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An evolutionary perspective on habenular asymmetry in humans

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ABSTRACT

The habenula (Hb) of vertebrates is a dorsal and bilateral diencephalic nuclear complex that works as an anatomical hub integrating cognitive, emotional and sensory networks to regulate mood, motivation and value-based decision-making, among other functions. Across vertebrates, the Hb organises into two conserved separate components (medial and lateral in mammals equivalent to dorsal and ventral in more basal vertebrate species), which are thought to subserve different functions based on a partial independence of their connectivity systems. As a complex, the Hb shows morphological, molecular and connectivity differences between the left and right sides in a wide range of vertebrate species, which in some cases extend to the functional and behavioural levels. Habenular asymmetries are particularly prominent in basal vertebrate species but become less evident in amniotes and particular mammals. In humans, recent evidence reveals that, under an overall symmetry morphology, the Hb shows lateral differences in volume, activation, metabolism and susceptibility to damage that suggest an asymmetric condition of this nuclear complex. Here, we review the evidence supporting this view and discuss the possible origin of this asymmetric trait in humans from an evolutionary developmental perspective.

The habenula as a key regulator of mood, motivation and decision-making

In the brain of vertebrates, the habenula (Hb) is a dorsal and bilateral diencephalic nuclear complex that works as an anatomical hub that integrates cognitive, emotional and sensory networks to regulate mood, motivation and value-based decision-making, among other processes. In mammals, the left and right sides of the Hb are formed by medial (Med-Hb) and lateral (Lat-Hb) components which are thought to subserve different functions based on a partial independence of their afferent and efferent connectivity systems (Figure 1A)[1,2]. The Med-Hb primarily receives inputs from the supracommissural septum and projects to the interpeduncular nucleus (IPN) in the ventral midbrain (Figure 1A, green)[3]. The Lat-Hb, on the other hand, has more widespread connectivity linking the basal ganglia and limbic forebrain with brainstem dopaminergic (substantia nigra pars compacta, SN; ventral tegmental area, VTA), serotonergic (raphe nuclei), histaminergic (hypothalamus) and gabaergic (rostro medial mesopontine tegmental nucleus, RMTg) centres (Figure 1A, red)[4,5]. Despite the significant amount of experimental data supporting the view of partial independence between the Med-Hb and Lat-Hb, there is nevertheless some degree of overlapping of afferent projections (i.e. descendent afferents from the accumbens and diagonal band nuclei, and ascendant afferents

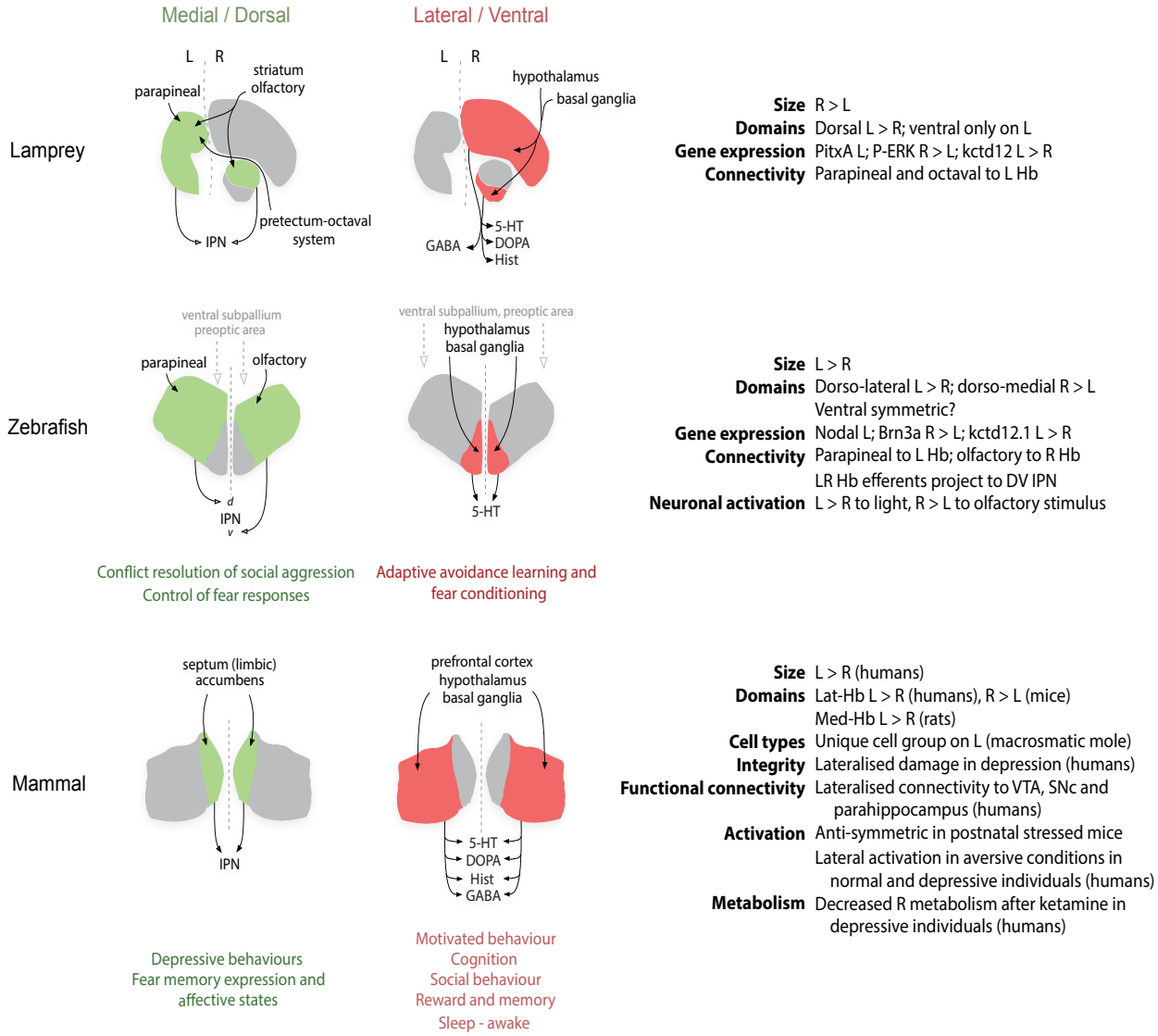

Figure 1: A comparative view of habenular connectivity, function and asymmetry in vertebrates.
(A) Organisation of connectivity and proposed function of the two main habenular pathways in vertebrates. Gene expression, neurochemistry and connectivity data from a basal vertebrate (lamprey), a modern teleost (zebrafish) and mammals (rodents and humans) support the existence of two partially independent habenular circuits. The medial habenular pathway of mammals is homologous to the dorsal habenular pathway of lampreys and zebrafish (left, green). On the other hand, the lateral habenular pathway of mammals is equivalent to the ventral habenular pathway of lampreys and zebrafish (right, red). The proposed motor-limbic and cognitive functions associated with each habenular domain are given below the schematics. (B) Left-right asymmetries of the Hb described at structural and functional levels in the lamprey, zebrafish and mammals (rodents and humans). Abbreviations: 5-HT (serotonergic), d (dorsal), DOPA (dopaminergic), GABA (gabaergic), Hist (histaminergic), IPN (interpeduncular nucleus), L (left), R (right), v (ventral). Details and references are given in the text.

from the VTA and locus coeruleus)[2,6] and interconnectivity[7] between the two Hb domains.

Given the efferent connectivity pattern and the connection of its afferent septal nuclei with specific sectors of the hippocampus and subiculum, the mammalian Med-Hb has been involved in learning associated with fear responses and mood and to nicotine addiction, among other functions[3]. In turn, studies in rats and monkeys have shown that projections from the Lat-Hb to the VTA and SN provide reward prediction error and value related signals to dopaminergic systems that are fundamental to learning[8,9]. Studies in humans support this view and reveal Hb activation and increased functional connectivity between the Hb, VTA and SN in the context of reward

predictor errors and negative motivation values associated with punishment[10-13]. In addition to learning, specific projections from the Lat-Hb to the serotonergic raphe nuclei provide long-term coding signals that appear to influence mood[6,14]. Consistently, structural and functional disruption of the Lat-Hb in humans has been linked to the origin of depression[15-22] and substance abuse (cocaine and alcohol)[23,24]. Furthermore, deep brain stimulation of the Lat-Hb has proven successful to alleviate depressive symptoms in patients with treatment-resistant major depression[25,26]. Together, these findings reveal that as a complex, the Hb is an anatomical hub integrating cognitive, emotional and sensory networks and that in this context participates in the modulation of a series of motivated behaviours, including mood, learning and value-based decision-making.

Evolution of habenular circuits in vertebrates

Across vertebrates, the structural organisation of the Hb into two separate components seems to be an ancestral character, which is also closely related to the conservation of two segregated systems of habenular connectivity[27-29]. Particularly, the primary outputs to the IPN and to dopaminergic/serotonergic systems that characterise the medial and lateral domains of the mammalian Hb, respectively,[2] are also present in the dorsal and ventral habenular domains of more basal vertebrate species such as lampreys and zebrafish (Figure 1A)[28-31]. However, such conservation of the output circuit design differs from the evolutionary shift of inputs from sensorial (e.g. olfactory, parapineal, octaval system) to limbic, which is seen in the medial/dorsal habenular domain from basal vertebrates to mammals[5,29,32-34]. This observation suggests a change in the contextual information that is used by different species to activate habenular circuits. Also, in the evolution towards amniotes and specifically in mammals we observe a striking diversification of input sources to the Lat-Hb[1,2], including the appearance of reciprocal projections from neuromodulatory monoaminergic habenular targets[1,35]. Interestingly, the relative size of the Lat-Hb is also significantly increased in humans compared with rats, such that it represents ~95% of the total Hb volume[36,37]. Thus, there appears to be a growing diversification of afferent sources to the lateral/ventral habenular domain during evolution, in particular in mammals, which suggests an increasingly complex modulation of this habenular circuit. Although detailed studies of habenular connectivity in other vertebrate species are still needed, this idea finds support in the extensive range of functional/behavioural domains (i.e. sensorial, motivational and cognitive) in which the Lat-Hb has been involved in mammals and especially in humans[5,9].

Asymmetry: a conserved but variable trait in the habenula of vertebrates

A noticeable and conserved feature of the bilateral Hb is the presence of morphological and molecular differences between the left and right sides (Figure 1B)[27]. Although studies on habenular asymmetry have comprised a wide range of vertebrate species, they have mostly referred to the Hb as a complex and little information is available on the contribution of the medial/dorsal and lateral/ventral components to habenular asymmetry across species. As a complex, habenular asymmetry is morphologically conspicuous in agnathans and most cartilaginous and bony fishes[27] and can involve both medial and lateral domains (e.g. lampreys)[29] or be confined to a single domain (e.g. medial/dorsal Hb zebrafish)[30]. In vertebrate species other than fishes, and in particular in amniotes such as birds and mammals, the morphological asymmetries of the Hb are much less pronounced with only a few exceptions (e.g. lizards)[27]. In mammals, the presence of small lateral differences in habenular volume has been described in the Med-Hb of rats[38] and the Lat-Hb of mice[39], while a unique small group of cells was described on the left Hb of the macrosmatic mole[40]. In primates and in particular in humans, the study of habenular asymmetry is still in its infancy due to the small size and internal position of this nuclear complex within the brain. In spite of this, a recent post-mortem volumetric analysis revealed that the human Hb is significantly larger on the left compared to the right in both genders, a condition that results from an enlargement of the left Lat-Hb[37]. Consistent with these findings, a volumetric study using high-resolution magnetic resonance imaging (MRI) showed a tendency of increased left habenular volume in healthy subjects and individuals with various neuropsychiatric conditions, although these differences were statistically non-significant possibly due to the resolution limitations of this imaging technique[17].

Asymmetry of the Hb does not restrict to the morphological and molecular domains but has also been observed at a functional level, suggesting that the Hb is involved in brain lateralisation. In zebrafish, for example, specific subsets of neurones on the dorsal Hb show differential calcium activation on the left and right sides in response to visual and olfactory stimuli, respectively[41]. Importantly, these functional asymmetries match the structural asymmetries in habenular morphology, gene expression and connectivity[30,41], which have also been associated with visual-guided lateralised behaviours[42]. In mammals, recent studies reveal that the left and right Hb become differentially activated under specific conditions, but the anatomical substrate underlying habenular asymmetric activation is still unknown. In mice, the Hb becomes asymmetrically activated in postnatal mice under stress as revealed by the expression of early response genes

in a transgenic background[43]. In humans, studies of high-resolution functional MRI have shown asymmetric blood oxygen level-dependent responses to aversive relative to neutral events[13] and to negative conditioned stimulus values[12]. Furthermore, a recent report based on high-resolution cardiac-gated resting state imaging revealed that the right and left Hb have distinct correlates of functional connectivity with the VTA, SN and the parahippocampus[44]. In turn, studies in depressive patients show a significant decrease in activation of the left Hb during the prediction or experience of monetary penalty[45], a decreased metabolism of the right Hb after ketamine treatment[18], and a reduction of volume, neuronal cell number and cell area in histological postmortem samples[16]. Together, these findings suggest that the human Hb has a previously unrecognised asymmetric condition that comprises both structural and functional levels, which might be relevant in contexts of health and disease. In summary, morphological, molecular and connectional observations across vertebrates reveal the presence of notorious asymmetries in more basal species, which in some cases is linked to the asymmetric response of the Hb to sensorial stimuli and lateralised behaviours. In contrast, in the context of subtle morphological asymmetries, the Hb of mammals and particularly humans often shows asymmetries at a functional level but the anatomical substrate underlying this condition remains unknown.

Coding asymmetries on habenular circuits

From a functional viewpoint, a relevant question is how the different types of asymmetries are coded into circuits. Asymmetric circuits involving paired neuronal structures such as the Hb can in principle use two main designs: exhibit left-right differences in the extent of similar types of neurones/connectivity present on left and right sides (class-I), or show unique neurones or connectivity patterns on only one side of the brain (class-II)[46]. The Hb appears to shows both types of circuit designs in vertebrates. For example, the left and right Hb of a modern teleost such as zebrafish exhibit different proportions of similar neurones based on molecular markers and connectivity[30]. The presence of volumetric differences between the left and right sides of the Hb in humans[37] and many other vertebrate species[27] could also be indicative of a class-I asymmetry. On the other hand, the Hb of lampreys, frogs and lizards show unilateral cellular domains, i.e. the ventral Hb of lampreys is only on the right side[29] while the laterodorsal and dorsomedial Hb domains of frogs[47] and lizards[48], respectively, are present only on the left[27]. On the other hand, a group of neurones of the olfactory bulb project only to the right Hb in zebrafish[33,34] while parapineal neurones reach only the left Hb in lampreys, zebrafish and lizards[32,48,49]. Noteworthy, the observation of sided activation of the human Hb in certain functional tasks, the unilateral metabolic response to drugs and lateral damage in certain neuropsychiatric conditions (see above) suggest the presence of class-II asymmetric circuits in the human Hb.

In the context of the different asymmetric habenular designs, some elaborate patterns of connectivity have emerged. A striking example is provided by zebrafish, where the spatial segregation of left-right habenular outputs along the dorsoventral axis of the IPN define parallel tunnels of habenular information directed to the griseum centrale and raphe nuclei, respectively[30,50]. Significantly, habenular asymmetry and its coding into segregated efferent connectivity tunnels have been associated in this species with the asymmetric processing of visual and olfactory stimuli[41,51], lateralised behaviours[42], and the behavioural responses to fear and anxiety[50,52]. Whether similar asymmetric patterns of functional connectivity and behavioural correlates are associated with the Hb of other vertebrate species including humans is yet to be determined.

Insights into the origin and impact of habenular asymmetry in humans

An important lesson from the comparative studies described here is the existence of multiple types of habenular asymmetries in different species affecting various organisational levels, from gene expression through morphology and connectivity to function. In this context, it does not appear sensible to provide a single explanation for the origin of habenular asymmetry in humans. On a developmental ground, studies in fishes have suggested that the Hb shows independent developmental programs on the left and right sides that can be modulated unilaterally by genetic and cellular inputs to generate asymmetry during ontogeny[53,54]. For example, the left-sided activation of the transforming growth factor-ß Nodal in the embryonic brain controls for development of morphological, molecular and connectional asymmetries in lampreys, catshark and zebrafish[53,55,56]. Nodal signalling is a conserved pathway that regulates the development of body, visceral and brain asymmetries across metazoans in a context-dependent manner[54,57,58], and in vertebrates, it has been associated with both enlarged and reduced habenular domains on the side of expression[53,55,56]. In addition to direct genetic inputs, the influence of an asymmetrically positioned cellular group, the parapineal organ (PpO), also plays a fundamental role in the elaboration of habenular asymmetries in zebrafish[32,59,60]. Notably, genetic (Nodal) and cellular (PpO) influences upon the developing Hb both seem to converge in the regulation of neurogenesis[56,61]. It is thus plausible that an asymmetric regulation of neurogenesis (via Nodal and other developmental inputs) is a conserved step in the origin of habenular asymmetry across vertebrates including humans. This idea is

consistent with the reduction or evolutionary loss of gross morphological asymmetries observed in vertebrate groups other than fishes including mammals[27], which follows the apparent loss of Nodal expression in the brain[54]. The mechanisms controlling habenular asymmetry in the absence of asymmetric Nodal signalling possibly exploit the sensitivity of the prospective Hb to spatial and temporal changes in genetic and cellular developmental inputs, as suggested by zebrafish studies[32,60-63]. These mechanisms could in principle generate structural and functional asymmetries in mammals beneath an apparent overall symmetric morphology of the Hb. The existence of a unique small group of cells on the left Hb of the macrosmatic mole[40], of lateral differences in volume described in the Hb of rodents and humans[37-39], of asymmetric functional connectivity in humans[44], and asymmetric activation of the rodent and human Hb in different contexts of health and disease[12,13,43,45] is consistent with this idea and supports the importance of considering other less evident types of habenular asymmetries in these species.

Functional studies involving areas such as the prefrontal cortex, amygdala, cerebellum and mesencephalon (i.e. optic tectum or colliculi) have shown that lateralisation is a key feature of the human brain[64]. In this context, demonstrating the existence of asymmetric circuit designs involving the human Hb is relevant to first understand the possible functional role of habenular asymmetry and then link this condition to a potential therapeutic use in the treatment of affective disorders. In contrast to sensorial asymmetries that in many cases associate with lateralised environmental stimuli, the mammalian Hb primarily integrates cognitive with sensorial and motivational information to generate an activation state that is contextually dependent, and thus the role of asymmetry in this process is less intuitive. The partial independence of left and right habenular circuits provides a substrate that could promote and perhaps explain the presence of sided activation and lateral susceptibility of the Hb to damage seen in humans. Should this is the case, it will become essential to distinguish the functions that the left and right Hb do in common from those that are unique to each of them. Future research will have to address these and other emerging questions and ascertain the presence and types of left-right asymmetric circuits in the human Hb and their correlates to habenular and brain function. To this aim, special efforts must be placed to improve the resolution of *in vivo* functional imaging and segmentation techniques, and to develop novel experimental designs that resolve left from right in the human Hb.

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