The Functional Neuroanatomy of the Limbic System

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Contents

G. Roth et al. (eds.), *Psychoneuroscience*, https://doi.org/10.1007/978-3-662-65774-4_2

2

In this chapter, we will review the anatomical components of the limbic system and its basic functions. The main structures of the brain will be presented in their morphology and neurochemistry as well as the connections of the limbic structures to each other and their links with motor and sensory-cognitive brain regions. The aim is to get to know the main functions of each limbic region, but also the overlapping and complementary functions with other limbic structures. Feelings, moods and affects are generated in limbic structures, and in complex cooperation with the other brain systems, emotional states, physical reactions, mental states and behavioural expressions are experienced as a unified whole. An important principle here is that of multiple networking and the formation of different networks of the limbic structures with the other brain systems, which act depending on the personal state of mind, the situational context and the external circumstances and requirements.

Learning Objectives

After reading this chapter, readers should know the main structures of the limbic system, be familiar with the respective functions of the limbic regions, understand the connections of limbic networks with the motor and sensory-cognitive systems and the associated control of emotions and behavior.

2.1 The Limbic System

The limbic system was considered the main centre for emotions by the American neurologist James Papez (1937). The reason for this view was the observation that diseases of this system often lead to severe emotional and psychological disorders. Papez included in this system the hypothalamus, including the mammillary bodies, the anterior thalamic nuclei, the cingulate gyrus, and the hippocampus. He considered these structures to be connected in a circle by powerful pathways and thus conceived of what is now called the "Papez circuit." The idea at the time that this circle was self-contained and closed off from the cerebral cortex is now considered to be refuted, even if the basic neuroanatomical features are correct.

The modern conception of the limbic system developed through the contributions of neuroanatomist Walle Nauta, who expanded the limbic system to include areas of the midbrain in the 1950s, and especially through the work of neuroanatomist Rudolf Nieuwenhuys, who included nuclei or areas of the pons and medulla oblongata (Nieuwenhuys 1985; Nieuwenhuys et al. 1991). Nieuwenhuys developed the fruitful concept of the "central limbic continuum" (Nieuwenhuys et al. 1991), which extends from the septum through the preoptic region and hypothalamus to the limbic centers of the ventral midbrain. At the subcortical level, the olfactory and vomeronasal systems, the amygdaloid complex, the pituitary gland, the habenula, and the limbic thalamic nuclei, and at the cortical level, the cingulate gyrus, the hippocampus, the parahippocampal gyrus, and the prepiriform cortex are directly associated with this central continuum (Fig. 2.1).

Terminology and Anatomical Methods

Neurons are grouped together as a nuclear group or nucleus (abbreviated Ncl.) if their cell bodies are close together and if they have the same connections from or to other brain areas, possess the same transmitters, or have other common characteristics. The axonal connections of a nuclear group to another brain structure are called projections. An *efferent* represents output from one nucleus to another; inputs to a nucleus are *afferents*. The location of neurons or nuclear groups, their positional relationships, and directional designations are described in anatomy relative to the body. Thus, neu-

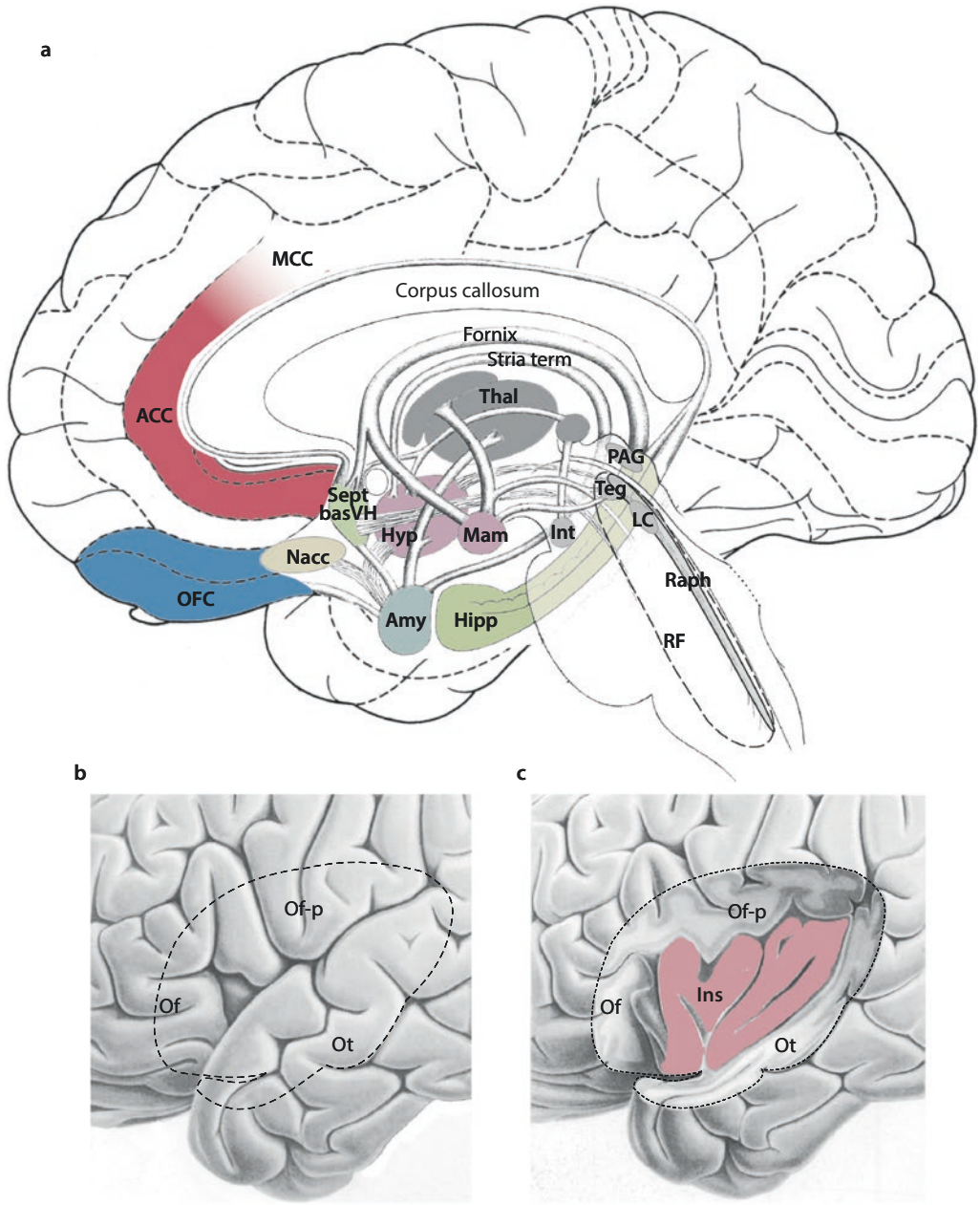

Fig. 2.1 **a** Main structures of the limbic system with fiber connections in a medial view of the right hemisphere (modified after Nieuwenhuys et al. 1988). Rostral is on the left. Internal structures include nuclei in the subcortical telencephalon (nucleus accumbens Nacc, septum and basal forebrain Sept/bas VH, amygdaloid complex Amy, hippocampus Hipp), diencephalon (thalamus Thal with habenula Hab, hypothalamus Hyp with mammillary body Mam), and brainstem (periaqueductal gray PAG, tegmentum Teg, ncl. interpeduncularis Int, locus coeruleus LC, raphe nuclei Raph, reticular formation RF; stria term = stria terminalis). The orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and insular cortex **b**, **c** are limbic cortices. Adjacent to the ACC is the midcingular cortex (MCC). **b** Detail of the lateral view of the left temporal, frontal, and fronto-parietal cortex. The dashed line indicates the area showing the underlying insular cortex in **c**. The temporal operculum (Ot), frontal (Ot), and fronto-parietal operculum (Of-p) cover the insular cortex (Ins)

rons are referred to as cells or groups of cells located *dorsally*, to the back or upper side, or *ventrally*, to the front or lower side. Structures located on the midline are median; they are *medial* if located close to the midline or *lateral* if located sideward. Structures located toward the tip of the frontal lobe are called *rostral* or, in humans, cranial, and those located to the back of the brain are called *caudal*. Within a nuclear group, subdivisions are often made representing a front or *anterior* portion, a hind or posterior portion, and a lower or *inferior* portion and an upper or *superior* portion.

In the following, the limbic structures in the rostrocaudal order of the subcortical structures of the end brain (telencephalon), the interbrain (diencephalon), the midbrain (mesencephalon), and the medulla oblongata, followed by the major cortical limbic centers of the prefrontal cortex including the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the insular cortex. The term brainstem subsumes the midbrain, pons, and medulla oblongata.

The anatomical connectivity (tracer) studies mentioned originate predominantly from experiments on macaque monkeys, only in a few cases data from rodents are cited. Cytological or immunohistochemical studies, as well as connectivity studies using imaging techniques, represent to a lesser extent the findings in humans. The taxon "primate" is used when homologous brain structures of monkeys and humans are presented.

2.1.1 Septal Region

The septum is a thin membrane in the middle of the brain between the two forebrain ventricles; the septal region refers to the adjacent nervous tissue on either side of this wall and borders the left and right ventricles. It is located in the subcortical telencephalon ventral to the corpus callosum and dorsal to the ncl. accumbens.

The septal region consists of different nuclei, which are divided into a *medial* and a *lateral septum*. The medial septum and the Ncl. of Broca's diagonal band (NDB) with a vertical and horizontal "limb" (abbreviated vertical and horizontal NDB, respectively) form the medial septal region. Neurons of the medial septum are cytoarchitecturally similar; they bear few or no *spines*. The largest group of neurons has the transmitter acetylcholine (ACh), others GABA or ACh and GABA, or GABA and the calcium-binding protein parvalbumin; still other neurons glutamate (Frotscher and Léránth 1985; Kiss et al. 1990a, b; Jakab and Leranth 1995; Hajszan et al. 2004). These neurons form a local network.

The *medial* septum receives afferents from the CA1-CA3 region of the hippocampus (▶ Sect. 2.1.3). The medial septal neurons project to the CA1 region of the hippocampus via the powerful fiber tract of the fimbria/fornix. GABAergic and glutamatergic neurons contact GABAergic hippocampal neurons, and cholinergic neurons contact pyramidal cells in CA1. This direct *septo-hippocampal loop* is critically involved in learning and memory; neurons in both areas show rhythmic activity in the theta frequency band (4–12 Hz); theta oscillations accompany voluntary movements, REM sleep, and states of arousal and attention. The cholinergic connection adjusts the excitability of hippocampal neurons in novel or familiar environments, glutamatergic septal neurons are involved in the initiation of locomotion, while GABAergic neurons influence or form theta rhythm and also provide information about the intensity of sensory stimuli (reviewed in Müller and Remy 2018). GABAergic and cholinergic neurons with projection to the hippocampus modulate different aspects of contextual fear as well as pain-related (nociceptive) informa-

tion. The affective nociceptive component is processed via the projection of the medial septum to the limbic cortex and then experienced as pain. Efferents of the medial septal region exist to the medial prefrontal cortex (mPFC) and to the anterior cingulate cortex (ACC), furthermore to the amygdala, to the Ncl. accumbens and to the spinal cord.

Reciprocal relationships exist between medial septum and lateral, posterior and medial hypothalamus, preoptic region and supramammillary nucleus. Vegetative and endocrine functions are regulated by this axis. Finally, the medial septum has reciprocal connections with dopaminergic midbrain structures as well as with cholinergic, serotonergic and noradrenergic nuclei of the brainstem (► Sect. 2.1.5) and receives afferents from the spinal cord.

The *lateral* septum is divided into a dorsal, intermediate and ventral part. The neurons are GABAergic and, in contrast to those of the medial septum, are covered with spines. A variety of neuropeptides as well as steroid hormones are present in the neurons. The lateral septal region, like the medial, is closely associated with the hippocampus and entorhinal cortex; however, these afferents are purely glutamatergic. In addition, the bed nucleus of the stria terminalis (BNST) and the amygdala, hypothalamus, and limbic nuclei of the midbrain and pons project to the lateral septum. Its efferents terminate in limbic cortical and subcortical areas. Projections to the medial and lateral hypothalamus are strongly developed. Efferents also run to the preoptic region, to limbic thalamic nuclei and to nuclei of the brainstem, especially to the central gray, also called periaqueductal gray (PAG).

The lateral septum is involved in emotional-motivational behavior; for example, it controls emotional-cognitive aspects of food intake via its connections to the hypothalamus (Sweeney and Yang 2015; Carus-Cadavieco et al. 2017) as well as exploration and territorial behavior including aggressive responses (Toth et al. 2010; Oldfield et al. 2015). Social fear conditioning (Zoicas et al. 2014) and social interaction in substance use disorders (Zernig and Pinheiro 2015) are regulated by a network between the ncl. accumbens, amygdala, midbrain dopaminergic nuclei, medial and lateral septum. Maternal caregiving behavior is also controlled by the lateral septum (Zhao and Gammie 2014); sexual and reproductive behavior is influenced via a projection of the lateral septum to the PAG (Tsukahara and Yamanouchi 2001; Veening et al. 2014).

The *basal forebrain is* located ventral to the septal region and the BNST and is a cholinergic cell group that extends ventrally to the Ncl. accumbens and dorsally to the amygdala from rostral to caudal. In the basal forebrain, four groups of cholinergic neurons are distinguished: in addition to the Ncl. basalis Meynert (CH4 group), cholinergic neurons are found in the medial septal nucleus (CH1 group) and the NDB (vertical NDB CH2 and horizontal NDB CH3 group). The Ncl. basalis Meynert receives input from limbic frontal, insular and temporal cortical areas, from the septal nuclei, the Ncl. accumbens and ventral pallidum, the amygdala, the hypothalamus and the parabrachial nucleus in the brainstem. In addition to projecting to the hippocampus, CH1 cells project to the interpeduncular nucleus, CH2 cells also project to the hypothalamus and dopaminergic midbrain. The projection of CH3 cells is to the olfactory bulb, that of CH4 cells to the basal amygdala as well as to the isocortex.

Functions of cholinergic projections involve learning and extinction of contextual or stimulus-associated fear responses in cortico-amygdalar and cortico-hippocampal circuits (Knox 2016; Wilson and Fadel 2017), as well as regulation of sleep-wake rhythms (Yang et al. 2017). Cholinergic modulation of attentional processes occurs via "top-down" control of the PFC over sensory cortical areas. In Alzheimer's disease or Parkinson's disease with dementia, degenera-

tion of cholinergic neurons, especially of the CH2 and CH4 groups, leads to attentional deficits, memory loss, language impairment, and, as degeneration progresses, further emotional-cognitive dysfunction (Liu et al. 2015; Ballinger et al. 2016).

2.1.2 Amygdala

The amygdala has historically been considered part of the limbic system, with predominant connections to the hypothalamus and brainstem. However, neuroanatomical studies from the last three decades show that the amygdala forms an extensive network with a variety of cortical and subcortical brain regions. The concept of the *extended* amygdala was developed by neuroanatomists Alheid and Heimer (1988) and includes, in addition to the classical amygdala nuclei, the aforementioned BNST and other nuclei lying between the amygdala and BNST. The extended amygdala complex is a heterogeneous group of nuclei located in the medial temporal lobe rostral to the hippocampal formation. There is little information on the anatomical connectivities of the amygdala in humans. However, the anatomical structure and connectivities of the macaque monkey amygdala are considered homologous to humans.

The following account of the classification of the nuclei of the amygdaloid complex is largely based on work in primates and follows the nomenclature of Freese and Amaral (2009). Up to 13 nuclei and cortical regions belong to the amygdaloid complex. They are divided into a deep and a superficial nuclear group. The deep lying group includes the lateral, basal, accessory basal, and paralaminar ncl; collectively, the lateral, basal, and accessory basal nuclei of the deep group are referred to as the *basolateral group*. The superficial group includes the medial, anterior, and posterior cortical ncl. as well as the ncl. of the lateral olfactory tract and the periamygdaloid ncl.; this nuclear group is also called the *cortical nucleus* without the medial ncl. or the *corticomedial nucleus* with it. The remaining nuclei are the anterior amygdaloid area, the central ncl. also called the central amygdala, the amygdalo-hippocampal area, and the nuclei intercalares (Freese and Amaral 2009). Central and medial nuclei are also grouped together as the *centromedial group*, depending on the author and species studied.

2.1.2.1 Deep Nuclei (Basolateral Group)

The *lateral nucleus* is subdivided into a dorsal, an intermediate and a ventral part due to the cell density and size of the neurons and its immunoreactivity for the acetylcholine-degrading enzyme AChE. The dorsal lateral nucleus is considered a polysensory part of the lateral nucleus because of its inputs from the sensory cortex. Its neurons project to the more densely located and more AchE-immunoreactive neurons of the ventral lateral nucleus. The *basal nucleus* is divided into a dorsal and caudal magnocellular part with large neurons, an intermediate part, and a small-cell, so-called parvicellular part, which is located most ventrally and rostrally. The flow of information within the basal nucleus is from the dorsally to the ventrally located neurons. The *accessory basal nucleus is* located most medially of all four nuclei of the deep group, and here, too, a more AChE-reactive magnocellular neuronal group and densely packed, strongly AChE-reactive neurons are found in the ventromedial part. The *paralaminar nucleus is* located at the ventral and rostral edges of the amygdaloid complex and is connected to the lateral and basal nuclei.

2.1.2.2 Superficial Nuclei (Corticomedial Group)

The *medial nucleus* lies within the amygdaloid complex caudally. It has a larger proportion of GABAergic neurons. The *posterior cortical nucleus* is also located caudally within the amygdaloid complex. The *anterior cortical nucleus* is rostral to the medial nucleus and is demarcated from the

medial nucleus, which has a demarcated layer II, because of its fusion of layers II and III. The *nucleus of the lateral olfactory tract* lies in the rostral part of the amygdaloid complex and is characterized by intense immunoreactivity for AChE. The *periamygdaloid nucleus*, also known as the periamygdaloid cortex, is located superficially medial and extends almost completely from rostral to caudal in the amygdaloid complex.

2.1.2.3 Central Amygdala and the Intercalated Nuclei

The *central nucleus is* located in the caudal half and is divided into medial and lateral divisions based on cytoarchitecture. The medial division is heterogeneous in terms of cell size and density, whereas the lateral division is more uniform in cell size and more densely packed. The prominent feature of the central nucleus is the presence of GABAergic neurons; accordingly, the projections of the central nucleus act predominantly inhibitory. In primates, the *nuclei intercalares* form a continuous inhibitory network of GABAergic neurons that lies between the basal nuclei and extends to the dorsally located anterior nuclei and the central and medial nuclei of the amygdaloid complex. *Spiny* neurons are found in greater numbers than *smooth* neurons.

The *BNST*, together with parts of the amygdaloid complex, is considered to be the "extended amygdala" and shares some similarities in terms of connections and chemoarchitecture (especially the presence of GABAergic neurons) with the central and medial nuclei of the amygdala. In humans, the BNST is divided into lateral, medial, central, and ventral portions and exhibits sexual dimorphism with up to 2.5-fold higher volume in males.

2.1.2.4 Intrinsic Connectivities of the Amygdalar Nuclei

The nuclei of the amygdaloid complex are closely interconnected. The lateral nucleus has projections to all other amygdalar nuclei; those to the basal, accessory basal, and periamygdaloid nuclei are particularly pronounced. The connection of the lateral to the central nucleus of the amygdala is weaker than that of the basal. In addition, the basal nucleus projects primarily to the medial and anterior cortical nuclei. Within the amygdala, the flow of information is generally from lateral to medial. The amygdala is connected to a variety of subcortical and cortical regions via the amygdalofugal fiber tract and stria terminalis. The fibers of the amygdaloid complex gather to form the ventral amygdalofugal fiber tract from rostral to caudal at the dorsomedial edge of the amygdala, while the stria terminalis is formed by fibers ventromedially in the caudal amygdala.

2.1.2.5 Extrinsic Connectivities and Functions of the Amygdalar Nuclei

The connections of the nuclei of the amygdaloid complex are primarily to the limbic cortical areas, to the other limbic subcortical brain structures, and to the thalamus and brainstem. The amydalar complex is involved in a variety of cognitive, emotional and affective-vegetative functions (◘ Fig. 2.2).

■ Olfactory System

The olfactory bulb and also the piriform cortex send axons to the anterior cortical nucleus, the nucleus of the lateral olfactory tract, and the periamygdaloid nucleus (Turner et al. 1978); the latter two nuclei also project to the olfactory bulb.

■ Connections to Areas of the Cortex

The majority of the basolateral group receives inputs from numerous areas in the frontal, insular, cingulate, and temporal cortex; extensive projections to a larger number of cortical areas (Brodmann areas, abbreviated BA) also originate from it. In general, the connections of the rostral areas of the cortical areas with the amygdalar nuclei are weaker. The cortical projections reach mainly the basolateral group of nuclei.

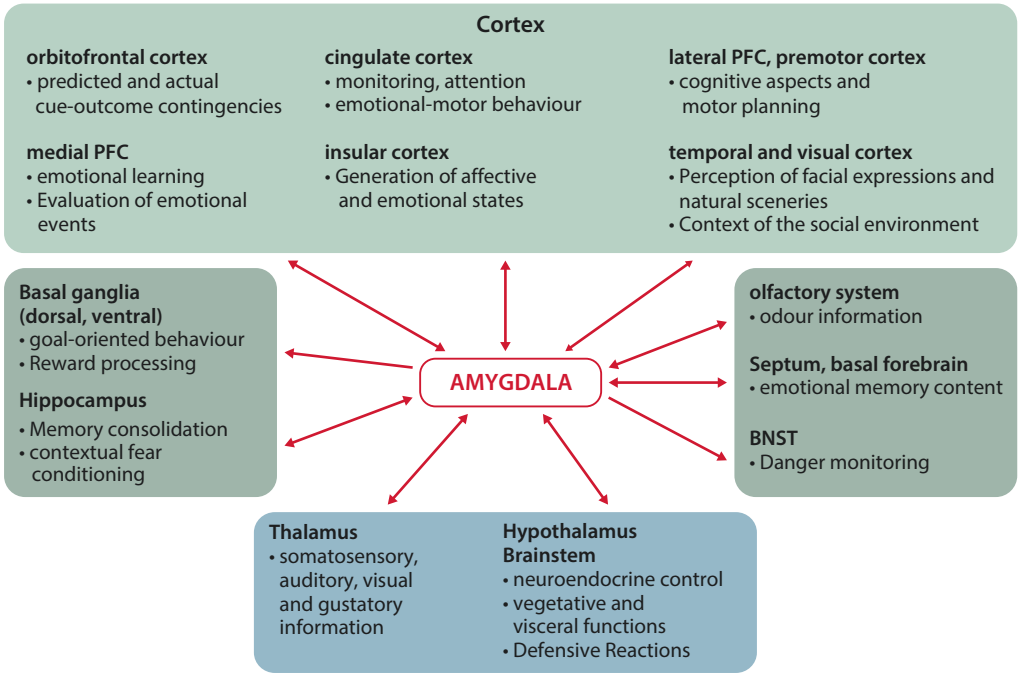

Fig. 2.2 Functional relationships of the amygdala to cortical areas (light green), subcortical telencephalic structures (dark green) and other brain parts (gray-blue). Reciprocal projections are indicated by arrows with two tips; the line width of the arrows indicates the strength of the connection

Inputs from the caudal OFC run stronger and more widely branched in the caudal than in the rostral amygdala. Projections from the OFC (BA 11, 13 and parts of 10, 12, 14, and 24) and from the medial prefrontal cortex (mPFC; BA 32, parts of 9, 10, 14, and 24) extend to the medial nucleus, cortical nuclei, periamygdalar nucleus, and central nucleus in addition to the basolateral group. Laterally located prefrontal areas (BA 8, 45, 46, parts of 9 and 12) as well as the premotor cortex (BA 6) project—although less strongly—to the basal nucleus. In terms of efferents, the basal nucleus of the amygdala has the strongest projection to the OFC and mediolateral cortex and a weaker one to the dorsolateral PFC; again, the terminations are more pronounced caudally in the OFC but also reach the frontal pole. The projection to the mPFC also emanates most strongly from the basal nucleus and less so from the accessory basal and medial nuclei and from the cortical nuclei. Only the basal nucleus has a projection, albeit small, to the dorsolateral PFC (Amaral and Insausti 1992; Carmichael and Price 1995a; Stefanacci and Amaral 2000; Ghashghaei and Barbas 2002).

The amygdala, together with the OFC and mediodorsal thalamus (▶ Sect. 2.1.5), encodes the specific identity of a predicted outcome (stimuli and/or actions) given an individual's current state (Rudebeck and Murray 2014). The basolateral amygdala thereby provides information about current stimulus-outcome contingencies, while the OFC forms a larger network of past and current associations that the basolateral amygdala can use for future learning episodes (Sharpe and Schoenbaum 2016).

One of the most important inputs to the amygdala is from the insular cortex. Projections from the rostral part of the insula (▶ Sect. 2.2.3) are stronger and reach

mainly the lateral, basal, and central nuclei (Freese and Amaral 2009). Except for the central nucleus, these projections are reciprocal. Caudal portions of insular cortex project to a lesser extent to the lateral and central nuclei; a moderately pronounced reciprocal projection originates from the nuclei of the basolateral group. Reciprocal, more pronounced projections also originate from the basolateral group of nuclei of the amygdala with the rostral cingulate cortex (BA 24 and 25). However, inputs also run to a lesser extent to the anterior amygdaloid area and central nucleus.

Reciprocal relationships also exist between the temporal cortex and the basolateral group. Regions around the superior temporal gyrus and sulcus project primarily to the lateral and basal nucleus and, to a lesser extent, to the corticomedial group. Inputs from region TE in the inferior and middle temporal gyrus and the caudally located region TEO of the posterior middle temporal gyrus also reach the basolateral group (Stefanacci and Amaral 2002). Regions TE, TEO, V4, V2, and V1, which form the ventral pathway of visual cortex from occipital to temporal cortex, receive projections from the basal nucleus of the amygdala. Thereby, a rostrocaudal topography exists between the amygdala nucleus and the visual regions (Freese and Amaral 2005). Emotional facial expressions and the perception of natural sceneries activate the amygdala as well as limbic cortex areas (Sabatinelli et al. 2011). Sensory processing of emotional stimuli occurs early in the amygdala and thus may influence subsequent sensory processing in other brain areas (Pourtois et al. 2013). The context of the social environment can also be modulated via this amygdala connection for regulation of social behavior (Adolphs and Spezio 2006).

Connections with the Basal Forebrain

The basolateral group projects to the lateral regions of the cholinergic Ncl. basalis Meynert and NDB of the basal forebrain; this projection also runs onward to other subcortical structures. The basolateral nuclei conversely receive powerful projections from the Ncl. basalis Meynert and are functionally involved in memory for contextual fear and extinction of fear. Cholinergic signaling is important in the generation of activity-dependent LTP in the amygdala and contributes to the maintenance of emotional memory content (Ballinger et al. 2016). Furthermore, the central nucleus of the amygdala projects to the Ncl. basalis Meynert, both structures have influence on fear conditioning processes (Knox 2016).

Connections with the Basal Ganglia

The amygdaloid complex, remarkably, receives no inputs from the striatum (Aggleton et al. 1980), but projects there. The basolateral group sends topographically ordered fibers to the caudate and putamen nuclei and to the ventral striatum and ncl. accumbens, respectively. Neurons of the small-cell portions of the two basal nuclei send their axons to the ncl. accumbens, while the magnocellular portions project to the caudate nucleus and rostroventral putamen, and the lateral nucleus projects to the caudoventral putamen and also to the tail of the caudate nucleus (Russchen et al. 1985).

Cho et al. (2013) distinguish three circuits that run from different cortical areas to the basal and accessory basal nuclei of the amygdala and from there to different regions of the striatum. A "primitive" pathway extends from BA 25 and 32 of the mPFC and from the agranular insula to the basal nuclei and thence to the rostral ventral striatum. This circuit presumably aligns internal emotional states with internal physiology and with motivation via attentional processes. An "intermediate" pathway runs from BA 24 and 14 of the mPFC and from the dysgranular as well as granular insula (► Sect. 2.2.3) via the basal nuclei also to the caudoventral striatum, the rostral body of the ventromedial striatum and the caudo-

ventral putamen. This pathway may control responses to social events, as BA 24 processes social contacts, the insula processes tactile stimulation, and the striatum processes facial and eye movements. A "developed" pathway extends from the OFC and BA 10 of the mPFC to the dorsal parts of the basal nuclei. The projection then proceeds to the dorsolateral and caudal body, knee, and tail of the striatum. This latter pathway may be responsible for sensory-guided changes in behavior, as the OFC and BA 10 process more complex cognitive functions such as updating and temporal aspects of behavior, and the striatal portions reached by this pathway also receive information from auditory and visual association cortices.

The amygdala's projection to the ventral striatum is also activated during reward processing, especially when previously rewarded stimuli are attenuated (devalued), or in contexts involving the threat of punishment. Other research finds that salient rather than rewarding events lead to amygdala activation. Responses to rewarding stimuli quickly attenuate in amygdala neurons (as they do to emotional stimuli in general), in contrast to those in the nucleus accumbens (reviewed in Haber and Knutson 2010). Motivational aspects are controlled via a network that includes direct amygdalo-ventrostriatal projections as well as cortico-striato-pallido-thalamic and hippocampo-striatal circuits. Actions and predictive stimuli are associated with the value of subsequent events; this larger network thus ensures adaptive behavior (Zorrilla and Koob 2013).

Connections with the Hippocampal Formation

Inputs from the hippocampus proper (the hippocampus in the strict sense, ▶ Sect. 2.1.3) originate primarily in the CA1 region and travel to the basal and cortical nuclei and to the paralaminar and periamygdaloid nuclei. The dentate gyrus does not appear to have direct connections with the amygdala. The projections from the amygdala to the CA1, CA2, and CA3 regions of the hippocampus are much stronger than those to the amygdala and originate from basal and cortical nuclei, while a projection from the basal and periamygdaloid nuclei also runs to the border region of the subiculum and CA1.

The entorhinal cortex (▶ Sect. 2.1.3) also projects to the lateral, basal, and periamygdaloid nuclei. In particular, the basal nucleus sends robust projections to the subiculum, para- and presubiculum of the hippocampal formation. Similarly, the lateral nucleus sends efferents to the parasubiculum, but influences the hippocampus proper primarily via a robust projection to the entorhinal cortex. Consolidation of memory content and reinforcement of declarative content of emotional events as well as (contextual) fear conditioning and extinction are important functions based on amygdalo-hippocampal interactions (McDonald and Mott 2017).

Connections to the Thalamus

Inputs from the thalamus to the basolateral group, medial nucleus, and central nucleus of the amygdala originate from the midline thalamic nuclei, e.g., the paraventricular and paratenial nuclei, which are activated during stressful situations, anxiety, and other affective behaviors. Projections of the thalamus from the Ncl. reuniens, the largest nucleus of the midline thalamic nuclei, and the intralaminar thalamic nuclei run to the medial, cortical, and central nuclei of the amygdala in addition to the basal nuclei. Strong inputs to the amygdala also arise from the nucleus centralis complex of the intralaminar thalamic nuclei (Aggleton et al. 1980; Mehler 1980).

The medial and central nuclei of the amygdala send projections to the reuniens nucleus. The latter has a massive connection to the hippocampus and limbic cortex areas, especially the mPFC (Vertes et al. 2015). The amygdala also projects strongly to the mediodorsal nucleus of the thalamus (▶ Sect.

2.1.5); the axons of the different amygdala nuclei terminate there separately (Russchen et al. 1987). The mediodorsal thalamic nucleus in turn has strong reciprocal relationships with limbic cortex areas, especially the mPFC, OFC, and insula. Similarly, the medial nucleus of the amygdala sends fibers to the central nuclei of the intralaminar thalamic nuclei, which are involved in attention and sensorimotor functions.

Reciprocal relationships exist between the amygdala and the pulvinar. The pulvinar is located in the caudal thalamus and has a strong connection to the visual cortex and is part of the visual attention system. The central nucleus projects to the pulvinar (Price and Amaral 1981), and the lateral nucleus of the amygdala receives a projection from the medial pulvinar (Aggleton et al. 1980).

■ Connections with the Hypothalamus

Strong reciprocal relationships exist between the ventromedial nucleus of the hypothalamus and the basal nuclei, central nucleus, and medial nucleus of the amygdala. The lateral hypothalamic region projects to the medial and central nuclei and to the cortical nuclei. The lateral mammillary nucleus of the hypothalamus innervates the central nucleus, and the supramammillary region innervates the medial nucleus.

The medial nucleus and parts of the cortical nuclei of the amygdala project to the preoptic region, the anterior hypothalamus, and to pre- and supramammillary regions of the hypothalamus. A strong projection of the central nucleus runs to the lateral hypothalamus and mammillary body. Neuroendocrine control, autonomic and visceral control, and defensive responses are major functions regulated by the amygdalo-hypothalamic axis.

■ Connections with the Brain Stem

In the central nucleus of the amygdala, dopaminergic projections terminate from the substantia nigra and the ventral tegmental area (VTA) of the midbrain, while the lateral and medial nuclei receive inputs from the peripeduncular nucleus. Inputs to the amygdaloid complex also originate from the serotonergic dorsal raphe nucleus and the PAG.

The central nucleus of the amygdala in turn sends projections to the dopaminergic midbrain nuclei, to the PAG and to the dorsal raphe nucleus and the ncl. raphe magnus. Reciprocal projections are also found between the central nucleus, the parabrachial nucleus, and the noradrenergic locus coeruleus. The central nucleus also projects to the reticular formation and to regions of the medulla oblongata up to the cervical spinal cord (Price and Amaral 1981; Amaral et al. 1982; Price 2003). Because the central nucleus has many GABAergic neurons, many of these long-descending projections to the brainstem likely have inhibitory effects. The connections of the central amygdala with the brainstem serve to regulate autonomic, visceral, and motor functions such as respiration, blood circulation, and defensive, avoidance, and escape behaviors.

2.1.2.6 Summary of the Functional Aspects of the Amygdaloid Complex

The amygdala is globally involved in emotional processing and is involved in motivation and memory. Information about external stimuli and the internal state of the organism is integrated by it and exerts an emotional influence on behavior via projection to other subcortical structures. This concerns olfactory signals directly mediated by the olfactory system and sensory information indirectly interconnected via the thalamus, such as taste, sight, hearing, touch. Vegetative centers, cardiovascular and respiratory centers from the brainstem as well as the hypothalamic neuroendocrine centers, visceral states and defensive reactions inform the amygdala about the internal state. The amygdala receives information about aspects of aggression and motivation processed in the septum and basal forebrain. These events and states influence actions, motivation, and reward behavior via projec-

tions to the dorsal and ventral striatum, anxiety via projections to the BNST, and learning and memory via those to the hippocampal formation.

The amygdala is strongly associated with the OFC and the mediodorsal PFC. These areas associate changes in the sensory environment relative to an individual's predicted and current state, mediating social signals to the amygdala, which influences social behavior via its projection to these cortices. The connections between the amygdala and insular cortex serve to detect and avoid danger in the environment as well as to regulate vegetative information. The recognition of emotional facial expressions and natural sceneries are integrated into behavior via the interaction between temporal visual areas and the amygdala. The amygdala is active in negative *and* positive emotional processing as well as in aversive and appetitive learning. However, it is unclear which nuclear groups and connections of the amygdala are relevant for appetitive, i.e. reward-oriented, signal processing (Correia and Goosens 2016; Kolada et al. 2017).

2.1.2.7 The Role of the BNST

The BNST is considered an important structure for fear responses in the presence of danger and for danger monitoring; it initiates the stress-relevant HPA (pituitary-hypothalamic-adrenal) axis in stress responses involving the medial PFC. In this context, the BNST appears to be activated in both imagined and actual danger, whereas the amygdala is activated only in the latter situation (Lebow and Chen 2016). The BNST is involved in an extensive limbic network via its connections, so that it is involved in many other functions such as mood, attention, sleep, appetite, but also in social interaction and reproductive behaviour (Lebow and Chen 2016).

2.1.3 Hippocampal Formation

The hippocampus proper is an elongated structure deep in the medial temporal lobe that resembles a seahorse (Greek hippocampus) in cross-section. It consists of four morphologically distinct subregions: the dentate gyrus (DG), the ammonic horn, Latin cornu ammonis, (CA) with four fields CA1 to CA4, presubiculum, and subiculum (Amaral and Lavenex 2006). The CA4 region is located in the inner curvature of the DG and is also referred to as CA4/DG in the primate brain. Based on neurochemical features, in primates the subiculum complex is divided into a prosubiculum and an actual subiculum (collectively referred to as the subiculum), a presubiculum and postsubiculum (collectively referred to as the presubiculum), and a parasubiculum. The subiculum complex is located between the hippocampus and entorhinal cortex. The three main subicular parts are characterized by different connections and functions. While the subiculum is the main output structure of the hippocampal formation and is involved in encoding and retrieval of long-term memory content, the presubiculum has functions in spatial orientation ("landmark navigation") and, together with the anterior thalamic nucleus, lateral mammillary nucleus, and retrosplenial cortex (BA 29, 30), is a main structure of the head orientation system. The parasubiculum has strong connections to the entorhinal cortex and generates theta EEG activity (reviewed in Ding 2013), i.e., the cells fire at a frequency of 4–12 Hz. Theta frequency oscillation is generated locally in the hippocampus and by the septo-hippocampal circuit. In the EEG, it is measurable in REM sleep and during exploratory behavior in rats.

Based on the size and morphology of glutamatergic pyramidal cells as the major cell types of hippocampal circuits, two main regions, CA1 and CA3, can be distinguished. A trisynaptic pathway extends from the DG to CA1 and CA3; axons of the DG pass through the CA4 region to CA3. The entorhinal cortex, which is properly located upstream of the hippocampus, sends axons via the so-called *perforant pathway* to the

granule cells of the DG, whose axons in turn terminate on the CA3 pyramidal cells via the so-called *mossy fiber tract*. The axons of the latter neurons form the *Schaffer collateral pathway*, which runs back to the subiculum and then to the entorhinal cortex. In addition to CA1, the axons of CA3 cells project to other CA3 neurons via axon collaterals, forming a recurrent collateral pathway. The CA3 region is therefore also considered to be an autoassociative, i.e., self-referral, memory system (Yau et al. 2015). CA3 cells also project back to the DG dentatus via excitatory mossy cells, so the pathways are not exclusively unidirectionally organized. In addition, recent data show that the CA2 region, previously considered a transition zone, represents a distinct functional unit equivalent to the CA1 and CA3 regions (Ding et al. 2010). CA2 and CA4 neurons are preferentially affected by degeneration processes in diseases such as chronic traumatic encephalopathy (McKee et al. 2016).

▪ Connections of the Hippocampal Formation

The parahippocampal region adjacent to the hippocampus proper comprises the entorhinal (BA 28), the parahippocampal (temporal areas TH and TF according to von Economo 1929) and the perirhinal cortex (BA 35, 36). The input structure for the hippocampus proper is the entorhinal cortex, which in turn has reciprocal connections with the perirhinal and parahippocampal cortex. The latter two cortices also project to each other. The perirhinal cortex is reciprocally connected with visual (associative) areas such as TE, TEO, and V4; however, it also has direct connections with the CA1 region and the subiculum. The parahippocampal cortex has reciprocal connections with the aforementioned visual cortical areas as well as with parietal and cingulate cortices. The parahippocampal cortex also has a direct input to the CA1 region and the subiculum.

The strongest hippocampal projections originate from the CA1 region and the subiculum complex; only the projections to the septum and ncl. accumbens also contain information from the CA3 region. Four groups of different efferents can be distinguished. Projections to the retrosplenial cortex, anterior, lateral dorsal, and midline nuclei of the thalamus, and mammillary bodies run almost exclusively from the subiculum; pre- and parasubiculum contribute partially. A second projection originates equally from the subiculum and CA1 and to a lesser extent from the pre- and parasubiculum; it reaches the OFC (BA 11, 13) and the mPFC (BA 14, 25, 32) in the PFC, the amygdala as well as areas TE and TG in the temporal cortex. Efferents of the third group originate from the CA1 region and the subiculum and extend to the entorhinal, perirhinal, and parahippocampal cortex. The fourth group of projections from the CA3 and CA1 regions reach the septum, the vertical limb of Broca's diagonal band, and the ncl. accumbens (Friedman et al. 2002; Aggleton 2012; Aggleton et al. 2012).

The discovery of *place cells* in the hippocampus and their associated *grid cells* in the entorhinal cortex of rats provided a picture of the origin of spatial orientation and the formation of spatial memory and explained spatial orientation deficits following hippocampal lesions. Functionally, studies in humans and animals revealed that the anterior hippocampus is involved within a larger network in *non-spatial functions* such as context coding, attention or reward expectation and the posterior (dorsal in rodents) part in *spatial navigation* or memory of spatial arrangements of a scene (Viard et al. 2011; Nadel et al. 2013).

2.1.4 Basal Ganglia and Mesolimbic System

In the telencephalon, the basal ganglia include the corpus striatum, which is composed of the caudate nucleus, the putamen and the ventral striatum including the

accumbens nucleus, and the globus pallidus. In the diencephalon, this includes the subthalamic nucleus and in the midbrain the substantia nigra, which in turn forms a functional unit with the ventral tegmental area. The basal ganglia are divided into a dorsal part with executive and sensorimotor functions, which prepares and controls motor actions, and a ventral part, which has emotional and motivational functions and belongs to the limbic system (for an overview, see Haber et al. 2012).

Nucleus Caudatus/Putamen

The caudate nucleus and the putamen together form a large subcortical structure and are separated from each other by the fiber tracts of the internal capsule and are directly contiguous only in the rostral part. The caudate nucleus lies medial to the putamen, is divided into a head, body and tail, and extends around the putamen from dorsal to ventrolateral.

The majority of neurons in the caudate nucleus and putamen are medium *spiny* cells, densely *spiny* in the middle and distal regions of the dendritic tree, and are therefore referred to as *medium spiny cells*. They possess the transmitter GABA and project inhibitory to the dorsal pallidum, substantia nigra and VTA. The interneurons of the striatum are cholinergic or GABAergic and immunoreactive for a number of neuropeptides and proteins such as neurotensin, enkephalin, somatostatin, substance P, vasoactive intestinal peptide (VIP), neuropeptide Y, calbindin and parvalbumin, and for NADPH diaphorase.

The striatum in primates exhibits compartmentalization into striosomes (also called *patches*) and a matrix (Graybiel and Ragsdale Jr 1978). The striosomes account for 10–20% of the cell mass and are 300–600 μm wide islands with low density of the enzyme acetylcholine esterase (AChE) and high density of opioid receptors, as well as high immunoreactivity for GABA, enkephalin, substance P and neurotensin. In contrast, the intervening matrix has a high density of AChE and strong calbindin and somatostatin immunoreactivity. This subdivision is distinct in the head of the caudate nucleus, where associative and limbic afferents enter, but only weakly evident in the posterior part and in the putamen with sensorimotor inputs. Striosomes specifically receive projections from the OFC, ACC, and insular cortex, while the matrix receives afferents from the entire frontal areas (Eblen and Graybiel 1995). The projections originating from the limbic cortical areas terminate insularly within the striatum; therefore, so-called microcircuits are thought to exist between the different cortical areas and striatum. At the same time, the insular projections of interconnected PFC areas overlap in the striatum, so that intra-cortical projections may also be represented in the striatum.

Ncl. Accumbens/Ventral Striatum

The ncl. accumbens comprises the rostral ventromedial part of the striatum and, together with the rostrally located olfactory tubercle and the ventrally located parts of the ncl. caudatus and putamen, is also considered the limbic part of the basal ganglia. It is anatomically and immunohistochemically subdivided into a ventromedial part, called shell, and a *core*, where the shell forms the dorsal and central part of the ncl. accumbens. The latter region is connected to the ventromedial part of the caudate nucleus and has similar histochemical features. The division into nucleus and shell is evident in primates only by the detection of histochemical markers (Meredith et al. 1996; Holt et al. 1997; Brauer et al. 2000). *Patches of* immunoreactivity for enkephalin or opioid receptors are found throughout the ncl. accumbens/ventral striatum. The shell shows stronger immunoreactivity for neurotensin and AChE and moderate calbindin and strong calretinin immunoreactivity, as well as weak presence of opioid receptors, whereas the core shows strong calbindin and only weak calretinin

immunoreactivity, as well as strong presence of opioid receptors. The core region of the ncl. accumbens receives afferents from the OFC (BA 12, 13), whereas the shell region receives projections from the subgenual and pregenual cingulate cortex (BA 25) (Haber et al. 1995). Based on the cortical projections, there is thus a separation, albeit not complete, into an *associative* territory in the medial part of the caudate nucleus and putamen with input from the lateral OFC and dorsal PFC, and a *limbic* territory in the ventral striatum with input from the limbic cortex areas (Buot and Yelnik 2012).

Subcortical inputs to the striatum originate from the basolateral amygdala primarily to the head of the ncl. caudatus and to a lesser extent to the anterior and ventral parts of the putamen; these inputs did not differ with respect to their termination in the striosome matrix portions of the striatum. In the ncl. accumbens, projections from the anterior part of the basolateral amygdala reach the core region, and projections from the posterior part together with those from the central amygdala reach the shell region of the ncl. accumbens. Again, an insular distribution of afferents is found. The hippocampal formation innervates the ncl. accumbens excitatory, further afferents originate from the limbic midline nuclei and intralaminar nuclei of the thalamus.

The Ncl. accumbens-ventral striatum complex is involved in dopaminergic circuits with the midbrain nuclei. Striosomes receiving limbic information project to the dopaminergic neurons of the substantia nigra pars compacta (SNc); the latter form afferents to the striosomes and matrix. Through a series of circuits between the striatum and SNc, ventral striatal regions can influence dorsal striatal regions and relay information between limbic medially located neurons and motor laterally located neurons (Haber et al. 2000). Substantia nigra and VTA connect the motor and limbic parts of the basal ganglia, which, remarkably, have no direct connections to each other.

Globus Pallidus

The globus pallidus, also known as the pallidum for short, consists of an external and internal segment, which, like the striatum, is divided into a dorsal motor and a ventral limbic part. The latter, together with the ventral striatum/ncl. accumbens complex, forms the ventral striato-pallidal system. The primate ventral pallidum is a crescent-shaped structure whose external segment is rich in enkephalin immunoreactivity and lies ventral to the commissura anterior. The globus pallidus contains predominantly GABAergic neurons that also express calretinin, calbindin, parvalbumin, neuropeptide Y, or somatostatin. The GABAergic neurons are strongly occupied by GABAergic boutons—they are therefore inhibited in turn.

The projections of the ncl. accumbens to the ventral pallidum are topographically ordered. The limbic portion of the pallidum has a ventromedial portion that is rich in neurotensin and receives afferents from the shell region of the ncl. accumbens. This projection from the ncl. accumbens continues to the extended amygdala and lateral hypothalamus. A projection from the lateral part of the shell region and the olfactory tubercle runs to a ventrolateral subregion that is devoid of neurotensin. The core region of the ncl. accumbens projects to a ventrolateral part of the ventral pallidum with strong calbindin immunoreactivity. Cholinergic neurons in the ventral pallidum also receive GABAergic input from the ncl. accumbens, are locally interconnected, and project to the basolateral amygdala and PFC. Efferents from the ventral pallidum to the ncl. accumbens originate equally from the dorsolateral and ventromedial portions of the ventral pallidum and reach the shell or core of the ncl. accumbens. Efferents to the basolateral amygdala originate mainly from cholinergic neurons in the ventral pallidum regulated by *mu*, *kappa*, and *delta opioid receptors*. Some of these cholinergic neurons also innervate the PFC and entorhinal cortex; however,

these do not appear to possess *kappa* or *delta opioid receptors*, so separate cholinergic ventropallidal projections to them appear to exist.

The neurons of the ventral pallidum have dopaminergic D1, D2, and D3 receptors. The dopaminergic inputs to the ventral pallidum are topographically ordered; a projection of the lateral VTA runs to the rostral, ventromedial, dorsolateral, and ventrolateral portions of the ventral pallidum, and that of the midline portion of the VTA to the medial ventral pallidum. Afferents from the substantia nigra are sparse.

The striosome and matrix neurons of the dorsal striatum form a so-called direct pathway through their projection to the internal segment of the dorsal pallidum to the substantia nigra pars reticulata (SNr) and an indirect pathway via the external segment of the dorsal pallidum to the subthalamic thalamus, which from there runs to the internal segment of the globus pallidus and further to the SNr. The majority of neurons projecting to the dorsal pallidum show immunoreactivity for GABA, neurotensin, and enkephalin and possess dopaminergic D2 receptors, whereas the majority of cells projecting to the SNc and SNr show immunoreactivity for GABA, dynorphin, neurotensin, and substance P and have dopaminergic D1 receptors. It is as yet unclear whether the strong efferent projection of the nucleus and core region of the ncl. accumbens also exhibits organization into a direct and indirect pathway.

Further subcortical connections exist to the thalamus and brainstem. Efferents of the ventral pallidum also reach the reticular nucleus of the thalamus. Another projection leads to the lateral habenula, which in turn projects to the mesopontine rostromedial tegmental nucleus (formerly also called the *tail of* the VTA), which is reciprocally connected to the ventral pallidum (Zahm and Root 2017). A projection to the lateral hypothalamus is topographically organized from medial to lateral; the ventral pallidum is also involved in the circuits of the medial preoptic nucleus. Projections exist to the pedunculopontine tegmental nucleus.

Functions of Limbic Circuits

The different functions within the ncl. accumbens/ventral pallidum complex are outlined in a review by Root et al. (2015) based on pharmacological microinjections into the ventral pallidum. The ventral pallidum is involved in a variety of motor behaviors such as unconscious reflexes, but also volitional actions, learning and memory, or reward-motivated actions. Consummatory behaviors such as food intake, food preference and taste responses, but also caring behaviors are also influenced by the ventral pallidum. Cognitive aspects during sensorimotor filtering mechanisms in the startle reflex, working memory and associative learning are affected in pharmacological microlesion, as well as reward mechanisms during self-stimulation and aversive behavior are regulated by ventral pallidal circuits.

The ventral striatum/ncl. accumbens appears to be more active in impulsive choice behavior than in inhibition of actions to be performed. However, the ncl. accumbens is not solely responsible for the regulation of impulsive behavior. In general, the pattern of neuronal activation in the ncl. accumbens appears to be partly genetically determined, partly learned, and has a strong influence on differences in impulsivity among individuals. Dopamine release by the VTA influences the strength of the neuronal representation and selection of the fronto-temporal limbic input to the ncl. accumbens and, via it, promotes either impulsive or controlled behavior depending on the relationship (contingency) of stimulus and reward, response and outcome (Basar et al. 2010).

Berridge and Kringelbach (2013) localize so-called hotspots in the ncl. accumbens and ventral pallidum, which are active for certain *hedonic aspects* such as liking and pleasure, while *wanting and craving for rewards* is represented in a larger and distributed dopaminergic network. Activation for valence

(appetence and aversion) is also localized in the ncl. accumbens, which generates corresponding intense motivation in the presence of positively valenced wanting or negatively valenced fear. Graded mixtures of affective wanting-fear activations are found in microstimulation along a rostrocaudal axis in the medial shell region; namely, from rostral beginning with desire for food to caudal with fearful fear responses. Subjective, consciously experienced pleasure, on the other hand, is encoded in the OFC, where there are also hedonic hotspots (Berridge and Kringelbach 2015).

■ Functions of the Basal Ganglia

The dorsal and ventral parts of the basal ganglia and their circuits are involved in motor and limbic functions, respectively. Initial models of cortical projections to the basal ganglia assumed five separate circuits that exist between frontal, oculomotor, dorsolateral frontal, lateral orbitofrontal, and anterior cingulate cortex and distinct regions in the striatum, pallidum/substantia nigra, and thalamus before returning to the cortical output area (e.g., Alexander and Crutcher 1990). However, the ventral striatum also receives inputs from auditory and visual associative parietal areas and from the temporal gyrus, so that a division into a limbic, an associative, and a sensorimotor territory is assumed (Parent and Hazrati 1995). The basal ganglia play a role in response and selection processes of declarative and procedural memory. The ncl. accumbens and olfactory tubercle are involved in unconditioned and conditioned responses. The ventral striatum supports selection and response during instrumental learning. Goal-directed actions and habits are controlled by the dorsal striatum (da Cunha et al. 2012; Liljeholm and O'Doherty 2012).

2.1.5 Thalamus

In the thalamus, three major cell masses are classically distinguished, namely so-called relay nuclei, limbic midline and intralaminar nuclei, and associative nuclei (Price 1995; Jones 1998; Groenewegen and Witter 2004). The relay nuclei receive sensory and motor information via ascending modality-specific pathways and project to distinct regions in the cortex. They are also referred to as *specific* nuclei. They include the lateral and medial geniculate complex (LGN, MGN), ventral posteromedial and posterolateral nuclei, a posterior nucleus, a ventral lateral, ventral anterior, and ventral medial nucleus. The *associative* nuclei consist of the mediodorsal, anterior, submedial, and lateral nuclei. They receive inputs from the somatosensory cortex and mediate these to associative cortical areas.

The *limbic* nuclei areas were originally called "nonspecific" because they have wide-ranging projections and could not be assigned a specific function. However, midline and intralaminar nuclei each receive specific afferent projections from the brainstem, and these nuclei in turn project to specific and poorly overlapping regions of the cortex and striatum (Pereira de Vasconcelos and Cassel 2015). The reticular nucleus of the thalamus is a separate complex that inhibits and modulates the thalamic relay nuclei and is under the control of topographically organized afferents from the cortex and thalamus and disseminated afferents from the basal forebrain and brainstem (Guillery and Harting 2003).

The midline nuclei and the intralaminar nuclei are spatially separated, the former along the midline and the latter within a medullary lamina. The midline nuclei consist of the rhomboid nucleus, a periventricular area, the intermediodorsal nucleus, paraventricular nucleus, nucleus reuniens, and paratenial nucleus. The intralaminar nuclei include various central and parafascicular nuclei.

■ Nucleus Reuniens and Nucleus Rhomboideus

The largest midline nucleus is the ncl. reuniens. Inputs originate from the medial PFC

(mPFC), anterior cingulate cortex, insular cortex, hippocampal formation, medial and anterior amygdala, lateral septum, and parts of the basal forebrain. Thalamic inputs from the reticular nucleus, corpus geniculatum laterale, and hypothalamic nuclei, as well as the brainstem (dopaminergic, serotonergic, and noradrenergic inputs; superior colliculus, periaqueductal gray, reticular formation, and other afferents) also reach this nucleus. Inputs to the rhomboid nucleus from the brainstem also originate from transmitter-specific nuclei and the reticular formation; from the cortex, projections originate from the mPFC and cingulate cortex as well as motor cortices and primary somatosensory cortex (Vertes et al. 2015).

Projections from the ncl. reuniens run to the rostral forebrain, especially to limbic cortices, most strongly to the mPFC. A topographically ordered projection runs to the CA1 region of the hippocampus and to the cortex surrounding it; a smaller proportion of neurons project parallel to the mPFC and to CA1. Efferents from the rhomboid nucleus also reach the ventral limbic frontal cortices, the cingulate cortex, and by extension, parts of the dorsal and ventral striatum, the lateral septum, and the core region of the ncl. accumbens. A dense projection terminates in the CA1 region of the dorsal hippocampus and in the surrounding cortex (Vertes et al. 2015).

The two aforementioned midline nuclei modulate circadian rhythms, eating behavior, and arousal states and are involved in stress and anxiety networks. According to Cassel et al. (2013), there is evidence for the involvement of the two nuclei in cognitive functions. These performances include attention, impulsivity, avoidance memory, (spatial) working memory as well as strategy switching and behavioral flexibility. These cognitive processes are influenced by the strong reciprocal connections of the two intralaminar nuclei with the medial PFC and the hippocampus. Thus, they may be a link between the mPFC and the hippocampus. Together with the rostral intralaminar nucleus, the Ncl. reuniens and Ncl. rhomboideus form a hippocampo-cortico-thalamic network for the consolidation of persistent declarative memory at the systemic level (Pereira de Vasconcelos and Cassel 2015).

Dorsally located midline nuclei such as the paraventricular and paratenial nuclei have strong reciprocal connections to a medial prefrontal network consisting of BA 25, 32, and parts of BA 14 as well as adjacent regions of BA 13 (Hsu and Price 2007). The paratenial nucleus, along with the central intermedial nucleus, is also strongly connected to BA 13 and 12, that is, the orbital and medial PFC. The medial prefrontal network, particularly the subgenual cortex, controls visceral and emotional states and is also involved in anxiety disorders. The strong connection between paraventricular nuclei and subgenual cortex provides a pathway for processing stress signals in prefrontal circuits.

The paraventricular nucleus is the only thalamic nucleus with strong projections to limbic centers such as the amygdala, BNST, and cingulate cortex, which play important roles in fear, anxiety, and reward behavior. Reciprocal connections also exist between the suprachiasmatic nucleus of the hypothalamus, as the brain's circadian pacemaker, and the paraventricular nucleus, which plays a role in arousal states via its dense innervation of orexin-containing neurons (Colavito et al. 2015). Through its connections, the paraventricular nucleus influences important limbic structures that control motivation and mood (reviewed in Hsu et al. 2014), as well as modulating functions related to chronic stress, addictive and reward behaviors through its connections to the medial PFC, ncl. accumbens and amygdala (Colavito et al. 2015). In the limbic thalamus, pain processing is modulated and emotional motor behavior is controlled (Vogt et al. 2008).

In humans, the intralaminar nuclei have been studied in their connectivities with

other brain centers using diffusion tensor imaging techniques (Jang et al. 2014). In particular, the PFC and the caudate nucleus of the basal ganglia, the primary motor and premotor cortex, the posterior parietal cortex, the globus pallidus, the basal forebrain and the hypothalamus as well as the reticular formation and the pedunculopontine nucleus in the brainstem are connected to the intralaminar nuclei; the cingulate cortex, however, has only minor connections. The connections are grouped by the authors into so-called "arousal" functions to control arousal states (PFC, brainstem, basal forebrain, and hypothalamus) and, for the PFC, also into an attentional function and into sensorimotor functions (motor cortices, parietal cortex, and basal ganglia).

2.1.6 Hypothalamus

At the base of the endbrain and diencephalon, the hypothalamus, including the preoptic region, forms the middle zone, which is bounded rostrally and medially by the anterior commissure and extends caudally to the ventral tegmental area and periaqueductal gray. The hypothalamus is a bilateral collection of nuclei divided into three longitudinal zones, periventricular, medial, and lateral. In the transverse plane, the medial zone is subdivided from rostral to caudal into a preoptic, supraoptic, tuberal, and mammillary zone (Mai et al. 2016). The hypothalamus is centrally located in the brain and connects to the cerebral cortex via the medial forebrain bundle, to the hippocampus via the fornix, and to the amygdala via the stria terminalis. The thalamus connects to the hypothalamus via the mammillo-thalamic tract, and the brainstem connects via the fasciculus longitudinalis dorsalis; the retinohypothalamic tract connects the retina and hypothalamus (Bear and Bollu 2018).

The longitudinal periventricular zone has a close relationship to the pituitary gland, and accordingly neurons that secrete "releasing factors" are found in this zone. At the rostral pole of the preoptic region, at the midline, lies the *Ncl. periventricularis*, which extends caudally along the supraoptic and tuberal regions. The periventricular ncl. controls the cardiovascular system and fluid balance and projects to the supraoptic-paraventricular nucleus complex. Attached to the periventricular nucleus laterally is a *preoptic nucleus group*. Ventral to it is the supraoptic region; within it are a *paraventricular nucleus* adjacent to the ventricle and an anterior *lateral hypothalamic nucleus*. A *supraoptic and retrochiasmatic ncl.* join ventrally.

The tuberal region contains a *juxtaparaventricular hypothalamic area*, a *dorsal hypothalamic area*, a *medial hypothalamic group*, an *arcuate ncl.*, a *lateral tuberal ncl.* and a ventrally located *median eminence*. The mammillary region consists of the dorsally located *posterior hypothalamic nucleus*, the posterior *lateral hypothalamic ncl.* and the ventrally located *supramammillary and mammillary nucleus*. Laterally, a *tuberomammillary ncl.* and a *lateral mammillary ncl.* are adjacent. Further caudally, the *retromammillary area* is adjacent (Ding et al. 2016).

In the anterior and tuberal hypothalamus, neuroendocrine neurons are located in the para- and periventricular ncl, the supraoptic ncl and the arcuate ncl. The hormones produced, except for the transmitter dopamine, are peptides such as oxytocin, vasopressin, releasing hormones (corticotropin, thyrotropin, growth hormone, gonadotropin), and somatostatin; these neurohormones are released into the bloodstream. The production of neuroendocrine hormones as well as the production of other non-neuroendocrine neuropeptides in other hypothalamic nuclei is regulated by a complex network of transcription factors (Alvarez-Bolado 2019).

In the preoptic region, temperature regulation and endocrine regulation of sexual behavior are carried out by the preoptic nucleus, while neuroendocrine and autonomic stress responses and secretion of

vasopressin and oxytocin are regulated in the hypothalamic paraventricular nucleus. The suprachiasmatic nucleus (SCN) regulates circadian rhythms, and the supraoptic nucleus secretes neurohypophyseal hormones. The tuberal region includes the arcuate nucleus, which monitors food intake, cardiovascular functions, and body adipose tissue, and the dorsomedial nucleus, with control over daily food timing, emotional stress responses, and libido. The ventromedial ncl. of the tuberal region is also involved in the control of food intake, weight loss and gain, fat digestion, and sexual behavior. In the mammillary region, the posterior nucleus organizes sympathetic nervous system responses and defensive and aggressive behaviors, while the tuberomammillary nucleus controls motivated behaviors related to food, fluid, sex, and intoxicants as well as wakefulness, and the mammillary nucleus is also active in encoding episodic memory content (Barbosa et al. 2017).

Eating Behavior

The control of the energy balance as well as the storage, use and conversion of nutrients is regulated by the *arcuate nucleus* (Joly-Amado et al. 2014). This is located close to the blood-brain barrier and controls hunger and satiety states via signals circulating in the blood (leptin, insulin, ghrelin). POMC (proopiomelanocortin) neurons of the Ncl. arcuatus reduce food intake and increase energy expenditure, while NPY/AgRP (neuropeptide Y/agouti-related protein) neurons are appetite-stimulating and anabolic. An extensive network controls eating behavior. The Ncl. arcuatus projects to other hypothalamic nuclei, the parabrachial nucleus, VTA and Ncl. solitarius in the brainstem. The latter are connected to limbic forebrain structures such as the ncl. accumbens, which acts as a guardian for the hedonic, or pleasure, value of food (Ferrario et al. 2016). The ncl. accumbens in turn projects to the lateral hypothalamus, which translates food signal-induced motivation into eating behavior; however, it also appears to be critical for the acquisition of signal-food associations and the retrieval of corresponding memory (Petrovich 2018). The PFC processes cognitive-emotional aspects of food signals for decision making, and dorsal parts of the basal ganglia control motor eating behavior. The amygdala and insular cortex integrate homeostatic, cognitive, and visceral inputs to modulate eating behavior (Andermann and Lowell 2017; Sweeney and Yang 2017). This network controls metabolic rate, endocrine hormone release, and ultimately food intake via the autonomic nervous system, and the hypothalamus also interfaces with motivational and cognitive aspects of eating behavior.

Sleep-Wake Rhythm

The lateral hypothalamus regulates the sleep-wake rhythm via neuron populations that produce the peptide orexin/hypocretin (Ox) or the neuropeptide melanin-concentrating hormone (MCH). Ox neurons are active during wakefulness and cause a rapid shift from non-REM (*rapid eye movement*) to REM sleep or from REM sleep to wakefulness during sleep. Loss of Ox neurons (normal is about 70,000 neurons in humans) produces narcolepsy, an excessive sleepiness. Ox neurons have extensive projections in the brain and spinal cord and activate, for example, the dopaminergic VTA, the noradrenergic locus coeruleus, and histaminergic neurons of the tuberomammillary nucleus. Activation of brainstem and basal forebrain cholinergic neurons are also critical for maintaining wakefulness (Schwartz and Kilduff 2015). MCH neurons are also involved in the regulation of eating behavior and increase the duration of REM sleep. MCH neurons also project to all parts of the brain; they appear to inhibit "waking" brain structures. Descending connections affect the generators of REM sleep located in the pons. Together with GABAergic neurons of the preoptic region and brainstem structures, MCH neurons regulate sleep.

The SCN is a circadian zeitgeber (timer) for many physiological and biochemical factors and also for the 24-h sleep-wake rhythm. The sleep-wake rhythm is organized indirectly by the SCN via multiple pathways (Fuller et al. 2006); these reach the lateral hypothalamus via an indirect projection to the dorsomedial hypothalamic nucleus. GABAergic afferents to the lateral hypothalamus come from the preoptic nucleus, lateral septum, basal forebrain, and ncl. accumbens, whereas the ventromedial hypothalamus and PFC act glutamatergically on the lateral hypothalamus. These inputs can have depolarizing or hyperpolarizing effects on Ox and MCH neurons, depending on the synaptic connection (Yamashita and Yamanaka 2017). Functional connectivity between the hypothalamic structures for food and eating behavior and sleep and wakefulness rhythms is also evident in the fact that, for example, leptin, a hormone for satiety signaling, can inhibit Ox neurons, while ghrelin, a hormone signaling hunger, activates Ox neurons.

2.1.7 Limbic Brainstem

In this section, we describe those structures of the limbic brainstem that have important connections with the limbic brain structures already shown (◘ Fig. 2.3).

▪ Periaqueductal Gray (Central Gray)

The periaqueductal gray (PAG) is located periventricularly and extends rostrocaudally from the third to the fourth ventricle in the pons. It is divided into a dorsomedial, dorsolateral, lateral, and ventrolateral longitudinal column (Bandler and Shipley 1994). Like almost all periventricularly located structures, the PAG is characterized by the presence of numerous peptidergic systems; these include fibers and/or receptors for opioids, substance P, neurotensin, somatostatin, neurophysin, oxytocin, vasopressin, VIP, CGRP, neuropeptide Y, and other peptides (reviewed in Carrive and Morgan 2012).

Afferents to the PAG originate from all regions of the PFC except the medial anterior part of the OFC, from the ACC, and from the insular cortex. The projections are topographically ordered; those from the medial PFC run to the dorsolateral column, those from the posterior OFC and anterior insular cortex to the ventrolateral column, and those from the ACC to the lateral, ventrolateral, and dorsomedial columns (An et al. 1998). According to an imaging study in humans, the ventrolateral region is predominantly connected to pain-modulating centers such as the ACC, and the lateral and dorsolateral regions are connected to executive centers such as the PFC and striatum (Coulombe et al. 2016), The network consisting of the PFC and PAG is consequently differentially organized for processing the various motivational and emotional aspects of behavior. Other strong connections come from amygdalar, limbic-thalamic, and hypothalamic nuclei; the latter are predominantly reciprocally connected to the PAG. Projections from the brainstem originate from sensory midbrain structures, from the dopaminergic, noradrenergic, and serotonergic nuclei, the ncl. solitarius, and the parabrachial nucleus. Inputs from the trigeminal nucleus and the dorsal horn of the spinal cord are somatotopically ordered, i.e., projections from the trigeminal system terminate in the rostral PAG, those from the cervical spinal cord in the intermediate and the lumbar spinal cord in the caudal PAG. This arrangement reflects the importance of processing visceral, somatic, and nociceptive inputs in the PAG (Carrive and Morgan 2012).

The efferents of the PAG do not run directly to the cortex, but terminate in the limbic thalamic nuclei, which serve as a relay station to the medial PFC, amygdala, and basal ganglia (Hsu and Price 2009). The reticular ncl. of the thalamus also receives inputs through which the influence of the

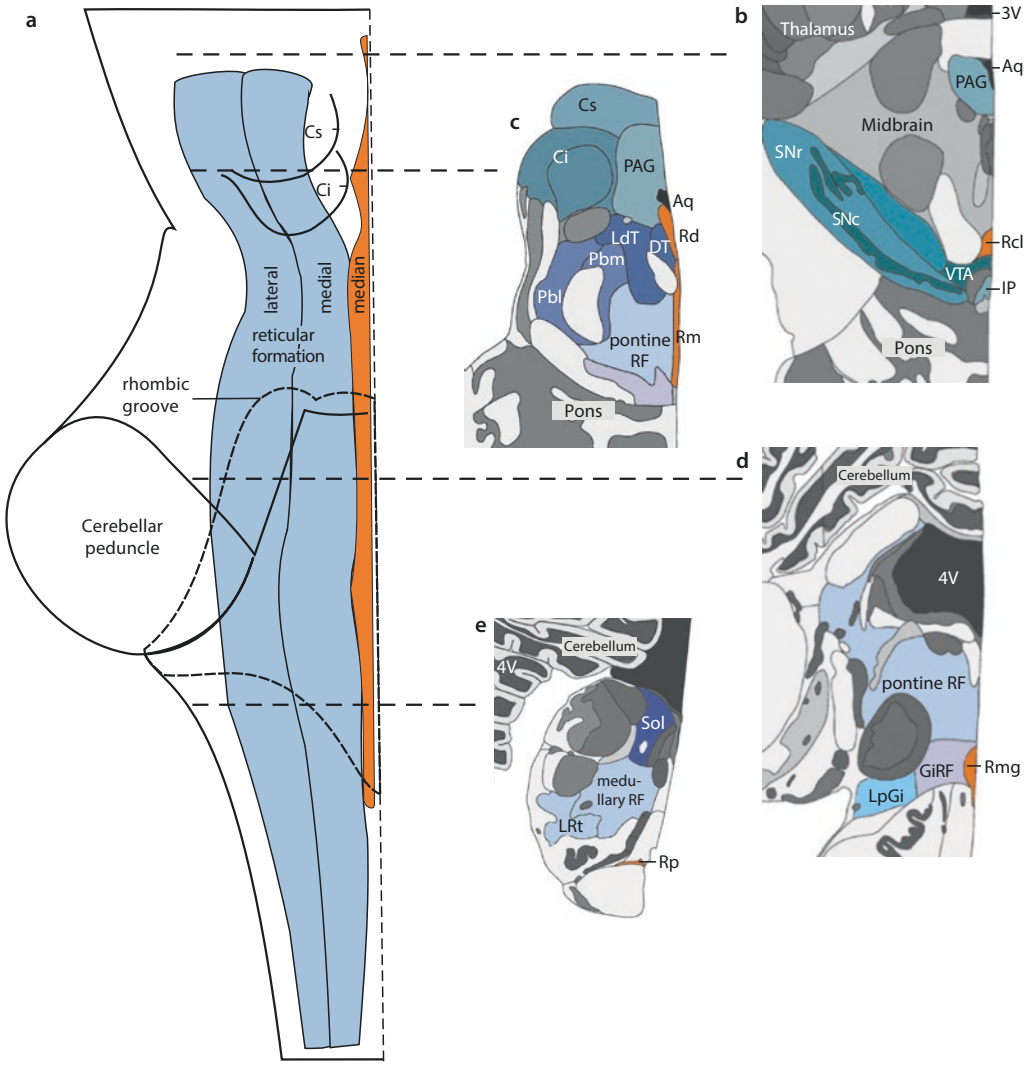

Fig. 2.3 **a** Schematic dorsal view of the left hemisphere of the brainstem. The overlying cerebellum is not shown. The midline is on the right; top is rostral. **b–e** Semi-schematic cross-sections through the brainstem from rostral to caudal show the gray and white matter. Major nuclei of the limbic brainstem are colored (modified from Ding et al. 2016). The serotonergic raphe nuclei (Rcl caudal linear raphe nucleus, Rd raphe dorsalis, Rm raphe medianis, Rmg raphe magnus, Rp raphe pallidus; orange) are located in the median reticular formation. Rostrally in the basal midbrain are dopaminergic nuclei (SNc substantia nigra pars compacta, VTA ventral tegmental area). 3V/4V third/fourth ventricle, Aq aqueduct, Cs/Ci superior/inferior colliculus, GiRF gigantocellular reticular formation, IP interpeduncular nucleus, LdT/DT laterodorsal and dorsal tegmental nuclei, LpGi lateral paragigantocellular nucleus, LRt lateral reticular nucleus, PAG periaqueductal gray, Pbm/Pbl medial and lateral parabrachial nucleus, RF reticular formation, SNr substantia nigra pars reticulata, Sol nucleus solitarius

thalamic nuclei on the cortex can be modulated. The hypothalamus is an important input structure for the efferents of the PAG as are the reticular formation, the transmitter-specific brainstem nuclei, numerous premotor nucleus areas, and also the spinal cord (Carrive and Morgan 2012).

Due to its connections to the emotion-related forebrain system and to vegetative centers, the PAG is a significant integration point for an ascending pain/body feeling system as well as for a descending limbic-emotional motor system. Overall, the PAG is involved in pain modulation, cardiovascular and other autonomic processes, emotional affective behavior including defensive and panic behavior as well as sexual behavior, emotional vocalization and micturition.

Substantia Nigra and Ventral Tegmental Area

The largest accumulation of dopaminergic neurons is found in the substantia nigra (SN), the ventral tegmental area (VTA), and the retrorubral field. In humans, approximately 600,000 dopaminergic neurons are found in the midbrain, with smaller numbers in the PAG, zona incerta, hypothalamus, olfactory bulb, and retina (group A9–A17; Dahlström and Fuxe 1964). The SN is located ventrally in the midbrain and has an elongated laminar architecture containing GABAergic neurons in a ventral row (pars reticulata) and overlying dopaminergic neurons in a ventral and dorsal row (pars compacta) (McRitchie et al. 1995). The dopaminergic neurons possess the namesake black pigment neuromelanin (Double et al. 2008). The VTA is located in the reticular formation of the midbrain, dorsal and medial to the substantia nigra in the human brain. The VTA is divided into ventromedial and dorsolateral zones; the former zone merges with the retrorubal field. The neurons of the VTA are less dense and smaller than those of the substantia nigra; 50% of the neurons of the VTA have neuromelanin.

Dopaminergic connections to the caudate ncl. and/or putamen originate from dorsal and ventral SN neurons. A mesostriatal projection originates from dorsolateral neurons of the VTA and from the retrorubral field. The latter also modulates the interaction between midbrain dopaminergic neurons via dopamine. The strong mesolimbic projection of the VTA to the Ncl. accumbens, amygdala, lateral hypothalamus and subgenual limbic PFC as well as to the dentate gyrus of the hippocampus is 75% dopaminergic and 25% GABAergic in humans; a smaller projection also extends to the septum, hippocampus and entorhinal cortex. The mesocortical projection of the VTA is 50% dopaminergic and 50% GABAergic and in primates extends to the dorsolateral PFC, motor, parietal, and temporal cortices in addition to all limbic cortices (Berger et al. 1991).

These compounds are involved in the regulation of a variety of motor and cognitive functions and promote learning and reward mechanisms. Dopamine modulates the membrane states of neurons via different receptor types (▶ Chap. 3). The function of the nigrostriatal projection is primarily movement control, while that of the mesolimbic/cortical projection is the control of emotional behavior and motivation (Halliday et al. 2012). Reinforcement learning, reward seeking, working memory performance, addictive behavior, action drive and motivation as well as hippocampal plasticity in learning processes are processes in which the transmitter dopamine plays an important role. Electrophysiological studies in monkeys show that dopaminergic neurons encode both positive and negative reward expectations (Satoh et al. 2003). Accordingly, they are active not only during reward and positive motivation, but also in non-reward situations such as aversive and alarming events (Bromberg-Martin et al. 2010).

Raphe Nuclei and Locus Coeruleus

The raphe nuclei are part of the median reticular formation and extend bilaterally along the midline of the tegmentum from the rostral midbrain to caudally just before the junction of the pyramidal tract. The raphe nuclei contain many serotonin (5-HT)-containing neurons. In the primate brain, some of the serotonergic neurons are also located laterally from the median reticular formation. Serotonin is synthesized by approximately 80% of neurons in the rostrally located ncl. raphe dorsalis and up to 10–20% of neurons in the caudal medullary raphe nuclei. The projections of the raphe nuclei have serotonergic and non-serotonergic components (GABA, glutamate, other monoamines such as dopamine). In neurons of the dorsal raphe nucleus, colocalizations of serotonin with substance P, the neuropeptide CRF or galanin are found. The serotonergic nuclei are divided into a rostral (caudal linear ncl, raphe dorsalis, raphe medianus, oral pontine ncl, supralemniscal ncl) and a caudal group (raphe magnus, raphe obscurus, raphe pallidus and neurons of the medullary reticular formation). The dorsal raphe nucleus contains the largest number, approximately 170,000 serotonergic neurons.

The connections of the rostral raphe nucleus group are wide ranging and predominantly serotonergic. The dorsal and median raphe nuclei project to the cortex, striatum, amygdala, BNST, lateral septum, hippocampus, entorhinal cortex, thalamus, SN, and various brainstem nuclei. The median raphe nucleus influences the basal ganglia and hippocampus via direct projections as well as indirect projections via the SN, septum, and mammillary nuclei. The caudal raphe nucleus projects to the caudal brainstem and spinal cord. Afferents to the dorsal and median raphe nuclei originate from the medial PFC, central amygdala, medial septum, NDB, ventral pallidum, lateral habenula, hypothalamic regions, from the PAG and other brainstem nuclei, and from the reticular formation (Hornung 2012).

Raphe nuclei and serotonergic neurons are involved in a variety of functions. These include synaptic maturation and migration of neurons in early brain development, modulation of sleep-wake rhythm, central modulation of pain stimuli along with the PAG, control of motor activity and emotional behavior when processing appetitive or aversive information (Hornung 2012; Hayashi et al. 2015; Luo et al. 2016). Pain-relieving effects are produced serotonergically (tonically activated during stress) or non-serotonergically (during non-stress states) depending on the stress state (Mitchell et al. 1998). The serotonergic system is implicated in affective disorders such as depression, in coping with stress, and also in drug addiction; important control of socio-affective behavior occurs through the ventromedial PFC and the serotonergic system, in part via direct circuits between them (Challis and Berton 2015). The axis between lateral habenula and rostral raphe nuclei is also affected in depression; an important factor in the pathophysiology appears to be impaired serotonin-dependent modulation with hyperactivation of the lateral habenula (Metzger et al. 2017). In general, the synaptic effects in the different circuits are complex due to the multitude of different serotonin receptors (5-HT) and partly also occur via the modulation of other transmitters.

A complex chain of excitation and inhibition involving serotonin is also found in stress processing. For example, in the presence of stressors, corticotropin release factors generated in the hypothalamus can inhibit or excite serotonergic neurons in the raphe nucleus, depending on the activated receptor type CRF1 or CRF2, which then excites or inhibits glutamatergic neurons in the medial PFC via 5-HT1A receptors. The mPFC neurons project back to the raphe nucleus and excite or inhibit GABAergic interneurons there. These in turn excite or inhibit serotonergic neurons, which in turn project to the basolateral amygdala and inhibit or excite GABAergic neurons there.

Via the amygdala, active or passive behaviors to cope with stress can be initiated in this way (Puglisi-Allegra and Andolina 2015). The dorsal serotonergic raphe nucleus is also instrumental in the suppression or execution of aggressive behavior via similarly complex neuronal interactions (Miczek et al. 2015).

Locus Coeruleus

The locus coeruleus (LC, Latin "blue place") is a highly pigmented nucleus in the dorsal wall of the rostral pons in the lateral floor of the fourth ventricle. It consists predominantly of monoaminergic neurons that synthesize the neurotransmitter/neuromodulator norepinephrine. Polymerization of norepinephrine leads to the formation of neuromelanin, which causes the bluish coloration. This nucleus represents the main source of noradrenergic projections to the other parts of the brain. The LC is involved with attentional and perceptual processing, memory performance, and motivation.

Afferents to the LC originate from the dorsolateral and dorsomedial PFC, the ACC, and the amygdala; the latter terminate on LC neurons expressing corticotropin and thyrotropin-secreting hormones. Hypocretin- and orexin-containing neurons of the posterior hypothalamus innervate the LC, as do neurons of the nociception-processing lamina of the spinal cord and processes of vasopressin-, somatostatin-, and neuropeptide Y-containing neurons. In part, the latter originate from the central amygdala. Serotonin, angiotensin, acetylcholine, and dopamine receptors are located on LC neurons, so it can be assumed that a wide range of subcortical and cortical afferents regulate LC activity, and modulations occur in part via feedback loops (Counts and Mufson 2012). In addition to noradrenaline, LC neurons express a number of neuropeptides such as neuropeptide Y, calcitonin gene-related peptides, cholecystokinin and somatostatin.

Approximately 45,000 neurons in the rostral LC have widely branching axonal projections to the forebrain (Counts and Mufson 2012). Projections run across two axonal systems. A dorsal tegmental bundle extends to the forebrain and a smaller portion of it to local brainstem structures and the spinal cord. Via a rostral periventricular bundle, ascending projections run to the rostral diencephalon, and descending tracts run to sensory-recipient brainstem structures such as the ncl. solitarius. Telencephalic projections of the LC reach the frontal, dorsal, and lateral cortex. The PFC and parietal cortex are moderately innervated, while somatosensory and motor cortices have a dense network of noradrenergic fibers. In the subcortical telencephalon, there are projections to the amygdala, entorhinal cortex, hippocampus, septum, NDB and Ncl. basalis Meynert. Norepinephrine can be released via synaptic contacts as well as extrasynaptically via volume transmission (Aoki et al. 1998). Receptors for norepinephrine (and simultaneously for epinephrine) form different classes of G protein-coupled receptors (► Chap. 3).

LC neurons exhibit a tonic and a phasic mode of activity that depend on an individual's activity state. Phasic activation is driven by sensory inputs and is important for alertness and efficient processing of salient information. Accordingly, the LC is considered a monitor for important events that require immediate attention (Berridge and Waterhouse 2003; Sara 2009). In this regard, the LC modulates the formation and experience-dependent changes in memory through cortical and subcortical attentional and memory circuits. The LC also plays an important role in stress and emotional memory. An intact emotional memory requires the LC to interact with the amygdala and hippocampus. Normal aging processes include a loss of noradrenergic cells with a rostrocaudal gradient and averages 30–50% in 70-year-olds. The decreased number of LC neurons with forebrain projection may also have an explanation for decreased attention and memory performance in old

age. In Alzheimer's disease, the loss is up to 80% of LC neurons. The reduction of LC neurons is associated with the occurrence of increased cortical plaque formation and neurofibrillary tangles; these phenomena correlate with the onset and progression of AD better than the loss of cholinergic neurons (Förstl et al. 1994; Zarow et al. 2003).

The Reticular Formation

The reticular formation (RF) is an extensive neuronal network along the rostrocaudal axis from the midbrain to the caudal medulla oblongata. It forms the inner core of the brainstem without conspicuous cytoarchitectonic boundaries; clearly delineated nuclei lie embedded within it. A median zone containing the raphe nuclei is distinguished from a medial large-cell and a lateral small-cell zone (Nieuwenhuys et al. 1991, 2008).

In the *medial RF*, due to the polarity of the cell bodies along a dorsomedial-ventrolateral axis and their main dendrites, an intermediate reticular zone is delineated by gigantocellular and parvicellular reticular nuclei with neurons of different orientations. The intermediate reticular zone contains catecholaminergic cells that have sympathetic cardiovascular and cardiorespiratory functions and control vasopressin release. Neuropeptide Y- and substance P-containing neurons as well as serotonergic neurons are present in this zone. The intermediate zone has ascending connections to the parabrachial region and descending connections to the ncl. solitarius and motor neurons of the phrenic nerve in the cervical medulla (Paxinos et al. 2012).

The gigantocellular ncl. and paragigantocellular ncl. of the medial RF contain serotonergic neurons that are larger than those in the intermediate reticular zone. They are involved in the inhibition of baroreflexes triggered by noxious stimuli in the nociceptive system. Adrenergic and noradrenergic neurons are also located in this zone. Unlike in rats or monkeys, no giant cells are found in the human gigantocellular nucleus. Descending projections of gigantocellular and paragigantocellular subnuclei to the spinal cord control structures of the autonomic system such as parasympathetic nuclei and neurons involved in the organization of reflexes of the pelvic floor (Hermann et al. 2003).

In the *lateral RF* is the parvicellular reticular nucleus with different subnuclei whose neurons are differentially immunoreactive for acetylcholine esterase (AChE). One subnucleus of this reticular nucleus has autonomic respiratory functions, as does the caudal medullary reticular nucleus. The parvocellular part with small compact cells and dense AChE reactivity contains dense neurokinin-containing fibers (Coveñas et al. 2003). In the caudal region lies the medullary reticular nucleus with a dorsal and ventral part, respectively. The dorsal medullary reticular nucleus is activated in response to noxious stimuli and is immunoreactive for opioids, neuropeptides, and monaminergic, catecholaminergic, and serotonergic transmitters/modulators. It is an important part of the pain control system and integrates excitatory and inhibitory inputs in nociceptive processing (Lima and Almeida 2002).

Inputs to the RF originate from many regions of the central nervous system. Cortical inputs originate from premotor, supplementary motor, and primary motor areas and innervate the RF ipsi- and contralaterally (Fregosi et al. 2017). Dorsal medial prefrontal areas and parietal areas of the cortex project to the pontine RF, and a projection from the central amygdala runs to the lateral RF (Price and Amaral 1981; Leichnetz et al. 1984). The cerebellum as well as the ascending spinoreticular tract from the spinal cord project to the RF.

The RF gives rise to descending tracts to the spinal cord and ascending tracts to brainstem and midbrain structures, the hypothalamus, the limbic thalamus, and the striatum (Angeles Fernández-Gil et al. 2010). The *ascending reticular activating sys-*

tem (ARAS) originates in the RF; major components of the ARAS consist of cholinergic nuclei in the brainstem and basal forebrain, noradrenergic nuclei, especially of the locus coeruleus, histaminergic and hypocretinergic hypothalamic projections, and dopaminergic and serotonergic projections from the brainstem and RF (Hobson and Pace-Schott 2002). The ARAS proceeds in a dorsal pathway via the limbic thalamic nuclei (intralaminar and midline nuclei and reticular thalamic nucleus) and in a ventral pathway via cholinergic nuclei in the basal forebrain. Via the ARAS originating from the thalamus, various projections extend to the ventromedial, dorso- and ventrolateral PFC, the OFC, the premotor cortex, the primary motor and somatosensory cortex, and the posterior parietal cortex. The most important function of the ARAS is the regulation of states of consciousness and wakefulness (Paus 2000; Jang and Kwak 2017); the ARAS also regulates related functions such as mood, motivation, attention, learning, memory, movement, and autonomic functions (Zeman and Coebergh 2013).

2.2 Limbic Cortical Areas

The orbitofrontal, cingulate and insular cortex are limbic structures in the frontal brain. They are named below according to the nomenclature of Ding et al. (2016). This study uses imaging, high-resolution cytoarchitectonic, and chemoarchitectonic data mapped to each other in a human brain. Brodmann's (1909) nomenclature of cortical areas is used as the primary reference and modified when necessary using nomenclature from a number of other studies of the human brain.

The entire prefrontal cortex (PFC) is divided into a frontopolar, dorsolateral prefrontal, ventrolateral prefrontal, orbitofrontal and a posterior frontal cortex. The frontopolar cortex (Brodmann area; BA 10) has a medial, lateral, and orbital area. The dorsolateral PFC has a rostral (BA 9), caudal (BA 8), intermediate (BA 9, 46), and rostroventral portion (BA 46). The ventrolateral PFC consists of a rostral (BA 45) and a caudal (BA 44) portion. The posterior frontal cortex is the motor cortex and contains the primary motor area (BA 4, also called area MI or area FA), the premotor cortex (BA 6 or area FB), which has laterodorsal, lateroventral, and medial (area MII) subdivisions, and a transitional area of premotor to cingulate cortex BA 6/32.

2.2.1 Orbitofrontal Cortex

According to Ding et al. (2016), the human orbitofrontal cortex (OFC) is divided into a medial, intermediate, and lateral area. The medial OFC (BA 14) has a rostral and caudal portion, while the intermediate OFC has a rostral, medial, and lateral portion (BA 11) and a caudal portion (BA 13). The lateral OFC (BA 12, 47) again has a medial and a lateral subdivision. The majority of the OFC connectivity studies presented here were conducted in macaque monkeys, whose OFC is divided into a frontopolar region, BA 10, and a lateral and medial OFC with different proportions of BA 11–14 (for a comparison, see Henssen et al. 2016).

The OFC has strong bidirectional connections within the cortex, especially with the other limbic cortical areas. Within the PFC, orbital, lateral, and medial prefrontal areas are intensely connected (Barbas and Pandya 1989; Carmichael and Price 1996). Limbic cortical areas connected to the OFC include the insular cortex, temporopolar cortex, and the medial-temporal hippocampal formation (Morecraft et al. 1992; Barbas 1993). This is indirectly connected to the OFC via the entorhinal and perirhinal cortex and the posteriorly located parahippocampal areas TF and TH and directly via the hippocampus proper (CA1, subiculum complex) (Cavada et al. 2000). The entorhinal cortex and the parahippocampal region,

i.e., the temporal pole (TP), the perirhinal cortex, and the posterior parahippocampal cortex, project to the caudal orbitofrontal part of BA 12 and to the caudal half of BA 13 of the OFC (Muñoz and Insausti 2005).

The OFC receives direct olfactory input via the primary olfactory cortex, and indirect input via the anterior insula and entorhinal cortex. Gustatory information enters the OFC via the orbitofrontal operculum and insula (Insausti et al. 1987; Morecraft et al. 1992). These areas receive gustatory and visceral information via thalamic relay nuclei (Carmichael and Price 1995b). Somatosensory inputs originate from primary areas BA1 and 2 and secondary S2 cortex as well as from the insula and parts of parietal area BA 7, where somatosensory inputs from the face and hand are processed. Axons enter the OFC from primary auditory areas and especially from secondary areas, the auditory associative areas and the superior-temporal polysensory area STP (Hackett et al. 1999).

Projections of the OFC run to the anterior temporal lobe (ATL), which includes the temporal polar cortex, the rostral part of the perirhinal cortex (BA 35 and 36), area TE to the tip of the superior temporal sulcus including the anterior border of the superior temporal gyrus. Area BA 13 of the OFC projects to the entire ATL with a weaker projection to BA 35 and 36, and the temporal polar cortex receives a stronger projection from BA 11 (Markowitsch et al. 1985; Moran et al. 1987; Mohedano-Moriano et al. 2015). The influence of the OFC on the ATL is direct, whereas the dorsolateral and ventrolateral PFC appear to influence the ATL via indirect pathways (Mohedano-Moriano et al. 2015).

Subcortical afferents of the OFC originate from the nucleus basalis Meynert, which innervates the OFC as well as other cortical regions in a cholinergic manner (Mesulam et al. 1983). Limbic cortices with projections to the Ncl. basalis Meynert such as the insular cortex or parahippocampal cortices are connected to the OFC (Mesulam and Mufson 1984; Öngür et al. 1998). Intermediate dopaminergic innervation of the OFC originates primarily from the VTA; noradrenergic bilateral innervation also reaches it from the locus coeruleus.

The OFC, as well as the entire medial prefrontal region, is strongly connected to the amygdala. The basolateral, cortical, medial groups, and periamygdaloid cortex project to the OFC, and these projections originate primarily from numerous neurons in the basal and accessory basal nuclei (Porrino et al. 1981; Amaral and Price 1984; Barbas and De Olmos 1990). The OFC projects back to the aforementioned nuclei of the amygdala and also to additional nuclei, such as the paralaminar and central nuclei of the amygdala (Cavada et al. 2000). In particular, the posterior OFC exhibits strong efferents to the amygdala (Ghashghaei et al. 2007), which in turn has a back-projection that excites the posterior OFC. The OFC and amygdala both project to the mediodorsal nucleus of the thalamus. The latter nucleus in turn innervates the posterior OFC (Aggleton and Mishkin 1984; McFarland and Haber 2002; Timbie and Barbas 2015). This tripartite network consisting of the OFC, amygdala, and mediodorsal thalamus can provide information about emotionally significant events and influence higher-order cortex areas that integrate emotional cognitive processes for decision-making and flexible behavior.

Dense projections of the OFC reach the caudate ncl. and putamen, especially ventromedial areas, and extend along a considerable longitudinal extent to the head, body, and tail of the caudate ncl. (Selemon and Goldman-Rakic 1985). The OFC projections are topographically ordered in different areas. Axons of BA 13 project to the central ventral striatum, whereas those of BA 13a, 13b, and 14 terminate primarily in the medial ventral striatum, those of BA 12 in the nuclear region of the ncl. accumbens, and those of BA 11 in both of the

above structures. In contrast, projections to the shell region of the ncl. accumbens originate predominantly in the anterior cingulate cortex (BA 32, 25; Haber et al. 1995). Projections from the OFC, as well as those from the other prefrontal areas also examined, appear to terminate predominantly in the striosomes. The topographic order of the projections is also maintained in the projections of the striatal areas to the medial and central globus pallidus, whereas the striatal projection to the substantia nigra is not topographically ordered.

Projections of the OFC to the thalamus, mostly reciprocal, reach the ipsilateral midline nuclei and intralaminar nuclei and, as already described, the mediodorsal nucleus of the medial nucleus group; but also parts of the pulvinar. The OFC has connections to autonomic centers in the hypothalamus and to the lateral and medial preoptic areas, as well as to the zona incerta and brainstem, here especially to the periaqueductal gray of the midbrain, the dopaminergic nuclei, and the interpeduncular nucleus (An et al. 1998; Rempel-Clower and Barbas 1998). The frontal cortex, like the amygdala, can exert rapid influence on autonomic systems responsible for the execution and expression of emotions through these connections (Barbas et al. 2003).

The OFC, with this multitude of connections to other limbic centers and to memory-processing and sensory structures, appears to form a special node where relevant past and present experiences, including their affective and social meanings, are collected and monitored. The OFC occupies an important role in the personality of individuals in the integration of complex memory contents and social adaptations. It involves comparing and processing personal experiences and intentions with contextual external stimuli to produce adapted and rational behavior. In general, the OFC is important in selecting appropriate behavior for the current context (Cavada et al. 2000; Wilkenheiser and Schoenbaum 2016).

The OFC integrates current information to make predictions or estimates about future outcomes. According to the group around Schoenbaum (Schoenbaum and Esber 2010; Schoenbaum et al. 2011), an important significance of the function of the OFC is that it is primarily important for outcome-guided and less for value-guided behavior. According to this view, in collaboration with the amygdala and hippocampus (and other brain structures), the OFC forms an extended network for processing past and present associations and forms new complex multidimensional associations specific to the current state. The amygdala updates information about signal-outcome conditions and accesses the associations of the OFC for use in future learning episodes (Sharpe and Schoenbaum 2016). The hippocampus, in turn, is a highly flexible system for rapidly grasping complex (directly experienced or deduced) features of the environment and encoding important information in such a way that higher-level spatial and relational information is retained. The hippocampus and OFC process parallel, but interactive, cognitive maps that capture the complex relationships between signals, actions, outcomes, and other environmental features. While the hippocampus provides abstract associations, information processing in the OFC concerns the direct biological relevance of events and objects (Wilkenheiser and Schoenbaum 2016).

The OFC, insula, and ACC, as well as subcortical regions such as the ncl. accumbens, ventral pallidum, and amygdala, form the brain's reward network. The anterior OFC seems to particularly register the feeling of subjective pleasure in different contexts (Gottfried et al. 2003; Grabenhorst and Rolls 2011; Rolls 2012) and is also active during sexual pleasure, the euphoric effects of drugs or music. An increase in the feeling of pleasure is regulated by opioid or orexin receptors in the hotspots of the OFC (Castro et al. 2014).

Koelsch et al. (2015) distinguish a total of four affective systems, namely a brainstem, a diencephalon, a hippocampus and an OFC-centered affective system. The OFC holds a number of functions, such as the integration of sensory information with stored memory content, decision-making, and preferences, which serve to motivate or inhibit a particular behavior. The OFC ensures that "somatic" markers in the sense of Damasio (1994), i.e. physical accompanying states, are used in this process. It modulates endocrine and vegetative processes in the hypothalamus and brainstem that contribute to the subjective feeling. Furthermore, the OFC flexibly processes rewards and punishments and generates "moral" affects based on representations of social norms and conventions. According to the authors' theory, the functions of the OFC in this context occur rapidly, automatically, and unconsciously. In contrast, the specific role of the OFC in states of consciousness is unclear. EEG findings in risk decision-making in humans show that OFC neurons encode a higher reward probability after 400–600 ms in response to cue stimuli, the OFC 1000–2000 ms after the decision is made produces a risk signal in the reward expectancy phase, and an evaluation signal 0–800 ms after the reward (Li et al. 2016). Conscious information processing is also likely to occur in this time window.

Lesion studies in macaque monkeys revealed that the lateral and medial OFC play different roles in choice behavior in uncertain and ambiguous situations, respectively. While the medial OFC tends to focus attention on the relevant decision variables for achieving a goal, the lateral OFC is required for rapid learning in fluctuating environments by associating a particular outcome with a particular decision (Walton et al. 2011). People with damage to the orbitofrontal and ventromedial cortex show weaknesses in decision making toward food, objects, object features, landscapes, or living things. Damage in the OFC appears to impair the accuracy of affective, value-based decision-making, without a large effect in the reaction time of a decision—nor impulsive action (Fellows 2011).

The functions of the OFC proposed by researchers were evaluated by Stalnaker et al. (2015), taking into account competing ideas and contradictory findings. Accordingly, response suppression, flexible associative coding, somatic markers for emotional states as well as value-based signal processing are *not* adequate explanations of the function of the OFC as a sole process. However, some of these functions such as response suppression, value calculation, error indication, or even their assignment to specific causes may be necessary in the formation of a so-called cognitive map in the current decision situation. A cognitive map contains the essential features of the current information and labels the current task state (Wilson et al. 2014). This shows that functions of the OFC clearly overlap with those of other limbic cortical areas.

2.2.2 Cingulate Cortex

The cingulate cortex is located in the medial wall of the cerebral hemisphere adjacent to the corpus callosum and is divided into anterior, middle, and posterior regions. These are divided into rostral and caudal as well as dorsal and ventral subregions.

In the *anterior* cingulate *cortex* (ACC), ventrodorsal BA 24 and a subcallosal or subgenual part BA 25 (lying below the corpus callosum or its "knee" or "genu") and dorsorostral BA 32 are distinguished. A ventral limbic series occupies the surface of the cingulate gyrus and contains BA 24a and 24b, subcallosal BA 25, and callosal part BA 33. A dorsal paralimbic row lies deep in the cingulate sulcus and corresponds to BA 24c and 32.

The *middle cingulate cortex* (MCC) is divided into an anterior part, again with a dorsal anterior (BA 32' and 24c'), a ventral

anterior (BA 24a' and 24b') and a callosal part (BA 33'). The posterior portion of the MCC includes BA 24c' and 24d located in the cingulate sulcus (Vogt et al. 2006; Vogt 2016). The cingulate motor areas (CMA) include rostral BA 24c, dorsal BA 6c, and ventral BA 23c.

The *posterior cingulate cortex* (PCC) includes BA 23a-c, the dorsally located BA 31. Ventral to these areas and closely associated with them is the retrosplenial cortex (BA 29 and 30; Vogt and Palomero-Gallagher 2012).

Inputs of the Cingulate Cortex

The anterior cingulate areas BA 25 and 24 are reciprocally connected and also receive inputs from the PCC. Both are innervated by the dorsolateral PFC and OFC and receive projections from the amygdala, hippocampus, and superior temporal sulcus. While BA 25 is also innervated by the superior temporal gyrus, BA 24 receives inputs from the temporal pole, parahippocampal areas, and the insula. Posterior BA 23 is connected to BA 24, is innervated by the dorsolateral PFC and OFC like the latter, but also receives inputs from the parietal and occipital cortex. The temporal inputs also originate from the superior temporal sulcus and parahippocampal areas (Vogt and Pandya 1987).

Outputs of the Cingulate Cortex

The most rostrally located BA 32 projects to the lateral PFC, the middle OFC, and the rostral part of the superior temporal gyrus. The anteriorly located area BA 24 innervates premotor cortical regions, the OFC, the rostral inferior parietal lobe, the anterior insula, the perirhinal cortex and the basolateral amygdala. The posteriorly located area BA 23 sends efferents to the dorsal PFC, rostral orbital cortex, parieto-temporal cortex (posterior inferior parietal lobe and superior temporal sulcus), and parahippocampal areas (Pandya et al. 1981). Medial and rostral areas 25 and 32 of the ACC send strong projections to all areas of the hypothalamus (Öngür et al. 1998).

BA 24c (also referred to as M3 in monkeys), located rostrally in the ACC, and BA23c (M4), located ventrally in the PCC, are characterized by strongly different patterns of connections from thalamic and intracortical inputs (Hatanaka et al. 2003). The efferents of both areas are equally somatotopically ordered to the primary and supplementary motor cortex (M1 and M2 in the macaque brain). Neurons located anteriorly in BA 24c and in BA 23c project to the face area in M1 and M2, neurons located in the middle part send their axons to the anterior limb area, and posteriorly located neurons to the posterior limb area (Morecraft and Van Hoesen 1993). Consequently, frontal associative and limbic areas have direct access to the part of the corticospinal projection arising from the middle cingulate (motor) cortex via the cingulate cortex. Rostral regions of BA 23c and 24c project not only to the face area in M1 and M2, but also parallel to the facial nucleus in the pons. BA 23c and 24c each contain their own face representations and directly influence facial expressions via efferents to cortical and subcortical centers (Morecraft et al. 1996). The efferents of the cingulate motor cortex partly extend into the cervical medulla (Dum and Strick 1996), and at the same time these areas receive information from the spinothalamic tract via thalamic relay nuclei (Dum et al. 2009), so that these areas are involved not only in sensorimotor functions but also in pain processing.

The basolateral group and cortical nucleus of the amygdala project to BA 24c (M3). The medial temporal lobe influences facial expressions and, to a lesser extent, arm movements through this amygdalar pathway to the cingulate cortex (Morecraft et al. 2007). The primary motor cortex, ventral lateral premotor cortex, and supplementary motor area control *voluntary* facial expressions, while the cingulate cortical areas regulate *involuntary* emotional facial

expressions due to their connection with limbic brain structures (Müri 2016).

Kunishio and Haber (1994) examined the projections of the cingulate cortex to the basal ganglia. Overall, medial regions of the cingulate cortex (BA 24c, 24c', 23c) project to the ventral striatum and to the shell region of the ncl. accumbens, whereas the lateral regions and the fundus of these areas project to the dorsal sensorimotor striatum. Thus, the fundus of the cingulate sulcus is involved in skeleto-motor functions through its connection to the dorsal striatum, whereas the medial region of the cingulate sulcus is involved with limbic and associative cortical functions.

Overall, the cingulate cortex has very extensive connections with limbic, parieto-temporal, and frontal associative areas (Morecraft et al. 2004). However, the ACC is also strongly connected to auditory associative areas and has a distinct connection to the amygdala as well as to a number of autonomic motor systems (Barbas et al. 1999; Öngür et al. 1998; Ghashghaei et al. 2007; García-Cabezas and Barbas 2017). ACC and posterior OFC are also strongly associated (Barbas and Pandya 1989; Cavada et al. 2000). A comparison of the strength of inputs and outputs reveals that the ACC has stronger projections to the amygdala than it receives from it; this is reversed for the posterior OFC (Ghashghaei et al. 2007). Due to its connections, the ACC shows strong involvement in the regulation of emotions and autonomic responses, whereas the functions of the MCC are in decision-making and skeleto-motor control (Vogt 2016). The ACC is active in attentional control and task-switching, and is particularly active when cognitive demands are high (Bush et al. 2000; Botvinick 2007). The ACC and area BA 10 are activated during mental tracking tasks (Burgess et al. 2007), so the network may be involved in maintaining concentration and, via it, supporting working memory and problem-solving.

The above findings are based primarily on studies in macaques. In humans, fMRI connectivity studies assume rostral and caudal as well as dorsal and ventral subregions of the ACC; these studies suggest functionally distinct networks (Margulies et al. 2007). The anterior MCC is active during the planning and execution of motor functions and also evaluates the outcome of an action via feedback detection (Picard and Strick 2001; Amiez and Petrides 2014; Procyk et al. 2016). Affective pain perception also occurs in the aMCC (Büchel et al. 2002; Rainville 2002). Increased activation of the aMCC and supplementary motor areas is also found when motor control and pain processing occur simultaneously (Misra and Coombes 2015). The cingulate cortex is also seen as an interface for the translation of intention and motivation into action: This explains the diversity of functions of the cingulate cortex (Paus 2001).

2.2.3 Insular Cortex

The insular cortex (also called insula) is located in the lateral wall of the cerebral hemisphere. It is deeply recessed between the frontal, parietal and temporal cortex and is externally overlaid by the operculum (Fig. 2.4). It is divided into dysgranular (Idg) and granular (Ig) insular cortex, each with rostral and caudal parts, and agranular insular cortex (Iag), which is divided into frontal (FI) and temporal (TI) parts. In primates, from ventral to dorsal, the insular cortex consists of a rostroventral agranular, a caudodorsal granular, and a broader intermediate dysgranular zone. Granular and agranular refers to the presence or absence of an internal granular layer IV characterized by the presence of small cells called granule cells. The intermediate dysgranular zone has fewer granular neurons and incomplete laminar differentiation (Mesulam and Mufson 1985; Friedman et al. 1986). In a subregion of the agranular insula (FI) and dorsal to the anterior dysgranular zone are the often-cited, spindle-shaped large "von

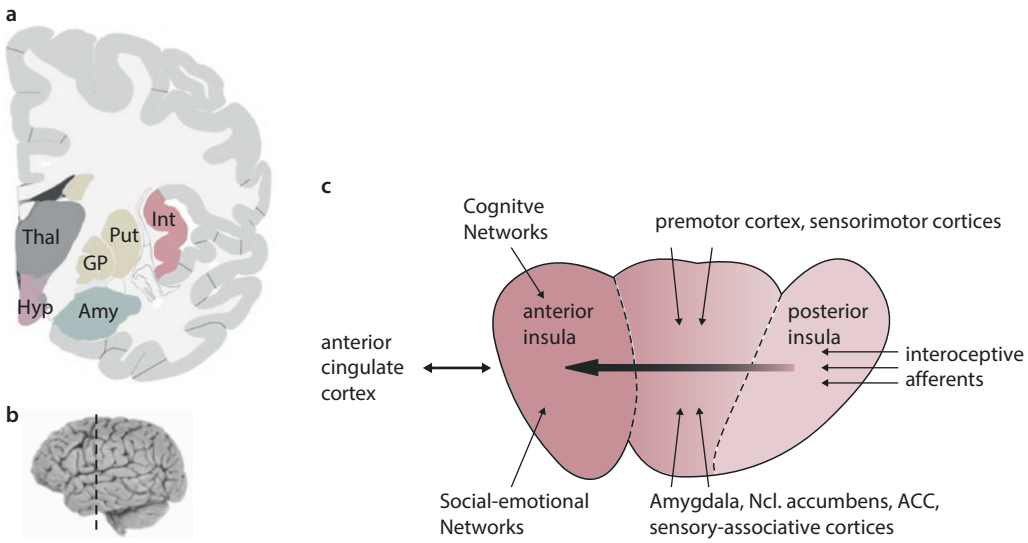

Fig. 2.4 **a** Semi-schematic representation of the location of the insula in one hemisphere of the human brain (modified after Ding et al. 2016). The insular cortex (Ins) is covered by the parietal and temporal operculum. Amygdala; GP globus pallidus; hyp hypothalamus; putamen; thal thalamus. Gray lines in the surrounding cortex separate functionally distinct cortical areas. **b** Lateral view of the human brain. The dashed line indicates the location of the cross-section in **a**. Rostral is left and caudal is right. **c** Schematic representation of the insular cortex in a lateral view after removal of the opercula (modified after Nieuwenhuys 2012). According to Craig's (2010) model, information processing within the insula progresses from posterior to anterior. Visceral states from the body are primarily processed in the posterior insula. Limbic, sensory, and cognitive influences are integrated in the interoceptive processing pathway to the anterior insula. The anterior insula encodes a "global emotional awareness" and works closely with the anterior cingulate cortex (ACC). The insular cortex generates emotions and (physical) awareness and the ACC motivation and self-efficacy. Together they form the core network for adaptive homeostatic control of the body and brain

Economo" cells (named after their discoverer von Economo), which are thought to be an important part of circuits for cognitive, complex social functions, and consciousness. However, these cells, e.g. also described in the ACC and dorsolateral PFC, have been found not only in primates with larger brains, but also in brains of other larger and smaller mammals with very different cognitive abilities, so that the actual function remains unclear.

The insular cortex receives inputs from the rostral, orbital and dorsolateral PFC, from regions in the parietal and temporal lobes, from the ACC, the olfactory system, the entorhinal cortex and the basal ganglia. Limbic structures such as the entorhinal cortex (BA 28), perirhinal areas (BA 35, 36), posterior orbitofrontal areas (BA 13, 14), temporopolar (BA 38) and cingulate (BA 23, 24) cortex, and the amygdaloid complex are strongly and reciprocally connected to the anterobasal region of the insula (Mesulam and Mufson 1982a, b; Mufson and Mesulam 1982; Augustine 1996). This limbic part also receives inputs from the superiorly located insular somatic associative cortex. Therefore, the limbic insula is considered a somatolimbic integration site where events in the extrapersonal environment are linked to motivational states. The efferents of the insular cortex to the amygdala as well as those to the limbic areas of the perihippocampal cortex are more pronounced than vice versa. Overall, a wide range of cortical and subcortical limbic con-

nections of the insula are found, as evidenced in macaque monkeys by tracing studies and in humans by imaging techniques (Ghaziri et al. 2017).

Efferents of the insular cortex run to the premotor cortex and the ventral and dorsal striatum. The agranular and ventral dysgranular zones project to the shell of the ncl. accumbens and to the medial ventral striatum, while the more dorsal and posterior parts of the agranular and dysgranular insula innervate the central ventral striatum. The dorsal dysgranular and granular insula project predominantly to the dorsolateral striatum (Chikama et al. 1997). Generally speaking, somatosensory information from the dorsal granular and dysgranular zone reaches the dorsolateral striatum, and limbic information about reward and memory content reaches the ventral striatum for feeding behavior. The agranular and rostral dysgranular parts of the anterior insula integrate sensory and amygdalar inputs and project to the caudal ventral striatum, which also receives projections from the amygdala. The posteromedial, lateral, and posterolateral portions of the agranular insula, which processes olfactory, gustatory, and visceral information, show particularly dense innervation of this striatal region (Fudge et al. 2005). After lesions of the insula, for example, conditioned feeding aversions are no longer maintained. Responses of the insula to visceral negative and positive stimuli can thus influence behavior organized by the caudal ventral striatum.

Sensory Processing

Inputs entering the insula transmit gustatory, visceral, nociceptive, thermoreceptive, vestibular, somatosensory, and olfactory information/sensory stimuli. A *primary gustatory cortex (GI)* in the granular anterosuperior part of the insula is distinguished from a *secondary gustatory cortex* underlying the GI in the dysgranular part of the insula. Posterior to the GI is the *insular viscerosensory cortex*, which processes general visceral information. Pain and temperature pathways terminate in the postero-superior insula, the *insular nociceptive and thermoreceptive cortex* (Brooks et al. 2005; Craig and Zhang 2006). Caudal to the latter, the postero-superior part contains the *parieto-insular vestibular cortex*, which receives information from the vestibular system. In the postero-superior insula, afferents from somatosensory, vestibular, and auditory cortices terminate in the *insular somatic associative cortex* (Nieuwenhuys 2012). The primary olfactory cortex, gustatory and viscerosensory insula project to the agranular anterior zone, which processes food-related information (Carmichael and Price 1996).

The visceral area of the insula processes taste information, regulates eating behavior, and has visceral motor autonomic functions (Augustine 1996). The somatosensory area of the insula plays a role in tactile perception, the pain-asymbolia syndrome that develops after stroke or trauma, i.e. the absence of normal pain-related motor and emotional responses and a sense of suffering despite pain recognition, and the thalamic pain syndrome, in which burning pain or cold pain occurs due to the disruption of thalamic connections.

In humans, four qualitatively and topographically different functional regions were described after electrical stimulation of the insula. A somatosensory representation was found in the posterior part, a representation of temperature and pain in a posterior superior part, and one for viscerosensory sensations anterior to the somatosensory representation. In a centrally located part of the insula, taste representations were localized, whereas no sensations were elicited upon stimulation of the anterior insula (Ostrowsky et al. 2002; Stephani et al. 2011).

Emotional and Cognitive Processing in the Insula

The anterior insula and especially its anterior basal region are involved in the processing of emotions and empathy (Kurth et al.

2010; Nieuwenhuys 2012). This involves the recognition of the emotional meaning of stimuli such as the (re)recognition of emotion in facial expressions and the subsequent generation of an affective state based on this (Phillips et al. 2003). These processes are regulated by a ventral system consisting of the amygdala, insula, ventral striatum, ventral ACC, and PFC. A dorsal system consisting of the hippocampus, dorsal ACC, and PFC regulates and modulates the affective state through cognitive aspects.

The empathic feeling for the pain of others is primarily accompanied by an activation of the anterior insula. Pain experiences are segregated in sensory-discriminative and vegetative-affective attributes (Singer et al. 2004). The activation of a core network consisting of the anterior insula and ACC reflects the emotional component that gives rise to our responses to pain and provides the neural basis for recognizing the feelings of others and our own feelings (Lamm et al. 2011). In this context, the insula is also activated in the prediction of emotional states, it enables error learning in emotional states and emotional uncertainty, and it modulates individual preferences in risk avoidance and contextual appraisals (Singer et al. 2009; Lamm and Singer 2010; Bernhardt and Singer 2012).

Decety and Michalska (2010) used imaging techniques to study children and adults while they observed a subject either experiencing an involuntary, self-inflicted, painful minor accident in everyday life (sympathy situation), behaving in a non-painful everyday situation, or experiencing pain intentionally induced by another (empathy situation). In all subjects, the perception of pain in the sympathy situation produced similar activations in the ACC, somatosensory cortex, periaqueductal gray, and insula, whereas the empathy situation activated different PFC regions. In the empathy situation, a stronger negative arousal was found in children than in young adults. This suggests a developmental aspect.

The insular cortex is also involved in reward processing. Thus, when listening to music, there is an activation of the mesolimbic system (Ncl. accumbens, VTA), the OFC, the hypothalamus and the insula. Vegetative and physiological adaptations in pleasant, rewarding and emotional situations are regulated by the latter two structures (Menon and Levitin 2005).

The Functional Network of the Insula

The insula is considered a major integrative cortex where multimodal information from somatosensory-limbic, insular-limbic, insular-orbital-temporal networks and from the axis between the PFC, basal ganglia, and basal forebrain converge (Shelley and Trimble 2004). Within the insula, homeostatic states appear to be connected to information from the sensory environment and to motivational, hedonic, and social information from different brain regions in a stepwise manner from posterior to anterior (Craig 2010).

The anterior insula is also a functionally complex area in humans, in which dorsal regions are involved with auditory-motor integration, while the ventral region is connected to the amygdala for the regulation of physiological parameters of emotional states (Mutschler et al. 2009). Cauda et al. (2011) used imaging techniques to investigate the connectivity of the insula in humans at rest and describe two complementary networks. In the first network, the ventral anterior insula has preferential connectivity to the middle and inferior temporal cortex and the ACC. This network controls arousal and attentional states that play a role in processing emotional stimuli and situations. In the second network, the middle posterior insula is connected to premotor, sensorimotor, supplementary motor cortices and the posterior cingulate cortex, has a more pronounced right-sided connection with the superior temporal and occipital cortex, and is functionally involved with sensorimotor integration.

Summary

In the endbrain, the limbic system comprises on the one hand the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC) and the insular cortex (insula), and on the other hand subcortical parts such as the septal region, the amygdaloid complex, the hippocampal formation, the habenula, parts of the basal ganglia and the mesolimbic system. The diencephalon contains limbic thalamic nuclei and the hypothalamus, and the midbrain contains the periaqueductal gray (PAG) with important limbic functions. The limbic brainstem contains transmitter-specific nuclei such as the dopaminergic ventral tegmental area (VTA), the serotonergic raphe nuclei, and the noradrenergic locus coeruleus. Other important limbic regions of the brainstem include the parabrachial nucleus, the nucleus solitarius, the reticular formation, and other smaller nuclei.

Functions of the limbic system involve emotional perception, evaluation, and behavioral control, which influence the cognitive and executive performances of the brain. Error detection and control, recognition of the emotional components of gestures, facial expressions, posture and language, learning and memory formation, as well as problem solving, action planning and attentional control, are substantially regulated by a limbic extensive network in the telencephalon. This consists of the OFC, ACC, medial septum, hippocampus, basal forebrain, amygdala, lateral habenula, ventral pallidum, and ncl. accumbens, and is closely intertwined with subcortical structures in the hypothalamus, transmitter-specific nuclei, and the reticular formation.

Emotional conditioning of behavior and motivational behavior control are also controlled by a functional unit consisting of the limbic cortical areas and especially the amygdala, ventral pallidum, and basal forebrain. These are interconnected in part by limbic thalamic nuclei and modulated by dopaminergic and serotonergic brainstem nuclei.

Affective states controlled by the limbic system include flight and avoidance behavior, defense, and attack, which are regulated by the amygdala, lateral septum, hypothalamus, PAG, and several nuclei in the brainstem, including transmitter-specific ones.

Control of feeding, reproduction, or sexual and caring behavior is by the lateral septum and ventral pallidum, hypothalamus, and PAG, whereas stress regulation and pain processing are controlled by the insula, ACC, hippocampus, limbic thalamus, and PAG; again, modulation by transmitter-specific and other brainstem nuclei.

The basic vegetative functions of the body, which include respiration, circulation, metabolism, digestion, hormonal balance, states of consciousness and arousal, and sleep-wake, are regulated by the hypothalamus and limbic brainstem nuclei and monitored and modulated by a telencephalic network of insula, ACC, and amygdala in cooperation with the limbic thalamus.

The limbic system exerts a direct influence (MCC) to a lesser extent and an indirect influence on the motor-executive and sensory-cognitive systems to a greater extent. According to current knowledge, these three systems are considered to be strongly interconnected. Intersections are e.g. the hippocampus, the (also cortical) far-reaching connections of the amygdala as well as the linkage of limbic cortical areas with PFC areas and thalamic regions, which establish direct and indirect connections to the sensory-cognitive system. Thus, the interaction of the three systems seems to be more dynamic than previously assumed. This is also increasingly reflected in the concepts and models of limbic networks.

The limbic system is the place of origin of affects and emotions and is considered the seat of the psyche. Mental illnesses may lie in disturbed functions of a particular limbic structure or in a disturbance of the balance between limbic centers. In many mental illnesses, alterations often also affect the transmitter/neuromodulator systems and the action of transmitters in their target areas.

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