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Circuits Regulating Pleasure and Happiness: A Focus on Addiction, Beyond the Ventral Striatum

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Additional information is available at the end of the chapter

Abstract

A recently developed anatomical model describes how the intensity of reward-seeking and misery-fleeing behaviours is regulated. The first type of behaviours is regulated within an extrapyramidal cortical–subcortical circuit containing as first relay stations, the caudate nucleus, putamen and core of the accumbens nucleus. The second type of behaviours is controlled by a limbic cortical–subcortical circuit with as first stations, the centromedial amygdala, extended amygdala, bed nucleus of the stria terminalis and shell of the accumbens nucleus. We hypothesize that sudden cessation of hyperactivity of the first circuit results in feelings of pleasure and of the second circuit in feelings of happiness. The insular cortex has probably an essential role in the perception of these and other emotions. Motivation to show these behaviours is regulated by monoaminergic neurons projecting to the accumbens from the midbrain: dopaminergic ventral tegmental nuclei, adrenergic locus coeruleus and serotonergic upper raphe nuclei. The activity of these monoaminergic nuclei is in turn regulated through a ventral pathway by the prefrontal cortex and through a dorsal pathway by the medial and lateral habenula. The habenula has this role since the first vertebrate human ancestors with a brain comparable to that of modern lampreys. The lateral habenula promotes or inhibits reward-seeking behaviours depending upon the gained reward being larger or smaller than expected. It is suggested that the ventral pathway is essential for maintaining addiction based on the observation of specific cues, while the dorsal pathway is essential for becoming addicted and relapsing during periods of abstinence.

Keywords: addiction, mood, habenula, basal ganglia, amygdala, insula

1. Introduction

The dominant view on the neuro-pathology of addiction is that of deficient control processes resulting from impaired prefrontal cortex function and increased saliency of drug-related cues over normal rewarding stimuli [1]. The latter results from altered reward processing in the ventral striatum [1]. An important starting point in this respect has been the work of Koob [2, 3], who integrated knowledge from different fields of science in order to describe a scheme for the neuro-circuitry of addiction. An important component of the work of Koob [4] is the characterization of anti-reward or negative reinforcement in particularly in the more advanced stages of addiction. In his work, he assigns a major role to the activation of the brain stress systems, the amygdala, in particular, in addiction. In line with Koob's work, we propose additional neuro-circuitry to be involved in addiction. In this review, we apply a neuro-evolutionary approach to addiction, in order to identify potential additional subcortical structures that might have relevance for addiction.

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 misery. As the human species currently exists, even our oldest ocean-dwelling ancestors living over 540 million years ago must have been capable to react to the environment to feed, evade predators, defend territory and reproduce. Thus, 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's brain almost completely lacked the human neocortex and the dorsal parts of the basal ganglia [5, 6]. These newer parts of the brain are believed to determine human behaviour to a high extent and consequently receive most attention in research of processes explaining the genesis of mental disorders. This contrasts the involvement in psychiatric 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 describe the anatomy of the forebrain of the earliest human vertebrate ancestors [6]. 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 centromedial (i.e. nuclear) amygdala. In anuran amphibians (frogs and toads), the lamprey's striatum is retrieved as central and medial amygdaloid nuclei, while a dorsal striatum for the first time appears in its direct vicinity [6, 7]. The lampreys 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 [8]. The habenula has received much attention because of it asymmetry in certain vertebrate species [9] and its role in mediating biorhythms [10]. The habenula regulates the intensity of reward-seeking and misery-fleeing behaviour probably in all our vertebrate ancestors. In lampreys, the activity of the lateral 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 [11]. These two circuits include the extrapyramidal and limbic basal ganglia, which are collaborating in a reciprocal (i.e. Yin-and-Yang) 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. Hijacking of the reward-seeking mechanism by certain substances such as alcohol or illicit drugs is considered the essential mechanism behind addiction.

In this chapter, we will describe the evolution of the vertebrate forebrain and the functioning of the described regulatory circuits in somewhat more detail. Thereafter, the putative role of the habenula in initiating addiction and causing relapse after abstinence is depicted. The described model also explains the mood and anxiety symptoms that accompany the addictive process. We will start with a brief description of the mechanism of the emotional process [11, 12].

2. Model for emotional regulation

A suitable model for the regulation of the emotional response can be derived from the paper of Terence and Mark Sewards [13]. According to their model, the control centre for emotional response types such as *sexual desire*, *hunger*, *thirst*, *fear*, *nurturance* and *sleep-need* drives and *power-dominance* drives is the hypothalamus. The output of the hypothalamus proceeds along three channels. The first route projects via the thalamus to the cortex, including a pathway that contributes to the perception of emotion and one for the initiation and planning of cognitive and motor responses (drives). The second output pathway is a projection at least partly via the periaqueductal grey (PAG) to several brainstem nuclei, including nuclei that regulate the autonomic components of the emotional response (e.g. increased circulation and respiration). The PAG also activates the serotonergic raphe nuclei, the adrenergic locus coeruleus complex and the dopaminergic ventral tegmental area. From these nuclei, projections pass back to the hypothalamus (e.g. regulating hypophysiotropic hormones) and through the medial forebrain bundle to the forebrain (activating the frontal cortex). The PAG also constitutes an important input structure generating signals to the emotional forebrain. Apart from hormone release mediated through various brainstem nuclei, a third direct hypothalamic projection system regulates the endocrine component of the emotional response (also by releasing hypophysio-tropic hormones), enabling adaptation of the milieu interne, or correction of a possible misbalance. The hypothalamus also exerts a receptor function for various substances in the circulating blood.

This model corresponds to a significant extent with the model of Liotti and Panksepp [14]. However, they follow a different approach, describing seven emotional systems for *seeking*, *rage*, *fear*, *panic* (separation distress and social bonding), *care* (nursing and empathy), *lust*

(sexual love) and *play* (joy and curiosity), which are not all regulated by the autonomic hypothalamus. Within the context of this article, the first three systems of Liotti and Panksepp deserve a more detailed description.

The appetitive motivation-*seeking* system stimulates the organism to acquire the many things needed for survival. This motivation is coupled to a reward feeling that can—but not necessarily does—result from these activities. The nature of the specific rewards is of a lesser importance; the system works equally well for seeking food, water, warmth, and illicit drugs, as well as for social goals such as sexual gratification, maternal engagement and playful entertainment. The system promotes interest, curiosity and desire for engagement with necessary daily life activities. The process of reward pursuing consists of at least three psychological components: learning to value (attentive salience), incentive salience or 'wanting' and experiencing pleasure resulting in 'liking'. The first component is believed to be addressed by the amygdala. The amygdala can 'learn' by conditioning to appreciate sensory appetitive information within the context of external and internal circumstances and to initiate a proper response. Incentive salience is regulated by mesocorticolimbic mechanisms, with a central role for the NAcb. Later, in this chapter, we will describe that the insula plays an essential role in perceiving pleasure.

The amygdala additionally takes a central position with respect to valuing aversive stimuli, playing a critical role in anxiety and aggression. The anger-promoting rage system is associated with irritation and frustration. In this system, the emotional circuit is stimulated by projections
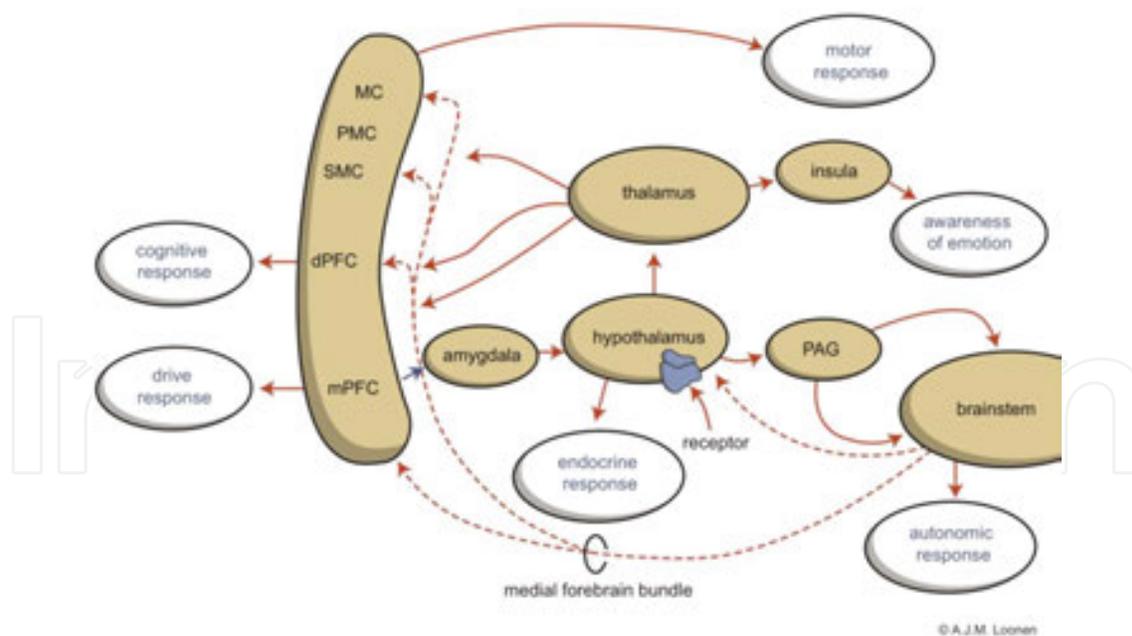

Figure 1. Simplified model for the regulation of emotional response. The hypothalamus is considered to be the principle controller and the amygdala the initiator of emotional response. In this depiction, the amygdala represents all limbic structures involved in emotional response. The amygdala is inhibited by the mPFC (blue arrow). MC = motor cortex, PAG = periaqueductal grey substance, dPFC = dorsolateral prefrontal cortex, mPFC = medial prefrontal cortex, PMC = premotor cortex, SMC = supplementary motor cortex.

between the medial amygdala and the medial hypothalamus via the stria terminalis. Neurons also project reciprocally between specific parts of the PAG in the mesencephalon and the medial hypothalamus. The fear system is organized in a fashion parallel to the rage system, in which both the amygdala and the PAG project to the medial hypothalamus. Activity within this system can lead to freezing or flight behaviour. Sustained fear (anxiety) is also mediated by the amygdala but follows a slightly different anatomical route and links the fear and stress systems.

Taken together, the regulation of the described forms of emotional output can be summarized and simplified into the scheme in **Figure 1**. The hypothalamus can be considered one of the principle control centres for emotional (non-behavioural) output (especially gratification, fear and aggression-driven). The hypothalamus regulates three components of this response: a thalamic one, a brainstem one and a pituitaric one. As explained above, the hypothalamus itself receives a stimulating input function from the amygdala, among other regions. The amygdala is responsible for the initiation of a suitable response type. In this process of initiating the emotional response, the amygdala is inhibited by the medial prefrontal cortex. This scheme describes the process of response selection, but another mechanism is regulating the level of motivation to exhibit the selected response type.

3. Perception of feelings of pleasure and happiness

According to Terence and Mark Sewards [13], the cortical representations of their emotional response types are located on the medial prefrontal and anterior cingulate areas. However, these cortical areas represent the fields initiating the corresponding drives for finding relief and are unlikely directly involved in the perception of feelings of thirst, hunger, sleepiness, somatic pain, etcetera, as these anterior cerebral areas are generally implicated in generating output. A better candidate for the perception of feelings of pleasure (reward) and happiness (euphoria) would be the insular cortex (**Figure 2**) as 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, such as anger, fear, happiness, sadness or disgust, and has been shown to display treatment-responsive changes of activity in different mood disorders [16]. However, the exact position of the insular cortex with respect to the perception of the discussed feelings remains unclear. The insular cortex, being located in the centre of the cerebral hemisphere, is reciprocally connected with almost every other input and output structure of the emotional response system. It could also be suggested that the insula's most important role is the integration and adjustment of the activities of such other brain structures without being primarily involved in the perception of emotional feelings itself.

However, yet another possibility comes into mind, which can be considered a revival of the late nineteenth century hypothesis developed independently by the US American William James (1842–1910) and the Dane Carl Lange (1834–1900) [17]. Their theories on the origin and nature of emotions states that once we become aware of the physiological bodily changes induced by, for example, danger, we feel the corresponding emotion of fear [18, 19]. So, the
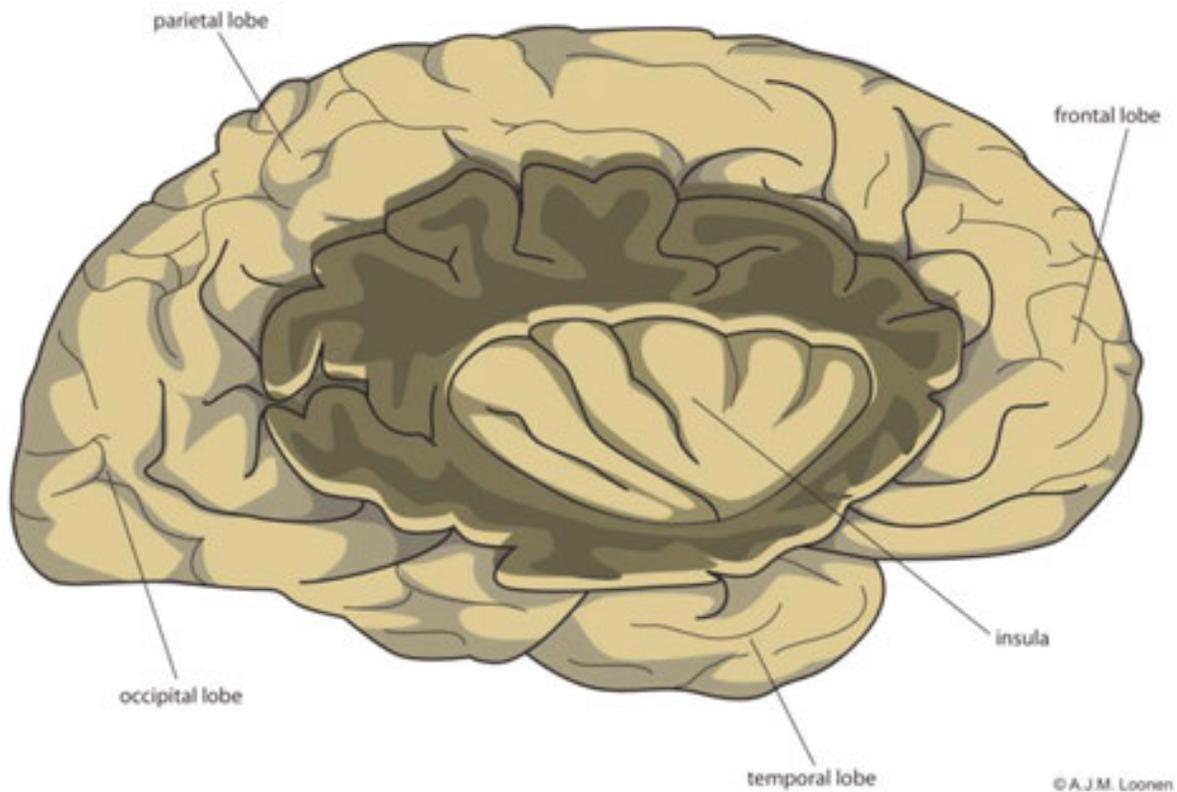
Figure 2. Position of the insular cortex. The human insular cortex forms a distinct, but entirely hidden cerebral lobe, situated in the depth of the Sylvian fissure. It is a phylogenetically ancient part of the cerebral hemisphere and entirely overgrown by adjacent regions of the hemispheres and the temporal lobe (cf. [15]).

basic premise of this theory is that the perception of interoceptive stimuli instigates the experience of an emotional feeling as well as its phenomenal consciousness. This could easily be expanded with the perception of other changes including environmental factors, which then would induce exteroceptive stimuli [19]. The anteriorly directed processing stream within the insula would make the anterior insula perfectly suitable to fulfil the requirements for the neuronal representative of such functions [20]. The upper part of the anterior insula is strongly and reciprocally connected with the anterior cingulate cortex, and the lower part is functionally linked to the adjacent caudal orbitofrontal cortex, which makes the anterior insula involved in food-related stimuli and the urge to take drugs as well [15].

The orbitofrontal cortex is the neuronal structure, which is most intricately involved in motivating for reward bringing behaviours [21, 22]. Perhaps the insula is involved in experiencing pleasure, but in our opinion, this is unlike to occur directly as sensing these positive feelings. As a matter of fact, the orbitofrontal cortex induces motivation to go for the possibility to obtain food, sex or drugs, which results in an unpleasant urge to exhibit this behaviour, called 'craving' [2–4]. This craving feeling results from hyperactivity of the motivational cortical–striatal–thalamic–cortical (CSTC) reentry circuit, running from the orbitofrontal cortex, through the core part of the NAcb, ventral pallidum and thalamus back to the orbitofrontal cortex [23]. It has been suggested that the NAcb itself is responsible for sensing pleasure,

but this is unlike to be true. Probably, the nucleus accumbens core (NAcbC) has a classical role of adapting the activity when reward is expected based upon information about other significant factors [24]. We want to hypothesize that the experience of pleasure is more likely related with the sudden ceasing of the urge to obtain the delightful objects once they are acquired.

Evidence for this last proposal can be derived from investigating neuro-activation during a very pleasurable activity; that is having sex. The activity pattern during sexual activity has been extensively studied [24, 25]. In women, first the medial amygdala and insula become activated, among other structures; then, the cingulate cortex is added to this activation; and then, at orgasm itself, the NAcb, paraventricular nucleus of the hypothalamus (secretes oxytocin) and hippocampus become active [25]. Specific experiments by Georgiadis and colleagues [26, 27] have shown that during orgasm, which is the moment that true pleasure is perceived, the activation of brain structures is very much the same in men and women. What is particularly interesting is that they found a profound deactivation in the anterior part of the orbitofrontal cortex (and also in the temporal lobe). Georgiades and colleagues [27] interpret the decreased activity of the orbitofrontal cortex and the temporal lobe to reflect the occurrence of satiety. But this idea may be too limited. In our opinion, they also make a case that the relief that accompanies the disappearance of the urge to reach orgasm is indeed the most important representation of pleasure itself. The reaction within the orbitofrontal cortex may be due to the loss of anticipating achieving the important goal (because it has been reached). The profound deactivation of the motivational reentry circuit would result in abrupt ceasing of craving, what in itself could result in pleasure. This would also indicate that without craving also pleasure cannot occur.

A prefrontal structure that has consistently been implicated in negative mood states (i.e. dysphoria) is the subgenual part of the anterior cingulate cortex (Brodmann's areas 25 and the caudal portions of Brodmann's areas 32 and 24). Anatomical studies have shown that the volume of the infralimbic sgACC is reduced in certain depressed groups [28]. Moreover, the activity of the sgACC is affected following successful treatment with SSRIs, electroconvulsive therapy, transcranial magnetic stimulation (rTMS), ablative surgery and deep brain stimulation [29]. Moreover, this sgACC has been found to be metabolically overactive in depressed states and reacts to the treatment with a decrease of its activity [30].

As shown in **Figure 3**, the infralimbic subgenual part of the anterior cingulate cortex is one of the structures, which feeds the shell part of the NAcb [31]. Hyperactivity of this structure might well result in hyperactivity within a putative emotional reentry circuit, which starts and ends within the anterior cingulate cortex. The subgenual cingulate gyrus sends efferents to all subcortical structures of our limbic basal ganglia and receives afferents from several hypothalamic and thalamic nuclei [32]. This hyperactivation of the subgenual cingulate gyrus might in turn results in increased stimulation of the anterior insula [32], which might lead to experiencing feelings of dysphoria. Abrupt termination of this hyperactivity might result in happiness in the same manner as ending craving would result in pleasure.
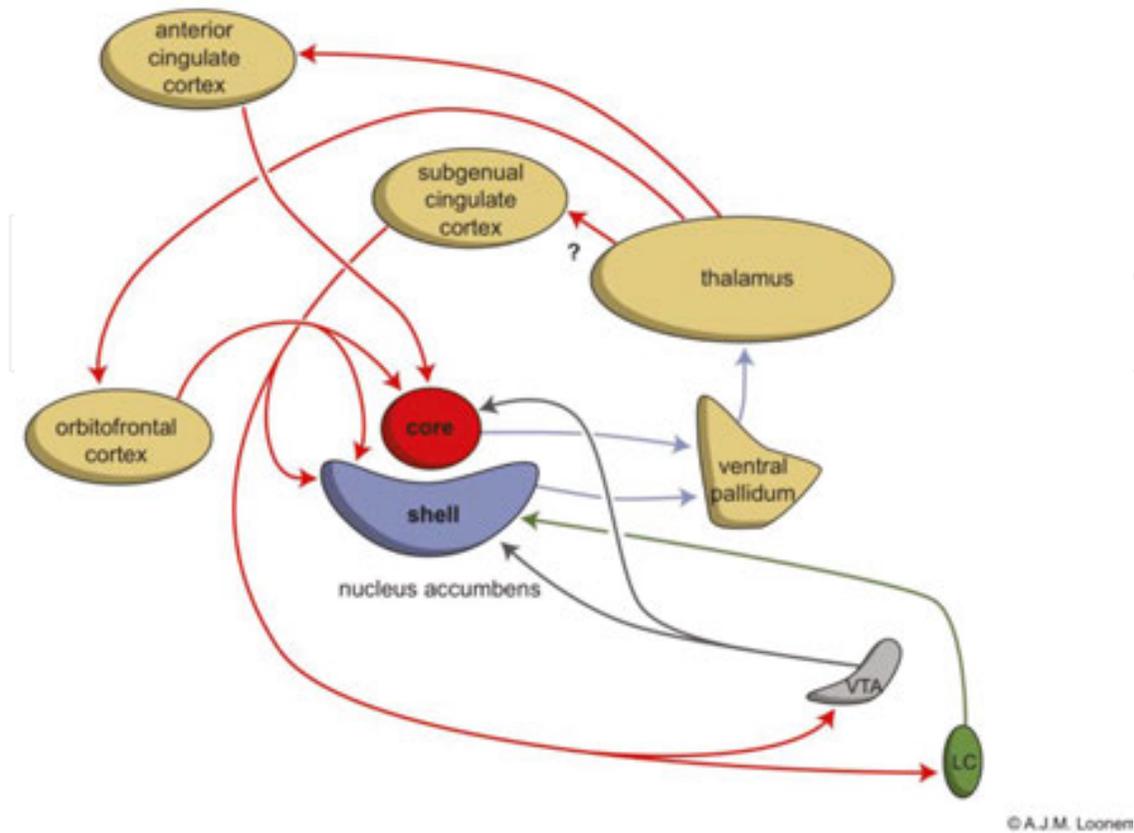
Figure 3. Stimulation of the core and shell of the nucleus accumbens. (Adapted from Ref. [31], reproduced with permission of the author). VTA = ventral tegmental area; LC = locus coeruleus. Red = glutamatergic, blue = GABAergic, grey = dopaminergic and green = adrenergic.

In conclusion, we want to hypothesize that two parallel cortical–subcortical reentry circuits regulate motivation to exert reward-bringing and misery-escaping behaviours, respectively. These circuits are involved in causing pleasure and happiness. Hyperactivity of the NAcb core-containing CSTC circuit induces craving and its abrupt ending is experienced as pleasure. Hyperactivity of the NAcb shell-containing CSTC circuit induces dysphoria and abrupt termination of the activity within this circuit would induce happiness.

4. Two complementary regulating circuits

In a previous paper, we have proposed to distinguish two separate circuits regulating skilled (cognitively controlled) and intuitive (emotionally controlled) behaviour: extrapyramidal and limbic circuits [11].

The 'extrapyramidal' circuit is often mainly associated with motor activity but also regulates other behavioural responses. The first relay station of this cortical–subcortical circuit is formed by the striatum, which consists of three parts that correspond to three parallel divisions of the extrapyramidal system: the caudate nucleus (cognitive system), putamen (motor system) and

ventral striatum (emotional/motivational system) [23, 33–35]. This last part is formed by the NAcb, which consists of a core (NAcbC) and a shell (NAcbS). The core belongs to the extrapyramidal basal ganglia and is primarily involved in motivating the organism to exhibit skilled behaviour. The shell belongs to the limbic basal ganglia and is primarily involved in facilitating intuitive (emotional) behaviour [23, 35].
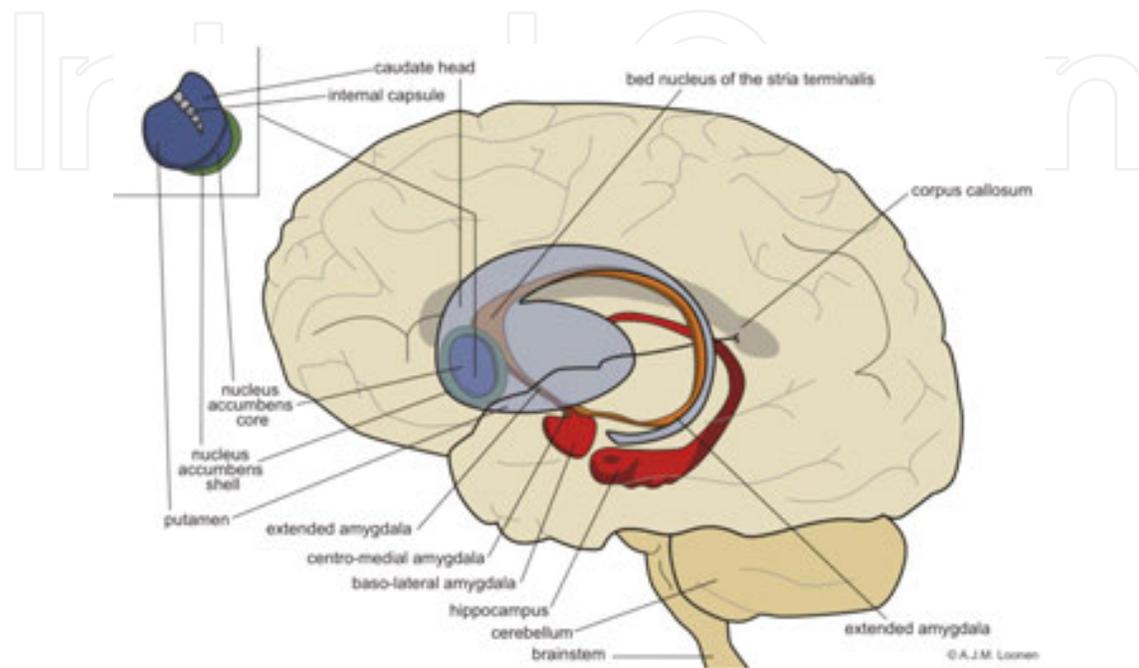

Figure 4. Position of the limbic basal ganglia (centromedial amygdala, extended amygdala, bed nucleus of the stria terminalis and nucleus accumbens shell) relative to the extrapyramidal basal ganglia (caudate nucleus, putamen, nucleus accumbens core) and hippocampus. The figure only shows the first relay stations of the extrapyramidal (light and dark blue) and limbic (orange and green) cortical–subcortical circuits.

The 'limbic' circuit is for a significant extent covered by the amygdala. The amygdala consists of a heterogeneous group of nuclei and cortical regions and is divided into cortical (basolateral) and ganglionic (centromedial) sections [36–38]. The various nuclei differ in the number and type of brain areas to which they are connected. Apart from extensive connectivity with a variety of cortical areas [37], the various parts of the complex are mutually massively connected with each other [37, 38]. Nevertheless, it is possible to consider the centromedial (ganglionic) part as an output channel to the diencephalon and brain stem, while the basolateral (cortical) part is more easily regarded as an input channel for cortical information. Moreover, the amygdaloid complex has widespread connectivity with many subcortical regions [37], including the dorsal and ventral striatum, the bed nucleus of the stria terminalis, and the basal forebrain nuclei. The centromedial amygdala is continuous with the extended amygdala, which is in turn continuous through the bed nucleus of the stria terminalis with the shell part of the NAcb [23, 39]. This extended amygdala takes a position to the allocortex (olfactory cortex and hippocampus) that is similar to that which the neocortex takes to the striatum [39]. This idea can be extended to distinguishing limbic and extrapyramidal basal ganglia. The centromedial amygdala, proper extended amygdala, bed nucleus of the stria terminalis, and

the shell of the NAcb form the limbic basal ganglia, with a function for the limbic cortex that reflects that of the extrapyramidal basal ganglia for the rest of the neocortex (**Figure 4**).

5. The evolution of the forebrain in vertebrates

We have developed an anatomical model how the intensity of reward-seeking and misery-fleeing behaviours is regulated. We propose that the first type of reward-seeking behaviours is controlled within a converging extrapyramidal neocortical–subcortical–frontocortical circuit containing as first stations, the caudate nucleus, putamen and core of the accumbens nucleus (NAcbC). The second type of misery-fleeing behaviours is then regulated by a limbic cortical–subcortical–frontocortical circuit containing as first relay stations, the centromedial amygdala, extended amygdala, bed nucleus of the stria terminalis and shell of the accumbens nucleus (NAcbS). As these types of behaviours must also have been exhibited by our most ancient ancestors, we studied the evolutionary development of the forebrain [6]. We found out that the earliest vertebrates, supposed to have a brain comparable with the modern lamprey, had an olfactory bulb, forebrain, diencephalon, brain stem and spinal cord, but not yet a true cerebellum. The forebrain of the lamprey contains a striatum with a modern extrapyramidal system, which is activated by dopaminergic mesostriatal fibres coming from the nucleus of the tuberculum posterior (NTP) [5], which is comparable with human ventral tegmental area
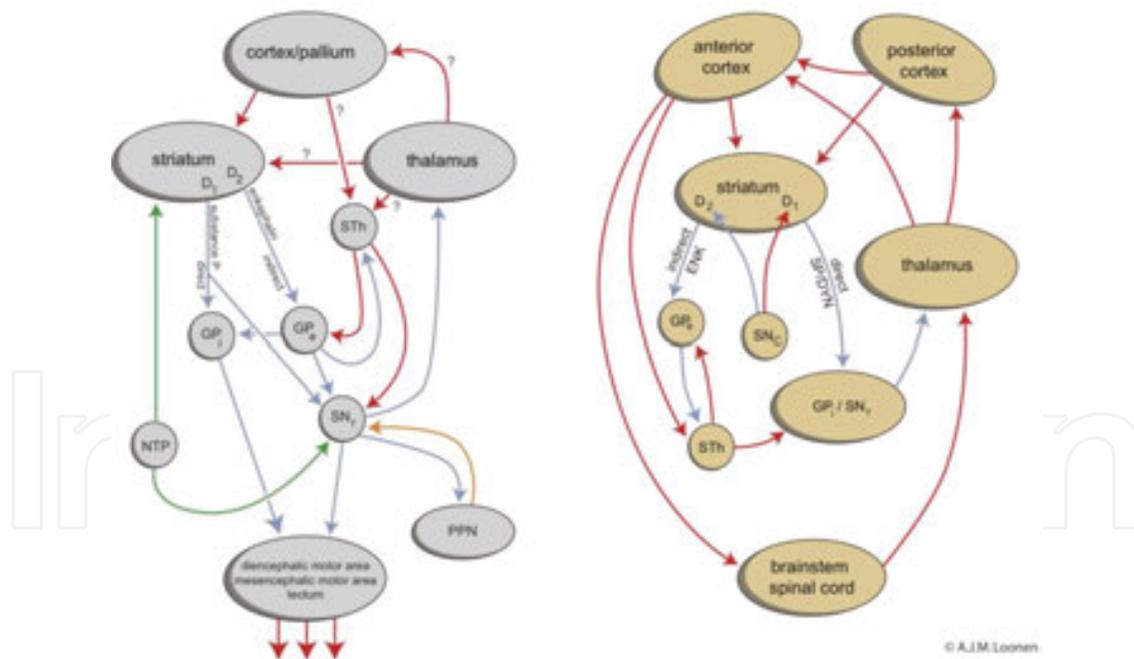

Figure 5. Simplified representation of the extrapyramidal system of lampreys (left) and humans (right). In lampreys, the internal and external parts of the globus pallidus are intermingled within the dorsal pallidum but functionally segregated. For further explanations, consult Refs. [33, 40, 41]. GPe = globus pallidus externa; GPi = globus pallidus interna; NTP = nucleus tuberculi posterior; PPN = pedunculopontine nucleus; SNr = substantia nigra pars reticulata; STh = subthalamic nucleus. Left figure: red = glutamatergic, blue = GABAergic, green = dopaminergic, orange = cholinergic; Right figure: red = excitatory, blue = inhibitory.

(VTA). An extrapyramidal circuit has not yet been developed and the extrapyramidal output ganglia directly activate motor control centres of the brainstem (**Figure 5**). In addition, the dorsal thalamus is very small and the forerunner of the neocortex has hardly developed.

It has been suggested that during evolution of vertebrates, the development of the cerebral cortex resulted in the successive addition of concise modules to the extrapyramidal basal ganglia, each regulating a newly acquired function of the species (**Figure 6**) [5]. What happened on the limbic side is not entirely clear. The amygdaloid complex was moved laterally to the pole of the temporal lobe. The centromedial amygdaloid nuclei can be considered to be a remaining part of the lampreys striatum, but whether the extended amygdala and the bed nucleus of the stria terminalis also evolved from this structure is uncertain. Amphibians already have a bed nucleus of the stria terminalis, which is closely associated with the central and medial nuclear amygdala [42]. The nucleus accumbens can be considered to be the interface between motor and limbic basal ganglia [35]. So, our theory is to a certain extent supported by these evolutionary considerations. We suggest that the core of the accumbens nucleus regulates the motivation to exhibit reward-driven (approach) behaviour and the shell of the accumbens nucleus regulates the motivation to exhibit misery-driven (avoidance) behaviour.
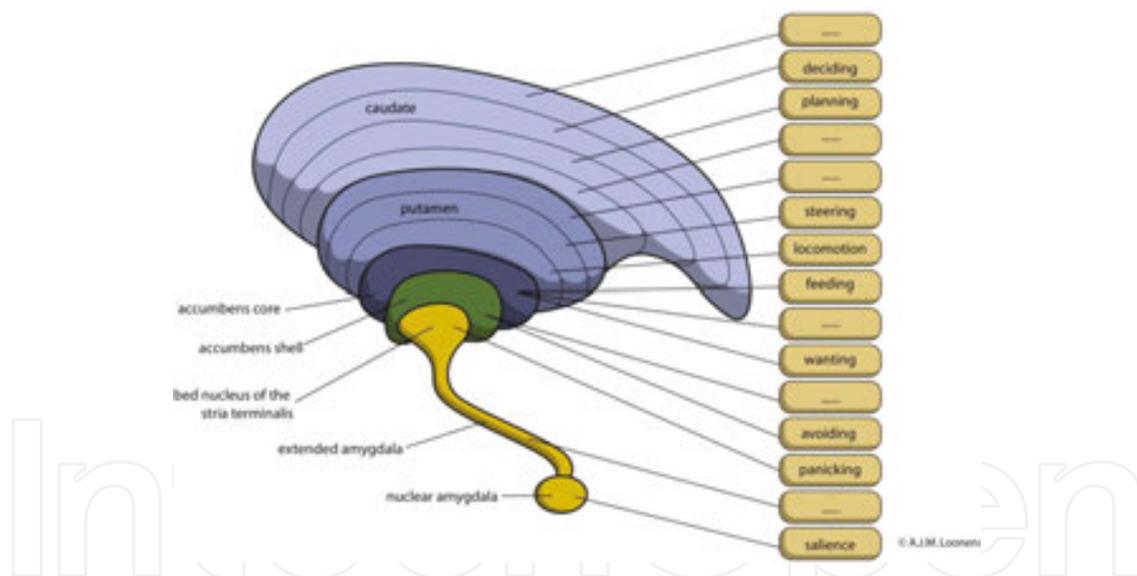

Figure 6. Modular expansion of the basal ganglia during evolution of vertebrates (adapted from [5]). The figure only shows the first relay stations of the extrapyramidal (light and dark blue) and limbic (yellow and green) cortical–subcortical circuits.

But how is this motivation to show these two types of behaviours adapted to the changing demands of environment? At this point, again, considering the forebrain of lampreys can shed some light on this matter. Within the lamprey's forebrain, a specific nuclear structure has been identified within the subhippocampal region, called the habenula-projecting globus pallidus (GPh) [6]. This nucleus receives inhibitory control from the striatum and excitatory input from both thalamus and pallium. It activates the lateral habenula, and from there, glutamatergic

fibres run directly to the dopaminergic NTP (excitatory) or indirectly via the GABAergic rostromedial tegmental nucleus (inhibitory). These dopaminergic fibres of the NTP regulate the activity of the striatum. So, in lampreys, the activity of the dopaminergic NTP is under the control of an evaluative system with input from the striatum and pallium in order to decide whether the locomotor activity should be increased or not (**Figure 7**). These structures increase activity during reward situations and decrease activity when an expected reward does not occur. A cholinergic circuitry from the medial habenula to the interpeduncular nucleus and periaqueductal grey regulates the fear/flight response.
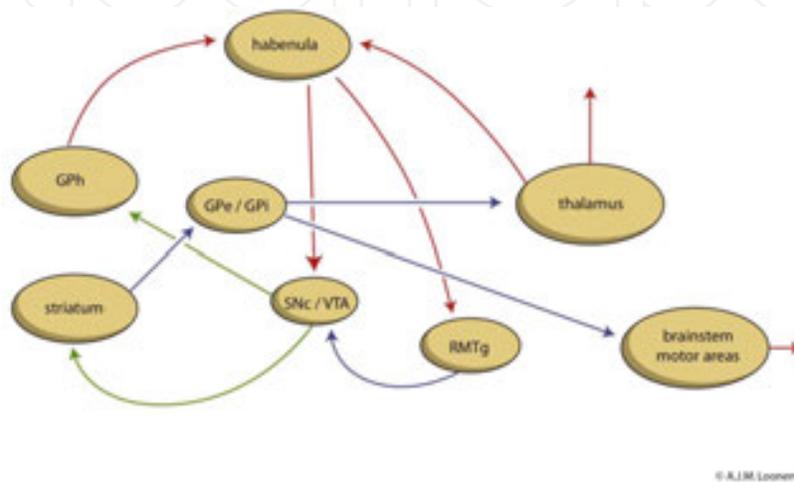

Figure 7. Circuitry of habenula-projecting globus pallidus of lampreys. Red = glutamatergic, blue = GABAergic, green = dopaminergic.

6. The habenula

The habenula in the epithalamus has recently received much attention for possibly playing a role in depression and addiction [43–47]. This is strongly related to the influence of the habenula on the activity of monoaminergic control centres of the brainstem [46, 47]. The habenula is subdivided into two nuclei: the medial habenula and lateral habenula. In lampreys, a direct pathway runs from the homologue of the lateral habenula to the nucleus of the tuberculum posterior (NTP; considered to be a homologue of the SNc/VTA), next to a pathway to a homologue of the GABAergic rostromedial tegmental nucleus (RMTg; which inhibits the NTP) [5, 48]. Other efferents of the lateral habenula run to (diencephalic) histaminergic and serotonergic areas. In lampreys, a projection system from the homologue of the medial habenula to the interpeduncular nucleus was also identified. These habenular output structures are well conserved across species. All the vertebrates examined possess the same efferent pathway, called fasciculus retroflexus, running to the ventral midbrain [9, 46, 47]. In mammals, the medial habenula projects, almost exclusively, to the cholinergic interpeduncular nucleus [49], whereas the lateral habenula projects to a variety of nuclei including the rostromedial tegmental nucleus (RMTg), raphe nuclei, substantia nigra, ventral tegmental area, and the

nucleus incertus [9]. Moreover, the medial habenula has direct output to the lateral habenula and may regulate the latter's activity [46, 47] (**Figure 8**).

However, the input to the epithalamus appears to be less well conserved during evolution. In lampreys, the input of the homologue of the medial habenula comes from the medial olfactory bulb, the parapineal organ, the pretectum and the striatum [48]. The input of the lateral habenula comes from subhippocampal lobe (habenula-projecting globus pallidus; GPh) and the lateral hypothalamus, but not from the diagonal band of Broca. Mammals do not have a distinct GPh. It has been suggested that its homologue in primates is localized in the border of the globus pallidus interna (GPb) [5, 50]. Whether the function of the lampreys' GPh is retained within this GPb, is far from certain. The mammalian habenula receives input via the stria medullaris from the posterior septum, as well as from the medial septum, the nucleus of the diagonal band and midbrain structures [47, 49]. Major input to the medial habenula arises from septal nuclei, which in turn receive the majority of their input from the hippocampus [48]. Afferents of the lateral habenula come from the hippocampus, ventral pallidum, lateral hypothalamus, globus pallidus and other basal ganglia structures [46]. It is hypothesized that during evolution from lampreys to mammals, the originally direct sensory innervation of the habenula has been replaced by inputs from the so-called limbic system (i.e. the septum and diagonal band of Broca) [48]. We prefer to say that this is not a replacement, but a maintainment as the human limbic system is considered to be a derivative of the lamprey's forebrain.
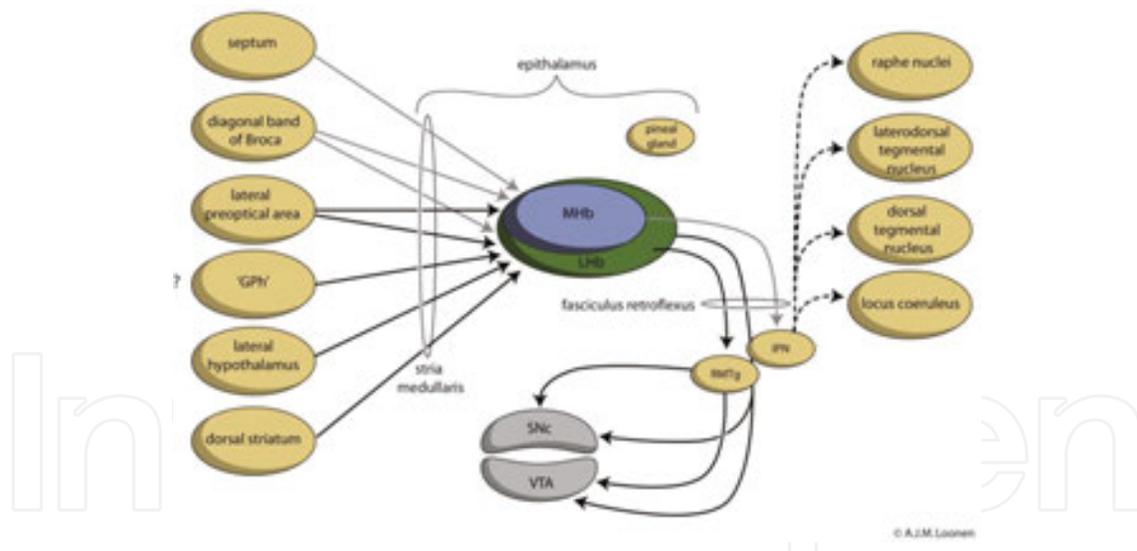

Figure 8. Connectivity through the epithalamus. GPh = habenula-projecting globus pallidus, IPN = interpeduncular nucleus, RMTg = rostromedial tegmental nucleus, SNc = substantia nigra, pars compacta, VTA = ventral tegmental nucleus (adapted from Ref. [47]).

In our opinion, the amygdala plays an essential role in value-based selection of behaviour (salience attribution) and this idea is supported by the history of the amygdaloid complex in our ancestors. When the habenula-projecting globus pallidus still exists and functions in humans, this structure should receive input from the amygdala and hippocampus and give glutamatergic output to the lateral habenula. The amygdala and hippocampus would then

regulate both the activity of the medial habenula (misery-fleeing behaviour) via septal nuclei as well as the activity of the lateral habenula (reward-seeking behaviour) via the homologue of the GPh. The amygdala and hippocampus should then be in an essential position for response selection of behaviour.

7. Idea for a possible role of habenula in addiction

In order to be considered to have a substance addiction, the individual must start to abuse a drug, he/she should maintain this abuse and/or he/she should relapse to abuse after a period of abstinence. Several lines of evidence suggest that indeed patients go through different stages of substance use, from intoxication, through repeated cycles of withdrawal and increasing tolerance to an end stage of addiction and relapse [3, 4]. It has also been shown that during this process, the motivation to use substances develops from 'liking' to 'wanting/needing' [3, 4]. In line with these findings, the neurobiological changes develop from more ventral striatal, reward-related, circuits to more dorsal striatal circuits involved in habit formation and stress [3, 4]. Moreover, addicted patients no longer use substances because it is nice (positive reinforcement), but because it reduces a negative affective state, related to increased activity of the brain stress systems, including the amygdala and hypothalamus-pituitary axis (negative reinforcement). This theory describes a development of addiction in three stages: *binge/ intoxication*, *withdrawal/negative affect* and *preoccupation/anticipation* [3, 4].

Our proposal of staging is slightly different in order to let it correspond better to the described primitive subcortical regulation of behaviour. Abuse is probably largely maintained by the pathological process of craving for drugs, which is activated by the observation of certain phenomena (cues), the getting involved in social and emotional circumstances or executing specific habits which all are related to the individuals' personal circumstances of drug abuse. We want to suggest that this mechanism (i.e. activation of craving by cues) explains the usage of the illicit drug by the individual on a regular basis. It has been described that the craving process is activated by stimulation of the dopaminergic input to the NAcb from the VTA. This VTA is in turn activated by glutamatergic fibres from the prefrontal cortex by a ventral connection, which are reacting upon analysis of the circumstances that predict the availability of the illicit drug [51]. The glutamatergic synapses with mesencephalic dopaminergic neurons carry nicotinic cholinergic receptors, which allow long term potentiation of this excitatory synaptic transmission [51].

The above mechanism explains how addiction is maintained, but not how it is initiated. We want to hypothesize that in this second process, the habenula is involved (for a description of the role of the habenula in addiction see Refs. [46, 47]). The lateral habenula stimulates or inhibits the VTA depending upon the result of the behaviour. It stimulates the behaviour when the result is more rewarding than expected [52, 53] and inhibits it when the behaviour has more or less disappointing results [54]. The lateral habenula also encodes reward probability, reward magnitude and the upcoming availability of information about reward [54, 55]. So, when an individual uses an illicit drug and the results are very rewarding (biological, psy-

chological or social) the habenula disinhibits the VTA to continue and expand this behaviour. The same is true concerning the rapid reactivation of craving for example tobacco, cocaine or GHB in the case of relapse after a period of abstinence. The lateral habenula could then signal vividly that the individual likes these effects very much. So it could be interesting to study the activity of the pathways during a phase of active drug abuse and after re-usage after a period of abstinence. This could also shed some light on the pharmacological mechanisms to prevent relapse.

Besides craving for the positive effects of substances, craving for addictive substances is also often accompanied by dysphoria and anxiety. This process has been described as the 'dark side of addiction' and has been associated with the development of a powerful negative reinforcement process [4]. This dysphoria is particularly true during relatively long-lasting periods of abstinence when even a clear depression can develop. Koob [4] has introduced the term 'anti-reward' to describe the background of this phenomenon. This is unfortunate, because it suggests a fictitious relationship with the reward-seeking system. However, this dysphoria could very well result from a dysfunction of another pathway connecting amygdaloid complex and hippocampus through the epithalamus with the midbrain. The misery-fleeing (fear/flight) response could be regulated via septal nuclei and medial habenula with the interpeduncular nucleus. Through this pathway, the medial habenula regulates the activity of the adrenergic locus coeruleus and the serotonergic dorsal raphe nucleus [47]. This could result in the activation of the misery-fleeing mechanism, causing dysphoria. The reward-seeking response could be regulated by a parallel pathway via a homologue of GPh and lateral habenula with the ventral tegmental area [56]. Hypoactivity of the reward-driven reentry circuit with as first station NAcbC would result in anhedonia and lack of energy, two main symptoms of depression.

8. Conclusions

Studying the evolution of the vertebrate's forebrain offers interesting clues about the mechanism of addiction. In lampreys, motor activity is regulated by a striatum, which can be considered to be the forerunner of the nuclear amygdala. The lamprey's striatum contains a quite modern extrapyramidal system (**Figure 5**). The activity of this striatum is regulated by dopaminergic fibres coming from the forerunner of the VTA in the midbrain. The activity of the VTA is in turn regulated by the habenula, with a connectivity that is very well conserved during the evolution into finally humans. During this evolution, the basal ganglia developed in a modular fashion with the addition of new layers on the dorsal side of the basal ganglia once new functions developed (**Figure 6**). The evolution of the ventral part of the basal ganglia is less certain, but these structures also became connected with parts of the (limbic) neocortex via the diencephalon. Therefore, it is possible to distinguish extrapyramidal and limbic CSTC circuits, which regulate the magnitude of reward-seeking and misery-fleeing behaviours. Motivation to express these two behaviours is regulated by the NAcbC and NAcbS, respectively. In turn, the VTA determines the activity of NAcb, and the locus coeruleus only of the NAcbS (**Figure 3**). Directly and indirectly, the upper raphe nuclei also determine the activity

of both parts of the NAcb [57]. As part of a dorsal pathway, the lateral habenula controls the activity of the VTA and the medial habenula the activity of locus coeruleus and raphe nuclei. The activity of both lateral and medial habenula is controlled by the amygdala and hippocampus. Via a ventral route, the prefrontal cortex also influences the activity of the VTA. We hypothesize that this ventral route is involved in maintaining substance abuse, while the dorsal route is primarily involved in initiating addiction and causing relapse into dependence after using illicit drugs after a period of abstinence.

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References

[1] Tang YY, Posner MI, Rothbart MK, Volkow ND. Circuitry of self-control and its role in reducing addiction. Trends Cogn Sci. 2015;19(8):43944. doi:10.1016/j.tics.2015.06.007

[2] Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278(5335):52–58. Stable URL: http://www.jstor.org/stable/2894498

[3] Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217–238. doi:10.1038/npp.2009.110

[4] Koob GF, Buck CL, Cohen A, Edwards S, Park PE, Schlosburg JE, Schmeichel B, Vendruscolo LF, Wade CL, Whitfield TW Jr, George O. Addiction as a stress surfeit disorder. Neuropharmacology. 2014;76 (Pt B):370–382. doi:10.1016/j.neuropharm. 2013.05.024

[5] Robertson B, Kardamakis A, Capantini Pérez-Fernández J, Suryanarayana SM, Wallén P, Stephenson-Jones M, Grillner S. The lamprey blueprint of the mammalian nervous system. Prog Brain Res. 2014;212:337–349. doi: 10.1016/B978-0-444-63488-7.00016-1

[6] Loonen AJM, Ivanova SA. Circuits regulating pleasure and happiness: the evolution of reward-seeking and missery-fleeing behavioral mechanisms in vertebrates. Front Neurosci. 2015;9:394. doi: 10.3389/fnins.2015.00394

[7] Moreno N, González A. The common organization of the amygdaloid complex in tetrapods: new concepts based on developmental, hodological and neurochemical data in anuran amphibians. Prog Neurobiol. 2006;78(2):61–90. doi: 10.1016/j.pneurobio.2005.12.005

[8] Benarroch EE. Habenula: recently recognized functions and potential clinical relevance. Neurology. 2015;85(11):992–1000. doi: 10.1212/WNL.0000000000001937

[9] Aizawa H. Habenula and the asymmetric development of the vertebrate brain. Anat Sci Int. 2013;88(1):1–9. doi: 10.1007/s12565-012-0158-6

[10] Salaberry NL, Mendoza J. Insights into the role of the habenular circadian clock in addiction. Front Psychiatry. 2015;6:179. doi: 10.3389/fpsyt.2015.00179

[11] Loonen AJM, Ivanova SA. Circuits regulating pleasure and happiness in major depression. Med Hypotheses. 2016;87(1):14–21. doi: 10.1016/j.mehy.2015.12.013

[12] Bruinsma F, Loonen A. Neurobiologie van cognitieve en emotionele motivatie. [Neurobiology of cognitive and emotional motivation] Neuropraxis. 2006;10(3):77–88. doi: 10.1007/BF03079087

[13] Sewards TV, Sewards MA. Representations of motivational drives in mesial cortex, medial thalamus, hypothalamus and midbrain. Brain Res Bull. 2003;61(1):25–49. doi: 10.1016/S0361-9230(03)00069-8

[14] Liotti M, Panksepp J. Imaging human emotions and affective feelings: implications for biological psychiatry. In: Panksepp J, editor. Textbook of biological psychiatry. Hoboken, NJ: Wiley-Liss; 2004. pp. 33–74. doi: 10.1002/0471468975.ch2

[15] Nieuwenhuys R. The insular cortex: a review. Prog Brain Res. 2012;195:123–163. doi: 10.1016/B978-0-444-53860-4.00007-6

[16] Nagai M, Kishi K, Kato S. Insular cortex and neuropsychiatric disorders: a review of recent literature. Eur Psychiatry. 2007;22(6):387–394. doi: 10.1016/j.eurpsy.2007.02.006

[17] Schioldann J. 'On periodical depressions and their pathogenesis' by Carl Lange (1886). Hist Psychiatry. 2011;22(1):108–130. doi: 10.1177/0957154X10396807

[18] Craig AD. Human feelings: why are some more aware than others? Trends Cogn Sci. 2004 Jun;8(6):239–241. doi: 10.1016/j.tics.2004.04.004

[19] Northoff G. From emotions to consciousness—a neuro-phenomenal and neuro-relational approach. Front Psychol. 2012;3:303. doi: 10.3389/fpsyg.2012.00303

[20] Craig AD. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10(1):59–70. doi: 10.1038/nrn2555

[21] Starkstein SE, Kremer J. The disinhibition syndrome and frontal-subcortical circuits. In: Lichter DF, Cummings JL, editors. Frontal-subcortical circuits in psychiatric and neurological disorders. New York, NY: Guilford Press; 2001. pp. 163–176. ISBN: 9781572306233.ch7

[22] Zald DH, Rauch SL, editors. The orbitofrontal cortex. Oxford: Oxford University Press, 2006. doi: 10.1093/acprof:oso/9780198565741.001.0001

[23] Heimer L. A new anatomical framework for neuropsychiatric disorders and drug abuse. Am J Psychiatry. 2003;160(10):1726–1739. doi: 10.1176/appi.ajp.160.10.1726

[24] Georgiadis JR, Kringelbach ML. The human sexual response cycle: brain imaging evidence linking sex to other pleasures. Prog Neurobiol. 2012;98(1):49–81. doi: 10.1016/j.pneurobio.2012.05.004

[25] Bianchi-Demicheli F, Ortigue S. Toward an understanding of the cerebral substrates of woman's orgasm. Neuropsychologia. 2007;45(12):2645–2659. doi: 10.1016/j.neuropsychologia.2007.04.016

[26] Georgiadis JR, Kortekaas R, Kuipers R, Nieuwenburg A, Pruim J, Reinders AA, Holstege G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. Eur J Neurosci. 2006;24(11):3305–3316. doi: 10.1111/j.1460-9568.2006.05206.x

[27] Georgiadis JR, Reinders AA, Paans AM, Renken R, Kortekaas R. Men versus women on sexual brain function: prominent differences during tactile genital stimulation, but not during orgasm. Hum Brain Mapp. 2009;30(10):3089–3101. doi: 10.1002/hbm.20733

[28] Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. J Psychiatr Res. 1997;31(4):393–432. doi: 10.1016/S0022-3956(97)00016-2

[29] Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. Br Med Bull. 2003;65(1):193–207. doi: 10.1093/bmb/65.1.193

[30] Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, Rafi-Tari S. Limbic-frontal circuitry in major depression: a path modeling metanalysis. Neuroimage. 2004;22(1):409–418. doi: 10.1016/j.neuroimage.2004.01.015

[31] Dalley JW, Mar AC, Economidou D, Robbins TW. Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. Pharmacol Biochem Behav. 2008;90(2):250–260. doi: 10.1016/j.pbb.2007.12.021

[32] Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM. The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry. 2011;69(4):301–308. doi: 10.1016/j.biopsych.2010.09.034

[33] Loonen AJ, Ivanova SA. New insights into the mechanism of drug-induced dyskinesia. CNS Spectr. 2013;18(1):15–20. doi: 10.1017/S1092852912000752

[34] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–381. doi: 10.1146/annurev.ne.09.030186.002041

[35] Groenewegen HJ, Trimble M. The ventral striatum as an interface between the limbic and motor systems. CNS Spectr. 2007;12(12):887–892. doi: 10.1017/S1092852900015650

[36] Balleine BW, Killcross S. Parallel incentive processing: an integrated view of amygdala function. Trends Neurosci. 2006;29(5):272–279. doi: 10.1016/j.tins.2006.03.002

[37] Freese JL, Amaral DG. Neuroanatomy of the primate amygdala. In: Whalen PJ, Phelps AE, editors. The human amygdala. New York, NY: Guildford Press; 2009. pp. 3–42. ISBN: 9781606230336.ch1

[38] Pitkänen A. Connectivity of the rat amygdaloid complex. In: Aggleton JP, editor. The Amygdala. A functional analysis. Oxford, UK: Oxford University Press; 2000: pp. 31–115. ISBN: 9780198505013.ch2

[39] Elias WJ, Ray DK, Jane JA. Lennart Heimer: concepts of the ventral striatum and extended amygdala. Neurosurg Focus. 2008;25(1):E8. doi: 10.3171/FOC/2008/25/7/E8

[40] Stephenson-Jones M, Samuelsson E, Ericsson J, Robertson B, Grillner S. Evolutionary conservation of the basal ganglia as a common vertebrate mechanism for action selection. Curr Biol. 2011;21(13):1081–1091. doi: 10.1016/j.cub.2011.05.001

[41] Stephenson-Jones M, Ericsson J, Robertson B, Grillner S. Evolution of the basal ganglia: dual-output pathways conserved throughout vertebrate phylogeny. J Comp Neurol. 2012;520(13):2957–2973. doi: 10.1002/cne.23087

[42] Moreno N, Morona R, López JM, Domínguez L, Joven A, Bandín S, González A. Characterization of the bed nucleus of the stria terminalis in the forebrain of anuran amphibians. J Comp Neurol. 2012;520(2):330–363. doi: 10.1002/cne.22694

[43] Belzung C, Willner P, Philippot P. Depression: from psychopathology to pathophysiology. Curr Opin Neurobiol. 2014;30C:24–30. doi: 10.1016/j.conb.2014.08.013

[44] Savitz JB, Nugent AC, Bogers W, Roiser JP, Bain EE, Neumeister A, Zarate CAJr, Manji HK, Cannon DM, Marrett S, Henn F, Charney DS, Drevets WC. Habenula volume in bipolar disorder and major depressive disorder: a high-resolution magnetic resonance imaging study. Biol Psychiatry. 2011;69(4):336–343. doi: 10.1016/j.biopsych.2010.09.027

[45] Schneider TM, Beynon C, Sartorius A, Unterberg AW, Kiening KL. Deep brain stimulation of the lateral habenular complex in treatment-resistant depression: traps

and pitfalls of trajectory choice. Neurosurgery. 2013;72(2 Suppl Operative):ons184–193. doi: 10.1227/NEU.0b013e318277a5aa

[46]   Velasquez KM, Molfese DL, Salas R. The role of the habenula in drug addiction. Front Hum Neurosci. 2014;8:174. doi: 10.3389/fnhum.2014.00174

[47]   Antolin-Fontes B, Ables JL, Görlich A, Ibañes-Tallon I. The habenulo-interpeduncular pathway in nicotine aversion and withdrawal. Neuropharmacology. 2015;96(Pt B):213–222. doi: 10.1016/j.neuropharm.2014.11.019.

[48]   Stephenson-Jones M, Floros O, Robertson B, Grillner S. Evolutionary conservation of the habenular nuclei and their circuitry controlling the dopamine and 5-hydroxytryptophan (5-HT) systems. Proc Natl Acad Sci USA. 2012;109(3):E164–E173. doi: 10.1073/pnas.1119348109.

[49]   Viswanath H, Carter AQ, Baldwin PR, Molfese DL, Salas R. The medial habenula: still neglected. Front Hum Neurosci. 2014;7:931. doi: 10.3389/fnhum.2013.00931

[50]   Grillner S, Robertson B. The basal ganglia downstream control of brainstem motor centres-an evolutionarily conserved strategy. Curr Opin Neurobiol. 2015;33:47–52. doi: 10.1016/j.conb.2015.01.019

[51]   Wu J, Gao M, Shen JX, Shi WX, Oster AM, Gutkin BS. Cortical control of VTA function and influence on nicotine reward. Biochem Pharmacol. 2013;86(8):1173–1180. doi: 10.1016/j.bcp.2013.07.013

[52]   Matsumoto M, Hikosaka O. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature. 2007;447(7148):1111–1115. doi: 10.1038/nature05860

[53]   Jhou TC, Good CH, Rowley CS, Xu SP, Wang H, Burnham NW, Hoffman AF, Lupica CR, Ikemoto S. Cocaine drives aversive conditioning via delayed activation of dopamine-responsive habenular and midbrain pathways. J Neurosci. 2013;33(17):7501–7512. doi: 10.1523/JNEUROSCI.3634-12.2013

[54]   Matsumoto M, Hikosaka O. Representation of negative motivational value in the primate lateral habenula. Nat Neurosci. 2009;12(1):77–84. doi: 10.1038/nn.2233

[55]   Bromberg-Martin ES, Matsumoto M, Hikosaka O. Distinct tonic and phasic anticipatory activity in lateral habenula and dopamine neurons. Neuron. 2010;67(1):144–155. doi: 10.1016/j.neuron.2010.06.016

[56]   Lecca S, Meye FJ, Mameli M. The lateral habenula in addiction and depression: an anatomical, synaptic and behavioral overview. Eur J Neurosci. 2014;39(7):1170–1178. doi: 10.1111/ejn.12480

[57]   Loonen AJM, Ivanova SA. Role of 5-HT2C receptors in dyskinesia. Int J Pharm Pharm Sci. 2016;8(1):5–10. http://innovareacademics.in/journals/index.php/ijpps/article/viewFile/8736/3470