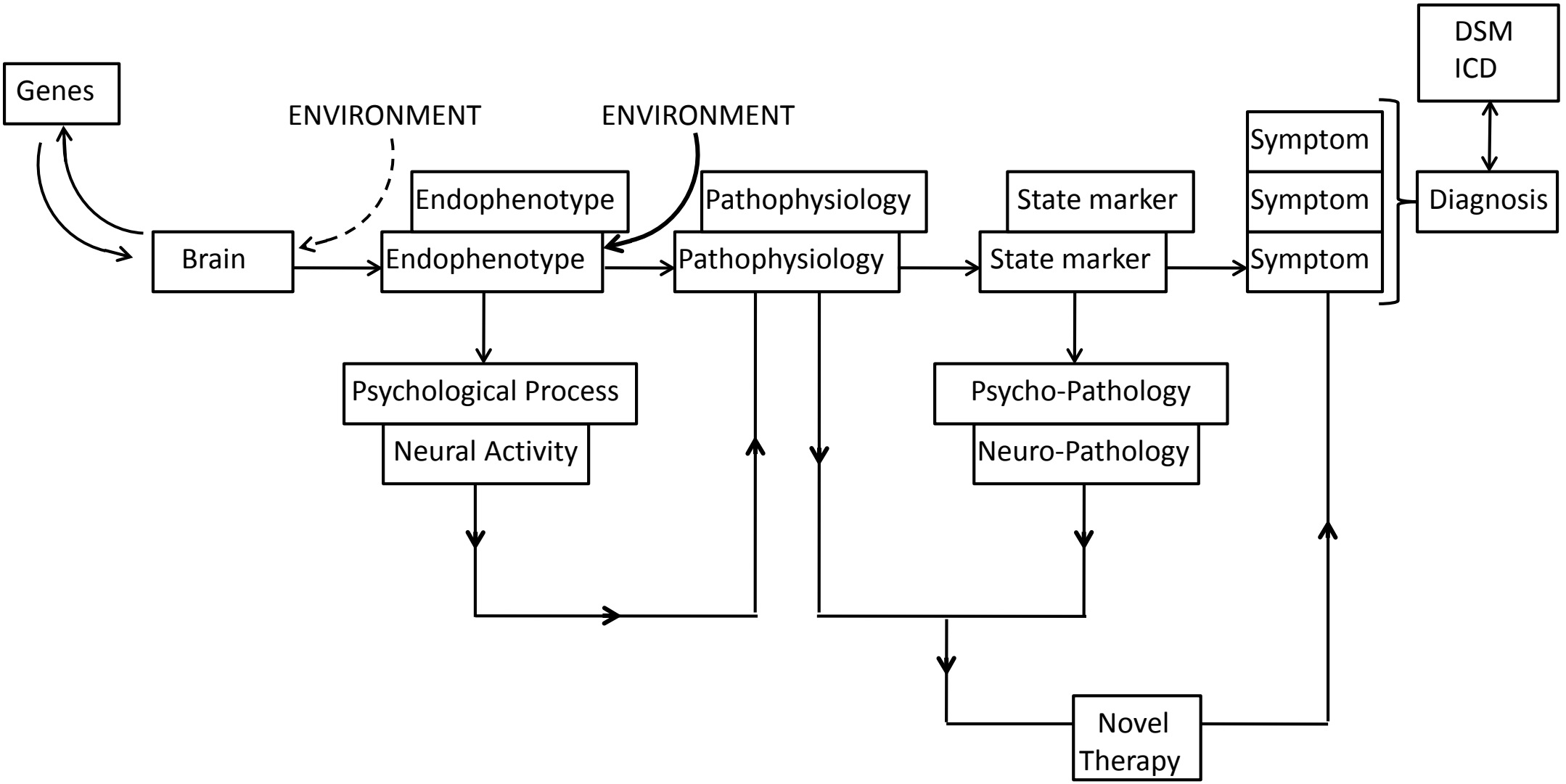
Animal models of human affective disorders:

Models relevant to psychiatric disorders

- Depression
- Animal model validity
- Rat/Mouse model of chronic unpredictable mild stress (CUMS) and reduced reward motivation
- Rat/Mouse model of CUMS and increased floating in forced swim test
- Rat/Mouse model of CUMS and decreased neuronal Plasticity in Hippocampus and PFC
- Mouse model of chronic social defeat (CSD) and hyper-fear conditioning
- Mouse model of CSD and Generalised Helplessness
- Mouse model of CSD and altered transcriptome expression in Amygdala
- Rat/Monkey model of early deprivation (ED) and reduced reward motivation
- Optogenetics and animal models of depression

Understanding a complex psychiatric disorder in terms of neuro-behavioural components



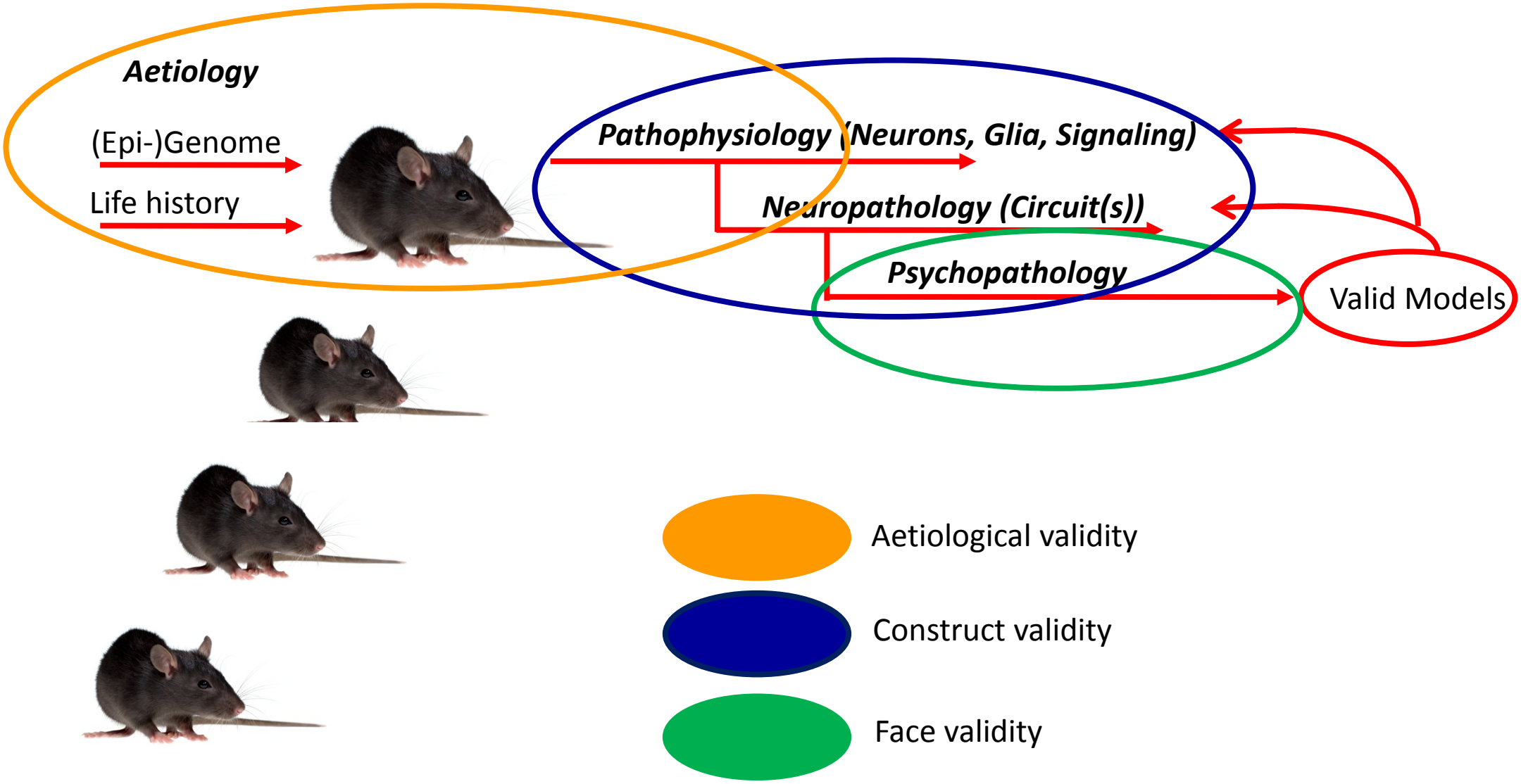
Depression is altered emotional processing of aversive and rewarding stimuli

Aversive life events/stimuli	Rewarding life events/stimuli
Reactivity to UCS (↑)	Motivation/Interest (↓)
Learning about CS (↑)	Learning about CS (↓)
Uncontrollability of stimuli (↑)	Uncontrollability of stimuli (↑)
Expectancy of stimuli (↑)	Expectancy of stimuli (↓)
Fatigue due to aversive stimuli (↑)	Pleasure from (=↓)

(↑) (↓) Direction of change, Depression vs Healthy control
(=↓) Evidence is not convincing
Not all patients will exhibit all symptoms/states

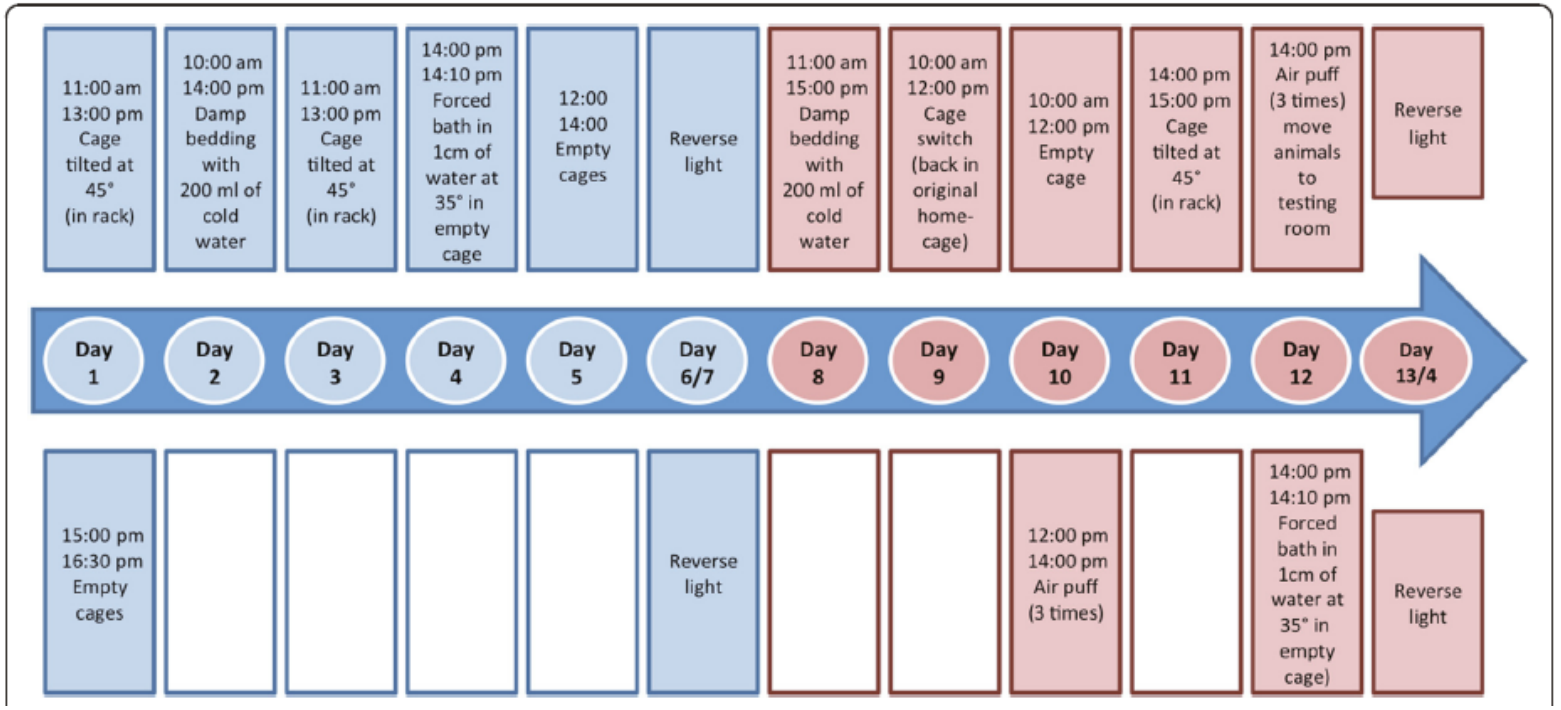
Pryce & Seifritz (2011) *Psychoneuroendocrinol* 36: 308

Animal models must have validity



Environmental manipulation: Chronic unpredictable mild stress (CUMS)

	Morning	Afternoon
Monday	8 AM 1-h confinement in restricted space	1 PM 1-h confinement in restricted space 4 PM overnight illumination
Tuesday	8 AM self-stimulation 11 AM 1-h confinement in restricted space	2 PM 1-h confinement in restricted space 4 PM food and water deprivation for 18 h
Wednesday	8 AM access to restricted food for 2 h	1 PM 1-h confinement in restricted space 4 PM water deprivation for 18 h
Thursday	8 AM exposure to empty bottle for 1 h 11 AM 1-h confinement in restricted space	2 PM 1-h confinement in restricted space 4 PM group-housed in soiled cage for 18 h
Friday	8 AM self-stimulation 11 AM 1-h confinement in restricted space	4 PM reversed light/dark cycle throughout the weekend

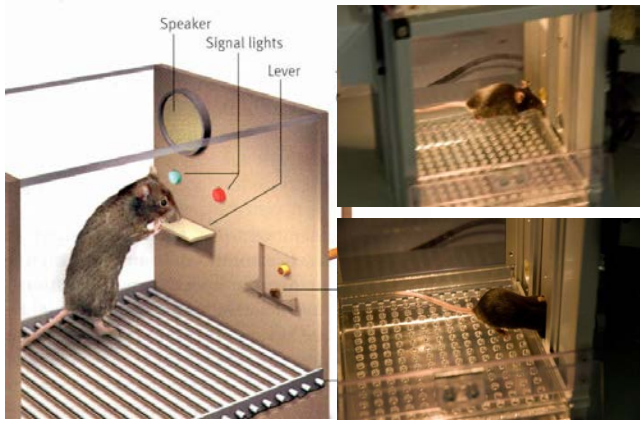


Food reward in Rodents – Adaptive goal-directed behaviours

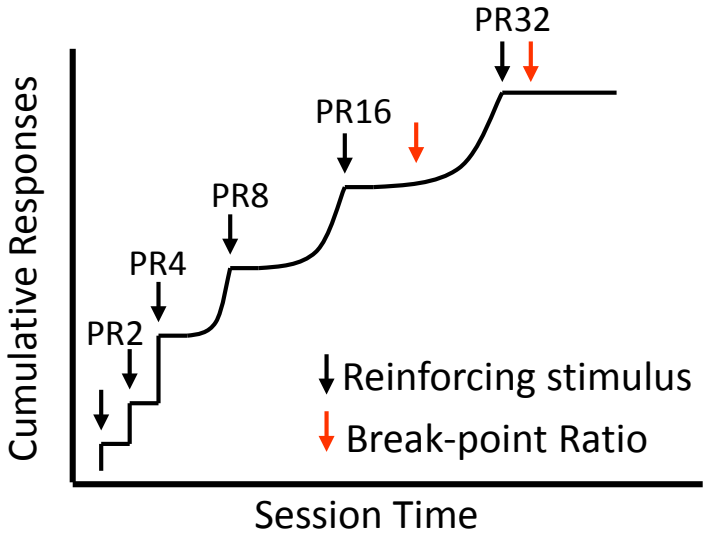
Major modulating function of mesocorticolimbic Dopamine system on Motivation

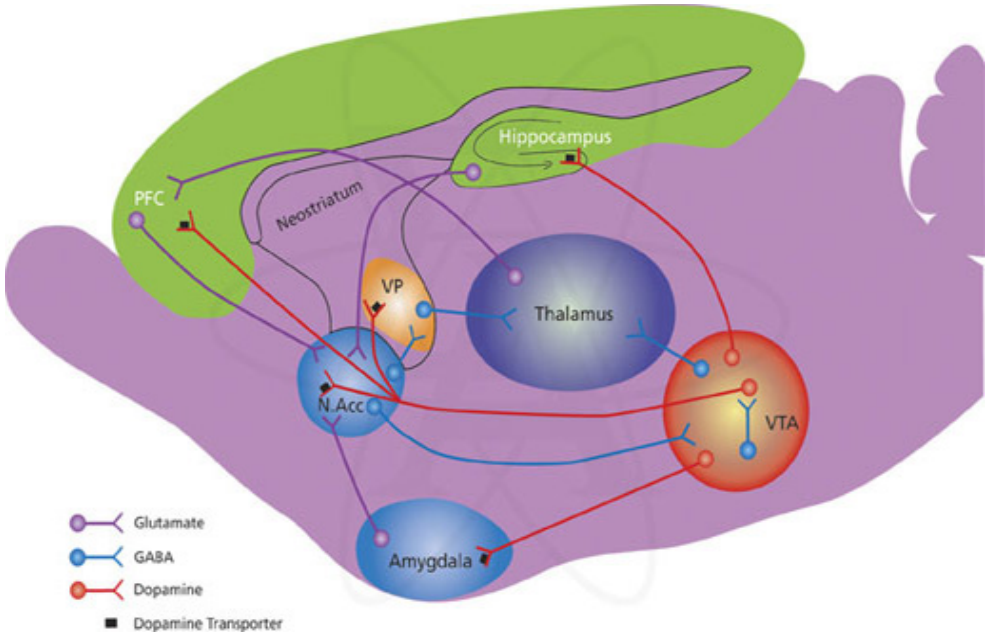
Consummation Tests

Operant Response-Outcome Tests



Progressive ratio schedule test



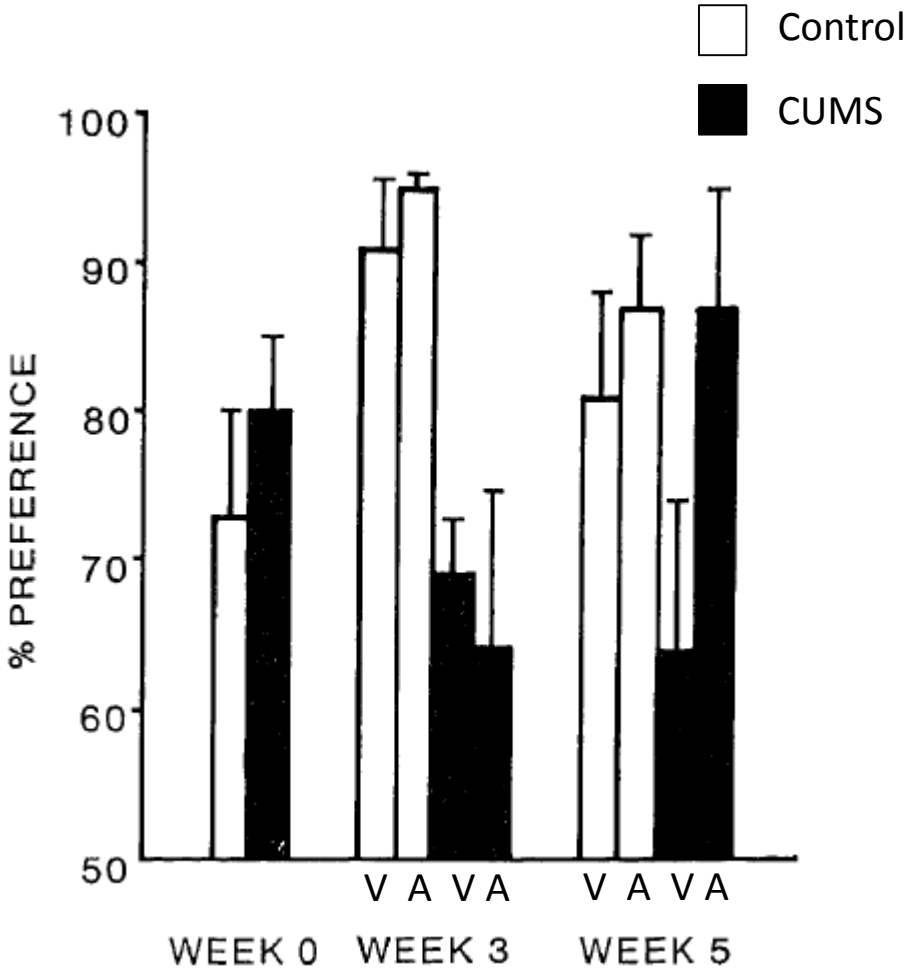


CUMS chronically reduces Sucrose-preference in Rats

2-bottle preference test

Sucrose preference =

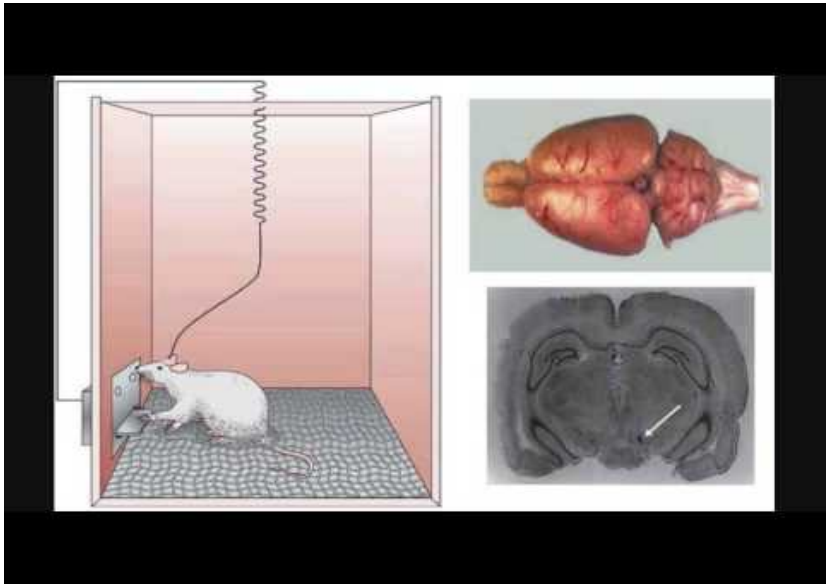
$$\frac{\text{Sucrose consumed}}{\text{Sucrose + Water consumed}}$$



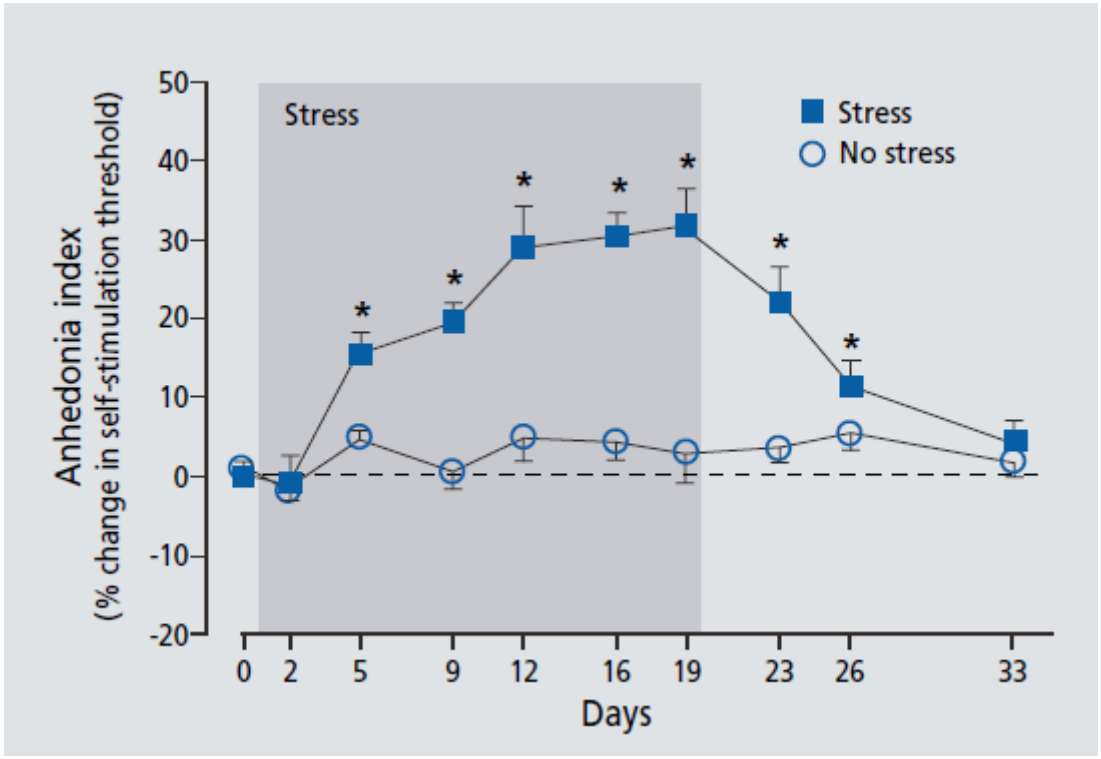
V, Vehicle
A, Antidepressant

Willner (1997) Psychopharmacology 134: 319

CUMS chronically reduces VTA self-stimulation in Rats



VTA = Ventral tegmental area

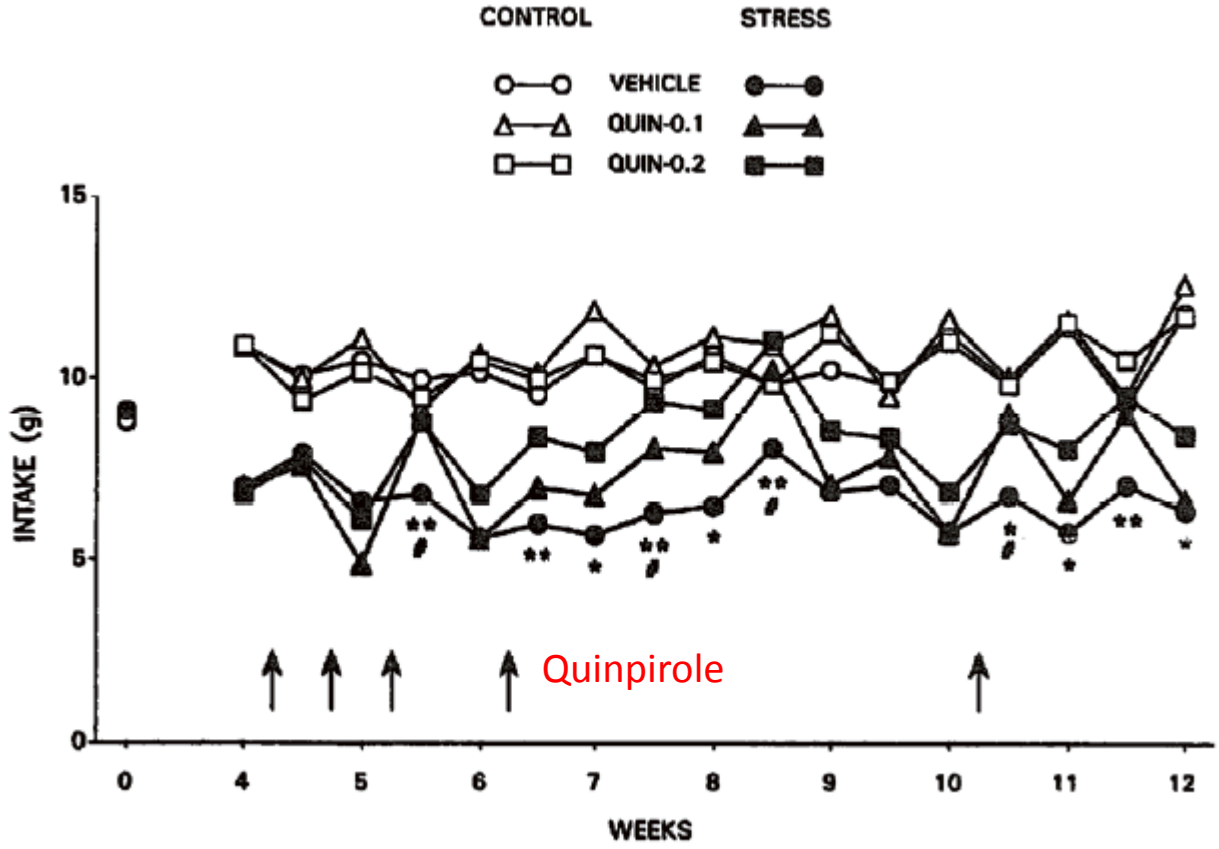


Moreau (2002) Dialog Clin Neurosci 4: 351

CUMS chronic reduction of Sucrose-Intake is reversed by Dopamine-receptor agonist in Rats

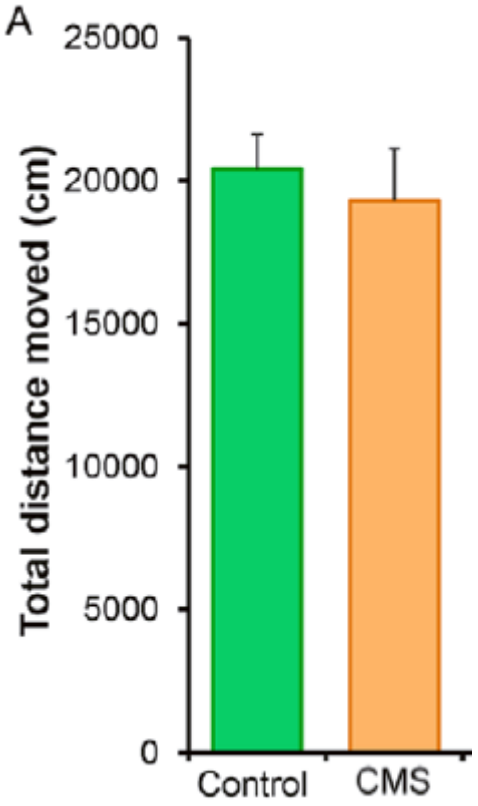
2-bottle test

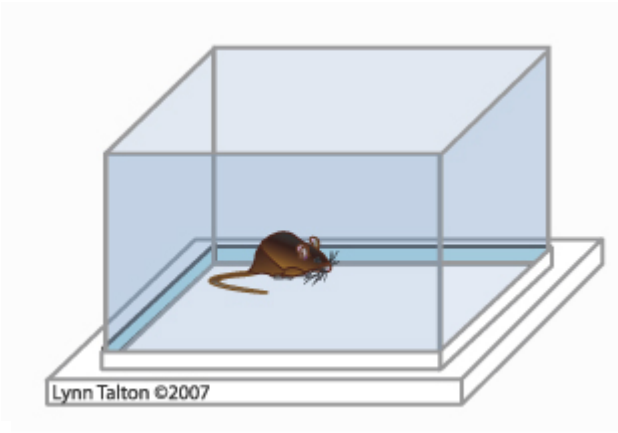
Sucrose consumed

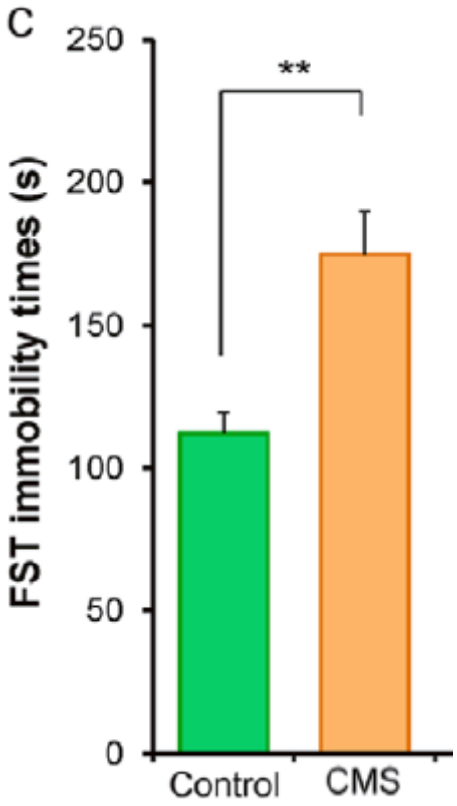


Muscat et al (1992) Biol Psychiatry 31: 937

CUMS increases floating in the Forced swim test in Mice



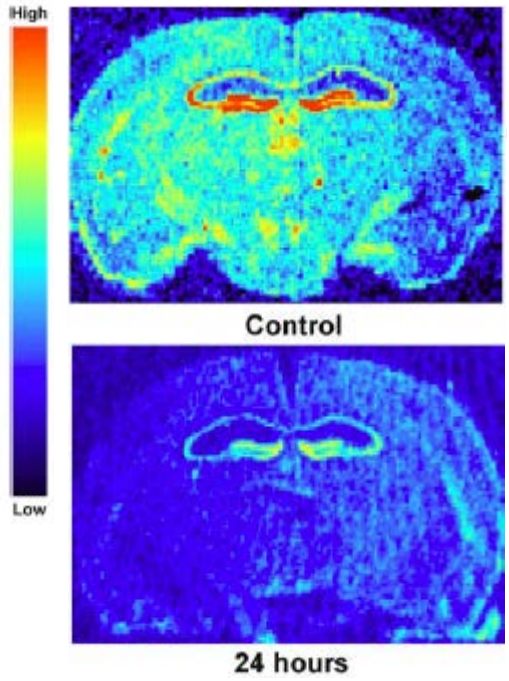


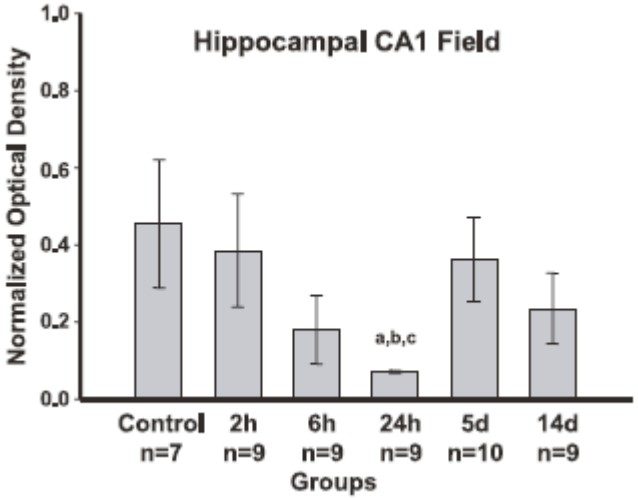


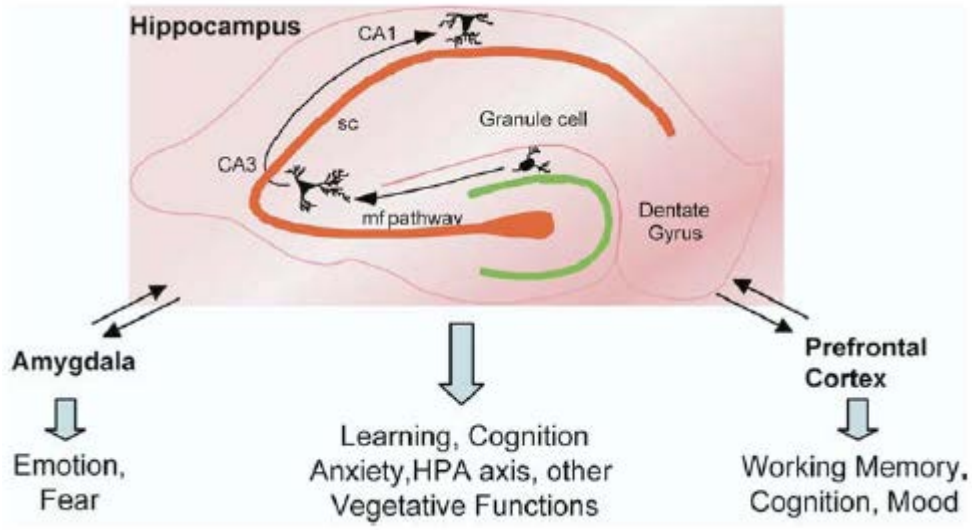
Ma et al. (2013) PLOS ONE 8: e56053

Stress decreases Neurotrophins and Synaptic Proteins in Hippocampus and Cortex

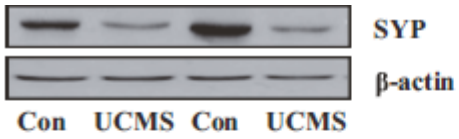
Brain-derived neurotrophic factor (BDNF)



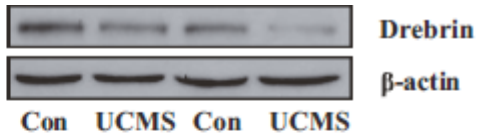


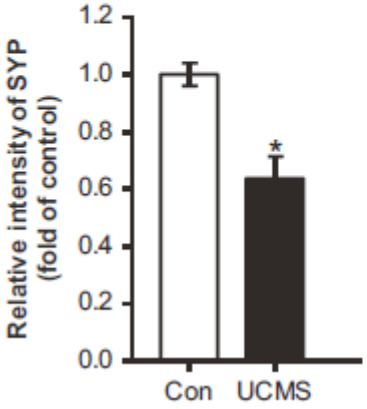


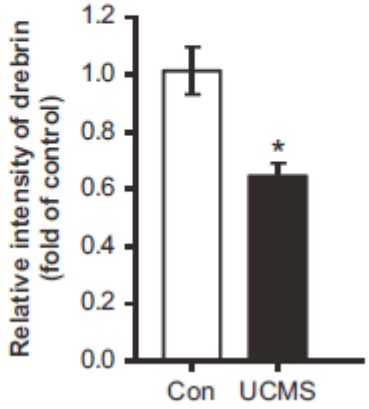
Pre-synaptic Synaptophysin

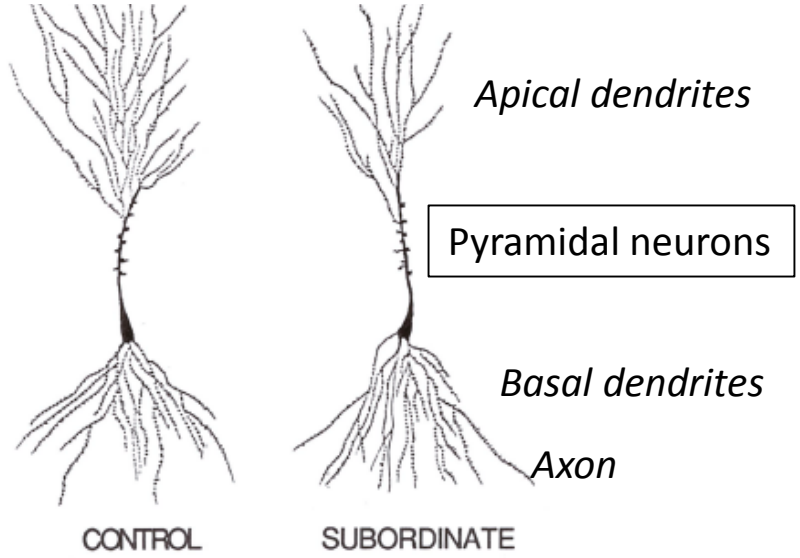


Post-synaptic Drebrin





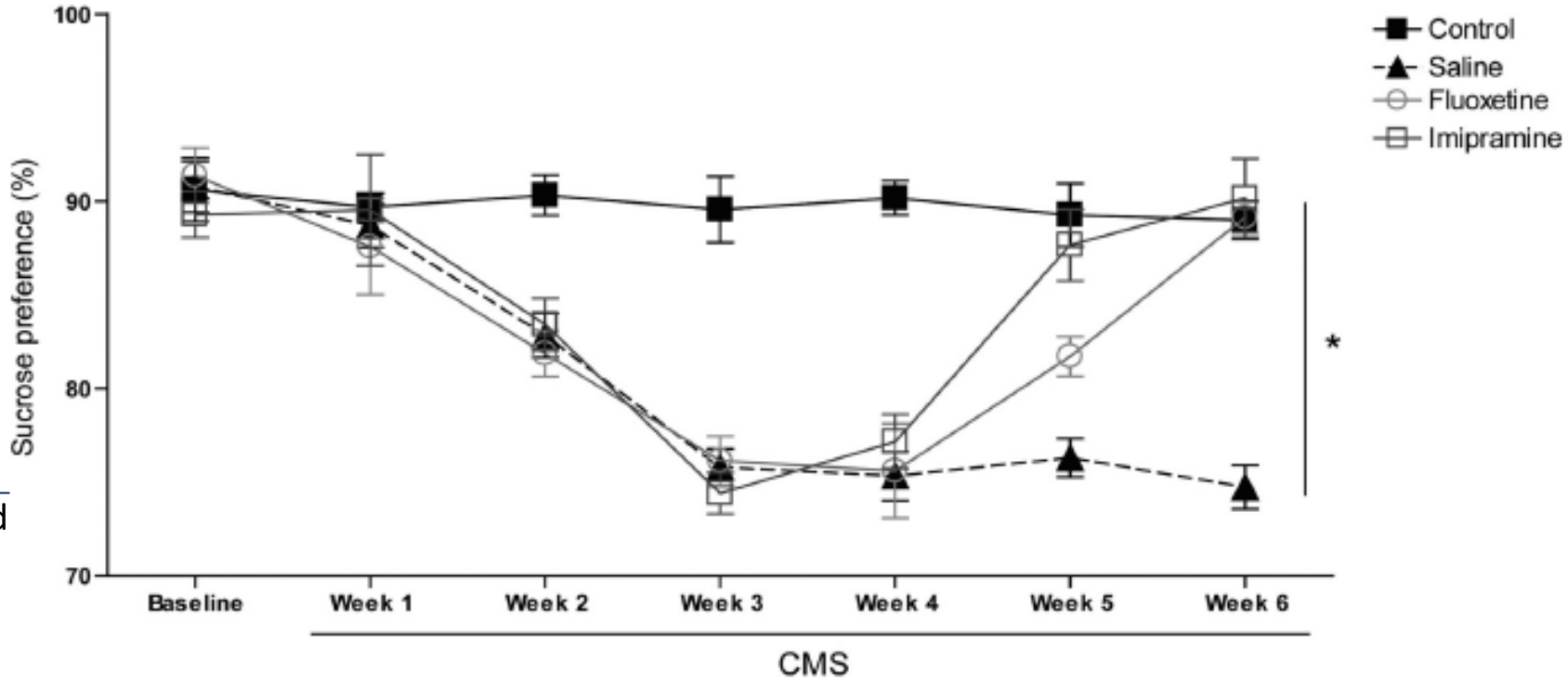




Pizarro et al (2004) Brain Res 1025: 10
Duman & Monteggia (2006) 59: 1116
Zhu et al. (2014) Brain Res 1576: 81

CUMS reduced sucrose preference in Rats is reversed by Antidepressants

Sucrose preference = Sucrose consumed / Sucrose + Water consumed



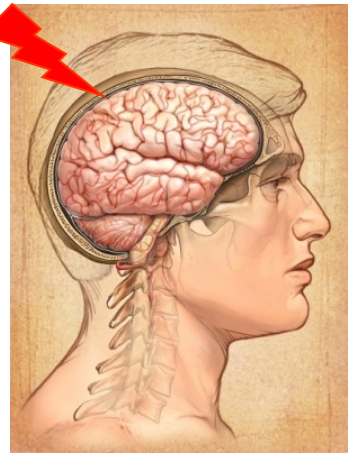
Bessa et al (2010) Front Behav Neurosci 3: 1

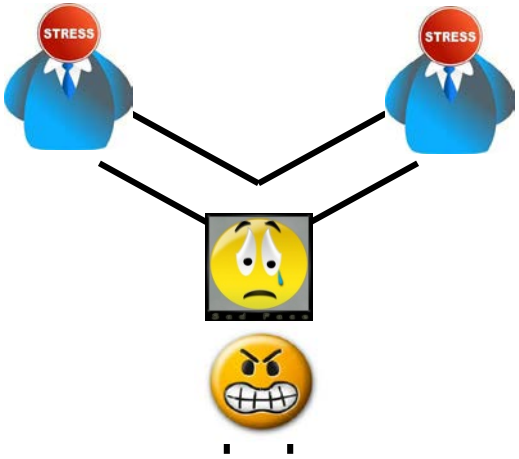
Environment: From Uncontrollability to Helplessness to emotional disorder

Aetiology

(Epi-)Genome

Life history





Uncontrollable Stressful life events:

- Employment
- Finance
- Health
- Housing
- Family
- Social relationships

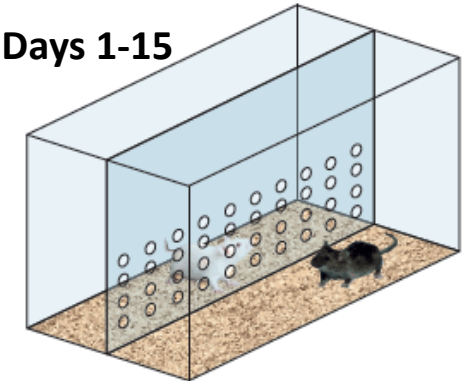
Aetiology

(Epi-)Genome

Life history

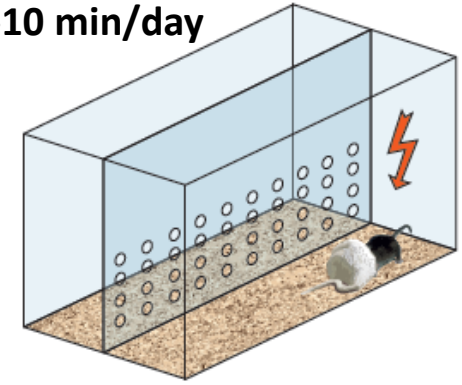
Chronic social defeat (CSD)

Days 1-15



Threat:
Visual
Olfactory
Auditory

1-10 min/day



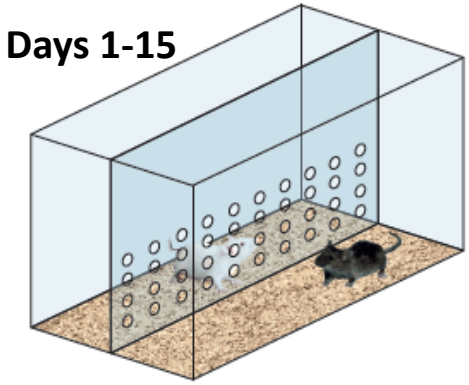
Threat+Attack:
Physical
No wounds

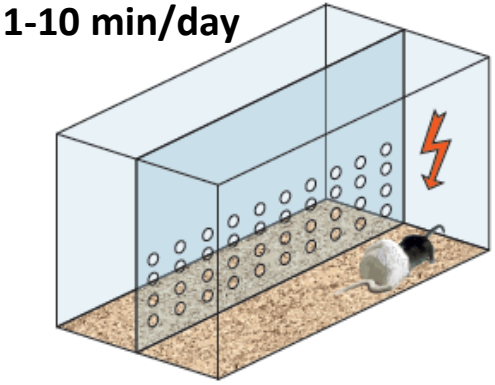
Lack of social control
= Helplessness

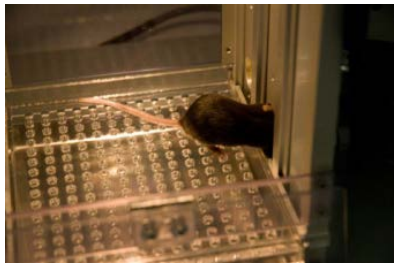
Chronic social defeat decreases Interest in Reward

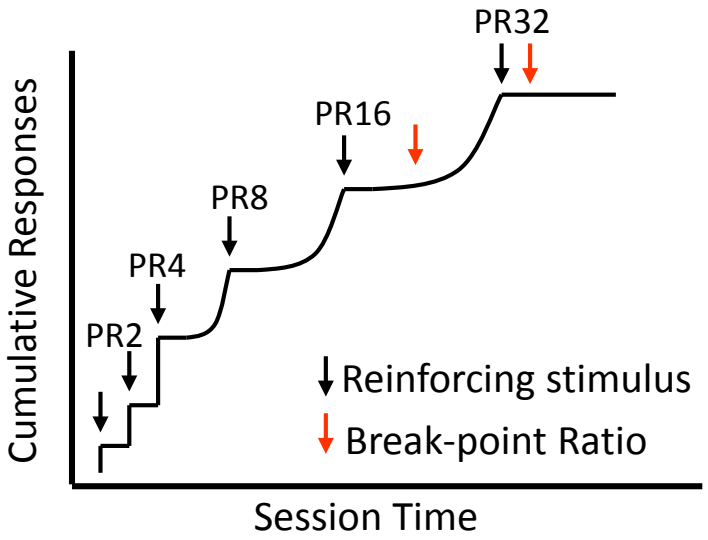
Chronic social defeat (CSD)

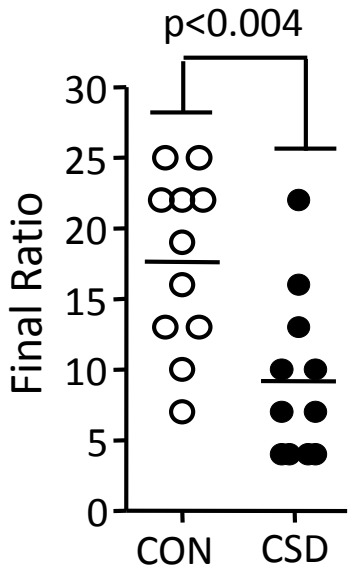
Progressive Ratio Schedule for sugar reinforcement

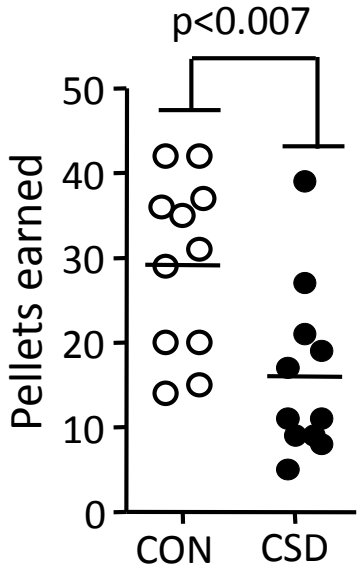


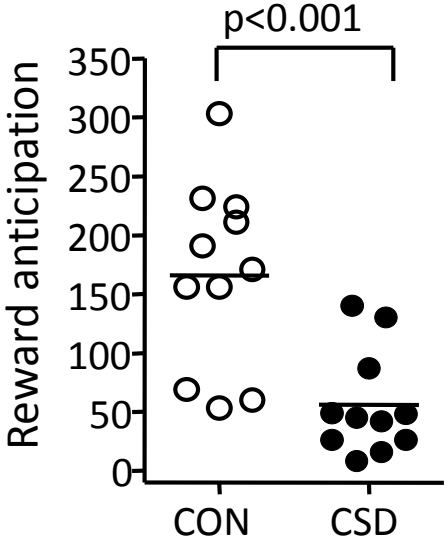










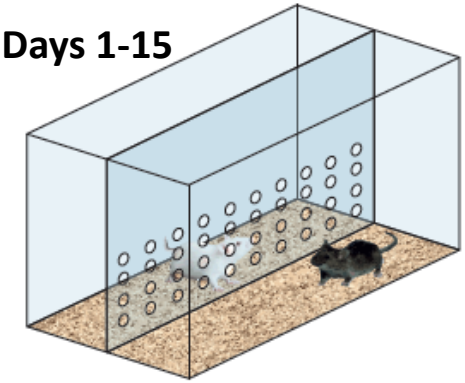


Chronic social defeat leads to Hyper-fear conditioning

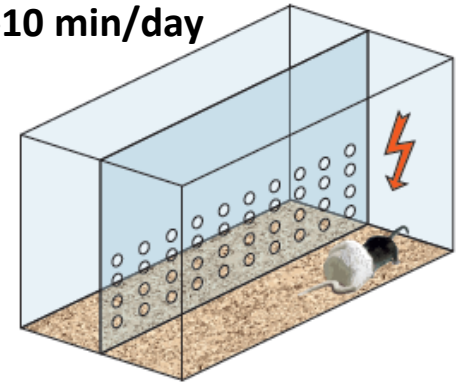
Chronic social defeat (CSD)

Fear Conditioned Freezing

Days 1-15



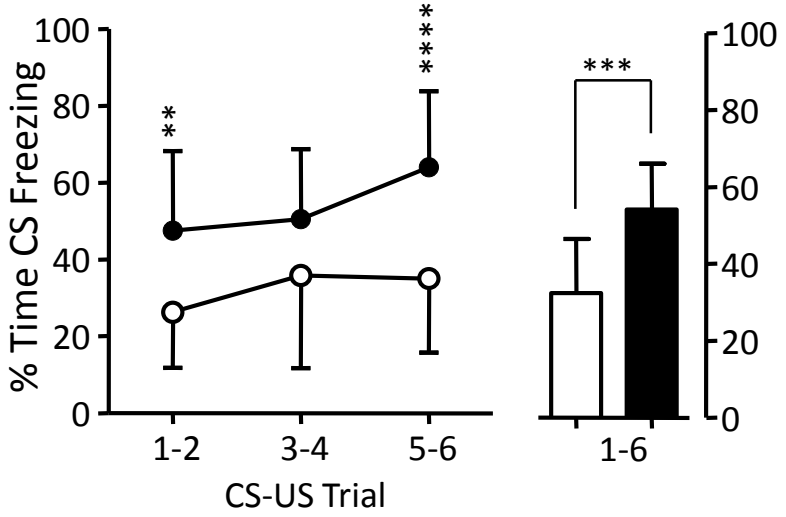
1-10 min/day

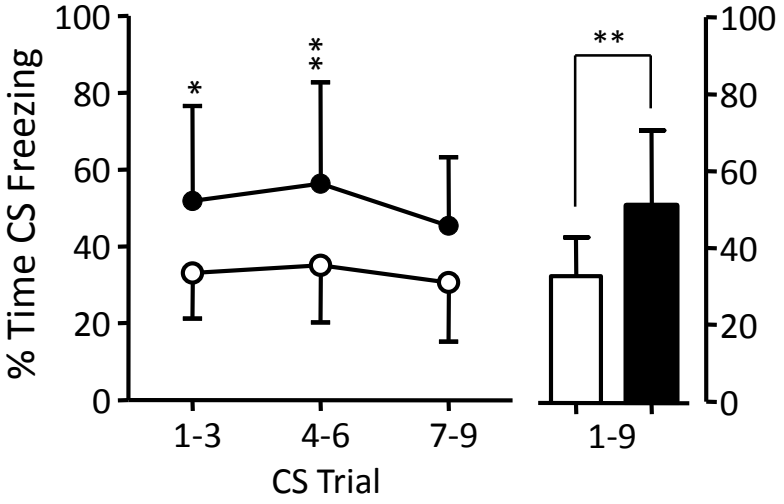


Day 16: Fear Conditioning

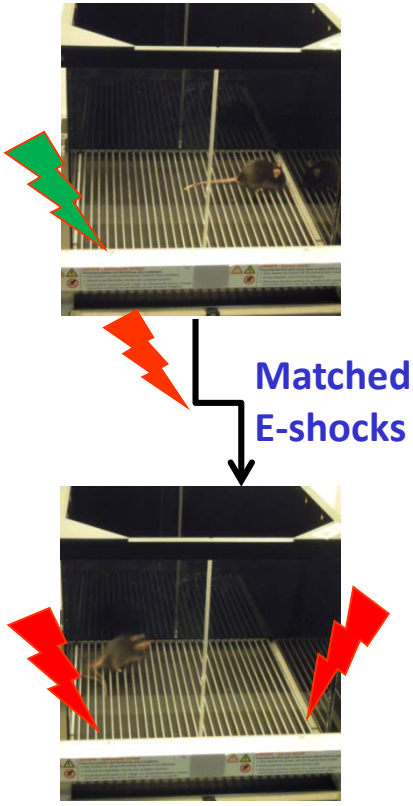
24 hr

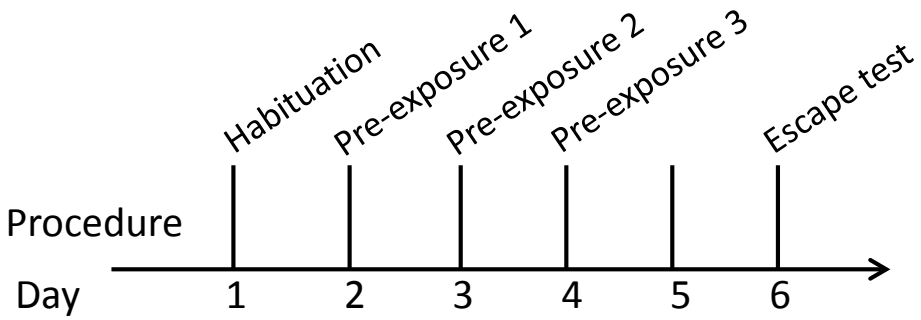
Day 17: Fear expression test

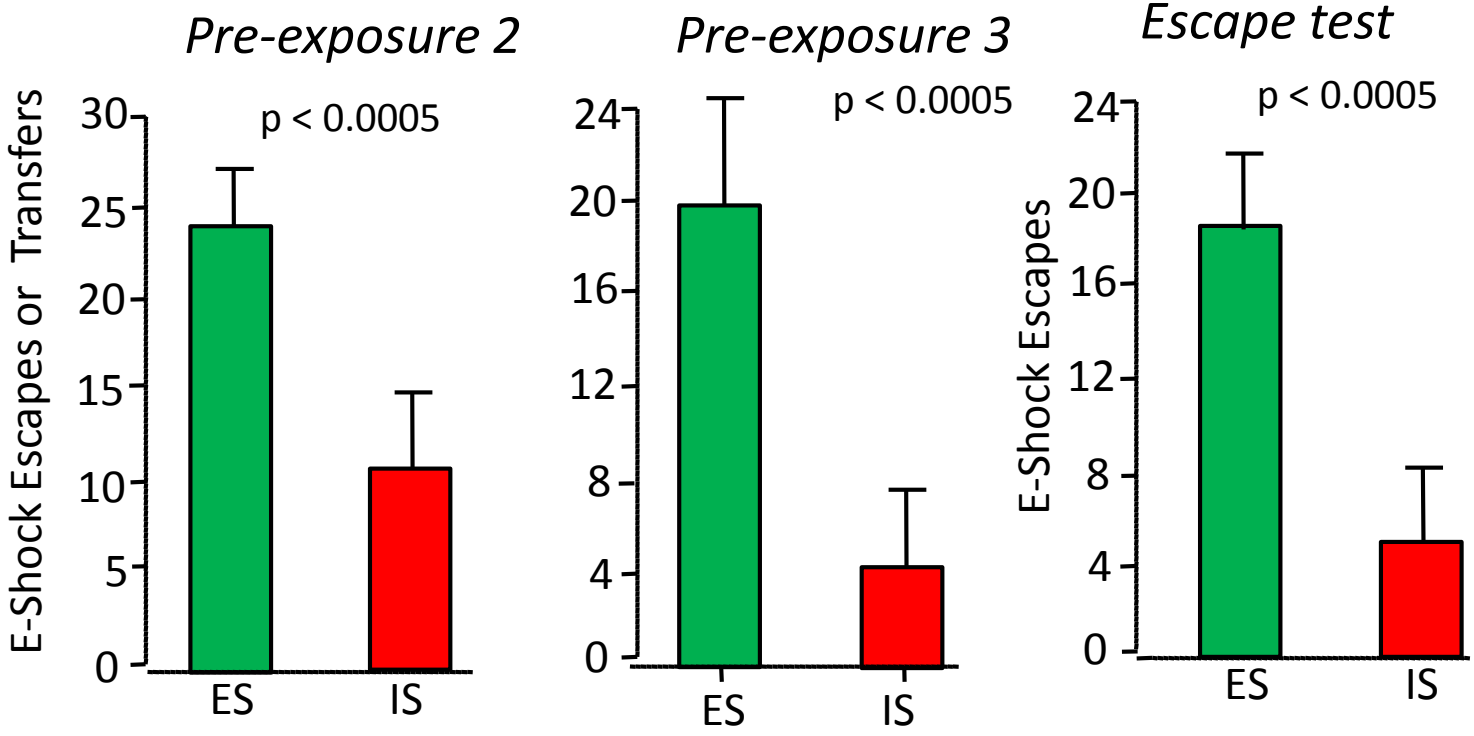




The specific learned helplessness effect in mice



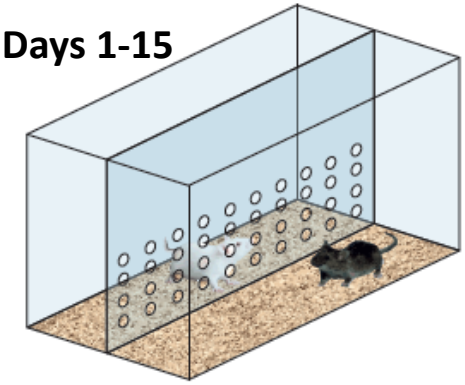




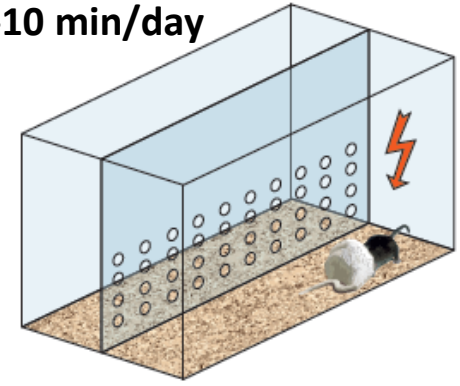
Chronic social defeat leads to Generalized helplessness

Chronic social defeat (CSD)

Days 1-15

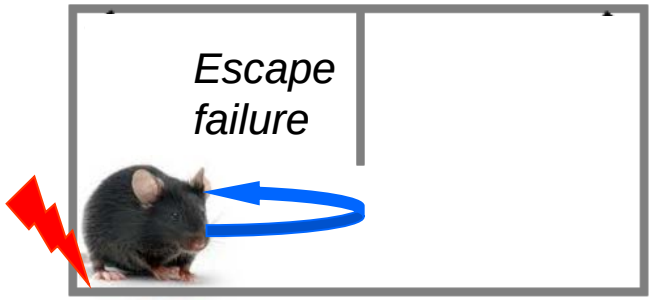


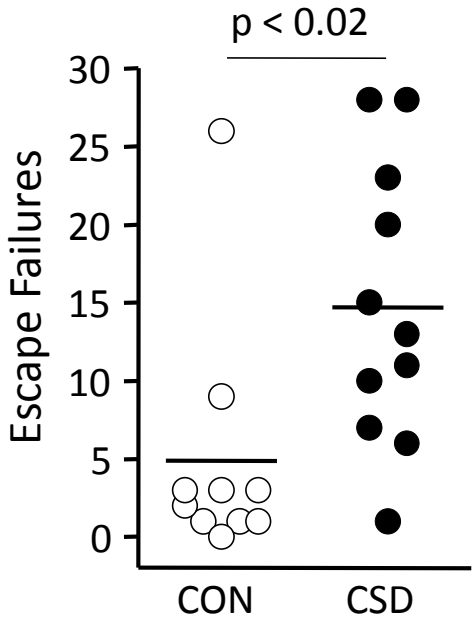
1-10 min/day



Helplessness

Day 20: Two-way Escape Test

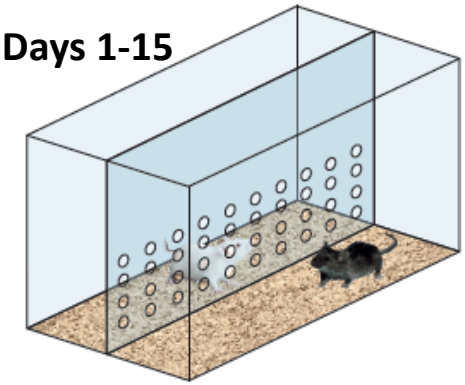




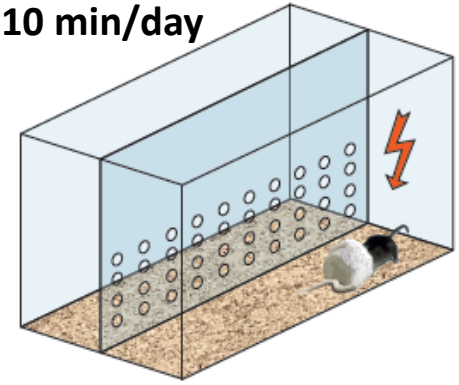
Effects of chronic social stress on CNS region-specific gene expression

Chronic social defeat (CSD)

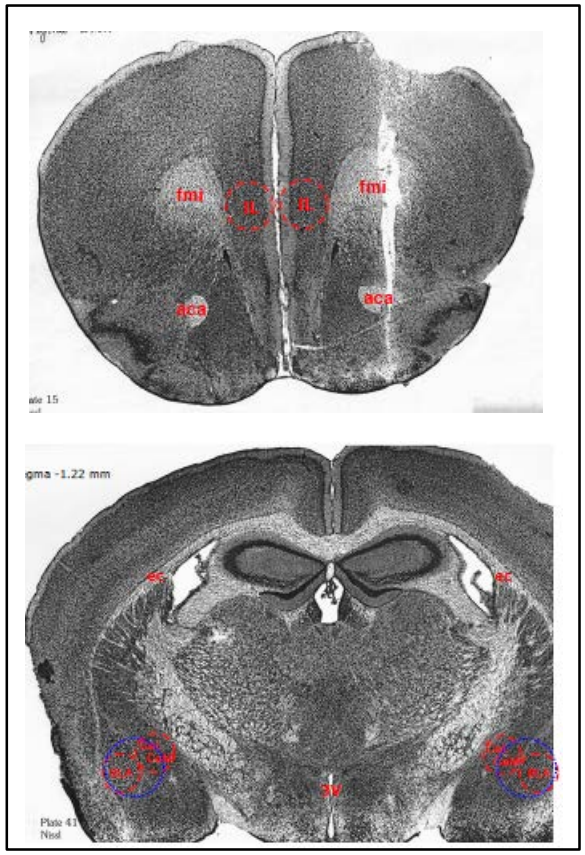
Days 1-15



10 min/day

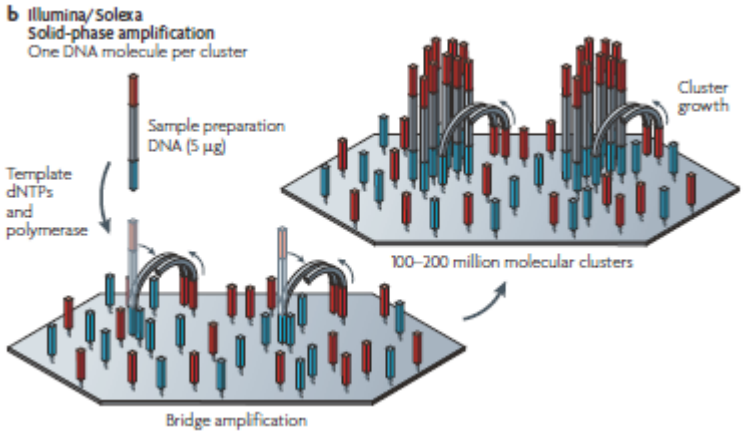


Brain ROI microdissection



Transcriptome RNA:
Amygdala
ventral Hippocampus
medial Prefrontal Cortex

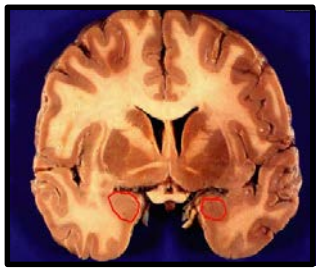
Next Generation Sequencing:
Gene expression data



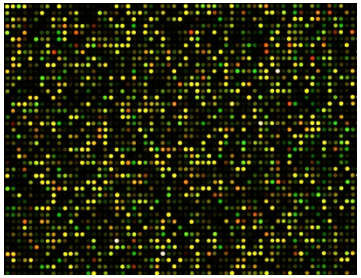
Mouse models for the study of stress effects on amygdala gene expression

Mouse

Human

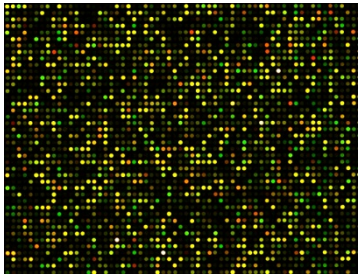


CUMS vs Control

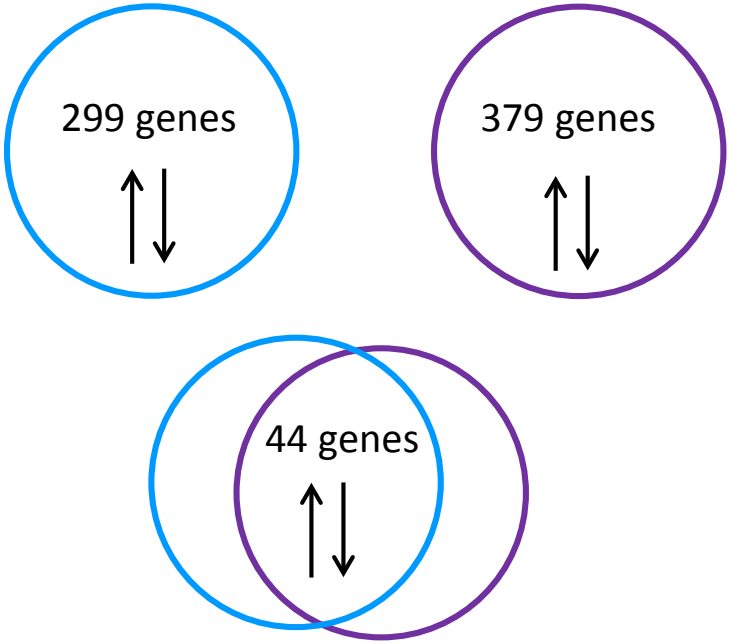


25’000 genes

Depression vs Control



20’000 genes



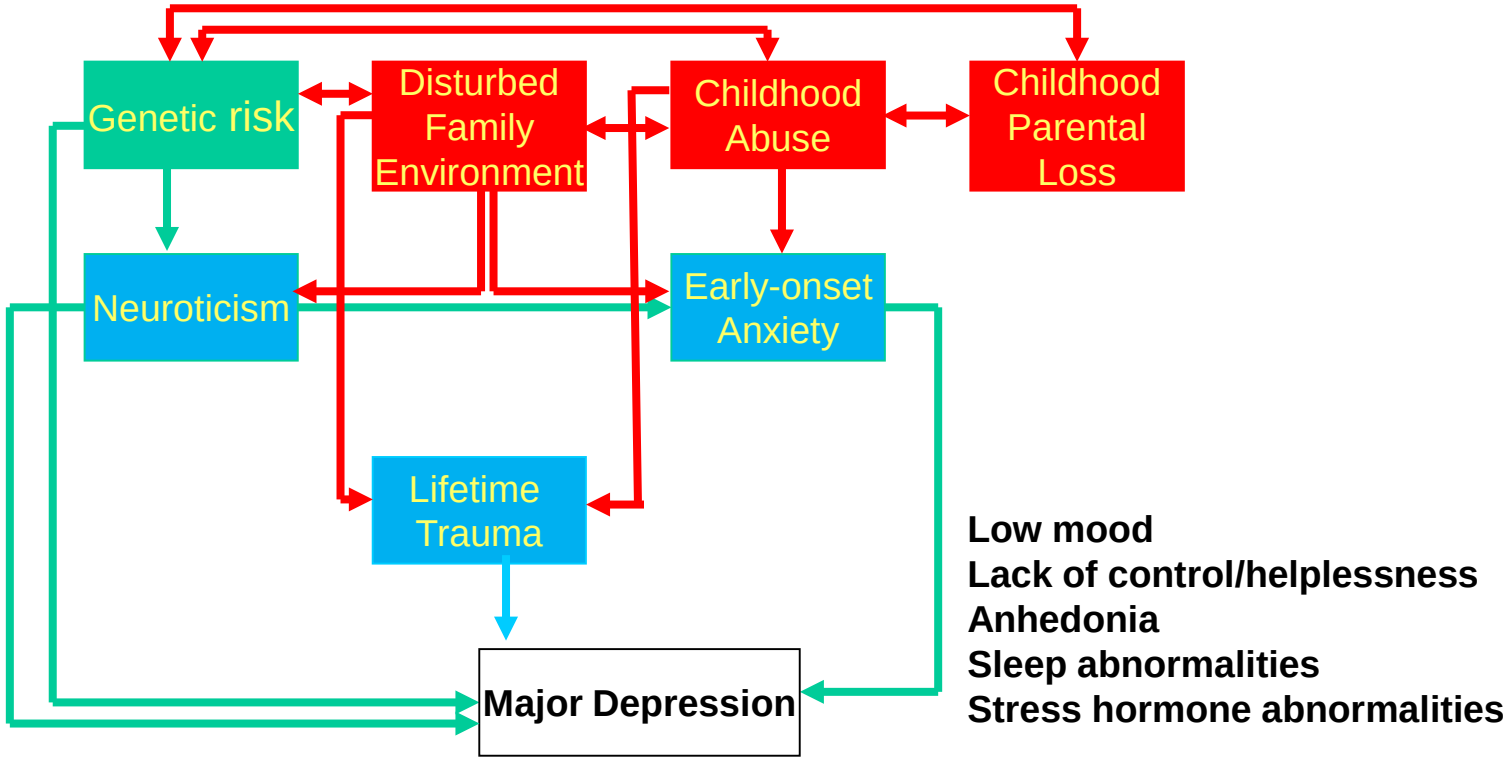
Gene Title	Gene Symbol	Entrez Gene	Human MDD: All MDD Subjects (alr)	Human MDD: MDD_{UCMS} Subjects (alr)	Human MDD: UCMS Effect (alr)
Calcium channel, voltage-dependent, beta 2 subunit[b]	CACNB2	783	0.02	0.49	0.37
Calcium/calmodulin-dependent protein kinase II delta	CAMK2D	817	0.08	1.07	0.54
Ankyrin repeat domain 43	ANKRD43	134548	0.06	0.28	0.44
Rho GTPase activating protein 6	ARHGAP6	395	0.42	0.75	0.45
Cadherin 13, H-cadherin (heart)	CDH13	1012	0.18	0.42	0.45
Diacylglycerol kinase, gamma 90kDa	DGKG	1608	0.34	0.44	0.46
Early growth response 1	EGR1	1958	−0.29	−0.30	−0.29
Neuronal pentraxin I	NPTX1	4884	0.10	0.35	0.35
V-jun sarcoma virus 17 oncogene homolog[b]	JUN	3725	0.19	0.66	0.39
Protein phosphatase 1, regulatory (inhibitor) subunit 16A	PPP1R16A	84988	−0.01	−0.23	−0.27
Transmembrane protein 17	TMEM17	200728	0.09	0.26	0.37
Rabphilin 3A homolog	RPH3A	22895	−0.36	−0.47	−0.33
Matrilin 2	MATN2	4147	0.33	0.64	0.80
Zinc finger protein 703	ZNF703	80139	−0.09	−0.24	−0.33
Chromosome 5 open reading frame 22	C5orf22	55322	0.02	0.60	0.34
Potassium channel tetramerisation domain containing 12[b]	KCTD12	115207	0.17	0.34	0.31
P18SRP protein[b]	P18SRP	285672	0.05	0.45	0.27
Carbohydrate (chondroitin) synthase 1	CHSY1	22856	0.02	0.30	0.30
Nuclear factor I/B	NFIB	4781	0.08	0.41	0.50
Integral membrane protein 2A[b]	ITM2A	9452	−0.15	−0.41	−0.35
Chromosome 5 open reading frame 13	C5orf13	9315	−0.16	−0.45	−0.46
Zinc finger protein, multitype 1	ZFPM1	161882	0.0	−0.25	−0.58
Copine family member IX	CPNE9	151835	−0.29	−0.65	−0.70
Myelin basic protein[b]	MBP	4155	−0.22	−0.41	−0.51
Aspartylglucosaminidase	AGA	175	−0.26	−0.19	−0.38
2',3'-cyclic nucleotide 3' phosphodiesterase[b]	CNP	1267	−0.12	−0.37	−0.56
Breast carcinoma amplified sequence 1	BCAS1	8537	0.02	−0.41	−0.65
Ectonucleotide pyrophosphatase/phosphodiesterase 2[b]	ENPP2	5168	−0.12	−0.29	−0.50
Plasma membrane proteolipid (plasmolipin)	PLLP	51090	−0.16	−0.40	−0.56
Endothelial differentiation, lysophosphatidic acid GPCR 2[b]	EDG2	1902	−0.10	−0.40	−0.85
G protein-coupled receptor 37	GPR37	2861	−0.31	−0.52	−0.50
Myelin-associated oligodendrocyte basic protein	MOBP	4336	−0.11	−0.51	−0.88

Gene expression up-regulated in depression/stress

Gene expression down-regulated in depression/stress

Sibille et al. (2009) Am J Psychiatry 166: 1011

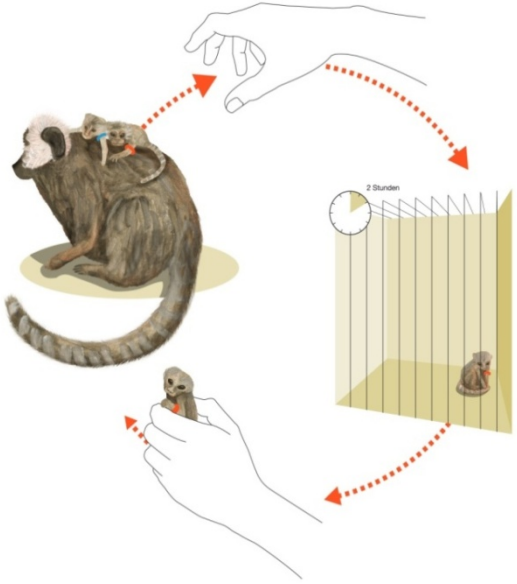
Early-life stress as an aetiological factor in depression

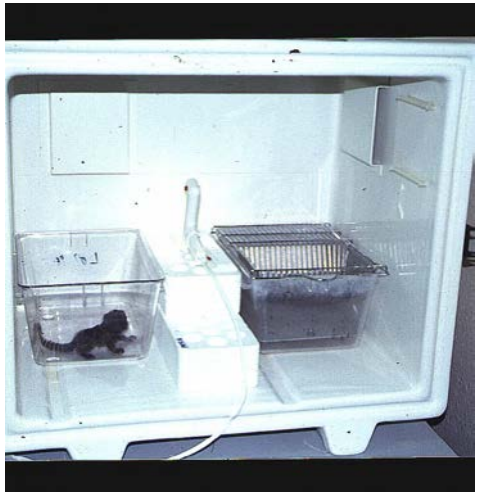


Kendler et al. (2002) Am J Psychiatry 159: 1133

Examples of manipulations of the early-life environment

Rat and marmoset early deprivation

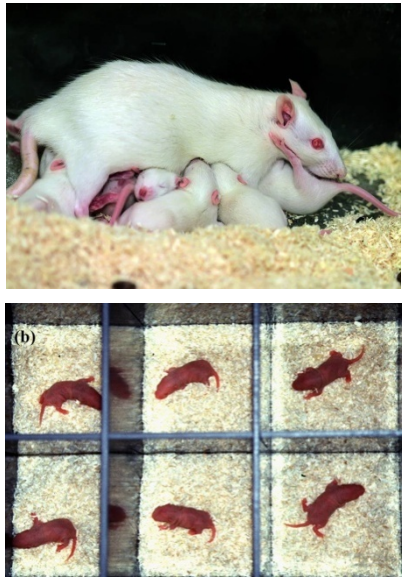


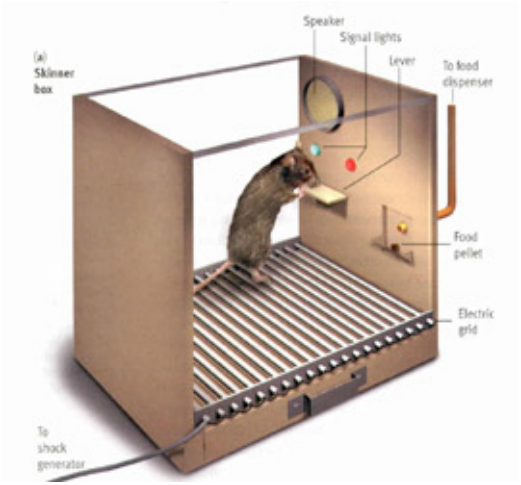


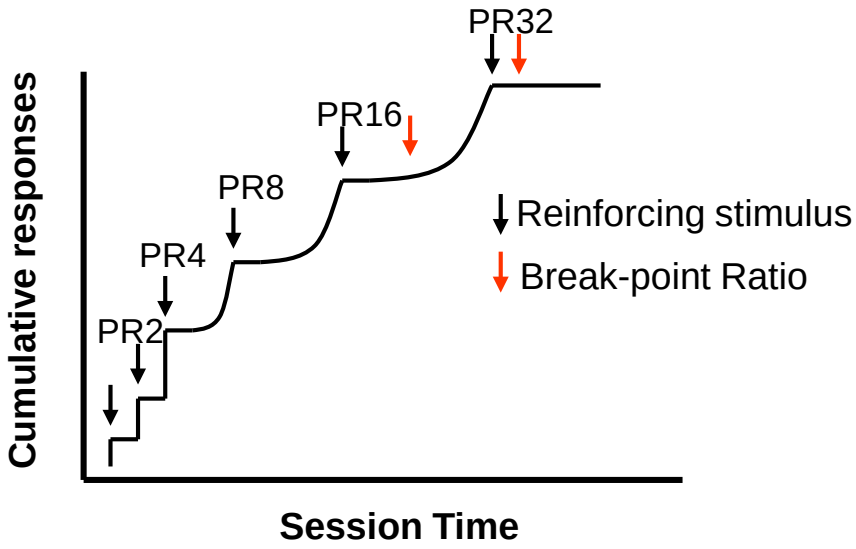
Pryce et al (2005) Neurosci Biobehav Rev 29: 649

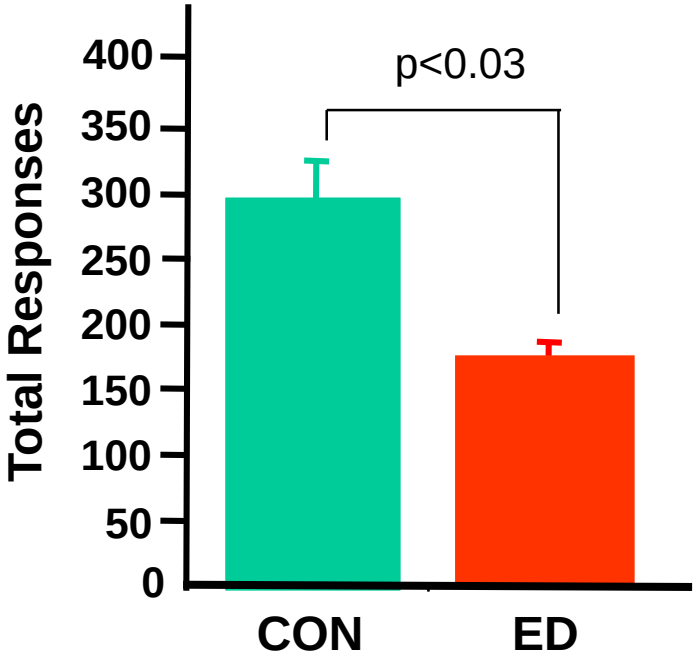
Krishnan & Nestler (2008) Nature 455: 894

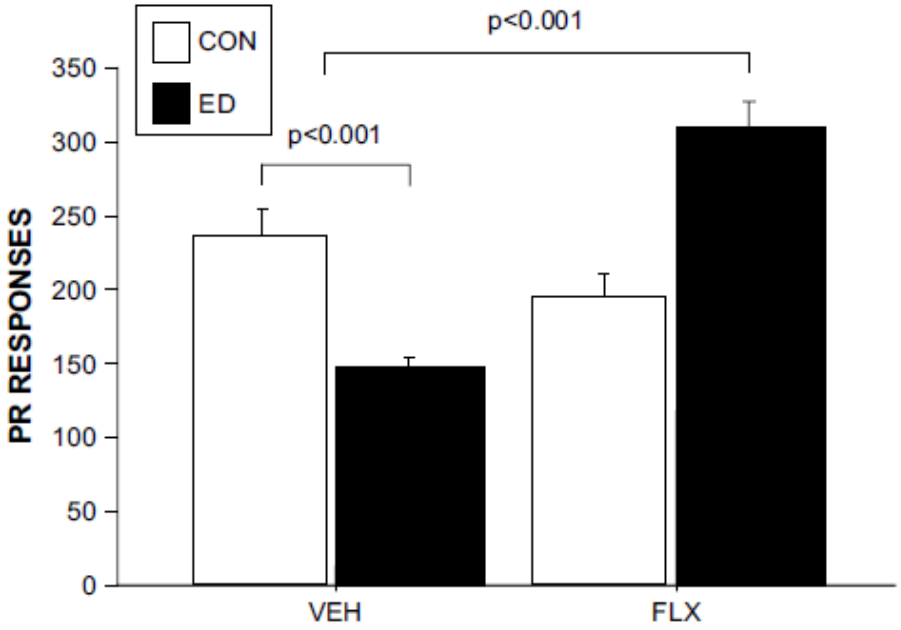
Long-term effects of early deprivation on reward wanting: progressive ratio reinforcement







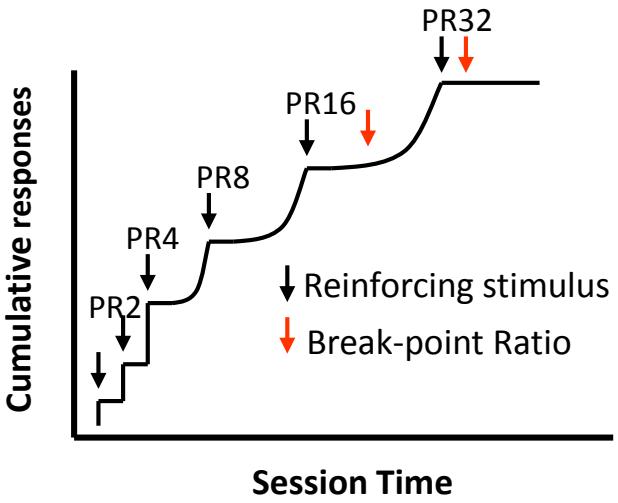




Rüedi-Bettschen et al. (2005) Behav Brain Res 156: 297

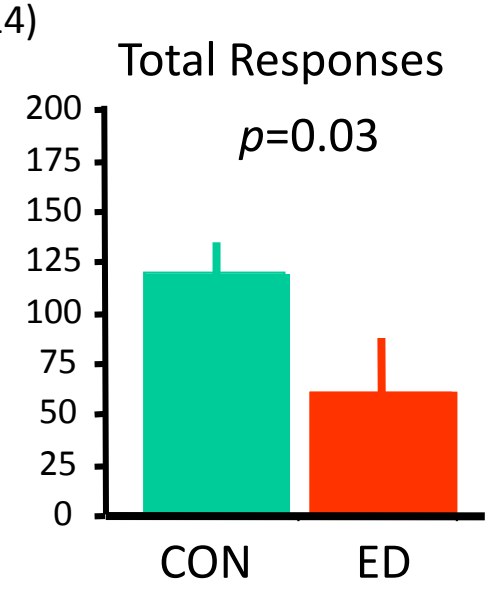
Leventopoulos et al. (2009) Neuropharmacol 56: 692

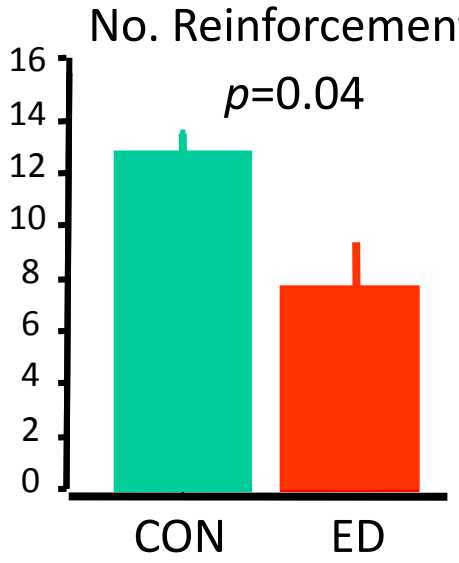
Effects of ED on Reward motivation: progressive ratio reinforcement task



- Rewarded with banana milkshake, no food/water deprivation
- Number of screen touches to obtain 0.1ml reward:
  1,2,3,4,5,6,7,8,10,12,14,16,18,20,22,24,28,32,36,40

CON (N= 14)
ED (N= 14)





„Free" reward (mL)	
CON	11.1 ± 1.6
ED	14.9 ± 2.8
	p>0.9
Body Weight (g)	
CON	346 ± 9
ED	331 ± 10
	p>0.17

Pryce et al. (2004) Biol Psychiatry 56: 72

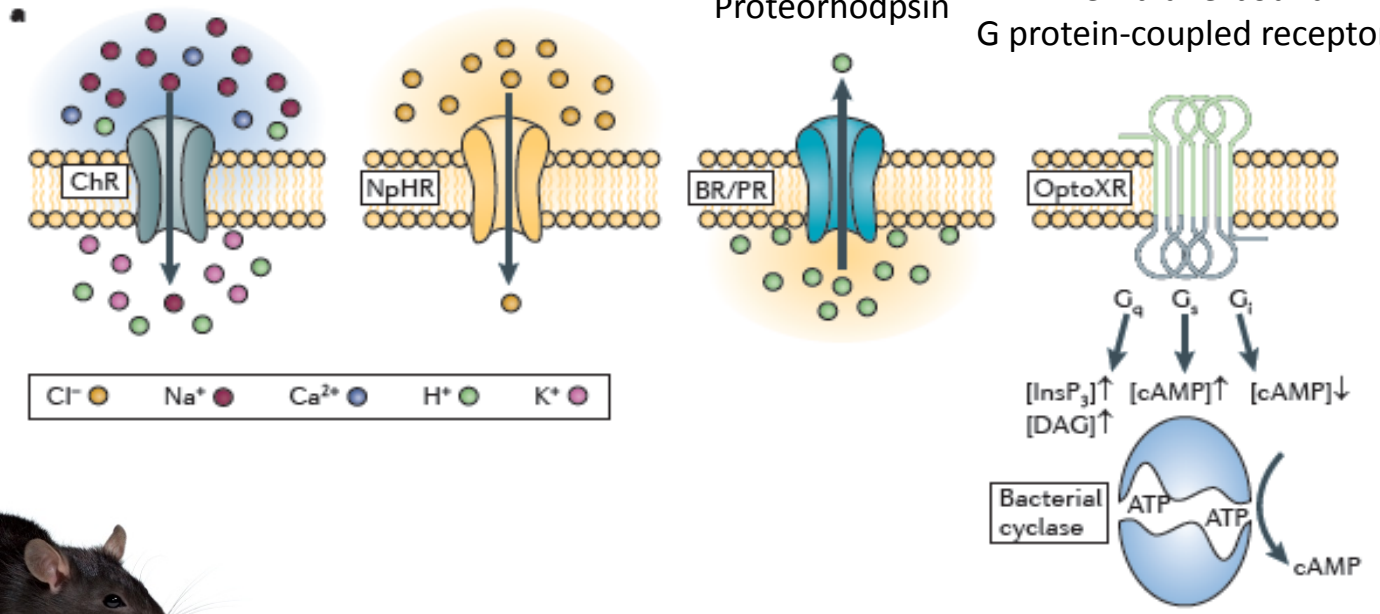
Optogenetic approach to investigation of neural circuits in animal models

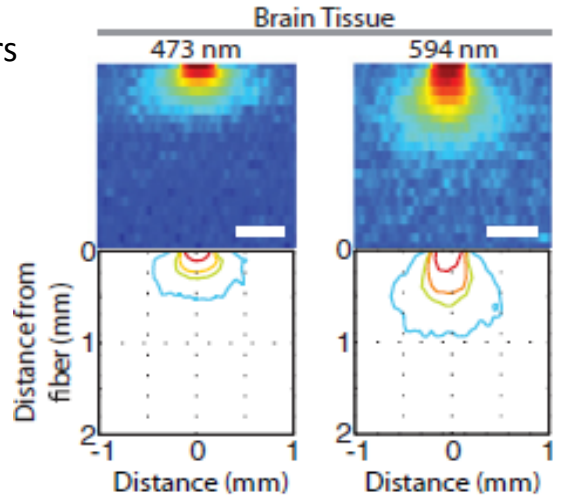
Channelrhodopsin

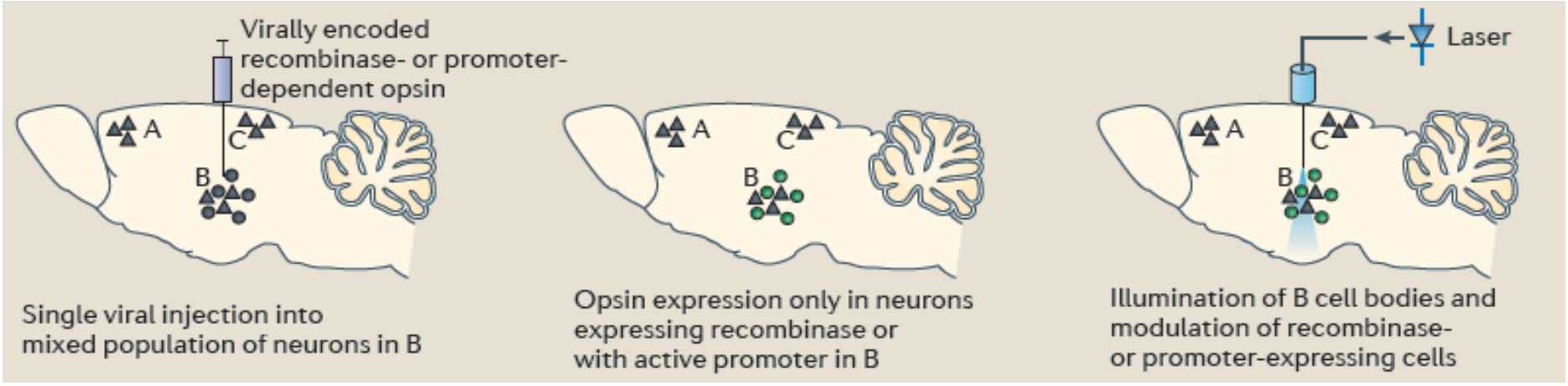
Halorhodopsin

Bacteriorhodopsin/
Proteorhodpsin

Light-activated
membrane-bound
G protein-coupled receptors





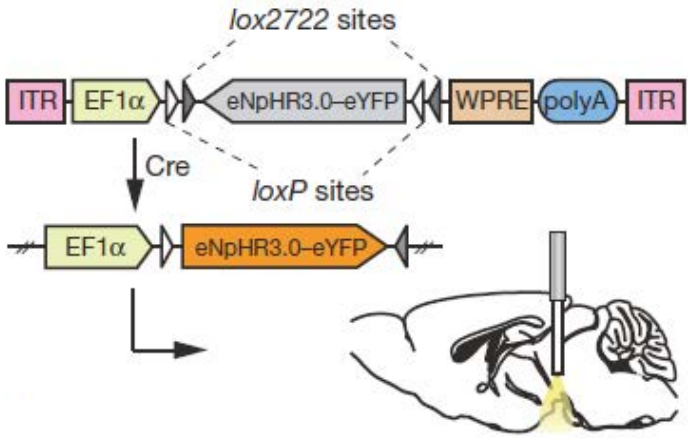


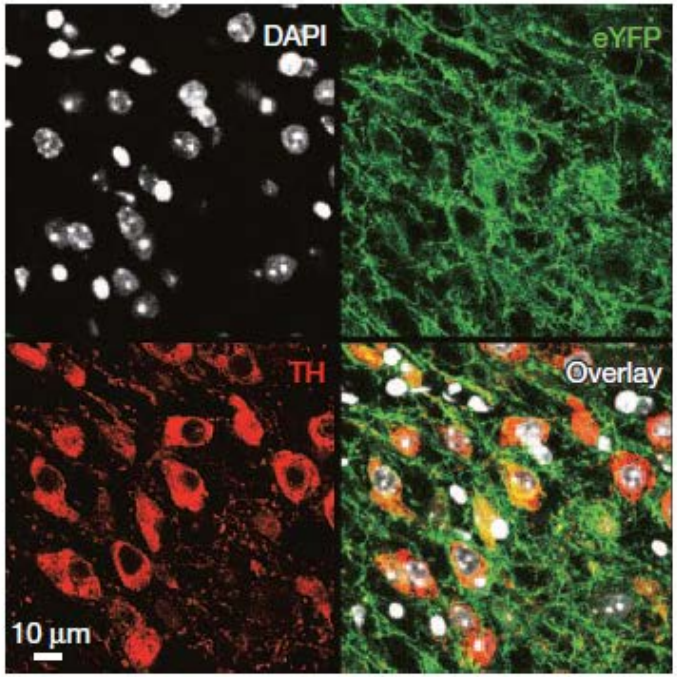
Tye & Deisseroth (2012) Nature Rev Neurosci 13: 251-266

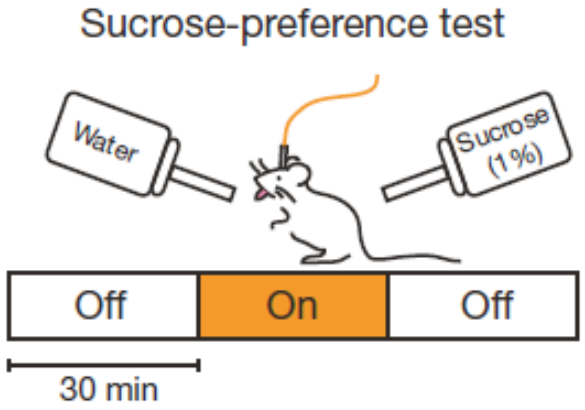
Selective inhibition of VTA dopamine neurons induces loss of sucrose preference in mouse

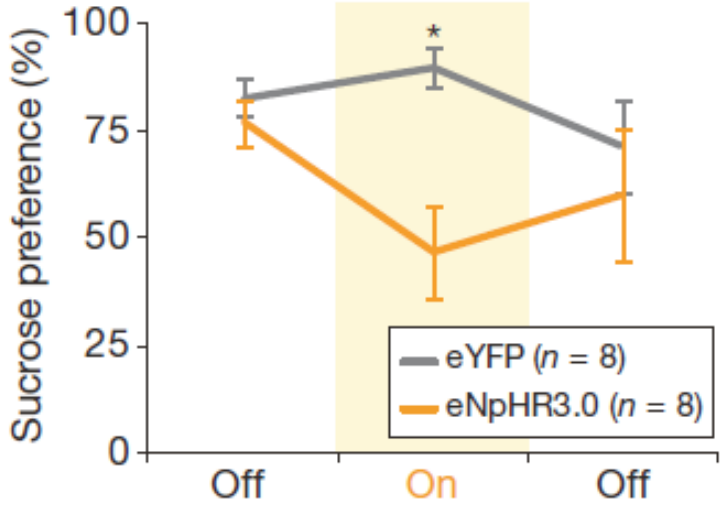
AAV Vector:
Halorhodopsin
loxP

Tyrosine hyroxylase::
Cre mice





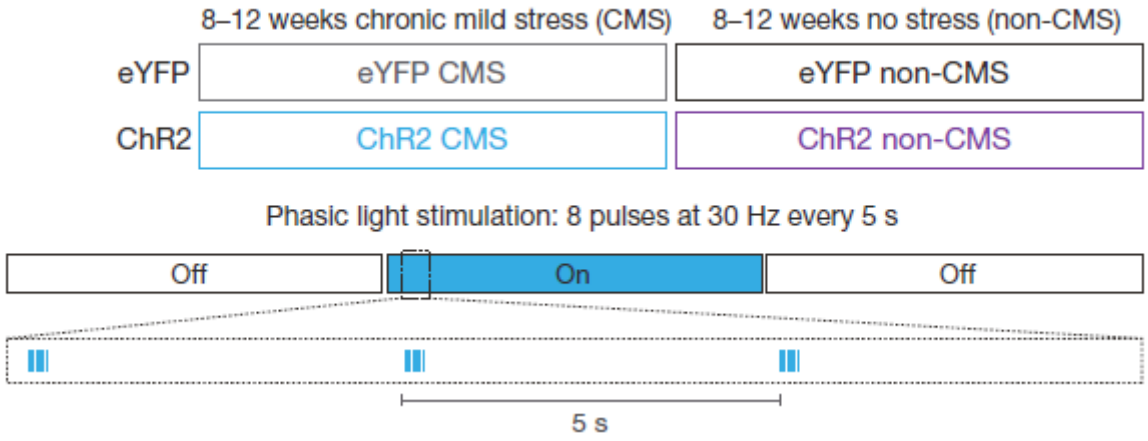


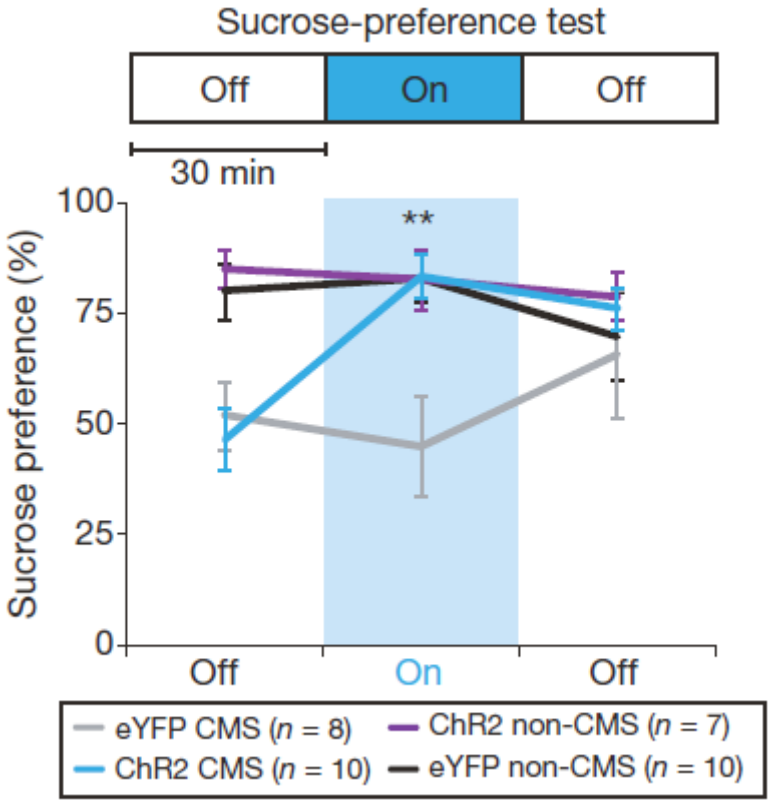


Tye et al. (2012) Nature 493: 537

Reversal of chronic-stress loss of sucrose preference by photoactivation of VTA dopamine neurons

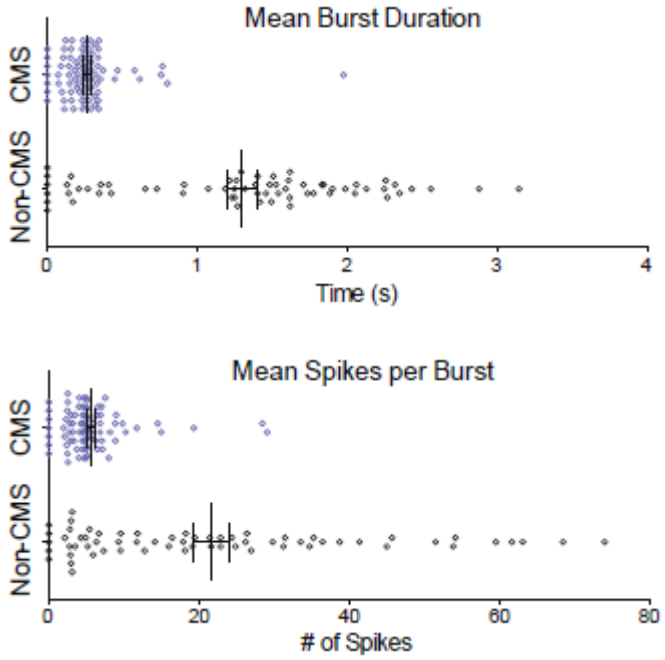
Phasic light stimulation of channelrhodopsin-2-expressing VTA dopamine neurons





Electrophysiological recording of VTA neurons

CMS leads to reduced cell firing in bursts



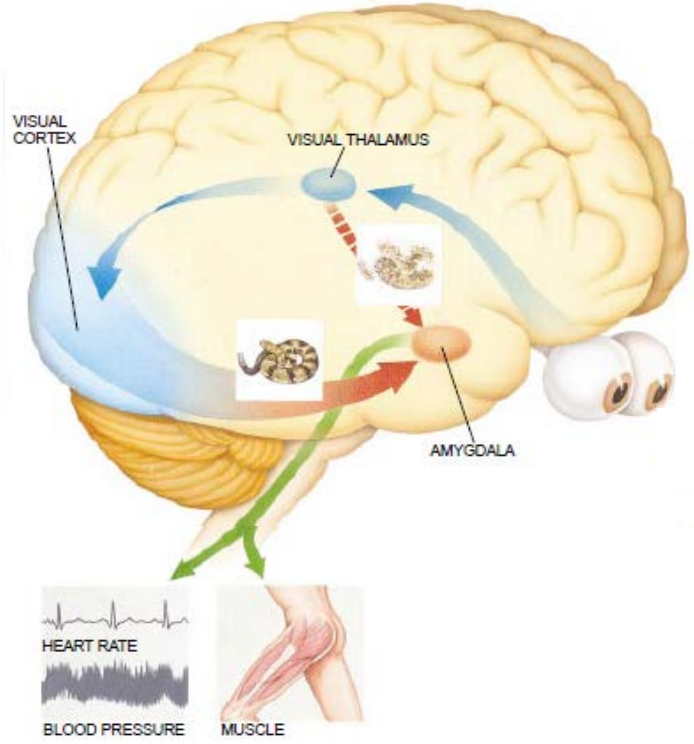
Tye et al. (2012) Nature 493: 537

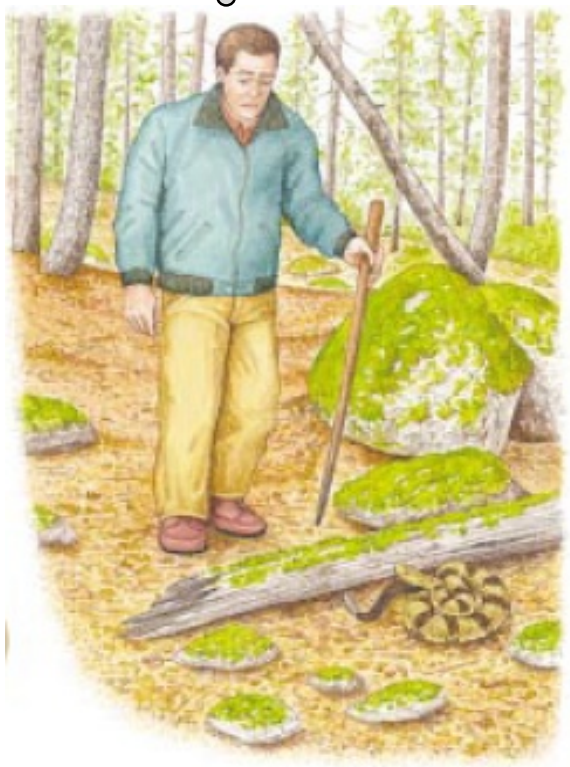
Human-unique features of emotions

- Due to cognitive-CNS evolution, emotional feelings are probably uniquely human -

"I feel afraid" = "I am afraid"

Self-consciousness
Language

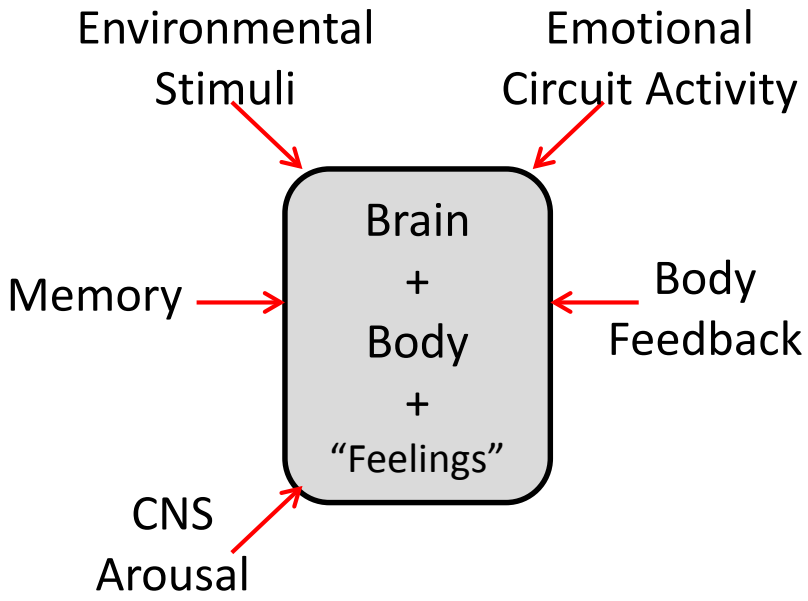


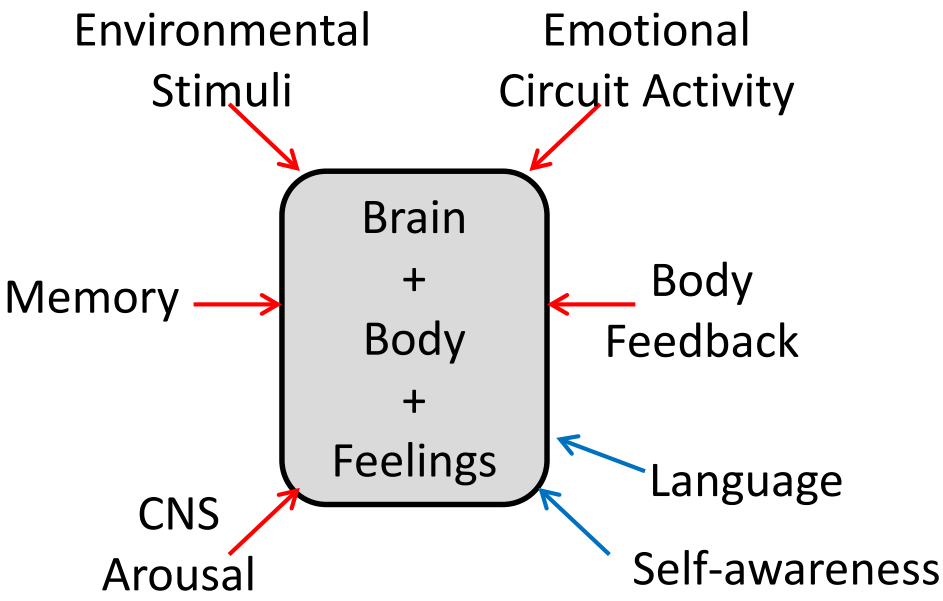


?

Summary of Universal and Human-unique features of emotions

- Much is universal, and what is universal is essential to that which is human -





Animal models relevant to psychiatric disorders

• Effects of environmental stress on behaviour and neurobiology are the most-studied animal model

• Combining CUMS with sucrose preference test/ICSS of VTA provides a model with aetiological and face validity for reduced interest/motivation. Associated neurobiology suggests importance of VTA-dopamine

• Combining CUMS with forced swim test provides a model with possible aetiological and face validity for helplessness.

• In addition to dopamine changes, CUMS causes decreased synaptic plasticity in Hippocampus and PFC

• Combining CSD with Fear conditioning or 2-way Avoid-Escape test provides a model with aetiological and face validity for Generalised helplessness. Associated neurobiology suggests importance of Amygdala Oligodendrocyte-Myelin function

• Combining early life stress with Test of reward wanting on a progressive ratio schedule provides a model with aetiological and face validity for reduced interest/motivation

• Optogenetics allows for the study of the importance of specific types of neurons in valid animal models of depression

• Animal models of disrupted emotional processing are valid in terms of subconscious/impersonal processes