

Reward processing by the lateral habenula in normal and depressive behaviors

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The brain reward circuit has a central role in reinforcing behaviors that are rewarding and preventing behaviors that lead to punishment. Recent work has shown that the lateral habenula is an important part of the reward circuit by providing 'negative value' signals to the dopaminergic and serotonergic systems. Studies have also suggested that dysfunction of the lateral habenula is associated with psychiatric disorders, including major depression. Here, we discuss insights gained from neuronal recordings in monkeys regarding how the lateral habenula processes reward-related information. We then highlight recent optogenetic experiments in rodents addressing normal and abnormal functions of the habenula. Finally, we discuss how deregulation of the lateral habenula may be involved in depressive behaviors.

One of the most conspicuous characteristics of any organism is its ability to react to salient stimuli with an appropriate behavioral response that maximizes survival and avoids threatening or unpleasant events. The brain reward system, which is thought to have a central role in controlling these behaviors, is a complex circuit containing the forebrain limbic system and its links to the midbrain aminergic (for example, dopaminergic and serotonergic) centers^{1–3}.

The habenula is a structure that has been preserved throughout evolution in vertebrates, being found in lamprey, fish, reptiles and mammals, suggesting that it regulates processes that are important for survival⁴. The habenula is located at the most caudal and dorsal part of the thalamus and, together with the pineal gland, forms the epithalamus. The stria medullaris provides most of the inputs to the habenula, whereas the fasciculus retroflexus is the main output. The stria medullaris, the habenula and the fasciculus retroflexus form the dorsal diencephalic conduction system⁵ that, together with the medial forebrain bundle⁶, transmit most of the cognitive and sensory information from the limbic system to aminergic midbrain areas involved in reward processing and affective control^{1,7,8}.

The habenula comprises two well-defined nuclei, the medial habenula (MHb, see below) and the lateral habenula (LHb). The LHb receives inputs from the basal ganglia, which participate in many functions, including selection of actions, as well as the limbic system, which, among other functions, controls emotions^{7,9}. The LHb sends efferents to dopaminergic centers¹⁰, serotonergic centers¹¹ and the GABAergic rostromedial tegmental nucleus (RMTg), which inhibits dopaminergic centers^{12,13}. Aminergic nuclei also send feedback projections to the LHb^{14,15}. The LHb is therefore well positioned to integrate emotion into the selection of actions.

Over the past several decades, a number of functions have been ascribed to the LHb: the regulation of sleep, maternal behavior, electromagnetic detection and navigation⁷. However, recent findings suggest that the LHb participates in the processing of reward-related information^{16,17}. LHb neurons encode negative reward prediction error: they are excited by unexpected non-rewarding or unpleasant events and inhibited by unexpected rewarding events^{16,17}. The LHb also provides aversive-related signals to the dopaminergic centers^{16,18}. These studies suggest that the LHb has a central role in goal-directed behaviors. Moreover, findings indicating that the LHb is activated by different type of stressors¹⁹ and that habenula lesions induce impaired behavioral responses in stress-related tasks²⁰ also suggest that the LHb might have a central function in behavioral response to stress or in avoidance of punishment.

Deregulation of aminergic centers have been proposed to be central in depressive disorders^{2,21}. Given that the LHb encodes reward-related information, responds to aversive stimuli and regulates aminergic centers, it has been suggested that deregulation of LHb function could underlie a number of psychiatric disorders, including schizophrenia, drug-induced psychosis, addiction and depression^{7,22,23}; we will focus on depression, as recent animal studies have provided insights into possible underlying neural mechanisms.

In this review, we first discuss how the LHb processes reward- and punishment-related information, based mainly on single neuronal recording in the macaque monkey. We then highlight recent optogenetic experiments examining LHb function and refining LHb circuits in rodents. Finally, we discuss how deregulation of the LHb may contribute to depressive behaviors.

Selective effects of LHb on heterogeneous DA systems

A prominent ability of animals is to predict rewards and punishments and to change their behavior accordingly. This gives animals a higher chance of survival. But, the manner in which behavior should be changed is different for prediction of reward and punishment.

When reward is predicted, a change in behavior depends mostly on the recent history of reward, which is often referred to as reward prediction error (RPE)²⁴. When the actual reward is larger than

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the predicted reward (that is, positive RPE), the action associated with the reward is facilitated (approach or Go). When the actual reward is smaller (that is, negative RPE), the action is suppressed (avoid or No Go).

LHb is important for the RPE-guided behavior: LHb neurons encode RPE by changing their activity phasically in response to the actual or estimated reward (that is, inhibition with positive RPE, excitation with negative RPE)¹⁶. The RPE signals in LHb neurons are transmitted, at least in part, to midbrain dopamine (DA) neurons^{16,25}. Given that the LHb-DA effect is largely mediated by RMTg, which consists of GABAergic inhibitory neurons^{12,13,25}, DA neurons are excited with positive RPE and inhibited with negative RPE²⁶. Behavioral changes would then be mediated by the striatum, which receives strong inputs from DA neurons: approach (or Go) by direct pathway neurons (via D1 receptors), avoidance (or No Go) by indirect pathway neurons (via D2 receptors)^{27,28}. The bidirectional effects of RPE on behavior help animals to maximize their rewards²⁹.

LHb neurons are also sensitive to punishment: they are excited by sensory cues predicting punishments¹⁷, similarly to their responses to negative RPE. This seems natural because both negative RPE and punishment are worthless or bad for animals. The punishment-predicting excitatory response of LHb neurons is translated into an inhibitory response of DA neurons³⁰, which would lead to avoidance or No Go.

However, simply suppressing actions while anticipating punishments may not always be good^{31,32}. In many cases, performing alternative actions would get the animal out of the bad situation. Indeed, the response of DA neurons to punishments is complex: some are excited and others are inhibited^{30,33–36}. In the rat ventral tegmental area (VTA), DA neurons in its dorsal part are inhibited, whereas DA neurons in its ventral part are excited, by foot shocks³³. Among putative DA neurons in the substantia nigra pars compacta (SNc) in the macaque monkey, neurons located medially are inhibited, whereas neurons located laterally are excited by a punishment or its predictor³⁰.

The heterogeneity of DA neurons is partly caused by the heterogeneous inputs from LHb. In the macaque monkey, LHb preferentially inhibits DA neurons located in the medial SNc, which are consequently inhibited by punishments and their predictors (Fig. 1). In other words, LHb-DA (medial) circuit suppresses actions leading to punishments³⁷, which is supported experimentally^{38–41}. In contrast, lateral DA neurons are excited by punishments and their predictors (partly because they receive inputs from brain areas that are sensitive to alert signals)⁴² and therefore facilitate actions evoked by the punishment predictions.

The LHb-DA (medial) circuit and the DA (lateral) circuit are also different in the way they treat reward uncertainty. When the reward outcome is unpredictable, medial DA neurons and LHb neurons show little response, reflecting its objective value, which implies that they promote no action³⁰. Indeed, they treat the resolution of uncertainty (that is, advanced information) more valuable than certainty (that is, no information)^{43,44}. In contrast, lateral DA neurons tend to be excited even when the reward outcome is uncertain³⁰, which implies that they promote actions. These data raise the possibility that LHb-DA (medial) circuit may guide risk-avoiding behavior, whereas the DA (lateral) circuit may support risk-preferring behavior. Possibly consistent with these observations, LHb inactivation produces a deficit in choice when the reward outcome is uncertain⁴⁵.

To summarize, the balance between the LHb-DA (medial) circuit and the DA (lateral) circuit in an animal (or human) may contribute to the behavioral and emotional trends of the animal (or person). If the LHb-DA (medial) circuit were to become overactive, the animal

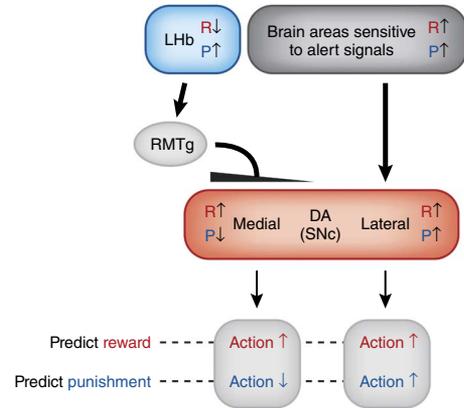


Figure 1 Inhibitory effects originating from the LHb create functional heterogeneity among DA neurons. LHb neurons encode negative motivational values (inhibited by reward and excited by punishment) and inhibit DA neurons in the SNc and VTA through the RMTg. In the monkey, the LHb-induced inhibition is stronger for DA neurons in the medial part of SNc. The medial DA neurons therefore signal positive values, and thereby facilitate reward-approaching actions (shown in red) when reward is predicted and suppress actions (blue) when punishment is predicted. In contrast, the lateral DA neurons are excited when either reward or punishment is predicted, and thereby facilitate both reward-approaching actions when reward is predicted (red) and punishment-avoiding actions when punishment is predicted (blue). R and P indicate reward and punishment. The punishment-related excitation of the lateral DA neurons may be caused by inputs from other brain areas sensitive to alert signals. Note that this scheme may not apply to all DA neurons; for example, some DA neurons in the rodent VTA receive excitatory inputs from the LHb.

may become less active, avoiding aversive or risky situations, becoming reluctant to explore and unwilling to initiate challenging actions. These phenomena may constitute some of the symptoms of major depression and other psychiatric disorders².

Differential monitoring of reward values by the LHb

The discussion thus far has focused on the effect of LHb on the DA system. However, it is known that LHb affects other neuromodulator systems^{7,46}. Particularly relevant to the current theme is serotonin (5HT). The LHb-DA circuit and the LHb-5HT circuit seem to be segregated mediolaterally (Fig. 2). The lateral part of LHb (LHb-l) receives inputs mainly from the basal ganglia through the border region of the globus pallidus (GPb)⁴⁷ and sends outputs mainly to the DA system (SNc and VTA) through RMTg⁴⁸. In contrast, the medial part of LHb (LHb-m) receives inputs from the limbic areas (for example, diagonal band of Broca)⁴⁷ and sends outputs mainly to the 5HT system (dorsal and median raphe nuclei, DRN and MRN)^{11,48,49}. Manipulations of LHb outputs (electrical stimulation, lesion, inactivation) induce changes in 5HT release in the 5HT nuclei and their target brain areas^{50–52}, which may lead to changes in behavior and possibly emotion^{53,54}. In human subjects, a transient depressive relapse, induced by acute tryptophan depletion, leads to a decrease in 5HT neurotransmission that is associated with covariation of DRN and habenula activity, particularly in individuals showing the greatest depression⁵⁵.

This LHb-5HT circuit seems to be important from the psychiatric viewpoint, as changes in 5HT neurotransmission are associated with changes in emotion⁸. However, little is known about how the LHb-5HT circuit might be involved in major depression. A fundamental, but unresolved, question is what kinds of information are transmitted through this circuit, especially by individual neurons. Recent data provide some hints as to the answer to this question.

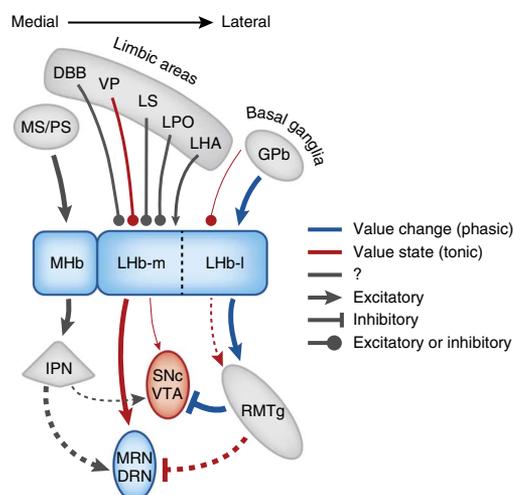


Figure 2 Both LHB and MHb control the dopaminergic and serotonergic systems. The lateral part of LHB (LHB-l) mainly influences the DA system (SNc and VTA) through the RMTg, whereas the medial part of LHB (LHB-m) mainly influences the 5HT system (MRN and DRN) directly. The RMTg-VTA/SNc connection is inhibitory; the other connections are mostly excitatory, although they may target inhibitory interneurons. MHb may influence the DA-5HT systems indirectly through the interpeduncular nucleus (IPN), although these connections need to be confirmed. Inputs to DA neurons may signal value change by changing their level phasically, whereas inputs to 5HT neurons may signal value state by changing their level tonically. It remains to be studied whether neurons in LHB and MHb transmit the phasic and tonic signals differentially to the DA-5HT systems. Dashed lines indicate connections that need to be confirmed and line thickness indicates the presumed strength of connection. DBB, diagonal band of Broca; LHA, lateral hypothalamic area; LPO, lateral preoptic area; LS, lateral septum; MS, medial septum; PS, posterior septum.

Neurons in the DRN in the macaque monkey encode reward values, but differently from DA neurons^{56,57}. Although DA neurons show phasic changes in activity every time reward value changes (that is, RPE), 5HT neurons show tonic changes in activity after reward value is updated. In other words, although DA neurons signal value changes, 5HT neurons signal value state. DA neurons alone may not indicate what the current value state is (for example, am I comfortable), and 5HT neurons alone may not indicate whether the value is increasing or decreasing (for example, am I on the right track). Combining these two kinds of signals would constitute a better mechanism that monitors and controls the value accurately and efficiently.

Previous studies of LHB neurons have emphasized their value change coding¹⁶. However, this may not be a universal feature of LHB neurons, as the LHB consists of many subnuclei that are characterized by molecular and chemical features^{58,59}. In particular, its medial division (LHB-m), which projects to the DRN/MRN directly, may contain neurons that encode value state; preliminary data support this hypothesis (Hong, S. & Hikosaka, O., unpublished data). Furthermore, brain areas upstream or downstream to LHB also contain neurons encoding value state. These upstream areas include the border region of the globus pallidus (GPb)^{60,61} and ventral pallidum (VP)^{62,63}. GPb contains two types of neurons, positive- and negative-value coding types, that project to LHB⁶⁴. The negative type encodes value change, whereas the positive type encodes value state. VP also contains positive- and negative-type neurons, but both encode value state⁶⁵, although it is unknown which type projects to the LHB. A prominent downstream area is RMTg, where neurons show negative-value coding and exert

GABAergic inhibitions on DA neurons¹². Some of them encode value change and other encode value state²⁵.

These results suggest that LHB conveys both value change and value state signals downstream, but the value change signal is selectively directed to DA neurons, whereas the value state signal is selectively directed to 5HT neurons (Fig. 2). This creates a system where value change and value state can be manipulated separately. The value change signal controlled by DA neurons may be related to motivation or wanting⁶⁶; the value state signal controlled by 5HT neurons may be related to mood or liking⁶⁷.

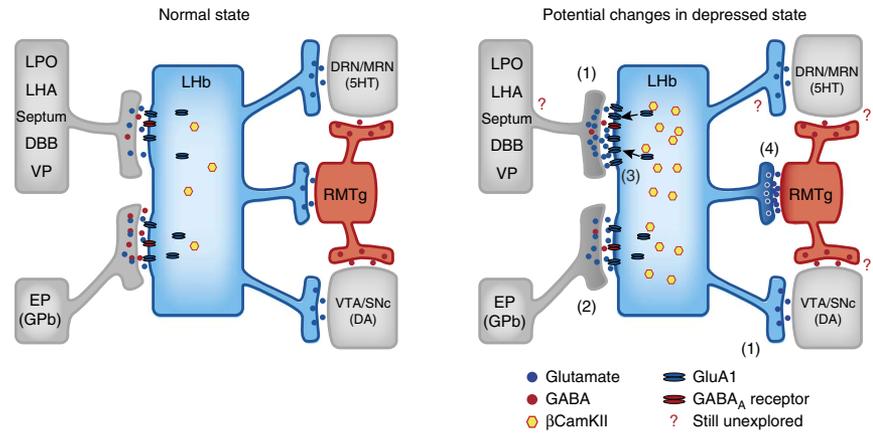
It is unknown, however, whether these LHB circuits controlling the DA and 5HT systems are essential for controlling motivation and mood. The amygdala, for example, is crucial for emotional control⁶⁸ and contains neurons encoding value state. However, little is known about whether and how the amygdala circuits and the LHB circuits might interact with each other⁶⁹.

Optogenetic assessment of the habenula circuits

Although studies in monkeys have provided rich information by correlating activity of LHB neurons to subtle behavioral contingencies, more versatile approaches are available for experiments using rodents that allow better dissection of neural circuits to assess the roles of specific pathways in different behavioral contexts, in normal and pathological states.

Recent studies in rodents have used optogenetic approaches⁷⁰ to examine the functional role of specific inputs and outputs of the LHB in processing reward and aversive information. One study examined the effects of selective activation of inputs to the LHB originating from the entopeduncular nucleus (EP), a basal ganglia nucleus corresponding to the GPb in monkeys. Optogenetic activation of EP terminals in the LHB produced aversion in a passive avoidance test⁷¹. As for outputs, optogenetic activation of LHB terminals contacting neurons in the RMTg produced passive, active and conditioned behavioral avoidance⁴¹. Although LHB activation of RMTg can reduce activity of DA neurons²⁵ (which may explain the generally opposite response properties of LHB and DA neurons in monkeys^{16,25}), LHB also sends direct excitatory projections to the VTA that activate DA neurons¹⁸. Surprisingly, optogenetic activation of this LHB-VTA pathway in mice is also aversive, and injection of a DA antagonist in the mPFC blocks the aversion induced by activation of the LHB-VTA pathway¹⁸. These results show that LHB activity can lead to reduced DA neuronal activity (by way of the RMTg) or increased DA neuronal activity (by direct pathways), but, in both cases, aversion is produced. One study recently identified in mice an inhibitory input to the LHB arising from a unique population of VTA neurons expressing dopaminergic markers⁷². Optogenetic activation of axon terminals from this VTA input releases GABA (and not DA) in the LHB, suppressing postsynaptic firing of LHB neurons. Activation of these terminals in the LHB also reduces firing activity of RMTg neurons, increases the spontaneous firing rate of dopaminergic neurons in the VTA and promotes reward-related behavioral responses⁷². By combining tract-tracing methods and immunohistochemistry, a previous study showed that LHB terminals, in addition to contacting onto VTA dopaminergic neurons, also contact onto VTA GABAergic neurons¹⁰. Optogenetic activation of VTA GABAergic neurons has been shown to disrupt reward consumption⁷³. How direct activation of GABAergic VTA neurons by the LHB affects dopaminergic activity and behavior still needs to be explored. These results demonstrate the intricate relationship between the LHB and the dopaminergic midbrain system and lead to the idea that some LHB neurons might project to this unique

Figure 3 Potential hyperactive synapses in human depression. Shown are schematics with main inputs and outputs from the LHB in normal state and potential cellular and molecular changes in depressed state. Dark shading represents overactive synapses. The depressed state may include an increase in excitatory drive onto the LHB (1–3) and increased LHB output to RMTg (4) and VTA (1) (1, ref. 78; 2, S. Shabel, C.D.P., J. Piriz and R.M., unpublished data; 3, ref. 80; 4, ref. 41). LPO, lateral preoptic area; LHA, lateral hypothalamic area; DBB, diagonal band of Broca.



dopaminergic population of VTA neurons⁷² that project back to, and inhibit, the LHB, offering a negative feedback mechanism to LHB neurons.

These new studies indicating that LHB activity can drive aversion support previous studies that linked LHB activity to the processing of different type of stressors^{19,74,75} and support electrophysiological recordings in macaque monkeys that have shown the central role of the LHB in the processing of negative reward-related information. Thus, aversive stimuli activate the LHB, which in turn triggers circuits that drive aversive behaviors.

LHB in depressive disorders

Monkey and rodent studies have linked the normal function of the LHB to the processing of rewarding/punishing information. In particular, the absence of reward (that is, disappointment) and the expectation of punishment (that is, sense of doom) are strong activators of the LHB. What occurs when the LHB functions incorrectly?

Several pieces of evidence have suggested that LHB hyperactivity may be important in depression. fMRI studies in depressed humans as well as metabolic labeling in animal models of depression have shown increased LHB activity^{55,76}, and LHB lesions in rodents reduce depressive behaviors^{53,77}. Perhaps most revealing, a clinical case study in which the habenula was inactivated by deep brain stimulation (DBS) resulted in a full remission (albeit with a several week delay period) of major depression in a therapy-refractory patient²². Notably, inadvertent stopping of DBS (which was unknown to the patient) brought back depressive symptoms within days, which were then ameliorated by restarting the DBS.

A number of recent studies in rodents have suggested that hyperactivity of LHB neurons may contribute to depression (Fig. 3). One study, in models of depression⁷⁸, detected enhanced excitatory synaptic inputs onto LHB neurons that project to the VTA. These LHB neurons may selectively excite mPFC-projecting dopaminergic VTA neurons that produce aversion in rodents¹⁸ and might be involved in cognitive disturbances observed in major depression⁷⁹. A separate study showed that exposure of mice to protocols that induce behaviors modeling depression increased LHB excitatory drive onto RMTg neurons⁴¹, which would be expected to reduce dopaminergic activity²⁵, and potentially be involved in depression².

Recent studies suggested two molecular mechanisms for the depression-related potentiation of depolarizing drive to LHB neurons: a biochemical change inside LHB neurons and a change in neurotransmitters targeting LHB neurons (Fig. 3). In the first mechanism, CaMKIIβ was identified as a potentially key molecular determinant of depression through a proteomic screen of LHB tissue in rodent models of depression⁸⁰. Increased levels of CaMKIIβ were detected in rat models of depression (Fig. 3). Experimentally increasing CaMKIIβ function in the LHB enhances synaptic efficacy

onto LHB neurons by phosphorylating and driving into synapses GluA1-type glutamate-sensitive receptors. This leads to increased spike output of LHB neurons and is sufficient to produce behaviors that model human depression. Conversely, downregulation of CaMKIIβ levels in the LHB is sufficient to reverse these behaviors. The second mechanism was found in the EP input to LHB neurons (S. Shabel, C.D.P., J. Piriz and R.M., unpublished data). The researchers found co-release of GABA (which is inhibitory) and glutamate (which is excitatory) from individual EP terminals and even vesicles. The GABA/glutamate ratio (Fig. 3) controlled LHB activity. Co-release of GABA was reduced in a model of depression, thereby increasing the net depolarizing drive to the LHB. In contrast, chronic treatment with an antidepressant increased the GABA/glutamate ratio. Taken together, studies examining the normal and abnormal function of the LHB in macaque monkeys and rodents suggest that aberrantly overactive LHB neurons may produce an unpleasant (that is aversive) state of constant disappointment or sense of doom, which may contribute to human depression.

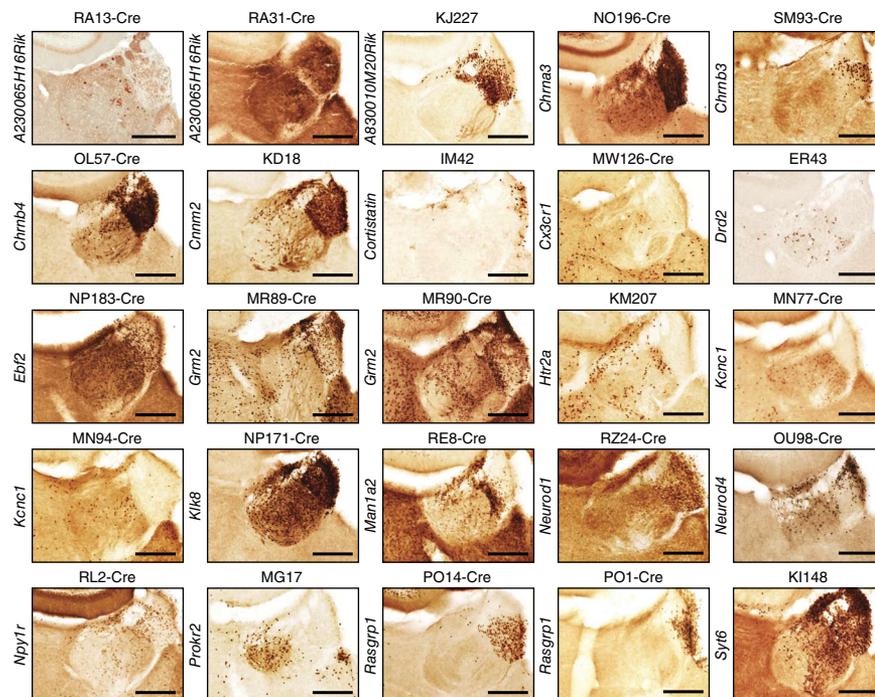
LHB and MHb

The habenula consists of two regions, LHB and MHb, and these two nuclei together constitute a unique structure that is distinguished from the surrounding thalamic areas, especially in terms of phylogeny^{4,81} and ontogeny⁸². A prominent difference between LHB and MHb is their chemical features. Most neurons in LHB are glutamatergic, whereas neurons in MHb use acetylcholine, substance P and glutamate as their neurotransmitters^{83,84}. The cholinergic effect of MHb neurons is mediated by nicotinic receptors⁸⁵ and is heavily involved in nicotine-related behavioral changes^{86,87}.

Despite the differences in chemical features, LHB and MHb seem to have shared or related functions. This is hinted at by similarities in malfunctions of LHB and MHb. In humans with major depression, both LHB and MHb are smaller than in control subjects⁸⁸. Furthermore, both LHB and MHb are hyperactive in rodent models of major depression⁷⁶. Experimental manipulations of MHb (as with LHB described above) cause changes in behavior, especially under stress or fear. Selective genetic ablation of MHb neurons in mice, which is associated with a decrease in ACh in the interpeduncular nucleus (IPN), induces hyperactive, impulsive and compulsive behaviors, effort aversion, and memory dysfunction⁸⁹. In zebrafish, genetic inactivation of the dorsal and ventral habenula, which correspond to MHb and LHB, respectively, changes the pattern of avoidance and freezing responses somewhat differently in anticipation of punishment⁹⁰. In short, both LHB and MHb may control motivation and emotion. This view may be supported by recent studies



Figure 4 Transgenic Cre-driver mouse lines from GENSAT that permit targeting of different neuronal ensemble in the LHB and MHB. A representative *in situ* histochemistry image encompassing the habenula is shown for different founder Cre lines (founder line name on top of each image) in which Cre expression is driven under specified gene promoter (gene name on the left of each images). The source of these images is the GENSAT website (<http://gensat.org/>). These lines are available from GENSAT. Scale bars represent 250 μ m.



suggesting that the MHB also has substantial influences on DA and 5HT neurons^{91,92}, which are largely mediated by the IPN (Fig. 2). Differences in the effects of LHB and MHB manipulations could be explained by their differential effects on DA and 5HT, or on other systems (for example, norepinephrine system, hippocampus, immune system)^{46,93–95}. It is possible that LHB and MHB have fundamentally different functions that have not yet been revealed.

Strategies for habenula targeting and manipulation

Histochemical and morphological analysis have distinguished at least ten subnuclei in the LHB and five subnuclei in the MHB^{58,59}. Moreover, as mentioned above, the LHB and MHB have distinct inputs and outputs (Figs. 2 and 3). This heterogeneity suggests that different habenular nuclei and subnuclei might be involved in different biological functions. The inability to manipulate specific habenular subnuclei by classic methods, such as electrical stimulation or pharmacological perturbation, likely contributes to the difficulty in clearly determining the biological function of the LHB and MHB.

To improve our understanding of the habenula, it will be important to delineate the precise nature of the circuitry of each of these nuclei/subnuclei, the manner in which manipulation of individual nuclei/subnuclei affects behavior during normal and stressful/aversive situations, and the changes that can be linked to specific pathological states. To answer these questions, it is critical to be able to specifically manipulate these nuclei and subnuclei.

Powerful ways of manipulating neuronal activity now exist. Optogenetic approaches use microbial opsins that, when expressed in neurons and illuminated, can rapidly generate time-locked action potentials or can rapidly block action potentials by hyperpolarizing neurons (see ref. 70 for a detailed description of optogenetic tools and technical strategies for optogenetic investigation in rodents). In cases in which long-lasting activation or inhibition of neuronal activity is preferable, an alternative approach is to use Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)⁹⁶.

An increasing collection of Cre-reporter transgenic lines are now available for driving expression of opsins or DREADDs in specific subset of neurons^{70,97}. A combinatorial approach, using Cre-driver mouse lines and viral delivery of Cre-dependent opsins or DREADDs, allows temporally and spatially specific manipulation of neuronal ensembles. Notably, a survey of available Cre-driver mouse lines from the Gene Expression Nervous System Atlas Project⁹⁸ (GENSAT, <http://gensat.org/>; Fig. 4) shows that many Cre-driver mouse lines may be readily used to target different subnuclei of either the LHB or the MHB. Viral delivery of Cre-dependent opsins or DREADDs into the habenula of

these Cre-driver mouse lines may greatly advance our understanding of habenular function in normal and pathological states.

Conclusions

In addition to the habenula, there are many brain areas that are involved in the control of emotion. Why then is the habenula in a pivotal position to guide or misguide emotional behaviors? It may be because the habenula acts as a hub of emotional information: it receives inputs widely and delivers outputs widely through multiple neuromodulator systems and brainstem circuits. Recent studies in monkeys and rodents have provided evidence that the LHB has important roles in decision-making by sending reward-related and aversive signals to the dopaminergic centers. By processing these signals as value state and value change, the LHB is centrally positioned to transform emotional information into proper behavioral responses, particularly during an aversive, stressful situation.

Human and non-human studies have both provided evidence that dysfunction of the LHB may be involved in depression. Hyperactivity of LHB neurons could reduce DA-related rewards signals, likely through intermediary actions of RMTg or by directly activating DA neurons that project to mPFC. Overactivity of these pathways may affect decision-making (for example, overprocessing of aversive events, reduced motivation, or altered learning from positive or negative reinforcement).

It is notable that the LHB also sends projections to serotonergic centers. In addition to reward value processing, 5HT has been implicated in the prediction of aversive events and in behavioral inhibition, as well as being centrally involved in depressive disorders. Little is known regarding how exactly the LHB affects these serotonergic centers. The type of signals provided by the LHB to these centers and their potential deregulation in depressive disorders should be investigated more extensively.

Hyperactivity of the LHB may contribute to depression, and its suppression may reduce depression symptoms. This provides a rationale and potential opportunity for treating depression. It will be important to identify how the LHB becomes hyperactive and which molecular

targets would permit selective reduction of LHB hyperactivity pharmacologically, and thereby reduce depressive symptoms. We hope that future studies elucidating molecular, cellular and circuit properties of the LHB, and how these are linked to behavior, will aid in addressing these issues.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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