normal
8 - 13 = Mild Depression
14-18 = Moderate Depression
19 - 22 = Severe Depression
≥ 23 = Very Severe Depression



Guilloux et al., 2011

Conclusions (I)

- A variety of models
- Models depending of species particularities
- Produce many scientific datas useful for the human pathologies
- Limits in the interpretation as well as for the human transposition

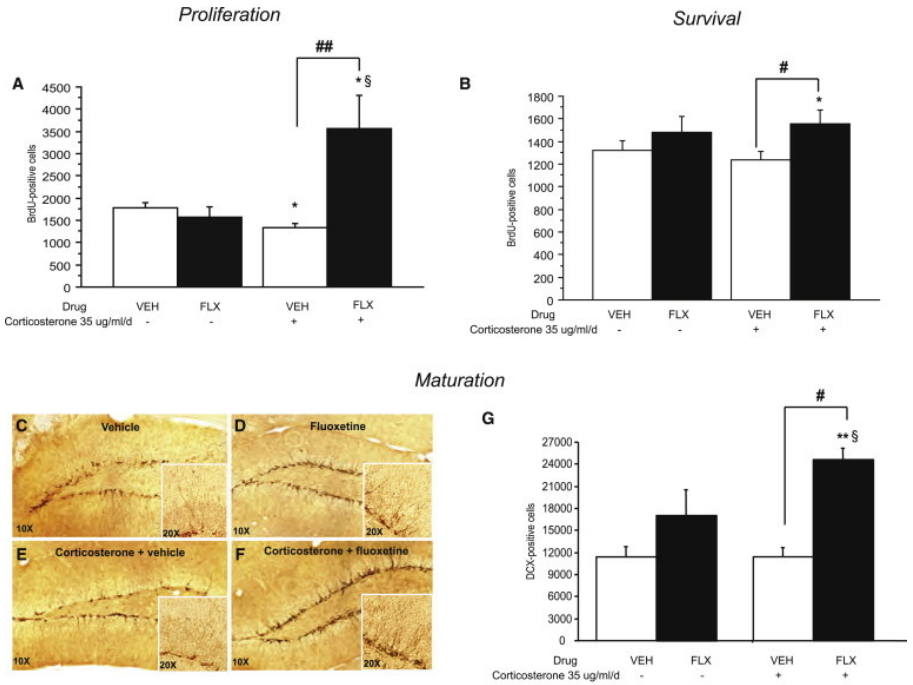
Conclusions (II)

II- Theoretical validity

- Several models can predict the effectiveness of a treatment (predictive validity)

- The mechanisms involved in the models and in humans must be evaluated

Theoretical validity : the example of the adult hippocampal neurogenesis



Adapted from David, al., (2009)

CORT model

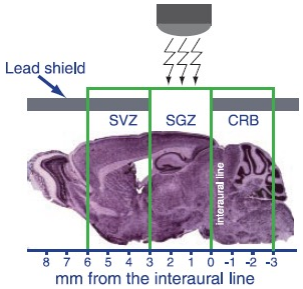
↓ Fluoxetine

↗ all the steps of AHN

↓

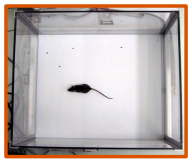
Consequences ???

Theoretical validity : the example of the adult hippocampal neurogenesis

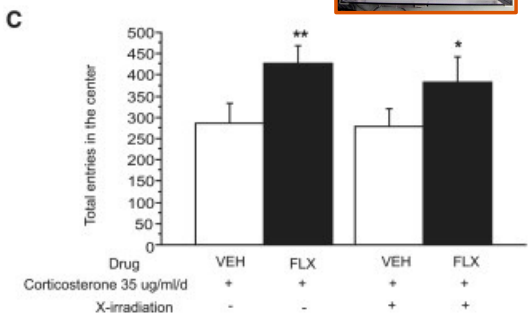


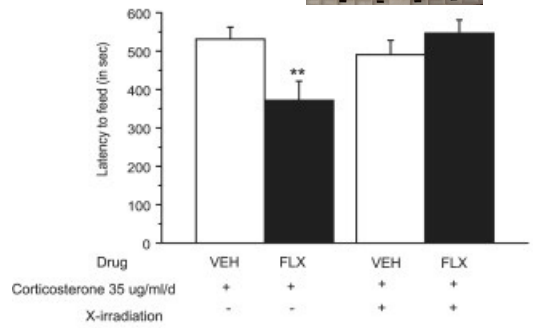
X ray irradiation to suppress the AHN

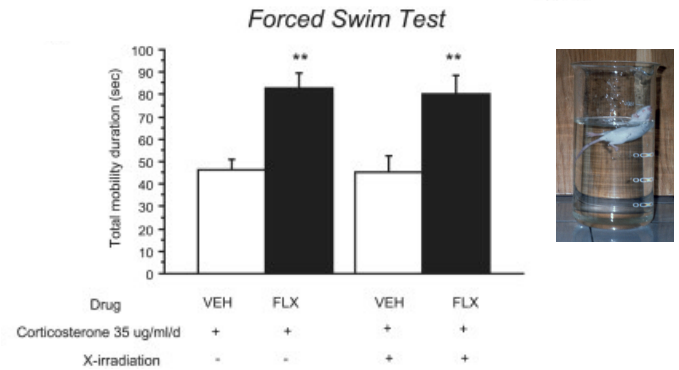
Openfield



NSF







Adapted from David, al., (2009)

CORT model

↓ Fluoxetine

↗ all the steps of AHN

↓

Behavioral effect (NSF)

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Theoretical validity : the example of the adult hippocampal neurogenesis : clinical data

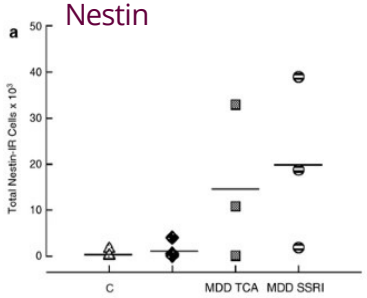
Neuropsychopharmacology (2009) 34, 2376–2389

www.neuropsychopharmacology.org

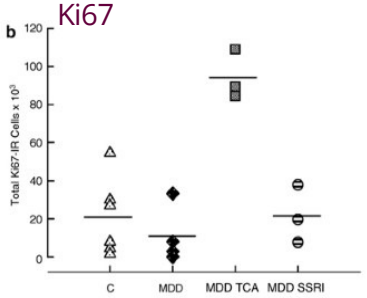
Antidepressants increase neural progenitor cells in the human hippocampus

Maura Boldrini[*1,2,3], Mark D Underwood[1,2], René Hen[1,4,5,6], Gorazd B Rosoklija[1,2,7], Andrew J Dwork[1,2,8], J John Mann[1,2] and Victoria Arango[1,2]

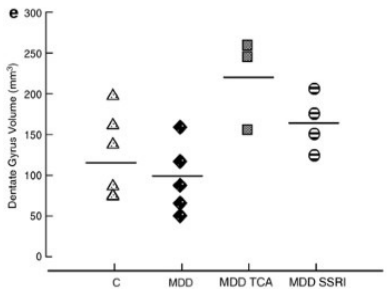
Nestin



Ki67



DG volume



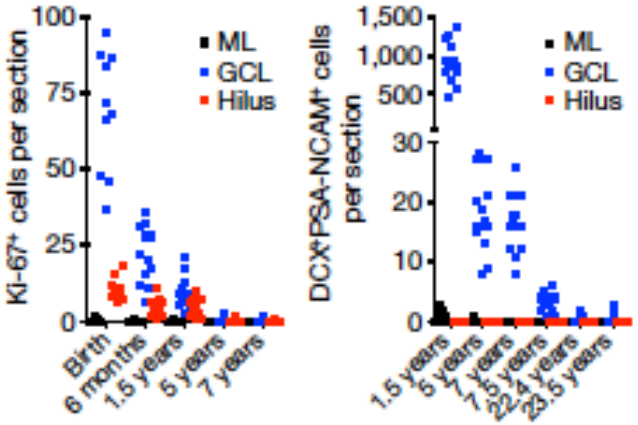
Controversy…

LETTER

doi:10.1038/nature25975

Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults

Shawn F. Sorrells[1,2*], Mercedes F. Paredes[1,3*], Arantxa Cebrian-Silla[4], Kadellyn Sandoval[1,3], Dashi Qi[5], Kevin W. Kelley[1], David James[1], Simone Mayer[1,3], Julia Chang[6], Kurtis I. Auguste[2], Edward F. Chang[2], Antonio J. Gutierrez[7], Arnold R. Kriegstein[1,3], Gary W. Mathern[8,9], Michael C. Oldham[1,2], Eric J. Huang[10], Jose Manuel Garcia-Verdugo[4], Zhengang Yang[5] & Arturo Alvarez-Buylla[1,2]



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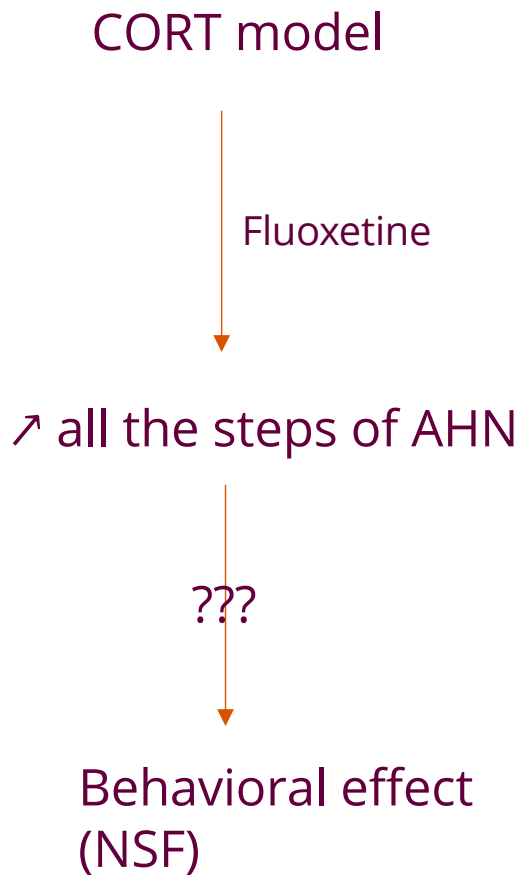
Theoretical validity : the example of the adult hippocampal neurogenesis : a way to go further in the mechanistic understanding



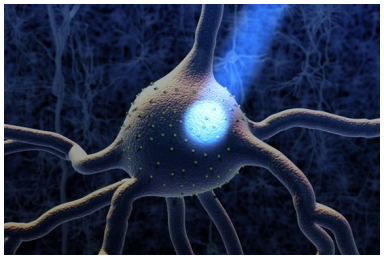
Theoretical validity : the example of the adult hippocampal neurogenesis : a way to go further in the mechanistic understanding

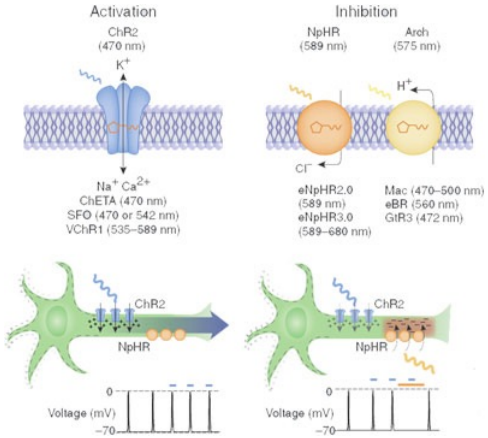
Manipulating the activity of adult born granule cells

optogenetics

Anatomical acuracy

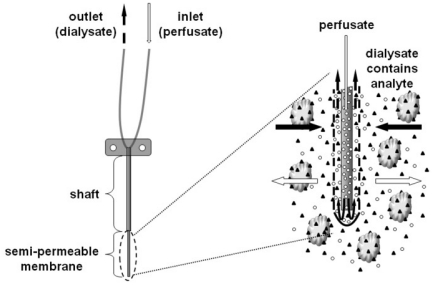
Selectivity for the cell type
(targeting 4 to 6-weeks-old cells)

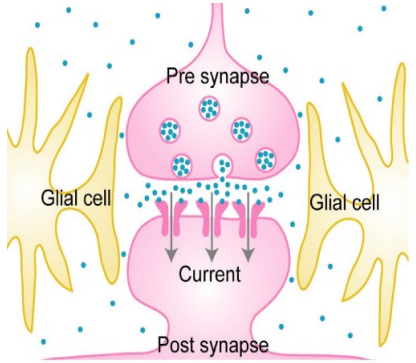




Neurochemical consequences

microdialysis





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Theoretical validity : the example of the adult hippocampal neurogenesis : a way to go further in the mechanistic understanding

Young neurons stimulation

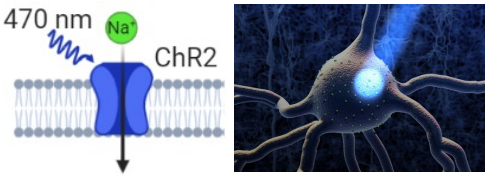
ChR2-YFP

STOP ChR2-YFP

Lox P Lox P

Tamoxifene-induced recombination

Nestine-ChR2-YFP



Nestine-CreER^{T2}

Nestine CreER^{T2}

Specific expression in young neurons

Young neurons inhibition

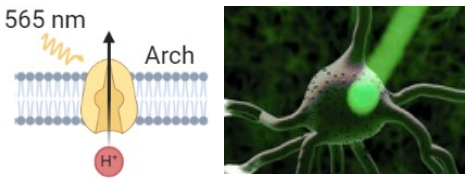
Arch-GFP

STOP Arch-GFP

Lox P Lox P

Tamoxifene-induced recombination

Nestine-Arch-GFP



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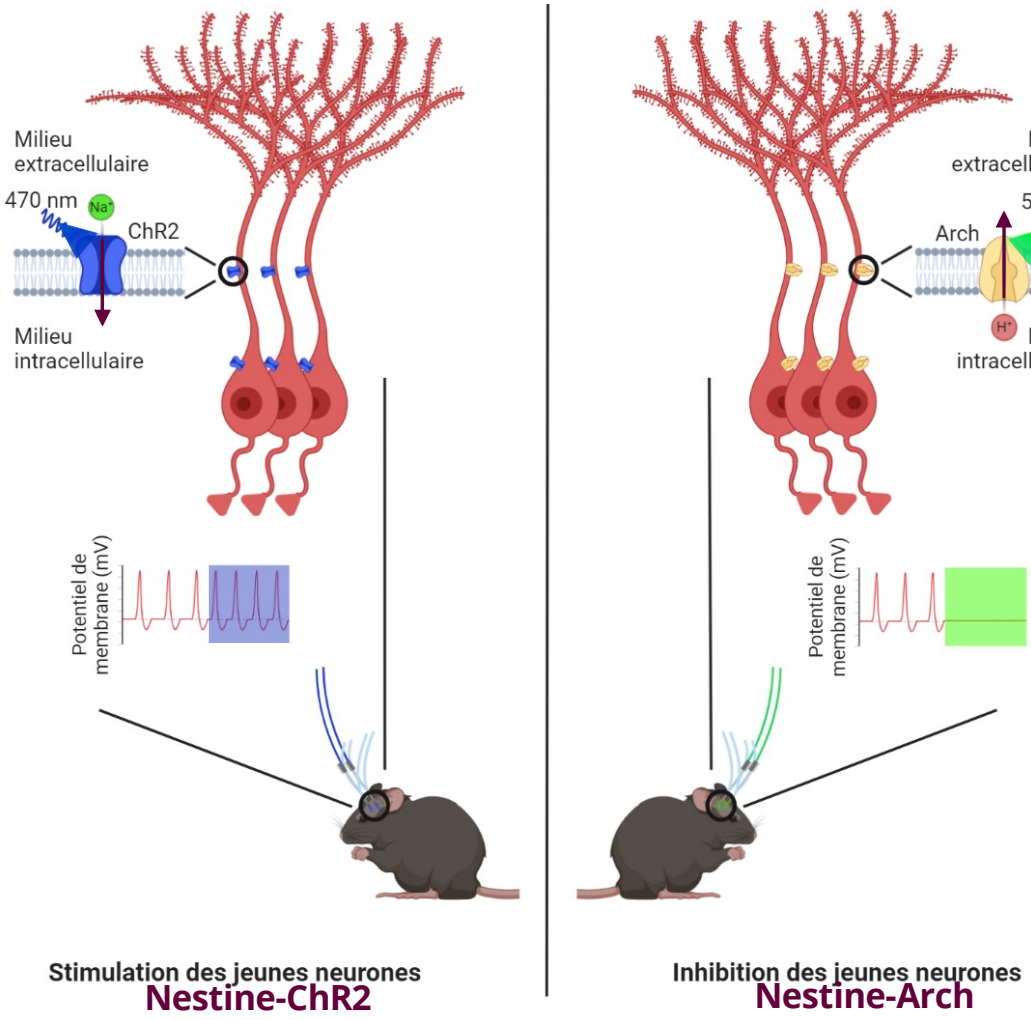
Theoretical validity : the example of the adult hippocampal neurogenesis : a way to go further in the mechanistic understanding

473 nm
20 mW
20 ms 10 Hz



Stimulation des jeunes neurones
Nestine-ChR2

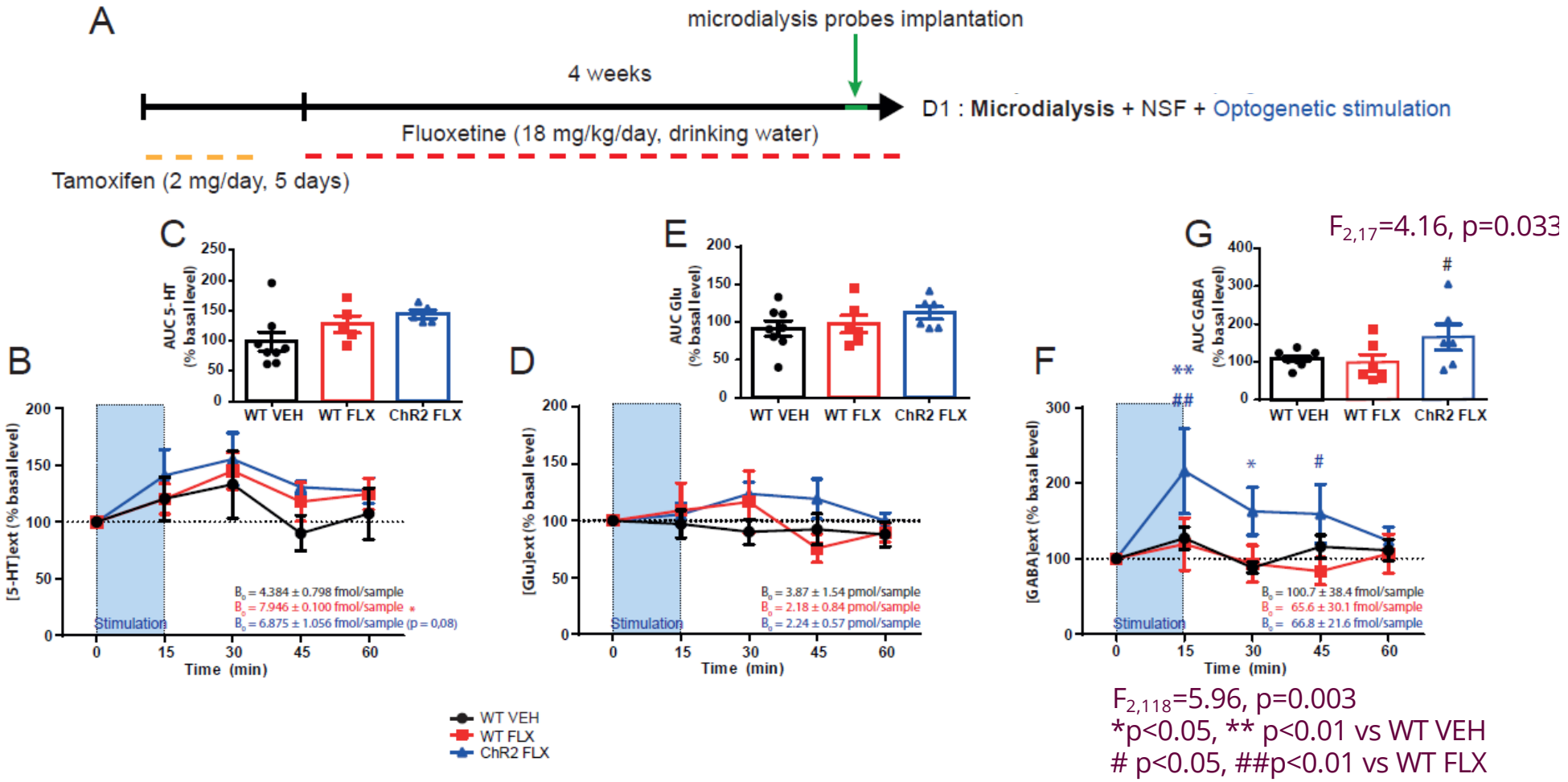
Inhibition des jeunes neurones
Nestine-Arch

532 nm
10 mW
en continu

Drew et al., 2016 ; Faye et al., 2020

Danielson et al., 2016 ; Faye et al., 2020

Theoretical validity : the example of the adult hippocampal neurogenesis : a way to go further in the mechanistic understanding



Adult-born Granule cells stimulation increases the GABA transmission in the DG

To take home :

Animal models: creative predictivity and theorical predictivity need to be taken into consideration

Several models in several tests are necessary

If « one mouse in no mouse » then you should apply the same « rule » for the models and the tests