Largely overlapping neuronal and molecular substrates of reactivity to drug and natural reward cues

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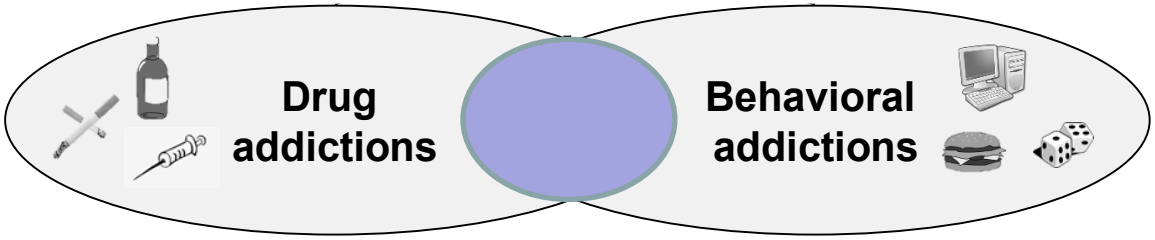
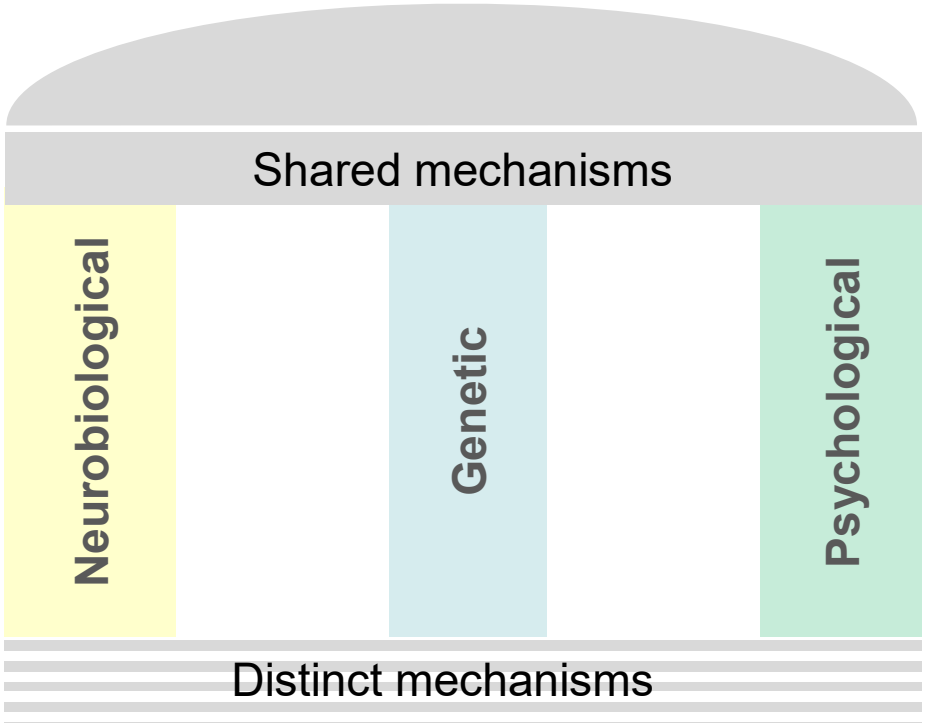
Shared and distinct pathomechanisms of drug addictions and behavioral addictions





Neuronal responses to drug and natural rewards

20 s: 5 x Alcohol /drug cues or cues for natural rewards

Noori et al. Eur Neuropsychopharmacol 2016


Hamid Noori

176 studies were included in the meta-analysis with n=5.573

	#Studies	#Cases	#Controls	Mean age ± SD (y)	% Male ± SD
Alcohol	44	1366	202	35.5 ± 10.4	65 ± 19
Cannabis	5	86	56	25.4 ± 7.9	59 ± 17
Cocaine	22	368	185	39.7 ± 4.7	83 ± 24
Heroin	11	207	133	35.9 ± 4.5	96 ± 9
Nicotine	33	930	192	31.9 ± 7.8	53 ± 33
Food	11		412	25 ± 6	18 ± 26
Sex	46		1318	28.1 ± 7.1	71 ± 38
Gambling	4	59	59	29.6 ± 5.7	100
Total	**176**	**3016**	**2557**	**31.4 ± 5.3**	**68 ± 26**

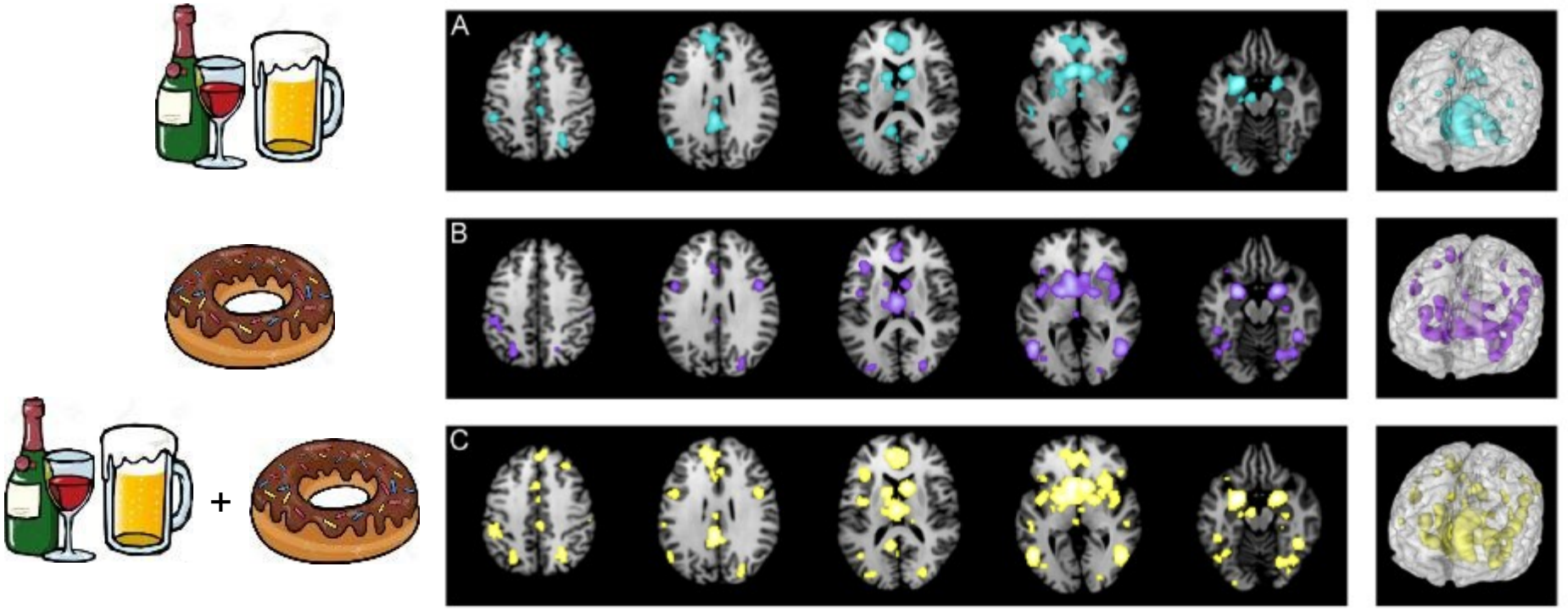
The activation likelihood estimation (ALE) approach

http://brainmap.org/ale

which provides weighted averages of stereotactic coordinates of clusters with respect to each particular cue.

Noori et al. Eur Neuropsychopharmacol 2016

Largely overlapping neuronal response pattern to drug and natural reward conditioned cues



Noori et al. Eur Neuropsychopharmacol 2016

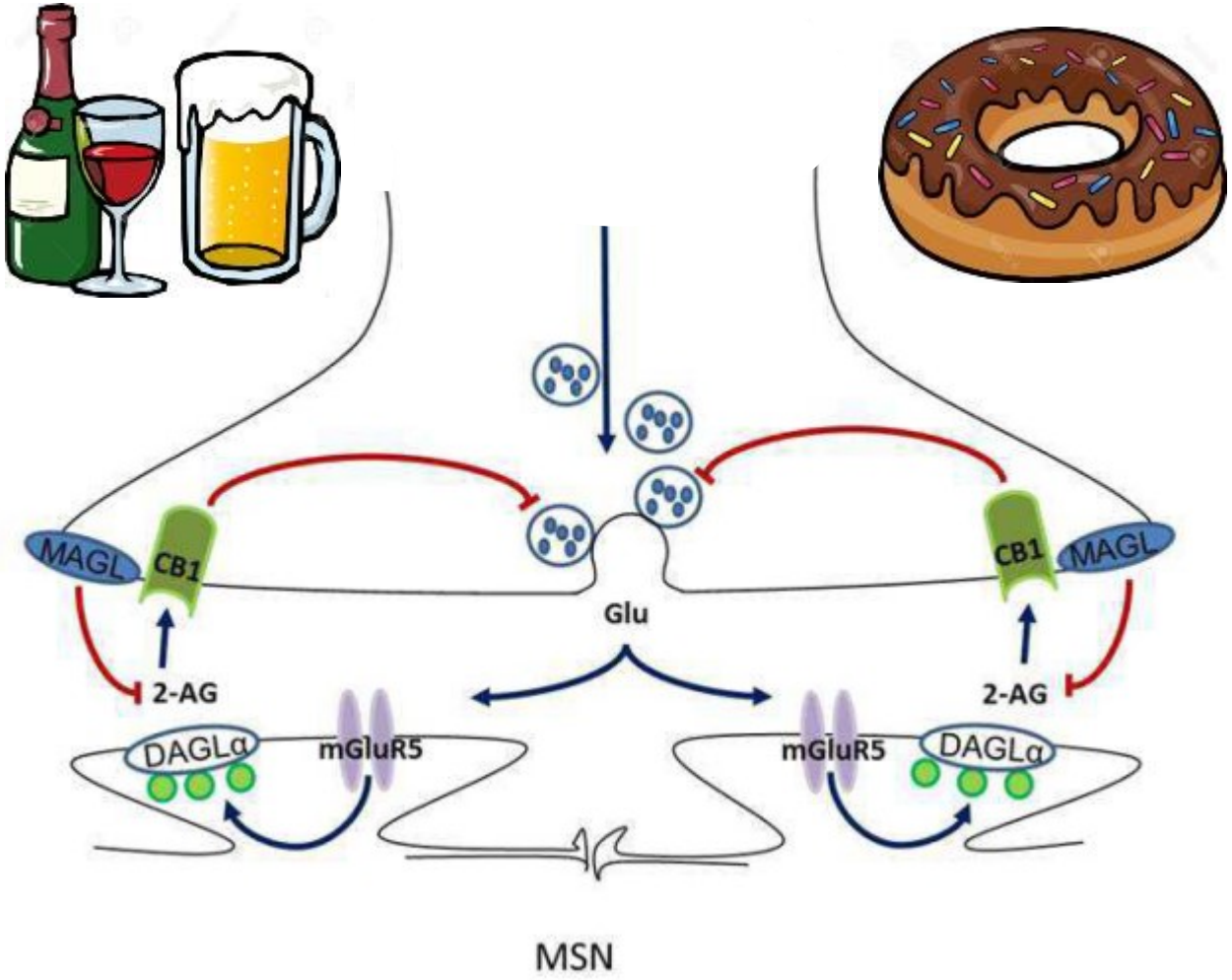
Conclusions

- Cue reactivity among all different types of stimuli is expressed by bilateral neuronal responses most dominantly within anterior cingulate gyrus, insula, caudate head, inferior frontal gyrus, middle frontal gyrus and cerebellum.

- Neuronal cue reactivity comprises areas regulating emotional responses (anterior cingulate, amygdala, and insula) and regions responsible for formation of habits (dorsal striatum and cerebellum).

- Neuronal cue reactivity among all different types of stimuli overlaps with neurocircuitries associated with non-declarative memory and habit learning, and obsessive-compulsive disorder.

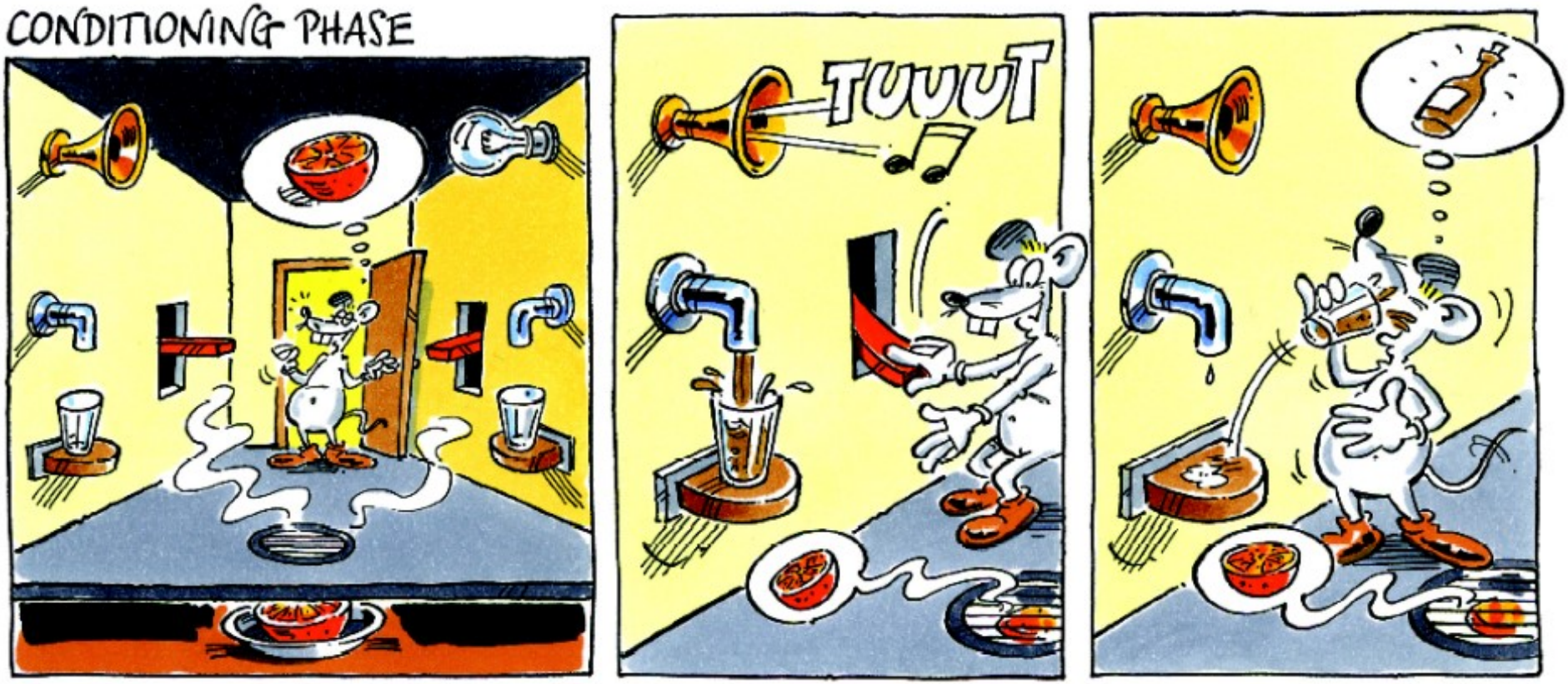
Common molecular cascade for processing drug and natural reward conditioned cues



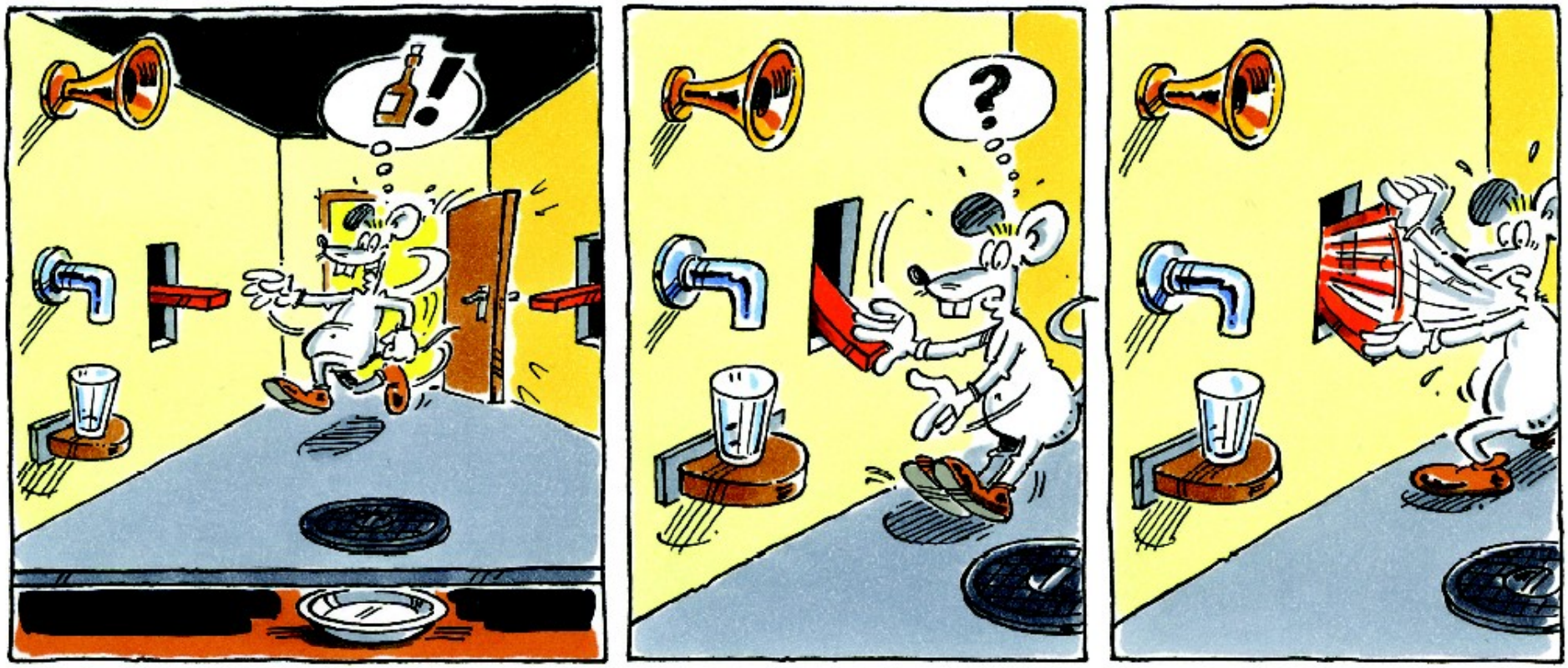
Bilbao et al. Neuron in revision

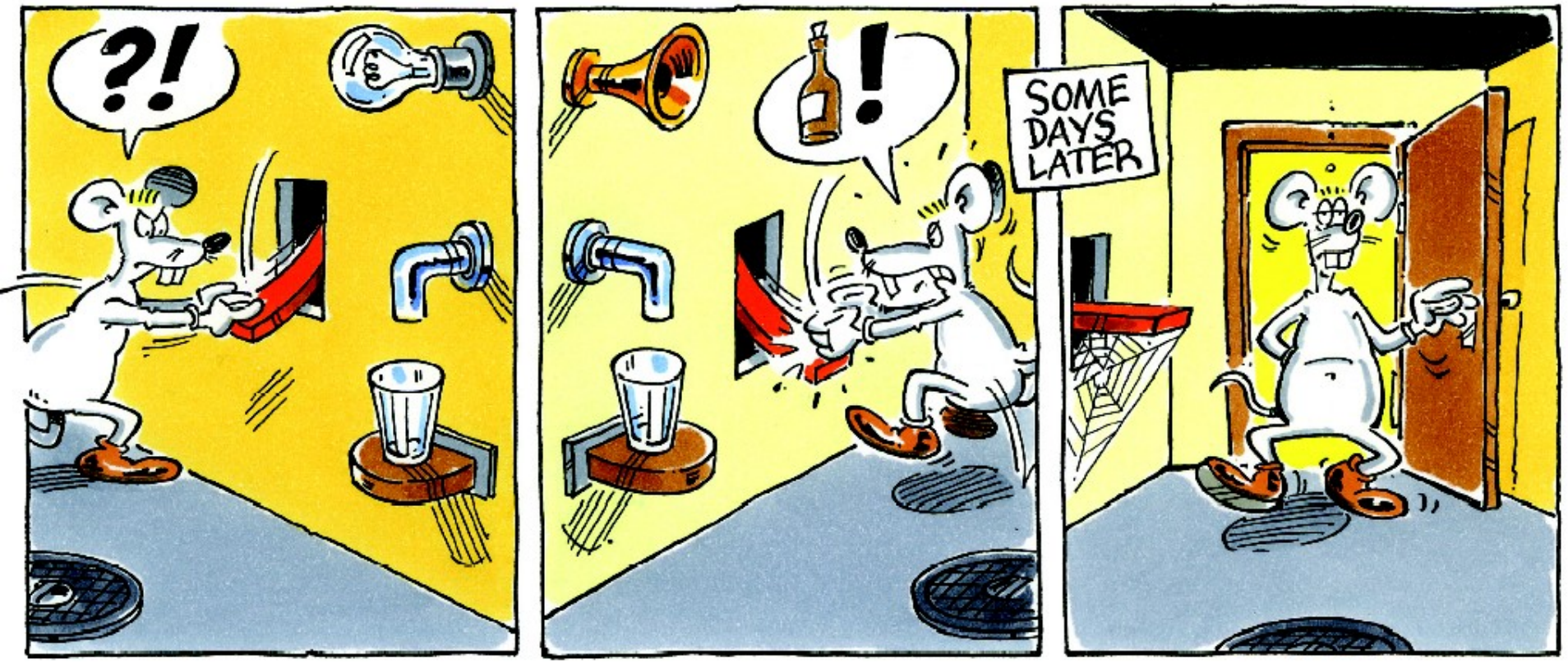
CUE-INDUCED REINSTATEMENT OF DRUG-SEEKING BEHAVIOR

CONDITIONING PHASE

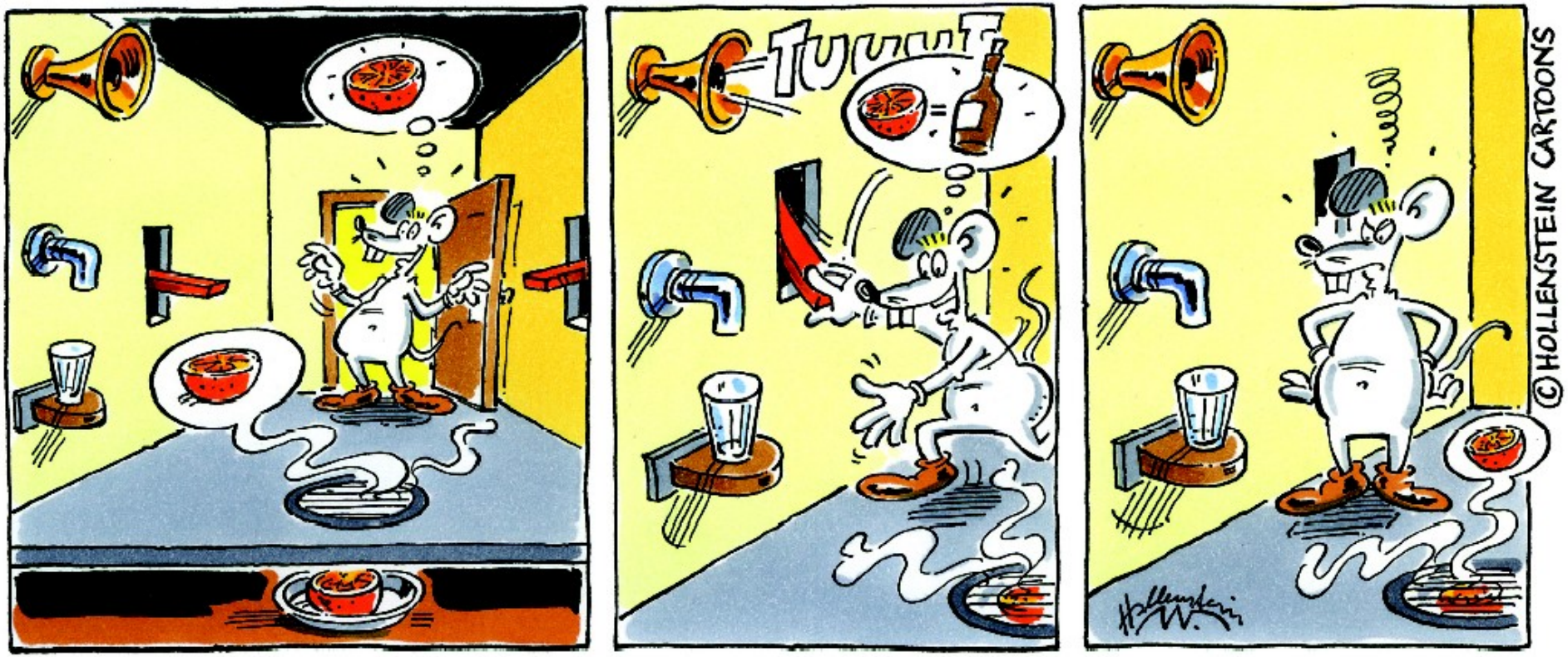


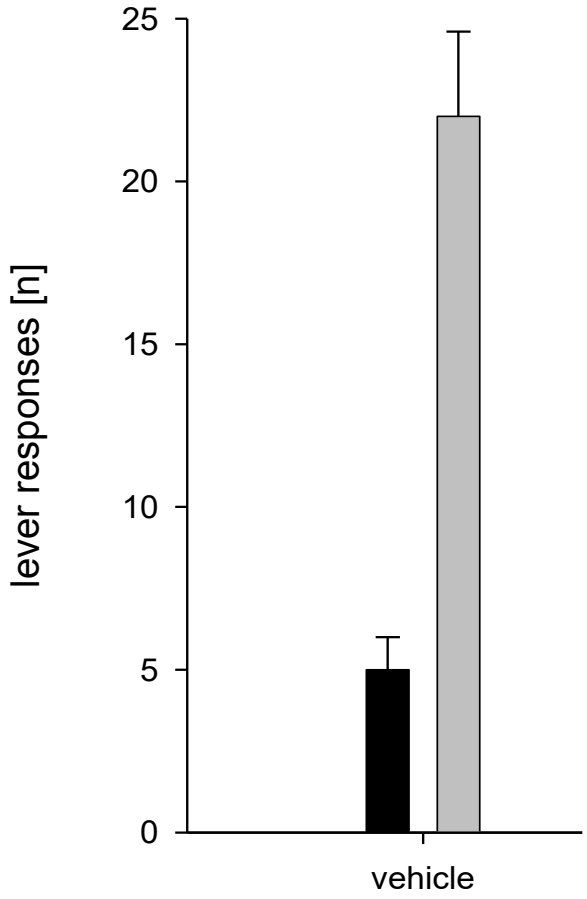
EXTINCTION




?!
!
SOME DAYS LATER

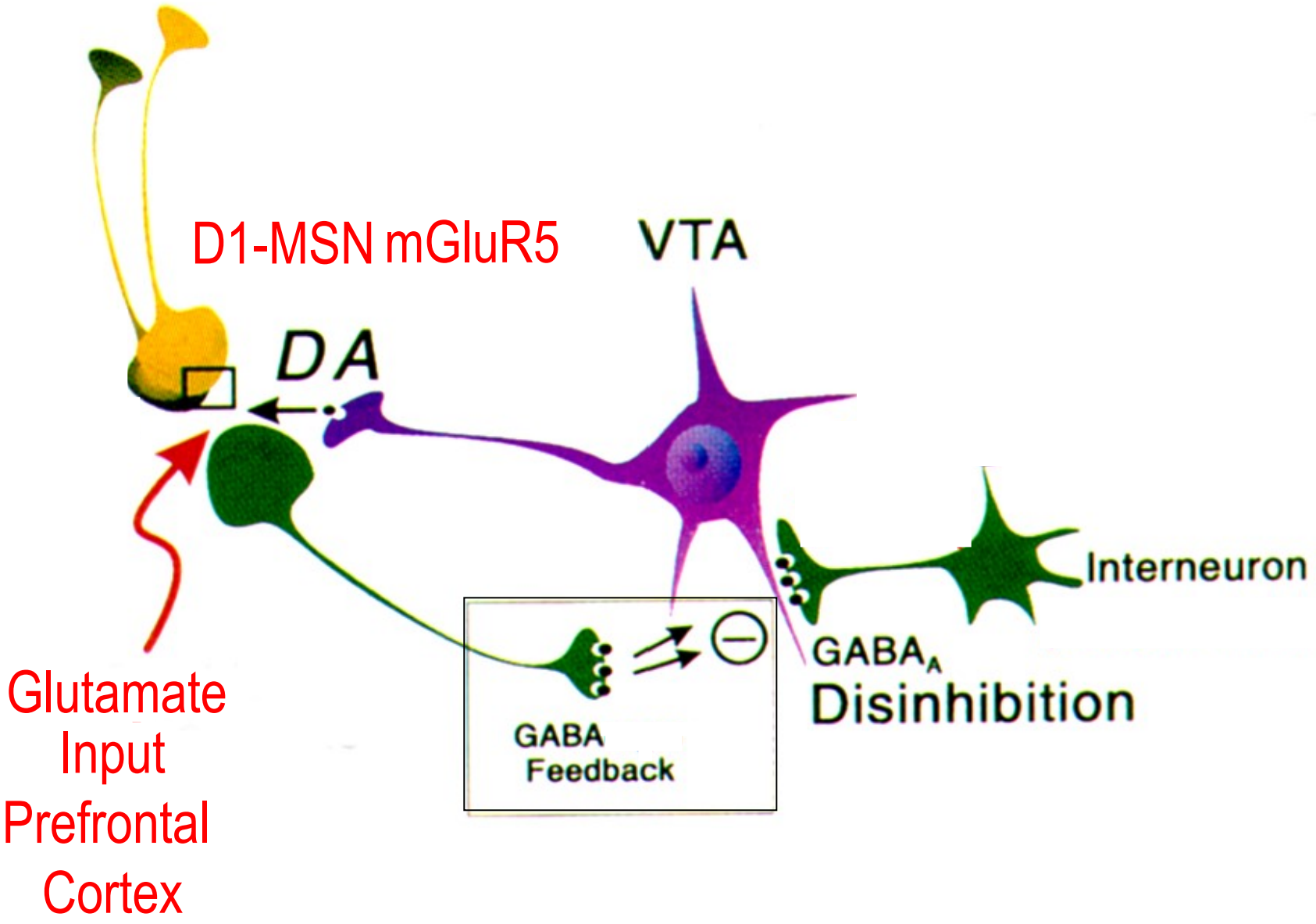
REINSTATEMENT





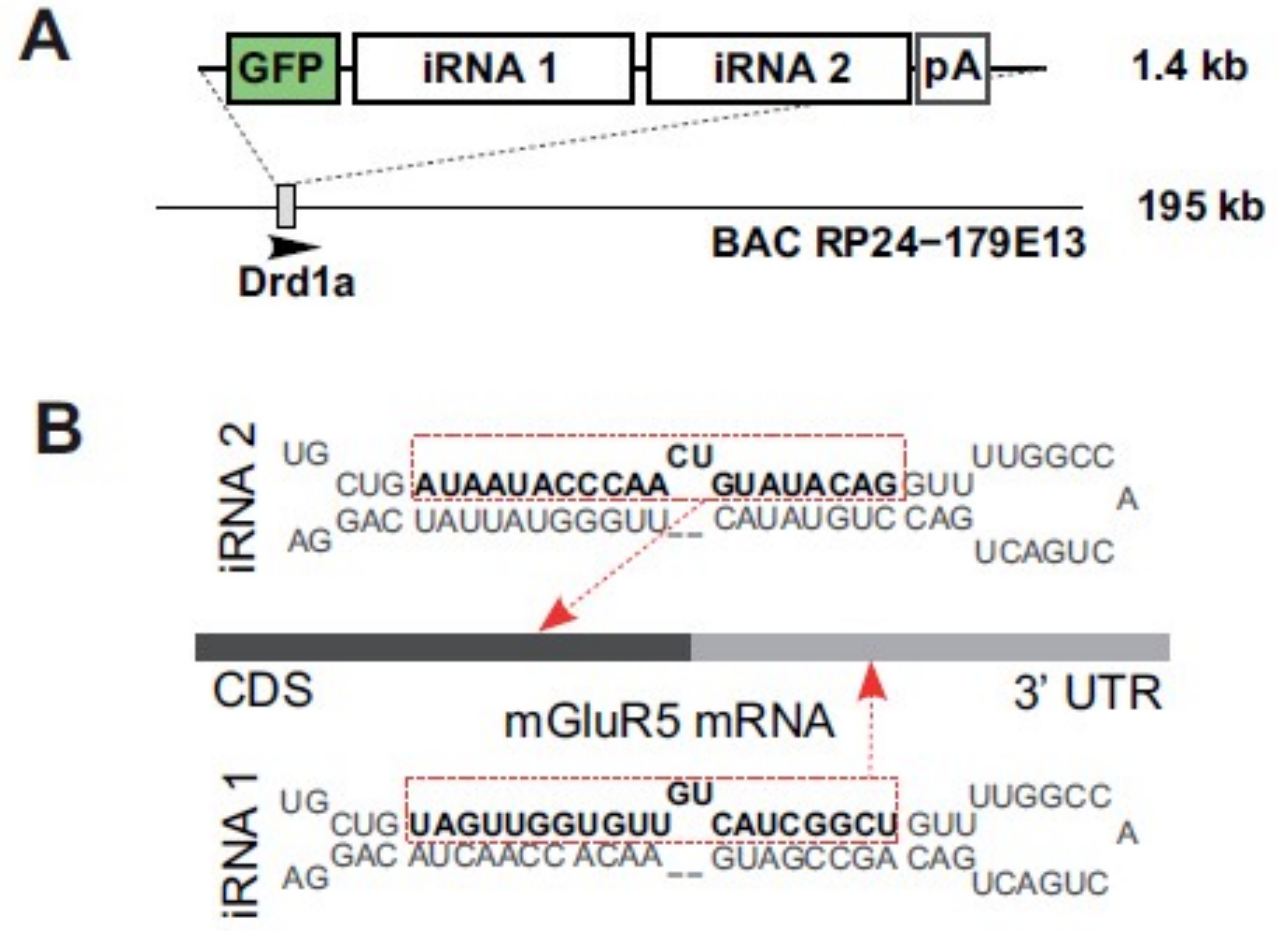
Bäckström et al., Neuropsychopharmacology 2004

Plasticity at glutamate synapses and reward-seeking



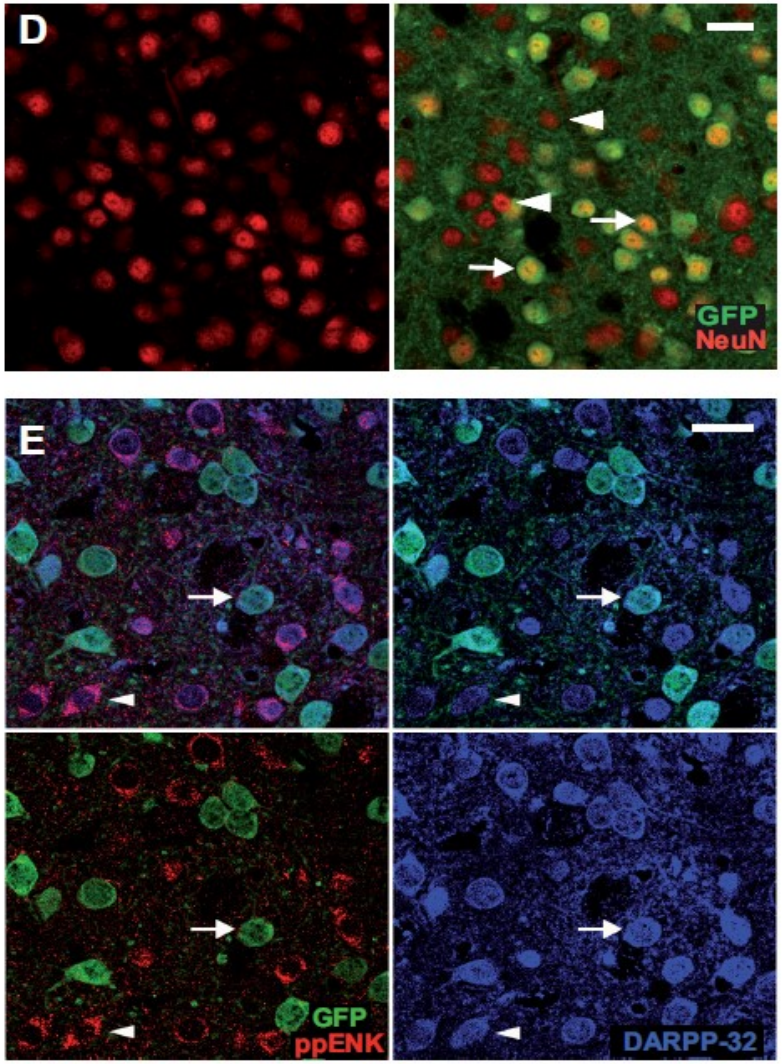

Ainhoa Bilbao

Transgenic mice expressing microRNAs targeting mGluR5



Novak et al., J Neurosci 2010

The transgene expression is selective for D1-MSN



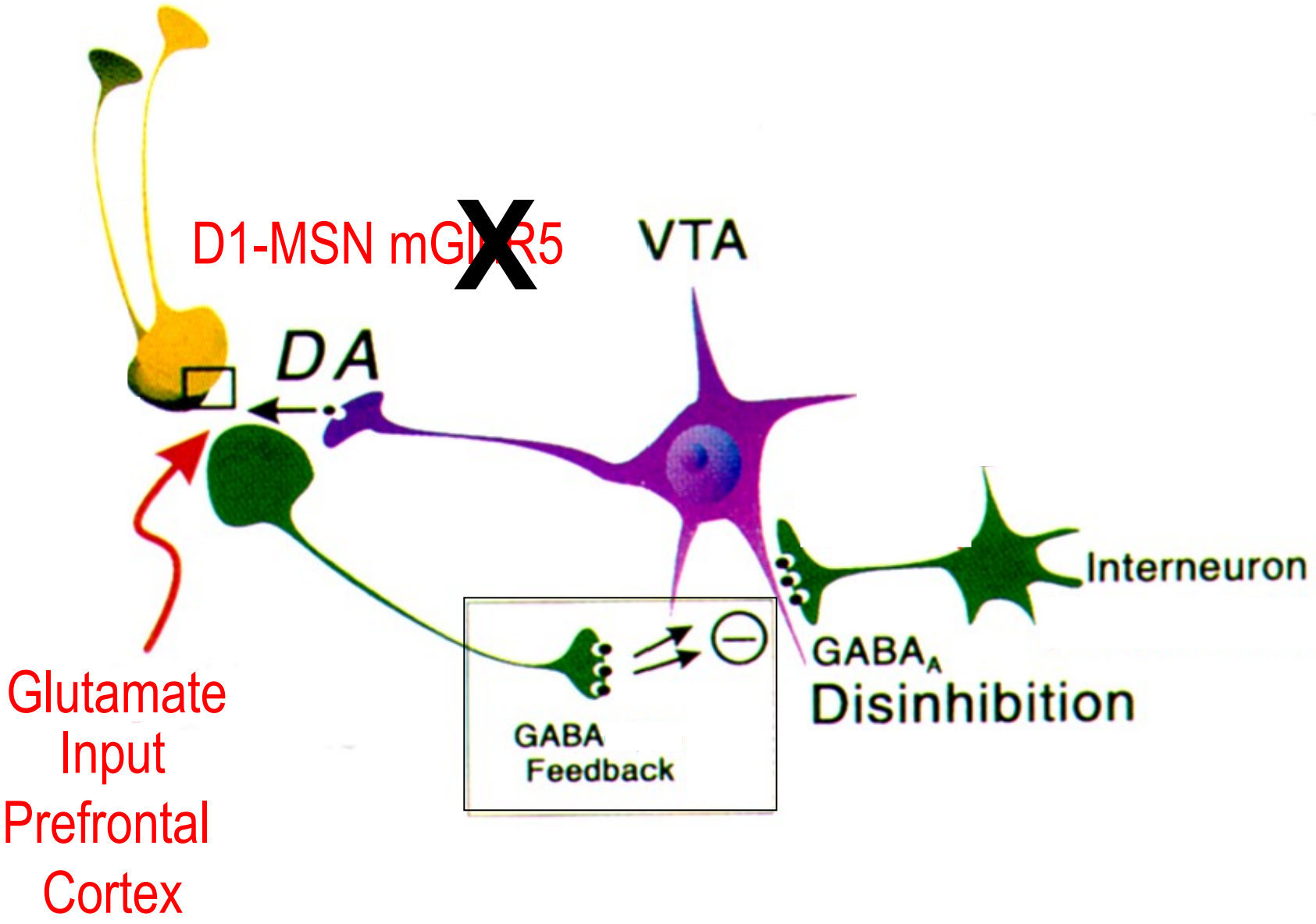
→ Neurons that contain the construct

→ Expression only in DARPP-32 MSN

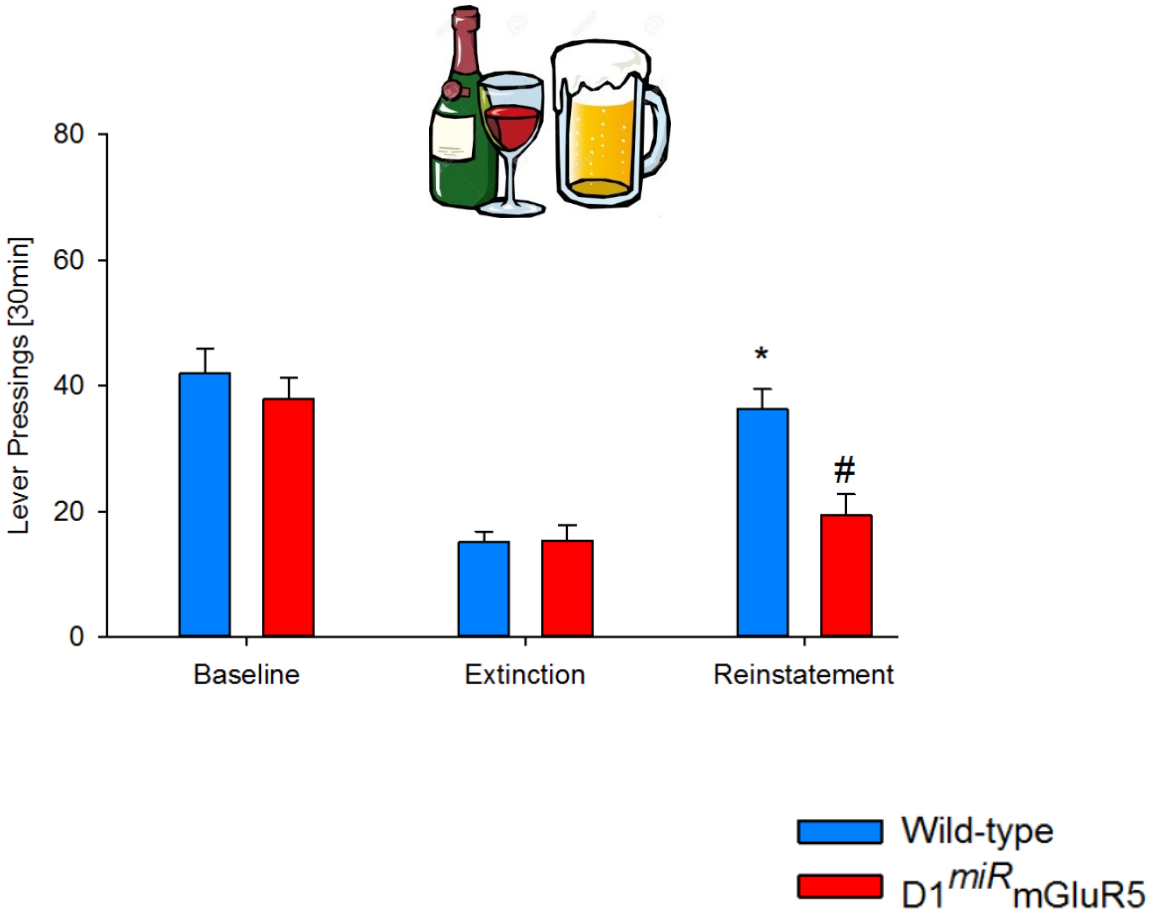
→ The transgene is expressed in ~53% of the striatal neurons

Novak et al., J Neurosci 2010

Plasticity at glutamate synapses and reward-seeking



Lack of cue-induced reinstatement of alcohol and sugar-seeking behavior in mGluR5$^{KD\text{-}D1}$



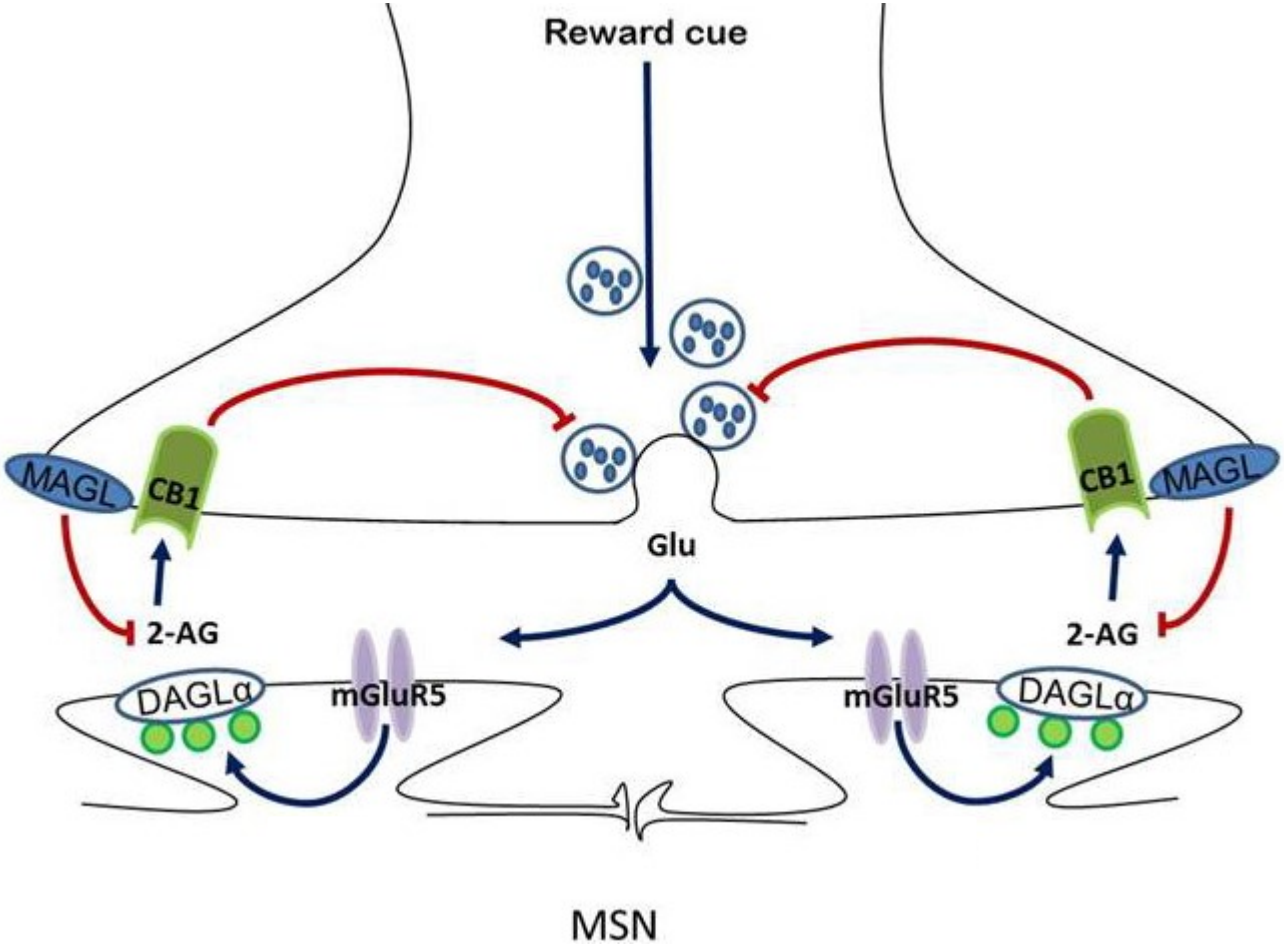
Blibao et al., unpublished

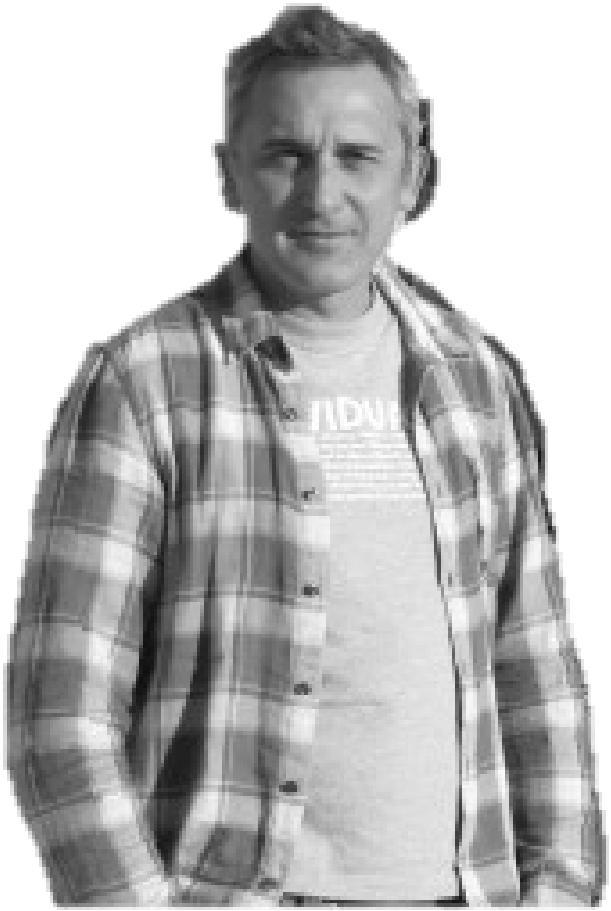
Which kind of synaptic learning mechanism may underlie cue-induced reward-seeking behavior?

One candidate mechanism may be endocannabinoid-mediated long-term depression (e-CB-LTD) because this synaptic learning mechanism depends on mGluR5R

Is eCB-LTD a mechanism involved in reward-seeking responses?

Glutamatergic corticostriatal projection neuron





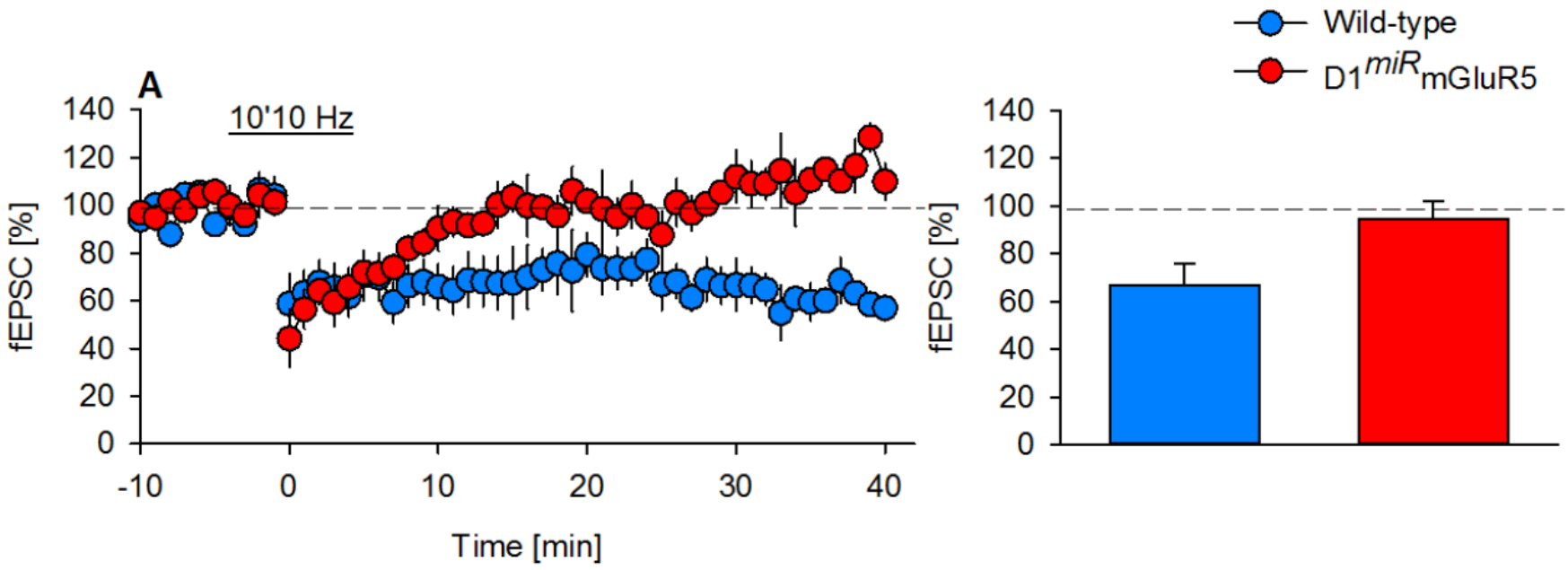
Olivier J. Manzoni

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

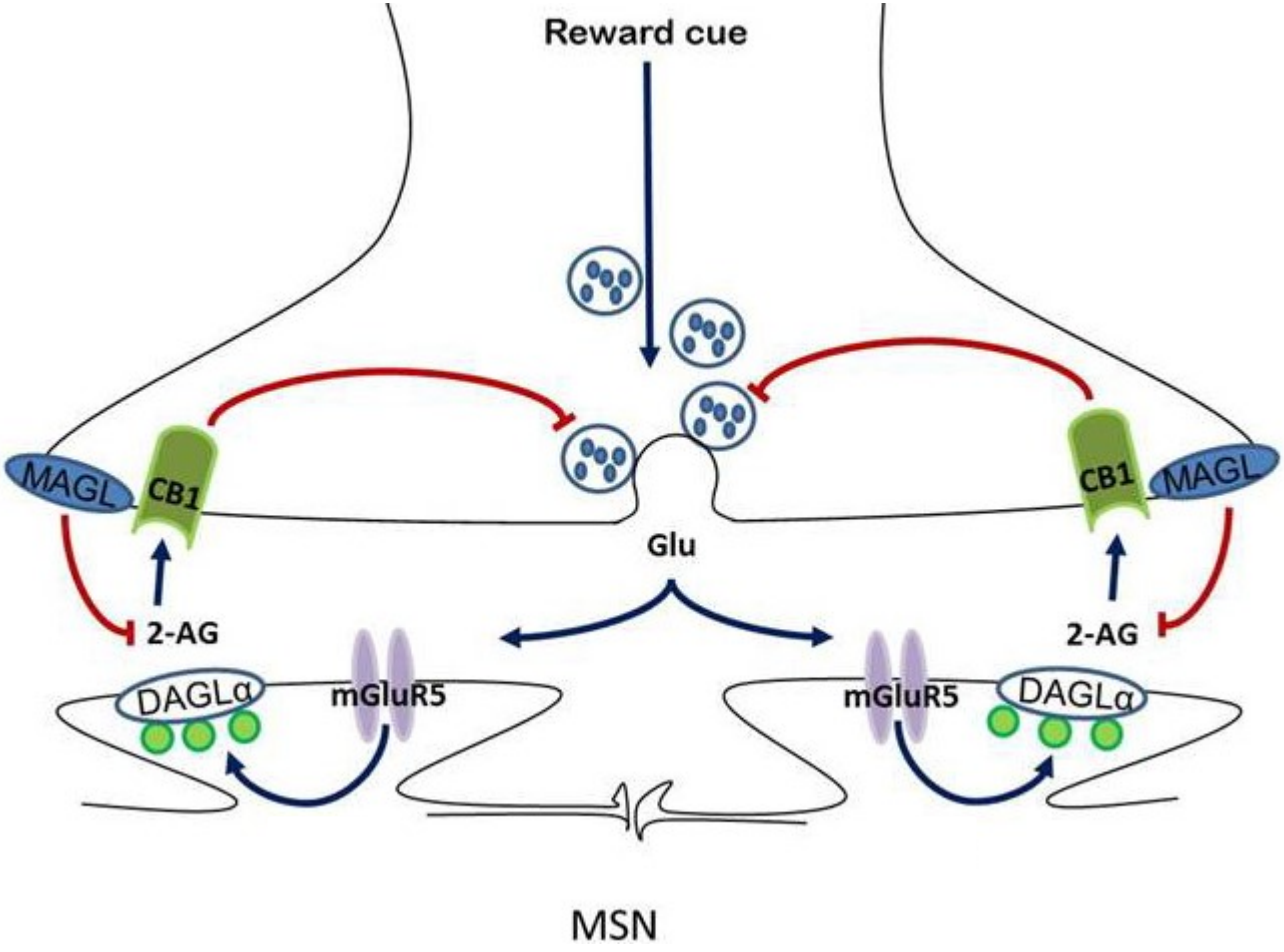
Accumbal eCB-LTD is absent in mGluR5$^{KD\text{-}D1}$ mutants



Olivier J. Manzoni, unpublished data

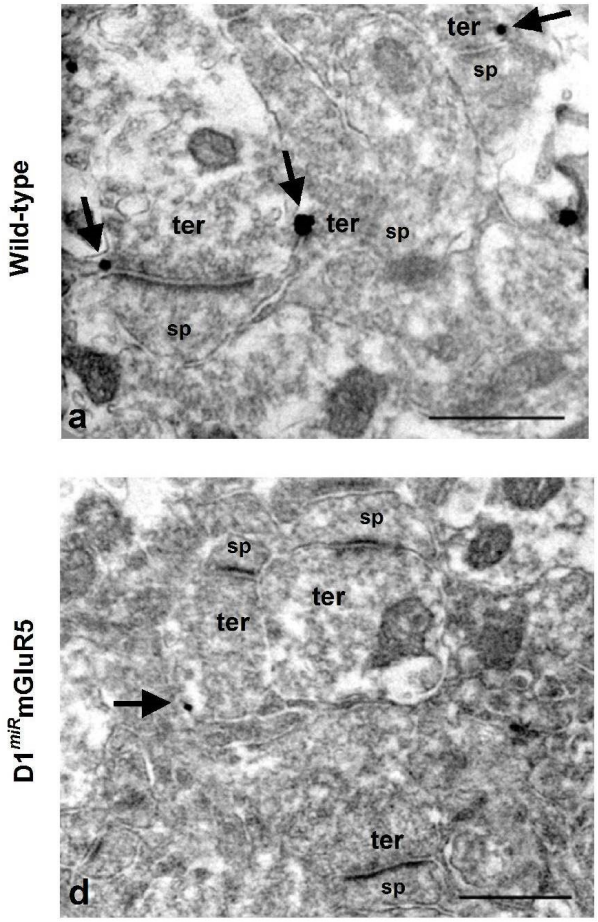
Is eCB-LTD a mechanism involved in reward-seeking responses?

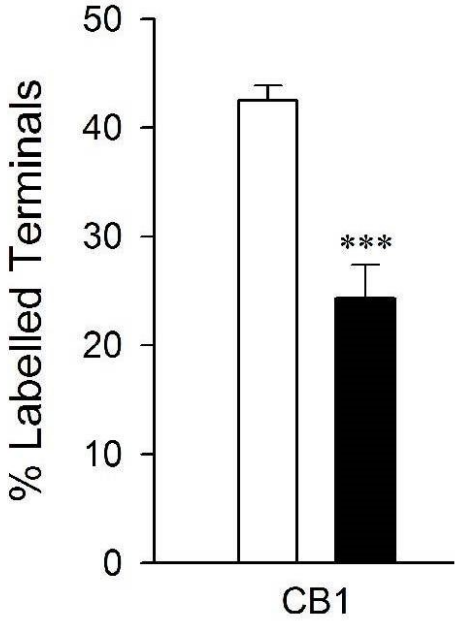
Glutamatergic corticostriatal projection neuron




nature neuroscience
Cannabinoid receptors in mitochondria
Cell-death agents in stroke
Integrating depth cues
probus
Panreac
eman ta zabal zazu
Universidad del País Vasco
Euskal Herriko Unibertsitatea
Pedro Grandes
Almudena Ramos-Uriarte

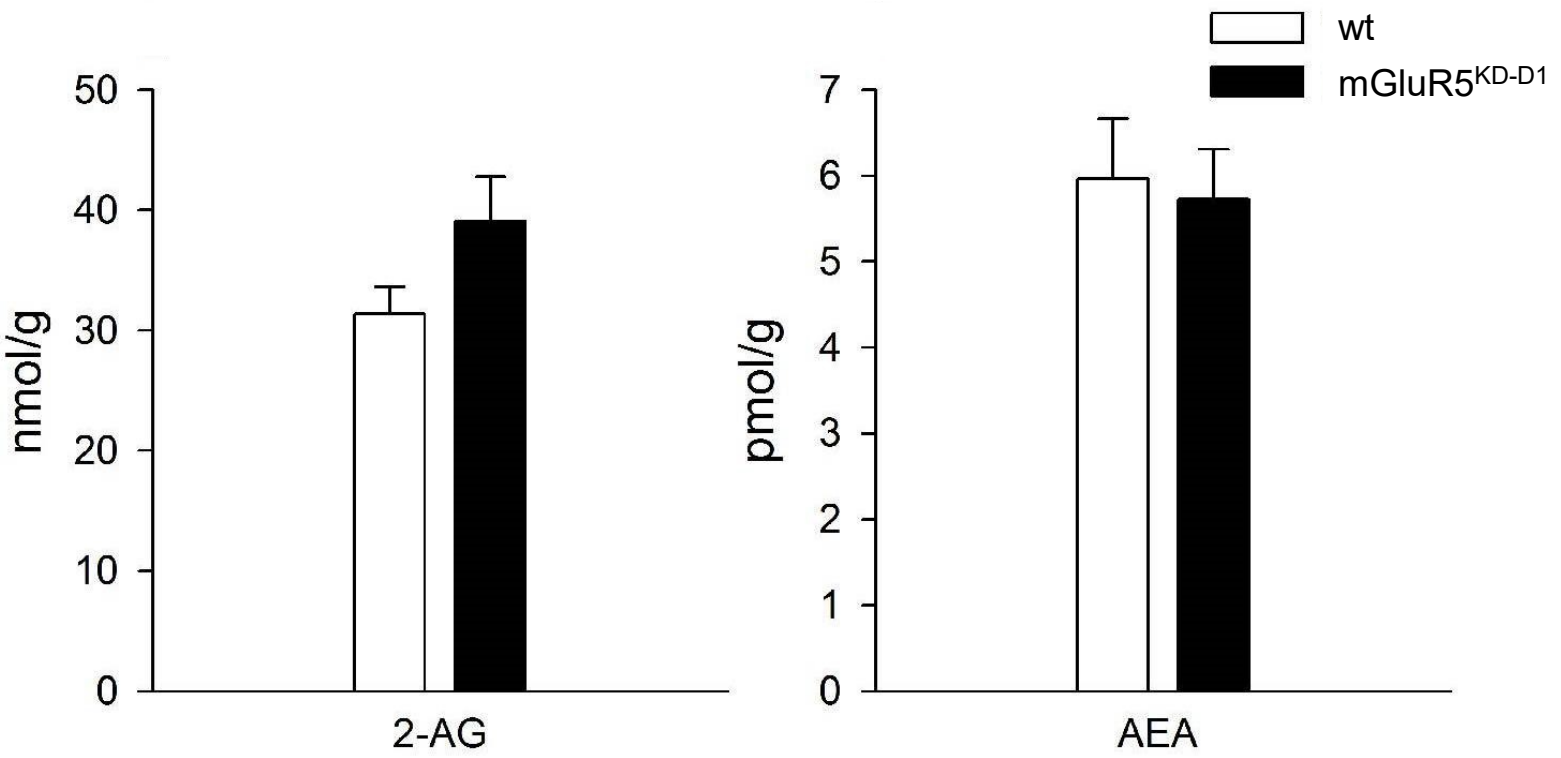
Ultrastructural analysis reveals strong down-regulation of presynaptic CB1 receptors in mGluR5$^{KD\text{-}D1}$





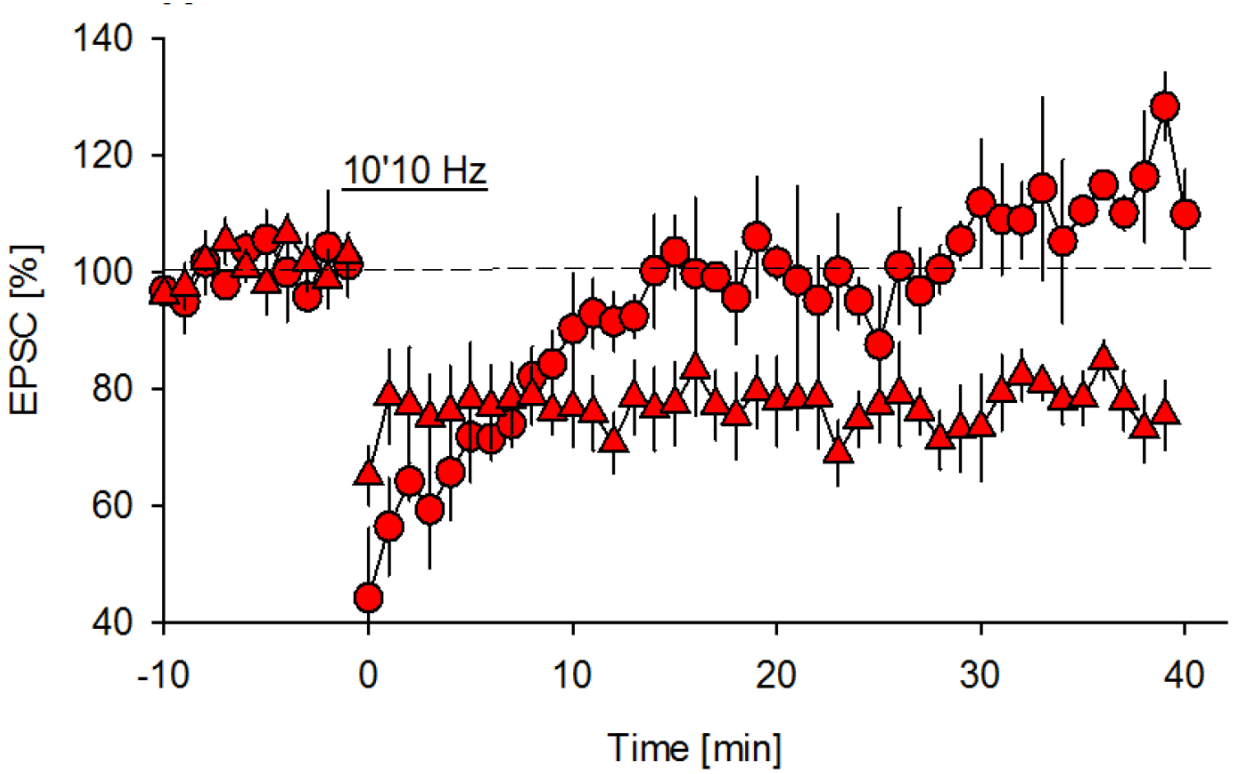
Pedro Grandes and Almudena Ramos-Uriarte, unpublished

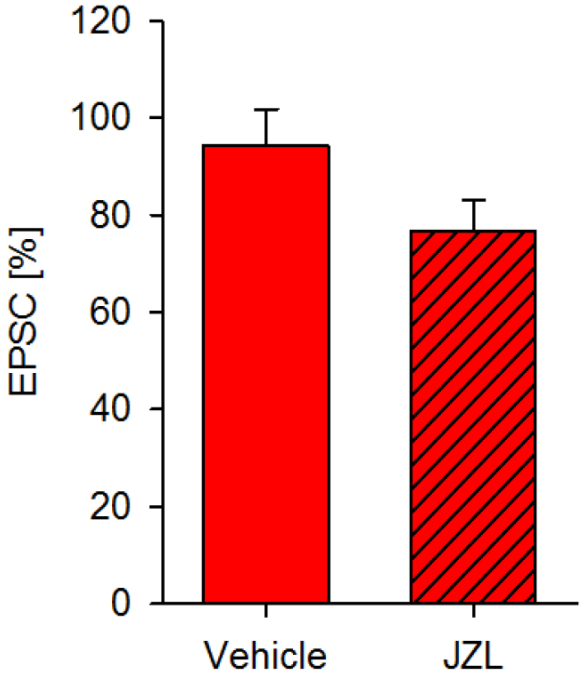
Basal eCB concentrations in the NAC of mGluR5^{KD-D1} mice are not affected



Ainhoa Bilbao, unpublished

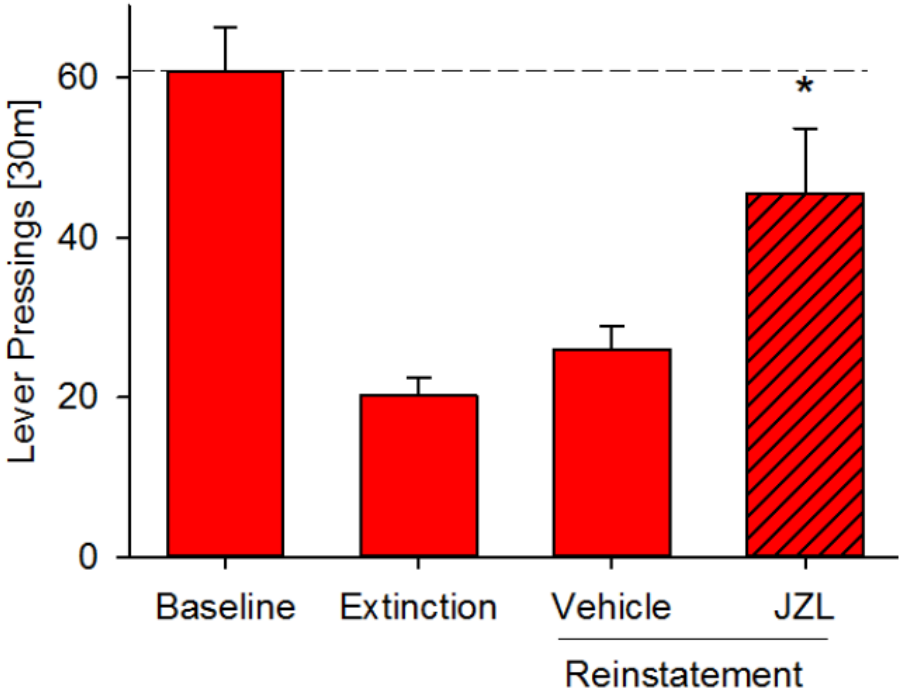
Increasing accumbal 2-AG levels by MAGL inhibiton restores LTD in mGluR5^{KD-D1} mice





Olivier J. Manzoni, unpublished data

Increasing 2-AG levels by MAGL inhibiton restores the reinstatement response in mGluR5^{KD-D1} mice



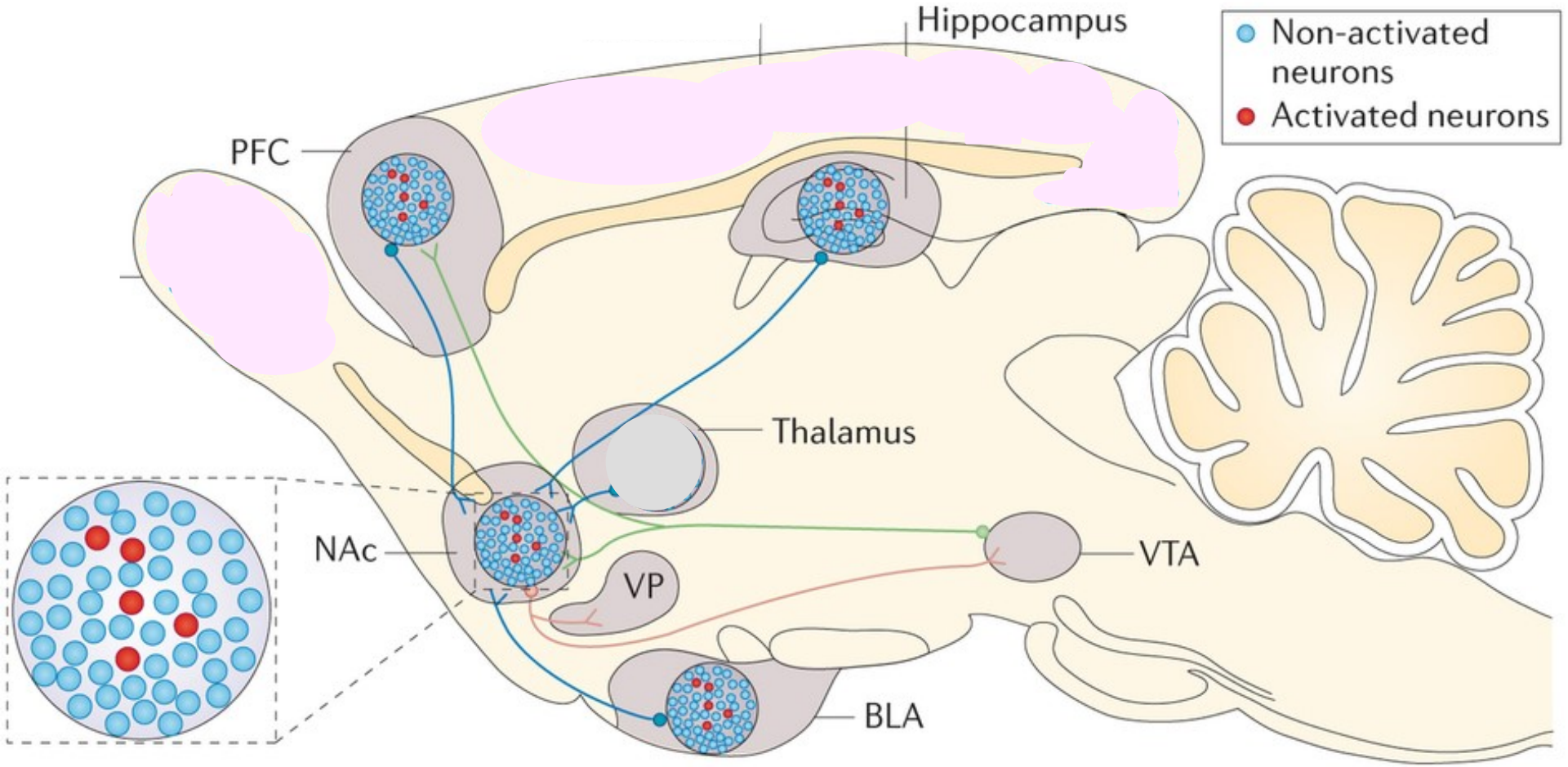
Bilbao et al. unpublished results

Conclusions

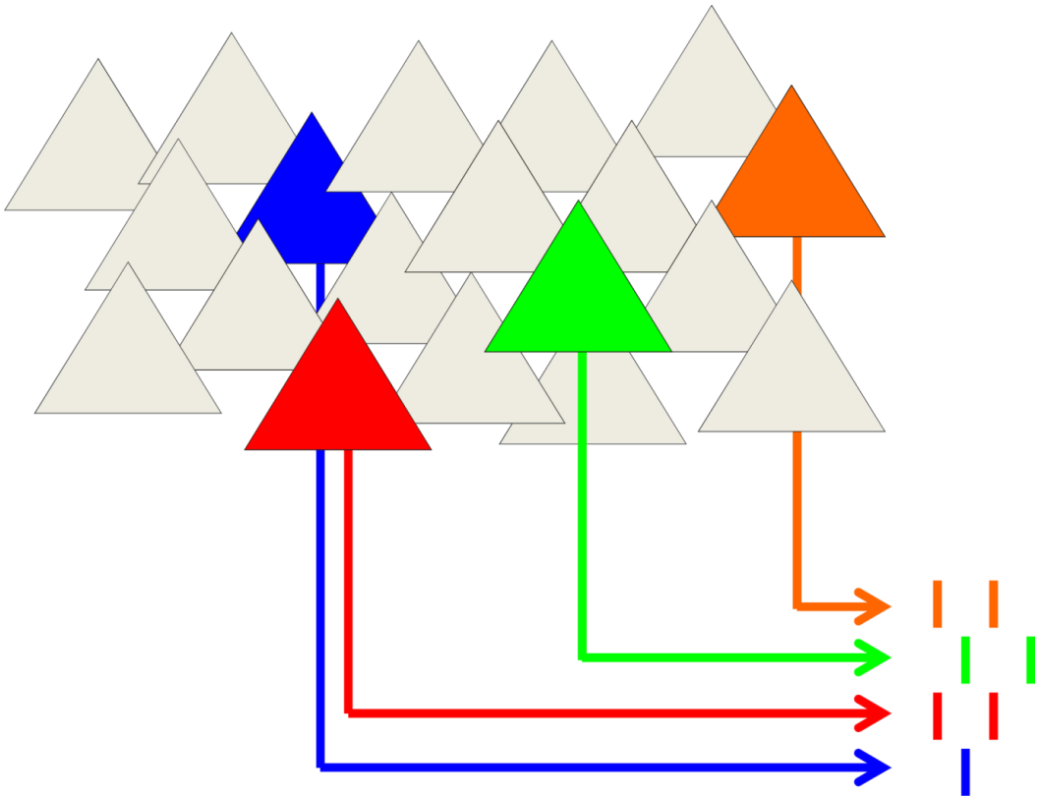
- Natural and drug rewards share the same molecular and physiological correlate for cue-induced reward-seeking responses, namely accumbal mGluR5-dependent eCB-induced LTD

- Because of this shared mechanism mGluR5 and CB1R inhibitors produce generalized effects on all kind of reward-seeking responses

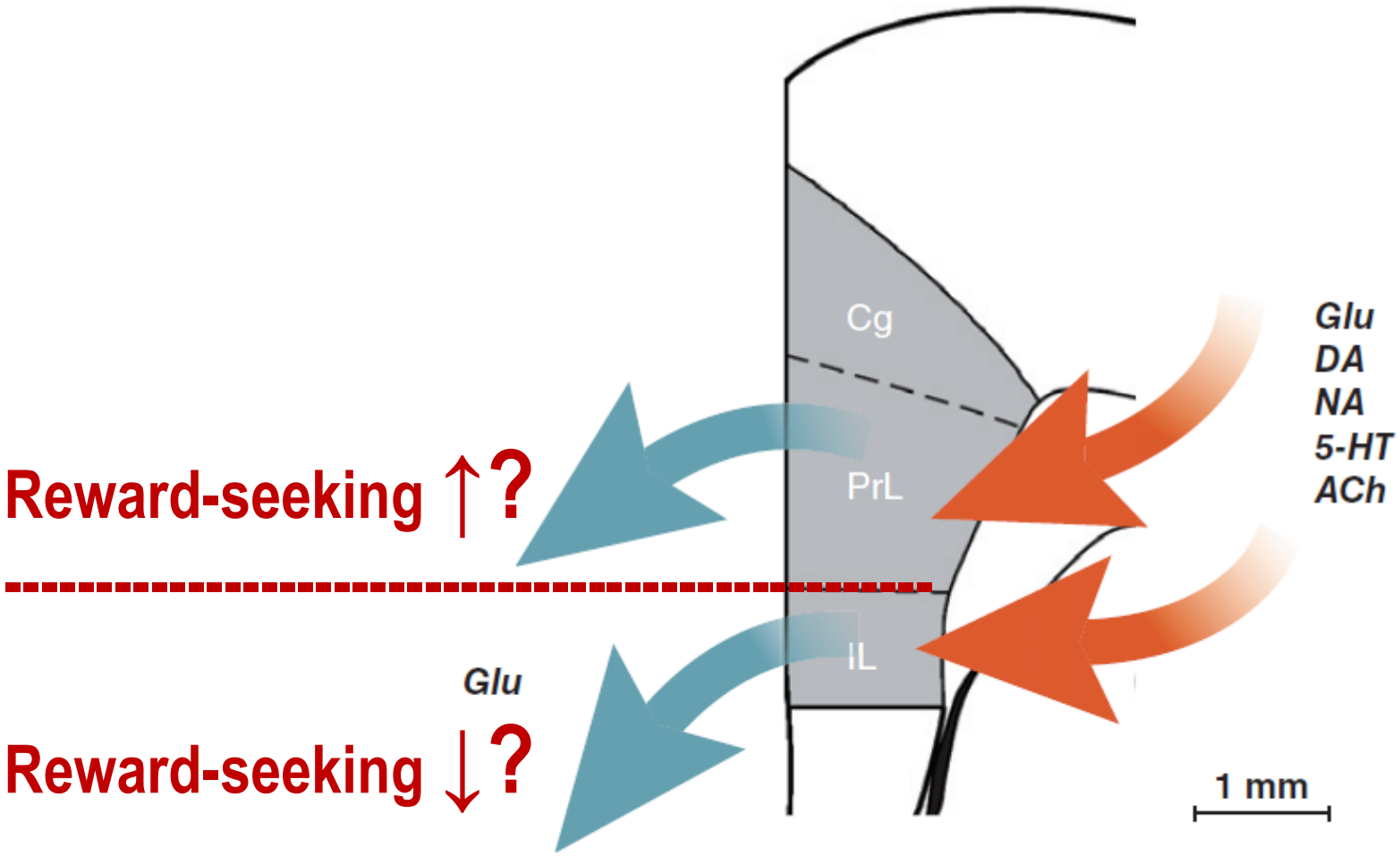
Activated neurons during cue-induced reinstatement of alcohol-seeking



Shared and distinct clusters of coherent active neurons (neuronal ensembles) during alcohol- vs. natural (e.g. saccharin) reward- seeking responses



Which are the neuronal ensembles that drive reinstatement of reward-seeking behavior?

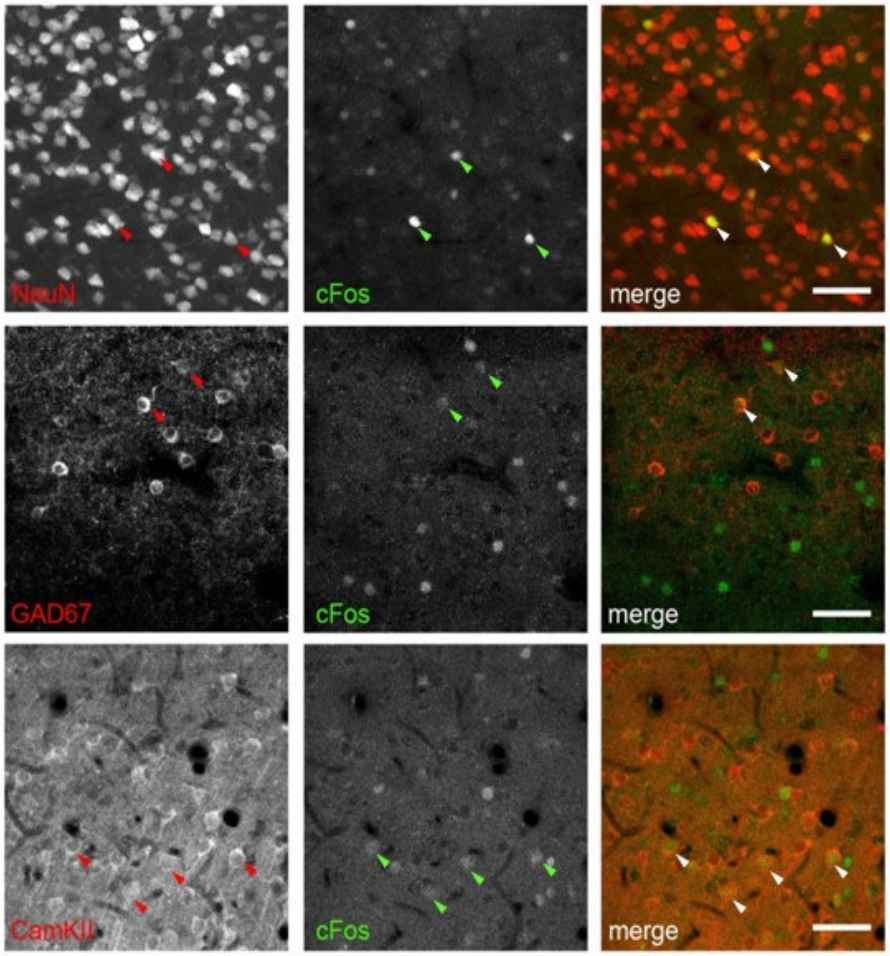


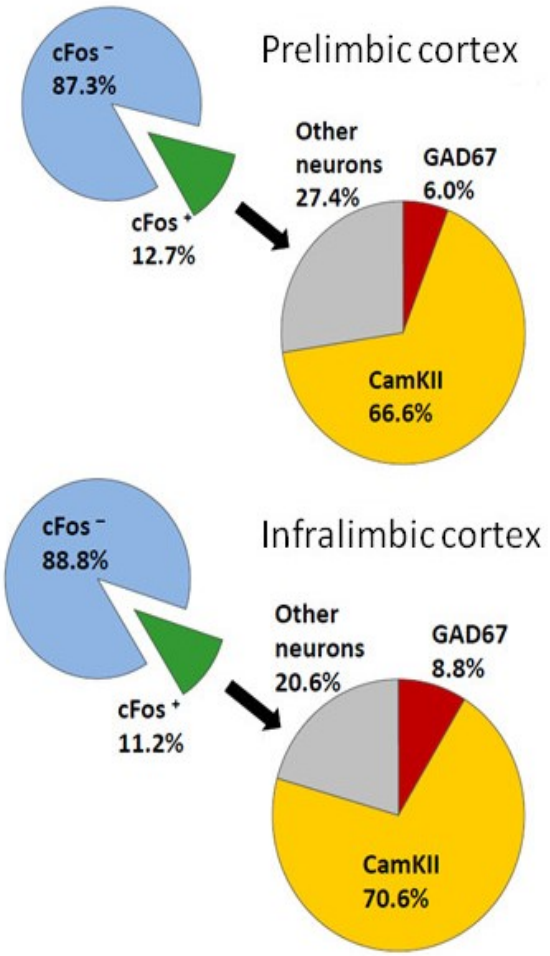
Marcus Meinhardt

Wolfgang Sommer


Simone Pfarr

Characterization of cue-responsive neurons in the prelimbic and infralimbic cortex after reinstatement of alcohol-seeking



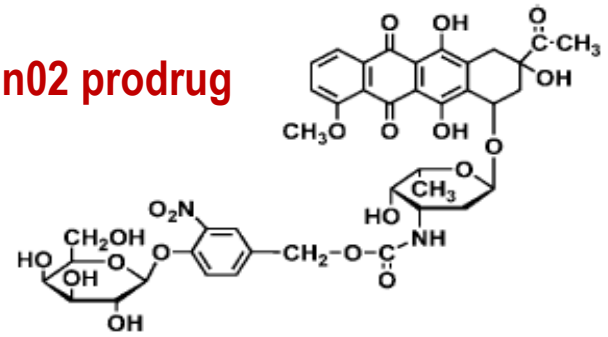


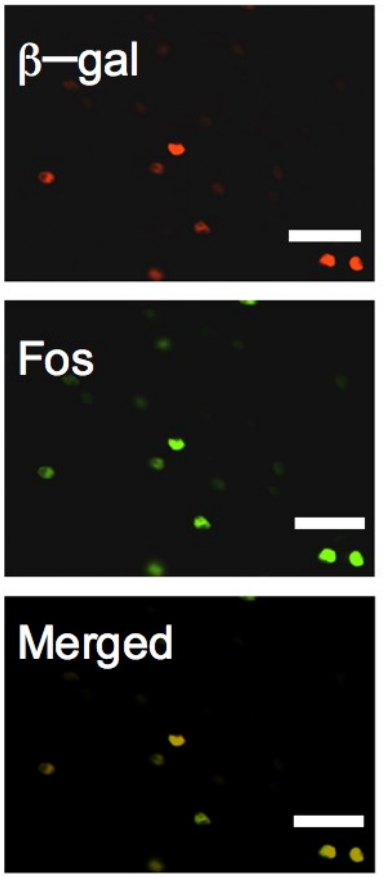
Pfarr et al. unpublished

Pharmacogenetic silencing with DaunO2

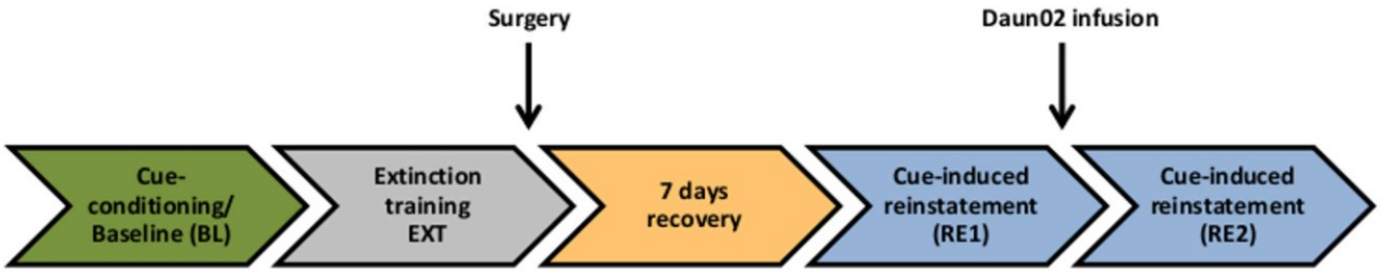
(see Cruz…Hope, Nat Rev Neurosci 2013)

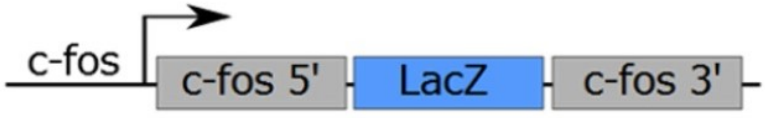
Daun02 prodrug



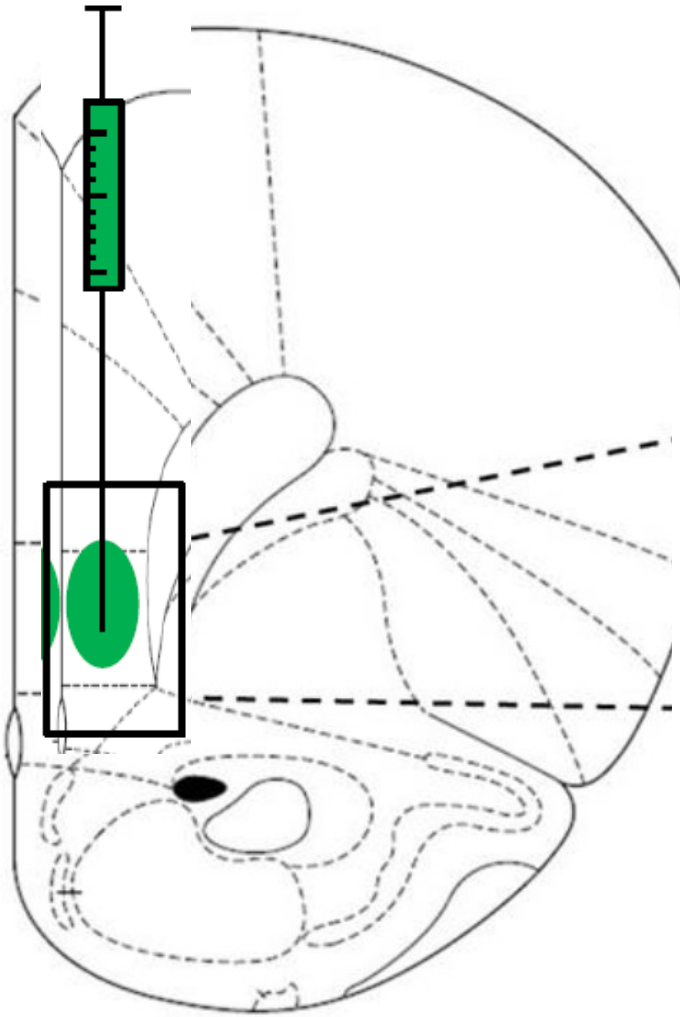


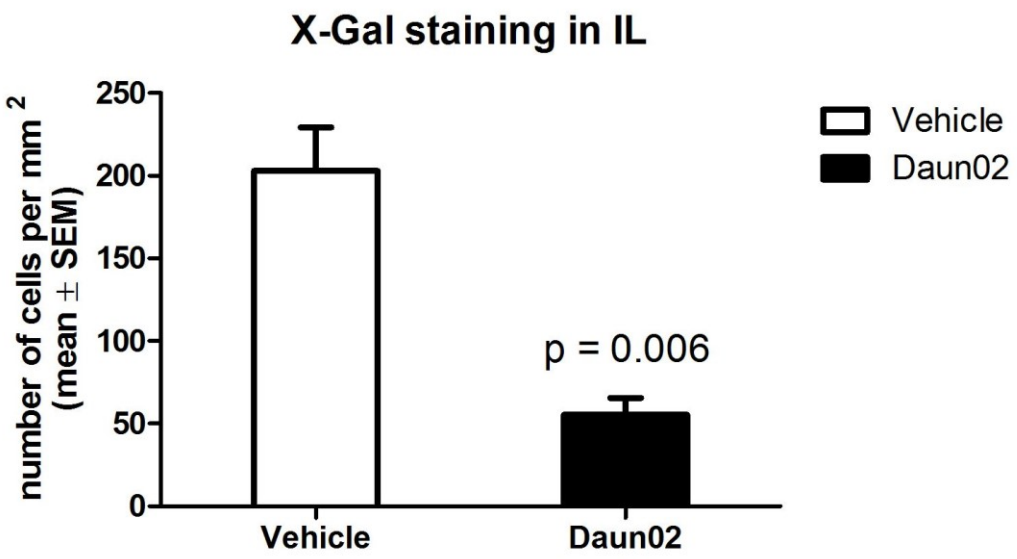
Pharmacogenetic silencing with DaunO2: experimental procedure





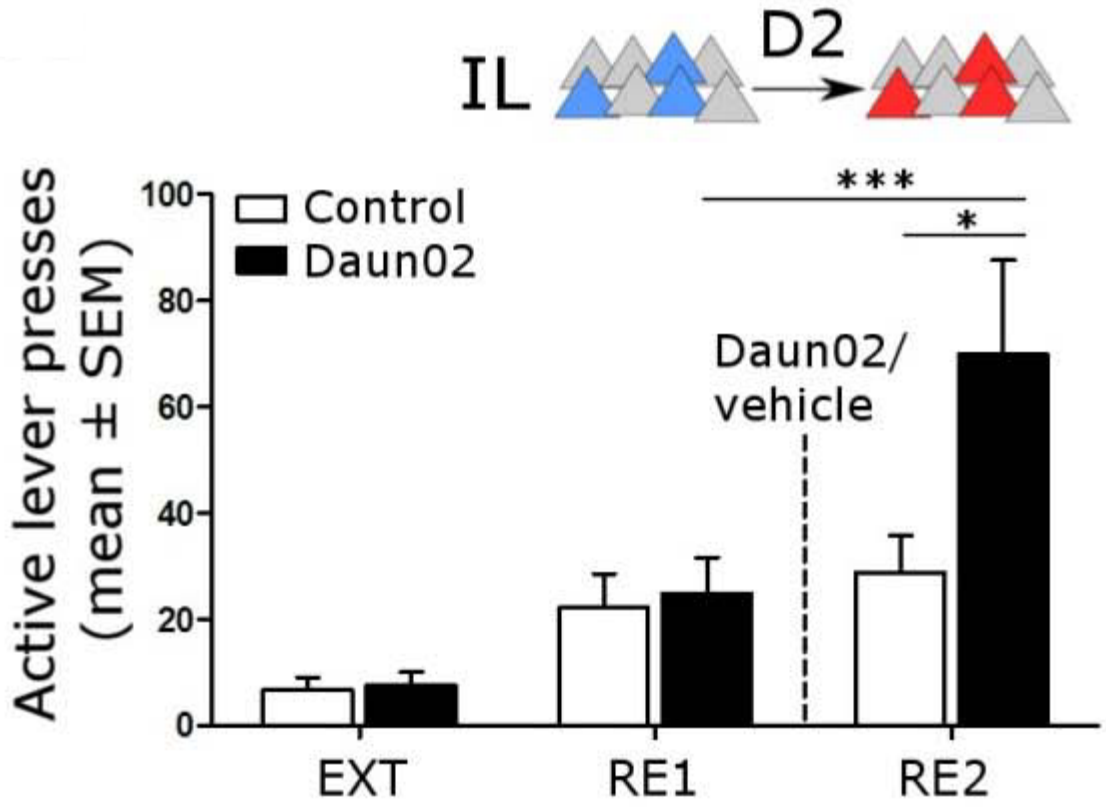
Pharmacogenetic silencing with DaunO2 erases activated neurons after cue-induced reinstatement





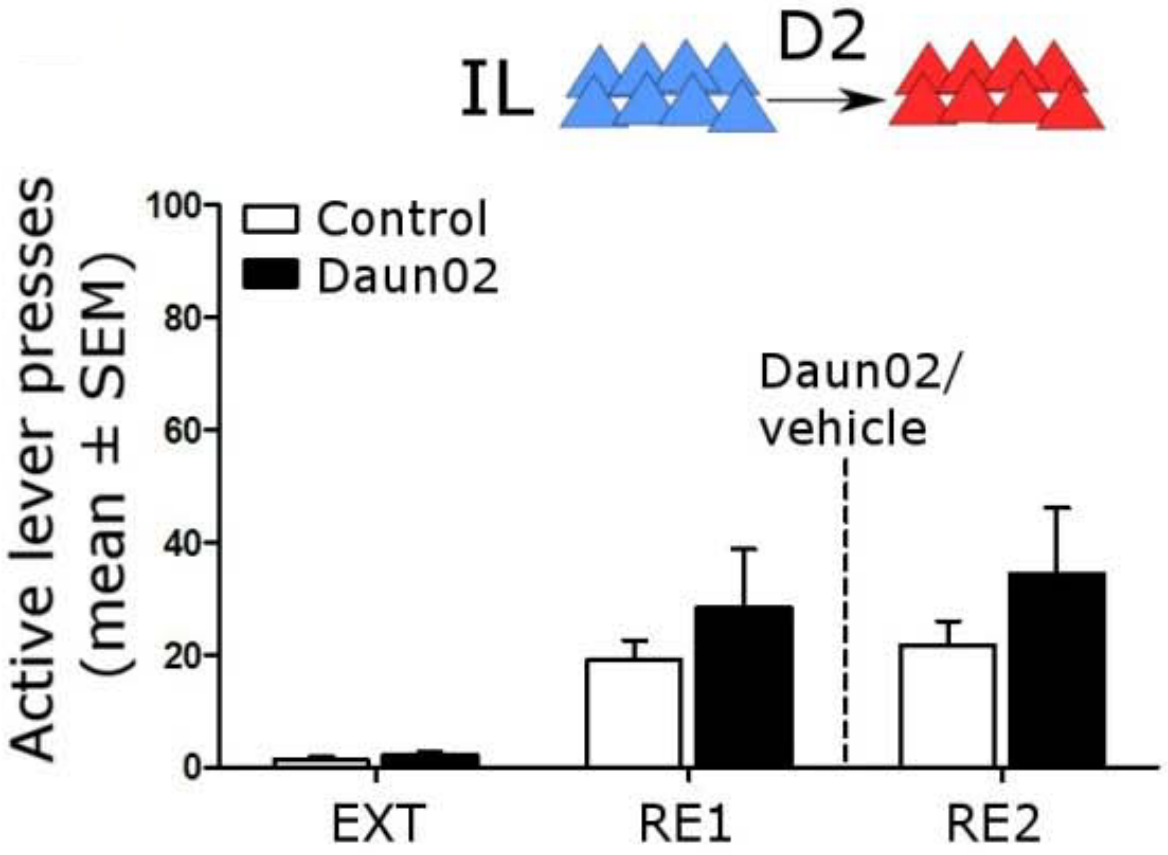
Pfarr et al., unpublished

DaunO2 silencing of infralimbic neuronal activity leads to enhanced alcohol-seeking



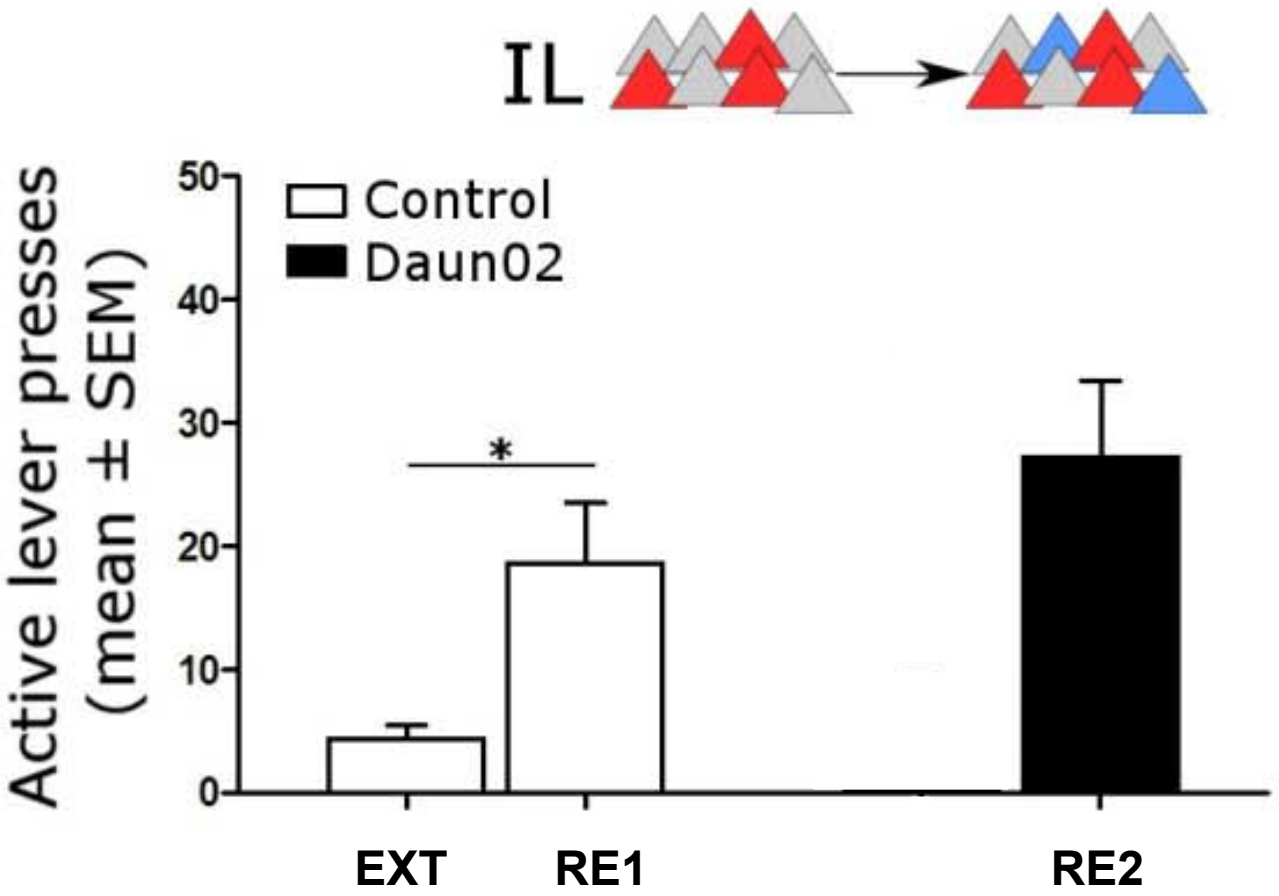
Pfarr et al., unpublished

Non-selective infralimbic inactivation by Daun02 in pCAG-lacZ rats does not affect alcohol-seeking



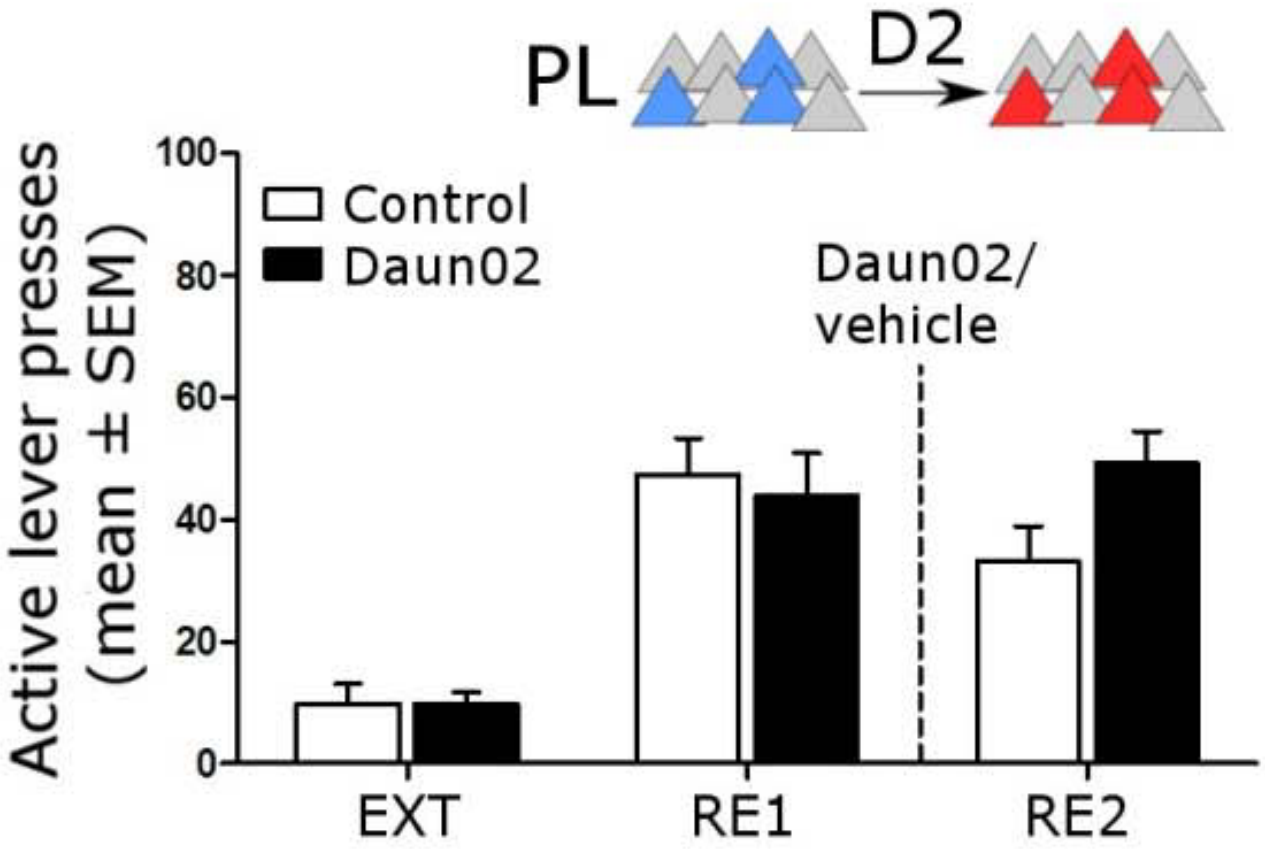
Pfarr et al., unpublished

DaunO2 silencing of alcohol cue driven infralimbic neuronal activity does not affect saccharin-seeking



Pfarr et al., unpublished

Prelimbic DaunO2 infusion does not alter reinstatement of alcohol-seeking behavior



Pfarr et al., unpublished

Conclusions

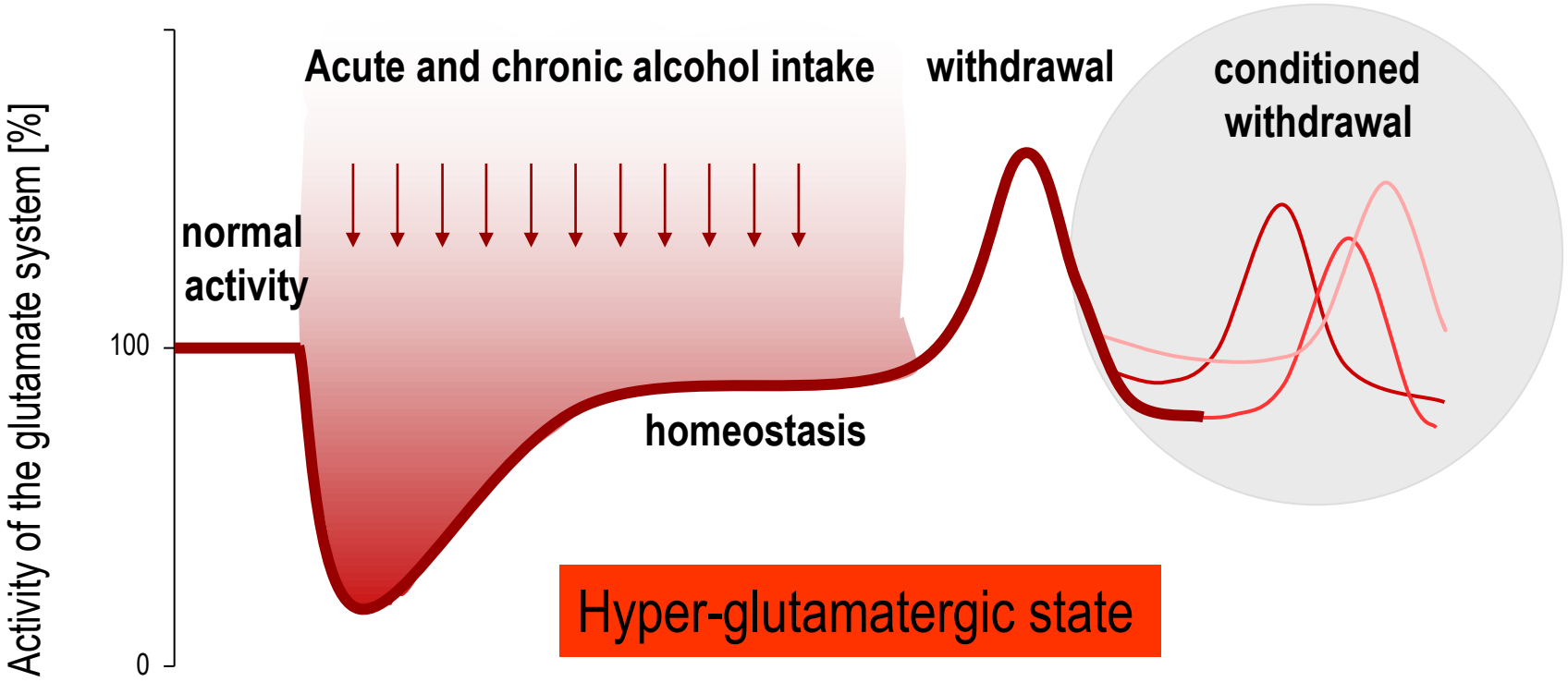
- Neuronal ensemble within the infralimbic PFC drives reinstatement of alcohol-seeking behavior

- This neuronal ensemble is distinct from the one that drives saccharin-seeking behavior

- Alcohol cue activated neurons within the prelimbic PFC are not involved in alcohol-seeking

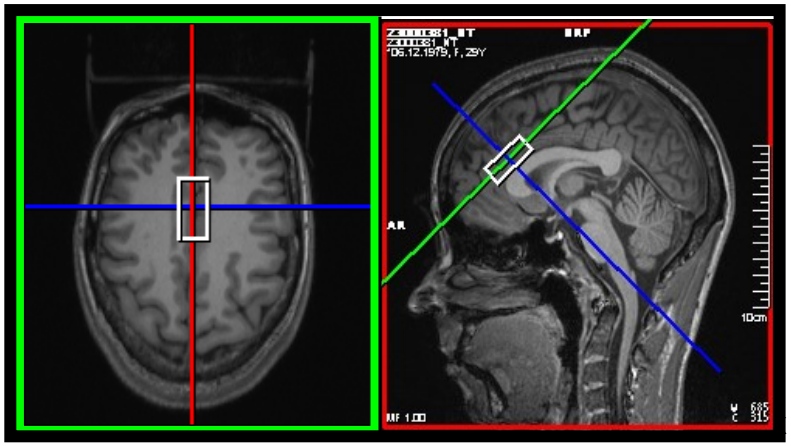
- Functional output depends on specific neuronal ensembles within a given brain region rather than on the global activity of that region

Enhanced glutamate levels are associated with cue-induced



Spanagel and Kiefer, Trends Pharmacol Sci 2008

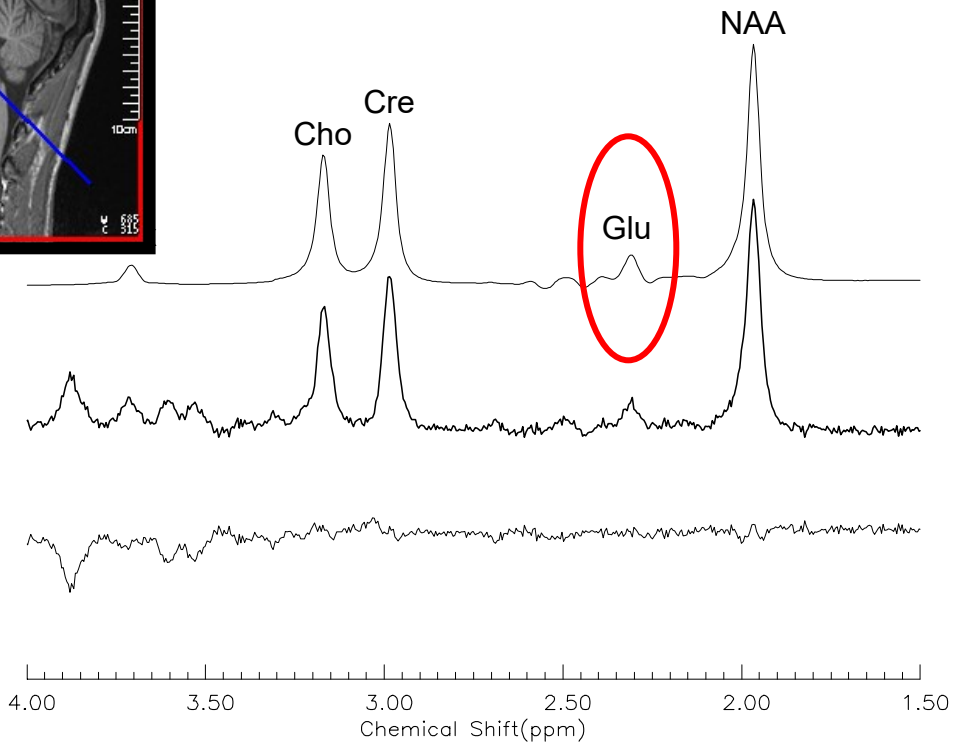
Glutamate spectroscopy (MRS) in the human brain at 3T



Anterior cingulate gyrus (ACC) Voxel: 15x30x12mm^3

Basal glutamte levels:

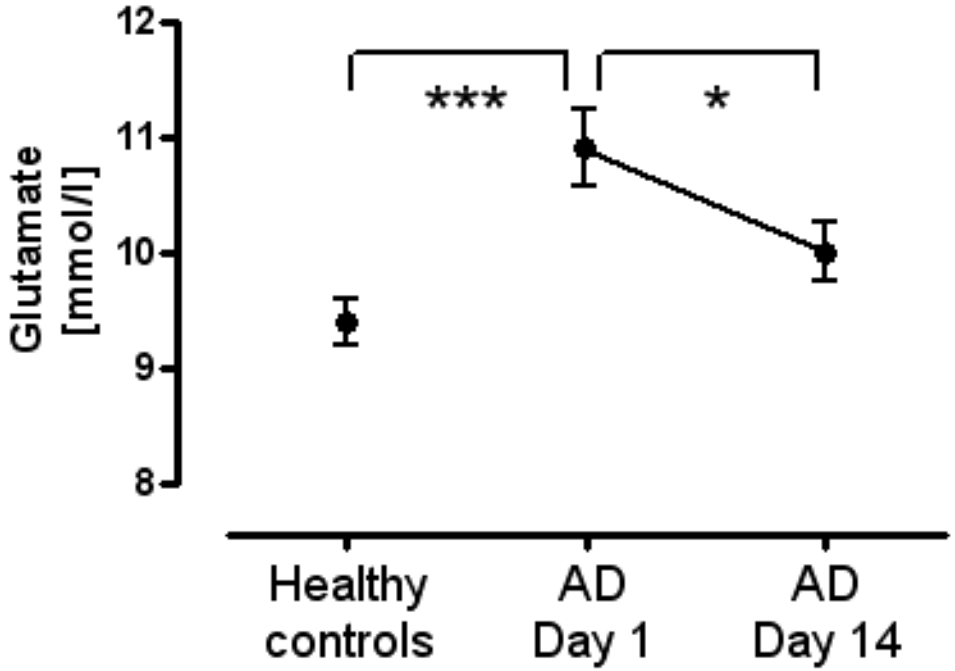
9.4 + 0.20 mmol/l



Herrmann et al., Biol Psychiatry 2012

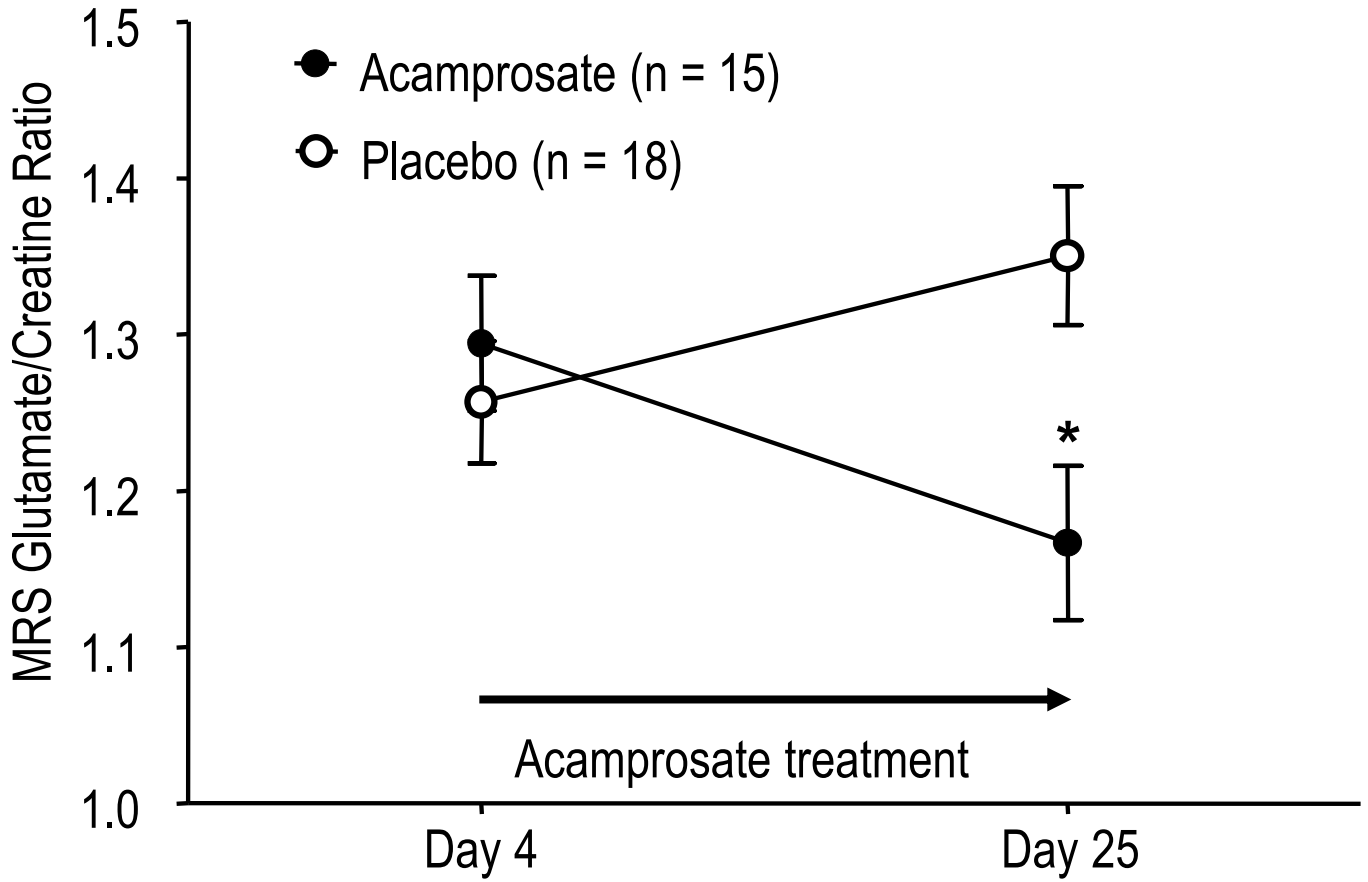
Increased glutamate levels in ACC of alcohol dependent patients during acute withdrawal

	M/F	Age	EtOH/day in g	AUDIT
Controls	32/13	44.2 ± 12	24 ± 18	3 ± 2
Patients	36/9	46.4 ± 10.5	207 ± 124	26.1 ± 6.5



Herrmann et al., Biol Psychiatry 2012

Acamprosate reduces enhanced glutamate levels in detoxified alcoholic patients



Umhau et al., Arch Gen Psychiatry 2010