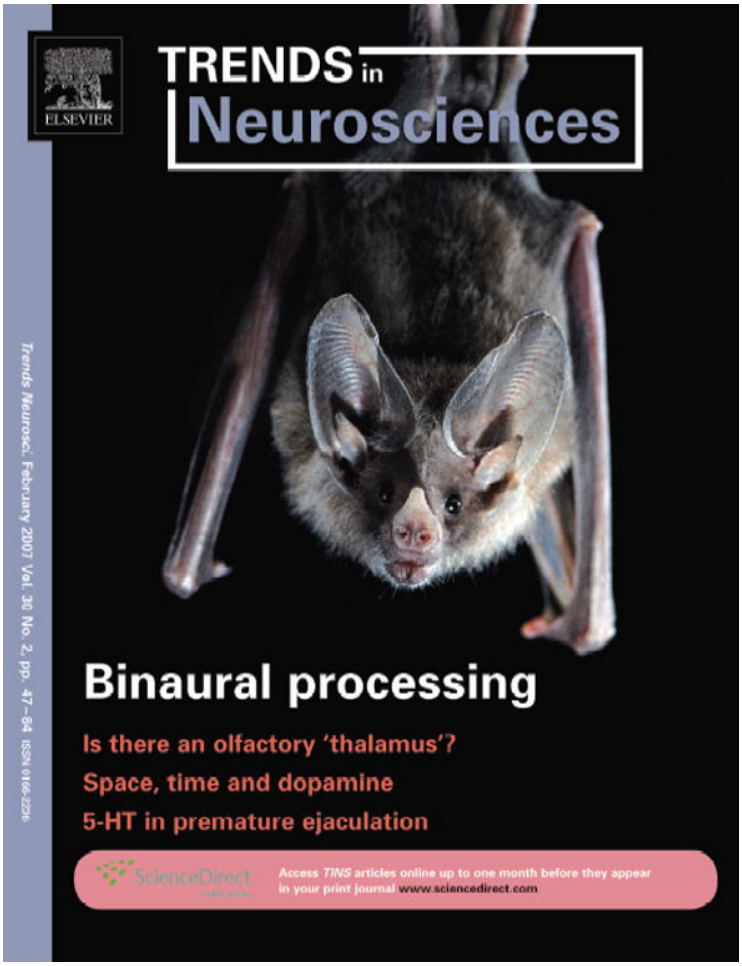

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An argument for an olfactory thalamus

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The mammalian olfactory system is unique in that sensory receptors synapse directly into the olfactory bulb of the forebrain without the thalamic relay that is common to all other sensory pathways. We argue that the olfactory bulb has an equivalent role to the thalamus, because the two regions have very similar structures and functions. Both the thalamus and the olfactory bulb are the final stage in sensory processing before reaching target cortical regions, at which there is a massive increase in neuron and synapse numbers. Thus, both structures act as a bottleneck that is a target for various modulatory inputs, and this arrangement enables efficient control of information flow before cortical processing occurs.

Introduction

In mammals, the central organization of the olfactory system differs from that of other sensory systems chiefly in regards to the thalamus: in the processing stage leading to the cortex, all other systems have a requisite thalamic relay, whereas olfactory information is sent to cortex without such a relay station. Another difference is that other sensory systems initially involve the neocortex, whereas the first cortical processing for olfaction is in paleocortex (including the olfactory bulb, anterior olfactory nucleus and piriform cortex). By the time olfactory information reaches neocortex, it does seem to be relayed via the thalamus, mostly via the medial dorsal nucleus.

The olfactory bulb has been labeled both as a 'retina' and as 'primary olfactory cortex', because of its intrinsic circuitry and its early cortical stage in olfactory processing, respectively [1–3]. We claim that the olfactory bulb is not a retina, owing to the presence of cortical and brainstem modulatory input to the bulb, which is absent in the mammalian retina. We also claim that it is not primary olfactory cortex; that role is better ascribed to the anterior olfactory nucleus. We recognize that other levels of sensory processing (e.g. spinal cord and brainstem) are subject to modulatory and feedback influences, but only the thalamus and the olfactory bulb represent the final, bottleneck stage of processing before the cortex. We argue that there is great value in having a thalamic relay, and that the olfactory bulb is the functional equivalent of an early thalamic relay. That is not to say that the olfactory bulb is precisely identical or homologous to the thalamus, with exactly matching cell and circuit properties (although many are very similar), but rather that the main functions of the thalamus are carried out by the olfactory bulb, and that this represents an example of convergent evolution.

Functions of the thalamus

In our discussion of thalamic function, we use as a model the lateral geniculate nucleus, which is the relay of retinal information to the cortex. This is a convenient model for all of the thalamus in terms of the main functions described here. For further details of the functional organization of the lateral geniculate nucleus specifically and the thalamus more generally, see Refs [4,5].

A major function of thalamus is to control the flow of information as a final common processing stage before the cortex. In the lateral geniculate nucleus, thalamic circuitry can control retinogeniculate gain, limiting the extent of information relayed; it can also affect the saliency of information by altering the firing mode between burst and tonic, and undoubtedly other forms of modulation remain to be elucidated. Important to its function is the fact that the thalamus represents a final anatomical bottleneck before the cortex. For example, there are ~1 000 000 relay cells in the lateral geniculate nucleus of the macaque monkey and ~160 000 000 neurons in the primary visual cortex [6], representing an increase of more than two orders of magnitude (see also Ref. [7]). It is much easier and more efficient to affect processing of all incoming sensory information at the level of thalamus before it reaches the cortex, and this is thought to be an important substrate for selective attention and vigilance.

The two main extrinsic sources of input to thalamus that modulate information flow are the cortex itself, in the form of a corticothalamic projection from layer 6, and inputs from numerous brainstem sites. In general, the corticothalamic feedback is organized to affect specific alterations in information flow that might be related to specific directed attention [8], whereas most of the brainstem inputs seem to be geared to modulate information flow more generally, for example as regards levels of arousal or sleep.

We argue below that the olfactory bulb represents many of these features of thalamus: it represents a final control of information flow as a last anatomical bottleneck before olfactory cortex is reached, and its functioning is heavily modulated by feedback from the cortex and inputs from brainstem. For the purposes of our argument, which does not rely on the thalamus being non-cortical (indeed, the thalamus and neocortex are so intimately related that they could be considered as one macroscopic functional unit), we use the term 'cortex' in olfactory areas to refer to cortical areas at higher hierarchical levels than the olfactory bulb.

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Structural and neurochemical comparison

There are gross structural similarities between the olfactory bulb and the lateral geniculate nucleus that at first attract one to the idea of similar function. Figure 1 summarizes many of the circuit features of both structures, indicating similarities and differences. For general information about this circuitry, see Refs [4,5] for the thalamus and Refs [2,9] for the olfactory bulb.

Sensory input

Sensory input in both systems is subject to amplification and attenuation at the afferent synapse. Both the olfactory bulb and the lateral geniculate nucleus receive sensory glutamatergic input onto principal neurons that project to sensory cortical areas. These neurons are mitral and tufted cells in the olfactory bulb and relay cells in the lateral geniculate nucleus (Figure 1). Mitral and tufted cells receive their sensory innervation within glial-ensheathed regions called glomeruli, and so do many thalamic relay cells.

Glomerular structure at the level of sensory input is a similar feature of both structures, but at a detailed functional level this similarity can be superficial. Synapses in the central nervous system typically are individually ensheathed by glial processes, and this probably limits the effect of neurotransmitter release on immediate postsynaptic structures. By contrast, a glomerulus can contain many synapses, and none has glial ensheathment; instead, the entire complex is surrounded by glial processes, suggesting that the effects of neurotransmitters within these circuits might extend beyond immediate structural targets. There is evidence for this in olfactory glomeruli [2,9]. However, a key difference is that, in olfactory bulb glomeruli, dendrites from several mitral and tufted cells are postsynaptic targets in a single glomerulus, whereas in the lateral geniculate nucleus only a single relay cell is postsynaptic.

Sensory axons also activate GABAergic interneurons that inhibit the principal neurons by activating $GABA_A$ (and possibly also $GABA_B$) receptors. In the olfactory bulb, these are periglomerular cells and other juxtaglomerular neurons; in the lateral geniculate nucleus, these are the local interneurons. In both systems, these inhibitory cells also receive inputs from sensory cortical areas: for the olfactory bulb, this is from the anterior olfactory nucleus, described by some as the most anterior part of the olfactory cortex [10]; and for the lateral geniculate nucleus, this is from layer 6 neurons in cortical area V1 [4,5]. Feedback cortical projections (Figure 1) are glutamatergic and target AMPA receptors on the interneurons. In the lateral geniculate nucleus the relay cells also receive inputs directly from descending layer 6 neurons, and these activate metabotropic and ionotropic glutamate receptors. This seems to be one major difference between the two systems, because

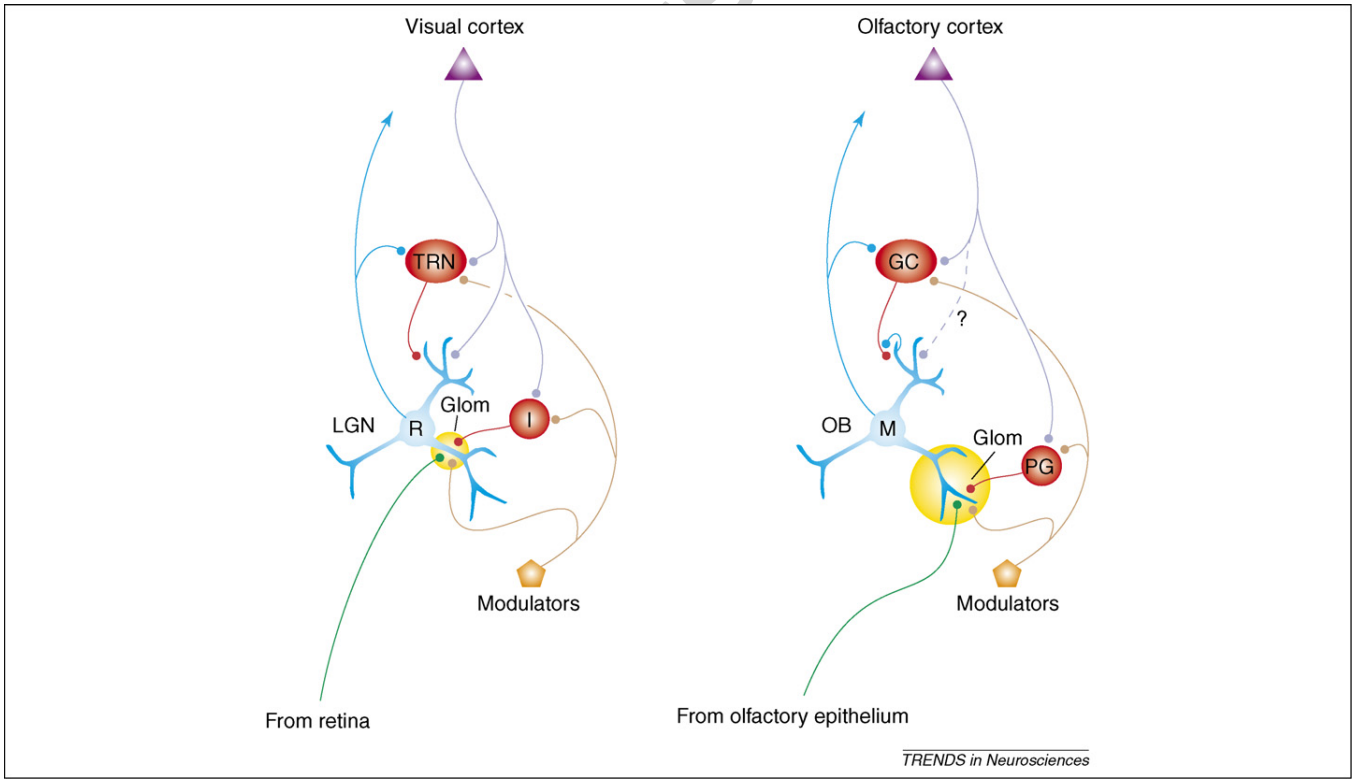

Figure 1. Structural similarities between the lateral geniculate nucleus (LGN) of the thalamus and the olfactory bulb (OB). Yellow circles signify glomerular structures (Glom). In the thalamus, these glomeruli surround individual synapses onto relay cells (R) that receive input from the retina, and in the olfactory bulb they surround the apical dendrites of ~25 mitral cells (M) that receive input from a single type of olfactory receptor neuron. Input from the anterior olfactory nucleus (described by some as being part of the olfactory cortex) directly to the mitral cells has not been shown to exist (broken line and question mark), but there are connections to the mitral cell layer in addition to the other layers of the olfactory bulb. Other structural similarities include input to the glomeruli from interneurons (I) in the visual system and from periglomerular cells (PG) in the olfactory system, and output to and input back from the thalamic reticular nucleus (TRN) in the visual system and granule cells (GC) in the granule cell layer of the olfactory bulb. Note the local reciprocal synapse between the granule cell and mitral cell. The two systems also receive input at equivalent points from higher cortical cortex and other modulatory areas. See text for details on neurotransmitters, modulators and specific synapses.

it is assumed that anterior olfactory nucleus neurons project only to GABAergic interneurons. However, there is no evidence that these axons do not synapse onto mitral and tufted cells, and portions of the anterior olfactory nucleus project to all layers of the olfactory bulb [10], whereas other cortical projections seem to be restricted to the granule cell layer.

Projections to primary sensory cortex

We have just described the bottleneck architecture of lateral geniculate nucleus projections to primary visual cortex, which produce a divergence from the smaller number of thalamic relay neurons to 2–3 orders of magnitude more neurons in primary visual cortex [7]. This anatomical feature of the sensory thalamus provides an efficient mechanism for total control over all incoming sensory information before it reaches the cortex. Although the numbers of neurons in the anterior olfactory nucleus and piriform cortex have not been quantified, the size of these cortical areas suggests that they contain at least an order of magnitude more neurons than the olfactory bulb.

Inhibitory modulation of sensory relays

The olfactory bulb contains a large population of inhibitory neurons deep to the mitral cell layer (Figure 1). These axonless interneurons (granule cells) are GABAergic and have reciprocal dendrodendritic synapses with mitral cell lateral dendrites outside of the glomeruli in the external plexiform layer; they inhibit the mitral cells via $GABA_A$ receptors and receive excitation at the same synapse via AMPA and NMDA receptors. Granule cells can provide inhibition over very small distances and even have local inhibitory effects within a single dendrite [11]. Their effects can also be wide, because they synapse onto the long lateral dendrites of multiple mitral cells. Granule cells do not receive direct input from the sensory afferent but do receive most of the synaptic input to the olfactory bulb from many cortical and subcortical regions. The densest inputs are from the anterior olfactory nucleus, considered by some to be primary olfactory cortex, and the anterior piriform cortex, which might be an olfactory association cortex [10], but other inputs come from the amygdala, posterior piriform cortex, entorhinal cortex and hippocampus.

The lateral geniculate nucleus does not have such an inhibitory cell population, but the thalamic reticular nucleus seems to have a very similar role based on anatomical relationships (Figure 1). This nucleus consists entirely of GABAergic cells that receive input from geniculate relay cells, via AMPA and NMDA receptors, and project back to these same relay cells [4,5]. This thus represents a relatively local feedback inhibitory circuit, much like the local inhibition that granule cells in the olfactory bulb accomplish through reciprocal synapses. The thalamic reticular nucleus also receives descending glutamatergic input from layer 6 neurons in visual cortical areas, similar to the type of input that the olfactory bulb granule cell layer receives from the olfactory cortex. Also, as noted in Figure 1, both GABAergic cell populations receive modulatory input from subcortical structures: granule cells are innervated by the basal forebrain, dorsal raphé nucleus and locus coeruleus, and thalamic reticular cells are innervated by various cell groups in the brainstem reticular formation.

The similarities in structure between the olfactory bulb granule cell layer and the thalamic reticular nucleus extend into finer structural and neurochemical detail. Olfactory bulb granule cells affect one another via electrical synapses [12]. Although GABAergic synapses between granule cells have been proposed in some models [13,14], there is as yet no evidence for these synapses, but GABAergic Blanes cells within the granule cell layer do form synapses with granule cells [15]. Thalamic reticular nucleus inhibitory neurons have local collaterals within the reticular nucleus and seem to have dendrodendritic synapses, which can provide recurrent inhibition [16–18]. These neurons also have electrical synapses [18,19].

More generally, the olfactory bulb and thalamus receive modulatory inputs from the brainstem and basal forebrain. GABAergic input comes into the olfactory bulb granule cell layer from the horizontal nucleus of the diagonal band in the basal forebrain [20] and to the thalamic reticular nucleus from the basal forebrain, globus pallidus, substantia nigra and pretectum [4,5]. Cholinergic input to the olfactory bulb comes from the horizontal nucleus of the diagonal band and to the thalamic reticular nucleus from the parabrachial region of the brainstem. These inputs target M_2 muscarinic ACh receptors on olfactory bulb granule cells and thalamic reticular nucleus neurons, and reduce the release of GABA in both cell populations [21–23]. Dopamine receptors also regulate GABA release and postsynaptic inhibition in both olfactory bulb granule cells and thalamic reticular neurons [24,25]. Dopaminergic input to the granule cell layer from the ventral tegmentum has been described in sheep but has not in rodents [26]. We still lack detail concerning the origin or neuronal targets of dopaminergic projections in the thalamus [5] (see also Ref. [27]). Both the olfactory bulb and thalamus receive noradrenergic and serotonergic fibers, from the locus coeruleus and dorsal raphé nucleus, respectively.

Physiological and functional comparison

Gain control and contrast enhancement

In both systems, there are multiple mechanisms that can be interpreted as gain control of the incoming sensory signals. One predominant mechanism is GABA-mediated inhibition of the principal neurons, with dual GABAergic inputs in both cases: periglomerular and granule cells for the olfactory bulb and interneurons and thalamic reticular cells for the lateral geniculate nucleus. There are also cortical feedback projections onto these GABAergic cell groups.

Additional gain control mechanisms operate presynaptically on sensory nerve terminals and postsynaptically on local interneurons. Both the olfactory nerve and retinal terminals express $GABA_B$ and D_2 dopamine receptors, which decrease the amount of glutamate released by sensory axons [28–31]. In the olfactory bulb, both GABA and dopamine are released by postsynaptic periglomerular cells. A complementary cholinergic mechanism might amplify sensory input within olfactory bulb and lateral geniculate nucleus glomeruli. Activation of M_2 receptors on periglomerular cells and lateral geniculate

interneurons decreases GABA release onto mitral cells and some relay cells [21,23,32]. Noradrenergic inputs from the locus coeruleus to α_1-adrenoceptors on principal neurons increase responses of mitral cells and relay neurons to weak inputs [33,34].

One way in which the olfactory bulb is like the retina concerns contrast enhancement within bulbar circuits. Lateral inhibition has been proposed by some as a mechanism of contrast enhancement, in which activated mitral and tufted cells suppress spatially adjacent cells via the GABAergic granule cells [35,36] (but see also Refs [37,38]). Lateral inhibition as a means of contrast enhancement is not restricted to the retina but is also apparent in the lateral geniculate nucleus [39,40].

Oscillatory processes

The olfactory bulb produces low-frequency respiratory-linked oscillations that can come under the influence of central cortical and brainstem areas [41,42]. Theta oscillations (4–12 Hz in rodents) might also represent arousal mechanisms within the olfactory system similar to arousal states in thalamocortical systems [43,44]. High-frequency oscillations are a signature of olfactory bulb responses to odors [45], and the circuitry involved is relatively well-described. Gamma oscillations (~70 Hz in rats and mice) have been shown by many researchers to arise from the reciprocal synapse between mitral and granule cells [46–48]. Removing fast oscillatory coupling in the analogous insect system impairs fine odor discrimination [49], and increasing oscillatory coupling in mice enhances fine odor discrimination [50], suggesting that fast oscillatory coordination among principal cell populations is important for close attention to sensory details. These fast oscillations are the focus of several olfactory coding models that utilize temporal precision in firing patterns as a feature of odor representations [51–53]. Similar oscillations have been noted in the thalamus, where fast oscillations (30–40 Hz) are coherent between thalamic nuclei and also between thalamic nuclei and neocortical areas in intact waking and sleeping animals [54,55], but there is as yet little information on the role of these oscillations in sensory processing.

Multiple lines of evidence suggest that the inhibitory networks of the olfactory bulb granule cells and thalamic reticular nucleus neurons are necessary to maintain fast oscillations [56]. The two systems might have similar mechanisms for adjusting the fine temporal structure of relay or mitral cell firing associated with fast oscillations. Loss of inhibitory drive to these inhibitory populations enhances fast oscillations significantly in both systems [50,57], suggesting that inhibitory drive to these GABAergic cells regulates the fine temporal firing patterns of principal neurons in both structures.

Attention-related changes

Lateral geniculate relay cells show characteristic burst and tonic modes, with the burst mode more common in sleep and inattentive states and tonic mode dominating in alert and attentive states [58]. Burst mode is associated with a greater signal-to-noise ratio and stronger cortical activation, and has been suggested to serve as a 'wake-up call' to the cortex that something has changed in the environment, eventually causing a switch to tonic mode for more faithful and linear relay of information [58]. These two modes depend on voltage-dependent intrinsic membrane conductances that are based on T-type Ca^{2+} channels and related to different depolarization states, with the tonic mode occurring in the depolarized state (e.g. roughly −65 mV or more depolarized) and burst mode in the hyperpolarized state (e.g. roughly −75 mV or more hyperpolarized). The transition from burst to tonic mode is facilitated by activation of metabotropic glutamate (mGlu) receptors and M_1 muscarinic ACh receptors on relay cells [59], and from tonic to burst mode by $GABA_B$ and possibly M_2 receptors [60,61].

In the olfactory bulb, most mitral and tufted cells respond with a burst of a few spikes upon inhalation when rats are breathing slowly (1–4 Hz) or during exploratory behavior (5–6 Hz) [62]. However, when rats attend to an odorant in a discrimination task, they sniff at high rates (6–12 Hz) [63], and mitral and tufted cells fire in tonic mode [62]. In anesthetized mice, during artificial higher-frequency respiration (~5 Hz), imaged glomeruli also lose most of their respiratory modulation [64]. The tonic attentive response is often discarded by researchers in favor of the more quantifiable burst firing mode during later periods of long odor exposures, which is associated with odor habituation [65].

Mitral cell burst firing might be supported by intrinsic and circuit properties. Bursting mitral cells show sustained depolarization in response to sensory nerve input, which might define the duration of a burst cycle [66]. One report showed that two-thirds of the mitral cells that were tested had intrinsic up states (more depolarized and near the threshold for spike generation) and down states (more hyperpolarized, no spiking) that were ~10 mV apart [67]. Metabotropic glutamate receptors on mitral cell dendrites are activated by sensory input and can modulate the up and down states of these cells and the duration of bursts [68].

No published reports have proposed a mechanism for the switch between burst and tonic firing of mitral cells, but several converging studies point at three possible sources: (i) the beginning of fast sniffing in odor-discrimination behavior coincides with entorhinal input to, and hippocampal coupling with, the olfactory bulb [42,69]; (ii) blocking K^+ currents that are sensitive to 4-aminopyridine (4-AP) transfers mitral cells to tonic firing mode in a slice preparation [70]; and (iii) sensory input frequency can change the firing mode, because mitral cells in slices uncouple from stimulation when the drive exceeds 8 Hz [66].

Despite the similarities in burst and tonic modes between thalamic relay neurons and mitral and tufted cells, there might be important differences. In the case of thalamic relay cells, the burst mode transmits the presence of a stimulus but does not convey precise information about the stimulus, which is transmitted in tonic mode as a linear representation of the stimulus [58]. Burst firing in olfactory bulb slices shows precise responses to electrical stimulation, whereas the tonic mode produces a less precise coupling of the firing pattern to the artificial

stimulation pattern [70]. Anterior piriform cortex pyramidal cells show state-dependent increases in sensory responses in urethane-anesthetized rats during neocortical fast wave states [71], similar to visual cortex neurons during relay cell tonic firing states. However, we still know relatively little about the temporal structure of mitral cell responses to odorants during attentive fast sniffing, making it difficult to evaluate precision in naturalistic situations. This should be the focus of future studies of olfactory bulb and olfactory cortex unit activity in behaving animals.

Summary

The similarities of these two systems suggest some general principles for sensory processing. Perhaps the most important similarity is that both the olfactory bulb and the thalamus represent a final stage of sensory processing before a major expansion into cortical tissue (Figure 2). This bottleneck in both cases is under modulatory control both of feedback from cortical targets and from other subcortical structures. This similarity as a final processing step exists even though sensory receptors innervate the olfactory bulb directly, whereas the thalamus represents a later stage in sensory processing. However, as shown in Figure 2, the extent of prethalamic processing varies widely between thalamic nuclei. For example, the lateral geniculate nucleus is innervated by retinal ganglion cells, which represent the result of considerable retinal processing, and the ventral posterior lateral nucleus is innervated by cells of the dorsal column nuclei, which are innervated by primary sensory afferents to the spinal cord (Figure 2).

At the olfactory bulb glomeruli and lateral geniculate nucleus, sensory signals of a common origin are grouped together, and the signal is amplified or attenuated by presynaptic action on sensory axons and other glomerular and interneuronal mechanisms. The second stage of this processing is driven by a large inhibitory population that does not receive direct sensory input (granule cells and thalamic reticular nucleus neurons). These neurons can coordinate activity that is associated with a common group of stimuli by inhibitory processes that might be involved in contrast enhancement and oscillatory coupling. These inhibitory structures receive synaptic and modulatory input from higher sensory areas and brainstem and basal forebrain areas, which can increase or decrease the amount and possibly precision of inhibitory drive to the principal neuron population. GABAergic circuits are common throughout the brain, and it is not clear whether there is anything unique about these circuits in the olfactory bulb or thalamus, but the point is that very similar GABAergic circuits do exist in thalamus and the olfactory bulb.

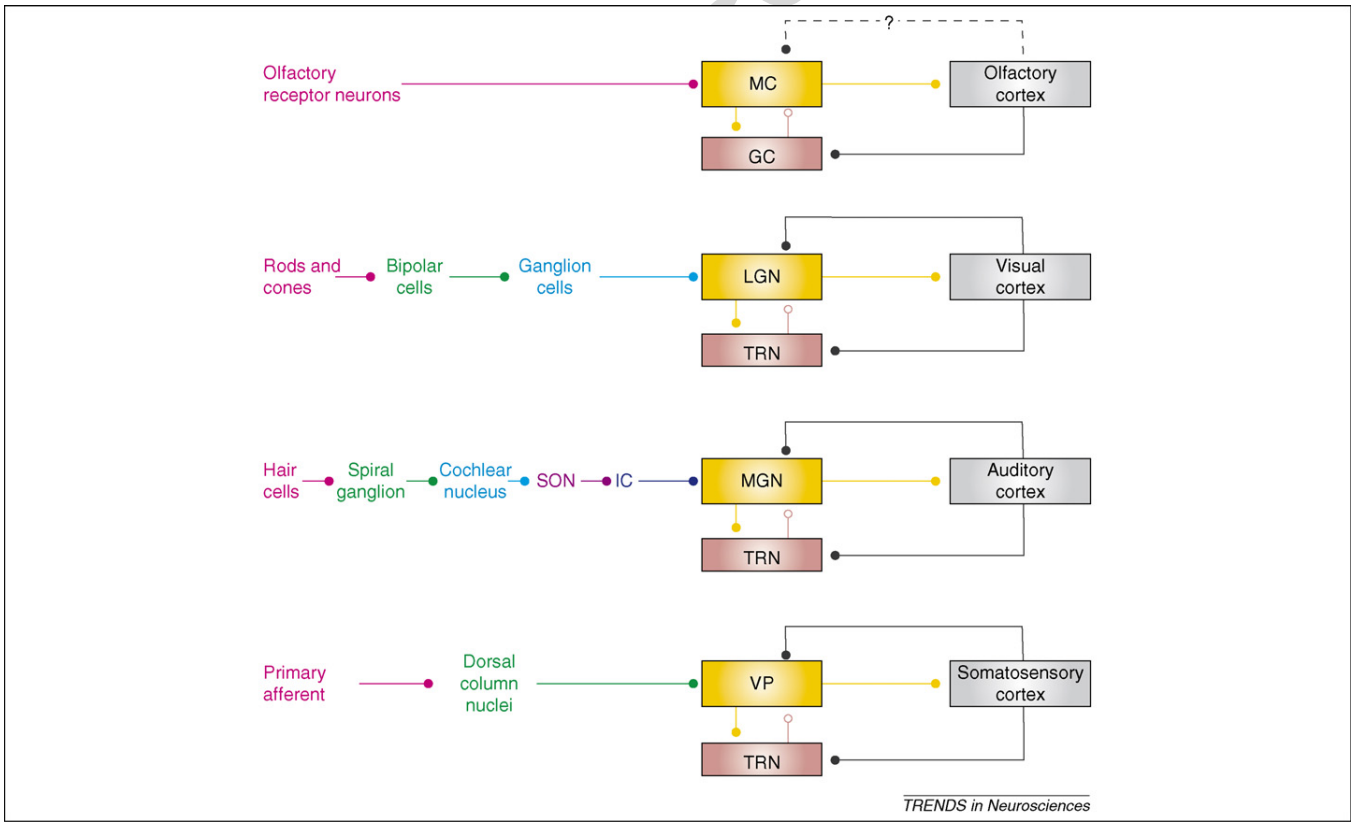

Figure 2. Sensory pathways through the thalamus for visual, auditory and somatosensory systems compared with the olfactory pathway. All four systems involve detection of sensory stimuli by primary receptors; the sensory systems then have a different number of processing steps, but all feature a circuit between two nuclei (shown in yellow and pink boxes) as a final stage before the cortex. In the olfactory system, these areas are cells in the mitral cell layer (MC) and granule cell layer (GC) of the olfactory bulb; in the other three systems shown the thalamic reticular nucleus (TRN) forms a circuit with the lateral geniculate nucleus (LGN; visual system), the medial geniculate nucleus (MGN; auditory system) and the ventral posterior nucleus (VP; somatosensory system). Filled circles are excitatory connections; open circles are inhibitory. The broken line and question mark indicate that a direct connection from the olfactory cortex (anterior olfactory nucleus) to mitral cells has not yet been demonstrated. Many of the prethalamic areas receive modulatory feedback (not shown). After the thalamic relay, there is a wide divergence to sensory cortex. Additional abbreviations: IC, inferior colliculus; SON, superior olivary nucleus.

The question arises of whether one structure might have arisen from the other. It is often claimed that the olfactory system is phylogenetically older than other sensory systems. However, there is little evidence of evolutionary precedence of one structure over the other, with both the diencephalon and olfactory bulb evident in the earliest jawless vertebrates, so we speculate that these structures might have arisen independently to solve a similar problem in sensory processing. The olfactory bulb is paleocortex and part of the telencephalon, whereas the thalamus comprises a large part of the diencephalon. Thus, we expect and find many differences in the two systems, but we maintain that both serve at least the common purposes that we have spelled out here. Future studies might shed light on the evolutionary pressures that gave rise to both structures.

Future perspectives

The different trajectories in olfactory and thalamic research have led to a different pattern of successes, raising the possibility that researchers in these two fields can learn significantly from each other. We suggest several immediate predictions and questions that arise from this analogy.

The decades of research into thalamic processing of sensory signals and the physiology of relays to sensory cortex suggest that it will be extremely informative for olfactory studies to follow the mechanisms and function of burst and tonic firing modes and other attention-related processes. If tonic firing modes are useful for faithful transmission of detailed information by the thalamus, then this might also be the case in the olfactory bulb. To this end, careful attention should be paid to role of fast sniffing periods during odor discrimination and the different coding properties of mitral cells during burst and tonic firing modes.

More than half a century of research into the nature and function of oscillatory processes in vertebrate olfactory systems, and new research in the analogous insect system, could help in the interpretation of similar processes in the thalamus. We know little about the role of fast oscillations in thalamic circuits but, if the olfactory bulb analogy holds, then these oscillations might represent precision in pattern discrimination. Future studies might benefit from interventions that abolish or enhance these fast oscillations and that are coupled with sensory psychophysics, as have already been used for the olfactory system [72].

It would be beneficial for both communities to understand better the effects of excitatory feedback. A few modeling and physiology studies have approached this topic in the olfactory literature, but much more research should be done from the anatomical to behavioral levels. We make a specific prediction that the projections that have been seen from the anterior olfactory nucleus to all layers of the olfactory bulb [10] will include direct excitatory synapses onto mitral or tufted cells.

The roles and mechanisms of processes involved in arousal and attention have received intense scrutiny by researchers investigating the thalamus. Both olfactory and thalamus researchers have described neuromodulatory mechanisms that are involved in these processes, but the focus has been different for the two systems. Thus, each would benefit from the other's knowledge about noradrenaline, 5-hydroxytryptamine (serotonin), dopamine, ACh, oxytocin, histamine and other modulator systems, many of which have effects at analogous locations in both systems. Both communities would benefit from combining what is known about the role of these systems at the synaptic and cellular levels with large-scale perceptual and cognitive effects.

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