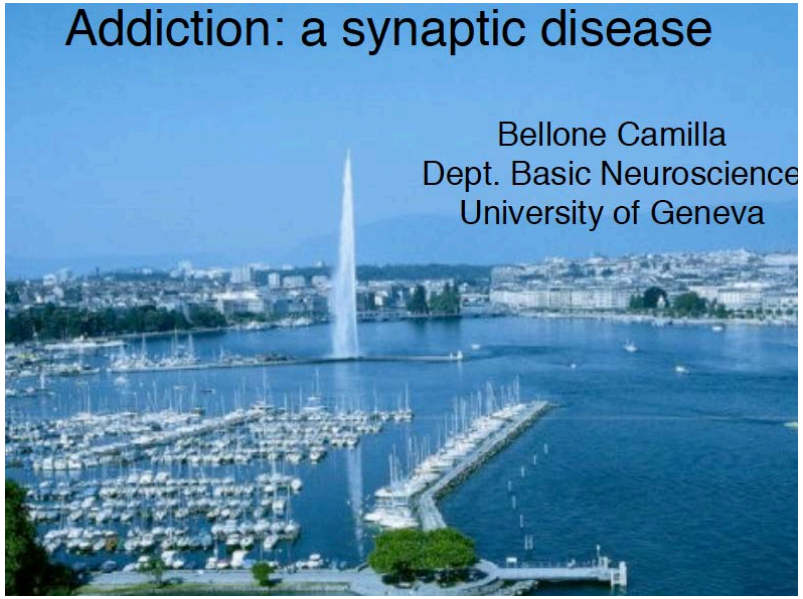
Addiction: a synaptic disease



Bellone Camilla
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Définitions

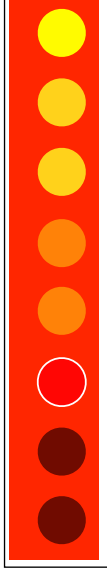
- **Addiction**: consommation compulsive en dépit de toutes conséquences négatives
- **Dépendance**: survenu d'un syndrome de sevrage à l'arrêt brusque de la drogue

Maladies du cerveau en Europe

EBC European Brain Council 2006	Cas en millions	**Coûts Mia€/an**
Dépression	21	**104**
Addiction (sans nicotine)	9	**57**
Demence (Alzheimer)	5	**55**
Troubles anxieux	41	**41**
Schizophrénie	3.5	**35**
Migraine	41	**27**
AVC	1	**22**
Epilepsie	3	**15**
Maladie de Parkinson	1.2	**11**

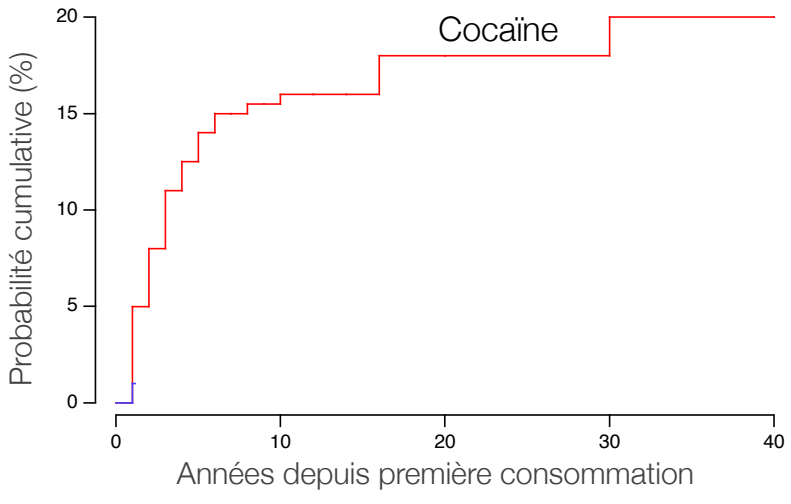
Risque relatif d'addiction

Goldstein & Kalant, Science 1990



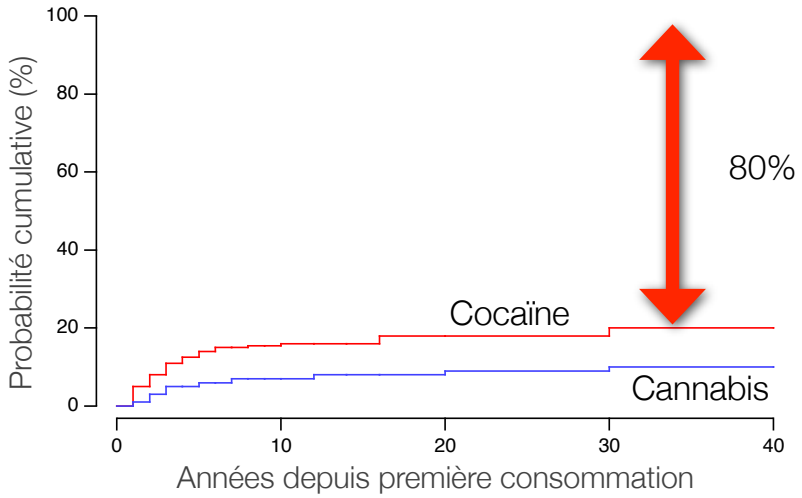
Hallucinogènes (LSD)	1
Cannabis (THC)	2
Benzodiazépines (BDZ)	2
Alcool	3
Nicotine	3
Opiacés (Morphine, Héroïne)	4
Amphétamines	5
Cocaïne	5

Addiction vs. consommation



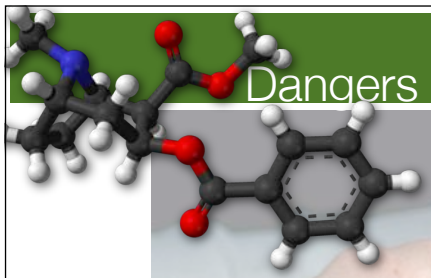
Wagner & Anthony, Neuropsychopharmacology, 2002

Addiction vs. consommation récréative



Wagner & Anthony, Neuropsychopharmacology, 2002

Dangers de la cocaïne



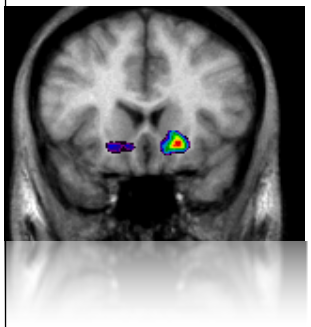
- Pression sanguine ↑↑
- Infarctus du myocarde
- Arythmie cardiaque
- Hémorragie cérébrale
- Addiction

Vulnérabilité individuelle ?


Cocaine
Morphine
Nicotine
Gambling
Chocolate
Addiction

Activation of the ventral striatum

Drugs

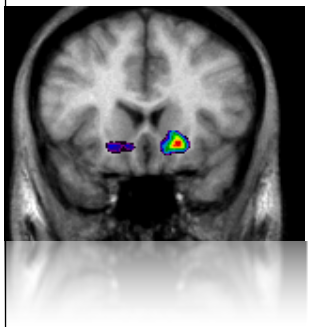


e.g.Amphetamines

Leyton et al., 2002

Activation of the ventral striatum

Drugs



e.g.Amphetamines

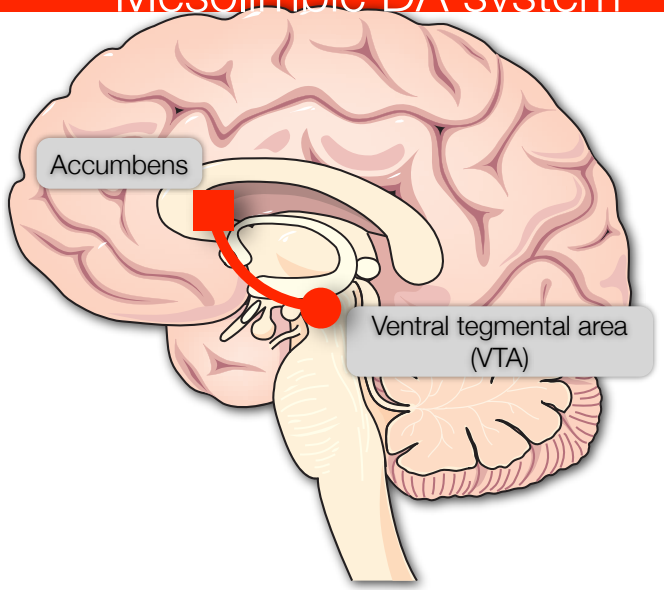
Leyton et al., 2002

Gambling

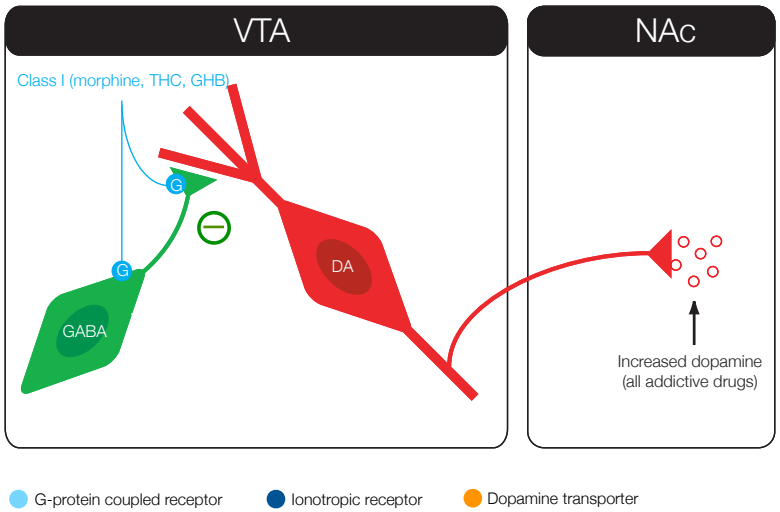
e.g.Poker

Boileau et al., 2003

Mesolimbic DA system

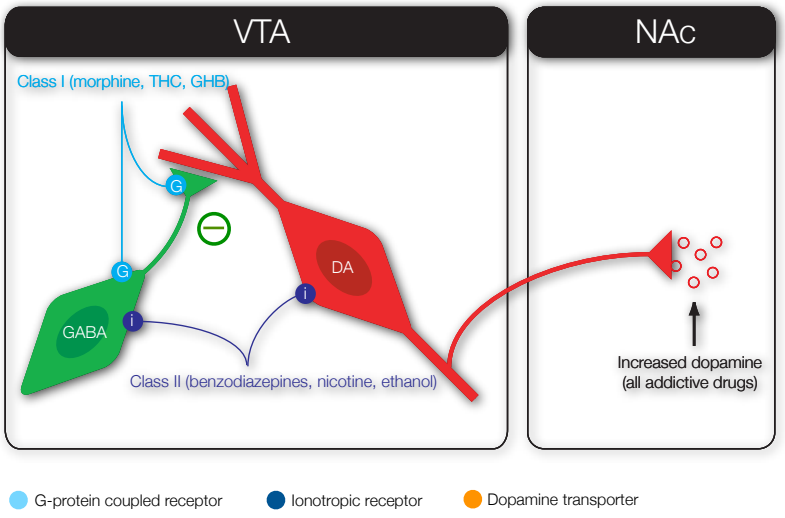


Ventral tegmental area



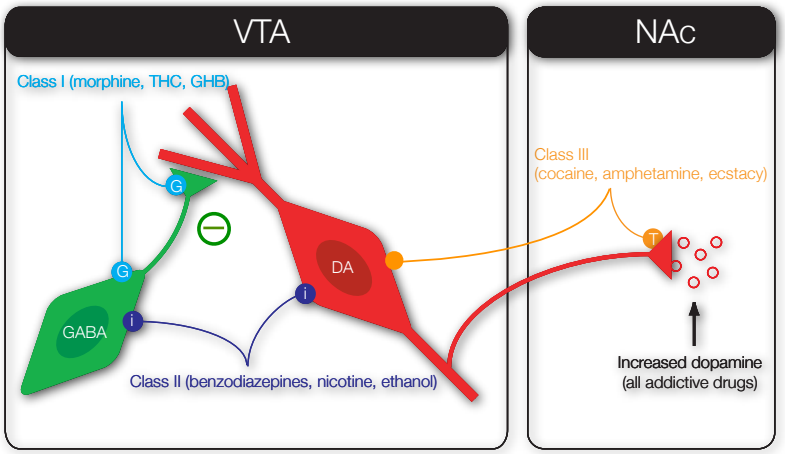
Lüscher & Ungless, PLoS, 2006

Ventral tegmental area



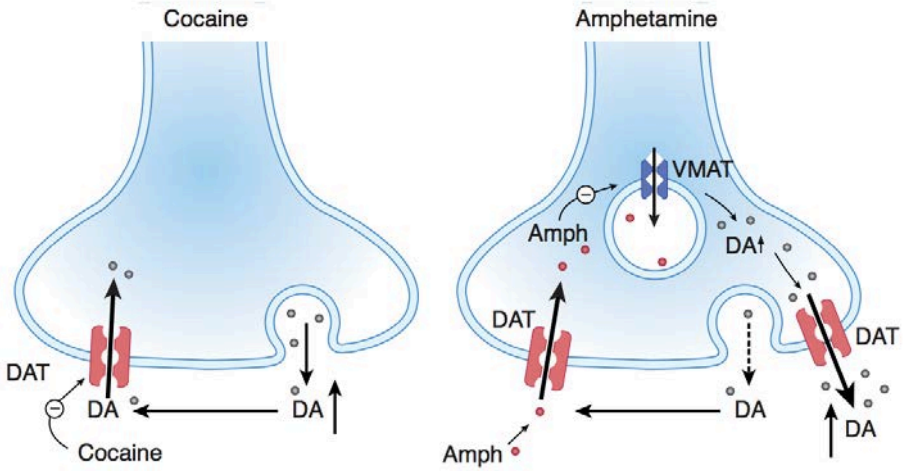
Lüscher & Ungless, PLoS, 2006

Ventral tegmental area



Lüscher & Ungless, PLoS, 2006

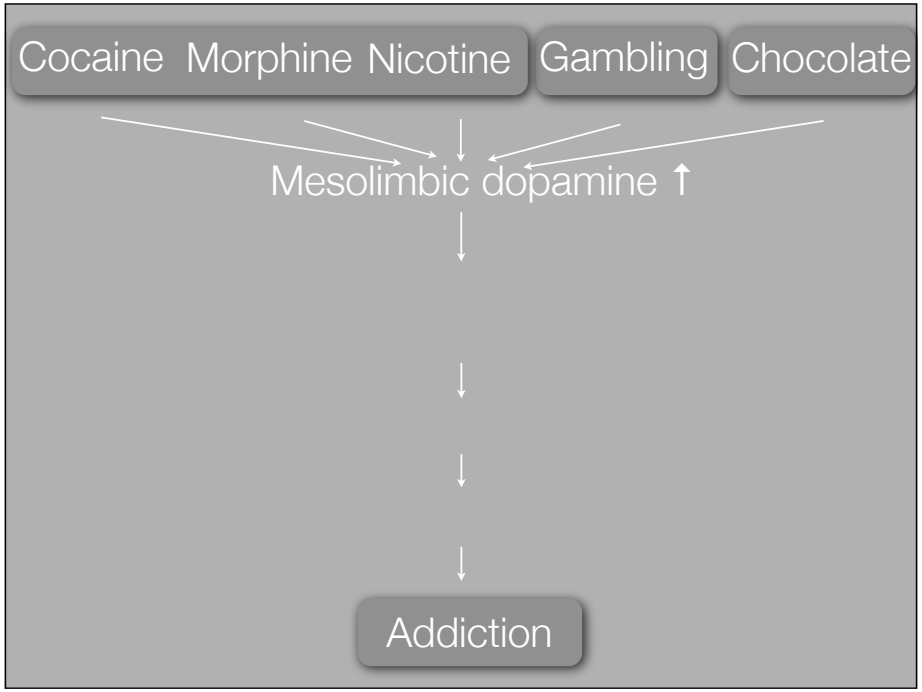
Classe III-drogues



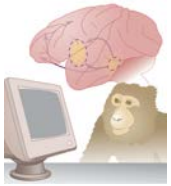
Mechanistic classification

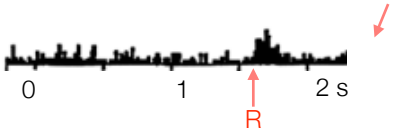
Class I: Drugs that activate G protein coupled receptors				
Name	Main molecular target	Pharmacology	Effect on dopamine neurons	RR
Opioids	μ-OR ($G_{i/o}$)	agonist	disinhibition	4
Cannabinoids	CB1R ($G_{i/o}$)	agonist	disinhibition	2
γ-hydroxy butyric acid (GHB)	$GABA_BR$ ($G_{i/o}$)	weak agonist	disinhibition	NA
LSD, Mescaline, Psilocybin	$5\text{-}HT_{1A}R$ ($G_{i/o}$)	partial agonist	-	↑
Class II: Drugs that bind to ionotropic receptors and ion channels				
Name	Main molecular target	Pharmacology	Effect on dopamine neurons	RR
Nicotine	nAChR ($\alpha4\beta2$)	agonist	excitation, disinhibition, modulates release	4
Alcohol	$GABA_AR$, $5\text{-}HT_3R$, nAChR, , NMDAR, K_v3 channels		excitation	3
Benzodiazepines	$GABA_AR$	positive modulator	disinhibition	3
Phencyclidine, Ketamine	NMDAR	antagonist	disinhibition (?)	↑
Class III: Drugs that bind to transporters of biogenic amines				
Name	Main molecular target	Pharmacology	Effect on dopamine neurons	RR
Cocaine	DAT, SERT and NET	inhibitor	blocks DA uptake	5
Amphetamine	DAT, NET and SERT, VMAT	reverses transport	blocks DA uptake, synaptic depletion, excitation	5
Ecstasy	SERT > DAT, NET	reverses transport	blocks DA uptake, synaptic depletion	NA

Lüscher and Ungless, PLOS Med, 2006


Cocaine
Morphine
Nicotine
Gambling
Chocolate
Mesolimbic dopamine ↑
Addiction

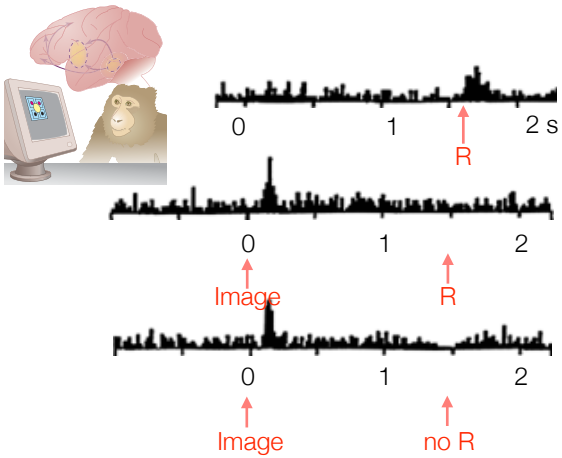
Prediction error



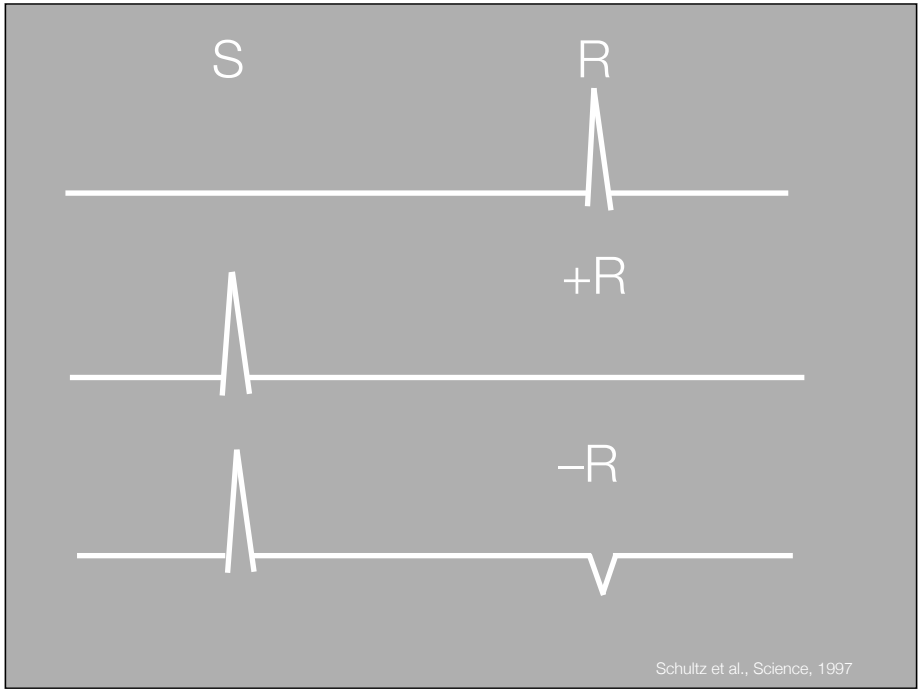


Schultz et al., Science 1997

Prediction error



Schultz et al., Science 1997


S
R
+R
–R
Schultz et al., Science, 1997

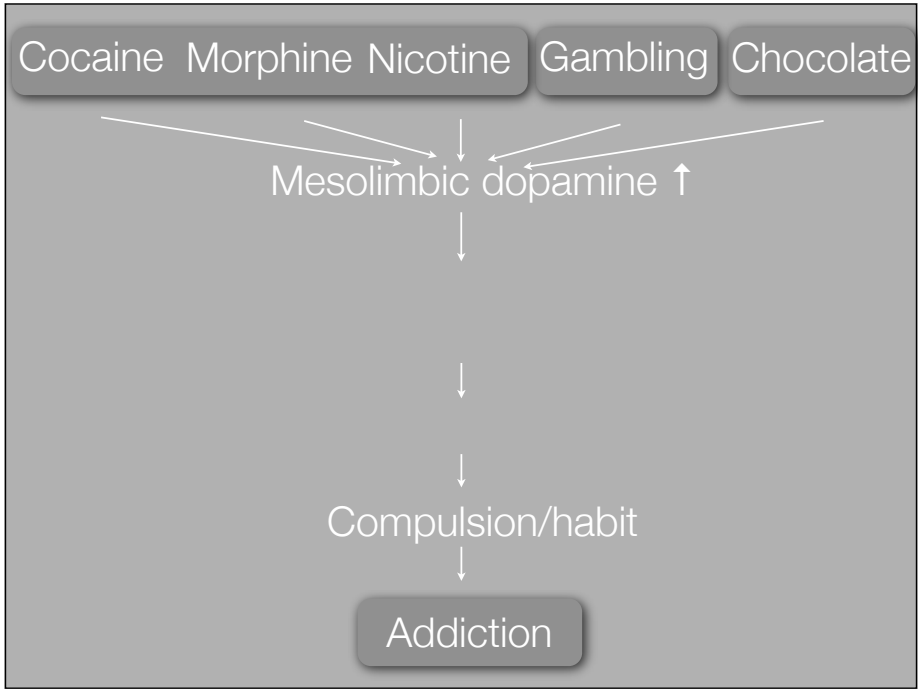
Addiction

Initiation | Repeated Consumption | Addiction

Context | **« Pleasure »** | **Automatisation/Habit**

Planned decision → Automatic decision/ Habit

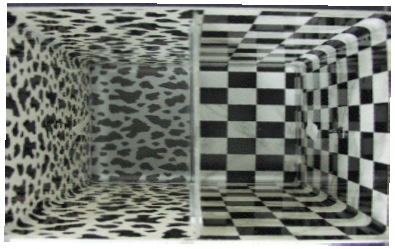
dopamine


Cocaine
Morphine
Nicotine
Gambling
Chocolate
Mesolimbic dopamine ↑
Compulsion/habit
Addiction

Animal models to study addiction

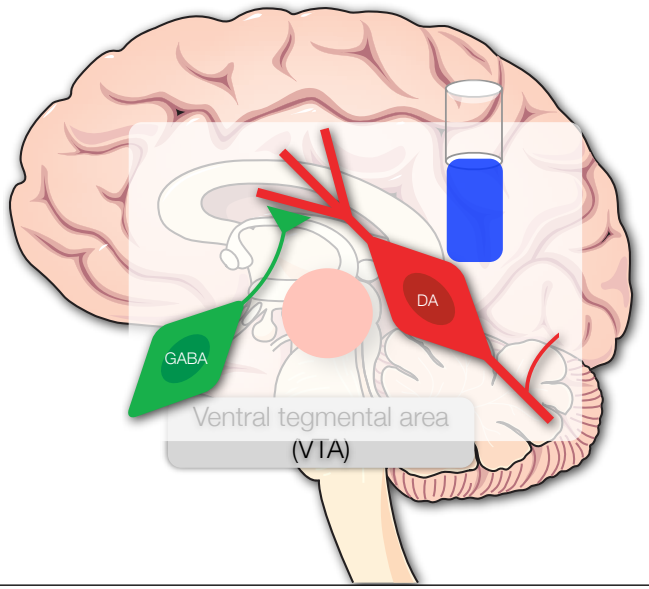
Memory trace in rodents

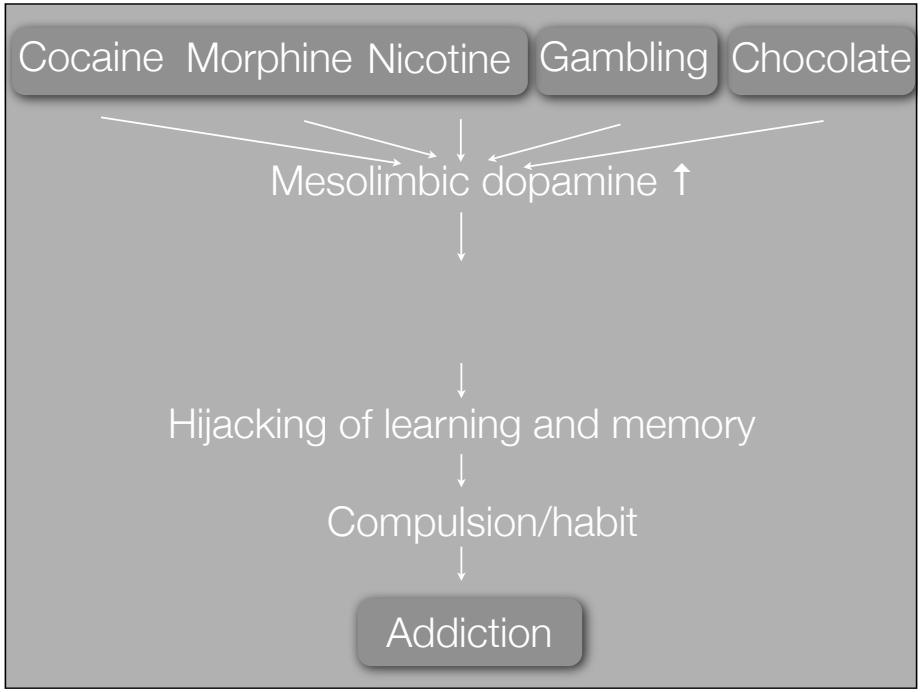
A B



A B

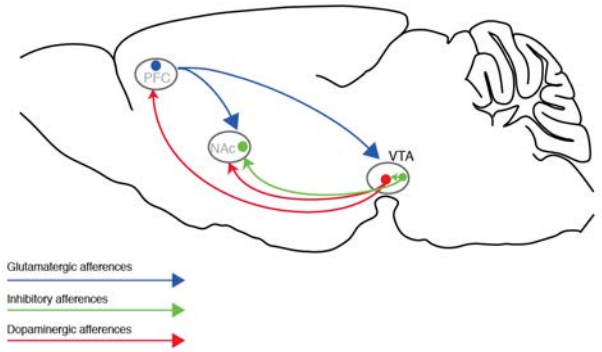
Excited by “blue light”



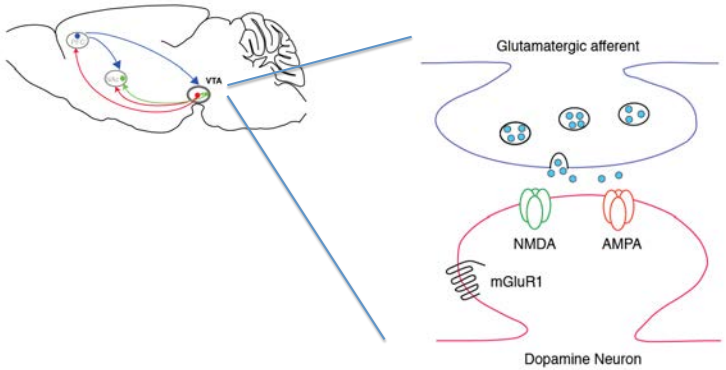


And here is what we have done over the last few years to experimentally test this hypothesis.

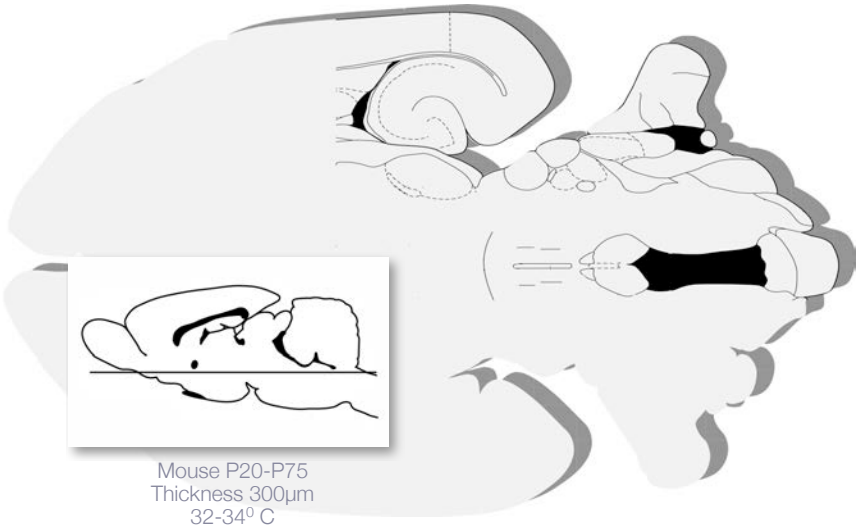
Mesocorticolimbic system



Excitatory transmission

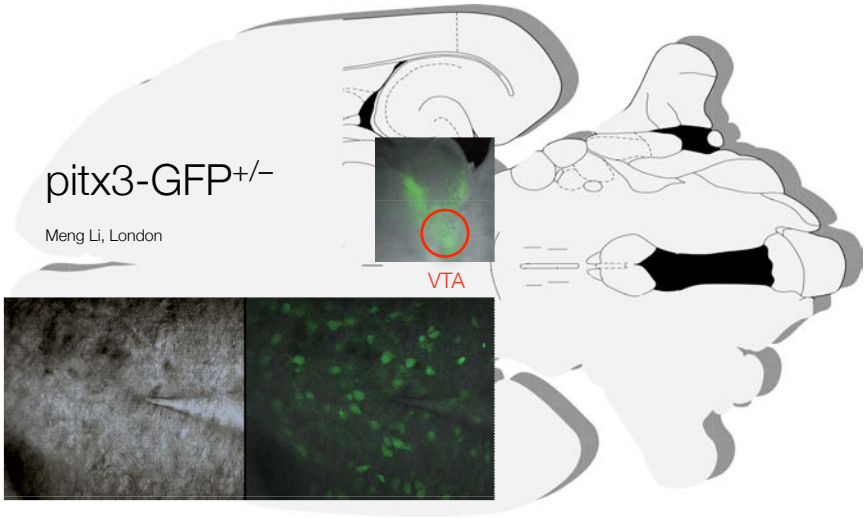


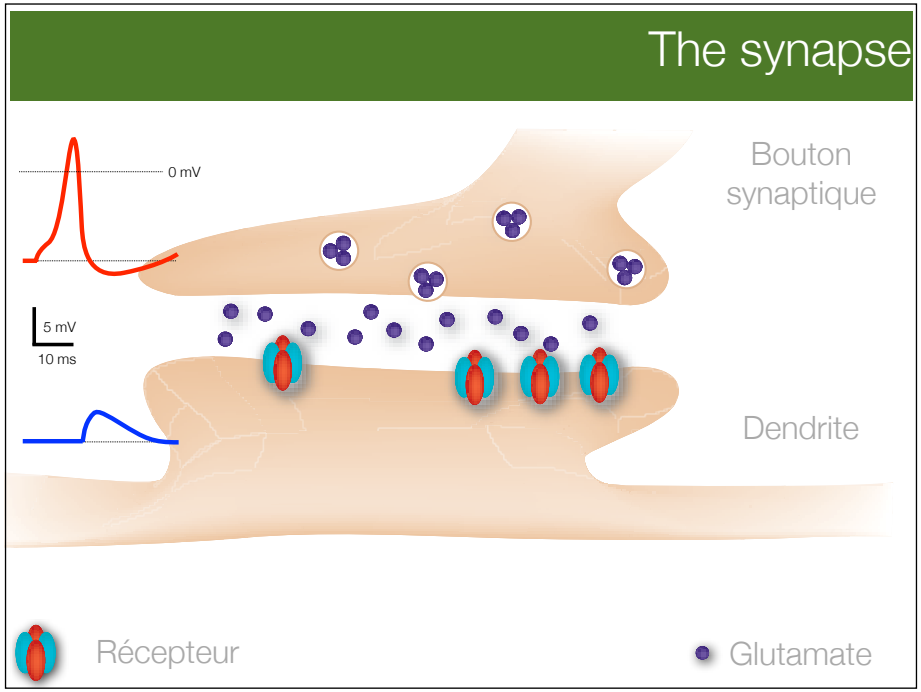
Slice preparation



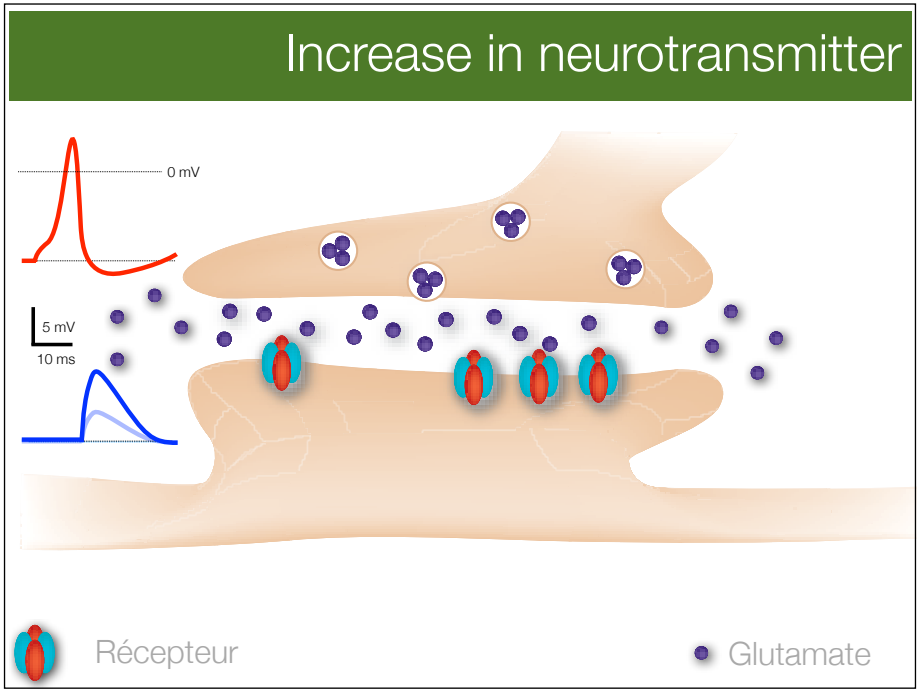
Mouse P20-P75
Thickness 300µm
32-34^{0} C

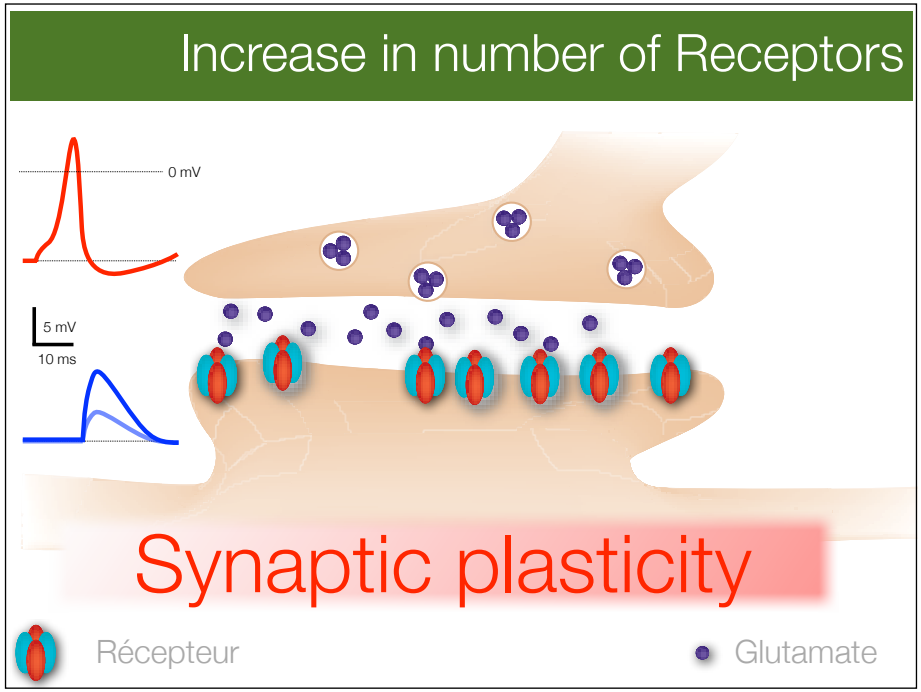
Slice preparation



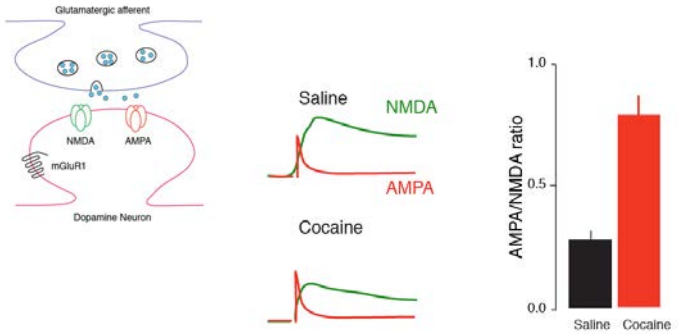

The synapse
0 mV
5 mV
10 ms
Bouton synaptique
Dendrite
Récepteur
Glutamate

Increase in neurotransmitter

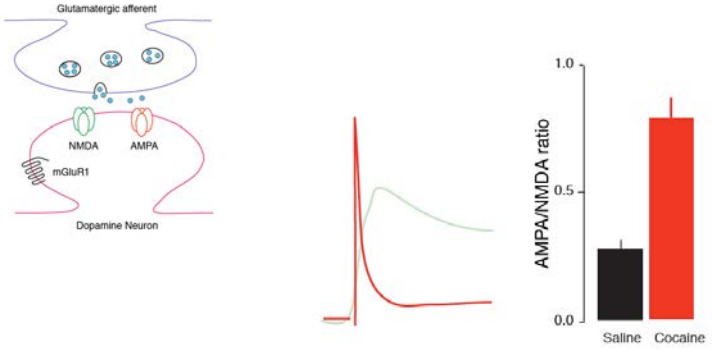



Increase in number of Receptors
0 mV
5 mV
10 ms
Synaptic plasticity
Récepteur
Glutamate

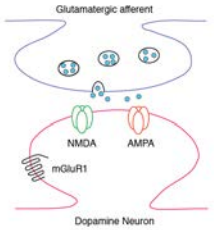
Cocaine:increase in AMPA/NMDA

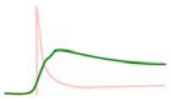


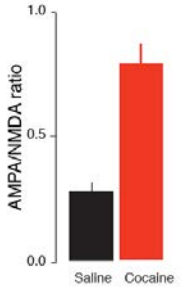
Cocaine:increase in AMPA/NMDA



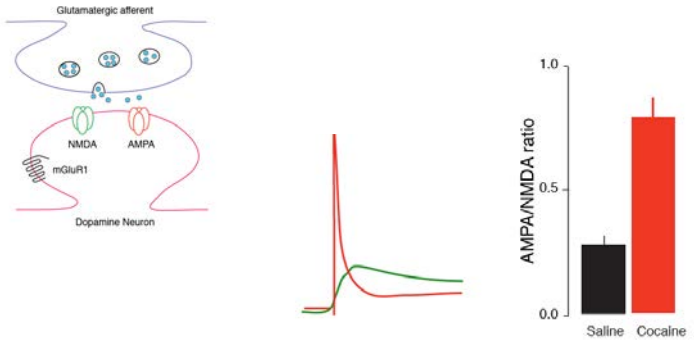
Cocaine:increase in AMPA/NMDA



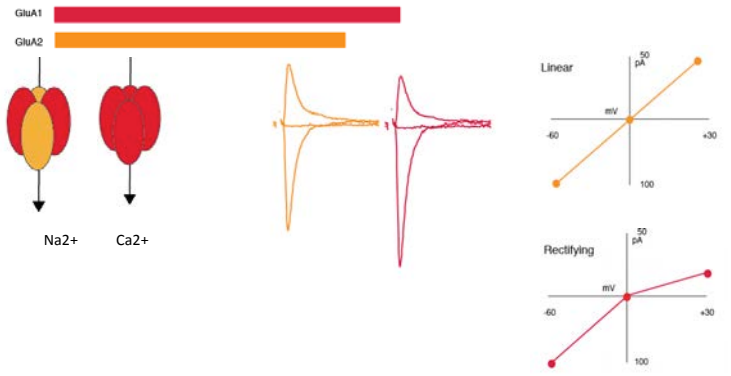




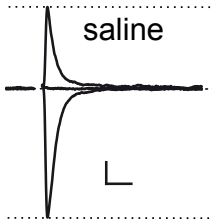
Cocaine:increase in AMPA/NMDA



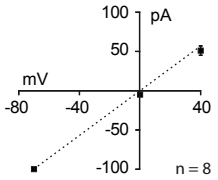
AMPARs

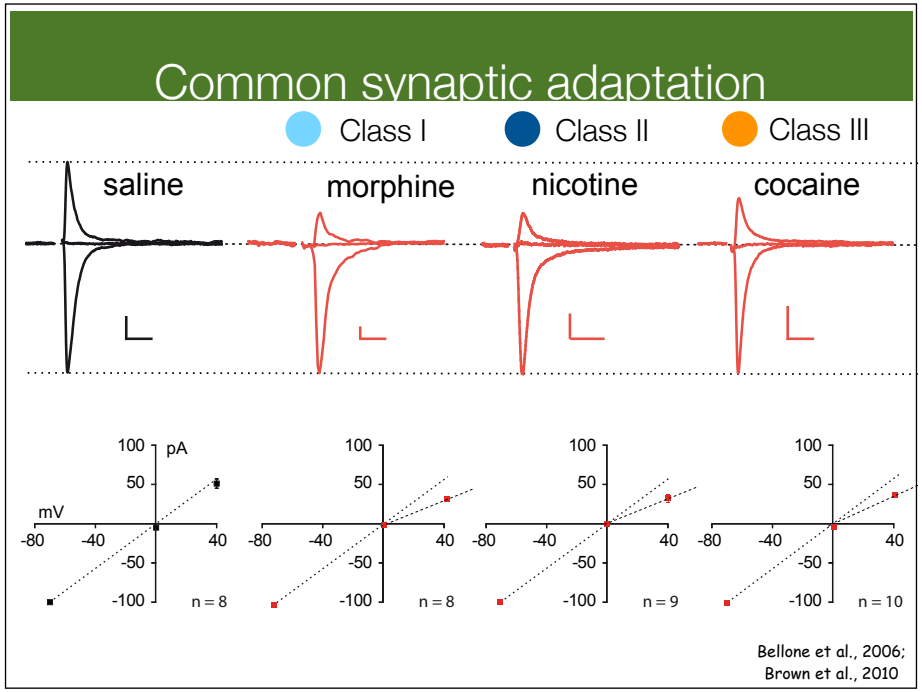

GluA1
GluA2
Na2+
Ca2+
Linear
50
pA
mV
-60
+30
100
Rectifying
50
pA
mV
-60
+30
100

Common synaptic adaptation



in d-APV




Common synaptic adaptation
Class I
Class II
Class III
saline
morphine
nicotine
cocaine
100
50
-50
-100
pA
mV
-80
-40
40
n = 8
n = 8
n = 9
n = 10
Bellone et al., 2006;
Brown et al., 2010

AMPAR subunit composition