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Short-Latency Single Unit Processing in Olfactory Cortex

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Abstract

■ Single-unit recording of layer II–III cells in olfactory (piriform) cortex was performed on awake, unrestrained rats actively engaged in learning novel odors in an olfactory discrimination task. Five of the 67 cells tested had very brief monophasic action potentials and high spontaneous firing rates (30–80 Hz); it is suggested that these units were interneurons. The remainder of the neurons had broader spikes and did not discharge for prolonged periods. Thirty-nine percent of the broad spike cells responded to at least one and usually more of the odors presented to the rats during either of the first two trials on which that odor was present, but, in most cases, these responses occurred only very infrequently over the course of subsequent trials. Six percent of the broad-spike group, however, continued firing robustly to a single odor but not to others.

From these results it appears that most cells in piriform cortex do not respond to most odors, i.e., coding is exceedingly sparse. A subgroup of the predominant broad-spike cell type does react to several odors but this response drops out with repeated exposure, perhaps because of training. However, a few members of this class (a small fraction of the total cell population) do go on responding to a particular odor, thus exhibiting a form of odor specificity. The results are discussed with regard to predictions from recently developed models of the olfactory cortex. ■

INTRODUCTION

Behavioral studies have shown that mammals in olfactory learning tasks are capable of very rapid locomotor responses (within 0.5 sec) to olfactory cues even though typical odor delivery systems take up to 100 msec from odor onset to time of reception at the epithelium (Staubli, Fraser, Faraday, & Lynch, 1987; Roman, Staubli, & Lynch, 1987; Eichenbaum, Kuperstein, Fagan, & Nagode, 1987). It is thus of interest to identify processes performed within this relatively narrow time window during which odors are detected and recognized, and appropriate responses are organized. Further interest has accrued to these questions in light of recent theoretical work generating conjectures about the nature of olfactory processing via simulation and modeling (e.g., Freeman, 1975; Haberly, 1985; Shepherd & Brayton, 1979; Li & Hopfield, 1989; Granger, Ambros-Ingerson, & Lynch, 1989; Ambros-Ingerson, Granger, & Lynch, 1990). Surprisingly few experimental studies have focused on the responses of single primary sensory cortical units during acquisition of novel olfactory stimuli in behaving, freely moving animals. We have previously (Lynch & Granger, 1989; Granger et al., 1989) forwarded a hypothesis of olfactory processing in which the characteristics of sparsely connected cells in competitive organizations (i.e., containing lateral inhibition) gave rise to extremely sparse firing patterns in the cortex, which were modified, via synaptic long-term potentiation (LTP), to generate stable odor-specific responses. The present study was motivated by these considerations in an attempt to characterize the behavior of single units in the period during which processing might actually be occurring, i.e., between reception and response.

RESULTS

Unit Classification and Distribution

Sixty-seven units in 20 animals were recorded during olfactory learning behavior, in 183 sessions that included from one to seven odor pairs for each unit. Two easily distinguished types of cells that gave short latency responses to LOT stimulation were recorded. Type I cells, which constituted by far the larger class (62/67), had relatively broad spikes ($\geq$ 500 μsec, unfiltered; Fig. 1a). Most of these occasionally emitted a burst: a high-frequency ($\geq$ 100 Hz) train of 2–5 spikes, resembling the complex-spike cells seen in hippocampal field CA1. These neurons had relatively low background discharge rates ($<$ 10/sec) and rarely fired for periods of more than 30–50 msec before becoming quiescent. The much less frequently encountered type II cells (5 of 67) had sharp monophasic action potentials ($<$ 400 μsec, unfil-

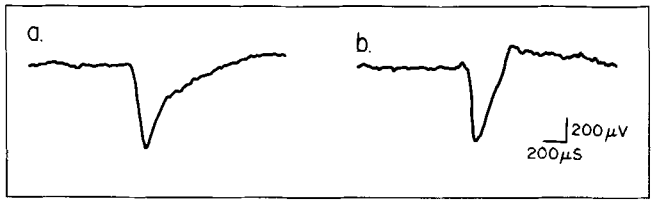

Figure 1. Comparison of unfiltered extracellular recordings of spontaneous discharges from two distinct cell types in pyriform cortex layer II. Type I cells (**a**) have relatively broad spike widths (≥ 500 μsec) whereas type II cells (**b**) have narrow spike widths (< 400 μsec).

tered; Fig. 1b) and a relatively high steady frequency (30–80 Hz). The 40 Hz EEG activity identified by Freeman and Schneider (1982) was routinely seen in unfiltered records but attempts were not made in the present study to correlate its presence or absence with the behavior of individual units.

Fixed Latency and Sparseness of Unit Responses

The two groups of units were also very different in how they responded to odors. Type II cells (sharp spikes) often exhibited a depression of firing during the 1-sec period prior to odor onset and for 100–150 msec after odor onset (recall that the cue onset begins at a fixed interval of 1 sec after the rat places its nose in the sampling port) and then resumed high-frequency sustained firing beginning at ~ 200 msec (Fig. 2a). This activity did not appear to be odor specific, since a given type II cell would behave similarly during exposure to any of several compounds (six of six tested in the case of one unit) but did vary in its intensity across trials even with the same odor. By analogy to results in hippocampus (Fox & Ranck, 1975), it is possible that the rarely encountered, high-frequency discharging type II units are inhibitory interneurons. The much more common type I cells (broad spikes) were largely unresponsive to odors. The typical neuron in this group was tested while the rat learned at least six odors ($\bar{x} = 7$), which usually involved 9–11 presentations of each odor cue. The median probability that a type I cell would emit a burst response in the period 100–300 msec after odor onset was less than 10%, i.e., across six odors and 60 or more trials the median cell would fire robustly on not more than one or two trials. The relative inactivity of piriform cortex during the period in which odors were presumably detected and recognized was the most striking aspect of the results obtained in this study.

Odor Specificity of Unit Responses

Twenty-four of the 62 type I units did respond to one or more odors on either the first or second trial on which the odor was presented; responses were defined as three

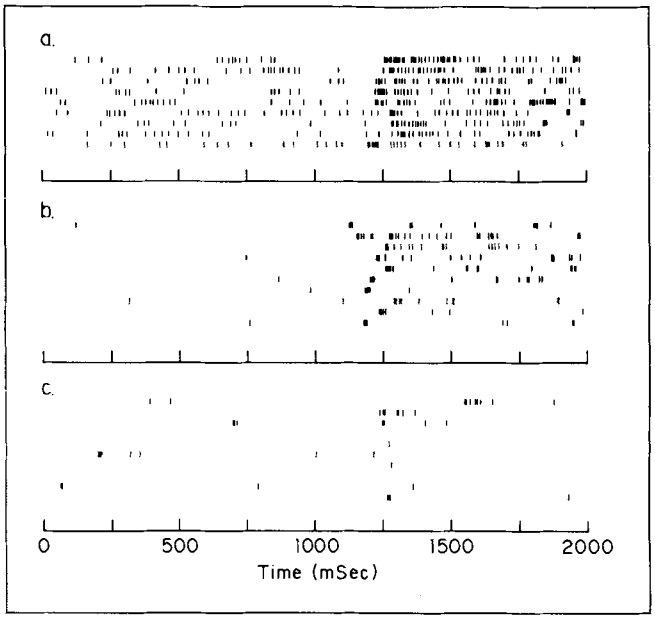

Figure 2. Peristimulus raster plots of unit activity during odor discrimination sessions. In each panel, rows of dashes indicate the time course of cell discharges for a series of trials for one odor. Odor onset begins at 1000 msec. (**a**) Type II cell. Firing rate decreased during the 1-sec period prior to odor onset, increased at odor onset, and then returned to the spontaneous rate later in each trial. (**b, c**) Type I cells. (**b**) Odor-specific burst discharges at about 200 msec after odor onset for the majority of trials. No reliable responses were seen for five other odors (not shown) tested on this cell. (**c**) Loss of odor responsiveness was seen after the second trial.

or more spikes occurring within 100 msec. Four of these odor-responsive cells exhibited a considerable degree of specificity. Figure 2b shows raster plots from a unit of this type. Note that the cell emitted a short, high-frequency (4 pulses in 40 msec) burst on the majority of the trials on which one of the odors in the pair was presented and that the onset of this burst was reasonably well time-locked to the cue. The neuron did not respond to the other member of the pair being learned, or to the odors in a second or third discrimination. One of the four responsive cells did fire to a second odor but not with the same degree of intensity or reliability as it did to its "primary" odor.

Twenty other cells (32% of the 62 cells) exhibited varying degrees of odor responsiveness. In all cases, this took the form of time-locked burst discharges to the first few presentations of an odor followed by a loss of responsiveness as the rat acquired the discrimination over 5 to 10 trials (Fig. 2c). The odor specificity of this effect was difficult to assess because of the small number of trials on which the bursts occurred. There were no differences in the distribution of spontaneous firing rates between those cells that did respond to an odor and those that did not; Figure 3 illustrates the distribution of interspike intervals (ISI) for "responding" and "nonresponding" class I neurons, as well as for class II neurons. It is seen that, whereas most of the class II units exhibited

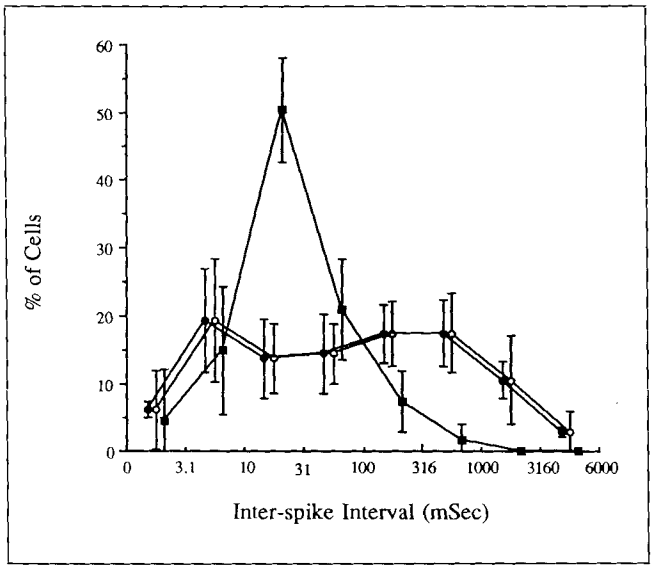

Figure 3. Distribution of interstimulus intervals (ISI) for class I units [both those (open circles) that exhibited odor-specific response, defined to occur when three or more spikes occurred within 100 msec and those (closed circles) that did not respond in this fashion to any odors tested] and class II units (closed squares). Class I responders and nonresponders exhibited no differences in ISI distribution; class II cells had a different distribution. The majority of class I neurons had ISIs of 100 msec or more, corresponding to mean firing rates of less than 10 Hz. In contrast, the majority of class II units had ISIs between 10 and 30 msec, corresponding to 30–100 Hz mean firing rates.

mean ISIs between 10 and 30 msec (i.e., 30–100 Hz), the majority of class I cells had ISIs of at least 100 msec, corresponding to spontaneous firing rates of less than 10 Hz.

DISCUSSION

Response Latencies

The present studies were undertaken in an attempt to identify the characteristics of single-cell responses in layer II piriform cortex during the salient period of information processing in that structure. That period is clearly defined via a number of disparate results. Average latency of first piriform layer II single unit responses after odor onset has been shown to be within 100–200 msec (Schwob, Haberly, & Price, 1984; Nemetz & Goldberg, 1983; Tanabe, Iino, & Takagi, 1975). Eichenbaum et al. (1987) found that cells in hippocampal field CA1 emit robust discharges at about 300 msec after odor onset in a task very much like that used in the present experiments. These experiments bracket the expected latency for piriform cortex layer II response to an odor stimulus presented in proximity to an attentive rat at 100–300 msec. The processing time needed for odor recognition must also be relatively short (at least for the readily distinguishable cues used in our studies) since the rat commits itself to a response based on recognition within about 500 msec after odor presentation. Combining these considerations we assumed that detection and processing related to recognition occurs in piriform during a 150–300 msec interval and investigated what types of unit responses were generated during that period.

It is worth noting that the present studies are not in conflict with those in which 40-Hz rhythmic activity is found in field potentials; 40-Hz activity corresponds to 25-msec latency between responses, and although this was not often found in single units, it was identified in unfiltered recordings, suggesting that mass activity may be occurring at this rhythm, as suggested by Freeman and Schneider (1982) in the olfactory system and by Gray and Singer (1989) in visual cortex.

Response Sparseness

As stated previously, responses in type I cells were defined to occur when three or more spikes occurred within 100 msec. The major finding of the present study was that very few cells in piriform cortex are responsive to any given odor, i.e., that the cortex uses very sparse coding. Nearly 80% of the predominant broad-spike cell group fired only rarely during the 150–300 msec window across several different odors that were clearly detected and learned by the rat. It should be recalled that each of these cells was located in a dense cell layer dorsal to the reversal point for field potentials evoked by lateral olfactory tract stimulation, almost all were driven by LOT stimulation, and all exhibited spontaneous firing (usually $\leq$ 5 per sec) when the rat was moving about in the cage. It appears that the great majority of the target cells of the olfactory bulb are not driven by most odors, or, put differently, that these cells are narrowly tuned. The bulbar-cortical projection exhibits little if any topography (Price, 1973; Haberly, & Price, 1977; Scott, McBride, & Schneider, 1980), and thus cells responsive to a particular pattern of bulb excitation are likely to be distributed with little evident order across the extent of the cortex.

Bringing a cell to its firing threshold will depend on three factors: (1) the number of active axons converging on it within an interval short enough for summation to occur, (2) the extent to which feedforward inhibition counteracts the excitatory input, and (3) the degree of lateral (recurrent) inhibition activated by cells that discharge to the input. It has been estimated that between 1 and 5% of the synapses on hippocampal pyramidal and granule cells must be active to depolarize one of those neurons sufficiently to overcome feedforward inhibition and cause an action potential (McNaughton, Barnes, & Andersen, 1981; Sayer, Redman, & Andersen, 1989). The percentage of layer II cells expected to respond to an odor can be roughly calculated by estimating the numbers of contacts in piriform layer I and the number of bulb mitral cells that fire in approximate synchrony to an odor. For fixed values of these quantities, the distribution of active synapses can be estimated via a hyper-

geometric probability density function (Granger et al., 1989). Figure 4 shows the predicted probability distribution of active cortical synapses (a) per cell in response to an odor, for a range of assumed values of synaptic connectivity (n) and input activity (A) across the total number of afferent fibers (N). The number of active synapses from these calculations ranges from 2 to 10% of the number of synapses per cell (see figure caption). Assuming, then, that from 1 to 5% of its synapses must be active for a cell to spike, this threshold would be readily reached by many cells, and, as seen in the figure, the number of active synapses is sensitive to relatively small changes in the values of n and A (the number of synapses per cell and the number of active afferents). Thus, if distribution of afferent activity onto excitatory synapses were the only factor determining cell response, then the number of cortical cells responding would be expected to vary greatly from odor to odor. However, simulation studies have shown that the lateral inhibitory network in cortex, operating over a confined

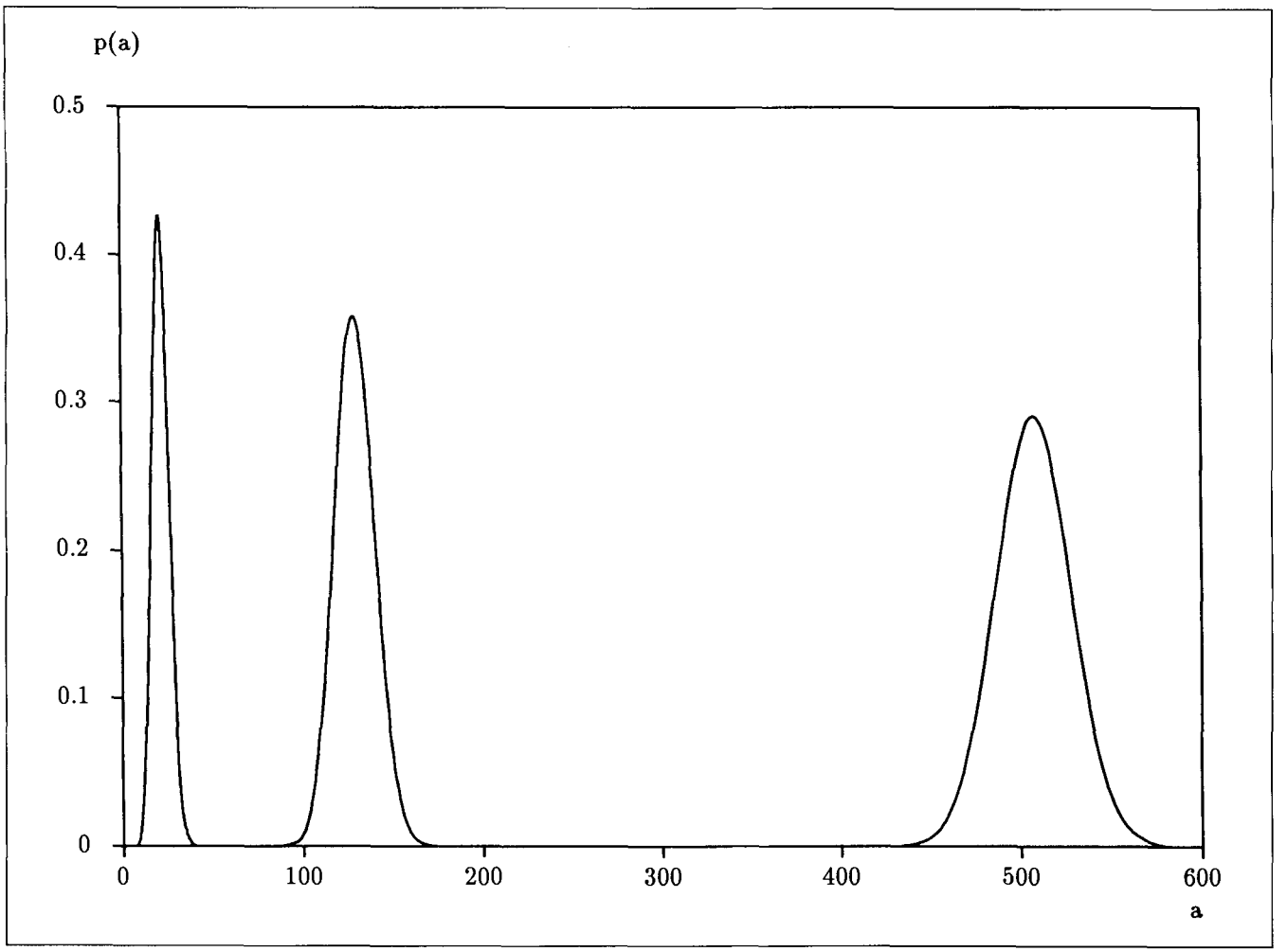

Figure 4. Calculated expected distribution of active cortical synapses (a) per cell in response to an odor, for a range of assumed values of synaptic connectivity (n) and input activity (A) across the total number of afferent fibers (N), via the hypergeometric probability density function $\mathcal{H}$ (see Granger et al., 1989). The PDF is given by

$$p(a \text{ active synapses}) = \mathcal{H}\binom{A\ N}{a\ n} = \frac{\binom{A}{a}\binom{N-A}{n-a}}{\binom{N}{n}}$$

The mean of this function is $\mu = nA/N$, and its variance is $\sigma^2 = nA(N - A)(N - n)/N^2(N - 1)$. The distribution roughly approximates a Gaussian for large μ, whereas it approximates a Poisson distribution for small μ. The three distributions of predicted active synapses a per cell correspond to three different settings of the values of the parameters n and A, with N = 50,000 total afferent input lines for all three curves. For the leftmost distribution, n = 1000 and A = 1000; for the middle curve, n and A both equal 2500, and for the rightmost curve, n and A are both 5000. (Other curves for any combinations of these values, e.g., n = 1000 and A = 2500, all fall roughly within the same range as the three curves shown.) For the leftmost curve, the mean value of a is 20, or 2% of the number of synapses per cell (1000). For the middle curve, the mean value of a is 125, or 5% of the number (2500) of synapses per cell. For the rightmost curve, the mean value of a is 500, or 10% of the number of synapses per cell (5000).

group of cells [perhaps "patches" or "islands" of the kind described by Van Hoesen and colleagues in lateral entorhinal cortex; e.g., Hyman, Van Hoesen, Kromer, & Damasio (1986)] can produce a situation in which cells within a group will "compete" to respond to any given odor; this arrangement would ensure that a small and relatively fixed number of neurons in any given area of cortex would fire to an input from the bulb (Coultrip, Granger, & Lynch, 1991). The present experimental findings are in accord with these simulation results.

Response Specificity

A subgroup of the class I (broad-spike) neurons did respond to varying numbers of odors on one or more of the early trials on which those odors were present. In almost all cases, these responses became less frequent over successive trials; 6% of the broad-spike neurons fired reliably to one odor (or for one unit, perhaps two odors) and discontinued responding to other odors. This could be explained by assuming that the degree to which LOT target neurons receive feedforward and/or feedback inhibition varies and that the convergence requirements for spiking in response to excitatory inputs vary accordingly. Thus, a cell with relatively few feedforward inhibitory contacts would appear to be broadly tuned since it would be brought to firing threshold much more readily (i.e., by many more patterns of input corresponding to cues) than would be the case for its neighbors that receive denser inhibitory innervation. This would not be unprecedented: anatomical studies on hippocampus indicate that the density of basket cell contacts, generally thought to be inhibitory, varies considerably across the granule cell layer (Ramón y Cajal, 1911; Lee, Gerbrandt, & Lynch, 1982).

The behavior of the type II units is worth noting. Three of the five recorded cells sharply decreased firing in the 1-sec period immediately prior to odor presentation, i.e., during the period when the animal was attentive but not receiving olfactory stimulation. If these units are inhibitory interneurons, this finding may indicate that the level of inhibition in the cortex is substantially reduced during anticipation of an odor.

Odors that differed from each other distinctly were used in the present studies, and the situation was arranged so that the rats could make very rapid responses. This had the advantage of defining a narrow interval in which detection and processing in cortex sufficient for recognition occurred, a feature necessary for a study of the physiological correlates of these events. However, our findings do not directly relate to what might happen with more difficult olfactory discrimination problems (e.g., when very similar odors are presented or an important cue is masked by a stronger odor). Rats and other small mammals typically employ a sinusoidal 4–8 Hz sniffing rhythm when sampling odors (Youngentob, Mozell, Shehe, & Hornung, 1986; Welker, 1964). This rhythmic response occurs in synchrony with (or, perhaps, is synchronized by) activity in the circuitry leading from bulb through hippocampus (Komisaruk, 1970; Macrides, 1975; Eichenbaum, Fagan, & Cohen, 1986). Computer simulation studies indicate that this rhythmic pattern enables several perceptual operations including the construction of odor categories and the detection of obscured or masked odors (Ambros-Ingerson et al., 1990; Granger, Ambros-Ingerson, Staubli, & Lynch, 1990). In particular, these simulations exhibit a series of distinct patterns of cell-firing response in olfactory cortex to a simulated odor over successive perceptual samples or sniffs. Analysis has shown that the sequence of cortical responses begins with a general "categorical" response to any of a set of similar odors, and becomes increasingly fine grained over successive sniffs, generating a multilevel hierarchical memory that uncovers statistical similarity relationships among learned cues, and sequentially traverses this hierarchical recognition memory during retrieval (Ambros-Ingerson et al., 1990). The model makes the specific prediction that different cortical cells should discharge over successive sampling cycles with progressively more selective tuning. The present study addresses only the antecedent questions of sparseness and odor specificity of cortical response; given the empirical support provided here that cortical responses are extremely sparse, testing of the progressive selectivity of cell tuning will likely require recording from thousands of cells. Experiments of the present type using behaviorally defined temporal windows, but with more complex olfactory problems, are needed to develop general hypotheses about the cortical correlates of odor perception. It should be noted that the theoretical findings mentioned above suggest that approximate hierarchical clustering will emerge as a fundamental property of memories based (at least in part) on LTP-like synaptic modifications in oscillatory networks of the type found in the olfactory system. The general architectural plan of the olfactory bulb–olfactory cortex system finds parallels in certain aspects of thalamocortical relations (Granger et al., 1991), raising the possibility that related mechanisms for perceptual recognition memory behavior may be present in neocortical sensory systems.

MATERIALS AND METHODS

Surgery

Twenty male Sprague–Dawley albino rats (200–300 g) were prepared for chronic unit recording using a lightweight removeable microdrive system described by Deadwyler, Bicla, Rose, West, and Lynch (1979). Rats were anesthetized with 50 mg/kg Ketoset and 10 mg/kg Rompun and mounted in a stereotaxic apparatus with toothbar set at −3.3 mm. A twisted bipolar stainless-steel stimulating electrode (0.005 in diameter, Teflon coated, 1.0 mm exposed tips) was implanted in the lateral olfac-

tory tract (LOT coordinates relative to bregma: AP +3.0 mm, L +3.2 mm; and approx. 7.0 mm below the dorsal surface of the brain). The microdrive holder and guide cannula were permanently affixed to the skull after establishing that the removable microelectrode recorded an appropriate laminar profile of field potentials in piriform cortex in response to LOT stimulation.

Behavioral Training

After 1 week of postoperative recovery, water-deprived animals were enclosed in a sound-attenuating wooden chamber containing a sniff-response port and a water-reward spout. Daily shaping sessions consisted of 60 trials in which animals were trained to poke the port, thereby interrupting a photobeam to initiate odor delivery through the port, in response to illumination of a "trial-initiation" light. A 1-sec delay period separated photobeam interruption and odor onset. Odorized air then flowed continuously until the animal triggered water delivery (0.05 ml) by interrupting a second photobeam positioned immediately above the water spout. Each trial ended when the animal finished drinking; intertrial intervals were at least 2 sec, during which the trial-initiation light was off and a nose-poke into the sniff port would not result in odor delivery and would delay the termination of the intertrial period by an additional 2 sec.

After 3 days of pretrial training, odor discrimination training was begun, which was similar to the pretrial training except that during a discrimination trial, one of two possible odors would be delivered, one of which (the "positive") odor was always associated with availability of water (as in the shaping trials) and the other (the "negative" odor) was not. After negative odor delivery, a water-spout lick (error response) extended the subsequent intertrial interval to a minimum of 6 sec. Failure to approach the water port within 10 sec was considered an error response for positive trials. Sessions ended when animals achieved a learning criterion of 18 correct responses out of 20 successive trials. Odorants were obtained from International Flavors and Fragrances, Inc. and Schilling/McCormick. Animals were selected for recording of piriform unit activity after attaining the learning criterion within 25 trials for at least two sessions.

Unit Recording

The microdrive assembly was loaded with an etched tungsten recording electrode (0.005 in diameter, epoxy coated, 1 MΩ, 200 pF), positioned over piriform cortex (AP 0.0 mm, L +4.2 mm) and lowered to approximately 8.0 mm below the dorsal surface. Position was adjusted to maximize the dendritic population EPSP in piriform layer I evoked by single pulse stimulation (2–10 V) of the LOT.

The electrode was then raised slightly above the reversal point (negative to positive) of the laminar profile of the field EPSP elicited by LOT stimulation and attempts made to isolate a cell responsive to the stimulation. Responses were considered to be from a single unit if they were evoked at a constant latency (between 5 and 15 msec after stimulation) and if there was an interspike interval of at least 2.5 msec, and by the appearance of a consistent waveform. Unit activity was amplified 10× at the head stage and filtered bandpass 300 Hz to 10 kHz. Isolated units (signal-to-noise ratio > 3/1) were recorded during exploration of the chamber: a rotating recording-cable/commutator allowed free movement of the rat during recording.

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