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Review

Information processing in the vertebrate habenula

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ABSTRACT

The habenula is a brain region that has gained increasing popularity over the recent years due to its role in processing value-related and experience-dependent information with a strong link to depression, addiction, sleep and social interactions. This small diencephalic nucleus is proposed to act as a multimodal hub or a switchboard, where inputs from different brain regions converge. These diverse inputs to the habenula carry information about the sensory world and the animal's internal state, such as reward expectation or mood. However, it is not clear how these diverse habenular inputs interact with each other and how such interactions contribute to the function of habenular circuits in regulating behavioral responses in various tasks and contexts. In this review, we aim to discuss how information processing in habenular circuits, can contribute to specific behavioral programs that are attributed to the habenula.

Contents

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The habenula (Hb) is an evolutionarily conserved diencephalic nucleus, connecting forebrain regions such as prefrontal cortex (PFC) [1], septohippocampal region [2] and the Basal Ganglia [3–6], with downstream monoaminergic nuclei, such as the ventral tegmental area/rostromedial tegmental nucleus (VTA/RMTg) [7–13] and the Raphe nuclei [2,6,11,14–16], as well as the interpeduncular nucleus (IPN) [6] (Fig. 1A,B).

Already in 1914, experimental evidence highlighted the role of the Hb in regulating the valence of behavioral outcomes. It was observed that electrostimulation of habenular efferents, in chimpanzees, induced a respiration pattern resembling laughter [17,18]. However, it was not until the eighties that researchers proposed the idea of the Hb steering emotionally involved behavior by the modulation of dopamine neurons [19]. With the refinement of experimental tools, as well as the advent of novel techniques such as optogenetics and molecular tools, it became possible to investigate and further subdivide the roles of the Hb in a broader range of behaviors related to learning, depression, addiction, sleep and social interactions.

The mammalian Hb consists of at least two functionally segregated subnuclei: the medial (MHb) and the lateral habenula (LHb). The MHb was suggested to play an important role in anxiety, fear, depression and nicotine addiction [20–24]. Moreover, MHb activity was shown to be regulated by circadian rhythm [25]. Yet, functional studies of the MHb have been difficult in mammals due to its small volume and deep location right next to the third ventricle [26]. On the other hand, a lot more studies have investigated the role of the LHb in brain function and animal behavior, with a strong focus on regulation of dopaminergic and serotonergic nuclei in order to shape both innate and conditioned behaviors [26].

Research on the Hb has been diverse, covering multiple questions ranging from the role of the Hb in learning and cognitive function, to its involvement in mood disorders and addiction in human patients. Moreover, the Hb has always been an attractive brain region for those who are interested in studying the development of brain asymmetries and their potential function. Finally, an increasing amount of evidence suggests an important role for the Hb in sensory information processing in several animal models. While all these exciting results contributed to our understanding of the habenular function in the brain, the link between these diverse disciplines of habenular research is not yet fully established. In this review, we aim to provide a broad overview of the research conducted on the Hb and try to link these studies that cover different disciplines of neuroscience.

In the following sections, we will first provide an overview of the inputs and outputs of the habenular circuitry and the role of these structures in different behaviors. Next, we will describe how sensory information is received and processed in the Hb. We then suggest several hypotheses about how neural information from different brain regions can be integrated at the level of the Hb. We propose that the ongoing activity observed in the Hb, plays an important role in reflecting the internal state of the animal, integrating information from a number of brain regions and the sensory systems.

1. The role of the habenula in generating complex behaviors

1.1. Learning, encoding errors and negative outcomes

Seminal studies, using single-unit recordings in primates, showed a direct involvement of the LHb in encoding prediction error. One of these studies reported that several LHb neurons were activated by no-reward predicting cues as well as the absence of the reward, while they were inhibited by reward and reward predicting stimuli [3]. The firing rate of neurons inhibited by reward and reward predicting cues, is also directly proportional to the probability of receiving the reward [27,28]. Moreover, the activity of LHb neurons is shown to follow the activity of the dopaminergic neurons in the substantia nigra pars compacta (SNc) in case of a reward and to precede it in case of reward omission [3,29].

Rodent studies have further unraveled the complexity of this interconnected circuit composed of feedback and feedforward signaling between the LHb, the monoaminergic brainstem nuclei and the basal ganglia. The LHb was shown to inhibit dopaminergic neurons of the VTA indirectly via the RMTg [8,12,30–33] or directly by exciting local GABAergic neurons in the VTA [12,34]. Exposure to aversive stimuli such as foot shocks, induces plasticity in the LHb-RMTg pathway [33] but also results in an increased firing in the GABAergic population of the VTA [35]. Stimulating LHb neurons directly induces place avoidance, a behavior characterized by reduced exploration of the stimulation-coupled area [35–37]. In addition, the role of the LHb has also been investigated in terms of cost-benefit decision making. Rats learnt to receive a greater benefit (four food pellets instead of one) when their waiting time was increased. When the probability of receiving the award was low, the cost of waiting became too high. Lesioning the LHb disabled the rats from making such cost-efficient decisions, without affecting the animal's ability to evaluate the magnitude of the immediate reward [32]. While VTA receives information directly or indirectly from LHb, it also sends feedback projections inhibiting LHb neurons [8]. Investigation of these projections reveals a co-release of glutamate and GABA [7,38], which suggests that modulating the co-release ratio can be a potential mechanism of tuning habenular activity. Interestingly, recordings of VTA neurons show two different populations encoding aversive and rewarding stimuli with different dynamics. The authors showed that, while most GABAergic VTA neurons respond to aversive stimuli, the majority of dopaminergic neurons respond to reward related information [39]. These results indicate that the LHb modulates and is modulated by the VTA, which plays a role in dopaminergic regulation of animal behavior. In addition to modulating dopaminergic signaling, the Hb was also shown to regulate serotonin release directly through LHb projections to the Raphe nuclei [32,40–42] and indirectly via the projections of the LHb and the MHb to the RMTg [16] and the IPN [42] respectively. The role of serotonin in reward processing and learning is still under investigation. However, accumulating evidence supports its involvement in these phenomena [43–47]. Taken together, these findings suggests that both dopamine and serotonin modulate the processing of stimulus-related information bidirectionally, shaping it based on the internal state of the animal in order to tune subsequent behavioral outcomes.

The mammalian lateral and medial Hb find their respective homologues as the ventral habenula (vHb) and the dorsal habenula (dHb) in zebrafish (Fig. 1C) [4,6]. Lesioning the dHb, was shown to prevent zebrafish from coping with threats in a stressful context and induces freezing (or helplessness), rather than escape or avoidance [48,49]. A complementary study [6] further showed that a population of vHb neurons encodes the negative expectation value that is associated with the conditioned stimulus, by increasing their tonic response to the conditioned stimulus during learning. In addition, the phasically active vHb neurons represent the prediction error. Along with this, the same study showed that lesioning the vHb impairs the ability of the fish to perform active avoidance, without affecting the switch from freezing to agitation as is the case for the dHb ablation. These results are in line with the two-factor theory of active avoidance. At first, an aversive stimulus is associated with a biologically neutral stimulus, resulting in a fear response when the neutral stimulus is presented (Pavlovian factor, association phase). Subsequently, the transition from an unsafe to a safe state can then be further associated to a specific performed

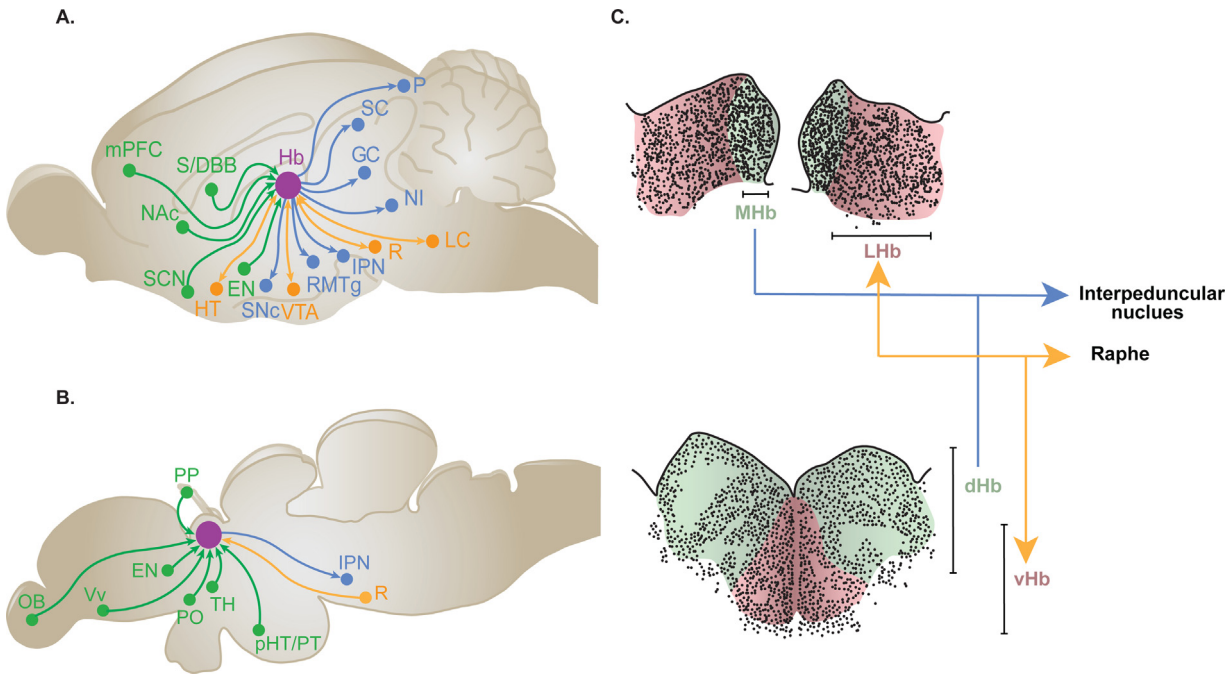

Fig. 1. Schematic overview of the habenula homologues in the mammalian and non-mammalian brain and their afferent and efferent neural pathways. Sagittal view of the rodent (A) and the zebrafish (B) brain showing that the habenula connects forebrain, midbrain and hindbrain nuclei in both vertebrates. Green: afferents, blue: efferents, yellow: bidirectional connections. Schematic representations of transverse views of both the rodent (rat) (top panel) and zebrafish (bottom panel) habenula showing the homologue habenula regions and their efferents (adapted from Amo et al. [6]) (C).Abbreviations: Hb, habenula; mHb, medial habenula; LHb, lateral habenula; dHb, dorsal habenula; vHb, ventral habenula; OB, olfactory bulb; EN, entopeduncular nucleus; PO, preoptic area; TH, thalamus; PP, parapineal organ; Vv, ventral area of the subpallium; pHT/PT, posterior hypothalamus/posterior tuberculum; IPN, interpeduncular nucleus; R, raphe; S/DBB, septum/diagonal band of Broca; RMTg, rostromedial tegmental nucleus; NAc, nucleus accumbens; LC, locus coeruleus; VTA, ventral tegmental area; SCN, suprachiasmatic nucleus; SNc; substantia nigra pars compacta; SC, superior colliculus; PAG, periaqueductal gray; NI, nucleus Incertus; P, pineal; mPFC medial prefrontal cortex;.

behavior, which can act as a surrogate reward (instrumental factor, goal-directed phase) [50,51]. Taken together, it appears that while the zebrafish dHb might be involved in the association phase of classical conditioning where a negative value is assigned to a previously neutral stimulus, the zebrafish vHb is involved in the goal-directed phase of operant conditioning, when the animal learns that a specific behavior gives the possibility of escape [6].

1.2. Addiction

In addition to the extensive literature linking the Hb to learned behaviors, the Hb is gaining popularity and receives increasing clinical interest, as a number of studies in humans [52] and rodents [52] have shown its involvement in addiction [53–55] to nicotine [55–59], cocaine [60,61] and ethanol [62]. The Hb-IPN pathway is particularly enriched with nicotinic acetylcholine receptors (nAChRs) [57,59,63,64]. In human studies, small changes in the genes encoding different subunits of these receptors, were linked to a predisposition to nicotine addiction [52]. In a rodent model, high doses of nicotine were shown to facilitate LHb excitation, by activating α6-nAChRs, while low doses inhibit the LHb via α4β2-nAChRs [65]. This dose-dependent effect of nicotine is also reflected in the behavior of the animal, since low doses of nicotine induce conditioned place preference [66] while high doses can induce place avoidance [59,67,68]. Moreover, nicotine has an excitatory influence on the activity of dopaminergic neurons, predominantly in the posterior VTA [69]. Similar behavioral effects are observed with ethanol, where low doses induce conditioned place aversion while higher doses induce place preference [62]. However, it is not clear if and how this dose-dependent behavioral switch is mediated by the Hb. It was suggested that the activation of dopaminergic neurons in the VTA, by high doses of ethanol, might counterbalance the aversion effect driven by the LHb [62]. In line with these results, cocaine self-administration was shown to increase LHb neuron excitability [61]. Moreover, cocaine withdrawal changes the GABA\Glutamate co-release ratio in the pathway between the entopeduncular nucleus and the LHb, resulting in a disinhibition of the LHb, which could potentially lead to a depressive-like state [5]. Interestingly, deep brain stimulation of the LHb was shown to reduce cocaine intake in rats, as well as cocaine and cocaine-cue related c-fos expression in the LHb [70], suggesting that the LHb could be an interesting target for ameliorating the behavioral symptoms of addiction.

1.3. Mood disorders and social behaviors

Since habenular circuits are involved in encoding prediction errors, coping with stress as well as controlling the activity of dopaminergic and serotonergic brain nuclei, it is not surprising that habenular dysfunction is associated with several mood disorders, ranging from anxiety [71] to depression [52]. Patients suffering from major depressive disorder were shown to have an altered habenular volume [72,73] and baseline activity [40,74]. More specifically, during a passive conditioning task where an initially neutral cue is associated with a negative stimulus (an electric shock), healthy participants show an increased cue-evoked activity in the Hb. Depressive patients however, show a decrease in habenular activity as the cue-stimulus association strengthens [75]. Excitingly, deep brain stimulation of the Hb was linked to reduced symptoms of depression in a human patient [76], which opens a range of therapeutic treatments for depression by interfering with habenular activity.

Despite these exciting results in humans, the neural mechanisms underlying the role of habenular circuits in mood disorders are still not fully understood. The dopaminergic neurons of the medial VTA show a reduced activity in a rodent model for major

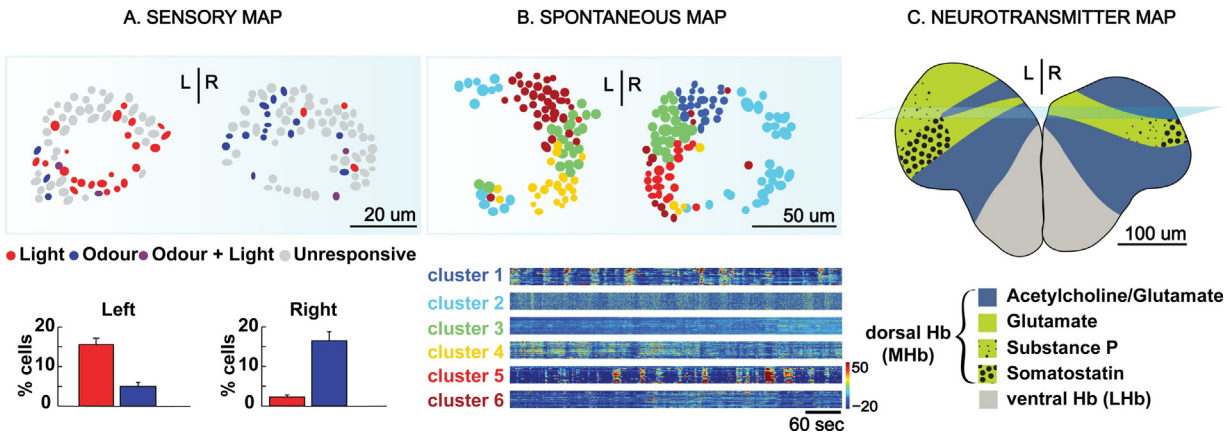

Fig. 2. Schematic overview of molecular and functional characteristics of the dHb in zebrafish. (A) Dorsal view of dHb neurons responding asymmetrically to light (red), odor (blue) or both (magenta) (adapted from Dreosti et al. [84]). L = left, R = right. Below are representative bar graphs of the percentage of light and odor- responsive neurons in the total dHB population, showing asymmetric distribution across hemispheres. (B) Dorsal view of spontaneously active neurons in the dHb of juvenile zebrafish (adapted from Jetti et al. [96]). The neurons are subdivided and color coded into six different clusters, based on their similarity of neural activity over time as visualized in the activity traces below. Neurons with similar neural activity are organized into spatial and functional clusters.(C) Transverse view of the neurotransmitter populations across the dHb in adult zebrafish (adapted from Decarvalho et al. [171]). The overall glutamatergic, cholinergic and peptidergic populations are asymmetrically distributed over the two hemispheres. Light blue plane shows the rough location of cross section in A and B.

depressive disorder based on chronic mild stress (CMS) [77]. Further investigation identified two potential drivers for this activity decrease in the VTA, the LHb and the infralimbic prefrontal cortex (ILPFC). While both the LHb and the ILPFC inhibit dopaminergic neurons in the VTA, the LHb preferentially inhibits the lateral VTA instead of the medial VTA [77]. This study therefore questions the involvement of the Hb in the modulation of dopaminergic neurons linked to the effects of CMS. However, parallel investigations show a direct link between habenular hyperactivity and a depression-like phenotype [78,79]. Interestingly, inhibiting glial glutamate reuptake in the LHb induces an increase in neural firing rate and c-fos expression, which again resulted in depressive-like symptoms [80].

A recent study in zebrafish, using another paradigm of inducing stress by social conflict, reveals a direct role of the dHb in regulating animal behavior. After a fight between two fish, local field potential recordings in the IPN showed that loser fish have reduced transmission in the pathway between the lateral dHb and the dorsal/intermediate IPN [81]. Complementary studies in rodents also report that social isolation can induce c-fos expression in the MHb. This effect could further be rescued by increasing the social interaction between animals [82,83].

Based on these findings Hb appears to have several roles in controlling mood and social interactions, which are tightly linked to one another. It is however not yet clear how neuronal signals are processed by the Hb and how they relate to controlling mood and social interactions in healthy individuals, as well as those who are suffering from major depressive disorder.

2. Sensory representations in the habenula

Several studies showed that a diverse range of sensory modalities can evoke robust responses in the non-mammalian Hb [14,84,85]. On the contrary, only a smaller number of works on the mammalian Hb report such sensory responses [86,87]. To gain more insight into the role of sensory processing in the Hb, a more thorough comparative approach is needed. Below we discuss different sensory modalities that are shown to be processed by habenular circuits in a diverse range of animal models.

2.1. Electroreception and vestibular system

Functional measurements of the MHb homologue in lampreys, showed that exposing lampreys to electric fields increases the activity of Hb neurons and can initiate responses that are typical for flight and freezing behavior [88]. Most likely, this information from the electroreceptive organ is transferred indirectly to the Hb via the pretectum. Retrograde tracing in the Hb indeed showed direct projections from the pretectum, while retrograde tracing in the pretectum itself showed direct projections from the electroreceptive organ [14].

2.2. Olfaction

Anatomical tracing studies in lampreys also demonstrated direct projections from the medial olfactory bulb (OB) to the MHb homologue [14]. Odor stimulation of these medial OB neurons was shown to activate spinal locomotor networks in lampreys [89], which suggests a potential link between MHb projecting OB neurons and the initiation of fast motor behaviors. Such characteristic movements that are tightly linked to odor cues are not only limited to lampreys, but were also observed in newborn rats, dogs, mice and zebrafish [90–93]. In line with studies in lampreys, tracing studies in salamanders and in zebrafish further confirmed the direct relay of olfactory information from OB to the MHb homologue [94,95]. Interestingly, it was also shown that zebrafish mitral cells from the mediodorsal OB send projections preferentially to the right dHb, the MHb homologue in zebrafish [95]. *In vivo* recordings further confirmed that odor responses in the dHb are asymmetric across the hemispheres with stronger odor responses in the right dHb [84,96] (Fig. 2a). However, it appears that while odor identity is precisely encoded by differential activation of zebrafish OB neurons [97,98], odor responses of dHb neurons are less odor specific and respond broadly to odors from different categories [96]. Moreover, a complementary study showed that dHb and vHb neurons display distinct temporal delays in response to different odorant categories and concentrations [85]. These results suggest that the non-mammalian Hb receives information from a distinct part of the olfactory system and relays olfactory information onto its downstream monoaminergic targets [84]. It is worth to note that despite this extensive work in the non-mammalian Hb, it remains unclear whether olfactory inputs are conserved in the mammalian

Hb. Further studies are needed to reveal whether the Hb receives olfactory information from the piriform cortex [99] or other parts of the higher olfactory system [95,100] and what role the Hb plays in olfactory processing within the context of behavioral plasticity and learning.

2.3. Photoreception and vision

The parapineal (Pp) is a sensory organ that contains photoreceptors conveying information about the ambient illumination to the brain and is thought to be involved in circadian rhythms [101–104]. This brain region is present in lampreys, bowfin, teleosts, reptiles and birds, but it is absent in other vertebrate groups [105–108]. In lampreys and in fish, the Pp projects asymmetrically to the left MHb homologue [109–113]. The influence of the Pp on the Hb was shown to contribute to asymmetries in gene expression, development and function between the left and the right dHb [84,114]. However, it is still unclear whether the Pp relays any information about ambient light conditions to Hb neurons or whether it is merely a regulator in habenular development. The first functional investigation of visual responses in the zebrafish dHb suggests that the majority (if not all) of the visual responses in the dHb do not arise from the Pp but likely from the retina [84]. Indeed, the authors showed that eye removal abolished all dHb visual responses, but laser ablation of the Pp did not have a significant effect on the dHb visual responses.

Intriguingly, dHb light responses, like odor responses, are asymmetric across habenular hemispheres [84]. Visual responses are more prominent on the left dHb while odor responses are predominantly observed in the right dHb (Fig. 2A). The asymmetric segregation of sensory modalities is also preserved in the dorsoventral organization of the Hb axonal targets in the IPN, which highlights the importance of sensory segregation in the Hb for information processing and controlling animal behavior. While the function of the dorsoventral segregation of visual and olfactory information in the IPN is not yet clear, the left-right segregation of sensory modalities in Hb suggests a division of labor across the habenular hemispheres. This could in principle increase the information processing capacity of the Hb, as distinct computations would be processed by a dedicated hemisphere rather than being duplicated in an alternatively symmetric and redundant system [115]. Several perturbations were also shown to interfere with these functional asymmetries between habenular hemispheres [84]. Such experimental manipulations could be used to further test whether disrupted habenular asymmetry leads to impairments in behavioral performance during visual, olfactory and mixed visio-olfactory tasks.

In the meantime, recent studies in fish have linked the visual responses in Hb to light-preference and circadian behaviors [116,117]. Furthermore, it was shown that a subpopulation of ON-responsive retinal ganglion cells activates the dorsal thalamic nuclei, which in turn activate and inhibit different populations of the left dHb neurons with complex temporal response patterns in a light intensity dependent manner [116,118]. In line with the role of the Hb in these observed behaviors, Hb lesions in quails were shown to be effective in suppressing inhibitory influences of light stimulation [119], suggesting the presence of visual processing, also in the bird Hb.

Only a limited number of studies have investigated sensory processing in the mammalian Hb [86,87]. While the Hb is located deep inside the mammalian brain, light-evoked responses were also reported in the rodent LHb and MHb [86]. *In vivo* recordings of both habenular subnuclei displayed excitatory and inhibitory characteristics in response to light stimuli, suggesting that different Hb neurons might encode light stimuli in different ways. Moreover, a higher tonic firing rate of Hb neurons was observed during the day compared to night-time [86]. When visual responses were measured during night-time, LHb neurons exhibit significantly stronger light responses compared to the MHb. Hence, visual responses through a retinoic pathway in the rodent Hb [120,121], might therefore be modulated by circadian rhythms related to day-night cycles and illumination levels.

Nonetheless, *in vivo* recordings of neural activity in the mammalian Hb remain challenging. It is thus unclear whether the sensory responses in the mammalian Hb are part of an evolutionarily conserved pathway or whether the afferent regulation of this circuitry has changed throughout evolution [14]. Higher-order brain areas that process more complex features of the sensory information in mammals, might have replaced the direct sensory input to the Hb that was observed in lampreys and teleosts. This could, in turn, help mammals to better adapt their behavioral response to contextual information that is not generated by direct sensory inputs. Even if so, the common mechanism in which the Hb generates motivated behaviors based on contextual information and updates the behavioral strategy to a more suitable outcome, is likely to be preserved across all species. Yet how sensory responses in the Hb and inputs from the limbic system or basal ganglia interact, remains elusive. Hence, it will be essential to continue comparing future results across different species, focusing on the role of habenular circuitry in the contextual modulation of sensory processing.

3. Ongoing spontaneous activity in the habenula

Almost all measurements of neural activity throughout the brain suggest that a significant amount of activity is generated independently from external sensory stimulation. This internally produced spontaneous activity was previously undervalued, as for a long time it was considered to be biophysical noise with no relevance in neuronal computations [122]. Yet, the ongoing spontaneous activity of neurons consumes a major part of the brain's energy and is arguably more than just an artifact [123]. Several studies have suggested key roles for these intrinsic activity dynamics in diverse neural processes from development and maturation of brain circuits to cognitive performance.

Spontaneous bursts of activity were detected in different parts of the nervous system across the animal kingdom. In the crustacean stomatogastric system [124] and in the vertebrate spinal cord [125], spontaneous activity is generally related to the generation of biological rhythms that control motor actions. However, the purpose of ongoing activity in the brain such as the vertebrate cortex [126–128], thalamus [129], hippocampus [130] and the Hb [96], or in neural parts of sensory organs such as the retina [131,132], are much more diverse and sometimes even elusive.

During development, spontaneous activity is important to form appropriate connections and to generate a mature network [129,131–133]. However, in mature networks, this activity has been linked to various functions such as replay [130] and processing of previous sensory experiences [134], memory consolidation [135,136], and event planning [137] as well as the reorganization of the synaptic weights of the network [138], bottom-up thalamic control [139] and top-down modulation [140]. Such spontaneous activity can be generated intrinsically within one brain area [141,142], by bottom up pathways [143] or by modulation from distal areas either top-down or subcortical [144]. Moreover, several studies suggest that spontaneous activity can reflect cortical states, which can 'gate' sensory information to higher brain areas [144].

In humans, highly correlated spontaneous brain activity, is suggested to reflect a 'default mode network' [145]. In this functionally defined network, ongoing brain activity is not elicited by one single brain region but is rather generated by dynamic interactions of several brain regions across the brain. When the human brain is

at rest or engaged in internally focused tasks, the default mode network' is thought to be spontaneously active. If and how the spontaneous activity of this network is altered by information from the external world is still investigated. It has been hypothesized that the spontaneous activity at rest can be counteracted or suppressed by competing activity from additional brain regions that are recruited during sensory processing or attention related tasks [146–150]. On the contrary, a handful of cognitive tasks were also shown to increase spontaneous activity [151]. In these cases ongoing spontaneous activity could support a broad level of attention when monitoring the external world for unexpected events [152]. While this idea of a functionally defined default mode network, was previously only applied to cortical areas, it is likely that other parts of the brain, such as Hb, might be part of similar networks with related network properties.

3.1. Implications of changing ongoing activity in habenular circuits

The link between spontaneous habenular activity (Fig. 2B) and habenular inputs coming from converging pathways across the brain is not well understood. Nonetheless, the hypothesis of the Hb encoding expected reward value by altering its activity compared to the baseline activity is now generally accepted [3,55]. Spontaneous activity in the Hb might therefore be a crucial feature, as is it might enable a bidirectional coding of the reward expectation value, as was observed with neurons encoding odors in the piriform cortex [153]. Such an increase in the dynamic range would not be possible without a baseline activity.

Furthermore, several studies have suggested that changes in spontaneous habenular activity might underlie behavioral symptoms observed in mood disorders or addiction. This is not very surprising as the Hb is regulating monoaminergic brain regions containing dopamine, serotonine and norepinephrine. Drugs like cocaine for example, evoke withdrawal symptoms by a hyperactivation of the LHb and strengthening of AMPAR-mediated synaptic transmission onto RMTg neurons [154]. Acute application of nicotine on the other hand, increases spontaneously occurring action potentials of the cholinergic neurons in the MHb via a specific subtype of nAChR [155]. Blocking of spontaneous firing in the MHb, was shown to induce withdrawal-like symptoms similar to nicotine withdrawal [155,156]. The effects of morphine, an opioid also inducing wirthdrawal-like symptoms, on the MHb activity are less clear, since low and high doses respectively increased and decreased spontaneous habenular activity [157,158]. It is highly likely that such pharmacological alterations do not only affect the Hb, instead this could alter the activity of a broadly dispersed brain network, where Hb plays a key role.

Furthermore stress-inducing stimuli also excite neurons in the LHb and prolonged stimulation could even generate anxiety and depression [49,159,160]. Multiple studies have shown that increased background activity of the LHb is linked to anhedonia (a behavioral symptom observed in some depressive patients), by decreasing the activity of dopaminergic neurons after positive events [76]. However, stress-induced activation of the LHb may not only lead to changes in dopaminergic signaling but also to alterations in the activity of serotonergic neurons located in the dorsal and medial raphe nuclei [161–163].

Under general anesthesia, the amount of habenular activity rises [164–166] which suggests that habenular activity can be modulated during the transition from sleep/low arousal states to awake/high arousal states. In line with this, fluctuations in the spontaneous activity of the Hb are regulated by circadian rhythms [86,167]. Precise mechanisms, which can underlie the role of the Hb during sleep, remain to be elucidated, but proposed roles point towards the control of serotonergic and possibly also dopaminergic neurons [168–170].

Taken together, the spontaneous activity in the Hb, both in LHb and MHb, appears to be altered in many different conditions ranging from substance abuse to stress, sleep, reward-based decision-making or even social behaviors. The baseline activity, which can be characterized as the ongoing activity in the Hb without any external stimulus, can therefore represent an internal state of the animal. Depending on the sensory inputs or internal information from other brain areas that are directly or indirectly projecting to the Hb, this activity can be modulated to eventually trigger behaviors that are better adapted to a given situation.

3.2. Interactions of spontaneous and sensory driven activity in the habenula

While all phenomena described above have a strong relation to changing levels of spontaneous habenular activity, it is less clear how sensory responses in the Hb and spontaneous habenular activity interact with each other. One possibility is that spontaneous activity alters sensory responses in the Hb and changes the way the Hb transmits sensory information to its monoaminergic targets. Alternatively, sensory responses in the Hb could also interfere with the spontaneous activity and therefore modulate the phenomena that are attributed to spontaneous habenular activity, such as cognitive function, depression, addiction, sleep or social behaviors.

Since the Hb receives inputs from both sensory and non-sensory regions of the forebrain, midbrain and hindbrain [1,2,4–16], one potential role of spontaneous habenular activity could be to serve as a gate or a switchboard. In such a model, the responsiveness of Hb neurons to sensory stimulation could be modulated (or gated) by the non-sensory inputs of the Hb that are shaping its ongoing activity. We have previously shown that spontaneous activity in the zebrafish dHb is not random, but rather spatially organized into different functionally and genetically distinct clusters [96] (Fig. 2B). Neurotransmitter maps of the dHb were shown to have a spatial organization that is asymmetric across habenular hemispheres and this organization is preserved in the targets of the Hb [171] (Fig. 2C). Hence, it would be interesting to classify what functional Hb clusters identified based on their ongoing activity, overlap with the neurotransmitter expression patterns observed in the Hb.

Additionally, we showed that the neurons belonging to a functional cluster during spontaneous habenular activity also respond similarly to sensory stimulation. Hence, in principle, modulating the spontaneous activity of a given Hb cluster could also alter the responsiveness of those Hb neurons to a given sensory modality, by increasing or decreasing their resting membrane potential. This process would in turn control if or when the sensory information should be passed to monoaminergic Hb targets in the locus coeruleus (LC), the VTA and the Raphe. Therefore, it will be interesting to modulate spontaneous habenular activity via direct stimulation of Hb inputs across the brain, or to utilize those behavioral phenomena that could regulate spontaneous habenular activity such as stress or sleep, to test whether altering spontaneous habenular activity can modulate sensory representations within the Hb and in turn alter the animal's behavioral response to sensory stimuli.

It is possible that the functional clusters observed in ongoing habenular activity could represent stable states of the network, marking the groups of neurons that are more likely to act together to recall a given behavioral program. In line with this hypothesis, functional clusters of Hb neurons with synchronized ongoing activity were shown to overlap with genetically labeled groups of Hb neurons [96], which were shown to be involved in associative fear learning [49]. It is exciting to speculate that these stable functional clusters of Hb neurons that are synchronized (or co-active) at

all times, represent favored states of the habenular circuits. These favored states of the habenular circuits resemble an attractor network, which is a network of recurrently connected neurons, whose dynamics settle to stable states. Such stable states are generally believed to be involved in decision making and provide the network with an increase in signal-to-noise ratio resulting in a better signal classification and discretisation [172–174]. In the mammalian cortex, attractor networks are proposed to be involved in gating and gain control of sensory information [175]. Hence, these principles could also apply to sensory processing within the Hb. For example odorant-evoked responses with different amplitudes and distinct representations in the OB, were no longer observed in dHb neurons. [96]. Instead dHb neurons are broadly tuned to odors which suggests that discrimination between odorant classes might no longer be relevant for Hb computations. A robust response that encodes saliency or presence of a broad odor signal could be achieved by keeping the network in a preferred excitable state. It is also possible that these stable states of the Hb networks can be entrained to increase the response likelihood of Hb neurons to a given sensory modality through an associative learning process. The Hb was indeed shown to be involved in such processes through reward prediction and error estimation. One way to test this hypothesis is to measure the changes in Hb spontaneous activity throughout the process of associative learning. Along with this hypothesis, the cognitive capacities involved in associative learning were shown to improve drastically within the first weeks of development [176]. As the Hb plays a role in this associative learning process, it is likely that the spontaneous activity of Hb circuits might change, as the Hb input regions across the brain mature throughout development. It would therefore be exciting to study the processes that regulate sensory responses and spontaneous activity of Hb neurons across different stages of development and test if different types of inputs to the Hb, from sensory, limbic and cortical brain regions arrive with a developmental order and whether spontaneous habenular activity shapes the fate and the function of Hb neurons.

One final possibility is that the spontaneous habenular activity constantly links the cortical or limbic inputs of the Hb to monoaminergic Hb targets. In this manner, the Hb receives information from these input regions about the animal's internal states (such as fear, stress, attention, learned outcomes) and spontaneous activity is regulated accordingly. The habenula can then act as a hub and relay the information received from Hb input regions to the neuromodulatory nuclei that control behavior. In this scenario, the sensory inputs to the Hb might interfere with ongoing habenular activity by potentiating or disengaging the link between Hb inputs and Hb targets. This can then allow to activate or suppress a given behavioral program in the presence of a salient sensory stimulus. The vast literature on the Hb and its function covers several disciplines. While most studies in the human, primate and rodent Hb focus on reward prediction, addiction and stress, work on the Hb of many lower vertebrates focuses on the representations of different sensory modalities in the Hb as well as the asymmetric architecture and function of habenular circuits. There is a strong parallelism in molecular and functional architecture of the vertebrate Hb as well as in its role in regulating behavior in general. However, further research is needed in order to understand the interplay between sensory information from the external world and the internally generated spontaneous activity of the Hb and how these interactions relate to the roles of the Hb in controlling animal behavior.

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