

# Crossmodal Associative Memory Representations in Rodent Orbitofrontal Cortex

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## Summary

Firing patterns of neurons in the orbitofrontal cortex (OF) were analyzed in rats trained to perform a task that encouraged incidental associations between distinct odors and the places where their occurrence was detected. Many of the neurons fired differentially when the animals were at a particular location or sampled particular odors. Furthermore, a substantial fraction of the cells exhibited odor-specific firing patterns prior to odor presentation, when the animal arrived at a location associated with that odor. These findings suggest that neurons in the OF encode cross-modal associations between odors and locations within long-term memory.

## Introduction

A central problem in memory research is the nature and locus of neural representations for learned associations. A strong candidate for associative memory is the prefrontal cortex, an area that receives multimodal inputs via several cortical and subcortical information processing streams and is intimately connected with hippocampal structures implicated in memory function. In the present study, we examined the extent to which neuronal activity in the agranular insular region of the orbitofrontal cortex (OF) reflects the processing of two prominent types of stimulus inputs, specifically from spatial and olfactory afferents, as well as behavioral events and learned associations between the multimodal stimuli.

The OF is intimately involved in olfactory information processing. This area receives olfactory inputs both directly from the pyriform cortex and indirectly through the central segment of the mediodorsal thalamic nucleus (Price et al., 1991; Barbas, 1993). Damage to OF results in impairments in odor-guided learning and memory in rodents and olfactory discrimination in humans (Eichenbaum et al., 1980; Zatorre and Jones-Gotman, 1991; Otto and Eichenbaum, 1992). Correspondingly, odor-selective evoked responses have been observed in the OF of rats and monkeys (Tanabe et al., 1975; Thorpe et al., 1993; Schoenbaum and Eichenbaum, 1995; Critchley and Rolls, 1996a; Rolls et al., 1996), and the OF is activated during odor processing in humans (Zatorre et al., 1992). There is also evidence that OF neurons exhibit associative properties; their activity is influenced by

learned associations with reward valence, gustatory stimuli, and other odors, in both rats and monkeys (Schoenbaum and Eichenbaum, 1995; Critchley and Rolls, 1996b).

In addition, OF receives spatial information indirectly via projections from the medial prefrontal cortex. This region of the rodent prefrontal cortex is the recipient of direct projections from the hippocampus and parahippocampal cortical regions, whose functions have been closely associated with spatial memory across species (O'Keefe and Nadel, 1978; Ono et al., 1993; Rolls et al., 1997; Maguire et al., 1998). Furthermore, damage to the medial prefrontal cortex in the rat results in impairments in spatial learning and memory (Eichenbaum et al., 1983; Kolb, 1984). This region of the prefrontal cortex sends strong projections throughout the OF (Deacon et al., 1983; Price et al., 1991; Barbas, 1993), suggesting that OF is the recipient of converging spatial and olfactory information. In addition, both olfactory and spatial information are processed by the entorhinal cortex, and this cortical area is strongly and bidirectionally interconnected with OF (Deacon et al., 1983). The present study focuses on the cross-modal associative coding properties of neurons in rat OF and specifically on the question of whether OF might be a site for odor-place associations.

Rats were trained to detect a unique odor at each of four different locations, allowing the formation of a set of odor-place associations (Figure 1). On each trial, the animal initially occupied a central position in a recording chamber, after which a panel light on one of the four walls of the chamber was illuminated. Then the rat approached a stimulus port on that wall, inserted its nose into the port, and awaited a particular odor that was presented only at that location. Subsequently, either the odor was presented and the rat could obtain a water reward for a sustained nose poke, or only clean air was presented and the reward was unavailable. Rats rapidly learned the significance of detecting an odor at the location where it was presented. We recorded the extracellular activity of OF neurons as rats performed this task and characterized cells that fired differentially when the animal was at the particular places where each odor detection was performed, as well as cells that were activated during odor presentation, some of which were activated differentially during the processing of specific odors. Additional analyses focused on the waiting period just prior to the presentation of the odors, when the animal's behavior was the same at each location, and during which the animal could anticipate a unique odor about to be experienced. During this preodor period, firing patterns of a substantial fraction of odor-responsive OF neurons reflected the associations between odors and places, as demonstrated by anticipatory odor-selective neural activity at the location where the odor was to be presented. These odor-place associations were "incidental" in the sense that they were not required for successful performance of the odor detection task. Nevertheless, their existence was revealed in the physiological data, as will be described below.

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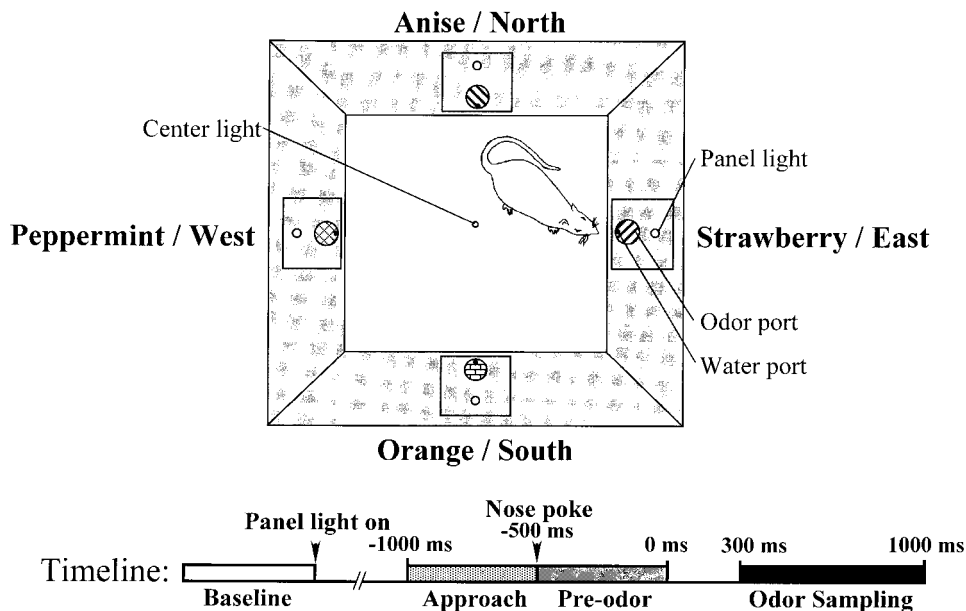


Figure 1. Schematic Drawing of the Testing Apparatus

The time line indicates the duration and order of the time periods over which neuronal responses were analyzed: baseline (before the illumination of the panel light), approach to the port, preodor period (nose poke in the odor port prior to odor or clean air delivery), and odor sampling period.

## Results

### Behavioral Performance

Animals performed on average between 88%–90% correct on the odor detection at all four odor ports for 243–291 trials across each of 7–13 recording sessions. For each animal, most mistakes involved errors of commission, that is, maintaining the nose poke response on clean air trials.

### Physiological Data

The activity of 245 neurons was recorded within layers 2 and 3, and the superficial portions of layer 5, of the lateral portion of the agranular insular region of the OF (Figure 2). The great majority of these cells exhibited regular-spiking firing patterns characteristic of pyramidal neurons. Out of those 245 cells, 209 exhibited task-related activity. To study location-related firing, we compared the cells' activity levels among the four odor ports while the animal waited with its nose in the odor port, prior to the presentation of an odor or clean air (the preodor period), as well as during the period when the animal approached the odor ports. Cells that fired differentially as the rats performed the same behaviors at each location were considered location selective. To study odor-related firing, we compared the activity levels of the cells among the four ports during the presentation of different odors versus clean air. Cells that increased firing on odor versus clean air trials were considered odor responsive, and cells that showed differential levels of activation among the odor set were considered odor selective.

### Location-Related Firing

A total of 186 cells, or 76% of all 245 neurons isolated, exhibited firing rates different from baseline on approach to an odor port or during the preodor period. Of

these, 52 cells, or 28%, were activated equally at all locations, reflecting some general aspect of all trials as animals performed the task. However, the majority of the cells, 134 or 72%, exhibited activity that differed between odor ports during the preodor period, the approach period, or both. These changes in firing rate were judged to reflect the animal's location, because the same sequence of approach and waiting behaviors were performed at each port. Examples of location-selective OF neurons are provided in Figure 3. For the cell shown in Figure 3A, the raster displays depict the time course and firing profile from 1500 ms prior to odor or clean air onset to 1500 ms after odor or clean air onset for all trials at each port. The firing rate of the cell began to increase ~500 ms prior to the initiation of a nose poke at the East port, reached its maximum level of activity during the preodor period, and then declined after presentation of the odor or clean air. The activity of this cell remained close to baseline when the rat awaited odors at other ports, even though the animal's behavior consistently involved a sustained nose poke at all ports. Also, it is important to note that the activity of this and other similar cells did not reflect only the animal's location but was influenced by the ongoing phase of the task. For example, the activity of this cell decreased when the odor or clean air was presented, even though the animal was still performing the same overt nose poke behavior at the same location.

A subset of OF location-selective neurons (23 or 17%) showed the same spatially selective activity across both the approach and preodor periods. For example, the cell shown in Figure 3A started firing during the approach to the East port and then increased firing when the rat entered that port. Two other examples provided in Figures 3B and 3C directly compare the mean firing rates during the approach and preodor analysis periods at each port. For both trial periods, the cell in Figure 3B

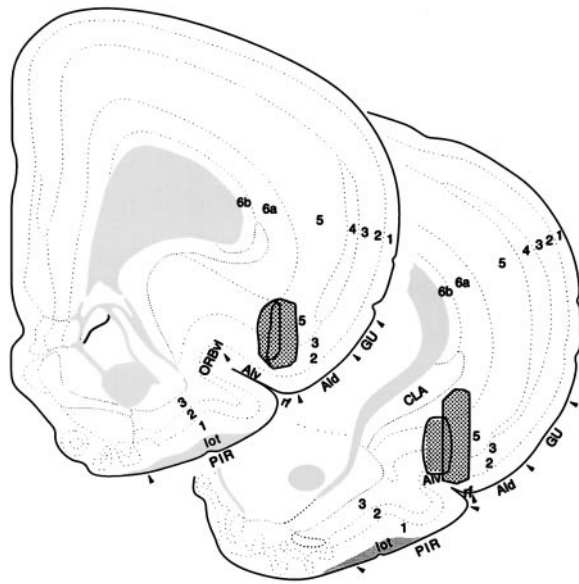


Figure 2. Neurons Were Recorded from the Agranular Insular Cortex Dorsal to the Rhinal Fissure

Stippled regions represent the approximate locations of the areas traversed by the 10-wire electrodes, the tips of which covered an area approximately 0.4 mm in diameter. Two electrode tracks (one from animal 1 and one from animal 2) are represented in the left, more rostral section, and two electrode tracks (from animals 1 and 3) are represented in the right, more caudal section. Abbreviations: Alv, agranular insula—ventral; CLA, claustrum; GU, gustatory cortex; ORbv, ventral orbital cortex; and rf, rhinal fissure. Numbers represent cortical layers. This figure is adapted from Swanson (1992).

was most active at the East port. The cell in Figure 3C was activated at the both East and South ports during both trial periods. These cells appeared to encode the same location-specific information across the multiple behaviors performed as the animal advanced toward the port and awaited the odors.

Other cells (30 or 21% of all location-selective neurons) that showed selective activity exhibited different patterns of spatial selectivity between the approach and preodor trial periods. For example, the cell in Figure 4A selectively fired as the rat approached the North port and then was transiently activated at the beginning of the nose poke at all ports. Subsequently, during the preodor period, the cell fired strongly at both the North and South ports. Figure 4B compares the mean firing rates during the approach and preodor periods for a different OF cell. This cell was selectively active during the approach to the North port and during the preodor period at the South port. The observation that the location-related properties of these cells changed between trial periods further emphasizes that these OF neurons are not simply encoding the animal's location, but rather that their activity also reflects task-related behaviors or information processing that differs across trial phases.

#### Odor-Related Firing

One hundred and fifty-one cells (62% of the total) were characterized as odor responsive because they reliably increased their firing rate during odor presentation but not during presentation of a clean air stream. Of these

odor-responsive cells, 115 (77%) exhibited differential responses among the odor set and were classified as odor selective. Because each odor occurred at only one location, it is possible that these odor-selective cells may have been encoding information about the location as well as about the odor.

Some of the odor-responsive cells (23 or 15%) first increased their firing during the odor sampling period. The example provided in Figure 5A showed a typical pattern. This cell increased firing beginning 300–500 ms after odor onset until 700–800 ms after odor onset and then continued to fire through the end of the reward delivery period. The firing rate did not increase above baseline during clean air presentations, indicating that the response involved information about the odor. Figure 5B shows an example of an odor-selective cell. This cell showed an increase in firing only during and just following the odor sampling period, and only on trials in which the odor presented was strawberry. This cell did not fire when clean air was presented at that or any other location, indicating that the cell was encoding information about the strawberry odor.

Most of the cells (128 or 85%) that responded to odors also showed increased firing during the preodor and/or the approach trial periods. Figure 6A shows an example of an odor-responsive neuron that fired during both the preodor and the odor sampling periods for each of the odors. This cell exhibited a characteristic complex response profile that included an initial firing increase during the preodor period, then a decline in the firing rate for the first 200–300 ms of the odor period, and then finally a second activation beginning 300–500 ms after odor onset and reaching a maximum ~800 ms after odor onset. The cell also initially increased firing during the preodor period on clean air trials but did not show the final activation and instead continued to decline in activity when no odor was presented, indicating that the final phase of activation was odor driven. A small number of these cells decreased, rather than increased, their rate of firing during the preodor and odor periods.

The majority of the odor-selective cells (81 or 70%) showed location-selective activity. Some of these cells showed different patterns of activation among the ports during the different trial periods. For example, the odor-responsive cell shown in Figure 6B responded selectively to the presentation of anise during the odor sampling period. This cell also fired during the preodor period at the North port, where anise was later presented, but it fired even more strongly during the preodor period at the East port, where activity during the odor sampling period was low. An example of a direct comparison of firing rates between these two periods for another cell of this type is provided in Figure 6C. This odor-responsive cell demonstrated odor-selective activity during the presentation of anise at the North port and location-selective activity during the preodor period at the South port. Other odor-responsive cells showed similar patterns of firing across ports during the preodor period and during the odor period, indicating that they might be encoding odor–location associations as described below.

#### Odor–Location Associations

Sixty-five odor-responsive cells (27% of the total) exhibited selective activity during both the odor sampling

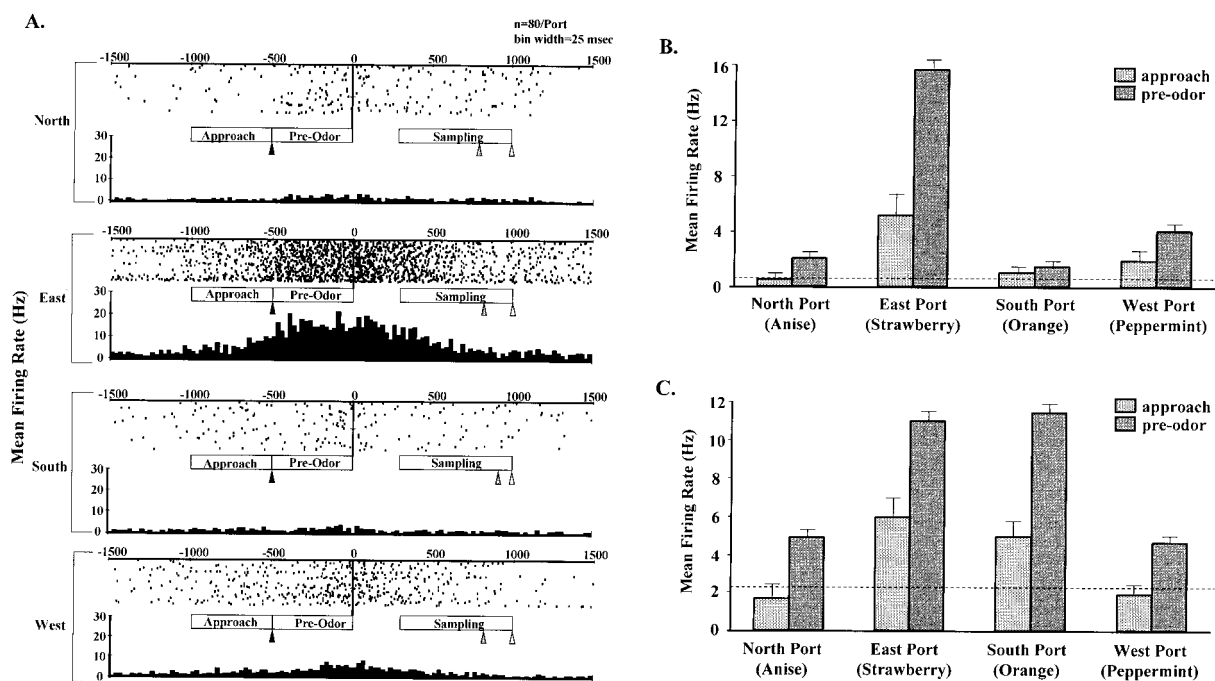


Figure 3. Examples of Location-Selective OF Neurons

(A) Raster displays of all trials plus summary histograms of firing rates for all trials at each of the four trial locations. This cell exhibited increased activity over baseline during the approach ( $F[1,317] = 156, p < 0.0001$ ) and preodor ( $F[1,317] = 578, p < 0.0001$ ) periods and differential activity among the odor ports during both trial periods (approach  $F[3,317] = 48, p < 0.0001$ ; preodor  $F[3,317] = 227, p < 0.0001$ ). Furthermore, the level of activation above baseline was significantly different across locations for both periods (approach  $F[1,317] = 49.7, p < 0.0001$ ; preodor  $F[1,317] = 208, p < 0.0001$ ). Trial periods used in statistical analyses are indicated by labeled boxes; black triangles indicate initiation of the nose poke; shaded triangles indicate the end of clean air delivery during correct clean air trials; and white triangles indicate the end of odor presentation for all correct odor trials. The vertical line in the raster display indicates the onset of odor or clean air delivery;  $n$  = the number of trials at each port.

(B and C) Mean firing rates during the approach and preodor analysis periods.

(B) This cell showed significantly different activity among ports during the approach period ( $F[3,317] = 56, p < 0.0001$ ) and during the preodor period ( $F[3,317] = 230, p < 0.0001$ ). Furthermore, the cell was highly selective at the East port relative to all three other locations during both the approach (all  $t_s > 6.2, p_s < 0.0001$ ) and preodor (all  $t_s > 14.6, p_s < 0.0001$ ) periods.

(C) This cell showed differential activation during the approach ( $F[3,283] = 42.4, p < 0.0001$ ) and preodor ( $F[3,283] = 64, p < 0.0001$ ) periods. Furthermore, activity at the East and South ports was greater than that at the North and West ports during approach (all  $t_s > 6.5, p_s < 0.0001$ ) and preodor (all  $t_s > 9.7, p_s < 0.0001$ ) periods. Horizontal dashed lines indicate the baseline firing rate.

period and during the preodor period immediately preceding it. These odor-responsive cells were further examined to determine whether their firing patterns were consistent with learned associations between odors and the unique locations where they were presented. We hypothesized that odor-place associations would be reflected in “prospective” activity—that is, the capacity of an odor-responsive cell to fire in anticipation of the presentation of an odor, based on the odor’s association with a particular place. In order to determine whether these neurons showed prospective coding properties, we examined neuronal activity among the four odor ports, comparing the activity profile during the preodor period with that during odor presentations. An odor-responsive cell was considered to show prospective coding of odors (that is, location-odor associations) if the pattern of mean firing rates during the preodor period matched that during odor sampling.

According to this analysis, 30 odor-responsive cells (46% of the 65 preodor and odor-selective cells, or 12% of all recorded neurons) demonstrated similar activity

profiles during the preodor and the odor sampling periods. This proportion was significantly greater than what would be expected by chance, as shown by a Monte Carlo analysis (30/65 observed versus 179/1000 expected,  $\chi^2 = 30.1, p < 0.0001$ ). An example is shown in Figure 7A. The response of this cell was strongest during the presentation of peppermint and substantially greater than responses during the presentation of each of the other odors ( $t_s > 2.2, p_s < 0.02$ ). This cell also fired more strongly during the preodor period when the rat was at the West port, prior to presentation of peppermint, than while the rat was at any of the other ports awaiting other odors ( $t_s > 3.9, p_s < 0.0001$ ). Importantly, the firing rate of this cell was significantly higher when sampling peppermint versus clean air at the West port ( $t > 3.4, p < 0.009$ ) but not at the other ports ( $t_s < 1.2, p_s > 0.3$ ), indicating that the response was linked to sampling the peppermint odor and not merely to the presence of the animal at the West port location. Similarly, the cell in Figure 7B was significantly more active when peppermint was presented than when other odors

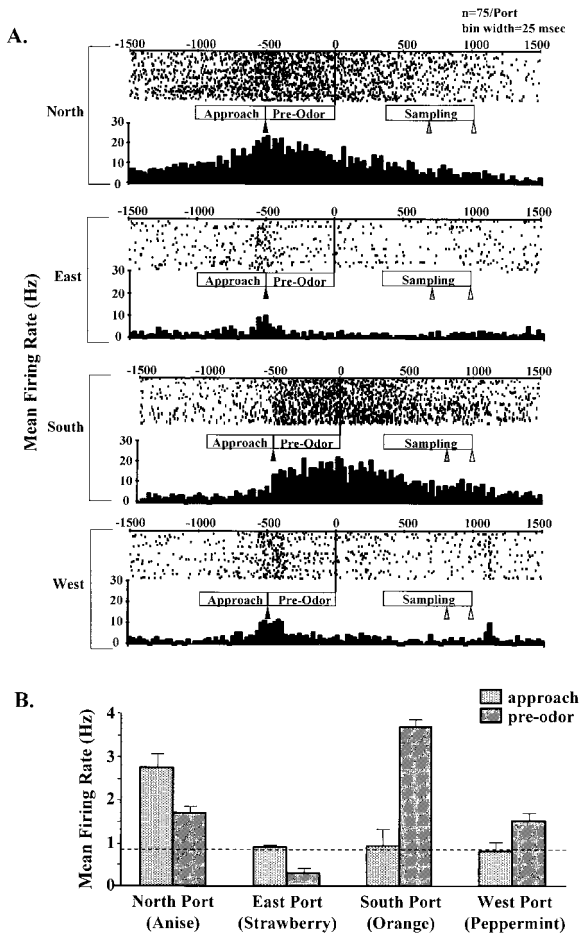


Figure 4. Examples of Neurons that Showed Different Location-Selective Activity Patterns during the Approach and Preodor Trial Periods across All Trials

(A) This neuron increased firing above baseline during both the approach ( $F[1,300] = 83, p < 0.0001$ ) and preodor ( $F[1,300] = 267, p < 0.0001$ ) periods and fired differentially among locations during both trial periods (approach  $F[3,300] = 38.6, p < 0.0001$ ; preodor  $F[3,300] = 98, p < 0.0001$ ). Furthermore, the level of activation above baseline significantly differed among locations for both trial periods (approach  $F[1,300] = 75, p < 0.0001$ ; preodor  $F[1,300] = 94, p < 0.0001$ ). The cell's activity as the rat approached the North port was significantly elevated relative to each of the other ports (all  $t_s > 11.8, p_s < 0.0001$ ) and was significantly elevated during the preodor period when the rat was at both the North and South ports relative to the other two ports (all  $t_s > 11.8, p_s < 0.0001$ ).

(B) This cell showed differential activity among the odor ports during both the approach ( $F[3,300] = 24, p < 0.0001$ ) and preodor ( $F[3,300] = 38, p < 0.0001$ ) periods. During the approach period, activity at the North port was significantly greater than that at each of the other ports (all  $t_s > 4.0, p_s < 0.001$ ), and during the preodor period activity at the South port was significantly greater than that at each of the other ports (all  $t_s > 2.9, p_s < 0.001$ ).

were presented ( $t_s > 7.3, p_s < 0.0001$ ). This cell also fired maximally during the preodor period when the rat was at the West port, prior to the presentation of peppermint, relative to the responses at other ports ( $t_s > 2.4, p_s < 0.02$ ). Its responses did not differentiate between the other three odors ( $t_s < 1.2, p_s > 0.1$ ) or the other three ports ( $t_s < 0.9, p_s > 0.4$ ). As above, the firing

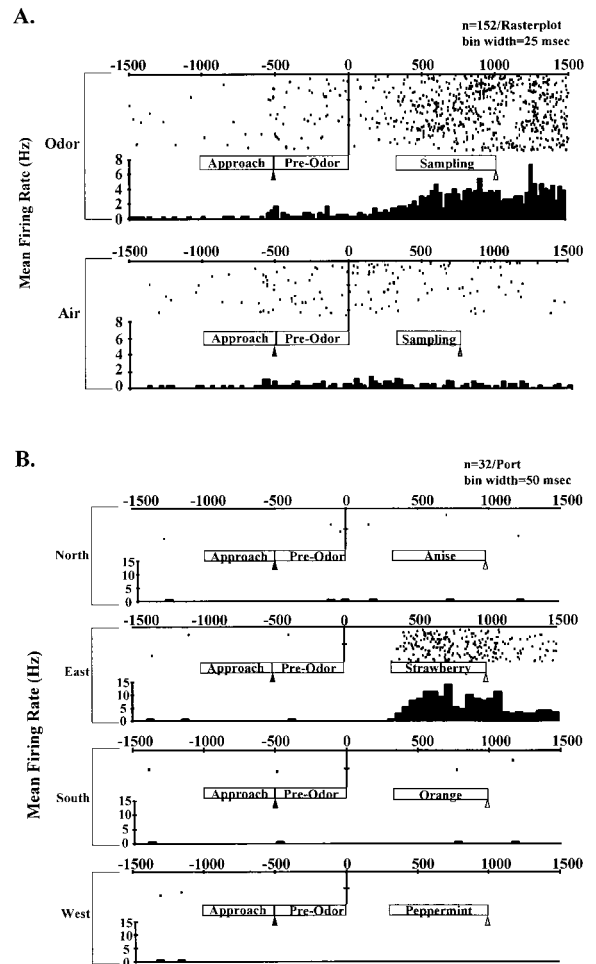


Figure 5. Examples of OF Neurons that Were Activated during the Odor Sampling Period

(A) An odor-responsive neuron. The firing rate of this cell increased during the sampling period for all odors relative to that during clean air trials ( $F[1,277] = 124, p < 0.0001$ ).

(B) An odor-selective neuron. During the odor sampling period, activity during odor trials was higher than that during clean air trials ( $F[1,203] = 86, p < 0.0001$ ) and activity levels differed among locations ( $F[3,203] = 97, p < 0.0001$ ), and the cell showed a differential level of activation over baseline among locations ( $F[3,203] = 99, p < 0.0001$ ). Furthermore, the cell exhibited highly selective activation during the presentation of strawberry relative to each of the other odors (all  $t_s > 10.8, p_s < 0.0001$ ). Mean firing rates during presentation of clean air at each port are as follows: North port, 0.06 Hz; East port, 0.125 Hz; South port, 0.05 Hz; and West port, 0.17 Hz.

rate was significantly higher when sampling peppermint versus clean air at the same location ( $t > 5.7, p < 0.0001$ ).

Of these 30 cells, 12 also exhibited the same selective firing patterns when the rats approached the odor ports, as well as during the preodor and odor presentation periods. That is, the firing rates increased in anticipation of the presentation of an odor even before the animal had reached the odor port. For example, the activity of the cell in Figure 7B was significantly higher during the approach and preodor periods at the West port, and during the presentation of peppermint at the West port, than for the three trial periods associated with any other

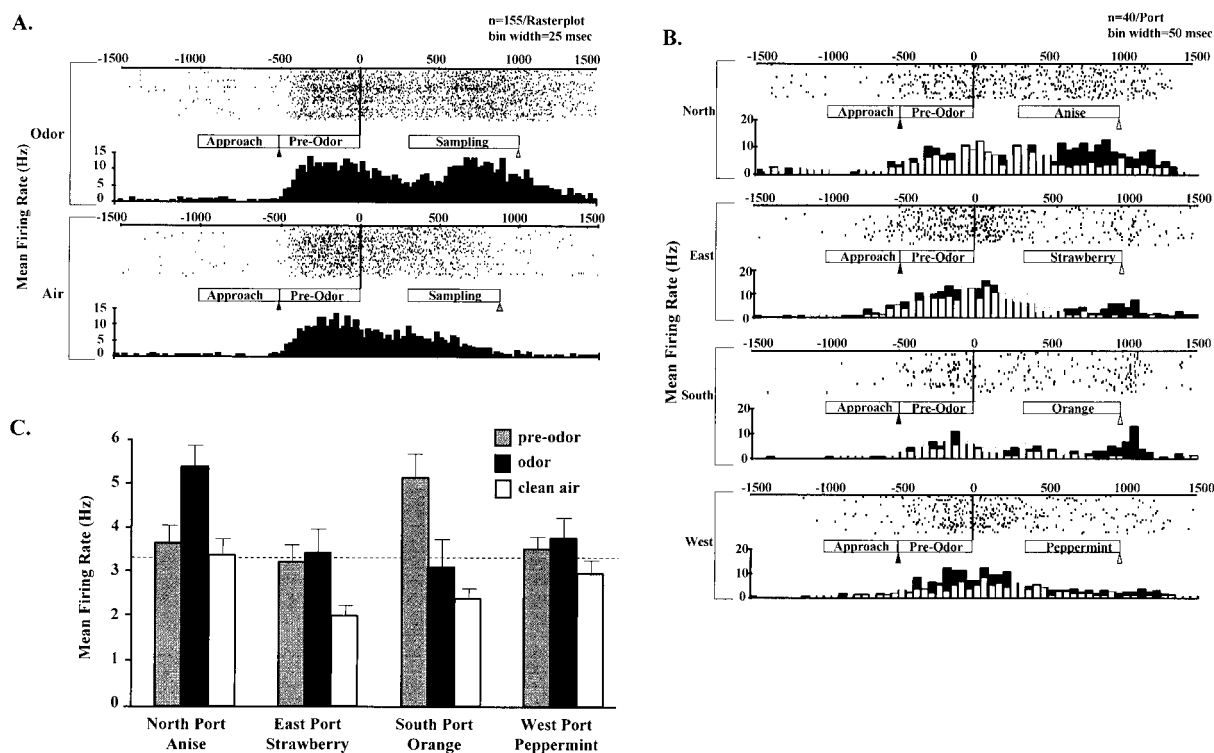


Figure 6. Examples of Odor-Responsive OF Neurons that Also Showed Selective Activity Patterns during Other Trial Periods

(A) An odor-responsive neuron that was also activated during the preodor period. Firing was greater during the preodor period than during baseline ( $F[1,308] = 731, p < 0.0001$ ), and the level of activation was higher for odor trials than for clean air trials during the sampling period ( $F[1,282] = 39, p < 0.0001$ ).

(B) An odor-selective neuron that exhibited elevated firing during the preodor period at all ports. During odor sampling, the cell fired differentially during presentation of odor versus clean air ( $F[1,222] = 14, p < 0.001$ ) and differentially among locations ( $F[3,222] = 19.6, p < 0.0001$ ), and the level of activation over clean air was different among locations ( $F[3,222] = 13, p < 0.001$ ). Furthermore, the cell was more active during the presentation of anise than during the presentation of any other odor (all  $ts > 7.4, ps < 0.0001$ ). During the preodor period, firing increased over baseline at each port ( $F[1,320] = 437, p < 0.0001$ ). Black bars indicate neuronal activity during odor trials; raster display indicates firing during odor trials; and white bars indicate neuronal activity during clean air trials.

(C) This cell showed differential activity among ports during the preodor ( $F[3,285] = 4.5, p < 0.005$ ) and odor sampling ( $F[3,133] = 6.6, p < 0.0005$ ) periods and was selectively activated during the preodor period at the South port over each of the other ports (all  $ts > 2.4, ps < 0.02$ ) and during odor sampling at the North port over each of the other ports (all  $ts > 2.8, ps < 0.006$ ). In addition, during odor sampling the cell fired differentially during presentation of odor versus clean air ( $F[1,273] = 21.3, p < 0.0001$ ).

odor or port (for the approach period,  $ts > 4.9, ps < 0.0001$ ; preodor,  $ts > 2.4, ps < 0.02$ ; odor sampling,  $ts > 7.3, ps < 0.0001$ ).

### Discussion

The present results show that OF neurons encode a broad variety of task-related events as rats perform an odor detection task. More than three quarters of all cells were activated during at least one of three designated trial periods: approach to an odor port, the preodor period, or the odor sampling period. In addition, the use of multiple odors and locations allowed for three additional important findings, discussed next.

First, we found that neuronal activity in OF discriminated among the locations where the rats performed the odor detection trials. A key characteristic of the present task that differentiates it from typical odor discrimination tasks is the use of multiple locations for stimulus presentation. Thus, neuronal activity associated with stereotyped behaviors performed at all odor

ports, such as the nose poke behavior, could be differentiated from firing that reflected the animal's presence at a particular port location. More than half of the cells exhibited differential firing related to the animal's location during the approach period or during the preodor period—that is, when the animal was at the port waiting for an odor or clean air.

Second, the present study confirmed that neuronal activity in OF reflects the detection of, and discrimination among, odors associated with the same behavioral responses and the same reward significance. We found that 61% of all cells recorded responded to odors (versus clean air) and that 47% of all cells responded differentially among odors. These observations are similar to other studies that examined the responses of OF neurons to olfactory stimuli (Schoenbaum and Eichenbaum, 1995; Schoenbaum et al., 1998), and these findings support the view that the OF is intimately involved in odor processing.

Third, we were able to compare profiles of neuronal activity among the ports and odors to reveal that OF

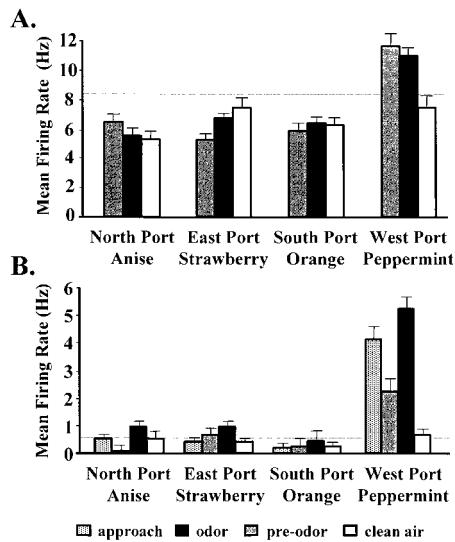


Figure 7. Examples of Neurons Whose Activity Reflected Odor-Place Associations

(A) This cell exhibited a prospective coding for peppermint, as revealed by comparisons of its activity profile for preodor and odor sampling periods. This cell was differentially active among the ports during the preodor (all trials  $F[3,240] = 14.23$ ,  $p < 0.0001$ ) and odor sampling (odor trials only  $F[3,82] = 4.31$ ,  $p < 0.01$ ) periods. Furthermore, the cell's activity was selectively increased at the West port over all other ports (all  $t_s > 3.9$ ,  $p_s < 0.0001$ ) during the preodor period and selectively activated during the presentation of peppermint over all other odors (all  $t_s > 2.2$ ,  $p_s < 0.02$ ) during the odor sampling period.

(B) This cell exhibited a prospective coding for peppermint, with the selective pattern of activation beginning as the animal approached the port where peppermint would be presented. The cell was differentially active during the approach ( $F[3,106] = 31.7$ ,  $p < 0.0001$ ), preodor ( $F[3,106] = 8.18$ ,  $p < 0.0001$ ), and odor sampling ( $F[3,42] = 46.2$ ,  $p < 0.0001$ ) periods. Furthermore, the cell's activity was greater at the West port than at each of the other three ports during the approach (all  $t_s > 6.1$ ,  $p_s < 0.0001$ ) and the preodor (all  $t_s > 2.4$ ,  $p < 0.02$ ) periods, and the cell was more active during the presentation of peppermint than each of the other odors (all  $t_s > 7.3$ ,  $p_s < 0.0001$ ). This cell's responses were not significantly different among the other three ports during the approach or preodor periods (all  $t_s < 0.9$ ,  $p_s > 0.4$ ) and were not significantly different among the presentations of the other three odors during odor sampling (all  $t_s < 1.2$ ,  $p_s > 0.1$ ). Horizontal dashed lines indicate the baseline firing rate.

neurons encode learned associations between odors and locations. Previous reports have indicated that OF cells can encode events predicted by specific olfactory cues, including other odors (Schoenbaum and Eichenbaum, 1995), and they encode rewards or punishments associated with odors (Schoenbaum et al., 1998) and other stimuli (Watanabe, 1996). The present finding of odor-specific firing patterns evoked at locations where odors are about to be presented extends OF representation to the expectation of odors based on nonolfactory cues.

#### Odor-Location Associations

Some of the neurons that responded selectively to odors showed increased firing not only when these odors were presented but also during the preodor period immediately preceding odor delivery—that is, when the animal

had arrived at the port and could anticipate the future delivery of the odor. This pattern of findings indicates a prospective coding of the odors during the preodor period. Thus, the activity of these cells during the preodor period appeared to reflect the retrieval of a stored representation of that particular odor based on predictable location cues.

We considered several alternatives to the possibility that these cells exhibited prospective coding of odors, and each was dismissed by analyzing control conditions incorporated into our behavioral paradigm. One possibility is that the cells were not coding the anticipated odors, but that the similarities in the activity profiles during the preodor and odor periods reflected either the consistent location alone or activation of the cell by residual odor traces at that location. These explanations can be ruled out by examining the activity of these cells during clean air trials (see Figure 7). If the cell was encoding only the location, or was activated by a residual odor trace, it would be expected that the elevated firing rate would continue during clean air sampling. Instead, the cells decreased their rate of firing to near baseline levels during this period, even though the rat was still located in the odor port and any odor traces would still be present. It also was possible that the repeated correction trials following errors provided an alternative source of predictability different from the spatial location. However, because these trials made up <5% of all odor trials, their contribution was undoubtedly minimal.

Another possibility was that the cells were responding to the expectancy of an upcoming reward (e.g., Critchley and Rolls, 1996a; Rolls et al., 1996; Watanabe, 1996). This explanation can be ruled out because each odor and port was associated equally with the same water reward, but the prospective responses were selective among the odors and locations. Innate preferences or aversions for particular odors might also have influenced the performance of the animals, which could potentially account for some measure of the observed odor-location associations. However, the distribution of prospective responses was 15 for anise, 12 for strawberry, 12 for orange, and 12 for peppermint. (This total is greater than 30, the number of cells, because many of these cells showed similarly high rates for more than one odor.) This even distribution among the odors suggests that any preferences or aversions the animals might have had did not provide a consistent influence over the firing patterns that reflected odor-location associations. In addition, we observed no systematic differences in response latencies or performance accuracy that could account for the patterns of prospective coding observed.

Finally, it was also possible that the cells were encoding not only olfactory cues but rather the combination of a particular odor and its place of presentation and reward. The design of this study purposely confounded the odors with the places at which they were presented, with the intention of encouraging consistent odor-place associations. However, this design leaves it unclear whether the odor selectivities observed reflect the identity of an odor per se or some combination of the odor, its place, and its reward status. Other data collected from studies where multiple odors were presented at

a single location and with equivalent rewards indicate that cells in OF respond differentially to odor identity (Schoenbaum and Eichenbaum, 1995). The firing latencies and proportions of odor-selective cells observed were similar to those described here, suggesting that the cells in this study were responding to the odors themselves. Importantly, even if the present responses do reflect the combinations of odors and their locations, the appearance of similar response profiles during the preodor period, when no odor was available, would constitute a prospective coding of an association of which the odor is a fundamental component.

Recently, evidence for visual-visual associations has been found in the form of prospective coding of visual information in the inferior temporal cortex, a higher order visual association area (Naya et al., 1996), and in the prefrontal cortex of monkeys (Watanabe, 1996; Rainer et al., 1997, *Soc. Neurosci.*, abstract). The prospective codes of these neurons reflected the retrieval of a visual target stimulus, or an expected reward, from long-term memory cued by other visual or spatial stimuli that the monkeys had learned to associate with the target. The present results extend the capacity of prospective coding by cortical neurons to rodents and extend the scope of prospective coding to cross-modal associations between locations and odors. These findings suggest that prospective coding of expected stimuli may be a general property of higher order association cortical areas. This type of association between predictive cues and expected future stimuli may constitute an example of memory for arbitrarily imposed relationships between stimuli, and the encoding of such arbitrary associations might be expected to depend on the hippocampal system (Eichenbaum et al., 1992).

### The Role of OF in the Representation of Odor Memories

There appear to be substantial similarities between the olfactory processing system of rodents, monkeys, and humans. Anatomical studies have revealed several similarities between the connections of the OF in the monkey with the connectivity of OF in the rodent (Tanabe et al., 1975; Price et al., 1991). Electrophysiological studies in monkeys support the idea that the OF is involved in higher-order olfactory processing. Cells in this area represent olfactory information (Rolls and Baylis, 1994; Critchley and Rolls, 1996a) as well as odor-reward associations (Critchley and Rolls, 1996a). Moreover, these responses vary with the internal state of the animal (Critchley and Rolls, 1996b). There is also evidence for multimodal processing in this area, since some of the cells in OF respond to visual or gustatory stimuli in addition to olfactory stimuli (Rolls and Baylis, 1994). Data from studies on humans also support this idea. Lesions to the OF in humans result in disturbances in the discrimination and identification of olfactory stimuli (Zatorre and Jones-Gotman, 1991), as is the case in rats (Eichenbaum et al., 1980). In addition, the presentation of odors results in the activation of the OF in humans (Zatorre et al., 1992).

However, in the present study, most cells were activated during multiple task phases, suggesting that cells

in OF are involved in coding representations of a broad range of behavioral events and stimuli. This indicates that OF processing is not limited to encoding the olfactory characteristics of a stimulus, as might be expected of a dedicated sensory processing area. Instead, it appears that OF cells participate in multiple cell assemblies that include neurons in widespread brain areas (Hebb, 1949). Thus, while many cells exhibited prospective coding properties, most of the cells that showed selective responses to locations and odors had responses that appeared unrelated from one task period to the next. The cells that showed different patterns of selectivity during the approach, preodor, and odor periods may well have been part of distinct neuronal ensembles that encoded task-relevant information and the animal's expectations at different phases of the task.

Together with these data, the results of the present study lend support to the view maintained by us and several investigators (Zatorre et al., 1992; Barbas, 1993; Rolls et al., 1996), based on evidence from anatomical, electrophysiological, and functional imaging studies, that the OF acts as both a secondary olfactory cortex and a higher order association cortex; the neural processing in this region reflects not only olfactory information but also cognitive operations involving the integration of past, present, and future experiences, enabling adequate performance in behavioral tasks, social situations, or situations involving survival.

### A Possible Functional Role of Prefrontal-Medial Temporal Connections

It is of interest to note the relatively long latency (300–500 ms) of the neurons' responses to odors. The OF has reciprocal connections with the pyriform cortex and receives direct projections from the olfactory bulb, entorhinal cortex, medial dorsal nucleus of the thalamus, and medial prefrontal cortex. The long response latencies of OF neurons to odor cues in the current task suggest that information represented by the firing patterns of these cells is influenced not only by forward projections from olfactory areas but also by projections from other areas that encode information about task conditions and the animal's state. The responses of neurons in hippocampus and entorhinal cortex can provide a prominent source for information subserving olfactory and spatial memory, as shown in studies of animals performing odor or place memory tasks (e.g., Wiener et al., 1989; Hampson et al., 1993; Young et al., 1997). These data, combined with current ideas regarding the function of medial temporal lobe structures in representing stimulus relations (Eichenbaum et al., 1992), lead to the suggestion that interactions between OF and medial temporal lobe structures might mediate the establishment or retrieval of predictive associations evident in OF neuronal response patterns.

### Experimental Procedures

#### Subjects, Surgery, and Histology

Subjects were three male Long-Evans rats, weighing 300 g at the start of training. The animals were allowed ad libitum access to food for the duration of the experiment but were restricted to 30 min of water per day before each training, testing, and recording session. The animals were maintained on a 12 hr light/dark cycle and were

housed with cagemates prior to surgery and individually after surgery.

Animals were anesthetized using halothane gas delivered in a 30:70 oxygen/nitrous oxide mixture. After placement in the stereotaxic apparatus, the skull was exposed and bregma and lambda were made level. Small holes were drilled over the appropriate sites for the placement of the electrodes, in addition to five holes for skull screws used for electrical ground and for securing the head stage. In one animal, drivable bundles of ten electrodes were implanted bilaterally just above the OF, at 3.2 mm anterior to bregma, 4.0 mm lateral to the midline suture, and 3.5–4.0 mm below the surface of the brain. In the other two animals, one bundle was implanted in only the right hemisphere. Dental cement was used to secure the electrode assembly to the skull screws and skull.

When the recordings were completed, each animal was deeply anesthetized with an overdose (100 mg/kg) of sodium pentobarbital. A 15 mA current was passed through each electrode. The animals were then perfused transcardially with 0.9% saline followed by a solution of 10% buffered formalin and 4% potassium ferrocyanide. A Prussian blue reaction resulted, marking the location of the electrodes. The brains were removed and stored in formalin for at least 24 hr prior to sectioning. The brains were sectioned coronally at 50  $\mu$ m on a freezing, sliding microtome and then mounted and stained with thionin.

#### Apparatus

The training arena consisted of a 38 cm square metal box, 30.5 cm high. An odor port was located 3.8 cm from the floor on each wall (Figure 1). A 24 V panel light was situated above each odor port. When illuminated, this light signaled the location where the next trial was to take place. A photodetector in the center of the box floor was used to determine when the animal was at that location. In addition, photodetectors at the entrance of each port were used to register when the animal had inserted his nose into an odor port. Although the box was nearly symmetrical, there were several auditory and visual cues by which the animal could orient itself while inside the box. In addition, there were a variety of cues that the rat could use to orient itself before entering the box, including the experimenter, a computer, fans, and the entry into the experimental room.

The timing and delivery of odors, clean air, and water were regulated by computer-controlled solenoid valves. The odors and the clean air were delivered at a rate of 0.5 l/min. After appropriate responses, 0.03 ml of water was delivered directly to the entrance of each port. A vacuum exhaust pulled the odor or air from each port at a rate of 2 l/min, ensuring that no odor escaped into the box and that none lingered in the port after each trial. In addition to the vacuum, air constantly flowed through all four ports at a rate of 0.5 l/min to ensure that no residual odor remained in the hose feeding into each odor port. This constant air flow was also intended to reduce or eliminate any difference in the physical perception of the air flow that might accompany the delivery of an odor or clean air. Only one odor was presented at each of the ports: anise in the North, strawberry in the East, orange in the South, and peppermint in the West. The odors were commercially available imitation food extracts diluted in deionized water to a concentration of 1:100, at which concentration the odors were just detectable to the experimenter.

#### Pretraining

Prior to the implantation of the recording electrodes, the animals were trained on all four odor/clean air discriminations. Pretraining included four stages of shaping. In the first stage, all four lights were turned on, and the animals were required to nose poke in any of the odor ports, without an odor present, for a reward of 0.03 ml of water. The light above the odor port that the animal had just visited was then turned off, and the animal was required to visit one of the other odor ports to receive a reward. When all four odor ports had been visited, all lights were again turned on to signal that reward was again available at all four ports. This shaping procedure required one 1 hr session of 50 trials.

In the second stage, which required two to four daily 200-trial sessions, the animals were trained to return to the center of the box

after each reward, in order to initiate the next trial. All the lights were turned off after a reward was delivered, and the animal needed to maintain a position at the center of the box for 500 ms, after which the start of the next trial was signaled by onset of the remaining panel lights. During this stage of training, the duration of the nose poke required to obtain a reward was increased gradually from 500 ms to 1500 ms. Clean air delivery was introduced in the third stage of training. In this stage, only one panel light was turned on for each trial, in a predetermined pseudorandom order. When the animal inserted its nose into the port, clean air was delivered, and the animal was required to maintain a nose poke for 1500 ms. This third stage required two to three daily 250-trial sessions.

In the fourth and final preoperative stage, the odors and their reward contingencies were introduced in the form of odor trials (rewarded) and clean air trials (not rewarded). To begin each trial, the animal was required to stand over the center light for 500 ms. This resulted in illumination of a panel light above one of the four odor ports selected in a predetermined pseudorandom order. Next, the animal approached the lit odor port and initiated a nose poke. For the first 500 ms, the preodor period, no odor was delivered and there was no indication of whether the trial would be an odor or clean air trial. If the animal left the port during the preodor period (a rare occurrence in the well-trained animals), the trial continued as though a nose poke had never occurred, the panel light remained on, and the clock was reset for the initial 500 ms. In the case of multiple incomplete nose pokes, the 500 ms prior to the last complete nose poke was used to compute the approach. Following the preodor period, either the assigned odor or clean air was delivered to the port according to a predetermined pseudorandom order of trials. There were equal numbers of odor and clean air trials at each port.

On odor trials, at the end of the preodor period the assigned odor was delivered to the port for 1000 ms. The animal received a water reward if it continued the nose poke for the 1000 ms odor sampling period, after which it could leave at any time. If the animal left the port before the end of the odor sampling period, the trial was counted as incorrect, and no reward was delivered. On clean air trials, at the end of the preodor period clean air was delivered for 1000 ms. A correct response on a clean air trial was to leave the port in less than 1000 ms. Typically, the animals left the odor port within 750–800 ms of the start of the clean air delivery. If the animal remained in the port at the end of the sampling period, the trial was counted as incorrect. During presurgical training sessions, incorrect responses on either odor or clean air trials were followed by up to two correction trials, which were repetitions of the trial. Only one correction trial followed an incorrect response during the recording sessions.

The final stage of training required 250 trials a day for 3–5 days for the animals to reach an 85% level of performance. Once criterion performance was reached, the animals underwent surgical implantation of the recording electrodes.

#### Electrophysiological Recordings

The drivable bundle of electrodes consisted of ten 30  $\mu$ m, Formvar-coated nichrome wires. The bundle of wires was threaded through a 27-gauge cannula, inserted into a custom-made microdrive assembly, attached to a 10-pin Augat connector, and secured to the skull using dental cement. The tips of the wires extended over a diameter of  $\sim$ 0.4 mm.

The animals were allowed to recover from surgery for 7–10 days, during which time they were given ad lib access to food and water. The animals were given 2 days of additional testing after recovery to get reacquainted with the task before recordings began. Animals were then screened every day for unit activity. If unit activity was observed, the animals performed the task for a session consisting of an average of 260 trials, during which unit activity was recorded. If no unit activity was observed, the bundle was advanced by 80  $\mu$ m, and at least 4 hr were allowed for the tissue to settle around the electrode tips before beginning another recording session. After each recording session, the bundle was advanced by 80  $\mu$ m. Neural activity was passed through a unity gain field effect transistor (JFET) in the headstage, differentially amplified (gain 8,500–10,000; Neuralynx Digital Amplifiers), band-pass filtered at 600–6,000 Hz, and digitized (28 kHz, Data Translation DT2821) using Enhanced Discovery software (DataWave Technologies) on an IBM-compatible Pentium-based personal computer. Offline, isolation and discrimination

of units were achieved using Autocut software (DataWave Technologies). Single units were isolated by defining clusters of spikes determined by eight distinct dimensions of waveform parameters: for example, spike height, spike width, peak time, valley time, etc. (McNaughton et al., 1989). If a particular unit maintained these established clusters throughout the session, the cell was considered for further analysis.

#### Data Analysis

Analysis of unit activity proceeded in three stages. Significance levels for all statistical tests were set at 0.05. Four time periods were used in these analyses (see Figure 1): baseline: the 500 ms before the start of each trial, while the rat was in the center of the box; approach to an odor port: the 500 ms prior to arrival at an odor port; preodor: the initial 500 ms at the odor port, before odor or clean air was delivered; and odor sampling: from 300 ms after the start of odor delivery until the animal stopped sampling the odor or clean air (that is, 1000 ms after the start of odor/clean air delivery or when the animal withdrew from the port, whichever occurred earlier on each individual trial). This time window started at 300 ms after odor onset because the latency for an odor response typically was 300–500 ms after the start of the odor sampling period. Trials in which the animal withdrew from the port before 300 ms after odor onset were not considered. Thus, the firing rate was calculated only for the period when the animal was in the port during odor or clean air presentation.

##### Stage 1: Location-Related Firing

We first examined whether the firing rate of the cells differed from baseline for the approach or preodor periods. For each period, a two-way ANOVA (period by port) was performed to compare the firing rate for that period to the baseline firing rate across the four odor ports. Cells were considered to show changes in firing rate with respect to baseline if the main effect of period or the interaction between trial period and odor port were significant. If a cell's firing rate differed from baseline for the approach or the preodor period, a one-way ANOVA across the four ports was performed. Cells were characterized as showing location-related firing if there was a significant main effect of port location in this analysis. A series of post hoc unpaired *t* tests, between all possible pairs of ports within a trial period, were performed on the cells that exhibited location-related firing to then identify, and support statistically, the ports at which these cells were most active.

##### Stage 2: Odor-Related Firing

Cells were considered odor responsive if, during the odor sampling period, the rate of firing was different during the delivery of an odor than during the delivery of clean air, as determined by a significant main effect of trial type (odor or clean air) or trial type-by-odor interaction in a two-way ANOVA. Only trials performed correctly were included in this analysis. Cells identified as odor responsive were further examined for odor selectivity. A cell was considered selective for odors if the firing rate during the odor sampling period was significantly different among the odors, as determined by a significant effect of odor in a one-way ANOVA. Only odor trials that were performed correctly were used in the odor-selective analysis. A series of post hoc unpaired *t* tests, between all possible pairs of odors, were performed on the cells that exhibited odor-selective activity to then identify, and support statistically, the odors to which these cells responded most.

##### Stage 3: Odor-Location Associations

Only odor-selective cells that also exhibited location-related firing during the preodor period were considered for this analysis. The analysis was designed to detect neural activity reflecting the anticipated presentation of a particular odor. In order to do this, we examined whether the profile of each cell's activity across the ports during the preodor period was similar to its activity profile across odors during the odor sampling period (on odor trials). The term "profile" refers here to the differences in an odor-selective cell's response to, for example, the four odors (e.g., high firing rate for orange and low firing rate for strawberry, anise, and peppermint). Two criteria had to be met before the activity profiles were judged sufficiently similar between the preodor and the odor sampling periods.

*Criterion 1.* First, we identified the preferred and least preferred odors of an odor-selective cell, (for example, orange [highest rate of firing] versus strawberry [lowest rate of firing]). Then, to meet the first criterion of a prospective response, the preodor firing rates at the ports where these odors were presented also had to differ significantly, in the same direction. In the above example, the preodor firing rate at the South port (orange) needed to be significantly greater than the preodor firing rate at the East port (strawberry).

*Criterion 2.* To examine in more detail the overall activity profile, we compared the results of unpaired *t* tests on firing rates between all possible pairs of ports during the preodor period to the results of equivalent pairwise tests between the associated odors during the odor sampling period. This analysis therefore included the results of six pairs of *t* tests: North versus East (preodor) and anise versus strawberry (odor); North versus South and anise versus orange; North versus West and anise versus peppermint; East versus South and strawberry versus orange; East versus West and strawberry versus peppermint; and South versus West and orange versus peppermint. We determined how many out of these six pairs of preodor and odor *t* tests matched (i.e., both tests were significant or both were nonsignificant). A cell was considered to meet the second criterion if at least three pairs of *t* tests matched.

These criteria ensured that the overall profiles were similar, while allowing for some variation in the responses between ports and odors that were associated with neither the highest nor the lowest neural activity. These criteria also allowed for some variation due to changes in the power of the *t* tests resulting from low firing rates or noise. Most of the cells that met these criteria were a match for four to six out of the six comparisons in criterion 2.

In addition, a Monte Carlo analysis was performed to establish whether the similarity in the activity profiles between the preodor and odor sampling periods could be due to chance. On each run of the analysis, two cells were randomly selected from the pool of 65 preodor and odor-selective cells. The activity profile for the preodor period of one cell was randomized across the four ports, and the activity profile for the odor sampling period of the other cell was randomized across the four odors. Then, the resultant profiles were compared to see if they met both of the criteria described above. This analysis was repeated 1000 times, and the proportion of cells that met both criteria in these analyses was then compared to the proportion found in the experimental data using a  $\chi^2$  test.

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