university of groningen

May 2016 | 1

CINP Course on Bipolar Disorder
It is all about the switch

› Prof. dr. Anton J.M. Loonen

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Pharmacotherapy and Pharmaceutical Care

Ladies and gentlemen,
This lecture was presented during the fourth CINP educational course, this time on the neurobiology of bipolar disorder, in Tomsk and Novosibirsk in May 2016.

university of groningen

May 2016 | 2

Agenda

- A new model for the regulation of pleasure and happiness
- Mechanism of unipolar depression
- Bipolar disorder is an activity switch disorder
- Biological mechanism behind bipolar disorder
- Conclusion:

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

In my lecture I will first describe a new model for the regulation of reward-seeking and misery-fleeing behaviour. Motivation to show these behaviours are associated with obtaining feelings of pleasure (hedonia) or happiness (euphoria). As these behaviours must be very ancient, the neurobiological mechanisms regulating them can be elucidated by describing the evolutionary development of the forebrain of vertebrates. I will show you that a small, but well conserved component of the forebrain, the habenula within the epithalamus, plays an essential role regulating these two types of behaviours.
Taking these mechanisms as a starting point, I will firstly describe the neurobiological background of unipolar depression, and thereafter explain that in bipolar disorder the mechanism regulating the misery-fleeing behaviour has variable effects on the magnitude of reward-seeking behaviour. This becomes evident best when we consider bipolar disorder as an activity switch disorder. This leads to the conclusion:

university of groningen

May 2016 | 3

Conclusion

› Similar mechanism causing depressive states in unipolar depression

combined with

› Unstable coupling to mechanism regulating reward-seeking behaviour

› Results in: euphoric (hypo)mania, dysphoric (hypo)mania, mixed manic/depressive states, bipolar depression or agitated depression

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

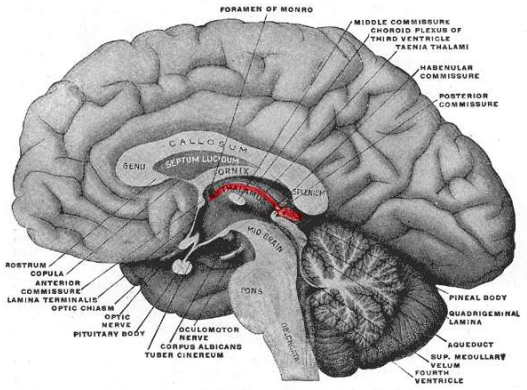
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

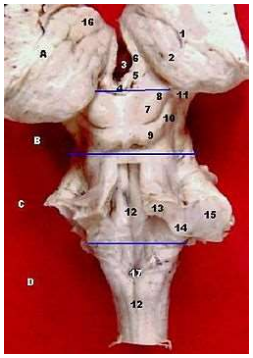
The same neurobiological mechanism which cause the continuous stimulation of misery-fleeing behaviour leading to unipolar depression are also operative in causing affective episodes in bipolar disorder. However, the reciprocal coupling between the activities of misery-fleeing and reward-seeking behaviours which causing the symptoms of unipolar depression is damaged in bipolar disorder. Variation of these two types of behaviour independent from one another may result in euphoric mania, dysphoric mania, mixed manic/depressive states, bipolar depression or agitated depression.

university of groningen

May 2016 | 4

Epithalamus: stria medullaris, habenula, epiphysis





GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

In this lecture I will describe that the habenula plays an essential role in regulating these two types of behaviours. Perhaps you have never heard of the habenula before, and therefore this brief introduction. The habenular nuclei are paired structures and belong to the epithalamus, which also harbours the pineal gland and the stria medullaris. On the left figure you see the position of the habenula and stria medullaris in red colour. The habenula is positioned near the midline in the caudal part of the epithalamus close to the midbrain. On the right figure the cerebellar and large parts of the cerebral hemispheres are removed, so you have a clear view on the thalamus, epithalamus, the roof of the midbrain and the fourth ventricle. The pineal gland has also been removed, but its stalk is still in place (number 4). Left and right to this stalk you see the habenula (number 5) and from rostral from it the stria medullaris (number 6). Functionally, the habenula is divided into lateral and medial parts. These complex nuclei are very small and until recently could not be measured in fMRI studies.

[Human: 1. Taenia choroidea (and lateral: Lamina affixa, Stria terminalis), 2. Thalamus, Pulvinar thalami, 3. Third ventricle, 4. Stalk of pineal gland, 5. Habenula, 6. Stria medullaris, 7. Superior colliculus, 8. Brachium of superior colliculus, 9. Inferior colliculus, 10. Brachium of inferior colliculus, 11. Medial geniculate nucleus, 12. Sulcus medianus, 13. Superior cerebellar peduncles, 14. Inferior cerebellar peduncle, 15. Middle cerebellar peduncles, 16. Tuberculum anterius thalami, 17. Obex, Area postrema.]

university of groningen

Circuits regulating pleasure and happiness

› 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 (distress driven)

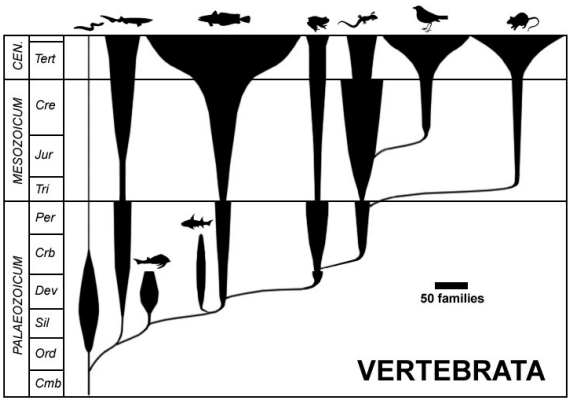
› Very ancient mechanisms regulating behaviour

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 to escape from threat and other sources of distress. These behaviours are so important that even the earliest free-living animals existing in the oceans must have been capable of displaying this behaviour in order to stay alive and have offspring.

university of groningen

May 2016 | 6

Evolution of the reward system (general overview)



GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

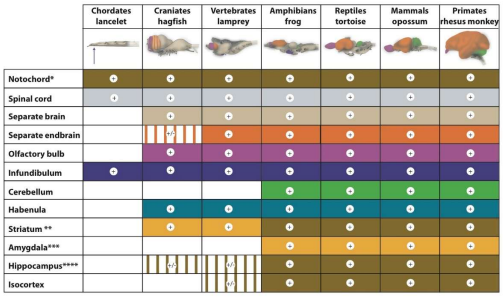
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

We can learn how the brain of these very early human ancestors looked like, because modern representatives exist of each stage of the evolution of vertebrates which maintained their earlier stage of development until now. This is shown in this figure. Hence, the brains of lampreys, sharks, lungfishes, frogs, turtles, opossums, rats, and monkeys can be believed to correspond to the brains of human ancestors from about 560 million years ago until now. The forebrain of lampreys is believed to correspond to the cerebrum of the very first animals having vertebrae, although these animals still lacked a lower jaw.

[This slide (source: https://en.wikipedia.org/wiki/Vertebrate_paleontology) shows you an accepted representation of the evolution of the vertebrates, which started with the first chordates comparible with the lancelet over 560 million years ago. The first vertebrates are supposed to be an animal comparable with the modern lamprey. This animal has a head containing a brain and vertebrates but not yet 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), Class Mammalia (mammals)]

university of groningen

Evolution of the brain of vertebrates



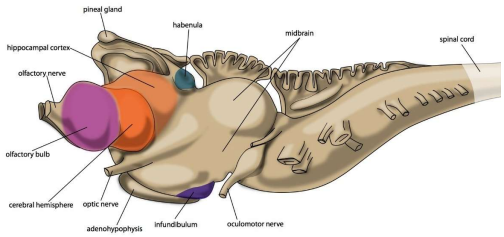
GUIDE Graduate School for Drug Exploration

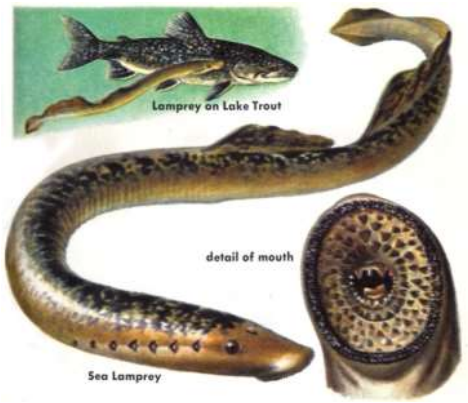
SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

This slide is showing you how the brain of these animals developed. I left out the (cartilagenous) fishes and the birds and started with the lancelet, an animal in which the brain cannot be morphologically distinguished yet 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





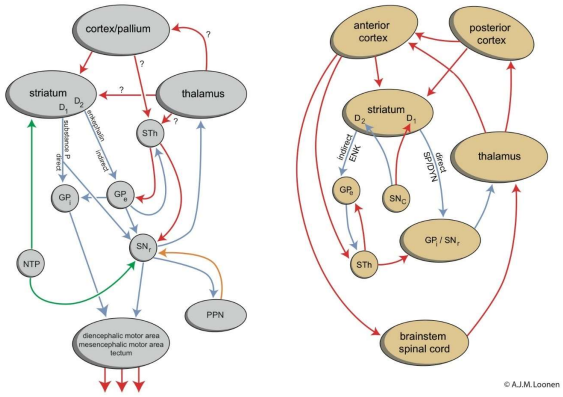
On the left you see a more detailed picture of the brain of the lamprey. This animal has a separate forebrain (orange), but this is relatively small in comparison to the olfactory bulb (purple) and anatomical thalamus (diencephalon). Note the prominent position of habenula (blue).

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 primates.

university of groningen

May 2016 | 9

Extrapyramidal systems of lampreys and humans



GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

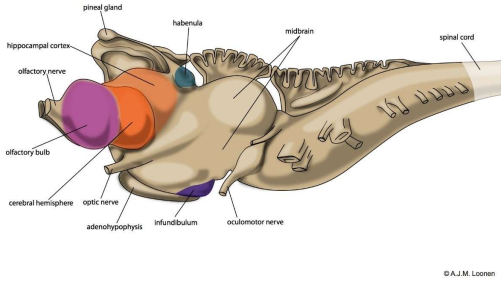
However, they also found important differences. In lampreys, the dorsal pallium (which is the forerunner of the majority of the mammalian cerebral cortex) has hardly been developed yet. Movement of the animal is not regulated by this dorsal pallium but by the extrapyramidal system, which directly influences motoric command centres in the midbrain. The majority of the input of the lamprey's striatum comes from secondary olfactory projection areas. So, motor behaviour is largely driven by olfactory sensory information.

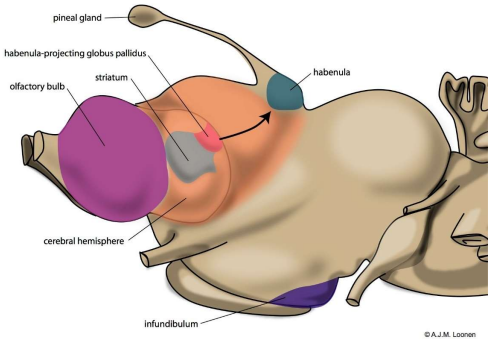
[GPe, globus pallidus externa; GPi, globus pallidus interna; NTP, nucleus tuberculi posterior; PPN, pedunculopontine nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STh, subthalamic nucleus]

university of groningen

May 2016 | 10

Position of the lamprey's habenula-projecting globus pallidus





GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

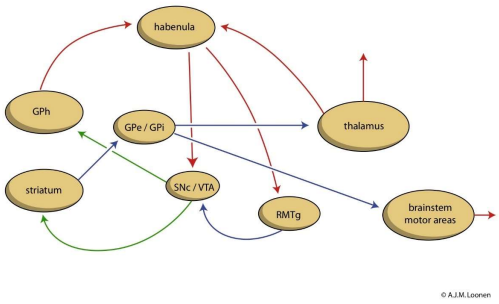
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

The forebrain of lampreys also contains a nucleus which plays an important role in deciding whether reward-seeking behaviour should be continued or not. This structure is shown on the right figure and is called the habenula-projecting globus pallidus.

However, evolution proceeded and these vertebrates first developed into bony fishes and thereafter into lobe-finned fishes and tetrapods which invaded the continents. The importance of olfactory information gradually decreased and the other senses became more important. Also, output became far more complex and its regulation made an important change necessary. However, our ancestors with an amphibian or turtle-like brain did not have a neocortex which analyses input from the senses and creates behavioural output yet. The amphibian dorsal pallium went up into the corticoid part of the amygdala and the limbic cortex of mammals.

university of groningen

Function of lamprey's GPh (reward-driven behaviour)



- Rhinocortex → striatum
- Striatum → motor centres
- GPh → habenula → SNc/VTA
- VTA → striatum

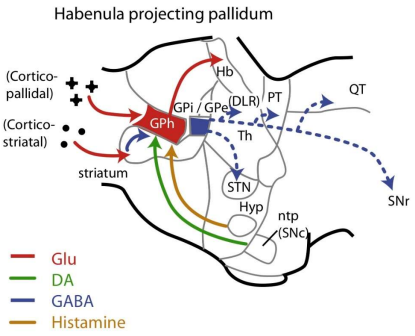
- Succesful → continue
- Unsuccessful → discontinue

The relevant connectivity is shown on this figure. The lamprey's striatum receives input from the rhinocortex and gives output to the globus pallidus (GPe/GPi). The globus pallidus gives output to thalamic and midbrain motor centres, which regulate locomotion. The habenula-projecting globus pallidus (GPh) receives input from the rhinocortex and the striatum and gives output to the habenula as its name indicates. In turn the habenula gives output to dopaminergic nuclei corresponding with the later ventral tegmental area and the substantia nigra pars compacta (SNc/VTA). The majority of the output of the habenula goes to the inhibitory rostromedial tegmental nucleus (RMTg), which inhibits these dopaminergic midbrain nuclei. Dopaminergic fibres from these last nuclei project to striatum and regulate the motor output of the animal. When ongoing behaviour does not result in achieving its goal, the activity is suspended.

university of groningen

May 2016 | 12

Connectivity of the GPh in Lamprey



- Input to GPh
  - Lateral pallium (cortex) (Glu)
  - Striatum (amygdala) (GABA)
  - Hypothalamus (histamine)
  - NTP (VTA/SNc) (dopamine)
- Output of GPh
  - Lateral habenula (glutamate)

GUIDE Graduate School for Drug Exploration | SHARE Graduate School for Health Research | Social Pharmacy, Pharmaco-epidemiology, Pharmacotherapy

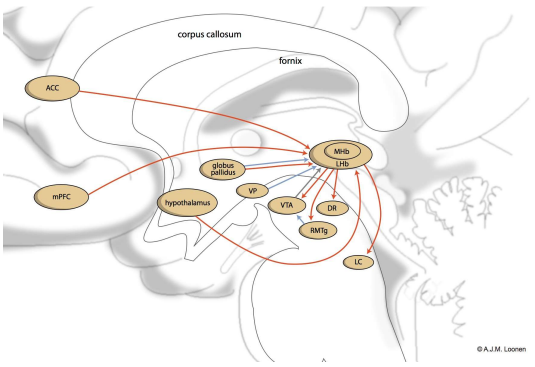
The complex influence of the habenula-projecting globus pallidus on several structures is more adequately shown in this figure, which is taken from Marcus Stephenson-Jones et al. (2013; doi: 10.1073/pnas.1314815110). In this figure the neurochemical identity of this connectivity is shown. The majority is glutamatergic (red, excitatory) and GABAergic (blue, inhibitory). In addition, histaminergic (orange) and dopaminergic (green) projections exist. The nucleus tuberculi posterior (NTP) is equivalent to the dopaminergic substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) of humans.

[It is worth noting that terminals in the lateral habenula have also been observed in mice that express both GABA and glutamate together and that stem from their pallidum and from the VTA (Root el al., 2018; doi: 10.1016/j.celrep.2018.05.063).]

university of groningen

May 2016 | 13

Connectivity of lateral habenula in humans



- Input to lateral habenula
  - Prefrontal cortex (Glutamate)
  - Hypothalamus (Glutamate)
  - Globus pallidus (Glutamate & GABA)
  - Medial habenula (unknown transmitter)
  - Ventral Tegmental Area (Dopamine)
- Output from lateral habenula
  - Ventral Tegmental Area (Glutamate)
  - RMTg (Glutamate)
  - Raphe nuclei (Glutamate)

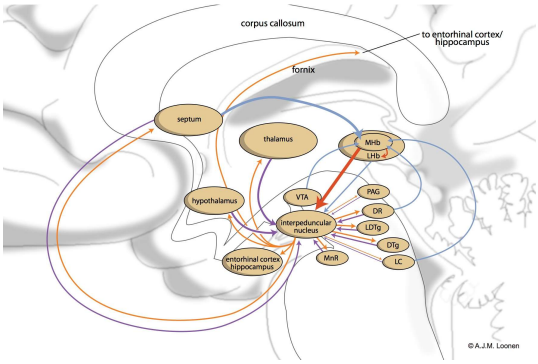
GUIDE Graduate School for Drug Exploration | SHARE Graduate School for Health Research | Social Pharmacy, Pharmaco-epidemiology, Pharmacotherapy

This figure is based on the article of Lecca et al. (2014; doi: 10.1111/ejn.12480), which deals with the connectivity of the lateral habenula in rodents. The connection of the hypothalamus (from the suprachiasmatic and the paraventricular nuclei) is more complex then shown in the figure. GABAergic input is not only originating in the globus pallidus as stated, but also coming from the diagonal band of Broca nucleus, the ventral pallidum, the ventral tegmental area, the nucleus accumbens and the substantia innominata. From the border region of the globus pallidus, the ventral pallidum and the bed nucleus of the stria terminalis, also glutamatergic neurons project to the lateral habenula. These probably correspond to the human equivalent of the habenula-projecting globus pallidus (GPh), described a few slides before. I extensively screened the literature to find out which type of neurons connect the medial habenula with the lateral habenula. However, I did not find a clear description. However, the existence of these connections has been described by Kim & Chang (2005; doi: 10.1002/cne.20410).

university of groningen

May 2016 | 14

Connectivity of the medial habenula in humans



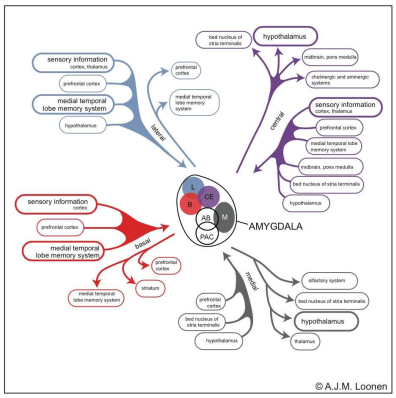
- Input to medial habenula (blue)
  - Septal nuclei (Glu/ATP, GABA, **ACh**)
  - Bed nucleus anterior commissure (**ACh**)
  - Ventral Tegmental Area (DA)
  - Upper raphe nuclei (5-HT)
  - Locus coeruleus complex (NE)
  - Superior cervical ganglion (NE)
- Output from medial habenula (red)
  - Lateral habenula (Unknown)
  - Interpeduncular nucleus (**SP**, **ACh**, Glu)

GUIDE Graduate School for Drug Exploration | SHARE Graduate School for Health Research | Social Pharmacy, Pharmaco-epidemiology, Pharmacotherapy

This figure is based on Artolin-Fontes et al. (2015; doi: 10.1016/j.neuropharm.2014.11.019), Klemm (Med Sci Monit. 2004 Nov;10(11):RA261-73) and Qin & Luo (2009; doi: 10.1016/j.neuroscience.2009.03.085). It shows the connectivity of medial habenula (MHb). The neurochemistry of this connectivity is more complex than that of the lateral habenula. Important input comes from the bed nucleus of the anterior commissure and the triangular nucleus in the posterior septum. These are cholinergic fibers which affect nicotine receptors within the medial habenula. Also the output of the medial habenula through the fasciculus retroflexus to the interpeduncular nucleus is cholinergic, next to peptidergic connections using substance P (SP) as neurotransmitter. The interpeduncular nucleus affects monoaminergic brainstem areas like the serotonergic raphe nuclei, dopaminergic ventral tegmental area and adrenergic locus coeruleus complex.

university of groningen

Connectivity of the amygdala to the habenula



- Lateral habenula
  - Bed nucleus stria terminalis (GPh)
- Medial habenula
  - Amygdalohippocampal complex via the septal nuclei

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

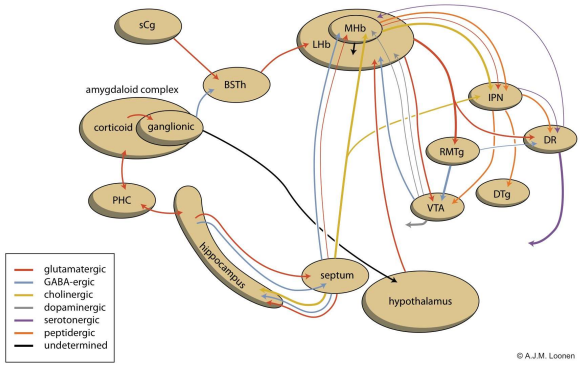
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

During evolution of vertebrates the striatum and globus pallidus of our lamprey-like ancestors went up into the extended amygdala consisting of nuclear amygdala, bed nucleus of the stria medularis and their extended amygdala connections. At least until and including our turtle-like ancestors, the neocortex had not yet developed. The entire pallium of amphibians went up into some limbic cortical areas, corticoid amygdala and hippocampal complex. This should be kept in mind when considering the connectivity of the human amygdala with the habenula. This figure shows the connectivity of the rodent amygdaloid complex according to Pitkänen (The amygdala. A functional analysis, ed. J.P. Aggleton (Oxford, UK: Oxford University Press), 31-115. ISBN 0 19 850501 9). The bed nucleus of the stria terminalis represents or contains the representative of the lamprey globus pallidus (Moreno et al., 2012; doi: 10.1002/cne.22694) and this may include the amygdaloid homologue of the habenula-projecting globus pallidus (GPh). This connects the amygdaloid complex with the lateral habenula. The amygdaloid complex is connected through hippocampus and fornix with the septal area. In turn this area is heavily connected with the medial habenula.

university of groningen

May 2016 | 16

Dorsal connection from limbic system → brainstem



GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

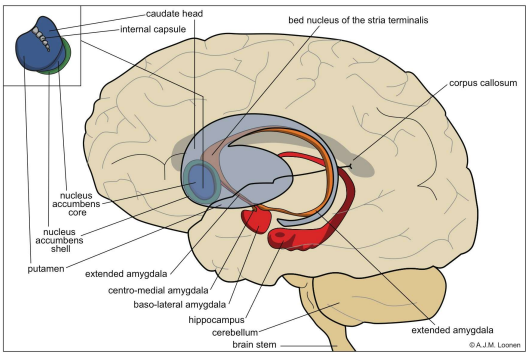
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

This figure presents a highly simplified overview of the Dorsal Diencephalic Connection System (DDCS). A word of caution should be added here. Many connections are still hypothetical. The existence of polysynaptic connections between the subgenual gyrus cinguli (sCg) and the lateral habenula (LHb) via the bed nucleus of the stria terminalis (BST) has yet to be demonstrated. The same applies to connections of the parahippocampal cortex (PHC) with the medial habenula (MHb) via the hippocampus/fornix and septal region. The amygdala/hippocampal complex is also connected to the lateral habenula via the lateral hypothalamus. These connections between the amygdaloid and habenuloid complexes are of great importance to us. In the amygdaloid complex, the relevance of sensory information for survival is determined and the primary processes of feeding, defending and reproducing are initiated on that basis. The DDCS is the phylogenetically equally ancient system for regulating the readiness for and intensity of initiated behaviours, and for increasing their efficiency by influencing the activity of monoaminergic centres in the upper brainstem. These two can therefore be considered as the original two structures in the forebrain that regulate the said primary behaviour. It is not unlikely that they still have this role in humans.

university of groningen

May 2016 | 17

Circuits regulating pleasure or happiness



- Motor basal ganglia
  - Caudate nucleus
  - Putamen
  - Nucleus accumbens - core
- Limbic basal ganglia
  - Nucleus accumbens – shell
  - Bed nucleus stria terminalis
  - Extended amygdala connections
  - Centromedial amygdala

GUIDE Graduate School for Drug Exploration

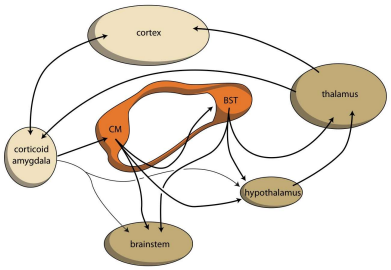
SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

The circuits that generate pleasure and happiness are referred to in the present presentation as extrapyramidal re-entry circuits. The cortico-striato-thalamo-cortical circuits can be broadly divided into the motor extrapyramidal and the limbic extrapyramidal circuits. The striatum of the former is formed by the caudate nucleus, putamen and core part of the nucleus accumbens. The limbic division consists of the shell part of the accumbens nucleus, the bed nucleus of the stria terminalis (BST) and the centromedial amygdala. Mentioning the BST as a striatal structure may not be entirely accurate. The BST and possibly the septal region may in part correspond to the globus pallidus of older ancestors.

university of groningen

Amygdaloid cortico-striato-pallido-thalamo-cortical circuit



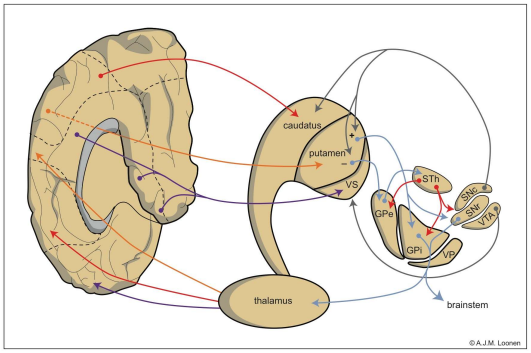
- Corticoid amygdala
  - Superficial nuclei
  - Deep nuclei
- Extended amygdala
  - Centromedial amygdala (striatum)
  - Bed nucleus stria terminalis (pallidum)
- CM → BST → thalamus → corticoid amygdala (original connectivity)
- Hypothalamus → thalamus → neocortex → corticoid amygdala (later during evolution)

In neuroscience, until the beginning of this century, the insight that the nuclear amygdala is as much a component of the extrapyramidal system as the caudate nucleus was systematically ignored. We now know that it is the oldest part of the extrapyramidal system that already regulated locomotion in the first vertebrates. This slide outlines what remains of this original cortico-striato-thalamo-cortical (CSTC) circuit in humans. The neocortex is of much later date than the corticoid amygdala. The connections through these new cortex parts was added to the original connections later during evolution. The original output is found in the connections of the corticoid amygdala, the centromedial nucleus, and the bed nucleus of the stria terminalis with the hypothalamus and brainstem. The original pathway was from corticoid amygdala to centromedial amygdala to BST to the motor centers in the hypothalamus and brainstem. The connections of the hypothalamus with the thalamus and so with the neocortex and then the corticoid amygdala date from a much later stage of evolution.

university of groningen

May 2016 | 19

The dorsal and ventral extrapyramidal system



- Circuit including caudate nucleus
  - Regulating reasoning/deciding
- Circuit including putamen
  - Regulating moving/motor behaviour
- Circuit including accumbens
  - Regulating motivation
    - Reward-seeking behaviour (core)
    - Missery-fleeing behaviour (shell)

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

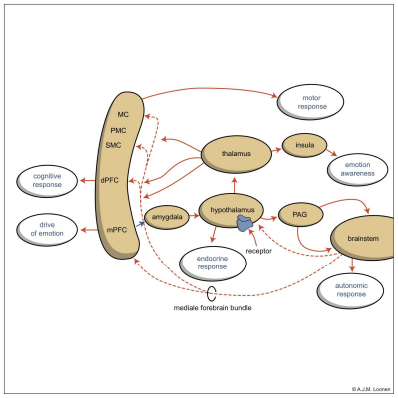
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

The extrapyramidal system regulates the magnitude and intensity of output. We can distinguish three divisions: the dorsal, the ventral, and the amygdaloid extrapyramidal system. The dorsal extrapyramidal system courses through the caudate nucleus and the putamen. The ventral system runs via the accumbens nucleus. The cognitive circuit via the caudate nucleus regulates the intensity of cognitive motions expressed in reasoning and decision making. The circuit via the putamen regulates the intensity of kinesis. The ventral extrapyramidal system consists of two parts. The part through the core of the nucleus regulates (heavily simplified) motivation to behaviours that lead to a reward feeling and the part through the shell to behaviours aimed at avoiding distress. When these functions are considered, we see that in mania the activity of the first three (via caudate, putamen and accumbens core) is increased and in bipolar depression is decreased. The activity of the circuit via accumbens shell is increased in both unipolar and bipolar depression.

university of groningen

May 2016 | 20

The limbic system (initiating fear and anger)



- Amygdala initiates
- Hypothalamus controls
  - Autonomic component
  - Endocrine component
  - Thalamic component
    - Perception (insula)
    - Frontal cortex
      - Motor response
      - Cognitive response
      - Drive

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

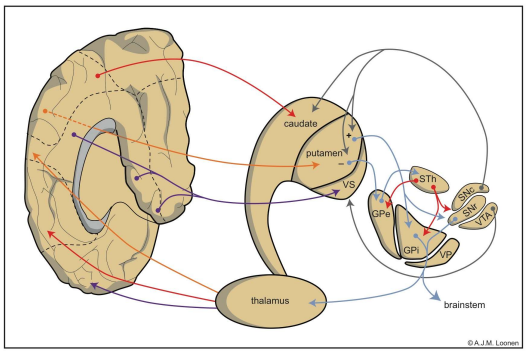
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

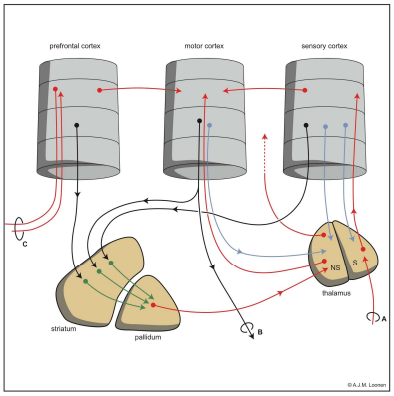
The amygdaloid extrapyramidal system existed long before cortex-like structures began to directly control locomotion. In the first vertebrates, movements were initiated by the precursor of the nuclear amygdala in response to various inputs from cortical and peripheral areas. In humans, this is also the case for the emotional response related to essential behaviours associated with feeding, defence, and reproduction in a broad sense. The amygdala initiates these behaviours by activating the hypothalamus and centres in the brainstem. The hypothalamus regulates the execution of the program which has three components (Sewards and Sewards, 2003; doi: 10.1016/s0361-9230(03)00069-8): an autonomic component (e.g. cardiovascular part of the response), an endocrine component (e.g. activation of the hypothalamus-pituitary-adrenal axis) and a component via the thalamus to the cerebral cortex. The amygdala is inhibited by the medial prefrontal cortex and thus in humans is under the control of free will.

university of groningen

May 2016 | 21

Convergence within the extrapyramidal circuits





GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

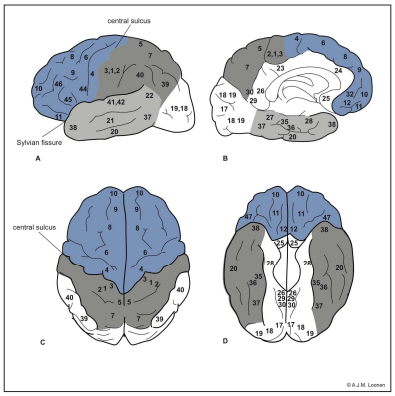
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

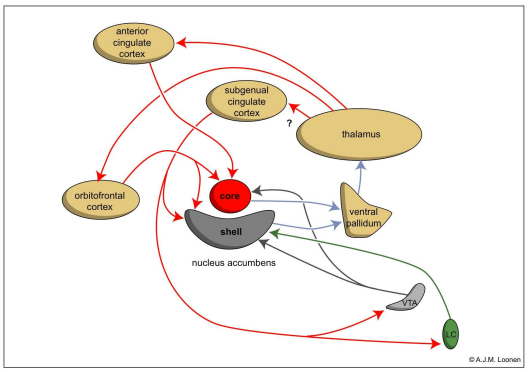
The cerebral cortex is not connected to the striatum in a random fashion. Moreover, the striatum is not uniform but consists of a continuous matrix containing isolated islands of so-called striosomes. The cortico-striato-thalamo-cortical (CSTC) circuits pass through the matrix. The striosomes receive all input from the prefrontal cortex. The input to the matrix topographically reflects the entire cerebral cortex. Within the striatal-pallidal-thalamic portion of the CSTC circuit, the circuits with origins in the posterior portion of the cerebral cortex converge with those with origins in the prefrontal portion and with those in the posterior frontal and prefrontal regions. This is shown in the right figure of this slide. This convergence exists on a microscale within the first part of the corticostriatal connections. Corticostriatal neurons from a small cortical area target a single striatal projection neuron. In the left figure of this slide, only the posterior part of the circuit is drawn. This convergent construction means that within each division of the output cortex there are also re-entry circuits, where circuits that originate in a particular part of the frontal cerebral cortex at the end of the circuit also exit into the same piece of the cerebral cortex.

university of groningen

May 2016 | 22

Relevant re-entry circuits (regulating motivation)





GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

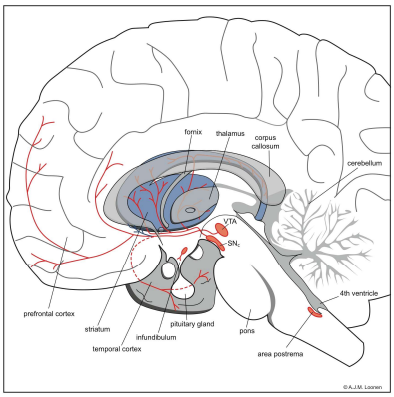
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

Two sets of re-entry circuits pass through the accumbens nucleus. The cortical start and end point is on the part of the frontal cerebral cortex that faces the midline: the mesial side (B on the left figure). These are the anterior cingulate cortex (area 24) and its subgenual part (area 25). The right figure shows that the former circuitry exits into the anterior cingulate cortex via mainly the core of the accumbens nucleus, the ventral pallidum and the thalamus. From the subgenual cingulate cortex, the re-entry circuits proceed mainly through the shell of the accumbens nucleus. In a highly simplified sketch, it can be postulated that the first circuits motivate behaviors that, when successful, result in a reward feeling (pleasure). The other circuits motivate to behavior that allows the individual to escape from misery which is accompanied by a feeling of happiness. These are the circuits that regulate pleasure and happiness.

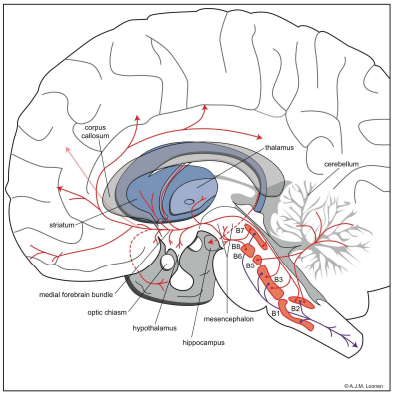
university of groningen

May 2016 | 23

Dopaminergic system



Serotonergic system



GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

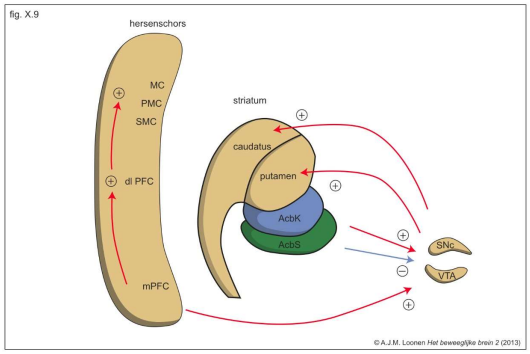
In the foregoing, we have focused primarily on how the anterior forebrain generates and regulates output, but these structures are also under the control of centers in the upper part of brainstem and cerebellum. Here we deal only with the ascending dopaminergic and serotonergic pathways. The cell bodies of the dopaminergic neurons are mainly located in the so-called substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). These are also called A9 and A10 areas. The fibers go to the frontal cerebral cortex, the hippocampus, the amygdala and the entire striatum. The cell bodies of the serotonergic neurons are located in nuclei that lie against the midline (raphes) of the brainstem. The most important is the dorsal raphe nucleus with fibers running to the same areas (even slightly more extensive in the cerebral cortex) as the dopaminergic fibers. The dopaminergic fibers stimulate the activity of the CSTC circuits, while the serotonergic ones inhibit them. The adrenergic neurons from the locus coeruleus complex, not shown on this slide, stimulate the shell part, but not the core part of the accumbens nucleus.

university of groningen

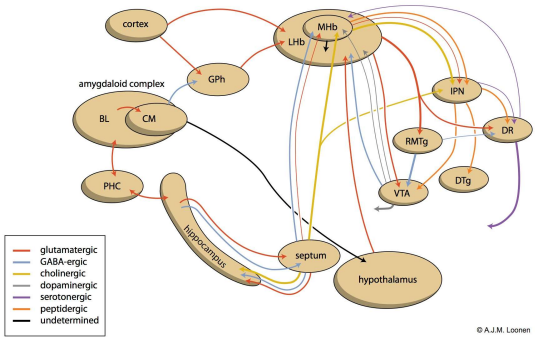
May 2016 | 24

Systems regulating dopaminergic activity

Ventral connection



Dorsal connection



GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

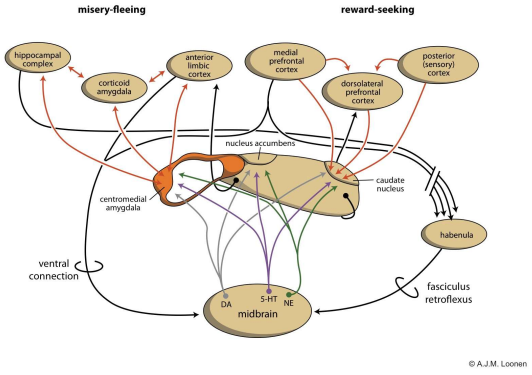
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

We can distinguish two descending systems that regulate the activity of dopaminergic input to the nucleus accumbens: the ventral and the dorsal connection systems. In both systems nicotinic receptors play an important role. In the ventral system, glutamatergic fibers from the prefrontal cortex pass through the medial forebrain bundle directly to dopaminergic neurons of the VTA. The stimulatory activity of these glutamatergic synapses is increased by axo-axonal synapses of cholinergic fibres using nicotine receptors. From the medial prefrontal cortex, glutamatergic fibers also run to striosomes of the ventral and dorsal striatum. From here, excitatory and inhibitory pathways run to the VTA and SNc. Their activity modulates not only the ventral, but also more dorsal striatal components. The dorsal diencephalic connection includes the amygdalohippocampal complex which is in turn also affected by the ventromedial prefrontal cortex. The habenula has an efferent pathway that runs to the ventral midbrain, called the fasciculus retroflexus. Together with the habenula and the pineal gland, the stria medullaris form the epithalamus. The habenula is the essential relay station of the dorsal connection system. It consists of two parts: the medial habenula and the lateral habenula. The pathway via the medial habenula is bound to increase the distress-avoiding response and the pathway via the lateral habenula inhibits the reward-seeking response. Especially the medial habenula is enriched with nicotine receptors.

university of groningen

May 2016 | 25

Overview of regulating system

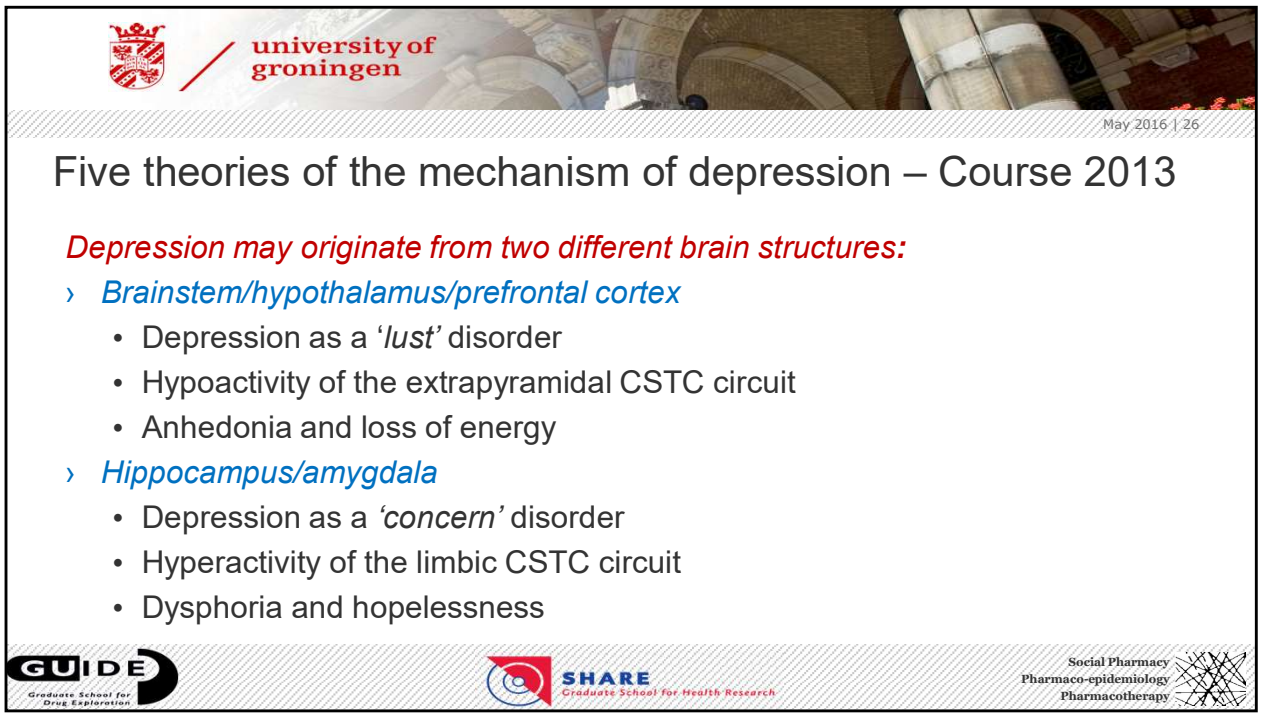


GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

This leads to the complex regulatory system depicted within this scheme. Two types of behaviours can be distinguished, which are initiated by the frontal cortex and corticoid amygdala, respectively. The first regulates skilled reward-seeking behaviour and the second instinctive misery-fleeing. These cortical structures stimulate basal ganglia, which are included in relevant CSTC circuits. The upper part of the brainstem is shown in the lower center, receiving input from the medial forebrain bundle (ventral connection) and from the fasciculus retroflexus (dorsal connection). The input from the ventral connection comes directly from parts of the prefrontal cortex and that from the dorsal connection from the habenula. The habenula in turn receives input from the hippocampus and the medial prefrontal cortex, among others. The amygdaloid, ventral and dorsal basal ganglia are shown in the middle. The striatal sections receive monoaminergic input from the upper brainstem, which regulates activity. From this it can be deduced that the oldest cerebral striatal parts have influence mainly through the dorsal connection and the somewhat younger ones through the ventral. Of course, despite its complexity, the figure is still a highly simplified representation.



After this detailed sketch of the organisation of the connections of the forebrain, I would now like to return to the 2013 presentation on the mechanism of depression (doi: 10.13140/RG.2.1.4317.0967). In it, an overview was provided of the content of five theories of the mechanism of depression. It was concluded that two structures in the brain can be distinguished that mediate two components of depression. The first is a system of the brainstem, the hypothalamus and the prefrontal cortex. These structures are involved in causing depression as a 'Lust' disorder, characterised by anhedonia and loss of energy. The other structure involved is the amygdala and the hippocampal complex. These cause the depression as a 'Worry' disorder, characterised by dysphoria and feelings of hopelessness. Of course, these two components should not be seen independently of each other. The first component may be associated mainly with reward-seeking behaviour and the second with misery-fleeing behaviour. This slide also shows that the extrapyramidal and the limbic cortico-striatal-thalamic-cortical (CSTC) circuits, respectively, regulate the activity of these two components. These circuits are activated by ascending monoaminergic neurons from the upper part of the brainstem. What we had not yet worked out in 2013 is that these components are regulated by the dorsal diencephalic connection system via the lateral and medial habenula, respectively.

university of groningen

May 2016 | 27

Dysregulation in major depressive disorder

Continuous stressful circumstances → persistent and excess activation of misery-fleeing behaviour

- Continuous challenging leads to increased sensitivity (kindling)
- Neurotrophins lead to increased sensitivity of amygdala
- Pro-inflammatory cytokines lead to decreased activity hippocampus
- Glucocorticoid steroids lead to decreased activity hippocampus

and

- Chronic antidepressant treatments increase expression protective BDNF

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

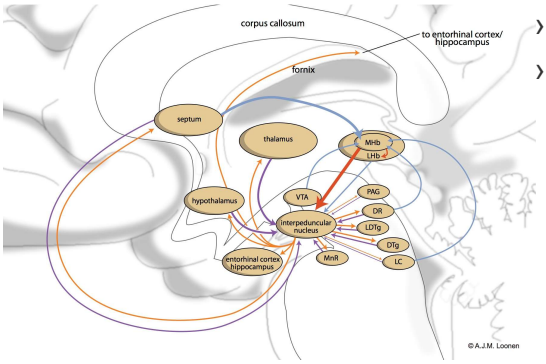
Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

Although a small proportion of depressive disorders may be entirely spontaneous, a significant part of depression according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) is related to living under stressful conditions that require the individual to be on guard and constantly worrying. According to the kindling hypothesis of depression, this results in an increased sensitivity of the system that initiates these behaviours and executes the components. This can be in various places in the system, with the amygdaloid and hippocampal complex, the ventral striatum, and the dorsal and ventral connection system as prime candidates. The effects of neurotrophic substances in the amygdaloid and hippocampal complex in people with depression and the influence of antidepressant treatment on the expression of brain-derived neurotrophic factor (BDNF) are in line with this.

university of groningen

May 2016 | 28

Dysregulation in major depressive disorder



- Disinhibition of septal nuclei (AChN)
- Activation of MHb (AChN/peptides)
  - Activation interpeduncular nucleus (GABA/peptides)
    - Periaqueductal gray substance (peptides)
    - Median and dorsal raphe nuclei (5-HT)
    - Locus coeruleus (NE)
    - Laterodorsal tegmental region (GABA/peptides)
  - Activation of lateral habenula (LHb)
    - Activation of RMTg (GABA) → inhibition VTA

GUIDE Graduate School for Drug Exploration | SHARE Graduate School for Health Research | Social Pharmacy, Pharmaco-epidemiology, Pharmacotherapy

On this slide, I take you one step further to a possible causative agent of major depressive disorder, namely the medial habenula (MHb). Via the septal nuclei, the MHb receives input from the primary forebrain and the mesial forebrain cortex. The output goes to the interpeduncular nucleus and from there to a variety of structures that play an essential role in the development or mediation of depression, such as the periaqueductal grey (PAG), the medial and dorsal raphe nuclei (MnR and DR), the locus coeruleus (LC), the laterodorsal tegmental nucleus (DLTg), the hypothalamus and the entorhinal, parahippocampal and hippocampal cortices. The medial habenula also has a link with the lateral habenula. Through the GABAergic rostromedial tegmental nucleus (RMTg) the lateral habenula inhibits the activity of the ventral tegmental area.

university of groningen

Dysregulation in major depressive disorder

- High activity missery-fleeing
  - Worrying/anxiety (mood)
  - Sadness or emptyness (mood)
  - Worthlessness or guilt (thought)
  - Hopelessness (thought)
  - Death becomes you (thought)
- Low activity reward-seeking
  - Anhedonia
  - Weight loss
  - Late night insomnia
  - Lack of energy/fatigue
  - Undecisiviness

This slide outlines the symptoms of depression associated with the two components that are mediated through the medial and lateral habenula. Of course, even this is not as absolute as it is shown here. For example, there is a strong case to be made that thoughts of death are also associated with a loss of energy and a loss of interest in life. There is also some disagreement with the suggestion that anxiety is primarily part of the depression and not an independent component.

university of groningen

May 2016 | 30

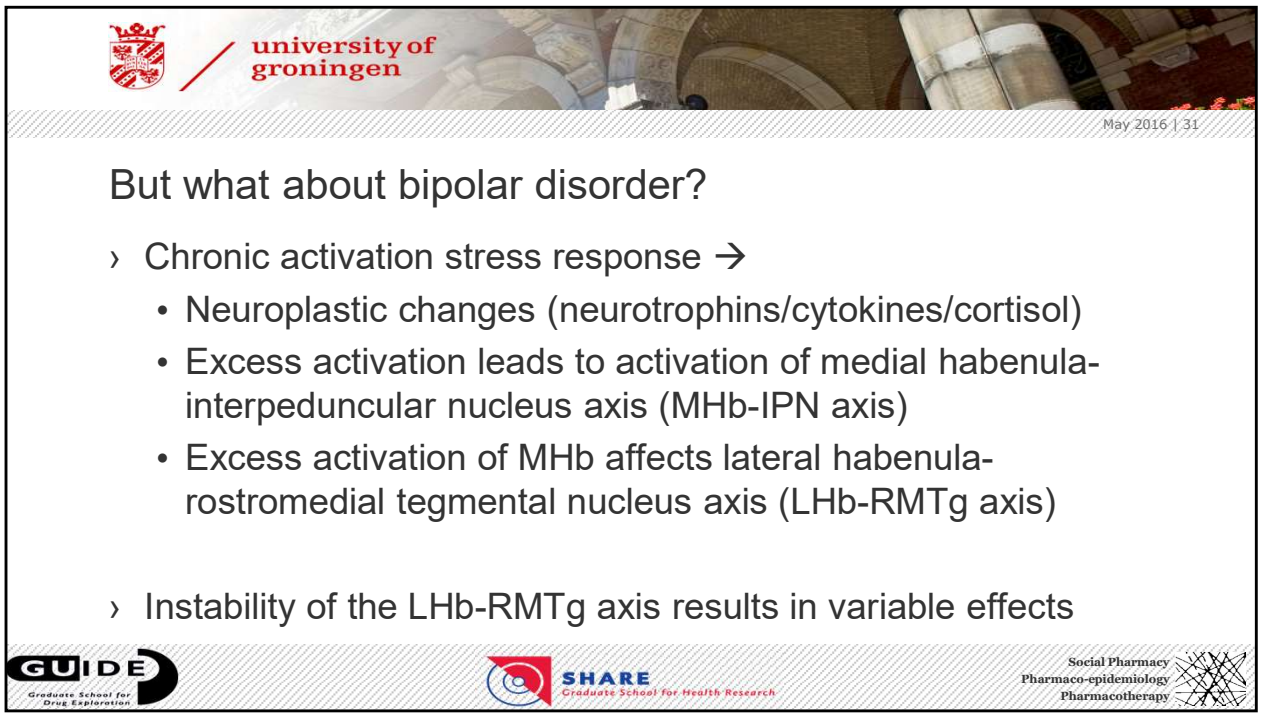
Putative mechanism in depressive disorder

› Continuous stressful circumstances → chronic activation stress response

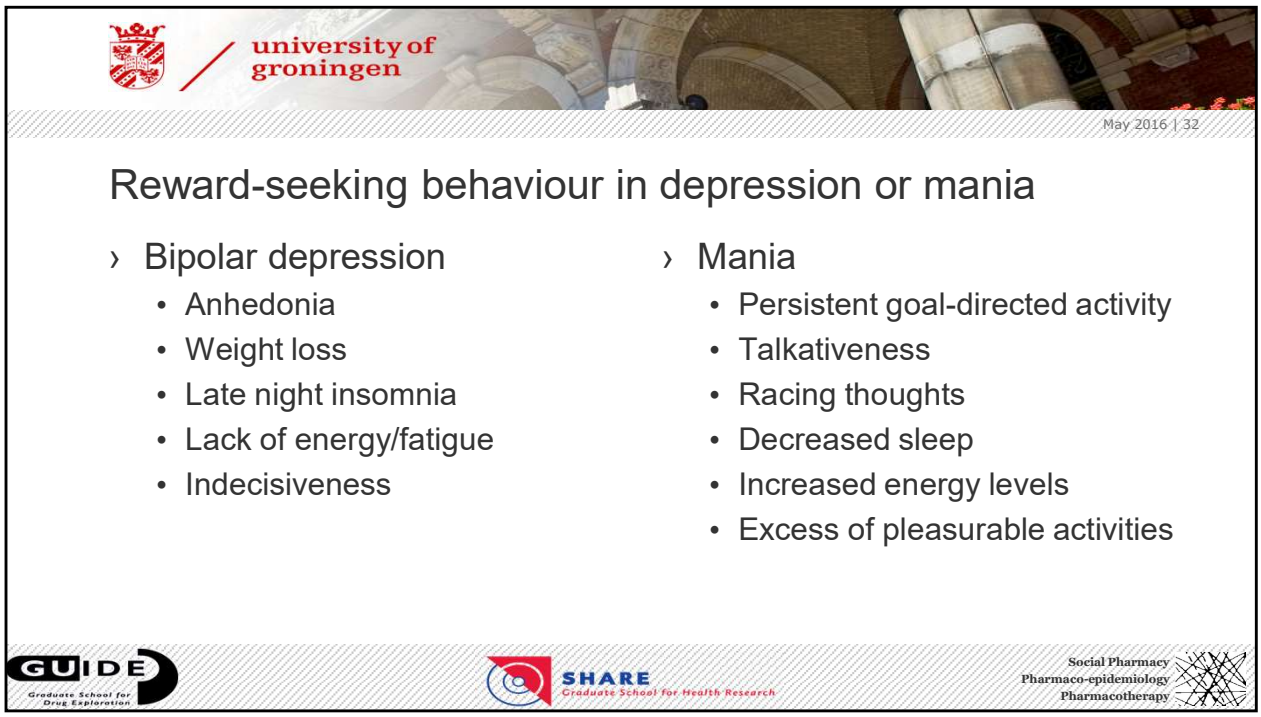
› Chronic activation stress response → neuroplastic changes (neurotrophins/cytokines/cortisol)
- Excess activation leads to activation of medial habenula-interpeduncular nucleus axis (MHb-IPN axis)
- Disinhibition of hippocampal influence leads to activation of MHb-IPN axis
- IPN activation leads to disproportional misery-fleeing behaviour
- Excess activation of MHb leads to activation of lateral habenula-rostromedial tegmental nucleus axis (LHb-RMTg axis)
- Excess activation of LHb-RMTg axis leads to decreased reward-seeking behaviour

GUIDE Graduate School for Drug Exploration | SHARE Graduate School for Health Research | Social Pharmacy, Pharmaco-epidemiology, Pharmacotherapy

This leads us to the following hypothesis about the origins of depression. The basis is a continuous activation of behaviour in response to distress and feelings of insecurity. This leads to chronic activation of the emotional stress response, which results in altered sensitivity of the system through neuroplastic changes. This leads primarily to excessive activation of the connection between the medial habenula and interpeduncular nucleus, which gives rise to the symptoms of depression as a worry disorder. The medial habenula also regulates the activity of the lateral habenula and this causes symptoms of depression as a pleasure disorder.



But how are things different in the bipolar disorder? It should be noted that bipolar depression, especially after the disorder has fully developed, more often has an autonomous course than 'unipolar' depression: the major depressive disorder of the DSM. Episodes of mania (Bipolar I disorder; BDI) or hypomania (BDII) also occur. It is striking that, especially in the initial phase, there is quite a lot of similarity. Most people with a bipolar disorder first experience one or more depressions. Often, in the beginning, sustained stressful life circumstances provide the trigger, and the depression only takes on an autonomous course later on (this is the core of the Kindling hypothesis). The neuroplastic changes that occur in the development of major depressive disorder and bipolar disorder show similarities and inconsistencies that suggest a common basis (Loonen et al., 2017; doi: 10.3389/fncir.2017.00035). For example, BDNF levels are reduced in both acute MDD and BD, and not different from healthy controls after reaching euthymia (Polyakova et al., 2015; doi: 10.1016/j.jad.2014.11.044). We would like to suggest that the neuroplastic changes in the dorsal diencephalic connection DDC system that occur in MDD and BD are largely similar. An important difference however lies in the stability of the coupling between the activity of the medial and lateral habenula.



A comparison of the symptoms of acute bipolar depression and mania shows that both have an important but opposite component in the field of reward-oriented (pleasure motivated) behaviour. The more primary component of distress avoiding (happiness motivated) behaviour, which is not shown on this slide, does appear to be the same. This raises the suspicion that the link between the two control activities in the two phases of the bipolar disorder have a different direction. Because this switch can occur very abruptly, the habenula is a good candidate where the responsible biological changes can take place. The lateral habenula regulates this type of behaviour.

university of groningen

Biological mechanism behind bipolar disorder

- Neurotoxicity damages the habenular connectivity (oxidative/nitrosative stress, tryptophan catabolites)
  - Possible the influence of lateral habenula-projecting pallidal neurons
  - More likely the integrity of the MHb-LHb connectivity
- Vulnerability to the pharmacological effects of antidepressants
  - MHb carries many nicotine ACh receptors → bipolar depression
  - Striatum carries many muscarine ACh depression → anti-dopaminergic effects
- Bipolar disorder and kindling (neuroplasticity/neurogenesis)
  - Many inconsistent findings
  - Many similarities with unipolar depression
- Bipolar disorder and biorhythms
  - Bipolar disorder is a biorhythm disorder (sleep, seasonal aspects, similar to animal migration)
  - Close association of the habenula with the pineal gland (melatonin)
  - Close association of the habenula with the hypothalamic suprachiasmatic nucleus (SCN)

This is all based on theoretical insights, but there are some experimental results that fit in somewhat. All kinds of neurotoxic factors have been linked to the pathogenesis of bipolar disorder. It can be assumed that their effects work on a number of neurons that occupy a key position in the dorsal diencephalic connection system. Some neuronal endings in the habenula show co-expression of glutamate and GABA. Under the influence of neurotoxic influences, but also by the action of, for example, cytokines, these can theoretically change their excitatory or inhibitory character. Also interesting in this context is the role of glial cells. Various neuronal synapses are in close contact with protrusions of astrocytes and neuroglia that determine the local environment. Neuroglia can also determine the structure of neuronal circuits by pruning synaptic connections. This slide also points out the interesting relationship with cholinergic neurotransmission and circadian aspects of bipolar mood disorders. It would be going too far to go into this in detail.

university of groningen

May 2016 | 34

Conclusion

› Similar mechanism causing depressive states in unipolar depression

combined with

› Unstable coupling to mechanism regulating reward-seeking behaviour

› Results in: euphoric (hypo)mania, dysphoric (hypo)mania, mixed manic/depressive states, bipolar depression or agitated depression

GUIDE Graduate School for Drug Exploration

SHARE Graduate School for Health Research

Social Pharmacy
Pharmaco-epidemiology
Pharmacotherapy

In this presentation I have outlined the background to the hypothesis that the depressive and bipolar disorders share the same biological mechanism as a causal factor. However, there is an important difference that in bipolar disorder some reward-related symptoms may be diametrically opposite to those in unipolar and bipolar depression. This may well be related to a disconnection within the functioning of the dorsal diencephalic connection system, which may be based on the dysfunction of a specific biological coupling mechanism in the habenula. This could also explain why this mechanism can switch from one state to another with an abrupt switch.

university of groningen

Thank you for your attention

SHARE Graduate School for Health Research

Pharmacotherapy & Pharmaceutical Care