The facets of olfactory learning
Janine K. Reinert and Izumi Fukunaga

Abstract
Volatile chemicals in the environment provide ethologically important information to many animals. However, how animals learn to use this information is only beginning to be understood. This review highlights recent experimental advances elucidating olfactory learning in rodents, ranging from adaptations to the environment to task-dependent refinement and multisensory associations. The broad range of phenomena, mechanisms, and brain areas involved demonstrate the complex and multifaceted nature of olfactory learning.

Addresses
Sensory and Behavioural Neuroscience Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa

Corresponding author: Fukunaga, Izumi (izumi.fukunaga@oist.jp)
Reinert J.K.
Fukunaga I.

Current Opinion in Neurobiology 2022, 76:102623
This review comes from a themed issue on Neurobiology of Learning and Plasticity 2023
Edited by Muming Poo and Thomas John McHugh
For complete overview of the section, please refer the article collection - Neurobiology of Learning and Plasticity 2023
Available online 20 August 2022
https://doi.org/10.1016/j.conb.2022.102623
0959-4388/© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Abbreviations
AON, Anterior olfactory nucleus; CA1, Cornu ammonis; COVID-19, Coronavirus disease of 2019; GABA, Gamma-aminobutyric acid.

The sense of smell may still be something of a mystery for many people. At least compared to sight and hearing losses, losing the sense of smell is considered less detrimental to human activities and communication, and yet, it is a source of enrichment for many, especially if one’s sense of smell is good enough to enjoy the subtle — or sometimes not so subtle — notes in fragrances, food, and beverages. Further, a vivid recollection of a scene, or even specific people, upon smelling a particular scent is a common experience. As we slowly crawl out of the current global pandemic, the loss of smell that accompanied many novel coronavirus (COVID-19) infections [1] has undoubtedly raised awareness of this sensory modality. While most people recover from this loss spontaneously, olfactory training is prescribed for more persistent cases [1–3], based on the capacity of the olfactory system to learn or change through experience and training.

Beyond regaining the ability to smell after temporary anosmia, how does the olfactory system learn? In this review, we argue that olfactory learning is not a single phenomenon attributable to one particular brain region. Instead, it manifests throughout the olfactory system, where the exact nature of change and its mechanism depends on its purpose. We highlight the diversity of olfactory learning involving many brain regions (Figure 1). Due to the limited space, we focus on recent mammalian literature, inevitably omitting many of the classics and with a heavy bias towards rodent works. Interested readers who wish to learn more about learning and plasticity in other organisms are recommended other excellent reviews [4,5].

Adapting to the environment
The chemical environment in which animals live is highly dynamic. The abundance of specific molecules in the environment changes constantly, for example, through living conditions or seasons. To best represent stimuli despite these constant fluctuations, olfactory systems are known to show homeostasis. That is, changes in the olfactory system happen in a way that counters the changes in the sensory inputs. Such adaptive responses start in the nasal epithelium, the site of sensory transduction. For instance, the olfactory sensory neurons that respond to semiochemicals involved in reproductive communication: Sex-specific semiochemicals are detected by specific olfactory receptor types (e.g., Olfr910, Olfr1295). When the semiochemicals are removed during development, for example, by separating male and female mice, the olfactory sensory neurons that express the corresponding receptor types become more numerous in a sexually dimorphic manner [6,7]. This proliferation may be achieved by regulating the chance of neuron survival or allelic selection during the turnover of sensory neurons in the nasal epithelium. In addition to controlling the number of olfactory sensory neurons this way, it is now clear that a large set of proteins within each olfactory sensory neuron is under transcriptional regulation in an activity-dependent manner [8**,9]. Many of these proteins are directly involved in olfactory transduction, such as voltage-gated ion channels, calcium-binding
proteins, and messenger molecules, whose expression levels are unique for a given olfactory receptor type. The result of activity-dependent transcriptional change is a calibrated transduction that reflects a history of sensory inputs experienced by each olfactory sensory neuron [8**].

The history of sensory inputs also substantially influences the properties of downstream neurons and circuits, for example, in the olfactory bulb. One drastic approach for changing the sensory statistics is in mice with a “monoclonal nose”, or M71 transgenic line [10]. In these mice, instead of the usual repertoire of >1000 receptor types, 95% of the sensory neurons express only one type of olfactory receptor (the olfactory receptor M71). Using these mice, it was shown that levels of hyperpolarisation-activated cation current (Ih) in olfactory bulb output neurons are more similar if the inputs are derived from the same olfactory receptor type, compared to neurons that do not share the history of sensory inputs this way [11]. As this depolarising current is activated at a resting membrane potential, this may regulate a neuron’s excitability and integration properties.

Moreover, differences in the general input levels also affect the interneurons of this region. When sensory input is lost, for example, by plugging the naris for one day, a structural change occurs in the axon initial segment — the segment of the axon close to the soma that initiates the action potential generation - of short axons cells [12*]. Sensory deprivation shortens the axon initial segment of these inhibitory neurons, requiring more input to generate action potentials. In other words, reduced sensory inputs may reduce the inhibitory drive within the olfactory bulb. Such a coupling of inhibitory drive was demonstrated in the M71 transgenic line mentioned above, where unusually prevalent inhibitory responses were observed in olfactory bulb output neurons following presentations of the M71 ligand acetophenone [13]. Thus, adjusting both network and intrinsic properties may be important mechanisms to adjust to environmental changes.

Representing structures in the olfactory stimulus space
Another way the sensory input may influence the olfactory representations in the brain is in the similarity of olfactory stimuli. Some molecules smell more alike — readers may find it easy to imagine categories of perceived qualities, such as fruitiness and woodiness. Methodologically, these categorical similarities are still challenging to study, partly due to the large number of olfactory receptor types involved and the inherent difficulty in relating molecules to each other. However, there are increasingly powerful, high-throughput behavioural methods for describing perceptual similarities [14,15], augmenting metrics based on physicochemical properties of odorants [16].

What is clear is that physicochemical properties do relate to the similarities of neuronal responses evoked by odours up to a point and that the brain additionally sculpts these representations. For example, in the olfactory bulb, the similarity of neuronal representations resembles the similarity of the respective odours as
described by the physicochemical metrics. However, downstream, such as in the piriform cortex, more abstract, generalised representations of similarities emerge [17]. Activity patterns to structurally similar odours tend to become even more similar, much like the emergence of perceptual categories. Even within the piriform cortex, the representation of odour similarity progressively changes from layer 2 to layer 3 due to recurrent interactions. Thus, a categorical representation may be one manifestation of experience-dependent representation predicted for this associative cortex [18]. It should be noted that another side of this circuit architecture, which constantly updates representations, is some drifts in representations, especially when the odours are not encountered frequently [19].

Categorical representations of odours in the brain need not always reflect the structural similarities of odours. Instead, they can also reflect learned categories of odours. For example, when mice and rats learn to group previously unrelated, structurally dissimilar odours as categories, responses in the olfactory bulb and the piriform cortex to these odorants can become more similar [20,21]. Thus, a component of active learning may be involved in establishing the pattern similarities, or “categories”, observed. As discussed below, active behavioural learning is accompanied by various changes across multiple brain regions.

Pushing the sensory limits with learning

While an important task for the olfactory system is adjusting to environmental changes and stimulus properties, behavioural demands are another prominent driver of change. What happens to the olfactory system when animals are required to push the sensory limits, for example, in odour detection and discrimination? The answer is a variety of changes. We first discuss detecting the presence of an odour of interest. Ultimately, whether or not an animal can detect a molecule of interest depends on the existence of corresponding receptors and the concentration of the odour [22–24]. In nature, though, an odour of interest typically occurs in the presence of other molecules - a noisy background. This poses a challenge, especially when there are many types of molecules in the background, and even more so when those molecules evoke overlapping activity patterns, masking the target pattern [25]. However, mice can be trained to overcome this initial challenge, learning to detect the target odour accurately despite the presence of a “difficult” background odour, at least in binary mixtures [26]. This behavioural improvement is accompanied by a refinement in the evoked responses in the olfactory bulb, with target response patterns becoming more separable from background patterns.

The second example of behaviourally driven refinement is in discriminating odours. Learning to perform olfactory discrimination is accompanied by various changes in the olfactory bulb. As mice learn, the amplitudes of output neurons’ responses to the odours generally decrease, and so does the fraction of neurons that respond [27–29]. However, as some of these changes are observed during passive exposures, adaptations like those discussed above may be involved, although this phenomenon is not observed in anaesthetized mice passively exposed to the same stimuli [28]. Some of the apparent learning-related changes may reflect changes in the stimulus sampling patterns, such as the frequency of sniffing and speed of inhalations [30]. However, learning-related changes in the olfactory bulb remain even when these factors are accounted for [27,29]. Notably, changes differ depending on the task difficulty [27,29]. A consequence is an emphasis on divergent, informative responses when mice learn to perform difficult but not easy discrimination [27,31]. Furthermore, when mice are trained to flexibly switch between coarse and fine discrimination tasks, a rapid modulation, or boosting of divergent responses during fine discrimination, is observed [31].

What mechanisms are involved in the refinement of sensory representations with learning? In the olfactory bulb, crucial players are inhibitory neurons, which are the dominant constituent of this region [32]. Additionally, they receive long-range connections, including feedback from secondary olfactory areas and projections from neuromodulatory areas. This connectivity may allow the inhibitory neurons to incorporate contextual signals when sculpting the output of the olfactory bulb. Amongst the inhibitory neurons, granule cells — the axonless, GABAergic interneurons — have received much attention because of their sheer number and the fact that they are the principal targets of those long-range feedback signals. It has been shown that boosting granule cell-mediated recurrent inhibition enables mice to accurately discriminate between similar odours more quickly while a reduced inhibitory drive impairs discrimination speed [33].

Further, the granule cells of the olfactory bulb undergo constant turnover in animals’ adulthood, being replenished by cells born in the subventricular zone and migrating towards the olfactory bulb. It is thought that the process of incorporating adult-born neurons into the existing olfactory bulb circuitry is used for learning-related plasticity and perceptual refinement [34]. The behavioural context matters in this process: Whether mice are passively exposed to odours or actively engaged in olfactory discrimination affects the number of adult-born neurons that become integrated, as well as their morphology [35,36]. Adult-born neurons seem particularly important for acquiring difficult olfactory discrimination tasks [37,38]. When adult-born neurons are chemically ablated, the detrimental effect is observed only when mice learn to distinguish between similar odours [38]. Intriguingly, optogenetic stimulation of adult-born cells in the olfactory bulb
during discrimination training results in faster acquisition of the task [39], possibly mimicking or amplifying contextual signals onto the granule cells. Again, this effect is seen only for learning difficult discrimination tasks. Overall, these studies point to a granule cell-mediated refinement in olfactory representations, particularly in mice actively performing difficult olfactory tasks.

As a sidenote, many learning-related changes have been described and interpreted in terms of firing rate changes. However, olfactory representations are distributed in space and precise in time. Recent studies have used precise optogenetic stimuli to mimic odour-evoked activity patterns to establish which aspects of olfactory bulb output patterns can be linked to odour perception at the behavioural level [40,41]. These studies demonstrated that subtle deviations in temporal or spatial patterns are perceptible to animals. Ultimately, this may relate to how the downstream areas read out the signals propagated by the olfactory bulb, as seen in the exquisite sensitivity of the piriform cortex neurons to specific latencies in the millisecond timescale [42]. For the piriform cortex, the largest olfactory cortex by volume, the readout mechanisms are starting to be understood [18,43–46], but they may differ between different cortical olfactory regions. An intriguing task for the future is to resolve how the learning-induced plasticity relates to olfactory representations at the level of relevant neural codes.

**Associating odours with hedonic values**

Having addressed various ways in which the olfactory system refines sensory representations, we turn now to formations of associations. The first is associating fear—one of the most potent drivers of behaviours. Mice are known to avoid some odours, such as trace amines like isopentalamine and 2-phenylethylamine, without being explicitly trained [47–49]. This innate avoidance involves the corticobasal amygdala [49] and the tail of the striatum [50]. While apparently innate, this behaviour seems to develop early in an animal’s life in an activity-dependent manner, since silencing the olfactory sensory neurons in juvenile mice prevents the normal emergence of this behaviour [48]. In addition, exposure to these odours during their development also reduces avoidance later [48].

In contrast, a more potent association occurs when fearful stimuli are used, such as pairing electric shocks with odours in olfactory fear conditioning paradigms. This experience results in visible consequences on the olfactory system, such as an increased number of olfactory sensory neurons and larger glomeruli associated with the receptor type that responds to the odour used [51]. In addition, neuronal responses to the conditioned odour become more enhanced [52,53], which may be due to an increased probability of synaptic release [54]. The etiological importance of associating a particular odour with fear may be appreciated when noting that this memory, in the form of enhanced representation of the conditional odour, may be inherited trans-generationally via an epigenetic mechanism conveyed by male gametes [51].

On the opposite end of value association is reinforcement learning—associating odours with reward. In general, the activity of dopaminergic neurons is largely believed to signal reward prediction error, which is thought to serve as the driver of learning-related changes such as synaptic plasticity [55,56]. In olfactory reinforcement learning, dopaminergic signals in the ventral striatum, dorsomedial striatum, and dorsolateral striatum can be well described using this model, explaining the rewarded-related responses that scale with the reward size, the emergence of responses driven by conditional stimulus (odour) with learning, and the choices that the animals make [57**]. However, reward-related signals are not restricted to these regions only. Among the olfactory cortices, the olfactory tubercle has consistently been shown to exhibit reward-related signals [58-60]. This is contrasted with the piriform cortex, where spiking activity correlates more with odour identities [58,60**,61]. A similar reward-related activity is observed in the orbitofrontal cortex, but only transiently, while a more stable form is found in the prefrontal cortex [61]. These value representations distributed over many areas may be related to each other. For example, the prefrontal cortex has connections to the olfactory tubercle [62]. Future investigations will clarify if this distributed, reward-related activity reflects different stages of value processing and its role in forming olfactory memory in the brain.

**Using olfactory cues for navigation**

Finally, for many animals, olfactory stimuli serve as important navigational cues. This includes scent tracking, as well as a more permanent form, which is to associate olfactory information with a place. As reviewed previously [63], tracking chemical signals in the environment is a highly conserved phenomenon. Gradients of concentrations towards the source, as well as fluctuations of molecules in the air—the plume dynamics—may provide useful information to guide animals’ navigation [63]. In addition to utilising the information available in the environment, animals actively adjust the stimulus sampling behaviour, such as sniffing patterns, as part of the strategy [64]. Remarkably, the mouse olfactory system can learn to resolve odour fluctuations faster than the sniffing frequency [65], possibly enabling the mice to make efficient use of plume dynamics, especially in the absence of smooth concentration gradients.

How might the sense of smell interact with, or even contribute to, representations of places? There is...
evidence of olfactory representation in the CA1 region of the hippocampus [66,67], a region well-known for its place cells [68]. Indeed, routes by which olfactory information may enter the hippocampus have been described, including via the lateral entorhinal cortex - a region reciprocally connected with primary and secondary olfactory areas [69] - through the dentate gyrus [70], or via the anterior olfactory nucleus [71]. In addition, a recent study demonstrated that olfactory cues contribute to defining a location, as shown by the enhancement of place-related activities in CA1 by olfactory stimuli that serve as landmarks [67].

Whether odours evoke responses in the hippocampus during spatial navigation, however, seems to depend on the relevance of the cue to the animals’ task [66]. For example, olfactory responses are observed when mice, moving in a virtual reality environment, learn to stop when olfactory stimuli indicate the arrival of a reward. When the task becomes a visually guided one, the occurrence of olfactory responses is negligible. This may suggest the existence of a gating mechanism that lets olfactory information into the CA1 region depending on the context. Gating mechanisms may also relate to learning-related coupling in oscillatory activities between olfactory regions and the CA1 region, as measured by coherence between the regions upon odour presentations [72,73]. For example, coherence between the lateral entorhinal cortex and CA1 changes as rats learn that olfactory stimuli instruct the location of a reward [72]. Alternatively, the integration of place information and olfactory signals could occur outside the hippocampus.

Figure 2

A variety of ways olfactory representations are adjusted through experience and training. Summary of the phenomena mentioned in the text. Olfaction learning in the brain manifests in various ways, ranging from gain changes in peripheral olfactory processing in response to environmental changes to associating complex information and in response to behavioural demands. Abbreviations: OSN, olfactory sensory neurons; OB, olfactory bulb; CA1, Cornu ammonis 1 of the hippocampus; LEC, lateral entorhinal cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex.
Intriguingly, the posterior piriform cortex has recently been shown to possess neurons with clear preferences for particular positions rather than identities of odours [74**]. That is, a conjunction of place and olfactory information may occur in areas that were traditionally classified as sensory cortices. Furthermore, these position-encoding neurons in the piriform cortex show stronger coherence with oscillatory activities in CA1 rather than respiratory rhythms, perhaps indicating their membership in a network of neurons representing the stronger coherence with oscillatory activities in CA1

**Conclusion**

The olfactory system learns to use volatile chemical information in a variety of ways, ranging from adaptation to the environment to active learning and multimodal stimulus integration (Figure 2). As demonstrated by a large volume of works, these facets of olfactory learning involve many mechanisms, as each brain region has its way of implementing changes. In conclusion, at any given point, an animal’s accumulated experience may be as much a part of its olfactory perception as the odours that it encounters.

**Conflict of interest statement**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Acknowledgments**

The authors thank Sander Lindeman, Josephine Reuschchenbach, and reviewers for comments on this manuscript. This work was supported by Okinawa Institute of Science and Technology Graduate University.

**References**

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Moën ST, Hashemian SM, Tabarsi P, Doty RL: Prevalence and reversibility of smell dysfunction measured psychophysically in a cohort of covid-19 patients. *International Forum of Allergy & Rhinology* 2020, 10:1127–1135.

2. Whitcroft KL, Hummel T: Olfactory dysfunction in covid-19: diagnosis and management. *JAMA* 2020, 323:2512–2514.

3. DeWeerdt S: How to bring back the sense of smell. *Nature* 2022, 606:S7–S9.

4. Kermen F, Franco L, Wyatt C, Yaksi E: Neural circuits medi- ating olfactory-driven behavior in fish. *Front Neural Circ* 2013, 7.

5. Modi MN, Shuai Y, Turner GC: The drosophila mushroom body: from architecture to algorithm in a learning circuit. *Ann Rev Neurosci* 2020, 43:465–484.

6. van der Linden CJ, Gupta P, Bhujiya AJ, Riddick KR, Hossain K, Santoro SW: Olfactory stimulation regulates the birth of neurons that express specific odorant receptors. *Cell Rep* 2020, 33.

7. Vihani A, Hu XS, Gundala S, Koyama S, Block E, Matsunami H: Semiochemical responsive olfactory sensory neurons are sexually dimorphic and plastic. *Elife* 2020, 9, e54501.

8. Tsukahara T, Brann DH, Pashkovski SL, Guichonts G, Bozza T, Datta SR: A transcriptional rheostat couples past activity to future sensory responses. *Cell* 2021, 184:6326–6343, e6332.

Using a combination of odour exposures with single-cell transcriptomic analysis and functional imaging, this study elegantly shows that olfactory sensory neurons dynamically change their transcriptome, adapting the transduction gain to inputs.

9. Horgue LF, Assens A, Fodoulian C, Marconi L, Tuberosa J, Haider A, Boillat M, Carleton A, Rodriguez I: Transcriptional adaptation of olfactory sensory neurons to gcpr identity and activity. *Nat Commun* 2022, 13:2359.

10. Fleischmann A, Shykind BM, Sosulski DL, Franks KM, Glinka ME, Mei DF, Sun Y, Kirkland J, Mendelsohn M, Albers MW, Axel R: *Mice with a “monoclonal nose”: perturbations in an olfactory map impair odor discrimination. Neuron* 2008, 60:1068–1081.

11. Angelo K, Rancz EA, Pimentel D, Hundahl C, Hannibal J, Fleischmann A, Pichler B, Margrie TW: A biophysical signature of network affiliation and sensory processing in mitral cells. *Nature* 2012, 488:375–379.

12. Galliano E, Hahn C, Browne LP, Villamayor PR, Tufo C, Crespo A, Grubb MS: Brief sensory deprivation triggers cell type-specific structural and functional plasticity in olfactory bulb neurons. *J Neurosci* 2021:1606–1620. JN-RM.

Sensory deprivation with just one day of naris occlusion causes the axon initial segment length to change selectively in inhibitory neurons located in the input layer of the olfactory bulb. The approach also gives a convenient experimental handle to study mechanisms of sensory adaptations.

13. Roland B, Jordan R, Sosulski DL, Diodato A, Fukunaga I, Wickersham I, Franks KM, Schaefer AT, Fleischmann A: Massive normalization of olfactory bulb output in mice with a “monoclonal nose.” *Elife* 2016, 5, e16335.

14. Manoel D, Makhlouf M, Arayata CJ, Sathappan A, Da Costa C, Jr, Abdelrahman D, Selvaraj S, Hasnah R, Mainland JD, Gerkin RC, Saravia LR: Deconstructing the mouse olfactory percept through an ethological atlas. *Curr Biol* 2021, 31: 2809–2818.

15. Nakayama H, Gerkin RC, Rinberg D: A behavioral paradigm for measuring perceptual distances in mice. *Cell Reports Methods* 2022, 2, 100233.

16. Ravia A, Snitz K, Honigstein D, Finkel M, Zirler R, Perl O, Secundo L, Buck L, Axel R: Cell-specific and plastic pattern recognition and behavioral sensory acuity. *Nature* 2012, 499: 6343. e6332.

This study investigates how odour representations develop along the olfactory processing hierarchy. By comparing the similarity relationships in the neuronal activity patterns in olfactory regions against those in the physico-chemical descriptors of odors, it was possible to demonstrate an emergence of abstract olfactory representations.

17. Passavanti SL, Iurilli G, Brann D, Chicharro D, Drummey K, Franks KM, Panzeri S, Datta SR: Structure and flexibility in cortical representations of odour space. *Nature* 2020, 583: 293–298.

18. Blazing RM, Franks KM: Olfod coding in piriform cortex: mechanistic insights into distributed coding. *Curr Opin Neurobiol* 2020, 64:96–102.

19. Schoonover CE, Ohashi SN, Axel R, Fink AJP: Representational drift in primary olfactory cortex. *Nature* 2021, 594:541–546.

20. Kudryavitskaya E, Marom E, Shani-Narkiss H, Pash D, Mizrahi A: Flexible categorization in the mouse olfactory bulb. *Curr Biol* 2021, 31:1616–1631. e1614.

21. Chapuis J, Wilson DA: Bidirectional plasticity of cortical pattern recognition and behavioral sensory acuity. *Nat Neurosci* 2012, 15:155–161.

22. Buck L, Axel R: A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 1991, 65:175–187.
23. Keller A, Zhuang H, Chi Q, Vossahl LB, Matsunami H: Genetic variation in a human odorant receptor alters odor perception. *Nature 2007, 449:468–472.

24. Dewan A, Cichy A, Zhang J, Miguel K, Feinstein P, Rinberg D, Bozza T: Single olfactory receptors set odor detection thresholds. *Nat Commun 2018, 9:2887.

25. Rokni D, Hemmelder V, Kapoor V, Murthy VN: An olfactory cocktail party: figure-ground segregation of odorants in rodents. *Nat Neurosci 2014, 17:1225–1232.

26. Adefuin AM, Lindeman S, Reintert JK, Fukunaga I: State-dependent representations of mixtures by the olfactory bulb. *Elife 2022, 11, e76882.

27. Chu Monica W, Li Wankun L, Komiyama T: Balancing the robustness and efficiency of odor representations during learning. *Neuron 2016, 92:174–186.

28. Kato Hiroyuki K, Chu Monica W, Isaacson Jeffry S, Komiyama T: Dynamic sensory representations in the olfactory bulb: modulation by wakefulness and experience. *Neuron 2012, 76:962–975.

29. Yamada Y, Bhaukaaurally K, Madarasz TJ, Pouget A, Rodriguez I, Carleton A: Context- and output layer-dependent long-term ensemble plasticity in a sensory circuit. *Neuron 2017, 93: 1198–1212. e1195.

30. Jordan R, Fukunaga I, Kollo M, Schaefer AT: Active sampling state dynamically enhances olfactory bulb odor representation. *Neuron 2018, 98:1214–1228. e1215.

31. Koldaeva A, Schaefer AT, Fukunaga I: Rapid task-dependent tuning of the mouse olfactory bulb. *Elife 2019, 8, e43558.

32. Burton SD: Inhibitory circuits of the mammalian main olfactory bulb. *J Neurophysiol 2017, 118:2034–2051.

33. Abraham NM, Egger V, Shimshek DR, Renden R, Fukunaga I, Sprengel R, Seeburg PH, Klugmann M, Margrie TW, Schaefer AT, Kuner T: Synaptic inhibition in the olfactory bulb accelerates odor discrimination in mice. *Neuron 2010, 65: 390–411.

34. Liedo P-M, Alonso M, Grubb MS: Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci 2006, 7:179–193.

35. MANDAIRON N, KUCZEWSKI N, KEREN F, FOREST J, MIDROIT M, LEDO P-M, ADEFUIN AM, LINDENMAN S, REINERT JK, FUKUNAGA I: State-dependent representations of mixtures by the olfactory bulb. *Nat Commun 2018, 9:2887.

36. Wu A, Yu B, Chen Q, Matthews Gillian A, Lu C, Campbell E, Tye Hori N, Murata K, Yoshikawa K, Yoshihara Y, Touhara K: Contribution of individual olfactory receptors to odor-induced attractive or aversive behavior in mice. *Nat Commun 2019, 10:209.

37. Burton SD: Inhibitory circuits of the mammalian main olfactory bulb. *J Neurophysiol 2017, 118:2034–2051.

38. Abraham NM, Egger V, Shimshek DR, Renden R, Fukunaga I, Sprengel R, Seeburg PH, Klugmann M, Margrie TW, Schaefer AT, Kuner T: Synaptic inhibition in the olfactory bulb accelerates odor discrimination in mice. *Neuron 2010, 65: 390–411.

39. Liedo P-M, Alonso M, Grubb MS: Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci 2006, 7:179–193.

40. MANDAIRON N, KUCZEWSKI N, KEREN F, FOREST J, MIDROIT M, LEDO P-M, ADEFUIN AM, LINDENMAN S, REINERT JK, FUKUNAGA I: State-dependent representations of mixtures by the olfactory bulb. *Nat Commun 2018, 9:2887.

41. Gill JV, Lerman GM, Zhao H, Stetter BJ, Rinberg D, Shoham S: Precise holographic manipulation of olfactory circuits reveals coding features determining perceptual detection. *Neuron 2020, 108:382–393. e385.*
Using a paradigm that makes mice learn an odour–reward association in less than 10 trials, the authors demonstrate that the representation of this association is prevalent in the olfactory tubercle, but not the piriform cortex.

61. Wang PY, Boboila C, Chin M, Higashi-Howard A, Shamash P, Wu Z, Stein NP, Abbott LF, Axel R: Transient and persistent representations of odor value in prefrontal cortex. Neuron 2020, 108:209–224.

62. Cansler HL, Zandt EE, Carlson KS, Khan WT, Ma M, Wesson DW: Organization and engagement of a prefrontal-olfactory network during olfactory selective attention. in ’t Cerebr Cortex 2022. bhac153.

63. Baker KL, Dickinson M, Findley TM, Gire DH, Louis M, Suver MP, Verhagen JV, Nagel KI, Smear MC: Algorithms for olfactory search across species. J Neurosci 2018, 38:9383.

64. Findley TM, Wyrick DG, Cramer JL, Brown MA, Holcomb B, Attey R, Yeh D, Monasevitch E, Nouboussi N, Cullen I, Songco JC, et al.: Sniff-synchronized, gradient-guided olfactory search by freely moving mice. Elife 2021, 10, e58523.

65. Ackels T, Erskine A, Dasgupta D, Marin AC, Warner TPA, Attey R, Yeh D, Monasevitch E, Nouboussi N, Cullen I, Songco JC, et al.: Sniff-synchronized, gradient-guided olfactory search by freely moving mice. Elife 2021, 10, e58523.

66. Radavansky BA, Oh JY, Climer JR, Dombec DA: Behavior determines the hippocampal spatial mapping of a multisensory environment. Cell Rep 2021, 36, 109444.

67. Fischler-Ruiz W, Clark DG, Joshi NR, Devi-Chou V, Kitch L, Schnitzer M, Abbott LF, Axel R: Olfactory landmarks and path integration converge to form a cognitive spatial map. Neuron 2021, 109:4036–4049. e4035.

68. O’Keefe J: Place units in the hippocampus of the freely moving rat. Exp Neurol 1976, 51:78–109.

69. Leitner FC, Melzer S, Lütcke H, Pinna R, Seeburg PH, Helmchen F, Monyer H: Spatially segregated feedforward and feedback neurons support differential odor processing in the lateral entorhinal cortex. Nat Neurosci 2016, 19:935–944.

70. Woods NI, Stefanini F, Apodaca-Montano DL, Tan IMC, Biane JS, Kheirbek MA: The dentate gyrus classifies cortical representations of learned stimuli. Neuron 2020, 107:173–184. e176.

71. Aqrabawi AJ, Kim JC: Hippocampal projections to the anterior olfactory nucleus differentially convey spatiotemporal information during episodic odor memory. Nat Commun 2016, 9:2735.

72. Igarashi KM, Lu L, Colgin LL, Moser M-B, Moser EI: Coordination of entorhinal–hippocampal ensemble activity during associative learning. Nature 2014, 510:143–147.

73. Martin C, Beshel J, Kay LM: An olfacto-hippocampal network is dynamically involved in odor-discrimination learning. J Neurophysiol 2007, 98:2196–2205.

74. Poo C, Agarwal G, Bonacchi N, Mainen ZF: Spatial maps in piriform cortex during olfactory navigation. Nature 2022, 601:596–599.

Using an ingenious behavioural paradigm that associated odours with particular locations, the authors demonstrate that the posterior piriform cortex contains neurons that represent place.