Behavioral/Systems/Cognitive

Olfactory Bulb Mitral–Tufted Cell Plasticity: Odorant-Specific Tuning Reflects Previous Odorant Exposure

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Olfactory system second-order neurons, mitral–tufted cells, have odorant receptive fields (ORFs) (molecular receptive ranges in odorant space for carbon chain length in organic odorant molecules). This study quantified several dimensions of these excitatory odorant receptive fields to novel odorants in rats and then examined the effects of passive odorant exposure on the shape of the ORF-tuning curve. ORFs for carbon chain length of novel ethyl esters (pure odorants that the animals had not been exposed to previously) were determined before and after a 50 sec prolonged exposure to one of the odorants. In response to novel odorants, quantitative analysis of mitral–tufted cell excitatory ORFs revealed that the median ORF width spanned 3– 4 carbons, generally with a single-most excitatory odorant. Exposure to either the most excitatory odorant (ON-PEAK) or an odorant that was two carbons longer (OFF-PEAK) for 50 sec produced whole ORF suppression immediately after the end of the prolonged exposure, with the ON-PEAK exposure producing the greatest suppression. These results are consistent with a feature-detecting function for mitral–tufted cells. Redetermination of the ORF 15 and 60 min after the exposure revealed that OFF-PEAK exposure produced a reduction in responsiveness to the best odorant and an increase in responsiveness to the exposed odorant. In contrast, exposure to the ON-PEAK odorant or no odorant did not affect ORFs. Given that mitral–tufted cells receive exclusive excitatory input from olfactory receptor neurons expressing identical receptor proteins, it is hypothesized that experience-induced mitral–tufted cell ORF changes reflect modulation of lateral and centrifugal olfactory bulb circuits.

Key words: **perceptual learning; olfactory memory; receptive field; odor coding; dynamic processing; mitral cell; habituation; adaptation; odorant receptive fields**

Introduction

Experience can influence both behavioral and physiological responses to sensory input. Both associative conditioning and, in certain circumstances, stimulus exposure alone can modify cortical sensory neuron receptive fields (RFs) and, consequently, behavioral sensory abilities (Gilbert et al., 2001). In thalamocortical sensory systems, RF plasticity is believed to be dependent on the heterogeneity and plasticity of afferent and association inputs (Hebb, 1949; Weinberger, 1995; Buonomano and Merzenich, 1998).

Similarly, mammalian olfactory system responses to odors can change with experience. For example, associative conditioning can alter olfactory bulb (OB) glomerular activity patterns (Leon, 1987; Wilson and Sullivan, 1994), OB output neuron (mitral–tufted cell) responses (Leon, 1987; Wilson and Sullivan, 1994; Faber et al., 1999), and local field potential oscillations (Freeman and Schneider, 1982; Kendrick et al., 1992; Ravel et al., 2003). OB odor response patterns can also be modified by simple odor exposure (Buonviso and Chaput, 2000; Spors and Grinvald, 2002) and by odor deprivation (Guthrie et al., 1990; Wilson and Sullivan, 1995). Experience can also modify odor response patterns in olfactory cortical neurons (Litaudon et al., 1997; McCollum et al., 1991; Schoenbaum et al., 1999; Wilson, 2000a). These changes in olfactory system response patterns may underlie both the memory for odors with acquired significance (Freeman and Schneider, 1982; Kendrick et al., 1992; Wilson and Sullivan, 1994; Ravel et al., 2003) and learned changes in behavioral olfactory acuity (Wilson and Stevenson, 2003).

Although changes in mitral–tufted cell responses to learned odors have been reported previously, the effects of odor experience on mitral–tufted cell odorant receptive fields (ORFs) have not. Mitral–tufted cell ORFs (molecular receptive range; Imamura et al., 1992; Mori and Yoshihara, 1995) are believed to primarily reflect the excitatory input that mitral–tufted cells receive on their apical dendritic tuft from a homogenous population of olfactory receptor neurons (ORNs), all expressing the same olfactory receptor protein (Vassar et al., 1994; Tsuboi et al., 1999). In mammals, individual mitral–tufted cells receive input from a single glomerulus and thus should have ORFs that primarily reflect the ORFs of their afferent receptor neurons (Bozza and Kauer, 1998; Luo and Katz, 2001). In addition to this excitatory receptor neuron input to the apical dendrite, mitral–tufted cell ORFs are also influenced by inputs to their extensive lateral dendrites. The inputs to lateral dendrites are primarily inhibitory (Yokoi et al., 1995; Shepherd and Greer, 1998), although there is evidence of excitatory (Isaacson, 1999) and autoexcitatory (Aroniadou-Anderjaska et al., 1999) activity.

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On the basis of hypothesized mechanisms of experience-induced change in RFs of cortical neurons in other sensory systems (Gilbert et al., 2001), the unique anatomy of the olfactory receptor neuron-glomerulus-mitral–tufted cell circuit might suggest unique consequences of experience on mitral–tufted cell ORFs. For example, given that mitral–tufted cells receive homogenous afferent receptor input, does this preclude experience-induced ORF shifts? The present experiment aimed at better understanding mitral–tufted cell ORFs and ORF plasticity. Mitral–tufted cell single-unit ORFs to a homologous series of ethyl esters were quantitatively characterized both before and after simple prolonged exposure to one of the odors. The results suggest that mitral–tufted cell ORFs to novel odorants can be shaped by previous exposure.

Materials and Methods

Subjects. Adult male Long–Evans hooded rats (Harlan Bioproducts for Science, Indianapolis, IN) were used as subjects. Rats were housed in polypropylene cages with water and food available *ad libitum*. Lights were maintained on a 12 hr light/dark cycle with testing taking place during the light hours. Animal care and protocols were approved by the University of Oklahoma Institutional Animal Care and Use Committee in accordance with National Institutes of Health guidelines. ORFs were mapped from a total of 72 cells in 56 animals with no more than three cells from each animal. Only cells that showed excitatory responses to at least one of the ethyl esters presented were used in this study.

Electrophysiology. Animals were anesthetized with urethane (1.5 gm/kg) and placed in a stereotaxic apparatus. After exposing the skull, a small hole was drilled over the left OB. Another hole was drilled over the lateral olfactory tract (LOT) posterior to the OB, allowing a tungsten-stimulating electrode to be inserted into the LOT. Respiratory activity was monitored throughout the experiment using a piezoelectric monitor strapped around the animals' chest. This output was then sent through a window discriminator allowing odorant pulse delivery to be timed to the transition of the inspiration–expiration cycle as reported previously (Wilson, 2000a).

For single-unit mitral–tufted cell recordings, a tungsten microelectrode (5–12 MΩ) was lowered into the dorsal region of the left OB normal to the dorsal surface. Recordings were made in the dorsomedial region of the OB known to be responsive to ethyl esters of differing hydrocarbon chains (Imamura et al., 1992; Uchida et al., 2000). Confirmation of recording electrode placement was verified by LOT electrical stimulation and histological confirmation of the recording electrode tip location. Unfortunately, given the superficial location of these recordings, most recording sites could not be reconstructed. Single units were amplified and bandpass filtered (300 Hz to 10 kHz) and then either directly isolated or extracted through template matching using Spike 2 software (Cambridge Electronics Design, Cambridge, UK).

Odorant receptive fields. The term receptive field is generally defined as that portion of the sensory epithelium or stimulus space to which a sensory neuron responds. In some systems, this corresponds to a precise spatial dimension in a description of the RF [e.g., somatosensory system (Mountcastle, 1957) or early stages of the visual pathway (Hubel and Weisel, 1959)], whereas in other systems, descriptions of RFs do not necessarily include a spatial dimension [e.g., frequency tuning in the central auditory system (Diamond and Weinberger, 1986; Weinberger, 1995) and object-oriented RFs of higher order visual system (Rolls et al., 2003)]. Although central olfactory system neurons can also display spatial RFs [e.g., mitral–tufted cells (Kauer and Moulton, 1974; Jiang and Holley, 1992) and piriform cortex neurons (Wilson, 1997)], a variety of terms have been used to describe the odorant stimulus tuning properties of these neurons and their underlying anatomy. These terms include odotopy (Shepherd and Greer, 1998), rhinotopy (Clancy et al., 1994), molecular receptive range (Mori and Yoshihara, 1995), and odorant receptive field (Wilson, 2000b; Luo and Katz, 2001; Sanchez-Montanes and Pearce, 2002). The two latter terms are generally considered analogous (Mori and Yoshihara, 1995; Luo and Katz, 2001) and refer to that region of odorant space to which an olfactory neuron responds. The ORF of a single unit in the central olfactory system is dependent on both the type of olfactory receptor neuron input it receives (influenced by precise anatomical projections from the receptor sheet) and central circuit processing (Kauer, 1991; Mori and Yoshihara, 1995; Luo and Katz, 2001). One dimension that has been routinely used to partially describe (map) ORFs is carbon chain length (Imamura et al., 1992). The present study uses the ORF terminology as described here to enhance comparison with published work from other sensory systems.

Odor stimulation. Odorants were delivered by passing a stream of humidified charcoal-filtered air through syringe filters saturated with specific odorants using a flow dilution olfactometer (1:10 dilution). Although higher odorant concentrations are known to elicit broader ORFs than lower concentrations, previous studies found the best (most effective) odorant of the ORF to be the same, regardless of concentration (Imamura et al., 1992, Sato et al., 1994). Odorants used were ethyl formate (E1), ethyl acetate (E2), ethyl propionate (E3), ethyl butyrate (E4), ethyl valerate (E5), ethyl hexanoate (E6), ethyl heptanoate, ethyl octanoate (E8), and isoamyl acetate (AA) (Sigma, St. Louis, MO). For all ORF determination, animals were given 2 sec odor pulses delivered in pseudorandom order. Odorant habituation (exposure) consisted of a single 50 sec odorant presentation to either the BEST-ODORANT (ON-PEAK) or the odorant that was two carbons longer in chain length than the BEST-ODORANT (OFF-PEAK). In all cases, odorants used for the 50 sec exposure were E3, E4, E5, or E6. All odorants were initially novel to the animals tested, and no animal received more than one 50 sec odorant exposure to allow examination of the effects of the initial odorant exposure on mitral–tufted cell ORFs, a design similar to our previous work (Wilson, 2000a).

Odor response analysis. A variety of quantification and classification schemes exist for odorant responses (Pager et al., 1972; Mair, 1982; Harrison and Scott, 1986; Meredith, 1986; Hamilton and Kauer, 1989; Wellis et al., 1989; Imamura et al., 1992; Buonviso and Chaput, 2000; Wilson, 2000b). Using these schemes, it has been shown that both the number of evoked spikes and temporal patterning of spike occurrence can vary with odorant stimulus quality and intensity. As a first approach to detecting ORF changes with exposure, we chose to focus on stimulus-evoked spike counts to facilitate comparison with results from other sensory systems (Weinberger et al., 1993; Rolls et al., 2003).

For the description of mitral–tufted cell ORFs to novel odorants, we used two different measures, one highly inclusive and liberal and one more conservative. Response magnitudes were calculated by subtracting the number of spikes during a 4 sec prestimulus period from the number of spikes during each 4 sec odorant presentation. Partial ORFs for the esters used here could then be mapped on the basis of changes in raw spike counts. For the more liberal response definition, cells were considered to show an excitatory response to an odorant if the mean response magnitude for that odorant was >0. This allowed characterization of ORFs with very inclusive criteria. The more conservative ORF measure involved statistical analysis of response magnitudes for each odorant response. For statistical ORF comparisons, cells were considered to respond to an odorant if the mean number of spikes during the 4 sec period beginning with the odorant presentation was significantly greater (0.25 sec bin width; t test; $p < 0.05$) than the number of spikes during the 4 sec prestimulus baseline activity.

For comparisons of individual ORFs as well as exposure-induced (i.e., 50 sec exposure) changes, it was necessary to normalize the ORFs relative to the response magnitude to the most excitatory (best) odorant. This allowed for comparisons of overall ORF-tuning curve shape. Normalized ORFs were obtained by calculating response magnitudes for each odorant as a percentage of the BEST-ODORANT response magnitude. The BEST-ODORANT was defined as the odorant that produced the largest response relative to the other odorants in the series at that time point. By normalizing responses, potential shifts in BEST-ODORANT could be seen by a shift in the postexperience ORF peak away from the pre-experience ORF peak while canceling simple changes in the overall firing rate to odorant presentations. Experience might not only shift the ORF toward a different peak odorant but also change the overall shape of the

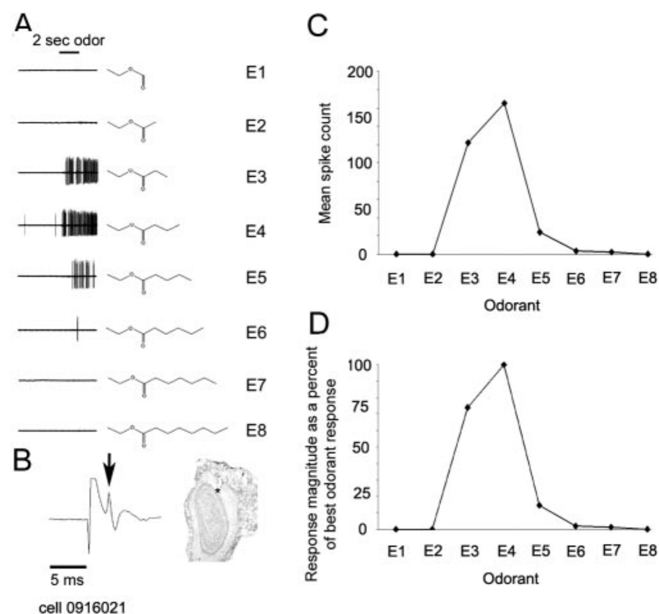

Figure 1. Representative example of single-unit mitral–tufted cell responses to a novel series of ethyl esters. *A*, Sample traces of spike activity before, during, and after 2 sec odorant presentations of a homologous series of ethyl esters differing in carbon chain length *B*, Antidromic LOT-evoked spike recorded from the neuron shown in *A* (arrow, evoked spike) and histological verification of electrode location near the mitral–tufted cell layer (asterisk, recording site). The time scale for antidromic response is 5 msec. *C*, ORF for cell in *A* is based on mean odorant-evoked changes in cell firing for each odorant. *D*, ORF of same cell remapped as a percentage of the BEST-ODORANT response (normalized). Replotting the ORF as a percentage of BEST-ODORANT response does not change overall ORF shape.

ORF. With ORFs normalized, a more precise relationship between odorant responses could be observed.

ORFs were remapped immediately, 15 and 60 min after the 50 sec odorant exposure stimulation. For preexposure, 15 min postexposure, and 60 min postexposure ORFs, response magnitudes were averaged across two presentations of each odorant. Because of time constraints of presenting eight odorants, ORFs immediately after the 50 sec exposure were based on responses to a single presentation of each odorant. The respiration rate, which could be indicative of changes in anesthetic level or animal condition over the course of the 60 min experiment, did not significantly change in the animals used for long-term testing [$t(18) = 0.10$; not significant].

For each cell, the 50 sec exposure odorant was chosen as either the BEST-ODORANT within the baseline ORF of that cell or an odorant that was two carbons longer in chain length than the BEST-ODORANT. Response magnitudes to each of the odorants were calculated for each time point in the same manner as the initial normalized ORFs. ORFs mapped before exposure, immediately after exposure, and 60 min after the 50 sec exposure were compared with three-way repeated measure ANOVA and *post hoc* comparisons.

Results

Odorant ORF mapping

Single-unit ORFs were mapped in odorant space along the carbon chain length dimension from 72 mitral–tufted cells to a homologous series of novel ethyl esters. Figure 1 shows a typical example of a single-unit excitatory ORF to ethyl esters. The recording in Figure 1*A* shows the spike discharge of the mitral–tufted cell before, during, and after a 2 sec odorant presentation. In this case, the cell responded to four of the eight ethyl esters presented, with vigorous firing to three of the odorants. For ORF determination along the dimension of carbon chain length, averaged single-unit responses were expressed for each odorant (Fig. 1*B*). To make comparisons between individual ORFs and potential experience-induced changes, all single-unit ORFs were also expressed as a percentage of the odorant eliciting the largest response for each cell (BEST-ODORANT) (Fig. 1*C*). Because the second phase of this study was concerned with comparing individual ORF changes, normalizing the ORF fields allowed for better comparisons of overall ORF-tuning curve shape over time. Expressing ORFs as a percentage of the BEST-ODORANT does not change the overall shape of the ORF, as shown in Figure 1.

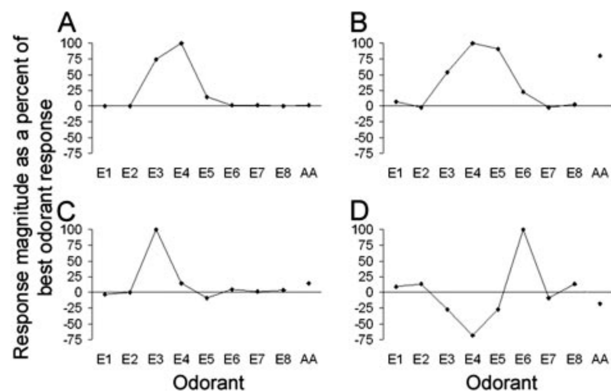

Figure 2. *A*--*D*, Individual examples of mitral–tufted cell ORFs to novel ethyl esters. Normalized ORFs were mapped as a percentage of the BEST-ODORANT response for each cell. Individual cells show differences in ORF shape and some have suppressive responses to odorants with longer and shorter chains surrounding excitatory stimuli. Responses to AA were also mapped. Some cells that responded to ethyl esters were also responsive to AA stimulation.

Representative ORFs to novel odorants from four different cells are shown in Figure 2. Individual cells differed in their ORFs to the esters presented. Differences between cells were observed in responses to odorants within the series, with most cells excited by only a subset of odorant chain lengths in the series. For example, the cell in Figure 2*A* responded to odorants E3–E5, with chain lengths outside of this range being ineffective. The cell in Figure 2*B* had a broader ORF with stronger responses to odorants E3–E6. This cell also displayed excitatory responses to isoamyl acetate, whereas AA appeared to be ineffective in exciting the cell in Figure 2*A*. Figure 2*C* shows an example of a cell with a sharper ORF, with the cell only responding to two of the chain lengths. This cell was somewhat inhibited by chain lengths immediately outside the range of excitatory odorants. Similarly, Figure 2*D* shows a cell with a very narrow ORF characterized by a single excitatory odorant and suppression to neighboring chain lengths.

The mean odor-evoked spike counts of all cells ($n = 72$) to all odorants were combined in Figure 3*A*. As a population, this group of cells responded most strongly to E3 and E4 with a slight skew toward longer chains (Fig. 3*A*). Using the liberal definition of excitatory odorant response as a simple increase in spike count during the stimulus compared with prestimulus count, most individual cells also responded to E3 and E4 (Fig. 3*B*). A majority of the cells tested also had excitatory responses when presented with isoamyl acetate (Fig. 3*B*). Furthermore, using the liberal definition of excitatory odorant responses, the majority of cells had excitatory ORF widths between four and seven odorants (Fig. 3*C*).

When the ORF responses were analyzed more conservatively on the basis of statistically significant changes in spike count, a slightly different picture of ORFs to novel odorants emerged. As might be expected, cells responded to substantially fewer odorants of the set than compared with liberal response definition (Fig. 4). Furthermore, the majority of cells had ORF widths between one and four odorants (Fig. 4*B*).

The conservative definition of odorant responses was also

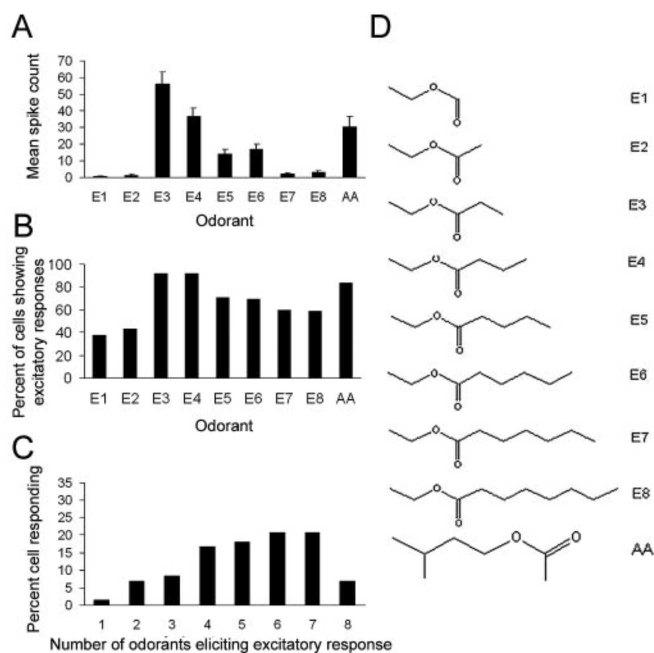

Figure 3. Response specificities of mitral–tufted cells to novel ethyl esters. A cell was considered to respond to an odorant if the odorant-evoked activity was >0 (see Materials and Methods). *A*, Mean novel responses for all cells ($n = 72$) based on odorant-evoked changes in cell firing to each ethyl ester and AA. *B*, Percentage of excitatory responses evoked by each odorant for all cells tested. *C*, Mean number of odorants eliciting responses in each cell. On the basis of excitatory responses alone, most cells displayed relatively broad RFs. *D*, Molecular structure and name of all odorants used.

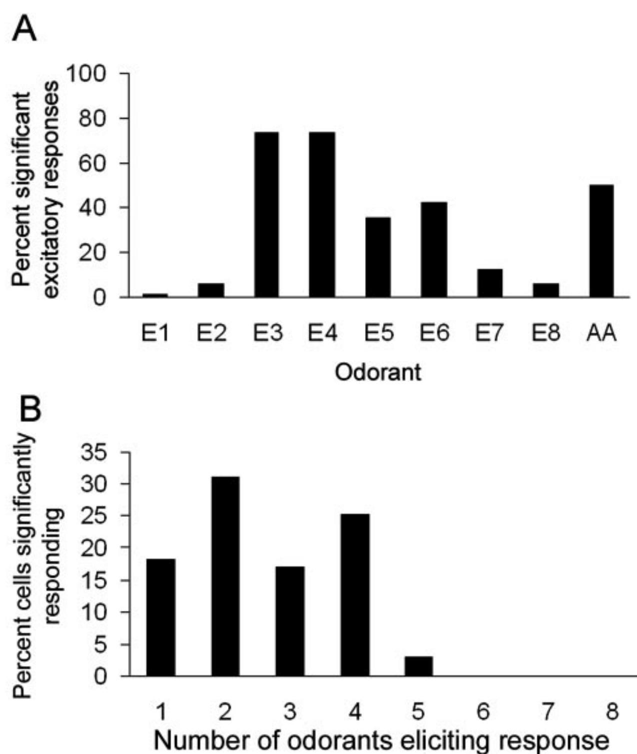

Figure 4. Response specificities of mitral–tufted cells based on statistically defined responses (see Materials and Methods). Responses were considered significant only if the odorant-evoked firing was statistically different from baseline activity. *A*, Mean novel responses for all cells based on significant odorant-evoked changes in cell firing to each ethyl ester and AA. *B*, Mean number of odorants eliciting responses in each cell. On the basis of significant response, most cells displayed more narrow ORFs with fewer odorants eliciting responses.

used to quantitatively characterize mitral–tufted cell ORFs by examining the conditional probability of responses to a particular odorant by a single cell, given that that same cell responds to another odorant. Thus, for example, we wanted to determine whether a cell that responds to an ester with a carbon chain length of four is equally likely to respond to esters with longer (E5) and shorter (E3) chain lengths, or whether there is an asymmetry in mitral–tufted cell ORFs for chain length. Data from olfactory receptor neuron recordings (Gaillard et al., 2002) and mitral–tufted cell cross-habituation studies (Wilson, 2000b) suggest that an asymmetry or bias exists in ORFs for chain length. Figure 5 shows probabilities of responses to ethyl esters on the basis of ORFs to novel odorants. Given the low response probability to E1 and E2, only data for E3–E8 are included. As shown, individual cells tend to respond to odorants of similar carbon chain length, although there is an asymmetry in relationship to carbon length preference. Thus, assuming a cell responds to a given chain length, it has a higher probability of responding to odorants with a shorter chain length than to odorants with a longer chain length. For example, of the cells that responded to E4, 80% also responded to E3, whereas only ~40% responded to E5. In contrast, of the cells that responded to E5, 80% also responded to E4, whereas ~50% responded only to E6.

These results suggest that a conservative estimate of mitral–tufted cell excitatory ORFs for novel esters includes odorants varying by a median of three carbons in length. Furthermore, a conditional probability analysis suggests that if a cell responds to an odorant of a particular carbon chain length, it is more likely to respond also to shorter chain odorants than longer chain odorants. The following analyses examined the effect of previous experience on these ORFs.

Odorant ORF short-term plasticity

After ORF determination to novel odorants, a subset of cells received a 50 sec odorant exposure to either the BEST-ODORANT for that cell (ON-PEAK; $n = 20$) or the odorant that was two carbons longer in chain length than the BEST-ODORANT for that cell (OFF-PEAK; $n = 28$). Given that most cells recorded here had BEST-ODORANTs of E3 or E4 and very few cells responded to E1 and E2, examination of the effects of exposure to shorter chain lengths was not possible. Immediately after the 50 sec exposure, ORFs were remapped. ORFs were normalized to the maximal response, as described in Materials and Methods, and aligned across cells to the BEST-ODORANT for each cell as determined during the preexposure mapping. Figure 6 shows the effects of a single 50 sec odorant stimulus on mitral–tufted cell raw spike-count ORFs mapped immediately after the termination of the prolonged exposure. Responses to the odorants after the 50 sec exposure were suppressed in both the ON-PEAK (Fig. 6*A*) and OFF-PEAK exposed (Fig. 6*B*) groups (ANOVA; main effect of trial, $F_{(1, 228)} = 52.1$; $p < 0.01$), with postexposure responses being suppressed more in the ON-PEAK group (ANOVA; trial × group interaction, $F_{(1, 228)} = 3.94$; $p < 0.05$). *Post hoc* Fisher tests revealed a significant difference between the ON-PEAK and OFF-PEAK postexposure responses to the BEST-ODORANT ($p < 0.05$), with responses in the ON-PEAK group showing greater suppression. The results show that immediately after a 50 sec exposure to an odorant within the ORF, responses across the ORF in both groups were suppressed.

By normalizing both preexposure and immediately postexposure ORFs, effects on the shape of the ORF can be better exam-

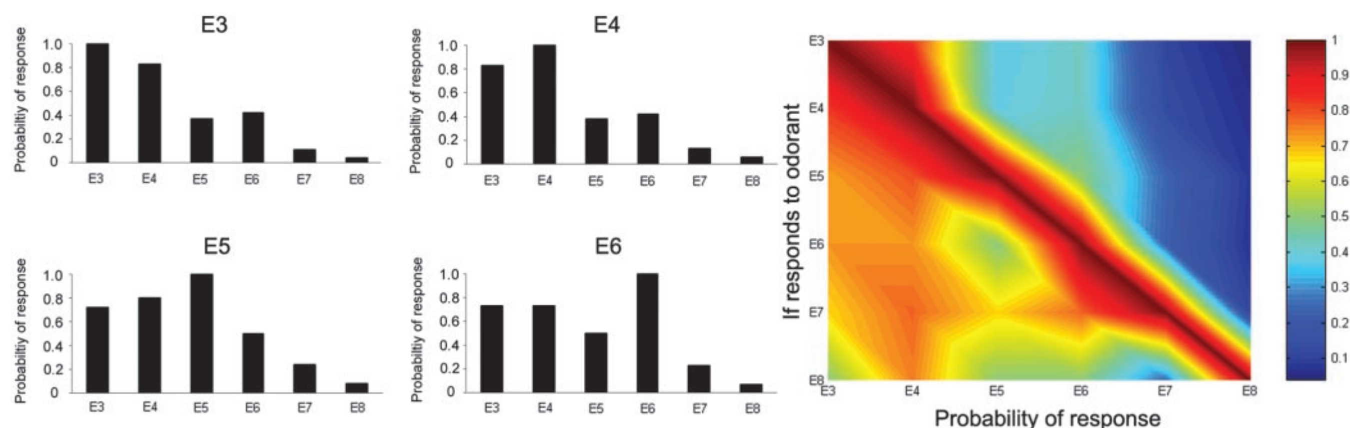

Figure 5. Conditional probability of an individual cell responding to specific odorants on the basis of all ORFs determined in this experiment ($n = 72$). Assuming a response to a given odorant (listed as the ordinate in the pseudocolor graph on the right), the probability of response to other odorants is displayed with higher probabilities (red). A histogram representation of the same data is shown on the left (odorant that the cell responds to is labeled above each histogram). If a given cell responded to an odorant of specific carbon chain length, it had a high probability of responding to shorter chained-related odorants. Response probabilities were based on odorant-induced responses that were statistically significant from baseline activity.

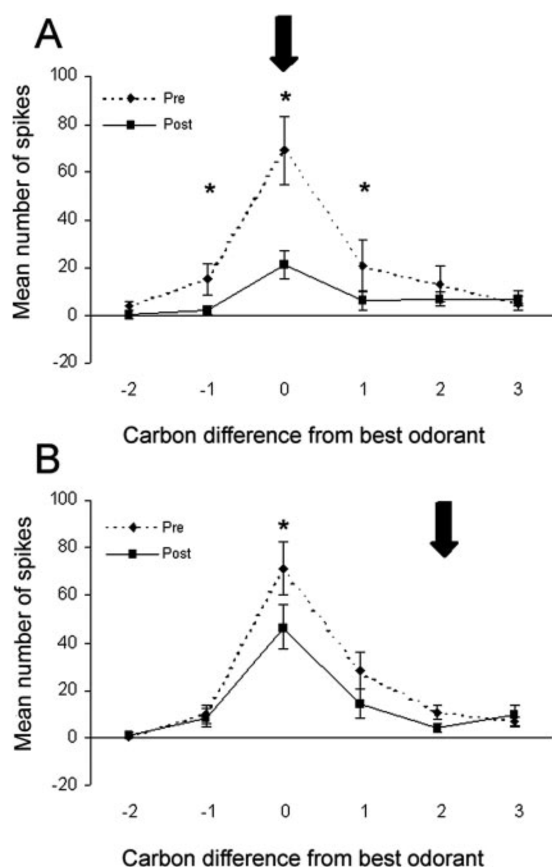

Figure 6. Mean single-unit ORF changes (odor-evoked spikes) immediately after 50 sec odorant exposure. *A*, Mean single-unit changes immediately after exposure to the ON-PEAK odorant ($n = 20$). *B*, Mean single-unit changes immediately after exposure to the OFF-PEAK odorant ($n = 28$). Arrows represent the carbon chain length of odorant presented during exposure. Asterisks represent a significant difference between postexposure odorant responses and preexposure responses ($p < 0.05$).

ined. Normalizing the pre-ORFs and post-ORFs again showed that a 50 sec odorant stimulus suppressed both the ON-PEAK and OFF-PEAK exposed ORFs (ANOVA; main effect of trial, $F_{(1,228)} = 21.5$; $p < 0.01$) (Fig. 7). Again, *post hoc* Fisher tests revealed a significant difference between the ON-PEAK and OFF-PEAK postexposure responses to the BEST-ODORANT ($p < 0.05$) with responses in the ON-PEAK group being lower. In the normalized ORFs, no significant difference in the amount of habituation was found between groups (ANOVA; significant trial × group interaction; $F_{(1,\ 228)} = 2.37$; not significant) or within odorant responses (ANOVA; trial × group × odor interaction; $F_{(4,\ 228)} = 2.04$; not significant). These results show that although there is a postexposure decrease in the response of both groups, no significant overall change in the shape of the ORF can be observed.

Odorant ORF long-term plasticity

In a subset of the animals used to describe short-term effects of odorant exposure, ORFs were remapped 15 and 60 min after the 50 sec odorant exposure. Figure 8 shows examples of individual normalized ORFs mapped before and 60 min after 50 sec exposure. The cell in Figure 8*A* was exposed to its BEST-ODORANT (ON-PEAK), whereas the cell in Figure 8*B* was exposed to the OFF-PEAK odorant. The ON-PEAK exposed cell shows no change in ORF BEST-ODORANT 60 min after exposure but does appear to narrow with the appearance of enhanced suppressive responses to longer and shorter odorant chains (Fig. 8*A*). In contrast, the OFF-PEAK exposed cell shows a marked shift ORF BEST-ODORANT away from the original BEST-ODORANT toward the exposure stimulus (Fig. 8*B*).

Mean ORF changes over time are shown in Figures 9 and 10. In the ON-PEAK exposed group ($n = 11$), little change occurs in the shape of the ORF over time (Figs. 9*A*, 10*A*). Although the ORF seems broader 15 min after the odorant exposure, within 1 hr the shape of the ORF is relatively unchanged. This suggests that odorant ORFs under the conditions here can be highly stable after exposure to the BEST-ODORANT. As an additional test of odorant ORF stability, the odorant ORFs of a small number of additional cells were monitored over repeated (range, 4–9) stimulation over the course of up to 60 min without an intervening 50 sec odorant exposure. In those cells, normalized ORFs did not significantly change over time ($n = 5$; repeated measures ANOVA; $F_{(2,24)} = 1.27$; not significant).

In contrast to the stability of odorant ORFs after ON-PEAK odorant exposure, in the OFF-PEAK exposed group ($n = 10$), there was a significant change in the overall odorant ORF shape with a shift in the peak toward the experienced odorant (ANOVA; trial × group × odorant interaction; $F_{(1,\ 57)} = 3.87$; $p < 0.05$). *Post hoc* Fisher tests revealed a significant drop in the

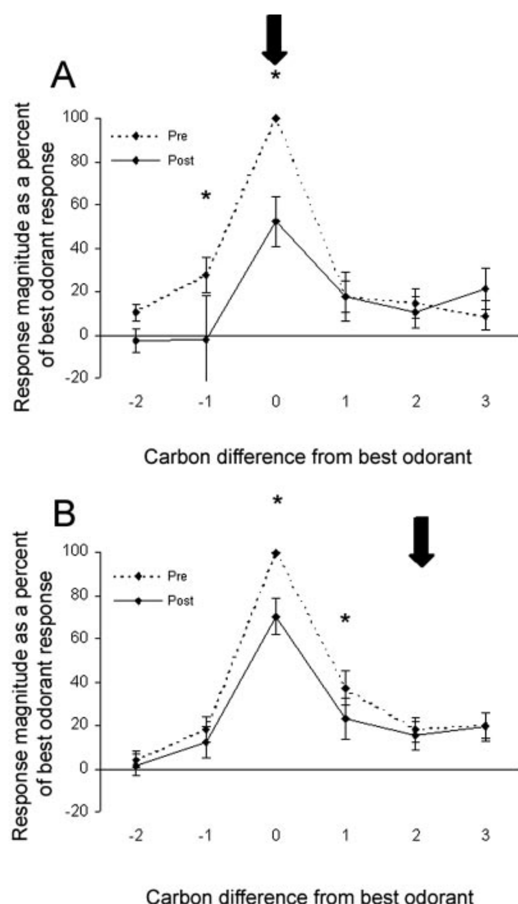

Figure 7. Mean normalized single-unit ORF changes immediately after 50 sec odorant exposure. ORFs from Figure 6 were normalized as a percentage of the preexposure BEST-ODORANT response. *A*, Mean single-unit changes immediately after exposure to the ON-PEAK odorant ($n = 20$). *B*, Mean single-unit changes immediately after exposure to the OFF-PEAK odorant ($n = 28$). Arrows represent the carbon chain length of odorant presented during exposure. Asterisks represent a significant difference between postexposure odorant responses and preexposure responses ($p < 0.05$).

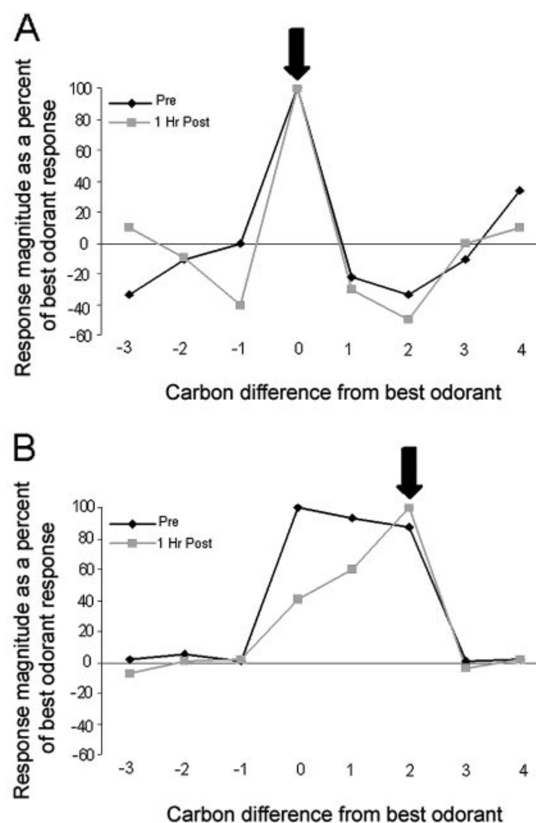

Figure 8. Examples of individual mitral–tufted cell odorant ORFs before and 60 min after a single 50 sec odorant exposure. ORFs are normalized on the basis of the preexposure BEST-ODORANT response. *A*, ORF changes in a mitral–tufted cell after ON-PEAK odorant exposure. In this case, the overall ORF shows little change, although with enhanced suppression of odorants similar to the BEST-ODORANT. *B*, ORF changes in a mitral–tufted cell with OFF-PEAK odorant exposure. In this cell, ORF changes were seen with an overall shift of the ORF toward the experienced odorant as well as suppression of the BEST-ODORANT response. Arrows represent the carbon chain length of the odorant presented during the 50 sec exposure.

BEST-ODORANT response and a significant increase in the exposure odorant response 60 min after odor exposure ($p < 0.05$) (Figs. 9*B*, 10*B*). These ORF shape changes after OFF-PEAK odorant exposure can develop over time with the ORF after 15 min of being intermediate between the pre-ORF and 60 min post-ORF (Fig. 9). Given the stability of odorant ORFs in ON-PEAK exposed animals and nonexposed CONTROL animals described above, the shifts in odorant ORF after OFF-PEAK exposure appear to be exposure-induced.

In addition to changes in BEST-ODORANT, selectivity of the exposed cells as a whole was also modified. As shown in Figure 11, as a population, mitral–tufted cells exposed to an ester for 50 sec showed a significant narrowing of responsiveness to other esters. A comparison of the percentage of cells responding to each odor for all cells combined showed a significant change 60 min after the 50 sec exposure (χ^2; df(8) = 18.91; $p < 0.05$).

In some animals, the response to isoamyl acetate was also measured after the odorant exposure. Similar to the other odorants immediately after a 50 sec exposure to one of the ethyl esters, responses to isoamyl acetate were significantly suppressed [$t(12) = 2.28$; $p < 0.05$]. The response to isoamyl acetate recovered over the course of the experiment, with responses returning to baseline within 60 min (ANOVA; $F_{(3,36)} = 0.64$; not significant) (Fig. 12).

Discussion

The current study quantified excitatory mitral–tufted ORFs to a homologous series of novel ethyl esters to investigate exposure-induced ORF plasticity. As described previously (Imamura et al., 1992; Mori et al., 1992), mitral–tufted cell responsiveness varied along the dimension of carbon chain length, generally showing a maximal responsiveness to a single carbon chain length (BEST-ODORANT). Median mitral–tufted cell excitatory ORFs spanned three to five of eight esters presented. There appeared to be an asymmetric conditional probability response bias, with cells more likely to respond to a given odorant and shorter carbon chain lengths than to longer chain lengths. Mitral–tufted cell ORFs to novel odorants demonstrated both long- and short-term plasticity after a 50 sec odorant exposure characterized by an immediate suppression across the ORF and followed by recovery and a long-term ORF shift toward the experienced odorant. These latter findings are very similar to RF plasticity in thalamocortical sensory systems (Weinberger, 1995; Buonomano and Merzenich, 1998; Gilbert et al., 2001), despite the unusual anatomy of afferent input to mitral–tufted cells.

Olfactory bulb odorant ORFs

These results are consistent with previously reported studies of mitral–tufted cell responses to odorants differing in carbon chain length (Imamura et al., 1992). In addition, a majority of cells

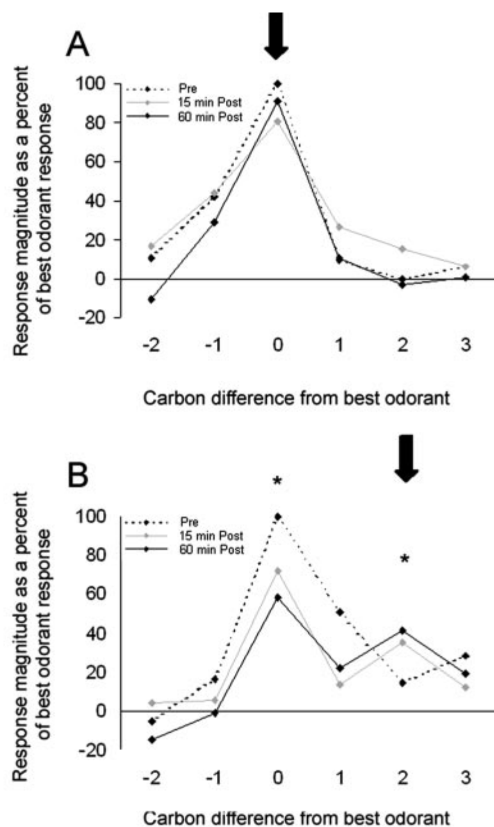

Figure 9. Mean single-unit odorant ORF changes after a single 50 sec odorant exposure. ORFs were normalized as a percentage of the preexposure BEST-ODORANT response. *A*, Mean single-unit changes 15 min and 1 hr after exposure to the ON-PEAK odorant ($n = 11$). *B*, Mean single-unit changes 15 min and 1 hr after experience to the OFF-PEAK odorant ($n = 10$). Arrows represent the carbon chain length of odorant presented during exposure. Asterisks represent a significant difference between postexposure odorant responses and preexposure responses ($p < 0.05$).

activated by ethyl esters also showed excitatory responses to isoamyl acetate (Fig. 3), which shares some structural similarities with ethyl esters used here. Note that the ORFs of the mitral–tufted cells recorded in this study have only been partially sampled and are presumably much larger, containing many more odorants differing not only in carbon chain length but possibly in type and position of functional groups within the odorant molecule as well (Hamilton and Kauer, 1989; Wellis et al., 1989; Imamura et al., 1992).

Mitral–tufted cell ORFs reflect both afferent input and central processing. Olfactory receptor neurons expressing homologous receptor genes project their axons to a small set of neighboring OB glomeruli, with individual glomeruli receiving exclusive input from receptor neurons expressing the same receptor gene (Vassar et al., 1994; Tsuboi et al., 1999). In turn, apical dendrites of rat mitral–tufted cells receive excitatory input from a single glomerulus (Shepherd and Greer, 1998). Thus, in the absence of local circuit inputs, excitatory ORFs of mitral–tufted cells to novel odorants should primarily reflect the ORF of the receptor neurons that innervate them. In fact, the quantified mitral–tufted cell excitatory ORFs described here, showing a median carbon chain length span of three to five, match well with qualitative and quantitative descriptions of olfactory receptor neuron ORFs for carbon chain length. Specifically, the mouse OR912–93 receptor only binds aliphatic odorants with a straight carbon chain length of more than four and with maximal specificity to a seven carbon chain (Gaillard et al., 2002). Many other studies have reported ORNs that are responsive to a series of homologous odorants spanning less than five carbons in chain length difference (Sato et al., 1994; Malnic et al., 1999; Araneda et al., 2000).

One surprising characteristic of the mitral–tufted cell excitatory ORFs described here was the asymmetry in conditional probability of responding to chain length. Within the sampled population, if a cell responded to a particular carbon chain length, it was more likely to also respond to shorter chains than longer chains. Similar phenomena have been reported for olfactory receptor neuron ORFs, in which, for example, a receptor may respond maximally to a given chain length but also to shorter chains (Gaillard et al., 2002). This type of receptor response could account for the asymmetry described here. However, there are several examples in the literature of the opposite effect, in which a receptor does not respond until a certain chain length is reached and then continues to respond as the chain length is increased (Malnic et al., 1999); although, these responses were not analyzed in detail. A more quantitative analysis of olfactory receptor neuron ORFs for carbon chain length, perhaps combined with mitral–tufted cell ORF mapping for the same odorant set and concentration, appears necessary to help isolate characteristics of mitral–tufted cell ORFs that result purely from OB processing, as opposed to those that primarily reflect afferent input.

Of course, mitral–tufted cell ORFs not only passively reflect excitatory olfactory receptor input but also reflect extensive lateral and feedback input to mitral–tufted cells from interneurons and centrifugal input from the rest of the brain (Shepherd and Greer, 1998; Mori et al., 1999). Through mechanisms such as lateral inhibition and centrifugal feedback, mitral–tufted cell ORFs can be sharpened to possibly enhance tuning specificities to odorant responses (Yokoi et al., 1995; Luo and Katz, 2001). Although previous reports have demonstrated that responses to particular odorants can be modified on the basis of behavioral state (Pager et al., 1972; Jiang et al., 1996) and past experience (Freeman and Schneider, 1982; Wilson and Sullivan, 1994, 1995; Brennan and Keverne, 1997; Kay and Laurent, 1999; Buonviso and Chaput, 2000), presumably through changes in central processing, the effects of experience on mitral–tufted cell ORFs have not been examined until now.

Odorant ORF plasticity: short-term effects of odorant exposure

As reported previously (Wilson 2000b), exposure to an odorant within a mitral–tufted cell ORF produced a widespread depression (habituation) of the odorant ORF, whereas the general shape of the ORF-tuning curve remained constant. Exposure to the BEST-ODORANT produced greater generalized habituation than exposure to an odorant near the edge of the ORF. These results are consistent with a feature detection model of mitral–tufted cell function in which habituation to one odorant (feature) within the ORF suppresses responses to all odorants sharing that feature (Mori and Yoshihara, 1995; Wilson 2000b). An odorant feature, perhaps less effective at stimulating the relevant receptors (OFF-PEAK), thus may produce less overall suppression, similar to the pharmacological concept of a partial agonist.

Odorant ORF plasticity: long-term effects of odorant exposure

The consequences of odorant exposure continued to emerge over the course of at least 60 min, as demonstrated by the OFF-PEAK exposed cells. In OFF-PEAK exposed cells, ORFs 60 min after exposure showed a decrease in responsiveness to the previously

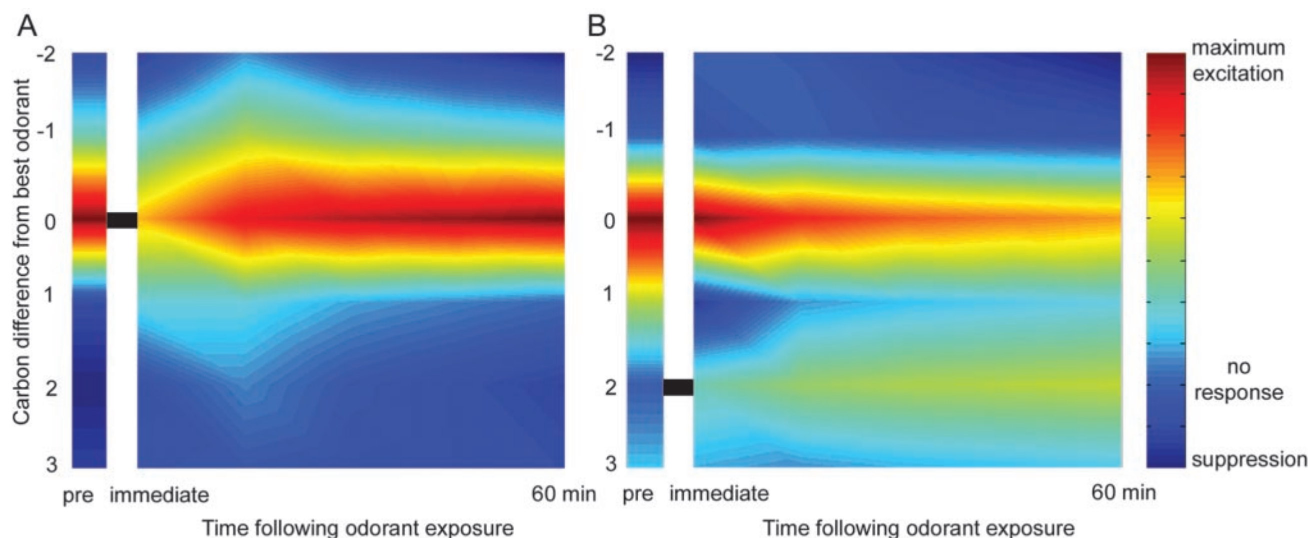

Figure 10. Pseudocolor representation of ORF changes over the course of 60 min after a single 50 sec odorant exposure. *A*, Mean single-unit changes after exposure to the ON-PEAK odorant ($n = 11$). Immediately after exposure, the ORF is suppressed but appears to recover within 15 min. After this, the ORF remains relatively stable over time, with no apparent shift, and the BEST-ODORANT remains the same. *B*, Mean single-unit changes after exposure to the OFF-PEAK odorant ($n = 10$). In contrast to the ON-PEAK exposed cells, after the initial suppression was brought about through OFF-PEAK exposure, the ORF displays major changes throughout the 60 min. The ORF shape changes with the responses to the BEST-ODORANT being suppressed, and responses to the experienced odorant being enhanced. The horizontal bar represents the carbon chain length of odorant presented during exposure. The color bar represents the amount of odorant-induced activity, with red being excitatory odorant responses and blue being suppression relative to baseline.

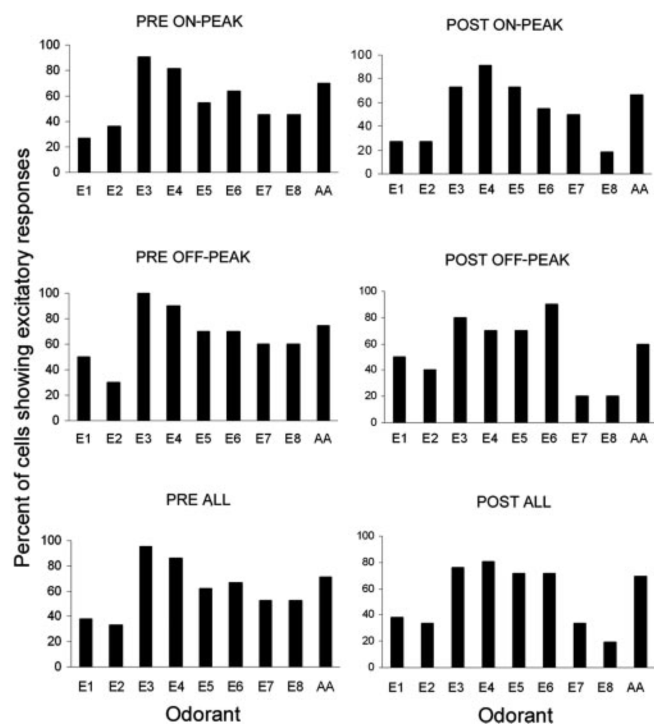

Figure 11. Mitral–tufted cells show narrowing of responsiveness to all esters after 50 sec of exposure with one of the esters in the series. As a population, both ON-PEAK- and OFF-PEAK exposed groups showed ORF narrowing with a significant decrease in the percentage of cells showing excitatory responses to the esters 60 min after the 50 sec odorant exposure. A statistical comparison revealed a significant difference between preexposure and postexposure for all cells ($p < 0.05$).

BEST-ODORANT and an increase in responsiveness to the exposed odorant. In some cells, these changes produced a complete shift in ORF peak toward the exposed odorant (Fig. 8*B*). In cells exposed to the BEST-ODORANT, ORFs maintained their preexposure BEST-ODORANT (Fig. 9*A*). In addition to changes in ORF peak, exposure to either the ON-PEAK or OFF-PEAK odorant produced a narrowing of the ORF. Thus, simple exposure to a novel odorant can focus mitral–tufted cell ORFs on the exposed odorant, conceivably enhancing odorant feature discrimination.

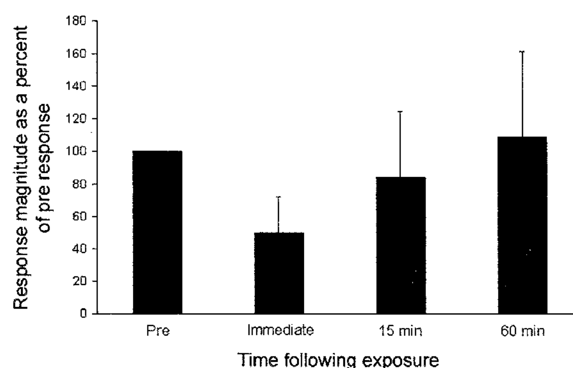

Figure 12. Responses to isoamyl acetate before and after experience with ethyl esters. Response magnitudes are expressed as a percentage of the initial isoamyl acetate response. Similar to the other odorants, adaptation to one of the ethyl esters caused responses to be significantly suppressed. The responses seemed to recover over the course of the experiment and being similar to baseline after 60 min ($n = 13$).

The experience-induced ORF changes reported here are similar to those found in other sensory systems in which experience can modify single-unit RFs and cortical representations (Weinberger, 1995; Buonomano and Merzenich, 1998; Gilbert et al., 2001) to enhance encoding of learned stimuli. The changes observed in the present study did not require specific associative training but used stimuli that the animals had never encountered before. Similar ORF changes may not occur in response to the exposure to well learned or familiar stimuli. The changes observed may represent an initial fine tuning of response patterns to novel stimuli and the first stage of olfactory perceptual learning. In both rats (Fletcher and Wilson, 2002) and humans (Rabin, 1988; Stevenson, 2001), discrimination of novel odorants can be enhanced through experience with those odorants. Although

perceptual learning is thought to be primarily a cortical event in most sensory systems (Gilbert et al., 2001; Wilson and Stevenson, 2003), the mitral–tufted cell ORF changes shown here could also contribute to this behavioral change.

Potential mechanisms of ORF change

Experience-induced changes in mitral–tufted cell excitatory ORFs is somewhat surprising, given that the afferent input to rat mitral–tufted cells is believed to be from a homogeneous population of olfactory receptor neurons. Although the receptor neuron-to-mitral–tufted cell synapse is capable of long-term potentiation (Ennis et al., 1998) and may contribute to the ORF changes seen here (C. Linster, M. L. Fletcher, and D. A. Wilson, unpublished observations), we hypothesize that plasticity in synaptic strength of interneuron connections and cortical feedback may be the major forces shaping mitral–tufted cell ORF experience-induced changes, as hypothesized for olfactory associative learning-induced OB changes (Freeman and Schneider, 1982; Gray et al., 1986; Sullivan et al., 1989; Ravel et al., 1990; McLean et al., 1993; Wilson and Sullivan, 1994; Brennan and Keverne, 1997; Kay and Laurent, 1999; Linster and Cleland 2002; Yuan et al., 2003).

The majority of centrifugal inputs to the OB terminate on inhibitory interneurons (Haberly and Price, 1978; Shepherd and Greer, 1998). Thus, we propose that experience-induced changes in mitral–tufted cell ORFs primarily reflect a change in inhibitory interneuron modulation of the olfactory receptor neuron-driven excitatory ORF. In this way, the BEST-ODORANT of an excitatory ORF of an individual mitral–tufted cell could be shifted between several odorants dependent on past experience. However, it is predicted that the extent of a possible shift will be entirely limited by the ORFs of the receptor neurons targeting the apical glomerulus and dendrite of that mitral–tufted cell. This dependence of coding plasticity on local "horizontal" circuits and descending input from higher processing centers is again highly reminiscent of plasticity in thalamocortical sensory systems (Gilbert et al., 2001).

In summary, mitral–tufted cell odorant ORFs, and thus OB output, are dynamic and can be modulated by odor experience. These ORF changes could affect OB spatiotemporal dynamics as well as cortical odor processing, ultimately resulting in modified perception of familiar odorants.

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