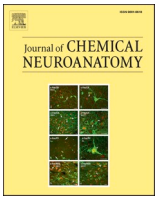
Journal of Chemical Neuroanatomy 136 (2024) 102392

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

journal homepage: www.elsevier.com/locate/jchemneu



The habenula in Parkinson's disease: Anatomy, function, and implications for mood disorders – A narrative review

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ARTICLE INFO

Keywords:
Habenula
Mood disorders
Neuroimaging
Parkinson's disease

ABSTRACT

Parkinson's disease (PD), a widespread neurodegenerative disorder, often coexists with mood disorders. Degeneration of serotonergic neurons in brainstem raphe nuclei have been linked to depression and anxiety. Additionally, the locus coeruleus and its noradrenergic neurons are among the first areas to degenerate in PD and contribute to stress, emotional memory, motor, sensory, and autonomic symptoms. Another brain region of interest is habenula, which is especially related to anti-reward processing, and its function has recently been linked to PD and to mood-related symptoms. There are several neuroimaging studies that investigated role of the habenula in mood disorders. Differences in habenular size and hemispheric symmetry were found in healthy controls compared to individuals with mood disorders. The lateral habenula, as a link between the dopaminergic and serotonergic systems, is thought to contribute to depressive symptoms in PD. However, there is only one imaging study about role of habenula in mood disorders in PD, although the relationship between PD and mood disorders is known. There is little known about habenula pathology in PD but given these observations, the question arises whether habenular dysfunction could play a role in PD and the development of PD-related mood disorders. In this review, we evaluate neuroimaging techniques and studies that investigated the habenula in the context of PD and mood disorders. Future studies are important to understand habenula's role in PD patients with mood disorders. Thus, new potential diagnostic and treatment opportunities would be found for mood disorders in PD.

1. Introduction

Parkinson's disease (PD) is a common degenerative neurological condition with an increasing incidence rate among adults 50 years and older (de Lau et al., 2004). One of the key neuropathological hallmarks is the progressive dopaminergic neuron loss within the substantia nigra pars compacta (SNc), which causes dopamine deficiency in the basal ganglia (Hirsch et al., 1988) and the emergence of typical PD motor symptoms, including bradykinesia and rigidity.

PD is often accompanied by non-motor mood disorders, such as depression, anxiety, apathy, and impulse control disorders (Antonelli et al., 2010; Antonini et al., 2017; Cummings and Masterman, 1999; Dissanayaka et al., 2010; Kano et al., 2011; Ray and Strafella, 2010; Tang and Strafella, 2012). The average estimated prevalence of depression and anxiety ranged from 2.7–90% and 6–55% in PD, respectively (Broen et al., 2016; Reijnders et al., 2008). Degeneration of SNc dopaminergic neurons is accompanied by the loss of other monoaminergic neurons. Degeneration of serotonergic (5-hydroxytryptamine; 5-HT) neurons in the brainstem raphe nuclei has been linked to depression and anxiety. The locus coeruleus and its noradrenergic neurons are among the first areas to degenerate in PD and contribute to stress, emotional memory, motor, sensory, and autonomic symptoms. Another brain region of interest is the habenula, which is an epithalamic structure especially related to anti-reward processing, and its function

Abbreviations: PFCx, prefrontal cortex; SM, stria medullaris; mHb, medial habenula; lHb, lateral habenula; FR, fasciculus retroflexus; RMTg, Rostro-medial tegmental nucleus; SNc, Subtantia nigra pars compacta; VTA, ventral tegmental area; LC, locus coeruleus; RN, raphe nucleus; NAc, nucleus accumbens.

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https://doi.org/10.1016/j.jchemneu.2024.102392
Received 5 December 2023; Received in revised form 7 January 2024; Accepted 12 January 2024
Available online 17 January 2024

has recently been linked to PD and in particular to mood-related symptoms.

There are several neuroimaging studies that investigated the role of the habenula in mood disorders. Differences in habenular size and hemispheric symmetry were found in healthy controls when compared to individuals with a history of depression (Carceller-Sindreu et al., 2015; Cho et al., 2021b; Savitz et al., 2011). A postmortem study also found decreased habenular volume in individuals with depression (Ranft et al., 2010).

There is relatively little known about habenula pathology in PD, but given these observations, the question arises whether habenular dysfunction might have a role in PD and the development of PD-related mood disorders. This manuscript presents a narrative review wherein we selectively examine and synthesize existing literature to provide a comprehensive overview of the role of the habenula in PD, with a particular focus on its association with mood disorders. Our literature search strategy involved a thorough examination of relevant studies and reviews published in major databases, including PubMed, Scopus, and Web of Science. Specifically, the literature search was conducted on January 1, 2023, using the key terms "habenula," "Parkinson's Disease," "mood disorders," "neuroimaging," and "neuropathology" to ensure a focused yet comprehensive coverage of the subject. The selection of literature was guided by the relevance to the habenula's anatomical and functional aspects, its role in PD, and its implications in mood disorders as observed in PD patients. Our review primarily encompasses neuroimaging studies, both in human subjects and animal models, to elucidate the habenula's involvement in PD-related mood disorders, alongside referencing key pathological and clinical studies that provide context to these imaging findings. The intent of this review is to collate and discuss the current understanding of the habenula in the context of PD, highlighting the gaps in knowledge and suggesting directions for future research.

2. Anatomy and circuitry of the habenula

The habenula is a bilateral epithalamic structure with boundaries formed anteriorly by the stria medullaris of the thalamus, posteroventrally by the posterior commissure, medially by the third ventricle, and dorsolateral by the thalamus (Fig. 1). The habenular nuclei consist of medial (MHb) and lateral (LHb) subdivisions, which are connected via the habenular commissure. They are components of the dorsal diencephalic conduction system, which links the forebrain and brainstem. Radiological and histological investigations have identified both the LHb and MHb, with the LHb being considerably larger than the MHb (Fore et al., 2018; Torrisi et al., 2017). The habenular nuclei receive inputs from the forebrain via the stria medullaris. The fasciculus retroflexus contains the habenular efferent projections to the midbrain.

The medial septum and limbic areas provide inputs to the MHb, and the diagonal band of Broca projects to the interpeduncular nucleus, which in turn targets the midbrain raphe nuclei, including the dorsal and median raphe and the dorsal tegmental region (Hikosaka et al., 2008) (Fig. 2). The frontal cortices, thalamus, hypothalamus, and globus pallidus internus (GPi) are the primary sources of projections to the LHb (Baker et al., 2016) (Fig. 2), and LHb can be further divided into a lateral and medial subdivision. The lateral LHb (LHb-L) receives excitatory inputs from the border zone of the globus pallidus and projects downward to the rostromedial tegmental nucleus (RMTg). These neurons are mainly glutamatergic and regulate DA neuronal activity predominantly by activating GABAergic neurons in the ventral tegmental area (VTA) and SNc. Both LHb-L and RMTg also project to the dorsal and median raphe nuclei. The medial LHb (LHb-M) receives inputs from the prefrontal cortex, ventral pallidum, lateral preoptic area, lateral hypothalamic area, lateral septum, and diagonal band nuclei, and primarily targets 5-HT neurons of the dorsal and median raphe nuclei (Benarroch, 2015).

Many of the neural circuits, known to regulate dopamine and serotonin release and to be associated with depression, anxiety, and other neuropsychiatric disorders, are linked to the striatum, a key component in mood regulation and motor control (Ikemoto, Yang and Tan, 2015). In rodents, it has been determined that subgroups of striosomal neurons project directly to the SNc (Crittenden et al., 2016) and indirectly to the LHb via the pallidum (Luo et al., 2015; Wallace et al., 2017). Hong et al. (2019) recently demonstrated a functional circuit between striosomes and LHb neurons in macaques that excites and inhibits LHb neurons. This circuit originates from dispersed striosomes in the caudate nucleus and putamen, with output converging on a relatively constrained region, the LHb.

Electrical stimulation of the LHb reduces the firing activity of the dopaminergic neurons (Ji and Shepard, 2007). LHb lesions are associated with dopaminergic neuronal disinhibition in the SNc (Sasaki et al., 1988). Moreover, dopamine neurotransmission can modulate LHb activity, particularly via D4 receptor activation. It was hypothesized that D4 receptor-mediated excitation of (RMTg-projecting) LHb neurons constitutes an indirect inhibitory feedback pathway that inhibits continued dopaminergic neuron activity (Good et al., 2013). In addition, Shen et al. (Shen, Ruan and Zhao, 2012) showed single-pulse and tetanic electrical stimuli of VTA and SNc to elicit suppression and increase the firing activity of LHb neurons, respectively.

Studying the habenula remains challenging because of the relatively small size (approximately 5–9 mm diameter and 31 mm^3 volume) and deep location. This is further complicated by hemispheric differences in volume (Ahumada-Galleguillos et al., 2017), asymmetric functional connectivity (Hetu et al., 2016), and asymmetric activation as a response to stress (Ichijo et al., 2015). A postmortem volumetric analysis revealed that the human habenula is significantly larger on the left side compared to the right side in both sexes, caused by enlargement of the left LHb

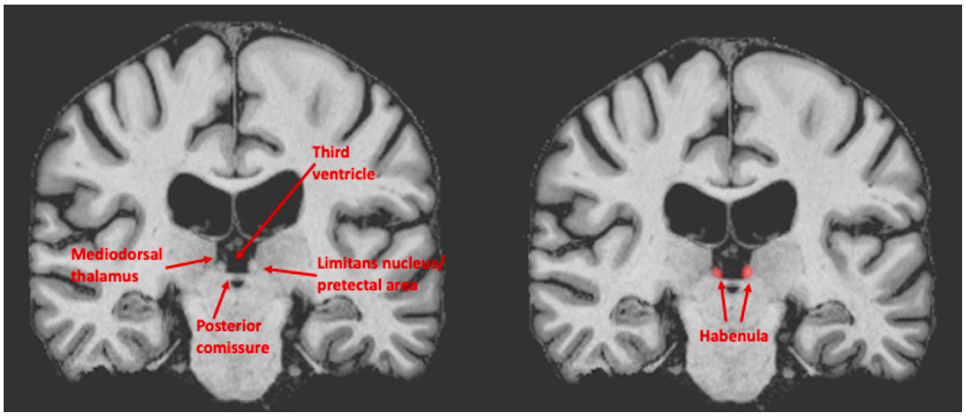

Fig. 1. Coronal MRI sections showing the habenula and the local anatomical landmarks for manual segmentation on 7 T MRI from TRACK-PD Study.

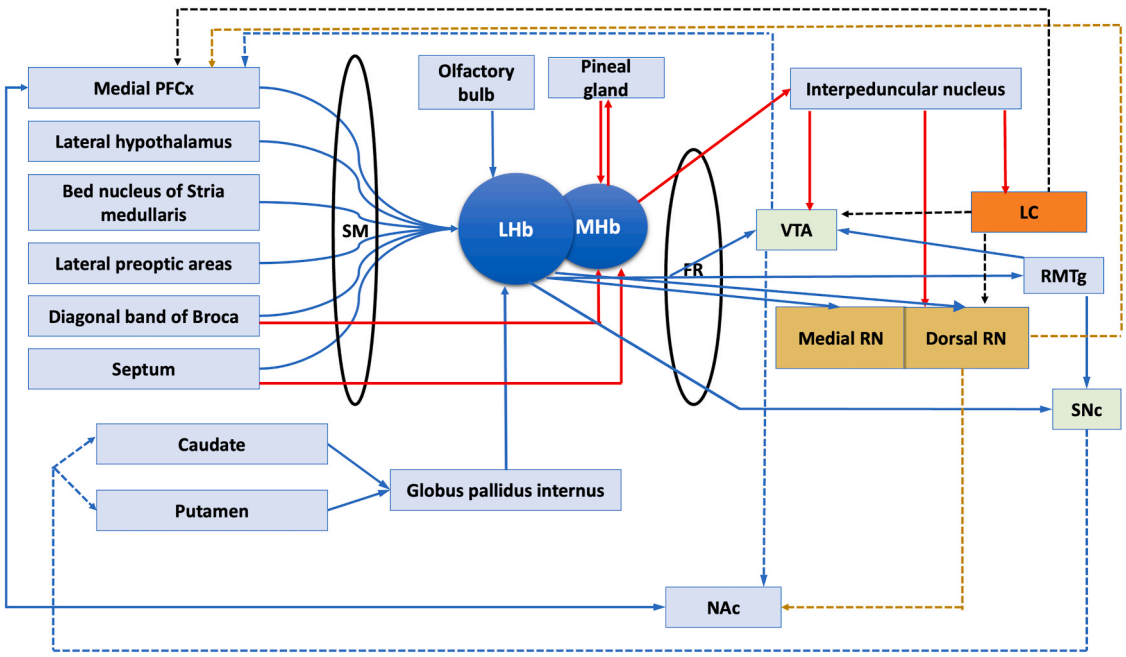

Fig. 2. Figure demonstrating inputs to and from the lateral and medial habenula. Blue arrows show the inputs and outputs of the lateral habenula; red arrows are the inputs and outputs of the medial habenula; light green boxes are the dopaminergic system; yellow boxes show the serotoninergic system, and orange box is the norepinephrine system. Dotted blue lines are the dopaminergic projections, dotted yellow lines are serotoninergic projections, and dotted black lines are norepinephrine projections.

(Ahumada-Galleguillos et al., 2017). In line with these findings, a volumetric study utilizing high-resolution MRI revealed a tendency for increased left habenular volume in both healthy controls (19.5 mm^3 for left, 17.0 mm^3 for right) and individuals with various neuropsychiatric disorders (19.1 mm^3 for left, 15.6 mm^3 for right in patients with major depressive disorder (MDD); 19.4 mm^3 for left, 16.8 mm^3 for right in patients with medicated bipolar disorder) (Savitz et al., 2011). The human habenula appears to have an asymmetry in functional connectivity as well. The left habenula was more functionally coupled with the right parahippocampal region and the right habenula towards the SNc/VTA (Hetu et al., 2016).

3. The function of the habenula

The human habenula is essential for (anti-)reward processing. Additionally, the habenula processes information from limbic regions and the GPi to produce goal-directed behavior. Research on non-human primates indicates that the LHb plays a crucial role in modulating dopaminergic neurons in the midbrain (Matsumoto and Hikosaka, 2007, 2009). LHb neurons are activated by negative reward prediction error and inhibited positive reward prediction error, which results in inhibition and excitation of DA neurons, respectively. A comparable neuronal response profile is observed in response to the outcomes, with LHb neurons responding with strong excitation to negative outcomes and inhibition to positive outcomes (Matsumoto and Hikosaka, 2009). The activity of LHb neurons is influenced by prediction and outcome mismatch, as shown by weaker excitatory responses when negative outcomes are entirely predictable, as compared to ambiguous outcomes. Additionally, greater negative prediction errors are correlated with a higher firing rate of LHb neurons. Therefore, the LHb responds to negative prediction errors and rewards, specifically negative motivational value, with the opposite encoding direction of dopaminergic neurons.

The challenge of detecting signal changes in small brain structures such as the habenula has restricted the use of task-based functional MRI (fMRI) in neuroimaging studies aiming to elucidate habenular function in humans. Using fMRI, Ullsperger and von Cramon (Ullsperger and von Cramon, 2003) conducted two experiments to explore the brain activity associated with negative and positive feedback in a dynamically adaptive motion prediction task. They discovered that receiving negative feedback led to the activation of the rostral cingulate motor area, the inferior anterior insula, and the habenular complex. Shepard et al. (Shepard, Holcomb and Gold, 2006) demonstrated that projections from the habenula to the midbrain could cause a temporary but almost complete suppression of dopaminergic neuron activity at the population level. This effect is comparable to what is seen in primates following an unanticipated negative outcome. Using fMRI, Salas et al. (Salas et al., 2010) found increased activity of the human habenula during negative prediction error events. Compared to reward anticipation, analysis of the regions of interest showed that anticipation of punishment increases left hemispheric habenula activity. However, the anticipation of rewarding rather than neutral outcomes had no effect on the left habenula signal change (Hennigan et al., 2015). Similar to primates, the human habenula is sensitive to probabilities. Cues indicating a high likelihood of losing points in a guessing game caused greater activation in the left-hemispheric habenula, but not in the right hemisphere (Furman and Gotlib, 2016). Another study showed that when presented with cues indicating a high versus low probability of upcoming punishment or monetary rewards, the habenula demonstrated bilateral activation when anticipating punishment, but a decrease in activation when anticipating monetary rewards (Lawson et al., 2014). Weidacker and colleagues (Weidacker et al., 2021) observed reduced activity in the habenula, in both hemispheres, when participants were presented with loss avoidance outcomes, which acted as a reward in comparison to neutral and monetary loss. The authors reported greater left habenula activity during monetary loss versus loss avoidance outcomes. When participants anticipated a loss compared to neutral outcomes, greater functional connectivity was found between the right habenula, subcallosal cingulate, and hippocampus. Yoshino et al. (2020) demonstrated that the bilateral habenula were active during aversive outcomes and that this activation was linked to aversive prediction errors. Finally, a study by Shelton et al. (2012) mapping the activation of the habenula after a painful thermal stimulus indicated a role in pain perception. It was later speculated that since the LHb controls the raphe nuclei, it may

regulate pain-associated depression. Li et al. (2017) found an increase in LHb activity and β calmodulin-dependent protein kinase type II expression and a reduction in neuronal activity in the dorsal raphe nucleus and 5-hydroxy indole acetic acid (5-HIAA)/5-HT ratios in rats with chronic constriction injury of the sciatic nerve, and these changes were accompanied by depression-like behaviors. The authors concluded that increases in the LHb-dorsal raphe nucleus pathway activity were a shared neurobiological mechanism for both pain and depression, which might clarify their co-occurrence.

In different animal models of depression, it has been demonstrated that the LHb becomes hyperactive (Caldecott-Hazard, Mazziotta and Phelps, 1988; Shumake et al., 2003; Shumake and Gonzalez-Lima, 2003, 2013). In both acute and congenital learned helplessness in rats, VTA-projecting habenular neurons exhibit increased synaptic activity (Li et al., 2011). In several human studies, habenula activity is increased and correlates positively with depression rating scales among humans with depression (Lawson et al., 2017; Morris et al., 1999). In the 6-hydroxydopamine rat model of PD, Luo et al. (2015) discovered increased activity in the LHb of rats with depressive-like behaviors. Additionally, LHb lesions reduced depressive-like behavior in the forced swim test of these PD rats expressed by a reduction in the duration of immobility and an increase in the duration of climbing and caused the increased 5-HT levels in raphe nuclei. The authors concluded that LHb mediates the effects of dopaminergic neurons in the substantia nigra and serotonergic neurons in the raphe nuclei, thereby contributing to depressive-like behavior in PD rats.

The habenula is a relatively new DBS target to treat various psychiatric disorders, including depression, and the procedure is mostly experimental for now. Habenula and stria medullaris stimulation, which is the primary afferent of the LHb, has been shown to alleviate depressive symptoms among a small number of patients diagnosed with treatment-refractory depression or bipolar disorder (BD) (Huang et al., 2021; Sartorius et al., 2010; Zhang et al., 2019). Human studies of DBS provide perhaps the most compelling evidence linking LHb dysregulation with MDD. Four months after bilateral LHb DBS surgery, remission of depressive symptoms was observed in a single female patient with chronic unremitting depression (Sartorius et al., 2010). In another case report, a 34-year-old patient with treatment-resistant depression (TRD) had significant improvement after bilateral Hb DBS surgery in mood, anxiety, sleep quality, and quality of life. Hamilton depression rating scale score was reported as 10 in the 12th week after surgery, while it was 23 preoperatively. With these case reports, Hb DBS seems to be a potentially effective therapy for individuals with TRD. Further research with a larger number of participants is necessary to establish the clinical significance and advantages of Hb-DBS.

In summary, various animal and human studies suggest that the habenula acts as a negative modulator of the reward system and that increased activity in the LHb is linked to symptoms of depression. However, the model systems employed in the literature should be carefully evaluated and interpreted. Studies in both rodents (Crittenden et al., 2016; Fore et al., 2018; Luo et al., 2015) and humans (Torrisi et al., 2017) have provided insights into these structural differences, though we note that direct comparisons between species must be approached with caution due to inherent anatomical and functional variations. Animals, especially common research models like rodents, have significant anatomical and physiological differences compared to humans. These differences can be particularly pronounced in brain structures and functions. For example, while the basic structure of the habenula might be conserved, its relative size, connectivity, and function could differ significantly between species. The human brain is more complex, and this complexity is not just anatomical but also functional, involving more intricate neural networks and higher-order cognitive processes. This makes it challenging to directly translate findings related to brain structures and functions. Besides, many aspects of human behavior and cognition, including emotions and higher-order thinking, are difficult to model in animals. This limits the ability to fully understand how findings in animals, especially concerning mood and cognitive functions related to the habenula, apply to humans.

On the other hand, human studies, such as those using high-resolution MRI to assess habenular volume in individuals with neuropsychiatric disorders (Savitz et al., 2011), offer more directly applicable insights into the human condition, albeit with their own methodological limitations, such as sample size and generalizability. Such studies with small sample sizes, while offering valuable insights, may have limitations in terms of potential biases and are prone to type II errors. Another issue is that neuroimaging studies that identify structural differences in the habenula (Ahumada-Galleguillos et al., 2017) must be evaluated in terms of their resolution and sensitivity, especially considering the small size and deep location of the habenula. Similarly, functional MRI studies exploring habenular activation in response to negative and positive feedback (Ullsperger and von Cramon, 2003) need careful interpretation, as the signal changes in small brain structures like the habenula can be challenging to detect.

Finally, there are studies presenting contrasting findings on the role and function of the habenula. These discrepancies underscore the complexity of this research area and necessitate a cautious approach to interpreting results. The divergent outcomes could be attributed to a variety of factors, including differences in study methodologies, variations in sample populations, and distinctions between experimental designs. For instance, while some neuroimaging studies suggest a specific pattern of habenular activation in mood disorders, others report contradictory results. These conflicting findings might be influenced by factors such as the resolution of imaging techniques, the demographic characteristics of study participants, or even the specific parameters used in the experiments. Given these considerations, it is essential to approach the existing literature on the habenula with an appreciation for its intricacies and an understanding that our current knowledge may be shaped by these varying perspectives. Future research in this field should aim to reconcile these differences, possibly through more standardized methodologies or larger, more diverse study populations, to build a more cohesive understanding of the habenula's role in neurological and psychiatric conditions.

4. Neuroimaging of the habenula

Acquiring in vivo habenula imaging data is challenging because of its central location, small size (Strotmann et al., 2014), and close proximity to the third ventricle. The latter causes partial volume effects, especially in clinical MRI scannners. The availability of high-resolution MRI has aided in detailing habenular morphology, connectivity, functional activation, and reduced magnetic susceptibility (Ely et al., 2016; He et al., 2020; Lawson et al., 2017; Savitz et al., 2011).

Ultra-high field MRI improves the spatial resolution and contrast-to-noise ratio (CNR) required to capture the habenula in detail. Previously, anatomical imaging of the human habenula counted on relaxation time contrasts generated by the high fiber myelination density. Increased myelin content leads to hyperintense T1-weighted (T1W) and hypointense T2-weighted (T2W) images (Kim et al., 2016). Schmidt et al. (Schmidt et al., 2017) made T1W maps and employed coronal landmarks to find the habenula but could not divide the habenula into medial and lateral parts. Another study employed T1W spin density and T2W to visualize the LHb, and reported that the habenula had lower T2W values compared to nearby regions, most likely due to the high iron content (Strotmann et al., 2014). Several combinations of inversion times, flip angles, echo times, and averaging can result in improved CNR in the images, while this frequently leads to a reduction in the signal-to-noise ratio (SNR) and the cost of longer acquisition times. As a result, the CNR is not enough to differentiate and definitively characterize the subdivisions, as well as to distinguish unequivocally the activity measured by fMRI thought to be associated with the LHb. T1W maps at 300 μm isotropic resolution and T2W images at 60 μm isotropic resolution were obtained in a human postmortem study at 7 T, and both

MHb and LHb could be differentiated (Strotmann et al., 2013). Schenck et al. (2015) discovered considerable magnetic susceptibility enhancement in the habenula in multiple volunteers researching **quantitative susceptibility mapping (QSM).** Considering the effectiveness of QSM in producing prominent contrast for areas of the basal ganglia that contain high levels of iron, these findings suggest the possibility that magnetic susceptibility could similarly provide anatomically functional contrast for human habenula imaging (Feng et al., 2017). He et al. (2020) used **susceptibility-weighted imaging (SWI)** and QSM to localize the LHb and exhibited bilateral signal alterations in the posterior region of the habenula relative to the anterior region at 3 T, which may imply increased putative iron concentrations in the LHb. The authors concluded that lateral component of the habenula could be identified using SWI and QSM at 3 T. One study used high-resolution ($0.5 \times 0.5 \times 0.8\ mm^3$) MRI of the human habenula with QSM at 3 T and suggested that QSM could be an effective method for in vivo substructure habenula imaging (Yoo et al., 2020). **T2W diffusion-weighted imaging (DWI)** MRI has been utilized to investigate axonal and myelin structure in white matter for over 15 years. Strotmann et al. (2014) described anatomical characteristics visible in high-resolution MR images (including DWI) of the human habenula, comparing in vivo and *ex vivo* findings and linking these to established histological maps. They concluded that high-resolution 7 T imaging of the human habenula provided sufficient SNR and contrast to enable identification of the LHb and MHb, and that high-resolution DWI at 7 T could differentiate LHb and MHb and detect major fiber tracts that connect the habenula with other brain regions. In general, the LHb appears to be predominantly connected with the frontal cortex and limbic system, whereas the MHb appears primarily linked with the brainstem and habenular commissure (Fakhoury, 2017; Strotmann et al., 2014). The few fMRI studies that have been conducted describe that the habenular nuclei are functionally related to the serotonergic system via the dorsal RN, to the dopaminergic system via the VTA and SNc, and to the noradrenergic system via the locus coeruleus (Hetu et al., 2016; Li et al., 2014; Skandalakis et al., 2018; Torrisi et al., 2017). Ely et al. (2019) recently identified significant habenula associations with brainstem regions, subcortical structures, and cortical areas related to the salience network and early sensory processing.

Volumetric assessment of the habenula is most commonly performed via manual segmentation (Savitz et al., 2011). The habenula is segmented by one or more blinded researchers in coronal planes and is visibly protruding into the third ventricle along the ventromedial part of the thalamus or located ventral and medial to the stria medullaris of the thalamus (Mai, Majtanik and Paxinos, 2015). The medial boundary is defined by the third ventricle, while the ventral border is defined by the white matter of the posterior commissure. The dorsal and lateral borders are determined by the white matter of the stria medullaris of the thalamus in anterior planes or by the mediodorsal thalamic nucleus, limitans nucleus, or pretectal area in posterior planes (Savitz et al., 2011). Another method is a geometric approach defined by three anatomical landmarks (Lawson et al., 2013). Firstly, the junction of the habenular medial margin and the posterior commissure is shown (Point A). Secondly, the dorsal point of the MHb border, where the curve of the medial boundary meets the medial-dorsal thalamus (Point B). Thirdly, the lateral portion of the mesopontine junction is close to the tentorial incisure (Point C). The lateral boundary of the habenula was determined in these slices by drawing a straight line between the second and third landmarks (Line z). The ventral boundary's medial extent is formed by drawing a straight line horizontally and laterally from the first landmark (Line x). The ventrolateral apex of the habenula is defined as the intersection of the Lines 'z' and 'x'. The medial boundary is defined by the CSF of the third ventricle in all slices and connected points A and B in posterior slices (Line y) (Fig. 3).

Kim et al. (2016) proposed a semi-automated habenular segmentation approach for in vivo 3 T T1W and T2W images, including histogram-based thresholding, region growing, geometric constraints,

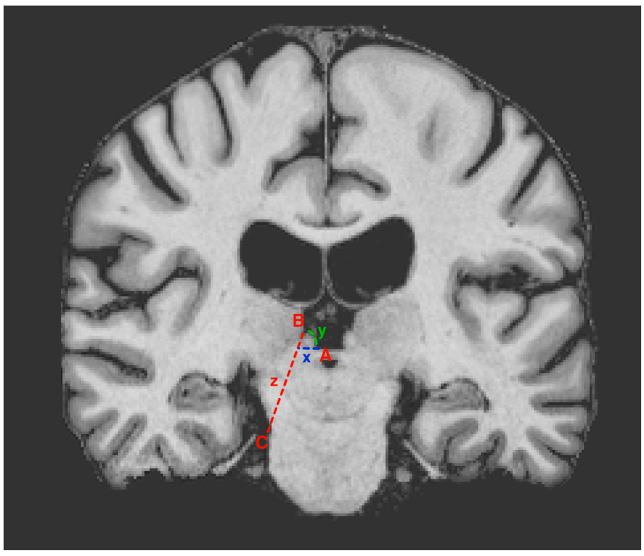

Fig. 3. Detail of the geometrically defined protocol for delineating the habenula on 7 T MR image from TRACK-PD Study. See text for definitions of points A, B and C, and connecting lines x, y, and z.

and partial volume estimation. This approach is based on the greater CNR of myelin-sensitive images due to the habenula's higher myelin content than the surrounding thalamus. More recently, fully automated habenular segmentation methods have been proposed, such as registration-based multi-atlas-driven and deep learning-based segmentation using T1W images (Germann et al., 2020; Kim and Xu, 2022; Lim et al., 2021). These are potentially quick, precise, and reproducible. However, the registration-based method by Germann et al. (108) depends on the registration quality of their atlases and takes long-time process. The deep learning method by Lim et al. (2021) requires 7 T T1 maps and manual pre-selection of slices. Kim and Xu (2022) suggested using 3D deep learning instead of 2D deep learning on T1W images. The potential and limitations of these methods are reviewed in Table 1.

In addition to the volumetric imaging of habenula, several studies at conventional fMRI resolutions reported habenular activation in response to aversive outcomes in controls (Garrison, Erdeniz and Done, 2013; Ide and Li, 2011; Li et al., 2008; Noonan, Mars and Rushworth, 2011; Schiffer et al., 2012; Ullsperger and von Cramon, 2003), in learning and motivation (Lawson et al., 2014), in the error detection process and its ability to modify accordingly (Ide and Li, 2011), as mentioned in the "Function of the Habenula" section above.

4.1. Neuroimaging of the habenula in Mood Disorders

4.1.1. Structural MRI findings

Over recent years neuroimaging studies have focussed on structural changes of the habenula in mood disorders (Table 2). Savitz et al. (2011) performed the first MRI volume examination in MDD and BD patients. The authors acquired high-resolution ($0.4\ mm^3$) images utilizing a 3 T scanner, and one rater manually segmented habenula. Seventy-four healthy controls were compared with medicated (n = 15) and unmedicated depressed BD (n = 22) patients, as well as unmedicated MDD patients (n = 28) and unmedicated MDD patients in remission (n = 32). They found significantly smaller absolute and normalized habenula volumes in unmedicated BD patients than in controls. They also detected smaller absolute habenula volumes in currently depressed women with MDD compared to female controls. The study concluded that a decrease in volume could have functional consequences that increase the risk of developing an affective disorder. Another study by Carceller-Sindreu et al. (2015) sought to determine whether habenular volume differed

Table 1
Pros and cons of various methods used for habenula segmentation.

Method	Field strength	Pros	Cons
Manual segmentation	3 T, 7 T	- No need for a secondary visual check for apparent erroneous segmentation - More common and accepted method	- Subjective (rater bias) - The rater must acquire a high level of technical ability and anatomical knowledge for accurate segmentation - Laborious - Not possible to separate the habenula into medial and lateral parts - Time-consuming
Geometric segmentation	3 T	- Use a subject-specific ROI approach	- Needs a training period - Laborious - Not possible to separate the habenula into medial and lateral parts - Involves manually reorienting each structural image into close alignment with the atlas
Myelin content-based segmentation	3 T, 7 T	- Combination of T1w and T2-weighted (T2w) anatomical images to improve the contrast-noise ratio for segmentation - Objective - Less prone to systematic signal variation	- Sometimes underestimates Hb near a less myelinated area but overestimates along highly myelinated fibers connected to the Hb (e.g., fasciculus retroflexus or stria medullaris)
Automated segmentation (registration-based multi-atlas-driven)	7 T	- Large datasets of images can be studied - Reproducible - Functional MRI, magnetic resonance spectroscopy and positron emission tomography imaging could be used	- Depends on the quality of the registration to the atlas - Takes a long process time - A visual inspection of each subject's segmentation to find obvious erroneous segmentation is required
Automated segmentation (deep learning-based)	7 T	- Versatile - Short processing time - Reproducible - Reducing atlas bias - -Averaging registration errors - Large datasets of images can be studied - Functional MRI, magnetic resonance spectroscopy and positron emission tomography imaging could be used	- Requires manual pre-selection of slices - Requires > 1000 of training data to achieve high accuracy and avoid overfitting - A visual inspection of each subject's segmentation to find obvious erroneous segmentation is required

between healthy controls and patients in various stages of unipolar MDD. Images were obtained from 34 healthy controls and 61 MDD patients utilizing a 3 T scanner. They found a higher white matter habenula volume in first-episode depressive women than in controls and chronic MDD. The authors reported that the habenular volume alterations may not be present in unipolar MDD, regardless of the disease stage, even among patients experiencing severe chronic depression. However, they also stated that the increased white matter volume seen in women with a first episode shows that habenula and its projections are involved in the early phases of recovery and the course of MDD. Johnston et al. (2015) observed reduced habenular volumes in individuals with TRD compared to healthy controls. In a recent study, Cho et al. (2021b) used high-resolution 7 T MRI data from 33 MDD patients and 36 healthy controls and stated that MDD patients had reduced right habenula volume compared to controls. In addition, the right habenula in the MDD group was smaller and had a lower T1 value than the left habenula. Contrary, Liu et al. (2017) discovered increased habenula volume in MDD patients, which was linked to anhedonic symptoms. Schafer et al. (2018) investigated the differences between BD and healthy controls and did not find such a longitudinal volumetric difference between the groups.

Elias et al. (2022) evaluated habenular volume in 32 patients treated with DBS with the subcallosal cingulate region as neurostimulation target for treatment-resistant mood disorders. Clinical response to DBS was strongly related to longitudinal habenula volume change. Responders had a tendency to exhibit an increase in habenular volume, while non-responders tended to have a decrease in volume.

In accordance with the imaging studies, a postmortem study by Ranft et al. (2010) demonstrated a decline in neuron count and density of the habenula in a mixed group of subjects who had a history of BD or MDD. In addition to the volumetric studies, Cho et al. (2021a) demonstrated that the ratio of the right ipsilateral tract between the thalamus and habenula was significantly higher in MDD patients compared to the left ipsilateral tract. They hypothesized that MDD is associated with the disintegration of the left thalamus-right habenula tract function, with a compensatory increase in the number of tracts.

In summary, there are different findings regarding habenula volume in mood disorders. The small number of participants and the relatively subjective manual habenula segmentation might be key methodological issues explaining inconsistencies in the volumetric analyses.

4.1.2. Functional MRI findings

fMRI studies indicate that the abnormal circuitry that contributes to TRD may involve affective, salience, auditory, visual networks, and language processing cortex (He et al., 2016). Recent research has found an abnormal functional correlation (FC) in the habenular nucleus, particularly with the default mode network (DMN) in TRD patients (Amiri et al., 2021; Luan et al., 2019). A recent study sought to map the intricate neural circuitry architecture of the habenula in order to detect the neural mechanisms of TRD (Barreiros et al., 2022). The authors performed FC analyses using the left and right habenula as seed regions, and whole-brain voxel-wise comparisons were used to compare the three groups (35 TRD patients, 35 patients with treatment-responsive depression, and 38 healthy controls). The TRD group showed increased connectivity in the left habenula, especially with the left precuneus and the right precentral gyrus, compared to the treatment-responsive group and the right precuneus, compared to the treatment-responsive and healthy control groups, indicating that an increased interplay between reward and DMN is associated with suicidality and may be a potential mechanism for anhedonia in TRD.

Increased habenula activation in depression has been demonstrated in an H2(15)O-PET study assessing different cognitive tasks involving either a paced word repetition task or a paced orthographic verbal fluency task alternating across the six scans in each session (Morris et al., 1999). Furthermore, an emotional-processing task during fMRI, along with the resting-state regional blood-flow measurement using arterial spin labeling, showed habenula hyperactivation in depression (Morris et al., 1999; Roiser et al., 2009). Furman and Gotlib (2016) observed that negative feedback responses activated the LHb more profoundly than positive feedback responses in MDD patients and healthy controls. A recent study investigating phasic habenular function by completing a

Table 2
Imaging studies investigating habenula in mood disorders.

Study	Number of participants	Type of assessment	Psychopathology	Strength of MRI	Sequences/Hb segmentation	Findings
(Ranft et al., 2010)	44 (13 HCs)	Postmortem	14 mood disorders 17 schizophrenia	N/A	N/A	Significantly reduced habenular volumes of the MHb and LHb in depressive patients in comparison to HC and schizophrenia patients.
(Savitz et al., 2011)	171 (74 HCs)	*In vivo*	37 BD 60 MDD	3 T	MPRAGE / manual	The unmedicated BD patients displayed significantly smaller absolute and normalized habenula volumes than the HC subjects.
(Carceller-Sindreu et al., 2015)	129 (34 HCs)	*In vivo*	95 MDD	3 T	3D-MPRAGE / manual	Women with a first-episode MDD had greater Hb-white matter volumes than HCs and patients with treatment-resistant/ chronic MDD.
(Johnston et al., 2015)	41 (21 HCs)	*In vivo*	20 TRD	3 T	MPRAGE	Significantly reduced grey matter volumes in regions corresponding to the habenula in TRD patients.
(Liu et al., 2017)	38 (17 HCs)	*In vivo*	21 unmedicated patients with major depression and 17 healthy participants.	3 T	T2 * weighted, echo planar single shot pulse sequence fMRI / manual	Activation in the left habenula during receipt of punishment in HCs. Attenuated left habenula activation to punishment in depressed patients. Greater left habenula activation was associated with more severe depressive symptoms and anhedonia. Greater habenula volume in patients with depression.
(Schafer et al., 2018)	140 (40 HCs)	*In vivo*	68 schizophrenia 32 BD	3 T	3D-MPRAGE / semi-automated	Case-control differences in Hb volume did not reach statistical significance.
(Cho et al., 2021a)	71 (37 HCs)	*In vivo*	34 MDD	3 T	DTI, MPRAGE	Higher right habenula-left mediodorsal thalamus tracts in patients with MDD than in HCs.
(Cho et al., 2021b)	69 (36 HCs)	*In vivo*	33 MDD	7 T	MPRAGE and MP2RAGE / manual	A smaller right Hb volume and left-right asymmetry of Hb volume in MDD.
(Elias et al., 2022)	32	*In vivo*	32 patients who received SCC-DBS	1.5 T and 3 T	3D-SPGR, GRE-EPI multiphase fMRI / automated	Increased Hb volume over time in responders, decreased Hb volume in non-responders. Active DBS was significantly associated with increased Hb connectivity to several prefrontal and corticolimbic regions.

HC: Healthy control, N/A: not available, MHb: Medial habenula, LHb: Lateral habenula, MDD: Major depressive disorder, DTI: diffusion tensor imaging, MPRAGE: magnetization-prepared rapid acquisition with gradient echo, BD: bipolar disorder, TRD: treatment-refractory depression, SCC-DBS: subcallosal cingulate area deep brain stimulation, SPGR: spoiled gradient recalled, GRE-EPI: gradient-recalled echo echo-planar imaging

passive (Pavlovian) conditioning task with appetitive (monetary gain) and aversive (monetary loss and electric shock) outcomes during high-resolution fMRI in MDD patients revealed decreased habenular responses within the patient group as the unconditioned stimulus became progressively more shock predicting (Lawson et al., 2017). In the TRD group, Luan et al. (2019) discovered a high correlation between the right habenular nucleus and the medial superior frontal gyrus, anterior cingulate cortex (ACC), and medial orbitofrontal cortex. They reported that TRD could be caused by dysfunction in the habenular nucleus-related circuitry for processing unpleasant emotions.

4.2. Neuroimaging of the mood disorders in Parkinson's disease

The present approach to diagnose PD relies on assessing clinical manifestations. Due to PD's heterogeneous presentation, early diagnosis can be challenging. At present, MRI is utilized in clinical settings to eliminate other possible reasons for parkinsonian symptoms, such as tumors. New MRI paradigms and ultra-high field imaging are being increasingly recognized for their potential in the diagnosis of PD in recent years (Lehericy et al., 2017). Numerous studies, including cross-sectional and cohort designs, have established links between MRI features and clinical manifestations in PD (Bae et al., 2016; Castellanos et al., 2015; Filippi et al., 2018; Reiter et al., 2015; Schwarz et al., 2014; Wolters et al., 2019). TRACK-PD is a longitudinal observational 7 T MRI study in the novo patients with PD (Wolters et al., 2020). The objective of this study was to offer significant insights into the diverse clinical presentations of PD and their corresponding MRI features. The ultimate goal of this study is to enhance the knowledge of PD and to develop novel biomarkers to track the progression of the disease, which will aid in developing new therapies. The first dataset of TRACK-PD is now complete and will be used to study habenula anatomy in PD patients compared to healthy controls.

Anxiety, depression, pain, and autonomic dysfunction are common non-motor symptoms observed in PD patients. In 2015, Wen et al. (2016) conducted a systematic review of neuroimaging findings in depression (38 studies), anxiety (8 studies), and apathy (14 studies) in PD. Other than PET/SPECT studies, four studies used T1W imaging (Feldmann et al., 2008; Kostic et al., 2010; van Mierlo et al., 2015), three used DTI (Huang et al., 2014; Li et al., 2010; Matsui et al., 2007), and six used resting state-fMRI (Hu et al., 2015; Lou et al., 2015; Luo et al., 2014; Sheng et al., 2014; Skidmore et al., 2013; Wen et al., 2013) in depression. There were also four studies reporting findings from structural T1W (Huang et al., 2013), DTI (Surdhar et al., 2012), task fMRI (Cardoso et al., 2009), and resting state-fMRI (Huang et al., 2015), respectively. Only one of the seven studies utilizing T1W revealed an increase in bilateral thalamic grey matter volume in PD patients with depression (dPDs) compared to PD patients without depression (Huang et al., 2015). Three studies did not observe any differences in gray matter volume between healthy controls and dPDs (Berg et al., 1999; Feldmann et al., 2008; Huang et al., 2013). On the other hand, three studies reported that dPD patients exhibited reduced gray matter volumes in areas such as the prefrontal, parietal, and insular regions, as well as the limbic system (ACC and amygdala) (Cardoso et al., 2009; Feldmann et al., 2008; Kostic et al., 2010) compared to healthy controls

or non-depressed PD patients. Furthermore, they discovered that the volume of the prefrontal and limbic regions had inverse correlations with depression (Kostic et al., 2010; van Mierlo et al., 2015). A study utilizing T2-weighted imaging revealed higher hyperintensity in the midline mesencephalic structure in patients with dPD, indicating a modification in the basal limbic system (Walter et al., 2007). Three out of four studies using DTI techniques reported reduced white matter connectivity, as indicated by decreased fractional anisotropy (FA), in various tracts such as the bilateral anterior cingulate cortex (ACC) and thalamus, as well as multiple tracts connecting the left frontal and deep temporal lobes (Huang et al., 2014; Li et al., 2010; Matsui et al., 2007). This FA decrease can indicate axonal degeneration, demyelination, or more complex fiber crossings. Compared to DTI results, studies using resting-state fMRI to investigate depression in PD revealed increased and decreased resting state neural activities in dPDs, compared to non-depressed PD patients and healthy controls. In dPDs, an increased FC between spatially distinct regions in the resting state was detected in the subcortical regions, such as the connectivity of the left amygdala with the bilateral mediodorsal thalamus. In contrast, connectivity between corticolimbic or corticocortical networks was reduced. The severity of depression was found to be inversely related to the FC between the amygdala and prefrontal and posterior cingulate cortices. Furthermore, there was a positive correlation between depression and the neural activity in the left amygdala, right cingulate and thalamus, and bilateral cerebellum prefrontal cortices. Regarding regional neural functional activity during the resting state, dPD patients demonstrated increased activity in the prefrontal, limbic, temporal, and parietal regions. These studies mostly imply that dPD patients have higher neural activity in the prefrontal regions and impaired FC between the prefrontal-limbic networks. Functional imaging studies found an inverse relationship between dopaminergic density in the caudate and putamen and the intensity of anxiety symptoms in PD, while there was no clear link between thalamic dopaminergic density and anxiety. Apathy and metabolism or activity in the striatum, amygdala, prefrontal, temporal, and parietal regions were found to have both positive and inverse associations. The authors reported no findings of the habenula, despite both nigrostriatal and extra-nigrostriatal pathways being affected in PD, particularly the frontal region and its connecting regions.

In a recent study, Liu et al. investigated the complexity of the spontaneous blood-oxygen-level-dependent (BOLD) of fMRI in dPDs. They found that the whole-brain complexity and complexity in 18 different regions of cognition and behavior were significantly lower in dPDs than in non-depressive PDs (Liu et al., 2022). Carey et al. (2021) reviewed neuroimaging features of anxiety in PD in 2020. They included studies using MRI, PET, and single-photon emission computed tomography. The cortico-striato-thalamo-cortical limbic and fear circuits were found to change depending on the anxiety's severity. Reduced FC between the striatum and ACC, decreased dopaminergic and noradrenergic activity in the striatum, thalamus, and locus coeruleus, and decreased serotoninergic activity in the thalamus have all been observed in the cortico-striato-thalamo-cortical limbic circuit.

5. Pathoanatomic staging studies on Parkinson's disease-related pathology in the habenula

For many years, PD was considered to have a relatively straightforward neuropathology; however, recent studies have significantly altered this perception. The progression of PD in the human nervous system spans several years, evolving into a fully developed clinical syndrome unless interrupted by death. The disease is marked by a steady increase in intraneuronal lesion severity and predictable distribution changes. These changes occur even in individuals with no recorded motor dysfunction symptoms, indicating presymptomatic and symptomatic phases in PD's progression.

PD primarily affects the limbic, visceromotor, and somatomotor systems and progresses through stages. Each stage is characterized by the ongoing development of distinct inclusion bodies. Braak et al. (2003) devised a neuropathological staging scheme for PD based on the progression of Lewy bodies (LBs). They proposed that PD likely originates in the olfactory bulb and the autonomic enteric nervous system, with a retrograde progression of Lewy body pathology (LBP) over time. This pathological spread eventually reaches the SNc, where it is believed to trigger the degeneration of DA neurons, a hallmark of PD. Although there is limited research on the epithalamus's role in PD, it is believed that significant PD-related pathological changes begin to manifest in this region at around Braak stage 4 (Braak et al., 2003; Hawkes, Del Tredici and Braak, 2010). In PD, it is suggested that the transition from the presymptomatic to the symptomatic phase likely occurs during stages 3–4 (Thal, Del Tredici and Braak, 2004). This phase involves severe lesions in the anteromedial temporal mesocortex, crucial for transferring data from sensory areas to the prefrontal cortex via limbic system centers. In a healthy brain, the limbic loop and the neocortex work together, with the neocortex processing sensory information and the limbic loop aiding in memory and importance categorization. Information from sensory areas passes through the temporal mesocortex to limbic structures and then to the prefrontal cortex. Impairments in this pathway can lead to memory and cognitive issues, and reduced limbic input to the prefrontal cortex can affect personal initiative and other cognitive functions (Dubois and Pillon, 1997).

While Braak's hypothesis on PD development receives support from various studies, including in vitro, in vivo, and clinical research, there is also skepticism about its applicability to all PD patients. This doubt stems from variations observed in the disease's progression among different individuals (Jellinger, 2008). A subgroup of young-onset, levodopa-responsive PD patients with predominantly motor symptoms and late-stage dementia aligns with Braak's staging. However, this staging does not consistently apply to other levodopa-responsive PD patients, indicating variability in the disease's progression (Halliday et al., 2008). Given this variability, it is plausible that habenular pathology may also exhibit variations among individuals.

6. The pathobiological basis of the habenula-related mood disorders in Parkinson's disease

PD is commonly known for its motor symptoms, but depression is a notable neuropsychiatric aspect of it (Aarsland et al., 2011). During the preclinical phases of PD, the dysfunction of the limbic loop of the basal ganglia and the lateral habenula, along with the interconnected network of dopaminergic, serotonergic, and adrenergic systems, have been implicated in the development of depression. This is discussed in studies by Borgonovo et al. (2017) and Wilson et al. (2019), which suggest that these neural components and pathways play a critical role in the early onset of depressive symptoms associated with PD.

Studies on rodents have shown that modifications in the dopaminergic pathways are correlated with the exhibition of behaviors that are characteristic of depression. In studies by Lyu et al. (2021) and Maillet et al. (2016), it was found that the downregulation of astroglial glutamate transporter in the habenula of 6-hydroxydopamine (OHDA)-lesioned rat models could be related to the degeneration of the nigrostriatal pathway, potentially playing a role in PD-related depression. Additionally, Hui et al. (2020) observed that unilateral 6-OHDA lesions in the SNc of rats involved presynaptic dopamine D4 receptors in the lateral habenula, which are crucial in regulating PD-related depression. Furthermore, Jiang et al. (2020) found that injections of the 5-HT1A receptor-agonist 8-hydroxy-2-(dipropylamino)tetralin hydrobromide into the dorsal hippocampus significantly elevated dopamine and 5-HT levels in the medial prefrontal cortex, habenula, ventral hippocampus, and amygdala, indicating that hippocampal 5-HT1A receptors might influence depression and PD-related depression. Other research has indicated that manipulating 5-HT4 receptor activity in the lateral habenula, either through activation or inhibition, can induce depressive-like behaviors in rats with 6-OHDA lesions (Guo

et al., 2021). This includes outcomes observed in forced swim tests and sucrose preference tests, suggesting a significant role of 5-HT4 in modulating mood-related responses in the context of PD models. The study by Luo et al. (2015) revealed that the lateral habenula plays a pivotal role in connecting the dopaminergic and serotonergic systems, contributing to depressive symptoms in PD rat models. This connection involves the lateral habenula mediating the effects of dopaminergic neurons in the SN on serotonergic neurons in the raphe nuclei, highlighting its significance in the neurobiology of depression in PD.

7. Neuroimaging of the habenula in Parkinson's disease

Only one human study reported on habenular imaging in PD with behavioral impairment. Markovic et al. (2017) acquired structural and resting state-fMRI in 22 patients with PD with punding, 30 patients with PD without any impulse control disorders matched for disease stage and duration, motor impairment, and cognitive status, and 30 healthy controls. A seed-based technique was used to examine the resting state-FC of the habenula and amygdala, and volumes of both and cortical thickness were calculated. They found that PD patients with punding had a high FC of the habenula and amygdala with the thalamus and striatum bilaterally and decreased connectivity between the bilateral habenula and the left frontal and precentral cortices. Lower FC between the right amygdala and the hippocampus was also seen in PD patients with punding compared to PD without punding. The volumes of the habenula and amygdala did not differ across groups. The authors concluded that a disruption in connection across critical nodes of the reward circuit (i.e., habenula, amygdala, BG, frontal cortex) might be a contributing cause of punding in PD. A review published by Borgonovo et al. (2017) explored the evidence of dysfunction in neural circuitry linked with depression in PD, focusing on the pre-clinical, pre-motor, and early motor stages of the disease. They argued that the early dysfunction of the neural circuitry related to depression in PD involves the limbic loop of the basal ganglia and LHb. They proposed that changes in the neural circuitry linked with emotional regulation could be indicative of the ongoing neurodegenerative process. New neuroimaging studies with a larger cohort about mood disorders in PD and habenula are needed to clarify the relationship.

8. Discussion and conclusion

The mood disorders significantly impact the quality of life and prognosis of individuals with PD. According to the most studies, the prevalence of clinically significant depressive symptoms in PD patients ranges from 30 to 35%. The underlying mechanism(s) responsible for the pathophysiology of depression in PD are not well understood, and multiple factors, such as genetic, inflammatory, cellular regulation, and signaling pathways, may be involved. The mood disorders linked with PD are connected to the malfunctioning of dopaminergic neurons in the substantia nigra, as well as alterations in 5-HT neurons in the raphe nuclei. The LHb is among the few areas that plays a role in regulating both DA and 5-HT-containing neurons (Hikosaka, 2010). There has been significant progress in comprehending the neural circuits and roles of the LHb. The habenula has a key role in the neural mechanisms of depression (Hu et al., 2020).

The habenula's connections to the brainstem nuclei that modulate key aspects of behavior (e.g., reward, mood, arousal) are well studied. A growing body of research indicates that the habenula, although tiny, is pivotal in enabling adaptive behavior. The capacity to accurately anticipate rewarding or aversive outcomes is a crucial adaptive behavior that promotes survival and facilitates avoidance of hazardous or disagreeable situations. This ability is thought to be attributed to an evolutionarily preserved hedonic neurocircuit, consisting of a network connecting various brain regions involved in the release of monoamines, spanning the forebrain, midbrain, and hindbrain regions. Within this hedonic neurocircuit, the LHb controls monoamine release and monoamine-controlled behaviors, such as reward learning. The complexity of this system has increased with the identification of heterogeneity in the roles of dopaminergic neurons in valence coding. The VTA and SNc contain at least two subpopulations of dopaminergic neurons based on their input-output pathways and cell body locations. These subpopulations include reward-activated and aversion-activated dopaminergic neurons. The LHb may also activate aversion-coding dopaminergic neurons in the medial VTA, which project to the mPFC, as well as inhibit reward-coding dopaminergic neurons. LHb neurons not only encode reward value but also reward probability and magnitude, which can facilitate complex decision-making by highlighting differences in reward magnitude and cost. Hyperactivity of LHb neurons could diminish dopamine-related reward signals, most likely via the intermediary actions of RMTg or by directly activating dopamine neurons that project to the mPFC. Such hyperactivity of these pathways may affect decision-making (e.g., overprocessing of aversive events, reduced motivation, or altered learning from positive or negative reinforcement).

Evidence from human and non-human studies shows that LHb dysfunction may play a role in depression. It is possible that LHb hyperactivity contributes to depression and that inhibiting LHb activity may alleviate depressive symptoms. Despite the link between habenula and depression, there are few imaging studies about the role of the habenula in mood disorders, probably due to its small size (Savitz et al., 2011). In one study, higher habenula volume in first-episode depressive women was shown (Carceller-Sindreu et al., 2015). Some imaging studies have reported activation of the habenula with aversive stimuli and negative feedback (Hennigan, D'Ardenne and McClure, 2015; Lawson et al., 2014; Ullsperger and von Cramon, 2003). Contrarily, in some studies, authors found attenuated habenula activation in depressive patients (Furman and Gotlib, 2016; Lawson et al., 2017; Morris et al., 1999). In another study, increased activation in the left habenula during the receipt of punishment was found in healthy individuals, while depressive patients had attenuated left habenula response. They also found greater habenula volumes in depressive patients and an association between greater left habenula activation and depression severity (Liu et al., 2017). As seen, the results are inconsistent, which could be related to patient differences, individual factors, disease severity and stages, and medication status. However, it is clear that we need much more studies with larger cohorts to understand the exact mechanism.

The imaging studies about mood disorders in PD mostly showed increased neural activity in the prefrontal regions and impaired FC between the prefrontal-limbic networks in dPD patients. In addition, an inverse relationship between dopaminergic density in the caudate and putamen and the intensity of anxiety symptoms in PD was found in functional imaging studies. However, there is only one imaging study about habenula's role in mood disorders in PD, although the relationship between PD and mood disorders is known. Markovic et al. (2017) conducted a study using structural and functional MRI and found that PD patients with punding had increased FC between the habenula and amygdala with the thalamus and striatum bilaterally, as well as decreased connectivity between the bilateral habenula and the left frontal and precentral cortices. However, the volumes of the habenula did not differ across groups. The authors claimed that a disruption in connection across critical nodes of the reward circuit, such as the habenula, amygdala, BG, and frontal cortex, might be a contributing cause of punding in PD. Nevertheless, there is still no human imaging study investigating habenula's role in depressive or anxious PD patients. The LHb, as a link between the dopaminergic and serotonergic systems, is thought to contribute to depressive symptoms in PD. Future studies are important to understand habenula's role in PD patients with mood disorders. Thus, new potential diagnostic and treatment opportunities would be found for mood disorders in PD.

Although extensive research has been conducted on animal models, reports on in vivo habenula imaging in humans have been scarce, likely

due in part to the habenula's location deep within the brain and its relatively small size in relation to the overall brain volume. Studies of the human habenular morphology, connectivity, functional activation, and magnetic susceptibility have been added to the growing body of in vivo human habenula research thanks to advances in high-resolution MRI. The primary method used in human habenula volumetric studies is manual segmentation. However, the conventional manual-based approaches are considered time-consuming and laborious, especially with large datasets. It is also difficult to produce segmented masks with precision due to the anatomical properties of the habenula. As a result, there is a wide range of variation in the results obtained from manual segmentation of the habenula by different observers, which makes it challenging to establish a definitive standard. Therefore, several semi- or fully automatic segmentation methods have been reported. The suggested automatic segmentation techniques are expected to aid in the automated segmentation and estimation of the volume of the habenula and other critical small brain areas for upcoming psychiatric neuroimaging research. The use of high-resolution MRI-assisted DBS in the habenula region has been suggested and implemented with promising outcomes as a potential treatment for TRD. We believe that neuroimaging studies with high-resolution MRI and a large patient population might make it easy to understand the pathophysiology under the non-motor, especially mood and behavioral findings in PD. Thus, early diagnosis of these findings and predicting the prognosis could be possible.

Ethics Approval and Consent to Participate

The authors confirm that the approval of an institutional review board was not required for this work.

Funding

None.

CRediT authorship contribution statement

Tan Sonny: Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Michielse Stijn:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Kuijf Mark L.:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Temel Yasin:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Samanci Bedia:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors confirm that the approval of an institutional review board was not required for this work. The authors declare no conflict of interest. There is no funding for this study.

Data availability

No data was used for the research described in the article.

Acknowledgments

None.

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