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From the top down: flexible reading of a fragmented odor map

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Animals that depend on smell for communication and survival extract multiple pieces of information from a single complex odor. Mice can collect information on sex, genotype, health and dietary status from urine scent marks, a stimulus made up of hundreds of molecules. This ability is all the more remarkable considering that natural odors are encountered against varying olfactory backgrounds; the olfactory system must therefore provide some mechanism for extracting the most relevant information. Here we discuss recent data indicating that the readout of olfactory input by mitral cells in the olfactory bulb can be modified by behavioral context. We speculate that the olfactory cortex plays a key role in tuning the readout of olfactory information from the olfactory bulb.

The means by which odorous volatile molecules detected in the periphery are transformed into an odor object representation in the cortex remains to be fully understood. According to the combinatorial coding hypothesis [1–3], odors detected in the nose are deconstructed into molecular features represented in a topographical pattern of glomerular activity termed an 'odor map' (Box 1). This representation is then processed and ultimately reconstructed into an odor 'object' in the olfactory cortex [4,5]. While this hypothesis for feedforward flow of information is often used to interpret experimental findings, it does not necessarily incorporate the influence of odor associations or 'meaning' on odor signal processing. An alternative hypothesis presented by Kay and Sherman [6] postulated that the olfactory bulb (OB) acts as a transiently modifiable (active) filter that shapes odor representations at the level of olfactory bulb output. The olfactory bulb/cortex circuit does not simply deconstruct, sharpen, and reconstruct complex odors. Instead, the circuitry in the olfactory bulb could extract the most relevant odor information, while filtering out parts of the signal that are not as important for the animal's current needs. Ramón y Cajal predicted more than a century ago [7] that the process of feature extraction by the olfactory bulb is modulated by what he termed centrifugal fibers originating in olfactory cortex and neuromodulatory centers in the brain (Figure 1). We speculate that odor associations or meaning affect the feedback circuit to the olfactory bulb from the olfactory cortex

(Figure 2a). By incorporating meaning into the feedback circuit, the cortex can then dynamically tune the readout of the odor map by the principal neurons of the bulb (tufted, T, and mitral, MT, cells) in behaviorally-relevant ways.

Lateral interactions could allow flexible readout of the fragmented chemotopic odor map

Sensory systems must optimize the processing of input to permit timely and efficient extraction of information. One elegant solution to this challenge is to organize information into a spatial map. In vision, for instance, the cornea focuses a spatial representation of an image onto the retinal surface in the eye, while in hearing the representation of sound is organized as a frequency map in the cochlea. Odor maps also appear to have a gross chemotopic arrangement. For example, carboxylic acids, methyl and ethyl esters stimulate a dorsal anterior domain in the olfactory bulb, while aromatic compounds stimulate a dorsal posterior domain [8,9].

Nevertheless, detailed comparison reveals fundamental differences between the chemotopic odor map and other sensory maps. On the one hand, auditory and visual systems have clear relationships along one- or two-dimensional space between neighboring neural elements and the stimuli being processed (e.g. the frequency scale or the visual field). In these systems, dense short-range interactions play an important role in the processing of signals. Objects analyzed by the auditory and visual systems can be very complex, but local processing of the stimulus in one or two dimensions respectively is an advantageous first step in analyzing the sensory input. In contrast, each chemical bond of a molecule is a dimension in the chemical structure, so there is no two-dimensional arrangement that would allow a glomerulus to have all 'similar' glomeruli nearby. Indeed, mathematical analysis shows that collapsing multidimensional maps onto two dimensions inevitably fragments the contiguous representation of an object [10]. Accordingly, the map must be fragmented because adjacent glomeruli are often not related in terms of stimulus tuning, and frequently respond to structurally disparate sets of odors [3,11]. In fact, a recent functional survey of approximately 30 unique glomeruli on the dorsal surface of the bulb revealed only a weak correlation between response and interglomerular distance in response to a large bank of odors [11]. Thus, the chemotopic structure of the map is 'loosely organized' [12]; this probably reflects the

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Box 1. Processing in the Olfactory Bulb

Each olfactory sensory neuron (OSN) in the main olfactory epithelium expresses one of ~1000 odorant receptors. Axons from OSNs synapse onto their second order targets in discrete ovoid neuropil called glomeruli. Each glomerulus receives only axons that express the same odorant receptor [51], so the pattern of glomerular activation on the surface of the bulb, called an odor map, is unique for each odor. Each glomerulus and its associated cells can be considered a functional 'column' because the input to these groups of cells is derived from a single odorant receptor [51,52]. The principal output neurons of the glomerulus, the tufted (T) and mitral (MT) cells, project to only one glomerulus (in mammals). The external tufted (ET) cells receive direct monosynaptic input from OSNs and drive synchronous activity in other cells innervating the glomerulus (including MT cells) (Figure I). In slices, these cells respond to electrical stimulation at a lower threshold and with a faster onset compared to MT cells [53–55]. The ET and MT cells could convey different information to olfactory cortex to be used for different purposes, including feedback to the olfactory bulb.

Activity in each glomerular column is regulated by inhibitory interneurons, the periglomerular (PG) and granule cells (GCs). PG cells influence both intra- and inter-glomerular modulation of column activation [12], while granule cells extend dendrites to the EPL and make reciprocal dendrodendritic synapses on the lengthy lateral dendrites of the MT and superficial middle tufted cells (see also Figure 2).

Dynamic inhibition of columns by the activation of GCs may create meaningful spatial and temporal patterns [56] or synchronization between columns [57], thereby encoding a stronger signal for downstream targets [34,35]. There is some evidence that proximal glomeruli are able to laterally inhibit each other and synchronize [58,59]. However, a recent survey of MT cell responsiveness to stimulation of multiple glomeruli in the dorsal olfactory bulb favors sparse glomerular column inputs to MT cells [60], consistent with the sparse columnar connections seen in viral tracings [52].
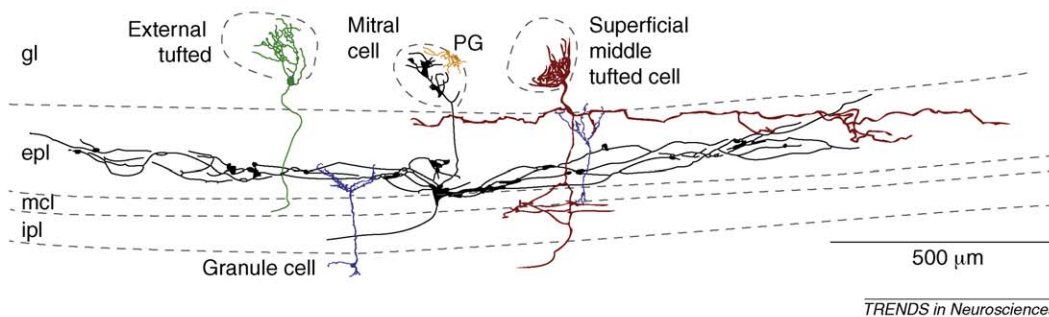

Figure I. Neural elements of the olfactory bulb (using nomenclature from Ezeh and co-workers, Ref. [61]) rendered from published data [62–64] with permission. gl, glomerular layer; epl, external plexiform layer; mcl, mitral cell layer; ipl, internal plexiform layer.

fact that behaviorally significant odors are complex mixtures of molecules often unrelated to previously encountered odors. For example, even if two adjacent glomeruli are functionally similar, the optimal processing of an incoming signal may change abruptly if a novel and behaviorally-relevant odor appears that contains an odor feature identified by one of the glomeruli but not the other. As such, a major problem for the olfactory system is the inherent unpredictability of potentially relevant stimuli. The problem lies not only in the large number of potential molecular features but also in the largely unlimited number of possible combinations [13].

Given that not all relationships between molecular features are represented by neighboring placement of glomeruli in a two-dimensional map, it is not surprising that processing in the olfactory bulb takes place through long-distance interactions mediated by lateral dendrites of MT cells or by long-range inter-glomerular interactions (Box 1). These lateral interactions could provide the flexibility needed for processing novel stimuli whose molecular features are represented by a different subset of distant glomeruli. Modulation of lateral interactions between glomeruli [12], or through MT cell lateral dendrites [14], might provide a mechanism for amplifying signals from some activated glomeruli while suppressing others. The combination of a loose chemotopic map with extensive lateral interactions provides a flexible circuit that can easily be modified through feedback from cortical or modulatory areas, so allowing optimal extraction of information from distinct subsets of glomeruli in different behavioral contexts.

Mitral cell odor responses are influenced by learning, behavior, and context

Evidence for top-down regulation of processing in the olfactory bulb was first provided by Kerr and Hagbarth [15] who showed that excitation of centrifugal fibers enhances the local field potential (LFP) activity of the olfactory bulb. The LFP, first described by Adrian, is a field potential recorded extracellularly in the olfactory bulb that reflects the oscillatory synchronous activity of neurons aligned on the average in the same direction [16,17]. Since 1955 other groups have shown that non-olfactory stimuli and olfactory learning tasks also alter odor-evoked LFP signals recorded in the bulb [18–21].

Substantial work has shown conclusively that learning is associated with a change in MT cell population responses to odors. Arguably, the most comprehensive work to date has focused on early olfactory learning (EOL). These studies demonstrated the involvement of noradrenaline in a rodent's preference learning of a conditioned odor when paired with an unconditioned stimulus such as stroking [22]. Moreover, Wilson and co-workers found that an increased fraction of population MT cell responses were suppressed in response to the conditioned odor [23]. Importantly, the changes in MT cell activity in EOL do not reflect the valence of the odor; conditioning with either aversive or appetitive unconditioned stimuli results in similar changes.

While studies in adult animals are not as comprehensive, many studies have shown changes in population MT activity due to learning. For example, Keverne and co-workers presented data suggesting that MT cells in ewes

Figure 1. Drawing by Ramón y Cajal showing the olfactory system from the olfactory epithelium to the olfactory cortex. He labeled the olfactory sensory neurons (A) and sustentacular cells (h) in the olfactory epithelium; glomeruli (B), mitral cells (C), tufted cells (a), granule cells (D), the lateral olfactory tract (E) in the olfactory bulb; and the olfactory cortex (F). Note the arrows that he drew implying the flow of information through the circuit. The fibers at the top of the drawing (what he called centrifugal fibers) have arrows that imply information flow in the direction of the olfactory bulb. These centrifugal fibers are now known to be centrifugal with respect to the olfactory cortex and neuromodulatory centers where they originate. Reproduced with permission from the original at the Cajal Institute CSIC, Madrid.
A statement from Ramón y Cajal (Ref. [7], translated by Diego Restrepo) reads 'It is fitting, in the current state of science, to conjecture that through them [thick centrifugal fibers] the sphenoidal region of the brain [olfactory cortex], or another undetermined cortical territory, sends nervous currents to the bulb, currents that flow primarily through the granules [granule cells] and flows into the cells with tufts [mitral and tufted cells]. These centrifugal impulses that Duval and Manoumelian ingeniously used to formulate their hypothesis of the *nervi nervorum*, could produce in the glomeruli some action indispensable for the normal interplay of the mechanism of transmission.'

respond to lamb odors more strongly after parturition [24]. In elegant multi-unit recordings in awake, behaving rodents, Pager showed that MT cells in hungry rats respond more strongly to odors associated with food [25], while Moulton showed that multiunit M/T cell activity in rabbits changed during learning in an odor discrimination task [26].

A key question is how individual MT cells change responsiveness during olfactory learning. The pioneering work of Kay and Laurent [27] described changes in MT cell odor responses during learning in an odor-discrimination task, but the sparseness of the responses in the awake, behaving animal [28] limited the strength of their conclusions. In a recent study, Fuentes and co-workers showed that the responses of MT cells to odors differ markedly depending on the behavioral task in terms of the percentage of cells responding and whether the responses are excitatory or inhibitory [29]. Finally, a recent study of MT cell activity during associative learning showed that responses of MT cells to odors change dramatically during the course of an odor discrimination task (Figure 3) [30]. While prescreening ensured that a large number of MT cells (~20%) were sensitive to the odors presented, initially most cells did not respond differentially to the two odors presented in the discrimination task. Even so, as the animal learned to discriminate between the two odors, MT cells started to respond differently to the rewarded and unrewarded odors. Divergence in the response to the two odors was transient, subsiding by the end of the

learning session. These experiments demonstrate that a profound change in MT cell responsiveness to odor takes place during learning.

There are several possible explanations for these changes in MT cell odor responses. First, input to the olfactory bulb could be modified by changes in sniffing (Box 2). Active sniffing is a way for animals to control voluntarily the input to the olfactory system, indeed fast sniffing has been shown to produce a different odor map compared to slow sniffing [31]. The intrinsic circuitry of the bulb could also contribute to changes in MT cell responses, notably through lateral interactions that could amplify, attenuate, or increase the contrast between activated glomeruli [12,14]. Finally, central modulation of the intrinsic OB network could elicit these behaviorally-relevant changes. Below we discuss changes in processing that occur intrinsically to the bulb, and those that are triggered by top-down regulation.

Local processing in the olfactory bulb is intrinsically dynamic
As discussed in Box 1, the spatio–temporal information contained in odor maps is processed by the interplay between the principal neurons of the bulb (tufted, T, and mitral, MT, cells) and the interneurons in the glomerular and external plexiform layers (EPL). This interplay gives rise to lateral inhibition [12,14], a potential mechanism for synchronizing MT cell firing. Synchronization of MT cells through reciprocal connections to granule cells has been
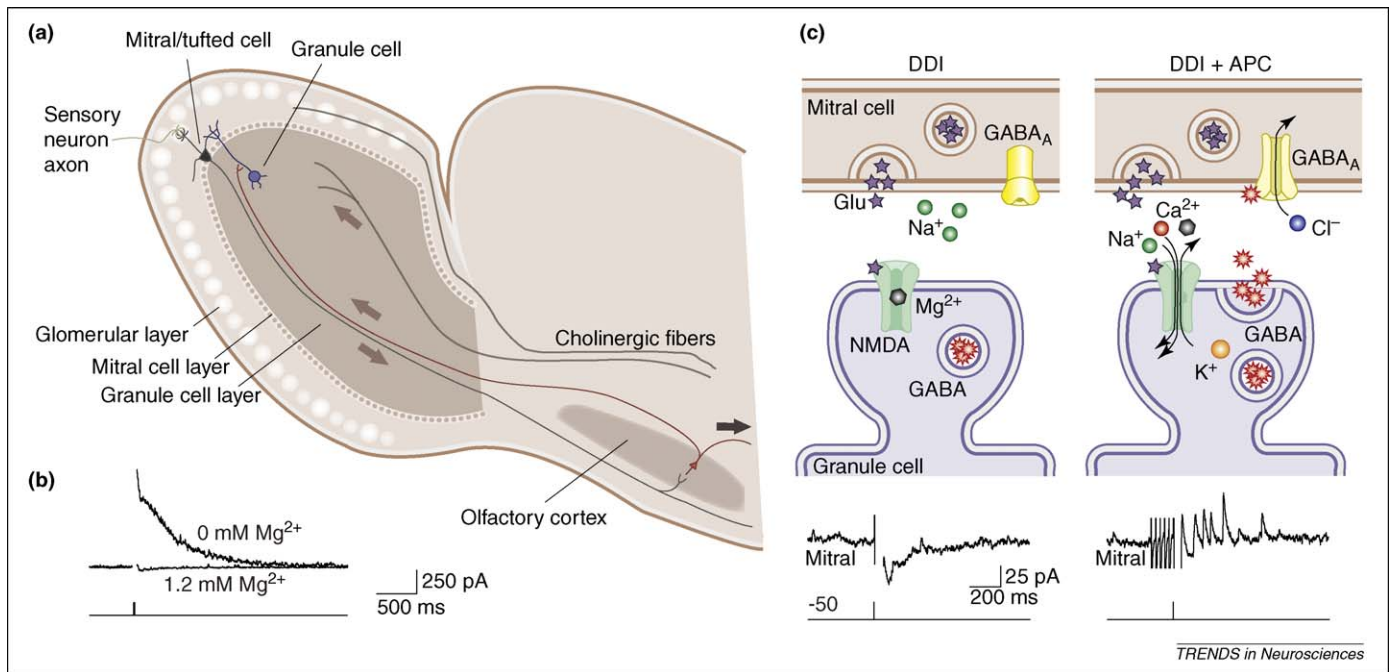
Figure 2. Near-coincident activation of centrifugal fibers from the olfactory cortex and depolarization of MT cells elicits enhanced dendrodendritic inhibition. **(a)** Diagram showing the arrangement of the olfactory bulb and olfactory cortex where MT cells send information to the cortex, where in turn principal neurons feed back onto the granule cells. In addition to centrifugal collaterals from olfactory cortex that innervate the proximal dendrites of granule cells, the diagram shows centrifugal feedback from one of the neuromodulatory brain areas (the cholinergic basal forebrain). Note that the lateral dendrites of the MT cells contact the distal dendrites of the granule cells where they form the reciprocal synapse shown schematically in panel (c). **(b)**. Data from Balu and co-workers [45] showing that removal of Mg^{2+} from the extracellular solution releases the block on NMDA receptor channels; the ensuing large dendrodendritic inhibitory currents (outward currents) then lead to 20 mV depolarization of the mitral cell. These dendrodendritic responses were blocked by the NMDAR blocker D-APV. **(c)** Top panels: schematic representation of the function of reciprocal synapses where MT cells release glutamate to excite distal dendrites of granule cells. The bottom panels display data from Balu and co-workers [45] showing that near coincident mitral cell depolarization (dendrodendritic inhibition-DDI) and anterior piriform cortex (APC) stimulation evokes outward inhibitory currents in mitral cells. Example responses to voltage-clamp depolarization alone (DDI, to +20 mV, 2 ms duration; left) and both intracellular depolarization and APC stimulation (DDI + APC, right) are shown. The diagram at the top shows that APC stimulation releases Mg^{2+} blockade of NMDA receptor channels in granule cells, thereby allowing synaptic activation of the granule cell distal synapse and release of GABA onto the mitral cell, in turn eliciting outward inhibitory currents in the mitral cell.

demonstrated in OB slices [32], and synchronized firing of MT cells has also been observed in anesthetized animals [33]. Local OB circuits can dynamically regulate the synchronization among MT cells, and synchronized firing of output cells leads to a more robust activation of principal cells in the olfactory cortex [34,35]. Thus, a change in the strength of lateral inhibition would be expected to affect the degree of synchronization, and hence the reliability of information transfer to the olfactory cortex.

Factors intrinsic to the bulb, such as a change in the basal level of MT cell excitation, can cause changes in the OB interneuron circuits that modify MT cell activity. Arevian and co-workers studied how the magnitude of lateral inhibition by neighboring MT cells through the granule cell circuit depended on the basal firing rate [36] in olfactory bulb slices. They found that the magnitude of granule cell lateral inhibition is entirely dependent on the activity level of the MT cell. The magnitude of lateral inhibition ranges parabolically from virtually no inhibition at low MT cell basal firing rates, to a maximum inhibition at intermediate firing rates, and then back down to no inhibition at high levels of activity. This profile results in a tendency for the circuit to optimize contrast among the active MT cells, an action that is advantageous in a system where the relationship between neighboring glomeruli can change unexpectedly.

Animals directly regulate input to the olfactory bulb by modifying their sniffing behavior: alterations in sniffing patterns could therefore underlie a change in the basal level of OB activation. Sniffing is affected by behavioral context [37,38], although it is not known whether changes in sniffing strategies (e.g. increased sniff frequency) affect information transfer at the level of the MT cells. Indeed, a recent study concluded that changes in sniffing do not influence low-level neural processing underlying odor perception [39]. However, the differences in MT cell odor responses depending on behavioral context reported by Fuentes et al [29] could be due to differences in sniffing patterns between the two tasks.

While both intrinsic bulb circuitry and the modulation of sniffing can alter MT cell odor responses, these mechanisms are unlikely to fully account for learning-induced changes in MT cell firing. Sniffing controls input to the entire olfactory bulb, and therefore can cause changes on a global scale, for instance by producing an overall increase in excitation or enhanced lateral inhibition [31]. It would be more difficult for sniffing to account for the differential firing patterns of MT cells observed during learning [30] because trials are shuffled randomly and animals do not know when they start sniffing whether the trial will be rewarded or not (Figure 3). Unfortunately, no study of MT single-unit odor responses during learning [27–30] has yet included recordings of sniffing patterns, and this remains an open question. Similarly, the intrinsic bulb circuitry, while optimally suited for contrast enhancement, would require input from a higher brain region to modify MT cell output in a behaviorally-relevant manner.
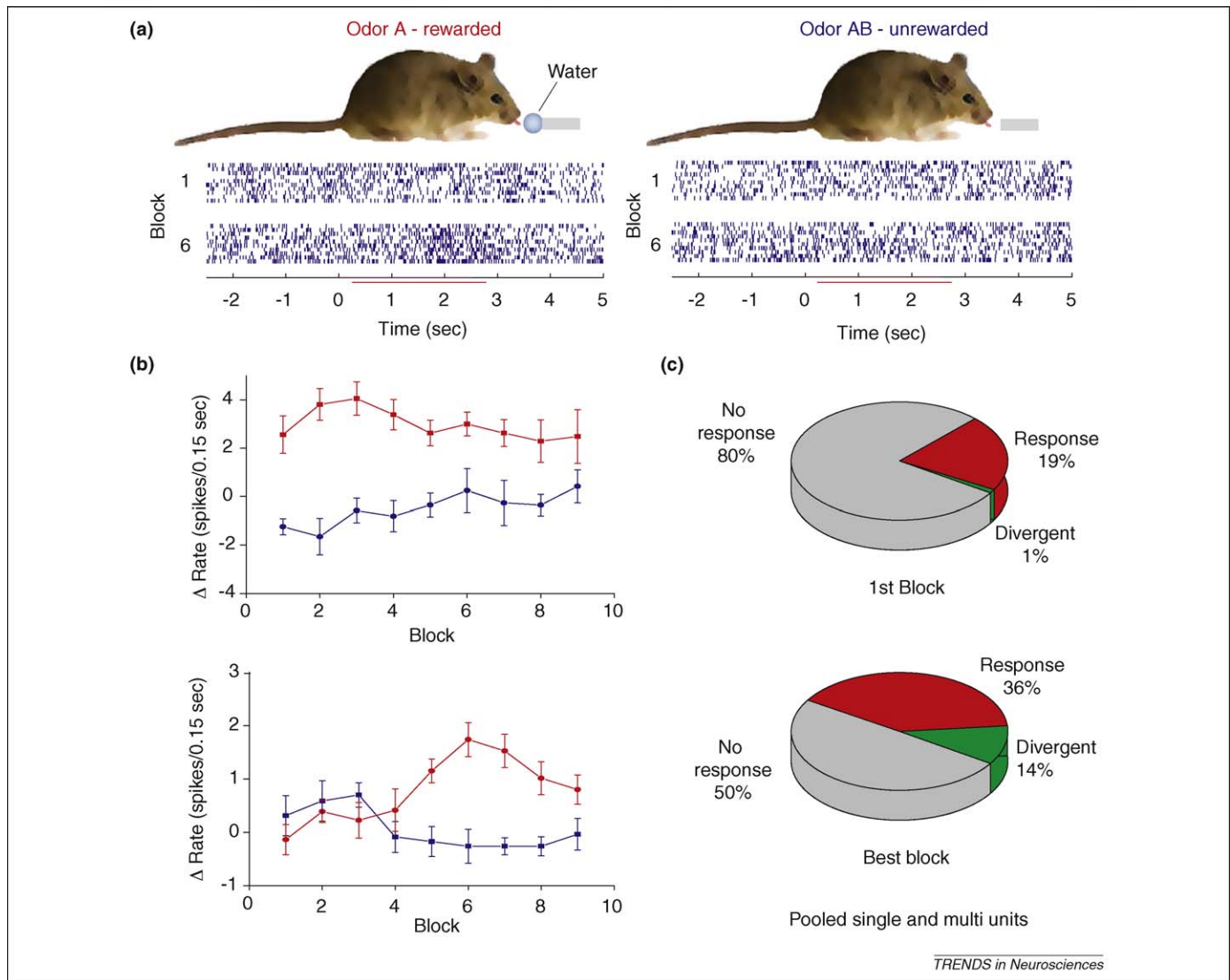
Figure 3. Divergence of MT cell responses during learning to discriminate between two novel odors. The data reproduced from Doucette and Restrepo [30] show that MT cells undergo a profound change in odor responsiveness during a session where animals learn to associate one odor with reward (rewarded; red) and another with no reward (unrewarded; blue). **(a)** A thirsty mouse learns to associate the reinforced odor with a water reward and the unreinforced odor with no reward. The mouse must lick on a metal tube for two seconds when presented with the rewarded odor so as to obtain the water reward. Rasters below the mouse show the responsiveness of a suspected mitral cell to the reinforced and unreinforced odors during the first block of 20 trials (10 reinforced and 10 unreinforced) and for block 6 (trials 100 to 120). During the first block the mouse responds randomly to the two odors, while in block 6 the mouse is responding correctly ∼80% of the time. **(b)** Examples of changes in odor responsiveness throughout the learning session. Red denotes rewarded odor; blue denotes unrewarded odor. The ordinate shows the odor-induced change in the number of spikes fired during a 0.15 sec interval. The top panel shows the odor responsiveness of a unit that responded differentially to the two odors from the onset of the session. This was rare (observed in only 2 of 660 units). The bottom panel shows the odor responsiveness of the cell whose responses are shown in (a). This cell developed a transient differential response to the two odors. This is representative of 93 of 660 units. **(c)** Pie charts showing the percent of units that responded to odors (red), and those that responded differently to the two odors (green). First block, the first 20 trials in the session; best block, 20 trials during the block where the unit displayed the largest difference in odor-evoked firing between reinforced and unreinforced odors.

Mechanisms for top-down regulation of mitral cell responsiveness

Modulation of MT cell responsiveness by adrenergic, cholinergic and serotonergic fibers is fairly well established [40]. In a recent study, Shea and co-workers found that odor-evoked increases in MT cell firing are suppressed in anesthetized mice when odor stimulation is paired with activation of the locus coeruleus (LC), the brainstem nucleus that houses the adrenergic neurons that innervate the olfactory bulb [41]. In another study, bulbar acetylcholine enhanced learning to discriminate between structurally-related odors; the effects on learning correlated with cholinergic sharpening of the odorant receptive field of MT cells [42]. It also stands to reason that divergent

firing of cells in neuromodulatory centers between rewarded and unrewarded odors [43] provides for differential modulation; this can therefore contribute to differential output from the olfactory bulb. Even the neuromodulatory systems that are thought to affect the entire olfactory bulb simultaneously, exemplified by the adrenergic system where all locus coeruleus neurons fire similarly [43], could result in the selective modulation of subsets of glomerular columns through mechanisms including nearly coincident odor responses and (slightly delayed) neuromodulatory inputs. Therefore, although the precise mechanisms remain unknown, intrinsic processing of contextual information conveyed by the neuromodulatory systems undoubtedly alters the processing of odor

Box 2. The role of sniffing in olfactory processing

The activation of olfactory sensory areas is intimately linked to respiration (breathing and/or sniffing). MT/T cells fire bursts of action potentials phase-locked to respiration in both anesthetized and, to a lesser degree, awake animals [65]. Similarly, oscillating field-potentials in the olfactory bulb appear to be driven by input to olfactory sensory neurons [65]. These respiration-driven oscillations can promote synchrony within a given cluster of MT/T cells corresponding to a single glomerulus [66,67] and have important implications for olfactory coding [68] (see Box 1). Whereas studies from anesthetized animals and tissue slices have provided most of the evidence for tight oscillatory coupling between olfactory bulb activity and respiration, recordings from MT/T cells in awake animals indicate a higher baseline firing rate with a variable degree of phase-locking to respiratory oscillations [27,28]. In addition, sniff frequencies above 4 Hz dramatically alter both olfactory nerve input and glomerular activation patterns [31] and decouple MT/T cell firing from respiration [27] in rats. Therefore, changes in respiration frequency cause dramatic changes in both input to the olfactory bulb and the response of cells in the circuit.

Animals commonly display fast sniffing during many natural behaviors [69], and often alternate between slow respiration and fast sniffing. By alternating their respiratory patterns, animals potentially extract different information from the same odorants. For example, the slow respiratory oscillations could promote synchronous firing, whereas fast sniffing could favor tonic input. In this fashion, the active modulation of sniff frequency represents yet another potential mechanism for the dynamic control of olfactory bulb circuit processing.

information in the olfactory bulb. It is also important to note that sniffing is governed by a subcortical motor control circuit that receives input from neuromodulatory systems (e.g. cholinergic and serotonergic) [44].

Alternatively, or in conjunction with neuromodulatory inputs, the cortical centrifugal input to the bulb could on/off gate MT cells as has been described in thalamocortical circuits [6]. Indeed, increasing evidence implicates the cortex in feedback regulation of the olfactory bulb circuit. Balu and co-workers [45] found that stimulation of cortical centrifugal fibers can relieve the tonic Mg^{2+} block of NMDA receptor channels at the MT/granule cell dendrodendritic synapses located at the distal end of the granule cell dendrites (Figure 2). These experiments effectively demonstrate that the centrifugal fibers originating from the olfactory cortex actively gate dendrodendritic inhibition of MT cells. The massive cortical centrifugal innervation of the olfactory bulb through the anterior commissure terminates mainly, but not exclusively, on the proximal synapses of granule cell dendrites [46].

Recent intriguing data, albeit inconclusive, suggest that (unlike neuromodulatory fibers in the olfactory bulb) cortical centrifugal fibers do not terminate across all areas in the granule cell layer, but terminate instead in small patches, presumably on individual glomerular columns [47]. If such a situation is indeed the case, then the cortical centrifugal fibers could gate the responses of different glomerular columns. Therefore, changes in the responsiveness of MT cells to odors during a learning task could be mediated by centrifugal feedback from the olfactory cortex. Such a feedback mechanism would be particularly effective in an odor discrimination task for MCs that send their primary dendrite to a single glomerulus that is activated by two similar odors. Cortical feedback could specifically relieve inhibition to these cells for one odor, but not the other, thereby increas-

ing the difference between the MT cell readout of the odor map for the two odors. Alternatively, this same type of feedback could increase the differential responses of cells initially responding differently to the two odors, so maximizing a difference that was always present.

Finally, recent evidence in olfactory bulb slices indicates that the input from cortical centrifugal fibers through proximal synapses in granule cells undergoes long-term potentiation (LTP, although there is some controversy on whether LTP occurs in mature *versus* newly-incorporated granule cells) [48,49]. This indicates that cortical centrifugal modulation of MT cell responsiveness can flip a switch on (and presumably off) for sustained periods of time.

The olfactory cortex receives information not only from the olfactory bulb, but also from other areas of the brain, and performs associative processing of the signal [50]. As such, it is conceivable that the olfactory cortex does not passively reconstruct the olfactory signal into an odor object. Rather, the olfactory cortex could serve as an active player that tunes the processing of glomerular columns in the olfactory bulb to optimize the readout of the odor-evoked olfactory glomerular map. In such a scenario, the glomerular layer of the olfactory bulb would be analogous to an orchestra whose instruments (the glomeruli) are being activated by odor features, and the olfactory cortex and/or neuromodulatory systems permit attention to be drawn to discrete voices or ensembles within the orchestra. We can hear a single violin, concentrate on the cello section, or listen to the complete orchestra. Analogously, an odor object resembles one such timbre that can be actively filtered out from the orchestra. In our opinion, cortical modulation of the readout of the odor map has the potential to allow exquisite context-dependent exploration of odor space.

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