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REVIEW ARTICLE

Processing of Odor Mixtures in the Mammalian Olfactory System

Venkatesh N. Murthy[1] and Dan Rokni[2]*

Abstract | Animals rarely encounter odors in isolation, and their olfactory systems generally operate in the context of complex mixtures of odorants. Individual objects typically emit a multitude of volatile chemicals that become their signature for identification. In addition, chemicals emitted from multiple objects mix in the air before reaching the nose. There is great interest, therefore, in understanding how mixtures are processed by the olfactory system to allow perceiving objects and segregating them from background odors. Studies comparing the neural responses to single odorants and their mixtures show that it is often not easy to predict the mixture response from the components, suggesting that cross-odorant interactions take place at multiple levels of the mammalian olfactory system. Experiments that relate cross-odorant interactions to perception may elucidate how mixture processing underlies object identification and background segregation.

1 Introduction

Natural objects typically emit many volatile chemicals that are detected by olfactory receptors . [18, 22, 53, 67] Moreover, objects are never in isolation—natural environments contain odors from many sources simultaneously. Our understanding of olfactory processing is, therefore, crucially reliant on understanding the processing of odorant mixtures. Although behavioral experiments have involved mixture stimuli, much of what we know about the neural processing of odors relies on experiments in which single-isolated odorants were presented. In this manuscript, we review what is known about the processing of mixtures at the perceptual level and at three levels of the mammalian olfactory system: sensory neurons, olfactory bulb, and olfactory cortex (see also[74]).

Significant advances have been made over the last few decades in our understanding of how smells are processed by the mammalian nervous system. Encoding of external odorant stimuli occurs at the nasal epithelium by specialized sensory neurons expressing olfactory receptor proteins.[4] An odorant will typically activate a broad subset of such sensory neurons and the subsets of sensory neurons representing different odors will often be overlapping.[1, 2, 25, 34, 49] Therefore, odorants may already interact at the level of sensory neurons. The encoded information is projected in an orderly fashion to the olfactory bulb, where axons of sensory neurons expressing the same olfactory receptor gene converge onto individual glomeruli.[57, 76] Basic universal transformations are thought to take place in the olfactory bulb such as input normalization and decorrelation. [12, 81]. In addition, plastic changes related to perceptual learning may also occur in the OB.[16,35, 82,84] Although the olfactory bulb principal neurons—mitral and tufted cells—receive their excitatory inputs predominantly from a single glomerulus, inter-glomerular interactions via local inhibitory circuits within the olfactory bulb may intensify inter-odorant interactions at this level.[3, 5, 19,48, 75] Neurons within olfactory cortex receive converging inputs from olfactory bulb projections representing multiple glomeruli,[55] perhaps providing the anatomical basis for further non-linear interaction in the processing of mixtures.

2 Perception

While we can often identify the smell of different spices in a dish, each emitting many odorants, we can typically not identify the different

Olfactory receptors: Proteins that sit at the membrane of olfactory sensory neurons and have the potential to bind certain volatile chemicals. Binding is the initial step in the transduction of chemical to electrical signals in sensory neurons.

Olfactory bulb: The part of the brain receiving direct input from olfactory sensory neurons. The olfactory bulb is thought to be the site, where general purpose processing occurs before information is relayed to the deeper olfactory cortex.

Olfactory cortex: several brain areas that all receive direct input from the olfactory bulb. Many of these brain areas project back to the olfactory bulb as well as to non-olfactory brain regions.

[1] Department of Molecular and Cellular Biology, and Center for Brain Science, Harvard University, Cambridge, MA, USA. [2] Department of Medical Neurobiology, Faculty of Medicine, Hebrew University, Jerusalem, Israel.
**danr@ekmd.huji.ac.il*

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constituents of the spice itself. Presumably, this is in part, because we are "trained" with these spices in different dishes, but never really encounter the molecular components of the spice individually. This introspection-based observation has been more formally studied psychophysically. Studies in humans demonstrated that our ability to tell apart the components of a mixture is rather limited.[28, 29, 41] Particularly, striking is the fact that humans can often not even tell whether a particular smell is a mixture or not.[42] This limited ability in analyzing mixtures gave rise to the view that olfaction is primarily a synthetic sense (as opposed to analytic), in which odorant mixtures are perceive as a new emergent odor and not as the sum of individual odorant percepts.

Assessing the ability of rodents to identify the constituents of odorant mixtures is more difficult. Studies have taken two different approaches. In the first, animal subjects are first trained to associate a mixture with an outcome (reward/punishment) and are then tested on a component of the mixture. If subjects identify the component as being part of the mixture, one may expect them to act according to the learnt association. Several studies using this approach have found that subjects often treat the isolated component as an unfamiliar stimulus, although this may depend on the similarity between mixture components.[13, 36, 37, 83] Another study, using a mixture of an actual and an artificial odorant (generated by light activation of olfactory cortical neurons) for training and then tested on either the real odorants or light stimulation, found that mice did act according to the learnt association.[11] In the second approach, animal subjects are trained to detect target odorants in a structured task in which odorant mixtures are presented. They are then tested on mixtures with varying degrees of difficulty (by varying the number and composition of components). A study employing this paradigm found that following training, mice can detect and identify target odorants from mixtures with extreme accuracy.[64]

Whether the different results obtained with humans and rodents reflect a real difference in olfactory processing and behavioral ability remains to be investigated. Although rodents (and other macrosmatic mammals) rely more heavily on the sense of smell for daily functions, it is possible that with training humans may prove to have similar capabilities.

Beyond the question of whether mixture components are perceived or is the mixture perceived as an emergent whole, some studies attempted to understand how the particular perceptual features of the components relate to the perceptual features of the mixture. Can we predict what a mixture would smell like based on the smells of its components? Features of odor perception are difficult to define and studies often turn to verbal descriptors.[38, 39, 86] The extent to which verbal descriptors are adequate measures of perception is debatable.[33, 44] A more tractable feature is perceived intensity and the related detection threshold. Studies in humans have shown that the perceived intensity of a mixture of an odor pair is typically lower than the sum of the perceived intensities of the individual components.[9, 31, 43] In some cases, perceived intensity is even less than the more potent component indicating that one odorant may suppress the perception of the other.[9] Another study has considered the possibility that different mixtures may be perceived similarly if they include odorants that span a wide enough range of chemical features—something akin to the concept of 'white'.[77] The authors concluded that about 30 properly picked odorants are enough to span the required chemical feature space.

The perception of an odorant mixture may also depend on our "training" that the mixture represents an object. For instance, although two oranges will never produce the exact same concentration profile of volatile chemicals, we will easily be able to tell that they are both oranges.[71] In a recent study, Wilson and colleagues have demonstrated that this behavioral generalization is in accordance with a neuronal generalization at the piriform cortex.[6]

3 Encoding of Mixtures by Sensory Neurons

Odorants are transduced into neural signals in the nasal epithelium by sensory neurons expressing olfactory receptor proteins.[4] These are G-protein-coupled receptors that upon binding of odorants activate an intracellular cascade that ends with the opening of ionic channels that depolarize the membrane thereby eliciting action potentials. Olfactory receptor proteins are encoded by the largest known gene family with about 400 functionally expressed genes in the human genome and over a thousand in the mouse genome.[56, 61] Each sensory neuron expresses only one receptor gene that defines the set of chemicals that will activate it.[2, 58] Sensory neurons expressing different receptor proteins are activated by different, yet overlapping sets of chemicals.[1, 25, 34, 49] In the presence of an odorant mixture, a particular sensory neuron may be activated by more than one odorant. To understand mixture responses, one would want to be able to predict the responses of sensory neurons to mixtures based on their responses to the individual mixture components. Systematic investigation of how sensory neurons respond to mixtures of odorants is challenging, because chemicals do not vary continuously along any dimension—i.e., chemicals are not easily described as points in a physico-chemical space. Studies, therefore, have to rely on a (somewhat) arbitrary set of odorants to be tested. Indeed, different types of interactions have been described for different binary mixtures, ranging from inhibitory interactions—i.e., the response to the mixture is less than the response to the single components, to synergistic interactions—i.e., the response to the mixture is more than the sum of the responses to the single components.[17, 60, 65] A particularly striking mode of interaction has been described in amphibians, where odorants were shown to suppress the responses of olfactory sensory neurons to other odorants.[40, 72] To test whether all these interactions can be understood within a single framework of olfactory sensory neuron odor responses, Marasco and colleagues attempted to fit the responses to individual odorants, such that they will also fit their binary mixtures, irrespective of the specific interaction class.[50] They found that fitting is possible if one assumes that the concentration response curve of odorant receptor pairs can be described with a sigmoidal function. Currently, the molecular logic that will allow predicting how a set of odorants will interact at the sensory neuron level is unknown. It remains to be explored what are the mechanisms responsible for non-linear interactions (such as synergy and inhibition). Their existence suggests that different odorants may bind onto different sites of the receptor protein. The binding of one odorant may affect the affinity of other odorants onto other binding sites.

How prevalent are the different interaction classes? Duchamp-Viret and colleagues[17] used a set of 14 odorants and their binary mixtures and found that the most prevalent interaction is hypoadditivity, in which the response to the mixture is similar to the most effective component (a max operation). The same group later showed that only about 50% of binary mixture responses can be estimated using the single component responses and a model in which they compete for the same binding site.[65] Other studies analyzed the responses of populations of sensory neurons by imaging olfactory glomerular responses to odorants and their mixtures. Several studies using intrinsic signal imaging indicated that the glomeruli that are activated by a mixture can be predicted as the union of the glomeruli that were activated by each component.[7, 26, 47] Similar results were obtained with imaging of pH changes that reflect synaptic release from sensory neurons.[54] In a recent study, we imaged glomerular responses to mixtures in mice expressing the Ca^{++} sensor GCaMP3 in all olfactory sensory neurons. We imaged the responses to a pool of 16 odorants and to a few hundred mixtures. We found that to a large extent mixture responses could be estimated as a saturating function of the linear sum of the responses to the individual components.[52] The exact extent to which inhibitory or synergic responses occurred was hard to estimate due to the variability in the responses to individual components.

4 Encoding of Mixtures in the Olfactory Bulb

Mixture responses of the second-order olfactory neurons have been studied much more extensively in invertebrates than in mammals.[15, 59, 66, 68, 69] The principal neurons of the olfactory bulb—mitral and tufted cells—receive direct excitatory input from a single glomerulus only. Their activity, therefore, reflects primarily the activity of one olfactory receptor type[73] and is, therefore, expected to inherit its mixture interactions. However, cross-odorant interactions may be enhanced via inhibitory circuitry that receives input from multiple glomeruli.[3, 5, 19, 48, 75]

Extracellular recordings from mitral and tufted cells in mice and rats show that responses to odor mixtures are often dominated by one component.[14, 24] However, the responses to the mixtures are in many cases suppressed compared to the responses to the dominating component, a phenomenon called mixture suppression.[14] This is also true in cases, where the dominating component is the only one evoking a response. These electrophysiological studies as well as an imaging study[20] show that one can predict which mitral cells will respond to a mixture based on their responses to the mixture components; however, predicting response magnitude is more difficult as it depends on the amount of cross-odorant interactions (mixture suppression predominantly). Given the non-linear interactions at the input stage as well as in the olfactory bulb, it was surprising that a recent study indicated that mitral cell responses to mixtures were predicted by linear summation of individual responses in anesthetized rats.[27] How general this is in awake, normally breathing animals, remains to be established.

Importantly, the olfactory bulb receives input from several central brain regions including the olfactory cortex. These inputs can strongly modulate mitral and tufted cell activity primarily via inhibitory circuits,[8, 51, 62] and may affect mixture responses in a context dependent manner. Complex mixture interactions may, therefore, be introduced in awake animals via this feedback, beyond those occurring at odorant receptors.

5 Encoding of Mixtures in the Olfactory Cortex

Olfactory cortex encompasses several brain regions that differ in many aspects including cell types, local connectivity, and input and output projections.[23, 80] A unifying theme in most of these regions is that individual neurons within them seem to integrate inputs from multiple glomeruli.[55] Cortical responses to odorant mixtures can therefore be expected to be highly non-linear.

The most studied olfactory cortex is the piriform cortex, where long range connections[21,30] along with local inhibitory circuits[63] may facilitate further cross-odorant interactions. Just a handful of studies compared piriform responses to pairs of single odors and their mixtures.[32, 70, 78, 85] Both sub- and supra-linear mixture responses were reported, with sublinear summation being the more common case. In a study using 2-photon microscopy to monitor the responses of a population of piriform neurons simultaneously, some cells that responded to the individual components failed to respond to the mixture, and some cells that did not respond to either of the components responded to the mixture.[70] Therefore, even predicting which cells will respond to a mixture based on single odorant responses is not trivial.

Another region that is considered to be part of olfactory cortex is the anterior olfactory nucleus (AON). A single study comparing single odorant and mixture responses in the AON found that mixture responses in the AON often exceed the linear sum of single odorant responses.[45]

Importantly, olfactory cortex may be a site of considerable plasticity[46, 79] and responses to mixtures may strongly depend on previous experience and behavioral context. One common hypothesis is that mixture processing in piriform cortex is primarily focused on identifying odor objects that are mixtures in nature. Piriform cortex may be involved in processes of pattern completion in which generalizations are made over variations in mixture profiles emitted by a certain object and pattern separation which allows discrimination among different objects.[6, 10] It has been suggested that pyramidal cells in piriform cortex receive converging inputs from many glomeruli to allow plasticity mechanisms to strengthen the ones that combine to represent object odors.[11, 71] This kind of object oriented representation may also explain the synthetic part of olfactory mixture perception discussed above.

6 Summary

The representations of volatile chemicals in the mammalian olfactory system interact at all levels of processing from sensory neurons in the nose, to the cortex. Although heuristic and mechanistic descriptions of these interactions are beginning to emerge, how these interactions underlie the perception of complex odorant mixtures remains to be elucidated.

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Venkatesh N. Murthy is a Professor and Chair of Molecular & Cellular Biology and member of the Center for Brain Science at Harvard University. His group's research is on the algorithms and neural processing underlying odor-guided behaviors. He obtained his Ph.D from the University of Washington and did his postdoctoral work at the Salk Institute before starting his independent faculty position at Harvard University.

Dan Rokni is an Assistant Professor at the Department of Medical Neurobiology, Faculty of Medicine at the Hebrew University of Jerusalem. His research is directed to understand the neural mechanisms underlying odor perception. He obtained his Ph.D from the Hebrew University of Jerusalem and then moved for postdoctoral training with Venkatesh N. Murthy at Harvard University.