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Article

Lack of correlation between odor composition and neuron response in the olfactory cortex of mice

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SUMMARY

In the mammalian brain, sensory circuits are usually organized in a topographical way, meaning that, for a given brain region, neighboring neurons respond to stimuli close to each other in their sensory space. Olfaction is a notable exception to this rule; projections to the olfactory system are sparse and dispersed, leading to no apparent topography. Here, we assessed the presence of a topographical map in the mouse olfactory cortex, using a previously generated online dataset of neuronal recordings. The dataset consisted of about 1,800 olfactory cortical neurons collected from 10 mice, stimulated with a panel of 15 odorants. If there is no odor topography in the olfactory cortex, there should be no correlation between the chemical composition of odorants and their evoked neuronal response. To test this hypothesis, we first calculated odor similarity between each pair of odorants, using their chemical traits. Then, for each odor pair, we computed the similarity between their evoked neuronal responses. Finally, we assessed the relationship between odor similarity and neuronal response similarity. We found little to no correlation between the two variables (R^2 averaged across all mice tested: 0.015), which suggests the lack of topography in the murine olfactory cortex and opens new questions into what other variables might play a role in odorant distinction.

INTRODUCTION

In mammals, the olfactory system serves several overlapping functions, such as identifying edible food sources (1,2), navigating their surroundings (2,3), and social interactions (4,5). An odor's pathway through the olfactory system starts at the nostrils or nares. After being inhaled, odors reach the olfactory epithelium at the back of the nostrils. The olfactory epithelium is a tight meshwork of pseudostratified columnar epithelial tissue, olfactory receptor neurons, and supporting neural tissue. The receptor neurons transduce the chemical signal of the odorant into patterns of action potentials, which are sent into the olfactory bulb (OB) (6-8).

In the forebrain, the OB is the only relay station between the olfactory epithelium and the rest of the brain. It consists of several subunits of axonal ends of neurons, known as glomeruli (7-9). Once electrical signals reach the glomeruli, the glomeruli relay them to the olfactory cortex, where odor information is further processed. In rodents, the olfactory cortex comprises several smaller sections in the ventral region of the forebrain, including the anterior olfactory nucleus (AON), anterior piriform cortex (APC), and posterior piriform cortex (PPC) (6,7,10).

The main sensory input that the olfactory system recognizes is odorant molecules. Odorant molecules are small, volatile compounds. One odor, such as a fruit or flower, can comprise several hundred different odorant molecules (7). Despite this diversity, there is at least some degree of perceptual consistency in odor detection. Namely, odorant molecules that we perceive similarly tend to share similar functional groups. For example, molecules with a carboxyl or hydroxyl group might share a similar sour or sweet odor, respectively (11,12). Furthermore, similar-smelling odorants can also have benzene ring arrangements, suggesting this structure may play a role in odor perception (11,12).

In the sensory circuits of the nervous system, neurons that respond to similar stimuli tend to be located near each other, giving rise to sensory maps in the brain, a phenomenon also known as brain topography (13-15). For example, in the visual system, visual stimuli located near on another in the visual field are perceived by neurons nearby in the retina (16). This topographical organization is called "retinotopy". It is also found in subsequent regions of the visual system (16). Likewise, in the auditory system, similar sound frequencies elicit neuronal activity in neighboring regions of the cochlea, creating an auditory topographical map called "tonotopy" that is conserved at the first stages of sound processing in the brain (17).

The olfactory system lacks the strict topographical structure found in the visual and auditory systems. There is some resemblance to a topographical map in the OB, where certain regions preferentially respond to specific chemical groups (11,18-20). Furthermore, tracing studies have shown that the OB sends axons to the outer region of the AON, called the AON *pars externa*, in a partially topographic manner (21-23). Besides the AON *pars externa*, the topographical maps of the OB appear to be largely lost in the olfactory cortex. Projections from the OB to other regions of the olfactory cortex (including the APC, PPC, and the inner part of the AON, also known as the AON *pars principalis*) are sparse and dispersed, meaning that there is little to no apparent structure in how distinct odorants activate different neurons (6,24-32). This absence of clear structure has led to the idea that most of the olfactory cortex lacks topography (6,25,30,32). However, recent functional studies show that the commissural projections between the two sides of the olfactory system are partially organized. In the OB, neurons receiving information from a given glomerulus may communicate with their contralateral equivalent through ordered axonal projections

Odor #	Odor Name	Nb of C	Nb of O	Irritant	Ester	Aldehyde	Alkene	Methyl/Allyl/Hexyl	Ether	Arene	Ketone	Fruity	Minty	Green	Cheesy	Anisic
1	Isopropyl tiglate	8	2	1	1	0	1	0	0	0	0	0	1	0	0	0
2	Ethyl Tiglate	7	2	0	1	0	0	1	0	0	0	1	0	0	0	0
3	Propyl acetate	5	2	1	1	0	1	1	0	0	0	1	0	0	0	0
4	Isoamyl Acetate	7	2	0	1	0	0	1	0	0	0	1	0	0	0	0
5	Ethyl Valerate	7	2	0	1	0	0	1	0	0	0	1	0	0	0	0
6	Hexanal	6	1	1	0	1	0	1	0	0	0	0	0	1	0	0
7	Heptanal	7	1	1	0	1	0	1	0	0	0	0	0	1	0	0
8	Allyl Butyrate	7	2	1	1	0	0	1	0	0	0	1	0	0	0	0
9	Citronellal	10	1	1	0	1	1	0	0	0	0	0	0	0	0	0
10	Hexyl tiglate	11	2	0	1	0	1	1	0	0	0	0	0	1	0	0
11	4-allyl anisole	10	1	1	0	0	0	1	0	1	0	0	0	0	0	1
12	Isobutyl Propionate	7	2	0	1	0	0	1	0	0	0	1	0	0	0	0
13	2-heptanone	7	1	1	0	0	0	1	0	0	1	0	0	0	1	0
14	Ethyl Propionate	5	2	0	1	0	0	1	0	0	0	1	0	0	0	0
15	Eucalyptol	10	1	1	0	0	0	0	1	0	0	0	1	0	0	0

Table 1: Structural and organoleptic information from the 15 odors. For each odorant, we listed the number of carbon and oxygen atoms ("Nb of C" and "Nb of O" respectively), as well as the presence of various functional groups and organoleptic qualities. For all categories except the atom counts, 1 means that the category is "true", while 0 means "false". For example, isopropyl tiglate is an irritant and contains at least one ester function, but no aldehyde function.

(33). In the olfactory cortex, a large fraction of neurons possesses a similar ipsilateral and contralateral odor tuning, suggesting that cortical microcircuits may have at least some degree of structure (34).

Therefore, we explored a potential topographical map in the olfactory cortex, using a dataset of neuronal recordings readily available online (35). If there is no odor topography in the olfactory cortex, there should be no correlation between the chemical composition of odorants and their evoked neuronal response. To test this hypothesis, we first computed odor similarity between each pair of the 15 monomolecular odorants based on their chemical structure and perceptual qualities (for example: cheesy, minty, fruity), referred to as their organoleptic characteristics. Then we measured, for each odorant pair, the similarity between their evoked neuronal response in the olfactory cortex. Finally, we assessed the relationship between odor similarity and neuronal response similarity, to determine if the chemical structure of odorants and the location of neuronal responses were linked. We found no correlation between the two categories. This observation held for all cortical regions investigated (AON, APC, and PPC). Our analysis indicates a lack of topography in the olfactory cortex and raises new questions about the mechanisms of odor perception and perceptual continuity.

RESULTS

Our main goal was to investigate odor topography in the olfactory cortex. We asked the following question: Do odors sharing similar features stimulate the same population of cortical neurons? We addressed this question by analyzing a dataset released online in 2020 (34). The dataset contained the extracellular recordings of about 1,800 olfactory cortical neurons gathered from 10 mice, recorded either in the AON (n = 3, 384 neurons), APC (n = 4, 931 neurons), or PPC (n = 3, 505 neurons) (34). In the original dataset, the mice were stimulated with a panel of 15 monomolecular odorants, while the neuronal activity of their olfactory cortex was monitored with implanted tetrodes (34).

Odor Similarity

Our first analysis focused on the odor panel. We asked how similar the 15 monomolecular odorants were to each other and quantified the similarity between each pair of odorants. We gathered various structural and organoleptic information from the 15 odorants using public online databases (**Table 1**) (36,37). We then calculated the odor similarity for each pair of odorants, which we defined as the number of chemical and organoleptic features that they shared (**Figure 1**).

Overall, we observed a wide range of odor similarity between the odorant pairs, with values going from 6 to 15 (9.8 ± 2.4, average ± standard deviation). For example, hexanal shared more features with heptanal with an odor similarity of 14 than with isopropyl tiglate with an odor similarity of 6.

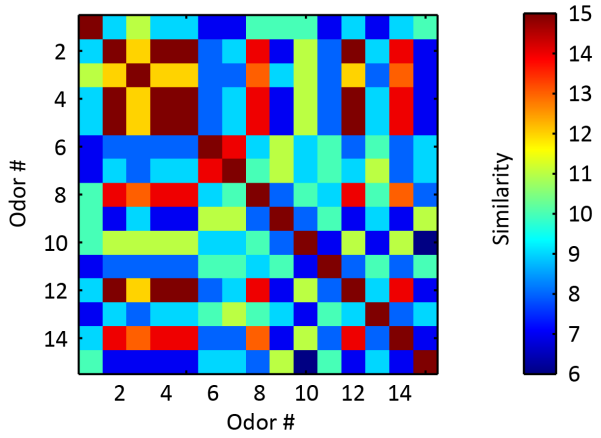

Figure 1: Odor similarity between odor pairs varies based on odor type. We calculated the odor similarity for each pair of odorants (n = 210 odorant pairs) (x- and y-axes), which we defined as the number of chemical and organoleptic features that they shared, as listed in Table 1. The higher the similarity, the more values shared. For example, odorants 4 and 2 have the same value for 15 out of 15 similarity categories, whereas odorants 1 and 2 share 9 out of 15 categories (average similarity ± SEM: 9.8 ± 0.17; similarities ranging from 6 to 15).

Some pairs, such as ethyl tiglate and ethyl valerate, showed an odor similarity of 15, meaning that they shared the same value for all the features we included in our analysis (**Figure 1**).

Neuron Response Similarity

We then asked how the response of the same neurons to different odorants compared. For each odorant pair, we performed a linear regression to compare the response of the neuron population to one odorant versus another. We used the coefficient of determination obtained from this regression to measure the neuronal response similarity (**Figure 2**). We repeated this analysis for each mouse separately.

We noted that the coefficient of determination varied widely across mice, with an average coefficient of determination ranging from 0.12 (mouse AON3) to 0.67 (mouse APC3) (**Figure 2A,B**). This variability was also observed for individual odorant pairs (**Figure 2C**).

The olfactory cortex is known to elicit partly inconsistent neuronal responses across repeats. More precisely, when the same odor is presented several times, the response of an olfactory cortical neuron to a given odor may vary greatly across repeats (34,38). If each odorant from our panel elicits a different degree of response variability, then the wide range of values that we observed in the neuronal response similarity may simply be an artifact of that response variability. To test this possibility, we computed the response variance across all seven repeats for each neuron and odorant. We then compared the distribution of variances across odorants for each cortical region (**Figure 3**). Overall, we found little to no difference in the response variance caused by the different odorants. Therefore, neuronal response variability alone could not explain the wide range of neuronal response similarity values.

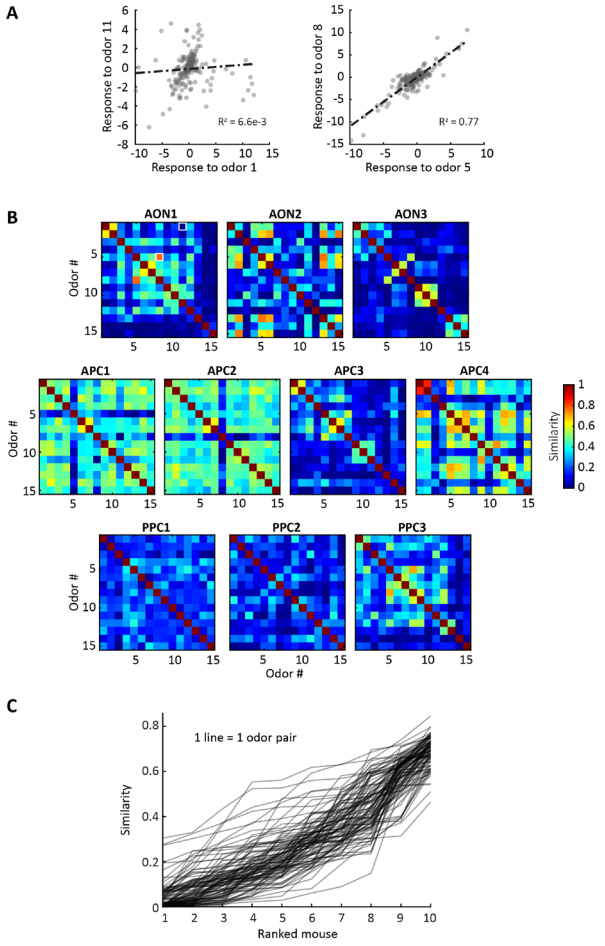

Figure 2: Neuron response similarity. (A) We computed, for each odorant pair, a linear regression to compare the response of the neuron population to one odorant versus the other. We used the coefficient of determination obtained from this regression as a measurement of the neuronal response similarity. Here we present, for mouse AON1, exemplar correlations from two different pairs of odorants. Each dot is a different neuron (n = 193 neurons; R^2 = 6.6e-3 when comparing odors 1 and 11; R^2 = 0.77 when comparing odors 5 and 8). (B) We repeated the process explained for panel (A) across all mice and all odorant pairs. Each matrix is a different mouse (n = 10 mice, 210 odorant pairs; average similarity per mouse ranging from 0.12 to 0.67). The white squares highlight the two examples shown in panel (A). (C) For each odorant pair, we sorted the similarity values calculated across all mice, from smallest to highest value. Each line is a different odorant pair (n = 210 odorant pairs). For a given odorant pair, similarity greatly varies across mice, ranging from 9.2e-7 to 0.85.

Odor Similarity Versus Neuron Response Similarity

Finally, we compared odor similarity (**Figure 1**) and neuron response similarity (**Figure 2**). To do so, we performed a linear regression of odor similarity versus neuron response similarity across all odorant pairs. We used the coefficient of determination as a proxy for similarity. We repeated this analysis for all mice and olfactory cortical regions (**Figure 4**). Overall, we found weak correlations between odor similarity and neuron response similarity. This result applied to all cortical regions and all mice (average R^2 = 0.015 ± 0.016; ranging from 3.7e-5 to 0.048) (**Figure 4**). We came to the same observation when we pooled the neuronal population from all mice for each olfactory cortical region (R^2 for the

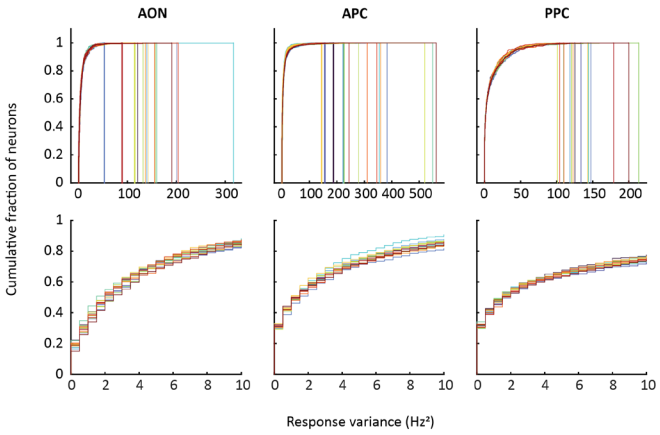

Figure 3: Odor response variance. For each neuron, each odorant, we calculated the response variance across all seven repeats. Here we display, for each cortical region, the variance across all neurons as a cumulative histogram (n = 384 neurons from the AON, 931 neurons from the APC, 505 neurons from the PPC). Each color is a different odorant. The top panels show the full range of variances, while the bottom panels present the same histograms zoomed in (variance values ranging from 0 to 561 Hz²). Overall, we find little to no visual difference in the response variances across odorants or regions.

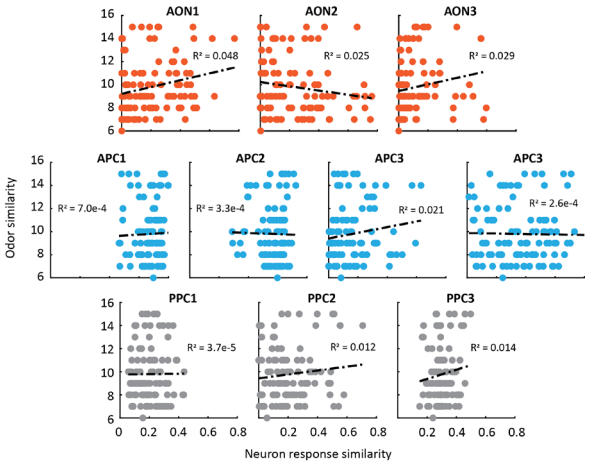

Figure 4: Odor similarity versus neuron response similarity. We compared odor similarity and neuron response similarity by performing a linear regression across all odorant pairs (n = 10 mice, 210 odorant pairs). We used the coefficient of determination as a proxy for similarity (average R^2 ± SEM across mice: 0.015 ± 0.016; values ranging from R^2 = 3.7e-5 to R^2 = 0.048).

AON = 0.023; APC = 0.022; PPC = 0.016), as well as when we pooled neurons from all mice, all regions (R^2 = 0.013). Therefore, two odorants sharing chemical or organoleptic features did not lead to them eliciting a similar pattern of neuronal activity in the olfactory cortex in this dataset.

DISCUSSION

Many mammals are capable of fine odor discrimination. For example, humans can discriminate a wide range of olfactory stimuli – the number of discriminable stimuli varies between 10,000 and one trillion depending on the study (39,40). Mice can easily solve complex "olfactory cocktail party" problems, where a target odorant is mixed with complex and variable odor mixtures (41). Dogs are capable of discriminating between "happy," "fearful," and "neutral" emotions in humans, based on the odorants present in a test subject's sweat (42). More recently, a cohort of dogs has been trained to diagnose COVID-19 from the smell of a patient's secretions (43).

It is unclear how the olfactory system reaches such a high level of odorant discrimination. Humans, for example, only express around 350 different olfactory receptors (44) – far less than the tens of thousands of odorant stimuli they can discriminate (39,40). Rather than exciting a single receptor, each odorant usually interacts with a unique combination of olfactory receptors (7,9). Therefore, we hypothesized that odorants sharing similar features would interact with similar combinations of olfactory receptors, leading to overlapping representations in the brain.

However, anatomical and functional data suggest that this hypothesis does not hold. While the OB shows some degree of olfactory topography (11,18-20), the olfactory cortex lacks this topography (6,24-32). Projections from the OB to the olfactory cortex are sparse and dispersed, apart from the AON *pars externa* (21-23), meaning that whichever topography forms in the bulb likely gets lost in the olfactory cortex, a region crucial for odorant discrimination (6,25,30,32). These sparse and dispersed projections suggest a paradox between perceptual continuity and an apparent lack of cortical topography: Odorants with similar chemical features tend to smell similar, however, their cortical representations are seemingly random. In this study, we used a readily available dataset to compare odor similarity and neuronal representation. First, for each pair of odorants from our panel, we quantified their "similarity" (i.e. how many chemical and organoleptic features they shared). Then we measured the strength of the correlation in the neuronal response to one odorant versus the other. Finally, we compared the odor similarity versus neuron response similarity. Overall, we found little correlation between these variables. In other words, it did not matter how many chemical or organoleptic features two odorants shared—they consistently elicited dissimilar patterns of neuronal activity in the olfactory cortex. Therefore, in accordance with previous anatomical and functional research, we found no apparent topography in the olfactory cortex.

While our study provides a sound approach to determining possible topographic representations in the olfactory cortex, our conclusions have limitations. First and foremost, we worked on a limited set of data. While the dataset contained more than 1,800 individual neurons recorded from 10 mice, each cortical region investigated (AON, APC, and PPC) was represented by 3 to 4 mice, and we could test 15 odorants only. Therefore, we must consider the possibility that the apparent absence of topography is due to our dataset being too small. For example, while more than 80% of all neurons contained in our dataset respond to at least one of the 15 odorants, most neurons respond to at most a few odorants (34). Ideally, this should be tested on a larger dataset, with more mice per region and more odorants.

Furthermore, while the AON, APC, and PPC are three of the largest regions of the olfactory cortex in mice, the olfactory cortex comprises of more regions, including the olfactory tubercle, entorhinal cortex, and cortical amygdala (6,7). If different regions of the olfactory cortex had been analyzed, the results might have been different.

Finally, we categorized odorants with two simple criteria: chemical composition and organoleptic features, though other criteria exist, such as the physical properties. Furthermore, various clustering methods, such as hierarchical clustering, might lend themselves to different trends (45,46). However, topography in the olfactory cortex may be based on other features, aside from chemical features. Generally, the sensory space in which the olfactory cortex projects and represents odors is not well understood (46,47) and remains an intriguing research topic (48,49). Without a clear comprehension of this sensory space, we cannot exclude the possibility that the olfactory cortex possesses topographical representations. Still, we may not be looking at its maps through the adequate sensory space.

In summary, our study provides a simple procedure to test the existence of a topographic representation in the recordings of olfactory neurons. Using a readily available dataset, we found a lack of apparent topography in three major regions of the olfactory cortex: the AON, APC, and PPC. Our results coincide with previous research, while opening new questions into what other variables might play a role in odorant discrimination.

MATERIALS AND METHODS

Neuronal Recording Dataset

The dataset used in this study (35) was made available online by the original publisher (34). Briefly, the researchers

wanted to investigate the bilateral projections across olfactory cortices. They recorded the activity of single neurons in the olfactory cortex of awake, head-fixed adult mice, while delivering various monomolecular odorants, one at a time, to the left or the right nostril. We listed the odorants in Table 1. In total, ten mice were recorded: three mice in the AON *pars principalis*, four mice in the APC, and three mice in the PPC (34).

The original dataset contains, for each mouse, each neuron, each odorant (including the solvent alone), each repetition, and each nostril (ipsilateral or contralateral to the tetrode implant), the neuronal response evoked by that odorant's presentation. Note that, in this study, we only used the neuronal responses to ipsilateral odorant presentations. The dataset was used with permission from the initial researchers.

Odor Similarity

To quantify odor similarity within our odorant panel, we first categorized each odorant based on various chemical and organoleptic criteria (**Table 1**). The chemical criteria were the number of carbon atoms, the number of oxygen atoms, as well as the presence or absence of the following functional groups: Ester, aldehyde, alkene, methyl / allyl / hexyl, ether, arene, and ketone. While the number of carbons and oxygens gave a proxy of the size of the molecule, we picked functional groups that have been hypothesized to influence odor recognition and odor topography in the OB (11). The chemical composition of the odorants was retrieved from PubChem (37).

The organoleptic criteria were the following: Fruity, minty, green, cheesy, and anisic. These categories correspond to the "odor types" used by the Good Scent Company's public database to classify odorants (36). We retrieved the organoleptic profile of the odorants from the Good Scent Company's database. We also noted whether the odorants were irritants using the same database.

In total, we considered 15 chemical and organoleptic categories (**Table 1**). For each pair of odorants, odor similarity was then defined as the number of properties for which both odorants share the same value (**Figure 1**).

Neuronal Response Similarity

For each mouse, each neuron, and each odorant, we calculated the average neuronal response using the same definition as (34):

$$average\ neuronal\ response = \frac{\sum_{repeats}[odor\ response] - \sum_{repeats}[blank\ response]}{number\ of\ repeats}$$

where *odor responses* are the neuronal responses to the seven repeats of the same odorant, while *blank responses* are the neuronal responses to the seven repeats of the solvent alone, as provided in the original database (35).

Then, for each mouse and each pair of odorants, we performed a linear regression to compare the response of the neuron population to one odorant versus the other. We used the coefficient of determination obtained from this regression as a measurement of the neuronal response similarity (**Figure 2**).

Odor Similarity Versus Neuronal Response Similarity

We assessed, for each pair of odorants, the relationship between odor similarity and neuronal response similarity, by performing a linear regression. We used the coefficient of determination obtained from this regression to investigate the relationship between odor similarity and cortical population response (**Figure 4**).

Code Availability

We performed all quantifications using custom scripts in MATLAB (MathWorks). All custom code written for this study is available on a dedicated GitHub repository (50).

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