ELSEVIER

Seminars in Cell & Developmental Biology 17 (2006) 454–461

seminars in
CELL & DEVELOPMENTAL
BIOLOGY

www.elsevier.com/locate/semcdb

Review

Olfactory neuronal dynamics in behaving animals

Dmitry Rinberg *, Alan Gelperin

Monell Chemical Senses Center, 3500 Market St., Philadelphia, PA 19104, United States

Available online 5 May 2006

Abstract

More than 50 years have passed since the first recording of neuronal responses to an odor stimulus from the primary olfactory brain area, the main olfactory bulb. During this time very little progress has been achieved in understanding neuronal dynamics in the olfactory bulb in awake behaving animals, which is very different from that in anesthetized preparations. In this paper we formulate a new framework containing the main reasons for studying olfactory neuronal dynamics in awake animals and review advances in the field within this new framework.

Keywords: Mitral cells; Olfactory bulb; Behavior; Learning; Sensory processing

Contents

1. Introduction

The vast majority of our knowledge about the functionality of different sensory systems has been obtained in anesthetized preparations. There is, however, increasing interest in studying sensory processing in the awake animal. Recording single units in the awake animal is the standard paradigm in primate vision [1–4], which also provides a model for the development of rigorous psychophysical methods [5] and neural data analysis in olfaction. There are three main reasons to study sensory information processing in the awake behaving animal:

(1) the neuronal dynamics in awake and anesthetized brains is very different: in the awake state feedback from higher brain areas is fully functional while it is suppressed in the anesthetized state. This feedback includes efferent projections from other brain areas, neuromodulatory control and input modulation (e.g., eye movements in vision and sniffing in olfaction);
(2) recordings in awake animals allow real-time tracking of the effects of learning and other experience-related changes in neural processing;
(3) in well-designed behavioral experiments, the animal can report the result of sensory information processing.

Recent interest in olfactory sensory processing has been stimulated by progress in molecular genetics [6–8] and the use of genetic model organisms in neurobiology, specifically mice, for which olfaction has very high behavioral relevance.

In this review we consider neural correlates of olfactory behavior. We limit ourselves to the direct study of neuronal responses in awake behaving animals, and specifically we consider information processing in the mammalian olfactory system at the level of the main olfactory bulb (MOB). Obviously, in the awake behaving animal any separation of the sequential stages of information processing is problematic, as many brain areas interact in shaping and controlling neural activity and behavior.

* Corresponding author. Tel.: +1 215 746 0261; fax: +1 215 898 2084.
E-mail address: drinberg@monell.org (D. Rinberg).

1084-9521/$ – see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcdb.2006.04.009

The MOB is subject to massive feedback from higher brain areas [9], and this feedback must be taken into account in the analysis of neural dynamics in the bulb.

There are a few recording techniques, with different temporal and spatial resolution, that are used to study neuronal activity in the olfactory bulb in the awake animal: EEG with surface electrodes [10], local field potential (LFP) recordings in the bulb [11,12], single and multiunit recordings [13–17], and recently fMRI in humans [18]. We will focus on single and multi-neuron recordings as neural correlates of odorant-elicited behavior recorded from cellular elements of the main olfactory bulb in the awake animal.

The mammalian olfactory system receives input from olfactory receptor neurons (ORNs) located in the nasal epithelium over which odorant-bearing air is moved by respiration or active sampling during sniffing [19,20]. All ORNs expressing the same odorant receptor converge onto one or two glomeruli in the MOB, where terminal axons of ORNs make excitatory synapses with apical dendrites of mitral/tufted cells, the output elements of the MOB. Multiple layers of lateral inhibitory connections allow center-surround suppression via periglomerular [21,22] and granule cells [23,24].

Of the cellular elements in the olfactory bulb, the mitral cells have the largest cell bodies aligned in a well-defined cell layer and therefore are most amenable to stable extracellular recording with high signal-to-noise ratio [25–27]. One of the earliest in vivo studies of olfactory processing in awake animals used chronically implanted electrodes in the olfactory bulbs of awake rabbits [15].

The location of the MOB at the rostral pole of the forebrain and its distinctive layering make it amenable to extracellular recording approaches. During a penetration normal to the surface, mitral cells and adjacent layers can be identified based on large-amplitude unit activity [28,29]. In the granule cell layer, in contrast, units are encountered infrequently and have small amplitudes. Typically, electrode tip position is verified by post-mortem lesion analysis [17].

We will now examine in more detail the three factors listed above that provide the main justification for studying neuronal dynamics in the awake behaving animal.

2. Awake and anesthetized brains are different

The first evidence that MOB activity is different in anesthetized and awake animals can be found in the pioneering work of Lord Adrian: “In very deep anaesthesia when the bulb is quiet, a moderate olfactory stimulus sets up a discharge of impulses in the mitral axons at each inspiration and there are no impulses between. . . . In less deep anaesthesia the olfactory discharges appear against a background of continuous irregular activity and as the anaesthesia lightens the continuous activity becomes more and more prominent until it may be no longer possible to detect any change due to the stimulus” [30]. Later he wrote: “We need more information also about the behaviour of the organ (olfactory bulb) when there is no anaesthetic to suppress spontaneous activity” [31].

In recent work Rinberg et al. [32] recorded the activity of the same mitral cells in awake behaving and anesthetized mice, and demonstrated dramatic differences in the responses of mitral cells in these two states. First, the spontaneous activity of the mitral cells is much higher in the awake mouse. Second, the odor responses are much sparser and weaker and sometimes have the opposite sign in awake mice.

What is known about the neuronal dynamics in the olfactory bulb in awake animals? Surprisingly, the main question that remains unknown is how odor stimuli are coded in the olfactory bulb of the awake animal. Mitral cells are the primary recipients of information from the ORNs. In the anesthetized state mitral/tufted cells are selectively activated by odors [33–38]. There are only a few reports of odor responses of mitral cells in the awake animal [14–17,32,39].

Moulton [15] found that odor stimulation caused very small changes in the firing rates of olfactory bulb neurons (presumably mitral/tufted cells). The odor response was usually masked by high spontaneous activity. Moreover, he measured odor responses in the bulb of the awake rabbit following unilateral transection of the connection between the MOB and higher olfactory areas. Odor responses which previously were hidden in the high background activity were revealed in recordings from the side of the MOB disconnected from higher brain areas: “On the side of the transection, spike discharges in response to odor stimulation stand out clearly against the low amplitude background activity” [15]. He argued that the high spontaneous activity was a result of efferent control of the MOB. This observation is similar to that made by Adrian [30] in experiments with the effects of deep and light levels of anesthesia: the olfactory bulb was much more active without anesthesia and odor responses were hidden by high spontaneous activity.

These observations raise an interesting question: if in the awake animal the MOB mitral/tufted cell odor-elicited firing rate responses are masked by high spontaneous activity, how is information about odor transmitted to other brain areas?

A few hypotheses have been discussed in the literature. In experiments on odor responses in awake animals only a small population of mitral/tufted cells and a limited number of odors were sampled. Perhaps there exist a small number of mitral cells with strong odor responses which are hard to find [17,32]. An alternative explanation mentioned in several papers dealing with awake odor responses [15,17,31,32,39] is that odor information is transmitted via the collective dynamics of multiple neurons. Brody and Hopfield [40] proposed a model in which odor information is transmitted by synchronous activity of mitral cells getting their inputs from different glomeruli. In their model the high spontaneous rate of mitral cells is advantageous for quickly changing the synchronous ensembles of cells transmitting odor information (see also [41,42]). Another possibility is that odor recognition associated with odor-guided behavior is sustained by neural assembles belonging to a set of reciprocally connected structures including olfactory bulb, piriform cortex, amygdala and orbito-frontal cortex. In this perspective what is observed at any level reflects both intra-areal and inter-areal processing [43].

The first attempt to analyze odor responses in the awake animal beyond simple comparison of firing rates was done in experiments by Bhalla and Bower [16]. Rats were passively exposed to different odor stimuli for periods of 5 s, while mitral cell spiking activity was recorded by implanted metal electrodes. Bhalla and Bower used several measures to compare mitral cell odor responses to their activity without odors: (1) mean-firing rate, similar to previous work; (2) phasic responses, the shape of the poststimulus histogram with 1 s bin size during stimulus presentation; and (3) respiration related responses, as deduced from the shape of the spike count histogram at different phases of the sniff cycle during odor exposure. The authors found odor responses and large non-odor specific variability in all measures, and argued for distributed odor coding.

A significant step forward is represented by the work of Kay and Laurent [17]. These authors recorded odor responses from the MOB of rats trained to discriminate two odors. For the first time it was directly demonstrated that the firing rate of mitral/tufted cells which were shown to respond to an odor stimulus was modulated by behavioral events associated with odor presentation. They found that only 11% of all recorded mitral/tufted cells responded during odor sampling by the rat. Two possible reasons for this low probability to find an odor response were proposed: first, the chosen odors might excite small subsets of mitral cells, and second, the odors are coded by dynamical states of multineuron firing patterns that are undetectable by measuring single cell firing rates.

Our recent work [32] directly confirmed the sparseness of mitral cell firing rate odor responses. Recording from the same mitral cell in anesthetized and awake states in the mouse olfactory bulb demonstrated that most of the cells lost their odor sensitivity at the transition from anesthetized to awake state.

Difficulties in finding odor responses in awake behaving animals led many researchers to focus on the factors which influence neuronal dynamics in the MOB, and in this way try to understand the function of this structure.

Early work with implanted extracellular electrodes in rabbits and rats showed that presumptive mitral/tufted cell activity, both multiunit and single unit, was modulated by hunger level. In rats habituated to having a single 2-h daily meal, multiunit activity in the MOB in response to food odors was increased before the daily meal compared to the same rats after their daily meal [28,44–46], reviewed in [47]. The higher excitability towards food odor in hungry rats resulted from a slower rate of habituation following repeated presentation. Rats fasted for 22 h for the first time show an enhanced food-odor reactivity of mitral cells compared to rats after 15 days of food restriction [48]. These differential effects of phasic and chronic food deprivation may be mediated by centrally-modulated release onto mitral cells of the feeding-related peptide orexin A [49]. Nutritional state also modulates the power in food odor-elicited local field potential oscillations in the MOB in the 15–30 Hz beta band [50], an effect dependent on feedback to the MOB from higher centers [12].

Other factors discussed in the literature are reproductive state and social interactions, although these factors have not been studied in the awake animal. Activation of units in the mitral cell layer of anesthetized rats by vaginocervical stimulation is specific to animals in proestrous-estrous [51]. This may be due to metamodulatory effects of estrogen level changes during the estrous cycle on noradrenaline and the glutamate/NO signaling pathway in the MOB [52]. Social transmission of food preference is a natural odor–odor association task [53,54] likely to be dependent on cholinergic modulation in the MOB [55–58] from basal forebrain cholinergic neurons originating in the diagonal band of Broca [59].

Results obtained in the awake animal point out the importance of feedback connections to the MOB. There are three main types of feedback connections: (1) direct efferent fibers from higher brain areas (e.g., piriform cortex) to the MOB; (2) neuromodulatory control (e.g., by cholinergic inputs) to the bulb; and (3) input modulation via control of breathing and sniffing. The latter feedback is often missed in neurobiological descriptions of the system, but it has a direct influence on the processing of olfactory information.

There is direct anatomical evidence for the presence of neuronal feedback to the bulb. Although numbers are not available, the projection from piriform cortex back to the olfactory bulb is much heavier than the forward projection from mitral/tufted cells to the piriform cortex [60,61]. Unilateral inactivation of the medial part of the olfactory peduncle by lidocaine infusion eliminated most of the feedback influences on the MOB and reduced the amplitude of odor learning-induced beta oscillation while enhancing gamma oscillations in the MOB [62].

Odorant-related behavioral modulations of MOB unit activity undoubtedly involve one or more of the numerous neuromodulatory inputs to the MOB from higher centers [63,64], particularly noradrenergic modulation, which has been shown to play a role in learned odor processing [65,66] and in a variety of other sensory processing systems [67,68]. Noradrenergic neurons in the locus coeruleus are activated by reward expectation during a Go/NoGo odor reward task [69]. Cholinergic modulation from the diagonal band of Broca [59,70,71] very likely also plays a role in behavioral modulation of MOB units. There is considerable heterogeneity between glomeruli in the density of cholinergic, noradrenergic and serotonergic [72] innervation from higher centers [73]. Dopaminergic modulation of MOB units has been shown to play a role in odor discrimination learning [74]. Increasingly the dissection of the role of intrinsic neurotransmitters and extrinsic neuromodulators will be done by spatially controlled switching of receptors, as in the recent demonstration of the differential role of AMPA receptors in olfactory discrimination and olfactory memory [75].

Feedback pathways in mammals link olfaction to the medullary centers controlling breathing [76], so that respiratory rate can be altered to optimize odorant sampling by sniffing [19]. Sniffing rate has direct effects on the access of highly mucous-soluble odorants to the interior recesses of the olfactory epithelium [77,78] that can be directly reflected in the accuracy of olfactory discrimination [79]. Sniffing rate evolves during odor learning, perhaps to improve behavioral performance [80,81]. Mitral/tufted cells are indirectly input modulated by changes in odorant access to receptors during nasal breathing and sniffing

[46,82,83]. The extent to which the sniff is a natural unit of olfactory perception and decision making is a topic of active research [84].

Mitral/tufted cells are the recipients of input from ORNs, thus in the absence of any feedback, they can send to the brain only information about the stimulus. However, as just described, mitral/tufted cells are involved in much broader neural computations, based on the additional input they receive via feedback. Moulton [15] directly demonstrated the differences in odor responses between the bulb connected to higher brain areas, i.e., with fully active feedback, and the bulb surgically isolated from feedback from higher brain centers. Pager [46] showed the modulation of mitral cell activity by the nutritional state of the animal, and by sniffing rate [14,85]. Karpov [39] and Kay and Laurent [17] were the first to measure the modulation of mitral cell responses by behavioral events and learning in the awake behaving animals.

Kay and Laurent [17] trained rats to associate odors with either sucrose (S+) or quinine (S−) solutions. Additional cues, like onset of a signal light or opening of the door to the odor port, signaled odor delivery. The authors reported robust mitral cell responses to these additional non-odor cues, on the trials when the rat was expecting that the odor stimulus had predictive value, (S+) or (S−). So, firing rate responses were modulated by non-olfactory cues associated with odor delivery when odor might signal a reward. Such modulations are possible only in awake behaving animals and may be explained by efferent and neuromodulatory inputs to the bulb [86–88]. These results emphasize the fact that the determinants of mitral cell activity in behaving animals are very similar to those observed in higher-level areas of olfactory processing, such as piriform cortex and orbito-frontal cortex [89].

Some of the modulatory effects observed by Kay and Laurent may be explained by changes of the breathing or sniffing pattern contingent on actual or expected odor delivery. The odor expectation may cause an increased sniffing rate and stronger activation of the receptors, even before delivery of the expected odor. The reflection of such 'feedforward' stimulation from sniffing will be seen as a modulation of mitral cell firing rate. However, we suggest that such an input to the bulb in an awake behaving animal is as important as direct neuronal and neuromodulatory feedback, and should be considered as feedback due to input modulation. Centrally initiated input modulation may be part of the strategy of animal odor perception. When solving an odor-related task, such as odor discrimination, detection, or navigation, an animal starts sniffing, and olfactory bulb dynamics is influenced by this feedback from input modulation. Also, from the point of view of the neurons in higher olfactory centers, which are recipients of information from the mitral/tufted cells, it may not matter what caused mitral/tufted cell modulation, sniffing or efferent feedback. The cells in higher centers need to interpret the mitral/tufted cell firing rate modulation and extract odor and behavior-related information coming from multiple mitral/tufted cells.

The importance of active aspects of olfactory perception and its refection in the neuronal dynamics was already emphasized in the work of Adrian [31].

3. Learning

The olfactory system is extremely plastic [90–92]. There is ample indirect evidence for learning-induced changes in the MOB based on measurements of LFPs in awake behaving rats [11,12,93,94] and EEG in awake rabbits [10,95,96]. Network architecture within the MOB gives rise to rhythmic activity in the gamma band (40–80 Hz) and beta band (12–30 Hz) which can be observed in slices [97,98] as well as in behaving animals [10,11,50,86]. Rhythmic respiration results in theta band (4–8 Hz) activity [99]. There is strong evidence that associative olfactory learning modifies odor-induced oscillatory responses in the MOB. Surprisingly, earlier studies in rabbit revealed changes in amplitude in gamma band responses [10] while recent experiments in rats showed that olfactory sampling is associated with a depression of the ongoing gamma activity and with emergence of an odor-locked beta response. Learning amplified both gamma depression and the beta response [11,12] The experimental demonstration of the relation between learning-induced changes in beta and gamma oscillation and simultaneously recorded mitral/tufted cell unit responses remains to be elucidated [100].

A particularly well-developed analysis is available for odor preference learning by rat pups, which leads to changes in mitral/tufted cell excitability as assessed in anesthetized preparations [101,102]. A detailed norepinephrine-dependent molecular mechanism for coincidence detection by mitral cells has been proposed [103,104]. Mitral cell recordings in awake behaving rat pups will be technically challenging but extremely informative, particularly given the lack of high frequency LFP oscillations in the MOB of these very young animals [105].

Kay and Laurent [17] showed that learning modulates responses to odors. In their experiments rats first were exposed to odors, which carried no information about reward. At the next stage rats learned to associate an odor with either positive or negative reinforcement. Responses of the same cell to the same two odors at these two stages were different. This observation does not identify the locus of new odor memory storage and learning. As we have already mentioned, mitral cell responses are modulated by behavior. If the rat knew the odor association and this memory was stored in higher brain areas then the odor responses recorded in the MOB by Kay and Laurent could be altered by learning due to feedback modulation. It would be very informative to know if learning-associated changes in mitral/tufted cell responses like those recorded by Kay and Laurent [17] survive application of anesthetics and/or disconnection of the MOB from higher centers as shown for beta oscillatory responses [62,106].

Additional experiments on learning and establishing a new stimulus reward association with precise timing analysis of neuronal and behavioral events are required to understand the neural correlates of olfactory learning.

4. Behavioral correlates of neural processing

Behavioral experiments provide a unique opportunity to ask questions about the correlation between neural processes related to stimulus perception and behavioral outcomes of such neural

processes. In other words, an experimenter may ask questions about the results of sensory information processing. Humans may be the best subjects for this work, however, there is still no technology available to record olfactory processing in normal human subjects, as opposed to epileptic patients [107,108], on the cellular level.

Great progress in finding behavioral correlates of neural processing has been achieved in vision research in primates. Single unit recording combined with behavioral tasks requiring decision making revealed the role of unit neuronal activity in forming behavioral actions [1].

The most relevant work in olfaction is Karpov's study in the rabbit [39]. Rabbits were trained to identify food by odor cues while OB unit responses were recorded. Among other factors, the author found correlations between neuronal responses and the animal's decision to act. The level of these experiments is much simpler than that performed in primate vision, but it is a promising direction for understanding neuronal computations in olfaction.

Recent behavioral studies in rodents on odor discrimination come close to the state of the art in psychophysics experiments in primate vision. Uchida and Mainen [109] and Abraham et al. [110] performed response time experiments in odor discriminations. Both groups tried to correlate glomerular imaging studies with mouse performance on odor discrimination tasks of different difficulties. Two olfactory stimuli which excited more overlapping dorsal glomerular patterns were harder to discriminate: in Uchida and Mainen's behavioral paradigm [109] rats performed at lower accuracy, and in Abraham et al.'s paradigm [110], mice spent longer times solving the harder discrimination problem. Not surprisingly, the difficulty of the odor discrimination task is higher when the pattern of primary receptor excitation is more similar. The discrimination power presumably depends on how similar patterns of glomerular activation are analyzed and processed further at the next stages of neural processing. In olfaction, decorrelation of similar patterns was demonstrated in the study of zebra-fish olfactory bulb at the level of mitral cell responses in acute preparations [111,112]. Analogous experiments in the mammalian olfactory system are still lacking.

While the first step in understanding neural mechanisms of olfactory perception and odor-guided behavior is looking for correlates between an average behavioral performance for multiple animals and the corresponding average neural processing, the next important step is establishing such correlates for the same animal during the same behavioral task, in the best case on trial by trial measurements.

5. Conclusion

For more than 50 years the study of olfactory information processing in behaving animals has progressed more slowly than audition and vision. The reasons for this are rather obvious: (1) we still lack basic understanding of olfactory stimulus space; (2) it is much harder to monitor and control olfactory stimuli than visual or auditory stimuli; (3) olfaction is usually considered less relevant to human behavior (but see [113]); (4) it is relatively hard to obtain single cell recordings from olfactory brain areas in behaving animals; and (5) in contrast to vision, olfactory peripheral neuronal dynamics in awake and anesthetized animals are vastly different, which makes their study much more difficult.

There are, however, factors that will accelerate this field. Fast progress in developing new genetic tools to monitor, control and modify brain circuits make mice very attractive for neurobiology research. Olfaction has very high behavioral relevance for mice. Recently developed olfactory behavioral paradigms [109,110,112,114,115] set a very high standard for psychophysical studies. Recording techniques suitable for studies of small awake behaving animals are becoming more available and reliable [32,116,117]. Like vision in primates, olfaction in mice will become a new window into the higher-level functions of the brain.

The first questions that need to be answered are (1) how are olfactory stimuli coded in the olfactory bulb of the awake animal? (2) How does learning modify the olfactory code? (3) What is the neuronal basis of decisions made during odor-guided tasks? (4) What information does the activity of MOB neurons convey to other parts of the brain?

Most of these questions were formulated in the pioneering works of Adrian [30,31]. Application of new recording technology, molecular genetic tools and quantitative psychophysical methods to the awake behaving animal during odor-guided computations is beginning to shed light on some of these basic questions.

Acknowledgements

Preparation of this article was supported by the Army Research Office and The Whitehall Foundation. We thank Diego Restrepo, Remi Gervais, Rainer Friedrich, and Ambarish Ghatpande for comments on the manuscript.

References

[1] Liu J, Newsome WT. Correlation between speed perception and neural activity in the middle temporal visual area. J Neurosci 2005;25:711–22.
[2] Gross CG. Processing the facial image: a brief history. Am Psychol 2005;60:755–63.
[3] Gilbert CD, Sigman M, Crist RE. The neural basis of perceptual learning. Neuron 2001;31:681–97.
[4] Gold JI, Shadlen MN. The influence of behavioral context on the representation of a perceptual decision in developing oculomotor commands. J Neurosci 2003;23:632–51.
[5] Thomson EE, Kristan WB. Quantifying stimulus discriminability: a comparison of information theory and ideal observer analysis. Neural Comput 2005;17:741–78.
[6] Buck LB. Unraveling the sense of smell (Nobel lecture). Angew Chem Int Ed Engl 2005;44:6128–40.
[7] Axel R. Scents and sensibility: a molecular logic of olfactory preception (Nobel lecture). Angew Chem Int Ed Engl 2005;44:6110–27.
[8] Mombaerts P. Genes and ligands for odorant, vomeronasal and taste receptors. Nat Rev Neurosci 2004;5:263–78.
[9] Shepherd GM, Chen WR, Greer CA. Olfactory bulb. In: Shepherd GM, editor. The synaptic organization of the brain. 5th ed. New York: Oxford University Press; 2004. p. 133–69.
[10] Freeman WJ, Skarda CA. Spatial EEG patterns, nonlinear dynamics and perception: the neo-Sherringtonian view. Brain Res Rev 1985;10:147–75.

[11] Ravel N, Chabaud P, Martin C, Gaveau V, Hugues E, Tallon-Baudry C, et al. Olfactory learning modifies the expression of odour-induced oscillatory responses in the gamma (60–90 Hz) and beta (15–40 Hz) bands in the rat olfactory bulb. Eur J Neurosci 2003;17(2):350–8.
[12] Martin C, Gervais R, Chabaud P, Messaoudi B, Ravel N. Learning-induced modulation of oscillatory activities in the mammalian olfactory system: the role of the centrifugal fibres. J Physiol Paris 2004;98:467–78.
[13] Gervais R, Pager J. Combined modulating effects of the general arousal and the specific hunger arousal on the olfactory bulb responses in the rat. Electroencephalogr Clin Neurophysiol 1979;46:87–94.
[14] Pager J. Unit responses changing with behavioral outcome in the olfactory bulb of unrestrained rats. Brain Res 1983;289(1–2):87–98.
[15] Moulton DG. Electrical activity in the olfactory system of rabbits with indwelling electrodes. In: Zotterman Y, editor. Olfaction and taste I. Oxford: Pergamon Press; 1963. p. 71–84.
[16] Bhalla US, Bower JM. Multiday recordings from olfactory bulb neurons in awake freely moving rats: spatially and temporally organized variability in odorant response properties. J Comput Neurosci 1997;4:221–56.
[17] Kay LM, Laurent G. Odor- and context-dependent modulation of mitral cell activity in behaving rats. Nature Neurosci 1999;2:1003–9.
[18] Zelano C, Sobel N. Humans as an animal model for systems-level organization of olfaction. Neuron 2005;48:431–54.
[19] Youngentob SL, Mozel MM, Sheehe PR, Hornung DE. A quantitative analysis of sniffing strategies in rats performing odor detection tasks. Physiol Behav 1987;41:59–69.
[20] Schoenfeld TA, Cleland TA. Anatomical contributions to odorant sampling and representation in rodents: zoning in on sniffing behavior. Chem Senses 2006;31:131–44.
[21] Pinching AJ, Powell TP. The neuron types of the glomerular layer of the olfactory bulb. J Cell Sci 1971;9:305–45.
[22] Aungst JL, Heyward PM, Puche AC, Karnup SV, Hayar A, Szabo G, et al. Centre-surround inhibition among olfactory bulb glomeruli. Nature 2003;426:623–9.
[23] Mori K, Nagao H, Yoshihara Y. The olfactory bulb: coding and processing of odor molecule information. Science 1999;286:711–5.
[24] Dietz SB, Murthy VN. Contrasting short-term plasticity at the two sides of the mitral-granule reciprocal synapse in the mammalian olfactory bulb. J Physiol Lond 2005;569:475–88.
[25] Adrian ED. Olfactory reactions in the brain of the hedgehog. J Physiol Lond 1942;100:459–73.
[26] Phillips CG, Powell TPS, Shepherd GM. Responses of mitral cells to stimulation of lateral olfactory tract in the rabbit. J Physiol Lond 1963;168:65–88.
[27] Mair RG. Response properties of rat olfactory bulb neurones. J Physiol 1982;326:341–59.
[28] Pager J. Ascending olfactory information and centrifugal influxes contributing to a nutritional modulation of the rat mitral cell responses. Brain Res 1978;140:251–69.
[29] Buonviso N, Amat C, Litauson S, Roux S, Royet J-P, Farget V, et al. Rhythm sequence through the olfactory bulb layers during the time window of a respiratory cycle. Eur J Neurosci 2003;17:1811–9.
[30] Adrian ED. The electrical activity of the mammalian olfactory bulb. Electroencephalogr Clin Neurophysiol 1950;2:377–88.
[31] Adrian ED. The action of the mammalian olfactory organ. J Laryngol Otol 1956;70:1–14.
[32] Rinberg D, Koulakov A, Ollinger F, Gelperin A. Mitral cell responses in awake and anesthetized mice. Program No. 139.11 2004 Abstract Viewer/Itinerary planner. Washington DC, Society for Neuroscience, 2004. Online.
[33] Wellis DP, Scott JW. Intracellular responses of identified rat olfactory bulb interneurons to electrical and odor stimulation. J Neurophysiol 1990;64:932–47.
[34] Harrison TA, Scott JW. Olfactory bulb responses to odor stimulation: analysis of response pattern and intensity relationships. J Neurophysiol 1986;56:1571–89.
[35] Hamilton KA, Kauer JS. Patterns of intracellular potentials in salamander mitral/tufted cells in response to odor stimulation in the olfactory bulb of the tiger salamander. J Neurophysiol 1989;62:609–25.
[36] Fletcher ML, Wilson DA. Olfactory bulb mitral cell-tufted cell plasticity: odorant-specific tuning reflects previous odorant exposure. J Neurosci 2003;23:6946–55.
[37] Cang J, Isaacson JS. In vivo whole-cell recording of odor-evoked synaptic transmission in the rat olfactory bulb. J Neurosci 2003;23:4108–16.
[38] Nagayama S, Takahashi YK, Yoshihara Y, Mori K. Mitral and tufted cells differ in the decoding manner of odor maps in the rat olfactory bulb. J Neurophysiol 2004;91:2532–40.
[39] Karpov AP. Analysis of neuron activity in the rabbit's olfactory bulb during food acquisition behavior. In: Thompson RF, Hicks LH, Shyrkov VB, editors. Neural mechanisms of goal-directed behavior and learning. New York: Academic Press; 1980. p. 273–82.
[40] Brody CD, Hopfield JJ. Simple networks for spike-timing-based computation, with application to olfactory processing. Neuron 2003;37(5):843–52.
[41] Mazor O, Laurent G. Transient dynamics versus fixed points in odor representations by locust antennal lobe projection neurons. Neuron 2005;48:661–73.
[42] Szyswzka P, Ditzen M, Galkin A, Galizia CG, Menzel R. Sparsening and temporal sharpening of olfactory representations in the honeybee mushroom bodies. J Neurophysiol 2005;94:3303–13.
[43] Ravel N, Mouly A-M, Chabaud P, Gervais R. Experience-induced changes reveal functional dissociation within olfactory pathways. In: Rouby C, Schaal B, Dubois D, Gervais R, Holley A, editors. Olfaction, taste, and cognition. Cambridge, UK: Cambridge University Press; 2002. p. 335–49.
[44] Le Magnen J. Olfaction and nutrition. In: Beidler LM, editor. Handbook of sensory physiology, vol. IV. Berlin: Springer Verlag; 1971. p. 465–82.
[45] Pager J, Giachetti I, Holley A, Le Magnen J. Selective control of olfactory bulb electrical activity in relation to food deprivation and satiety in rats. Physiol Behav 1972;9:573–9.
[46] Pager J. Nutritional states, food odors, and olfactory function. In: Kare MR, Maller O, editors. The chemical senses and nutrition. New York: Academic Press; 1977. p. 51–68.
[47] Pager J. Neural correlates of odor-guided behaviors. Experientia 1986;42:250–6.
[48] Apelbaum AF, Chaput MA. Rats habituated to chronic feeding restriction show a smaller increase in olfactory bulb reactivity compared to newly fasted rats. Chem Senses 2003;28:389–95.
[49] Apelbaum AF, Perrut A, Chaput M. Orexin A effects on the olfactory bulb spontaneous activity and odor responsiveness in freely breathing rats. Reg Pept 2005;129:49–61.
[50] Chabaud P, Ravel N, Wilson DA, Mouly AM, Vigouroux M, Farget V, et al. Exposure to behaviourally relevant odour reveals differential characteristics in rat central olfactory pathways as studied through oscillatory activities. Chem Senses 2000;25:561–73.
[51] Guevara-Guzman R, Barrera-Mera B, Weiss ML. Effect of the estrous cycle on olfactory bulb response to vaginocervical stimulation in the rat: results from electrophysiology and Fos immunocytochemistry experiments. Brain Res Bull 1997;44:141–9.
[52] Sanchez-Andrade G, James BM, Kendrick KM. Neural encoding of olfactory recognition memory. J Reprod Dev 2005;51:547–58.
[53] Galef BG, Wigmor SW. Transfer of information concerning distant foods: a laboratory investigation of the 'information-centre' hypothesis. Anim Behav 1983;31:748–58.
[54] Wrenn CC, Harris AP, Saavedra MC, Crawley JN. Social transmission of food preference in mice: methodology and application to galanin-overexpressing transgenic mice. Behav Neurosci 2003;117:21–31.
[55] Ravel N, Akaoka H, Gervais R, Chouvet G. The effect of acetylcholine on rat olfactory-bulb unit-activity. Brain Res Bull 1990;24:151–5.
[56] Elaagouby A, Ravel N, Gervais R. Cholinergic modulation of excitability in the rat olfactory bulb: effect of local application of cholinergic agents on evoked field potentials. Neurosci 1991;45:653–62.
[57] Linster C, Cleland TA. Cholinergic modulation of sensory representation in the olfactory bulb. Neural Networks 2002;15:709–17.
[58] Wilson DA, Fletcher ML, Sullivan RM. Acetylcholine and olfactory perceptual learning. Learn Mem 2004;11:28–34.

[59] Linster C, Hasselmo ME. Neural activity in the horizontal limb of the diagonal band of Broca can be modulated by electrical stimulation of the olfactory bulb and cortex in rats. Neurosci Lett 2000;282:157–60.
[60] Luskin MB, Price JL. The topographic organization of associational fibers of the olfactory system in the rat, including centrifugal fibers to the olfactory bulb. J Comp Neurol 1983;216:264–91.
[61] Neville KR, Haberly LB. Olfactory cortex. In: Shepherd GM, editor. The synaptic organization of the brain. 5th ed. New York: Oxford University Press; 2004. p. 415–54.
[62] Martin C, Gervais R, Messaoudi B, Ravel N. Learning-induced oscillatory activities correlated to odour recognition: a network activity. Eur J Neurosci 2006;23:1801–10.
[63] Heimer L. Synaptic distributions of centripetal and centrifugal nerve fibers in the olfactory system of the rat. An experimental anatomical study. J Anat Lond 1968;103:413–32.
[64] Shipley MT, Ennis M. Functional organization of olfactory system. J Neurobiol 1995;30:123–76.
[65] Gervais R, Holley A, Keverne B. The importance of central noradrenergic influences on the olfactory bulb in the processing of learned olfactory cues. Chem Senses 1988;13:3–12.
[66] Dluzen DE, Muraoka S, Engelmann M, Ebner K, Landgraf R. Oxytocin induces preservation of social recognition in male rats by activating alpha-adenoreceptors of the olfactory bulb. Eur J Neurosci 2000;12:760–6.
[67] Hurley LM, Devilbiss DM, Waterhouse BD. A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks. Curr Opin Neurobiol 2004;14:488–95.
[68] Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Ann Rev Neurosci 2005;28:403–50.
[69] Bouret S, Sara SJ. Reward expectation, orientation of attention and locus coeruleus-medial frontal cortex interplay during learning. Eur J Neurosci 2004;20:791–802.
[70] Mechawar N, Saghatelyan A, Grailhe R, Scoriels L, Gheusi G, Gabellec MM, et al. Nicotinic receptors regulate the survival of newborn neurons in the adult olfactory bulb. Proc Natl Acad Sci USA 2004;101:9822–6.
[71] Ghatpande A, Sivaraaman K, Vijayaraghavan S. Store calcium mediates cholinergic effects on mIPSCs in the rat main olfactory bulb. J Neurophysiol 2006;95:1345–55.
[72] Hardy AB, Palouzier-Paulignan B, Duchamp A, Royet JP, Duchamp-Viret P. 5-Hydroxytryptamine action in the rat olfactory bulb: in vitro electrophysiological patch-clamp recordings of juxtaglomerular and mitral cells. Neuroscience 2005;131:717–31.
[73] Gomez C, Brinon JG, Barbado M, Weruaga E, Valero J, Alonso J. Heterogeneous targeting of centrifugal inputs to the glomerular layer of the main olfactory bulb. J Chem Anat 2005;29:238–54.
[74] Yue EL, Cleland TA, Pavlis M, Linster C. Opposing effects of D-1 and D-2 receptor activation on odor discrimination learning. Behav Neurosci 2004;118:184–90.
[75] Shimshek DR, Bus T, Kim JH, Mihaljevic A, Mack V, Seeburg PH, et al. Enhanced odor discrimination and impaired olfactory memory by spatially controlled switch of AMPA receptors. PLoS Biol 2005;3: e354.
[76] du Pont JS. Firing patterns of bulbar respiratory neurons during sniffing in the conscious, non-paralyzed rabbit. Brain Res 1987;414:163–8.
[77] Schoenfeld TA, Cleland TA. The anatomical logic of smell. Trends Neurosci 2005;28:620–7.
[78] Scott JW. Sniffing and spatiotemporal coding in olfaction. Chem Senses 2006;31:119–30.
[79] Kent PF, Mozell MM, Youngentob SL, Yurco P. Mucosal activity patterns as a basis for olfactory discrimination: comparing behavior and optical recordings. Brain Res 2003;981:1–11.
[80] Macrides F, Eichenbaum HB, Forbes WB. Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. J Neurosci 1982;2:1705–17.
[81] Freeman WJ, Viana di Prisco G, Davis GW, Whitney TM. Conditioning of relative frequency of sniffing by rabbits to odors. J Comp Psychol 1983;97:12–23.
[82] Sobel EC, Tank DW. Timing of odor stimulation does not alter patterning of olfactory bulb unit activity in freely breathing rats. J Neurophysiol 1993;69:1331–7.
[83] Buonviso N, Amat C, Litaudon P. Respiratory modulation of olfactory neurons in the rodent brain. Chem Senses 2006;31:145–54.
[84] Kepecs A, Uchida N, Mainen ZF. The sniff as a unit of olfactory processing. Chem Senses 2006;31:167–79.
[85] Pager J. Respiration and olfactory bulb unit activity in the unrestrained rat: statements and reappraisals. Behav Brain Res 1985;16:81–94.
[86] Freeman WJ. The physiology of perception. Sci Am 1991;264:78–85.
[87] Kay LM, Lancaster IR, Freeman WJ. Reafference and attractors in the olfactory system during odor recognition. Int J Neural Syst 1996;7:489–95.
[88] Kay LM, Freeman WJ. Bidirectional processing in the olfactory-limbic axis during olfactory behavior. Behav Neurosci 1998;112:541–53.
[89] Schoenbaum G, Eichenbaum H. Information coding in the rodent pefrontal cortex. 1. Single-neuron activity in orbitofrontal cortex compared with that in pyriform cotex. J Neurophysiol 1995;74:733–50.
[90] Gelperin A. Oscillatory dynamics and information processing in olfactory systems. J Exp Biol 1999;202:1855–64.
[91] Wilson DA, Stevenson RJ. The fundamental role of memory in olfactory perception. Trends Neurosci 2003;26:243–7.
[92] Wilson DA, Best AR, Sullivan RM. Plasticity in the olfactory system: lessons for the neurobiology of memory. Neuroscientist 2004;10:513–24.
[93] Mouly AM, Fort A, Ben-Boutayab N, Gevais R. Olfactory learning induces differential long-lasting changes in rat central olfactory pathways. Neuroscience 2001;102:11–21.
[94] Mouly AM, Gervais R. Polysynaptic potentiation at different levels of rat olfactory pathways following learning. Learn Mem 2002;9:66–75.
[95] Gray CM, Freeman WJ, Skinner JE. Chemical dependencies of learning in the rabbit olfactory bulb: acquisition of the transient spatial pattern change depends on norepinephrine. Behav Neurosci 1986;100:585–96.
[96] Grajski KA, Freeman WJ. Spatial EEG correlates of nonassociative and associative olfactory learning in rabbits. Behav Neurosci 1989;103:790–804.
[97] Lagier S, Carleton A, Lledo P-M. Interplay between local GABAergic interneurons and relay neurons generates gamma oscillations in the rat olfactory bulb. J Neurosci 2004;24:4382–92.
[98] Schoppa NE. Synchronization of olfactory bulb mitral cells by precisely timed inhibitory inputs. Neuron 2006;49:271–83.
[99] Margrie TW, Schaefer AT. Theta oscillation coupled spike latencies yield computational vigor in a mammalian sensory system. J Physiol 2003;546:363–74.
[100] Eeckman FH, Freeman WJ. Correlations between unit firing and EEG in the rat olfactory system. Brain Res 1990;528:238–44.
[101] Sullivan RM, Leon M. One-trial olfactory learning enhances olfactory bulb responses to an appetitive conditioned odor in 7-day old rats. Brain Res 1987;432:307–11.
[102] Wilson DA, Leon M. Spatial patterns of olfactory bulb single-unit responses to learned olfactory cues in young rats. J Neurophysiol 1988;59:1770–82.
[103] Sullivan RM, Wilson DA. Molecular biology of early olfactory memory. Learn Mem 2003;10:1–4.
[104] Harley CW, Daby-King A, McCann J, McLean JH. Beta 1-adrenoreceptor or alpha 1-adrenoreceptor activation initiates early odor preference learning in rat pups: support for the mitral cell/cAMP model of odor preference learning. Learn Mem 2006;13:8–13.
[105] Fletcher ML, Smith AM, Best AR, Wilson DA. High-frequency oscillations are not necessary for simple olfactory discriminations in young rats. J Neurosci 2005;25:792–8.
[106] Martin C, Gervais R, Hugues E, Messaoudi B, Ravel N. Learning modulation of odor-induced oscillatory responses in the rat olfactory bulb: a correlate of odor recognition? J Neurosci 2004;24(2):389–97.
[107] Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I. Invariant visual representation by single neurons in the human brain. Nature 2005;435:1102–7.
[108] Jung J, Hudry J, Ryvlin P, Royet JP, Bertrand O, Lachaux JP. Functional significance of olfactory-induced oscillations in the human amygdala. Cereb Cortex 2006;16:1–8.

[109] Uchida N, Mainen ZF. Speed and accuracy of olfactory discrimination in the rat. Nat Neurosci 2003;6:1224–9.
[110] Abraham NM, Spors H, Carleton A, Margrie TW, Kuner T, Schaefer AT. Maintaining accuracy at the expense of speed: stimulus similarity defines odor discrimination time in mice. Neuron 2004;44:865–76.
[111] Friedrich RW, Habermann CJ, Laurent G. Multiplexing using synchrony in the zebrafish olfactory bulb. Nat Neurosci 2004;7(8):862–71.
[112] Friedrich RW. Mechanisms of odor discrimination: neurophysiological and behavioral approaches. TINS 2005;29:40–7.
[113] Shepherd GM. The human sense of smell: are we better than we think? PLoS Biol 2004;2:572–5.
[114] Bodyak N, Slotnick B. Performance of mice in an automated olfactometer: odor detection, discrimination and odor memory. Chem Senses 1999;24:637–45.
[115] Clevenger AC, Restrepo D. Evaluation of the validity of a maximum likelihood adaptive staircase procedure for measurement of olfactory detection threshold in mice. Chem Senses 2006;31:9–26.
[116] Fee MS, Leonardo A. Miniature motorized microdrive and commutator system for chronic neural recording in small animals. J Neurosci Methods 2001;112:83–94.
[117] Luo M, Fee MS, Katz LC. Encoding pheromonal signals in the accessory olfactory bulb of behaving mice. Science 2003;299:1196–201.