Chapter 6

Circuits Regulating Pleasure and Happiness in Schizophrenia: The Neurobiological Mechanism of Delusions

Anton J.M. Loonen and Svetlana A. Ivanova

Additional information is available at the end of the chapter

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Abstract

A recently developed model describes how evolutionary old neuronal systems allow free-moving animals, including humans, to escape from threats and discomfort and to acquire sufficient necessities to maintain life and to continue as a species. The amygdala has an essential role in regulating these fundamental reward-seeking and misery-fleeing behaviours. This is probably related to the ancient character of the corticoid and ganglionic parts of the amygdaloid complex. During evolution almost the entire ventral and lateral pallium (cortex) of the first vertebrates went up into the superficial and deep amygdalar nuclei, and their entire striatum and pallidum went up into the extended amygdala. An important role of the amygdala is selecting the sensory cues which are relevant for reward-seeking and misery-fleeing behaviour and should be paid attention to in order to increase the animal's chances. This corresponds to attentive salience. Disturbances of this process in humans may lead to delusions. It has been suggested that in patients with schizophrenia this aberrant salience results from dopaminergic hyperactivity. The authors of this chapter believe that aberrant salience can result from dysfunctions everywhere within the chain: neocortex, corticoid amygdala, hippocampal complex, medial septum, medial habenula, midbrain nuclei and ventral tegmental area.

Keywords: amygdala, hippocampus, habenula, salience, delusions, subcortical network

1. Introduction

Two basic principles of animal life are essential for survival of the individual and as a species. Firstly, the animal should be motivated to obtain food, warmth, sexual gratification and

comfort. Secondly, the animal should be motivated to escape from predators, cold, sexual competitors and other forms of adversity. To survive as an individual and a species, even our oldest ocean-dwelling ancestors living over 560 million years ago must have been able to react to the environment to feed, evade predators, defend territory and reproduce. Hence, their primitive nervous systems must have regulated the necessary behaviours and incorporated the most essential structures of all today's freely moving Animalia. However, since then the human brain passed through a long evolutionary pathway during which particularly the forebrain showed major changes. The earliest vertebrate brain almost completely lacked the forerunner of the human neocortex and the dorsal parts of the basal ganglia [1, 2]. These newer parts of the brain are believed to determine human behaviour to a high degree and consequently receive most attention in research of processes explaining the genesis of mental disorders (see, e.g. Ref. [3]). This contrasts the involvement in psychic disorders of those behavioural processes described above as also being displayed by the most primitive vertebrates. We want to suggest that these actions are still regulated in humans by brain structures derived from the primitive forebrain of the earliest vertebrates. Therefore, we described the anatomy of the forebrain of the earliest human vertebrate ancestors, which is believed to be comparable with the brain of lampreys [2]. From a comparison of the striatum of lampreys to that of anuran amphibians and younger vertebrates, it can be concluded that the striatum of lampreys is the forerunner of the human nuclear amygdala [4]. In anuran amphibians (frogs and toads), the lamprey's striatum is retrieved as central and medial amygdaloid nuclei, while a later ventral striatum for the first time appears in its direct vicinity [2, 4]. The lamprey's forebrain also contains a structure of which the connections are very well conserved in more recent human ancestors: the habenula. The habenula constitutes—together with the stria medullaris and pineal gland—the epithalamus and consists of medial and lateral parts [5]. The habenula regulates the intensity of reward-seeking and misery-fleeing behaviour probably in all our vertebrate ancestors. In lampreys the activity of the habenula is in turn regulated by a specific structure: the habenula-projecting globus pallidus. It is tempting to speculate that this structure has a similar role in humans, but a clear anatomical human equivalent with the same function has not yet been identified. Based upon the evolution of the basal ganglia in vertebrates and the mechanism of the emotional response, we postulate the existence of two systems regulating the intensity of the aforementioned behaviours [6, 7]. These two circuits include the activities of extrapyramidal and limbic basal ganglia and are collaborating in a yin-and-yang-like fashion. The two basal ganglia systems are linked together by the core and shell parts of the nucleus accumbens (NAcb), which regulates motivation to show reward-seeking and misery-fleeing behaviour, respectively.

The amygdala is believed to address the ability of learning to value sensory information (attentive salience). This capacity is essential to determine which sensory information is of vital importance to react on with reward-seeking or misery-fleeing behaviour. Aberrant salience is believed to be a crucial component of the mechanism of (schizophrenic) psychosis and the antipsychotic effects of dopamine antagonists [8]. We believe that the amygdala regulates the behavioural output by affecting the connection of the ancient forebrain (amygdala, hippocampus) with the monoaminergic centres of the midbrain through the

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medial and lateral habenula. Therefore, we will describe the evolution of the amygdaloid complex and its final anatomy and functioning. Subsequently, we will integrate these findings with our model of neuronal circuits regulating pleasure and happiness and give an explanation how the connection between amygdala and habenula is involved regulating these behaviours.

2. Evolution of the amygdaloid complex in vertebrates

An important reason for us to become interested in the embryology, connectivity and neuroanatomy of primitive vertebrates is the scientific notion that their primitive brains may reflect earlier evolutionary stages of the current human brain. Hence, the brains of lampreys, sharks, lungfishes, frogs, turtles, opossums, rats and monkeys correspond to the brains of human ancestors from about 560 million years ago until now [9]. The very first vertebrate is supposed to be an animal comparable with modern lamprey [2]. This animal has a head containing a brain and it has vertebrates, but not yet a lower jaw. The lamprey forebrain consists of olfactory bulbs, medial and lateral pallium, subpallium and diencephalon (extensive thalamus). The lateral pallium already forms a primitive hemisphere (**Figure 1**). However, some controversy exists how to divide it into different fields. The question emerges whether the lamprey has a dorsal pallium, a structure which gives rise to the majority of the neocortex in mammals. We have concluded that our earliest vertebrate ancestor (comparable with lamprey) must already have had a dorsal pallium, but it functions as an extension of the medial pallium. Lamprey medial pallium is considered to give rise to the hippocampal complex in tetrapods [10]. The ventral pallium which appears to be present in all vertebrates, but also in hagfishes, is related to olfactory structures. It is included as part of the amygdala in tetrapods [10].

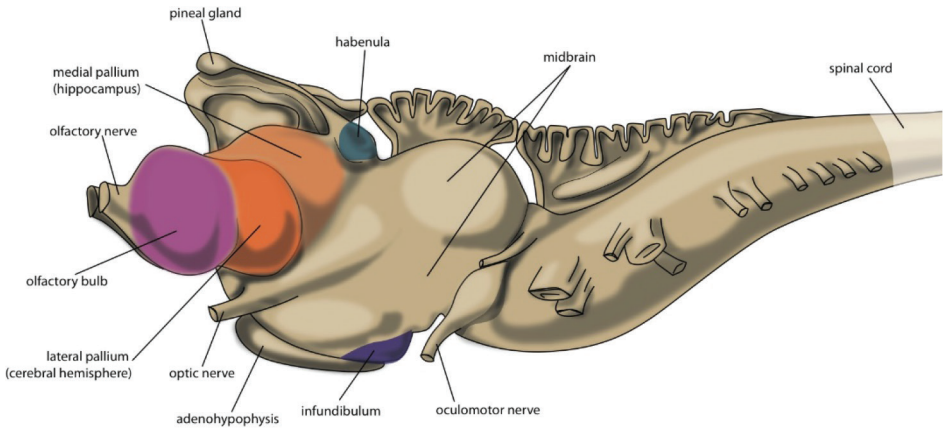

Figure 1. Central nervous system of lamprey.

2.1. Evolution of the cerebral cortex

Studying the development of the human cerebral cortex during subsequent steps of evolution brings a few typical problems. Firstly, in reptiles and birds, the neocortex developed in another direction than in mammals [10]. Secondly, a large part of the cerebral cortex in mammals is laminated (organised in three or six different layers), while the pallium in non-mammals is primary organised in a non-laminar fashion. However, by integrating comparative neuroanatomy with comparative embryology and developmental genetics, a clear picture can be created on the evolutionary development of human cerebral cortex [10–12].

In human embryos the future insula is the first 'neo'cortical structure to develop [13, 14]. The primordial insula is initially located on the free lateral surface of the cerebral hemisphere and adjoining the cortical amygdaloid regions on one side and olfactory cortical regions on the other [13, 15]. This is highly comparable to the position of the dorsal pallium in lamprey hemispheres [16]. According to the von Baerian theory, embryos of later-descendent species resemble the embryos of earlier-descendant species to the point of their divergence. So, it may be concluded that the human insula is the most ancient part of the neocortex. In addition, the lamprey has a small but well-developed dorsal thalamus (the part forming the proper so-called thalamus in humans), which connects the tectum (e.g. somatosensory and viscerosensory information) and optic tract (visual information) with caudal parts of the pallium (mainly hippocampal primordium and subhippocampal lobe, i.e. medial pallium) [17].

In amphibians, the dorsal pallium has significantly expanded in comparison to lamprey dorsal pallium, and it covers almost the entire roof of the hemisphere in these animals [18]. Fibres of neurons within these dorsal pallial fields run ipsilaterally to other pallial regions (medial, lateral, ventral), to the septum and to the amphibian striatopallidum [18]. However, fibres running from the thalamus to the primitive cerebral cortex are certainly not restricted to the newly present dorsal fields [19–21]. Anterior parts of the anuran thalamus are projecting widely within the forebrain, while, e.g. visual information is also projected to the hypothalamus and brainstem [19]. From electrical recording and anatomical labelling experiments, it can be concluded that the anuran dorsal pallium does not yet has achieved its human input processing and output generating role [19–21] but is still part of a more extensive 'limbic' behavioural control system including almost all pallial and subpallial regions.

In more recent jawed vertebrates, the input to the dorsal thalamus largely increases and this leads to a significant expansion of the dorsal pallium [22, 23]. However, this expansion occurs along different lines in non-synapsid (reptiles, birds) and synapsid (mammals) animals [12, 23]. Both groups derive from a common sauropsid ancestor with a turtle-like brain. The dorsal thalamus consists of two divisions called lemnothalamus and collothalamus, dependent upon their brainstem input structures. Within the mammalian line, both thalamic divisions with their corresponding cortical fields developed [23]. These cortical fields comprise the subicular, cingulate, prefrontal, sensorimotor and related cortices of mammals. The described expansion resulted probably in a total displacement of ventral and medial pallial fields. The medial pallium became hippocampus and the ventral pallium became the most caudal edge of the frontal lobe (including olfactory tubercle) and cortical regions of the amygdaloid complex in the temporal lobe.

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Secondary to the described synapsid development of the dorsal pallium, lamination of the cerebral cortex occurred [10, 24]. This lamination is absent in non-mammals and not restricted to new, originally dorsal, pallial fields [10]. Due to this lamination, the human neocortex consists of horizontal layers, intersected by vertical (or radial) columns that are stereotypically interconnected in the vertical dimension and comprise processing units [24, 25]. The expansion and elaboration of the cerebral neocortex during evolutionary development from primitive mammals to humans resulted in formation of new areas with new connections creating numerous extensive networks regulating different new or more sophisticated types of behaviour [24]. However, the majority of this progress is of relatively recent date.

2.2. Evolution of subcortical structures

The lamprey telencephalon can be divided into a dorsal, pallial region and a ventral, subpallial region. This subpallial part largely consists from the striatum, septum and preoptic area [17]. Sten Grillner and collaborators have demonstrated that the complete basal ganglia circuitry is already present in these phylogenetically oldest vertebrates [26, 27]. Moreover, these animals possess a subpallial structure (**Figure 2**), the habenula-projecting globus pallidus (GPh), which has an essential role in selecting behaviours that are either rewarding and should be continued or are not rewarding and should be abandoned [28]. We have hypothesised that lamprey striatal subpallium is included in nuclear amygdala of mammals [2]. However, some controversy exists concerning the fate of the GPh in more recent vertebrates. Lamprey also

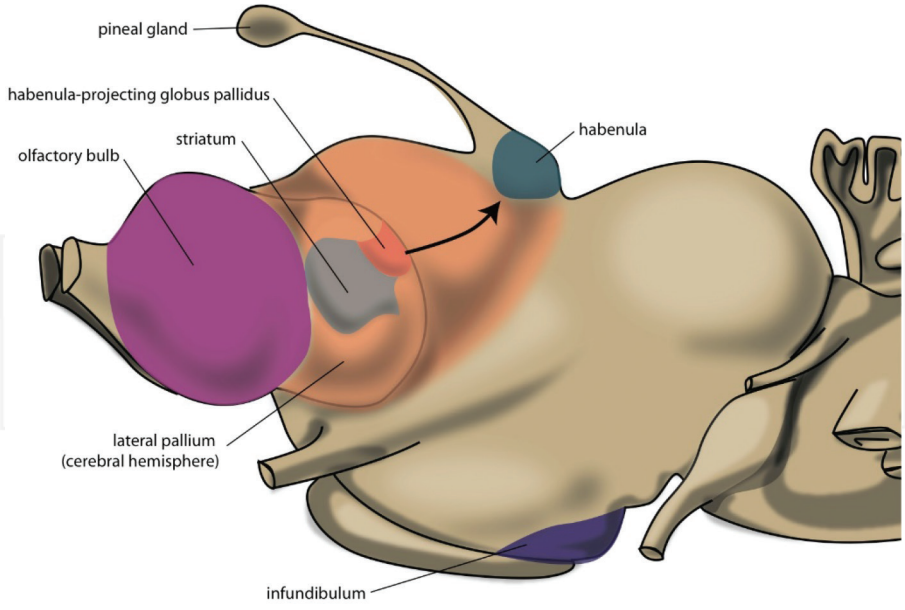

Figure 2. Position of the striatum and habenula-projecting globus pallidus of lamprey.

have an epithalamus which is very similar to its homologue in more modern animals [2]. This includes the output structures of the habenula via fasciculus retroflexus to midbrain nuclei.

It was formerly believed that the forebrain (especially its basal ganglia) underwent important changes during the evolution from anamniotes (lampreys, fishes, amphibians) to amniotes (reptiles, birds and mammals). However, the organisation of the basal ganglia is more conserved than previously thought [29]. The two main components of the basal ganglia develop embryologically from two different areas: the lateral ganglionic eminence (giving rise to the striatum) and the medial ganglionic eminence (giving rise to the pallidum). During embryological development different genes are brought to expression in order to regulate the regionalisation of these two areas. In particular, the transcription factor Nkx2.1 is expressed in the medial ganglionic eminence (and not the lateral one), and the expression of this gene in combination with that of others has been used to characterise pallidal basal ganglia in embryos of amniotes and anamniotes [29]. These authors were able to identify striatal and pallidal regions in cartilaginous fishes, ray-finned fishes, lungfishes and amphibians. However, in the subpallium of lampreys, a pallidal region could not be identified because these animals lack an Nkx2.1-expressing zone. Therefore, it was suggested that the pallidum is still absent in agnathans and first appeared during or after the transition from jawless to jawed vertebrates [30]. However, since Stephenson-Jones and colleagues [26, 27] have demonstrated the existence of a complete extrapyramidal circuitry in the subpallium of lamprey, this proposal of Moreno and co-workers [30] has to be rejected. In lampreys pallidal structures do exist in spite of the absence of expression of Nkx2.1 during the embryonic development of this structure.

The nuclear part of the amygdaloid complex is another derivative of the lateral ganglionic eminence, and the development of the amphibian amygdaloid complex has been studied in detail by Moreno and González [4, 31–33]. Within the anuran forebrain, the striatum (anterior) is continuous with the central and medial amygdala (posterior) and clearly separated from pallidum, bed nucleus of the stria terminalis and septum [4]. In humans, the bed nucleus of the stria terminalis is continuous with the connecting extended amygdala on one side and with the shell part of the nucleus accumbens (NAcbS) on the other [2, 25]. As a matter of fact, the original concept described the centromedial amygdala and bed nucleus of the stria terminalis both as part of the extended amygdala [34]. The investigations made clear that the organisation of the ancestral tetrapod (amphibian-like) amygdaloid complex is retained within more recent ancestors [35]. Evolution of the anamnio-amniotic (mammalian) striatum probably occurred in a modular sense when a more lateral part of the striatum was added every time when a cortical part with a new function was added to the expanding the neocortex [1, 36]. The amygdaloid complex derives from pallial and subpallial territories. Pallial (corticoid) structures include the cortical amygdala (olfactory and vomeronasal) and the basolateral complex deep to it [37]. These pallial components originate from lateral and ventral pallial regions and are also maintained during evolution of amniotic vertebrates [35, 37].

An important discovery during studying the embryological development of anuran basal ganglia was the finding that the bed nucleus of the stria terminalis (BST) and part of the septum are also of pallidal instead of striatal origin [29, 38]. This is interesting because the BST is a suitable structure to execute the functions of the limbic component of lamprey

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habenula-projecting globus pallidus. The architecture and connectivity of the rat BST has been studied in detail by Larry Swanson and collaborators. It becomes evident that the BST is an extremely complex set of nuclei, which can be separated into dorsal, lateral and ventral areas [39]. These nuclei receive input from the central amygdaloid nucleus (innervating various parts of the anterior BST division) and medial amygdaloid nucleus (preferentially innervating the posterior BST division), but not from the superficial and deep corticoid nuclei of the amygdala [40]. It is concluded that BST is a rostral differentiation of the pallidum receiving massive GABAergic input from centromedial amygdala and giving again GABAergic output to brainstem motor systems and thalamocortical re-entrant loops [40]. Viewed broadly, BST posterior division cell groups share massive bidirectional connections with the medial amygdaloid nucleus and other amygdaloid components of the accessory olfactory system, and they send massive projections to hypothalamic control centres regulating reproduction and defence [41]. The BST anterolateral group projects to the ventral autonomic control network, to midbrain structures modulating the expression of orofacial and locomotor somatosensory responses and to the ventral striatopallidal system. This suggests that the anterolateral group is primary involved in appetitive feeding (eating and drinking) behaviour [41]. The lateral habenula hardly receives any fibres from these BST areas. However, the anteromedial BST division projects to the lateral habenula [41, 42]. In our opinion, it is very well possible that the anteromedial division of the rat BST contains glutamatergic neurons which are running to the lateral habenula and have similar function as lamprey GPh neurons. Moreover, the anterior BST division receives input from hippocampus (ventral subiculum) and infralimbic cortex (comparable with the human subgenual anterior cingulate cortex, Brodmann area 25 (BA25)). This connectivity probably corresponds to the cortical input to the habenula-projecting globus pallidus.

2.3. Conclusion: evolution of the amygdaloid complex

The endbrain (telencephalon) of the very first vertebrates can be considered to be the evolutionary starting point of the human amygdaloid complex. Its pallium largely consisted of ventral, lateral and medial fields. Its dorsal pallium was not contributing to a very significant extent. Its subpallium contained a striatopallidal complex for motor control and a habenula-projecting globus pallidus for decision-making. During evolution to an amphibian-like ancestor, the dorsal pallium developed to a significant extent, but it can still be considered an extension of the medial pallium. This can be concluded from its connectivity with other pallial and subpallial structures as well as from its input received from the dorsal thalamus. The medial pallium later developed into the hippocampus. At a subpallidal level, the primitive striatopallidal complex becomes nuclear amygdala and bed nucleus of the stria terminalis, respectively. This limbic striatopallidal structure will later become the human extended amygdala of Heimer [34]. Next to the amygdaloid complex, a new ventral and dorsal striatopallidal complex arises in amphibians which will form the extrapyramidal system in our mammalian ancestors. In our opinion it actually took until the evolution of our mammalian ancestors before the dorsal pallium was actually transformed into the current neocortex. The massive growth of this neocortex resulted in a C-shaped and outside-inward curving of the cerebral hemispheres. The medial pallium became hippocampus and the ventral pallium

superficial and deep corticoid amygdala. This means that almost the entire cerebral hemisphere is of quite recent origin. This is probably also true for the limbic cortical-subcorti-

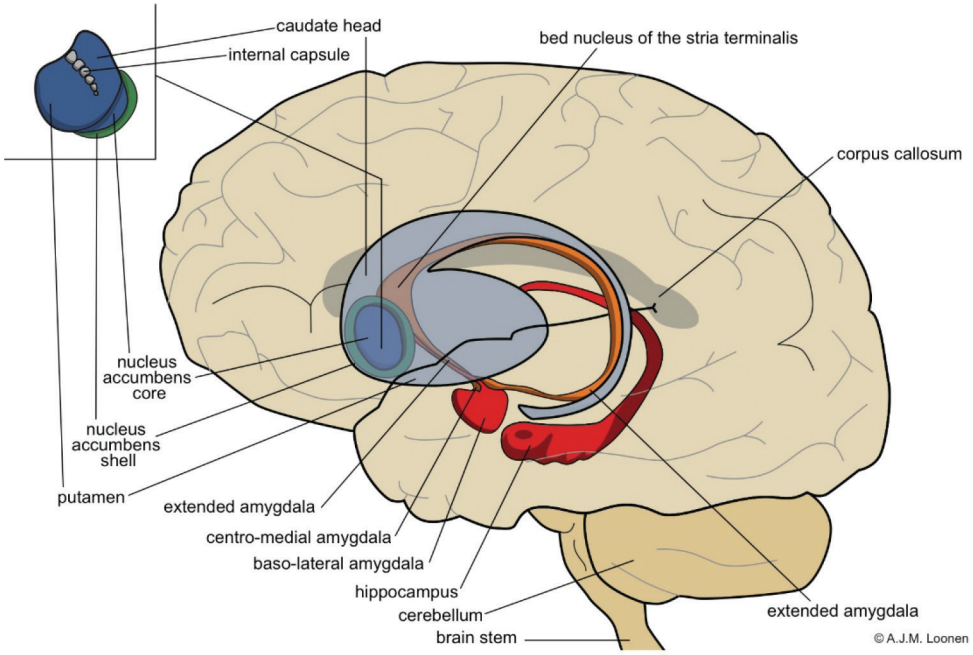

Figure 3. Position of the limbic basal ganglia (extended amygdala and nucleus accumbens shell) relative to the extrapyramidal striatum (caudate nucleus, putamen, nucleus accumbens core) and hippocampus.

cal-cortical connectivity we have previously suggested [2, 6]. Corticoid amygdaloid output reaches the hypothalamus and brainstem (to minor extent directly and) largely along nuclear amygdala (striatal amygdala) and bed nucleus of the stria terminalis (pallidal amygdala). This directly results from the regulation of vegetative and motor behaviour by the striatum instead of the pallium in lamprey [2]. However, the human frontal neocortex is reached through connectivity with the dorsal thalamus. This last connectivity must have developed later during the evolution of the mammalian forebrain. The amygdaloid equivalent of the habenula-projecting globus pallidus is probably localised within the bed nucleus of the stria terminalis.

The final picture of the position of the human limbic and extrapyramidal basal ganglia is given in **Figure 3**.

3. Connectivity of the amygdaloid complex

The amygdaloid complex is a heterogeneous group of 13 nuclei and cortical areas located in the medial temporal lobe just rostral to the hippocampal formation [43]. The complex can

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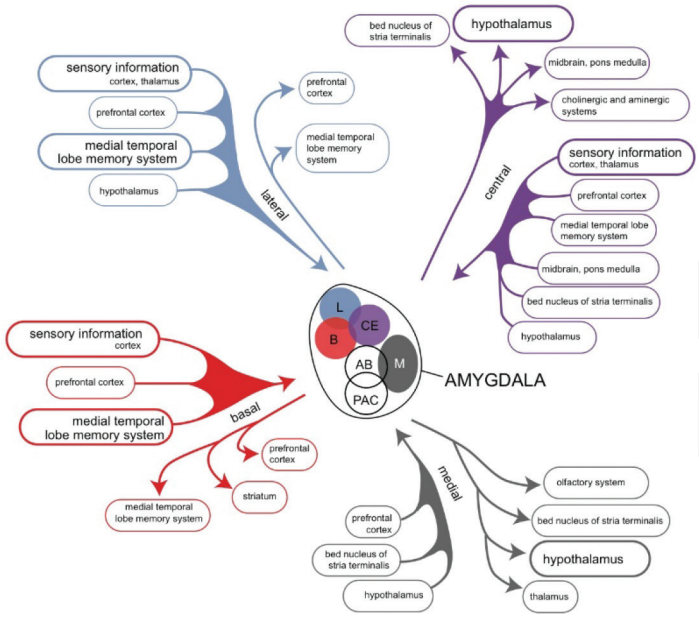

Figure 4. Overview of the connectivity of the rat amygdaloid complex [adapted from Ref. [45] with permission of the author].

neuroanatomically be divided into 'deep nuclei', 'superficial nuclei' and 'remaining nuclei' [43]. Both the cortical amygdalar nuclei and the basolateral amygdalar nuclear complex, which is located deep to it, have cortex-like cell types [44]. In contrast, the so-called extended amygdalar nuclei contain predominantly GABAergic spiny projection neurons, like the striatum [44]. In order to simplify, we usually divide the amygdala in a corticoid basolateral and a nuclear centromedial part (**Figure 3**). Each nucleus of the amygdala has a characteristic set of interconnections with other amygdalar nuclei and extrinsic brain regions (**Figure 4**) [43, 45]. Within the amygdalar nuclear complex, the primary flow is from corticoid to nuclear structures [46].

An unambiguous description of the structure and connectivity of the human amygdaloid amygdala is hampered by the existence of a predominance of contradictory, confusing, and unsubstantiated viewpoints both in recent and old scientific literature [47–49]. Moreover, the connections of the amygdaloid complex have been studied in mammalian animal species (mainly rats, cats and monkeys), which differ with respect to the extensiveness of their neocortex [48]. This large size of the neocortex causes dominance of projections from and to neocortical areas. Again looking into the connectivity of putative homologues of the amygdaloid complex in our early vertebrate ancestors may be of help. In amphibians, the amygdaloid complex is divided into three components: the vomeronasal amygdala, the olfactory/multimodal amygdala and the autonomic amygdala [4]. It should be realised that anuran species probably do not possess a true homologue of the human neocortex yet (see above). However,

the anterior, lateral and medial areas of the anuran amygdaloid complex reveal connectivity which is roughly running ahead of the connectivity of the neocortex associated with amygdaloid complex [4, 50]. This includes output of the later deep corticoid and medial amygdaloid nucleus to the medial pallium, which is the later hippocampus.

Based on these start points, three or four components of amygdaloid connectivity can be distinguished: the accessory olfactory division, the main olfactory division, the autonomic division and the frontotemporal division [47, 48]. As possession of a true vomeronasal organ, which is originally the main source of input to the accessory olfactory division, by humans is still controversial, the first two may be added together in humans. The frontotemporal division is often primarily associated with strong bidirectional interactions with the prefrontal cortex and hippocampal formation [45, 46], but the amygdalo-hippocampal system can also be considered to be an output channel of the amygdaloid complex. The connectivity of the deep corticoid amygdaloid complex from and to the hippocampal complex is mediated through parahippocampal regions [51]. Via the fornix the hippocampus sends a GABAergic connection to the medial septum and a glutamatergic connection to the lateral septum [52, 53]. Reciprocally, cholinergic and to a far less extent GABAergic and glutamatergic fibres coming from the medial septum-diagonal band of Broca complex run through the fornix to the hippocampus [52, 53].

The four divisions of the amygdaloid system have more conjoined than separated functional significance. All regulate in combination with each other several components of instinctive, emotional behaviour. The accessory olfactory component is perhaps somewhat more involved in social behaviour related to reproduction and the autonomic part somewhat more with the regulation of visceral aspects of the emotional response. However, the abundancy of the interactions between separate amygdaloid areas and the extensive mixed connectivity with other brain structures [43–45] make that separate pathways cannot be clearly distinguished. An important part of this amygdaloid output is delivered, either directly or via hippocampus indirectly, to hypothalamic structures regulating reward-gaining and misery-fleeing behaviour [6, 54, 55]. These hypothalamic areas are also reached via the non-centromedial parts of the extended amygdala (including the bed nucleus of the stria terminalis) [49, 56]. However, a major role is played by the deep corticoid complex (mainly basolateral nuclei) in bidirectional interaction with prefrontal cortical areas, the hippocampal complex, as well as sensory cortical areas [44, 46, 57–59]. An essential characteristic of this bidirectional amygdaloid connectivity is the capability to learn from experiences through associative learning, complex response conditioning, episodic memorisation and so on [46]. The best description of the function of the amygdaloid complex is to analyse the complex input concerning the actual daily life situation within the individual's biotope (nature, flora, fauna, social circumstances) and to select the sensory input which deserves more attention in order to improve the current chances (misery fleeing and reward seeking). The amygdala also receives information about the environment from the sensory thalamus and sensory cortices. The input is compared with memorised information and modulated by programmes concerning implicit and explicit behavioural output. This includes direct inhibition of the amygdala-dependent emotional response when this is expected to be more profitable. This last function is primarily attributed to ventromedial areas of the prefrontal cortex [6, 60, 61]. Traditionally, the amygdala is supposed to

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induce an emotional response mainly by giving output to the hypothalamus and brainstem via the centromedial nucleus after this validation process has been completed [46]. We want to suggest that the significant part of output is additionally given via the hippocampus and fornix to medial and lateral septal areas [52, 53]. After comparison with memorised experiences in the hippocampus and processing within the septal area, this information may reach the medial habenula (MHb). The septum, particularly the medial septum and the adjacent nucleus of the diagonal band of Broca, is the main input to the MHb [5, 62, 63]. Although the MHb has been far less extensively studied than the lateral habenula (LHb), experimental data support hyperactivity of the MHb to be associated with depression, anxiety and fear [63]. The MHb projects through the inner area of the fasciculus retroflexus to the interpeduncular nucleus within the midbrain [5, 62, 64, 65]. The interpeduncular nucleus is a singular, unpaired structure located at the ventral midline of the midbrain [62, 66]. The major efferent pathways originating in the interpeduncular nucleus project to the dorsal tegmental nucleus [66], the ventral tegmental area [62] and the raphe nuclei [62, 64]. However, the interpeduncular nucleus is well known for its widespread projections both ascending and descending [62, 66]. Hence, the above pathway from the corticoid amygdala, via hippocampus, septal nuclei, medial habenula and interpeduncular nucleus to ventral tegmental area and raphe nuclei, may represent a primary regulation mechanism to increase or decrease the intensity of the emotional misery-fleeing response.

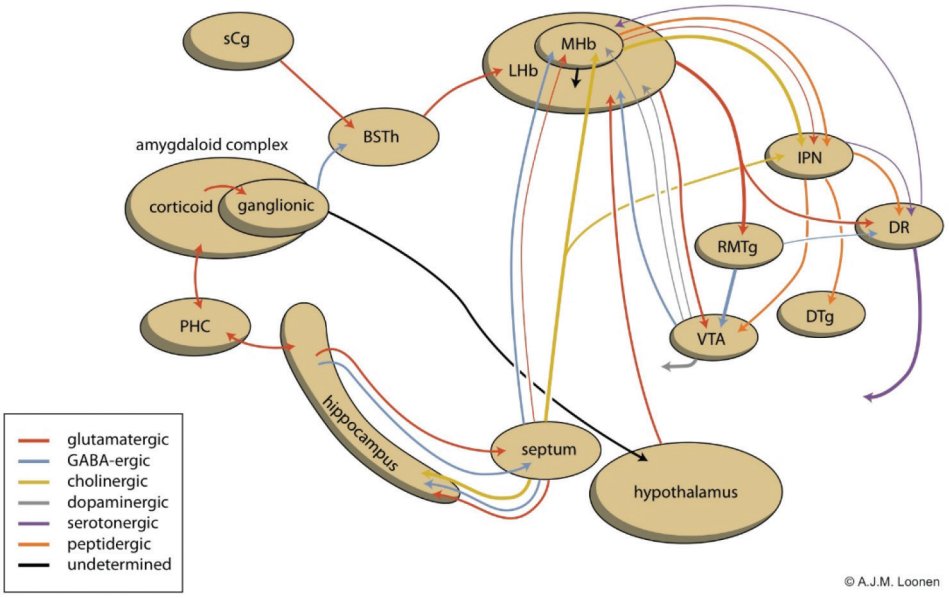

Figure 5. Scheme showing the connectivity of limbic (cortical) system to the midbrain through the habenular complex. BSTh, habenula-projecting part of the bed nucleus of the stria terminalis; DR, dorsal raphe nucleus; DTg, dorsal tegmental nucleus; IPN, interpeduncular nucleus; LHb, lateral habenula; MHb, medial habenula; PHC, parahippocampal cortex; RMTg, rostromedial tegmental nucleus; sCg, subgenual cingulate gyrus; and VTA, ventral tegmental area.

In addition, the amygdala affects the activity of the ventral tegmental area through a pathway including the lateral habenula. We want to suggest that anteromedial division of the bed nucleus of the stria terminalis contains the human limbic equivalent of the lamprey habenula-projecting globus pallidus (GPh). This area receives input from GABAergic projection neurons originating within the central amygdaloid nucleus [40] and gives output to medial and caudal regions of the lateral habenula [41, 42]. When this limbic GPh is functioning similar to lamprey GPh, the amygdala can inhibit reward-seeking behaviour by stimulating the pathway, which runs from corticoid amygdala, through central amygdala, anteromedial bed nucleus of the stria terminalis, lateral habenula and rostromedial tegmental nucleus to ventral tegmental area (**Figure 5**).

In conclusion, the amygdaloid complex plays an essential role in fear and anger control, perception and attention to relevant sensory input (including, e.g. facial expression in order to allow adequate social functioning), by validating this input with respect to their significance for reward-seeking and misery-fleeing behaviour. The activity of this emotional response is regulated through a pathway including the habenula, in which two routes can be distinguished: one including the hippocampus, septal nuclei and medial habenula and the other including central amygdala, bed nucleus of the stria terminalis and lateral habenula.

4. A model for the regulation of pleasure and happiness

4.1. Cortical regulation of behaviour

Behaviour can be considered a mechanism where the brain manages input to create a specific output, which enables the organism to adapt to changed circumstances within the biosphere. In humans, input from the senses is primarily translated within the cerebral cortex into a specific behavioural output. Sensory information is processed within the posterior cerebral cortex in a stepwise fashion [25, 67]. Specific information is integrated with other sensory information and transmitted from the primary sensory cortex to the secondary sensory cortex, from there to the association cortex and so on. Within the anterior cerebral cortex, a similar now diverging flow of information occurs, which leads to the activation of specific brain regions, e.g. the motor cortex. Apart from this stepwise analysis, other fibres connect to more distant regions that run in parallel. Every neural connection is capable of learning, due to the characteristics of glutamatergic transmission, which can increase or decrease the sensitivity of connecting synapses by inducing long-term potentiation (LTP) or long-term depression (LTD). Therefore, the cortex can 'learn' to transmit specific sensory information to a specific output unit via a 'preferred' cortical tract. Accordingly, the cerebral cortex learns to interpret sensory information and produce a specific behavioural response.

4.2. Subcortical regulation of behaviour

Although this process is expedient, it can be expected to be highly sensitive to dysregulation, both in routine functions and in learning. Therefore, a parallel circuit has evolved, which includes subcortical structures. All processing units in the cerebral cortex also send information to the

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basal ganglia [68]. The route through the basal ganglia and thalamus leads to corresponding processing units in the anterior cortex [69]. This parallel circuit has stimulatory and inhibitory pathways, and its glutamatergic synapses can also induce LTP and LTD. Therefore, this parallel route through the basal ganglia enables the brain to correct serially transmitted information, when it arrives at the 'final' destination. Moreover, the connection through the basal ganglia is convergent [69]. Hence, the processing units in the posterior and anterior cortices and their outputs converge within this subcortical circuit to the same output unit. Again, the 'learning' ability of glutamatergic synapses within this framework makes it possible to process a constantly varying input and produce very complex, sophisticated output patterns, in a reproducible, precise fashion.

This organisation of connections is well known as the extrapyramidal system, which regulates cognition and movements [70]. In our mental function model, we suggest that a similar organisation can be distinguished within the limbic cortex, although here, the structure is more complex and less modular, due to the ancient origins of these structures. To simplify, we propose the corticoid regions of the amygdala to represent the primary limbic cortex. These corticoid regions are connected with many other cortical areas. The superficial (cortical) and deep (basolateral) corticoid regions of the amygdaloid complex can be considered input areas, and the centromedial (ganglionic or nuclear) region can be considered the output area of the amygdaloid complex [46]. In the earliest vertebrate ancestors, the striatum directly manages autonomic and motor control centres in lower diencephalon and brainstem [2]. In the lamprey very limited connectivity exists between pallial (cortex) areas and diencephalic and brainstem control centres. This is also true within the corresponding system in mammals: only light connectivity has been found between corticoid amygdalar areas and the hypothalamus or brainstem [45]. The stria terminalis connects the 'striatal' centromedial amygdala with its corresponding pallidum (bed nucleus of the stria terminalis) and also directly with the hypothalamus and brainstem [45]. Although the majority of output from the limbic basal ganglia flows to the brainstem, also connectivity exists with the (dorsal) thalamus and cerebral cortex. This is true for the output of the bed nucleus of the stria terminalis [40, 49] and for the output of the hypothalamus, which is probably related to affect the motor output of higher vertebrates, including humans, by inducing the drive to seek food, warmth, comfort, etc., or to escape from pain, thirst, misery, etc. [55]. This finally results in a limbic cortical-subcortical circuit that is more complex, but nevertheless essentially similar, to the well-known extrapyramidal system, provided that one realises that the cerebral neocortex was included within the circuit on a later evolutionary moment (**Figure 6**).

Hence, two types of cortical-subcortical circuits may be distinguished: extrapyramidal and limbic circuits. These systems have different ganglionic relay stations: the extrapyramidal circuit includes the dorsal and ventral striatum, and the limbic circuit includes the extended amygdala (as defined in Ref. [34]). These circuits are linked to each other by means of the nucleus accumbens, which serves as an interface between the two circuits [71]. The core part belongs to the extrapyramidal and the shell parts more to the limbic circuit. The extrapyramidal circuit regulates rational, cognitively constructed, skilled behaviour, which is often goal oriented and includes decision-making. The limbic circuit regulates emotional (instinctive and automatic) behaviours, which are often defensive, and this regulation includes (attentive)

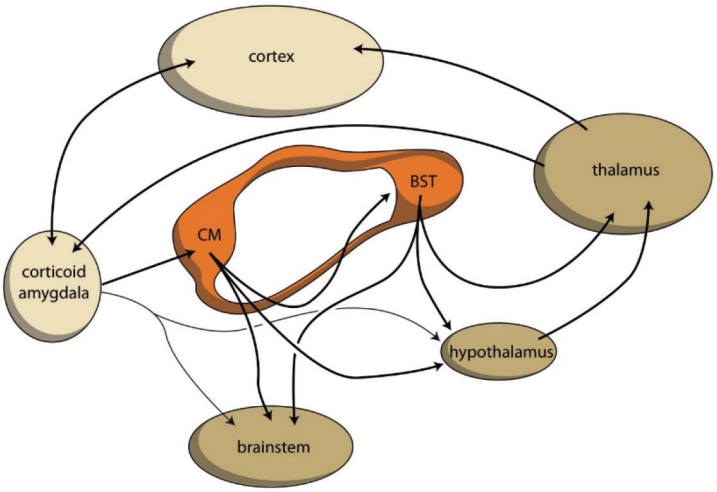

Figure 6. Limbic cortical-subcortical regulatory circuit. BST, bed nucleus of the stria terminalis; CM, centromedial amygdala; orange, extended amygdala; dark yellow, diencephalon and brainstem; and light yellow, corticoid amygdala and neocortex.

salience. The two systems influence each other in a reciprocal (yin-and-yang-like) fashion; moreover, both systems can inhibit or activate, as the situation demands. It is generally accepted that the prefrontal cortex (PFC) is in control of selecting the appropriate response [72, 73]. The dorsolateral PFC is particularly important for controlling rational responses, and the medial PFC controls emotional responses. Within the medial PFC, the orbitofrontal cortex (OFC) plays a particularly noteworthy role, because it is essential for regulating the direction of motivation [74].

4.3. Motivation to reward-seeking and misery-fleeing behaviour

Behaviour can be a reaction to an influence in the environment, or it can also be generated by the individual. To enable this proactive instead of reactive behaviour, motivation comes into play [73, 75]. Three stages of behavioural motivation can be distinguished: general motivation, initiative and selective precedence conveying (via inhibition). The OFC plays a significant role in regulating these processes by delivering input to the ventral striatum, the anterior cingulate cortex and the amygdala [74].

Although the extrapyramidal and limbic circuits regulate two different types of behaviour (constructed/rational and instinctive/intuitive, respectively), the individual must be highly motivated to express these conducts. This motivation requires the involvement of two specific structures: the NAcbC and the NAcbS (**Figure 7**) [71, 76, 77]. The NAcbC motivates the individual to show behaviour that may lead to a feeling of reward. The NAcbS motivates the individual to show behaviour that may lead to escape from adversity [6]. When high stimulation of these motivations suddenly ceases as its goal is obtained, the individual experiences feelings of pleasure (NAcbC) or feelings of happiness (NAcbS). Therefore, we dis-

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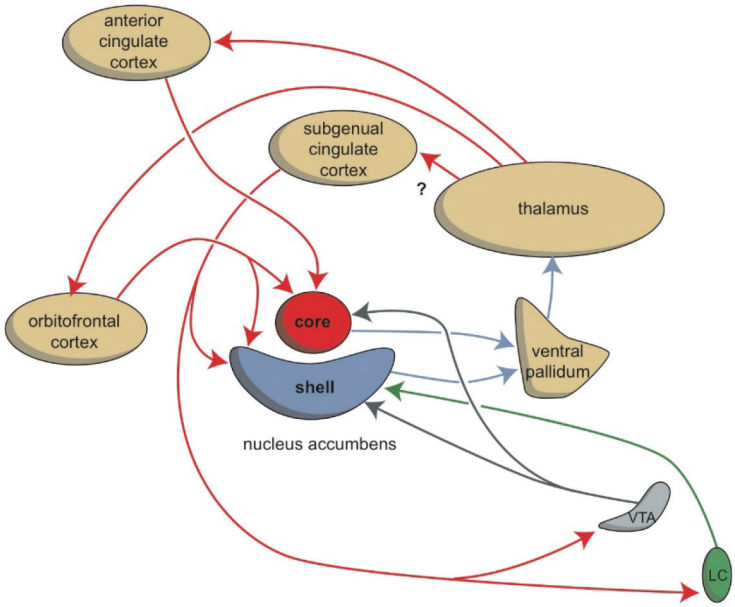

Figure 7. Stimulation of the core and shell of the nucleus accumbens (adapted from Ref. [76] with permission of the author). VTA, ventral tegmental area; LC, locus coeruleus. Red arrows, glutamatergic; blue arrows, GABAergic; grey arrows, dopaminergic; and green arrow, adrenergic.

tinguish between circuits that regulate pleasure and circuits that regulate happiness [6]. We have hypothesised that the best candidate for the perception of feelings of pleasure (reward) and happiness (euphoria) would be the insular cortex [7]. The posterior part of the insula contains areas for gustation, thermo-sensation, pain, somato-sensation and viscera-sensation [15]. Indeed, the insular cortex has been demonstrated to be involved in processing emotions like anger, fear, happiness, sadness or disgust and has been shown to display treatment-responsive changes of activity in different mood disorders [78].

4.4. Brainstem regulation of behaviour

The activities of the NAcbC and NAcbS, in turn, are regulated by monoaminergic nuclei within the midbrain. These nuclei transmit signals through dopaminergic (ventral tegmental area), adrenergic (norepinephrine, locus coeruleus) and serotonergic (raphe nuclei) tracts. In addition to their direct regulation of the NAcbC and/or NAcbS [6, 7], these monoaminergic nuclei regulate the activity of other, first relay station, basal ganglia and important parts of other areas in the forebrain. Therefore, it may be concluded that behavioural output is controlled at three levels within the brain. The highest level is the cerebral cortex (isocortex, limbic cortex, corticoid (cortical, basolateral) amygdala and hippocampal complex). The second level is the subcortical forebrain (dorsal striatum, ventral striatum, extended amygdala). The third level of control is the midbrain (monoaminergic regulation centres).

4.5. Habenular regulation of behaviour

As part of our model, we suggest that a fourth regulatory system exists, the habenula, which connects the cerebral cortex and midbrain systems (**Figure 8**) [6, 7]. Based on the regulation of appetitive behaviour in lampreys, we suggest the lateral habenula also to have an important regulatory function in humans [6]. In the lamprey, when a behaviour is particularly rewarding, the lateral habenula promotes this behaviour by intensifying stimulation of the phylogenetic homologue of the ventral tegmental area. However, when the reward is smaller than expected or absent, the behaviour is inhibited by affecting the ventral tegmental area equivalent of the lamprey. The medial habenula appears to play a similar role with respect to misery-fleeing behaviour as the lateral habenula with respect to reward-seeking activities.

The habenula belongs to the epithalamus, which also harbours the pineal gland and the stria medullaris. The habenula's projections to the midbrain were very well conserved during vertebrate evolution [7, 79], but its input structures are not so easily to be traced back from the anatomy of earlier vertebrates. The septum, particularly the medial septum and the adjacent nucleus of the diagonal band of Broca, is the main input structure of the medial habenula [5, 62, 63]. We suggest that by means of this pathway the corticoid amygdala (cortical and basolateral areas of the amygdaloid complex) gives input to the medial habenula (via hippocampal complex and fornix) (**Figure 5**). Although probably an important part of the functional

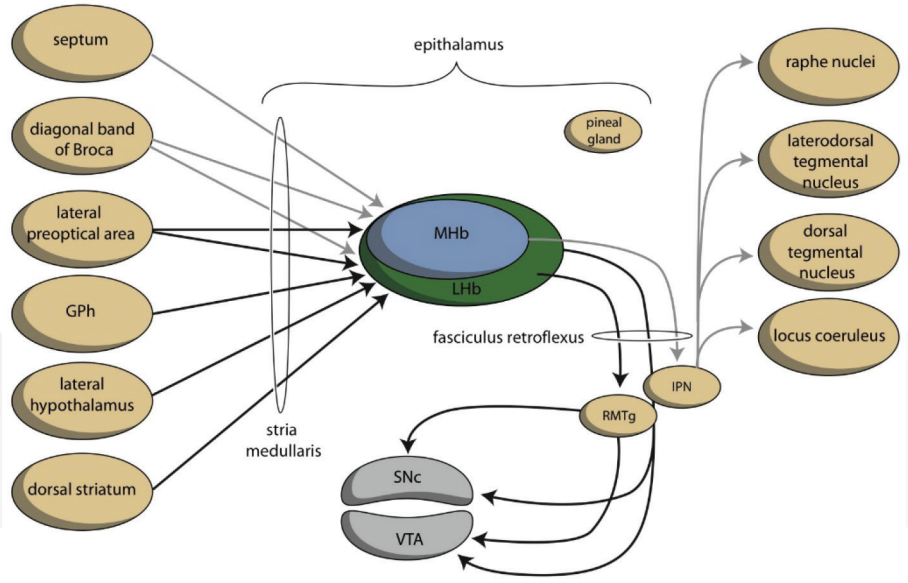

Figure 8. Simplified representation of the connectivity through the epithalamus (adapted with permission from Ref. [79]). GPh, habenula-projecting globus pallidus; IPN, interpeduncular nucleus; RMTg, rostromedial tegmental nucleus; SNc, substantia nigra, pars compacta; and VTA, ventral tegmental area. GPh depends upon the cortical-subcortical circuit being considered. GPh is localised within the bed nucleus of the stria terminalis in the limbic circuit, within the ventral pallidum concerning the motivational circuit and within the globus pallidus (border region, GPb) within the extrapyramidal circuit.

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input to the lateral habenula has not yet been elucidated, this nucleus is known to receive excitatory input from the preoptic area, lateral hypothalamus and globus pallidus and from anterior cingulate and the medial prefrontal cortex [5, 80, 81]. Moreover, the lateral habenula also receives strong GABAergic innervations from various brain regions [82]. In addition, the medial habenula is directly giving input to the lateral habenula [83]. The striatopallidal (extended) amygdala is heavily (directly and indirectly) connected to the lateral hypothalamus. We suggest that the activity of the lateral habenula is modulated by this pathway. In addition, the bed nucleus of the stria terminalis contains the human equivalent of lamprey habenula-projecting globus pallidus, as we have argued above.

The corticoid amygdaloid complex is in a perfect position to increase the magnitude of misery-fleeing (happiness) over reward-seeking (pleasure) behaviour. This limbic cortex regulates the activity of monoaminergic centres within the midbrain by affecting the medial and lateral habenula. In addition, the amygdaloid complex regulates instinctive motivation to gain certain essential prerequisites to maintain life (such as food, water, warmth, etc.) by affecting the lateral hypothalamus.

4.6. Model for the regulation of behaviour

In conclusion, the extrapyramidal and limbic cortical systems regulate cognitive (rational) and instinctive behaviours, respectively. The intensity of behaviour that ultimately leads to reward is controlled by the cortico-striato-thalamo-cortical (CSTC) circuit that includes the NAcbC. The intensity of behaviour that ultimately leads to safety is controlled by the CSTC circuit that includes the NAcbS. On the temporal side of the brain, the amygdala determines

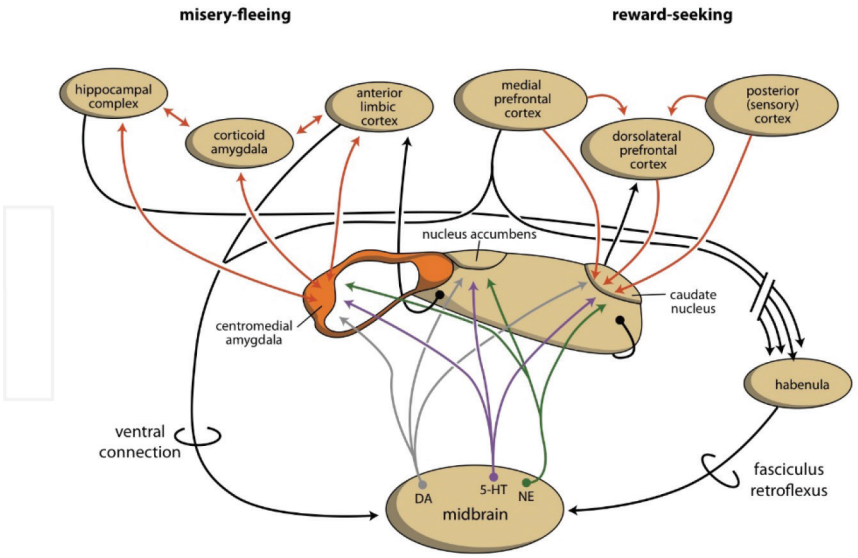

Figure 9. Overview of model for the regulation of behaviour.

the appropriateness of flight, fight, or appetitive responses. Based on attentive salience, it initiates the proper emotional component of behaviour. On the dorsal side of the brain, the caudate nucleus determines the suitability of the available repertoire of skilled behaviours; it selects the proper motor response to achieve the intended goals. The motivation to express these behaviours is regulated by monoaminergic centres within the midbrain. In turn, these monoaminergic centres are regulated by old and new parts of the cerebral cortex through a dorsal connection that travels through the medial and lateral habenula. Of note, the monoaminergic centres are also regulated by the medial prefrontal cortex via a direct ventral connection, which possibly travels through the medial forebrain bundle [7] (**Figure 9**).

5. From aberrant salience to schizophrenic psychosis

Salience attribution is the process of events and thoughts that come to grab attention, drive the actions and determine behaviour because of their associations with reward or punishment [84]. This corresponds very well to the role of the amygdaloid complex described in a few pages above: playing an essential role in fear and anger control by perception and paying attention to relevant sensory input (including, e.g. facial expression in order to allow adequate social functioning), by validating this input with respect to their significance for reward-seeking and misery-fleeing behaviour. As until mammals the neocortex was not capable of playing its input-processing and output-organising role as in humans, salience attribution was taken care of by the pallium of our anamniote and turtle-like ancestors. As described above this ancient pallium essentially corresponds with the superficial and deep corticoid amygdala and associated hippocampal areas. Later during evolution the interaction of the corticoid amygdala with neocortical areas became involved in the process, and in humans probably no part of the neocortex can be excluded from participating.

At the beginning of this century, Shitij Kapur [8, 85–88] proposed a model for the development of delusional systems in psychiatric disorders due to aberrant attribution of salience to objects and associations, which would normally be meaningless, but now are interpreted as being significant and to be dealt with considerable carefulness. Due to a dysregulated, hyperdopaminergic state this theory holds, environmental events and internal representations become associated with important elements of one's experiences and induce the creation of a cognitive construct (the delusion) to explain these strange occurrences. Hallucinations are believed to reflect the direct observation of these salient internal representations [85]. Antipsychotics decrease the salience of the abnormal experiences by blocking dopamine transmission and allow their resolution by making them unimportant. Howes and Kapur integrated vast experimental findings to this pathophysiological context of causing psychosis by inducing aberrant salience [88].

The model may correspond to the observation that delusions and hallucinations are not uncommon in the general population and not always result in a full-blown psychosis [89]. Substantial evidence suggests that psychotic-like experiences exist along a continuum in the general population [90]. Moreover, stress from life hassles can provoke delusional ideation [90]. In line with this, Jim van Os has suggested to replace the concept of schizophrenia being an illness with the model that it is a salience dysregulation syndrome [91–93].

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An important limitation of the model is that the corticoid amygdala is integrated within at least four cortical networks regulating salience-involving processes [61, 84]. Within this context, especially, the interaction between the ventromedial prefrontal cortex and the corticoid amygdala may be essential. Therefore, the corticoid amygdala cannot be considered to be a separate salience-attributing structure, but is having this role in interaction with other cortical structures participating in the network [61].

6. Application of our model to explain the pathogenesis of schizophrenic psychosis

In our opinion, a weak point of Kapur's model is the starting point that the aberrant salience attribution is due to a dysregulated, hyperdopaminergic state. This is not necessarily true. Actually, the hyperdopaminergic state could result from dysregulation on every level within the corticoid amygdala to midbrain monoaminergic area chain, including input from neocortical areas to the corticoid amygdala and the influence of the habenula to relevant midbrain structures. In most psychotic disorders, the hyperdopaminergic state may not induce aberrant salience, but may result from it. This does not exclude that increased sensitivity to the effects of dopaminergic transmission may increase the vulnerability to become psychotic.

So, we propose that the primary dysregulation which causes psychotic symptoms in 'schizophrenia' is localised within the interaction between the corticoid amygdala, in interaction with neocortical fields, with midbrain monoaminergic centres. The ventromedial prefrontal cortex may be the principle pathway for the corticoid amygdala to interact with these other cortical areas. Via connections through the habenula, the amygdaloid complex regulates the activity of the midbrain monoaminergic centres which in turn regulate motivation to exhibit reward-seeking or misery-fleeing behaviour. Increased dopaminergic input to the basal ganglia may induce behavioural hyperactivity and to the parahippocampal region may lead to hallucinations [94]. The amygdaloid complex is also innervated with dopaminergic fibres. Dopamine may lead to increased sensitivity of the amygdala to induce an emotional response. Psychotic disorders may be due to increased dopaminergic activity within the amygdaloid complex, aberrant salience attribution due to genetic or learned (conditioned) neuronal faults or aberrant inhibition by the dorsomedial prefrontal cortex due to neurodegenerative network failure. However, the hyperdopaminergic state is probably not the essential factor causing schizophrenic psychosis, and this may explain why antidopaminergic agents, as are all current antipsychotic drugs, are not always effective in treating schizophrenic psychosis.

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Author details

Anton J.M. Loonen[1, 2]* and Svetlana A. Ivanova[3, 4]

*Address all correspondence to: a.j.m.loonen@rug.nl

1 Department of Pharmacy, University of Groningen, Groningen, The Netherlands

2 Mental Health Institute GGZ Westelijk Noord-Brabant, Halsteren, The Netherlands

3 Tomsk National Research Medical Center of the Russian Academy of Sciences, Mental Health Research Institute, Russian Federation

4 National Research Tomsk Polytechnic University, Tomsk, Russian Federation

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