

INVITED REVIEW ARTICLE

Food memory: neuronal involvement in food recognition

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Previous studies indicate that ablation of the temporal cortex including the amygdala (AM) and hippocampal formation (HF) induce the Klüver-Bucy syndrome in which animals cannot discriminate food from nonfood. Of 710 AM neurons tested, 129 (18.2%) responded to single sensory stimulation (48 to vision, 32 to audition, 49 to ingestion), 142 (20.0%) to multimodal stimulation and 20 to only one item with affective significance. Eight food related AM neurons were tested in reversal by salting food or introducing saline, and all responses were modulated by reversal. In HF and parahippocampal cortices (PH), 864 neurons were recorded, and 160 (18.5%) responded to the sight of certain objects. Of these, 23 responded predominantly to food-related rewarding objects, 13 to several aversive objects such as a spider model, syringe, objects associated with weak electric shock, ten to one object or one kind of object, seven to unfamiliar objects. Of 14 rewarding or aversive object-related neurons tested, responses of seven to the same test object did not change in extinction or reversal tests. Although responses of the other seven decreased in extinction or reversal tests, the magnitude of response remaining in five of those seven still exceeded that of responses to other categories. Results suggest complementary AM and HF-PH functions. The AM may be important in ongoing recognition of the affective significance of complex stimuli (food-nonfood discrimination) and the HF-PH in sustaining past affective significance

Introduction

The mammalian limbic system and hypothalamus are important interacting structures in the control of functions such as feeding behavior^{3,11,33}. The limbic system affects the behavior of an organism mainly through parts of the brainstem and diencephalon such as the hypothalamus⁸. The amygdala (AM), the hippocampal formation (HF) and parahippocampal cortices (PH) are the principal limbic regions, in which various exteroceptive sensations converge^{6,14}. Various exteroceptive information may reach the lateral hypothalamic area (LHA), feeding center and ventromedial hypothalamic nucleus (VMH), satiety center through the AM and HF that send efferent fibers to these two centers^{22,27,28}. Lesion studies indicate some contributions of both the AM and HF to learning and recognition of rewarding objects such as food in some situations⁸. For example, the animals with bilateral hippocampal lesions had deficits in forming association of conditioned stimuli with unconditioned stimuli, ie reward, if delay time was introduced between conditioned and unconditioned stimuli⁸. Bilateral lesions of the temporal cortices including the AM produce the Klüver-Bucy syndrome^{7,13}. All animals with these deficits excessively examined objects whether food or nonfood, by touching, tasting and smelling. These animals seem to be indifferent to the reward value of a stimulus¹².

We have been investigating neuronal responses in rat and monkey AM, HF and LHA during discrimination of rewarding and aversive stimuli, such as food and nonfood. A series of our experiments reveal functional

roles of each of these areas, and indicate sequential visual information processing for recognition of a rewarding object, ie food,^{20,23}. We review here our recent results in monkey experiments^{18,19,37}.

Experimental setup and data analysis

Eight monkeys (*Macaca fuscata*, 4-6 kg) were studied. Each was restrained painlessly in a stereotaxic apparatus by a previously prepared surgically fixed head holder designed in our laboratory^{24,25} for single unit recording. They sat in a chair facing a panel containing shutters and an operant response bar (Fig. 1A). Juice, water, and saline were made available through a small spout with an electromagnetic valve. Aversive stimulation was by a weak electric shock applied between the ear lobes. The task included visual discrimination (feeding, drinking, and active avoidance), and auditory discrimination, which led to presentation of food or nonfood, or various sensory stimuli associated with food, juice or water (Fig. 1B, C)^{18,19}. During a recording session behavior and eye movement were monitored by TV cameras or electrooculography, or both, as well as by direct observation by the experimenter.

Two task situations, an original one and a modified version of this, were used. In the original version of the feeding task an opaque shutter (W1) was opened at

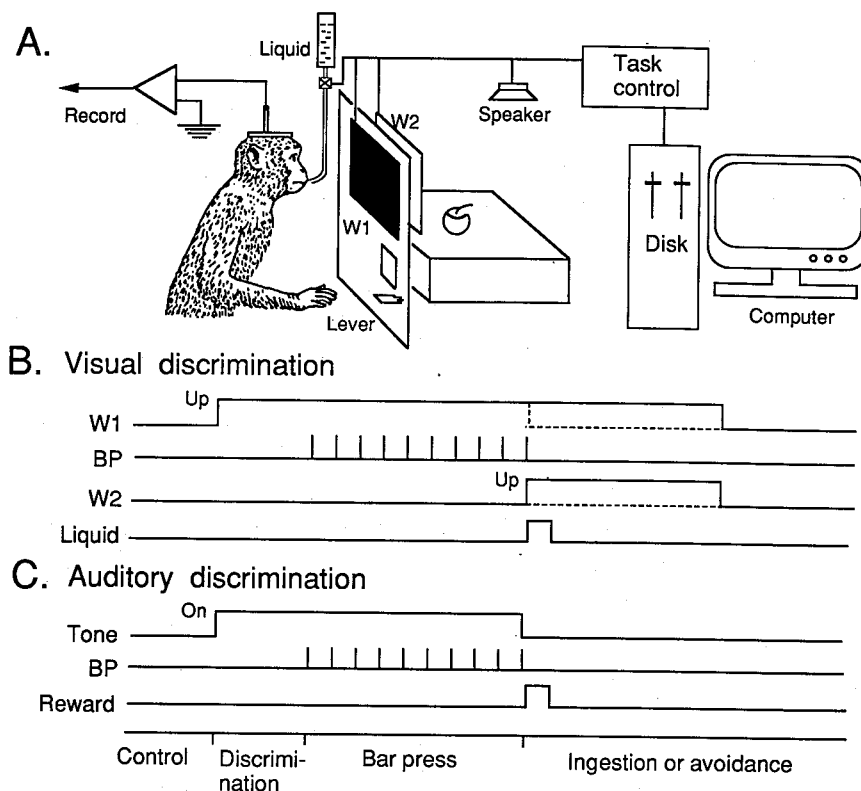


Fig. 1. Schema of an experimental setup (A) and time sequences of two operant tasks (B,C). A: monkey sat in a chair facing a panel with a bar, and a window covered by two shutters (W1, an opaque shutter; W2, a transparent shutter) in front of a stage. Liquid could be obtained from a spout near the monkey's mouth. B: time sequence of visual discrimination tasks that involved feeding (—), drinking (---), or avoidance (---). W1 and W2 opened at Up. C: time sequence

of auditory discrimination task. Tone started at On. BP: indications of individual bar presses and time during which they occurred (B, C). Liquid was dispensed from spout after last bar press if a particular object was presented. Tone indicated availability of reward in auditory discrimination test (C). Reward: drop of juice dispensed from spout after last bar press, or cookie or raisin on stage became available by simultaneous opening of W1 and W2 after last bar press.

random intervals to reveal a transparent shutter (W2) in front of a stage. By pressing the bar a pre-determined number of times (fixed ratio, FR 10–30) monkeys could take an object seen through W2 and in the case of desirable food ingest it (Fig. 1B, solid line). Similarly, when the FR criterion was met in a drinking task, W1 was automatically closed and a drop of potable liquid such as juice or water, portended by a symbolic object such as a column or cube could be licked from a small spout (Fig. 1B, dashed line); eg a white cylinder was usually associated with juice and a red cylinder was associated with water. In active avoidance tasks a brown cylinder was usually associated with a weak electric shock. On seeing the brown cylinder and hearing a 1200 Hz tone monkeys had to complete a FR schedule within 4–6 seconds to avoid electric shock. The required bar press procedure closed W1 without producing the shock (Fig. 1B, dashed line). In the auditory discrimination task a buzzer noise was associated with food, ie cookies or raisins, and a tone with a fundamental frequency of 800 Hz was associated with a drop of juice (Fig. 1C). On hearing the buzzer or the 800 Hz tone the monkey had to complete a FR schedule to obtain the corresponding food or juice, as in the feeding task. Two pure tones (2800 or 4300 Hz) were introduced as neutral stimuli associated with neither reward nor electric shock and the food or test objects not being visible behind the shutter W1.

In a modified version of the task the monkey could see an object on a stage through a one-way mirror (S1) in front of the stage when a light behind the mirror was turned on. However, a second shutter (S2) prevented access to the bar. After a delay of at least 2 seconds, S2 was opened automatically so the bar could be pressed. The S1 shutter was opened by the last bar press. The monkey's behavior and the neuronal responses were essentially the same in this and the previously described situation. The task comprised three phases (Fig. 1C): (1) control; (2) discrimination visual or auditory discrimination of an object or situation; (3) operant responding (bar pressing), and (4) ingestion or avoidance.

We focused on possible discharge patterns of single AM, HF or PH neurons when these different rewarding (food) and aversive stimuli were presented. Some neurons were tested by changing the affective (rewarding or aversive) significance of a stimulus.

Amygdalar neuron responses

Of 710 AM neurons tested, 380 responded to at least one stimulus. Based on their responsiveness to sensory modalities, 291 of these 380 neurons fell into one of five categories: vision-related, audition-related, ingestion-related, multimodal and selective.

Forty-eight neurons responded, all positively to visual stimuli, but not to auditory, oral sensory or somesthetic

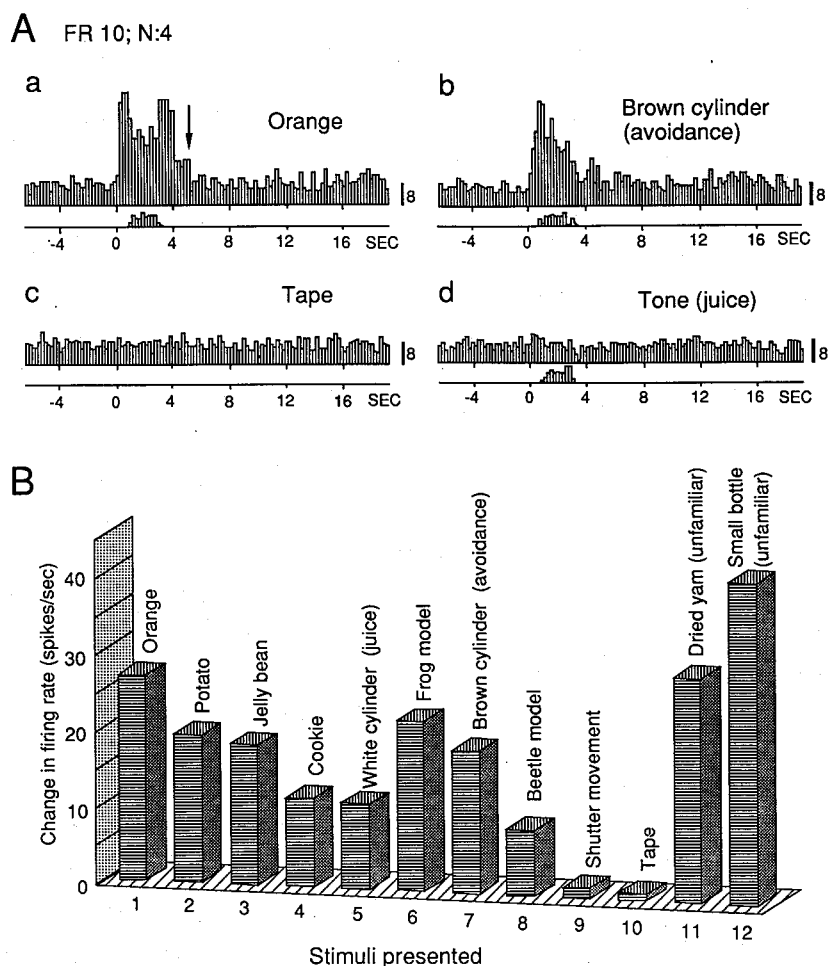


Fig. 2. Responses of Vis-I AM neuron. A: activity increased at the sight of positive (a) and negative (b) affect-related, but not neutral, objects (c). However, neuron did not respond to positive affect-related auditory stimuli (800 Hz fundamental frequency tone) (d). Note absence of neuronal response after animal put orange into mouth (arrow in Aa). Bar presses shown by histograms on time scales (W1 opened at time 0). Responses are shown as the sum of 4 trials. Calibration at right of each histogram: number of spikes in each bin. B: Comparison of Vis-I neuron responses to various objects.

stimuli. These neurons responded clearly to the sight of unfamiliar objects, regardless of whether they were food or nonfood, and to the sight of some familiar nonfood objects. Of 48 vision-related neurons, 31 — Vis-I type — responded consistently both to rewarding objects, such as familiar food and red or white cylinders associated with water or juice, and to certain nonfood items such as a brown cylinder associated with electric shock, or a syringe, glove or other object, but not to familiar neutral nonfood stimuli, ie tape. The remaining 17 vision-related neurons — Vis-II type — responded similarly to unfamiliar objects and to certain familiar negative objects, but not to familiar reward-related objects, ie foods and red and white cylinders associated with water and juice. Figure 2 illustrates responses of a typical Vis-I neuron. This neuron responded strongly to both familiar positive (Aa, orange) and negative (Ab, brown cylinder) objects, but not to familiar neutral tape (Ac, tape). In contrast to its responses to visual stimuli, this neuron did not respond to any auditory stimuli. An example of no response to a familiar positive auditory stimulus is

shown in Fig. 2Ad. Those stimuli did, however, elicit various overt reactions, such as bar pressing. Figure 2Aa shows no response after putting orange into the mouth (indicated by arrow), so this neuron did not respond to oral sensory stimuli. Responses of this particular neuron to various food and nonfood objects are compared in Fig. 2B. The degree of preference for different kinds of food was estimated from evaluation of the animal's overt behavior when the different food items were made available to it. The neuron responded significantly more strongly to more preferred food than to less preferred food.

The response profile of Vis-I neurons indicates that although the response magnitude may vary, these neurons respond to biologically significant objects regardless of whether they can be considered rewarding or aversive. To investigate this inference, the neuron shown in Fig. 2 was also studied in various situations in which affective significance of the stimulus was altered (Fig. 3). Responses to an unfamiliar object, dried yam which the monkey apparently did not consider to be food, habitu-

Each column rearranged here to compare among different foods (columns 1–5), various nonfood objects (columns 6–8), neutral (columns 9, 10), and unfamiliar objects (columns 11, 12) shows response magnitude after the indicated objects were revealed, ie the mean discharge rate (spikes/sec) of four 5-sec firing rates minus spontaneous rate. Unfamiliar stimuli evoked the greatest responses. Neuronal responses to objects shown here (and to other objects not shown) correlated with rates of behavioral responses.

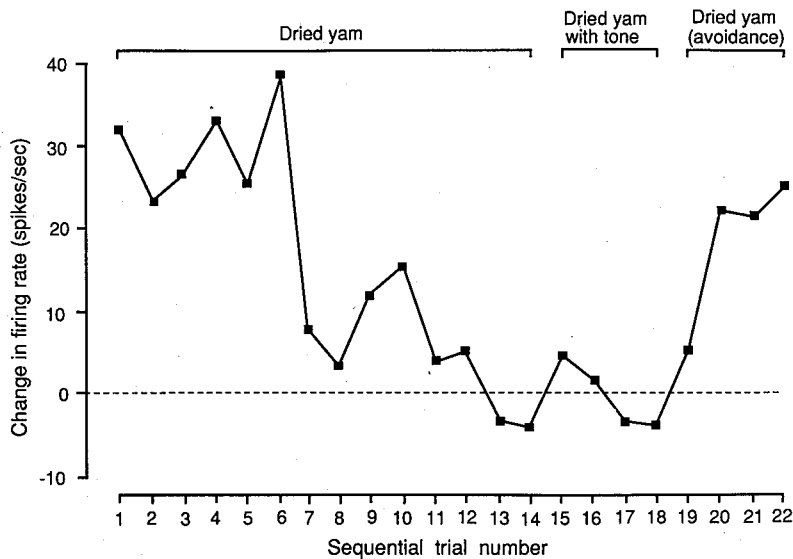


Fig. 3. Modulation of Vis-I neuron responses to a new food, dried yam. The dried yam, which was handled and smelled but never tasted, finally was not accepted by the monkey as food. In trials 1–14 the response gradually habituated. In trials 15–18 the dried yam was presented with the 1200 Hz tone used in the active avoidance task. In trials 19–22 the

response appeared again after association with electric shock (in trials 19 and 20 electric shock was applied). Shock was avoided in trials 21 and 22. ■ indicates mean response magnitude (net response minus spontaneous firing rate) during 5 sec presentation of the dried yam.

ated gradually in trials 1 to 14 as the object became familiar and meaningless. In trials 13 and 14 the monkey never pressed the bar (not shown), which indicates that it learned that the object was biologically meaningless. When the dried yam plus the 1200 Hz tone was presented instead of the brown cylinder plus the 1200 Hz tone (avoidance task) without electric shock, the initial response was slight, and quickly habituated in trials 15 to 18 as the monkey learned that the dried yam was still meaningless. In trial 19 the dried yam plus the tone was followed by electric shock. In trial 20 the neuronal response was elicited without bar pressing for avoidance. In trials 21 and 22 both neuronal and behavioral responses were elicited. The bar press data are not shown here. Thus, the neuronal response to the sight of dried yam was modified when associated with other stimuli (1200 Hz tone and electric shock) evincing overt avoidance behavior.

Thirty-two neurons responded exclusively to auditory stimuli with the same responsiveness to affective significance as vision-related neurons. All of these 32 neurons responded vigorously to unfamiliar sounds and habituated to certain auditory stimuli in repeated trials; none responded to familiar pure tones used as controls. These neurons were subdivided into two groups: 11 that responded to familiar cue tones associated with a cookie or juice reward, as well as to unfamiliar sounds (aud-I); and 21 that responded to unfamiliar sounds but not to cue tones associated with cookie or juice (aud-II). Forty-nine neurons responded primarily during the ingestion phase of the tasks. According to responsiveness to other stimuli, this group was subdivided into three groups: 32 oral sensory, 13 oral sensory plus vision, and four oral sensory plus audition. The responses of 142 neurons were multimodal. Of these, 48 responded phasically and nonspecifically to various sensory stimuli. These responses were independent of the nature of the stimuli. In contrast to the phasic type neurons, 94 neurons re-

sponded tonically to biologically significant stimuli, but not to familiar neutral stimuli.

Responses of 20 neurons were highly selective for only particular familiar objects or sounds: nine were selective for one specific food item or for cylinders associated with potables, eight were selective for one specific nonfood item, and three were selective for one specific sound. Examples of responses that indicated selectivity for one specific food item are shown in Fig. 4. This neuron was tested with 16 objects and seven somesthetic and auditory stimuli (not all shown), and the magnitude of its responses to any other stimulus relatively insignificant (Fig. 4A). The responses of this neuron to the sight of watermelon were also modulated by the affective significance (Fig. 4B). This neuron responded consistently to the sight of watermelon in trials 1 and 2. In trials 7–11, after four intervening trials, salted watermelon reversibly modified the neuronal activity. The salted watermelon was visually indistinguishable from unsalted watermelon and in trial 7 the neuron responded as previously. However, as soon as the salted watermelon was ingested, the activity suddenly decreased (not shown). In trials 8–11 the response to the sight of watermelon rapidly decreased and finally disappeared. In trials 8 and 9 bar pressing failed to meet the FR criterion to obtain the watermelon and in trials 10 and 11 bar pressing stopped entirely (not shown). After the experimenter gave a piece of unsalted watermelon to the animal by hand, neuronal and bar pressing responses (not shown) resumed in trials 12 and 13.

The responses of eight rewarding-stimuli-related neurons (four oral sensory plus vision and four selective) and their related behavioral responses were suppressed in the same way in reversal tests. During the tests neuronal and integrated behavioral responses not individual bar presses, were well correlated. The responses of both types of neurons were first suppressed during the initial ingestion of salted food, suppression

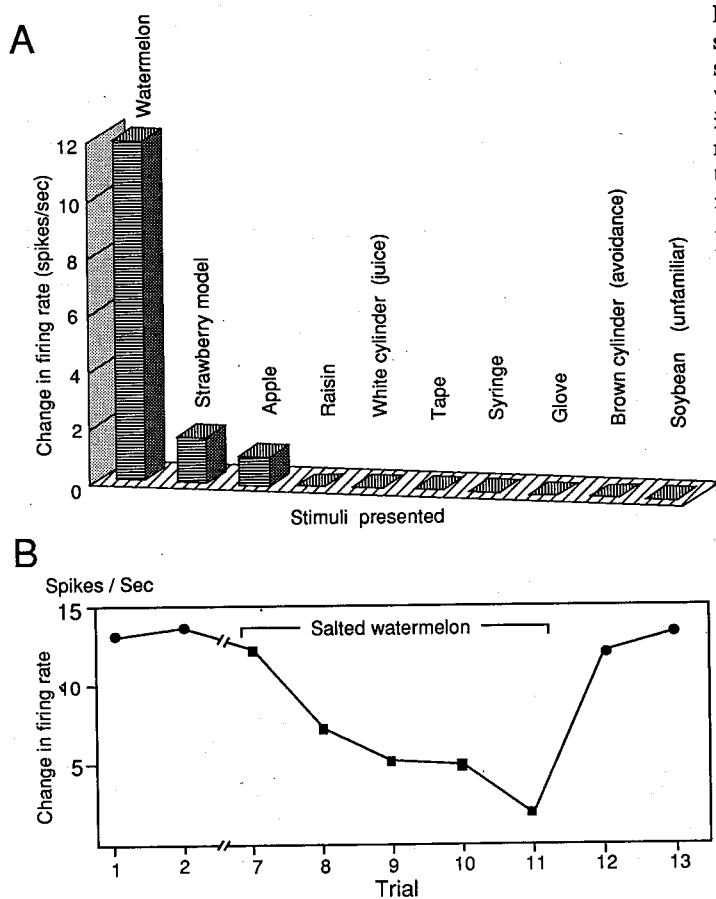


Fig. 4. Responses of selective AM neuron. A: responses of neuron selective to watermelon. Other descriptions as for Fig. 2B. B: Modulation of responses to watermelon by salting. Neuron responded to sight and ingestion of normal watermelon in trials 1 and 2. Note neuronal response to watermelon decreased after the trial 7 in which the animal put salted watermelon into its mouth. In trials 8-11 the neuronal responses gradually decreased and finally disappeared. Other descriptions as for Fig. 3.

of visual responses then followed although appearance of the food was not changed. In preliminary experiments, we observed suppression of gustatory responses by quinine, and those results were similar to the suppression by salt that is reported here. The gustation phase of ingestion is important in the evaluation of food palatability^{2, 21}. The evidence suggests that the suppression of visual responses by ingestion, as discussed here, is related to aversion to the taste of salted food. This speculation is reasonable since behavioral responses were also suppressed after the first of a series of salted food trials. This dependence of visual responses on sensation during ingestion suggests that these neurons were related to visual-oral sensory, possibly gustatory, association^{18, 19}. Geschwind⁵ suggested that visual-gustatory association in the limbic system was essential for stimulus-reinforcement association. Such associations may partially account for the deficits in discrimination of food and nonfood that are observed in the Klüver-Bucy syndrome caused by lesion of the temporal cortex, including the amygdala (AM)¹³. The AM may be important in ongoing recognition of the affective significance of complex stimuli involved in food-nonfood discrimination.

Some vision-related, audition-related, and multimodal tonic neurons responded equally to rewarding and aversive stimuli, but did not respond to familiar neutral stimuli. The responses of those neurons were easily modulated by extinction or by changing the affective significance of the stimulus (Fig. 3). Neurons with those characteristics may discriminate stimuli that are biologically significant from stimuli that are nonsignifi-

cant. This rapid and flexible change could be a neurophysiological basis of the role of the basolateral amygdala in acquisition of fear-potentiated startle, depending on the affective significance of the stimulus¹⁵. Those response changes may also be part of attention, reflected by the animal's concentration on one biologically significant stimulus among various exteroceptive stimuli^{18, 19, 23, 26}.

Responses of HF and PH neurons

Of 864 neurons recorded during performance of an operant task coupled to the presentation of rewarding, aversive or unfamiliar objects, 160 (18.5%) responded to the sight of certain object(s)³⁷. Of these 160, 73 (61 excited; 12 inhibited) responded to virtually all objects with no significant difference in response magnitude (nondifferential neurons). Eighty-seven neurons (66 excited, 11 inhibited, ten excited or inhibited depending on the kind of objects) responded differentially to different objects with significant differences in response magnitude or direction — 'differential' neurons.

Of these 87 differential neurons, 23 responded significantly more to rewarding objects than to aversive objects or to unfamiliar objects — 'rewarding-object-dominant' neurons. An example of this type of neuron is shown in Fig. 5A. Responses to rewarding objects (apple, raisin, cookie, and a red cylinder associated with juice) were stronger than those to aversive objects (syringe, spider model, centipede model, white cylinder associated with shock) or those to unfamiliar objects (car model, clip). However, the order of magnitude of responses to reward-

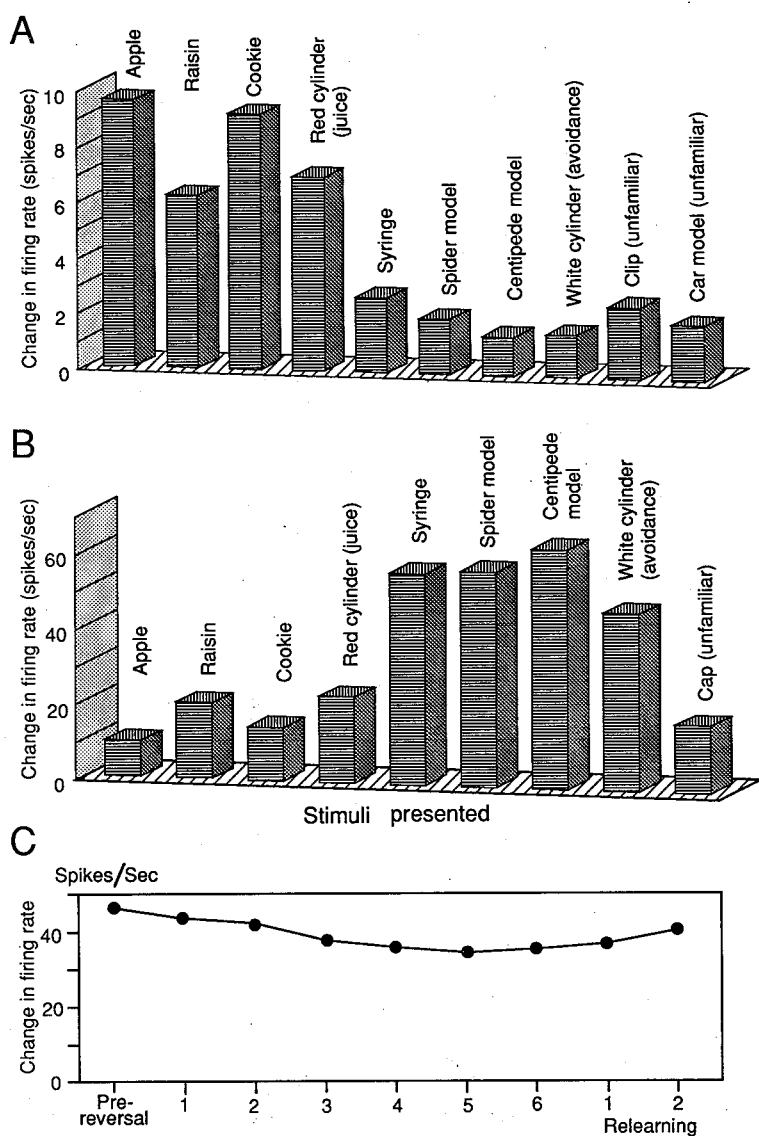


Fig. 5. Responses of HF and PH neurons to various food and nonfood objects. A: Responses of rewarding-object-dominant neuron. B: Responses of aversive-object-dominant neuron. Each column indicates response magnitude (mean of 1.0 sec firing rate after visual stimulation minus 1.0 sec firing rate before visual stimulation). C: Responses of an aversive-object-dominant neuron in the HF to white cylinder that was usually associated with electric shock in pre-reversal block, each reversal block, and two relearning blocks. Each response indicated by a filled circle shows a mean response size of five trials.

ing objects (food) did not necessarily correspond to the order of the animal's preference for the objects. Thirteen neurons responded more to aversive objects than to rewarding objects or unfamiliar objects 'aversive-object-dominant' neurons. Figure 5B shows an example of aversive-object-dominant neuron responses. The magnitudes of responses to aversive objects (syringe, spider model, centipede model and white cylinder associated with shock) were significantly larger than those to objects in the rewarding or unfamiliar groups. Seven differential neurons responded significantly more to unfamiliar than to familiar objects 'unfamiliar-object-dominant' neurons. Ten differential neurons each responded strongly to only one object or to one category of object.

Fourteen rewarding-object- and aversive-object-dominant neurons were tested in extinction or reversal tests. Responses of seven neurons to the same test objects did not change in extinction or reversal tests. Although responses of the other seven neurons decreased in extinction or reversal tests, the remaining magnitude of responses of five of these seven still exceeded the magnitudes of their responses to objects in other categories. Figure 5C shows the data of an aversive-object-dominant neuron that responded strongly during reversal

learning to the white cylinder associated with electric shock. In reversal learning, a white cylinder usually associated with electric shock was changed to be associated with juice reward. Though the response magnitude weakened slightly in the last five trials, this neuron continued to respond with significantly greater magnitude to the white cylinder than to the red cylinder, which elicited the greatest magnitude of response of all of the normal reward-related stimuli (Fig. 5B).

The absence of modulation of the differential responses of HF and PH neurons by reversal or extinction was in contrast to the action of AM neurons. This is consistent with the lesion study by Jones and Mishkin¹⁰ in which HF lesion had no effect on the performance of monkeys in stimulus-reward association tasks. The results suggest that activity of these neurons might not be directly related to ongoing recognition of affective significance, but might be related to past memory of affective significance. This agrees with human studies in which lesion of ventromedial parts of the temporal cortex including the HF resulted in retrograde amnesia for a few years³⁶. This part of memory might be related to a kind of 'temporal buffer memory'³⁰ before being encoded into long-term memory. Neurophysiological and

anatomical studies suggest that activity of these neurons might be involved in the control of feeding behavior. Neurophysiologically, the HF has profound influence on the hypothalamic ventromedial nucleus and the perifornical area¹⁴ partially by way of AM projections to the hypothalamus²⁷. A recent anatomical study indicates direct reciprocal connections between the AM and the HF indicating that the AM and HF may work in coordination. Thus the HF may transfer some past affective significance of an object to the AM for ongoing recognition of food and nonfood.

Neural mechanisms for discrimination of food and nonfood

Although AM-lesioned animals cannot discriminate food from nonfood immediately after the operation, they eventually reacquire the ability to discriminate food⁹. Furthermore, AM-lesioned animals can learn visual discrimination^{7, 29, 32, 39}, albeit gradually^{35, 38}. Discrimination of food and nonfood can depend on simple visual discrimination³⁸. It has been suggested that the temporal stem³⁸ or direct visual projection from the visual cortex to the striatum¹⁶ is responsible for such simple discrimination. Mishkin and his colleagues^{16, 35} suggested that this inferotemporal-striatal system corresponds to a neural counterpart of habit or procedural memory⁴, whereas the inferotemporal-AM system is responsible for associative memory by which animals discriminate positive and negative affective objects. AM-lesioned animals may plastically substitute the inferotemporal-striatal system for the ITCx-AM system. Food-responsive neurons have been reported in the rostroventral putamen¹⁷, an area that receives afferents from both the ITCx and the AM^{31, 34}. In contrast to the responses of AM food-responsive neurons, responses of the putamen neurons were highly task-dependent and not multimodal, ie they did not respond during the ingestion phase. These characteristics suggest strong relations of such neurons to a procedural memory system^{17, 23}.

The ratio of selective neurons found in the AM and HF to the total number of tested, 30/1574, appears to be very small in relation to the total number of items or objects with which the animals were familiar. However, if we consider that the number of items used to test each neuron was probably insignificant compared to the total admittedly relatively limited experience of laboratory animals the activity of selective neurons remained very low when tested with any other than the selective item. Thus we can draw two conclusions: (1) the number of selective neurons identified was very small compared to the unknown but probably very large population of such neurons, and (2) only by using an almost infinite number of test items would it be possible to measure approximately the actual ratio of selective neurons in the AM and HF. It appears to be necessary therefore to content ourselves with knowledge that these selective neurons exist in these two centres and not to attempt the meaningless task of evaluation of the populations of neurons concerned.

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扁桃体および海馬体を含む側頭葉の破壊により、食物と非食物の識別が不能になるクリューバー・ビューシー症候群を呈することが知られている。本研究では、サル扁桃体および海馬体から単一ニューロン活動を記録し、食物や非食物を含む種々の呈示物体や、ジュースや水と連合した音刺激の識別課題に対するニューロンの応答様式を解析した。扁桃体より総数710個のニューロン活動を記録し、そのうち、129個が単一感覚種の刺激に(視覚応答型、48個; 聴覚応答型、32個; 摂食応答型、49個)、142個が多感覚種の刺激に応答した。20個は生物学的に意味のある特定の物体または音の1つだけに特異的に応答した。さらに、食物に応答した8個の扁桃体ニューロンに対し、嫌悪性の塩あるいは食塩水を食物に添付することにより逆転学習を行った。その結果、8個すべての扁桃体ニューロンの応答が減弱あるいは消失した。

海馬体および海馬傍回より864個のニューロン活動を記録し、そのうち160個が視覚刺激(物体)に応答した。このうち、23個は主として報酬物体(種々の食物やジュースと連合した茶色円柱など)に、13個は主として嫌悪物体(クモのモデル、注射器、電気ショックと連合した白色円柱)に、10個は特定の物体に、7個は新奇物体に特異的に応答した。これら報酬および嫌悪物体に応答した14個の海馬体および海馬傍回ニューロンに対して、扁桃体と同様の消去または逆転学習をテストした。このうち7個のニューロンでは、応答がほとんど変化しなかった。5個のニューロンでは、有意な応答の減弱を示したが、他の物体に対する応答と比較すると依然として強い応答を示した。これらの結果より、扁桃体および海馬体の相補的な機能的役割りが示唆された。すなわち、扁桃体は目前の物体の生物学的価値評価と情動的意味の認知(たとえば、食物と非食物の識別など)に、海馬体は過去の物体の情動的意味の保持に関与すると考えられる。

Food memory: neuronal involvement in food recognition

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研究顯示部份切除動物顳葉皮層包括杏仁核和海馬回可誘發Klüver-Bucy綜合症，以致該動物不能區別食物與非食物。作者用710個杏仁核的神經元作檢驗，結果發現有129個（18.2%）對簡單的感覺刺激有反應（其中48個對視覺、32對聽覺、49個對攝食），（142個（20%）對多方式的刺激有反應和20個僅對感情方面的刺激有反應。用咸食物或鹽水導入對八種與杏仁核神經元有關的食物做反向試驗，發現所有反應均被反向調整。作者在海馬回和副海馬回皮層中的864個神經元進行試驗，結果發現160個（18.5%）對某些物体有反應，其中23個對主要喜歡的物体有反應，13個對幾種厭惡的物体（如蜘蛛模型、注射器、與弱電休克有關的物体）有反應，10個對一種或一類物体有反應，7個對陌生的物体有反應。用14種與神經元有關的喜歡或厭惡的物体作試驗，結果發現7種在消退或反向試驗中不改變，然而其它7種在試驗中減少。作者認為杏仁核可能在復染刺激（辨別食物與非食物）的感情方面的繼續認識起重要作用，而海馬回 - 副海馬回則可能對過去感情方面的記憶起作用。