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# Untangling the dorsal diencephalic conduction system: a review of structure and function of the stria medullaris, habenula and fasciculus retroflexus

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## Abstract

The often-overlooked dorsal diencephalic conduction system (DDCS) is a highly conserved pathway linking the basal forebrain and the monoaminergic brainstem. It consists of three key structures; the stria medullaris, the habenula and the fasciculus retroflexus. The first component of the DDCS, the stria medullaris, is a discrete bilateral tract composed of fibers from the basal forebrain that terminate in the triangular eminence of the stalk of the pineal gland, known as the habenula. The habenula acts as a relay hub where incoming signals from the stria medullaris are processed and subsequently relayed to the midbrain and hindbrain monoaminergic nuclei through the fasciculus retroflexus. As a result of its wide-ranging connections, the DDCS has recently been implicated in a wide range of behaviors related to reward processing, aversion and motivation. As such, an understanding of the structure and connections of the DDCS may help illuminate the pathophysiology of neuropsychiatric disorders such as depression, addiction and pain. This is the first review of all three components of the DDCS, the stria medullaris, the habenula and the fasciculus retroflexus, with particular focus on their anatomy, function and development.

**Keywords** Dorsal diencephalic conduction system · Stria medullaris · Habenula · Fasciculus retroflexus

## Introduction

The dorsal diencephalic conduction system (DDCS) is a highly conserved integrative and modulatory pathway present in all vertebrates (Sutherland 1982). This bilateral assembly consists of two white matter tracts with an

intervening nucleus and is a key conduit connecting the cognitive-emotional basal forebrain to the modulatory monoamine areas of the brainstem (Sutherland 1982; Gardon et al. 2014). It is often overlooked in favor of its more ventral and larger companion, the medial forebrain bundle, which also connects the fore- and hindbrain regions. The similarity in connections (forebrain limbic–striatal to monoaminergic brainstem) and the fact that they converge upon each other anteriorly and posteriorly despite straddling either the dorsal (epithalamic route) or ventral (hypothalamic route) thalamus (Fig. 1) led Nauta to suggest that they may have similar functions with respect to reward behaviors (Nauta 1958). The DDCS first revealed a role in reward in 1970 (Boyd and Celso 1970) and subsequently also showed functionality in the ‘top-down’ modulation of motivation, mood and pain. Highly conserved amongst vertebrates, (Beretta et al. 2012; Concha and Wilson 2001) this system, unlike the singular component of the medial forebrain that forms direct connections (Coenen et al. 2018), is composed of three structures: the white matter stria medullaris, the intervening habenular nucleus and the white matter fasciculus

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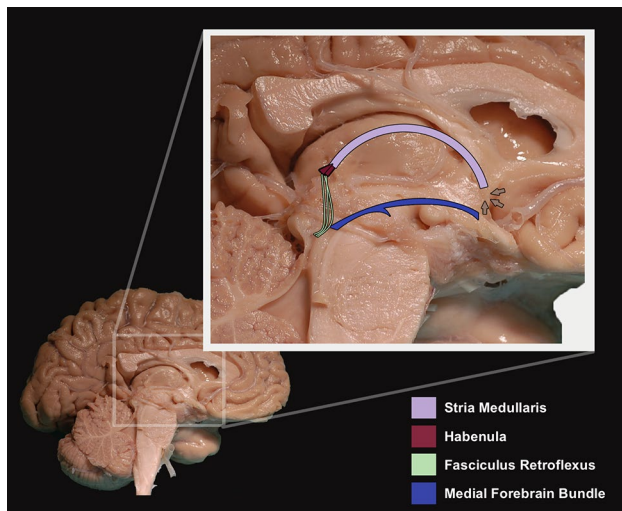
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**Fig. 1** The dorsal diencephalic conduction system, with the stria medullaris, habenula and fasciculus retroflexus highlighted. The SM can be seen arching over the thalamus and terminating in the Hb. The larger more wedged-shaped LHb is labeled and can be distinguished from the smaller MHb. The FR can also be identified with fibers arising from the MHb running through the core of the FR and fibers arising from the LHb traveling in the mantle of the FR. Brain photography courtesy of Professor Paul Tierney, Head of Discipline, Department of Anatomy, Trinity College Dublin. *SM* Stria Medullaris, *Hb* habenula, *FR* Fasciculus Retroflexus, *LHb* Lateral Habenula, *MHb* Medial Habenula

retroflexus. Gathering inputs from diverse frontal areas including the septal nuclei (pleasure and motivation), hypothalamus (arousal and pain), fronto-cortical regions (decision-making), and basal ganglia (motor and behavioral control), the stria medullaris funnels information from these regions into the habenula, situated at the dorso-caudal end of the thalamus (Parent et al. 1981; Geisler and Trimble 2008). Information flow in the SM is almost entirely unidirectional (forebrain to habenula), apart from some reciprocal fibers arising from the lateral preoptic and lateral hypothalamic areas (Yamadori 1969; Champney 2015; Patestas and Gartner 2016). After integrating these inputs and relaying in the habenula, output fibers project down through the fasciculus retroflexus to synapse among brainstem monoamine areas including the midbrain ventral tegmental area and hindbrain raphe nuclei. Through this system, distinct frontolimbic areas can modulate monoaminergic release in the brainstem and consequently influence whole brain monoaminergic tone.

In recent years, the DDCS has received increasing attention (Gardon et al. 2014; Fakhoury et al. 2016b; Roddy et al. 2018; Fore and Yaksi 2019; Ichijo and Toyama 2015), with research suggesting a particular role in neuropsychiatric disorders due to its function in monoamine regulation (Fakhoury 2017). This is the first review to collate the literature on the known anatomy, function and development of the

human DDCS as a whole, as opposed to reviews which have focused exclusively on the habenula alone (Hikosaka et al. 2008; Hikosaka 2010; Fakhoury 2017; Bianco and Wilson 2009). Although initially aimed as a review of the human DDCS, due to the relative dearth of human studies, the review will be complemented by other vertebrate studies throughout.

## Methods

A comprehensive literature search to investigate the range and destination (medial/lateral) of habenular inputs was undertaken for the purpose of this review. Online sources including PubMed/MEDLINE, Google Scholar, EMBASE, OVID, and PsycINFO were systematically searched by the primary and senior authors (ER and DWR) using the terms “HABENULA”/“DORSAL DEINCEPHALIC CONDUCTION SYSTEM”/“FASCICULUS RETROFLEXUS”/“HABENULOPEDUNCULAR TRACT”/“HABENULOINTERPEDUNCULAR TRACT” + “INPUT”/“EFFERENT”/“TRACING”/“CONNECTIONS”/“MIDBRAIN”/“HINDBRAIN”. No time limit was imposed on search results. Once areas were identified, the search was rerun for each area separately, e.g., “HABENULA” + “HYPOTHALAMUS”, “HABENULA” + “AMYGDALA”. All vertebrate species were included in the search. For each article, references were checked and accessed if considered potentially relevant. A physical search of older literature and books archived in the Department of Anatomy, Trinity College Dublin was also undertaken. All studies were collated, and the data extracted and crosschecked by two researchers (ER and JW).

To determine the mean volume of the habenula, we analyzed data from 14 studies examining normal habenulae (i.e., studies examining habenulae volumes in normal individuals, or control data from clinical studies) in a total of 356 subjects (excluding data from repeated studies). Data were extracted from the results of these studies, and the authors contacted if the raw data was unavailable from published sources. Many study data sets were unavailable and, therefore, mean habenular volumes could not be calculated. As such using the SPSS 24 “compute” command, the MEAN function was used to generate an available analysis (AIA) scale for the missing data (Parent 2013).

## Stria medullaris

(*Latin; inner strip/furrow*) The stria medullaris (SM), also known as stria medullaris thalami or habenular stria, is a discrete bilateral white matter tract forming the first part of the dorsal diencephalic conduction system (Sutherland 1982).



An unlabeled drawing of the SM can be clearly seen in Vesalius' texts (Vesalius 1543), but was first designated as the *medullary stria* by Wenzel and Wenzel (1812). Other terms over the years include the *columna medullaris* (Tarin 1750), the *markiger Streisen* (von Soemmerring 1791) and *rené* (reins) (Cruveilhier 1836). Previously considered part of the olfactory system due to its origins around the basal forebrain regions (Ramon y Cajal 1911), it is now well established that the SM is the primary afferent of the behavior modifying DDCS (Fakhoury et al. 2016a).

## Anatomy

The stria medullaris first appears as a bilateral compact fascicle just posterior to the anterior commissure (Buchanan and Newton 1948). At this point, it is in contact with the fornix and stria terminalis as all three tracts converge around the anterior commissure. The SM runs caudally along the roof of the third ventricle, attached to the tela chordae (Faucette 1969) and arches dorsally over the thalamus. Coursing along the dorsomedial border of the thalamus, it forms a distinct horizontal ridge. In the 80% of individuals where an interthalamic adhesion is present (Allen and Gorski 1991; Carpenter 1991), it arches superior to this. The SM then descends caudally, its lateral fibers terminating in the habenula (Buchanan and Frazer 1937; Díaz et al. 2011). Cadaveric measurements place the diameter of the stria medullaris at between 1.5 and 2.5 mm across its length (Roddy et al. 2018), being widest caudally where it merges with the habenula. Both the SM and habenula can be seen as a combined rod-like structure on the posteromedial aspect of the thalamus, protruding into the lateral ventricle with an expansion towards the caudal thalamus. The SM white matter tract occupies 30% of the cross-sectional area of the habenula in humans. This SM–habenular interface is greatly enlarged in humans compared to that in rodents, with the SM taking up only 12% of the cross-sectional area in rats (Díaz et al. 2011).

In contrast to the lateral fibers, the medial SM fibers flex inwards towards the base of the pineal gland and cross to the opposite side. These terminate in the contralateral habenula (Buchanan and Frazer 1937; Naidich and Duvernoy 2009; Díaz et al. 2011). This decussation is known as the habenular commissure (Strotmann et al. 2014). Note that the nearby posterior commissure found in the inferior part of the pineal stalk is not anatomically or functionally part of the DDCS. The habenular commissure lying across the superior part of the pineal stalk together with the SM and habenulae form what is anatomically known as the habenular trigone (Strotmann et al. 2014). The lateral habenula also contributes to the habenular commissure in rats (Kim 2009); however, in humans, it is unclear what proportion of these commissural fibers derive from the SM, medial or lateral habenulae.

Three distinct groups of fibers are found in the human stria medullaris. Within the dorsolateral cross section of the tract travel fibers originating from the amygdala and striatal regions (Marburg 1944). Fibers from the basal forebrain areas lie dorsomedial and centrally within the SM; whereas, fibers that originate from the thalamus and hypothalamus are found ventrally. The course and relative position of these fibers remain unchanged through the SM as far as the habenula (Marburg 1944) and correspond with the general trend of lateral habenula fibers being more striatal in origin, and medial fibers being more basal forebrain/septal in origin.

The stria medullaris is also reported to have its own nucleus. A small compact group of cells thought to be the bed nucleus of the stria medullaris (BSM) was first reported in mice by Ramon y Cajal (1911). The nucleus, embedded among myelinated axons of the stria medullaris, is found caudally to the bed nucleus of the anterior commissure and between the stria medullaris and the fornix in rodents (Risold and Swanson 1995; Ramon y Cajal 1911). As a caudal extension of the septal region (Risold and Swanson 1995), the BSM is reported to contain small multipolar neurons and dense collaterals thought to arise from the fornix (Ramon y Cajal 1911). It has also been alluded to by others (Gurdjian 1927; Watson and Paxinos 1986; Jacobowitz and Palkovits 1974); however, borders have been difficult to identify (Risold and Swanson 1995) and connections of BSM itself have been difficult to establish, with only projections to the medial habenula identified thus far (Shinoda and Tohyama 1987).

Due to the thinness of the tract, the SM is often missed on standard resolution clinical MR imaging. As this tract has been identified as a potential therapeutic target for deep brain stimulation in depression and other neuropsychiatric diseases (Sartorius and Henn 2007), recent efforts have focused in localizing the trajectory of the tract for stereotactic neurosurgery using diffusion-weighted imaging (Kochanski et al. 2016; Roddy et al. 2018).

## Function

In general, the SM gathers fibers from frontal, septal, striatal and hypothalamic areas and relays information from these areas through a single tract to the lateral and medial habenulae. Information is transmitted through the tract in a mostly unidirectional manner from the forebrain regions to the habenula. To date, however, there have been no fiber tracing or staining studies of the human SM.

The first-order inputs to the lateral habenula through the stria medullaris include the lateral preoptic area, the lateral hypothalamus, anterior hypothalamic nucleus, bed nucleus of the stria terminalis, the internal segment of the globus pallidus, substantia innominata and septum (Klemm 2004; Hikosaka et al. 2008). Second- and further-order inputs



arise from medial, lateral and preoptic hypothalamic areas (Klemm 2004). The SM also inputs information from the nucleus of the diagonal band of Broca, lateral hypothalamus, lateral preoptic area and medial septal nuclei into the medial habenula (Akagi and Powell 1968; Klemm 2004). SM afferents are primarily cholinergic, glutamatergic and GABAergic, with primary GABAergic and cholinergic input into the habenula being supplied by the nucleus of the diagonal band of Broca via the SM (Viswanath et al. 2013; Klemm 2004). This was supported when bilateral transection of the SM in rodents induced a 50% decrease in choline acetyltransferase, an enzyme responsible for acetylcholine synthesis, in the habenulae and the downstream interpeduncular nucleus, as well as a 65% decrease of glutamate decarboxylase in the habenula (Contestabile and Fonnum 1983).

The stria medullaris has recently been suggested as a therapeutic target for the treatment of depression and other neuropsychiatry diseases using deep brain stimulation (Sartorius and Henn 2007). Even though modulation of the lateral habenula is the proposed mechanism of this technique, electrode placement occurs at the caudal end of the SM, just beside the habenula. To date, two patients with intractable depression have shown marked improvement with modulation of the DDCS through SM stimulation (Sartorius et al. 2010; Kiening and Sartorius 2013).

The SM and habenula, although discrete structures, are essentially a functional unit and defining a function for the SM independent of the habenula is impossible. As such, the function of the SM will be integrated in the below section.

## Habenula

(Latin; *little reign*) The trigonum habenulae is a small triangular eminence encompassed by the pineal gland, the posterior part of the stria medullaris and the adjacent part of the thalamus (Buchanan and Frazer 1937; Naidich and Duvernoy 2009). A slight swelling in this trigone indicates the position of the evolutionary conserved gray matter structure called the habenula (also known as the habenular complex, due to being composed of multiple nuclei) (Nolte 2002). It was first named by Meynert who described a small mass of gray matter on the posteromedial aspect of the thalamus (Meynert 1872). Originally considered anatomically and functionally the stalk of the adjacent pineal gland, it refers to two distinct groups of nuclei at the caudal end of the stria medullaris.

The habenula is the central component of the DDCS and has been well conserved throughout vertebrate evolution (Loonen et al. 2017). It acts as a hub, with limbic pathways traversing the stria medullaris to relay to the habenula prior to transmitting signals to brainstem modulatory areas (Carpenter 1991). As such, it is vital for integrating motor,

cognitive, emotional and sensory processing within a single locus to influence motivational processes and value-based decision-making (Gardoni et al. 2014). Recent studies highlighting the function of the habenula in encoding reward and aversive behavior have renewed the interest into this small structure.

## Anatomy

The habenula, like many limbic structures, was initially believed to have primarily olfactory connections (Ramon y Cajal 1911); however, repeated studies have revealed its connections with a wide variety of regions across the brain (Rausch and Long 1971; Powell et al. 1965; Greatrex and Phillipson 1982; Gamble 1952). The habenula has both medial and lateral nuclei (see below). The literature strategy revealed that 135 studies have investigated habenular connections in diverse vertebrates from lizards to primates. Only one study to date has traced the connections of the human habenular complex (Marburg 1944). The results are presented in Table 1. Although some overlap, broadly speaking, motor, frontal, thalamic, hypothalamic, basal ganglia and associated areas (e.g., ventral tegmental area) project to the lateral habenula; whereas, septal and limbic associated areas (e.g., hippocampus) project to the medial habenula.

Although easily distinguishable as the thick caudal expansion of the combined SM–habenula rod-like structure that protrudes into the lateral ventricle, defining the rostral most boundaries of the habenula is challenging in gross dissections. This is because the SM tapers caudally and dorsally into the habenula. Regional microscopic differences in cellular distribution, however, allow the habenula to be distinguished from the white matter fibers of the SM and the multipolar cells of the adjacent thalamus (Marburg 1944; Díaz et al. 2011). The habenular width is approximately 5–9 mm across (Strotmann et al. 2014), as such the structure is difficult to visualize accurately using standard clinical MRI. However, using high-resolution magnetic resonance imaging (resolution  $< 1.5\text{mm}^3$ ), it has recently been possible to determine the mean habenular volumes in a number of studies (Table 2a). Extrapolated mean values for left and right habenular complex volumes were found to be  $21.9\text{ mm}^3$  ( $\text{SD} \pm 6.5\text{ mm}^3$ ) and  $20.6\text{ mm}^3$  ( $\text{SD} \pm 6.7\text{ mm}^3$ ), respectively. A single post-mortem study has investigated habenular volumes (Ranft et al. 2010). This study suggested larger habenular volumes revealing lateral volumes of  $27.57\text{ mm}$  ( $\text{SD} \pm 5.05\text{ mm}$ ) and  $29.59\text{ mm}$  ( $\text{SD} \pm 4.83\text{ mm}$ ) and medial volumes of  $3.35\text{ mm}$  ( $\text{SD} \pm 1.33\text{ mm}$ ) and  $3.64\text{ mm}$  ( $\text{SD} \pm 0.97\text{ mm}$ ) for left and right sides, respectively. MRI resolution limitations, age variation and differences in measurement techniques between post-mortem and MRI studies could potentially account for the difference between the two methods of volume estimation.



**Table 1** Habenular inputs collated from previous tracing studies

Area of input	Nucleus	References
<b>Cortical regions</b>		
Piriform cortex	Medial/lateral	(Gurdjian 1925) (rat), (Carl Huber and Crosby 1929) (bird), (Hines 1929) (platypus), (Loo 1931) (Opossum), (Young 1936) (rabbit), (Humphrey 1936) (bat), (Marburg 1944) (human), (Herrick 1948) (tiger salamander), (Gamble 1952) (lizard), (Gamble 1956) (tortoise), (Ban 1962) (rat), (Powell et al. 1965) (rat), (Millhouse 1969) (mouse), (Parent et al. 1981) (rat, cat and monkey), (Kim and Lee 2012) (rat)
Hippocampus	Medial	(Hines 1929) (platypus), (Young 1936) (rabbit), (Humphrey 1936) (bat), (Marburg 1944) (human)
Amygdala	Medial/lateral	“Nucleus Taenia” (Carl Huber and Crosby 1929) (bird), (Young 1936) (rabbit), (Humphrey 1936) (bat), (Marburg 1944) (human), (Herrick 1948) (tiger salamander), (Gamble 1952) (lizard), (Laursen 1955) (monkey), (Kusama and Hagino 1961) (rabbit), (Mitchell 1963) (cats), (Cowan et al. 1965) (rat), (Johnson 1965) (cat), (Millhouse 1969) (mouse), (Leonard and Scott 1971) (rats), (Iwahori 1977) (cat), (Parent et al. 1981) (rat, cat and monkey), (Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)
Prelimbic cortex	Lateral	(Gamble 1952) (lizard), (Kim and Lee 2012) (rat)
Infralimbic cortex	Lateral	(Kim and Lee 2012) (rat)
Anterior cingulate cortex	Lateral	(Kim and Lee 2012) (rat)
Anterior insular cortex	Lateral	(Vertes 2002) (rat), (Vertes 2004) (rat), (Kim and Lee 2012) (rat)
<b>Basal forebrain</b>		
Septum undifferentiated	Medial/lateral	(Gurdjian 1925) (rat), (Carl Huber and Crosby 1929) (bird), (Humphrey 1936) (bat), (Nauta 1956) (Rat), (Nauta 1958) (cat), (Valenstein and Nauta 1959) (Rat, guinea pig, cat and monkey), (Guillery 1959) (Cat), (Cragg 1961) (rabbit, rat and cat), (Ban 1962) (rat), (Powell 1963) (rat), (Zyo 1963) (rabbit), (Mitchell 1963) (cats), (Johnson 1965) (cat), (Raisman 1966) (rat), (Powell 1966) (cat), (Powell 1968) (Rat, cat and monkey), (Mizuno et al. 1969) (cat), (Genton 1969) (mouse), (Price and Powell 1970) (Rat), (Smaha and Kaelber 1973) (opossum and cat), (Herkenham and Nauta 1977) (rat), (Iwahori 1977) (cat), (Meibach and Siegel 1977) (rat), (Swanson and Cowan 1979) (rat), (Gottesfeld and Jacobowitz 1979) (rat), (Parent et al. 1981) (rat, cat and monkey), (Hoogland 1982) (lizard), (Shinoda and Tohyama 1987) (rat), (Kawaja et al. 1990) (rat), “septal nucleus impar” (Díaz and Puelles 1992) (Lizard), (Li et al. 1993) (rat), (Felton et al. 1999) (rat), (Yetnikoff et al. 2015) (rat)
Medial septum	Medial/lateral	(Powell 1966) (cat), (Qin and Luo 2009) (mouse)
Lateral septum	Medial/lateral	(Marburg 1944) (human), (Powell 1963) (rat), (Powell 1966) (cat), (Powell 1968) (Rat, cat and monkey), (Herkenham and Nauta 1977) (rat), (Gottesfeld and Jacobowitz 1979) (rat), (Sim and Joseph 1991) (rats), (Li et al. 1993) (rat), (Risold and Swanson 1997) (rat), (Yetnikoff et al. 2015) (rat)
Posterior septum	Medial	(Powell 1966) (cat), (Powell 1968) (Rat, cat and monkey)
Septofimbrial nucleus	Medial	(Loo 1931) (Opossum), (Young 1936) (rabbit), (Herkenham and Nauta 1977) (rat), (Parent et al. 1981) (rat, cat and monkey), (Staines et al. 1988) (Rat), (Kawaja et al. 1990) (rat), (Li et al. 1993) (rat)
Triangular nucleus of septum	Medial	(Herkenham and Nauta 1977) (rat), (Staines et al. 1988) (Rat), (Kawaja et al. 1990) (rat), (Qin and Luo 2009) (mouse)
Precommissural septum	Medial/lateral/unspecified	(Zyo 1963) (rabbit), (Johnson 1965) (cat), “rostral septum” (Powell 1966) (cat), “rostral septum” (Powell 1968) (Rat, cat and monkey)



**Table 1** (continued)

Area of input	Nucleus	References
Supracommissural septum	Medial	(Nauta 1956) (Rat), (Herkenham and Nauta 1977) (rat), (Yañez and Anadón 1996) (rainbow trout)
Postcommissural septum	Medial	(Cragg 1961) (rabbit, rat and cat), (Ban 1962) (rat), (Johnson 1965) (cat), (Herkenham and Nauta 1977) (rat), (Parent et al. 1981) (rat, cat and monkey), (Staines et al. 1988) (Rat)
Diagonal band of Broca	Medial/lateral	(Loo 1931) (Opossum), (Marburg 1944) (human), (Guillery 1959) (Cat), (Powell 1966) (cat), (Price and Powell 1970) (Rat), (Conrad and Pfaff 1976b) (rat), (Herkenham and Nauta 1977) (rat), (Meibach and Siegel 1977) (rat), (Gottesfeld and Jacobowitz 1979) (rat), (Parent et al. 1981) (rat, cat and monkey), (Staines et al. 1988) (Rat), (Díaz and Puelles 1992) (Lizard), (Li et al. 1993) (rat), (Qin and Luo 2009) (mouse), (Yetnikoff et al. 2015) (rat)
Susbtantia innominata	Lateral	(Cragg 1961) (rabbit, rat and cat), (Kim et al. 1976) (monkey), “nucleus basalis” (Herkenham and Nauta 1977) (rat), (Troiano and Siegel 1978a) (cat), (Parent et al. 1981) (rat, cat and monkey)
Nucleus accumbens	Unspecified	“pars medialis of nucleus accumbens” (Loo 1931) (Opossum), (Powell 1966) (cat), (Powell and Leman 1976) (monkey), (Conrad and Pfaff 1976b) (Rat), (Herkenham and Nauta 1977) (rat), (Troiano and Siegel 1978a) (cat), (Li et al. 1993) (rat), (Felton et al. 1999) (rat), (Yetnikoff et al. 2015) (rat)
Anterior olfactory nucleus	Unspecified	(Gurdjian 1925) (rat), (Humphrey 1936) (bat), (Gamble 1952) (lizard), (Gamble 1956) (tortoise), (Millhouse 1969) (mouse), (Ferrer 1969) (hamster), (Heimer 1972) (rat)
Olfactory tubercle	Unspecified	(Loo 1931) (Opossum), (Morin 1950) (Guinea Pig), (Kusama and Hagino 1961) (rabbit), (Ban 1962) (rat), (Millhouse 1969) (mouse), (Heimer 1972) (rat), (Iwahori 1977) (cat), (Parent et al. 1981) (rat, cat and monkey)
Olfactory bulb	Unspecified	(Ramon y Cajal 1911) (vertebrates), (Herrick 1948) (tiger salamander)
Central white matter nuclei		
Nucleus of posterior pallial commissure	Medial	(Díaz and Puelles 1992) (Lizard)
Bed nucleus of anterior commissure	Medial/lateral	(Carl Huber and Crosby 1929) (bird), Herrick 1948 (tiger salamander), (Staines et al. 1988) (Rat), (Díaz and Puelles 1992) (Lizard)
Bed nucleus of stria terminalis	Medial/lateral	(Marburg 1944) (human), (Cragg 1961) (Rabbit), (Conrad and Pfaff 1976b) (Albino Rats), (Swanson and Cowan 1979) (rat), (Parent et al. 1981) (rat, cat and monkey), (Weller and Smith 1982) (rat), (Staines et al. 1988) (Rat), (Díaz and Puelles 1992) (Lizard), (Li et al. 1993) (rat), (Dong and Swanson 2006) (rats), (Yetnikoff et al. 2015) (rat)
Basal Ganglia		
Globus pallidus externa	Lateral/unspecified	(Ranson and Ranson 1941) (monkey), (Mitchell 1963) (cats), (Nauta and Mehler 1966) (monkey), (Kim et al. 1976) (monkey), (Gottesfeld et al. 1977) (rat), (Herkenham and Nauta 1977) (Rat), (Parent et al. 1981) (rat, cat and monkey), (Hoogland 1982) (lizard), (Araki et al. 1984) (rat), (Li et al. 1993) (rat), (Felton et al. 1999) (rat)



**Table 1** (continued)

Area of input	Nucleus	References
Globus Pallidus interna (Entopeduncular Nucleus)	Lateral/unspecified	(Mitchell 1963) (cat), (Herrick 1948) (tiger salamander), (Nauta and Mehler 1966) (Monkey), (Kim et al. 1976) (monkey), (Iwahori 1977) (cat), (Herkenham and Nauta 1977) (rat), (Gottesfeld et al. 1977) (rat), (Nagy et al. 1978) (rat), (Filion and Harnois 1978) (cat), (Carter and Fibiger 1978) (rat), (Larsen and Sutin 1978) (cat), (Parent 1979) (squirrel monkey), (Larsen and McBride 1979) (cat), (Parent et al. 1981) (rat, cat and monkey), (Van Der Kooy and Carter 1981) (rat), (McBride 1981) (cat), (Hoogland 1982) (lizard), (Vincent et al. 1982) (rat), (Garland and Mogenson 1983) (rats), (Araki et al. 1984) (Rat), (Vincent and Brown 1986) (Rat), (Shinoda and Tohyama 1987) (rat), (Hazrati and Parent 1991) (squirrel monkey), (Moriizumi and Hattori 1992) (rat), “lobus subhippocampus” (Yañez and Anadón 1994) (Lamprey), “rostral thalamus” (Yañez and Anadón 1996) (rainbow trout), (Kha et al. 2000) (rats), (Parent et al. 2001) (monkey), (Folgueira et al. 2004) (rainbow trout), (Wallace et al. 2017) (mice)
Ventral Pallidum	Unspecified	(Kim et al. 1976) (monkey), (Herkenham and Nauta 1977) (rat), (Troiano and Siegel 1978b) (cat), (Parent 1979) (squirrel monkey), (Groenewegen et al. 1993) (rat), (Li et al. 1993) (rat), (Haber et al. 1993) (monkey), (Zahm et al. 1996) (rats), (Hendricks and Jesuthasan 2007) (Zebrafish), (Tripathi et al. 2013) (rat)
Thalamic nuclei		
Thalamus undifferentiated	Medial/lateral	(Hines 1929) (platypus), “dorsal thalamus” (Herrick 1948) (tiger salamander), (Mitchell 1963) (cats), (Smaha and Kaelber 1973) (opossum and cat), “dorsal thalamus” (Díaz and Puelles 1992) (Lizard), “thalamic eminence” (Krug et al. 1993) (Axolotl—fish), “thalamic eminence” (Hendricks and Jesuthasan 2007) (Zebrafish)
Anterior Group	Lateral	(Cragg 1961) (rabbit), (Smaha and Kaelber 1973) (opossum and cat)
Anterodorsal nucleus	Unspecified	(Yañez and Anadón 1994) (Lamprey)
Anteroventral nucleus	Lateral	(Yetnikoff et al. 2015) (rat)
Paramedian thalamus	Medial	(Cragg 1961) (rabbit), (Hoogland 1982) (lizard)
Reticular nucleus	Lateral	(Felton et al. 1999) (rat)
Epithalamus	Unspecified	“Pineal gland” (Yañez and Anadón 1996) (rainbow trout)
Hypothalamus		
Hypothalamus undifferentiated	Medial/lateral	(Carl Huber and Crosby 1929) (bird), (Humphrey 1936) (bat), (Marburg 1944) (human), (Mitchell 1963) (cats), (Zyo 1963) (rabbit), (Parent et al. 1981) (rat, cat and monkey), (Li et al. 1993) (rat), (Yañez and Anadón 1996) (rainbow trout), (Felton et al. 1999) (rat), (Yetnikoff et al. 2015) (rat)
Lateral nucleus	Medial/lateral	(Nauta 1958) (cat), (Kusama and Hagino 1961) (rabbit), (Zyo 1963) (rabbit), (Wolf and Sutin 1966) (Rat), (Mizuno et al. 1969) (cat), (Smaha and Kaelber 1973) (opossum and cat), (Troiano and Siegel 1975) (cat), (Swanson 1976) (rat), (Iwahori 1977) (cat), (Herkenham and Nauta 1977) (Rat), (Parent 1979) monkey), (Saper et al. 1979) (rat), (McBride 1981) (cat), (Parent et al. 1981) (rat, cat and monkey), (Berk and Finkelstein 1982) (Rat), (Araki et al. 1984) (Rat), (Shinoda and Tohyama 1987) (rat), (Díaz and Puelles 1992) (Lizard), (Li et al. 1993) (rat), (Yañez and Anadón 1996) (rainbow trout), (Felton et al. 1999) (rat), (Kowski et al. 2008) (rat), (Hahn and Swanson 2010) (rat), (Hahn and Swanson 2012) (rat), (Yetnikoff et al. 2015) (rat)
Dorsomedial nucleus	Lateral	(Li et al. 1993) (rat)



**Table 1** (continued)

Area of input	Nucleus	References
Paraventricular nucleus	Unspecified	“magnocellular nucleus” (Loo 1931) (Opossum), (Smaha and Kaelber 1973) (opossum and cat), (von Bartheld and Meyer 1990) (lungfish), (Li et al. 1993) (rat)
Suprachiasmatic nucleus	Lateral	(Buijs 1978) (rats), (Sofroniew et al. 1981) (rats)
Ventromedial nucleus	Lateral	(Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)
Anterior nucleus	Lateral	(Conrad and Pfaff 1976b) (Albino Rats), (McBride 1981) (cat), (Parent et al. 1981) (rat, cat and monkey), (Li et al. 1993) (rat), (Risold et al. 1994) (rat)
Supraoptic nucleus	Unspecified	(Humphrey 1936) (bat)
Posterior nucleus	Lateral	(McBride 1981) (cat)
Preoptic hypothalamus undifferentiated	Medial/lateral	(Gurdjian 1925) (rat), (Gurdjian 1927) (rat), (Hines 1929) (platypus), (Carl Huber and Crosby 1929) (bird), (Loo 1931) (Opossum), (Humphrey 1936) (bat), (Marburg 1944) (human), (Herrick 1948) (tiger salamander), (Zyo 1963) (rabbit), (Smaha and Kaelber 1973) (opossum and cat), (Herkenham and Nauta 1977) (Rat), (McBride 1981) (cat), (Li et al. 1993) (rat), (Yañez and Anadón 1996) (rainbow trout)
Medial preoptic nucleus	Lateral	(Gurdjian 1925) (rat), (Young 1936) (rabbit), (Marburg 1944) (human), (Conrad and Pfaff 1976a) (Albino Rat), (Anderson and Shen 1980) (guinea pig), (Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)
Lateral preoptic nucleus	Lateral	(Young 1936) (rabbit), (Nauta 1958) (cat), (Cragg 1961) (Rabbit), (Kusama and Hagino 1961) (rabbit), (Zyo 1963) (rabbit), (Cowan et al. 1965) (rat), (Wolf and Sutin 1966) (rat), (Mizuno et al. 1969) (cat), (Troiano and Siegel 1975) (cat), (Swanson 1976) (rat), (Iwahori 1977) (cat), (Herkenham and Nauta 1977) (rat), (Troiano and Siegel 1978b) (cat), (Parent et al. 1981) (rat, cat and monkey), (Garland and Mogenson 1983) (rats), (Díaz and Puelles 1992) (Lizard), (Li et al. 1993) (rat), (Felton et al. 1999) (rat), (Kowski et al. 2008) (Rat), (Yetnikoff et al. 2015) (rat)
Mammillary bodies	Lateral	(Parent et al. 1981) (rat, cat and monkey), (Díaz and Puelles 1992) (Lizard)
Premammillary nucleus	Lateral	(Li et al. 1993) (rat)
Brainstem		
Tectum	Unspecified	(Marburg 1944) (human), (Herrick 1948) (tiger salamander)
Tegmentum undifferentiated	Unspecified	(Hoogland 1982) (lizard)
Laterodorsal tegmental nucleus	Medial/lateral/unspecified	“Nucleus isthmi” (Hoogland 1982) (lizard), (Cornwall et al. 1990) (rat), (Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)
Dorsal tegmental area	Lateral	(Goto et al. 2001) (rat), (Olucha-Bordonau et al. 2003) (rat)
Ventral tegmental area	Medial/lateral	(Lindvall and Björklund 1974) (rat), (Kizer et al. 1976) (rat), (Herkenham and Nauta 1977) (rat), “ventral tegmental pars lateralis” (Simon et al. 1979) (rat), (Beckstead et al. 1979) (rat), “ventral tegmental interfascicular nucleus” and “ventral tegmental median paranigral” (Phillipson and Griffith 1980) (rat), (Parent et al. 1981) (rat, cat and monkey), (Phillipson and Pycock 1982) (rat), (Swanson 1982) (rat), (Skagerberg et al. 1984) (rat), (Díaz and Puelles 1992) (Lizard), (Li et al. 1993) (rat), (Gruber et al. 2007) (rat), (Yetnikoff et al. 2015) (rat)
Pretectal area	Unspecified	(Herrick 1948) (tiger salamander)
Periaqueductal gray	Lateral	(Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)
Locus coeruleus	Unspecified	(Hoogland 1982) (lizard), (Gottesfeld 1983) (rat), (Yañez and Anadón 1996) (rainbow trout), (Gruber et al. 2007) (rat), (Yetnikoff et al. 2015) (rat)
Substantia nigra compacta	Lateral	(Kizer et al. 1976) (rat), (Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)



**Table 1** (continued)

Area of input	Nucleus	References
Interpeduncular nucleus	Lateral	(Massopust Jr and Thompson 1962) (rats and cats), (Mitchell 1963) (cats)
Raphe Nuclei undifferentiated	Lateral	(Herkenham and Nauta 1977) (rat), (Moore et al. 1978) (rat), (McBride 1981) (cat), (Li et al. 1993) (rat), (Morin and Meyer-Bernstein 1999) (hamster), (Felton et al. 1999) (rat), (Yetnikoff et al. 2015) (rat), (Muzerelle et al. 2016) (mouse)
Raphe nuclei dorsal	Medial/lateral	(Conrad et al. 1974) (rat), (Pierce et al. 1976) (cat), (Azmitia and Segal 1978) (rat), (Li et al. 1993) (rat)
Raphe nuclei median	Medial/lateral	(Conrad et al. 1974) (rat), “superior raphe” (Bobillier et al. 1975) (cat), “superior raphe” (Bobillier et al. 1976) (cat), (Herkenham and Nauta 1977) (rat), (Azmitia and Segal 1978) (rat), “superior raphe” (Bobillier et al. 1979) (rat), “superior raphe” (Hoogland 1982) (lizard), (Hallanger et al. 1987) (rat), (Vertes and Martin 1988) (rat), (Vertes et al. 1999) (rat), (Li et al. 1993) (rat), (Yetnikoff et al. 2015) (rat)
Interfascicular nucleus	Lateral	(Li et al. 1993) (rat)
Superior Cervical ganglion	Medial	(Björklund et al. 1972) (rat), (Lindvall and Björklund 1974) (rat), (Gottesfeld 1983) (rat)

Literature review methods detailed in the text

**Table 2** (A and B) Summary of habenular volumes given in mm<sup>3</sup> in the current literature

Name	Participants	Total volume		SD	Left volume		SD	Right volume		SD
(A) Magnetic resonance imaging										
Kim et al. (2016)	50	–		–		21.1	5.2	21.3		4.5
Kim et al. (2016)	6	–		–		18.3	2.3	17.9		2.1
Lawson et al. (2013)	24	–		–		29.4	4.7	29.3		3.7
Hétu et al. (2016)	34	–		–		27.88	8.49	28.03		8.18
Carceller-Sindreu et al. (2015)	34	42.99		9.4		–	–	–		–
Furman and Gotlib (2016)	13	–		–		28.7	2.5	27.3		7
Lawson et al. (2017)	25	22.31		9.29		–	–	–		–
Savitz et al. (2011a)	75	36.9		8.5		19.8	5.1	17.1		4.6
Savitz et al. (2011b)	74	36.5		8.7		19.5	5.2	17		4.7
Schmidt et al. (2017)	20	34.92		11.34		17.63	5.49	17.29		6.12
Zhang et al. (2017)	16	–		–		24.02	3.2	20.42		3.46
Bocchetta et al. (2016)	15	–		–		23.6	2.2	23.3		2.2
Torrise et al. (2017)	32	–		–		18.8	6	14.9		4
Hennigan et al. (2015)	18	35.35		13.3		–	–	–		–
Extrapolated mean values		36.3		10.98		21.89	6.47	20.62		6.71
Name	Participants	Left habenula volume				Right habenula volume				
		Medial	SD	Lateral	SD	Medial	SD	Lateral	SD	
(B) Postmortem	13	3.35	1.33	27.57	5.05	3.64	0.97	29.59		4.83

(A) Whole, lateral and medial mean habenular volumes extrapolated from 14 high resolution magnetic resonance imaging studies with a total of 356 subjects. See text for further details. (B) Postmortem medial and lateral habenular volumes in 13 participants are reported. SD, standard deviation.

In mammals, the habenula comprises of two functionally segregated nuclei, the medial habenula (MHb) and lateral habenula (LHb). The lateral is the larger of the two and is

further divided into medial and lateral portions in humans and other mammals (Torrise et al. 2017; Fore et al. 2017; Carpenter 1991). These nuclei share many similar sources of



afferent inputs and efferent nuclei but have distinct anatomy and connectivity within brain networks (Fakhoury 2017; Bianco and Wilson 2009; Gardon et al. 2014).

### Medial habenula

The medial habenula is the smaller and least studied of the two nuclei (Viswanath et al. 2013; Iwahori 1977; Ramon y Cajal 1911). It borders the wall of the third ventricle and contains a more homogeneously densely packed array of cells when compared to the LHb. MHB volumes in human postmortem studies are reported in Table 2b. The human MHB can be subdivided into five subnuclei, which can be most easily distinguished from each other in terms of cell packing density, as opposed to cell type. This is because

most cells in each of the five nuclei are small round cells (Table 3) (Diaz et al. 2011). These cells have a soma diameter of 8.85.

The medial habenula is richly innervated from multiple neuronal types. In animals, the predominant innervations to the MHB come from septal regions and are largely inhibitory through the action of GABAergic neurons (Torrisi et al. 2017; Benarroch 2015; Batalla et al. 2017). Indeed, the medial habenula contains some of the highest concentration of GABA-B receptors in the rat brain (Wang et al. 2006; Bischoff et al. 1999; Durkin et al. 1999; Charles et al. 2001). However, other afferents terminate as cholinergic (Contestabile and Fonnum 1983), substance P (Contestabile et al. 1987) and glutamate (Qin and Luo 2009). Additionally, the medial habenula abundantly expresses nicotinic

**Table 3** Summary of reported sub-nucleic histological characteristics of the human habenula

Subnuclei	Cell shape and size	Cellular distribution	Fiber distribution	Cell packing	References
<b>Undifferentiated Habenula</b>					
Ventromedial	Very small celled, spindle shaped	-	-	Densely packed	Marburg (1944)
Medial	Small celled, larger and fewer cells, spindle shaped,	-	-	Loosely packed	Marburg (1944)
Dorsomedial	Small celled, larger and fewer cells, spindle shaped	-	-	Loosely packed	Marburg (1944)
Dorsolateral	Small spindle shaped and medium sized cells, polygonal, containing well-developed nuclei and trigoid bodies	-	-	-	Marburg (1944)
Lateral	Large celled	-	-	-	Marburg (1944)
<b>Medial habenula</b>					
Dorsal	Small round	Heterogenous with myelinated fibers	Few fibers, forming bundles	Intermediately packed	Diaz et al. (2011)
Medial	Small round	Homogenous	Few fibers and very thin	Loosely packed	Diaz et al. (2011)
Intermediate	Small round	Homogenous	Few fibers, forming a loose network	Densely packed	Diaz et al. (2011)
Lateral	Small round	Homogenous	Few fibers and very thin	Densely packed	Diaz et al. (2011)
Ventral	Small round, medium round	Homogenous	Thin, with fibers emerging as fasciculus retroflexus	Densely packed	Diaz et al. (2011)
<b>Lateral habenula</b>					
Dorsal	All cell types	Heterogenous with myelinated fibers	Many fibers, forming thick bundles	Loosely packed	Diaz et al. (2011)
Medial	Small round, medium round	Heterogenous, with occasional clumping	Very thin, reticulated pattern	Loosely packed	Diaz et al. (2011)
Intermediate	Small round, medium elongated, medium multipolar	Heterogenous	Few fibers and very thin, forming reticulated pattern	Loosely packed	Diaz et al. (2011)
Lateral	Small round, small large multipolar	Heterogenous with clumping	Many fibers, forming a reticulated pattern	Intermediately packed	Diaz et al. (2011)
Ventral	Small round, medium round and a few medium elongated	Heterogenous	Many fibers, thin, with fibers emerging as fasciculus retroflexus	Intermediately packed	(Diaz et al. 2011)



acetylcholine receptors (Sheffield et al. 2000). Monoamine inputs such as serotonin (Herkenham and Nauta 1977), noradrenaline (Gottesfeld 1983) and dopamine (Phillipson and Pycock 1982) also target the MHb through feedback projections from the midbrain.

The MHb outputs extend through the core of the fasciculus retroflexus to the midbrain and hindbrain. MHb neurons are predominantly excitatory, releasing the neurotransmitters acetylcholine, substance P and glutamate (Aizawa et al. 2012; Viswanath et al. 2013). These neurons primarily target the serotonergic neurons of the median raphe nuclei directly or indirectly via interpeduncular nucleus (IPN) (Koppenssteiner et al. 2016; Contestabile et al. 1987) and noradrenergic inputs from the locus coeruleus (Benarroch 2015; Díaz et al. 2011; Fakhoury 2017; Bianco and Wilson 2009). The IPN also provides feedback projections to brain areas that target the MHb such as the septal regions through the medial forebrain bundle (Hayakawa et al. 1981) as well as the MHb itself (Benarroch 2015). Of note, there are two principal subnuclei that can be identified using the transmitter acetylcholine in the ventral MHb and the expression of substance P in the dorsal MHb (Contestabile et al. 1987; Hsu et al. 2016). While they both project to the IPN, they innervate distinct structures within it (Hsu et al. 2014).

### Lateral habenula

The lateral habenula lies between the medial habenula and the thalamus. It is considerably larger than the MHb in most species and can be distinguished from the smaller structure microscopically by having a much less compacted and more heterogeneous cell population overall (Díaz et al. 2011). The human LHB is greatly expanded compared to the MHb, with the LHB being about 8 times bigger than the MHb (Table 2). This suggests an increased influence of limbic and striatal afferents upon the DCSS in humans. The LHB can be further subdivided into medial LHB and lateral LHB subdomains. Five separate nuclei are observed in the LHB and these can be distinguished from each other in terms of the heterogeneous cell shapes and sizes seen in the LHB as opposed to the packing density distinctions seen in the MHb (Table 3) (Díaz et al. 2011). The cellular organization within the LHB shows a larger degree of variability among individuals than the MHb and the distinction between nuclei is less precise; however, the broad overall cellular organization within the LHB is medial parvocellular and lateral magnocellular regions (Marburg 1944).

The LHB innervations are generally more dispersed and heterogeneous than MHb afferents. Primary excitatory glutamatergic innervations originate from the prefrontal cortex, basal ganglia and lateral hypothalamus (Baker et al. 2016; Batalla et al. 2017). The majority of the fast-mediating excitatory transmission identified in the LHB is

through the AMPA-type glutamate receptors (Meye et al. 2013; Li et al. 2013). The LHB receives strong inhibitory GABAergic inputs arising through long-range projections from areas such as the nucleus accumbens, diagonal band of Broca, the lateral preoptic area, substantia innominate and the ventral pallidum (Meye et al. 2013; Benarroch 2015). The medial globus pallidus GABA projections preferentially innervate the lateral portion of the LHB, whilst the diagonal band of Broca and lateral preoptic areas primarily target the medial portion (Herkenham and Nauta 1977). Additionally, midbrain and hindbrain targets of the LHB provide dopaminergic (ventral tegmental area), noradrenergic (locus coeruleus) and serotonergic (median raphe nucleus) feedback projections, suggesting that dopamine, noradrenaline and serotonin have modulatory effects on the LHB (Meye et al. 2013; Benarroch 2015). Other inputs arise from the suprachiasmatic nucleus, providing GABA/vasopressinergic innervations into the LHB (Benarroch 2015).

In spite of sharing a singular output tract, there appears to be little overlap between efferents and function of the MHb and LHB (Quina et al. 2015). Through the external mantle of the FR, the LHB projects to multiple monoaminergic mesencephalic areas such as the ventral tegmental area (VTA) and periaqueductal gray and rhombencephalic areas such as raphe nucleus and locus coeruleus. In rodents, there exists a structure called the rostromedial tegmental nucleus (RMTg) which is essentially an inhibitory tail (Kaufling et al. 2009) of the VTA (Holstege 2009). It has been shown that most glutamatergic axons from the LHB primarily target the GABAergic neurons of the VTA and RMTg, leading to an overall inhibitory effect (Brinschwitz et al. 2010). RMTg in particular exhibits a high density of habenular efferents, despite only accounting for less than 20% of the total outputs of the LHB to the hindbrain (Quina et al. 2015). The RMTg inhibits the nearby dopaminergic neurons of the VTA and substantia nigra pars compacta (SNc) directly and the serotonergic neurons of the raphe nuclei indirectly (Díaz et al. 2011; Fakhoury 2017). This intermediary structure has not been isolated as yet in human post-mortem studies (Héту et al. 2016). There are also direct bilateral innervations of the LHB to the VTA, with electrical stimulation of the LHB causing direct orthodromic reduction of dopaminergic tone in the VTA and its axons to the nucleus accumbens (Ji and Shepard 2007; Christoph et al. 1986). Similarly, lesioning the LHB causes an increase in serotonergic activity in the dorsal raphe by activating the local GABAergic neurons (Varga et al. 2003; Amat et al. 2001). Retrograde studies have also identified the median raphe, caudal dorsal raphe, and pontine central gray as LHB targets (Quina et al. 2015). LHB efferents also feedback to the lateral hypothalamic area, septum and several thalamus nuclei (Benarroch 2015; Batalla et al. 2017).



## Function

Despite overlapping sources of connectivity, the medial and lateral habenula appear to represent largely distinct functional subcircuits within the DDCCS. The MHb regulates inhibitory controls, cognition-dependent executive functions and place aversion learning (Gardoni et al. 2014). The MHb also has a role with respect to misery-fleeing behavior, stress responses, neural control of sleep and analgesia (Loonen et al. 2017; Díaz et al. 2011). These functions correspond with the inputs from the pleasure and motivational centers of the forebrain.

Although the MHb has remained largely unstudied, it is proposed that two subnuclei, the ventral and dorsal subnuclei, are largely responsible for its functions. The ventral MHb, containing cholinergic neurons, has been associated with the somatic symptoms of nicotine withdrawal by inhibiting serotonin and dopamine within the IPN (Zhao-Shea et al. 2013; Lee et al. 2019). Whereas, the substance P containing dorsal MHb is implicated in fear responses (Lee et al. 2019). A study in rodents demonstrated a reduction in activity of the dorsal medial habenula with fear conditioning. The authors suggested that diminished MHb may result due to interference with medial raphe nucleus activity, including hippocampal ripple activity and fear memory consolidation (Koppensteiner et al. 2016).

The LHb is involved in rewards signals, aversion and behavioral avoidance (Gardoni et al. 2014). These functions were first suggested following studies which revealed that the habenula was involved in reward through brain stimulation (Boyd and Celso 1970). With the LHb long considered as the ‘missing link’ in the mechanisms of reward pathways (Brinschwitz et al. 2010), efforts have been made to further uncover its exact functionality and underlying mechanisms. Studies in the lamprey show that when there is rewarding behavior, the LHb promotes the behaviour by intensifying stimulation of the phylogenetic homolog of the VTA (Loonen et al. 2017). However, when the reward is smaller than expected or absent, the behavior is inhibited by affecting the VTA equivalent. Furthermore, the habenula has been implicated in circadian behaviour due to its connections with the nearby pineal and suprachiasmatic nucleus, with both MHb and in particular LHb cells showing increased firing during the day than night (Zhao and Rusak 2005).

Peptidomic analysis has identified a total of 262 and 177 neuropeptides in the medial and lateral habenula, respectively, with 126 present in both regions (Yang et al. 2018). One of the peptides identified was somatostatin, often associated with chronic stress. Previously, stressed rats were reported to have significantly upregulated somatostatin receptors on the medial habenula (Faron-Górecka et al. 2016). Additionally, multiple pain-related peptides (nociception, pro-enkephalin-A, pro-dynorphin-related prohormones)

were also detected (Yang et al. 2018). These peptides are involved in pain signaling mechanisms through the binding of opioid and nociception receptors. Such findings are consistent with current literature on habenular involvement in pain and analgesia (Shelton et al. 2012a; Levins et al. 2019).

Significant findings from these extensive studies conducted in animals have led to investigations of the habenula in humans. All studies investigating the function of the human habenula have taken place using magnetic resonance imaging. Imaging the habenula suffers from resolution issues due to the size and shape of the structure and the resolution of standard functional MRI imaging. Also, due to position and shape, imaging this structure is further complicated as a result of its proximity to the third ventricle and subsequent partial volume effects. As such functional imaging studies of this structure are small in number and limited in scope. However, the habenula has been implicated in processing aversive stimuli (Lawson et al. 2014; Hennigan et al. 2015) and error detection (Ullsperger and von Cramon 2003; Li et al. 2008; Salas et al. 2010; Ide and Li 2011). The human habenula has been found to be functionally coupled with the insula, septum, thalamus, striatum, pons, substantia nigra/ventral tegmental area, periaqueductal gray, stria terminalis and parahippocampal regions (Héту et al. 2016; Torrisi et al. 2017). The structure has also been functionally linked with pain responses (Shelton et al. 2012b) subclinical depressive symptoms (Ely et al. 2016), and anxious thoughts (Najafi et al. 2017) in normal individuals. A promising new field of clinical research examining the habenula is underway with many studies implicating this diminutive structure in depression (Lawson et al. 2017; Schmidt et al. 2017), anxiety (Savitz et al. 2011a), schizophrenia (Shepard et al. 2006), frontotemporal dementia (Bocchetta et al. 2016), addictions (Curtis et al. 2017; Rose et al. 2017) and chronic pain (Erpelding et al. 2014), cancer-associated weight loss (Maldonado et al. 2018) and Parkinson’s disease (Markovic et al. 2017).

## Habenular asymmetry

Many species exhibit asymmetries in size, anatomical organization and function (Schmidt and Pasterkamp 2017; Bianco and Wilson 2009; Concha and Ahumada-Galleguillos 2016; Dreosti et al. 2014; Ichijo et al. 2015). The significance of this is unknown; however, an intriguing functional impact of left–right habenular differences has been found in zebrafish (Dreosti et al. 2014; Krishnan et al. 2014; Ichijo et al. 2017; Halpern et al. 2003) and in mice (Ichijo et al. 2015, 2017). In Zebrafish, lateralization appears more structurally fixed (Ichijo et al. 2017), with habenular neurons shown to respond to light more frequently on the left; whereas, responses to odor were more likely to be found in the right habenula (Dreosti et al. 2014). Meanwhile, in



mice LHb lateralization appears more functionally flexible and occurs during postnatal development and in response to water-immersion restraint stress (Ichijo et al. 2015, 2017). However, small volume differences have also been described in mammals, including small asymmetries in the LHb in mice (Zilles et al. 1976) and the MHb in rats (Wree et al. 1981). Interestingly, a unique clump of cells has also been described on the left habenula only in the macrosomatic mole (Kemali 1984).

In primates and humans, the study of subtle habenular volume asymmetry is more difficult due to the small relative size of the habenula and its internal position deep within the brain. However, left–right asymmetry appears to occur in the lateral habenula in humans (independent of age, brain weight and total habenular size) and is more prominent in women (Ahumada-Galleguillos et al. 2017). There also appears to be a functional asymmetry in the human habenula as evidenced by apparent differences in connectivity between left and right habenulae with the left habenula more coupled with the right parahippocampal regions and the right habenula more coupled with the substantia nigra/ventral tegmental regions (Héту et al. 2016). Additionally, a high-resolution volumetric MR study found a trend (but not of significance) towards a larger left habenula volume in both healthy controls and patients with depression and bipolar affective disorder (Savitz et al. 2011b).

## Fasciculus retroflexus

(Lt; *backwards turning bunch/bundle*) The fasciculus retroflexus, also known as the fasciculus retroflexus of Meynert, habenulointerpeduncular tract, habenulopeduncular tract or retroflex tract, is the final component of the DDCS and principal efferent of the habenula, running ventrally from the habenula to the ventral midbrain and hindbrain (Aizawa et al. 2011). Although originally described in 1872 as a tract originating from the habenula by Meynert (1872), Van Gehuchten was the first to define its distal end as joining the IPN (Van Gehuchten 1894). Similar to the SM, the FR is also bidirectional tract and contains fibers originating from both the lateral and medial habenula (Herkenham 1981).

## Anatomy

Although described since 1892 by Meynert, specific anatomical information regarding the precise trajectory of this tract in humans is sparse. This is due to the bending nature of the tract as well as the fact that it traverses a particularly structurally dense white matter region of the midbrain. Overall, the FR appears to take a lyre shape as it descends from the habenula to the IPN (Naidich and Duvernoy 2009). In contrast to rats, where MHb fibers directly join the FR, human

MHb fibers initially travel along the ventral part of the LHb before descending to unite with the FR (Díaz et al. 2011). From the ventral aspect of the LHb, the FR travels down through the caudal thalamus, remaining medial to the centromedial nuclei (Naidich and Duvernoy 2009). It then curves medially, continuing ventrally in front of the pretectal area along the rostromedial border of the red nucleus, penetrating the nucleus near its rostral pole. At the level of the basal plate, it subsequently turns at 90° caudally, to enter the IPN beneath the red nucleus. The abrupt change in direction is what gives this tract its name (retroflexus meaning recurve). Note that the FR enters the IPN from its rostral and dorsal borders (Naidich and Duvernoy 2009). The fibers here cross and recross the midline IPN several times forming a figure eight pattern (Morley 1986). Here they generate synapses and appear to innervate both the ipsilateral and contralateral IPN (Contestabile and Flumerfelt 1981; Moreno-Bravo et al. 2016). An ill-defined nucleus of the interpeduncular tract has been documented in both animals (Rioch 1931) and humans (Marburg 1944). This nucleus consists of scattered neurons that lie between the medial and lateral parts of the tract and is of unknown function or significance.

Structurally, the FR consists of two concentric regions. A bundle of very thin unmyelinated axons originating exclusively from the MHb travel through its core, and terminate after criss-crossing in both the contra and ipsilateral interpeduncular nuclei (Benarroch 2015; Herkenham and Nauta 1979; Moreno-Bravo et al. 2016). Axons arising from the individual MHb subnuclei project down to specific regions of the IPN; dorsal MHb axons project to the lateral IPN, medial MHb axons to the ventral IPN, and lateral MHb axons to the dorsal IPN (Herkenham and Nauta 1979; Ichijo and Toyama 2015; Koppensteiner et al. 2016). Projections from MHb to IPN decrease caudally, with no afferents of the MHb reaching the caudal pole of the IPN (Contestabile and Flumerfelt 1981). The ventral MHb contains cholinergic neurons (Aizawa et al. 2012) and the dorsal MHb contain Substance P neurons of the dorsal MHb (Contestabile et al. 1987). The thicker myelinated fibers on the outer (mantle) FR emerge from the LHb (Benarroch 2015; Herkenham 1981), and to terminate directly in multiple monoaminergic nuclei including the ventral tegmental area, raphe nuclei, ventral periaqueductal gray and reticular formation. Note that the FR does not just consist of habenular efferents. Similar to other animals, the human FR also contains thalamic (pulvinar/midline nuclear group) fibers as well as ascending tectum fibers (Marburg 1944).

## Function

Information relayed from the SM through the habenula is ultimately transmitted through the FR (Batalla et al. 2017) to the brainstem. Little specific information is available from



human studies on the exact connectivity and function of the FR and as such most of its function is inferred from animal studies. Broadly speaking, the FR participates in inhibitory control of monoaminergic regions (Ellison 2002).

The core of the FR (i.e., originating from the MHb) is the principal cholinergic input of the interpeduncular nucleus (Hattori et al. 1977). The IPN is well known for its widespread connections including ascending projections to the limbic system (hippocampus, entorhinal cortex and septal areas) and descending projections to the brainstem monoaminergic regions (VTA, raphe and periaqueductal gray) (Morley 1986). The IPN outputs that synapse with these modulatory regions are GABAergic (Lima et al. 2017). As such the MHb through the FR core exerts tonic inhibitory control on ascending monoaminergic neurons (Nishikawa et al. 1986). Blocking muscarinic cholinergic transmission in the IPN results in increased levels of dopamine metabolism in more frontal areas such as the medial prefrontal cortex and nucleus accumbens (Nishikawa et al. 1986). Bilateral lesioning of the FR in mice demonstrated a chronic increase in serotonin, noradrenaline and dopamine in the IPN (Takishita et al. 1990). Following lesioning, there was evidence of hyperinnervation of the IPN by the afferent fibers from the locus coeruleus (NA) (Battisti et al. 1987), raphe nucleus (serotonin) and other central areas (Takishita et al. 1990). This progressive alteration in monoamines within the IPN is suggested to be implicated in cognitive processes, specifically the deterioration of choice accuracy (Bianco and Wilson 2009).

The FR mediates most of the negative feedback between the dopamine-receiving forebrain and the dopamine-releasing brainstem through the lateral habenula (Ellison 2002). Continuous injections of dopaminergics, such as cocaine, MDMA, cathinone and amphetamine, in animals induced degeneration of the FR, particularly the outer sheath (Ellison 2002). The disintegration of the FR may also underlie the development of progressive neuropsychiatric effects associated with repeated binges in addiction disorders, including paranoia (Carlson et al. 2000; Ellison 1994).

Studies have demonstrated that the fasciculus retroflexus also has reciprocal ascending monoaminergic axons targeting the habenula (Smaha and Kaelber 1973; Skagerberg et al. 1984; Li et al. 1993). These axons are confined to the outer sheath of the FR and as such specifically connect with the lateral habenula (Skagerberg et al. 1984). The FR provides dense DA innervations to the LHb, particularly its medial region, from the VTA and substantia nigra pars compacta (Skagerberg et al. 1984; Li et al. 1993; Shen et al. 2012). Previous literature suggest that DA has an inhibitory role in LHb and potentially is involved in the regulation of the habenular response to aversive and painful stimuli (Brown and Shepard 2013; Shen et al. 2012). Lesions of the FR weakened the density of dopaminergic nerve terminals

in the LHb in rats (Shen et al. 2012; Skagerberg et al. 1984), indicating that the FR must be intact to transmit positive reward signals from the brainstem dopaminergic system to the LHb.

## Development

As the name suggests, the DDCS is embryologically part of the diencephalon, a prosencephalic (forebrain) structure between the telencephalon and mesen- and rhombencephalon. Indeed, the main function of the DDCS components are as processing conduits to relay information between telencephalic and mesen/rhombencephalic structures. Similar to the development of other epithalamic gray matter structures, initially the habenular nuclei form early on, closely followed by their efferent and then followed by their afferent connections (Cho et al. 2014; Altman and Bayer 1979).

The diencephalon is formed of distinct segments, prosomeres (p1, p2 and p3) and neuromeres (D1, D2, D3, and D4), with circumferential axonal tracts forming around the neuromere boundaries (Funato et al. 2000). The habenula forms from the alar plate of p2 (Schmidt and Pasterkamp 2017), the SM is formed along D2 (Lim and Golden 2007) and the FR is formed along the p1/p2 boundary (Funato et al. 2000). Axon guidance molecules are expressed in adjacent neuromeres guiding the axonal growth (Funato et al. 2000). Among these molecules is the repulsive axon guidance molecule Sema3F. This is found in the diencephalon and is expressed in p1, leading to repulsion from habenular explants. Whereas Netrin-1, an attractant, is expressed from the caudal to the ventral regions of the diencephalon (Funato et al. 2000).

The larger neurons of the lateral nucleus develop before the smaller neurons of the medial nucleus in rodents (Angevine 1970), resulting in the establishment of a clear latero-medial or “outside-in” progression. This gradient appears to exist both across the whole habenula and within each lateral and medial habenular nuclei (Altman and Bayer 1979). In humans, habenular cytogenesis starts around the fifth week and is completed by approximately weeks 7–8 (Muller and O’Rahilly 1997) with the habenular commissure also present in most embryos by the start of the eighth week (Muller and O’Rahilly 1990).

The efferent white matter FR is characterized by immediate growth of axons from the developing habenula, with the FR extending towards the mesen/rhombencephalon and rapidly reaching the interpeduncular nucleus around the end of week 6. The relationship of the FR and the parvocellular red nucleus is variable during development (Cho et al. 2014); however, the newly formed tract appears to migrate gradually towards the red nucleus to lodge into a deep groove on the medial aspect of the red nucleus sometime after week



12 (Yamaguchi and Goto 2008). Embryologically, the FR appears to develop its complex trajectory along three decision points: (1) repulsive signals *Sema3F* and *Sema5A* complement the attractive signal *Netrin1* to funnel the developing FR along a corridor in front of the pretectum allowing dorsoventral extension from the habenula, (2) sudden retroflexion caudally due to *Slit1* repulsion from the floor plate, and (3) finally criss-crossing across the IPN complexes (Moreno-Bravo et al. 2016). Myelination of the FR occurs much later in development, with completion sometime after 35 weeks (Yamaguchi and Goto 2008). Similar to other epithalamic structures, the afferent tract develops slightly later, with the SM forming from the telencephalic nuclei and eventually reaching the habenula around week 8 (Muller and O’Rahilly 1990).

## Conclusion

This is the first review to describe in-depth all the components of the dorsal diencephalic conduction system: the stria medullaris, habenula and fasciculus retroflexus. The anatomy and connections of the DDCS reflect its function as an integrator of reward, motivational, cognitive and emotional information from diffuse basal forebrain regions within the habenular relay. From this hub, habenular outputs can modulate the regulatory brainstem regions. Despite the potential importance of this circuit in neuropsychiatric disorders, this review highlights the clear lack of human studies into the DDCS and its components in humans. What is known of the human DDCS appears inconsistent, particularly the specific networks of the habenular afferents and efferents. While there is an abundance of animal studies on the DDCS connections, there has been just one study that has physically traced the connections in humans (Marburg 1944), as such it is not clear whether many of these animal networks map accurately onto the larger human forebrain (Herculano-Houzel 2009). Furthermore, habenular function in humans has not been clearly defined, specifically with regards to the functional importance of known habenular laterality (Héту et al. 2016), which appears to be of particular significance in other vertebrates (Ahumada-Galleguillos et al. 2017; Concha and Ahumada-Galleguillos 2016). The difficulty of studying such small anatomical structures in humans is without a doubt a contributor to the lack of replicable research of this system. This is particularly relevant for human in vivo studies, where imaging techniques struggle to capture the structures at current resolutions. New advances in neuroimaging such as increased scanner strengths, image acquisition improvements, and higher-order diffusion tractography (Tournier et al. 2011), functional imaging (Cradock et al. 2015) and magnetic resonance spectroscopy protocol refinements (Drago et al. 2018) may aid future

investigations into the structure and function of the DDCS in humans in vivo. Additionally, more human post-mortem studies using established (e.g., DiI, horseradish peroxidase) (Von Bartheld et al. 1990; Schmued 1994; Tardif and Clarke 2001) and pioneering neurotracing methods (e.g., viral tracers) (Schmued 2016; Lai et al. 2018) to determine the diffuse basal forebrain connections of the DDCS neurocircuitry are needed to reveal the complicated habenular connectome. Further exploration of this pivotal system may progress our insight into the pathophysiology of many neuropsychiatric disorders, particularly major depressive disorders, anxiety disorders, addiction and pain disorders, and open novel therapeutics targets for investigation.

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