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# Getting out the caliper: Behavioral quantification of perceptual odor similarity

Tobias Ackels[1,2,*] and Andreas T. Schaefer[1,2,*]
[1]Sensory Circuits and Neurotechnology Lab, The Francis Crick Institute, London, UK
[2]Department of Neuroscience, Physiology and Pharmacology, University College, London, UK
*Correspondence: tobias.ackels@crick.ac.uk (T.A.), andreas.schaefer@crick.ac.uk (A.T.S.)
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**Rigorously quantifying perceptual similarity is essential to link sensory stimuli to neural activity and to define the dimensionality of perceptual space, which is challenging for the chemical senses in particular. Nakayama, Gerkin, and Rinberg present an efficient delayed match-to-sample behavioral paradigm that promises to provide a metric for odor similarity.**

In recent years, large-scale electrical and optical recordings from mammalian brains have become increasingly common. Together with the development of versatile methods for targeted and patterned manipulation of neural activity, this promises the opportunity to probe models of circuit function with increasing detail. To link circuit function to perception requires similarly quantitative and fine-grained analyses of psychophysics and behavior. Behavioral analysis has indeed seen several waves of quantification of increased rigor and complexity, in particular when assessing aspects such as animal movement or body postures (Mathis et al., 2018; Wiltschko et al., 2015). However, often motor movement is observed in constrained operant tasks, or, in sensory neuroscience experiments, only limited numbers of stimuli are used to challenge the brain and assess neural computation. In such situations, it is surprisingly difficult to ensure an adequately high-dimensional stimulus set (Gao et al., 2017). This is particularly the case for olfaction, where a plethora of different kinds of odorous molecules, as well as the large number of olfactory receptor genes (about 1,000 in mice), has generated a notion of a "high-dimensional" sense—yet evidence for this putative high dimensionality has been lacking (Meister, 2015).

In order to systematically and quantitatively link stimuli to neural activity, as well as to obtain a measure of dimensionality, one central approach is to quantify stimulus similarity for a large number of stimulus pairs (Meister, 2015). This, however, is notoriously difficult in olfaction as conventional behavioral paradigms such as go/no-go (GNG), two-alternative forced-choice (2-AFC), or preference tasks that aim to measure perceptual similarity are time-consuming, require large numbers of animals to obtain quantitative measures for individual stimulus pairs, or lack the quantitative rigor needed for such analysis.

In a recent paper, Rinberg and colleagues have built on their deep quantitative experience in sensory behavior and physiology (e.g., Chong et al., 2020) and developed an innovative new paradigm that promises to tackle this challenge (Nakayama et al., 2022). Their variant of an olfactory delayed match-to-sample (DMTS; Figure 1A) task (e.g., Wu et al., 2020) allowed them to assess many odor pairs (n = 276), permitting a robust psychophysical measurement of pairwise perceptual similarity (Figures 1B and 1C). In addition, it provided insight into the comparability of olfactory perceptual space across individual mice. When grouping odors by chemical class (for example, into acids and non-acids), the authors confirmed results from human psychophysics studies that found that perceptual distance between acids was significantly smaller than between different classes (Figure 1C). Thus, in this case, chemical similarity served as a reliable indicator of perceptual similarity. Varying the concentration of the odors and the order of presentation ensured that chemical similarity, rather than another factor such as perceived intensity or sequence, was the key indicator of perceptual similarity. Importantly, the measured perceptual distances were comparable between animals, symmetric (perceptual distance between odors A and B was the same as between B and A), and consistent with the triangle inequality (perceptual distance between two odors A and B was smaller or equal to the distance between odors A and C plus the distance between C and B). This suggests that perceptual distance as measured in the DMTS paradigm can be used as a mathematically proper distance metric.

Their olfactory DMTS task is a hybrid of the conventional 2-AFC and GNG assays that combines the advantages and eliminates many of the disadvantages of both classical tasks. Specifically, this new paradigm uses two water reward ports, but, in contrast to a classical 2-AFC task, animals are not forced to actively pick a reward port. They can instead passively receive a water reward after a correct no-go response. This modification makes it easier to train animals, even for challenging tasks, and allows for a higher number of stimuli to be tested with more experimental animals. Training mice on a larger number of odors, in turn, makes it possible to measure the perceptual similarity for novel odors without explicit prior training, considerably increasing experimental throughput, generalizability, and avoiding potential confounds due to overtraining on specific odor pairs. The DMTS paradigm further abolishes the performance asymmetry that comes with a GNG task, where animals tend to respond to any stimulus with default licking. Having two distinct reward ports brings

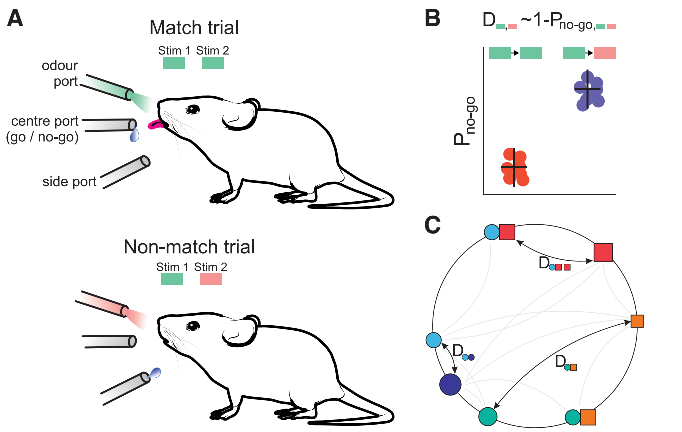


**Figure 1. Olfactory delayed match-to-sample (DMTS) paradigm used to measure perceptual similarity.**

(A) Illustration of the delayed match-to-sample task. For match trials (top), the animal can obtain a water reward from the center port. A correct response for non-match trials (bottom) is when the animal refrains from licking the center port; instead, it receives a free water reward from the side port.
(B) Normalized fraction of successful non-match trials ($P_{no\text{-}go}$) yields a measure of perceptual distance (D).
(C) Example schematic of distances between odors: perceptual distance is generally longer between odors of different chemical groups ($D_{\bullet\blacksquare}$) than for chemically similar odor pairs ($D_{\bullet\circ}$) or for binary mixtures and their component odors ($D_{\bullet\blacksquare\ \blacksquare}$)

another advantage, as both correct and incorrect go responses, as well as anticipatory licking during go trials, can be distinguished. Thus, the paradigm introduced by Nakayama et al. creates improved conditions for more efficient training and generates data in a high-throughput fashion with better interpretability compared to conventional GNG or 2-AFC assays.

In its present form, the perceptual distance DMTS task is developed for individual animals trained in a head-fixed setting, making it well suited for combination with optogenetic manipulation or physiological recordings. Applying the DMTS task systematically to increasing numbers of odors will make it possible to probe how chemical similarity maps onto perceptual similarity (and importantly where it doesn't). To reach even higher throughput, the same task and training strategy could be combined with group-housed home cage operant conditioning systems (Erskine et al., 2019). This would enable systematically defining the dimensionality of odor space for a variety of chemical classes and help build a perceptual map that could be used to measure against (and alter) neural activity in olfactory areas. Moreover, high-throughput approaches would allow the extension of the notion of "chemical space" to other stimulus features that are critical for the perception of the olfactory world. These include odor intensities or the temporal structure of odors that are thought to play a key role in the perception of the spatial structure of the environment (Ackels et al., 2021; Crimaldi et al., 2021).

Systematically determining the perceived similarities of odor stimuli using the paradigm developed by Rinberg and colleagues will substantially facilitate quantitatively linking neural activity to stimuli. Moreover, it could enable systematic identification of perceptual invariances in stimulus space that, in turn, will provide critical stimulus sets to further understand the often elusive link between the external world, neural activity and perception.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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