Flavour and Fragrance Journal

WILEY

REVIEW ARTICLE

A Short Glance at the Role of Olfactory Tubercle in Odour Processing

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Received: 30 July 2024 | **Revised:** 25 August 2024 | **Accepted:** 14 September 2024

Funding: This study was supported by the National Natural Science Foundation of China (No. 82371515), and the State Key Laboratory of Integrated Management of Pest Insects and Rodents (No. IPM2301) China.

Keywords: neural circuits | odour detection | odour processing | olfactory system | olfactory tubercle

ABSTRACT

The mammalian olfactory system is one of the most precocious sensory systems during development and is innately endowed with versatile functions distinct from other sensory systems. Perception of time-locked olfaction-related stimuli quickly from the external environment and encoding them accurately via the olfactory system is paramount for the survival and reproduction in the animal kingdom. The olfactory system of mammals encompasses the main and accessory parts. As one key component of the ventral striatum, the olfactory tubercle (OT), is also an important as well as indispensable sub-region of the main olfactory system and plays a crucial role in the central processing of odours. The OT also serves as a hub linking the olfactory system with the reward system in the brain. Although extensive research has underscored the involvement of the ventral striatum in the reward and punishment process as well as motivational behaviour, the encoding mechanism of neural circuits engaged in odour detection and recognition by the OT is still largely unknown. Herein, we make a brief overview of the olfactory system and underscore the crucial role of olfactory receptors in odour detection. We also emphasize the structural and functional characterisations of the OT and corresponding neural circuits involved in odour processing.

1 | The Olfactory System in Mammals

Mammals are able to identify and recognize chemical signals in the environment via their olfactory system, which in turn affects their behaviours and is essential for survival and reproduction [1]. Compared to other sensory systems, the olfactory system is one of the most precocious sensory systems developed in embryos. In the past few decades, a wide array of breakthroughs has been made in both the structure and function of the olfactory system [2–4]. The olfactory system is mainly divided into the peripheral and central parts. The peripheral olfactory system includes the olfactory epithelium and nerve bundles. After passing through the sieve plate, the axons of olfactory sensory neurons converge to form olfactory nerves, one of the 12 pairs of brain nerves in humans. The olfactory tract is bulbous and locates below the frontal lobe of each hemisphere and the olfactory

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nerve enters the olfactory bulb (OB), the primary centre of sensory processing in the olfactory system. The OB belongs to the telencephalon, with a layered structure composed of external plexiform layer (EPL), granule cell layer (GCL), glomerular layer (GL) and mitral cell layer (MCL) [5, 6]. In the OB, the main mitral and tufted (M/T) cells belonging to a unique glomerulus are activated by specific molecular features of individual odorants.

The olfactory system of mammals is endowed with comprehensive functions including but not limited to physiological regulation, emotional response (such as anxiety, fear and pleasure), reproductive function (such as sexual and maternal behaviour) and social behaviour [7–10]. For example, dysfunctions of the olfactory system are closely related to mood disorders in mice, which is supported by the finding that linalool had an anxiolytic effect on normal mice, but no such effect on mice with anosmia [11]. In addition, there is evidence showing that the main olfactory system (MOS) could also detect a wide array of volatile odorants that functioned as pheromones to facilitate mate recognition and activated the hypothalamic–pituitary–gonadal neuroendocrine axis [7]. Moreover, it has been reported that blocking vasopressin-expressing interneurons in the OB impaired the social recognition abilities of rats, further supporting the undoubtedly important role of the olfactory system in social behaviour [12]. The proper realization of these versatile functions relies on both the main and the accessory olfactory system (AOS). In the MOS of rodents, odorants enter the nasal cavity, where they are first detected by olfactory sensory neurons (OSNs) located in the main olfactory epithelium. Subsequently, axons from these OSNs project to the main olfactory bulb (MOB), where information pertaining to odorant molecules is converted into neuronal signals and transmitted to various brain regions within the olfactory cortex, such as the anterior olfactory nucleus (AON), piriform cortex (PCX), olfactory tubercle (OT), cortical amygdala (CoA) and entorhinal cortex (ECX) [12]. Similar to the MOS, in the AOS, once pheromone-related odours are detected by the vomeronasal organ [13], a single axon is projected from the vomeronasal organ (VNO) to the accessory olfactory bulb (AOB) where neuronal signals are filtered and then transmitted to downstream regions including the bed nucleus of stria terminalis (BNST), the medial amygdala (MeA) and the posteromedial cortical amygdala (PMCo) [14, 15] (Figure 1). The VNO or AOS has been implicated in a wide range of studies on the processing of sex pheromones and predator odours and it regulates mammalian sexual and avoidance behaviour through neuronal connections to downstream brain regions [16]. One study on mouse urine pheromones shows that male and female mice sense volatile and non-volatile sex pheromones to generate sexual attraction through vomeronasal receptor type 1 and type 2 (V1R and V2R) receptors in vomeronasal sensory neurons [17]. Another study on mouse glandular secretions reveals that the exocrine gland secreting peptide 1 (ESP1), which is secreted from the eyes of male mice, was sensed by the vomeronasal organ of female mice through physical contact. This stimulation activated V2R-expressing neurons in the vomeronasal organ, leading to the release of electrical signals [18]. It has also been reported that c-fos expression in AOB significantly increased when rats were exposed to objects with cat-like odours [19]. Additionally, after undergoing a surgical procedure called 'vomeronasal removal surgery', mice spent significantly more time exploring predator odours compared to the sham-operation group [20]. Together, these studies demonstrate the important role of both the MOS and AOS in mammalian reproduction and survival.

The appropriate performance of olfaction-related behaviours relies heavily on the accurate detection of external odours via the olfactory epithelium. The olfactory epithelium is mainly composed of three types of cells: OSNs, supporting cells (a type of glial cell with microvilli on its apical surface) and stem cell populations of basal cells (capable of producing new OSNs). The exquisite performance of OSNs in odour detection relies on the olfactory receptors (ORs). The ORs, also known as odour receptors, are chemical receptors expressed in the cell membrane of OSNs, responsible for detecting odour molecules that produce

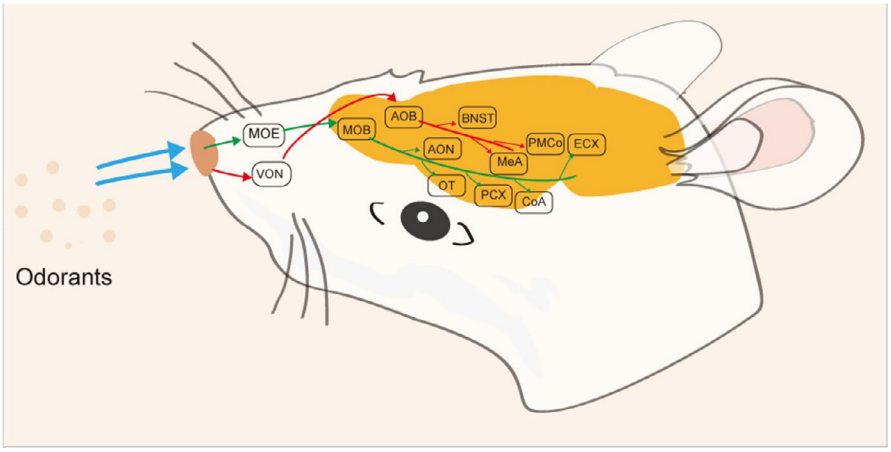

FIGURE 1 | Schematic illustrating the neural pathway of the main (green) and accessory (red) olfactory system of rodents. The olfactory system of mice is divided into MOS and AOS. In the MOS, odours are received by olfactory receptors in the MOE and send neuronal axons to the MOB, which then transmit neuronal signals to the olfactory cortex regions of the AON, OT, PCX, CoA and ECX [12]. In the AOS, after odours are sensed by the VON, the vomeronasal organ sends neuronal axons to the AOB, after which the AOB transmits neuronal signals to the BNST, MeA and PMCo [14, 15]. AOB, accessory olfactory bulb; AON, anterior olfactory nucleus; AOS, accessory olfactory system; BNST, bed nucleus of the stria terminalis; CoA, cortical amygdala; ECX, entorhinal cortex; MeA, medial amygdala; MOB, main olfactory bulb; MOE, main olfactory epithelium; MOS, main olfactory system; OT, olfactory tubercle; PCX, piriform cortex; PMCo, posteromedial cortical amygdala; VON, vomeronasal organ.

smell. The ORs are located within the olfactory epithelium and are distributed at the top of the nasal cavity, upper part of the nasal septum and upper part of the upper turbinate. The ORs are members of the A-class rhodopsin family of G protein-coupled receptors (GPCRs). Once the ORs are activated, they trigger nerve impulses to transmit information about odours to the brain [1, 21–25]. The olfactory receptor forms a multi-gene family consisting of approximately 400 genes from humans and 1200 genes from mice [26, 27]. In vertebrates, ORs are in the cilia and synapses of OSNs, as well as in the epithelial cells of human airways. In insects, ORs are located on the antennae and other chemical sensory organs. It has been reported that humans can distinguish as many as 1012 types of odours, while visual perception can only distinguish 107 types of colours [28]. Due to the undoubtedly crucial role of ORs, the Nobel Prize in Physiology or Medicine of 2004 was awarded to Linda B Buck and Richard Axel for their pioneered and enormous contributions to studies related to ORs [29]. Interestingly, two years later after the announcement of the Nobel Prize to the olfactory research, another study discovered a second receptor family in the olfactory epithelium of mice. The genes encoding these receptors are called trace amine-associated receptors (TAARs), which are evolutionally conserved and also exist in humans, mice and fish and can be used to detect volatile amines. Except for TAAR1, all functional TAARs in humans are expressed in olfactory epithelial cells [30]. The third type of olfactory receptor, known as the vomeronasal receptor, has also been identified. The function of the vomeronasal receptor is presumed to be one kind of pheromone receptor [31, 32]. Like many other GPCRs, the current structural information of ORs is based on homology modelling methods and still lacks atomic-level structural information. ORs do not bind to specific ligands but exhibit varying degrees of affinity towards a range of odour molecules. It is noteworthy that a single odour molecule can bind to many ORs with different affinities, depending on the physical and chemical properties of the molecule [33–36]. Once the odour agent binds to the OR, the receptor undergoes structural changes and binds to activate the olfactory G protein inside the olfactory receptor-expressing neurons. G protein activates adenylyl cyclases to convert ATP into cyclic AMP (cAMP) [37]. cAMP opens cyclic nucleotide-gated ion channels, allowing calcium and sodium ions to enter cells, depolarizing olfactory receptor-expressing neurons and generating action potentials, transmitting information to the central nervous system [38, 39], such as the OT.

2 | Anatomical and Functional Characterization of the OT

The OT, also called tubular striatum [40–42], is a sub-region of the ventral striatum, which directly receives information inputs from the OB and other brain regions. OT brain regions are enriched in the expression of dopamine receptor 1 (D1R), dopamine receptor 2 (D2R) and dopamine receptor 3 (D3R), with D3R mainly expressed in Islands of Calleja (IC) [43–48]. The IC is also known as 'interface islands' and 'granular islands', which are characterised by the dense core of small 'glial like' granular cells belonging to the smallest neurons in the OT [49, 50]. In general, 90%–95% of the neurons in the OT are D1R/D2R medium spiny neurons (MSNs), most of which express the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [51, 52]. The structure of the OT can be roughly divided into three layers (layers 1, 2 and 3) from the outside to the inside [53]. In the layer 1, also referred as the molecular layer, there are dendrites of dopamine receptor 1 or 2-expressing medium spiny neurons (D1 or D2 MSNs) present. In general, cell bodies of D1 and D2 MSNs predominantly compose the secondary dense cell layer (DCL, layer 2). The multiform layer (layer 3), situated below the DCL, is characterized by a substantial abundance of densely packed clusters comprising granular cells, the Islands of Calleja (IC). Interestingly, D1 and D2 MSNs, more or less, are also present in the multiform layer [52, 54] (Figure 2).

Compared to the fruitful anatomical of the OT, its functional role is relatively limited. Our recent study reveals that the OT was an important factor in the regulation of self-grooming (one typical asocial behaviour), social attraction and depressive phenotypes in mice [55]. Additionally, there is evidence showing that OT plays a crucial role in odour perception in the anterior piriform cortex (aPCX)-OT pathway [48]. The OT is also involved in the

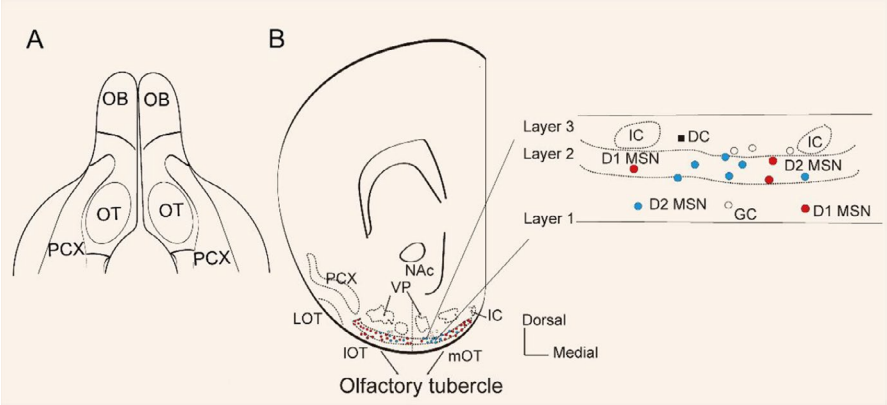

FIGURE 2 | Schematic illustrating the olfactory tubercle (OT) in rodents. (A) A ventral view of the anatomical location of the OT in the brain. (B) A coronal view of local anatomy and structure of the OT. The OT is one sub-region of the ventral striatum and is located below the VP and NAc, close to the PCX and LOT. The OT can be roughly divided into three layers from the ventral to the dorsal. There are 90%–95% of neurons in the OT are D1 and D2 MSNs [52]. There are also ICs with dense granule cells with rich expression of D3 receptor. D1 or D2 MSNs, dopamine receptor 1 or 2 (D1R/D2R)-expressing medium spiny neurons; DC, dwarf cell; GC, granule cell; LOT, lateral olfactory tract; lOT, lateral olfactory tubercle; mOT, medial olfactory tubercle; NAc, nucleus accumbens; OB, olfactory bulb; PCX, piriform cortex; VP, ventral pallidum.

VTA-OT pathway mediating odour preference and a variety of naturalistic reward processes [56]. Furthermore, it has also been demonstrated that OT-projecting Fezf2^{BLA} neurons provide positive valence or motivation information [57]. Though these great progresses have been made, research on the function of OT-related neural circuits still remains much to be explored. Thus, in light of the relatively limited studies aforementioned, more physiological roles of OT and corresponding neural circuits are warranted to be further unveiled.

3 | The Role of OT in Odour Processing

The OT plays a pivotal role in odour recognition and regulation in rodents and actively participates in odour-induced motivational responses [58, 59]. Specific odours could elicit distinct behavioural motivations in mice. The odorants emitted from predators can induce fear and avoidance responses in rodents. For example, both rats and mice displayed avoidance behaviour towards the biogenic amine 2-phenylethylamine identified from bobcat urine [60]. The trimethyl-thiazoline (TMT), a volatile substance secreted from the anal glands of mice's natural predator, the fox, elicited pronounced fear responses and avoidance behaviours in both mice and rats [61–63]. The 4-methylthiazol (4MT), as a structural analogue of TMT, was also an innate aversive odour in mice [64]. The valeraldehyde and 2-methylbutyric acid (2 MB), which are pungent odours produced by rotting food, induced concentration-dependent distinct behaviours in mice. Higher concentrations of 2 MB produced aversive behaviour while lower concentrations triggered neutral behaviour [61, 65]. This is probably due to the fact that the odours produced by rotting food include fatty acids, fatty aldehydes and alkylamines, all of which are undesirable to mice [61]. In contrast, the limonene and heptaldehyde have been demonstrated to trigger a distinct preference for specific locations in mice [66, 67]. In fact, the odorant preferences of mice exhibit plasticity and could be manipulated via modulating the OT neural activity. It has been reported that bilateral stimulations of the OT region by electrodes changed mice's initial preference for their favourite peanut odour [68]. Moreover, the preference of female mice in estrus towards male mice urine was abolished following the inhibition of neuronal activity in the mOT via chemogenetic manipulations [69]. In addition, local administration of the 17 beta-estradiol (E2) inhibitor letrozole into the OT resulted in gonadectomised female mice exhibiting a remarkable preference for intact female mouse urine, while not significantly affecting their recognition of other odours [70]. Altogether, these studies suggest that the mOT is involved in the recognition and processing of both social- and non-social-related odours in mice.

The OT exhibits region-dependent variances in odour processing and related behaviours. Odour regulation varies across different sub-regions of the OT. The D1 MSNs in the mOT were implicated in regulating attractive, eating and reward-related motivational behaviours, while D2 MSNs exhibited contrasting effects. Conversely, the lOT was involved in modulating aversive behaviour elicited by odour stimuli, with D1 and D2 MSNs playing opposing roles to those in the mOT [59, 71, 72]. It is noteworthy that D1 MSNs exhibited heightened sensitivity to odour concentrations, while D2 MSNs demonstrated a greater propensity for discriminating between different types of odours. Consequently, D1 and D2 MSNs manifested distinct responses when exposed to olfactory stimuli [72, 73]. The proper and exquisite function of the OT in odour processing and odour-guided behaviours depends on a plethora of neurotransmitters produced locally or released from other OT-projecting brain areas. Dopamine, a neurotransmitter in the OT, plays a crucial role in regulating reward-induced motivational behaviour. Previous studies employing the 6-hydroxydopamine (6-OHDA), a catecholaminergic neuronal toxin causing dopaminergic denervation, have successfully induced bilateral mOT lesions in mice, resulting in the complete elimination of preference for attractive odours [67, 74–76]. These findings provide compelling evidence that dopamine release within the OT modulates odour preference in mice. Moreover, one study showed that the perception of some attractive odorants was declined in older mice while the appreciation of unattractive odorants did not change. Intriguingly, neural activity in the OT of older mice was consistently altered when attraction to pleasant odorants was impaired while maintained when the odorants kept their attractivity, further strengthening the pivotal role of the OT in odour processing and regulation and indicating the neural plasticity of OT in odour processing during ageing in rodents [77].

4 | OT-Related Neural Circuits Involved in Odour Processing

The OB serves as the primary sensory structure responsible for receiving and transmitting olfactory information. Upon the arrival of perceived odour molecules, they undergo conversion into neuronal signals within the axons located in the OB before being transmitted to various brain regions associated with olfaction [78]. The OT can function as intermediate relay stations for processing diverse odour information, receiving neuronal inputs from both the MOB and the auxiliary olfactory pathway of the OB. In mice, odour information is conveyed to the OT via mitral cells (MC) and tufted cells (TC) in the OB [79]. The robust behavioural responses to odours in rodents heavily rely on intricate interactions among neural circuits formed between specific brain regions. Several olfactory and reward-related brain areas, including the OB, PCX, AON, OT, amygdala, ventral tegmental area (VTA), lateral olfactory tract (LOT), ventral pallidum (VP), NAc and other olfactory cortices, all play pivotal roles in odour recognition and processing. Additionally, some other brain regions that have connections with the OT, such as the prefrontal cortex (PFC) and ECX, are also involved in odour processing which is potentially realized through the modulation of OT [53, 80, 81]. The following descriptions will elucidate the formation of neural circuitry between these aforementioned brain regions implicated in odour processing and their interactions with the OT [74]. Among these neuronal pathways, the pathway connecting the amygdala to the striatum, including the OT, was implicated in the recognition and attraction of mammalian sex pheromones [82]. Both anterograde and retrograde tracer techniques were leveraged to ascertain that the posteromedial cortical amygdaloid nucleus projected to the OT [83]. The processing of sex pheromone odours played a crucial role in the courtship and reproduction in rats, particularly in females,

wherein the amygdala was assumed to play a pivotal function [84]. During this process, efferents from the amygdala projected to various regions of the ventral striatum, including the nucleus accumbens core (AcbC) and shell (AcbSh), VP, mOT and IC [74]. Another study demonstrated the pivotal role of the OT in processing olfactory information, with a particular focus on the extensive projection of neurons from the amygdala into the mOT, as confirmed via Fluoro-Gold injection into this specific region [85]. It is also suggested that the neural circuits involved in both indirect and direct synaptic connections between the anteromedial amygdala and OT may potentially contribute to the investigation of these odours in female mice [86]. Rodents process odour information not only through sex pheromones but also via other non-pheromonal cues, which can be broadly categorized into pleasant and unpleasant odour processing. In addition, the OT also served as a pivotal hub for dopamine signalling in the midbrain, thereby playing a crucial role in odour processing and reward-related behaviours [87, 88].

The anterior and posterior parts of the OB (aOB and pOB, respectively) could exert distinct effects via projections to different regions of the OT. Optogenetic activation of neurons in the pOB to mOT pathway enhanced mice's attraction to unpleasant odours, indicating a reversal in their odour preference [66]. However, optogenetic activation of the aOB to lOT pathway did not elicit corresponding changes. As a component of the olfactory sensory cortex, the PCX served as a primary centre for olfaction and received direct inputs from the OB [89, 90]. The PCX transmitted odour-related information to the downstream OT in the striatum [47]. Consequently, the neural pathway connecting the PCX to OT played a crucial role in processing olfactory information. Intriguingly, a substantial population of neurons in the PCX projected to the OT, whereas reciprocal projections from the OT to the PCX were absent. Optogenetic activating neuronal fibres originating from the aPCX could modulate neuronal activity within the OT and influenced odour-evoked responses. Notably, both D1 and D2 MSNs in the OT received direct synaptic inputs from glutamatergic neurons originating from aPCX [48]. Interestingly, the activation of neuronal fibres projecting from aPCX to different regions of the OT elicited distinct effects. The activation of neuronal fibres projecting from the aPCX to the mOT induced both rewarding and attractive behaviours, whereas the activation of neuronal fibres originating from the aPCX and targeting the lOT was associated with aversive behaviours [91]. Moreover, neuronal projections from the VTA to OT primarily involved VTA's medial neurons projecting to the anteromedial region of the OT, while its lateral neurons projected to the lateral region of the OT [92]. The mOT was implicated in reward and olfactory information processing, whereas dopaminergic neurons in the VTA were believed to play a role in reward and motivation. Optogenetic activation of VTA-mOT projections elicited preference for spatial, positional and neutral odours in mice [56]. In addition, neuronal projections from specific brain regions to the OT could modulate olfactory information recognition. For example, the LOT is projected to dwarf cell cap regions of the OT and the LOT-OT pathway is potentially involved in non-pheromonal processes such as feeding [93, 94]. Besides, mice exhibited innate fear and stress responses towards natural predators, such as the scent of cat and fox urine, due to their heightened sensitivity to olfactory cues from these enemies. Upon detection of predator odours, odour ORs in the olfactory epithelium and TAARs received the olfactory signals, which were then transmitted to the MOB. Subsequently, the MOB conveyed input signals from olfactory neurons to the aPCX for perception and encoding of odour information [30, 95–97]. Additionally, the PCX encoded familiarity and similarity of odours while facilitating recognition of mixed odours [98, 99]. The bed nucleus of the stria terminalis (BNST) and amygdala were also involved in fear stress behaviour elicited by natural enemy odour [99, 100]. Upon detection of natural enemy odour, olfactory information was perceived by the MOS and transmitted to the MOB, which then projects to the medial BNST via the medial amygdala and to the lateral BNST via the central amygdala [97] (Figure 3). Furthermore, exposure to predator odour activated the trigeminal nervous system, autonomic nervous system and neuroendocrine stress system in rodents [101], which could also potentially involve the OT during odour processing.

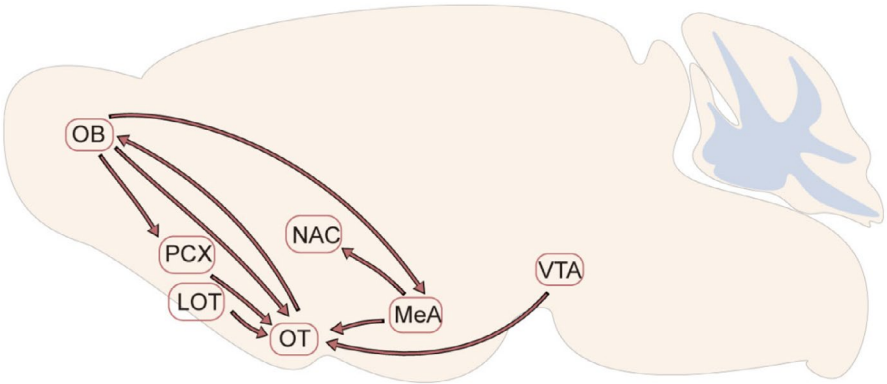

FIGURE 3 | Schematic illustrating the OT-related neural circuits involved in odour processing in rodents. When rodents engage in courtship, sex pheromone odour messages are sent by receptor neurons to the OB, then project to the amygdala and from the amygdala to the OT and NAc. The OB-PCX pathway was activated when mice smelled predators [30, 95–97]. Optogenetic activating the pOB-mOT pathway made mice be attractive to unpleasant odours [89]. Activation of the aPCX-mOT pathway triggered attractive behaviour, while activation of the aPCX-lOT pathway induced aversive behaviour [48]. Optogenetic activation of the VTA-mOT pathway induced neutral odour preference in mice [56]. In addition, some brain regions also project OT, such as the LOT [93, 94]. LOT, lateral olfactory tract; MeA, medial amygdala; NAc, nucleus accumbens; OB, olfactory bulb; OT, olfactory tubercle; PCX, piriform cortex; VTA, ventral tegmental area.

5 | Concluding Remarks and Perspectives

The mammalian olfactory system is one of the most precocious systems during development and is endowed with versatile functions distinct from other sensory systems. As the key component of both the olfactory system and the ventral striatum, the OT and related neural pathways play paramount roles in olfactory transmission and odour-guided behaviours that are crucial for the survival and production of animals. Though great progresses have been made regarding the function of the OT in the past few decades, information pertaining to unappreciated physiological roles of the OT and corresponding neural circuits is still lacking, for example, (1) What is the role of OT and the underlying neural mechanisms responsible for feeding? (2) How the OT integrates peripheral olfactory inputs with midbrain rewarding information to affect emotion-related behaviours? (3) How the local neural circuits work compatibly in the OT during odour processing? and etc. More delineated work focusing on OT is warranted in the future.

Author Contributions

Yanbiao Zhong, Haiping Wang and Yun-Feng Zhang designed and supervised the project. All authors were involved in collecting related references, drafting subsections individually/cooperatively and preparing the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 82371515) and the State Key Laboratory of Integrated Management of Pest Insects and Rodents (No. IPM2301), China.

Ethics Statement

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data supporting the findings of this study are available within the paper.

References

1. S. Firestein, "How the Olfactory System Makes Sense of Scents," *Nature* 413 (2001): 211–218, https://doi.org/10.1038/35093026.

2. T. D. Smith and K. P. Bhatnagar, "Anatomy of the Olfactory System," *Handbook of Clinical Neurology* 164 (2019): 17–28, https://doi.org/10.1016/B978-0-444-63855-7.00002-2.

3. A. Fang and C. R. Yu, "Activity-Dependent Formation of the Topographic Map and the Critical Period in the Development of Mammalian Olfactory System," *Genesis* 62 (2024): e23586, https://doi.org/10.1002/dvg.23586.

4. K. A. Fulton, D. Zimmerman, A. Samuel, K. Vogt, and S. R. Datta, "Common Principles for Odour Coding Across Vertebrates and Invertebrates," *Nature Reviews. Neuroscience* 25 (2024): 453–472, https://doi.org/10.1038/s41583-024-00822-0.

5. M. Migliore, F. Cavarretta, A. Marasco, E. Tulumello, M. L. Hines, and G. M. Shepherd, "Synaptic Clusters Function as Odor Operators in the Olfactory Bulb," *Proceedings of the National Academy of Sciences of the United States of America* 112 (2015): 8499–8504, https://doi.org/10.1073/pnas.1502513112.

6. A. M. Boyd, J. F. Sturgill, C. Poo, and J. S. Isaacson, "Cortical Feedback Control of Olfactory Bulb Circuits," *Neuron* 76 (2012): 1161–1174, https://doi.org/10.1016/j.neuron.2012.10.020.

7. L. B. Buck, "The Molecular Architecture of Odor and Pheromone Sensing in Mammals," *Cell* 100 (2000): 611–618, https://doi.org/10.1016/s0092-8674(00)80698-4.

8. M. J. Baum and J. A. Cherry, "Processing by the Main Olfactory System of Chemosignals That Facilitate Mammalian Reproduction," *Hormones and Behavior* 68 (2015): 53–64, https://doi.org/10.1016/j.yhbeh.2014.06.003.

9. V. A. Tobin, H. Hashimoto, D. W. Wacker, et al., "An Intrinsic Vasopressin System in the Olfactory Bulb Is Involved in Social Recognition," *Nature* 464 (2010): 413–417, https://doi.org/10.1038/nature08826.

10. K. C. Persaud, *Neuromorphic Olfaction Frontiers in Neuroengineering*, eds. K. C. Persaud, S. Marco and A. Gutierrez-Galvez, (Boca Raton, FL: CRC Press, 2013).

11. H. Harada, H. Kashiwadani, Y. Kanmura, and T. Kuwaki, "Linalool Odor-Induced Anxiolytic Effects in Mice," *Frontiers in Behavioral Neuroscience* 12 (2018): 241, https://doi.org/10.3389/fnbeh.2018.00241.

12. K. Mori and H. Sakano, "How Is the Olfactory Map Formed and Interpreted in the Mammalian Brain?," *Annual Review of Neuroscience* 34 (2011): 467–499, https://doi.org/10.1146/annurev-neuro-112210-112917.

13. K. Trinh and D. R. Storm, "Detection of Odorants Through the Main Olfactory Epithelium and Vomeronasal Organ of Mice," *Nutrition Reviews* 62 (2004): S189–S192, discussion S224-141, https://doi.org/10.1111/j.1753-4887.2004.tb00098.x.

14. C. Dulac and A. T. Torello, "Molecular Detection of Pheromone Signals in Mammals: From Genes to Behaviour," *Nature Reviews. Neuroscience* 4 (2003): 551–562, https://doi.org/10.1038/nrn1140.

15. K. K. Ishii and K. Touhara, "Neural Circuits Regulating Sexual Behaviors Via the Olfactory System in Mice," *Neuroscience Research* 140 (2019): 59–76, https://doi.org/10.1016/j.neures.2018.10.009.

16. M. Keller, M. J. Baum, O. Brock, P. A. Brennan, and J. Bakker, "The Main and the Accessory Olfactory Systems Interact in the Control of Mate Recognition and Sexual Behavior," *Behavioural Brain Research* 200 (2009): 268–276, https://doi.org/10.1016/j.bbr.2009.01.020.

17. S. A. Roberts, D. M. Simpson, S. D. Armstrong, et al., "Darcin: A Male Pheromone That Stimulates Female Memory and Sexual Attraction to an Individual Male's Odour," *BMC Biology* 8 (2010): 75, https://doi.org/10.1186/1741-7007-8-75.

18. H. Kimoto, S. Haga, K. Sato, and K. Touhara, "Sex-Specific Peptides From Exocrine Glands Stimulate Mouse Vomeronasal Sensory Neurons," *Nature* 437 (2005): 898–901, https://doi.org/10.1038/nature04033.

19. I. S. McGregor, G. A. Hargreaves, R. Apfelbach, and G. E. Hunt, "Neural Correlates of cat Odor-Induced Anxiety in Rats: Region-Specific Effects of the Benzodiazepine Midazolam," *Journal of Neuroscience* 24 (2004): 4134–4144, https://doi.org/10.1523/jneurosci.0187-04.2004.

20. C. L. Samuelsen and M. Meredith, "The Vomeronasal Organ Is Required for the Male Mouse Medial Amygdala Response to Chemical-Communication Signals, as Assessed by Immediate Early Gene Expression," *Neuroscience* 164 (2009): 1468–1476, https://doi.org/10.1016/j.neuroscience.2009.09.030.

21. L. B. Buck, "Olfactory Receptors and Odor Coding in Mammals," *Nutrition Reviews* 62 (2004): S184–S188, discussion S224-141, https://doi.org/10.1111/j.1753-4887.2004.tb00097.x.

22. T. Tesileanu, S. Cocco, R. Monasson, and V. Balasubramanian, "Adaptation of Olfactory Receptor Abundances for Efficient Coding," *eLife* 8 (2019): e39279, https://doi.org/10.7554/eLife.39279.

23. C. Mucignat-Caretta, "The Rodent Accessory Olfactory System," *Journal of Comparative Physiology. A, Neuroethology, Sensory, Neural, and Behavioral Physiology* 196 (2010): 767–777, https://doi.org/10.1007/s00359-010-0555-z.

24. P. M. Lledo, G. Gheusi, and J. D. Vincent, "Information Processing in the Mammalian Olfactory System," *Physiological Reviews* 85 (2005): 281–317, https://doi.org/10.1152/physrev.00008.2004.

25. T. E. Holy, "The Accessory Olfactory System: Innately Specialized or Microcosm of Mammalian Circuitry?," *Annual Review of Neuroscience* 41 (2018): 501–525, https://doi.org/10.1146/annurev-neuro-080317-061916.

26. I. Rodriguez, "Singular Expression of Olfactory Receptor Genes," *Cell* 155 (2013): 274–277, https://doi.org/10.1016/j.cell.2013.09.032.

27. M. Spehr and S. D. Munger, "Olfactory Receptors: G Protein-Coupled Receptors and Beyond," *Journal of Neurochemistry* 109 (2009): 1570–1583, https://doi.org/10.1111/j.1471-4159.2009.06085.x.

28. C. Bushdid, M. O. Magnasco, L. B. Vosshall, and A. Keller, "Humans Can Discriminate More Than 1 Trillion Olfactory Stimuli," *Science* 343 (2014): 1370–1372, https://doi.org/10.1126/science.1249168.

29. A. S. Barwich, "What Makes a Discovery Successful? The Story of Linda Buck and the Olfactory Receptors," *Cell* 181 (2020): 749–753, https://doi.org/10.1016/j.cell.2020.04.040.

30. S. D. Liberles and L. B. Buck, "A Second Class of Chemosensory Receptors in the Olfactory Epithelium," *Nature* 442 (2006): 645–650, https://doi.org/10.1038/nature05066.

31. K. Del Punta, T. Leinders-Zufall, I. Rodriguez, et al., "Deficient Pheromone Responses in Mice Lacking a Cluster of Vomeronasal Receptor Genes," *Nature* 419 (2002): 70–74, https://doi.org/10.1038/nature00955.

32. E. B. Keverne, "The Vomeronasal Organ," *Science* 286 (1999): 716–720, https://doi.org/10.1126/science.286.5440.716.

33. C. Wu, M. Xu, J. Dong, W. Cui, and S. Yuan, "The Structure and Function of Olfactory Receptors," *Trends in Pharmacological Sciences* 45 (2024): 268–280, https://doi.org/10.1016/j.tips.2024.01.004.

34. L. Guo, J. Cheng, S. Lian, et al., "Structural Basis of Amine Odorant Perception by a Mammal Olfactory Receptor," *Nature* 618 (2023): 193–200, https://doi.org/10.1038/s41586-023-06106-4.

35. J. Del Marmol, M. A. Yedlin, and V. Ruta, "The Structural Basis of Odorant Recognition in Insect Olfactory Receptors," *Nature* 597 (2021): 126–131, https://doi.org/10.1038/s41586-021-03794-8.

36. C. B. Billesbolle, C. A. de March, W. J. van der Velden, et al., "Structural Basis of Odorant Recognition by a Human Odorant Receptor," *Nature* 615 (2023): 742–749, https://doi.org/10.1038/s41586-023-05798-y.

37. D. Schuster, B. Khanppnavar, I. Kantarci, V. Mehta, and V. M. Korkhov, "Structural Insights Into Membrane Adenylyl Cyclases, Initiators of cAMP Signaling," *Trends in Biochemical Sciences* 49 (2024): 156–168, https://doi.org/10.1016/j.tibs.2023.12.002.

38. T. Imai, M. Suzuki, and H. Sakano, "Odorant Receptor-Derived cAMP Signals Direct Axonal Targeting," *Science* 314 (2006): 657–661, https://doi.org/10.1126/science.1131794.

39. M. Maritan, G. Monaco, I. Zamparo, M. Zaccolo, T. Pozzan, and C. Lodovichi, "Odorant Receptors at the Growth Cone Are Coupled to Localized cAMP and Ca^{2+} Increases," *Proceedings of the National Academy of Sciences of the United States of America* 106 (2009): 3537–3542, https://doi.org/10.1073/pnas.0813224106.

40. D. W. Wesson, "The Tubular Striatum," *Journal of Neuroscience* 40 (2020): 7379–7386, https://doi.org/10.1523/JNEUROSCI.1109-20.2020.

41. A. Xiong and D. W. Wesson, "Illustrated Review of the Ventral Striatum's Olfactory Tubercle," *Chemical Senses* 41 (2016): 549–555, https://doi.org/10.1093/chemse/bjw069.

42. M. Yamaguchi, "Connectivity of the Olfactory Tubercle: Inputs, Outputs, and Their Plasticity," *Frontiers in Neural Circuits* 18 (2024): 1423505, https://doi.org/10.3389/fncir.2024.1423505.

43. S. Ridray, N. Griffon, V. Mignon, et al., "Coexpression of Dopamine D1 and D3 Receptors in Islands of Calleja and Shell of Nucleus Accumbens of the Rat: Opposite and Synergistic Functional Interactions," *European Journal of Neuroscience* 10 (1998): 1676–1686, https://doi.org/10.1046/j.1460-9568.1998.00173.x.

44. G. Mengod, M. T. Villaró, G. B. Landwehrmeyer, et al., "Visualization of Dopamine D1, D2 and D3 Receptor mRNAs in Human and Rat Brain," *Neurochemistry International* 20, no. Suppl (1992): 33S–43S, https://doi.org/10.1016/0197-0186(92)90208-9.

45. Y. F. Zhang, L. Vargas Cifuentes, K. N. Wright, et al., "Publisher Correction: Ventral Striatal Islands of Calleja Neurons Control Grooming in Mice," *Nature Neuroscience* 25 (2022): 264, https://doi.org/10.1038/s41593-021-01003-3.

46. N. Martiros, V. Kapoor, S. E. Kim, and V. N. Murthy, "Distinct Representation of Cue-Outcome Association by D1 and D2 Neurons in the Ventral striatum's Olfactory Tubercle," *eLife* 11 (2022): e75463, https://doi.org/10.7554/eLife.75463.

47. Z. Zhang, H. Zhang, P. Wen, et al., "Whole-Brain Mapping of the Inputs and Outputs of the Medial Part of the Olfactory Tubercle," *Frontiers in Neural Circuits* 11 (2017): 52, https://doi.org/10.3389/fncir.2017.00052.

48. K. A. White, Y. F. Zhang, Z. Zhang, et al., "Glutamatergic Neurons in the Piriform Cortex Influence the Activity of D1- and D2-Type Receptor-Expressing Olfactory Tubercle Neurons," *Journal of Neuroscience* 39 (2019): 9546–9559, https://doi.org/10.1523/jneurosci.1444-19.2019.

49. O. E. Millhouse, "Granule Cells of the Olfactory Tubercle and the Question of the Islands of Calleja," *Journal of Comparative Neurology* 265 (1987): 1–24, https://doi.org/10.1002/cne.902650102.

50. Chapter 3 Islands of Calleja (Insulae Terminalis)," *Handbook of Clinical Neurology* 79 (2003): 61–62, https://doi.org/10.1016/S0072-9752(03)80010-6.

51. M. L. Perreault, A. Hasbi, B. F. O'Dowd, and S. R. George, "The Dopamine d1-d2 Receptor Heteromer in Striatal Medium Spiny Neurons: Evidence for a Third Distinct Neuronal Pathway in Basal Ganglia," *Frontiers in Neuroanatomy* 5 (2011): 31, https://doi.org/10.3389/fnana.2011.00031.

52. H. L. Cansler, K. N. Wright, L. A. Stetzik, and D. W. Wesson, "Neurochemical Organization of the Ventral striatum's Olfactory Tubercle," *Journal of Neurochemistry* 152 (2020): 425–448, https://doi.org/10.1111/jnc.14919.

53. M. Yamaguchi, "Functional sub-Circuits of the Olfactory System Viewed From the Olfactory Bulb and the Olfactory Tubercle," *Frontiers in Neuroanatomy* 11 (2017): 33, https://doi.org/10.3389/fnana.2017.00033.

54. A. J. Giessel and S. R. Datta, "Olfactory Maps, Circuits and Computations," *Current Opinion in Neurobiology* 24 (2014): 120–132, https://doi.org/10.1016/j.conb.2013.09.010.

55. Y. F. Zhang, J. Wu, Y. Wang, et al., "Ventral Striatal Islands of Calleja Neurons Bidirectionally Mediate Depression-Like Behaviors in Mice," *Nature Communications* 14 (2023): 6887, https://doi.org/10.1038/s41467-023-42662-z.

56. Z. Zhang, Q. Liu, P. Wen, et al., "Activation of the Dopaminergic Pathway From VTA to the Medial Olfactory Tubercle Generates Odor-Preference and Reward," *Elife* 6 (2017): e25423, https://doi.org/10.7554/eLife.25423.

57. X. Zhang, W. Guan, T. Yang, et al., "Genetically Identified Amygdala-Striatal Circuits for Valence-Specific Behaviors," *Nature Neuroscience* 24 (2021): 1586–1600, https://doi.org/10.1038/s41593-021-00927-0.

58. M. A. Gadziola, K. A. Tylicki, D. L. Christian, and D. W. Wesson, "The Olfactory Tubercle Encodes Odor Valence in Behaving Mice," *Journal of Neuroscience* 35 (2015): 4515–4527, https://doi.org/10.1523/JNEUROSCI.4750-14.2015.

59. K. Murata, M. Kanno, N. Ieki, K. Mori, and M. Yamaguchi, "Mapping of Learned Odor-Induced Motivated Behaviors in the Mouse Olfactory Tubercle," *Journal of Neuroscience* 35 (2015): 10581–10599, https://doi.org/10.1523/JNEUROSCI.0073-15.2015.

60. D. M. Ferrero, J. K. Lemon, D. Fluegge, et al., "Detection and Avoidance of a Carnivore Odor by Prey," *Proceedings of the National Academy of Sciences of the United States of America* 108 (2011): 11235–11240, https://doi.org/10.1073/pnas.1103317108.

61. K. Kobayakawa, R. Kobayakawa, H. Matsumoto, et al., "Innate Versus Learned Odour Processing in the Mouse Olfactory Bulb," *Nature* 450 (2007): 503–508, https://doi.org/10.1038/nature06281.

62. A. L. Hebb, R. M. Zacharko, H. Dominguez, F. Trudel, S. Laforest, and G. Drolet, "Odor-Induced Variation in Anxiety-Like Behavior in Mice Is Associated With Discrete and Differential Effects on Mesocorticolimbic Cholecystokinin mRNA Expression," *Neuropsychopharmacology* 27 (2002): 744–755, https://doi.org/10.1016/S0893-133X(02)00354-8.

63. B. A. Morrow, A. J. Redmond, R. H. Roth, and J. D. Elsworth, "The Predator Odor, TMT, Displays a Unique, Stress-Like Pattern of Dopaminergic and Endocrinological Activation in the Rat," *Brain Research* 864 (2000): 146–151, https://doi.org/10.1016/s0006-8993(00)02174-0.

64. K. Mori and H. Sakano, "Processing of Odor Information During the Respiratory Cycle in Mice," *Frontiers in Neural Circuits* 16 (2022): 861800, https://doi.org/10.3389/fncir.2022.861800.

65. K. Sung, M. Kim, J. Hyun, Y. Kim, and K. Kim, "Possible Effects of Nitric Oxide Synthases on Odor-Induced Behavioral Changes in Mice," *Neuroscience Letters* 569 (2014): 158–162, https://doi.org/10.1016/j.neulet.2014.04.005.

66. M. Midroit, L. Chalençon, N. Renier, et al., "Neural Processing of the Reward Value of Pleasant Odorants," *Current Biology* 31 (2021): 1592–1605, e1599, https://doi.org/10.1016/j.cub.2021.01.066.

67. P. Valle-Leija and R. Drucker-Colin, "Unilateral Olfactory Deficit in a hemiparkinson's Disease Mouse Model," *Neuroreport* 25 (2014): 948–953, https://doi.org/10.1097/WNR.0000000000000218.

68. B. J. Fitzgerald, K. Richardson, and D. W. Wesson, "Olfactory Tubercle Stimulation Alters Odor Preference Behavior and Recruits Forebrain Reward and Motivational Centers," *Frontiers in Behavioral Neuroscience* 8 (2014): 81, https://doi.org/10.3389/fnbeh.2014.00081.

69. B. T. DiBenedictis, A. O. Olugbemi, M. J. Baum, and J. A. Cherry, "DREADD-Induced Silencing of the Medial Olfactory Tubercle Disrupts the Preference of Female Mice for Opposite-Sex Chemosignals (1,2,3)," *eNeuro* 2 (2015): 25423, https://doi.org/10.1523/ENEURO.0078-15.2015.

70. K. N. Wright, N. L. Johnson, A. M. Dossat, J. T. Wilson, and D. W. Wesson, "Reducing Local Synthesis of Estrogen in the Tubular Striatum Promotes Attraction to Same-Sex Odors in Female Mice," *Hormones and Behavior* 140 (2022): 105122, https://doi.org/10.1016/j.yhbeh.2022.105122.

71. K. Murata, "Hypothetical Roles of the Olfactory Tubercle in Odor-Guided Eating Behavior," *Frontiers in Neural Circuits* 14 (2020): 577880, https://doi.org/10.3389/fncir.2020.577880.

72. K. Murata, T. Kinoshita, Y. Fukazawa, et al., "Opposing Roles of Dopamine Receptor D1- and D2-Expressing Neurons in the Anteromedial Olfactory Tubercle in Acquisition of Place Preference in Mice," *Frontiers in Behavioral Neuroscience* 13 (2019): 50, https://doi.org/10.3389/fnbeh.2019.00050.

73. A. Maegawa, K. Murata, K. Kuroda, S. Fujieda, and Y. Fukazawa, "Cellular Profiles of Prodynorphin and Preproenkephalin mRNA-Expressing Neurons in the Anterior Olfactory Tubercle of Mice," *Frontiers in Neural Circuits* 16 (2022): 908964, https://doi.org/10.3389/fncir.2022.908964.

74. B. T. DiBenedictis, A. O. Olugbemi, M. J. Baum, and J. A. Cherry, "6-Hydroxydopamine Lesions of the Anteromedial Ventral Striatum Impair Opposite-Sex Urinary Odor Preference in Female Mice," *Behavioural Brain Research* 274 (2014): 243–247, https://doi.org/10.1016/j.bbr.2014.08.024.

75. M. O. Klein, D. S. Battagello, A. R. Cardoso, D. N. Hauser, J. C. Bittencourt, and R. G. Correa, "Dopamine: Functions, Signaling, and Association With Neurological Diseases," *Cellular and Molecular Neurobiology* 39 (2019): 31–59, https://doi.org/10.1007/s10571-018-0632-3.

76. J. Cui, D. Zhao, M. Xu, et al., "Characterization of Graded 6-Hydroxydopamine Unilateral Lesion in Medial Forebrain Bundle of Mice," *Scientific Reports* 14 (2024): 3721, https://doi.org/10.1038/s41598-024-54066-0.

77. L. Chalencon, M. Midroit, A. Athanassi, et al., "Age-Related Differences in Perception and Coding of Attractive Odorants in Mice," *Neurobiology of Aging* 137 (2024): 8–18, https://doi.org/10.1016/j.neurobiolaging.2024.02.003.

78. K. Mori, H. Nagao, and Y. Yoshihara, "The Olfactory Bulb: Coding and Processing of Odor Molecule Information," *Science* 286 (1999): 711–715, https://doi.org/10.1126/science.286.5440.711.

79. K. M. Igarashi, N. Ieki, M. An, et al., "Parallel Mitral and Tufted Cell Pathways Route Distinct Odor Information to Different Targets in the Olfactory Cortex," *Journal of Neuroscience* 32 (2012): 7970–7985, https://doi.org/10.1523/JNEUROSCI.0154-12.2012.

80. A. K. Bepari, K. Watanabe, M. Yamaguchi, N. Tamamaki, and H. Takebayashi, "Visualization of Odor-Induced Neuronal Activity by Immediate Early Gene Expression," *BMC Neuroscience* 13 (2012): 140, https://doi.org/10.1186/1471-2202-13-140.

81. F. de Castro, "Wiring Olfaction: The Cellular and Molecular Mechanisms That Guide the Development of Synaptic Connections From the Nose to the Cortex," *Frontiers in Neuroscience* 3 (2009): 52, https://doi.org/10.3389/neuro.22.004.2009.

82. E. Lanuza, A. Novejarque, J. Martínez-Ricós, J. Martínez-Hernández, C. Agustín-Pavón, and F. Martínez-García, "Sexual Pheromones and the Evolution of the Reward System of the Brain: The Chemosensory Function of the Amygdala," *Brain Research Bulletin* 75 (2008): 460–466, https://doi.org/10.1016/j.brainresbull.2007.10.042.

83. I. Ubeda-Banon, A. Novejarque, A. Mohedano-Moriano, et al., "Vomeronasal Inputs to the Rodent Ventral Striatum," *Brain Research Bulletin* 75 (2008): 467–473, https://doi.org/10.1016/j.brainresbull.2007.10.028.

84. C. Pardo-Bellver, B. Cadiz-Moretti, A. Novejarque, F. Martinez-Garcia, and E. Lanuza, "Differential Efferent Projections of the Anterior, Posteroventral, and Posterodorsal Subdivisions of the Medial Amygdala in Mice," *Frontiers in Neuroanatomy* 6 (2012): 33, https://doi.org/10.3389/fnana.2012.00033.

85. I. Ubeda-Banon, A. Novejarque, A. Mohedano-Moriano, et al., "Projections From the Posterolateral Olfactory Amygdala to the Ventral Striatum: Neural Basis for Reinforcing Properties of Chemical Stimuli," *BMC Neuroscience* 8 (2007): 103, https://doi.org/10.1186/1471-2202-8-103.

86. B. T. DiBenedictis, A. I. Helfand, M. J. Baum, and J. A. Cherry, "A Quantitative Comparison of the Efferent Projections of the Anterior and Posterior Subdivisions of the Medial Amygdala in Female Mice," *Brain Research* 1543 (2014): 101–108, https://doi.org/10.1016/j.brainres.2013.10.046.

87. D. W. Wesson and D. A. Wilson, "Sniffing out the Contributions of the Olfactory Tubercle to the Sense of Smell: Hedonics, Sensory Integration, and More?," *Neuroscience and Biobehavioral Reviews* 35 (2011): 655–668, https://doi.org/10.1016/j.neubiorev.2010.08.004.

88. J. W. Scott, R. L. McBride, and S. P. Schneider, "The Organization of Projections From the Olfactory Bulb to the Piriform Cortex and Olfactory Tubercle in the Rat," *Journal of Comparative Neurology* 194 (1980): 519–534, https://doi.org/10.1002/cne.901940304.

89. K. A. Bolding and K. M. Franks, "Recurrent Cortical Circuits Implement Concentration-Invariant Odor Coding," *Science* 361 (2018): eaat6904, https://doi.org/10.1126/science.aat6904.

90. L. B. Haberly, "Parallel-Distributed Processing in Olfactory Cortex: New Insights From Morphological and Physiological Analysis of Neuronal Circuitry," *Chemical Senses* 26 (2001): 551–576, https://doi.org/10.1093/chemse/26.5.551.

91. M. F. R. Sha, Y. Koga, Y. Murata, M. Taniguchi, and M. Yamaguchi, "Learning-Dependent Structural Plasticity of Intracortical and Sensory Connections to Functional Domains of the Olfactory Tubercle," *Frontiers in Neuroscience* 17 (2023): 1247375, https://doi.org/10.3389/fnins.2023.1247375.

92. S. Ikemoto, "Dopamine Reward Circuitry: Two Projection Systems From the Ventral Midbrain to the Nucleus Accumbens-Olfactory Tubercle Complex," *Brain Research Reviews* 56 (2007): 27–78, https://doi.org/10.1016/j.brainresrev.2007.05.004.

93. A. C. Santiago and S. J. Shammah-Lagnado, "Efferent Connections of the Nucleus of the Lateral Olfactory Tract in the Rat," *Journal of Comparative Neurology* 471 (2004): 314–332, https://doi.org/10.1002/cne.20028.

94. G. Zhou, G. Lane, T. Kahnt, and C. Zelano, "Structural Connectivity Between Olfactory Tubercle and Ventrolateral Periaqueductal Gray Implicated in Human Feeding Behavior," *Journal of Neuroscience* 44 (2024): e2342232024, https://doi.org/10.1523/jneurosci.2342-23.2024.

95. C. B. Wilson, L. D. McLaughlin, P. J. Ebenezer, A. R. Nair, and J. Francis, "Valproic Acid Effects in the Hippocampus and Prefrontal Cortex in an Animal Model of Post-Traumatic Stress Disorder," *Behavioural Brain Research* 268 (2014): 72–80, https://doi.org/10.1016/j.bbr.2014.03.029.

96. H. E. Day, C. V. Masini, and S. Campeau, "The Pattern of Brain c-Fos mRNA Induced by a Component of Fox Odor, 2,5-Dihydro-2,4,5-Trim ethylthiazoline (TMT), in Rats, Suggests Both Systemic and Processive Stress Characteristics," *Brain Research* 1025 (2004): 139–151, https://doi.org/10.1016/j.brainres.2004.07.079.

97. M. Matsukawa, M. Yoshikawa, N. Katsuyama, S. Aizawa, and T. Sato, "The Anterior Piriform Cortex and Predator Odor Responses: Modulation by Inhibitory Circuits," *Frontiers in Behavioral Neuroscience* 16 (2022): 896525, https://doi.org/10.3389/fnbeh.2022.896525.

98. M. Kadohisa and D. A. Wilson, "Separate Encoding of Identity and Similarity of Complex Familiar Odors in Piriform Cortex," *Proceedings of the National Academy of Sciences of the United States of America* 103 (2006): 15206–15211, https://doi.org/10.1073/pnas.0604313103.

99. T. D. Goode and S. Maren, "Role of the Bed Nucleus of the Stria Terminalis in Aversive Learning and Memory," *Learning & Memory* 24 (2017): 480–491, https://doi.org/10.1101/lm.044206.116.

100. D. R. Collins, "Synthetic Versus Natural Cat Odorant Effects on Rodent Behavior and Medial Amygdala Plasticity," *Behavioral Neuroscience* 125 (2011): 124–129, https://doi.org/10.1037/a0021955.

101. L. K. Takahashi, "Olfactory Systems and Neural Circuits That Modulate Predator Odor Fear," *Frontiers in Behavioral Neuroscience* 8 (2014): 72, https://doi.org/10.3389/fnbeh.2014.00072.