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Activity-dependent gating of lateral inhibition in the mouse olfactory bulb

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Lateral inhibition is a circuit motif found throughout the nervous system that often generates contrast enhancement and center-surround receptive fields. We investigated the functional properties of the circuits mediating lateral inhibition between olfactory bulb principal neurons (mitral cells) *in vitro*. We found that the lateral inhibition received by mitral cells is gated by postsynaptic firing, such that a minimum threshold of postsynaptic activity is required before effective lateral inhibition is recruited. This dynamic regulation allows the strength of lateral inhibition to be enhanced between cells with correlated activity. Simulations show that this regulation of lateral inhibition causes decorrelation of mitral cell activity that is evoked by similar stimuli, even when stimuli have no clear spatial structure. These results show that this previously unknown mechanism for specifying lateral inhibitory connections allows functional inhibitory connectivity to be dynamically remapped to relevant populations of neurons.

Lateral inhibitory circuits are known to enhance contrast, facilitate discrimination of similar stimuli and mediate competitive interactions between active neurons[1,2]. These properties are the results of reductions in the degree to which input-driven activity is correlated across neurons responding to stimuli[3]. However, for lateral inhibition to function effectively in this manner, inhibition must be stronger between cells that are activated by similar stimuli (that is, between cells having correlated activity)[4]. When information is represented topographically, similar stimuli activate nearby neurons, so local inhibitory interactions are an effective means for contrast enhancement. This arrangement ensures that cells with correlated activity have strong inhibitory connectivity[5]. However, there are alternative strategies for specifying effective lateral inhibitory connectivity. For example, neurons with similar receptive fields can be connected specifically, independent of their proximity[6]. In this study, we investigate a third possibility, in which the strength of lateral inhibition is dynamically enhanced between neurons with correlated activity.

On the basis of the known properties of olfactory bulb circuits, we hypothesized that such a dynamic specification of inhibitory connectivity may be possible and functionally useful in the olfactory bulb[7]. At the level of olfactory receptor–neuron input to the olfactory bulb, stimuli are thought to be represented combinatorially with discontinuous topography[8–11]. Connectivity between mitral cells (the principal neurons of the olfactory bulb) lacks obvious patterning[12,13]. Single-molecule odorants activate many glomeruli that are distributed widely across the surface of the bulb. Unrelated odors can activate glomeruli in nearby areas and structural similarity of odorant molecules is often only weakly correlated with the relative position of the activated glomeruli[8,10,14,15].

Lateral inhibition in the olfactory bulb is mediated largely by reciprocal dendrodendritic synaptic connections between mitral-cell lateral dendrites and the dendrites of inhibitory granule cells[16,17]. Mitral-cell dendritic trees are radially symmetric, spanning an area up to 2 mm in diameter, connecting (disynaptically via the granule cells) a single mitral cell with as many as half of all the other mitral cells in the bulb[18,19]. These lateral dendrites release glutamate that depolarizes granule cell dendrites, which in turn release GABA back onto the presynaptic mitral cell (recurrent inhibition), as well as onto other mitral cells (lateral inhibition)[17]. The same population of granule cell–to–mitral cell synapses mediates both recurrent and lateral inhibition[20]. This suggests that when multiple mitral cells are active, recurrent and lateral inhibition will interact because multiple mitral cells will excite overlapping populations of granule cells (see **Supplementary Figs. 1** and **2** online). Such an arrangement may allow mitral cells to regulate (via their own activity and the input they provide to granule cells) the effectiveness of the lateral inhibition that they receive. Specifically, we predicted that the output of weakly activated granule cells would be facilitated by the activity of a given mitral cell, enhancing the lateral inhibition that this cell receives, similar to what has been reported recently in cortical circuits[21]. In contrast, when granule cells are strongly active, additional input to these cells will not generate additional output.

The functional properties of inhibitory circuitry in the olfactory bulb are not well understood and the role of this circuitry in stimulus coding is controversial[22]. Here we show that the efficacy of lateral inhibition from an active mitral cell is enhanced when the postsynaptic mitral cell is also firing (that is, when the mitral cells show correlated activity). We used simulations to demonstrate that this activity-dependent

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