



# Editorial: The Habenula and Its Role in Neuropsychiatric Symptoms

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## Editorial on the Research Topic

### The Habenula and Its Role in Neuropsychiatric Symptoms

The habenula (Hb) is a small epithalamic structure that, through its downstream connectivity controls major neurotransmitters, such as the cholinergic and monoaminergic systems (Hikosaka, 2010; Hu et al., 2020). The Hb contributes to a wide range of behaviors e.g. social behavior (van Kerkhof et al., 2013; Ogawa and Parhar, 2021), circadian rhythms (Liu et al., 2021; Salaberry and Mendoza, 2022), reward processing (Lalive et al., 2022; Mondoloni et al., 2022), decision-making (Stopper et al., 2014; Baker et al., 2015, 2017; Nuno-Perez et al., 2021), cognitive flexibility (Vadovičová, 2014; Baker et al., 2015, 2017), and is implicated in the neurobiology of a number of psychiatric disorders and neuropsychiatric symptoms (Hu et al., 2020). Recent findings confirmed the importance of the Hb in schizophrenia (Schafer et al., 2018; Li et al., 2019; Germann et al., 2020; Wang et al., 2020), bipolar disorder (Schafer et al., 2018; Zhang et al., 2019; Germann et al., 2020; Sonkusare et al., 2022), autism (Germann et al., 2021; Murru et al., 2021), depression (Yang et al., 2018; Barreiros et al., 2022; Zhang et al., 2022; Young et al.), and eating disorders (Maldonado et al., 2018; Wills et al., 2020; Carlson et al., 2022), and implicated the Hb in neuropsychiatric symptoms such as sleep disturbances (Aizawa et al., 2013; Ge et al., 2021), and agitation/aggressive behavior (Flanigan et al., 2017, 2020; Gan et al., 2019).

Thus, this timely special issue provided the space and opportunity for both clinical and pre-clinical researchers to have an up to date discussion of the important and broad role of the Hb in the various neuropsychiatric disorders and symptoms. In total, 60 authors from 8 different countries participated.

Emphasizing the broad role of the Hb, Baker et al. highlight some of the less explored aspects of lateral habenula (LHb) function in contextual memory, sleep, and behavioral flexibility, by providing evidence that the LHb is well-situated to integrate different internal states and multimodal sensory information. The authors focus on the impact of early life stress on LHb function to illustrate how dysregulations on LHb systems promote anhedonia and motivational deficits, and stress the importance of ethologically-relevant behaviors to further understand LHb involvement in a wide range of psychiatric illnesses. Illustrating the important role of the LHb in motivation Sevigny et al. using a unique behavioral paradigm that requires rats to climb a physical barrier in order to receive a large reinforcement or to opt for a smaller reward without the need to climb a barrier, show that pharmacological inactivation of the LHb results in fewer choices for the high-effort-high-reward option, demonstrating that the LHb is part of the circuit responsible for integrating external information on a trial-by-trial basis. This work points to the involvement of the LHb in the ability to discriminate rewards specifically when contingencies change in an unpredictable manner. This supports a growing body of experimental evidence arguing for a

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relevant contribution of the Hb in diverse facets of reward encoding (Stopper et al., 2014; Lalive et al., 2022).

Considering the important role of eye contact as the starting point of interactions in many social animals, Lee and Hikosaka recorded eye movement and LHb activity while monkeys viewed faces in the context of Pavlovian and instrumental conditioning tasks. The results show that faces associated with larger rewards elicited longer periods of eye contact and are associated with suppression of LHb neurons. Faces signaling low values are associated with excitation of LHb neurons. The authors conclude that the reward encoding of LHb contributes to social behavior and disorders, as a sequential goal-directed behavior. Webster et al., in their review, provide an up-to-date summary of the current state of knowledge on LHb neuronal activity and its association with Major Depressive Disorder (MDD). They discuss the growing body of literature on LHb excitatory and inhibitory neurons, downstream connections with the rostromedial tegmental nucleus, and involvement of the reward system, arguing that normalizing inhibitory signaling within the LHb may be a potential therapeutic strategy for MDD. Further studies are necessary to better understand the exact pharmacological and neural circuit mechanisms underlying inhibitory signaling within the LHb.

Another line of research associating Hb activity and MDD, involves circadian rhythms and light signals that affect the LHb. Young et al. review the literature regarding neuronal activity in the LHb during altered circadian rhythms and link it to mental disorders, including depression. The authors, however, highlight the need for further research before firm conclusions can be drawn regarding the importance of changes in the circadian function of the LHb in the etiology of depression and antidepressant treatments. New research by Elias et al. on the role of the Hb in the therapeutic effect of Deep Brain Stimulation (DBS) for MDD, showed clinical response to treatment was significantly associated with Hb volume changes, with responders showing increased Hb volume over time, and non-responders showing the opposite. Furthermore, functional MRI analysis showed DBS treatment to be significantly associated with increased Hb connectivity to several prefrontal and corticolimbic regions, areas previously implicated in the neurocircuitry of depression.

DBS targeting the Hb has been trialed for a number of psychiatric disorders as outlined in the review article by Germann et al. Merging the knowledge from pre-clinical and clinical observations, and using both the published literature as well as registered clinical trials the work highlights the important role of the Hb in mental health. The outcomes of the ongoing clinical trials for treating schizophrenia, depression, obsessive-compulsive disorder, and bipolar disorder will provide further knowledge that will be necessary to confirm the clinical benefit of

this promising intervention. To investigate possible mechanisms of action of Hb-DBS, Zhang et al. explored the transient effects of Hb stimulation in patients with bipolar disorder and schizophrenia. Commonly elicited effects of stimulation were numbness, heart rate changes, pain, and involuntary movements and these showed a pattern suggesting a potential somatosensory organization of the Hb.

Expanding on the involvement of the Hb in psychiatric disorders, Lee and Goto in their perspective review hypothesize that an initially hypoactive Hb during childhood in individuals with Attention-Deficit-Hyperactivity-Disorder (ADHD) may undergo compensatory changes during development, priming the Hb to be hyperactive in response to stress exposure and thereby increasing vulnerability to MDD in adulthood. They suggest that the Hb is involved in the neural network of both MDD and ADHD, via direct and indirect connections with dopaminergic and serotonergic neurons in midbrain nuclei. Suggesting a role of the Hb in anxiety disorders, Liu et al. find that ovariectomized (OVX)-induced anxiety-like behavior is associated with increased LHb activity. Moreover, their results showed that estrogen-treated OVX rats present less anxiety-like behavior, higher levels of monoamines in dopaminergic and serotonergic nuclei, and reduced neuronal activity in the LHb, as compared to non-treated OVS rats. This effect is also observed following intra-LHb injections of estrogen receptor agonist in OVX rats. Gouveia and Ibrahim explore the anatomical organization of the Hb and discuss several distinct mechanisms by which the Hb is involved in the modulation of aggressive behaviors. They propose new investigations for the development of innovative neuromodulatory techniques targeting the Hb to reduce aggressive behaviors. Along those lines, Marks et al. propose that the LHb plays a critical role in the transition from suicidal ideations to self-harm. The authors argue that a multidisciplinary group of researchers is necessary to better understand the role of the LHb, and its long-term modulation, in response to the negative affect in suicidal behavior, to discern the underlying neural mechanisms of this contribution.

The studies presented in this special topic, highlight broad and important roles of the Hb in the neural-networks of several psychiatric disorders and neuropsychiatric symptoms, in both animal models and humans. This body of research points to the new experimental actions needed to further shed light on Hb cellular and molecular mechanisms, and its repercussions for physiological and pathological behaviors.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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