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Review article

The role of the habenula in the transition from reward to misery in substance use and mood disorders

Albert Batalla[a,b,*], Judith R. Homberg[c], Tatiana V. Lipina[d,e], Guillaume Sescousse[f], Maartje Luijten[g], Svetlana A. Ivanova[h,i], Arnt F.A. Schellekens[a,b,f], Anton J.M. Loonen[j,k]

[a] Radboud University Medical Center, Department of Psychiatry, Reinier Postlaan 10, 6500 HB, Nijmegen, The Netherlands
[b] Radboud University, Nijmegen Institute for Scientist-Practitioners in Addiction, Toernooiveld 5, 6525 ED, Nijmegen, The Netherlands
[c] Radboud University Medical Center, Department of Cognitive Neuroscience, PO Box 9101, 6500 HB, Nijmegen, The Netherlands
[d] Federal State Budgetary Scientific Institution, Scientific Research Institute of Physiology and Basic Medicine, Timakova 4, 630117, Novosibirsk, Russia
[e] Novosibirsk State University, Pirogova 2, 630090, Novosibirsk, Russia
[f] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Kapittelweg 29, 6525 EN, Nijmegen, The Netherlands
[g] Behavioural Science Institute, Radboud University, Montessorilaan 3, 6525 HR, Nijmegen, The Netherlands
[h] Mental Health Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, Aleutskaya street 4, 634014, Tomsk, Russian Federation
[i] National Research Tomsk Polytechnic University, Lenin Avenue, 30, 634050, Tomsk, Russian Federation
[j] Groningen Research Institute of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713AV, Groningen, The Netherlands
[k] GGZ Westelijk Noord-Brabant, Hoofdlaan 8, 4661AA, Halsteren, The Netherlands

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ABSTRACT

The habenula (Hb) is an evolutionary well-conserved structure located in the epithalamus. The Hb receives inputs from the septum, basal ganglia, hypothalamus, anterior cingulate and medial prefrontal cortex, and projects to several midbrain centers, most importantly the inhibitory rostromedial tegmental nucleus (RMTg) and the excitatory interpeduncular nucleus (IPN), which regulate the activity of midbrain monoaminergic nuclei. The Hb is postulated to play a key role in reward and aversion processing across species, including humans, and to be implicated in the different stages of transition from recreational drug intake to addiction and co-morbid mood disorders. The Hb is divided into two anatomically and functionally distinct nuclei, the lateral (LHb) and the medial (MHb), which are primarily involved in reward-seeking (LHb) and misery-fleeing (MHb) behavior by controlling the RMTg and IPN, respectively. This review provides a neuroanatomical description of the Hb, discusses preclinical and human findings regarding its role in the development of addiction and co-morbid mood disorders, and addresses future directions in this area.

1. Introduction

The habenula (Hb) (from the Latin, little rein) is a phylogenetically old structure highly conserved among vertebrates located in the dorsomedial portion of the thalamus (Benarroch, 2015; Loonen and Ivanova, 2015). The habenular nuclei are paired structures and belong to the epithalamus, which also harbors the pineal gland and the stria medullaris. The Hb is considered to be an important relay between cortical and subcortical structures implicated in emotion and reward processing (Hetu et al., 2016). The Hb receives inputs from the septum, basal ganglia, lateral hypothalamus, anterior cingulate and medial prefrontal cortex, and projects to several midbrain centers, most importantly the tail of the ventral tegmental area (also known as the rostromedial tegmental nucleus [RMTg]) and to the interpeduncular nucleus, which regulate the activity of midbrain monoaminergic nuclei (Bianco and Wilson, 2009; Herkenham and Nauta, 1977). As emotional and reward-related impairments are relevant across psychiatric disorders, particularly within addiction and mood disorders (Goya-Maldonado et al., 2015; Jentsch and Pennington, 2014), the function of the Hb in humans is of great clinical importance.

Functionally, the Hb is divided into lateral (LHb) and medial (MHb) parts (Benarroch, 2015; Klemm, 2004). The MHb is connected to the amygdalo-hippocampal system through fornix and medial septal area and to the LHb via the striatopallidal (i.e. extended) amygdala and lateral hypothalamus (Loonen and Ivanova, 2016b). The LHb plays an important role in brain reward responses, and has been linked to drug

* Corresponding author at: Department of Psychiatry, Radboud University Medical Center, Reinier Postlaan 10, Route 966, 6500 HB, Nijmegen, The Netherlands.
E-mail addresses: abatallacases@gmail.com (A. Batalla), judith.homberg@radboudumc.nl (J.R. Homberg), lipina@physiol.ru (T.V. Lipina), g.sescousse@fcdonders.ru.nl (G. Sescousse), m.luijten@pwo.ru.nl (M. Luijten), svetlana@mail.tomsknet.ru (S.A. Ivanova), arnt.schellekens@radboudumc.nl (A.F.A. Schellekens), a.j.m.loonen@rug.nl (A.J.M. Loonen).

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addiction, as well as reward-related processes in major depression (Matsumoto and Hikosaka, 2007; Sartorius et al., 2010). The MHb – which has not yet been studied as extensively as the LHb – has been mainly associated with the regulation of nicotine intake (Fowler et al., 2011; Salas et al., 2009) and may also be implicated in the regulation of depressive mood (Viswanath et al., 2013). It has been postulated that the LHb might be more implicated in the initial stages of recreational drug intake (associated with positive reinforcement), while the gradual shift towards compulsive drug use in addiction, strongly associated with negative affect (negative reinforcement), might be mediated by an enhanced activity of the LHb and a gradually greater involvement of the MHb (Loonen et al., 2017; Loonen et al., 2016).

The structure and function of the Hb have been mainly explored in preclinical studies using rodent and monkey models. The study of the Hb in humans has been hampered by its small size and difficulties resolving its boundaries (Ely et al., 2016; Kim et al., 2016; Lawson et al., 2013). Despite this limitation, several groups have attempted to study the Hb at conventional fMRI resolutions (Erpelding et al., 2014; Garrison et al., 2013; Ide and Li, 2011; Li et al., 2008; Noonan et al., 2011; Schiffer et al., 2012; Ullsperger and von Cramon, 2003) and more recently at high resolutions (Ely et al., 2016; Hennigan et al., 2015; Hetu et al., 2016; Lawson et al., 2016; Lawson et al., 2014; Salas et al., 2010), providing fairly consistent findings of Hb activation when studying punishment and reward processing.

The present review focuses on the neuroanatomical description of the Hb, and discussion of preclinical and human findings regarding the role of the Hb in the transition from recreational drug intake to addiction and co-morbid mood disorders. We first describe the neuroanatomical properties of the LHb and MHb together with their afferent and efferent projections. Second, we review animal studies showing how the Hb is involved in reward processes and aversive states, and how this may mediate the transition from recreational to compulsive drug use and development of co-morbid mood disorders. Third, we review neuroimaging studies investigating the structure and function of the Hb in humans, as well as its role in reward, aversive states, addiction and depression. Finally, we propose a model of transition from recreational drug use to substance use and mood disorders, we discuss the limitations of the existing findings and we offer suggestions for future work in this area.

2. Habenula neuroanatomy

2.1. Connections of the habenula with other brain structures

2.1.1. Inputs

The Hb receives signals from the septum, hippocampus, ventral pallidum, lateral hypothalamus, global pallidus, and other areas of the basal ganglia (Fig. 1). The main input to the MHb comes from the septum, particularly the medial septum and the adjacent nucleus of the diagonal band of Broca (Benarroch, 2015; Klemm, 2004). The input to the MHb from these septal areas is primarily cholinergic and gamma-aminobutyric acid (GABA)ergic, although some inputs are glutamatergic (Benarroch, 2015). Moreover, the MHb receives dopaminergic input from the ventral tegmental area (VTA), adrenergic (norepinephrine) input from the locus coeruleus and serotonergic (5-hydroxytryptamine, 5-HT) input from the raphe nuclei (Benarroch, 2015; Bianco and Wilson, 2009; Xie et al., 2016). The LHb primarily receives glutamatergic afferents from the preoptic area, lateral hypothalamus, the entopeduncular nucleus (EPN; analog of globus pallidus in primates), the anterior cingulate and medial prefrontal cortex (Benarroch, 2015). The LHb also receives strong GABAergic innervations (Poller et al., 2013) from various other brain regions, including e.g. the EPN, nucleus accumbens and VTA. However, most of the inputs of the Hb functional inputs are still unknown (Shabel et al., 2012). Hence, there is a large heterogeneity in GABAergic inputs onto LHb neurons. Although the input from the basal ganglia is thought to be primarily inhibitory, Shabel et al. (2012) have shown that transmission from the basal ganglia to the LHb can also be excitatory glutamatergic, and suppressed by serotonin. These neurons may correspond to part of the habenula-projecting globus pallidus (GPh) of human's earliest vertebrates ancestors, a structure primarily involved in decision making in reward-driven behavior (Loonen and Ivanova, 2015). Additionally, the LHb receives dopaminergic innervation from the VTA, serotonergic innervation from the medial raphe nucleus, and adrenergic input from the locus coeruleus (Benarroch, 2015; Stamatakis et al., 2013). The LHb neurons express tyrosine hydroxylase (TH) and DA type 2 and 4 receptors (Aizawa et al., 2012; Geisler et al., 2003; Good et al., 2013; Gruber et al., 2007). A single-pulse stimulation of the VTA inhibits the firing of ~90% of the LHb neurons, whereas tetanic stimulation increases the activity of LHb units (Shen et al., 2012). Although the MHb sends projections to the LHb, there is no connection from LHb to the MHb (Kim and Chang, 2005).

2.1.2. Outputs

Information encoded by the LHb and the MHb is transmitted through the fasciculus retroflexus (FR) axon bundle to several midbrain monoaminergic nuclei (Hikosaka, 2010). However, the majority of the output is given to two specific midbrain areas: the rostromedial tegmental nucleus (RMTg) and the interpeduncular nucleus (IPN) (Fig. 1).

The FR is divided into two regions, the *outer* and the *inner* areas. The *outer* region originates in the LHb and projects mainly to the RMTg, next to numerous monoaminergic nuclei in the mid- and hindbrain (Bianco and Wilson, 2009). These efferents are predominantly glutamatergic, but some are GABAergic and cholinergic (Bianco and Wilson, 2009). The RMTg is a small nucleus that contains mainly inhibitory GABAergic cells and thereby regulates activity of VTA/substantia nigra compacta (SNc) and the dorsal raphe nucleus (Benarroch, 2015). More specifically, LHb neurons predominantly inhibit dopaminergic (DA) neurons of the midbrain (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). Electrical stimulation of LHb abolished the firing of ~ 90% of DA neurons of VTA and SNc (Christoph et al., 1986; Matsumoto and Hikosaka, 2007). Vice versa, lesion of LHb increased DA turnover in terminal projection areas of these midbrain nuclei (Lecourtier et al., 2008). Similarly, through its RMTg projection, stimulation of the LHb caused transient inhibition of the firing activity of serotonergic neurons in the raphe nucleus (Wang and Aghajanian, 1977). LHb neurons also directly target the DA VTA (Lammel et al., 2012) and substantia nigra pars compacta, the serotonergic medial and dorsal raphe nuclei, cholinergic laterodorsal tegmentum and noradrenergic locus coeruleus (Herkenham and Nauta, 1979).

The *inner* area of the FR originates in the MHb and projects to the IPN (Benarroch, 2015; Bianco and Wilson, 2009; Klemm, 2004; Sutherland, 1982). The MHb contains both cholinergic neurons (in its ventral two-thirds) and dorsally located substance P-containing neurons, which innervate the ventral and dorsal versus the lateral IPN, respectively (Artymyshyn and Murray, 1985; Contestabile et al., 1987). This neuronal pathway is highly conserved across various species (Broms et al., 2015). The results of Qin and Luo (2009) suggest that, at least in mice, also glutamate is used as a neurotransmitter next to acetylcholine and substance P (Qin and Luo, 2009). The MHb is the main source of input for the IPN (Bianco and Wilson, 2009; Klemm, 2004; Morley, 1986), although cholinergic fibers may also originate in the posterior septum (Contestabile and Fonnum, 1983; Fonnum and Contestabile, 1984). The IPN is a singular, unpaired structure located at the ventral midline of the midbrain (Klemm, 2004; Morley, 1986). The major efferent pathways originating in the IPN project to the dorsal tegmental nucleus (Morley, 1986), the VTA (Klemm, 2004) and the raphe nuclei (Bianco and Wilson, 2009; Klemm, 2004). However, the IPN is well known for its widespread ascending and descending projections (Klemm, 2004; Morley, 1986). Apart from a low number of serotonergic neurons (continuous with the B8 cell group of the medial raphe nucleus) numerous peptidergic neurons (substance P, met-

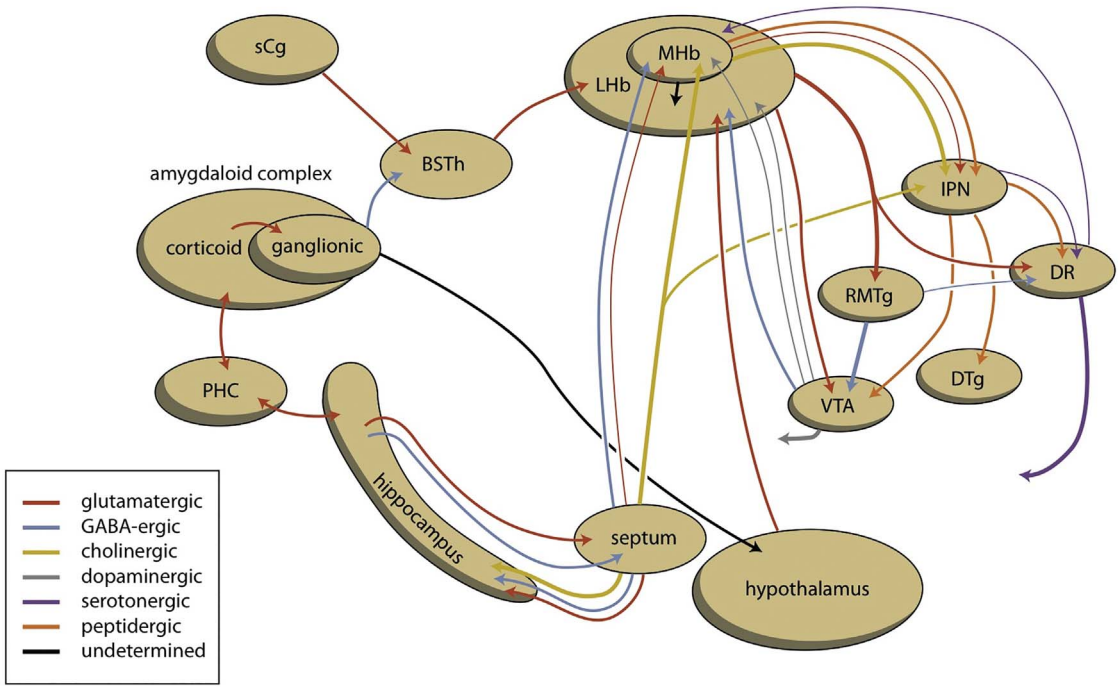

Fig. 1. Scheme showing the connectivity of the amygdalo-hippocampal system to the midbrain through the habenular complex.
BST = bed nucleus of the stria terminalis; DR = dorsal raphe nucleus; DTg = dorsal tegmental nucleus; IPN = interpeduncular nucleus; LHb = lateral habenula; MHb = medial habenula; PHC = parahippocampal cortex; RMTg = rostromedial tegmental nucleus; sCg = subgenual cingulate gyrus; VTA = ventral tegmental area. Reproduced from Loonen and Ivanova (doi: in press) with permission of the copyright owner.

enkephalin, somatostatin) have been identified within the IPN (Morley, 1986).

2.2. Neurons in the LHb and MHb

Most of the LHb neurons are glutamatergic, with enriched expression of vesicular glutamate transporter (VGluT2) (Li et al., 2011; Stamatakis and Stuber, 2012). Also, there is a small population of inhibitory GABAergic interneurons (Smith et al., 1987). Both $GABA_A$ and $GABA_B$ receptors were detected in the rodent LHb (Liang et al., 2000; Rodriguez-Pallares et al., 2001). LHb cells showed various firing patterns, including regular pace-making, irregular discharge activity or spontaneously occurring trains of bursts (Kowski et al., 2009; Weiss and Veh, 2011). Electrophysiological experiments indicate that excitatory transmission onto LHb neurons is mainly induced by a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), with a low expression of *N*-methyl-D-aspartate receptors (NMDAR) (Li et al., 2011; Maroteaux and Mameli, 2012).

The MHb is distinctive from the LHb in that it co-expresses the mRNA of α3, α5, and β4 nAChRs subunits at very high (α3 and β4) or moderate (α5) levels (Bierut, 2011). The IPN, main the output from the MHb, is also enriched in α5 and β4 nAChR subunits expression. Furthermore, muscarinic cholinergic receptors have been identified within the IPN (Kuhar et al., 1975), though less extensively distributed than nAChRs (Rotter et al., 1979; Schwartz, 1986). Spencer et al. (1986) demonstrated that within the IPN muscarinic receptors were almost exclusively M2-class (inhibitory) autoreceptors on cholinergic terminals (Spencer et al., 1986).

3. Functional role of the habenula in aversive states and reward processing

3.1. Role of the LHb

The most important function of the LHb is to convey aversive states (Hikosaka, 2010). For instance, the anticipation or (unexpected) experience of air puffs in the eye have been shown to cause a strong excitation of the LHb neurons recorded by in vivo electrophysiology in monkeys (Matsumoto and Hikosaka, 2009). Notably, LHb neuronal firing occurs in response to unpredicted aversive events, also known as negative prediction errors; when a punishment could be predicted, LHb firing was much less pronounced (Matsumoto and Hikosaka, 2009). In line with this role in processing negative prediction errors, LHb neuronal firing is also increased by the omission of an expected reward (i.e., disappointment) (Matsumoto and Hikosaka, 2009).

Li et al. (2011) reported that enhanced excitatory synaptic transmission onto VTA-projecting LHb neurons positively correlated with the degree of helpless behavior, and that deep brain stimulation of the LHb, resulting in decreased excitatory synaptic transmission, acutely reversed "learned helplessness" (Li et al., 2011), a rodent model of human major depression (Shumake et al., 2003). Similarly, Yang et al. (2008) found that rats with electrolytic lesions of the LHb displayed a decrease in immobility time and an increase in climbing time in the forced swim test, indicative for decreased depression-like mood (Yang et al., 2008). Along this lines, Stamatakis and Stuber (2012) exposed mice to aversive stimuli (footshocks), used to induce depressive-like phenotypes in rodents. They found an increase in the frequency of miniature excitatory post-synaptic potentials, and a decrease in paired-pulse ratio in the LHb (Stamatakis and Stuber, 2012), suggesting that exposure to footshock stress enhanced activity of LHb neurons projecting to the RMTg. Additionally, activating this projection induced passive avoidance and conditioned place aversion (Stamatakis and Stuber, 2012). Vice versa, inhibition of the LHb using Designer Receptor Exclusively Activated by Designer Drugs (DREADD) technology had anti-depressant effects in the forced swim test (Nair et al., 2013).

The LHb is also involved in the regulation of reward processes. For instance, it has been demonstrated that the activity of LHb neurons is diminished by unexpected rewards or their cues (Jhou et al., 2009; Matsumoto and Hikosaka, 2007). The LHb is believed to encode reward probability, reward value and the availability of information about potential rewards (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009). However, this is not necessarily encoded by the LHb

itself, but can also be mediated along a pathway including the LHb. It has also been demonstrated that activation of the VTA-LHb inhibitory pathway resulted in place preference behavior, which was prevented by intra-LHb microinjections of GABAa antagonist and disinhibition of VTA dopaminergic neurons (Stamatakis et al., 2013).

Overall, current results suggest that the LHb plays an important role in processing of aversive and rewarding stimuli. LHb activation is associated with aversive states and stimuli, while LHb deactivation is related to rewarding states and stimuli, functioning as an anti-reward node.

3.2. Role of the MHb

Studies into the functional role of the MHb are limited. A distinct/specific role of the MHb in the motivational aspects of mood and anxiety disorders has been suggested (Viswanath et al., 2013). This is, for example, concluded from altered metabolic activity in the MHb in rat studies of "learned helplessness", a test measuring the motivation to escape a stressor (Shumake et al., 2003). Furthermore, it was demonstrated that mice lacking the dorsal MHb perform poorly in motivation-based locomotor behaviors, such as voluntary wheel running and the accelerating rotarod, without abnormalities in gait, balance and basal locomotion. These mice also showed reduced sucrose preference (indicative for reduced motivation), but no changes in forced swim test performance, measuring depressive mood (Hsu et al., 2014). This suggests that the MHb is implicated in motivation, but not in depression-like mood.

MHb-mediated motivation to undertake action is probably related to projections of the MHb to the IPN. Indeed, recent studies suggest that the MHb-IPN pathway should be included as part of several well-known circuitries regulating the aversive states associated with drug withdrawal (Koob and Volkow, 2010; Lobo and Nestler, 2011). As outlined previously, the MHb is characterized by a striking high level of nAChR expression. The β2 and α6 nAChRs present in MHb-IPN pathway are involved in the affective symptoms of nicotine withdrawal. For instance, animal studies in mice have shown that knockout of the β2 nAChR subunit, mainly/highly expressed within the MHb-IPN pathway, reduced anxiety and conditioned place aversion during nicotine withdrawal from chronic nicotine exposure (Jackson et al., 2008). This effect has also been observed in mice after administration of α6 nAChR antagonist; nicotine-induced conditioned place preference was blocked as well as withdrawal-associated conditioned place aversion and anxiety (Jackson et al., 2009). Overall, animal studies indicate that α2, β2, α6 contribute to the affective domain of aversive symptoms of nicotine withdrawal (Fowler et al., 2008) but the specific role of the MHb in aversive states still needs to be clarified.

The assumed involvement of the MHb in reward-related processes is largely based on animal studies with nicotine administration (Viswanath et al., 2014). For instance, it has been shown that mice without choline acetyltransferase (ChAT; responsible for acetylcholine synthesis) in habenular neurons were resistant to nicotine-induced reward as measured by acute nicotine-induced psychomotor activity (Frahm et al., 2015). This implies that acetylcholine in the MHb is important for (nicotine) reward and highlights the role of the MHb in motivational aspects associated with reward processes (e.g. translating motivation into action).

Several mouse lines lacking nAChR subunits have been generated. For instance, mice without β4 subunit did not self-administer nicotine. These animals also showed absence of nicotine-induced dopamine release in the ventral striatum (Picciotto et al., 1998). These effects could at least in part be mediated by alterations in MHb function. The α4 subunit is also important for regulation of reward in mice (Tapper et al., 2004). Activation of α4 subunit of AChRs by a low dose of nicotine in α4 mutant mice carrying a point mutation causing substitution of leucine to alanine at 9th amino acid and thereby mimicking hypersensitivity to nicotine, induced reinforcing effects of acute nicotine administration (Tapper et al., 2004). Hence, β4 and α4 subunits of A-ChRs can be considered as "addiction targets".

In sum, current results suggest that the LHb plays a role in processing aversive and rewarding stimuli, whilethe MHb plays a role in reward processing and motivation. While LHb activation is associated with aversion, LHb deactivation is associated with reward. On the other hand, MHb activation seems to be associated with reward and motivation and deactivation with the lack of both.

4. The habenula in substance use disorders and associated aversive (mood) states: pathways to addiction and mood disorders

4.1. Transition to substance abuse and mood disorders

Drug addiction is a chronic relapsing disorder characterized by a loss of control over drug use, a high motivation for obtaining the drug, and maintaining drug use despite negative consequences (American Psychiatric Association, 2013). It has been proposed that drug addiction, in contrast to recreational drug use, involves a dysregulation of the neural circuits mediating reinforcement, reflecting two parallel mechanisms: dysfunction of the brain reward systems that normally mediate natural rewards and the recruitment of brain stress systems that drive aversive states (Koob and Volkow, 2010; Wise and Koob, 2014). Addiction is often conceptualized as a three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (Munro, 2015). These stages of the addiction cycle feed into each other, become more intense, and ultimately lead to the pathological state known as addiction. During this transition the positive reinforcement of the early stages of drug use turns into negative reinforcement, which ultimately predominates (Koob and Volkow, 2010). Not surprisingly, there is a high comorbidity between depression and drug addiction: subjects suffering from cocaine addiction are twice as likely to be depressed (National Survey on Drug Use and Health, 2012) compared with healthy controls.

The transition from positive to negative reinforcement during the development of addiction is where the Hb may play a key role. Positive reinforcement is defined as a learning process related to experiencing positive affective states (rewards). Negative reinforcement is defined as a learning process related to the alleviating of negative affective states (removal of an aversive stimulus). The aversive, negative emotional state that drives the negative reinforcement of addiction is produced by two opponent processes. First, the negative affective state is hypothesized to be mediated by deficits in the brain systems that mediate reward. Second, the negative affective state is thought to be mediated by recruitment of brain stress systems, i.e. the frontotemporal amygdalohippocampal complex (Wise and Koob, 2014).

It is generally acknowledged that drugs of abuse modulate the activity of dopaminergic neurons in the VTA (Luscher and Malenka, 2011), leading to increased dopamine release in the nucleus accumbens, which plays a central role in positive reinforcement (Wise, 2004). Negative reinforcement is thought to be mediated by the neuroadaptive changes that occur during drug withdrawal. These involve changes in the mesolimbic dopamine system, changes in corticotropin-releasing factor (CRF), norepinephrine, and dynorphin in the extended amygdala, and changes in the dynorphin-κ opioid system in the nucleus accumbens and extended amygdala (Wise and Koob, 2014). Given the functional profile of the habenula, neuroadaptive changes in this area may be added to this list.

4.2. The specific role of the LHb

Since glutamatergic neurons of the LHb display relatively high rates of spontaneous activity allowing disinhibition in rewarding circumstances (Hong et al., 2011; Matsumoto and Hikosaka, 2007) and LHb firing increases in cases of reward omissions or other unpleasant events, the LHb may serve as an"anti-reward"center. In reward states,

habenular activity is generally below average, and in aversive states (e.g., during disappointing events), the habenular signal is above the spontaneous level (Velasquez et al., 2014). In addition, expectation of aversive events results in increased phasic firing of LHb neurons, which is reduced after positive outcomes (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2007, 2009). Therefore, the LHb functioning corresponds to what occurs during the addictive state according to the anti-reward process theory (Koob and Volkow, 2010). This is in line with the findings that LHb stimulation promotes conditioned avoidance and reduces reward-related responding (Lammel et al., 2012; Stamatakis and Stuber, 2012). This is linked to addiction as mouse experiments revealed that cocaine enhanced glutamatergic transmission in LHb neurons targeting the RMTg (Meye et al., 2015). Disrupting this mechanism prevented development of depressive-like symptoms (that is, depression-like mood as measured in the forced swim test) during withdrawal from repeated cocaine administration (Meye et al., 2015). A limitation of this elegant study is that repeated systemic drug administration as employed in this study was insufficient to trigger an addictive state. Nonetheless, these findings do shed some light on the effect of drugs of abuse on LHb function under non-pathological conditions. Taken together, these results suggest that anti-reward signals carried by the LHb may serve as a key factor to continue drug seeking. Supporting this hypothesis, deep brain stimulation of the LHb can reduce cocaine intake, facilitate extinction and attenuate drug-induced relapse in rats trained to self-administer cocaine (Friedman et al., 2011).

How do drugs of abuse disturb the activity of the LHb? It has been recently demonstrated that the EPN (the mouse equivalent of the globus pallidus) projects to a subset of LHb neurons innervating the RMTg. Of interest, this EPN-to-LHb (probably the mouse homologue of the earlier mentioned GPh) excitatory signaling was limited by GABAergic co-transmission, and this inhibitory component decreased during cocaine withdrawal as a result of reduced presynaptic vesicular GABA transporter (VGAT). This shifted the EPN-to-LHb GABA/glutamate balance to glutamate, disinhibiting EPN-driven LHb activity. If signals coming out of the LHb are tonically amplified after cocaine exposure, VTA dopamine neurons receive a greater amount of tonic inhibition from the RMTg and therefore less DA is released from VTA neurons. Thus, excitatory activity of LHb neurons and their afferents may be elevated as a form of homeostatic regulation, to counteract the robust increase in dopaminergic firing following intense cocaine exposure (Jhou et al., 2013; Zahm et al., 2010). Suppression of signaling the value of events would then be expected to lead to an incapability to decide what option – e.g. drug or other relevant events – may be'better' in terms of survival. Whereas under non-pathological conditions organisms prefer food over drugs (Lenoir et al., 2007), when LHb function gets disrupted the drug may get progressively the overhand relative to food intake (and other events important for survival) (Lenoir et al., 2013), particularly when dysfunction of the MHb gets gradually involved (see Sections 4.3 and 6).

Serotonin is also implicated in the behavioral effects mediated by the LHb, although serotonin's role only has been investigated in relation to anxiety and mood, and not in relation to the effects of drugs of abuse. In vivo microdialysis studies indicated that serotonin levels in the DRN in animals displaying behavioral despair induced by chronic unpredictable stress were significantly lower than in control animals (Yang et al., 2008), which is in accordance with the inhibitory control of the LHb over midbrain/brainstem areas like the DRN and the key role of serotonin in anxiety and mood. Serotonin also influences LHb input; serotonin has an inhibitory effect on the excitatory input from the EPN (i.e. from GPh) to the LHb (Shabel et al., 2012). This is in line with the finding that negative prediction errors can be modulated by serotonin (Fischer et al., 2015) and suggests that reduced serotonin release in the raphe nuclei upon LHb stimulation leads to disinhibition of LHb input, as a self-regulating loop to maintain homeostasis.

4.3. The specific role of the MHb

Evidence for the role of the MHb in drug addiction is derived from studies focusing on morphine and tobacco addiction. For instance, chronic morphine administration has been found to decrease c-fos activity in the MHb whereas morphine withdrawal elevates c-fos protein levels in the LHb (Neugebauer et al., 2013). Furthermore, the MHb expresses mRNA for all three of α3, α5, and β4 nAChRs subunits at very high (α3 and β4) or moderate (α5) levels (Bierut, 2011), and genome-wide association studies (GWAS) found consistent results across distinct laboratories showing an association between α3, α5, and β4 nAChRs gene cluster and tobacco use and addiction (Amos, 2007; Berrettini et al., 2008). Of interest, no change in the basal or nicotine-induced neuronal firing was observed in cholinergic MHb neurons from mice chronically treated with nicotine, while during withdrawal (associated with negative affect) re-exposure to nicotine doubled the firing of cholinergic neurons (Gorlich et al., 2013). Furthermore, nicotine withdrawal-induced anxiety increases activity of neurons in the interpeduncular intermediate (IPI), a subregion of the IPN, through its glutamatergic input from MHb (Zhao-Shea et al., 2015). MHb cholinergic neurons regulate nicotine withdrawal-induced anxiety via increased signaling through nicotinic receptors containing the α6 subunit. This was demonstrated using mice expressing these gain-of-function nAChRs. The mice exhibited increased nicotine-withdrawal induced anxiety-like behavior that was alleviated by blockade with a nAChR antagonist (Pang et al., 2016). These findings demonstrate that cholinergic MHb neurons particularly control aversive states associated with withdrawal.

The MHb may regulate nicotine reward by directly controlling glutamate release in the IPN. Mice characterized by local elimination of choline acetyltransferase (Chat) in the MHb neurons were found to be insensitive to nicotine-conditioned reward and withdrawal, due to the absence of ACh control over the quantal size and release frequency of glutamate at habenular synapses in the IPN (Frahm et al., 2015). The IPN, on its turn, may control dopamine release in the striatum through projections to the VTA (Groenewegen et al., 1986; Klemm, 2004). Indeed, injections of β4 antagonists into the MHb prevented nicotine-induced dopamine release in the nucleus accumbens (McCallum et al., 2012), and micro-infusion of an alpha3beta4 nicotinic antagonist into the MHb prevented nicotine-induced behavioral sensitization and sensitization-related dopamine release in the nucleus accumbens (Eggan and McCallum, 2016). As to whether the MHb is also implicated in substance use disorders other than tobacco addiction is an outstanding question for future research. Since mu opioid receptor expression is weak in the LHb but strong in the septum, MHb (co-localization with substance P and Ach neurons), fasciculus retroflexus (fr) and IPN (Gardon et al., 2014), also opiate dependence may be driven by the MHb. In support, chronic morphine administration with escalating doses (20, 40, 60, 80, 100, 100, and 100 mg/kg, IP, 3 times a day (08.30, 13.00, and 18.30 h) caused a reduction in acetylcholinesterase (AChE) activity in the MHb (Neugebauer et al., 2013), while a higher dose of morphine (150 mg/kg three times a day) injected for a longer period of time increased AChE activity in the MHb (Mohanakumar and Sood, 1983). Notably, during morphine withdrawal, AChE activity in MHb recovered to baseline (Neugebauer et al., 2013).

Apart from acetylcholine and catecholamines, also the serotonergic system is intricately involved in mood and anxiety regulation. The MHb is via IPN connected with the serotonergic upper raphe nuclei, which in turn project to ventral and dorsal striatum, to the extended amygdala, to the amygdalo-hippocampal complex and to the prefrontal cortex (Nieuwenhuys, 1985). These serotonergic fibres inhibit dopamine release from its terminals. In turn, the amygdalo-hippocampal system is probably an important source of input to the MHb via fornix and medial septum (Loonen and Ivanova, 2016b). This circuit is believed to have an important role in the regulation of the stress/anxiety response system. The septohippocampal system can also be considered as the neural

substrate regulating the behavioral inhibition system that modulates reaction to stimuli indicating adverse events (Hahn et al., 2010). It has been demonstrated anticipation of monetary loss elicited activation in the hippocampus as well as in the amygdala (Hahn et al., 2010).

Furthermore, conditional deletion of cannabinoid type 1 receptors (CB1R) from MHb neurons reduced fear-conditioned freezing and abolished conditioned odor aversion in mice, without affecting neutral or reward-related memories. Local inhibition of nicotinic, but not glutamatergic receptors in the IPN before retrieval, rescued these phenotypes and optogenetic electrophysiological recordings of MHb-to-IPN circuitry revealed that blockade of CB1R specifically enhances cholinergic, but not glutamatergic, neurotransmission (Soria-Gomez et al., 2015). Thus, a dysfunction of the MHb-mediated fear without affecting reward-related memories could drive to a selective motivation for drug use above other rewards.

4.4. The specific role of the fasciculus retroflexus

On the long-term, when drugs are used for a substantial period of time, the increased excitability of LHb glutamatergic efferents may lead to dysfunction of the outer area of the fasciculus retroflexus. It has been reported that substance use disorders and rats with a history of cocaine self-administration are characterized by degeneration of the fasciculus retroflexus (Ellison, 2002; Lax et al., 2013). In rats this was reflected by a decreased number of LHb neurons labeled with a retrograde tracer injected into the VTA (Lax et al., 2013). Cocaine may cause damage to brain tissue via oxidative stress and mitochrondial impairment (Cunha-Oliveira et al., 2008; Numa et al., 2008; Poon et al., 2007). Since a dysregulation of glutamate neurotransmission can lead to abnormal levels of glutathione, an antioxidant, and oxidative stress can lead to degeneration of myelination (Kulak et al., 2013), the excessive glutamate release may be one cause of fasciculus retroflexus degeneration. A recent study demonstrated that nicotine self-administration in mice was associated with differential (i.e. opposing) expression of micro-RNAs in the LHb and MHb, which target various genes of cell signaling pathways related to the degeneration of the fasciculus retroflexus (e.g. mmu-miR-669c-3p regulated the sortilin 1 (Sort1)), one of the receptors involved in cell-death signaling (Lee et al., 2015). Hence, micro-RNAs may provide another pathway by which long-term self-administration of drugs of abuse can lead to degeneration of the outer area of the fasciculus retroflexus. It is tempting to speculate that under these conditions less efficient efferent function of the LHb, leads to an increase of the relative contribution of the MHb to behavior.

5. Function of the habenula in human neuroimaging studies

Despite the considerable amount of data available from preclinical and experimental animal studies (Bianco and Wilson, 2009), the functional role of the Hb in humans remains largely unexplored (Ely et al., 2016; Furman and Gotlib, 2016; Hennigan et al., 2015; Hetu et al., 2016; Lawson et al., 2016; Lawson et al., 2014). An important limitation has been the small size of the structure, which is reported to be approximately 30 mm3 in each hemisphere (LHb plus MHb) post-mortem (Ranft et al., 2010). However, in vivo estimates report sizes around 18.5 mm^3 per hemisphere (Savitz et al., 2011), which means that in each hemisphere the Hb may be even smaller than the standard functional MRI voxel size (i.e. 27 mm^3, with a resolution of 3 mm isotropic voxels). Recently, several groups have employed a high-resolution fMRI approach to examine resting state (Ely et al., 2016; Hetu et al., 2016) and task-related (Furman and Gotlib, 2016; Hennigan et al., 2015; Lawson et al., 2016; Lawson et al., 2014) Hb activity with ≤ 2 mm isotropic voxel sizes, providing novel and more reliable information about the Hb network in humans. Because this resolution is still coarse to study in the Hb in detail, these studies cannot distinguish between the lateral and medial parts as in animal studies.

5.1. Functional connectivity of habenula during resting state

Resting-state high-resolution fMRI studies indicate that the Hb is functionally connected with several cortical and subcortical regions involved in reward and aversion processing (Ely et al., 2016; Hetu et al., 2016). At the cortical level, the Hb has shown to be functionally coupled to the insula and somatosensory and motor regions, which are involved in interoception and sensorimotor planning, respectively. The Hb is also functionally coupled to areas of the default mode network, including the PCC, retrosplenial cortex, pregenual ACC, and parahippocampal gyrus (Ely et al., 2016; Hetu et al., 2016). At the subcortical level, the thalamus, striatum (caudate body), pons, SN/VTA complex, periaqueductal gray (PAG) and locus coeruleus have been shown to be functionally connected with the Hb (Ely et al., 2016; Hetu et al., 2016).

These results are consistent with observations from animal studies, highlighting the VTA, thalamus, (para)hippocampus and ACC as the main Hb afferents, and the SN, VTA and raphe nuclei as the main (indirect) efferents (Benarroch, 2015; Bianco and Wilson, 2009). In particular, evidence of Hb connectivity with the VTA in humans adds to the growing body of evidence that the Hb functionally interacts with the midbrain dopaminergic reward system (Benarroch, 2015; Ely et al., 2016; Hetu et al., 2016). In addition, clusters of activity within the dorsal medial pons in the vicinity of the dorsal raphe nuclei support the connection of the Hb with the primary serotonergic target reported in the preclinical literature (Benarroch, 2015; Ely et al., 2016). Finally, the network activity of the Hb appears to also extend into the noradrenergic locus coeruleus, which is known to be bi-directionally connected with both the MHb and LHb (Ely et al., 2016) (see Section 2.1. for details).

In summary, the functional coupling between the Hb and cortical/subcortical regions is in agreement with the proposed role of the Hb as a relay between cognitive/sensory processing structures and the aminergic regions of the midbrain involved in affective and reward processing (Bianco and Wilson, 2009; Hikosaka, 2010; Proulx et al., 2014).

5.2. Functional role of habenula in aversive processing

As stated in previous sections, several animal studies have shown that the Hb plays an important role in the processing of aversive stimuli and negative prediction errors (Lammel et al., 2012; Matsumoto and Hikosaka, 2007, 2009; Stamatakis and Stuber, 2012). High-resolution fMRI studies in humans have revealed that regions known to be involved in emotional processing, such as the posterior insula, the PAG and the limbic system, are functionally connected with the Hb (Ely et al., 2016; Hetu et al., 2016). Task-related high-resolution fMRI studies have extended these findings by showing that the Hb is involved in the processing of cues predicting noxious stimuli in humans. Lawson et al. (2014, 2016) demonstrated in two studies that the Hb encodes the negative conditioned value of stimuli predicting electric shocks, with greater activation elicited by greater expectation of receiving a painful electric shock (Lawson et al., 2016; Lawson et al., 2014). In Lawson et al. (2014), the (right) Hb also displayed increased functional connectivity with several structures including the amygdala with increasing aversive value of the conditioned stimulus (Lawson et al., 2014). Consistent with these results, Hennigan et al. (2015) showed increased Hb activation in anticipation of electric shocks as compared with neutral stimuli, as well as increased functional connectivity with the VTA (Hennigan et al., 2015). These results suggest that the functional connections identified in resting-state studies between the Hb and the VTA/limbic system are most likely part of the functional network processing aversive stimuli (Ely et al., 2016; Hennigan et al., 2015; Hetu et al., 2016; Lawson et al., 2016; Lawson et al., 2014).

Finally, two studies explored the functional connectivity of the Hb in individuals with subclinical depression (Ely et al., 2016) as well as with major depression (Lawson et al., 2016). Ely et al. (2016) reported that depressed mood was associated with stronger resting-state Hb

connectivity with default mode network regions (dmPFC, anterior middle temporal gyrus, temporal pole, and inferior lateral parietal cortex) and weaker connectivity with salience network areas (anterior insula, amygdala, and mid-cingulate cortex). However, these results must be treated with caution due to the lack of correction for multiple comparisons. Intriguingly, the study by Lawson et al. (2016) found that, in contrast to healthy controls, the Hb of patients with major depression showed decreasing activation as the expectation of receiving a painful electric shock increased (Lawson et al., 2016). This result, which is at odds with current models of depression based on animal studies, may suggest that major depression is characterized by a loss of capacity to avoid negative cues.

5.3. Connectivity with structures associated with reward processes

Neuroimaging studies have revealed that the Hb is functionally connected with the striatum and the SN/VTA complex in humans (Ely et al., 2016; Hetu et al., 2016), which is in line with its role in reward learning and goal-directed actions (Bianco and Wilson, 2009; Hikosaka, 2010; Proulx et al., 2014). Animal studies have shown that the Hb plays a major role in controlling the activity of dopamine neurons in the SNc and the VTA (Matsumoto and Hikosaka, 2007). More precisely, the firing rate of Hb neurons increases following unexpected aversive stimuli and decreases following unexpected reward (Matsumoto and Hikosaka, 2007) (see Sections 3.1 and 3.2), while the firing rate of dopamine neurons increases in response to unexpected rewards (see Sections 4.2 and 4.5). Both structures are known to be part of the same circuit, where the GABAergic RMTg −located in the caudal section of the VTA- has been proposed to play a mediating role, translating activation/inhibition in the Hb into inhibition/activation in the SN/VTA (see Sections 2.1.2 and 4.2).

Using fMRI, Hetu et al. (2016) have shown that activity in the right Hb was negatively coupled with activity in the right VTA left caudate during rest (although note that the left Hb was *positively* coupled with regions in the bilateral SN/VTA complex) (Hetu et al., 2016). These results suggest a similar functional architecture in humans as observed in animal studies, i.e. an inhibitory influence of the Hb on the dopamine system possibly mediated by the RMTg, which in turn reduces activity within the striatum (Bianco and Wilson, 2009; Hikosaka, 2010; Proulx et al., 2014). However, this finding has not been replicated so far. Ely et al. (2016) identified functional connectivity between the Hb and dorsal ACC, a key region for reward and emotion processing that has been consistently implicated in major depression (Ely et al., 2016).

Consistent with the animal literature, high-resolution task-related studies have reported decreased Hb activity during the experience of rewarding stimuli (e.g., juice), but increased Hb activity following negative prediction errors, induced by exposure to noxious stimuli (e.g. electric shocks) or experience of negative feedback (e.g. monetary penalties) (Furman and Gotlib, 2016; Hennigan et al., 2015; Lawson et al., 2014; Salas et al., 2010).

5.4. Limitations of current neuroimaging studies

In order to obtain high spatial resolution while maintaining reasonable temporal resolution, the reviewed studies herein were frequently only able to achieve partial brain coverage (Hennigan et al., 2015; Hetu et al., 2016; Lawson et al., 2016; Lawson et al., 2014). As a result, the functional relationship of the Hb with the entire brain remains an open question. Although current neuroimaging data provide strong evidence that the Hb is functionally coupled to the VTA in humans during rest, they cannot inform us on the exact nature of these connections, as it is difficult to precisely identify which subpopulation of neurons within the VTA is functionally connected with the Hb in humans using fMRI (Hetu et al., 2016). In addition, it is important to note that since BOLD (Blood Oxygen Level Dependent) signal is only an indirect measure of neuronal activity (Logothetis et al., 2001), caution is needed when interpreting positive/negative correlations as excitatory/inhibitory influences (Hetu et al., 2016).

From animal studies it is known that the Hb can be further divided into two functional parts, the MHb and LHb, which have different inputs and outputs and different functions (Lecca et al., 2011; Viswanath et al., 2013) (see Sections 2 and 3). Unfortunately, current limitations of neuroimaging methods (i.e. relatively low anatomical MRI contrast and low functional resolution) do not allow to reliably distinguishing these sub-parts on a structural image. This limitation raises the possibility that Hb activity picked up with fMRI reflects an intermixing of signals from functionally distinct regions (Ely et al., 2016; Furman and Gotlib, 2016; Hetu et al., 2016; Lawson et al., 2016; Lawson et al., 2014). In addition, although there is agreement that the left and the right Hb do not differ morphologically in humans (Ely et al., 2016; Lawson et al., 2013; Ranft et al., 2010), differences in the delineating techniques that often consider different boundaries (Kim et al., 2016; Lawson et al., 2013; Savitz et al., 2011) might result in volume differences (left vs. right) and identification discrepancies of the Hb among the studies. Furthermore, standard pre-processing steps (e.g. normalization and spatial smoothing) might lead to localization errors (Lawson et al., 2013), making the signal from the Hb difficult to distinguish from adjacent structures.

6. Model of gradually enhanced activity of LHb and MHb

The human prefrontal cortex is connected to the midbrain monoaminergic nuclei through a ventral route (passing through the medial forebrain bundle) and a dorsal pathway (including the habenula and RMTg/IPN). We have recently developed a model of how the activity of this dorsal connection is regulated in addiction (Loonen et al., 2017; Loonen et al., 2016) and depression (Loonen and Ivanova, 2016a). Of interest, it has been proposed that depression, and in particular bipolar depression, involves a dysregulation of the catecholaminergic and cholinergic systems (Loonen et al., 2017; van Enkhuizen et al., 2015). Evidence from neuroimaging studies, neuropharmacological interventions, and genetic associations supports the notion that increased cholinergic functioning underlies depressive mood, whereas increased release of catecholamines (dopamine and norepinephrine) underlies the behavioral activity changes of mania (van Enkhuizen et al., 2015). Decreased activity of the latter is also likely to be implicated in core motivational symptoms such as anhedonia (loss of enjoyment or pleasure), commonly present in both addiction and mood disorders (i.e. unipolar and bipolar depression), which points at a common neural substrate (Lawson et al., 2016). Given that the LHb regulates the catecholaminergic system, and that the MHb is enriched with nicotinic cholinergic receptors and regulates the IPN, this view implies that the transition from recreational drug use to substance abuse and mood disorders, which is driven by negative reinforcement mechanistically, could involve an enhanced activity of the LHb, with a gradually greater involvement of the MHb.

Here we propose a model where the Hb plays a crucial role in the transition from recreational drug use to addiction, by (1) development of a negative affective state (contributing to negative reinforcement of drug use) and (2) development of selective motivation for compulsive drug use. In the early stages of drug use, the use of drugs has rewarding effects, resulting in positive reinforcement learning. Based on the functional roles of the LHb and MHb, we propose that during this phase of recreational drug use, LHb activity is reduced upon drug intake, whereas MHb activity is increased. This results in a positive affective state and an increasing motivation to obtain the drug.

In the subsequent development of drug addiction, the LHb would become steadily more activated in some individuals, due to homeostatic processes, counteracting the repeated de-activation by ongoing drug use. Drug use becomes then a way to compensate for this LHb hyperactivity, by temporarily relieving the associated negative affective state (negative reinforcement). At the same time, the progressive enhanced

activity of the MHb might contribute to reduced sensitivity for rewards other than drugs of abuse, resulting in a selective motivation to obtain these drugs of abuse. An increased MHb activity would also further enhance the activity of the LHb, leading to increased negative affective states and contributing to the development of core motivational symptoms involved in addiction and mood disorders, such as anhedonia. Finally, a progressive dysfunction of the fasciculus retroflexus, that is, a less efficient efferent function of the LHb, might further increase the relative contribution of the MHb and therefore aggravate the Hb dysfunction, intensifying the negative mood states (LHb) and the selective motivation for using drugs of abuse above other rewards (MHb).

7. Future perspectives

Testing our model of gradually enhanced LHb and MHb activity during the transition from recreational substance use to addiction and associate aversive states requires that future research considers a number of important factors. First of all, rodents should not be addicted when being administered a drug in the early stages, or when self-administering a drug on a regular basis. Rather, rats have to display a gradual loss of control over self-administration behavior, as is typically measured using the extended access model for drug self-administration (Ahmed and Koob, 1998). Furthermore, it is important to emphasize that only those animals showing an increased motivation to self-administer the drug, while being insensitive to conditioned suppression of drug self-administration and continuing drug seeking behavior during extinction, fulfill critical DSM-5 criteria for substance use disorders and can be 'diagnosed' as being addicted (Deroche-Gamonet et al., 2004). Likewise, the proper measurement of an aversive state, like depression, is critical. Depression is a heterogeneous disorder, diagnosed based on 11 DSM-5 criteria (American Psychiatric Association, 2013). Although not all of the depression-related criteria can be measured in rodents, several of them can, like depressive mood, anhedonia, loss of energy, changes in body weight, changes in activity, changes in circadian rhythm and decreased cognitive functioning. Yet, most rodent studies capture only a few of these and study the degree of dysfunction, which is often insufficient for conclusions regarding depression understood as a categorical disorder. It has been acknowledged that the integration of dimensional (domains of dysfunction) with categorical (class of disorder) criteria is crucial in clinical and preclinical research in psychiatry (Kraemer, 2015; Millan et al., 2015). We therefore recommend the application of categorical approaches (e.g. DSM-5) to define depression in rodents, while studying domains of dysfunction. In addition it is clear that there is a need to elaborate studies on the role of the MHb in addiction beyond nicotine as substance. Moreover, differences between type of processes driving MHb and LHb into encoding aversive states should be clarified in experimental studies. The function of the LHb is related to reward motivated behaviors and the MHb to stress/danger motivated conducts. Depression consists of changes of both components (Loonen and Ivanova, 2016a). When using animal models of depressive-like behavior the relationship with these two components should be explicitly considered in order to disentangle the contribution of both parts of the Hb. At the neuroanatomical level, investigation of changes in the structural and functional connectivity from the LHb to the RMTg, VTA and DRN, the MHb to the LHb, and the MHb to the IPN will be crucial to support our model. Novel technologies like cell-type specific Rabies Virus monosynaptic retrograde tracing to characterize anatomical projections, followed by their optogenetic or chemogenetic manipulation to assess their function and contribution to behavior are very suitable.

High-resolution fMRI offers the only non-invasive method to investigate the function of the Hb in humans, and provides a vital link from animal models to clinical symptoms in humans. In the same way, the integration of dimensional and categorical approaches is essential in order to better classify trans-diagnostic dimensions of disease within a biological framework and promote the detection of potential biomarkers. Human neuroimaging studies on the Hb will benefit from the use of standardized segmentation methods that have shown to be robust and objective for selecting Hb seed voxels for functional and diffusion MRI using 3T (Kim et al., 2016). Future studies are needed to evaluate the reproducibility of such segmentation scheme under various acquisition and contrast conditions both in healthy controls and psychiatric patients, including patients suffering from substance use and mood disorders. High-resolution and high contrast 7T Hb imaging (Strotmann et al., 2014) and associated segmentation schemes represent a promising future research direction for more accurate Hb morphological and functional evaluation. Such techniques could shed light on the functional activity of the LHb and MHb in humans. As the Hb is increasingly considered as a potential target for treatment of psychiatric disorders, neuroimaging studies revealing the functional coupling of this structure in humans are essential. A better understanding of the altered networks involved in psychiatric conditions is of major importance to identify the correlational and/or potential causal relationships among specific symptoms domains (i.e. anhedonia), categorical disorders (i.e. substance use and mood disorders) and treatment options. Such knowledge will contribute to the development of treatment and prevention strategies for those vulnerable individuals.

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