UNIVERSITY OF CAMBRIDGE

Cambridge Laboratory for Research on Impulsive/Compulsive Disorders

On the multifaceted nature of compulsive drug-seeking habits in addiction: Insights from preclinical research

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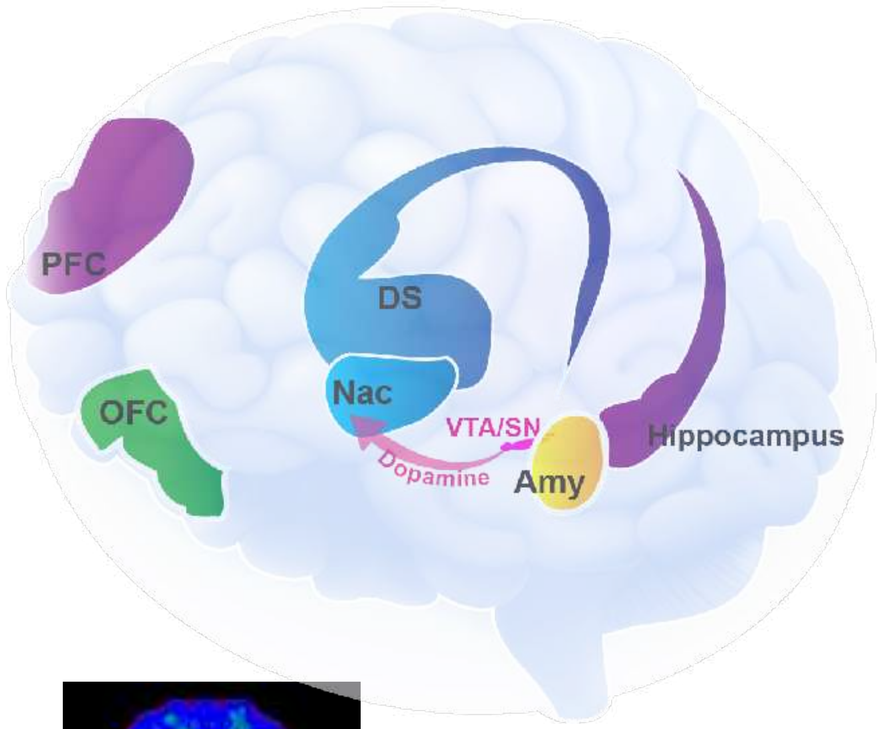
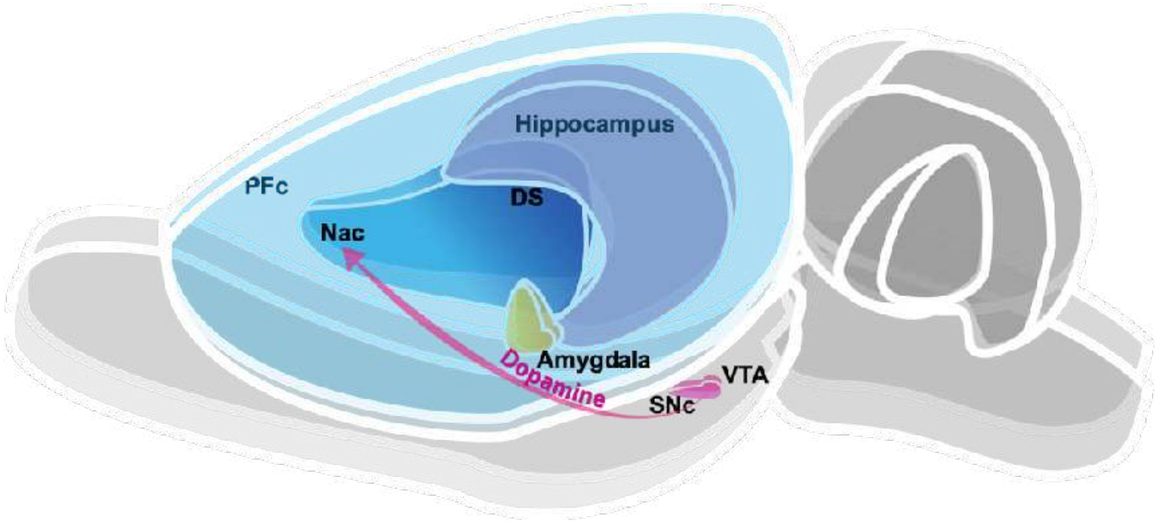
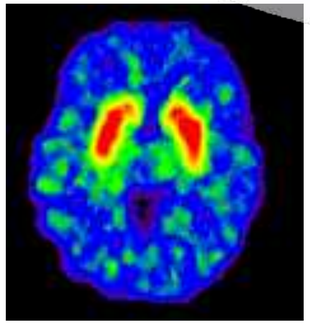
University of Cambridge

Addictive drugs increase $[DA]_{ext}$ in the nucleus accumbens (NAc)

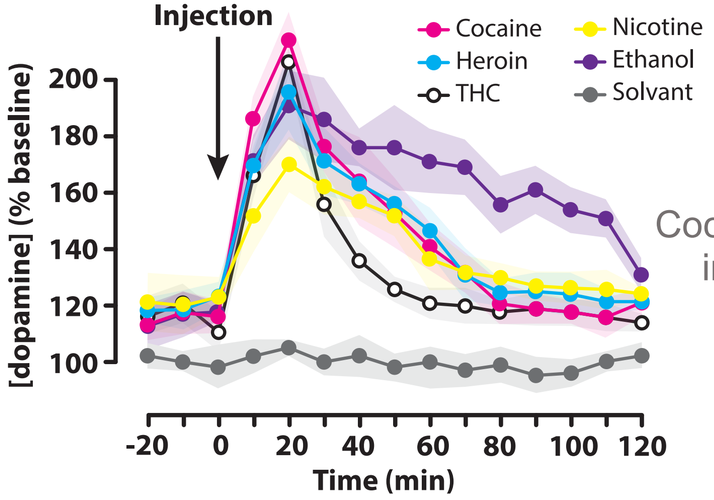






Cocaine-induced increase in DA in human striatum

Volkow et al., 2010



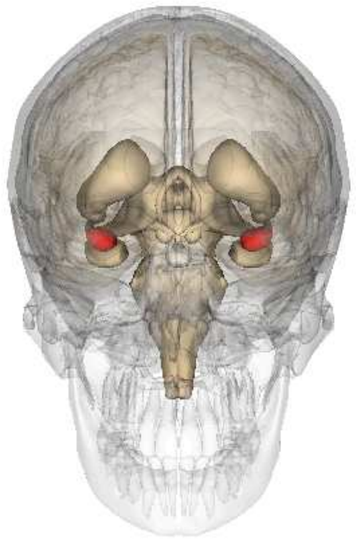
Cocaine-induced increase in $[DA]_{ext}$ in rat NAc

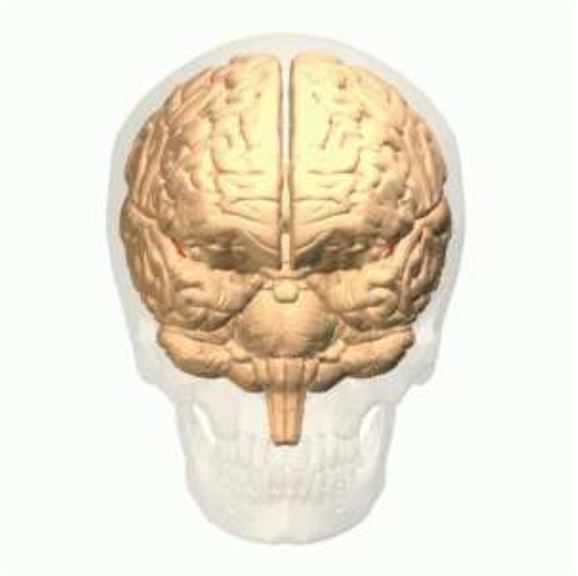
Di Chiara & Imperato, 1988

➔ Common reinforcing effect partly explains why addictive drugs are initially & repeatedly taken

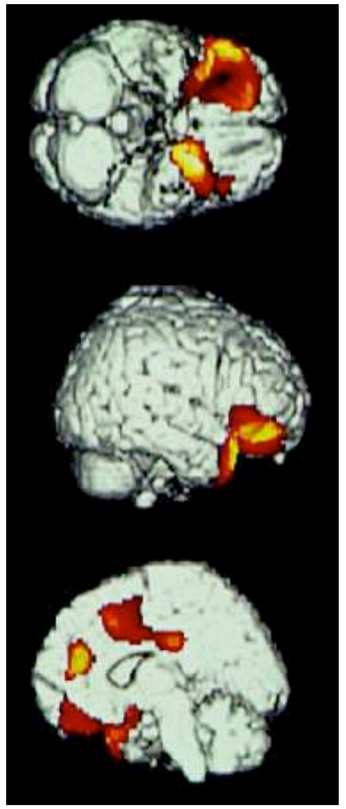
Psychological processes involved in addiction: Pavlovian conditioning

Amygdala & insula





- Pavlovian conditioned stimuli (CSs)
- Drug (unconditioned stimulus, US)

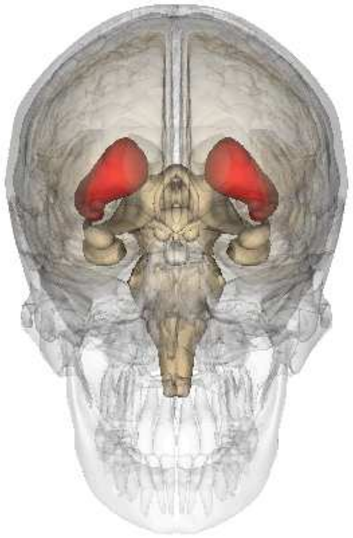


Childress et al., 2000

Motivation, craving, and invigoration of foraging behaviour

Psychological processes involved in addiction: habits

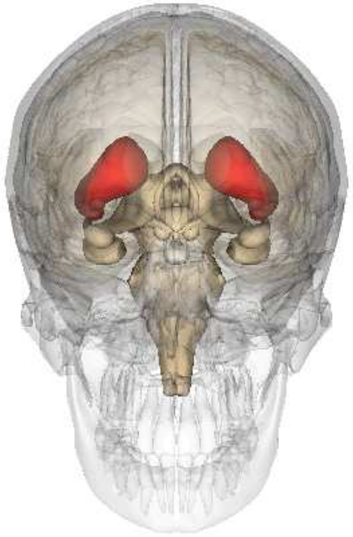
The striatum



Habits:
Stimulus-bound
Rigid enactment of behavioural sequences
Depend on the dorsolateral striatum (DLS)

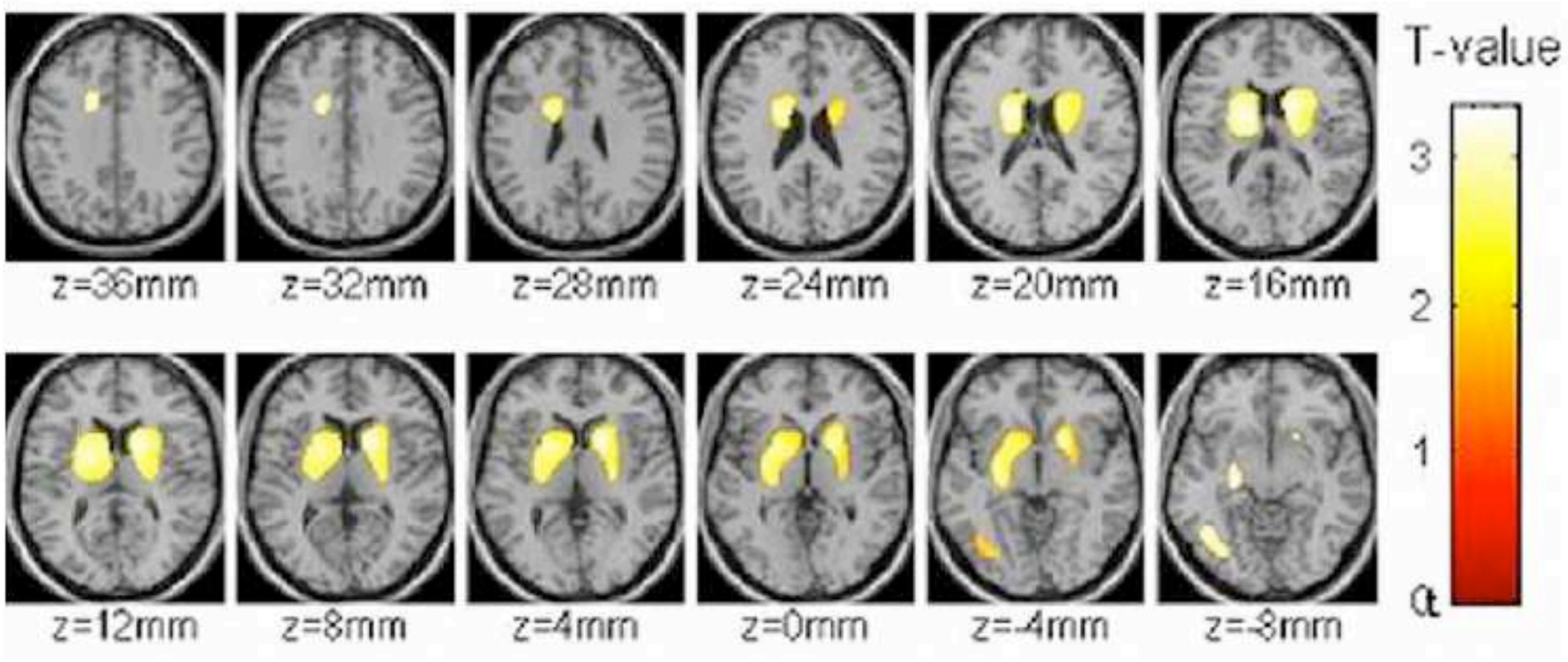
Habits: behavioural manifestation

The striatum



Addiction: engagement of the DLS DA-dependent habit system

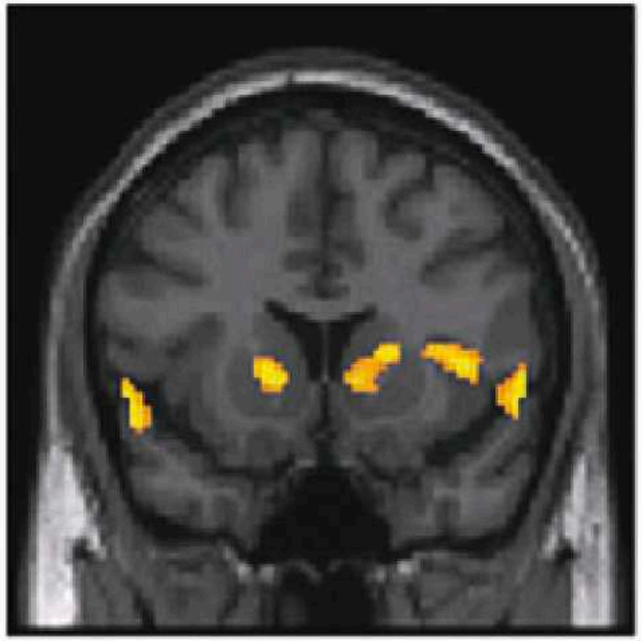
Craving is associated with increased DA transmission in the dorsal striatum in humans



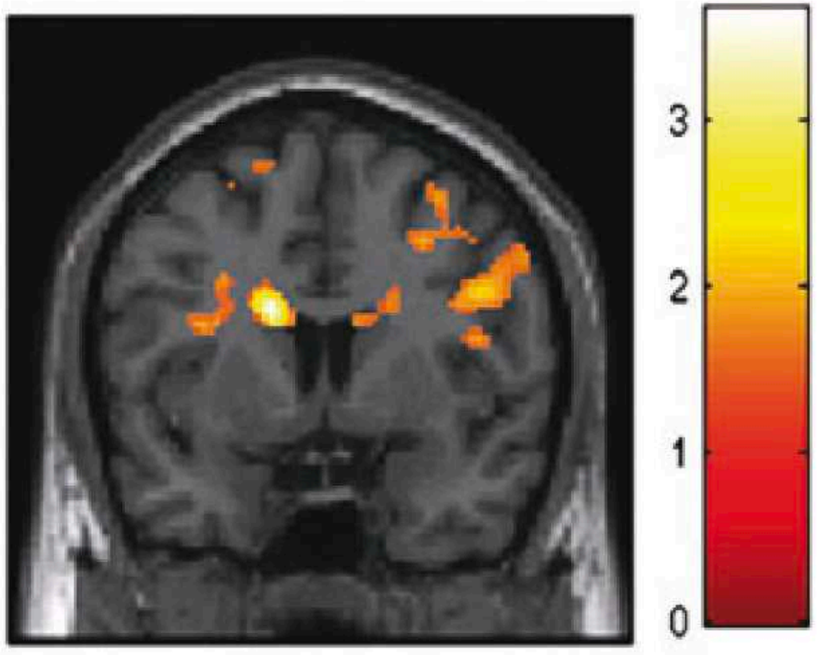
Volkow et al., J. Neurosci. 2006

Engagement of the dorsolateral striatum in heavy alcohol drinkers

Recreational user



Heavy drinker



Vollstadt-Klein et al., 2010

Intrastriatal functional shifts: does it matter?

Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum

Sabine Vollstädt-Klein[1], Svenja Wichert[1], Juri Rabinstein[1], Mira Bühler[1], Oliver Klein[1], Gabriele Ende[2], Derik Hermann[1] & Karl Mann[1]

Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany[1] and Department Neuroimaging, Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany[2]

Original Paper

Smoking addiction: the shift from head to hands: Approach bias towards smoking-related cues in low-dependent versus dependent smokers

Sandrine Detandt[1], Ariane Bazan[1], Etienne Quertemont[2] and Paul Verbanck[3]

Psychopharm

Journal of Psychopharmacology
2017, Vol. 31(7) 819–829

DOI: 10.1177/0269881117699606
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Cocaine Cue-Induced Dopamine Release in Recreational Cocaine Users

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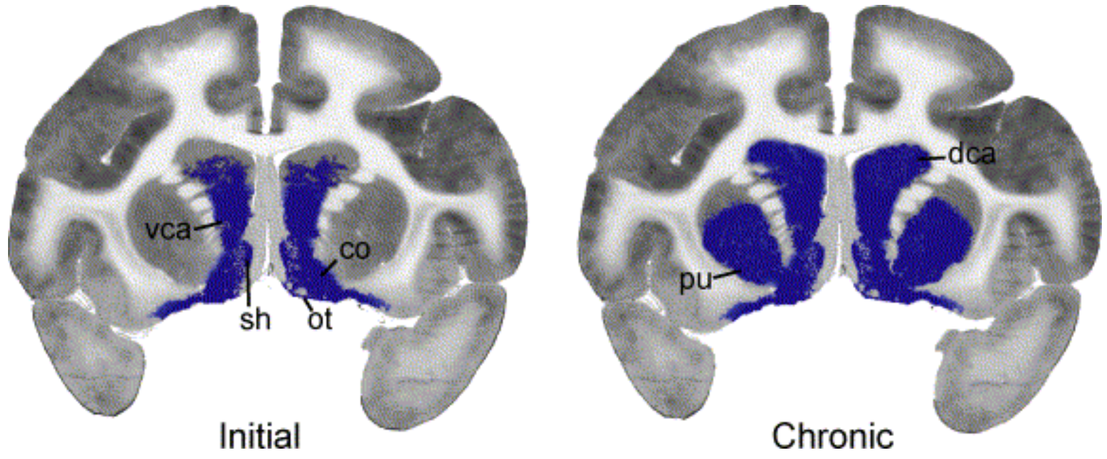
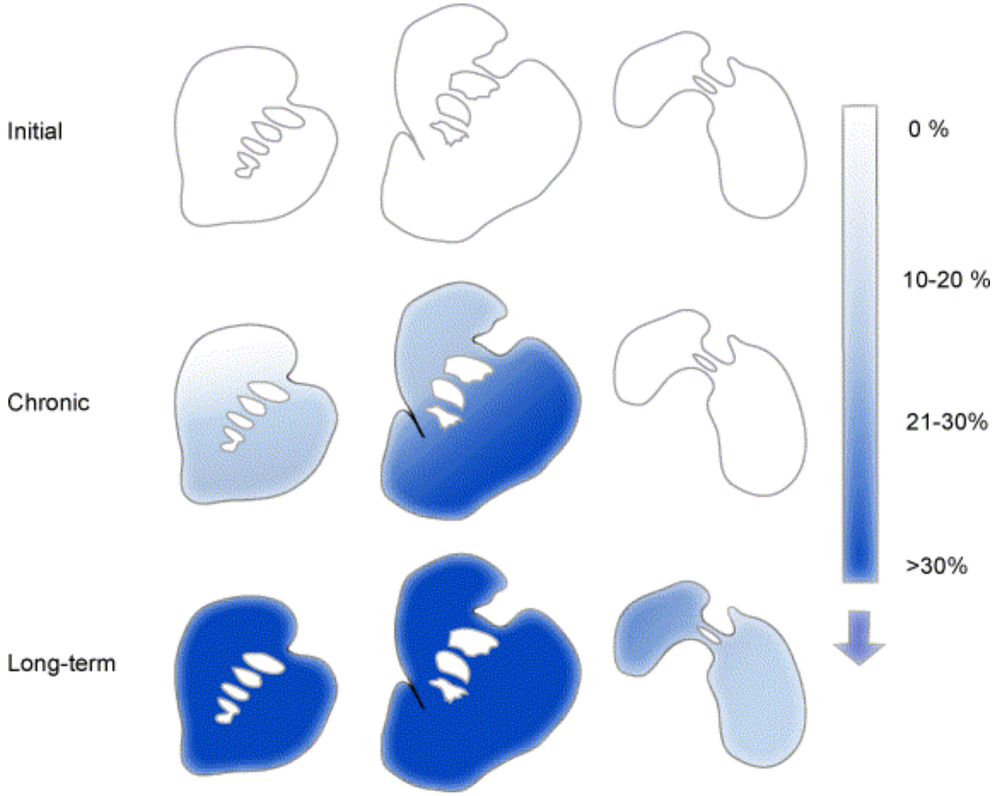
Published: 26 April 2017

Sylvia M. L. Cox[1], Yvonne Yau[2], Kevin Larcher[2], France Durand[1], Theodore Kolivakis[1], J. Scott Delaney[3], Alain Dagher[2], Chawki Benkelfat[1,2] & Marco Leyton[1,2]

Engagement of the aDLS-dependent habit system: non-human primates





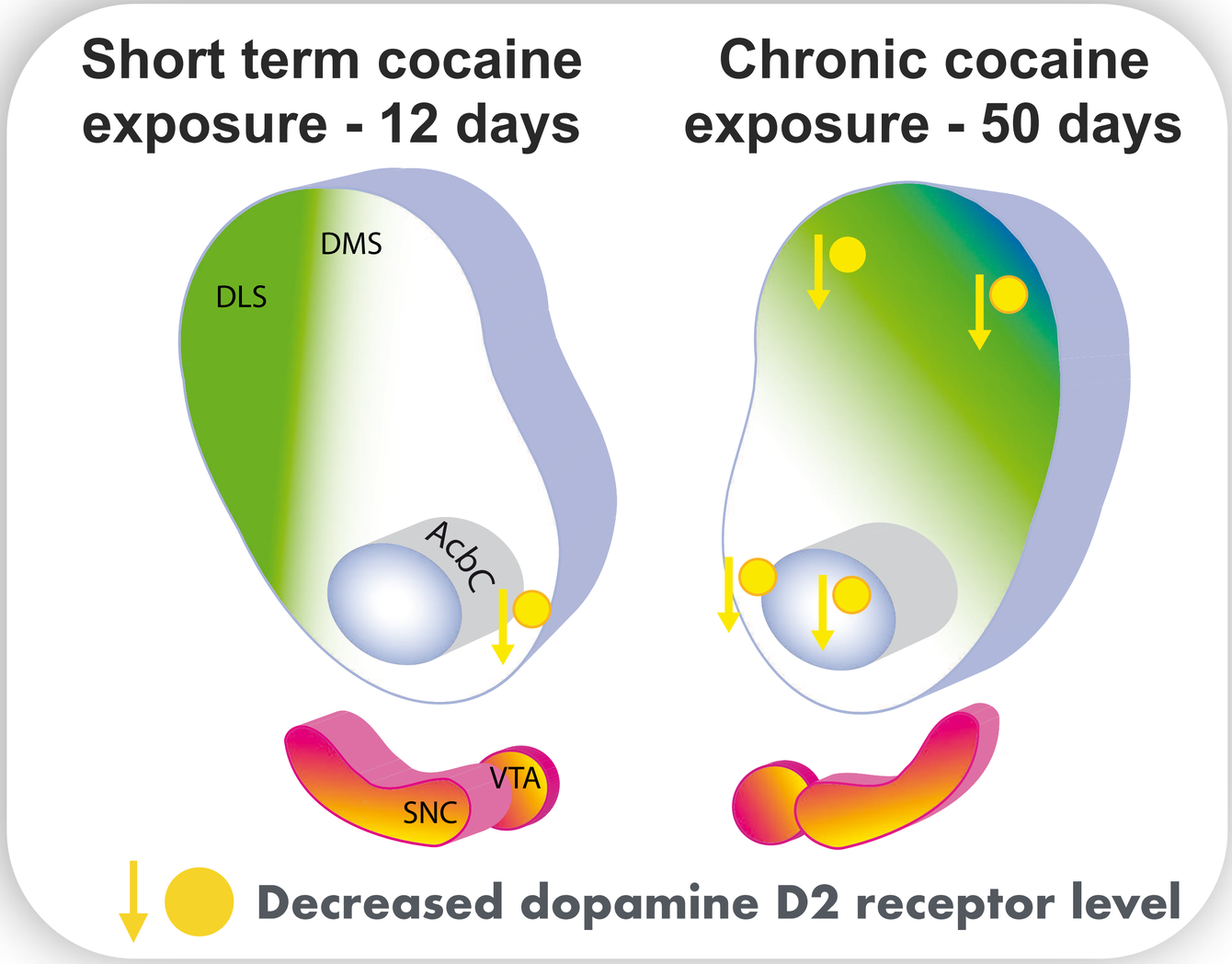
2DG metabolic activity decreases

D2 binding site decreases

Porrino L. 2004

Engagement of the dDLS-dependent habit system: rodents

In situ hybridisation
of the D2 dopamine receptor

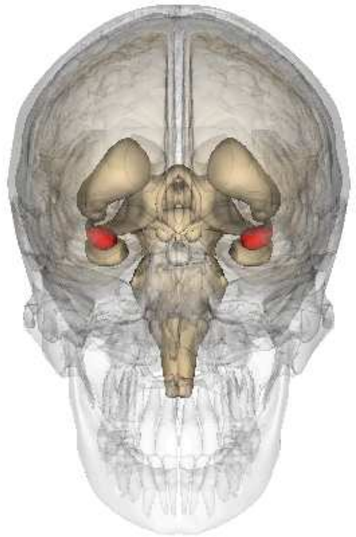


Besson et al., Neuropsychopharmacology, 2013

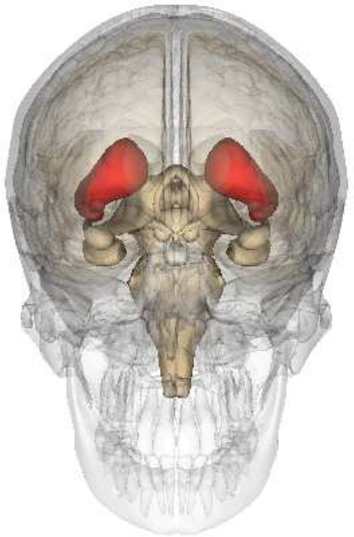
Amygdalo-striatal mechanisms in addiction: real life drug foraging

What mechanisms underlie the development of drug seeking habits in addiction?

The amygdala: motivation/ urges



The dorsolateral striatum: habits



The amygdala does not project directly to the dorsolateral striatum!

Amygdalo-striatal mechanisms in addiction: real life drug foraging

How do we operationalise drug foraging in non human mammals?

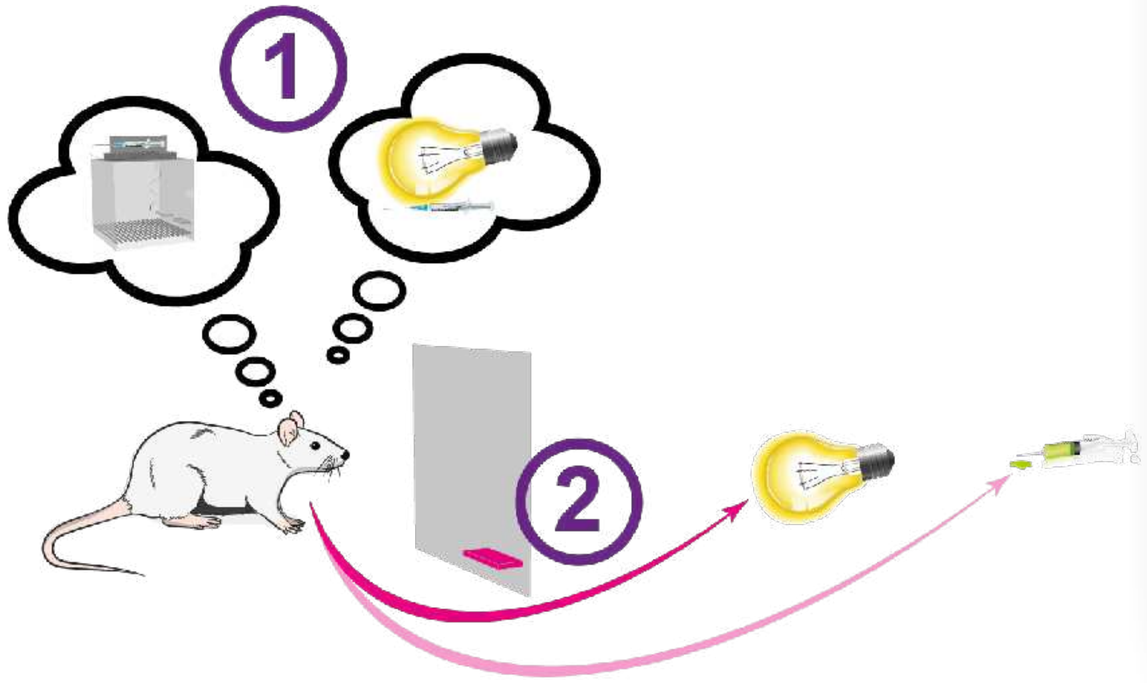
Importance of conditioned reinforcement

In the real world, habits are not divorced from cues: conditioned reinforcement

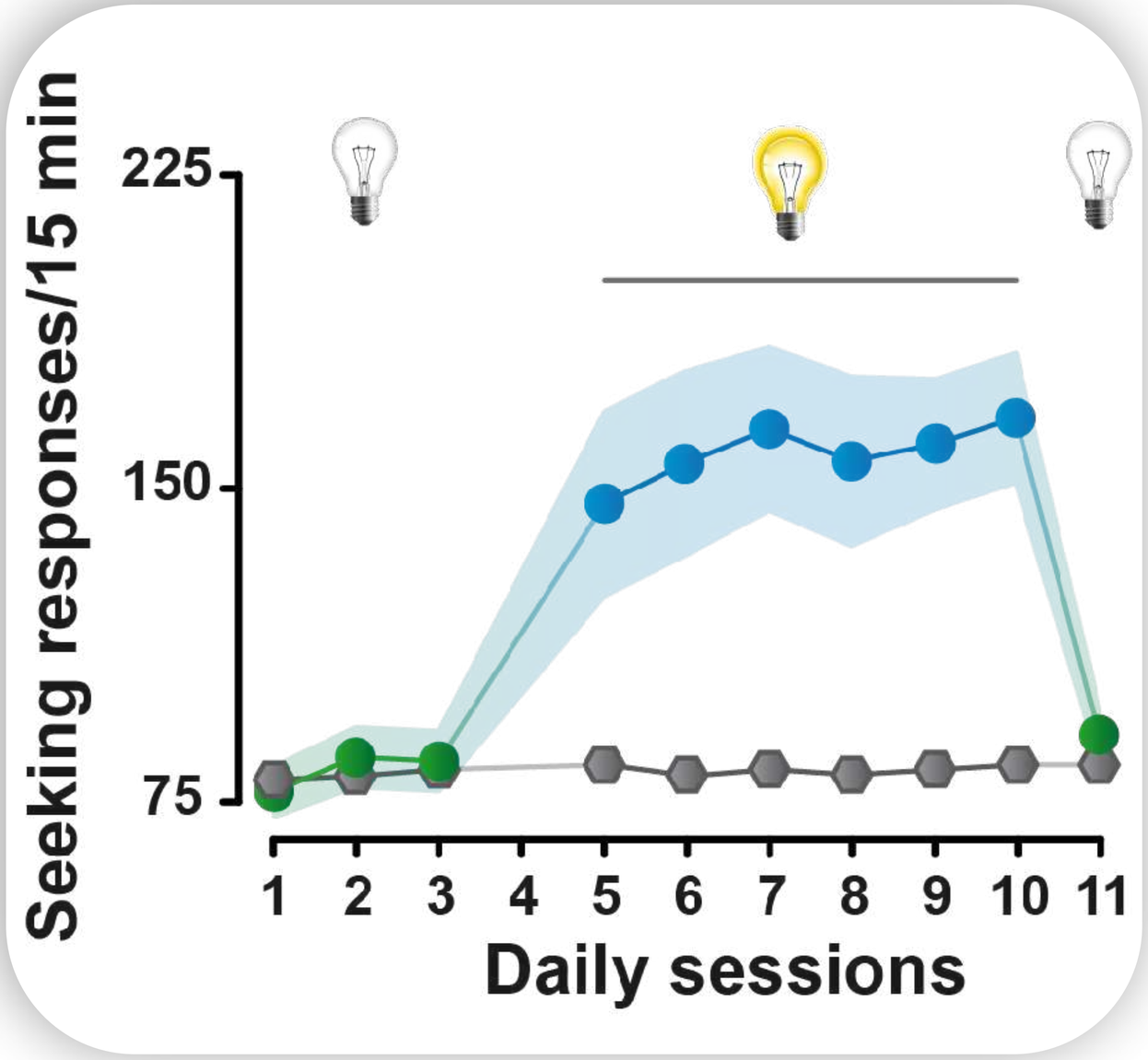
Cue-controlled drug seeking

Second order schedule of reinforcement

A model of drug seeking that measures the impact of drug CSs over delays to drug taking (conditioned reinforcement)



Conditioned reinforcement



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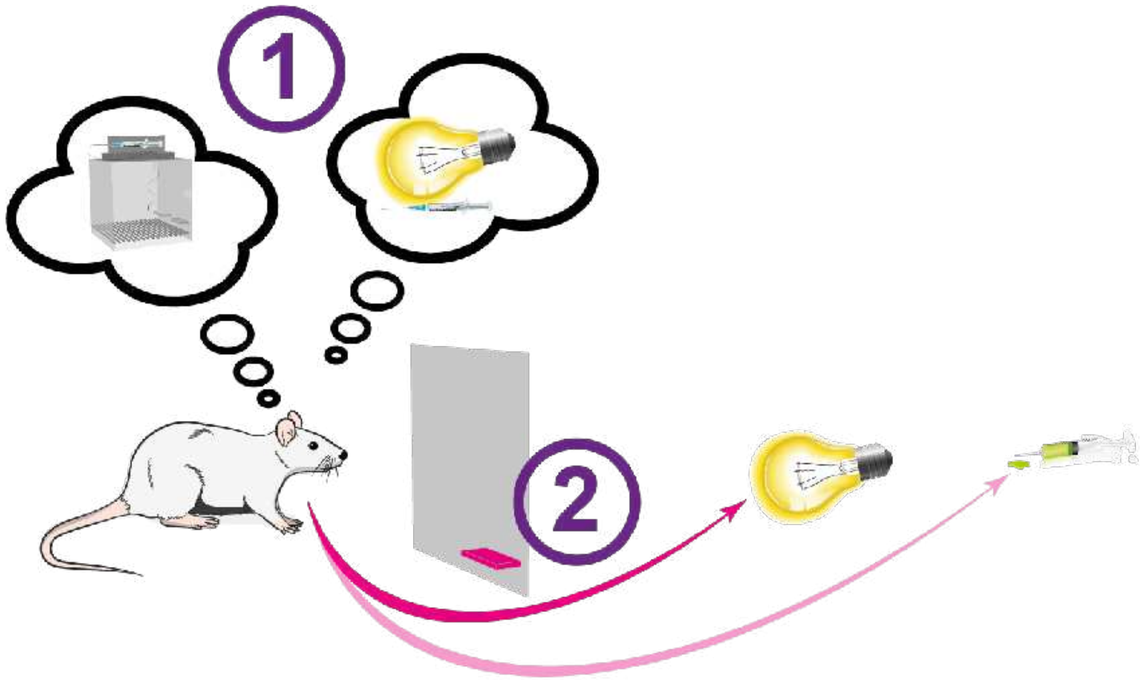
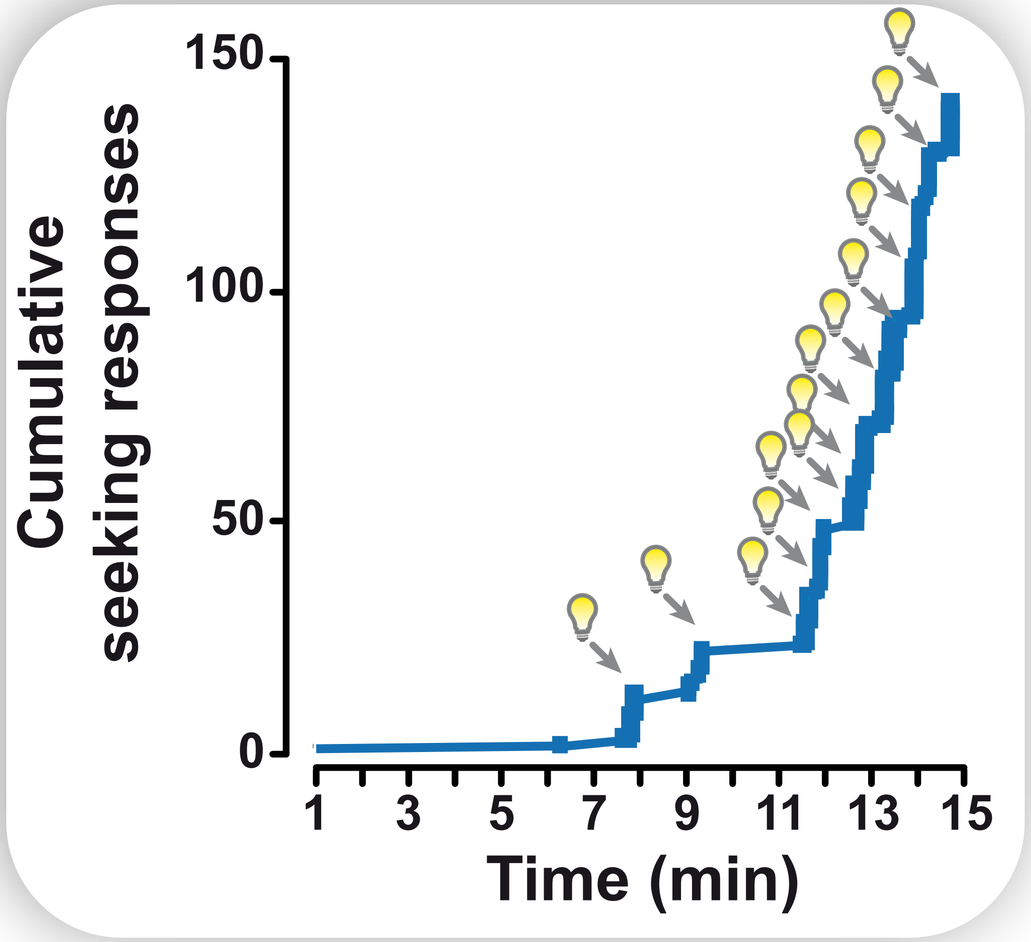
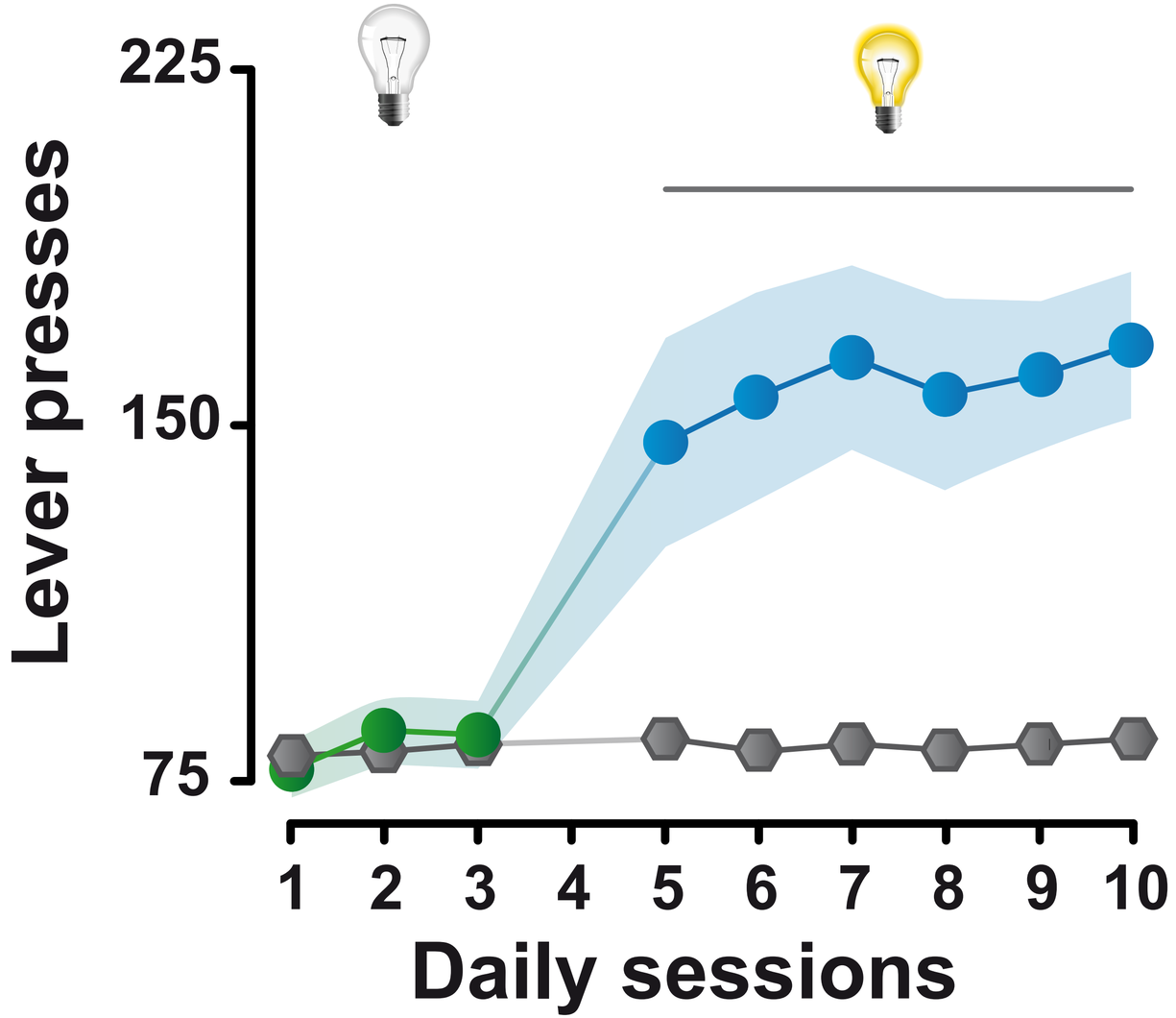


Conditioned reinforcement



Incentive habits

Cue-controlled drug seeking behaviour



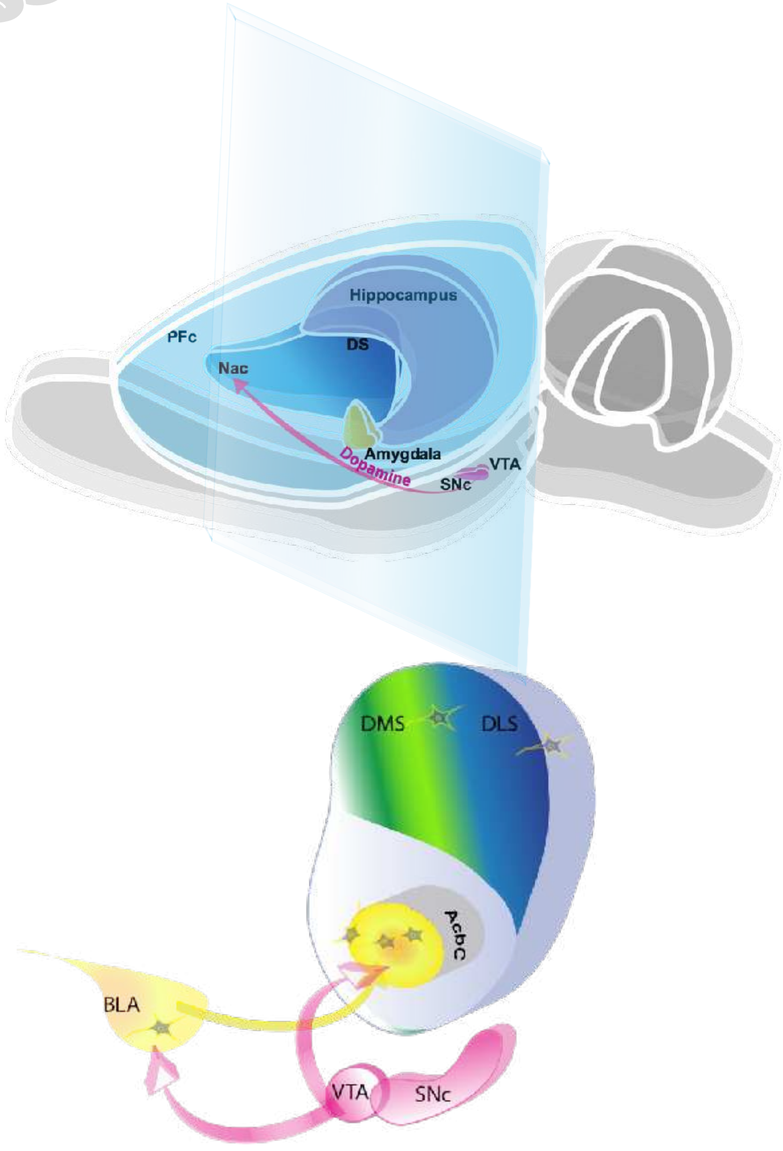
Incentive Habit (SOR)

Habit (FI15)

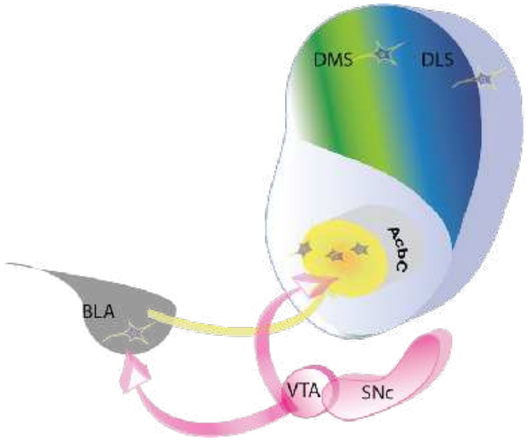
Incentive habits

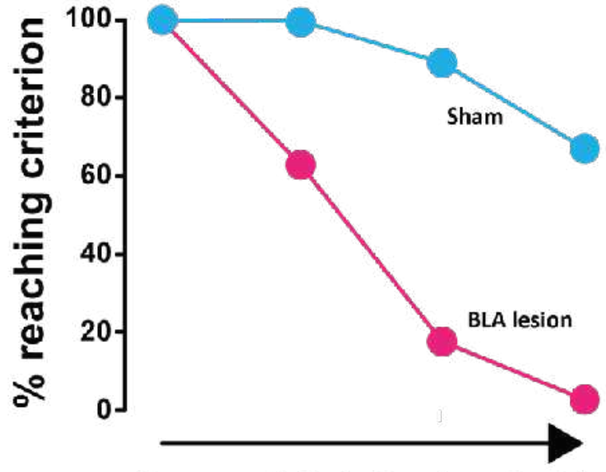
Neural basis of the acquisition of cue-controlled drug seeking

Cue-controlled drug seeking: role of the basolateral amygdala and of the NAc Core



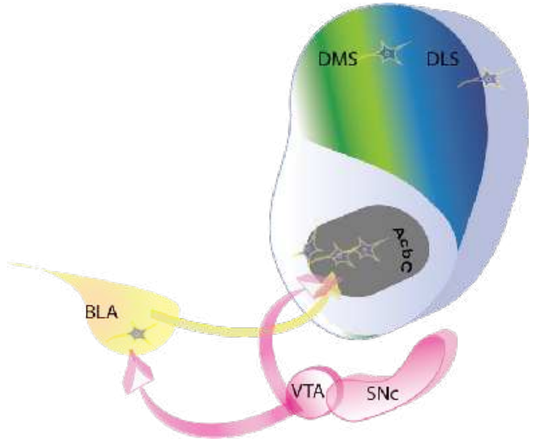
BLA lesion or inactivation

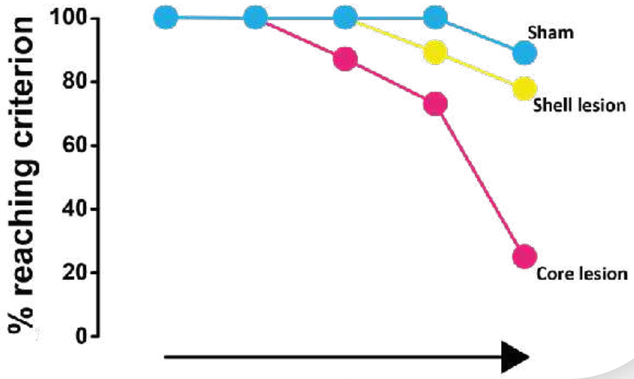




Whitelaw et al., 1996

NAc core or Shell lesion

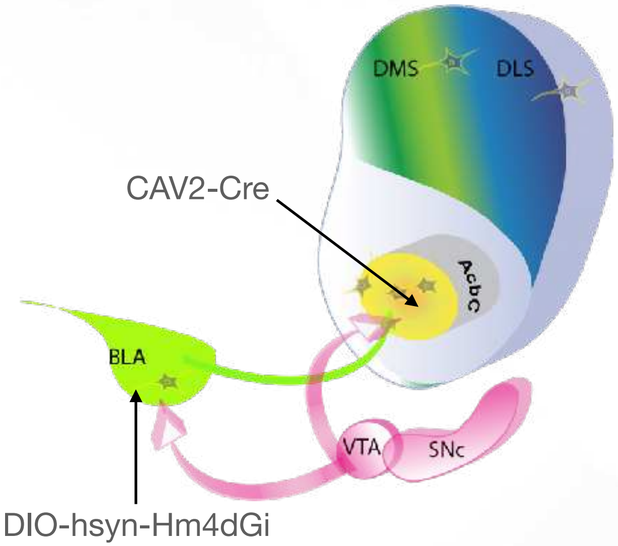


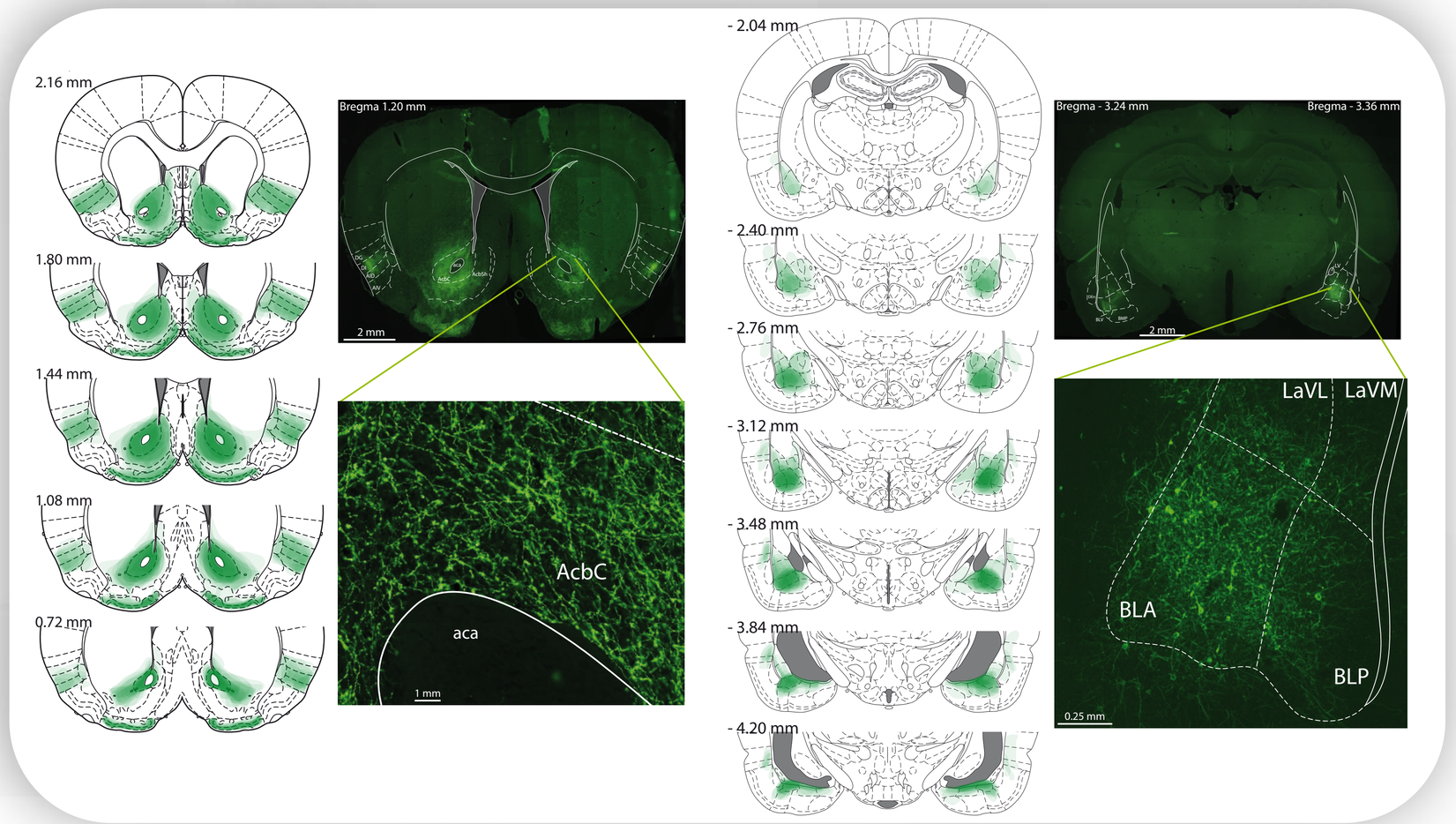


Ito et al., 2002

Cue-controlled drug seeking: a BLA - NAcC circuit underlies the impact of drug CSs on cocaine seeking

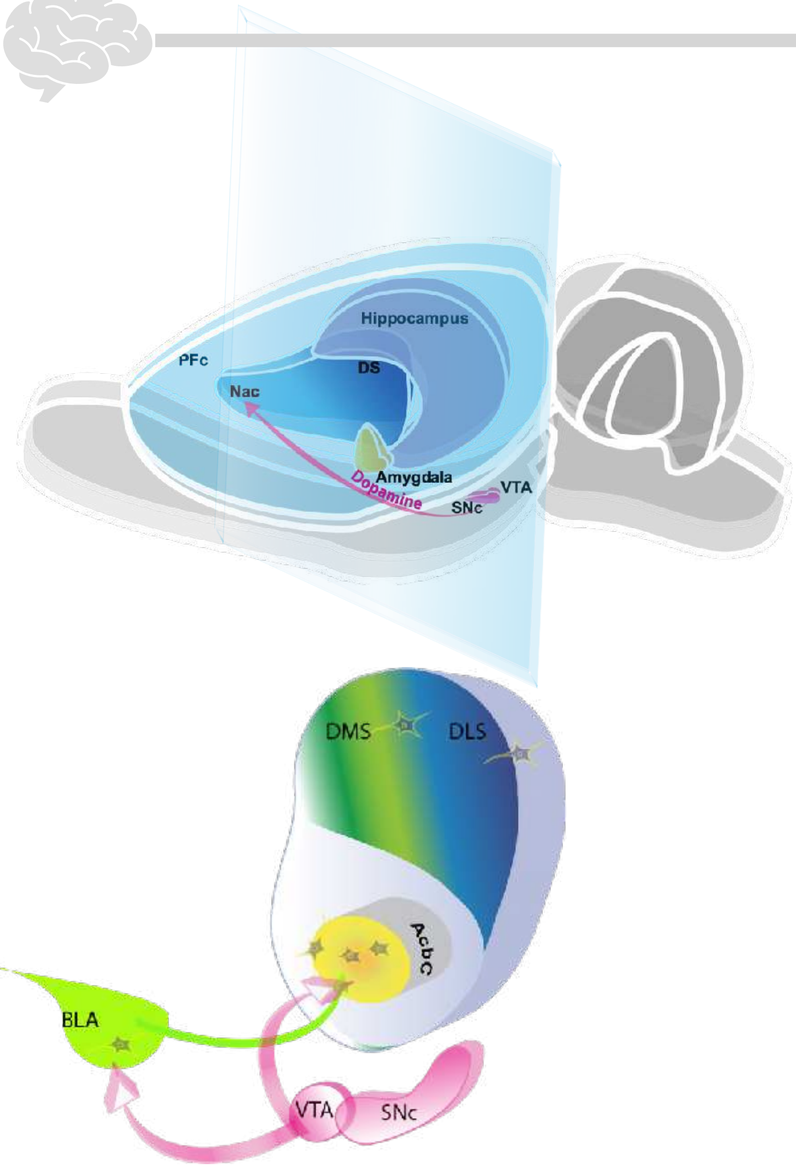
Circuit mapping: DREADDs Designer receptor exclusively activated by a designer drug



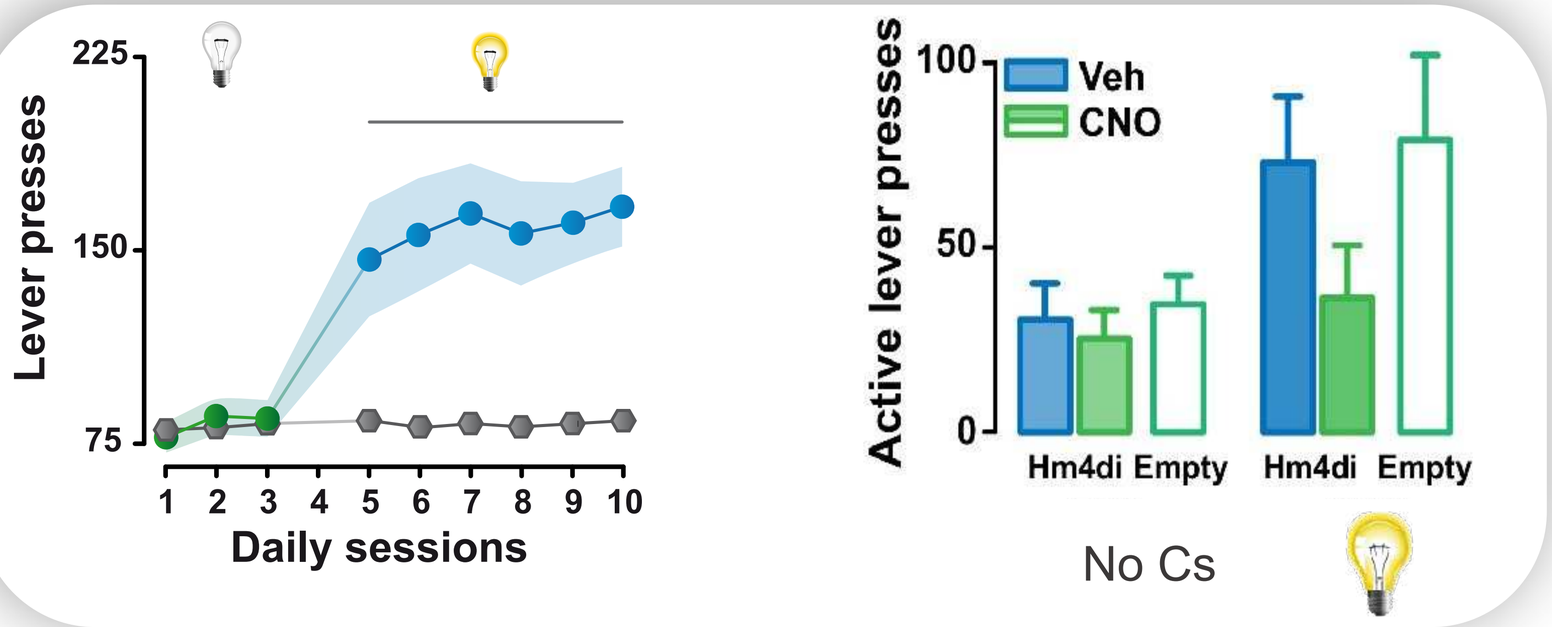


Puaud et al., Biol. Psychiatry, 2021

Cue-controlled drug seeking: a BLA - NAcC circuit underlies the impact of drug CSs on cocaine seeking



Selective inhibition of the neurons of the BLA-AcbC pathway prevents the development of cue-controlled cocaine seeking



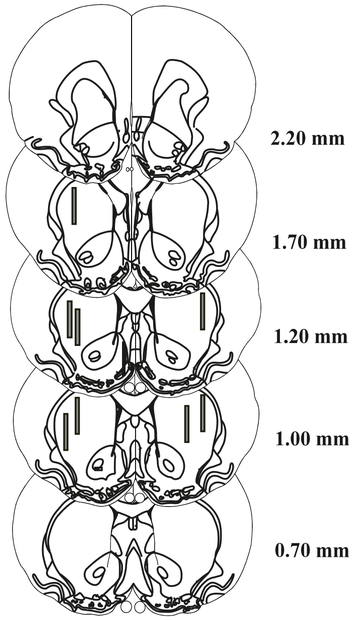
Puaud et al., Biol. Psychiatry, 2021

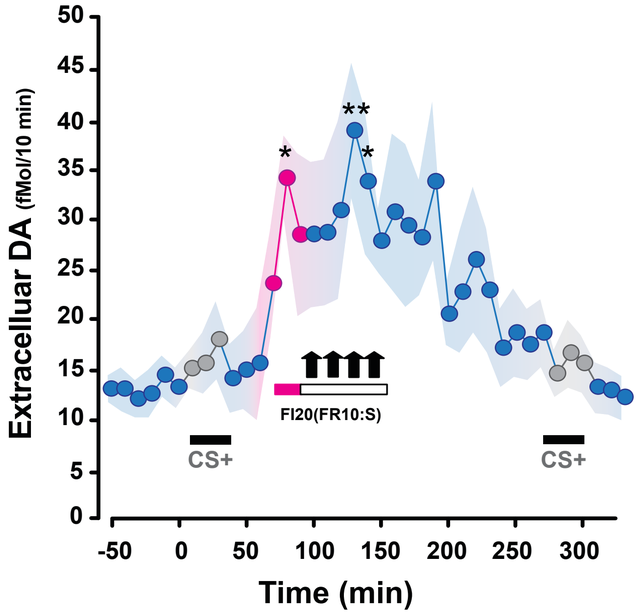
Incentive habits

When cue-controlled drug seeking becomes well establihsed, its control devolves to the aDLS

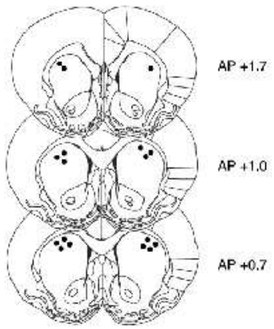
Cue-controlled drug seeking becomes reliant on aDLS Dopamine

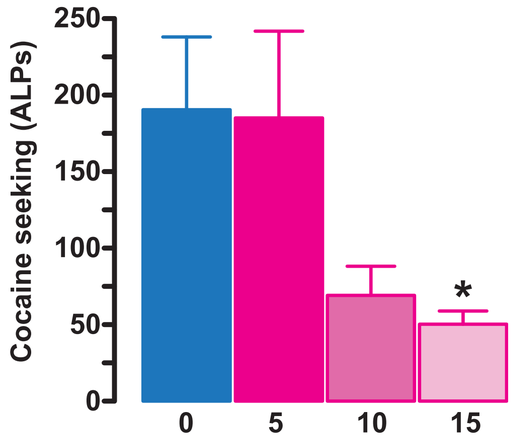
Incentive cocaine seeking habits





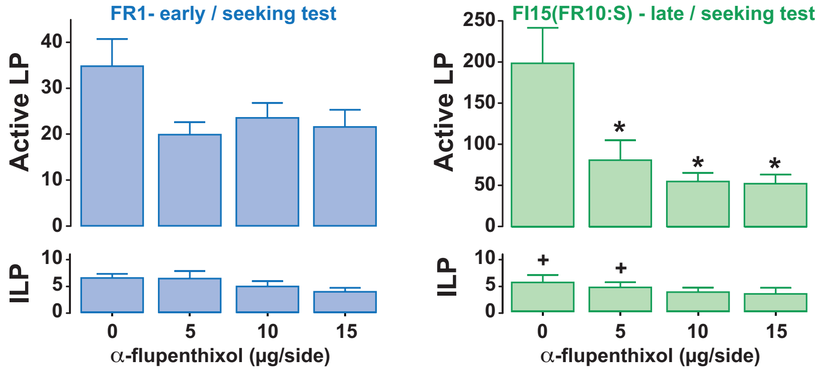
Ito et al., J Neurosci. 2002

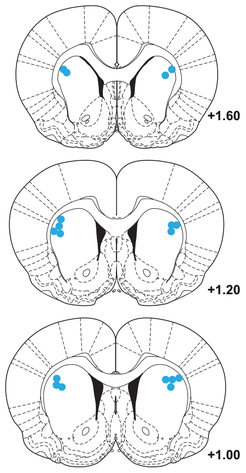


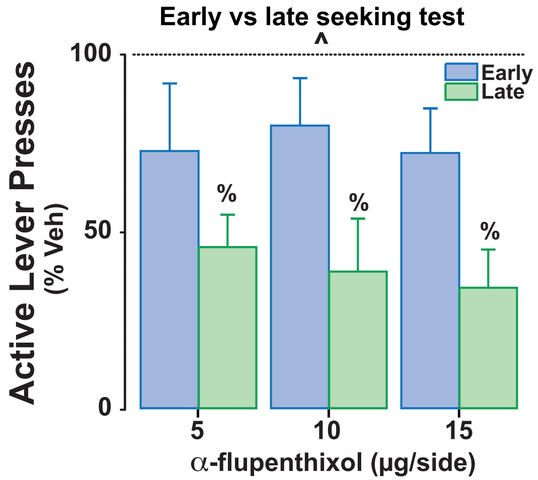


Vanderschuren et al.. J Neurosci. 2005

Incentive heroin seeking habits



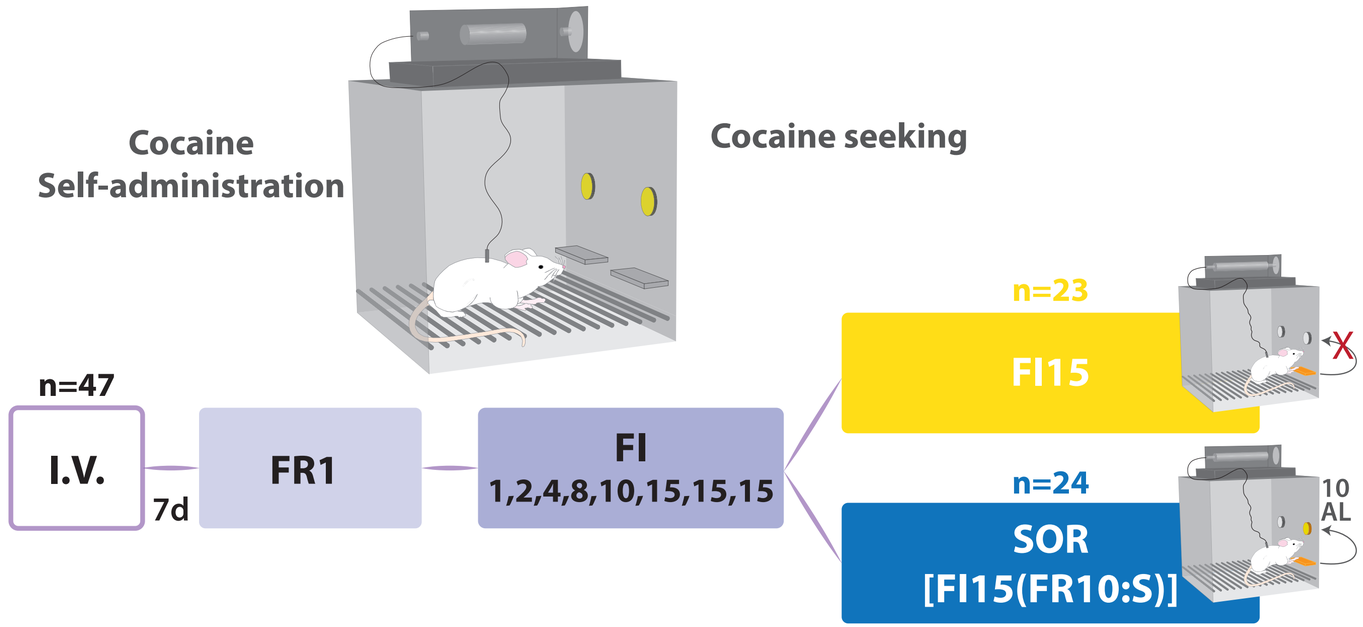


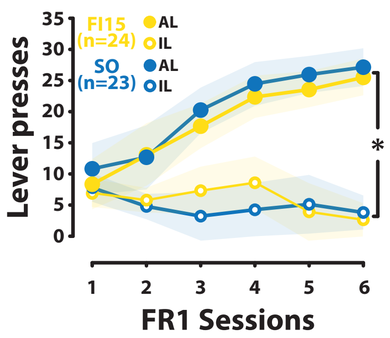


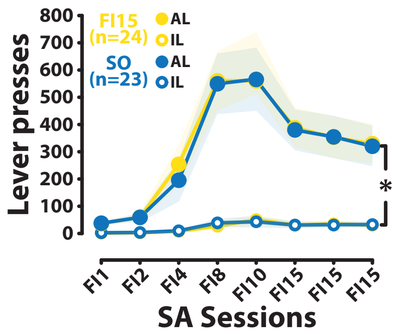
Hodebourg et al., EJN 2019

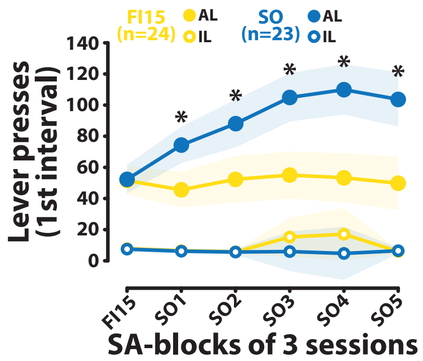
Incentive habits: the path to compulsion?

Instrumental deprivation effect: forced abstinence in cocaine seeking









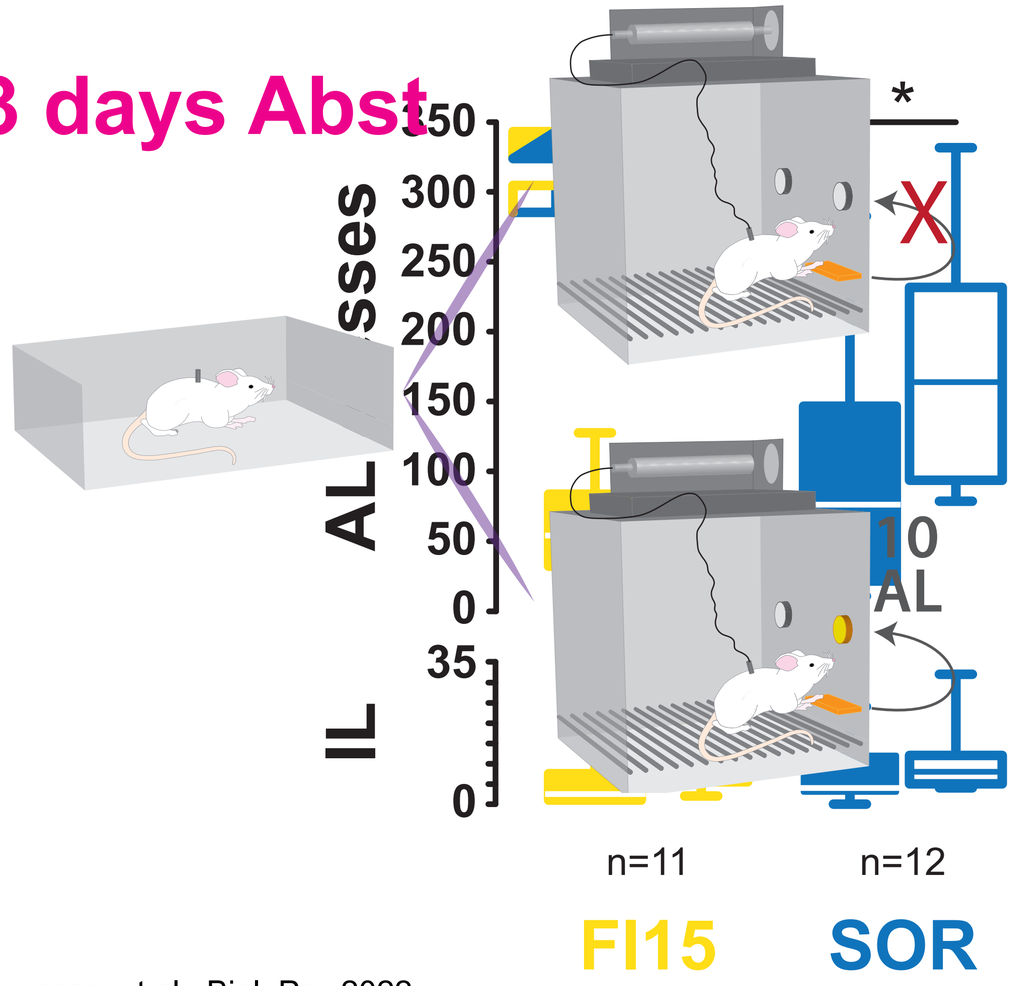
Fouyssac et al., Biol. Psy 2022

Incentive habits promote compulsive relapse

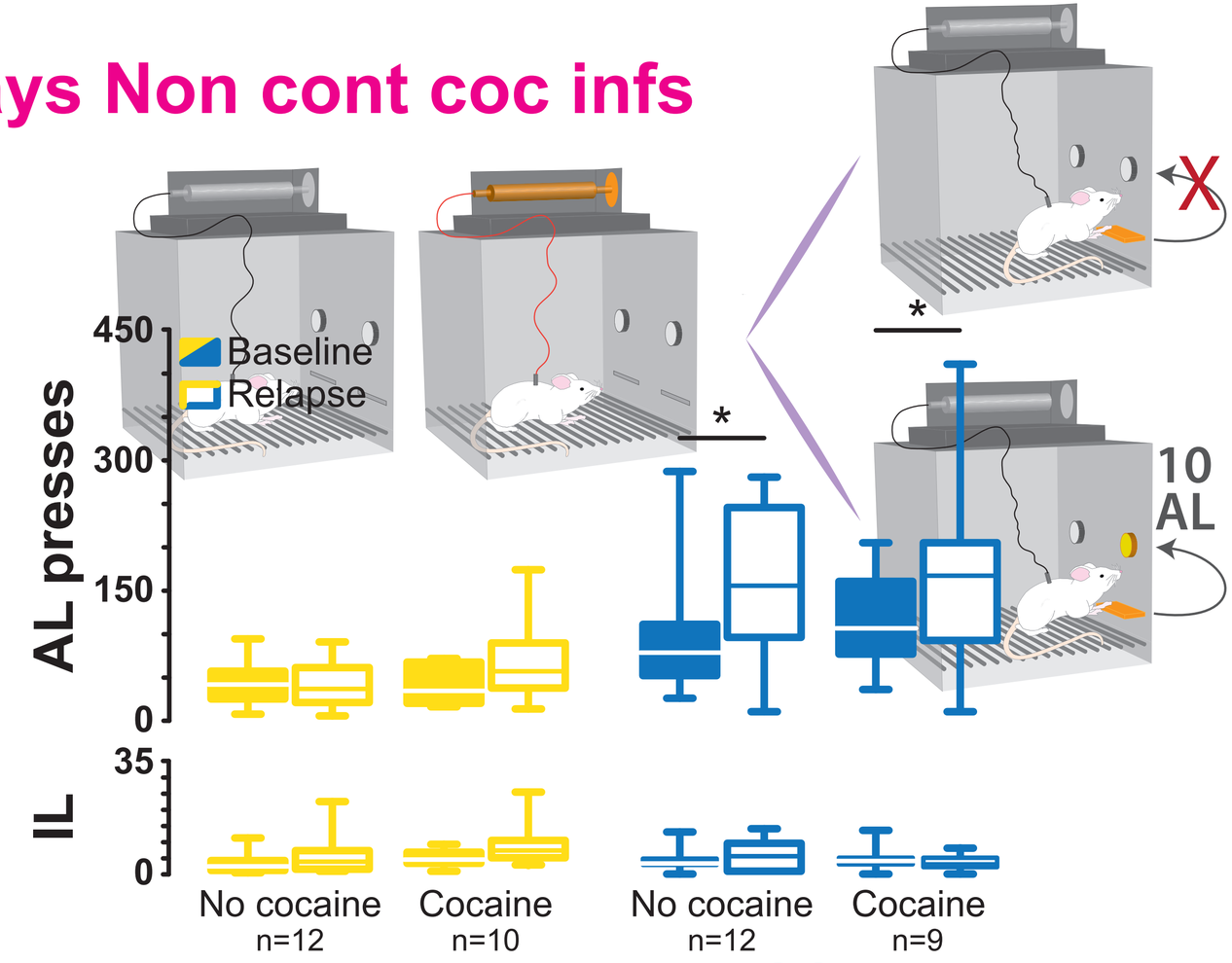
Incentive habits promote aberrant relapse…

Independently of pharmacological withdrawal

3 days Abst



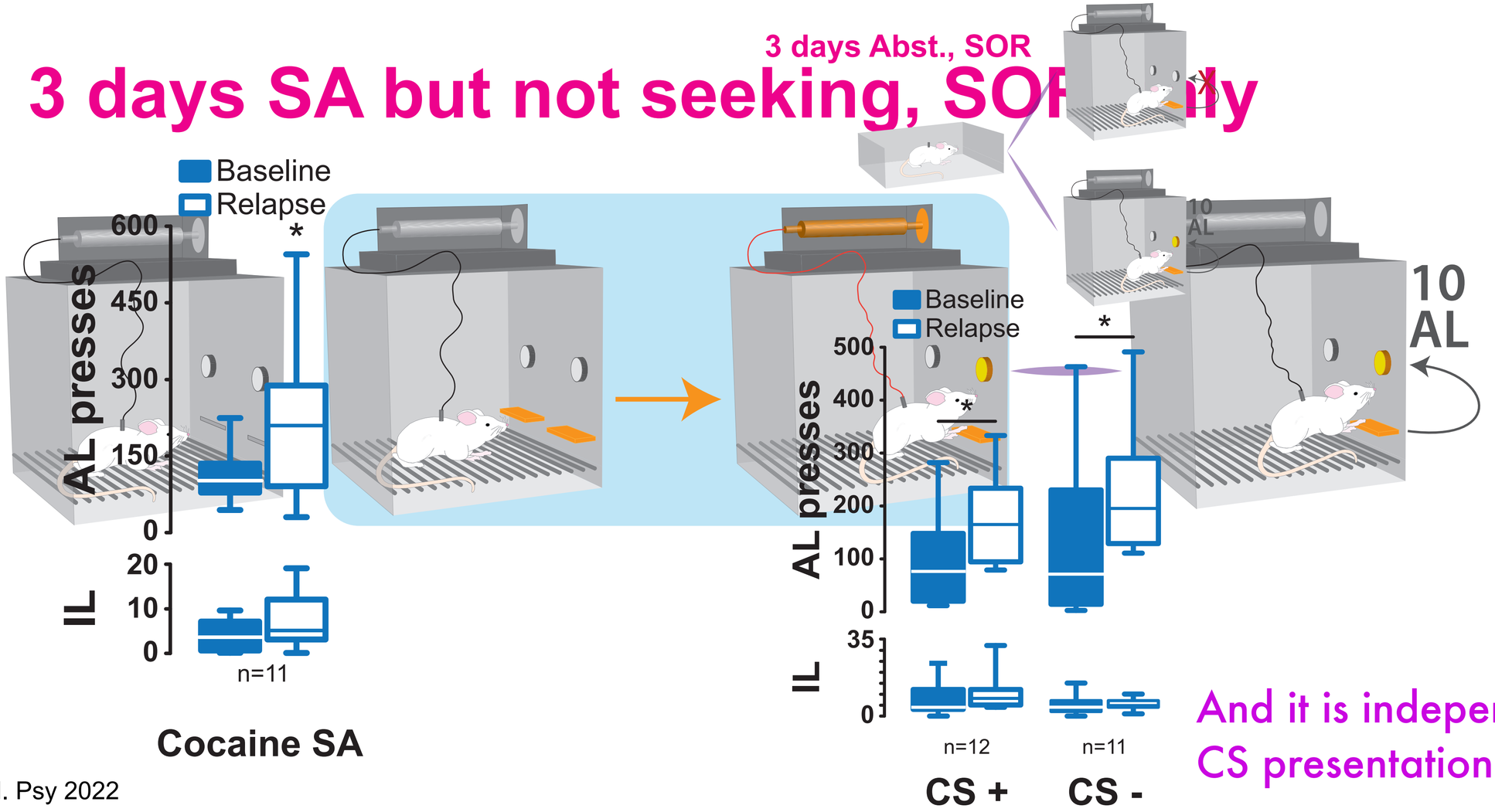
3 days Non cont coc infs



Fouyssac et al., Biol. Psy 2022

Incentive habits promote compulsive relapse

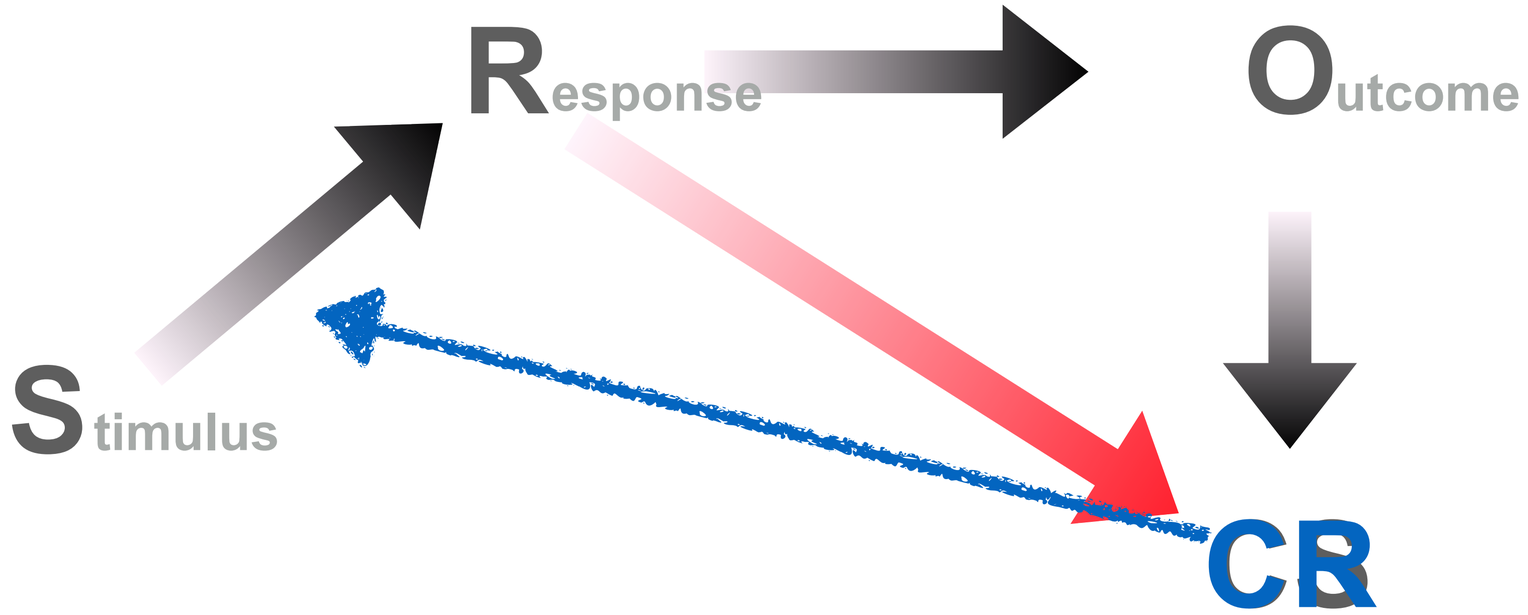
Incentive habits-mediated relapse occurs when SEEKING, but not TAKING is prevented



And it is independent of CS presentation at relapse

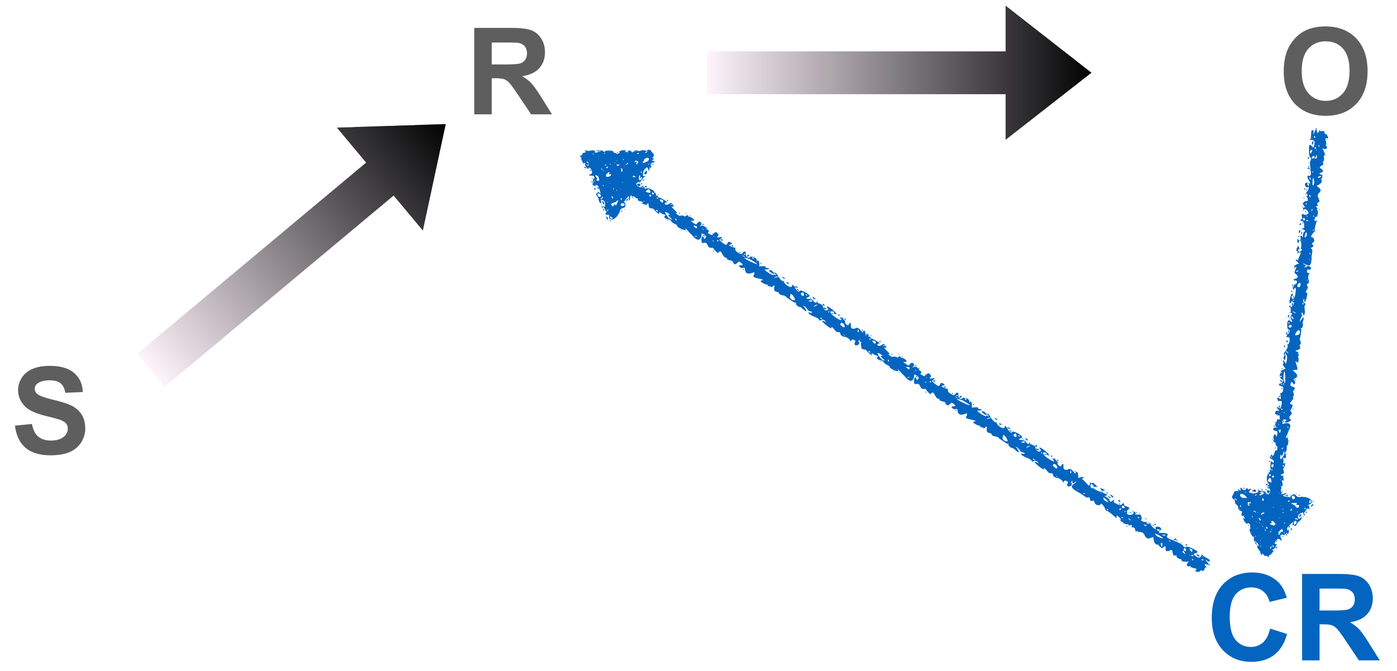
Fouyssac et al., Biol. Psy 2022

Incentive habits: hypothetical associative model



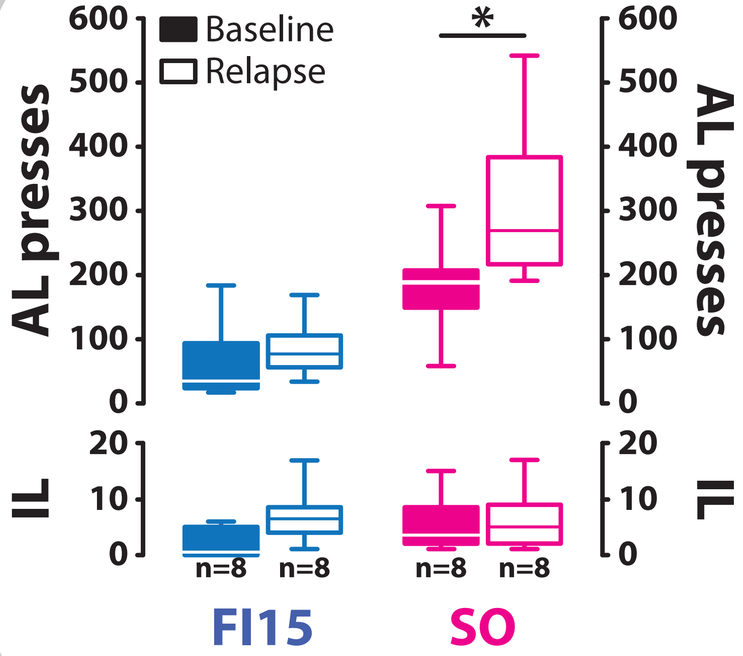
Independent of the value of the drug

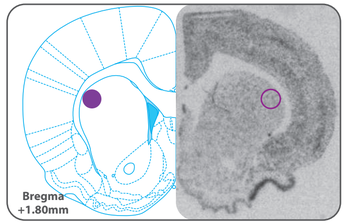
Incentive habits: hypothetical associative model



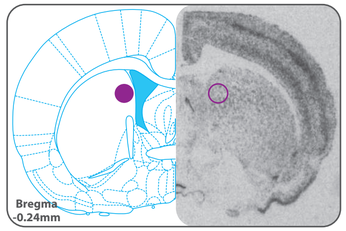
Second order
Interdimensional
Conditioning

Incentive habits: flexibility in the inflexibility - neural correlates

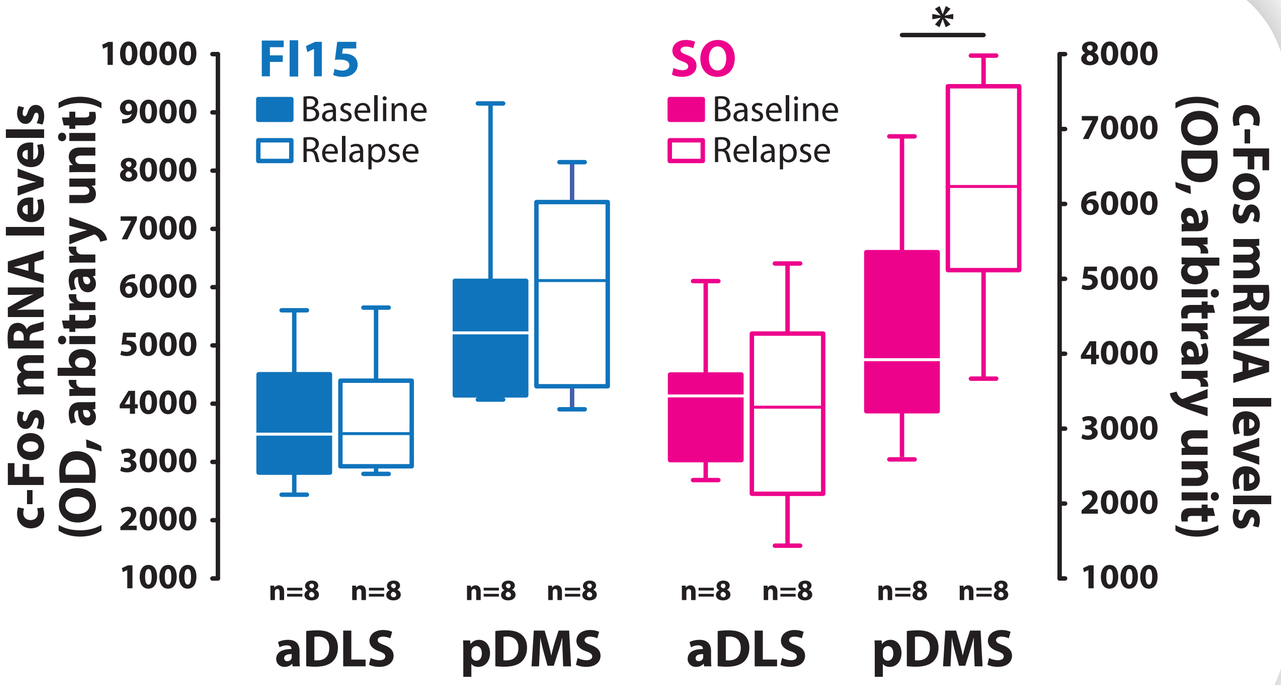




aDLS



pDMS

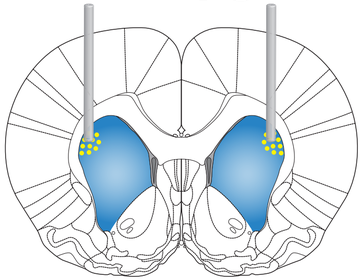


Instrumental deprivation effect: a new goal-directed schemata the goal of which is responding leading to the alleviation of an aversive internal state associated with negative urgency

Fouyssac et al., Biol. Psy 2022

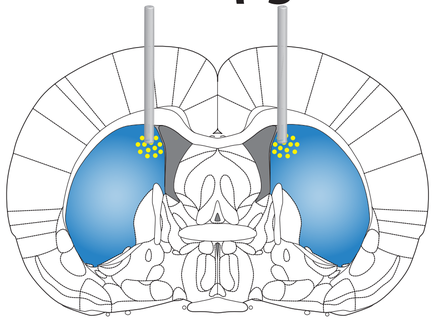
Incentive habits: flexibility in the inflexibility - causal evidence

α-Flu: 10µg/side



aDLS

α-Flu: 10µg/side



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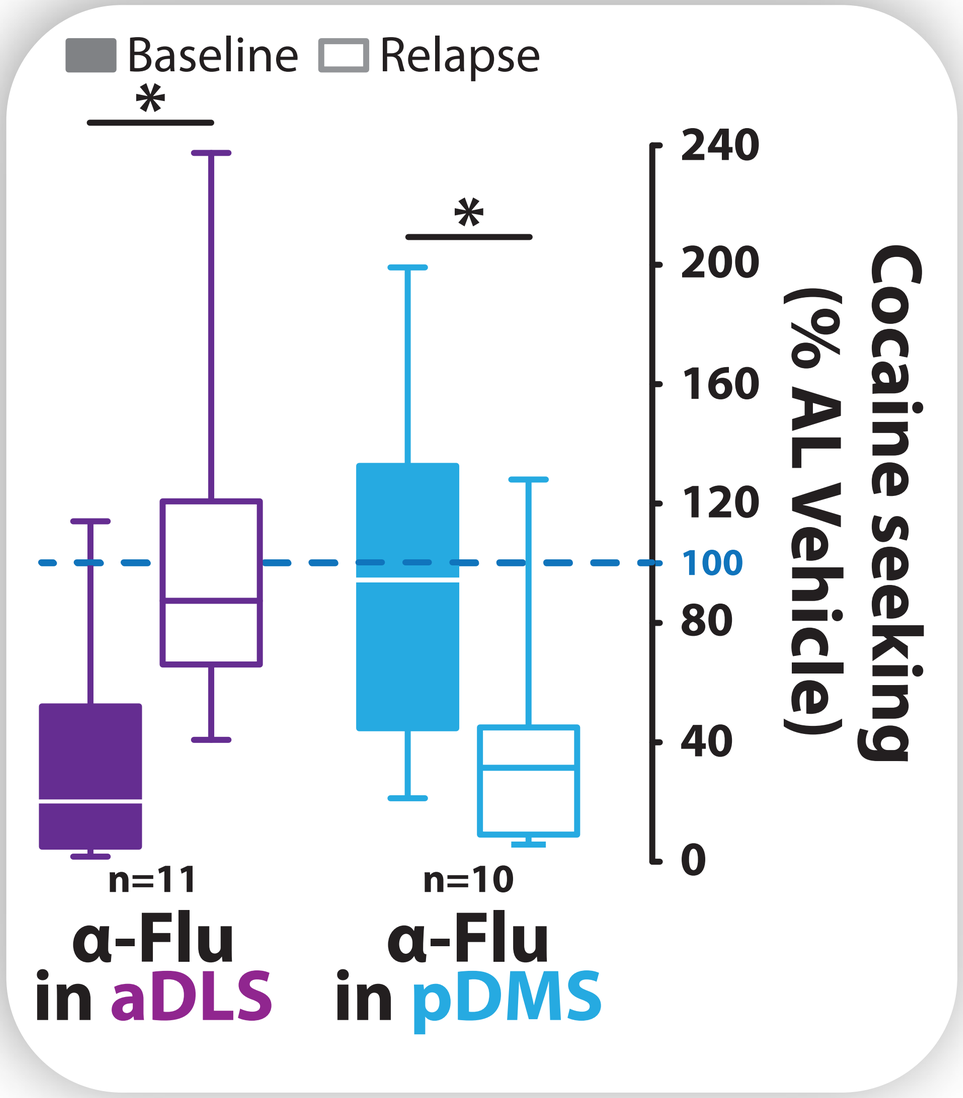
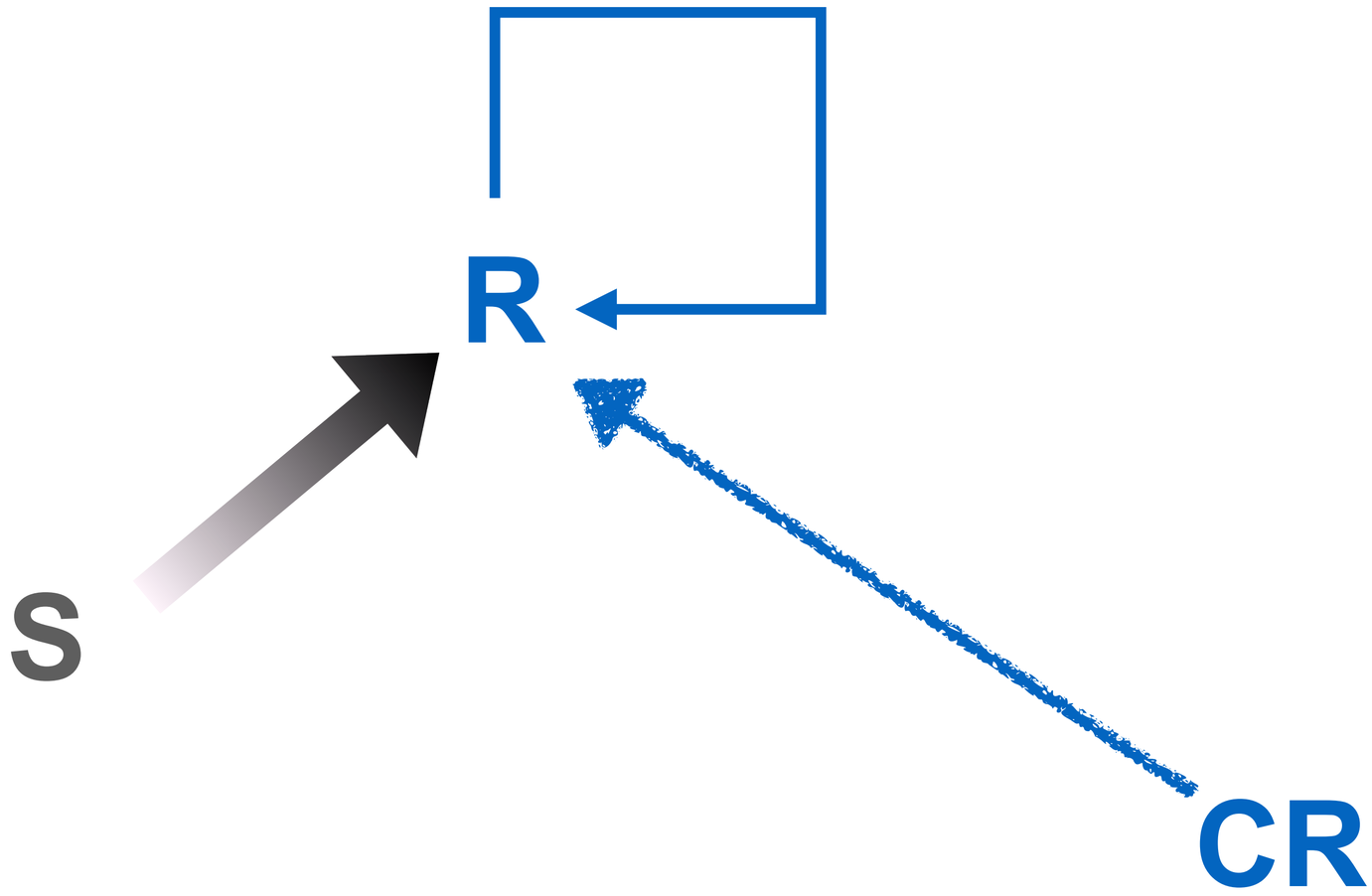


Fouyssac et al., Biol. Psy 2022

Incentive habits: flexibility in the inflexibility

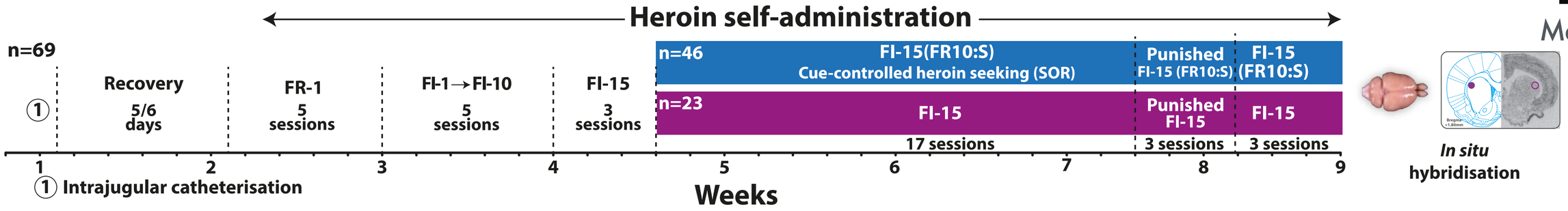


Compulsion resulting from a response aiming at reducing distress and alleviating the urge for action: negative reinforcement beyond withdrawal.

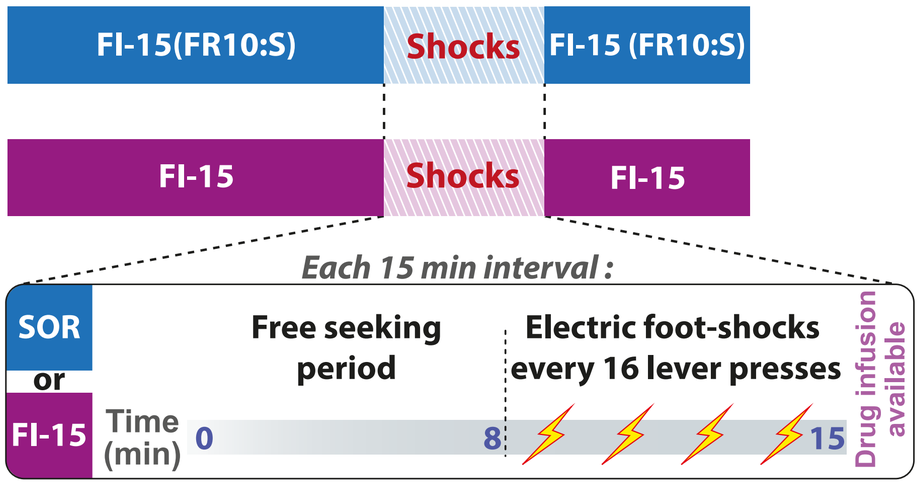
Incentive habits and compulsive behaviours in OUD

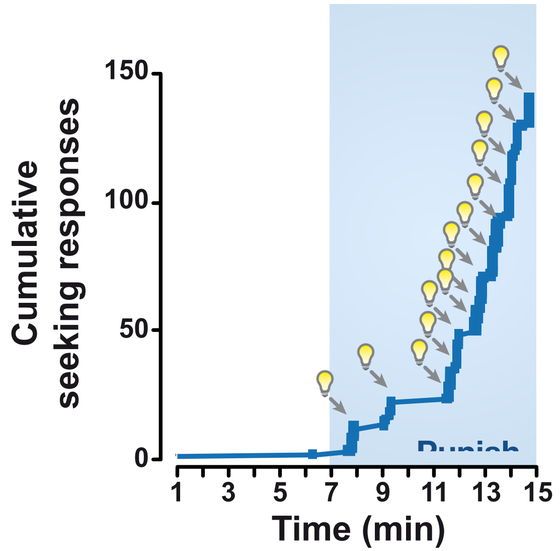
Instrumental deprivation effect: voluntary abstinence in heroin seeking

Maxime Fouyssac



In situ hybridisation

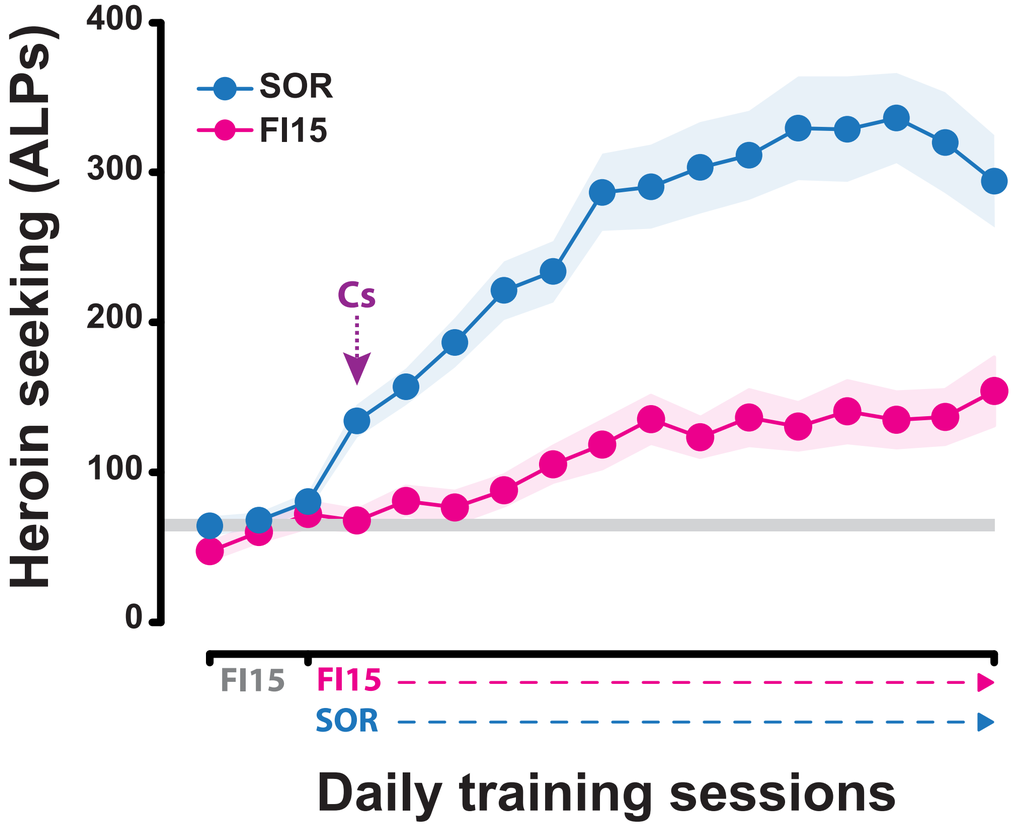


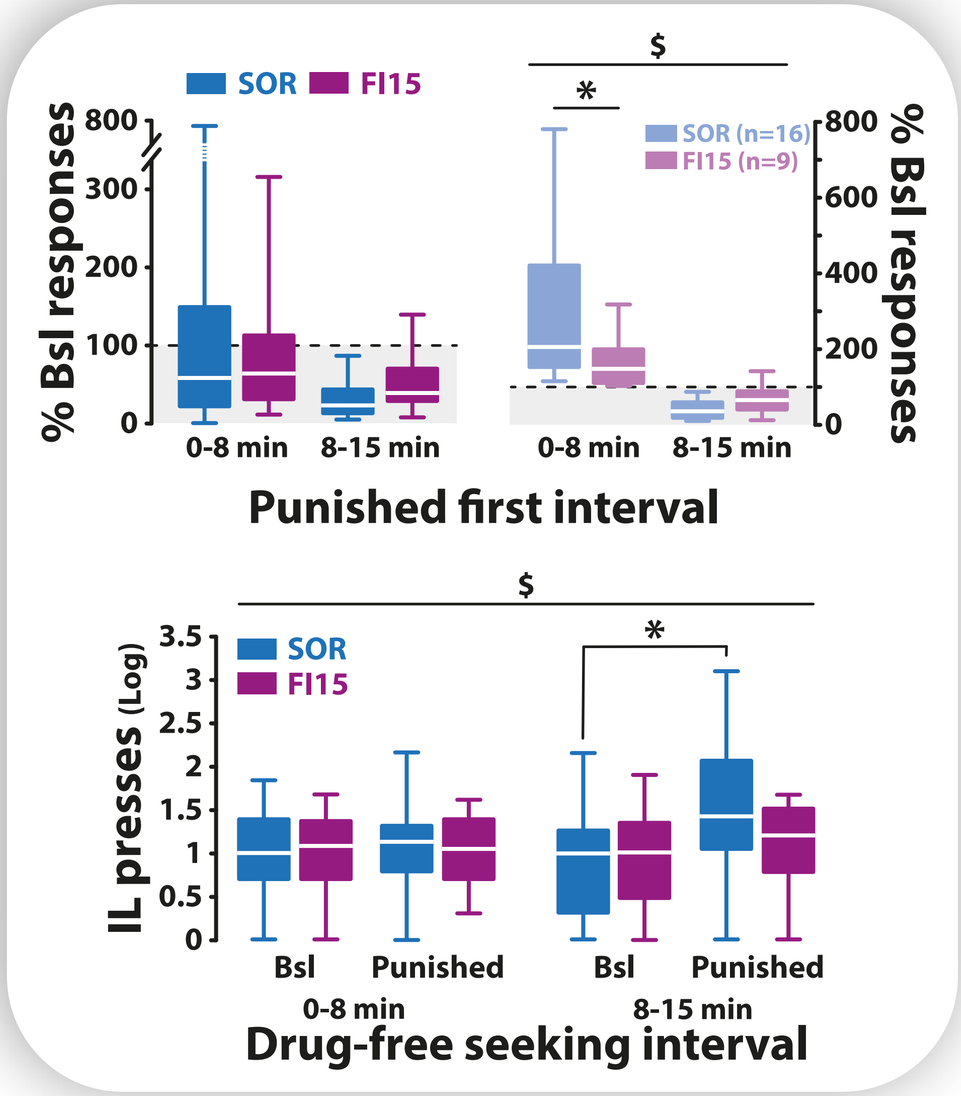


Fouyssac et al., Unpublished

Incentive habits and compulsive behaviours in OUD

Incentive habits promote a compulsion to respond maladaptively in anticipation of, and under, punishment

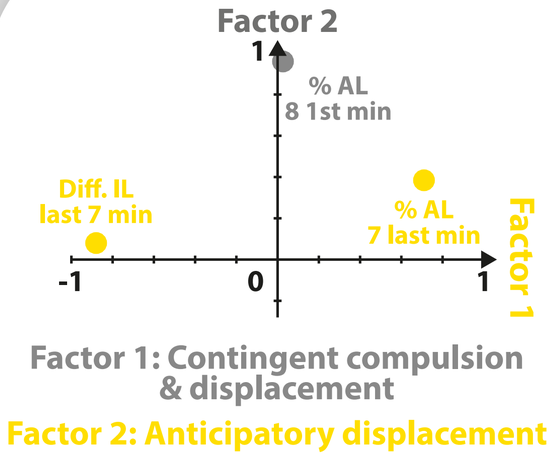




Fouyssac et al., Unpublished

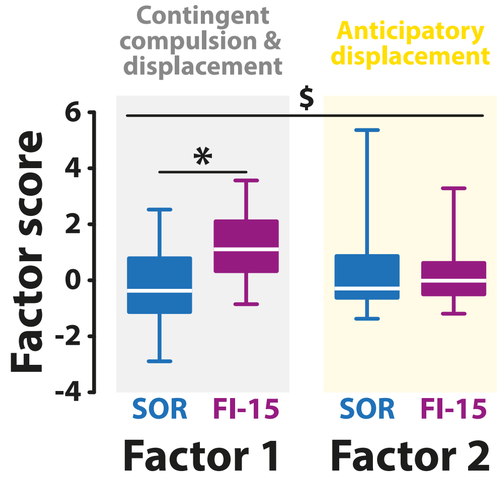
Incentive habits and compulsive behaviours in OUD

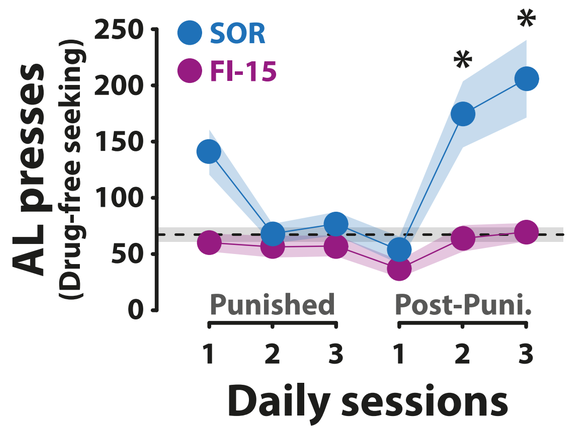
The compulsion to respond maladaptively in anticipation of, and under, punishment predicts compulsive relapse in individuals with an incentive heroin-seeking habit

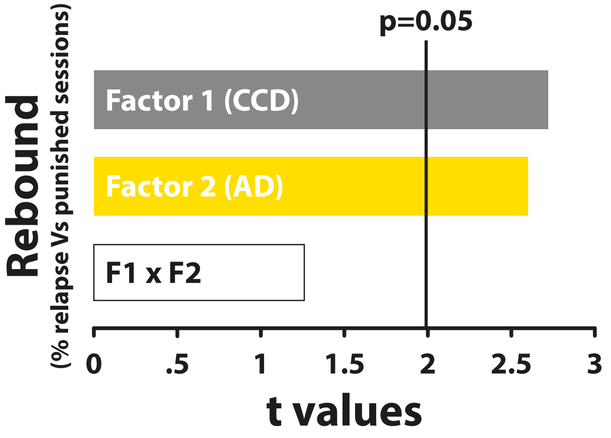


Factor 1: Contingent compulsion & displacement

Factor 2: Anticipatory displacement







Fouyssac et al., Unpublished

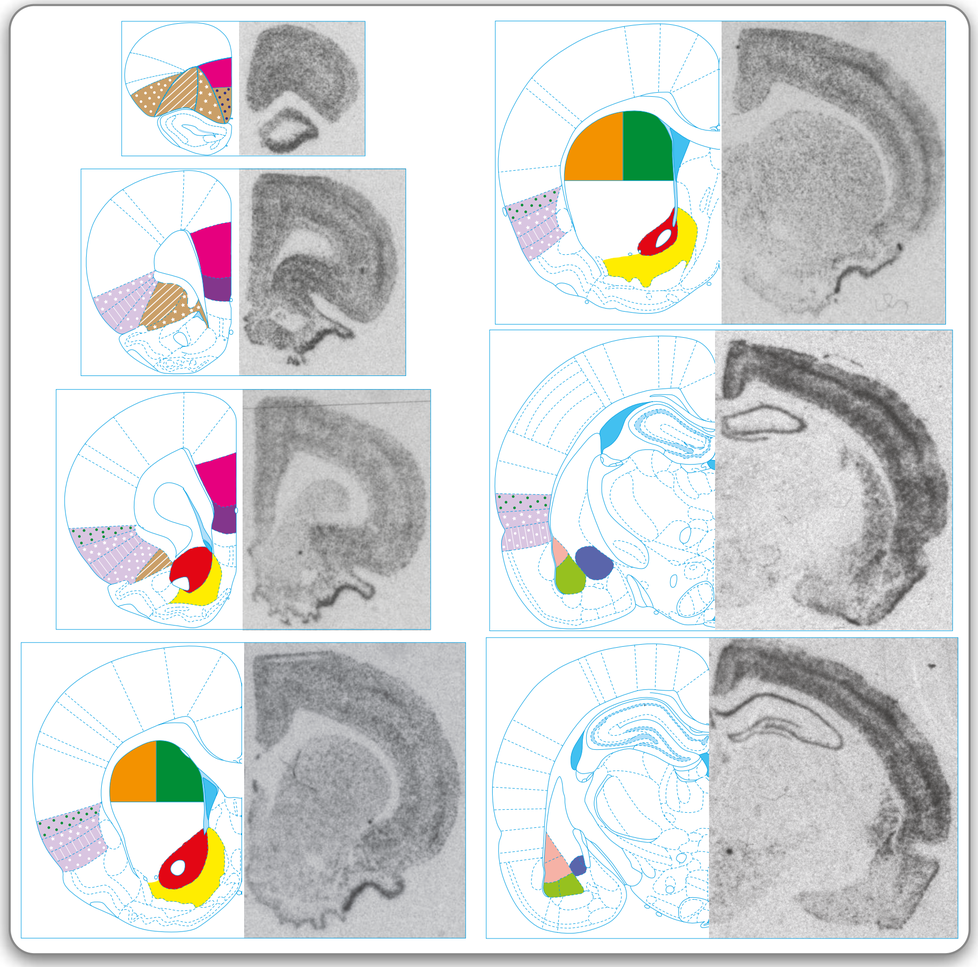
Incentive habits

Neural basis of incentive heroin seeking habits and their compulsive manifestations

Incentive habits: neural signature of incentive heroin seeking habits

Functional convergence matrices of Zif268 mRNA levels in discrete regions

In Situ hybridisation targeting ZIF-268 mRNA



OFC
- Dorsolateral
- Lateral
- Ventral
- Medial

Insular Cortex
- Agranular ventral
- Agranular dorsal
- Dysgranular
- Granular

mPFC
- Infralimbic cortex
- Prelimbic cortex

Amygdala
- Central Amygdala
- Lateral Amygdala
- Basolateral Amygdala

Striatum
- Dorsolateral striatum
- Dorsomedial striatum
- Nucleus accumbens core
- Nucleus accumbens shell

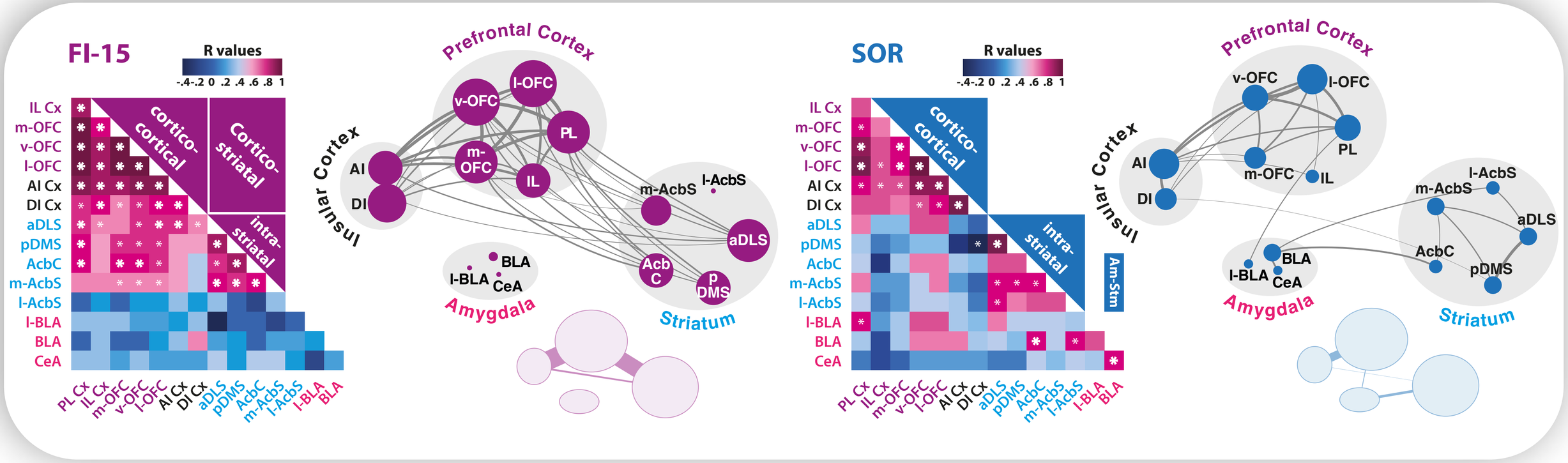
Fouyssac et al., In preparation

Incentive habits: neural signature of incentive heroin seeking habits

Functional convergence matrices of Zif268 mRNA levels in discrete regions

Habits

Incentive habits



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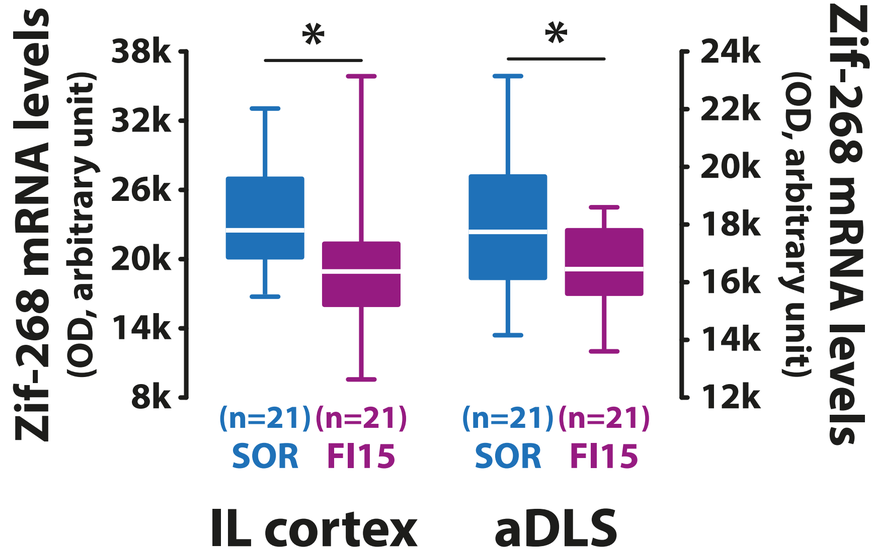
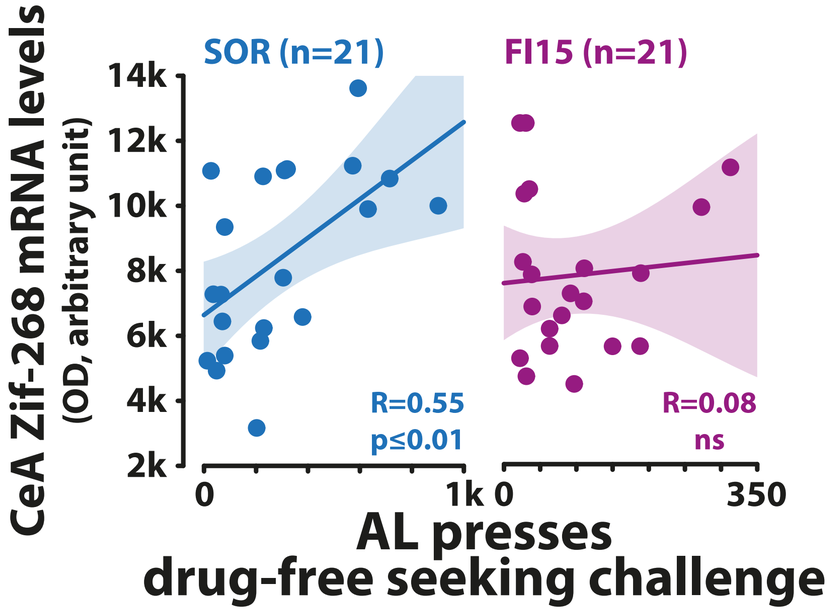
Incentive habits: neural signature of incentive heroin seeking habits

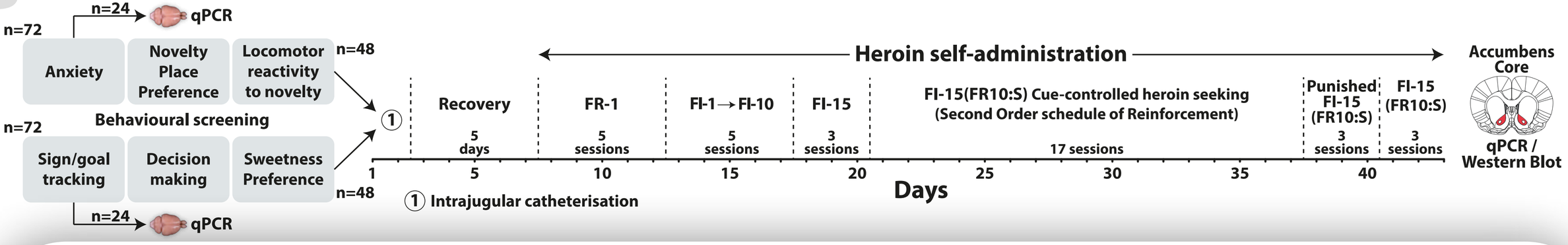
Greater plasticity in the habit system in incentive habits

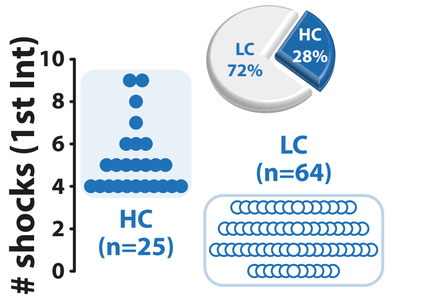


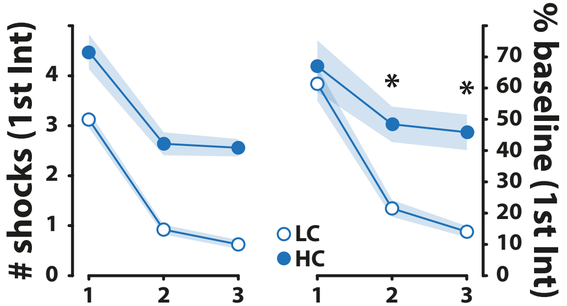


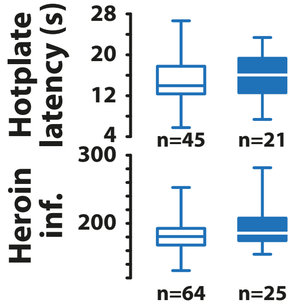
Fouyssac et al., In preparation

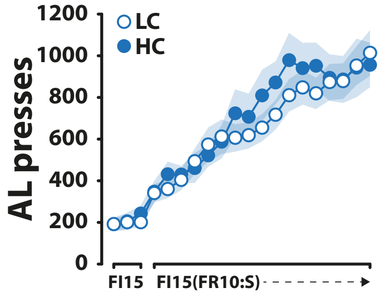
Compulsive incentive habits

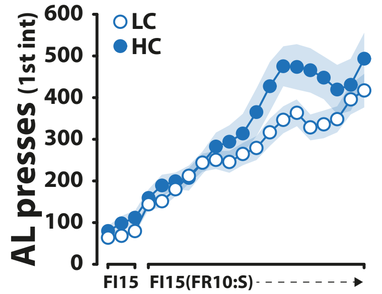


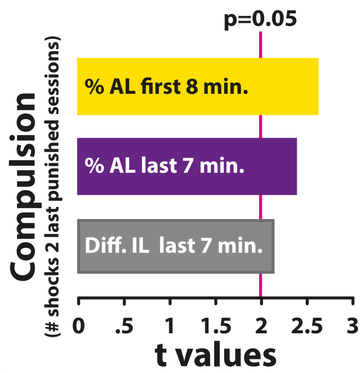


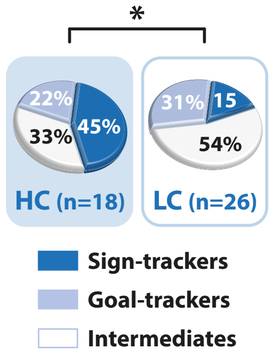


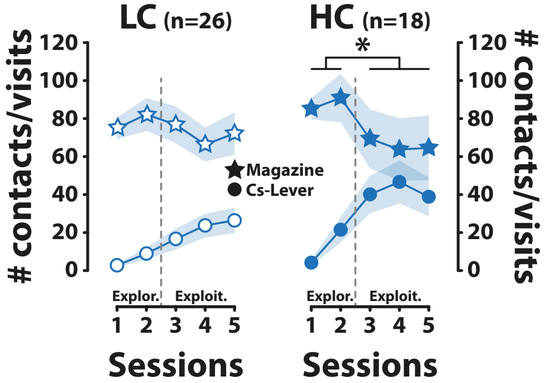


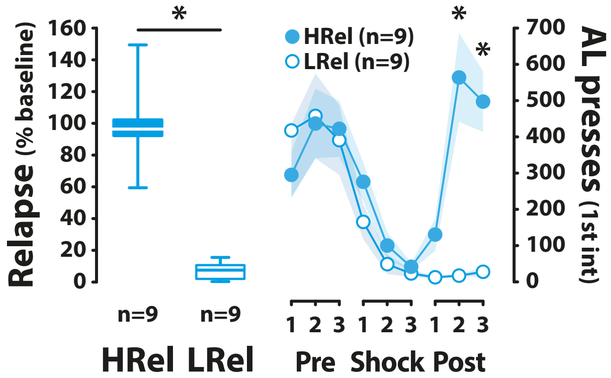


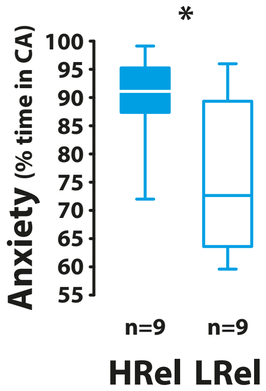








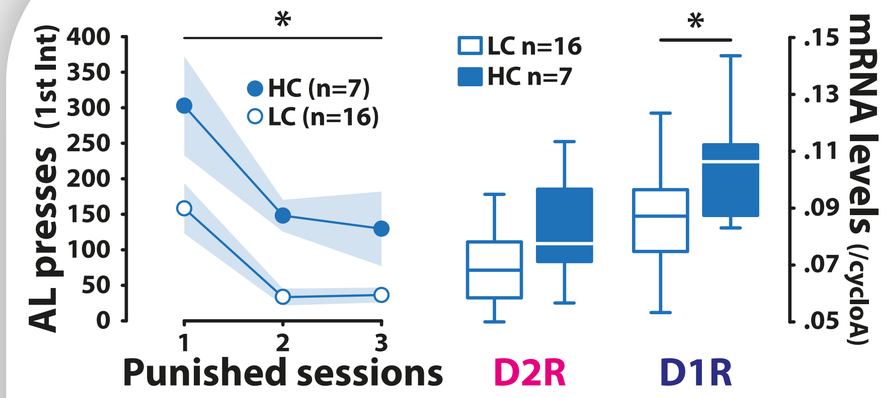


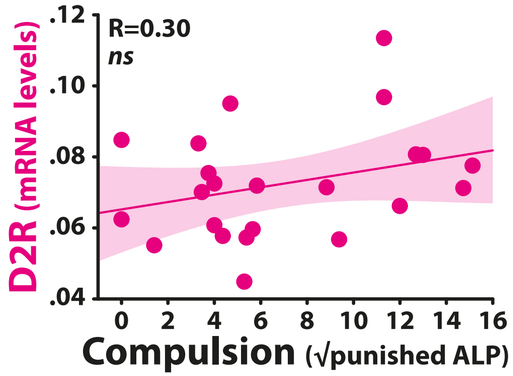


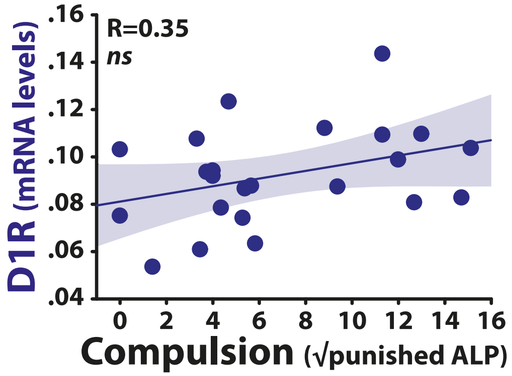
Fouyssac et al., In preparation

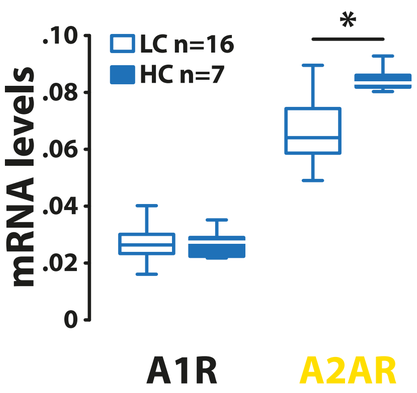
Compulsive incentive habits: purinergic mechanisms

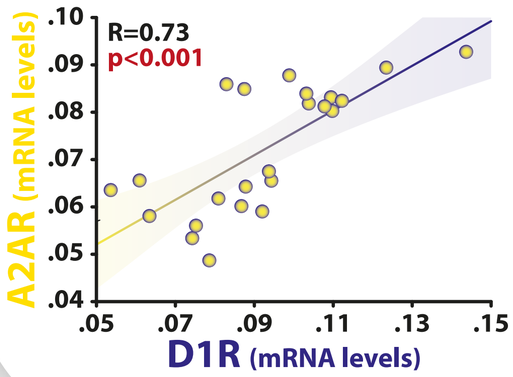
Compulsion is associated with A2AR mRNA and protein levels in the NacC

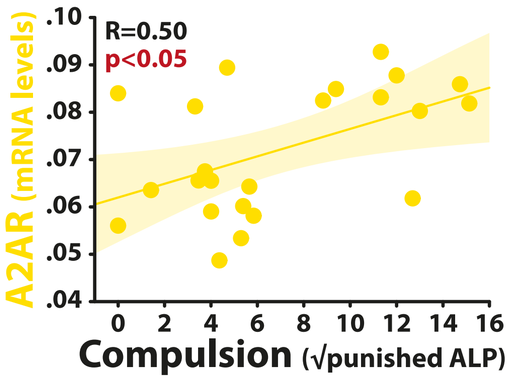


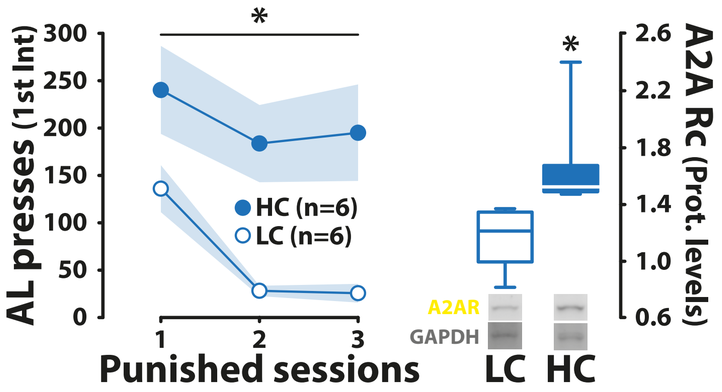


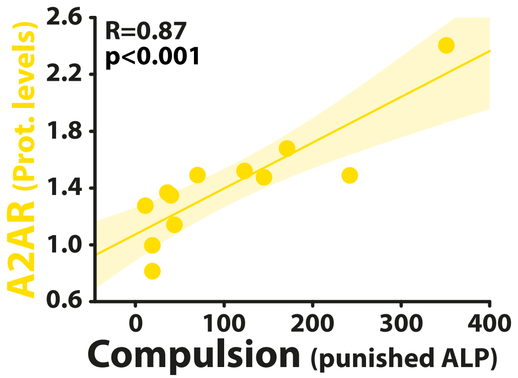








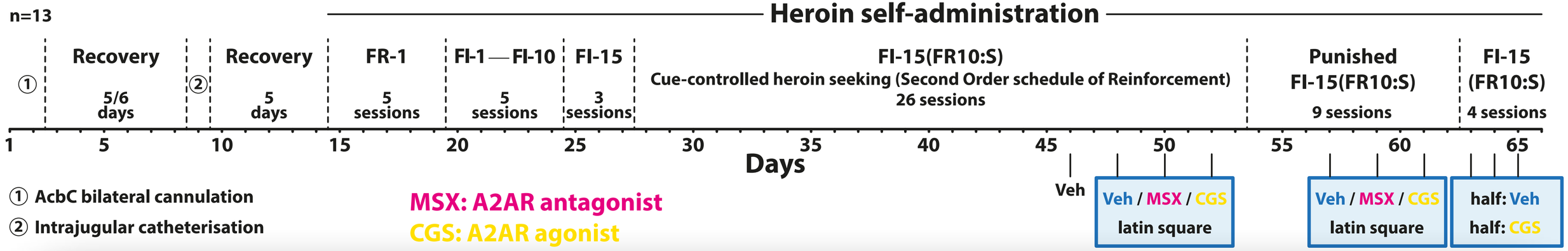


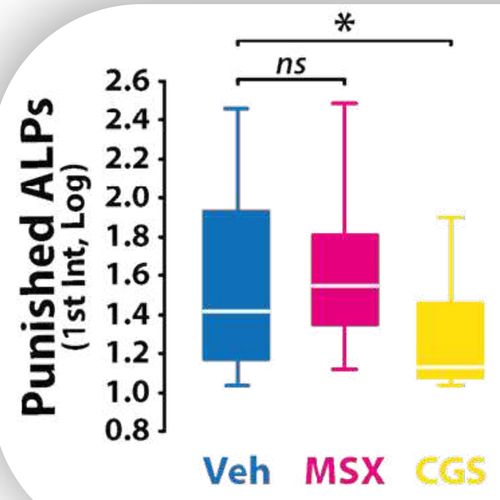


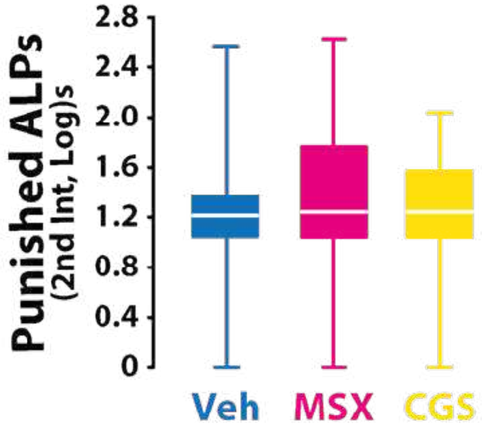
Fouyssac et al., In preparation

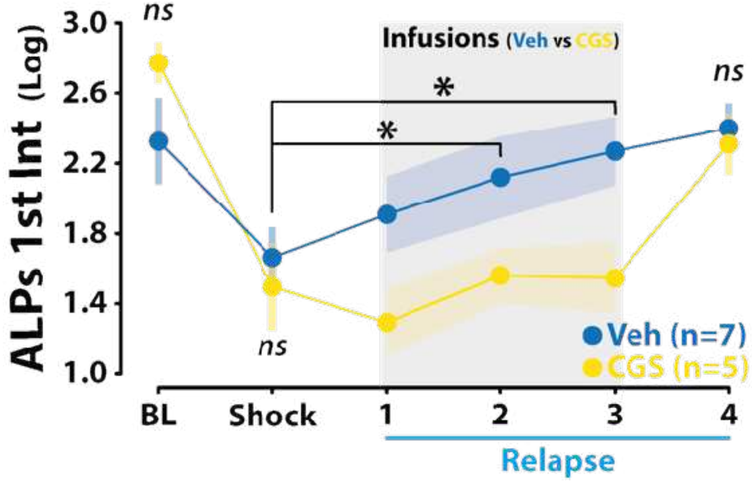
Compulsive incentive habits: purinergic mechanisms

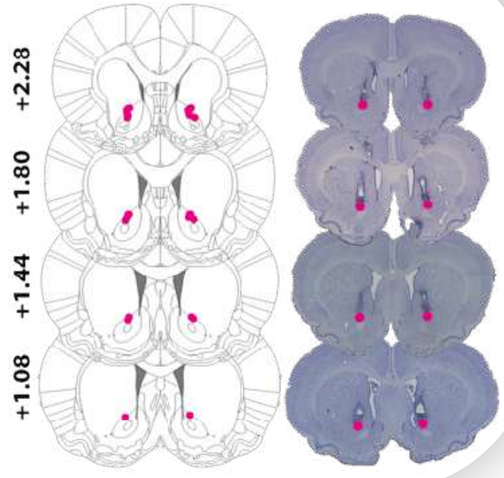
Causal evidence for a role of A2ARs in compulsive incentive heroin seeking habits and relapse











Fouyssac et al., In preparation

Conclusions

A long history of drug seeking under the control of the conditioned reinforcing properties of the drug-paired cues results in incentive habits.

Individuals prevented from enacting their incentive habits experience and urge to respond that is mediated by a new goal-directed schemata, the goal of which is not the drug, but the response.

This promotes responding in the face of future negative consequences that will result in an inability to fulfil the incentive habit and an increased tendency to relapse following self-imposed abstinence.

Incentive habits are associated with a specific corticostriatal functional signature similar to that observed in humans with SUD and purinergic mechanisms in the NacC.

Acknowledgements

Dr Aude Belin-Rauscent
Dr Maxime Fouyssac
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Dr Sue Jones

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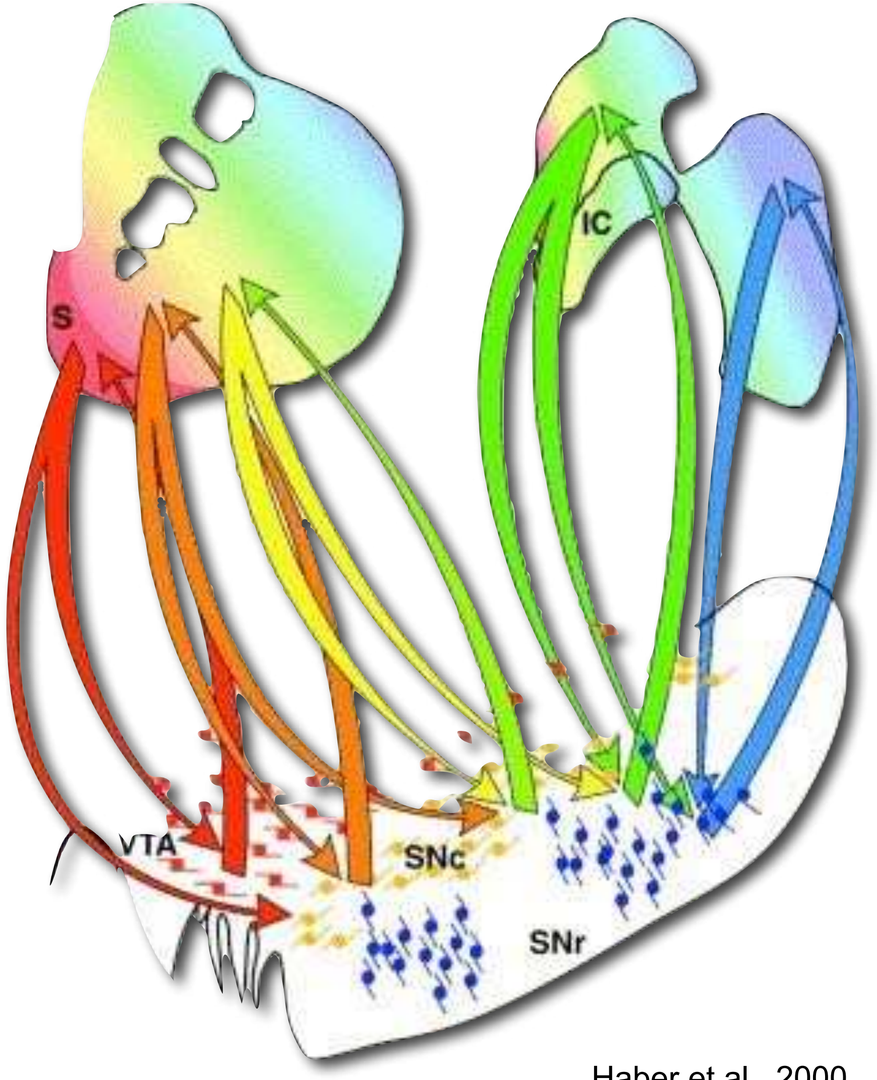
Dr Jenn Murray
Dr Alejandro Higuera-Matas

Professor Barry Everitt

Incentive habits

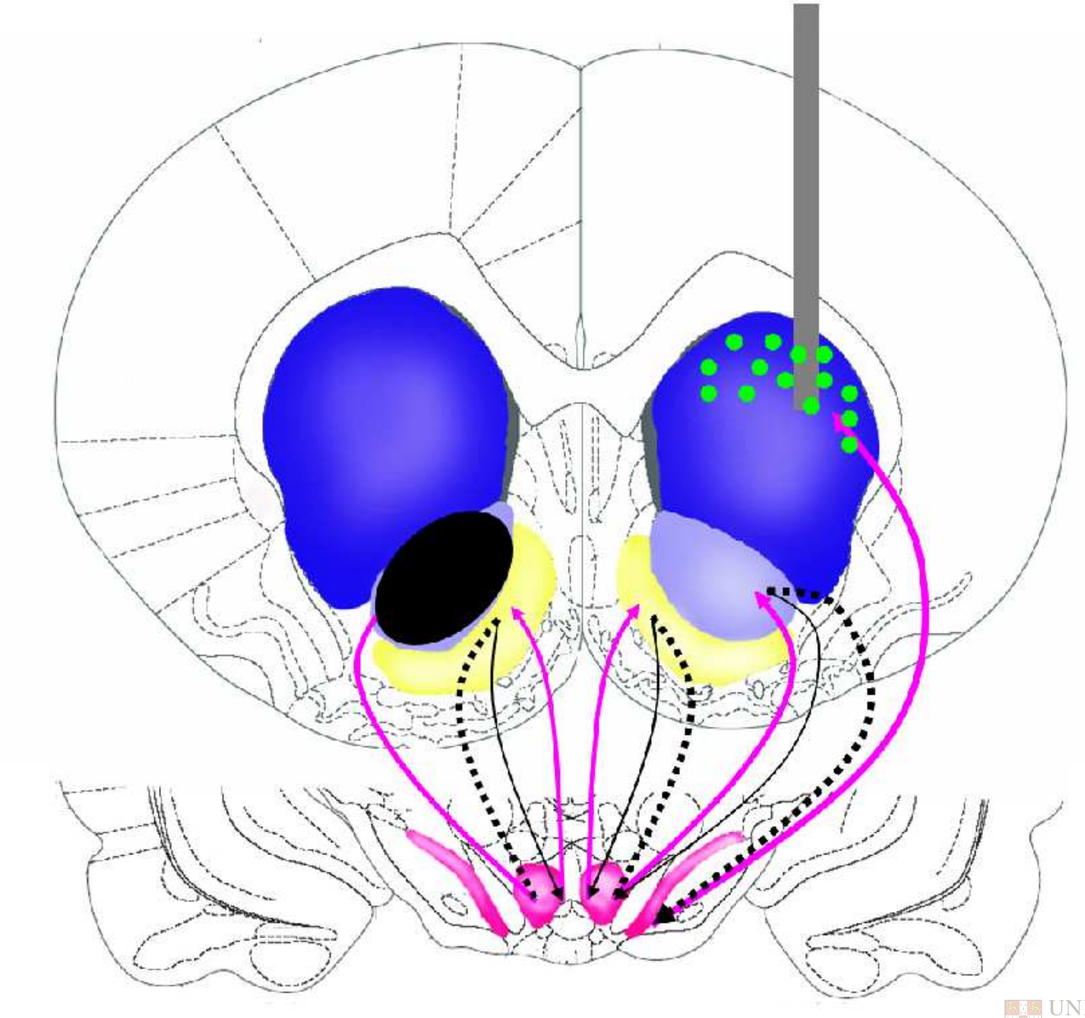
Neural basis of the ventral to dorsolateral striatal shift in the locus of control over cue-controlled drg seeking when it becomes habitual

Intrastriatal mechanisms of drug seeking habits

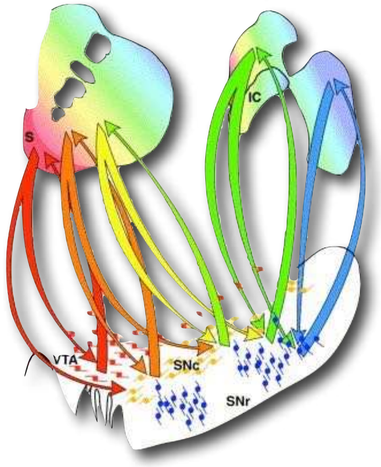


Haber et al., 2000

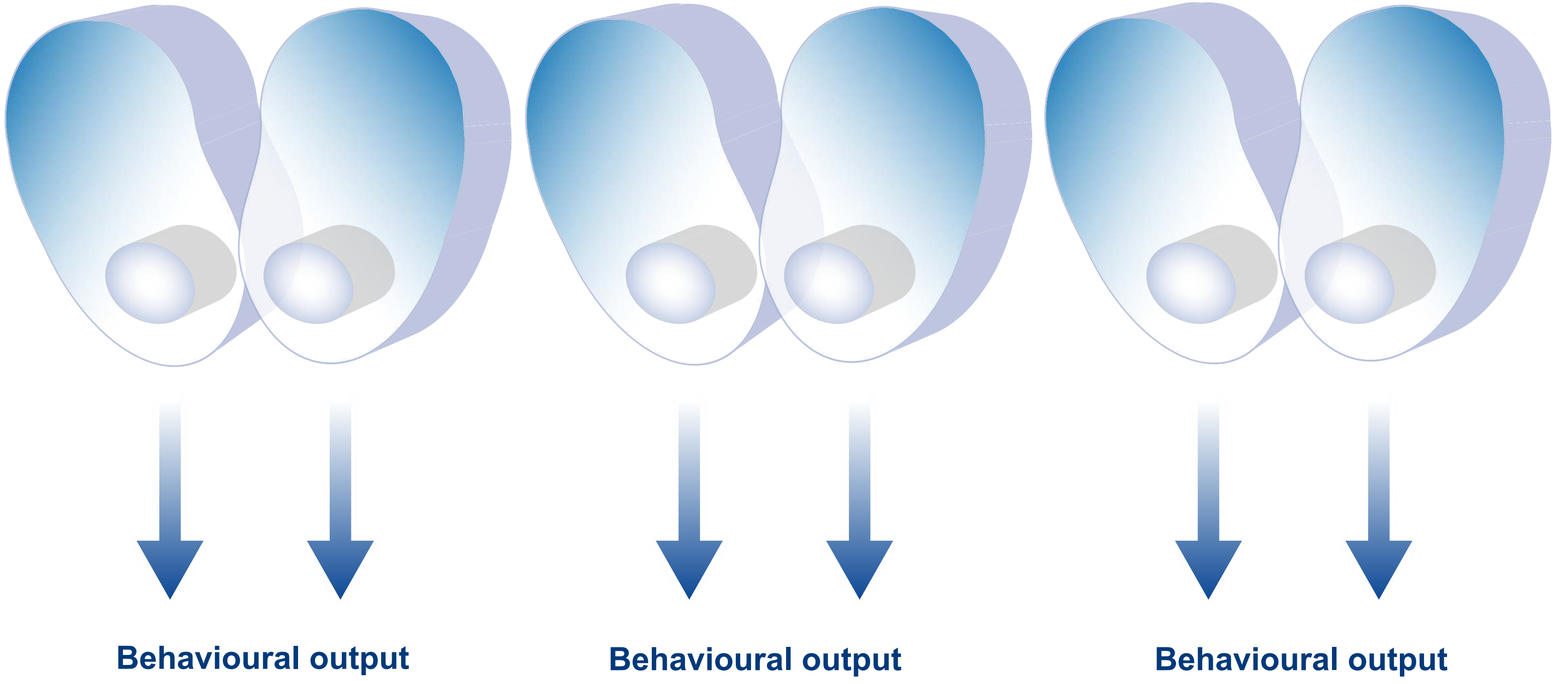
Intrastriatal functional disconnection



Functional disconnections

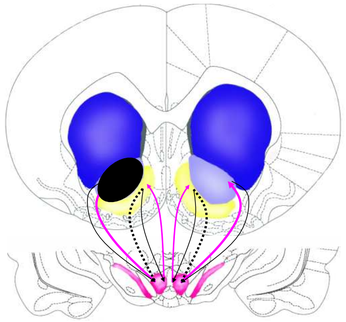


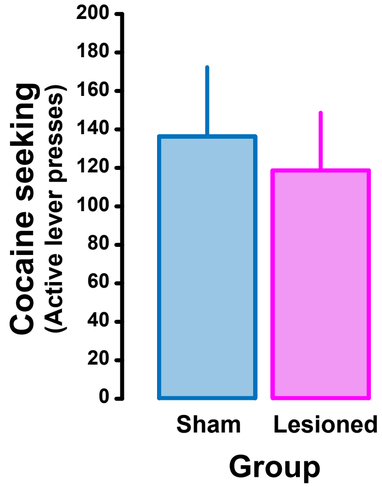
Haber et al., 2000

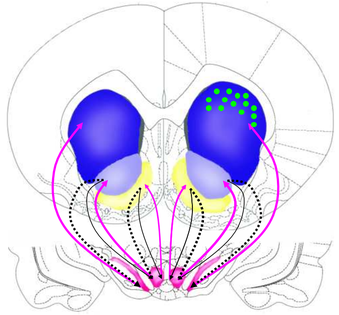


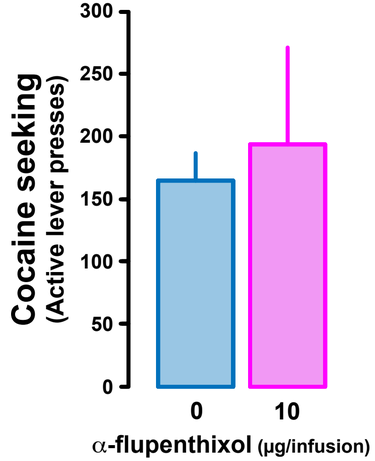
Intrastriatal mechanisms of cocaine seeking habits

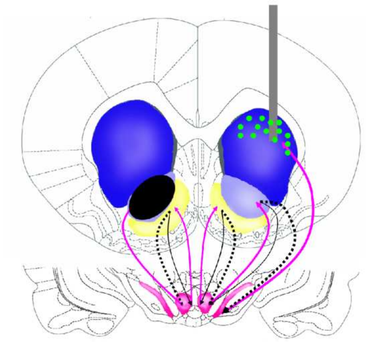
Cocaine seeking habits depend upon functional interactions between the ventral and the dorsolateral striatum

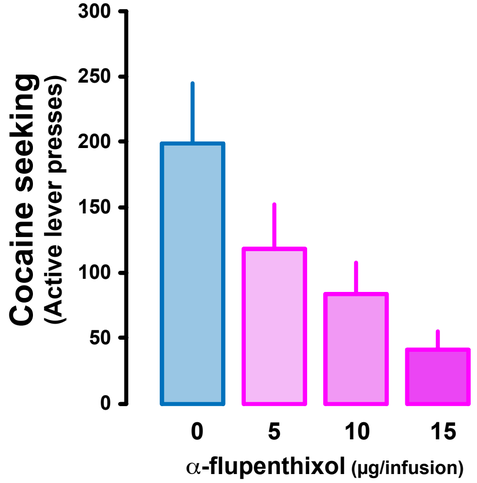


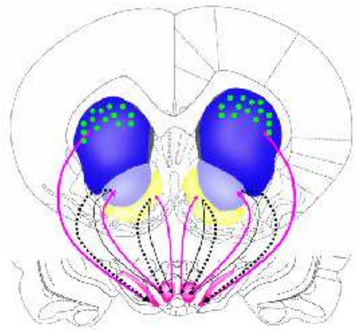


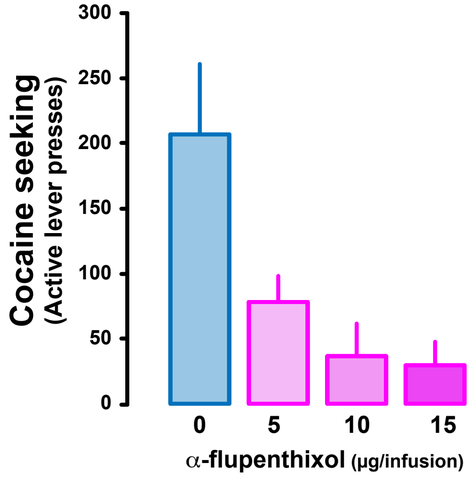












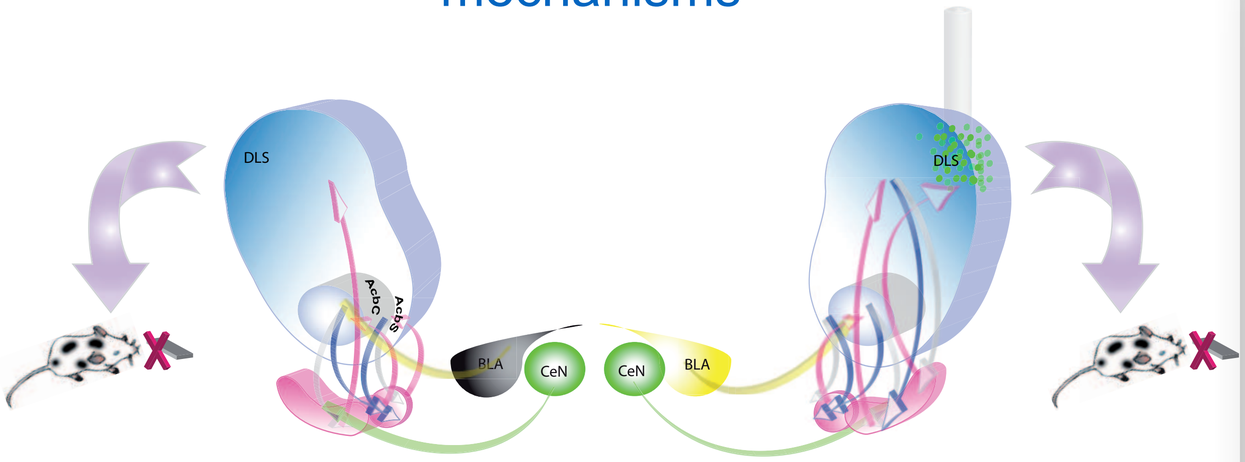
Belin & Everitt, Neuron 2008

Incentive habits

But, what drives this shift?

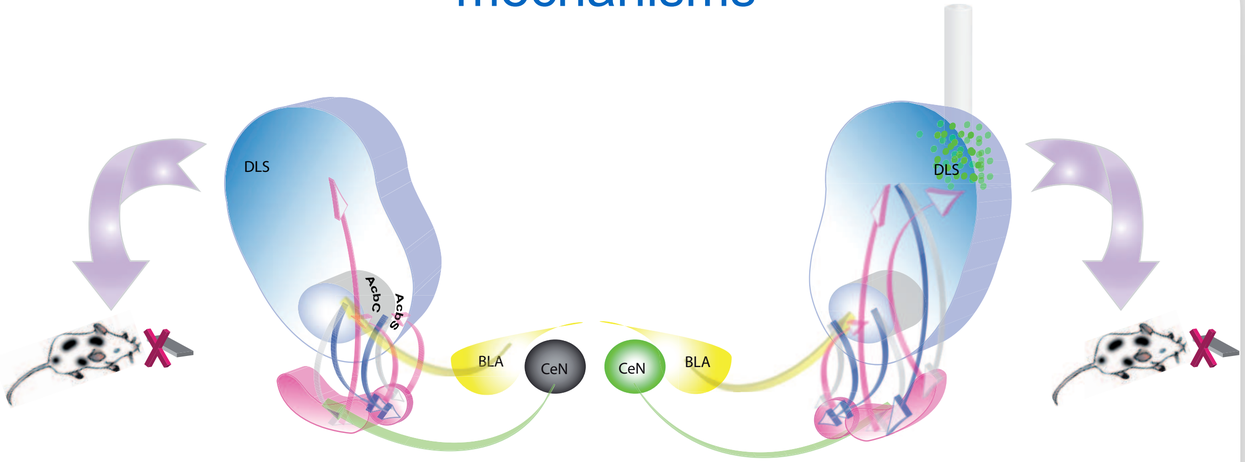
The BLA recruits aDLS-dependent control via antecedent glutamatergic mechanisms in the NAcC

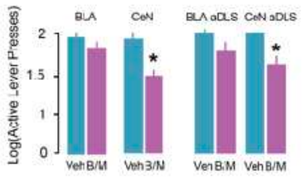
Disconnecting BLA from aDLS DA mechanisms



Prevents acquisition of incentive habits but not they long term expression

Disconnecting CeN from aDLS DA mechanisms

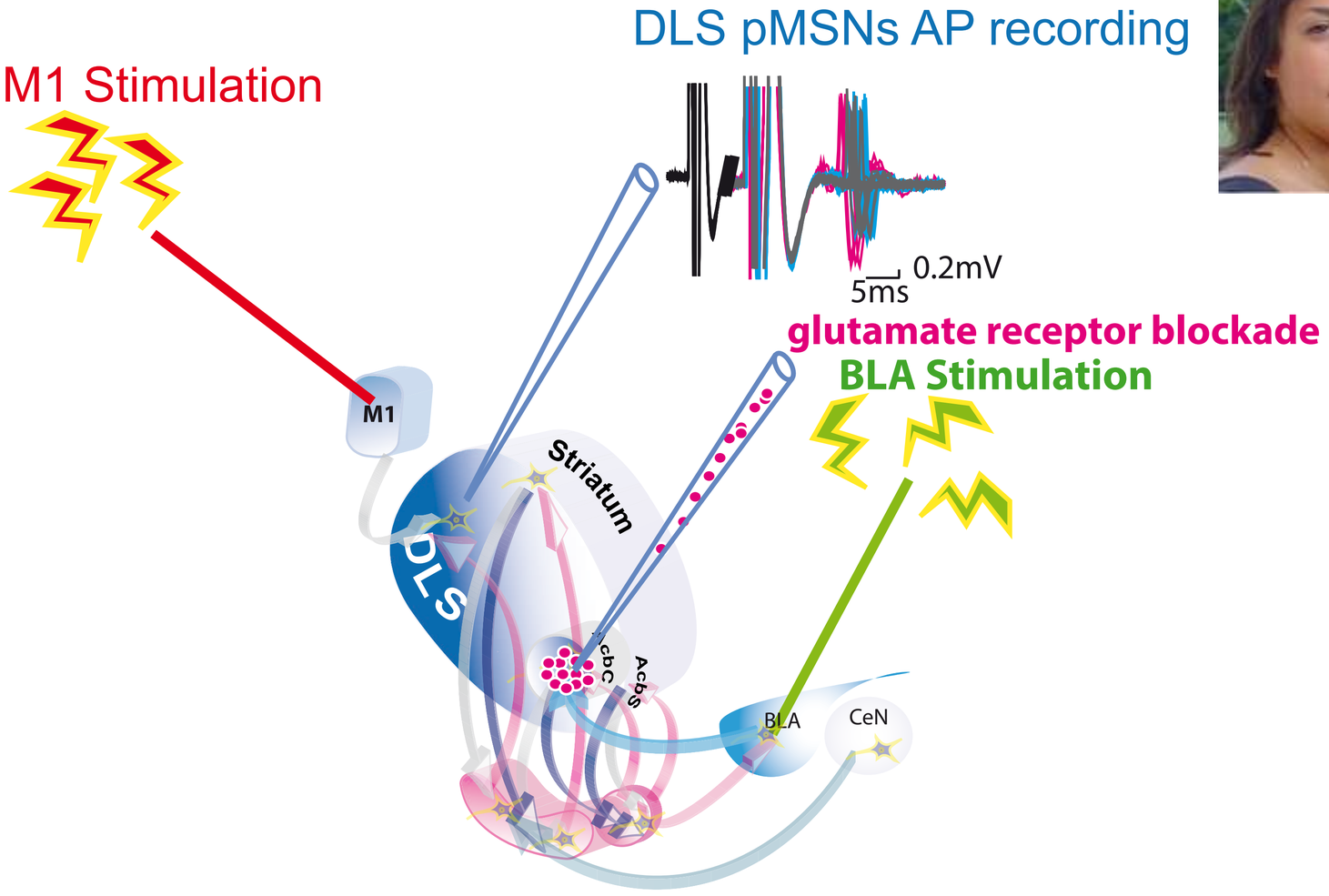


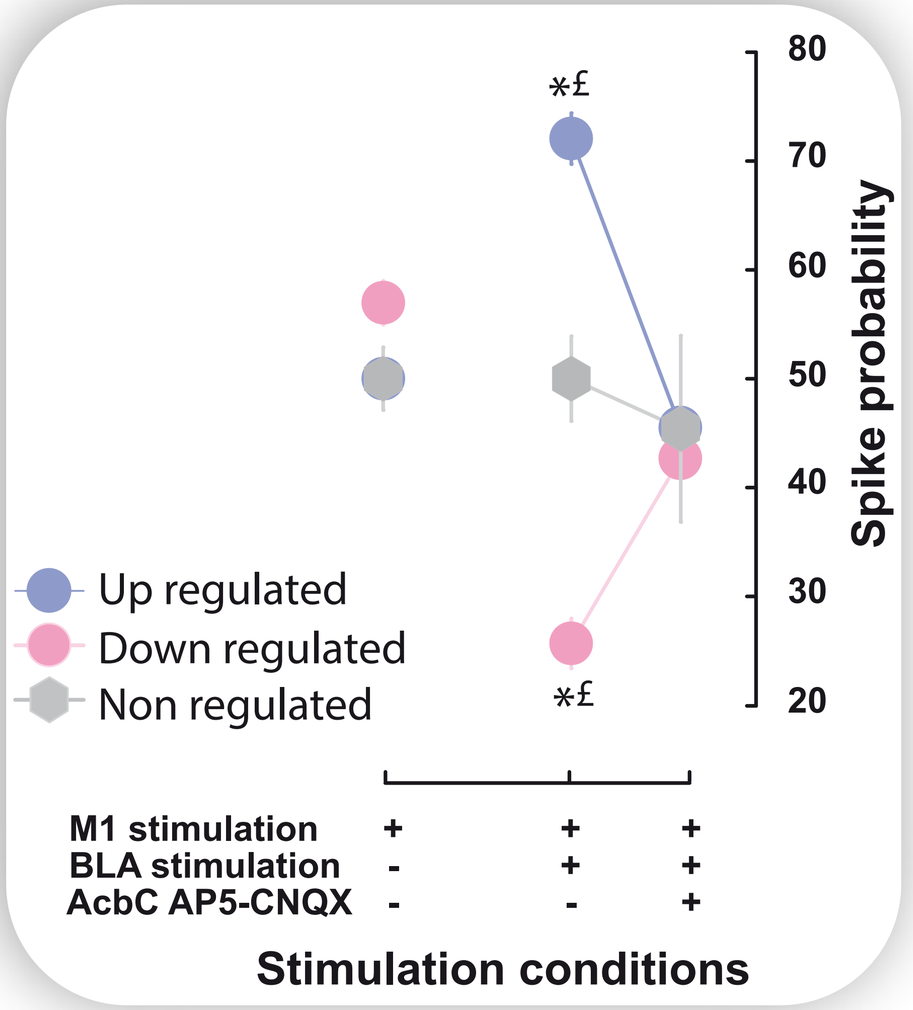


Prevents long term expression of incentive habits but not their development

Murray J., Belin-Rauscent A. et al. Nature Comm. 2015

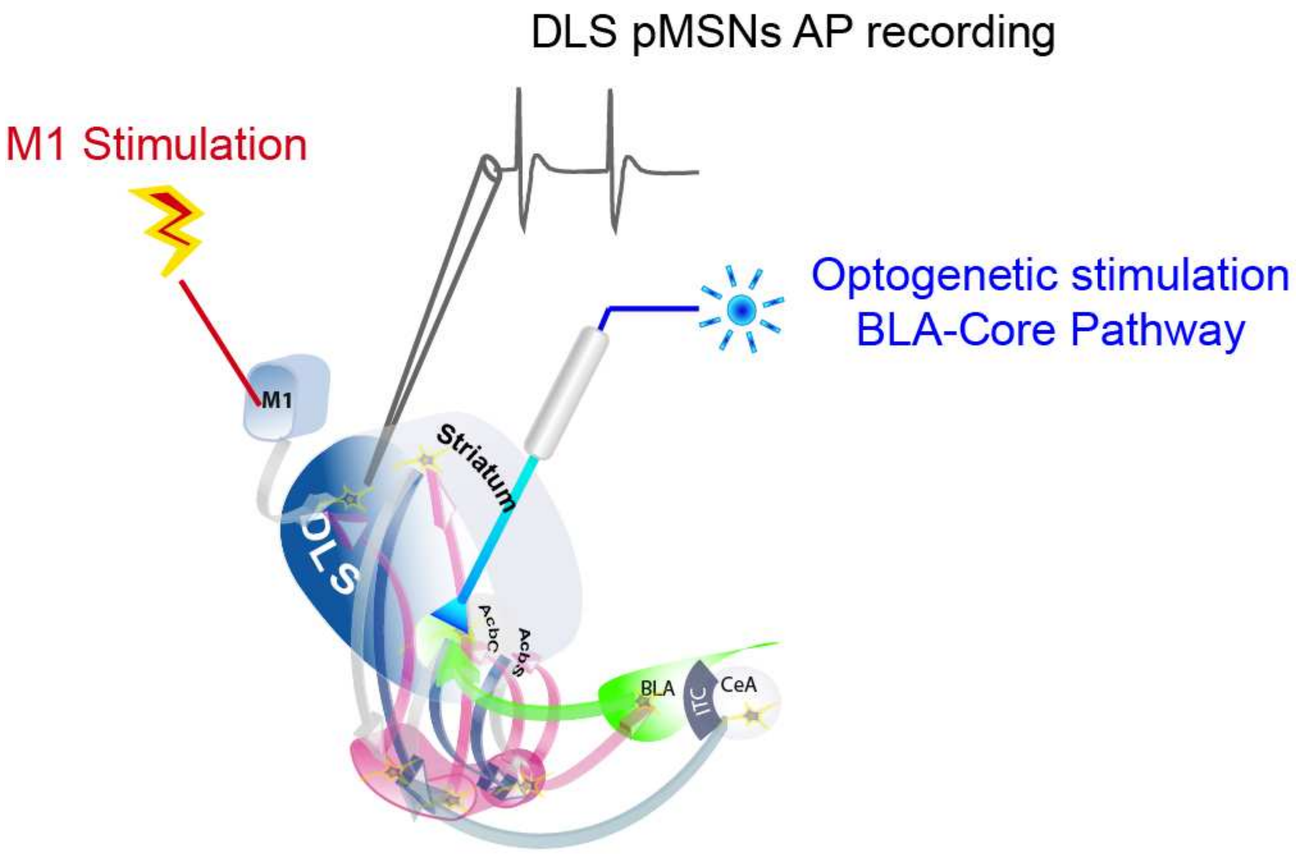
The BLA remotely controls aDLS-MSNs via glutamatergic mechanisms in the NAcC

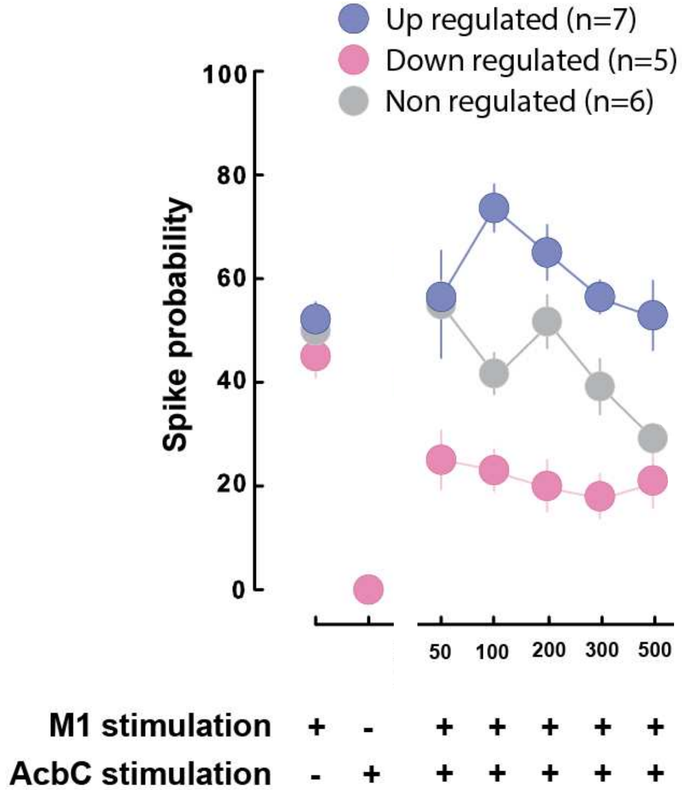




Murray J., Belin-Rauscent A. et al. Nature Comm. 2015

Photostimulation of BLA terminals in the NAcC controls the activity of aDLS MSNs





Belin-Rauscent A. et al. unpublished

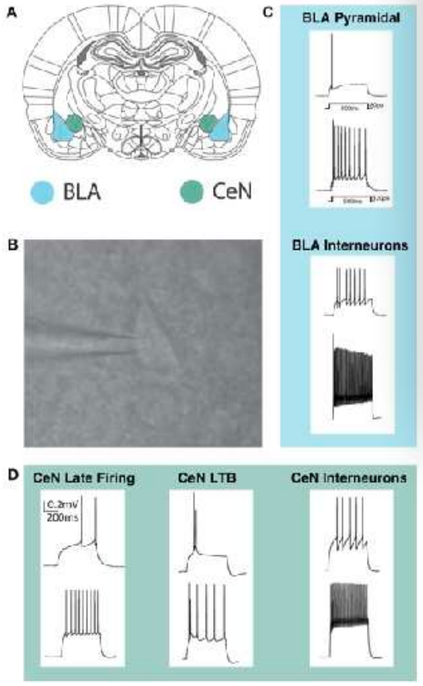
Incentive habits

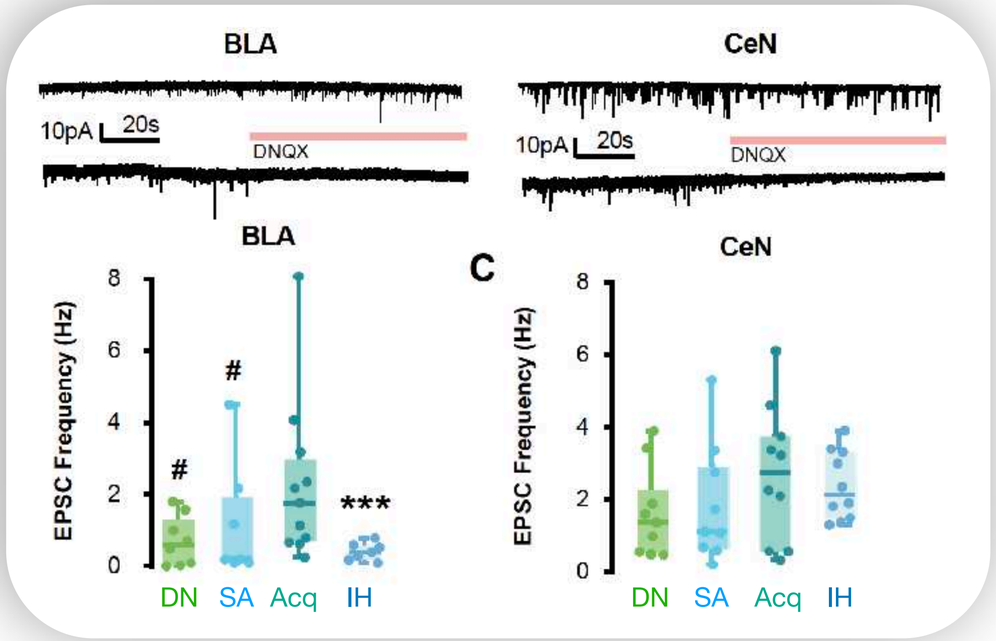
Cellular mechanisms in the BLA underlying the expression of incentive drug seeking habits

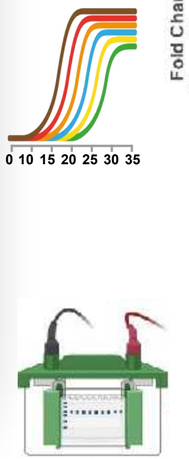
Sue Jones

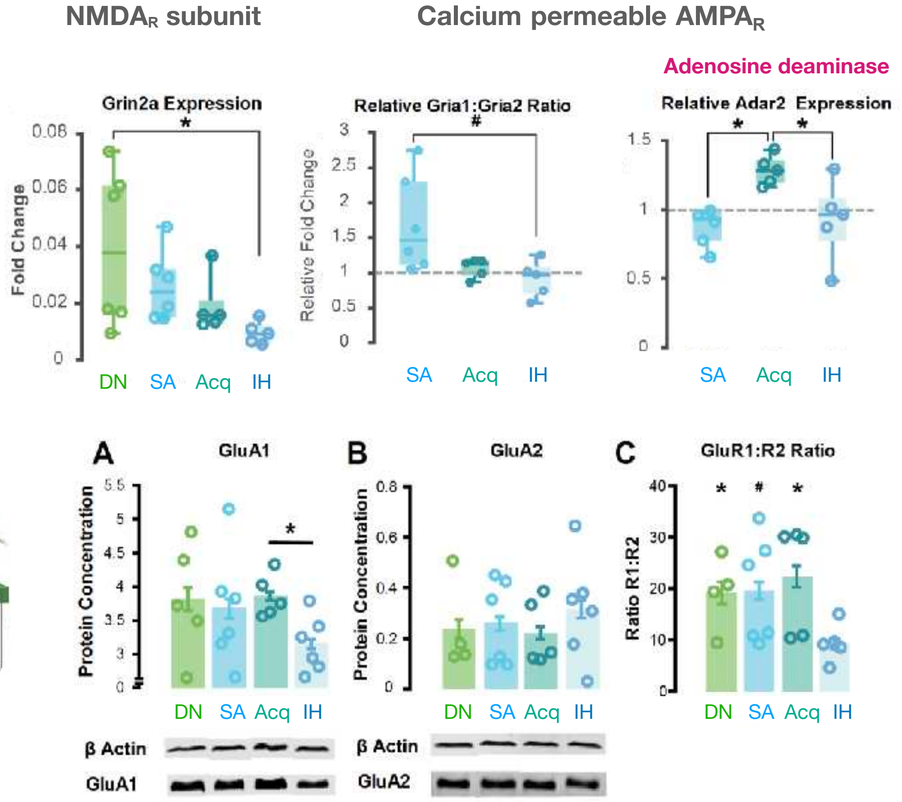
Changes in synaptic activity in the BLA over the course of the development of aDLS-dependent cocaine seeking habits

BLA synaptic activity increases during acquisition before decreasing during the habitual expression of cue-controlled cocaine seeking









Drug naive controls (DN)

Self-administration controls (SA)

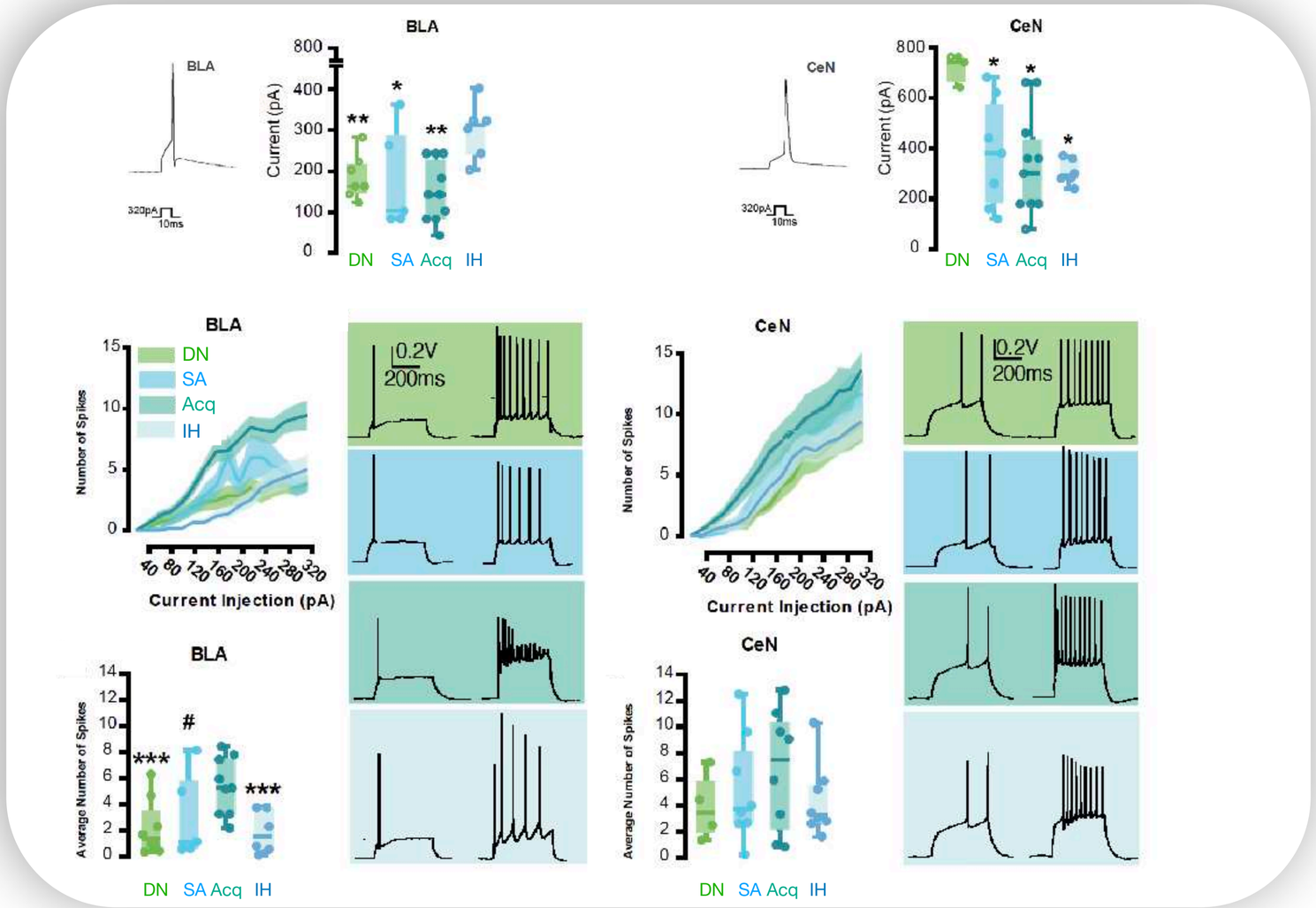
Acquisition of cue-controlled cocaine seeking (Acq)

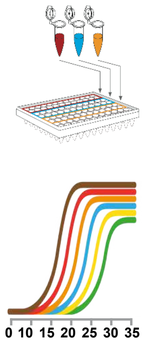
Incentive cocaine seeking habits (IH)

Stiebahl, Puaud, Jones, Belin, unpublished

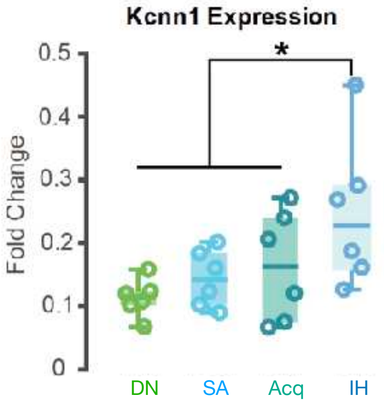
Changes in BLA excitibility over the course of the decelopment of aDLS-dependent cocaine seeking habits

BLA excitability increases during acquisition of cue-controlled cocaine seeking before decreasing when it becomes habitual





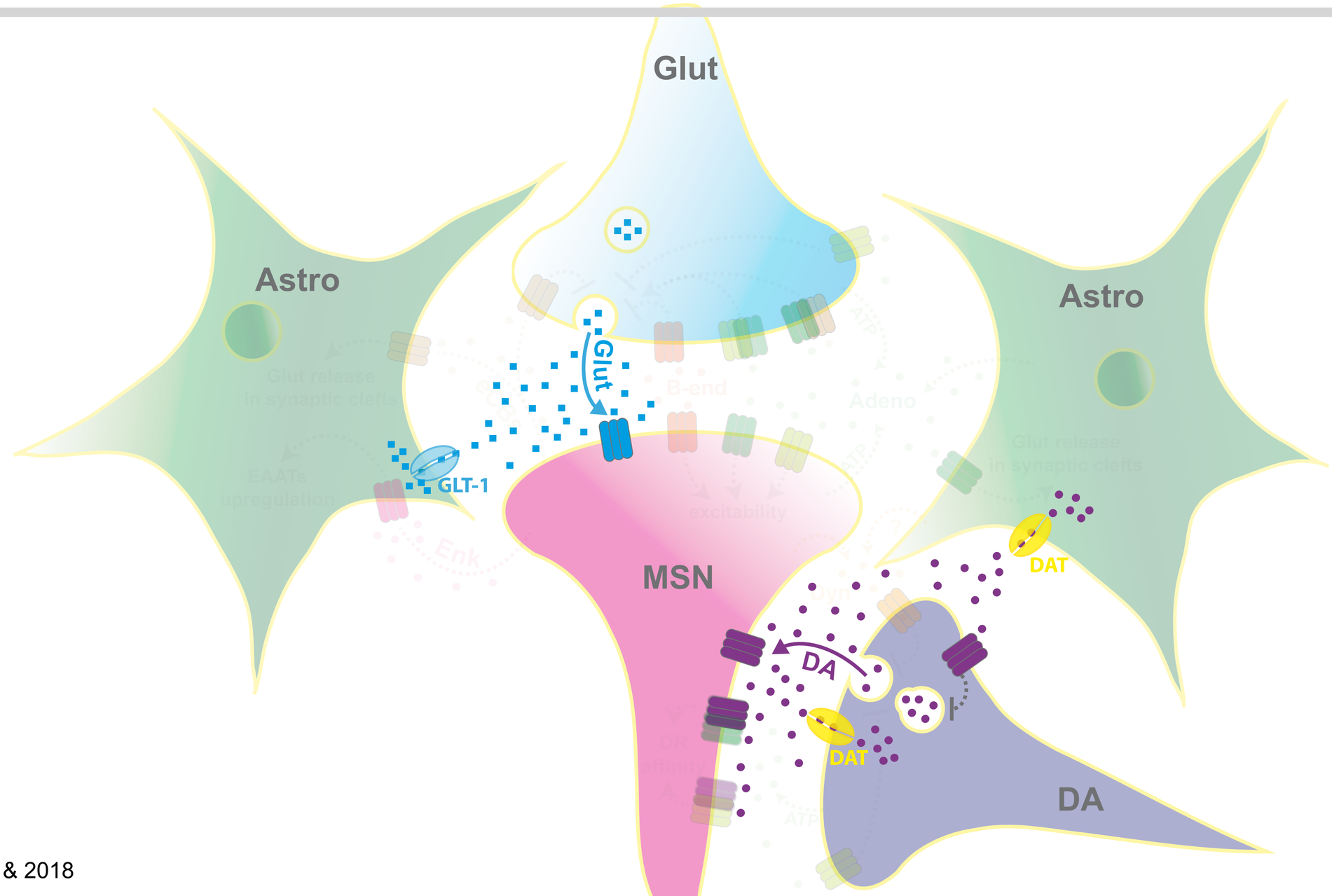
Calcium-gated potassium channel



Incentive habits

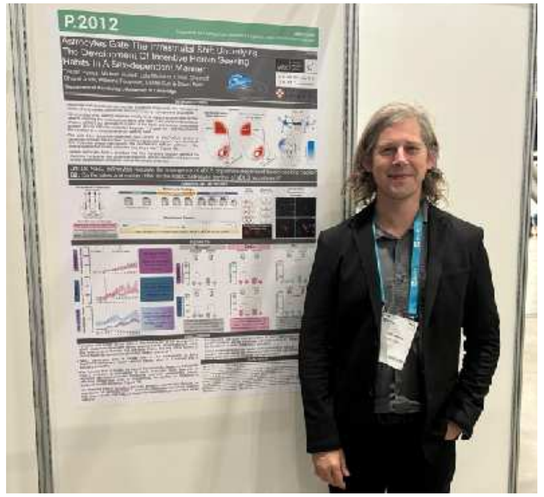
The unexpected guest: more to incentive habits than neural systems

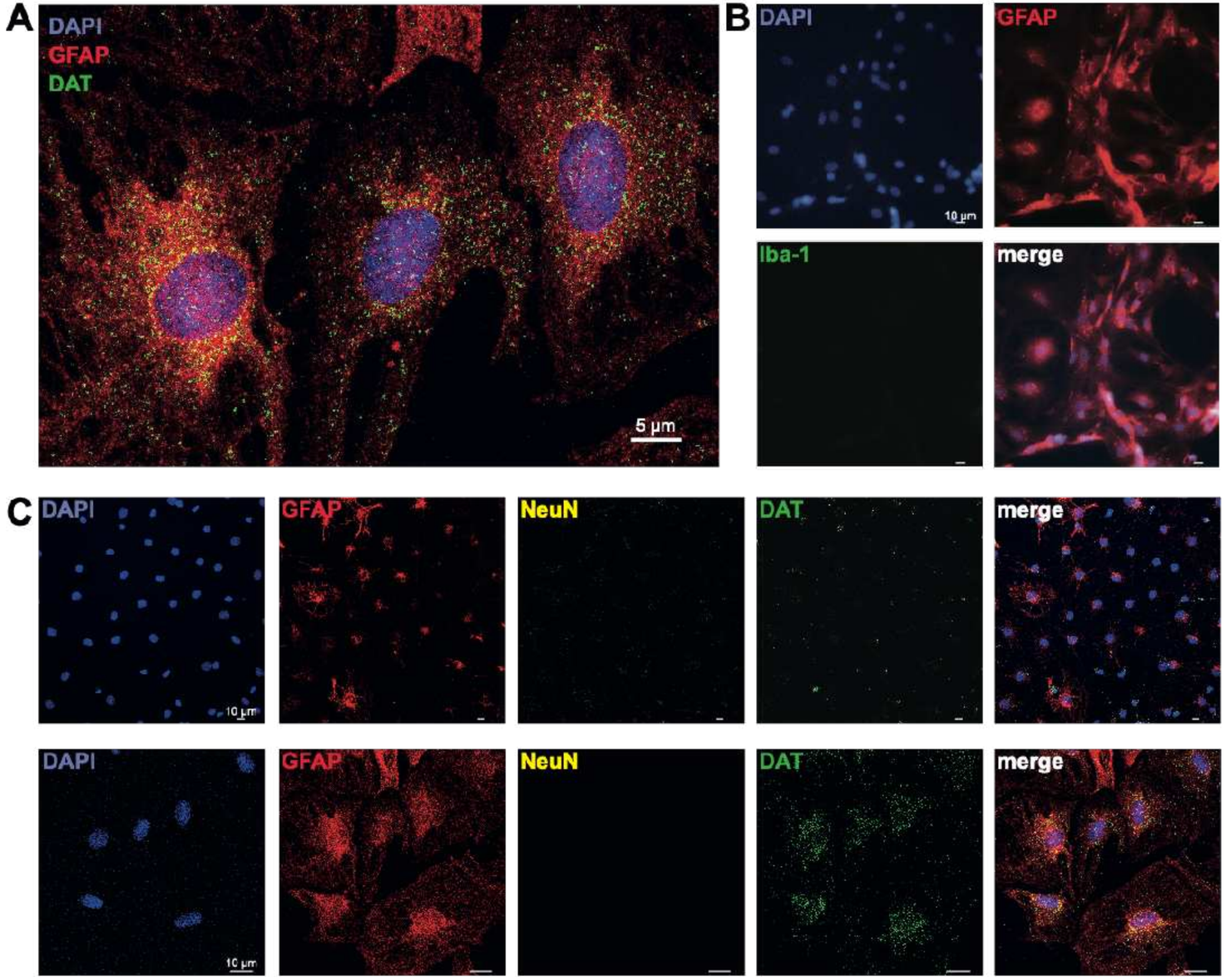
Striatal quadripartite synaptic microenvironment



Fouyssac et al., 2017 & 2018

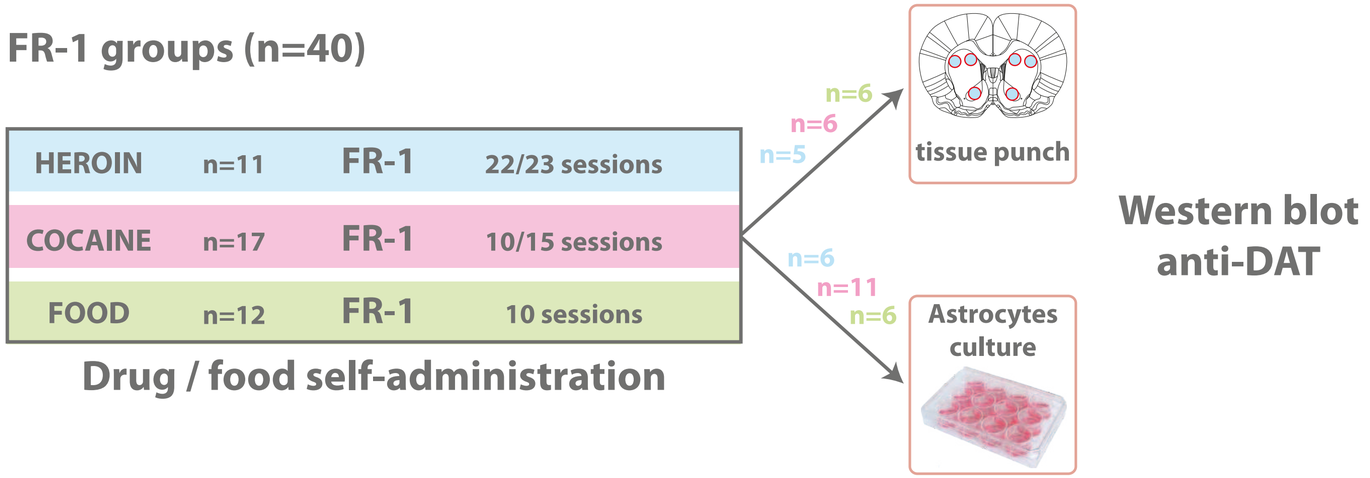
Striatal astrocytes express DAT





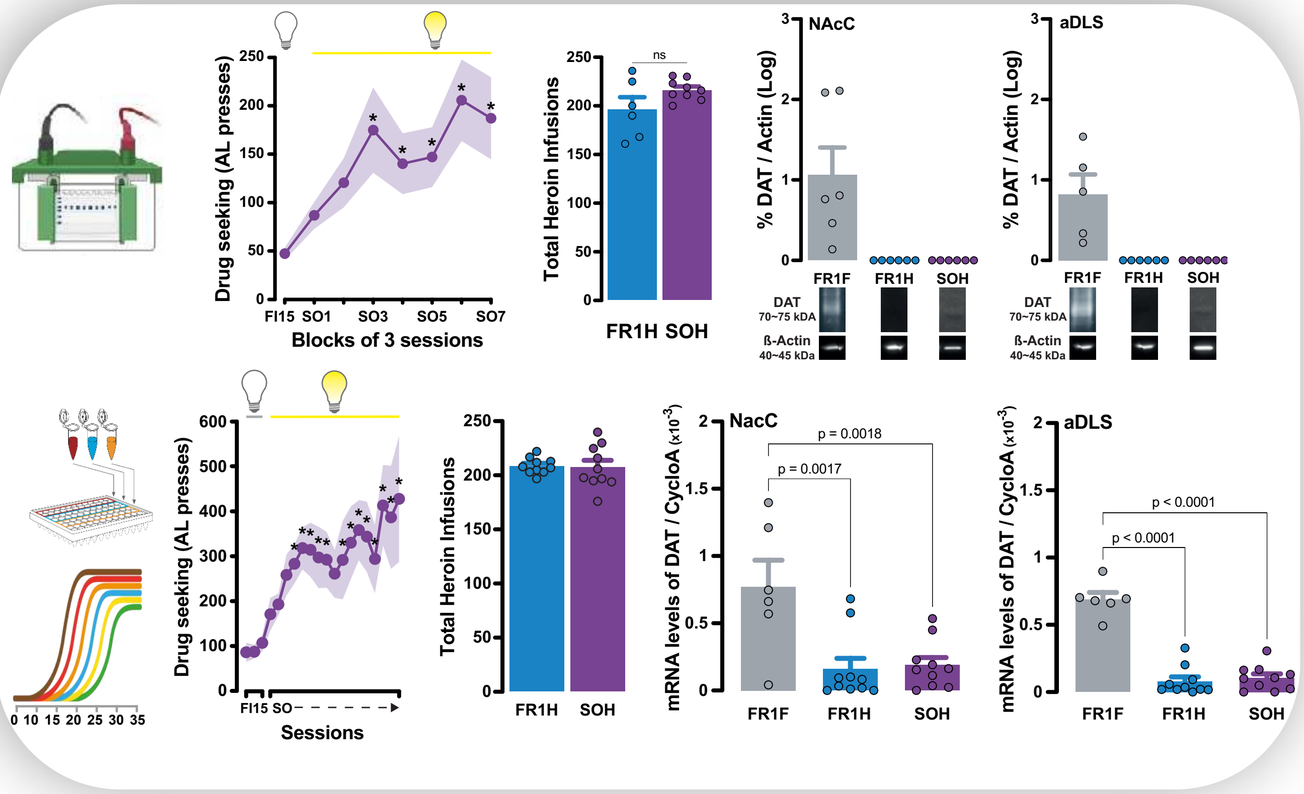
Hynes, Fouyssac et al., 2024 EJN

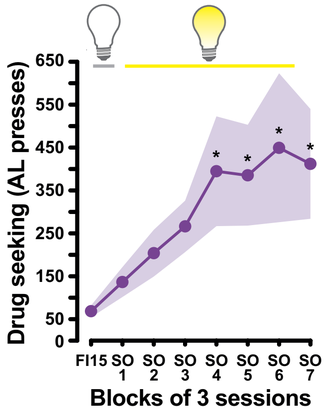
Investigating the effect of drug exposure on striatal astrocytic DAT

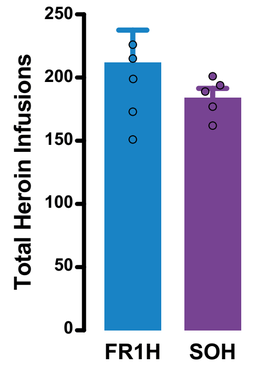


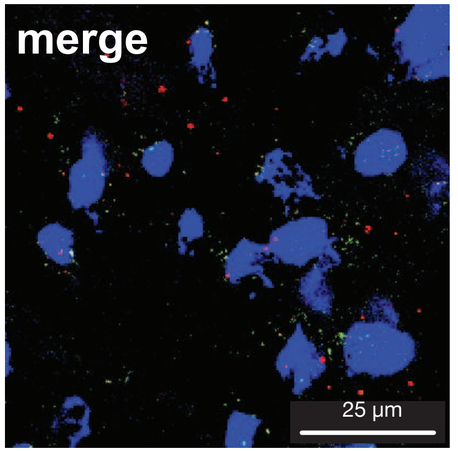
Hynes, Fouyssac et al., 2024 EJN

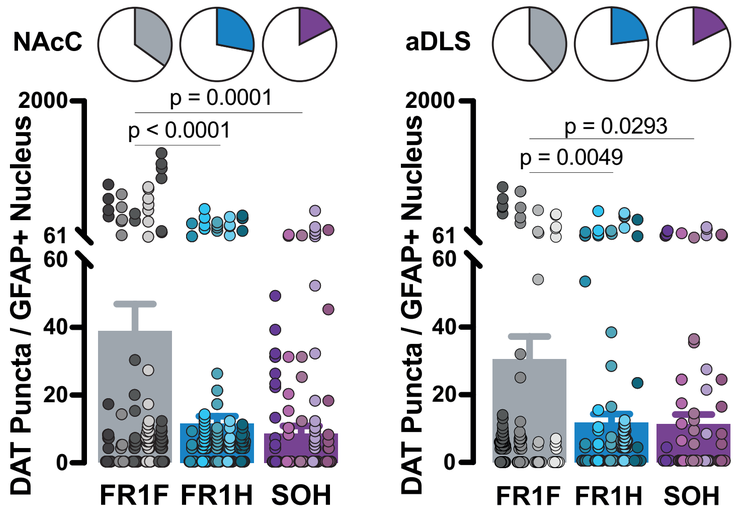
Astrocytic DAT expression is downregulated by drug exposure throughout the striatum









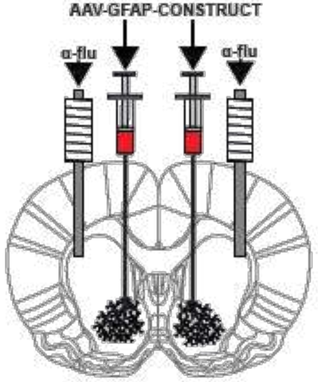


Hynes, Fouyssac et al., 2024 EJN

NAcC astrocytes regulate the development of aDLS DA-dependent incentive drug seeking habits

Experimental Timeline

Intracranial Preparation



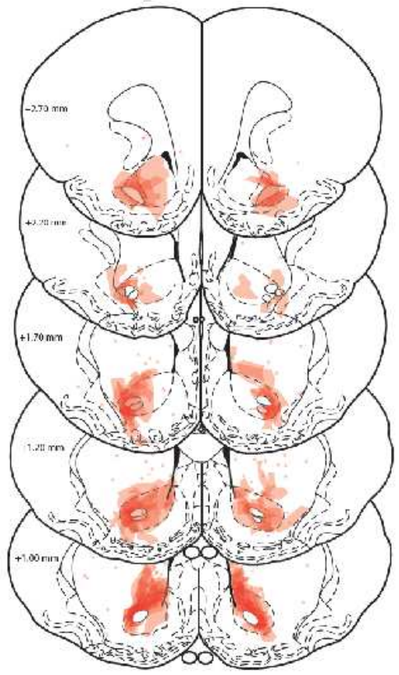
Viral Construct Groups

CalEx: Astrocytic inhibition via Calcium Extruder
(AAV-GFAP-hPMCA2w/b-mCherry)

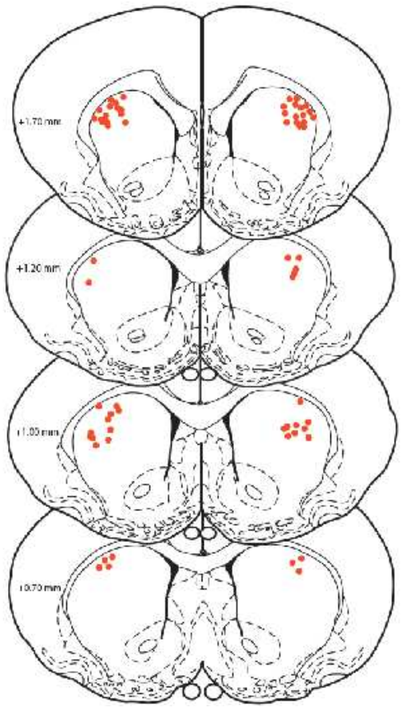
Gq: Astrocytic activation via hM3(Gq) DREADD
(AAV-GFAP-hM3D(Gq)-mCherry)

Control: Control fluorophore mCherry or Gq-VEH
(pAAV-GFAP-mCherry or AAV-GFAP-hM3D(Gq)-mCherry)

Viral spread



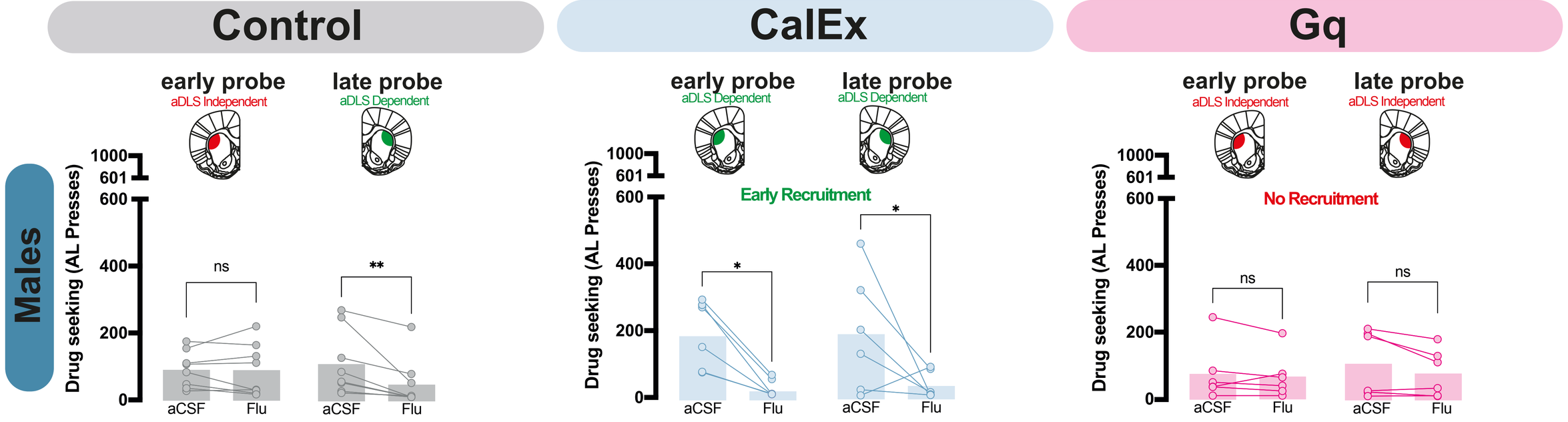
Cannulae placement



NAcC astrocytes regulate the development of aDLS DA-dependent incentive drug seeking habits

- Inhibition of astrocytic striatal syncytium facilitates the recruitment of aDLS DA-dependent control of drug seeking

- Activation of astrocytic striatal syncytium prevents the recruitment of aDLS DA-dependent control of drug seeking



Conclusions

A long history of drug seeking under the control of the conditioned reinforcing properties of the drug-paired cues results in incentive habits.

Individuals prevented from enacting their incentive habits experience and urge to respond that is mediated by a new goal-directed schemata, the goal of which is not the drug, but the response.

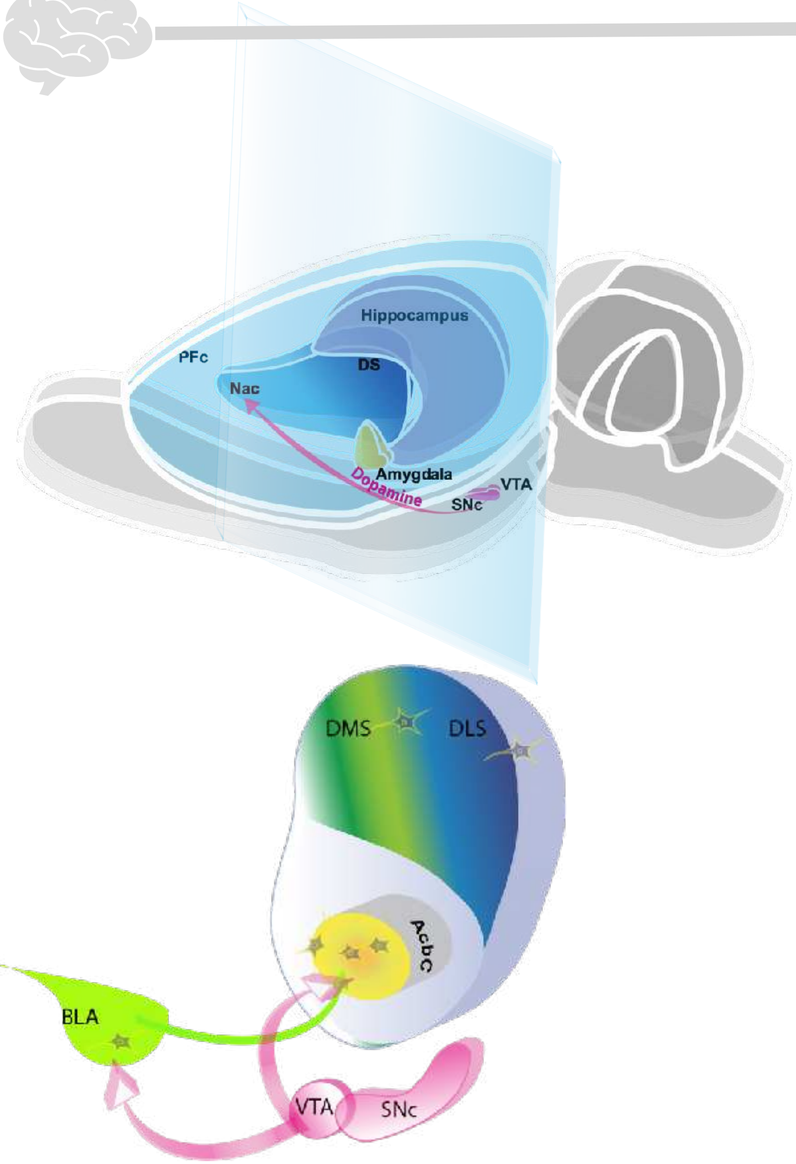
This promotes responding in the face of future negative consequences that will result in an inability to fulfil the incentive habit and an increased tendency to relapse following self-imposed abstinence.

Incentive habits are associated with a specific corticostriatal functional signature similar to that observed in humans with SUD and purinergic mechanisms in the NacC.

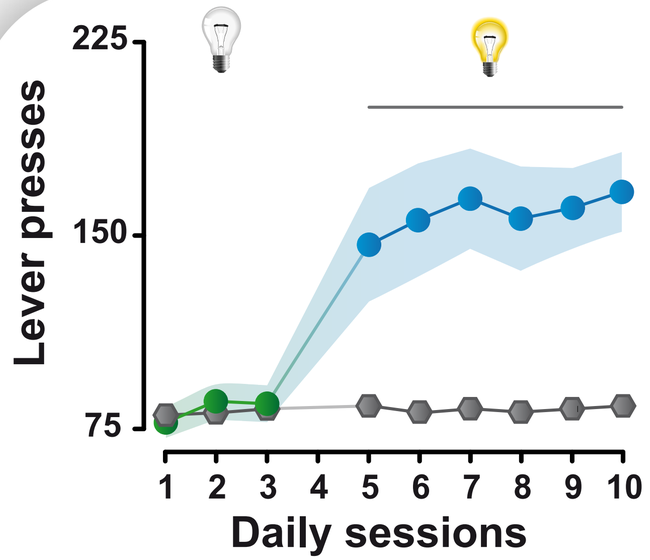
Differential cellular and synaptic plasticity in the BLA accompany the acquisition of cue-controlled drug seeking and the expression of incentive drug seeking habits

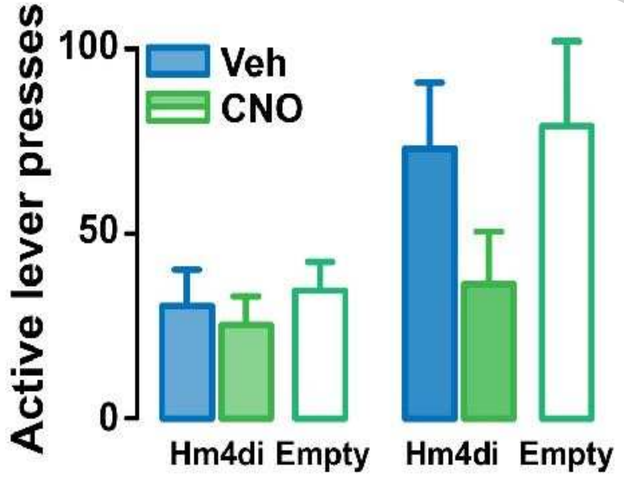
Striatal astrocytes play an unexpected role in the recruitment by the NAcC of aDLS DA-dependent incentive habits of aDLS

Cue-controlled drug seeking: a BLA - NAcC circuit underlies the impact of drug CSs on cocaine seeking

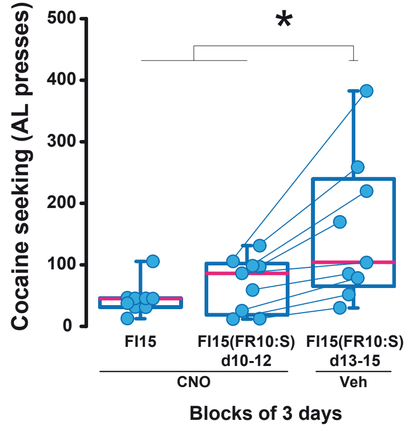


Selective inhibition of the neurons of the BLA-AcbC pathway prevents the development of cue-controlled cocaine seeking



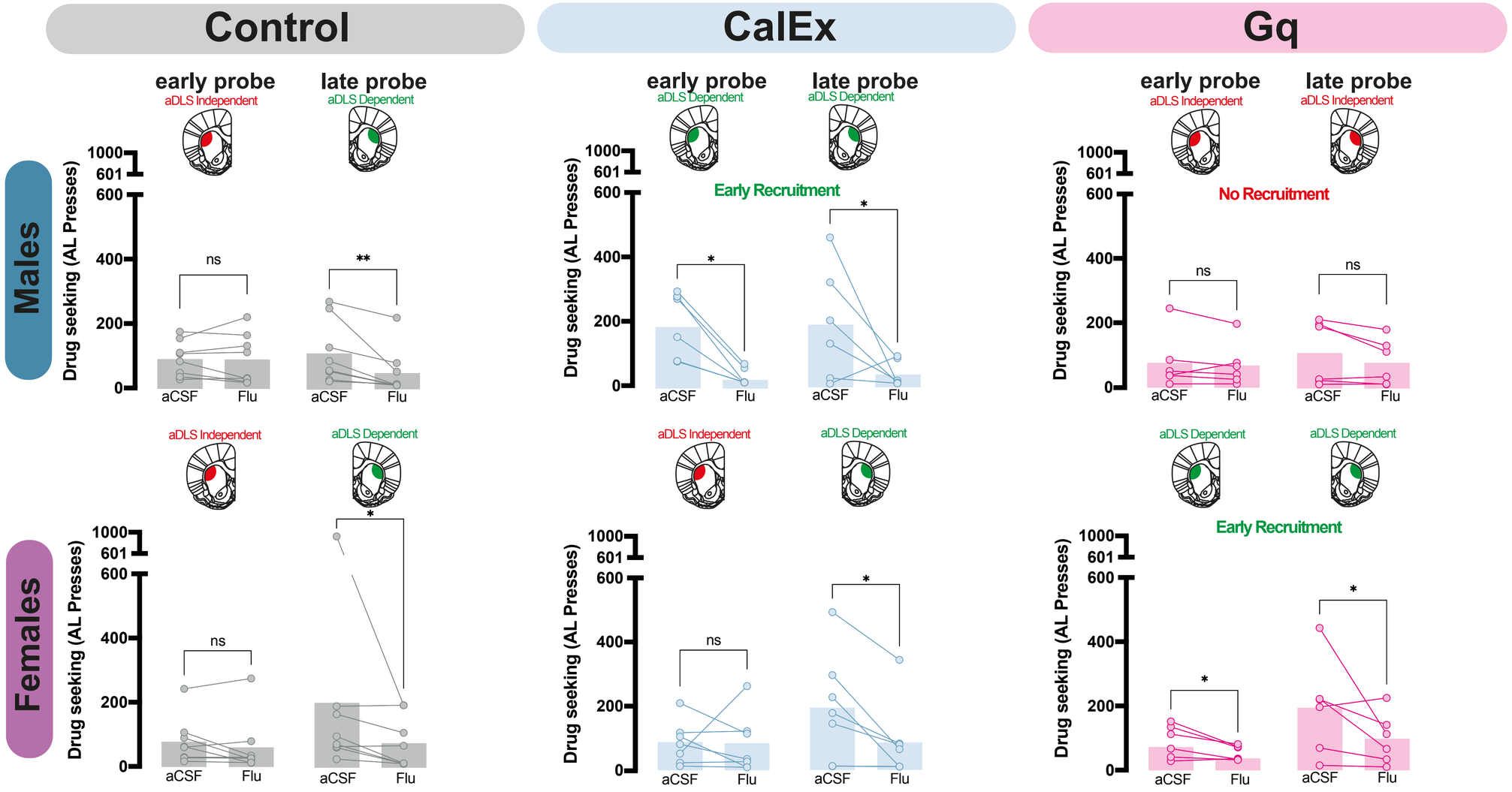


No Cs



Puaud et al., Biol. Psychiatry, 2021

NAcC astrocytes regulate the development of aDLS DA-dependent incentive drug seeking habits



Diagnosis of substance use disorder

A chronic relapsing disorder characterised by the compulsive engagement in drug seeking and taking behaviour, the inability to control drug use and the experience of negative affective states on withdrawal

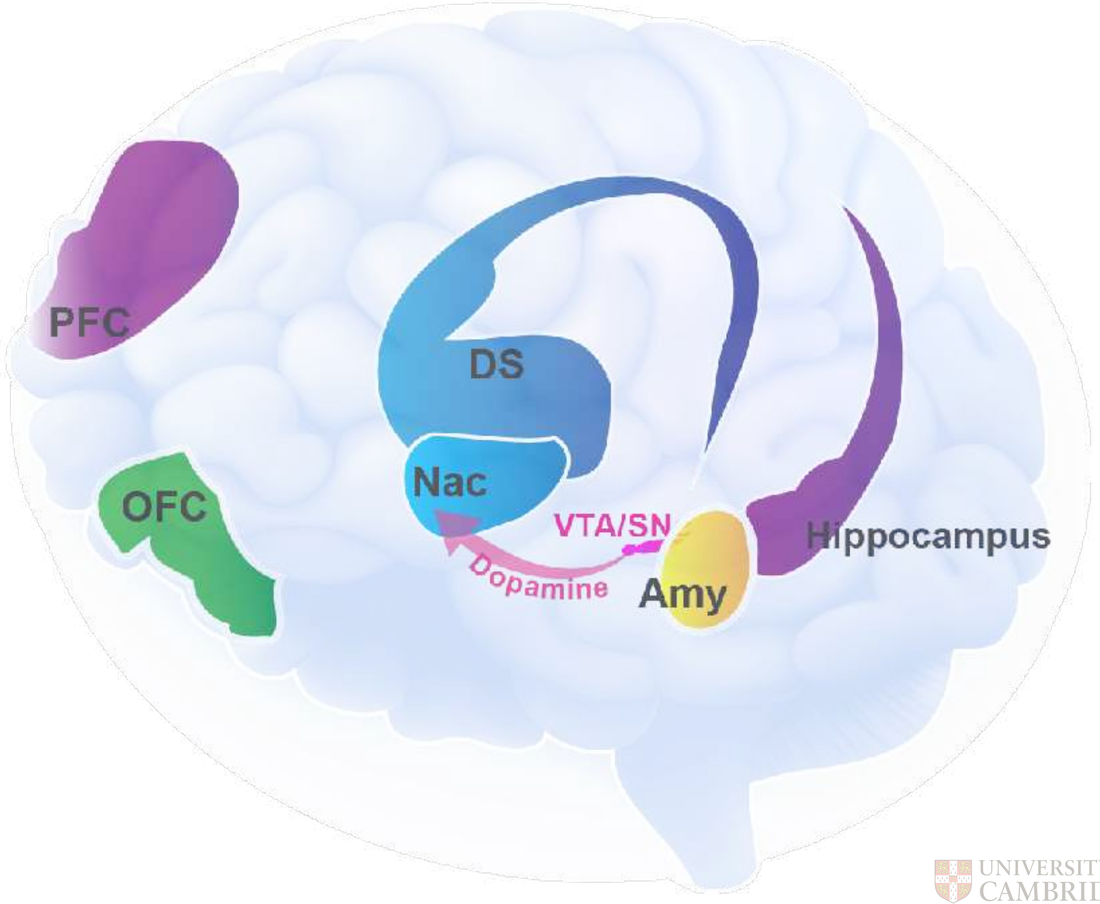
DSM 5: Substance use disorder

1. Taking more drug than intended
2. Unsuccessful efforts to cut down
3. Strong urges & craving for the drug (cues)
4. Excessive time spent acquiring drug
5. Activities given up because of use
6. Failure to fulfill major role obligations
7. Use despite negative effects
8. Recurrent use in hazardous situations
9. Continued use despite consistent social or interpersonal problems
10. Tolerance to drug effect
11. Withdrawal signs

Severity measured by the number of symptoms

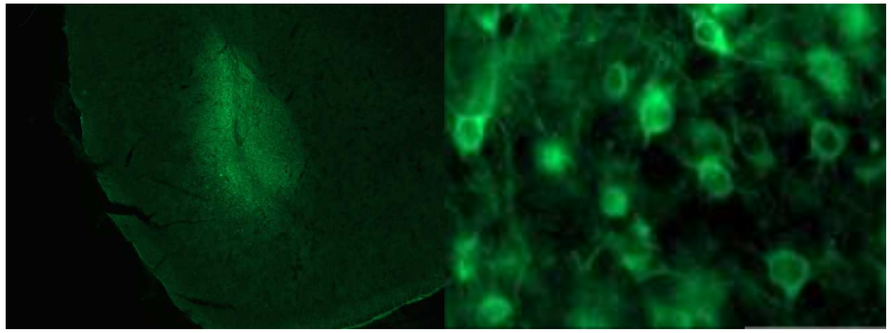
Mild (2-3)
Moderate (4-6)
Severe (7-11)

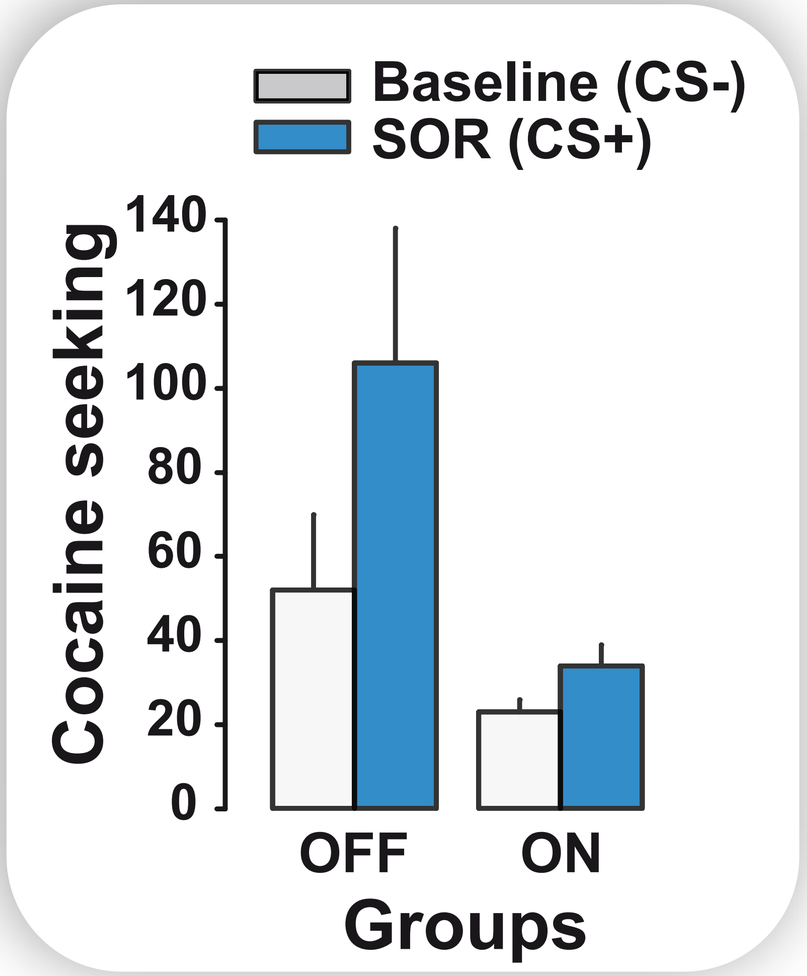
Multiple brain systems and circuits are involved in addiction



Amygdalo-striatal mechanisms and incentive habits

Optogenetic inhibition of the BLA prevents the development of cue-controlled cocaine seeking

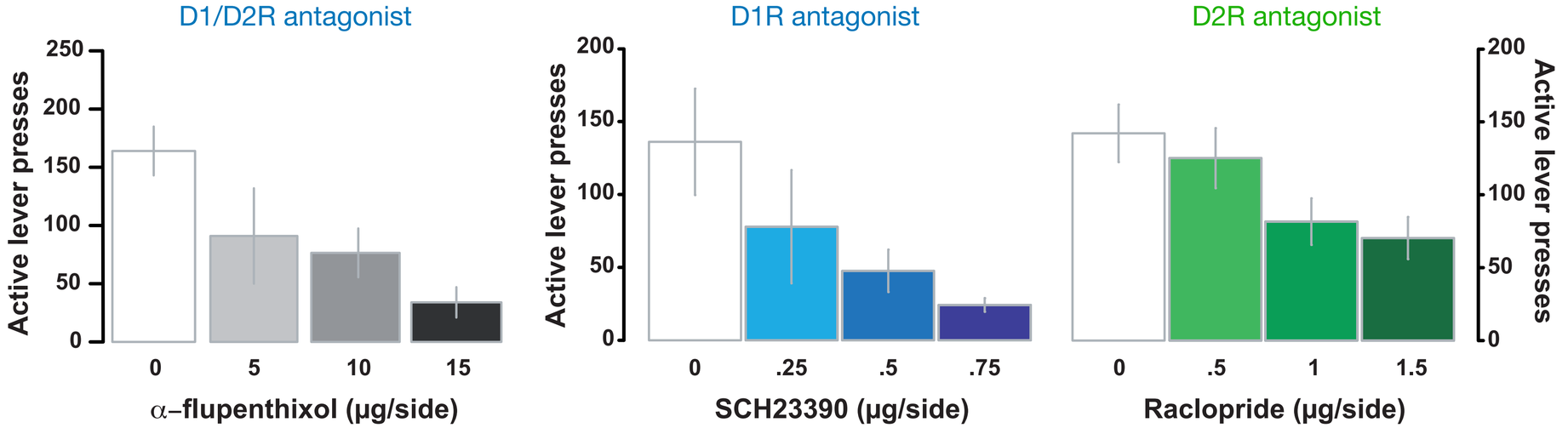




Puaud et al. Unpublished

Cue-controlled drug seeking becomes reliant on aDLS Dopamine

Well-established cue-controlled cocaine seeking: role of both D1 and D2 dopamine receptors in the aDLS



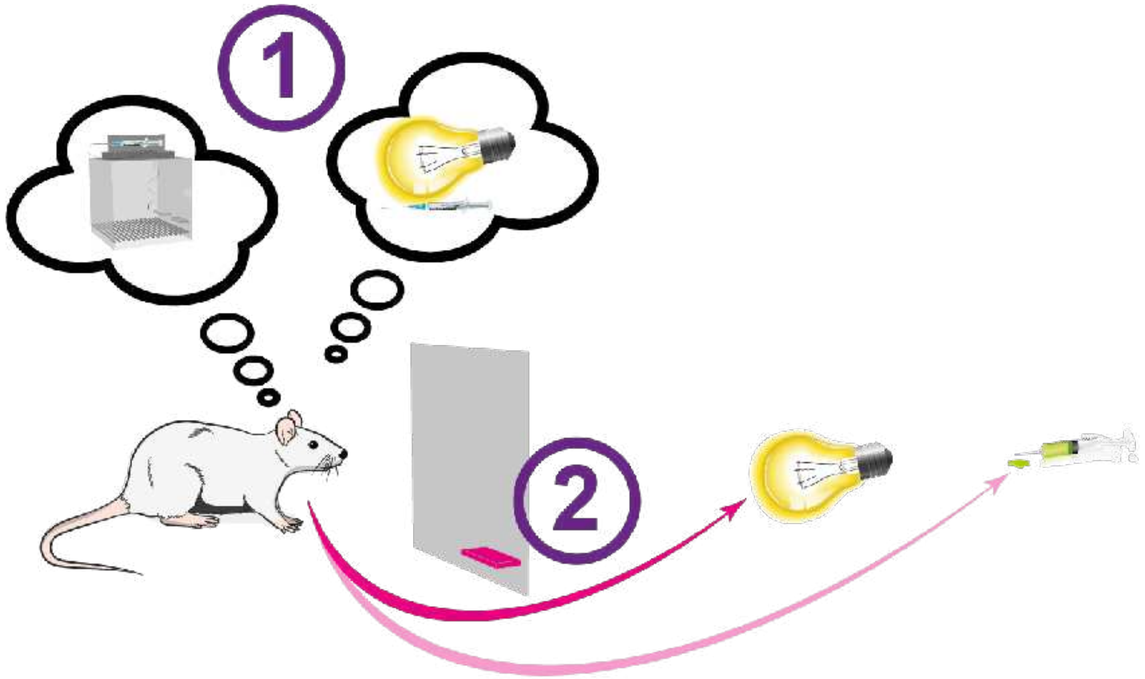
Murray, Belin-Rauscent et al. Nat Comm, 2015

In the real world, habits are not divorced from cues: conditioned reinforcement

Cue-controlled drug seeking

Second order schedule of reinforcement

A model of drug seeking that measures the impact of drug CSs over delays to drug taking (conditioned reinforcement)



Conditioned reinforcement