Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Sniffing out the contributions of the olfactory tubercle to the sense of smell: Hedonics, sensory integration, and more?

Daniel W. Wesson [a,b,*], Donald A. Wilson [a,b,c]

[a] Emotional Brain Institute, Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY 10962, United States
[b] Department of Child & Adolescent Psychiatry, New York University School of Medicine, 577 First Avenue, New York, NY 10016, United States
[c] Center for Neural Science, New York University, 4 Washington Place, New York, NY 10003, United States

ARTICLE INFO

ABSTRACT

Since its designation in 1896 as a putative olfactory structure, the olfactory tubercle has received little attention in terms of elucidating its role in the processing and perception of odors. Instead, research on the olfactory tubercle has mostly focused on its relationship with the reward system. Here we provide a comprehensive review of research on the olfactory tubercle—with an emphasis on the likely role of this region in olfactory processing and its contributions to perception. Further, we propose several testable hypotheses regarding the likely involvement of the olfactory tubercle in both basic (odor detection, discrimination, parallel processing of olfactory information) and higher-order (social odor processing, hedonics, multi-modal integration) functions. Together, the information within this review highlights an understudied yet potentially critical component in central odor processing.

© 2010 Elsevier Ltd. All rights reserved.

Contents

* Corresponding author at: Emotional Brain Institute, Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Building 35, Orangeburg, NY 10962, United States. Tel.: +1 845 398 5455; fax: +1 845 398 2193.
E-mail address: dwesson@nki.rfmh.org (D.W. Wesson).

1. Introduction

The formation of a sensory percept results from the processing of information across a distributed network of brain regions—each contributing uniquely to perception. In some cases the processing builds hierarchically as the information flows from one region to the next, with later regions building on the outcomes of earlier regions. This mode is exemplified by, for instance, the increasing complexity and size of visual receptive fields as information travels from the retina to the visual cortex. In other cases, different components are specialized for specific information content (e.g., visual movement versus visual objects). Within these schemata, extensive reciprocal and feedback connections within and between the sensory system and other systems further contribute to the emergence of the percept. A complete understanding of perception, therefore, will only result from understanding the role of every component across the entire network.

Olfaction is dependent on a large network of multiple primary and secondary processing centers which are connected in both serial and parallel manners. Adding to the complexity, some of these centers are reciprocally connected with non-olfactory regions. At the simplest level, olfactory receptor neurons project into the olfactory bulb and the output of the olfactory bulb projects to the olfactory cortex. The olfactory cortex – those areas with direct afferents from the olfactory bulb – is a three layered cortex composed of several distinct subregions, the largest of which is the piriform cortex (Haberly, 1998). The two other major components of the olfactory cortex are the anterior olfactory cortex (also termed 'anterior olfactory nucleus' (Haberly, 2001; Brunjes et al., 2005) and the subject of this review, the olfactory tubercle.

The olfactory tubercle [*tuberculum olfactorium*] was first described in 1896 by Rudolf Albert von Kölliker (Kölliker, 1896). Its reception of major olfactory bulb input has been known for over 50 years (White, 1965). However, with the exception of extensive research on its general anatomy, neurochemistry, and role in the reward system, almost nothing is known about the sensory processing functions of the olfactory tubercle. There are several excellent recent reviews of the role of olfactory tubercle in reward (e.g., (Heimer, 2003; Ikemoto, 2007), though these rightfully ignore the sensory role of this structure. The purpose of this review, therefore, is two-fold. First, we will summarize the relatively sparse data pertaining to the olfactory processing functions of the olfactory tubercle. Second, we will use this data as a basis to postulate some testable hypotheses regarding the contributions of the olfactory tubercle to olfaction and behavior. This review is intended to not only serve as a necessary foundation to understanding the olfactory tubercle, but also to spark future investigations into the role of this enigmatic structure in olfaction.

2. Where is the olfactory tubercle?

The olfactory tubercle differs in location and relative size between humans, non-human primates, rodents and other animals. In most cases, the olfactory tubercle is identifiable as a round bulge along the basal forebrain, posterior to the olfactory peduncle yet anterior to the optic chiasm. For instance, in rodents (i.e., rats, mice and hamsters) and birds (i.e., pigeons and quail) the olfactory tubercle is readily identifiable as a large, pronounced, elliptical bulge nested between the lateral olfactory tract, the optic chiasm and the hemispheric midline ridge (Fig. 1A) (Millhouse and Heimer, 1984). Indeed, the olfactory tubercle occupies a considerably large portion of the basal forebrain in these animals (Fig. 1A and B).

On the other hand, visual identification of the olfactory tubercle in humans and non-human primates is not as easy. This difficulty in identifying the olfactory tubercle stems from the fact that the
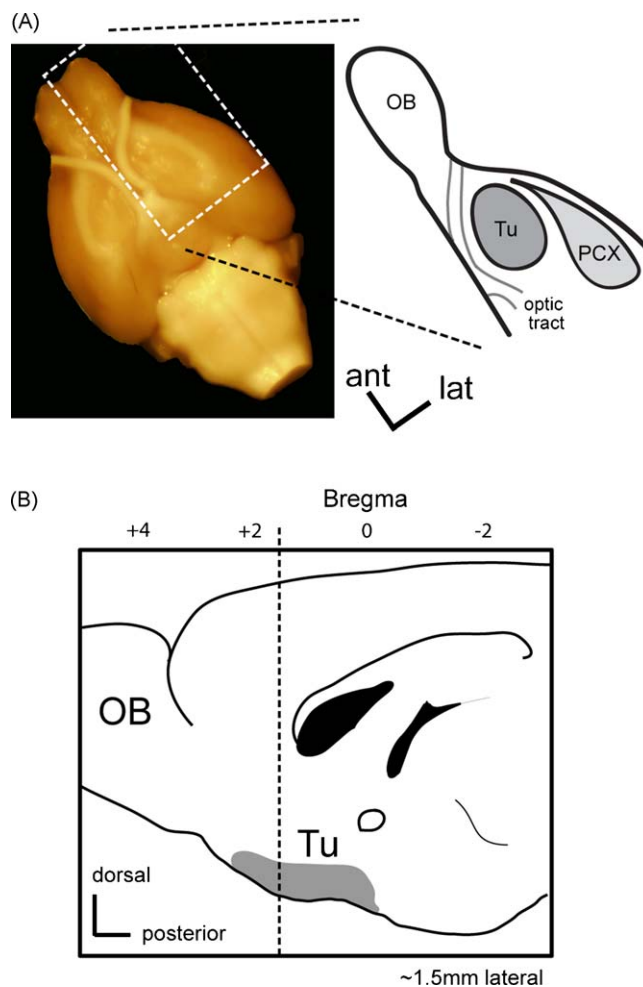

Fig. 1. Gross anatomy of the olfactory tubercle. (A) Image (left) and rendering (right) of the ventral surface of the mouse (mus musculus) brain showing the anatomical locations of the olfactory bulb (OB), olfactory tubercle (Tu) and piriform cortex (PCX). Sensory information from the OB travels into the Tu and PCX via the lateral olfactory tract. The Tu in the mouse (and other rodents) is identifiable as a pronounced region nested between the optic and lateral olfactory tracts. (B) Sagittal rendering of the rodent brain, designating the location of the Tu in the basal forebrain (gray shaded region). Drawing in (B) is adapted from (Paxinos and Franklin, 2000).

basal forebrain bulge is small, if not mostly absent in these species. Thus, anatomical definitions of the olfactory tubercle in these cases are not consistent. For example, whereas some have considered the human olfactory tubercle to include all of the anterior perforated space (Rose, 1927; Crosby and Humphrey, 1941), others have designated the slightly more-prominent region of the perforated space, posterior to the olfactory stalk, as the olfactory tubercle (Nauta and Haymaker, 1969; Stephan, 1975). In more recent human brain imaging studies (Sobel et al., 2000; Weismann et al., 2001) the olfactory tubercle is identified as a small zone nested between the uncus and the medial forebrain bundle, ventral to the anterior olfactory cortex. In non-human primates, the olfactory tubercle is usually identified as a small region immediately posterior to the olfactory stalk. Importantly, only a portion of this region in non-human primates receives direct olfactory input from the olfactory bulb (Carmichael et al., 1994). Thus, as part of the olfactory cortex, the designation of the olfactory tubercle ideally should be based upon these regional distinctions in combination with histological verification of direct, monosynaptic input from the olfactory bulb (as discussed in more detail later).

In terms of functional anatomy, the olfactory tubercle can be considered part of at least three larger networks. First, based on

its location along the rostral ventral region of the brain, the olfactory tubercle is considered part of the basal forebrain, along with diagonal band nuclei, nucleus accumbens, and amygdaloid nuclei (Alheid and Heimer, 1988). Second, the focus of this review stems from the olfactory tubercle as a component of the olfactory cortex as defined by receiving direct input from the olfactory bulb. This olfactory input makes odor a likely major driving force of olfactory tubercle activity. Finally, based on embryology, anatomy and neurochemical data (Alheid and Heimer, 1988; Voorn et al., 2004), the olfactory tubercle is considered part of the ventral striatum. Like other parts of the striatum, the olfactory tubercle is interconnected with the ventral pallidum, and has a number of similarities with other striatal regions including neuropeptide expression and cell morphology. Some authors also divide the olfactory tubercle into medial and lateral subdivisions, with the medial region aligned with the extended amygdala (Alheid and Heimer, 1988; Voorn et al., 2004). However, terminology and neuroanatomical boundaries within the striatum and rostral basal forebrain are by no means fixed (Swanson and Petrovich, 1998; Voorn et al., 2004). Understanding commonalities and differences between the olfactory tubercle and its surrounding structures will be helpful in identifying possible functions of this region.

3. Neurodevelopment of the tubercle

Compared to other cortical structures, the olfactory tubercle has an unusual cytoarchitecture which includes both cortical and nuclear organization (Pigache, 1970). Whereas the ventral portion of the olfactory tubercle is tri-laminar and cortical-like, the dorsal portion contains dense cell clusters (the islands of Calleja and cell bridges) and adjoins (even contains) the ventral pallidum. Several studies have contributed to understanding neurogenesis of the olfactory tubercle and the greater olfactory cortex (Hinds and Angevine, 1965; Smart and Smart, 1977; Bayer, 1985, 1986; Ashwell et al., 2008; Garcia-Moreno et al., 2008). Migrating cells from multiple developmental sites converge to form the olfactory tubercle (Garcia-Moreno et al., 2008) including the ventral lateral ganglionic eminence and the rostromedial telencephalic wall. Notably, whereas subsets of cells from the rostromedial telencephalic wall also project to the neighboring piriform cortex, the input of cells from the ventral lateral ganglionic eminence to the olfactory tubercle is apparently unique amongst olfactory cortical regions (Garcia-Moreno et al., 2008).

Early autoradiographic work by Bayer (1985) showed that olfactory tubercle neurons originate as early as embryonic day 13 (E13). Further, the time-course of cell development/placement occurs in a layer specific manner. In particular, large neurons in layer III (the multiform layer) originate from E13 to E16. Cells in layer II (dense cell layer), the small–medium cells in layer III, and the striatal bridges originate between E15 and E20. These previous cell groups develop along a lateral to medial gradient. Island of Calleja granule cells originate between E19 and E22, although neurogenesis and migration of these granule cells into the islands of Calleja continues until well after birth in the mouse (De Marchis et al., 2004) and primate (Bedard et al., 2002). Citing analogies to the time-course of neurogenesis in the striatum, globus pallidus, and substantia innominata, Bayer (1985) postulated that the olfactory tubercle should be considered more like a striatal-pallido region, versus an olfactory one.

This development of the olfactory tubercle coincides closely with the development of olfactory bulb input (Schwob and Price, 1984a,b). The emergence of the 3 main layers of the olfactory tubercle begins approximately simultaneously. Further, this happens around the same time as the emergence of the layers in the piriform cortex (Schwob and Price, 1984a). In particular, around E17
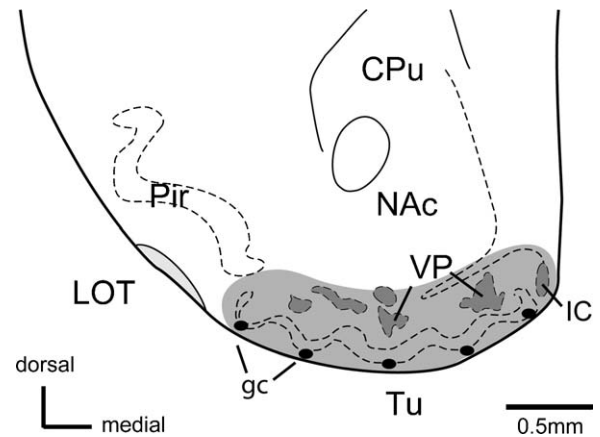

Fig. 2. Local anatomy of the olfactory tubercle. Coronal diagram of the basal forebrain in a mouse (*Mus musculus*) showing detailed anatomy of the olfactory tubercle (Tu, gray shaded region). As discussed within the text, the Tu 'cortical' zone contains a trilamilar region wherein the dense cell layer (layer II, dashed region) possesses numerous gyrating 'hills'. At the trough of these hills are small granule cell clusters (gc). Within the cap region of the tubercle are projections from the ventral pallidum (VP) and also small dense cell clusters called the islands of Calleja (IC), some of which are off-shoots of the nucleus accumbens (NAc). CPu—caudate putamen, Pir—piriform cortex, LOT—lateral olfactory tract. Drawing adapted from (Paxinos and Franklin, 2000), at the anterior/posterior location indicated in Fig. 1B (dashed line).

fibers from the lateral olfactory tract begin to branch into the olfactory tubercle. The lateral olfactory tubercle (adjoining the lateral olfactory tract) receives the densest fiber input, whereas the medial olfactory tubercle receives only light fiber projections (Schwob and Price, 1984a). Such fiber distribution patterns are seemingly complete by the end of the first postnatal week. Notably, these two areas (the olfactory tubercle and piriform cortex) develop lamination prior to the anterior olfactory cortex (Schwob and Price, 1984a)—perhaps suggesting greater maturity (and function) of the olfactory tubercle and piriform network early in life in comparison to the anterior olfactory cortex. Functional mapping of olfactory system activation by odors with [14c]-2-deoxy-D-glucose (2DG) analysis, however, has revealed that the olfactory tubercle is activated along with other secondary olfactory structures (including the anterior olfactory cortex) starting as early as postnatal day 1 (Astic and Saucier, 1981). In summary, these data demonstrate that the cellular and network components of the olfactory tubercle are assembled in a manner allowing functional input of olfactory information, even early in life.

4. Morphological and neurochemical features of the olfactory tubercle

Originally, the olfactory tubercle was classified as a primitive cortex ('cortex primitivus') (Brodmann, 1909). However, some later anatomical investigations of the olfactory tubercle did not classify it as cortical (e.g., (Gray, 1924)). Unlike other archicortical structures, the olfactory tubercle is not a 'simple' trilaminar region. Instead, the olfactory tubercle is a trilaminar structure in the anterior-most aspects, which, in the more ventral areas becomes a peculiar gyrating structure with anatomically defined 'hills' (gyri and sulci) and 'islands' (Fig. 2). A somewhat poetic description of the tubercle was given by Gray (1924): "a broad band of densely crowded, granular cells pursues a tortuous course across this region". This picture painted by Gray highlights the 'hills' created by the dense cell layer of the tubercle. Further, unlike other olfactory cortical areas (piriform and anterior olfactory cortex), the olfactory tubercle does not possess an association fiber system (Haberly and Price, 1978).
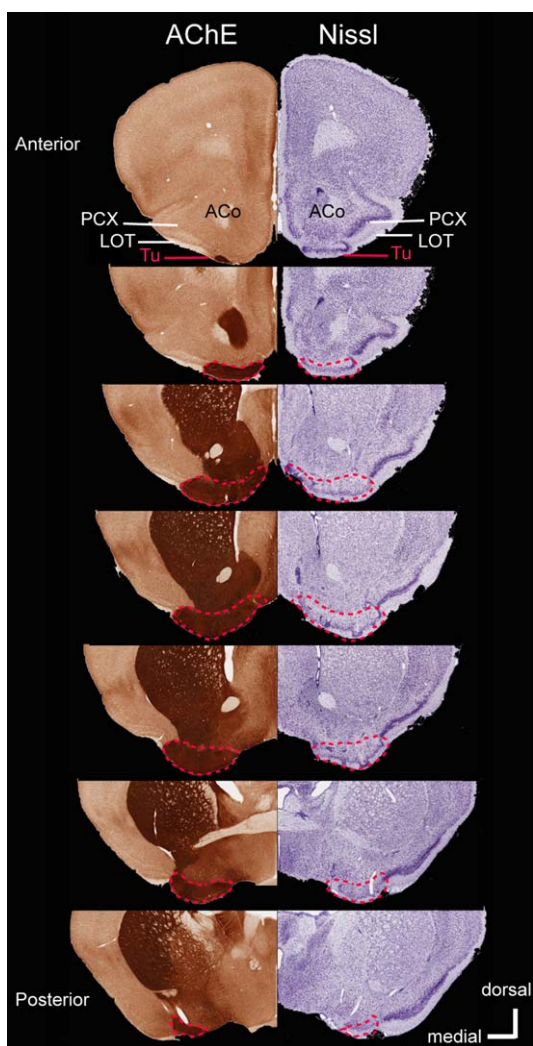
Fig. 3. Olfactory tubercle cytoarchitecture. Serial coronal sections of the forebrain of mice (*Mus musculus*; spanning from apx. +2.5 to −0.5 mm relative to bregma) showing the cytoarchitecture of the olfactory tubercle (Tu) with both acetylcholinesterase (AchE) and Nissl staining. PCX—piriform cortex, LOT—lateral olfactory tract, ACo—anterior commisure. Red dashed zone indicates the approximate region of the Tu. Images adapted from http://brainmaps.org.

At least in higher mammals (e.g., cats) the olfactory tubercle can be divided into two main components, a cortical zone and a cap/hilus zone (Meyer and Wahle, 1986). Whereas in higher mammals (Meyer and Wahle, 1986) these components are more discretely identifiable, in smaller macrosomats these regions may be contiguous—perhaps being separated by <500 μm distance (see Fig. 2). The cap region forms ∼5 gyri (in rodents) which reside ventral to the islands of Calleja. Such gyrations are less pronounced in the more anterior aspects of the olfactory tubercle.

One of the most striking features of the olfactory tubercle are tightly packed cell clusters which reside dorsally to the dense cell layer (see Figs. 2 and 3). Named after Julián Calleja y Sánchez from anatomical studies in rabbits (Calleja, 1893), these "islands" are rod-like structures which extend rostro-caudally through the majority of the olfactory tubercle (de Vente et al., 2001). The islands of Calleja have many GABA-ergic granule cells with short, sparse processes, as well as a population of larger cells with longer dendrites (Ribak and Fallon, 1982; Krieger et al., 1983; Millhouse, 1987; Meyer et al., 1989). The outer-most cells of the islands of Calleja are innervated by dopaminergic projections from the nucleus accumbens and the substantia nigra compacta (Fallon et al., 1978). The

most medially positioned island of Calleja is in fact an extension of the nucleus accumbens (Talbot et al., 1988b). The neuropil surrounding the islands is innervated by vast cholinergic projections and the islands of Calleja stain heavily for acetylcholinesterase (e.g., as shown in Fig. 3) and choline acetyltransferace (Talbot et al., 1988a). The neuropil of the islands of Calleja also contains nitric oxide synthase (Vincent and Kimura, 1992). The olfactory tubercle is also dense in other neurochemicals and their respective receptors (Rieger and Heller, 1979; Alheid and Heimer, 1988; Riedel et al., 2002). Yet as current reviews on this subject are already available (Alheid and Heimer, 1988; Ikemoto, 2007) we will not go into further detail here.

Using Golgi methods in rats, Millhouse and Heimer (1984) found several distinct cell types in the olfactory tubercle (in addition to those reviewed above within the islands of Calleja) (see Fig. 4). These cell types are classified based upon somatic size and dendritic structure. Further, the cells reside often in one or one to two cell layers of the tubercle. The most common cell type in the olfactory tubercle is the medium-sized dense-spine cell. The soma of this cell type is found predominately in the dense cell layer (layer II) and as the name implies, its dendrites are covered in spi axons into the dorsal multiform layer (Millhouse and Heimer, 1984). Medium-sized dense-spine cells also project into the nucleus accumbens and the caudate putamen (Fallon, 1983a)—linking the olfactory tubercle within the pallidum. The largest cell in the olfactory tubercle is the crescent cell, named after its crescent-shaped cell body. The crescent cells are found within both the multiform (layer III) and dense cell layers (layer II). Two additional morphologies of medium-sized cells reside in the multiform and dense cell layers, including spine-poor neurons and spindle cells—both types set apart from the medium-sized dense-spine cells due to their sparse dendritic trees. Finally, there are three classes of small cells in the olfactory tubercle, found mostly in the dense cell (layer II) and molecular layers (layer I). First, there are pial cells which resemble miniature medium-sized densely spined cells. Pial cells are named due to their location near the pial surface. Second, radiate cells are identified by their numerous multi-directional spineless dendrites. Third, similar to pial cells, small spine-rich cells also look like medium-sized spine-rich cells yet are not located near the pial surface (Ribak and Fallon, 1982).

Work in the olfactory tubercle of larger mammals has shown that small pyramidal-like cells (perhaps the medium-sized dense-spine cells from (Millhouse and Heimer, 1984)) project from the dense cell layer of the cortical zone of the olfactory tubercle into both the hilus region and the accumbens part of the ventral pallidum (Meyer and Wahle, 1986). Perhaps in relation to this, similarities between the morphology of olfactory tubercle cells with those in the accumbens has resulted in speculation that some cells in the olfactory tubercle are ventral pallidum cells (Millhouse and Heimer, 1984). Indeed, due to its interconnections with the mesocorticolimbic system, the olfactory tubercle along with the nucleus accumbens make up the anatomical region of the ventral striatum (Heimer and Wilson, 1975). This is especially evident upon examination of acetylcholinesterase staining of coronal sections through the forebrain – wherein the staining forms a clear continuum between the accumbens and the olfactory tubercle (see Fig. 3). This same neurochemical phenotype supports a differentiation between the olfactory tubercle and the neighboring piriform cortex, which is not dense in acetylcholinesterase (Fig. 3).

5. Olfactory input into the olfactory tubercle

The olfactory tubercle receives monosynaptic olfactory input from both the olfactory bulb and the piriform cortex (White, 1965; Haberly and Price, 1977; Luskin and Price, 1983; Schwob and Price, 1984a; Johnson et al., 2000). Axons of olfactory bulb second order
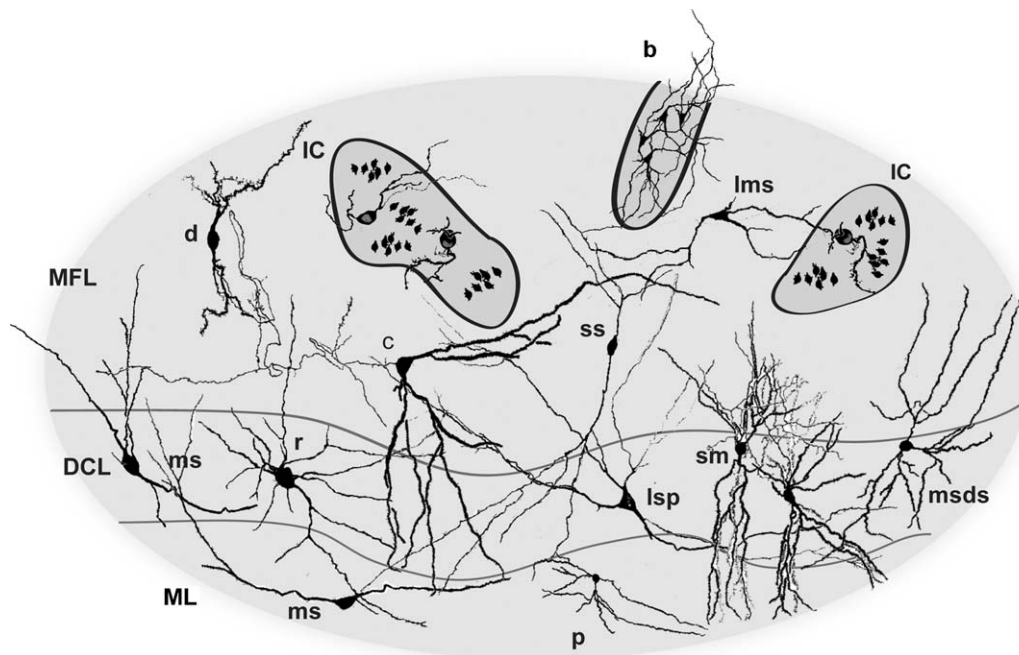
Fig. 4. Cellular diversity in the olfactory tubercle. Golgi impregnated cells from the olfactory tubercles of rats (adapted, modified, and classified based on original work by Millhouse and Heimer (1984) and Millhouse (1987) reconstructed together within a single diagram. The three cell layers ML (molecular layer), DCL (dense cell layer), and MFL (multi-form layer) are indicated. Cells include granule cells (located within the islands of Calleja (IC), crescent cells (c), dwarf cells (d), radiate cells (r), pial cells (p), spindle-shaped cells (ss), medium-sized, moderately spiny cells (ms), large, spine-poor cells (lsp), medium-sized densely spined cells (msds), symmetrical, medium-sized densely spined cells (sm) and large, moderately spined cells (lms). Some medium cells also compose a cell bridge (b) between the olfactory tubercle and the ventral striatum. While ICs are composed mostly of g cells, they also contain sparse lms cells. g cell bodies are approximately 5–8 μm. lsp and lms cell bodies reach up to 20 μm in diameter. Cell body sizes are not precise to scale. Due to space, this image does not reflect the 'hills' created by the dense cell layer as it spans the lateral–medial distance (see Fig. 2).

neurons (mitral and tufted cells) fasciculate to form the lateral olfactory tract which travels along the ventral–lateral aspect of the brain. A subset of lateral olfactory tract axons enter the molecular layer of the olfactory tubercle (layer I) where they likely synapse onto olfactory tubercle principle neurons in the dense cell layer (see Fig. 5) (Scott et al., 1980). Whereas the piriform cortex is mostly innervated by mitral cells, tufted cells from the ventral portion of the olfactory bulb send a large, if not dominant, dominant projection into the olfactory tubercle (Scott et al., 1980) (see Fig. 6). Thus, there are two 'sources' of output from the olfactory bulb. Given that tufted cells display enhanced sensitivity to odors at lower concentrations, enhanced entrainment to respiratory cycles, and broader receptive fields in comparison to mitral cells (Mori and Shepherd, 1994; Shepherd et al., 2004), the olfactory tubercle may be integral to a parallel processing network for olfactory information alongside the piriform cortex.

There is recent functional evidence for dual pathways of olfactory input into the olfactory tubercle (Carriero et al., 2009). Carriero et al. (2009) showed that lateral olfactory tract stimulation results in a biphasic voltage sensitive dye response in the olfactory tubercle. In support of the hypothesis that each phase of this response was due to unique input from the olfactory bulb and piriform cortex separately, the authors revealed that severing the lateral olfactory tract projection into the piriform cortex reduced the olfactory tubercle's secondary biphasic response. Also, possibly answering whether the olfactory tubercle is more or less homogenously activated in response to odors (here modeled with electrical simulation of the lateral olfactory tract), these experiments demonstrated that the voltage spread across the surface of the olfactory tubercle travels in a more-or-less homogenous gradient from lateral (adjacent to the lateral olfactory tract) to medial (Carriero et al., 2009). Such observations are consistent with the fact that more olfactory bulb afferent fibers terminate in the lateral versus medial molecular layer of the olfactory tubercle (Schwob and Price, 1984a) (see Fig. 5). Alternative hypotheses for compartmentalization of odor processing in the olfactory tubercle exist (Josephson et al., 1997). For example, based on axonal tracing data, sub-regions of the olfactory tubercle may have reduced levels of olfactory sensory input (Josephson et al., 1997). Indeed, as shown in Fig. 5, the zone of the olfactory tubercle most distal from the lateral olfactory tract is only sparsely innervated by olfactory bulb input.

The olfactory tubercle also receives indirect input from the accessory olfactory system (Ubeda-Bañona et al., 2007b; Ubeda-Bañona et al., 2007a). The accessory olfactory bulb projects into the posteromedial cortical amygdaloid nucleus in rodents (Kevetter and Winans, 1981). In turn, the posteromedial cortical amygdaloid nucleus projects into the ventral striatum, including the olfactory tubercle (especially the medial olfactory tubercle and the islands of Calleja) (Ubeda-Bañona et al., 2007b). Unlike in the main olfactory system, we are not aware of evidence for direct (monosynaptic) input to the olfactory tubercle from the accessory olfactory bulb. Thus, both accessory and main olfactory systems converge in the olfactory tubercle—presenting this structure as a 'mixed' olfactory cortex (Martinez-Marcos, 2009). These anatomical points highlight the likely role of the tubercle in the processing of odors.

6. Interconnections of the tubercle with other regions

As shown in Fig. 7, the olfactory tubercle is interconnected with sensory, cognitive, endocrine, and reward-related centers in the brain. As previously discussed, major olfactory sensory input arrives in the olfactory tubercle via direct projections from the olfactory bulb output neurons (Fig. 6) (White, 1965; Scott et al., 1980), the nucleus of the lateral olfactory tract (Santiago and Shammah-Lagnado, 2004), and association fiber input from the piriform cortex (Luskin and Price, 1983). The olfactory tubercle additionally receives fibers from the agranular insular cortex (Reep and Winans, 1982), endopiriform nucleus (Fallon, 1983b; Behan
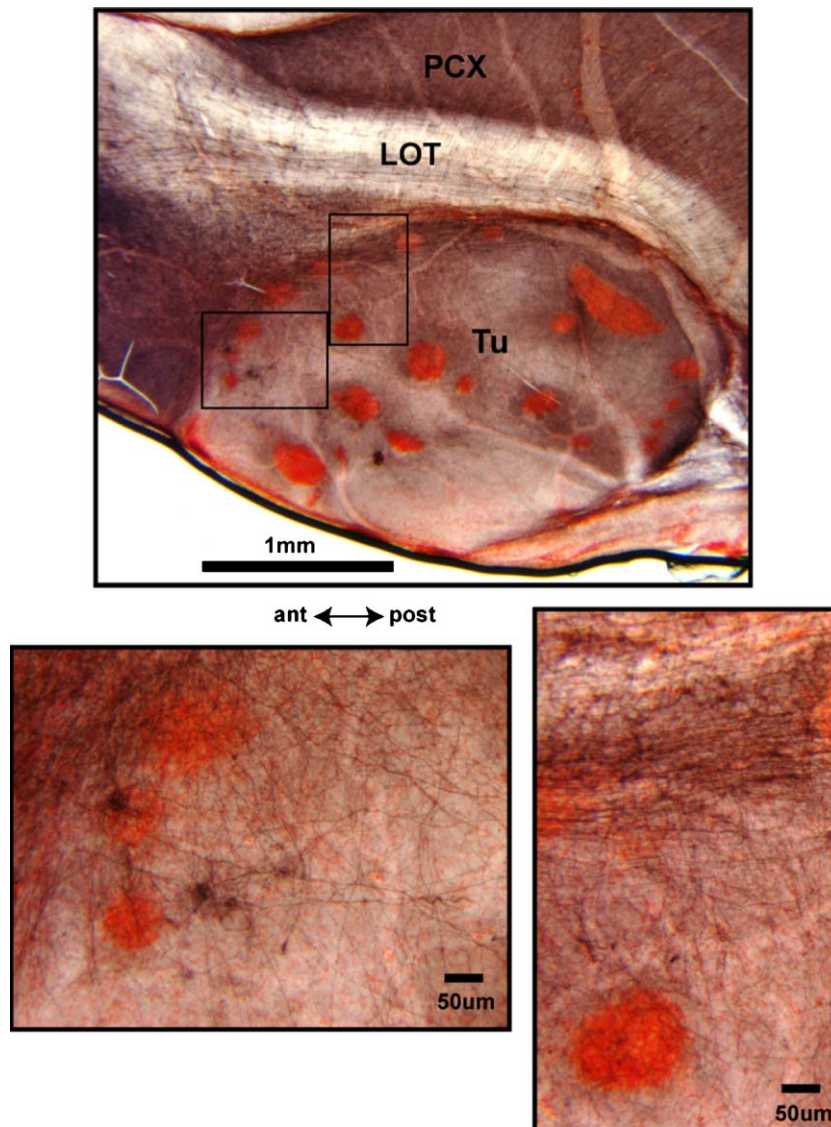
Fig. 5. Olfactory fiber input into the olfactory tubercle. 'Flattened cortex' image through the mouse (*Mus musculus*) forebrain with olfactory sensory fibers loaded with PHA-L (*Phaseolus vulgaris* leucoagglutinin, by injection into the ventral main olfactory bulb) and visualized with DAB (3,3'-diaminobenzidine; brown) after anti-PHA-L immunohistochemistry. Cell nuclei are counterstained with Vector Nuclear Fast Red (red) which readily identifies spherical granule cell clusters (the islands of Calleja). LOT—lateral olfactory tract. Tu—olfactory tubercle. PCX—anterior piriform cortex. Anatomical input is most dense near the LOT and in the anterior Tu (near the olfactory bulb). Images courtesy of Ningdong Kang and Michael Baum (Boston University).

and Haberly, 1999) and entorhinal cortex (Haberly and Price, 1978). Also as discussed earlier, indirect accessory olfactory input also arrives in the olfactory tubercle from the amygdala (which receives direct input from the accessory olfactory bulb) (Ubeda-Bañona et al., 2007b).

The olfactory tubercle is heavily interconnected with the reward system (for review see Ikemoto, 2007). Reward system projections into the olfactory tubercle include the rostral linear nucleus of the ventral tegmental area (Del-Fava et al., 2007), the nucleus accumbens (Zahm and Heimer, 1993), the medial forebrain bundle (Gaykema et al., 1990) and the substantia nigra (Fallon et al., 1978). Also, the olfactory tubercle receives additional input from the amygdala, including the medial nucleus (Usunoff et al., 2009), posterolateral olfactory amygdala (Ubeda-Bañona et al., 2007b), posterior nucleus, periamygdaloid cortex and the cortical nuclei of the amygdala (Fallon, 1983b). Finally, the olfactory tubercle is innervated by the thalamus and hypothalamus, including the paraventricular and paratenial nuclei of the dorsal midline thalamus (Vertes and Hoover, 2008), the lateral hypothalamus (Fallon, 1983b), the subthalamic nucleus (Groenewegen and Berendse, 1990) and the septum (Fallon, 1983b).

Hippocampal regions also target the olfactory tubercle. The posteromedial molecular layer of the olfactory tubercle receives fibers from the hilar region of the dentate gyrus (Kunzle, 2005). The subiculum also projects into the medial olfactory tubercle (Groenewegen et al., 1987). Given the olfactory tubercle's place in the reward system (Heimer, 2003; Ikemoto, 2007), this may provide an anatomical pathway for the involvement of the subiculum in reward behavior (Martin-Fardon et al., 2007).

Auditory and visual sensory fibers converge in the olfactory tubercle in manners which might contribute to multi-sensory convergence and integration. Auditory sensory fibers may arrive in the olfactory tubercle via general associative networks involving the hippocampus (Deadwyler et al., 1987) or ventral pallidum (Budinger et al., 2008) or directly from the auditory cortex (Budinger et al., 2006). Visual sensory fibers arrive directly from retinal ganglion cells (Mick et al., 1993). Thus, as discussed in detail later, the olfactory tubercle is not a 'simple' olfac-
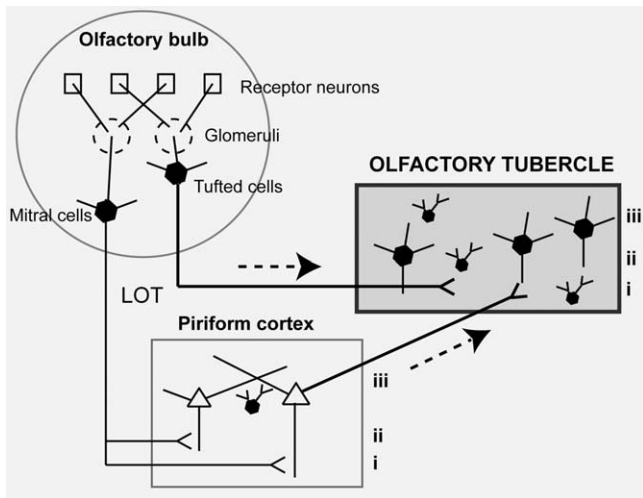
Fig. 6. Olfactory sensory input into the olfactory tubercle. Schematic representation of olfactory sensory input into the olfactory tubercle. Mitral and tufted cells depart the olfactory bulb carrying odor information along the lateral olfactory tract (LOT). Mitral cell axons mostly terminate in the piriform cortex. Tufted cell axons mostly terminate into layer I of the olfactory tubercle (Scott et al., 1980), allowing monosynaptic olfactory input. PCX association fibers project partly into the olfactory tubercle, allowing di-synaptic olfactory input. These pathways represent possible parallel input of olfactory sensory signals into the tubercle.

tory sensory structure but instead may integrate multi-modal information.

The olfactory tubercle is innervated by numerous neuromodulatory sites. Dense innervation by locus coeruleus afferents (Solano-Flores et al., 1980; Guevara-Aguilar et al., 1982) and serotonergic fibers from the dorsal and ventral aspects of the raphe nuclei (Guevara-Aguilar et al., 1982) both terminate in the olfactory

Fig. 7. The olfactory tubercle is a highly interconnected brain region. Diagram of brain regions which are anatomically connected with the olfactory tubercle. Direction of arrows indicates known directions of information flow. References for each connection can be found within the text. LOT—lateral olfactory tract.

tubercle. The olfactory tubercle also receives local acetylcholinergic fibers from the horizontal limb of the diagonal band (Price and Powell, 1970). Thus the olfactory tubercle is a likely contributor to state dependent olfactory processing, which may itself be modulated by state (see Section 9).

The olfactory tubercle has extensive efferent projections (Fig. 7). The olfactory tubercle sends centrifugal input to the both olfactory bulbs (ipsi- and contralateral) and the anterior olfactory cortex (ipsi- and contralateral), particularly the dorsomedial and pars lateralis zones (Heimer, 1968; Shafa and Meisami, 1977; Brunjes et al., 2005). The olfactory tubercle projects to the mediodorsal (Young et al., 1984) and submedial nuclei of the thalamus (Fallon, 1983b; Price and Slotnick, 1983) as well as the lateral hypothalamus (Price et al., 1991), Forel's field H (Fallon, 1983b), the supramammillary complex (Fallon, 1983b), the nuclei Gemini (Scott and Chafin, 1975; Heimer et al., 1990) and the ventromedial nucleus of the hypothalamus (Groenewegen et al., 1993). The tubercle also densely innervates the nucleus accumbens, ventral pallidum, and to a lesser-extent the caudate putamen (Heimer and Wilson, 1975). Projections from the Islands of Calleja innervate the ventral tegmental area and the mediodorsal nucleus of the thalamus (Fallon, 1983b). An additional structure involved in reward/reinforcement signaling (i.e., the presence of punishment or the absence of reward) (Matsumoto and Hikosaka, 2009) to which the olfactory tubercle projects is the lateral habenula (Fallon, 1983b). Finally, the olfactory tubercle projects into the orbitofrontal cortex (Barbas, 1993; Illig, 2005).

In summary, the olfactory tubercle is interconnected with numerous brain regions. Especially prominent are connections with sensory (olfactory bulb, piriform cortex, and anterior olfactory cortex) and arousal/reward centers (the nucleus accumbens, ventral tegmental area and caudate putamen). This connectivity pattern overlaps with, but is distinct from, that reported for the piriform cortex. The olfactory tubercle's afferent and efferent anatomy situates it as a potentially critical interface between sensory processing and behavioral response.
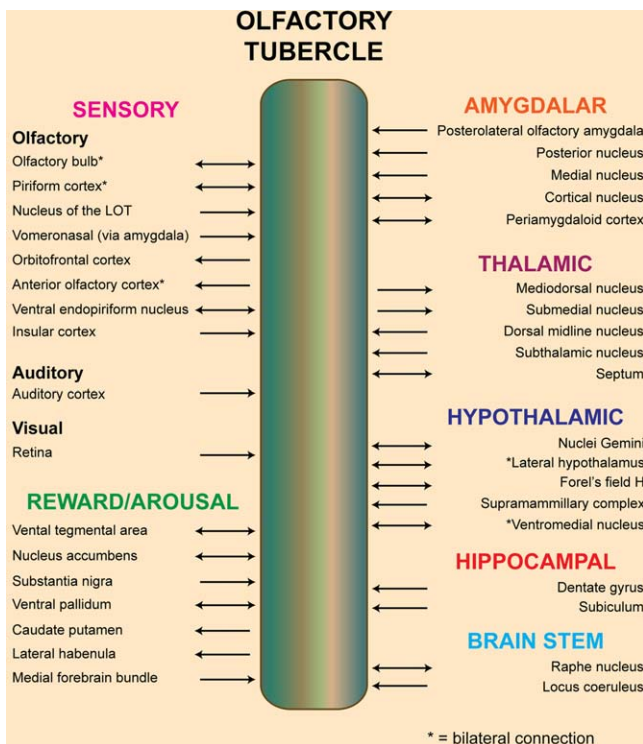
7. The role of the olfactory tubercle in odor information processing

The role of the olfactory tubercle in olfactory coding has received relatively little attention. This may be due to historical patterns of research interest in the olfactory bulb and piriform cortex leading future researchers to follow in suit. Regardless, as a major structure in olfactory system, understanding the role of the olfactory tubercle in olfaction will be important in an ultimate understanding of the sense of smell.

Human functional imaging by Zelano et al. (2007) suggests that the olfactory tubercle may be crucial in determining the source of olfactory information (trigeminal irritants vs. pure olfactory odors). This is in contrast to the piriform cortex, which their data suggest represents the valence of odors but not the source (Zelano et al., 2007). Work from the same group has also shown that the olfactory tubercle responds to odor inhalations which were attended to more-so than unattended inhalations (Zelano et al., 2005). Thus, the olfactory tubercle may be involved in attentional modulation of the early olfactory code.

In cellular-level studies the olfactory tubercle has been found to display *in vivo* paired-pulse facilitation (McNamara et al., 2004), indicative of at least short-term plasticity. Furthermore, based on *in vitro* field potential responses to stimulation of the molecular (afferent fibers) and multiform (intrinsic and association fibers) layers we know that the multiform, but not molecular layer synapses are modulated by ACh (Owen and Halliwell, 2001), similar to that observed in piriform cortex (Hasselmo and Bower, 1992).

Perhaps the most detailed physiological work to date comes from Chiang and Strowbridge (2007). In this work, the authors used *in vitro* whole-cell patch-clamp experiments to characterize the intrinsic properties of olfactory tubercle neurons (dense cell and multiform layers) and to relate the patterns of neural activity with cellular morphology (Chiang and Strowbridge, 2007). Three distinct firing modes were observed. "Regular spiking" neurons display action potentials at a consistent frequency throughout a current pulse. "Intermittently discharging" cells display high frequency bursts of action potentials, separated by pauses in firing (~100–800 ms). Finally, "bursting neurons" in the olfactory tubercle display brief bursts of high frequency action potentials immediately upon the current step, which terminate within approximately the first 500 ms. Chiang and Strowbridge (2007) suggest that the rapid spiking neurons (found mostly in the dense cell layer) may be the common medium-size densely spiny neurons of Millhouse and Heimer (1984) (Fig. 4). Due to spiking pattern similarities with pyramidal cells in the neighboring piriform cortex, the authors suggest that these cells may be glutamatergic (Chiang and Strowbridge, 2007). In contrast, the spine-poor neurons of Millhouse and Heimer (1984) are likely intermittent and regular spiking cells (and perhaps GABA-ergic). Of notable interest to this review, the authors also used a current-injection protocol to mimic respiratory rhythm-related responses in the cells to see if olfactory tubercle neurons display a respiratory phase-dependent activity which is commonly observed within other olfactory areas (Chaput, 1986; Sobel and Tank, 1993; Wilson, 1998; Spors et al., 2006; Carey et al., 2009). Indeed, both intermittent and regular spiking cells showed phasic responses with each 'sniff-like' current pulse (Chiang and Strowbridge, 2007). Thus, while not exploring the role of the olfactory tubercle in odor processing *per se*, these *in vitro* data suggest that olfactory tubercle units have the functional capabilities of other olfactory center neurons. Further, while no detailed dual immunolabeling studies are available, these results suggest that the network functions of the olfactory tubercle are likely shaped by both excitatory (glutamate) and inhibitory (GABA) systems.

Including recent work from our group, we are aware of only two studies which have recorded *in vivo* odor-evoked tubercle unit responses (Murakami et al., 2005; Wesson and Wilson, 2010). Both of these studies utilized multi- and single-unit extracellular recordings in urethane anesthetized rodents. Though not the focus of their work, Murakami et al. (2005) showed that rat olfactory tubercle neurons display odorant-evoked responses (increase rate of action potentials). More recently our group further explored odor-evoked activity in mouse olfactory tubercle units (Wesson and Wilson, 2010). As shown in Fig. 8, this work showed that individual olfactory tubercle units robustly respond to odors. Further, individual units appear capable of odor-selective responses. For example, the first unit in Fig. 8 (top) only shows a significant response to one odor. This is in contrast with the lower unit (Fig. 8) which displays significant responses to three of the five odorants. These apparently odor-selective responses suggest that the olfactory tubercle may contribute to odor discrimination (Wesson and Wilson, 2010).

While not reflecting odor processing *within* the olfactory tubercle, an early prediction for the role of the olfactory tubercle in olfaction was that it modulates centrifugal control over the olfactory bulb (Gervais, 1979). Gervais tested this hypothesis in a study of mitral cell responses in awake rats with and without olfactory tubercle lesions. Unilateral olfactory tubercle lesions affected the spontaneous and odor-evoked activity of olfactory bulb mitral cells (both ipsi- and contralateral). Further, during slow-wave sleep, olfactory tubercle lesioned rats showed increased cortical desynchronization (arousal) during odor presentation (Gervais, 1979). Thus, Gervais hypothesized that the olfactory tubercle may be important in modulating both descending state-dependent control over olfactory bulb activity, and olfactory-mediated neocortical arousal (Gervais, 1979). This state-dependent modulation may be mediated in part by noradrenergic input from the locus coeruleus or serotonergic input from the raphe nucleus (as shown in Fig. 7), both of which influence olfactory tubercle activity in rats (Inokuchi et al., 1988; Hadley and Halliwell, 2010).

In summary, these data suggest that the olfactory tubercle, like the piriform cortex (Haberly, 1998) and olfactory bulb (Wilson and Mainen, 2006), displays numerous features linking it to a possible role in the processing of odors. Olfactory tubercle single-units respond in an odor-specific manner (Wesson and Wilson, 2010) – thus they likely contribute to odor discrimination. This response is state/attention-dependent (Zelano et al., 2005). Finally, the olfactory tubercle may be involved in state-dependent modulation of olfactory bulb odor responses and odor-evoked neocortical arousal (Gervais, 1979). These physiological manifestations appear in line with what might be predicted based on the anatomical description outlined above; i.e., an interface between sensory inputs and sensory evoked arousal and motivated responses. However, many significant questions remain. For instance, how does sensory phys-
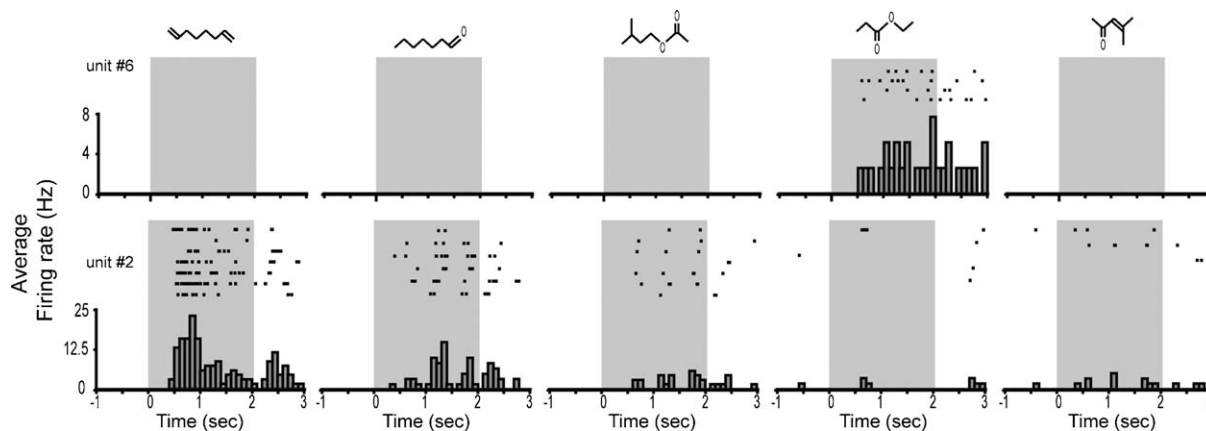

Fig. 8. Selective olfactory responses in the olfactory tubercle may allow for odor discrimination. Olfactory tubercle single-unit spike raster plots and peri-stimulus time histograms from 2 units (2 separate mice) throughout multiple presentations with 5 different odorants (gray shaded regions) in urethane anesthetized mice. Top halves of each panel shows spike activity as raster plots (dots) of single units in response to each of the 5 odorants across multiple trials (*Y*-axis, each row is a single trial). Summarizing each raster plot is a peri-stimulus time histogram with average firing rate (Hz) on the *Y*-axis. Odorants (from left to right): 1,7-octadiene, heptanal, ethyl propionate, isoamyl acetate, and 4-methyl-3-penten-2-one. Histograms—100 ms time bins.
Adapted from Wesson and Wilson (2010).

iology and odor responsiveness align with the reported biophysical differences between morphologically identified cell types? Do odor response properties within the olfactory tubercle match those of the piriform cortex or anterior olfactory cortex, or as might be assumed based on differences in afferent input and local circuitry, do these subregions of the olfactory cortex respond to odor (quality, intensity, familiarity, hedonics, etc.) differently? Furthermore, more detailed and sensitive behavioral assays should be used to examine how odor perception and odor-guided behavior are modified by olfactory tubercle lesions. These assays may be particularly informative if specific cell types (e.g., granule cells of the Islands of Calleja or medium sized cells in the dense cell layer) can be silenced or lesioned.

8. The olfactory tubercle as a multi-sensory processing center

The role of 'early' cortical structures in the multimodal processing of information is becoming more prominent (Kayser and Logothetis, 2007; Lakatos et al., 2007). Olfactory cortices are no exception to this. Indeed, olfactory processing regions within 2-3 synapses from the nose are integral in the multimodal processing of sensory information. These regions include the piriform cortex, endopiriform nucleus and orbitofrontal cortex (Gottfried and Dolan, 2003; Fu et al., 2004; Rolls, 2004; Small, 2004; Verhagen and Engelen, 2006). For instance, visual input during olfactory sampling alters olfactory perception which is associated with changes in piriform cortex activity (Gottfried and Dolan, 2003).

Recent evidence from our group suggests that the olfactory tubercle plays a functional role in the integration of olfactory information with extramodal senses. As described earlier, auditory sensory information may arrive at the olfactory tubercle via general associative networks involving the hippocampus (Deadwyler et al., 1987) or ventral pallidum (Budinger et al., 2008) or directly from the auditory cortex (Budinger et al., 2006). Thus, the olfactory tubercle may play a role in olfactory–auditory sensory integration. In support of this, we recently found that olfactory tubercle units display olfactory–auditory convergence (Wesson and Wilson, 2010). Approximately 19% of the tubercle units examined showed significant responses to an auditory stimulus (a pure sine-wave tone) (see Fig. 9) (Wesson and Wilson, 2010). In contrast, no auditory responses were observed in olfactory bulb units (Wesson and Wilson, 2010)—suggesting that the auditory input arrives within the olfactory tubercle, not before. This work also found that individual olfactory tubercle units can display sometimes supra-additive or suppressive responses to the simultaneous presentation of an odor and tone, depending upon the unit, compared to responses to either tone or odor alone (Fig. 10) (Wesson and Wilson, 2010). In conclusion, these recent and exciting data suggest that similar to the piriform cortex (Gottfried and Dolan, 2003) and orbitofrontal cortex (Rolls, 2004; Small, 2004; Verhagen and Engelen, 2006), the olfactory tubercle is involved in merging information across the senses—perhaps in a behaviorally relevant manner. Indeed, the magnitude of auditory input has been shown to influence food perception in human studies (Zampini and Spence, 2010). Based upon retinal projections into the olfactory tubercle (Mick et al., 1993), further experiments on olfactory–visual integration in the tubercle may yield new insights into the role of the olfactory tubercle in multisensory processing. Finally, whether multisensory integration in the olfactory tubercle may impact odor processing in neighboring cortical areas is a topic which will likely have large impacts on models of odor coding.

These findings place the olfactory tubercle among other established multisensory regions. For instance, the superior colliculus and auditory cortex both play multisensory roles in the process-
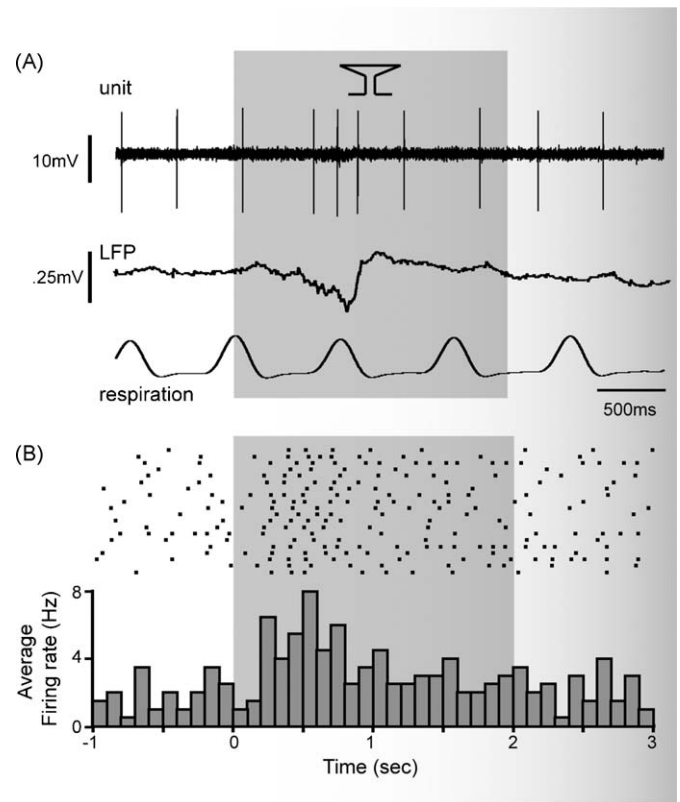

Fig. 9. Auditory sensory responses in the olfactory tubercle. (A) Traces showing multi-unit activity in the olfactory tubercle, local field potential (LFP) and respiration in a urethane anesthetized mouse. Inhalation—upward deflection. Time of tone—shaded box. (B) Spike raster plot and peri-stimulus time histogram from a single unit throughout multiple presentations of an auditory tone.
Adapted from Wesson and Wilson (2010).

ing of visual–spatial and auditory–visual information respectively (Stein and Meredith, 1993; Calvert et al., 2004). While our understanding of the olfactory tubercle in multisensory processing is still in its infancy, it will be exciting to see how integration in the olfactory tubercle may contribute to complex behaviors such as odor tracking.

9. The role of the olfactory tubercle in behavior

The behavioral contributions of the olfactory tubercle have received considerable attention regarding its position in the mesocorticolimbic system. Unilateral lesions of the olfactory tubercle alter attention, social and sensory responsiveness and even locomotor behavior (Hitt et al., 1973; Hagamen et al., 1977; Gervais, 1979). Bilateral lesions of the olfactory tubercle reduce copulatory behavior in male rats (Hitt et al., 1973). Combined 6-hydroxydopamine lesions of the olfactory tubercle and nucleus accumbens in rats result in hyperphagia and also an attenuation in normal d-amphetamine—induced locomotor behavior (Koob et al., 1978). These results support the hypothesis that, as part of the ventral striatum, the olfactory tubercle may be necessary for behavioral flexibility (Koob et al., 1978) and/or stimulus hedonics. More recently, Ikemoto (2003) has shown that the olfactory tubercle is especially involved in reward and addictive behaviors. In particular, rats self-administer cocaine into the olfactory tubercle more-so than into the ventral pallidum or nucleus accumbens. In addition, intracerebral infusions of cocaine into the olfactory tubercle, but not ventral pallidum or nucleus accumbens induces conditioned place preference (Ikemoto, 2003). Finally, amphetamine
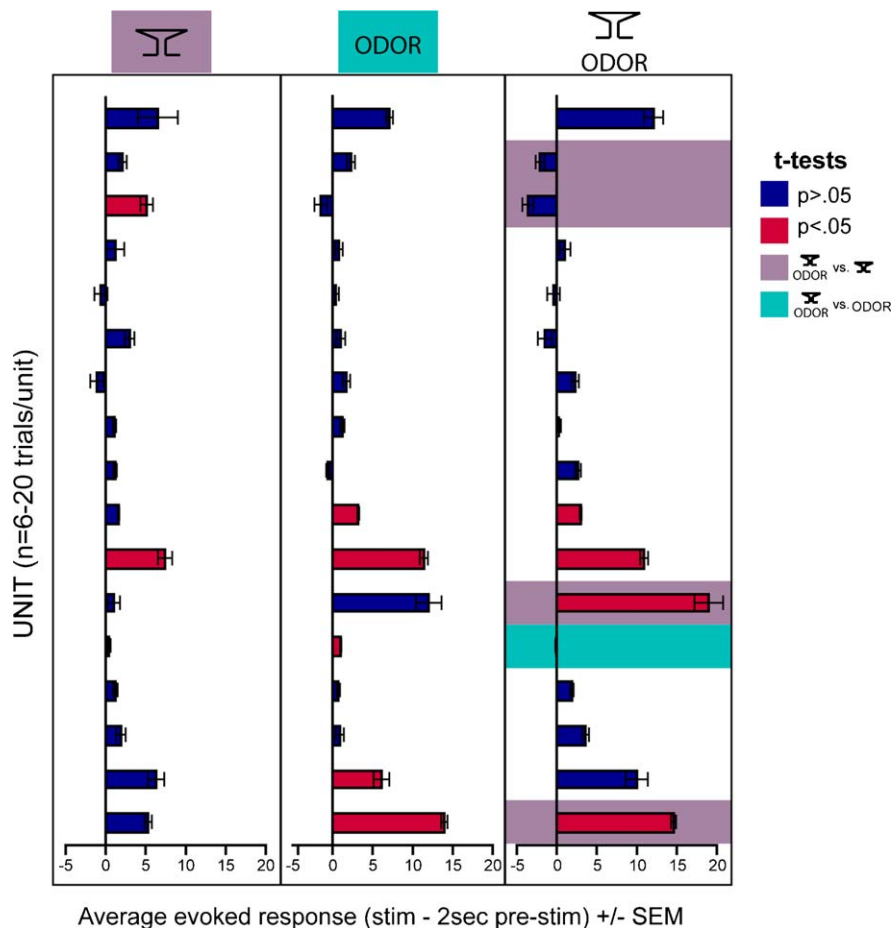
Fig. 10. Olfactory-auditory sensory integration in the olfactory tubercle. Bar graphs of average stimulus evoked responses across 17 units in response to tone (left), odor (middle, see methods for odor) and simultaneous tone and odor presentations (right column). Red bars indicate significant responses of that unit across all trials ($p < .05$, two-tailed t-test, 2 s pre-stim vs. 2 s during stim). Blue bars are insignificant ($p > .05$). Purple background color behind bars—response of that unit is significantly different from responses of that unit to tone alone ($p < .05$, two-tailed t-test). Blue background color behind bars—response of that unit is significantly different from responses of that unit to odor alone ($p < .05$, two-tailed t-test). Whereas some tubercle units showed supra-additive responses to both stimuli simultaneously, others showed suppressive responses.

Adapted from Wesson and Wilson (2010).

infusions into the medial olfactory tubercle enhance behavioral interaction/attention towards unconditioned sensory stimuli (Shin et al., 2010). Thus, as discussed in detail elsewhere (Ikemoto, 2007), the olfactory tubercle is an integral part of the reward/motivation behavior system, while also influencing sensory guided behavior.

Whether or not the olfactory and reward/motivation aspects of tubercle function interact is unclear. However, in olfactory bulbectomized animals, both dopamine D2 receptor gene expression and pre- pro-enkephalin mRNA level are upregulated in the olfactory tubercle (Holmes, 1999), and the reward properties of d-amphetamine are modified (Holmes et al., 2002; Romeas et al., 2009), suggesting that olfactory input to the tubercle could modulate reward/motivation circuit function. It is currently unknown whether the olfactory tubercle contributes to hedonic responses to odor.

What does the olfactory tubercle functionally contribute to olfaction? Current views of the olfactory system include distributed functionality across diverse components. The olfactory bulb is critical for initial odor-specific spatiotemporal patterns required for odor discrimination (Sharp et al., 1975; Rubin and Katz, 2001; Wachowiak and Cohen, 2001; Mori et al., 2006; Johnson and Leon, 2007; Verhagen et al., 2007; Restrepo et al., 2009). The olfactory bulb also contributes to gain control (Ennis et al., 2001; McGann et al., 2005), state-dependent modulation of odor responses (Pager

et al., 1972; Murakami et al., 2005; Tsuno et al., 2008), learned odor responses (Karpov, 1980; Sullivan et al., 1987; Wilson and Leon, 1988; Linster and Hasselmo, 1997; Doucette and Restrepo, 2008), odor-background segmentation (Verhagen et al., 2007), and long-term habituation (Wilson and Linster, 2008). Downstream, the piriform cortex contributes to pattern recognition of the odor-specific olfactory bulb output (Haberly, 2001; Illig and Haberly, 2003; Kadohisa and Wilson, 2006; Barnes et al., 2008; Howard et al., 2009), short-term habituation (Wilson, 1998), odor memory (Hasselmo et al., 1990; Schoenbaum and Eichenbaum, 1995; Barkai and Saar, 2001; Mouly et al., 2001; Cohen et al., 2008; Chapuis et al., 2009) and perceptual learning (Wilson and Stevenson, 2006; Li et al., 2008). What is left for the olfactory tubercle?

Perhaps the best sources of evidence for perceptual roles of the olfactory tubercle stem from human functional imaging studies (Zelano et al., 2005, 2007). The olfactory tubercle, along with the piriform cortex, is highly activated during tasks engaging attention (Zelano et al., 2005). This finding is in parallel to the earlier rodent work linking the olfactory tubercle to arousal-related systems (see Gervais, 1979; Ikemoto, 2007). Additional work from the same group (Zelano et al., 2007) suggests that the olfactory tubercle may be crucial in sorting out the source of olfactory information (trigeminal stimulants vs. pure olfactory). These findings suggest that the olfactory tubercle serves diverse roles in olfactory per-

ception and odor-guided behavior. Particularly likely, the olfactory tubercle may link odor perception with action through its connections with attentional, reward, and motivation systems of the basal forebrain.

10. Outlook and conclusions

This review has outlined >100 years of research on the anatomy, physiology and possible functions of the olfactory tubercle in odor information processing and behavior. Based upon the research presented above, we make the following four predictions regarding the contributions of the olfactory tubercle to olfactory perception and behavior:

Prediction 1: The tubercle expresses odor processing capabilities distinct from other olfactory cortical areas. Odor information in the olfactory tubercle may be modulated based upon sensory input from the piriform cortex (Carriero et al., 2009)—suggesting that the piriform cortex may help shape olfactory tubercle odor responses. However, whereas olfactory bulb input to the piriform cortex mostly stems from mitral cells, olfactory bulb input to the olfactory tubercle originates predominately from tufted cells (Scott et al., 1980). This differential input into the olfactory tubercle sets the stage for distinct odor processing schemes. Given that mitral and tufted cells differ in their odor response thresholds (Wellis et al., 1989; Mori and Shepherd, 1994), width of odor receptive fields (Mori and Shepherd, 1994), and local connectivity to interneuron networks (Shepherd et al., 2004; Wachowiak and Shipley, 2006), we predict that olfactory tubercle odor responses will differ from those of the piriform cortex, perhaps as two components of a parallel processing stream. For example, we predict that the olfactory tubercle will be responsive to odors at much lower thresholds than piriform cortex. Further, the lack of a local association fiber system within the tubercle in contrast to the extensive and highly plastic association fiber system within the piriform cortex suggests fundamentally different computational properties of these two structures. Namely, we predict that the olfactory tubercle's capacity for plasticity (i.e., adaptation to prolonged odor exposure, experience-dependent changes in acuity, etc.) will be markedly less than the piriform cortex. Following similar logic, we predict odor representations in the olfactory tubercle will also significantly differ from those in the anterior olfactory cortex. These differences may allow for distinct contributions of the olfactory tubercle to olfactory behaviors. Further studies exploring the principles of odor coding in the olfactory tubercle in comparison to neighboring olfactory cortex regions will be critical in understanding basic aspects of odor information processing in the brain.

Prediction 2: The olfactory tubercle is crucial in odor hedonics and odor-motivated behavior. As a component of the ventral striatum, the olfactory tubercle is intimately interconnected with numerous reward, affective, and motivation-related brain centers (see section 6)(Heimer, 2003; Ikemoto, 2007). The olfactory tubercle sits at the interface between olfactory sensory input and state-dependent and hedonic behavioral modulatory circuits. Thus, the olfactory tubercle may play an important role in mediating odor approach/avoidance behaviors, potentially in a state-dependent manner (Gervais, 1979), and further may help regulate activity within other olfactory areas (e.g., olfactory bulb) through feedback connections. If this is so, then we predict state, motivational and affective regulation of odor-evoked activity within the olfactory tubercle. Further, we predict that disruption of normal odor guided behaviors (e.g., novel odor investigation, odor avoidance) will occur following olfactory tubercle disruption. Finally, related to this, we predict that damage to the olfactory

tubercle induced by disease, addiction or aging will result in an impairment of normal state/motivational modulation of other olfactory areas. Likewise, we predict that disturbances in olfactory input could disrupt normal motivated behavior. This may be evident in psychiatric disorders including schizophrenia (Rupp, 2010), dementia (Mesholam et al., 1998; Murphy et al., 2009) and depression (Negoias et al., 2010) wherein olfactory and affective dysfunction is common.

Prediction 3: The olfactory tubercle is necessary for social odor processing. Rodent social odors (e.g., urinary odors) are largely represented in the ventral olfactory bulb (Restrepo et al., 2004; Martel and Baum, 2007). Interestingly, tufted cells in the ventral olfactory bulb mainly project into the olfactory tubercle (Scott et al., 1980) (see Fig. 6). This, along with previous work showing that the olfactory tubercle is important in sexual responsiveness (Hitt et al., 1973; Talbot et al., 1988a), leads us to predict that the olfactory tubercle may be critical site for social odor processing. This predicted function is further supported by presence of both estrogen and androgen receptors in the olfactory tubercle (Pfaff, 1968; Rainbow et al., 1982) – allowing for modulation of sensory signals in accordance with fluctuating sex hormone levels. The indirect input from the accessory olfactory bulb to the olfactory tubercle in rodents further backs this hypothesis. To our knowledge there have been no examinations of natural biological odor stimulation on olfactory tubercle activity or how such activity may be modulated by sex hormone levels.

Prediction 4: The olfactory tubercle is a critical site for multisensory integration. As discussed earlier, simultaneous presentation of an odor and tone enhances odor-evoked responses in the olfactory tubercle (Wesson and Wilson, 2010). Anatomical data suggests that the olfactory tubercle may also receive visual information (Mick et al., 1993). Based upon this, we predict that auditory and/or visual input may enhance odor detection thresholds and perhaps odor discrimination abilities via convergence within olfactory tubercle. This integration may add to the possible role of the olfactory tubercle in odor detection as postulated in Prediction 1. Further, if demonstrated to be behaviorally relevant, this sensory integration in the olfactory tubercle may be especially advantageous in rapid decision making given the olfactory tubercle's close association with numerous higher-order brain regions (as shown in Fig. 7) and in consequence will place the olfactory tubercle among other established multisensory regions.

In conclusion, the olfactory tubercle not only receives strong and direct olfactory input as part of the olfactory cortex, but also is an integral component of the ventral striatal reward/arousal complex (Heimer, 2003; Ikemoto, 2007). Thus, the olfactory tubercle not only likely is involved in basic aspects of odor processing (e.g., discrimination) but also may be an integral site for the pairing of odors with states and stimuli signaling valence. Thus, the olfactory tubercle likely modulates odor preference and aversion, and helps link odors to action. This likely function may designate the olfactory tubercle as a critical site in the processing of social and food-related odors wherein the pairing of odor information with reward-related neural input may result in emotionally distinct stimuli and drive odor-guided behaviors. Therefore, future studies of the role of the olfactory tubercle in both basic odor processing and higher-order events may provide significant insights into olfactory perception and odor-guided behaviors.

Conflicts of interest

The authors have no conflicting commercial or financial interest in writing this review.

Acknowledgments

References

Alheid, G.F., Heimer, L., 1988. New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience 27, 1–39.

Ashwell, K.W., Marotte, L.R., Cheng, G., 2008. Development of the olfactory system in a wallaby (Macropus eugenii). Brain Behav. Evol. 71, 216–230.

Astic, L., Saucier, D., 1981. Metabolic mapping of functional activity in the olfactory projections of the rat: ontogenetic study. Brain Res. 254, 141–156.

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

Barkai, E., Saar, D., 2001. Cellular correlates of olfactory learning in the rat piriform cortex. Rev. Neurosci. 12, 111–120.

Barnes, D.C., Hofacer, R.D., Zaman, A.R., Rennaker, R.L., Wilson, D.A., 2008. Olfactory perceptual stability and discrimination. Nat. Neurosci. 11, 1378–1380.

Bayer, S.A., 1985. Neurogenesis in the olfactory tubercle and islands of Calleja in the rat. Int. J. Dev. Neurosci. 3, 135–147.

Bayer, S.A., 1986. Neurogenesis in rat primary olfactory cortex. Int. J. Dev. Neurosci. 4, 251–271.

Bedard, A., Levesque, M., Bernier, P.J., Parent, A., 2002. The rostral migratory stream in adult squirrel monkeys: contribution of new neurons to the olfactory tubercle and involvement of the antiapoptotic protein Bcl-2. Eur. J. Neurosci. 16, 1917–1924.

Behan, M., Haberly, L.B., 1999. Intrinsic and efferent connections of the endopiriform nucleus in rat. J. Comp. Neurol. 408, 532–548.

Brodmann, K., 1909. Vergleichende lokalisationslehre der grobhirnrinde in ihren principien dargestellt auf grund des zellenbaues. Barth, Leipzig.

Brunjes, P.C., Illig, K.R., Meyer, E.A., 2005. A field guide to the anterior olfactory nucleus (cortex). Brain Res. Brain Res. Rev. 50, 305–335.

Budinger, E., Heil, P., Hess, A., Scheich, H., 2006. Multisensory processing via early cortical stages: Connections of the primary auditory cortical field with other sensory systems. Neuroscience 143, 1065–1083.

Budinger, E., Laszcz, A., Lison, H., Scheich, H., Ohl, F.W., 2008. Non-sensory cortical and subcortical connections of the primary auditory cortex in Mongolian gerbils: Bottom-up and top-down processing of neuronal information via field AI. Brain Res. 1220, 2–32.

Calleja, C., 1893. La region olfactoria del cerebro. Nicolas Moya, Madrid.

Calvert, G.A., Spence, C., Stein, B.E. (Eds.), 2004. The Handbook of Multisensory Processes. MIT Press, Cambridge, MA.

Carey, R.M., Verhagen, J.V., Wesson, D.W., Pirez, N., Wachowiak, M., 2009. Temporal structure of receptor neuron input to the olfactory bulb imaged in behaving rats. J. Neurophysiol. 101, 1073–1088.

Carmichael, S.T., Clugnet, M.C., Price, J.L., 1994. Central olfactory connections in the macaque monkey. J. Comp. Neurol. 346, 403–434.

Carriero, G., Uva, L., Gnatkovsky, V., de Curtis, M., 2009. Distribution of the olfactory fiber input into the olfactory tubercle of the in vitro isolated guinea pig brain. J. Neurophysiol. 101, 1613–1619.

Chapuis, J., Garcia, S., Messaoudi, B., Thevenet, M., Ferreira, G., Gervais, R., Ravel, N., 2009. The way an odor is experienced during aversive conditioning determines the extent of the network recruited during retrieval: a multisite electrophysiological study in rats. J. Neurosci. 29, 10287–10298.

Chaput, M.A., 1986. Respiratory-phase-related coding of olfactory information in the olfactory bulb of awake freely breathing rabbits. Physiol. Behav. 36, 319–324.

Chiang, E., Strowbridge, B.W., 2007. Diversity of neural signals mediated by multiple, burst-firing mechanisms in rat olfactory tubercle neurons. J. Neurophysiol. 98, 2716–2728.

Cohen, Y., Reuveni, I., Barkai, E., Maroun, M., 2008. Olfactory learning-induced long-lasting enhancement of descending and ascending synaptic transmission to the piriform cortex. J. Neurosci. 28, 6664–6669.

Crosby, E.C., Humphrey, T., 1941. Studies of the vertebrate telencephalon II. The nuclear pattern of the anterior olfactory nucleus, tuberculum olfactorium, and the amygdaloid complex in adult man. J. Comp. Neurol. 74, 309–352.

De Marchis, S., Fasolo, A., Puche, A.C., 2004. Subventricular zone-derived neuronal progenitors migrate into the subcortical forebrain of postnatal mice. J. Comp. Neurol. 476, 290–300.

de Vente, J., Hani, L., Steinbusch, H.E., Steinbusch, H.W.M., 2001. The three dimensional structure of the islands of Calleja: a single heterogenous cell complex. Neuroreport 12, 565–568.

Deadwyler, S.A., Foster, T.C., Hampson, R.E., 1987. Processing of sensory information in the hippocampus. CRC Crit. Rev. Clin. Neurobiol. 2, 335–355.

Del-Fava, F., Hasue, R.H., Ferreira, J.G.P., Shammah-Lagnado, S.J., 2007. Efferent connections of the rostral linear nucleus of the ventral tegmental area in the rat. Neuroscience 145, 1059–1076.

Doucette, W., Restrepo, D., 2008. Profound context-dependent plasticity of mitral cell responses in olfactory bulb. PLoS Biol. 6, e258.

Ennis, M., Zhou, F.-M., Ciombor, K.J., Aroniadou-Anderjaska, V., Hayar, A., Borrelli, E., Zimmer, L.A., Margolis, F., Shipley, M.T., 2001. Dopamine D2 receptor-mediated presynaptic inhibition of olfactory nerve terminals. J. Neurophysiol. 86, 2986–2997.

Fallon, J.H., 1983a. The islands of Calleja complex of rat basal forebrain II: connections of medium and large sized cells. Brain Res. Bull. 10, 775–793.

Fallon, J.H., 1983b. The islands of Calleja complex of rat basal forebrain II. Connections of medium and large sized cells. Brain Res. Bull. 10, 179–199.

Fallon, J.H., Riley, J.N., Sipe, J.C., Moore, R.Y., 1978. The islands of Calleja: organization and connections. J. Comp. Neurol. 181, 375–395.

Fu, W., Sugai, T., Yoshimura, H., Onoda, N., 2004. Convergence of olfactory and gustatory connections onto the endopiriform nucleus in the rat. Neuroscience 126, 1033–1041.

Garcia-Moreno, F., Lopez-Mascaraque, L., de Carlos, J.A., 2008. Early telencephalic migration topographically converging in the olfactory cortex. Cereb. Cortex 18, 1239–1252.

Gaykema, R.P., Luiten, P., Nyakas, C., Traber, J., 1990. Cortical projection patterns of the medial septum-diagonal band complex. J. Comp. Neurol. 293, 103–124.

Gervais, G., 1979. Unilateral lesions of the olfactory tubercle modifying general arousal effects in the rat olfactory bulb. Electroencephalogr. Clin. Neurophysiol. 46, 665–674.

Gottfried, J.A., Dolan, R.J., 2003. The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. Neuron 39, 375–386.

Gray, P.A., 1924. The cortical lamination pattern of the opossum (Didelphys virginiana). J. Comp. Neurol. 37, 221–263.

Groenewegen, H.J., Berendse, H.W., 1990. Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. J. Comp. Neurol. 294, 607–622.

Groenewegen, H.J., Berendse, H.W., Haber, S.N., 1993. Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. Neuroscience 57, 113–142.

Groenewegen, H.J., der Zee, E.V.-V., te Kortschot, A., Witter, M.P., 1987. Organization of the projections from the subiculum to the ventral striatum in the rat A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. Neuroscience 23, 103–120.

Guevara-Aguilar, R., Solano-Flores, L.P., Donatti-Albarran, O.A., Aguilar-Baturoni, H.U., 1982. Differential projections from locus coeruleus to olfactory bulb and olfactory tubercle: an HRP study. Brain Res. Bull. 8, 711–719.

Haberly, L.B., 1998. Olfactory cortex. In: Shepherd, G.M. (Ed.), The Synaptic Organization of the Brain, fourth ed. Oxford University Press, New York, pp. 377–416.

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

Haberly, L.B., Price, J.L., 1977. The axonal projection patterns of the mitral and tufted cells of the olfactory bulb in the rat. Brain Res. 129, 152–157.

Haberly, L.B., Price, J.L., 1978. Association and commissural fiber systems of the olfactory cortex of the rat I. systems originating in the piriform cortex and adjacent areas. J. Comp. Neurol. 178, 711–740.

Hadley, J.K., Halliwell, J.V., 2010. Serotonin modulates glutamatergic transmission in the rat olfactory tubercle. Eur. J. Neurosci. 31, 659–672.

Hagamen, T.C., Greeley, H.P., Hagamen, W.D., Reeves, A.G., 1977. Behavioral asymmetries following olfactory tubercle lesions in cats. Brain Behav. Evol. 14, 241–250.

Hasselmo, M.E., Bower, J.M., 1992. Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex. J. Neurophysiol. 67, 1222–1229.

Hasselmo, M.E., Wilson, M.A., Anderson, B.P., Bower, J.M., 1990. Associative memory function in piriform (olfactory) cortex: computational modeling and neuropharmacology. Cold Spring Harb. Symp. Quant. Biol. 55, 599–610.

Heimer, L., 1968. Synaptic distribution of centripedal and centrifugal nerve fibers in the olfactory system in the rat. J. Anat. 103, 413–432.

Heimer, L., 2003. A new neuroanatomical framework for neuropsychiatric disorders and drug abuse. Am. J. Psychiatry 160, 1726–1739.

Heimer, L., Wilson, R.D., 1975. The Subcortical Projections of the Allocortex: Similarities in the Neural Connections of the Hippocampus, the Piriform Cortex and the Neocortex. New York, Raven.

Heimer, L., Zahm, D.S., Schmued, L.C., 1990. The basal forebrain projection to the region of the nuclei gemini in the rat; A combined light and electron microscopic study employing horseradish peroxidase, fluorescent tracers and Phaseolus vulgaris-leucoagglutinin. Neuroscience 34, 707–731.

Hinds, J.W., Angevine, J.B., 1965. Autoradiographic study of the histogenesis in area pyriformis and claustrum in mouse. Anat. Rec. 151, 456.

Hitt, J.C., Bryon, D.M., Modianos, D.T., 1973. Effects of rostral medial forebrain bundle and olfactory tubercle lesions upon sexual behavior of male rats. J. Comp. Physiol. Psychol. 82, 30–36.

Holmes, P., Masini, C., Primeaux, S., Garrett, J., Zellner, A., Stogner, K., Duncan, A., Crystal, J., 2002. Intravenous self-administration of amphetamine is increased in a rat model of depression. Synapse 46, 4–10.

Holmes, P.V., 1999. Olfactory bulbectomy increases prepro-enkephalin mRNA levels in the ventral striatum in rats. Neuropeptides 33, 206–211.

Howard, J.D., Plailly, J., Grueschow, M., Haynes, J.-D., Gottfried, J.A., 2009. Odor quality coding and categorization in human posterior piriform cortex. Nat. Neurosci. 12, 932–938.

Ikemoto, S., 2003. Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. J. Neurosci. 23, 9305–9311.

Ikemoto, S., 2007. Dopamine reward circuitry: Two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. Brain Res. Rev. 56, 27–78.

Illig, K.R., 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.

Illig, K.R., Haberly, L.B., 2003. Odor-evoked activity is spatially distributed in piriform cortex. J. Comp. Neurol. 457, 361–373.

Inokuchi, A., Boran, T.V., Kimmelman, C.P., Snow, J.B.J., 1988. Effects of locus ceruleus and olfactory bulb stimulation on rat olfactory tubercle neuron activity. Otolaryngol. Head Neck Surg. 98, 116–120.

Johnson, B.A., Leon, M., 2007. Chemotopic odorant coding in a mammalian olfactory system. J. Comp. Neurol. 503, 1–34.

Johnson, D.M., Illig, K.R., Behan, M., Haberly, L.B., 2000. New features of connectivity in piriform cortex visualized by intracellular injection of pyramidal cells suggest that "primary" olfactory cortex functions like "association" cortex in other sensory systems. J. Neurosci. 20, 6974–6982.

Josephson, E., Padgett, M.L., Buxton, D.F., 1997. The lateral and medial compartments of the olfactory tubercle and their relation to olfactory-related input as determined by artificial neural network analysis. Brain Res. 744, 253–271.

Kadohisa, M., Wilson, D.A., 2006. Separate encoding of identity and similarity of complex familiar odors in piriform cortex. Proc. Natl. Acad. Sci. U. S. A. 103, 15206–15211.

Karpov, A.P., 1980. Analysis of neuron activity in the rabbit's olfactory bulb during food-acquisition behavior. In: Thompson, R.F., Hicks, L.H., Shvyrkov, V.B. (Eds.), Neural Mechanisms of Goal-Directed Behavior and Learning. Academic Press, New York, pp. 273–282.

Kayser, C., Logothetis, N.K., 2007. Do early sensory cortices integrate cross-modal information? Brain Struct. Funct. 212, 121–132.

Kevetter, G.A., Winans, S.S., 1981. Connections of the corticomedial amygdala in the golden hamster I. Efferents of the "vomeronasal amygdala". J. Comp. Neurol. 197, 81–98.

Kölliker, V.A., 1896. Handbuch der Gewebelehre des Menschen, sixth ed. Leipzig, W. Engelmann.

Koob, G.F., Riley, S.J., Smith, S.C., Robbins, T.W., 1978. Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. J. Comp. Physiol. Psychol. 92, 917–927.

Krieger, N.R., Megill, J.R., Sterling, P., 1983. Granule cells in the rat olfactory tubercle accumulate 3H-gamma-aminobutyric acid. J. Comp. Neurol. 215, 465–471.

Kunzle, H., 2005. An extrahippocampal projection from the dentate gyrus to the olfactory tubercle. BMC Neurosci. 6, 1–10.

Lakatos, P., Chen, C.M., O'Connell, M.N., Mills, A., Schroeder, C.E., 2007. Neuronal oscillations and multisensory interaction in primary auditory cortex. Neuron 53, 279–292.

Li, W., Howard, J.D., Parrish, T.B., Gottfried, J.A., 2008. Aversive learning enhances perceptual and cortical discrimination of indiscriminable odor cues. Science 319, 1842–1845.

Linster, C., Hasselmo, M., 1997. Modulation of inhibition in a model of olfactory bulb reduces overlap in the neural representation of olfactory stimuli. Behav. Brain Res. 84, 117–127.

Luskin, M.B., Price, J.L., 1983. 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.

Martel, K.L., Baum, M.J., 2007. Sexually dimorphic activation of the accessory, but not the main, olfactory bulb in mice by urinary volatiles. Eur. J. Neurosci. 26, 463–475.

Martin-Fardon, R., Ciccocioppo, R., Aujla, H., Weiss, F., 2007. The dorsal subiculum mediates the acquisition of conditioned reinstatement of cocaine-seeking. Neuropsychopharmacology 33, 1827–1834.

Martinez-Marcos, A., 2009. On the organization of olfactory and vomeronasal cortices. Prog. Neurobiol. 87, 21–30.

Matsumoto, M., Hikosaka, O., 2009. Representation of negative motivational value in the primate lateral habenula. Nat. Neurosci. 12, 77–84.

McGann, J.P., Pirez, N., Gainey, M.A., Muratore, C., Elias, A.S., Wachowiak, M., 2005. Odorant representations are modulated by intra- but not interglomerular presynaptic inhibition of olfactory sensory neurons. Neuron 48, 1039–1053.

McNamara, A.M., Cleland, T.A., Linster, C., 2004. Characterization of the synaptic properties of olfactory bulb projections. Chem. Senses 29, 225–233.

Mesholam, R.I., Moberg, P.J., Mahr, R.N., Doty, R.L., 1998. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's Diseases. Arch. Neurol. 55, 84–90.

Meyer, G., Wahle, P., 1986. The olfactory tubercle of the cat I. Morphological components. Exp. Brain Res. 62, 515–527.

Meyer, G., Gonzalez-Hernandez, T., Carrillo-Padilla, F., Ferres-Torres, R., 1989. Aggregations of granule cells in the basal forebrain (islands of Calleja): Golgi and cytoarchitectonic study in different mammals, including man. J. Comp. Neurol. 284, 405–428.

Mick, G., Cooper, H., Magnin, M., 1993. Retinal projection to the olfactory tubercle and basal telencephalon in primates. J. Comp. Neurol. 327, 205–219.

Millhouse, O.E., 1987. Granule cells of the olfactory tubercle and the question of the islands of calleja. J. Comp. Neurol. 265, 1–24.

Millhouse, O.E., Heimer, L., 1984. Cell configurations in the olfactory tubercle of the rat. J. Comp. Neurol. 228, 571–597.

Mori, K., Shepherd, G.M., 1994. Emerging principles of molecular signal processing by mitral/tufted cells in the olfactory bulb. Semin. Cell Biol. 5, 65–74.

Mori, K., Takahashi, Y.K., Igarashi, K.M., Yamaguchi, M., 2006. Maps of odorant molecular features in the Mammalian olfactory bulb. Physiol. Rev. 86, 409–433.

Mouly, A.M., Fort, A., Ben-Boutayab, N., Gervais, R., 2001. Olfactory learning induces differential long-lasting changes in rat central olfactory pathways. Neuroscience 102, 11–21.

Murakami, M., Kashiwadani, H., Kirino, Y., Mori, K., 2005. State-dependent sensory gating in olfactory cortex. Neuron 46, 285–296.

Murphy, C., Solomon, E., Haase, L., Wang, M., Morgan, C., 2009. Olfaction in Aging and Alzheimer's Disease. Ann. N. Y. Acad. Sci. 1170, 647–657.

Nauta, W.J.H., Haymaker, W., 1969. Hypothalamic nuclei and fiber connections. In: Nauta, W.J.H., Haymaker, W. (Eds.), The Hypothalamus. Thomas, Springfield, pp. 136–209.

Negoias, S., Croy, I., Gerber, J., Puschmann, S., Petrowski, K., Joraschky, P., Hummel, T., 2010. Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. Neuroscience 169, 415–421.

Owen, G.S., Halliwell, J.V., 2001. Electrophysiological characterization of laminar synaptic inputs to the olfactory tubercle of the rat studied *in vitro*: modulation of glutamatergic transmission by cholinergic agents is pathway-specific. Eur. J. Neurosci. 13, 1767–1780.

Pager, J., Giachetti, I., Holley, A., Le Magnen, J., 1972. A selective control of olfactory bulb electrical activity in relation to food deprivation and satiety in rats. Physiol. Behav. 9, 573–579.

Paxinos, G., Franklin, K., 2000. The Mouse Brain in Stereotaxic Coordinates, second ed. Academic Press, San Diego.

Pfaff, D.W., 1968. Autoradiographic localization of testosterone-3H in the female rat brain and estradiol-3H in the male rat brain. Cell. Mol. Life Sci. 24, 958–959.

Pigache, R.M., 1970. The anatomy of "paleocortex" A critical review. Ergeb. Anat. Entwicklungsgesch. 43, 3–62.

Price, J.L., Powell, T.P., 1970. An experimental study of the origin and the course of the centrifugal fibres to the olfactory bulb in the rat. J. Anat. 107, 215–237.

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

Price, J.L., Slotnick, B.M., Revial, M.F., 1991. Olfactory projections to the hypothalamus. J. Comp. Neurol. 306, 447–461.

Rainbow, T.C., Parsons, B., MacLusky, N.J., McEwen, B.S., 1982. Estradiol receptor levels in rat hypothalamic and limbic nuclei. J. Neurosci. 2, 1439–1445.

Reep, R.L., Winans, S.S., 1982. Efferent connections of dorsal and ventral agranular insular cortex in the hamster, *Mesocricetus auratus*. Neuroscience 7, 2609–2635.

Restrepo, D., Arellano, J., Oliva, A.M., Schaefer, M.L., Lin, W., 2004. Emerging views on the distinct but related roles of the main and accessory olfactory systems in responsiveness to chemosensory signals in mice. Horm. Behav. 46, 247–256.

Restrepo, D., Doucette, W., Whitesell, J.D., McTavish, T.S., Salcedo, E., 2009. From the top down: flexible reading of a fragmented odor map. Trends Neurosci. 32, 525–531.

Ribak, C.E., Fallon, J.H., 1982. The island of Calleja complex of rat basal forebrain I. Light and electron microscopic observations. J. Comp. Neurol. 205, 207–218.

Riedel, A., Härtig, W., Seeger, G., Gärtner, U., Brauer, K., Arendt, T., 2002. Principles of rat subcortical forebrain organization: a study using histological techniques and multiple fluorescence labeling. J. Chem. Neuroanat. 23, 75–104.

Rieger, N., Heller, J.S., 1979. Localization of glutamic acid decarboxylase within laminae of the rat olfactory tubercle. J. Neurochem. 33, 299–302.

Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain Cogn. 55, 11–29.

Romeas, T., Morissette, M.-C., Mnie-Filali, O., Pieyro, G., Boye, S., 2009. Simultaneous anhedonia and exaggerated locomotor activation in an animal model of depression. Psychopharmacology 205, 293–303.

Rose, M., 1927. Die sog. Riechrinde beim Menschen und beim Affen. J. Psychol. Neurol. Lpz. 34, 261–401.

Rubin, B.D., Katz, L.C., 2001. Spatial coding of enantiomers in the rat olfactory bulb. Nat. Neurosci. 4, 355–356.

Rupp, C., 2010. Olfactory function and schizophrenia: an update. Curr. Opin. Psychiatry 23, 97–102.

Santiago, A.C., Shammah-Lagnado, S.J., 2004. Efferent connections of the nucleus of the lateral olfactory tract in the rat. J. Comp. Neurol. 471, 314–332.

Schoenbaum, G., Eichenbaum, H., 1995. Information coding in the rodent prefrontal cortex I. Single-neuron activity in orbitofrontal cortex compared with that in pyriform cortex. J. Neurophysiol. 74, 733–750.

Schwob, J.E., Price, J.L., 1984a. The development of axonal connections in the central olfactory system of rats. J. Comp. Neurol. 223, 177–202.

Schwob, J.E., Price, J.L., 1984b. The development of lamination of afferent fibers to the olfactory cortex in rats, with additional observations in the adult. J. Comp. Neurol. 223, 203–222.

Scott, J.W., Chafin, B.R., 1975. Origin of olfactory projections to lateral hypothalamus and nuclei gemini of the rat. Brain Res. 88, 64–68.

Scott, J.W., McBride, R.L., Schneider, S.P., 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.

Shafa, F., Meisami, E., 1977. A horseradish peroxidase study of the origin of central projections to the rat olfactory bulb. Brain Res. 136, 355–359.

Sharp, F.R., Kauer, J.S., Shepherd, G.M., 1975. Local sites of activity-related glucose metabolism in rat olfactory bulb during olfactory stimulation. Brain Res. 98, 596–600.

Shepherd, G.M., Chen, W.R., Greer, C.A., 2004. Olfactory bulb. In: Shepherd, G.M. (Ed.), The Synaptic Organization of the Brain, fifth ed. Oxford University Press, Oxford, pp. 165–216.

Shin, R., Cao, J., Webb, S.M., Ikemoto, S., 2010. Amphetamine administration into the ventral striatum facilitates behavioral interaction with unconditioned visual signals in rats. PLoS ONE 5, e8741.

Small, D.A., 2004. Crossmodal integration—insights from the chemical senses. Trends Neurosci. 27, 120–123 (discussion 123–124).

Smart, I.H., Smart, M., 1977. The location of nuclei of different labelling intensities in autoradiographs of the anterior forebrain of postnatial mice injected with [3H]thymidine on the eleventh and twelfth days post-conception. J. Anat. 123, 515–525.

Sobel, E.C., Tank, D.W., 1993. Timing of odor stimulation does not alter patterning of olfactory bulb unit activity in freely breathing rats. J. Neurophysiol. 69, 1331–1337.

Sobel, N., Prabhakaran, V., Zhao, Z., Desmond, J.E., Glover, G.H., Sullivan, E.V., Gabrieli, J.D., 2000. Time course of odorant-induced activation in the human primary olfactory cortex. J. Neurophysiol. 83, 537–551.

Solano-Flores, L.P., Aguilar-Baturoni, H.U., Guevara-Aguilar, R., 1980. Locus coeruleus influences upon the olfactory tubercle. Brain Res. Bull. 5, 383–389.

Spors, H., Wachowiak, M., Cohen, L.B., Friedrich, R.W., 2006. Temporal dynamics and latency patterns of receptor neuron input to the olfactory bulb. J. Neurosci. 26, 1247–1259.

Stein, B.E., Meredith, M.A. (Eds.), 1993. The Merging of the Senses. MIT Press, Cambridge, MA.

Stephan, H., 1975. Allocortex. Springer-Verlag, Berlin & New York.

Sullivan, R.M., Wilson, D.A., Kim, M., Leon, M., 1987. Enhanced olfactory-bulb response to learned attractive odors in the absence of altered respiratory response. Chem. Senses 12, 703–1703.

Swanson, L.W., Petrovich, G.D., 1998. What is the amygdala? Trends Neurosci. 21, 323–331.

Talbot, K., Woolf, N.J., Butcher, L.L., 1988a. Feline islands of Calleja complex: II Cholinergic and cholinesterasic features. J. Comp. Neurol. 275, 580–603.

Talbot, K., Woolf, N.J., Butcher, L.L., 1988b. Feline islands of Calleja complex: I Cytoarchitectural organization and comparative anatomy. J. Comp. Neurol. 275, 553–579.

Tsuno, Y., Kashiwadani, H., Mori, K., 2008. Behavioral state regulation of dendrodendritic synaptic inhibition in the olfactory bulb. J. Neurosci. 28, 9227–9238.

Ubeda-Bañona, I., Novejarqueb, A., Mohedano-Morianoa, A., Pro-Sistiagaa, P., Insaustia, R., Martinez-Garciab, F., Lanuzac, E., Martinez-Marcos, A., 2007a. Vomeronasal inputs to the rodent ventral striatum. Brain Res. Bull. 75, 467–473.

Ubeda-Bañona, I., Novejarque, A., Mohedano-Moriano, A., Pro-Sistiaga, P., de la Rosa-Prieto, C., Insausti, R., Martinez-Garcia, F., Lanuza, E., Martinez-Marcos, A., 2007b. Projections from the posterolateral olfactory amygdala to the ventral striatum: neural basis for reinforcing properties of chemical stimuli. BMC Neurosci. 8, 103.

Usunoff, K.G., Schmitt, O., Itzev, D.E., Haas, S.J.P., Lazarov, N.E., Rolfs, A., Wree, A., 2009. Efferent projections of the anterior and posterodorsal regions of the medial nucleus of the amygdala in the mouse. Cells Tissues Organs 190, 256–285.

Verhagen, J.V., Engelen, L., 2006. The neurocognitive bases of human multimodal food perception: Sensory integration. Neurosci. Biobehav. Rev. 30, 613–650.

Verhagen, J.V., Wesson, D.W., Netoff, T.I., White, J.A., Wachowiak, M., 2007. Sniffing controls an adaptive filter of sensory input to the olfactory bulb. Nat. Neurosci. 10, 631–639.

Vertes, R.P., Hoover, W.B., 2008. Projections of the paraventricular and paratenial nuclei of the dorsal midline thalamus in the rat. J. Comp. Neurol. 508, 212–237.

Vincent, S.R., Kimura, H., 1992. Histochemical mapping of nitric oxide synthase in the rat brain. Neuroscience 46, 755–784.

Voorn, P., Vanderschuren, L.J.M.J., Groenewegen, H.J., Robbins, T.W., Pennartz, C.M.A., 2004. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci. 27, 468–474.

Wachowiak, M., Cohen, L.B., 2001. Representation of odorants by receptor neuron input to the mouse olfactory bulb. Neuron 32, 723–735.

Wachowiak, M., Shipley, M.T., 2006. Coding and synaptic processing of sensory information in the glomerular layer of the olfactory bulb. Semin. Cell Dev. Biol. 17, 411–423.

Weismann, M., Yousry, I., Heuberger, E., Nolte, A., Ilmberger, J., Kobal, G., Yousry, T.A., Kettenmann, B., Naidich, T.P., 2001. Functional magnetic resonance imaging of human olfaction. Neuroimaging Clin. N. Am. 11, 237–250, viii.

Wellis, D.P., Scott, J.W., Harrison, T.A., 1989. Discrimination among odorants by single neurons of the rat olfactory bulb. J. Neurophysiol. 61, 1161–1177.

Wesson, D.W., Wilson, D.A., 2010. Smelling sounds: olfactory-auditory sensory convergence in the olfactory tubercle. J. Neurosci. 30, 3013–3021.

White, L.E., 1965. Olfactory bulb projections of the rat. Anat. Rec. 152, 465–479.

Wilson, D.A., 1998. Habituation of odor responses in the rat anterior piriform cortex. J. Neurophysiol. 79, 1425–1440.

Wilson, D.A., Leon, M., 1988. Spatial patterns of olfactory bulb single-unit responses to learned olfactory cues in young rats. J. Neurophysiol. 59, 1770–1782.

Wilson, D.A., Stevenson, R.J., 2006. Learning to Smell: Olfactory Perception from Neurobiology to Behavior. Johns Hopkins University Press, Baltimore.

Wilson, D.A., Linster, C., 2008. Neurobiology of a simple memory. J. Neurophysiol. 100, 2–7.

Wilson, R.I., Mainen, Z.F., 2006. Early events in olfactory processing. Annu. Rev. Neurosci. 29, 163–201.

Young, W.S., Alheid, G.F., Heimer, L., 1984. The ventral pallidal projection to the mediodorsal thalamus: a study with fluorescent retrograde tracers and immunohistofluorescence. J. Neurosci. 4, 1626–1638.

Zahm, D.S., 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.

Zampini, M., Spence, C., 2010. Assessing the role of sound in the perception of food and drink. Chemosensory Percept. 3, 57–67.

Zelano, C., Montag, J., Johnson, B., Khan, R., Sobel, N., 2007. Dissociated representations of irritation and valence in human primary olfactory cortex. J. Neurophysiol. 97, 1969–1976.

Zelano, C., Bensafi, M., Porter, J., Mainland, J., Johnson, B., Bremner, E., Telles, C., Khan, R., Sobel, N., 2005. Attentional modulation in human primary olfactory cortex. Nat. Neurosci. 8, 114–120.