Handbook of Clinical Neurology, Vol. 164 (3rd series)
Smell and Taste
R.L. Doty, Editor
https://doi.org/10.1016/B978-0-444-63855-7.00006-X

Chapter 6

Central olfactory structures

THOMAS A. CLELAND[1]* AND CHRISTIANE LINSTER[2]
[1]*Department of Psychology, Cornell University, Ithaca, NY, United States*
[2]*Department of Neurobiology and Behavior, Cornell University, Ithaca, NY, United States*

Abstract

Axons from the olfactory bulb (OB) project to multiple central structures of the brain, many of which, in turn, send axons back into the OB and/or to one another. These secondary sensory regions underlie many aspects of odor representation, valence, and learning, as well as serving some nonolfactory functions, though many details remain unclear. We here describe the connectivity and essential structural and functional properties of these postbulbar olfactory regions in the mammalian brain.

INTRODUCTION

The involvement of central olfactory structures in clinical disorders is poorly understood, and many disorders of olfaction appear to reflect damage to the peripheral elements of the olfactory pathways, most notably the olfactory epithelium. However, as with other sensory systems, a basic understanding of the complex anatomy of the central processes involved in olfactory function is necessary to understand the full range of olfactory disorders in the general population. This is particularly true for neurodegenerative diseases such as Alzheimer's and Parkinson's, in which subtle changes in olfactory function can occur years before the onset of the classic clinical pathologies. The goal of this chapter is to provide a broad-based overview of central olfactory structures and their function so as to provide the reader with a basic understanding of the elements of central olfactory function. Clinical disorders, per se, are not addressed; the reader is referred to other chapters in this volume for information regarding such disorders.

The commonality among vertebrate species in terms of central olfactory anatomy is remarkable, as will be noted and stressed throughout the chapter, although obviously exceptions exist. *Secondary olfactory structures* include all areas of the brain to which mitral and/or tufted cell axons from the olfactory bulb (OB) directly project. This term is synonymous with the term *primary olfactory cortices* often used in the literature (de Olmos et al., 1978; see also Price, 1973, 1987; Halasz, 1990; Shipley, 1995; Haberly, 2001); however, recognition of the OB as a cortical structure has rendered this latter term ambiguous. The centripetal projection patterns of bulbar mitral and tufted neurons have been described in several mammalian species, among them rat (Price, 1973), mouse (Shipley and Adamek, 1984), opossum (Scalia and Winans, 1975; Meyer, 1981; Shammah-Lagnado and Negrao, 1981), monkey (Turner et al., 1978; Turner and Mishkin, 1978), hamster (Davis et al., 1978), rabbit (Broadwell, 1975a), tree shrew (Skeen and Hall, 1977), and hedgehog (Radtke-Schuller and Kunzle, 2000), as well as in several nonmammalian vertebrates including bullfrog (Northcutt and Royce, 1975; Kemali and Guglielmotti, 1987; Scalia et al., 1991), and snake (Halpern, 1976).

The major secondary olfactory structures described in mammals and discussed herein include (listed roughly rostrocaudally): the anterior olfactory nucleus (AON), a group of rostromedial cortices including the ventral tenia tecta, anterior hippocampal continuation, and indusium griseum, the olfactory tubercle, the anterior and posterior piriform cortices and endopiriform nucleus, the periamygdaloid cortex and anterior cortical nucleus of the amygdala, and the lateral entorhinal cortex (Fig. 6.1). Despite

*Correspondence to: Thomas A. Cleland, Ph.D., Professor, Psychology, Cornell University, Ithaca, NY 14853, United States. Tel: +1-607-255-8099, E-mail: tac29@cornell.edu

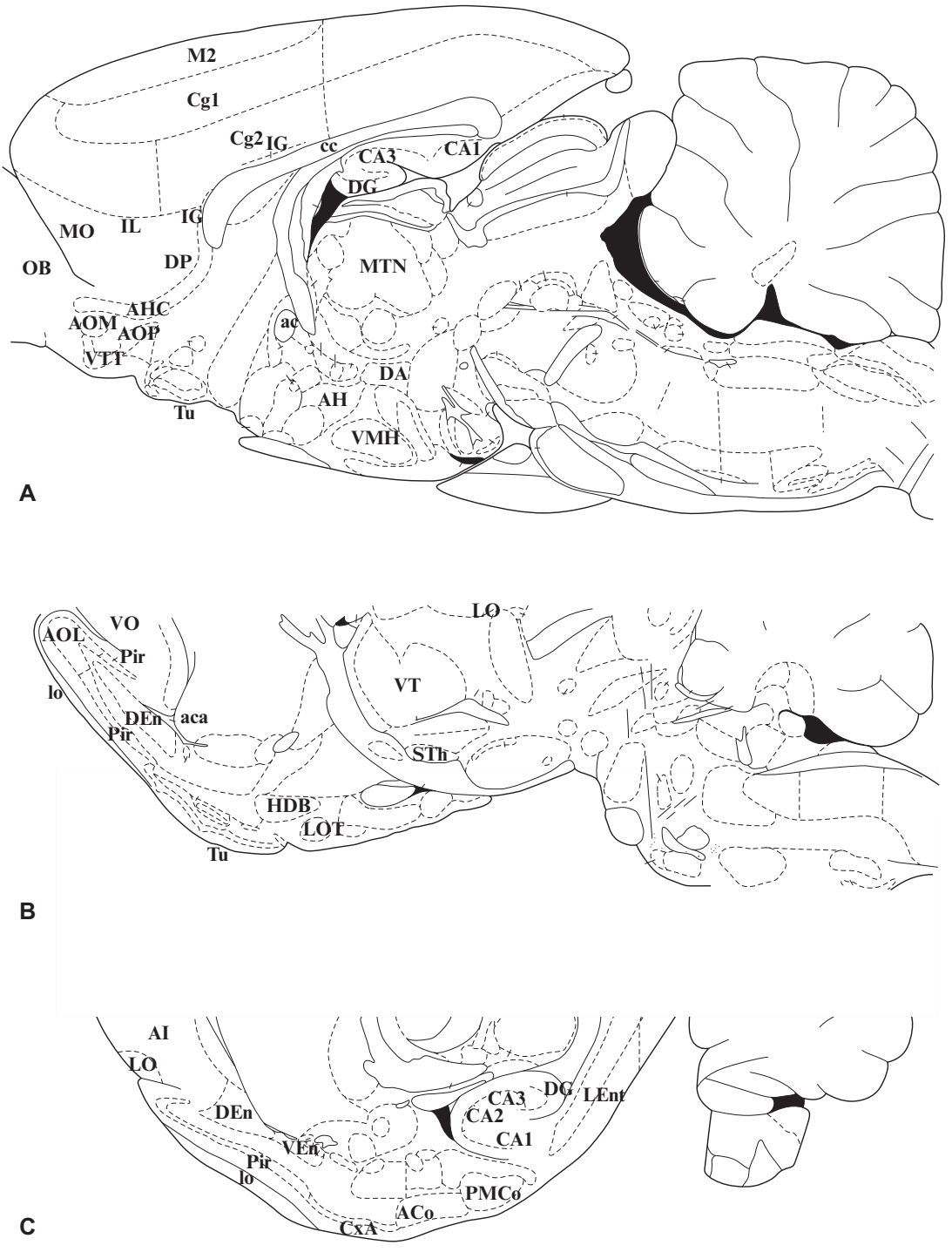

Fig. 6.1. Overview of olfactory structures. Each of the panels shows a sagittal section through a rat brain at different lateral coordinates. (A) Sagittal section at 0.4 mm lateral from bregma, showing rostromedial olfactory cortices and the olfactory tubercle. *ac*, anterior commissure; *AHC*, anterior hippocampal continuation (also known as dorsal tenia tecta); *AOM*, *AOP*, medial and posterior anterior olfactory nucleus; *CA1, CA3, DG*, hippocampus; *Cg1* and *Cg2*, cingulate cortex; *DA* and *AH*, dorsal and anterior hypothalamic areas; *DP*, dorsal peduncular cortex; *IG*, indusium griseum; *IL*, infralimbic cortex; *MO*, medial orbitofrontal cortex; *MTN*, medial thalamic nuclei; *OB*, olfactory bulb; *Tu*, olfactory tubercle; *VMH*, ventromedial hypothalamic nucleus; *VTT*, ventral tenia tecta. (B) Sagittal section at 2.4 mm lateral from bregma. *aca*, anterior part of the anterior commissure; *AOL*, lateral anterior olfactory nucleus; *DEn*, dorsal endopiriform nucleus; *HDB*, nucleus of the horizontal limb of the diagonal band; *lo*, lateral olfactory tract; *LOT*, nucleus of the lateral olfactory tract; *Pir*, piriform cortex; *STh*, subthalamic nuclei; *VO*, ventral orbitofrontal cortex; *VT*, ventral thalamic nuclei. (C) Sagittal section at 3.9 mm lateral from bregma. *ACo*, anterior cortical amygdaloid nucleus; *CA1, CA2, CA3, DG*, hippocampus; *CxA*, periamygdaloid cortex (also known as the cortex-amygdala transition zone); *DEn* and *VEn*, dorsal and ventral endopiriform nucleus; *LEnt*, lateral entorhinal cortex; *lo*, lateral olfactory tract; *LO*, lateral orbitofrontal cortex; *Pir*, piriform cortex; *PMCo*, posteromedial cortical amygdaloid nucleus. Adapted from Paxinos, G., Watson, C., 1986. The rat brain in stereotaxic coordinates. San Diego: Academic Press, with permission.

a basic conservation of bulbar projection patterns among vertebrates, and particularly among mammals, there are, nonetheless, important species differences that may provide insight into the multiple mechanisms by which different species may employ olfactory information to solve similar adaptive problems and, ultimately, contribute to an understanding of the respective roles played by the diverse central structures receiving olfactory information. In general, the canonical features of the secondary olfactory projections described in this review are derived primarily from studies in rat and secondarily from studies in mouse and primates; however, data from other species also are described to emphasize specific points and highlight the commonalities and diversity of the vertebrate radiation.

All secondary olfactory structures are paired, except for interhemispheric commissures; there is no evidence of asymmetry in the anatomy or function of any of these areas. The axons of mitral cells and several classes of tufted cells emerge from the OB, forming the *olfactory peduncle* (Brunjes et al., 2011; Brunjes, 2012); this path is also the route of the *rostral migratory stream*, along which new presumptive OB interneurons migrate throughout life into the OB from progenitor cells in the subventricular zone (Meisami and Hamedi, 1986; Jankovski et al., 1998; Lepousez et al., 2013). Within the olfactory peduncle and immediately caudal to the OB lies the *AON*, actually a cortical structure incorporating several morphologically diverse subdivisions with characteristic projection patterns (Brunjes et al., 2005; Brunjes and Kenerson, 2010). Among other functions, the AON (via the anterior commissure) mediates interhemispheric communication between the OBs in mammals. The AON is predominantly two-layered (with superficial plexiform and deep cellular layers), but gradually assumes a trilaminar form near its caudal extreme, adjacent to the anterior commissure (Valverde et al., 1989; Halasz, 1990). At this caudal extreme, the AON adjoins the ventral tenia tecta (rostromedially) and the anterior piriform cortex (laterally); OB projection fibers in the most superficial layer of AON (layer Ia) here divide into distinct rostromedial and lateral pathways projecting to other secondary olfactory structures (Shipley and Adamek, 1984; Scott et al., 1985). The lateral branch develops into the *lateral olfactory tract* (LOT).

Dorsomedial to the AON and medial to the LOT, the rostromedial pathway projects in series to three secondary olfactory structures collectively termed the rostromedial olfactory cortices: the *ventral tenia tecta*, which medially adjoins the caudal AON, the *anterior hippocampal continuation* (also known as the *dorsal tenia tecta*), and the *indusium griseum* (also known as the *dorsal hippocampal continuation* or the *supracallosal gyrus*) (Haberly and Price, 1978a; Luskin and Price, 1983b; Wyss and Sripanidkulchai, 1983; Shipley and Adamek, 1984; Carmichael et al., 1994; Kier et al., 1995). The dorsomedial peduncular cortex also is sometimes included in this group (Haberly and Price, 1977; Halasz, 1990; Haberly, 1998). The anterior hippocampal continuation and indusium griseum are structurally comparable to, and often considered part of, the hippocampal formation (Wyss and Sripanidkulchai, 1983; Adamek et al., 1984); they probably derive from the medial (limbic) pallium, as does the ventral tenia tecta (Kier et al., 1995).

Laterally, bulbar mitral and tufted cell axons exit the peduncular region following the LOT. The LOT is heavily myelinated, though it also contains numerous unmyelinated fibers, which, at least in cat, may outnumber the myelinated axons (Price and Sprich, 1975; Willey et al., 1983). Collaterals from these axons enter the *anterior* and *posterior piriform cortices* (Haberly, 1985, 1998, 2001) and the *lateral entorhinal cortex*, all derivatives of the lateral pallium, as well as the transitional *periamygdaloid cortex* and the *anterior cortical nucleus* of the corticomedial division of the amygdaloid complex. The piriform cortex is a three-layered allocortex (Haberly and Price, 1978a), incorporating a superficial plexiform layer and two cell body layers, that has been extensively studied in the context of olfactory function (Haberly, 1985, 1998; reviewed in Bekkers and Suzuki, 2013). It is sometimes referred to in the literature as *pyriform cortex* or, loosely, *olfactory cortex*. Deep to the piriform cortex lies the *endopiriform nucleus*, which some scholars regard as layer IV of piriform cortex, either alone or in conjunction with the deep portion of layer III (Valverde, 1965; Tseng and Haberly, 1989). Within the amygdaloid complex, bulbar collaterals from the LOT innervate the anterior cortical nucleus and periamygdaloid cortex; the latter adjoins and is sometimes also considered part of the piriform cortex (Paxinos and Watson, 1986). While these amygdaloid structures exhibit trilaminar structures similar to that of piriform cortex, their layers II and III are somewhat underdeveloped in comparison (Krettek and Price, 1978). The *lateral entorhinal cortex* is the most caudal target of OB axons (Heimer, 1968; Price, 1973; Scalia and Winans, 1975; Davis et al., 1978). Entorhinal cortex, which includes medial, lateral, and intermediate divisions, has six layers as opposed to the three (or four) layers observed in piriform cortex, though these six layers do not correspond to the six layers of mammalian isocortex. The piriform, entorhinal, and periamygdaloid cortices can be collectively termed the *lateral olfactory cortices*.

In mice, axons from OB projection neurons (probably mitral cells) also traverse piriform cortex layer Ia, extending beyond its dorsal limit to innervate the posterior insular cortex, within which they converge with gustatory

and visceral information received from the parabrachial nucleus of the pons and the gustatory thalamus (Shipley and Adamek, 1984; Shipley and Geinisman, 1984). This projection may also exist in rat and opossum (Scalia and Winans, 1975; de Olmos et al., 1978), but is absent in hamsters (Davis et al., 1978) and has not been observed in primates. Because of this uncertainty, insular cortex is not here considered a canonical secondary olfactory structure. However, the insular cortex consistently receives strong tertiary olfactory innervation via the piriform cortex in diverse mammalian species (Gerfen and Clavier, 1979; Motokizawa and Ino, 1983; Carmichael et al., 1994), as well as, indirectly, via the thalamus.

Just caudal to the olfactory peduncle, and medial to the LOT and cortices, lies the distinctive *olfactory tubercle*. The olfactory tubercle is innervated by collaterals from the LOT, though in garter snake the branch innervating the tubercle is more distinct and is labeled separately as the intermediate olfactory tract (Lanuza and Halpern, 1998). The olfactory tubercle, like the amygdaloid complex and the (other) basal ganglia, is derived from the striatal subpallium (Heimer and Wilson, 1975; Butler and Hodos, 1996), though in architecture it varies between cortical (predominant in the lateral tubercle, adjacent to the LOT) and striatal (predominant in the medial tubercle) organization (Heimer and Wilson, 1975; Millhouse and Heimer, 1984). Indeed, its striatal portion is an integral part of the ventral striatum, closely integrated with the nucleus accumbens and, as such, receiving dense dopaminergic projections from the ventral tegmental area. Consequently, the tubercle must be considered both as a secondary olfactory cortex and as a component of the basal ganglia (reviewed in Wesson and Wilson, 2011). The olfactory tubercle caudally adjoins the rostromedial olfactory cortices and receives associational fibers from the ventral tenia tecta (Luskin and Price, 1983b), thereby bridging the rostromedial and lateral branches of the OB projection. Indeed, the tubercle sometimes has been grouped together with the rostromedial cortices, differentiating them collectively from the AON and from the lateral olfactory cortices (Shipley, 1995; Haberly, 2001). However, it is probably better to consider the olfactory tubercle (with its subpallial and diencephalic projections and close integration with the nucleus accumbens) as a distinct OB target structure, separate from both the rostromedial cortices (with their probable medial pallial derivation and interconnectivity with the hippocampal formation) and the lateral cortices (with their lateral pallial derivation). The transitional structure of the olfactory tubercle may, in time, be clarified by improved knowledge regarding its anatomical and functional heterogeneity, including its segregation of afferent inputs from mitral and tufted cells (Igarashi et al., 2012; Payton et al., 2012).

CENTRIPETAL PROJECTIONS FROM OLFACTORY BULB

The diverse cortices receiving direct input from the OB exhibit some fundamental similarities in their architectures. Each, for example, consists of a superficial plexiform layer (layer I) and one or more deeply located cell layers. Afferent inputs from the OB and associational inputs from other regions project to layer I, where they synapse with pyramidal cell dendrites as well as with local interneurons. In the lateral cortices, bulbar afferents are sharply restricted to the most superficial portion of the layer, layer Ia, while associational projections from other regions arborize within the deeper portion of this plexiform layer, termed layer Ib (Price, 1973). In the anterior hippocampal continuation and indusium griseum of the rostromedial pathway, in contrast, bulbar afferents and associational projections mix within layer I (Wyss and Sripanidkulchai, 1983). The AON is organized similarly to the lateral cortices, although in the rhesus monkey, a microsmatic primate, afferents from the OB to the AON terminate throughout that structure rather than being restricted to layer I (Turner et al., 1978). Deeper layers in secondary olfactory cortices are all cell body layers—one in the AON, two in the piriform cortex (or three if the endopiriform nucleus is included), four in the indusium griseum and anterior hippocampal continuation—except for the six-layered entorhinal cortex, which, in the nomenclature of Amaral and Witter (1995), includes four cellular layers and one additional plexiform layer (the lamina dissecans).

Bulbar projections to the rostromedial cortices emerge from the superficial plexiform layer of the AON, which is continuous with that of the ventral tenia tecta, and extend dorsally along the midline within the superficial plexiform layers of the ventral tenia tecta, anterior hippocampal continuation and indusium griseum (Adamek et al., 1984; Shipley and Adamek, 1984). In contrast, bulbar afferents to the lateral cortices, olfactory tubercle, and amygdaloid complex in mammals project caudally via the LOT and the superficial plexiform layers of these cortices (Fig. 6.2A). In the LOT, both the number and the diameter of bulbar axons decrease as the projections extend further caudally (Price and Sprich, 1975); furthermore, the density of innervation of secondary olfactory structures by LOT axon collaterals parallels the developmental sequence of innervation, being greatest near the LOT and sparsest in the medial olfactory tubercle (Schwob and Price, 1984). Whereas both mitral and tufted cells project to the AON and to the anterior piriform cortex and olfactory tubercle (Haberly and Price, 1977; Schoenfeld and Macrides, 1984), the bulbar projection to more caudal lateral olfactory cortices becomes progressively dominated by

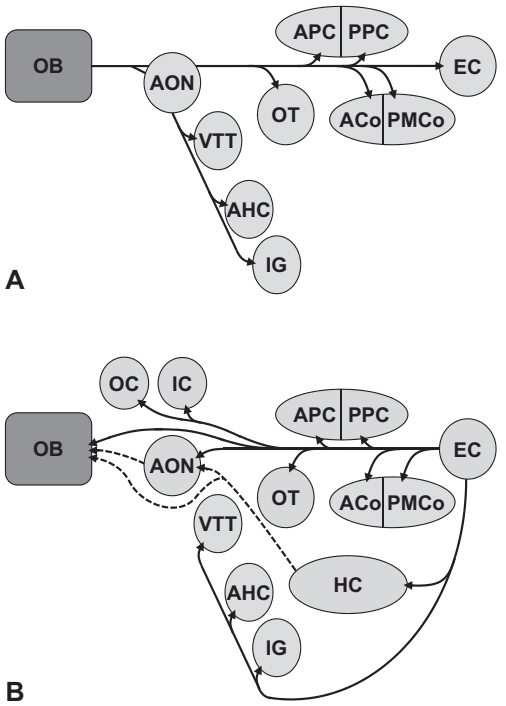

Fig. 6.2. Schematic depiction of canonical secondary olfactory projections. Pathways depicted represent the most commonly reported connections and are neither exhaustive nor universal. (A) Projections from the OB to secondary olfactory structures. All secondary structures depicted, with the exception of the IG, also project back to the OB. (B) Projections from entorhinal cortex to olfactory-related structures. In addition to direct projections, the indirect projections to OB and AON via the hippocampus also are depicted (*dotted lines*). Other hippocampal outputs are not depicted. *ACo, PMCo*, anterior and posteromedial cortical amygdaloid nuclei; *AHC*, anterior hippocampal continuation; *AON*, anterior olfactory nucleus; *APC, PPC*, anterior and posterior piriform cortices; *EC*, entorhinal cortex; *HC*, hippocampus; *IC*, insular cortex; *IG*, indusium griseum; *OB*, olfactory bulb; *OC*, orbitofrontal cortex; *OT*, olfactory tubercle; *VTT*, ventral tenia tecta.

mitral cells (Haberly and Price, 1977), and recent work has suggested a substantial segregation of mitral versus tufted cell axonal targeting within and among secondary olfactory structures (Igarashi et al., 2012).

Other than the short-latency interbulbar projection via the pars externa of the AON (Haberly and Price, 1978b), no clear topographic organization of bulbar projections to secondary olfactory structures is in evidence. Rather, (1) the limited topographic regularity immediately caudal to the OB is lost before the LOT emerges from the olfactory peduncle (Price and Sprich, 1975); (2) small regions of the OB project to large secondary areas, while small areas within olfactory cortex receive projections from widely distributed areas in the OB (Haberly and Price, 1977; Stettler and Axel, 2009); and (3) individual mitral and tufted cells can innervate multiple secondary regions (Scott, 1981; Luskin and Price, 1982; Igarashi et al., 2012; but see Scott et al., 1980). For example, in rabbit, individual mitral cells project axon collaterals into multiple secondary olfactory structures—typically arborizing in both the AON and the anterior piriform cortex, with one quarter of the neurons studied additionally projecting into the olfactory tubercle. However, within each of the innervated structures, each neuron's multiple dense terminal arborizations are highly localized, exhibiting a patchy distribution (Ojima et al., 1984). Consequently, while bulbar projections are clearly diverse, they also are likely to be highly organized. Furthermore, the collateral architecture ensures that multiple, widely spaced secondary olfactory structures could receive similar input patterns from the same set of activated mitral cells (Ojima et al., 1984).

The LOT in mammals is thought to contain all of the bulbar axons projecting caudally to the lateral olfactory cortices and olfactory tubercle. However, medial and lateral subdivisions are apparent within the rabbit LOT, reflecting the distinct "intermediate" and lateral tracts observed in garter snake (Lanuza and Halpern, 1998). Specifically, in rabbit, one type of mitral cell axon collateral courses through the LOT and terminates within the lateral olfactory cortices and the lateral, more cortically organized, portion of olfactory tubercle. A second type of axon collateral branches from the main axon within the OB, travels through the ventromedial olfactory peduncle, remaining medial to the LOT, and innervates the medial, more striatally organized portion of the olfactory tubercle (Ojima et al., 1984). In nonmammalian tetrapods, while evolutionary divergence renders it challenging to compare olfactory systems in specific detail, there are many conserved characters that can shed light on the probable plesiomorphic organization of these projections. In the garter snake, *Thamnophis sirtalis*, bulbar projections are clearly segregated into three tracts: a LOT that projects to lateral (piriform) cortex and rostral amygdala, an intermediate olfactory tract that projects to the olfactory tubercle, and a medial tract that projects ipsilaterally to the dorsomedial retrobulbar formation (Lanuza and Halpern, 1998). These three projections are comparable to the lateral and medial portions of the rabbit LOT and the projection to the mammalian rostromedial cortices, respectively. In bullfrogs (*Rana* spp.), two distinct tracts are observed, one lateral tract corresponding to the LOT (in that it projects to lateral pallium, dorsal striatum including the cortical amygdaloid nucleus, and a ventral portion of dorsal pallium) and one medial tract projecting to the medial pallium (corresponding to the mammalian rostromedial cortices) as well as to multiple septal nuclei (Northcutt and Royce, 1975; Scalia et al., 1991).

Many more species-specific deviations from the canonical bulbar projection have been described. Lateral

fiber projections extend across piriform cortex layer Ia to innervate insular (gustatory) cortex in mice, but not hamsters, as described earlier (Shipley and Adamek, 1984; Shipley and Geinisman, 1984). In the lesser hedgehog tenrec (*Echinops telfairi*), reciprocal connections have been observed between the OB and frontal isocortex (specifically, the sulcal and orbitofrontal cortices). These cortices, therefore, constitute secondary olfactory structures in this species (Radtke-Schuller and Kunzle, 2000), unlike most species studied to date in which orbitofrontal cortex is a tertiary recipient of olfactory information (Barbas, 1993, 2007; Carmichael et al., 1994). In both macaque monkeys (*Macaca* spp.) and in hedgehog (*Erinaceus europaeus*), a direct projection from the OB to the nucleus of the horizontal limb of the diagonal band of Broca that is not evident in most species studied has been described (de Carlos et al., 1989; Carmichael et al., 1994). A direct projection from the OB to the supraoptic nucleus of the hypothalamus has been reported in rats (Smithson et al., 1989). Finally, in the lemur (*Microcebus murinus*), in addition to the canonical projections, bulbar fibers also directly and bilaterally innervate the hippocampus proper (usually considered a tertiary projection area) as well as the septum, dorsal striatum (caudate nucleus and putamen), and, via the medial forebrain bundle, several hypothalamic nuclei and two mesencephalic neuromodulatory centers (the locus coeruleus and the raphe nuclei; Mestre et al., 1992).

CENTRIFUGAL AND ASSOCIATIONAL PROJECTIONS FROM SECONDARY OLFACTORY STRUCTURES

Centrifugal projections

Excepting the indusium griseum—the most distal projection target along the rostromedial branch of OB output—all of the secondary olfactory structures described herein are known to send direct feedback projections to the OB (Davis et al., 1978; de Olmos et al., 1978; Haberly and Price, 1978a, b; Davis and Macrides, 1981; Luskin and Price, 1983b; Wyss and Sripanidkulchai, 1983; Shipley and Adamek, 1984; Carmichael et al., 1994). Among the secondary structures innervated by the LOT, corticobulbar feedback projections are much heavier from rostral areas (AON and anterior piriform cortex) than from posterior piriform cortex and other caudal areas (Carson, 1984; Shipley and Adamek, 1984) and arise mainly from layer II and III pyramidal cells. Most of these feedback projections appear to terminate on granule cells in the OB, though some extend into the glomerular layer (Matsutani, 2010; Rothermel and Wachowiak, 2014). Within their layers of termination, these projections are widely distributed and responsive to odor presentations (Boyd et al., 2015). As with centripetal projections from OB, most feedback projections are ipsilateral, with the notable exception of those originating in the AON, which project bilaterally. In addition to direct feedback projections from secondary olfactory structures, the OB is also indirectly connected to the hippocampus, via entorhinal cortex, and receives projections from area CA1 (van Groen and Wyss, 1990; Cenquizca and Swanson, 2007; Fig. 6.2B).

Associational connections among secondary olfactory structures

Extensive connections, termed *associational* fibers, project between secondary olfactory cortices; their axons arborize in layer I as do the bulbar afferents, although, in the lateral cortices, they are sharply segregated from the afferents, projecting into the deeper portion of that layer (layer Ib) and also into the two superficial cell body layers (layers II and III; Luskin and Price, 1983a). These associational connections have been grouped into two classes: *local* (or *intrinsic*; short connections between neurons in different layers of a given cortical structure) and *associative* (connections between different cortices; Shipley, 1995). In piriform cortex, local connections are mediated by a variety of excitatory and inhibitory interneurons as well as pyramidal cell collaterals (Poo and Isaacson, 2009; Isaacson, 2010; Large et al., 2016). Associative connections among olfactory cortical structures are extensive and exhibit a degree of laminar and regional organization. Most associative projections among secondary olfactory structures can be classified into one of two fiber systems according to their laminar pattern of termination (Luskin and Price, 1983a, b). The first of these fiber systems, termed the *layer Ib fiber system*, includes projections from the AON and the piriform and entorhinal cortices, which terminate in layer Ib; the projections from each of these different structures are typically concentrated at different characteristic levels within layer Ib. The second fiber system, termed the *layer II-deep Ib fiber system*, originates from the dorsal peduncular cortex, ventral tenia tecta, and periamygdaloid cortex, and terminates in layer II. Projections from the anterior cortical nucleus of the amygdaloid complex arborize throughout layer I. A second system of classification is apparent based on the origins of these projections: projections from layer II pyramidal cells tend to project to more caudal sites, whereas pyramidal cells in layer III target more rostral sites. Layer II cells of anterior piriform cortex also send commissural projections contralaterally, though these are limited in number and distribution compared to ipsilateral projections (Haberly and Price, 1978a, b; Luskin and Price, 1983a, b).

Projections to tertiary olfactory structures

Olfactory information is also distributed from secondary olfactory structures to several other regions of the brain, including but not limited to, orbitofrontal cortex, insular cortex, the mediodorsal, submedial, and anterior nuclei of the thalamus, the hypothalamus, the amygdaloid complex, and the hippocampus (Krettek and Price, 1977a; Reep and Winans, 1982; Luskin and Price, 1983b; Price and Slotnick, 1983; Cavada and Reinoso-Suarez, 1985; Price, 1985; Takagi, 1986; Smithson et al., 1989; Price et al., 1991; Barbas, 1993; Carmichael et al., 1994; Datiche and Cattarelli, 1996; Cavada et al., 2000; Illig, 2005). Generally, corticocortical projections from secondary olfactory structures originate in more superficially located cell layers (typically layer II), while corticodiencephalic projections originate from deeper layers (e.g., the endopiriform nucleus, the striatal zone of the olfactory tubercle, deep cells within periamygdaloid and entorhinal cortices (Price and Slotnick, 1983; Price, 1985). Different secondary olfactory structures projecting to common tertiary structures typically project to discrete subregions; e.g., olfactory projections to the thalamus include both highly convergent projections from the lateral olfactory cortices to the mediodorsal and submedial thalamic nuclei (Price and Slotnick, 1983; Price, 1987) as well as projections from the indusium griseum and anterior hippocampal continuation to the anterior thalamic nuclei (Wyss and Sripanidkulchai, 1983). Tertiary olfactohypothalamic projections arise from the AON, the piriform cortex, the olfactory tubercle, and the amygdaloid nuclei (Price et al., 1991). Notably, in rat, the piriform cortex provides input by way of the mediodorsal thalamic nucleus to the same prefrontal areas to which it projects directly (Ray et al., 1992). In contrast, no corticothalamic projections from the piriform cortex have been observed in cat or rabbit (Motokizawa and Ino, 1983), though the olfactory tubercle, amygdala, and insular cortex do project to the mediodorsal thalamic nucleus in those species.

CONNECTIVITY OF SECONDARY OLFACTORY STRUCTURES

Anterior olfactory nucleus

The AON, a portion of which has also been termed anterior olfactory cortex (Brunjes et al., 2005), is a laminated structure embedded within the olfactory peduncle. The AON has been divided into several subregions with distinct architectures and connectivities (Broadwell, 1975a; de Olmos et al., 1978; Haberly and Price, 1978b; Davis and Macrides, 1981; Shipley and Adamek, 1984; Shipley, 1995; Brunjes et al., 2005; Brunjes and Kenerson, 2010). It is predominantly two-layered, consisting of a superficial plexiform layer containing incoming projection fibers and the apical dendrites of its intrinsic neurons and a tightly packed cell body layer (Haberly and Price, 1978b), but gradually assumes a trilaminar form near its caudal extreme adjacent to the anterior commissure (Valverde et al., 1989; Halasz, 1990). The AON receives projections from OB mitral and tufted cells in its superficial plexiform layer, layer Ia (Scott et al., 1985); bulbar afferents also course along this superficial layer into the superficial plexiform layers of the adjoining ventral tenia tecta (medially) and anterior piriform cortex (laterally; Shipley and Adamek, 1984), the latter forming the LOT.

The AON is the major source of centrifugal and feedback connections to the OB from any source (Carson, 1984). All subdivisions of the AON project to both the ipsilateral and the contralateral OB, except for pars externa, which projects only to the contralateral OB via the anterior commissure (Broadwell, 1975a; Haberly and Price, 1978b; Davis and Macrides, 1981). The AON also projects to the piriform cortex, olfactory tubercle, ventral tenia tecta, orbitofrontal cortex, and hypothalamus (Luskin and Price, 1983b; Price et al., 1991; Barbas, 1993) and receives projections from several structures including the piriform and entorhinal cortices (Wyss, 1981; Luskin and Price, 1983b), the orbitofrontal cortices (Hoover and Vertes, 2011), and the ventral CA1 region of the hippocampal formation (Cenquizca and Swanson, 2007). While no clear topographic organization is apparent in most of these projections (e.g., Price and Sprich, 1975; Luskin and Price, 1982), a few are clearly topographic. Bulbar projections to the AON pars externa, and that structure's projections to the contralateral OB, are both strictly topographic (Schoenfeld and Macrides, 1984; Scott et al., 1985); the pars lateralis also may exhibit some topographic organization (Scott et al., 1985). Finally, the AON receives topographically organized inputs from the ventral tenia tecta (Luskin and Price, 1983b). The regions and connections of the AON have been reviewed in detail by Brunjes et al. (2005) and Brunjes and Kenerson (2010).

Direct bulbobulbar contralateral projections that bypass the AON also have been demonstrated in several species including cat, rabbit, caiman, turtle, and fish but are believed to be absent in others such as rat, mouse, rhesus monkey, hamster, guinea pig, frog (*Rana* spp.), and some lizards (reviewed in Turner et al., 1978; Shipley and Adamek, 1984; Kemali and Guglielmotti, 1987; Halasz, 1990; Scalia et al., 1991; but see Leveteau et al., 1993). Moreover, in frogs (*Rana esculenta*), primary olfactory receptor neurons themselves have been shown to project bilaterally and innervate both OBs; this contralateral projection is mediated by an interbulbar adhesion distinct from the anterior and habenular commissures (Leveteau et al., 1992).

Until recently, relatively little has been known about the functional role of the AON for olfactory processing, save that it mediates most or all bilateral bulbobulbar communication in many species and thus presumably is important for the bilateral integration of olfactory information. Odor responses recorded in rabbit AON neurons appeared less odor selective than those recorded in the OB (Boulet et al., 1978), with odor responses distributed and not topographically organized (Kay et al., 2011). When adult rats were trained on simple discrimination tasks, changes in odor-evoked neural activity (as measured by 2-deoxyglucose histology) were observed in the AON of the trained animals compared to their untrained counterparts; interestingly, no changes in 2-deoxyglucose uptake were observed in the piriform cortex in this experiment (Hamrick et al., 1993). Enhanced *c*-fos expression has also been observed in the AON of rats that received forward pairing of odors with a foot shock stimulus, demonstrating that odor-induced *c*-fos expression can be modified through aversive conditioning in the AON as well as in the OB (Funk and Amir, 2000). *C*-fos expression within OB odor-activated regions was also reduced bilaterally when centrifugal afferents were severed by unilateral section of the olfactory peduncle or by application of noradrenergic antagonists within the OB, whereas 2-deoxyglucose uptake patterns were unaffected (Sallaz and Jourdan, 1993, 1996).

More recent evidence has demonstrated the direct regulation of OB processing by AON activity. For example, during social odor processing, AON modulation by the neuropeptide oxytocin activates excitatory projections onto inhibitory granule cell interneurons in the OB, thereby increasing the signal-to-noise ratio of OB principal neuron odor representations (Oettl et al., 2016). However, broad chemogenetic activation of the AON pars medialis impaired the detection of very low concentration odors, whereas chemogenetic inhibition of the same structure improved odor detection at very low concentrations and enhanced olfaction-dependent social interactions (Aqrabawi et al., 2016). These emerging data suggest that the AON is a plastic structure that exerts strong top-down effects on OB processing and is likely to regulate odor learning in concert with the OB and other secondary olfactory structures (see also Rothermel and Wachowiak, 2014).

Rostromedial olfactory structures

The ventral tenia tecta, anterior hippocampal continuation and indusium griseum receive input from the OB in their small molecular layers (de Olmos et al., 1978; Wyss and Sripanidkulchai, 1983; Adamek et al., 1984; Shipley and Adamek, 1984; Levy et al., 1999); in addition, the latter two (perihippocampal) structures receive input from the entorhinal cortex (Luskin and Price, 1983b). Because the anterior hippocampal continuation and indusium griseum have been considered part of the hippocampal formation, their inputs from the OB, while relatively sparse, have been suggested to provide a more direct olfactory input to the hippocampus proper than that via the entorhinal cortex (Adamek et al., 1984). While there are feedback projections from the ventral tenia tecta and anterior hippocampal continuation to the OB, the indusium griseum has not been shown to project back to the OB. The ventral tenia tecta also projects heavily to the AON (and receives projections from it) and, additionally, sends projections to the anterior piriform cortex and the olfactory tubercle (Luskin and Price, 1983a; Santiago and Shammah-Lagnado, 2005), whereas the indusium griseum receives additional input from the piriform cortex (Luskin and Price, 1983b; Wyss and Sripanidkulchai, 1983; Adamek et al., 1984). Interestingly, connections from the OB to the ventral tenia tecta are absent in the microsmatic rhesus monkey (Turner and Mishkin, 1978).

Olfactory tubercle

The *olfactory tubercle* in mammals is a prominent bulge on the base of the brain just caudal to the olfactory peduncle and medial to the LOT, receiving direct afferent input from OB mitral and tufted cells (Heimer, 1968; de Olmos et al., 1978; Scott et al., 1980). Notably, whereas both mitral and tufted cells project to the olfactory tubercle, they appear to innervate different discrete regions within that structure, as they do within the AON (Igarashi et al., 2012). The tubercle also receives indirect afferent input via association fibers from piriform cortex (Fallon et al., 1978; Luskin and Price, 1983a; Gaykema et al., 1991; Wesson and Wilson, 2011), the endopiriform nucleus (Behan and Haberly, 1999), and entorhinal cortex (Haberly and Price, 1978a). Nonolfactory inputs to the olfactory tubercle arise from the hippocampus, from other sensory regions (perhaps contributing to multisensory integration; Wesson and Wilson, 2010), and, most prominently, from the "reward system," including the ventral tegmental area and nucleus accumbens (Zahm and Heimer, 1993; Del-Fava et al., 2007; Wesson and Wilson, 2011). Indeed, the deep, striatal portion of the olfactory tubercle merges into the nucleus accumbens, and these two structures are considered to collectively comprise the ventral striatum, a component of the basal ganglia. Like the nucleus accumbens, the striatal olfactory tubercle is a major target of dopaminergic fibers from the ventral tegmental area (Santiago and Shammah-Lagnado, 2005). The tubercle also receives associational fibers from the ventral tenia tecta (Luskin and Price, 1983b), thereby potentially integrating the separate dorsomedial and lateral projection pathways arising from the OB.

Projections emerging from the olfactory tubercle are directed toward the mediodorsal and submedial nuclei of the thalamus (Price and Slotnick, 1983), the ventral pallidum and nucleus accumbens (Heimer and Wilson, 1975; Luskin and Price, 1983b), and other areas (reviewed in Wesson and Wilson, 2011). In monkeys, the tubercle also projects to the orbitofrontal cortex (Barbas, 1993). The tubercle also projects bilaterally back to the AON (Brunjes et al., 2005) and the OB (Mohedano-Moriano et al., 2012). The islands of Calleja within the striatal tubercle project to, and receive projections from, the piriform cortex (Fallon et al., 1978; but see Luskin and Price, 1983b) and also receive inputs from the amygdalar targets of the vomeronasal chemosensory pathway (Fallon et al., 1978)

The inputs and projections to and from the olfactory tubercle can vary substantially among species; e.g., in many macrosmatic animals (in which the olfactory sense is well developed), the olfactory tubercle receives copious direct bulbar input, and cell bridges exist between the olfactory tubercle and other striatal structures (Butler and Hodos, 1996), whereas, in humans and other microsmatic primates, the region of the tubercle receiving afferent input from the OB is greatly reduced (Carmichael et al., 1994). Current understandings of the roles and connections of the olfactory tubercle have been reviewed in detail recently (Wesson and Wilson, 2011; Xia et al., 2015).

The olfactory tubercle exhibits a superficial plexiform layer like the lateral and rostromedial olfactory cortices, but its cellular architecture varies substantially. Medially, it resembles other striatopallidal complexes, whereas, laterally (adjoining the piriform cortex), it exhibits a trilaminar cortical organization (Heimer and Wilson, 1975; Millhouse and Heimer, 1984). The distinctive islands of Calleja within the deep tubercle are closely associated with the nucleus accumbens, to the extent that, in microsomatic primates, in which the olfactory tubercle is substantially reduced and difficult to identify, the islands of Calleja sometimes have been interpreted to lie within the nucleus accumbens itself. That said, the nomenclature and defining features of the olfactory tubercle vary (Wesson and Wilson, 2011), so this distinction is less categorical than it may seem.

Neurons in the olfactory tubercle of rats can respond to electrical stimulation of the OB, as suggested by their direct bulbar inputs. Both excitatory and inhibitory responses have been observed and are modulated by the application of dopamine (Inokuchi et al., 1987, 1988). Similarly, the olfactory tubercle exhibits strong responses to presented odors; these responses are less prone to adaptation than those recorded in the piriform cortex (Xia et al., 2015), and they are strongly modulated by the valence or behavioral significance of these odors (Gadziola et al., 2015). Electrical stimulation of the olfactory tubercle can modulate odor preferences and act as a rewarding stimulus (Fitzgerald et al., 2014), suggesting a role in reward processing, as befits its close association with the nucleus accumbens. Finally, the olfactory tubercle also responds to auditory inputs, suggesting a role in multisensory integration (Wesson and Wilson, 2010), though this now appears to be a more general property of the lateral olfactory cortices (specifically olfactory tubercle and piriform cortex; Varga and Wesson, 2013).

Piriform cortex and endopiriform nucleus

Of all secondary olfactory structures, the piriform cortex has been most intensively studied with respect to olfactory function (Poo and Isaacson, 2009; Stettler and Axel, 2009; Isaacson, 2010; Payton et al., 2012; Bekkers and Suzuki, 2013; Boyd et al., 2015; Xia et al., 2015). This three-layered allocortex receives abundant afferent input from the OB as well as inputs from other secondary olfactory cortices (Krettek and Price, 1977a; Wyss, 1981; Luskin and Price, 1983b; Kowianski et al., 1999). It is traditionally divided into *anterior piriform cortex,* which projects densely back to the OB and has a less dense association fiber network, and *posterior piriform cortex,* which projects less densely to the OB and has a more extensive association fiber network (reviewed in Bekkers and Suzuki, 2013). Additionally, the anterior piriform cortex has been further subdivided into *ventrorostral* and *dorsal* subdivisions based both on intrinsic cellular properties and on their different densities of innervation by associative fibers from ventrolateral orbitofrontal cortex (Illig, 2005).

Mitral and tufted cells project to the piriform cortex by way of the LOT and arborize exclusively in layer Ia. The piriform cortex also receives input from the orbitofrontal and insular cortices, hippocampal formation, basal forebrain, brainstem, thalamus, hypothalamus, and amygdala (Kemppainen et al., 2002; Illig, 2005), and sends extensive projections back to the OB (de Olmos et al., 1978; Haberly and Price, 1978a, b; Luskin and Price, 1983a; Carmichael et al., 1994; Mohedano-Moriano et al., 2012). These feedback projections terminate mainly on or near OB granule cell interneurons, which inhibit mitral and tufted projection neurons in the OB (Boyd et al., 2012). Many projections from the piriform cortex to other regions also have been described (Haberly and Price, 1978a; Takagi, 1986; Price et al., 1991; Carmichael et al., 1994; Kowianski et al., 1999), including projections to other secondary olfactory structures as well as to the hippocampal formation, orbitofrontal and insular isocortices, the amygdaloid complex, the hypothalamus, and the mediodorsal and submedial nuclei of the thalamus.

Physiologic responses in the piriform cortex have been studied more extensively than in other secondary olfactory cortices (reviewed in Wilson et al., 2006; Bekkers and Suzuki, 2013). While odor responses in these areas are widely distributed and display no evident topography (Stettler and Axel, 2009), individual neurons in anterior piriform cortex can exhibit receptive fields comparable to those reported in the OB (Wilson, 2000), and undergo rapid adaptation that underlies behavioral habituation (Kadohisa and Wilson, 2006; Linster et al., 2009). Piriform cortical neurons also exhibit response plasticity during olfactory learning tasks (Calu et al., 2007; Roesch et al., 2007). From a theoretical perspective, PC has long been proposed to function as an associative memory network (Haberly and Bower, 1989); this hypothesis has been extensively modeled (Linster and Hasselmo, 2001; Linster et al., 2003; Mandairon et al., 2014; de Almeida et al., 2015) and empirically investigated (Barnes et al., 2008; Wilson, 2009). Notably, due to their different patterns of connectivity with other cortices, the anterior and posterior piriform cortices are thought to have distinct functions (reviewed in Bekkers and Suzuki, 2013).

Deep to the piriform cortex lies the endopiriform nucleus, a large group of multipolar cells that is interconnected with the overlying cortex to the extent that it, either alone or in combination with the deep portion of layer III, is considered layer IV of piriform cortex by some authors (Valverde, 1965; Tseng and Haberly, 1989). The function of the endopiriform nucleus is unknown; however, studies with animal models suggest that it plays an important role in temporal lobe epileptogenesis (Behan and Haberly, 1999). The input and output connections of the endopiriform nucleus are very similar to those of the piriform cortex (Kowianski et al., 1999); however, efferents from the endopiriform nucleus lack the precise laminar order of those from the piriform cortex and form a heavy caudorostral pathway that the piriform cortex lacks (Behan and Haberly, 1999).

Periamygdaloid cortex and the anterior cortical nucleus of the amygdaloid complex

In mammals, axons from the main OB project to the periamygdaloid cortex (considered part of the piriform cortex by some; Paxinos and Watson, 1986) and the anterior cortical nucleus of the amygdaloid complex. (While the accessory OB also projects to the amygdaloid complex, its target regions are not shared with those of the main OB; Haberly and Price, 1978a; Krettek and Price, 1978; Luskin and Price, 1983b.) These "extended amygdalar" structures exhibit a characteristic trilaminar structure, although layers II and III are somewhat less developed than in the piriform cortex (Krettek and Price, 1978). Olfactory targets of projections from the periamygdaloid cortex and the anterior cortical nucleus include the piriform cortex, entorhinal cortex, infralimbic area, ventral agranular insular area, and perirhinal area (Krettek and Price, 1977b; Kevetter and Winans, 1981; Wyss, 1981; Kowianski et al., 1999; Kunzle and Radtke-Schuller, 2000), whereas the posterior cortical nucleus also projects to piriform cortex (Kemppainen et al., 2002). A third, superficial corticoid structure within the amygdaloid complex, adjoining the anterior cortical nucleus, is the *nucleus of the LOT*; this structure exhibits a trilaminar structure similar to that of the anterior cortical nucleus, though its interconnectivity with other secondary olfactory structures is less well established.

Research in rats and in monkeys has shown that, in awake, behaving animals, neurons in the amygdaloid complex respond selectively to olfactory stimulation. In rats, neurons in the basolateral amygdala responded to odors (Cain and Bindra, 1972; Cain, 1975), displayed selective odor responses in an odor discrimination task, and rapidly reversed this selectivity during reversal learning (Schoenbaum et al., 1998). In monkeys, odor selectivity in medial amygdalar neurons could be obtained without training (Tanabe et al., 1975). In hamsters, conspecific olfactory signals mediate neural activity in the amygdalar complex (Westberry and Meredith, 2016). In mice, the activation of projections from amygdala to piriform cortex modulates odor-induced activity; given the importance of the amygdala for valence representation, this may be a pathway to transmit valence information to olfactory cortex (Sadrian and Wilson, 2015). The amygdala also is implicated in the mediation of innate aversion to odor signals (Root et al., 2014) and in olfactory fear conditioning (Hegoburu et al., 2014). In PET studies of humans, aversive odors activate the amygdala in both hemispheres (Zald and Pardo, 2000).

In neonatal rats, the amygdala is strongly implicated in the development of odor hedonics (Perry et al., 2016). Lesions of the amygdaloid complex in neonatal rats blocked the acquisition of odor preferences in a conditioned odor association paradigm, although this impairment could be overcome by overtraining (Sullivan and Wilson, 1993). In contrast, in adult rats, lesions of either the LOT inputs to the amygdala or of the amygdala itself did not affect simple odor discrimination learning (Slotnick, 1985; Slotnick and Risser, 1990; Sutherland and McDonald, 1990). Lesions of the bed nucleus of the stria terminalis (described in Broadwell, 1975b; Krettek and Price, 1978; Turner and Zimmer, 1984) specifically blocked activation of the hypothalamic paraventricular nucleus (PVN), which regulates adrenocortical secretion, by olfactory stimuli, while sparing activation of the PVN via other sensory modalities (Mor et al., 1987).

Entorhinal cortex

The lateral portion of the entorhinal cortex is the most caudal projection of axons from OB (Heimer, 1968; Price, 1973; Scalia and Winans, 1975; Davis et al., 1978). Entorhinal cortex is divided into medial, lateral, and intermediate divisions and is commonly categorized into six layers (or seven; there is some disagreement between the primate and rat literatures; Amaral and Witter, 1995), as opposed to the three (or four) layers seen in piriform cortex. Entorhinal cortex has been considered transitional between olfactory allocortices and the isocortex, although its six layers do not directly correspond to the six layers of mammalian isocortex. While entorhinal cortex projects back to the OB and also to other olfactory cortical structures, including the AON, ventral tenia tecta, indusium griseum, piriform cortex, endopiriform nucleus, olfactory tubercle, and amygdaloid cortices (Wyss, 1981; Luskin and Price, 1983a, b; Kowianski et al., 1999; Santiago and Shammah-Lagnado, 2005), its strongest projection is to the hippocampal formation (Fig. 6.2B).

A number of studies have shown that olfactory stimuli can modulate neural activity in the entorhinal cortex of behaving rats (Kay and Freeman, 1998; Chabaud et al., 2000; Mouly et al., 2001; Xu and Wilson, 2012). Highly coherent dynamic neural responses from piriform cortex and entorhinal cortex have been evoked by odor application, and these dynamics change in the entorhinal cortex as a function of the behavioral relevance of a given odor stimulus (Kay and Freeman, 1998; Chabaud et al., 2000; Mouly et al., 2001). While these data suggest the functional relevance of entorhinal cortex to olfactory processing, behavioral lesion studies have demonstrated that rats with posterior sections of the LOT (severing bulbar projections to the entorhinal and amygdaloid cortices) are not noticeably impaired in simple odor discrimination tasks (Slotnick and Risser, 1990; Thanos and Slotnick, 1997; Zhang et al., 1998). While these data may superficially suggest that the entorhinal cortex is not a crucial structure for olfactory discrimination learning, it also is clear that entorhinal cortex receives olfactory input from many other secondary olfactory structures as well as the OB; i.e., posterior LOT lesions may not eliminate the participation of the entorhinal cortex in olfactory stimulus processing. Finally, it has been reported that short-term memory for olfactory stimuli in a delayed nonmatch-to-sample task in rats can be *increased* in duration by lateral entorhinal cortex lesions (Ferry et al., 1996; Wirth et al., 1998). These results could of course also be interpreted as a reduction in the rats' ability to extinguish associations likely to be no longer appropriate due to the passage of time, suggesting that such lesions would impair reversal learning.

FUNCTIONAL PROPERTIES OF SECONDARY OLFACTORY STRUCTURES

The anatomy of the olfactory pathways described in this chapter clearly shows that olfactory processing involves a large number of structures, heavily interconnected with one another, and incorporating complex networks of feedforward and feedback interactions. As early as in the OB, feedback projections from more central brain structures influence neural dynamics and are crucial for normal olfactory learning and odor recognition. Whole-brain imaging studies in humans have shown that multiple diverse neural structures become activated during tasks involving olfactory stimulation, that the correspondence between activation in these structures and particular odor stimulus attributes can differ (Fournel et al., 2016), and that the nature of the task strongly influences which of these structures become most activated. For example, in studies measuring regional cerebral blood flow increases using PET, the presentation of single odors increased activity in the piriform, periamygdaloid, orbitofrontal, insular and cingulate cortices as well as in the thalamus, indicating that olfactory stimuli activate diverse regions throughout the human brain. When subjects were tested on olfactory discrimination and memory tasks, additional regions were activated, including the cerebellum (Savic et al., 2000). In a similar PET study, the orbitofrontal cortex was differentially activated when subjects were asked to make judgments about odor presence, familiarity, intensity, hedonicity, or edibility; furthermore, this activation could be differentially lateralized (Royet et al., 2000, 2001; Sorokowska et al., 2016). Aversive odor stimuli have been shown to increase regional cerebral blood flow in the orbitofrontal cortex; highly aversive odor stimuli additionally evoked such increases in the amygdaloid complex (Zald and Pardo, 1997). Finally, in a functional magnetic resonance imaging study differentiating the effects of odor stimulation per se from those deriving from motor and other correlates of odor sampling behaviors, Sobel et al. (1998) showed that active sniffing, either in the absence or in the presence of an odor, induced activation in the piriform and the medial and posterior orbitofrontal cortices; in contrast, smelling an odor, irrespective of sniffing activity, induced activation mainly in the lateral and anterior orbitofrontal cortex. These results emphasize a crucial caveat to imaging and other physiologic studies: regions in which activity correlates with or is shown to mediate important features of an olfactory task are not necessarily chemosensory in nature.

Physiologic and behavioral data from nonhuman animals also have offered considerable insight into the functional roles of various secondary olfactory

structures in odor acquisition, processing, and memory (Wilson et al., 2004, 2006). Neural responses evoked or modulated by olfactory stimulation have been reported in all secondary olfactory cortices studied and in several tertiary structures as well; examples include the amygdala (Schoenbaum et al., 1998; Perry et al., 2016), orbitofrontal cortex (Tanabe et al., 1975; Schoenbaum et al., 1998, 2000; Lipton et al., 1999; Ramus and Eichenbaum, 2000), and hypothalamus (Courtiol and Wilson, 2014, 2015; Wilson et al., 2014). Together, these data demonstrate that animals' experiences and expectations regarding odors can persistently alter the odor-evoked response patterns of individual neurons, the neural ensembles activated in response to odorant presentation, and the dynamics of the interplay of neural populations. However, it remains unclear just what factors are being encoded or what the functional meanings of the observed changes might be.

Behavioral lesion studies also can yield valuable information about the putative contributions of various structures to tasks such as odor detection, identification, discrimination, responsivity, and learning. Behavioral lesion studies suggest that deficits in odor detection and learning are related to the extent to which the OB is disconnected from the forebrain. For example, transections of only the LOT, the anterior limb of the anterior commissure, or the olfactory tubercle had little effect on performance of a simple odor discrimination task, whereas combined lesions of these structures produced severe impairments (Slotnick and Schoonover, 1992). Interestingly, transections of the LOT, sparing the more rostromedially directed outputs of the OB, had little effect on odor retention, suggesting that rostromedial olfactory projections can suffice for performance of certain olfactory tasks (Slotnick and Berman, 1980). Lesions of either the lateral or rostromedial portions of the olfactory peduncle impaired rats' performance in a two-choice behavioral test, whereas rostromedial lesions specifically impaired isocortical responsivity to food odor presentation during slow-wave sleep (Gervais and Pager, 1982). Finally, specific lesions of centrifugal projections back to the OB from lateral secondary olfactory structures significantly modulated bulbar oscillatory dynamics (Martin et al., 2004) and impaired odor-reward associations (Kiselycznyk et al., 2006). More posterior lesions of the LOT, disconnecting the amygdaloid complex and entorhinal cortex from direct OB inputs, had no detectable effects either on retention of a previously learned odor detection task or on the acquisition of a simple odor discrimination (Slotnick, 1985; Slotnick and Risser, 1990). However, substantial associational projections to the entorhinal cortex from multiple secondary olfactory structures remained intact under this procedure, such that the contribution of entorhinal cortex activity to the olfactory task may not have been eliminated by the LOT lesions. Indeed, in some types of olfactory memory tasks, lesions of the entorhinal cortex can be interpreted to facilitate olfactory recognition. In an olfactory habituation task, rats with aspirative entorhinal cortex lesions displayed recognition of a previously investigated odor at shorter latencies than control rats (Wirth et al., 1998). Similar results have been obtained using conditioned odor aversion, in which entorhinal cortex lesions lengthened the time window during which an association between the odor stimulus and the subsequent aversive stimulus could be formed (Ferry et al., 1996, 1999). Lesions of the mediodorsal thalamic nucleus, in contrast, impaired both acquisition of an odor discrimination task and its reversal (Slotnick and Risser, 1990). Finally, lesions of the olfactory inputs to the amygdala did not impair performance on olfactory detection and discrimination tasks (Slotnick, 1985); however, odor preferences that were affected by bilateral amygdalar lesions in neonatal rats could be restored by extensive training (Sullivan and Wilson, 1993).

FURTHER DEVELOPMENT AND RECOMMENDATIONS

Olfactory sensory input pathways diverge immensely after emerging from the relative bottleneck of the OB. As reviewed herein, these secondary olfactory projections innervate a broad diversity of structures deriving from several distinct telencephalic pallial and subpallial tissues as well as diencephalic, midbrain, and brainstem structures. Many of these structures are highly interconnected with one another via associational projections, and each receives characteristic extrinsic and neuromodulatory inputs from other regions of the brain that can influence neuronal responses and complex behavior (e.g., Oettl et al., 2016). While these structures and projections are remarkably conserved among vertebrates, there also are numerous species-specific variations that presumably derive from the divergent adaptive needs of each species, both in terms of novel or absent projections and in terms of the relative densities of projection patterns among secondary and tertiary olfactory structures. Lacking specific knowledge of what purposes most of these structures serve, or even of the physiologic and adaptive tasks that must be performed by the organism and for which it requires olfactory perceptual information, which framework for analysis is likely to be the most conducive to elucidating an understanding of these structures over time?

It may be counterproductive to think of secondary olfactory structures as primarily "olfactory" in nature. In particular, it may be misleading to judge such structures primarily on the basis of the purported odor selectivity of individual neurons, or even of ensembles.

Aside from the typically unwarranted assumptions about mechanism that necessarily underlie statistical measures of selectivity, it is unlikely that ever-increasing specificity is the general goal of all secondary processing. Rather, a functional approach is likely to be stronger: for what various purposes might a given organism require olfactory sensory data, and what elements of those data are needed for the organism to respond adaptively? How precise must an olfactory identification be to meet the organism's needs, and what are the probable costs of false positive errors compared with false negatives? Even if maximally specific odor identification were prerequisite to all decision processes utilizing olfactory information—an unlikely possibility—neural activity based increasingly on contingency and less on the physical characteristics of the stimulus would be expected as the response cascade proceeds beyond primary sensory areas in the brain. In some tissues, studying how the categorization of different olfactory stimuli changes, for example, may be more indicative than measuring how theoretically orthogonal their representations may be.

In short, a functional approach to understanding the contributions of secondary olfactory structures to cognition and human health might be to hypothesize an information-processing task to which a given structure might contribute, to assess what elements of olfactory sensory information would be required in order for it to fulfill that task, and to predict what cellular and network mechanisms would be required in order to extract this information from the ensemble activity of the projection neurons that innervate it. Given the known involvement of olfactory structures in many brain disorders, including epilepsy (Restrepo et al., 2014; Vaughan and Jackson, 2014), Alzheimer's disease (Velayudhan and Lovestone, 2009; Roberts et al., 2016), and Parkinson's disease (Zhu et al., 2016), a more complete understanding of these interacting systems is crucial to our understanding of the function and vulnerabilities of the healthy brain (Wilson et al., 2014).

References

Adamek GD, Shipley MT, Sanders MS (1984). The indusium griseum in the mouse: architecture, Timm's histochemistry and some afferent connections. Brain Res Bull 12: 657–668.

Amaral DG, Witter MP (1995). Hippocampal formation. In: G Paxinos (Ed.), The rat nervous system, Academic Press, San Diego, pp. 443–493.

Aqrabawi AJ, Browne CJ, Dargaei Z et al. (2016). Top-down modulation of olfactory-guided behaviours by the anterior olfactory nucleus pars medialis and ventral hippocampus. Nat Commun 7: 13721.

Barbas H (1993). Organization of cortical afferent input to orbitofrontal areas in the rhesus monkey. Neuroscience 56: 841–864.

Barbas H (2007). Specialized elements of orbitofrontal cortex in primates. Ann N Y Acad Sci 1121: 10–32.

Barnes DC, Hofacer RD, Zaman AR et al. (2008). Olfactory perceptual stability and discrimination. Nat Neurosci 11: 1378–1380.

Behan M, Haberly LB (1999). Intrinsic and efferent connections of the endopiriform nucleus in rat. J Comp Neurol 408: 532–548.

Bekkers JM, Suzuki N (2013). Neurons and circuits for odor processing in the piriform cortex. Trends Neurosci 36: 429–438.

Boulet M, Daval G, Leveteau J (1978). Qualitative and quantitative odour discrimation by mitral cells as compared to anterior olfactory nucleus cells. Brain Res 142: 123–134.

Boyd AM, Sturgill JF, Poo C et al. (2012). Cortical feedback control of olfactory bulb circuits. Neuron 76: 1161–1174.

Boyd AM, Kato HK, Komiyama T et al. (2015). Broadcasting of cortical activity to the olfactory bulb. Cell Rep 10: 1032–1039.

Broadwell RD (1975a). Olfactory relationships of the telencephalon and diencephalon in the rabbit. I. An autoradiographic study of the efferent connections of the main and accessory olfactory bulbs. J Comp Neurol 163: 329–345.

Broadwell RD (1975b). Olfactory relationships of the telencephalon and diencephalon in the rabbit. II. An autoradiographic and horseradish peroxidase study of the efferent connections of the anterior olfactory nucleus. J Comp Neurol 164: 389–409.

Brunjes PC (2012). The mouse olfactory peduncle. 2. The anterior limb of the anterior commissure. Front Neuroanat 6: 51.

Brunjes PC, Kenerson MC (2010). The anterior olfactory nucleus: quantitative study of dendritic morphology. J Comp Neurol 518: 1603–1616.

Brunjes PC, Illig KR, Meyer EA (2005). A field guide to the anterior olfactory nucleus (cortex). Brain Res Brain Res Rev 50: 305–335.

Brunjes PC, Kay RB, Arrivillaga JP (2011). The mouse olfactory peduncle. J Comp Neurol 519: 2870–2886.

Butler AB, Hodos W (1996). Comparative vertebrate anatomy: evolution and adaptation, Wiley-Liss, New York.

Cain DP (1975). Effects of insulin injection on responses of olfactory bulb and amygdala single units to odors. Brain Res 99: 69–83.

Cain DP, Bindra D (1972). Responses of amygdala single units to odors in the rat. Exp Neurol 35: 98–110.

Calu DJ, Roesch MR, Stalnaker TA et al. (2007). Associative encoding in posterior piriform cortex during odor discrimination and reversal learning. Cereb Cortex 17: 1342–1349.

Carmichael ST, Clugnet MC, Price JL (1994). Central olfactory connections in the macaque monkey. J Comp Neurol 346: 403–434.

Carson KA (1984). Quantitative localization of neurons projecting to the mouse main olfactory bulb. Brain Res Bull 12: 629–634.

Cavada C, Reinoso-Suarez F (1985). Topographical organization of the cortical afferent connections of the prefrontal cortex in the cat. J Comp Neurol 242: 293–324.

Cavada C, Company T, Tejedor J et al. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10: 220–242.

Cenquizca LA, Swanson LW (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. Brain Res Rev 56: 1–26.

Chabaud P, Ravel N, Wilson DA et al. (2000). Exposure to behaviourally relevant odour reveals differential characteristics in rat central olfactory pathways as studied through oscillatory activities. Chem Senses 25: 561–573.

Courtiol E, Wilson DA (2014). Thalamic olfaction: characterizing odor processing in the mediodorsal thalamus of the rat. J Neurophysiol 111: 1274–1285.

Courtiol E, Wilson DA (2015). The olfactory thalamus: unanswered questions about the role of the mediodorsal thalamic nucleus in olfaction. Front Neural Circuits 9: 49.

Datiche F, Cattarelli M (1996). Reciprocal and topographic connections between the piriform and prefrontal cortices in the rat: a tracing study using the B subunit of the cholera toxin. Brain Res Bull 41: 391–398.

Davis BJ, Macrides F (1981). The organization of centrifugal projections from the anterior olfactory nucleus, ventral hippocampal rudiment, and piriform cortex to the main olfactory bulb in the hamster: an autoradiographic study. J Comp Neurol 203: 475–493.

Davis BJ, Macrides F, Youngs WM et al. (1978). Efferents and centrifugal afferents of the main and accessory olfactory bulbs in the hamster. Brain Res Bull 3: 59–72.

de Almeida L, Reiner SJ, Ennis M et al. (2015). Computational modeling suggests distinct, location-specific function of norepinephrine in olfactory bulb and piriform cortex. Front Comput Neurosci 9: 73.

de Carlos JA, Lopez-Mascaraque L, Valverde F (1989). Connections of the olfactory bulb and nucleus olfactorius anterior in the hedgehog (Erinaceus europaeus): fluorescent tracers and HRP study. J Comp Neurol 279: 601–618.

de Olmos J, Hardy H, Heimer L (1978). The afferent connections of the main and the accessory olfactory bulb formations in the rat: an experimental HRP-study. J Comp Neurol 181: 213–244.

Del-Fava F, Hasue RH, Ferreira JG et al. (2007). Efferent connections of the rostral linear nucleus of the ventral tegmental area in the rat. Neuroscience 145: 1059–1076.

Fallon JH, Riley JN, Sipe JC et al. (1978). The islands of Calleja: organization and connections. J Comp Neurol 181: 375–395.

Ferry B, Oberling P, Jarrard LE et al. (1996). Facilitation of conditioned odor aversion by entorhinal cortex lesions in the rat. Behav Neurosci 110: 443–450.

Ferry B, Wirth S, Di Scala G (1999). Functional interaction between entorhinal cortex and basolateral amygdala during trace conditioning of odor aversion in the rat. Behav Neurosci 113: 118–125.

Fitzgerald BJ, Richardson K, Wesson DW (2014). Olfactory tubercle stimulation alters odor preference behavior and recruits forebrain reward and motivational centers. Front Behav Neurosci 8: 81.

Fournel A, Ferdenzi C, Sezille C et al. (2016). Multidimensional representation of odors in the human olfactory cortex. Hum Brain Mapp 37: 2161–2172.

Funk D, Amir S (2000). Enhanced fos expression within the primary olfactory and limbic pathways induced by an aversive conditioned odor stimulus. Neuroscience 98: 403–406.

Gadziola MA, Tylicki KA, Christian DL et al. (2015). The olfactory tubercle encodes odor valence in behaving mice. J Neurosci 35: 4515–4527.

Gaykema RP, van Weeghel R, Hersh LB et al. (1991). Prefrontal cortical projections to the cholinergic neurons in the basal forebrain. J Comp Neurol 303: 563–583.

Gerfen CR, Clavier RM (1979). Neural inputs to the prefrontal agranular insular cortex in the rat: horseradish peroxidase study. Brain Res Bull 4: 347–353.

Gervais R, Pager J (1982). Functional changes in waking and sleeping rats after lesions in the olfactory pathways. Physiol Behav 29: 7–15.

Haberly LB (1985). Neuronal circuitry in olfactory cortex: anatomy and functional implications. Chem Senses 10: 219–238.

Haberly LB (1998). Olfactory cortex. In: GM Shepherd (Ed.), The synaptic organization of the brain. Oxford University Press, New York, pp. 377–417.

Haberly LB (2001). Parallel-distributed processing in olfactory cortex: new insights from morphological and physiological analysis of neuronal circuitry. Chem Senses 26: 551–576.

Haberly LB, Bower JM (1989). Olfactory cortex: model circuit for study of associative memory? Trends Neurosci 12: 258–264.

Haberly LB, Price JL (1977). The axonal projection patterns of the mitral and tufted cells of the olfactory bulb in the rat. Brain Res 129: 152–157.

Haberly LB, Price JL (1978a). Association and commissural fiber systems of the olfactory cortex of the rat. J Comp Neurol 178: 711–740.

Haberly LB, Price JL (1978b). Association and commissural fiber systems of the olfactory cortex of the rat. II. Systems originating in the olfactory peduncle. J Comp Neurol 181: 781–807.

Halasz N (1990). The vertebrate olfactory system, Akademia Kiado, Budapest.

Halpern M (1976). The efferent connections of the olfactory bulb and accessory olfactory bulb in the snakes, Thamnophis sirtalis and Thamnophis radix. J Morphol 150: 553–578.

Hamrick WD, Wilson DA, Sullivan RM (1993). Neural correlates of memory for odor detection conditioning in adult rats. Neurosci Lett 163: 36–40.

Hegoburu C, Parrot S, Ferreira G et al. (2014). Differential involvement of amygdala and cortical NMDA receptors activation upon encoding in odor fear memory. Learn Mem 21: 651–655.

Heimer L (1968). Synaptic distribution of centripetal and centrifugal nerve fibres in the olfactory system of the rat. An experimental anatomical study. J Anat 103: 413–432.

Heimer L, Wilson RD (1975). The subcortical projections of the allocortex: similarities in the neural connections of the hippocampus, the piriform cortex and the neocortex. In: M Santini (Ed.), Perspectives in neurobiology, Raven, New York, pp. 177–193.

Hoover WB, Vertes RP (2011). Projections of the medial orbital and ventral orbital cortex in the rat. J Comp Neurol 519: 3766–3801.

Igarashi KM, Ieki N, An M et al. (2012). Parallel mitral and tufted cell pathways route distinct odor information to different targets in the olfactory cortex. J Neurosci 32: 7970–7985.

Illig KR (2005). Projections from orbitofrontal cortex to anterior piriform cortex in the rat suggest a role in olfactory information processing. J Comp Neurol 488: 224–231.

Inokuchi A, Mooney KE, Snow Jr JB (1987). Dopaminergic modulation of bulbofugal projections in the rat olfactory tubercle. Am J Otolaryngol 8: 214–218.

Inokuchi A, Boran TV, Kimmelman CP et al. (1988). Effects of locus ceruleus and olfactory bulb stimulation on rat olfactory tubercle neuron activity. Otolaryngol Head Neck Surg 98: 116–120.

Isaacson JS (2010). Odor representations in mammalian cortical circuits. Curr Opin Neurobiol 20: 328–331.

Jankovski A, Garcia C, Soriano E et al. (1998). Proliferation, migration and differentiation of neuronal progenitor cells in the adult mouse subventricular zone surgically separated from its olfactory bulb. Eur J Neurosci 10: 3853–3868.

Kadohisa M, Wilson DA (2006). Olfactory cortical adaptation facilitates detection of odors against background. J Neurophysiol 95: 1888–1896.

Kay LM, Freeman WJ (1998). Bidirectional processing in the olfactory-limbic axis during olfactory behavior. Behav Neurosci 112: 541–553.

Kay RB, Meyer EA, Illig KR et al. (2011). Spatial distribution of neural activity in the anterior olfactory nucleus evoked by odor and electrical stimulation. J Comp Neurol 519: 277–289.

Kemali M, Guglielmotti V (1987). A horseradish peroxidase study of the olfactory system of the frog, Rana esculenta. J Comp Neurol 263: 400–417.

Kemppainen S, Jolkkonen E, Pitkanen A (2002). Projections from the posterior cortical nucleus of the amygdala to the hippocampal formation and parahippocampal region in rat. Hippocampus 12: 735–755.

Kevetter GA, Winans SS (1981). Connections of the corticomedial amygdala in the golden hamster. II. Efferents of the "olfactory amygdala". J Comp Neurol 197: 99–111.

Kier EL, Fulbright RK, Bronen RA (1995). Limbic lobe embryology and anatomy: dissection and MR of the medial surface of the fetal cerebral hemisphere. Am J Neuroradiol 16: 1847–1853.

Kiselycznyk CL, Zhang S, Linster C (2006). Role of centrifugal projections to the olfactory bulb in olfactory processing. Learn Mem 13: 575–579.

Kowianski P, Lipowska M, Morys J (1999). The piriform cortex and the endopiriform nucleus in the rat reveal generally similar pattern of connections. Folia Morphol 58: 9–19.

Krettek JE, Price JL (1977a). Projections from the amygdaloid complex and adjacent olfactory structures to the entorhinal cortex and to the subiculum in the rat and cat. J Comp Neurol 172: 723–752.

Krettek JE, Price JL (1977b). Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. J Comp Neurol 172: 687–722.

Krettek JE, Price JL (1978). A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections. J Comp Neurol 178: 255–280.

Kunzle H, Radtke-Schuller S (2000). Basal telencephalic regions connected with the olfactory bulb in a Madagascan hedgehog tenrec. J Comp Neurol 423: 706–726.

Lanuza E, Halpern M (1998). Efferents and centrifugal afferents of the main and accessory olfactory bulbs in the snake Thamnophis sirtalis. Brain Behav Evol 51: 1–22.

Large AM, Vogler NW, Mielo S et al. (2016). Balanced feedforward inhibition and dominant recurrent inhibition in olfactory cortex. Proc Natl Acad Sci U S A 113: 2276–2281.

Lepousez G, Valley MT, Lledo PM (2013). The impact of adult neurogenesis on olfactory bulb circuits and computations. Annu Rev Physiol 75: 339–363.

Leveteau J, Andriason I, Mac Leod P (1992). The bilateral bulbar projections of the primary olfactory neurons in the frog. Exp Brain Res 89: 93–104.

Leveteau J, Andriason I, Mac Leod P (1993). Interbulbar reciprocal inhibition in frog olfaction. Behav Brain Res 54: 103–106.

Levy F, Meurisse M, Ferreira G et al. (1999). Afferents to the rostral olfactory bulb in sheep with special emphasis on the cholinergic, noradrenergic and serotonergic connections. J Chem Neuroanat 16: 245–263.

Linster C, Hasselmo ME (2001). Neuromodulation and the functional dynamics of piriform cortex. Chem Senses 26: 585–594.

Linster C, Maloney M, Patil M et al. (2003). Enhanced cholinergic suppression of previously strengthened synapses enables the formation of self-organized representations in olfactory cortex. Neurobiol Learn Mem 80: 302–314.

Linster C, Menon AV, Singh CY et al. (2009). Odor-specific habituation arises from interaction of afferent synaptic adaptation and intrinsic synaptic potentiation in olfactory cortex. Learn Mem 16: 452–459.

Lipton PA, Alvarez P, Eichenbaum H (1999). Crossmodal associative memory representations in rodent orbitofrontal cortex. Neuron 22: 349–359.

Luskin MB, Price JL (1982). The distribution of axon collaterals from the olfactory bulb and the nucleus of the horizontal limb of the diagonal band to the olfactory cortex, demonstrated by double retrograde labeling techniques. J Comp Neurol 209: 249–263.

Luskin MB, Price JL (1983a). The laminar distribution of intracortical fibers originating in the olfactory cortex of the rat. J Comp Neurol 216: 292–302.

Luskin MB, Price JL (1983b). The topographic organization of associational fibers of the olfactory system in the rat, including centrifugal fibers to the olfactory bulb. J Comp Neurol 216: 264–291.

Mandairon N, Kermen F, Charpentier C et al. (2014). Context-driven activation of odor representations in the absence of olfactory stimuli in the olfactory bulb and piriform cortex. Front Behav Neurosci 8: 138.

Martin C, Gervais R, Chabaud P et al. (2004). Learning-induced modulation of oscillatory activities in the mammalian olfactory system: the role of the centrifugal fibres. J Physiol Paris 98: 467–478.

Matsutani S (2010). Trajectory and terminal distribution of single centrifugal axons from olfactory cortical areas in the rat olfactory bulb. Neuroscience 169: 436–448.

Meisami E, Hamedi S (1986). Relative contribution of brain and peripheral connections to postnatal growth and cell accretion in the rat olfactory bulb. Brain Res 394: 282–286.

Mestre N, Petter A, Bons N (1992). Systematisation of the olfactory bulb efferent projections in a lemurian primate: Microcebus murinus. J Hirnforsch 33: 173–184.

Meyer RP (1981). Central connections of the olfactory bulb in the American opossum (Didelphys virginiana): a light microscopic degeneration study. Anat Rec 201: 141–156.

Millhouse OE, Heimer L (1984). Cell configurations in the olfactory tubercle of the rat. J Comp Neurol 228: 571–597.

Mohedano-Moriano A, de la Rosa-Prieto C, Saiz-Sanchez D et al. (2012). Centrifugal telencephalic afferent connections to the main and accessory olfactory bulbs. Front Neuroanat 6: 19.

Mor G, Saphier D, Feldman S (1987). Neural pathways that mediate the effects of afferent stimuli on paraventricular nucleus multiunit activity in freely moving rats. J Neurosci Res 17: 452–458.

Motokizawa F, Ino Y (1983). A non-thalamic olfactory pathway to the orbital gyrus in the cat. Brain Res Bull 10: 83–88.

Mouly AM, Fort A, Ben-Boutayab N et al. (2001). Olfactory learning induces differential long-lasting changes in rat central olfactory pathways. Neuroscience 102: 11–21.

Northcutt RG, Royce GJ (1975). Olfactory bulb projections in the bullfrog Rana catesbeiana. J Morphol 145: 251–267.

Oettl LL, Ravi N, Schneider M et al. (2016). Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. Neuron 90: 609–621.

Ojima H, Mori K, Kishi K (1984). The trajectory of mitral cell axons in the rabbit olfactory cortex revealed by intracellular HRP injection. J Comp Neurol 230: 77–87.

Paxinos G, Watson C (1986). The rat brain in stereotaxic coordinates, Academic Press, San Diego.

Payton CA, Wilson DA, Wesson DW (2012). Parallel odor processing by two anatomically distinct olfactory bulb target structures. PLoS One 7e34926.

Perry RE, Al Ain S, Raineki C et al. (2016). Development of odor hedonics: experience-dependent ontogeny of circuits supporting maternal and predator odor responses in rats. J Neurosci 36: 6634–6650.

Poo C, Isaacson JS (2009). Odor representations in olfactory cortex: "sparse" coding, global inhibition, and oscillations. Neuron 62: 850–861.

Price JL (1973). An autoradiographic study of complementary laminar patterns of termination of afferent fibers to the olfactory cortex. J Comp Neurol 150: 87–108.

Price JL (1985). Beyond the primary olfactory cortex: olfactory related areas in the neocortex, thalamus and hypothalamus. Chem Senses 10: 239–258.

Price JL (1987). The central olfactory and accessory olfactory systems. In: TE Finger, WL Silver (Eds.), Neurobiology of taste and smell. John Wiley & Sons, New York, pp. 179–204.

Price JL, Slotnick BM (1983). Dual olfactory representation in the rat thalamus: an anatomical and electrophysiological study. J Comp Neurol 215: 63–77.

Price JL, Sprich WW (1975). Observations on the lateral olfactory tract of the rat. J Comp Neurol 162: 321–336.

Price JL, Slotnick BM, Revial MF (1991). Olfactory projections to the hypothalamus. J Comp Neurol 306: 447–461.

Radtke-Schuller S, Kunzle H (2000). Olfactory bulb and retrobulbar regions in the hedgehog tenrec: organization and interconnections. J Comp Neurol 423: 687–705.

Ramus SJ, Eichenbaum H (2000). Neural correlates of olfactory recognition memory in the rat orbitofrontal cortex. J Neurosci 20: 8199–8208.

Ray JP, Russchen FT, Fuller TA et al. (1992). Sources of presumptive glutamatergic/aspartatergic afferents to the mediodorsal nucleus of the thalamus in the rat. J Comp Neurol 320: 435–456.

Reep RL, Winans SS (1982). Afferent connections of dorsal and ventral agranular insular cortex in the hamster Mesocricetus auratus. Neuroscience 7: 1265–1288.

Restrepo D, Hellier JL, Salcedo E (2014). Complex metabolically demanding sensory processing in the olfactory system: implications for epilepsy. Epilepsy Behav 38: 37–42.

Roberts RO, Christianson TJ, Kremers WK et al. (2016). Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. JAMA Neurol 73: 93–101.

Roesch MR, Stalnaker TA, Schoenbaum G (2007). Associative encoding in anterior piriform cortex versus orbitofrontal cortex during odor discrimination and reversal learning. Cereb Cortex 17: 643–652.

Root CM, Denny CA, Hen R et al. (2014). The participation of cortical amygdala in innate, odour-driven behaviour. Nature 515: 269–273.

Rothermel M, Wachowiak M (2014). Functional imaging of cortical feedback projections to the olfactory bulb. Front Neural Circuits 8: 73.

Royet JP, Zald D, Versace R et al. (2000). Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: a positron emission tomography study. J Neurosci 20: 7752–7759.

Royet JP, Hudry J, Zald DH et al. (2001). Functional neuroanatomy of different olfactory judgments. Neuroimage 13: 506–519.

Sadrian B, Wilson DA (2015). Optogenetic stimulation of lateral amygdala input to posterior piriform cortex modulates single-unit and ensemble odor processing. Front Neural Circuits 9: 81.

Sallaz M, Jourdan F (1993). c-Fos expression and 2-deoxyglucose uptake in the olfactory bulb of odour-stimulated awake rats. Neuroreport 4: 55–58.

Sallaz M, Jourdan F (1996). Odour-induced c-fos expression in the rat olfactory bulb: involvement of centrifugal afferents. Brain Res 721: 66–75.

Santiago AC, Shammah-Lagnado SJ (2005). Afferent connections of the amygdalopiriform transition area in the rat. J Comp Neurol 489: 349–371.

Savic I, Gulyas B, Larsson M et al. (2000). Olfactory functions are mediated by parallel and hierarchical processing. Neuron 26: 735–745.

Scalia F, Winans SS (1975). The differential projections of the olfactory bulb and accessory olfactory bulb in mammals. J Comp Neurol 161: 31–55.

Scalia F, Gallousis G, Roca S (1991). Differential projections of the main and accessory olfactory bulb in the frog. J Comp Neurol 305: 443–461.

Schoenbaum G, Chiba AA, Gallagher M (1998). Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. Nat Neurosci 1: 155–159.

Schoenbaum G, Chiba AA, Gallagher M (2000). Changes in functional connectivity in orbitofrontal cortex and basolateral amygdala during learning and reversal training. J Neurosci 20: 5179–5189.

Schoenfeld TA, Macrides F (1984). Topographic organization of connections between the main olfactory bulb and pars externa of the anterior olfactory nucleus in the hamster. J Comp Neurol 227: 121–135.

Schwob JE, Price JL (1984). The development of axonal connections in the central olfactory system of rats. J Comp Neurol 223: 177–202.

Scott JW (1981). Electrophysiological identification of mitral and tufted cells and distributions of their axons in olfactory system of the rat. J Neurophysiol 46: 918–931.

Scott JW, McBride RL, Schneider SP (1980). The organization of projections from the olfactory bulb to the piriform cortex and olfactory tubercle in the rat. J Comp Neurol 194: 519–534.

Scott JW, Ranier EC, Pemberton JL et al. (1985). Pattern of rat olfactory bulb mitral and tufted cell connections to the anterior olfactory nucleus pars externa. J Comp Neurol 242: 415–424.

Shammah-Lagnado SJ, Negrao N (1981). Efferent connections of the olfactory bulb in the opossum (Didelphis marsupialis aurita): a Fink–Heimer study. J Comp Neurol 201: 51–63.

Shipley MT (1995). Olfactory system. In: G Paxinos (Ed.), The rat nervous system, second ed. Academic Press, Sydney, pp. 899–928.

Shipley MT, Adamek GD (1984). The connections of the mouse olfactory bulb: a study using orthograde and retrograde transport of wheat germ agglutinin conjugated to horseradish peroxidase. Brain Res Bull 12: 669–688.

Shipley MT, Geinisman Y (1984). Anatomical evidence for convergence of olfactory, gustatory, and visceral afferent pathways in mouse cerebral cortex. Brain Res Bull 12: 221–226.

Skeen LC, Hall WC (1977). Efferent projections of the main and the accessory olfactory bulb in the tree shrew (Tupaia glis). J Comp Neurol 172: 1–35.

Slotnick BM (1985). Olfactory discrimination in rats with anterior amygdala lesions. Behav Neurosci 99: 956–963.

Slotnick BM, Berman EJ (1980). Transection of the lateral olfactory tract does not produce anosmia. Brain Res Bull 5: 141–145.

Slotnick BM, Risser JM (1990). Odor memory and odor learning in rats with lesions of the lateral olfactory tract and mediodorsal thalamic nucleus. Brain Res 529: 23–29.

Slotnick BM, Schoonover FW (1992). Olfactory pathways and the sense of smell. Neurosci Biobehav Rev 16: 453–472.

Smithson KG, Weiss ML, Hatton GI (1989). Supraoptic nucleus afferents from the main olfactory bulb—I. Anatomical evidence from anterograde and retrograde tracers in rat. Neuroscience 31: 277–287.

Sobel N, Prabhakaran V, Desmond JE et al. (1998). Sniffing and smelling: separate subsystems in the human olfactory cortex. Nature 392: 282–286.

Sorokowska A, Negoias S, Hartwig S et al. (2016). Differences in the central-nervous processing of olfactory stimuli according to their hedonic and arousal characteristics. Neuroscience 324: 62–68.

Stettler DD, Axel R (2009). Representations of odor in the piriform cortex. Neuron 63: 854–864.

Sullivan RM, Wilson DA (1993). Role of the amygdala complex in early olfactory associative learning. Behav Neurosci 107: 254–263.

Sutherland RJ, McDonald RJ (1990). Hippocampus, amygdala, and memory deficits in rats. Behav Brain Res 37: 57–79.

Takagi SF (1986). Studies on the olfactory nervous system of the old world monkey. Prog Neurobiol 27: 195–250.

Tanabe T, Iino M, Takagi SF (1975). Discrimination of odors in olfactory bulb, pyriform-amygdaloid areas, and orbitofrontal cortex of the monkey. J Neurophysiol 38: 1284–1296.

Thanos PK, Slotnick BM (1997). Short-term odor memory: effects of posterior transection of the lateral olfactory tract in the rat. Physiol Behav 61: 903–906.

Tseng GF, Haberly LB (1989). Deep neurons in piriform cortex. I. Morphology and synaptically evoked responses including a unique high-amplitude paired shock facilitation. J Neurophysiol 62: 369–385.

Turner BH, Mishkin M (1978). A reassessment of the direct projections of the olfactory bulb. Brain Res 151: 375–380.

Turner BH, Zimmer J (1984). The architecture and some of the interconnections of the rat's amygdala and lateral periallocortex. J Comp Neurol 227: 540–557.

Turner BH, Gupta KC, Mishkin M (1978). The locus and cytoarchitecture of the projection areas of the olfactory bulb in Macaca mulatta. J Comp Neurol 177: 381–396.

Valverde F (1965). Studies on the piriform lobe, Harvard University Press, Cambrdige.

Valverde F, Lopez-Mascaraque L, De Carlos JA (1989). Structure of the nucleus olfactorius anterior of the hedgehog (Erinaceus europaeus). J Comp Neurol 279: 581–600.

van Groen T, Wyss JM (1990). Extrinsic projections from area CA1 of the rat hippocampus: olfactory, cortical, subcortical, and bilateral hippocampal formation projections. J Comp Neurol 302: 515–528.

Varga AG, Wesson DW (2013). Distributed auditory sensory input within the mouse olfactory cortex. Eur J Neurosci 37: 564–571.

Vaughan DN, Jackson GD (2014). The piriform cortex and human focal epilepsy. Front Neurol 5: 259.

Velayudhan L, Lovestone S (2009). Smell identification test as a treatment response marker in patients with Alzheimer disease receiving donepezil. J Clin Psychopharmacol 29: 387–390.

Wesson DW, Wilson DA (2010). Smelling sounds: olfactory-auditory sensory convergence in the olfactory tubercle. J Neurosci 30: 3013–3021.

Wesson DW, Wilson DA (2011). Sniffing out the contributions of the olfactory tubercle to the sense of smell: hedonics, sensory integration, and more? Neurosci Biobehav Rev 35: 655–668.

Westberry JM, Meredith M (2016). GABAergic mechanisms contributing to categorical amygdala responses to chemosensory signals. Neuroscience 331: 186–196.

Willey TJ, Maeda G, Schultz RL et al. (1983). The principal projection pathway between the olfactory bulb and the prepyriform cortex in the cat. J Neurosci Res 9: 253–277.

Wilson DA (2000). Comparison of odor receptive field plasticity in the rat olfactory bulb and anterior piriform cortex. J Neurophysiol 84: 3036–3042.

Wilson DA (2009). Pattern separation and completion in olfaction. Ann N Y Acad Sci 1170: 306–312.

Wilson DA, Best AR, Sullivan RM (2004). Plasticity in the olfactory system: lessons for the neurobiology of memory. Neuroscientist 10: 513–524.

Wilson DA, Kadohisa M, Fletcher ML (2006). Cortical contributions to olfaction: plasticity and perception. Semin Cell Dev Biol 17: 462–470.

Wilson DA, Xu W, Sadrian B et al. (2014). Cortical odor processing in health and disease. Prog Brain Res 208: 275–305.

Wirth S, Ferry B, Di Scala G (1998). Facilitation of olfactory recognition by lateral entorhinal cortex lesion in rats. Behav Brain Res 91: 49–59.

Wyss JM (1981). An autoradiographic study of the efferent connections of the entorhinal cortex in the rat. J Comp Neurol 199: 495–512.

Wyss JM, Sripanidkulchai K (1983). The indusium griseum and anterior hippocampal continuation in the rat. J Comp Neurol 219: 251–272.

Xia CZ, Adjei S, Wesson DW (2015). Coding of odor stimulus features among secondary olfactory structures. J Neurophysiol 114: 736–745.

Xu W, Wilson DA (2012). Odor-evoked activity in the mouse lateral entorhinal cortex. Neuroscience 223: 12–20.

Zahm DS, Heimer L (1993). Specificity in the efferent projections of the nucleus accumbens in the rat: comparison of the rostral pole projection patterns with those of the core and shell. J Comp Neurol 327: 220–232.

Zald DH, Pardo JV (1997). Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. Proc Natl Acad Sci U S A 94: 4119–4124.

Zald DH, Pardo JV (2000). Functional neuroimaging of the olfactory system in humans. Int J Psychophysiol 36: 165–181.

Zhang Y, Burk JA, Glode BM et al. (1998). Effects of thalamic and olfactory cortical lesions on continuous olfactory delayed nonmatching-to-sample and olfactory discrimination in rats (Rattus norvegicus). Behav Neurosci 112: 39–53.

Zhu M, Li M, Ye D et al. (2016). Sensory symptoms in Parkinson's disease: clinical features, pathophysiology, and treatment. J Neurosci Res 94: 685–692.

HANDBOOK OF CLINICAL NEUROLOGY

Series Editors

MICHAEL J. AMINOFF, FRANÇOIS BOLLER, AND DICK F. SWAAB

VOLUME 164

ELSEVIER

SMELL AND TASTE

Series Editors

MICHAEL J. AMINOFF, FRANÇOIS BOLLER, AND DICK F. SWAAB

Volume Editor

RICHARD L. DOTY

VOLUME 164

3rd Series

ELSEVIER

ELSEVIER
Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-444-63855-7

Publisher: Nikki Levy
Editorial Project Manager: Kristi Anderson
Production Project Manager: Sujatha Thirugnana Sambandam
Cover Designer: Alan Studholme

Typeset by SPi Global, India