

Post-eclosion odor experience modifies olfactory receptor neuron coding in *Drosophila*

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Olfactory responses of *Drosophila* undergo pronounced changes after eclosion. The flies develop attraction to odors to which they are exposed and aversion to other odors. Behavioral adaptation is correlated with changes in the firing pattern of olfactory receptor neurons (ORNs). In this article, we present an information-theoretic analysis of the firing pattern of ORNs. Flies reared in a synthetic odorless medium were transferred after eclosion to three different media: (i) a synthetic medium relatively devoid of odor cues, (ii) synthetic medium infused with a single odorant, and (iii) complex cornmeal medium rich in odors. Recordings were made from an identified sensillum (type II), and the Jensen–Shannon divergence (D_{JS}) was used to assess quantitatively the differences between ensemble spike responses to different odors. Analysis shows that prolonged exposure to ethyl acetate and several related esters increases sensitivity to these esters but does not improve the ability of the fly to distinguish between them. Flies exposed to cornmeal display varied sensitivity to these odorants and at the same time develop greater capacity to distinguish between odors. Deprivation of odor experience on an odorless synthetic medium leads to a loss of both sensitivity and acuity. Rich olfactory experience thus helps to shape the ORNs response and enhances its discriminative power. The experiments presented here demonstrate an experience-dependent adaptation at the level of the receptor neuron.

imaginal conditioning | sensory adaptation | odor imprinting | Jensen–Shannon divergence | chemo receptor tuning

Olfaction in the fruit fly, *Drosophila melanogaster*, is crucial for a variety of behaviors, including associative learning (1, 2), courtship (3), foraging (4), and flight (5, 6). Odorants are detected by approximately 1,300 olfactory receptor neurons (ORNs), which are housed in sensilla on the third antennal segment and individually express one of approximately 50 functional odor receptors in adults (7–9). All ORNs expressing the same olfactory receptor project to one of approximately 50 glomeruli in the antennal lobe, where they synapse with a set of projection neurons (PNs) (10, 11). The activity of ORNs, either excitation or inhibition, provides behaviorally relevant information about odorants such as their identity, concentration, and source. The information transduced by an ORN is processed in the antennal lobe (12, 13) and sent via PNs to the mushroom bodies, which are believed to be centers for olfactory learning and memory (14, 15).

Experience-dependent modifiability (i.e., plasticity) of olfactory representation at the level of the central nervous system is well known (2, 16, 17). Relatively little attention has been paid to long-term changes in sensory neuron activity resulting from odor experiences. It was previously shown that exposure of newly born imago to a particular set of odorants alters their responses to these odors (18, 19). The flies develop an attraction to the chemicals to which they are exposed and an aversion to other chemicals. We have called this phenomenon imaginal conditioning. The term refers to effects of odor experiences after eclosion and involves experience-dependent plasticity at the level of ORN, an uncommon instance of odor imprinting on receptor

neurons (19). Here we present an analysis, based on information theory, of the changes in single-unit response patterns to some esters as a result of conditioning.

The effects of conditioning were examined by recording the spiking activity of ORNs. We employed a synthetic medium (19) devoid of complex odor cues present in normal cornmeal medium (20) that could be infused with specific odorants. The larvae were raised on synthetic medium, and the emerging flies were transferred to bottles containing the conditioning medium with specified odors. The effect of the odor environment was examined by recording the pattern of spiking activity from a well characterized sensillum, type II (ab2). This large basiconic sensillum contains two neurons, easily distinguishable by their spike patterns, that express the olfactory receptors Or59b and Or85a, respectively (9, 19, 21). In search of a robust quantitative measure sensitive to the differences in ORN firing patterns resulting from different odor experiences, we used the Jensen–Shannon divergence (D_{JS}), a metric widely used in information theory (22, 23) as a quantitative measure of dissimilarity between pairs of spike patterns. The D_{JS} contrasts the differences in the probability of spike occurrence along a response time course, rather than the average firing rate or the total spike count. We show that odor experience changes sensitivity and acuity in distinguishing between different odors.

Results

Imaginal Conditioning Modulates the Sensitivity of ORNs. Sensilla basiconica in *Drosophila* mediate the detection of a variety of general odors (21) and have been classified into seven types. Type I houses four different neurons (i.e., ORNs) and type II contains two neurons (IIa and IIb). This study analyses the effect of imaginal conditioning on firing dynamics of IIa expressing the functional receptor Or59b, responding to a number of odorants. Fig. 1A shows representative traces of type IIa responses to different dilutions of ethyl acetate (EA) in flies conditioned on three different media. Newly eclosed adults raised on odorless synthetic medium were reared on synthetic medium, EA-supplemented synthetic medium, or cornmeal medium. To compare differences in rise and decay kinetics in the ORN firing patterns, we grouped the traces into 50-ms bins and aligned them by the bin with the highest spike number and then compared them with spontaneous firing (SF) treated in the same manner (Fig. 1B). The overall temporal pattern of firing under the three conditions appeared to be similar. A rapid increase followed by a gradual decline in firing.

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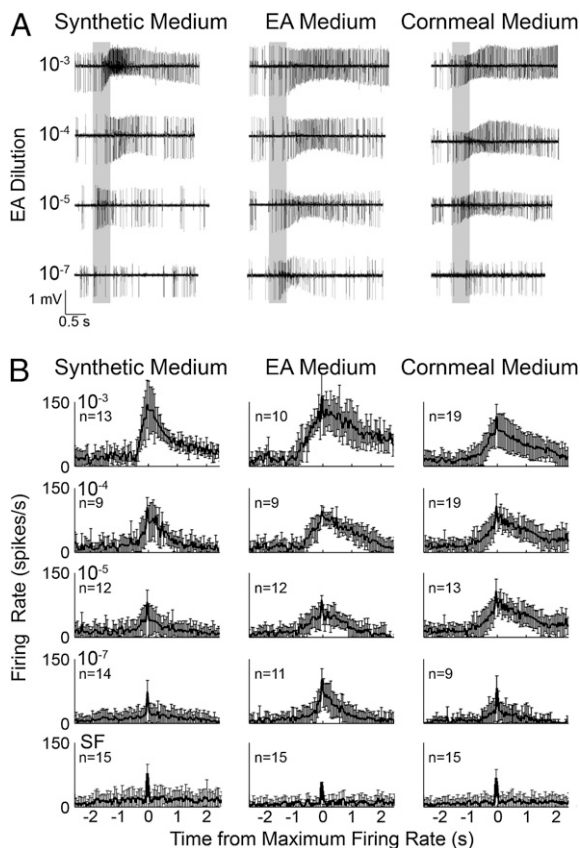


Fig. 1. Responses to EA in type II (ab2) sensilla. (A) Representative traces of extracellular single-unit recordings of type II responses to a 500-ms presentation of EA (gray bar) at dilutions of 10^{-3} , 10^{-4} , 10^{-5} , and 10^{-7} in flies raised on synthetic, synthetic + 10^{-4} EA, or cornmeal medium. (B) Mean and SD firing frequencies of type IIa ORNs are shown in response to EA (from 10^{-3} to 10^{-7} dilutions), or of SF in 50-ms bins aligned by the bin with the maximum firing rate ($n = 9$ – 19 traces).

However, closer examination of the response characteristics reveals marked differences under different conditions based on D_{JS} .

To better describe the changes in response patterns arising from imaginal odor conditioning, we compared several methods applicable to the analysis of response patterns. In addition to previously used measures such as the maximum spiking rate (24) and total spike count (9, 19) within the time course of the response (Fig. 2*A* and *B*), we also explored the “total information gain” as measured by D_{JS} , which has been used in time series analysis of discrete events (25) and appeared to be suitable for quantifying differences between spike trains (Fig. 2). This statistical treatment is a symmetrical version of the Kullback–Leibler divergence (26), and is robust in quantifying distinction between two series of discrete events based on differences in probability distribution of event occurrence within each sequential time interval. We first compared odor responses to SF within a fixed time period to assess the robustness of the responses to an odor. Later, by using the same procedure, we compared the responses to different dilutions of an odor as well as responses to different odors.

After collecting a number of spike trains in response to a particular odor, we determined the spike occurrence within each sequential time bin for the responses to obtain the probability distribution of the spike counts ($i = 0, 1, 2, \dots$) within the bin (50 ms). This was repeated for the responses to each odor. In a pair-wise comparison of odor responses, if two spike count distributions in a particular time bin overlap completely, the D_{JS} is 0 (Eq. 1), signifying that the spike count for this bin does not

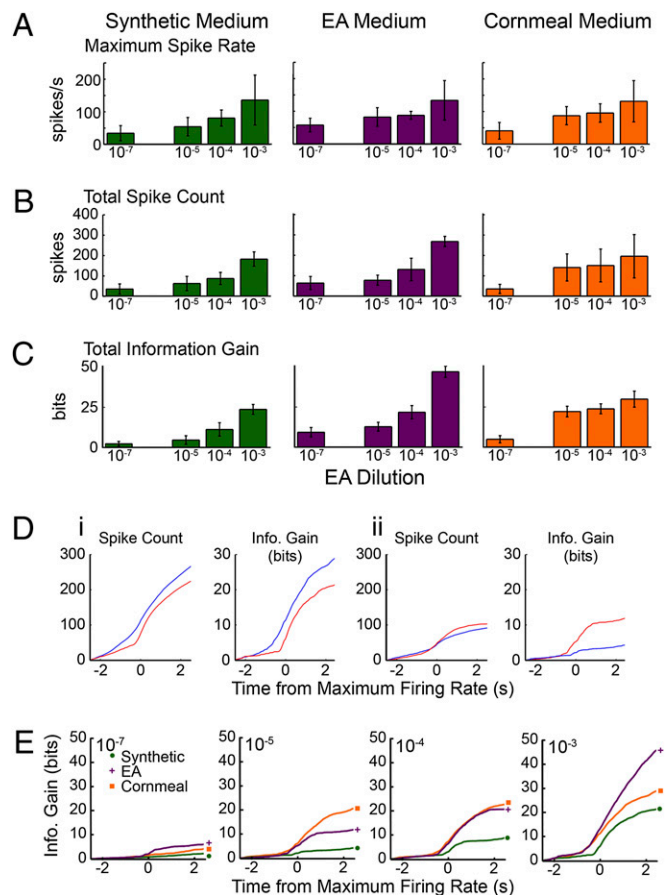


Fig. 2. Quantitative descriptions of type IIA ORN sensitivity to EA after imaginal odor conditioning. Three ways to quantify conditioning effects on odor responses to EA dilutions are by the maximum spike rate (A), total spike count over the response (B), and total information gain based on ΣD_{JS} (C), between the EA response ensembles against SF ensembles (in a 5-s window centered around the time of maximum spiking). The same data sets shown in Fig. 1*B* are compared using these methods. The cumulative information gain was calculated by the bin-by-bin sum of D_{JS} between the EA responses against SF. The values at the end of this 5-s window yield the total information gain for the respective pairs of spike train samples. Error bars indicate SD of observations. (D) Cumulative plots of both the spike count and the information gain along the 5-s window can be used to describe the temporal characteristics of ORN response ensembles. Plotted are examples (i) in which information gain was marginally more effective than spike counts (cornmeal medium conditioning effect on responses to EA at 10^{-3}) and (ii) in a case in which the cumulative information gain produced a drastically improved distinction (EA conditioning effect on responses to EA at 10^{-5} dilution). (E) Cumulative plots of ΣD_{JS} of response ensembles to EA dilutions (against SF) provide a measure of the ability to differentiate between an odor response and SF over the course of the 5-s window.

contribute to the differentiation between the odor stimuli. If, on the contrary, the distributions do not overlap at all, the D_{JS} between them is one bit, implying complete certainty of the odor identity corresponding to each spike train.

The D_{JS} for each time bin along the odor response time course was accumulated as the cumulative information gain (ΣD_{JS}), and total information gain at the end of the 5-s response was compared with the corresponding total spike count (Fig. 2*C* vs. Fig. 2*B*). As used previously for other information theoretic measures (26), the robustness of the total information gain was assessed by using nonparametric bootstrap resampling (27, 28). We found in most cases that the differences between pairs of odor response ensembles over time were more clearly illustrated in their ΣD_{JS}

measures, as resampling of the response ensembles produced relatively small variation in the ΣD_{JS} in comparison with the SD of the other methods relying on simple spike counts. Although the value of ΣD_{JS} is dependent on the bin size and number of bins in the response, the characteristic shape of the ΣD_{JS} values between two ensemble responses are qualitatively similar over a practical range around the adopted 50-ms bin size (12.5–200 ms; Fig. S1).

The cumulative spike count and the cumulative information gain measured by the ΣD_{JS} along the response time course both quantify dynamic features of the odor responses (Fig. 2D); however, there are differences between these measures—particularly when processing the responses to highly dilute odors (compare *i* vs. *i* in Fig. 2D). The cumulative spike count simply reflects the amount of spiking, whereas the D_{JS} determines the distinction in spiking distribution in a small bin. Thus, the ΣD_{JS} provides a measure of the magnitude and timing of differences between two response ensembles in the context of information theory.

Flies raised in any of the three conditions were sensitive to EA at high concentration, although EA medium and cornmeal medium–raised flies showed greater divergence from SF (Fig. 2E). As the EA odor stimulus became more dilute, the sensitivity of flies raised on the odorless synthetic medium dropped first—barely diverging from SF at 10^{-5} dilution. Sensory adaptation after acute exposure to a stimulus would normally be expected to reduce the magnitude of subsequent responses. Surprisingly, long-term exposure in EA media led to the greatest sensitivity to EA-robust responses to EA at 10^{-7} , not seen in other two groups. Conversely, depriving odor experience with synthetic medium led to the least sensitivity to EA stimuli, barely responding at 10^{-5} . Cornmeal medium–raised flies showed a mean level of sensitivity between the other two conditions (Fig. 2E).

Conditioning Does Not Change the SF Pattern of Ila ORNs. Histograms of SF frequency of flies from the three conditioning schemes fit Poisson distributions (Fig. S2), and showed no significant differences among them (χ^2 test, $P > 0.05$). This suggests that the mechanism altering the coding of Ila as a result of conditioning has little effect on the “system noise,” the basal level of transduction and excitability of the receptor cell that generates SF.

ORN Concentration Discrimination Is Modified by Imaginal Conditioning. Another important feature of olfactory perception is the ability to detect minute differences in the concentration of an odor. Greater acuity in detecting differences in odor dilutions indicates a greater capacity of the ORN to code precisely the concentration of an odor. To determine the dynamic range of the dilution-response relationships (shown in Fig. 2C for the three conditioning protocols), we examined the ratio of the information gain (against SF) of the most divergent dilution (10^{-3}) to the average information gain for all dilutions. Both synthetic and EA medium raised flies had similarly large ratios (1.91 and 2.04, respectively) compared with cornmeal medium–raised flies (1.47), suggesting that the former groups could code differences in EA concentration over a greater range.

To confirm the conclusions drawn from the dilution-response relationships (Fig. 2C), we directly assessed the pair-wise information gain (ΣD_{JS}) between different dilutions of EA (Fig. 3A). Importantly, direct pair-wise assessment between EA dilutions revealed similar cumulative information gain in both magnitude and pattern when comparing synthetic and EA medium–raised flies, even though the information gain against SF was much greater for EA medium–raised flies (Fig. 2C). Another feature illustrated in Fig. 3A is that in cornmeal medium–raised flies, substantial distinction of 10^{-3} dilution from other dilutions occurs before the peak firing rate ($t = 0$ s), implying that the initial phase of the odor response contributes substantially to their dilution distinction, despite the more limited total information gain for

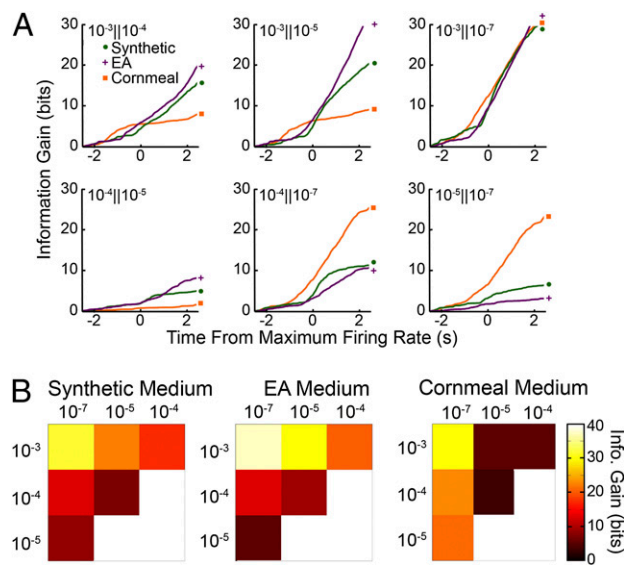


Fig. 3. Imaginal conditioning effects on concentration discrimination based on type Ila ORN responses. (A) Cumulative plots of information gain between responses to different dilutions of EA (10^{-3} to 10^{-7}) demonstrate that the ability to differentiate between the dilutions at different time points along the response is modified by imaginal odor conditioning. (B) Matrices of the total information gain show the pair-wise ability to differentiate among EA dilutions for the three conditioning protocols. The color intensity represents the total information gain between the respective EA dilutions. Table S1 shows the values used.

10^{-3} against 10^{-4} or 10^{-5} . The total information gain between EA dilutions (endpoints of the cumulative information gain in Fig. 3A) are shown in Fig. 3B. It is evident that the complex odor experience of cornmeal medium rearing led to a characteristically different dilution distinction profile, whereas the other two conditioning schemes led to similar profiles. Also in cornmeal medium–raised flies, there is diminished dilution acuity between higher concentrations of EA, accompanied with higher dilution acuity between lower concentrations, in contrast to the results on synthetic medium and single odor exposure on EA medium.

Cross Conditioning: Modification of the Sensitivity to Other Esters.

We also characterized the responses to three other esters—ethyl butyrate (EB), isoamyl butyrate (IB), and isoamyl isovalerate (IV)—that can excite Ila ORNs in terms of the ΣD_{JS} measure. Fig. 4 shows a comparison of responses to different odors at the same dilution (10^{-4}) processed in the same manner as our analysis of EA dilution responses. In Fig. 5, the information gain, based on the ΣD_{JS} , is presented in the same manner as our earlier analysis of EA dilution responses. Conditioning with EA increased the sensitivity to all other esters studied compared with synthetic or cornmeal medium ($\Sigma D_{JS} > 10$ bits over 5 s). However, EA conditioning did not increase the ability to distinguish between other esters.

We also examined the effect of conditioning on synthetic media infused with EB and IV on Ila coding (Fig. S3). As with EA conditioning, EB and IV conditioning led to enhanced response to EB and IV, respectively. Each ester used for conditioning increased sensitivity to all esters compared with odor-deficient synthetic medium. Exposure to a single ester increases sensitivity to all esters activating the Or59b receptor, although not necessarily to the same extent.

Enriched odor experiences on cornmeal medium result in a very different Ila sensitivity scheme. Although EA sensitivity remains high (ΣD_{JS} of approximately 22 bits over 5.0 s), sensitivity to other esters was lowest compared with the responses in

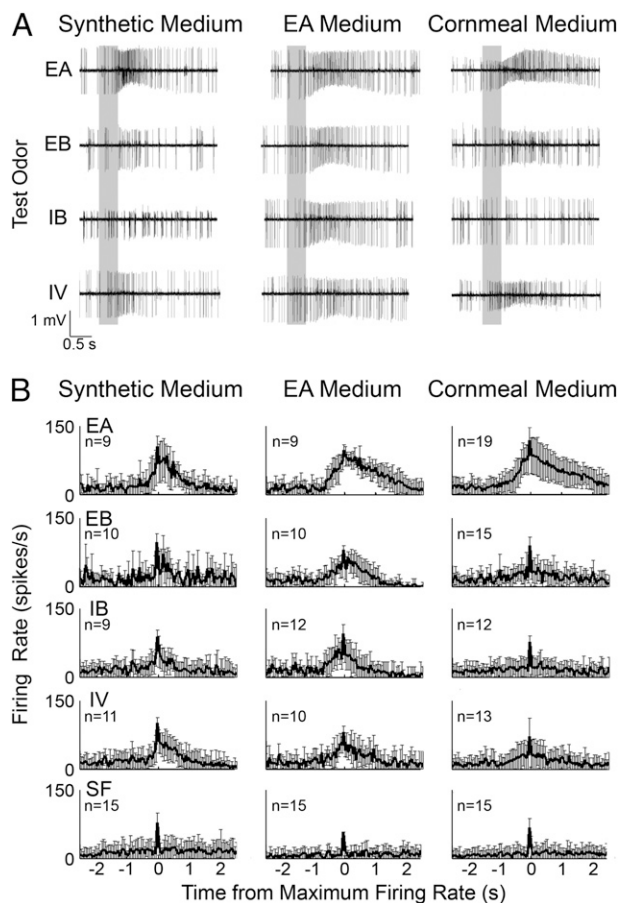


Fig. 4. Cross-conditioning effects on type IIA responses to other esters. (A) Representative traces of four acetate esters—EA, EB, IB, and IV—at 10^{-4} dilution in flies raised on synthetic, EA, or cornmeal media (gray bar indicates 500-ms odor presentation). (B) The firing frequency ensemble of the responses to odors, represented in the same manner as Fig 1 (mean \pm SD; $n = 9$ –19 traces).

flies raised on synthetic and EA supplemented media ($\Sigma D_{JS} < 8$ bits over 5.0 s; Fig. 5). Accordingly, the ratio of information gain from SF of the best separated odor (EA) and the average information gain for all esters tested in cornmeal medium–raised flies (2.12), is much greater than those for odor-deprived (1.23) and single odor–exposed flies (1.54 for EA medium rearing). We therefore infer that enriched odor experiences are important for a sharper tuning of IIA ORN responses to EA among esters.

Coding Space Map of Odor Discrimination Under Different Conditioning Schemes.

So far we have presented only pair-wise discrimination between the response to a particular odor and SF or the response to another odor. We seek to present a global map of the relationships among odor responses following our conditioning schemes. Because D_{JS} provides a distance metric for pair-wise comparisons for each conditioning regime, we constructed a matrix of distances, mapping the relationships among all responses to different odors and concentrations (Table S2). Using the nonlinear ISOMAP algorithm (29), we were able to reduce the dimensionality of the data such that, in a 2D plot, the overall relationship of the ΣD_{JS} for the different esters at two dilutions (10^{-4} and 10^{-5}) can be clearly visualized. In this algorithm, the first axis of the plot can be thought of as the axis most sensitive in distinguishing the odor responses and the second axis as being the second best. In Fig. 6, the nine dimensions required to describe the spike ensembles collected under different conditions (four odors at two dilutions and SF) are

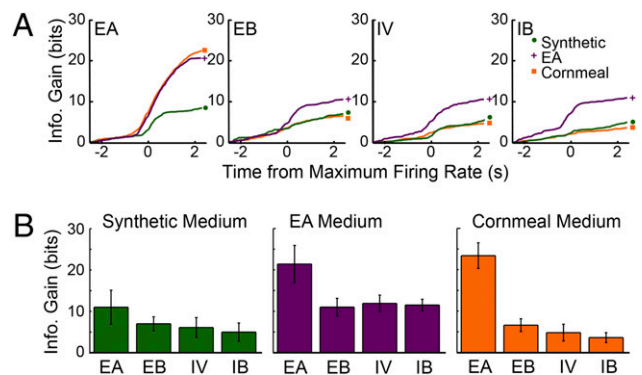


Fig. 5. Information gain measures of the cross conditioning effect on type IIA ORNs ester response sensitivity. (A) Cumulative plots of the information gain of odor responses against SF, based on the data shown in Fig. 4, and plotted in the same manner as in Fig. 2E and Fig. 3A, show that single odor (EA) conditioning increased the sensitivity not only to EA, but also to the esters IB, EB, and IV, compared with flies raised on synthetic medium. In contrast, the enriched odor experience of cornmeal medium–raised flies selectively tuned responses to EA. (B) Bar plots of the total information gain (in the 5-s response window) display the increased sensitivity to different esters in EA medium–raised flies and increased tuning of EA-specific responses in cornmeal medium–raised flies compared with synthetic medium–raised flies (error bars indicate SD).

transformed into 2D maps of best distinction and are displayed at three time points during the spike train ensembles (1.25 s before, at the time of peak firing rate, and 1.25 s afterward). For the sake of clarity, we overlay 200 resampled matrices for each of the nine dimensions reduced using the ISOMAP algorithm (Fig. S4).

The ΣD_{JS} based on IIA ORN responses transformed by the ISOMAP algorithm elucidate the conditioning effects on odor discrimination. As shown in Fig. 6, the plots show that synthetic medium–raised flies show the least separation of odor responses from one another and from SF, consistent with the idea that odor deprivation affects both the sensitivity to odors and identification of odors. In contrast, odor sensitivity is boosted by single-ester exposure, as EA medium–raised flies separate SF from responses to different esters the most. However EA medium–raised flies are not effective in separating a particular acetate ester from the others as they are all clustered together. Enriched odor experience with cornmeal medium conditioning tunes the IIA code for EA particularly well among the tested odors, i.e., the corresponding points are well segregated from the points corresponding to other esters, making IIA ORNs effective detectors of EA.

Discussion

The effects of sensory experience on the function of the central nervous system have been studied in many animals. We have extended the concept of experience-dependent plasticity of information processing to primary sensory neurons by examining the effect of long-term odor deprivation or odor exposure on ORN coding. The key observations discussed in this article are: (i) odor deprivation reduces odor sensitivity, (ii) single-odor exposure increases odor sensitivity broadly to a set of related odors, and (iii) complex odor enrichment tunes ORN sensitivity to a particular odor. These findings are paralleled by studies showing that olfactory sensilla undergo significant morphological changes that result from odor deprivation in *Caenorhabditis elegans* (30), and odor imprinting in zebrafish is correlated with changes in gene expression in their ORNs (31). In addition to plasticity resulting from imprinting or conditioning, other studies in *Diptera* indicate that odor coding may display circadian variation (32, 33), and depend on age, sex, and hunger level (34). Furthermore, short-term priming by certain ketones and alde-

with each other in a pair-wise manner to determine the ability to discriminate between the ensembles.

By using the data shown in Figs. 1 and 4, the following bootstrap resampling procedure was used to assess the robustness of the total information gain measure between two response ensembles (or between a response ensemble and SF): (i) 1,000 resampled ensemble pairs were created by drawing, with replacement from each respective original ensembles, a set of traces; (ii) the ΣD_{JS} over the entire response was calculated for each of the 1,000 resampled response ensembles pairs; and (iii) the mean and SD of the 1,000 resampled ΣD_{JS} values was found.

ISOMAP visualization was done using code adapted from Tenenbaum et al. (29) applied to sets of 1,000 matrices of ΣD_{JS} values between odor response ensembles at three different time points along the odor responses for each conditioning scheme. Each of the 1,000 matrices (9×9) in a set were

created by resampling the ΣD_{JS} between all pairs of response ensembles at the particular time point as previously described. The ISOMAP algorithm, using the four nearest neighbors among the nine odor-dilution combinations used, was applied for each bootstrapped matrix. The resulting points for each matrix were normalized by the SF point and overlaid upon each other (for Fig. 6, 200 maps were used).

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