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Addiction as a Reward System Disease

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Agenda

- › The evolution of the motivating system
- › Regulation of motivation to appetitive behaviour
- › Similarity between animal migration and addiction
- › Three basic pharmacological mechanism of addiction
- › Addiction is a reward system disease



Five components of addiction disorder

- › Lust (pleasure, high) – CINP Course 2013 → [MHRI website](#)
- › Tolerance
- › Withdrawal
- › **Craving**
- › Relapse

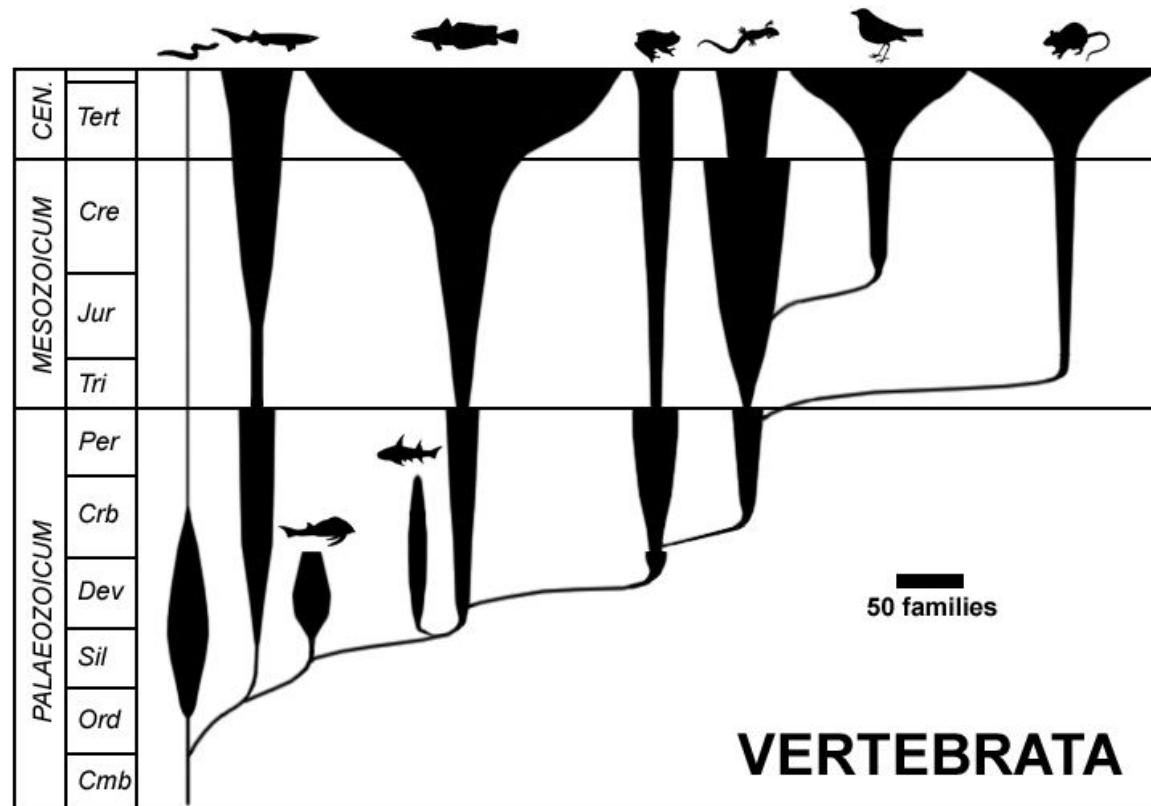


Craving is the driving force of addiction

- › Motivation to seek for addictive substance
- › Hijacking the mechanism to stimulate appetitive behaviour
- › Two essential forces necessary for survival of the individual and species
 - Motivation to obtain food, water, warmth, comfort (reward driven)
 - Motivation to escape from threat, heat, cold (misery driven)
- › Very ancient mechanisms regulating behaviour










Evolution of the reward system (general overview)





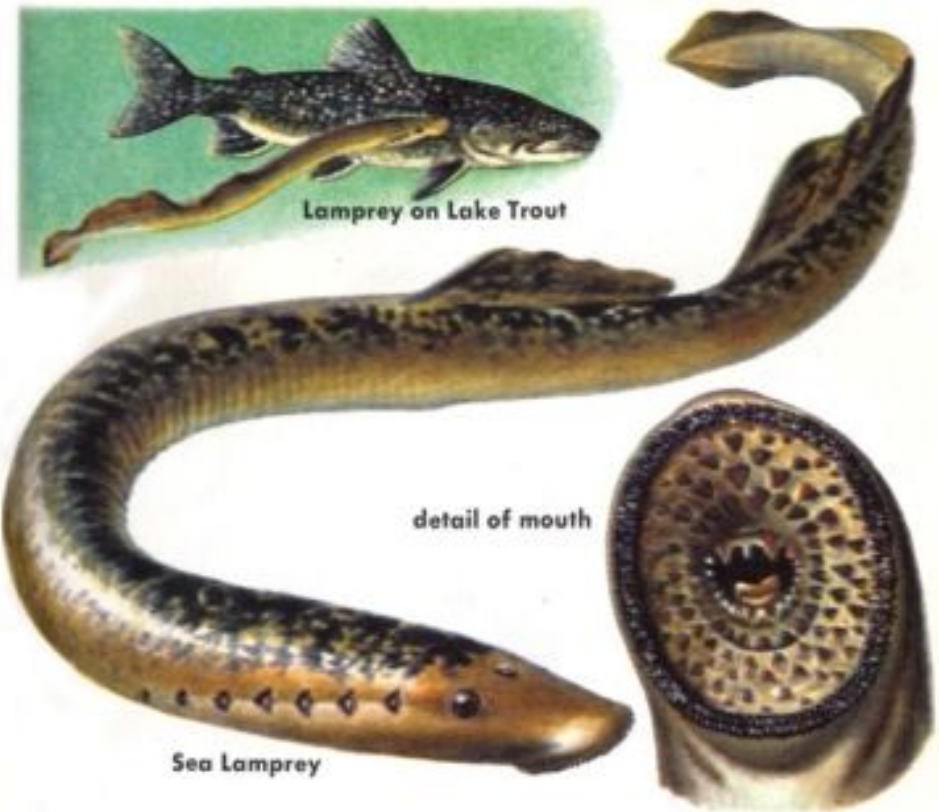
Evolution of the brain of vertebrates

	Chordates lancelet	Craniates hagfish	Vertebrates lamprey	Amphibians frog	Reptiles tortoise	Mammals opossum	Primates rhesus monkey
							
Notochord*	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+
Separate brain		+	+	+	+	+	+
Separate endbrain		+	+	+	+	+	+
Olfactory bulb		+	+	+	+	+	+
Infundibulum	+	+	+	+	+	+	+
Cerebellum				+	+	+	+
Habenula		+	+	+	+	+	+
Striatum **		+	+	+	+	+	+
Amygdala***				+	+	+	+
Hippocampus****		+	+	+	+	+	+
Isocortex			+	+	+	+	+



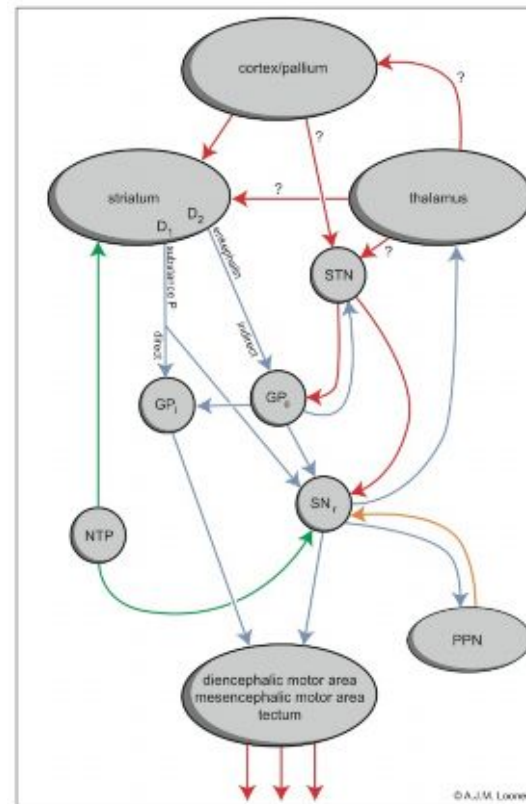
Brain of the lamprey

lamprey brain



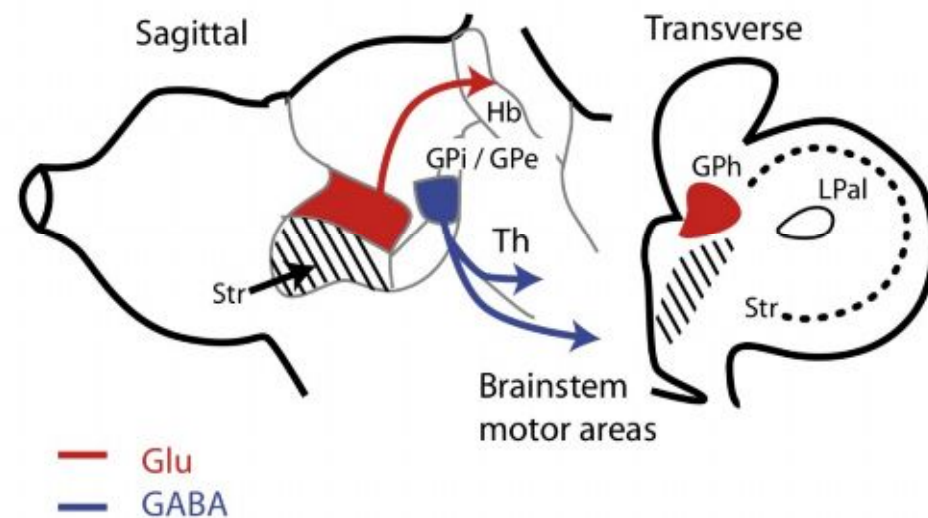


Extrapyramidal system of the lamprey

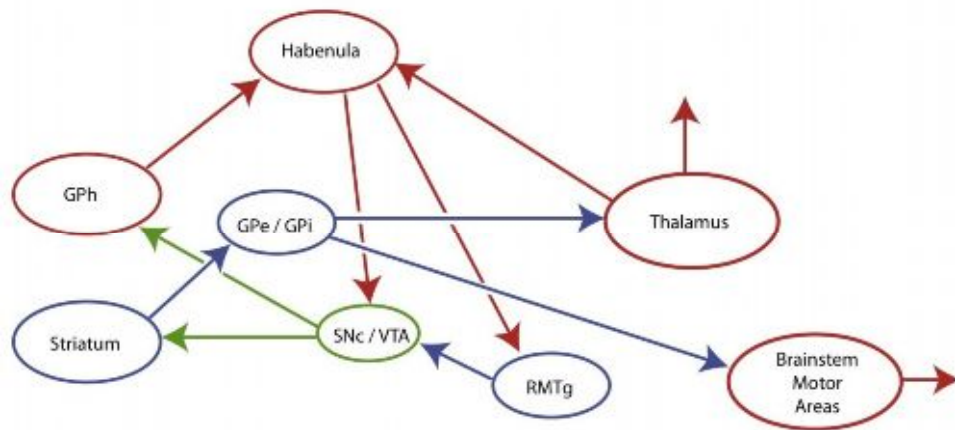


Habenula-projecting globus pallidus (GPh)

lamprey brain

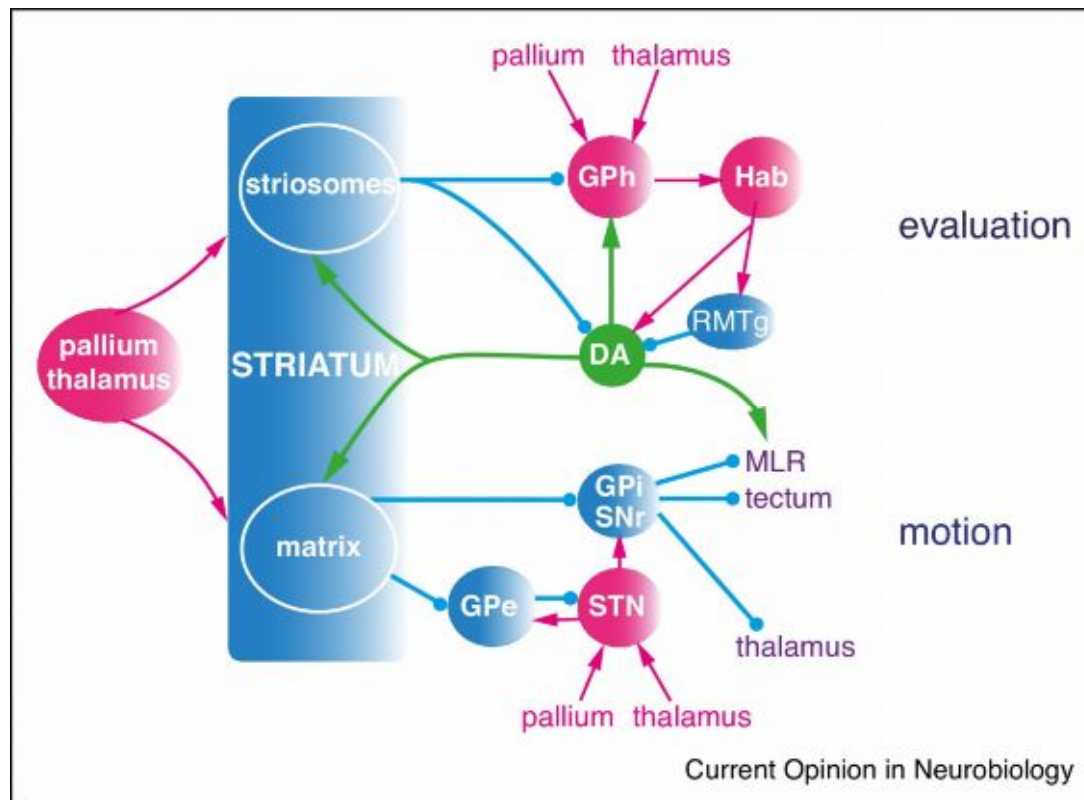


Regulation of response selection in lampreys



- › GPh stimulates lateral habenula
 - Stimulates SNc/VTA (increase activity)
 - Stimulates RMTg (inhibit activity)
- › Activation depends upon result
 - Food obtained: continue activity
 - Food not obtained: discontinue
- › Striatum directs motor activity

Regulation of response selection



› Evaluative circuit

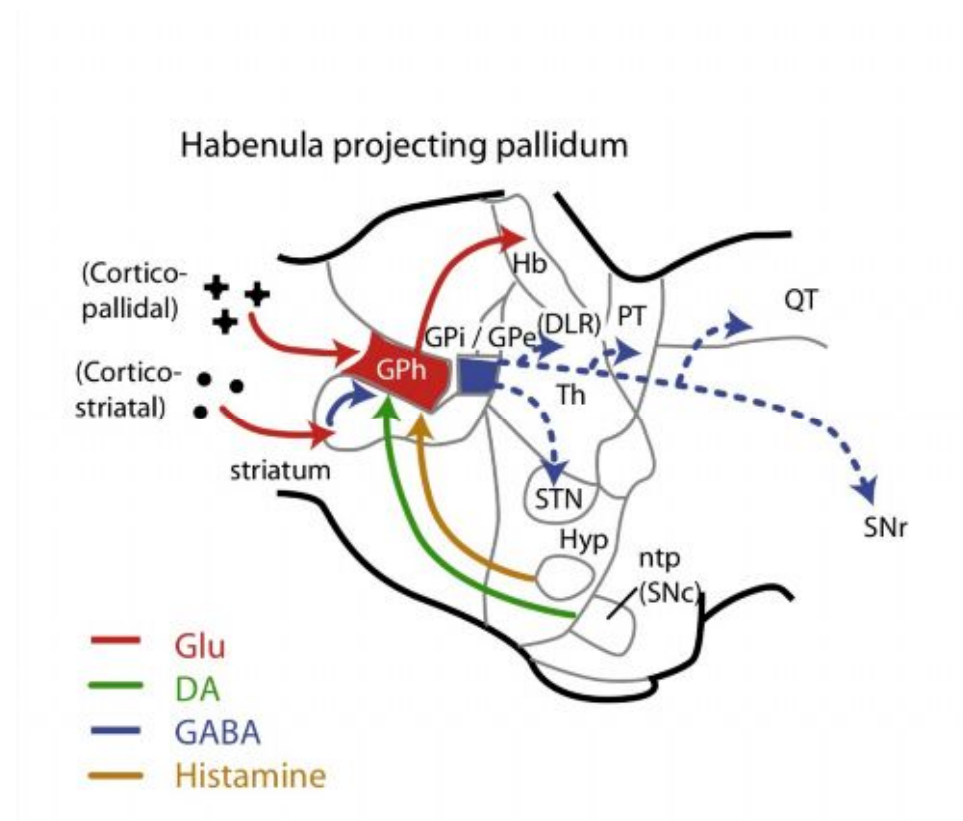
- GPh
- Habenula
- SNc/VTA
- Striatum

› Induce motor activity

- Striatum
- Globus pallidus output channel
- Midbrain motor centres



Position of the lamprey's habenula-projecting globus pallidus





Forebrain changes from lamprey to man

- › Development of the dorsal pallium to cerebral cortex
 - Input analysis from complex sensory input by posterior cortex
 - Complex behavioural output generation by anterior cortex
- › Development of the cerebellar system
- › Development of the extrapyramidal circuit
- › Inclusion of ventromedial pallium and striatum into amygdala
 - Development of basolateral cortical amygdala
 - Development of centromedial striatal amygdala
 - Development of the hippocampal complex
- › But where did the habenula-projecting globus pallidus go?

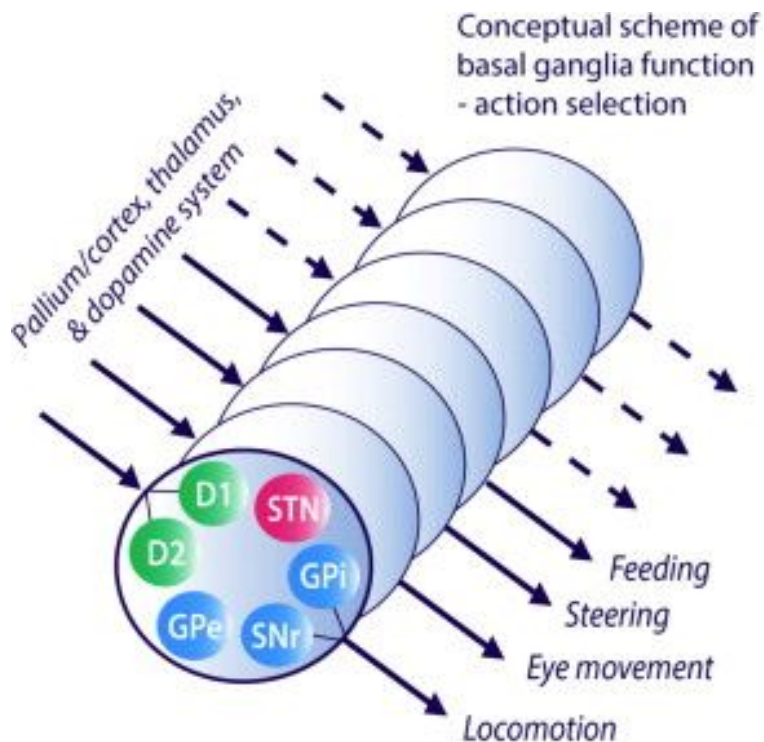
Modular organization of the basal ganglia

› Limbic basal ganglia

- Fight
- Flight
- Nucleus accumbens shell
- Nucleus accumbens core
 - feeding

› Extrapyramidal basal ganglia

- Steering
- Eye movement
- Locomotion

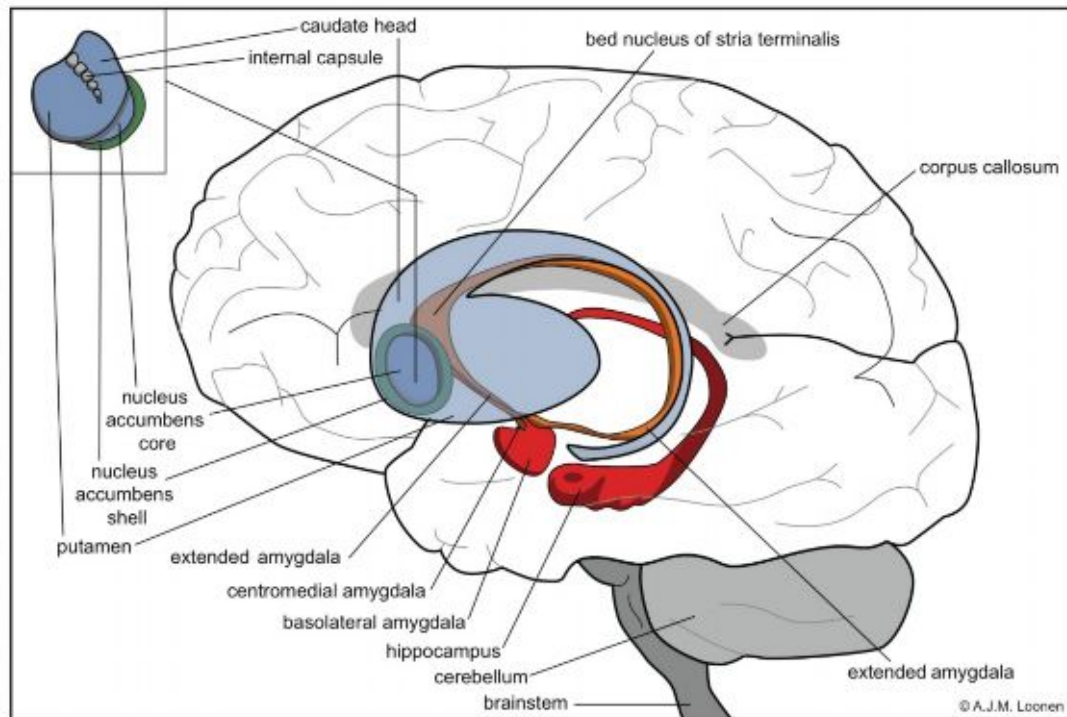




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Basal ganglia in humans



› Dorsal striatum

- Caudate nucleus
- Putamen

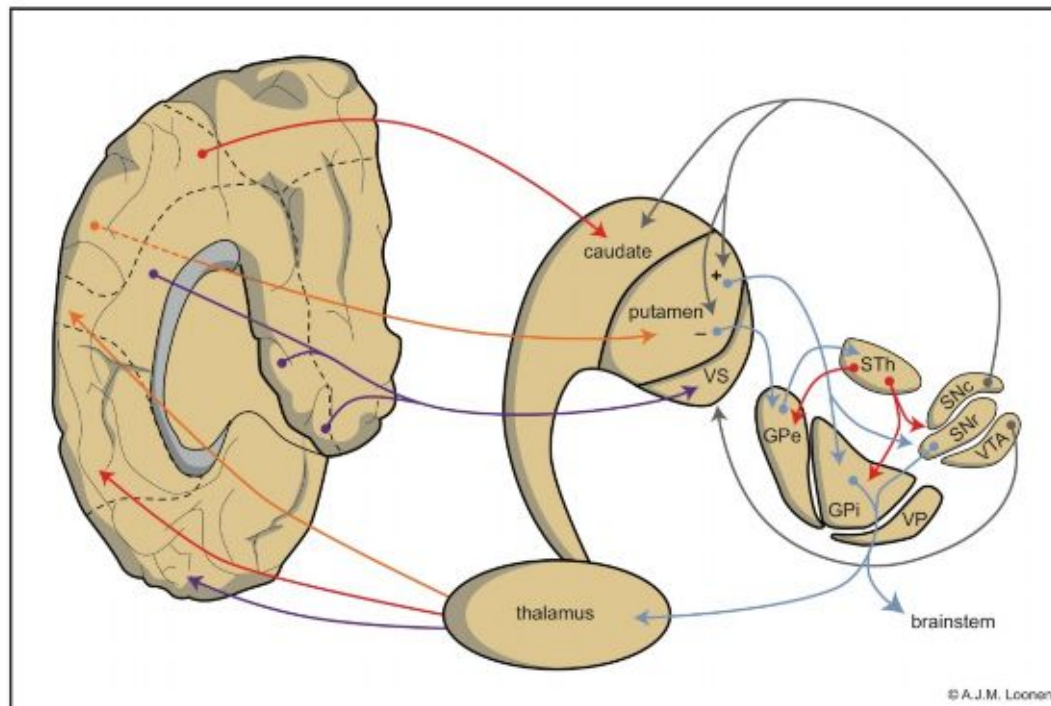
- Nucleus accumbens core
- Nucleus accumbens shell

› Nuclear and extended amygdala

› Basolateral amygdala

› Hippocampal complex

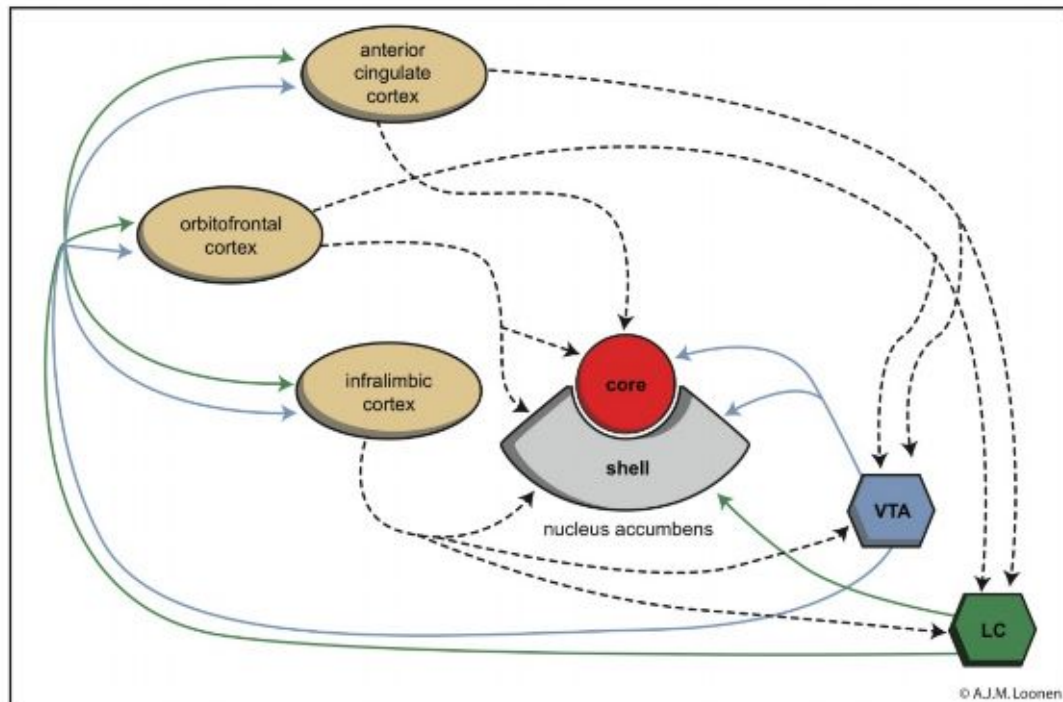
Posterior loop of parallel extrapyramidal circuits



› Motivational circuit

- Limbic cortex/amygdala
- Ventral striatum (Nucleus Accumbens)
- Ventral pallidum
- Thalamus
- Medial prefrontal cortex

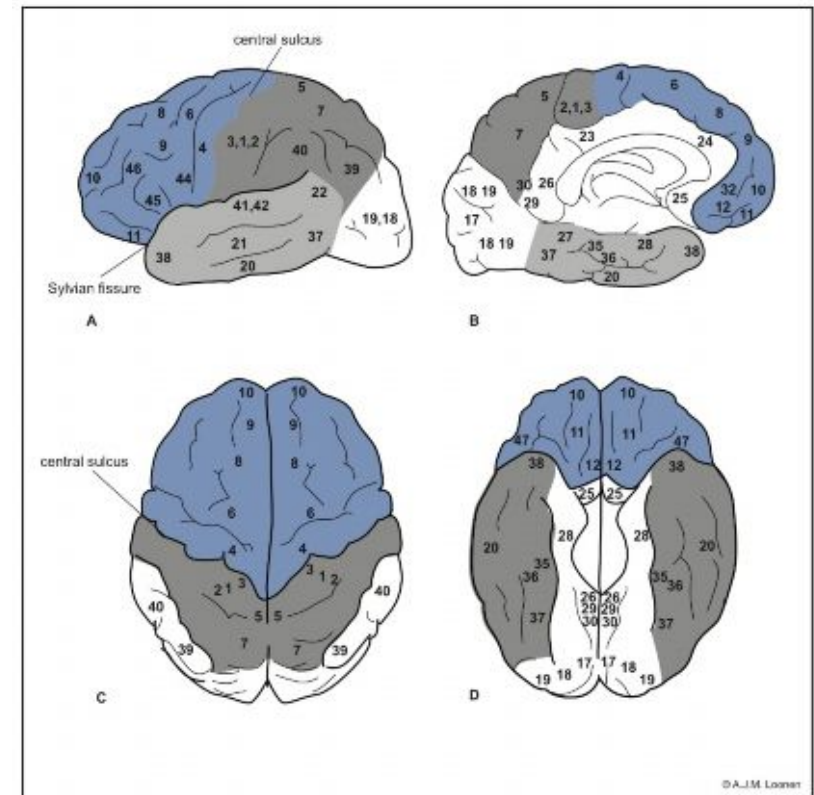
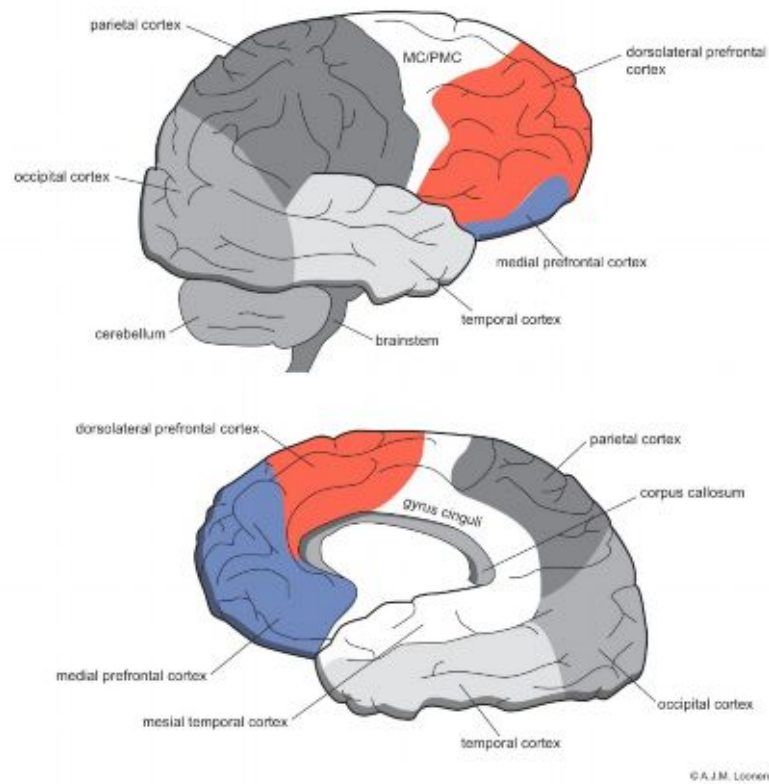
Structures affecting the nucleus accumbens



- › Limbic cortical areas
 - Anterior cingulate cortex
 - Subgenual cingulate cortex
 - Orbitofrontal cortex
- › Dopaminergic input (D2)
- › Adrenergic input (β)



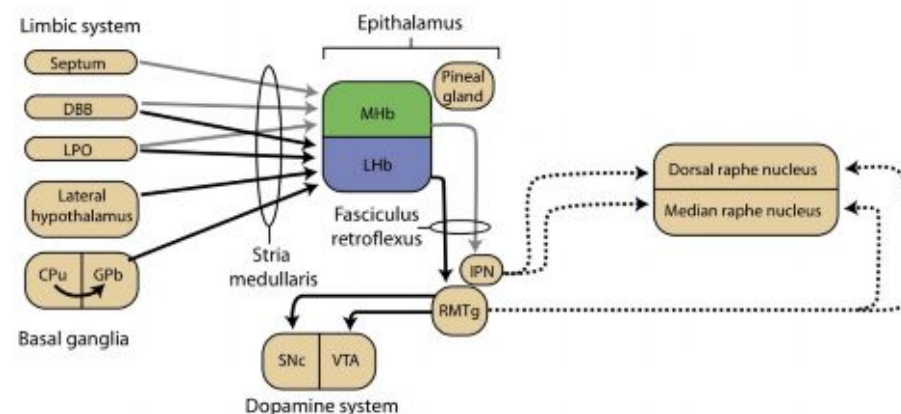
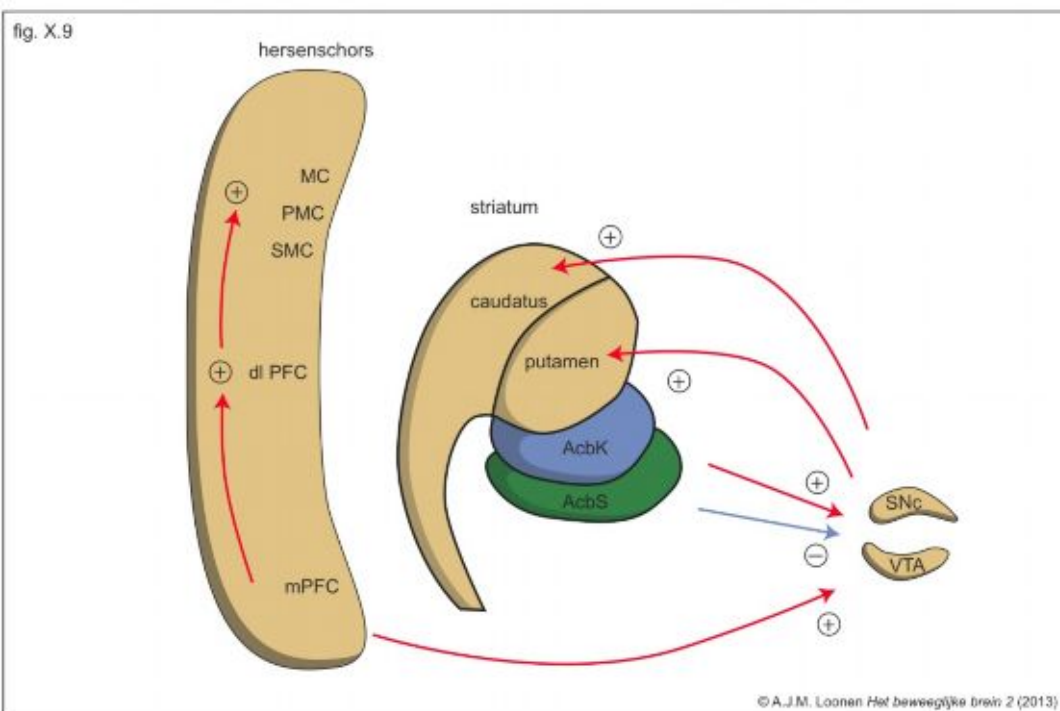
Position on the cerebral cortex



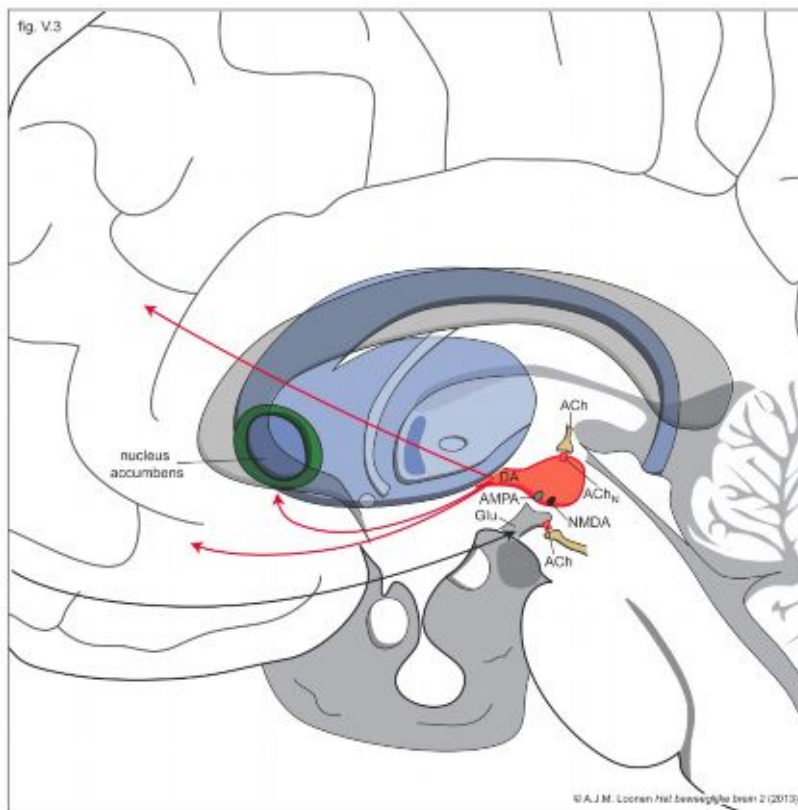
Systems regulating dopaminergic activity

Ventral connection

Dorsal connection



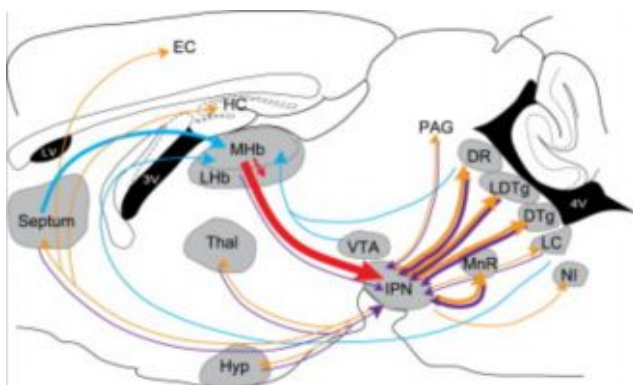
Connectivity of the medial prefrontal cortex



- › Specific cues activate mPFC (Glu)
- › Stimulation of VTA (Glu)
 - LTP/LTD induces memorization
- › Presynaptic input on synapses
 - ACh_N facilitation of memorization



Connectivity of the medial habenula



› Input from

- Septal areas (ACh, SP)

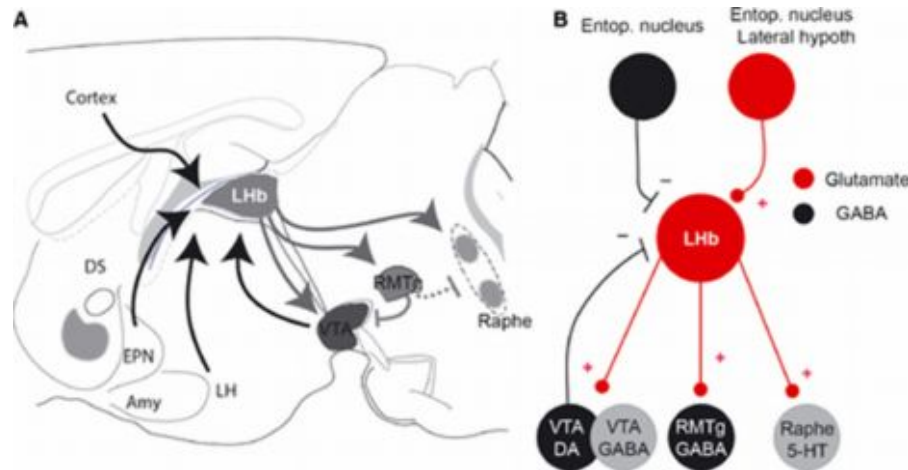
› Output to (ACh, SP, Glu)

- Lateral habenula (LHb)
- Interpeduncular nucleus (IPN) (ACh, SP, Glu)
 - Dorsal raphe (DR)
 - Laterodorsal tegmental nucleus (LDTg)
 - Dorsal tegmental nucleus (DTg)
 - Locus coeruleus (LC)

Connectivity of the lateral habenula

› Input from

- Lateral hypothalamus
- Entopeduncular nucleus (EPN)
- Prefrontal cortex
- EPN/ventral pallidum
- Diagonal Band of Broca nucleus



› Output through fasc. Retroflexus

- Brainstem monoaminergic nuclei
- Rostromedial tegmental nucleus (RMTg)



Physiological role of lateral habenula

- › Reward-based decision-making (reinforcement learning)
 - Disinhibition of DA in larger than expected rewards
 - Inhibition of DA in smaller than expected rewards
- › Encoding of aversive stimuli (avoidance learning)
 - Inhibition of DA in aversively conditioned stimuli
- › Behavioural response to stress (in relationship to medial habenula?)
- › Sleep-regulatory function (in relationship to pineal gland)
- › Navigation
- › Maternal behaviour



Preliminary conclusion

- › Behaviour is facilitated by increasing activity of motivational CSTC circuit
- › Activity of CSTC circuit is regulated by midbrain DA nuclei (SNc/VTa)
- › Activity of SNc/VTa system is regulated by two descending pathways:
 - PFC via medial forebrain bundle (MFB) to brainstem nuclei
 - Lateral habenula through fasciculus retroflexus to brainstem nuclei
 - Input from prefrontal cortex through septal nuclei
 - Input from hippocampus through septal nuclei
 - Input from basal ganglia through border region globus pallidus (GP)



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Seasonal animal migration as an example

Fitis migration



Wildebeest migration





Motivation to start migration

- › Precedes the actual need to obtain food (corresponding to hunger)
- › Based on various physical, emotional and cognitive cues
 - Internal cues (metabolism, autonomic, endocrine, immunological)
 - External cues (environment, social system)
- › Overrules other needs and activities



Craving for alcohol or illicit drugs

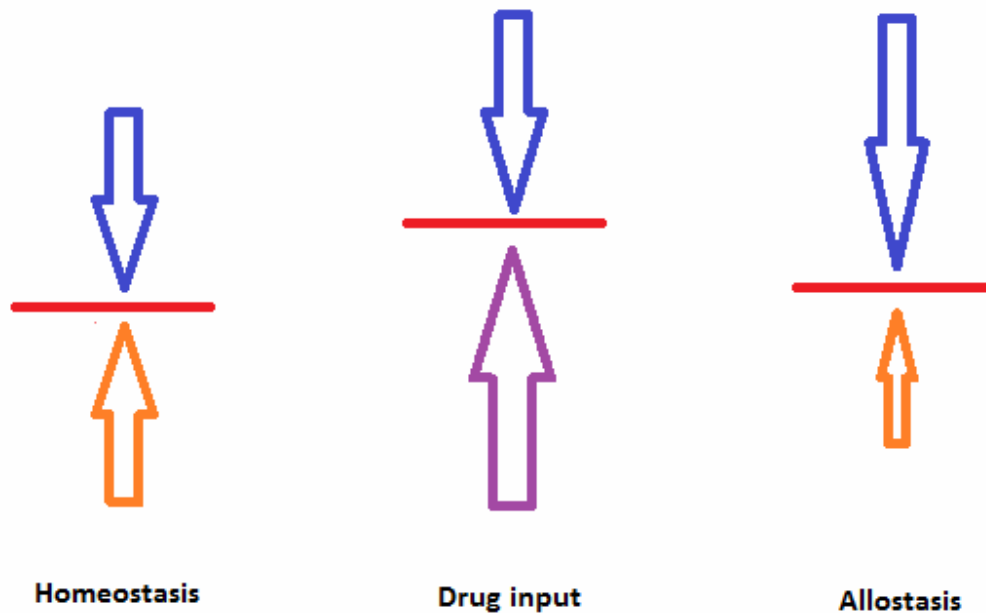
- › Motivation to obtain substance without an actual need is present
- › Based on various physical, emotional and cognitive cues
 - Physical: allostasis → withdrawal reactions
 - Emotional: mood symptoms → anxiety, depression
 - Cognitive: preoccupation with alcohol/illicit drug use
- › Overrules other needs and activities (hijacks the reward system)



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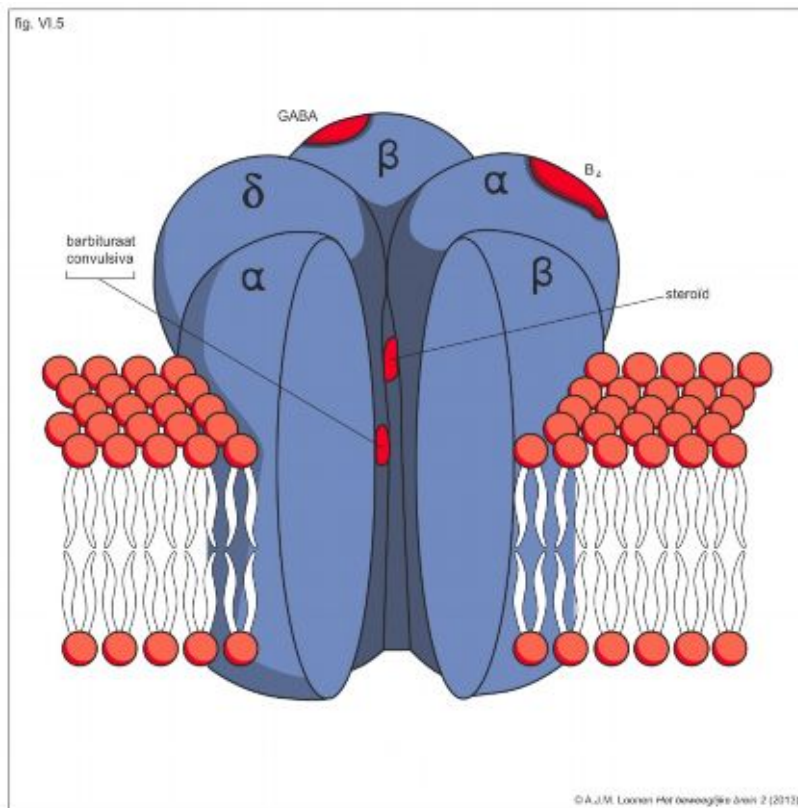
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Mechanism of allostatis



- › Homeostasis = set-point in equilibrium
- › Drug effect = shift of set-point
- › Allostasis = set-point in disequilibrium
 - Withdrawal reactions
 - Dysphoria and anxiety
 - Motivation to solve the problem

Mechanism of tolerance



› Normal situation

- GABA binds to receptor protein
- Flux of chloride ions alters

› With alcohol

- Alcohol binds to channel protein
- Flux of chloride ions alters
- Sensitivity to conformation changes altered

› Alcohol withdrawal

- Sensitivity to alcohol is altered
- Sensitivity to GABA is altered



Mechanism of relapse

Narcotic cues → craving

- Slowly decreasing in magnitude

Renewed use → intense craving

- Rapid reactivation to original level
- Less slowly decreasing in magnitude

Recurrent drug use

- Complicates detoxification
- Complicates maintaining abstinence

› PFC → stimulation of VTA → NAcb

› Habenula → powerful disinhibition VTA

- Increased sensitivity of NAcb
- Increased sensitivity to these relevant cues

› Repeated drug use

- Intensified craving induced by relevant cues
- More slowly desensitization after stopping



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Addiction is a reward system disease

- › Craving is an essential component of addiction
- › Craving is increased motivation to obtain alcohol or illicit drug
- › Craving is derived of a normal function of the reward system
- › The dorsal descending pathway (via habenula) has an essential role
 - Initiation of craving for a compound with unexpected rewarding effect
 - Invigorating craving after reusing substance following abstinence
- › The ventral descending pathway (via MFB) maintains craving in regular
- › Conclusion: addiction is a reward system disease.



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Thank you for your attention