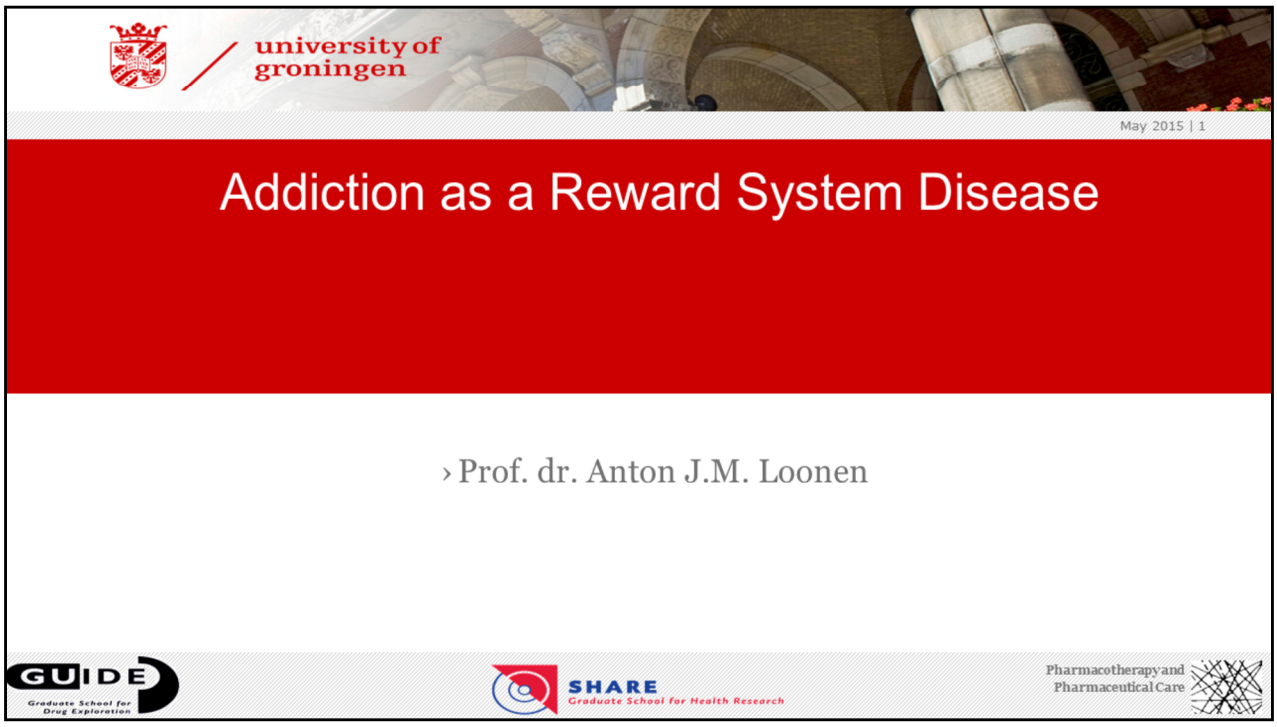

Ladies and gentlemen,

This lecture was presented during the third CINP educational course, this time on the neurobiology of addiction, in Tomsk and Novosibirsk in May 2015.

In my lecture I will first describe the evolutionary development of the forebrain of vertebrates. I will specifically pay attention to the systems regulating motivation to obtain food. Thereafter, I will describe how motivation to appetitive behaviour is regulated in humans.
In my opinion an important similarity exists between hypermotivation to obtain alcohol, tobacco or illicit drugs and the well-known phenomenon of animal migration shown by several birds and mammals. Describing this similarity will result in a description of addiction as a reward system disease. In addiction the mechanism to obtain necessities for the survival of the individual or the species is hijacked by alcohol, tobacco or illicit drugs.

Five components determine the character of addiction. Only one of them is truly essential to addiction, which is craving. The other effects are also shown by other drugs or processes which are not addictive in nature.

Having pleasure is one of the most important processes in life. We can experience much pleasure when we find relief from pain or other disease symptoms. For this reason, many effective drugs used for treating somatic conditions cause pleasure. On the other hand, persons who are seriously addicted often reach the stage where they do not become high after having taken the addictive substance.

Tolerance and withdrawal are very common effects of drugs. Side effects of drugs are usually more severe just after initiating treatment. In SSRIs this tolerance to stress-inducing impulses is probably the main mechanism of action. It also results in withdrawal symptoms, but SSRIs are not addictive at all.

Relapse is a phenomenon we will end with, so let's now turn to craving.

Craving is an essential driving force leading to addiction behaviour. It is defined as giving preference to behaviour which leads to the acquiring of the substance or process the individual is addicted to. In reality, craving abuses a mechanism which is essential for keeping alive and healthy. Two forces are essential for maintaining life: the first is the force that motivates the individual to obtain food and so on; displaying this behaviour leads to a reward feeling. The second force motivates the escape from threat and other sources of misery.

These behaviours are so important that even the earliest free living animals existing in the oceans some 540 mya must have been capable of displaying this behaviour in order to stay alive and have offspring.

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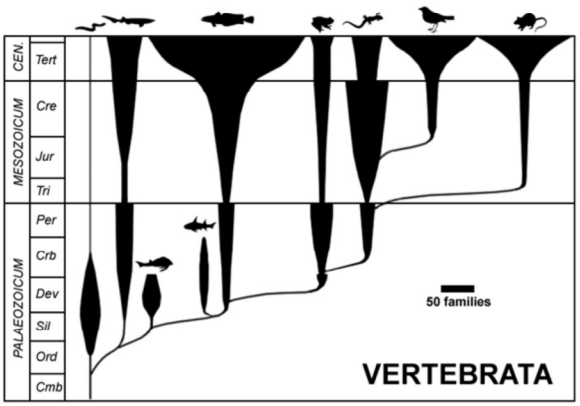
Evolution of the reward system (general overview)



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This slide shows you an accepted representation of the evolution of the vertebrates, which started with the first chordates comparable with the lancelet over 540 million years ago. The first vertebrate is supposed to be an animal which is comparable with the modern lamprey. This animal had a head containing a brain and vertebrates, but did not yet have a lower jaw. These animals are therefore called agnathans (jawless fishes).

[All family classes of the subphylum vertebrata are from left to right): Class Agnatha (jawless fishes); Class Chondrichthyes (cartilaginous fishes); Class Osteichthyes (bony fishes); Class Amphibia (amphibians); Class Reptilia (reptiles), Class Aves (birds) and Class Mammalia (mammals)]

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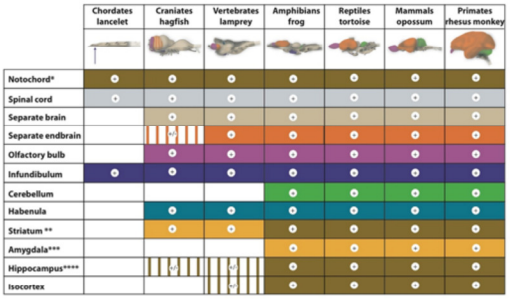
Evolution of the brain of vertebrates



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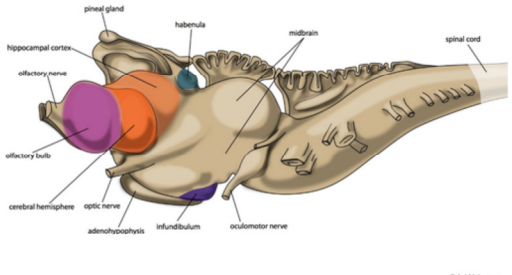
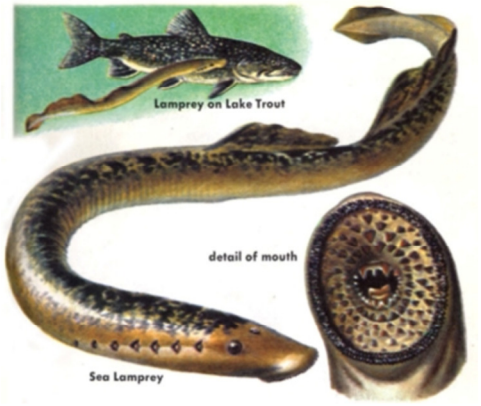
This slide shows how the brain of these animals developed. I left out the birds and started with the lancelet, an animal in which the brain cannot yet be morphologically distinguished from the spinal cord. As can be seen, the first animal with an actual forebrain is the lamprey. The hagfish, which represents an earlier stage of development and who do not possess true backbone, already have a striatum. However, it should be kept in mind that the striatum of both hagfish and lamprey develop into the nuclear amygdala in later animals.

Brain of the lamprey





This is a more detailed picture of the brain of the lamprey. This animal has a separate forebrain (orange), but this is relatively small in comparison to the olfactory bulb (purple) and thalamus. The hippocampal part of the forebrain is coloured pale orange on this figure. Note the prominent position of habenula (blue).

The lamprey (sometimes also called lamprey eel) is characterized by a toothed, funnel-like sucking mouth. Lampreys are well known for boring into the flesh of other fish to suck their blood, but in fact only a minority of the about 38 known extant species actually do so.

[The group of Sten Grillner (particularly Marcus Stephenson-Jones and Brita Robertson) of the Department of Neuroscience, Karolinska Institutet, SE-17177 Stockholm, Sweden have studied the extrapyramidal system of the lamprey and have found that it shows major similarities to the extrapyramidal system of mammals.]

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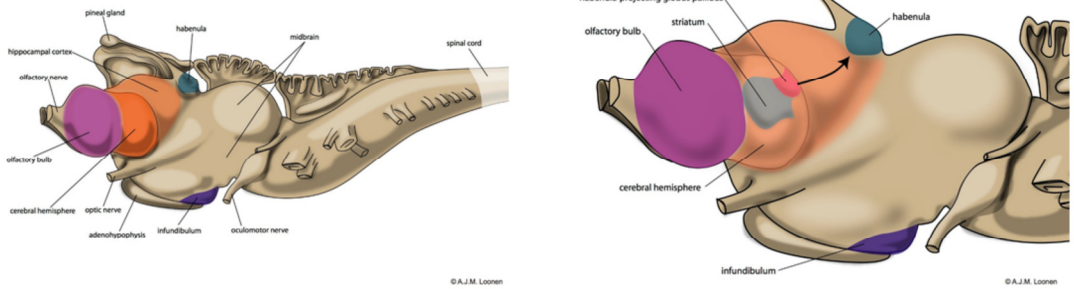
Habenula-projecting globus pallidus (GPh)



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On the right figure the relation is shown of the hippocampal lobe with a special structure which is specifically influencing the lateral habenula. This structure is positioned in the medial wall of the forebrain within the subhippocampal lobe and is termed the habenula-projecting globus pallidus (GPh). Glutamatergic fibres run from this GPh and stimulate the lateral habenula to influence two specific structures in the midbrain: the nucleus of the tuberculum posterior (NTP; considered to be a homologue of the substantia nigra, pars compacta (SNc) and ventral tegmental area (VTA).

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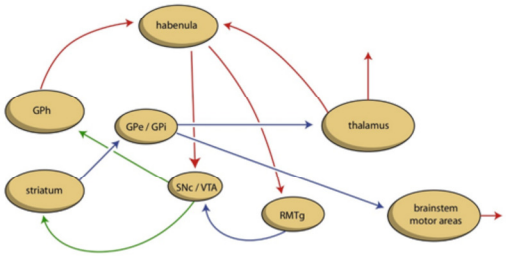
Regulation of response selection in lampreys



- 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

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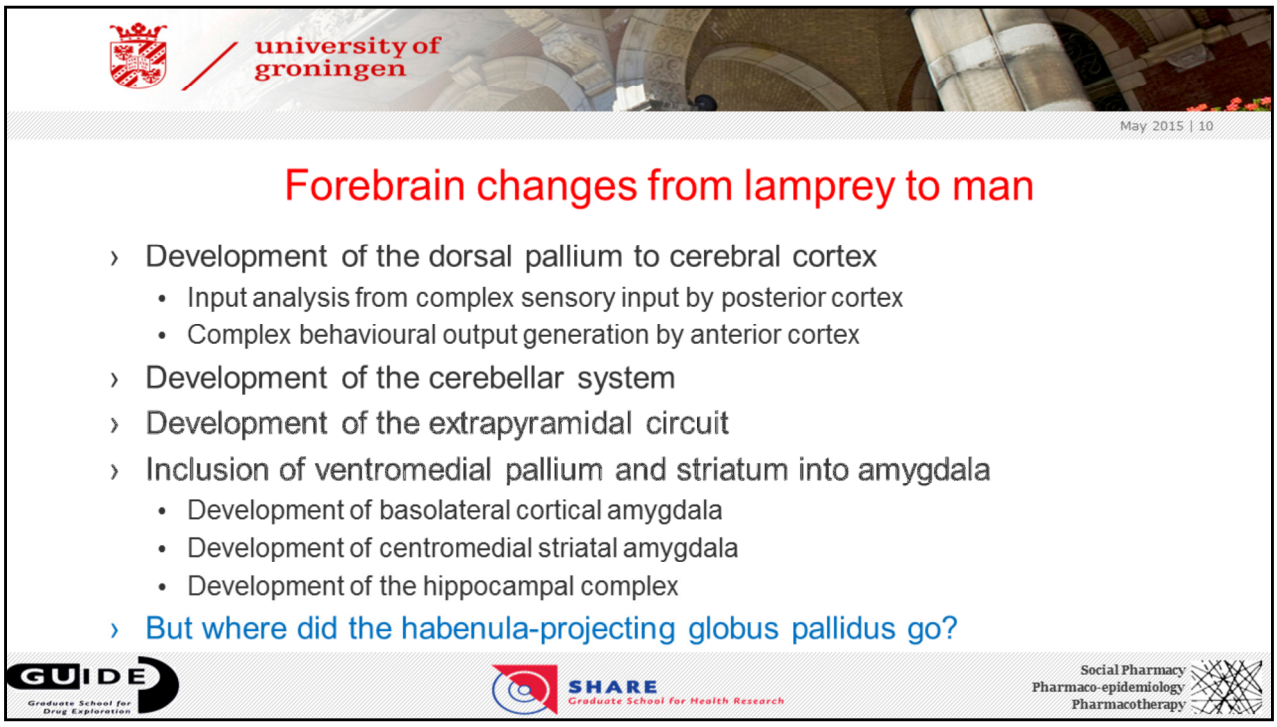
In this scheme, two separate regulatory systems are distinguished. One system starts in the lamprey's striatum and affects the extrapyramidal output ganglia. Activation of this system is induced by olfactory and other sensory information and results in increased motor activity. A second system is the regulation of whether the activity is successful and whether it should be continued or not. When it is not very rewarding, it could probably best be suspended in order to allow other, potentially more beneficial activities. This is a circuit starting in the so called habenula-projecting globus pallidus (GPh) and stimulating the lateral habenula. From there, the dopaminergic nucleus of the tuberculum posterior - which is similar to the human ventral tegmental area (VTA) - is stimulated directly or inhibited indirectly by activation of the rostromedial tegmental nucleus (RMTg). Dopaminergic fibres activate the striatum and habenula-projecting globus pallidus.



Of course, during evolution from the very first vertebrates (represented by the lamprey) to human beings, the forebrain changed extensively. The most important change is obviously the development of the cerebral cortex as the main structure dealing with sensory input and producing behavioural output. Parallel to this structure the cerebellar and extrapyramidal systems developed to adapt the behavioural output as needed. The pallium and striatum of the primitive agnathans have been included within the emotional brain: the hippocampal complex, the amygdaloid complex and a small part of the limbic cortex.

I cannot give you the answer to the last question on this slide. As far as I know, the habenula-projecting globus pallidus is lost in the mammalian brain; it has been suggested that in mammals it is the border region of the globus pallidus (GPb), but this is not definite yet. In my opinion, the relation with the hippocampal complex should probably be retained within the human equivalent of the GPh, but I am not sure that this is the case for this border region of the globus pallidus.

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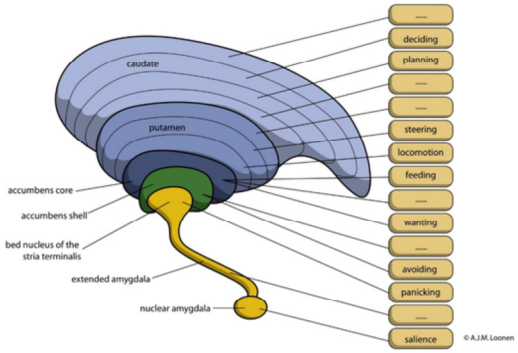
Modular organization of the basal ganglia



- Limbic basal ganglia
  - Fight
  - Flight
  - Nucleus accumbens shell
  - Nucleus accumbens core
    - Feeding
- Extrapyramidal basal ganglia
  - Steering
  - Eye movement
  - Locomotion

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According to Brita Robertson and colleagues [The lamprey blueprint of the mammalian nervous system, Progress in Brain Research, Volume 212, 2014, 337 – 349], during evolution, one by one modules regulating certain movements and behaviour were added to the extrapyramidal system. I myself would suggest that this might have happened at the side of the limbic striatum (amygdala in humans) and of the extrapyramidal striatum (dorsal and ventral striatum in humans). The interface of these two is formed by the nucleus accumbens. The core of this nucleus belongs more to the extrapyramidal striatum and the shell part to the limbic striatum.

In the next part of my presentation I will describe how appetitive behaviour is regulated in humans.

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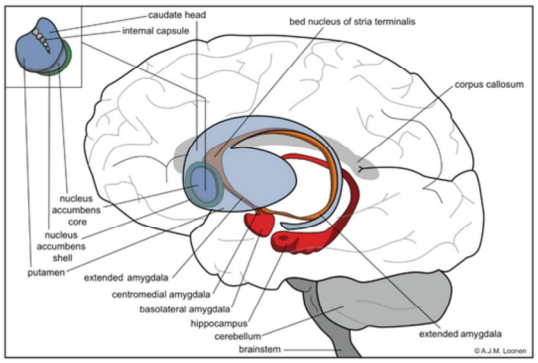
Basal ganglia in humans



- Dorsal striatum
  - Caudate nucleus
  - Putamen
  - Nucleus accumbens core
  - Nucleus accumbens shell
- Nuclear and extended amygdala
- Basolateral amygdala
- Hippocampal complex

I will start with the description of the subcortical structures involved. This slide shows you the position of the basal ganglia in the human brain. During the rest of this lecture we will concentrate on the ventral striatum or nucleus accumbens. This structure has a major role in promoting behaviour that might lead to reward.

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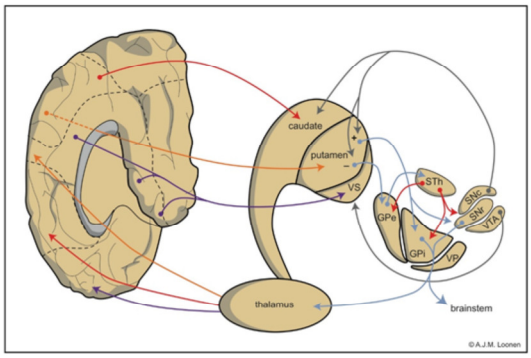
Posterior loop of parallel extrapyramidal circuits



› Motivational circuit (purple)

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

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Just to refresh your memory: the extrapyramidal circuit consists of several segregated, parallel sub-circuits, one of which is the motivational/emotional circuit running from the limbic cortex via the ventral striatum and ventral pallidum to thalamus and then to the medial prefrontal cortex. This circuit is relevant for this lecture because it regulates the amount of motivation required to display appetitive reward directed behaviour.

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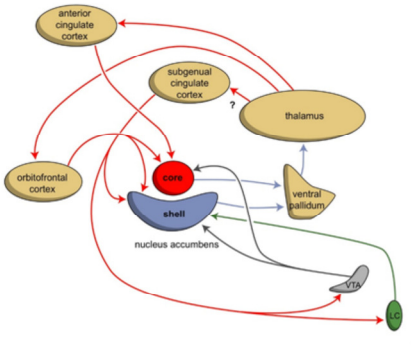
Structures affecting the nucleus accumbens



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

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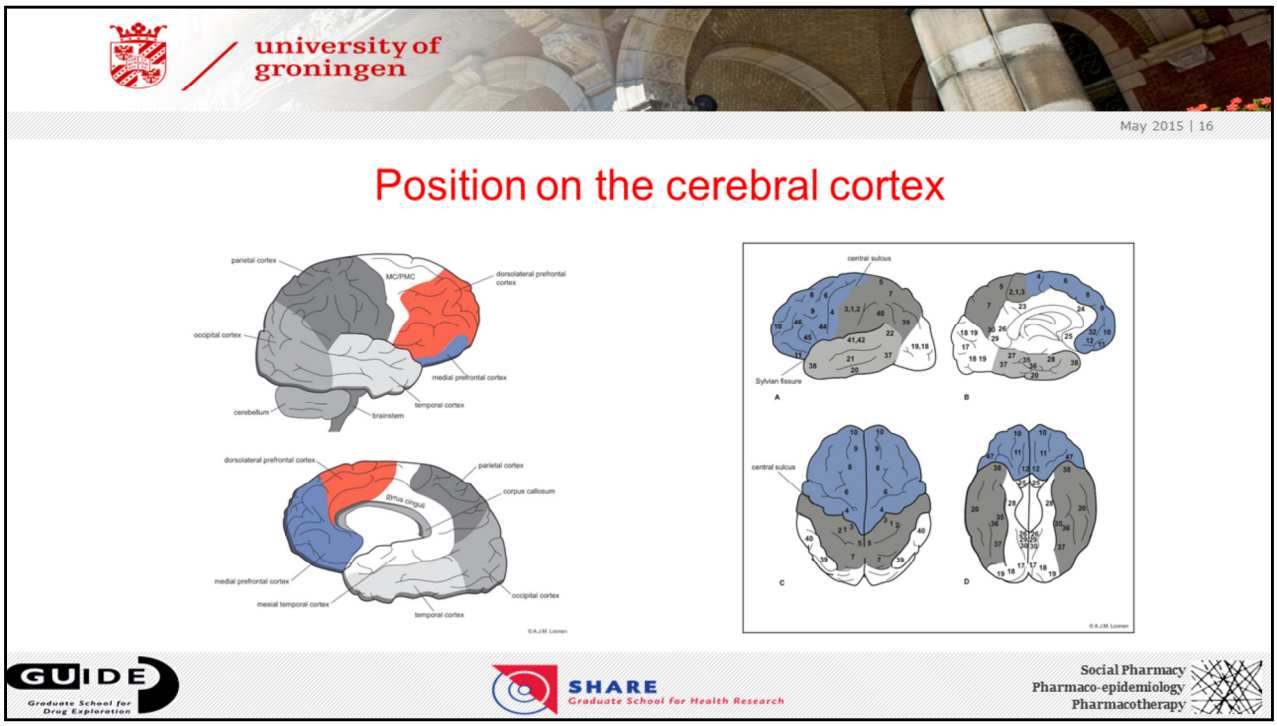
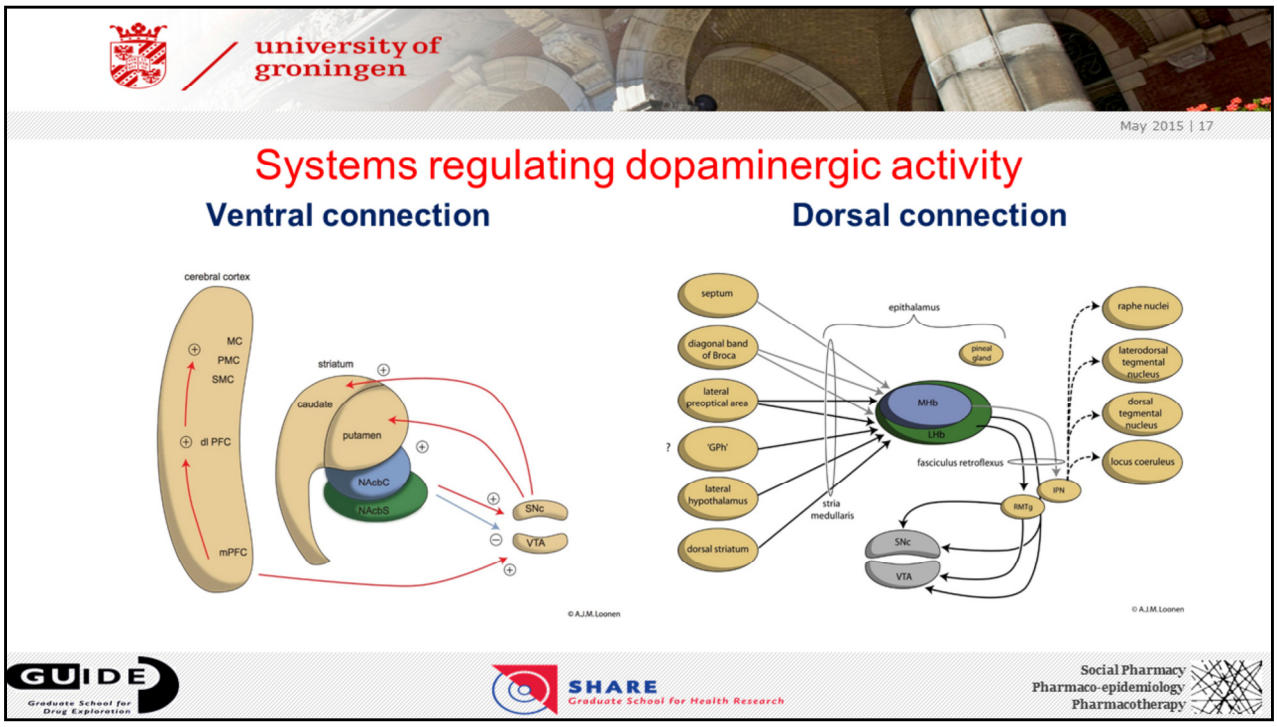
As is shown on this slide, the nucleus accumbens receives information from different limbic cortical areas. The activity of the circuits is regulated by dopaminergic input from the midbrain ventral tegmental area. The nucleus accumbens shell also receives adrenergic input from the locus coeruleus, but this will not be considered any further here. The nucleus accumbens core motivates the individual to display behaviour which will lead to a reward. The nucleus accumbens shell is active when obtaining a reward is less certain and this causes stress.



The cortical areas I am referring to are on the prefrontal cortex. This is in red (dorsolateral part) and blue (medial part) on the figure on the left. In the figure on the right the Brodmann areas are depicted. The anterior cingulate cortex is Brodmann area 24, the infralimbic cortex or the subgenual cingulate cortex is Brodmann area 25, and the orbitofrontal cortex is Brodmann area 11.



We can distinguish two systems regulating the activity of the dopaminergic input to the nucleus accumbens: the prefrontal cortex and the habenular complex. In both systems, nicotinic receptors play an important role. The habenula consists of two parts: the medial habenula and the lateral habenula. The habenula has an efferent pathway running to the ventral midbrain, called the fasciculus retroflexus. At the input side fibres come from the basal ganglia and septal areas and run through the stria medullaris. Together with habenula and pineal gland, the stria medullaris constitutes the epithalamus. The habenula is one of two important pathways linking cortical structures with the midbrain monoaminergic nuclei. The other one follows the medial forebrain bundle.

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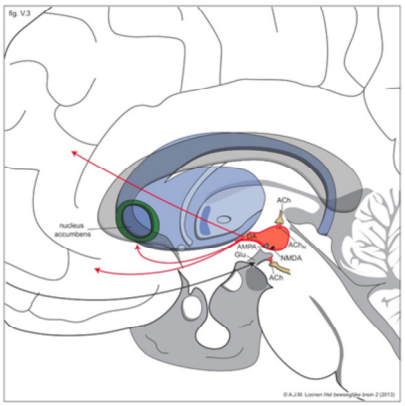
Connectivity of the medial prefrontal cortex



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

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Glutamatergic projections from the medial prefrontal cortex stimulate dopaminergic cell bodies within the midbrain. The learning ability of glutamatergic networks (LTP/LTD) results in activation of the system based on specific cues. Cholinergic input from the brainstem facilitates this learning ability by the stimulation of nicotinic receptors.

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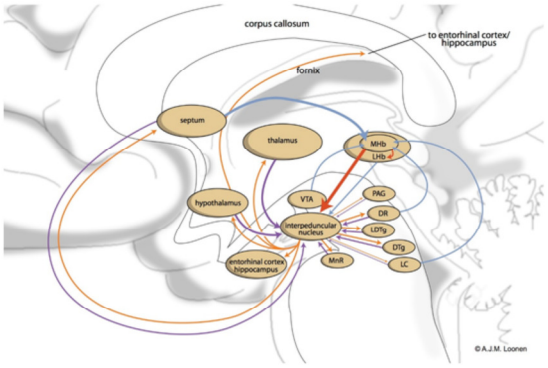
Connectivity of the medial habenula



- Input from
  - Septal areas (ACh, SP)
- Output to (ACh, SP, Glu)
  - Lateral habenula (LHb)
  - Interpeduncular nucleus (IPN) (ACh)
    - Dorsal raphe (DR)
    - Laterodorsal tegmental nucleus (LDTg)
    - Dorsal tegmental nucleus (DTg)
    - Locus coeruleus (LC)

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The medial habenula receives input from several brain areas, but mainly from septal nuclei. Most of these fibres terminate as cholinergic or substance P-ergic synapses in the medial habenula, but others are glutamatergic, GABAergic or monoaminergic. The MHb is also widely known for its abundance of nicotinic acetylcholine receptors (nAChRs). It is estimated that 90 – 100% of the neurons in the medial habenula express sub-units of the nicotinic receptors. The output of the medial habenula goes largely to the cholinergic interpeduncular nucleus by the fasciculus retroflexus. These efferent fibres use three neurotransmitters in a strictly organized manner: acetylcholine, substance P and glutamate.

A growing literature suggests that the medial habenula plays an important role in mood disorders, anxiety, stress, memory, and nicotine withdrawal as well as in cocaine, methamphetamine, and alcohol addiction. However, the mechanism of this role has only been partly elucidated.

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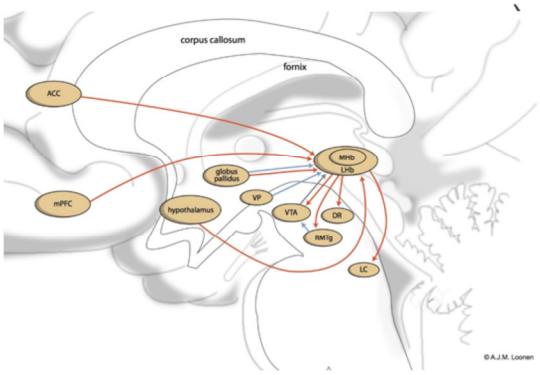
Connectivity of the lateral habenula



Input from

- Lateral hypothalamus
- Globus pallidus
- Prefrontal cortex
- Globus pallidus/ventral pallidum
- Diagonal Band of Broca nucleus

Output through fasc. Retroflexus

- Brainstem monoaminergic nuclei
- Rostromedial tegmental nucleus (RMTg)

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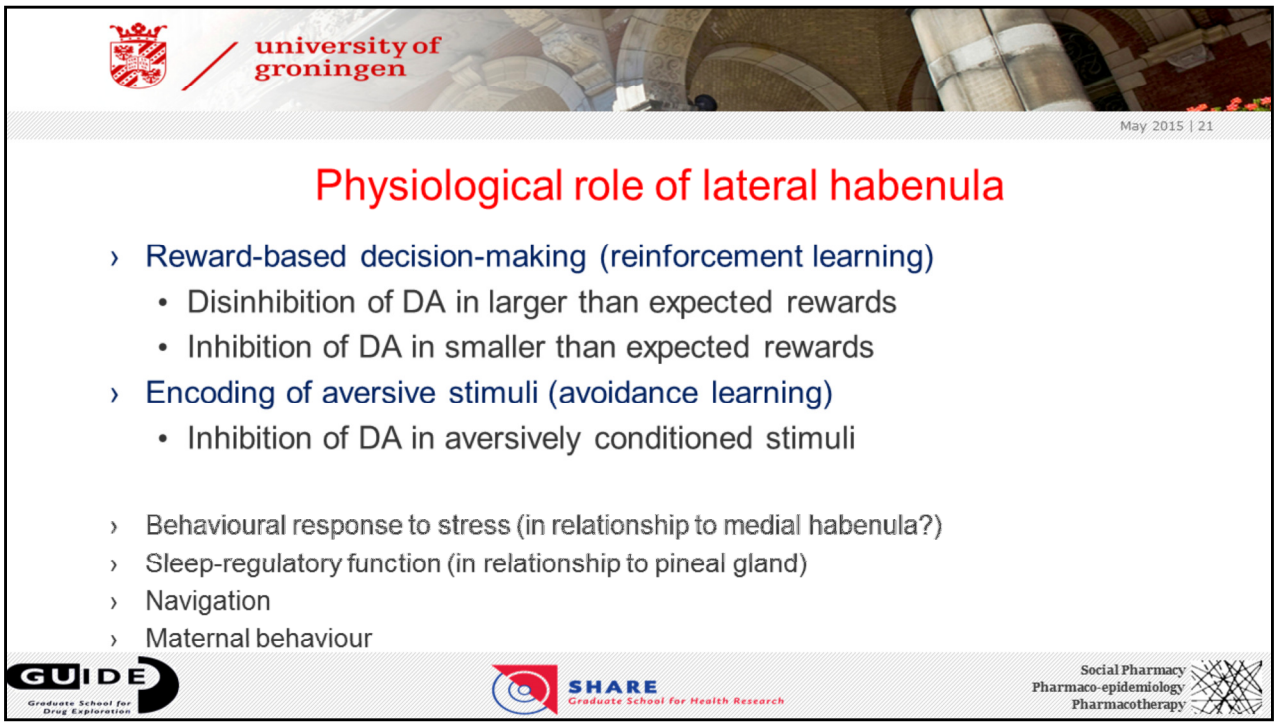
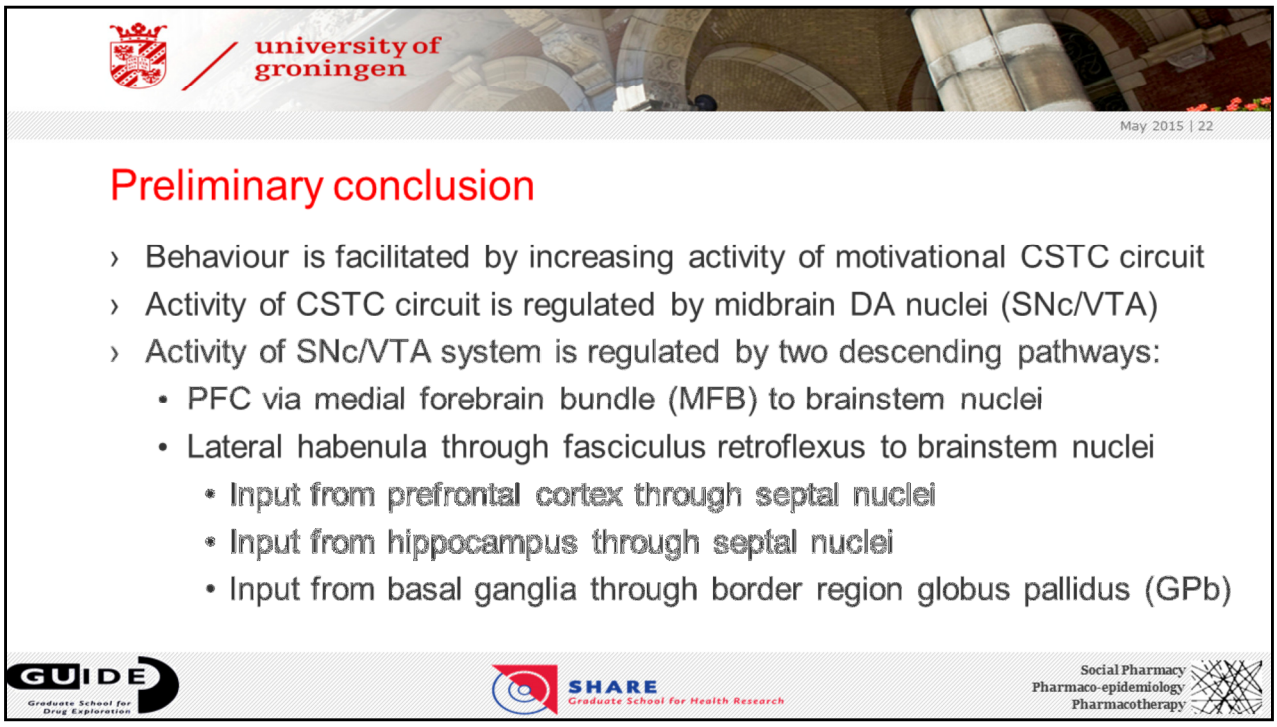
The connectivity of the lateral habenula is shown in this figure. Glutamatergic input is received from the lateral hypothalamus, the medial globus pallidus and several parts of the prefrontal cortex (ACC, mPFC). GABAergic input is received from the medial globus pallidus, ventral pallidum and the nucleus of the diagnonal band of Broca. All output from the lateral habenula is glutamatergic. The output is given to the monoaminergic nuclei of the brainstem (ventral tegmental area, raphe nuclei, locus coeruleus complex) and also to the GABA-ergic rostromedial tegmental nucleus. This nucleus inhibits the activity of the dopaminergic nuclei of the midbrain.

This brings me to the most important function of the lateral habenula: i.e. the inhibition of activity of the individual.



In monkeys the function of the habenula is not very different from that in lampreys. The lateral habenula increases firing when an aversive state is detected, especially when this aversive state is unexpected. This is similar, but less sophisticated, to the situation in lampreys where lack of reward induces inhibition of the current behaviour. Increased firing of the lateral habenula results in the inhibition of the ventral tegmental area, and therefore of the current behaviour. Interestingly, a stimulus does not need to be intrinsically aversive in order to lead to stimulation of the habenula. Indeed, the omission of an expected reward also increases LHb neuronal activity, suggesting a role of LHb in encoding 'disappointment'.

On the other hand, the lateral habenula is inhibited by unexpected delivery of rewards or their cues. Due to this response, the ventral tegmental area is disinhibited, and this results in a strong promotion of the on-going behaviour. This might explain why the lateral habenula is considered to play a prominent role in promoting craving for illicit drugs.



This brings me to the following conclusions: appetitive behaviour is facilitated by increasing the activity of motivational cortico-striato-thalamo-cortical (CSTC) subcircuit. In turn, the activity of the CSTC subcircuit is regulated by dopaminerge fibres coming from the ventral tegmental area (VTA) in the midbrain. The activity of the VTA is regulated by two descending pathways: the ventral pathway comes from the medial prefrontal cortex (mPFC) via the medial forebrain bundle, and the dorsal pathway comes via the lateral habenula and fasciculus retroflexus. The input to the dorsal pathway is probably coming in part from the mammalian equivalent of the lamprey's habenula-projecting globus pallidus (GPh).

In order to explain the biological background of craving it can be useful to consider the mechanism of animal migration. Animal migration is the relatively long-distance movement of individual animals, usually on a seasonal basis. It is found in all major animal groups, including birds, mammals, fish, reptiles, amphibians, insects, and crustaceans. The trigger for the migration may be the local climate, local availability of food, the season of the year or for mating reasons.

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Seasonal animal migration as an example

Fitis migration

Wildebeest migration

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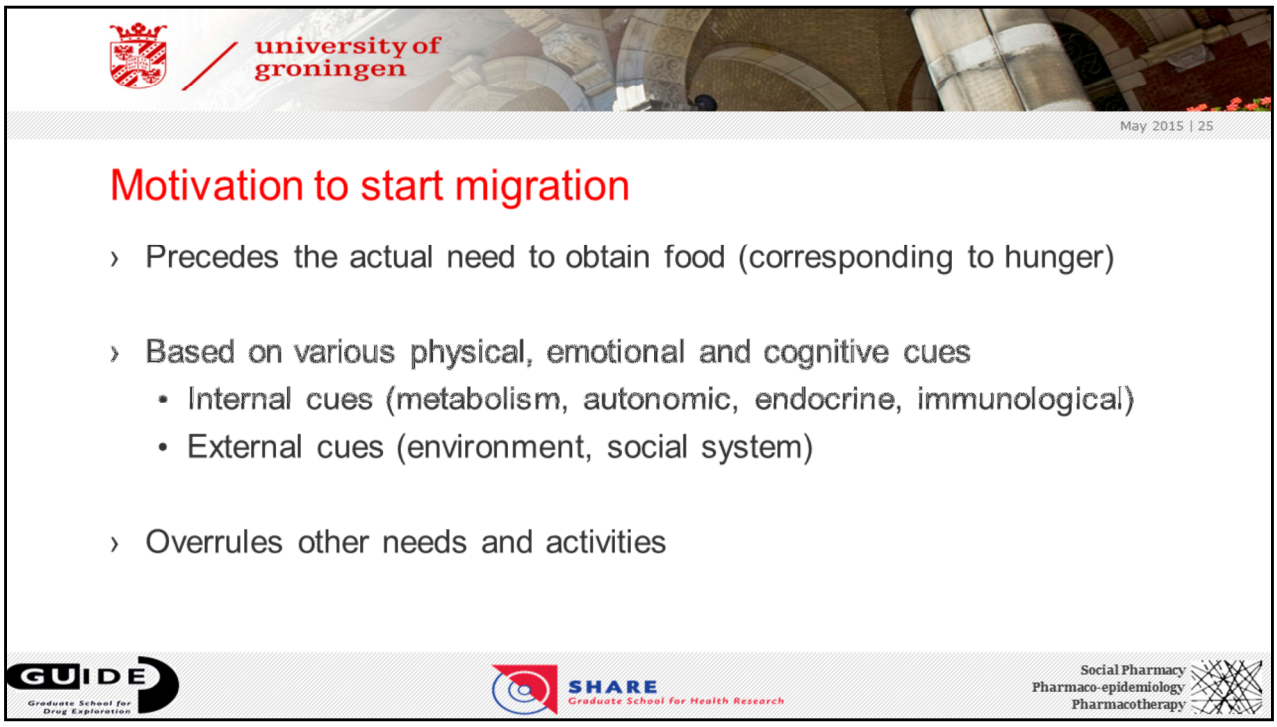
This slide shows two typical examples of animals migrating every season over a large distance. The East-Siberian Fitis bird migrates from Northern and Eastern Siberia to East Africa, while its Western European brothers and sisters migrate from Norway to South-East Asia and Indonesia. In East Africa, the annual migration of big herds of wildebeests offers a good example of mammals which perform an annual migration to new grazing grounds.

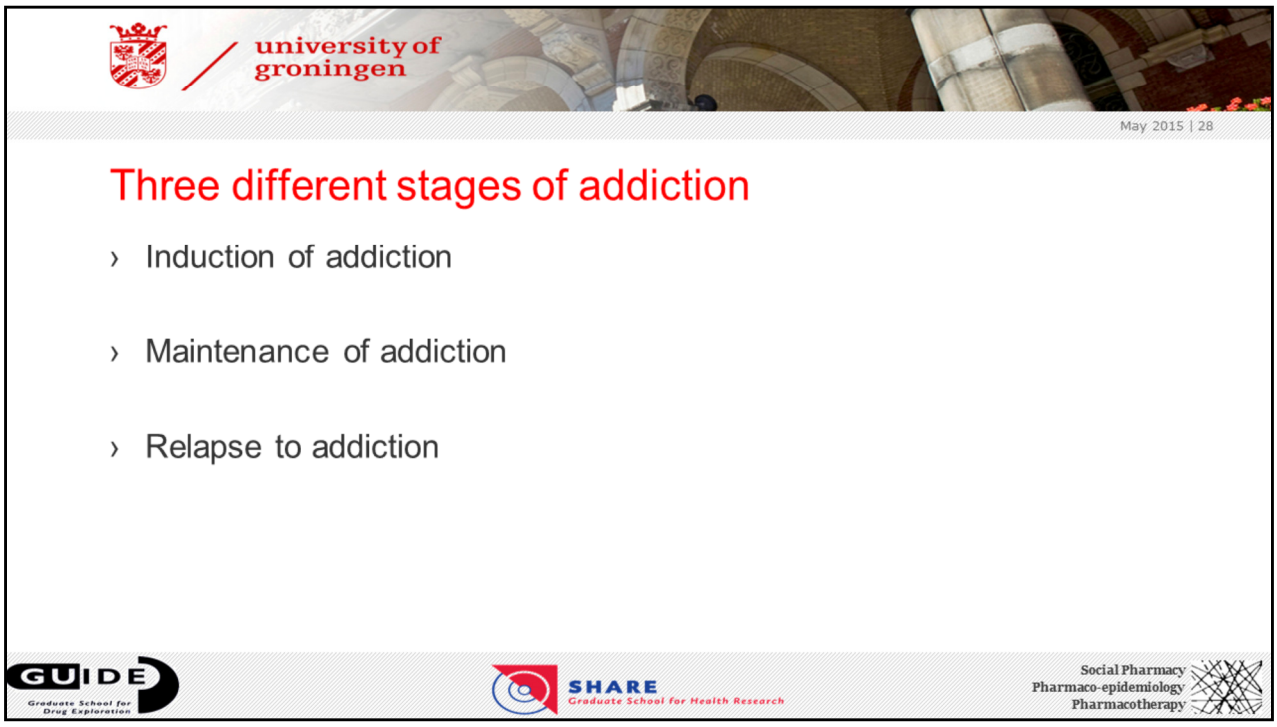


When we compare the mechanisms which lead to animal migration, a strong similarity with craving for illicit drugs becomes evident. In animal migration, certain changes within the animal's biosphere and internal circumstances are detected, which induce an urge to 'get going'.

By the way, it is not peculiar at all to think of the epithalamus when considering animal migration. Many animals can detect changes in electric or magnetic fields and use this information to navigate. In the lamprey, this electromagnetic-induced behaviour seems to be controlled by the habenula. Moreover, the close association of the habenula with the epiphysis may explain the seasonal patterns, as the pineal gland is part of the system regulating biorhythms.

Comparison of animal migration with craving for illicit drugs shows the similarity: this is also independent from the actual need for the drug and is induced by physical, emotional and cognitive cues.

It is necessary, however, to distinguish two separate processes: induction and maintenance of craving. This can be best illustrated by considering the phenomena occurring during relapse. I want to hypothesize that the dorsal route via the habenula is particularly important during the inducement of craving and also during relapse after a period of abstinence.



During regular use of illicit drugs, craving is maintained by specific sensory information, or 'narcotic cues', which are associated with the circumstance of obtaining or using these drugs. After abstaining from taking the drug, the craving intensity slowly tapers down, but it may take years to disappear or to become 'neglectable', e.g., consider craving from tobacco smoking. However, when the drug is used again after a period of abstinence, the craving process is rapidly reactivated and may become severe in a short period of time. It is tempting to speculate that the dorsal pathway is involved, because this corresponds very well to the earlier described reaction of the habenula to the unexpected delivery of rewards or their cues. The dorsal route seems capable of inducing a major change in behaviour, comparable in starting migration in some animal species.

This brings me to the conclusion of my presentation: addiction is a reward system disease.

As I have discussed, craving can be considered the essential force behind the process of addiction. Actually, craving is the hijacking of a normal function of the reward system serving to obtain things the animal needs to survive both as an individual and as a species. The intensity of the craving phenomenon is regulated by the ventral cortico-striato-thalamo-cortical system, and this is in turn regulated by the dopaminergic nuclei within the midbrain, particularly the ventral tegmental area (VTA). Two descending pathways regulate the activity of the VTA: a ventral and a dorsal route. The ventral route is mainly involved in maintaining craving during regular drug usage. The dorsal route is involved in initiating craving and reactivating it after a period of abstinence. In lampreys, the habenula-projecting globus pallidus (GPh) has an essential role in regulating the activity of the lateral habenula. It might be interesting to describe and study the human equivalent of this GPh in order to find new treatment to prevent relapse in drug addiction.

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Thank you for your attention

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