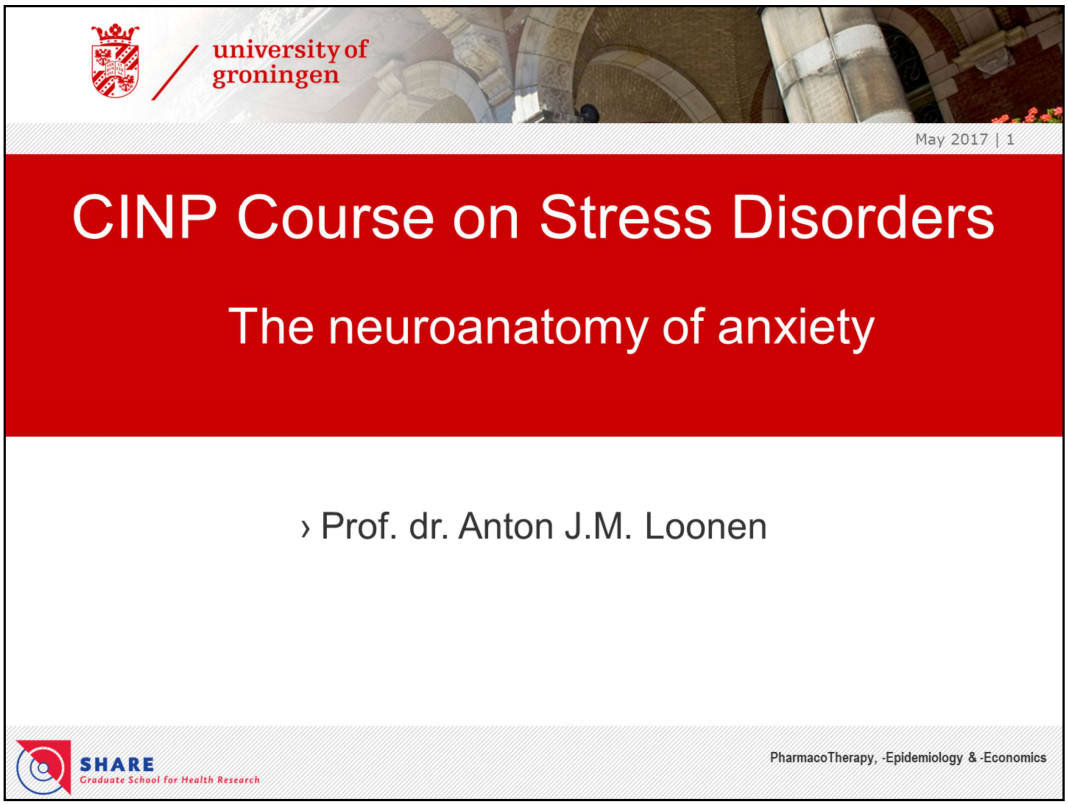
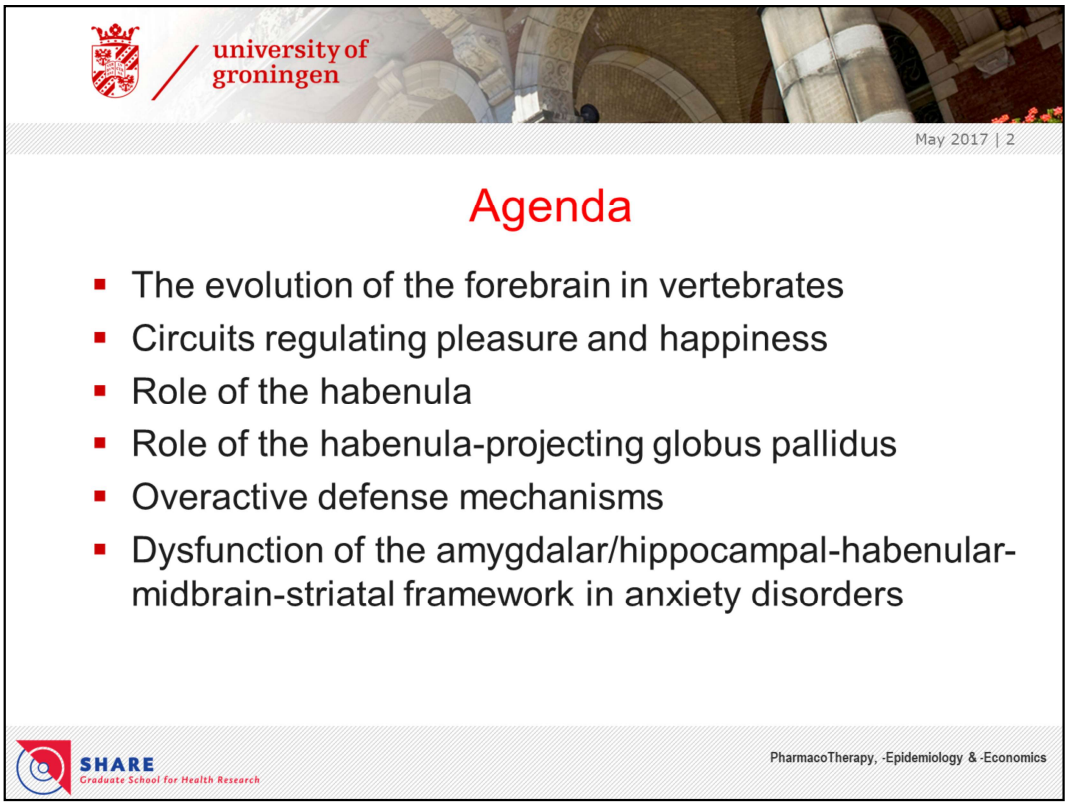
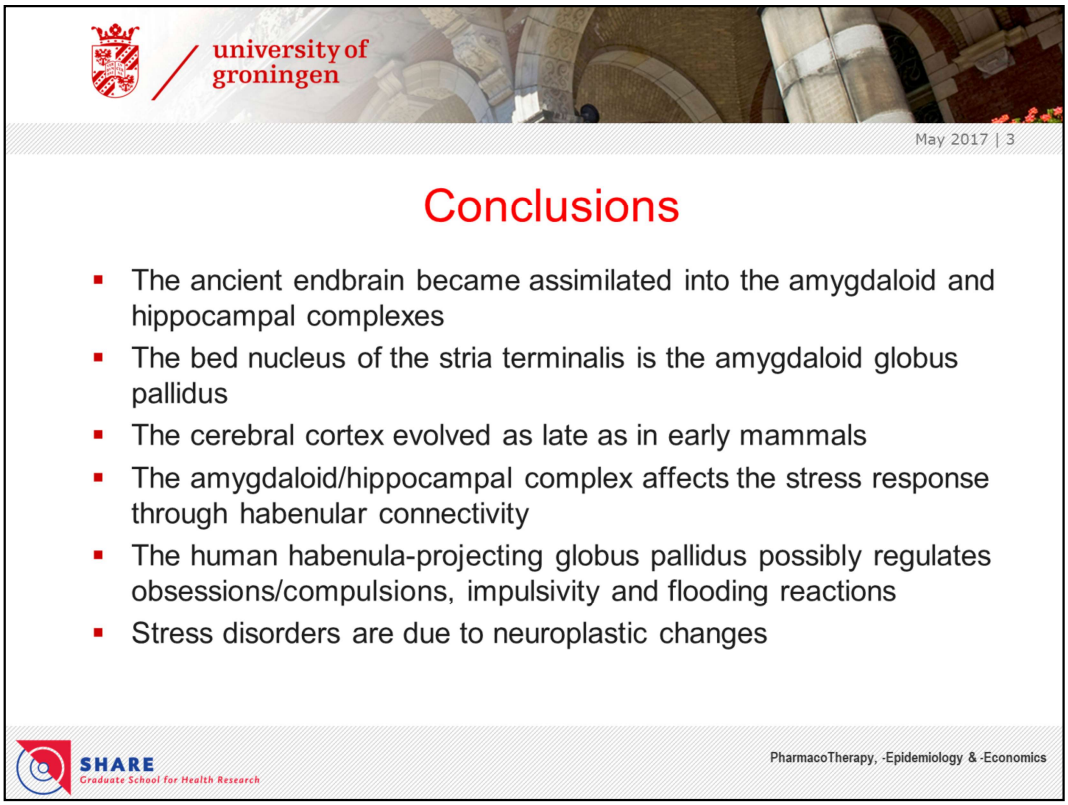


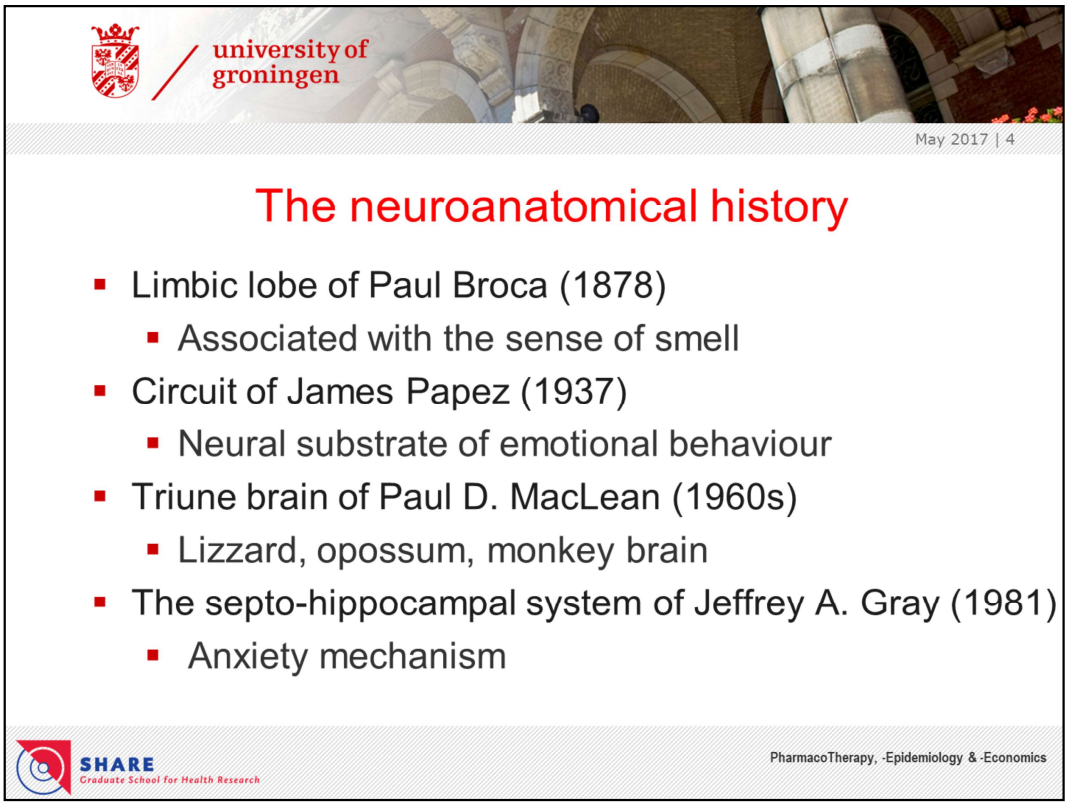
This presentation is a modified version as that of my lecture "Neuronal cascades regulating pleasure and happiness in stress disorders" that I delivered at the International Education Courses "Modern problems of neurobiology and psychopharmacology of post-traumatic stress disorder and anxiety disorders" in Tomsk, Kemerovo and Novosibirsk on 15-19 May 2017.



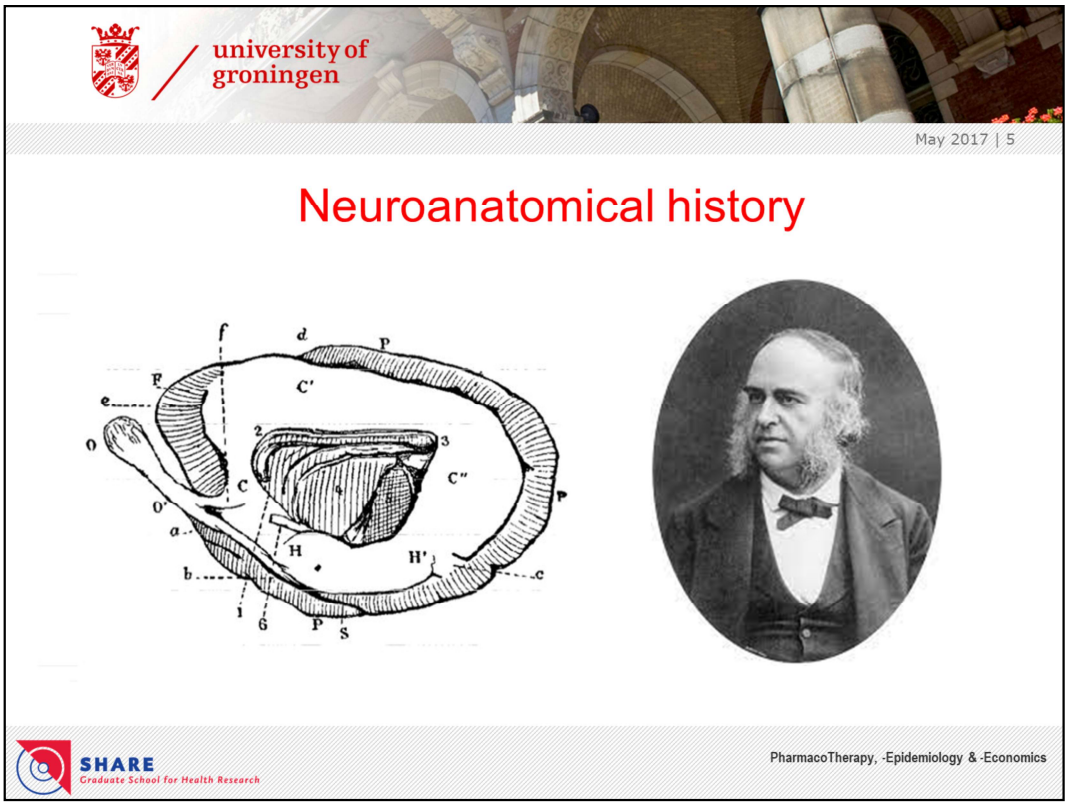
In this presentation, I will discuss new developments in our understanding of the neuroanatomy of stress disorders. Recently, we have developed some new ideas about the organization of the subcortical forebrain by studying its evolution from the earliest vertebrates until humans (Loonen and Ivanova, 2018; doi: 10.1017/neu.2017.8). We discovered that the cerebral structures regulating behaviour leading to pleasure and happiness in our earliest vertebrate ancestors can be retrieved within the current human brain. These structures probably display the same function in humans as they do in lampreys, which are modern representatives of these ancestors living about 560 million years ago. An important function is exhibited by a tiny nuclear complex close to the pineal gland: the habenula. Therefore, I will start from a model in which an important role is reserved for the dorsal diencephalic connection (DDC) system in which the habenuloid complex plays an essential role. In humans, the forebrain of the first vertebrates with a brain similar to that of the lamprey is found mainly in the amygdaloid and hippocampal complex, the septal region and various parts of the anatomical thalamus (the diencephalon). This primary part of the forebrain initiates the complex emotional response including the compound stress response that plays an essential role in the development of anxiety and stress disorders.



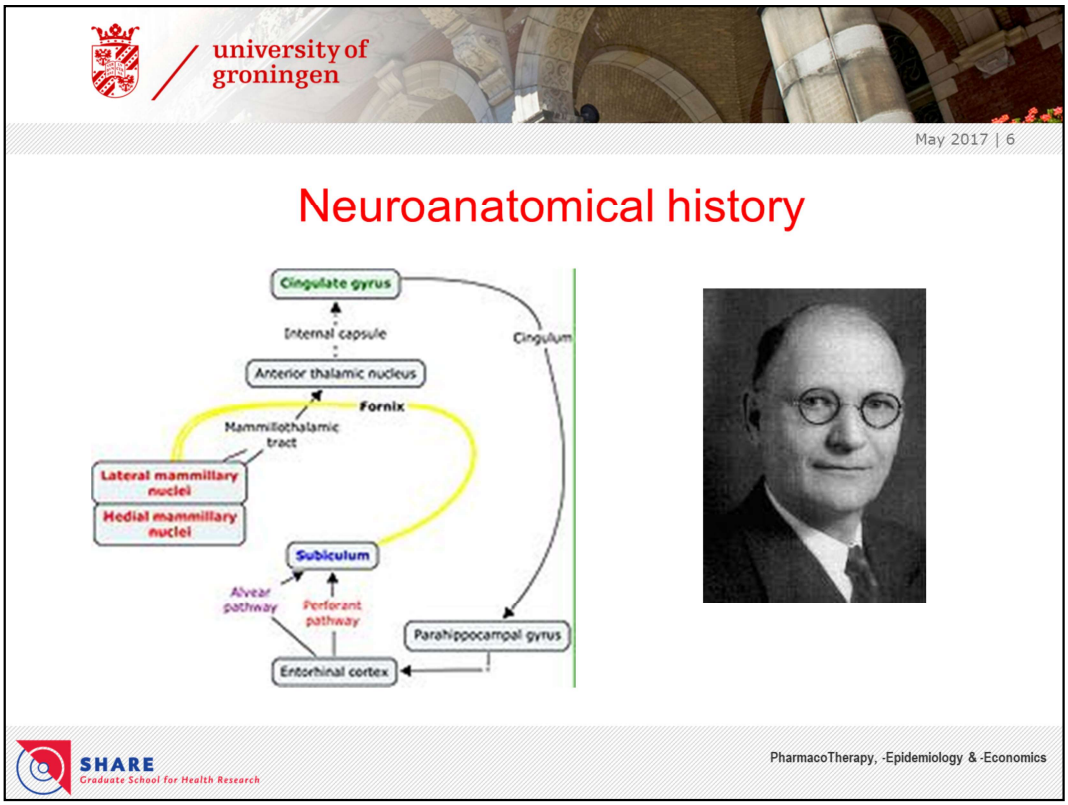
The take-home messages from my lecture are written on this slide. We have obtained evidence that the primitive forebrain of our earliest vertebrate ancestors became incorporated into the current amygdaloid and hippocampal complexes (Loonen and Ivanova, 2015, 2016; doi: 10.3389/fnins.2015.00394, doi: 10.3389/fnins.2016.00539). Similar to the rest of the hemisphere, this amygdaloid complex consists of a corticoid (cortical) and a striatopallidal (subcortical) part. The bed nucleus of the stria terminalis corresponds to the globus pallidus of this amygdaloid complex. In the lamprey, this globus pallidus contains a structure that decides whether the reward-seeking behaviour is productive enough to be continued. This structure influences the activity of the habenula, which in turn regulates the monoaminergic centres in the midbrain. The human habenula-projecting globus pallidus may be involved in regulating obsessions/compulsions, impulsivity and flooding reactions. It must be realised that the cerebral cortex, which plays a dominant role in influencing behaviour in humans, is a relatively new cerebral structure. Therefore, it is unlikely to play an essential role in regulating behaviours that are crucial to sustaining life in ancestors who lacked this structure. Since the amygdaloid/hippocampal complex influences the stress response via habenular connectivity and had this role very early in evolution, it is tempting to speculate that the mechanism of the flight response is essentially the same in all successive vertebrates, including humans. However, the mechanism that regulates fear and anxiety sensations in humans is probably of much later date. But I will start with a little history of the ideas about the origin of anxiety disorders. As we all know, the stress response is of vital importance to survival of the individual and its species. However, in humans an inadequate duration and intensity of this response can also become a burden since it can result in invalidating mood and anxiety disorders, which might result from the occurrence of neuroplastic changes.



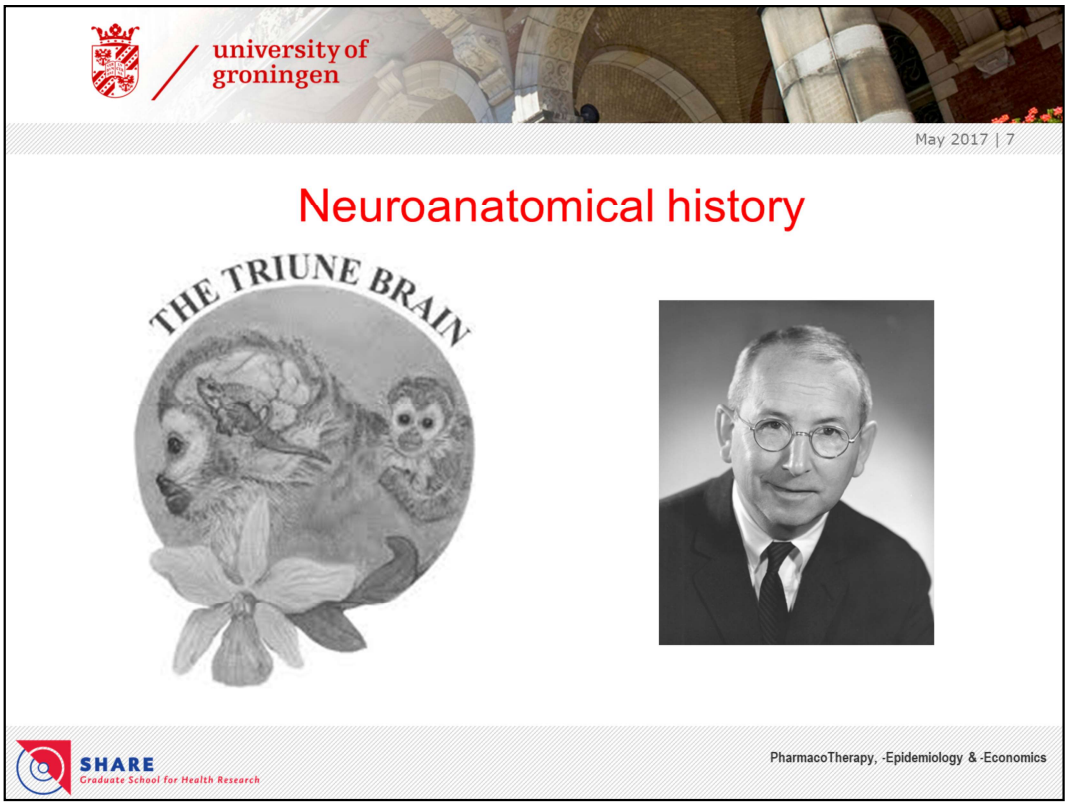
These emotions were traditionally believed to be regulated by the so-called limbic lobe, which was first defined by Paul Broca in 1878, who was associating it with the sense of smell. The limbic loop was for the first time described by James Papez in 1937 as the circuit constituting the neural substrate of emotional behavior [Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatr 1937;38:725-743]. The limbic system also appears in the Triune Brain model of Paul D. MacLean [MacLean PD. The Triune Brain in Evolution. Role in Paleocerebral Functions. Plenum, New York, 1990]. As a starting point for delineating the neurocircuitry of pathological and non-pathological anxiety also the pioneering work of Jeffrey A. Gray should be mentioned, which was described in his book published in 1981 [Gray JA. The neuropsychology of anxiety: an enquiry Into the functions of the septo-hippocampal system. Oxford: Oxford University Press, 1981].



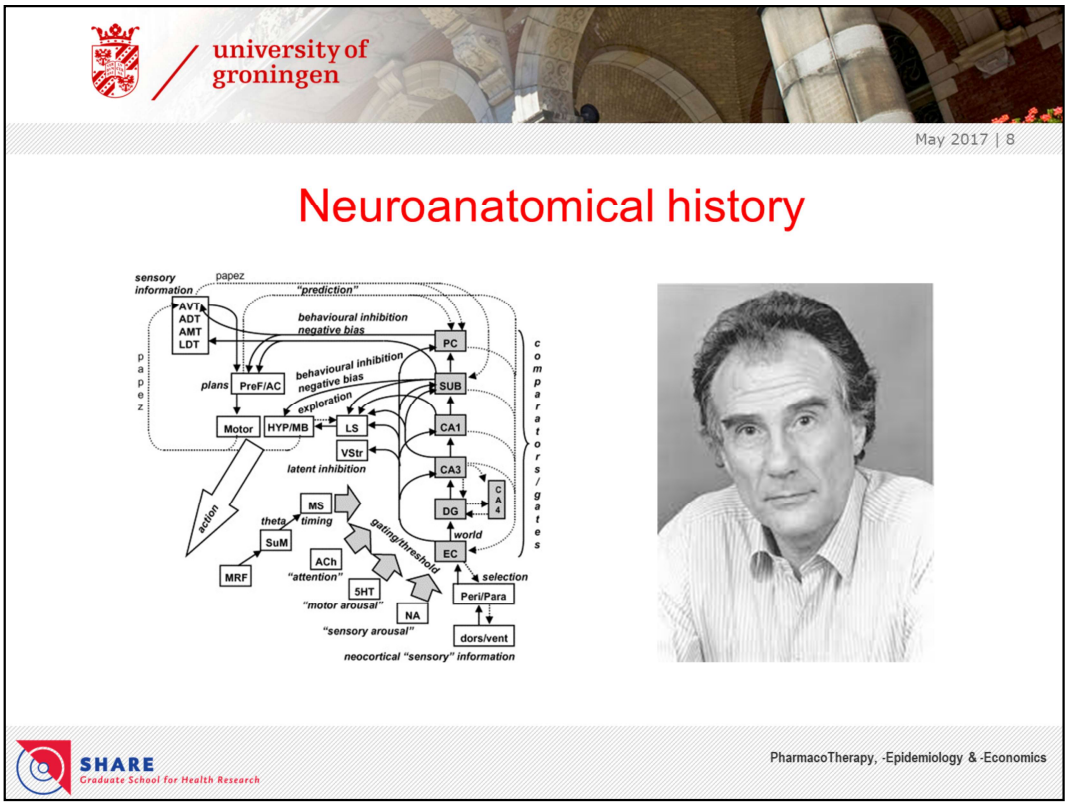
Paul Pierre Broca (1824-1880) is best known for the speech centre named after him but is mentioned here for his comparative anatomical brain research in more than 30 different mammalian species [Pessoa and Hof, 2015; doi: 10.1002/cne.23840]. He compared the construction of the mesial plane of the brain, which is the part of the two hemispheres of the brain facing the midline and opposite each other. A great merit of this was that he was able to demonstrate the analogy of this construction from more primitive mammals to humans. He began his treatise by describing the mesial surface of the otter (left figure), where the relationship of the limbic lobe to smell is very clear. In this figure, C, C', and C'' indicate what Broca called the lobe of the corpus callosum. O is the olfactory lobe and O' is the olfactory peduncle. Broca concluded that all mammals possess a large limbic lobe, but that in primates the olfactory lobe has become rudimentary and that on the nasal side the frontal lobe has developed enormously at the expense of limbic lobe.



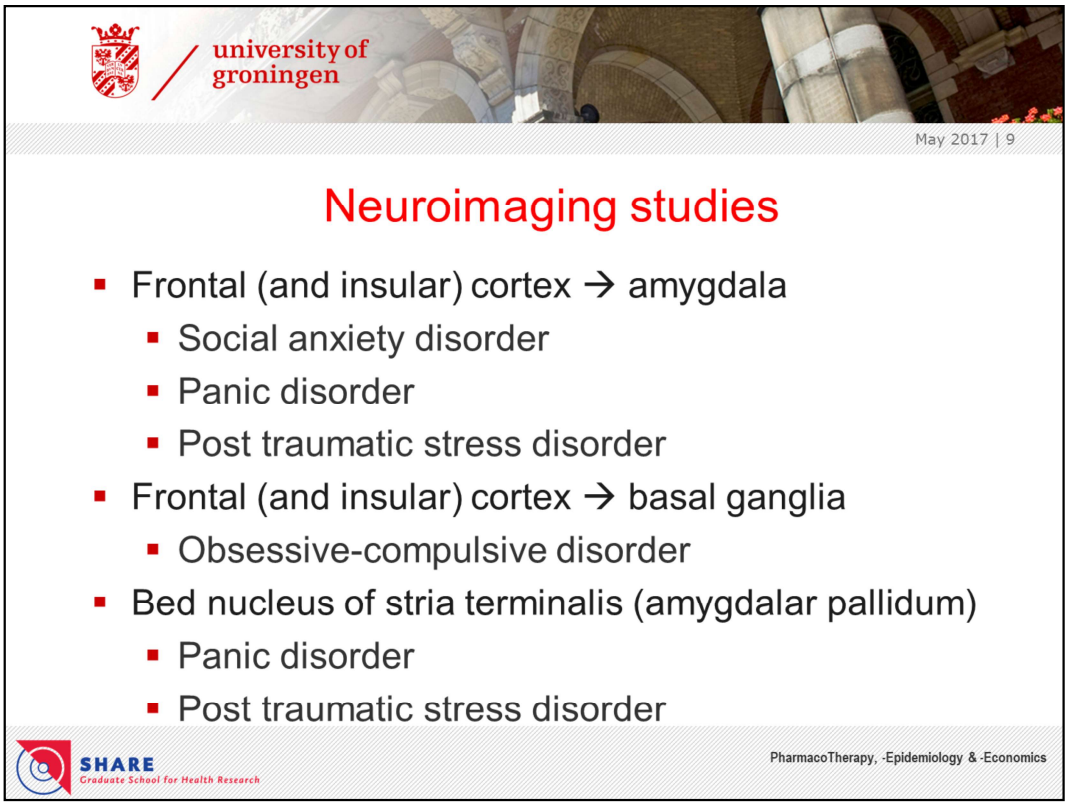
In 1937, the American neuroscientist James Wenceslaus Papez (1883-1958) described the circuitry named after him, to which he attributed an important role in the generation of emotions (Bhattacharyya, 2017; doi: 10.4103/aian.AIAN_487_16). Papez based his ideas on experiments in which he injected rabies virus into the hippocampus of cats and then followed the course of the infection through the brain in brain sections. He postulated that the emotional process is built up in the hippocampal formation and is then conducted from the subiculum through the fornix to the mammillary bodies of the hypothalamus. The signal is then transmitted via the Vicq d' Azir tract (mammillothalamic tract) to the anterior thalamic nuclei and from there to the cortex of the gyrus cinguli (see diagram in left figure). He hypothesised that radiating the emotive process from the gyrus cinguli to other areas in the cerebral cortex would add emotional coloration to psychic processes that are controlled elsewhere.



Papez's idea was later modified somewhat by Paul Donald MacLean (1913 - 2007), who introduced the name limbic system in 1952 (Bhattacharyya, 2017; doi: 10.4103/aian.AIAN_487_16). In the Triune Brain model introduced by McLean, the forebrain consists of a reptilian complex or the R complex (basal ganglia), a palaeomammalian complex or the limbic system (the septum, amygdala, hypothalamus, hippocampal complex, and cingulate cortex), and the neomammalian complex or neocortex. This idea was immediately embraced in the popular press, suggesting erroneously that these three units functioned independently of each other. But this was not the only problem. From an evolutionary perspective, the idea was false. Reptiles such as the crocodile and the lizard are not the ancestors of primates at all, but are in a separate lineage, along with the birds as an offshoot of them. Reptiles and birds have no mammalian-like cerebral cortex, because in these non-synapsid animals the forebrain has developed in a different direction (Loonen and Ivanova, 2016; doi: 10.3389/fnins.2016.00539). Also, the functions that MacLean ascribed to the different parts do not make sense in retrospect. The theory has therefore been abandoned, but in some respects that is a pity, as we shall see later.



A reference to the work of the British psychologist Jeffrey Alan Gray (1934 - 2004) should not be missing from this brief sketch. In 1981 his book "The neuropsychology of anxiety" was published and in 2000 a revision appeared with new implications that he wrote together with Neil McNaughton. Gray formulates his ideas in a rather difficult way. I remember the bewilderment in the eyes of the psychiatric residents when we went through and discussed this book together as part of the biological psychiatry course. I no longer have the book and make a reference to an article by McNaughton (2006; doi: 10.1016/j.bbr.2006.05.037). What I find very interesting about Gray and McNaughton's work is that they attribute an important role to the interaction between the hippocampus and the septal nuclei. The medial septal area is anatomically and functionally closely and reciprocally linked to the hippocampal complex (Ang et al., 2017; doi: 10.1016/j.nlm.2016.07.017). Gray and McNaughton talk about the septo-hippocampal system (SHS) with a central role for the subiculum. We believe that, in addition, there is also a phylogenetically much older system in which (olfactory) sensory information is routed via hippocampus, fornix, posterior septal nuclei to the medial habenula.



Much work has been done in recent years by applying the results of neuroimaging studies. Combined with animal experiments, these studies indicate that a network consisting of parts of the frontal (and insular) cortex is connected to the amygdala for social anxiety disorder, panic disorder, and posttraumatic stress disorder (Kent and Rauch, 2003; doi: 10. 1007/s11920-003-0055-8; Taylor and Whalen, 2015; doi: 10.1007/s11920-015-0586-9) and connected to the basal ganglia (particularly the nucleus caudatus) for obsessive-compulsive disorder (Huey et al, 2008; doi: 10.1176/jnp.2008 .20.4.390). Another structure that should not be overlooked for playing a role in panic disorder and posttraumatic stress disorder is the bed nucleus of the stria terminalis (Johnson et al, 2008; doi: 10.1038/sj.npp.1301621; Lebow and Chow, 2016; doi: 10.1038/mp.2016.1). However, in both the pathophysiology of panic disorder and post-traumatic stress disorder, the essential role of the prefrontal-amygdaloid so-called "fear network" has also been questioned (Sobanski and Wagner, 2017; doi: 10.5498/wjp.v7.i1.12; Patel et al., 2012; doi: 10.1016/j.neubiorev.2012.06.003). A major problem is the multiplicity of anxiety and anxiety disorders and that researchers often do not know what they are talking about and do not pay attention to placing the knowledge in a larger anatomical and behavioral organizational context. It is also far from certain to us that anxiety disorders may be dealt with in this context in a categorical manner as is done in the DSM and ICD.

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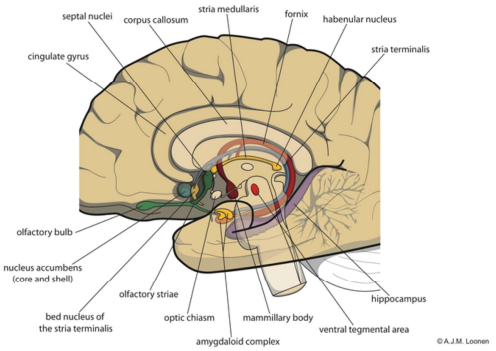
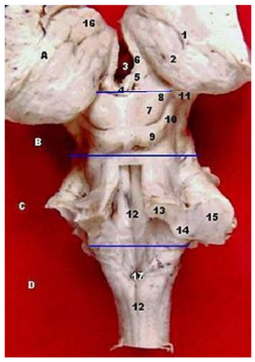
Epithalamus





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We would like to focus on the phylogenetic oldest flight system in this presentation. Actually, it is not so sure that this can be called a fear or anxiety system. We are concerned here with the system that motivates the individual to free himself from less pleasant circumstances. That could be anxiety, but this emotion might be phylogenetically younger that the origin of distress-avoiding behaviour. Nevertheless, the system may also have a significant role in human anxiety disorders.

Just for orientation I show you the position of this habenular complex within the human brain. The figure on the left gives you a midsagittal view. The habenula is localized within the posterior part of the epithalamus and connected with the septal area through the stria medullaris. The right side figure gives you a view on the brainstem and epithalamus after removal of the cerebellum and the overlying cerebral hemispheres. Also the pineal gland has been removed but no. 4 is the remainder of its stalk. The habenula is marked with ‘5’ and the stria medullaris with ‘6’. In humans the habenula is almost symmetrical and tiny. The complete complex measures about 20-30 mm3 on each side. About 95% of it is taken by the lateral division. This is too small to be visualised with normal neuroimaging techniques and therefore its function has hardly been studied so far.

[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].

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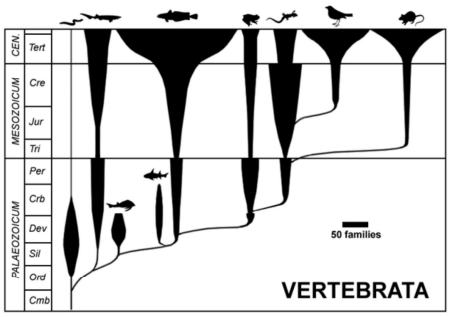
Evolution of the forebrain in vertebrates



- Jawless fishes - lamprey
- Cartilaginous fishes - shark
- Bony fishes - zebrafish
- Amphibians - frog
- Reptiles – turtle
  - Reptiles
  - Birds
- Mammals
  - Marsupialia - opossum
  - Rodents – mouse
  - Primates – macaque monkey

In order to study the history of the human forebrain we apply the theory that during evolution representatives of our vertebrate ancestors are still living today. Hence, we consider the brains of lampreys, sharks, zebrafishes, frogs, turtles, opossums, mice, macaques to represent earlier stages of the human brain during its evolution. This diagram shows this evolutionary development graphically. The vertical axis shows the emergence of the species within the periods of a geological time scale. On this diagram, it can be seen that the mammals originated from early reptiles (these were turtle-like creatures) and that the birds later split off from the reptiles as flying dinosaurs. This is, of course, all for illustrative purposes only.

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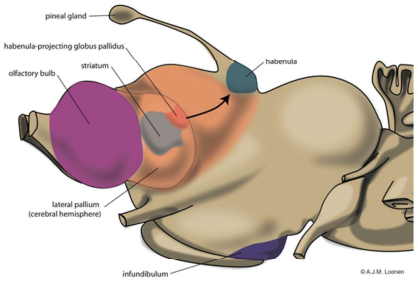
Forebrain of the lamprey



- Dominant olfactory bulb
- Small hemisphere
  - Striatum → pallidum → brainstem
  - GPh → habenula → brainstem
- Medial pallium (hippocampus)
- Hypothalamus (output)
- Upper brainstem (output)
  - Motor output
  - Monoaminergic feedback

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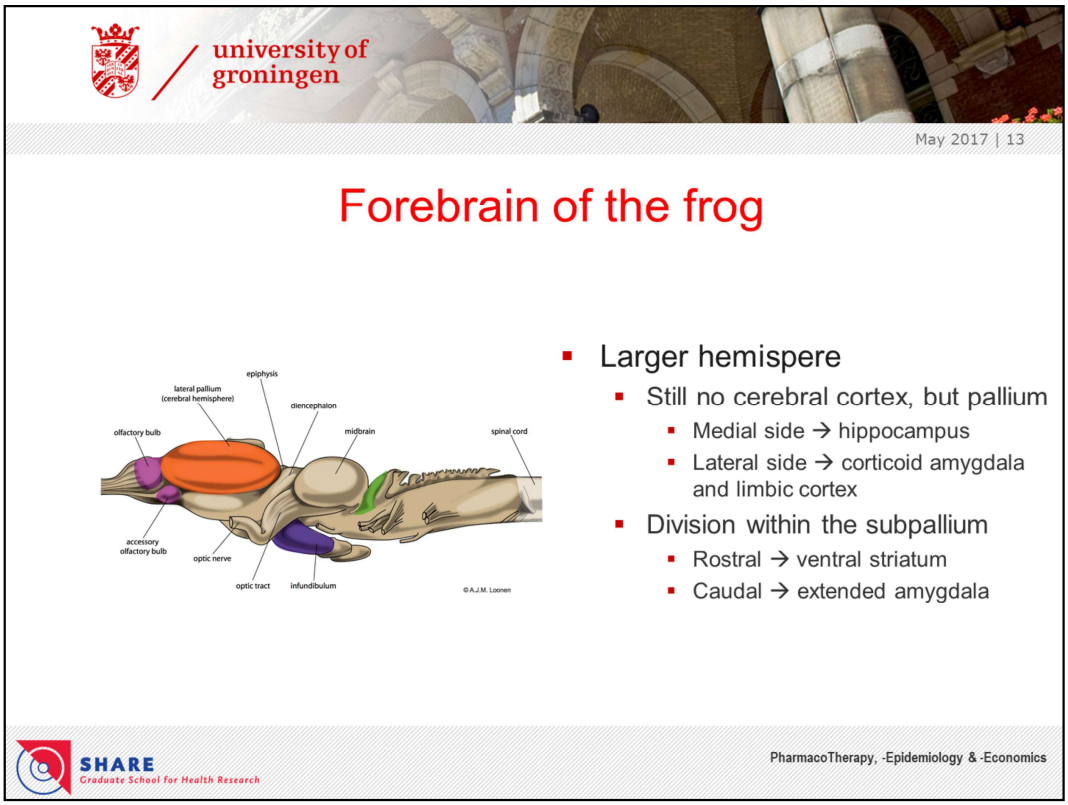
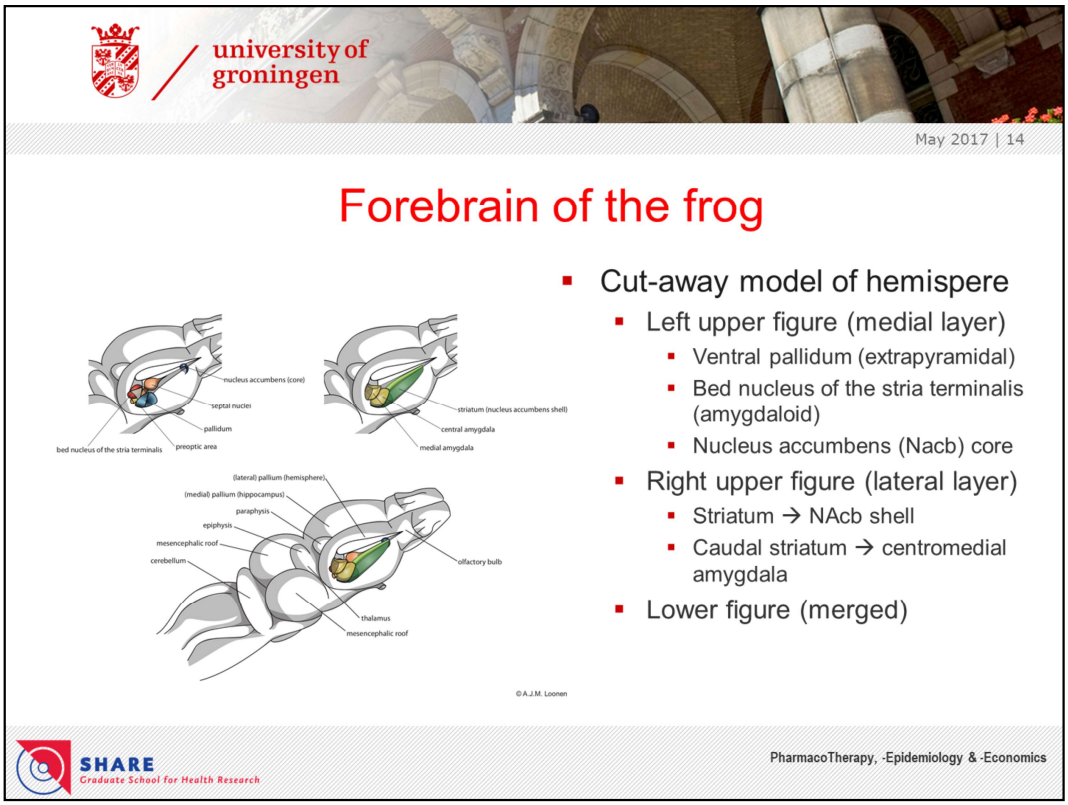
Looking at the lamprey brain, it is striking that the later cerebral hemisphere ('lateral pallium') is still very small, for example, compared to the olfactory bulb. Nevertheless, it contains a striatum, which has been shown to be part of a fairly modern extrapyramidal system (Grillner et al., 2013; doi: 10.1113/jphysiol.2012.246660; Robertson et al., 2014; doi: 10.1016/B978-0-444-63488-7.00016-1; Grillner and Robertson, 2016; doi: 10.1016/j.cub.2016.06.041). As is well known, the human extrapyramidal system corrects the speed and amplitude of movements initiated in the frontal cerebral cortex. However, lampreys lack the human cerebral cortex and movements are initiated by the striatum itself. The striatopallidal system of the lamprey activates motor centres in the lower hypothalamus and the upper brainstem. In the forebrain of the lamprey, in addition to the hemisphere, a relatively large 'medial pallium' is also seen that is coloured pink in the figure. From this piece of cortex-like tissue, the hippocampus will later develop.

Another important structure is a part of the animal's globus pallidus that is connected to the lateral part of the habenular complex (Stephenson-Jones et al., 2013; doi: 10.1073/pnas.1314815110). These habenula-projecting globus pallidus (GPh) neurons were found to be part of a separate circuit that evaluates the outcome of actions. The habenula is connected to the upper brainstem via the fasciculus retroflexus and regulates the activity of the monoaminergic centres in the midbrain. As in humans, dopaminergic terminals run from the midbrain to the striatum and stimulate motor activity.



In our overview of the evolutionary development, we will skip the cartilaginous and bony fishes, because the cerebral hemisphere developed differently in them. From lungfish, the amphibians were the first land animals to evolve. The brain of frogs can be considered to represent the brain of this developmental stage. In frogs, the hemisphere is considerably larger compared to the rest of the brain. However, these animals still lack a cerebral cortex like that found in humans. The corticoid tissue of these animals has a different organisation and has a different significance for behaviour. This tissue should therefore be considered the ancestor of the corticoid amygdalar complex and the limbic cortex of humans.

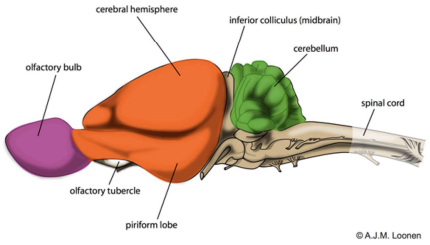
Another important finding was that the cerebral hemisphere of frogs and toads (Anura) contains both a striatum and a "centromedial" amygdala nucleus (Moreno and González, 2006; doi: 10.1016/j.pneurobio.2005.12.005). This can be interpreted as the first separation between the amygdaloid and the extrapyramidal striatopallidal system. However, the anura-striatum is still part of a limbic "extrapyramidal" system. In humans, this is reflected in the emotional part of the ventral extrapyramidal system. In mammals, this limbic connectivity is well preserved with projections from the corticoid amygdala and hippocampus to the shell of the nucleus accumbens (Heilbronner et al., 2016; doi: 10.1016/j.biopsych.2016.05.012).



That the frog's subpallium contains two separate striatopallidal systems is also illustrated in this open-cut model of the frog brain. In the upper right figure, the frog's striatum is shown in green, which will later develop into the shell part of the nucleus accumbens (NAcbS). In yellow, the central and medial nuclei of the amygdala are drawn. These correspond to the striatum of the lamprey and can therefore be considered the striatum part of the extended amygdala. On the left upper figure the more medially situated nuclei are drawn. The (blue) pallidum of the frog develops later into the ventral pallidum of humans and belongs to the ventral extrapyramidal system. An important discovery during the study of the embryological development of the basal ganglia of the anura was the finding that the bed nucleus of the stria terminalis (BST) and part of the septum are of pallidal rather than striatal origin (Moreno et al., 2012; doi: 10.1002/cne.22694; González et al., 2014; doi: 10.1159/000357754). This makes that the BST (red in the figure) can be understood as the pallidum part of the amygdaloid "extrapyramidal" division.

[This is also interesting because the BST is a suitable structure for the execution of the amygdaloid component of the habenula-projecting globus pallidus (GPh) of the lamprey. Indeed, in rats, medial and caudal regions of the lateral habenula receive significant input from the anteromedial zone (BSTamg), and even more extensively from the dorsomedial nucleus (BSTdm) of the anteromedial BST division (Dong and Swanson, 2006a,b: doi: 10.1002/cne.20790 and doi: 10.1002/cne.20788). However, it is still unclear whether this includes glutamatergic neurons in addition to GABAergic ones. In the ventral pallidum both GABAergic and glutamatergic neurons have been found with fibres running to the lateral habenula (Wulff et al., 2019; 10.1016/j.brainres.2018.10.010), but whether these correspond to GPh neurons of the lamprey is still unclear].

Forebrain of opossum



- Olfactory bulb
- Cerebral cortex
  - Cerebral hemisphere
  - Piriform lobe
- Colliculus (midbrain)
- Cerebellum

When we now look at the brain of an early mammal, represented by the opossum, we see a dramatic increase in both cerebral hemisphere and cerebellum. Mammals evolved from amphibian ancestors through a turtle-like intermediate stage. In the opossum, the forebrain is covered by a cerebral cortex (Wong and Kaas, 2009; doi: 10.1159/000225381). However, a separate temporal lobe is not yet present (Voogd et al. In: the central nervous system of vertebrates. Berlin; Heidelberg: Springer-Verlag, 1998;1637-2097). The amygdala, hippocampus, basal ganglia and thalamus are fully enveloped within this external covering of the forebrain.

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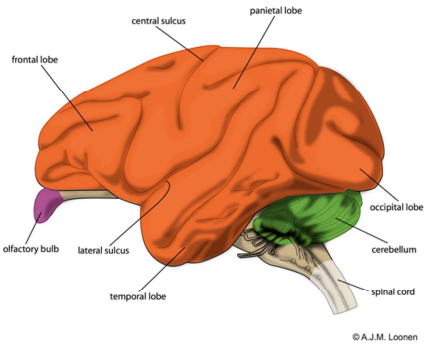
Forebrain of rhesus monkey



- Small olfactory bulb
- Cerebral cortex
  - Frontal lobe
  - Parietal lobe
  - Occipital lobe
  - Temporal lobe
- Cerebellum
- Small brainstem

The same applies to the brains of primates. Macaques are often studied here, as their brains are already very similar to those of humans. In these animals, the cerebral cortex can be divided into the same parts as in humans and the dorsal extrapyramidal system is almost as developed in them as in humans. We can therefore distinguish three divisions of the extrapyramidal system in them just as in humans: an amygdaloid, a ventral and a dorsal "extrapyramidal" system. The dorsal system regulates the intensity of motor activity and cognitions.

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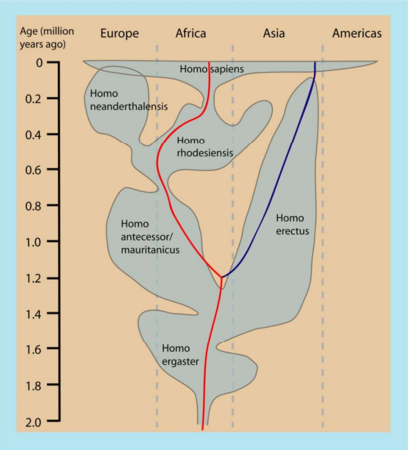
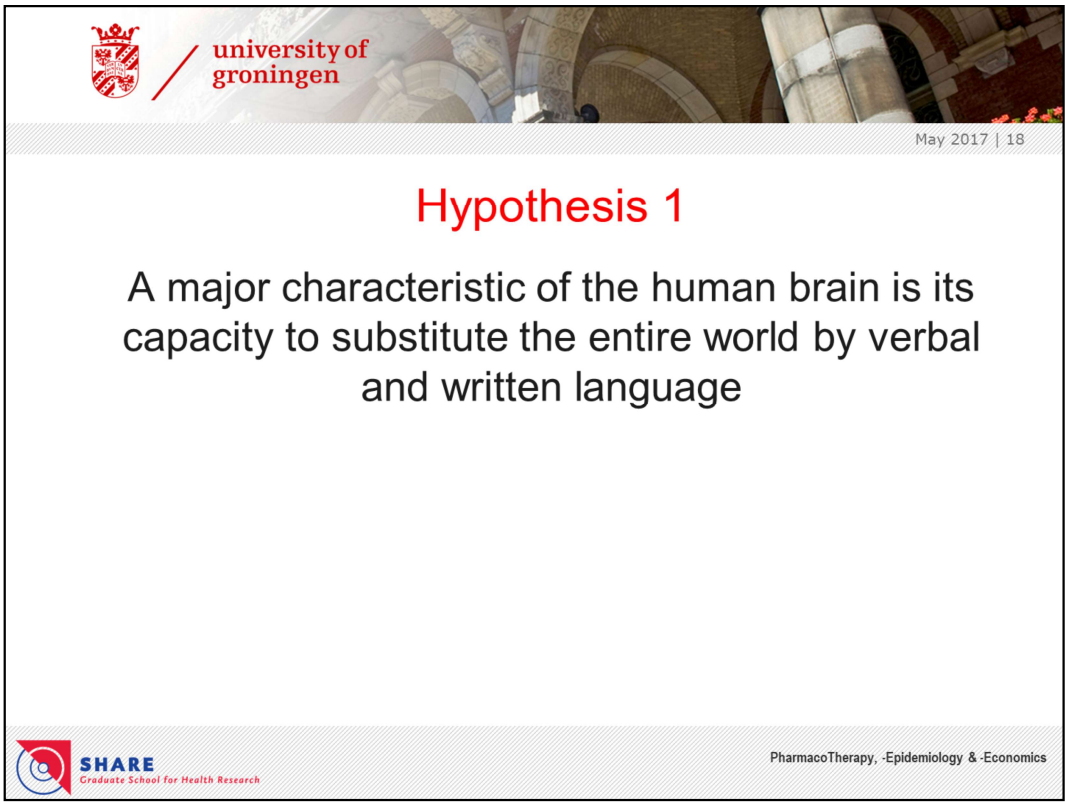
History of humans



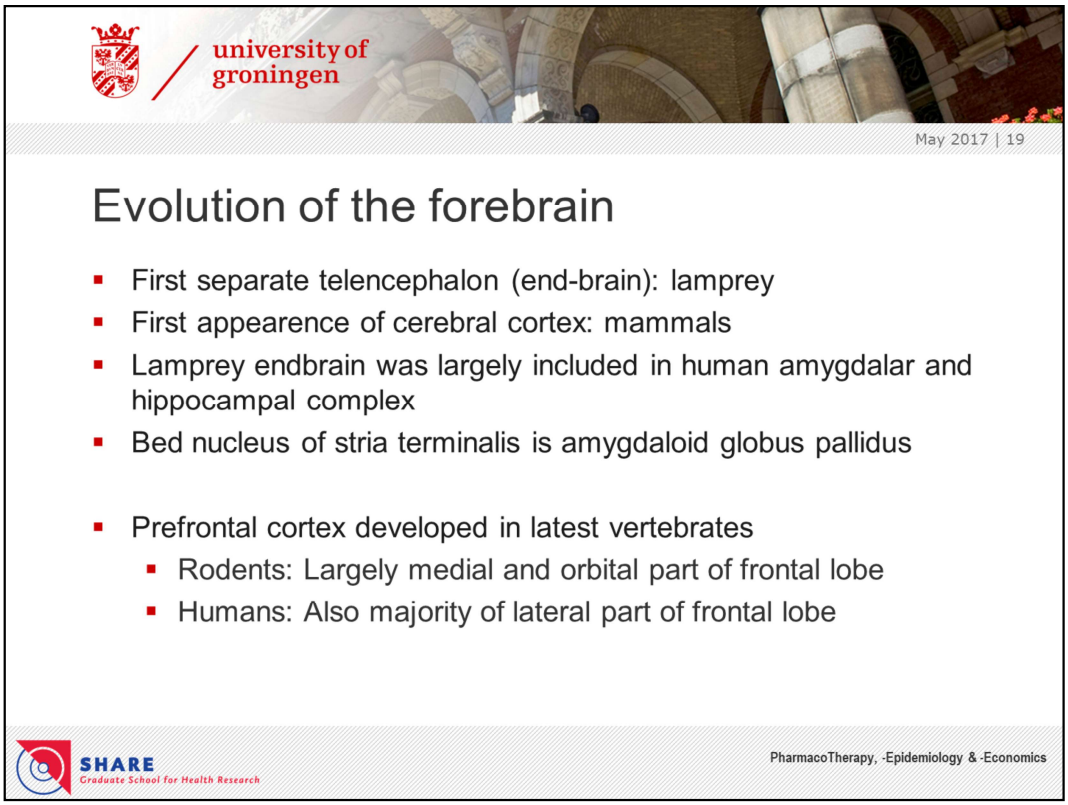
- Homo neanderthalensis: 380.000 – 32.000 ya (Africa, Europe, Siberia)
- Homo denisova: 100.000 - ?? ya (Siberia)
- Homo erectus: 1.000.000 - ?? Ya (Asia)

- Kenya, Africa: 195.000 ya
- Levant, Asia: 80.000 ya
- Indonesia: 60.000 ya
- Europe/Siberia: 40.000 ya
- America: 18.000 ya

But then the history of modern humans. This slide shows a largely outdated view that homo sapiens began with a small group of no more than 2,000 individuals somewhere in southern Kenya (McDougall et al., 2005; doi: 10.1038/nature03258). However, more recent information shows a more gradual evolution of the human globular brain over the last 500,000 to 50,000 years (Neubauer et al., 2018; doi: 10.1126/sciadv.aao5961). Other Homo species are much older, as can be seen. Neanderthals have vanished, but we cannot be sure that Homo denisova and Homo erectus have completely disappeared. Remains of Denisova human were found only a few years ago in the remote Denisova cave in the Altai Mountains of Siberia. Not much is known about this species or subspecies in the genus Homo. Much more is known about Homo erectus, or "upright man", which had a very long reign; the earliest fossil evidence dates back 1.9 million years and may go as far as 35,000 years. Contrary to what is shown on this slide, genetic data indicate a population split between modern humans on the one hand and Neandertals and Denisovans on the other more than 500,000 years ago (in Africa). However, Homo sapiens did spread around the world more effectively than any other hominin before him and was also able to at least eradicate Neanderthals. It is striking that the cultural evolution of man (art, fishing, animal domestication, agriculture, writing) has taken place entirely within a time frame of the last 40,000 years. This suggests that another change took place in the brains of humans, through which they acquired skills that are lacking in other apes.



This hypothesis is the first of five that will be given as an interlude during this talk. In my opinion, the sophisticated use of language is one of the most important characteristics of the human being. The ability to produce and perceive language is a property of the cerebral cortex. As human beings, we are able to hear and remember stories and produce fantasies. These brain products can be regarded as sensory input that does not come from the "real world". The processing of this input can result in verbal or written behaviour suitable for influencing other people. Moreover, this input causes pressure to perform and fear of failure; this is similar to the stress observed in more primitive animals. It may well be (and in my view probably is) the case that humans are not unique in the animal kingdom in having the ability to use language in such an advanced way. But the development of writing - the oldest known writing is the cuneiform script from Mesopotamia and is 5,000 - 10,000 years old - and the later use of writing for recording laws and regulations, for historiography and for transferring technical skills and knowledge in manuals, textbooks, journals and other publications did bring about an unprecedented cultural evolution.



To summarise the evolutionary development of the human brain: our earliest vertebrate ancestor had a brain similar to that of the present lamprey with a separate diencephalon (anatomical thalamus) and telencephalon (end-brain). In their direct ancestor, with a brain like that of the hagfish, these parts of the brain were still partly mixed up. The human cerebral cortex was missing in the brain until the first mammals. In birds and reptiles a different structure developed. In amphibians, almost the entire subpallidal end-brain of the oldest vertebrates is included in the amygdaloid complex. The medial pallium, from which the hippocampus later develops, is then included in the hemisphere. The amygdaloid system of humans consists of a corticoid and a striatopallidal part. The centromedial nucleus is homologous to the striatum and the bed nucleus of the stria terminalis is so to the globus pallidus of the lamprey. The prefrontal cortex, which is of great importance in determining behavioural output, is largely developed in the most recent mammals.

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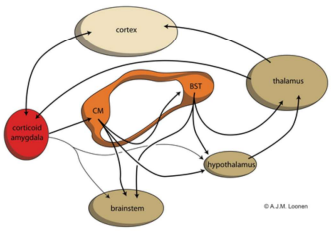
Amygdalar 'extrapyramidal' circuit



- Amygdaloid complex
  - Corticoid amygdala (red)
  - Extended amygdala (orange)
    - Striatal: centromedial nucleus (CM)
    - Pallidal: bed nucleus stria terminalis (BST)
- Thalamus → corticoid amygdala
- Hypothalamus→ thalamus →
  - Cortex → corticoid amygdala
  - Corticoid amygdala
- Hypothalamic output centres
- Brainstem output centres

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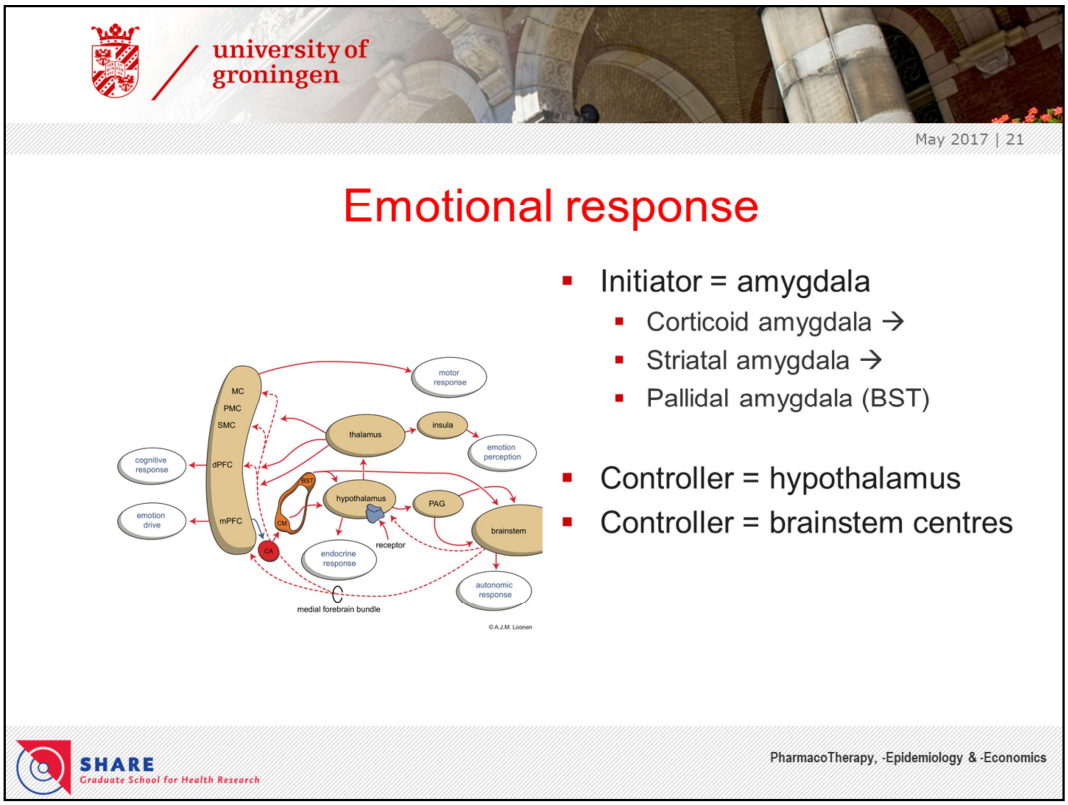
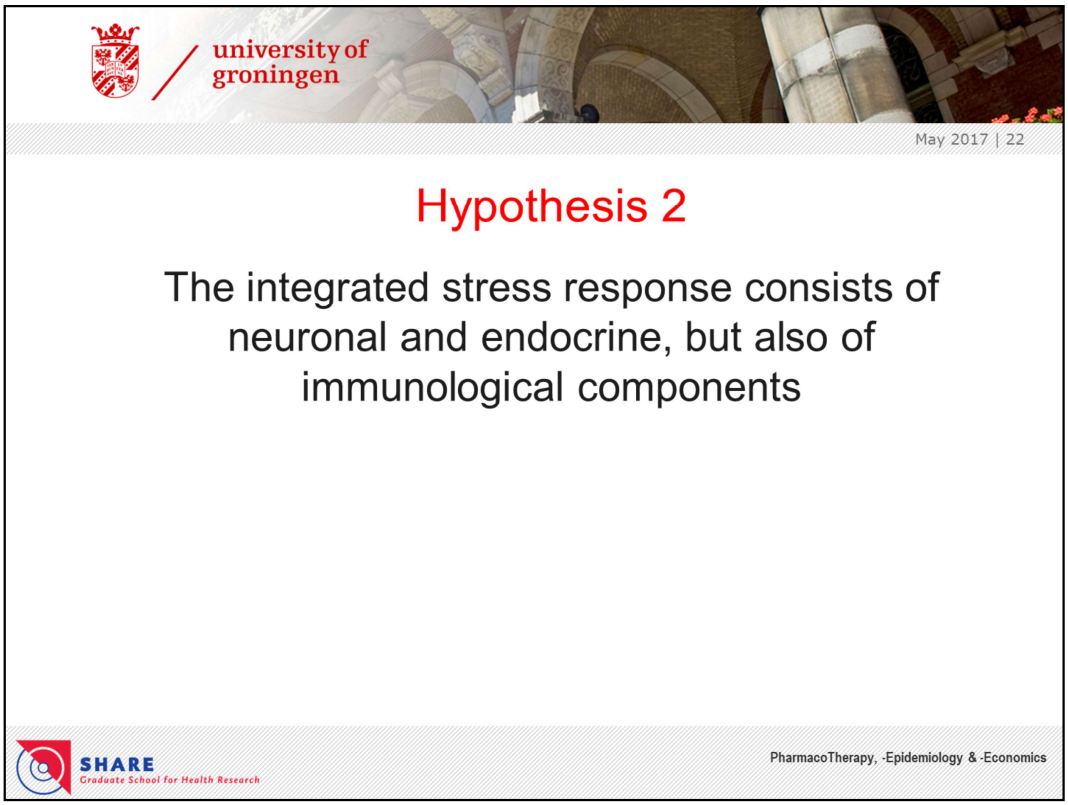
We propose that in the course of vertebrate evolution also an amygdalar extrapyramidal circuit has developed. The corresponding basal ganglia are represented by the so-called extended amygdala (Heimer and Van Hoesen, 2006; doi: 10.1016/j.neubiorev.2005.06.006): the central and medial amygdaloid nuclei, the bed nucleus of the stria terminalis (BST) and their connecting parts. [Note that the extended amygdala is defined differently by some authors]. Both the centromedial nucleus and the BST give output to brainstem centres and the hypothalamus, which probably corresponds to their organization in early vertebrates. What is new is that the BST also provides output to the thalamus as part of an extrapyramidal circuit that begins and ends in the corticoid amygdala. Later during the evolution of the forebrain, the hypothalamus became connected to the prefrontal forebrain. This connectivity may play a role in regulating the drive component of the emotional response (Sewards and Sewards, 2003; doi: 10.1016/s0361-9230(03)00069-8).



This form of organization should be kept in mind when interpreting the present diagram depicting the organization of the emotional response system (interpreted from Sewards and Sewards, 2003; doi: 10.1016/s0361-9230(03)00069-8). The emotional response is initiated by the amygdaloid complex: corticoid and extended amygdala. This explains why the corticoid part of the amygdala plays such an important role in selecting the sensory input vital for survival: representing (attentive) salience. It is likely that the motor centres in the midbrain lost their importance when the frontal cortex began to determine motor output. The dorsal thalamus developed in parallel with the cerebral cortex (see Butler, 1994a,b; doi: 10.1016/0165-0173(94)90003-5 and doi: 10.1016/0165-0173(94)90004-3) and probably the hypothalamic centers began to control motor output through their connectivity with the dorsal thalamus, largely taking over this role from the brainstem motor centers. In the human brain, the three components of the emotional response are largely controlled by the hypothalamus; the endocrine component by the hypothalamus itself, the autonomic component by connectivity with the brainstem, and the cortical component by connectivity with the dorsal thalamus. However, this simplification should not lead to ignoring the putative role of the BST.



A teleological explanation could be that in most animal species, the stress response is primarily activated in circumstances where the individual is at high risk of being physically traumatised. Due to the high burden of micro-organisms that can enter the body in these circumstances, activation of the immune system as part of the stress response would increase the chances of surviving this trauma. Therefore, activation of the immune response is a likely part of the integrated stress response that results in a good defence mechanism. More deontologically, the explanation could be that, in addition to the neuronal and endocrine, immunology is the third major operating system that determines behavioural output. It must therefore also be involved in the stress response. There is also much empirical evidence for this.

The starting point in creating our new theoretical framework to explain the pathogenesis of mental disorders was the recognition that two behavioural forces are essential for the maintenance of an individual's life and for the survival of the species: first motivation to seek to obtain essential nutrients and second motivation to seek to escape from potential threats. These behaviours are driven by the possibility of obtaining rewards and avoiding suffering, respectively. The nucleus accumbens plays a crucial role in regulating the intensity of these two behaviours. In all freely moving animals, these two forces must come into play and, if we limit ourselves to vertebrates, just as much in jawless fish as in apes and hominids.

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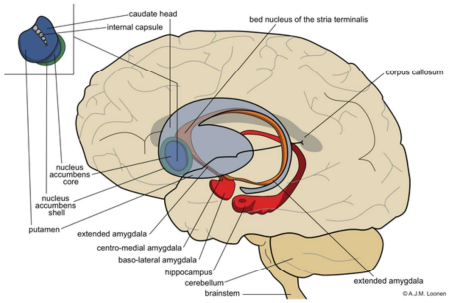
Dorsal and ventral striatum



- Dorsal striatum (light blue)
  - Caudate nucleus
  - Putamen
- Ventral striatum
  - Nucleus accumbens core (blue)
  - Nucleus accumbens shell (green)

This slide shows a transparent representation of the human brain. The temporal lobe contains the corticoid amygdala and the hippocampus (drawn in red). The hippocampus is connected via the fornix (also drawn in red) to the anterior thalamus, the septal nuclei and the mammillary bodies in the hypothalamus (not drawn). The extended amygdala is shown in orange. The part closest to the corticoid amygdala is the centromedial nucleus of the amygdala and the part near the nucleus accumbens is the bed nucleus of the stria terminalis. These two parts also belong to the extended amygdala. The dorsal striatum (shown in light blue) consists of the caudate nucleus and the putamen. The nucleus accumbens (what this slide is actually about) is stuck to this on the ventral forehead side pointing to the midline (see the insert). The nucleus accumbens comprises the ventral fraction of the striatum and consists of core section enveloped by a shell part. As can be seen on this slide, it is localised at the ventromedial border of the dorsal striatum and aligns with the bed nucleus of the stria terminalis on the other side.

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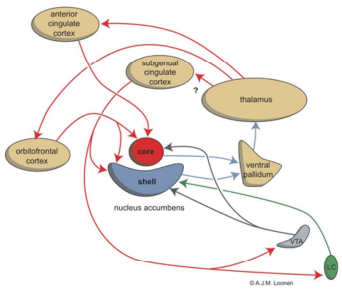
Ventral extrapyramidal re-entry circuits



- Motivating reward-seeking behaviour
  - Accumbens core (red)
  - Successful → pleasure
- Motivating misery-fleeing behaviour
  - Accumbens shell (blue)
  - Successful → happiness

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We have developed a model in which the motivation to engage in reward-driven or distress-avoiding behaviour corresponds to the activity within two cortical-striatal-pallidal-thalamic-cortical re-entry circuits that include the nucleus accumbens core (in red) or shell (in blue), respectively (Loonen and Ivanova, 2006; doi: 10.1016/j.mehy.2015.12.013). As shown on this slide, these re-entry circuits begin and end within the anterior (Brodmann Area 24) or subgenual (BA25) part of the cingulate cortex. [Note: this is of course a simplification: in reality a band runs from the ventroanterior part of the cingulate cortex via the subgenual part to the anterior insular cortex and the circuits are also much less clearly divided over the core and shell parts of the accumbens nucleus]. The activity within these two circuits depends on the activity of dopaminergic, serotonergic and partly adrenergic fibres that originate in the midbrain. The activity of these ascending monoaminergic pathways is originally regulated by the habenula.

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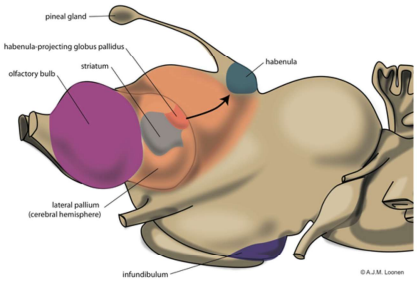
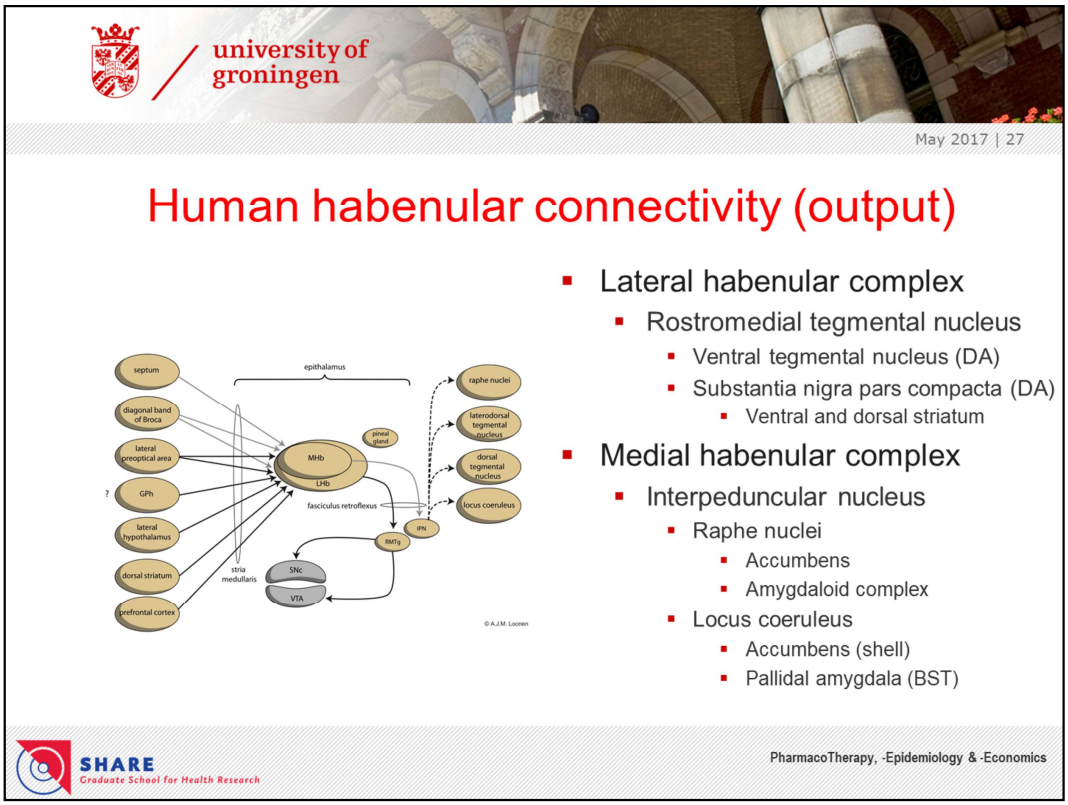
Function of lamprey GPh



- Lamprey extrapyramidal system
  - Pallium → striatum
  - Striatum → pallidum
  - Pallidum → brainstem motor centres
- Lamprey GPh system
  - Pallium → GPh
  - Striatum → GPh
    - GPh → LHb → RMTg → VTA → striatum
- Evaluation reward-driven behaviour
  - Behaviour successful → continue
  - Behaviour unsuccessful → abandon

In lampreys, motor activity is regulated by an "extrapyramidal system" that is very similar to the human extrapyramidal system. However, in lampreys movements are initiated by the striatum instead of the - still missing - cerebral cortex. The cortex-like pallium provides sensory input to the striatum, but does not initiate movements. Moreover, output from the striatopallidal system goes to motor centres in the hypothalamus and brainstem. In these primitive vertebrates, the activity of the extrapyramidal system is also regulated by monoaminergic centres in the upper brainstem, similar to the situation in humans. Dopaminergic centres thus increase the motor activity of the animal by stimulating the striatum. In turn, the activity of these monoaminergic centres in the midbrain depends on the activity of the lateral and medial habenula. In lampreys, the habenula-projecting nucleus of the globus pallidus inhibits the behaviour when it is evaluated and appears to be unsuccessful, whereas the behaviour is facilitated by disinhibition of the dopaminergic centres when it is effective.



The habenula output is well conserved across species during evolution (Batalla et al., 2017; doi: 10.1016/j.neubiorev.2017.03.019). This is shown in the right side of this scheme (an adaptation of a figure of Hikosaka, 2010; doi: 10.1038/nrn2866). The habenular nuclei are paired structures consisting of a large lateral (LHb) and a small medial (MHb) division, each of which consists of a complex set of subregions and subnuclei. Information processed by the LHb and the MHb is transmitted via the axon bundle of the fasciculus retroflexus to monoaminergic nuclei in the midbrain, such as the dopaminergic ventral tegmental area and the substantia nigra pars compacta, and the serotonergic raphe nuclei. The fasciculus retroflexus is divided into two regions: the outer region originates in the LHb and projects mainly to the rostromedial tegmental nucleus (RMTg), in addition to numerous monoaminergic nuclei in the mid- and hindbrain. The rostromedial tegmental nucleus, which is also called the "tail" of the ventral tegmental area, is a small nucleus that contains mainly inhibitory GABAergic cells and therefore regulates the activity of the ventral tegmental area/substantia nigra pars compacta and the dorsal raphe nucleus. LHb neurons also directly target the dopaminergic ventral tegmental area and substantia nigra pars compacta itself (also targeting GABAergic interneurons there), as well as the serotonergic median and dorsal raphe nucleus, the cholinergic laterodorsal tegmentum, and the noradrenergic locus coeruleus. The MHb sends almost all of its output to the predominantly GABAergic (and peptidergic) interpeduncular nucleus and from there to various brainstem nuclei.

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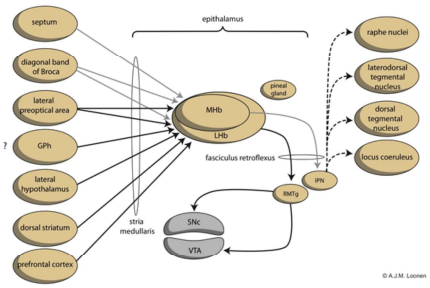
Human habenular connectivity (input)



- Medial habenular complex
  - Septal area
- Lateral habenular complex
  - Prefrontal cortex
  - Striatum
  - Pallidum (GPh)
    - Border globus pallidus (GPb)
    - Ventral pallidum (VPh)
    - Bed nucleus stria terminalis (BSTh)
  - Hypothalamus

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The input to the habenula is much less easy to summarise. In the course of evolution the composition of the forebrain has changed radically and this has had consequences for the connectivity with the habenular complex. In the left part of the diagram some of the input areas are named [Note: The input to this diagram from 2010 is now largely obsolete]. The input reaches the habenula via the stria medullaris. The MHb receives input primarily from the bed nucleus of the anterior commissure and the triangular nucleus, both in the posterior septum (Aizawa and Zhu, 2019; doi: 10.1111/pcn.12892). Most of the input to the lateral habenula comes from a LPO-LHT continuum of nuclei that extends from the lateral preoptical to the lateral hypothalamic region and probably includes the ventral pallidum and the bed nucleus of the stria terminalis (Zahm and Root, 2017; doi: 10.1016/j.pbb.2017.06.004). In addition, moderate LHb input comes from the mesial prefrontal cortex, the globus pallidus interna and the upper part of the brainstem.

[Note 1: The area of the mesial prefrontal cortex refers to the same band that extends from the anterior part (BA24) of the Cingulate cortex and then through the subgenual part (BA25) to the anterior insular cortex as that mentioned on slide 25 as the beginning and end point of the extrapyramidal re-entry circuits via the nucleus accumbens].

[Note 2: The lateral habenula also receives glutamatergic input from the habenula-projecting globus pallidus (GPh), which in humans is represented by the border region of the globus pallidus (GPb), an area within the ventral pallidum (possibly VPh) and even more hypothetically by the habenula-projecting part of the bed nucleus of the stria terminalis (BSTh). Evidence regarding a GPh function of GPb neurons has been provided in mice (Stephenson-Jones et al., 2016; doi: 10.1038/nature19845), but whether the glutamatergic habenula-projecting neurons of the ventral pallidum (Wulff et al., 2019; doi: 10.1016/j.brainres.2018.10.010) are homologues to lamprey GPh remains to be proven].

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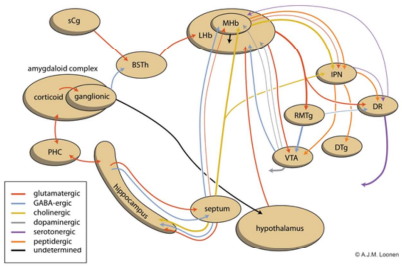
Amygdalo/hippocampal – habenular connection



- Lateral habenula
  - Corticoid amygdala
  - Nuclear amygdala
  - Bed nucleus stria terminalis (BST)
    - Hypothalamus and (possibly) BSTh
  - *Reward-driven behaviour*
- Medial habenula
  - Corticoid amygdala
  - Hippocampus
  - Posterior septal area
    - *Misery-avoiding behaviour*

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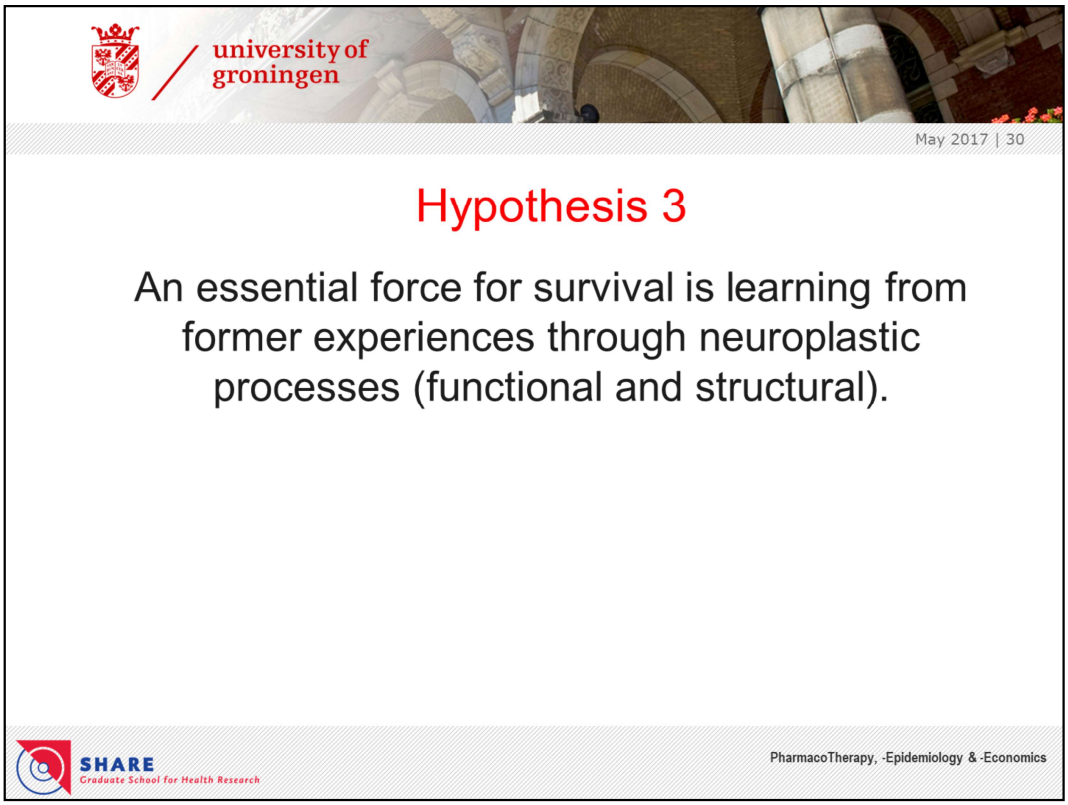
This slide provides a possible neuroanatomical framework for the involvement of the habenula in the regulation of the emotional behavioural response. This is a sketch with many loose ends: the existence of some of the connections mentioned has yet to be established. It is likely that the corticoid amygdala is connected to the MHb via the hippocampus, the fornix and the posterior septal nuclei. The LHb receives input from the corticoid amygdala via the extended amygdala and the LPO-LHT continuum of the previous slide. Hypothetically, the lateral habenula is also influenced by a habenula projecting part of the bed nucleus of the stria terminalis (BSTh). This BSTh (if it exists) is expected to receive input from the striatal part of the extended amygdala (CM, centromedial nucleus). Whether this BSTh also receives input directly from the subgenual Cingulate cortex (sCg) as indicated in the figure remains to be seen.

The essence of our proposal on this slide is that the amygdala is connected to the habenula in two ways. First, via the hippocampus and the posterior septal nuclei with the MHb. This route influences the intensity of distress avoidance behaviour. Second, through the (still hypothetical) BSTh connection with the LHb, and through this route reward-oriented behaviour is modulated. In addition, extensive connections exist from the amygdala to the LHb via the LPO-LHT continuum.

[Note: connections of the IPN with the other brainstem nuclei have not yet been elaborated in this scheme (see Metzger et al., 2021; doi: 10.1111/ejn.14647)]



The statement of this slide can hardly be considered a hypothesis. It is clear that we learn from past experiences by changing the excitability of neuronal connections. This kind of neuroplasticity is induced, for example, by long-term potentiation (LTP) at glutamatergic synapses or the influence of certain neurotrophic factors such as brain-derived neurotrophic factor (BDNF). The same applies, of course, to natural defence mechanisms involving the immune system. Immunological memory is an essential component of adaptive immune defence against viruses and other pathogenic entities. A combination of the two is found in the connection of innate immunity with neuroplastic changes. Cytokines contribute to the behavioural immune response by modifying the structure and activity of neuronal circuits. Finally, we would like to point out the role of microglia in the embryological development and regulation of neuroplastic changes in the adult brain. Microglia represent the immune system within the blood-brain barrier. The importance of the memory function in amygdala and hippocampus in the development of fear and anxiety is widely recognised. Immune factors also play an essential role in the responsible neuroplastic changes.

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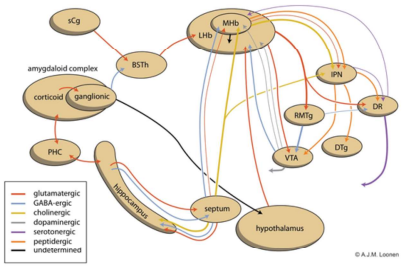
But what is the role of the habenula in anxiety?



- Lateral habenula
  - Corticoid amygdala
  - Nuclear amygdala
  - Bed nucleus stria terminalis (BST)
    - Hypothalamus and (possibly) BSTh
  - *Reward-driven behaviour*
- Medial habenula
  - Corticoid amygdala
  - Hippocampus
  - Posterior septal area
    - *Misery-avoiding behaviour*

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Looking through the various mechanisms of the last slides, one can conclude that the involvement of the dorsal diencephalic connection system (DDCS) in the development of anxiety and fear is possible, but also somewhat artificial and to a large extent too hypothetical to accept just like that. The scientific literature also speaks rather easily of anxiety, whereas it may be more about a more fundamental feeling of uneasiness such as occurs in depression and addiction. Depression and addiction are often accompanied by symptoms of anxiety and it is perhaps in this area that the DDCS plays a particular role. This could be more bottom-up by activating brainstem centres that in turn activate the amygdala and the septo-hippocampal system (SHS). Another role might be inhibition of reward-oriented behaviour, when a targeted fear response is preferable. Importantly, the MHb has a strong activating influence on the LHb and the LHb inhibits the activity of midbrain centres inducing more intense reward-seeking behaviour.

More philosophically, the idea is that fear may be more 'modern' than the feeling of discomfort in which the DDCS plays an important role. Older vertebrates, such as bony fish, naturally show an escape response to threat, but whether this is the same as a human fear response (as in human anxiety disorders) remains to be seen. It is suspected that the latter requires a relatively well-developed brain in which the amygdala and hippocampus have been upgraded by the development of the cerebral cortex in mammals and the ventricular ridge in reptiles and birds.

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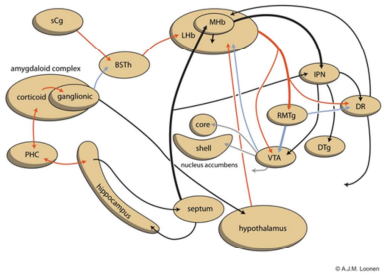
Overview



- Amygdaloid complex
  - Primitive forebrain
    - Corticoid part = pallium
    - Extended part = striatopallidum
    - Hypothetical BSTh = GPh
  - Corticoid amygdala
    - Salience
    - Initiating stress response
  - Extended amygdala
    - Decision making
    - Executing stress response
- Hippocampal complex
  - Contextual memory

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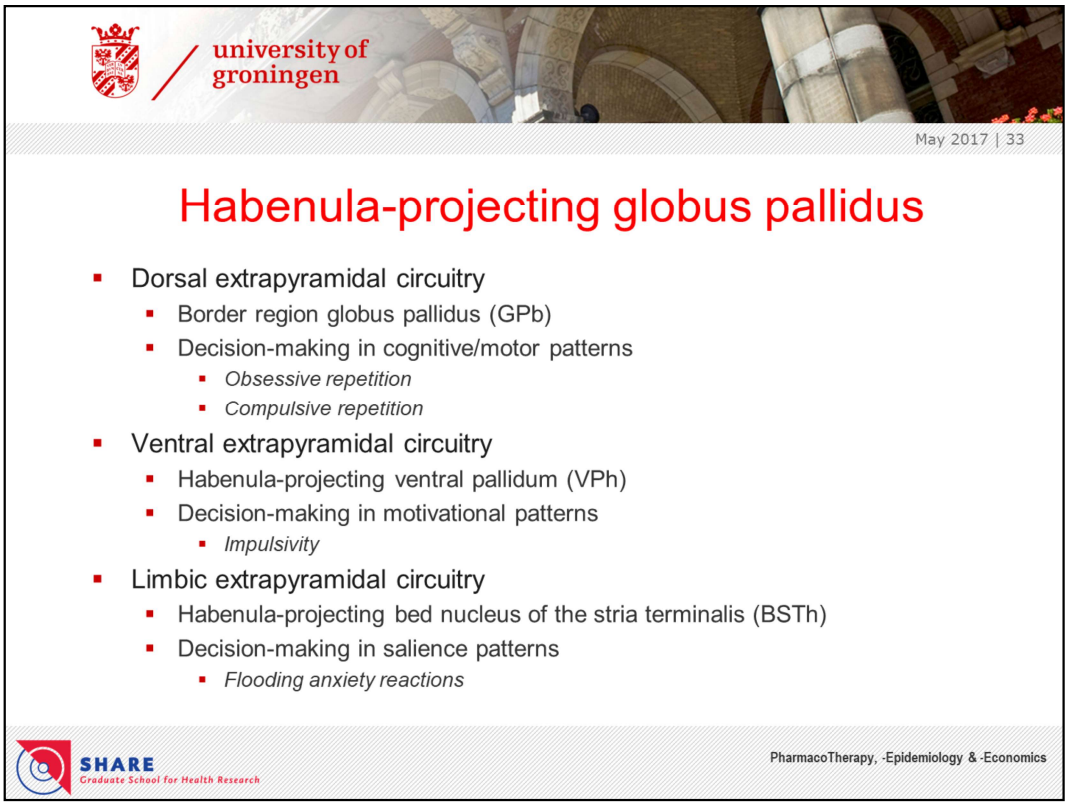
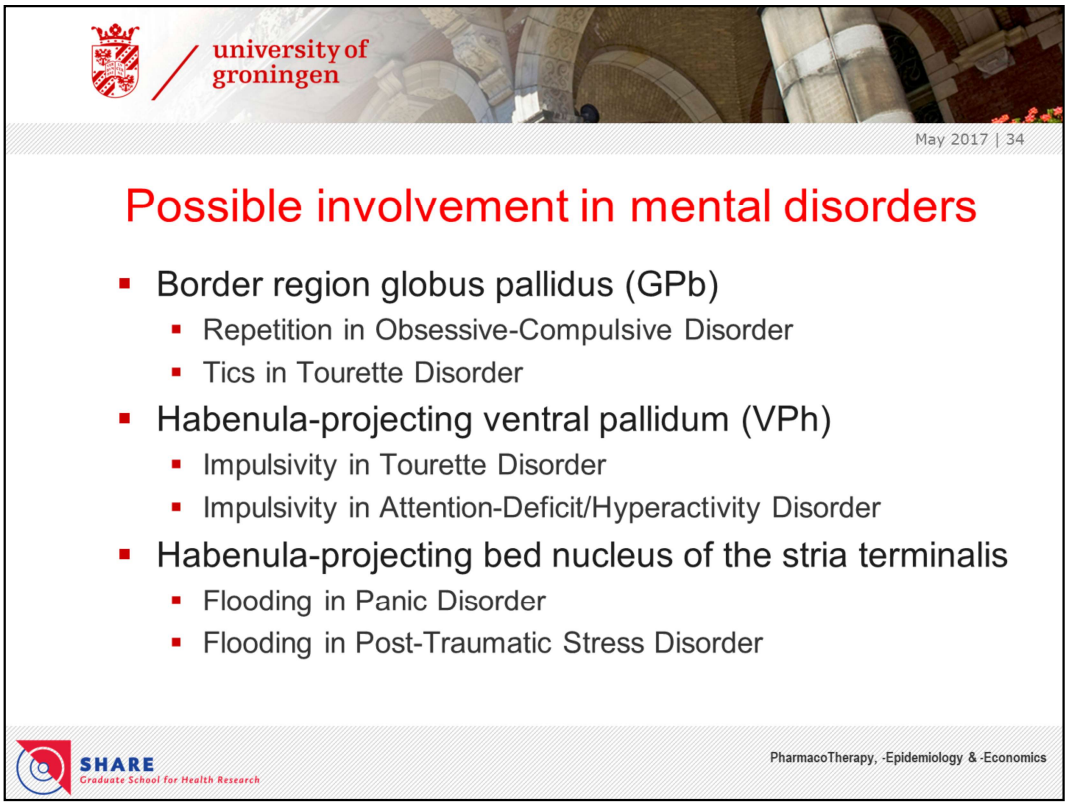
Now let's go back to the scheme and look at the rest of the picture. The amygdaloid and hippocampal complexes correspond to the forebrain of our earliest vertebrate ancestors. A large part of their cortex-like pallium became the corticoid amygdala and their subpallium, or striatopallidum, became the extended amygdala. Their medial pallium gave rise to the hippocampus. Considering this evolutionary origin is also useful to explain the function of these structures. The corticoid amygdala is involved in noticing the most relevant input signals to respond to, which corresponds to (attentive) salience. The hippocampus compares current input signals with past experiences, leading to contextual memory. Interactions within a septo-hippocampal regulatory system of the medial septum and the hippocampus (the SHS that usually gives output through the subiculum) initiate a range of behavioural processes elsewhere in the brain, such as curiosity and also various aspects of learning and memory (McNaughton, 2006; doi:10.1016/j.bbr.2006.05.037). These include various components of anxiety and fear.

The amygdaloid complex initiates the composite stress response by acting on the regulators of this response in the hypothalamus and the brainstem (see diagram on slide 21). The intensity of the stress response is regulated by influencing the medial habenula via the hippocampus and the posterior septal region, and the lateral habenula via the hypothalamus and (still hypothetical) the BSTh. The habenula regulates the activity of monoaminergic centres of the midbrain. These in turn regulate the activity of a limbic circuit that controls the intensity of the stress response.

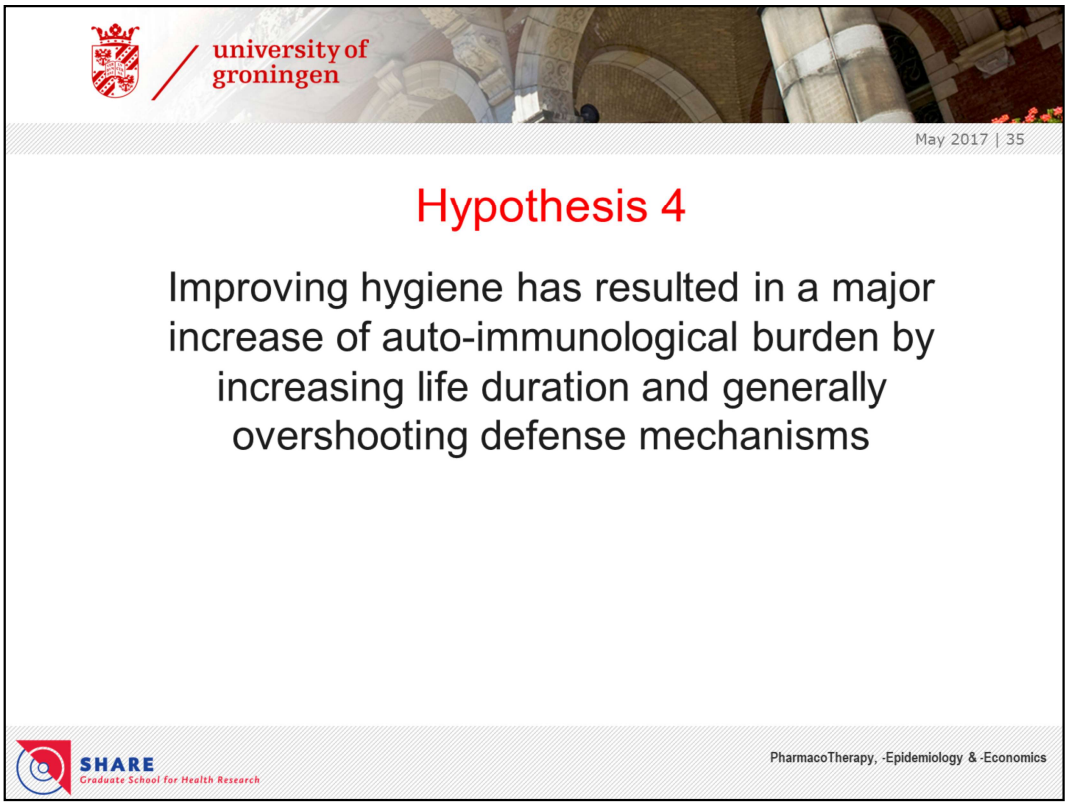
[Note that the composite stress response is of a much more fundamental level than the neuropsychological fear response and plays a role in various mental disorders].



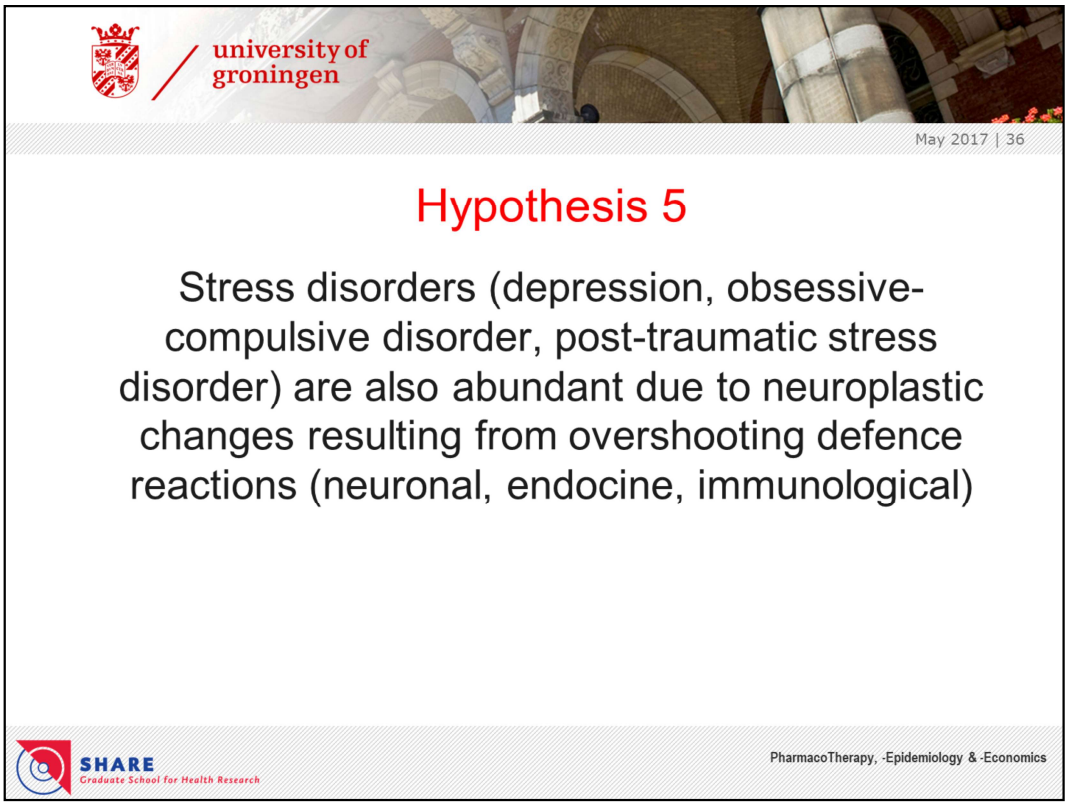
Clearly, we would like to speculate on a possible role of the human successor of the habenula-projecting globus pallidus (GPh). In our earliest vertebrate ancestors, the GPh was probably a single nuclear structure, receiving input from the striatum and pallium. We would like to hypothesize that in humans, three more diffuse structures may correspond to this GPh, which correspond to the dorsal, ventral and amygdaloid extrapyramidal circuits, respectively: a. the border region of the globus pallidus (GPb), b. the habenula-projecting ventral pallidum (VPh) and c. the habenula-projecting part of the bed nucleus of the stria terminalis (BSTh). If these three structures are still involved in decision-making in humans, they could be related to obsessive-compulsive repetition, impulsivity and flooding reactions, respectively. However, we would like to emphasise that this is still entirely speculative. Primate studies on this subject and high-resolution human MRI studies comparing patients with control subjects may resolve this uncertainty.



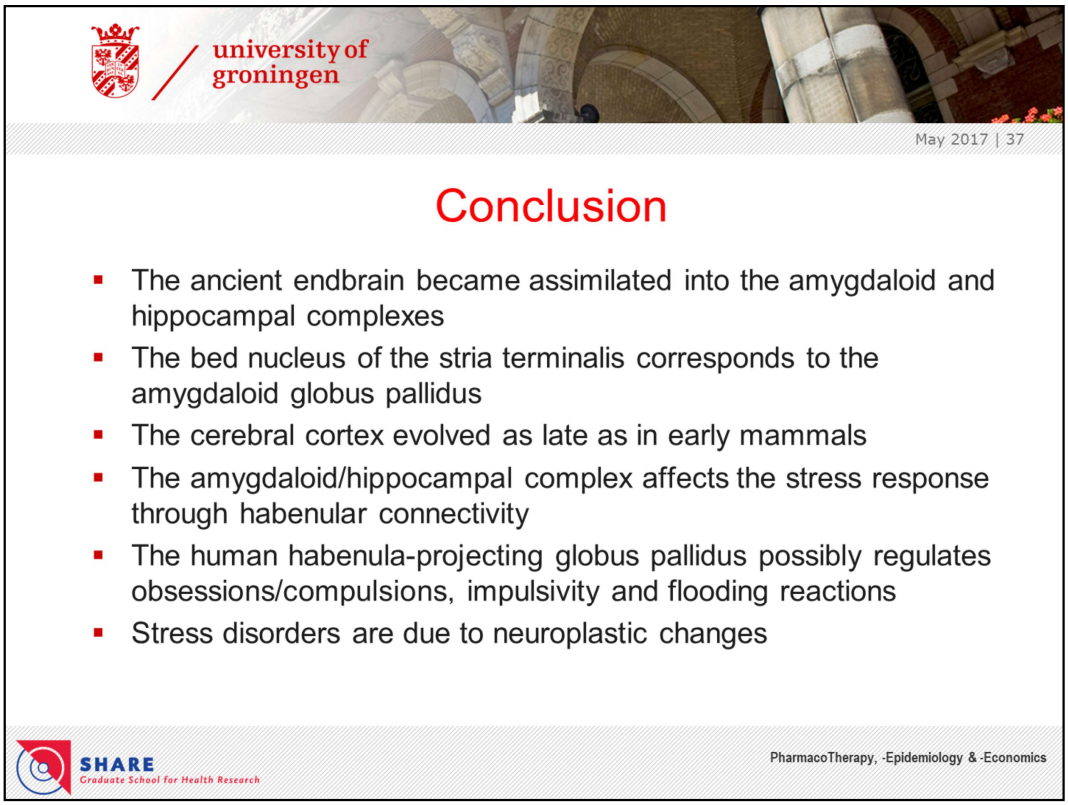
Despite this uncertainty, we believe that the successor to the habenula-projecting globus pallidus (GPh) of the first vertebrates may be associated with specific symptoms of certain anxiety disorders: the GPb in the dorsal striatopallidum may be associated with obsessive-compulsive disorder, the VPh in the ventral striatopallidum with Tourette's syndrome and attention deficit hyperactivity disorder, and the BSTh with panic disorder and post-traumatic stress disorder. How this matches up with other theories on the pathogenesis of these disorders remains to be determined.



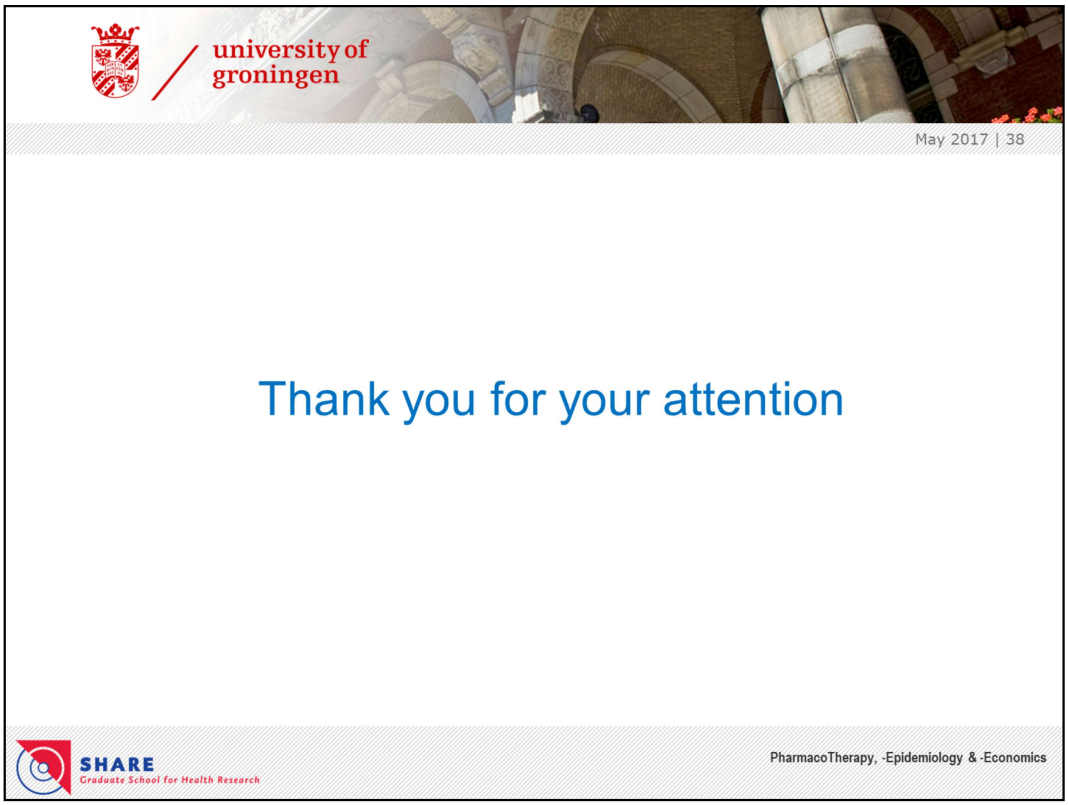
The fourth hypothesis is supported by evidence presented in our review article on the mechanisms of depression (Loonen and Ivanova, 2016; doi: 10.3389/fnhum.2016.00571). Up to and including the Middle Ages, life expectancy after birth was about 25 years (Bocquet-Appel and Bacro, 1997; doi: 10.1002/(SICI)1096-8644(199704)102:4<569::AID-AJPA11>3.0.CO;2-Z; Eshed et al., 2004; doi: 10.1002/(SICI)1096-8644(199704)102:4<569::AID-AJPA11>3.0.CO;2-Z; Nagaoka et al., 2006; doi: 10.1002/ajpa.20402), and this increased until 45 years after 1900 AD (Mackenbach and Looman, 2013; doi: 10.1093/ije/dyt122). Most people at that time probably died of infectious diseases because people lived in very unhygienic conditions (Miller and Raison, 2015; doi: 10.1038/nri.2015.5). Therefore, in order to survive as individuals and as a species, humans needed a very good immune system. Today, the conditions are completely different. In the absence of an abundance of dirt, bacteria and fungi, the immune system can attack common proteins and other macromolecules that can cause allergies and autoimmune diseases. Therefore, it is possible that our immune system is currently overreacting and may even be causing more diseases than it is fighting.



The second part of this theory states that overshooting neuronal, endocrine and immunological immune responses may be partly responsible for the aberrant neuroplastic changes that cause mental stress disorders, such as obsessive-compulsive and post-traumatic stress disorder. It is likely that these and other mood and anxiety disorders are so prevalent today, at least in part, due to the strain of our particularly over-hygienic and over-long-term health lifestyle.



When we try to summarise the data of this presentation, it can be concluded that considering the evolution of the human forebrain, the forebrain of our earliest vertebrate ancestors was likely assimilated into the human amygdaloid and hippocampal complexes. The bed nucleus of the stria terminalis corresponds to the amygdaloid globus pallidus. The cerebral cortex evolved rather late and is therefore not essential for regulating the human stress response, but may be essential for the human complex neuropsychological anxiety response. It may be thought that the amygdaloid/hippocampal complex regulates the stress response and influences its intensity via habenular connectivity. It can be postulated that the human habenula projecting globus pallidus may be responsible for inducing obsessions/compulsions, impulsivity and overwhelm reactions in anxiety disorders. Very important for the pathogenesis of the emotional disorders may be aberrant neuroplastic changes due to overactive defence mechanisms.



This 2017 presentation was extensively edited in April 2022. Thank you for reading and I welcome your comments.