CHAPTER 9

Priming contributes to concentration invariance in early olfactory circuits

Object recognition requires both specificity, to ensure that stimuli with distinct behavioral relevance are distinguished, and invariance, to ensure that different instances of the same stimulus are recognized as the same under varied conditions (intensity, pitch, position, etc.). In olfaction, the question of stimulus specificity has received considerable attention[1-13]. Psychophysical studies also show that individual odors can be perceived as identical over significant ranges of concentrations[14,15]. Whether concentration invariance results, at least in part, from low-level neural phenomena rather than cognitive grouping is so far unknown. Using locusts, we found that projection neurons in the antennal lobe (the first olfactory relay) are sensitive to odor concentration differences, but often in a history-dependent manner. In ~50% of recordings, exposure to a high concentration modified subsequent responses to lower concentrations such that responses to lower concentrations became more similar to responses to the higher con-

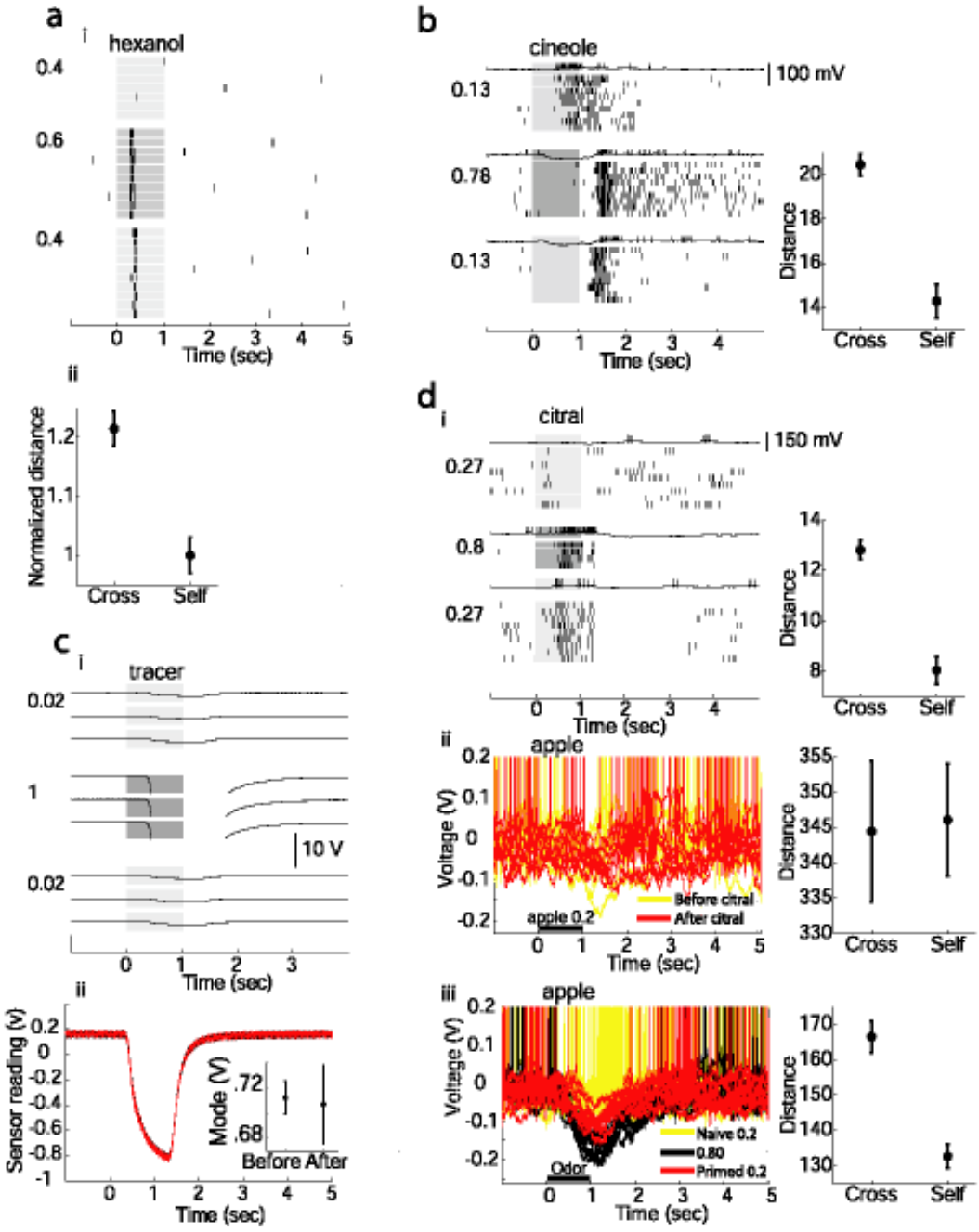
centration recently experienced. This hysteresis, which we called priming, was odor-specific, lasted 15 to 30 minutes, and was not disrupted by exposure to different odors. Priming might provide a mechanism to 'tune in' or bias responses towards an odor likely to be sampled in the near future and contribute to the invariance of neuronal responses across concentrations.

Olfactory systems operate effectively over a very wide dynamic range of concentrations. Insects, for example, can sometimes detect single molecules[16], but also discriminate odors at saturated vapor concentration, such as inside a flower[17]. Odors at different concentrations are sometimes perceived as different[14] and can even acquire a different hedonic valence[18]. Electrophysiological studies in the olfactory bulb (OB) of vertebrates, indeed, indicate that mitral cells (MC) responses generally change with stimulus concentration[13,19-21]. Nevertheless, behavioral studies also show that animals can normally recognize an odor across a range of concentrations[14,15]. Concentration invariance has so far not been described at the level of single neurons.

The antennal lobe, the insect analog of the vertebrate olfactory bulb, is the site of projection of olfactory receptor neurons. In locusts, it forms a compact (830 output neurons) and dynamic representation of odors[22]. We carried out intracellular recordings from projection neurons (PNs), the insect analog of mitral cells, in the antennal lobe of awake locusts, while presenting series of 1-sec-long odor puffs of varying concentrations using a computerized delivery system. The stimulus sequence was delivered to an initially naïve animal, that is, one that had no prior experience with the odor tested.

PNs in naïve locusts generally proved to be concentration sensitive (responses to two concentrations were significantly different in 58 out of 62 responsive odor/cell pairs tested, Distance test, see Methods). Responses increased in contrast relative to baseline with increasing concentration. Increasing concentrations strengthened excitatory responses ($p<10^{-4}$, n=62, see Methods) and inhibitory responses as seen in a lengthening and deepening of subthreshold inhibitory periods ($p<10^{-3}$ for both, Wilcoxon test, n=49; see Methods) (Fig. 8.3; see also Figs. 9.1-9.4).

We observed, however, that PN response differences across concentrations depended on the animal's past history of stimulation. Exposure to between five and ten 1-sec-long pulses of high concentration induced significant changes in odor responses to lower concentrations in 28 out of the 49 concentration-sensitive PN-odor pairs tested ($p<<10^{-6}$, Fig. 9.1a). This proportion is a lower bound, for only a small set of concentrations was tested with each PN-odor pair. These changes included the induction of responses to previously ineffective concentrations (Fig. 9.1a) as well as changes in preexisting responses (Fig. 9.1b). Priming affected both inhibitory and excitatory responses (Fig. 9.1b). Each PN's response was affected in ways more complex than a simple increase or decrease in firing rate; instead, priming made the response to lower concentrations seemingly more similar to the response to a higher concentration (Fig. 9.1b and see below). We call these high concentration-induced changes priming. Priming was not due to hysteresis in the odor delivery system, because responses of a detector to the same low concentration presented before or after high concentration


a
i
hexanol
0.4
0.6
0.4
Time (sec)
ii
Normalized distance
Cross
Self
b
cineole
100 mV
0.13
0.78
0.13
Distance
Cross
Self
Time (sec)
c
i
tracer
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Sensor reading (v)
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Naive 0.2
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Primed 0.2
Distance
Cross
Self
Time (sec)

Figure 9.1. **Exposure to a higher concentration primes PNs' excitatory and inhibitory response to lower concentrations in an odor specific manner. a,** Exposure to a suprathreshold concentration sensitizes PNs to previously subthreshold concentrations. **i,** Trials were presented (top to bottom) with 10 seconds between the onset of each trial and 1 minute in between concentrations (0.4 and 0.6, fration of saturated vapour) for purging the odor delivery system. **ii,** Responses after priming with a suprathreshold concentration were significantly different from responses to the same stimulus before priming ($p«10^{-6}$, Distance test, n=49 cell-odor pairs with significant concentration sensitivity in the naïve state tested for priming). **b,** Priming affects inhibitory components of responses as well as excitatory ones. A different PN's response to cineole before and after priming with a stimulus at a higher concentration. Responses to 0.13 before and after priming (computed for t=0-1 s and t=1-2 s periods) were significantly different ($p<10^{-4}$, Distance test). **c,** Priming is not due to hysteresis in the odor delivery system. **i,** Concentrations delivered in response to identical pulses of 2% of saturation (0.02) before and after a series of saturated vapour (1) pulses are statistically indistinguishable ($p>0.6$, Welch test and T-test). Signal caused by high concentration stimulus off scale. **ii,** Overlaid detected sensor responses from 16 trials at a concentration of 0.02 before (black) and after (red) delivery of high concentration. **Inset,** Mean and standard deviation of mode concentration readings for pulses at 0.02 concentration, before and after delivery of high concentration are overlapping. **d,** Priming is odor-specific and excitatory and inhibitory responses to different odors can be independently primed in the same cell. Exposure to citral at a concentration of 0.8 primes excitatory responses of another PN to citral at a concentration of 0.27 (i) but does not prime responses to apple (ii). The same PN can be primed to respond with inhibition to apple by exposure to apple at a concentration of 0.8 (iii). **Left**: **i,** Intracellular traces (top) and rasters obtained in response to 0.27 citral in a naïve animal, followed by 0.8 and then 0.27 again. **ii,** Superimposed intracellular voltage traces for ten trials of 0.2 apple before (yellow) and after (red) exposure to 0.8 citral. **iii,** Superimposed intracellular voltage traces for ten trials each of 0.2 apple before (yellow) and after (red) exposure to ten trials of 0.8 apple (black). Inhibition of priming affects both hyperpolarization and firing rates: notice spikes present during the odor response in the naïve animal (yellow) disappear after priming (red). **Right**: Distance test (see Methods): (i) $p<10^{-4}$; (ii) $p=0.9$; (iii) $p<10^{-5}$.

pulses were statistically indistinguishable (Fig. 9.1c). Both gas chromatography-mass spectroscopy (GCMS) and polycaprolactone/carbon black (80:20 wt/wt) composite polymers[23] confirmed this result. Priming was specific to odor-responses and could not be attributed to changes in basal firing rate (the changes observed over odor responses were significantly greater than any trends in basal period, $p<<10^{-6}$, Distance test, n=49 cell-odor pairs).

To test whether priming is odor-specific, we presented the following stimulus sequence: A low → B low → B high → B low → A low → A high → A low, where X low stands for odor X at the lower concentration and X high stands for odor X at the higher concentration. Priming was odor-specific: presentation of one odor at the higher concentration caused PNs to respond to previously ineffective concentrations of that odor ($p<0.0005$, n=12 cell-odor pairs, Distance test, Fig. 9.1di), while leaving responses to similar (or even greater) concentrations of a second odor unchanged ($p>0.1$, n=12 cell-odor pairs, Distance test, Fig. 9.1dii). This was true even when responses to the second odor could be primed by subsequent high concentration exposure with that odor ($p<10^{-5}$, Distance test between lower concentration of second odor before and after exposure to higher concentration, Fig. 9.1diii). Priming did not extend across chemically similar (citral (an aldehyde) and its corresponding alcohol, geraniol; hexanol and octanol) or structurally different odorants. Thus, different responses to multiple odors could be enhanced independently in the same neuron. Indeed, a given neuron could exhibit priming of excitation for one odor and priming of inhibition for nother (n=9 odor pairs in 5 cells; see Fig. 9.1d), suggesting that priming is not caused by an intrinsic change in PN excitability.

To quantify whether priming contributed to creating a representation of odor identity that is less dependent on concentration, we asked whether primed responses to low concentrations were more similar to the responses to the (higher) priming concentration trials than the initial responses to low concentrations were. We assayed similarity between responses by calculating the mean distance, using a cost-based metric[24], between spike trains of individual trials for each concentration, in the primed and naïve conditions. After priming, PNs' responses were more similar across different concentrations ($p<0.005$, Distance test, n=49 cell-odor pairs; see Fig. 9.2c), both in firing rates (Fig. 9.2a) and interestingly, in response patterning (Fig. 9.2b-c and see below). Exposure to a high concentration decreased PNs' sensitivity to concentration and thus contributed to concentration invariance. The extent of priming, measured as the across/within-groups distance ratio for odor responses divided by that for the baseline period preceding odor present, was significantly and positively correlated with the concentration sensitivity in the naïve neuron ($r=0.87$ for all 51 cell-odor pairs, $r=0.93$ for concentration-sensitive datasets): the more different responses were to different concentrations in the naïve animal, the more the response to lower concentrations changed in response to priming (see also Fig. 9.2d). None of the PN-odor pairs that were not sensitive to con-

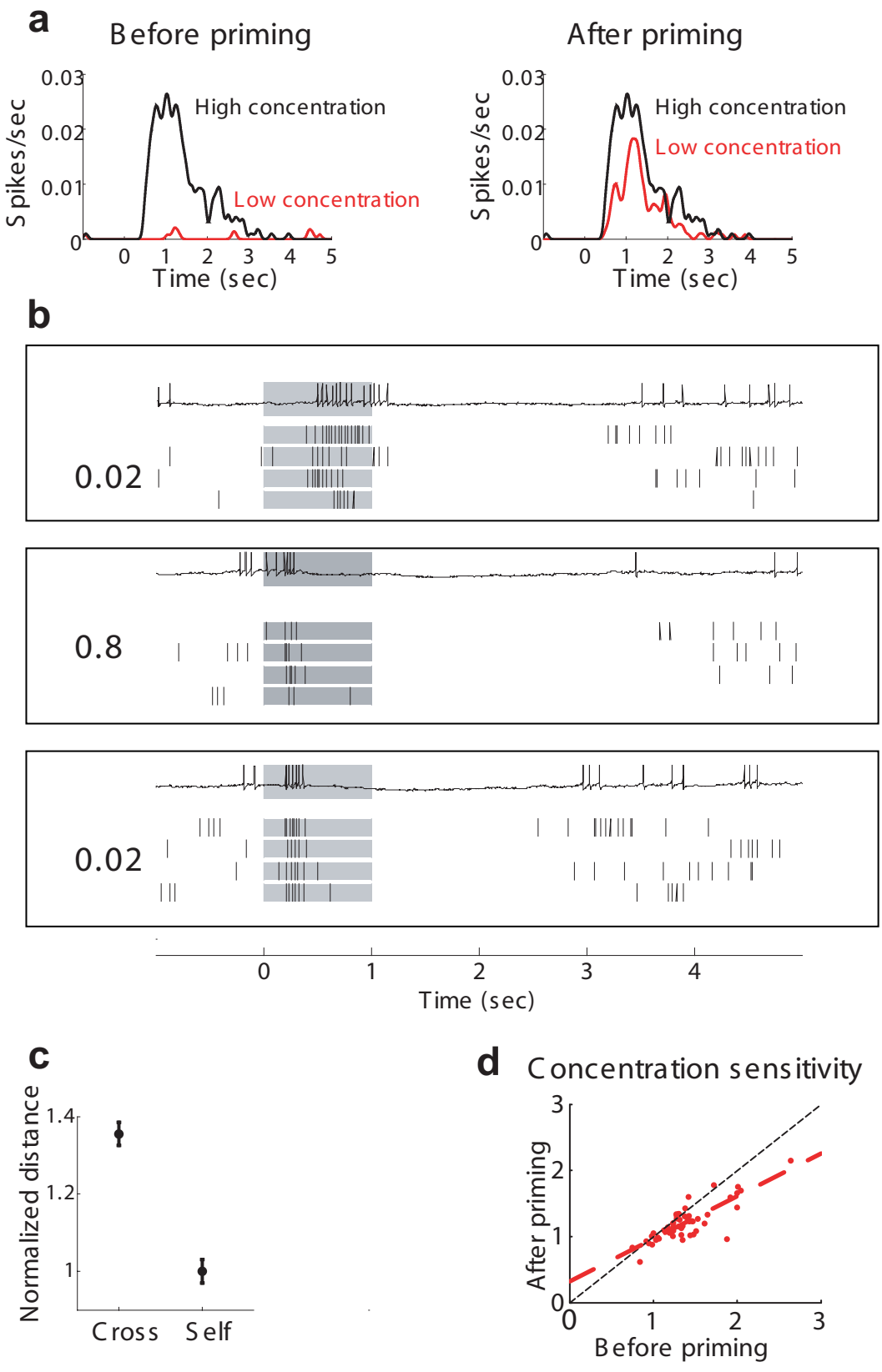

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Figure 9.2. **Priming makes a PN's response more invariant to concentration**. **a,** A PN's firing rate at low and high concentration before and after priming. **b,** Priming makes the response pattern of a PN to lower concentrations more similar to that at higher concentrations ($p<10^{-4}$, Distance test). **c,** Response patterning is affected by priming even when firing rate information is eliminated by normalization ($p<<10^{-6}$, Distance test, n=51 PN-odor pairs). **d,** Scatter plot of the concentration sensitivity of each PN-odor pair before (x-axis) and after (y-axis) exposure to high concentration. All 51 datasets are shown, regardless of whether they were affected by priming or not. Concentration sensitivity is defined by the mean ratio of across-group/within-group distances over all trials (see Methods). The black diagonal line denotes identity (y=x). Note that the population of PN-odor pairs is shifted toward the right of the diagonal, indicating a shift toward greater concentration invariance (concentration sensitivity was significantly reduced by exposure to high concentration, $p<0.005$, Wilcoxon ranksum test, n=51). The red dashed line represents the best linear fit to the data. Its intercept with y=x at x=0.97 indicates that the concentration sensitivity of PN-odor pairs that are initially not concentration-sensitive is not affected by priming. Its slope (0.32) indicates that the most concentration-sensitive PN-odor pairs are affected the most by priming. See also Figs. 9.1 and 9.3.

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centration in the naïve state (i.e., which did not respond to the odor at any concentration when first exposed or whose responses to the two concentrations were not significantly different) were affected by priming (see also Fig. 9.2d). We then tested explicitly whether priming could contribute to identification of odor identity robustly across concentrations. We classified the response of each trial as indicating the odor whose responses across all concentrations tested were on average most similar to those of the trial being classified[25], using the cost-based metric[24] to assay similarity. We found that priming significantly improves classification among odors presented at multiple concentrations ($p<0.05$, n=28 cell-odor pairs that underwent significant priming, as defined by exhibiting primed responses significantly different from naïve responses).

To quantify whether the temporal patterns in PN responses were affected above and beyond the effect on mean firing rates, we calculated a peri-stimulus time histogram (PSTH) for every trial (using a range of s.d. values from 25 to 250 msec), normalized so that the mean firing rates of all trials were identical, and then assayed priming as described above, using the sum squared difference between PSTHs as the distance metric. Exposure to high concentration significantly changed the temporal response patterns evoked by low concentrations ($p<<10^{-6}$, Distance test, n=51 PN-odor pairs, Fig. 9.2c).

To assay whether priming was due to the intervening block of high concentration trials or to the passage of time alone, we carried out experiments presenting three successive blocks of trials of the same odor at the same low concentration (low→low→low) and compared the responses obtained in the third block of trials to those obtained, with the same neuron, after exposure to a high concen-

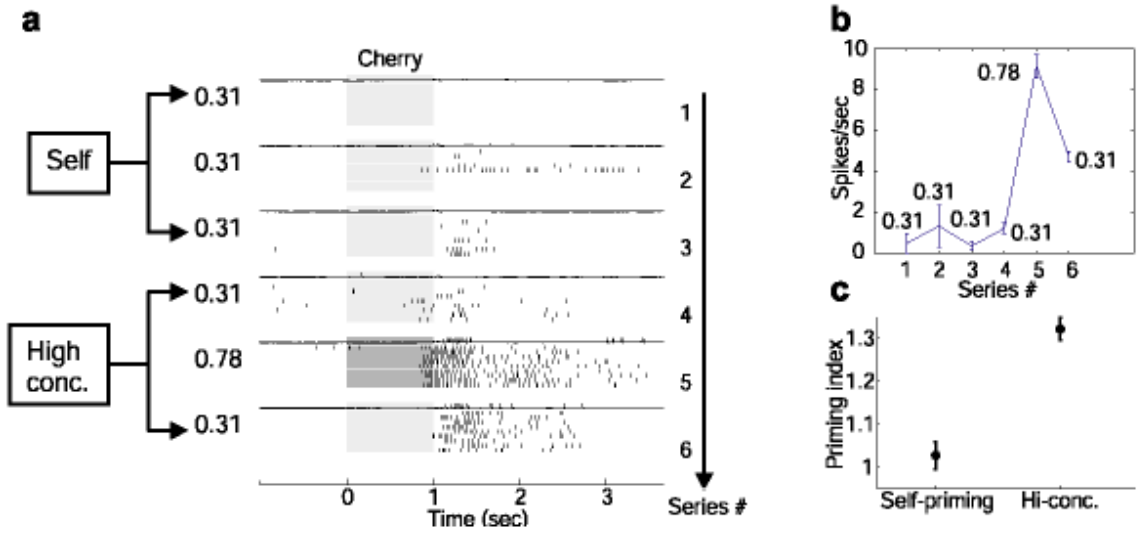

Figure 9.3. **Repeated presentation of an odor at the lower concentration is not sufficient to elicit the priming caused by exposure to a higher-concentration primer. a,** 40 trials of cherry at a concentration of 31% of saturation were presented (left panel), followed by 10 trials of a concentration of 78% of saturation, followed by a final series at 31%. **b,** Mean firing rate during the response period (computed over 0.5-3.5 s interval) for each series on the left panel. **c,** The change in response to the lower concentration, measured by a priming index equal to the ratio of mean across-series distance over mean within-series distance, is significantly larger after exposure to a higher, suprathreshold concentration (right bar) than it is after an equivalent time period with exposure to the lower concentration (left bar) ($p<<10^{-6}$, Distance test, n=6 cell-odor pairs).

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tration (low→high→low) (Fig. 9.3). Neither time nor repeated presentation of the odor at low concentration was sufficient to elicit the changes induced by exposure to high concentration ($p<10^{-5}$, binomial test, n=6, see Methods). Even after equating the total quantity of odorant to which the animal was exposed in each condition by prolonging the number of exposures to low concentration (low-low-low-low-high-low), exposure to high concentration was more effective in inducing priming than a more prolonged exposure to a lower concentration ($p<10^{-4}$, Distance test). Exposure to a higher concentration thus appears to be needed for rapid priming. Conversely, experiments were carried out where the sequence of concentrations presented in the three successive trial blocks was reversed (high-low-high). Priming by the low concentration was never observed under these circum-

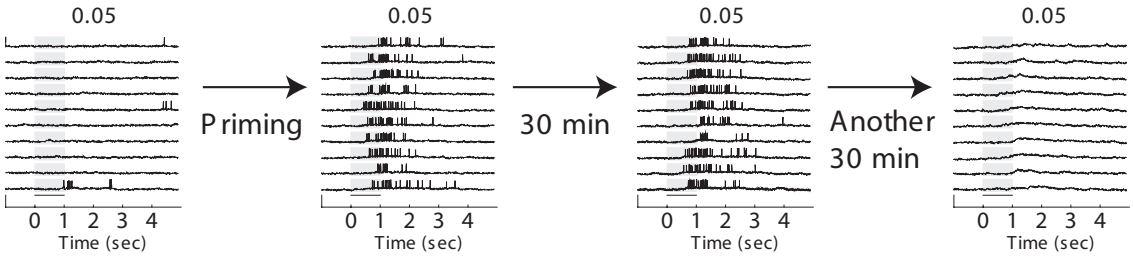

Figure 9.4. **Priming persists for half an hour, but is for the most part reversed 1 h after exposure to high concentration.** A PN's response to the odor geraniol at 0.05 concentration before, immediately after, 30 and 60 minutes after exposure to a higher concentration (0.31). After the neuron stopped firing in response to geraniol at 0.05, the higher concentration continued to evoke suprathreshold responses (data not shown).

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stances ($p>0.38$, Distance test, n=20 concentration-sensitive cell-odor pairs). Priming is thus induced on low concentration responses by exposure to higher concentrations and not the reverse.

We next investigated the duration of this memory. An animal was challenged with a set of low concentration trials, primed with higher concentrations and then stimulated with another set of low concentration trials after variable delays. The effect of priming on PNs was present 15 to 30 minutes after exposure to the primer ($p<<10^{-6}$, Distance test, n=5 cell-odor pairs) but was generally gone an hour later (priming absent 52±32 min after exposure to high concentration, $p>0.3$, Distance test, n=6 cell-odor pairs, all originally significantly primed) (Fig. 9.4). Responses to the higher concentration were present throughout the recording session, ensuring that the loss of the priming effect was not due to deteriorating recording quality. Moreover, priming was not disrupted by intervening exposure to a different odor ($p<<10^{-6}$, Distance test, n=7 cell-odor pairs).

In summary, exposure to a high concentration was found to prime responses to lower concentrations, including previously ineffective ones, in an odor-specific manner. Priming could enhance both excitatory and inhibitory responses or response phases and affected the timing and patterning of responses, making odor responses more invariant to concentration. The effects lasted over 15 minutes but disappeared within approximately 1 hour.

Our results have several implications. Olfactory sampling is serial and intermittent, due both to the turbulent nature of odor plumes[33] and to periodic sampling given by sniffing[28,29] in vertebrates or by

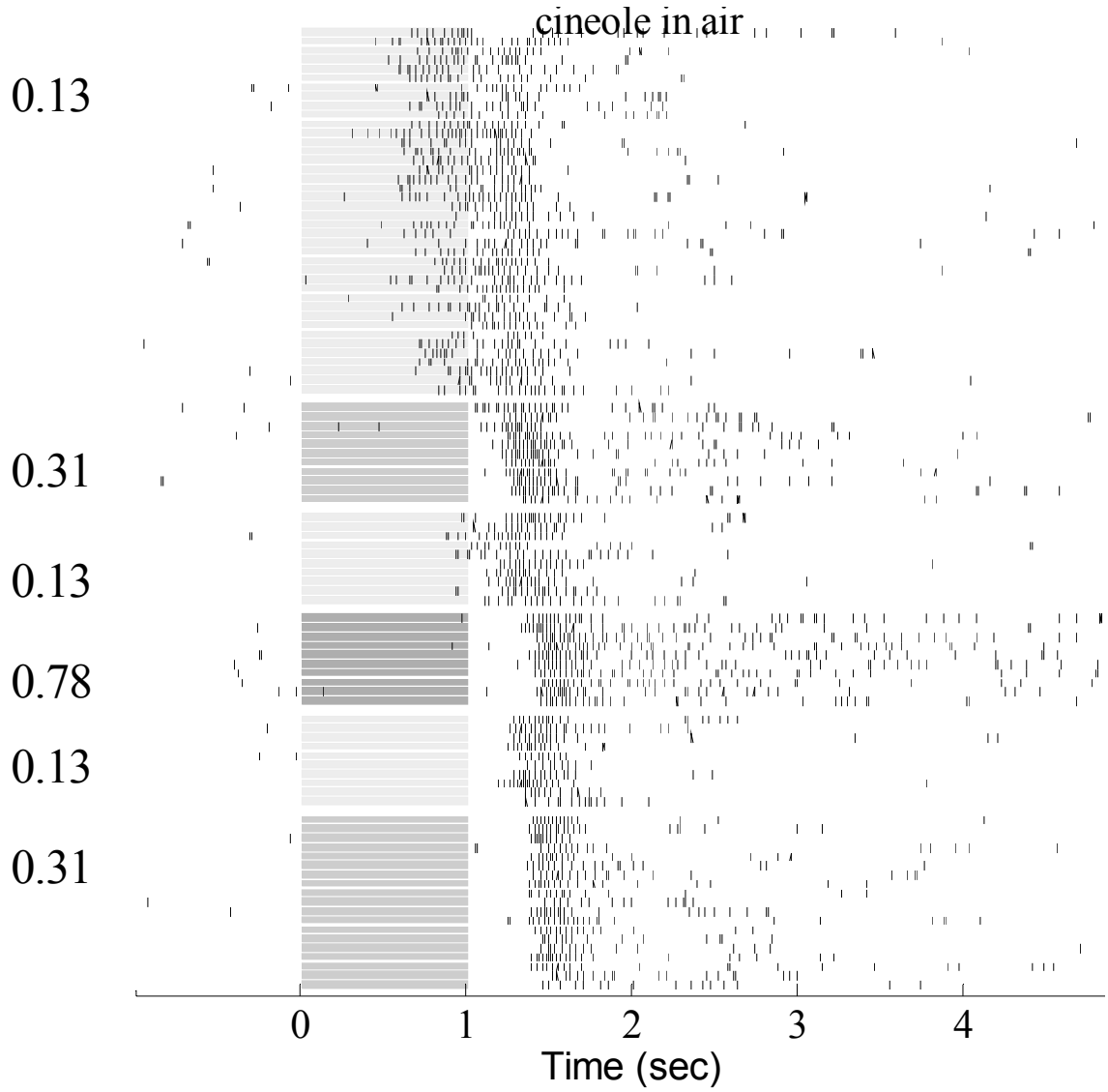

Figure 9.5. **Odor pulses of cineole at varying concentrations, shown in order of presentation from top to bottom.** Note the relative similarity of responses to different concentrations after priming compared to naive responses.

antennal movements in arthropods[30]. Clearly, taking the results of previous samples into account can be advantageous. In natural odor plumes, filaments of higher odor concentration alternate with ones of lower concentration[26,27]. By lowering response thresholds to an odor detected with certainty in the recent past, priming might provide a way to 'tune in' or bias responses towards correct identification of an odor likely to be sampled in the near future.

Prolonged exposure to an odor has been previously shown to enhance sensitivity and discrimination both at the behavioral[31-37] and peripheral neural[38-40] levels. Such a sensitization, however, occurred over days to weeks rather than seconds to minutes as in our experiments. Exposure for 20 continuous min/day for a week, on the contrary, has been seen to decrease responsiveness of mitral/tufted cells in the rat olfactory bulb non-specifically[41,42]. The difference between these results and ours, using brief pulsed stimuli, suggests that intermittent odor stimuli, like those encountered in natural odor plumes[26,27], may be differentially recognized by early olfactory circuits. It also suggests that olfactory circuits likely change over many different time scales, each adapted to input statistics.

Our results suggest that the response of early sensory circuits to a stimulus can be influenced for relatively long periods by the recent history of stimulation, and that exposure to a stimulus can change subsequent neuronal responses not only to the same stimulus[43], but also to weaker stimuli with the same odor identity. Note that the short-term plasticity previously described by Stopfer and Laurent[43] in the same neurons is quite different from that described here: the former affects the synchronization of PNs over repeated trials at one concentration, while priming reduces the variance of response patterns across concentrations. The timescales of the two phenomena are also different: the effects on synchronization last less than 12 minutes, while priming persists for at least 15-30 min. Whether the changes we describe here are particular to the olfactory system or are more general remains to be seen (but see ref. [44]); because priming has been observed behaviorally both with vision and hearing[45,46], similar cellular effects might be found in those systems as well.

Our results also suggest a solution to the tradeoff between representing odor concentrations and identity. Over all PNs, sensitivity to odor concentration is greater in naïve PNs than after repeated exposure. After exposure to high concentrations, the system may switch to a mode at once more sensitive (response threshold is lowered) and more invariant to concentration. Because priming was seen to affect only 57% of tested PN-odor pairs, it is also possible that different subcircuits within the antennal lobe subserve different roles.

The mechanisms behind priming are, as of now, unknown. Our results appear to contradict what one would predict from knowledge of the adaptation of olfactory receptor neurons[47-50], mitral cells[51]

and olfactory perception[52]. An explanation is that adaptation is a more rapid phenomenon (both on and off)[50]. Adaptation and priming may coexist. Indeed, 3 PN-odor pairs exhibited adaptation in our experiments. These PNs were the same that exhibited priming, both for other odors and for the odor that caused adaptation. Adaptation lasted only seconds to a few minutes, and affected concentrations lower than those that were affected by priming.

Our results lead to testable behavioral predictions. If the behavior of projection neurons is echoed by downstream neurons involved in recognition by the animal, one would expect that exposure to an odor at high concentration would rapidly, transiently and specifically lower the animal's detection threshold for that odor, enhance recognition of that odor in a noisy environment, and do so in a transient manner. Such behavioral improvement of detection in the face of noise after exposure to a stronger version of the stimulus is well known in visual psychophysics[53], but to our knowledge remains to be tested in olfaction.

Methods

Specimens, odor stimulation and electrophysiology

Intracellular recordings were obtained from 46 PNs (150 PN-odor pairs) of 21 locusts, *Schistocerca americana*. Surgery and recordings were performed as previously described[54,55]. Delivery of eight odors, including pure compounds as well as ethologically relevant blends, was performed using a gaseous dilution computerized odor-delivery system. We could deliver arbitrary concentrations by mixing a stream carrying saturated odor vapor with a second stream carrying pure air. The concentration of the odor delivered was regulated by controlling the relative flow rates of both streams[56]. The system was purged between presentation of different stimuli.

The odor timecourse and magnitude was measured by using CO_2 as a tracer in the air line carrying the odor while the diluting stream carried ambient air, and measuring the CO_2 concentration at the nozzle[56]. Direct measurement of the odorant concentration with GCMS also showed that concentration returned to baseline within 1 minute of purging.

Analysis of sensitivity to concentration

Each cell-odor pair was challenged with multiple trials (n_5; n_10 for most datasets) at each of at least two concentrations between 2 and 100% of saturated vapor pressure. The firing rates for different concentrations (Fig. 1a) were compared using a paired T-test comparing maximum (over

time) mean (over trials) firing rates for the highest and lowest concentration tested for each cell-odor pair during 4 sec following odor onset, for the 62 cell-odor pairs with purely excitatory responses. A response was defined as excitatory if one or more epochs (300 or 500 msec, shifted in 100 msec steps, to account for short responses with high temporal precision as well as longer responses with more variance in spike times) exhibited a firing rate increase to at least 3 standard deviations above the mean baseline rate.

The low baseline firing rates of PNs (2-6 Hz) prevented an accurate evaluation of inhibition using firing frequency alone. Instead, the intracellular voltage traces for successive trials of the same concentrations were aligned on the mean voltage during the second preceding odor delivery for each trial. An odor was said to elicit an inhibitory response at a given concentration if there was any period (evaluated with sliding windows of 500 msec shifted in 100 msec steps) during which firing was suppressed and the mean voltage was at least 3 standard deviations below the mean voltage during the period preceding odor delivery. 35% of datasets showed some period of inhibition and individual responses often contained a period of excitation and a period of inhibition. The depth and duration of inhibition were quantified for each concentration. Depth was the mean voltage during all inhibited epochs. Duration was defined as the total duration of all epochs during which inhibition was detected.

Distance test

To further quantify the degree to which each PN was sensitive to the concentration of a novel odor (Fig. 1e), we calculated, for each cell-odor pair, the mean distance between each trial and all other trials for the same concentration (*within-group or self-distance)* and that between each trial and all trials of a different concentration (*across-groups or cross-distance*). The responses to two concentrations were said to be significantly different if the mean across-groups distances, measuring the effect of concentration, were significantly greater than the mean within-group distances, measuring the variability of responses within trials with one concentration. Significance was evaluated with a Wilcoxon ranksum nonparametric test. Distances were calculated using a cost-based metric[24], which measures the difference between two spike trains taking both the number and timing of spikes into account. This distance is defined as the cost paid to transform one spike train into the other using three elementary steps: insertion; deletion of a spike (each at a cost of 1); and displacement of a spike by 1 ms (cost of 2/*T* for each displacement). T thus dictates how far two spikes can be for them to be considered 'similar' in timing. We used a range for *T* between 10 and Infinity, with qualitatively similar results for T>=25 ms (data shown for T=250 throughout the text)[31]. For inhibi-

tory responses, traces were low-pass filtered with a cutoff of 20 Hz, aligned on their mean voltage during the period preceding stimulation, and the distance between two traces taken to be the mean square difference between the traces. To discount any nonspecific change in a neuron's firing rate, two conditions were considered significantly different only if their cross/self distance ratios were significantly greater for the odor response than for the baseline period preceding odor stimulation. For brevity, we call these tests the Distance test throughout the text. Charts show the mean self- and cross-distances for the groups compared and the standard error of the means.

We applied the same test to quantify the extent to which priming had modified responses to lower concentrations (Fig. 2a,c,d and 4c), and the degree to which priming diminished the concentration sensitivity of PNs (Fig. 3c). In this case, the two conditions compared were responses before priming vs. after priming, rather than responses to different concentrations.

Effect of time vs. concentration

All 6 cell-odor pairs showed more change after a high concentration primer than after an equal period with repeated exposures to the same odor at low concentration. For 5 of the 6, the mean across/within distance ratio was significantly larger for the experimental condition with an intervening high concentration than for the control condition without one ($p<10^{-5}$, binomial test). Additionally, a paired T-test on the mean cross/self distance ratios for each dataset showed those ratios to be significantly higher for the experimental condition than for the control one ($p<0.005$, paired T-test).

Decrease in concentration sensitivity

Concentration sensitivity is defined as

$$S = \frac{< \text{across - series distance} >}{< \text{within - series distance} >}$$

where the across-series distance is computed between naïve low and primer high before priming, and between primed low and primer high after priming, and the within-series distances are averaged across the two corresponding series.

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