

Review

Adjusting neurophysiological computations in the adult olfactory bulb

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Abstract

The olfactory bulb receives signals from olfactory sensory neurons and conveys them to higher centers. The mapping of the sensory inputs generates a reproducible spatial pattern in the glomerular layer of the olfactory bulb for each odorant. Then, this restricted activation is transformed into highly distributed patterns by lateral interactions between relay neurons and local interneurons. Thus, odor information processing requires the spatial patterning of both sensory inputs and synaptic interactions. In other words, odor representation is highly dynamic and temporally orchestrated. Here, we describe how the local inhibitory network shapes the global oscillations and the precise synchronization of relay neurons. We discuss how local inhibitory interneurons transpose the spatial dimension into temporal patterning. Remarkably, this transposition is not fixed but highly flexible to continuously optimize olfactory information processing.

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1. Introduction

More than a thousand airborne volatile molecules, called odorants, can diffuse through the nasal mucus layer of mammals and then bind to olfactory receptors expressed on sensory neurons located in the olfactory epithelium. This sensory organ projects to the main olfactory bulb (referred hereafter as the olfactory bulb or OB), which processes the odorant informa-

tion. The understanding of olfactory transduction has increased over the last decade. Yet, the question of how odor coding takes place is by no means solved and is currently an area of vigorous debate and experimentation.

Molecular approaches have revealed valuable information on the organization of the olfactory system. From these studies, we now know how the sensory organ connects to the OB. In this first relay, the axons of sensory neurons form glutamatergic excitatory synapses in regions known as glomeruli, which are analogous to the multineuronal ‘barrels’ in cerebral cortex (Fig. 1A) [1]. As well as relaying sensory inputs to the olfactory cortex, the OB also actively takes part in sensory information

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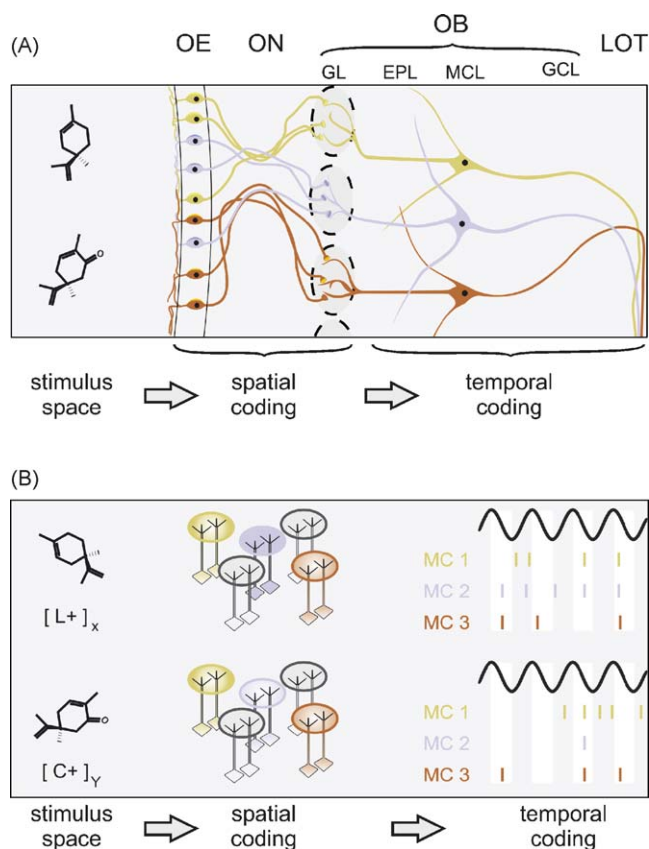


Fig. 1. Early olfactory processing at the first stages of the olfactory system. (A) Schematic organization of the connections between olfactory sensory neurons (whose cell bodies lie in the olfactory epithelium, OE) and olfactory bulb relay neurons (whose cell bodies lie in the mitral cell layer, MCL). Olfactory sensory neurons axons fasciculate to form the olfactory nerve (ON) between the olfactory epithelium and the olfactory bulb (OB). Sensory neurons axons synapse onto bulbar neurons, including OB relay neurons, in spherical structures called glomeruli. Relay neurons send then their axons in the lateral olfactory tract (LOT), toward higher brain structures. Olfactory sensory neurons express one or very few odorant receptors, conferring them a specific “identity”. All the sensory neurons endowed with the same identity project onto few distinct glomeruli within the OB. Olfactory sensory neurons position, identity and projection pattern into the OB constitute the morphological basis of the early processing of the sensory inputs defined as “spatial coding”. Lateral interactions between bulbar relay neurons and local neurons constitute the morphological basis of another subsequent processing of sensory information defined as “temporal coding”. GL: glomerular layer; EPL: external plexiform layer; GCL: granule cell layer. (B) Schematic definition of spatial and temporal coding of olfactory information. Given the olfactory sensory neuron pattern of projections, the presentation of an olfactory stimulus (defined by a chemical identity and a concentration) leads to the activation of a subset of glomeruli (the degree of activation is represented in the figure by the degree of color filling, grey glomeruli being not activated), specific to the stimulus (in the example, (+)-limonene at a given concentration, and (+)-carvone at another concentration). The temporal aspect of the olfactory sensory coding relies in the temporal organization of relay neurons activity. The activity of three different neurons (MC 1–3) is presented in addition to local field potential oscillations, which reflect the odor-induced response of a bulbar neuronal population. Relay neurons are either activated or silenced subsequently to stimulus presentation. Their spikes could either be phase-locked to the field oscillation (i.e., occurring in the falling phase of the field potential oscillation, like spikes of MC 3 after limonene presentation) or not (out of the falling phase of the oscillation, like most of spikes of MC 1 in response to carvone). On top of the population oscillation, individual neuron synchronization or desynchronization and their dynamics reflect the specificity of stimulus.

processing. This occurs through a series of critical steps in anatomically distinct places [2–5] and involving two classes of local inhibitory interneurons: periglomerular cells and granule cells. The periglomerular cells (GABAergic and dopaminergic interneurons), the projections of which are restricted to one or few glomeruli, interact with olfactory nerve terminals and/or primary dendrites of relay neurons [6].

Local processing also depends on the interneuron circuit located in the external plexiform layer of the OB, in which other dendrodendritic reciprocal synapses are heavily distributed [7]. There, individual relay neurons extend lateral dendrites over distances of up to 1000 μm [8,9] to form synapses with apical dendrites of granule cells [10,11]. As granule cells are the largest group of bulbar interneurons, synaptic transmission between dendrites is the principal synaptic interaction in the OB [3]. These interneurons help to spread the activity, allowing input patterns to be shaped and relay neuron activity to be synchronized (see below).

Not surprisingly, the bulbar interneuron populations are subjected to complex functional regulation due to their important role in OB functions. First, extensive centrifugal fibers innervating the bulb primarily contact local interneurons. These numerous centrifugal systems include the piriform cortex, the telencephalic basal ganglion, the magnocellular basal forebrain nuclei and the brain stem locus coeruleus [1,12,13]. Second, both periglomerular and granule cells are continuously renewed throughout the lifespan of mammals [14], with more than 30,000 newborn interneurons reaching the OB every day, while some others are eliminated [15]. This continuous neuronal replacement provides a support for a high degree of plasticity in the bulbar microcircuit [16]. Therefore, the previously reported high degree of plasticity of OB networks (e.g., [17,18]), leading to changes in odor discrimination and learning, results from a combination of a dual process: neuromodulation and neurogenesis. The striking similarity between separately evolved olfactory systems, from insects to mammals, in the organization of the olfactory pathway suggests there is an optimal solution to detecting, discriminating and learning odors ([19], see also Kay and Stopfer, this issue).

2. Neurophysiological computations at the first information processing stage

Sensory information is first transduced in the olfactory system by specialized sensory neurons located in the nasal epithelium (Fig. 1A). Local circuits in the second- and third-order brain areas then process and convert the simple monophasic sensory signals from the sensory neurons into a multi-dimensional code [2,20–23]. In the bulb, the incoming signals are first transformed, and then sent to multiple central targets [4,20,24,25]. The relative importance of spatial versus temporal patterns is still to be decided (see [26–29]). As we will not provide a critical or comprehensive assessment of all the studies here, several recent reviews may be consulted for a more complete perspective on this area [2,5,21–23,29–32].

A general picture has emerged nevertheless from data collected in distinct model systems: odorants activate an array

of olfactory receptor types resulting in a chemotopically fragmented map of activated glomeruli due to the precise convergence of sensory neuron axons depending on the receptor type they express [33–38]. This suggests that the spatial assemblies of output neurons encode odors in the OB (Fig. 1B). Remarkably, glomerular maps of primary sensory input to the OB are temporally dynamic [39]. They depend on the timing of the input from the olfactory epithelium and on synaptic interactions within glomeruli and between neurons in adjacent glomeruli. These spatially restricted activation maps are then transformed in subglomerular layers through complex synaptic interactions that are partly mediated by lateral dendrites of the relay neurons that extend over long distances.

The spatial and the temporal features of olfactory input encoding have been opposed for a long time. However, both should be considered as two sides of the same coin. The initial spatially organized odorant-activated pattern of relay neurons – sometimes ambiguous for similar odorants – evolves in time, and diverges from the initial pattern following a trajectory in the coding space that is characteristic of a given odorant and a given concentration. Thus, each odor representation can be thought of as a high-dimensional vector of relay neuron states that evolves with time in a stimulus-specific manner [2,31]. This holds at least for insects where individual projection neurons in the antennal lobe typically respond to a large number of odorants [40] and project to Kenyon cells in the mushroom body, which respond to very few odorants, indicating a “sparsening” of the olfactory code [40]. However, although the striking similarity in the anatomical organization of olfactory systems across different phyla may suggest a common, optimal strategy for odor detection and discrimination, important differences in coding strategies between systems are beginning to emerge. For instance, in contrast to insects, some individual relay neurons in mammals are very narrowly tuned, responding to singular chemical features of an odor [41]. Because each of these relay neurons has diffuse and overlapping projections in the olfactory cortex, and only a few relay neurons are required to drive cortical action potentials [42], the olfactory code in the mammalian cortex seems instead broadened and distributed.

A component of the temporal encoding of olfactory information requires the relay neurons to synchronize their firing between each other, resulting in a global oscillation of the local field potential (LFP). It has long been suggested that synchronous fast oscillations in central sensory systems help neural assemblies representing sensory objects to form [28]. However, we are still far from understanding the function of these oscillations. Yet, the computational richness and evolutionary conservation of network oscillations suggest that they are used in neural information processing.

It was Sir Adrian whom first reported odor-evoked fast oscillations (≈ 40 Hz) of LFP in the mammalian OB [43], and the underlying mechanisms have been investigated in considerable detail. Regarding the types of computations that could be performed during oscillatory activity, studies in invertebrates have been particularly helpful [44]. In insects, the information conveyed by the synchronization of relay neurons is related to fine odor discrimination [2]. In vertebrates, however, synchronous

relay neuron spiking conveys information only about odor categories, with the specific odor identity being conveyed by asynchronous spikes that define the slow decorrelation of sensory inputs [45]. It appears that both correlation (or synchronization) and decorrelation (or desynchronization) processes occur simultaneously. Although the relative contribution of the correlation and decorrelation processes in olfactory psychophysics is still poorly understood, the neurophysiological mechanism underlying the generation of oscillations has started to be determined. We will now present a detailed analysis of the various rhythms present in the mammalian OB.

3. Network dynamics in the olfactory bulb and downstream structures

LFP recordings in the OB of many vertebrates revealed that rhythmic activities are a universal feature of olfactory sensory processing across species [43,46–51]. For a given odor stimulus, the “induced rhythm” (as first coined by Adrian) appears transiently and only among a neural subpopulation selectively responsive to that particular odorant. The inhalation of odor molecules triggers oscillations in the bulb with different frequency ranges (e.g., [43,48,52,53]). The classical features of odor information processing in mammals are a robust pair of fast oscillations, called gamma (30–80 Hz) and beta (15–40 Hz) waves, and a slower one called the theta (3–12 Hz) rhythm. All of these rhythms are present not only in the OB but also in the olfactory cortex [54–56].

Gamma and beta waves are induced by odor inputs, whereas, the theta frequency band seems to be phase-locked with the breathing rhythm [48,52]. Each of these rhythms is generated in a specific location. Theta oscillations are conveyed from the sensory organ to the OB through rhythmic inputs. Beta oscillations are generated by interactions between the bulb and the olfactory cortex, whereas, gamma oscillations are generated within the OB circuitry. Thus, when the olfactory peduncle is blocked by cooling [53] or by surgical interruption [54], gamma oscillations are preserved in the bulb, whereas, beta oscillations disappear.

The involvement of gamma oscillations in sensory processing has been extensively studied in invertebrates, in which rhythm supports fine discrimination between similar stimuli. In the *Limax* procerebral lobe, a disruption of relay neuron synchronization impaired the discrimination between similar stimuli [57]. A similar result was obtained in insects [58] where it was further demonstrated that a combination of the intrinsic properties of relay neuron targets and rhythmic inputs with feed-forward inhibition define short integration windows [59]. Such precise frames allow readout of the information contained within each gamma cycle and an elimination of all the activity, which is out of these frames [2]. It is tempting to compare this mechanism with the one observed in vertebrate OB where relay neuron firing occur only within narrow time frames [60]. As a result, a distinct set of synaptic responses is expected to occur within each fast oscillation cycle [61]. Finally, it is worth noting that studies of an olfactory-based learning task in which beta oscillations were seen to increase while gamma oscillations decrease in the OB suggested that oscillations play a role

in learning [50,53,56,62,63]. The progressive domination of beta over gamma oscillations may be due to an increase in the top-down control of the OB by the olfactory cortex.

In sum, synchronized oscillations of neuronal assemblies of the olfactory system may be involved in the following processes: creating a periodic clock which allows neurons to follow the phase in which they fire, filtering noise, refining the coding space of a response, fine discrimination between odorants using overlapping spatial representations in the bulb, and changes in odor representations attributable to learning. Alternatively, the oscillations may be epiphenomenal. A more careful examination of the correlation between the odor-induced oscillations in the bulb and in downstream structures, as well as the behavior of conscious animals are required to propose more specific hypotheses on the meaning of rhythms.

4. Inhibitory local interneurons of the olfactory bulb mediate complex functions

Network oscillations in olfactory systems involving a manipulation of local inhibitory interneurons have proven useful in the study of their computational roles. For instance, a specific loss of odor discrimination was reported in mutant mice in which the number of bulbar interneurons was reduced [64] or in which GABA_A receptor-mediated synaptic inhibition was altered [65]. Among the local inhibitory interneurons of the mammalian OB, the granule and periglomerular cells are the largest cell populations [66,67]. Periglomerular cells receive inputs from olfactory sensory axons, relay neurons and short axon cells

(i.e., a group of excitatory interneurons). In turn, periglomerular cells contact mitral cells through reciprocal dendrodendritic synapses or through axo-dendritic synapses within a glomerulus. As periglomerular cells are also targeted by short-axon cells, they play some role in interglomerular interactions and lateral inhibition [68]. As a result, during initial OB processing, sensory information is transmitted both vertically across the glomerular relay between sensory neurons and relay neurons, and horizontally through local interneuron connections that are activated in odor-specific patterns.

Granule cells are the most numerous populations of interneurons in the OB (Fig. 2A), representing 90% of the total population of bulbar interneurons. The ratio between granule cells and relay neurons is about 100 to 1 [1]. These interneurons lack an axon, with all contacts being made and received through either their apical or basal dendrites. Granule cells interact with relay neurons principally through reciprocal dendrodendritic synapses (Fig. 2B). These anatomical features support four properties of signal integration and transmitter release between granule cells and relay neurons (Fig. 2A). The first one represents the so-called *recurrent inhibition* [69,70] in which the Ca²⁺ influx required to trigger GABA release directly back onto the relay neurons is mediated by voltage-dependent Ca²⁺ channels [70–72] and/or NMDA receptors [73–75] (Fig. 2B). Granule cells also support a *local lateral inhibition* among neighboring relay neurons when the activation of granule cell spines is strong enough to elicit a local spread of depolarization [76], Ca²⁺ signals or dendritic Na⁺ spikes [77–79] through the granule cell dendritic tree (Fig. 2A). Both recurrent and local lateral mechanisms, which

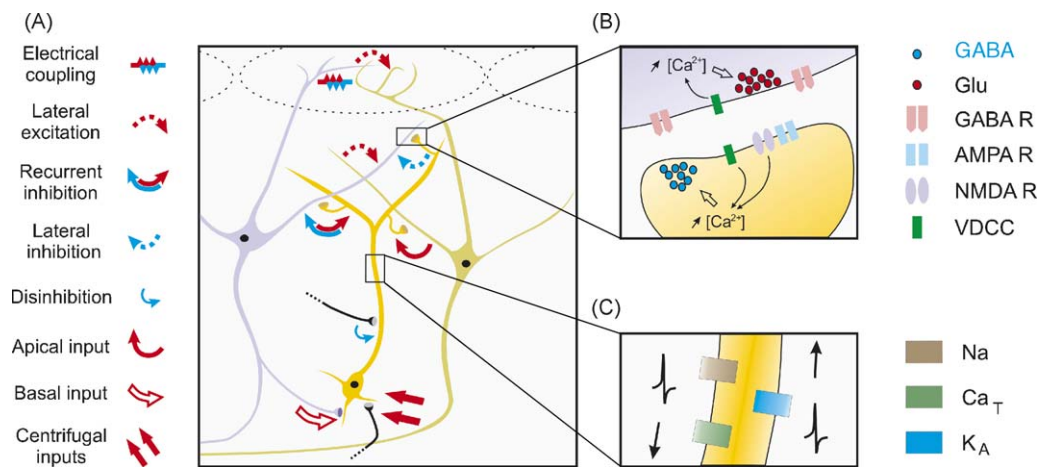


Fig. 2. Olfactory bulb microcircuit and connectivity. (A) Relay neurons communicate directly between each other through electrical coupling within a glomerulus and through glutamate spillover between their lateral dendrites. Granule cells receive excitatory inputs from relay neurons. These inputs are coming from relay neurons lateral dendrites onto granule cell spines, on their apical dendrites (apical input) and from relay neuron axon collaterals onto granule cell basal dendrites (basal input). All apical inputs lead to a negative inhibitory feedback onto the activated relay neuron, via dendro-dendritic reciprocal synapses, called recurrent inhibition. Moderate inputs could propagate into portions of granule cell apical dendritic tree and yield to the activation of spines contacting neighboring relay neurons, giving thus rise to lateral inhibition. Strong input could elicit granule cell somatic spikes, which will propagate into the entire dendritic tree, supporting global lateral inhibition. Granule cells receive also inhibitory inputs from bulbar interneurons (e.g., granule cells, Blanes cells, Golgi cells, ...). Lastly, granule cells receive a large panel of centrifugal inputs, coming from the piriform cortex, the locus coeruleus, the telencephalic basal ganglion and the magnocellular basal forebrain nuclei [1,66]. (B) Organization of the dendrodendritic reciprocal synapse between relay neurons and granule cells. Glutamate is released from relay neuron dendrites after an increase in intracellular calcium concentration (due either to the depolarisation carried by a spike or by the propagation of a calcium signal along the dendrite). Once released, glutamate binds to both AMPA and NMDA receptors present on the granule cell spine. The GABA liberation by a granule cell could come from a local calcium signal, coming from NMDA receptors and/or voltage-dependent calcium channels (VDCC) or from a global signal, which could be a calcium or a sodium spike. (C) Granule cell dendrites are able to carry calcium spikes (via T-type channels) and sodium spikes (through fast sodium channels) both forward and backward. The propagation and integration properties of granule cells are mainly under the control of A-type potassium channels.

do not require somatic action potentials, provide a graded inhibition (Fig. 2B). Third, the synaptic activation of the granule cell spines may be strong enough to propagate to the soma and to elicit a somatic action potential that might backpropagate through the entire dendritic tree and releasing GABA from hundreds of granule cell spines [77–79]. This represents a *global lateral inhibition* (Fig. 2C). Finally, granule cells may receive excitatory inputs on their proximal dendrites from relay neuron collaterals [9,75], thus providing a *feedforward inhibition* [for more details see Urban and Egger, this issue].

The numerous effects of granule cell inhibition on a relay neuron depend on both the location and strength of the inhibitory input, and its impact on local signaling processes. Reciprocal synapses are widely distributed over the soma, the apical and lateral dendrites, and the axonal hillock and initial segment [10,80–83]. A synapse located on the initial segment could shift the site of spike initiation up to the apical dendrite or could completely block somatic spike output [84]. GABAergic synapses located on the lateral dendrite might also block action potential initiation depending on their distance from the soma and the level of shunting current needed to control action potential propagation. In this case, lateral inhibition relies on bidirectional signaling. The lateral dendrite of the relay neuron transmits excitatory outputs from the soma in the form of centrifugally back-propagating action potentials and receives GABAergic inputs centripetally conducted to the soma.

As lateral dendrites have large projection fields and extensive reciprocal connections with interneurons, dendrodendritic interactions provide both a fast and graded feedback inhibition as well as a unique mechanism for lateral inhibition between relay neurons innervating different glomeruli [69,70,85–88]. Consequently, it has been shown that bulbar projecting neurons that are connected to different glomerular units and respond to a wide range of related odor molecules also receive inhibitory inputs from neighboring glomerular units via lateral inhibition at dendrodendritic connections [3,20]. According to this principle, lateral connections enhance contrast and therefore improve discrimination and learning of similar odors.

It is also worth noting that in virtually all models of the OB, lateral inhibition plays a dominant role in establishing spatiotemporal dynamics (e.g., [28,89]). Electrophysiological studies have provided further experimental supports to these models [90–92]. We now focus this review on the critical function specifically played by granule cells in generating fast gamma oscillations.

5. Microcircuits generating gamma oscillations

In the OB, odor-evoked gamma oscillations arise when the relay neurons are depolarized due to sensory neurons activity. This is supported by the temporal relationship between theta oscillations and relay neuron depolarization [93,94] and between the occurrence of theta and gamma oscillations in vivo [95]. In OB slices, oscillations and relay neuron depolarization are clearly correlated [91]. A single stimulation of the sensory afferent inputs causes long-lasting oscillations of up to three seconds [91]. Such a prolonged network activity may result from numerous intrinsic and synaptic factors including: (i) the amplification

of olfactory nerve inputs occurring in the glomerular layer by recurrent excitation [96] and excitation between neighboring relay neurons [51,97–99]; (ii) lateral interglomerular excitation between neighboring relay neurons in the external plexiform layer [100,101]; (iii) the existence of a bi-stability in the relay neuron potentials that can prolong the duration of the initial depolarization [102]. All of these mechanisms may contribute to the maintenance of the oscillations through amplification of the inputs and prolongation of relay neuron excitation.

It is worth mentioning that for generating fast oscillations, at least three major cellular mechanisms can be postulated:

- (a) *Intrinsic resonant properties of relay neurons.* In the OB, relay neurons are particularly prone to voltage-dependent oscillations. Subthreshold oscillations, in the range of 15–60 Hz, are generated by a TTX-sensitive Na^+ conductance that operates within a range of voltages above and below the spike threshold [103]. These oscillations are crucial for spike timing and for integrating excitatory postsynaptic potentials [103]. This membrane resonance and subthreshold oscillations once again indicates that relay neurons are not passive relays of incoming synaptic events but rather participate in sculpting their output. The role of other voltage-dependent conductance in generating subthreshold oscillations has yet to be determined. During the gamma cycle, the magnitude of the membrane potential can change considerably. Therefore, distinct voltage-dependent conductance may be sequentially activated. This activation could exert an important effect on the firing patterns of the relay neurons. Whatever the nature of ionic channels involved, it has been suggested that the subthreshold oscillatory activity of the membrane potential may precisely control the timing of spiking activity (see [104]) and thereby provide a mechanism of synchronizing the firing patterns.
- (b) *Electrical coupling.* The presence of gap junctions between granule cells of the OB remains an open debate (see [105,106]) despite some arguments in favor of electrical coupling being functionally implicated in gamma oscillation generation [107]. By contrast, gap junctions between relay neurons projecting into the same glomerulus are now well established (Fig. 2A) [99]. This coupling is known to support the synchronization of relay neuron firing [99,108]. Yet, this remains to be demonstrated for the generation of gamma oscillations.
- (c) *Synaptic interactions.* As a canonical neural circuit consists of two major cell types – excitatory relay neurons and inhibitory local interneurons – it follows that three types of synchronization mechanisms by chemical synapses are theoretically possible: feedback inhibition through an excitatory–inhibitory loop, lateral excitation, and mutual inhibition between interneurons. Modeling approaches have suggested that the gamma rhythm in the mammalian OB [53,109] is generated by a negative feedback loop between excitatory neurons and local inhibitory interneurons. The phase relationship between unit activity and the field potential in the OB is consistent with this [60]. Granule cells appear to be the key players among the bulbar interneurons

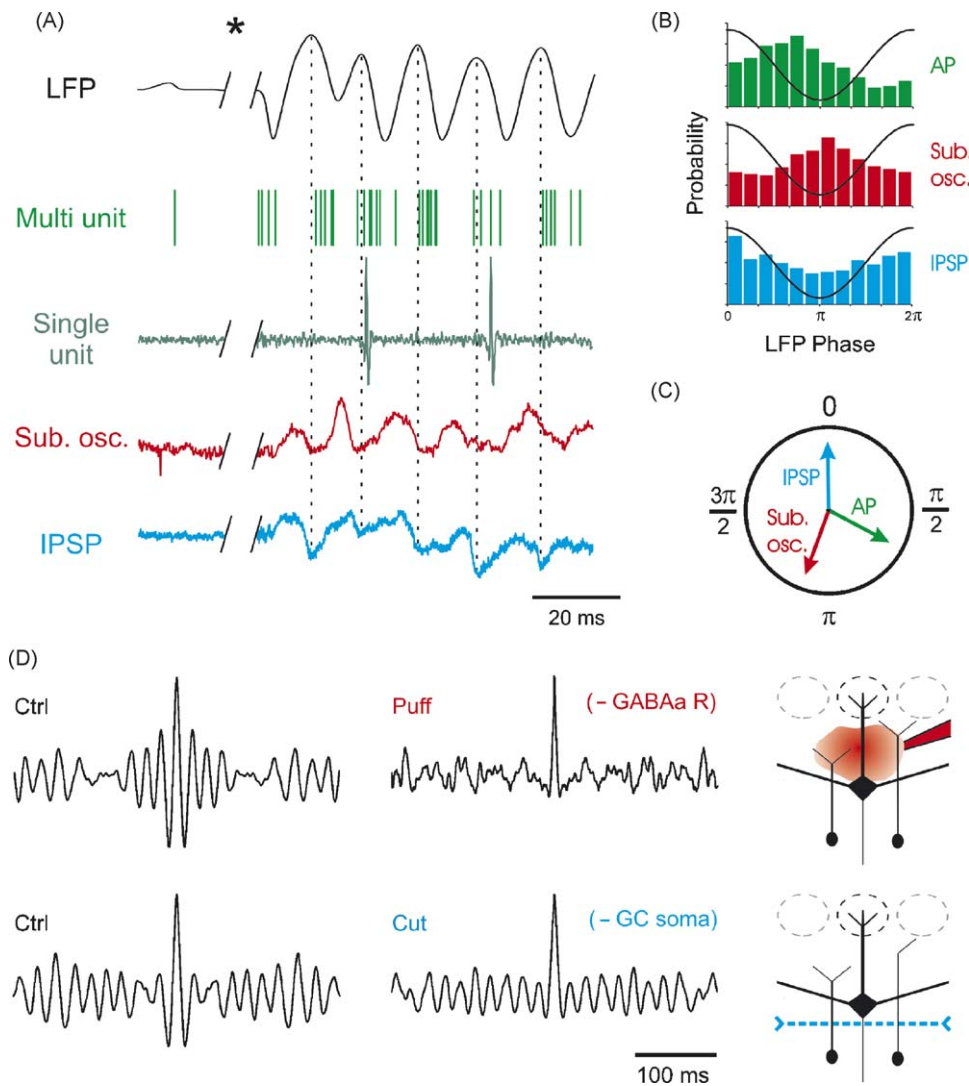


Fig. 3. Field potential fast oscillations recorded in rodent olfactory bulb slices. (A) Temporal relationship between local field potential (LFP) relay neurons activity. Relay neuron suprathreshold activity (shown here in multi- and single-unit recordings), membrane subthreshold oscillations (shown here with an intracellular recording) and inhibitory post-synaptic potentials (IPSP) they received are phase-locked with LFP oscillations. The star indicates the timing of the stimulation. (B) Summary plots of relay neurons spikes (AP, in green), subthreshold oscillations (sub. osc., in red) and IPSP (in blue) occurrence probability according to LFP (represented as a black line) phase. (C) Summary of the LFP cycle phase preference of relay neurons spikes (AP, in green), subthreshold oscillations (sub. osc., in red) and IPSP (in blue). Relay neurons spikes occur preferentially in the falling phase of the field potential oscillations, peaks of subthreshold oscillations just after the troughs of the field potential oscillations, and troughs of IPSPs on peaks of the field potential oscillations. (D) Auto-correlograms of LFP recordings in control conditions (Ctrl), after local application of a GABA_A receptor antagonist on synapses between granule cells and relay neurons (Puff) and after a section of the slice below relay neurons cell body (Cut). Note the disruption of the oscillations after the drug application and the absence of consequences after the isolation of granule cell dendritic trees.

for network synchronization. Inhibition from granule cells may arise either from parts of their dendritic tree, mediating both reciprocal and lateral inhibition, or from action potentials generated in the soma that backpropagate through the entire dendritic tree [72,79]. Experiments in which only the dendrites of granule cells remain intact have shown that somatic action potentials were not necessary for generating LFP oscillations [91] (Fig. 3D). However, the involvement of spikes generated locally in their dendrites [79] cannot be ruled out. Granule cells possess several intrinsic properties that may explain their crucial role in generating LFP oscillations. First, certain granule cells interact with relay neurons very close to their cell body. Therefore, these synapses are

more likely to control the spiking activity of the relay neurons [92] than remote synapses made by other local interneurons. Second, there are relay neuron lateral dendrites that can extend as far as one-third of the length of the OB [9], providing the long connectivity necessary for synchronizing a large population of relay neurons. This is supported by results from experiments showing that GABAergic reciprocal inhibition contributes to the synchronization of relay neuron activity [103,110] primarily through granule cell activity [91,92].

As aforementioned, lateral connections may include both lateral inhibitory coupling and also lateral excitatory coupling in

the OB. The question of the relative contribution of excitatory and inhibitory coupling mechanisms has been recently investigated using a physiologically based network model of the OB circuit combined with experimental approaches [111]. The precise synaptic organization and properties driving evoked gamma rhythms was investigated. Lateral inhibitory coupling was found to provide a strong and reliable mechanism for generating and maintaining gamma oscillations and population synchrony in the bulbar network [111]. A network coupled purely by excitation was found to oscillate slower, in the beta frequency ranges [111]. Therefore, as excitatory connections between relay neurons occur primarily within a single glomerulus, the main function of lateral excitation may be to render these functional units more homogeneous.

Finally, consistent with a primary role of the OB in olfactory discrimination and learning, several studies proposed that local interneuron connections might evolve with time. Both a model of olfactory memory [112] and a number of experimental studies (e.g., [113,114]) pointed to the plastic nature of dendrodendritic reciprocal synapses. In addition to this synaptic plasticity, adult neurogenesis, which provides the OB circuit with newborn interneurons, plays also part in the neuronal adaptation of the OB network. Therefore, the degree of synchronization among specific subsets of relay neurons might evolve through the combined action of neuromodulators, synaptic plasticity, and adult neurogenesis. This continuous adjustment may lead to changes in the strength of the temporal binding of signals originating from different odorant receptors. This might be critical not only for adjusting the level of odor discrimination but also for perceptual learning [115].

6. Adjusting synchronized oscillatory activity in the olfactory bulb network

A general physiological mechanism seems to operate within the OB during olfactory learning in different contexts and different species. This widespread mechanism relies on fine-tuning the excitatory–inhibitory balance of the OB network. Alteration in this balance has been extensively documented both in the OB and the accessory bulb in various conditions such as memory of the mating male's pheromone, olfactory learning in neonatal rats and olfactory conditioning in adult mice (reviewed in [113,114]). By highlighting the plastic nature of the dendrodendritic synaptic connections, previous studies have indicated that the degree of synchronization among specific subsets of output neurons might change according to the history of previous sensory inputs. In other words, a plastic change in the dendrodendritic synaptic interactions, triggered by a learning process, might result in a modification in the strength of temporal binding of signals originating from similar or different odorant receptors.

6.1. Modulation of the reciprocal synaptic activity by centrifugal fibers

As bulbar interneurons play a key role in inducing and maintaining oscillations, it should not be surprising that they rep-

resent the primary target of centrifugal fibers innervating the OB [116,117]. These fibers include excitatory inputs from the olfactory cortex [118] and inhibitory inputs from the nucleus of the horizontal limb of the diagonal band [119]. Therefore, not only the OB processes sensory information from the external world but it also integrates signals from centrifugal projections originated from numerous central structures [12,66].

Among the various neuronal types of bulbar circuit, the cortical feedback mainly targets the granule cells [118]. Since centrifugal input primarily arrives onto their basal dendrites [117], it is likely that it either enhances putative mutual inhibition via excitatory inputs to the granule cells or inhibits the granule cells via direct GABAergic inputs. As a consequence, the bulbar neuromodulators play important roles in emerging computational functions of synchronized oscillatory activity. For instance, interactions between central noradrenergic and cholinergic fibres with granule cells have been suggested to occur in olfactory learning-related local mechanisms of neuronal plasticity [120–125]. The spatial and temporal coincidence of centripetal sensory inputs and centrifugal afferents may be the conditions needed for triggering bulbar interneuron plasticity. In this respect, the centrifugal influences on local inhibitory interneurons might provide the contextual information required for sensory formatting of odor representations by early olfactory circuits [126].

6.2. Structural changes underlying cellular plasticity of the local inhibitory network

To ensure that the mature nervous system's control of behavior is adaptive and flexible in the face of a constantly varying environment, morphological and physiological changes are possible at all levels including molecules, spines, dendrites and axons. Remarkably, this plasticity was thought to be limited, in sensory areas, to a period in early postnatal life known as the critical period. Hubel and Wiesel, who found that the balance of input from the two eyes could be altered by restricting visual experience to one eye, discovered the cortical basis of critical period plasticity (reviewed in [127]). The capacity for the cortex to undergo this change is limited to the first few months or years of life, depending on the species. Then, this capacity vanishes during the adulthood. The discovery of neurogenesis in the adult brain has challenged this view. It confronted the sturdy assumption that adult neurons did undergo proliferation and therefore that brain structure might also be changed that way. The existence of the phenomenon being established in two central areas, the hippocampus and the OB, the important step has been to understand what triggered and inhibited it, and how it was regulated. Identifying the functional roles of these newly generated neurons in the context of the brain structure–function relationships are starting to receive new insights [128]. Below we discuss whether neurogenesis in the OB directly acts on neuronal information processing in a specific and functional manner or whether it prepares the host circuits for general experiences and increased general challenges.

6.3. Functional implications of bulbar neurogenesis

In addition to the massive regulation of interneuron activity by neuromodulators, adult neurogenesis represents another means by which the OB can make changes to its own functional circuitry. Remarkably, this cell-level renovation is not static or merely restorative; instead, neurogenesis in the adult OB constitutes an adaptive response to challenges imposed by an animal's environment and/or its internal state. It is becoming clear that newborn interneurons continue to be added to the adult circuit of the OB, yet understanding the functional meaning of this cell turnover remains a challenge [128]. The generation of new neurons in adult circuits may be part of a large repertoire of neuroadaptive responses, which adapt neuronal networks to sensory experience by continuously replacing old neurons by new ones [16]. As granule cells are the largest neuronal population in the OB [1] and as one granule cell contacts several hundreds of relay neurons, which in turn contacts many pyramidal cells from the piriform cortex, interneuron renewal occurring upstream is ideal for amplifying the neurogenic effect within the entire olfactory pathway.

One has to wonder the functional meaning of adult neurogenesis. A growing numbers of studies have already discussed important results suggesting that newborn neurons in the adult OB are vital for certain aspects of sensory performance, learning or memory [4]. They all imply a high degree of plasticity brought to adult circuits by newborn cells and the replaceable ones. Next, one might wonder whether neurogenesis acts directly on neuronal information processing in a specific manner, or whether it prepares host circuits for general experiences and increased general challenges [129]. Exploring the functional differences between new cell generation in the developing and in the mature OB might be helpful to sketch concepts about the functional consequences of adult neurogenesis [130].

One of the major functions of adult neurogenesis may be to bring plasticity to mature pre-existing networks. Sensory deprivation has recently been shown to drastically decrease the number, dendritic length and spine density of newborn granule cells [131]. These effects contrast with the lack of morphological changes occurring in pre-existing granule cells. A cohort of newborn granule cells allows therefore the OB circuit to continuously cope with novel sensory experiences. In line with this, it is worth noting that bulbar neurogenesis occurs in a neuronal network in which sensory afferents are also subjected to continuous replacement. Indeed, mature olfactory sensory neurons have only a limited life span – about 90 days in rodents – and this rate is tightly regulated by environmental factors. One could speculate that bulbar neurogenesis could represent a mechanism by which the processing of sensory information in the brain could be adjusted in response to ever-changing sensory afferents. This could happen even if the morphology of the apical arborization of relay neurons, which receive sensory afferents is not affected by their renewal. More experiments are needed to clearly establish whether neurogenesis of sensory neurons and bulbar neurogenesis are tightly correlated, and whether the generation of new olfactory sensory neurons influence changes in bulbar circuits.

Postdevelopmental neurogenesis in the OB is conserved across evolutionary boundaries from crustaceans to higher vertebrates including primates and humans. Since bulbar neurogenesis is a rather conserved biological phenomenon, its adaptive functions deserve to be explored. However, most of the studies have as yet focused on the physiological processes underlying adult neurogenesis and, except for the seminal papers by Nottebohm and his group in song birds [132], very few experiments have addressed the question of its adaptive role. According to the common view, new neurons produced in mammals are beneficial. One must ask therefore what could be the advantages of this late neurogenesis in term of fitness. A first glance at the evolutionary scale reveals that the degree of late neurogenesis rather decreased with increase brain complexity. It is worth mentioning that adult neurogenesis in lower vertebrates, such as lizards, provides *additional supply* of neurons and can regenerate entire brain parts. In contrast, mammalian neurogenesis is restricted to a few regions only where it provides neuronal *replacement*. It seems therefore that they might be a trade-off between benefits accrued from newborn neurons and the problems they generate for the network circuit into which they integrate. Obviously, understanding the balance between the functional benefits and the deleterious effects becomes a central issue today for better understanding of how neurophysiological computations are continuously adjusted in the adult OB.

7. Concluding remarks

Relay neurons of the mammalian OB circuit readily synchronize their firing and generate gamma oscillations in response to olfactory nerve inputs. Due to its basic architecture and its synaptic organization, the local inhibitory network provides the OB with a unique form of inhibition that can induce and maintain gamma oscillations. This inhibitory function results from the unique GABA release mechanism by granule cells, which provides lateral inhibitory coupling between neighboring relay neurons. Therefore, GABAergic interneurons both synchronize relay neuron outputs and distribute the information within the bulbar circuitry, allowing relay neuron responses to be enhanced through lateral inhibition.

We conclude therefore that granule cells operate as transducers, transforming the spatial dimension of the sensory information reaching the OB into more complex spatio-temporal patterns. The continuous integration of new GABAergic interneurons and elimination of other ones, together with the action of neuromodulators, bring a unique degree of circuit adaptation based on the fine-tuning of lateral inhibitory coupling into the operational bulbar network.

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