

ORBITOFRONTAL CORTEX: MODELING PREFRONTAL FUNCTION IN RATS

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Running head: Modeling prefrontal function in rats

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a common functional identity is determined by the same type of structure and connections, whatever the mammal examined. ... stratiographic analogy, grossly appreciated in Nissl or Weigert preparations, constitutes a valuable data point, but it is not completely decisive or infallible. – Cajal (1988, p 524).

Introduction

In histological preparations, a signature granular cell layer distinguishes a broad expanse of prefrontal cortex positioned rostral to motor cortex in both human and nonhuman primate brains. While cytoarchitectonic criteria originally provided a basis for defining cortical areas (Brodmann 1909), it was recognized in early writings that ‘functional identity’ of structures between different species would ultimately depend on data, then largely unavailable, regarding specific anatomical connections and physiology rather than ‘stratiographic analogy’ (Cajal, 1988). Since the middle of the last century the definition of prefrontal cortex has been influenced by a wealth of new information on neuroanatomical connections gained from tract tracing studies (see Preuss, 1995 for review). As Cajal envisioned, these new data indicate that prefrontal areas share functions in different species even in the absence of a granular cell layer.

Early on, Rose and Woolsey (1949) proposed that projections from mediodorsal (MD) thalamus defined prefrontal cortex. Indeed, the cytoarchitectonic definition of prefrontal cortex in the nonhuman primate corresponded well with the topography of innervation from MD. Since then it has become clear that an additional defining feature of prefrontal cortex is its rich interconnections with other brain systems, including other “association” areas of posterior and temporal neocortex, limbic structures such as the hippocampus and amygdala, and major efferent projections to striatum (Preuss, 1995; Ongur and Price, 2000). This connective anatomy has provided an important basis for further subdividing regions of prefrontal cortex and guiding functional analysis of prefrontal systems. The prefrontal cortex in the primate, which constitutes nearly a third of the neocortex, is now widely recognized to comprise three main subdivisions: a

dorsolateral region (Brodmann's cytoarchitectonic area 46 and lateral parts of areas 8, 9, 10, and 11), a medial region (areas 12, 24, and 32), and finally, an orbitofrontal region (areas 13, 47, and inferior aspects of areas 10, 11, and 13) (Fuster, 2000). This chapter focuses on the orbitofrontal division of prefrontal cortex, providing an overview of recent research that suggests strong functional homologies between orbitofrontal cortex in primate brain and a region in the rat brain that shares similar anatomical connectivity.

In the rat, mediodorsal thalamus can be divided into three segments (Krettek and Price, 1977a; Groenewegen, 1988). Projections from the medial and central segments of MD define a region that includes orbital areas and the ventral and dorsal agranular insular cortices (Leonard, 1969; Krettek and Price, 1977a; Kolb, 1984; Groenewegen, 1988). These regions of MD in rat receive direct afferents from amygdala, medial temporal lobe, and the ventral pallidum/ventral tegmental area; and olfactory input from the piriform cortex additionally innervates the central segment of MD (Krettek and Price, 1977a; Groenewegen, 1988; Ray and Price, 1992). The primate orbitofrontal region is defined by the projections of the medially-located, magnocellular division of MD (Kievit and Kuypers, 1977; Goldman-Rakic and Porrino, 1985; Russchen et al., 1987). Like the medial and central segments of rat MD, this region of primate MD also receives afferents from limbic structures such as amygdala and regions in the medial temporal lobe, olfactory structures such as piriform cortex, and ventral pallidum (Russchen et al., 1987). These data indicate that a defined region in rat cortex is likely to receive input from thalamus very similar to that reaching the primate orbitofrontal cortex. Based in part on this pattern of input, the projection fields of medial and central MD in the orbital and agranular insular areas of rat prefrontal cortex have been proposed as homologous to the primate orbitofrontal region (Leonard, 1969; Groenewegen, 1988; Preuss, 1995; Ongur and Price, 2000).

Other neuroanatomical studies in the past two decades have confirmed that in addition to receiving projections from regions of MD, orbitofrontal cortex in rat also has direct connections with a number of other structures that resemble those found in primate brain. Perhaps most notable are reciprocal connections with the basolateral complex of the amygdala, a region thought to be involved preferentially in affective or motivational aspects of learning (Gallagher and

Holland, 1999; Davis, 2000; LeDoux, 1995; Everett and Robbins, 1992). In primate, these connections (Price et al., 1987) have been invoked to explain certain similarities in behavioral abnormalities resulting from damage to either orbitofrontal cortex or amygdala (for example see Jones and Mishkin, 1972; Gaffan and Murray, 1990; Damasio, 1994; Fuster, 1997). Reciprocal connections between basolateral amygdala and areas within rat orbitofrontal cortex (Krettek and Price, 1977b; Kolb, 1984; Kita and Kitai, 1990; Shi and Cassell, 1998) suggest that interactions between these structures may have a similar importance for regulation of behavioral functions in rats as well.

Additional similarities between rat and primate connectional anatomy provide another basis for functional parallels involving orbitofrontal cortex. For example, in both species orbitofrontal cortex provides a strong efferent projection to ventral striatum, overlapping with innervation from limbic structures such as the amygdala and subiculum (Groenewegen et al., 1987; Groenewegen et al., 1990; McDonald, 1991; Haber et al., 1995). In fact, the specific circuitry connecting the orbitofrontal region, limbic structures and ventral striatum represents a striking parallel across species that suggests possible similarities in functional interaction among these major components of the forebrain (Groenewegen et al., 1990; McDonald, 1991; O'Donnell, 1999).

Of course, obvious differences in cortico-cortical connections of the orbitofrontal region are evident in comparing primates and rats, in line with the expansion of cortical processing systems in the primate brain. Rat orbitofrontal cortex is nonetheless multimodal with respect to input from cortical sensory processing streams (Kolb, 1990; Reep et al., 1996; Ongur and Price, 2000). In addition, orbitofrontal cortex receives direct projections from piriform cortex as well as olfactory-related regions of MD in both species (Yarita et al., 1980; Cinelli et al., 1985; Takagi, 1986; Price et al., 1991; Barbas, 1993; Carmichael et al., 1994).

The conservation of many features of anatomical connectivity across species provides a strong foundation for studies of functional similarities. Such an approach has already revealed that homologies in connectional circuits between primate and rat orbitofrontal regions are accompanied by homologies in function and in information processing. From these data, it

appears that in both rat and primate the orbitofrontal cortex serves a role in the strategic use of motivational information that is encoded with reference to prior experience, current context, and expectations regarding predicted events. This functional description of orbitofrontal cortex provides a basis for its central role in guiding goal-directed behavior and may be tied to broader conceptualizations of the role of prefrontal cortex in executive function, a topic we return to at the end of this chapter.

From clinical descriptions to experimental paradigms for orbitofrontal function

The most famous clinical case, which set the stage for much subsequent investigation, was that of Phineas Gage, a railroad foreman in the 1800's who suffered a traumatic injury thought to involve the orbitofrontal region (Harlow, 1868; Damasio, 1994). Following his injury, Gage became unable to continue productive work and exhibited a remarkable change in personality, characterized by socially impulsive behavior. Descriptions of patients with damage to orbitofrontal cortex have continued to identify maladaptive actions as a hallmark of the clinical syndrome. In nonhuman primates and rats, damage to orbitofrontal cortex likewise produces behavioral abnormalities in a social context. A seemingly invariable consequence of such lesions in monkeys is a loss of social rank (Butter et al., 1968; Butter and Snyder, 1972). It has also been noted that rats display abnormalities in social behavior and changes in aggressiveness after orbitofrontal damage (Kolb and Nonneman, 1974; Kolb, 1984).

Socially inappropriate and impulsive behaviors after orbitofrontal damage were initially studied as instances of a more general manifestation of "disinhibition". Indeed, early experimental studies focused on deficits in response inhibition as the hallmark of damage to orbitofrontal cortex (Mishkin, 1964). For example, primates with orbitofrontal lesions are impaired in acquisition or reversal of discriminations in which cues are paired with reinforcement, and where different responses must be executed to receive reward (Butter, 1969; Jones and Mishkin, 1972; Tanabe et al., 1975b; Gaffan and Murray, 1990; Diaz et al., 1996). Typically the behavioral deficit is manifest as an inability to withhold inappropriate responses, and impairment is particularly apparent on tasks or in situations that require a modification of the normal response

set or tendency (Mishkin, 1964). The important distinction made in these studies was that impairment was in the persistence of an old (or prepotent) pattern of responding rather than in an inability to learn new patterns (Jones and Mishkin, 1972).

Deficits in discrimination performance are also observed in rats after damage to orbitofrontal cortex. For example, rats with orbitofrontal lesions are impaired at discriminations involving olfactory cues (Eichenbaum et al., 1983; Whishaw et al., 1992). Impaired performance on discriminations is observed despite normal odor detection, and like primates with orbital lesions, rats exhibit perseverative responding (Eichenbaum et al., 1983). Rats are also impaired at using odor cues to guide performance in a delayed-non-matching task (Otto and Eichenbaum, 1992) and in object discrimination performance (DeCoteau et al., 1997). The olfactory modality used in this research with rats exploits the heavy involvement of rat orbitofrontal cortex in olfactory processing. Encoding of olfactory information is also well documented by single cell recording in monkey orbitofrontal cortex (Tanabe et al., 1975a; Thorpe et al., 1983; Rolls et al., 1996).

Although response inhibition was an important theme early on, more recent research, noting the connections of the orbitofrontal cortex with the amygdala, has focused on alterations in motivational and affective processes as a key component of the behavioral deficits associated with orbitofrontal damage. In support of this general perspective, a syndrome similar to that seen after orbital damage, in which monkeys lose social rank, has also been observed after damage to the amygdala (Rosvold et al., 1954; but see Emery et al., 2001). Further support for this perspective has come from a series of recent laboratory investigations with patients and experimental studies using monkeys and rats.

In work with patients, Damasio and colleagues devised a gambling task in which observations of behavioral performance were made along with measures of autonomic arousal. In this experimental setting, as in their lives, patients with orbitofrontal damage were prone to making disadvantageous decisions (Bechara et al., 1997). Notably, they also failed to display measures of increased autonomic arousal that were routinely observed in control subjects prior to choices that were likely to be costly in comparison with choices that led to more reliable gains.

While these deficits appear to be specific to damage in the orbitofrontal region within prefrontal cortex (Bechara et al., 1998), they are also observed in patients with amygdala damage (Bechara et al., 1999). These findings are consistent with the idea that orbitofrontal cortex plays a critical role in processing motivational information that is based on prior experience and that processing in this region provides a strategic guide for expectations about predicted events. Moreover, the evidence suggests that this function depends on orbitofrontal interconnections with the amygdala.

Alongside the intriguing findings from such research with patients, other recent studies have shown that interference with normal function of this circuitry in animals (monkeys and rats) can selectively impair goal-directed behavior, when such deficits are isolated from other performance- and learning-related factors. These studies have employed learning tasks that permit associations between cues to be assessed along with the current incentive value of events or outcomes predicted by those cues. These associations between cues, responses, or contextual information and the incentive properties of outcomes provide an important basis for the expectancy that guides goal-directed behavior.

One such task (Figure 1) exploits the ability of rats to modify responses toward a goal based on information about the value of the predicted outcome. Initially, rats are trained to expect food delivery at a food-cup following presentation of a 10-second light conditioned stimulus (CS). As a consequence of learning, rats approach the food-cup in the presence of the light CS (Figure 1A). In a second phase of the protocol (Figure 1B), rats are given food, identical to that delivered in the learning task, in their home cage; consumption of this food is followed by induction of illness by injection of lithium chloride. Rats thus acquire a taste aversion and subsequently refrain from consumption of the food that led to illness. In the final phase of the experimental protocol the effects of “devaluation” of the food are assessed on goal-directed behavior in the original training apparatus (Figure 1C). Control rats reduce their responding toward the food cup in the presence of the light CS in non-reinforced trials. In contrast, rats with orbitofrontal damage (Gallagher et al., 1999) fail to show this change in food-cup responses after food devaluation (Figure 1C). This deficit is notable because lesioned rats, like normal rats, refrain from consuming the food that led to illness (Figure 1B). Thus, rats with orbitofrontal damage can inhibit a pre-potent response, i.e.

food consumption, but they fail to use this information to guide behavior in response to cues that predict the devalued food. Like patients in the gambling task, rats with orbitofrontal damage continue to make responses that will lead to an undesirable outcome. It is also notable that in rats, as in human clinical cases, the behavioral deficit in modifying goal-directed responses after orbitofrontal damage is reproduced by damage to the amygdala (Hatfield et al., 1996). In the case of rats, this deficit is observed after highly selective neurotoxic lesions of the basolateral amygdala, the origin of direct projections to orbitofrontal cortex.

Other research using devaluation protocols has demonstrated the involvement of amygdala/orbitofrontal circuitry in monkeys. In those studies a change in incentive value was induced by selectively overfeeding a food item that was used as a reinforcer. After such satiation, normal monkeys were less likely to select a visually-presented object that had been reinforced with the “devalued” food in earlier discrimination training. This change in responding, however, was absent in monkeys that had lesions of the amygdala (Malkova et al., 1997) or lesions that disconnected the amygdala and orbitofrontal regions (Baxter et al., 2000). As in rats, monkeys with damage to this circuitry appear to be unable to use the motivational guidance provided by an expected outcome to guide goal-directed behavior. In the next section we consider studies of information encoding by orbitofrontal neurons that may serve as a basis for the adaptive regulation of goal-directed behavior that appears to be organized by this region.

Homologies in information processing between rat and primate orbitofrontal cortex

A number of recording studies have been conducted in recent years examining the properties of orbitofrontal neurons in monkeys and rats while they perform relevant behavioral tasks. The results of these investigations suggest strong similarities in the properties of orbitofrontal neurons across species and in the features of information encoding that are likely to serve as a basis for the critical role of orbitofrontal cortex in guiding goal-directed behavior.

Some of the earliest recording studies in orbitofrontal cortex noted the importance of the biological significance of stimuli in determining the firing properties of neurons. For example, although neurons do respond to specific olfactory cues (Tanabe et al., 1975a; Schoenbaum and

Eichenbaum, 1995a; Yonemori et al., 2000), they appear to be most responsive to odors with some biological importance, such as odors of urine, feces, or other animals (Onoda et al., 1984). Food odors and visual features of food items also evoke activity in orbitofrontal neurons (Thorpe et al., 1983). Moreover, such responses are sensitive to motivational state. For example, satiation decreases the responsiveness of orbitofrontal neurons to food-related cues (Critchley and Rolls, 1996b).

In monkeys, neutral cues that signal rewarding or aversive contingencies also strongly activate orbitofrontal neurons (Rosenkilde et al., 1981; Thorpe et al., 1983; Critchley and Rolls 1996a, Tremblay and Schultz, 1999). Similarly, in rats orbitofrontal cortex appears to encode the acquired significance of cues. For example, in rats trained to perform an 8-odor go, no-go discrimination task, many orbitofrontal cortex neurons fired selectively during sampling of the odor cues (Figure 2). In this task, rats learned that four of the odors were reinforced (water was provided to thirsty rats) while the other four odors were not reinforced (Schoenbaum and Eichenbaum, 1995a, 1995b). As illustrated in Figure 2, odor-responsive activity recorded in well-trained rats typically discriminated among odor cues based upon their association with reinforcement rather than based on their sensory properties. Similar findings have been reported in primates trained to perform an odor discrimination task (Critchley and Rolls, 1996a). Orbitofrontal neurons also respond similarly to different complex visual cues (different pattern stimuli) that signal the same reward (Tremblay and Schultz, 1999). It is important to note that neurons in orbitofrontal cortex are not solely attuned to the positive or rewarding significance of cues. For example, in Figure 2 several neurons fire most strongly to odors associated with non-reinforcement, and other studies (Critchley and Rolls, 1996a; Schoenbaum et al., 1999) have reported that orbitofrontal neurons are selectively active during sampling of cues associated with an aversive outcome (delivery of aversive saline in monkeys or quinine in rats).

The notion that neurons in orbitofrontal cortex are specialized for encoding the motivational significance or value of the events associated with cues is consistent with evidence that the activity in orbitofrontal cortex that is established in associative learning is dramatically affected when contingencies are modified. In an odor discrimination task for rats in which different

odors predict either sucrose or quinine, reversal of the reinforcement contingencies alters the encoding properties of neurons (Figure 3), thereby indicating the dependence of neural activity on the value (rewarding/aversive) of the predicted events (Schoenbaum et al., 1999). Reversal training in monkeys likewise alters the responsiveness of orbitofrontal neurons to olfactory cues (Rolls et al., 1996). In addition, it has been shown that the encoding properties of orbitofrontal neurons in monkeys are altered by more subtle variations in the incentive value of predicted outcomes. For example, orbitofrontal neurons respond more strongly to cues that predict preferred food items than to less preferred food items (Tremblay and Schultz, 1999). This encoding can also reflect relative preferences among the items that are available at a given time. For example, a neuron that fires more robustly to the cue that predicts a preferred outcome in one block of trials will decrease firing to that cue in a subsequent trial block when a more preferred reward is introduced (Tremblay and Schultz, 1999). The dependence of encoding during cue presentation on relative preference has yet to be tested in rats. However, other important features of encoding that reflect the anticipation of expected rewards during delay intervals can be observed in both species.

Orbitofrontal neurons are active in both rats and primates during short delays interposed between responses and delivery of reinforcement (Schoenbaum et al., 1998; Tremblay and Schultz, 1999, 2000a) or in some cases during delays between cue presentation and responses to instructions preceding reinforcer delivery (Hikosaka and Watanabe, 2000). This activity appears to encode expectancy of an impending outcome, independent of the response made to gain access to the outcome (Figure 4). Like neuronal activity during presentation of predictive cues, differential firing during delays emerges with learning (Schoenbaum et al., 1998, 1999; Tremblay and Schultz, 2000b) and is linked to the incentive value rather than to the specific identity of the impending reward (Tremblay and Schultz, 1999, 2000a; Hikosaka and Watanabe, 2000). The dependence of these correlates on the incentive value of the reward appears to distinguish anticipatory delay-activity in orbitofrontal cortex from similar activity in dorsolateral prefrontal regions (Watanabe, 1996; Hikosaka and Watanabe, 2000).

In each of these studies, it is particularly interesting, given the multimodal input to orbitofrontal cortex, that neural encoding of incentive value appears to be independent of the physical attributes of either the signaling event or the impending outcome. For example, cues with different physical features (different odors or different complex visual stimuli) can evoke similar responses when those cues predict similar rewards (Schoenbaum and Eichenbaum, 1995a; Tremblay and Schultz, 1999). Moreover neuronal firing in anticipation of reinforcers differs according to incentive value rather than the nature of the reward (Hikosaka and Watanabe, 2000). The independence of encoding in orbitofrontal cortex from the physical features of cues is also evident for more abstract “cues”. For example, firing in orbitofrontal cortex can encode incentive value based on apparent conjunctions between places and odors (Lipton et al., 1999) or based on whether the odor matches one presented on the preceding trial (Ramus and Eichenbaum, 2000). Such encoding was prominent when the demands of the task required those features to guide performance. For example in the study by Ramus and Eichenbaum (2000), rats sampled an odor on each trial and were rewarded for responding if the odor did not match the sampled odor on the immediately preceding trial. Although odor identity is important in determining whether a match is made, the identity of the odor is not, by itself, correlated with outcome. In this setting, a high proportion of neurons recorded in orbitofrontal cortex (64%) had differential activity depending on whether the odor sampled was a match or a non-match. Few cells fired selectively to odors based on their identity, and almost no neurons fired independently of whether an odor was a match. Thus, orbitofrontal neurons are capable of representing more abstract conjunctions between cues if these representations are reliably associated with outcomes.

The features of information encoding by orbitofrontal neurons illustrated by these recording studies are consistent with the view that in both rat and nonhuman primates this region serves a role in the strategic use of motivational information that is encoded in reference to prior experience, current context, and expectations about predicted events. Moreover, the close relationship of encoding to the incentive value of expected outcomes is consistent with a central role of orbitofrontal cortex in guiding goal-directed behavior based on how incentive value and

outcomes are represented. Impairments in devaluation studies in both rats and monkeys with orbitofrontal lesions, as well as the maladaptive responses made by neurological patients with orbitofrontal damage, may reflect the loss of such representations or the inability to use them effectively to guide behavior.

Conclusions

New evidence indicates that the orbitofrontal region is especially important for prospective encoding of outcome value. This role is evident in the effect of lesions, which impair behaviors that depend on the appropriate use of that information, and in the properties of orbitofrontal neurons, which represent incentive value independent of physical attributes of predicted events. Recent research demonstrates a remarkable parallel across primates and rats in this characteristic of the orbitofrontal region, providing a basis for functional homology across species.

The incentive value of anticipated events encoded in orbitofrontal cortex is likely to be used in conjunction with information represented in other prefrontal regions to guide behavior. For example, cells in dorsolateral prefrontal cortex in the primate represent physical features of information in the environment, including object identity and spatial location (Wilson et al., 1993). The information used to guide behavior, therefore, has a distributed representation with specialization in different prefrontal regions, at least in part, reflecting differences in connectivity with other cortical and subcortical systems. Although we have emphasized the importance of orbitofrontal connections with amygdala in this chapter (see also Schoenbaum et al., 1998, 1999; Gallagher et al., 1999), the influence of connections with other structures is also evident in the properties of orbitofrontal neurons (Schoenbaum and Eichenbaum, 1995a; Lipton et al., 1999; Ramus and Eichenbaum, 2000). As in other prefrontal regions, representations in orbitofrontal cortex generally develop with accurate task performance (Schoenbaum and Eichenbaum, 1995b; Schoenbaum et al, 1999; Rainer et al., 1998; Asaad et al., 2000), and neural activity persists during delays to anticipate outcomes (Schoenbaum et al., 1998; Tremblay and Schultz, 1999; Hikosaka and Watanabe, 2000). Within a framework that assigns a role for prefrontal cortex in

executive functions, orbitofrontal cortex may now be viewed as an important component of the prefrontal system. Additional comparative research will help to illuminate both the similarities and distinctive features of prefrontal cortex across mammalian species.

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Figure Captions

Figure 1: Effects of neurotoxic lesions of orbitofrontal cortex on performance in a devaluation task. As illustrated (A, upper panel), control rats and rats with bilateral neurotoxic lesions of orbitofrontal cortex were trained to associate a conditioned stimulus (light CS) with an unconditioned stimulus (food US). Over several sessions (1-4), both lesioned (circles) and control (squares) rats developed a conditioned response at the food cup to the light (A, lower panel). This food cup response is represented as the percentage of total behavior. There was no effect of the lesion on the development of the food cup response. The rats then received presentations of the food item in their home cages followed by illness induced by lithium chloride (LiCl) injection (B, upper panel). Some rats in each group received paired presentations of food and illness (dark circles and squares), while others received unpaired presentations (light circles and squares). Rats that received paired presentations stopped consuming the food item (B, lower panel). Again no effect of lesion was observed. The following day the rats were returned to the training environment, and conditioned responses to the light cue were measured (C, upper panel). When exposed to the light CS (C, lower panel), control rats that had received paired presentations of food and illness reduced conditioned responses to the food cup relative to unpaired controls. Rats with orbitofrontal lesions did not show this decrease in conditioned responding as a result of reinforcer devaluation.

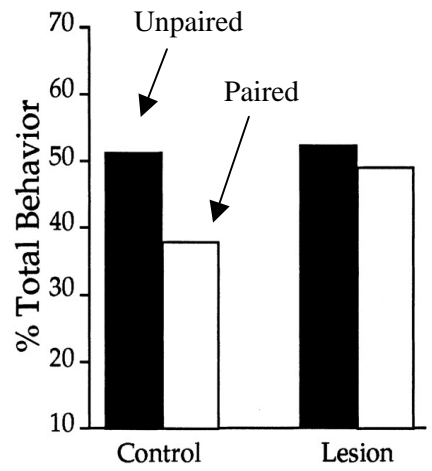
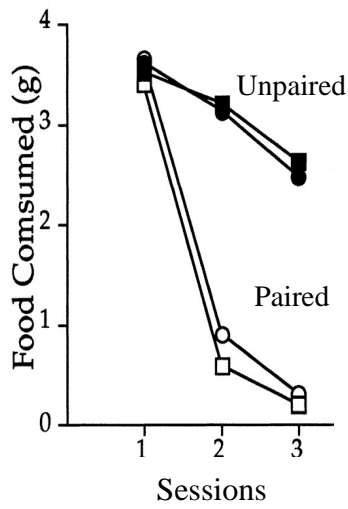
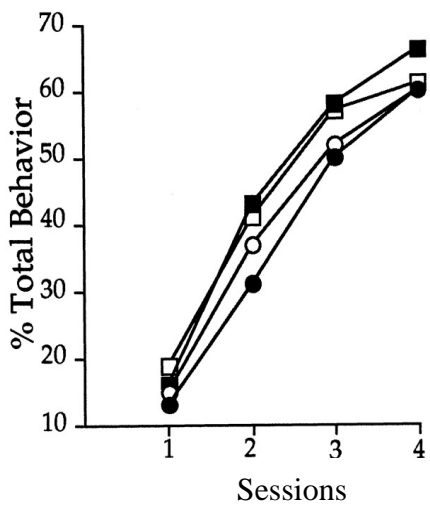
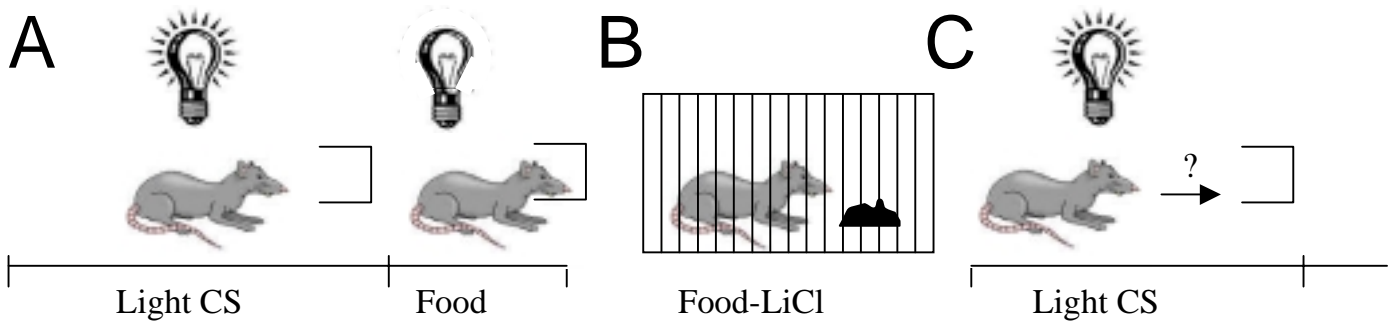
Figure 2: Encoding of associated outcome rather than sensory features of cues in orbitofrontal cortex revealed by neural activity during odor sampling. Neurons in rat orbitofrontal cortex were recorded during performance of an 8-odor go, no-go odor discrimination task. On each trial, one odor was presented. After odor sampling, a response could be made at a nearby fluid well for a water reward. Four odors were positive, indicating that a response would be rewarded; and four odors were negative, indicating that no reward would be given for responding. Rats were well-trained on the discrimination prior to recording, responding to positive odors and rarely to negative odors. Activity in orbitofrontal cortex is shown in spikes/second during odor sampling for 5 different neurons. Each panel shows activity for a different neuron to each of the 8 different

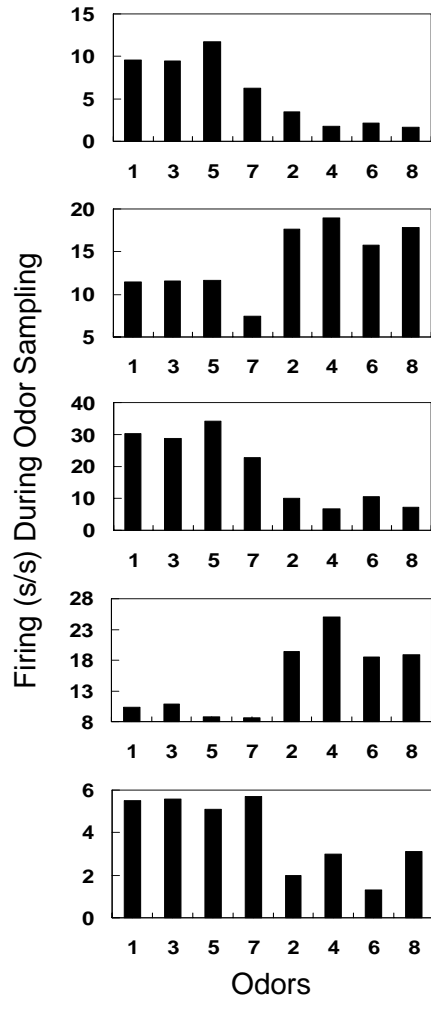
odors presented in each session. Positive odors 1⁺, 3⁺, 5⁺, and 7⁺ are on the left of each panel, and negative odors 2⁻, 4⁻, 6⁻, and 8⁻ are on the right of each panel. Note that the cells responded to all positive or all negative odors and did not distinguish between odors that were associated with the same outcome.

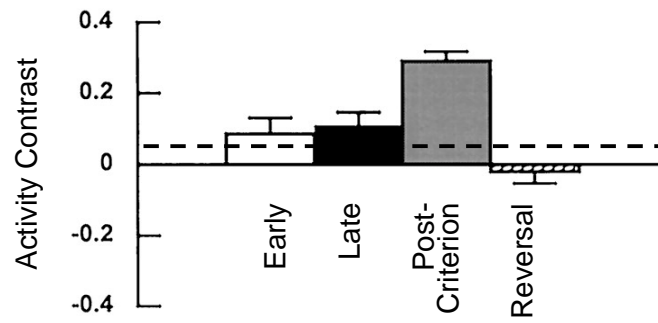
Figure 3: Representation of incentive value in orbitofrontal cortex revealed by neural activity during discrimination and reversal training. Neurons in rat orbitofrontal cortex were recorded during acquisition and reversal of new 2-odor discrimination problems in a go, no-go paradigm. On each trial, an odor was presented. Responses after sampling of the positive odor resulted in delivery of a sucrose solution; responses after sampling of the negative odor resulted in delivery of a quinine solution. Rats were presented with a novel odor pair in each session. Neural activity was recorded as the rats learned to withhold responses to the negative cue to avoid the quinine solution, during accurate performance, and then during reversal training where the reinforcers paired with the odor cues were switched. A. Contrast in population activity during odor sampling calculated for the 96 of 328 orbitofrontal neurons that exhibited selective firing to odor cues during accurate performance. Differential activity in these cells (illustrated in B) developed only during odor sampling in the post-criterion phase of pre-reversal training and disappeared after reversal. Activity contrast was calculated as the difference in firing to positive and negative odors, referenced to the polarity of this difference during post-criterion trials, and normalized by the sum of those rates in each training phase. The dotted line represents a baseline value calculated from neural activity recorded between trials. Selectivity in this population of neurons differed significantly from baseline only during the post-criterion phase. B. An example of a neuron with differential firing during odor sampling that developed during acquisition of the discrimination and was evident only before reversal. Neural activity is shown for representative trials in raster format. Trials are shown sequentially for each odor. Activity on each trial begins with odor onset, is synchronized to odor offset, and ends with a response or after 1500 ms for no-go trials (faded). This cell developed selective firing to odor 1 in the post-criterion trial block, during accurate

performance on the discrimination. This selective response diminished rapidly after reversal and disappeared.

Figure 4: Representation of incentive value in orbitofrontal cortex during delays after cue sampling and during the response at the fluid well up to the time of reinforcer delivery. Neurons were recorded in the same experiment described in Figure 3. A. Contrast in population activity during the delay after responding at the fluid well but before reinforcer delivery, calculated for the 74 of 328 orbitofrontal neurons that exhibited selective firing during this period (illustrated in B). Selective firing during the delay in this population of neurons developed rapidly during training and increased significantly with learning between the early and late phases of pre-criterion training. Activity contrast was calculated by comparing firing during the delay on positive and negative trials as described for Figure 3. B. This figure shows an example of a neuron that did not fire differentially during odor sampling but did fire differentially later in each trial, namely during a brief delay after a response had been made but before reinforcement was delivered. This selective activity appears to anticipate delivery of the quinine solution. Neural activity is shown for representative trials in raster format. Trials are shown sequentially for each odor. Activity on each trial begins with odor offset, is synchronized to the response at the fluid well and ends with reinforcer delivery. Only go responses made during pre-criterion training are shown.





A**B**