1. Animal learning and memory

    Classical/Pavlovian conditioning

    Operant conditioning and Goal-directed behaviour

    Memory

2. **Emotional and cognitive stimulus processing**

    Processing of rewarding stimuli

    Aversive stimuli, fear and the amygdala

    Stress, learning and memory

3. Animal models of human affective disorders

    Translational experimental psychiatry

    Manipulations and readouts

    Animal models relevant to anxiety and depression

    Immune system and depression

4. Pre-clinical psychopharmacology

    SSRIs and affective disorders

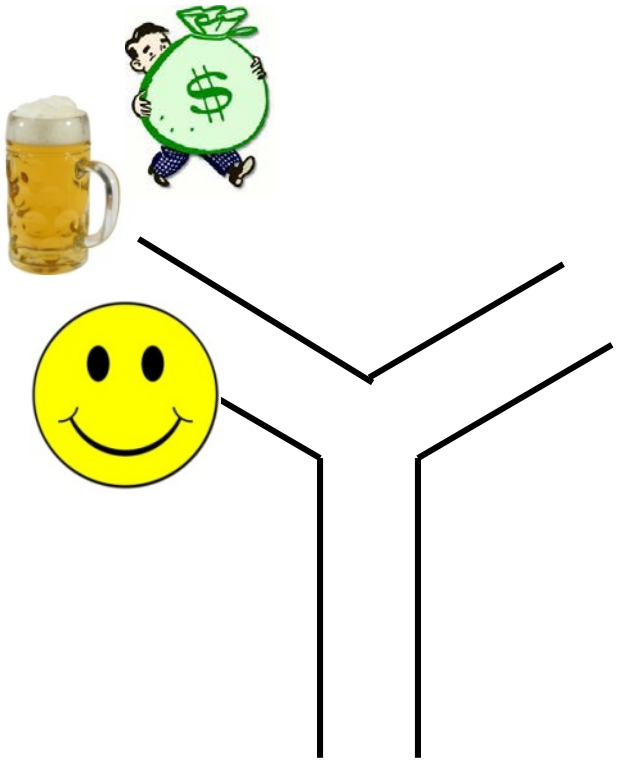
    Anti-depressants: the next generation?

Emotional and cognitive stimulus processing:

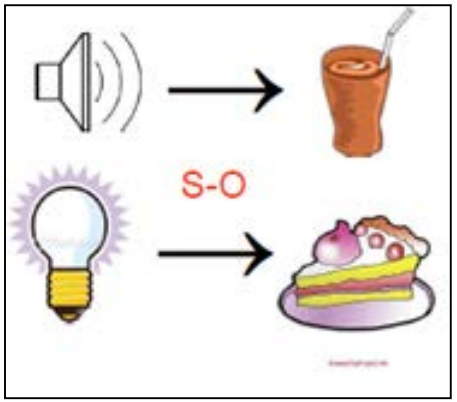
Processing of rewarding stimuli

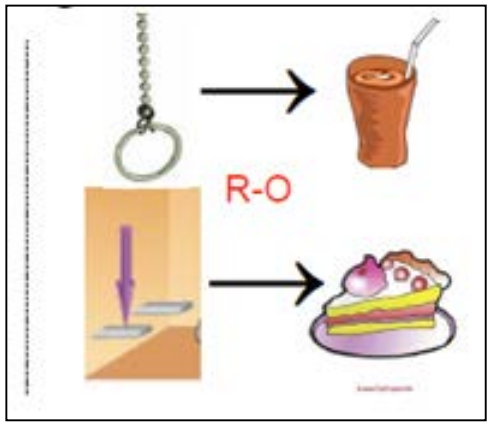
- Psychological components of reward
- Neurobiology of reward
- Dopamine and Reward learning
- GABA and Reward learning
- Dopamine and Reward motivation
- Opioid and Reward motivation
- Opioid and Reward liking

Individuals respond to and learn efficiently about environmental factors



Approaching/Consuming Reward



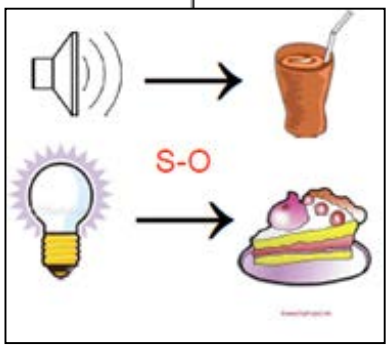


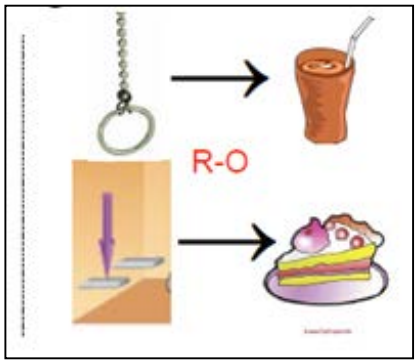
brain can put the two together to make the third one

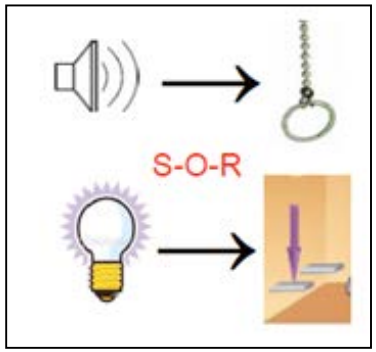
Psychological components of reward e.g. Food and feeding

Major categories

Learning

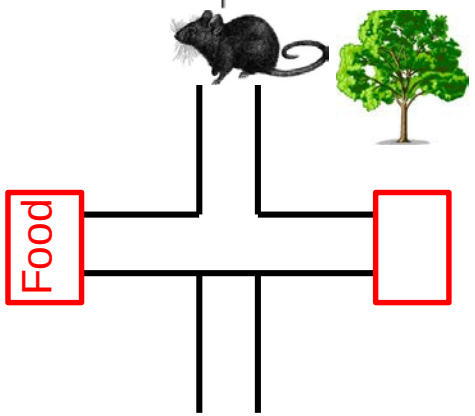


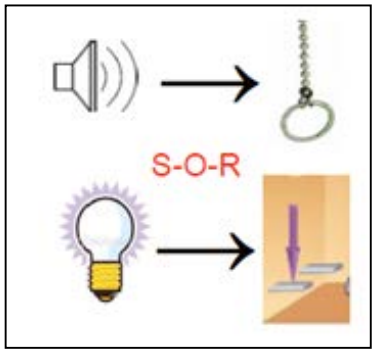




Motivation

wanting





Emotion or affect

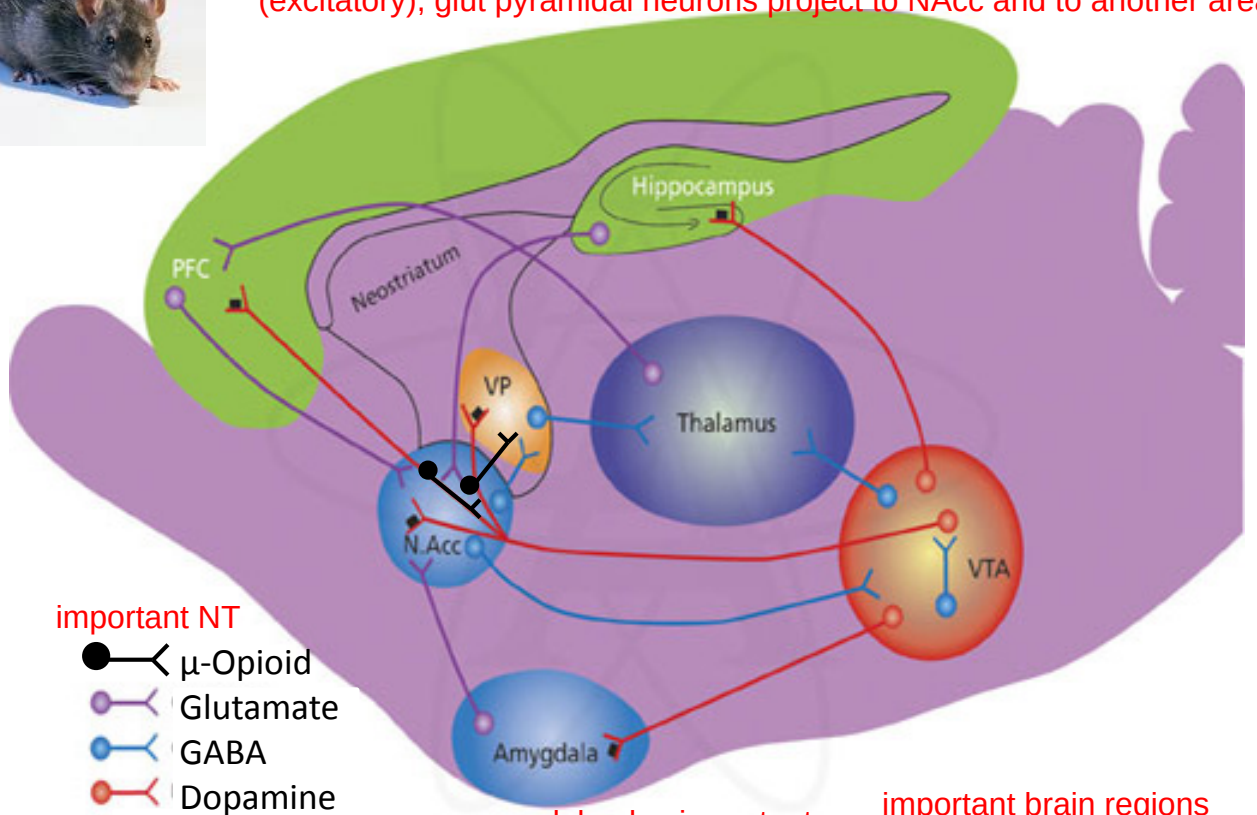
liking

psychiatrix disorders involve pathology with the reard system. depression; reduced interest in everyday events. no more motivation for college, work, socialization
=> significant motivational reduction.
but when put in situation, like going to social event, then emotional response is normal:
motivation affected, but likinf unaffected

Berridge & Robinson (2003) TINS 26: 507

Brain regions and neurotransmitters for processing rewarding stimuli

important structures: VTA communicates via dopamine system to the NAcc
Ventral pallidium (=: VP) receives from VTA and NAcc. it is inhibitory(GABA)(?)
PFC: goal directed behaviour no longer possible when inactivated. uses primarily glutamate (excitatory), glut pyramidal neurons project to NAcc and to another area (next slide)

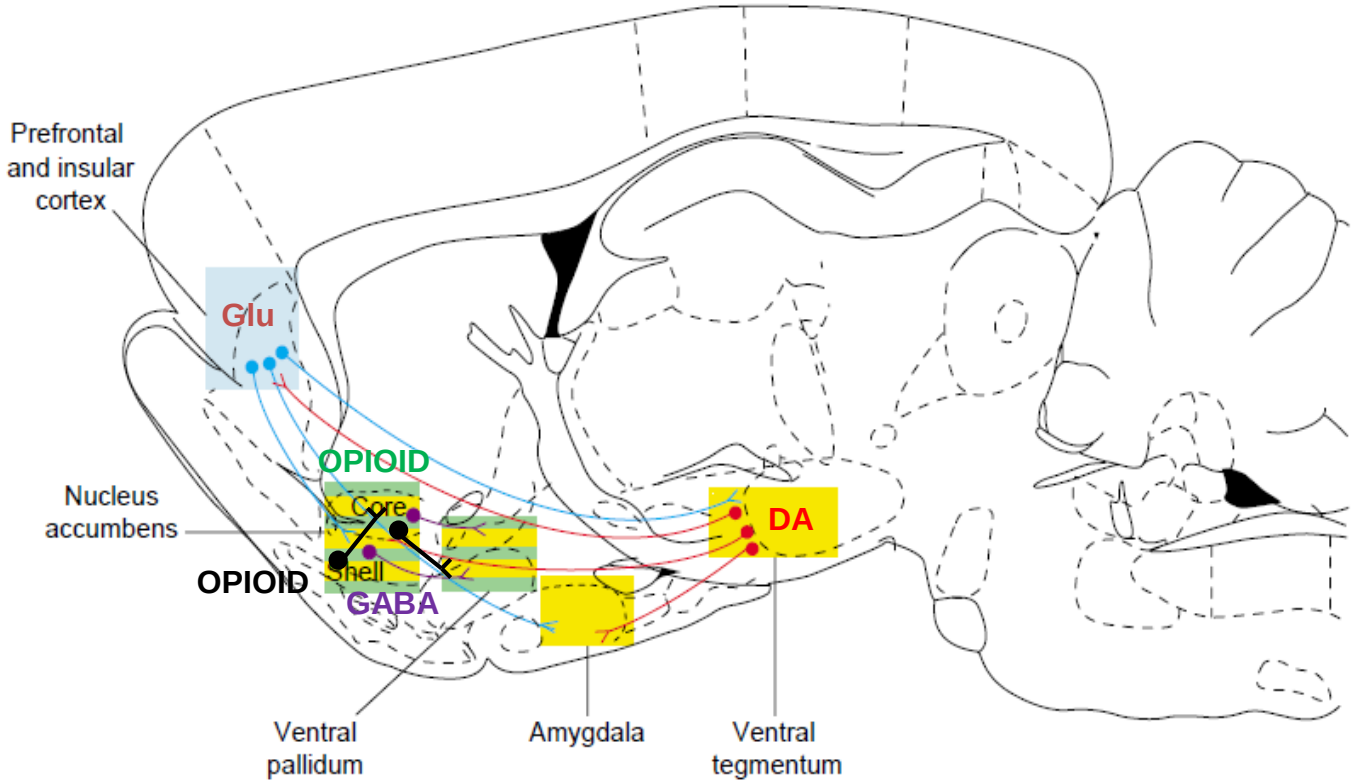


important NT
- μ-Opioid
- Glutamate
- GABA
- Dopamine

amygdala also important, but omitted due to time reasons

important brain regions
VTA, Ventral tegmental area
N Acc, Nucleus accumbens
VP, Ventral pallidum
PFC, Prefrontal cortex

Brain substrates of the different components of reward



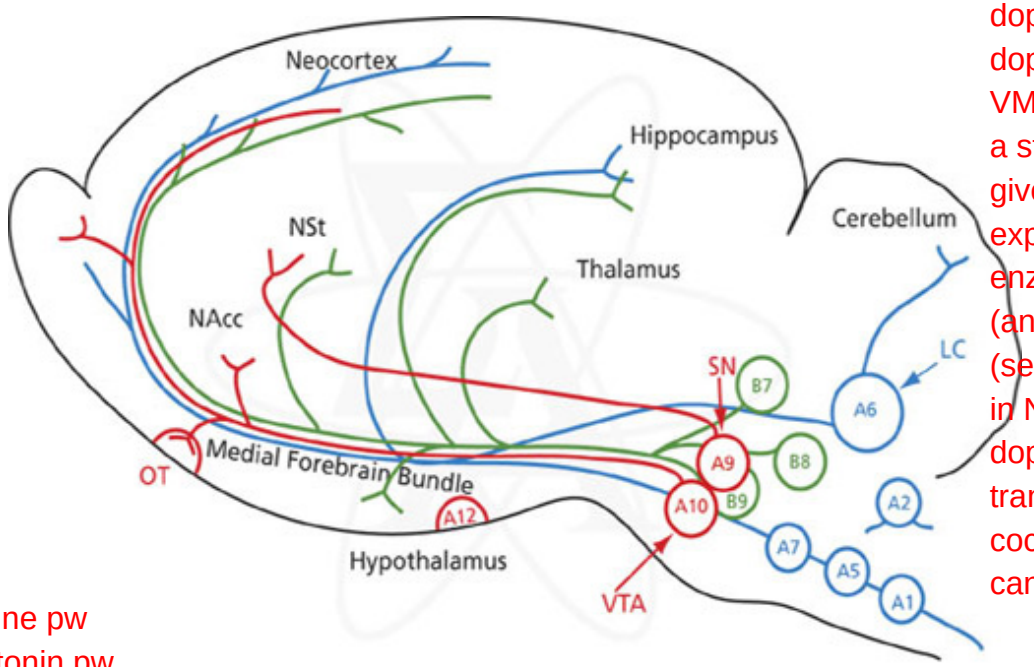
Response-Goal/Outcome

Emotion Reward Liking

CS-US Learning Motivation Reward Wanting

Berridge & Robinson (2003) TINS 26: 507

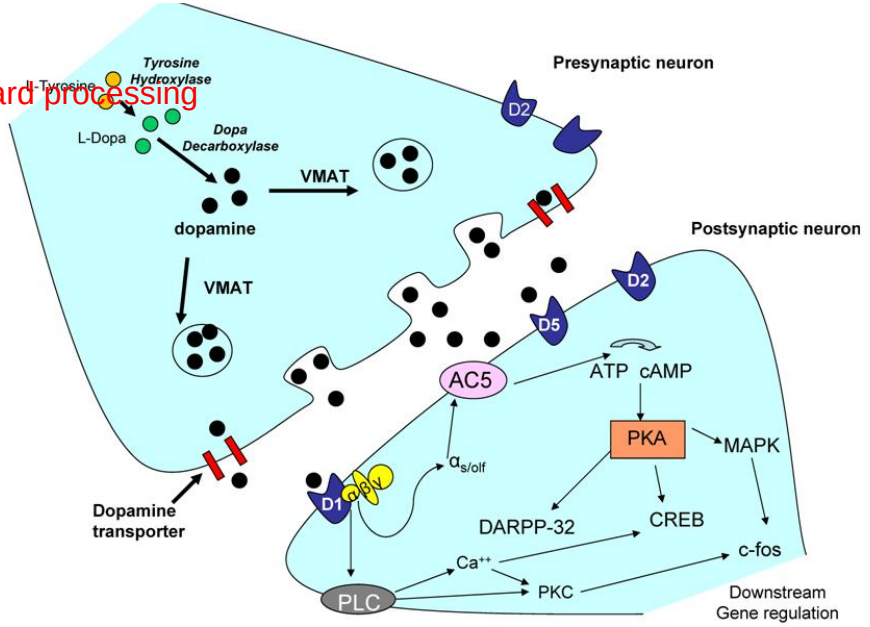
Dopamine neuron cell bodies, forebrain projections and synaptic signalling



dopamine neurons project on NAcc, PFC etc.
dopmaine synthesized in presyn, then transported in VMAT to the presyn membrane. now dopamine has a starting point in tyrosine + tyrosine hydroxylase gives L-DOPA. only occurs if the neurons are able to express the enzyme. the presence of this spec enzyme is almost exclusive to dopamine neurons (and to noradrenaline neurons). a second enzyme (see below) makes dopamine.
in NAcc, D1/2 are the receptors. any non-bound dopamine neurons are bound to dopamine transporter which is reuptook into the presyn axon.
cocaine: blocks dopamine transporter, such that it cannot be retaken up anymore.

red: dopamine pw
green: serotonin pw
blue: noradrenaline pw
A9: substantia nigra - control of MS
A10: ventral tagmental area(?) - main region for regulation of reward processing

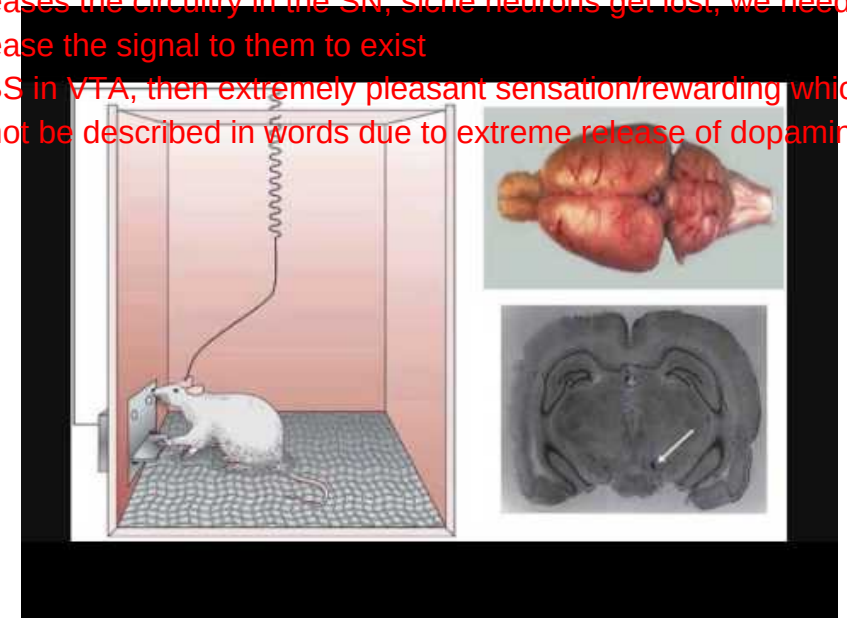
L-DOPA = Dihydroxyphenylalanine
VMAT = Vesicular monoamine transporter
AC5 Adenylate cyclase 5
PLC = Phospholipase C
DARPP-32 = Dopamine and cyclic AMP-regulated phosphoprotein



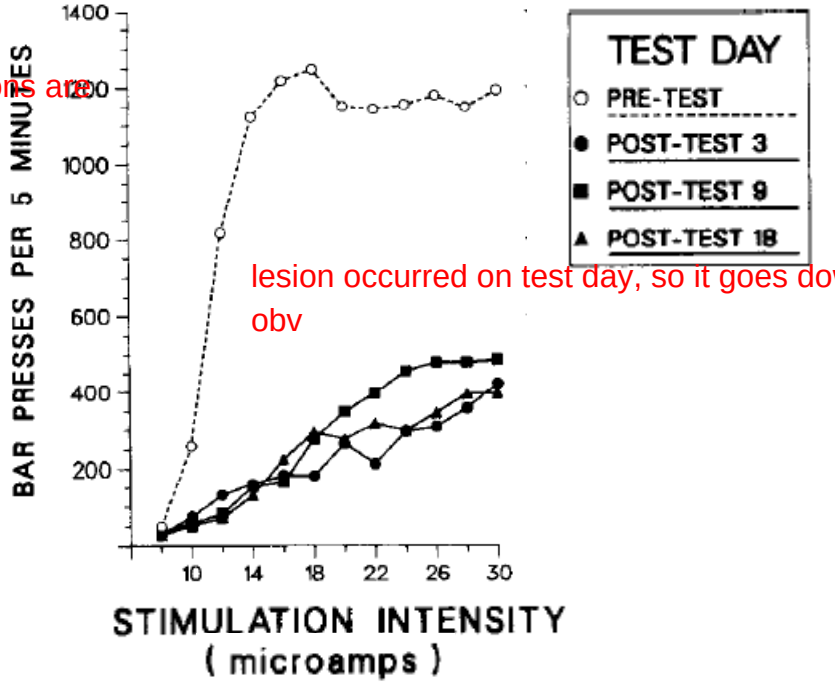
Dopamine release from ventral tegmental area regulates goal-directed behaviour: Operant intra-cranial self-stimulation

VTA := ventral tagmental area

PD: DBS best treatment, targets the substantia nigra where dopa neurons are, increases the circuitry in the SN, sicne neurons get lost, we need to increase the signal to them to exist
if DBS in VTA, then extremely pleasant sensation/rewarding which cannot be described in words due to extreme release of dopamine



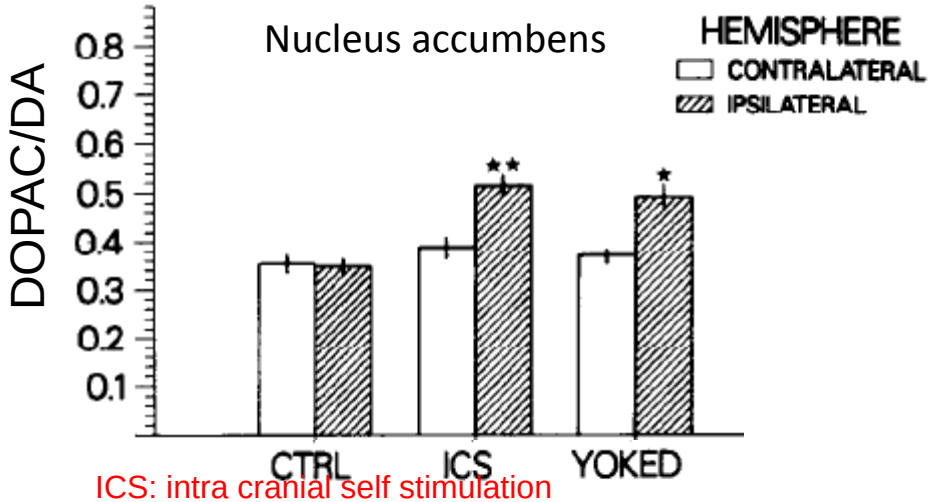
VTA DA lesions



lesion occurred on test day, so it goes down obv

↑DA Rewarding
↑ DA Motivating
↑ DA promotes Learning

specifically, the learning of pressing the lever to get rewarded



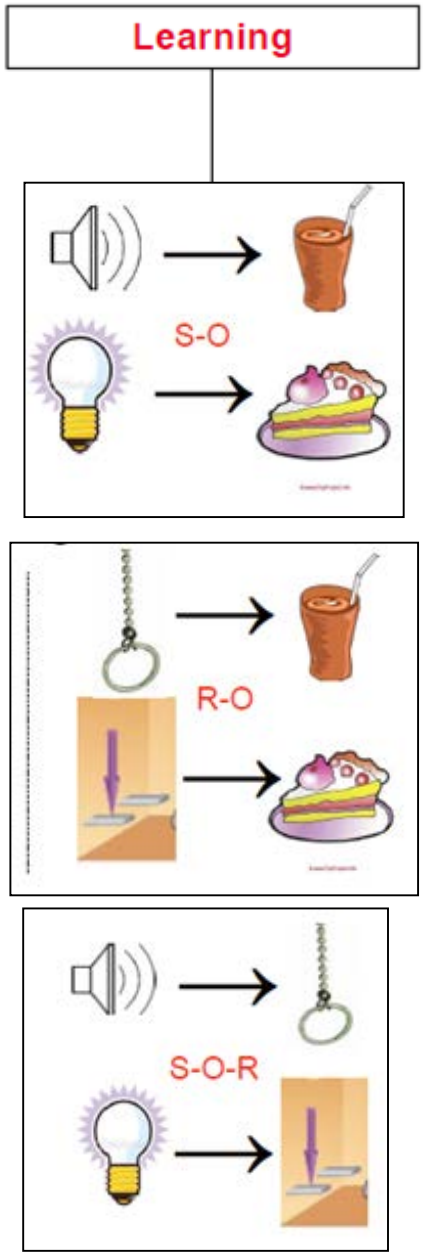
DOPAC = Dihydroxyphenylacetic acid

ICS: intra cranial self stimulation

Psychological components of reward e.g. Food and feeding

(basically ignored slide)

Major categories



Berridge & Robinson (2003) TINS 26: 507

Classical conditioning models: Rescorla-Wagner "surprise" model

$\Delta V = \alpha(\lambda - V)$

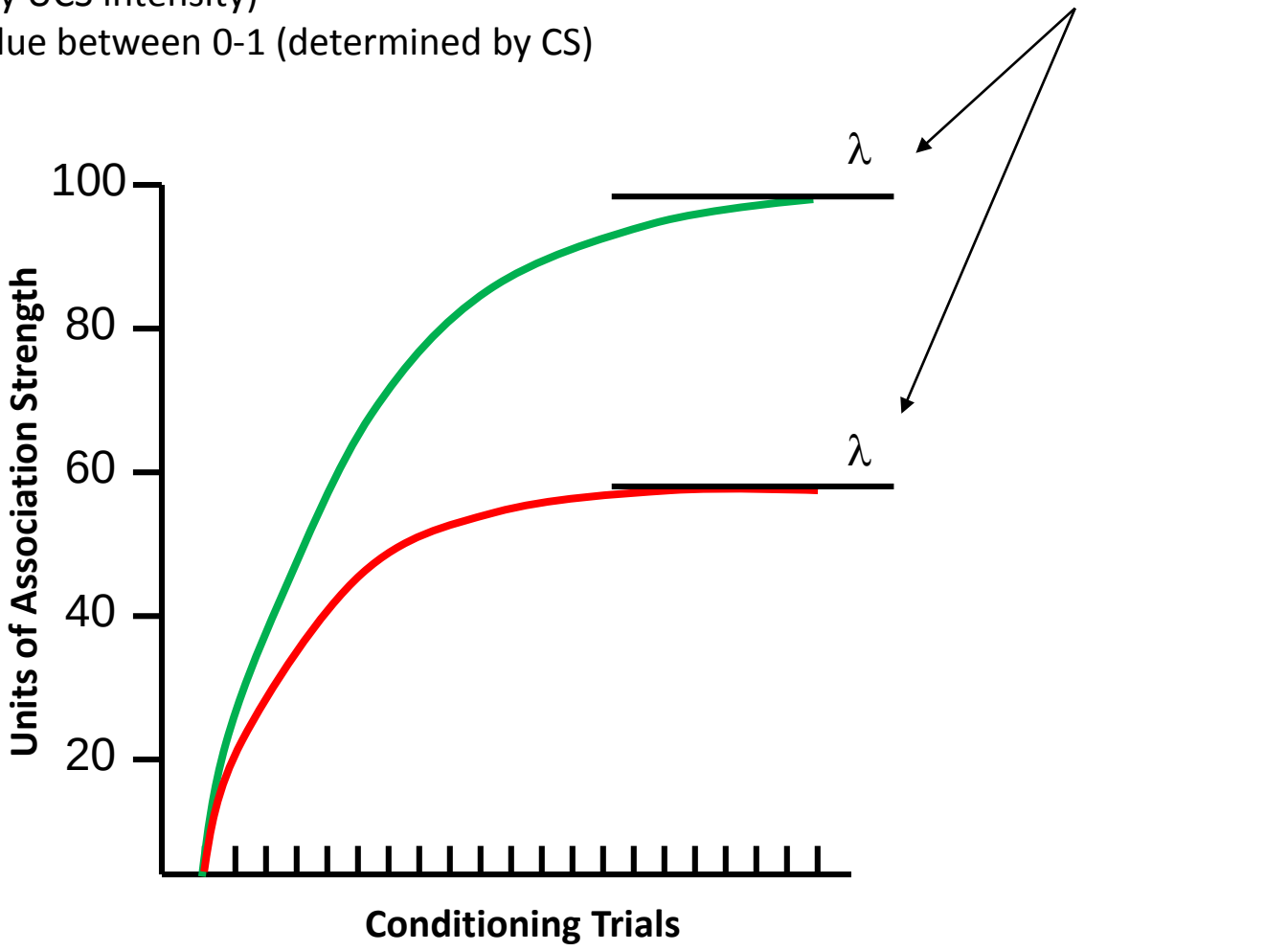
V, strength of CS-UCS association

ΔV, change in strength for any trial

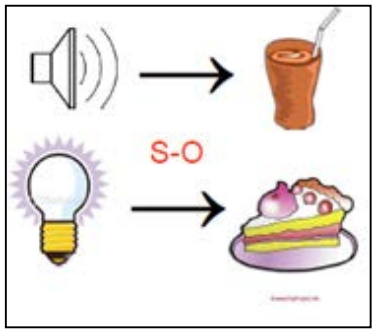
λ (lambda), maximum CS-UCS association strength (determined by UCS intensity)

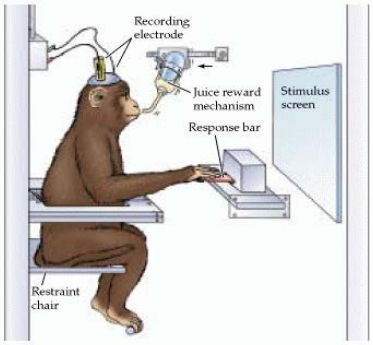
α, constant value between 0-1 (determined by CS)

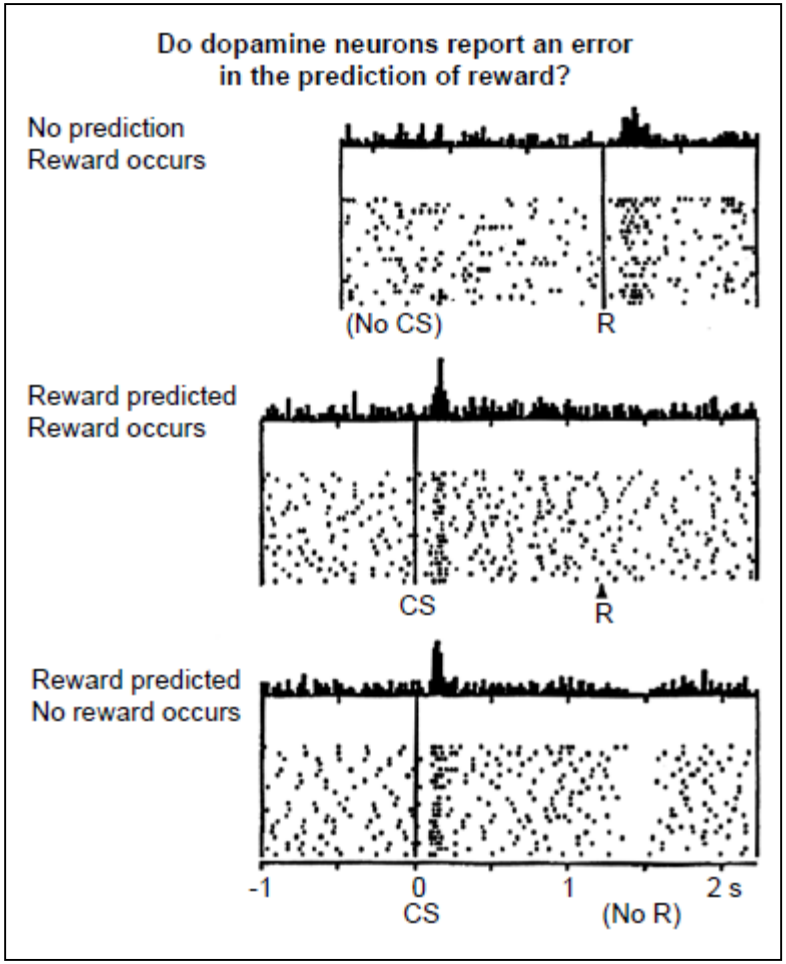
The UCS is completely predicted by the CS

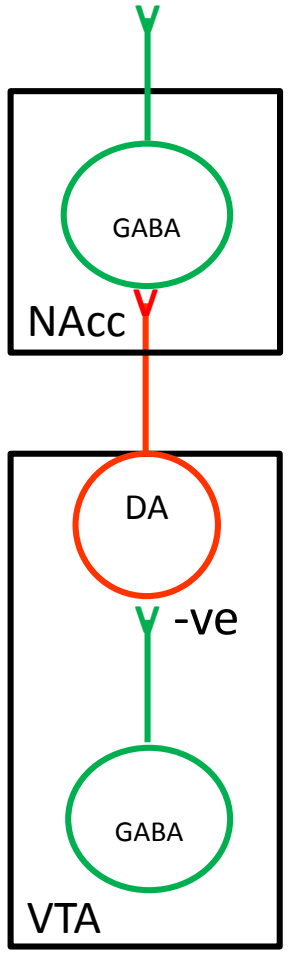


VTA-nucleus accumbens dopamine neurons: a neural substrate for CS-Reward Conditioning
Rescorla-Wagner surprise model / Reward prediction error







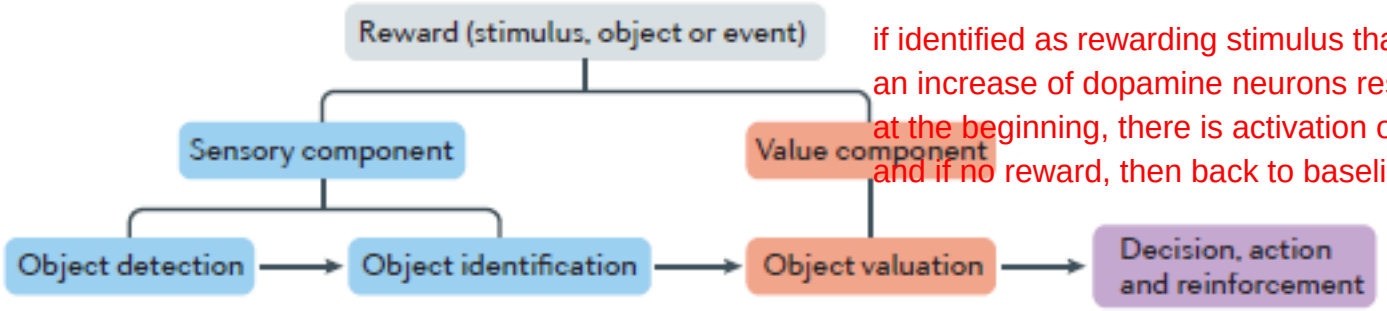


1. No CS-UCS conditioning: Reward unexpected and dopamine neuron activated by Reward
2. After CS-UCS conditioning: Dopamine neuron activated by CS; Reward is expected and dopamine neuron is not activated (remains at baseline)
3. CS-UCS extinction: Dopamine neuron activated by CS; Reward is expected but is not delivered and dopamine neuron reduces activity from baseline

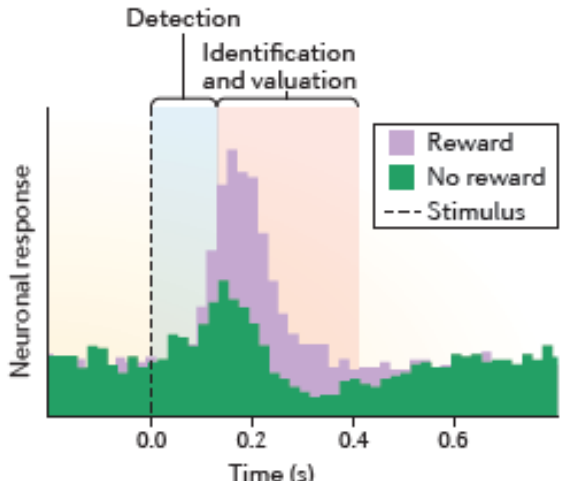
not getting a reward and feeling disappoint reduces activity and it feels unpleasant

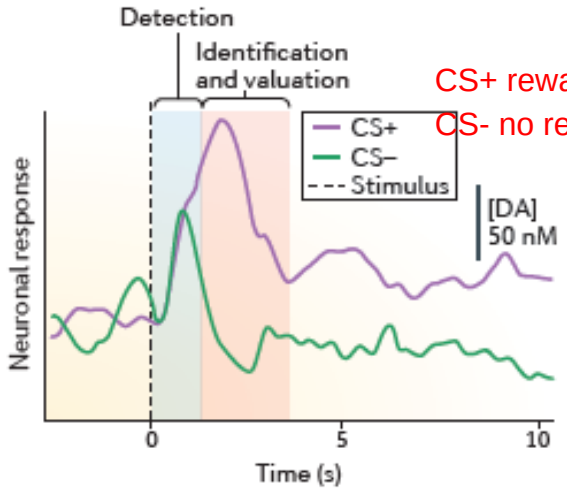
Schultz et al (1997) Nature 275: 1593

Dopamine reward prediction-error signalling: a two-component response

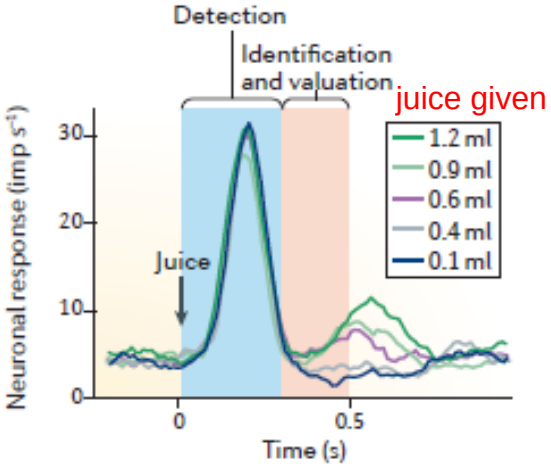


if identified as rewarding stimulus than there is even an increase of dopamine neurons response
at the beginning, there is activation of them anyway, and if no reward, then back to baseline

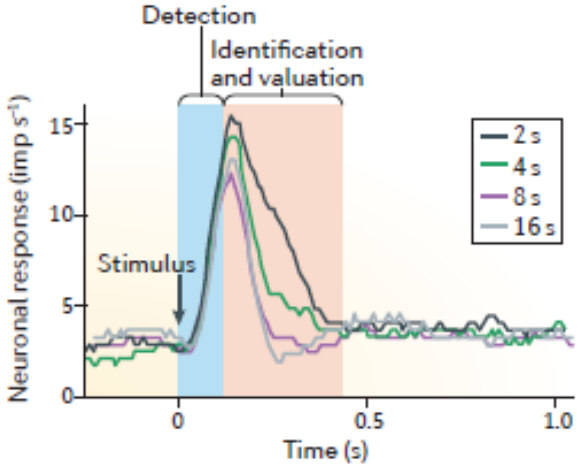




CS+ reward
CS- no reward

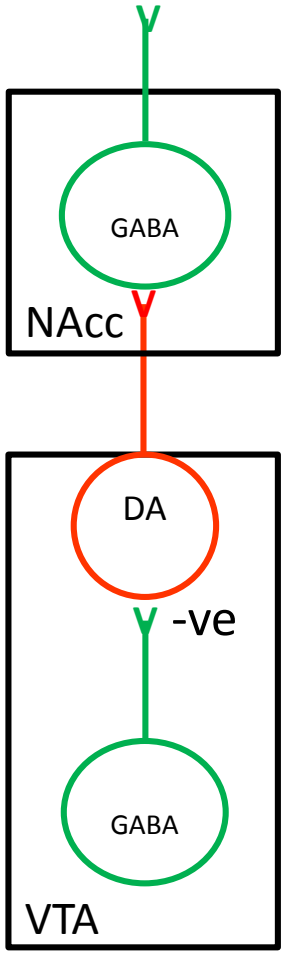


juice given



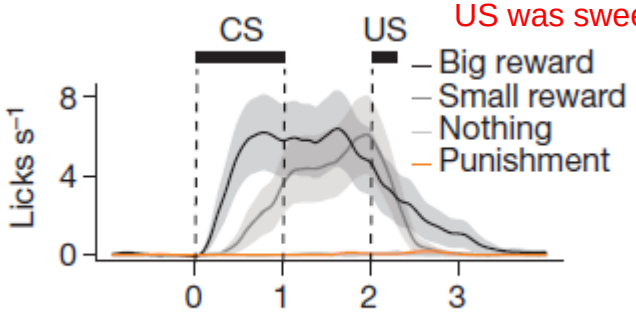
Schultz et al (2016) Nature Rev Neurosci 17: 183

Neuron-specific signalling of reward in the mouse ventral tegmental area: a mechanism for Reward prediction error



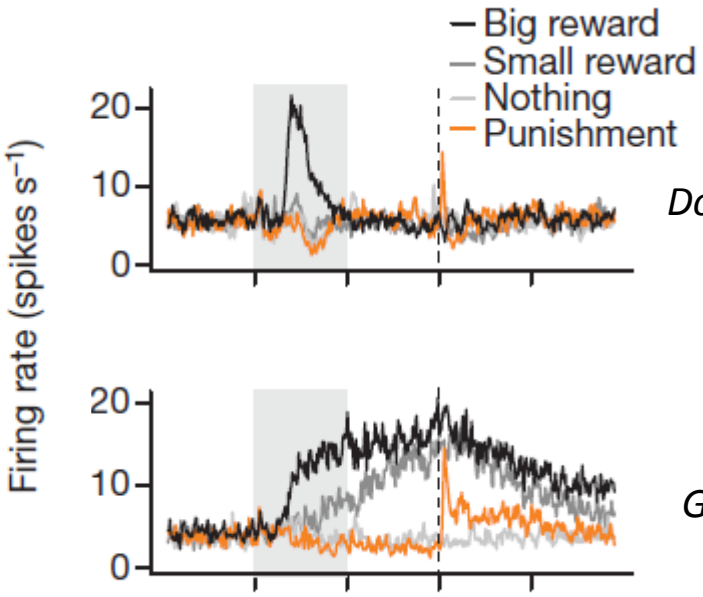
CS: *Odour – Outcome conditioning task*

US was sweet tasting solution



CS caused licking behaviour

= Air Puff



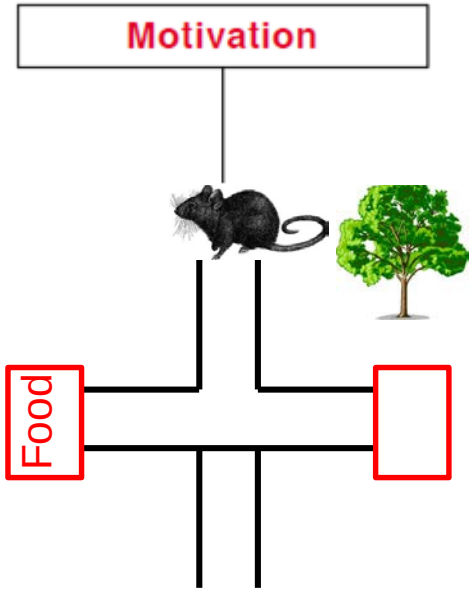
Dopaminergic neurons

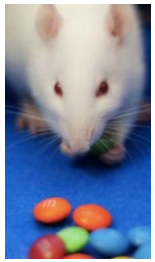
GABAergic neurons

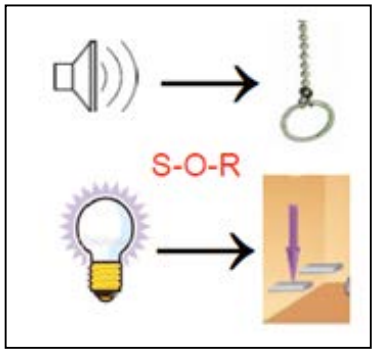
Cohen et al. (2012) Nature 482: 85

Psychological components of reward e.g. Food and feeding

Major categories





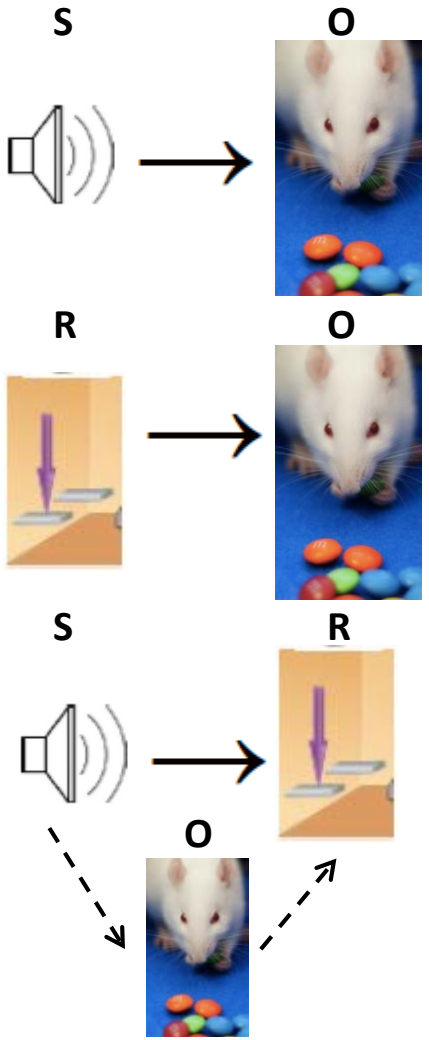


Berridge & Robinson (2003) TINS 26: 507

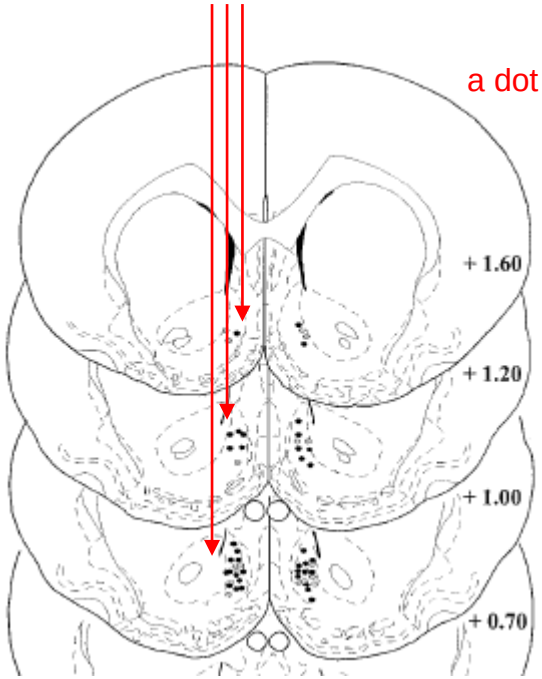
Incentive motivation for Reward (Wanting) is increased by Dopamine: Using Pavlovian-to-Instrumental transfer to measure motivation

amphi: more dopamine release, here injection in NAcc

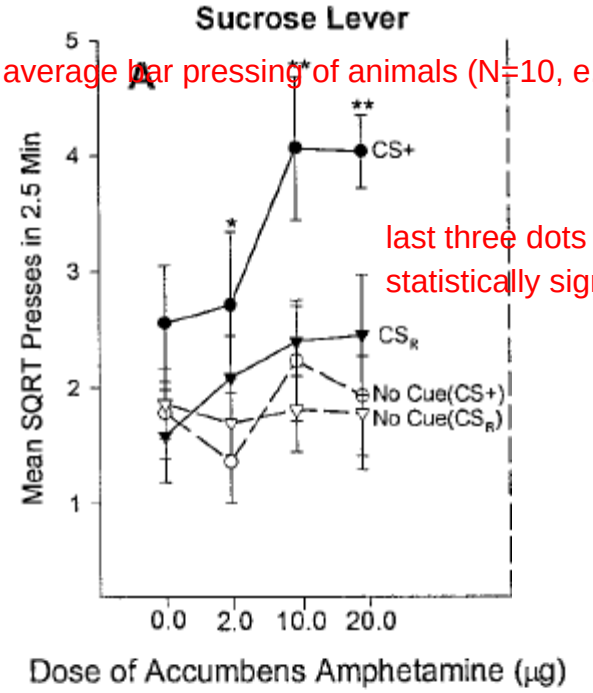
controls: water solution simply.
pavlivoian-to-instrumental transfer occurs also without amphis.



Amphetamine into Nucleus accumbens:
Dopamine releaser at D1 and D2 receptors



a dot is the average bar pressing of animals (N=10, e.g.)



last three dots are statistically signif.

○ Period before CS switched ON

● Tone CS associated with sucrose

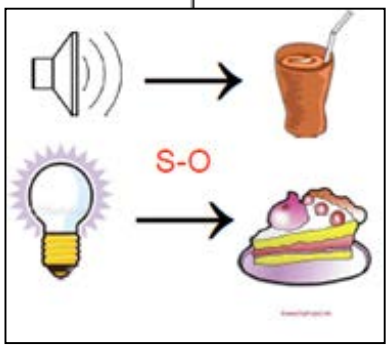
▼ Random CS NOT associated with sucrose

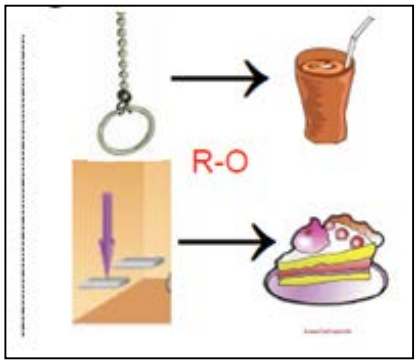
Wyvell & Berridge (2000) J Neurosci 20: 8122

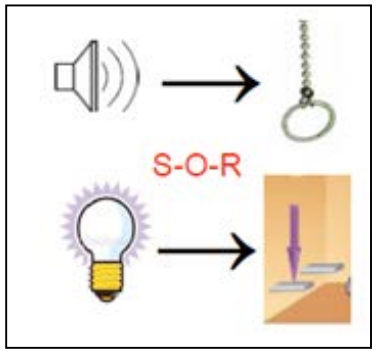
Psychological components of reward e.g. Food and feeding

Major categories

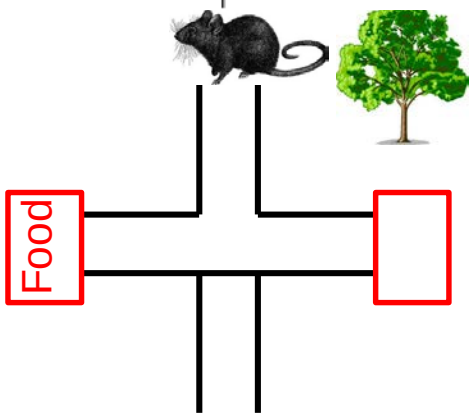
Learning

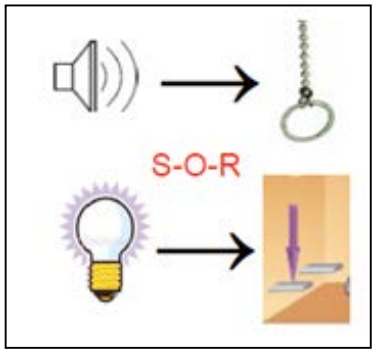






Motivation

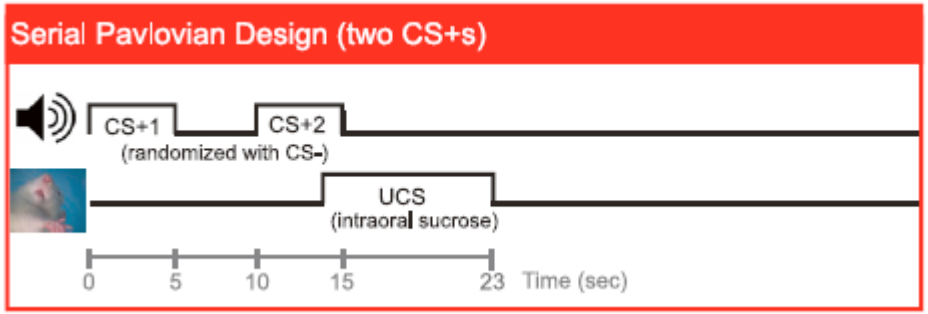


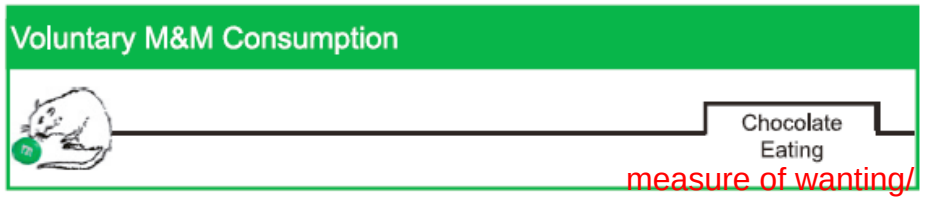


Emotion or affect

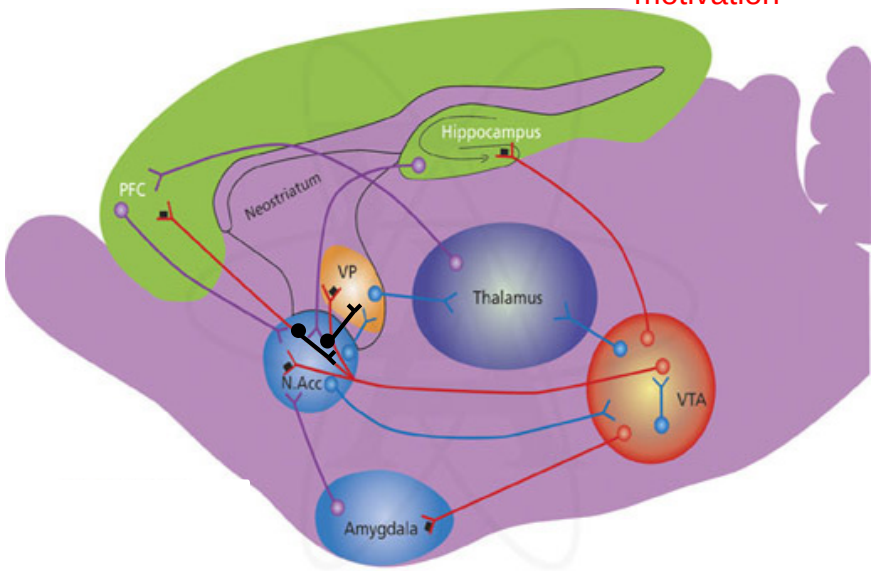
Berridge & Robinson (2003) TINS 26: 507

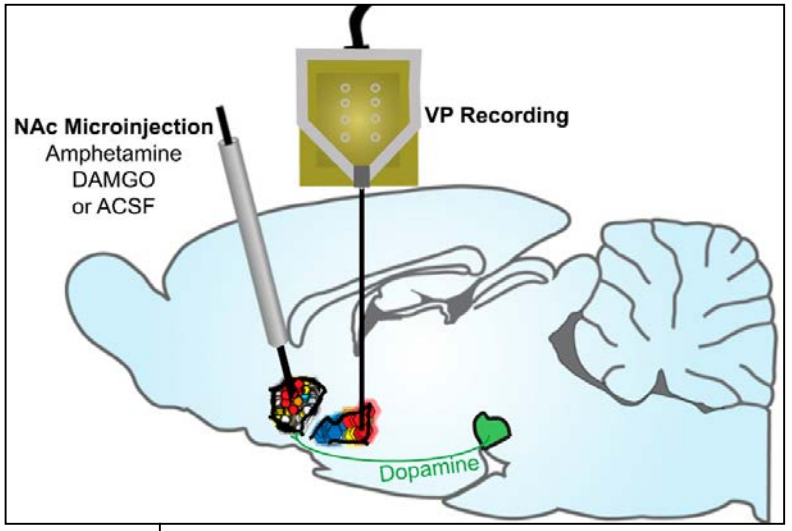
Evidence that learning (CS-UCS), reward motivation (wanting) and emotion (liking) have different neurobiological substrates





measure of wanting/ motivation





Nucleus accumbens:

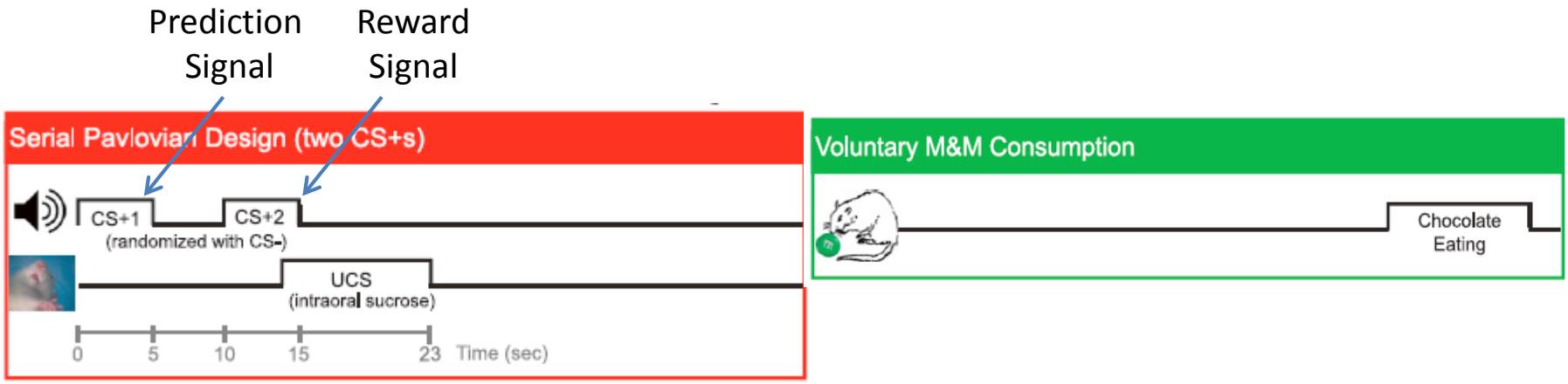
- Dopamine-stimulating drug (Amphetamine)
- Mu Opioid agonist drug (DAMGO)

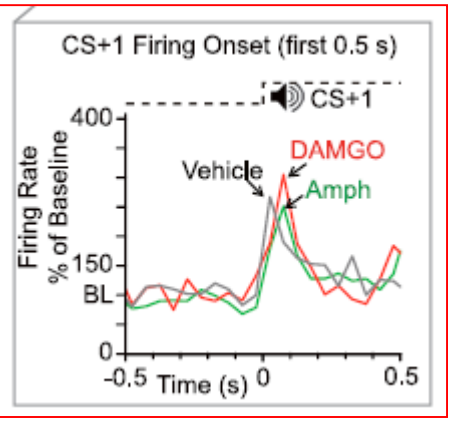
Ventral Pallidum:

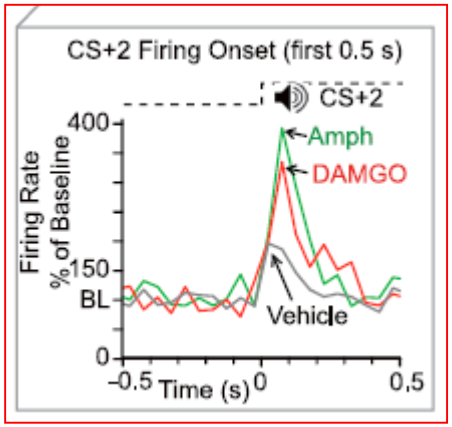
- Single unit electrophysiological recording in Ventral Pallidum

Smith et al. (2011) PNAS 108: E255

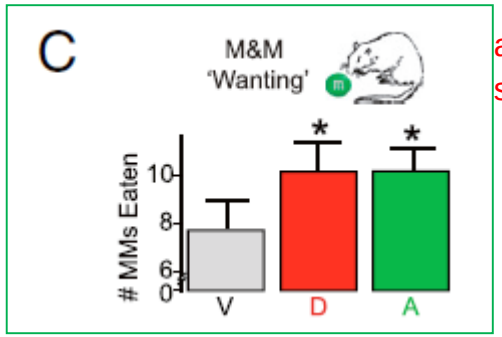
Increasing dopamine or opioid neurotransmission in nucleus accumbens: No effect on reward prediction signal and increased reward motivation signal







similar response as in vehicle cond
no further increase in VTA when CS1 presented



they eat more m&ms

- <u>Vehicle-NAcc conditions</u>:

CS+1 induces large increase in VP neuron firing
CS+2 induces small increase in VP neuron firing
Low level of Reward wanting = Eating

- <u>High Dopamine-NAcc neurotransmission</u>:

CS+1 No further increase in VP neuron firing
CS+2 induces large increase in VP neuron firing
Increased Reward wanting = Eating

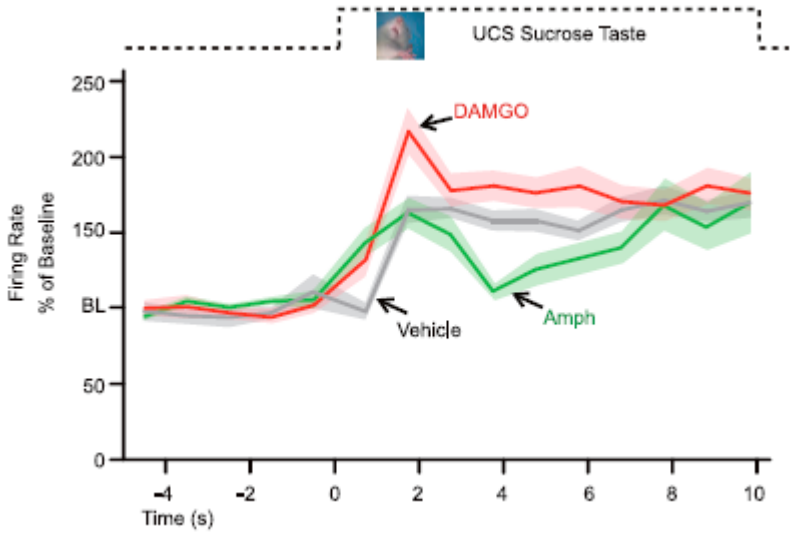
artificial increase in CS2 even though it was predicted by CS1, system taken out of equilibirum

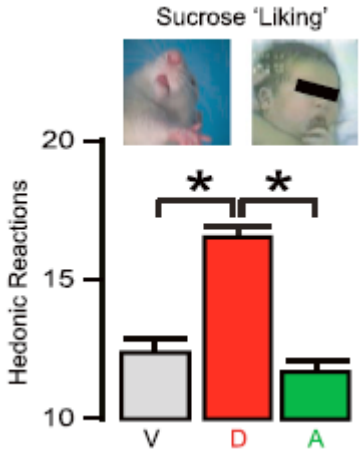
- <u>High Opioid-NAcc neurotransmission</u>:

CS+1 No further increase in VP neuron firing
CS+2 induces large increase in VP neuron firing
Increased Reward wanting = Eating

Smith et al. (2011) PNAS 108: E255

Increasing dopamine or opioid neurotransmission in nucleus accumbens: Opioid-specific effect on reward liking





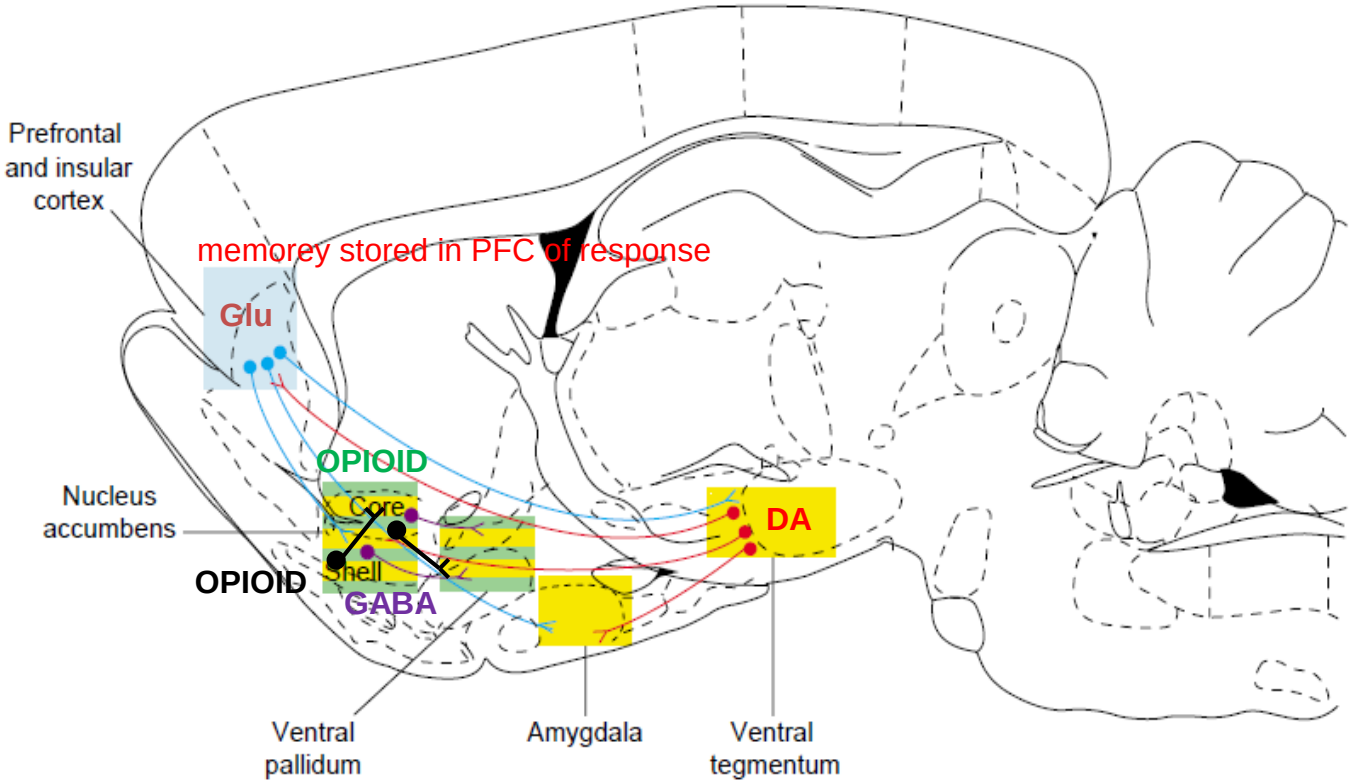
• <u>Vehicle-NAcc conditions</u>:
UCS Sucrose induces slow increase in VP firing
Low level of orofacial liking reactions

• <u>High Dopamine-NAcc neurotransmission</u>:
No increase in VP firing to Sucrose
No increase in orofacial liking reactions

• <u>High Opioid-NAcc neurotransmission</u>:
Increase in VP firing to Sucrose
Increased orofacial liking reactions

Smith et al. (2011) PNAS 108: E255

Brain substrates for the different components of reward



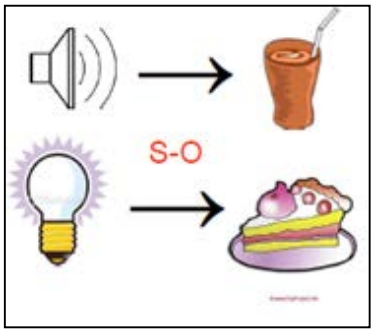
Response-Goal/Outcome

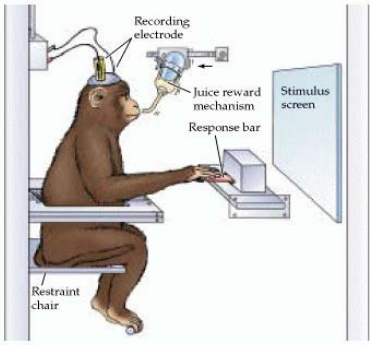
Emotion Reward Liking

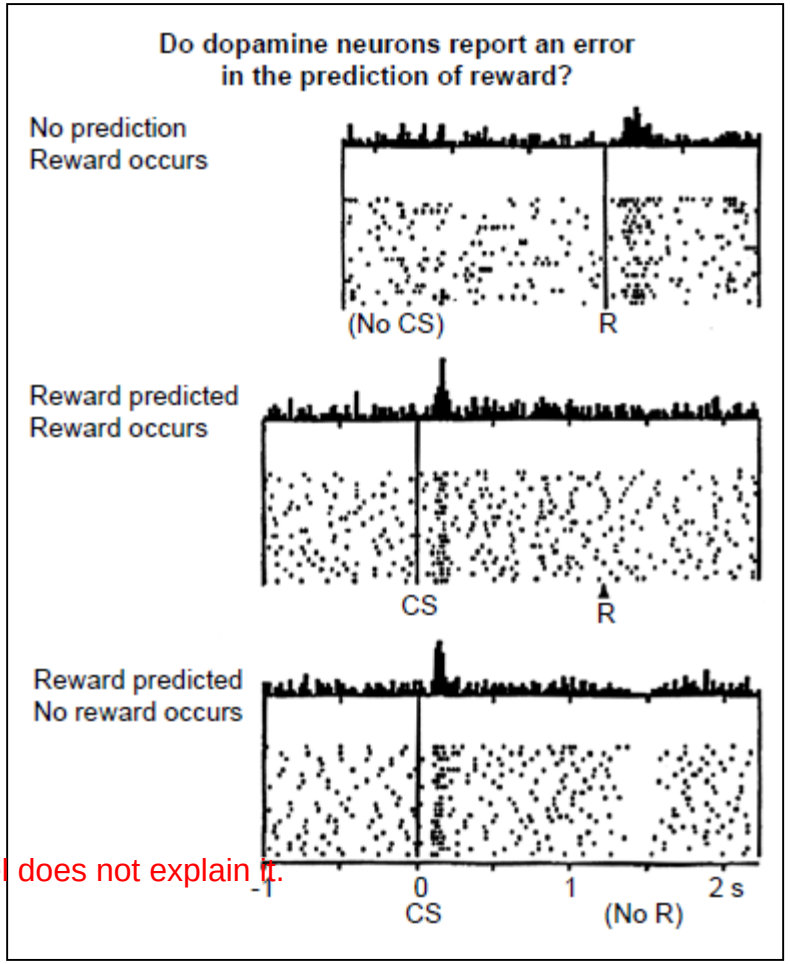
CS-US Learning Motivation Reward Wanting

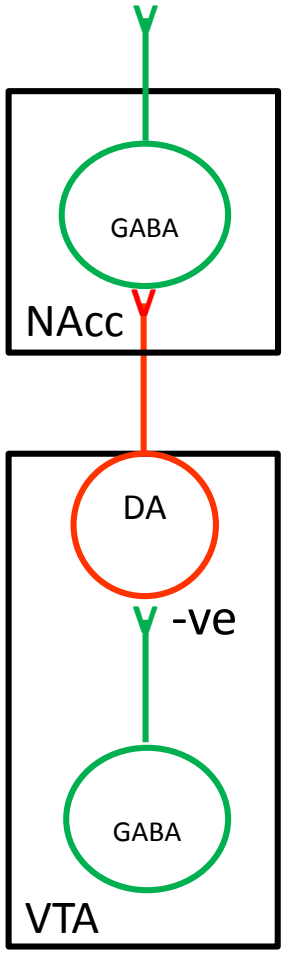
Berridge & Robinson (2003) TINS 26: 507

VTA-nucleus accumbens dopamine neurons: a neural substrate for CS-Reward Conditioning
Rescorla-Wagner surprise model / Reward prediction error









why is there response to CS - this model does not explain it.
answer: next slide

1. No CS-UCS conditioning: Reward unexpected and dopamine neuron activated by Reward
2. After CS-UCS conditioning: Dopamine neuron activated by CS; Reward is expected and dopamine neuron is not activated (remains at baseline)
3. CS-UCS extinction: Dopamine neuron activated by CS; Reward is expected but is not delivered and dopamine neuron reduces activity from baseline

Schultz et al (1997) Nature 275: 1593

Is Dopamine signalling past events or predicting future events?

Rescorla-Wagner model: learn the value of previous events

if nothing rewarding happens a the brain monitors the environemnt, dopamine goes down to base levels and responds if there is a stimulus and we get to CS and then to UCS

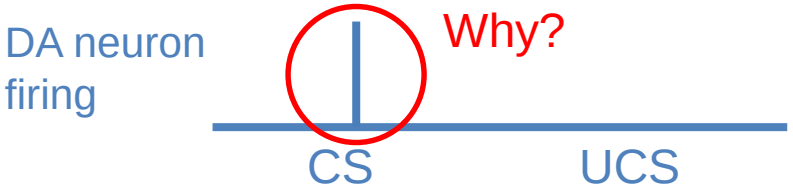
Expected CS-UCS association → Observed **CS-UCS** associations
based on previous CS-UCS pairs

↓

Reward prediction error

Low CS-UCS

High CS-UCS



Temporal Difference model: predict value of the future

Expected future reward → Observed **CS or UCS**
(UCS ..... CS, UCS)

↓

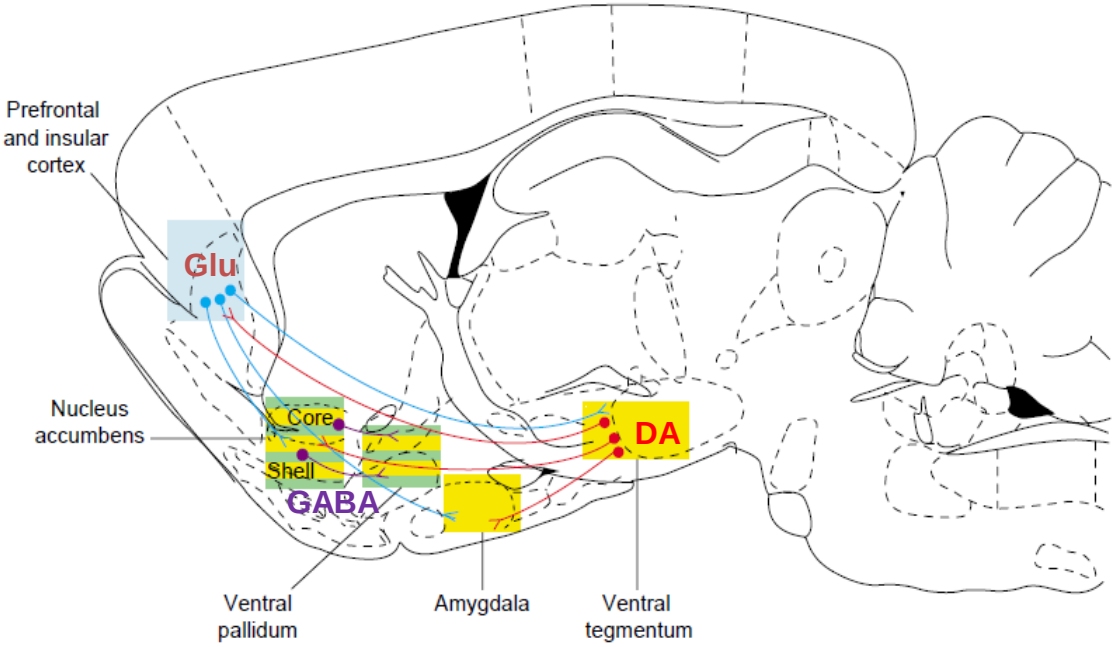
Reward prediction error

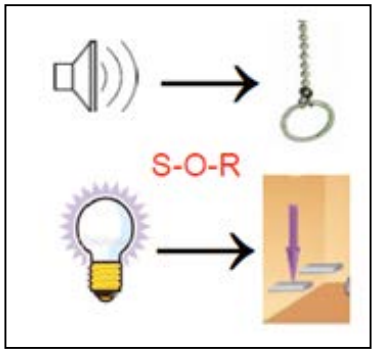
Low CS-UCS

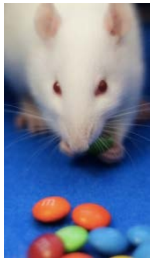
High CS-UCS

Glimcher (2011) PNAS 108: 15647

Temporal Difference model: Behaviour that brings the individual closer to a CS will release dopamine and be reinforced







Behaviour → Expected future reward (UCS ..... CS, UCS) → Observed CS or UCS

↓

Reward prediction error

↓

Dopamine release

↑ (Behaviour)

Glimcher (2011) PNAS 108: 15647

Processing rewarding stimuli

• The psychological components of reward are Learning, Motivation (Wanting) and emotion/affect (Liking)

• Learning involves classical conditioning, instrumental conditioning, and Pavlovian-to-instrumental transfer

• Motivation involves appetitive behaviour (e.g. Approach, Pavlovian-to-instrumental transfer) and consummatory behaviour (e.g. eat)

• Emotion involves enjoying the stimulus

• The brain circuitry of reward includes the ventral tegmental area (Motivation), Nucleus accumbens (Motivation, Emotion), Ventral pallidum (Motivation, Emotion), Amygdala (Motivation), Prefrontal cortex (Learning)

• The VTA dopamine system is a major neurotransmitter in: experiencing rewards as rewarding, learning about rewards, and motivation for reward

• VTA-nucleus accumbens dopamine neurons fire on receiving a reward UCS if unexpected. If expected, the neurons fire to the predictive CS and not to the UCS. This reward prediction error corresponds to the Rescorla-Wagner model of classical conditioning: no further learning if the UCS is completely expected

• GABA neurons in the VTA respond to the CS and could be responsible for inhibiting dopamine neuron response to the UCS

• Stimulating dopamine receptors in nucleus accumbens increases reward motivation/wanting

• Stimulating dopamine receptors in nucleus accumbens increases firing of ventral pallidum neurons to a CS that predicts reward and increases eating. However, it does not increase firing of ventral pallidum neurons to sucrose UCS and does not increase sucrose liking

• Stimulating opioid receptors in nucleus accumbens increases firing of ventral pallidum neurons to a CS that predicts reward and increases eating. It also increases firing of ventral pallidum neurons to sucrose UCS and increases sucrose liking

• The temporal difference model of dopamine signalling explains why the CS that predicts reward increases firing of dopamine neurons: it is because the CS is unexpected. According to this model dopamine is signalling whenever an unexpected CS or UCS reward is encountered in the environment, and thereby brings the animal ever closer to the reward