

The Psychological and neural basis of adaptive and maladaptive motivation

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Course Overview

- **What are the neural bases of motivation, emotion and learning?**
- **An introduction to the methods of behavioural neuroscience.**
- **The use of converging evidence across species and techniques.**
- **Relating brain mechanisms, including chemical neurotransmitter systems, to psychological constructs including motivation & learning**
- **Evaluate putative animal models of obesity and cognitive impairment**
- **Focus on incentive learning, Pavlovian and instrumental associations and their interaction in motivation**
- **Evaluate the utility of concepts such as the “limbic system”**

Lecture 1: Drive, incentive and the hypothalamus

Part I

Objectives:

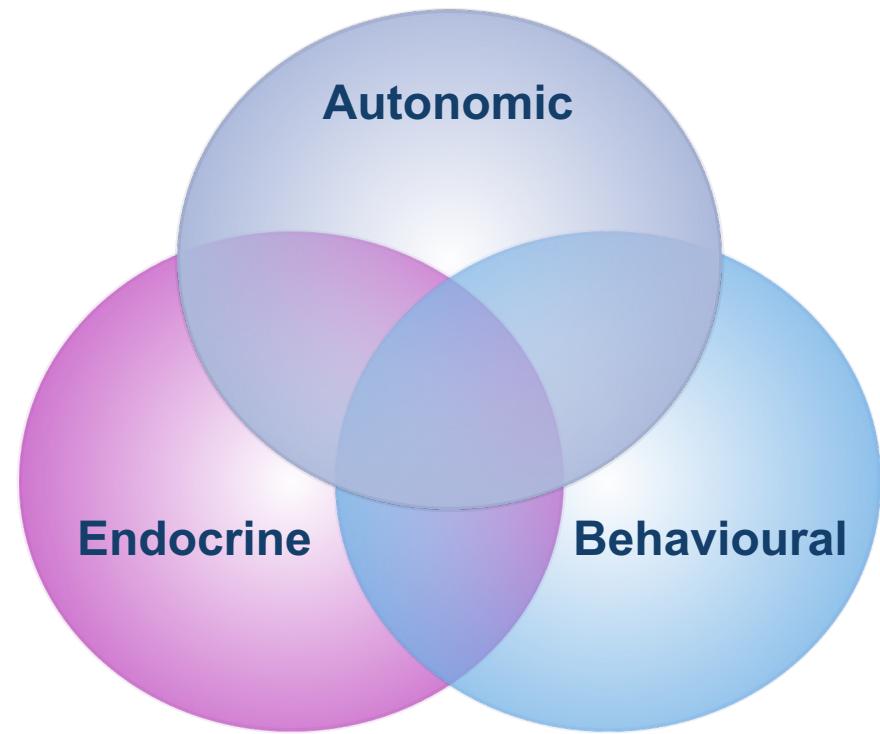
Historical perspective of research into motivation.

- **Different forms of motivation and how they are expressed**
 - e.g. the role of the hypothalamus
- **Reconsider the utility of mapping psychological constructs onto neural structures.**
- **Use of converging approaches/ techniques in behavioural neuroscience, including psychology, physiology, electrophysiology, psychopharmacology etc..**
- **Validity of animal models of human conditions (e.g. obesity)**

Motivation

Motivation: a set of psychological and underlying neural processes that promote biological and behavioural responses necessary for the survival of the organism, aiming either to obtain appetitive stimuli or to avoid aversive stimuli

Impact at **three major levels**

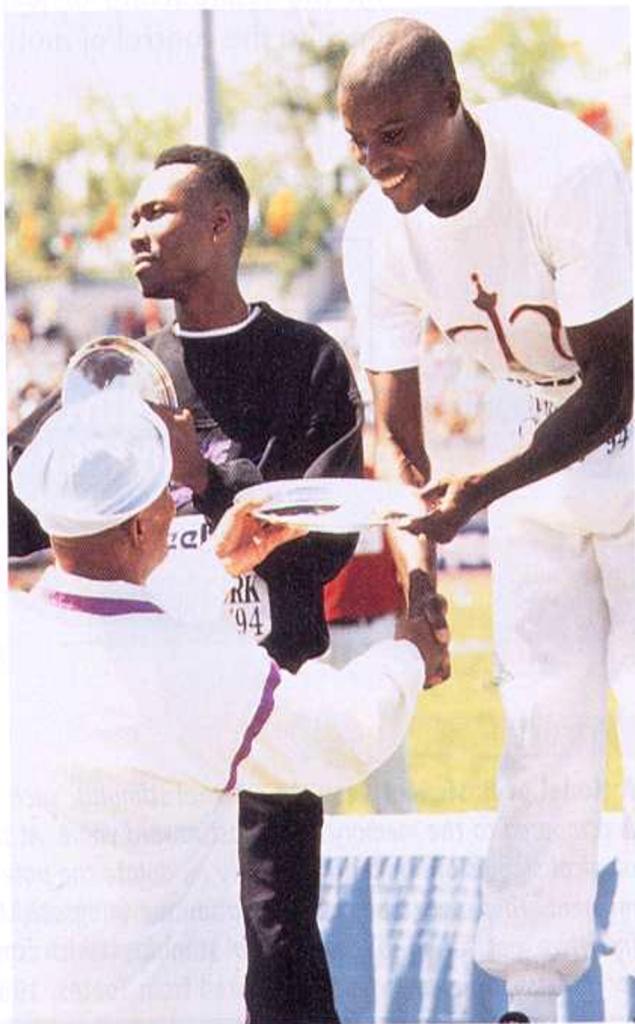
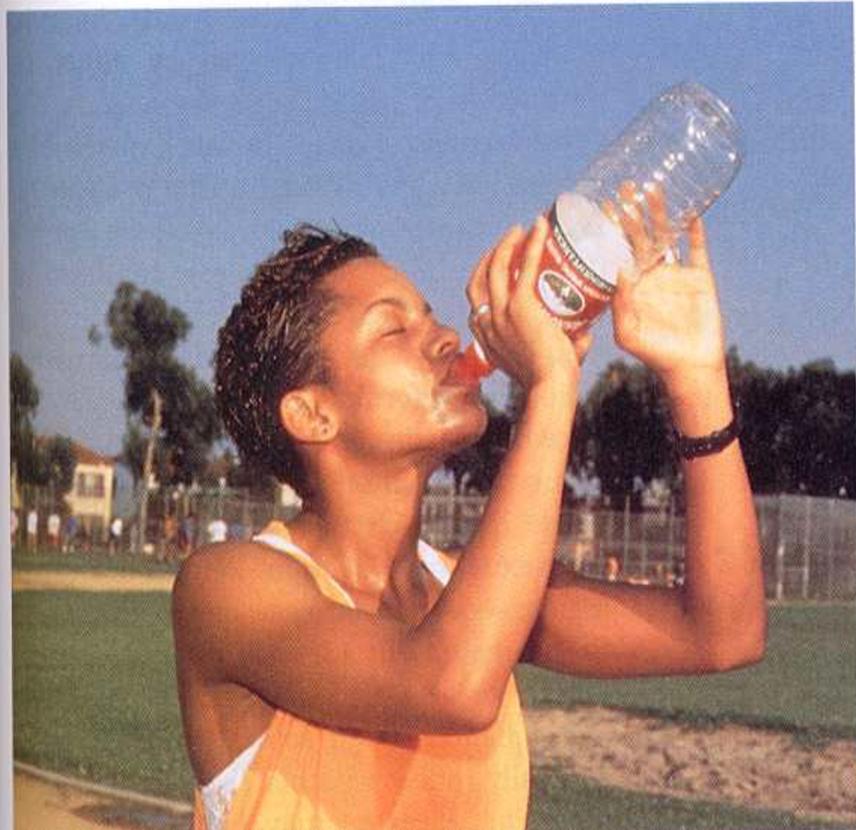


What are the component mechanisms of a particular motivation?
How are the components **coordinated** in order to produce **integrated** behavioural and physiological responses?

The **hypothalamus** may be the organisation and integration centre.

Drives vs incentives

The causes of motivation range from physiological events such as thirst to social aspirations and cultural influences such as those that create the desire to excel.



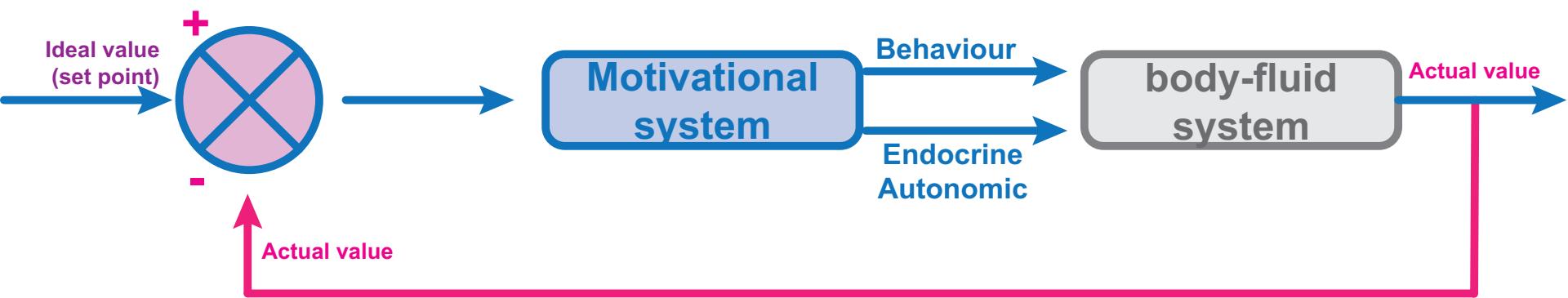
Drives vs incentives: important distinctions

- Motivation can **push** behaviour → **DRIVE**
- Motivation can **pull** behaviour → **INCENTIVE**
- Motivation involves
 - Preparatory responses (anticipatory mechanisms, seeking) → Pavlovian & instrumental mechanisms
 - OR
 - Consummatory responses (taking) → ingestive responses, e.g. eating, drinking, lordosis, mounting

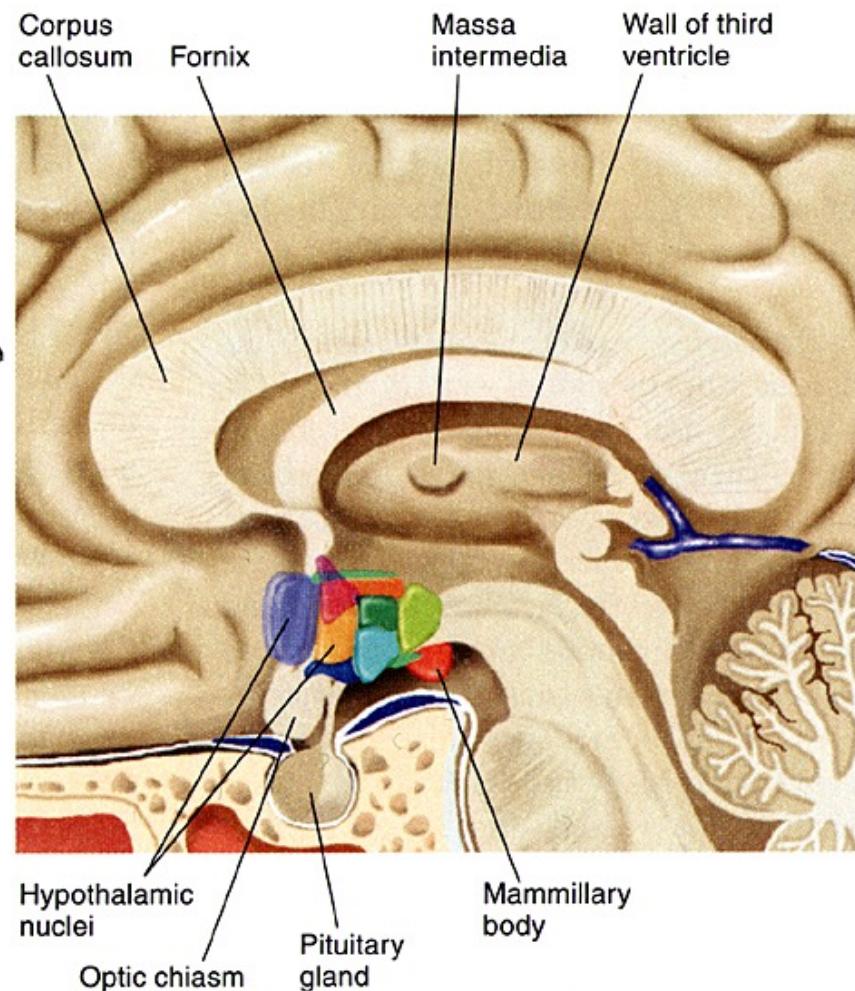
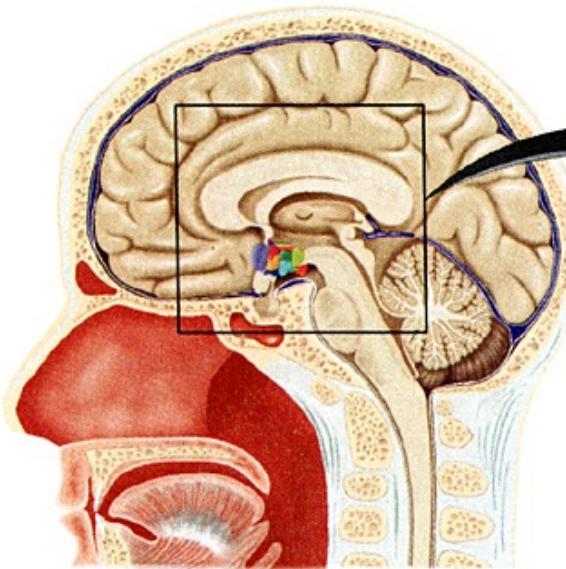
Drive and the hypothalamus

Motivation

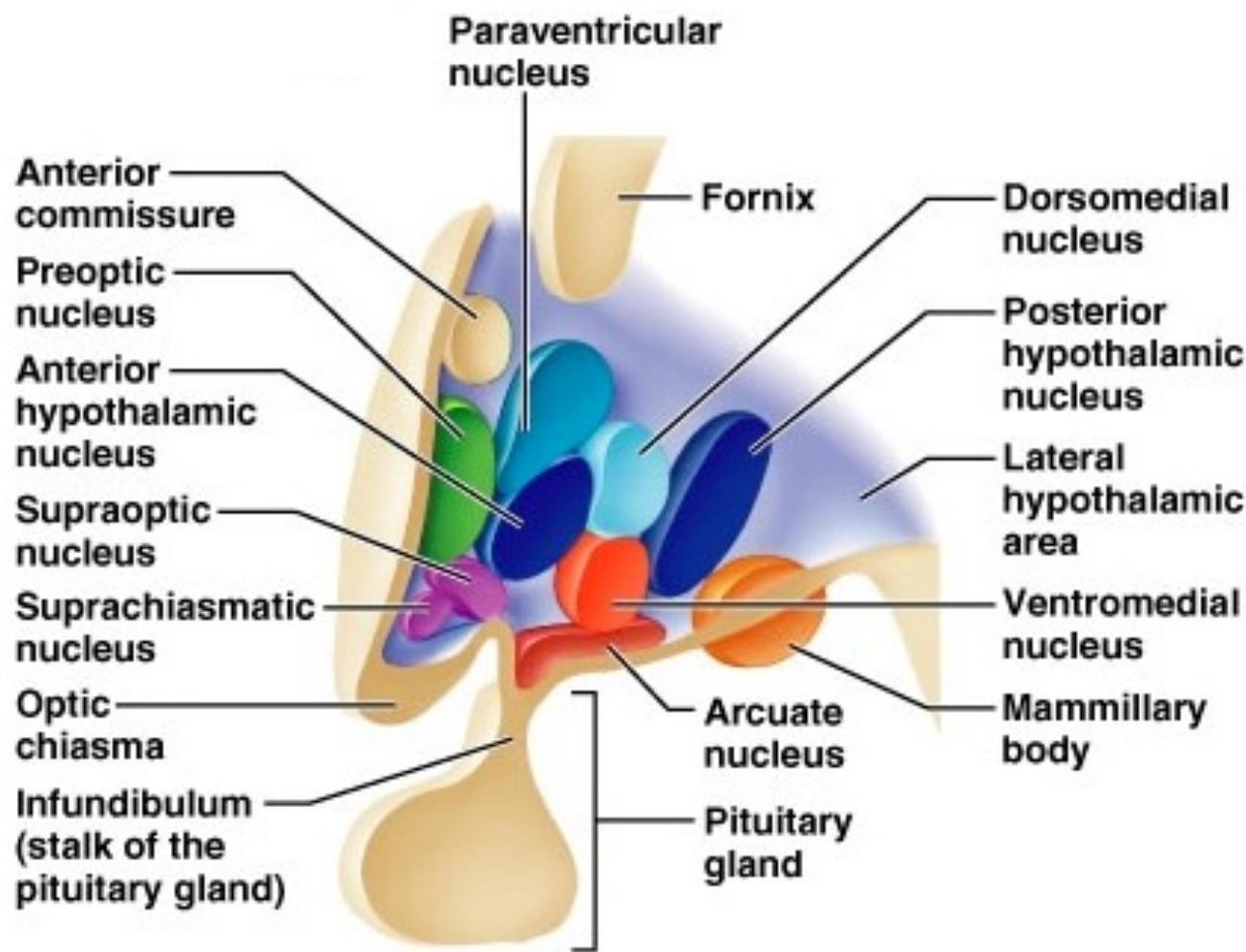
Homeostatic regulation (need, DRIVE reduction in the context of the body fluid system)



The hypothalamus: anatomy



The hypothalamus: anatomy

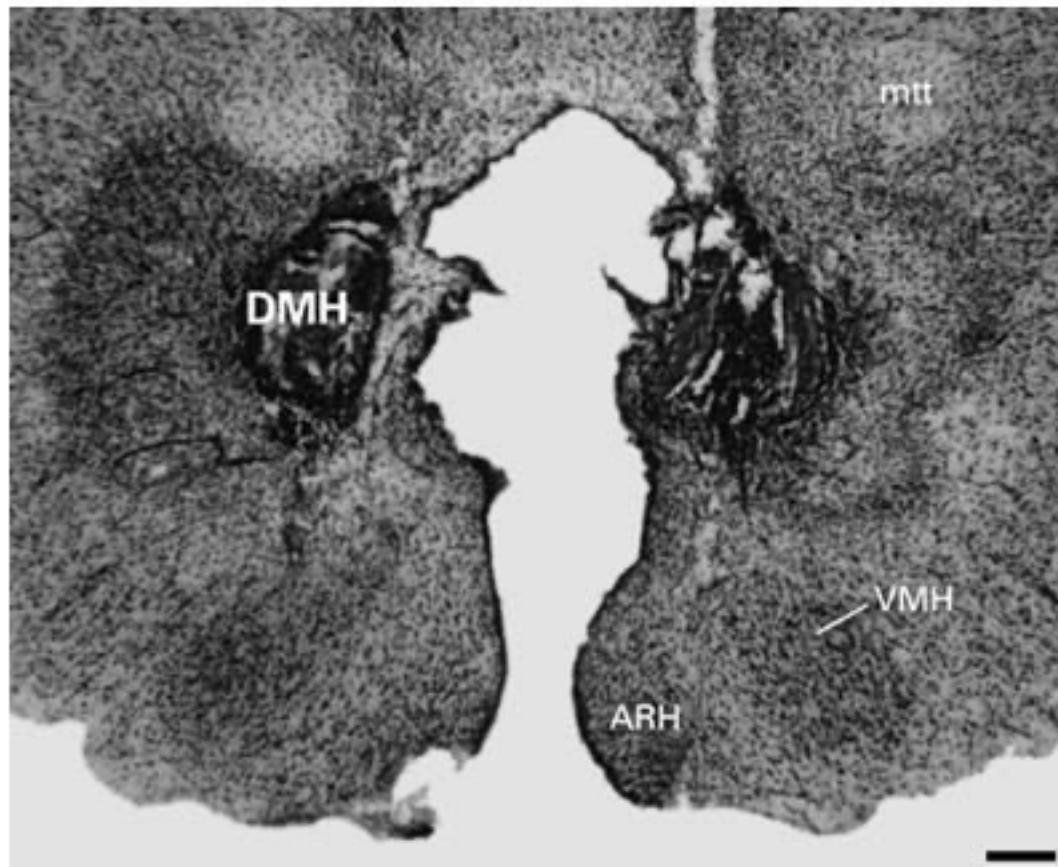


Drive and the hypothalamus: early insights into the control of feeding

Hypothalamic drive centres (Stellar)

The hypothalamus: early causal manipulations

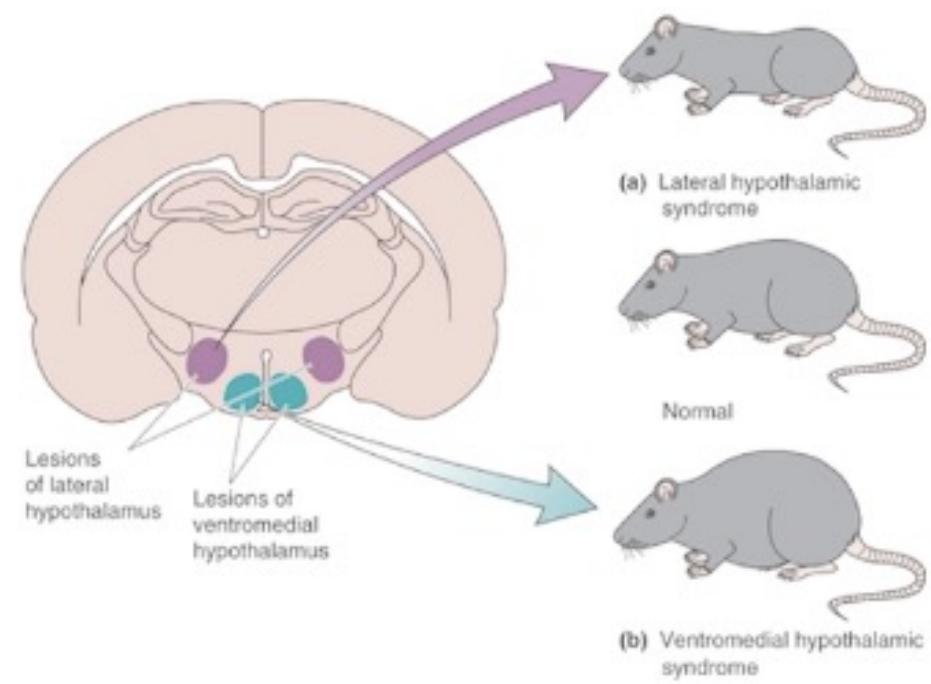
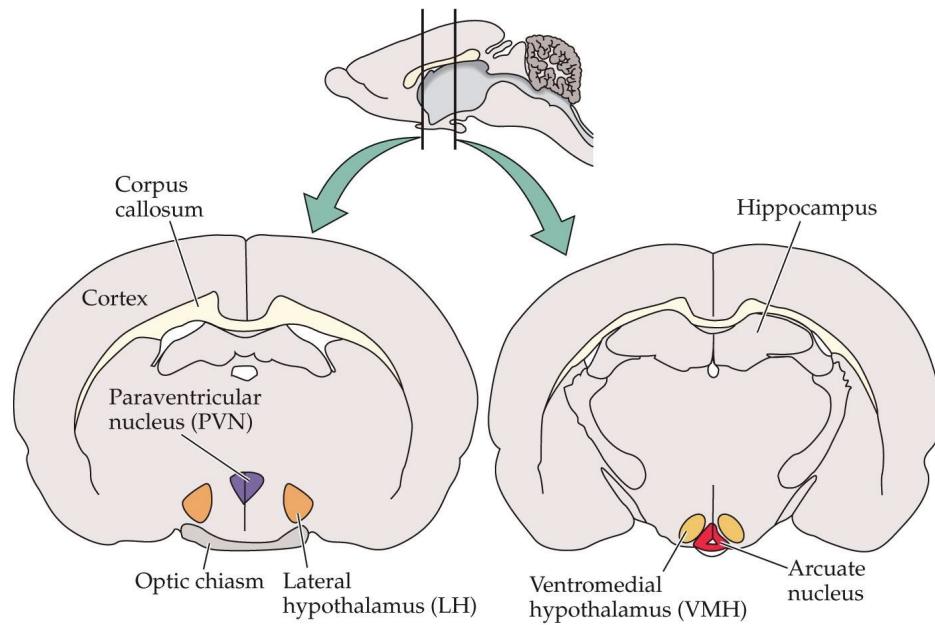
Electrolytic lesions



DOI: [10.1159/000054628](https://doi.org/10.1159/000054628)

Hypothalamic drive centres (Stellar)

Early concepts of modular hypothalamic function



Hypothalamic drive centres (Stellar)

Early concepts of modular hypothalamic function

Lateral hypothalamus (LH) → the “feeding” centre

- Lesions produce aphagia (Anand & Brobeck, PMCID: PMC2599116)
- Electrical stimulation induces eating in sated rats (Hoebel, PMID: 13907995)
- Chemical stimulation (NA) also induces eating (Grossman, Leibowitz, PMID: 13829706)
- Electrophysiology → neurons sensitive to the sight or taste of food when hungry; also to glucose (Rolls, PMID: 819286)

Ventromedial hypothalamus (VMH) → the “satiety” centre

- Lesions produce hyperphagia and obesity
- VMH neurons respond to gastric distension

Drive and the hypothalamus: control of drinking

Physiological control of thirst & drinking



Osmometric thirst

When interstitial fluid becomes hypertonic (e.g. NaCl injection)

- Osmoreceptors respond to and mediate drinking and **vasopressin** secretion
- Osmoreceptors are found in the anterior region of the 3rd ventricle (**AV3V**) and the **OVLT** (organum vasculosum of the lamina terminalis)

Volumetric thirst

Blood volume decreases (e.g. haemorrhage, vomiting)

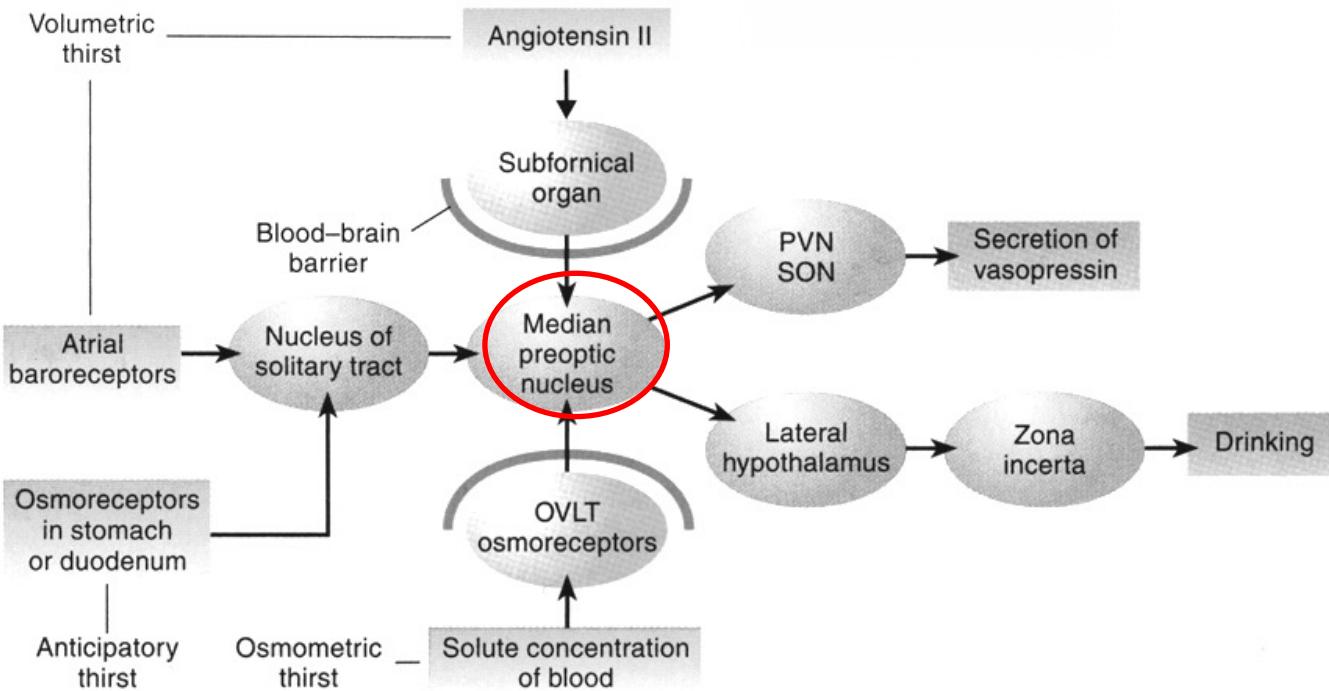
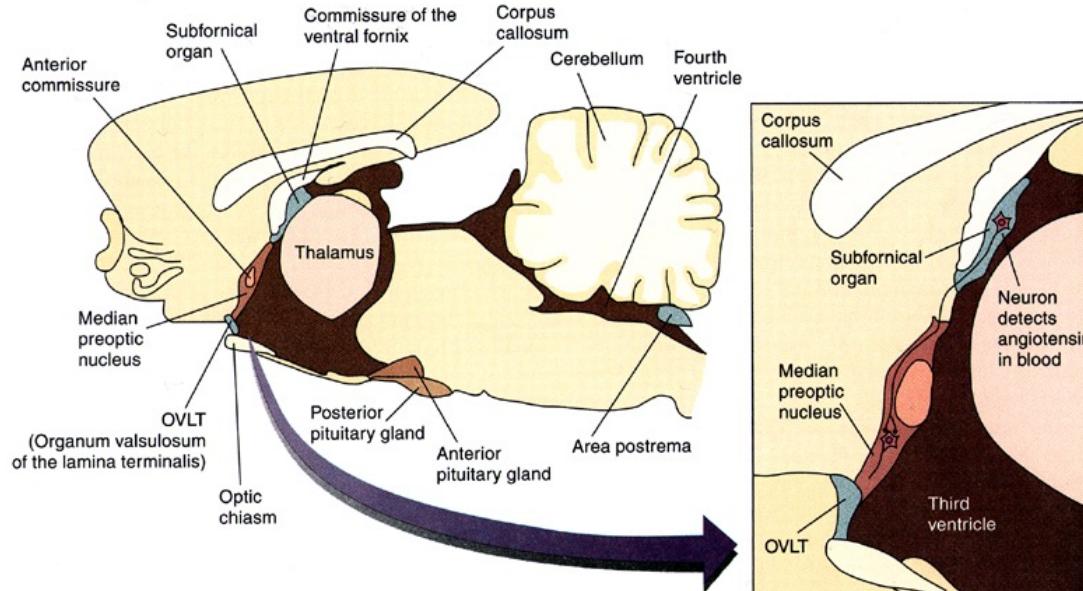
- Decrease in blood pressure

→ atrial baroreceptors activated and vagal afferents convey information to the **AV3V** via the nucleus of the solitary tract (NTS)

→ Renal juxtaglomerular apparatus (JGA) secretes renin and initiating the angiotensin II cascade.

→ Angiotensin II coordinates drinking and coordinated physiological responses via the subfornical organ (**SFO**)

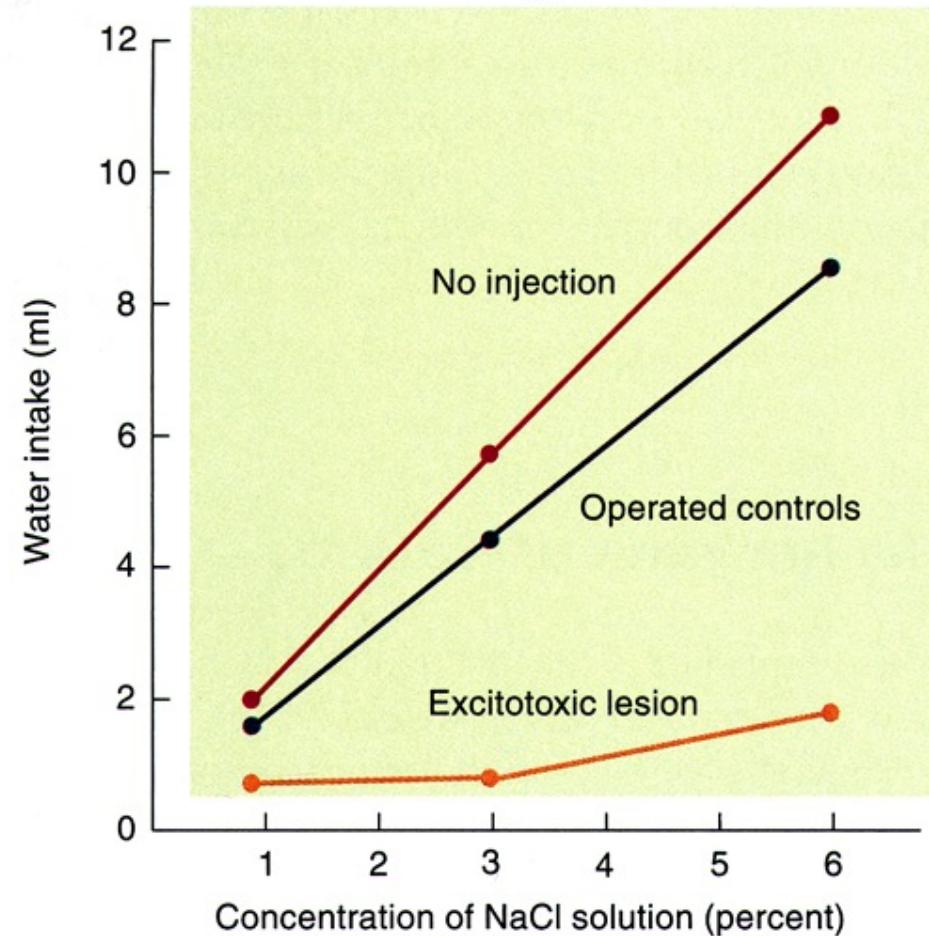
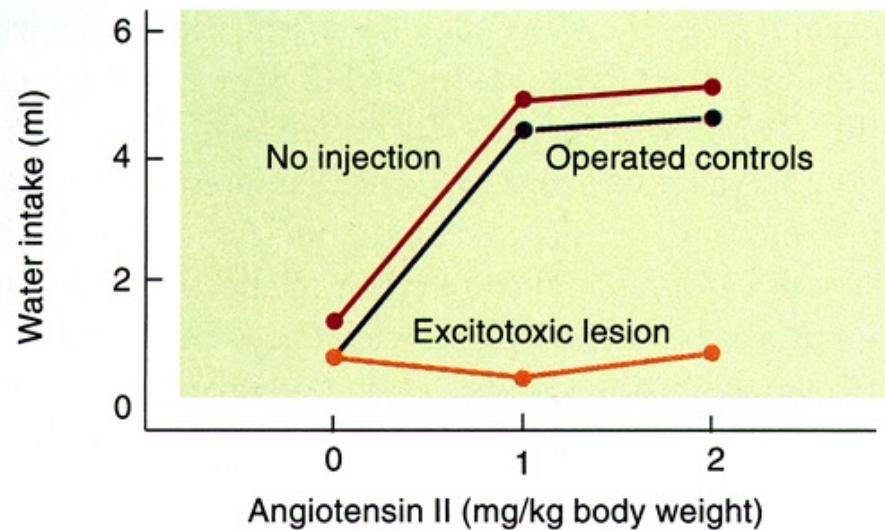
Neural control of thirst & drinking



Neural control of thirst & drinking

The median preoptic area is important for thirst

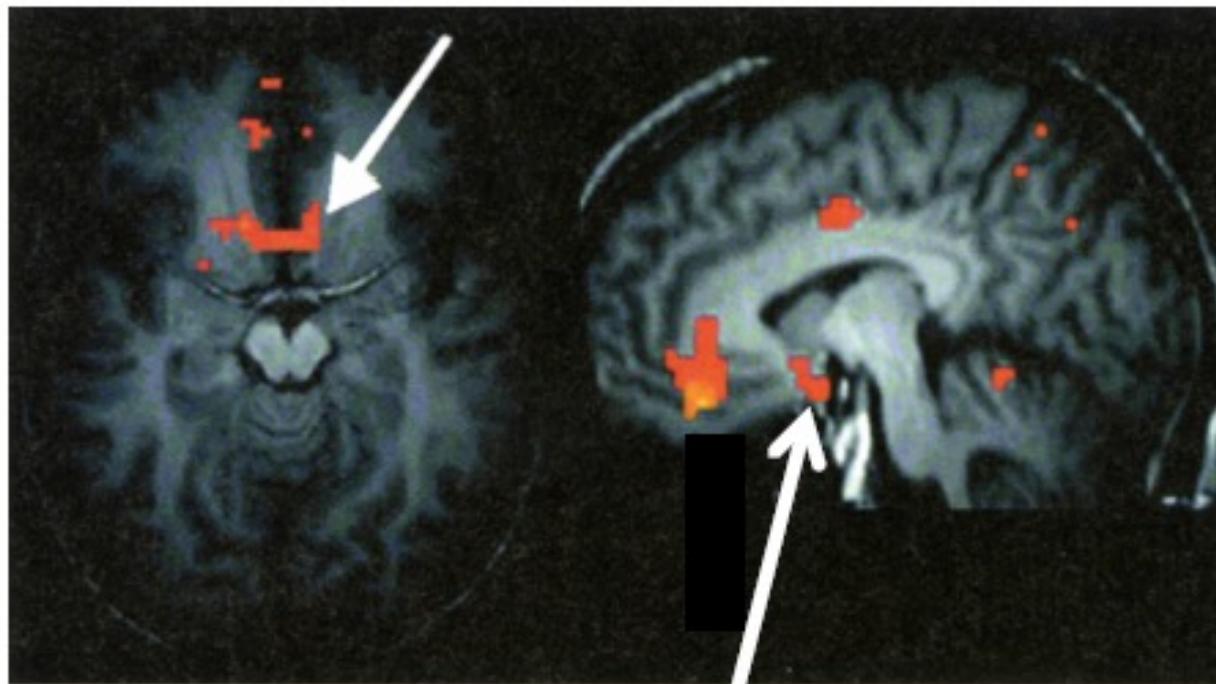
Median preoptic nucleus (**mPOA**) lesions impair drinking produced by injections of hypertonic saline (right – osmometric thirst) and AII (below – volumetric thirst).



Cunningham et al 1992, PMID: 1504809

Functional imaging of thirst in humans

Hypothalamus



lamina terminalis region

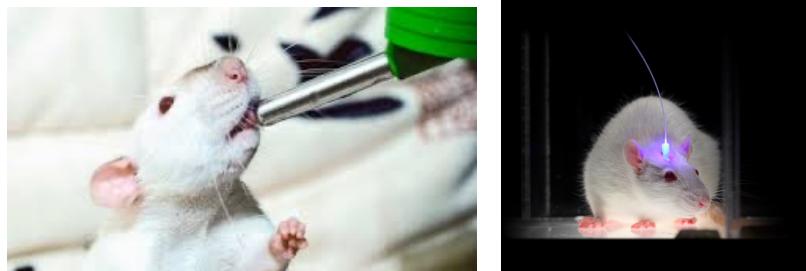
DOI: [10.1073/pnas.2136650100](https://doi.org/10.1073/pnas.2136650100)

Neural control of thirst: neuronal ensembles

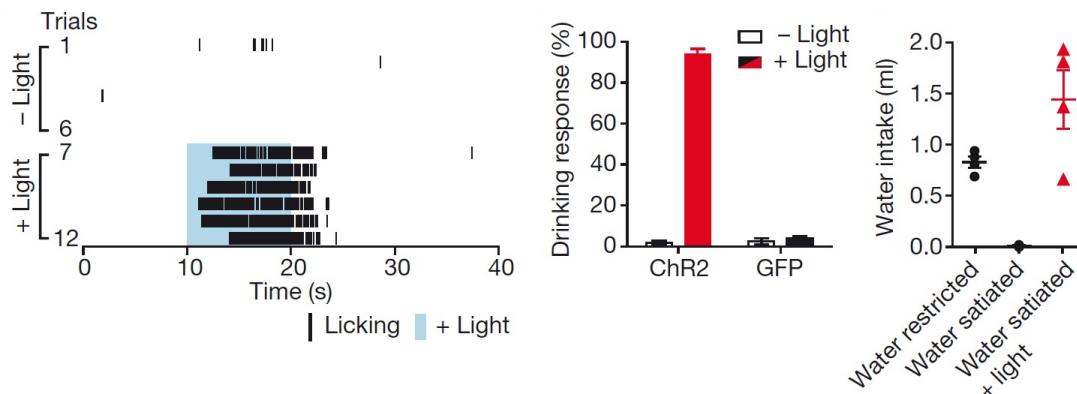


From structures to
circuits and neuronal
ensembles

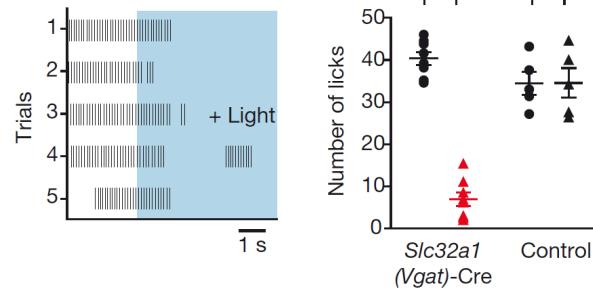
Two distinct neural populations in the SFO control thirst



Optogenetic activation of CamKII-positive (Glutamatergic) SFO neurons triggers thirst



Optogenetic activation of Vgat-positive (GABAergic) neurons in the SFO suppresses thirst

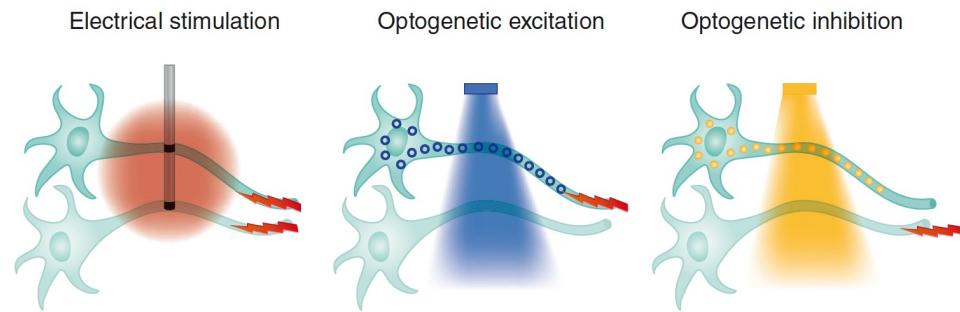
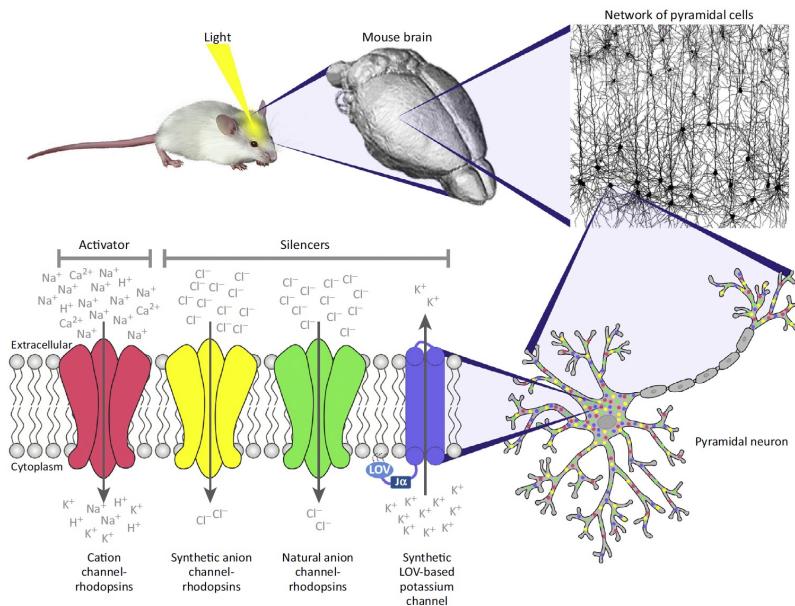
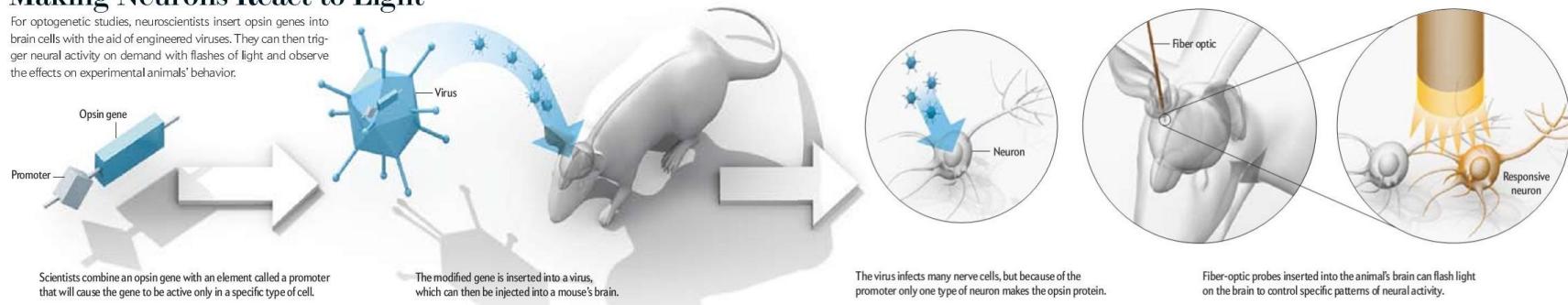


doi:10.1038/nature14108

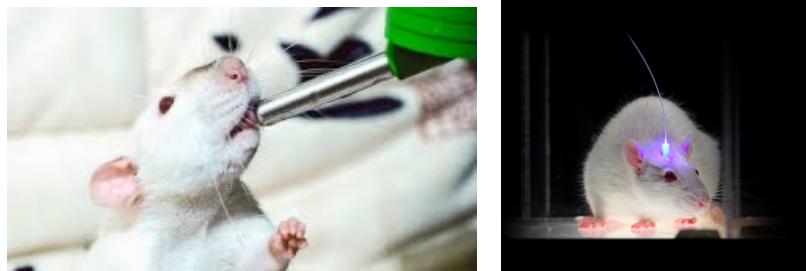
What is optogenetics

Making Neurons React to Light

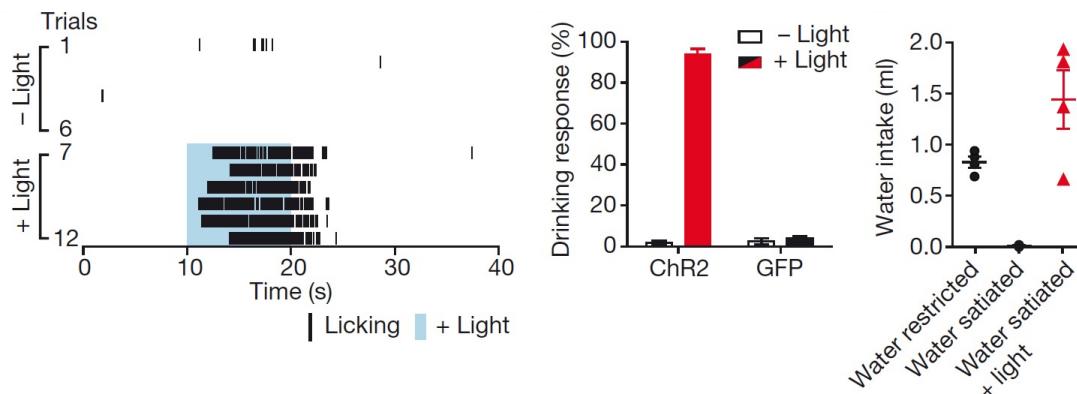
For optogenetic studies, neuroscientists insert opsin genes into brain cells with the aid of engineered viruses. They can then trigger neural activity on demand with flashes of light and observe the effects on experimental animals' behavior.



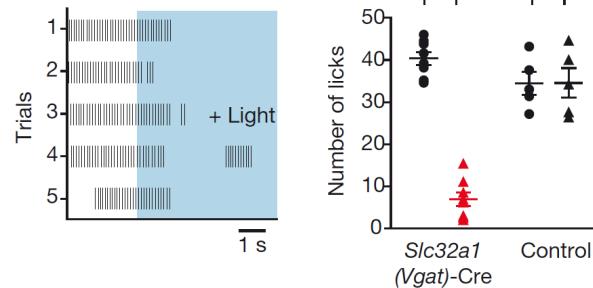
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Motivation: not just drive reduction

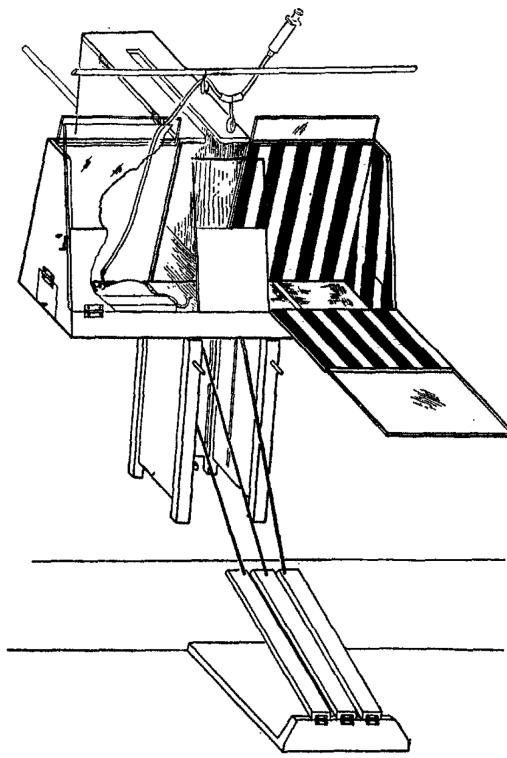


FIG. 1. THE T MAZE

The starting box has a false back which can be pushed forward by a rod projecting through the back. The starting box and each of the goal boxes have doors sliding up from below, which are operated by foot pedals. Opening the door to the starting box closes a microswitch and starts a clock which is stopped when the animal steps across the small gap in the floor of either goal box and operates an electronic relay. The top $7\frac{1}{2}$ in. of the front of the apparatus is transparent plastic to allow the experimenter to observe the animal. In the diagram the hinged front of the right goal box is opened; a portion of the left one is cut out so that an animal can be seen being injected with milk via fistula. Hinged doors at the end of each goal box allow dishes of milk or saline to be inserted.

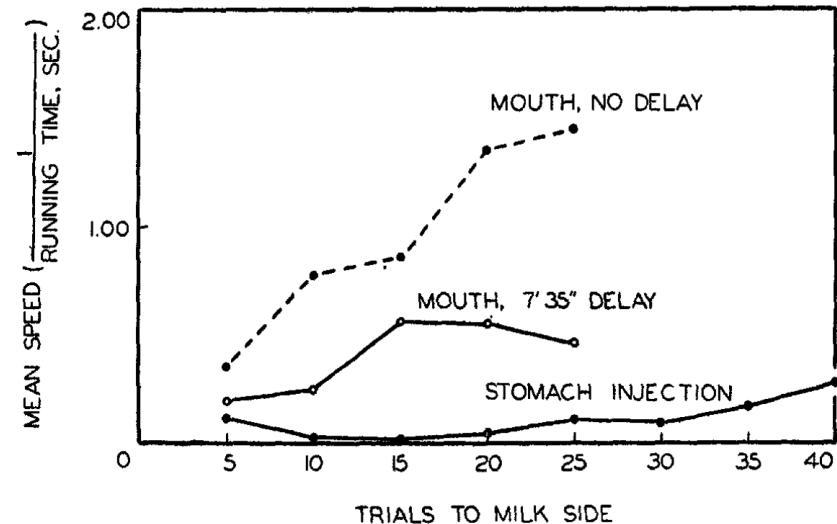
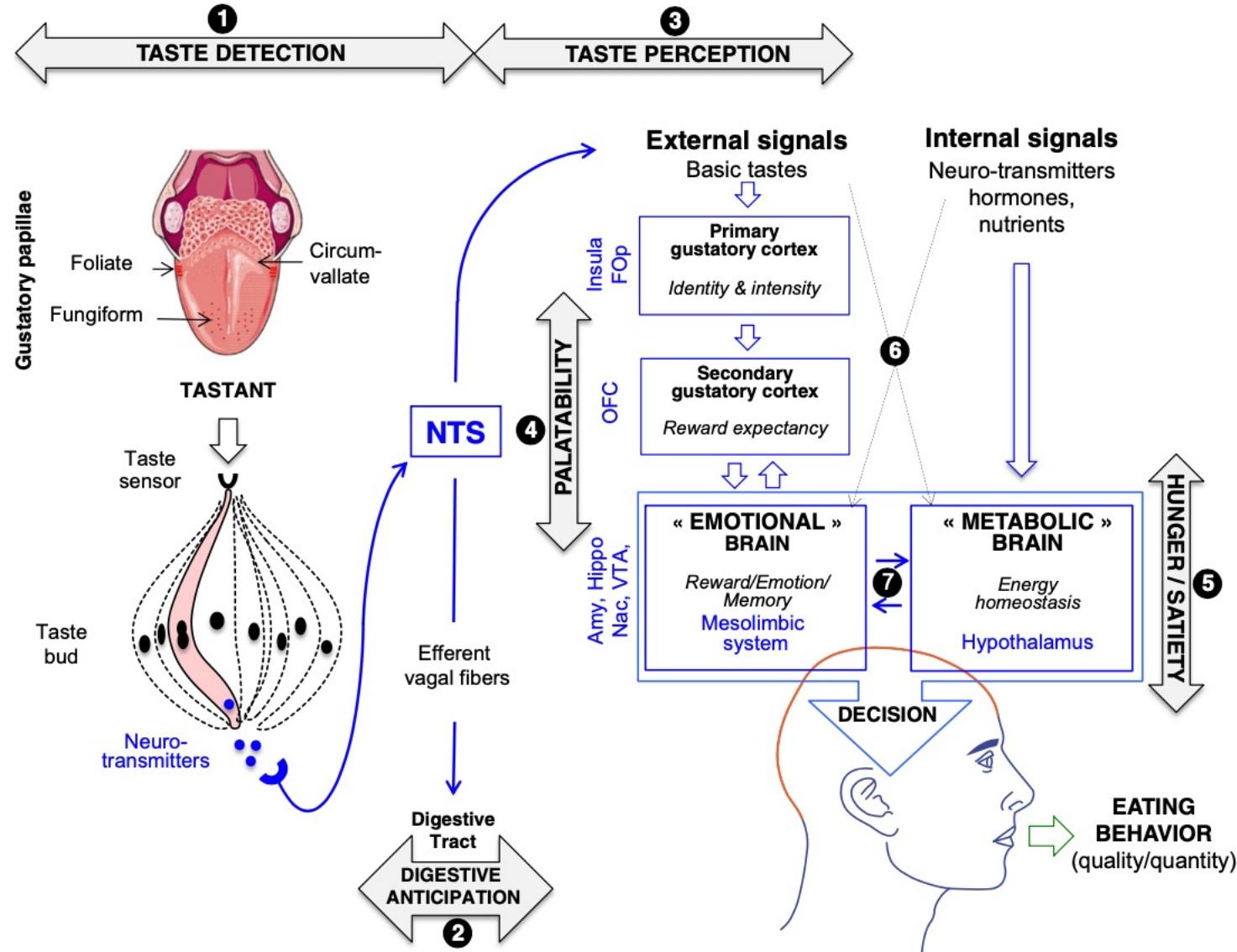


FIG. 3. SPEED OF RUNNING TO THE COMPARTMENT IN WHICH MILK WAS GIVEN

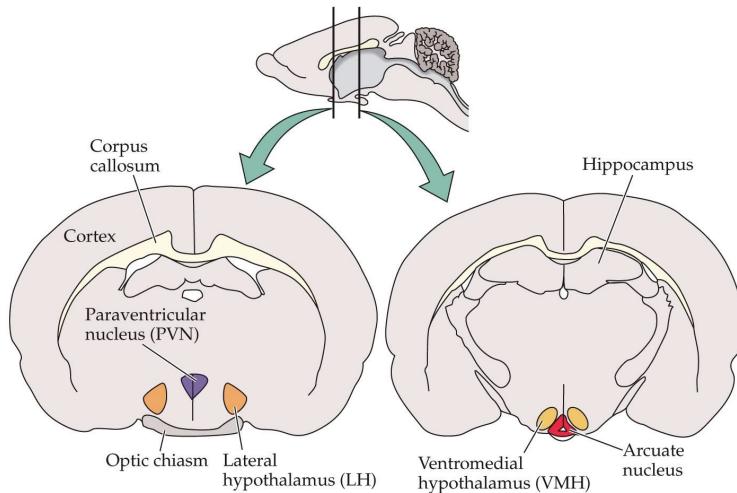
Motivation: not just drive reduction



DOI: [10.1007/s11154-016-9355-2](https://doi.org/10.1007/s11154-016-9355-2)

*Dissociable control of aggression in the LH and
VMH*

Neural control of aggression



Predatory ('quiet')

Quiet stalking and killing
Elicited by stimulation of LH (in opossum, rat, cat)
“Enhanced sensori-motor reflexes’ hypothesis (Flynn)
Projections to ventral PAG (midbrain)

Defensive (affective)

Autonomic components, hissing, piloerection, etc
Elicited by electrical stimulation of VMH
VMH projects to dorsal PAG (midbrain)
Chi and Flynn tract-tracing experiment

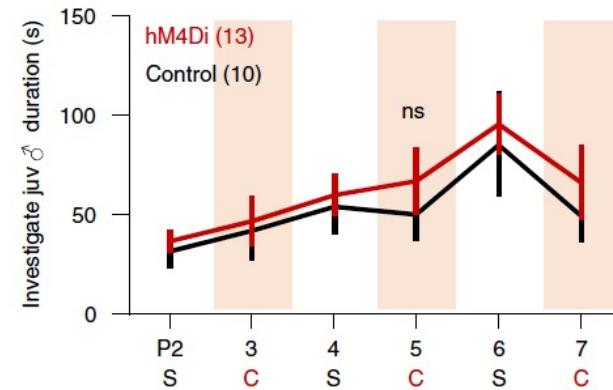
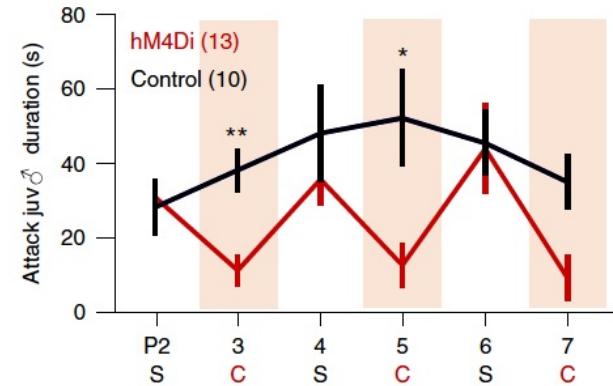
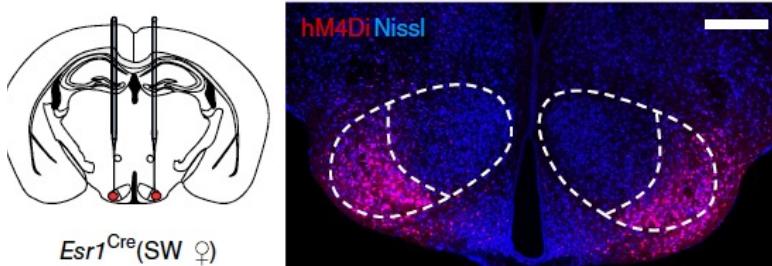
Neural control of aggression



From structures to
circuits and neuronal
ensembles

Neural control of aggression

Cell-specific DREADD-mediated chemogenetic inhibition of neurons expressing the oestrogen receptor in the VMHvl reveals they are necessary for female aggression



What are DREADDS??

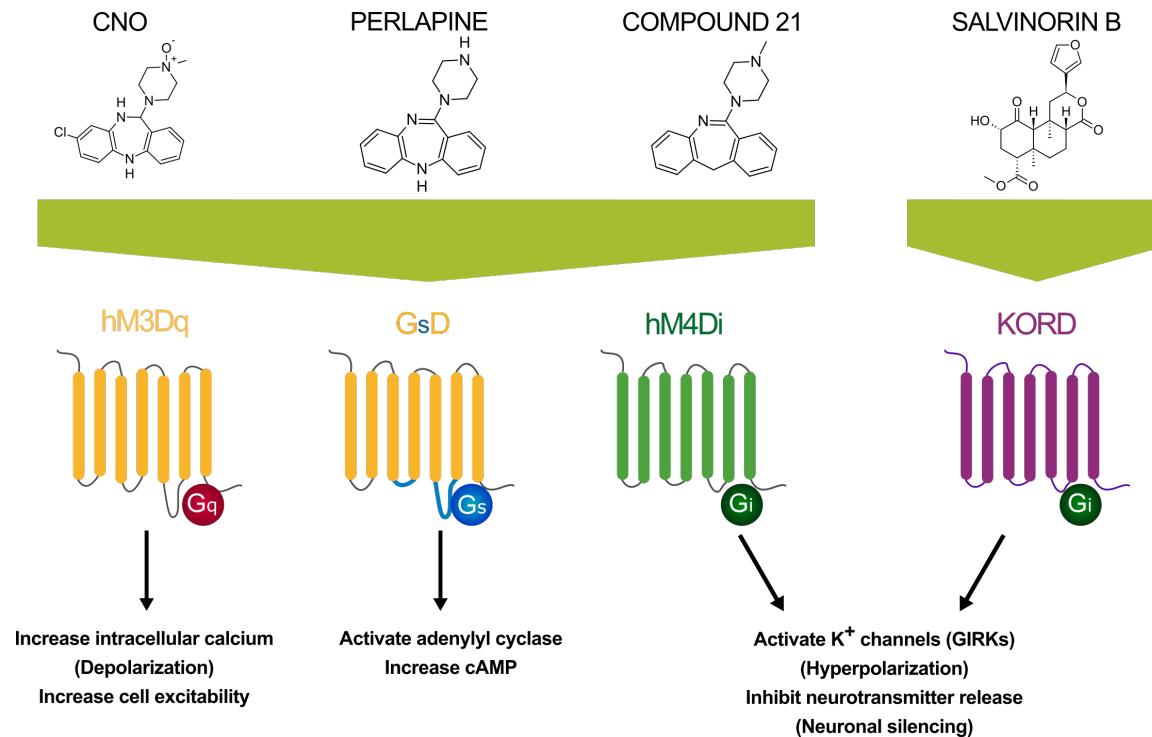
(Designer receptors exclusively activated by designer drugs)

Advances in genetics → modification of G-protein coupled receptors (GPCRs)

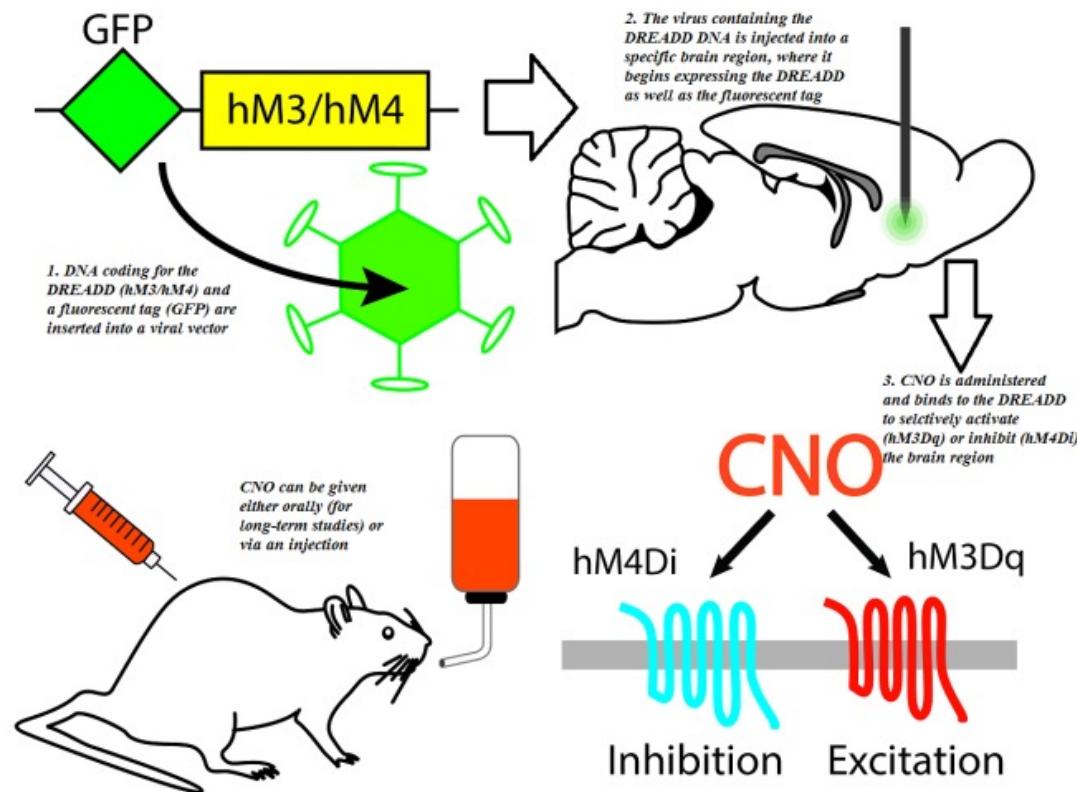
- Preservation of much of the receptor's native functionality

- while altering specific properties such as agonist binding.

DREADDs are genetically engineered GPCRs (muscarinic receptors) activated by physiologically inert synthetic small molecules (designer drugs) but not their former endogenous ligand.

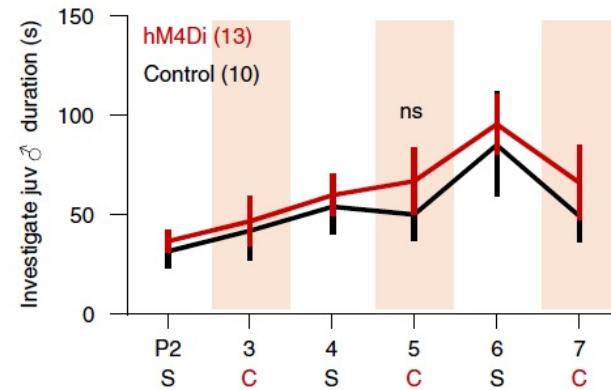
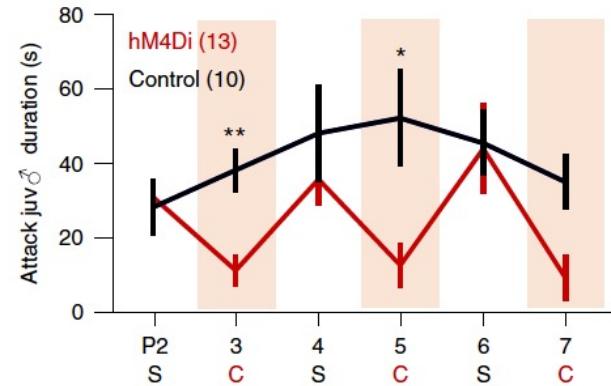
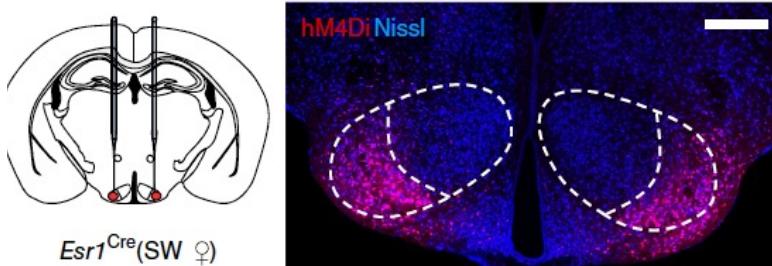


What are DREADDS??



Neural control of aggression

Cell-specific DREADD-mediated chemogenetic inhibition of neurons expressing the oestrogen receptor in the VMHvl reveals they are necessary for female aggression



Neural control of sexual behaviour

Hypothalamus and sexual behaviour

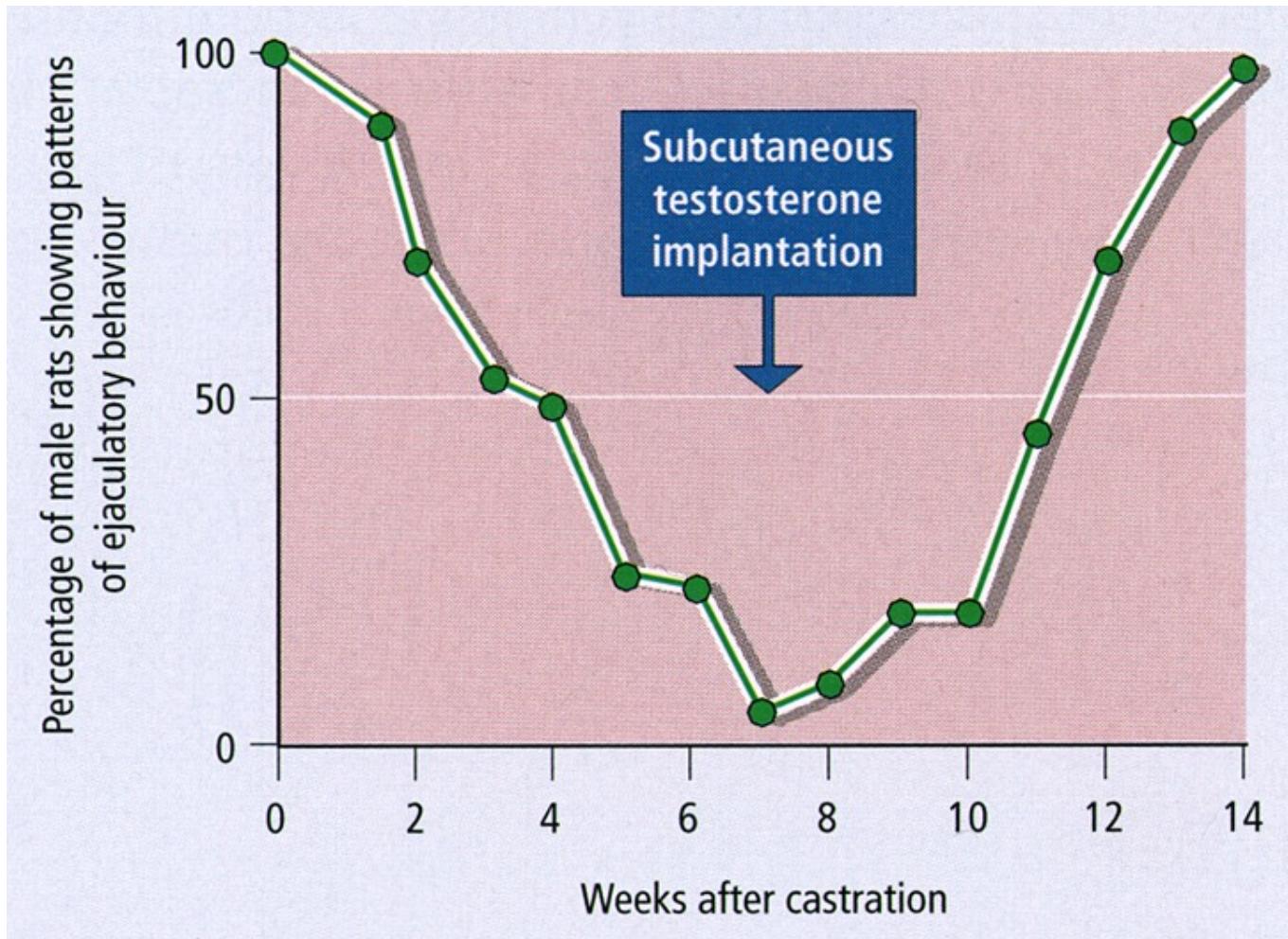
The hypothalamus is clearly involved in mediating regulatory (homeostatic) processes underlying motivation and coordinating behavioural, endocrine and autonomic responses.

What about non-regulatory motivations such as sex?



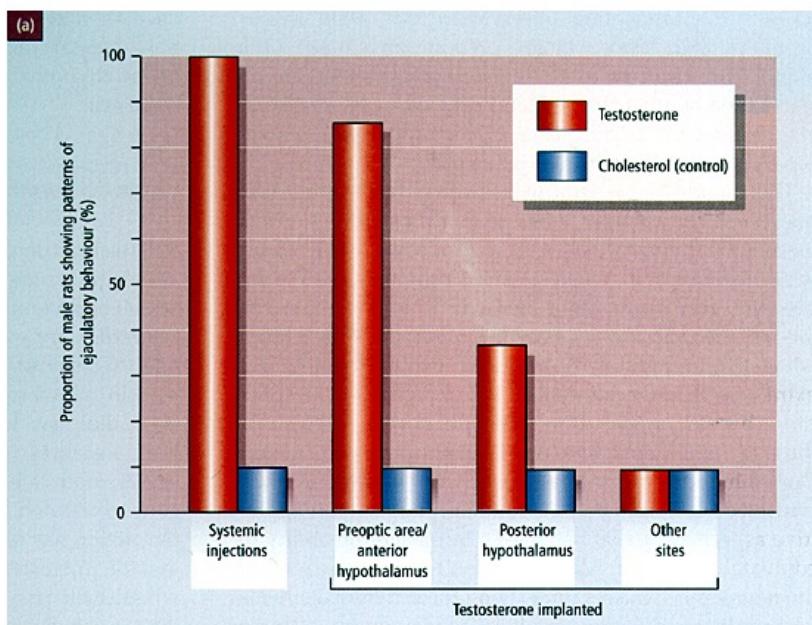
Lordosis is the female's reflex response of raising the rear quarters in response to tactile stimulation of the hind quarters from the male

Sexual behaviour is hormone-dependent



Sexual dimorphism in the hypothalamus & sexual behaviour

The medial preoptic area (mPOA) is important for sexual behaviour in male rats



Testosterone implanted in the mPOA restores sexual behaviour in castrated males.

while the ventromedial hypothalamus (VMH) is important for sexual behaviour in female rats.

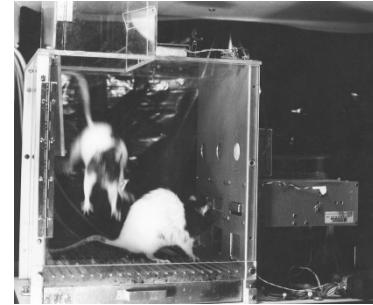
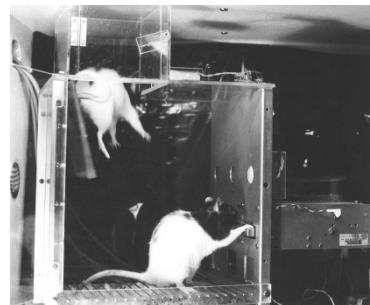
In female rats, the VMH similarly mediates the effects of oestradiol and progesterone on lordosis and proceptive behaviour.

Sexual behaviour – dissociable mechanisms



Some components of ‘motivation’ are intact following *more selective* hypothalamic damage:
e.g. dissociation of preparatory versus consummatory behaviour

Effects of mPOA lesions vs castration on appetitive and consummatory responses in male rats



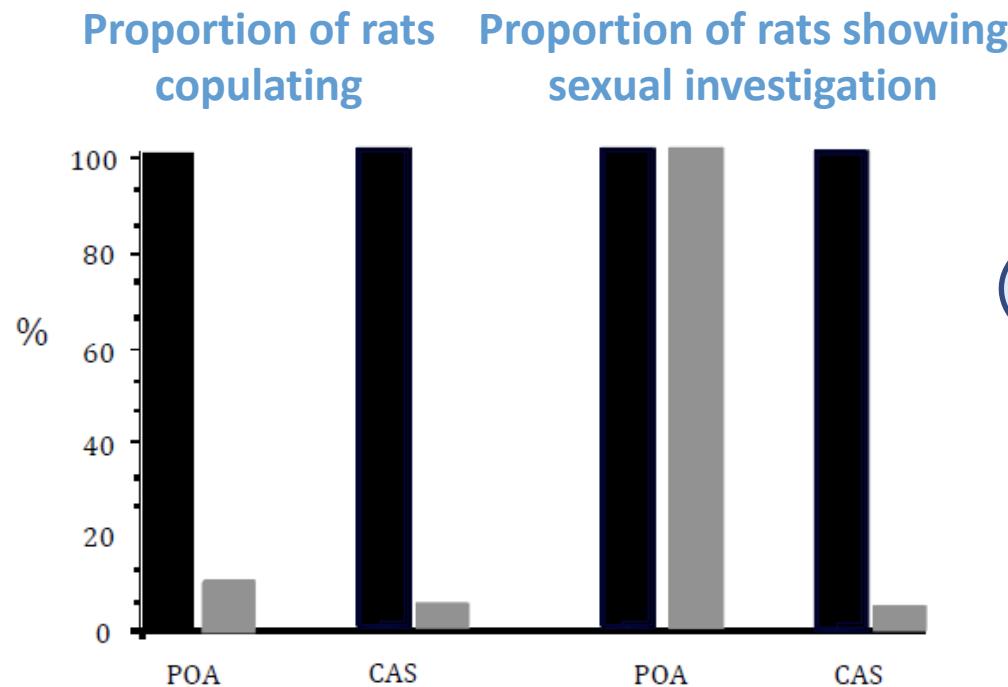
Everitt et al., 1987 PMID: 3691063

Sexual behaviour – dissociable mechanisms



Some components of ‘motivation’ are intact following *more selective* hypothalamic damage:
e.g. dissociation of preparatory versus consummatory behaviour

Effects of mPOA lesions vs castration on appetitive and consummatory responses in male rats



Double dissociation:
Basolateral amygdala lesions
→ Deficits in anticipatory but not consummatory responses

Everitt et al., 1987 PMID: 3691063

Summary & conclusions

The hypothalamus provides critical neural mechanisms for integration of motivated behavioural responses with neuroendocrine and physiological responses serving homeostatic regulation.

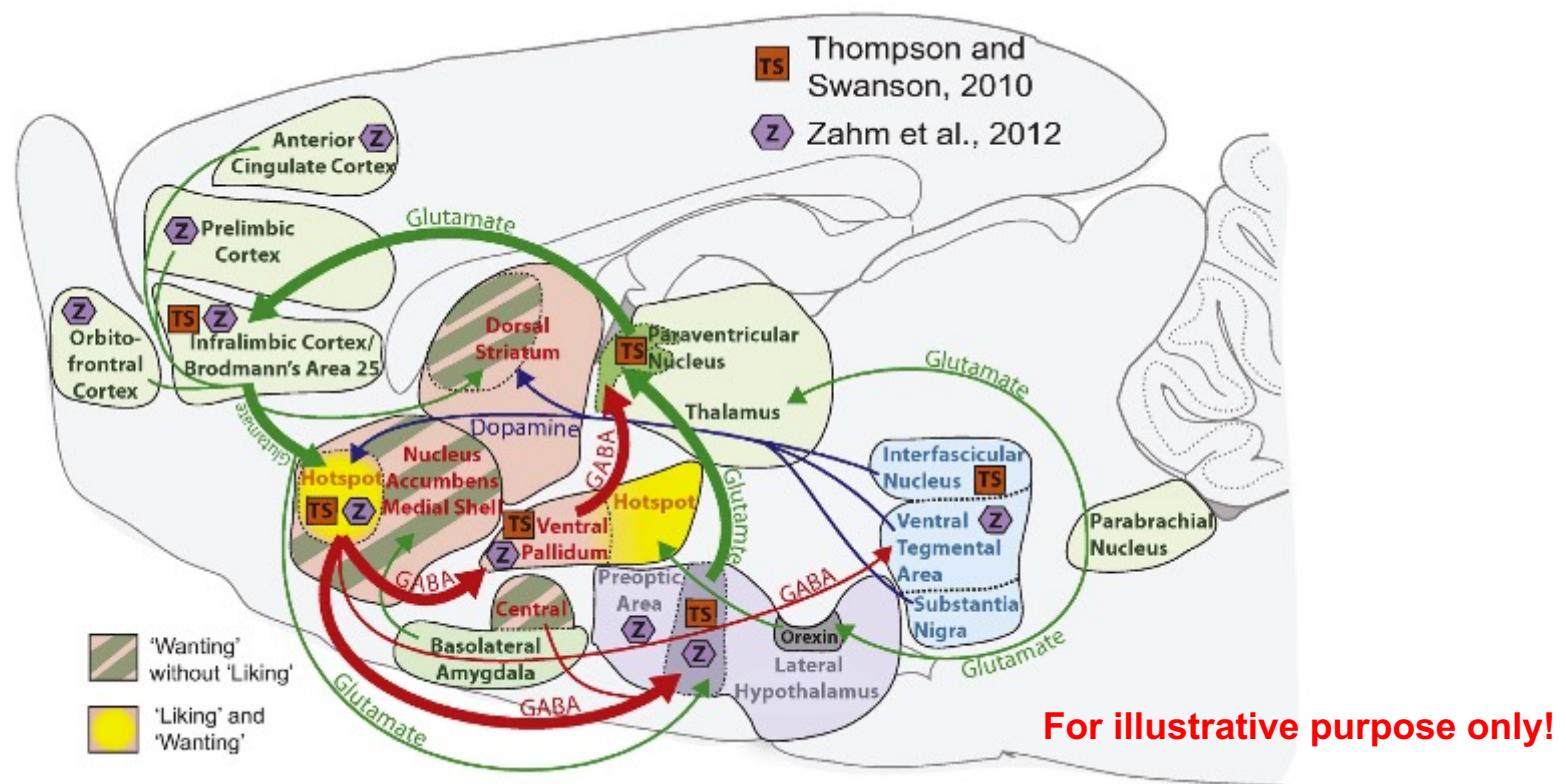
BUT following hypothalamic lesions a variety of flexible, voluntary appetitive responses are spared e.g. instrumental responses for food, warm or cool air, and sex in the face of impaired ingestive thermoregulatory and sexual consummatory responses.

Many behaviours have no obvious deficit state



Summary & conclusions: hierarchical control of motivation

Motivation is co-ordinated in a hierarchical fashion; the hypothalamus is one structure within this greater scheme



So, which brain areas are important for the flexible, voluntary appetitive responses?

Lecture 2: Monoamines, reinforcement and incentive motivation

Overview – monoamines and incentive motivation

The lateral hypothalamic (LH) syndrome revisited

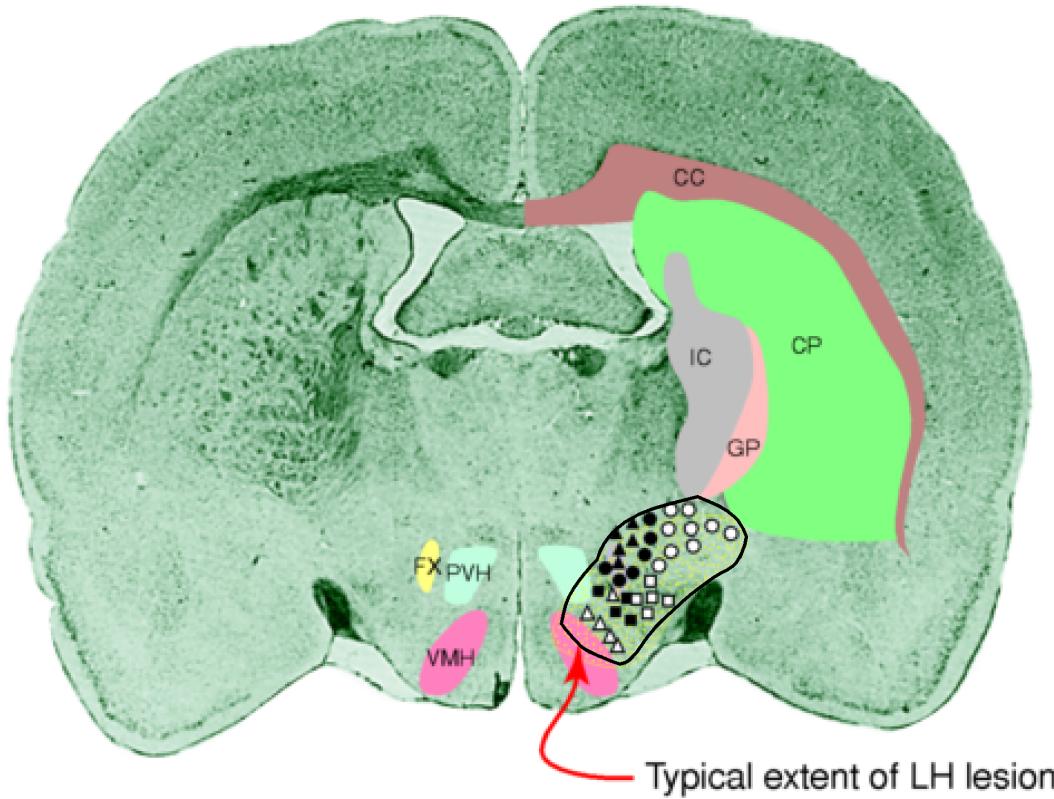
- importance of ascending monoamines (especially dopamine)
- Monoaminergic systems: function and regulation
- Focus on dopamine

Dopamine denervation syndrome

- sensory / motor / sensorimotor deficits
- behavioural activation

Part I The LH syndrome revisited

Critique of the drive centre hypothesis



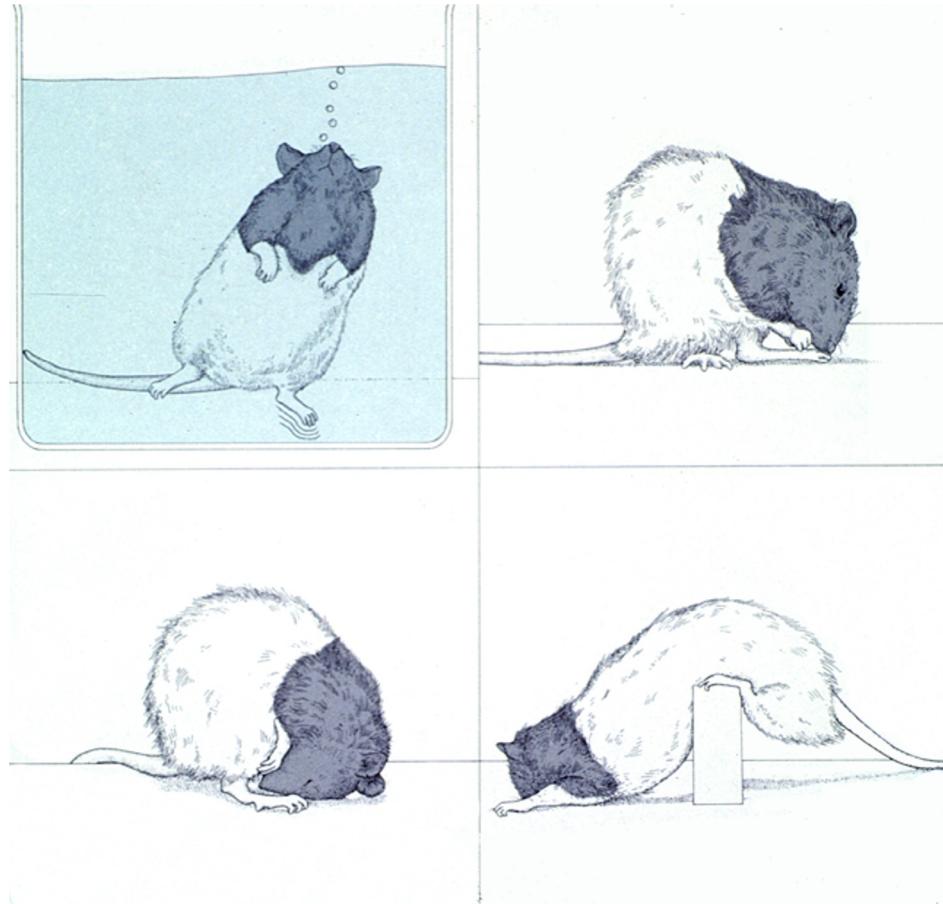
- Mesostriatal dopamine projection
- Mesolimbic dopamine projection
- ▲ Ceruleo-cortical noradrenergic projection
- △ Ventral noradrenergic ascending projection
- Medial 5-HT projection
- Lateral 5-HT projection

Coincidental damage to axons of monoamine and other neurons passing through the medial forebrain bundle in the lateral hypothalamus leads to some aspects of the LH syndrome.

→ Warranting to revisit of the function of the hypothalamus



Behavioural changes following electrolytic LH lesions that also induce aphagia and adipsia



Levitt & Teitelbaum (1975)

Critique of the drive centre hypothesis

Over-selective interpretation of effects of hypothalamic lesions

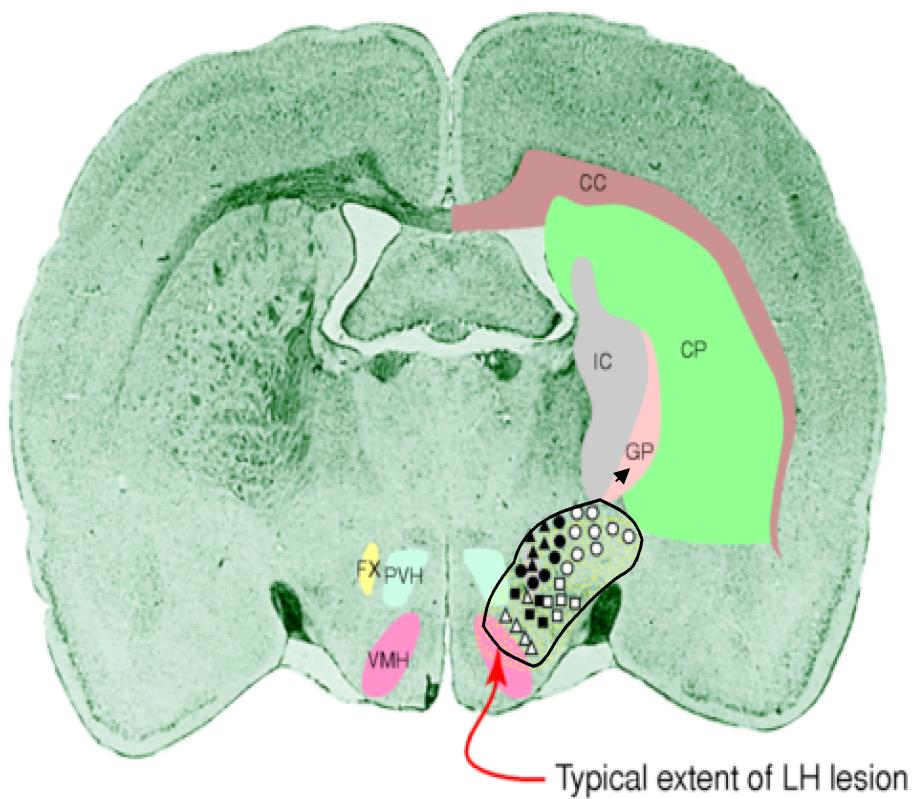
Undue emphasis on the role of the hypothalamus as necessary and sufficient structure for motivated behaviour

e.g.

1. Problem of interpretation of lesions:

- Non specific effects with electrolytic lesions which destruct the fibers of passage
- Recovery of function (re-organisation and compensation as well as intrinsic recovery of damaged brain systems)

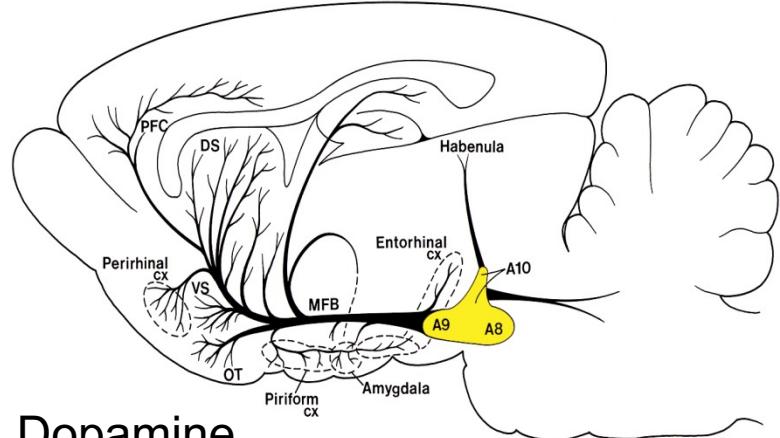
LH electrolytic lesions affect the ascending monoaminergic fibres of passage



- Mesostriatal dopamine projection
- Mesolimbic dopamine projection
- ▲ Ceruleo-cortical noradrenergic projection
- △ Ventral noradrenergic ascending projection
- Medial 5-HT projection
- Lateral 5-HT projection

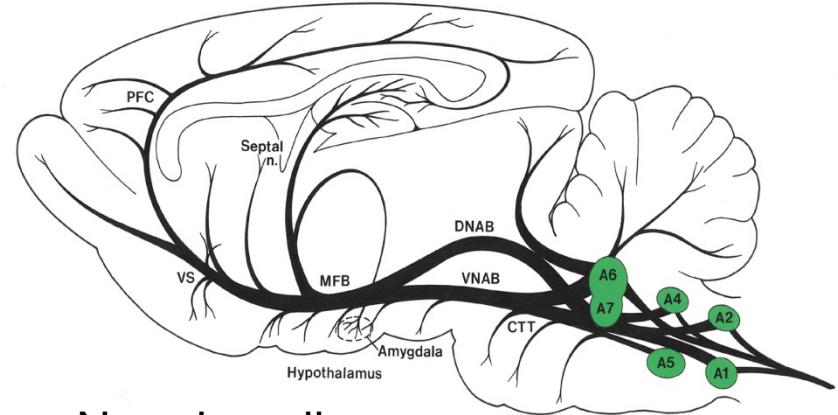
From Koob, Everitt & Robbins (Fundamental Neuroscience)

The ascending monoaminergic systems pass through the lateral hypothalamus



Dopamine

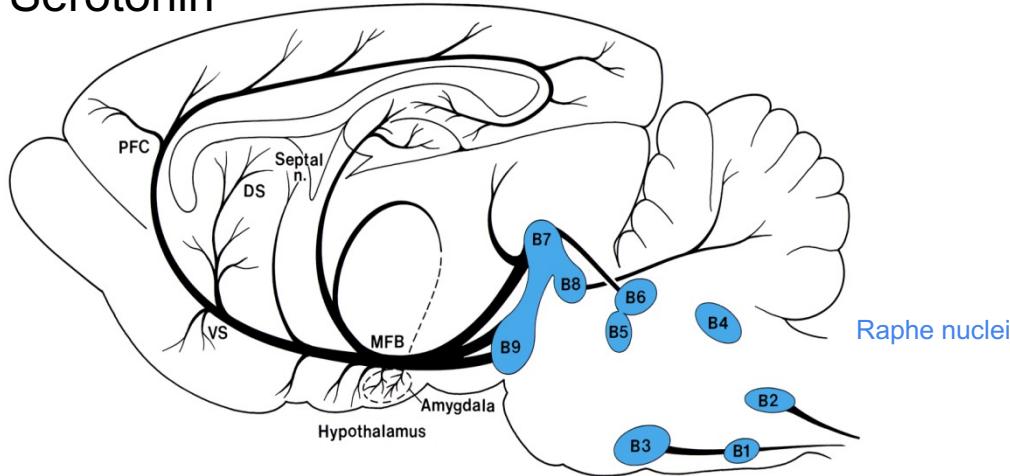
A9: substantia nigra compacta (SNC)
A10: ventral tegmental area (VTA)



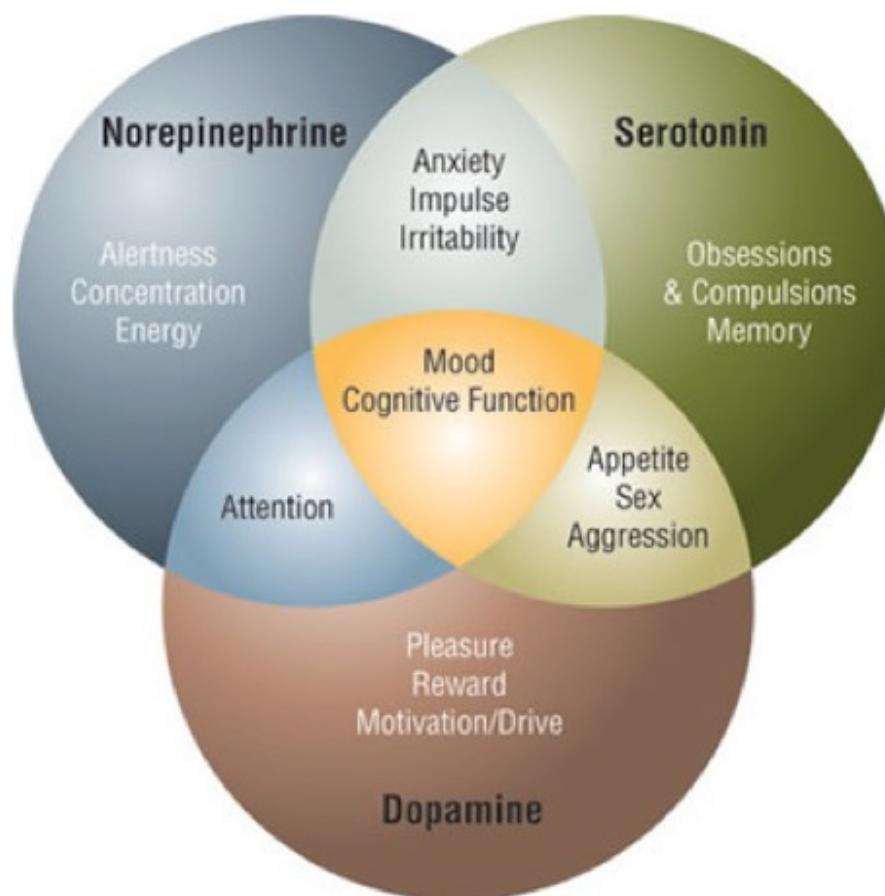
Noradrenaline

A6: Locus Coeruleus
A2: NTS

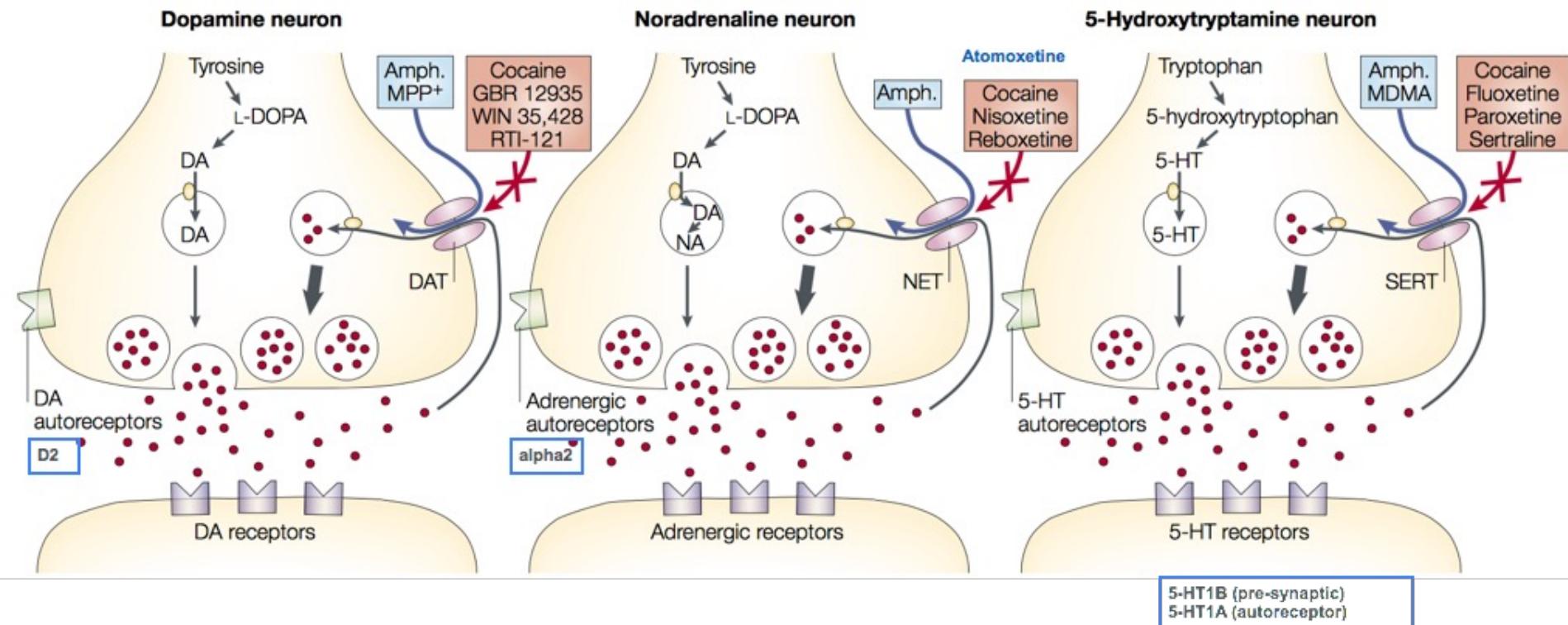
Serotonin



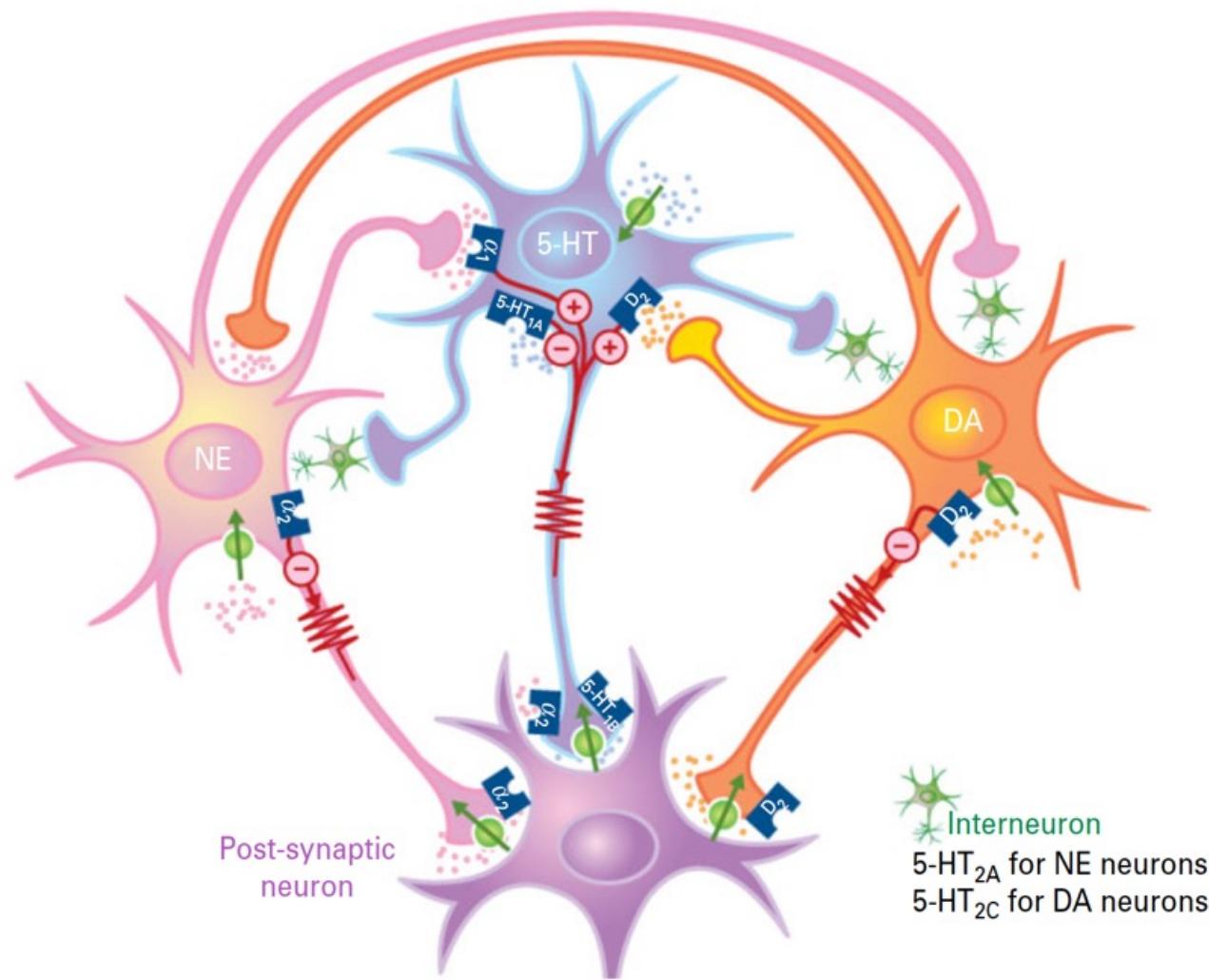
Monoamines: ascending regulatory systems



Regulation of monoaminergic synapses

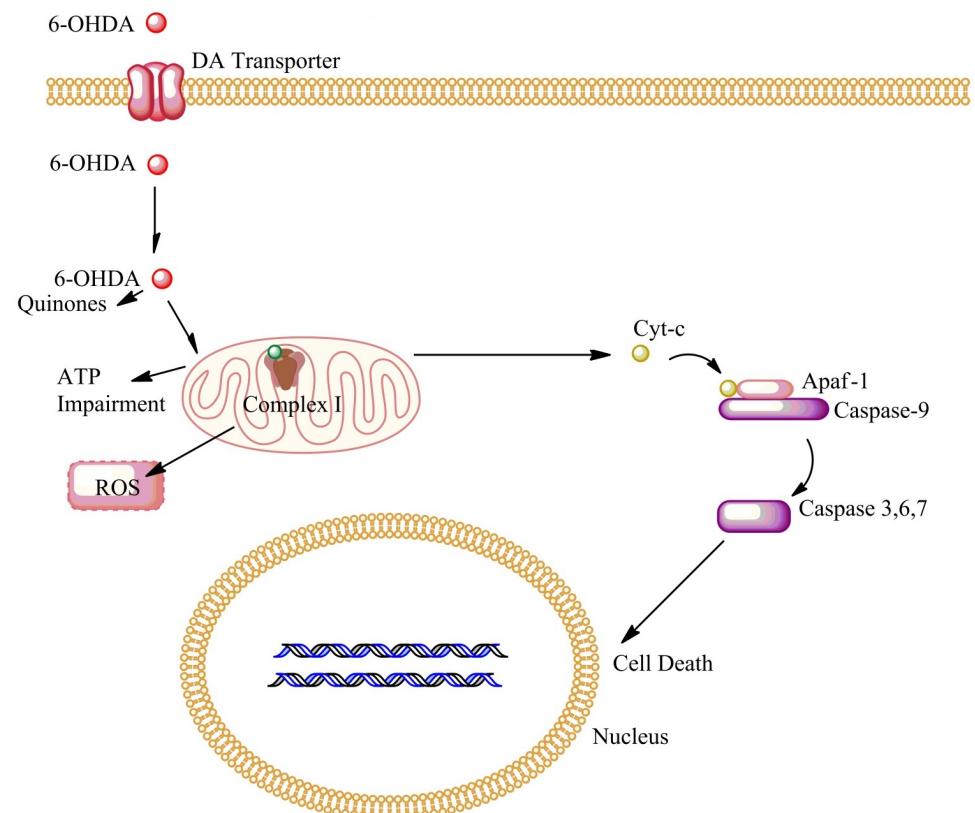
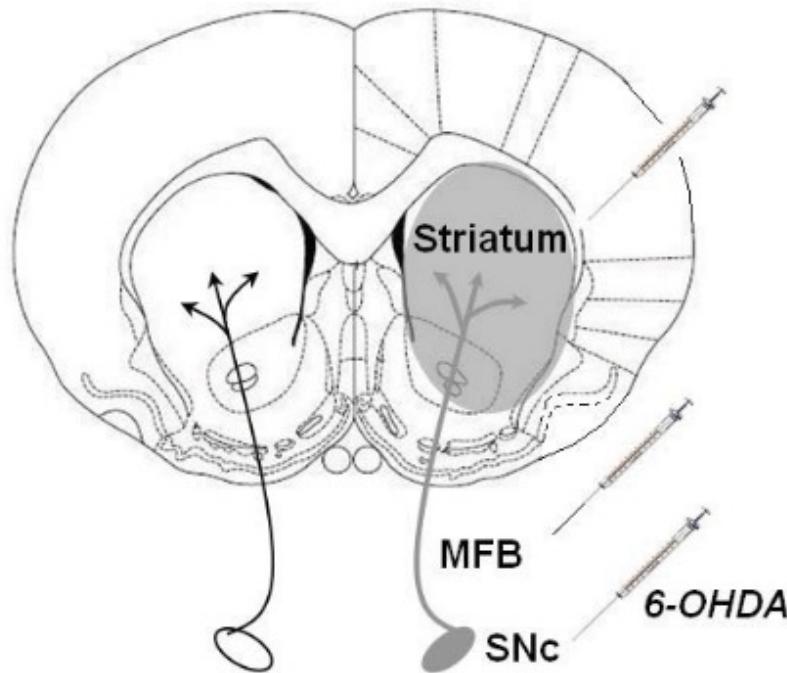


Reciprocal interactions between dopamine, serotonin and noradrenaline



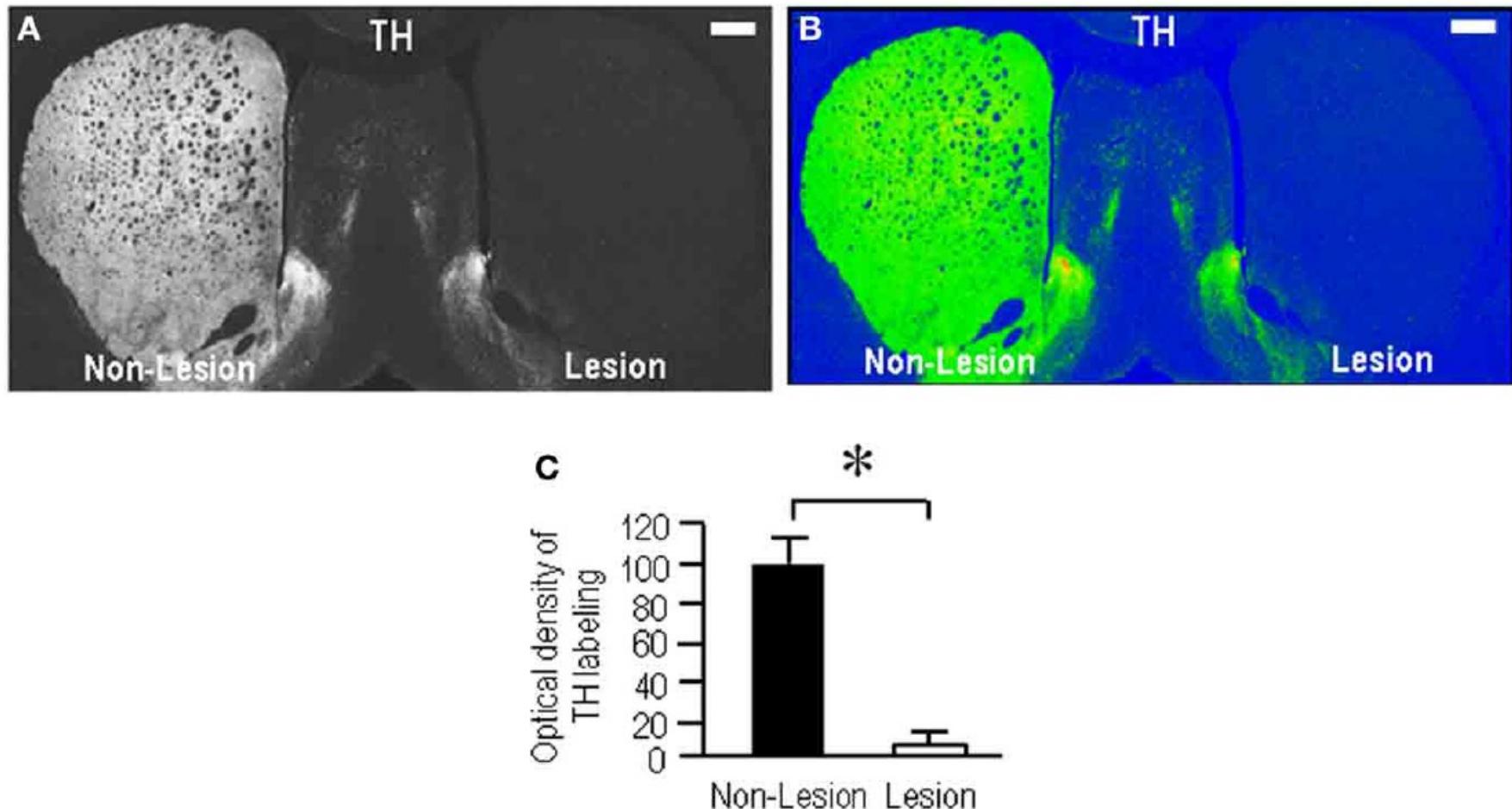
Focus on dopamine: the dopamine denervation syndrome

6-hydroxydopamine (6-OHDA) is a neurotoxin that selectively “kills” catecholaminergic neurons

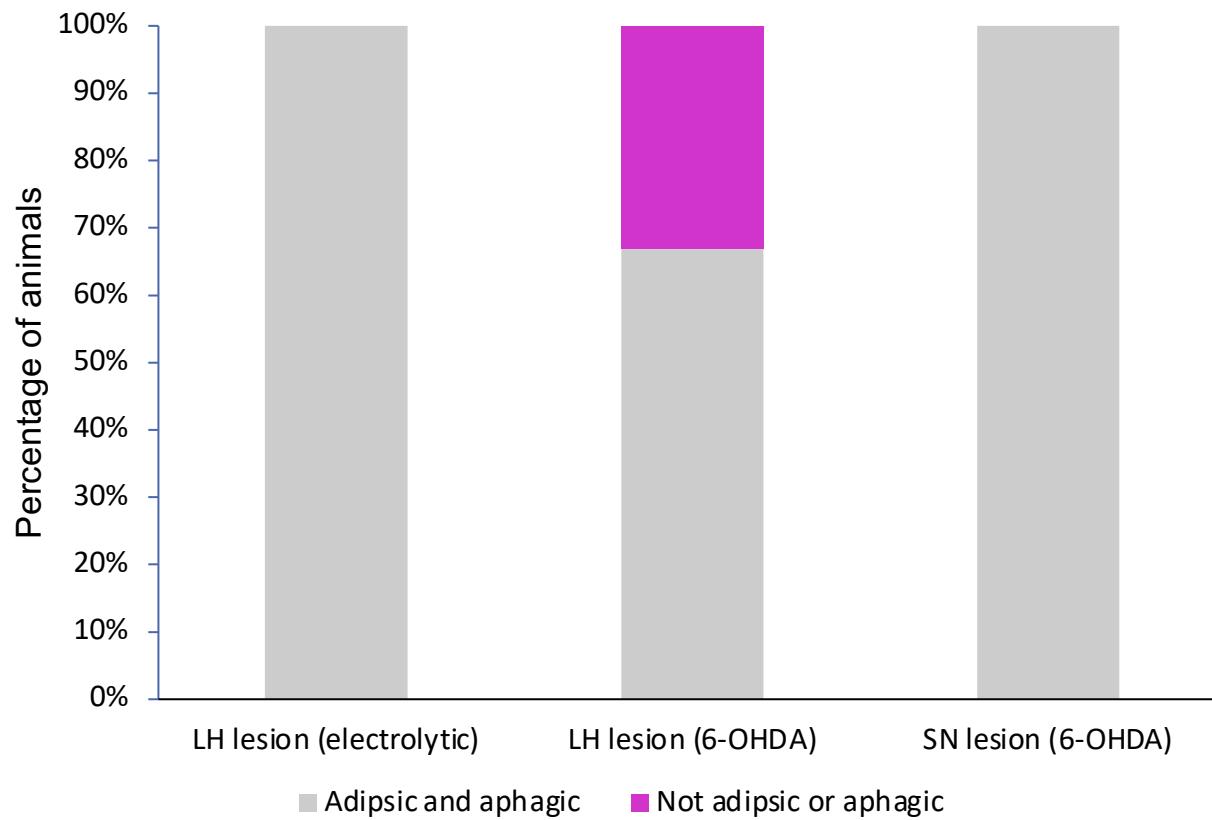


Focus on dopamine: the dopamine denervation syndrome

6-OHDA-induced dopamine depletion in the striatum:



Depletion of catecholamines and LH syndrome



Very similar effects to LH syndrome...

BUT – dopaminergic projections don't actually synapse in the LH, but rather in the striatum. Is the LH syndrome actually caused by depletion of DA in the striatum?

Data replotted from Ungerstedt (1971)

Lesions with 6-OHDA in the LH produce profound DA depletion in the striatum

Brain region	Concentration ng/mg \pm s.e.m.			Mean % depletion
	Ipsi	Contra		
Anterior caudate	1.13 \pm 0.9	12.75 \pm 3.0		90.6
Posterior Caudate	0.75 \pm 0.8	13.98 \pm 2.2		93.9
Tail of Caudate	1.30 \pm 0.9	5.08 \pm 1.8		31.2
Nucleus accumbens	4.70 \pm 1.7	8.61 \pm 3/6		40.8

So – is LH syndrome actually produced by depletion of dopamine in the striatum, rather than damage to the LH itself?

Similarities in the effects of electrolytic LH lesions and 6-OHDA lesions

Acute aphagia and adipsia

1. Recovery through predictable stages:
 - Stage 1 - aphagia and adipsia
 - Stage 2 - anorexia and adipsia
 - Stage 3 - adipsia with dehydration aphagia
 - Stage 4 - partial recovery - prandial drinking only
2. Residual deficits to physiological challenges
glucoprivation; osmotic challenge

Hypokinesia and catalepsy

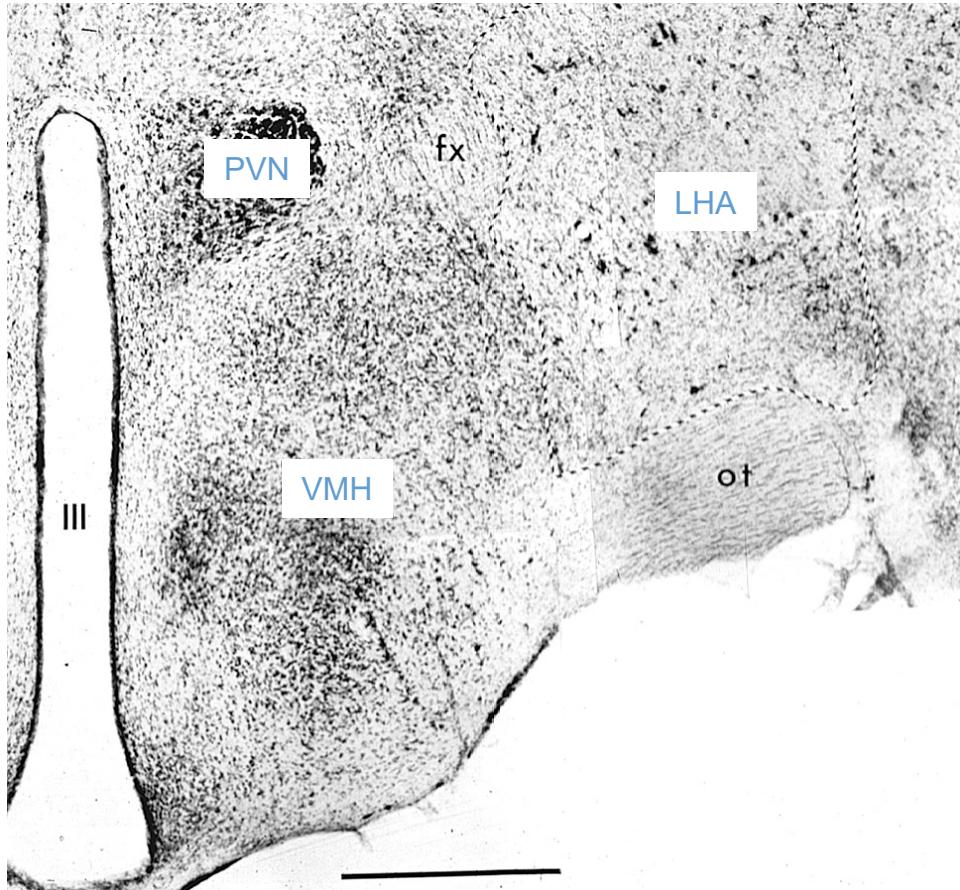
‘Sensory neglect’

...but some important differences between electrolytic LH lesions and 6-OHDA lesions

1. 6-OHDA rats are not somnolent
2. 6-OHDA rats are less finicky, even though the ingestive deficit is still significant
3. 6-OHDA rats have no deficits in taste aversion learning or in thermoregulation
4. LH lesions producing the full syndrome reveal striatal DA depletions of 50% or more on subsequent biochemical assay

(By contrast, 6-OHDA lesions must yield striatal DA depletions in excess of 90-95% in order to result in the full syndrome of impairments.)

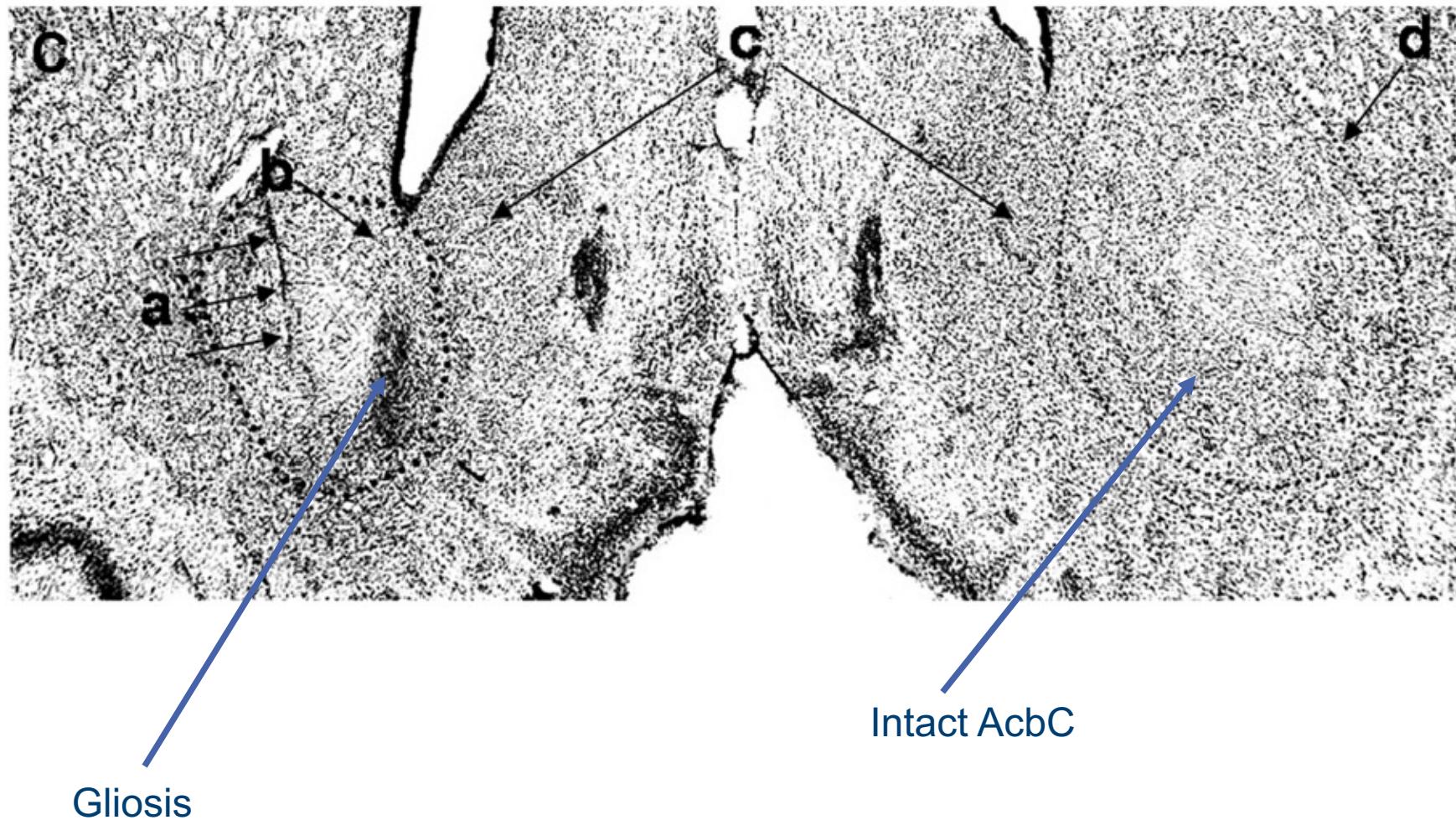
Excitotoxic lesions → examination of function of the LH vs. fibres of passage



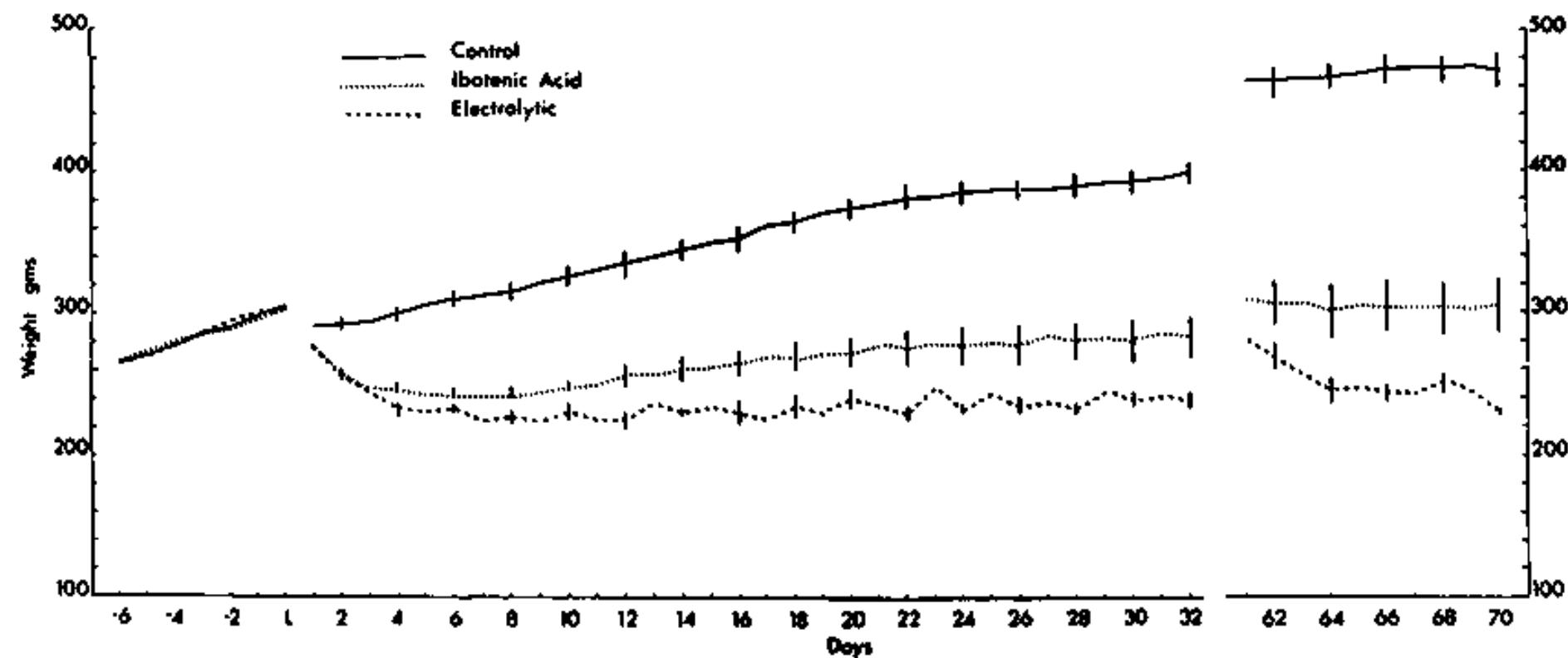
Excitotoxic lesions destroy neurons through overexcitation, and they **only target cell bodies** (not fibres of passage).

Originally **kainic acid** was used, but later **ibotenic acid** and **quinolinic acid** were favoured
→ more specific (less aggressive) lesions.

Excitotoxic lesions → examination of function of the LH vs. fibres of passage



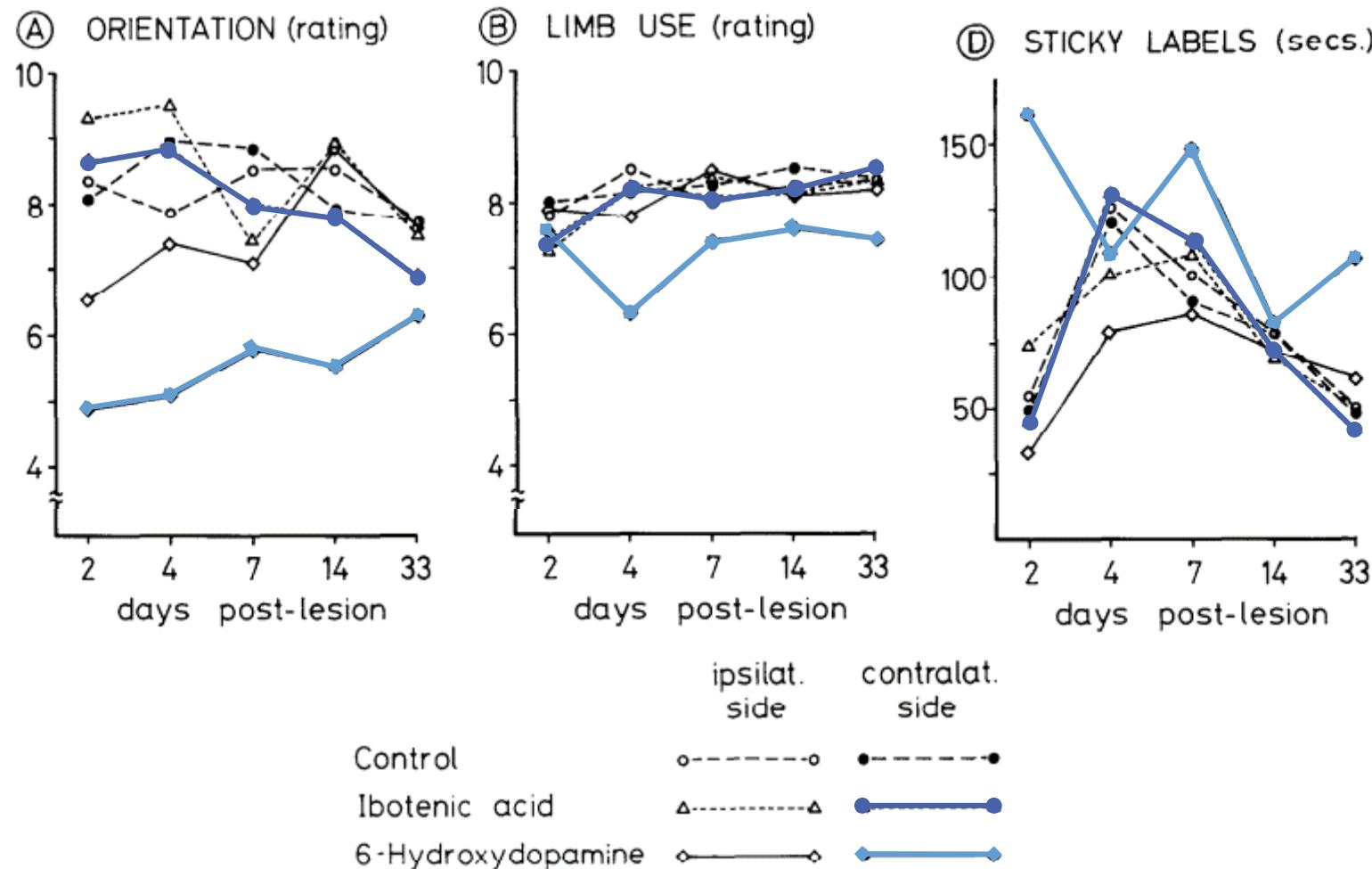
Ibotenic acid lesions of the LH: reduction of body weight but with some recovery



Electrolytic: all rats stopped eating straight after lesion; 4/9 required intragastric feeding; 5 died; remaining 4 would not eat more than 5g food

Ibotenic: all rats stopped eating straight after lesion; 8/11 returned to normal feeding; 3/11 were as impaired as electrolytic lesioned animals

Ibotenic acid lesions of the LH: no motor symptoms as compared to 6-OHDA



Dunnett et al. (1985)

Summary: effects of electrolytic, 6-OHDA, and excitotoxic lesions of the LH

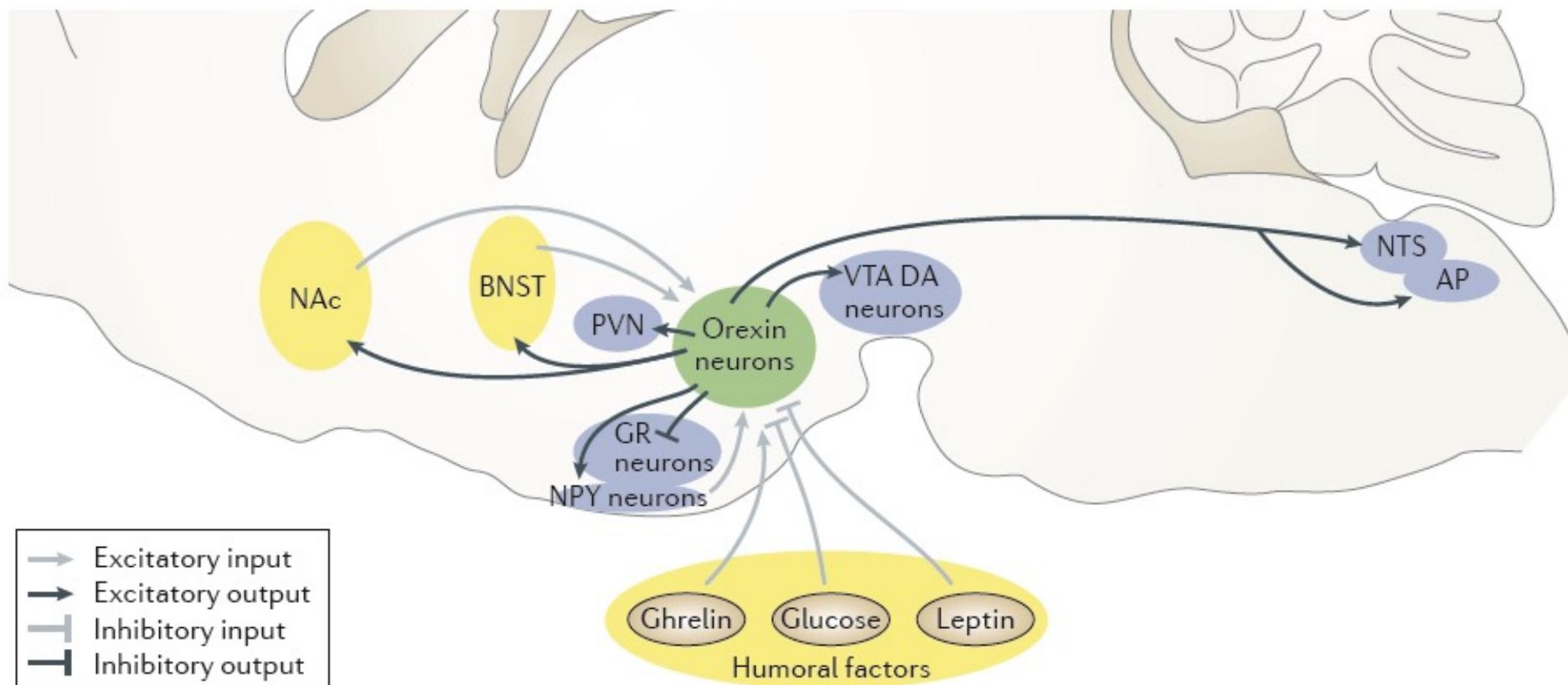
Behavioural test	Electrolytic lesion	6-OHDA lesion	Excitotoxic lesion
Basic regulation – feeding, drinking, maintenance of body weight	Substantial	Initially substantial, but recovers	Mild
Physiological challenges – dehydration with hypertonic saline or polyethylene glycol, drinking induced by angiotensin II, feeding induced with glucoprivation	Substantial	Moderate	Substantial
Tests of deprivation – 24hr water deprivation, 24hr food deprivation, prandial drinking	Substantial	Substantial	None
Diet adulteration – taste reactivity	Substantial	None	None
Motivation and activation – locomotion, sensorimotor tests, operant responding	Substantial	Substantial	None

Adapted from Winn (1995)

Separating the functions of the LH from those of ascending monoamines

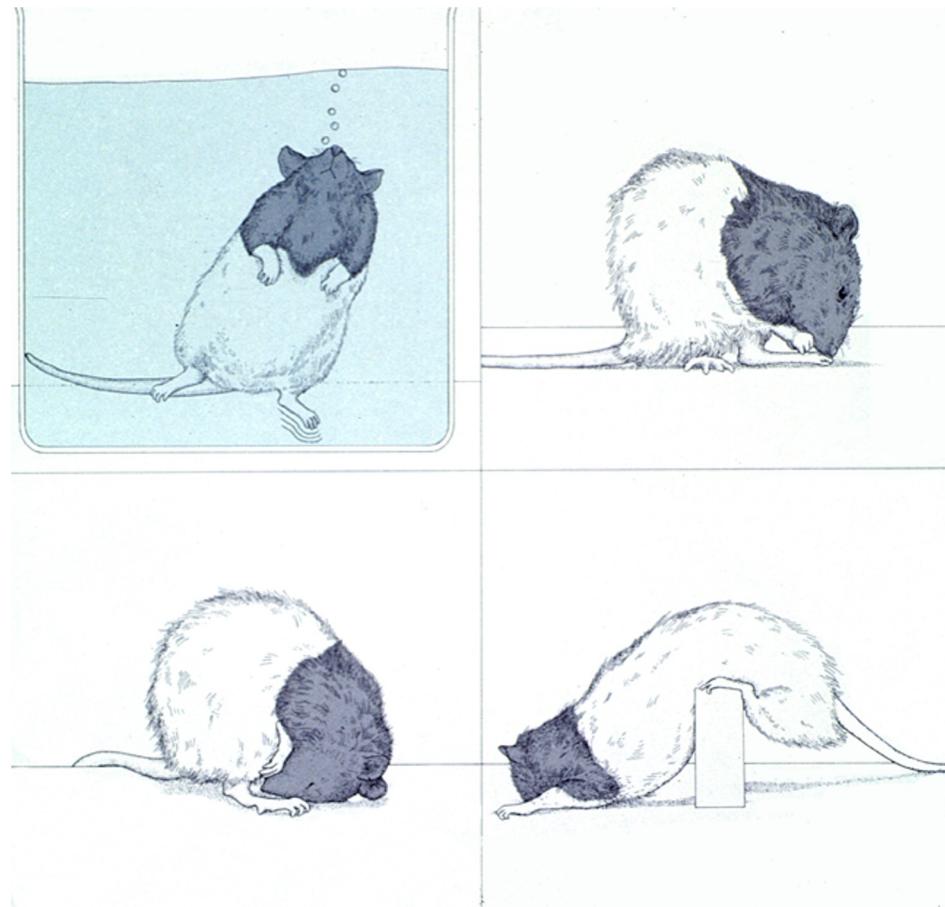
1. Akinesia and sensorimotor deficits are DA related, independent of intrinsic LH cells.
2. Regulatory mechanisms for feeding, drinking, temperature regulation etc. have a hypothalamic substrate - or involve non-dopaminergic projections in the mfb which are damaged by the gross lesions.
3. For feeding and drinking (though not thermoregulation) the functional LH outputs may converge on the dopamine system via LH to substantia nigra pars compacta and hence the nigrostriatal DA projections.
4. Cell body lesions of the LH and 6-OHDA lesions of the DA bundle disrupt different levels of the same system. → **LH projections to the VTA contain the peptide orexin and regulate DA neuron activity. Not clear whether these same neurons regulate the nigral DA neurons.**

LH orexin neurons: the link between the LH and the DA system in regulating feeding?



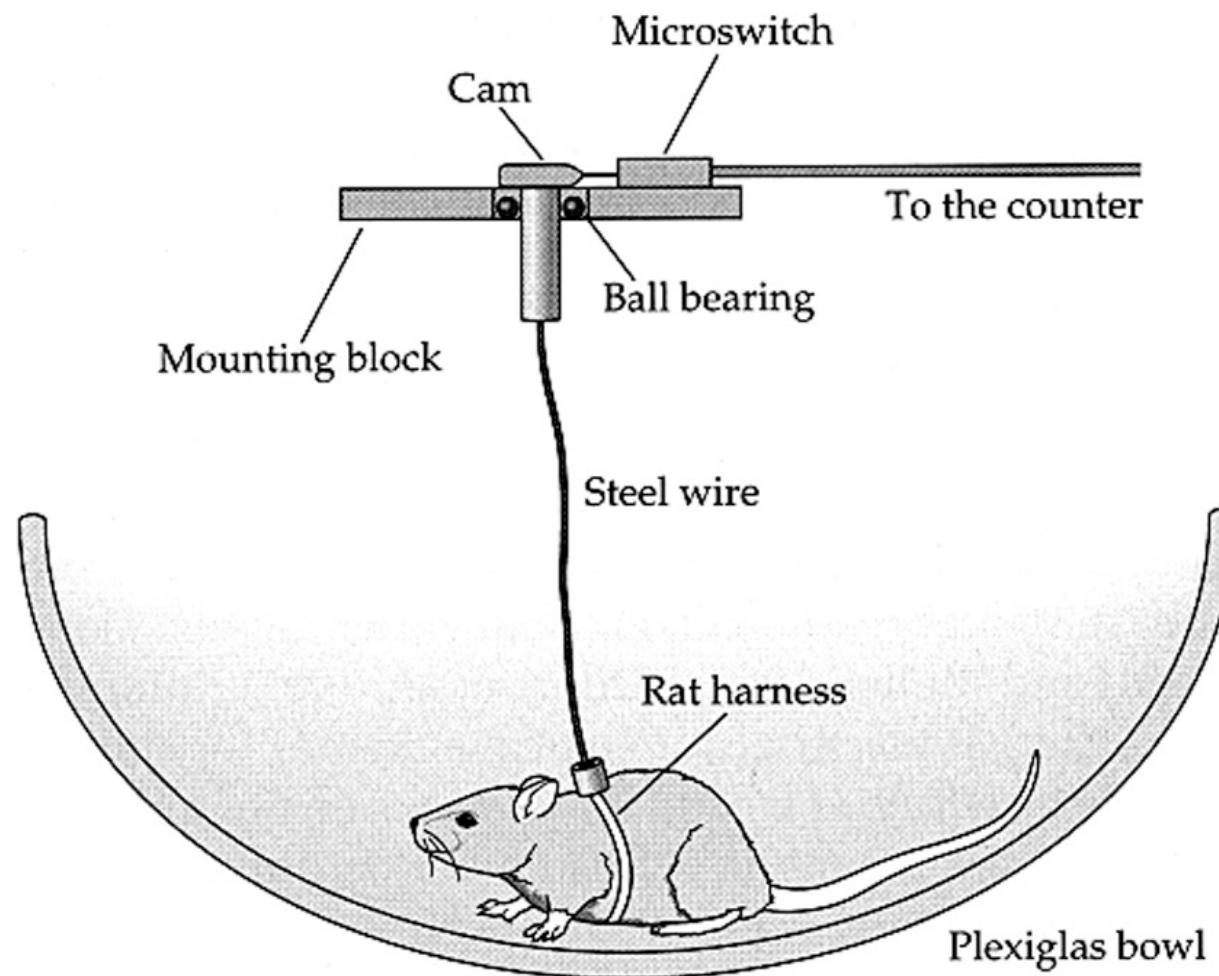
Part II Behavioural interpretations of the dopamine denervation syndrome

Non-specific effects of electrolytic LH lesions: primarily motoric



Levitt & Teitelbaum (1975)

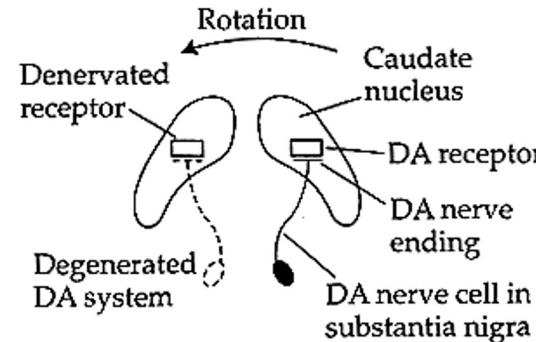
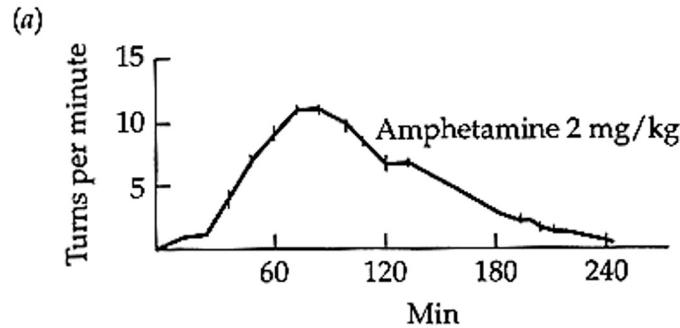
Quantifying rotation in rats – surprisingly useful for understanding recovery from motivational deficits



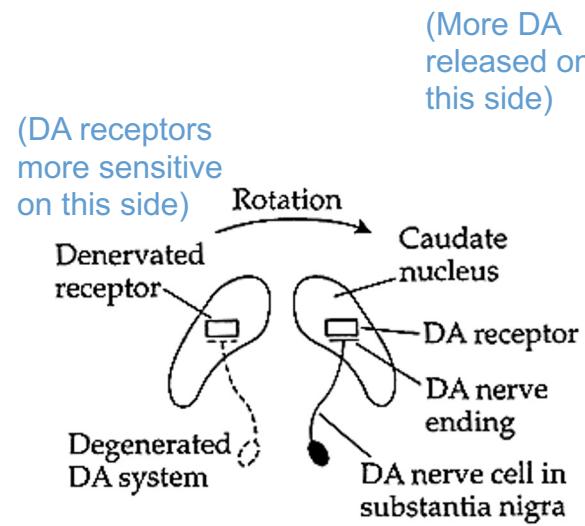
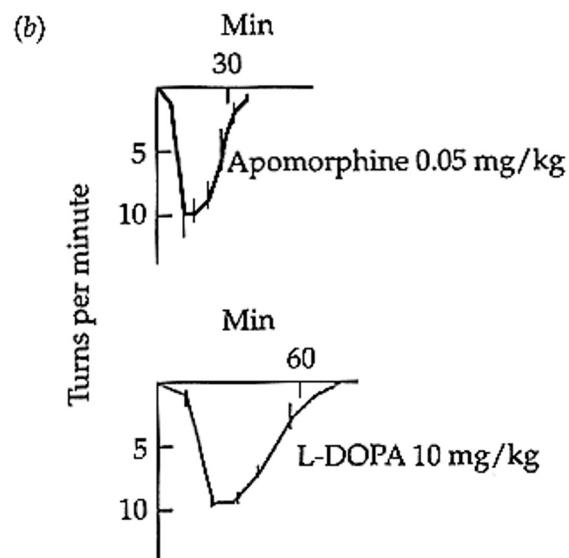
Ungerstedt & Arbuthnott (1970)

Rats with 6-OHDA lesions of the nigrostriatal pathway: rotations following dopaminergic drug administration

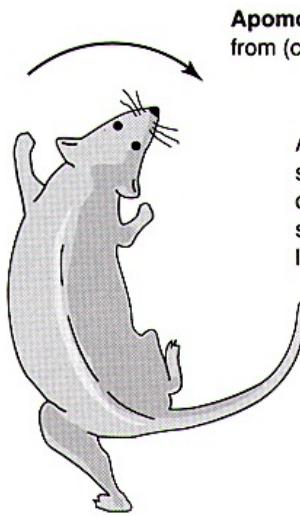
Indirect
agonist:



Direct
agonist:

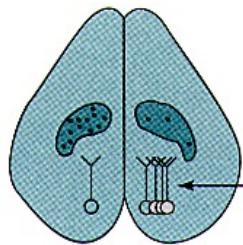
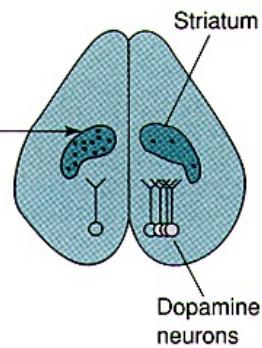


Direct and indirect dopamine receptor agonists: rotation in opposite directions in unilateral 6-OHDA rats



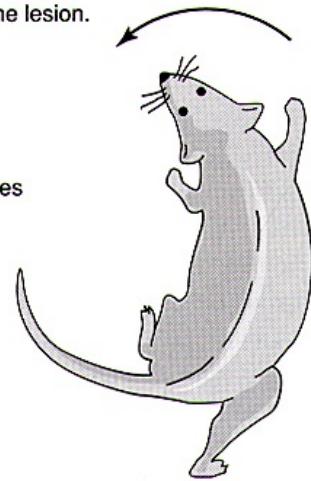
Apomorphine causes rotation away from (contralateral to) the lesion.

Apomorphine activates supersensitive dopamine receptor signaling on lesioned side



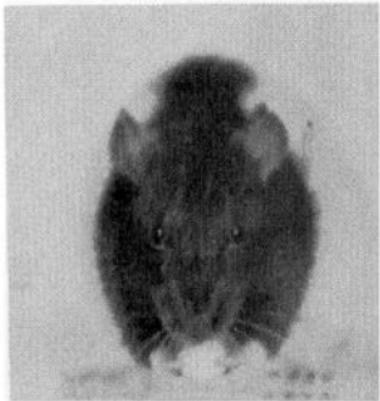
Amphetamine causes rotation toward (ipsilateral to) the lesion.

Amphetamine causes more dopamine release from unlesioned side

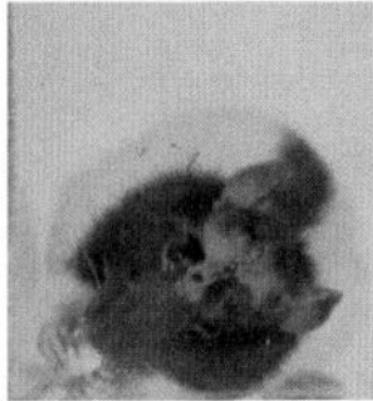


Unilateral lesions of the LH or the nigrostriatal dopamine system produce postural asymmetry

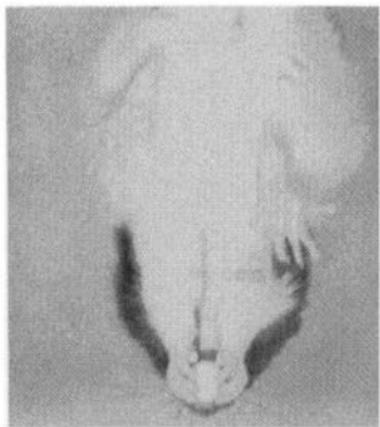
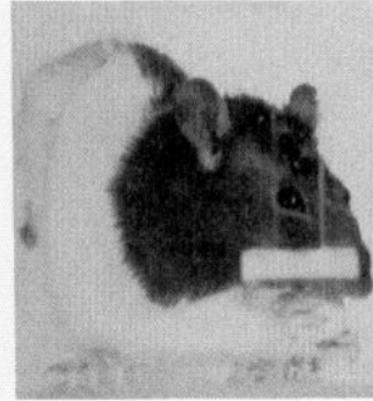
A. Presurgery



B. Day 3



C. Day 60



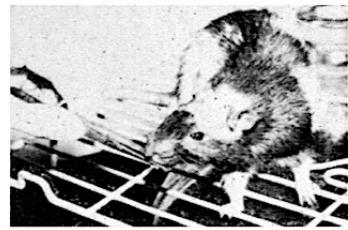
Unilateral lesions of the LH or the nigrostriatal dopamine system produces ‘unilateral neglect’

Ipsilesional
(‘good’) side

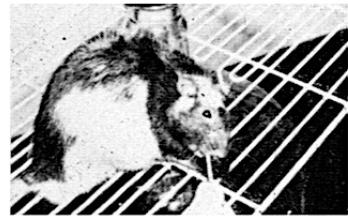
WHISKER
TOUCH



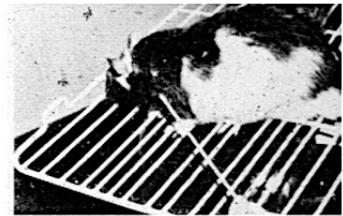
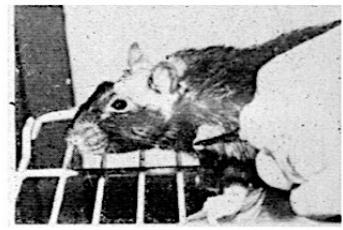
ODOR



BODY
TOUCH



Contralesional
(‘bad’) side

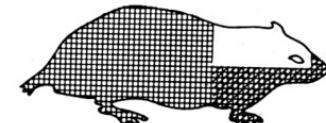


Days
Post-op

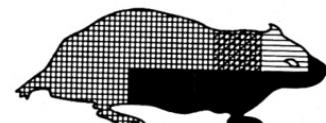
1



3



9

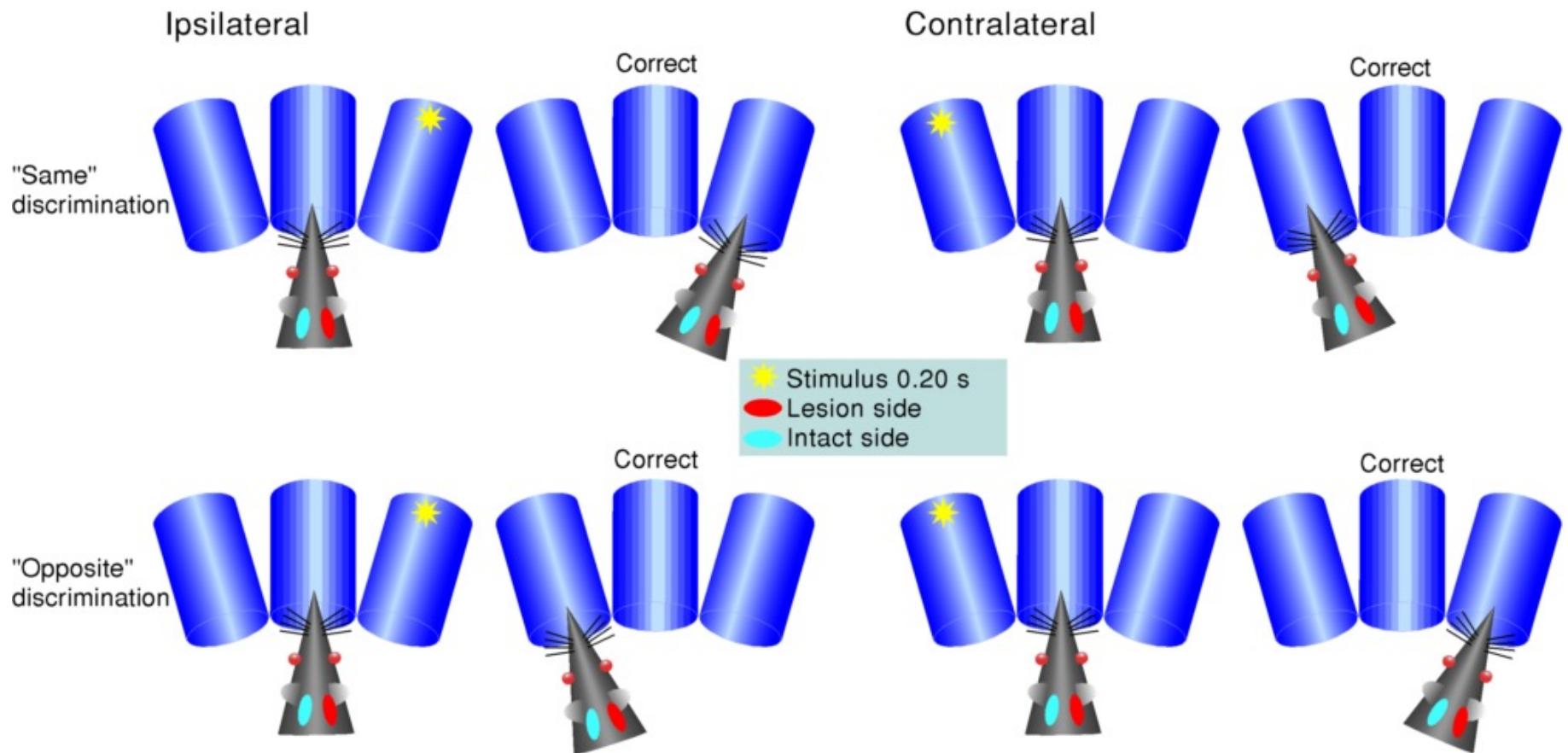


30



- Directed Head Orientation with biting
- Directed Head Orientation without biting
- Vague Orientation
- Scratching Stimulus Away
- No Oriented Response

Dopamine depletion from the striatum: sensory deficit, motor deficit, or sensorimotor deficit?



Carli et al. (1985)

Dopamine depletion from the striatum: sensory deficit, motor deficit, or sensorimotor deficit?

Remember:
IPSI = 'good'
side, CONTRA
= 'bad' side.

Sensory Neglect

STIMULUS

Motor Neglect

STIMULUS

Sensorimotor integration

STIMULUS

RESPONSE

IPSI CONTRA

IPSI
CONTRA

IPSI CONTRA

IPSI
CONTRA

IPSI CONTRA

IPSI
CONTRA

Dopamine depletion from the striatum: sensory deficit, motor deficit, or sensorimotor deficit?

Remember:
IPSI = 'good'
side, CONTRA
= 'bad' side.

Sensory Neglect

STIMULUS

Motor Neglect

STIMULUS

Sensorimotor integration

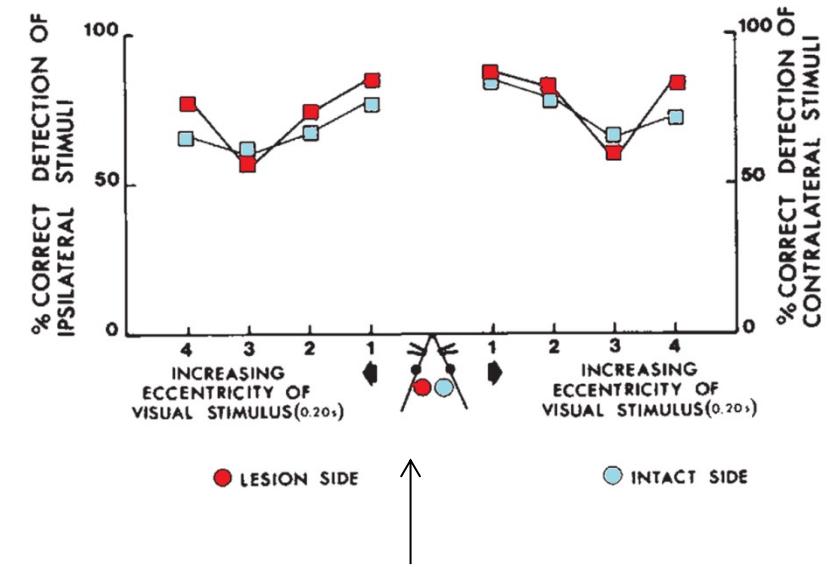
STIMULUS

		RESPONSE	
		IPSI	CONTRA
IPSI	IPSI	✓	✓
	CONTRA	✗	✗

		IPSI	CONTRA
IPSI	IPSI	✓	✗
	CONTRA	✓	✗

		IPSI	CONTRA
IPSI	IPSI	✓	✓
	CONTRA	✓	✗

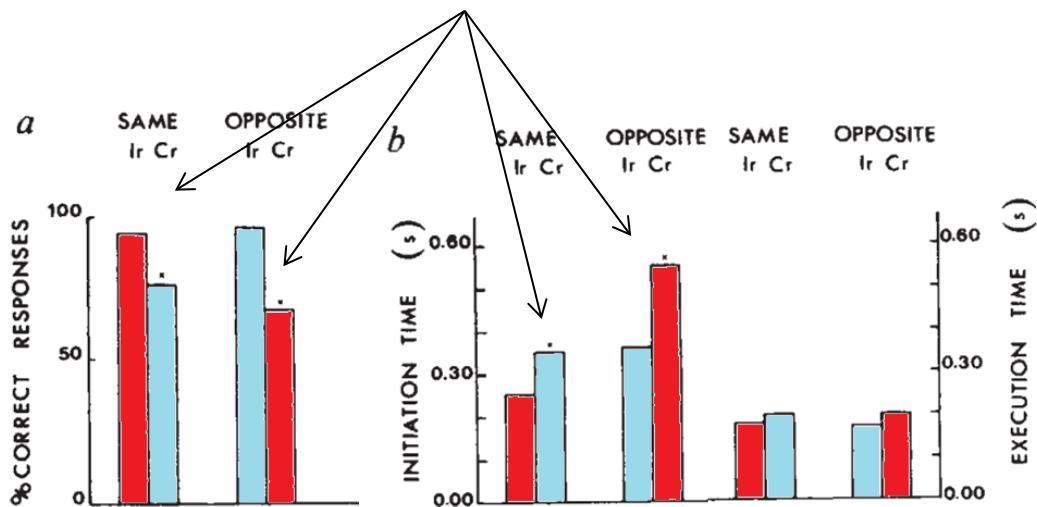
Unilateral dopamine depletion from the striatum: deficits consistent with motor response initiation in rats



Carli et al. found no differences in the ability to detect visual stimuli on either side of space.



There were problems in initiating responses on the contralesional side, suggestive of a motor deficit.



Carli et al. (1985)

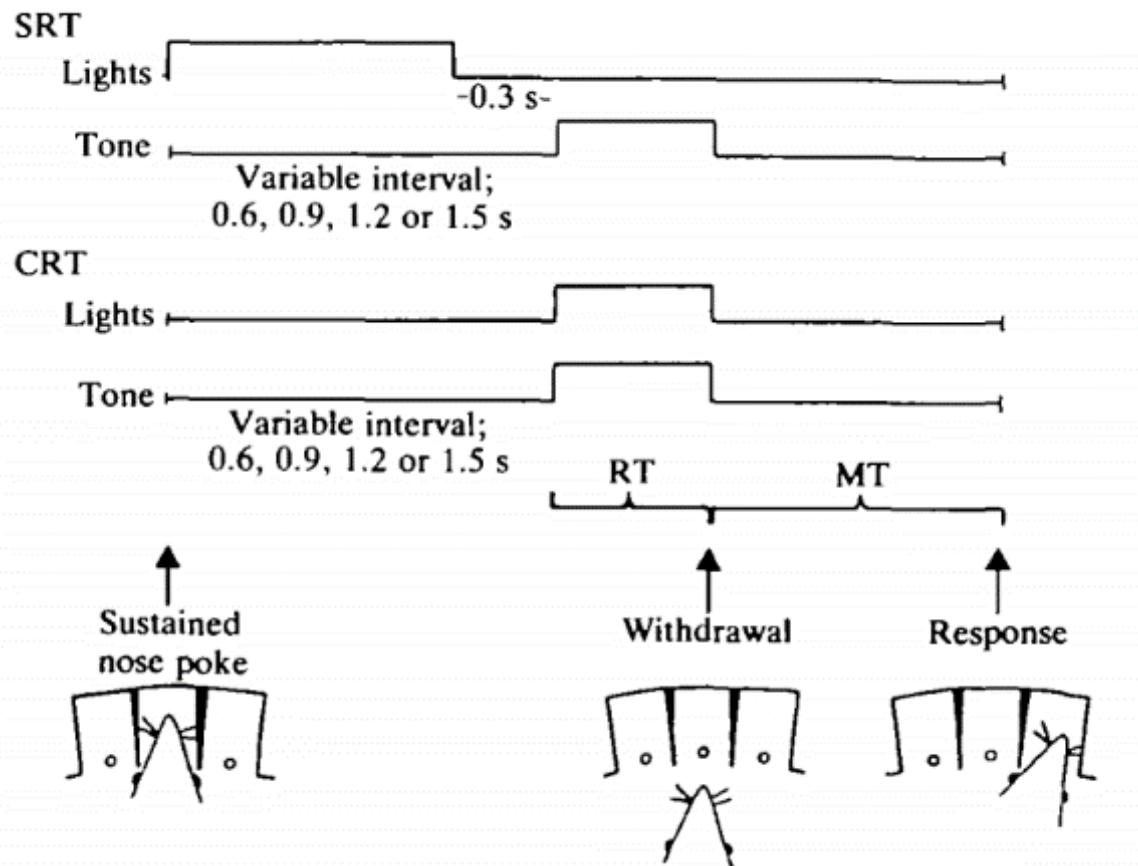
Unilateral striatal dopamine depletion: impaired motor readiness or 'activation' rather than movement per se

Lights presented on both sides:

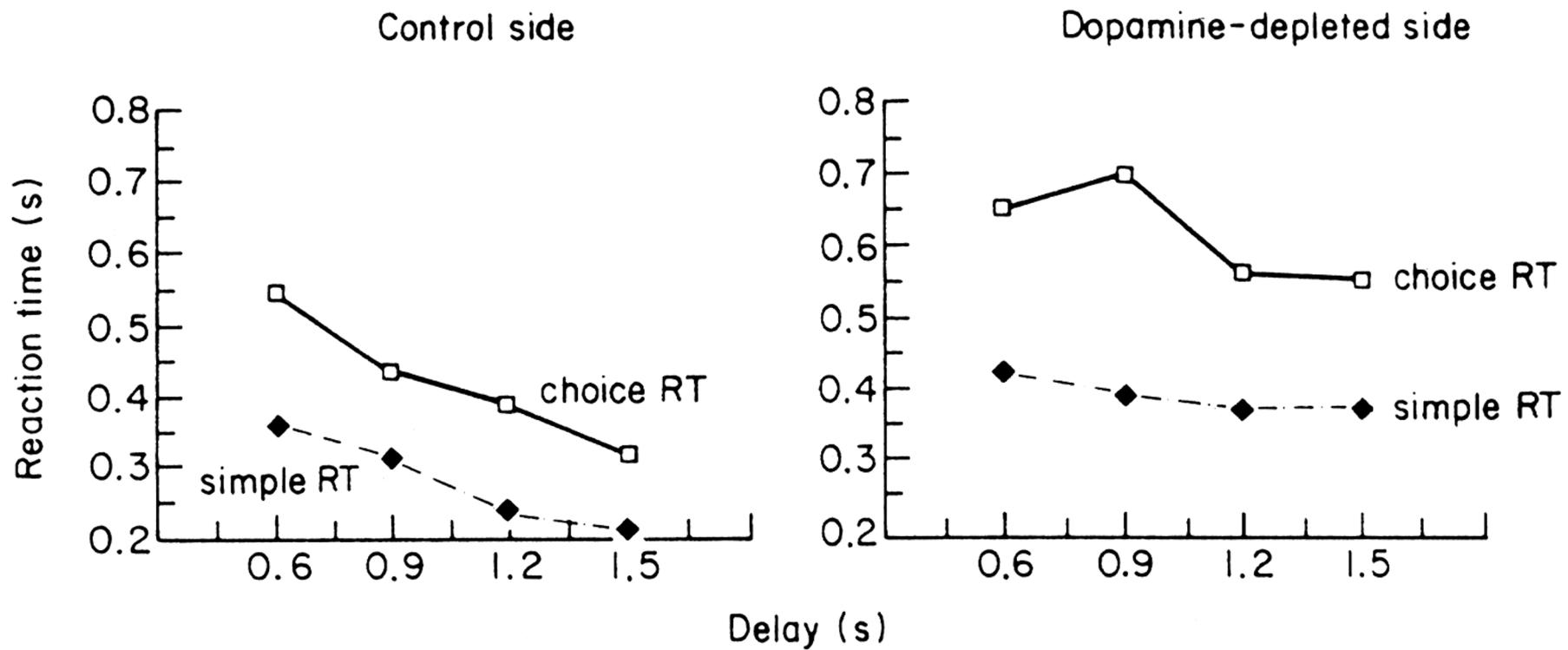
- Bright → Go left
- Dim → Go right

Tone signalled when to make response:

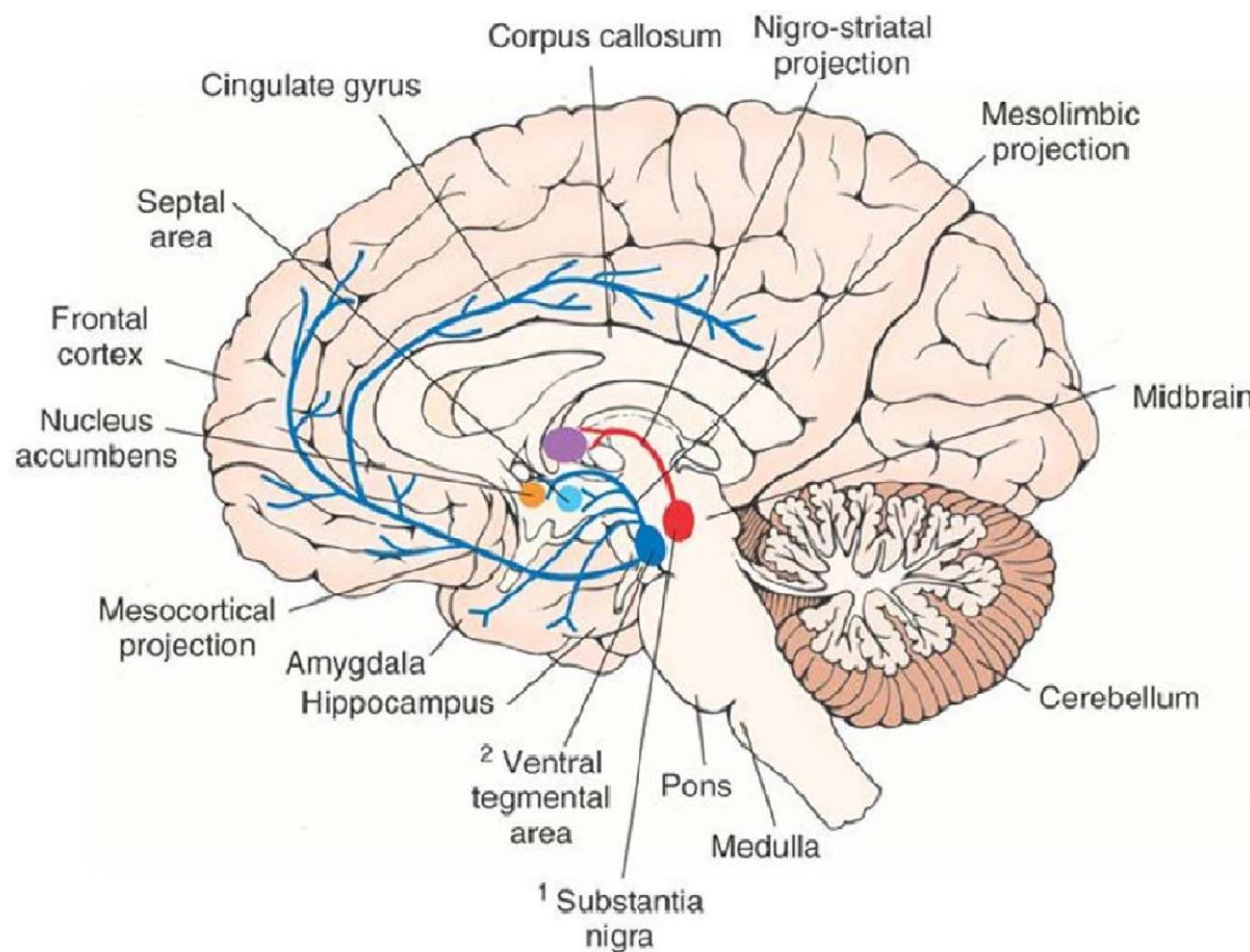
- After lights went out for Simple RT task (advance information)
- When lights came on for Choice RT task (no advance information)



Unilateral striatal dopamine depletion: impaired motor readiness or 'activation' rather than movement per se



Nigrostriatal, mesolimbic and mesocortical DA systems: different roles in motivation



Part III Central reward systems

Overview – central reward mechanisms

- **Intracranial self-stimulation (ICSS)**
- **The neural basis of ICSS (and its link to dopamine)**
- **Reward thresholds as measures of “hedonic states”**
- **Drugs of abuse as rewards**
- **A more general dopaminergic theory of reward (Wise)**

Reward vs. reinforcement



Reward

**Actively enjoyed;
has hedonic value.**



Reinforcement

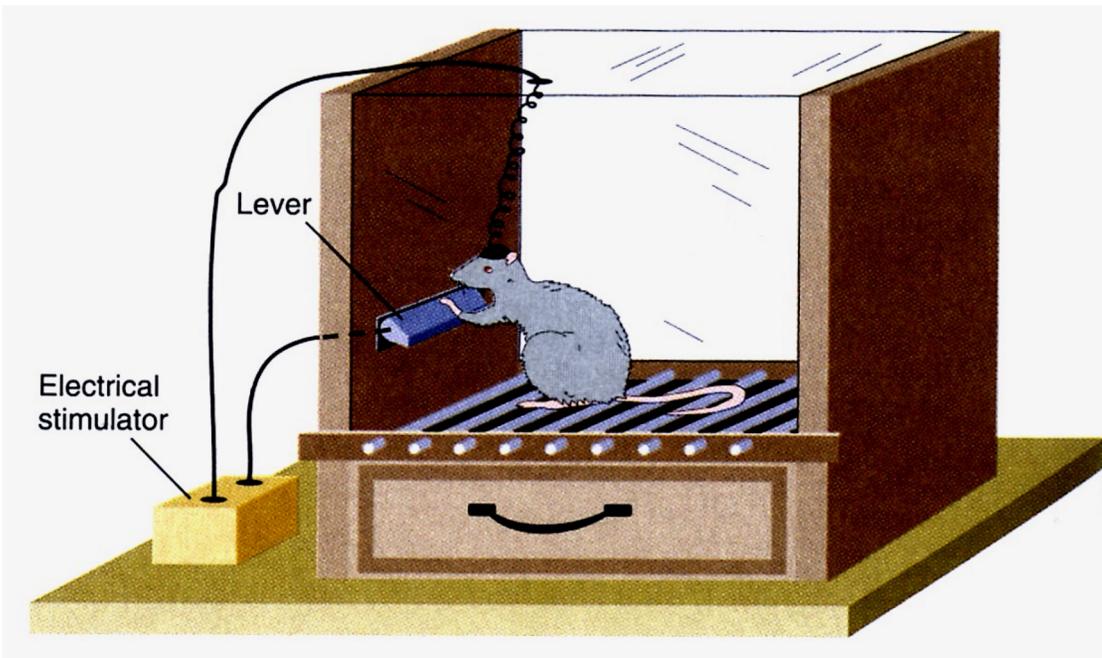
**Likely to elicit
behaviour again.**

Probing brain mechanisms of reinforcement: Intracranial self-stimulation (ICSS)

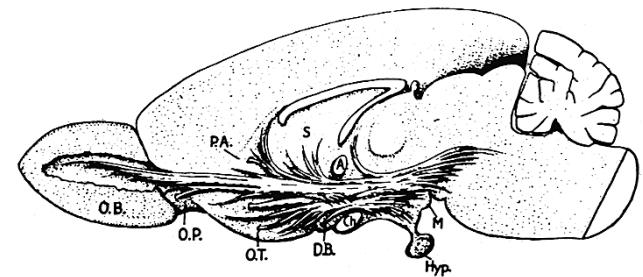
Electrical self-stimulation of the brain



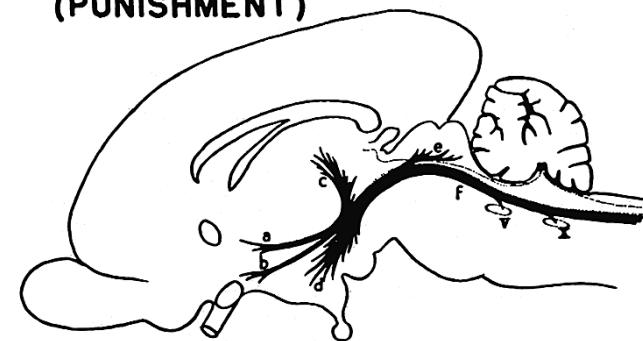
Electrical self-stimulation of the brain



MEDIAL FOREBRAIN BUNDLE
(REWARD)



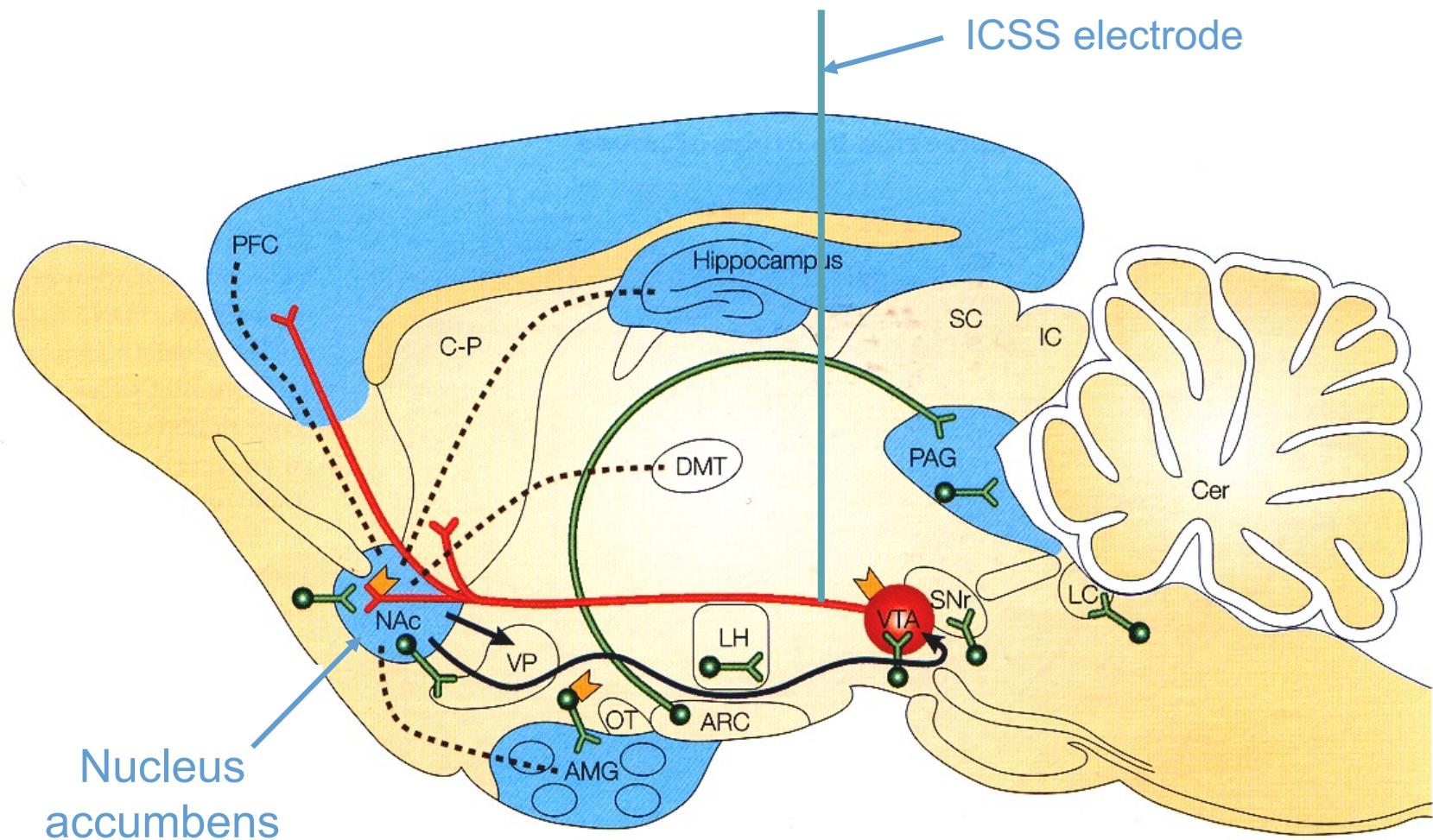
PERIVENTRICULAR SYSTEM
(PUNISHMENT)



DIAGRAMS OF LE GROS CLARK

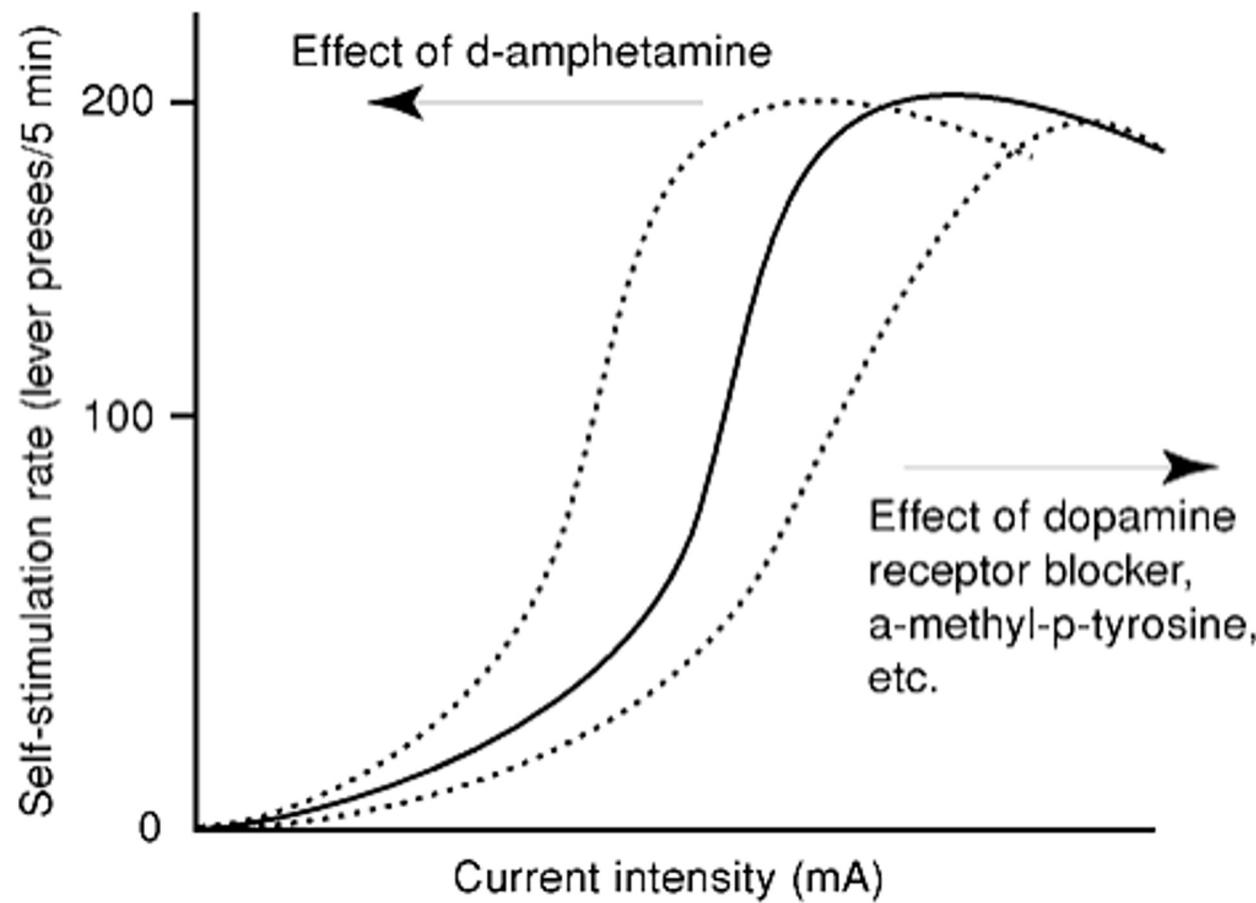
Olds & Milner (1954)

ICSS sites overlap with the mesolimbic dopamine system

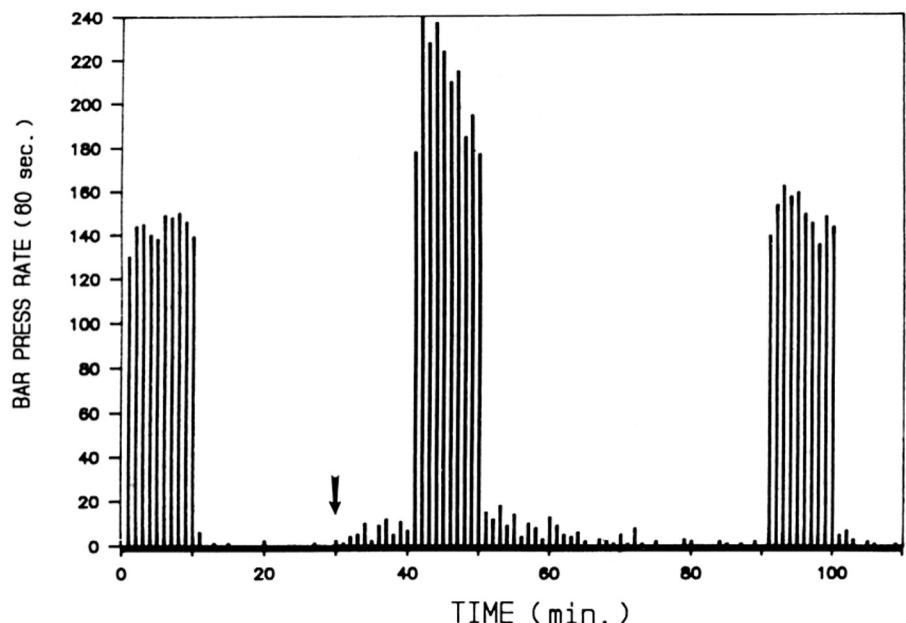
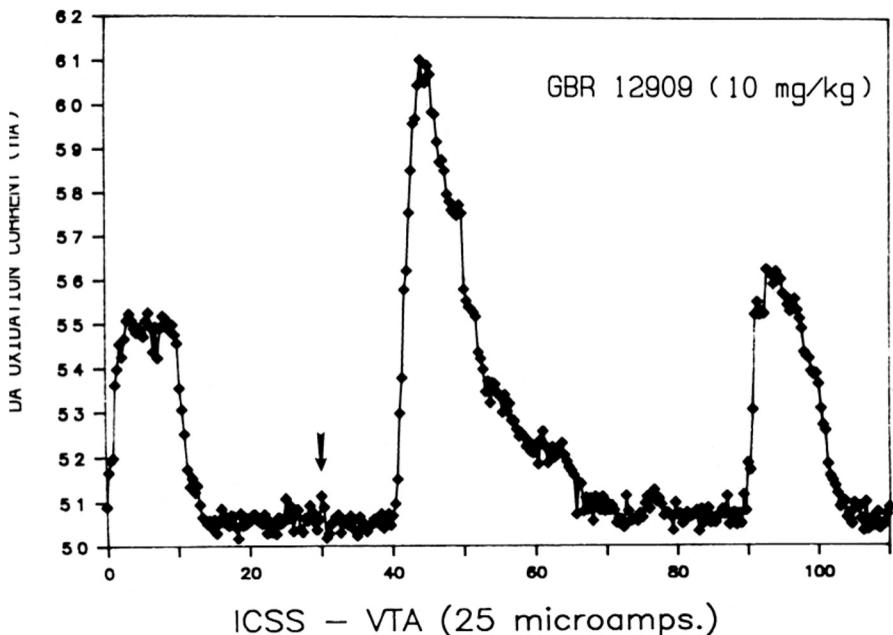


The neurochemical basis of ICSS: link with dopamine?

ICSS was rendered more rewarding/reinforcing by drugs that increase dopamine transmission, and less rewarding/reinforcing by drugs that decrease dopamine transmission.

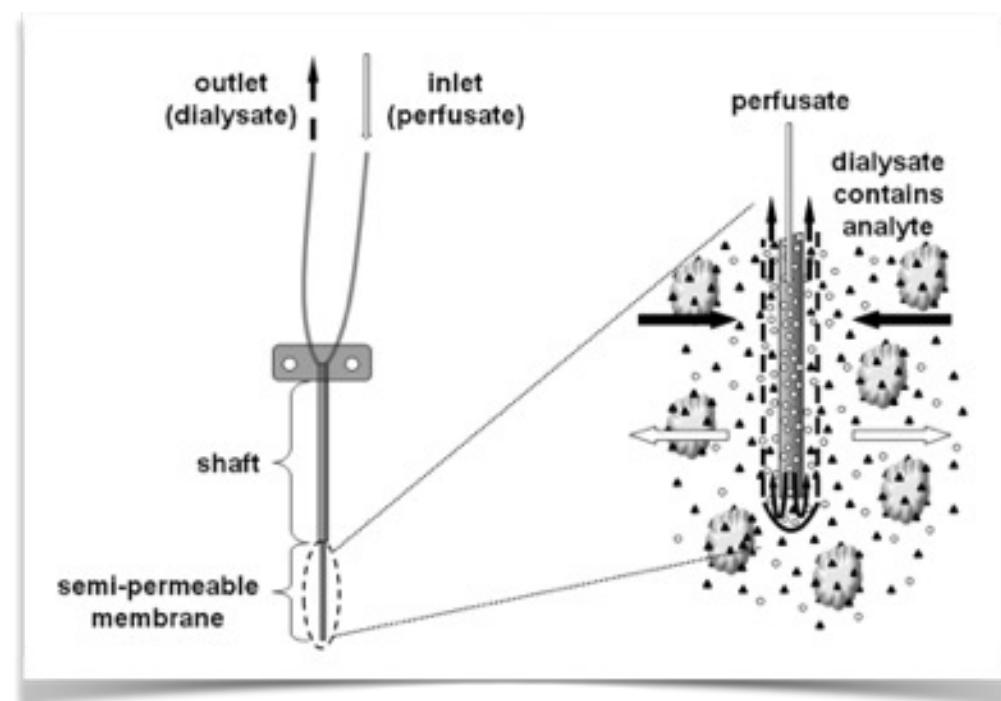
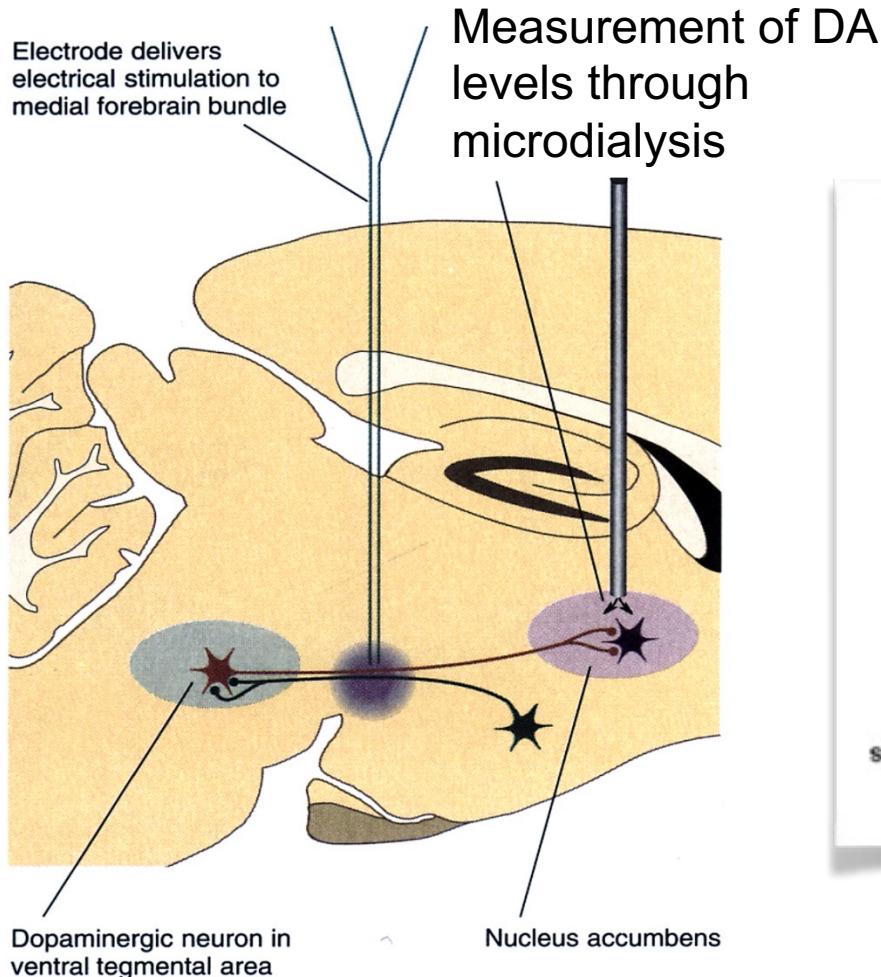


Potentiating DA release in accumbens enhances ICSS



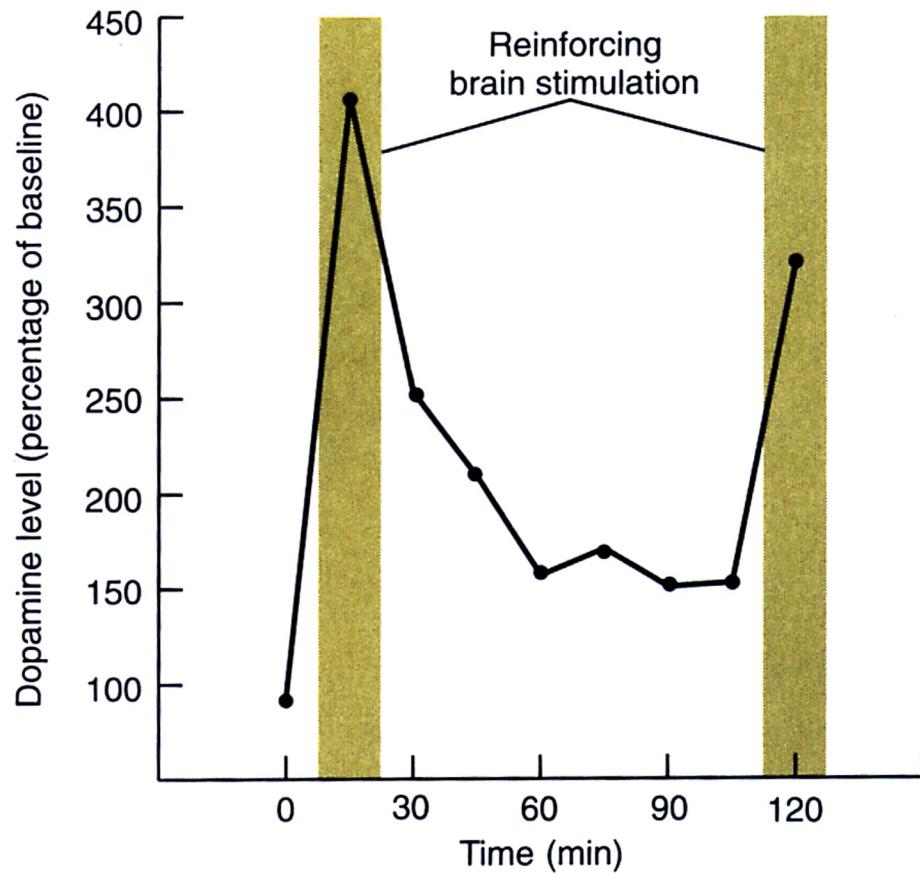
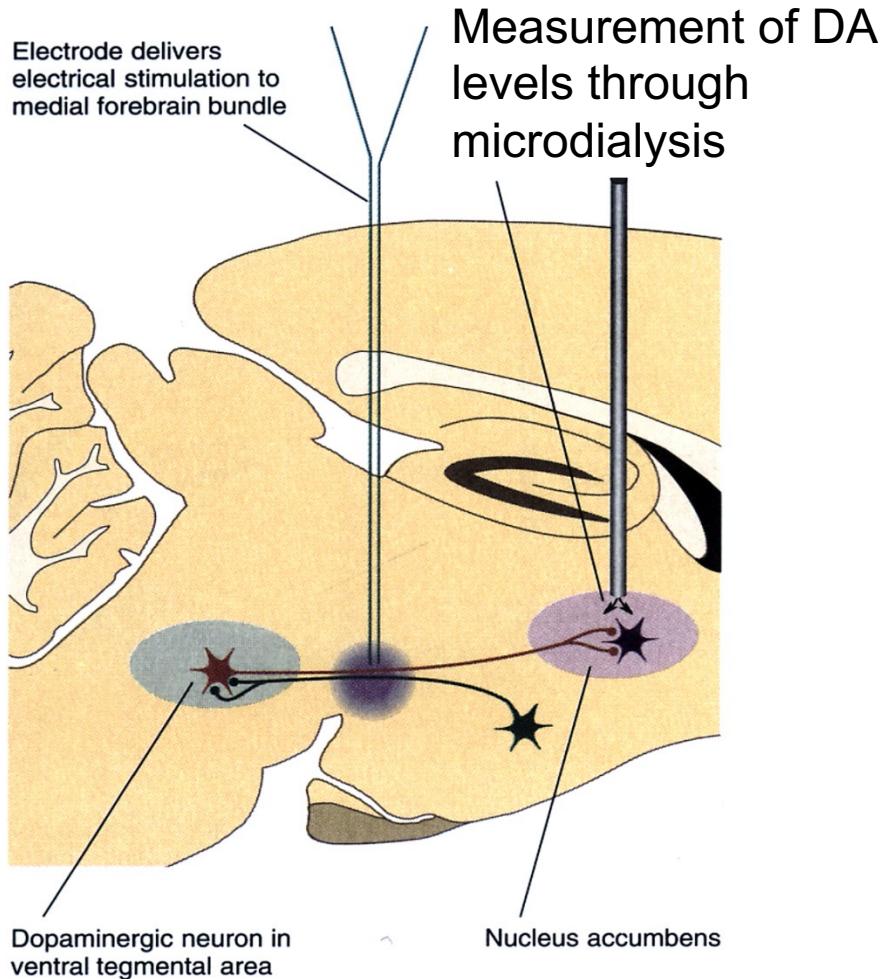
GBR 12909 (a dopamine uptake blocker) potentiates DA levels in the nucleus accumbens measured by **chronoamperometry**, and enhances lever pressing for ICSS.

Nucleus accumbens DA levels increase during ICSS



Microdialysis: measure of extra-synaptic concentrations of neurotransmitters

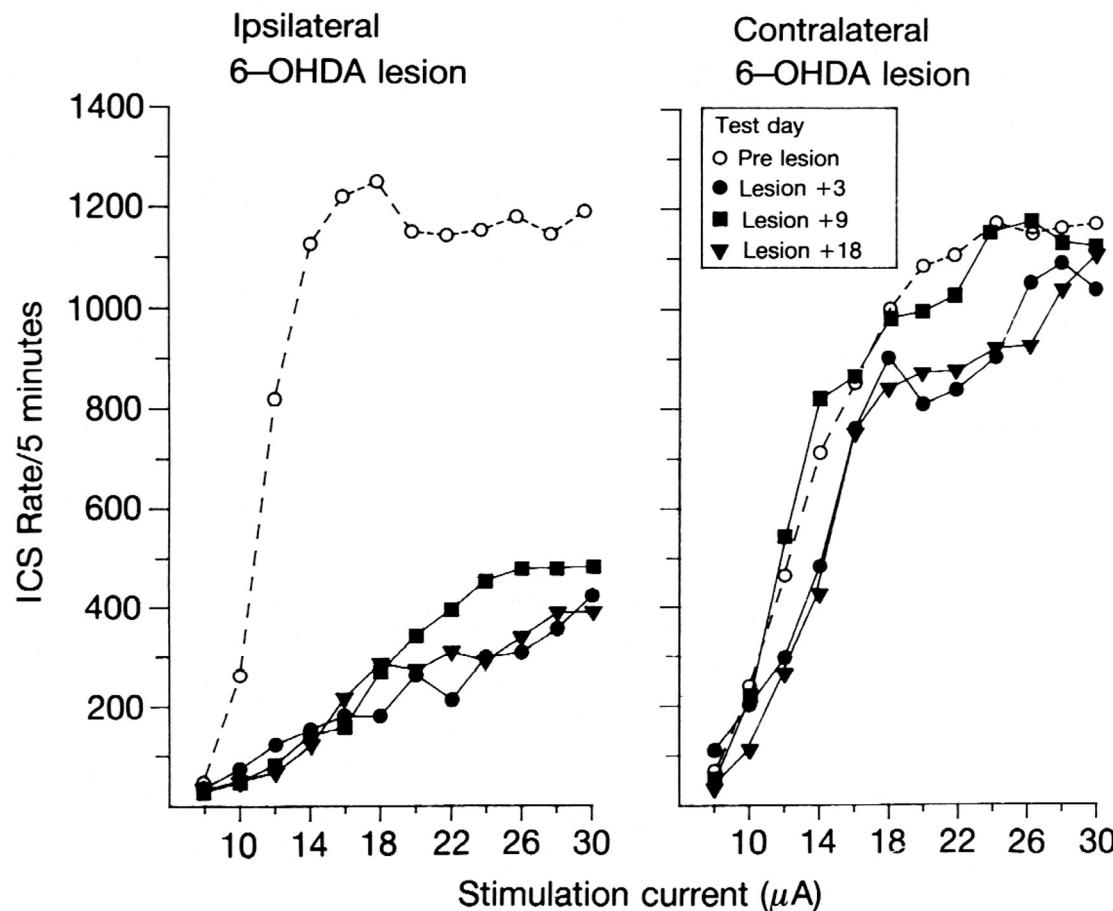
Nucleus accumbens DA levels increase during ICSS



Separating motor and limbic effects of DA in ICSS

Unilateral dopamine depletion impairs ICSS if electrodes are on ipsilesional side, but not if on contralateral side.

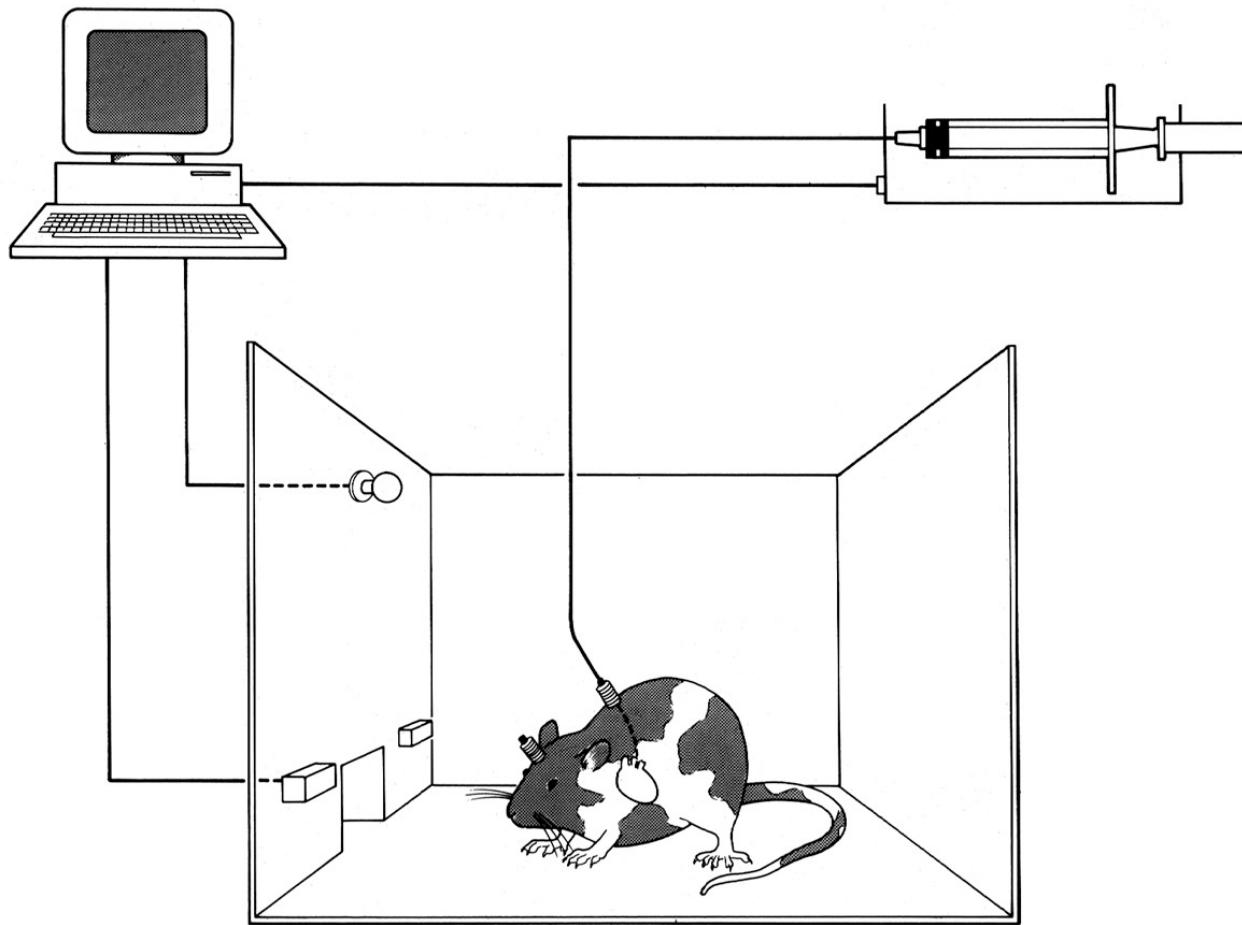
If deficits in ICSS performance were simply due to motor deficits, a unilateral lesion should impair behaviour regardless of the side of electrode implantation.



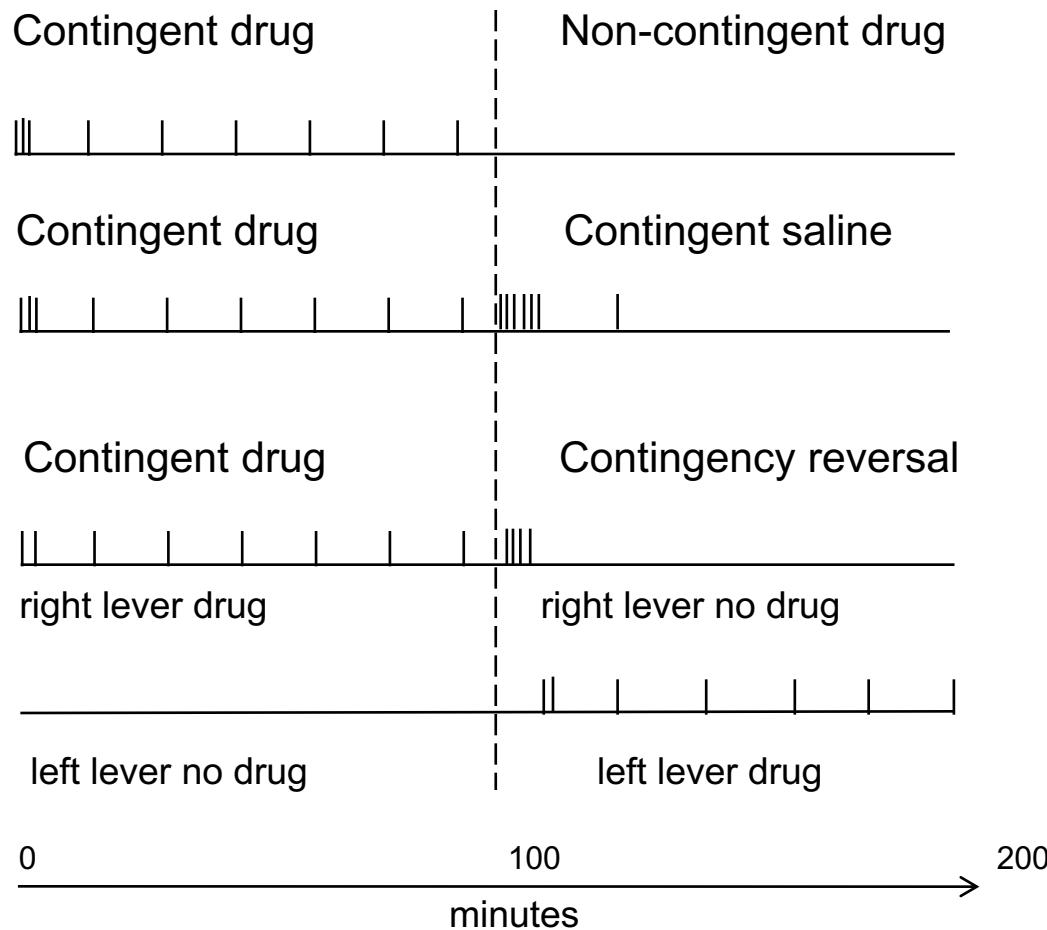
Fibiger et al. (1987)

Drugs of abuse as rewards

Drugs of abuse are self-administered by rats and monkeys



Drugs of abuse act as positive reinforcers / rewards



Pickens & Thompson (1968)

Drug self-administration is regular and regulated: titration

Titration: maintenance of an optimal level of reinforcement across a wide range of unit doses

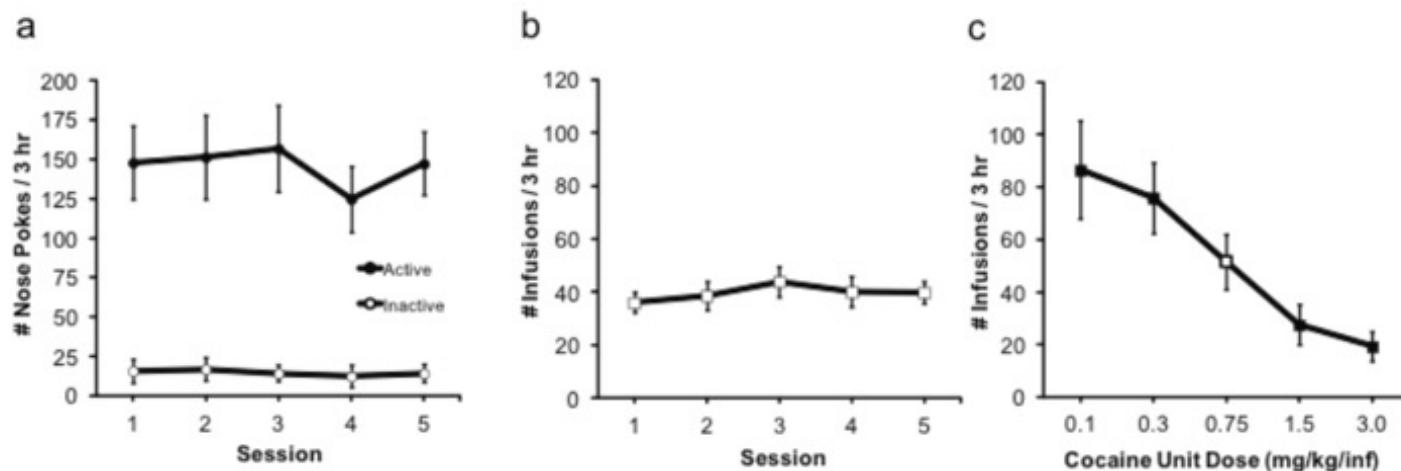
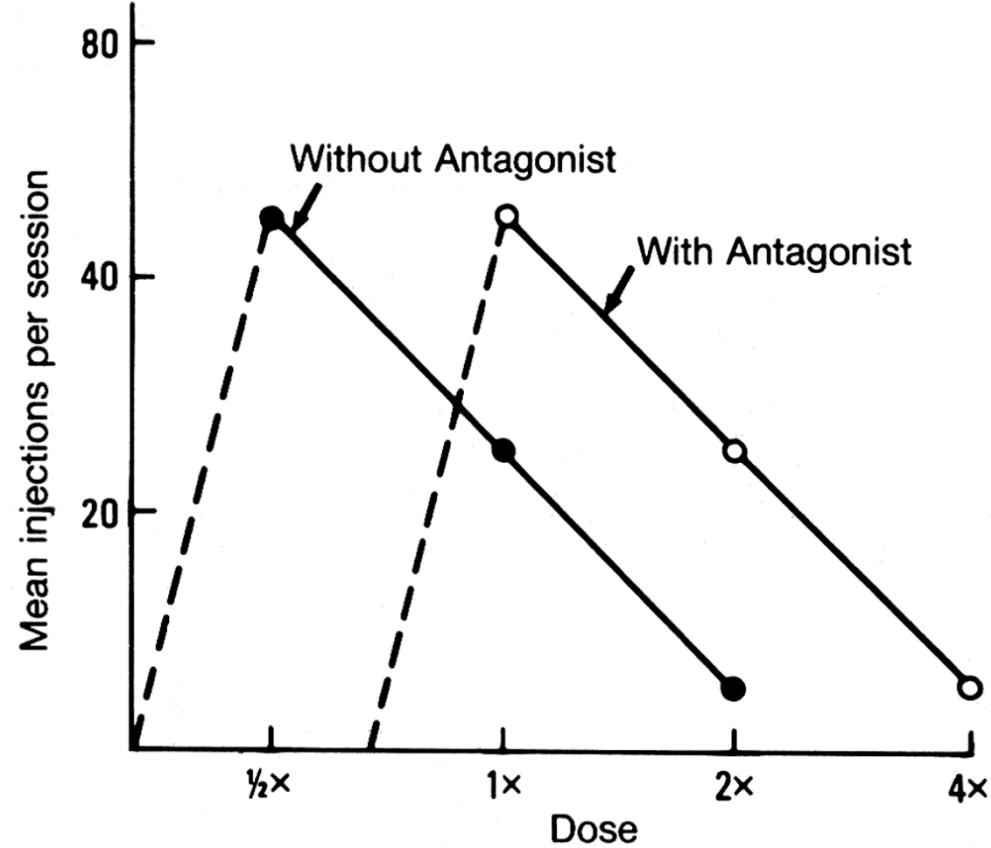
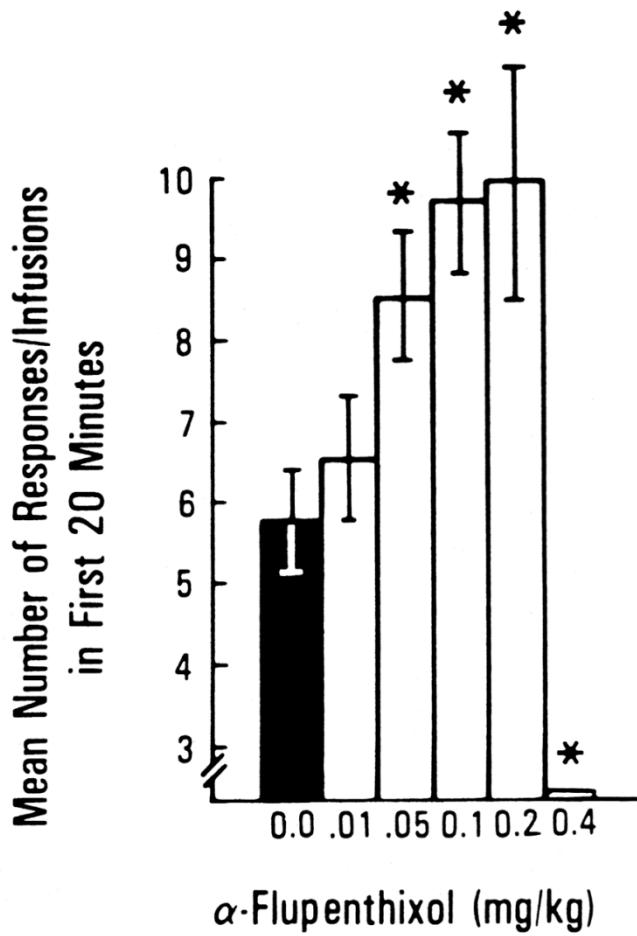


TABLE 1
MEAN (\pm SEM) POSTINFUSION PAUSE AS A FUNCTION OF INFUSION DOSE (IN SECONDS)

Rat	Cocaine Unit Dose (mg/kg)			Rat	Heroin Unit Dose (μ g/kg)		
	0.5	1.0	2.0		25	50	100
117	142 \pm 14	280 \pm 10	699 \pm 41	223	439 \pm 105	748 \pm 113	1113 \pm 115
144	219 \pm 19	424 \pm 13	555 \pm 18	227	423 \pm 125	1174 \pm 370	1372 \pm 289
145	302 \pm 50	399 \pm 32	664 \pm 76	228	458 \pm 65	730 \pm 75	933 \pm 100
170	251 \pm 43	640 \pm 47	876 \pm 32	264	313 \pm 70	1221 \pm 189	1954 \pm 273
191	208 \pm 22	332 \pm 19	452 \pm 42	267	298 \pm 43	425 \pm 53	776 \pm 89
226	206 \pm 24	389 \pm 19	462 \pm 39	282	155 \pm 40	1178 \pm 302	1570 \pm 202

Drug self-administration: role of dopamine

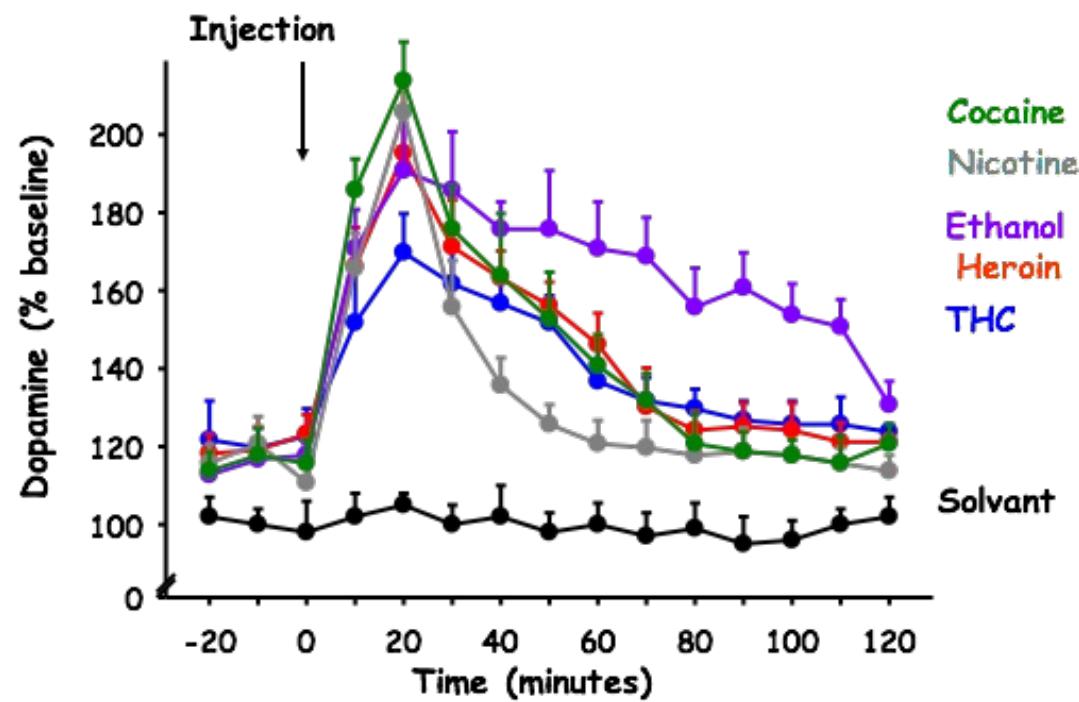
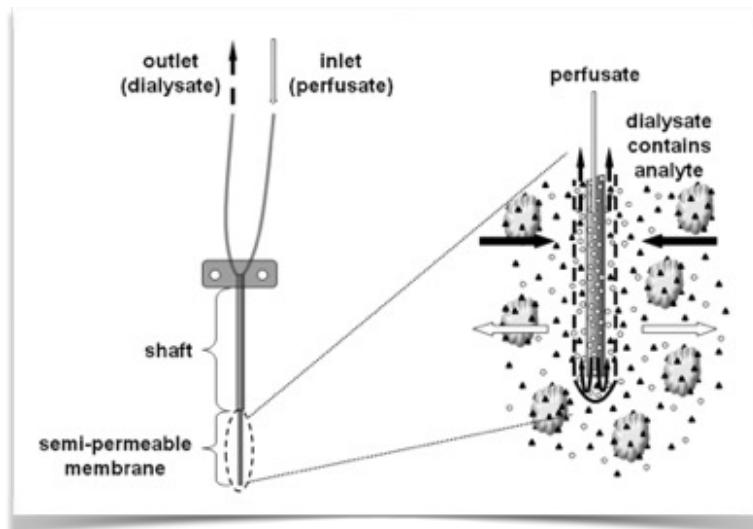
Dopamine receptor antagonists: right-shift of the dose-response curves



Drug self-administration: role of dopamine

All addictive drugs increase DA concentration in the Nucleus accumbens (NAc)

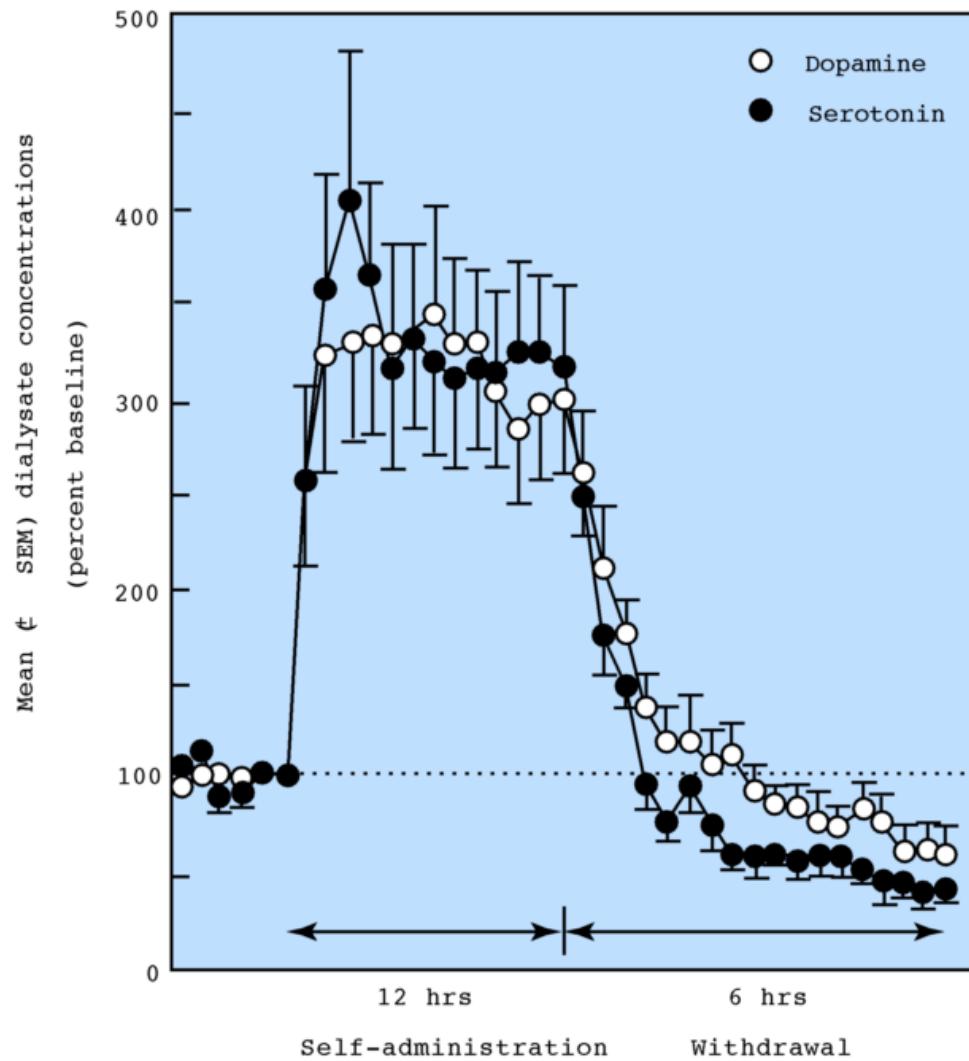
Microdialysis: measure of extra-synaptic concentrations of neurotransmitters



Di Chiara, G. & Imperato, A. (1988)

Drug self-administration: role of dopamine

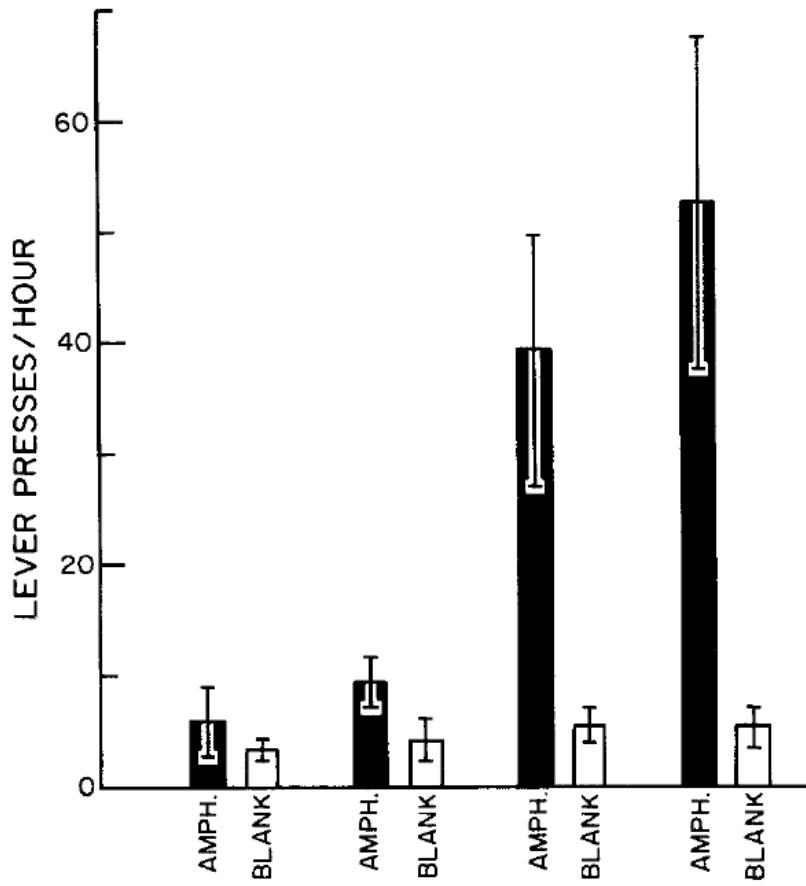
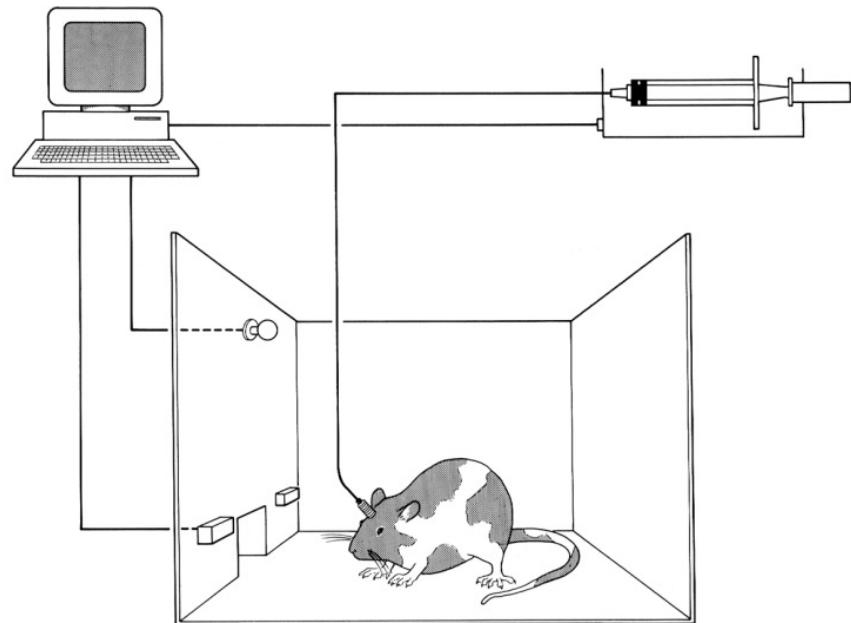
NAc DA levels increase during cocaine self-administration



Parsons et al. (1995)

Drug self-administration: role of dopamine

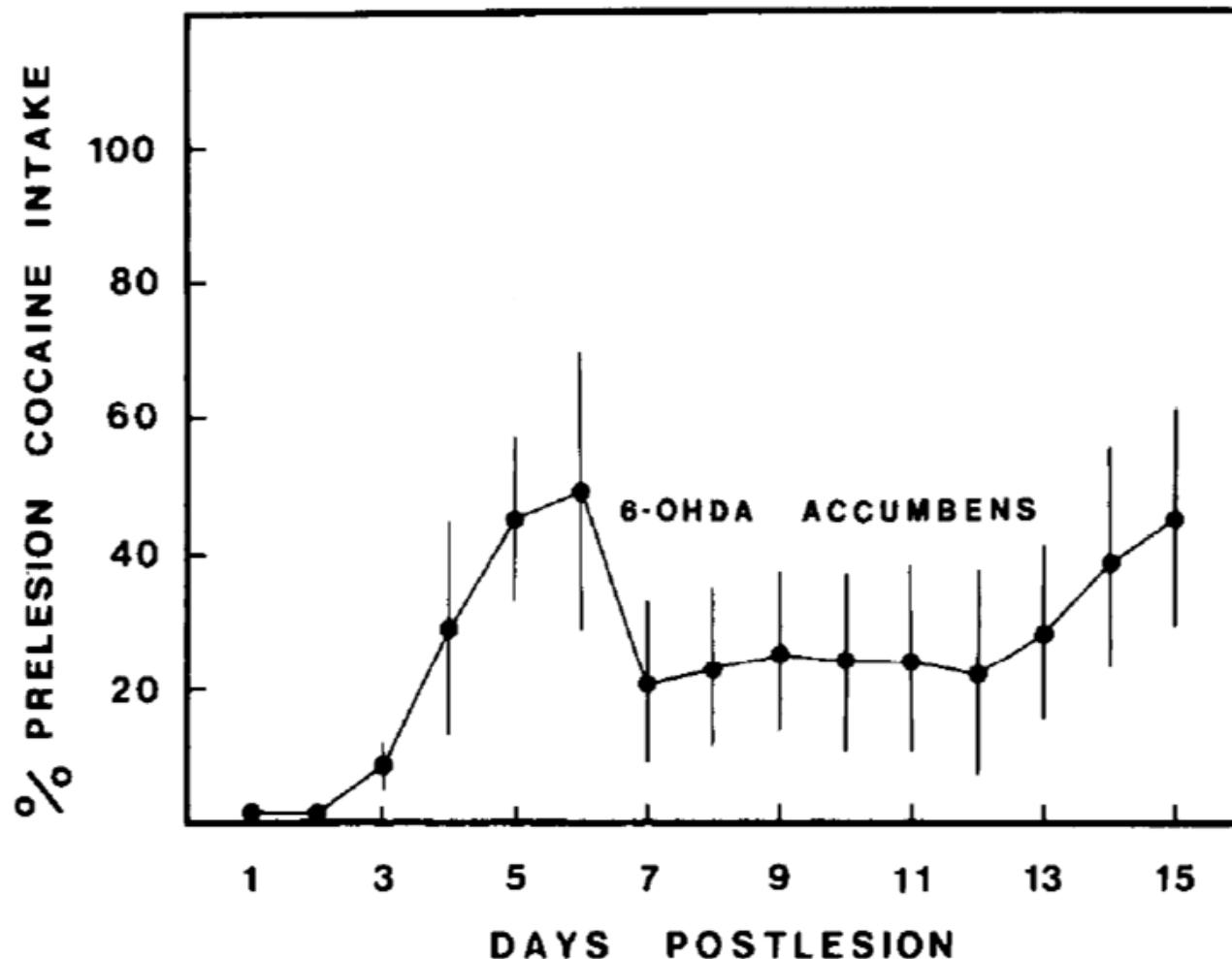
Rats will self-administer amphetamine directly into the NAc in nanolitre quantities



Hoebel et al. (1983)

Drug self-administration: role of dopamine

Dopamine depletion within the NAc reduces cocaine self-administration

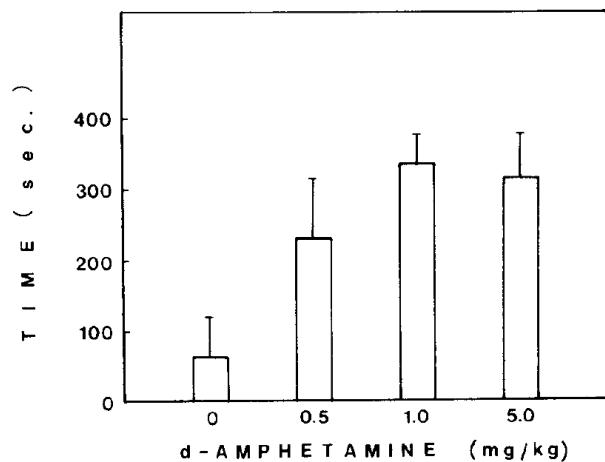
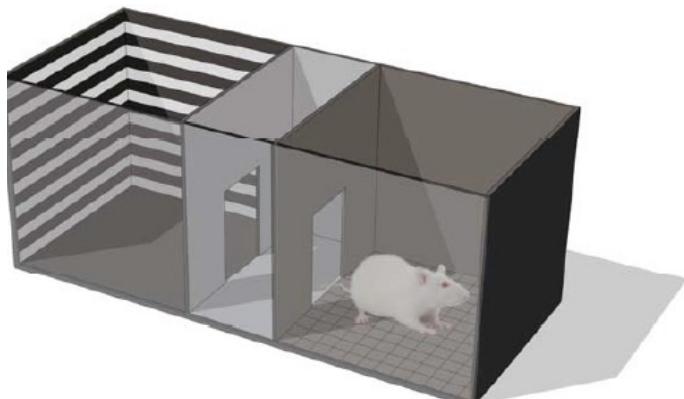


Roberts et al. (1977)

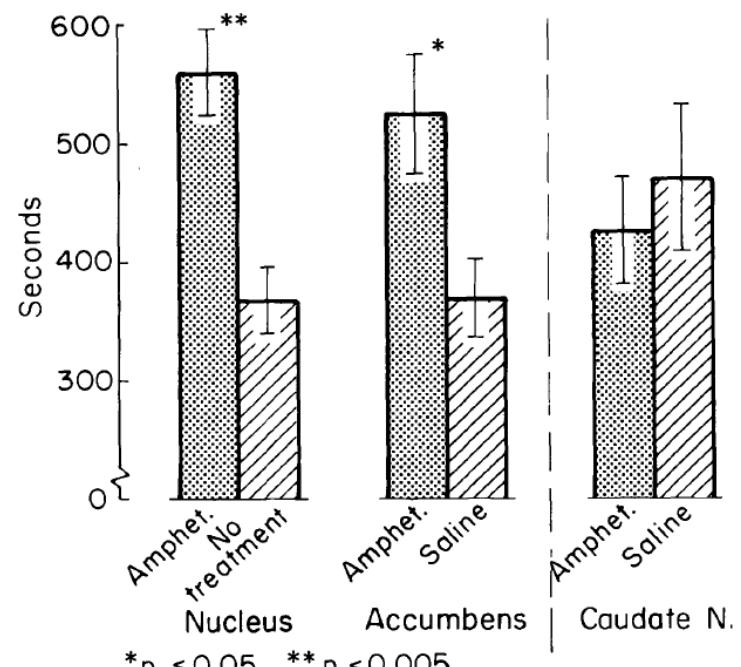
Drug self-administration: role of dopamine

Rats show a place preference for a compartment previously associated with amphetamine (conditioned place preference, CPP)

Systemic amphetamine (i.p.)



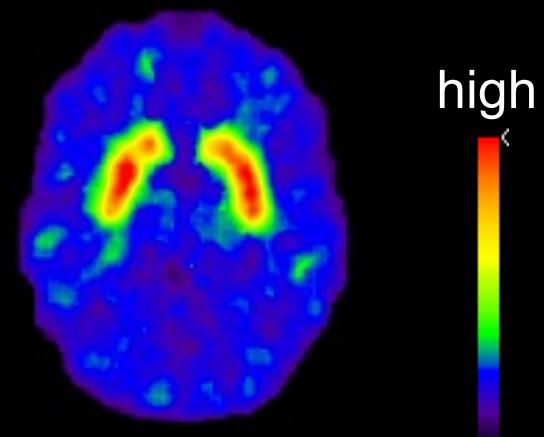
Intra-accumbens amphetamine



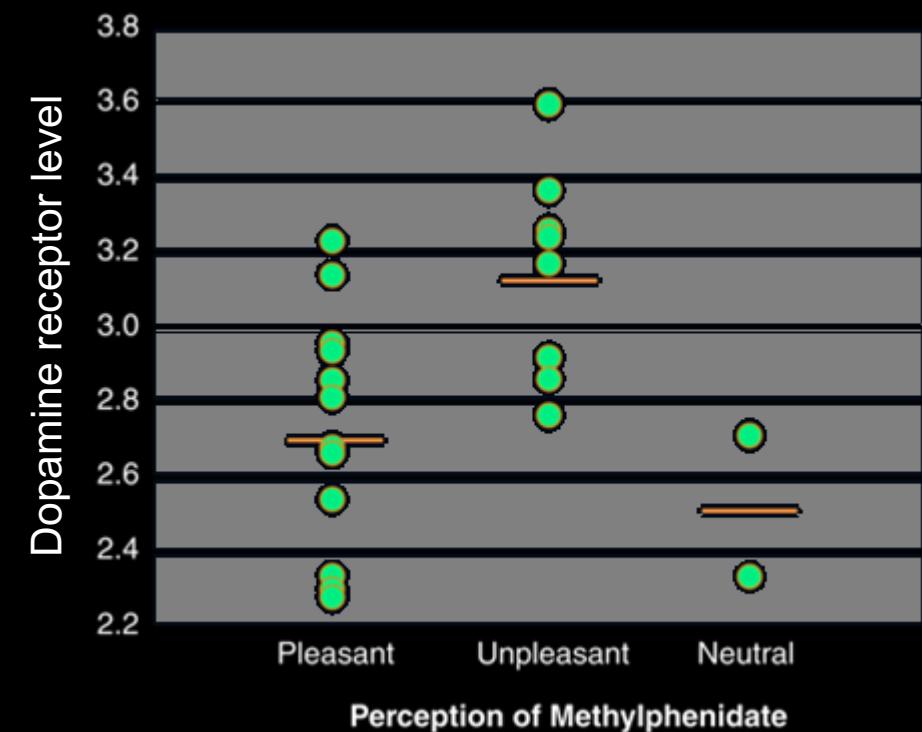
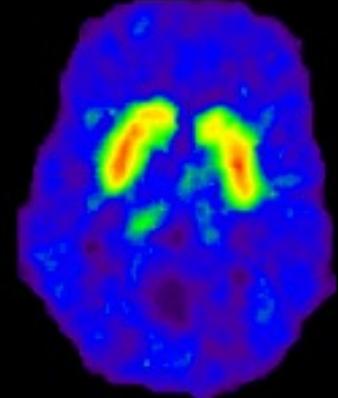
Sprakai et al. (1982); Carr & White (1983)

Individual variations in the subjective response to drugs of abuse – possibly linked to mood / arousal

High DA D2 receptor

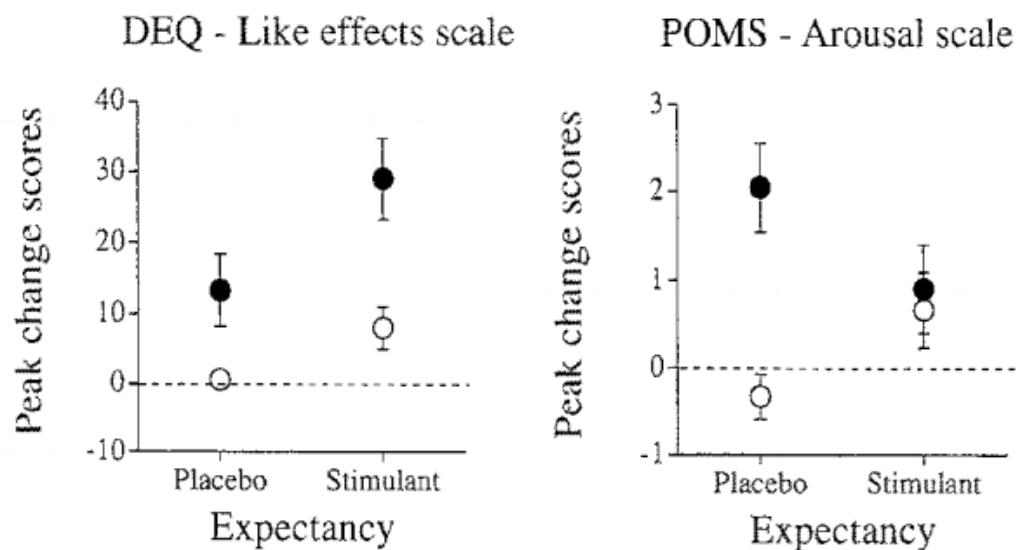
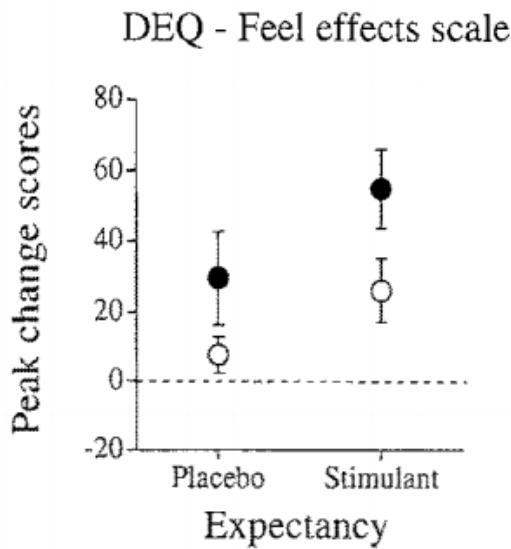


Low DA D2 receptor



As a group, subjects with low receptor levels found methylphenidate pleasant while those with high levels found it unpleasant.

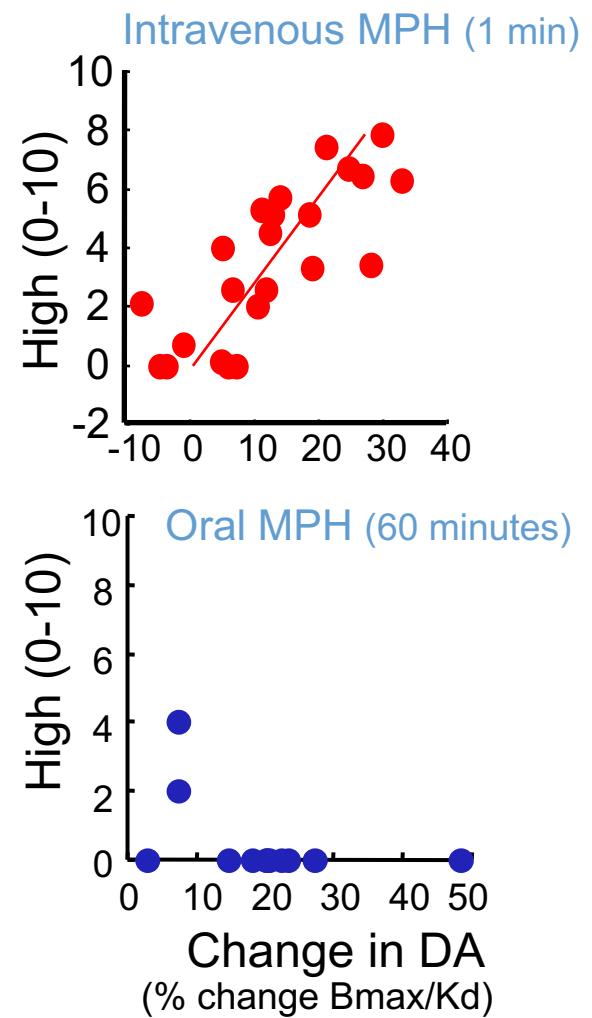
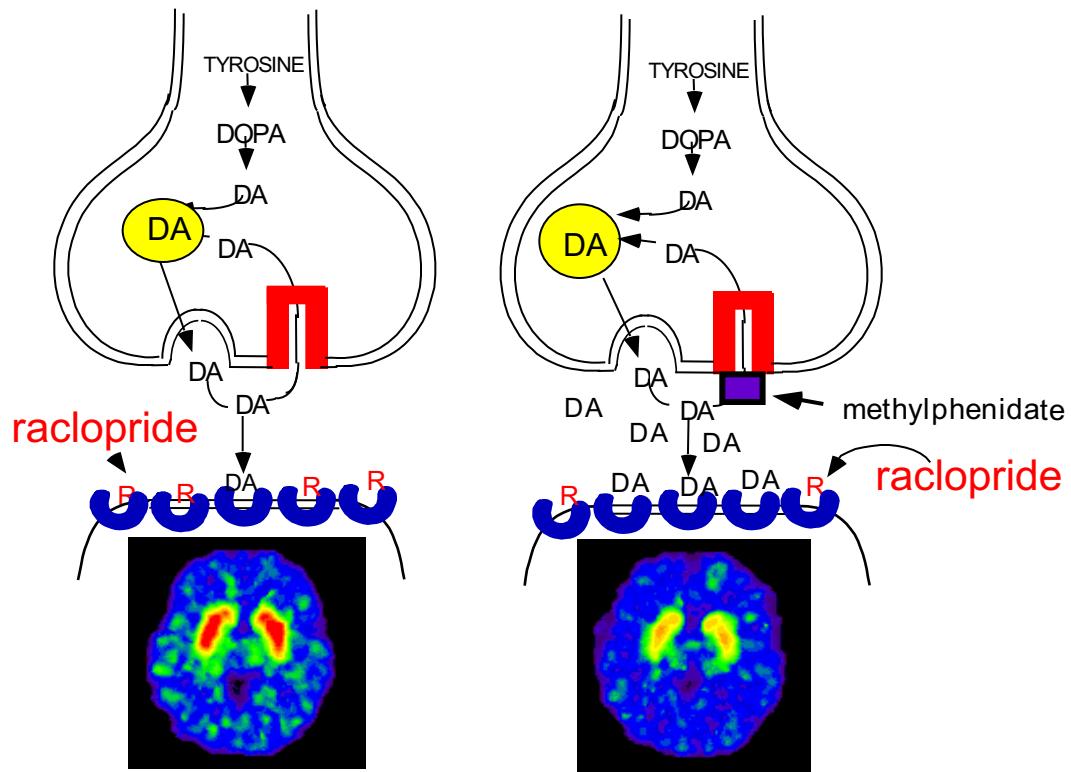
Effect of expectancy on the subjective response to amphetamine



● Got Stimulant ○ Got Placebo

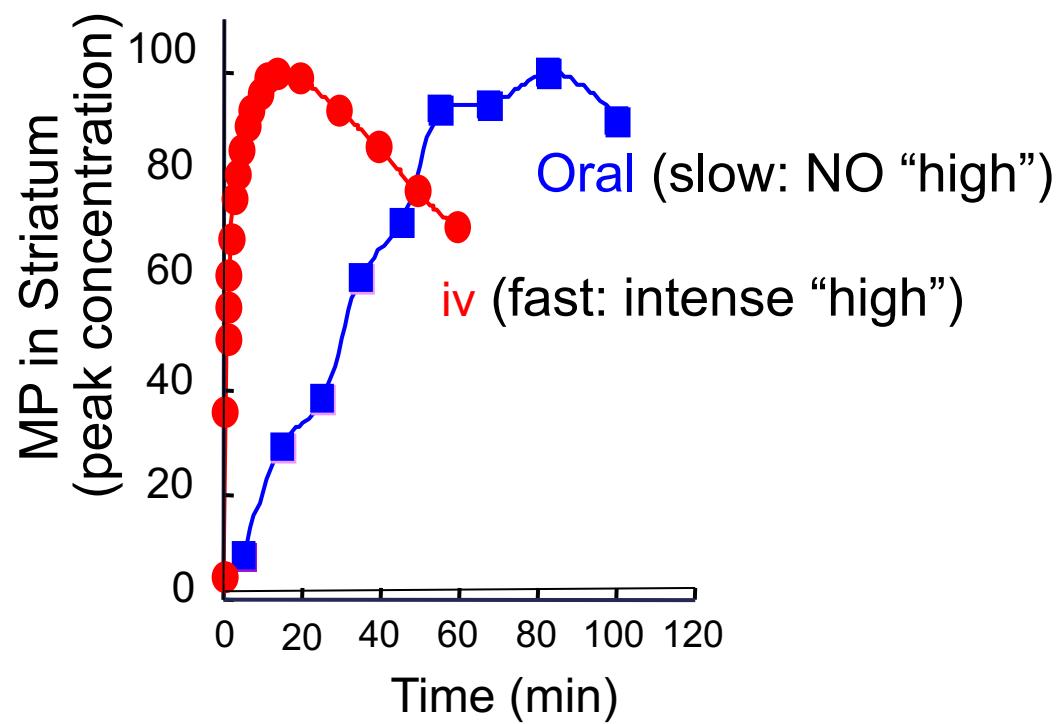
The subjective response to drugs of abuse depends upon expectancy as well as the drug's pharmacological mechanism of action.

Displacement PET studies using methylphenidate (MPH) in humans



The kinetics of binding to the D2-subtype of dopamine receptors in the striatum correlates with drug ‘high’

The reinforcing effects of drugs are probably due to their ability to induce **fast increases in DA** that emulate phasic DA cell signalling (15-30 Hz), which are implicated in reward and conditioning, rather than tonic DA cell signalling (2-10 Hz).



See Volkow et al. (2009) for review

Drugs of abuse and dopaminergic signalling in the Nac

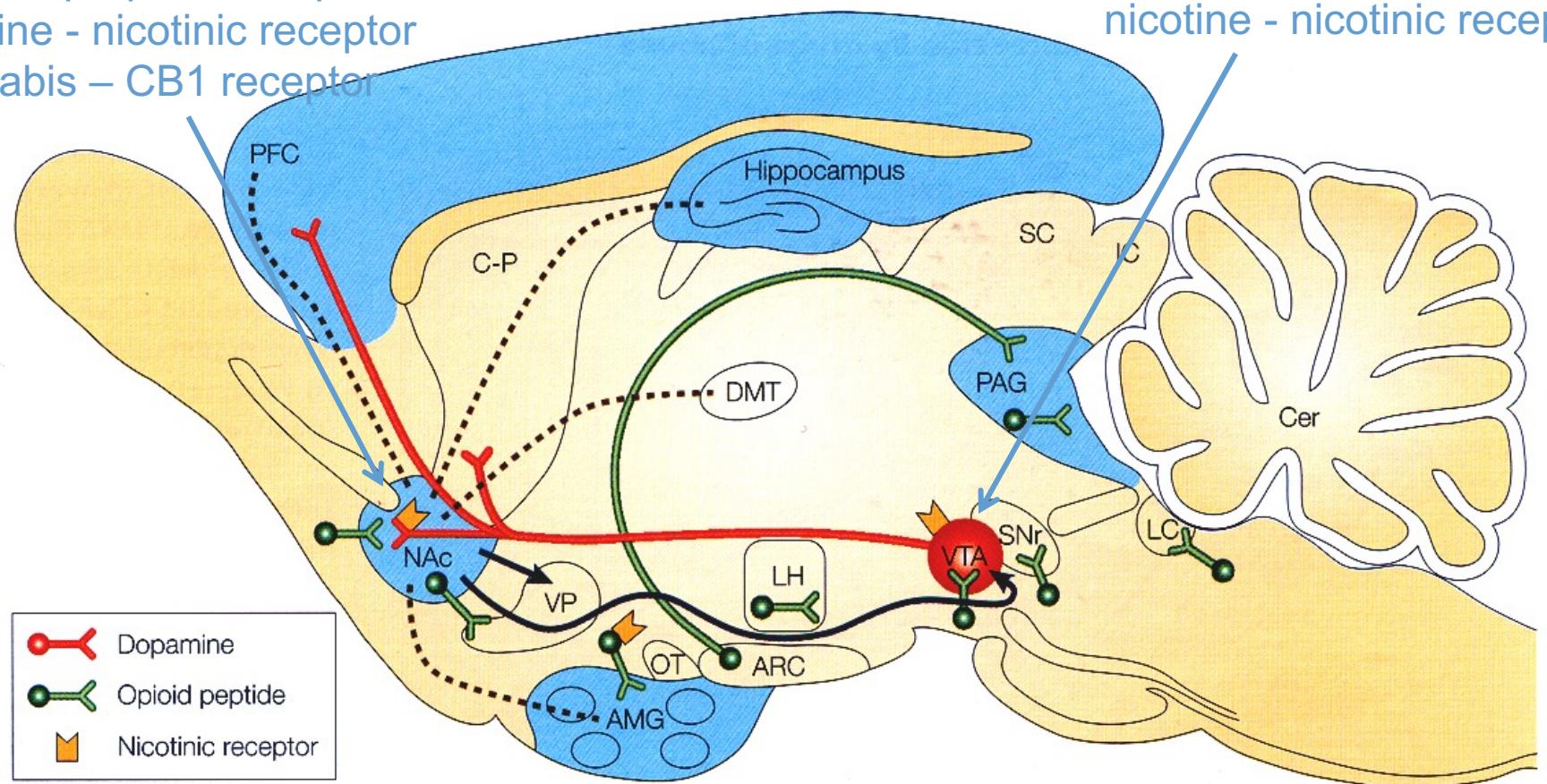
cocaine - dopamine transporter

heroin - μ -opiate receptor

nicotine - nicotinic receptor

cannabis – CB1 receptor

heroin - μ -opiate receptor
nicotine - nicotinic receptor



Broadening it out: a more general dopaminergic theory of reward

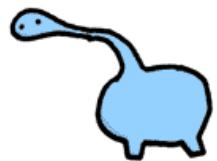
Wise's dopaminergic theory of reward

All rewards - whether natural or artificial - have a common action to increase dopaminergic activity in the nucleus accumbens.

Originally, this theory equated reward with subjective pleasure (hedonic responses).

Note that addictive drugs 'usurp' or 'hijack' the brain's reward system.

SEROTONIN & DOPAMINE



Technically, the only two things you enjoy

Wise's dopaminergic theory of reward

Are dopamine levels correlated with reward?

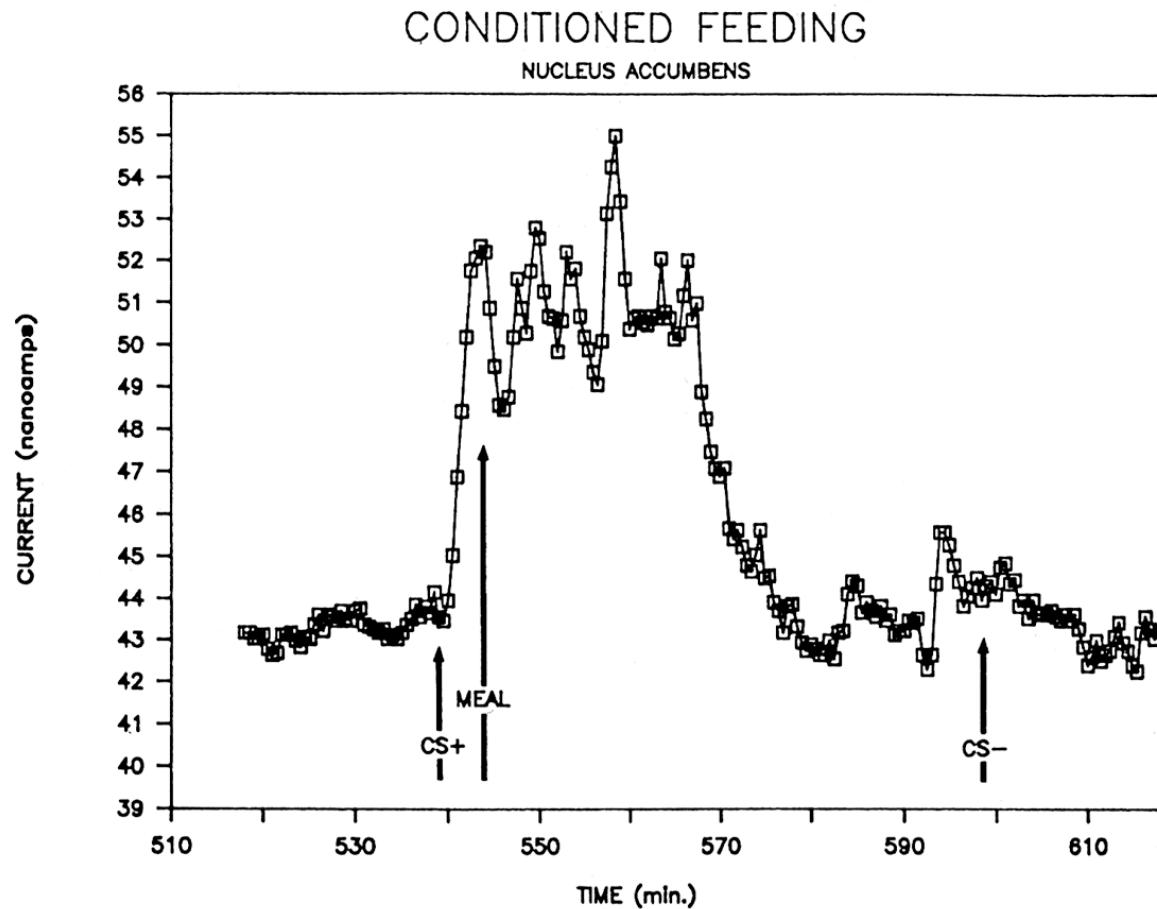
Yes – ICSS is supported if dopaminergic pathways are stimulated

Yes – drugs of abuse increase dopamine in the nucleus accumbens

Is dopamine sufficient for reward?

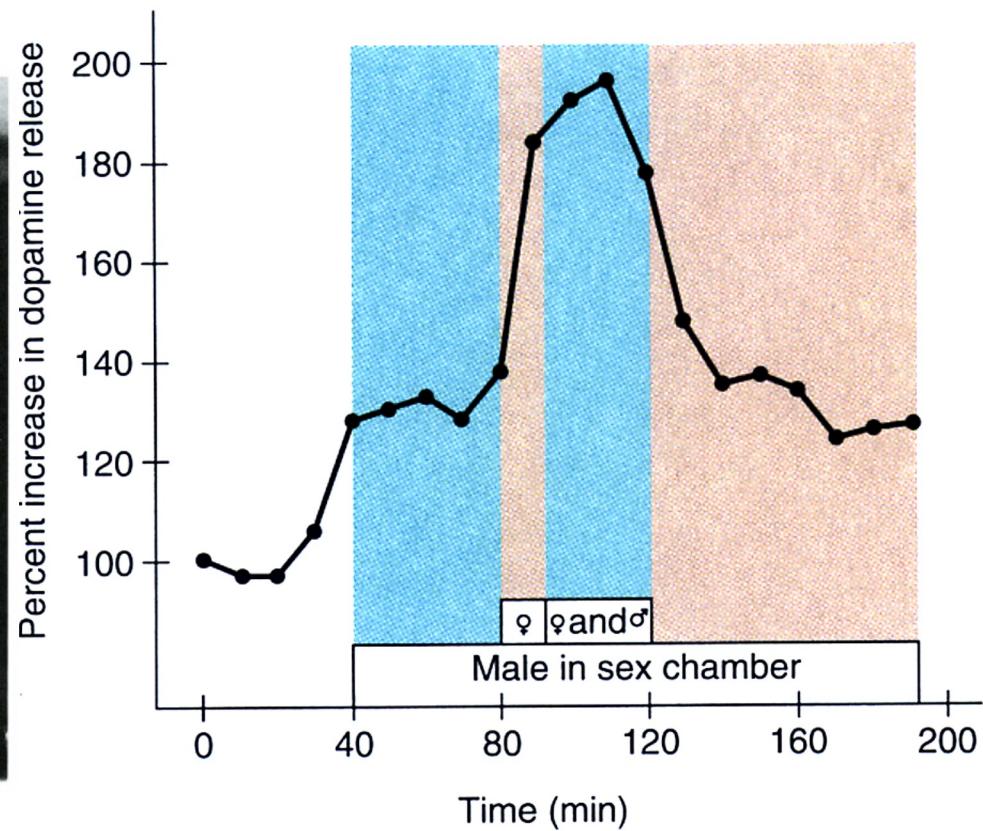
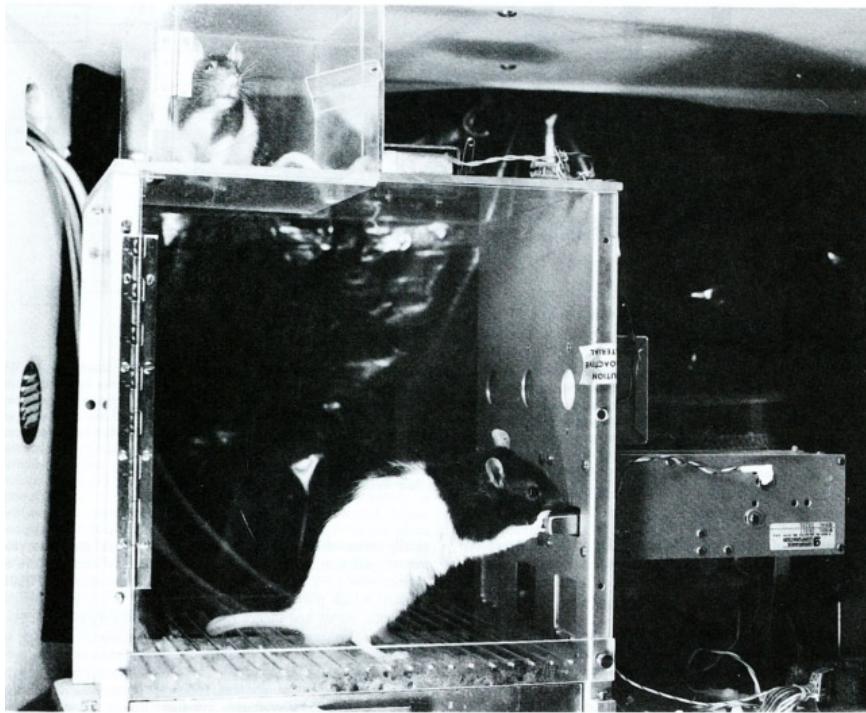
Is dopamine necessary for reward?

DA levels increase in the accumbens when eating a preferred food – and in the presence of a food CS



Phillips et al. (1993)

DA levels increase in the accumbens during sexual behaviour – and in anticipation of sex



Pfau et al. (1990)

Wise's dopaminergic theory of reward

Are dopamine levels correlated with reward?

Yes – ICSS is supported if dopaminergic pathways are stimulated

Yes – drugs of abuse increase dopamine in the nucleus accumbens

Yes – natural rewards (food and sex) increase DA in the nucleus accumbens

Is dopamine sufficient for reward?

Yes – ICSS appears to act through dopaminergic pathways

Yes – drugs that enhance dopamine in accumbens are self-administered

Is dopamine necessary for reward?

Yes – blocking dopamine receptors alters reward-seeking behaviour

Is it really 'reward', and not 'reinforcement'? Or something else entirely?

Wise's dopaminergic theory of reward

Is it only dopamine that is correlated with reward?

Drugs of abuse have distinct, primary molecular targets

Drug	Molecular targets relevant to addiction
1. Opioids (e.g. morphine, heroin)	μ opiate receptors
2. Psychomotor stimulants (cocaine, amphetamine, methamphetamine)	DA transporter (cocaine) and synaptic vesicle amine transporter (amphetamine). Also 5-HT and NA transporter.
3. 'Legal highs' (e.g. mephedrone)	Unknown
4. Cannabinoids	CB1 cannabinoid receptors
5. Nicotine	Nicotinic acetylcholine receptor
6. Ethanol	GABA _A receptor (facilitates) and NMDA receptor (inhibits) / μ -OR (through its metabolite salsolinol)
7. Phencyclidine (PCP), ketamine	NMDA receptor (inhibits)
8. Benzodiazepines and barbiturates	GABA _A receptors
9. Inhalants	Unknown

Wise's dopaminergic theory of reward

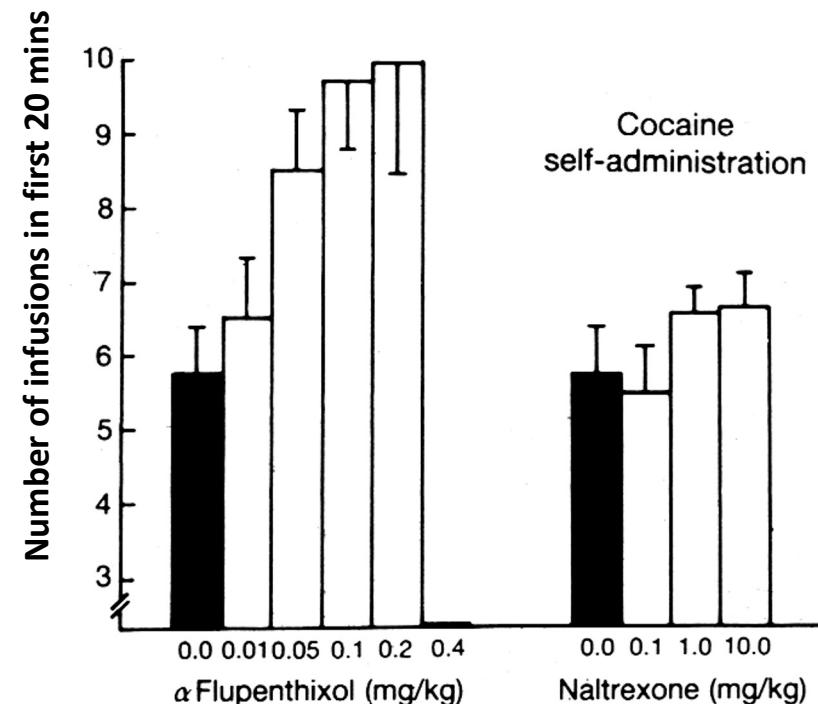
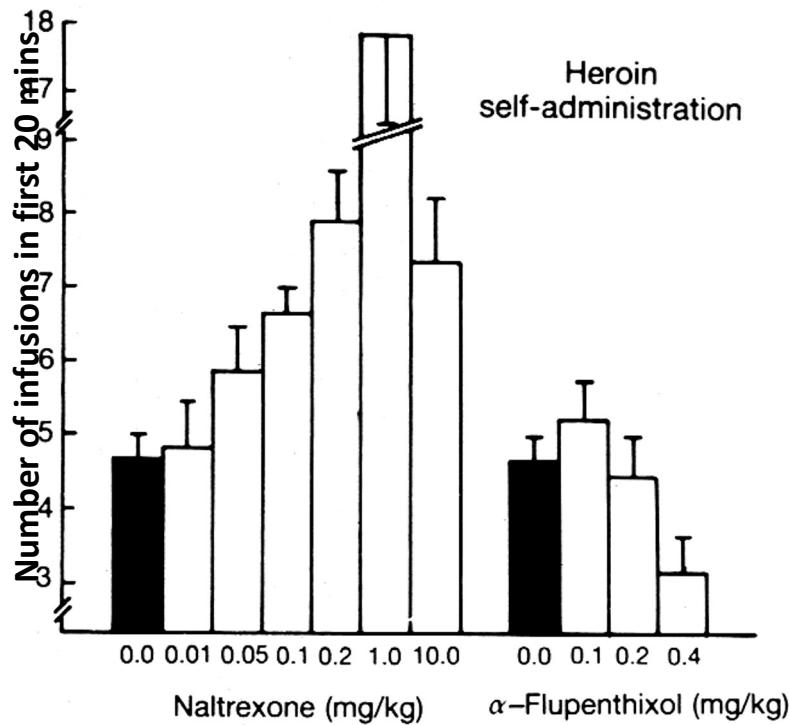
Is it only dopamine that is correlated with reward?

No – drugs of abuse have multiple molecular targets

Is dopamine sufficient for reward?

Is dopamine sufficient for reward?

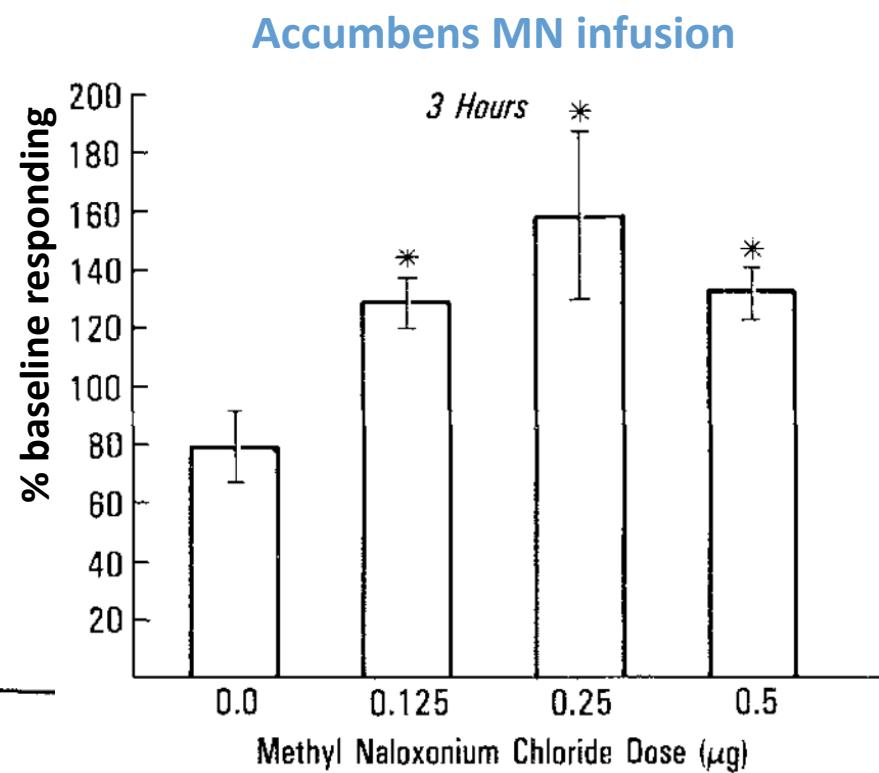
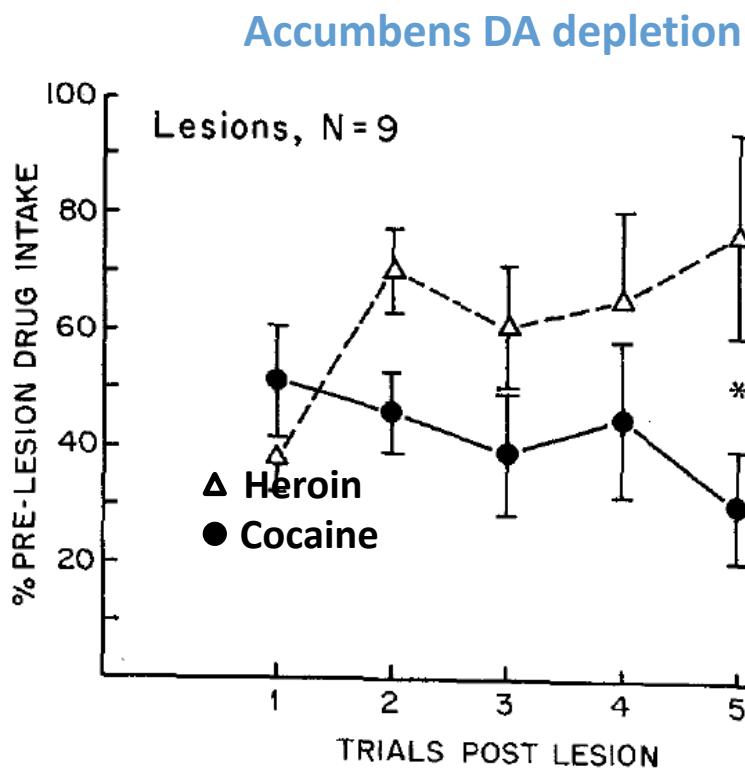
Dopamine receptor antagonists do not modulate much heroin SA



There is a double dissociation in the effects of the opiate receptor antagonist naltrexone and the dopamine receptor antagonist α -flupenthixol on heroin and cocaine self-administration.

Is dopamine sufficient for reward?

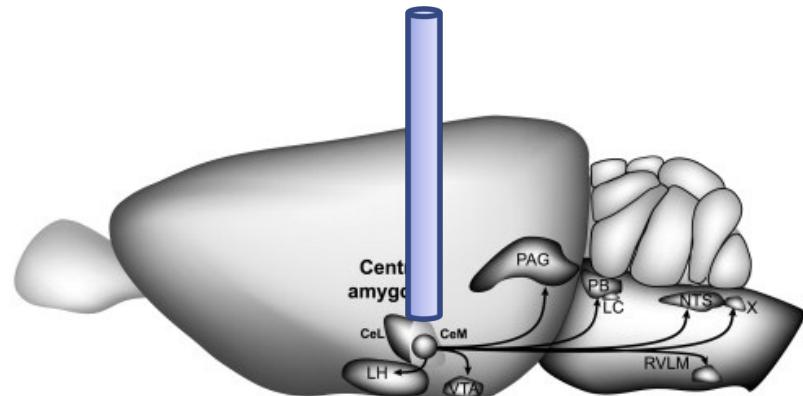
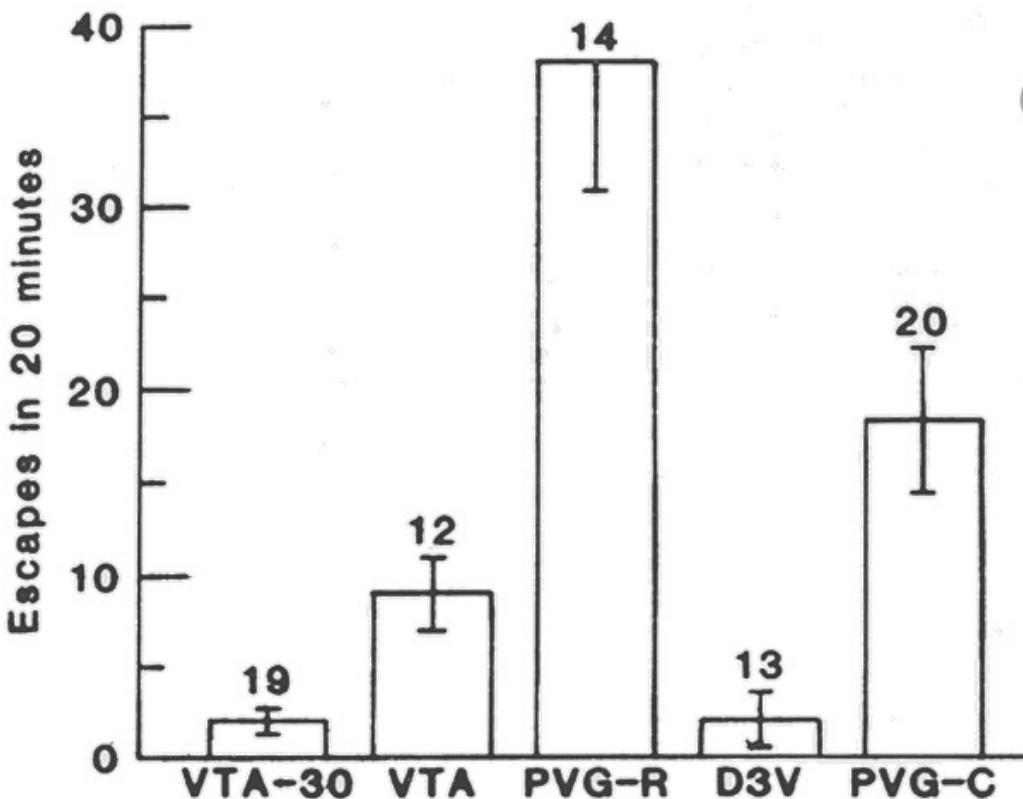
Methylnaloxonium, but not dopamine depletion, in the nucleus accumbens modulates heroin self-administration



Pettit et al. (1984); Vaccarino et al. (1985)

Is dopamine sufficient for reward?

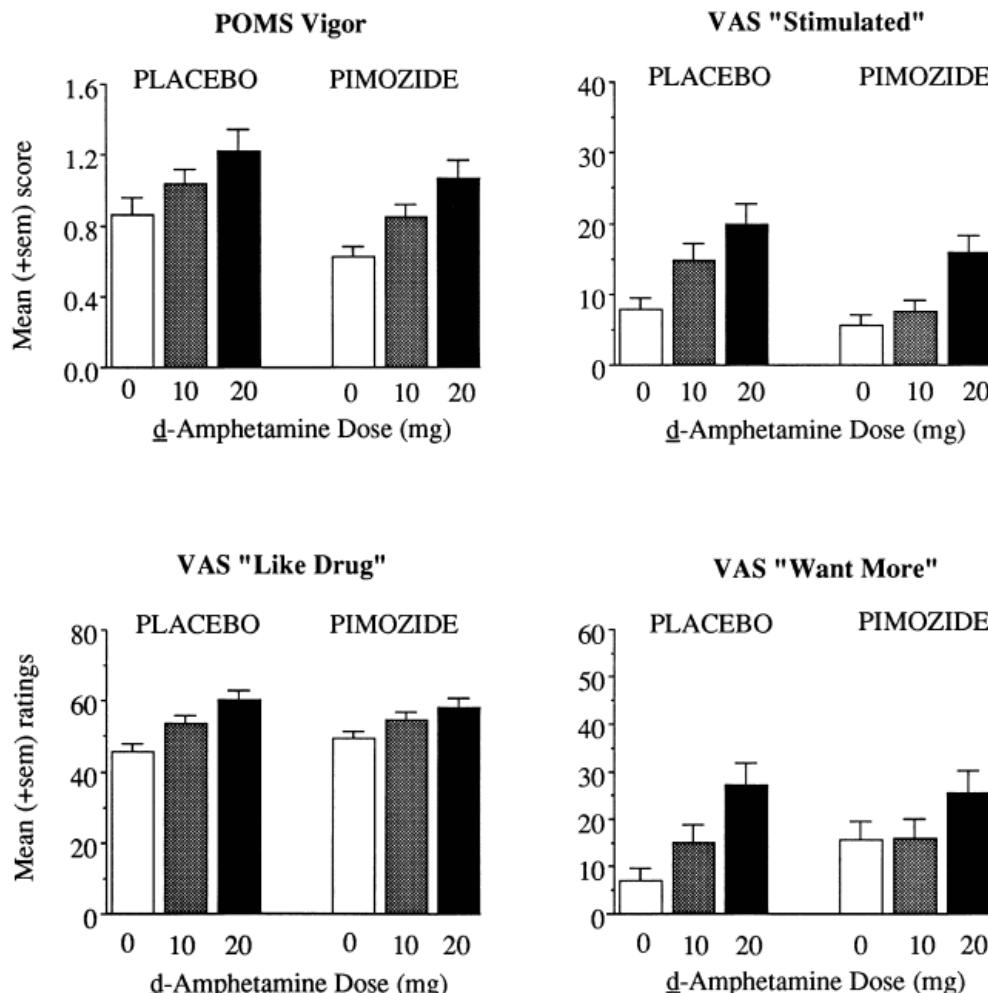
Opiates produce neural adaptations in areas other than the nucleus accumbens and ventral tegmental area



	VTA	PAG
Self-admin	✓	✗
Physical dependence	✗	✓

Is dopamine sufficient for reward?

Dopamine receptor antagonists do not affect the hedonic response to psychostimulants



Dopamine receptor antagonism with pimozide affected feelings of 'stimulation' and 'wanting', but importantly did not affect 'drug liking'.

Wise's dopaminergic theory of reward

Is it only dopamine that is correlated with reward?

No – drugs of abuse have multiple molecular targets

Is dopamine sufficient for reward?

No – activation of opiate receptors is required for heroin reward

Is dopamine necessary for reward?

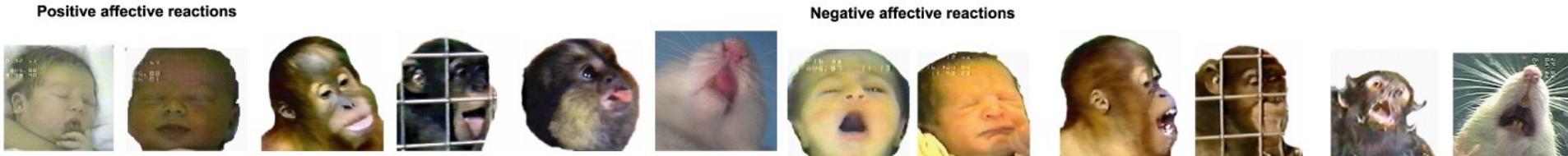
No – blocking dopamine receptors does not affect heroin-seeking

No – blocking dopamine receptors does not affect hedonic reactions to amphetamine

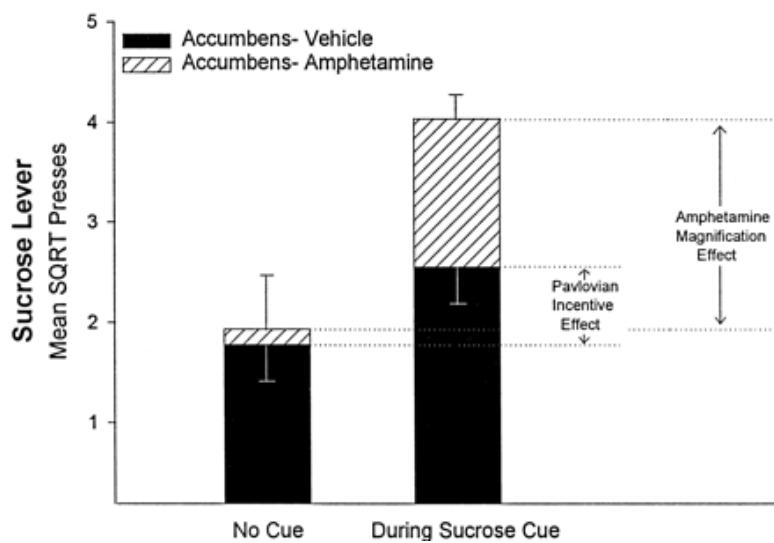
Is it really ‘reward’, and not ‘reinforcement’? Or something else entirely?

Is it really ‘reward’, and not ‘reinforcement’? Or something else entirely?

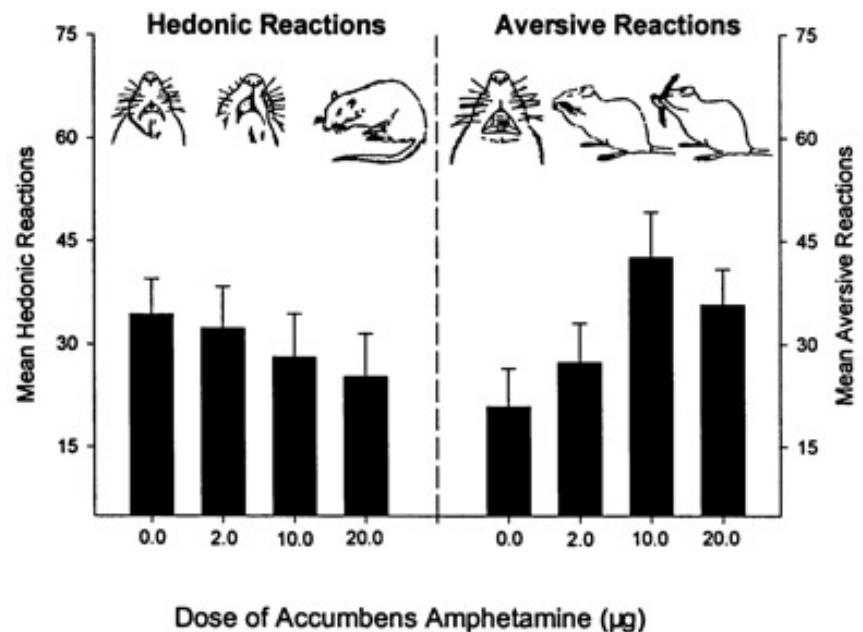
Dopamine – hedonic impact, reward learning, or incentive salience?



Amphetamine enhances ‘wanting’...



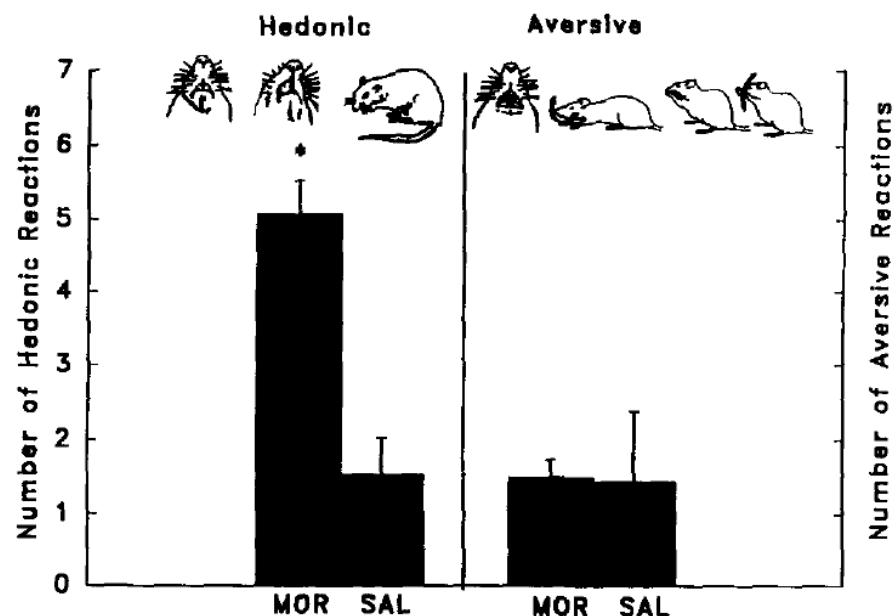
...without enhancing ‘liking’



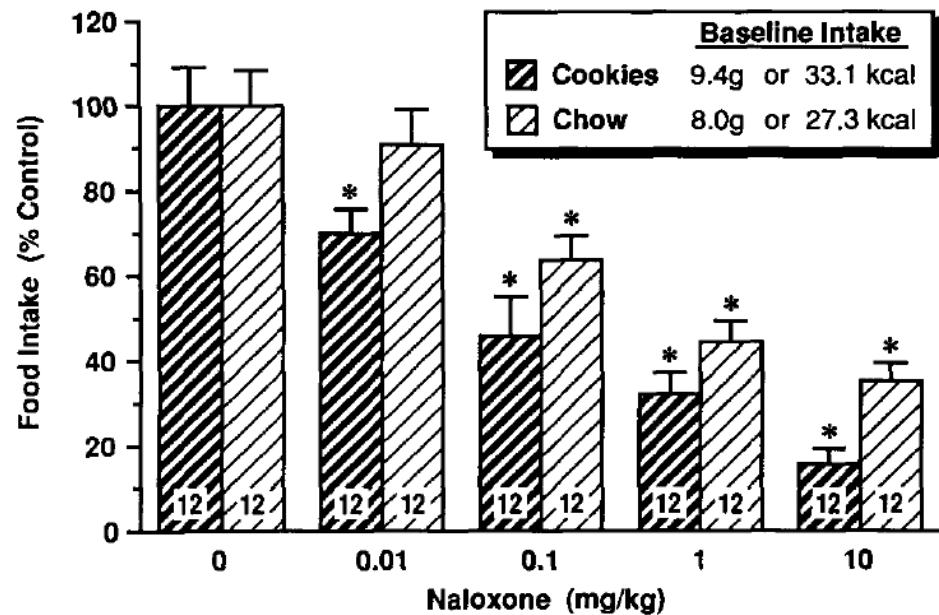
Wyvill & Berridge (2000)

Is it really ‘reward’, and not ‘reinforcement’? Or something else entirely?

Hedonics may be more dependent on opiate signalling



Morphine enhances hedonic taste reactions to palatable food.

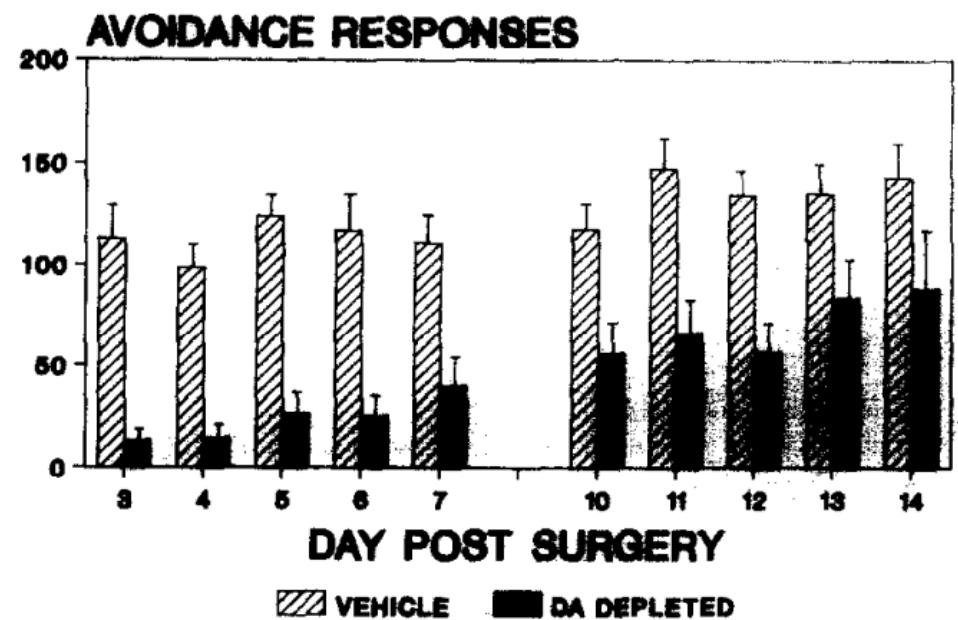
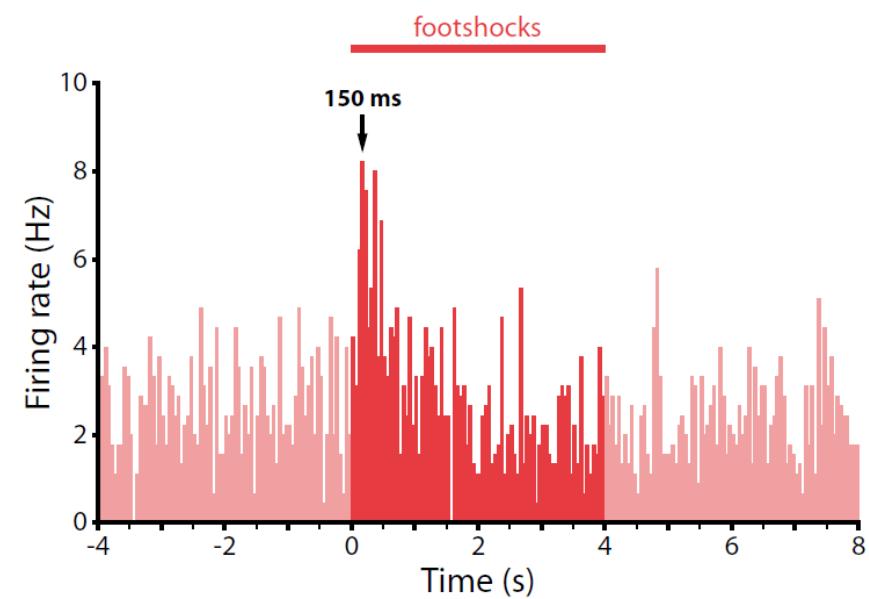


Naloxone has relatively selective effects on reducing *palatable* food consumption.

Doyle et al. (1993); Giraudo et al. (1993)

Is it really ‘reward’, and not ‘reinforcement’? Or something else entirely?

Dopamine levels increase in aversive situations

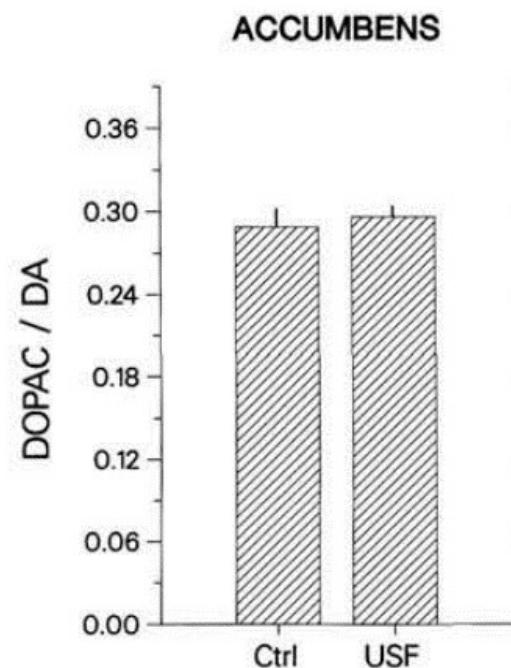
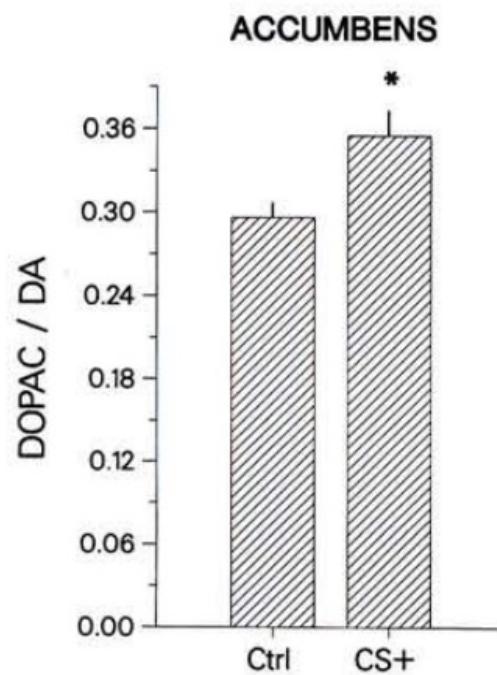


VTA dopamine neurons respond to noxious stimuli.

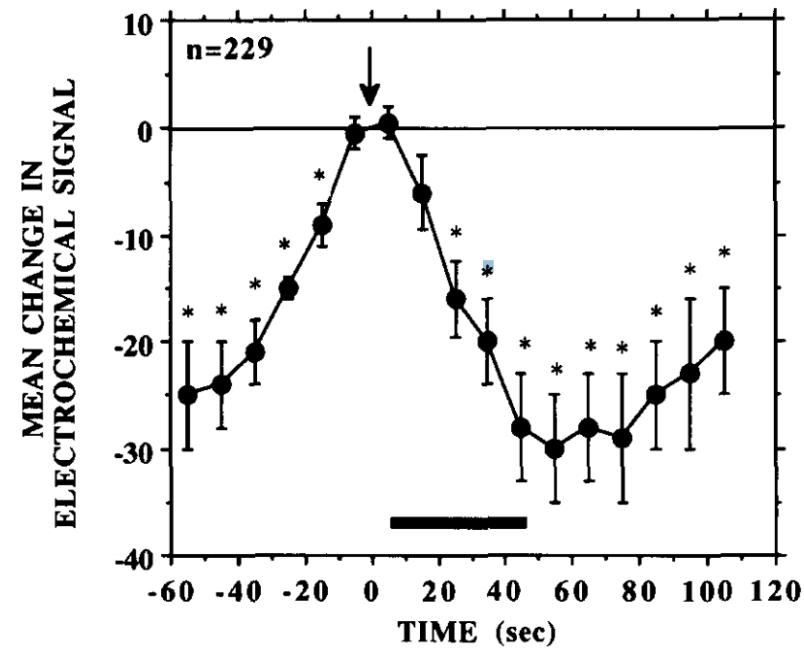
Animals with dopamine depletion in the nucleus accumbens are impaired at avoidance learning.

Is it really ‘reward’, and not ‘reinforcement’? Or something else entirely?

Dopamine levels in accumbens correlate with the anticipation of motivationally relevant events



Microdialysis → DA levels (metabolism) increase in the Nac in response to a food-associated CS (CS+) but not to consumption of unsignalled food (USF).



Chronoamperometry shows that accumbens dopamine levels peak just before a food pellet is consumed (black bar).

Blackburn et al. (1989); Kiyatkin & Gratton (1994)

Wise's dopaminergic theory of reward

Is it only dopamine that is correlated with reward?

No – drugs of abuse have multiple molecular targets

Is dopamine sufficient for reward?

No – activation of opiate receptors is required for heroin reward

Is dopamine necessary for reward?

No – blocking dopamine receptors does not affect heroin-seeking

No – blocking dopamine receptors does not affect hedonic reactions to amphetamine

Is it really ‘reward’, and not ‘reinforcement’? Or something else entirely?

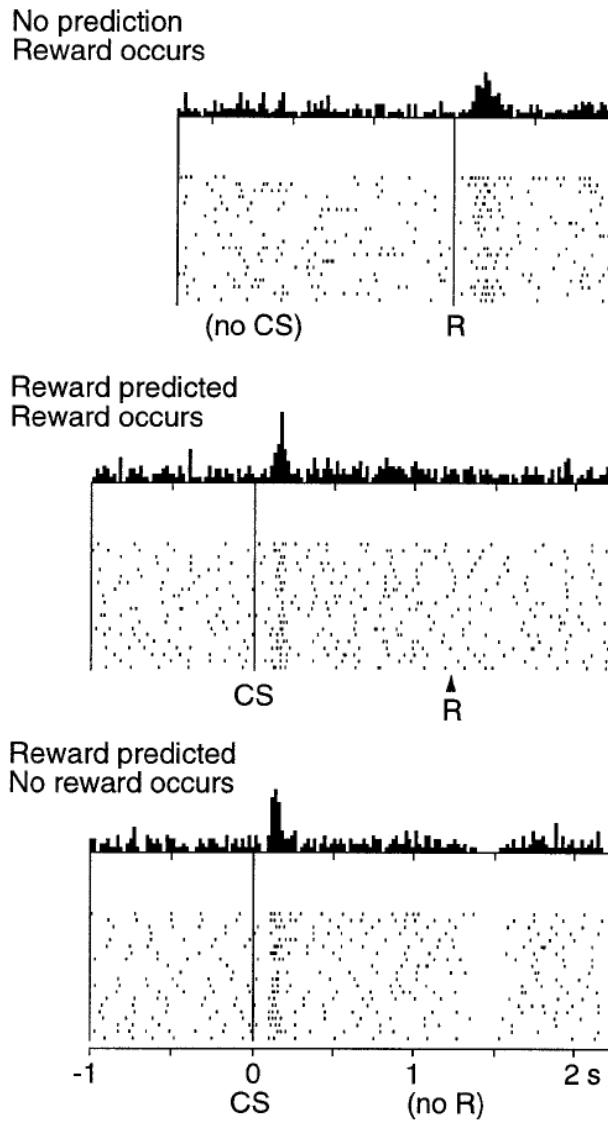
No – dopamine levels don't affect hedonic taste reactions

No – dopamine levels also increase with aversive stimuli

No – dopamine levels peak with stimuli *predictive* of motivationally relevant outcomes

Dopamine and incentive motivation

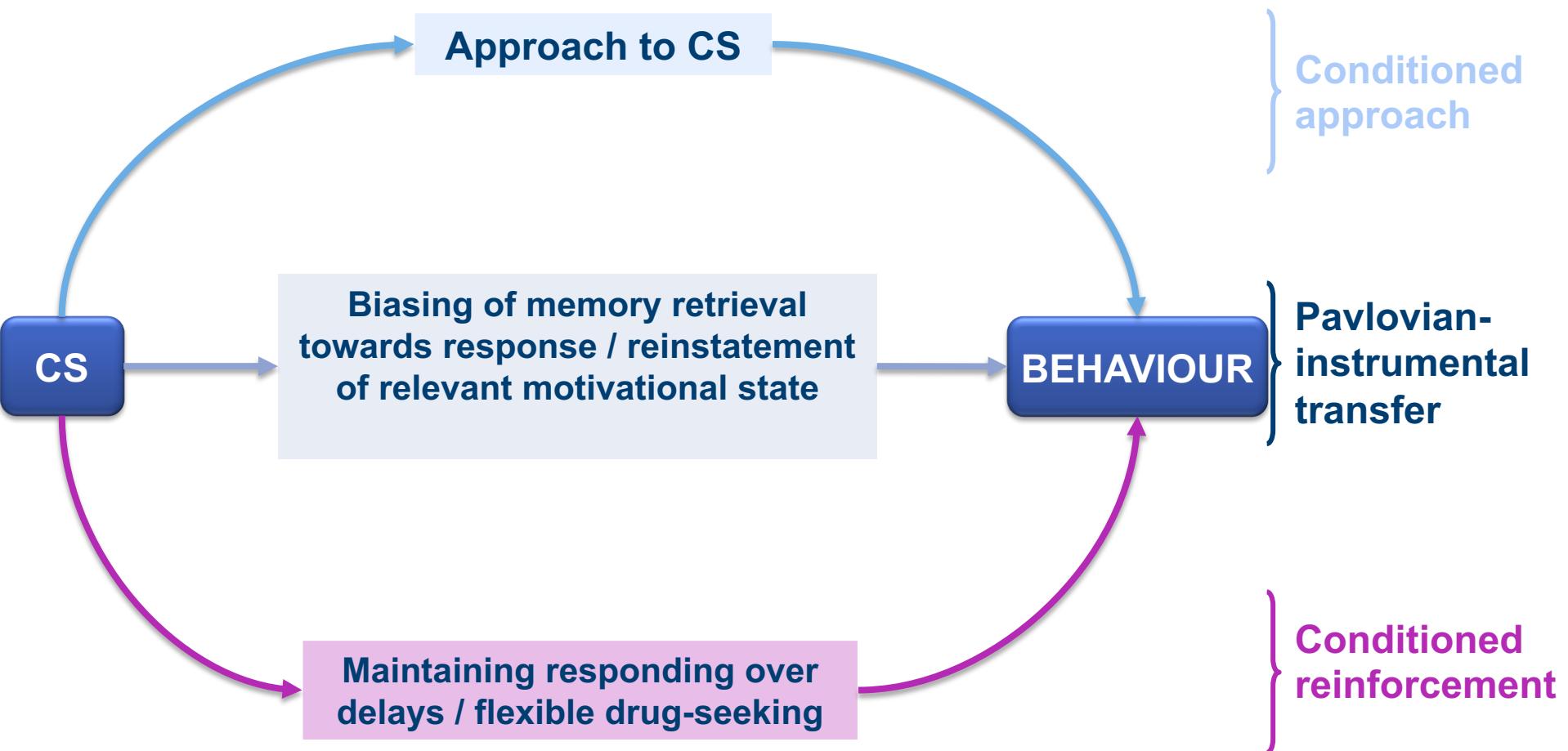
Dopamine neurons initially fire to primary reward, but later fire to stimuli *predictive* of reward



The firing of VTA dopamine neurons correlate with '**prediction error**:

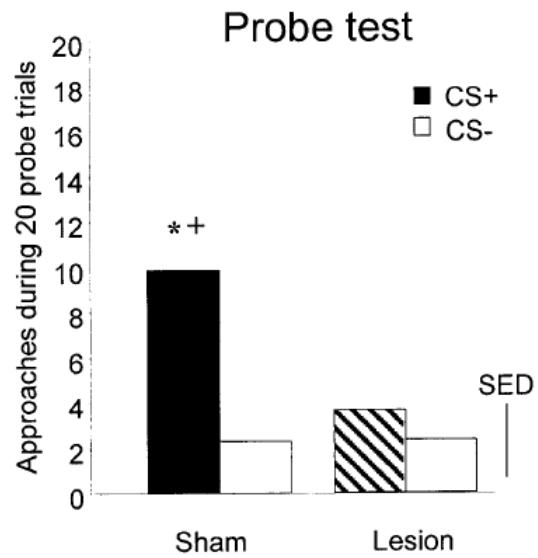
- If rewards are as expected, firing remains at the tonic baseline rate.
- If rewards are better than expected (positive prediction error) then there is a phasic increase in firing.
- If rewards are worse than expected (negative prediction error) then there is a pause in firing.

Dopamine may be required for the effects of pavlovian CSs on instrumental behaviour

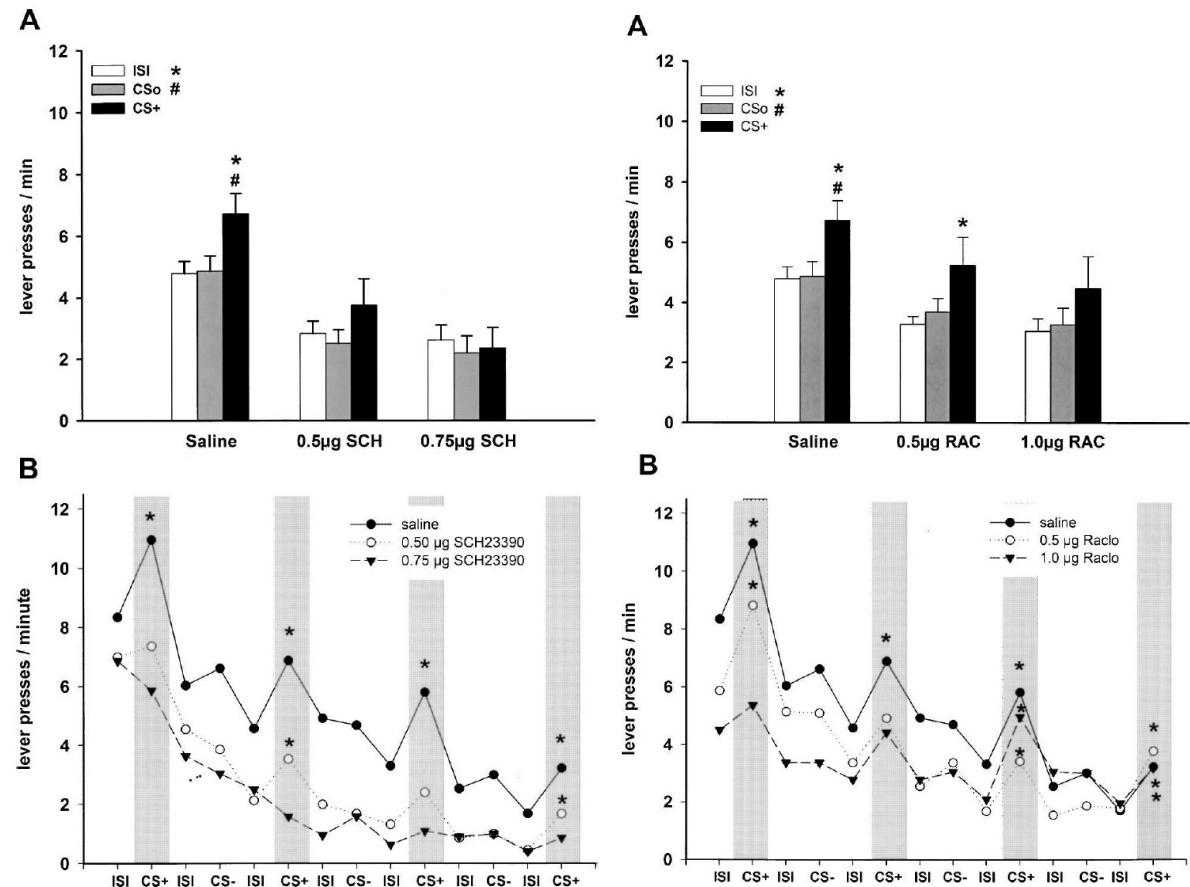


Nucleus accumbens dopamine is required for pavlovian stimuli to influence instrumental behaviour

Autoshaping



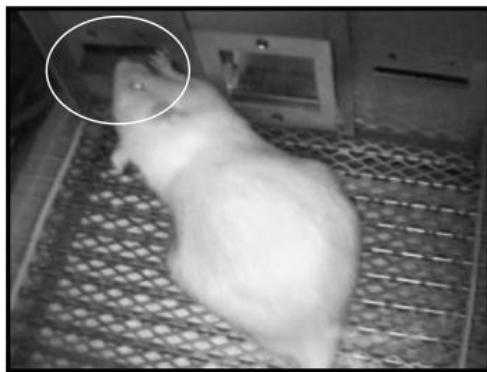
Pavlovian-instrumental transfer



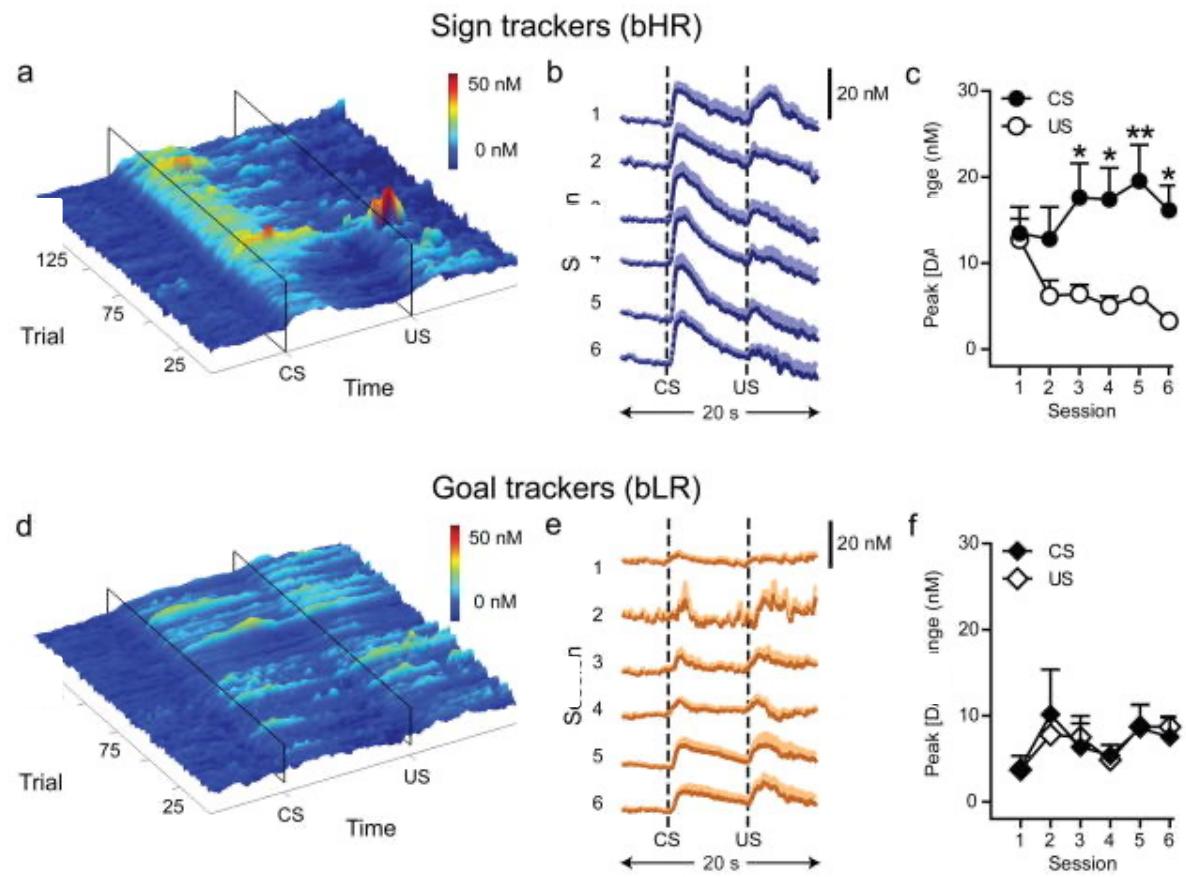
Parkinson et al. (2002); Lex & Hauber (2008)

Individual differences in Nac dopamine may affect CS influences on behaviour

Sign-tracking

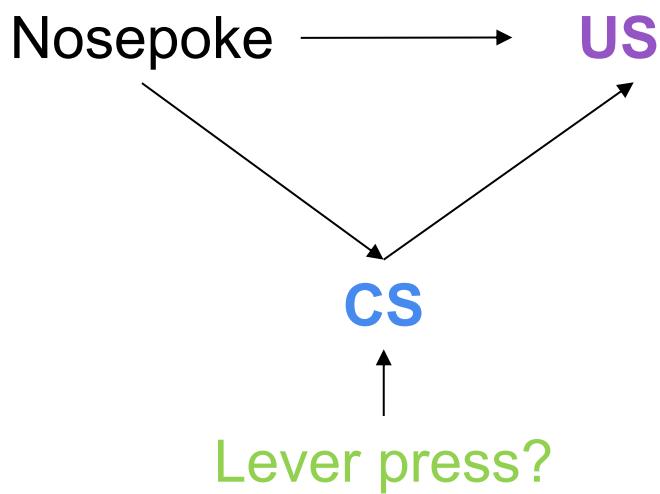


Goal-tracking



→ Inter-individual differences in the attribution of incentive motivational value to CSs

The acquisition of a new instrumental response for conditioned reinforcement (ANR)



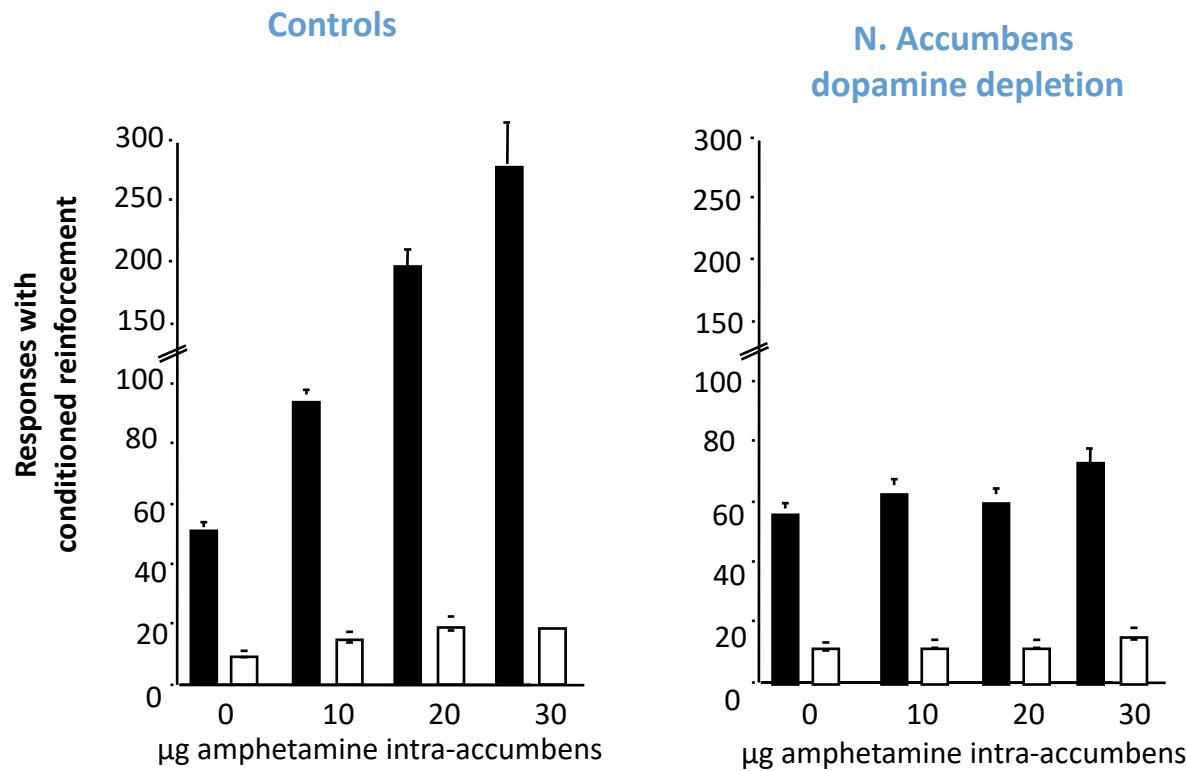
Stage 1: pavlovian conditioning: CS-reward pairings

Stage 2: instrumental conditioning: a lever press response for the conditioned reinforcer in extinction

'Active' lever → conditioned reinforcer

'Inactive' lever → no consequence

Nac dopamine potentiates responding for conditioned reinforcement



Taylor & Robbins (1984; 1986)

Lecture 3: Preparatory responses: Pavlovian and Instrumental conditioning – role of the striatum



Classical or Pavlovian
Conditioning

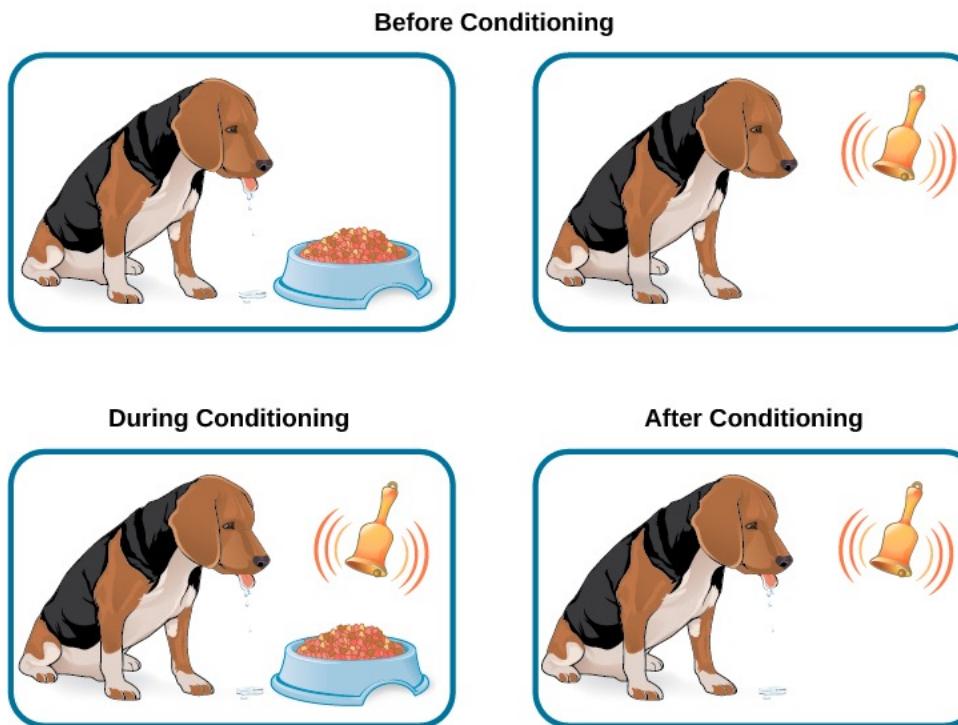


Instrumental or Operant
Conditioning

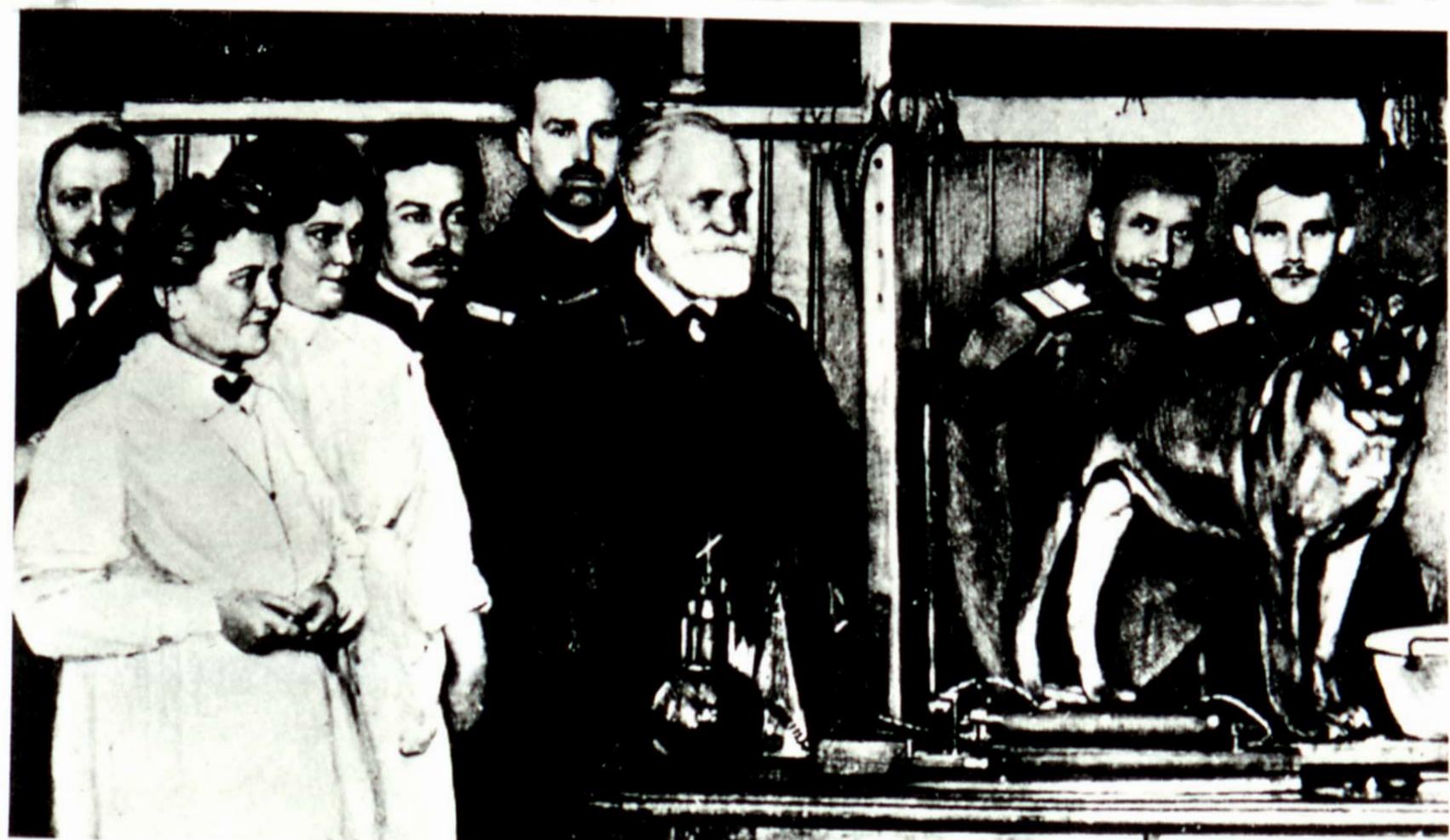
Pavlovian Conditioning

Classical or Pavlovian conditioning: definition

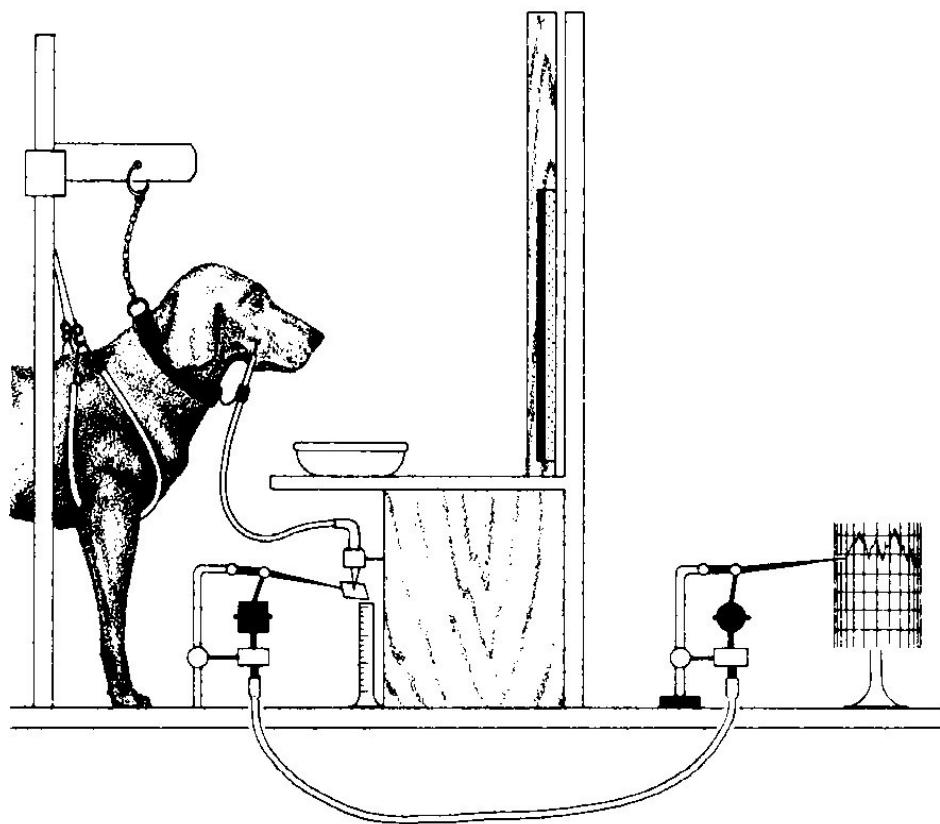
- A behavioural change caused by a predictive relationship between a previously irrelevant stimulus (e.g. a sound, a light) and a naturally relevant stimulus (e.g. food, sex, pain) when the two are reliably paired



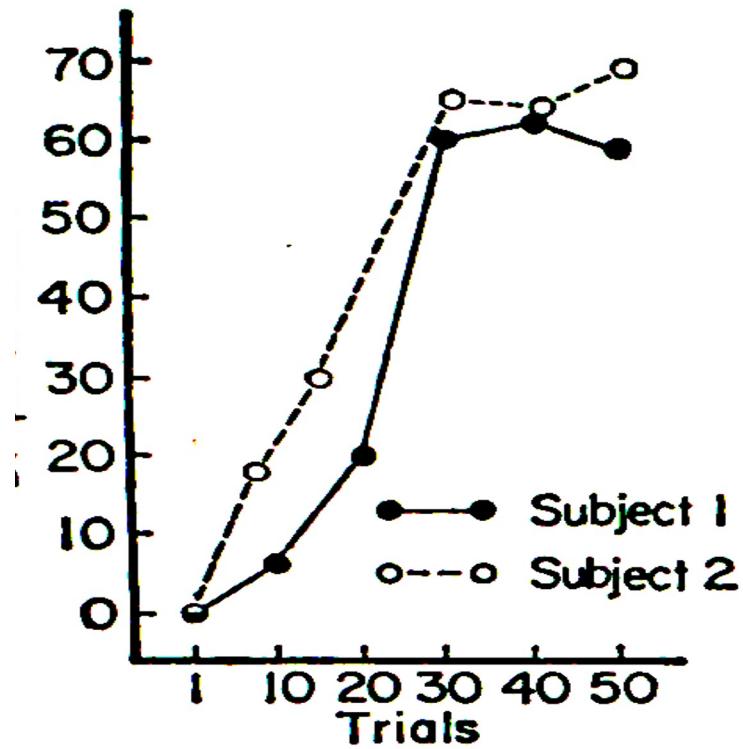
Pavlov's seminal experiments with dogs



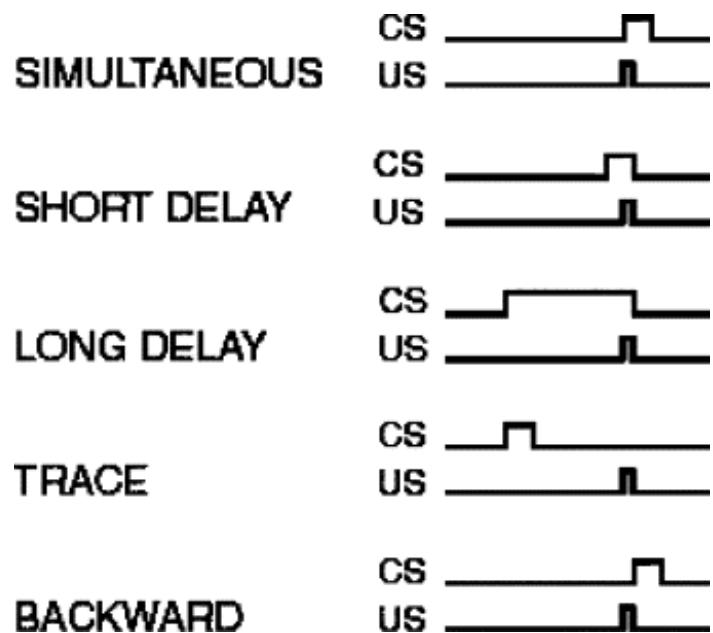
Pavlov's seminal experiments with dogs



(a) Salivary conditioning



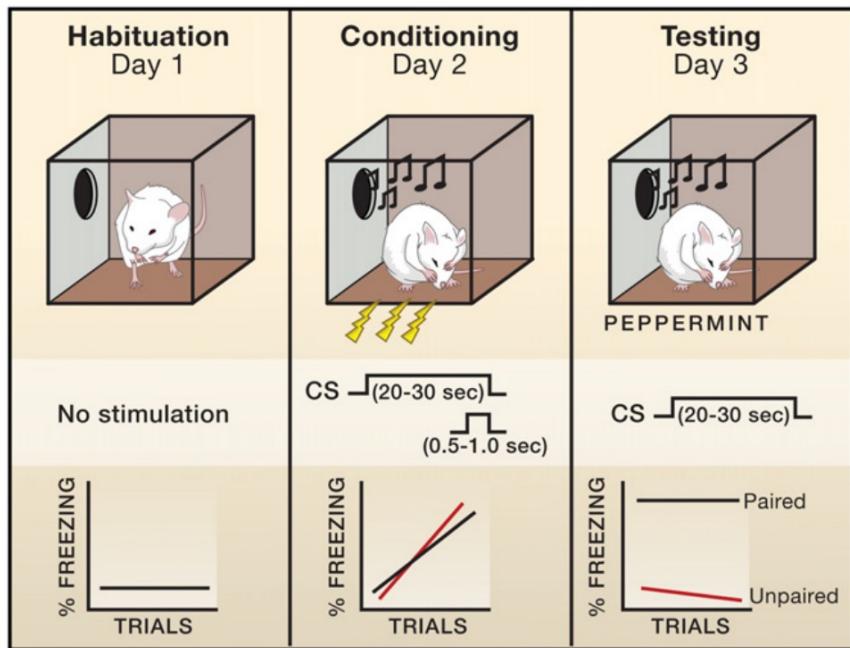
Pavlovian conditioning: a CS predicts the occurrence of a US



- Simultaneous pairing procedures rarely lead to any evidence of conditioning.
- Both delay and trace procedures lead to robust conditioning, with the delay conditioning procedure being superior at long intervals between CS and US onset
- The backward pairing procedure again rarely leads to any acquisition of conditioned responses.

These basic outcomes have been advanced as proof that the CS must provide some information regarding the onset of the US before any conditioning can occur.

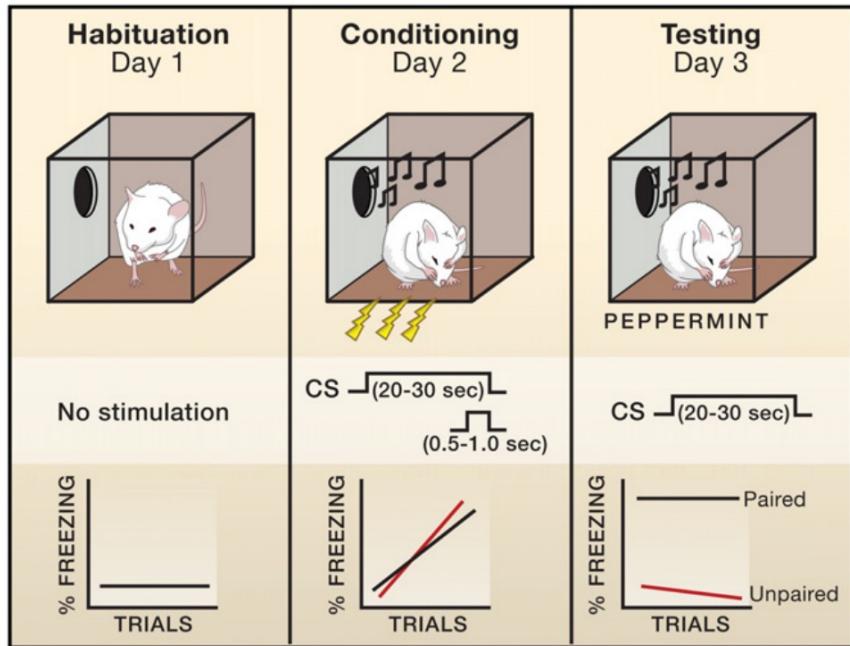
Conditioned fear and prediction error



Conditioned fear and prediction error



Conditioned fear and prediction error



When something happens that we didn't predict, we find it surprising. The more well predicted something is, the less surprising we find it.

The more surprised we are: the more we learn. The first time a CS is followed by a US, this is very surprising and there is a lot of learning. The second time, it is less surprising and there is less learning....etc.

Learning proceeds as a negatively accelerating learning curve, as the presentation of the US following the CS becomes less surprising over trials.

Learning is complete when responding reaches asymptote

Pavlovian conditioning: learning and prediction error

Rescorla-Wagner Rule

Learning as a reduction in prediction error over trials

$$\delta V = \alpha \beta (\lambda - \sum V)$$

↓ ↓ ↓ ↓ ↓ ↓
Change in Associative Learning Asymptote Sum of Associative strength rate strength

- V = the associative strength of CS
- $\alpha\beta$ = learning rate parameters
- λ = the associative strength required to fully predict the outcome (asymptote)
- so that $(\lambda - \sum V)$ is the prediction error, and learning stops when $(\lambda - \sum V) = 0$

Pavlovian conditioning: learning and prediction error

$$\delta V = \alpha \beta (\lambda - \Sigma V)$$

1) $\delta V_A = .25 (1 - 0)$

$$\delta V_A = .25$$

2) $\delta V_A = .25 (1 - .25)$

$$\delta V_A = .19$$

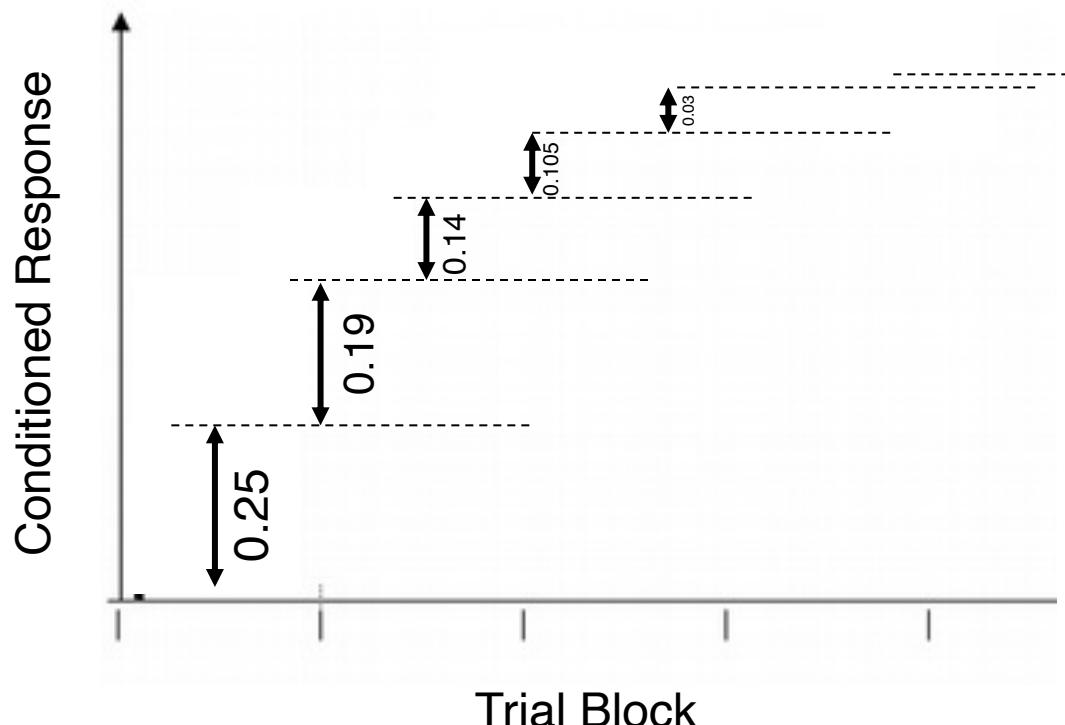
3) $\delta V_A = .25 (1 - .44)$

$$\delta V_A = .14$$

...Etc. until...

N) $\delta V_A = .25 (1 - 1)$

$$\delta V_A = 0$$



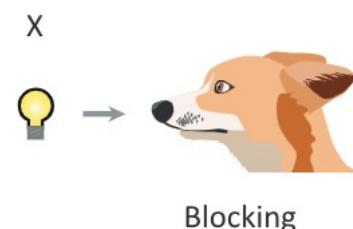
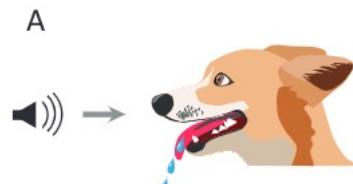
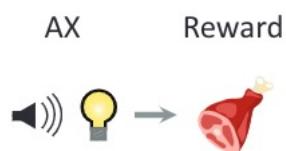
Pavlovian conditioning: prediction error and blocking

If a CS comes into predicting the US enough, any new stimulus presented contingently upon the CS will fail to enter new learning= blocking

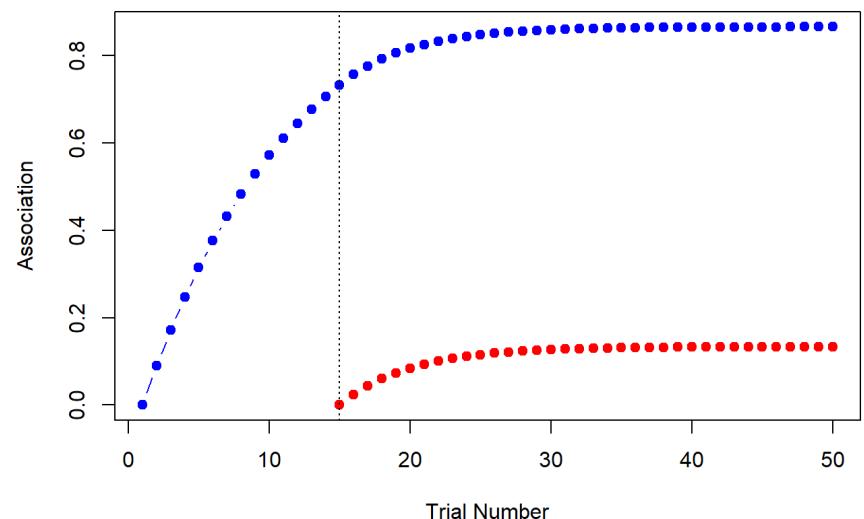
(1) First conditioning



(2) Second conditioning

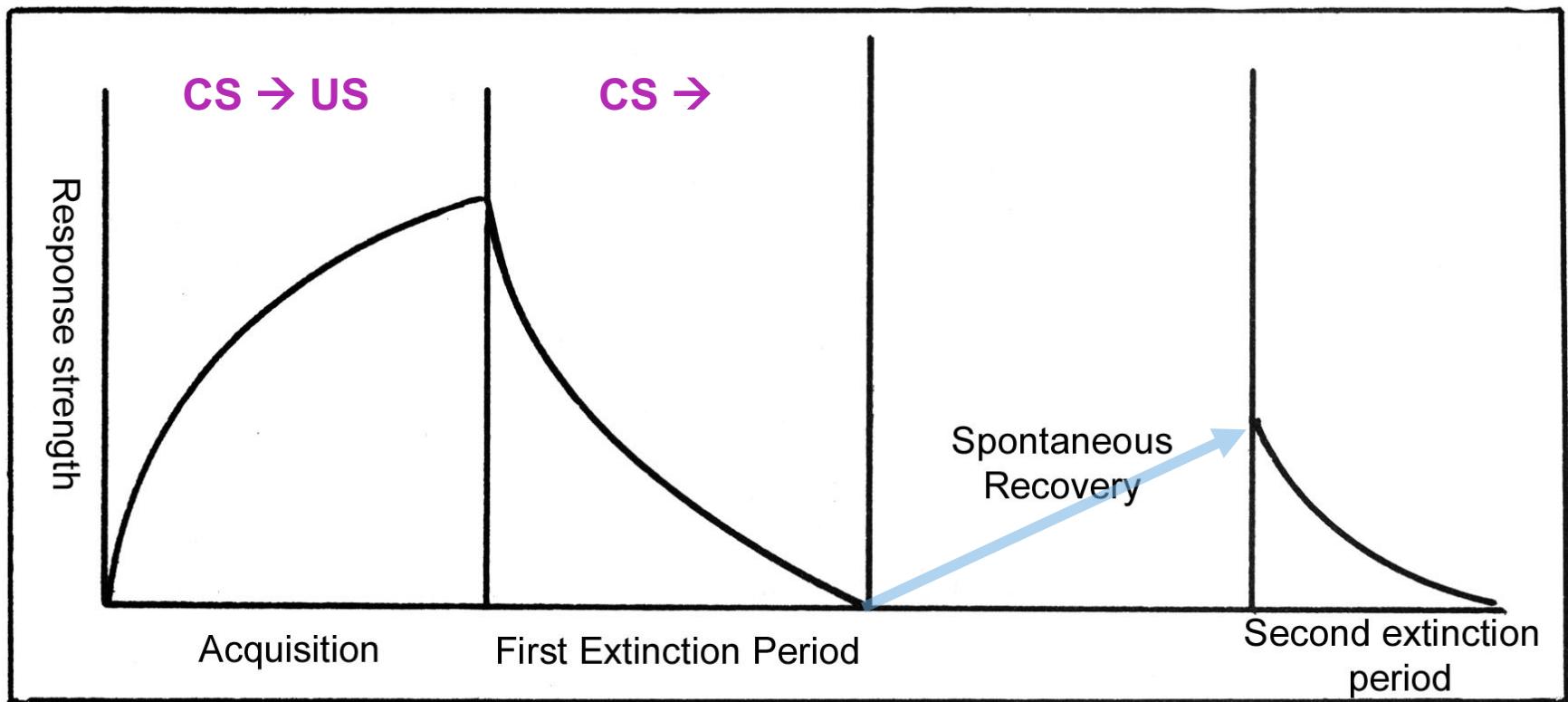


Blocking



Tobler et al (2006)

Extinction of Pavlovian associations



Extinction:

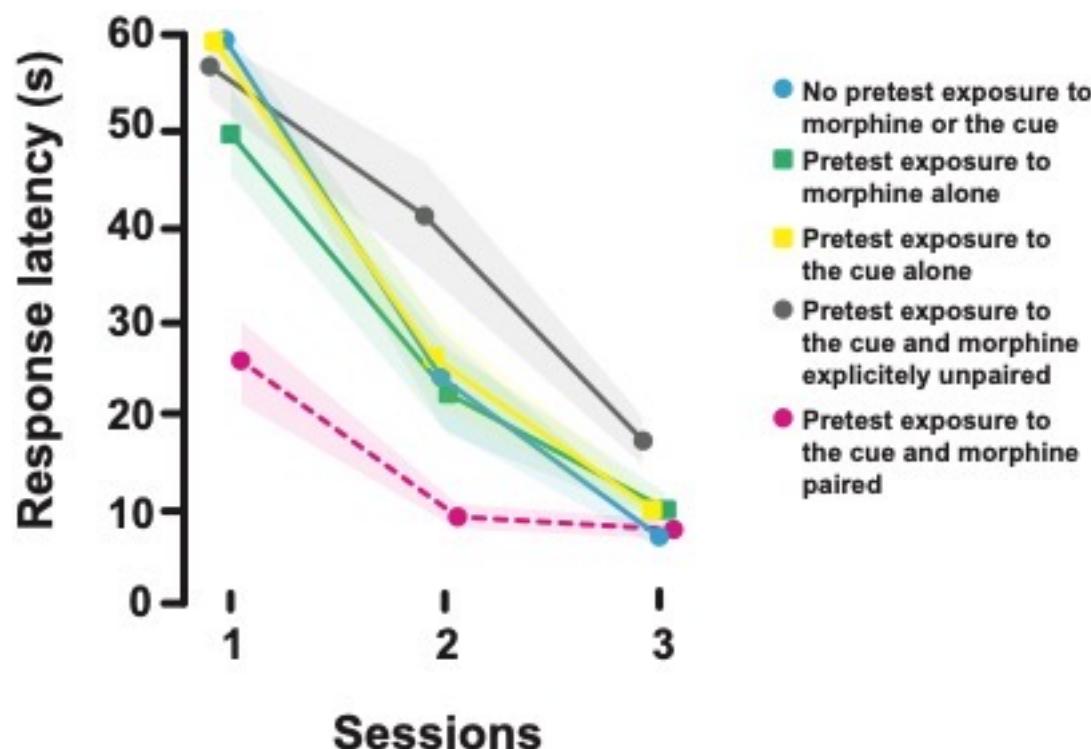
- weakening of the original CS → US association
- learning of a new CS → No US association in a specific context (renewal effect)

Conditioned responses: compensatory mechanisms

Cephalic phase of digestion:

- prepares the organism to interact with the outcome (US)

Conditioned tolerance to the analgesic effects of morphine:



Siegel (1983)

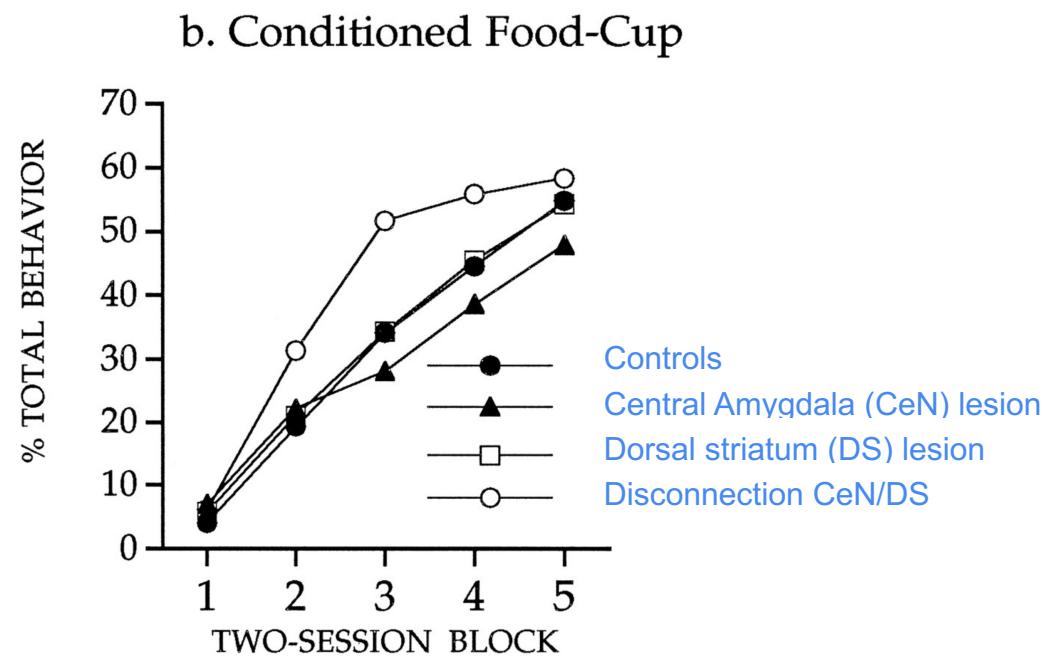
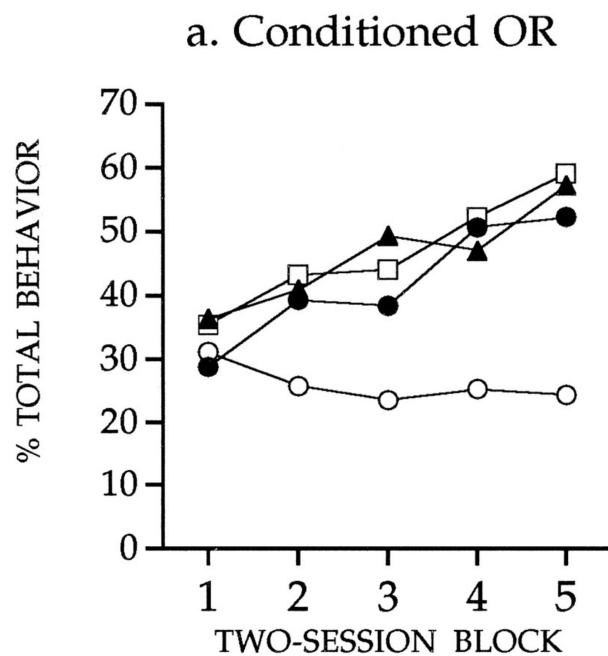
Conditioned responses: conditioned orientation / approach

Pavlovian responses can also be of a behavioural nature:
conditioned orientation and conditioned approach

→ Bring the animal closer to sources of reinforcement

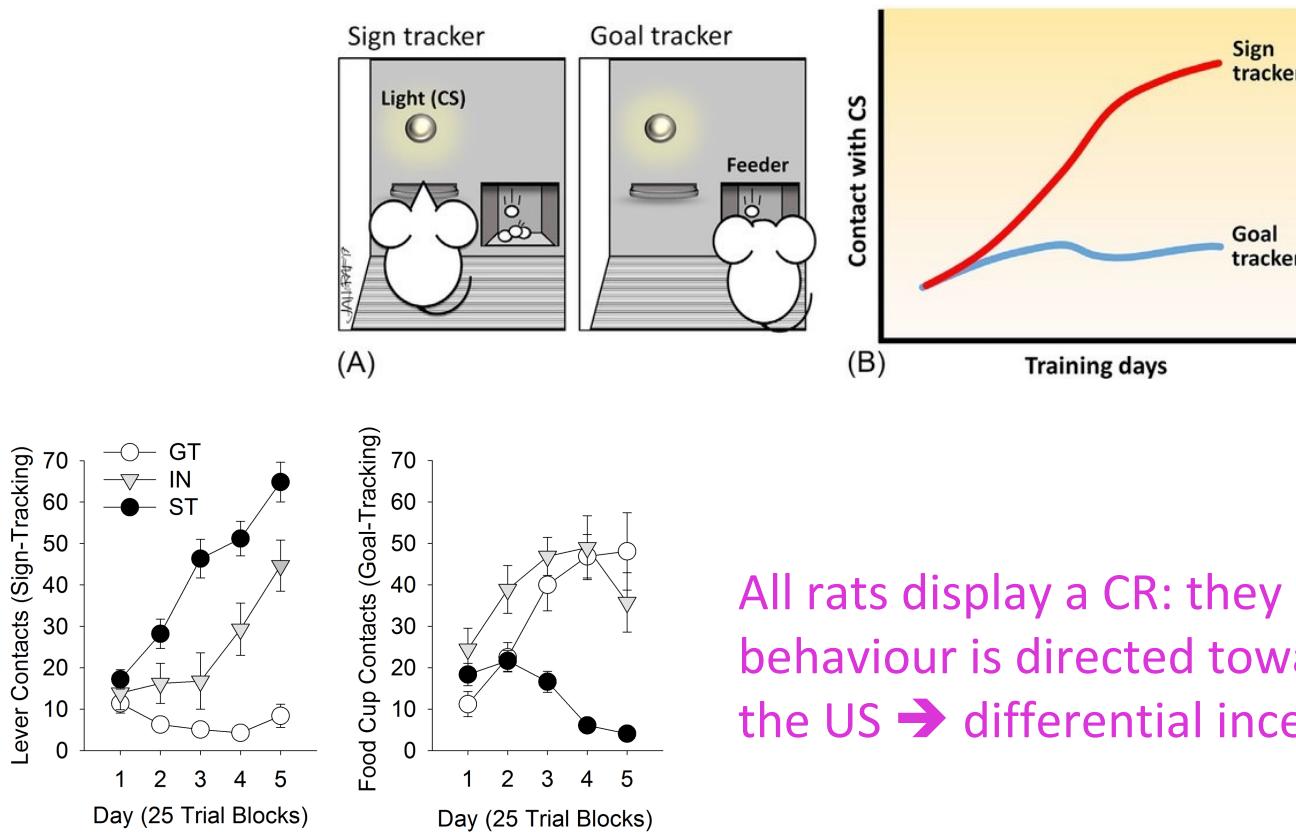
Conditioned responses: conditioned orientation / approach

Conditioned orientation but not approach depends on the functional
Interactions between the central amygdala and the dorsal striatum:



Conditioned responses: conditioned orientation / approach

Inter-individual differences in conditioned approach:
Sign-tracking vs Goal tracking



All rats display a CR: they approach! But their behaviour is directed towards either the CS or the US → differential incentive learning

Instrumental Conditioning

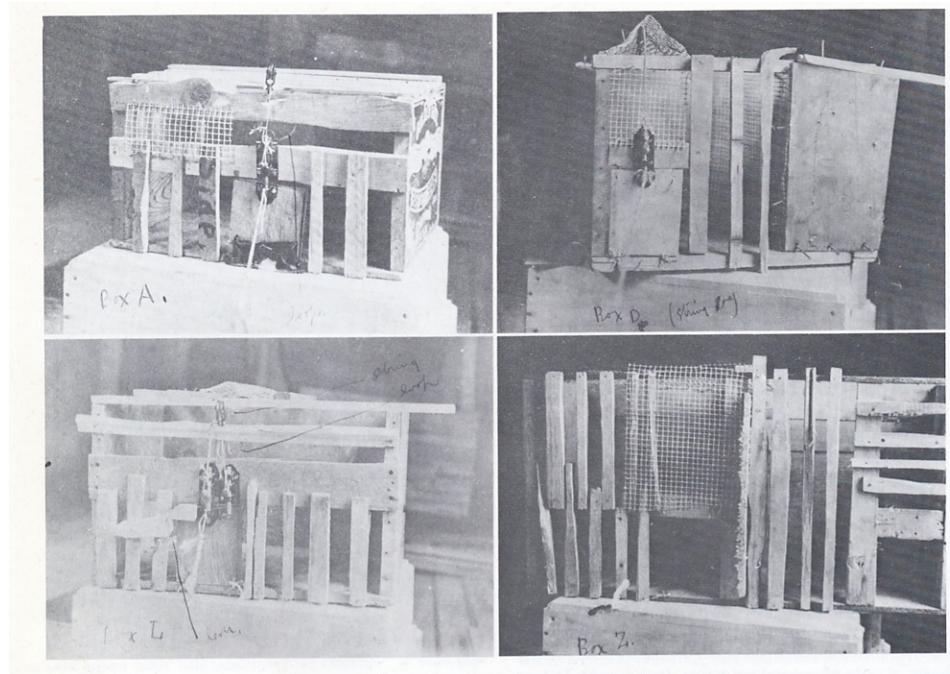
Instrumental conditioning

Pavlovian responses are about helping the organism interact with the US/outcome (including physiologically)

Instrumental/operant responses are about working to get the US/outcome

Law of effect: habits

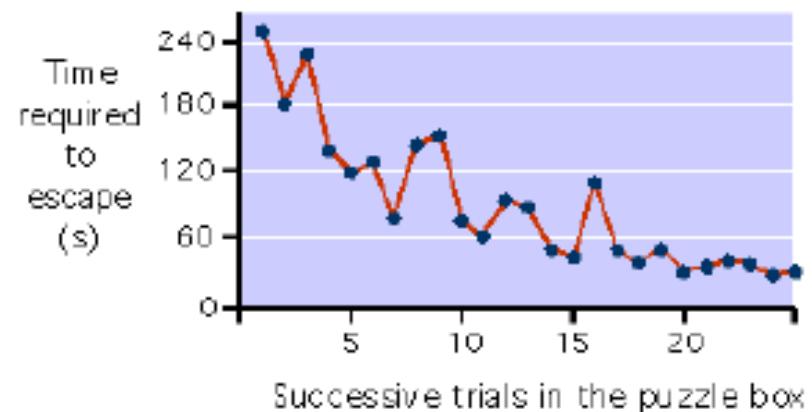
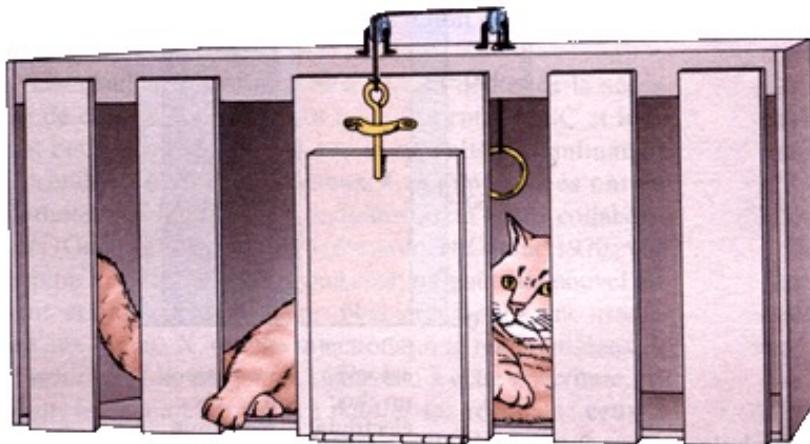
Initial understanding of instrumental/operant conditioning: Thorndike's law of effect



Edward Thorndike

Law of effect: habits

Initial understanding of instrumental/operant conditioning: Thorndike's law of effect



Law of effect: habits

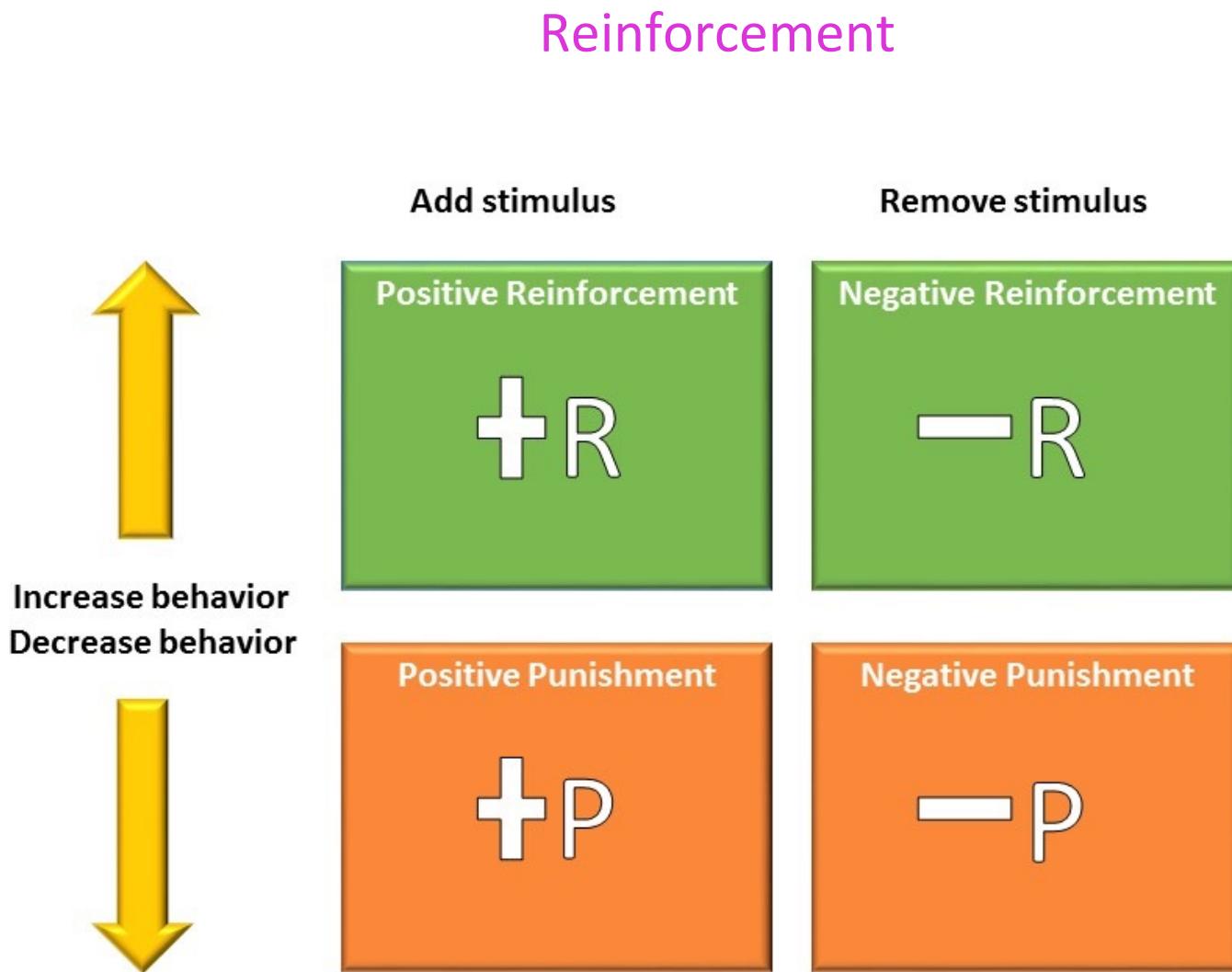
Initial understanding of instrumental/operant conditioning: Thorndike's law of effect

THORNDIKE'S LAW OF EFFECT

(from *Animal Intelligence* 1911)

"Of several responses made to the same situation, those which are accompanied or closely followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it recurs, they will be more likely to recur; those which are accompanied or closely followed by discomfort to the animal will, other things being equal, have their connections with that situation weakened, so that, when it recurs, they will be less likely to occur. The greater the satisfaction or discomfort, the greater the strengthening or weakening of the bond."

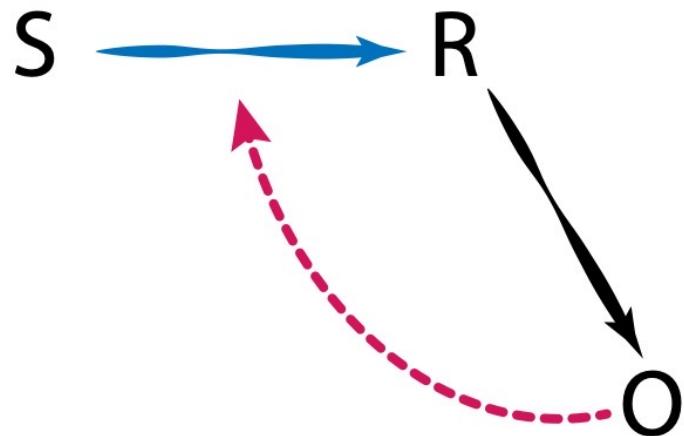
Law of effect: habits



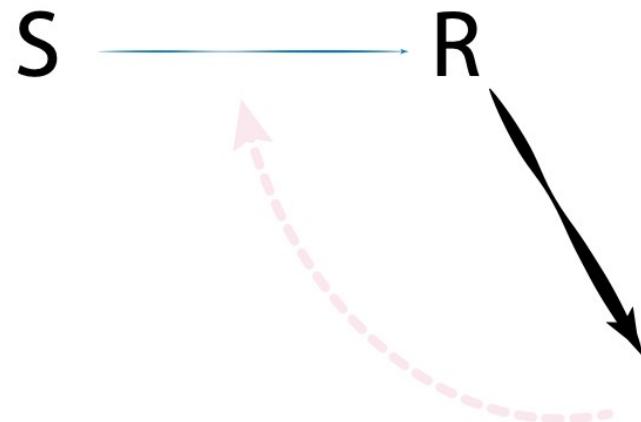
Law of effect: habits

Thorndike's law of effect → instrumental habits
mediated by S-R associations

Reinforcement



Extinction

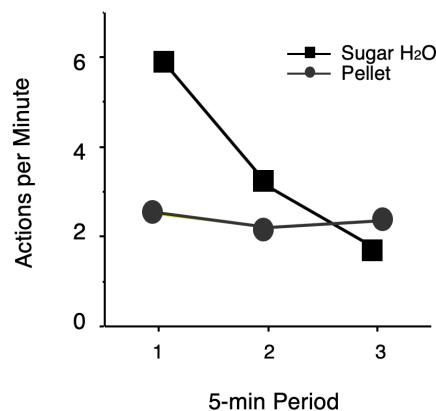


From habits to goal-directed behaviours

Instrumental habits:

Impervious to value of outcomes → problem with flexible behaviour displayed by many species in response to changes in the value of the outcome and choice....

Training: Hunger	Test: Thirst
$L_p \rightarrow \text{Pellet}$ $C_p \rightarrow \text{Sugar H}_2\text{O}$ or $L_p \rightarrow \text{Sugar H}_2\text{O}$ $C_p \rightarrow \text{Pellet}$	$L_p \rightarrow 0$ vs $C_p \rightarrow 0$

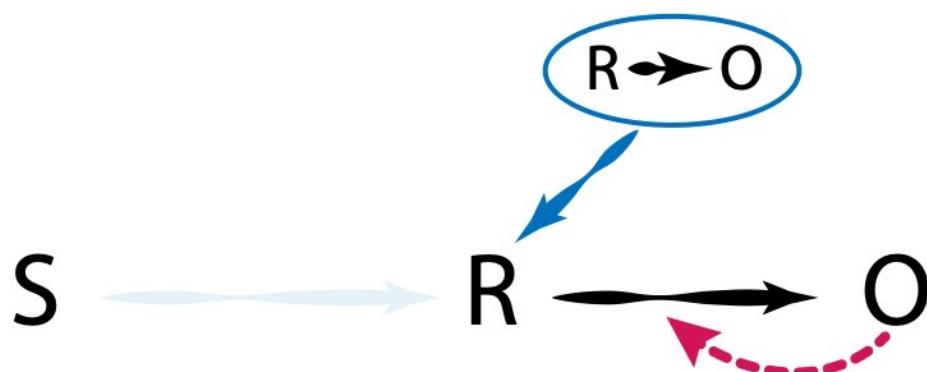


Dickinson & Watt, 1997

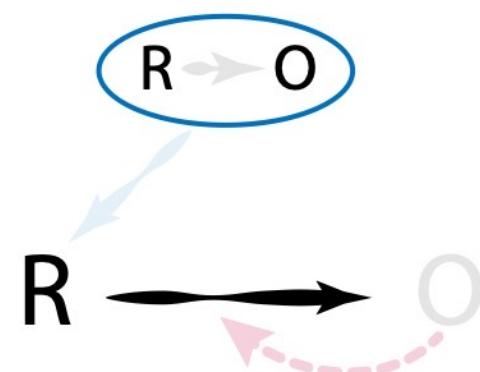
From habits to goal-directed behaviours

Goal-directed behaviours and A-O associations:

Reinforcement

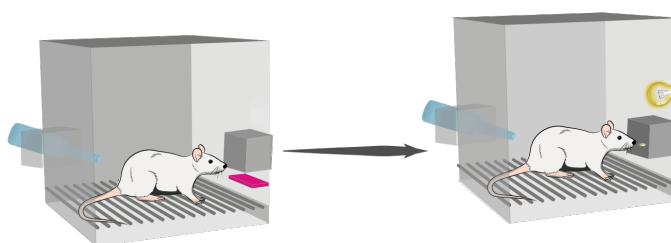


Extinction



From habits to goal-directed behaviours

Sensitivity to outcome devaluation and contingency degradation: the signature of goal-directed behaviour



Devaluation of the outcome

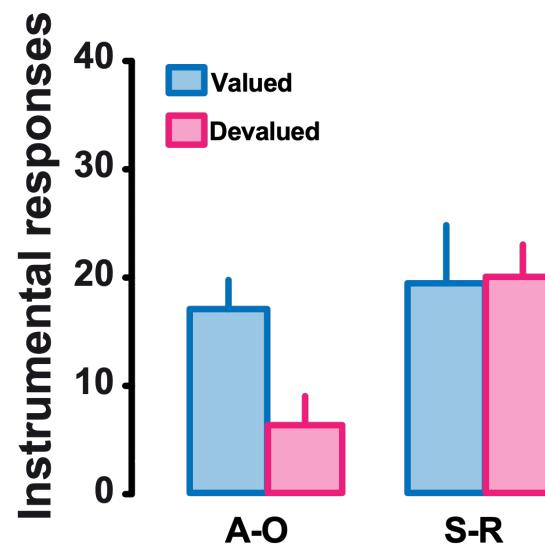
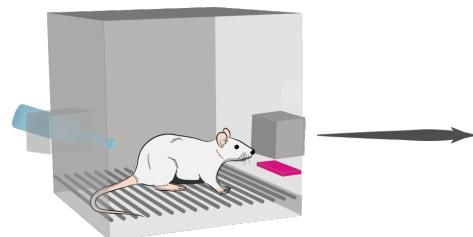


Pre-feeding satiety

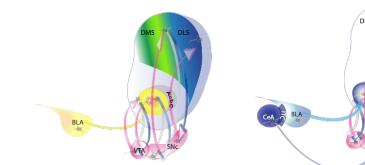
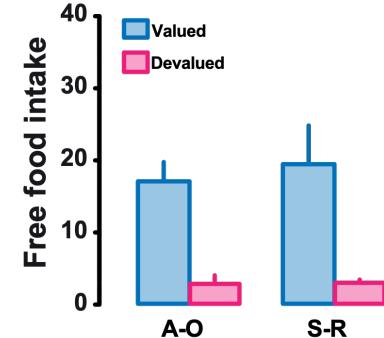


Taste aversion

Test under extinction conditions



Post-challenge consummatory test



Measure seeking responses!

From habits to goal-directed behaviours

Evidence for sensitivity to outcome devaluation:

Following instrumental training with a particular food, an aversion can be established to that food by pairing its consumption with an injection of lithium chloride (LiCl). If instrumental performance is controlled by knowledge about the consequences of the action, the animal should be less ready to perform this action following food-aversion training.

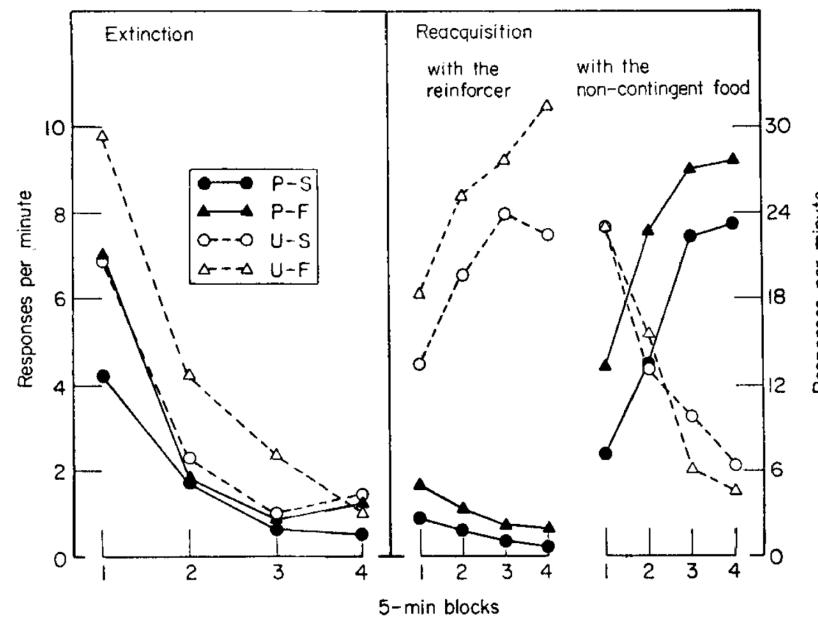
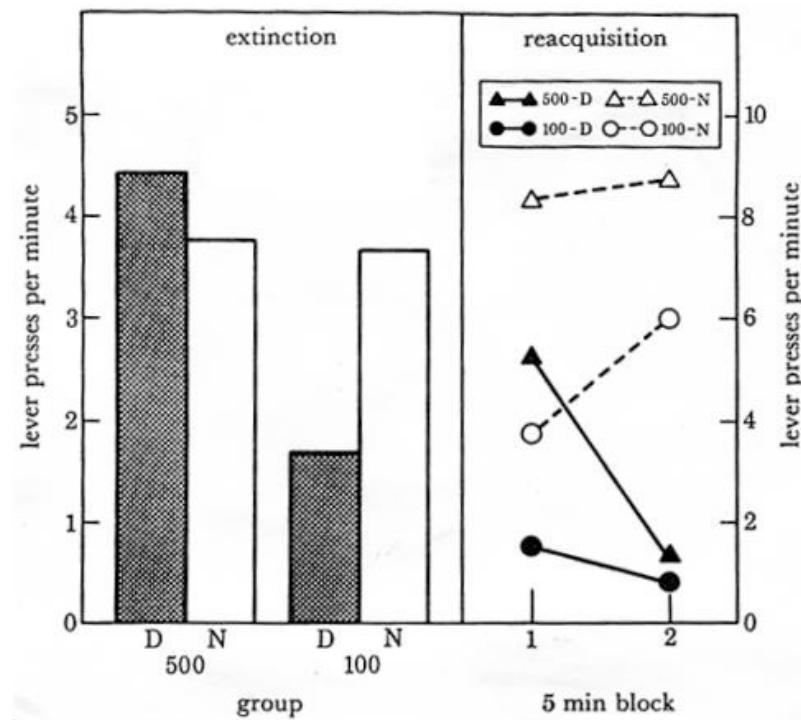
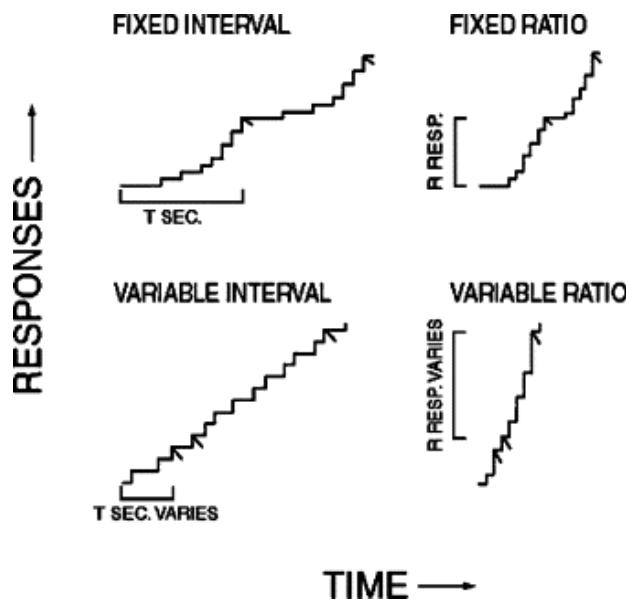


FIGURE 2. Experiment II: mean response rates in 5-min blocks of all groups during extinction and reacquisition sessions. P-S: paired-sucrose reinforcer; P-F: paired-mixed composition food reinforcer; U-S: unpaired-sucrose reinforcer; U-F: paired mixed composition food reinforcer.

From habits to goal-directed behaviours

Habits are
resistant to outcome devaluation
predominant under interval schedules of reinforcement and following
overtraining

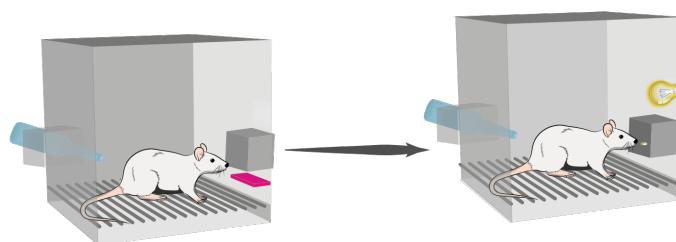


Ratio schedules: strong contingency → A-O
Interval schedules: no contingency → S-R

Adams et al., 1982

From habits to goal-directed behaviours

How to determine the associative nature of instrumental responses?



Devaluation of the outcome

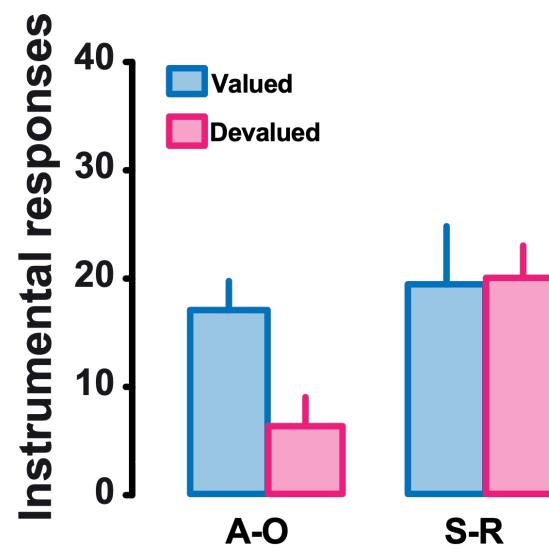
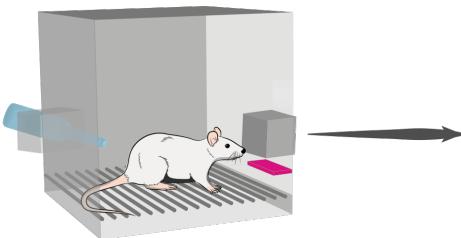


Pre-feeding satiety

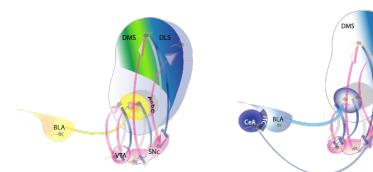
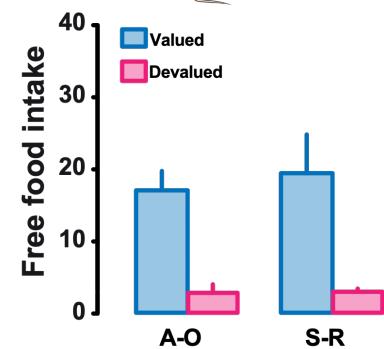


Taste aversion

Test under extinction conditions



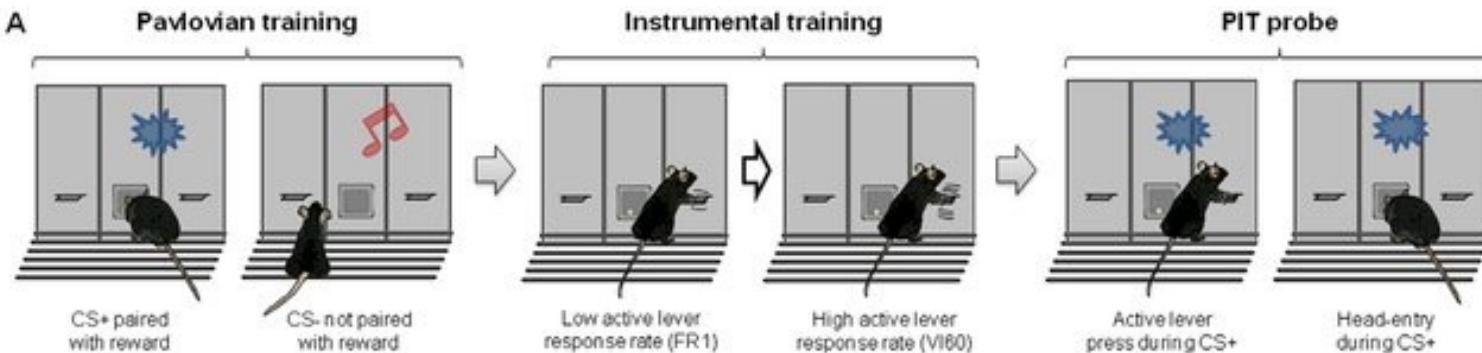
Post-challenge consummatory test



Measure seeking responses!

Pavlovian/instrumental interactions

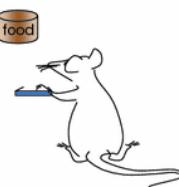
Pavlovian to instrumental transfer (PIT)



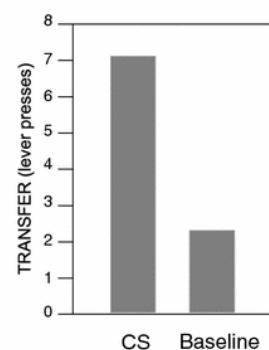
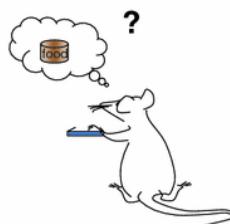
1. Pavlovian Training
S-O association



2. Instrumental Training
R-O association



3. Extinction Test

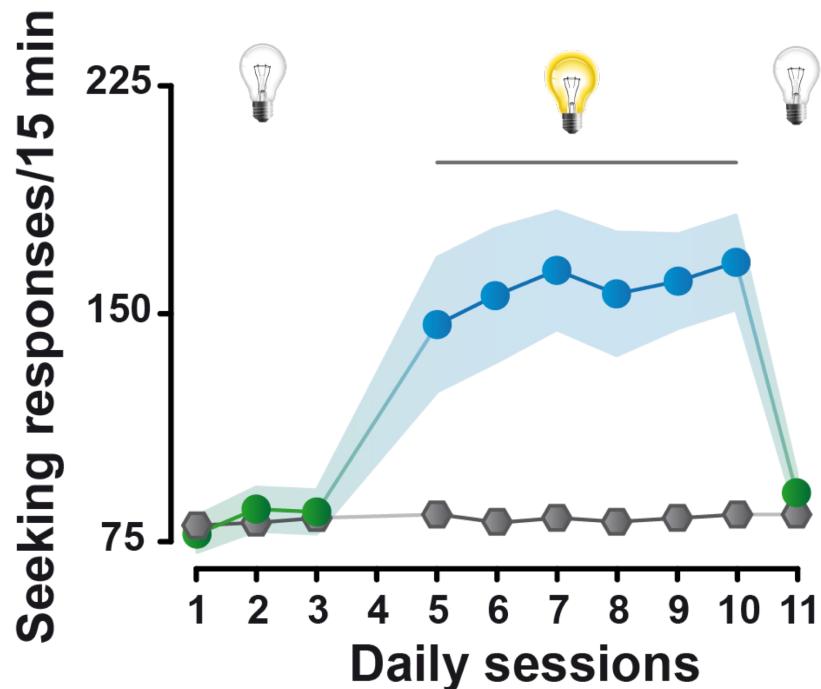
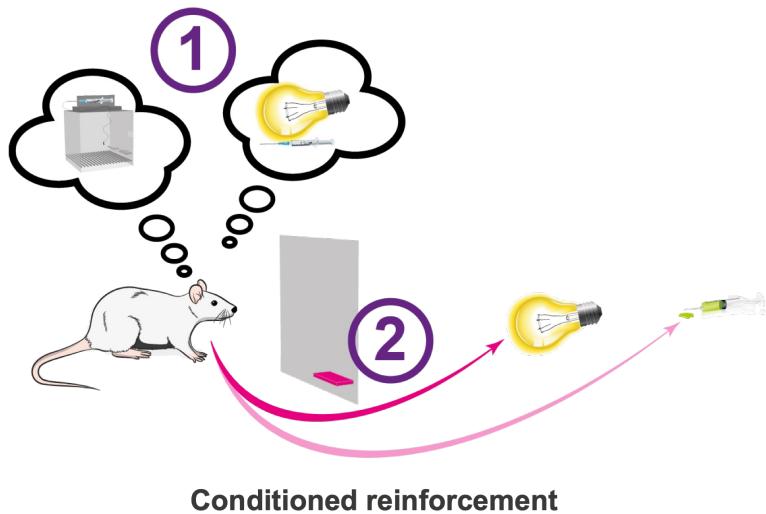


Conditioned reinforcement

In conditioned reinforcement CSs are response produced and become CRs!

Second order schedule of reinforcement

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



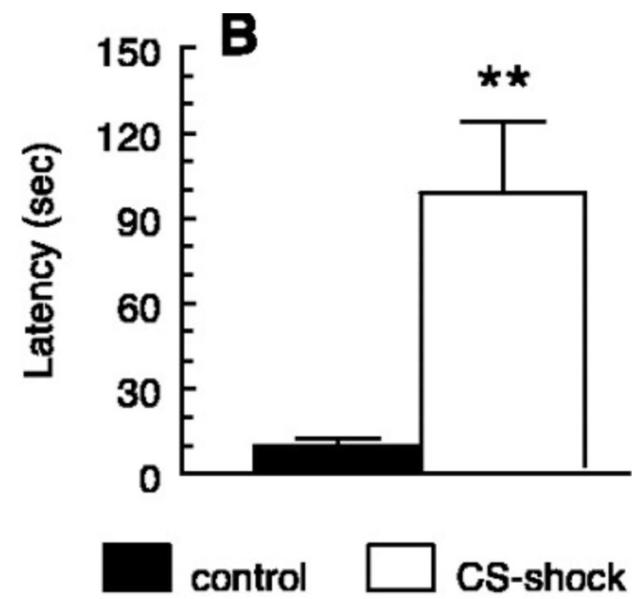
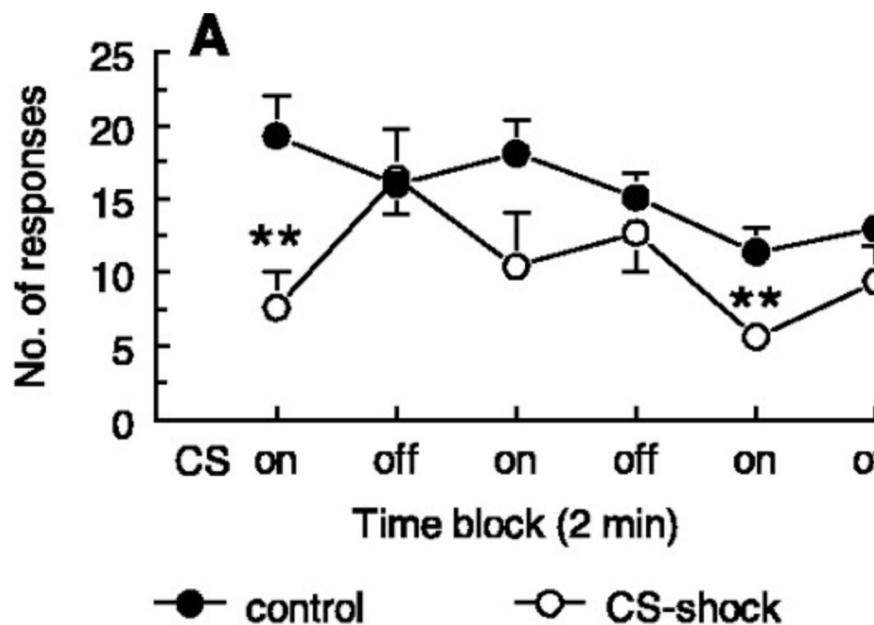
Conditioned reinforcers

- bridge delays to reinforcement
- invigorate responding over prolonged periods of time
- are resistant to devaluation of the outcome
- support the acquisition of new instrumental responses

Arroyo et al., 1998

Conditioned suppression: negative PIT

A shock-associated CS presented non contingently decreases cocaine seeking
→ Conditioned suppression



Conclusions

Pavlovian responses are inflexible: useful to prepare to interact with the outcome and be able to CHOOSE your actions

Instrumental conditioning is where the response CAUSES the outcome.

Sometimes this is a S-R association (the stimulus elicits the response) – this is a HABIT

Sometimes this is a R-O association (you perform the action in order to bring about the outcome) – this is GOAL DIRECTED

Pavlovian cues can influence (invigorate or suppress) instrumental responses

These Pavlovian and instrumental mechanisms and their interactions all rely on the striatum

Part II The functional anatomy of the striatum

Overview – functions of the striatum

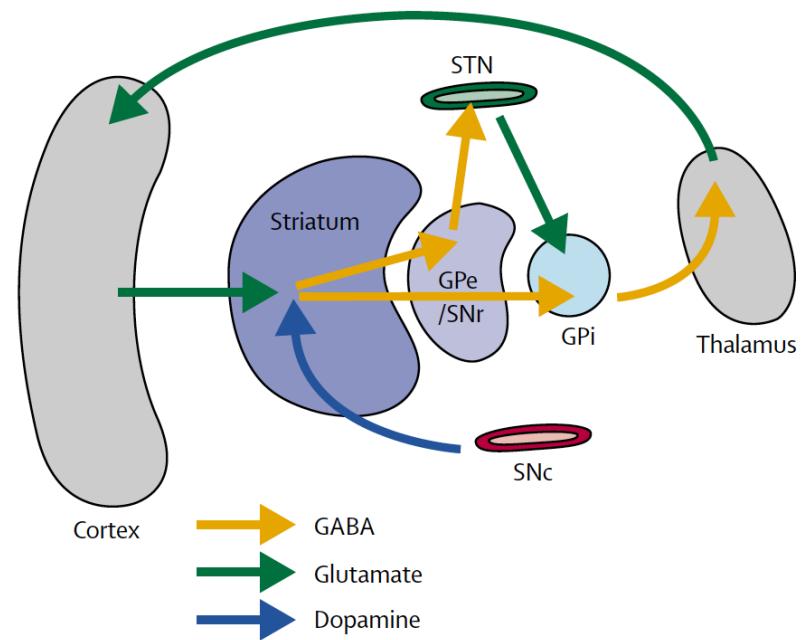
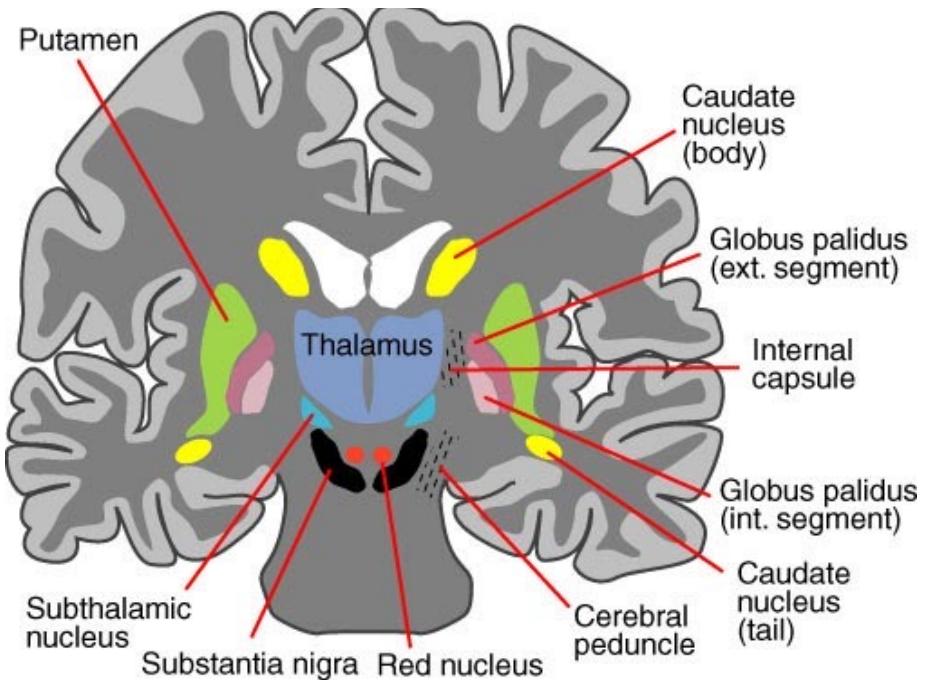
Organisation of the striatum

1. Different, parallel 'loops'
2. Ventral vs dorsal streams
→ actor-critic model

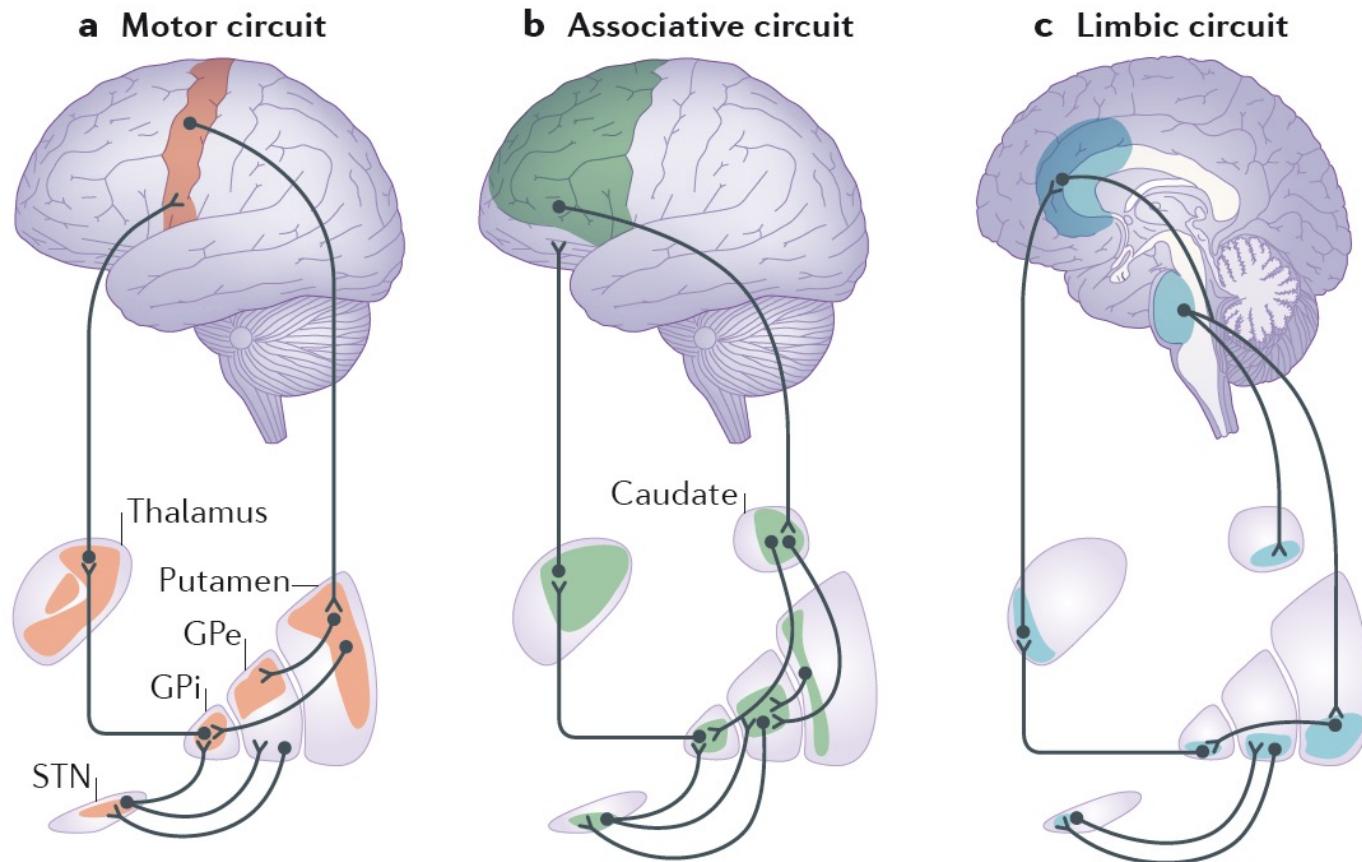
3. Ventral striatum/nucleus accumbens:
→ limbic/motor interface
→ Role in Pavlovian/instrumental interactions

4. Dorsal striatum: control over instrumental behaviour
→ actions and habits, DMS and DLS
→ direct and indirect pathways in the dorsal striatum
→ Parkinson's disease

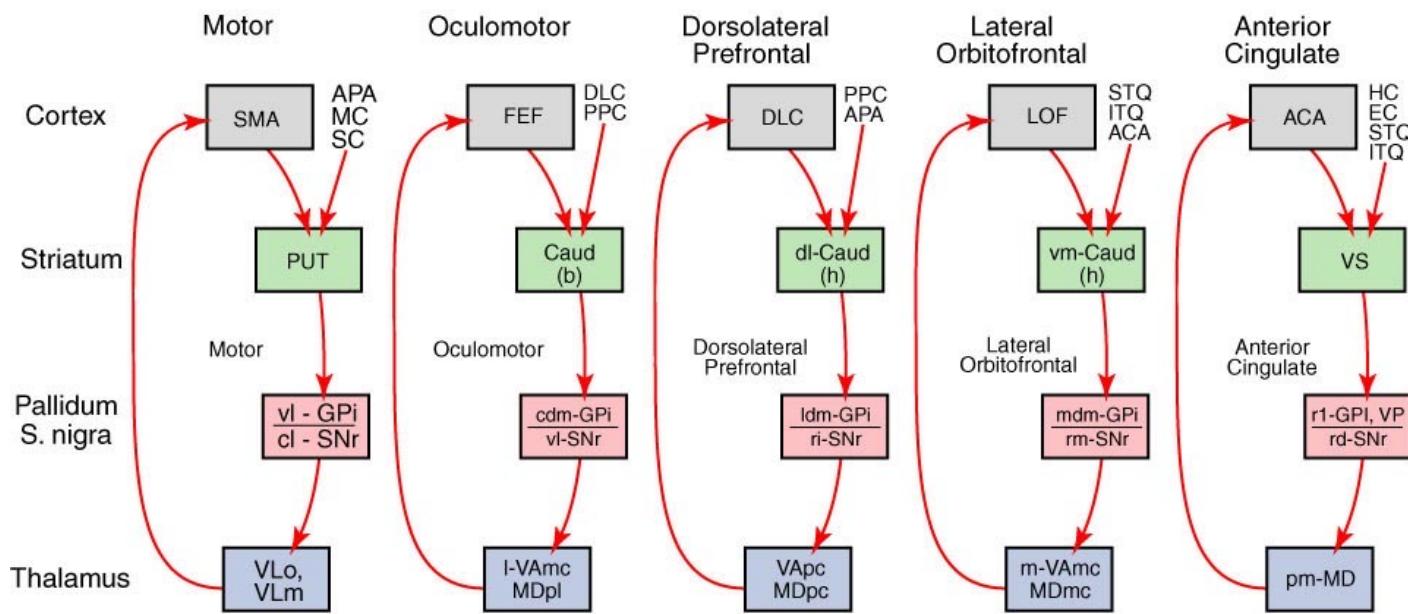
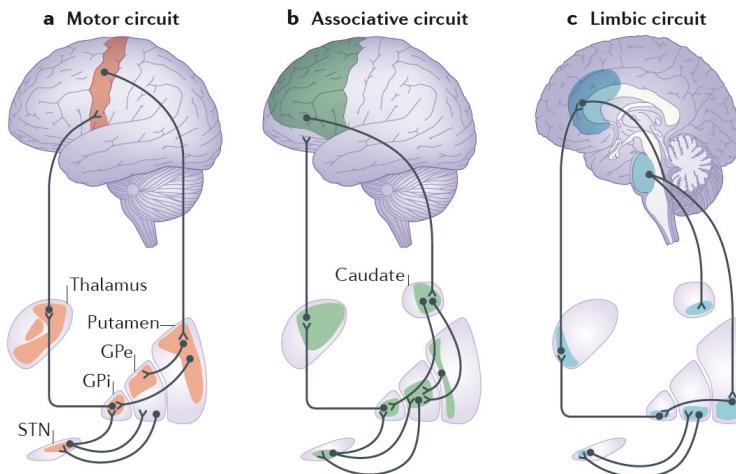
The basal ganglia: subcortical nuclei that participate in functional ‘loops’ with cortical areas



The corticostriatal loops of Alexander & DeLong – parallel functional loops

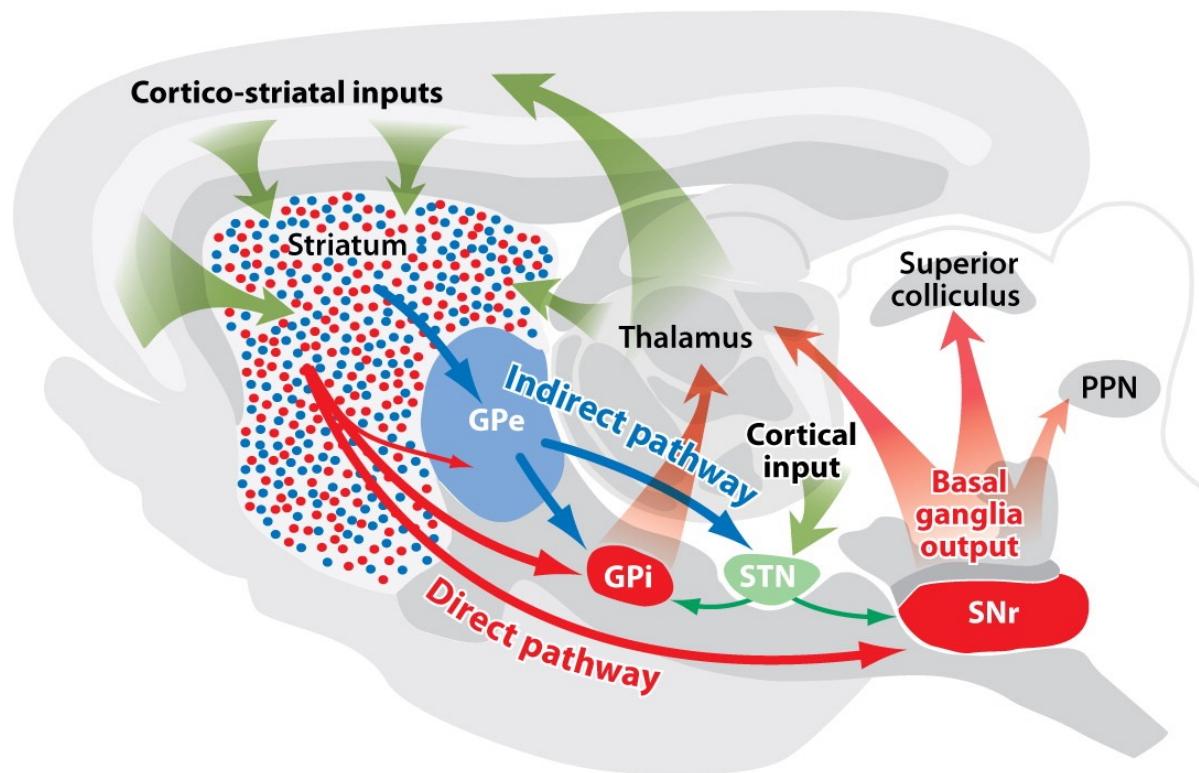


The corticostriatal loops of Alexander & DeLong – parallel functional loops



Alexander et al. (1986)

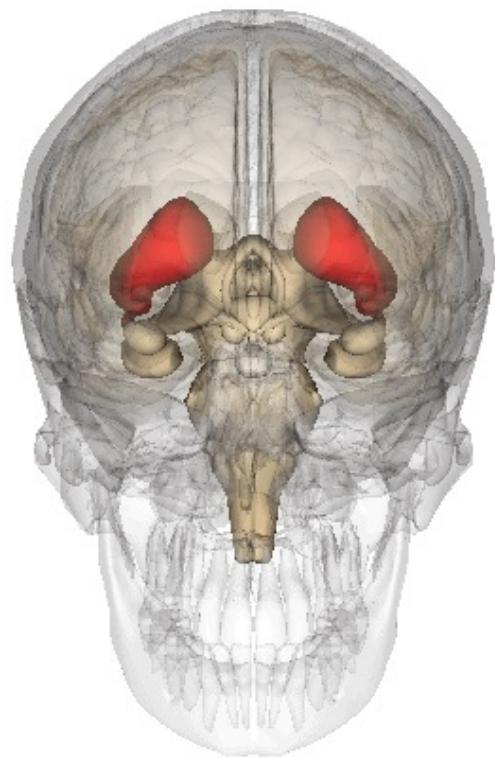
The corticostriatal loops of Alexander & DeLong – similar functional organisation in rodents



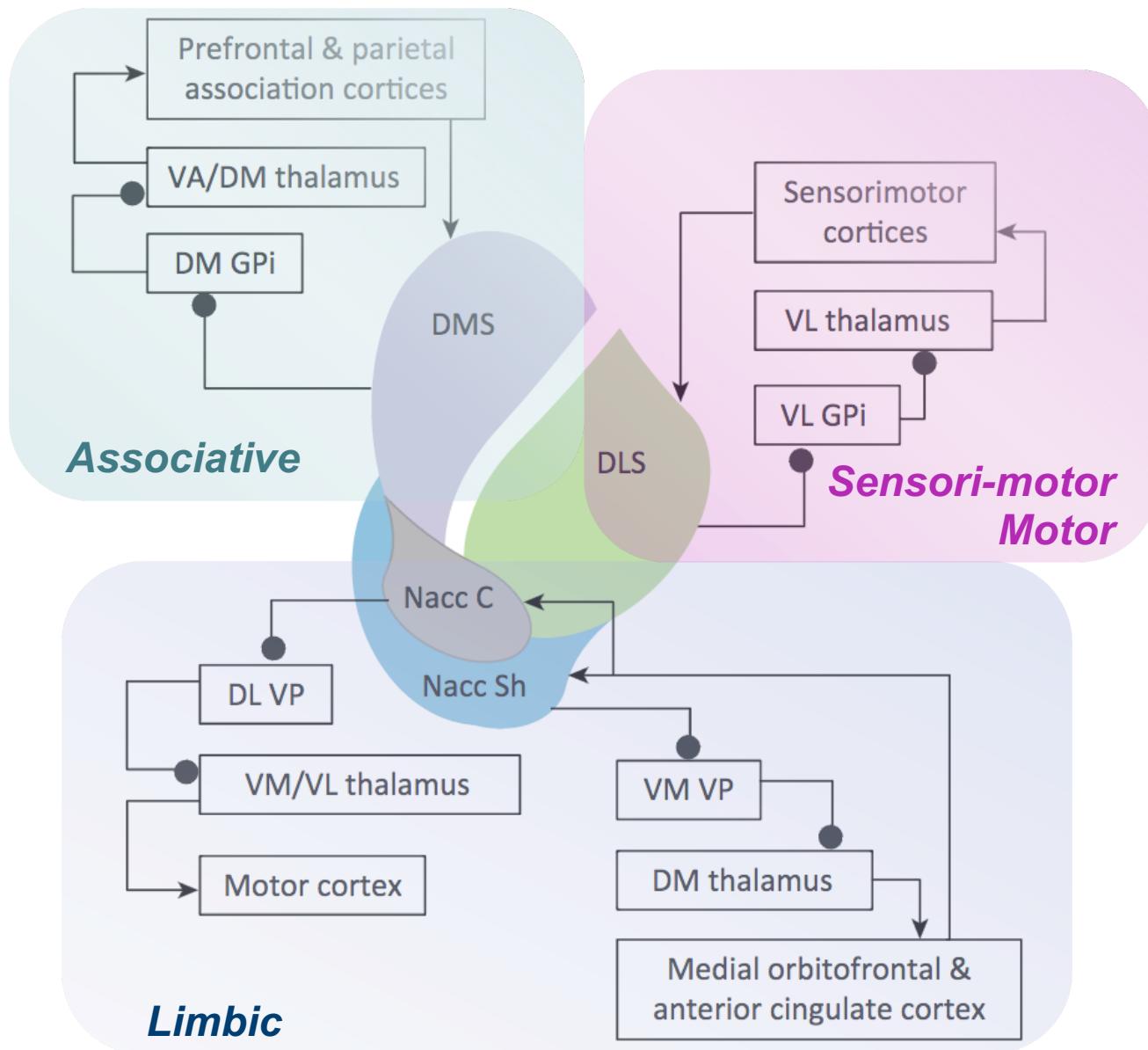
Note SNr – substantia nigra pars reticulata = GPi (in primate brain)
EP = entopeduncular nucleus = GPi (in primate brain)

The organisation of the striatum

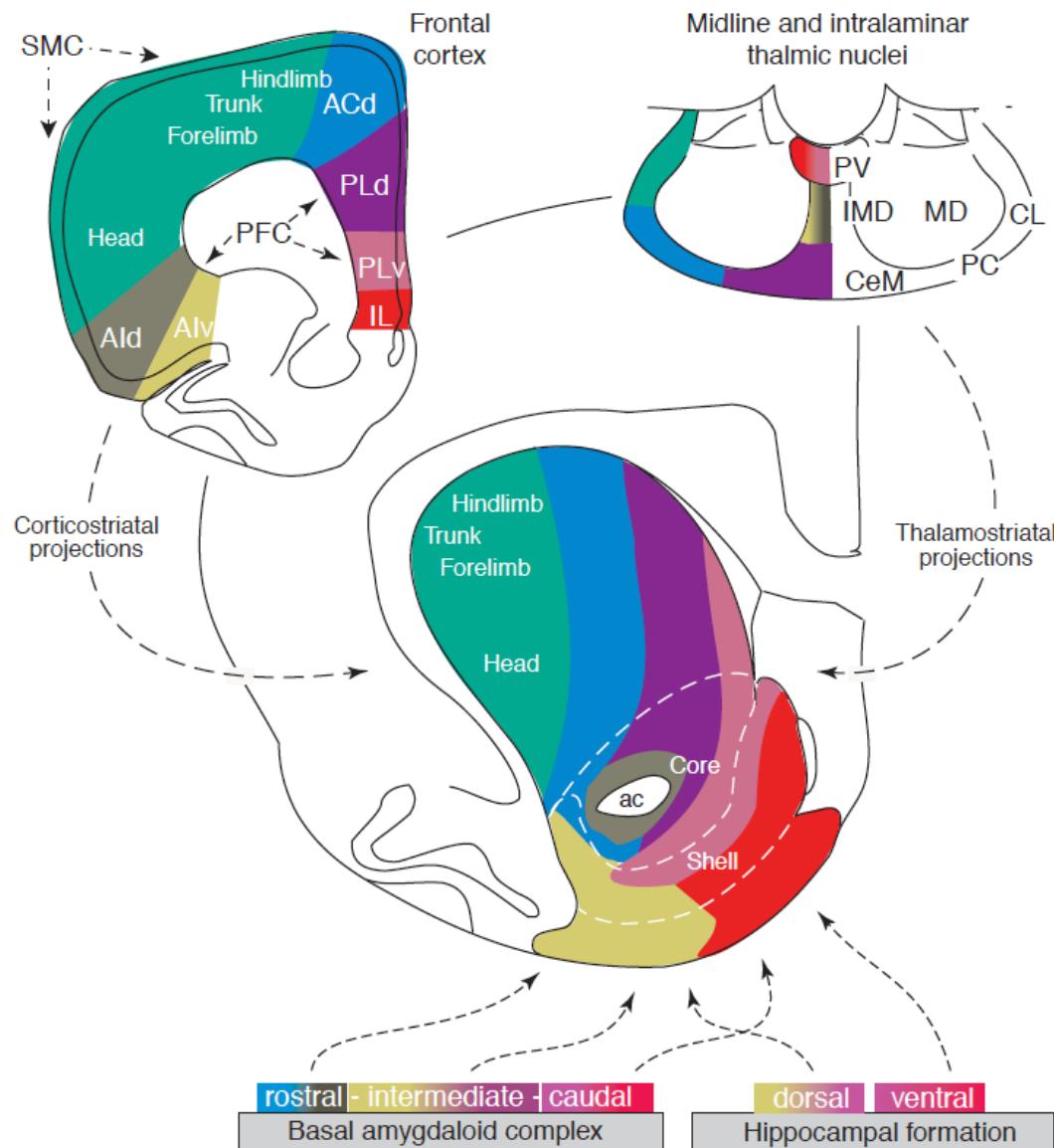
The striatum: anatomical and functional heterogeneity



The striatum: anatomical and functional heterogeneity

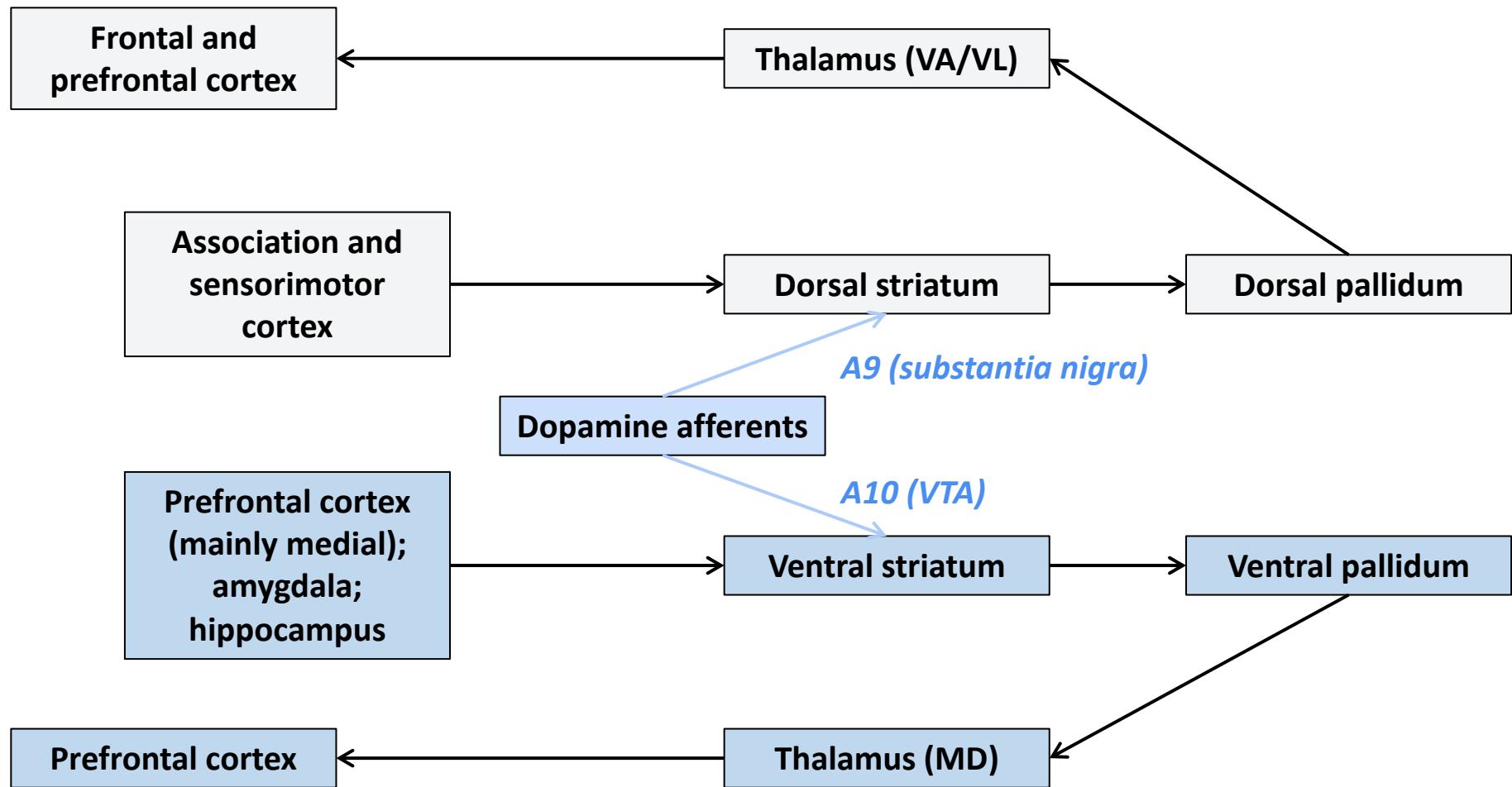


The striatum: anatomical and functional heterogeneity

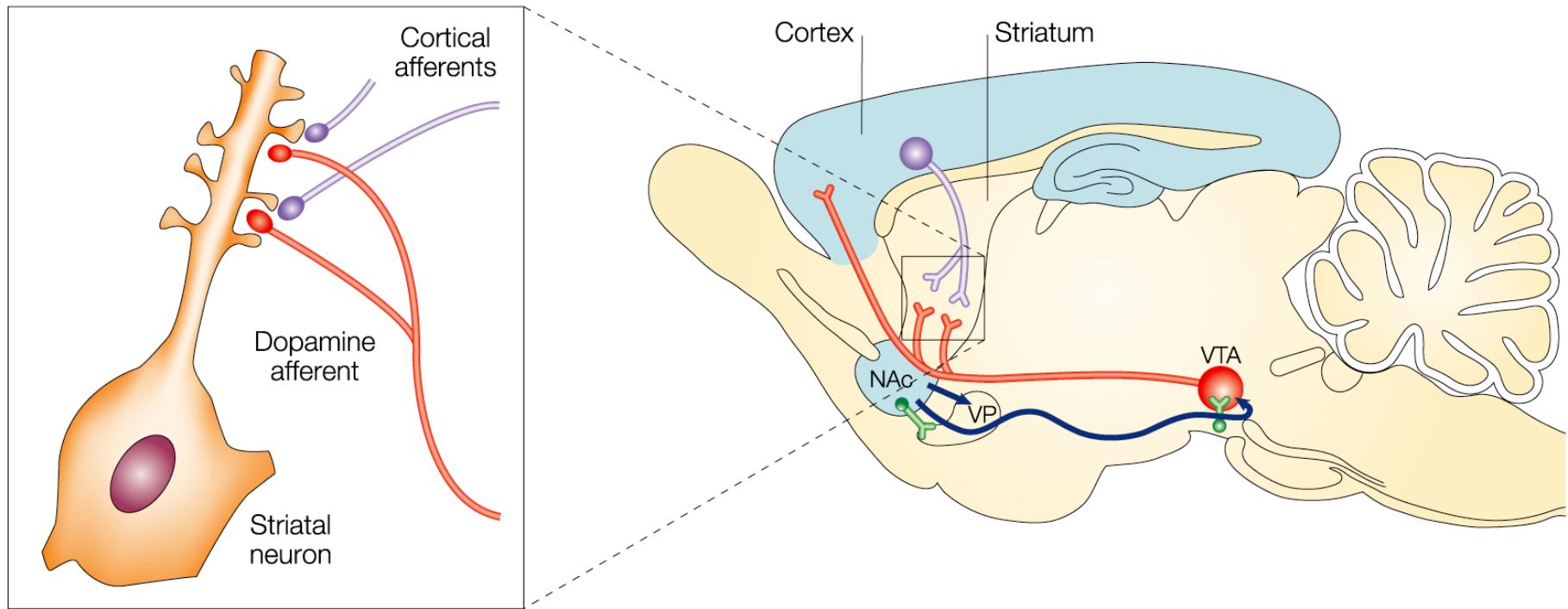


Voorn et al., 2004
10.1016/j.tins.2004.06.006

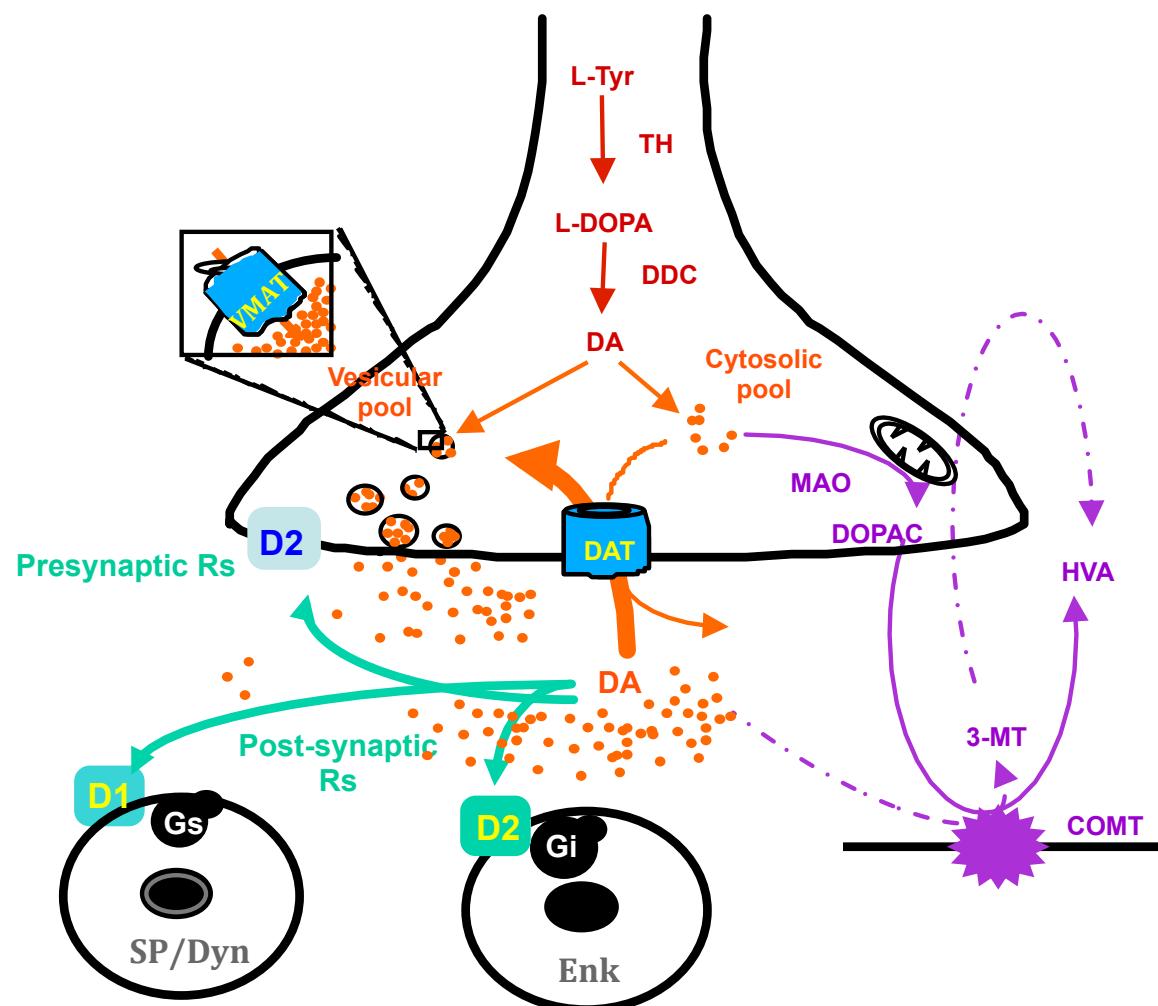
Lennart Heimer drew parallels between the dorsal and ventral striatal circuitry



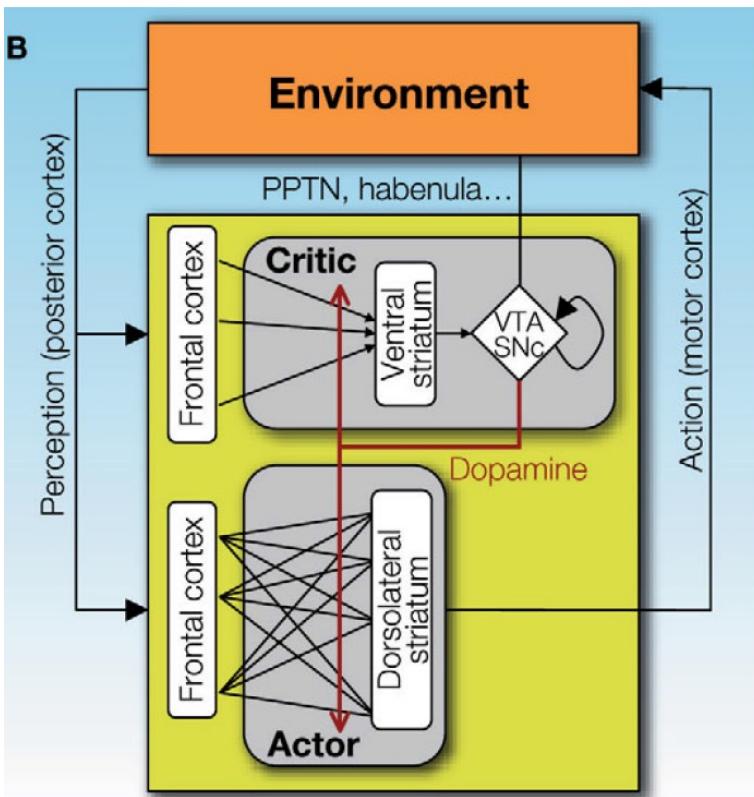
Dopamine acts on striatal medium spiny neurons



MSNs in the direct pathway express mainly the D₁-subtype, and the indirect pathway the D₂-subtype of DARs



The Actor/Critic model of the striatum



The actor (dorsal striatum)

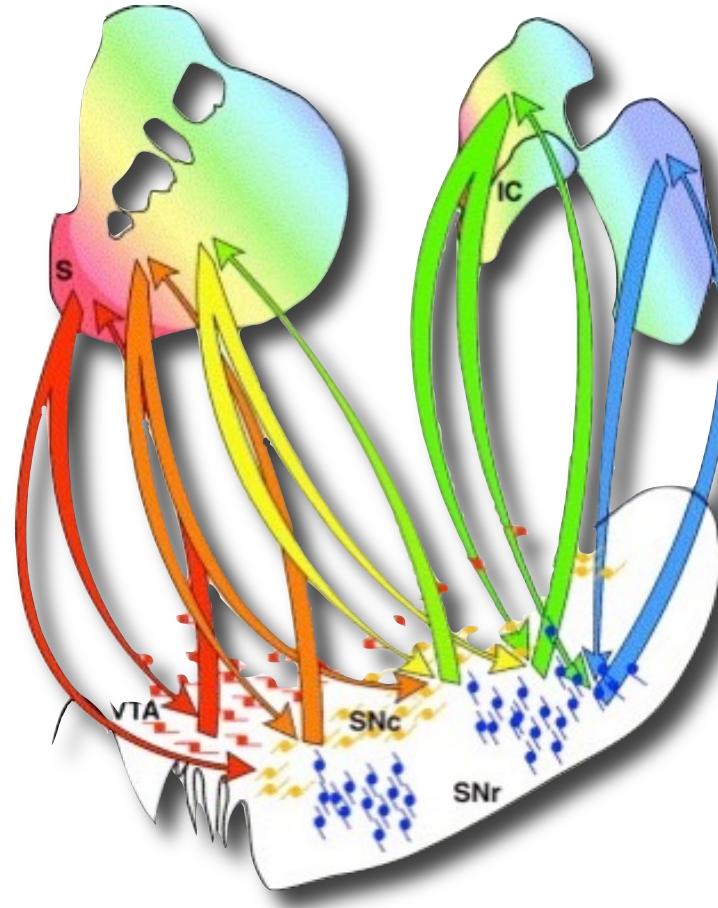
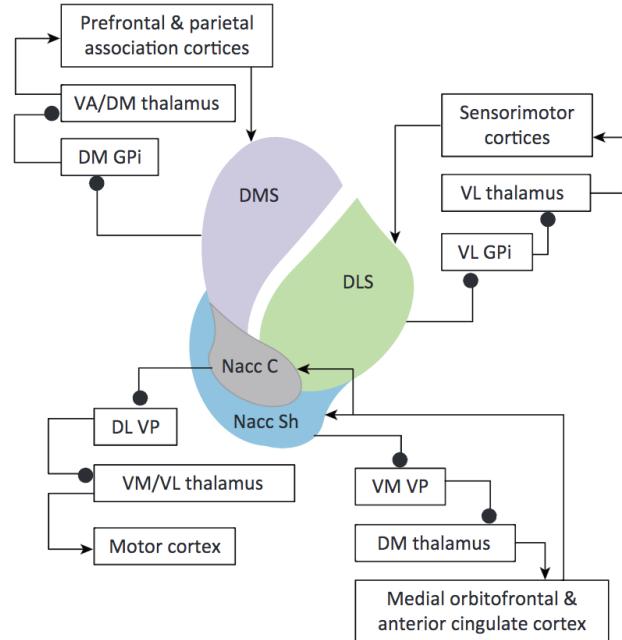
- Model-free (maps states and action propensities)
 - Decides how to perform an action
 - Under the control of the critic

The critic (Nac)

- Models (model-based) whether it is worth doing something for the possibility of a reward
 - Relies on prediction/error (Dopamine)
 - Says Go to the Actor
 - Assesses post-hoc the utility of the action
 - The coach of the actor

Striato-nigral-striatal pathways lead to ascending spirals from accumbens shell to accumbens core to dorsal striatum

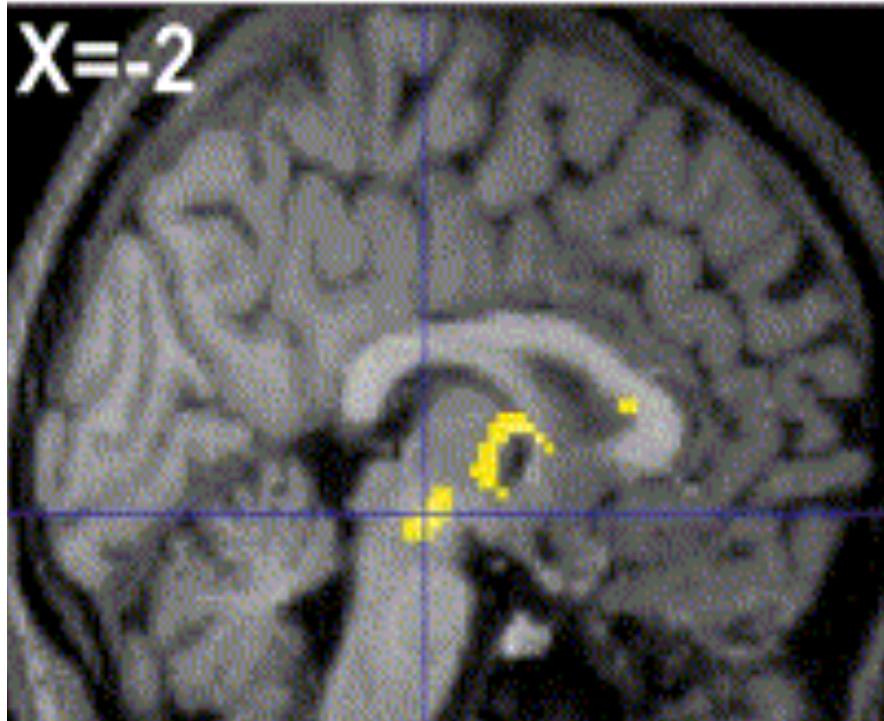
A potential anatomical organisation for an intrastriatal Actor/Critic system



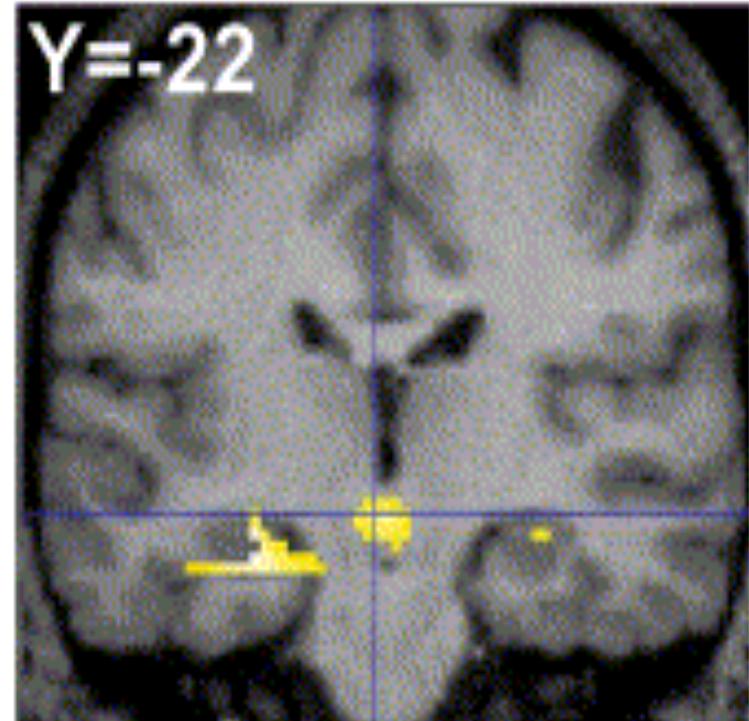
The nucleus accumbens: a limbic/motor interface

Nucleus accumbens and Pavlovian responses

Nucleus accumbens

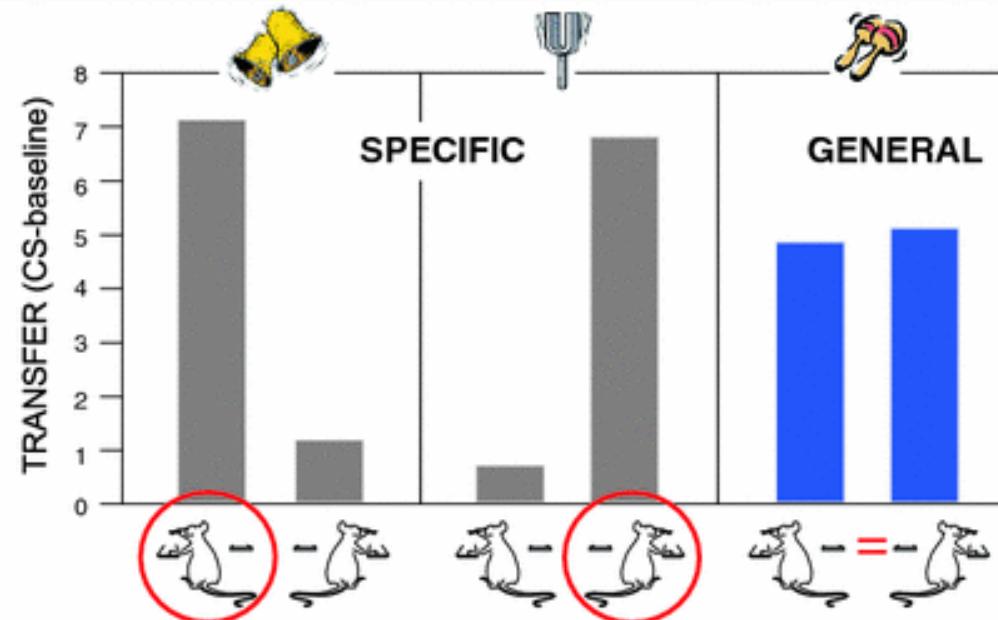
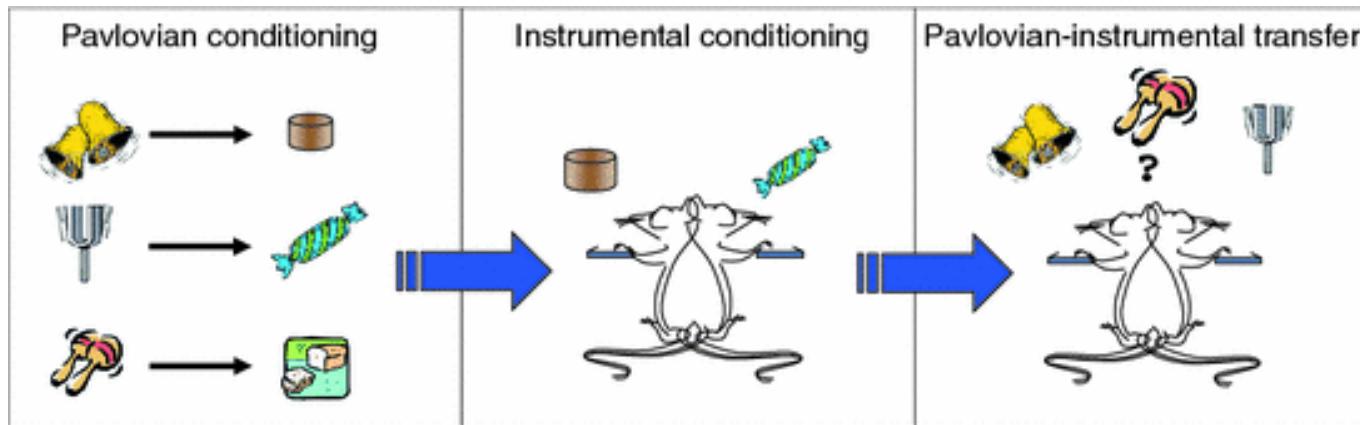


Amygdala



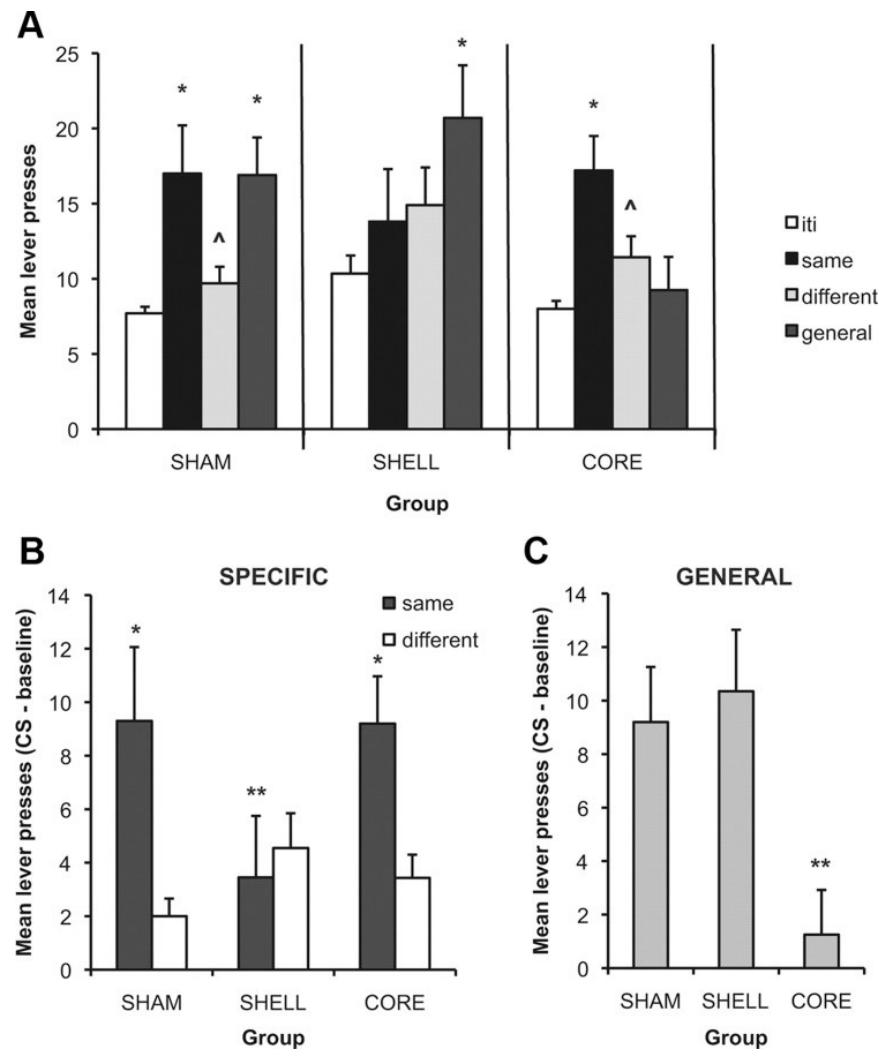
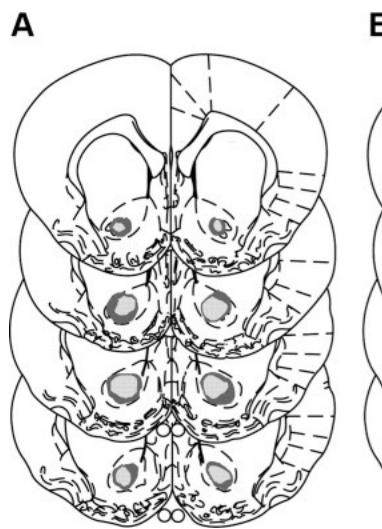
Brain areas more active during anticipation than receipt of glucose

Nucleus accumbens and PIT



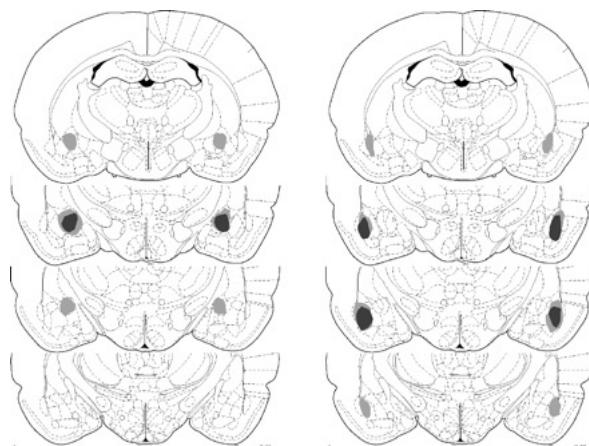
Corbit and Balleine, 2005

Nucleus accumbens and PIT

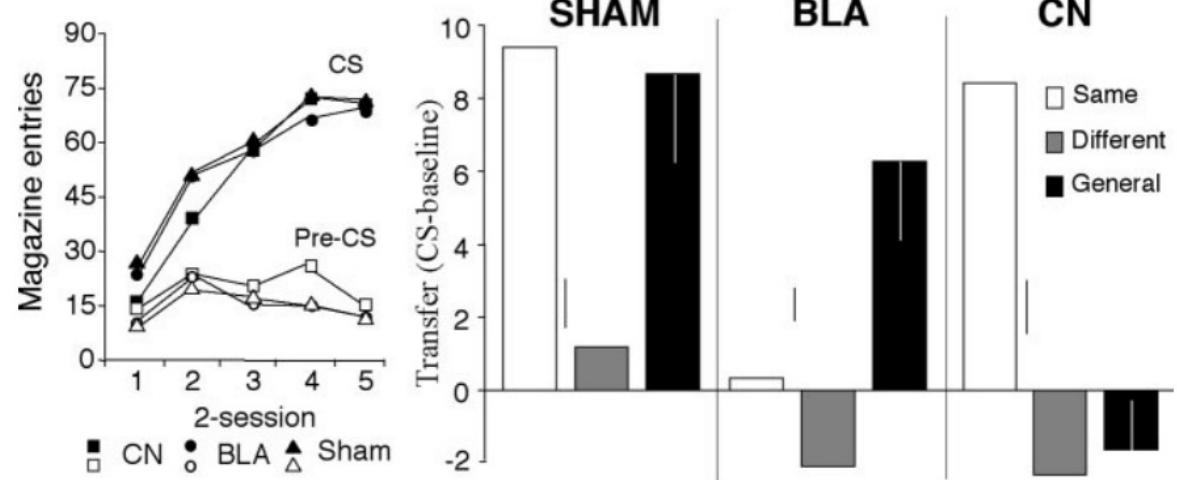


Corbit and Balleine, 2011

Amygdala and PIT

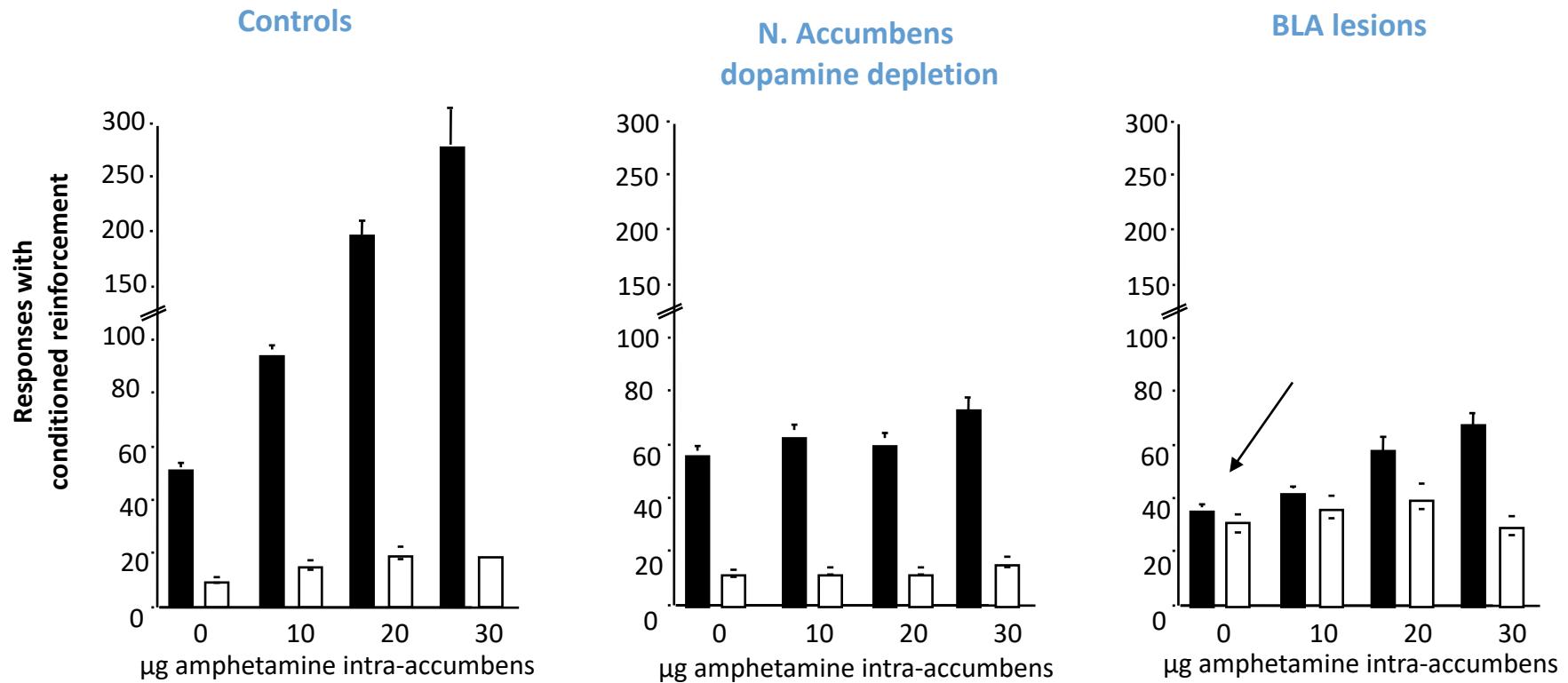


	training	conditioning	transfer test
$R1 \rightarrow O1; R2 \rightarrow O2$		S1-O1 S2-O2 S3-O3	S1: R1, R2 S2: R1, R2 S3: R1, R2



Corbit and Balleine, 2005

NAc dopamine potentiates responding for conditioned reinforcement



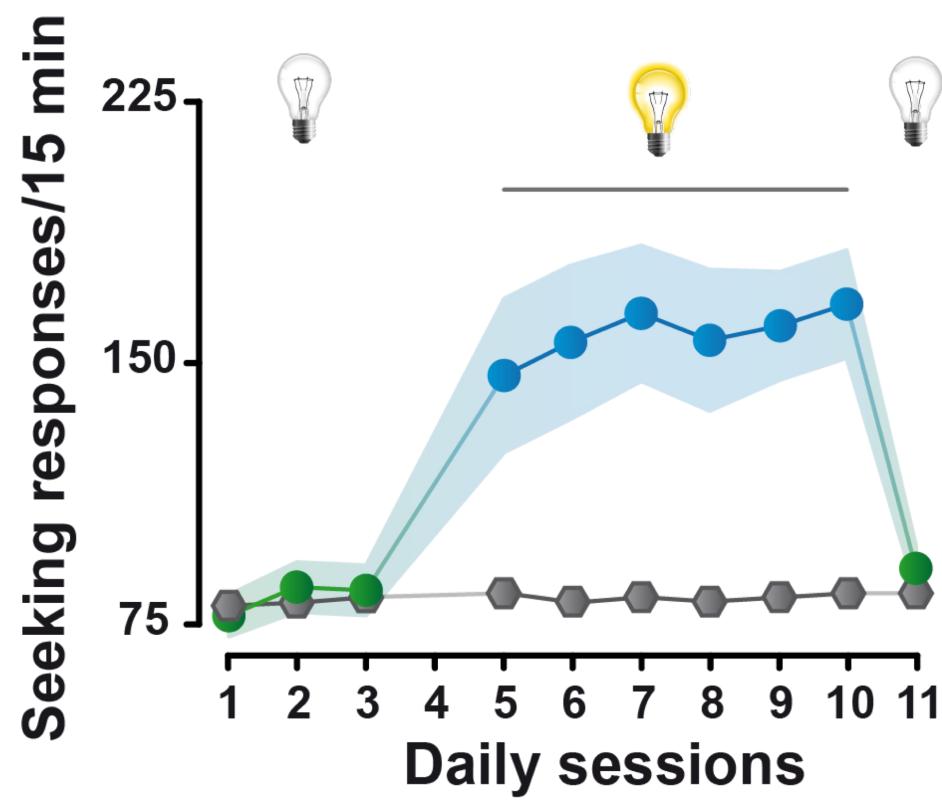
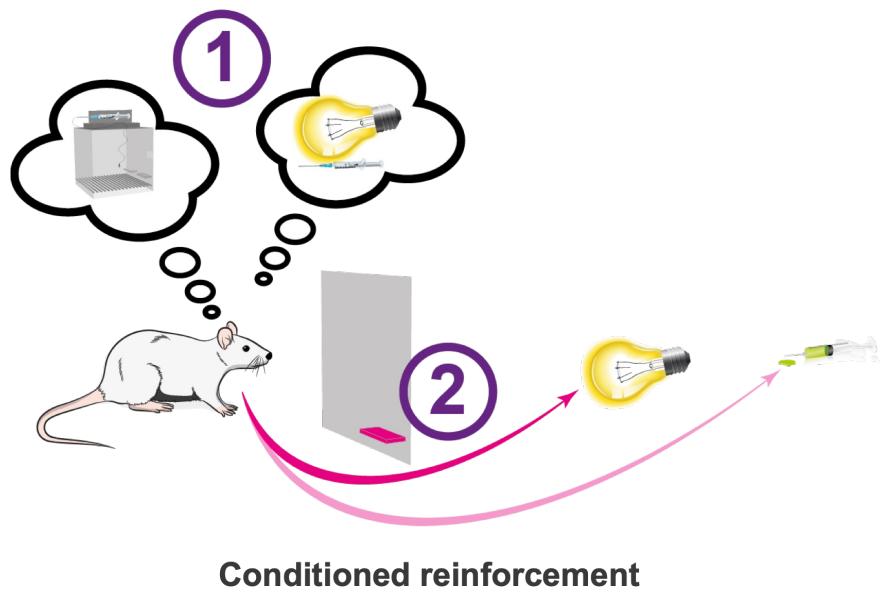
Taylor & Robbins (1984; 1986)

Pavlovian CSs and drug-seeking behaviour

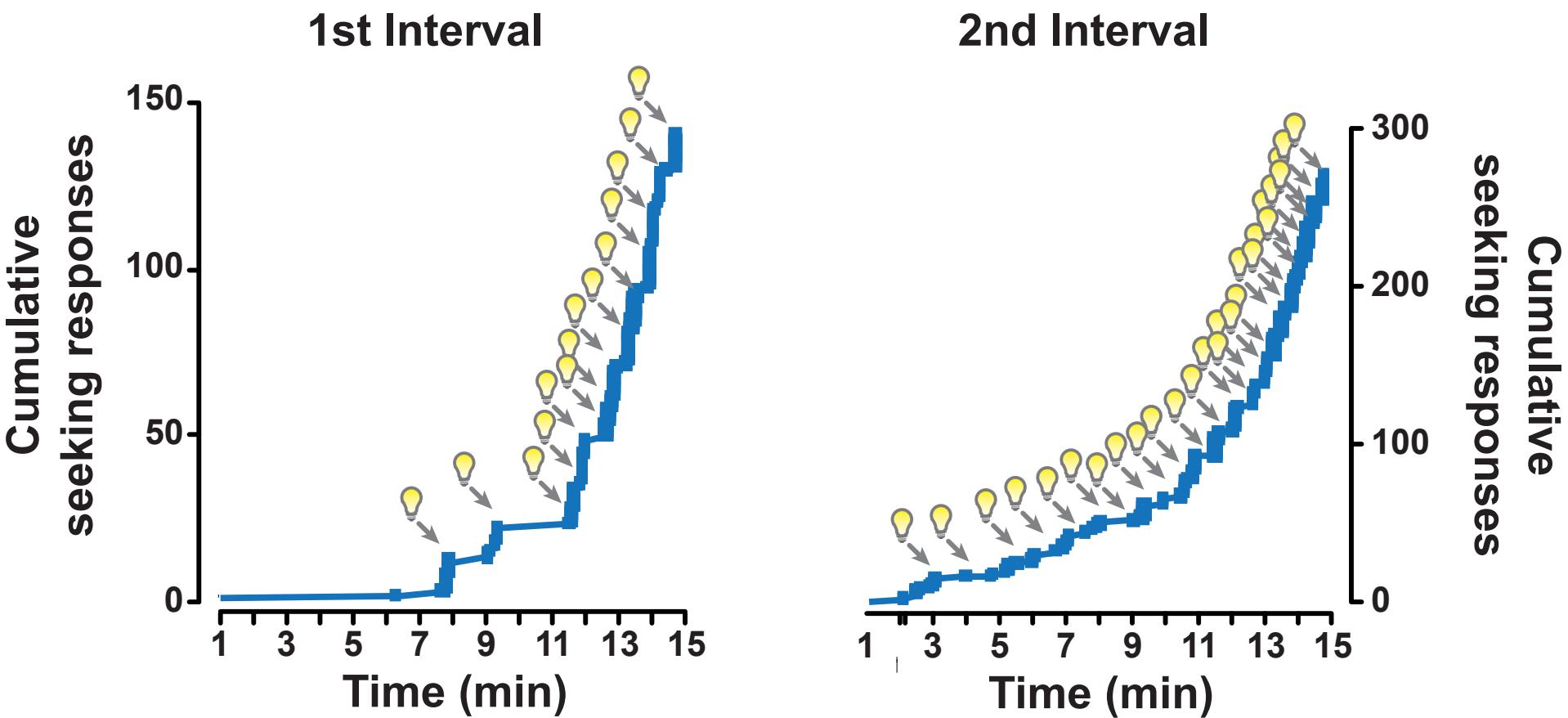
Cue-controlled drug seeking

Second order schedule of reinforcement

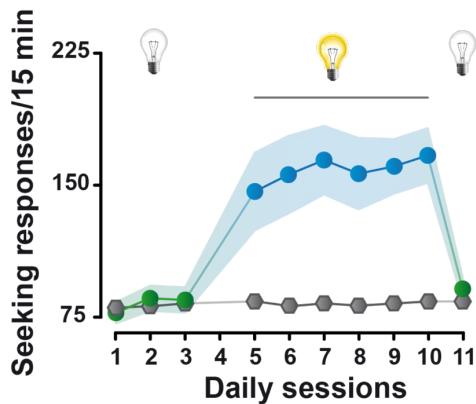
A model of drug seeking that measures the impact of drug CSs over delays to drug taking (conditioned reinforcement)



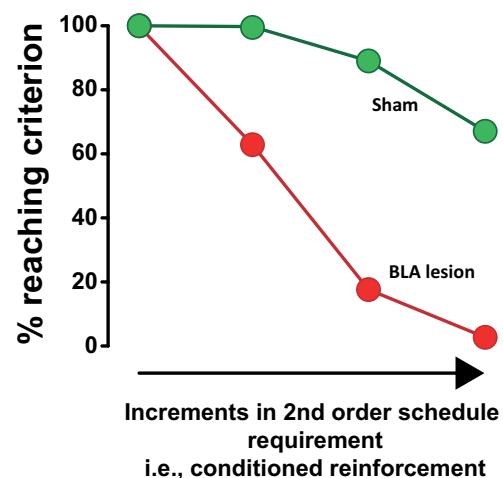
Instrumental responding under a second-order schedule of reinforcement



Acquisition of cue-controlled cocaine-seeking depends upon the basolateral amygdala and nucleus accumbens core

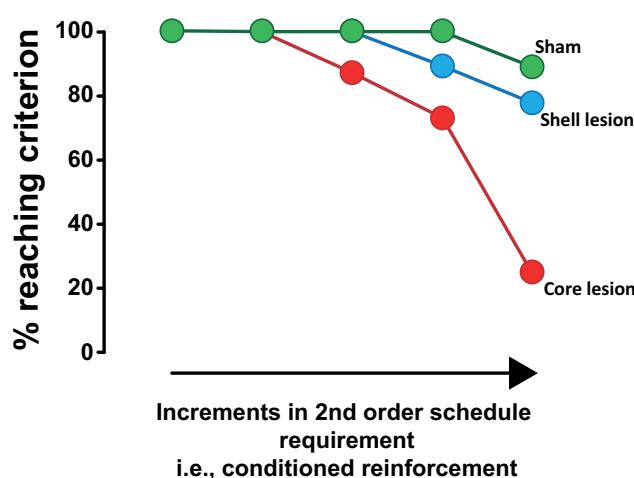


BLA lesion/inactivation

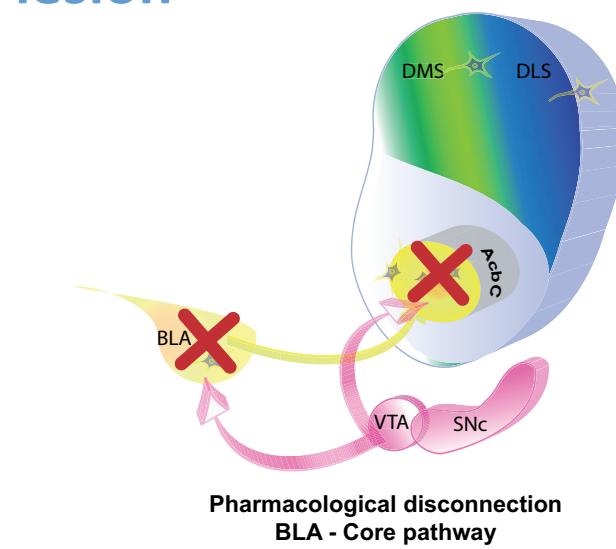


Whitelaw et al., 1996

NAcb core or shell lesion

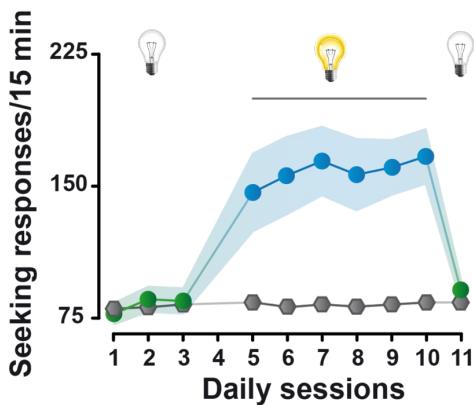


Ito et al., 2002



Di Ciano et al., 2004

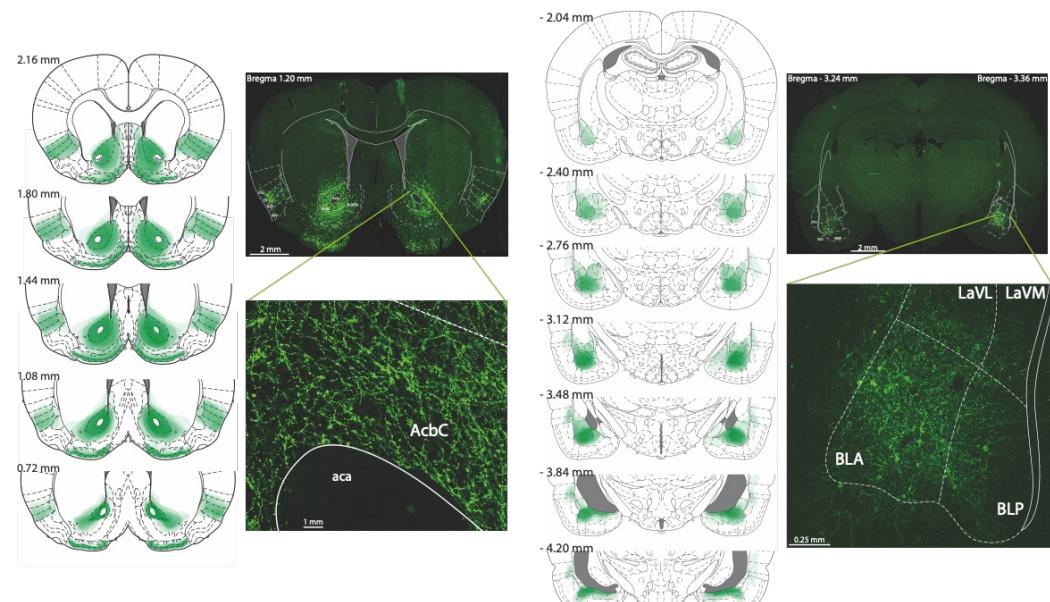
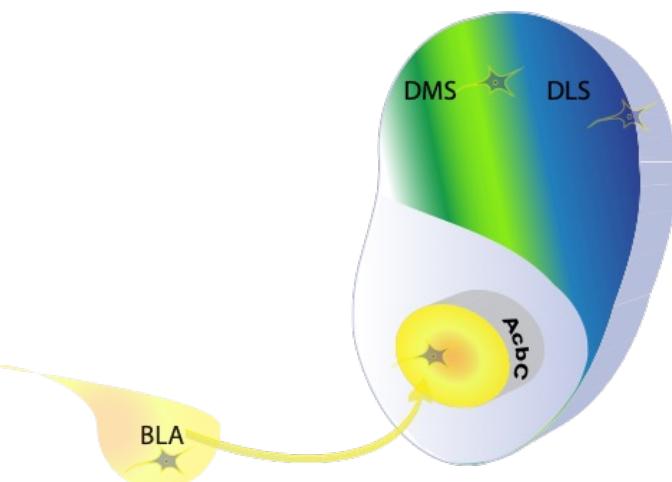
Acquisition of cue-controlled cocaine-seeking depends upon the basolateral amygdala and nucleus accumbens core



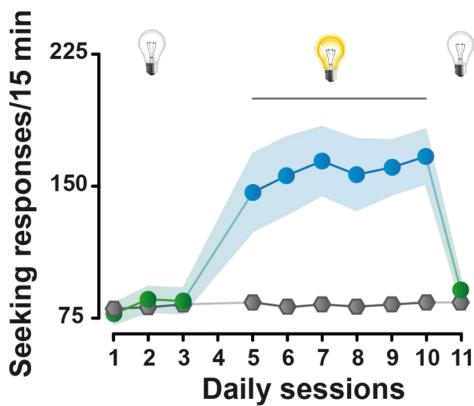
Selective inhibition of the neurons of the BLA-AcbC pathway prevents the development of cue-controlled cocaine seeking

Circuit mapping: DREADDs

Designer receptor exclusively activated by a designer drug



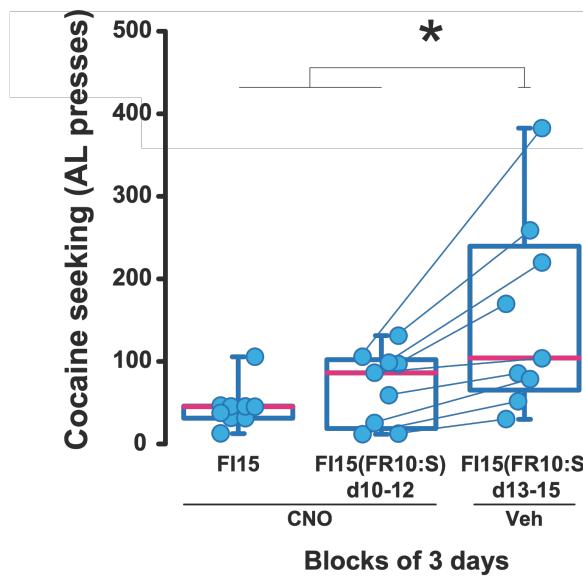
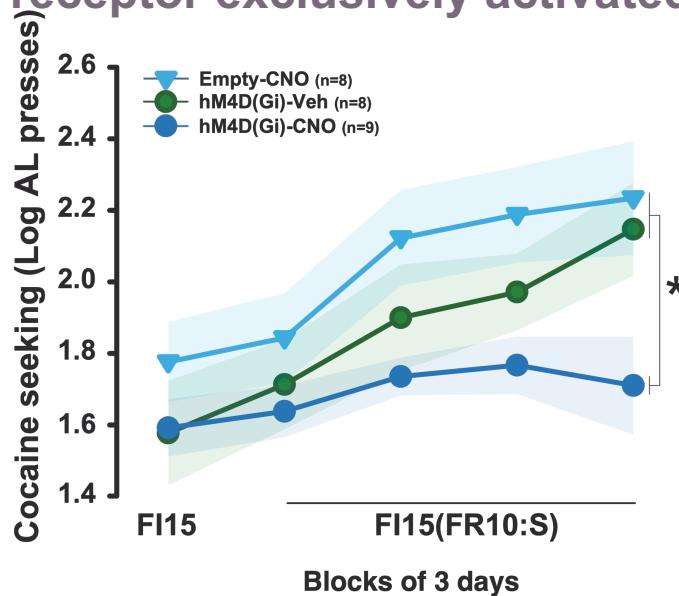
Acquisition of cue-controlled cocaine-seeking depends upon the basolateral amygdala and nucleus accumbens core



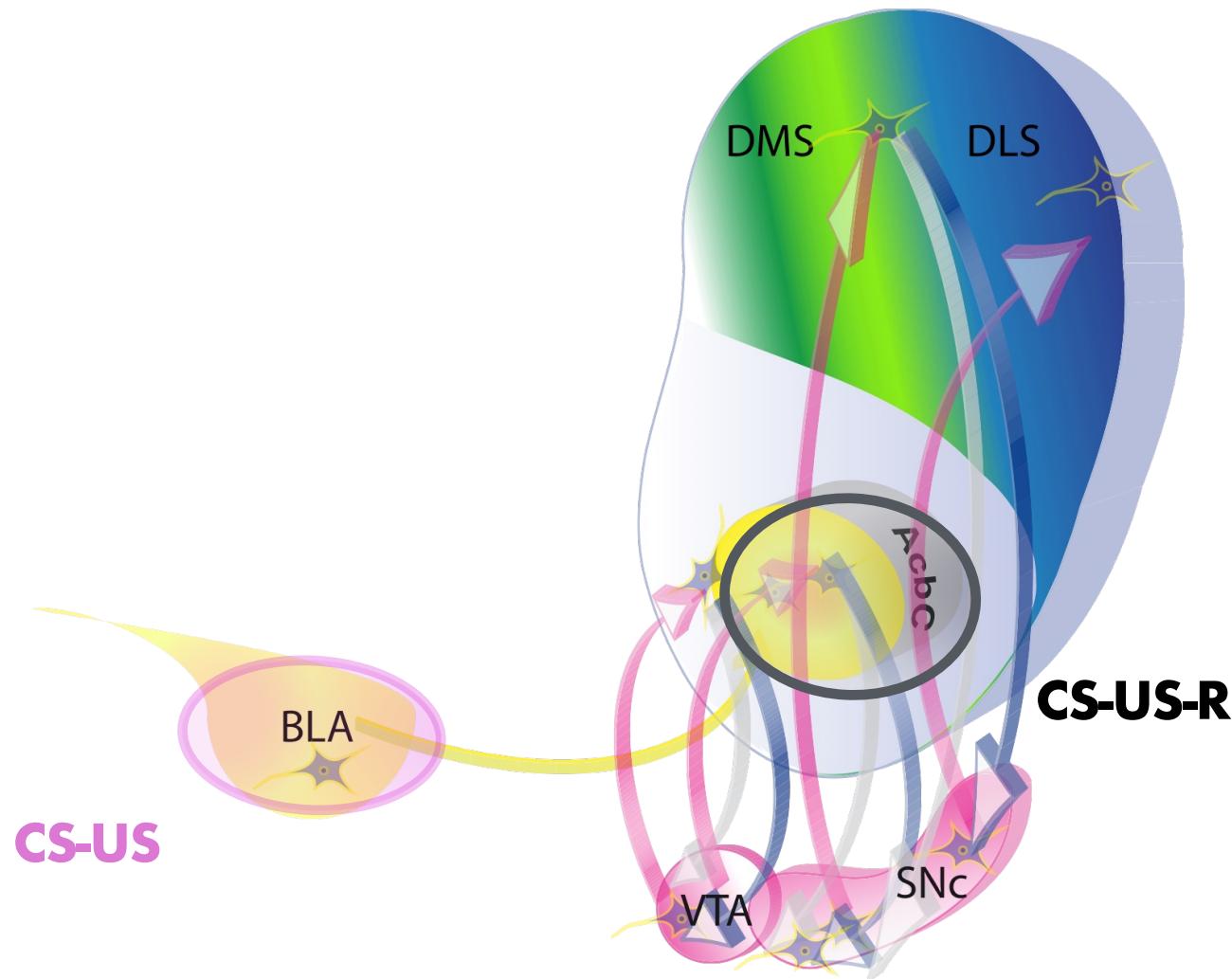
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Circuit mapping: DREADDs

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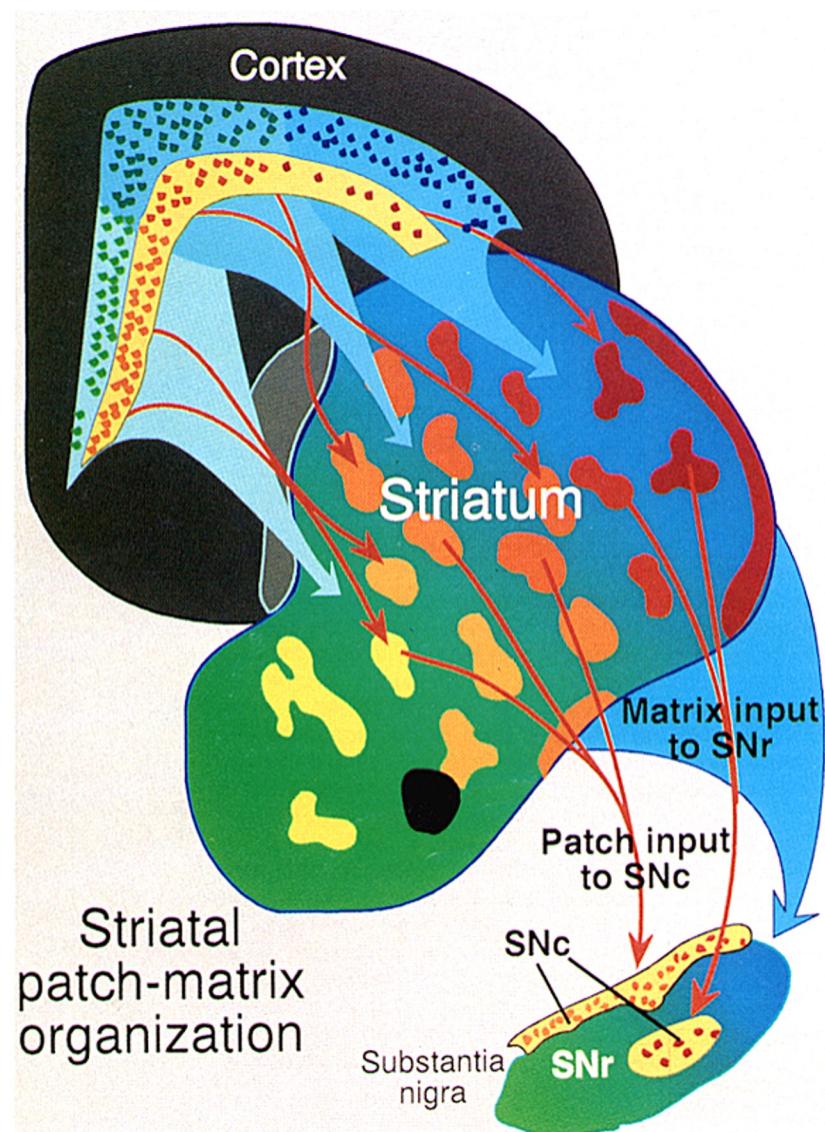


Incentive motivational processes depend upon the ‘limbic’ corticostriatal circuitry



*The dorsal striatum, motor control,
actions and habits*

The striatum is not homogenous; rather it is divided into patch and matrix compartments



The dorsal striatum can be subdivided on the basis of neurochemical markers into:

Patch (striosome) compartments

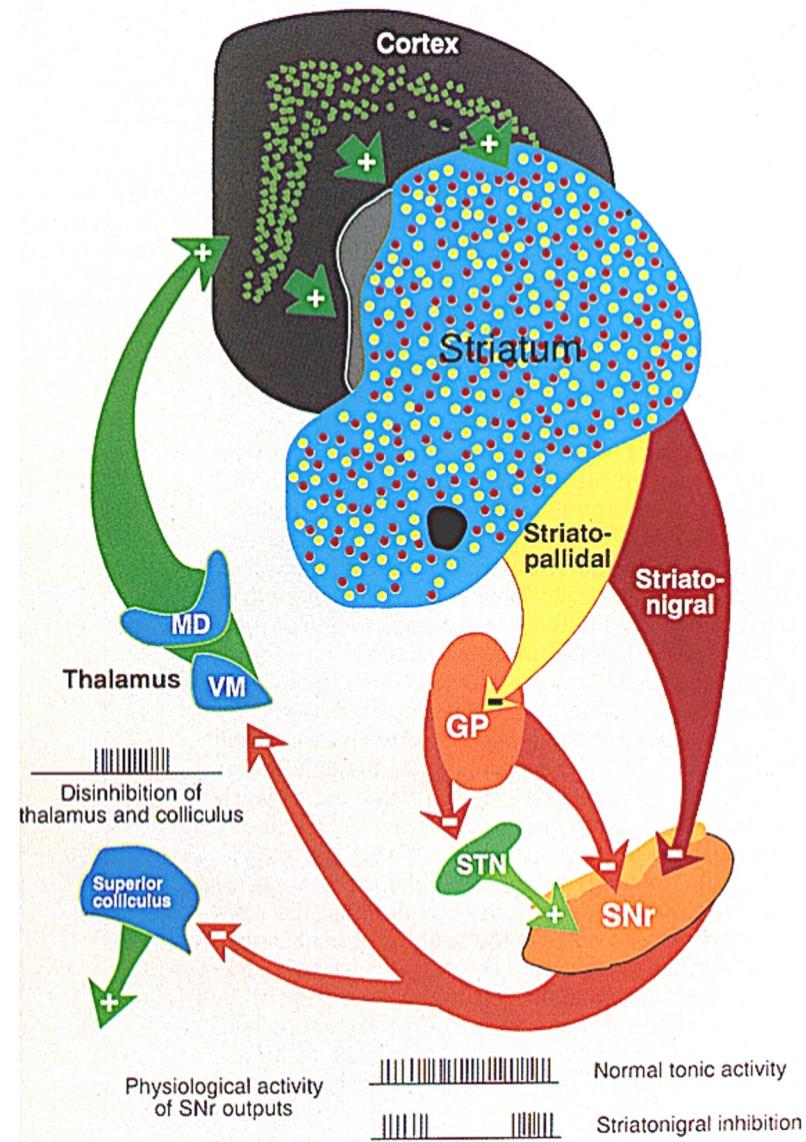
Rich in μ opiate receptors and neuropeptides
Projects to substantia nigra pars compacta

Matrix compartments

Rich in acetylcholinesterase, somatostatin and calbindin
Projects to the substantia nigra pars reticulata/GPi

(Note that the patches of the ventral striatum project to the cholinergic nucleus basalis)

The outflow of the dorsal striatum is divided into ‘direct’ and ‘indirect’ pathways



The direct pathway disinhibits the thalamus (i.e. facilitates movement):

Cortex → Striatum → GP_i/SNpr → Thalamus

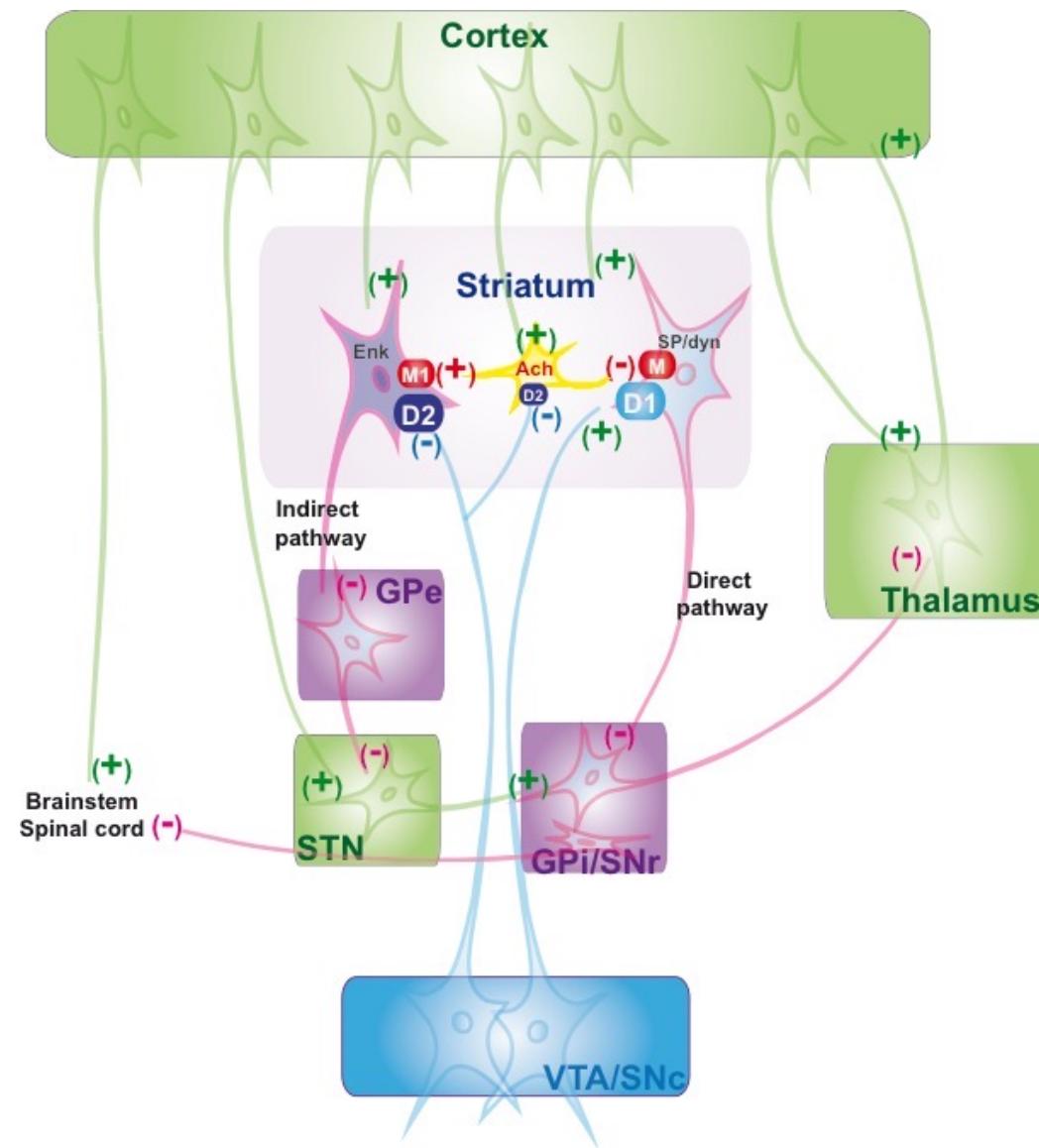
The indirect pathway disinhibits the subthalamic nucleus (i.e. inhibits movement):

Cortex → Striatum → GP_e → STN → GP_i/SNpr → Thalamus

The balance of activity between the direct and indirect pathways is determined by neuromodulators (particularly dopamine).

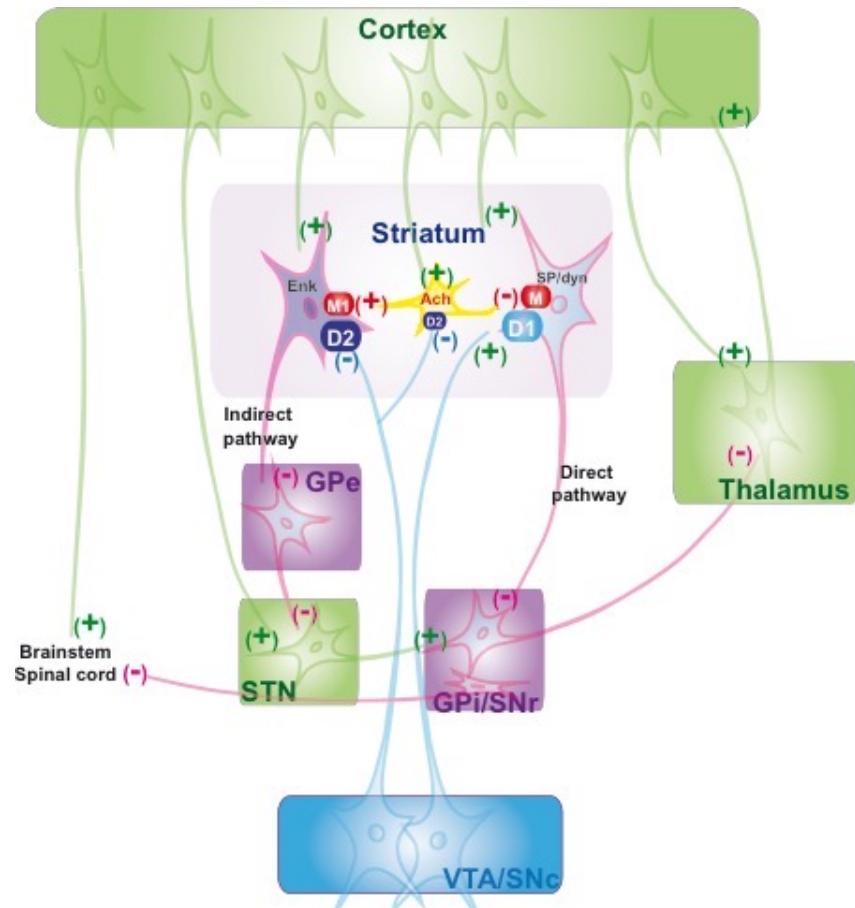
The role of dopamine in striatal function

The outflow of the dorsal striatum is divided into ‘direct’ and ‘indirect’ pathways modulated by dopamine

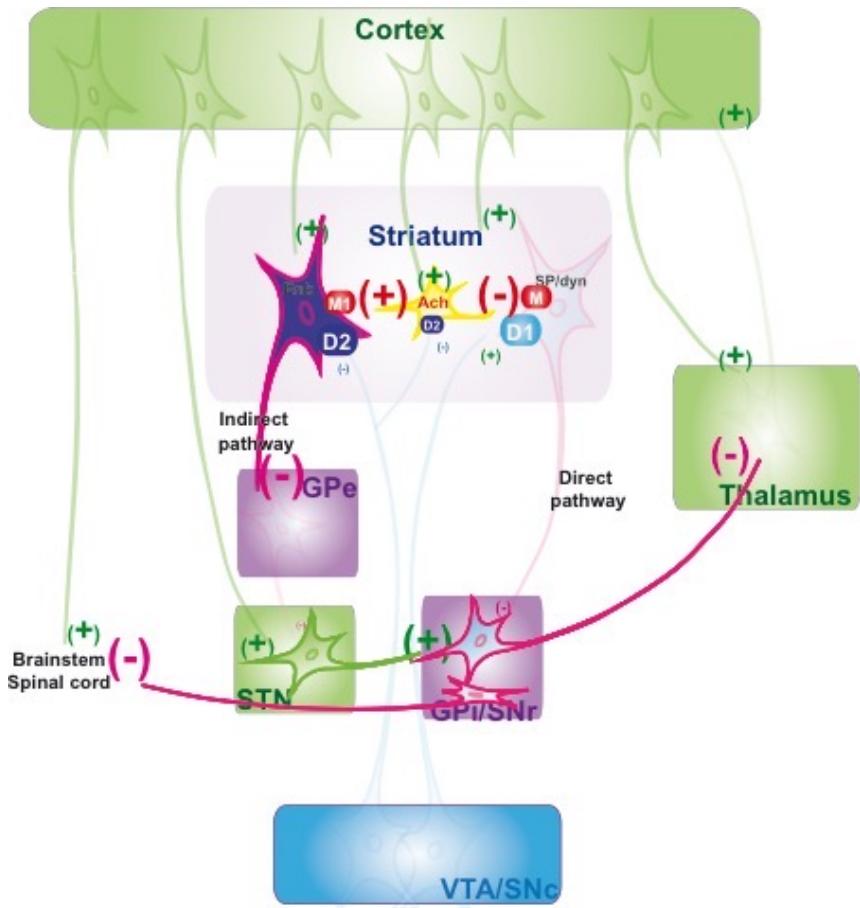


Altered activity of the ‘motor’ loop in Parkinson’s Disease

Control



Parkinson's Disease



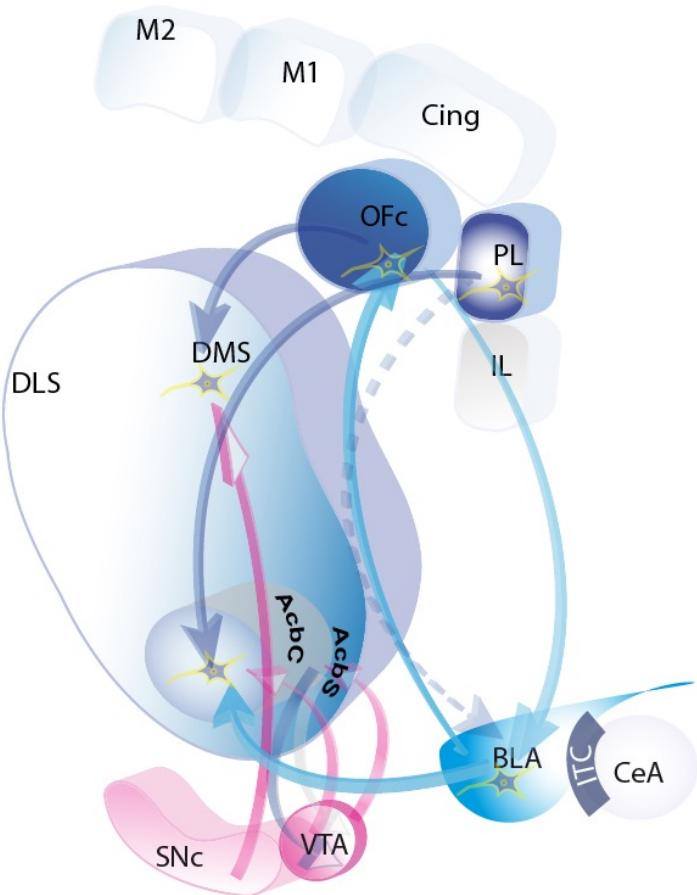
Degeneration of the substantia nigra → loss of dopamine innervation to the dorsal striatum:

- Reduced excitation of the direct pathway through D₁Rs
- Reduced inhibition of the indirect pathway through D₂Rs

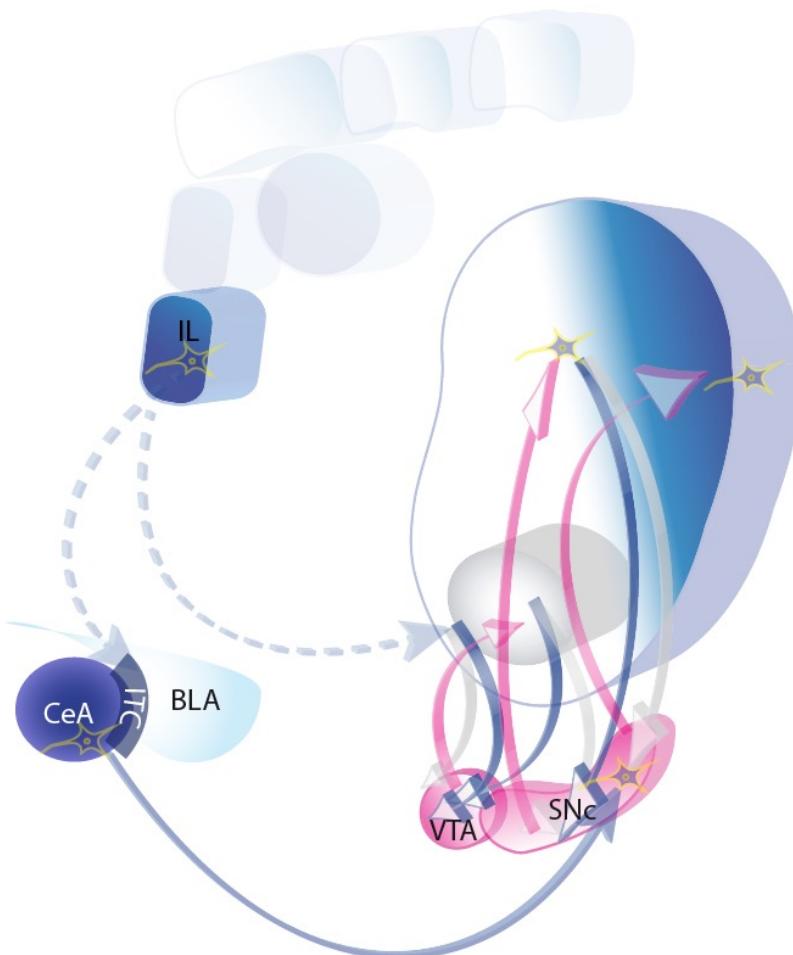
Overall, there is a reduction in the capacity to initiate movement.

Motor function of the striatum: DMS vs DLS

Goal-directed → DMS



Habitual → DLS



Motor function of the striatum: DMS vs DLS

Instrumental performance = $f(\text{representation of the motivational value of the outcome}) \rightarrow$
Sensitivity to devaluation \rightarrow Goal-directed (Action-Outcome)

Instrumental performance **independent of** representation of the motivational value of the outcome \rightarrow insensitivity to devaluation \rightarrow habitual (stimulus-response)

B Drug seeking under Action-Outcome control

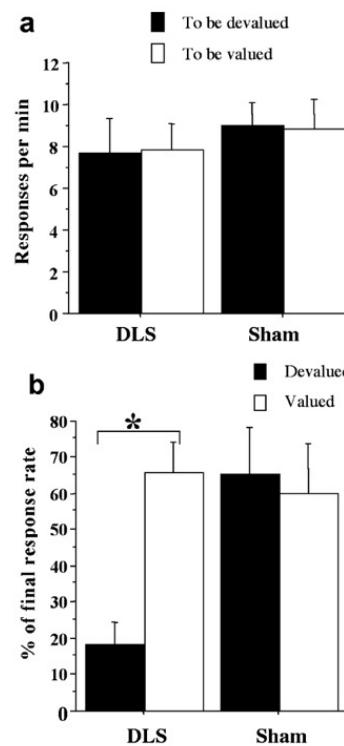
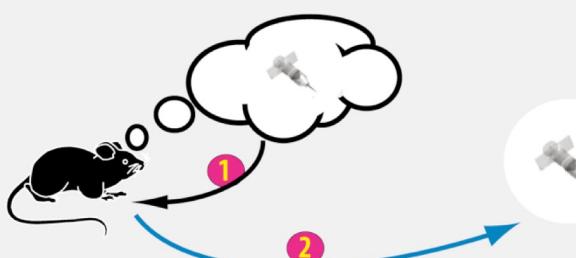


Fig. 4. Performance on a 5-min extinction test. (a) Response rates on the last day of training, on an RI-60 schedule. (b) Response rate during a 5-min extinction test after outcome devaluation as a percentage of the response rate on the last day of training. Error bars show one SEM; * $P < 0.05$; DLS, dorsolateral striatal lesioned group; Sham, sham operated controls.

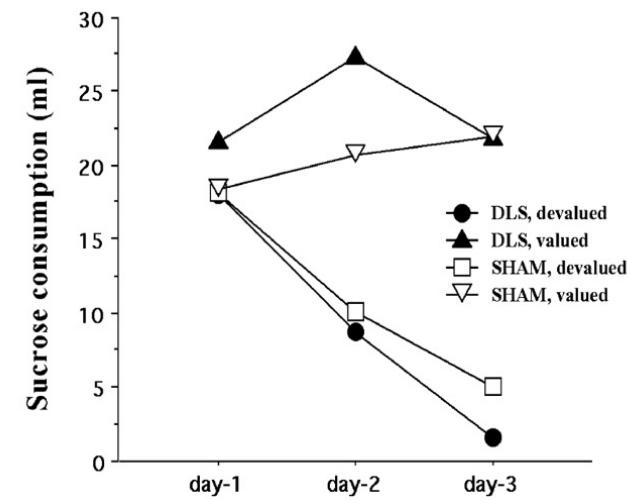
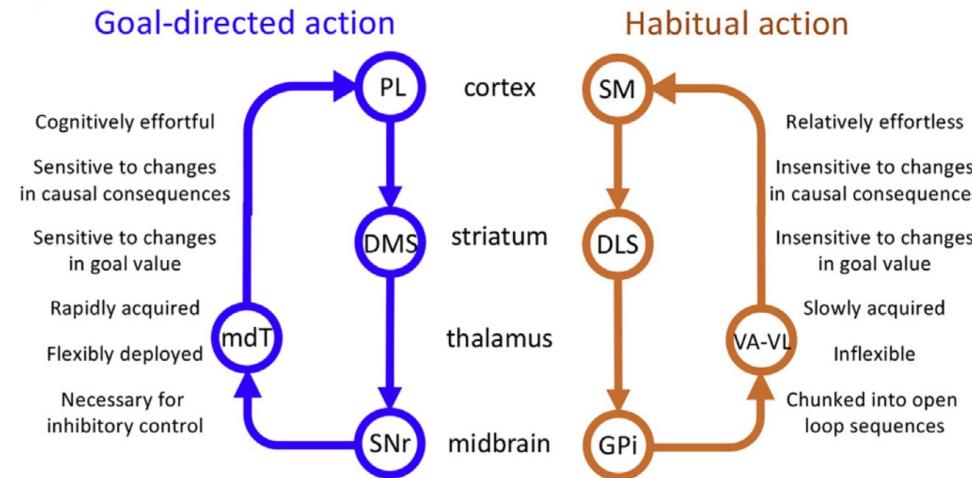


Fig. 3. Sucrose consumption over 3 days of taste aversion training for rats receiving LiCl injections (devalued) and saline injections (valued). DLS, dorsolateral striatum lesioned group; SHAM, sham operated controls.

Motor function of the striatum: DMS vs DLS



Goal-directed → DMS

Lesions/inactivation of the DMS → habitual control

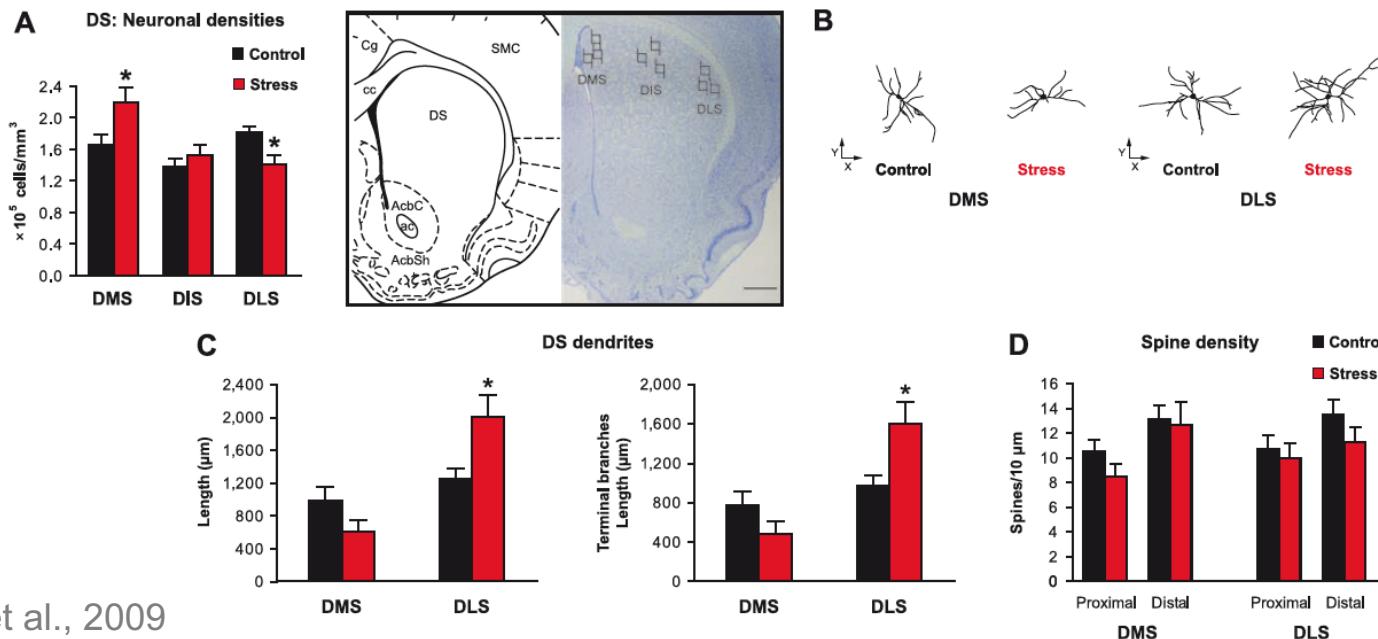
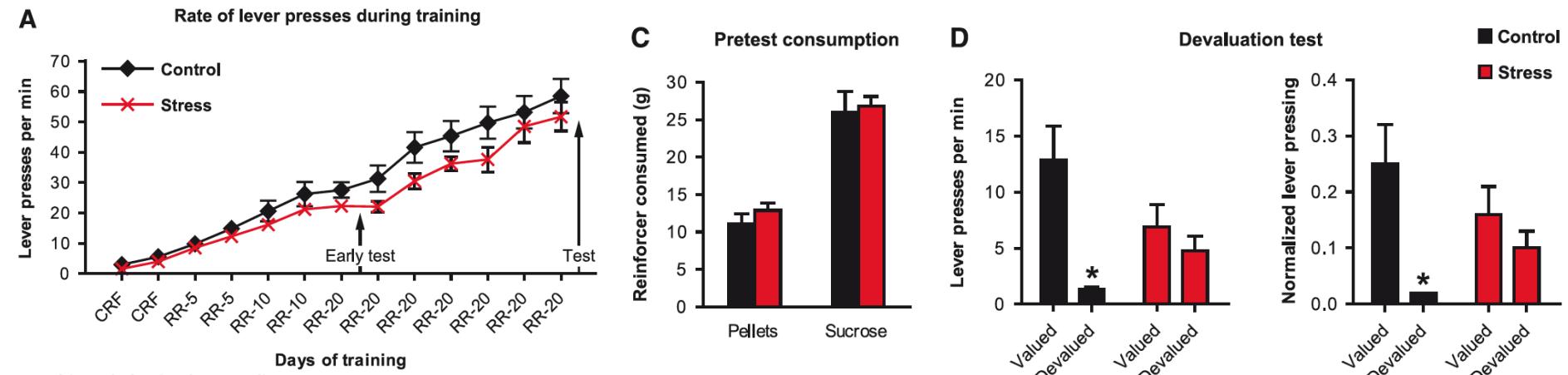
Lesions/inactivation of the prelimbic cortex → habitual control

Habitual → DLS

Lesions/inactivation of the DLS → goal-directed behaviour

Lesions/inactivation of the infralimbic cortex or CeA → goal-directed behaviour

Motor function of the striatum: stress facilitates DLS-dependent habits



Dias-Ferreira et al., 2009

Conclusions

1. The striatum is an heterogenous structure involved in different, parallel 'loops'
2. Ventral vs dorsal streams → actor-critic model
3. Dorsal striatum: control over instrumental behaviour
 - direct and indirect pathways in the dorsal striatum
 - Dopamine facilitates movement
 - Parkinson's disease = loss of movement initiation
 - actions and habits, DMS and DLS

Lecture 4

Feeding, obesity & cognition

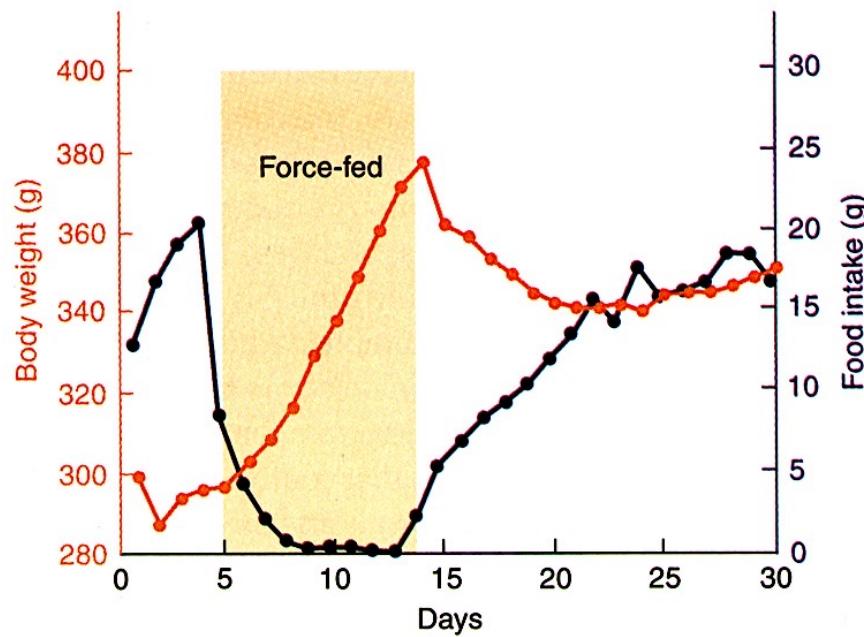
This lecture

- The neural basis of hypothalamic control of feeding
- Taste Perception and the Brainstem
- The Cephalic Phase Response
- Learning
- Social Context
- The bidirectional relationship between obesity, the hippocampus and consumption regulation
- Dieting: replacing calories

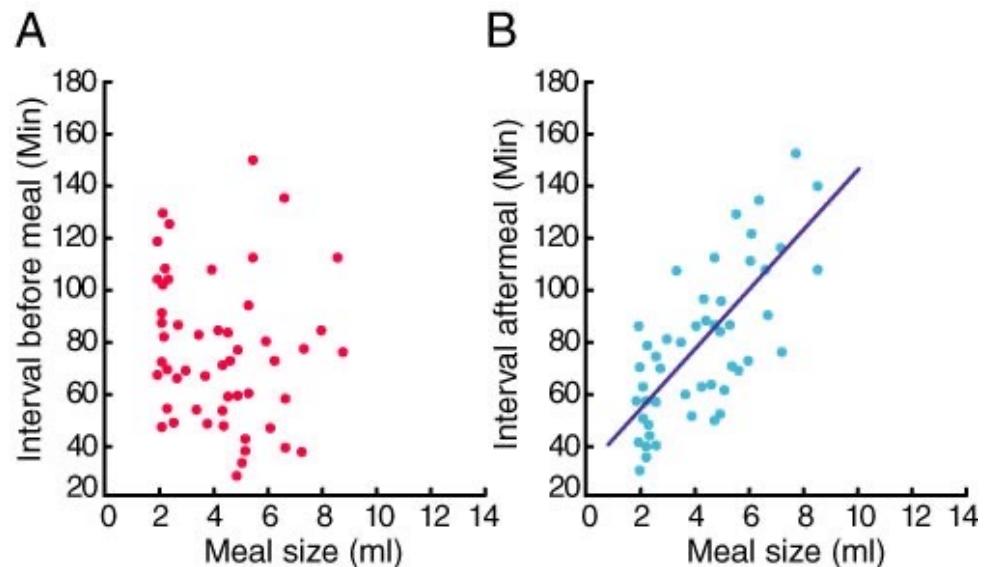
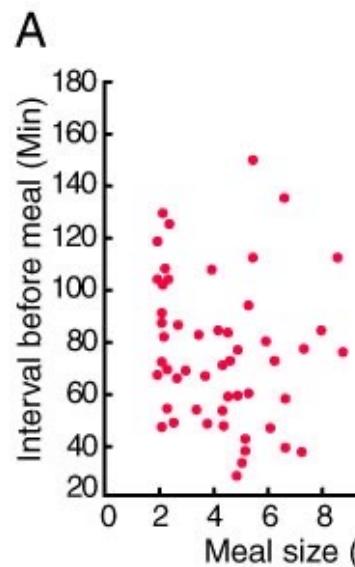
Part I

Hypothalamus, feeding and obesity

Homeostatic control of weight and feeding behaviour

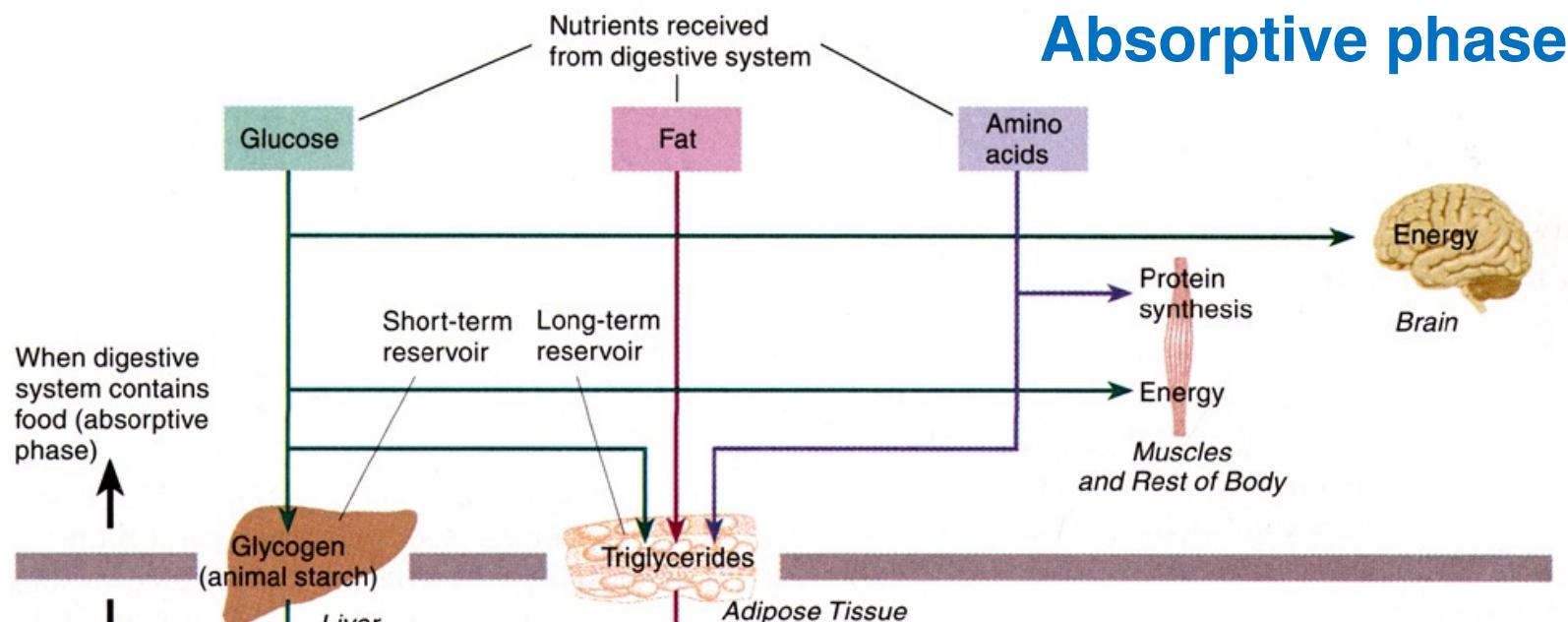


Pre-meal intervals do not predict meal sizes whereas meal sizes predict post-meal intervals



Homeostatic control of weight and feeding behaviour

Absorptive phase

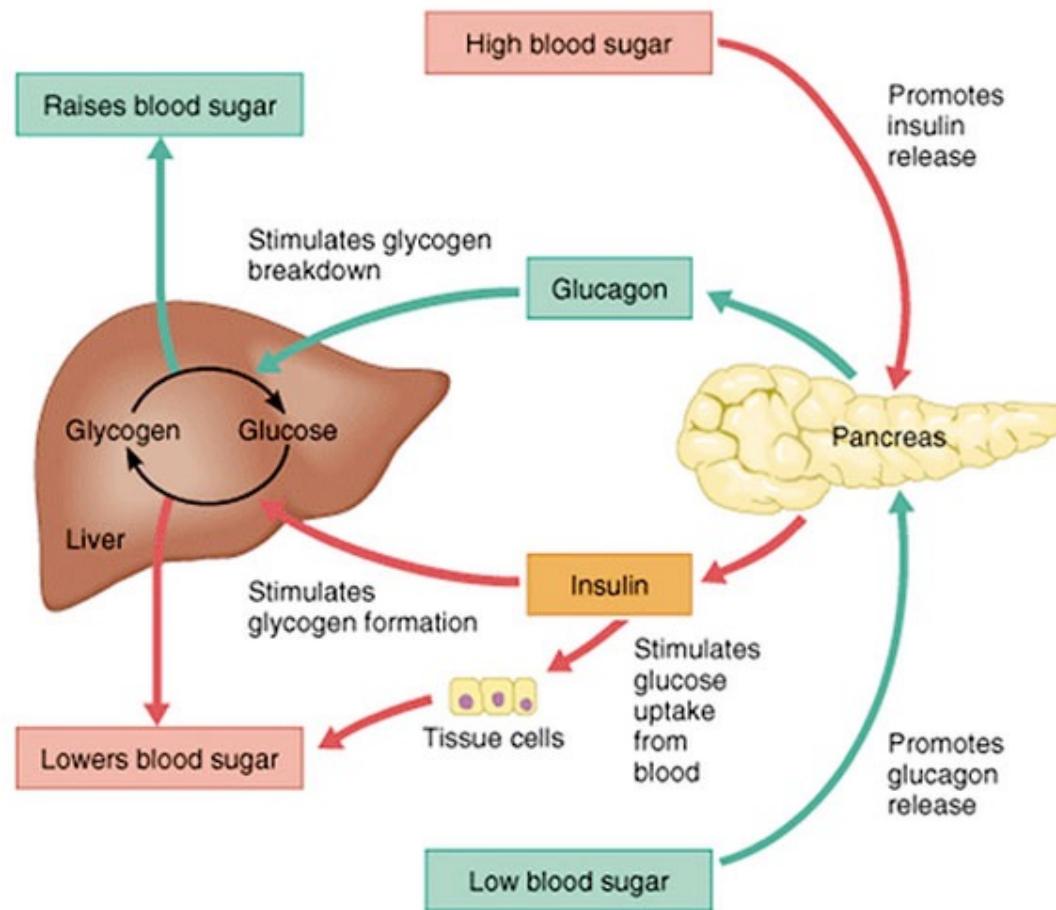


When digestive system is empty (fasting phase)

Fasting phase



Insulin/glucagon regulation of glucose



Nb. Insulin also increases glucose uptake into cells and produces a state of glucoprivation in the plasma

Hypothalamic mechanisms of hunger and satiety: initiation of a meal

Initiation of a meal: environmental and physiological stimuli can initiate eating.

Environmental stimuli

Smell, sight and especially the taste of food

Conditioned stimuli associated with food through pavlovian conditioning

Physiological factors

Low levels of blood glucose and fatty acids, i.e. animals eat in response to glucoprivation and lipoprivation

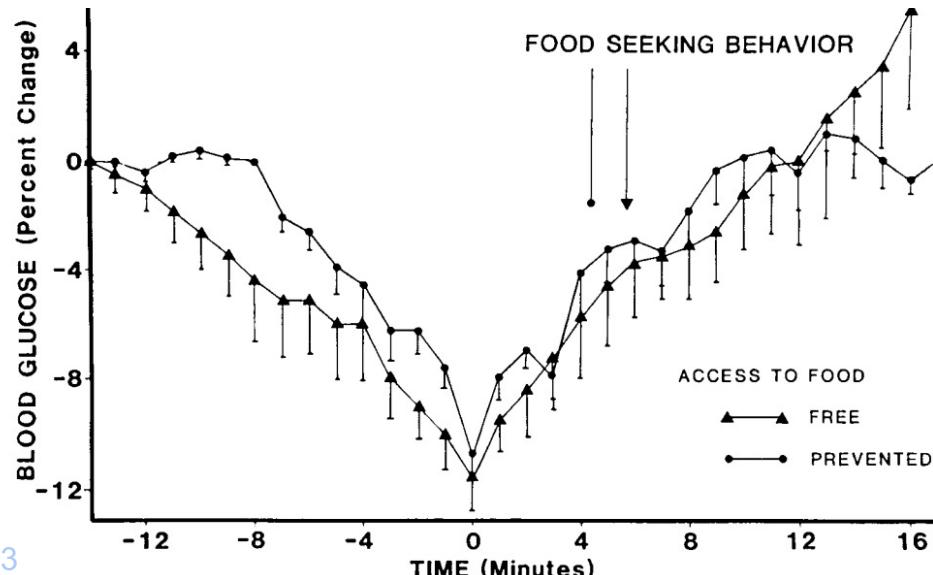
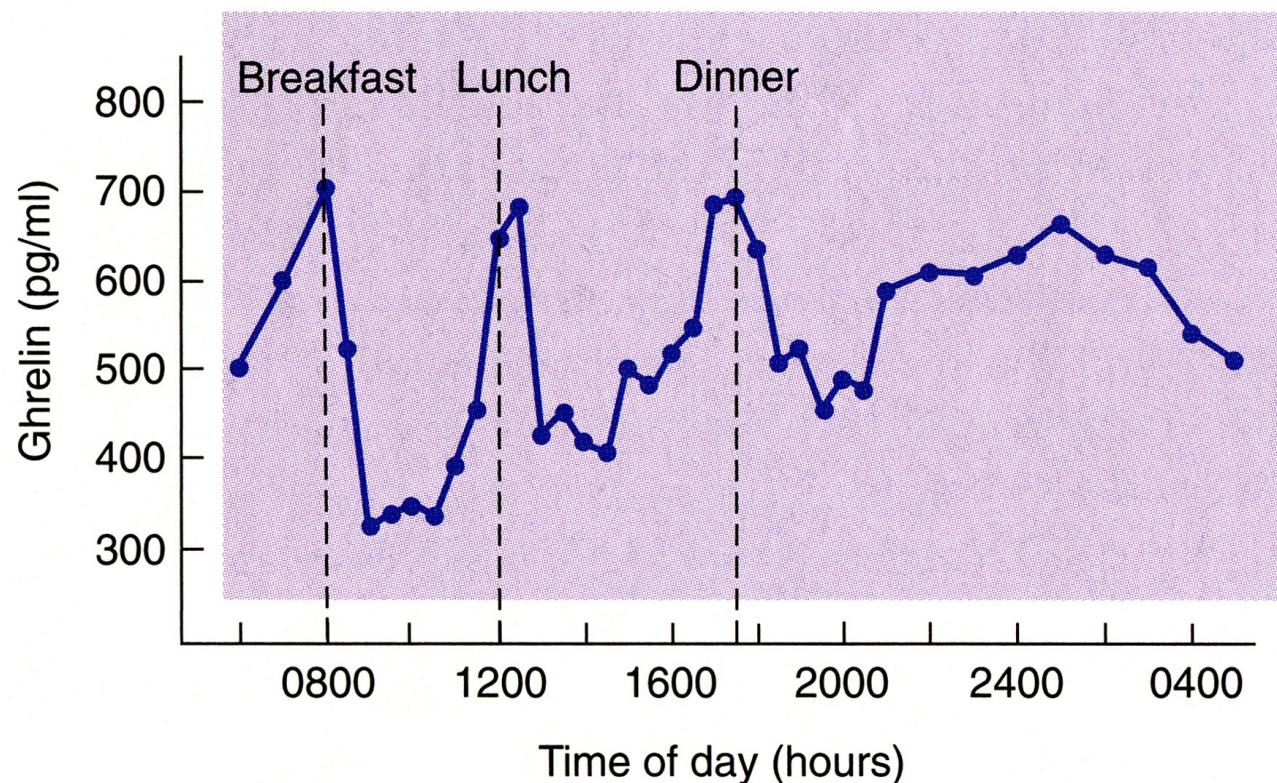


FIG. 5. Average time course of the transient decline in blood glucose when access to food was free or prevented. Blood glucose concentrations are expressed as percent change from the intermeal baseline concentrations in this figure. The minimum glucose concentration has been taken as the *time 0* reference. Data were selected each minute from the reference point and averaged in each of nine experiments. Data are means \pm SE. The onset of food-seeking behavior is indicated by the vertical arrows in free access (\blacktriangle) and prevented access (\bullet) groups. Mean baseline glucose concentrations were 104 ± 5 and 96 ± 3 mg/dl, respectively. Note the similar time course of blood glucose and onset of food-seeking behavior when food access was free and prevented. [From Campfield and Smith (18), with permission from Elsevier Science.]

Hypothalamic mechanisms of hunger and satiety: initiation of a meal

→ Ghrelin

A 24-amino acid peptide hormone produced mainly by cells lining the fundus of the stomach and epsilon cells in the pancreas. Effects on appetite mediated by actions in the hypothalamus.



Hypothalamic mechanisms of hunger and satiety: stopping a meal

Stopping a meal: satiety mechanisms – short- and long-term satiety signals.

Short-term satiety signals:

Feedback from tasting, smelling and swallowing food

Conditioned satiety

Humoral factors: e.g. **cholecystokinin (CCK)**

- ➔ a peptide hormone released by the duodenum when it receives fat-rich food
- ➔ acts on receptors in the pylorus and the information is transmitted to the brainstem via the vagus (relaying in the NTS) and from here to the hypothalamus
- ➔ produces a “post-prandial behavioural response in rats

Enterostatin

- ➔ A peptide derived from a proenzyme in the gastrointestinal tract called procolipase
- ➔ controls fat intake
- ➔ Triggers: 1) reduction of **insulin secretion**, 2) increase in sympathetic drive to **BAT** (brown adipose tissue), 3) stimulation of adrenal corticosteroid secretion.
- ➔ Initiates a sensation of fullness of stomach
- ➔ Requires CCK 1 receptors

Hypothalamic mechanisms of hunger and satiety: stopping a meal

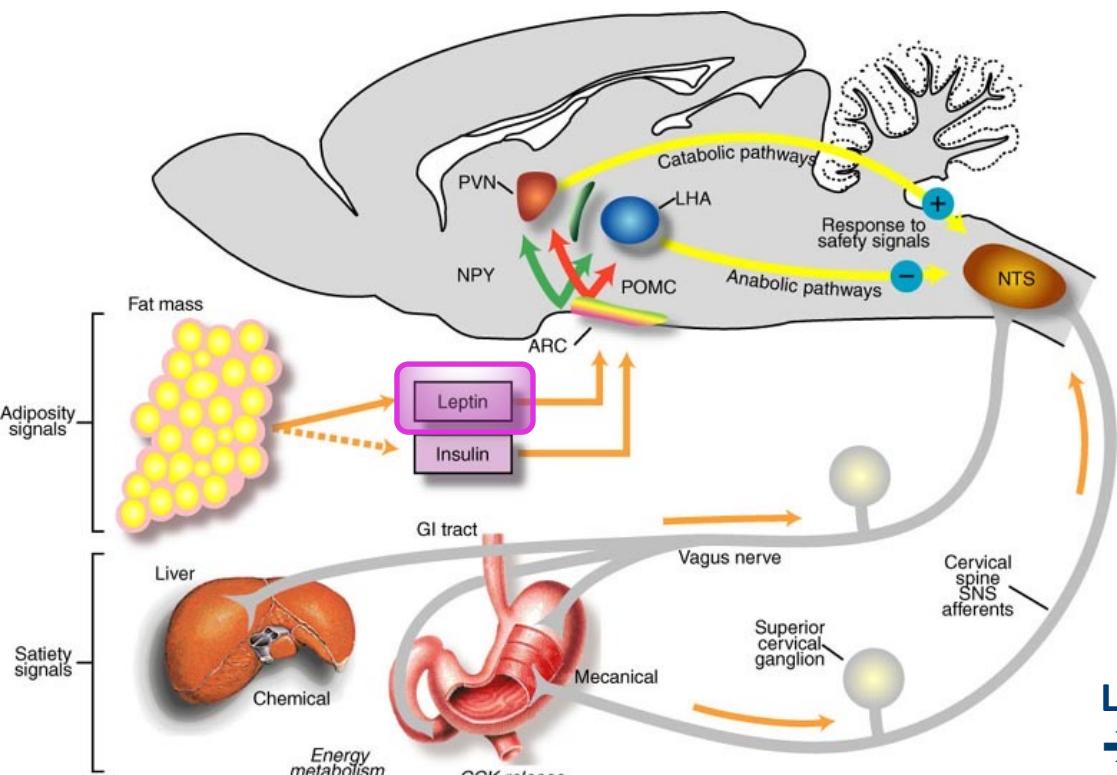
Stopping a meal: satiety mechanisms – short- and long-term satiety signals.

Long-term satiety signals - Leptin:

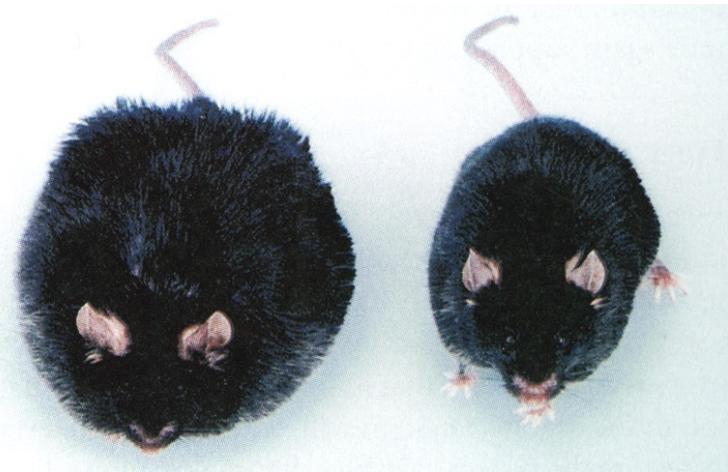
- Leptin: peptide secreted by well-nourished adipose tissue; it increases metabolic rate and decreases food intake.
- The obese (ob/ob) mouse is deficient in leptin and is obese. Leptin normally acts to decrease meal size and increase the brain's sensitivity to short-term satiety signals such as CCK.

Hypothalamic mechanisms of hunger and satiety: stopping a meal

Stopping a meal: satiety mechanisms – short- and long-term satiety signals.



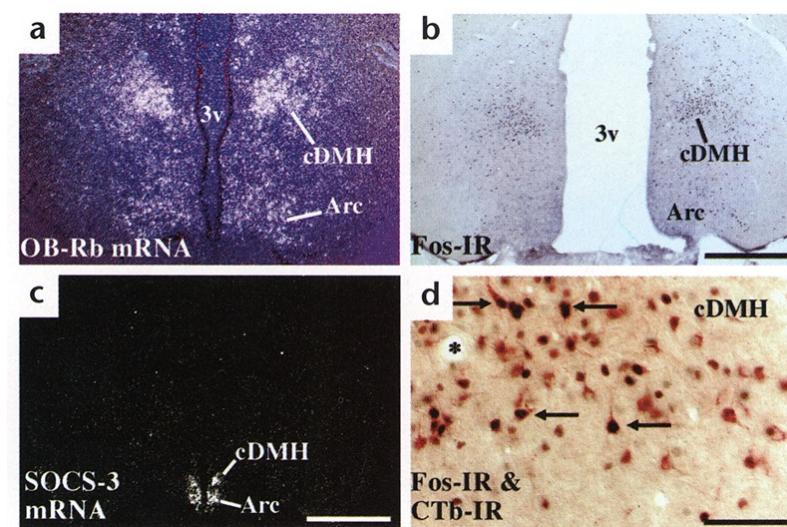
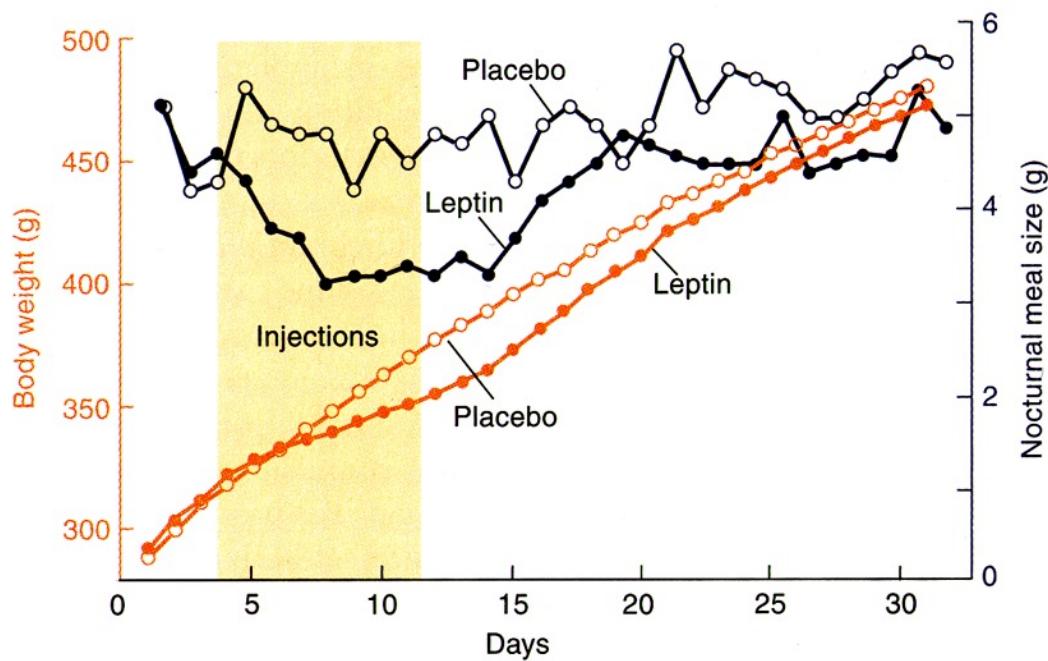
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Leptin and the obese (ob/ob) mouse
→ cannot produce leptin
→ overeat and becomes obese.
If treated with leptin, the mutants eat normally.

Hypothalamic mechanisms of hunger and satiety: stopping a meal

Effects of leptin injections on body weight and meal size and cellular activity in the hypothalamus



a. Leptin receptors in dorsomedial HT and ARC

b. Early gene expression in HT after iv leptin

d. as b but in PVH

Hypothalamic mechanisms of hunger and satiety: stopping a meal

Response to leptin in congenital leptin deficiency



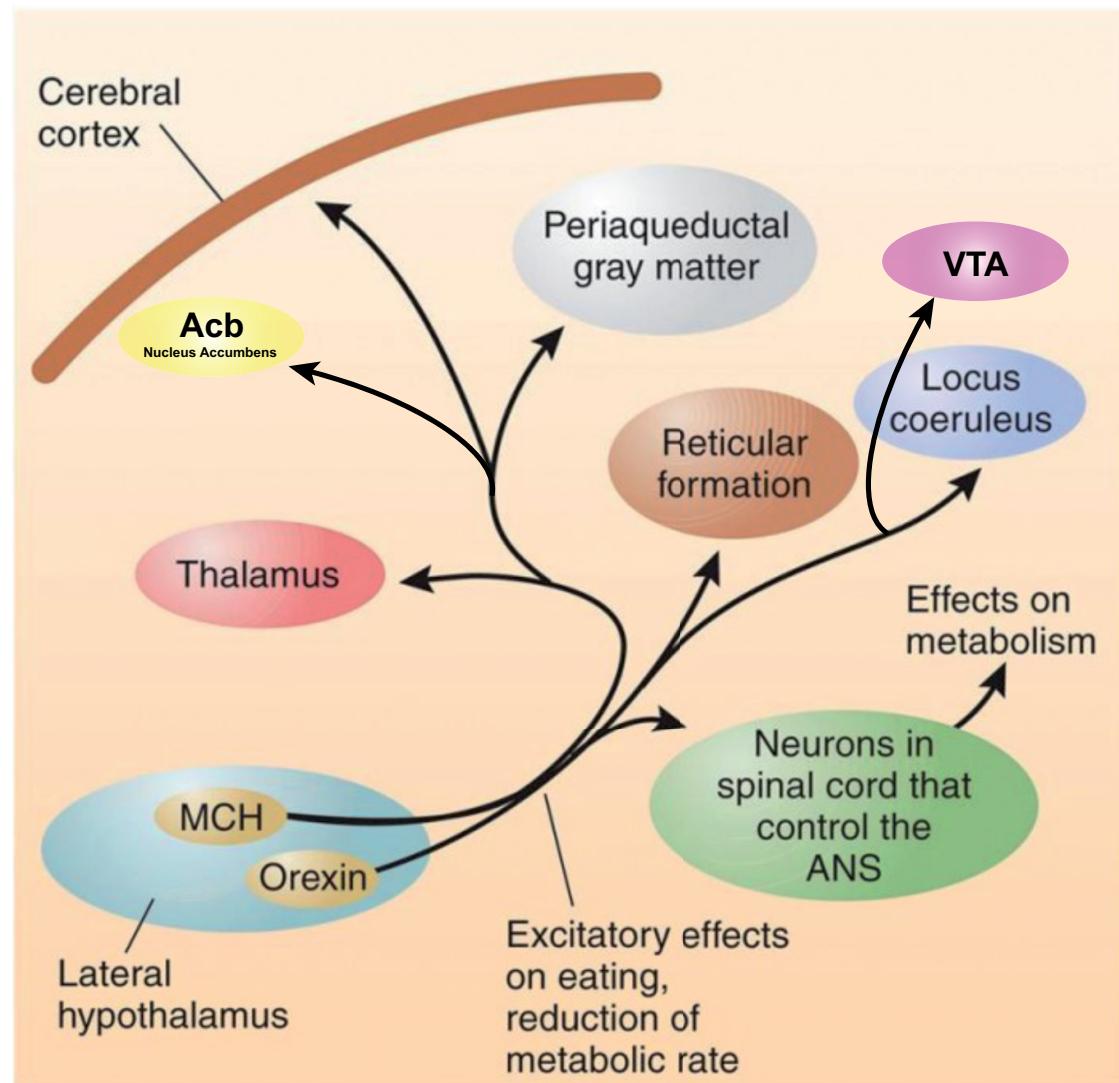
*Deciphering the hypothalamic circuits of control
of feeding*

Orexin and MCH neurons in the LH: influence on hunger and feeding

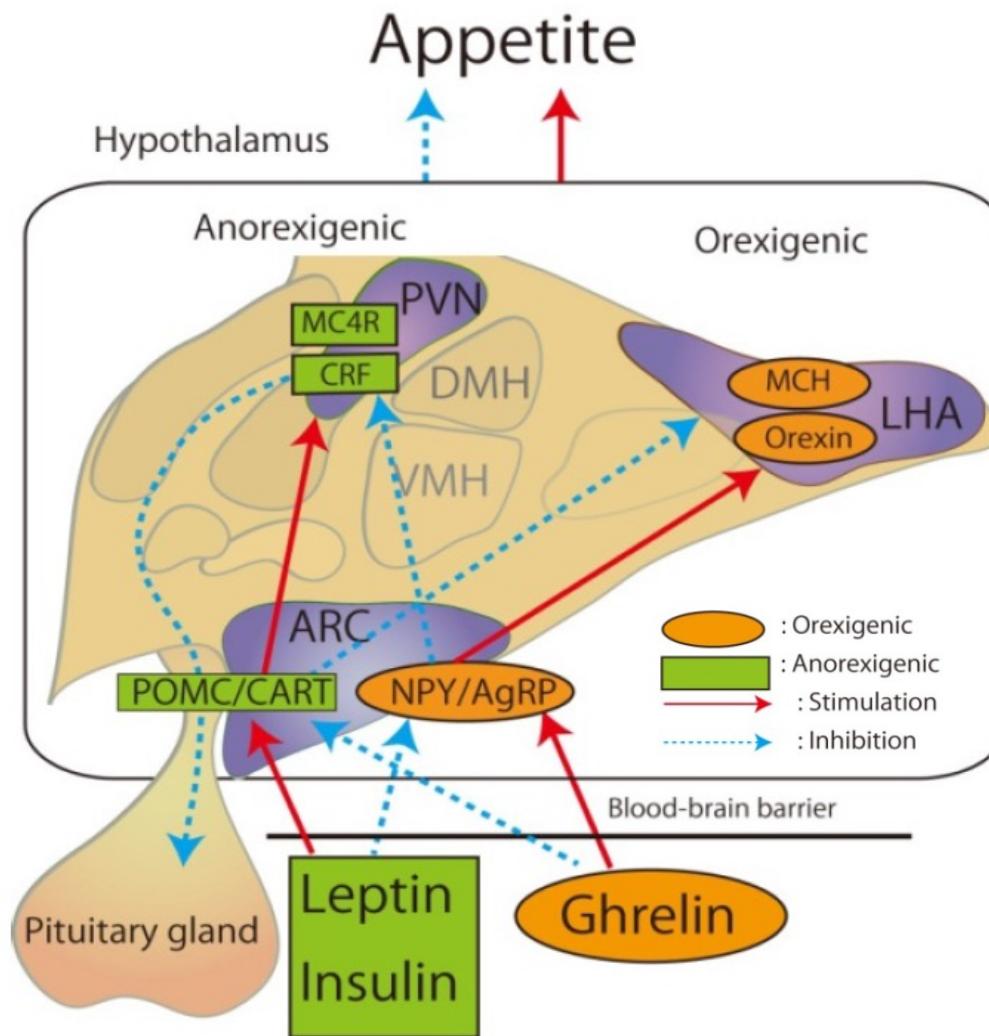
Melanin-concentrating Hormone (MCH) and orexin infusions in lateral ventricle and in extra-hypothalamic sites increase feeding.

Food deprivation increases MCH and orexin mRNA.

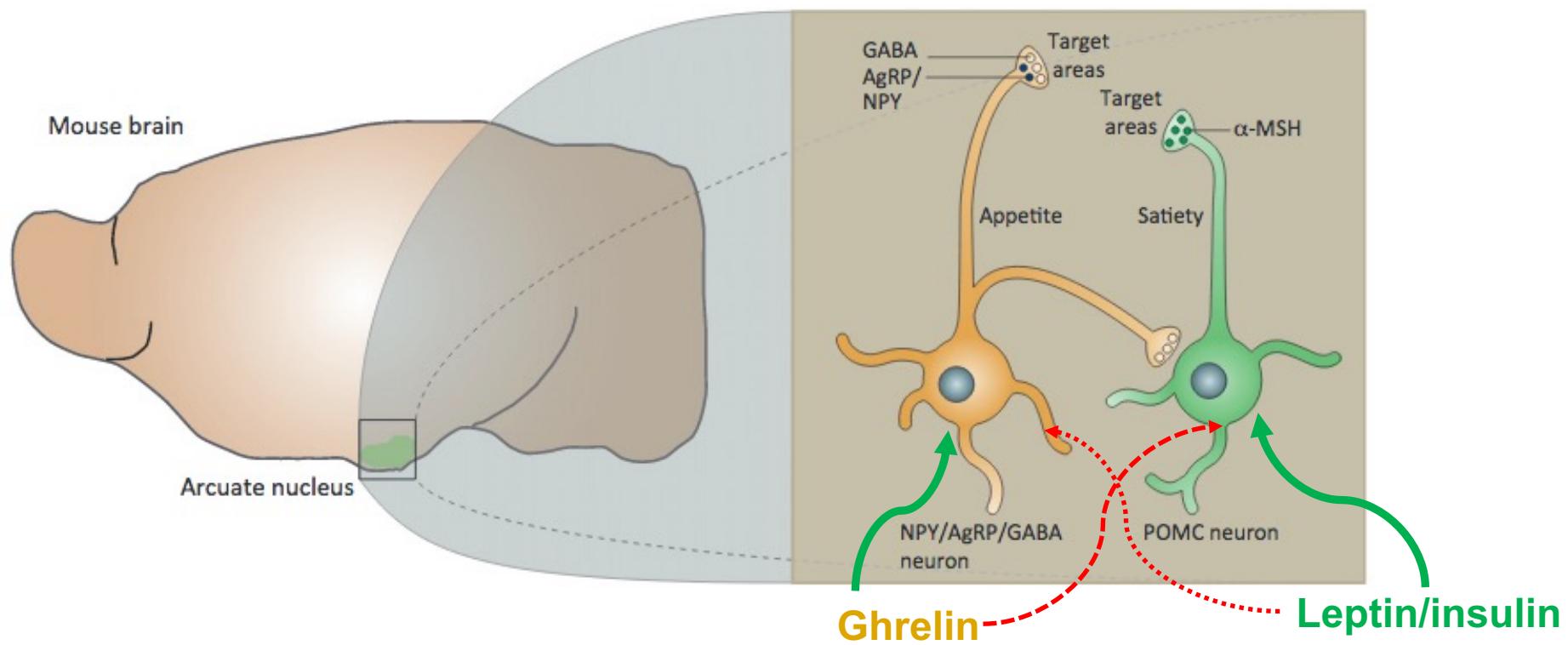
(Note connection to nucleus accumbens; it is newly discovered and functionally important)



Ghrelin, insulin and leptin: influence of LH through ARC neurons



Ghrelin, insulin and leptin: differential influence on ARC neurons



Arc projects to LH and PVN

Neuropeptide Y (**NPY**)/ Agouti-related peptide (**AgRP**)-containing neurons → **orexinergic** (hunger, promote feeding)

POMC (proopiomelanocortin)/ α -Melanocyte-Stimulating Hormone (α -MSH) containing neurons → **anorexinergic**

NPY and feeding

Arcuate NPY neurons project to:

- (i) LH orexin and MCH neurons to stimulate feeding
- (ii) PVN neurons to decrease insulin secretion and decrease metabolism

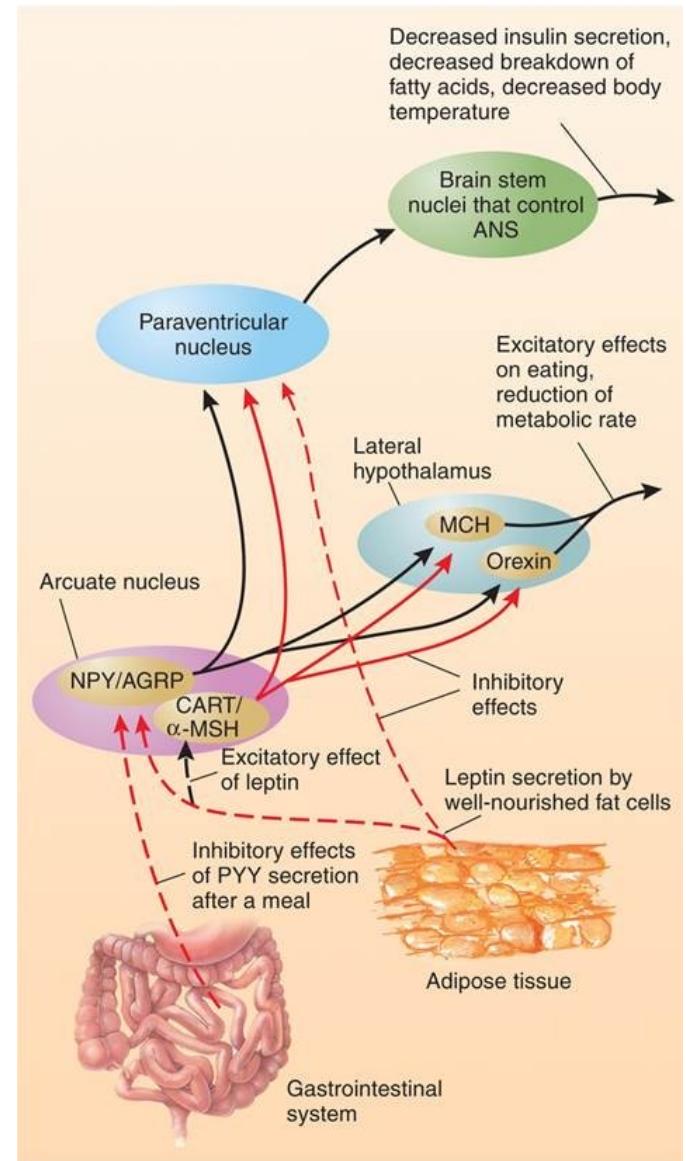
Food deprivation increases NPY

Food ingestion decreases NPY

Leptin (and insulin) decrease NPY

Ghrelin stimulates NPY neurons

NPY neurons also receive afferents from the brainstem that are sensitive to changes in nutrient (glucose) levels. These neurons also use NPY as a transmitter.



Mechanisms underlying satiety

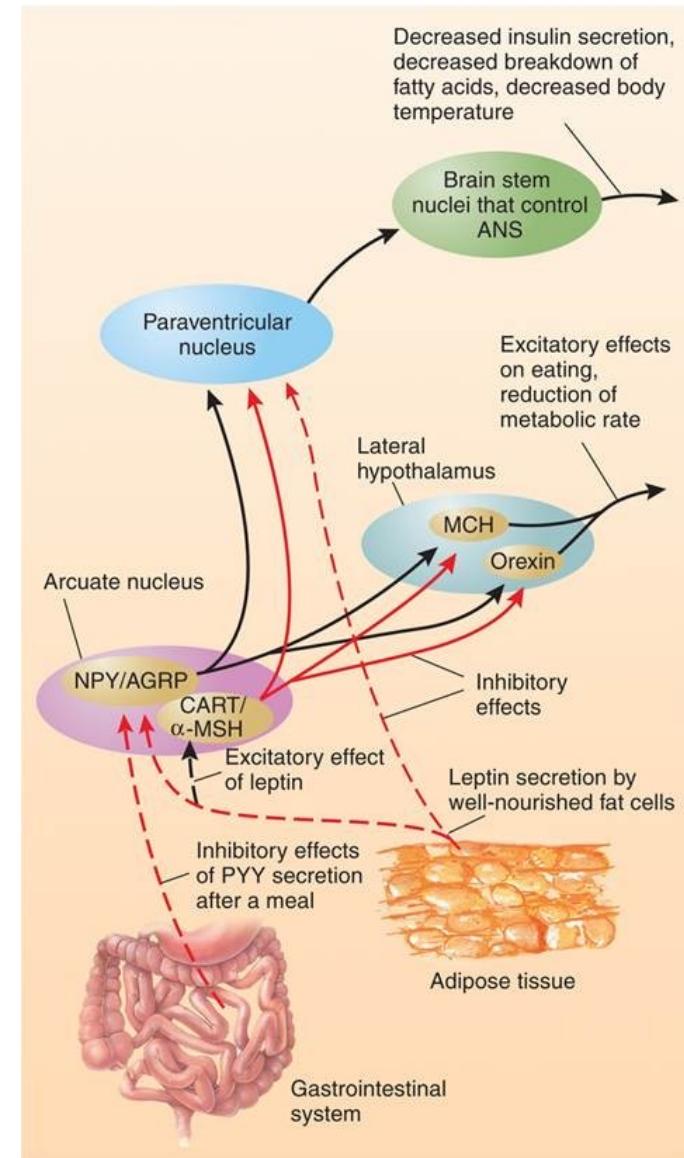
CART/ α -MSH inhibit orexin and MCH neurons in the LH, thereby reducing eating.

α -MSH acts at melanocortin-4 (**MC-4**) receptors on LH neurons. Mutations in the MC-4 gene are associated with obesity.

Leptin activates CART/ α -MSH neurons in the ARC.

Leptin binds to receptors on arcuate NPY/AGRP neurons and inhibits NPY synthesis → inhibits NPY stimulation of hunger / eating and prevents NPY influence on metabolic rate.

Leptin also directly inhibits PVN neurons and blocks their regulation of metabolic rate.



Re-evaluating the role of the hypothalamus

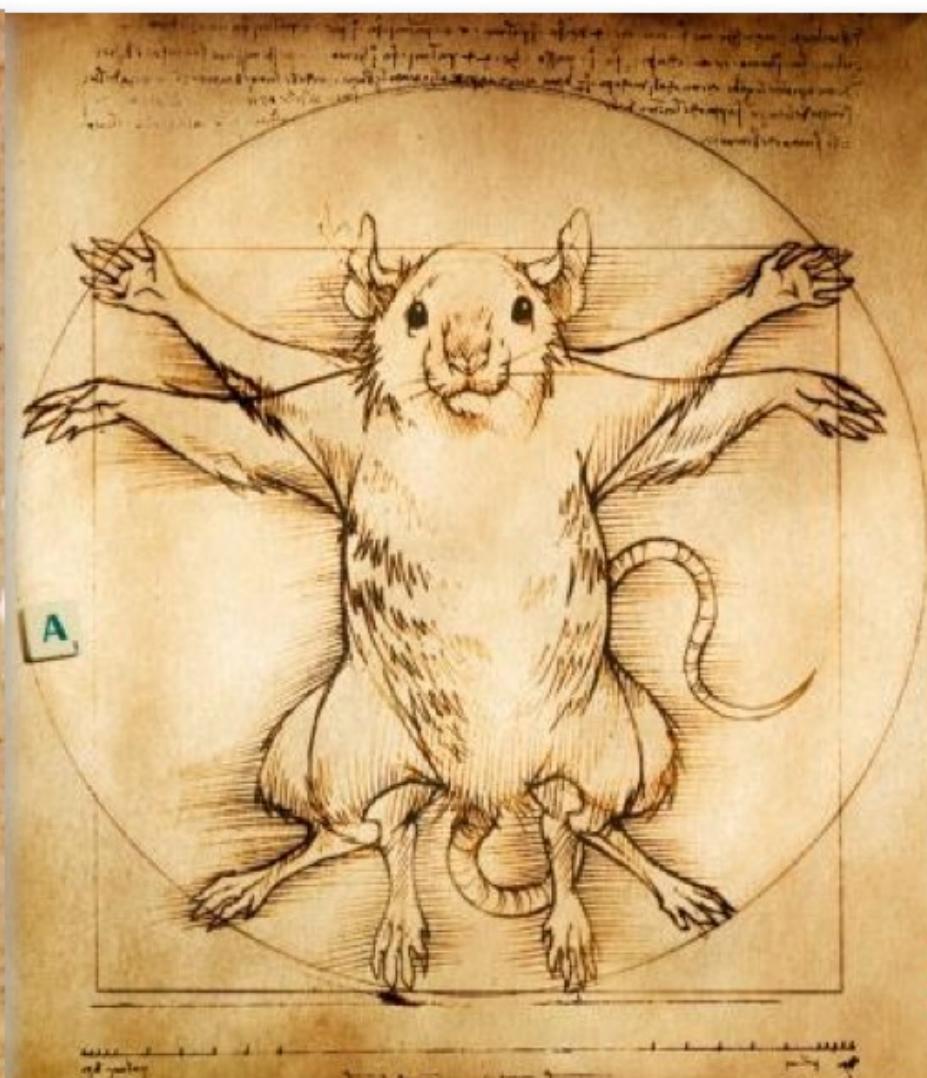
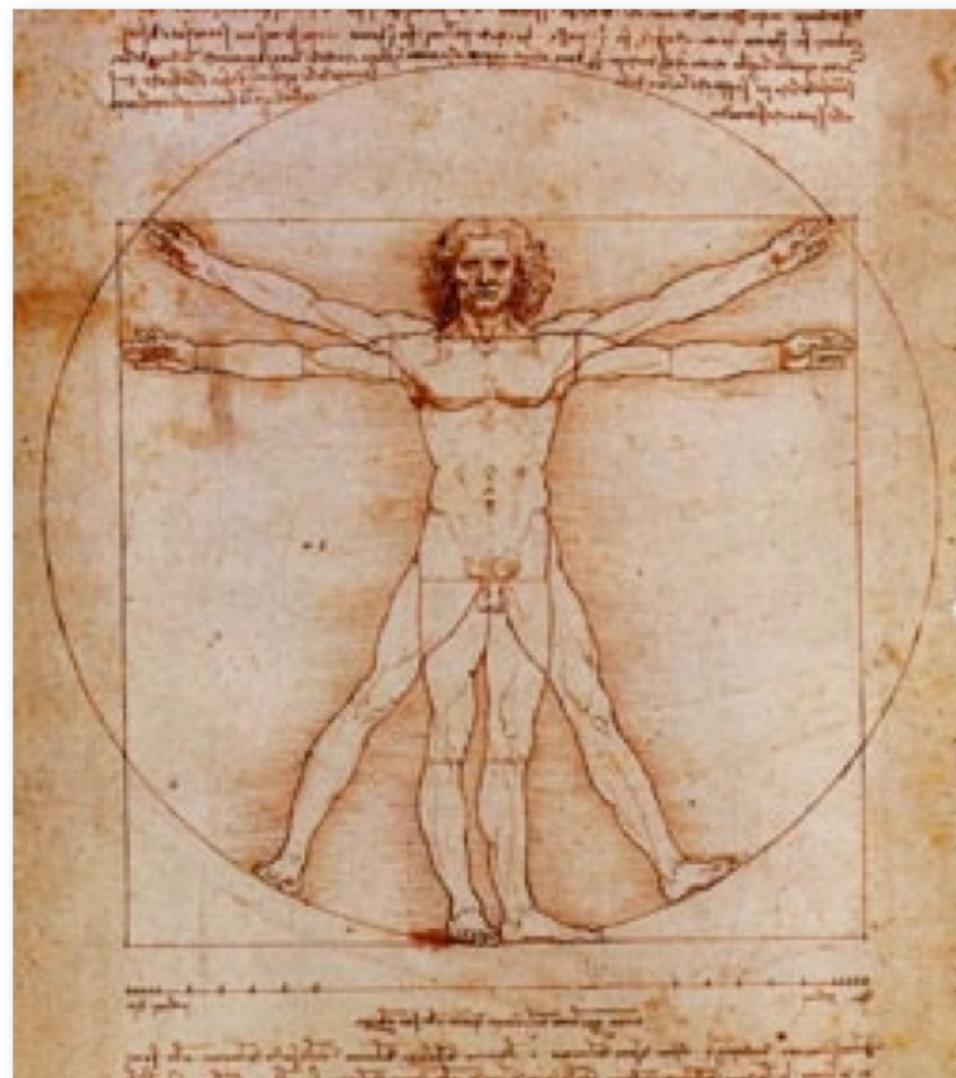
Several hypothalamic nuclei contribute to the regulation of hunger and feeding.

The lateral hypothalamic peptidergic systems regulating eating and metabolic rate are controlled by ventromedial (arcuate) peptidergic neurons.

It was these systems that were grossly affected by electrolytic lesions in earlier studies.

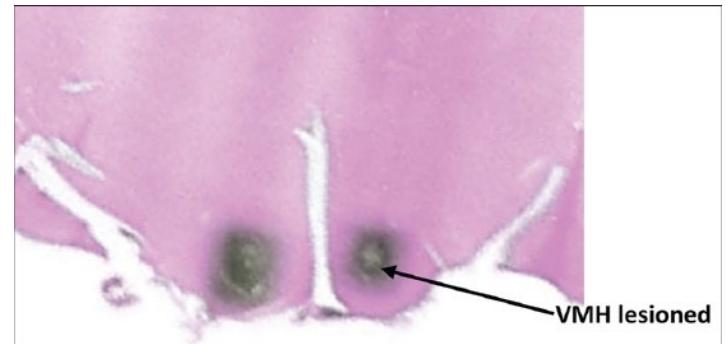
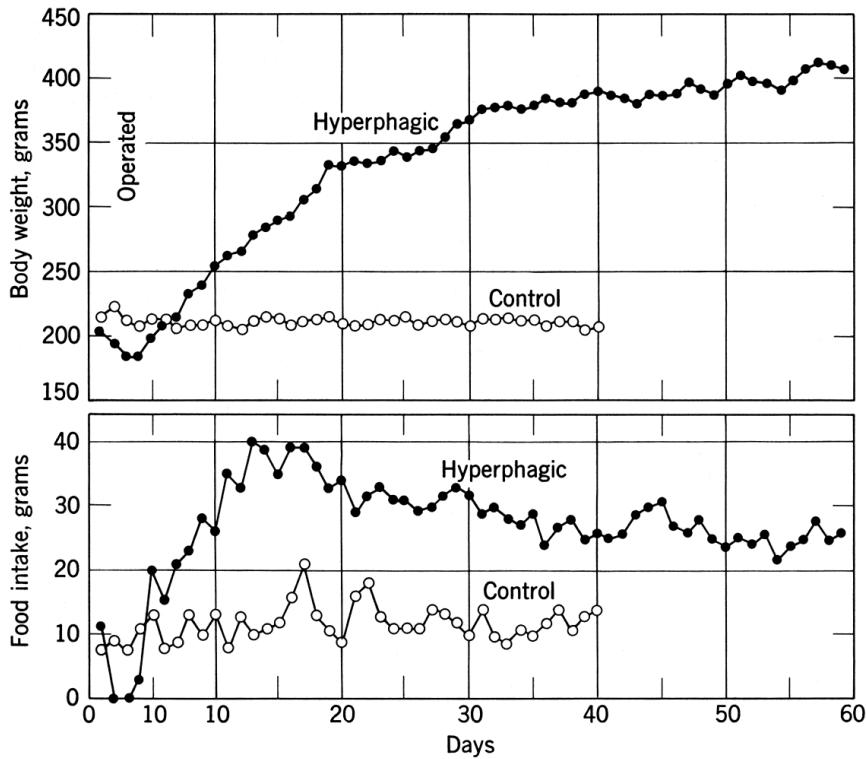
These peptidergic neural systems integrate metabolic signals (ghrelin, glucose, leptin, insulin, fatty acids, visceral afferents) and coordinate behavioural, neuroendocrine and metabolic responses in the regulation of hunger and satiety.

The hypothalamus & obesity



Models of obesity: hypothalamic obesity

VMH lesions and obesity: dynamic and static phases



Babinski & Frohlich
→ tumours in humans

Hetherington & Hanson
→ VMH lesions

Disruption of the satiety
'centre'?

Models of obesity: hypothalamic obesity

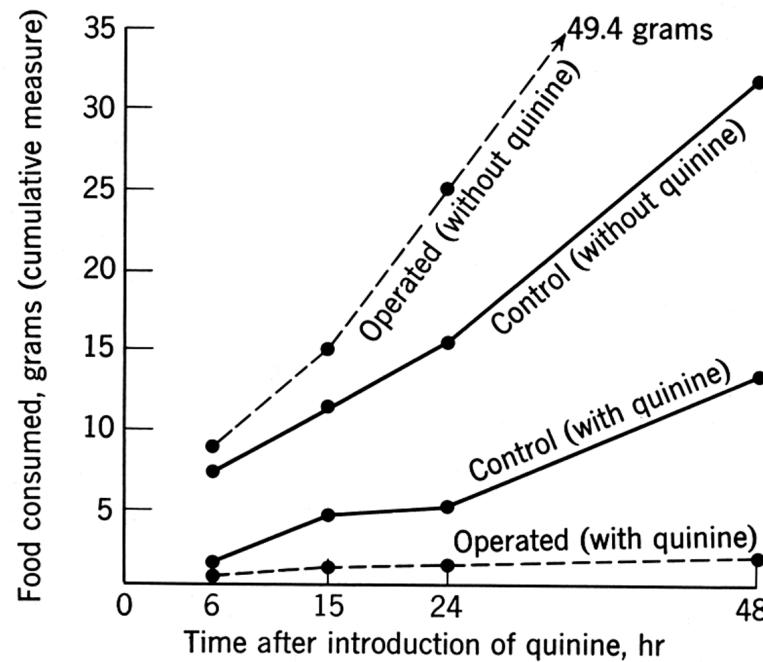
VMN (VMH) → satiety centre; inhibits LH

e.g. gastric distension increases firing in VMN neurons

But:

- VMN lesioned rats are not over-motivated (in fact, *less so!*)

Finickiness in the VMH-lesioned rat



Models of obesity: hypothalamic obesity

VMN (VMH) → satiety centre; inhibits LH

e.g. gastric distension increases firing in VMN neurons

But:

- VMN lesioned rats are not over-motivated (in fact, *less* so!)
- Glucose loads still produce short-term satiety in lesioned rats
- Obesity can be seen in the *absence* of hyperphagia
- Disconnection lesions between VMH and LH do not cause obesity (Sclafani)

Thus VMH obesity may be due to primary effects on endocrine/ autonomic system

(NOT through increased consumption or hyperphagia)!

Models of obesity: hypothalamic obesity

Endocrine and autonomic dysfunction following hypothalamic damage

Shifted sympathetic → PARASYMPATHETIC balance: e.g.

hyperinsulinaemia (not prevented by controlled feeding); blocked by vagotomy (reduces weight gain)

smaller salivary glands

reduced glucagon secretion

reduced BAT activity

impaired lipolysis

fast stomach

Autonomic control over insulin secretion and *not* hyperphagia → obesity
Enhanced *utilisation* of glucose produced by the hyperinsulinaemia → hyperphagia !

(Friedman & Stricker)

The hypothalamus and obesity

- Actual hypothalamic damage (e.g. to VMN) is unlikely to underlie obesity in general
- Hypothalamic dysfunction and abnormal regulation of endocrine system may contribute to obesity

Two models are of interest:

1. **Genetic predisposition**
(leptin)
2. **Cafeteria diet model**
(Pima Indians)



Recent findings provide strong evidence of a genetic basis for obesity.



Models of obesity: genetic models

The leptin-deficient ob/ob mice



1986

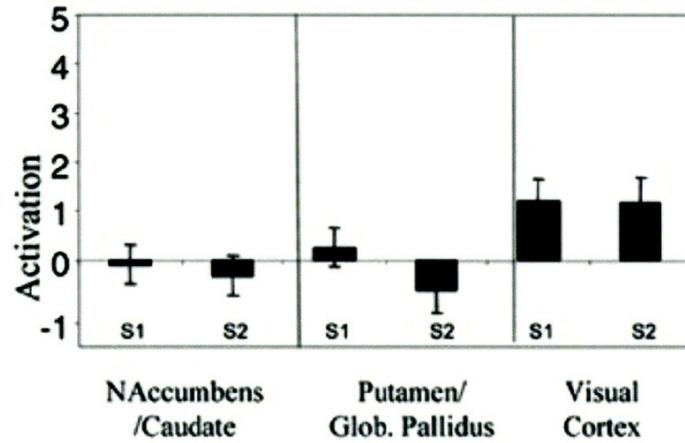
Lep^{ob}

- Hyperinsulinaemia → promotes fat synthesis *and hyperphagia*
- Reductions in BAT activity
- Deficit in circulating leptin (hormone from adipose tissue)
- Also increases in other (hypothalamic) hormones e.g. MCH implicated in *stimulating* feeding

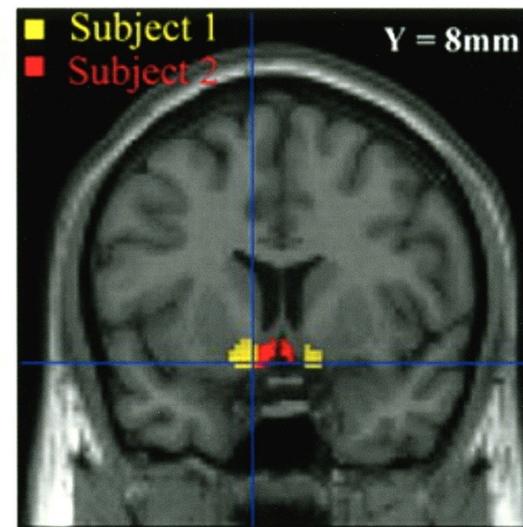
Linking homeostasis via leptin to limbic reward mechanisms: A brain imaging study in humans

A

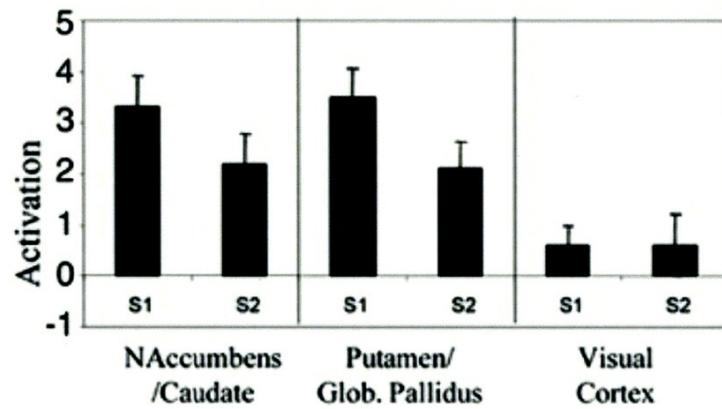
Post-leptin treatment



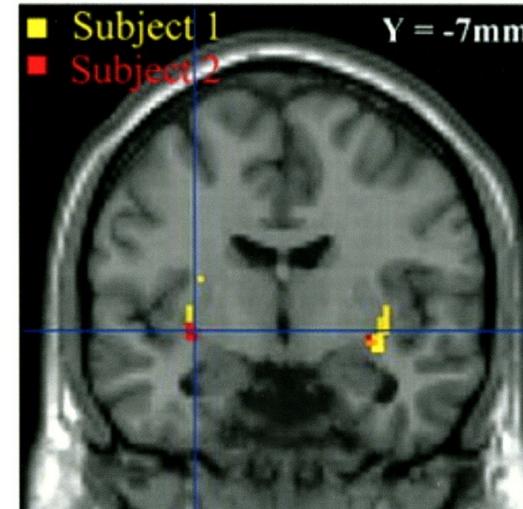
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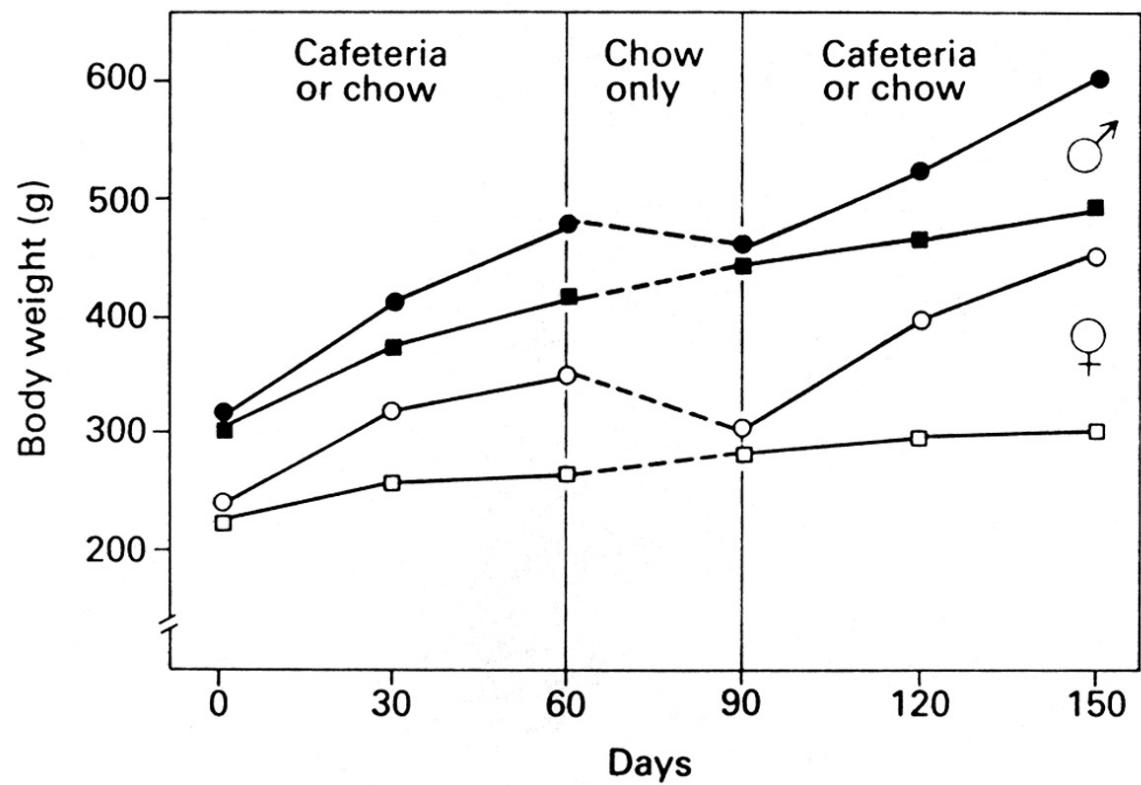
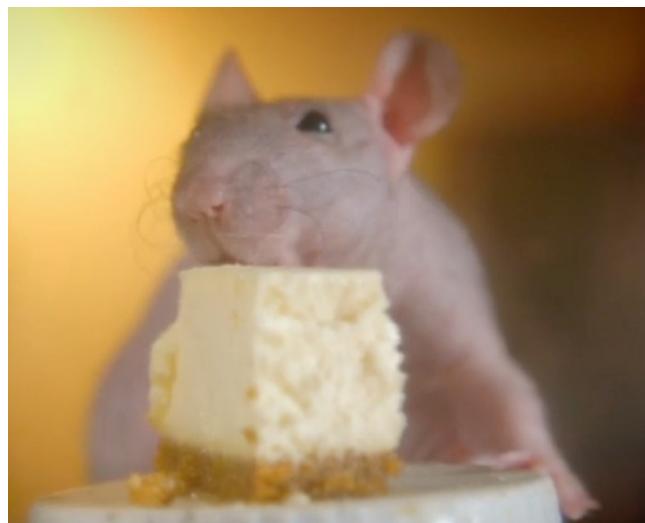
Leptin deficient state



C



Models of obesity: the cafeteria model



Sclafani and Springer

Models of obesity: the cafeteria model

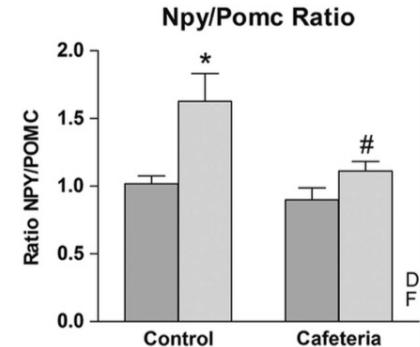
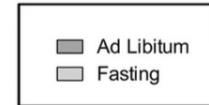
Adaptations to cafeteria obesity

- Large increase in caloric input
- Large increase in energy expenditure
- Large increase in Brown Adipose Tissue (BAT) activity (driven by the sympathetic nervous system; dietary thermogenesis)
- Enormous variation by genetic strain

Table 1. Overnight food intake, body weight, fat content, weight of different WAT and liver, and circulating glucose, leptin, insulin, NEFAs and triglycerides of 22-day-old male rats fed a control or a cafeteria diet from day 10 of life and killed under *ad libitum* feeding conditions and after 12 h fasting.

	Control diet		Cafeteria diet		Anova
	Ad libitum	Fasting	Ad libitum	Fasting	
Food intake (kcal)	23.4 ± 2.2	—	70.6 ± 2.0 ^a	—	
Body weight (g)	54.7 ± 1.5	45.6 ± 1.1 ^b	52.6 ± 1.5	48.7 ± 1.2 ^{a,b}	F
Body fat mass (g)	4.4 ± 0.3	2.2 ± 0.1 ^b	8.0 ± 0.5 ^a	6.3 ± 0.5 ^{a,b}	D, F
Body fat content (%)	8.0 ± 0.4	4.9 ± 0.2 ^b	15.2 ± 0.7 ^a	12.7 ± 0.7 ^{a,b}	DxF
Inguinal WAT (mg)	501 ± 29	375 ± 32 ^b	844 ± 81 ^a	862 ± 72 ^a	D
Mesenteric WAT (mg)	203 ± 17	164 ± 16	331 ± 31 ^a	334 ± 21 ^a	D
Retroperitoneal WAT (mg)	80 ± 7	51 ± 5 ^b	216 ± 18 ^a	184 ± 19 ^a	D, F
Epididymal WAT (mg)	97 ± 8	68 ± 10 ^b	200 ± 15 ^a	178 ± 17 ^a	D
Liver (g)	2.387 ± 0.096	1.362 ± 0.042 ^b	2.212 ± 0.084 ^a	1.546 ± 0.059 ^b	DxF
Glucose (mg dl ⁻¹)	171 ± 6	121 ± 5 ^b	156 ± 4 ^a	120 ± 5 ^b	F
Leptin (pg ml ⁻¹)	1423 ± 144	171 ± 33 ^b	4418 ± 334 ^a	739 ± 72 ^{a,b}	D, F
Insulin (μg l ⁻¹)	0.087 ± 0.021	0.072 ± 0.021	0.062 ± 0.010	0.049 ± 0.006	
Triglycerides (mg ml ⁻¹)	0.934 ± 0.170	0.467 ± 0.045 ^b	1.010 ± 0.168	0.746 ± 0.097 ^a	D
NEFAs (mM)	0.550 ± 0.086	0.992 ± 0.112 ^b	0.721 ± 0.152	0.970 ± 0.094	D

Abbreviations: NEFA, non-esterified fatty acids; WAT, white adipose tissue. ^aCafeteria versus control diet ($P < 0.05$, Student's *t*-test). ^bFasting versus *ad libitum* feeding ($P < 0.05$, Student's *t*-test). Data are mean ± s.e.m. ($n = 10\text{--}13$). Statistics: F, effect of feeding conditions (*ad libitum* feeding/fasting); D, effect of diet (control/cafeteria); DxF, interactive effect between diet and feeding conditions, ($P < 0.05$, two-way ANOVA).



Castro et al., 2015

Psychological theories of human obesity

How do they relate to metabolic accounts?

- ‘Externality’ → dependence of feeding on environmental (rather than internal) cues (Schacter & Rodin)
- Finickiness → enhanced cephalic phase responses (saliva, insulin) e.g. to a sizzling steak (Rodin)
- Stress – arousal-induced feeding, stress reduction? (Slochower)
- Eating ‘styles’ → ‘restrained’ (dieting) vs ‘unrestrained’ (Herman & Polivy): role of self-control
- Possible links to drug addiction and other forms of compulsive behaviour (Volkow and Wise, 2005)

Psychological theories of human obesity

Stress-induced feeding in the obese

EMOTIONAL LABELING AND OVEREATING

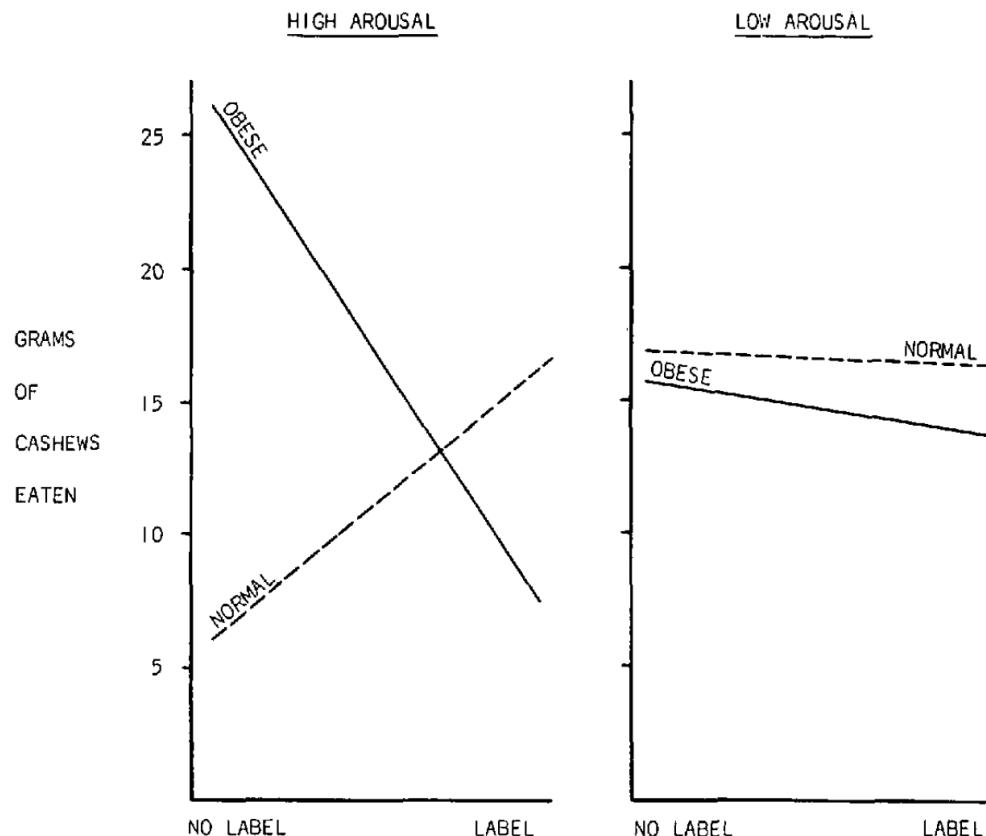
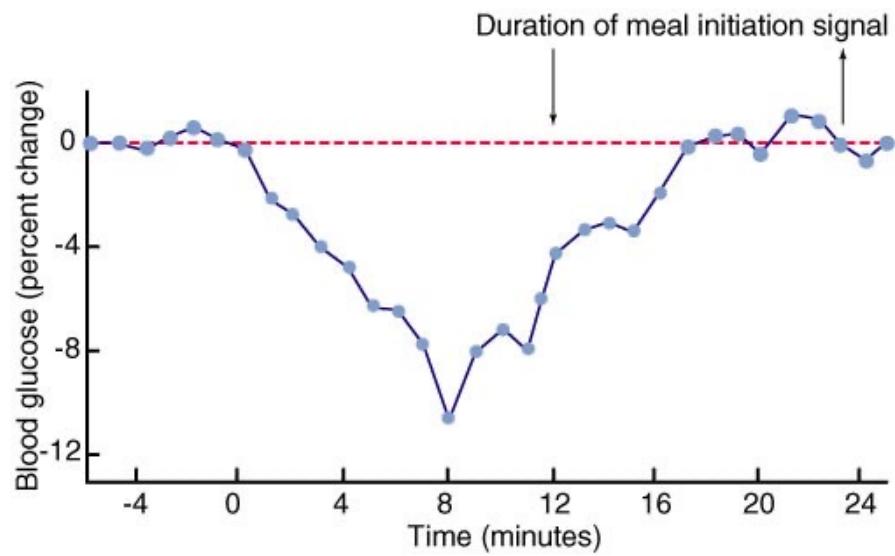
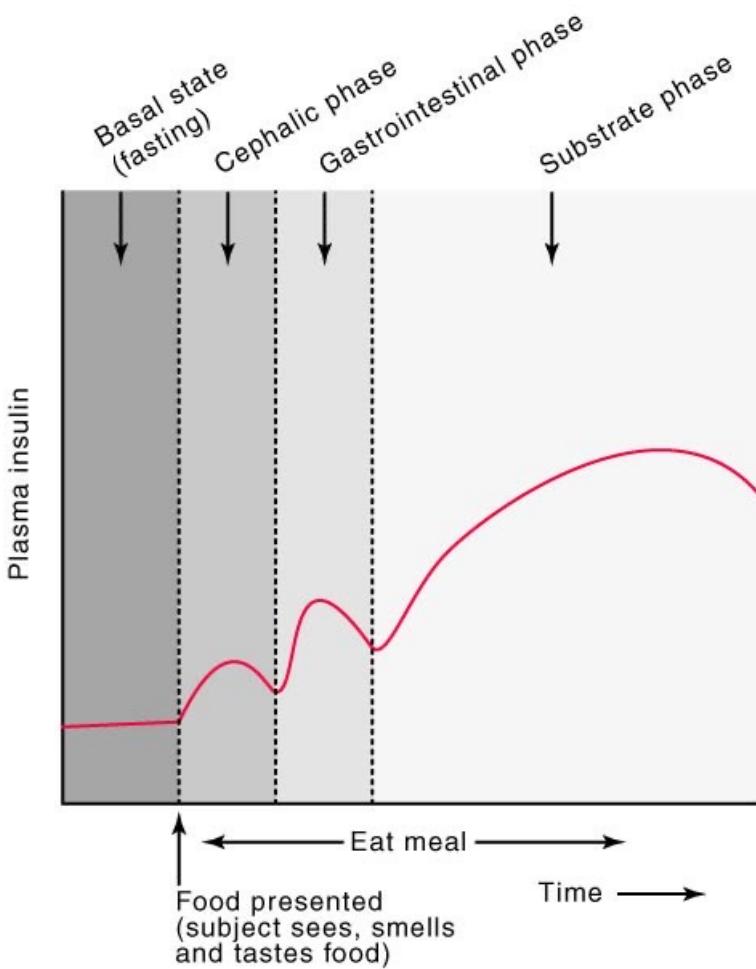


Fig. 1. Mean grams of cashews eaten by obese and normal subjects.

Psychosomatic Medicine 1976

Psychological theories of human obesity

Insulin responses: The cephalic phase



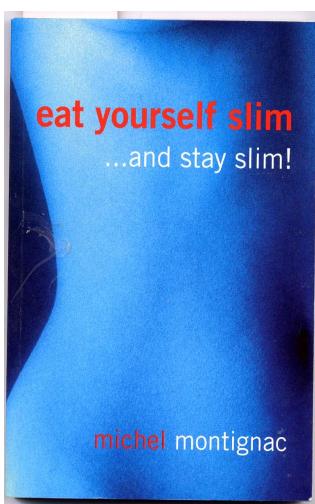
Psychological theories of human obesity: cephalic phase and loss of dietary restraint

Cephalic phase hypothesis

Hyperinsulinaemia leads to hyperphagia and an increase in fat storage

Enhanced insulin response is under psychological control

1. Sensitised response to external cues (sizzling steak)
2. Abnormal baseline (VMN rat/ genetic predisposition in humans)
3. Heightened response through stress



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Summary & conclusions

The hypothalamus → complex peptidergic regulation of integrated circuits.

Homeostasis interacts with motivational systems beyond caloric regulation

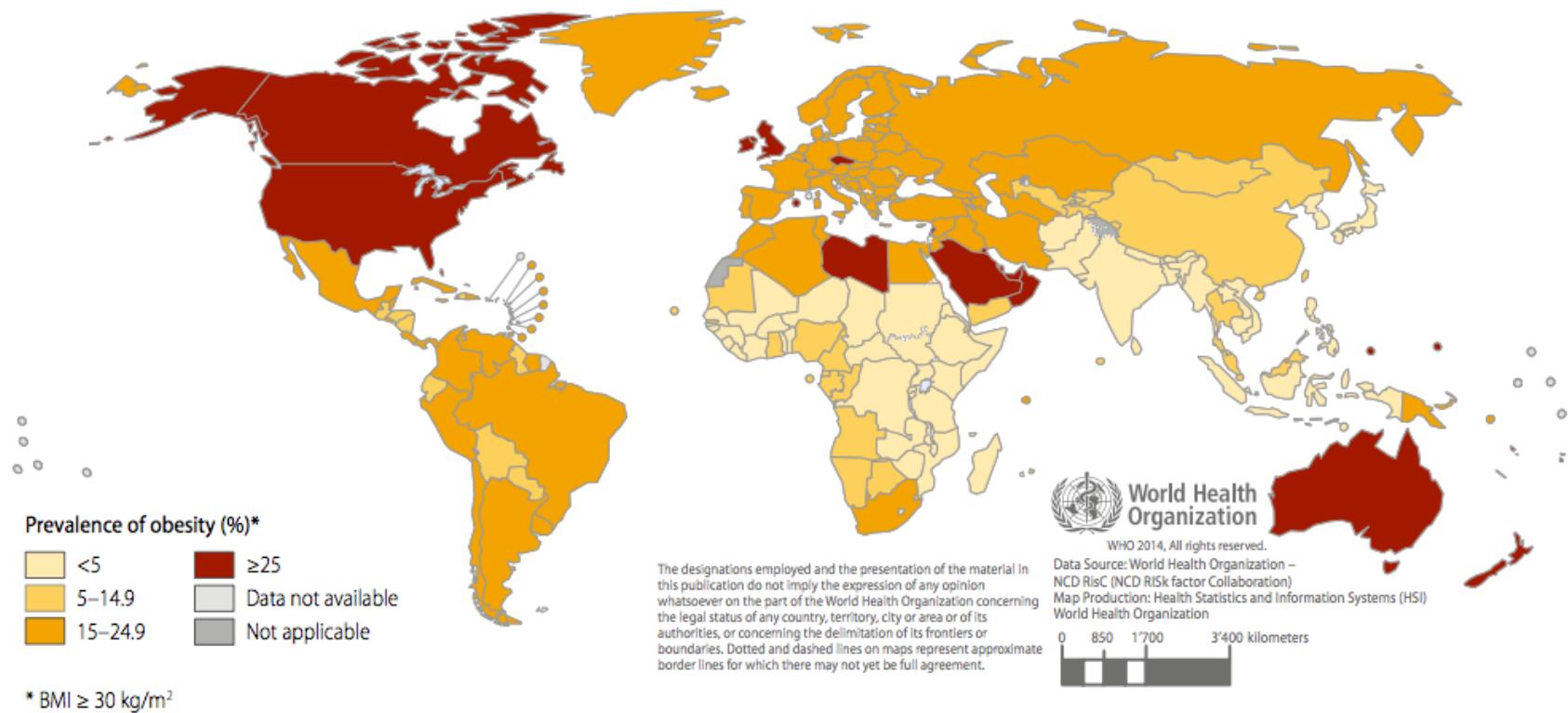
Obesity: genetic, environmental and psychological factors

Many behaviours have no obvious deficit state



Obesity

Fig. 7.1 Age-standardized prevalence of obesity in men aged 18 years and over ($\text{BMI} \geq 30 \text{ kg/m}^2$), 2014



- Obesity → most significant health issue facing the western world.
- In the United Kingdom, around 65% of adults are overweight, and 25% are obese ([WHO, 2010](#)).
- Obesity → a major risk factor for premature mortality ([Kopelman, 2000](#))

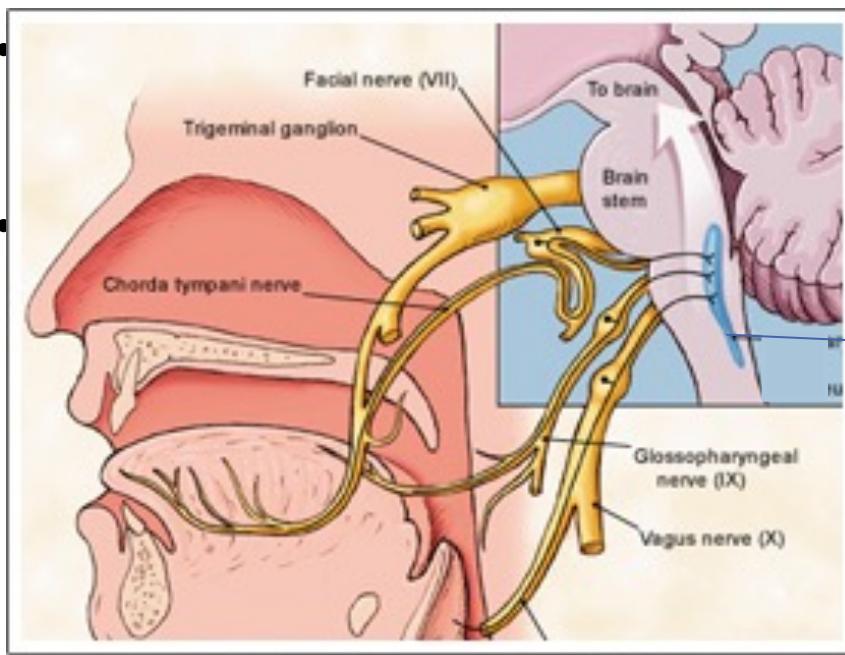
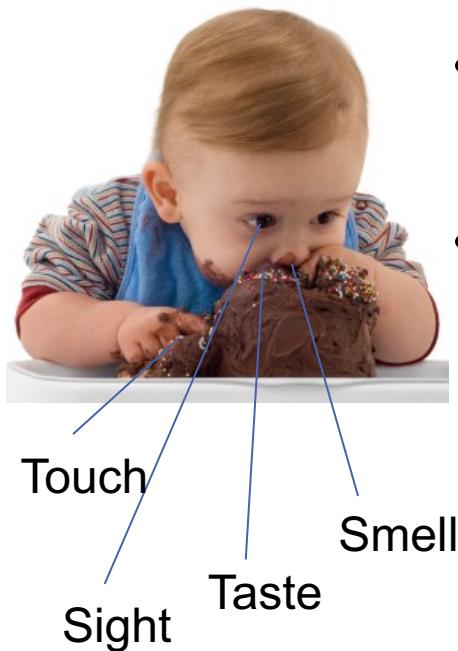
Obesity & cognition

There is more to obesity than meets the eye:

- there may be a significant psychological and neurological element to the obese syndrome
- cognitive deficits may occur both as a result of obesity, and potentially as a causal factor in its emergence.

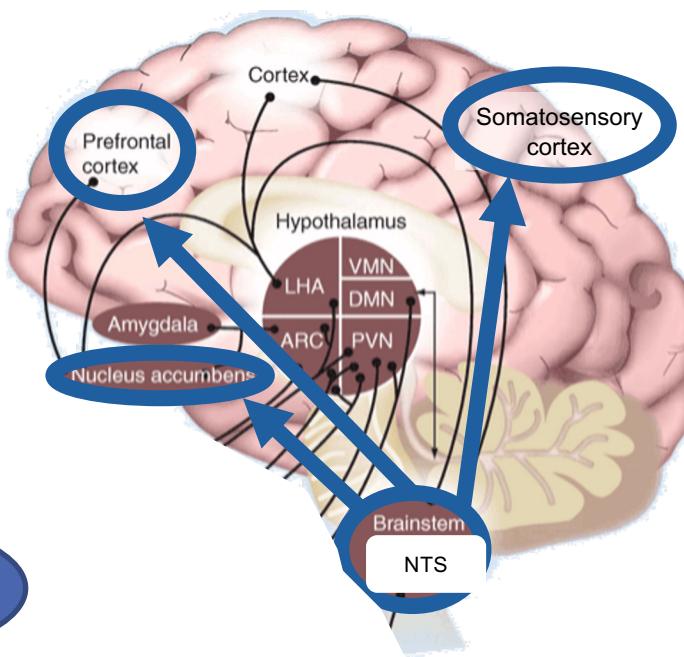
It all starts with Taste Perception

Information about the taste of food is passed from taste receptors in the tongue and processed by the nucleus of the solitary tract (NST) in the brainstem

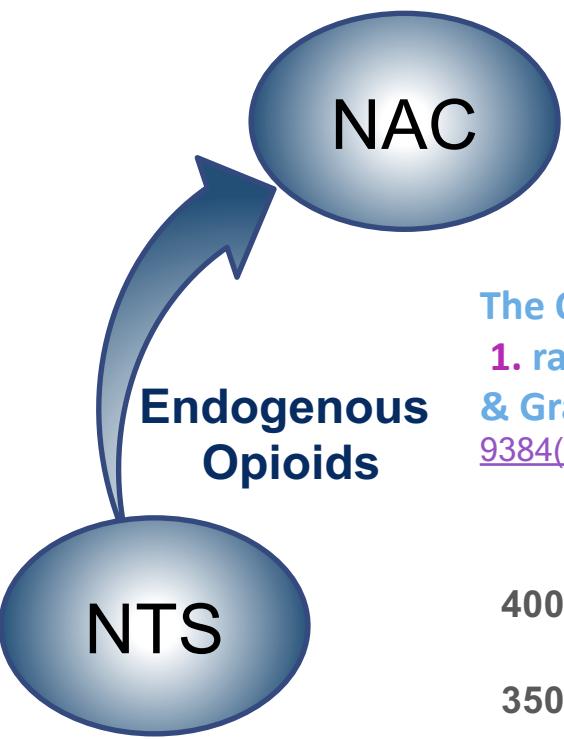


It all starts with Taste Perception

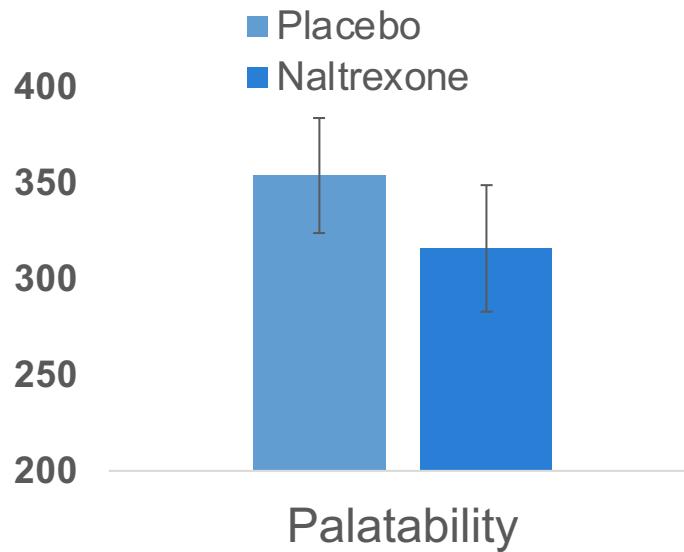
- Neurotransmitter signals from the **NST** terminate in:
- The **Somatosensory cortex** in the parietal lobe, which works on identifying specific flavours
- The **Nucleus Accumbens, amygdala and prefrontal cortex** which have a significant role in motivation and reward.



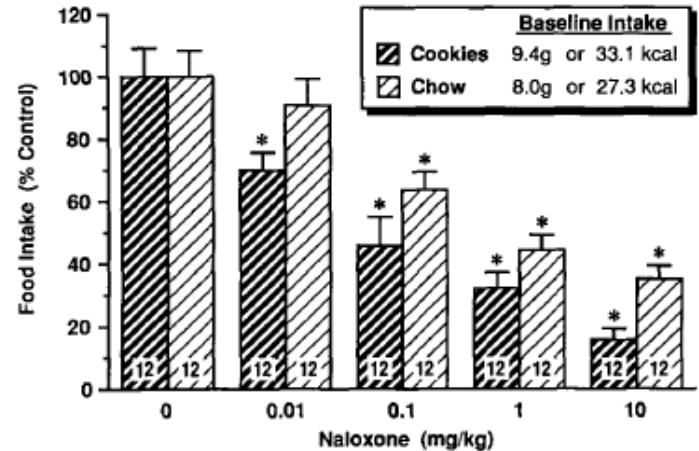
Taste perception: Opioids and palatability



The Opioid antagonists reduce
1. rated palatability of food (Yeomans & Gray, 1997) [https://doi.org/10.1016/S0031-9384\(97\)00101-7](https://doi.org/10.1016/S0031-9384(97)00101-7)



And 2. consumption of highly palatable foods (Giraudo et al. 1993) PMID: 8309972

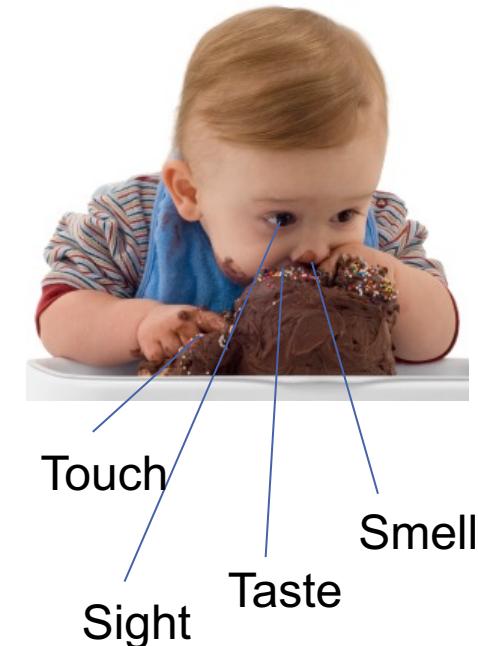
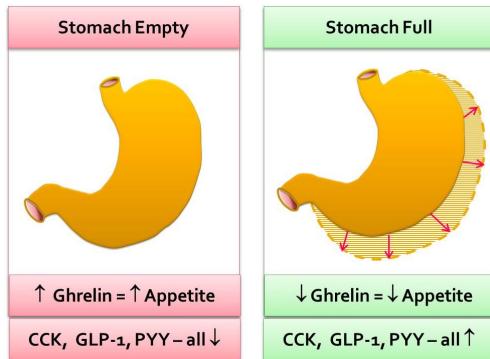
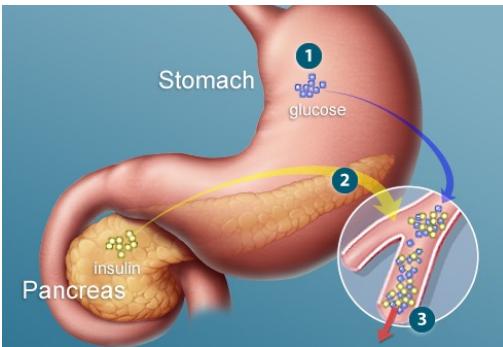


The cephalic phase response

We have seen how hormones, such as insulin are produced in response to a rise of glucose in the blood and how CCK is released in response to the presence of fat and protein in the intestine.

However, as discussed previously, release of these hormones can be elicited in response to the detection of food in the environment

→ This “preparatory” release is called the “cephalic phase response / reflex”



The cephalic phase response: insulin

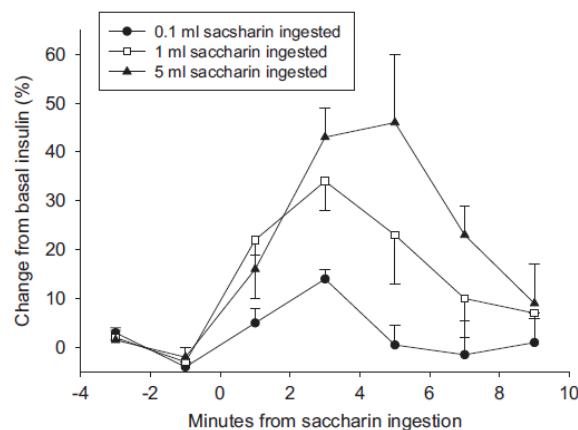
Rats and humans → cephalic insulin response

→ Gives the body a head start

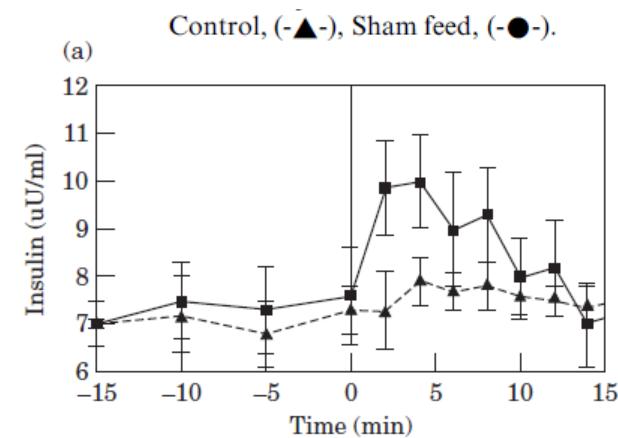
The most powerful stimuli that induces this response is the experience of a sweet flavour in the mouth

Although humans appear to need to also chew a food along with a sweet taste to get a large insulin response

However, cephalic insulin (and other hormonal) responses don't only occur in response to having food in your mouth

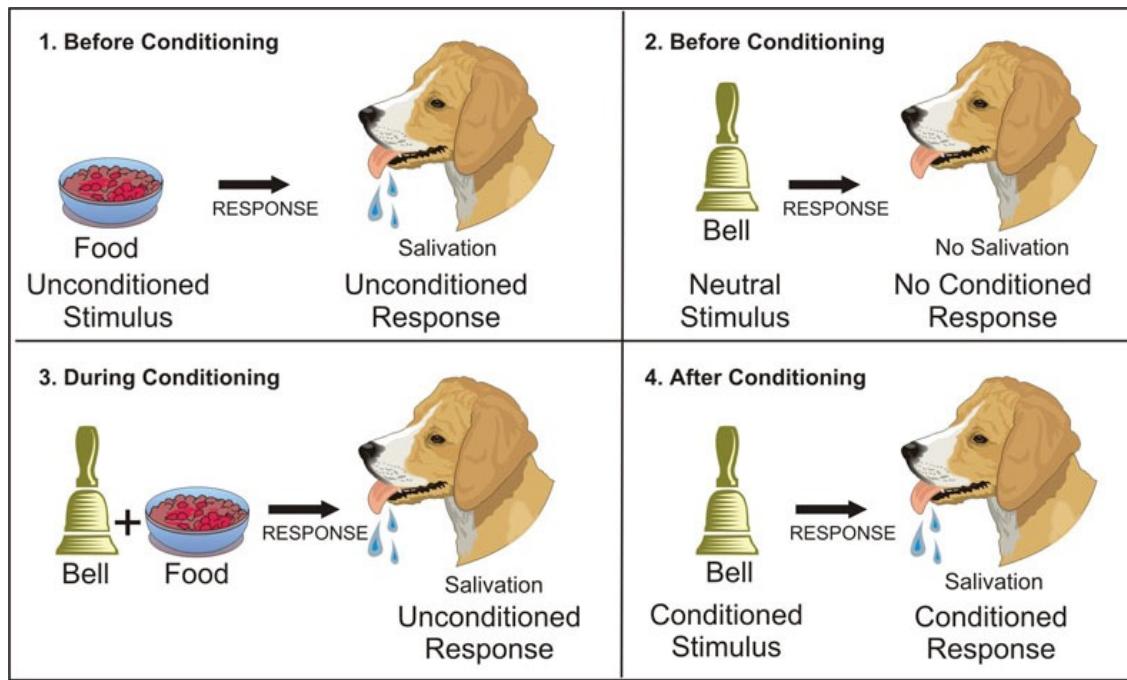


Sweet taste increases basal insulin in rats (Powley & Berthoud, 1985)
doi: [10.1016/j.appet.2007.10.006](https://doi.org/10.1016/j.appet.2007.10.006)



Sham-feeding (chewing and tasting, but not consuming) increases plasma insulin in humans (Teff, 2000)
<https://doi.org/10.1006/appc.1999.0282>

The cephalic phase response



One of the earliest demonstrations of a cephalic phase digestive response was that of Pavlov's dogs. Pavlov originally termed the conditioned salivation response "Psychic secretions". He extended this work beyond salivation to gastric secretions, showing that they too could be conditioned.

→ Shown by a number of digestive hormones including Ghrelin in response to stimuli associated with food:
sights, smells or sounds reliably paired with food as well as timings related to food

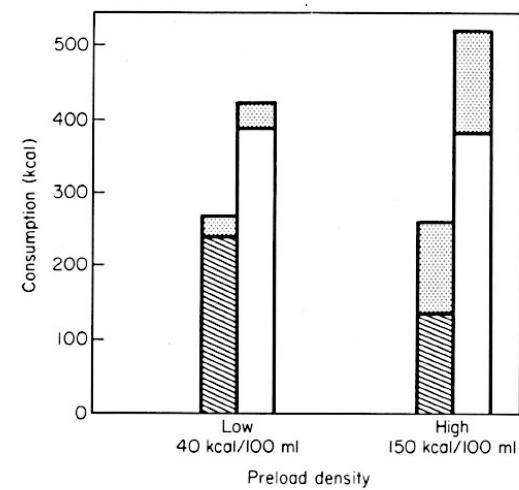
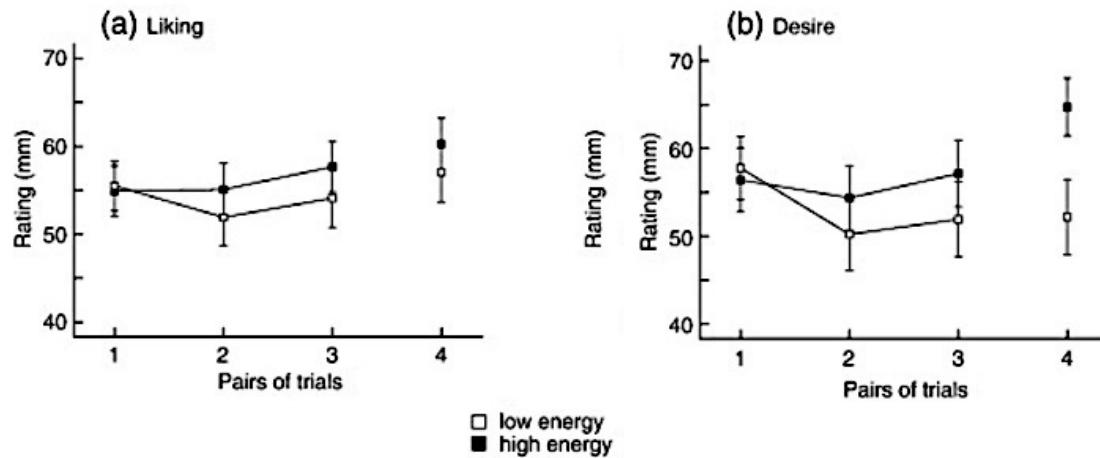
Flavour-nutrient learning

We learn about food: particular flavours → post-ingestive consequences

After weaning, children learn to associate a particular taste with the potential energy, satiation and satiety repercussions of consuming it.

In general, this translates into an increased liking for flavours that are associated with greater energy density

We also learn in some circumstances to adapt how much we eat to maintain a balanced energy intake



Even when initially equally preferred, humans learn to prefer food that is higher in energy (Brunstrom & Mitchell, 2007).

FIGURE 1. *Ad libitum* lunch consumption and high and low caloric density preload consumption (kcal) by children and adults. ▨, Preload; □, lunch, children, $N=21$; □, lunch, adults, $N=26$.

Children adapt their food intake after a preload to keep energy intake constant (Birch & Deysher, 1986).

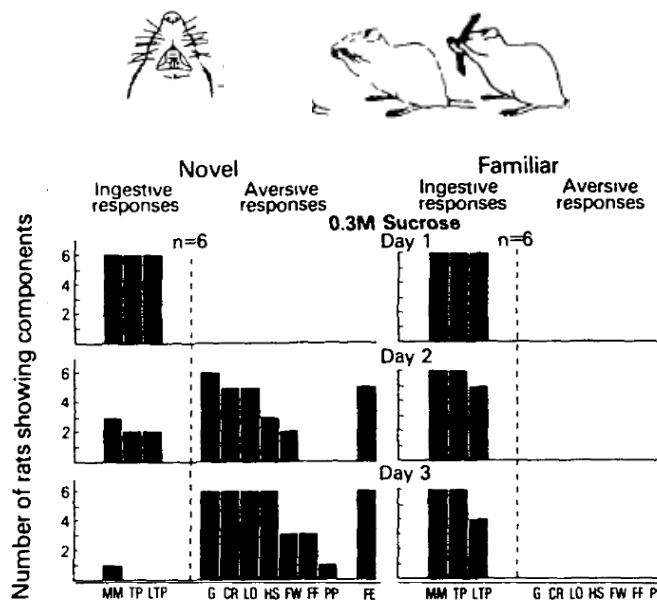
Taste aversion learning

→ particularly powerful form of flavour learning

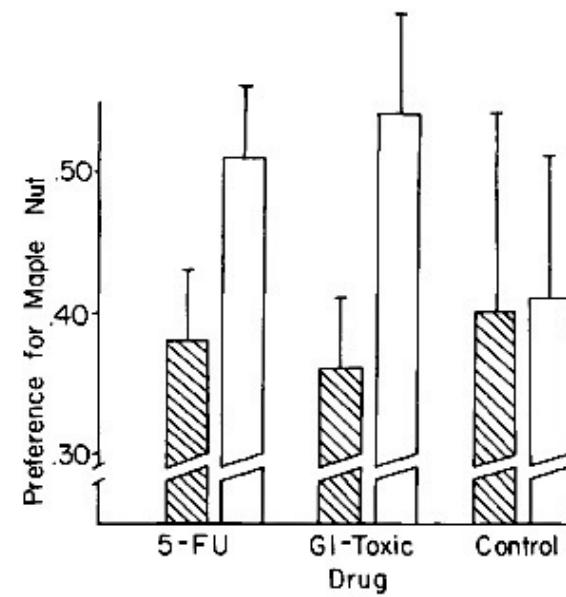
Only a single pairing of a particular flavour with gastric distress (e.g. nausea, vomiting) is often required for an individual to display rejection behaviours.

This “Garcia-type” learning (Garcia, 1977) follows a different timeline to other forms of associative learning, as flavours can be paired with sickness that occurs hours later.

→ can lead to misplaced taste aversions.



Naive rats display aversion responses to sucrose solution after a single pairing with lithium chloride (Berridge et al., 1981)



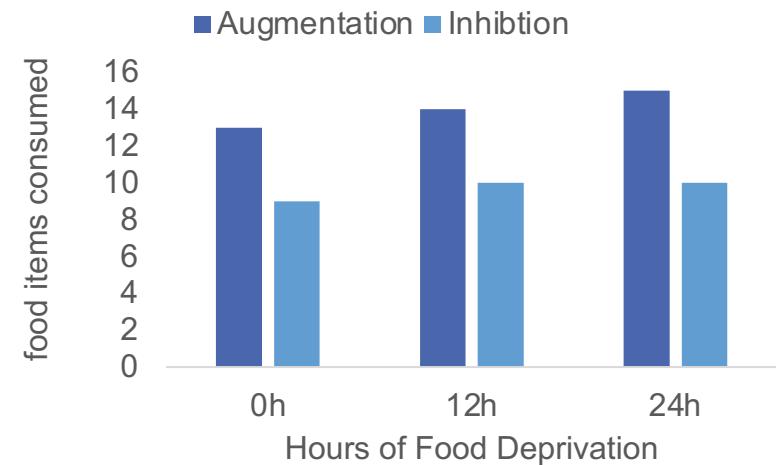
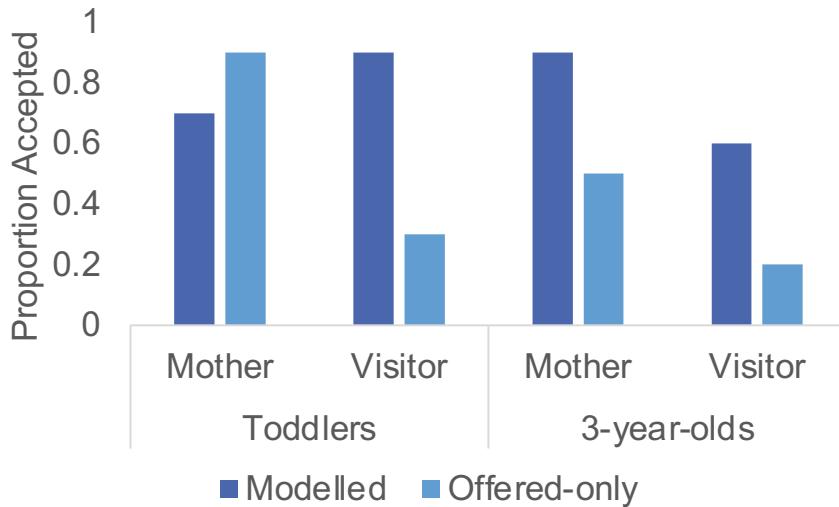
Chemo patients who tried a novel flavour of ice-cream before drug administration displayed reduced preference for that flavour (Burnstein & Webster, 1980).

Social context: modelling

Parents attempt to encourage consumption of certain foods through **modelling**

Modelling is also highly effective on adults: people eat considerably more if with a confederate modelling higher consumption.

This effect is even powerful when individual is highly food deprived



In pre-schoolers (but not just weaned toddlers) modelling encourages eating over just being offered, mother more effective modeller than stranger (recreated from Harper & Sanders, 1975)
[https://doi.org/10.1016/0022-0965\(75\)90098-3](https://doi.org/10.1016/0022-0965(75)90098-3)

Modelling can augment or inhibit amount consumed even when an individual is food deprived (from Goldman et al, 1991)
[https://doi.org/10.1016/0195-6663\(91\)90068-4](https://doi.org/10.1016/0195-6663(91)90068-4)

Social context: norms and stereotypes

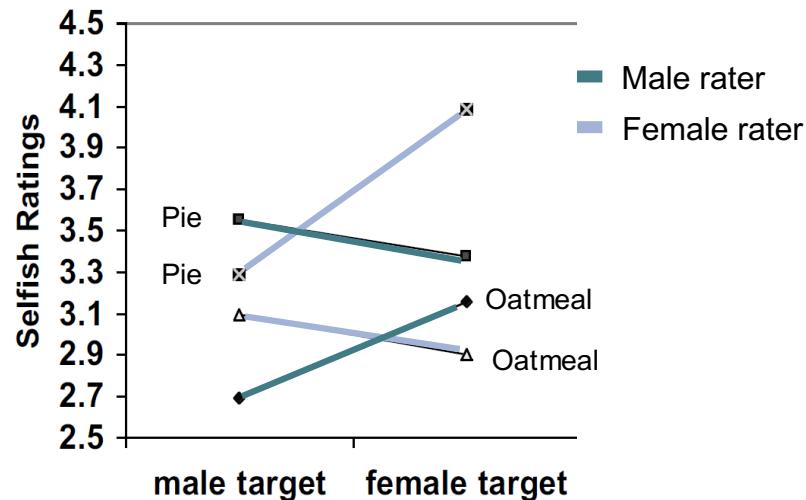
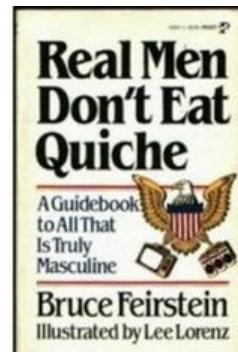
Social norms and shared values affect a great deal of human behaviour.

A person's social group will therefore inform what they consider "acceptable" food

Individuals will adapt their eating in an attempt at "impression management" (Vartanian et al., 2007).

Low fat food more stereotypically "female" food, while higher fat, protein rich diets stereotypically more "male"

Food choice heavily tied with morality. E.g. Healthier food more "moral"



Individuals' personality and morality is judged by others relative to healthiness of food and group conformity (Oakes & Slotterback, 2004) <https://doi.org/10.1007/s12144-004-1001-6>

Summary

- Eating behaviour is a complex phenomenon affected by physiology, neuroscience and psychology
- No system works in a vacuum: the brain is affected by the body and the body is affected by the brain
- Learning plays an important role in dictating what, when and how much we eat, but also affects our ability to digest that food once consumed.
- Social context can have a considerable impact on what and how much we eat.

➔ When things go awry....

Obesity and the brain: structural differences

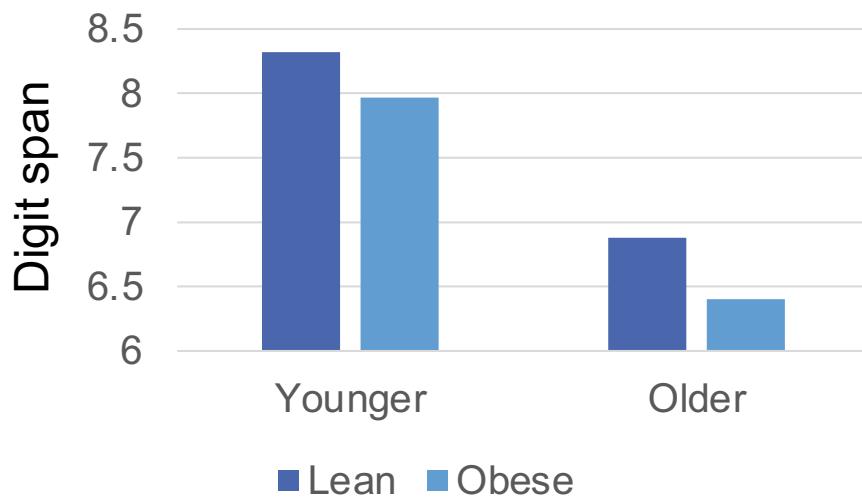
Across all ages, higher body fat is associated with grey matter atrophy in the frontal lobe, particularly in the prefrontal cortex

In middle aged and older adults, higher adiposity is associated with parietal and temporal lobe atrophy (Willete & Kapogiannis, 2015 doi: [10.1016/j.arr.2014.03.007](https://doi.org/10.1016/j.arr.2014.03.007).)

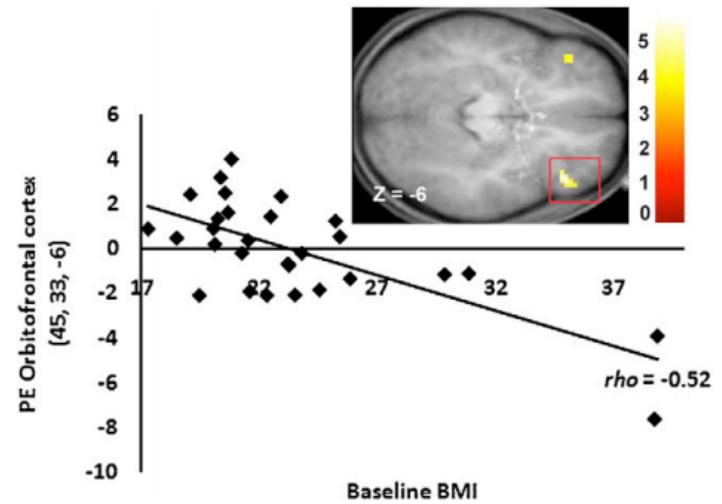


Obesity and the brain

Changes in frontal lobe structure and function are associated with deficits in executive function (a set of cognitive processes – including attentional control, inhibitory control, working memory, and cognitive flexibility, that help an individual regulate behaviour)



Obesity is associated with reduced working memory performance, particularly in older adults
(Gunstad et al., 2007, doi:
[10.1016/j.comppsych.2006.05.001](https://doi.org/10.1016/j.comppsych.2006.05.001))



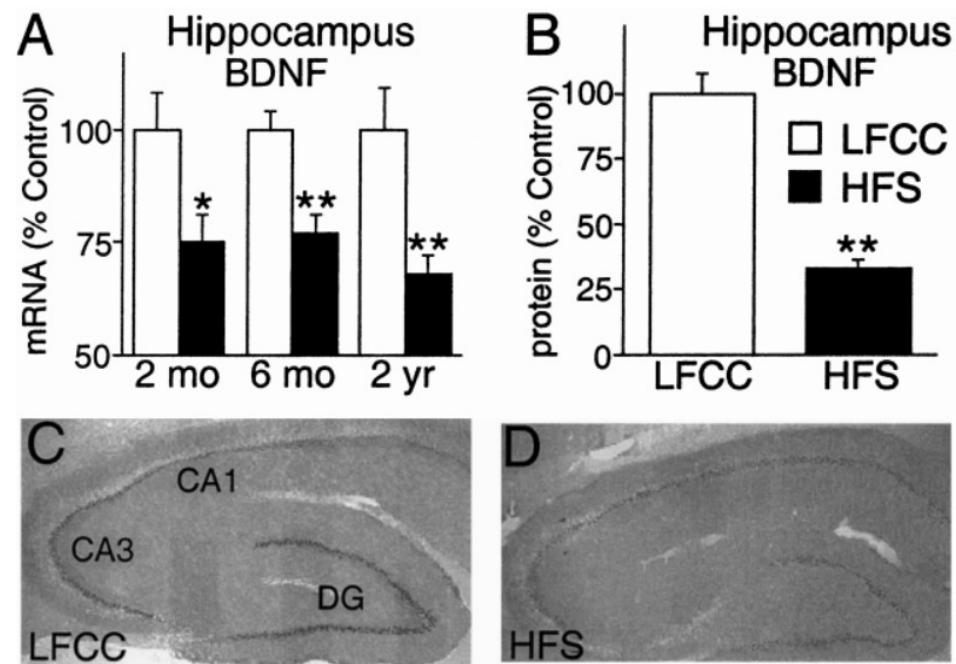
Higher BMI is associated with reduced orbitofrontal activation and poorer performance while performing a go-no-go task
(Batterink et al., 2010, doi:
[10.1016/j.neuroimage.2010.05.059](https://doi.org/10.1016/j.neuroimage.2010.05.059))

Western diet and the hippocampus

Western Diet = Energy dense diets that are high in saturated fat and refined sugar (also referred to as HFS or HE)

Rats on a western diet: several markers of damage to the hippocampus →

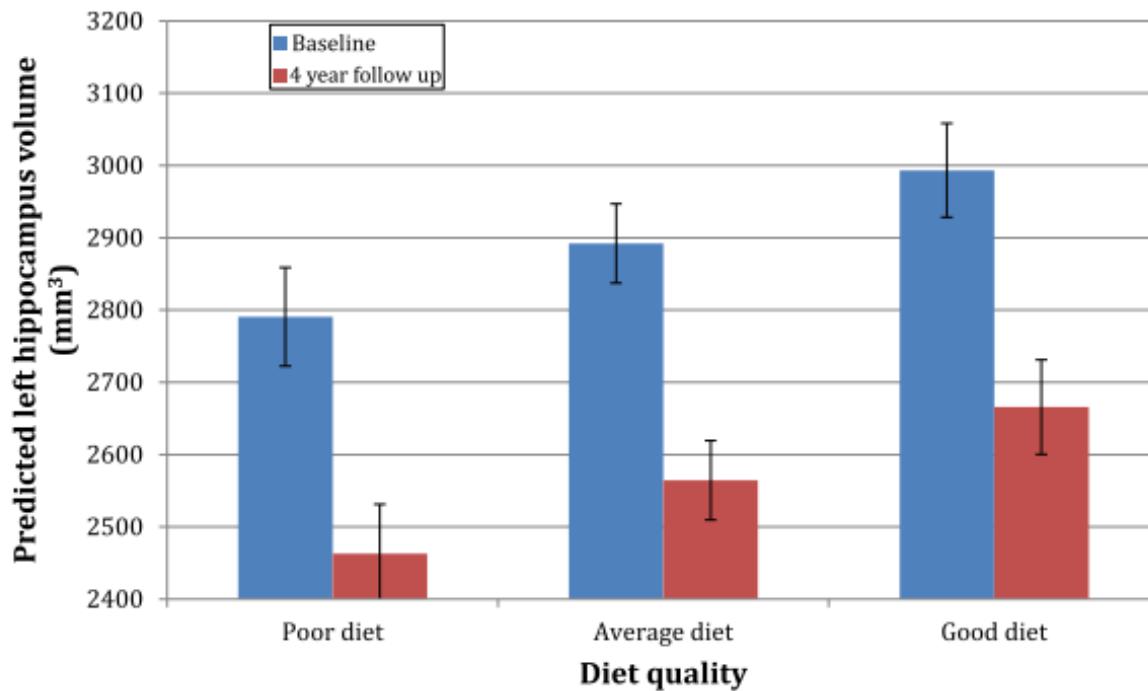
- Reduced hippocampal BDNF (Molteni et al., 2002; Kanoski et al., 2007)
- Reduced hippocampal neurogenesis (Park et al., 2010)
- Increased hippocampal inflammation (Puig et al., 2012; Herculano et al., 2013)



Reduced BDNF in hippocampus after 2 months on HFS
(Molteni et al., 2002) [https://doi.org/10.1016/S0306-4522\(02\)00123-9](https://doi.org/10.1016/S0306-4522(02)00123-9)

Western diet and the hippocampus

Diets lower in healthy elements (e.g. vegetables, whole grains, fish, etc) and those higher in unhealthy elements (saturated fat and refined sugar) are independently associated with reduced hippocampal volume in older humans (Jacka et al., 2015).



- Some evidence suggests that it is not the diet itself, but the **obesity** it causes that leads to deficits.
- See later with obese and resistant rats

Older adults (60-64) with an unhealthy diet show reduced hippocampal volume compared to those with a healthy diet (Jacka et al., 2015)

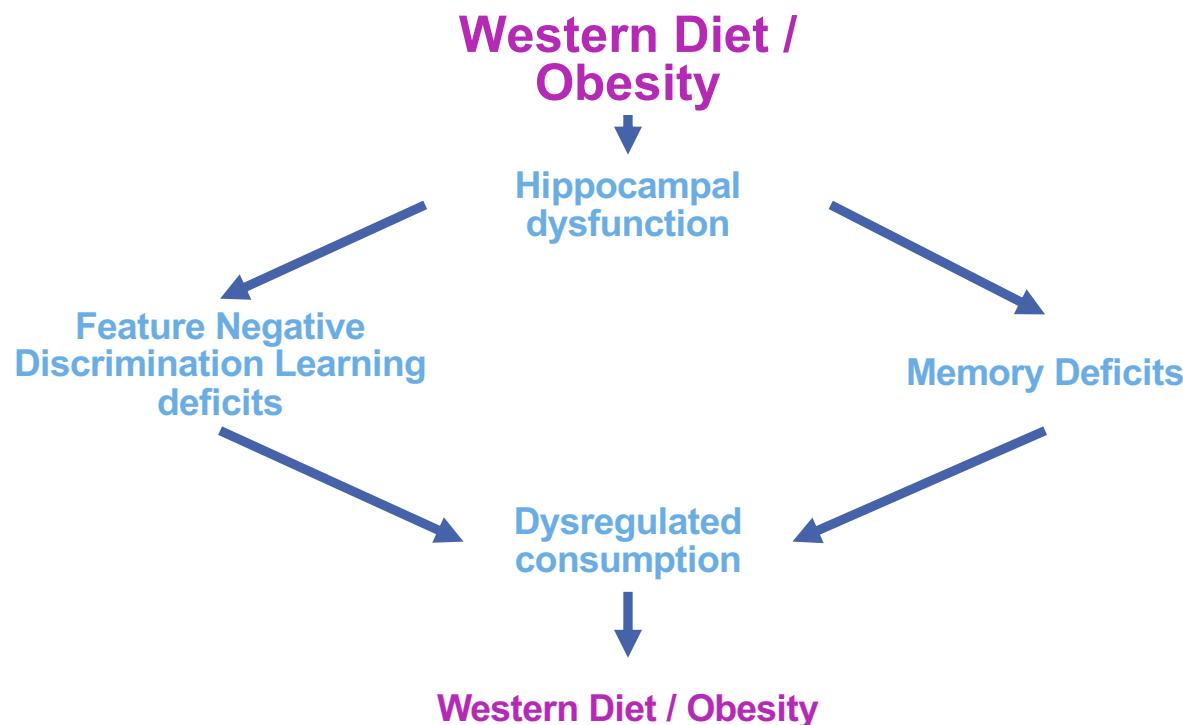
<https://doi.org/10.1186/s12916-015-0461-x>

Western diet, obesity and hippocampus dysfunction

The hippocampus performs a number of functions, but is centrally important for learning and memory → a range of different cognitive deficits if function altered.

→ We will explore two particular cognitive functions: Feature Negative Discrimination Learning and Memory.

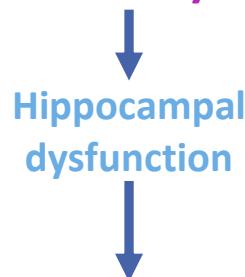
Deficits in these abilities may also lead to dysregulated consumption



Feature negative discrimination learning

Feature Negative Discrimination learning = the ability to learn that a particular stimulus is rewarded in some contexts but not in others.

Western Diet /
Obesity



Feature Negative
Discrimination Learning
deficits

X → Reward

Y → X → No Reward

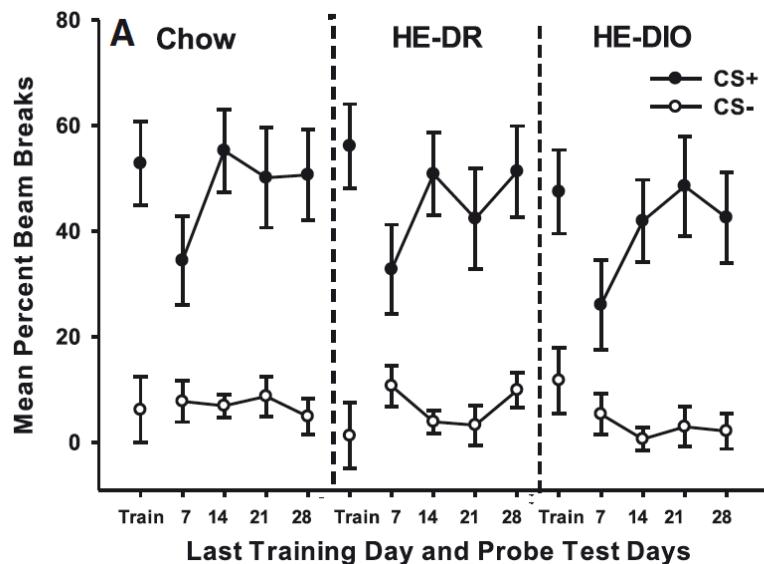
The ability to learn an association between a stimulus and an outcome is generally not dependant on the hippocampus

However, the ability to learn that the same stimulus is NOT rewarded in the presence of a second stimulus (or in a given context) IS hippocampal-dependant

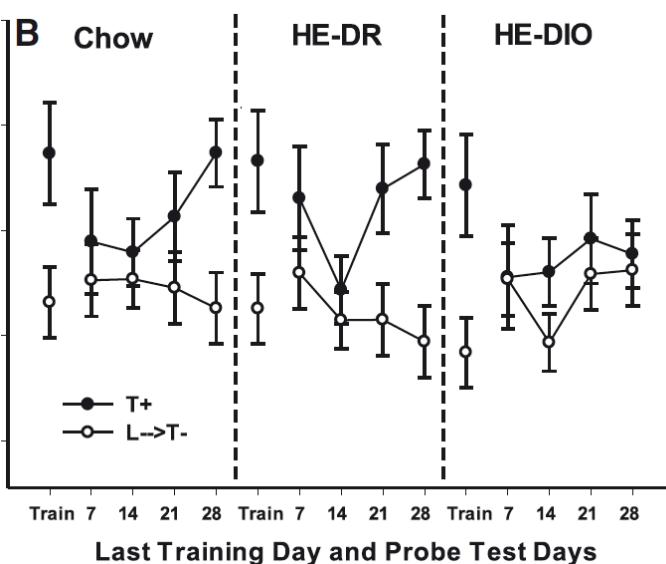
Hippocampus dysfunction: FND learning

Simple Discrimination

Not all rats exposed to western diet become overweight. Thus rats exposed to the same diet can be classed as “diet-induced obese” (DIO) or diet-resistant (DR)



FN Discrimination

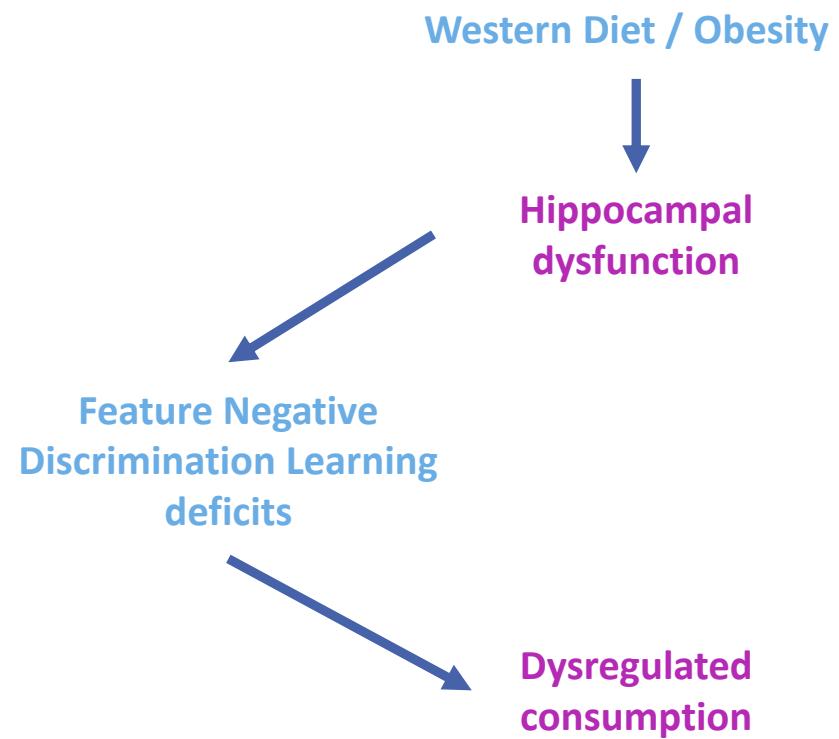


Rats maintained on a high energy diet (HE) that became obese (DIO) were just as able to learn a simple discrimination as rats maintained on the same diet that didn't become obese (DR) and rats maintained on chow, but were specifically impaired on feature negative discrimination learning (Davidson et al., 2012)

BUT... Rats maintained on a high fat, low carbohydrate diet (KETO) that become obese (DIO) do not show this effect (Davidson et al., 2013)

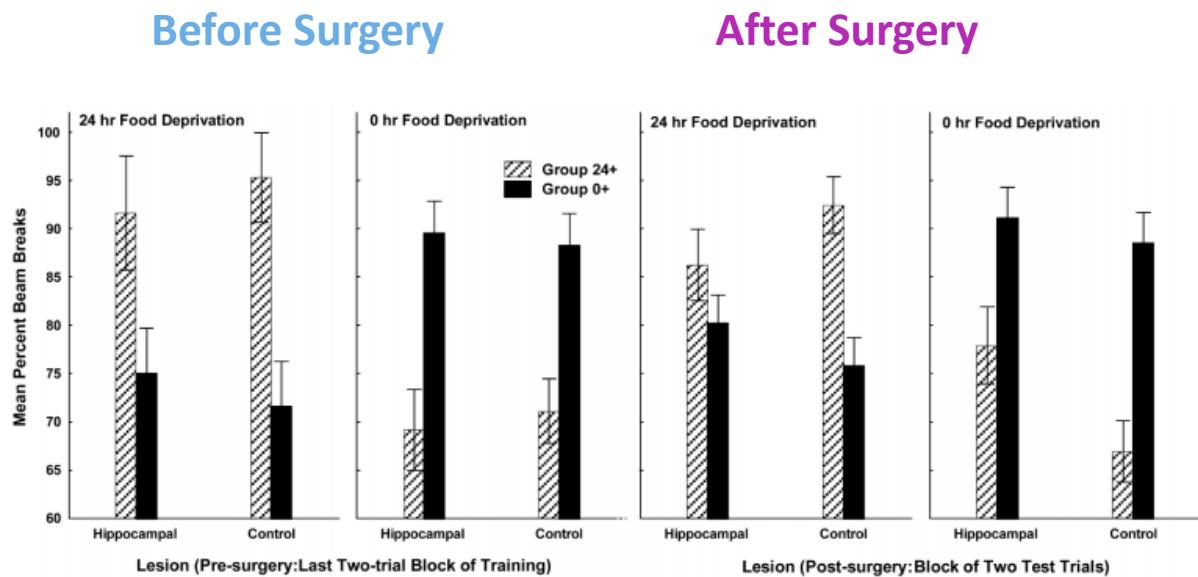
FND learning and consumption regulation

- FN discrimination important for regulating dietary intake?
 - Woods 2004: Most eating is initiated by environmental food-cues (and physiological hunger cues play a more minor role)
 - Feelings of satiation act as a feature negative cue: stimuli predictive of food are highly rewarding UNLESS they are in the context of satiety
 - Disrupted FN learning may lead individuals to continue to respond appetitively to food cues even in the context of satiety (Kanoski & Davidson, 2011).



FND learning and consumption regulation

- Hippocampal lesions
 - elevated appetitive response to food cues in sated rats relative to intact controls (Schmelzeis et al., 1996).
 - Impaired use of internal state to predict the availability of food (Davidson et al., 2010)



Rats were taught that they would be given sucrose pellets either when they had gone 0 hours without food or when they had gone 24 hours without food (Davidson et al., 2010)

After surgery, rats with hippocampal lesions were less able to use their own deprivation-state to predict when food would arrive (Davidson et al., 2010)

Obesity and memory: rodents

Rats maintained on a western diet → spatial and nonspatial memory deficits

Western Diet /

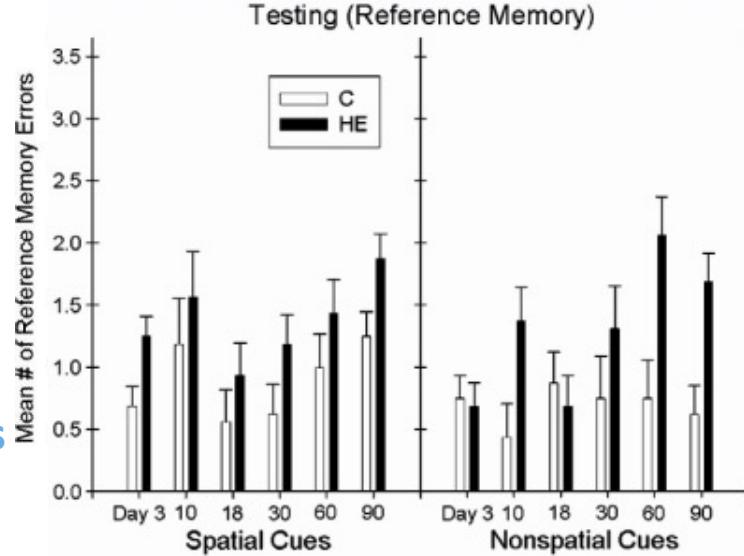
Obesity



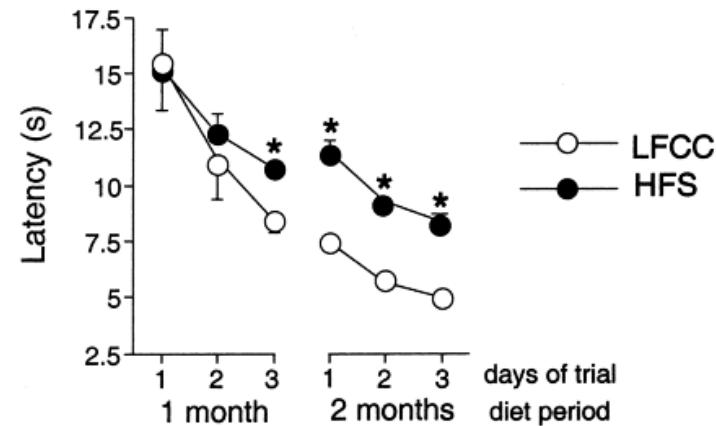
Hippocampal dysfunction



Memory Deficits



Spatial memory (radial arm maze)
deficits emerge after only 72h on a high
energy diet, and nonspatial memory
deficits after around 60 days (Kanoski &
Davidson, 2011)



Performance on the Morris
water maze reduces
significantly after 1-2 months
on a high fat, high sugar diet
(Molteni et al., 2002)

Obesity and memory: rodents

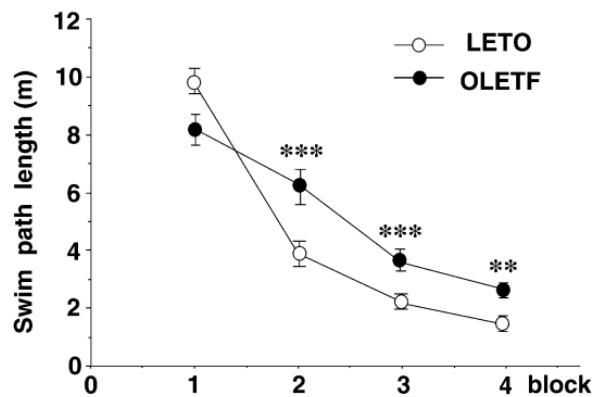
Genetic Obesity



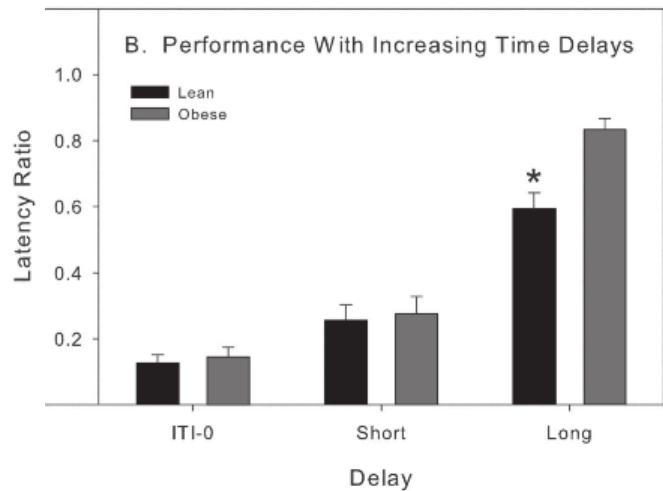
Hippocampal dysfunction



Memory Deficits



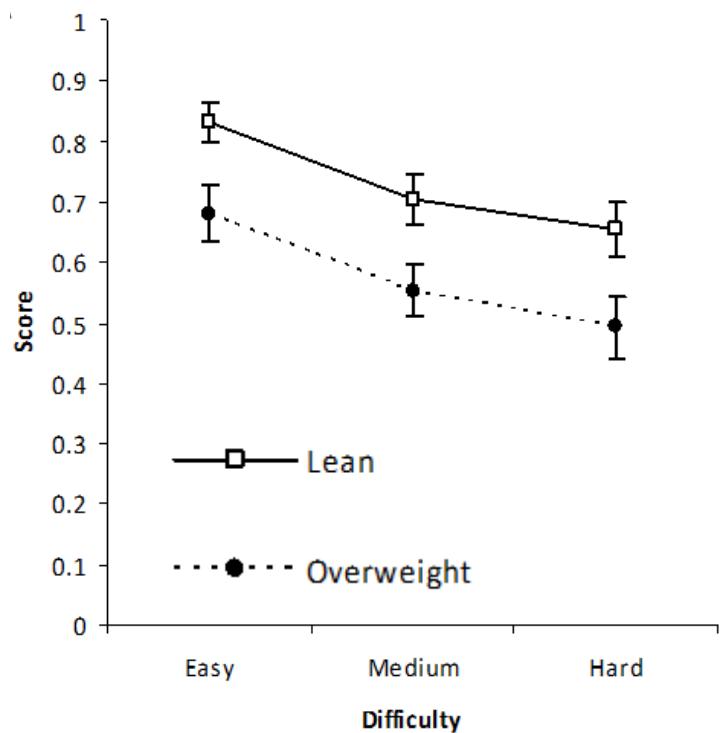
Genetically obese OLETF rats are significantly impaired compared to lean animals on the Morris water maze (Li et al., 2002)



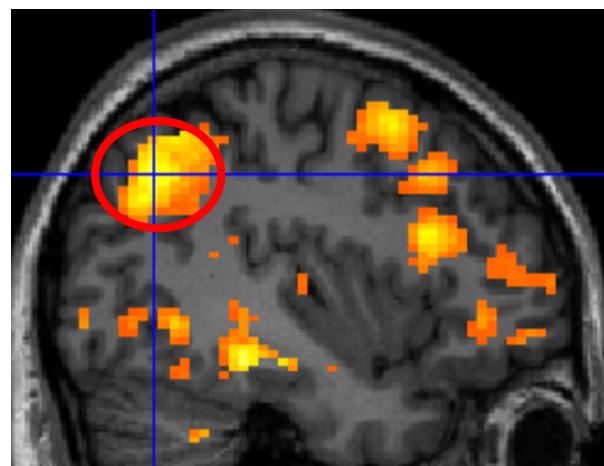
Genetically obese Zucker fa/fa rats are significantly impaired when required to remember information over long intervals (Winocur et al., 2005)

Obesity and memory: humans

Obesity has also been associated with memory deficits in humans



Otherwise healthy young (18-35) overweight adults perform significantly worse on a episodic memory test compared to lean controls (Cheke et al., 2016)



And show reduced activity in memory-related brain areas while performing this task (Cheke et al., 2017)

Memory and consumption regulation?

Western Diet /

Obesity



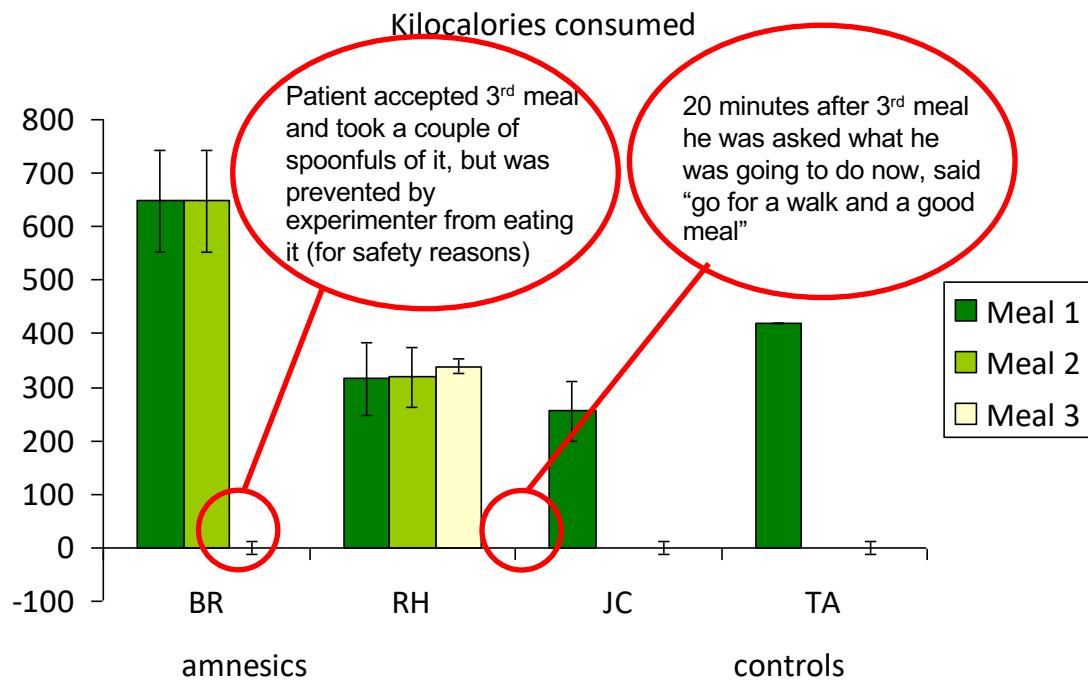
Hippocampal dysfunction



Memory Deficits



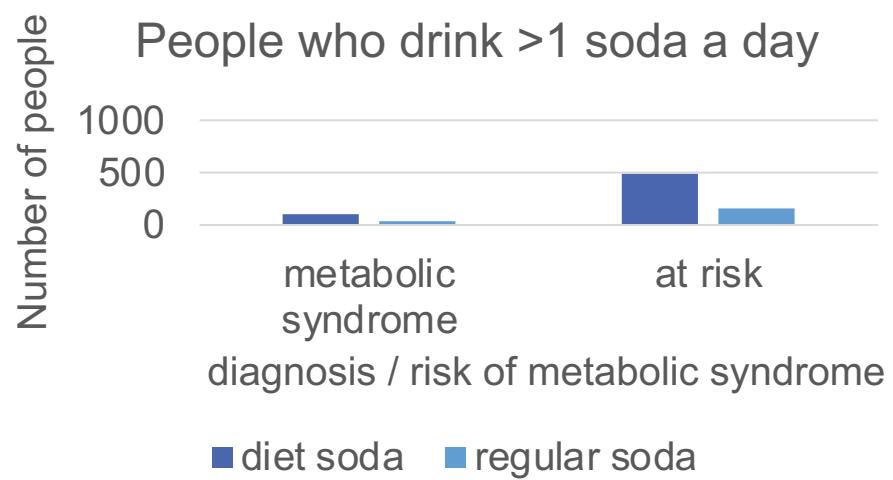
Dysregulated consumption



Amnesic patients are willing to eat several meals consecutively (Rozin et al., 1998)

Replacing calories: artificial sweeteners

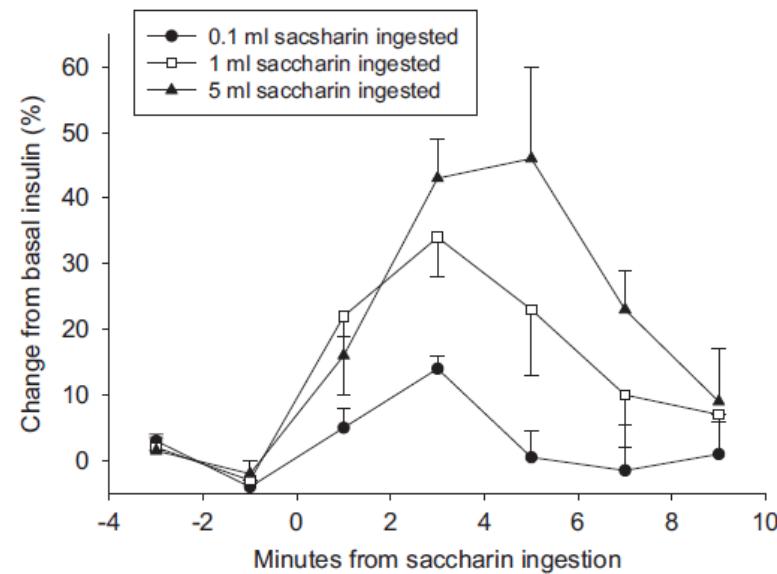
- Logic:
 - replacing sugar with artificial sweeteners reduces the calories
 - reducing caloric intake will produce weight loss
 - sweet flavour reduces need for self control / restraint.
- BUT: growing evidence that consumption of artificial sweeteners is associated with weight GAIN rather than weight loss (Dhingra et al., 2007; Fowler et al., 2008; Fung et al., 2009; Lutsey, Steffen, & Stevens, 2008).



In people who regularly drink soda, those who drink diet soda are more likely to have or show risk factors for metabolic syndrome (Dhingra et al., 2007)

Artificial sweeteners and the cephalic phase response

- The efficiency of energy regulation depends, at least in part, on the elicitation of cephalic-phase responses
- We know that a cephalic response can be elicited by non-nutritive sweeteners (e.g. Powley & Berthold, 1985)
- If the elicitation of cephalic-phase responses depends, in part, on the ability of sweet tastes to signal calories, then experiences that weaken this signalling or predictive relationship might also disturb the efficiency of energy regulation by disrupting the cephalic phase response.



Effect of sweet taste on basal insulin in rats (Powley & Berthoud, 1985)

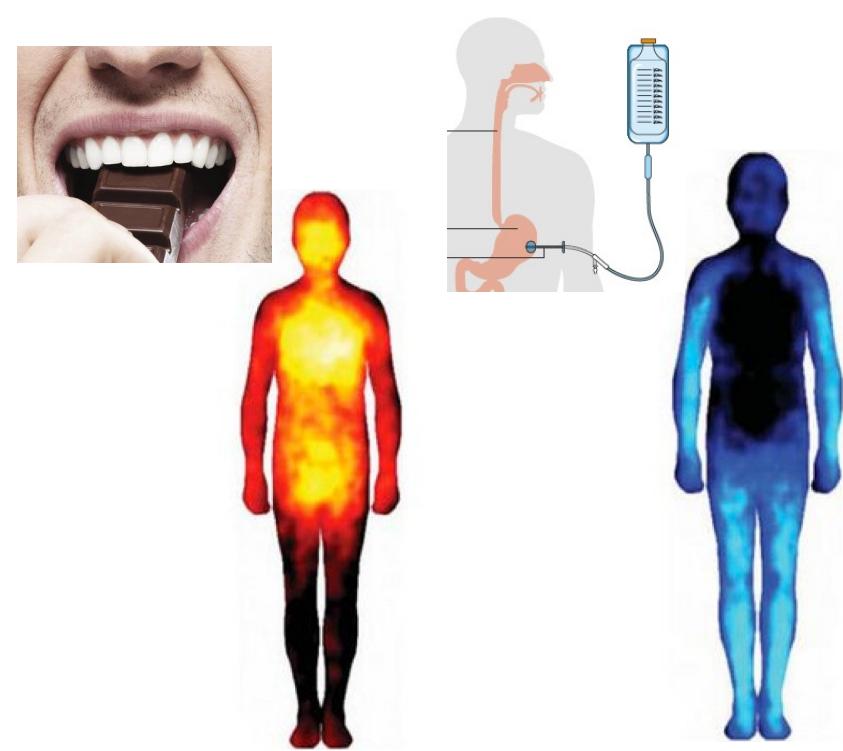
Artificial sweeteners and the cephalic phase response

- Ingestion of food → reflexive thermogenic response (i.e: increases body temperature: Jequier, 1983; Tappy, 1996)

= a form of cephalic response – when food is tasted but not swallowed, the change in temperature can match, or even exceed, that produced by a normal meal (Diamond et al., 1985; LeBlanc & Cabanac, 1989).

In contrast, when food goes straight into the stomach, the thermogenic response either does not occur or is much weaker (Diamond et al., 1985; LeBlanc, Cabanac, & Samson, 1984).

→ this thermogenic effect may be due to the body anticipating the energy it will expend during digestion and the increased utilization of calories that is normally produced by nutrient absorption.



Artificial sweeteners and the cephalic phase response

- Rats who'd experienced a predictive relationship between sweet taste and calories showed a normal cephalic thermogenic response, but those who had experienced a non predictive relationship showed a reduced response

→ Those rats who had exposure to a nonpredictive relationship between sweet taste and calories had a blunted cephalic phase response.

Women assigned to either regular or irregular meals for 2 weeks. Those on irregular meals showed significant reduction in temperature and energy burned after a meal compared to those with regular meals (Farschi et al., 2004)

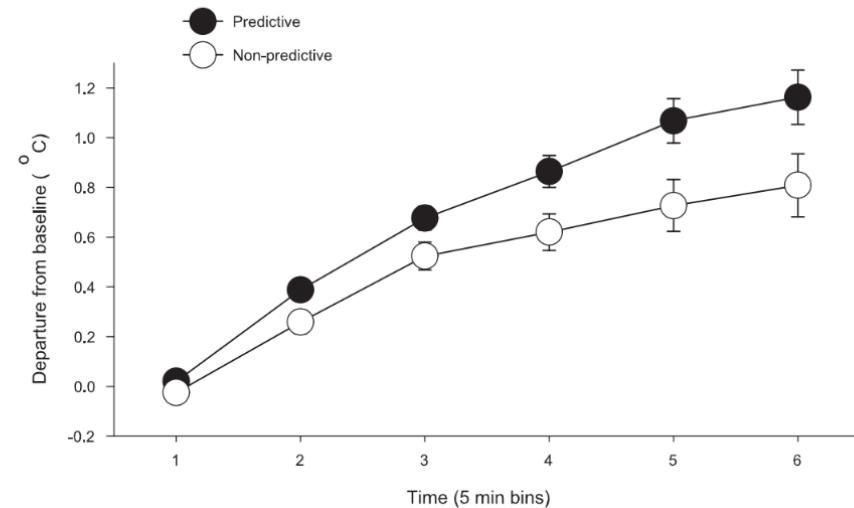
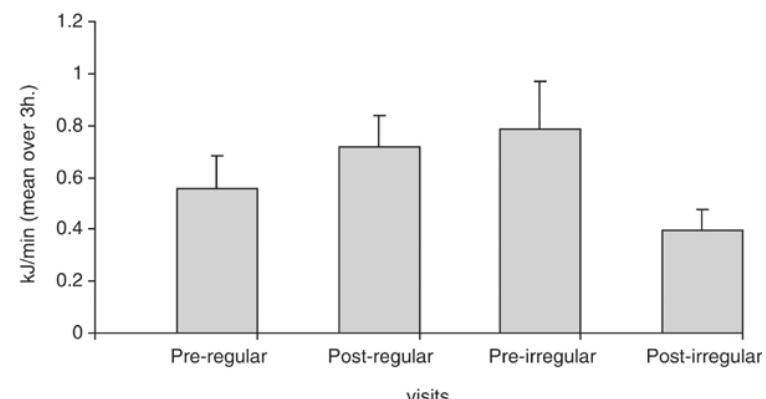
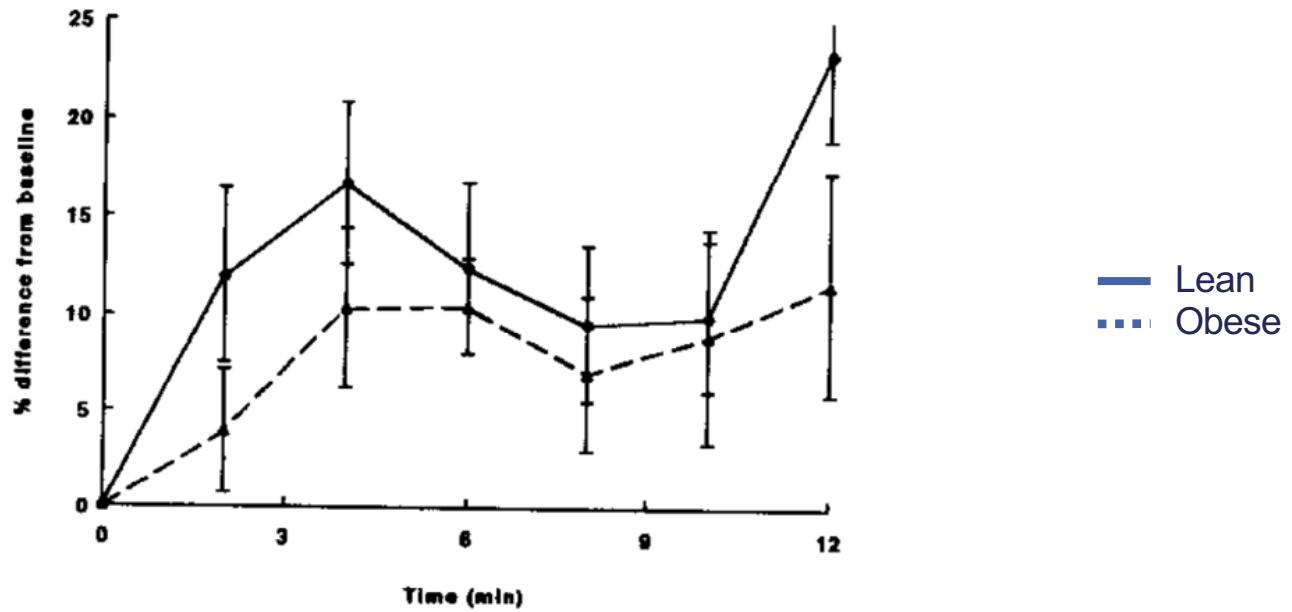


Figure 9. Changes in core body temperature during the first 30 min following presentation of the same novel, sweet premeal to sweet predictive and sweet nonpredictive rats. Sweet predictive rats showed significantly greater increases in core body temperature than did sweet nonpredictive rats.



Blunted cephalic phase response leads to obesity?



Obese individuals show altered cephalic insulin response (Teff et al., 1993)

Blunted cephalic phase response leads to obesity?

- It is possible that factors that lead to a blunting of the cephalic response may be a primary factor in the development of obesity and diabetes (Storlein & Bruce, 1989)
- Storlein & Bruce argue that disruption of the cephalic phase insulin response will lead to increased post-meal hyperglycaemia (because the body doesn't process glucose from the blood as efficiently) and reduced thermogenesis
- Over time, these effects will lead to insulin resistance (from persistent hyperglycaemia), and weight gain (due to reduced energy expenditure via thermogenesis).



Summary

- Obesity is associated with functional and structural changes to the brain
- These changes are associated with cognitive deficits
- Some cognitive deficits (e.g. learning and memory) may lead to problems regulating consumption
- Obesity and cognitive deficits may be mutually perpetuating
- Attempting to reduce or replace calories can have counterintuitive and counterproductive impacts on consumption and weight gain.

Lecture 5: Interoception, the insula, decision making and emotion regulation

Overview - interoception

Interoception: what is it?

Implicit and explicit mechanisms:

conditioning

awareness, sensitivity and accuracy: role in emotions
and emotional regulation

Somatic markers and homeostatic priors: interoception as a teaching signal for adaptive behaviours

Neural basis of interoception: the insula

Role of the insula in decision making

Interoception: definition (s)

→ Perception and interpretation of bodily signals

Interoception refers to the process of how the brain senses and integrates signals originating from inside the body, providing a moment by moment mapping of the body's internal landscape.

This crosstalk gives rise to urges, feelings, drives and emotional experiences under certain conditions, highlighting the importance of interoception for the maintenance of homeostatic functioning, body regulation, and survival.

Interoception: from perception to subjective experience

Dimensions of Interoception

Interoceptive accuracy

Objective performance

Performance on
behavioural tests

e.g. heartbeat detection tests

Start *Silent counting* End



Schandry (1981)

Interoceptive sensibility

Subjective belief

Self report

e.g. questionnaire

BODY PERCEPTION QUESTIONNAIRE

Read the instructions for each sub-test and answer (a - e) next to each item

I: AWARENESS (Image how aware you are of your body processes)

Select the answer that most accurately describes you. Rate your awareness on each of the characteristics described below using the following 5-point scale:

- a) never b) occasionally c) sometimes d) usually e) always

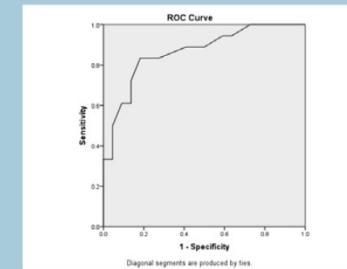
Porges (1993)

Interoceptive awareness

Metacognitive accuracy

Insight into performance
aptitude

e.g. confidence-accuracy correspondence,
area under ROC curve



Garfinkel et al. (2015)

Garfinkel et al., 2016

Interoception: from perception to subjective experience

Feature	Definition
Attention	Observing internal body sensations
Detection	Presence or absence of conscious report
Magnitude	Perceived intensity
Discrimination	Localize sensation to a specific channel or organ system and differentiate it from other sensations
Accuracy (Sensitivity)	Correct and precise monitoring
Insight	Metacognitive evaluation of experience/ performance (e.g., confidence–accuracy correspondence)
Sensibility	Self-perceived tendency to focus on interoceptive stimuli (trait measure)
Self-report Scales	Psychometric assessment via questionnaire (state/trait measure)

Interoception: definition (s)

Interoception is measured with the Multidimensional Assessment of Interoceptive Awareness questionnaire (MAIA), a 32-item self-report questionnaire → interoceptive bodily awareness (Mehling et al., 2012).

Questions are answered on a 6-point Likert scale ranging from 0 (never) to 5 (always).

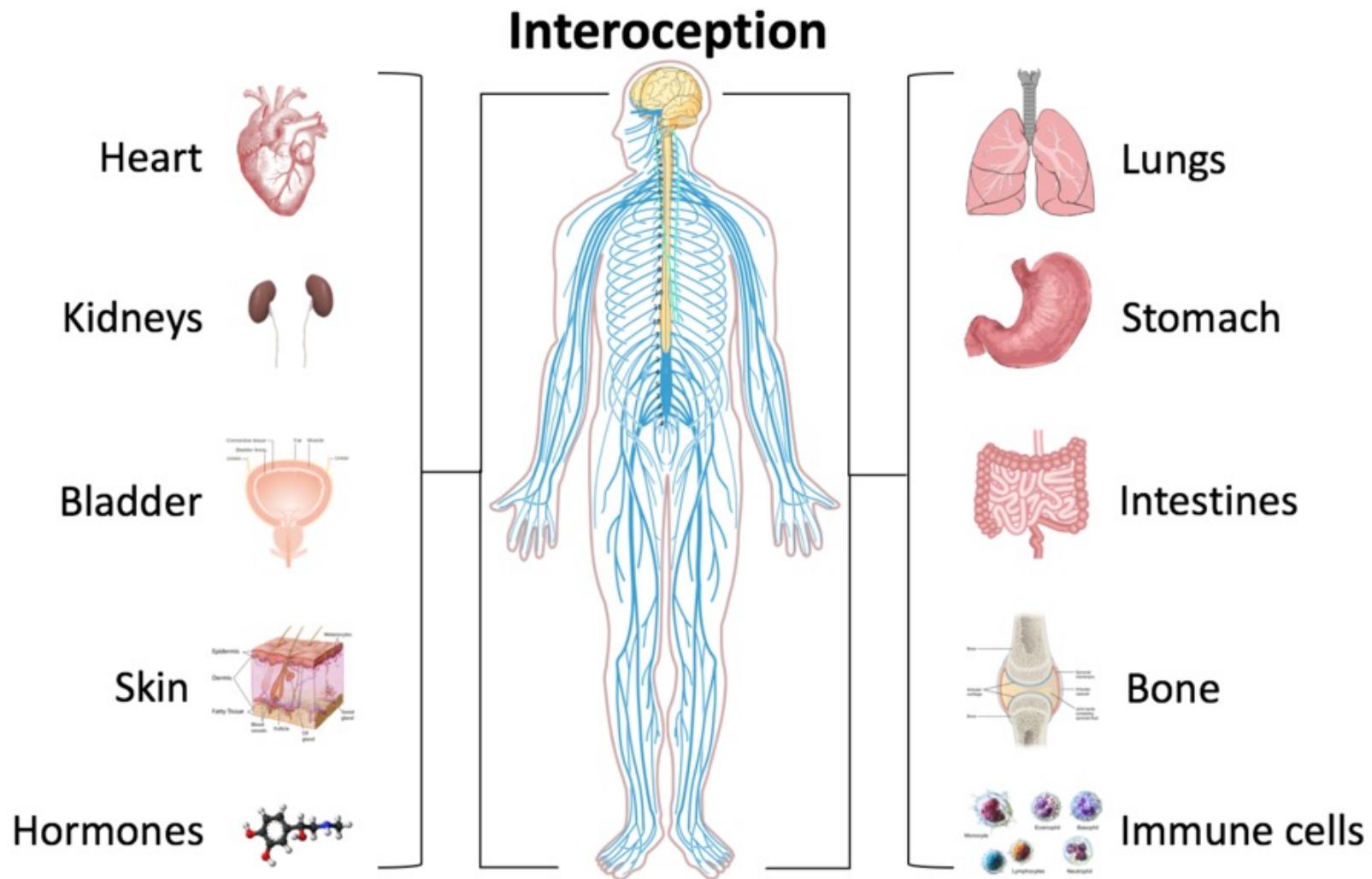
The MAIA has eight dimensions:

1. noticing (e.g., “I notice where in my body I am comfortable”),
2. not-distracting (e.g., “when I feel pain or discomfort, I try to power through it”)
3. not-worrying (e.g., “I can notice an unpleasant body sensation without worrying about it”),
4. attention regulation (e.g., “I can return awareness to my body if I am distracted”),
5. emotional awareness (e.g., “I notice how my body changes when I am angry”),
6. self-regulation (e.g., “I can use my breath to reduce tension”),
7. body listening (e.g., “I listen for information from my body about my emotional state”)
8. trusting (e.g., “I trust my body sensations”).

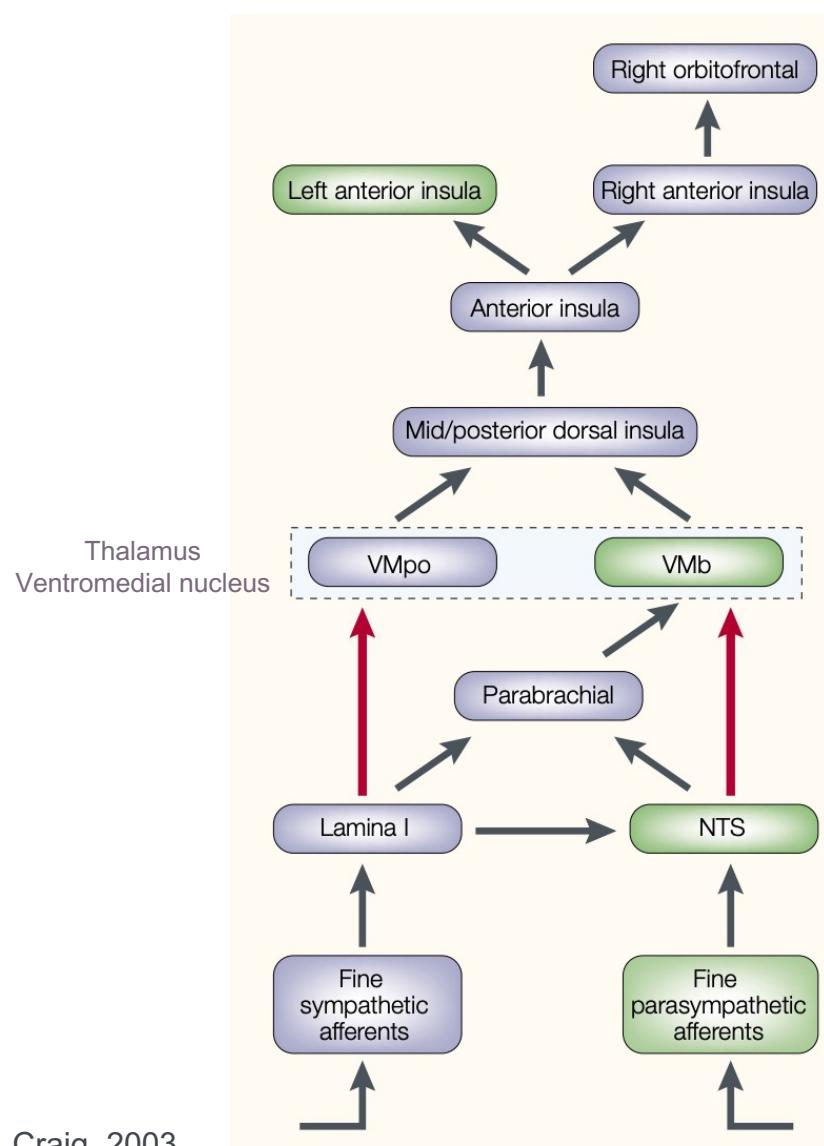
Interoception: role in psychiatric disorders

Psychiatric Disorder	Symptoms	Signs
Panic Disorder	Palpitations, chest pain, dyspnea, choking, nausea, dizziness, flushing, depersonalization/derealization	Elevated heart rate and/or blood pressure, exaggerated escape, startle, and flinching
Depression	Increased or decreased appetite, fatigue, lethargy	Weight gain, weight loss, psychomotor slowing
Eating Disorders	Hunger insensitivity, food anxiety, gastrointestinal complaints	Severe food restriction, severe weight loss, binging, purging, compulsive exercise
Somatic Symptom Disorders	Multiple current physical and nociceptive symptoms	Medical observations do not correspond with symptom report
Substance Use Disorders	Physical symptoms associated with craving, intoxication, and/or withdrawal (drug specific)	Elevated/decreased: heart rate, respiratory rate, and/or blood pressure, pupil dilation/constriction, others (drug specific)
Posttraumatic Stress Disorder	Autonomic hypervigilance, depersonalization/derealization	Exaggerated startle, flinching, and/or escape responses, elevated heart rate and/or blood pressure
Generalized Anxiety Disorder	Muscle tension, headaches, fatigue, gastrointestinal complaints, pain	Trembling, twitching, shaking, sweating, nausea, exaggerated startle
Depersonalization/Derealization Disorder	Detachment from one's body, head fullness, tingling, lightheadedness	Physiological hyporeactivity to emotional stimuli
Autism Spectrum Disorders	Skin hypersensitivity	Selective clothing preferences

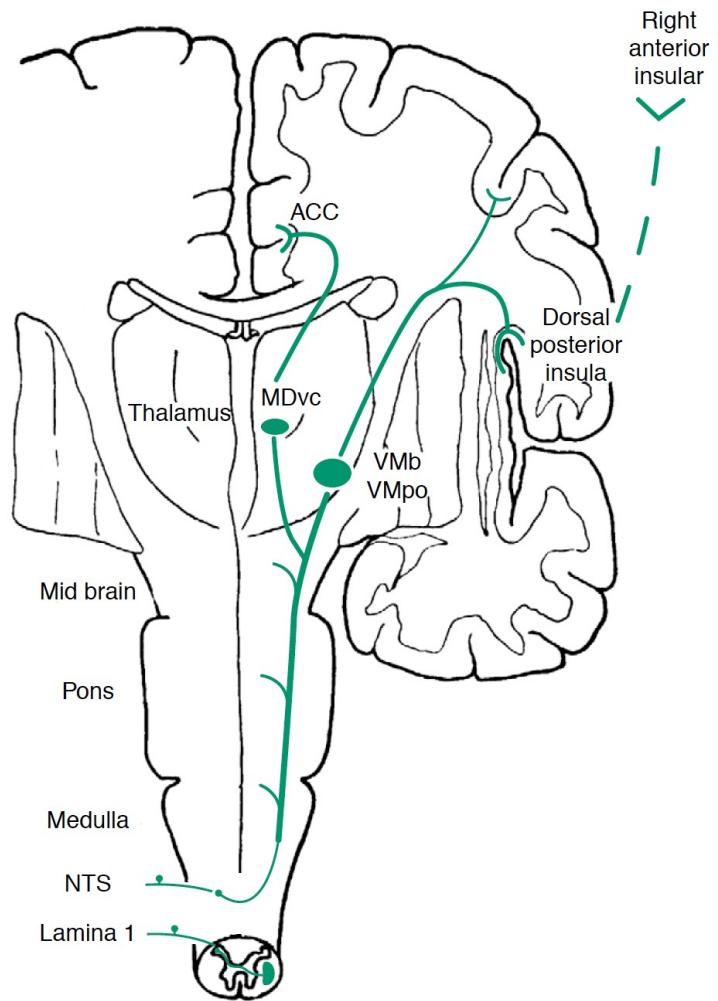
Interoception: visceral ascending pathways



Interoception: visceral ascending pathways

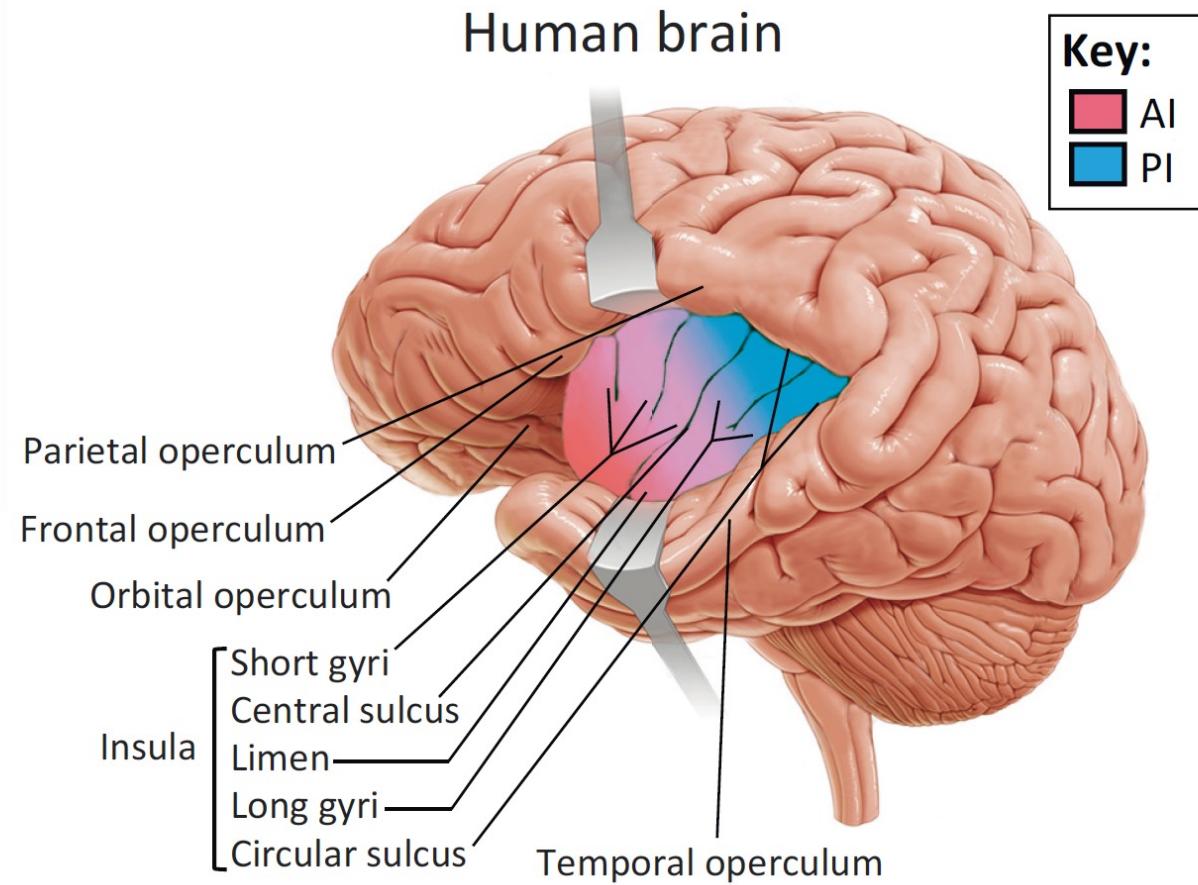


Craig, 2003

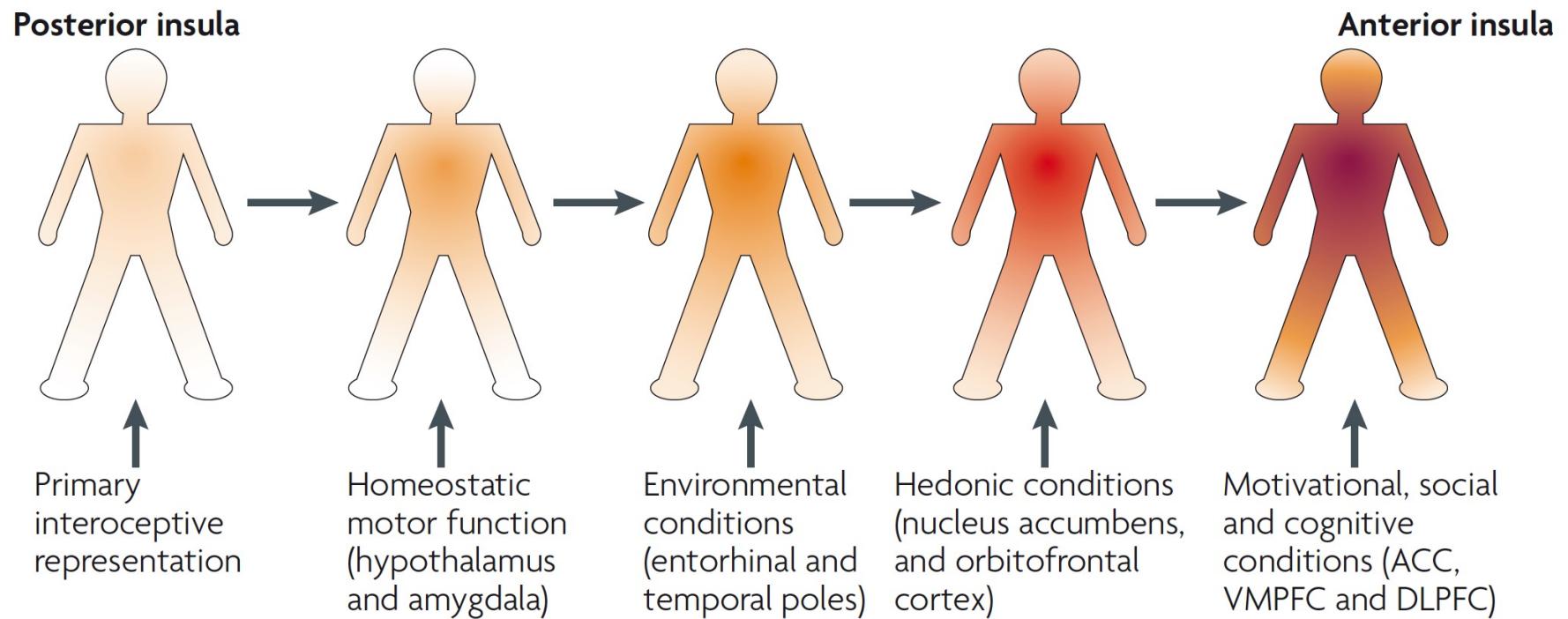


Craig, 2004

Interoception: the insula

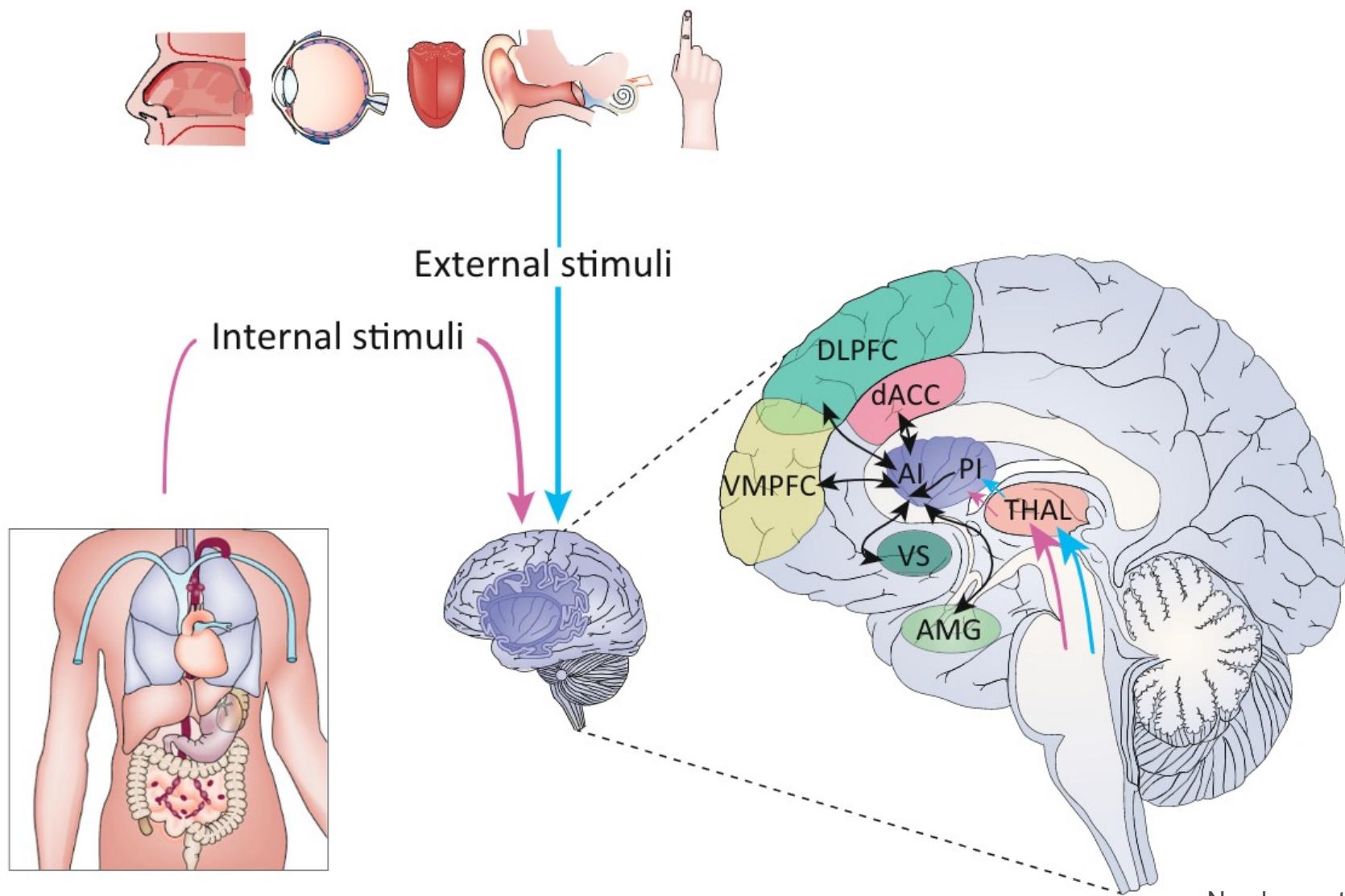


Interoception & insula



Craig, 2004

Interoception: integration of bodily experiences and external cues



Namkung et al., 2017

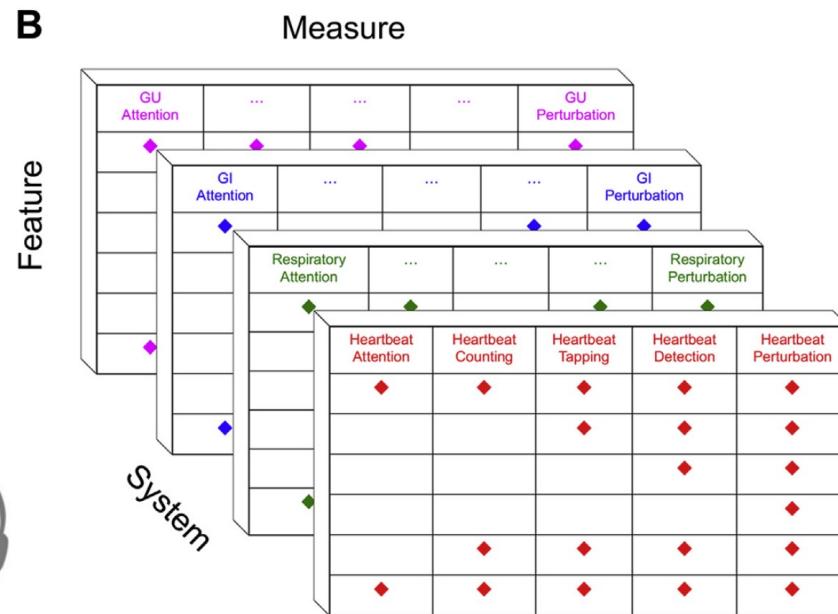
The insula: from sensations to predictions

The insula: from sensations to predictions

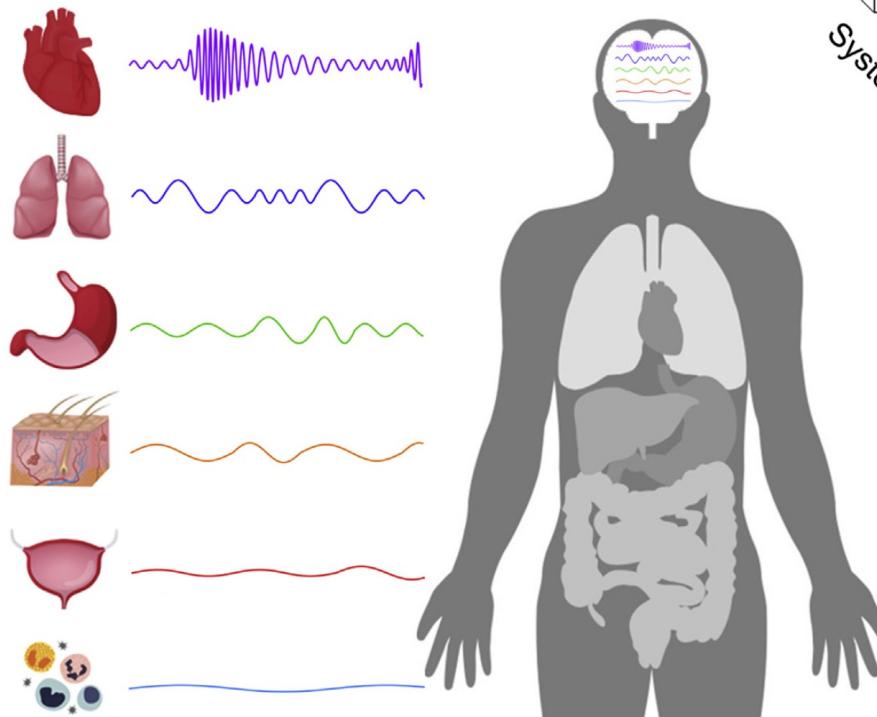
A

Feature	Heartbeat Attention	Heartbeat Counting	Heartbeat Tapping	Heartbeat Detection	Heartbeat Perturbation
Attention	♦	♦	♦	♦	♦
Detection			♦	♦	♦
Discrimination				♦	♦
Intensity					♦
Accuracy		♦	♦	♦	♦
Self report	♦	♦	♦	♦	♦

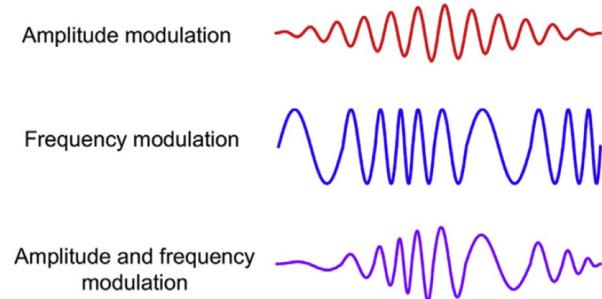
B



C

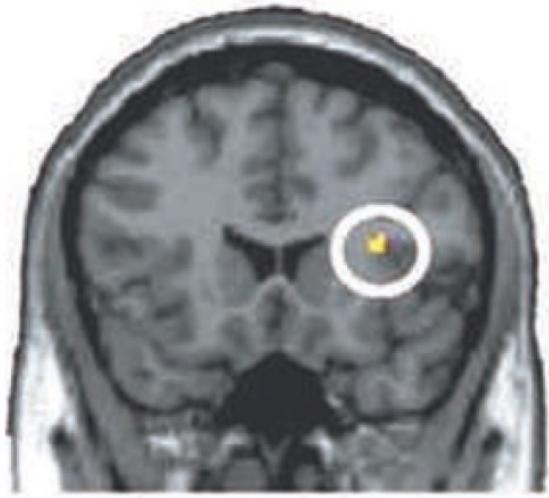


D

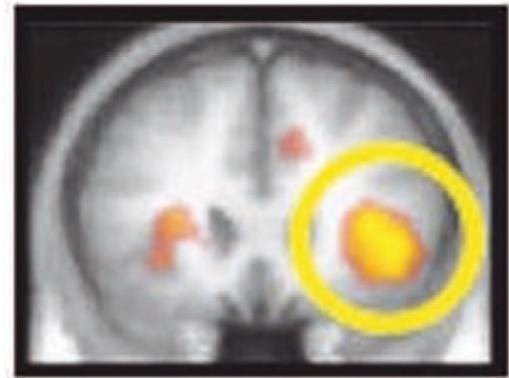


Subjective appraisal of interoceptive cues

Heartbeat awareness



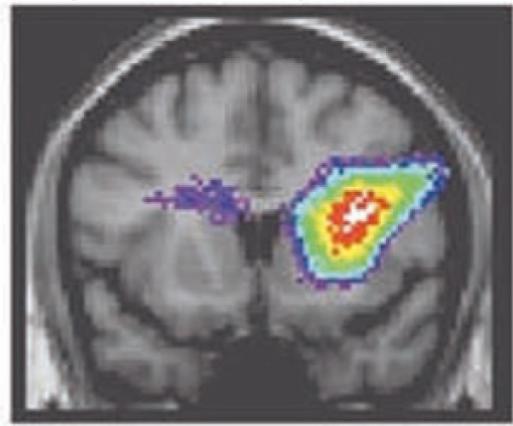
Attention to heat pain



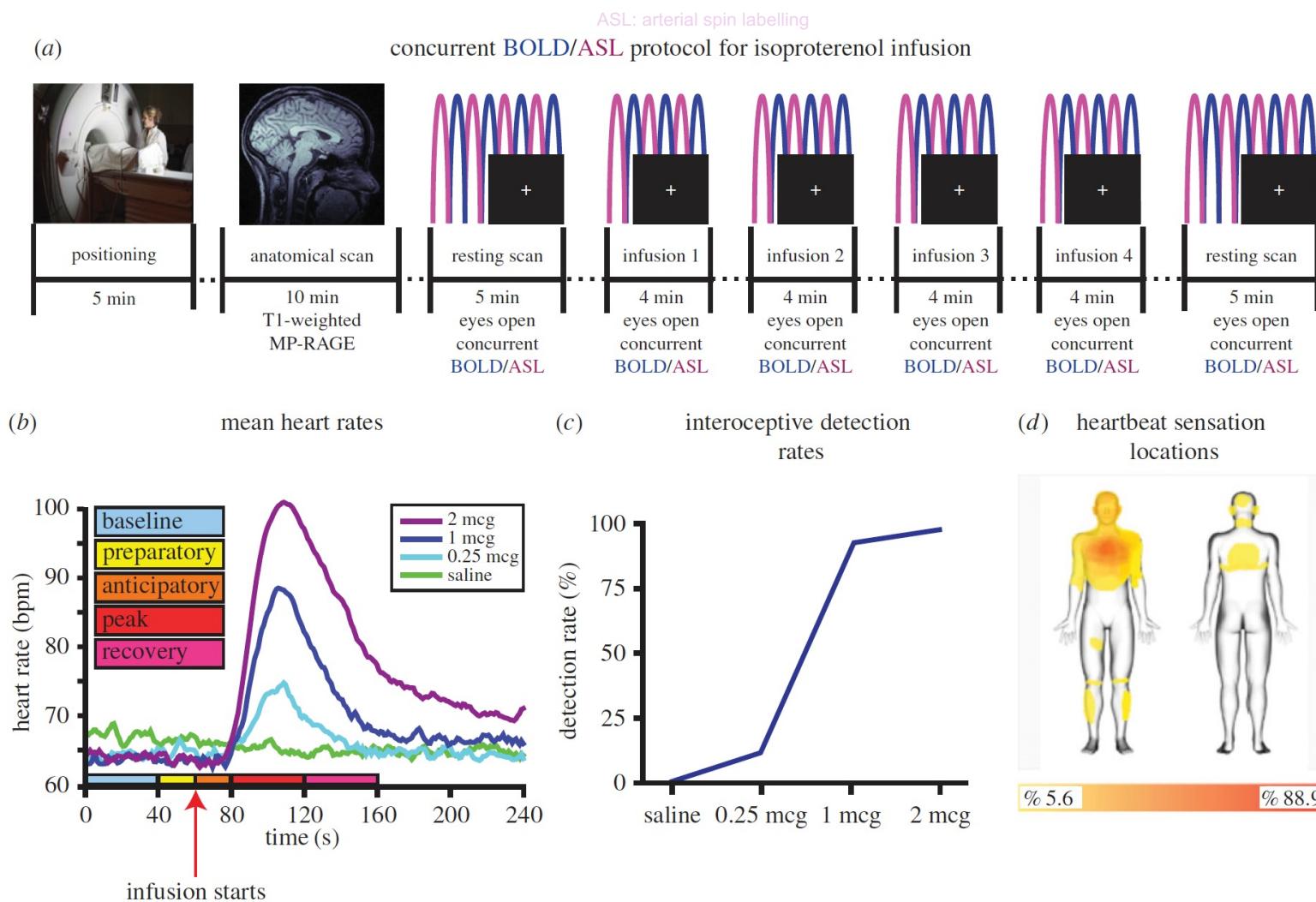
Learned pain 'now'



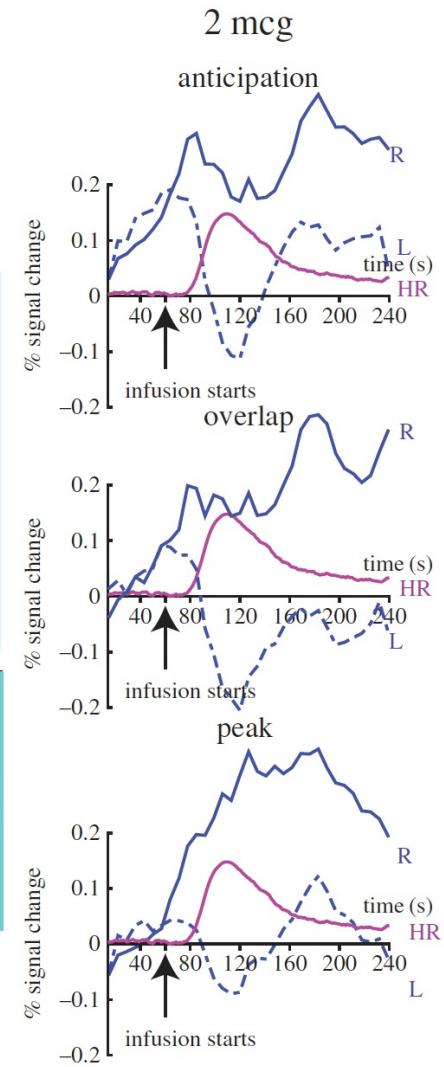
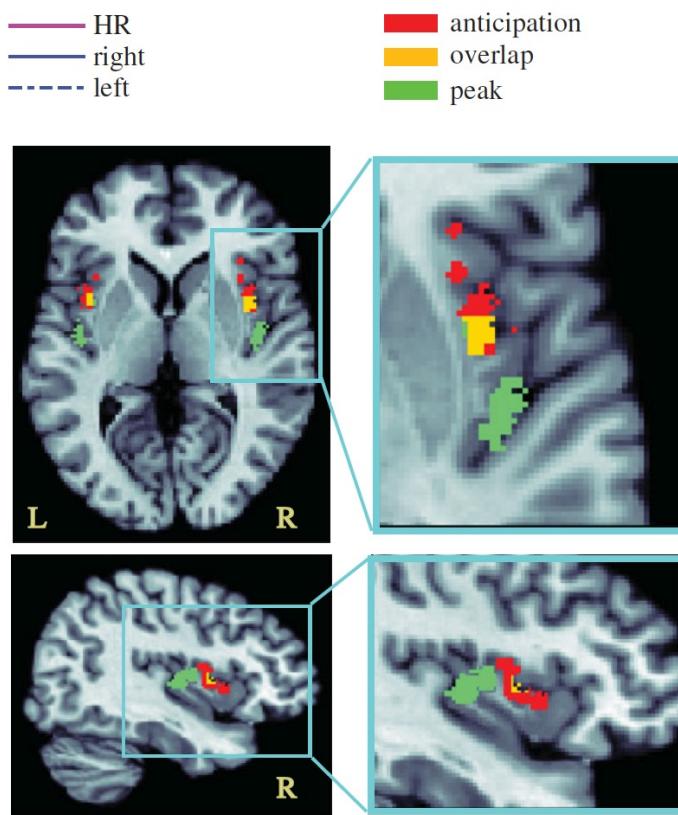
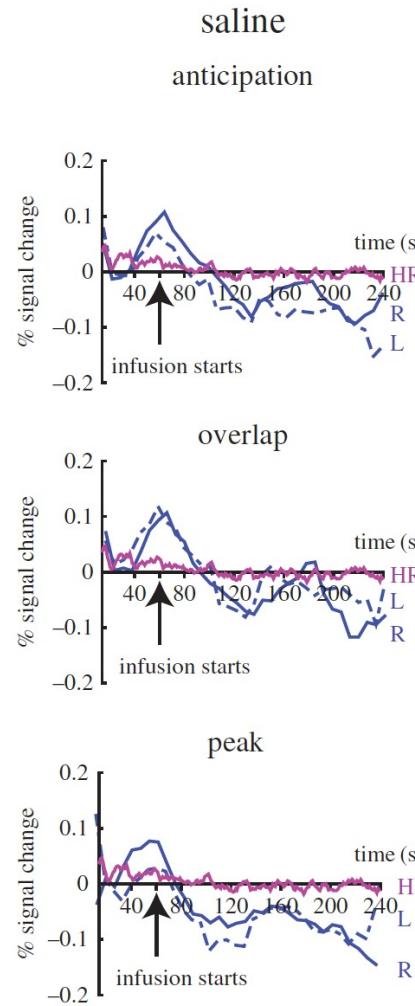
Subjective cooling



Subjective appraisal of interoceptive cues: cardiovascular interoception

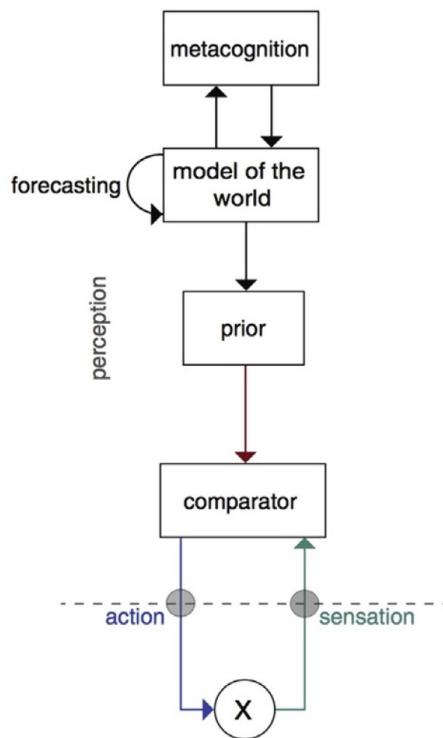


Subjective appraisal of interoceptive cues: cardiovascular interoception and prediction

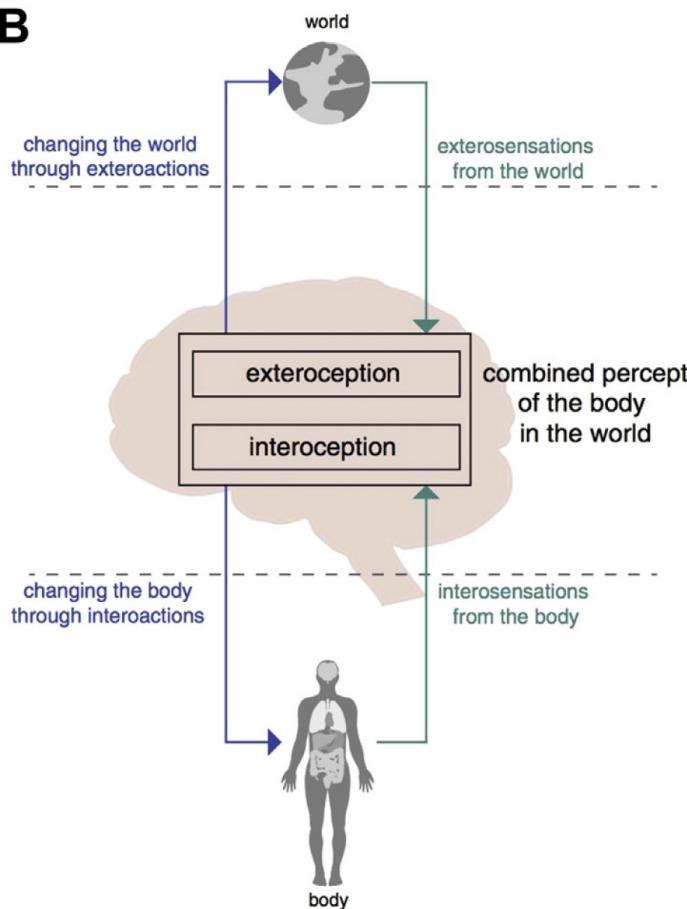


The insula: from sensations to predictions

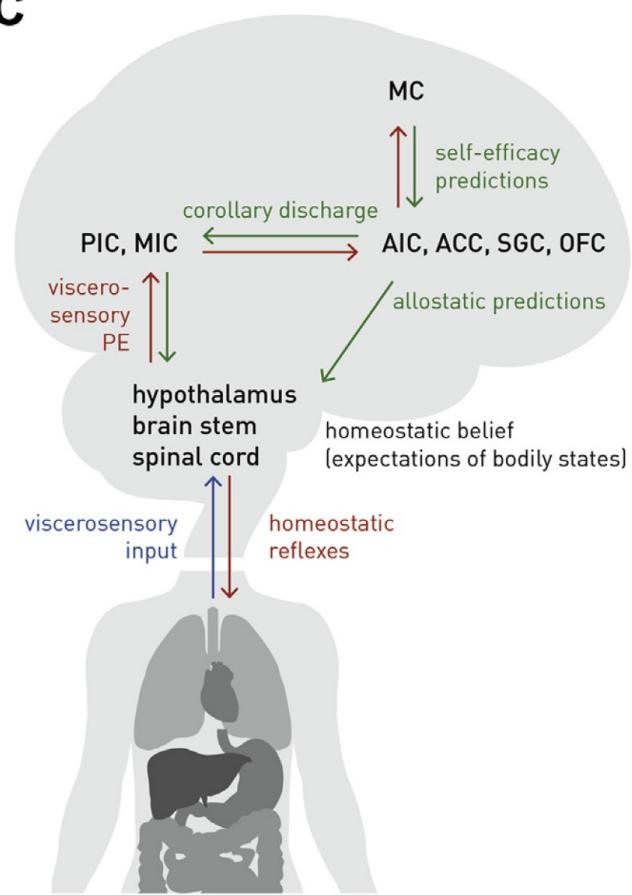
A



B



C



ACC, anterior cingulate cortex; AIC, anterior insular cortex; MC, metacognitive layer; MIC, midinsular cortex; OFC, orbitofrontal cortex; PE, prediction error; PIC, posterior insular cortex; SGC, subgenual cortex

Towards a somatic marker hypothesis

Somatic markers (SM) are a special instance of feelings generated from secondary emotions.

Those emotions and feelings have been connected by learning to predicted future outcomes of certain scenarios.

When a negative SM is juxtaposed to a particular future outcome the combination functions as an alarm bell. When a positive SM is juxtaposed instead, it becomes a beacon of incentive.

This is the essence of the SMH.

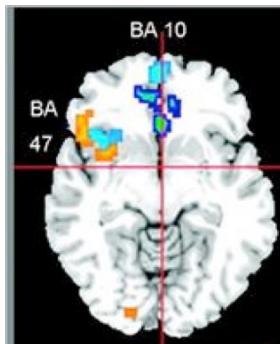
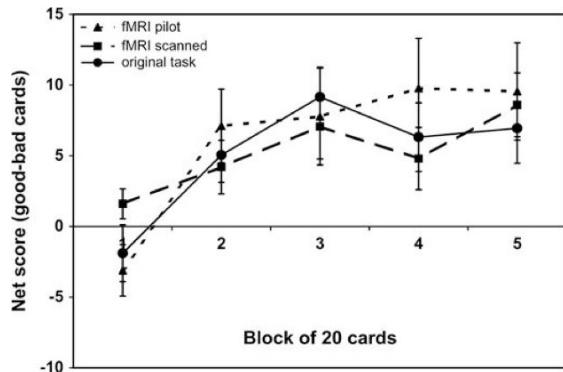
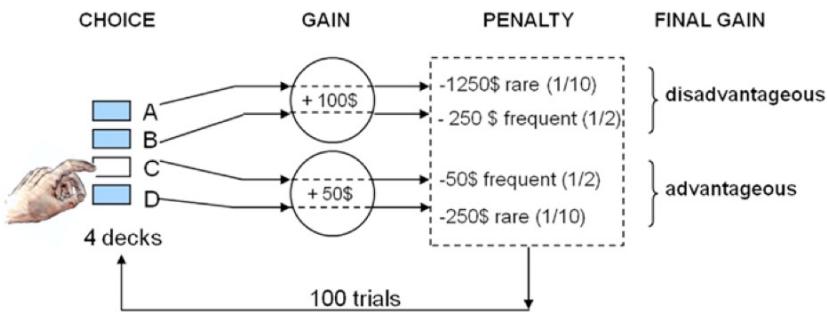
On occasion SMs may operate covertly (without coming to consciousness) and may utilize an 'as-if-loop'.

The insula, interoception and decision making

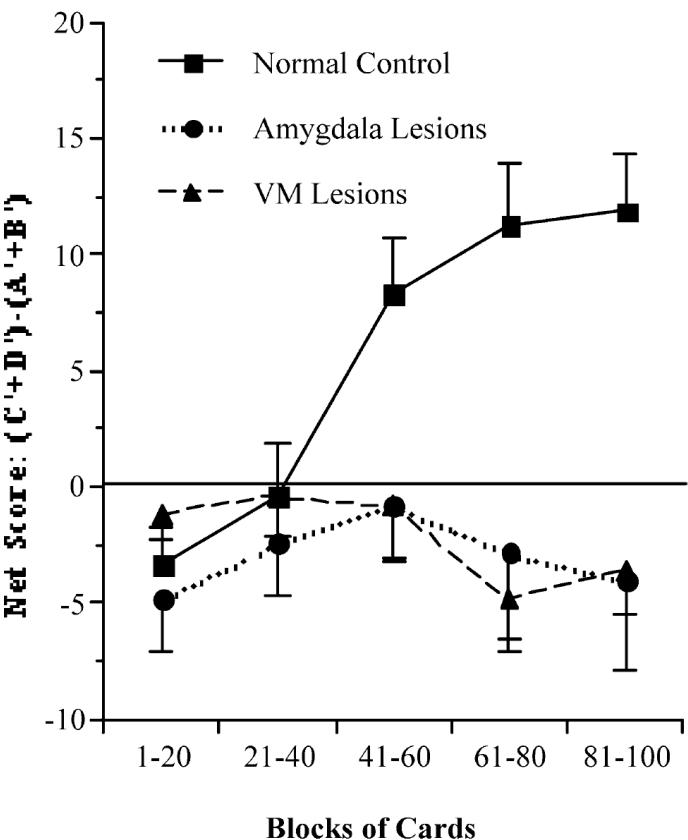


The insula, interoception and decision making

Iowa Gambling Task



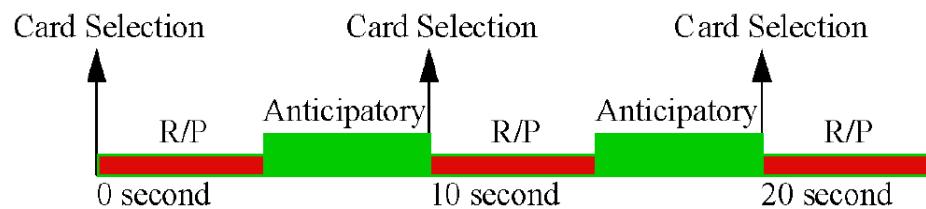
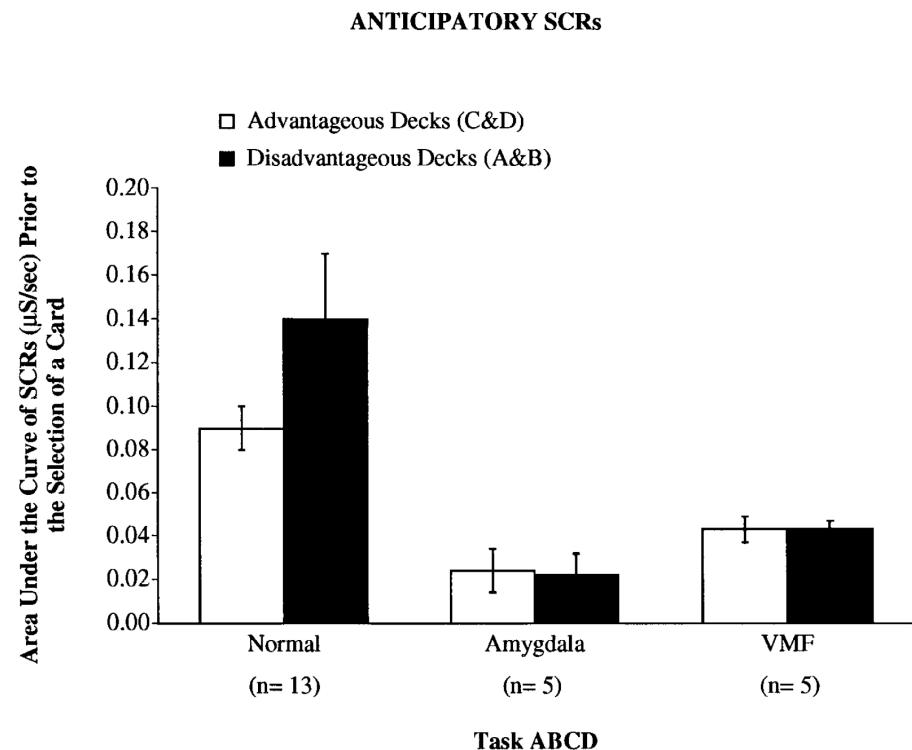
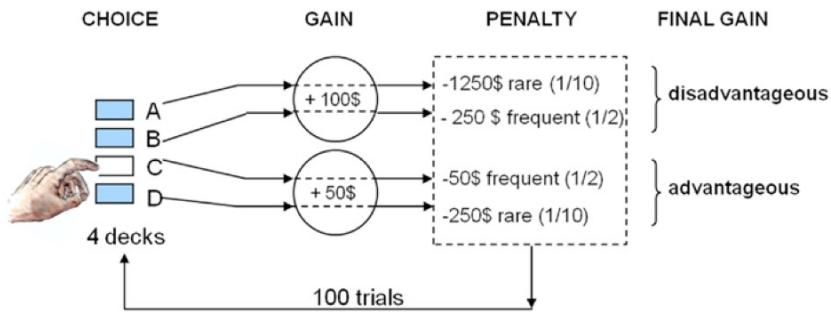
Behavioral Performance on A'B'C'D'



Bechara & Damasio, 2005

The insula, interoception and decision making

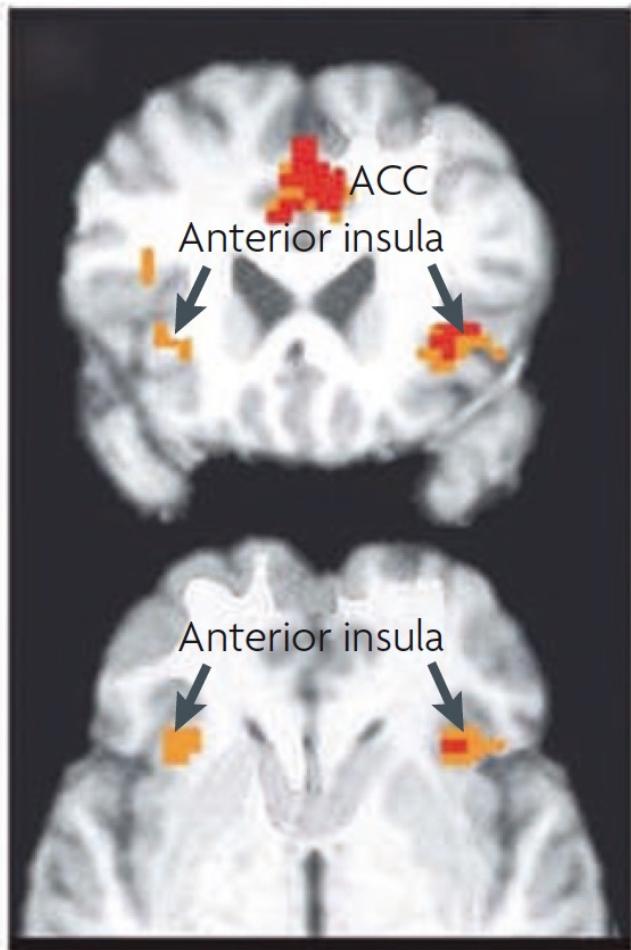
Iowa Gambling Task



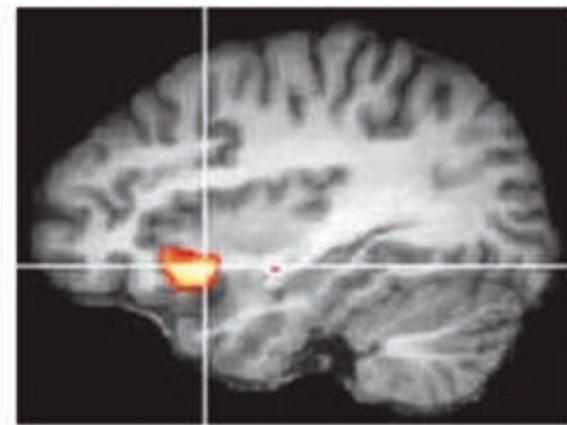
Bechara et al., 1999;
Bechara & Damasio, 2005

The insula, interoception and decision making

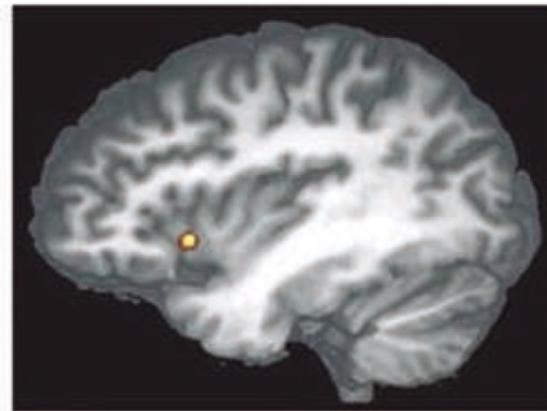
Decision making



"Free won't"

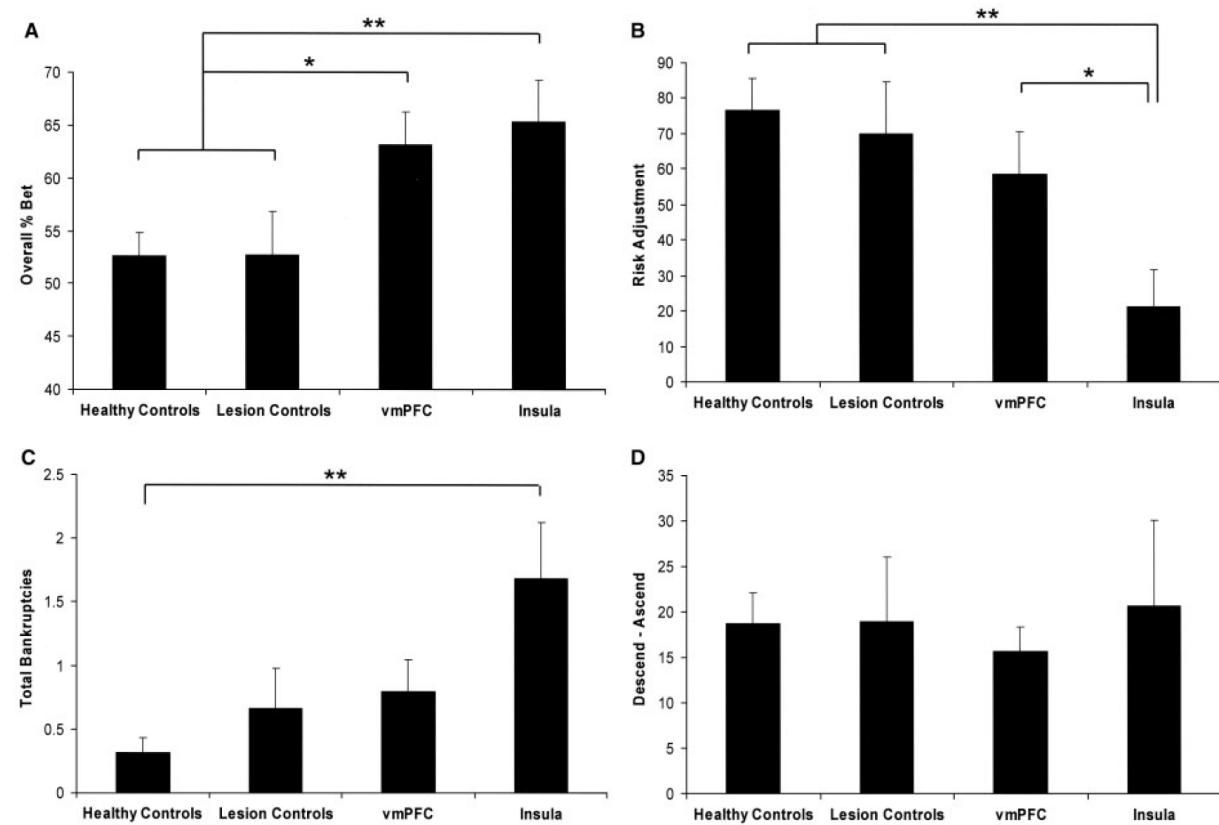
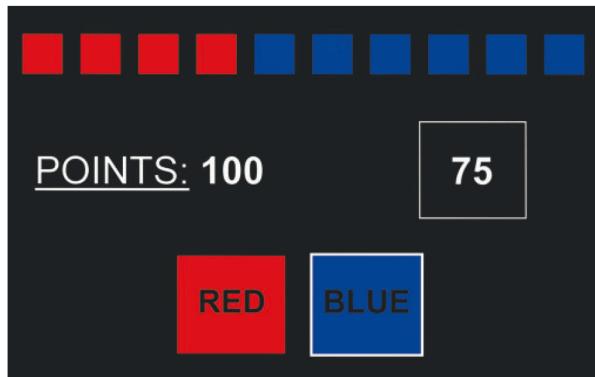


Error awareness



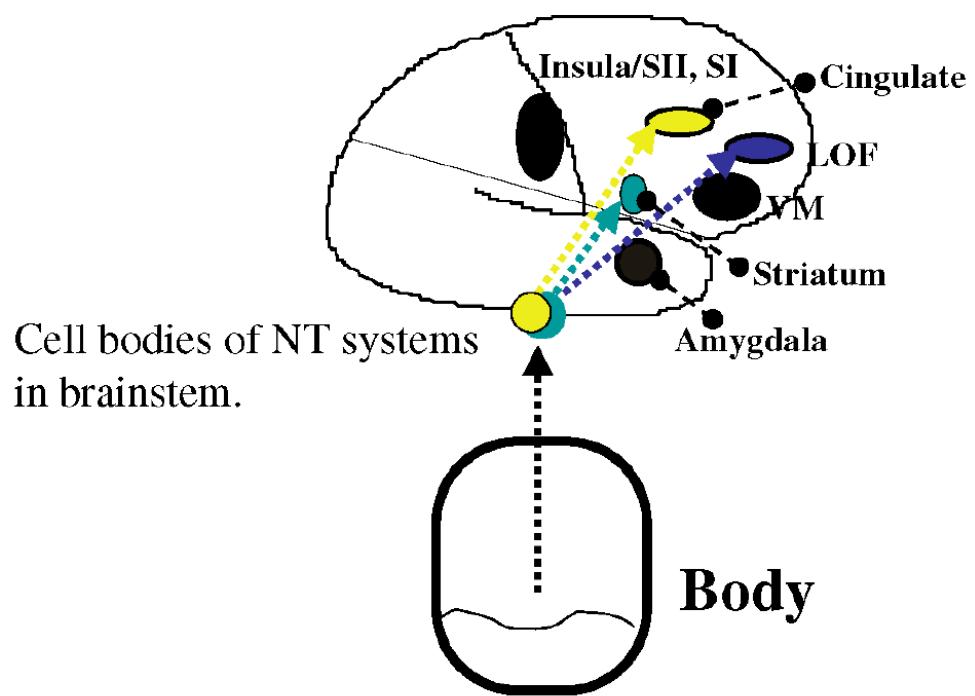
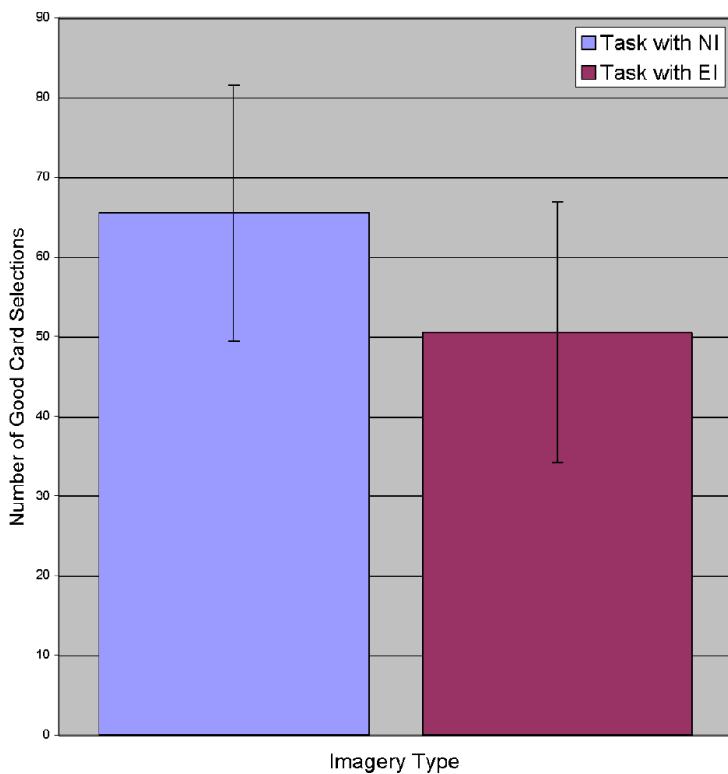
The insula, interoception and decision making

Decision-making under risk: The Cambridge Gamble task

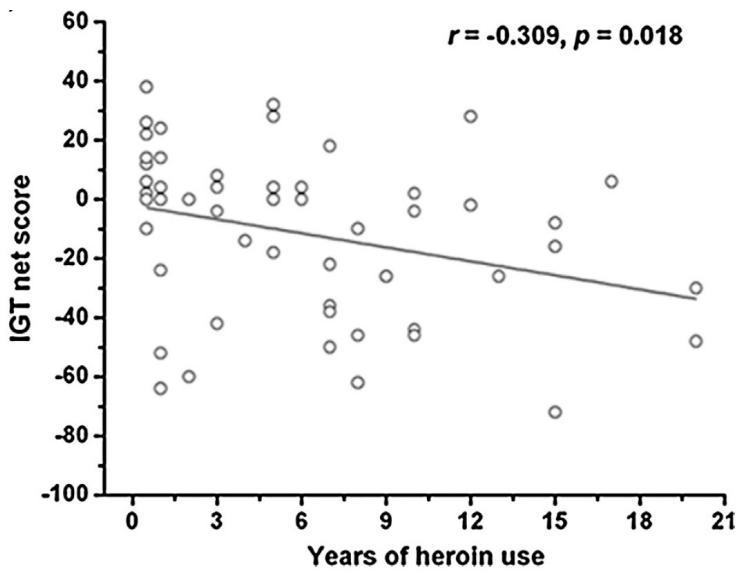
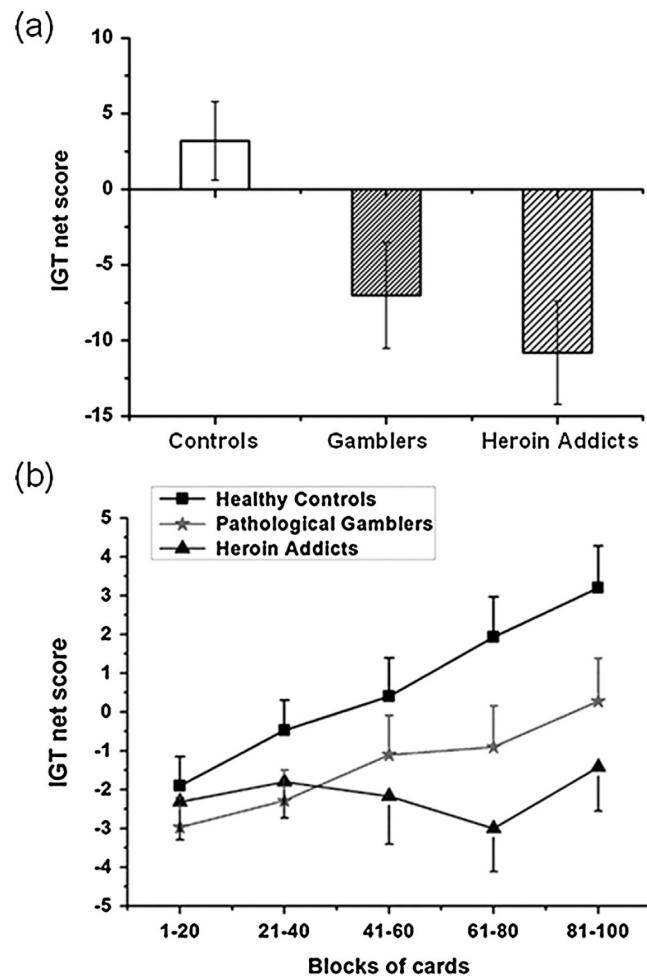


Emotional influence on decision making

Average Gambling Task Performance Following
Neutral Imagery vs. Emotion Imagery



Decision making is impaired in drug addiction and pathological gambling



→ Alteration of somatic markers in Impulsive/Compulsive Disorders (see lecture 4)

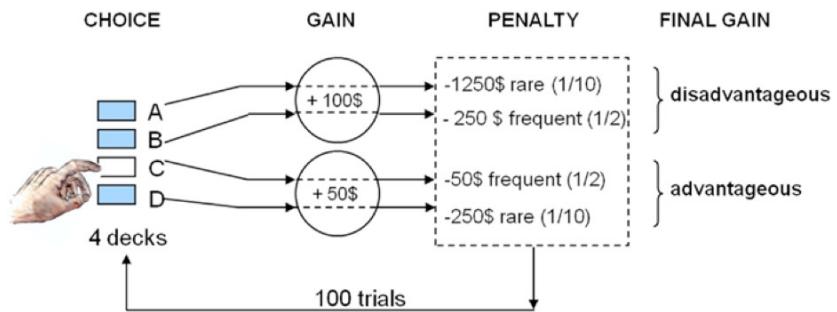
Yan et al., 2014

The insula, interoception and decision making

Causal evidence in human studies is always limited by the specificity of the lesion

The anterior insula contributes to decision making in the rat

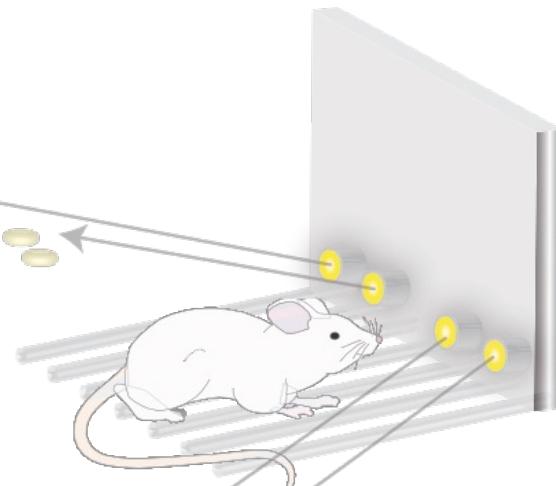
Iowa Gambling Task



Rat Gambling Task

Disadvantageous choices

$$P(444s \text{ TO}) = 0.25 + \text{yellow circle}$$
$$P(222s \text{ TO}) = 0.5 + \text{yellow circle}$$

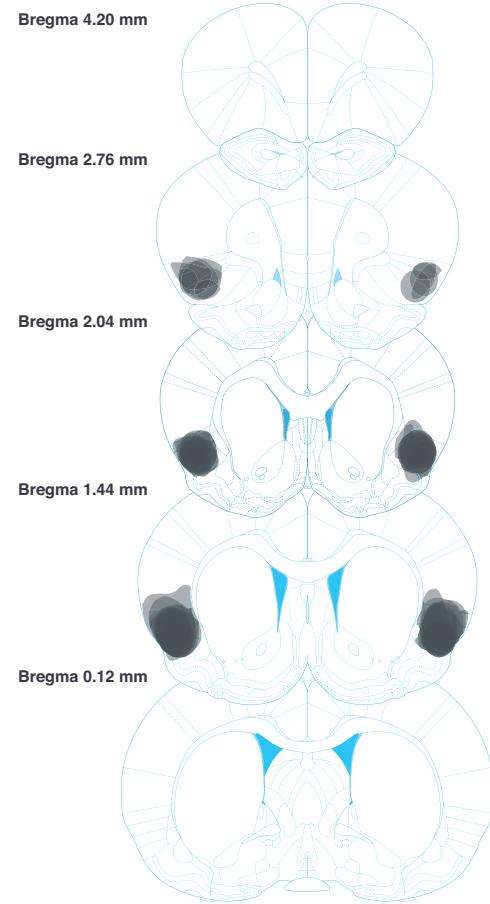
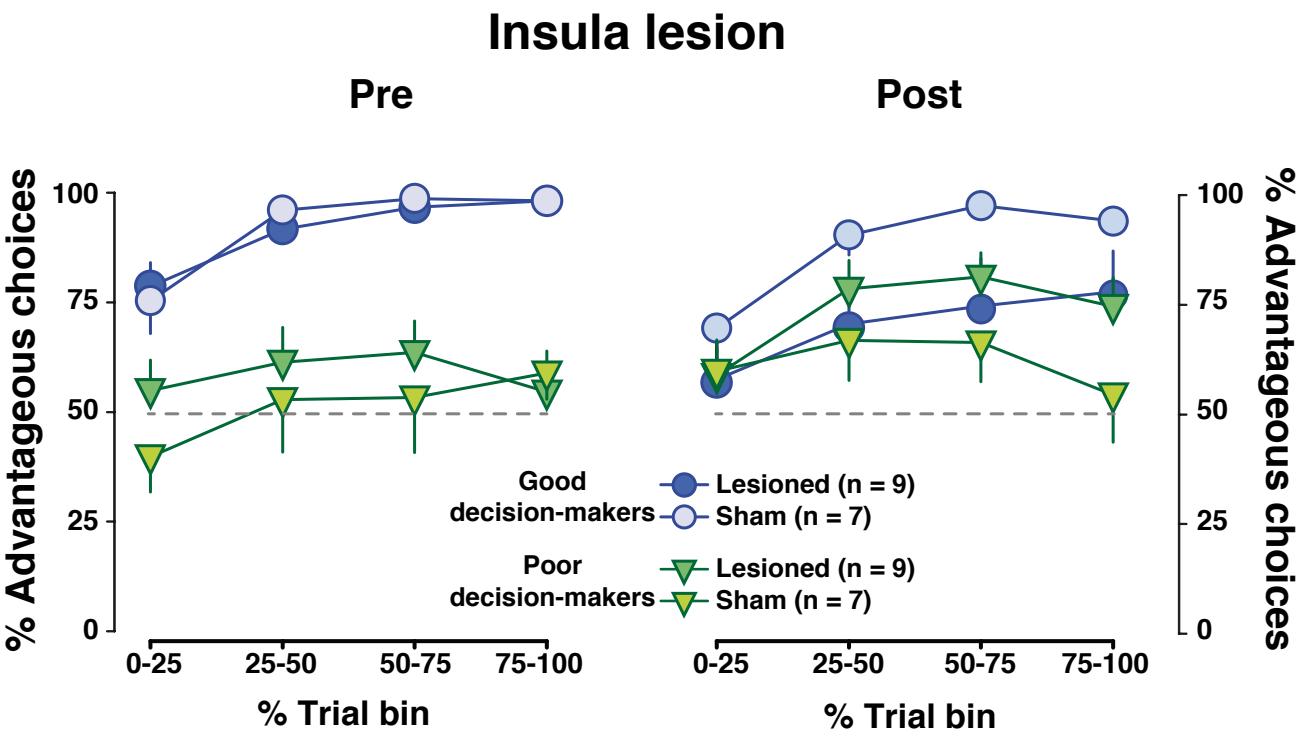
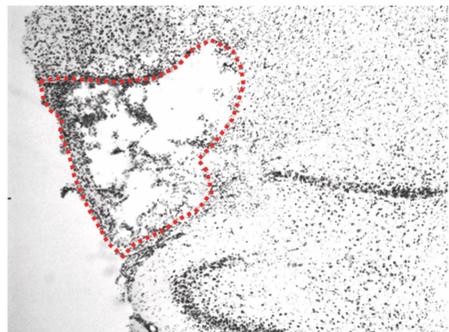


Advantageous choices

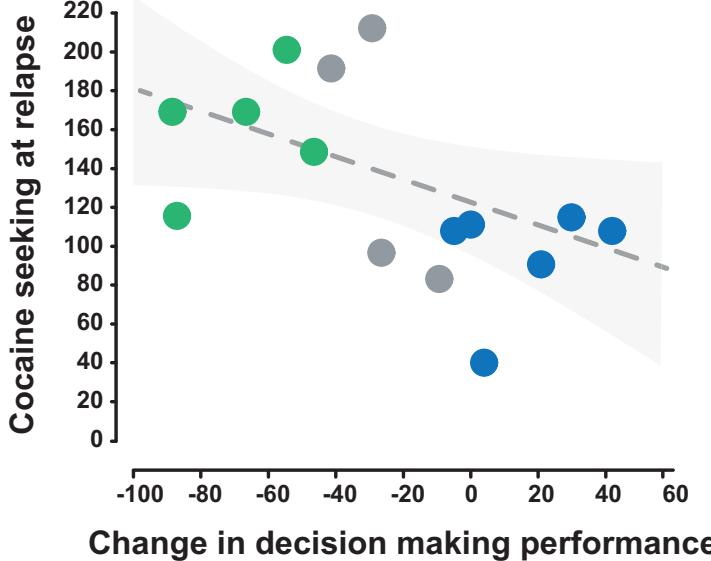
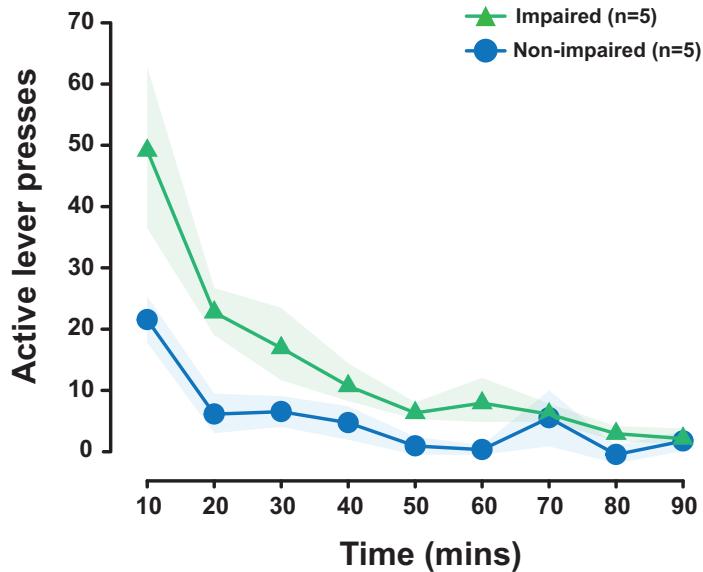
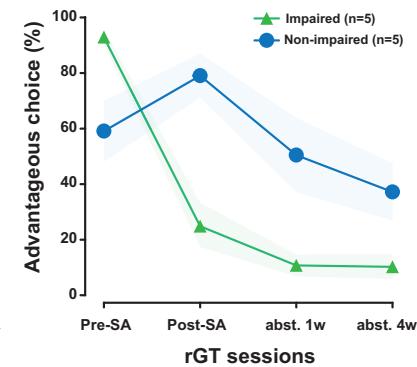
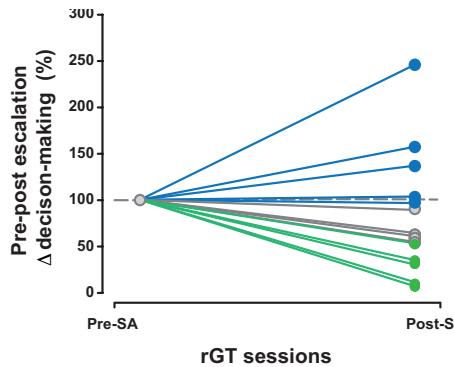
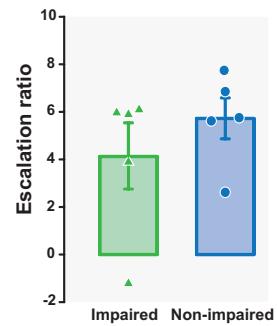
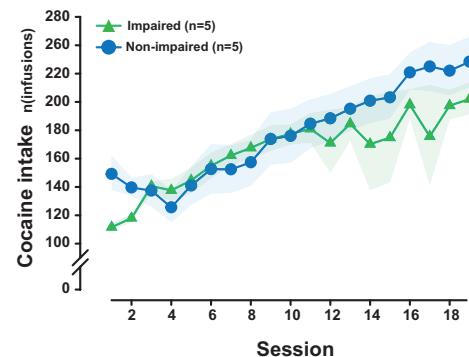
$$P(6s \text{ TO}) = 0.5 + \text{yellow circle}$$
$$P(12s \text{ TO}) = 0.25 + \text{yellow circle}$$



The anterior insula contributes to decision making in the rat



Drug-induced impairment in decision making predicts vulnerability to relapse in the rat



Conclusions

Interoception: the sense of the physiological condition of the body

Interoceptive mechanisms can be implicit or explicit (requires attention)

Interoceptive mechanisms can be used as predictors of emotionally significant outcomes following associative learning (prediction-error)
→ teaching signal / Somatic marker hypothesis

Interoceptive mechanisms depend on a brain network involving the VMPFC, ACC, Amygdala and the **insula**

The Insula is the interoceptive cortex and it is involved in (almost) every interoceptive mechanism and associated emotions as well as in their influence on executive functions such as decision making

Interoception and emotion regulation

Emotion regulation involves a coherent relationship with the self, specifically effective communication between body, mind, and feelings.

→ The processes by which individuals modulate their emotional experiences, expressions, and the situations giving rise to the emotion

Effective emotion regulation involves the ability to accurately detect and evaluate cues related to physiological reactions to stressful events, accompanied by appropriate regulation strategies that temper and influence the emotional response.

→ As emotions unfold over time, emotion regulation strategies are often differentiated along the timeline of the emotion-generative process

→ Consequently, two types of regulation strategies can be defined on the basis of whether they are used

before response tendencies become active

(i.e., antecedent-focused)

or once the emotional response has been triggered (i.e., response-focused).

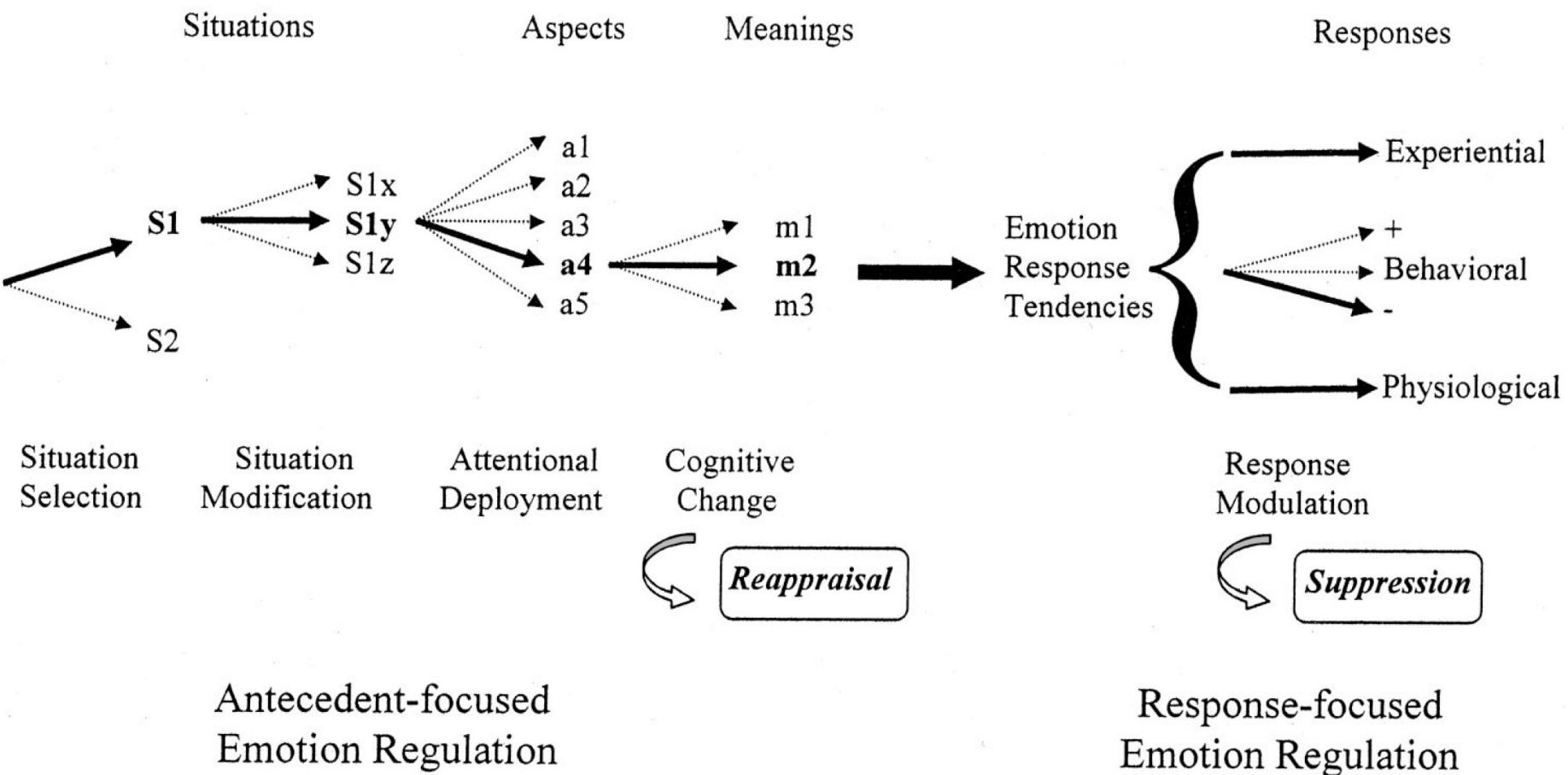
→ Requires assessment of interoceptive cues and their emotional valence

Interoception and emotion regulation

There is compelling evidence demonstrating links between poor or disrupted awareness of sensory information, or interoceptive awareness, and difficulties with emotion regulation.

→ Anxiety may result from fear of interoceptive emotional inputs

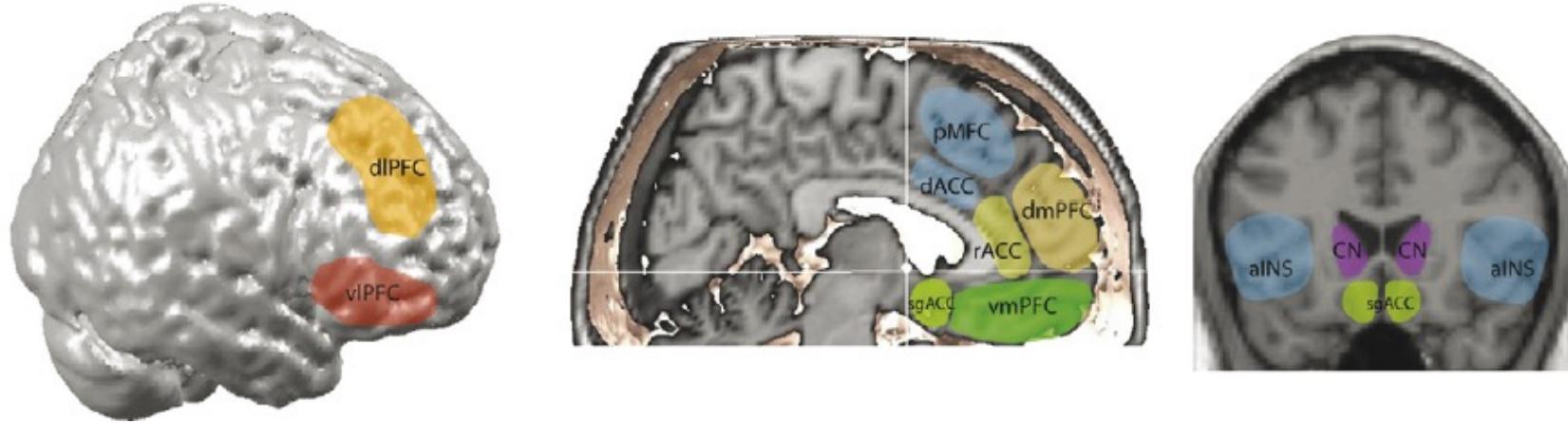
Interoception and emotion regulation



➔ Reappraisal and suppression are a successful regulation strategies that pertain to positive emotion regulation in everyday life

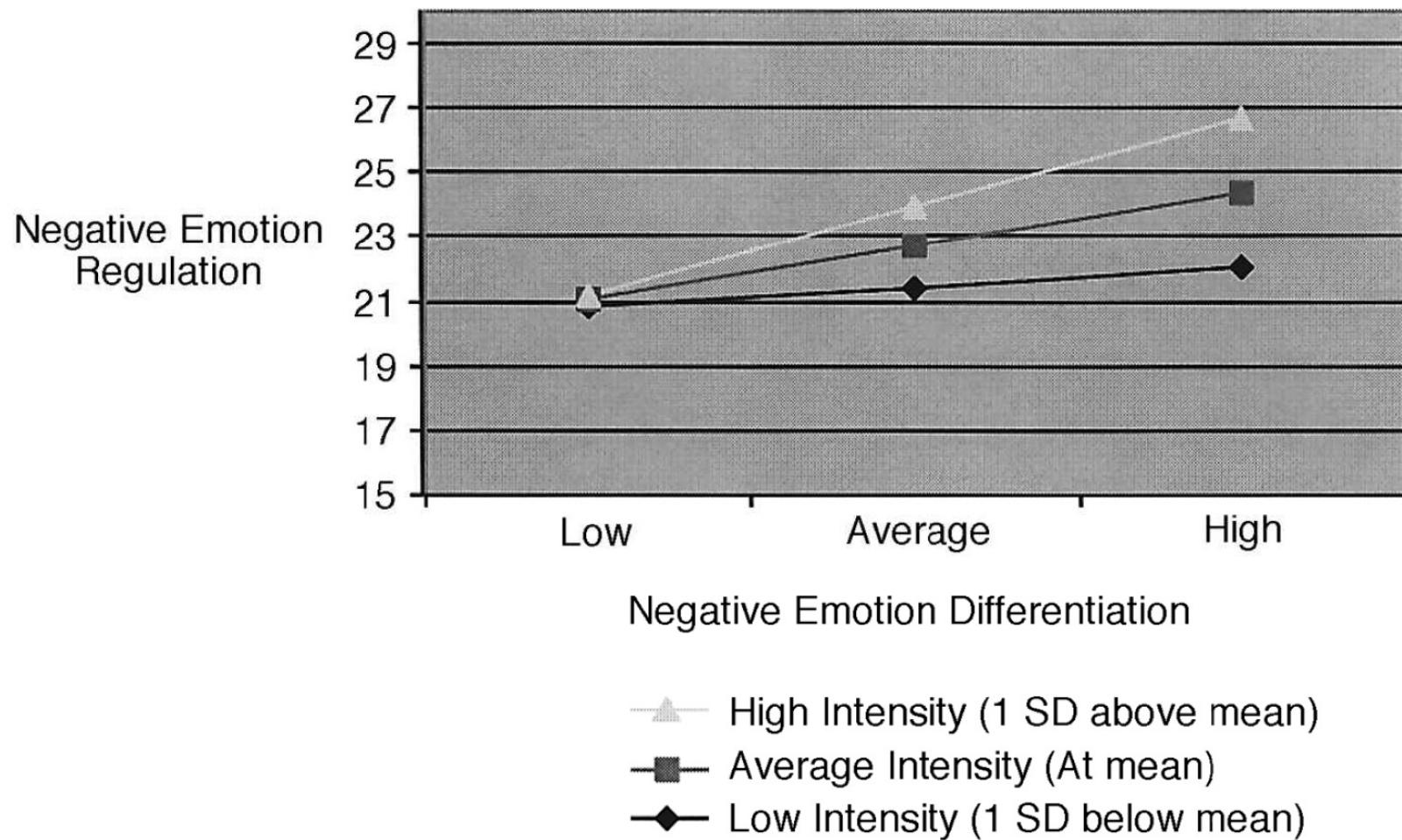
Gross & John, 2003

Emotion regulation, cognition/emotion interactions and the insula



Taylor & Liberzon 2007

Interoception accuracy predicts emotion regulation

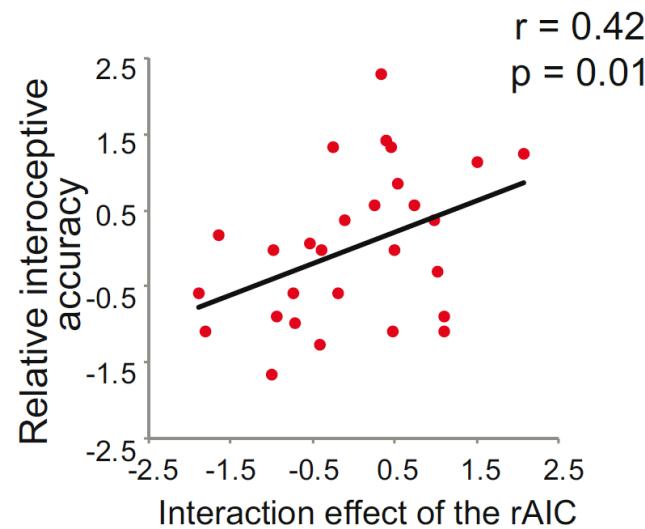
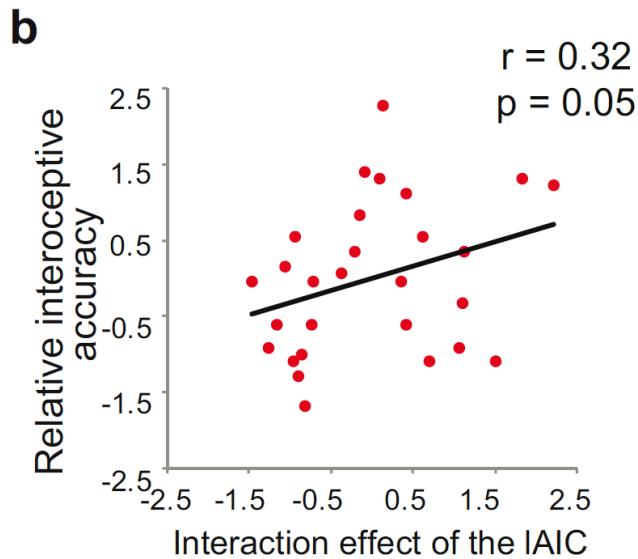
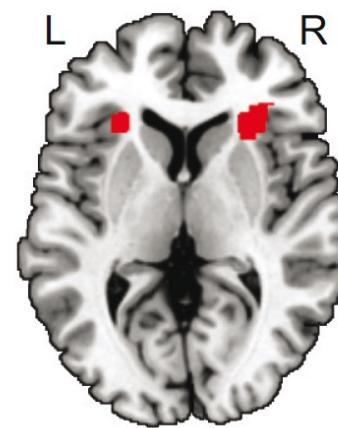
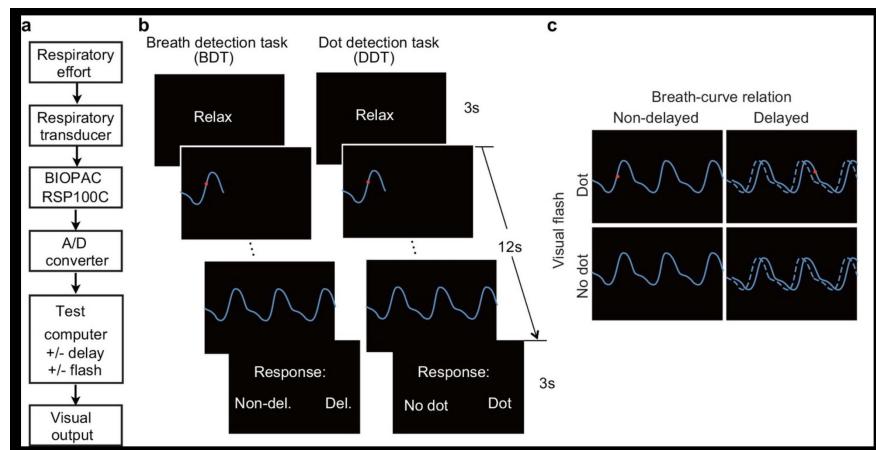


Emotion regulation: repetitive body-focused behaviours

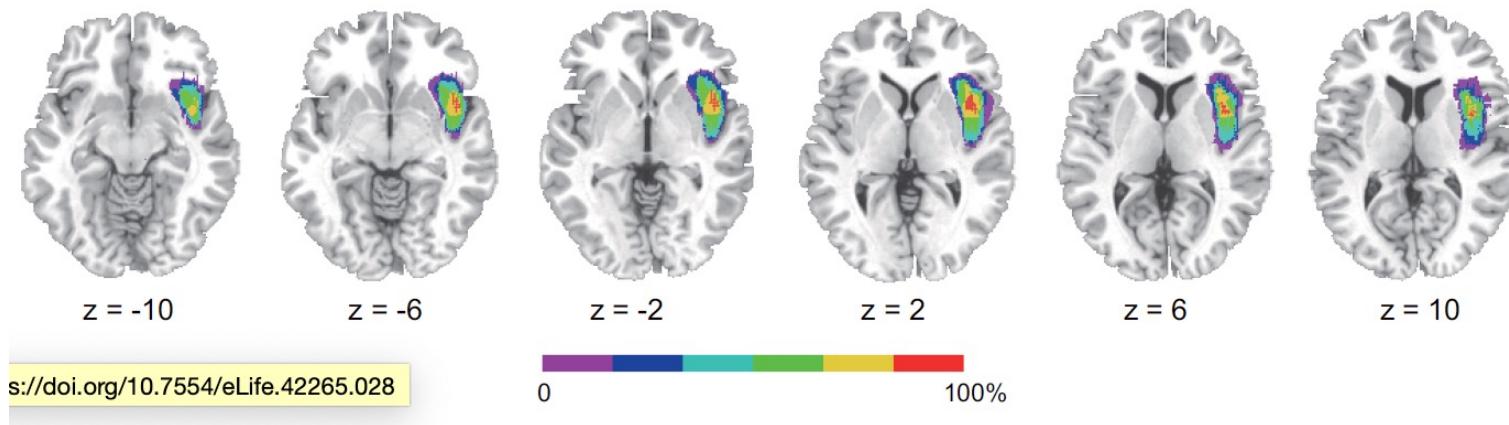


Roberts et al., 2013

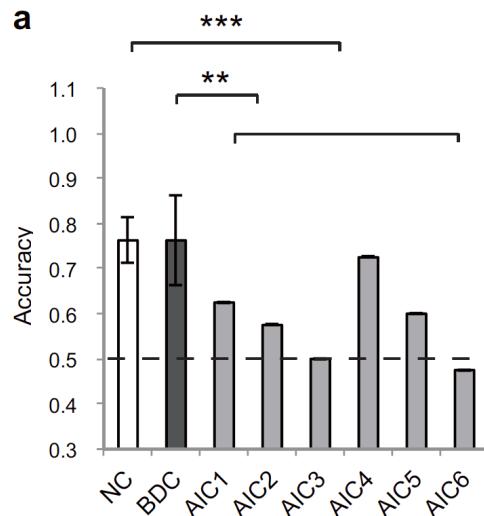
The insula: neural locus of attention to interoceptive cues



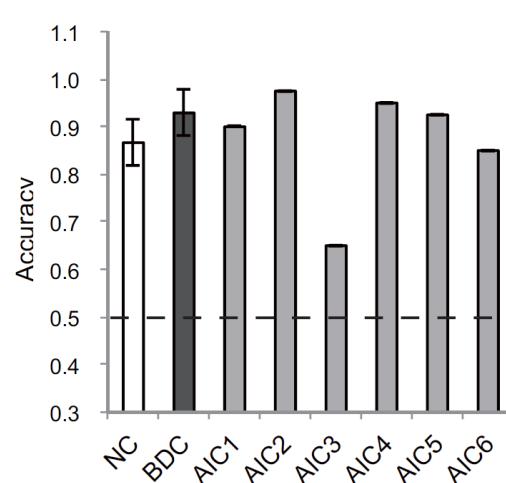
The insula: neural locus of attention to interoceptive cues



Interoception

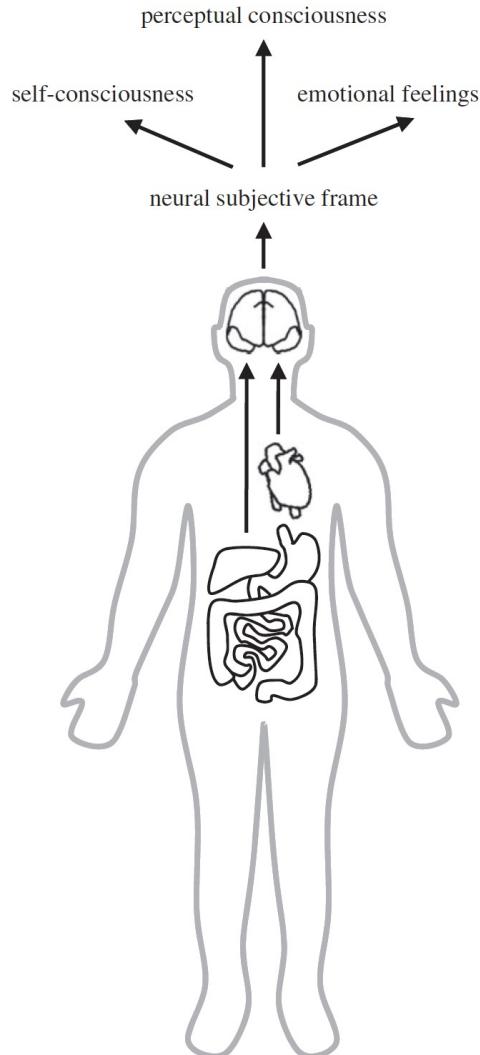


Exteroception



Wang et al., 2019

Interoception and the neural subjective frame



→ Detection of exteroceptive cues

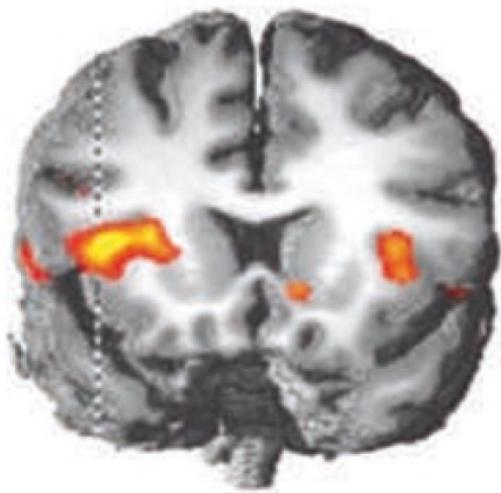
→ memory

→ Emotional labelling/assessment

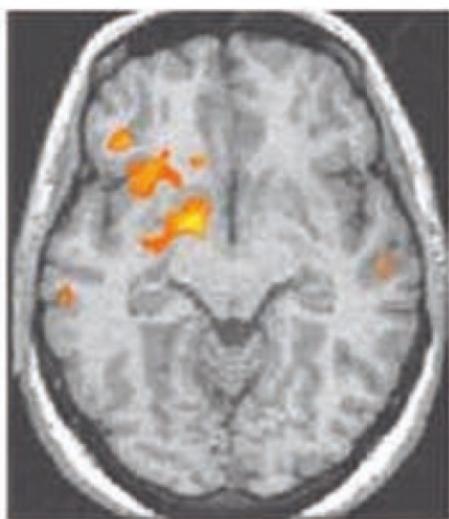
→ Internal cues have priority over external ones

Subjective appraisal of emotionally relevant exteroceptive cues

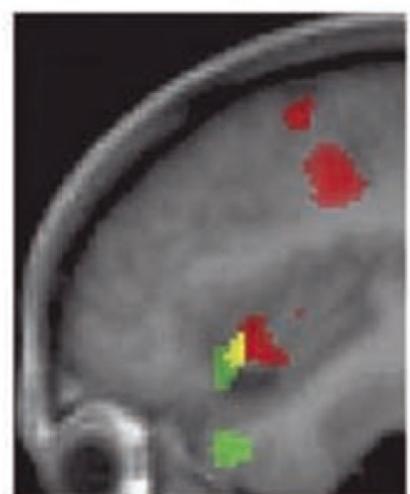
Pleasant music



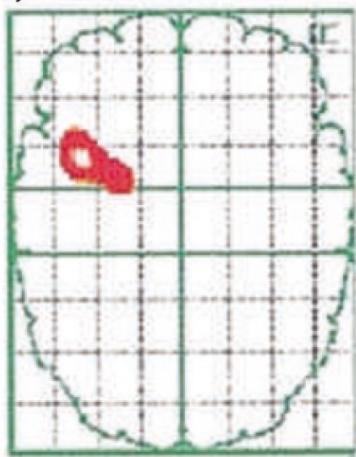
Maternal affiliation



Seeing or making a smile



Rhythm



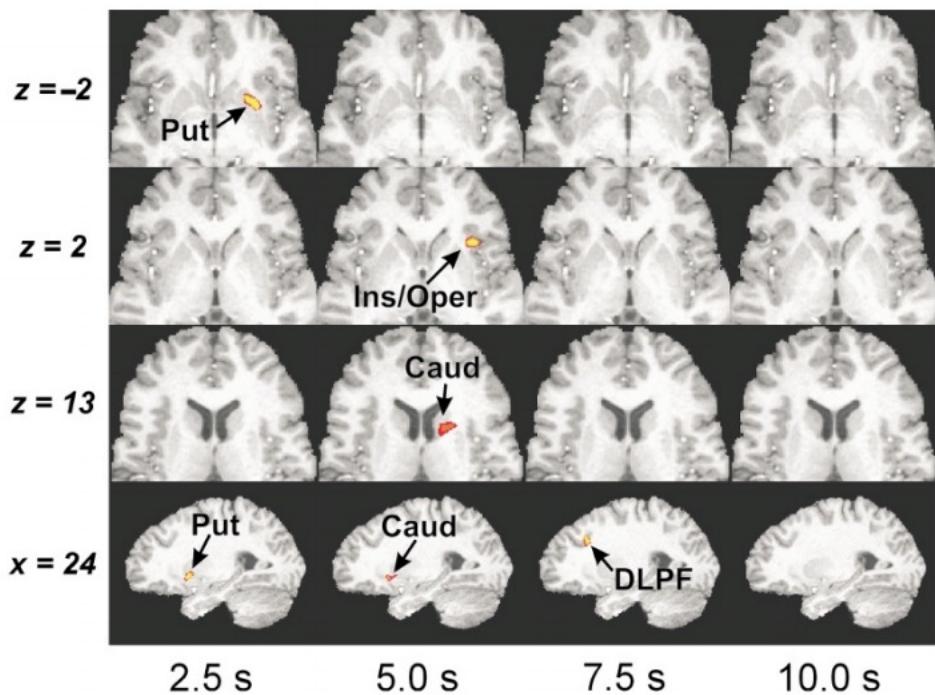
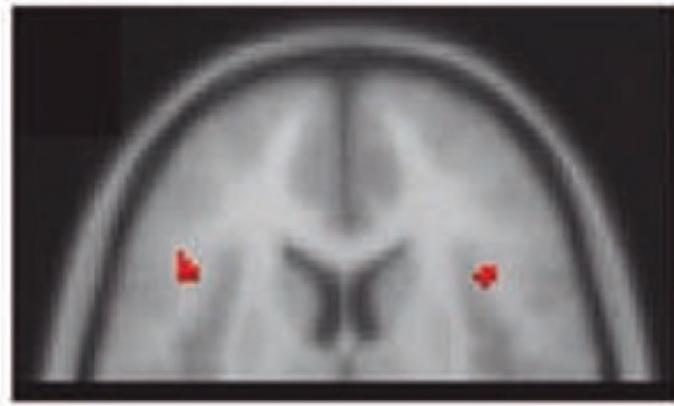
Happy voices



Craig, 2009

The insula and time perception

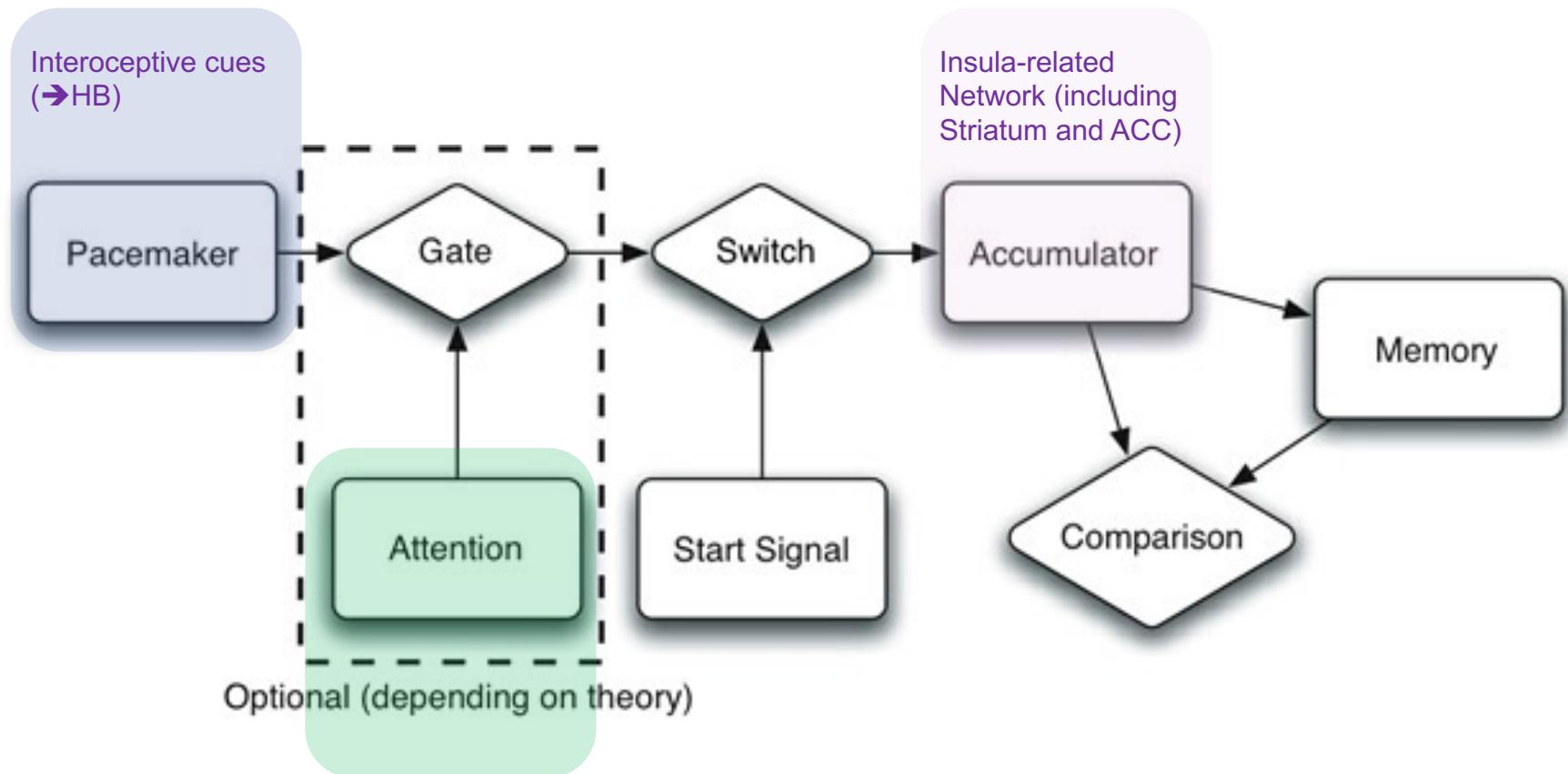
Time perception



Livesey et al., 2007

Rao et al., 2001

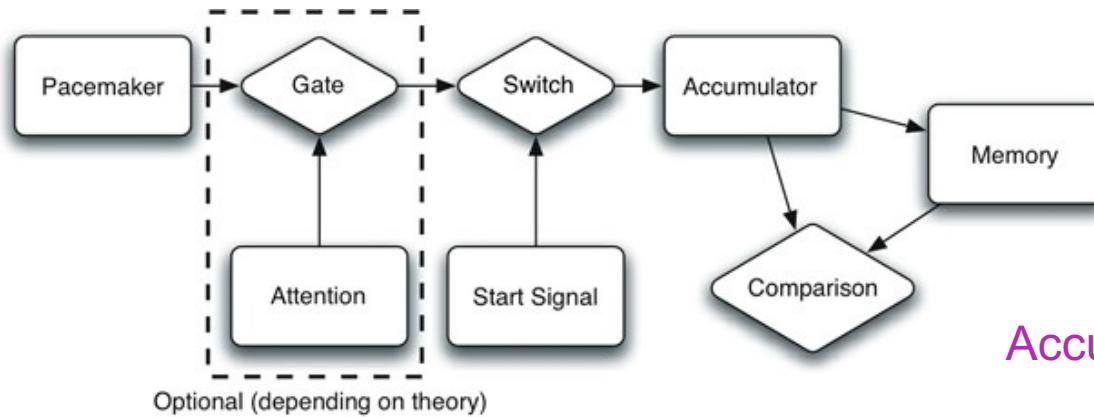
The insula, time perception and boredom



Attention directed inwards
and weak exteroceptive
input → time passes slowly

Block & Zakay, 1997

The insula, time perception and boredom



Accumulation of activity in the insula encodes subjective time

Interoceptive focus shapes the experience of time

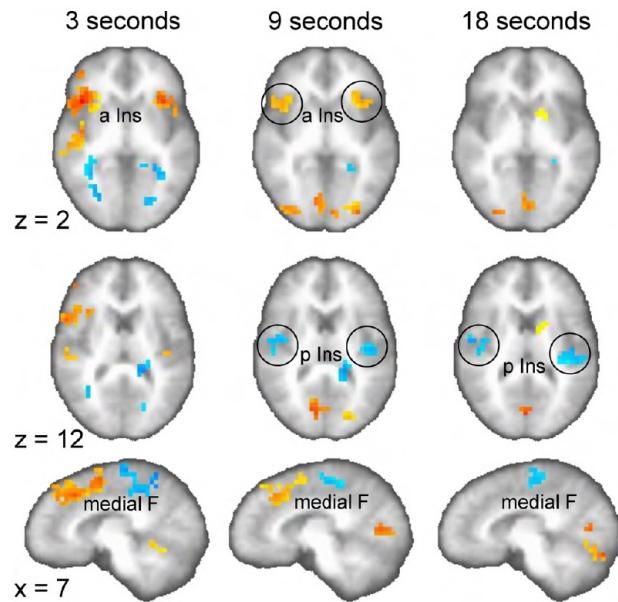
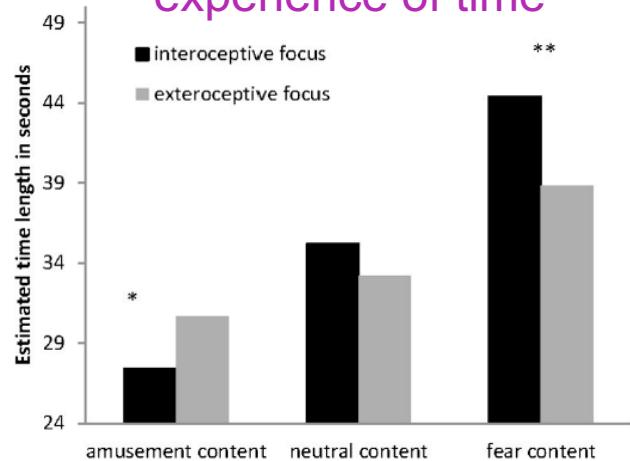


Fig. 4. Significant brain activation for the contrast reproduction versus encoding phase ($p < 0.01$, corrected) on two axial ($z = 2$ and 12) and one sagittal plane ($x = 7$). Stronger activation in the reproduction phase is colored in yellow to red (focus point: bilateral anterior insula, a Ins), stronger activation in the encoding phase is coded in blue (focus point: bilateral posterior insula, p Ins).

Boredom as an aversive emotional state

Boredom is a common experience that is associated with a strong desire to change or escape the current situation. It is generally defined as an aversive motivational state resulting from an unfulfilled desire to be engaged in satisfying activity

→ Lack of exteroceptive input



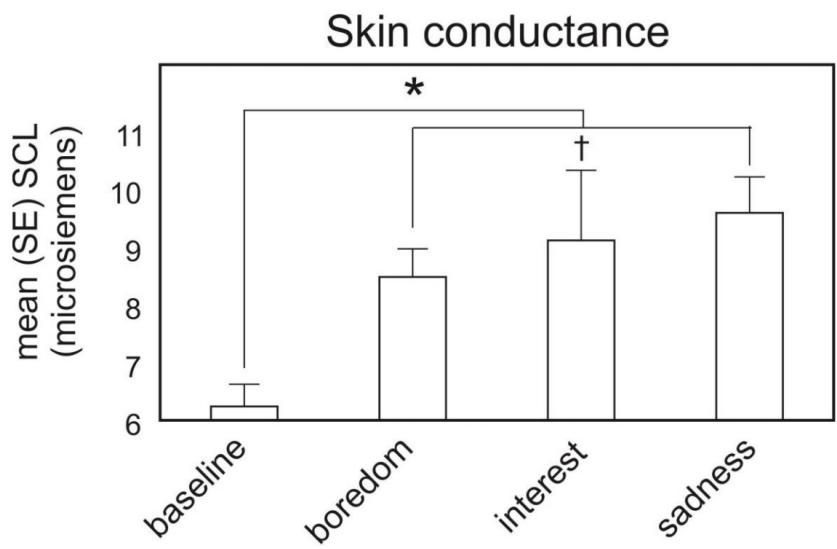
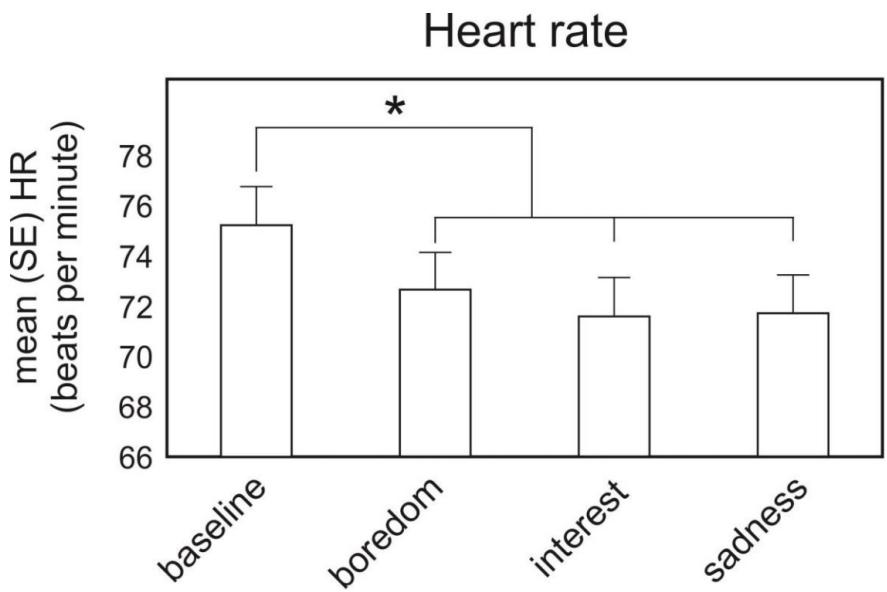
Boredom proneness is related to time perception and is a powerful negative reinforcer!

→ Humans would self-administer electric shocks to escape boredom

→ Boredom a gateway to maladaptive coping strategies?

In a 2003 survey among North-American youth 91% of the respondents reported experiencing boredom. In another 2009 British survey, respondents reported feeling bored on average for approximately 6 h per week

Boredom as an aversive interoceptive and emotional state

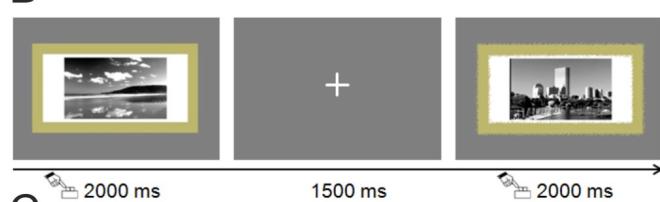


Avoiding boredom: gateway for maladaptive coping strategies?

A



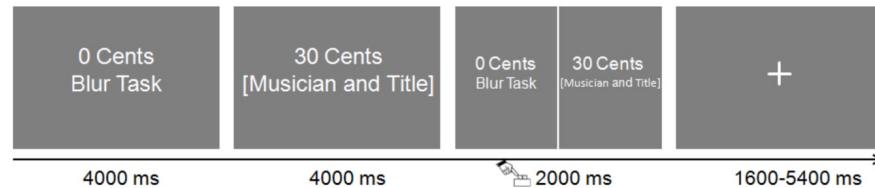
B



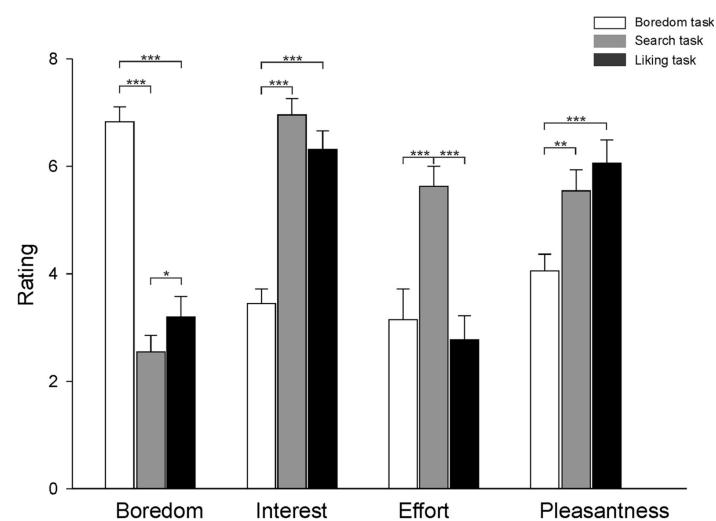
C



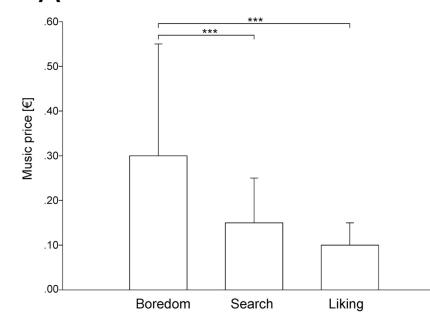
D



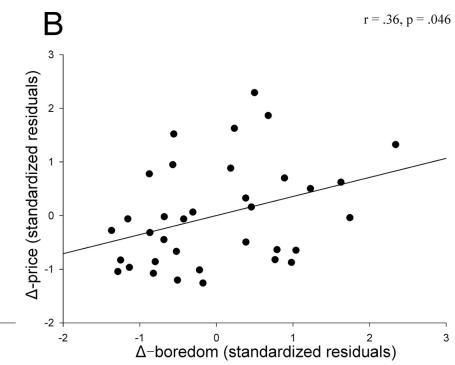
Humans pay to avoid boring things



A



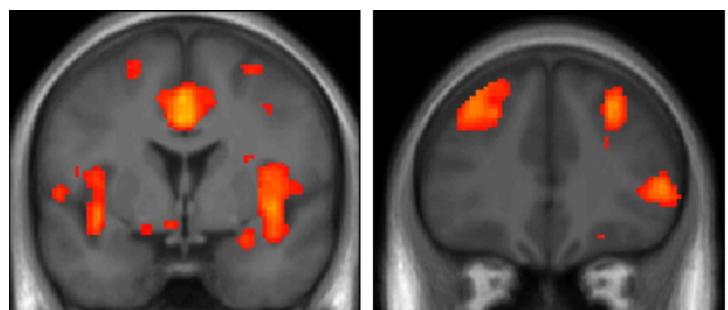
B



Dal Mas & Wittmann, 2017

Avoiding boredom: gateway for maladaptive coping strategies?

Neural response to experienced boredom

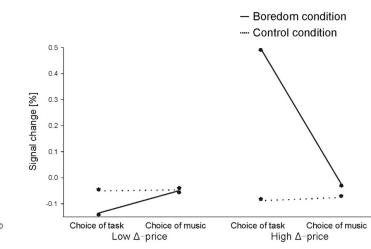
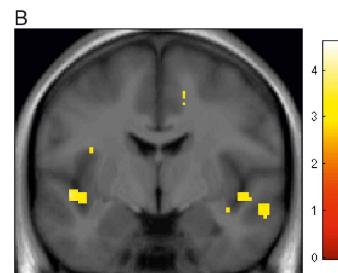
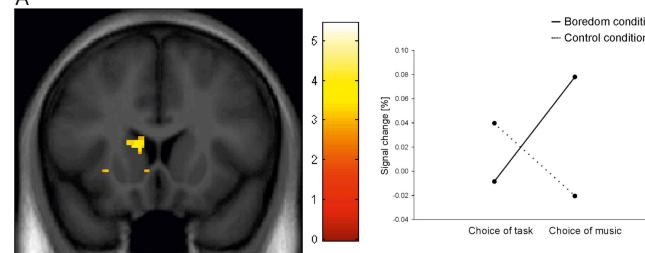


→ bilateral DLPFC,
right VLPFC
bilateral insula/dACC
amygdala ROI



Neural response to boredom-motivated decisions

→ bilateral insula/caudate



Dal Mas & Wittmann, 2017

Maladaptive coping strategies

TABLE 1
PEARSON CORRELATION COEFFICIENTS BETWEEN BOREDOM PRONENESS
AND MAACL SCORES ($N = 153$)

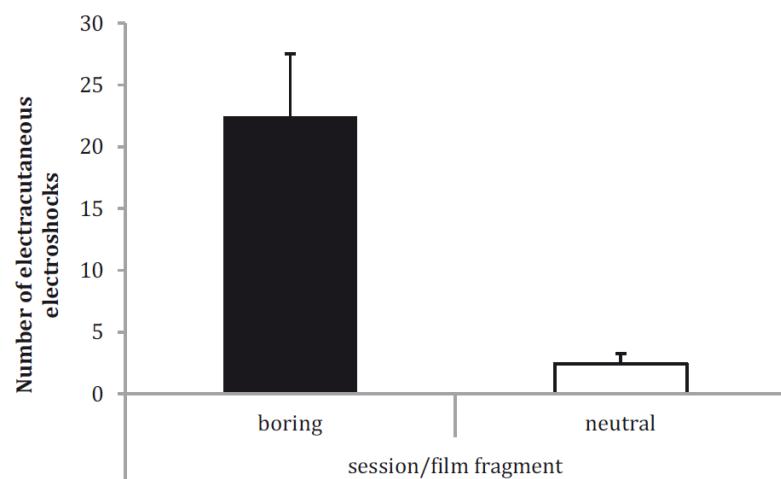
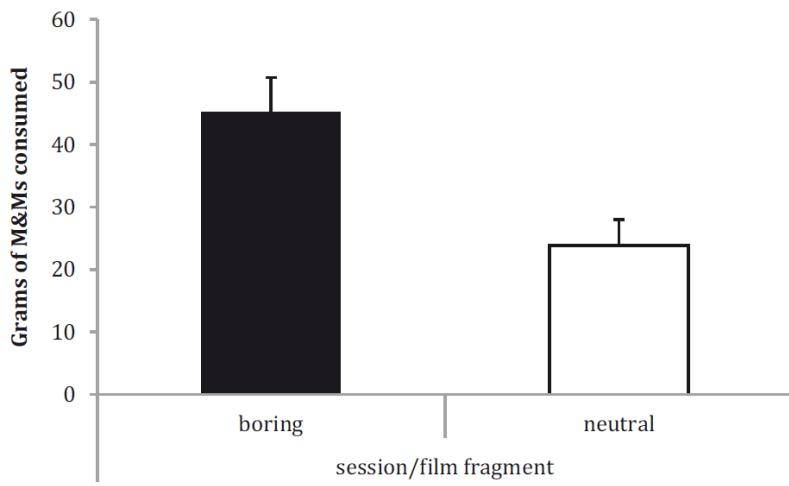
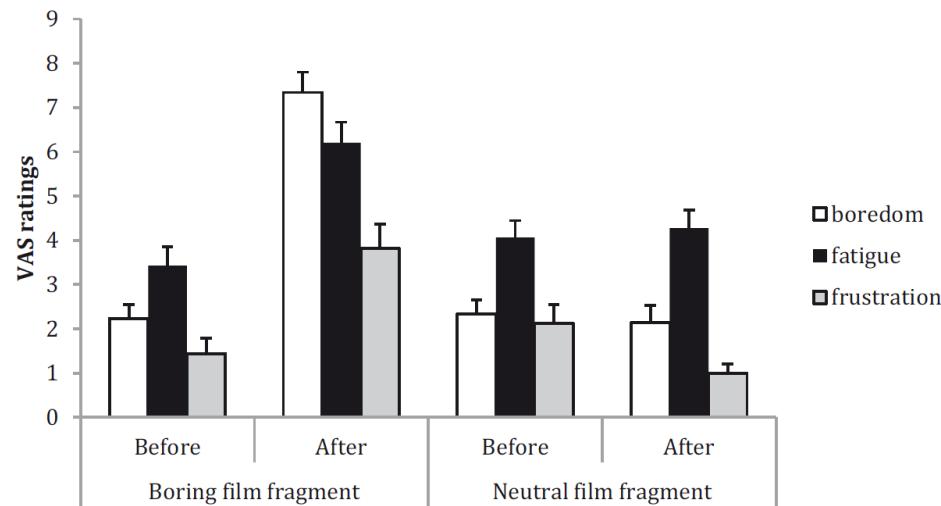
MAACL Scores	Boredom Proneness Scores					
	Total	External Stimulation	Internal Stimulation	Affective Experience	Perception of Time	Constraint
Anxiety	.23*	.18	.08	.13	.14	.38*
Depression	.33*	.29†	.09	.26†	.27†	.15
Hostility	.37†	.18*	.15	.18*	.39†	.38†
Positive Affect	-.39†	-.34†	-.09	-.21*	-.31†	-.28†
Sensation Seeking	-.19*	.13	-.35†	-.32†	-.21†	.18*
Dysphoria	.40†	.24†	.15	.24†	.34†	.40†
PASS‡	-.37†	-.18*	-.23†	-.31†	-.33†	-.11

* $p < .05$. † $p < .01$.

‡PASS is the Composite score of positive affect and sensation seeking.

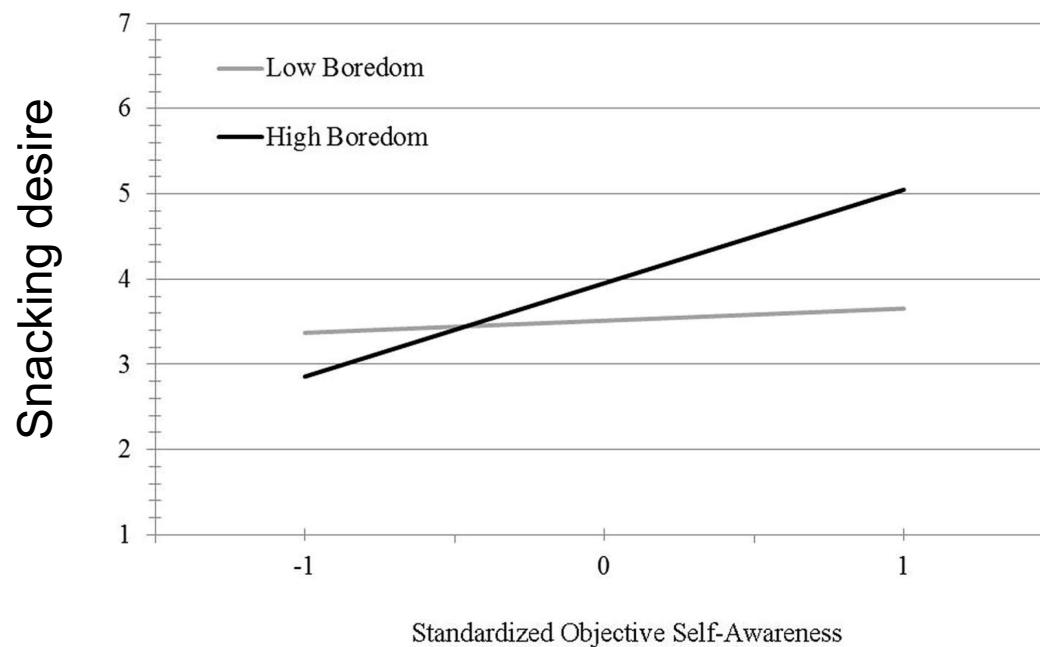
The Multiple Affect Adjective Checklist (MAACL)

Maladaptive coping strategies



Vodanovich & Verner, 1991

Maladaptive coping strategies



Conclusions

Interoception is a key feature of the individual ability adaptively to regulate emotions

Emotion regulation requires a broad system that involves the insula, the anterior cingulate cortex, the amygdala, the striatum as well as the entire prefrontal cortex

Interoceptive mechanisms contribute to the identification of distress and the establishment of coping strategies

Interoception is the primary mechanism contributing to biological time and subjective representation of time

- ➔ Interoception contributes to boredom (which is an aversive state) and associated coping strategies
- ➔ negative urges and underlying insular mechanism contribute to rash behaviours

Alteration in interoceptive accuracy contributes to maladaptive coping: eating and drug use as self-medication strategies...

Drug addiction 1: From the incentive sensitisation to the opponent process and the maladaptive habit theories of addiction

Overview - addiction

Addiction as a disorder

Drugs and dopamine:

incentive learning

incentive sensitisation theory

Drug withdrawal and Wikler's theory of relapse

Opponent process theories of addiction

hedonic allostasis

dysphoria

Maladaptive habit theory of addiction

Addiction: compulsive drug use despite adverse consequences, a chronic and relapsing disorder

Loss of control

Larger amounts
Longer time

High motivation for drug

Obtaining, using or recovering
Other activities reduced

Persistence despite negative consequences

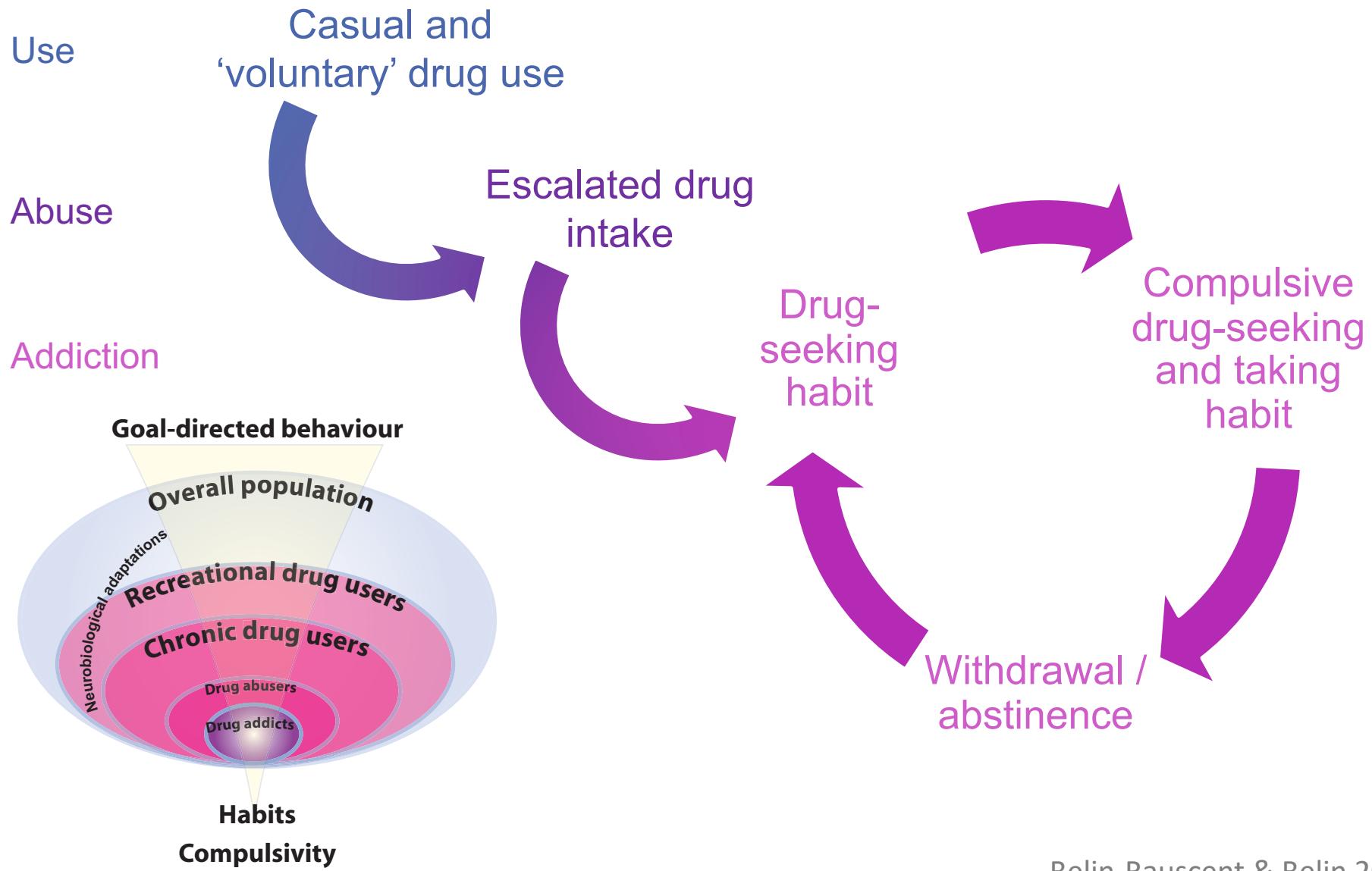
Psychological problems
Physical problems

Physiological adaptations

Tolerance
Withdrawal



The development of drug addiction



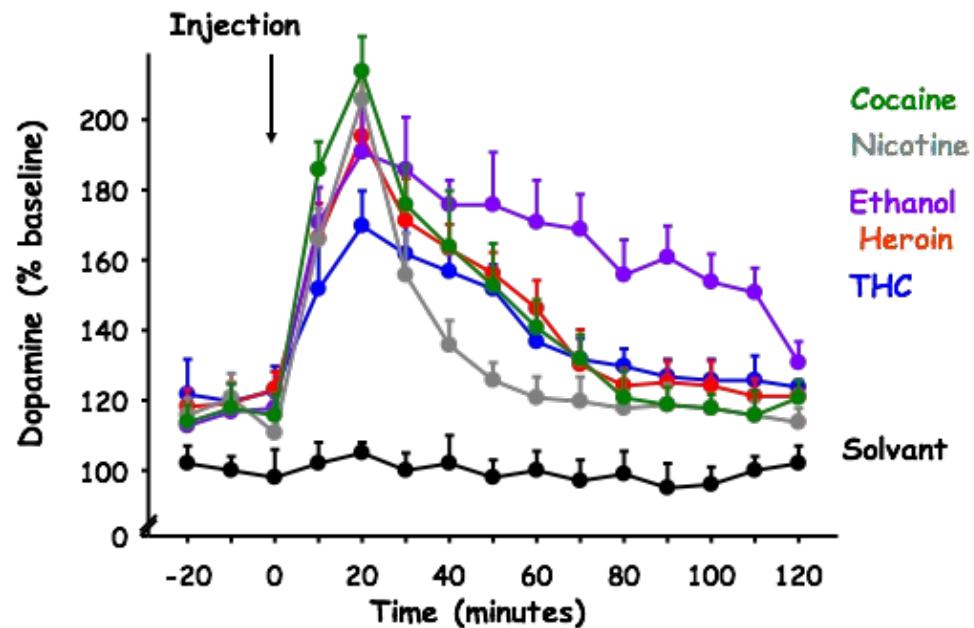
Two important hypotheses

1. Addictive drugs from different classes act on a common brain mechanism: concept of a “**reward system**” in the brain → Important for the **initiation of drug use** and abuse.
2. Drug addiction is manifested as a set of **neuroadaptive, compensatory responses in the brain** to chronically self-administered drugs.
→ **Adaptations contribute to the development of compulsive drug-seeking and taking.**

Incentive motivational theories of addiction

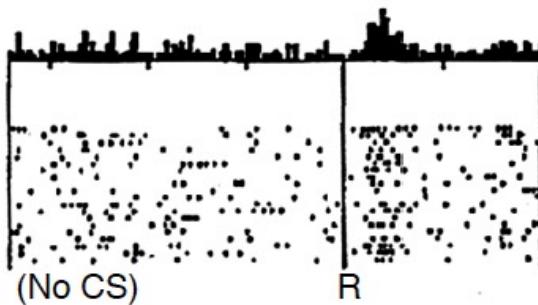
All addictive drugs result in an increase in extrasynaptic [DA] in the nucleus accumbens.

→ addictive drugs ‘usurp’ or ‘hijack’ the brain’s reward system.

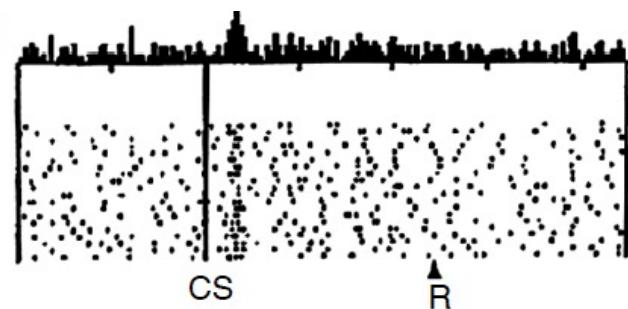


Incentive motivational theories of addiction

No prediction
Reward occurs

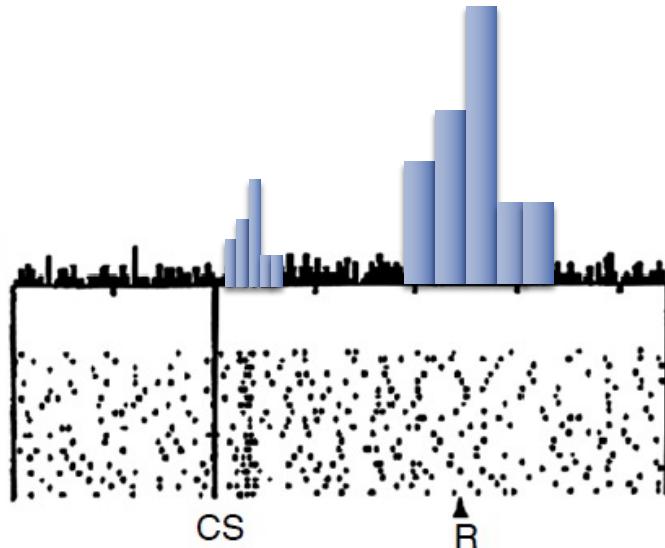


Reward predicted
Reward occurs



With drugs

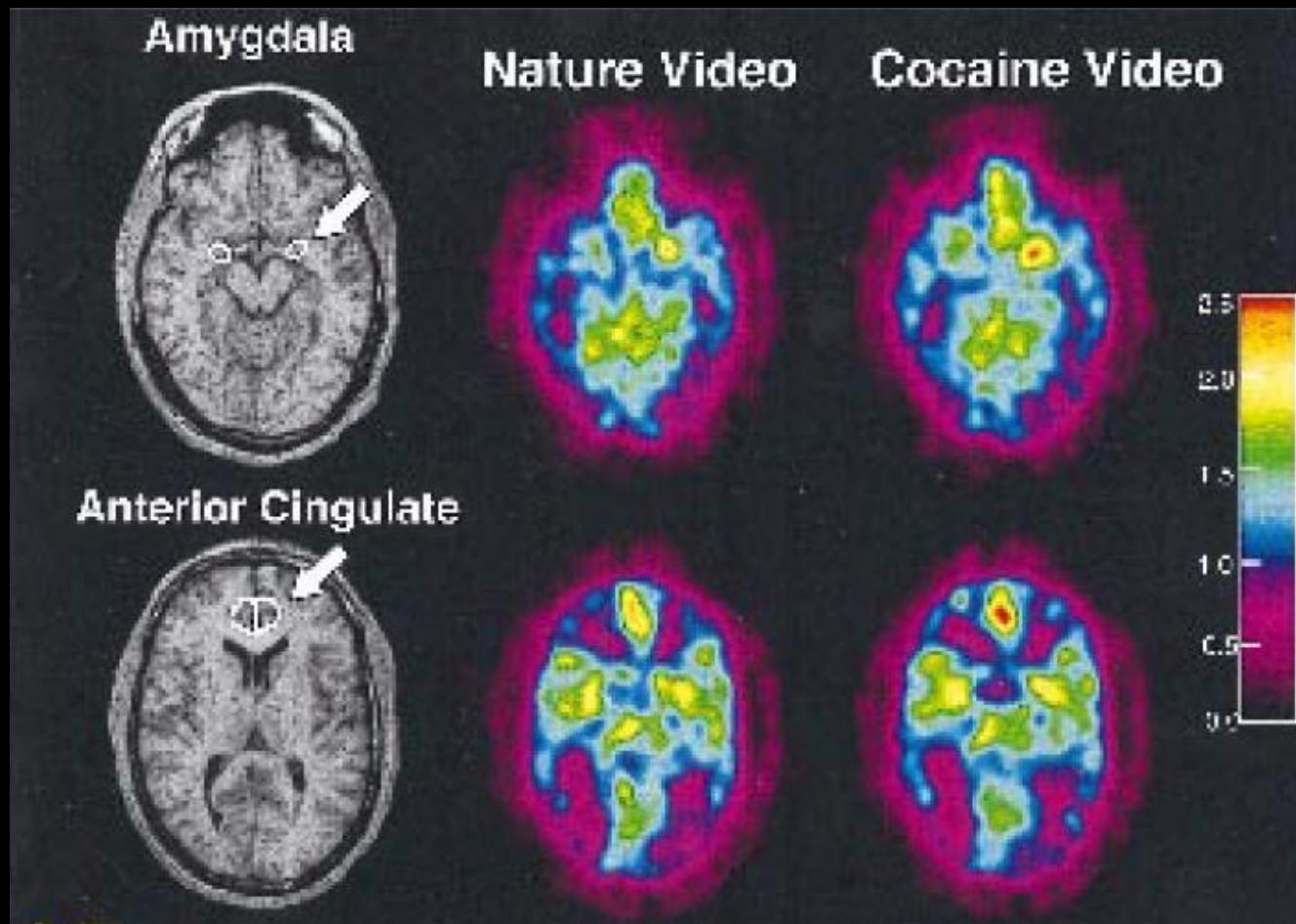
Reward predicted
Reward occurs



Always better than
expected

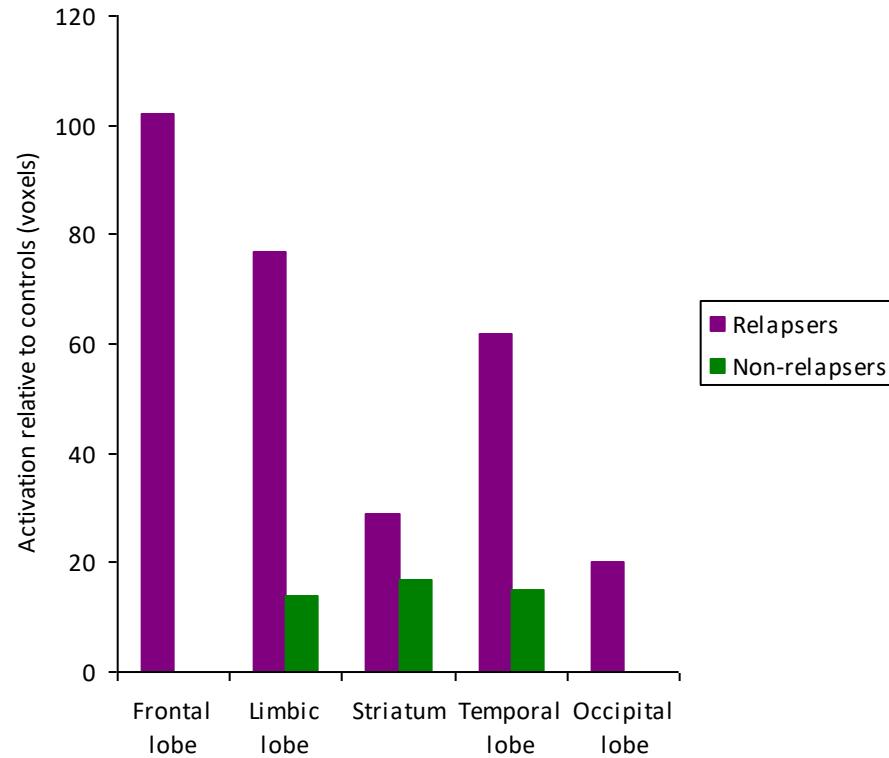
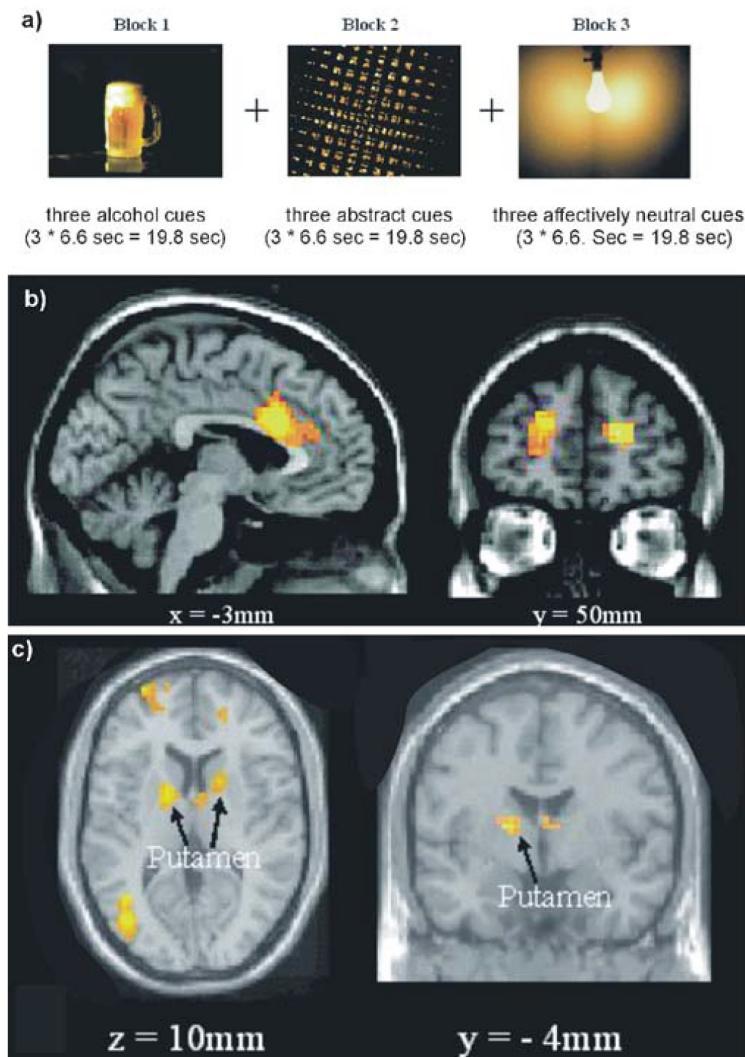
Jane Stewart - emphasizes the way conditioned stimuli boost activity in the meso-accumbens dopamine system to produce drug craving (in humans), drug-seeking & relapse

Presentation of drug-paired CSs → activation of the limbic corticostriatal circuitry



Childress et al. (1999)

Greater activation of the striatum by drug CSs predicts risk of relapse



Replotted from Grüsser et al. (2004)

Incentive sensitisation (Robinson & Berridge)

Incentive motivational theories of addiction

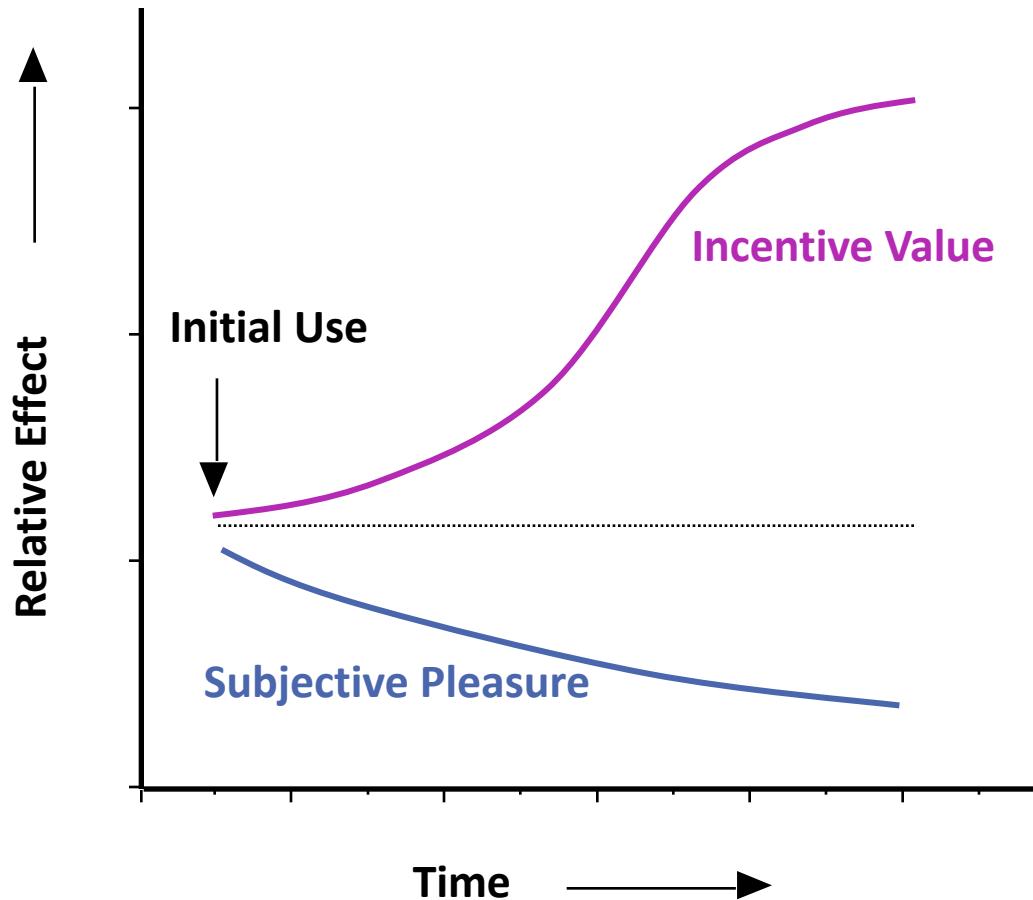
→ Jane Stewart

emphasizes the way conditioned stimuli boost activity in the mesoaccumbens dopamine system to produce drug craving (in humans), drug-seeking & relapse

→ Robinson & Berridge (1993) - Incentive Sensitisation Theory

emphasizes the sensitization of incentive motivational processes, especially the **increased salience of drug cues that elicit “drug “wanting”, rather than “liking”** and hence drug-seeking and relapse.

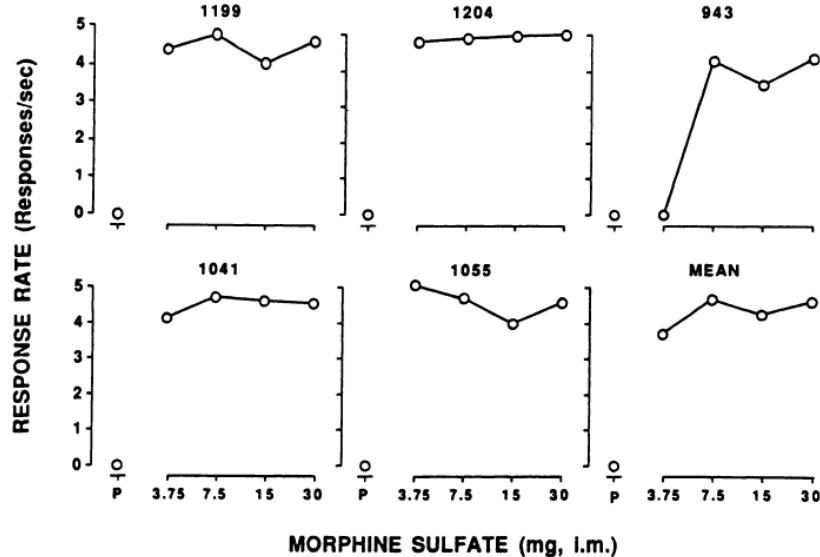
Hypothetical relationship between drug 'wanting' and 'liking'



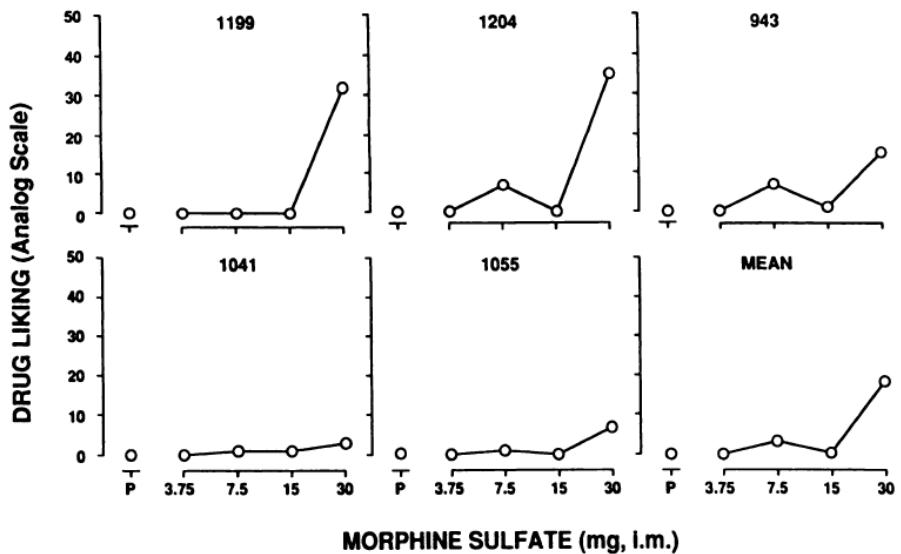
Robinson & Berridge, 1993

Morphine abusers will work for doses of drug that they don't subjectively like

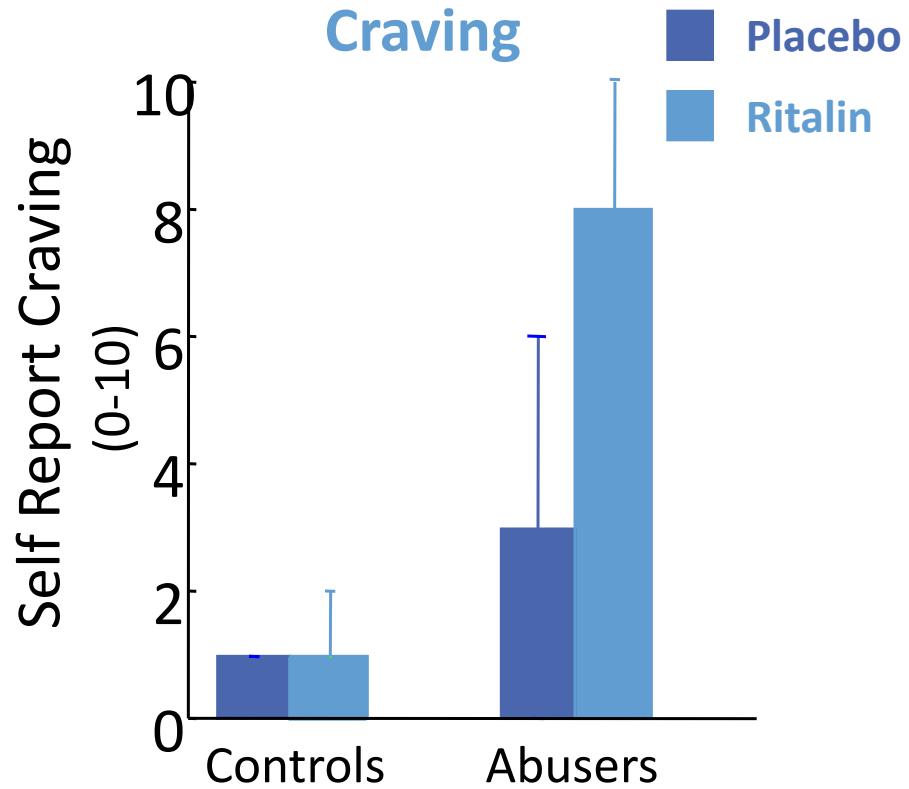
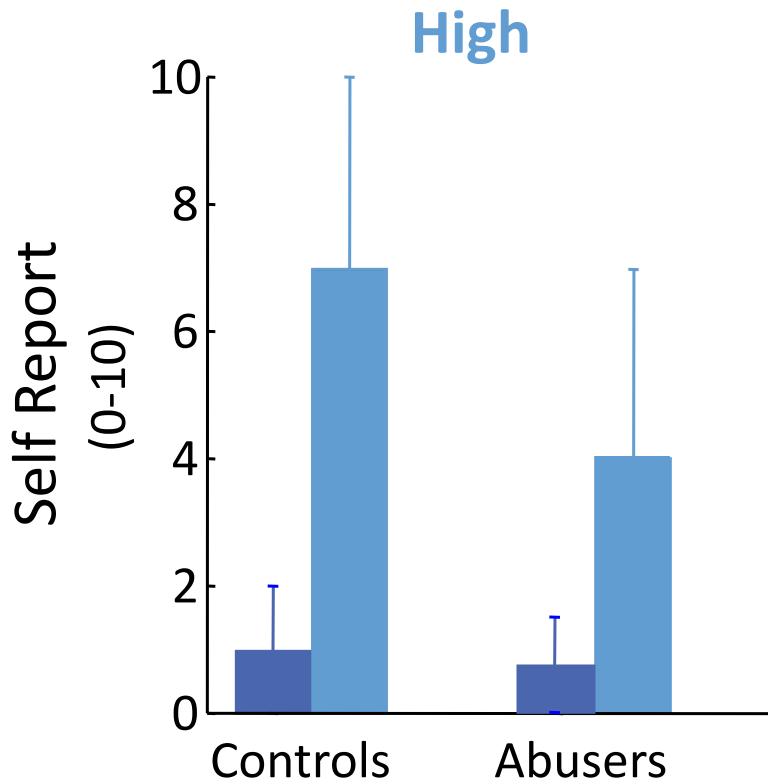
Drug 'wanting'



Drug 'liking'



Self-reported drug effects of Ritalin (methylphenidate) in controls and detoxified cocaine abusers



Cocaine abusers showed decreased drug induced increases in subjective 'high', but increased drug craving.

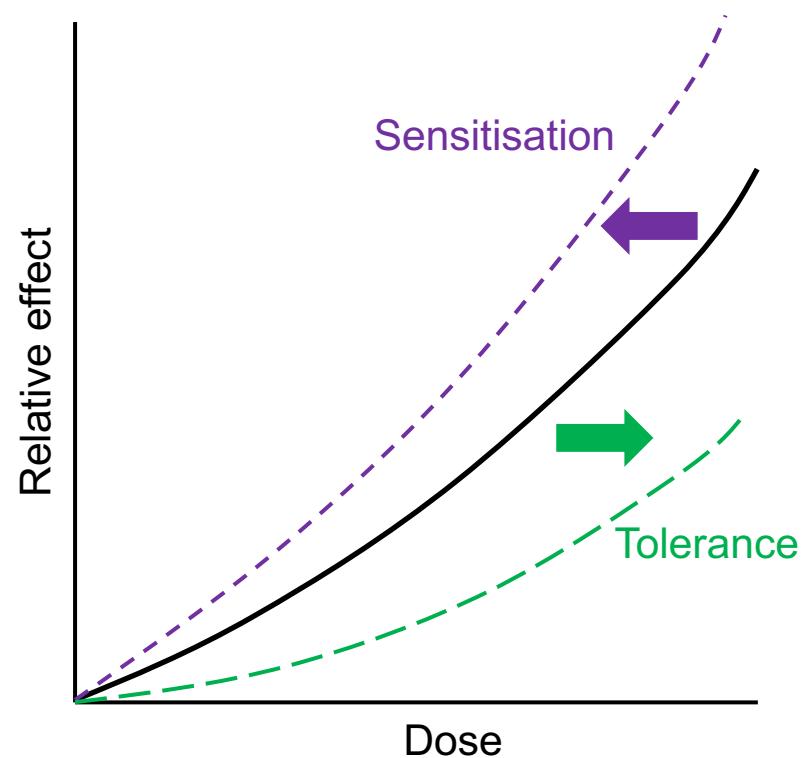
Sensitisation

Sometimes called ‘inverse tolerance’

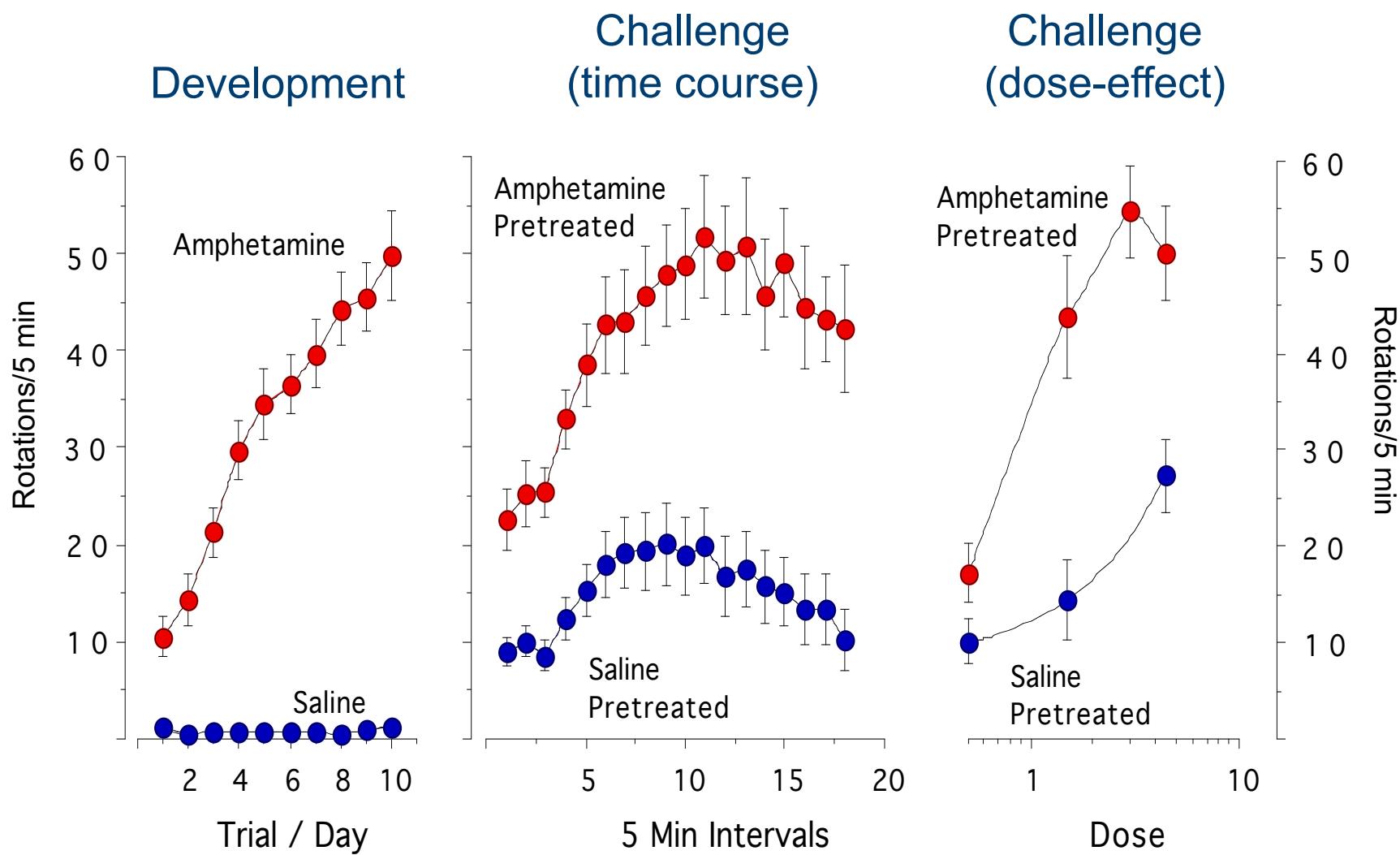
sensitisation manifests as an **increased response** to the same dose over time (i.e. shift of the dose-response curve to the left or upwards).

Supported by:

- (i) Molecular / cellular adaptations
 - similar to LTP
- (ii) Conditioning processes.

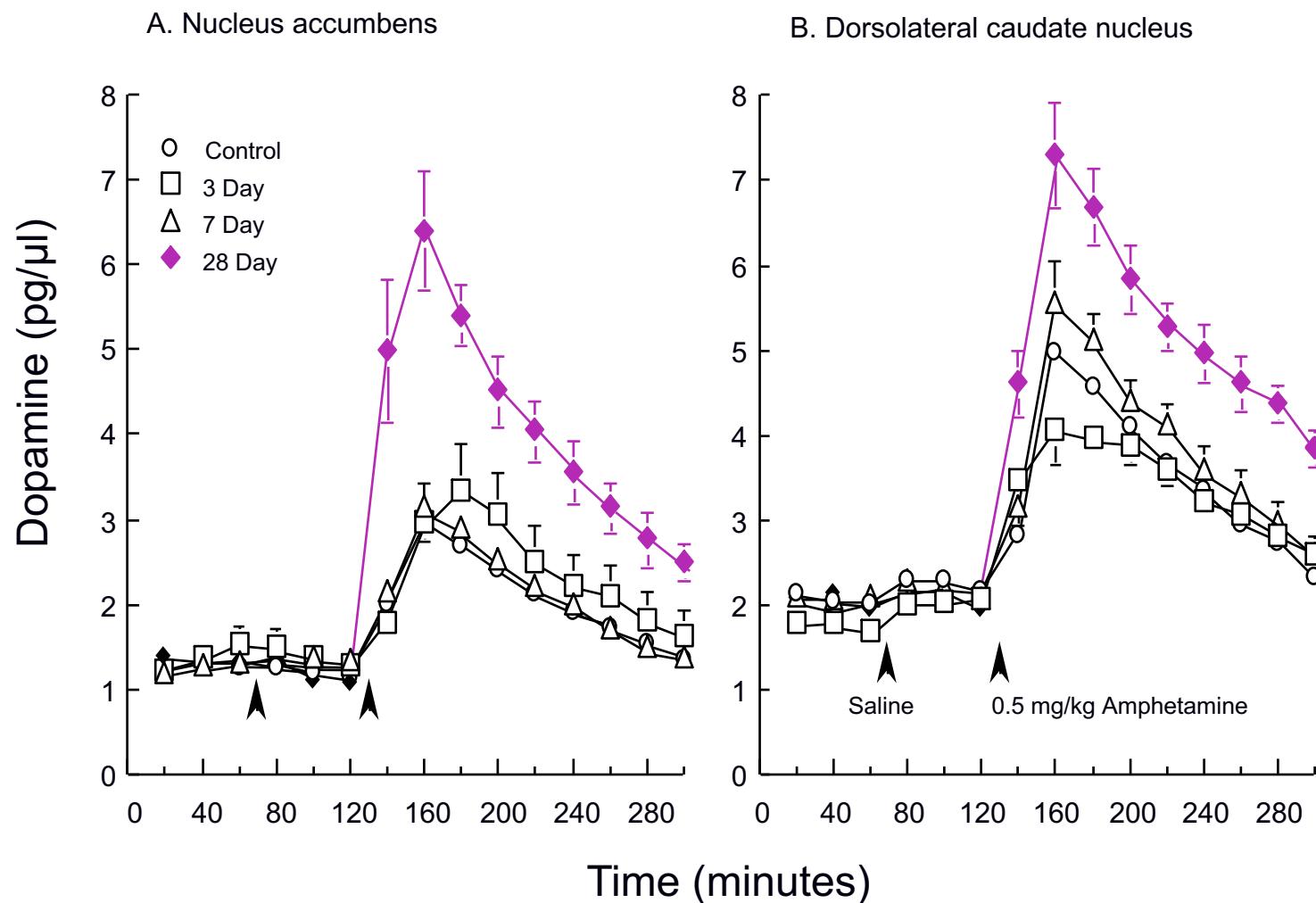


Psychomotor sensitisation is the increase in response to repeated injection of drug (usually psychostimulants)



Anagnostaras & Robinson (1996)

Rats show greater DA release following an injection of amphetamine the longer they are into withdrawal



Paulson & Robinson (1995)

Drug withdrawal, and Wikler's theory of relapse

Symptoms of withdrawal from drugs

Physical withdrawal - e.g. from heroin/morphine

Lacrimation, rhinorrhoea, piloerection,
shivering, perspiration, vomiting, diarrhoea



Psychological withdrawal - seen with all drugs

Dysphoria, anhedonia, anxiety



Addiction as withdrawal avoidance

Wikler's two-factor theory of addiction to heroin:

Relapse, following a period of rehabilitation and abstinence, is associated with the individual having self-administered heroin in the past in order to avoid the distress of withdrawal.

More formally stated, this is a two-factor conditioning theory with pavlovian and instrumental components:

1. Conditioning of withdrawal phenomena (UCR) to environmental stimuli or contexts (CSs);
2. Previous negative reinforcement of drug-taking behaviour through a reduction in withdrawal symptoms.

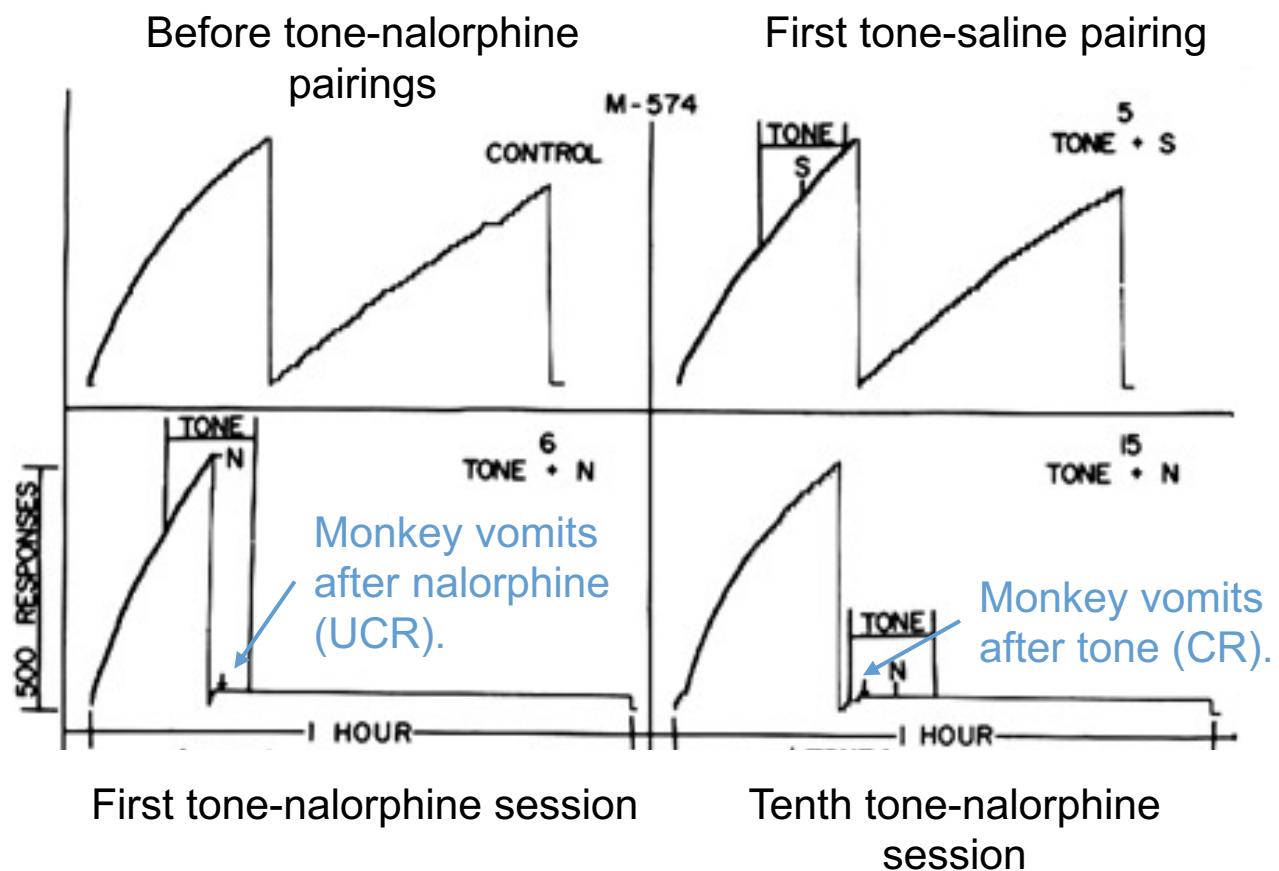
Conditioned opiate withdrawal: precipitation of withdrawal by nalorphine in morphine-dependent monkeys or rats

Nalorphine counteracts many pharmacological and behavioral effects of morphine.

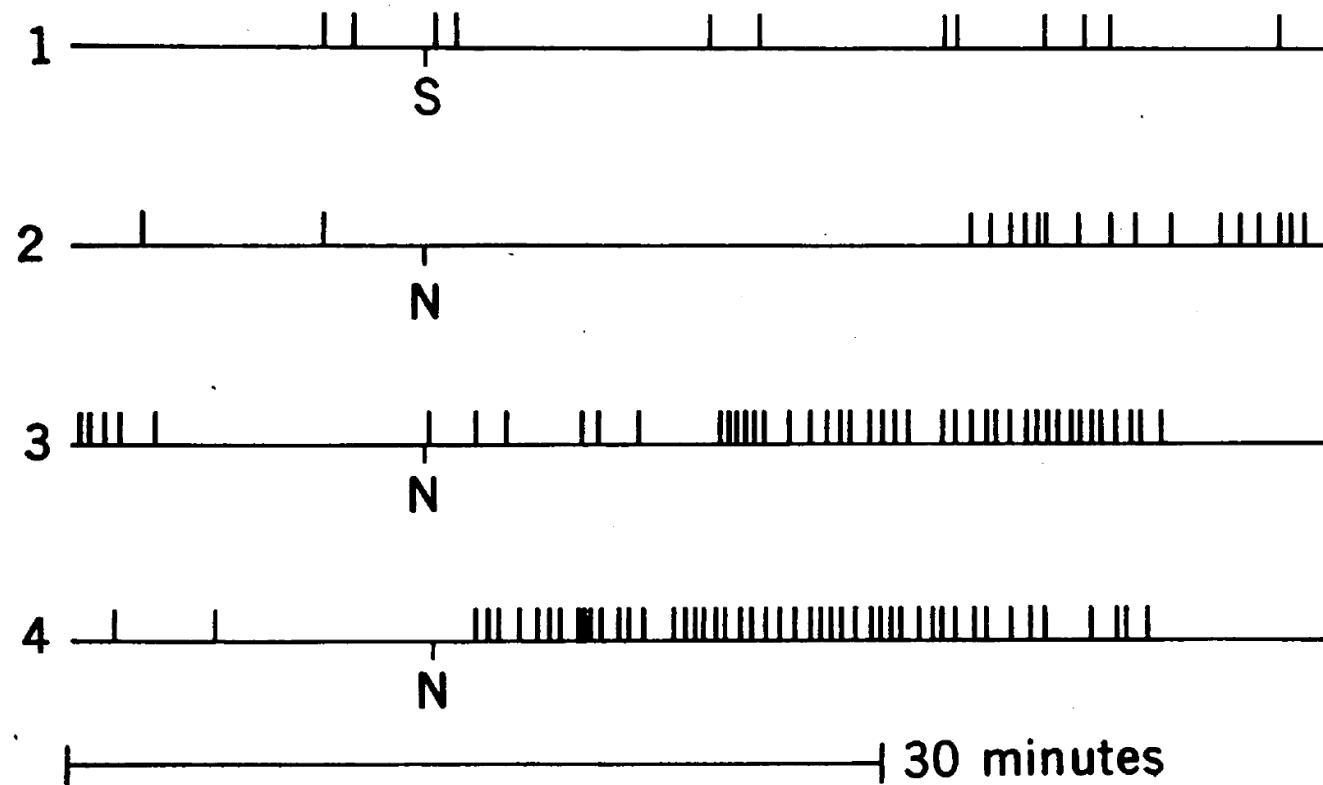
In organisms dependent upon morphine, nalorphine induces a severe withdrawal syndrome, which includes restlessness, piloerection, vomiting, salivation, body tremors, and general irritability.

Conditioned opiate withdrawal in monkeys

Morphine-dependent monkeys were trained to respond for food (FR10) and responses assessed in presence of neutral tone (paired with saline) and tone CS (paired with μ opiate receptor antagonist nalorphine).

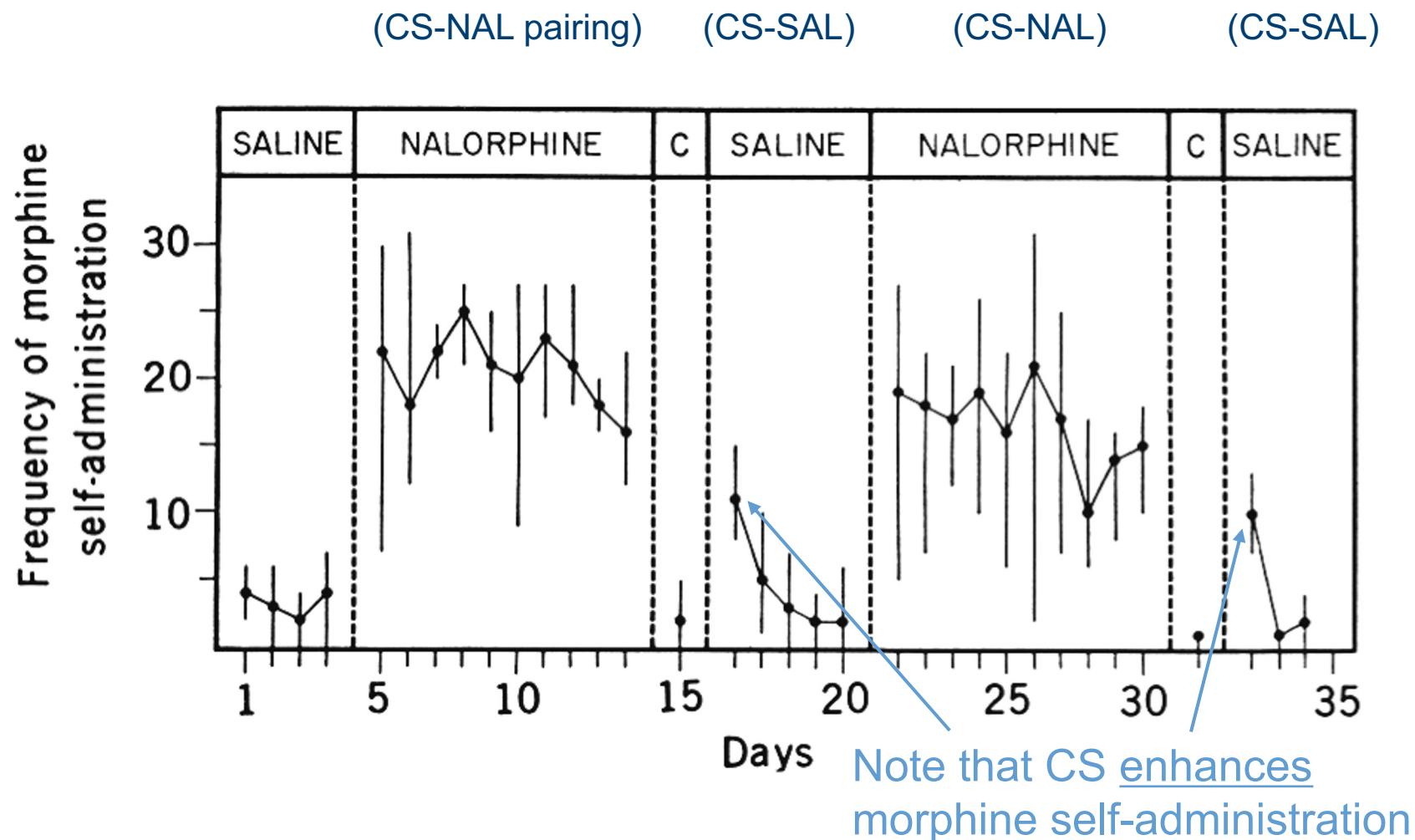


Increased morphine self-administration during conditioned withdrawal



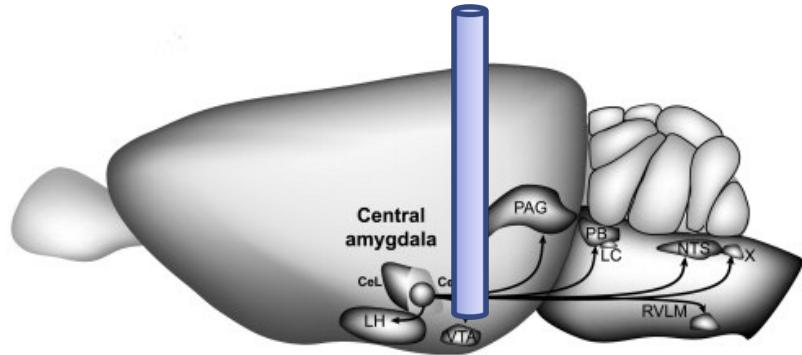
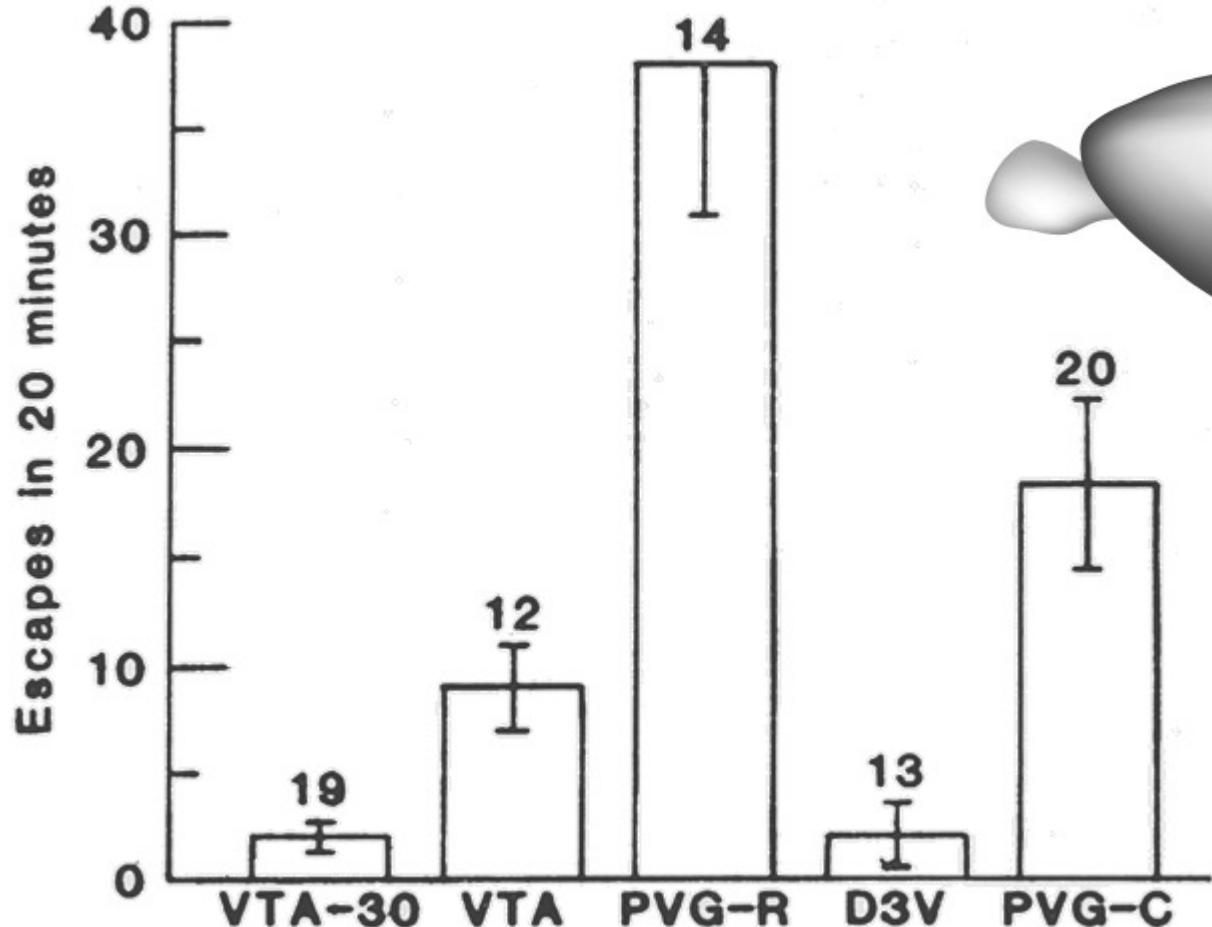
Goldberg et al. (1969)

Increased morphine self-administration during conditioned withdrawal



Goldberg et al. (1969)

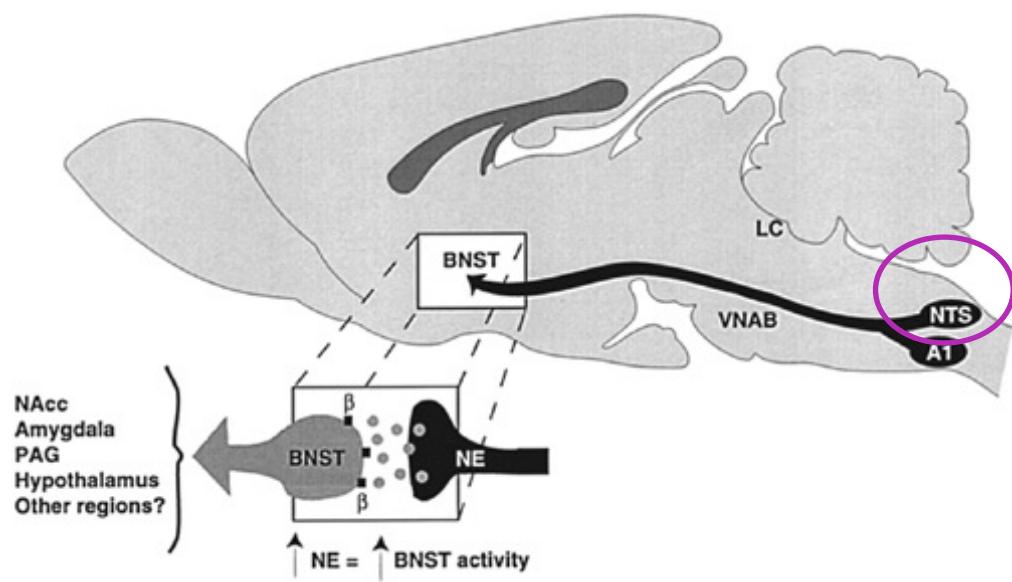
Physical withdrawal from opiates and opiate reward depend upon different neural substrates



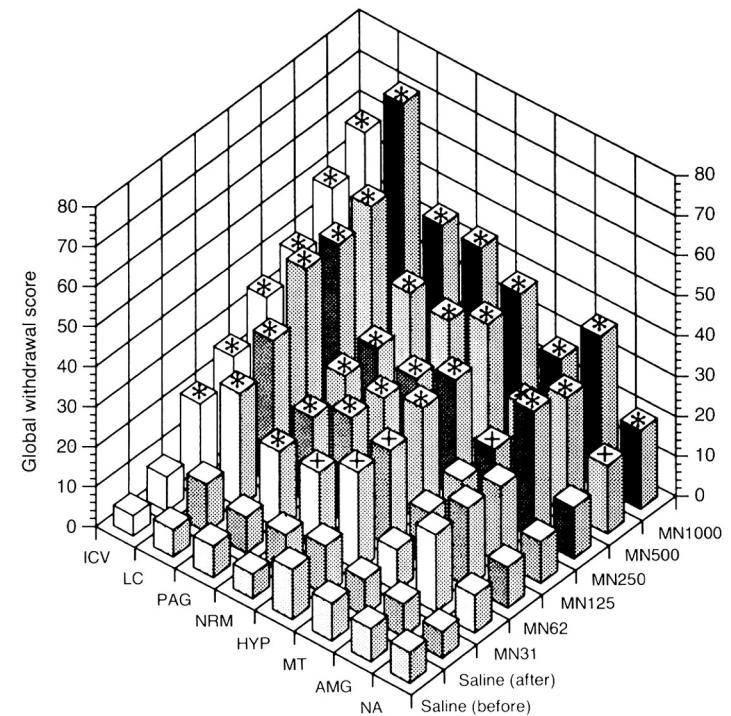
	VTA	PAG
Self-admin	✓	✗
Physical dependence	✗	✓

Bozarth & Wise (1984)

Physical withdrawal from opiates depends upon the locus coeruleus and other distributed structures including the NTS!



Smith and Aston-Jones (2008)



MN: methynaloxonium (opiate receptor antagonist)

Maldonado et al. (1992)

Addiction as withdrawal avoidance?

Some findings go against this view:

1. Many individuals addicted to heroin do not experience physical withdrawal, and do not report that they take heroin to avoid or escape physical withdrawal distress.
2. No physical withdrawal syndrome is seen following abstinence from stimulants (cocaine, amphetamine, nicotine).

So, a unifying theory of compulsive drug-seeking/taking (i.e. addiction) therefore cannot be based on avoidance of the rebound syndrome of physical withdrawal alone.

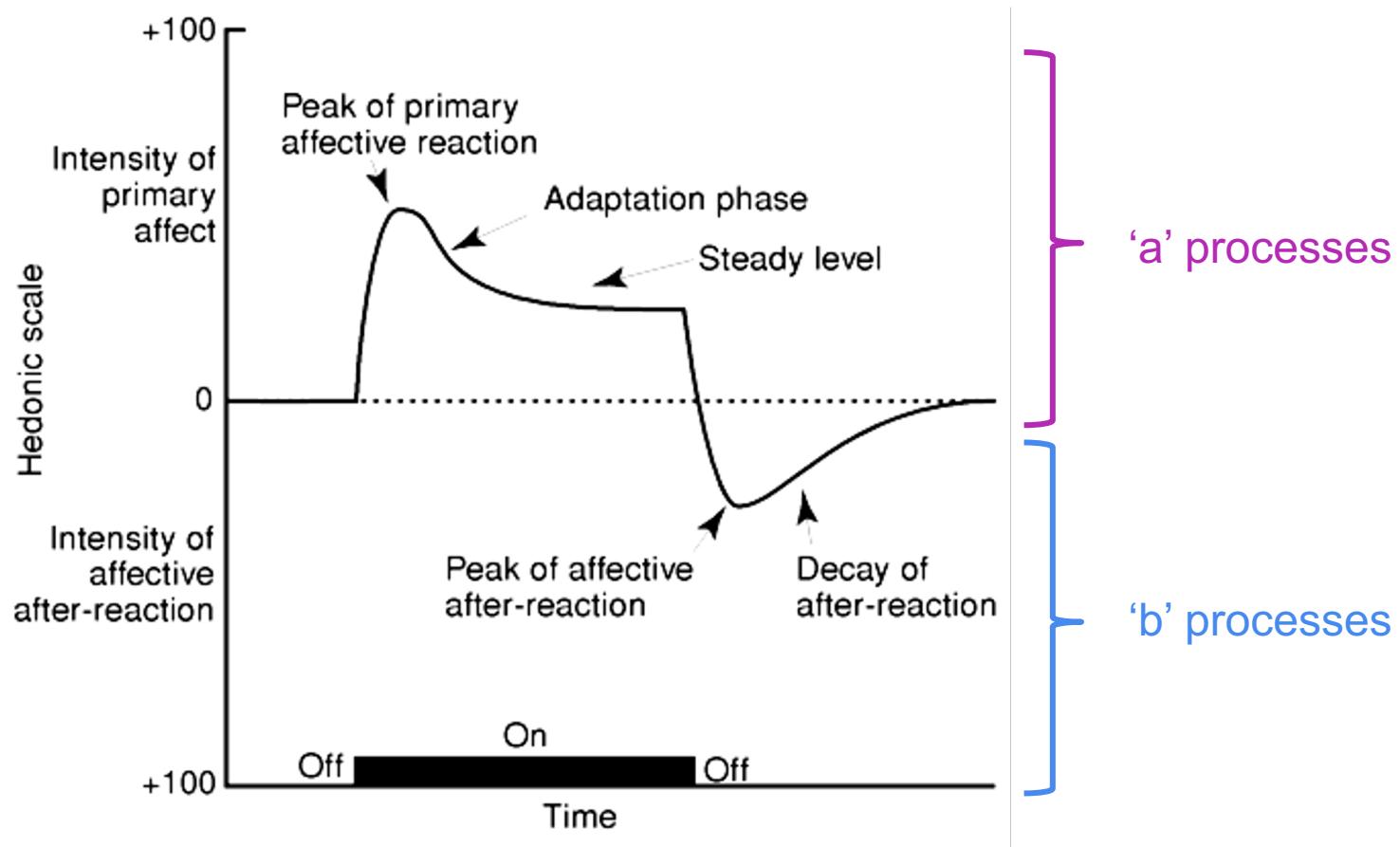
But avoidance of psychological withdrawal (dysphoria, anhedonia) is common to withdrawal from all drugs of abuse, and so may be an important factor in the development of addiction.

Diagnostic criteria for drug withdrawal (DSM-IV)

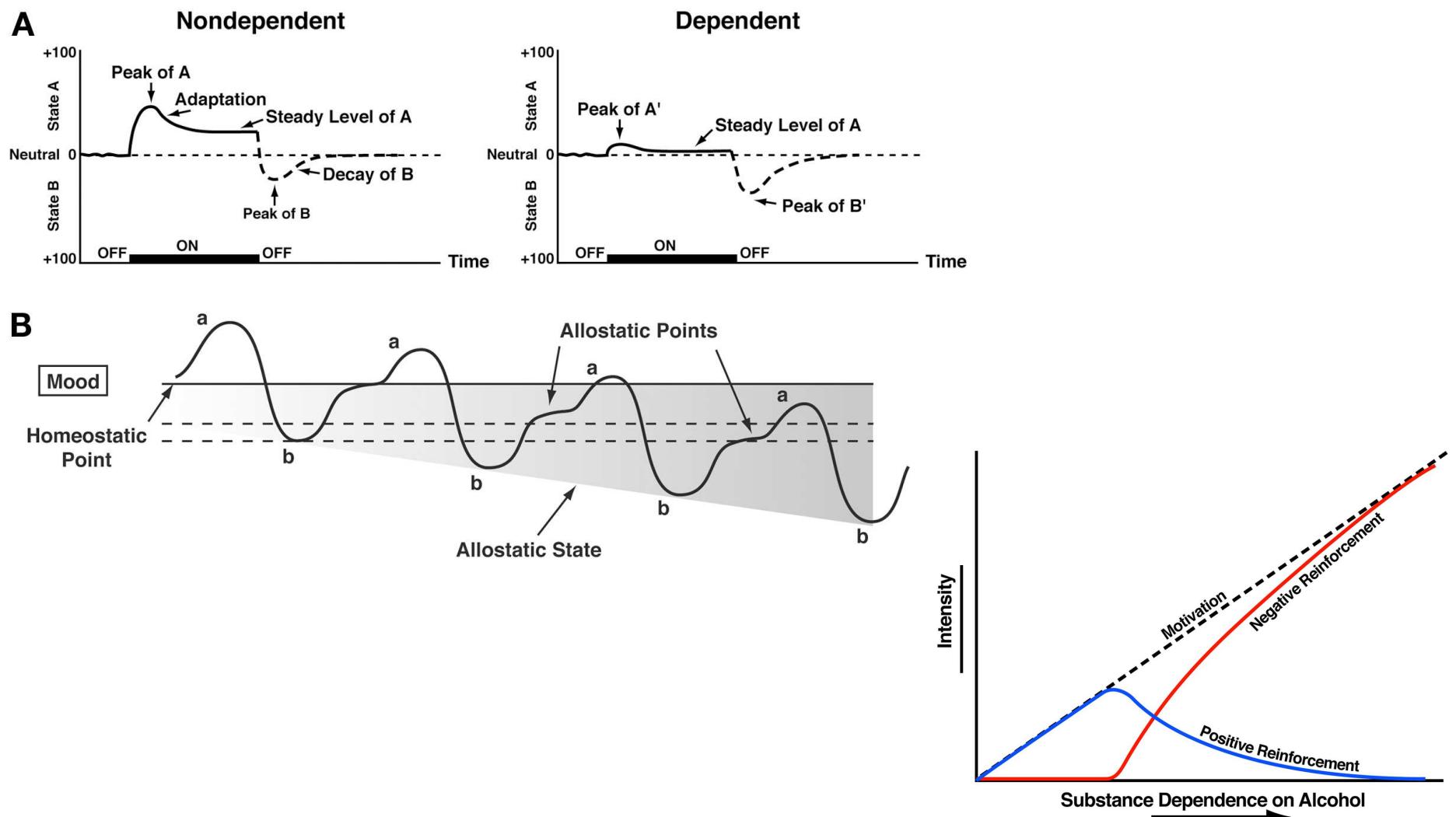
Opioid	Alcohol	Cocaine	Nicotine
Dysphoric mood Nausea or vomiting Muscle aches Lacrimation Rhinorrhea Pupillary dilation Piloerection Sweating Diarrhea Yawning Fever Insomnia	Autonomic hyperactivity Hand tremor Insomnia Nausea or vomiting Hallucinations Illusions Psychomotor agitation Anxiety Seizures	Dysphoric mood Fatigue Unpleasant dreams Insomnia or hypersomnia Increased appetite Psychomotor retardation or agitation	Dysphoric or depressed mood Insomnia Irritability Anxiety Difficulty concentrating Restlessness Decreased heart rate Increased appetite Weight gain

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, D.C., 1995.

Solomon's 'Opponent Process Theory'

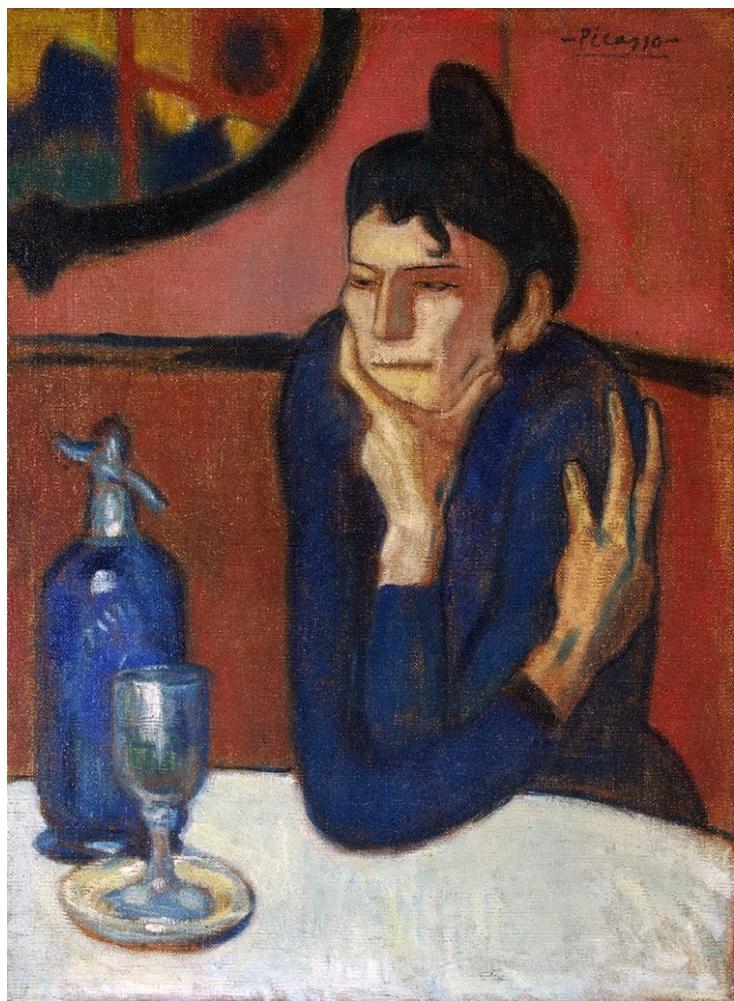


Koob and Le Moal's negative reinforcement model

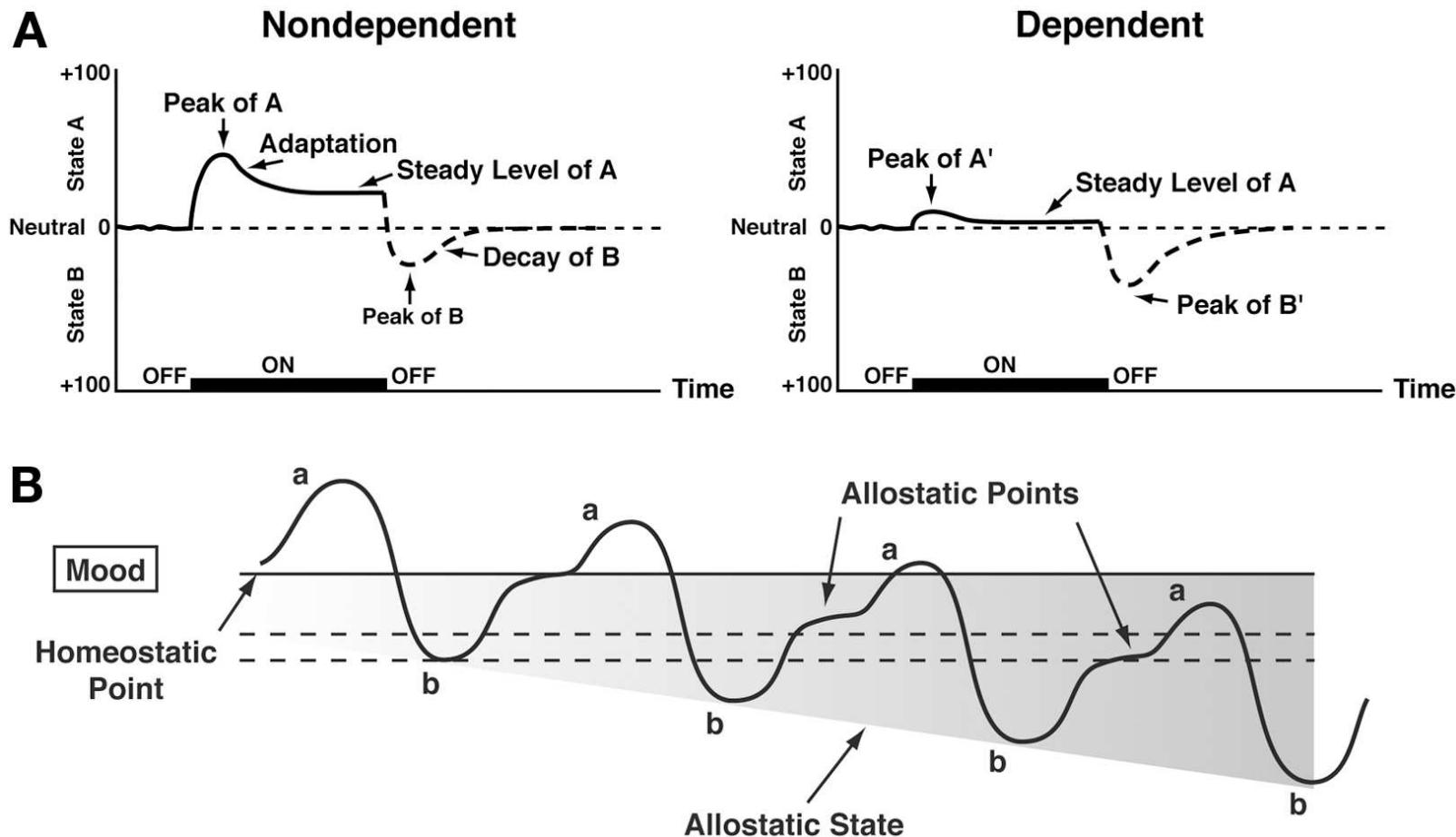


Koob (2013)

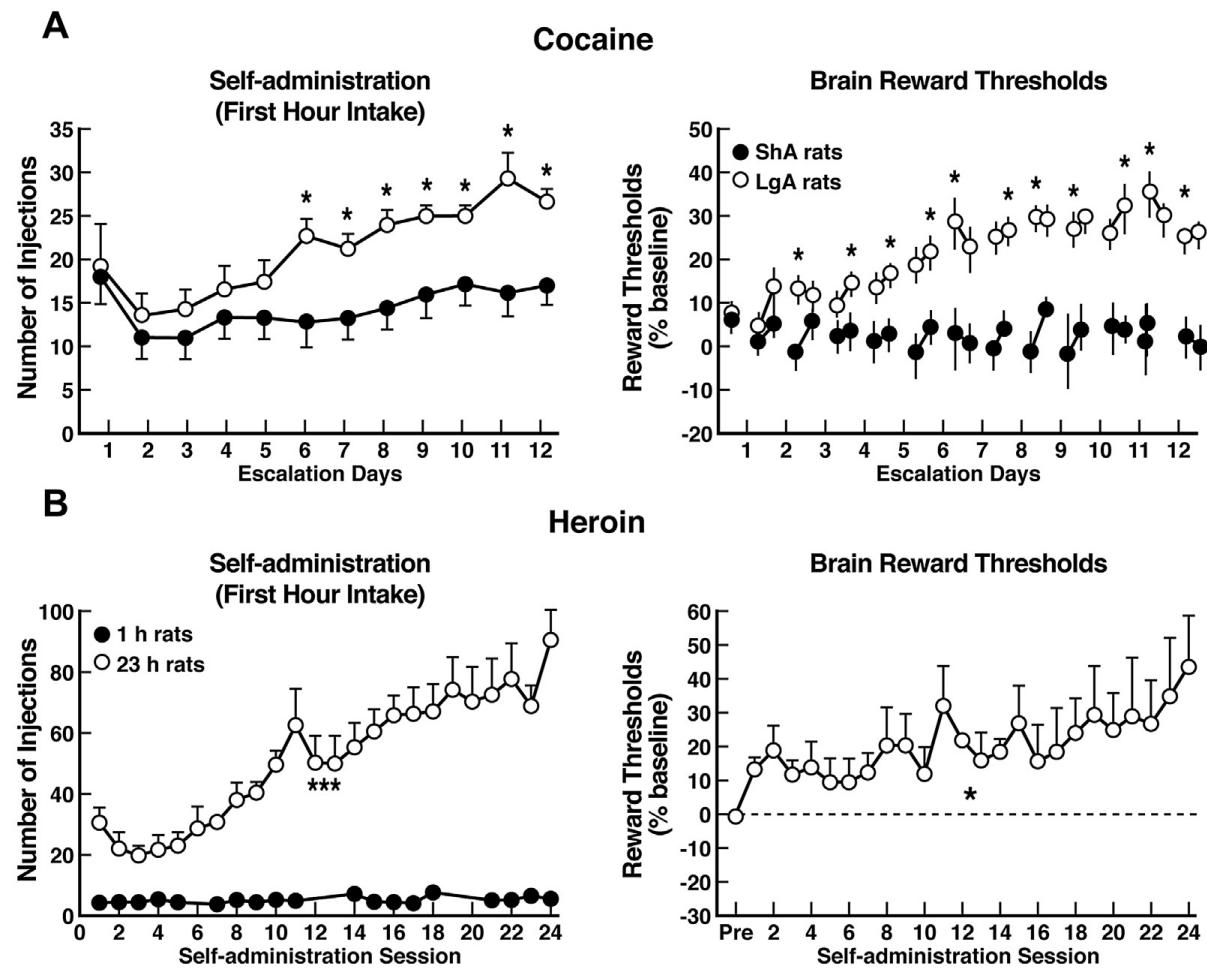
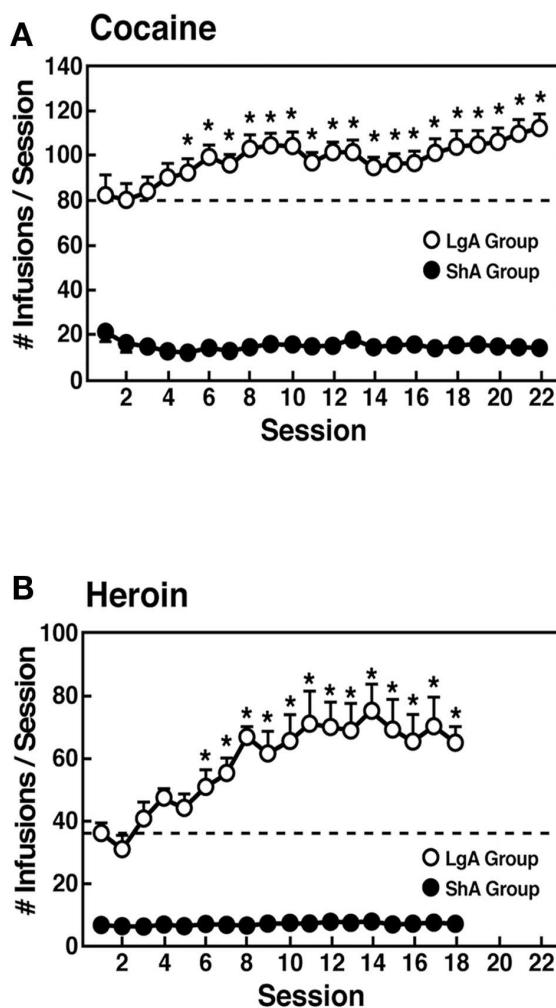
Opponent processes of addiction: Dysphoria and
‘hedonic homeostatic dysregulation’



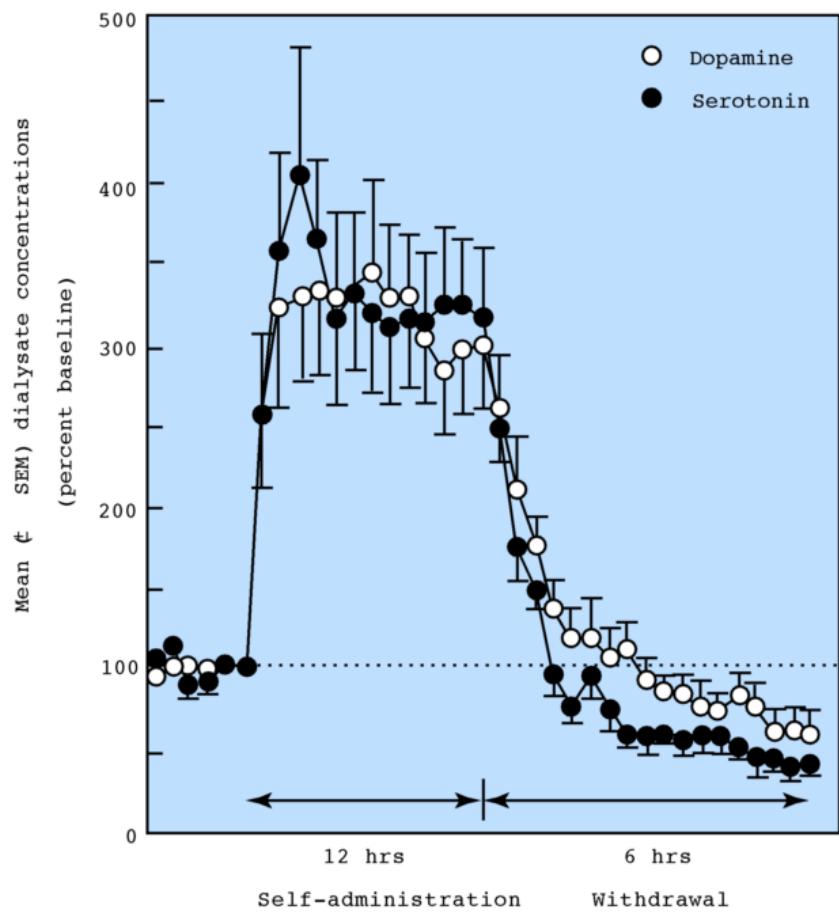
Changes in the magnitude of the 'a' and 'b' processes following repeated exposure to drugs of abuse



Loss of control over drug intake: changes in brain reward thresholds (= dysphoria/anhedonia?)



DA and 5HT levels decrease in nucleus accumbens in rats following withdrawal from self-administered cocaine

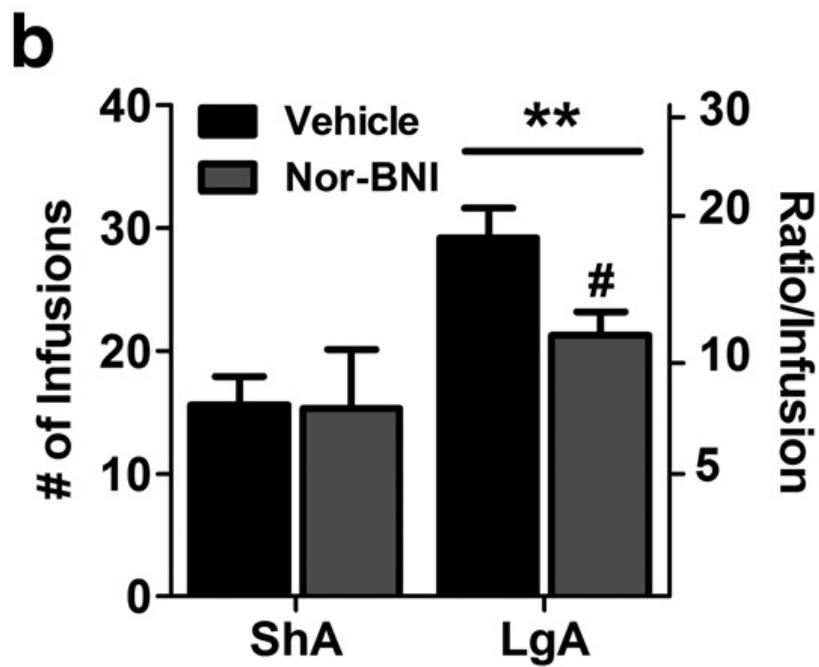
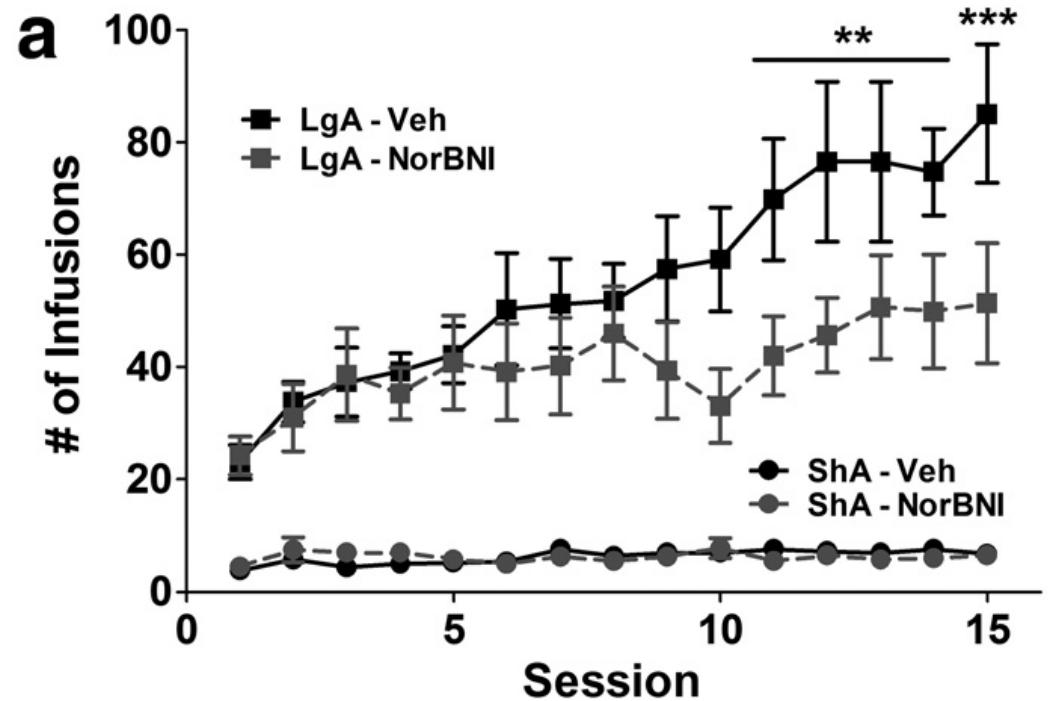


Decrease
in levels below
baseline - associated
with an increased
reward threshold.

Parsons et al. (1995)

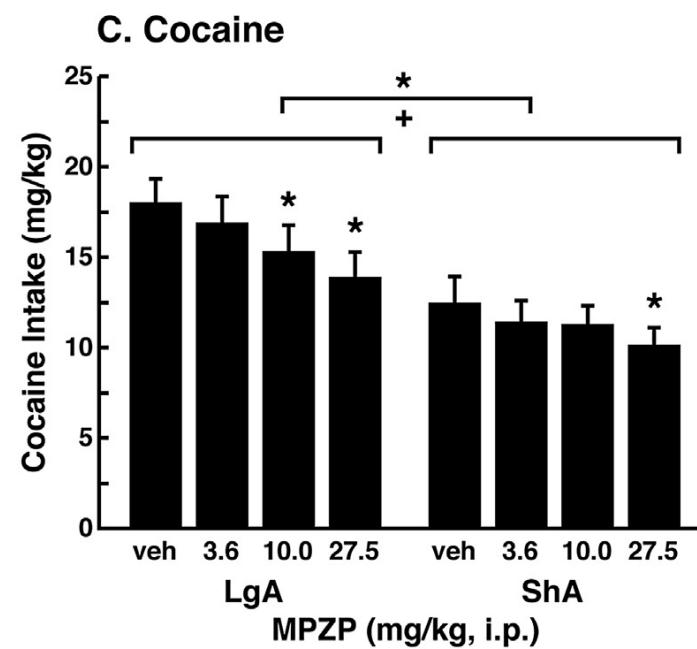
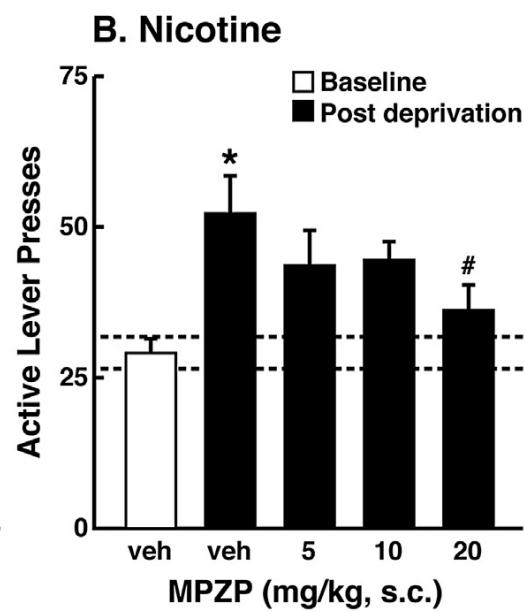
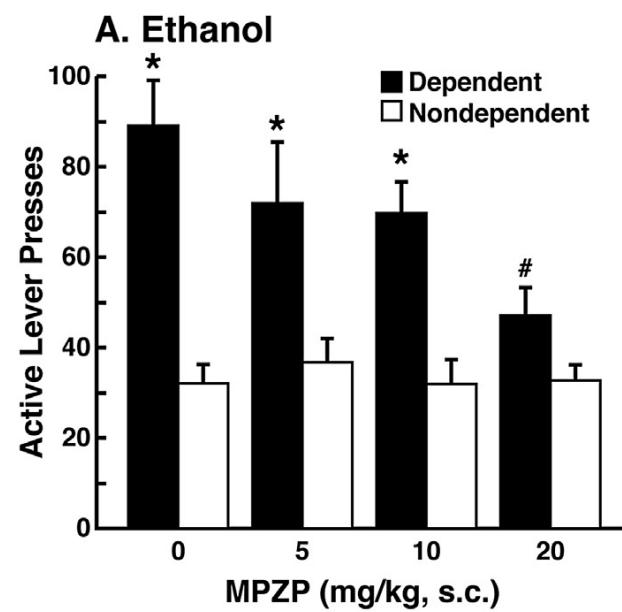
Weiss et al. (1992)

Escalation of drug intake depends on the dynorphin/kappa system



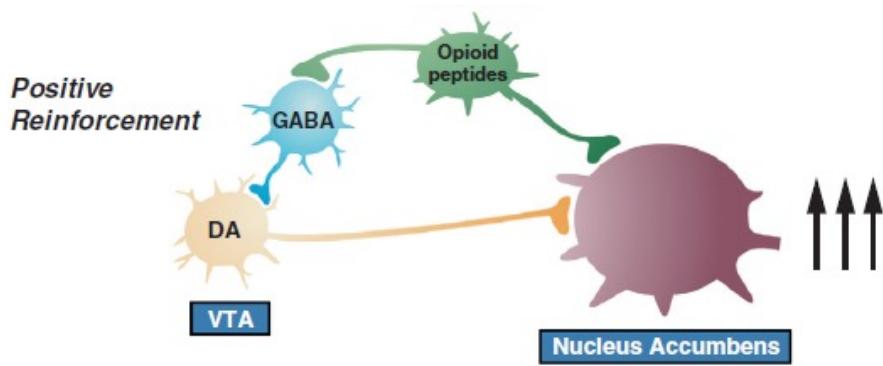
Escalation of drug intake depends on CRF (especially in the amygdala)

CRF₁ Antagonism in Dependent Rats

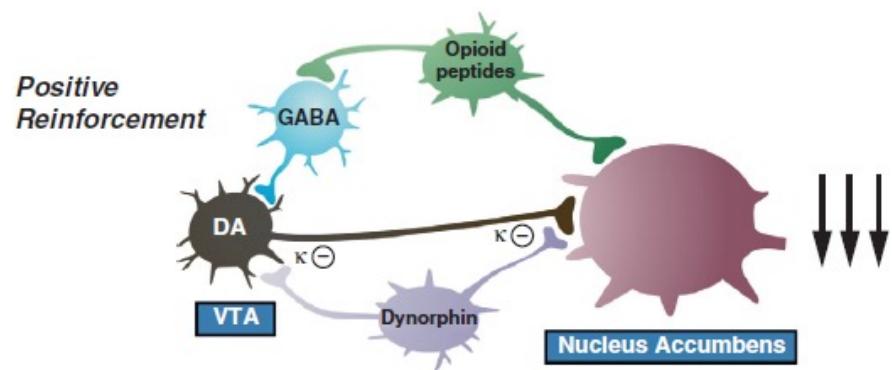


The ‘dark side’ of addiction: within- and between-systems neuroadaptations

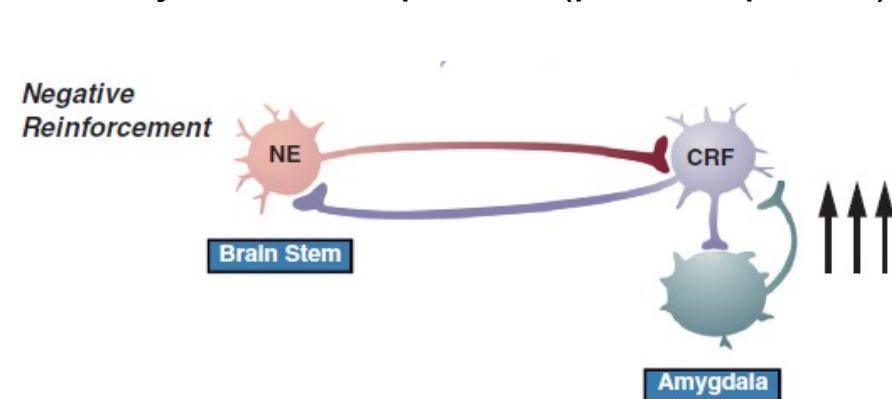
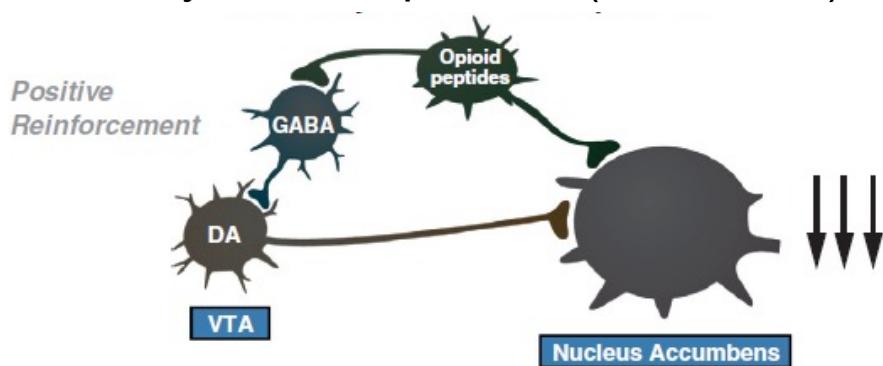
Reward (binge intoxication)



Between-systems adaptation (repeated withdrawal)



Within-system adaptations (withdrawal)



Koob (2013)

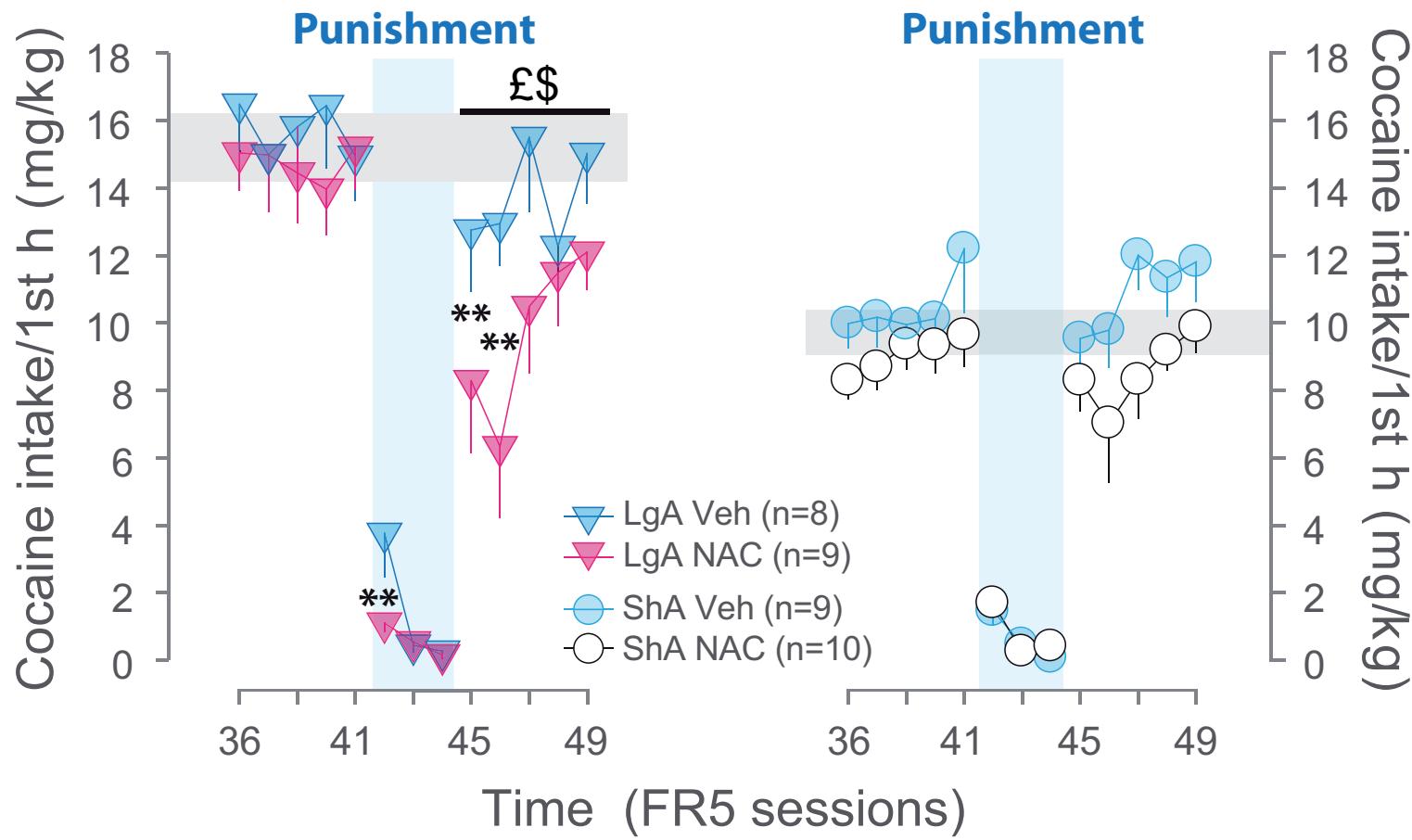
Neural correlates of dysphoria and anhedonia

Withdrawal from stimulants, opiates and ethanol produces persistent neuroadaptations within the reward system i.e. in the mesolimbic dopamine neurons and the nucleus accumbens neurons that they innervate.

These manifest as:

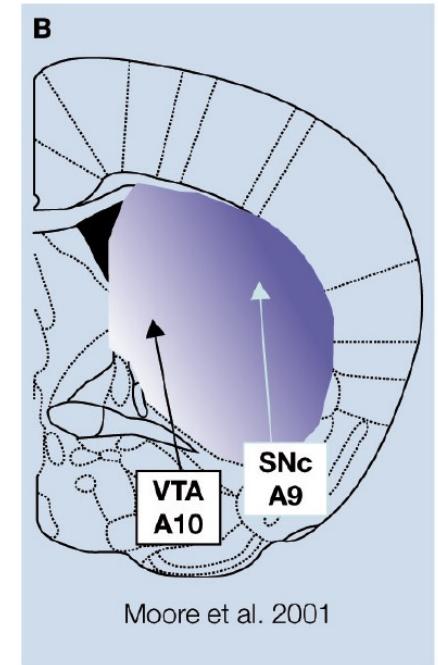
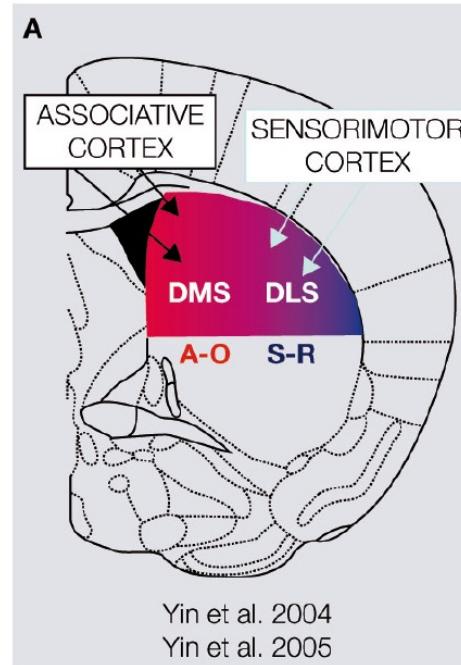
- (i) Decreases in neurotransmitter levels (e.g. dopamine and serotonin)
- (ii) Changes in intracellular & molecular signalling cascades
- (iii) Changes in dopamine receptor expression (e.g. decreased D2 dopamine receptors)

But... Escalation of drug intake does not necessarily predict compulsivity



Addiction: loss of control over maladaptive habits

Individuals suffering from an addiction FORAGE for the drug



Goal-directed → DMS

Lesions/inactivation of the DMS → habitual control

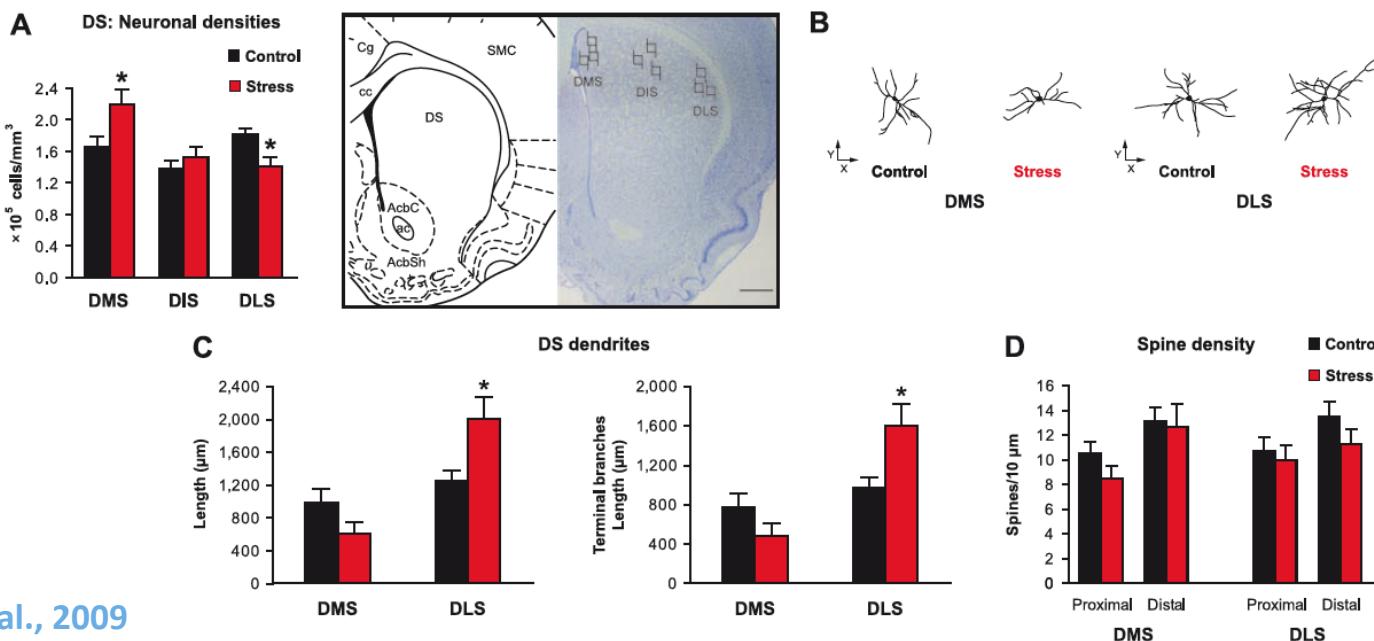
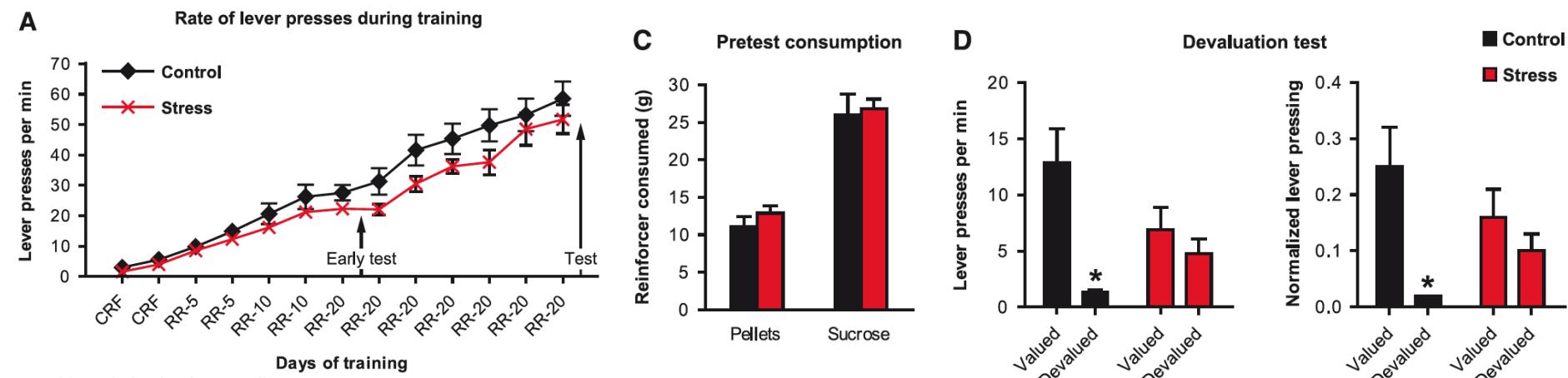
Lesions/inactivation of the prelimbic cortex → habitual control

Habitual → DLS

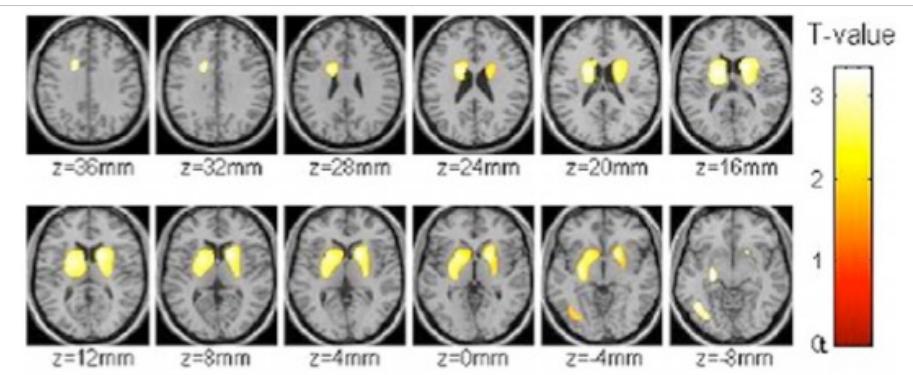
Lesions/inactivation of the DLS → goal-directed behaviour

Lesions/inactivation of the infralimbic cortex or CeA → goal-directed behaviour

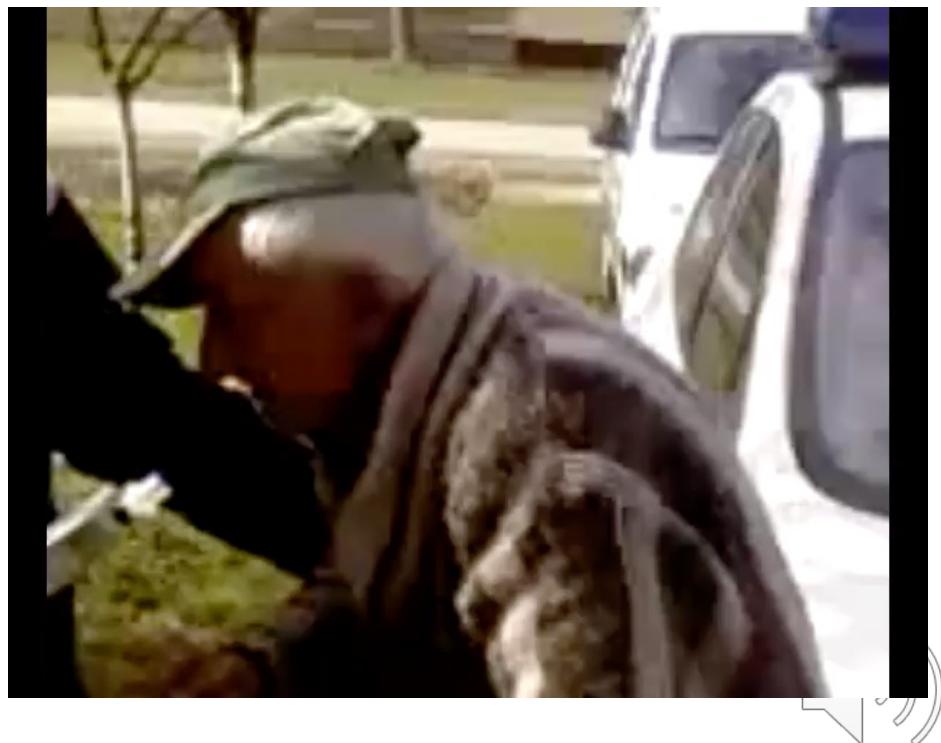
Stress facilitates DLS-dependent instrumental habits



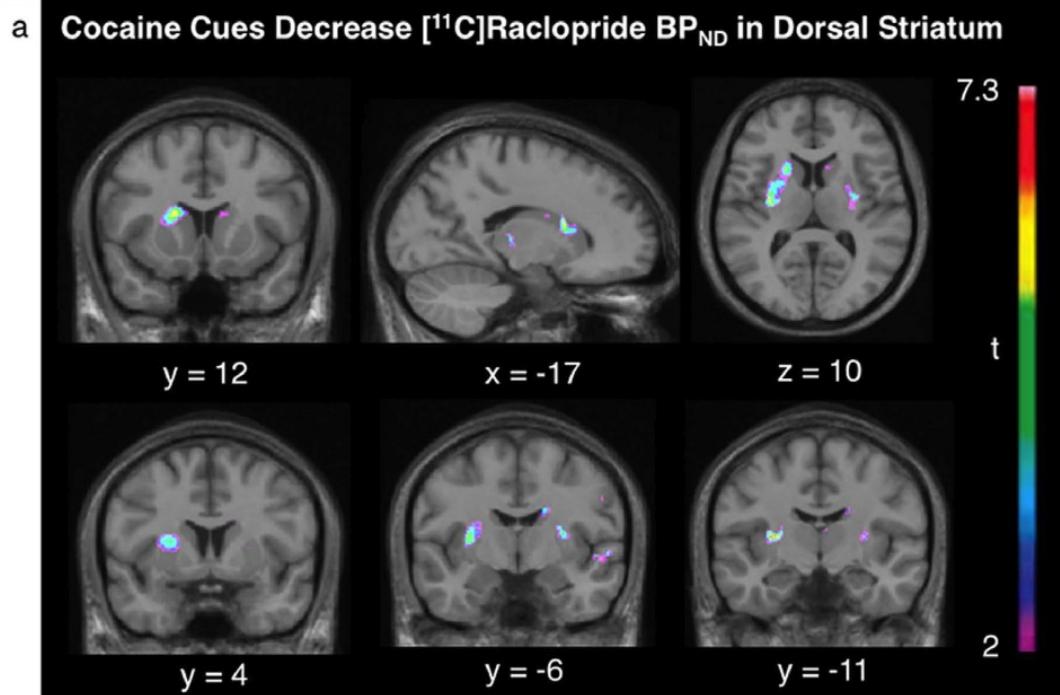
Dopamine release in the DLS in human addicts presented with drug-paired CSs: habits??



Volkow et al., J. Neurosci. 2006



Drug-related cues trigger dopamine release in the DLS of recreational cocaine users



Cocaine cues decreased [^{11}C] raclopride BPND in the dorsal striatum.

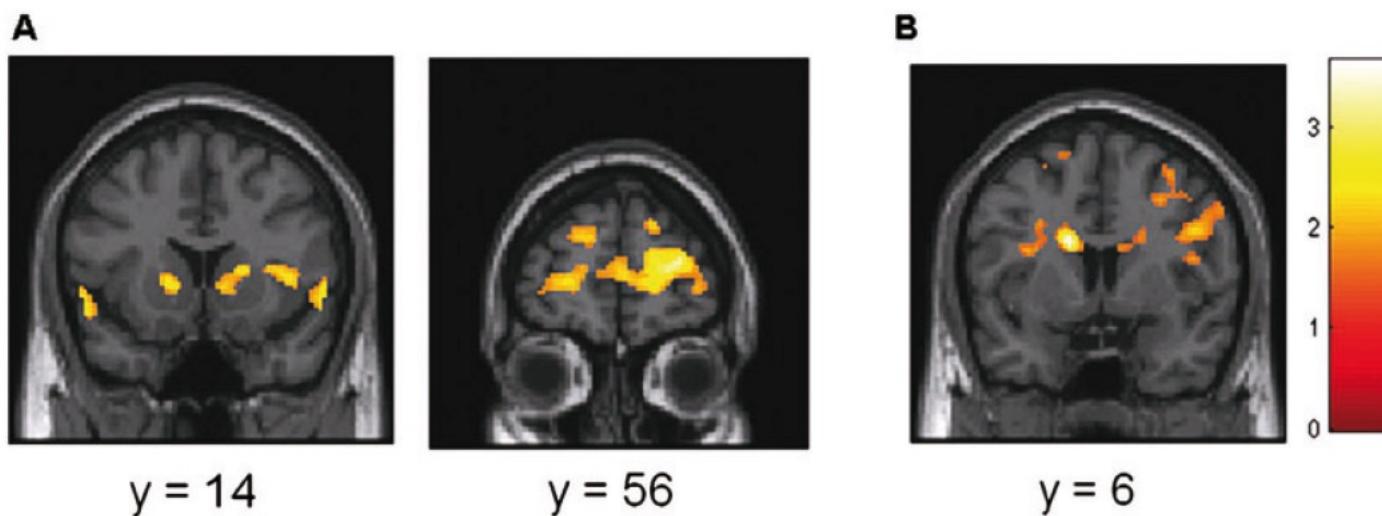
(a) T-map illustrating significant decrease in [^{11}C] raclopride BPND in response to cocaine vs. neutral cues

(b) Regions showing significant decrease in [^{11}C]raclopride BPND in response to cocaine vs. neutral cues

b

Region	Peak Coordinates (x, y, z)	Peak t-value	Cluster size, n voxels (mm^3)	$\Delta \text{BP}_{\text{ND}} (\%)$
Putamen				
Left Posterior	-31, -11, 9	7.31	124 (994)	15.21 (19.6)
Left Anterior	-25, 4, 12			14.0 (19.5)
Right posterior	30, -7, 11	5.61	21 (168)	15.7 (11.5)
Caudate				
Left Anterior	-17, 12, 14	6.56	48 (387)	16.1 (19.2)

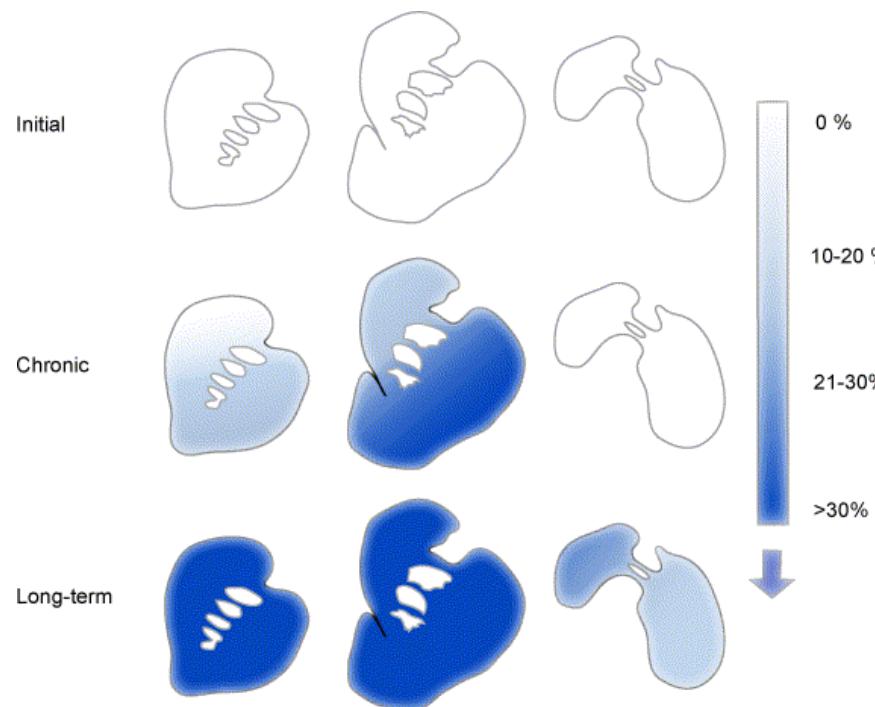
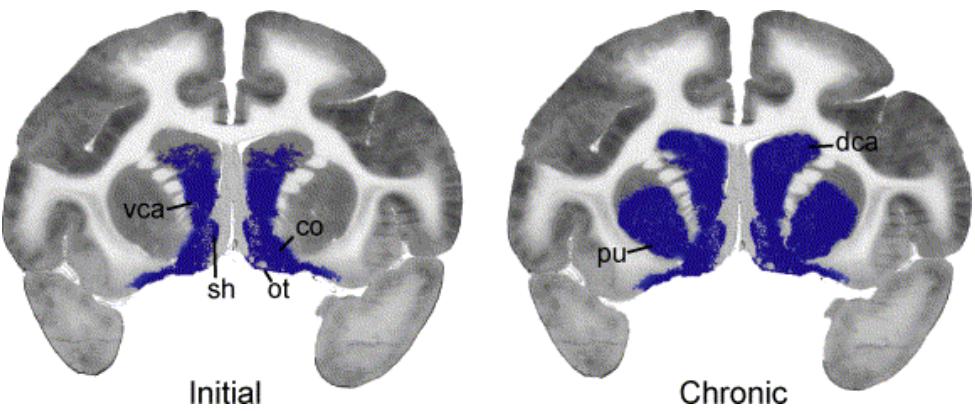
Progressive recruitment of DLS mechanisms in alcohol addiction



Alcohol cue-induced brain activation (contrast ‘favourite drinks versus neutral cues’) in light social drinkers compared to heavy social drinkers

- (a) increased activation in light social drinkers in the ventral striatum and the prefrontal cortex
- (b) heavy drinkers showed enhanced activation in the dorsal striatum

Intrastriatal shifts following cocaine exposure

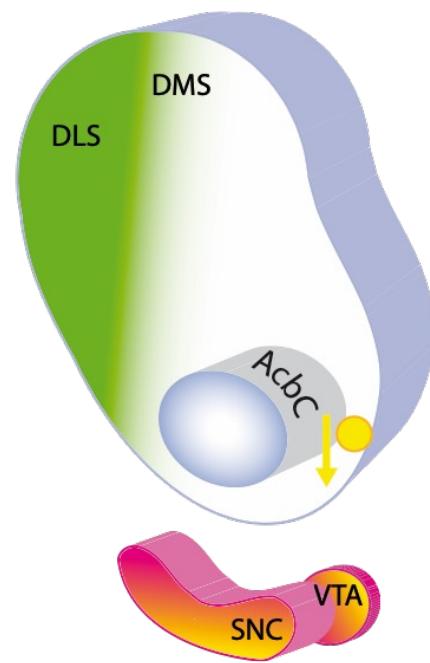


2DG metabolic activity decreases

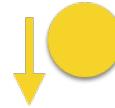
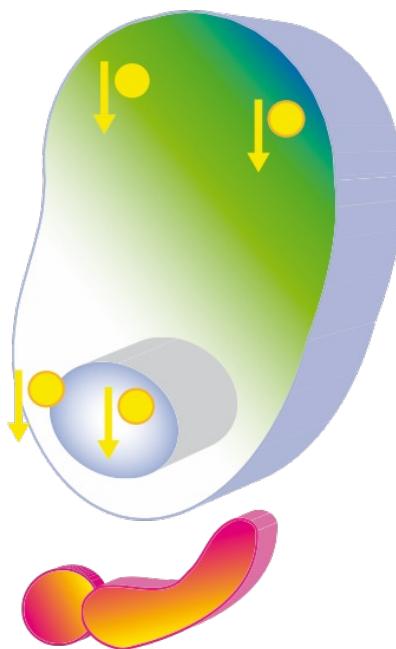
D2 binding site decreases

Intrastriatal shifts following cocaine exposure

Short term cocaine exposure



Chronic cocaine exposure



**Decreased dopamine D2
receptor level**

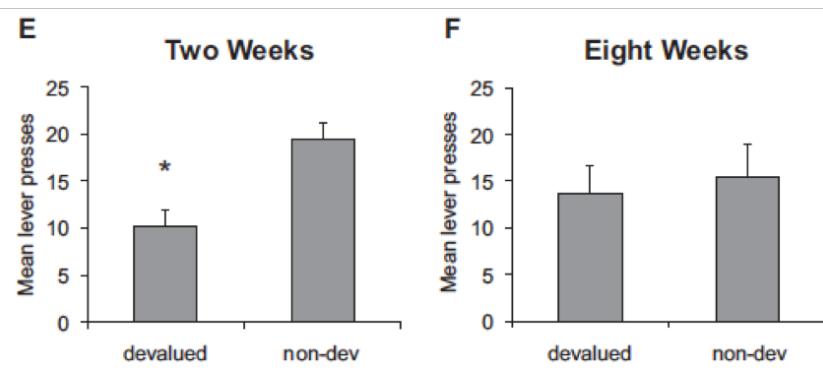
Besson et al., 2013

Drugs facilitate habit formation

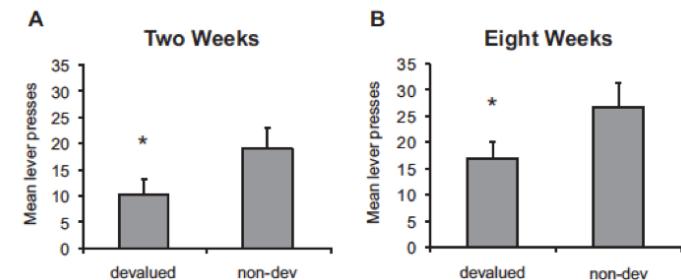
Goal-directed → DMS

Habitual → DLS

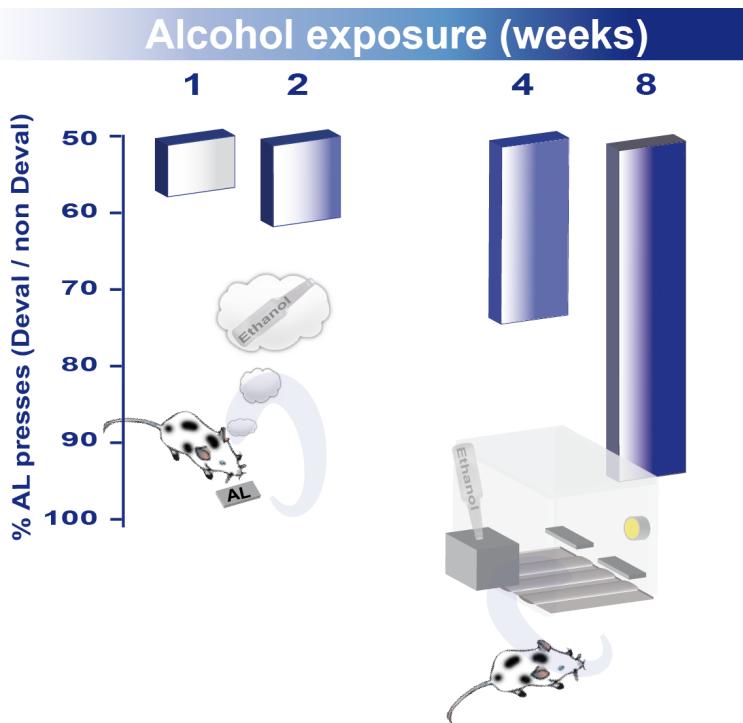
Alcohol



Sucrose



Outcome devaluation



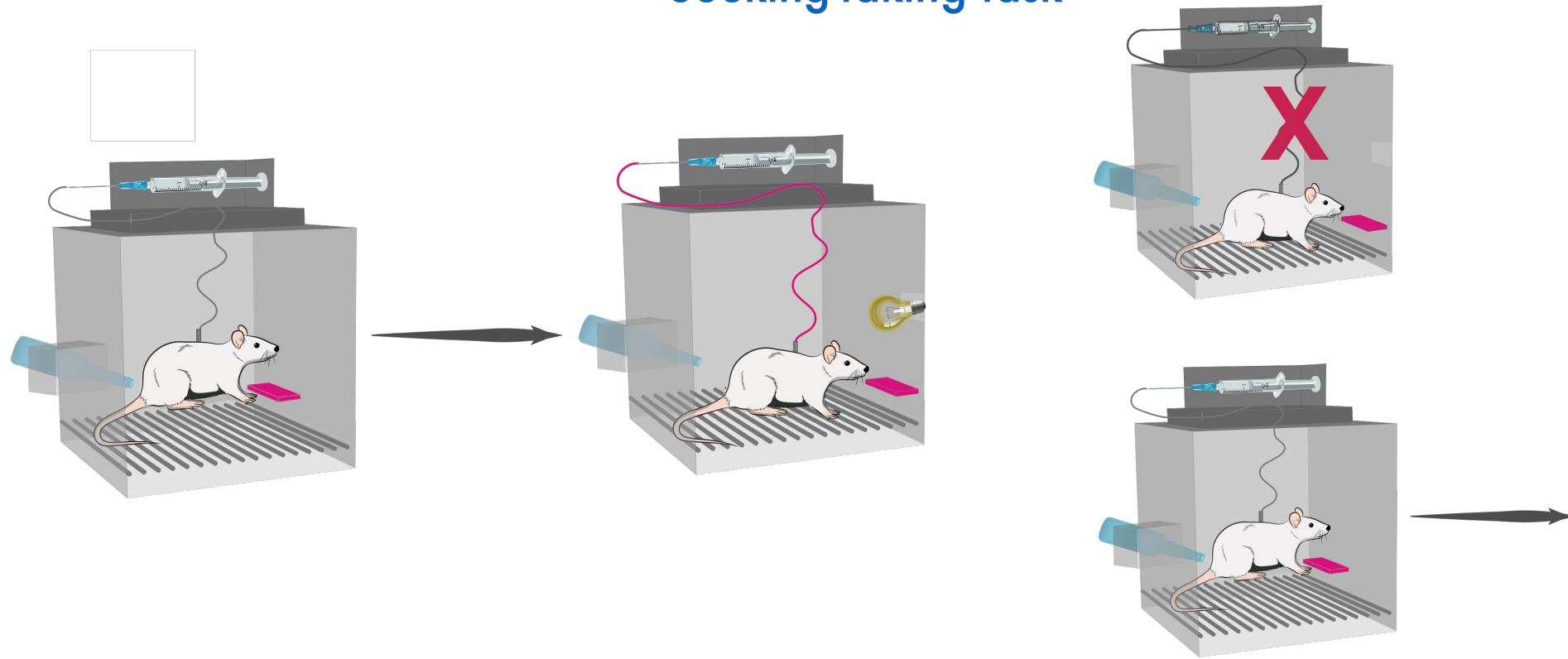
Corbit LH et al. Biol Psychiatry. 2012

Belin-Rauscent et al., 2012

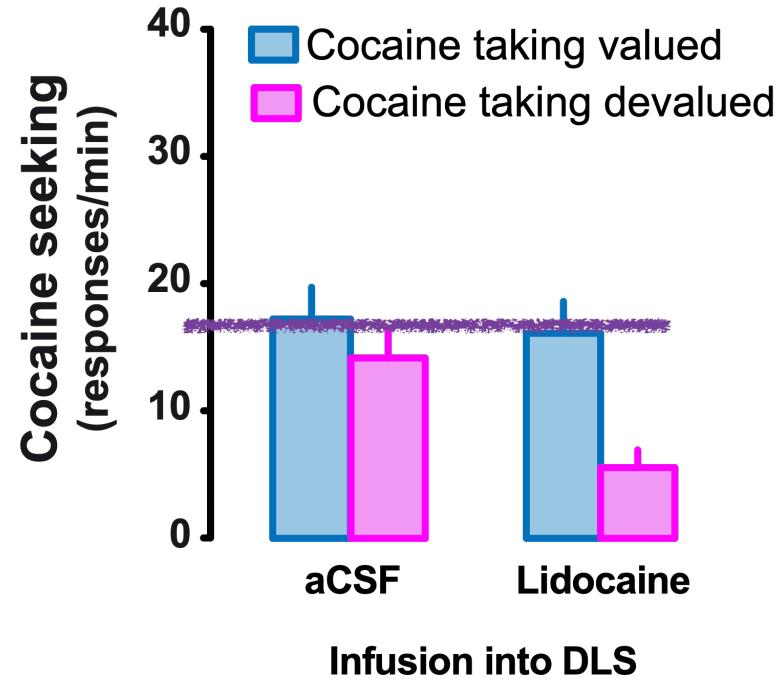
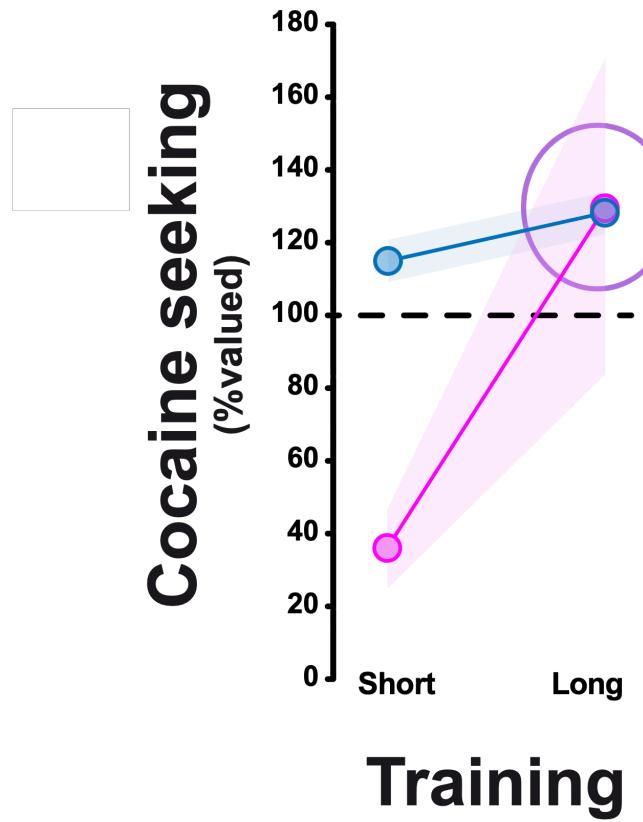
DLS-dependent habits emerge following overtraining (or interval schedules of reinforcement)

Assessing the associative nature of cocaine seeking

Seeking-taking task



DLS-dependent habits emerge following overtraining (or interval schedules of reinforcement)

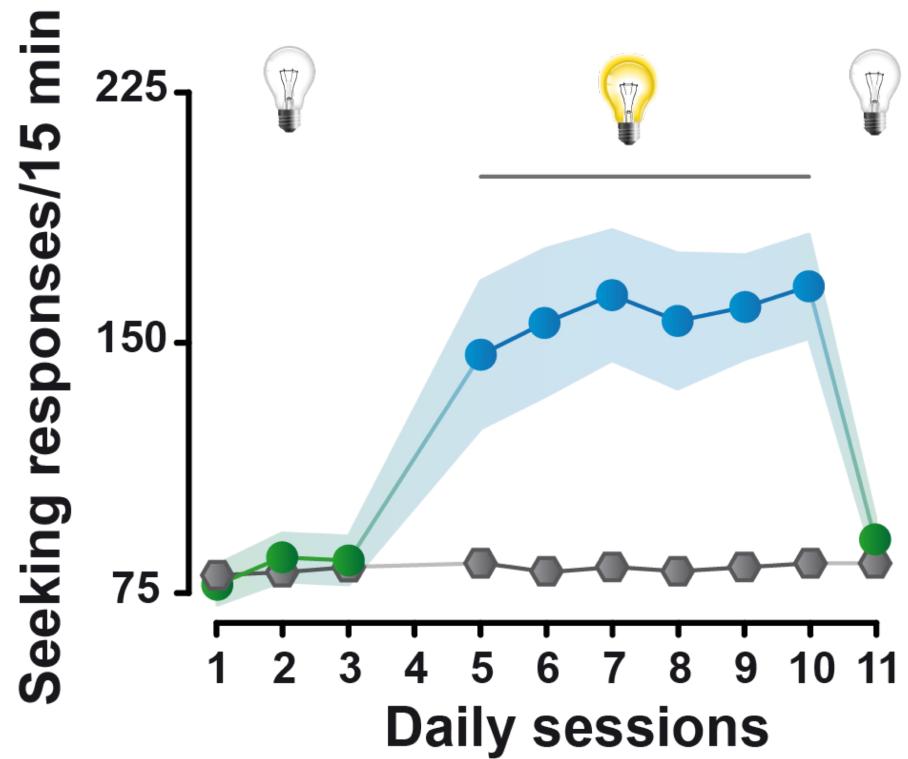
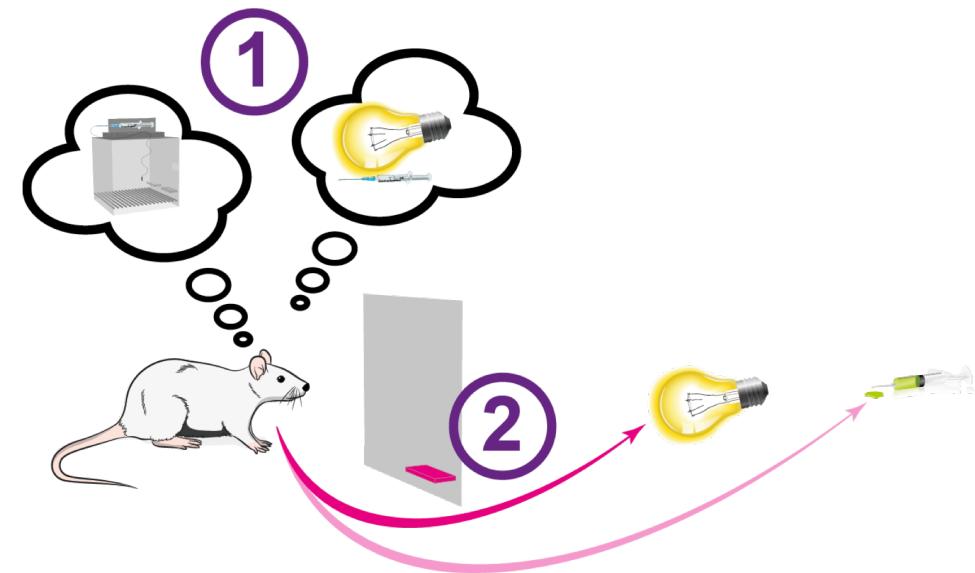


Zapata et al., J Neurosci. 2010

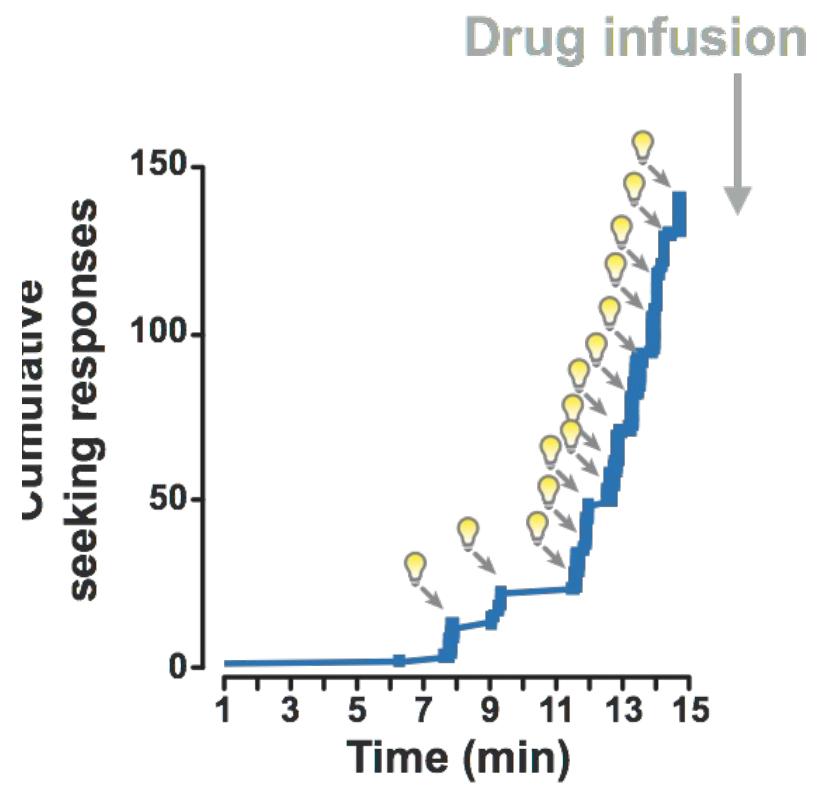
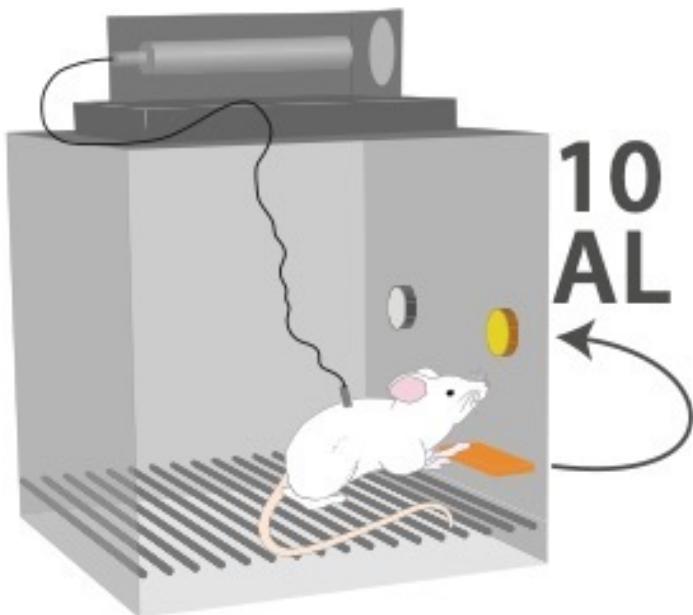
Inactivation DLS = restauration of sensitivity to devaluation

Intrastriatal functional shifts and drug seeking habits: a necessary step towards addiction?

Measuring cue-controlled drug seeking behaviour: second-order schedules of reinforcement

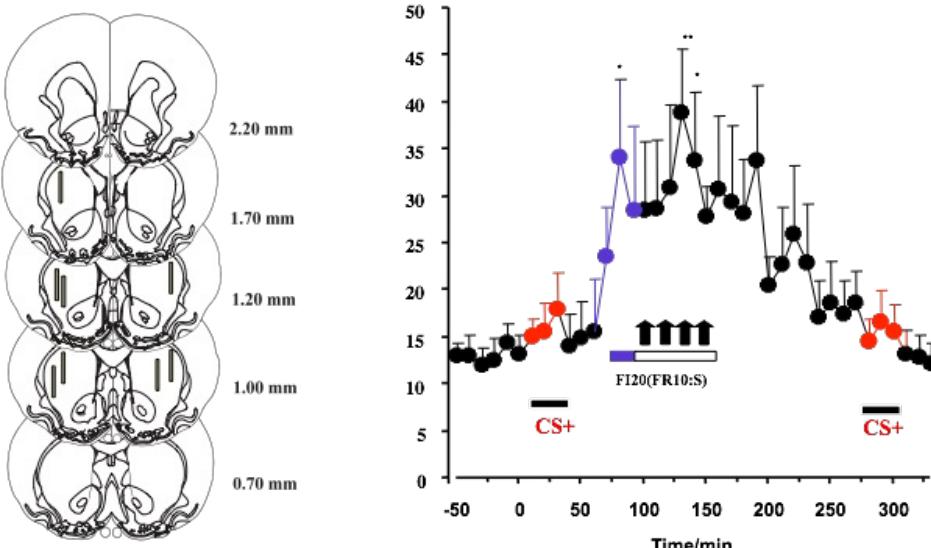


Measuring cue-controlled drug seeking behaviour: second-order schedules of reinforcement

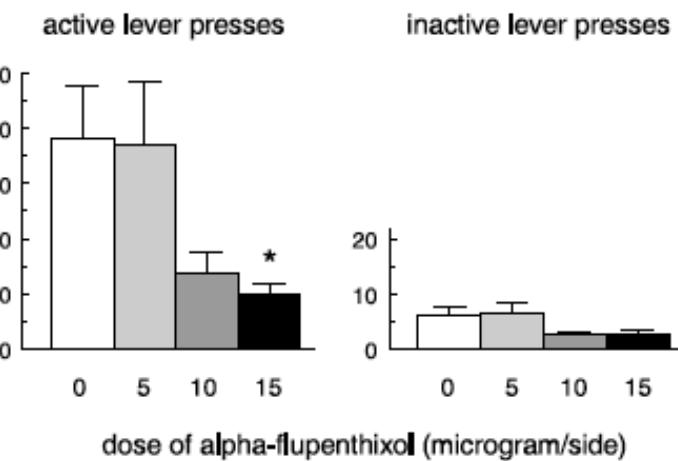
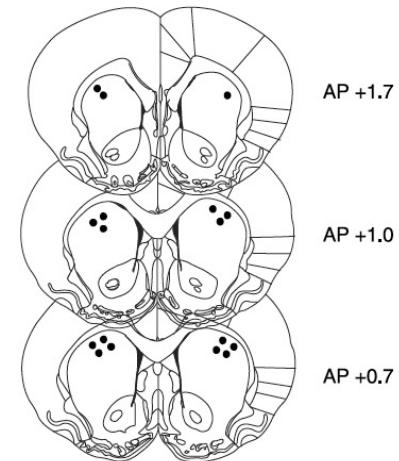


Drug seeking for prolonged periods of time reinforced by the conditioned reinforcing properties of drug-associated CSs

Well established, habitual cocaine-seeking depends dopaminergic mechanisms in the DLS



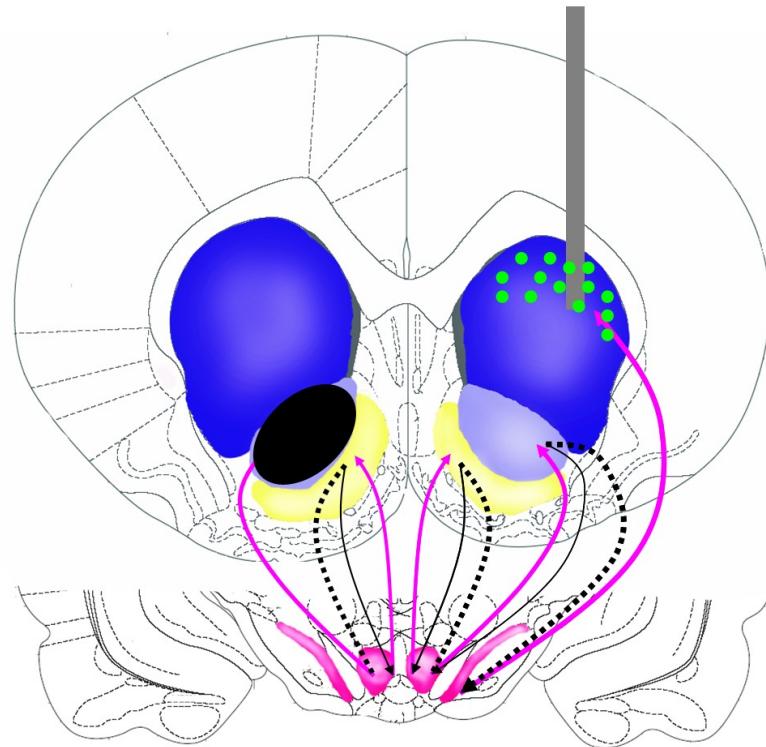
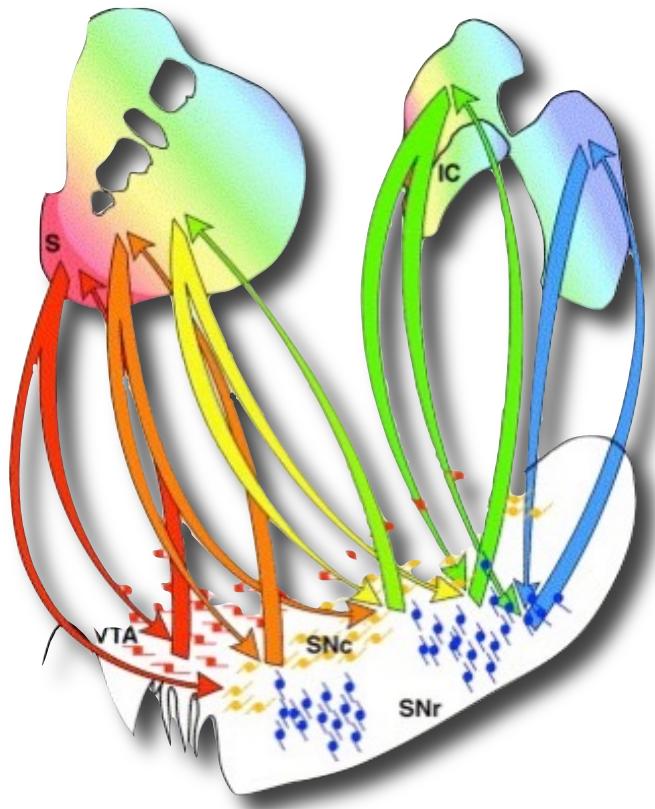
Ito R. et al. (2002)



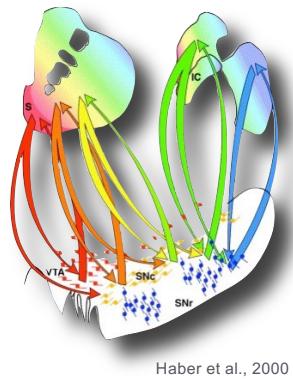
Vanderschuren LJ et al. (2005)

Intrastriatal functional shifts in the control over cue-controlled drug seeking: development of maladaptive habits

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

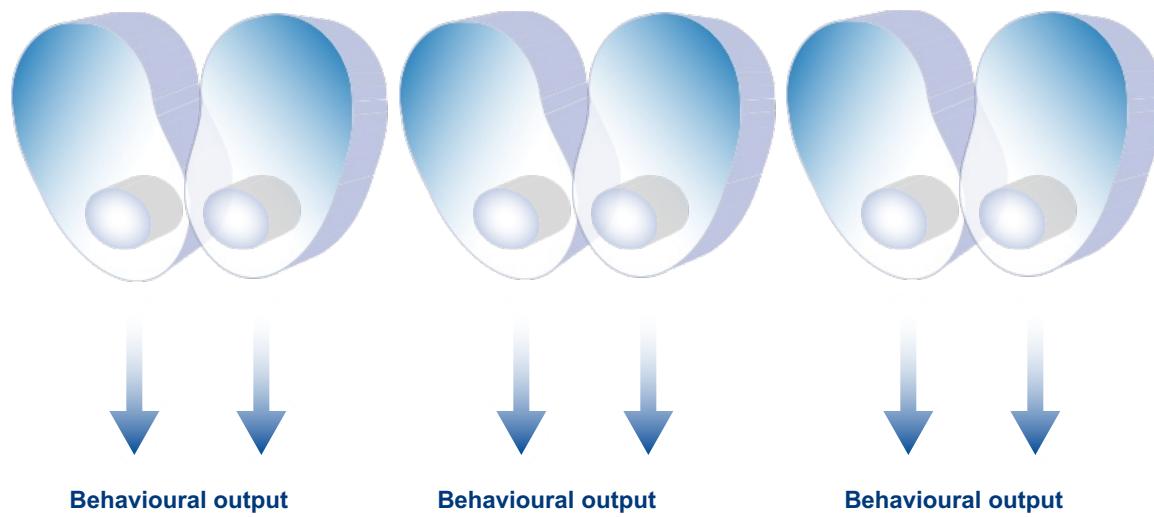


Intrastriatal functional shifts in the control over cue-controlled drug seeking: development of maladaptive habits



Haber et al., 2000

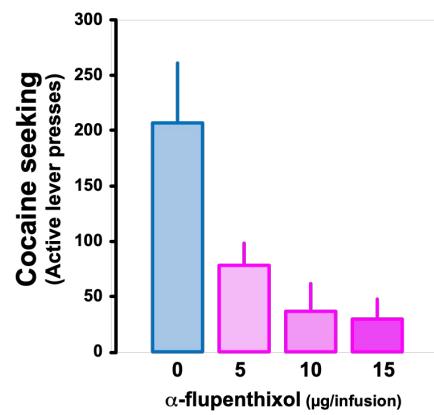
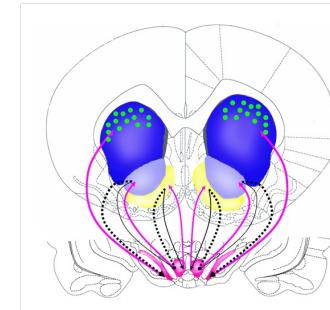
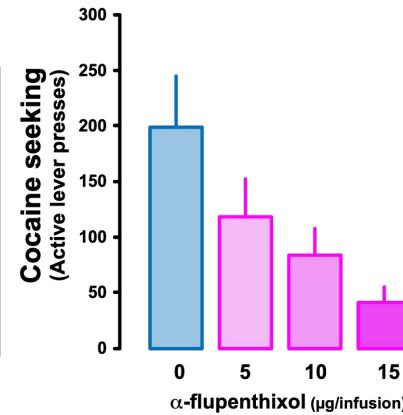
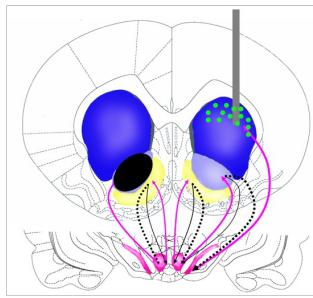
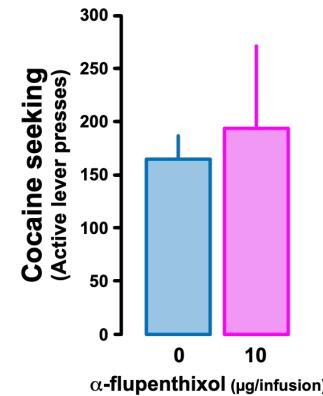
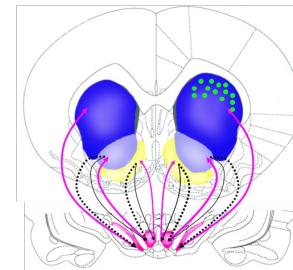
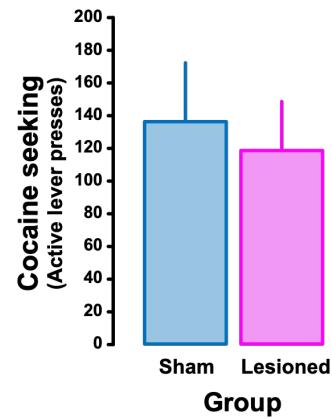
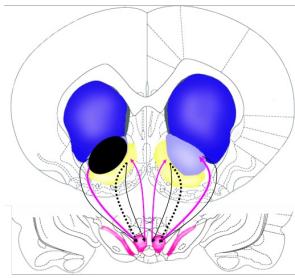
Functional disconnections



Belin & Everitt, Neuron 2008

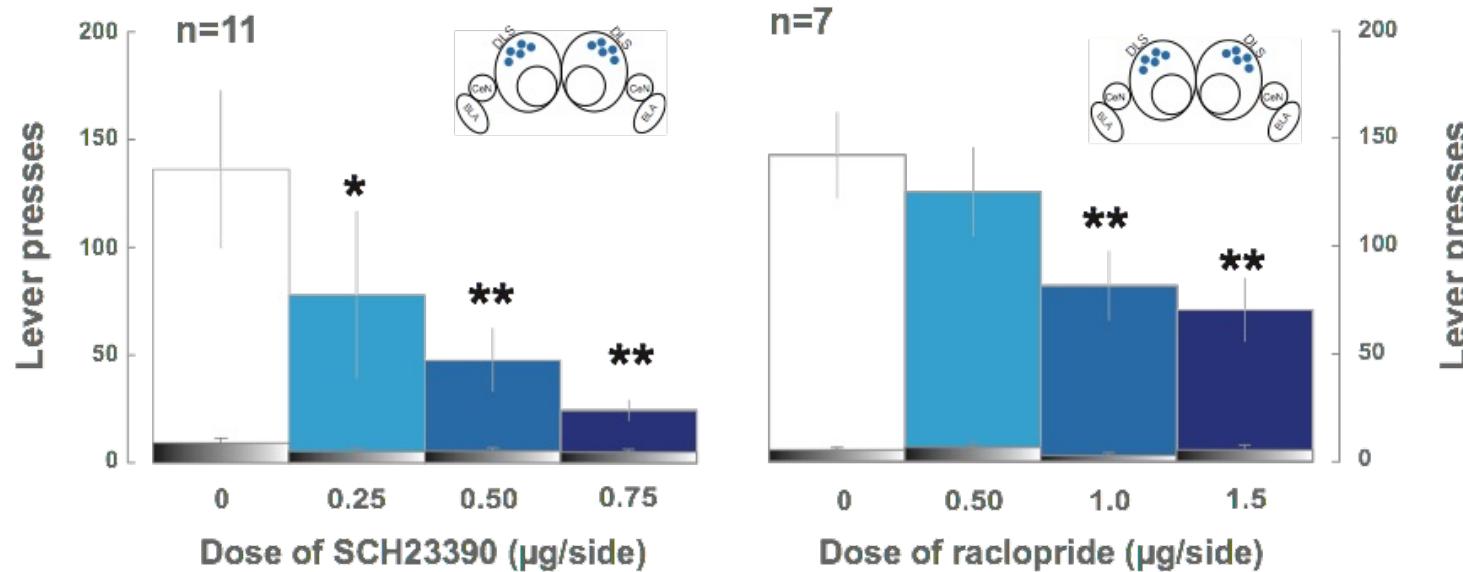
Intrastriatal functional shifts in the control over cue-controlled drug seeking: development of maladaptive habits

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

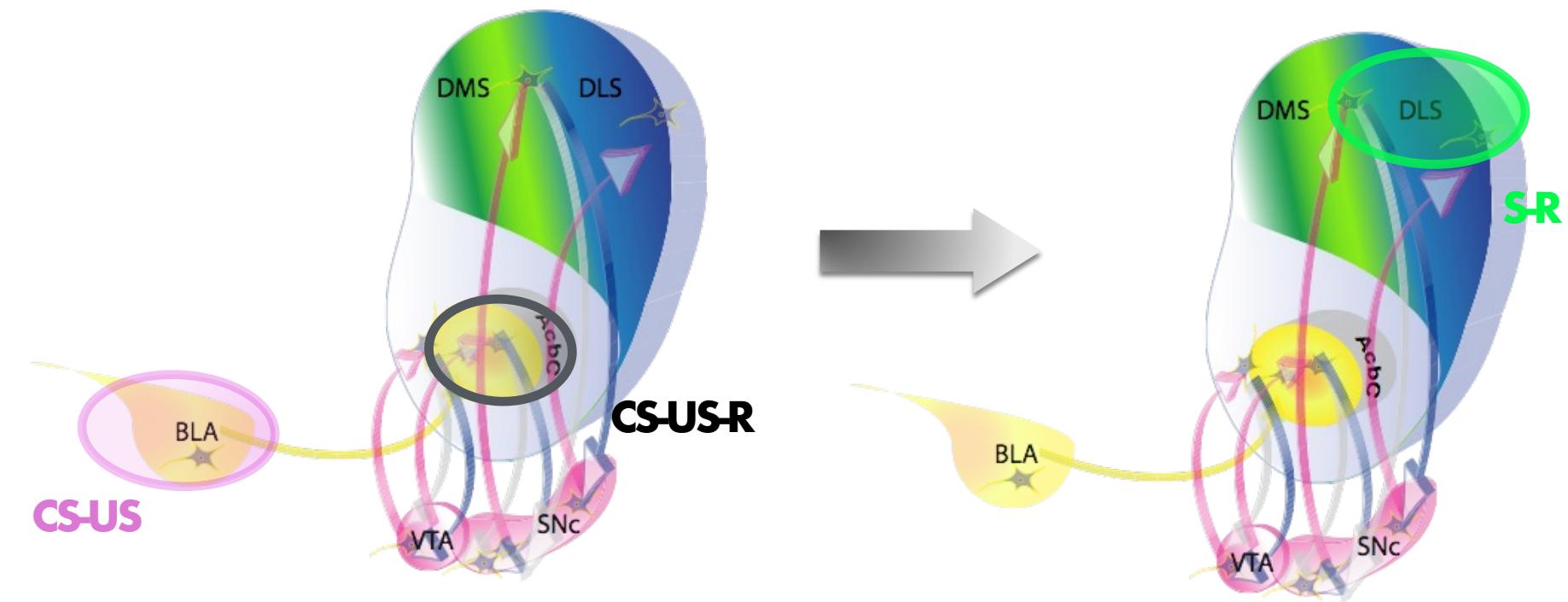


Intrastriatal functional shifts in the control over cue-controlled drug seeking: development of maladaptive habits

Cocaine seeking habits depend upon D1 and D2 dopamine receptors in the dorsolateral striatum



Intrastriatal functional shifts in the control over cue-controlled drug seeking: development of maladaptive habits



Belin et al., 2013

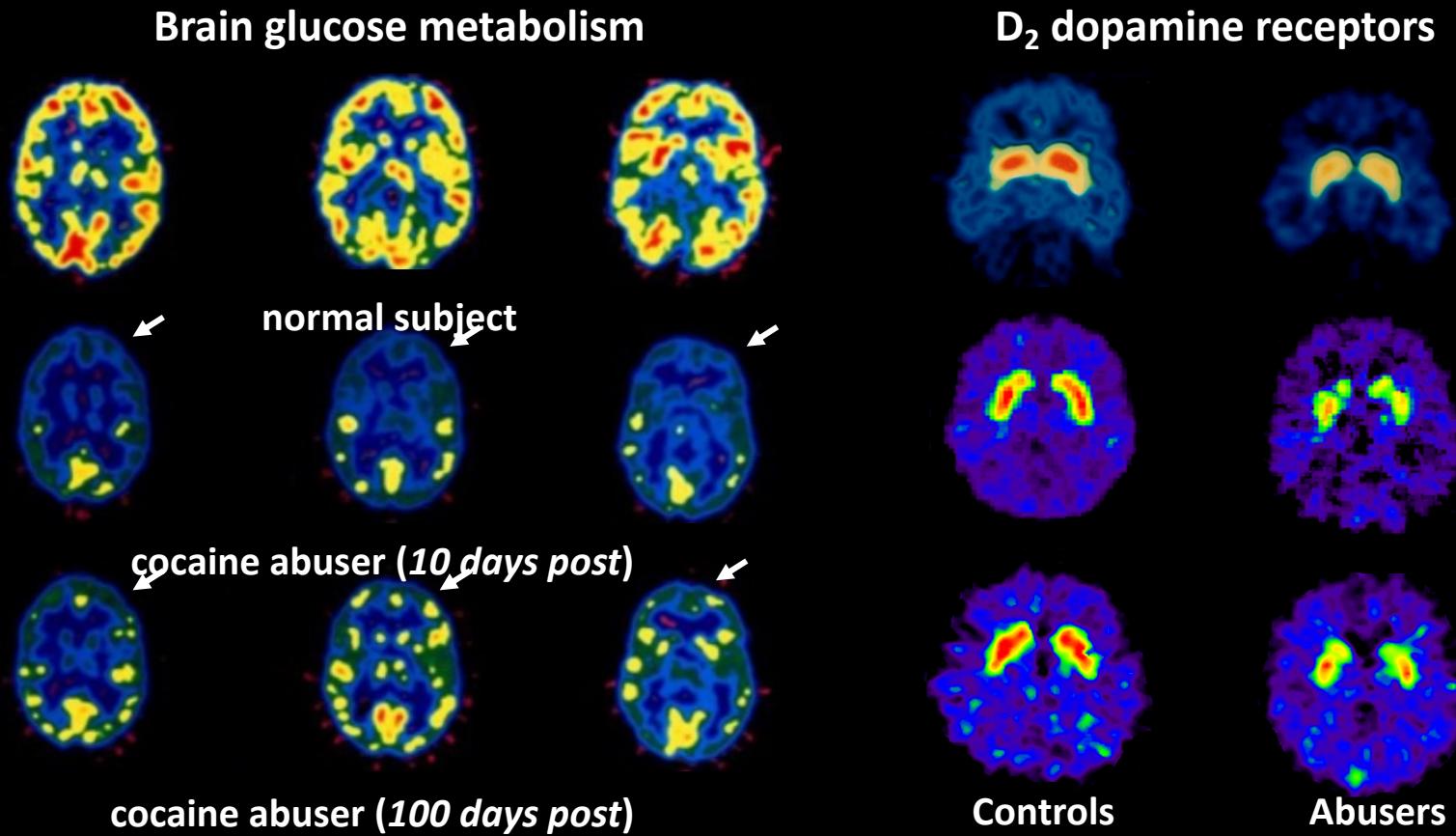
Conclusions

- Chronic exposure to drugs and associated withdrawal recruit within- and between- systems adaptations
- These adaptations involve the functional engagement of the endogenous stress system (NA, CRF, dynorphin...) and mediate dysphoria, anhedonia and escalation of drug intake
- But stress also facilitates the control of drug foraging by the DLS-dependent habit system
- Drugs facilitate habits and promote the functional recruitment of DLS control over behaviour
- Drug seeking habits depend on DLS dopamine dependent mechanisms, the recruitment of which is mediated by the ascending spiralling circuitry.

Lecture 8: individual vulnerability to addiction

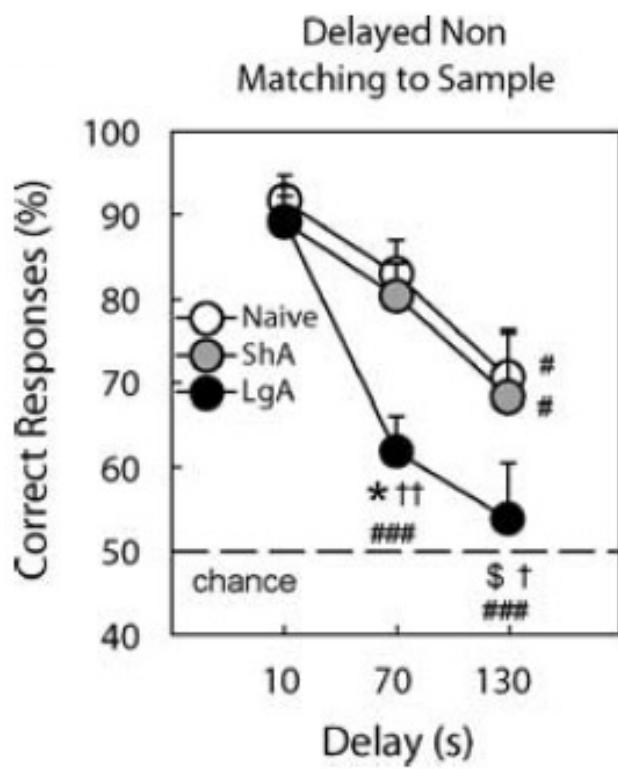
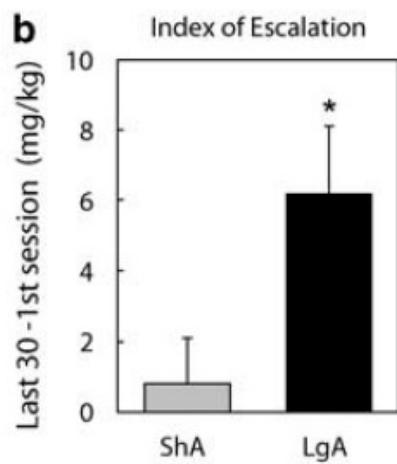
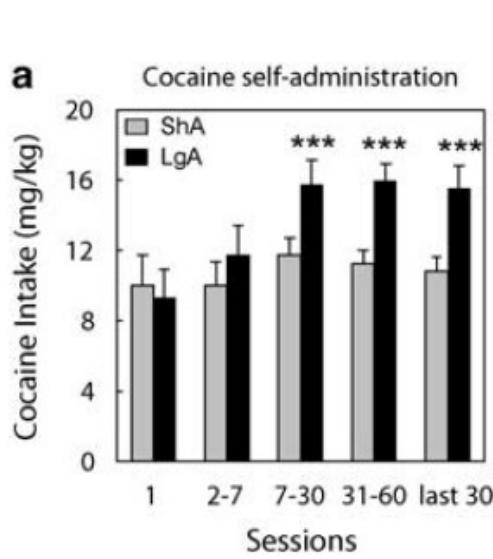
What is the neural basis of a compulsive drug-seeking and drug-taking habit?

Addicted individuals show reduced prefrontal cortical metabolic activity and a correlated decrease in dorsal striatal dopamine D₂ receptors.



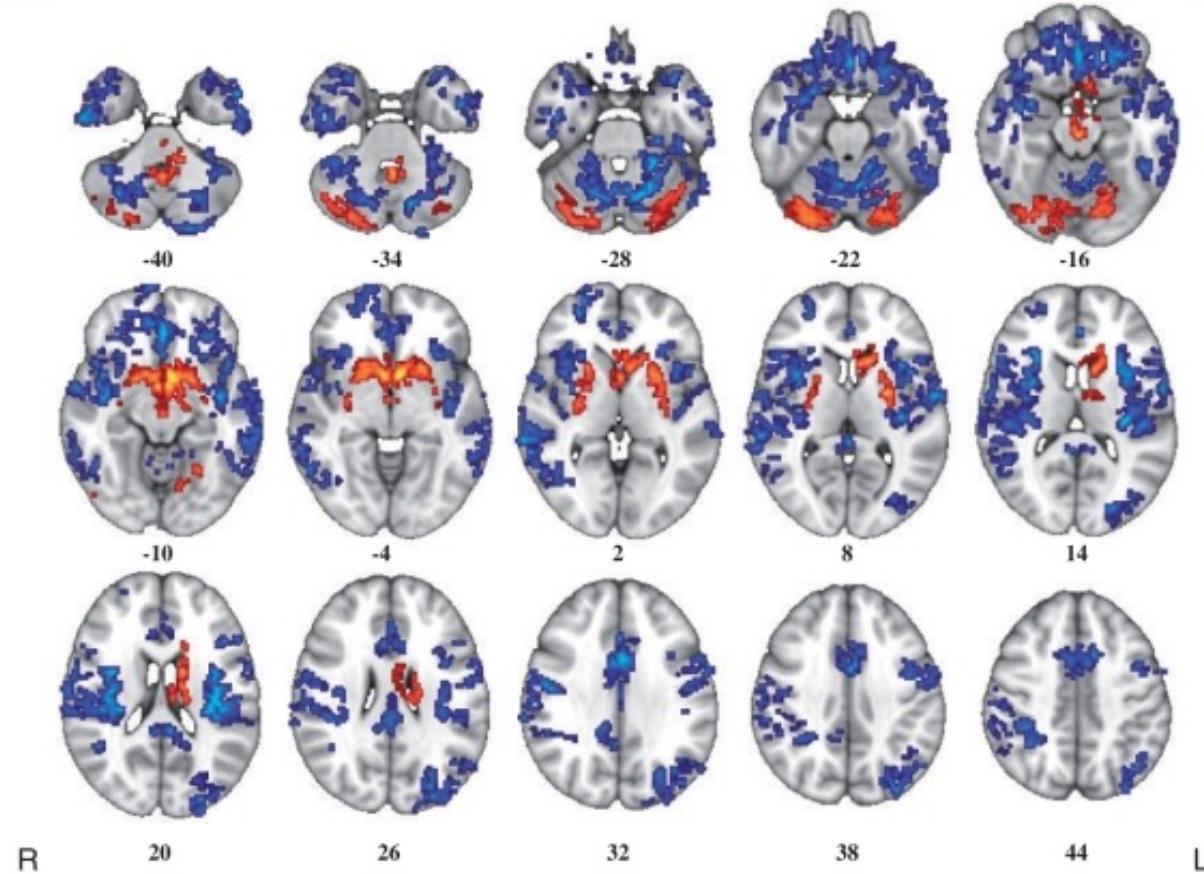
data from Volkow & colleagues

Extended exposure to cocaine impairs PFC-dependent functions



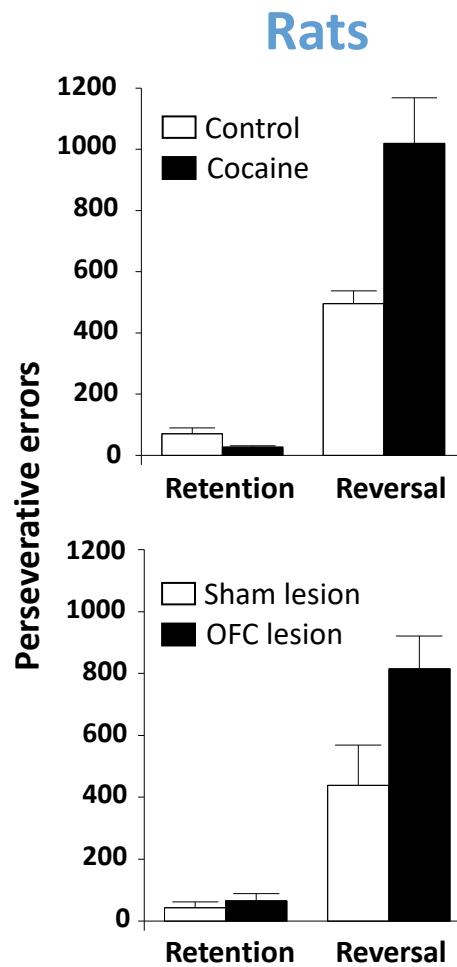
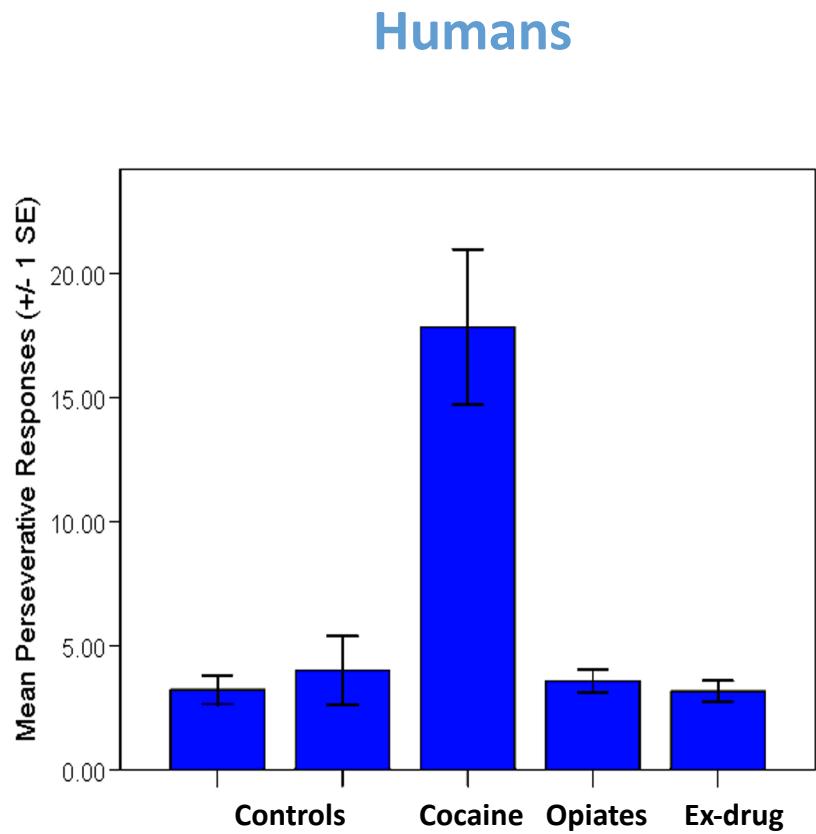
George et al. (2008)

Prolonged drug abuse correlates with reduced grey matter volume in the prefrontal cortex



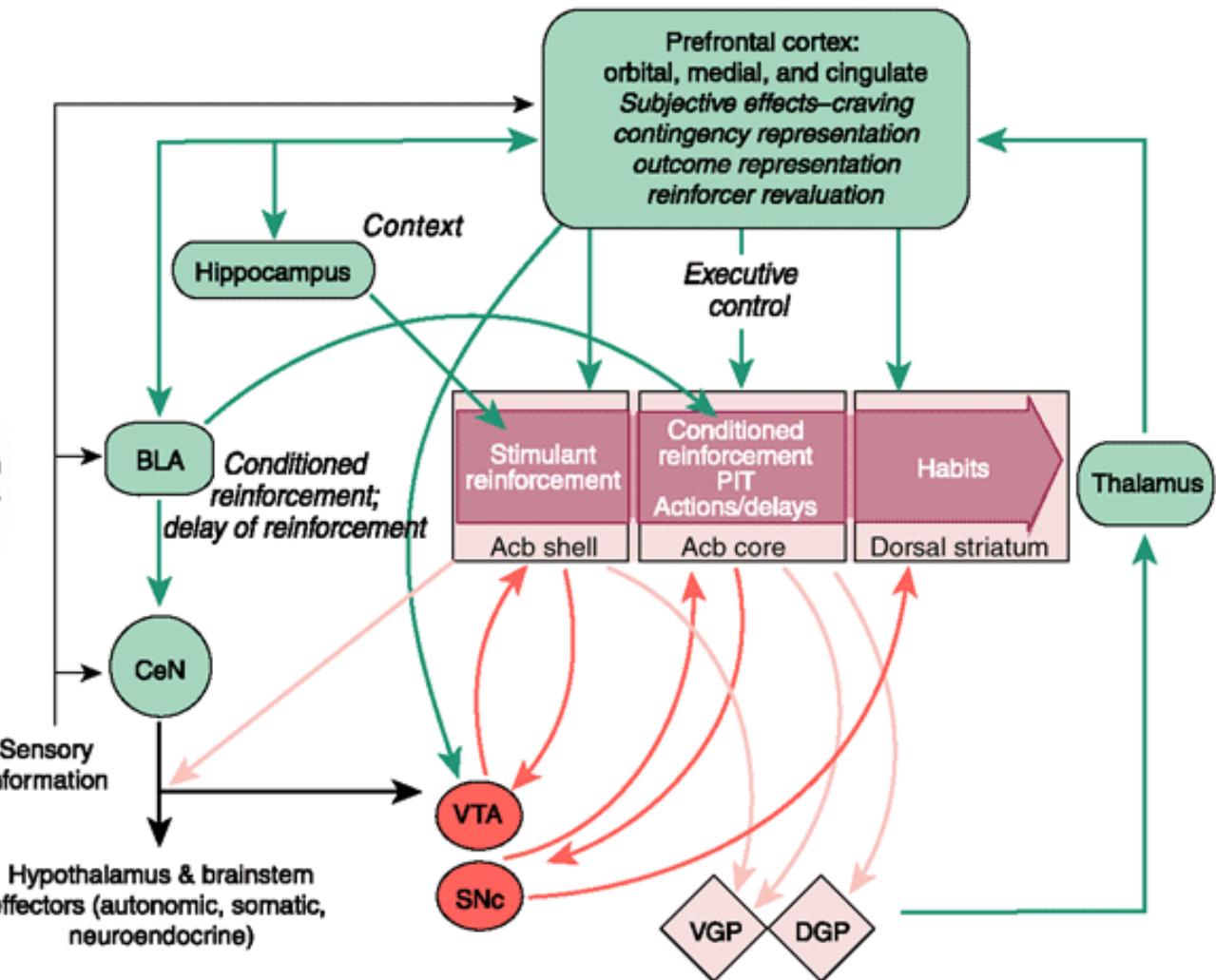
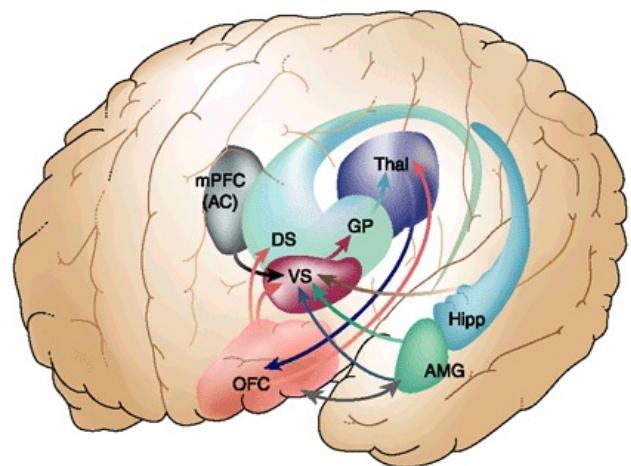
Ersche et al. (2011)

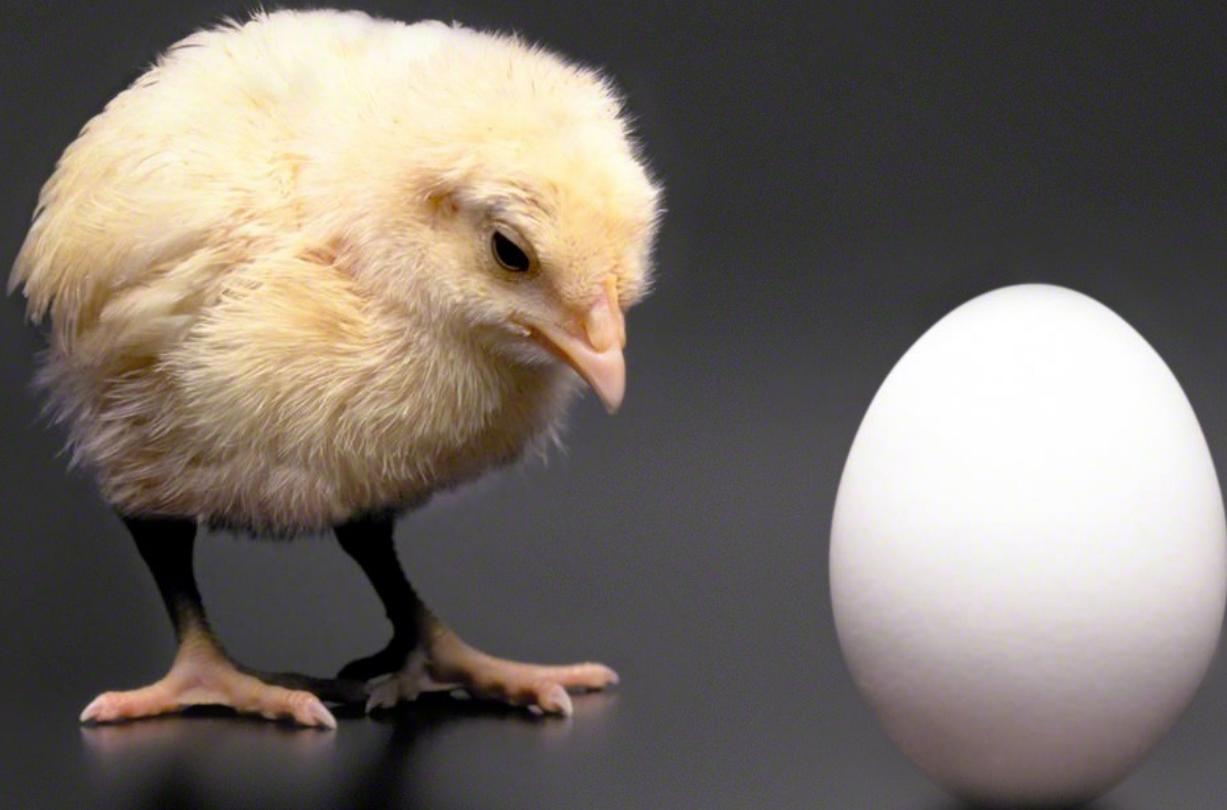
Reduced prefrontal function produces deficits on tests of cognitive flexibility, such as reversal learning



Ersche et al. (2007); Stalnaker et al. (2009)

Addiction: from actions to habits to compulsion





Are the brain changes observed in addiction a cause or consequence of taking drugs of abuse?

We are not equally vulnerable to addiction



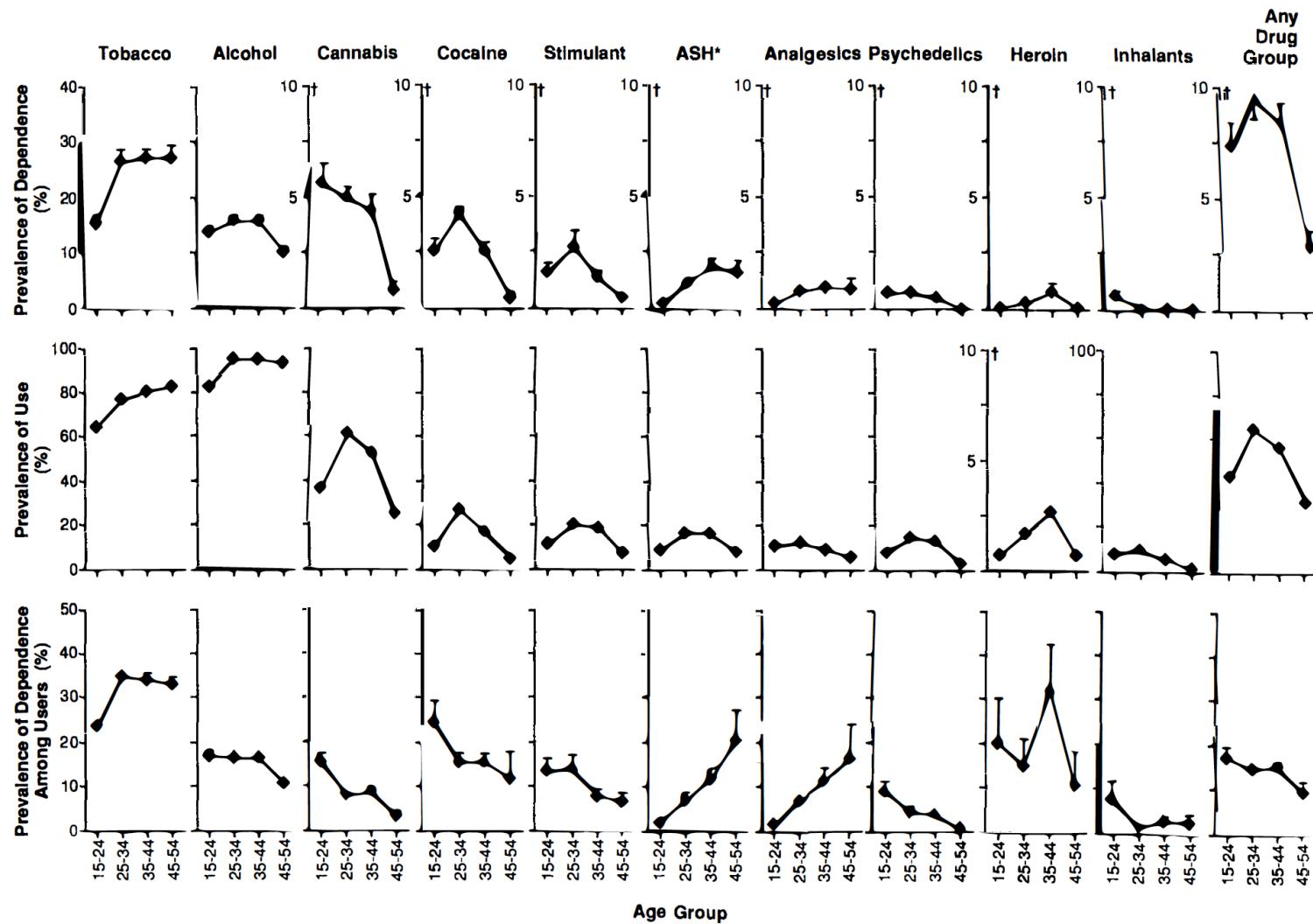
Potential drug
users

First drug use/
recreational use

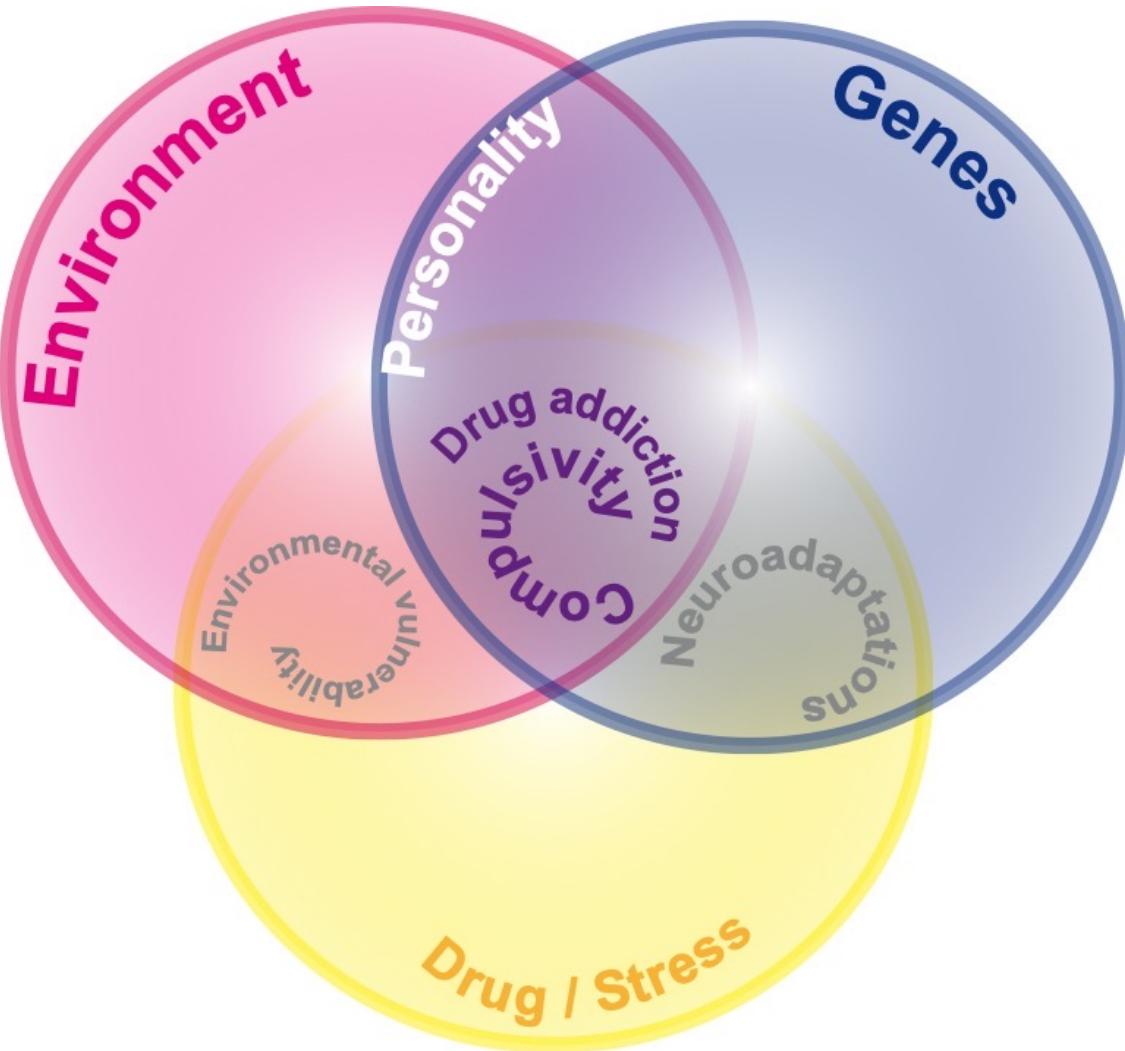
Abuse

Addiction

We are not equally vulnerable to addiction



Anthony et al., 1994



We are not equally vulnerable to addiction

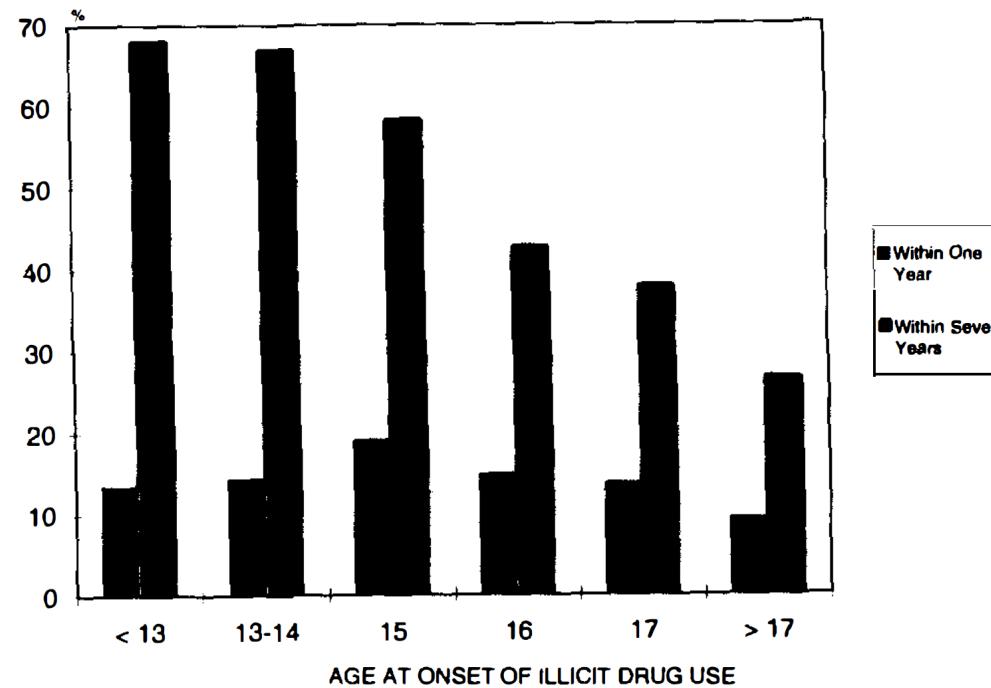
DSM V Diagnostic Criteria: Substance Use Disorder

SEVERITY: 2-3: mild 4-5: moderate 6 or more: severe

1. Taking the substance in larger amounts or for longer than you meant to.
 2. Wanting to cut down or stop using the substance but not managing to do so.
 3. Spending a lot of time getting, using, or recovering from use of the substance
 4. Cravings and urges to use the substance
 5. Not managing to do what you should at home, work, or school because of substance use
 6. Continuing to use, even when it causes problems in relationships
 7. Giving up important social, occupational, or recreational activities because of substance use
 8. Using substances again and again, even when it puts you in danger
 9. Continuing to use, even if you have a physical or psychological problem that could have been caused or made worse by the substance
 - *10. Needing more of the substance to get the effect you want (tolerance)
 - *11. Development of withdrawal symptoms, which can be relieved by taking more of the substance
- *Criteria not met if taking prescribed drugs under supervision

Neurodevelopmental and psychoaffective factors of vulnerability

Early age of onset of drug use predicts subsequent transition to addiction



Neurodevelopmental and psychoaffective factors of vulnerability

Drug use as a coping strategy: self-medication and addiction

Table 2

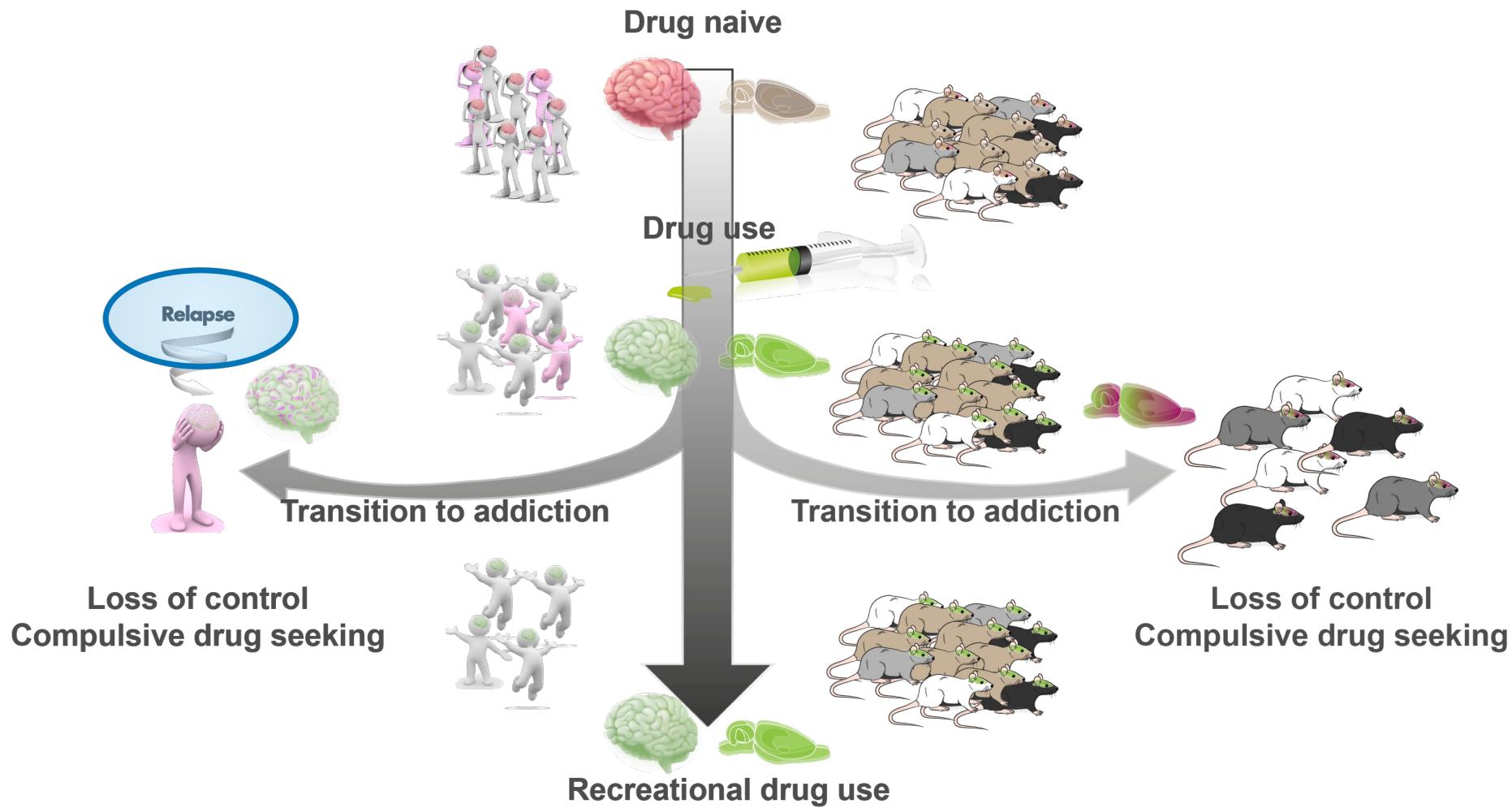
Summary of hierarchical multiple regressions using demographic (Block 1) and personality (Block 2) variables to predict "risky" coping, conformity, and enhancement residualized motive scores for (a) alcohol use, (b) cigarette smoking, and (c) marijuana use

	Coping		Conformity		Enhancement	
	DR ²	β	DR ²	β	DR ²	β
<i>(a) Alcohol (DMQ)</i>						
Demographic predictors	.041*		.062***		.011	
Age		.077		-.184		.190
Family income		-.040		-.016		.038
Gender		.122		-.259***		.103
Grade		-.188		.017		-.120
Personality predictors	.060**		.034*		.049*	
AISS-I		.088		-.098		.142*
AISS-N		-.017		-.028		-.027
CASI		-.010		.166*		-.182*
STAIC-T		.258***		-.028		.005
Overall F and df for model	4.24****	(8, 303)	4.02****	(8, 303)	2.41*	(8, 303)
<i>(b) Smoking (TSMQ)</i>						
Demographic predictors	.099***		.130****		.029	
Age		-.031		-.152		-.135
Family income		-.197**		-.059		.094
Gender		.148		-.200		-.078
Grade		.093		-.154		.026
Personality predictors	.082**		.002		.004	
AISS-I		.003		.031		-.021
AISS-N		.037		.005		-.036
CASI		.029		.002		-.078
STAIC-T		.292***		-.017		.019
Overall F and df for model	5.04****	(8, 183)	3.47***	(8, 183)	0.79	(8, 183)
<i>(c) Marijuana (TMMQ)</i>						
Demographic predictors	.073		.129****		.030	
Age		-.138		.286		.253
Family income		.158		-.177*		.056
Gender		.007		-.119		.092
Grade		.069		-.478***		-.149
Personality predictors	-.019		.051 ^t		.055	
AISS-I		-.083		.124		-.106
AISS-N		.039		-.113		-.068
CASI		.015		.230*		-.142
STAIC-T		.130		-.073		-.112
Overall F and df for model	1.42	(8, 145)	3.99****	(8, 145)	1.68	(8, 145)

Anxiety → coping

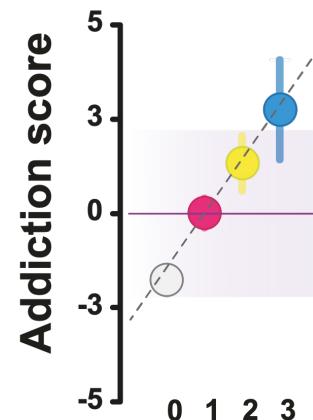
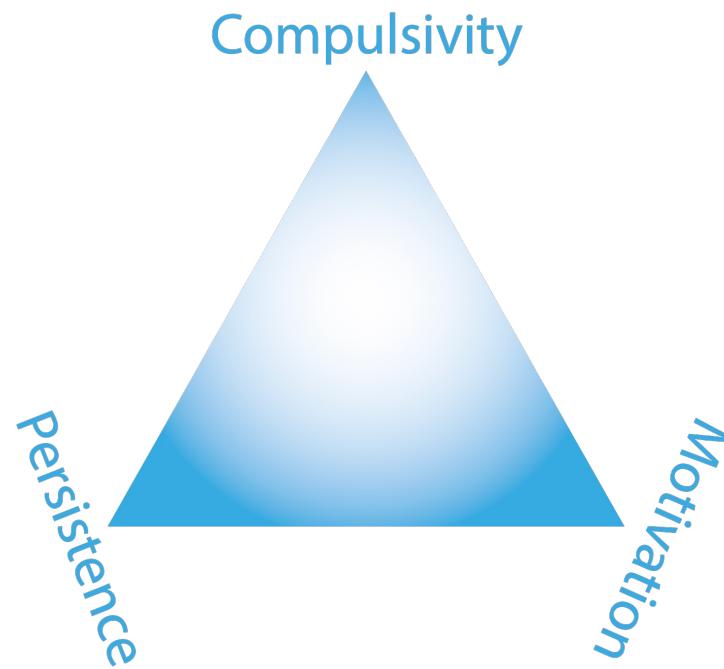
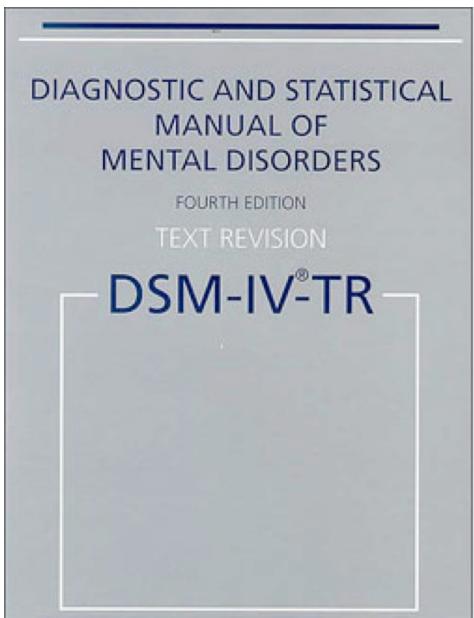
Sensation seeking → enhancement

Measuring addiction-like behaviour in the rat



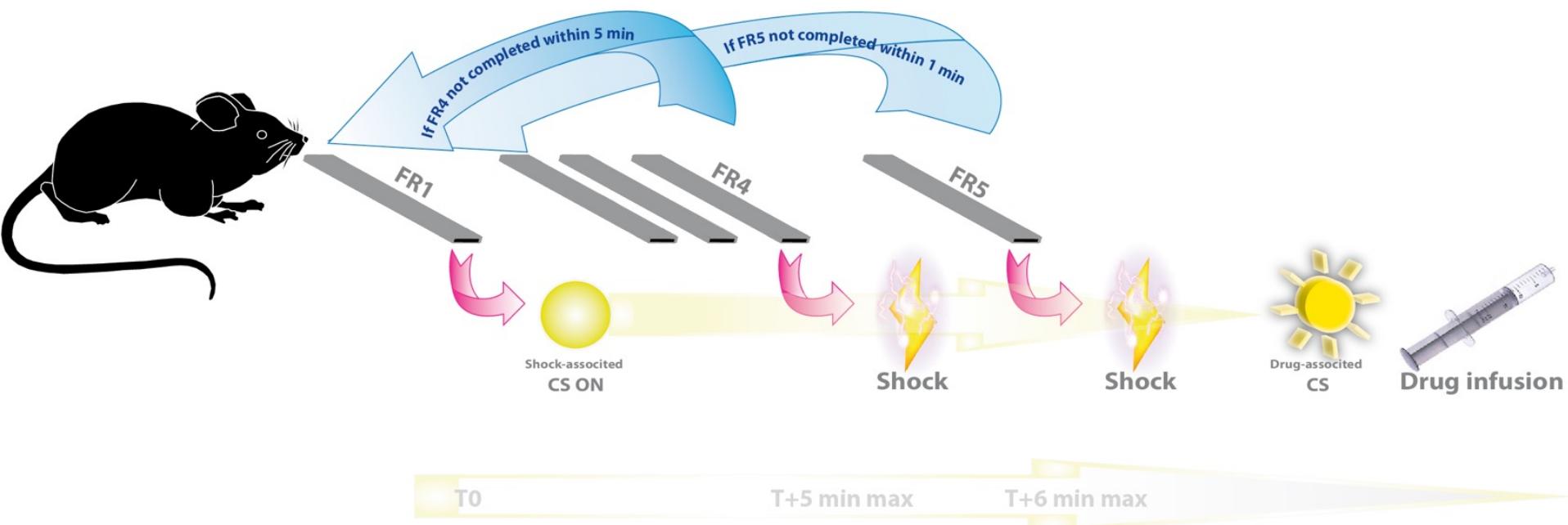
Belin et al. (2004, 2008, 2010, 2011)

Measuring addiction-like behaviour in the rat



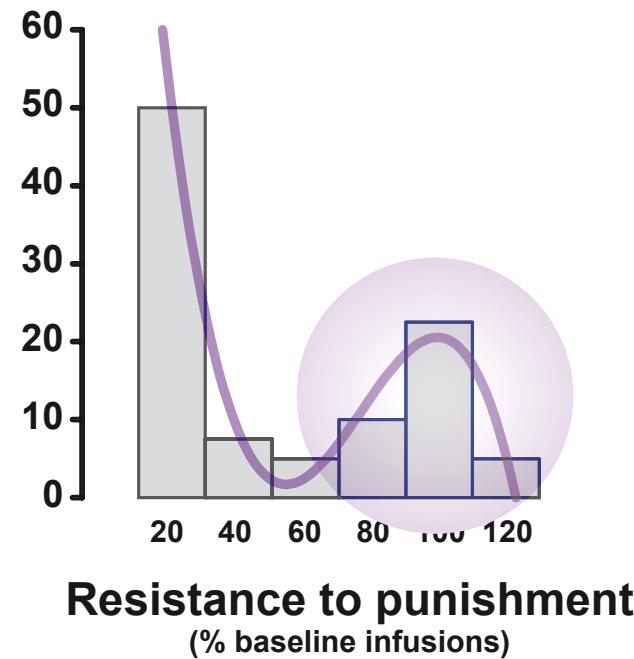
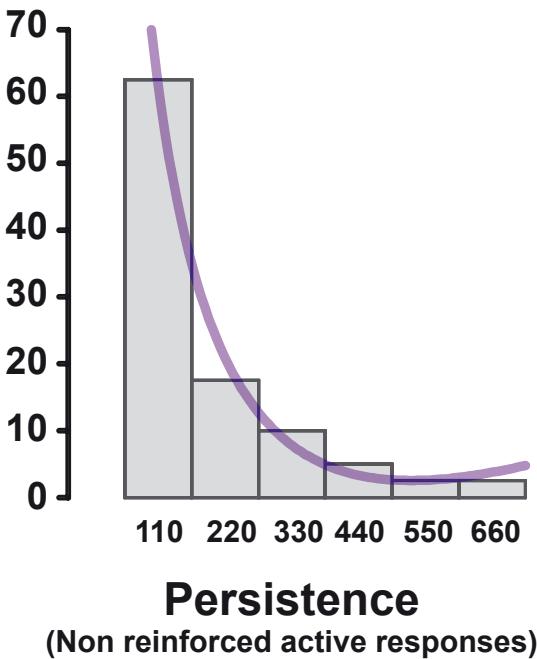
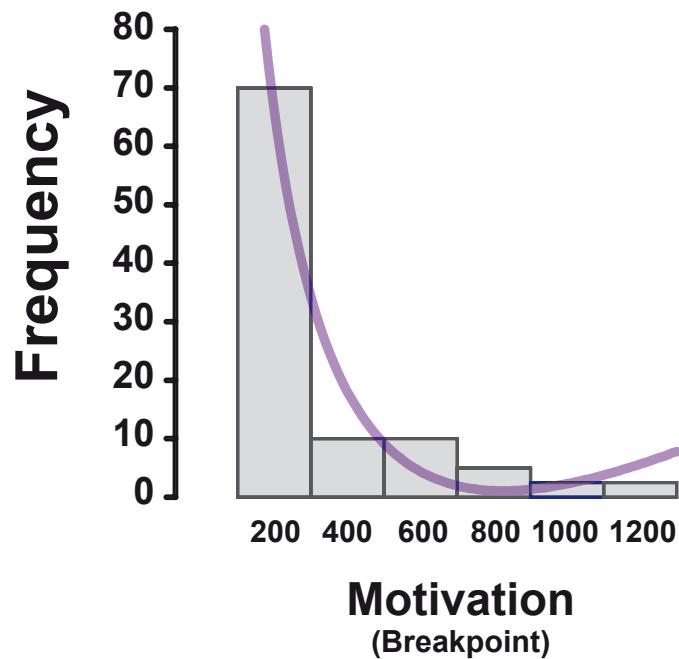
Belin et al. (2004, 2008, 2010, 2011);
Fouyssac et al., 2021

Measuring addiction-like behaviour in the rat

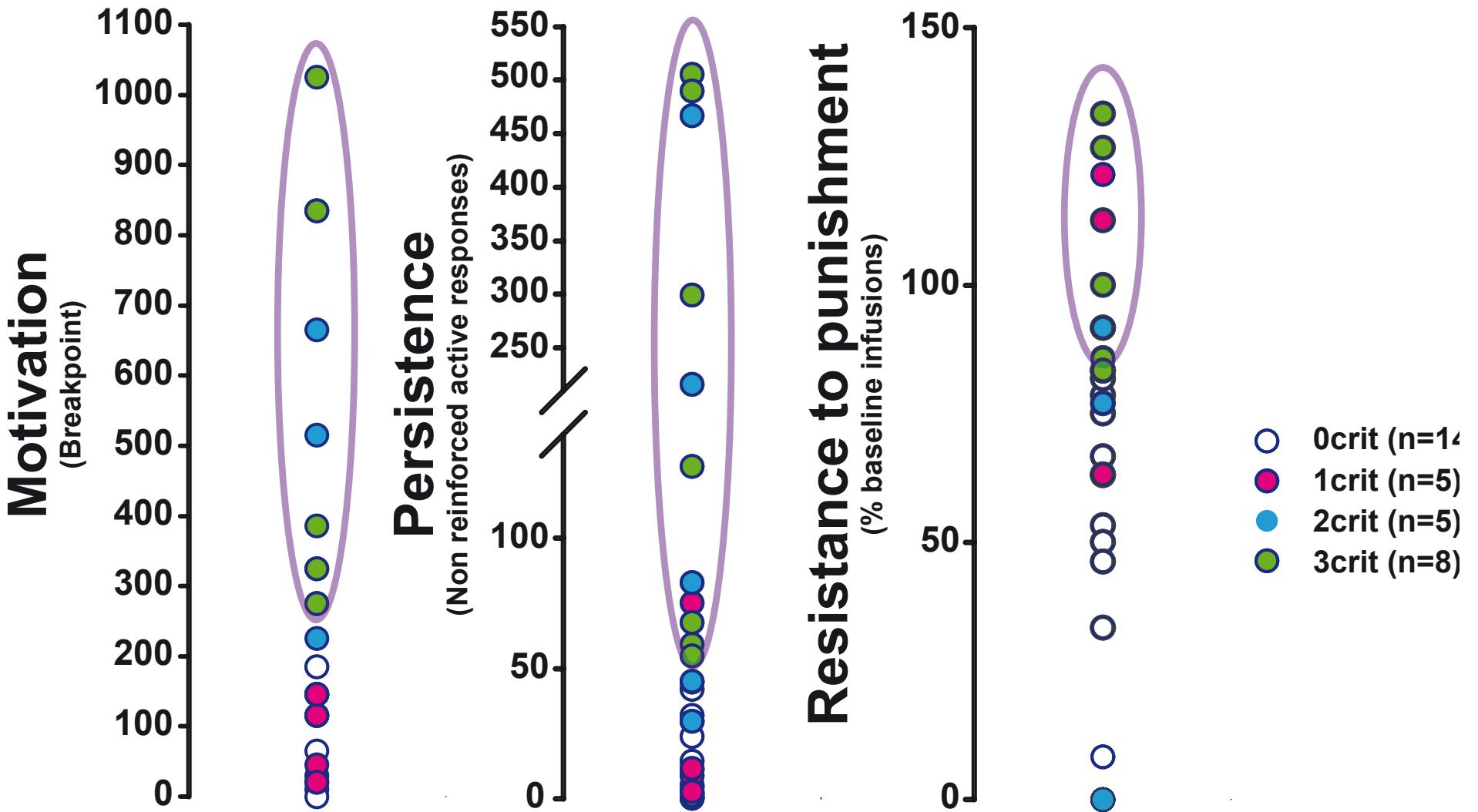


Belin et al. (2004, 2008, 2010, 2011)

Measuring addiction-like behaviour in the rat

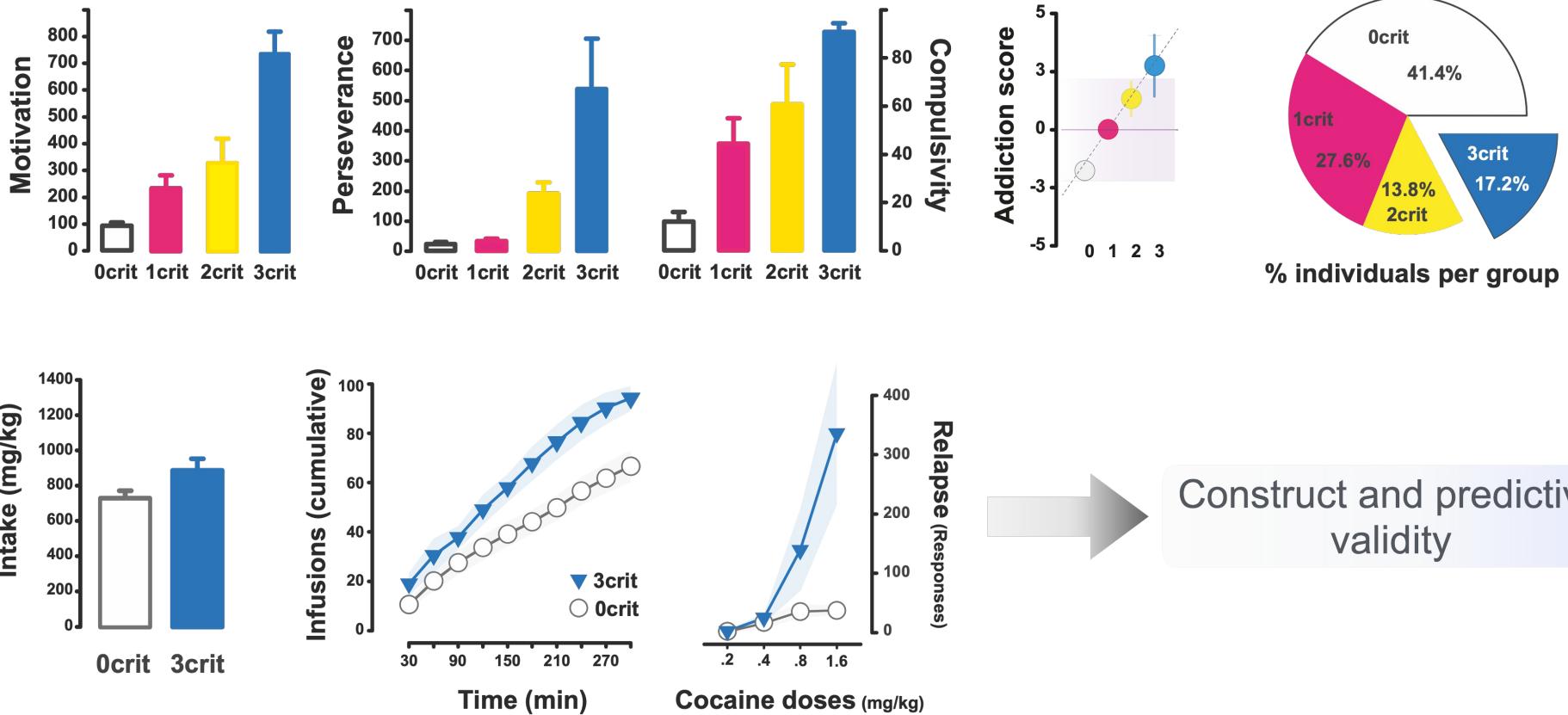


Measuring addiction-like behaviour in the rat



Belin et al. (2004, 2008, 2010, 2011)

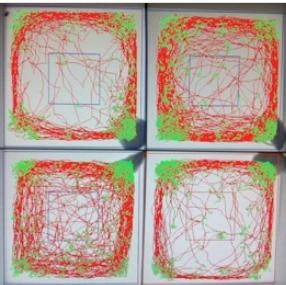
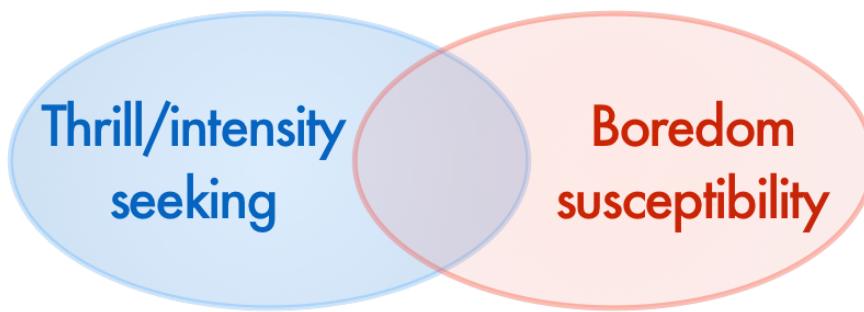
Measuring addiction-like behaviour in the rat



Belin et al. (2004, 2008, 2010, 2011)

Identifying behavioural endophenotypes of vulnerability

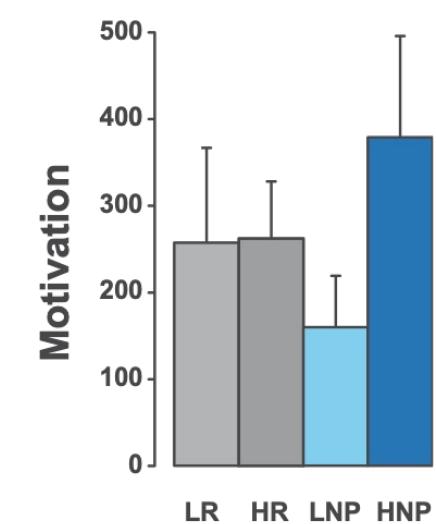
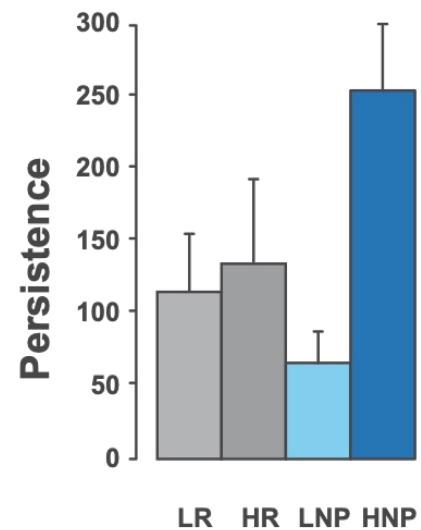
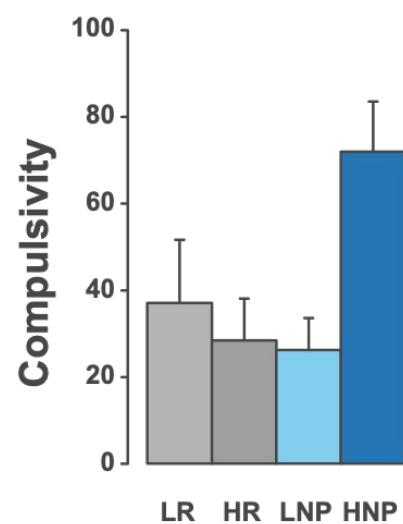
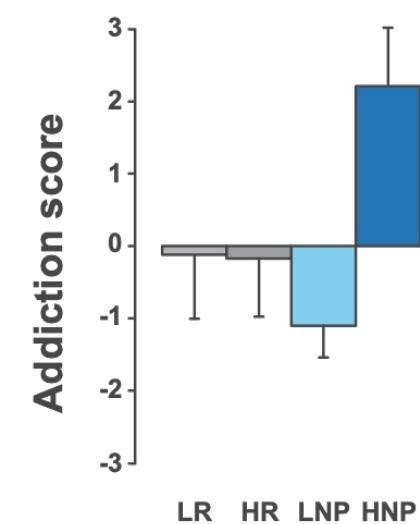
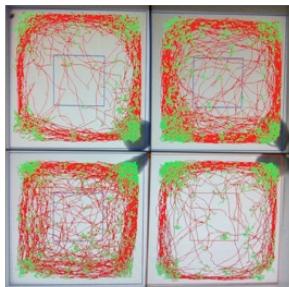
Investigating sub dimensions of sensation seeking



Belin et al. (2004, 2008, 2010, 2011)

Identifying behavioural endophenotypes of vulnerability

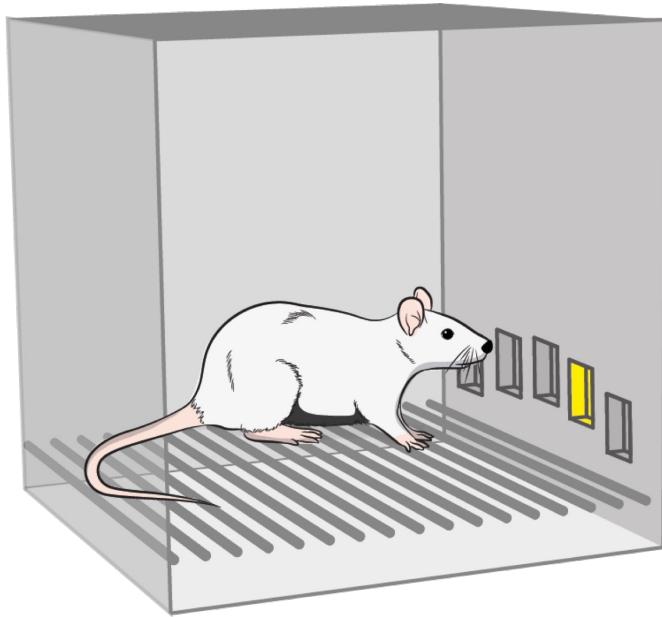
Investigating sub dimensions of sensation seeking



Belin et al. (2004, 2008, 2010, 2011)

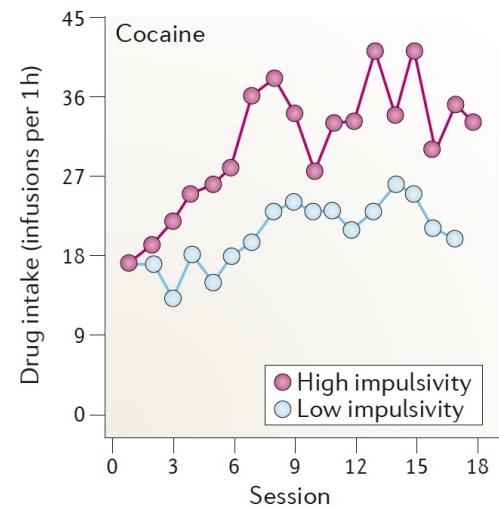
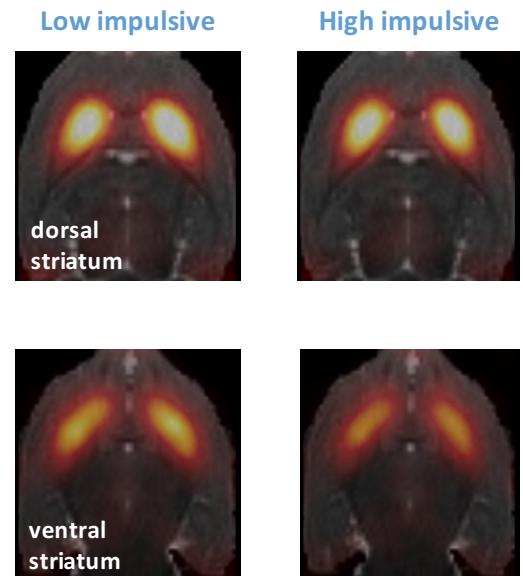
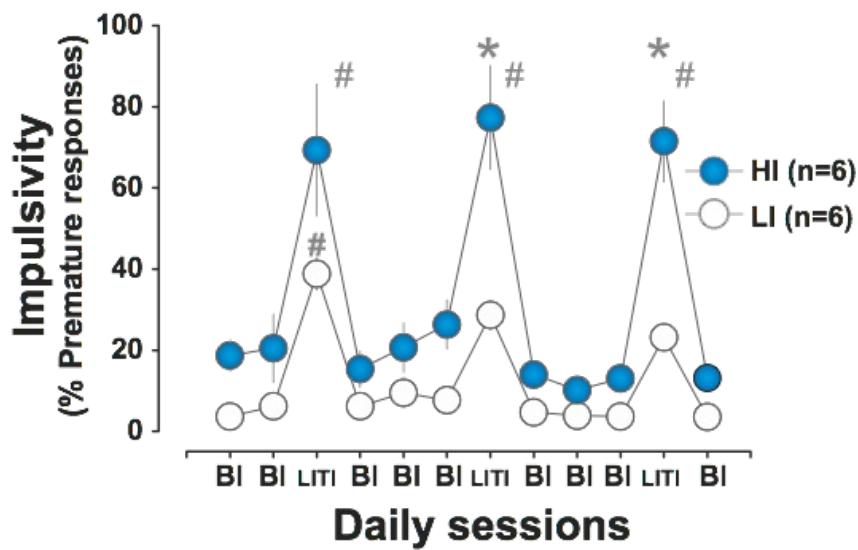
From impulsivity to compulsivity

5-choice serial reaction time task



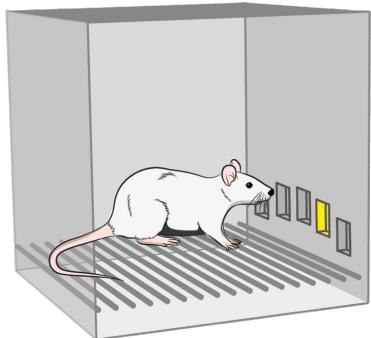
From impulsivity to compulsivity

High impulsivity trait: decreased dopamine D2 receptor levels in the Acb and exacerbated escalation of cocaine SA

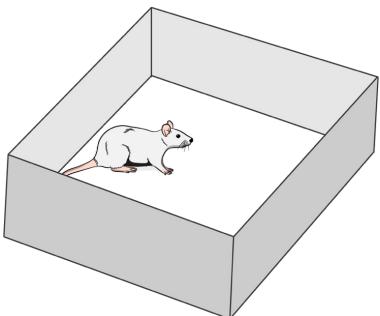


From impulsivity to compulsion

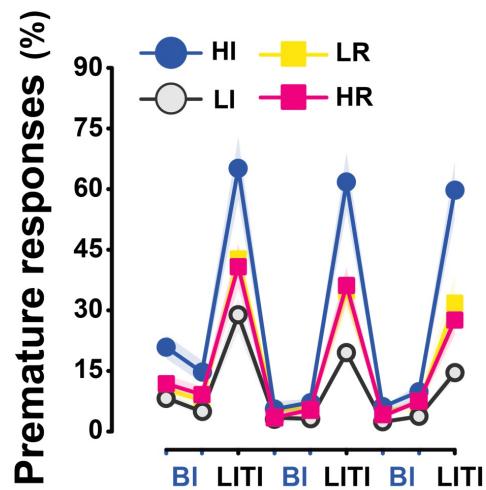
Impulsivity



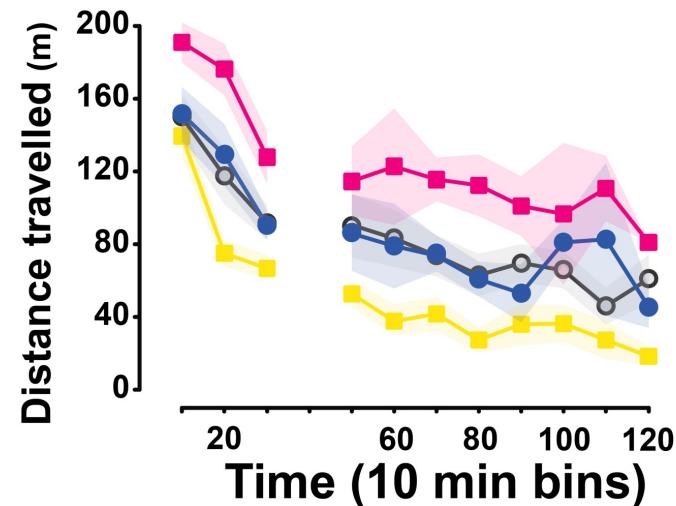
Sensation seeking



Impulsivity

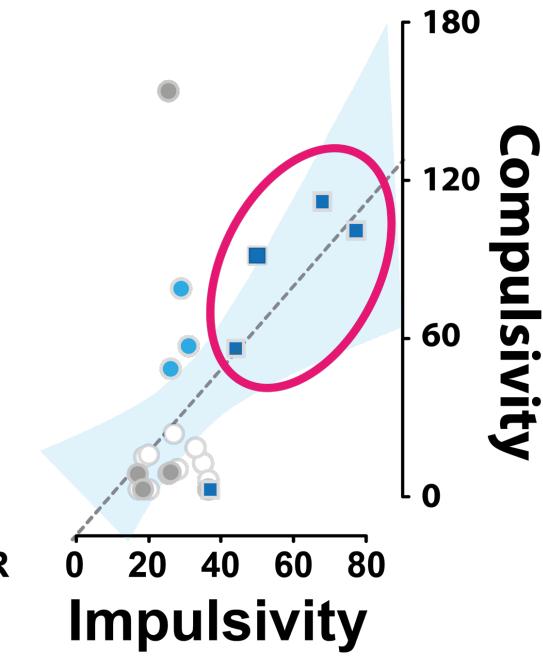
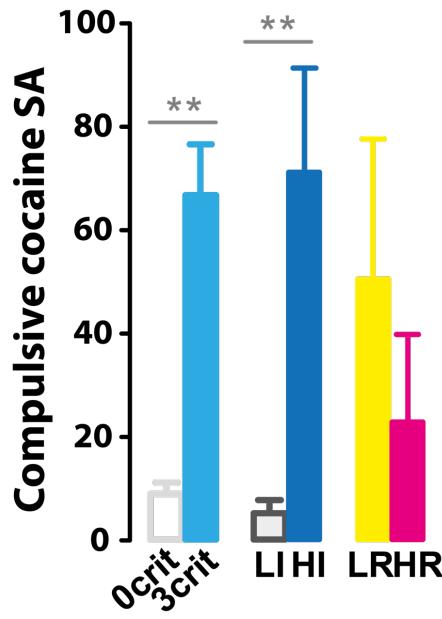
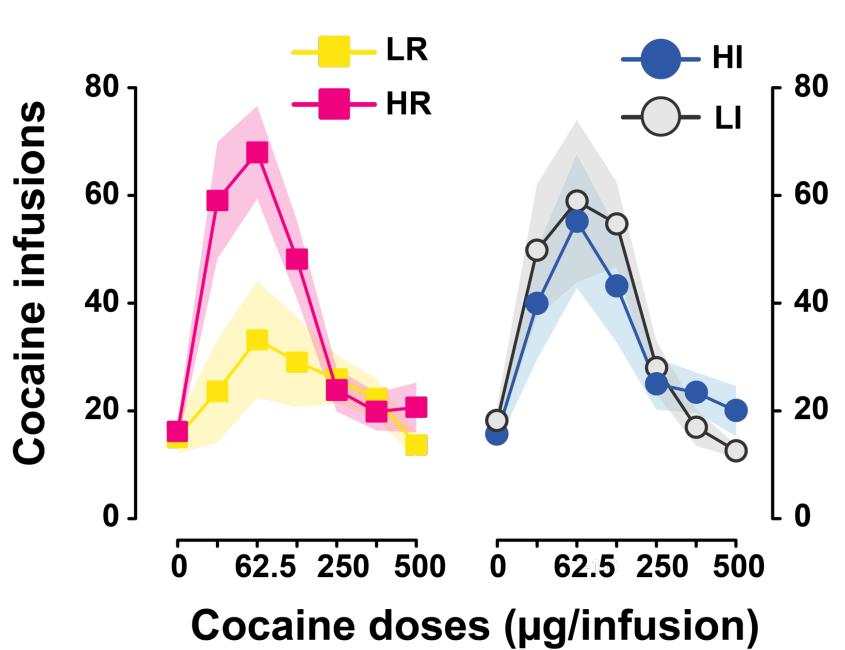


Sensation seeking



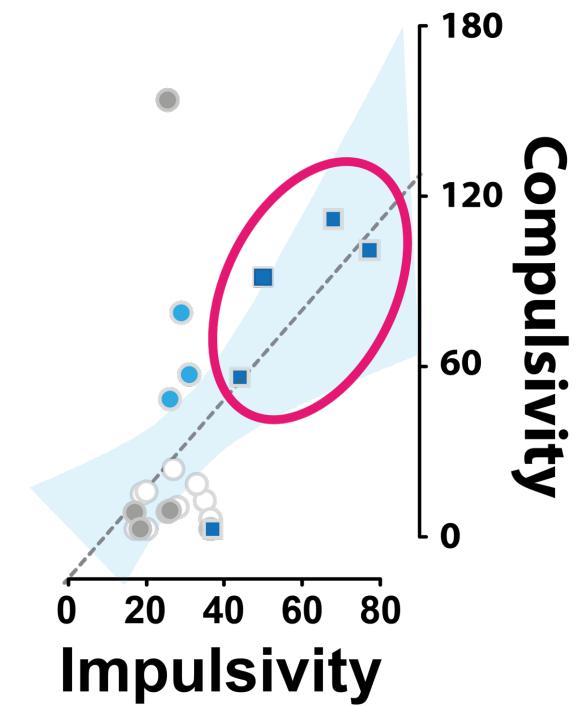
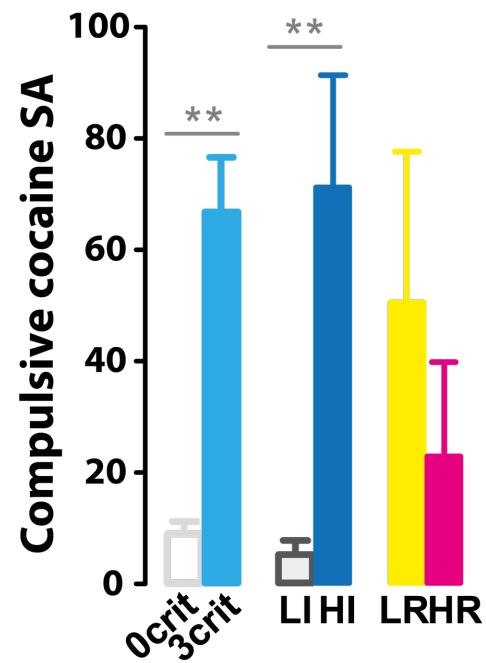
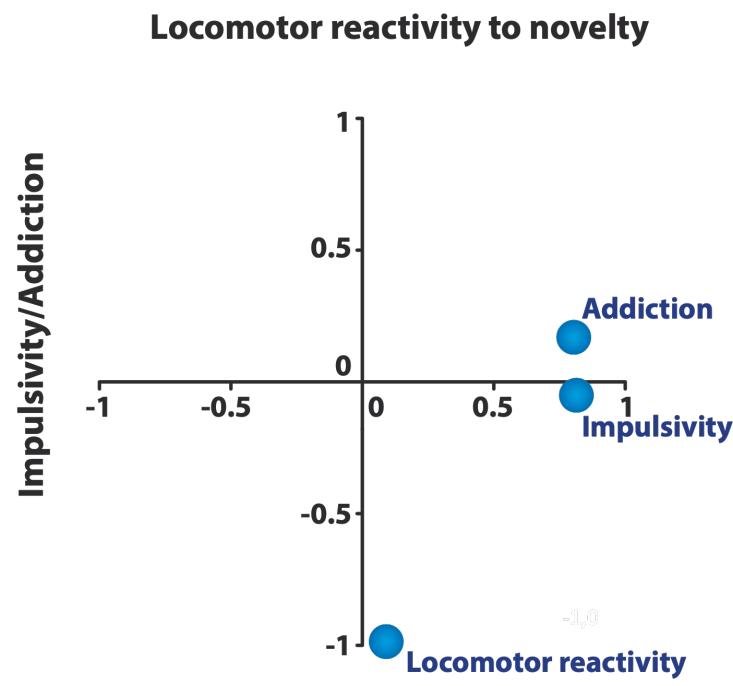
From impulsivity to compulsivity

High impulsivity, but not sensation seeking trait: a factor of vulnerability to addiction

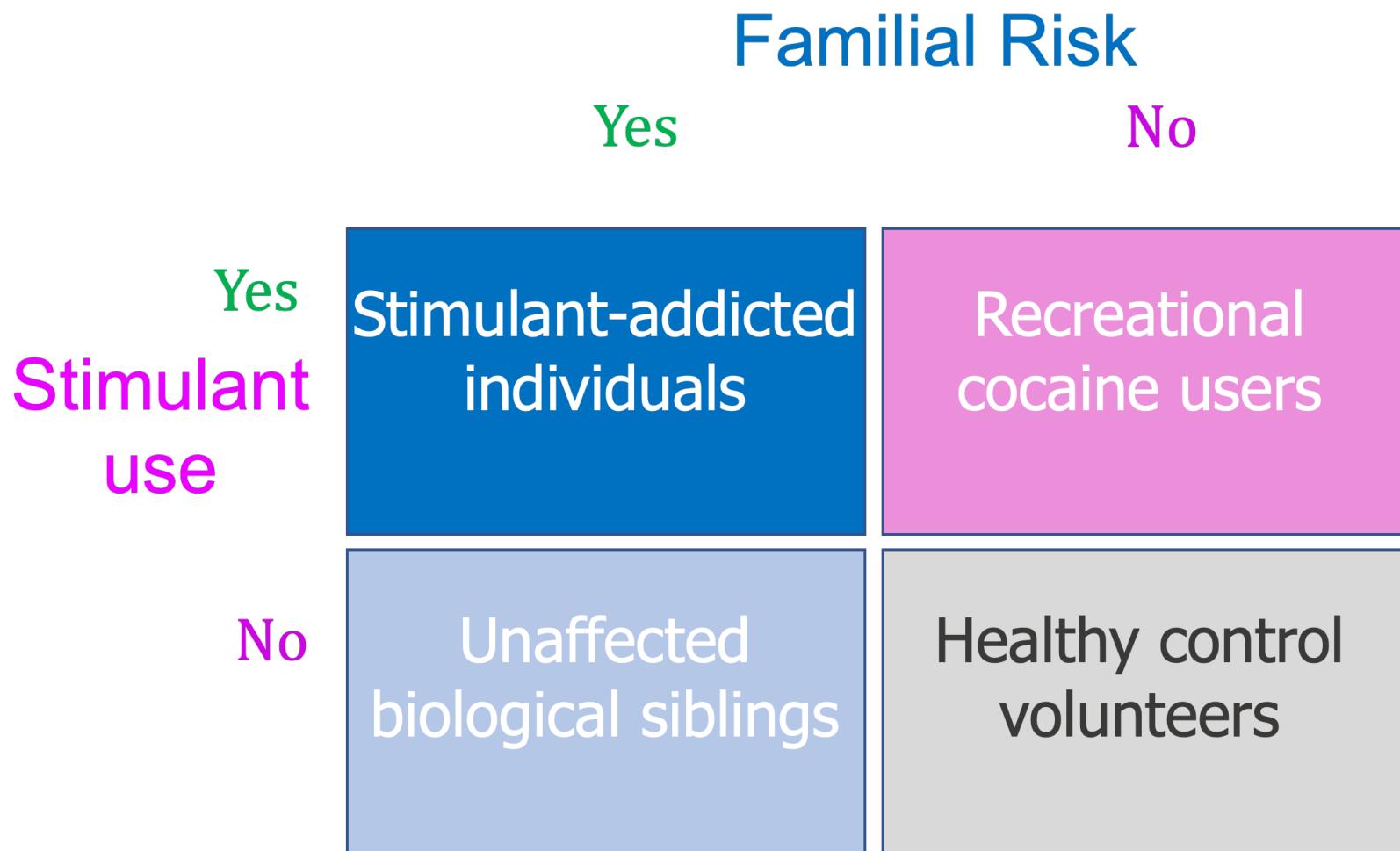


From impulsivity to compulsivity

High impulsivity, but not sensation seeking trait: a factor of vulnerability to addiction



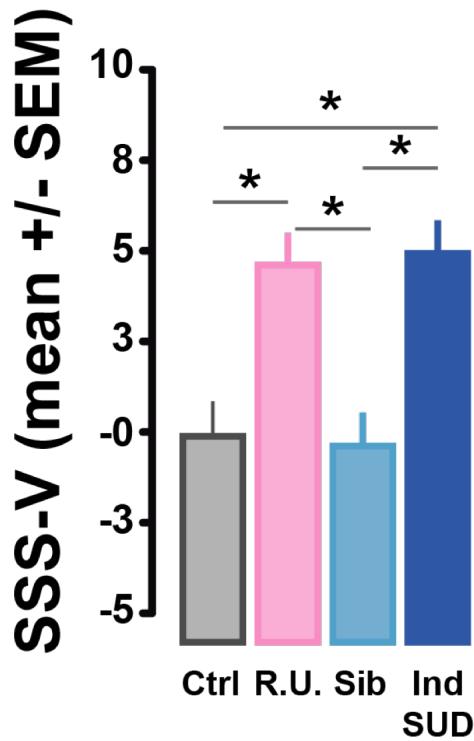
Impulsivity in humans predicts becoming addicted to drugs, while sensation-seeking predicts likelihood of trying drugs



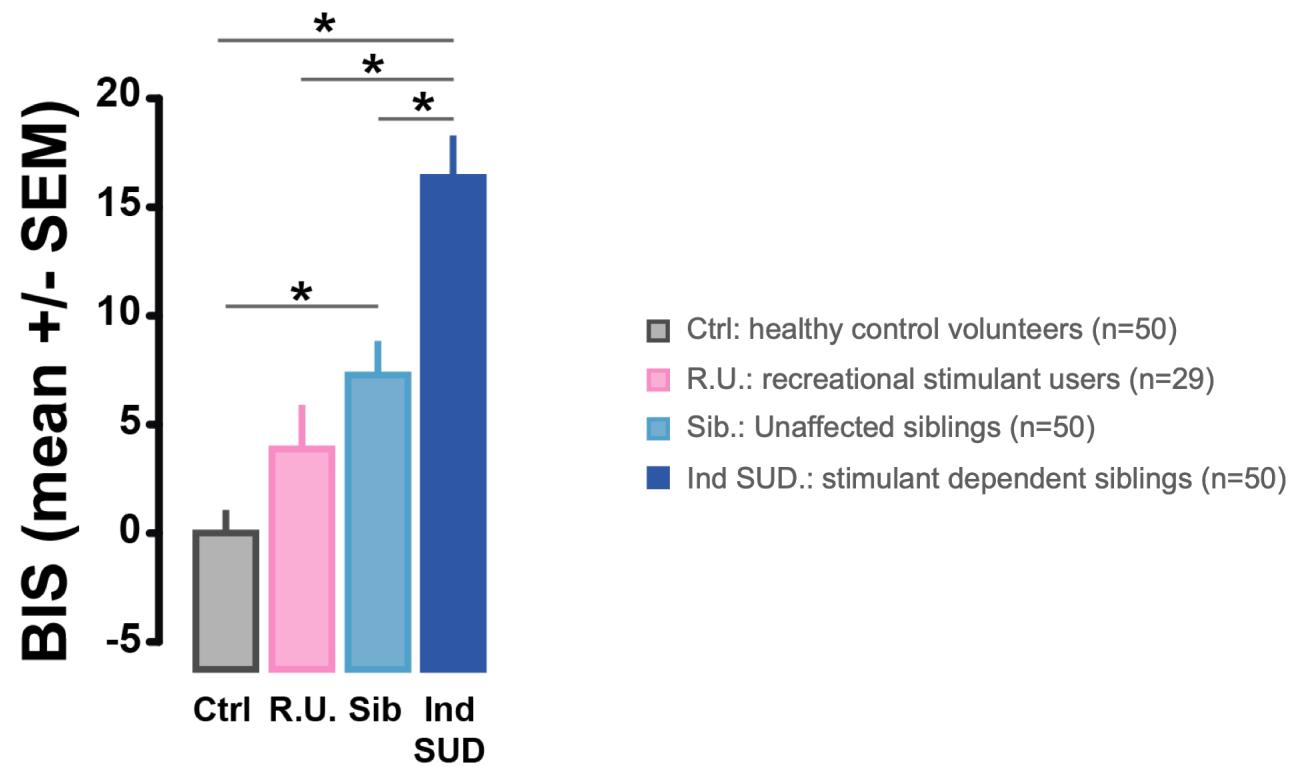
Ersche et al. (2010; 2013)

Impulsivity in humans predicts becoming addicted to drugs, while sensation-seeking predicts likelihood of trying drugs

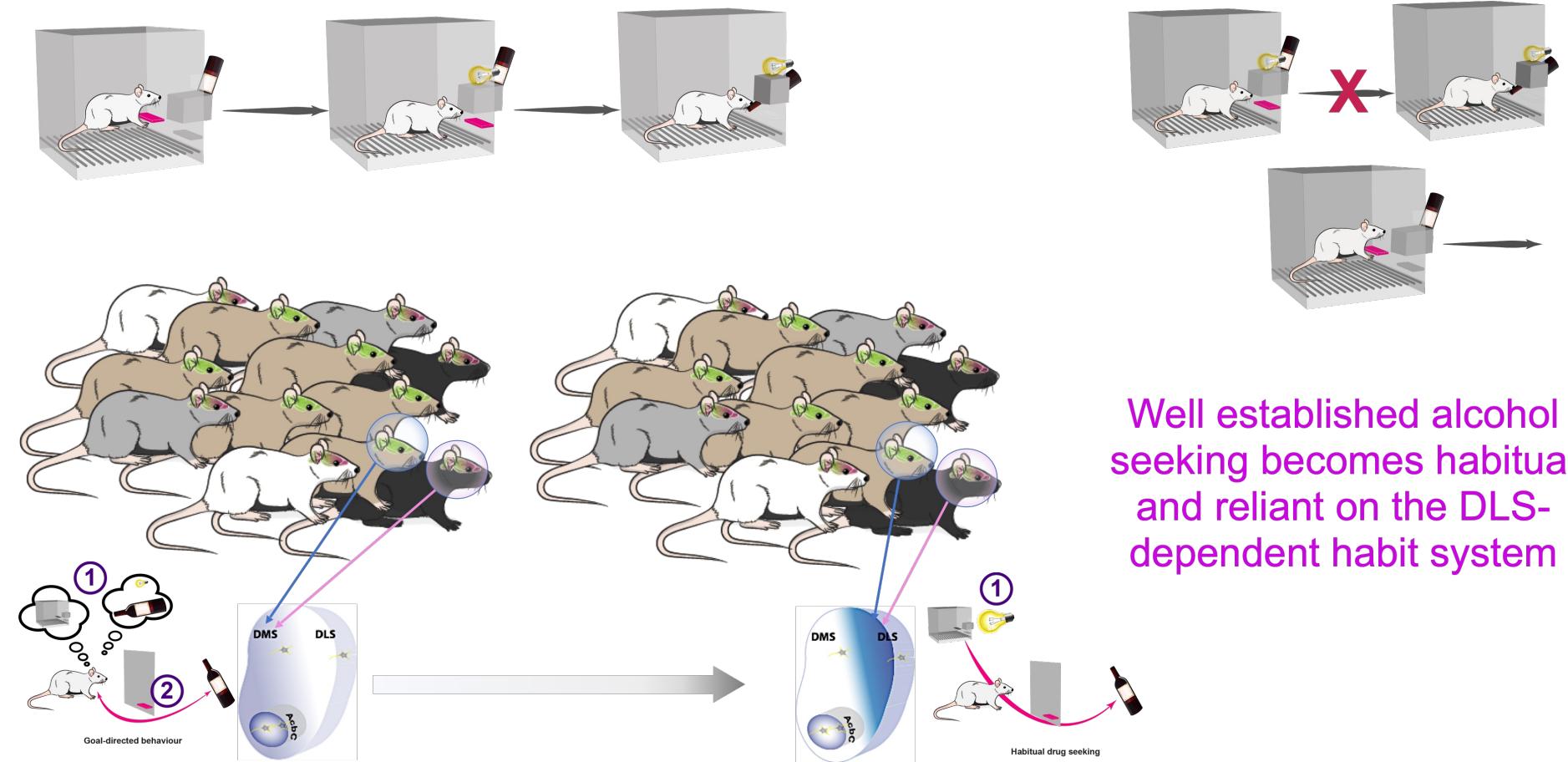
Sensation seeking



Impulsivity



Vulnerability to compulsive alcohol seeking is associated with an inability to disengage aDLS control over behaviour



Vulnerability to compulsive alcohol seeking is associated with an inability to disengage aDLS control over behaviour

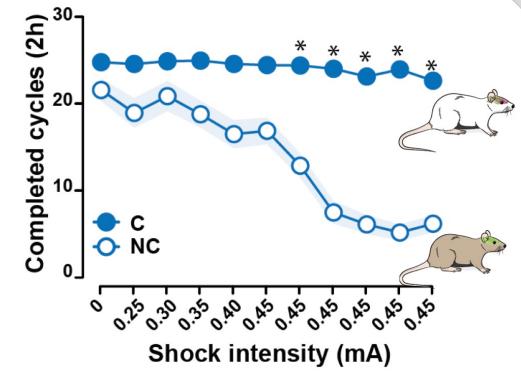
→ Rats must run the risk of punishment to access and drink alcohol

75% of seeking cycles result in access to the taking lever

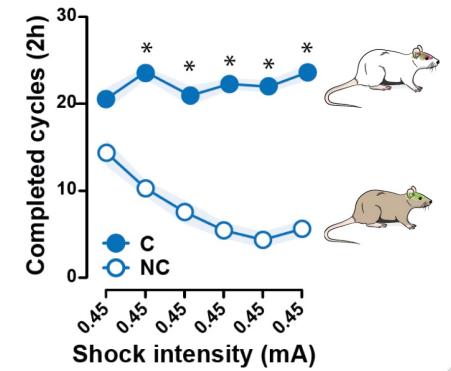


25% of seeking cycles result in unpredictable punishment

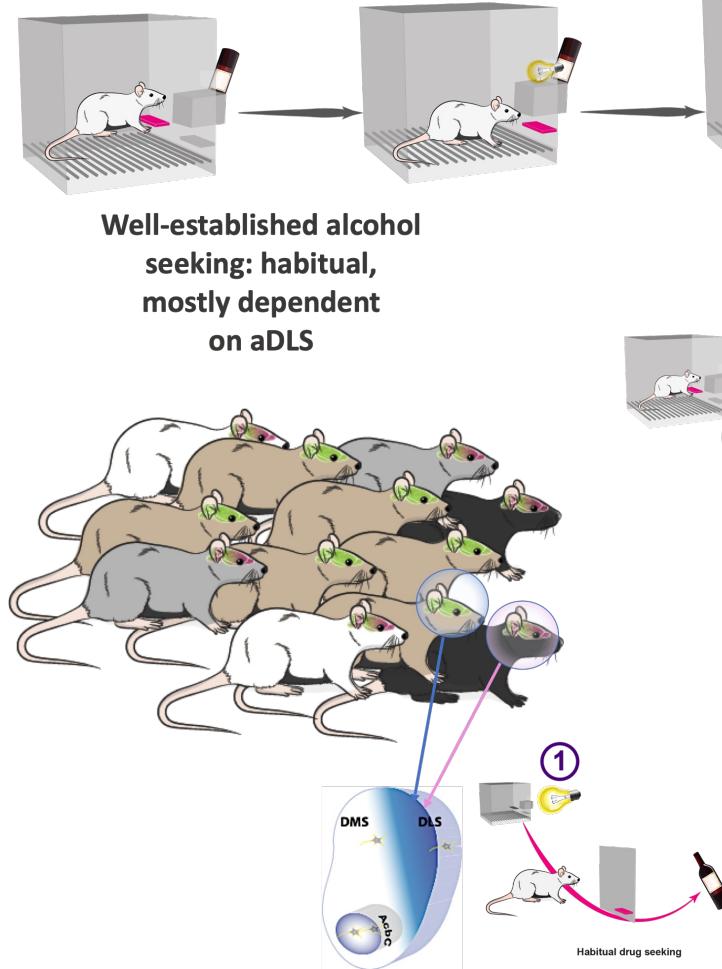
→ (NB punishment is never paired with the drug)



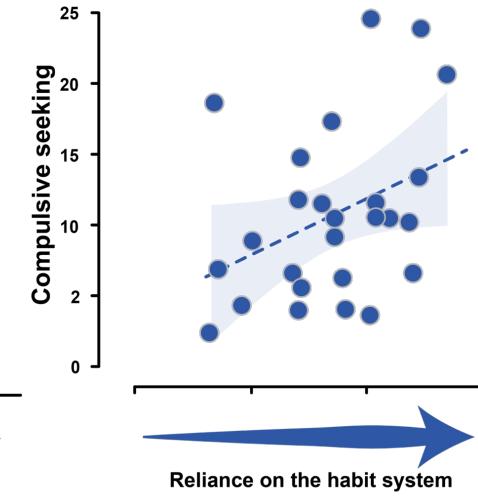
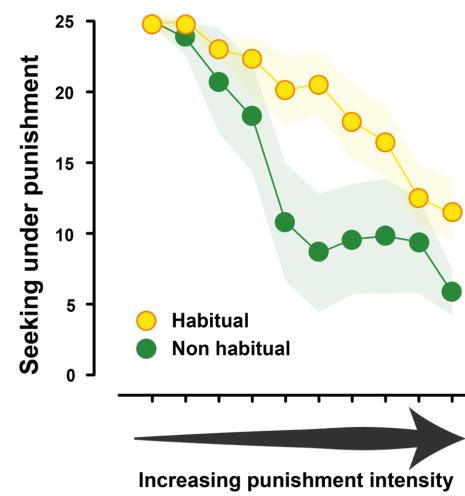
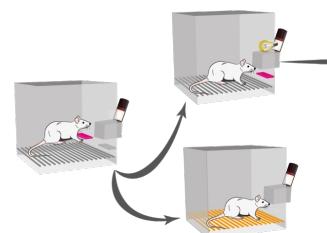
10 Months Later



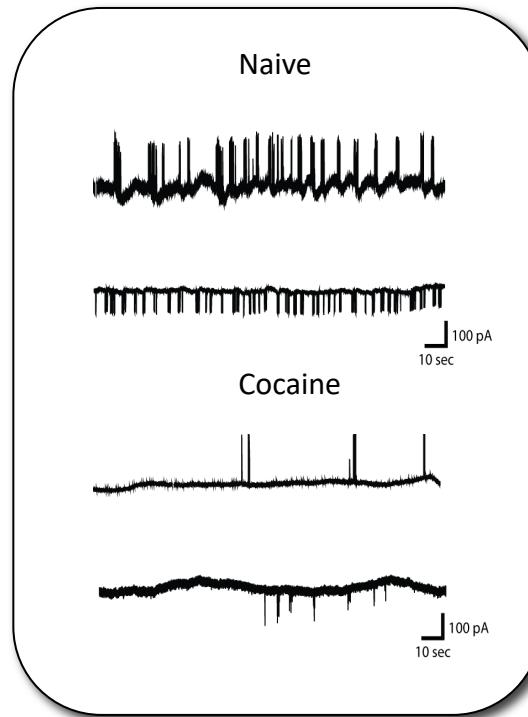
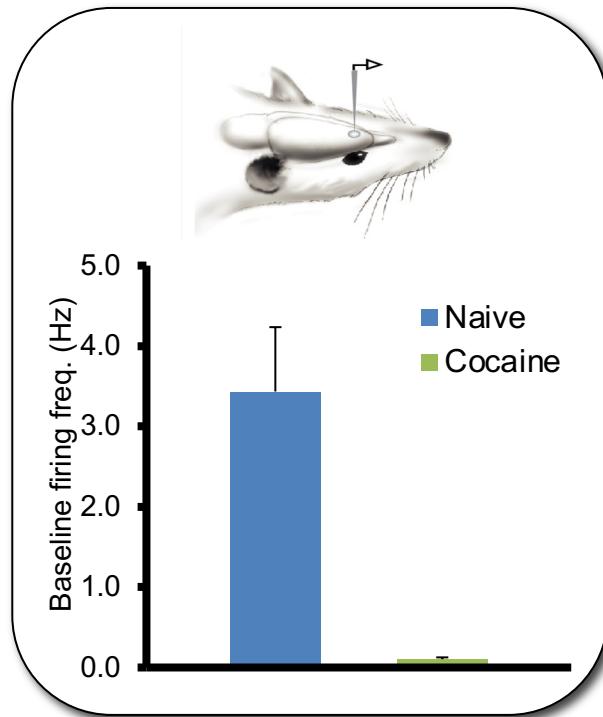
Vulnerability to compulsive alcohol seeking is associated with an inability to disengage aDLS control over behaviour



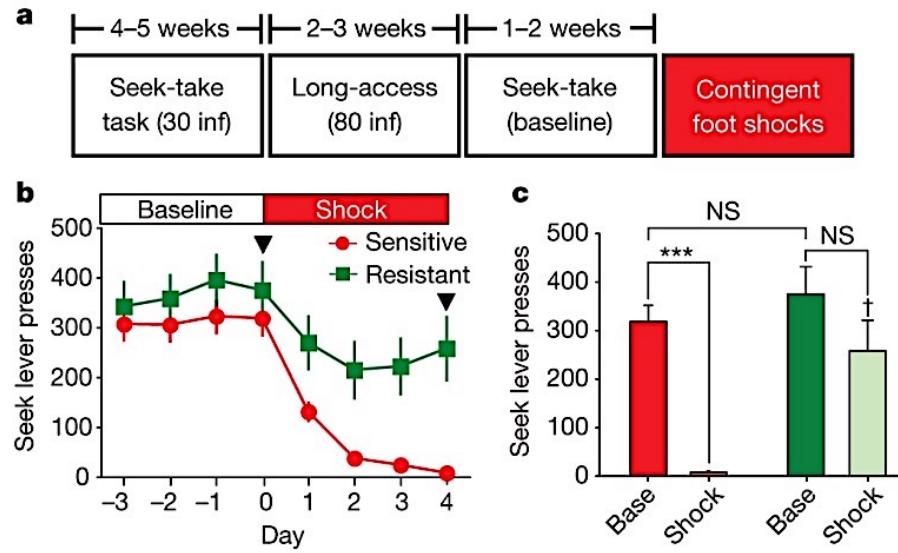
Compulsive alcohol seeking:
inability to disengage DLS control
in the face of punishment



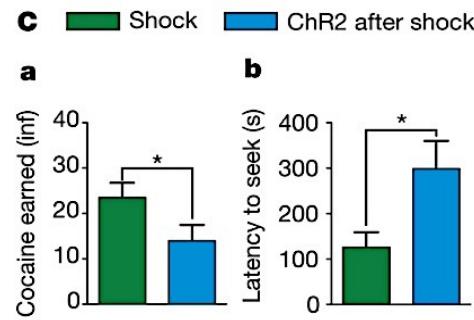
Vulnerability to compulsive cocaine seeking is associated with hypofunction of the prelimbic cortex in the rat



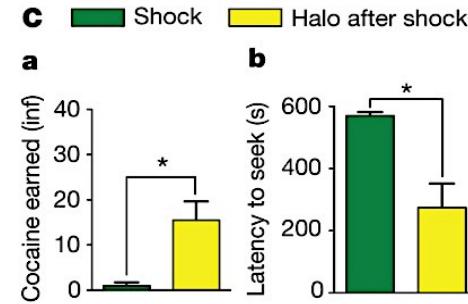
Vulnerability to compulsive cocaine seeking is associated with hypofunction of the prelimbic cortex in the rat



Optogenetic stimulation (channelrhodopsin) of prelimbic cortex decreases compulsive cocaine seeking



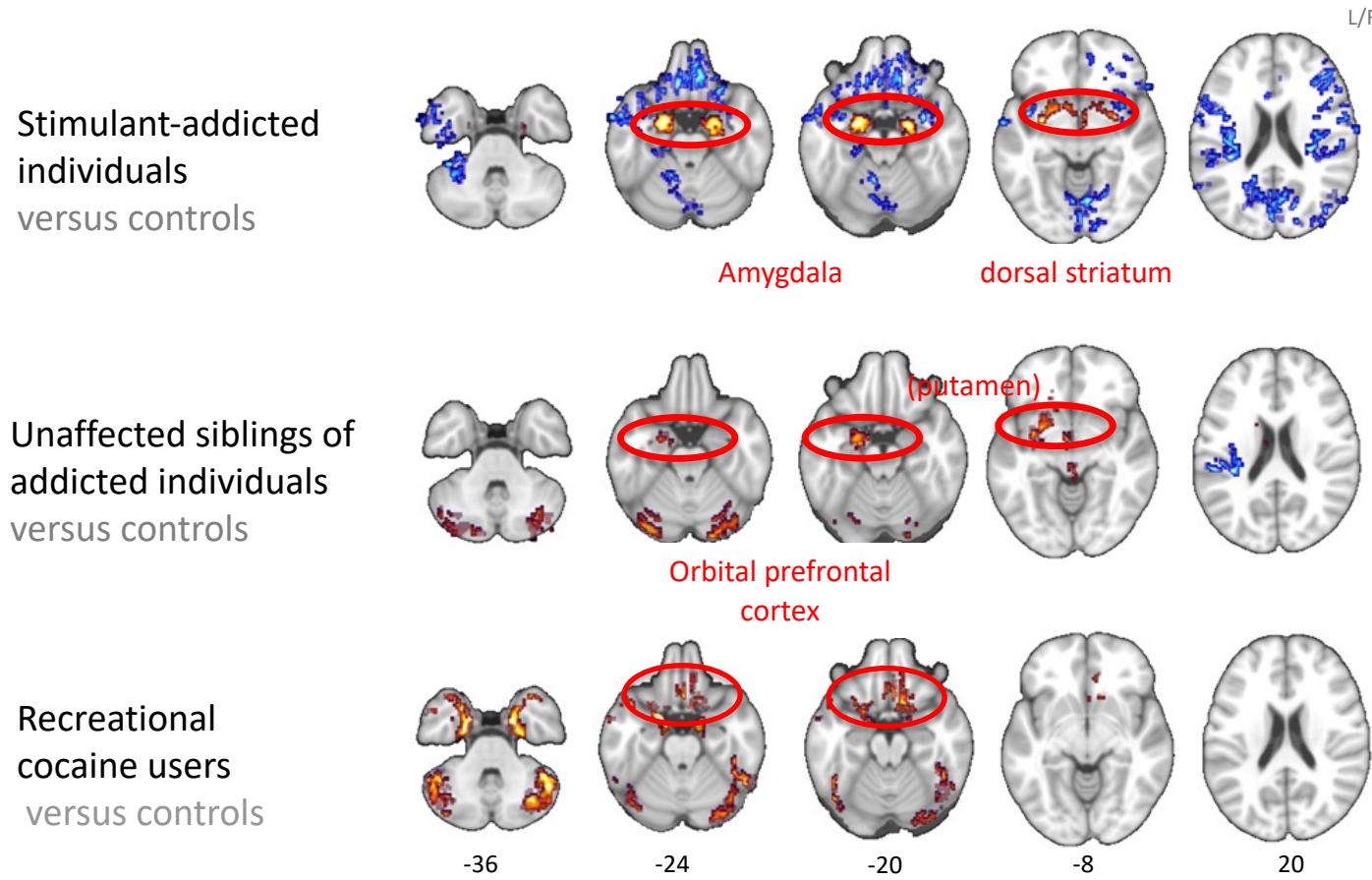
Optogenetic inhibition (halorhodopsin) of prelimbic cortex in non-compulsive rats causes compulsive cocaine seeking



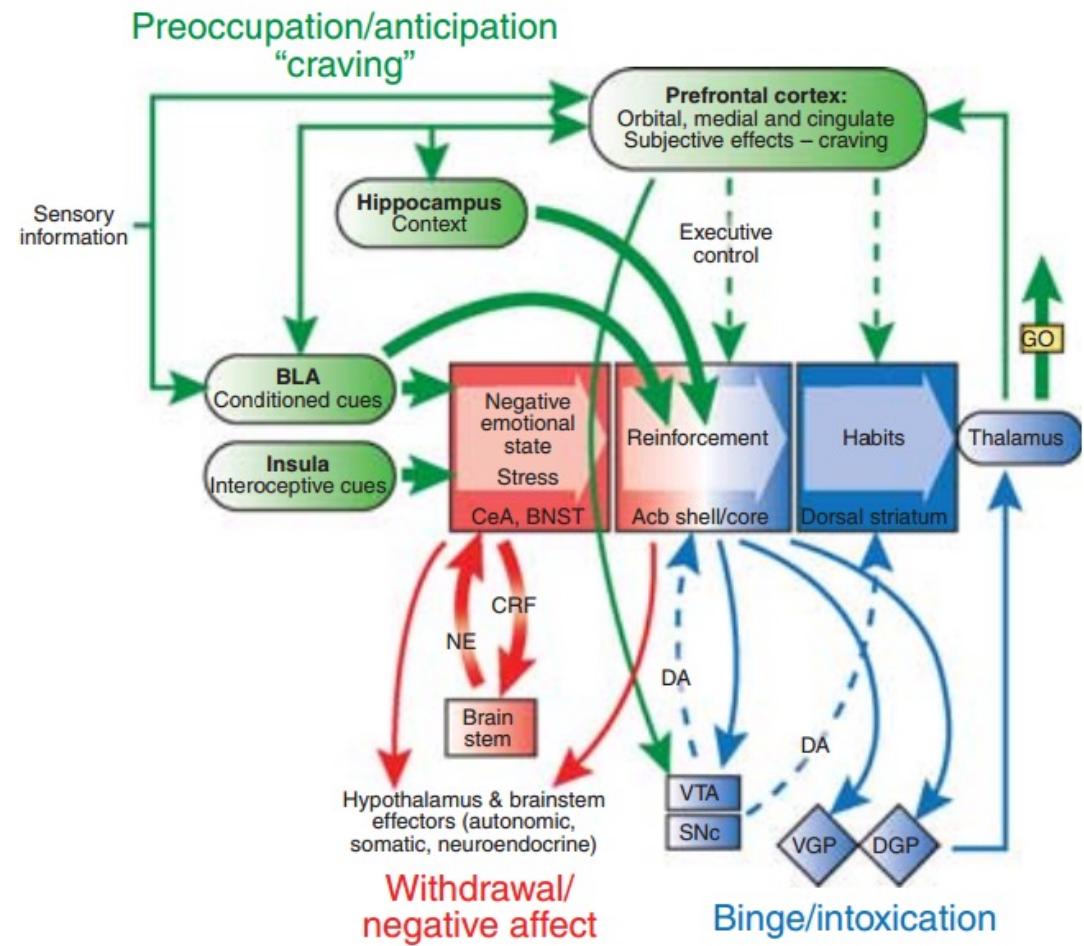
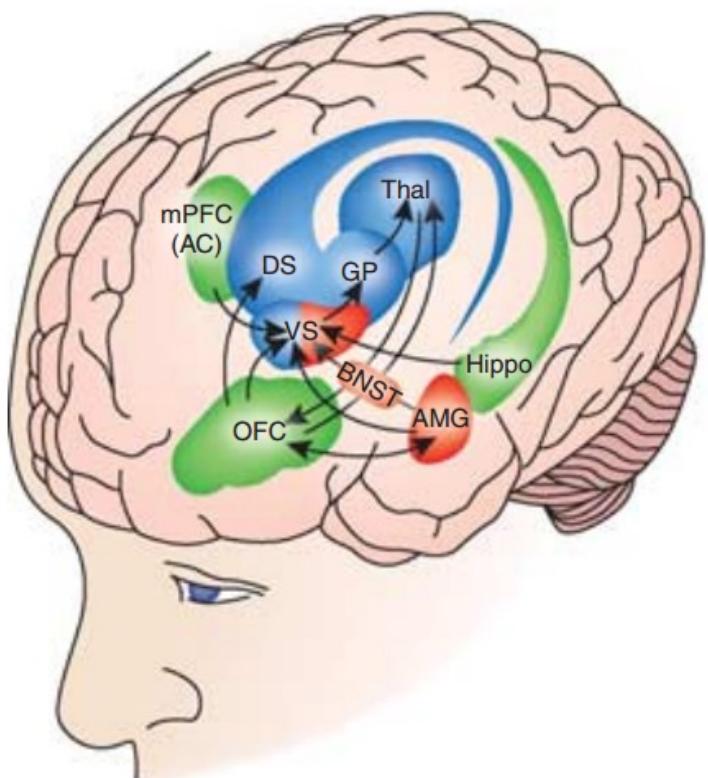
Vulnerability to addiction: wrapping things up

Are the shifting brain systems engaged during the transition to addiction the consequences or causes of habitual and compulsive drug use?

→ Grey matter anomalies in stimulant addicts and their siblings



Putting it all together



Koob, Everitt & Robbins (2008)