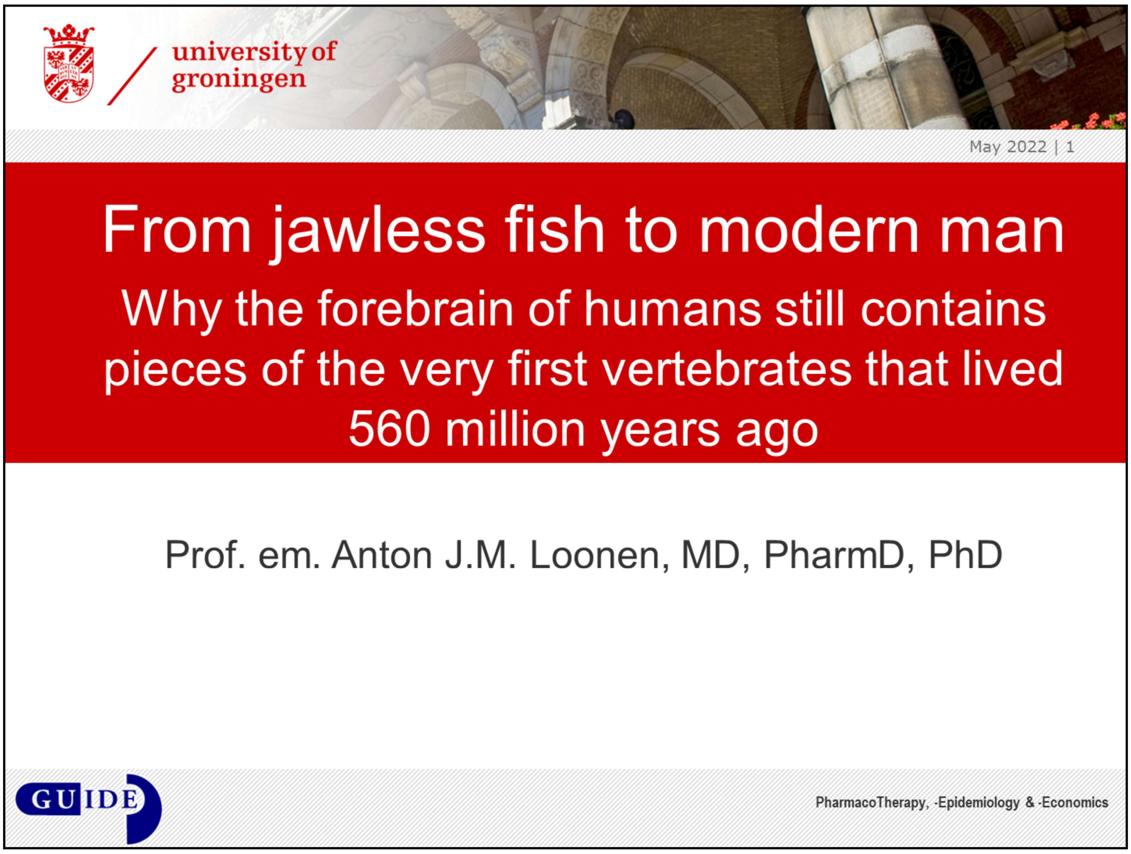


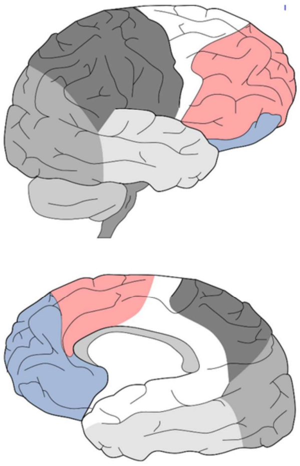
In this video I will explain why a piece of the brain of our early ancestors can still be found in the human brain. These oldest parts of the human brain are important for the development of some mental disorders, such as anxiety, depression, addiction and psychosis.

But first let me introduce myself a little. I am a retired professor from the University of Groningen and have a lot of experience in treating people with mental illnesses with medication. From 1980 to 1997 I worked as a hospital pharmacist and clinical pharmacologist and from 1997 to 2019 as a medical doctor and clinical pharmacologist in psychiatric hospitals in the Netherlands. Nowadays, these are called GGZ institutions, by the way. I have always been very interested in the mechanics of the brain and the mechanisms of the effects of psychotropic drugs.

university of groningen

May 2022 | 3

The human brain



- Side view (lateral view)
  - Hemisphere
  - Cerebellum
  - Brainstem
- Midline view (mesial view)
  - Cerebral cortex
  - Corpus callosum
  - Thalamus (not on picture)
  - Basal forebrain (not on picture)
  - Brainstem (not on picture)

GUIDE

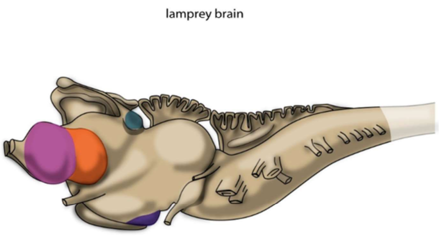
PharmacoTherapy, -Epidemiology & -Economics

We start with showing you a picture of the human brain. The top figure is a view from the side. On the right is the side of the forehead and on the left the back of the head. Most of the brain consists of two hemispheres, which are lined with cerebral cortex. These hemispheres are turned toward each other in the midline. The lower figure shows the view from the midline, after the two hemispheres have been separated there. In doing so, the corpus callosum (in grey in the middle) connecting the two hemispheres has been severed, as well as the joint part below it that is not shown on this figure.

university of groningen

May 2022 | 4

The lamprey brain

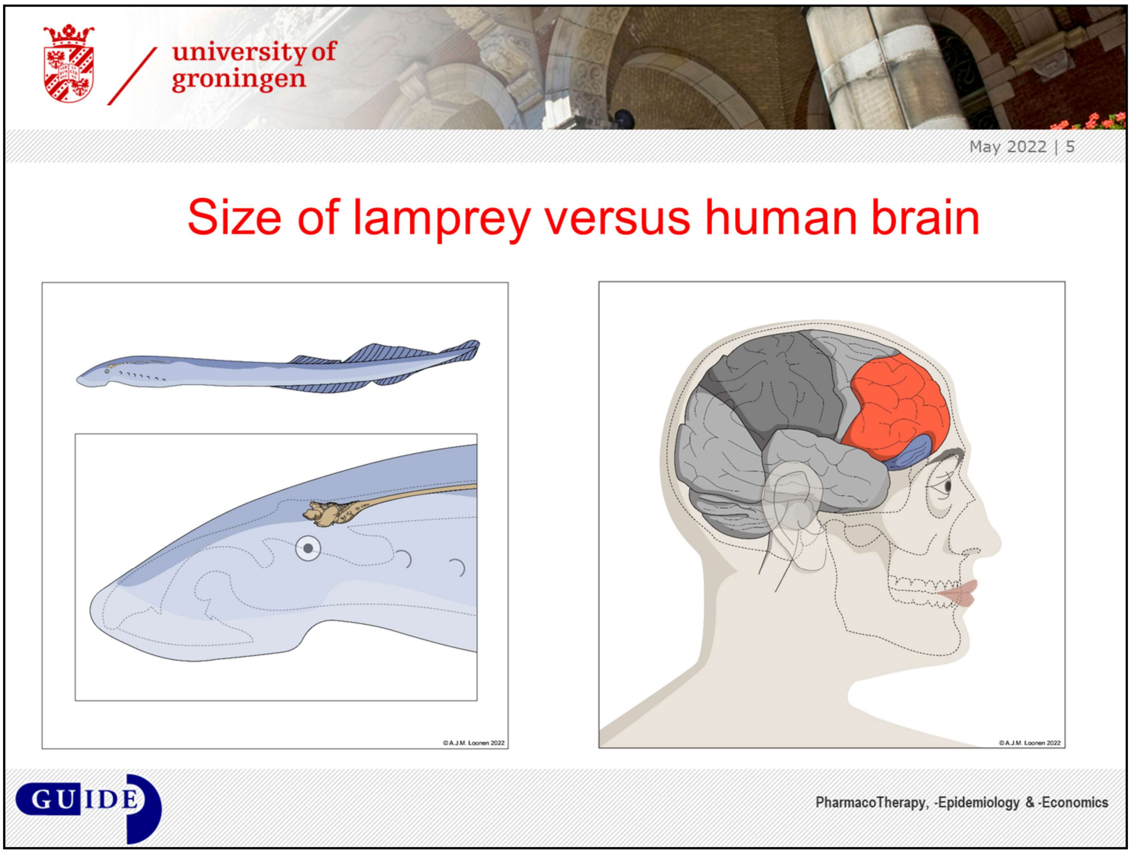


- Most primitive animal with a backbone (vertebrate)
- Corresponds with jawlish fish living 560 million years ago
- Small brain (mainly brainstem and hypothalamus)
- Pronounced olfactory bulb (purple) for processing of smell information
- Modest hemisphere (orange) dominated by the rest

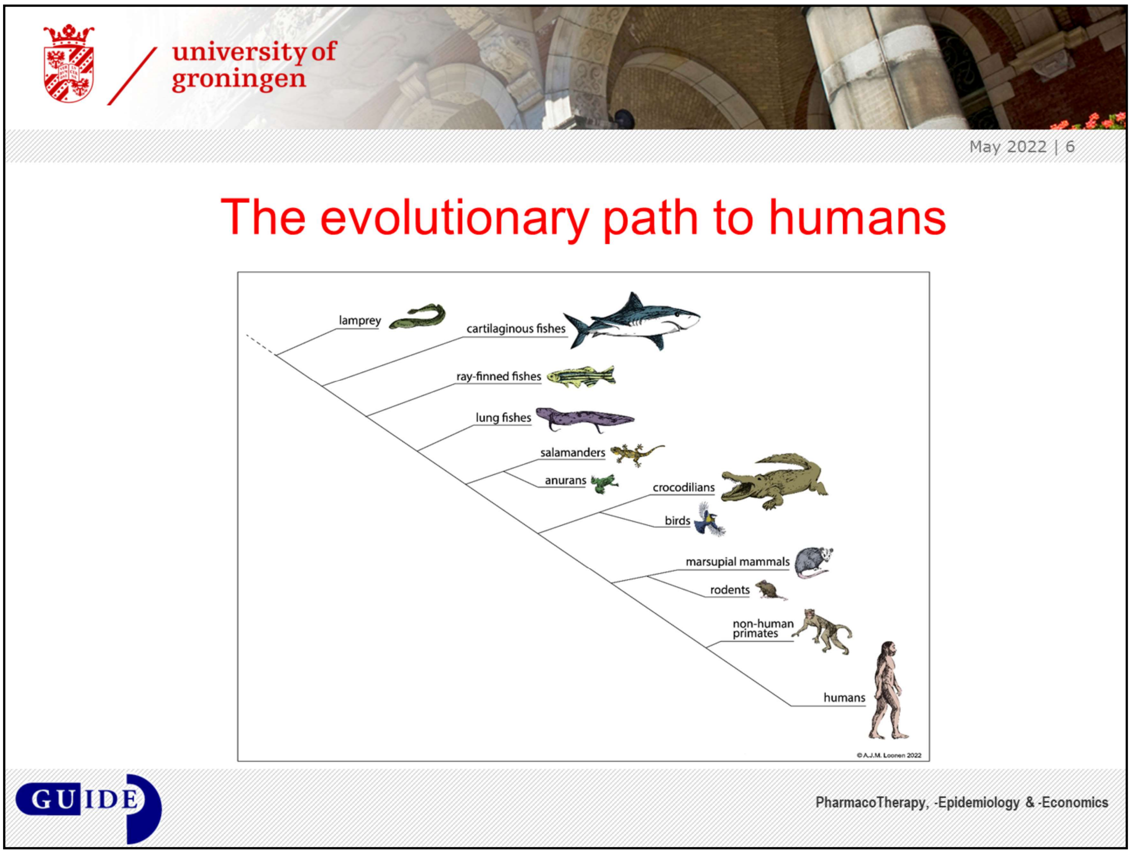
GUIDE

PharmacoTherapy, -Epidemiology & -Economics

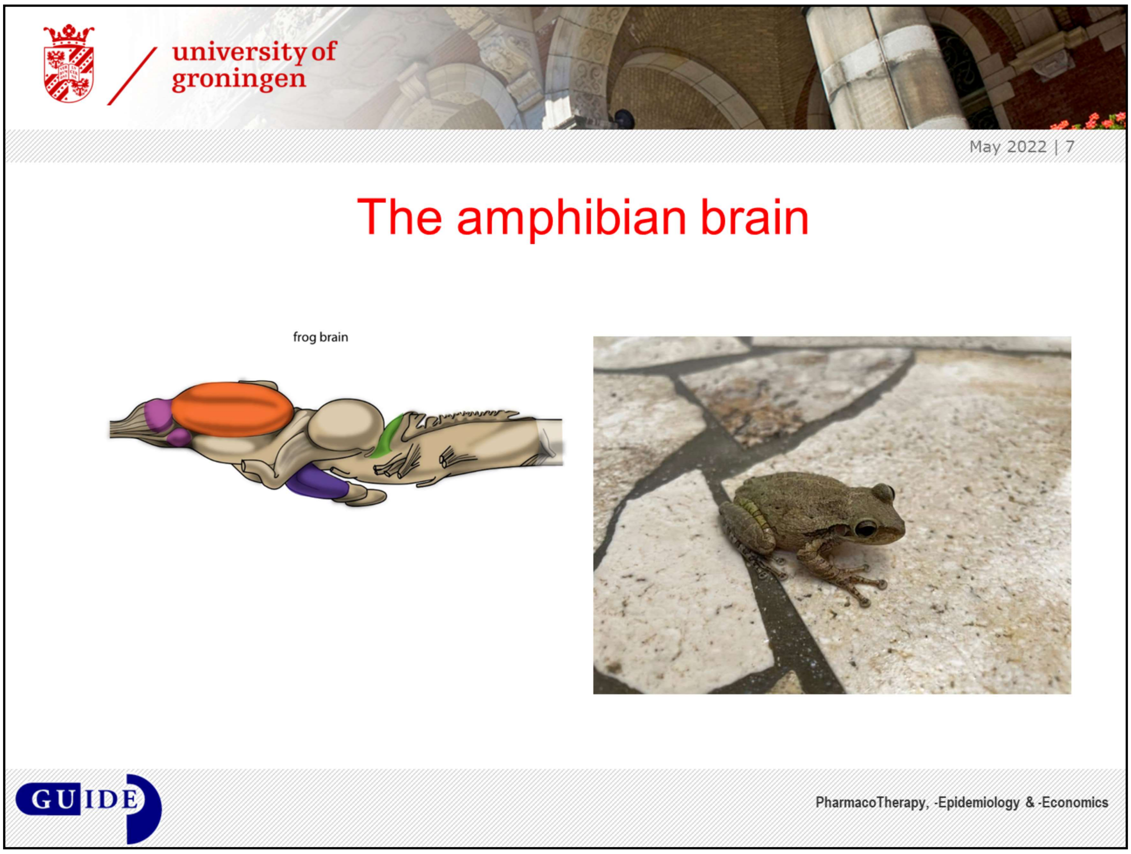
Now compare the human brain with the brain of the lamprey in this slide. The lamprey is a jawless fish that can be considered the most primitive member of the vertebrates. The brain of this lamprey corresponds to the first vertebrates that emerged during evolution about 560 million years ago. It is striking that in this lamprey brain, the purple olfactory bulb is larger than the orange hemisphere. This olfactory ganglion processes the information from the olfactory organ before it is sent to the rest of the brain. Smell is very important for these animals.



Their brain is also comparatively very small. This slide shows the head of the lamprey on the left and the human head with the brain inside on the right. You can clearly see that the brain of the lamprey takes up only a very small part of the body. Yet this small brain regulates all the functions that are essential for the preservation of life and the survival of the species. These are the behaviours that lead to the acquisition of food, to the escape from threats and to the acquisition of offspring. The human brain also regulates these essential behaviours, but it can do much more. These extras have been added to the essential behaviours over the course of evolution, so that the newly created species can perform them more efficiently and successfully.



The lamprey represents a preliminary stage in the evolution to man. This slide shows this evolution. We can follow the evolutionary development because representatives of the various stages are still alive. We will in the following only look at the lamprey as a starting point, the frog, the turtle, the opossum, the rhesus monkey (rhesus macaque) and the human, so we will go through this evolution by leaps and bounds.



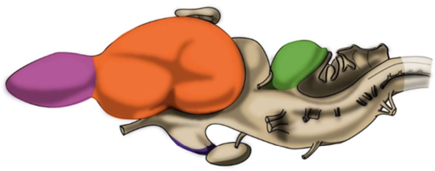
We use the frog as an example of an animal whose brain has the same appearance as in the amphibian ancestor of man evolving about 370 million years ago. In the brain of the adult frog, the orange hemisphere is much larger than the purple olfactory bulb which by the way consists of two parts here. This hemisphere is lined with cortex-like tissue, but this does not yet fulfil the same role as the cerebral cortex in humans. In humans, the posterior part of the cortex processes all sensory input and the anterior part generates all cognitive and motor output. In the frog, the hemisphere can be regarded as a single unit that regulates the animal's behaviour on the basis of all kinds of input.

university of groningen

May 2022 | 8

The last pre-mammalian brain

tortoise brain



GUIDE

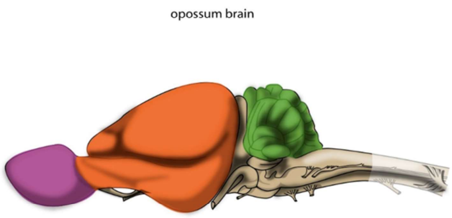
PharmacoTherapy, -Epidemiology & -Economics

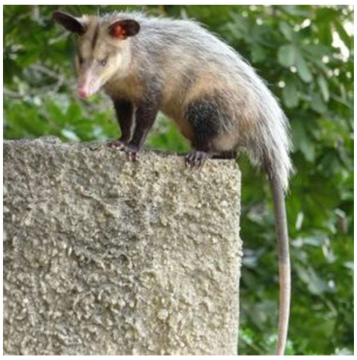
The turtle can be considered as a predecessor of both reptiles and birds on one side and of mammals on the other. In the case of mammals, a cerebral cortex similar to that of humans emerged for the first time from the cortex-like coverage of the hemisphere in more primitive animals. In reptiles and birds, the development of this so-called pallium follows a different route and is less broad than in mammals. In the tortoise in this picture, the hemisphere is slightly larger and the (green) cerebellum is also more developed. The cerebellum had also been developed in cartilaginous fish and bony fish, but we have skipped them because the hemisphere had turned outside instead of inside during their development.

university of groningen

May 2022 | 9

The earliest mammalian brain

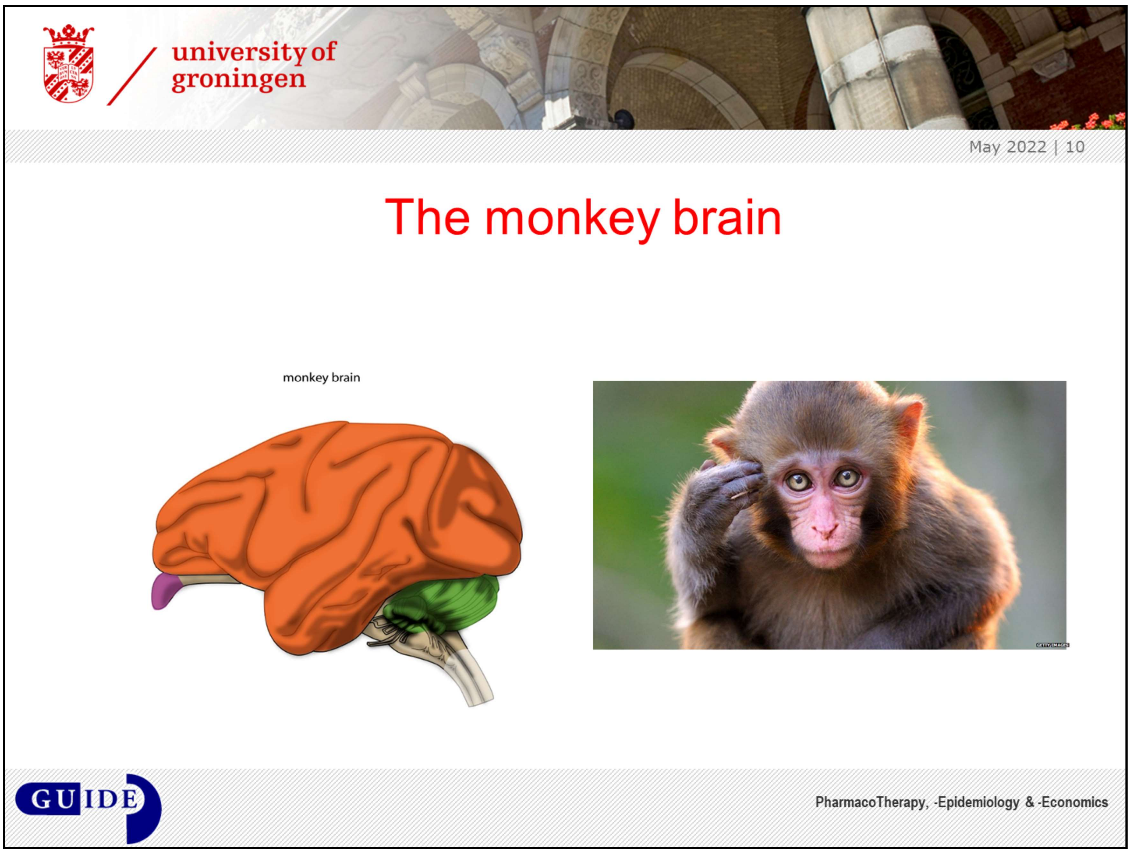




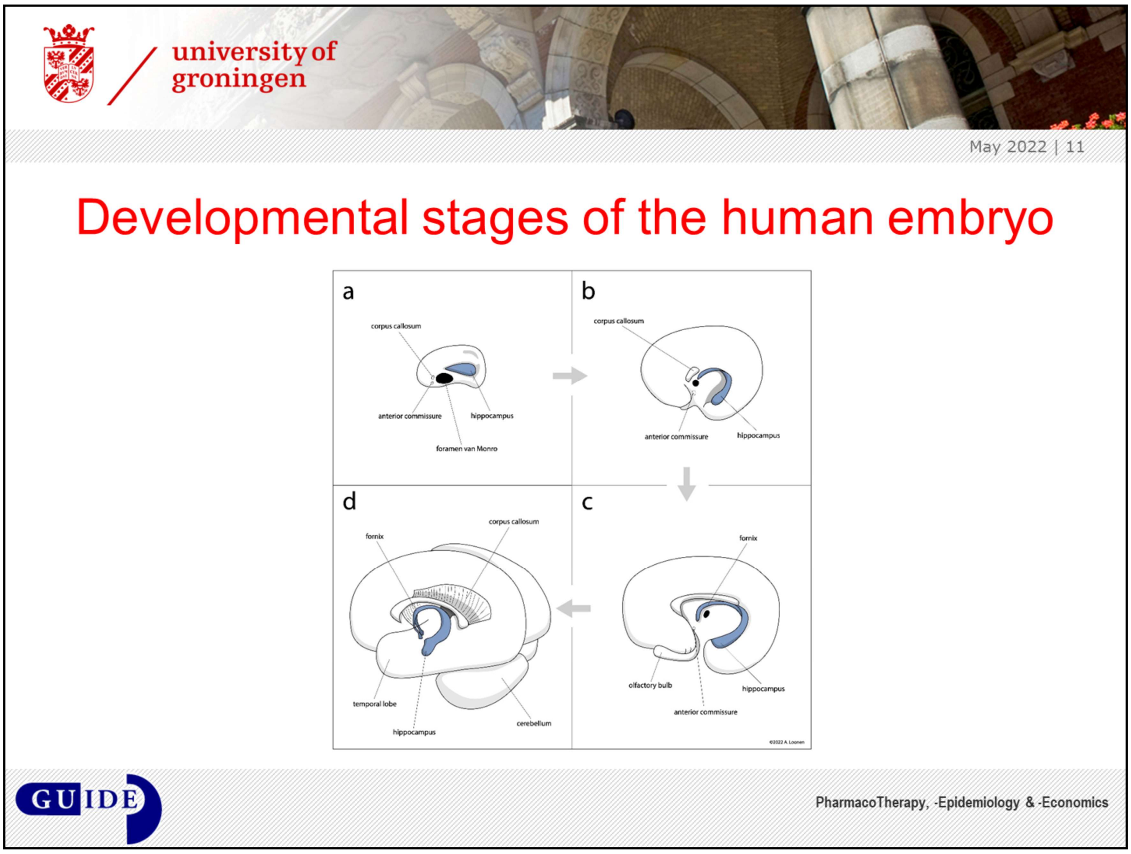
GUIDE

PharmacoTherapy, -Epidemiology & -Economics

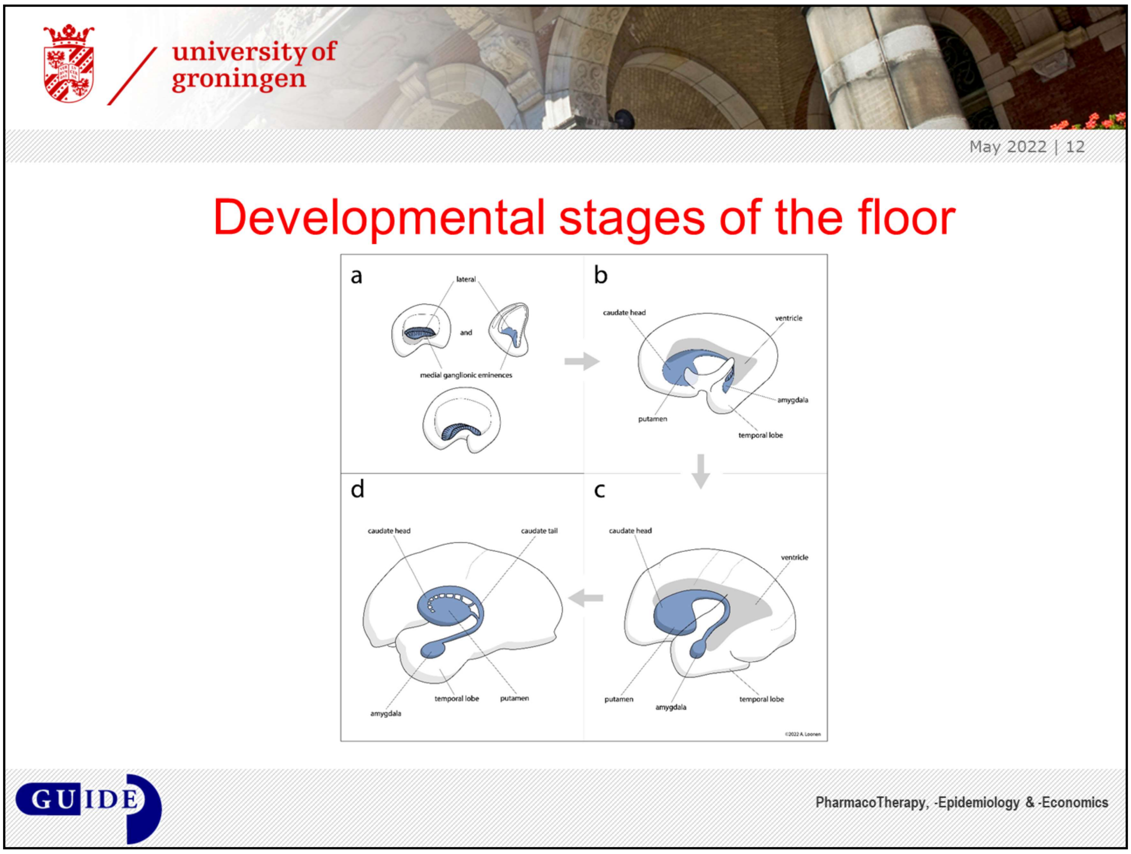
The opossum's brain could pass for a representative of early mammals. Actually, Australian egg-laying monotremes, such as the platypus or duckbill, represent the oldest mammals, which arose about 145 million years ago. In the brain of the opossum, it can already be seen that in mammals the upper (dorsal) part of the hemisphere extends backwards and sideways, which later results in a C-shaped curvature of the hemisphere. This expansion of the cerebral cortex is an important feature of the evolutionary development of mammals. The mesial (turned towards the midline) part of the frog's cerebral cortex is moved so far outwards and underneath rolled inwards on the outside that in humans it is found in the so-called hippocampus.



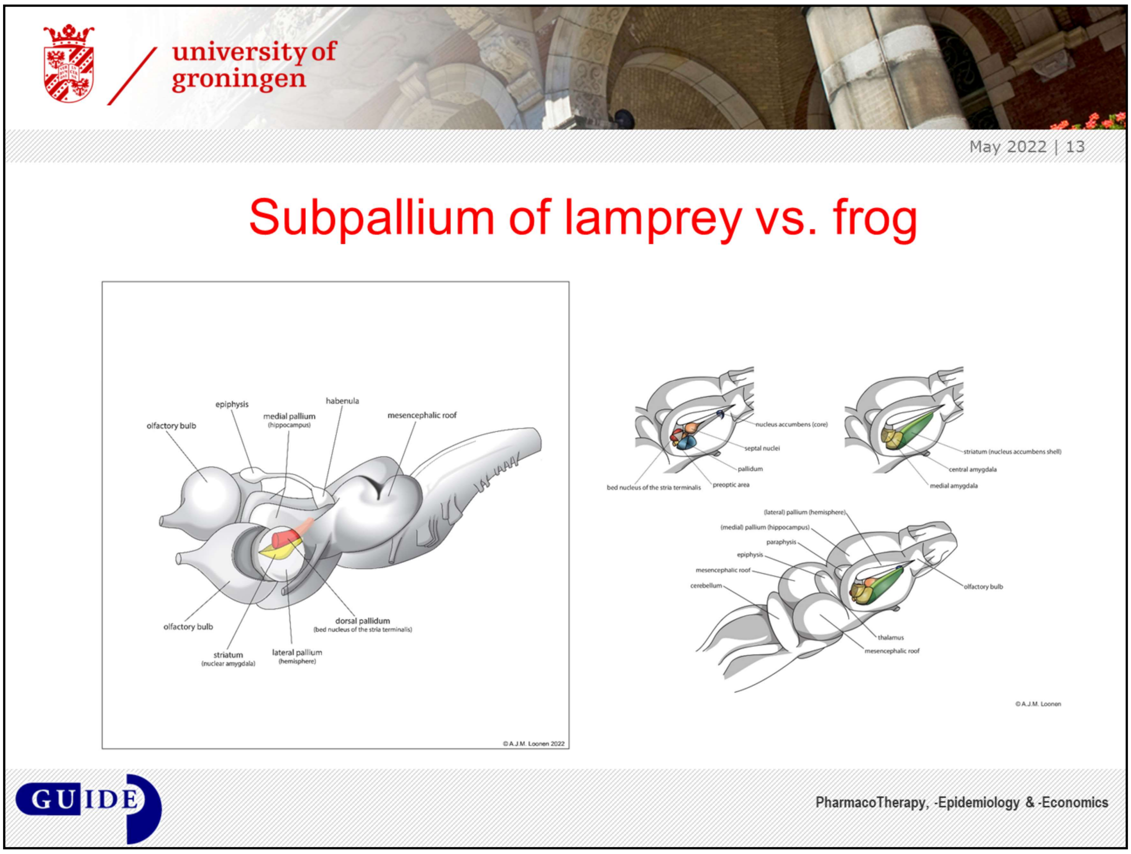
The first primates arose as ancestors of prosimians about 65 million years ago. From these, monkeys emerged about 55 million years ago and great apes about 20 million years ago. The closest relative to humans is the chimpanzee. They each went their own way in evolution over 6 million years ago. In the brain of the rhesus monkey or (rhesus) macaque as shown on this slide, the relationship with the human brain is clearly recognisable. The expansion of the cerebral cortex already goes so far that the temporal lobe expands beneath and aside part of the rest of the hemisphere in a forward direction. The olfactory ganglion which is shown in purple is, however, still much larger than in humans.



What took place during evolution over hundreds of millions of years is more or less repeated during the embryonic development of every human being. The left top picture (a) shows the primitive hemisphere of a human embryo of about 35 days old as seen from the midline. In blue it shows the first formation of the hippocampus. During the embryo's later development depicted in b, via c to d , the hemisphere grows out in a C-shaped curve, forming the temporal lobe. The left bottom picture shows the situation in the adult brain. The fact that evolution repeats itself during embryonic development refers to the principle of Karl Ernst von Baer.



Something similar happens inside the early embryonic development of the cerebral hemisphere. The left upper picture (a) shows a cross-section through this lateral vesicle on the right and on the left a longitudinal section indicating the lateral and medial ganglionic eminences. These structures in the bottom of the lateral vesicle are making up of the first formation of the so-called 'basal ganglia', which in the adult brain play an important role in, among other things, the regulation and intensity of voluntary movements. A well-known disease of the basal ganglia is Parkinson's disease. The pictures of the longitudinal section below and following the arrows from (a) to (b), to (c) and to (d), show their development in the basal ganglia in the adult brain. In the adult brain the right (posterior) part of the bottom of the cerebral vesicle is located in the temporal lobe, while the left (anterior) part is located inside the forehead. The part in the forehead is called the striatum and globus pallidus and the part in the temporal lobe is termed ‘nuclear amygdala.'

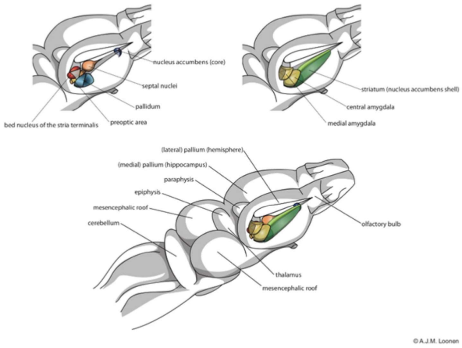


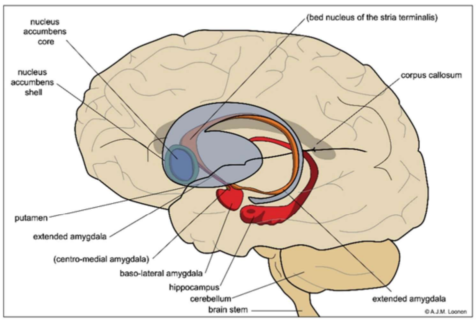
This slide shows the brain of the lamprey and the frog again, but now from a completely different perspective. In the medial wall of the hemisphere of the lamprey we see a single set of basal ganglia. The yellow nucleus is called striatum and in extension to it, in red, lies the dorsal pallidum (which later become the nuclear part of the amygdala and the bed nucleus of the stria terminalis). In the picture on the right, we see the brain of the frog. The yellow and red basal ganglia are also present, but now there is also a green striatum and a blue pallidum. In the frog, the basal ganglia of the lamprey are now part of the extended amygdala, which in humans is located in the temporal lobe of the brain. The green and blue basal ganglia are the first instance of the basal ganglia in the frontal lobe.

university of groningen

May 2022 | 14

Subpallium of frog vs. human

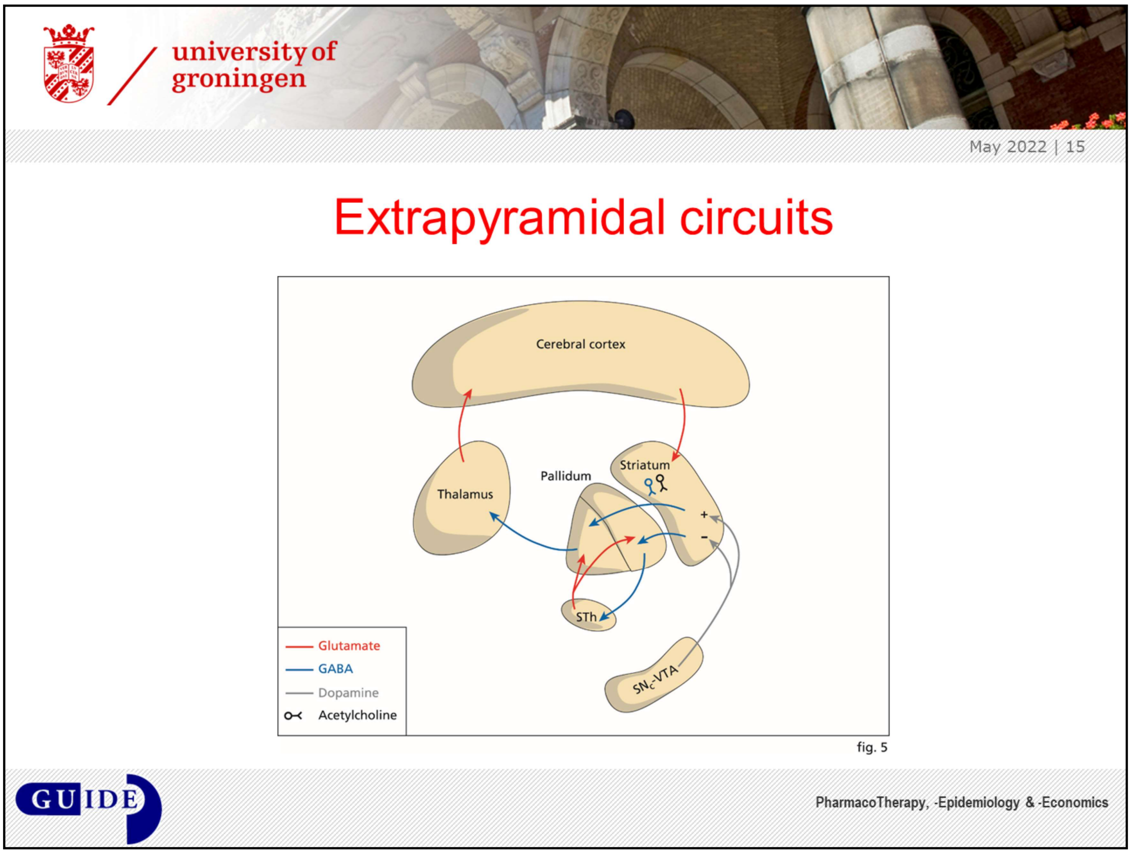




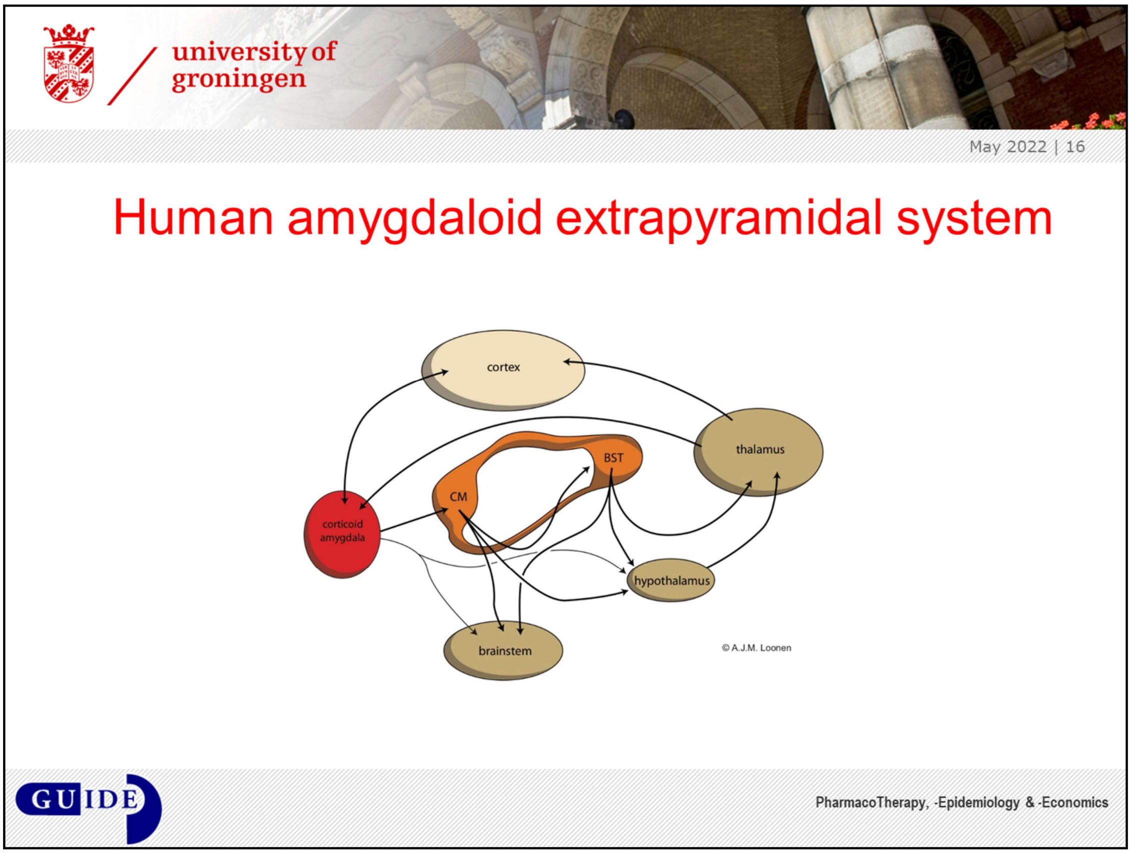
GUIDE

PharmacoTherapy, -Epidemiology & -Economics

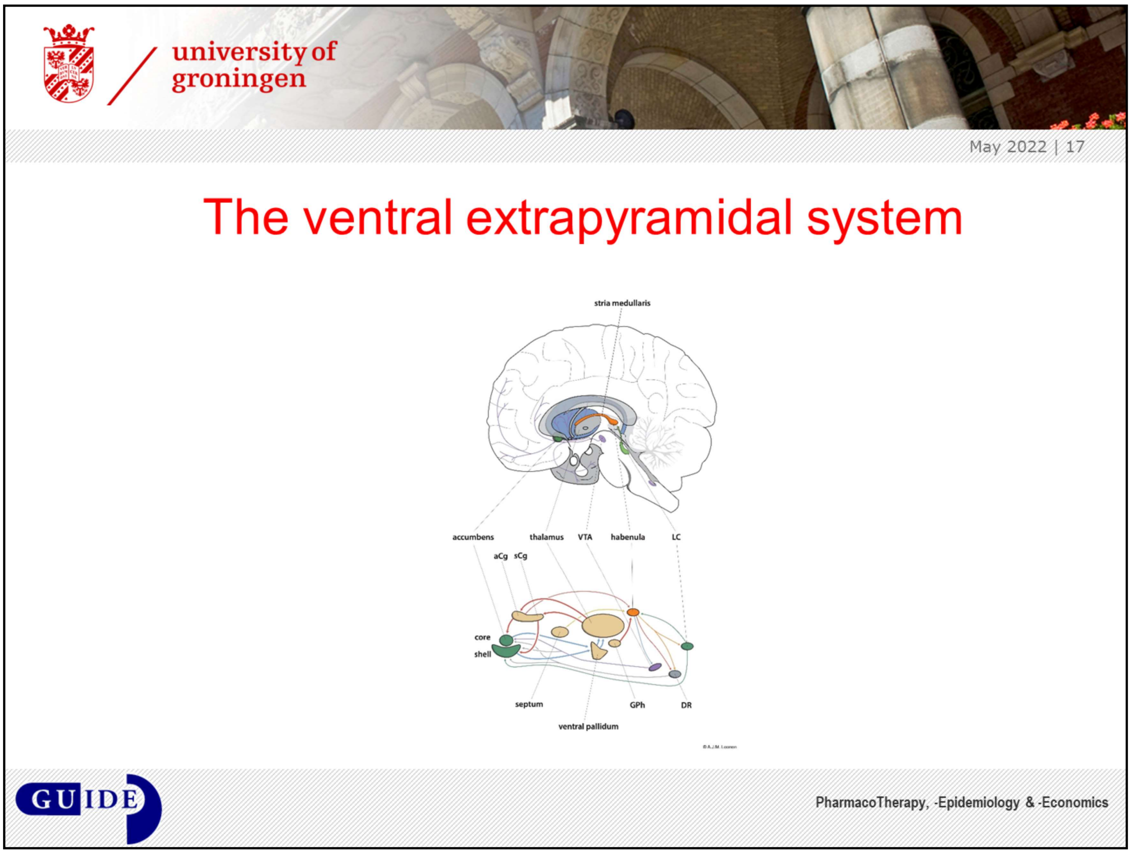
Now we compare the brain of the frog with that of man and see that in man a large third system has been added (in light blue). This is the dorsal striatum which is divided into two parts; the caudate nucleus and the putamen. In this figure the ventral pallidum and the dorsal pallidum (globus pallidus) have been omitted. This dorsal striatum arises from the nucleus accumbens of the frog. We see this in dark blue in the upper left image of the frog's brain. So in humans, the so-called basal ganglia consists of three parts. First a part in the amygdala complex (coloured ochre in this slide) that already existed in the very first vertebrates, second a part that already functioned in ancestors such as amphibians and corresponds to the nucleus accumbens (green and dark blue) in humans and third a part (in light blue) that in mammals has gradually developed: the putamen and the caudate nucleus.



The basal ganglia consist of two types of nuclei: the striatum and the pallidum. This figure outlines that dorsal striatum and dorsal pallidum (the latter commonly called globus pallidus) are part of a circuit that starts in the cerebral cortex and also ends in the cerebral cortex at the end. This means that output from the cerebral cortex is also routed back to the output nerve cells, modulating their activity. Several neurotransmitter substances are involved in this process. Essential to the activity within the circuit is the neurotransmitter substance dopamine. It regulates the activity within the circuit by opening or closing a kind of valve function in the striatum. When dopaminergic fibers are active the valve is open and the cerebral cortex is strongly activated. If little dopamine is active then the activity of the cerebral cortex is reduced. Thus, one of the functions of the extrapyramidal system is to adjust the strength and rate of output of specific parts of the cerebral cortex according to actual need.



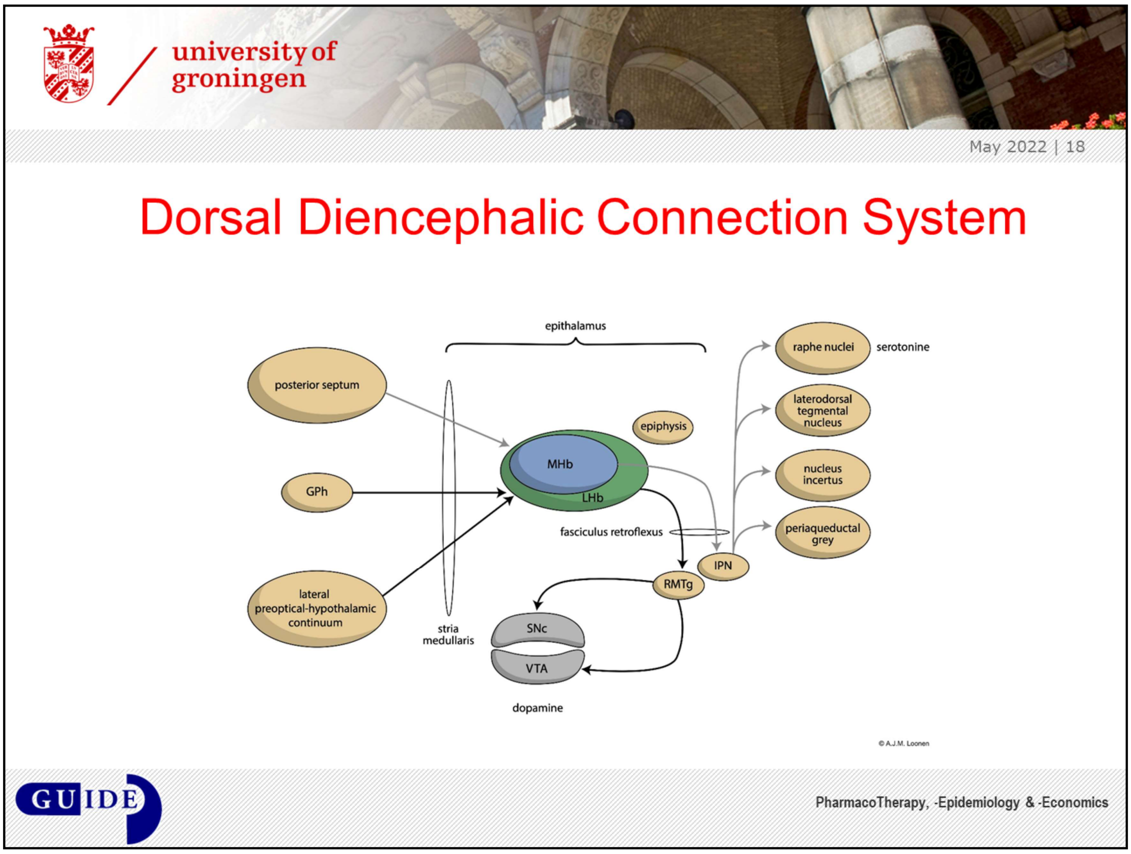
In the structure of the extrapyramidal system of the amygdala complex, this architecture can also still be recognized. The amygdala consists of more than 10 nuclei that can be divided into a corticoid and a nuclear complex. The corticoid complex is similar to the cerebral cortex in humans. In this figure CM represents the centromedial nucleus which can be considered the striatum. BST stands for bed nucleus of the stria terminalis and corresponds to the pallidum. The circuits continue through the thalamus, that in turn is connected to the corticoid part of the amygdala. Two other things can be seen in this figure: first, a significant portion of the output of the centromedial amygdala and the BST goes to the brainstem and hypothalamus. Along these lines, the amygdala initiates the essential behaviours associated with feeding, defending, and reproducing. The second thing that is somewhat indicated is that the amygdaloid complex is connected and incorporated into structures that arose later during evolution. This oldest part of the brain does not function independently of the newer parts, but in constant concert with them. Because the amygdala along with the hippocampus are the oldest parts of the forebrain and regulate functions that are prerequisites for the existence of any species, I call these parts the primary forebrain.



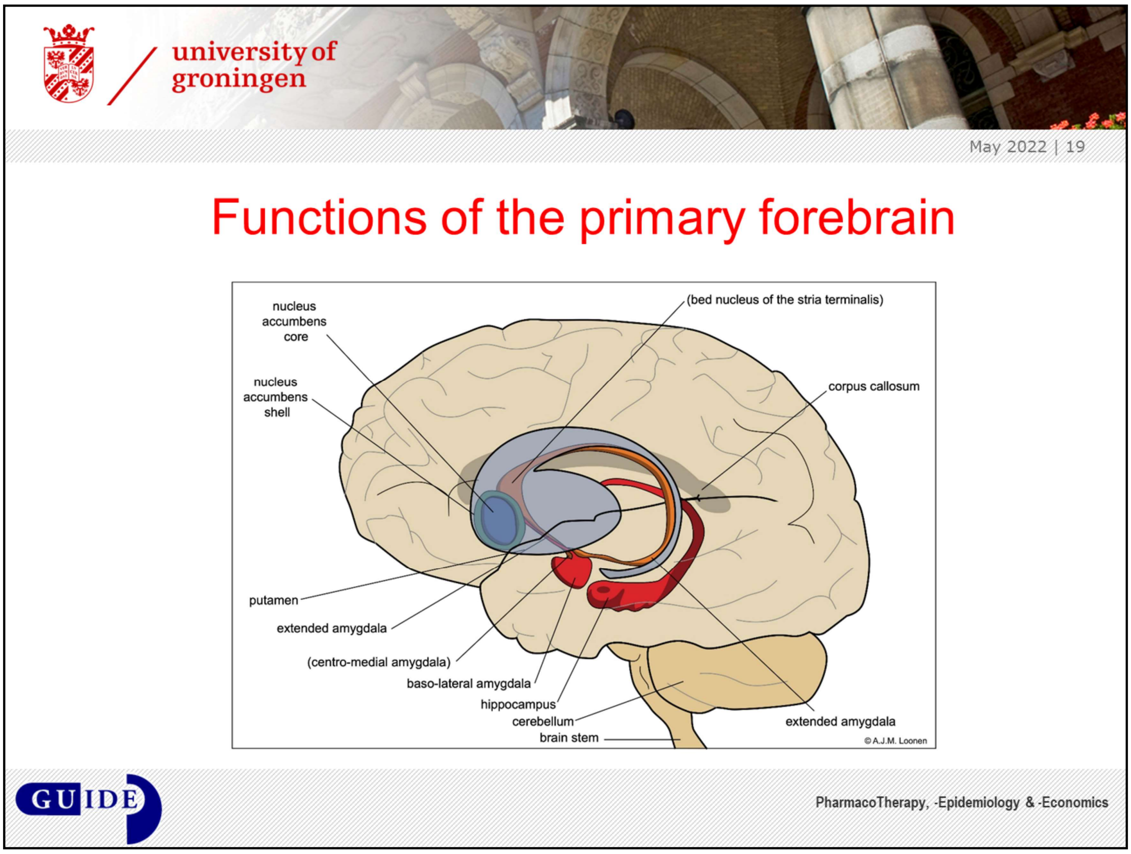
Representing the extrapyramidal circuit of the secondary forebrain is somewhat more complex. It is shown schematically in the lower half of this figure, and the location of the mentioned structures in the human brain is indicated in the upper half.

The ventral circuit is drawn in the lower left: it begins and as well ends in the limbic cortex (denoted here by aCg and sCg), into which it ends after running via the core and shell of the nucleus accumbens, the ventral pallidum and the thalamus. Note: this is greatly simplified. In fact, many more ventral extrapyramidal circuits exist and there are many connections to the primary and tertiary forebrain.

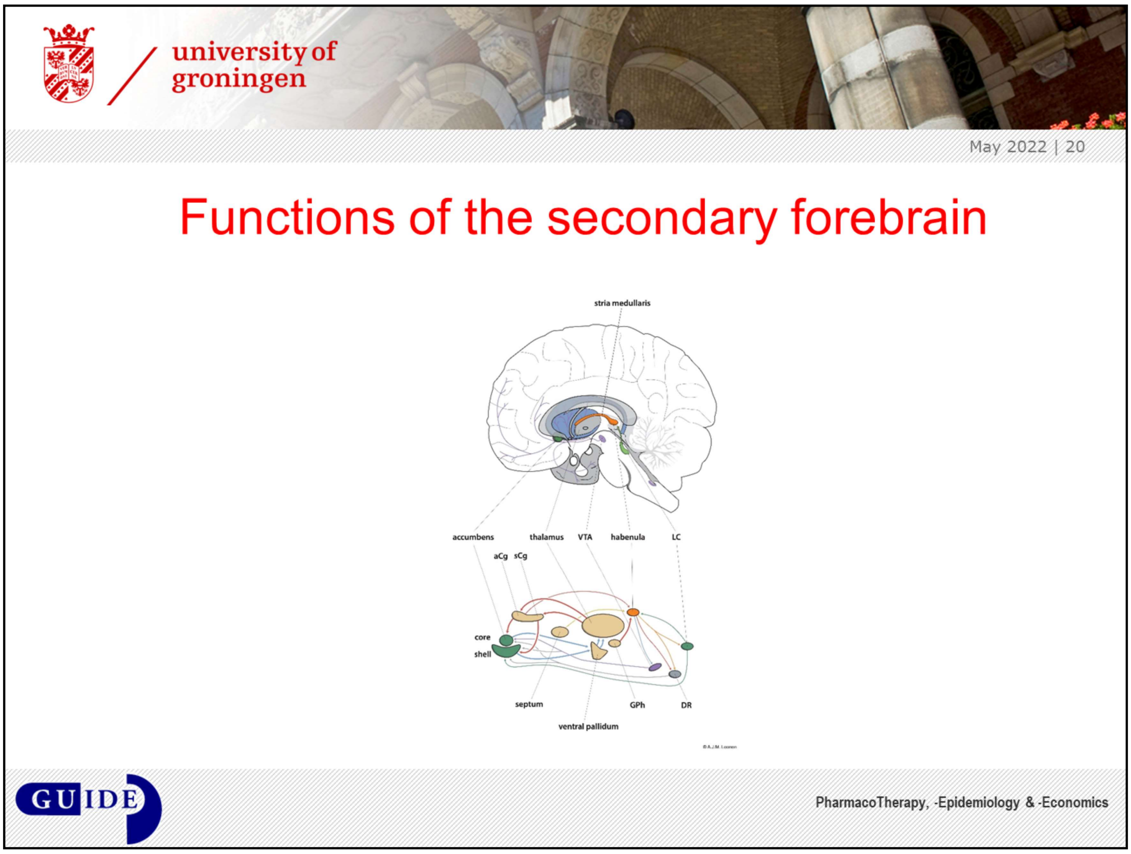
In the lower right corner, the diagram shows the habenula. This complex of nuclei is already present in the invertebrate ancestors of our earliest vertebrate ancestors and especially important for the functioning of the primary and secondary brain. It is a nuclear station that relays information from the forebrain to nuclei in the midbrain. From one of these midbrain nuclei, dopamine-using fibres run up into the primary, secondary and tertiary forebrain and increase their activity. So it is an important regulatory system: the so-called dorsal diencephalic connection system. The habenula also regulates the activity of fibers that use serotonin, norepinephrine and acetylcholine as neurotransmitter substances and that run from the midbrain to the forebrain.



This rather complex diagram shows the DDC system in more detail. The habenula in the middle consists of two divisions: a small medial habenula (labelled MHb) and a large lateral habenula (LHb). Like the epiphysis (pineal gland), the habenula is part of the epithalamus. The medial habenula receives input primarily from the posterior septum and gives output via the interpeduncular nucleus to a number of nuclei in the midbrain including those that use serotonin as a neurotransmitter. The lateral habenula is 20 times larger than the medial division and receives input from several areas in the forebrain. Via the so-called RMTg, the output goes mainly to nuclear areas from which dopaminergic nerve fibres run to various areas in the forebrain. This dopaminergic activity is inhibited when the lateral habenula is very active. This is why the lateral habenula is called an anti-reward centre, but the influence on behaviour leading to a reward feeling is only a part of the activity of the ascending dopaminergic pathways.



This figure does not show the habenula, but does show the entire primary forebrain consisting of the amygdaloid complex and the hippocampus. In humans, the primary forebrain values perceptions from the point of view of their significance on the probability of survival. This is called salience. This applies to all forms of feeding, defending and reproducing, but can be most clearly explained by the alarm triggered by the threat of danger. A person does not need to constantly scan the environment for possible relevant sources of danger, but the sight of a blue flashing light immediately calls attention to it. The dopamine secreted in the amygdala by fibres from the midbrain sharpens the functioning of the forebrain in this respect. Over-activity of dopamine makes it far too easy to attach great value to all kinds of perceptions. This leads to false beliefs about one's own importance or imminent danger that are not at all correct; these then become delusions. Through the activity of dopamine-using fibres that run from the midbrain to the primary forebrain, the habenula can regulate the occurrence of psychotic phenomena.

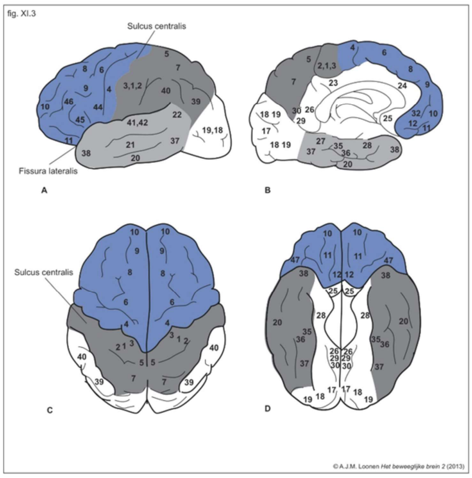


The diagram in this figure shows an important part of the secondary forebrain. The secondary forebrain consists mainly of ventral extrapyramidal circuits that run parallel to each other via the nucleus accumbens. The diagram shows two of these circuits starting and ending in a particular part of the limbic cortex, here indicated by the symbols aCg (anterior cingulate cortex) and sCg (subgenual cingulate cortex). This part of the cerebral cortex is also connected to the habenula. The secondary forebrain controls the willingness to engage in behaviour that leads to a feeling of reward or lets you escape from unpleasant circumstances. The degree, the intensity, of that behaviour is also regulated. According to my previous definitions, when the first type of behaviour is successful, the individual experiences pleasure and when the second type of behaviour is successful, happiness. Inappropriate activity within the secondary forebrain plays an important role in (relapse to) addiction, in excessive and prolonged stress and in mood problems.

university of groningen

May 2022 | 21

Functions of the tertiary forebrain



PharmacoTherapy, -Epidemiology & -Economics

The tertiary forebrain consists of the rest of the cerebral cortex and the associated thalamus and basal ganglia. This figure shows the cerebral cortex from all sides. The areas are numbered by German neurologist Korbinian Brodmann. The posterior half of the cerebral cortex analyses and interprets the input from the 5 senses and the blue anterior half (including the part behind the forehead) controls the output in the form of movements and reasoning. The cerebral cortex consists of a dense network of nerve cells embedded in a tissue of supporting cells. Different parts of the cerebral cortex are interconnected in the network within each hemisphere. There are also many connections between the left and right hemispheres, mainly through the corpus callosum. In addition, there are many connections back and forth to the thalamus and much of the output goes directly to the spinal cord, brainstem and hands with fingers. There are also many connections back and forth with the primary and secondary forebrain. Besides analysing sensory input and causing movements, the tertiary brain is also responsible for thinking, knowing, imagining and remembering. In humans, every observation and movement can also be replaced by a thought.

It is not unlikely that other species besides humans can think and remember in one form or another, because they have a similar complex cerebral cortex as humans. But humans have the rather unique ability to read and write. This allows humans to learn from and build on the skills and experiences of other humans, which has resulted in tremendous technological evolution. This thinking requires a well-functioning brain, but the content is not so concretely laid down in the hardware. Reasoning is learned and circumstances can be recognised, but the thinking itself is organised in thought patterns separate from the hardware (in my opinion). The thinking of the individual human being is also not entirely self-contained. It depends on what each person has internalised from upbringing and former living conditions, what is learned from religious or legal writings, what is learned during schooling and education and what is provided by the current social context. The fact that the thinking of the individual human being is partly independently organised from the physical brain, but can influence and is influenced by it, is frequently applied during psychotherapeutic interventions. Participating in a community gives a strong impulse to think and behave in a similar way. During psychotherapy, this very mechanism is used to help people recover from mental disorders. Medication serves to create the space within the functioning of the brain that this is also possible.

Sources for professionals

- Lectures
  - https://antonloonen.nl/presentations/
- Articles
  - https://doi.org/10.1017/neu.2017.8
  - https://doi.org/10.1017/S1092852917000748
  - https://doi.org/10.1177/0269881118798617
  - https://doi.org/10.1017/neu.2022.15

Contributions

Scientific Background

Anton Loonen

Text

Anton Loonen

Figures

Lizanne Hennessey

Technical realization

Thomas Muller