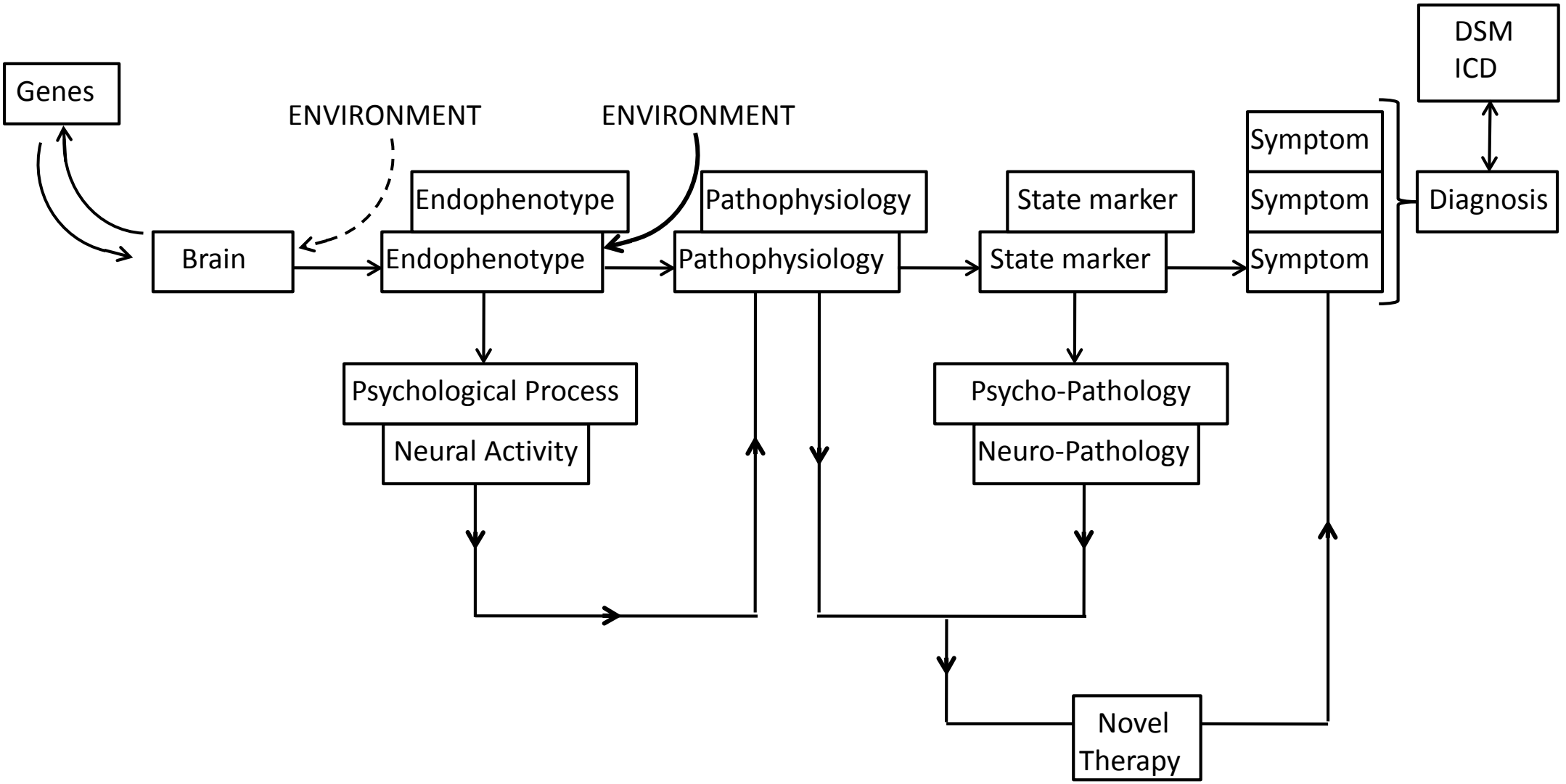
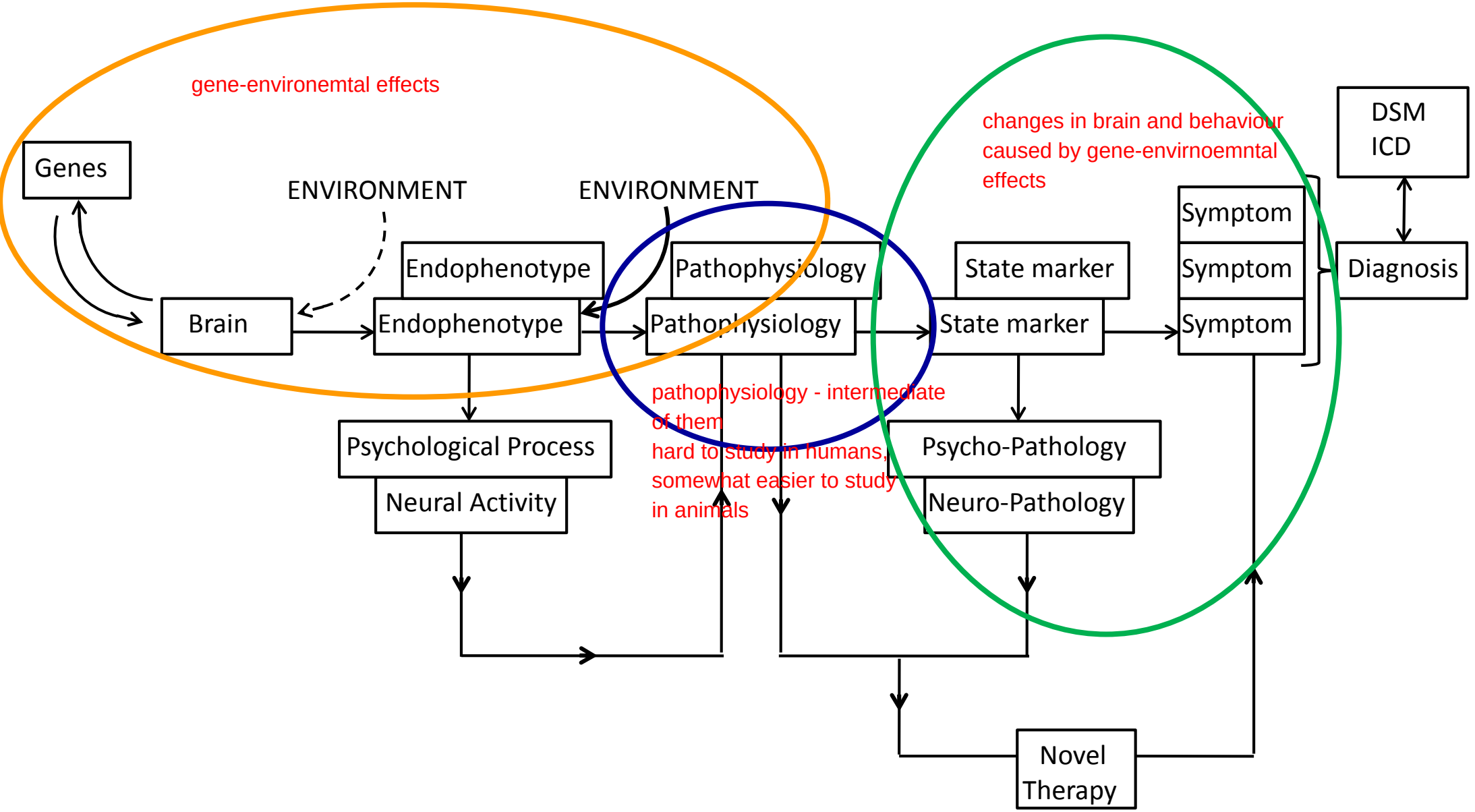
Animal models of human affective disorders: Manipulations and Readouts

- Aetiology, Pathophysiology, Psychopathology
- Gene x environment causation (aetiology)
- Animal model validity: Aetiological, Construct, Face
- Genetic aetiology (G)
- Environmental aetiology (E)
- Examples of valid animal models of G, E and GxE aetiology
- Face validity
- Behavioural readout tests

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



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



Dividing a complex disorder into translational components: e.g. Depression

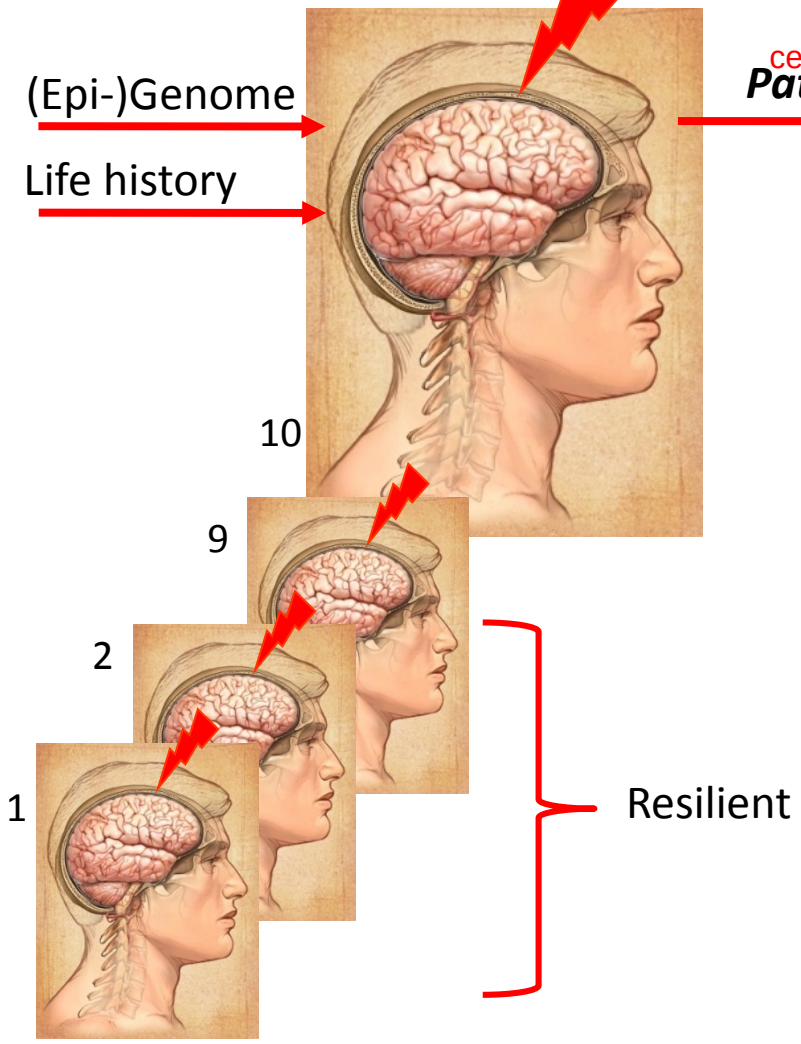
causation/causal factors

Aetiology

Uncontrollable Stressor(s)

(Epi-)Genome

Life history



Resilient

cellular level

Pathophysiology (Neurons, Glia, Signaling) normally studied post mortem

Neuropathology (Circuit(s))

Psychopathology (Diverse)

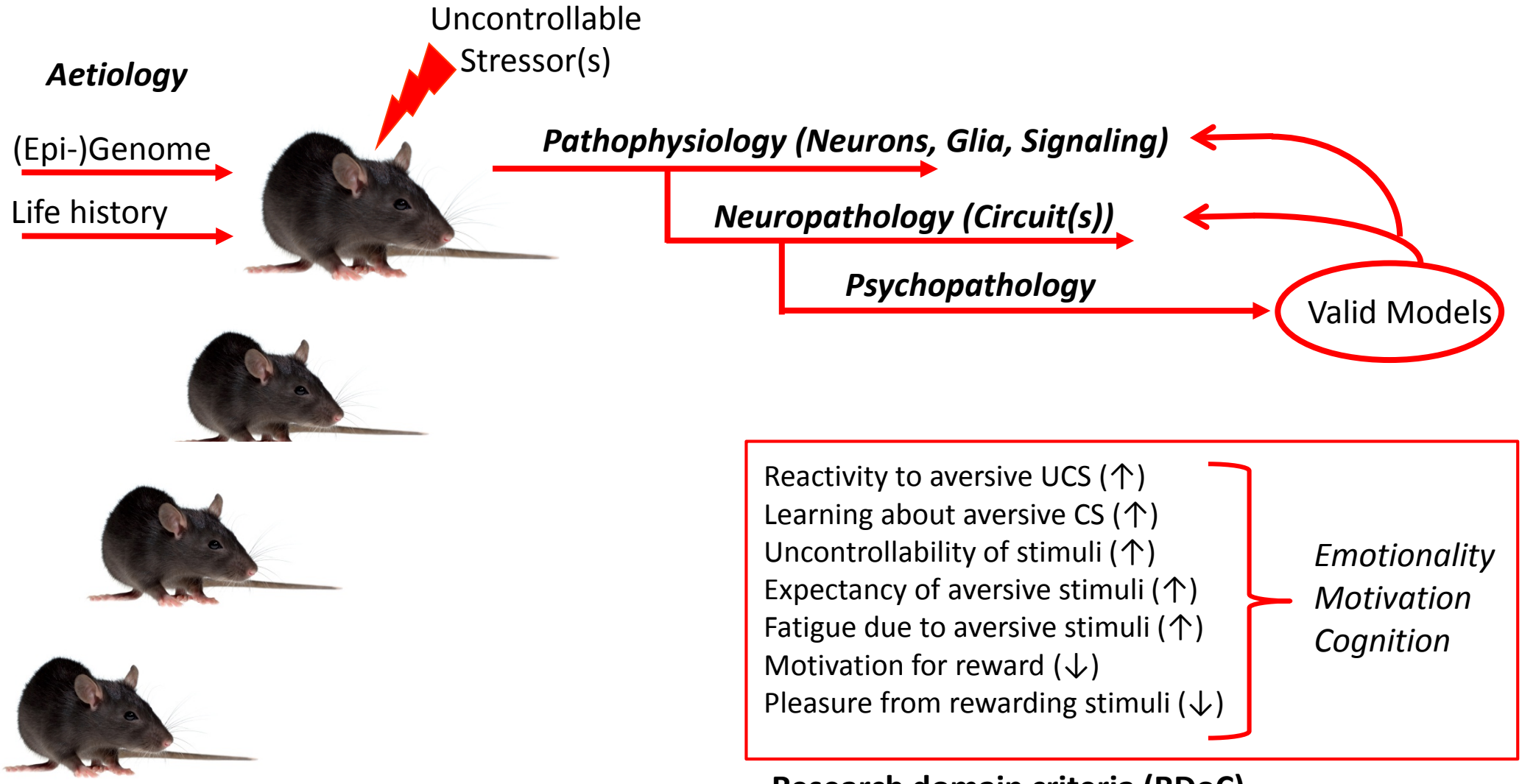
Diagnosis

Reactivity to aversive UCS (↑)
Learning about aversive CS (↑)
Uncontrollability of stimuli (↑)
Expectancy of aversive stimuli (↑)
Fatigue due to aversive stimuli (↑)
Motivation for reward (↓)
Pleasure from rewarding stimuli (↓)

Emotionality
Motivation
Cognition

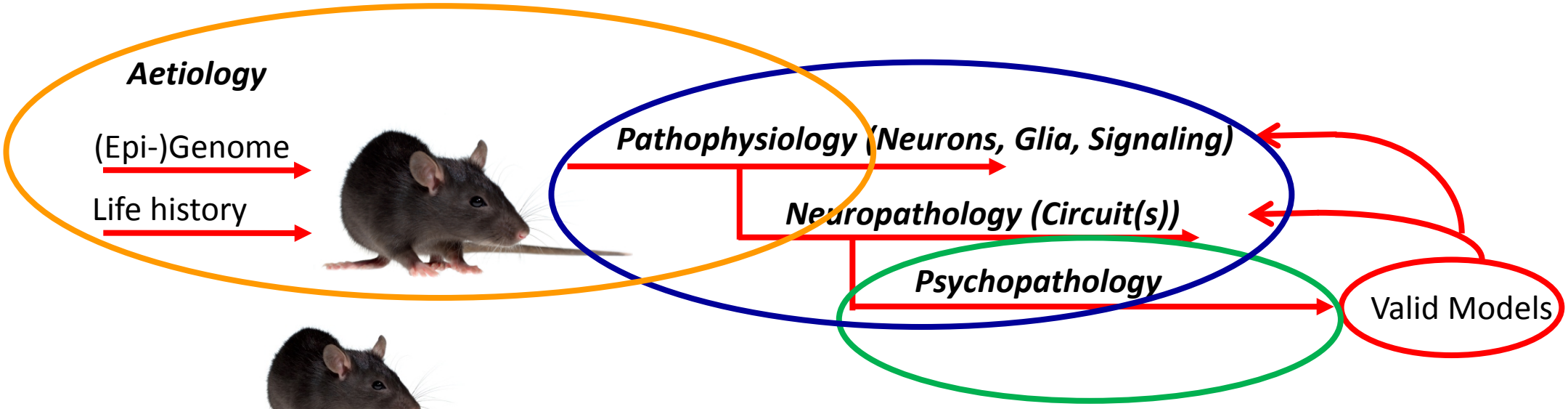
Research domain criteria (RDoC)

Studying translational components in Animal models e.g. Depression



Research domain criteria (RDoC)

Animal models must have validity



Aetiological validity

are the changes that we cause to animal in terms of genetics and life history valid to the human situation (or are they irrelevant and therefore useless for human patients)

Construct validity

cellular/circuit changes in animal need to have relevance to the human patients. so changes of mouse brain need to have similarity to human disorder - but we know little about the human case

it's hard to have construct validity in animal models, so we cant be strict there, since we dont know what it is in humans and what should be similar

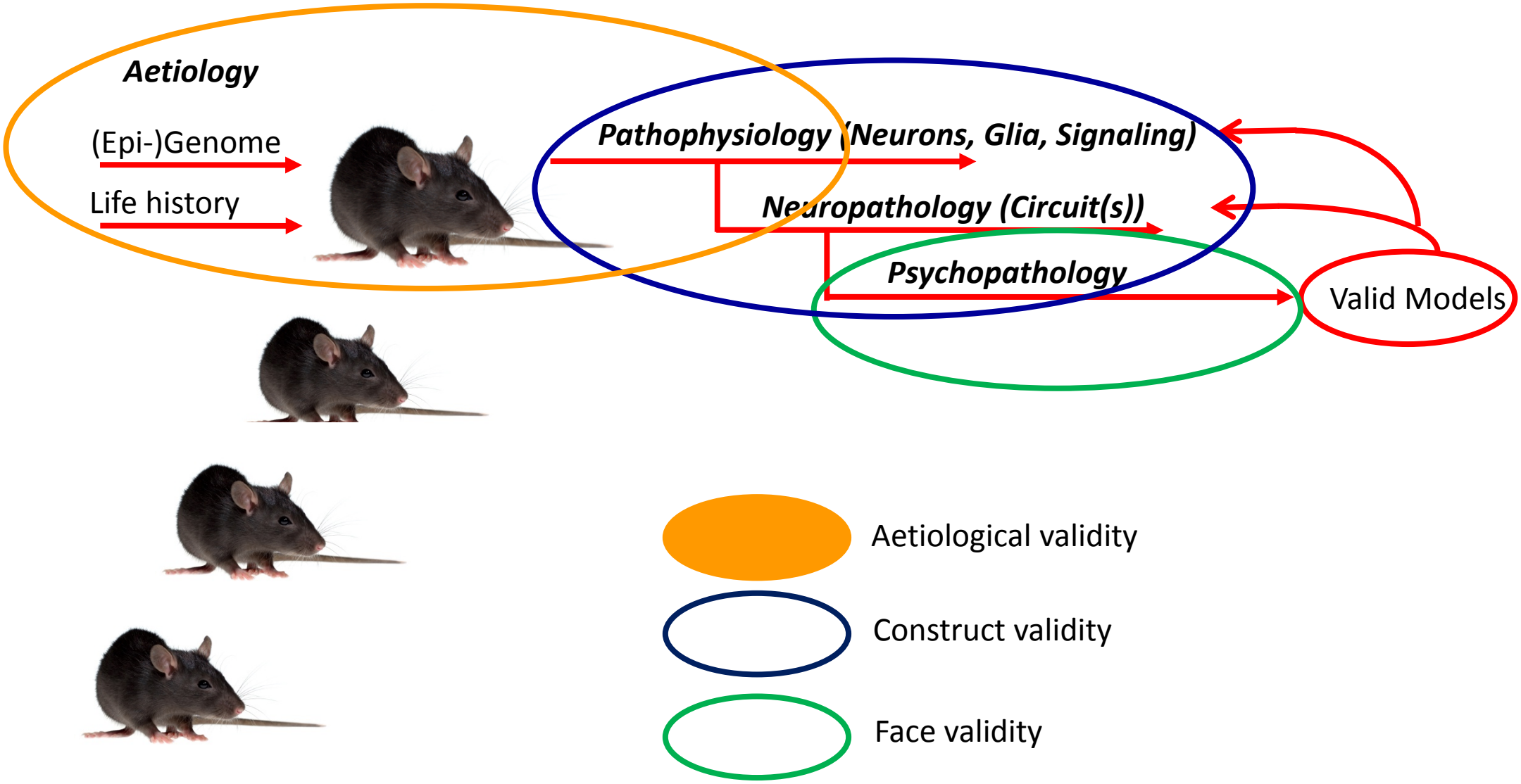
Face validity

changes in behaviour of animal: how similar are they to the psychopathology of human patients. it can basically be observed by mere eye

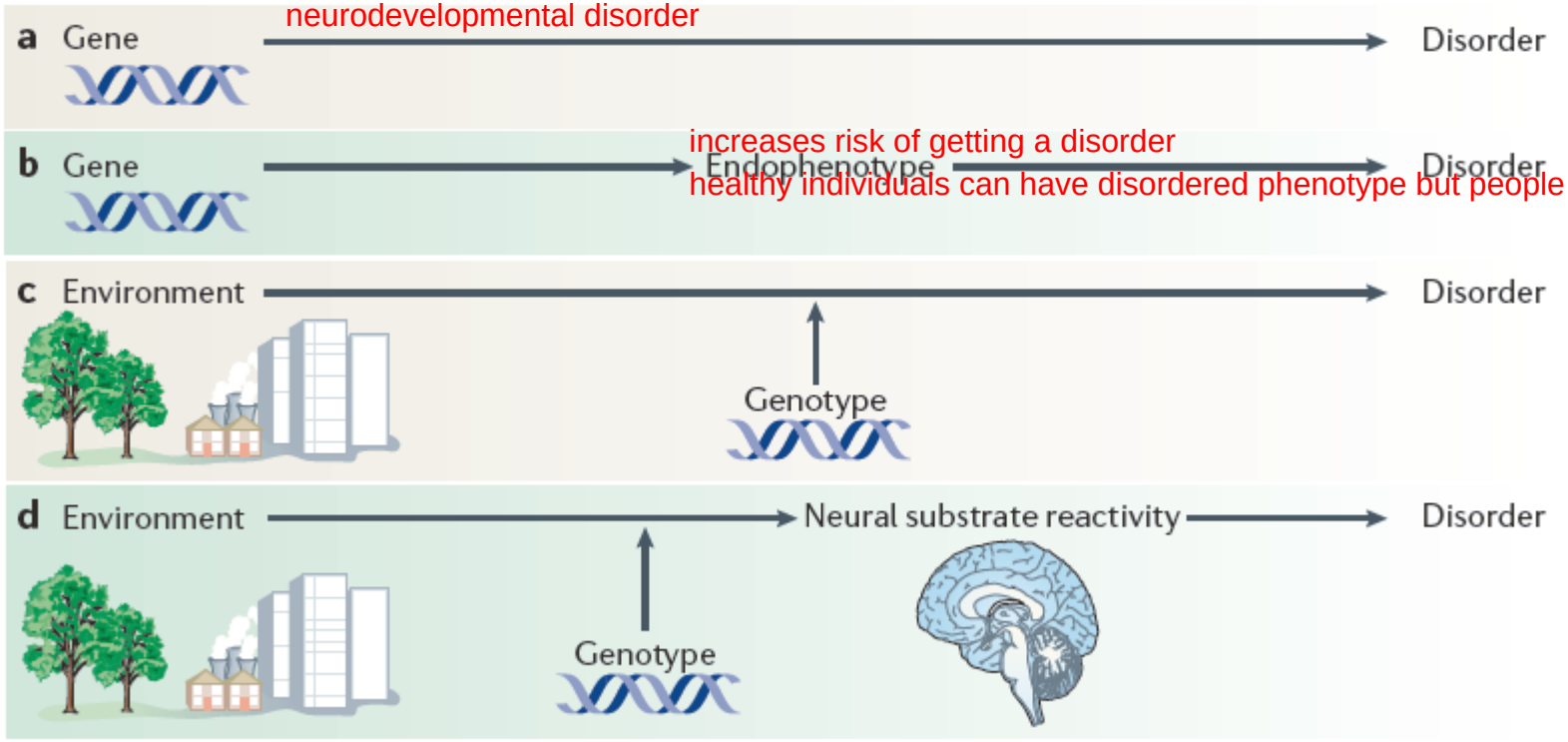
we only want to understand
some of human psychopathology.
we assume it's already unrealistic to produce
a depressed mouse etc.

skipped

Animal models must have validity: Aetiological validity



Approaches to studying Genes and Environments important in depression



Caspi & Moffitt(2006) Nature Reviews Neurosci 7: 5830

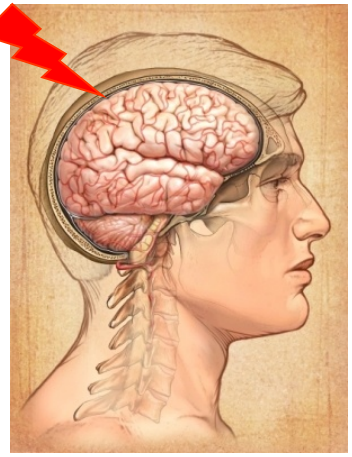
seritonin transp gene prom region

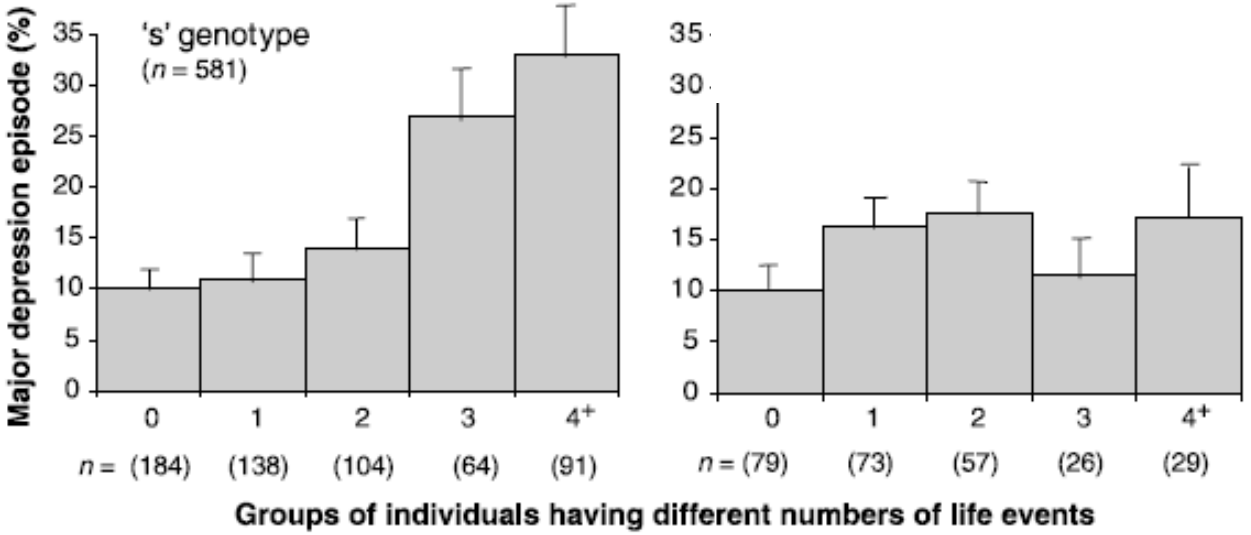
5-HTTLPR polymorphism interacts with stressful life events to increase prevalence of depression

Aetiology

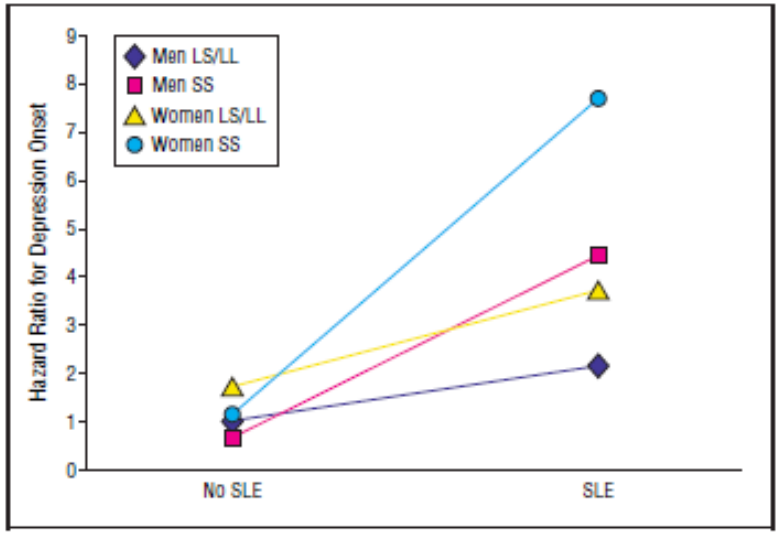
(Epi-)Genome

Life history





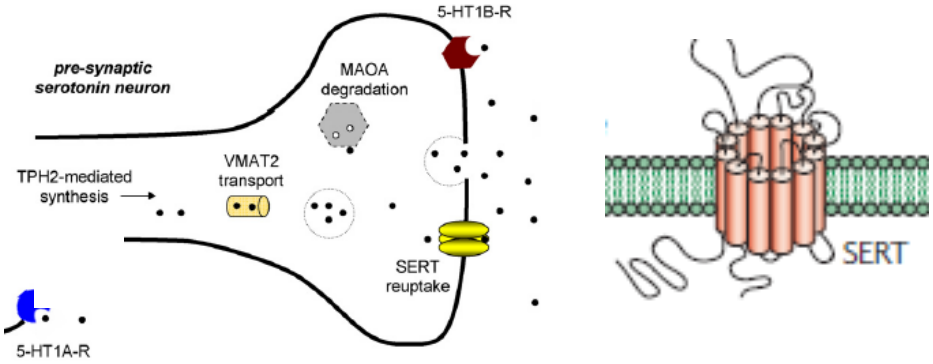
Caspi et al. (2003) Science 301: 386

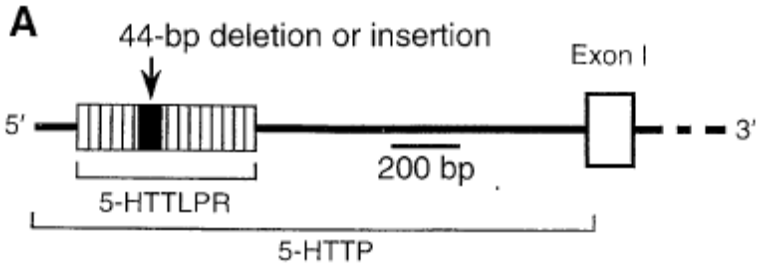


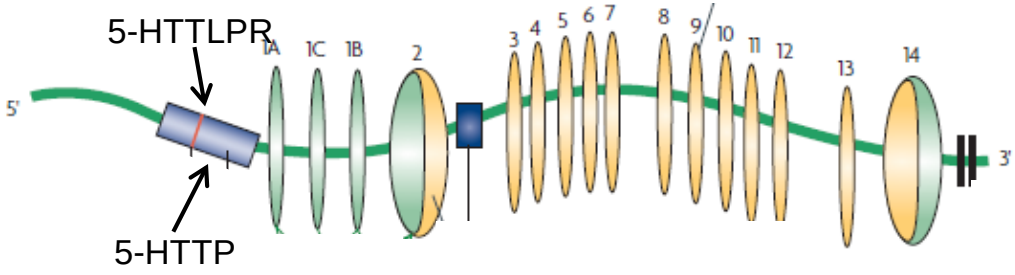
SLE = stressful life events

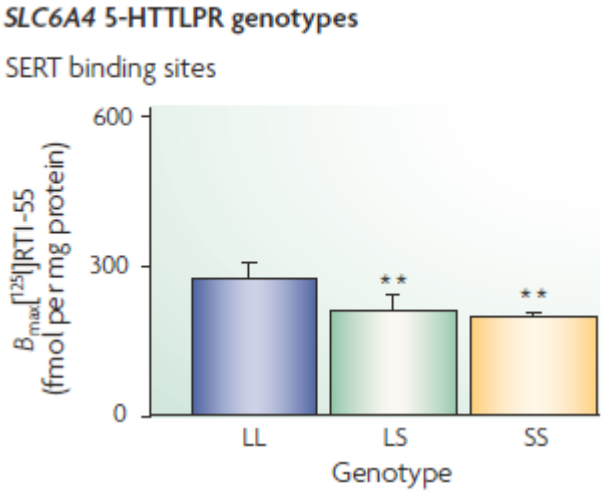
Kendler et al. (2005) Arch Gen Psych 62: 529

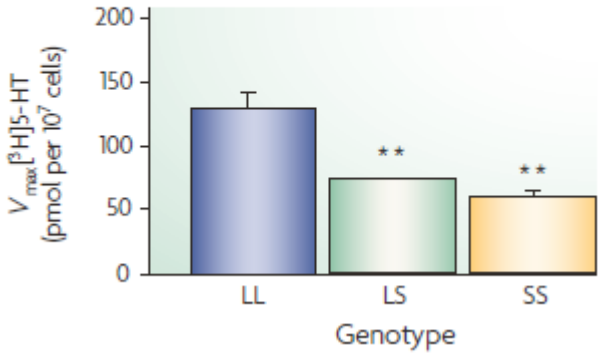
Serotonin transporter promoter (5-HTTP) gene-linked polymorphic region (5-HTTLPR):
modelling (s)hort and (l)ong genotypes in mouse using gene knockout

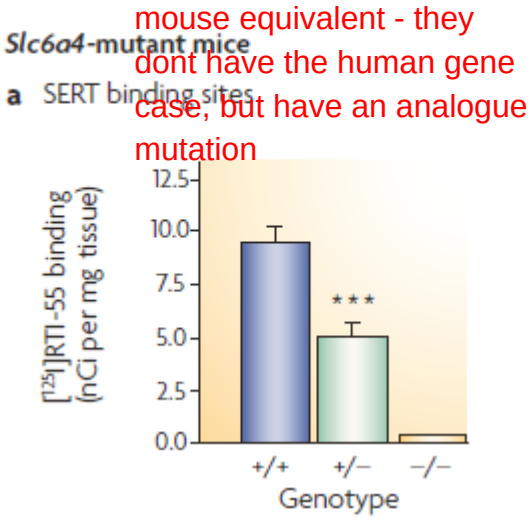




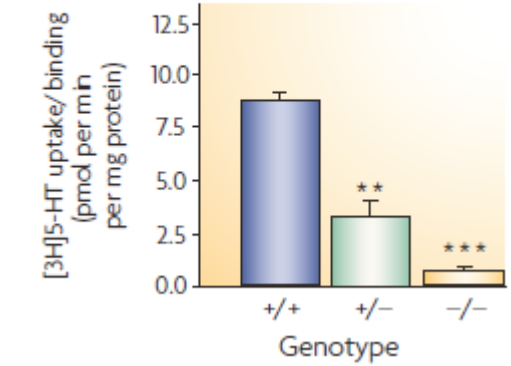








mouse equivalent - they dont have the human gene case, but have an analogue mutation

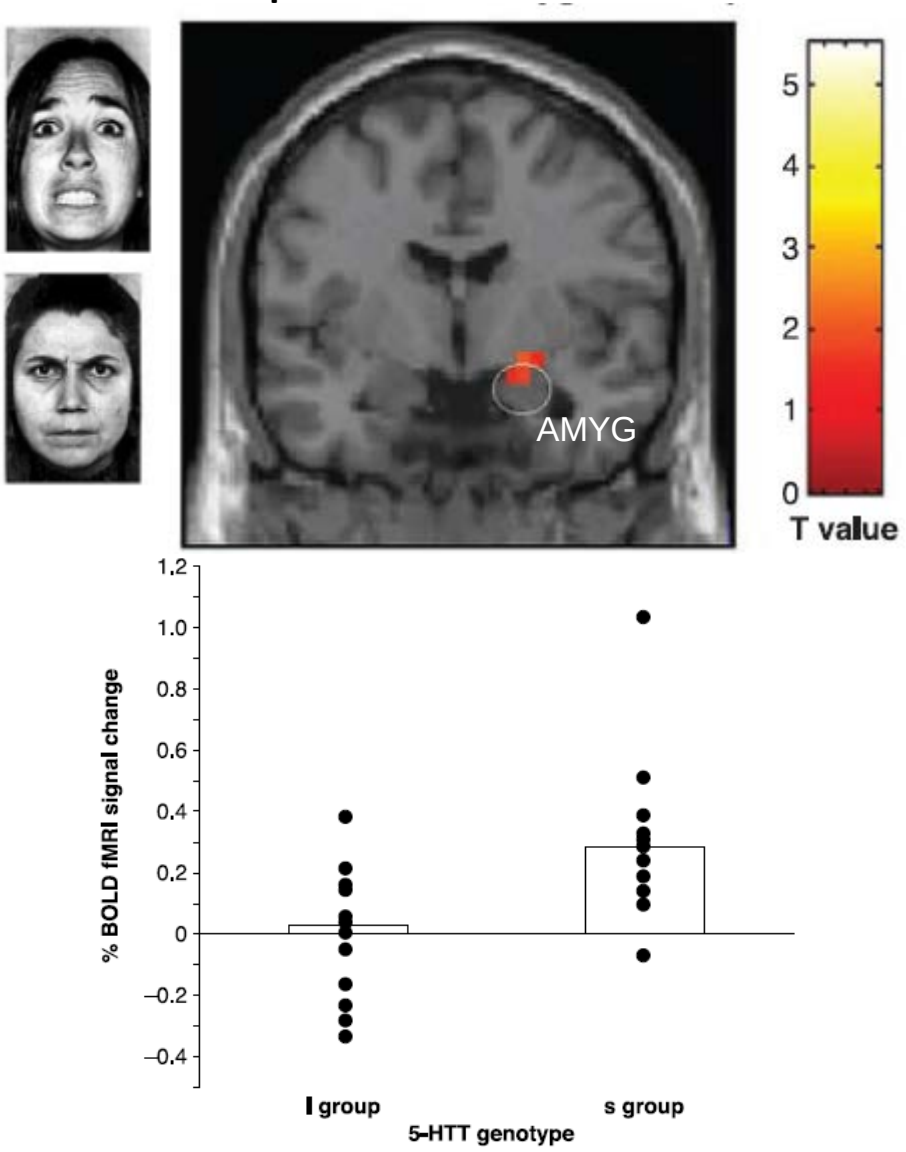


Murphy & Lesch (2008) Nature Rev Neurosci 9: 85

quick

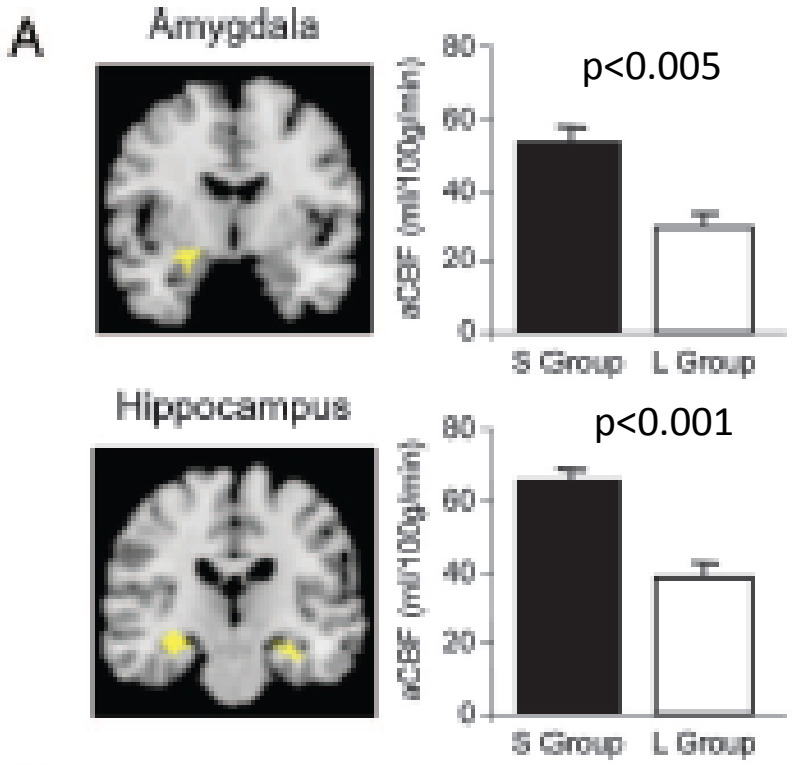
5-HTTLPR genotype and Brain Endophenotype for depression in healthy subjects

BOLD fMRI response to fearful face



Hariri et al. (2002) Science 297: 400

Absolute Cerebral Blood Flow at Rest



Canli et al (2006) PNAS 103: 16033

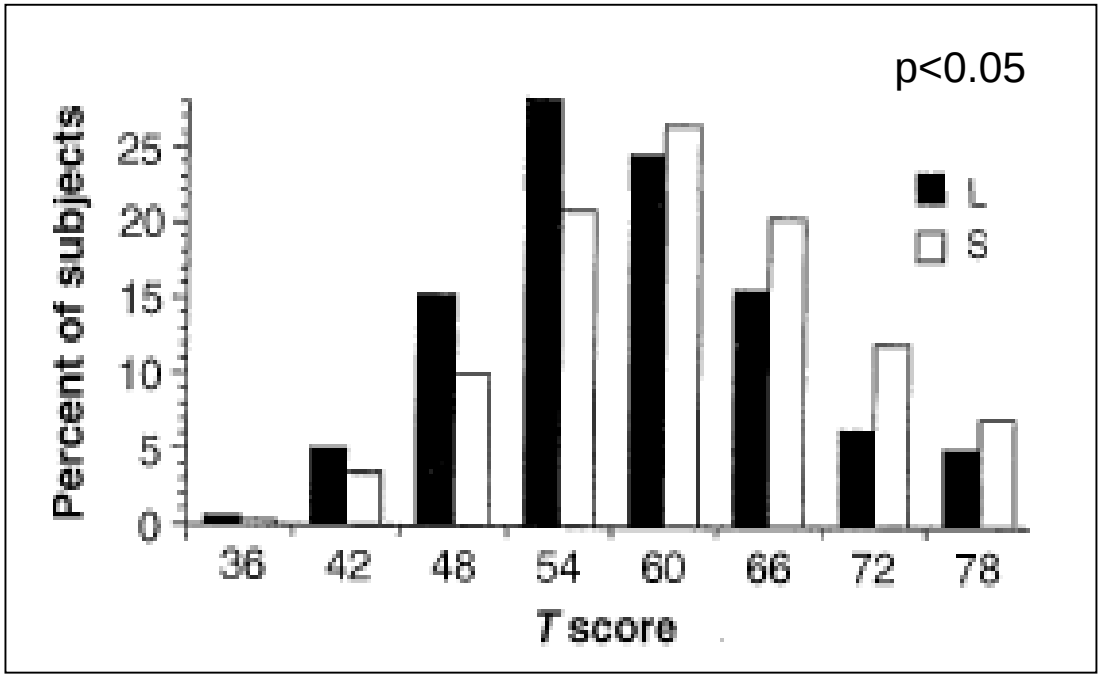
Evidence from human and mouse for fear endophenotype associated with low-activity 5-HTT genotype

measure personality in animals

the higher T score the higher neuroticiism

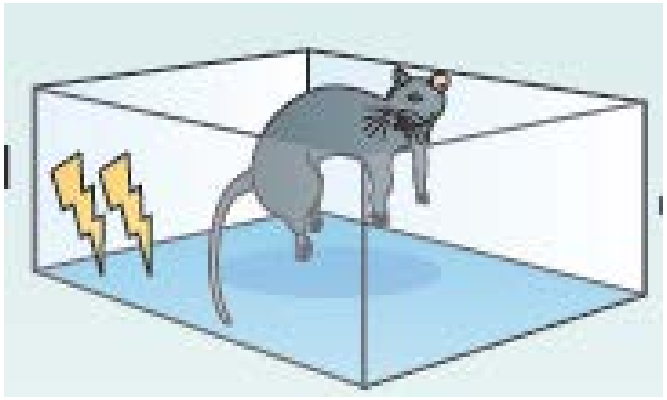
Human Neuroticism personality trait scores

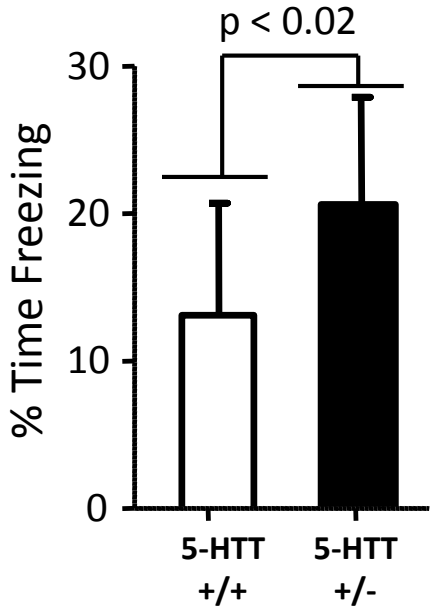
people who are neurotic probably carry S allele for SERT



Lesch et al. (1996) Science 274: 1527

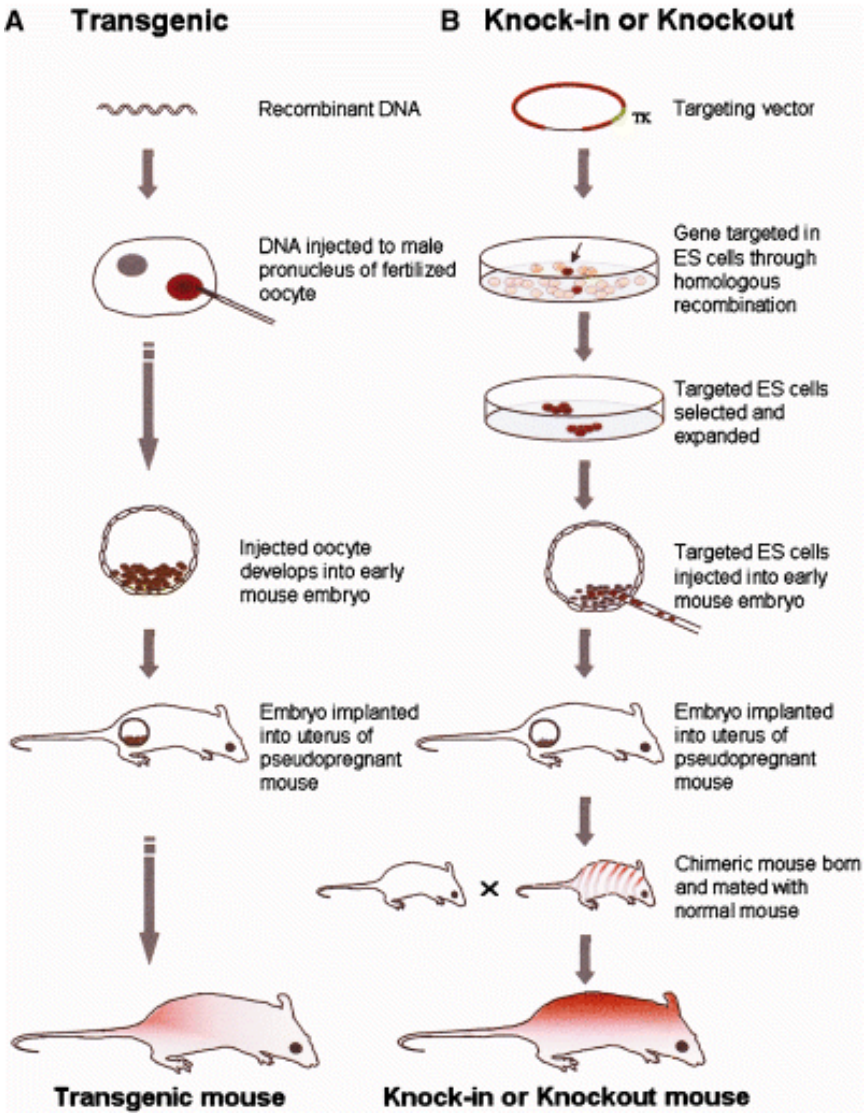
5-HTT heterozygous knockout mouse
Conditioned freezing to context





Pryce et al. (2012) Neuropharmacol 62: 358

Methods of gene manipulation in animals for study of gene-to-phenotype relationships



used when not interested
in where the transgenic gene
is inserted

Gene knockout via homologous recombination

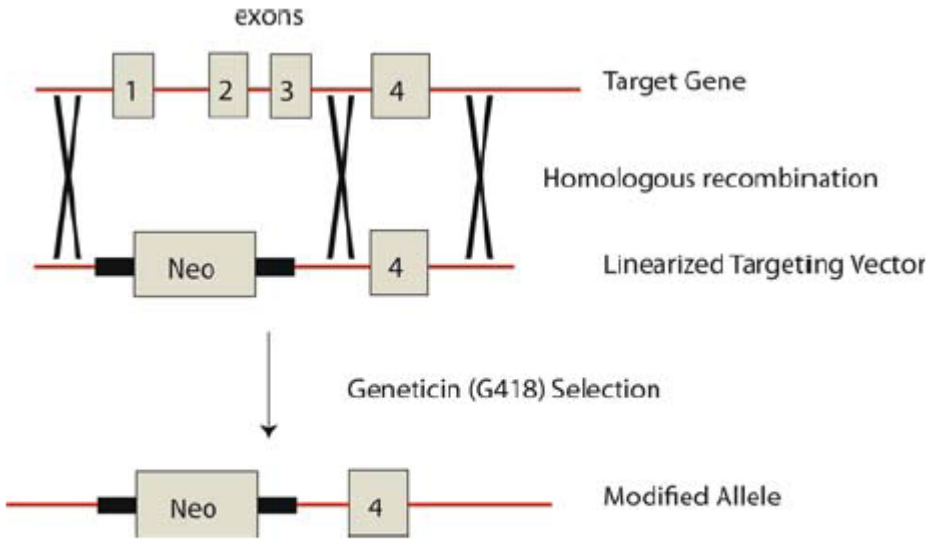
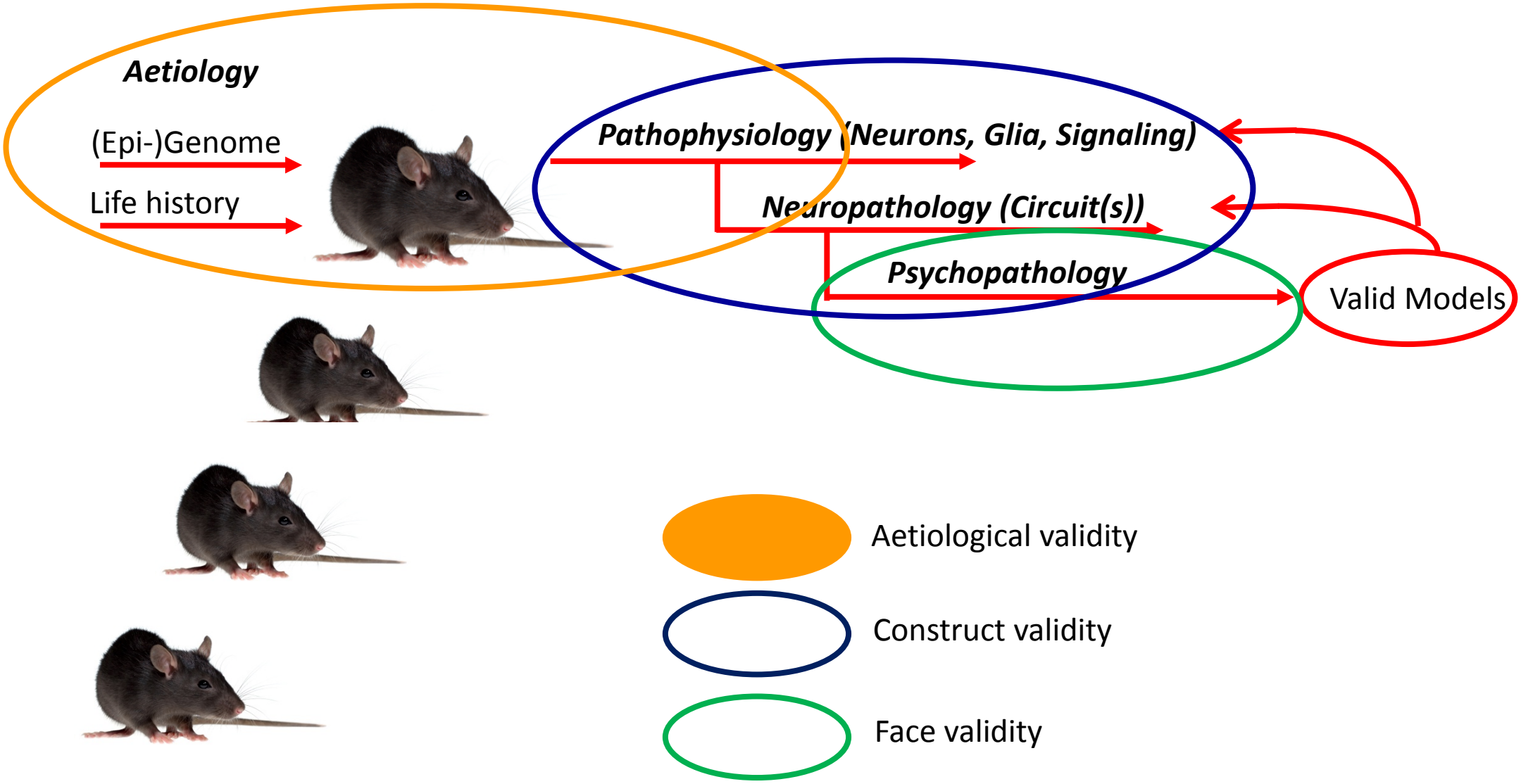


Fig. 1 Homologous recombination. In the example above the homologous recombination results in a gene knockout

Animal models must have validity: Aetiological validity

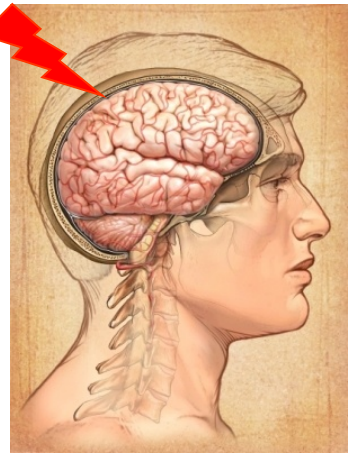


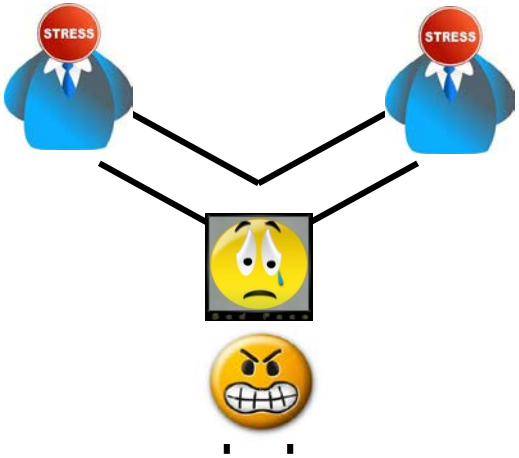
Environment: From Uncontrollability to Helplessness to Emotional disorder

Aetiology

(Epi-)Genome

Life history





Uncontrollable Stressful life events:

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

we never evolved a mechanism, because environemnt was either controllable or your dead (so no mechanism can even evolve).
no cns copes with the events to the left

Aetiology

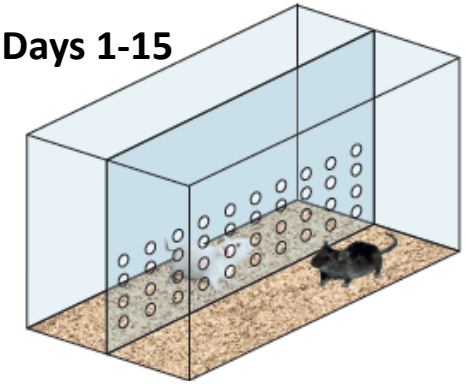
(Epi-)Genome

Life history

Chronic social defeat (CSD)

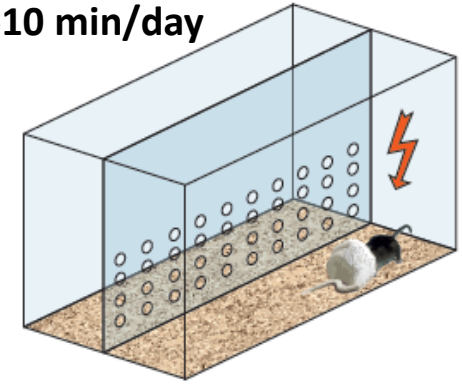
Days 1-15

white submissive
black dominant and very aggressive



Threat:
Visual
Olfactory
Auditory

1-10 min/day

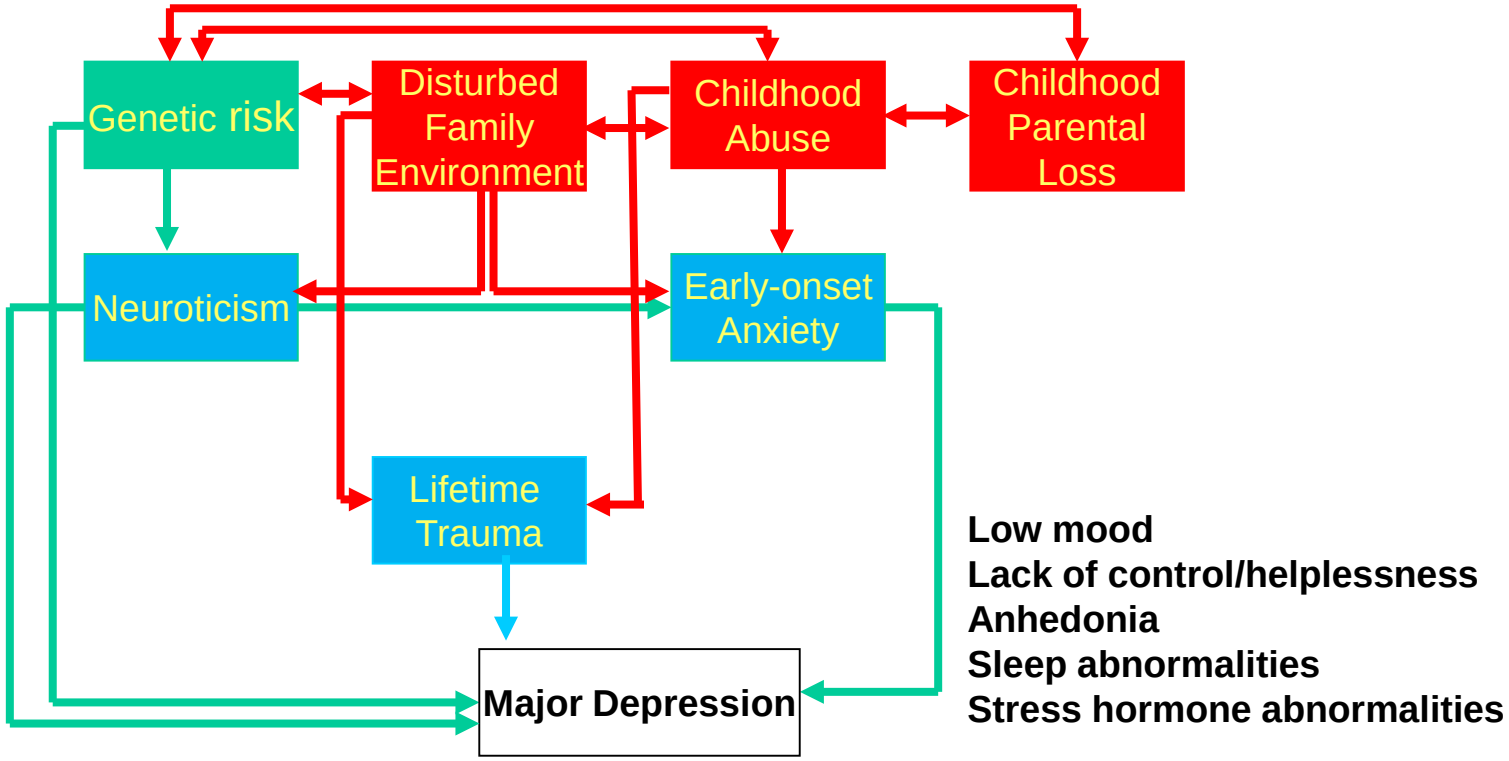


Threat+Attack:
Physical
No wounds

Lack of social control
= Helplessness (in humans)

Pryce et al. (2011) *Pharm Therapeut* 132: 242

Early-life stress as an aetiological factor in depression

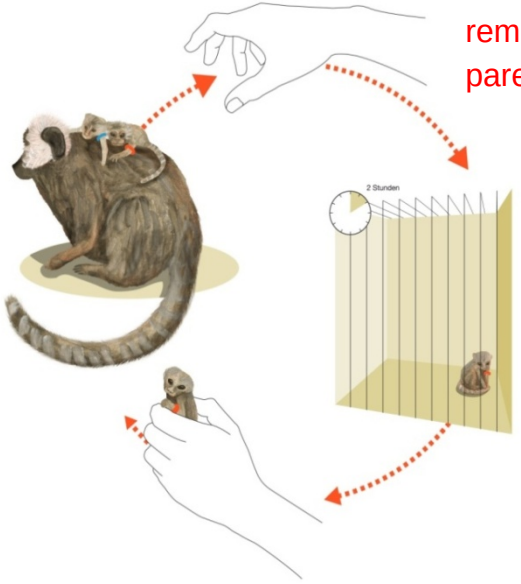


Kendler et al. (2002) Am J Psychiatry 159: 1133

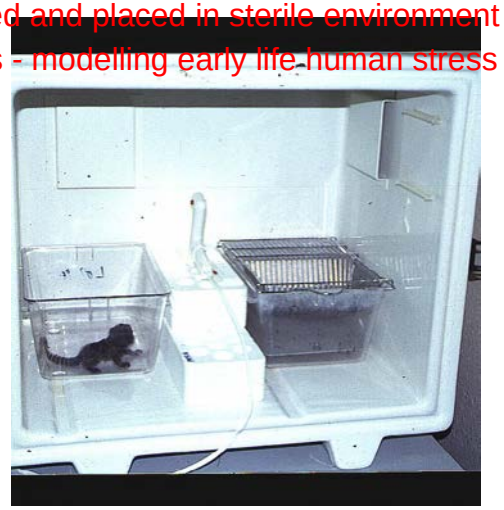
Examples of manipulations of the early-life environment

(environmental manipulations)

Rat and marmoset early deprivation



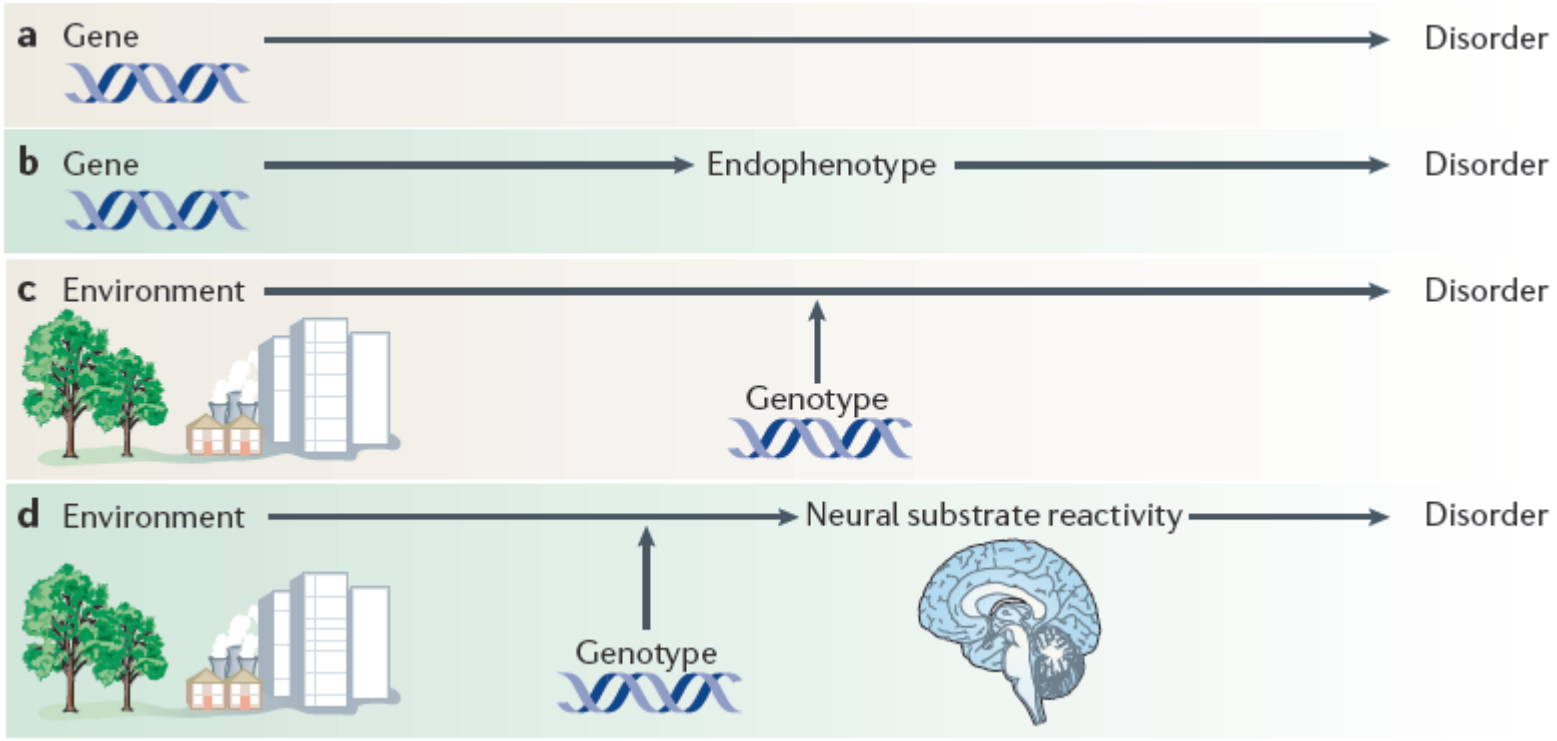
removed and placed in sterile environment for aorund 30mins before returned to parents - modelling early life human stress in animals



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

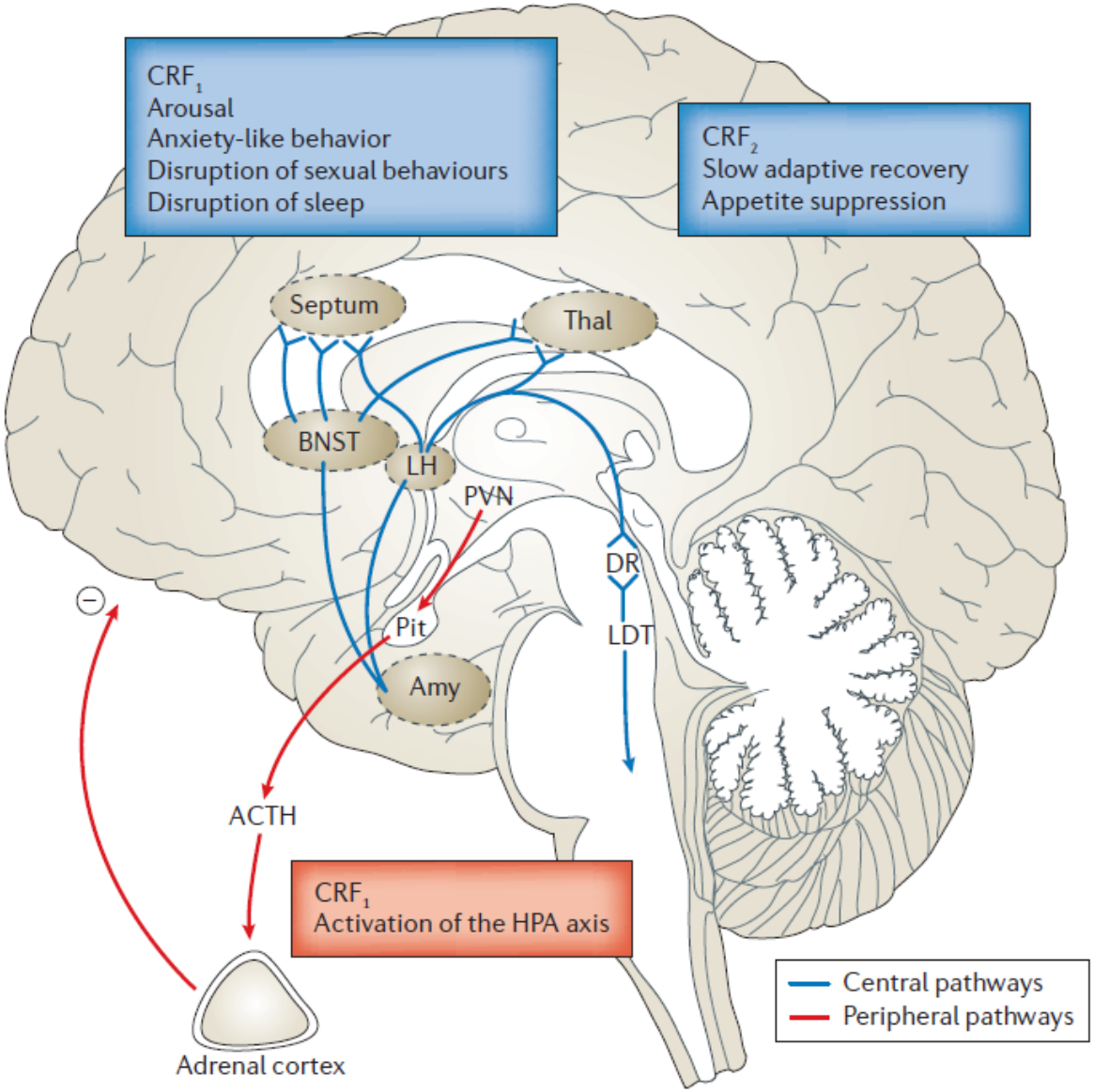
Krishnan & Nestler (2008) Nature 455: 894

Approaches to studying Genes and Environments important in depression



Caspi & Moffitt(2006) Nature Reviews Neurosci 7: 5830

Corticotrophin Releasing Factor (CRF) is a Neurotransmitter and Neurohormone



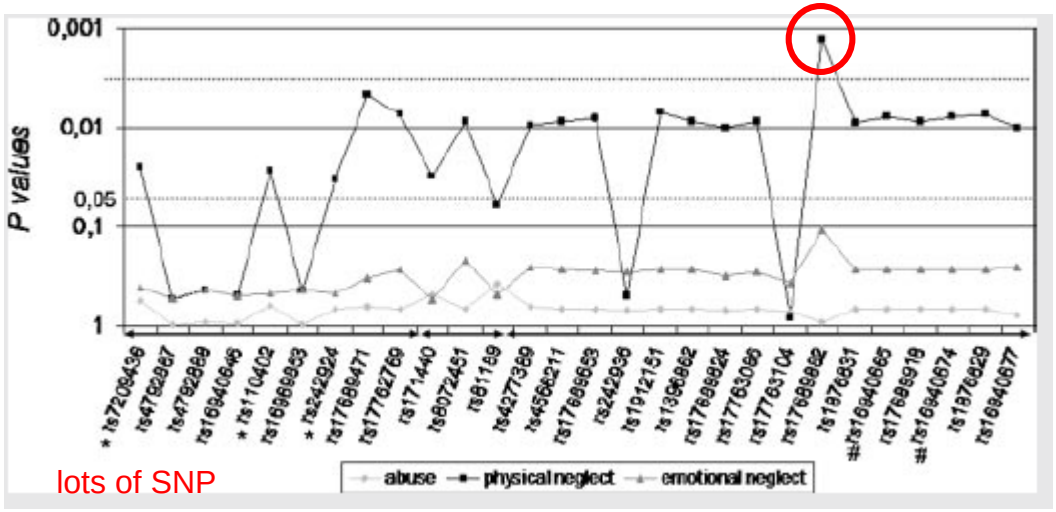
LH, Lateral hypothalamus
BNST, Bed nucleus of stria terminalis
Thal, Thalamus
DR, Dorsal raphe nucleus
Amy, Amygdala

Berton & Nestler (2006) Nature Rev Neurosci 7: 137

Interaction between the CRF receptor 1 genotype and childhood stressful life events in depression aetiology

CRF := corticotrophin releasing factor

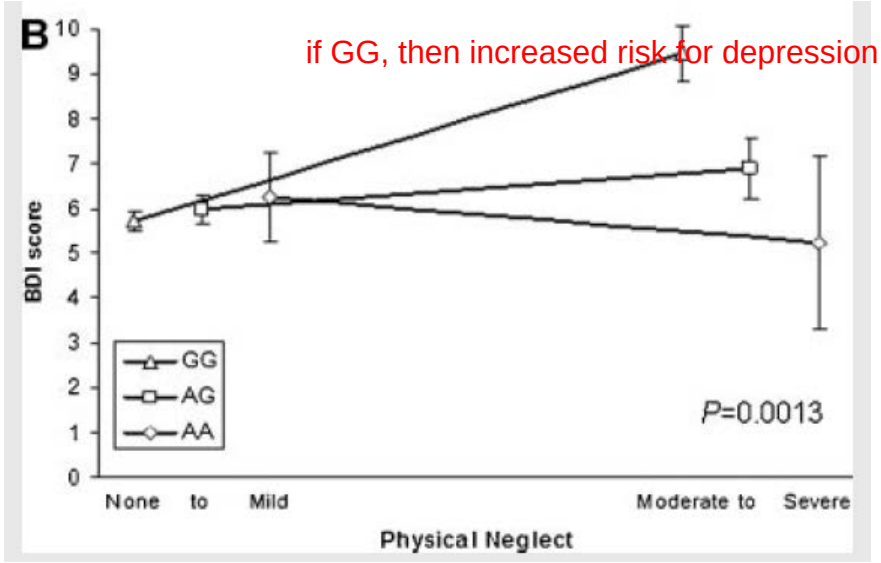
Probability of GxE Interaction for CRFR1 SNPs



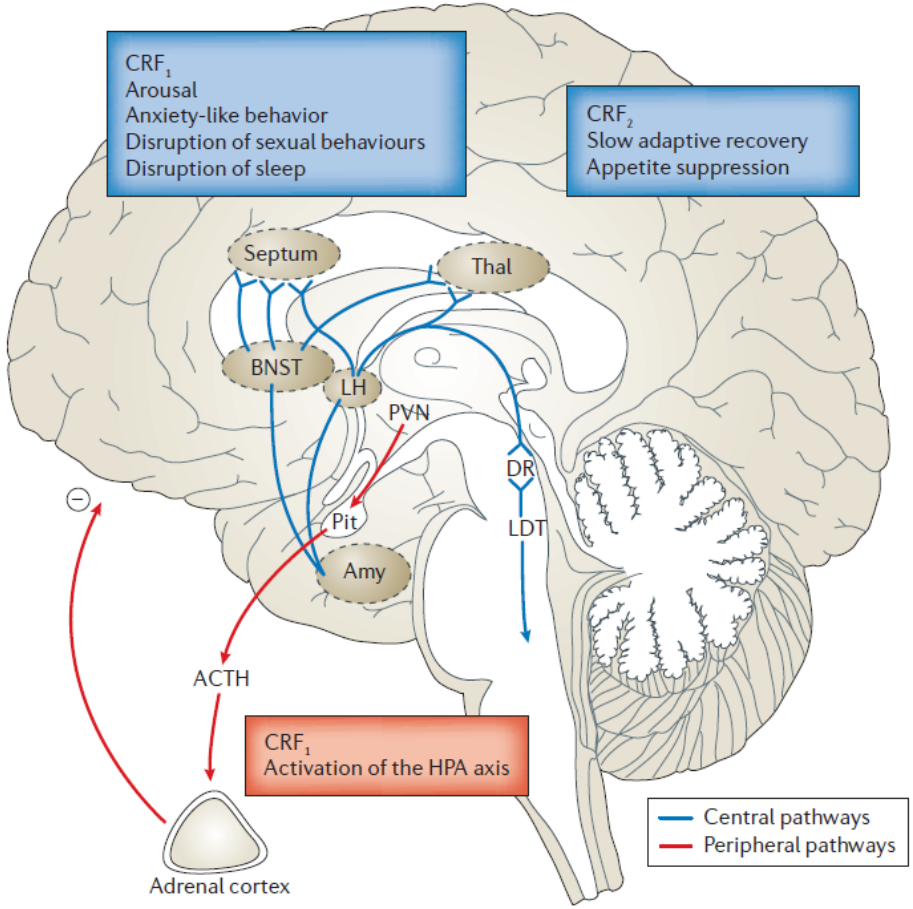
lots of SNP

this one was identified:

GxE Interaction for SNP rs17689882

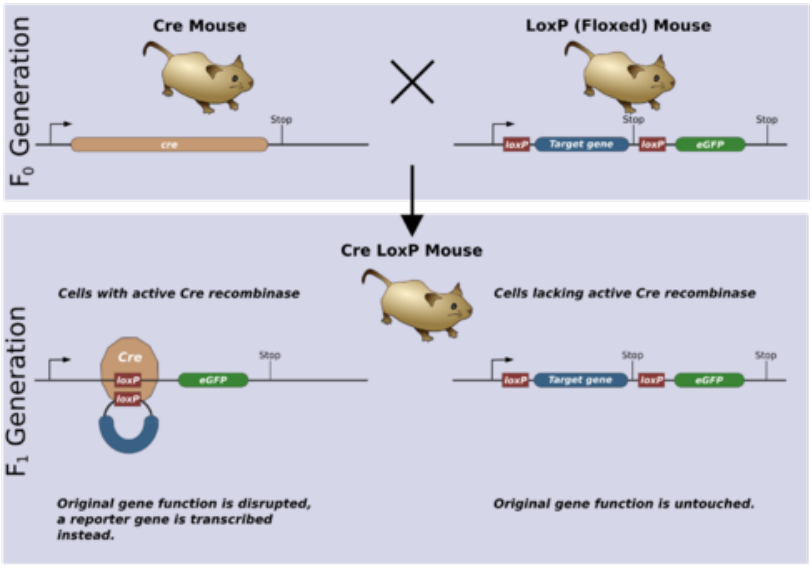


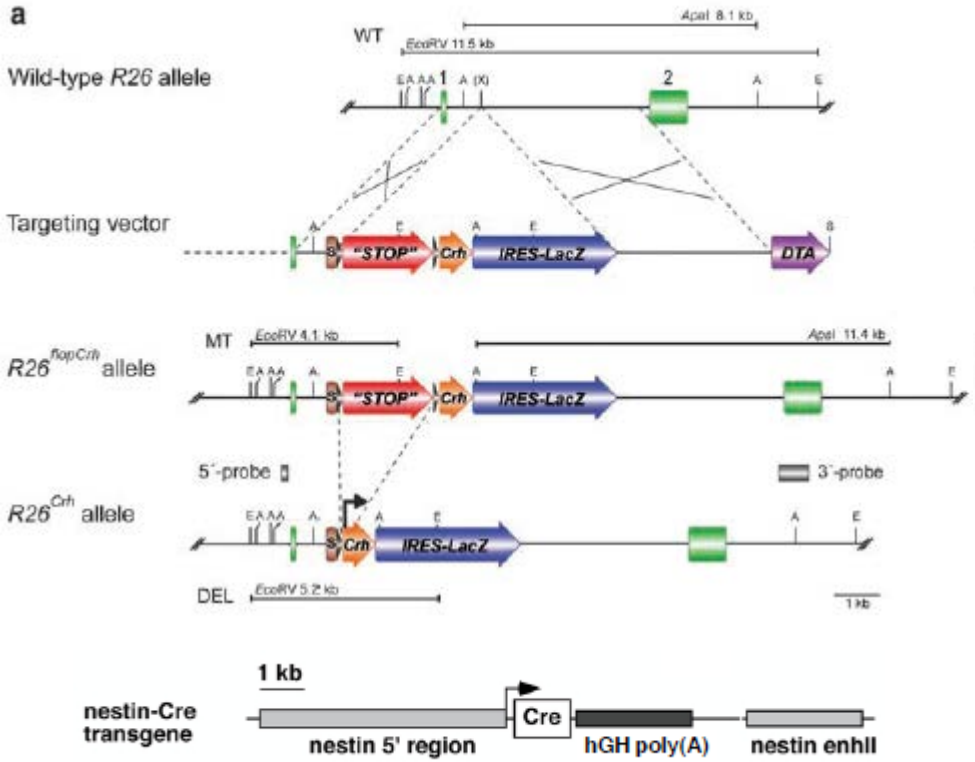
if GG, then increased risk for depression

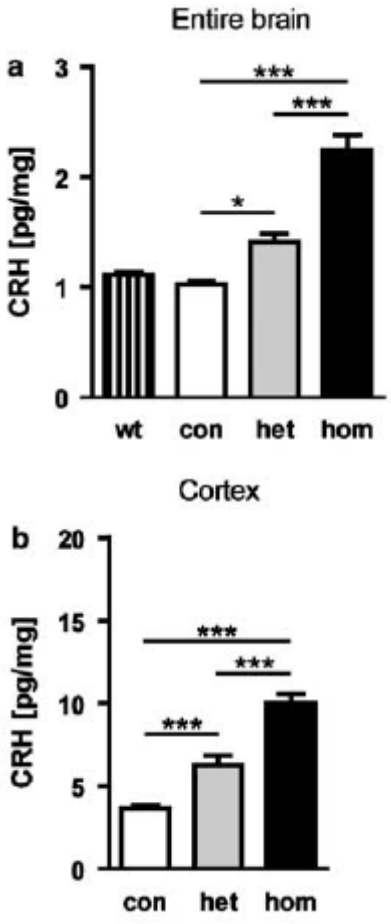


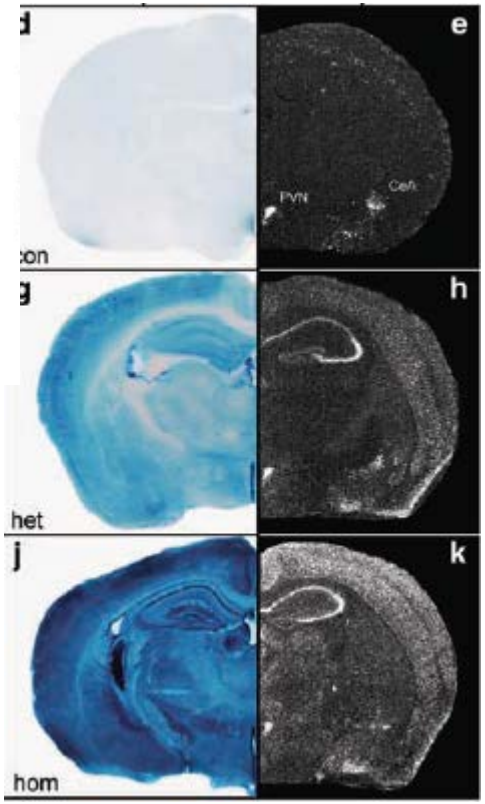
Grabe et al. (2010) Am J Med Genet B 153B: 1483

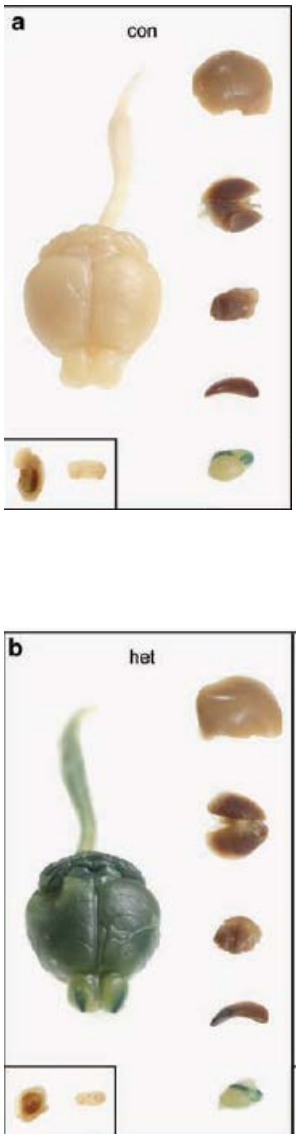
CNS-specific transgenic over-expression of corticotropin releasing factor in mice





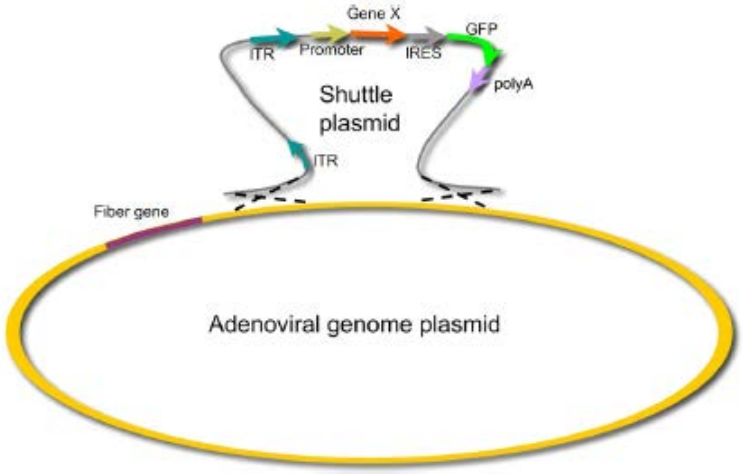


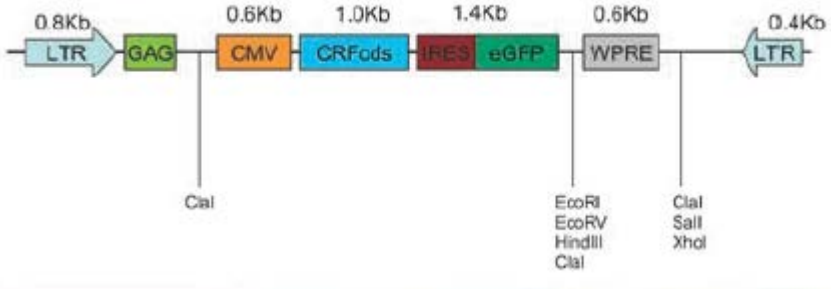




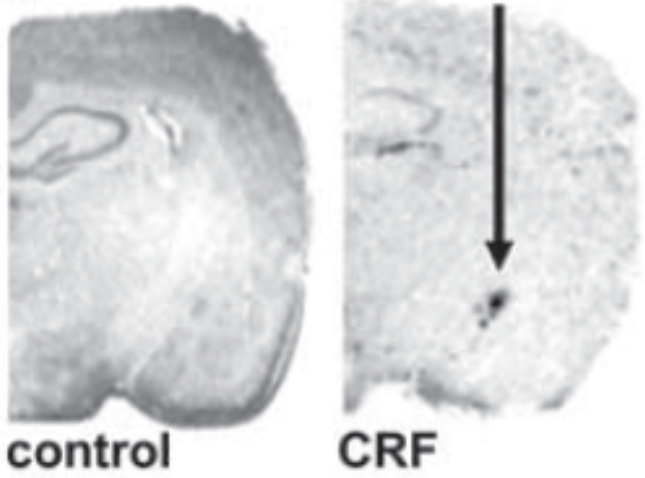
Lu et al. (2008) Mol Psychiatry 13: 1028

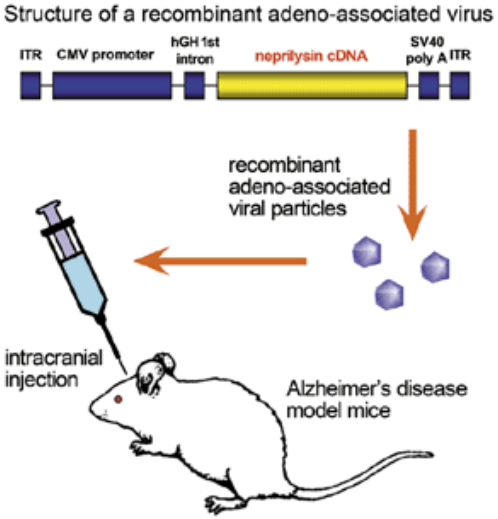
Viral vector-induced gene-over expression: high spatial and temporal resolution

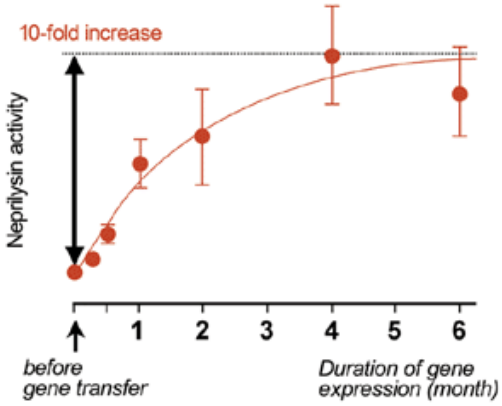


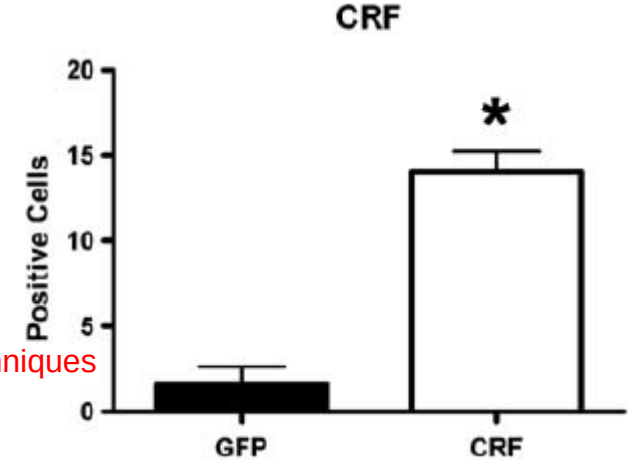


Control = Green fluorescent protein (GFP)









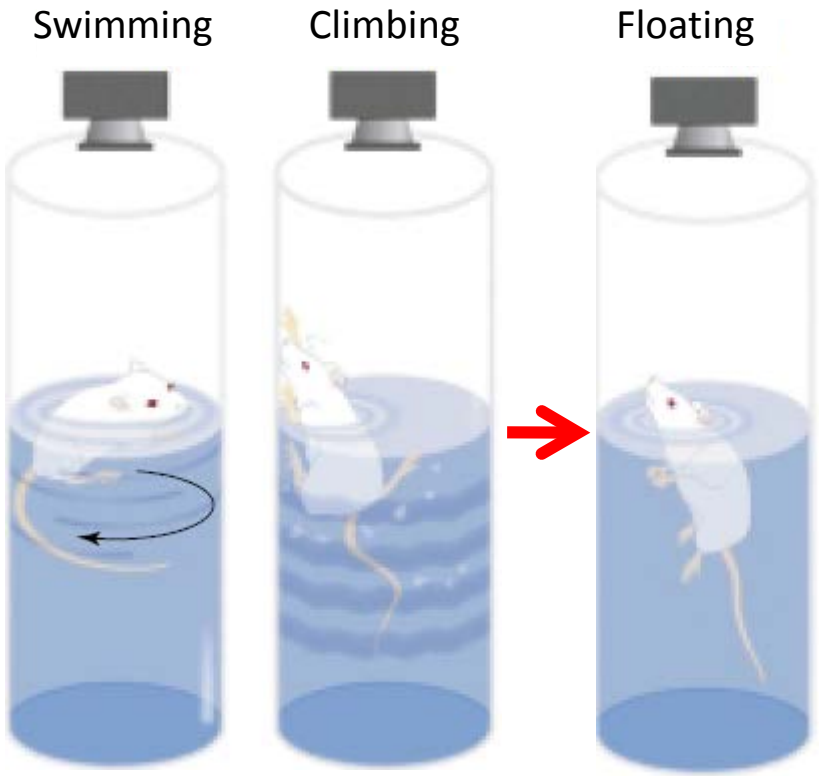
increase of CRF in these animals using gene techniques

Järäs et al. (2007) Exp Hematol 35: 343

Keen-Rhinehart et al. (2009) Mol Psychiatry 14: 37

The rodent forced swim test

test if effect of CRF has effect on behaviour: test performed was rodent forced swim test: take large cyling and fill with warm water.observe swimming, climbing and floating behvaiour for 6 mins. during last 4 mins, is there swimming or floating.

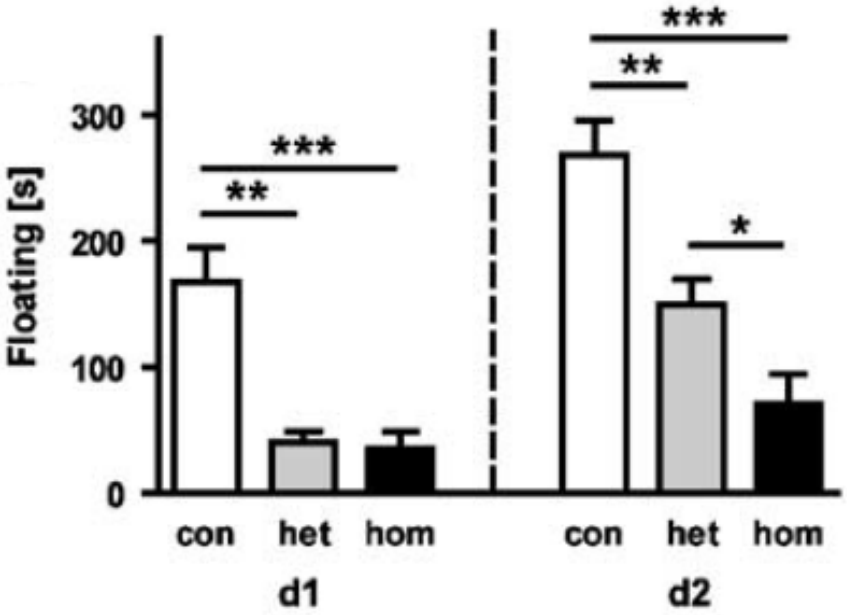


CRF and Forced swim test: interpreting the findings to fit the hypothesis

lec: forced swim test is useless in his opinion - no face validity

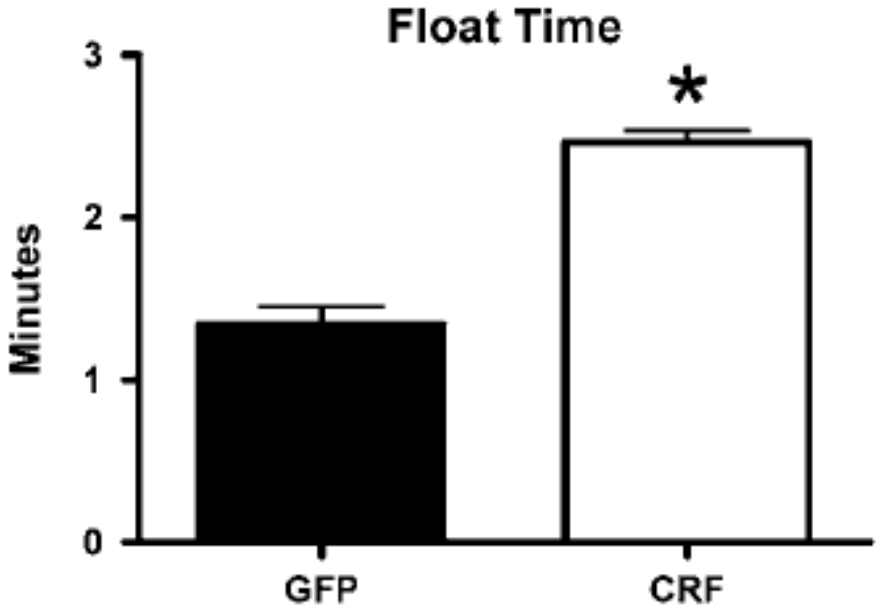
Transgenic CRF over-expression in mouse

the more CRF, the less floating and the more swimming



Viral-vector CRF over-expression in rat

here there was more floating, the opposite result



"Decreased floating reflects increased stress responsiveness and active coping"

"Increased floating reflects depressive-like behaviour"

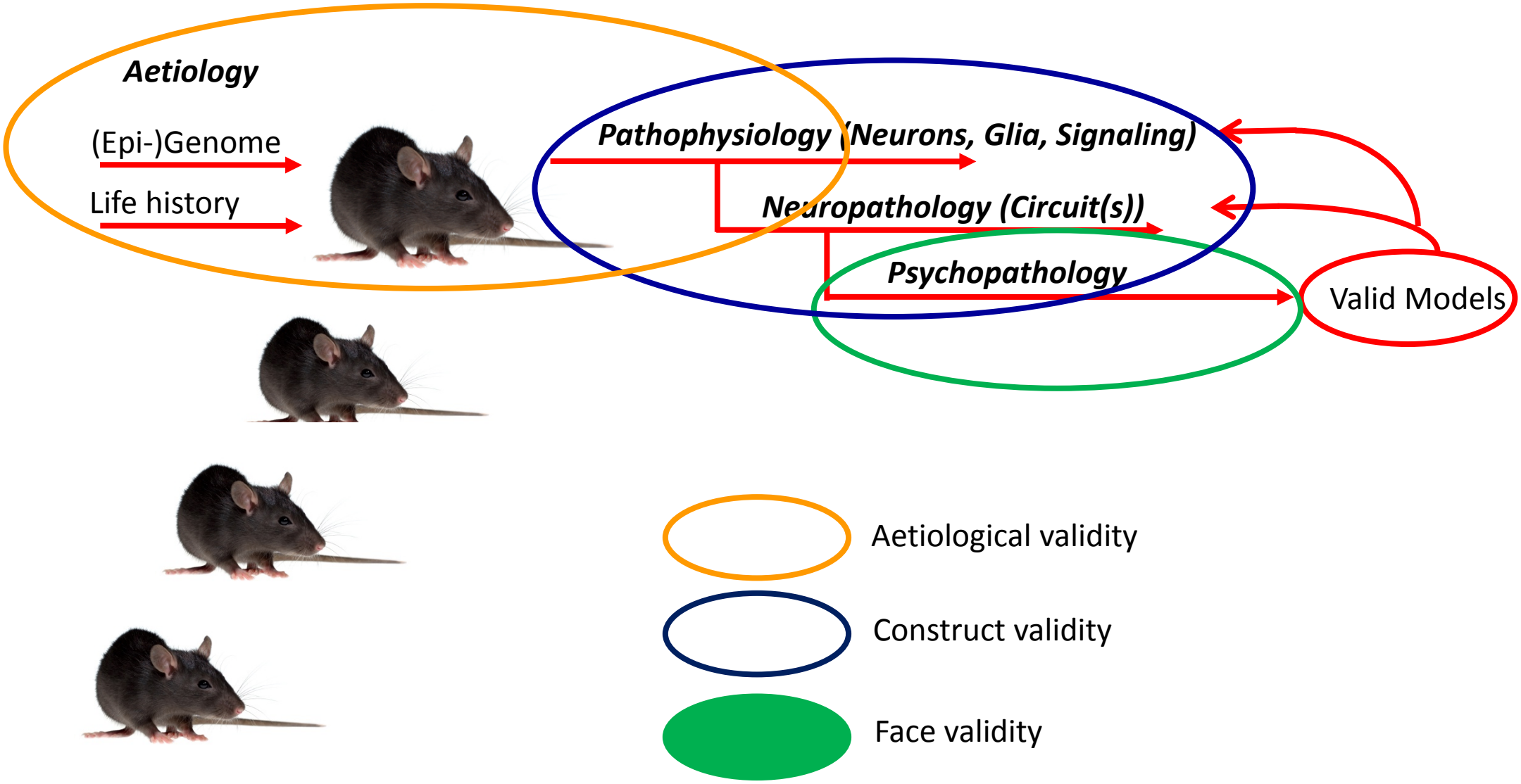
Lu et al. (2008) Mol Psychiatry 13: 1028

very good journal

Keen-Rhinehart et al. (2009) Mol Psychiatry 14: 37

skipped

Animal models must have validity: Face Validity



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

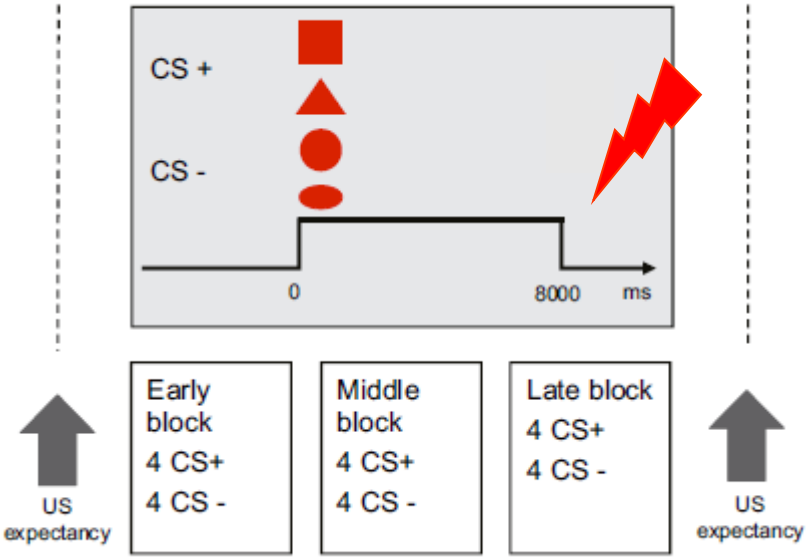
Pryce & Seifritz (2011) *Psychoneuroendocrinol* 36: 308

Example of a State Marker in Depression:
Increased conditioned fear responses in depressed patients relative to healthy controls

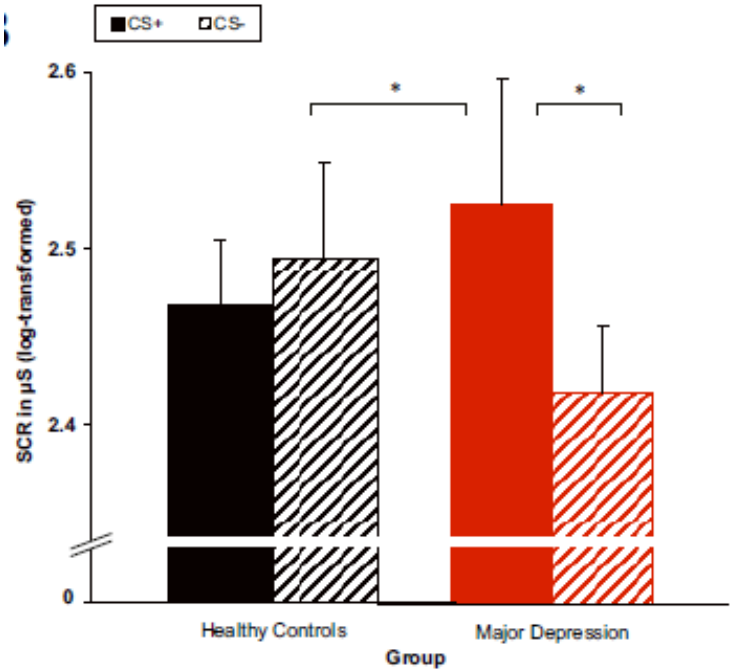
Depressed patients exhibit increased CS-UCS fear conditioning, measured using skin conductance

Depressed patients and healthy controls show similar and accurate expectancy of UCS depending on CS

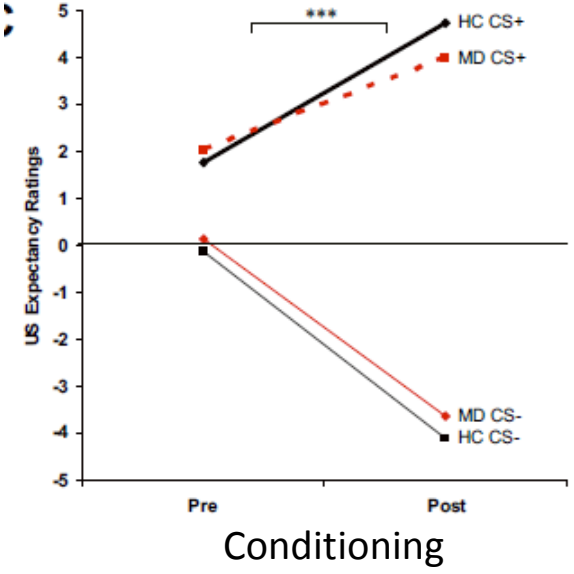
Fear Conditioning Protocol



Skin Conductance Response



UCS Expectancy Rating

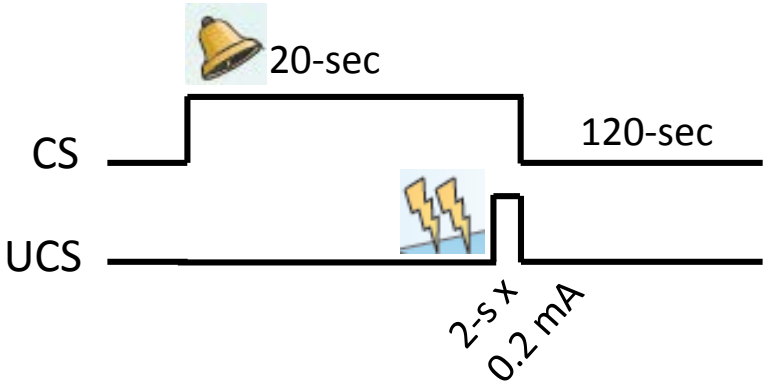


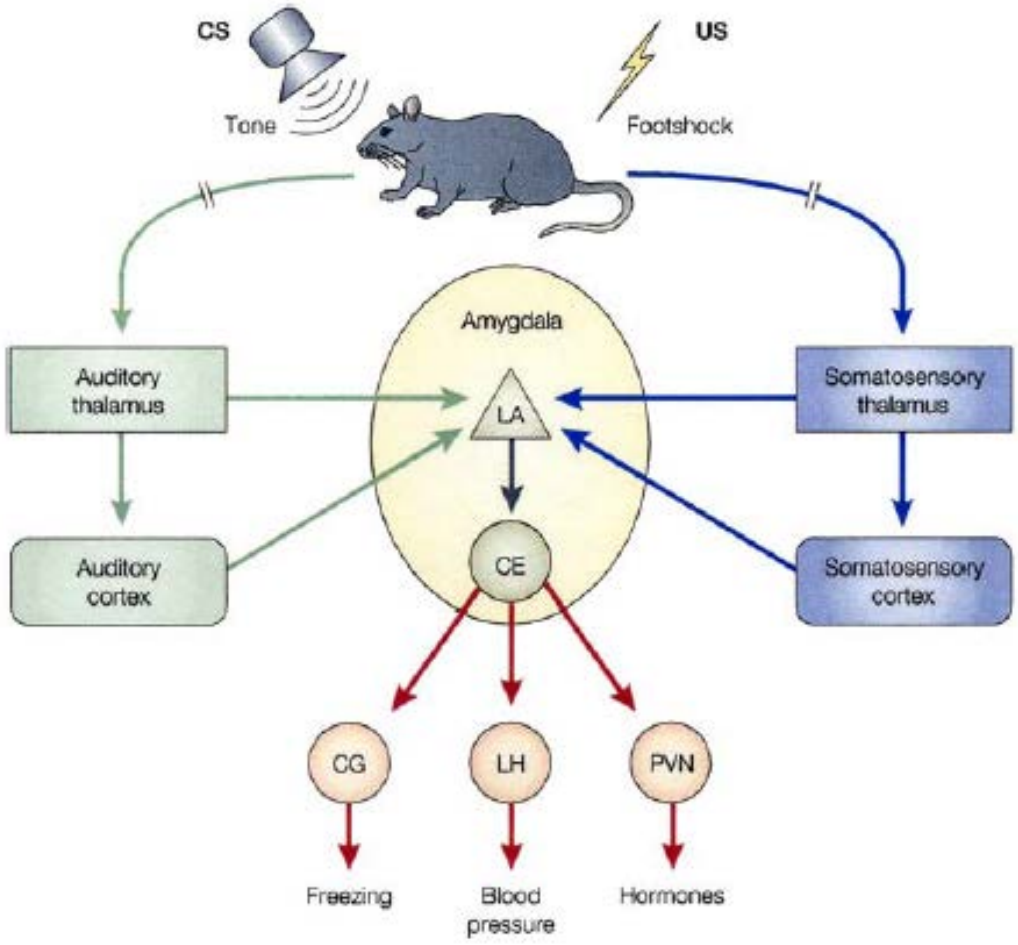
Nissan et al (2010) Biol Psychiatry 68: 544

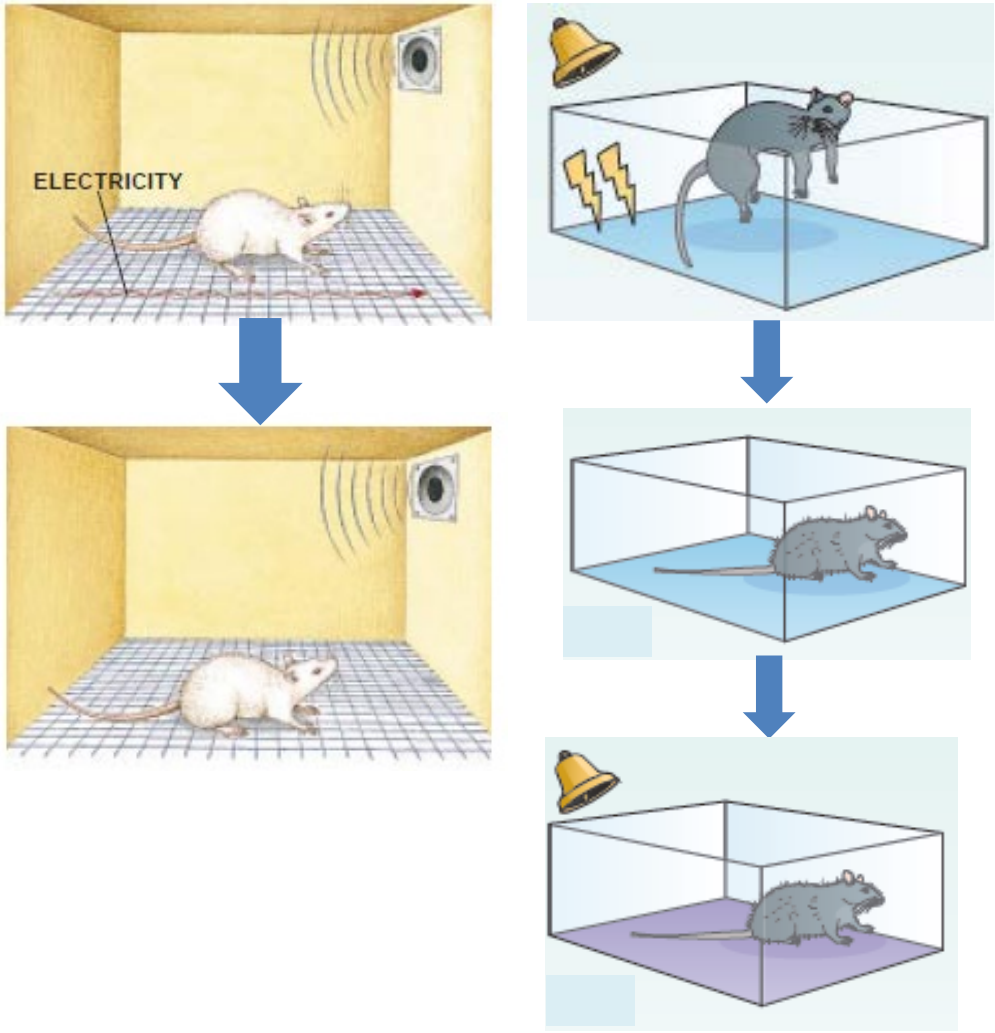
Fear conditioned Freezing in Rodents – Adaptive emotional behaviour

Convergence of CS and UCS sensory neuron inputs at the lateral amygdala

why not do fear conditioning for CRF to see what was the case with CRF changes





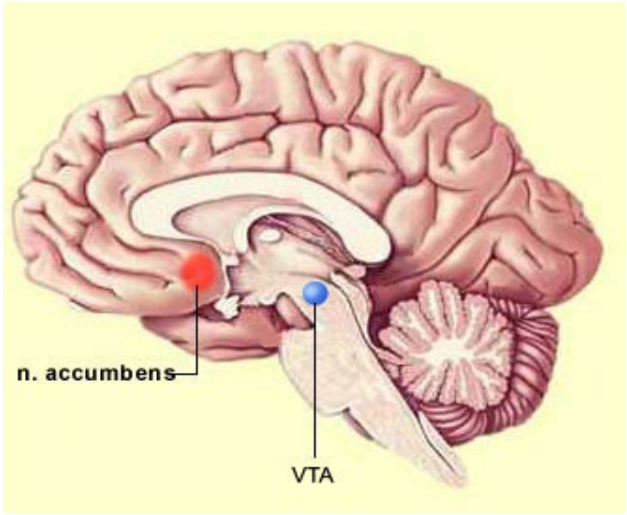


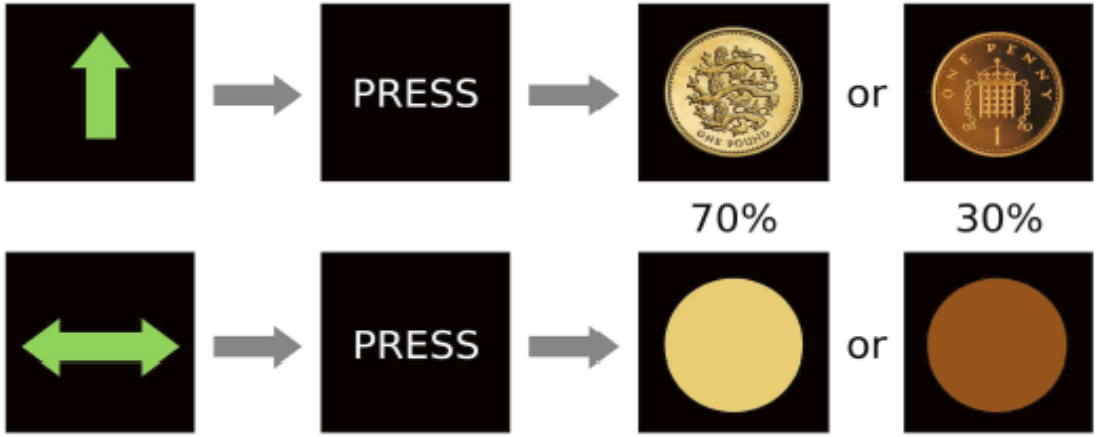
Phelps & LeDoux (2005) Neuron 48: 175

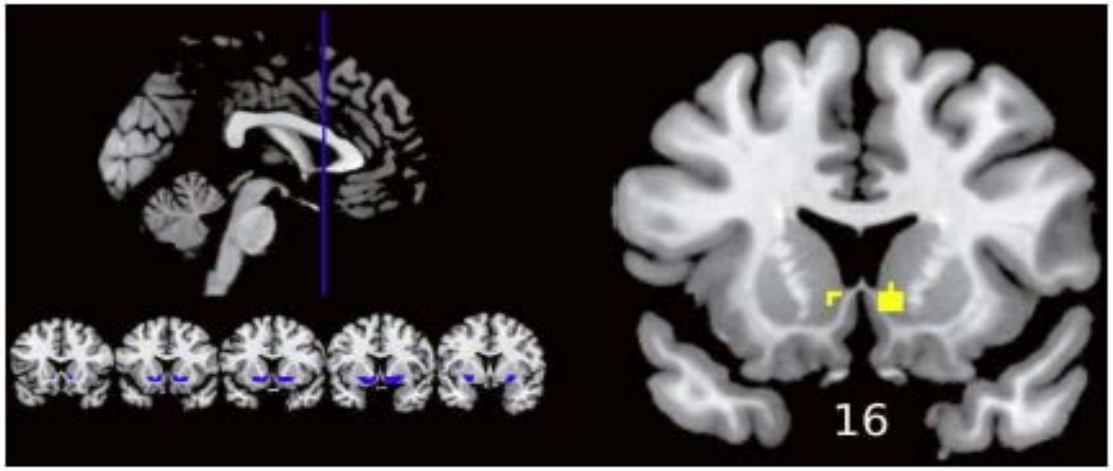
CRF could have been done on reward motivation too

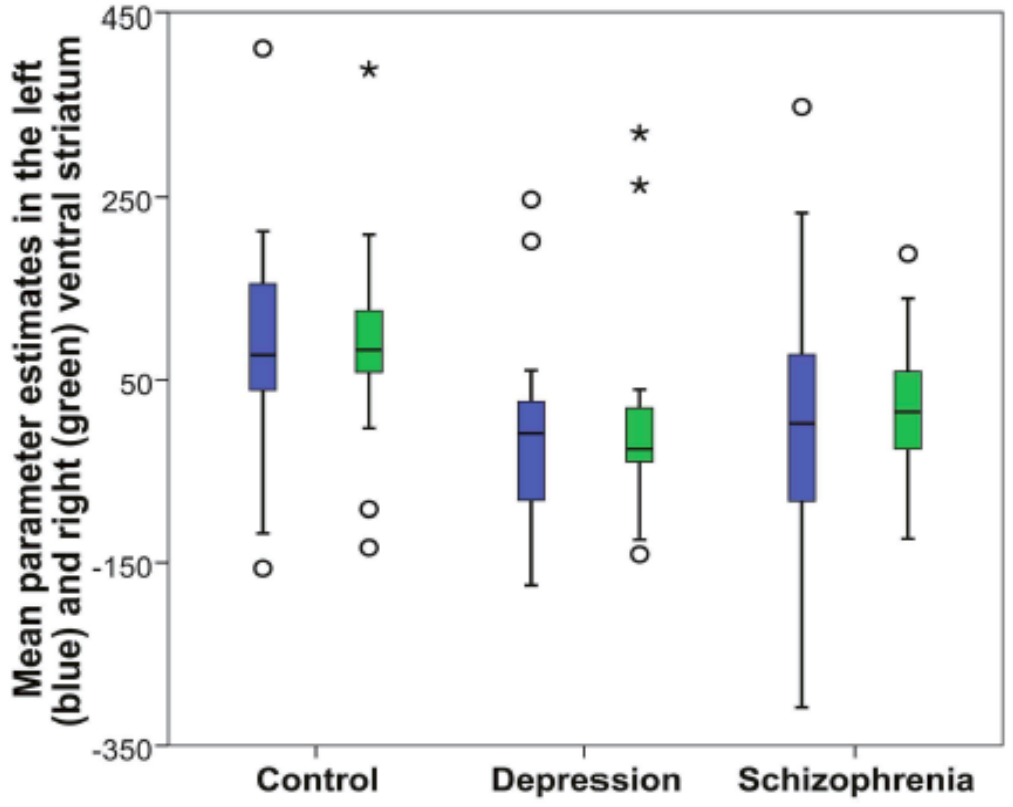
Example of a State marker in depression

Decreased nucleus accumbens response to reward in depression









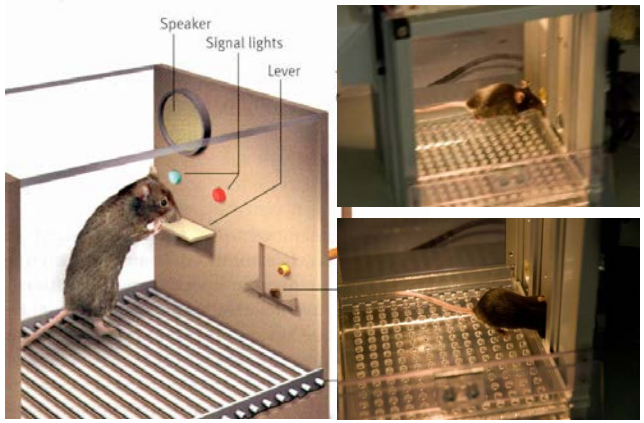
Arrondo et al. (2015) *Front Psychol* 6: 1280

Food reward in Rodents – Adaptive goal-directed behaviours

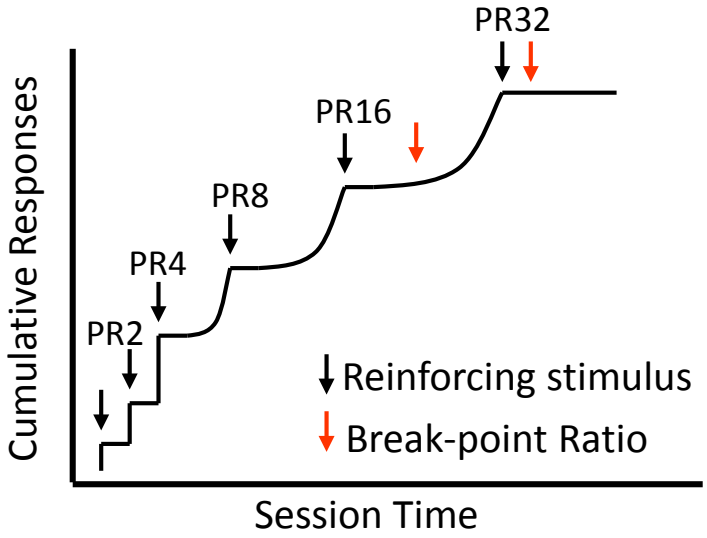
Major modulating function of mesocorticolimbic Dopamine system on Motivation

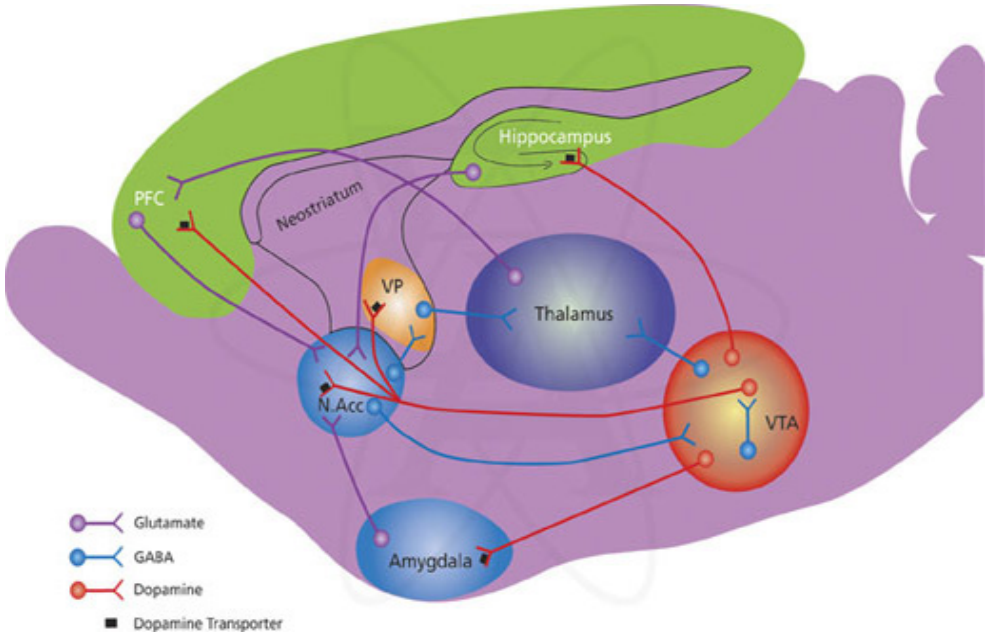
Consumption Tests

Operant Response-Outcome Tests



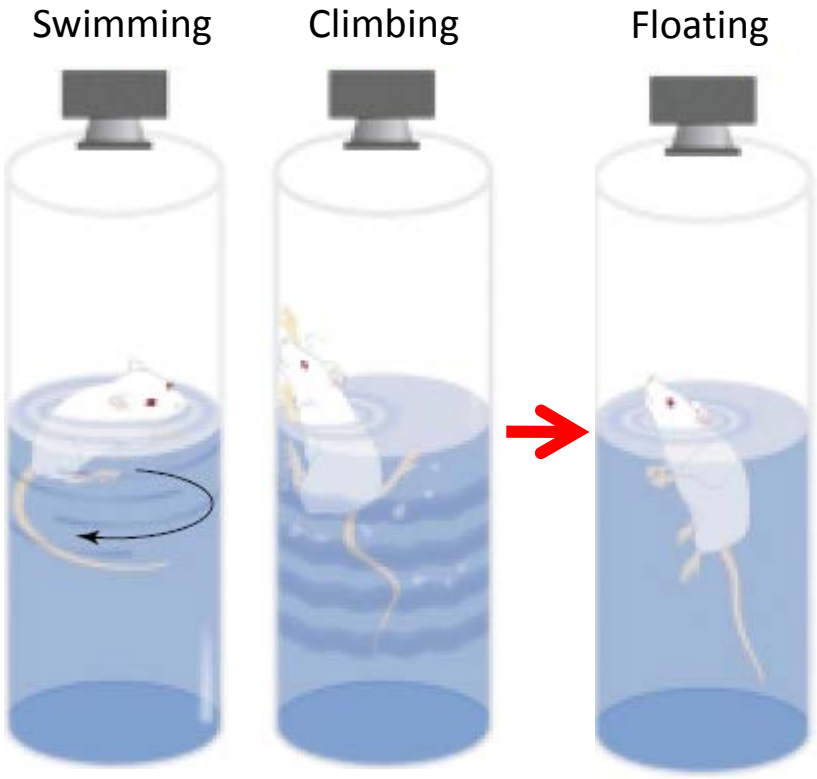
Progressive ratio schedule test

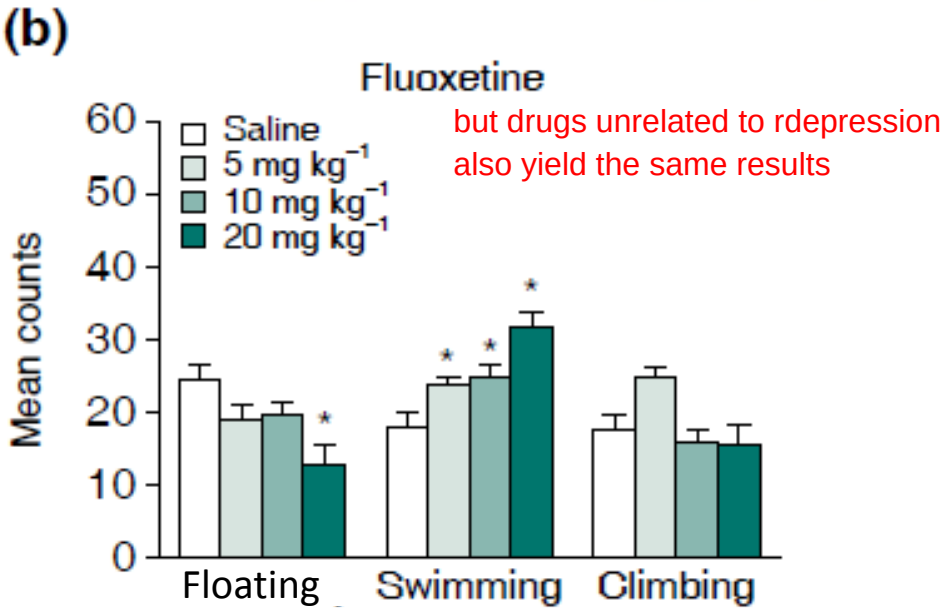




The forced swim test in depression research

the forced swim test is sensitive to antidepressants





but drugs unrelated to rdepression also yield the same results

Aetiological Validity:

Uncontrollable stress

Face Validity:

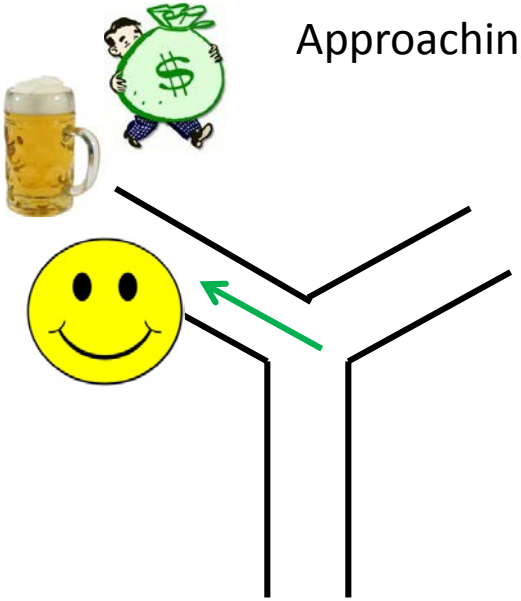
Uncontrollable stress → Despair → Floating

human interpretation of human observation

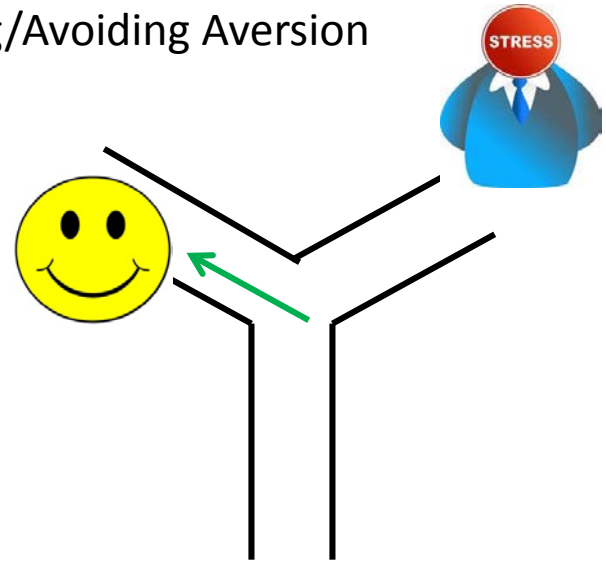
- Really the Uncontrollability?
- Really Despair?

Emotional stimuli ("life events"): the special case of uncontrollability

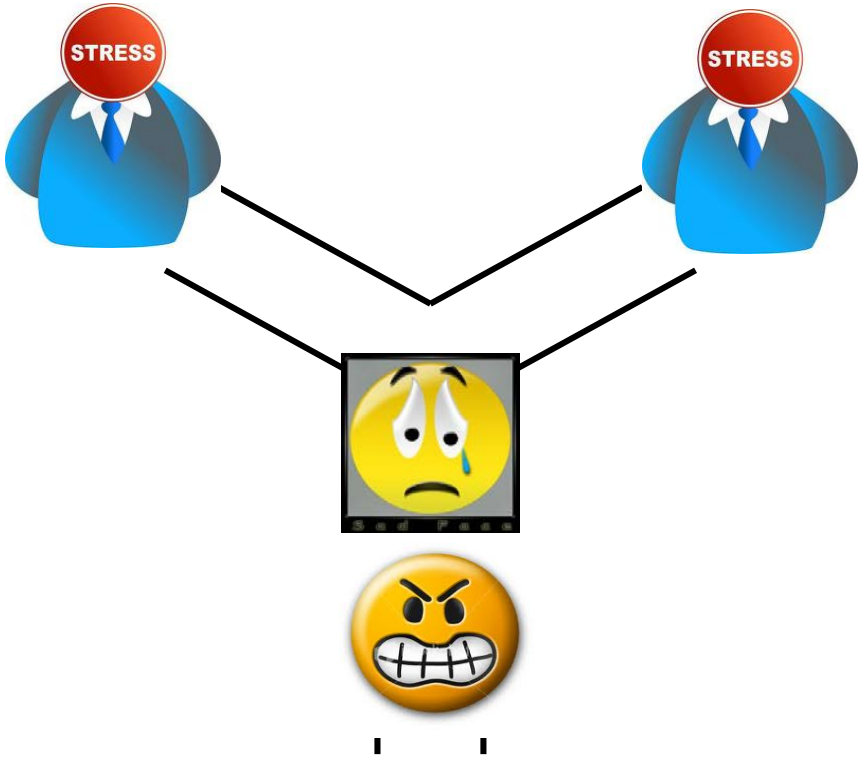
Approaching/Consuming Reward



Escaping/Avoiding Aversion



Uncontrollable Aversion (or Reward)



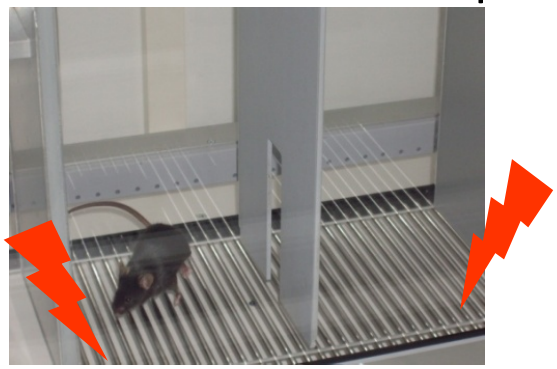
Contexts for Stressful life events:

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

Translational research into depression needs valid animal models of emotional-cognitive function

thats the test for the previous slide

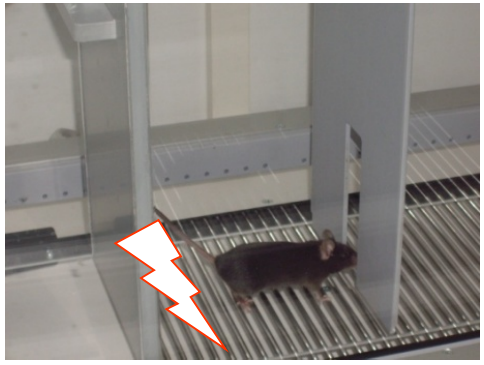
(Un)controllable foot shock escape test



Footshock pre-exposure:

Controllable Uncontrollable None

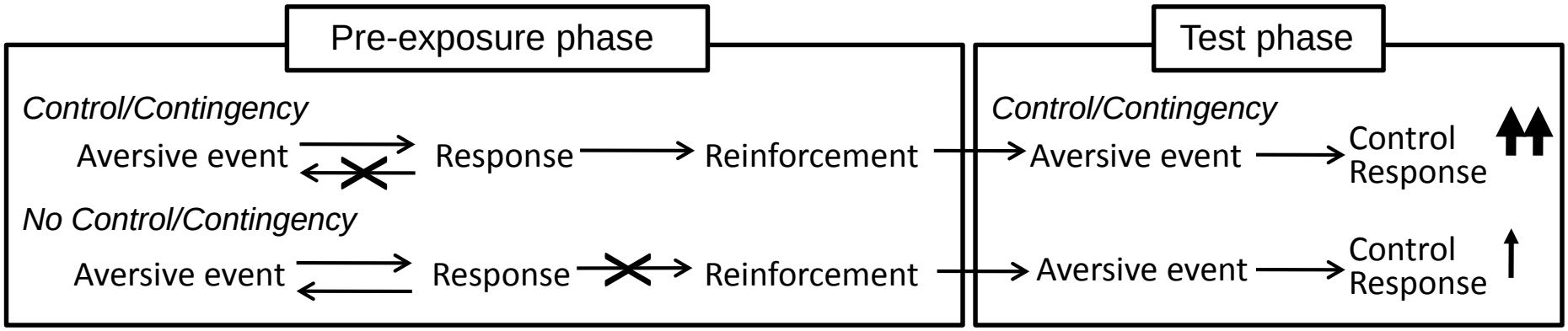
Footshock escape test:

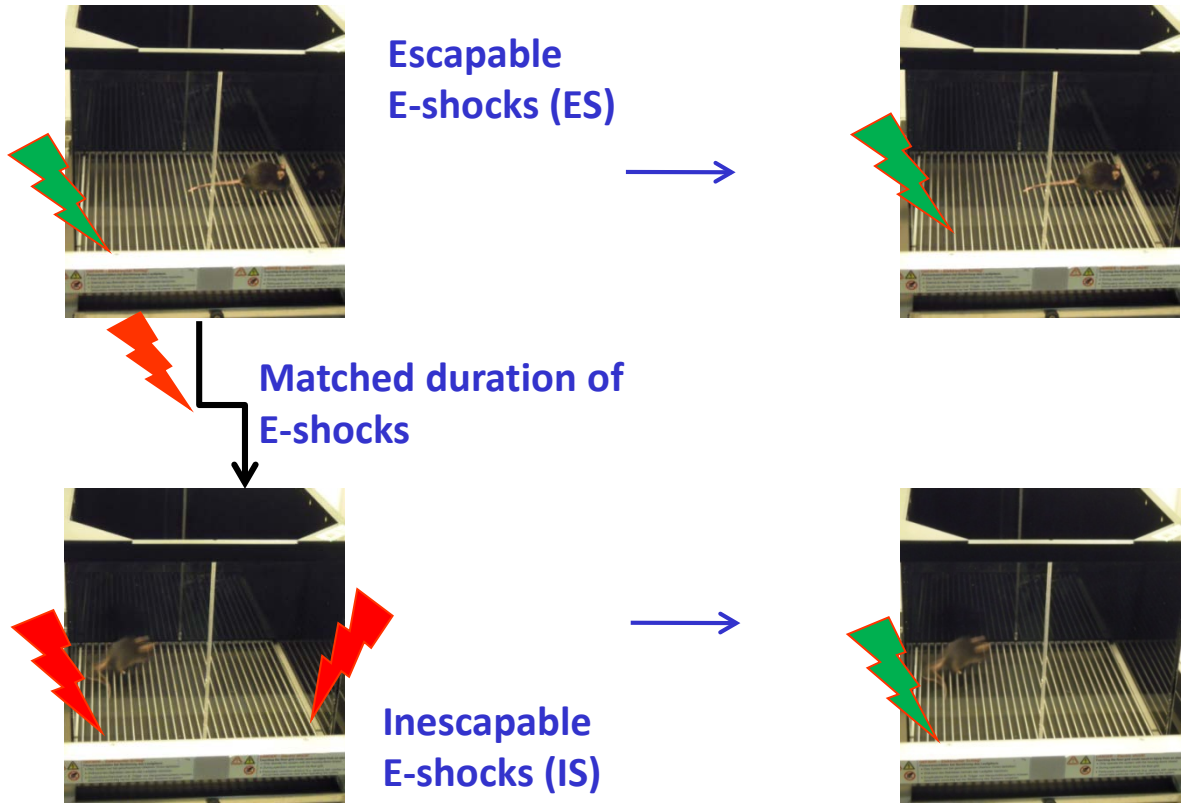


Uncontrollable stress → Escape failure

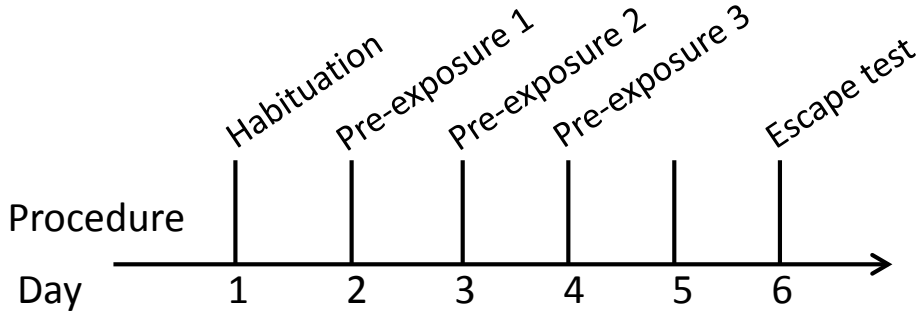
- Really the Uncontrollability? YES
- Really learned helplessness?

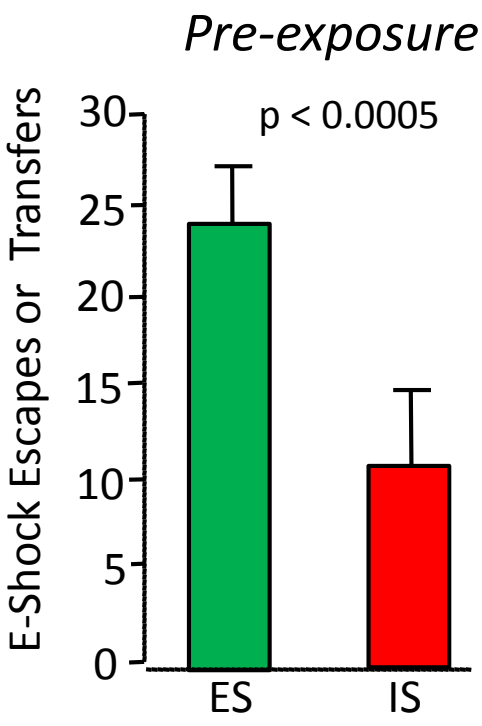
Demonstrating the learning of uncontrollability in mice

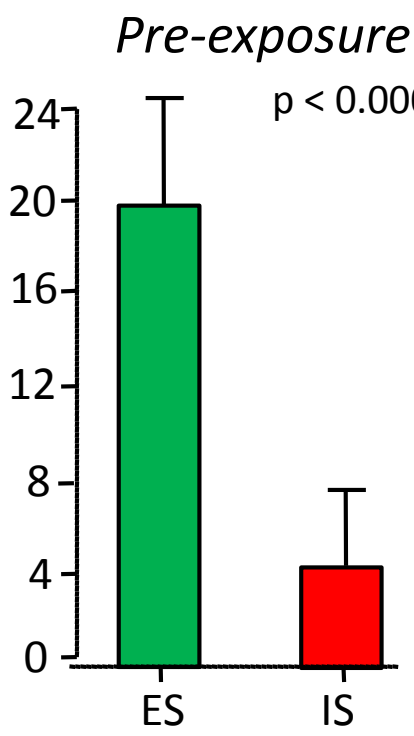


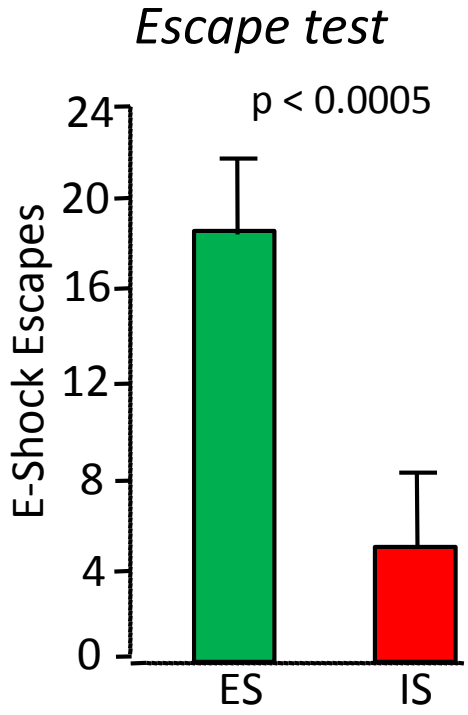


Evidence for the specific learned helplessness effect in mice









Manipulations and Readouts

- Complex psychiatric disorders need to be divided into translational components for their scientific study
- Animal models of human brain-behaviour disorders must satisfy specific validity criteria to be models
- Genes, environments, and their interactions, are the causes (aetiology) of depression
- Aetiological validity: G(ene), E(nvironment), GxE
- Serotonin transporter polymorphism x developmental stressful life events: *the* major example of GxE
- 5-HTT knockout mice have G-Endophenotype validity
- Genetic manipulations in laboratory animals: Transgenic, Gene knockout, knockin, Viral vector gene delivery
- Emotional stimuli ("life events") that are uncontrollable are severe and chronic
- The example of CRF, CRF receptor 1 and developmental stressful life events: human evidence and mouse models
- Face validity: Behavioural readout tests of specific psychopathologies
- Forced swim test: Not a model, only a readout test, and no face validity (only predictive validity)
- Learned helplessness: Not a model, only a readout test, but with face validity
- Universal neurobiology for processing emotional (important) stimuli across mammals is important for studying animals to understand adaptive/healthy human emotion and also human emotional disorders