

Making scents out of how olfactory neurons are ordered in space

Nathan E Schoppa

Many sensory brain areas are characterized by a specific spatial organization, with neurons being ordered according to their similarity in receptive field properties. A surprising new study provides evidence that the organization of glomeruli in the olfactory bulb violates this anatomical principle, suggesting that olfaction might work by a different set of rules.

The way our mind senses the world around us depends a lot on how neurons are organized in space. For example, in the visual system, retinal ganglion cells are ordered according to the visual field, with neighboring cells being responsive to neighboring parts of the visual field. This organization, known as the retinotopic map, is believed to promote the sharpening of images through center-surround contrast enhancement¹. A similar spatial order is seen in the auditory system, where the organization of neurons by sound frequency (a tonotopic map) is believed to narrow frequency tuning. Likewise, a somatotopic map exists in the somatosensory system. For olfaction, however, the question remains as to whether there is a chemotopic map. Are neurons that prefer similar chemical odor molecules located close together in space?

In this issue, Soucy and colleagues² provide evidence that, surprisingly, there is not much of a chemotopic map, or at least certainly nothing like the order that is seen in other sensory systems. They specifically examined the positions of many of the ~2,000 glomeruli that line the outer surface of the olfactory bulb. Glomeruli are neuropil structures, ~50–100 μm in diameter, that contain both the axon terminals of olfactory receptor neurons (ORNs) arriving from the nose and dendrites of a number of neuron-types including output mitral cells. Each glomerulus receives inputs from ORNs that express only one type of odorant receptor,

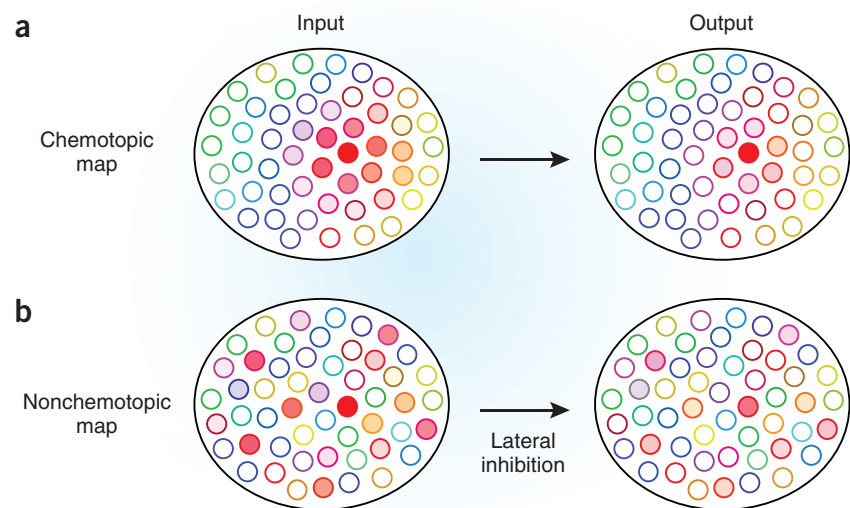


Figure 1 Effect of the lack of chemotopy on lateral inhibition during presentation of a simple odor. (a) When inputs into the olfactory bulb are ordered chemotopically, lateral inhibition generates a center-surround effect, whereby the activity of the most strongly activated glomerulus (shown as darkest red) dominates the output. In the diagram, each circle for the 'input' is meant to reflect a glomerulus specific for one odorant receptor in the nose, whereas each circle for the 'output' reflects the population of mitral cells associated with each glomerulus. Color reflects the similarity in odorant receptors and the darkness of the filled-coloring reflects the degree of activation. (b) In the absence of chemotopy, lateral inhibition causes a more uniform reduction in activity across all glomeruli, including the most strongly active glomerulus.

and hence the population of glomeruli across the bulb reflects the population of odorant receptors in the nose (typically 2 glomeruli per odorant receptor). To test for the presence of a chemotopic map, or chemotopy, the experimenters exposed rodents (mice or rats) to a battery of ~100 diverse odors and developed an odor spectrum (the pattern of responses to a range of odors) for each glomerulus. They then performed pair-wise comparisons across all tested glomeruli to address how the similarity in odor spectra

between glomeruli depended on their physical separation.

What they found was quite striking. When odor spectra similarity was plotted as a function of glomerular separation, there was a small tendency (only about 2–3% of all glomerular pairs tested) for pairs separated by less than approximately 1 mm to have more similar spectra. However, there was little evidence for a fine-scale chemotopic map. Glomeruli that were immediately adjacent to each other were not much more likely to have

The author is in the Department of Physiology and Biophysics, University of Colorado at Denver, Anschutz Medical Campus, Mail Stop 8307, P.O. Box 6511, Aurora, CO 80045 USA.
e-mail: nathan.schoppa@uchsc.edu

similar odor spectra as compared with those located several hundred microns apart.

These were not easy studies. Besides being computationally intensive, tens of thousands of glomerular pair-wise calculations were required; the experimenters had to overcome one factor that has confounded olfactory physiologists: the difficulty of controlling a chemical odor stimulus. Soucy *et al.*² sampled many odors by using a custom-made machine in which odorized air could be quickly applied and switched between odors. An additional advantage was offered by the two different optical probes that were used in their measurements of glomerular activity. One of these, called an intrinsic signal, reflects activity-dependent changes in the optical properties of tissue, probably the result of factors such as changes in hemoglobin absorption. The second probe was genetically encoded synaptopHluorin, a protein associated with synaptic vesicles that changes fluorescence as a function of activity-dependent neurotransmitter release^{3,4}. SynaptopHluorin was specifically targeted to mouse ORNs that expressed olfactory marker protein. Notably, neither of the optical probes require an exogenous indicator and thus are less susceptible to stimulus-dependent signal degradation, a factor that greatly facilitated the long experiments required for developing the complete glomerular odor spectra.

Several groups have performed similar experiments in the past^{5–8}, finding evidence for clustering of glomeruli on the basis of particular chemical features of odor molecules. This clustering, a form of chemotopy, can be seen, for example, in the positioning of glomeruli responsive to aliphatic aldehydes of different carbon chain length. Soucy *et al.*² analyzed glomerular receptive fields in a somewhat different way, examining responses to a large set of diverse odors rather than focusing on particular molecular features. Nevertheless, as they point out, the loose chemotopic map that they saw on a ~1-mm spatial scale may very well reflect the glomerular clusters that were seen previously. Their most interesting result is the near-complete absence of chemotopy at a fine scale. Soucy *et al.*² are the first, to the best of our knowledge, to systematically examine the relationship between odor response similarity and glomerular spatial separation, which is the key analysis that allowed them to test for fine-scale chemotopy.

If olfactory bulb glomeruli do not show fine-scale chemotopy, then what makes olfaction different from other sensory systems? One explanation is that olfactory

bulb processing does not depend on the spatial order of neurons; for example, the bulb might be more focused on introducing a timing component to an odorant response⁹. However, such a conclusion is inconsistent with experiments that Soucy *et al.*² report in much of the earlier part of their study, where comparisons of glomerular maps were made between olfactory bulbs of different animals. A prediction of a model in which space does not matter is that there might be substantial developmental ‘noise’ in the positioning of glomeruli. In fact, glomerular maps were found to be highly precise between animals, with deviations of only 1–2 glomerular spacings. Similarities in glomerular maps were even found when interspecies comparisons were made between rats and mice. The observed precision in the glomerular maps suggests that space does matter, even if glomeruli do not form an ordered chemotopic map on the basis of receptive field.

What might then be the implications of having a nonchemotopic order in glomeruli? Soucy *et al.*² argue that it might be important for lateral inhibition. Lateral inhibition is the circuit mechanism that underlies center-surround contrast enhancement in the visual system and there are extensive networks of GABAergic interneurons in the olfactory bulb that appear to be capable of driving lateral inhibition between different glomeruli^{10,11}. With chemotopy, lateral inhibition might do exactly what you would expect on the basis of the example of the visual system. The ‘preferred’ glomerulus, reflecting the most strongly active odorant receptor, would laterally inhibit surrounding weakly activated glomeruli, such that the output of the bulb would be dominated by the preferred glomerulus (Fig. 1). In contrast, lateral inhibition in the absence of chemotopy might cause a more uniform reduction in activity across all glomeruli. Such a mechanism, which has been shown to be at least feasible in modeling studies¹², might act as a form of gain control, preserving information about odor identity with varying odor concentration. One way of understanding the different effects of lateral inhibition in the two schemes is to assume that the strength of lateral inhibition between glomeruli is dependent on physical separation. In the case of chemotopy, the preferred glomerulus is well positioned to turn off near-neighbor weakly-activated glomeruli, whereas in the nonchemotopic situation, it is not. Because weakly active glomeruli are less inhibited, they can in turn inhibit the preferred glomerulus, thus leading to a more uniform activity reduction.

Lateral inhibition is, of course, only one of many functional possibilities to consider when searching for the meaning of a nonchemotopic map, although it should be pointed out that there are other independent lines of evidence that support the notion that lateral inhibition in the bulb functions in a somewhat atypical fashion. For example, two studies examining the spatial relationship between active mitral cells and active glomeruli during odor-evoked responses^{13,14} found that the sphere of influence onto mitral cells was quite dispersed. Mitral cells were not substantially more influenced by nearby glomeruli, as might be expected if lateral inhibition were operating on a local scale, as in the visual system.

There are, of course, other unresolved issues that will need to be tackled in the future, in addition to trying to understand the effect of lateral inhibition. For example, the just-described gain-control mechanism suggests one possible advantage of having no fine-scale chemotopy in the bulb, yet it does not at all explain the animal-to-animal precision in the spatial glomerular maps, which implies that glomeruli need to be ‘unordered’ in a very specific way. In addition, there remains the issue of contrast enhancement. A previous study¹⁵ showed more than a decade ago that the olfactory bulb circuitry can introduce a form of olfactory contrast enhancement, making neurons more finely tuned to specific odors. If local lateral inhibitory mechanisms are unable to mediate contrast enhancement in the bulb, owing to the lack of fine-scale chemotopy, what are possible alternate mechanisms?

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