Studies on Single Neurons in Dorsal Hippocampal Formation and Septum in Unrestrained Rats

Part I. Behavioral Correlates and Firing Repertoires

JAMES B. RANCK, JR.

The University of Michigan Medical School, Medical Science Building, Ann Arbor, Michigan 48104

Received May 9, 1973

INTRODUCTION

This study on hippocampal formation of rat is modelled after an approach used so successfully in the visual and somatosensory systems. In these sensory systems the receptive fields of individual neurons at various stages of the system have been determined, and subsequently, inferences have been made about how the processing of information occurs at each stage. For a neuron many synapses removed from sensory receptors or motor effectors, the analog of receptive field will be the behavioral correlate of a neuron, i.e., the sensory inputs and motor outputs of a rat which are associated with a given frequency or pattern of firing of a single neuron. Let us call this search for the behavioral correlates of single neurons "microphrenology."

It may not be possible to find a behavioral correlate of a neuron, for its firing may signal something not directly related to overt behavior, such as drive state, or some idea the rat has, or the blood level of some substance. The firing of the neuron might be part of some internal timing mechanism, or a mechanism in memory retrieval. The firing of the neuron might be significant only in some neural net, and therefore, firing of a single neuron may not be interpretable. However, in the hippocampal formation and septum, clear behavioral correlates can be determined for almost all neurons.

When the behavioral correlates of a group of neurons are known, we can try to define various behavioral types, groups of neurons with similar behavioral correlates. Among neurons of the same behavioral type, particular care will be taken to look for differences in behavioral correlates, for in the visual and somatosensory systems topographic location is reflected in the *difference* in receptive field between neurons.

The receptive field of a lateral geniculate neuron is (roughly) a spot or anulus of light, but the function of these neurons is not to respond to anuli or spots of light. To know its function we must know how the inputs of that region differ from the outputs to see how that region transforms the information. Similarly, to be able to apply this approach to hippocampal formation we must know behavioral correlates of almost all inputs and outputs of the system and see what transformations occur. The data reported here includes most of the inputs and presumably almost all of the outputs. While not complete, these data still allow many inferences on processing of information to be developed.

As in the case of the analog in sensory systems, we cannot simply record the firing of the neuron in a variety of predetermined conditions. Rather we must look for those conditions in which the neuron fires. In the early stages of the study *the behavior of the neuron shapes the behavior of the experimenter.* This first stage of the study is inadequate by itself. Most of the neurons reported here were studied in a second stage which included a systematic protocol, derived from the results of the first stage.

The firing repertoire of a neuron, i.e., the range of frequencies and pattern in which it fires in a fairly wide range of situations, is also studied. It is shown that the firing repertoire is distinctly different in different neurons.

The description of both behavioral correlates and firing repertoires involve a somewhat naturalistic approach, i.e., describing behavioral correlates and firing repertoires in general terms in a fairly wide range of behavior. It is necessary to go through this initial stage to know what questions will be worth asking more precisely. One of the groups of neurons discovered in this initial study was studied more incisively and results are reported separately (29). The questions in this later study could not have been formulated until this group of cells had been identified and its general characteristics described.

METHODS

A. Surgery and Electrodes

Electrodes were implanted in male Sprague–Dawley rats weighing 350–450 g under pentobarbital anesthesia to measure electrooculogram (EOG), dorsal neck muscle electromyogram (EMG), and electrocorticogram (EEG) (from stainless steel screws through the skull). Devices enabling recordings from single neurons to be made with a movable microelectrode were also implanted. The details of the movable microelectrode have been published (86). Briefly, it was tungsten wire with an etched tip, insulated to within 10–20 μm of the tip and mounted on a 1-72 stainless steel screw. The microelectrode was lowered through a silastic-covered hole in the skull by turning the screw (one turn equals 356 μm). The microelectrode was

removable so that multiple tracts could be made through the same hole. The system was sufficiently stable so that neurons could regularly be held when the electrode was hit against the side of the cage, or the rat picked up in the experimenter's hand.

B. Recording

General. Recording was made differentially between the movable microelectrode and a fixed microelectrode with a tip in the adjacent neocortex to reduce the EMG from jaw muscles recorded during chewing. This artifact can be large enough in a rat to obscure action potentials because his large jaw muscles are a comparatively small distance from any spot in brain. The wire from each electrode plugs into a Field Effect Transistor on the connector on the rat's head. This system is almost completely free of movement artifact. Both action potentials and slow waves of publishable quality record can be routinely obtained during the most vigorous movement of a rat. The regular slow wave theta rhythm activity recordable from the indifferent fixed microelectrode was tested in each rat by observing these slow waves when the movable microelectrode had just entered neocortex. In all cases it was less than 200 μv.

Recordings were routinely made on an oscilloscope of unit activity on a narrow band (flat 1000–5000 Hz) and slow waves and unit activity on a broad band (flat 1.0–20,000 Hz). Notch filters of 60 Hz were *not* used.[1] The shape and duration of all action potentials were examined. Since slow waves in the hippocampus in slow-wave sleep are often about 2–3 mv, and action potentials are often only 200 μv, it is sometimes difficult to catch an action potential on a storage scope with sufficient gain to examine it except with a narrow band amplification, where shape and duration are seriously distorted.

The EEG, neck EMG, EOG, and the slow waves from the microelectrode were recorded on a polygraph continually. Photographs of the oscilloscope trace of action potentials and the slow waves from the microelectrode were made of representative types of activity. Some were also recorded on magnetic tape.[2]

The microelectrode was lowered while the rat was in his cage. He readily adapted to the situation and sometimes slept while the microelectrode was moved. Below the silastic, electrical contact was made. By counting the number of turns below silastic, the approximate depth of the microelectrode was known. The accurate depth was determined at histology.

[1] Very sharp filtering was used in the narrow band channel, falling off 8.6 db per octave below 500 Hz and 14.4 db per octave below 70 Hz.

[2] The EMG of the dorsal neck muscles of a rat changes with every movement, so this recording is particularly useful in determining the timing of movements.

Problems of Isolation. Isolation is particularly difficult in parts of hippocampal formation as compared to, for instance, neocortex. This is not surprising when one looks at the very close packing of cell bodies in the granular cell layer of fascia dentata and the pyramidal cell layer of Ammon's horn. Since the pyramidal cells of CA1 are smaller than those of CA3, it is not surprising that extracellularly recorded action potentials are smaller and isolation is more difficult in CA1 than in other parts of Ammon's horn. The cells of fascia dentata are also more difficult to record from than CA3, no doubt for similar reasons.

Since so many cells fired in complex spikes in which the size of the extracellularly recorded action potential decreases during the burst, a simple spike-height window discriminator cannot always be used. Therefore, it is important to have especially good isolation of a cell. This isolation was achieved by moving the electrode up and down once a neuron had been found. In many cases more than one neuron was recorded at one time, but often the firing of a single neuron could be distinguished from the others because of a distinctive sound on the speaker, or with the aid of a spike-height window discriminator, or by checking with photographs of firing later. The criteria that a single cell was recorded from were: all amplitudes were within 20% of each other and shapes of action potentials as observed on a fast sweep were the same. These criteria do not assure that only single neurons are reported. Some of the data may in fact be from two neurons, but it is surely a small proportion of the cells.

Rarely Firing Neurons. Many neurons in hippocampal formation did not fire at all for minutes if their behavioral correlate did not occur. Three special procedures were used to find these rarely firing neurons. (a) During slow-wave sleep the electrode was moved in an increment of 10 μm and action potentials were looked for for 30 sec after each advance of the microelectrode. Only two neurons have been found which did not fire at least once in 30 sec in slow-wave sleep. Most fire at least every 5 sec (see Results). Notice there is a circularity in the reasoning: almost all neurons fire in slow-wave sleep, but many of them were found in slow-wave sleep. Therefore, this procedure is not enough. (b) When the electrode was near where action potentials were being recorded, but none were present, the rat was induced to produce those behaviors which are often associated with firing. Notice there is a circularity in this procedure also. (c) When recording from a neuron, the rare firing of other neurons was carefully watched for. When other neurons were found, they were studied whenever possible.

Neuron Damage. Damage to a neuron by a microelectrode in Ammon's horn and fascia dentata is very different from that in neocortex and many other parts of brain. Only two neurons have been seen to die in a high frequency discharge, and less than 20 have developed "notches" on action

potentials. Often I recorded from a neuron, which seemed to be firing in a normal fashion and which then suddenly did not fire anymore. This usually occurred within the first 15 sec of recording, but could occur any time. Therefore, whether or not a neuron had been damaged was not as clear as it is in recording from neocortex, from which many of our conventional standards seem to have been derived. The special case of complex spikes will be dealt with in Section A of Results.

The possibility of damage must be considered even more seriously since the amplitude of the action potential often changed, suggesting that the electrode sometimes moved with respect to the cell. Usually the change occurred gradually over the course of an hour or more and was not associated with particular behaviors. The effects of this damage over many minutes was tested in the following way. Slow-wave sleep is an easily obtainable behavior, two episodes of which are presumably very much alike if there are similar EEG and deprivation states (46), during which almost all units fire and during which unit firing is relatively constant when averaged over a few seconds. Therefore, unit firing was observed in two or more episodes of slow-wave sleep which bracketed some other behaviors in all the first 50 neurons and in many later neurons. Photographs of the firing of the cell in different episodes of slow-wave sleep were compared by visual inspection.[3] In only one neuron was a change seen. Therefore, if there was any long-term damage to neurons, its effect on firing was constant over the times observed.[4]

Since some changes in firing of a neuron were associated with movement of the rat, there is a possibility that some change in rate of firing was due to movement of the electrode with respect to the neuron, thereby changing the degree of damage to the neuron. This seems unlikely for three reasons: (a) Almost all changes in rate were not associated with changes in size of the recorded action potential. (b) As will be shown, the changes in rate are best related to the kind of thing the rat is doing, rather than how he is doing it or his position, i.e., sniffing with head up or head down. Yet when changes in amplitude of action potential were seen over periods of less than a few seconds, it was associated with changes in body position. (c) All reported changes were reproducible over periods of several hours in many cells. All exceptional cases are mentioned in the Results section. Some of these may have been due to damage. Fortunately, the number of exceptional neurons is small, so the issue can remain open without influencing the major conclusions.

[3] This method will pick up changes of greater than about 50% in rate and gross changes in pattern.

[4] This repetition of slow-wave sleep also gave greater assurance that the recording was from the same cell throughout, but continual observation of the cell by the experimenter provided the most important evidence that it was the same cell.

C. Behavioral Procedure and Data Acquisition

Training of Rats and General Procedure. Before being run, all rats were trained for at least 3 days. Training involved food and water deprivation from about 5:30 PM until 8:00 AM. During the day individual pellets of food were presented at irregular intervals. A water bottle was present only for about five 2-min periods. The rats learned to eat and drink immediately upon presentation of food and water. During this time the rats were also deprived of paradoxical sleep by the inverted-flowerpot-in-water method. Quinine was added to the water (0.01%) so the rat did not drink it. The rats received normal total amounts of food and water during this time. When a rat was being run he was on a similar food–water–sleep deprivation schedule. The advantage of this is that the rats would eat and drink immediately upon presentation of food or water so observations of these acts could occur whenever the experimenter desired. The water deprivation allowed the passive avoidance test to be run (see below). Paradoxical sleep deprivation ensured frequent episodes of both slow-wave sleep and paradoxical sleep. The recording time on a rat for a single day was a maximum of 8 hr. This enabled the rat to get some sleep prior to the 12–14-hr food–water–sleep deprivation. Rats were allowed to eat and drink to satiety at the end of each recording day. Eight rats were also trained to bar-press for food and water on continuous reinforcement before recording. The electrodes were left in place for many days, and could be moved up or down over this time. All the recording was done by the same experimenter. All runs were not necessarily on consecutive days. Recordings from a single rat were usually made over about 1 wk. Rats were kept in glass acquaria in a laboratory with windows. Thus, they were on the seasonal light–dark cycle. All data were taken in the daytime.

The running box was 60 cm long, 30 cm deep, and 30 cm high. Three of the sides were wooden. The fourth, which faced the experimenter, consisted of a fine-mesh screen. There was no top. This box permitted observation of the animal by the experimenter at all times. The box contained a bar which operated a food dispenser, a bar which operated a water dipper, and a hole into which a water bottle spout was sometimes placed. Much of the experiment was performed while the experimenter was listening to the cell firing on a loudspeaker and watching the rat. This made it easier to find correlations between the two than if it were necessary to watch both. It also made it easier to work out details of timing of the two. However, it made even greater demands on good isolation of a single cell.

Stages of the Experiment. In Ammon's horn and fascia dentata there were two stages of the investigation. The first 102 of the 310 cells studied in Ammon's horn and fascia dentata were used in the first stage and were used to discover the various behavioral types and develop the running pro-

tocol. Since a type could not be defined until a group of them had been studied individually, the classification of behavioral type of many of these early cells was done retrospectively, although in almost all cases the descriptions were adequate to make an unambigous retrospective classification. Once the behavioral types had been defined and the protocol developed, cells were studied in the second stage. The next 208 cells were classified at the time of observation. This second stage was important for five reasons. (a) All cells were subjected to the same protocol. (b) It allowed the important question "are there any cells which do not fit these types?" to be asked. (c) It attenuated some important sampling bias, since finding a cell is somewhat dependent on what one is looking for, especially if the cell fires rarely (see Methods B). (d) After a behavioral type had been defined, the validity of the descriptive categories was retested many times. (e) When a cell had been classified during observation, the ability of this classification to then *predict* the firing of that cell in the whole range of behaviors observed was then tested. The ability to predict was not tested quantitatively, but it is nevertheless a far stronger demand on classification than retrospective generalization of data from many cells. It also forces observations on each cell to be replicated. In the first stage of the investigation the approach was very open-ended with an attempt to see what could be seen. The second stage used a systematic protocol, but even in the second stage it was important to watch the rat and cell continually, not only during items of the protocol. For the descriptions that follow are an attempt to describe all the firing of a neuron in the context of the experiment. Any firing which was not predicted was a failure of the description and will be reported. Averaging across presumably similar episodes of a behavior in the same cell, in different cells was thus not done. This study rather concentrated on the logical prior question of determining which episodes of behavior could indeed be considered to be similar in the context of the neurons studied.

The data reported in this paper on 157 cells from septum, subiculum, presubiculum, parasubiculum, and medial entorhinal cortex only used the first stage of description. Many cells were classified retrospectively. All of the septal cells were studied after the cells of Ammon's horn and fascia dentata and the same running protocol was used. The cells in subiculum, presubiculum, parasubiculum, and medial entorhinal cortex were studied before the first stage of hippocampal investigation was completed.

Protocol of Data Acquisition. All cells in the second stage were studied on all parts of the protocol below except items a, b, q, and the bar-pressing behavior of items i and k. The running protocol was: (a) The rat is in slow-wave sleep. (b) The rat is in paradoxical sleep. The relation of phasic episodes of paradoxical sleep to cell firing was determined in two ways: during a run the cell was listened to and the rat, especially his vibrissae, was watched; and eye movements were recorded on a polygraph

and were later correlated with photographic records of the cell. (c) The rat is in quite arousal. (d) The rat smells amyl acetate, or camphor, or turpentine, or wintergreen on a Q-tip. Usually only two of these were tested. (e) The experimenter moves his hand in front of rat's face, flashes a flashlight, and moves the light across the rat's visual field. (f) The experimenter snaps a cricket (aversive), and bangs cans or claps hands (this startles the rat). (g) The experimenter touches all parts of rat's skin. This is done in the form of petting him. (h) The rat grooms his face, legs and body, and genitalia. (i) Eating behavior: The rat approaches a 1–2 g food pellet, picks up the pellet, carries the pellet across the cage, eats, explores the floor after finishing the pellet, and follows a pellet as it is moved in the experimenter's fingers. On continuous reinforcement, the rat bar-presses for 45-mg food pellets delivered by a chute. (j) Response to novel nonnutritive objects (paper, wood, pencils, etc.) is observed. (k) Drinking behavior: The rat approaches the water bottle, explores the water bottle, drinks, and explores the water hole after removal of water bottle. This is compared with drinking from a small cup and lapping up drops of water on the floor. The rat bar-presses for water or continuous reinforcement, drinking from a dipper. (l) The experimenter interrupts the rat's eating or drinking by putting his hand in cage, and, if necessary, making noise. (m) The rat explores the cage, including sniffing at the floor and sniffing while standing on his hind feet, i.e., sniffing when there is no apparent object to sniff. (n) The rat is picked up in experimenter's hand. (o) The experimenter blows on the rat. Rats try to escape from this. (p) The experimenter pinches rat's tail. This causes vocalization and escape. After his tail has been pinched once or twice, when his tail is picked up the rat runs off (avoids). (q) Passive avoidance: The rat had been trained so that he drank immediately and almost continuously during the few brief periods when the water bottle was present. The waterspout is then hooked to a 0.27-ma 60-Hz current and the grid floor of the cage grounded so that the rat is shocked when he drinks. This is enough current so that the rat usually does not return to the water bottle for as much as 30 sec, and often not for minutes after the second shock. When he is shocked he gets little or no water for he backs off immediately. The spout is shielded so that the 60 Hz interference does not obscure the electrical record if the rat is more than about 5 cm away from the spout. The microelectrode is disconnected when the rat is shocked, for it can be shown that as much as 10^{-8} amp may flow through the microelectrode during the shock which could affect the activity of the cell. This disconnection is readily accomplished so that only 2 or 3 sec of recording time is lost. If the disconnection is not made, the cell is not studied any further since the cell may have been damaged by current through the microelectrode.

Thus, in the context of this experiment, consummatory behavior includes

eating, drinking (which will include licking the floor), sleeping, and grooming. Another consummatory behavior, automatic sniffing will be defined below in Section B of Results. In the descriptions of behavioral correlates of neuronal firing which follow almost all descriptive categories of the most common type of cell (complex spike cells) are tied to consummatory behavior. Even though descriptions are based on observations of a single experimenter, each of these consummatory behaviors are unequivocally recognizable.[5]

As will be seen, none of the descriptions of behavioral correlates given require an interpretation by the observer (although a few of the words used do make some implications, for instance, "orient," "successful," and "unsuccessful"). Thus, all descriptions are behavioristic. Indeed, as will be seen the rat need not be observed for more than 1 or 2 sec for the discriptions to be made. All of the classifying categories used are unambiguous, and all or none. All observations were made by one observer, so the likelihood of subjective bias was present. These observations must receive further validation from multiple observers and quantitative tests of predictability in the future. Nevertheless, for the reasons given above, errors due to subjective factors have been kept within bounds.

D. Histology

After electrode tracks were completed on both sides of the brain, a 100-μm lesion was burned in each tract, the rats were perfused with saline then formol–saline, and cresyl-violet-stained frozen sections were examined to determine where the recordings had been made. In most rats only one track was made on each side of the brain.

The anatomical terminology used will be that of Blackstadt (16). Sharp demarcation between presubiculum, area retrosplenalis E parasubiculum, and entorhinal cortex can be made with silver stains, but not with Nissl stains which were used in this study. Therefore the term area retrosplenalis E will not be used and the other three will be identified by general region only. Field CA2 will not be recognized, but will be convenient to speak of the upper and lower branches of dorsal CA3, the upper branch including all of what others would consider CA2 and called upper CA2-3. By hippocampal formation, I mean Ammon's horn, fascia dentata, subiculum, presubiculum, parasubiculum, and entorhinal cortex.

RESULTS

This paper will report data from 372 neurons in dorsal hippocampal formation in 35 rats. All neurons recorded in CA1 were in anterior CA1 of

[5] Sleep and its various stages are not unequivocally recognizable from overt behavior alone, but neocortical EEG, hippocampal slow waves, neck muscle EMG and EOG were always recorded.

TABLE 1

DORSAL AMMON'S HORN AND DORSAL FASCIA DENTATA

	Theta cells	Complex spike cells
1a. Complex spikes	Never	All have some
b. Simple action potentials	Always	All have some
2. Duration of extracellular negative spike (distorted)	All 0.15–0.25 msec	All 0.3–0.5 msec in single spikes and spikes of complex spikes
3. Rate of firing most of the time awake and SWS	Almost all >8/sec	All <12/sec, most <2/sec, many off[a]
4. Maximum rate of firing	29–147/sec, sustained for many seconds	All <40/sec, most <20/sec sustained for less than 2 sec[a]
5. Patterns of firing	Comparatively regular	Irregular
6. During theta rhythm in slow waves in paradoxical sleep or awake		
a. Rate	At maximum rate if and only if theta rhythm is present	No simple relation usually <1/sec[a]
b. Phase relations	Most have clear phase relation	Most have clear phase relation

[a] A complex spike is counted as a single potential.

Raisman, Cowan, and Powell (84, 85). All cells in dorsal fascia dentata were in the dorsal blade. Data from 95 neurons in medial and lateral septal nuclei in 14 rats will be reported.

A. Theta Cells and Complex Spike Cells of Dorsal Ammon's Horn and Dorsal Fascia Dentata: Firing Repertoire

In dorsal Ammon's horn and fascia dentata all of the neurons belong unequivocally to one of two groups. These groups differ from each other in many ways. These differences are listed in Table 1. There are equally clear differences in the behavioral correlates of the two groups. Picking only one of the possible characteristics by which to name these cells, I will call one group "theta cells," the other "complex spike cells." Each of the characteristics of Table 1 will be discussed.

Complex Spikes. A "simple spike" is the usual single spike action potential of neurons. Both types of neurons have these action potentials.

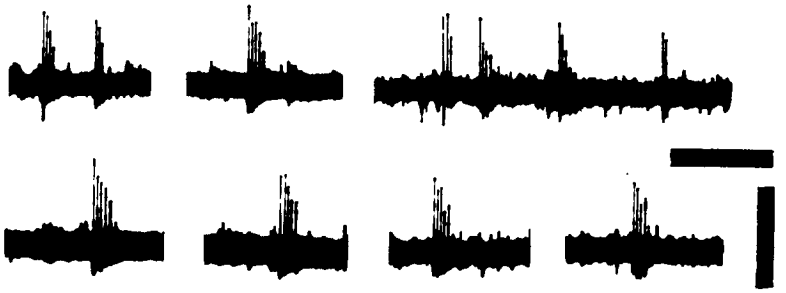


FIG. 1. A complex spike cell from CA1. All of these occurred within 5 sec during slow-wave sleep. Negative up. Voltage calibration 360 μv; time 0.1 sec.

A "complex spike," which *all* complex spike cells have at some time and which theta cells *never* have, is a series of two to seven individual spikes with 1.5–6 msec interspike intervals, in which the amplitude of individual extracellularly recorded spikes changes during the series, usually decreasing. Complex spikes were first reported in hippocampus in 1940 in the first report of recordings from single neurons in mammalian central nervous system by Renshaw, Forbes, and Morrison (87). They have been seen by many others since. They have been studied with intracellular recording (50), demonstrating they are not just firing from several adjacent cells. They occur in other parts of brain but are especially common in Ammon's horn and fascia dentata.

Complex spikes have not been studied systematically but certain facts are clear. For a given neuron the complex spike continually changed. Figure 1 shows all the action potentials of a neuron over a 5-sec period; no two are alike. Some complex spike cells fired more complex spikes than simple spikes, others fired many more simple than complex spikes. Many complex spike cells fired a larger proportion of complex spikes in slow-wave sleep than in any other behavior. Indeed, some cells never fired complex spikes except in slow-wave sleep. One should not say a cell does not have complex spikes unless the cell has been observed in slow-wave sleep. During a complex spike the duration of the individual extracellularly recorded spikes increased. During a complex spike the interspike interval usually increased. Sometimes the first interspike interval of a complex spike was the longest, the second was the shortest, and subsequent interspike intervals progressively lengthened. Both patterns are seen in Fig. 1 in the same cell.

Complex spikes can also be seen in neocortex above Ammon's horn. However, we have only once been able to record a complex spike in neocortex for more than 5 min, and almost all could only be recorded in the first 30 sec of recording. Therefore, in neocortex a complex spike may well be an artifact of injury. In Ammon's horn and fascia dentata we have never seen any change in frequency of complex spikes in relation to a given behavior.

over periods of up to 4 hr, although we have done no quantitative studies. Since the proportion of spikes which are complex spikes is highest in slow-wave sleep in many neurons, it seems unlikely that complex spikes are an artifact in Ammon's horn and fascia dentata. Thus the presence or absence of complex spikes is a real electrophysiological difference between these two groups of cells, and probably the clearest defining characteristic. In practice this is not the easiest characteristic to use to distinguish the two groups, for some complex spike cells may not fire a complex spike for many minutes, especially when the rat is awake. Rate of firing and behavioral correlates are the most practical defining characteristics. A few cells were classified as complex spike cells, even though a complex spike was not seen, if all the other defining characteristics were met, and the cell was not observed during slow wave sleep. One exceptional cell has been found, a cell with all the characteristics of a complex spike cell (including behavioral correlate) except that a complex spike was never seen, although the cell was observed continually for 69 min including slow-wave sleep.

Duration of Action Potentials. The extracellularly recorded action potentials of all theta cells were negative–positive. The initial negative spike of all theta cells had a duration of 0.15–0.25 msec on the narrow band filter usually used. This filter distorts the shape and duration of the spike. On a broad band-filter a theta cell with a 0.2-msec negative (distorted) spike had a negative–positive action potential of 0.6–0.7 msec (undistorted). Theta cells with 0.2–0.25 msec duration negative (distorted) spikes could be held for hours and could be recorded from as the microelectrode was moved 100 μm. Theta cells with 0.15 msec duration negative (distorted) spike were either hard to hold for more than about a minute or developed 0.2-msec duration spike with time or further movement of the electrode. These 0.15-msec duration negative spike cells may have been from axons and are excluded from this study. Identification of the reported theta cells is discussed in Section D of Discussion.

Almost all complex spike cells had negative–positive action potentials. The duration of the negative spike was 0.3–0.5 msec when recorded through the narrow band-filter. Five exceptions were found: Three complex spike cells which had durations of the negative spike of 0.2 msec (distorted), and two theta cells which had durations of 0.4 msec (distorted).

Rate and Pattern of Firing. The most obvious differences between these groups was rate and pattern. There was some overlap in rates, but almost all complex spike cells never fired faster than 10/sec (counting a complex spike as one event), and almost all theta cells almost always fired faster than 10/sec. When theta cells slowed to less than 10/sec it was for less than about 4 sec. When complex spike cells increased to greater than 10/sec it was for less than about 2 sec. Therefore, for periods of greater than about 3 sec there was almost no overlap in rate of the two groups. Some

complex spike cells did not fire at all for minutes at a time, and many fired at less than once in 10 sec most of the time while the rat was awake.

No quantitative studies of patterns of firing have been made, but from inspection of the figures it is clear that as compared to complex spike cells, the interspike intervals of theta cells were more uniform and consecutive interspike intervals were likely to be similar. This holds in all theta cells in all modes of firing.

Relation to the Theta Rhythm. Theta cells increased their rates of firing *if and only if* there was regular 6–10/sec slow waves in hippocampal formation, during both paradoxical sleep or wakefulness—hence the name of these cells. These regular slow waves will be called by the usual term "theta rhythm" even though the frequency may be faster than the 4–8/sec theta range. This relation between the slow-wave theta rhythm and increased neuron firing was absolutely invariable when the rat was awake—there were no exceptional cells and no exceptional instances within a cell. In paradoxical sleep there were five exceptions described in Results, Section B below. The greater the frequency of the theta rhythm, the more rapid the firing of the theta cell.

The phase relations of most theta cells with the locally recorded regular theta rhythm slow wave were easily determined by simple inspection. For a given cell this relationship is constant with a theta rhythm at various frequencies, (1, 28) and is the same during either wakefulness or paradoxical sleep (Figs. 3, 4). A changing phase relation as reported by Noda, Manohar, and Adey (69) was never seen. In some theta cells the phase relations were not obvious (Figs. 5, 6). In one exceptional cell no phase relation could be seen. Rapidly firing cells in phase with the theta rhythm in hippocampus were first discovered by Green and Machne (36). Noda *et al.* (69) studied interspike interval histograms, autocorrelations of cell firing and cross-correlations of action potentials to slow waves in what are clearly theta cells in Ammon's horn of cat (Discussion, Section B). Macadar *et al.* (60) and Morales *et al.* (68) made similar studies of theta cells in medial septum of rat. With the exception noted above in Discussion, Section B, this study agrees with these other, more quantitative, studies.

There was no simple relation between the existence of a slow-wave theta rhythm and the firing of a complex spike cell. Most complex spike cells fired at some time when a theta rhythm was present, but only in certain special situations as described below for the behavioral correlates of complex spike cells. When a complex spike cell fired during a theta rhythm, the firing was usually in phase with the locally recorded slow-wave theta rhythm (Figs. 13, 16, 17). For a given cell the same phase relation held in wakefulness and paradoxical sleep. In some cells there was no obvious phase relation to the slow waves, but quantitative studies have not been done. Thus whenever either theta cells or complex spike cells fired during

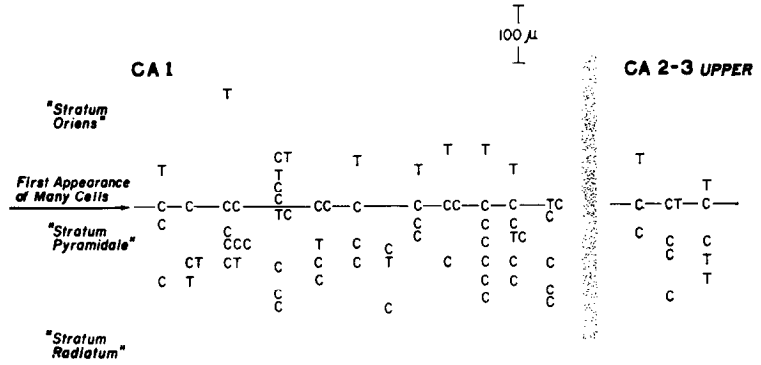


FIG. 2. Location of theta and complex spike cells. Each vertical line of letters is a single tract. T = theta cell, C = complex spike cells. The first appearance of many cells (i.e., isolation problems) was considered the beginning of stratum pyramidale. This was always in general agreement with the location of stratum pyramidale by histology.

a theta rhythm, there was usually a phase relation between firing and slow waves. The distinguishing feature is that the behavioral correlate of rapid firing in theta cells is identical to the behavioral correlate of the theta rhythm, while the behavioral correlates of complex spike cells and the theta rhythm are unrelated. The slow-wave theta rhythm has different phase relations in different parts of the hippocampus (37, 78). Therefore phase relations of units to the local slow wave theta rhythm do not have a simple interpretation and further details of these relations will not be given in this paper.

A slow-wave theta rhythm could not always be recorded from the fascia dentata, especially in the molecular layer. There were instead irregular waves of 1–4/sec of 1–3 mv amplitude. This may just have obscured a smaller amplitude theta. A theta rhythm also could not be recorded from septum, and the slow waves were less than 100 uv amplitude. Therefore, theta cells can be found in some sites where there is no regular slow theta rhythm.

Location of Cells. Almost all complex spike cells were only seen in a region from which many other large action potentials were also recorded, which I take to be either the stratum pyramidale of Ammon's horn or stratum granulosum of fascia dentata. Some theta cells were found alone and others were found with complex spike cells. Figure 2 shows the location of theta and complex spike cells in CA1 and upper CA2-3 in all tracts in the second stage of this study when the classification of all cells was clear. Theta cells in stratum radiatum and stratum moleculare of fascia dentata are reported elsewhere (29). In stratum radiatum, and lacunosum-moleculare of CA1, and in the lower branch of dorsal CA3 and fascia dentata,

much of the data is not adequate for this analysis. Since the localization study is incomplete, localization does not appear in Table 1.

Theta cells were also found in subiculum (6 out of 29); presubiculum, parasubiculum, and medial entorhinal cortex (8 out of 33); medial nucleus of septum (13 out of 30); nucleus of diagonal band (1 out of 17); septofimbrial nucleus (3 out of 16); and bed nucleus of stria terminalis (2 out of 16). Other data from these last three regions are not reported in this paper. Theta cells in medial nucleus of septum and nucleus of diagonal band have been studied by others (60, 68, 79). No theta cells were seen in lateral septum out of the 65 cells studied. I cannot see any difference between theta cells in any of these locations. However, the sample is small and the methods barely quantitative so real differences may well exist. Macadar *et al.* (60) suggested there are differences between these cells in medial septum and hippocamus.

Number of Cells Seen. The numbers of theta cells and complex spike cells seen in various parts of Ammon's horn and fascia dentata are listed in Table 3. Of all "late" cells, 28% were theta cells. No cells are included for which there is any ambiguity about histological location. All cells which might have been in CA4 had some ambiguity about location. Thirty-one cells, 9 (29%) of which were theta, 22 (71%) of which were complex spike, are excluded from the study because of uncertain location, but none of these demonstrate an exception to the descriptions given above.

A sampling bias has lead to a large overrepresentation of theta cells for the following reasons. (a) Rapidly firing cells are easier to hear than more slowly firing cells, especially when some slow cells are off for many seconds to minutes. (b) The striking rhythmicity of most theta cells during a theta rhythm is easy to hear and recognize. (c) A short duration action potential makes a sharper noise on a speaker. (d) Because of their high rate of firing, theta cells can be studied with little error even if they are not isolated from a slowly firing cell (Fig. 5, 6) but the reverse is not true. (e) Complex spike cells are more difficult to isolate from each other. I have never recorded from two theta cells at the same time (although others working in this laboratory have), and I almost always record from at least two complex spike cells at the same time. I do not know what the proportion of theta cells is, but it is surely much less than the 28% found in this study. From these data it is not possible to say if there are significantly different proportions of theta cells in the various fields of Ammon's horn and fascia dentata.

B. Behavioral Correlates of Theta Cells

Since theta cells increased their rates of firing if and only if there was a slow-wave theta rhythm, the behavioral correlate of rapid firing of a theta cell was identical with the behavioral correlate of the theta rhythm.

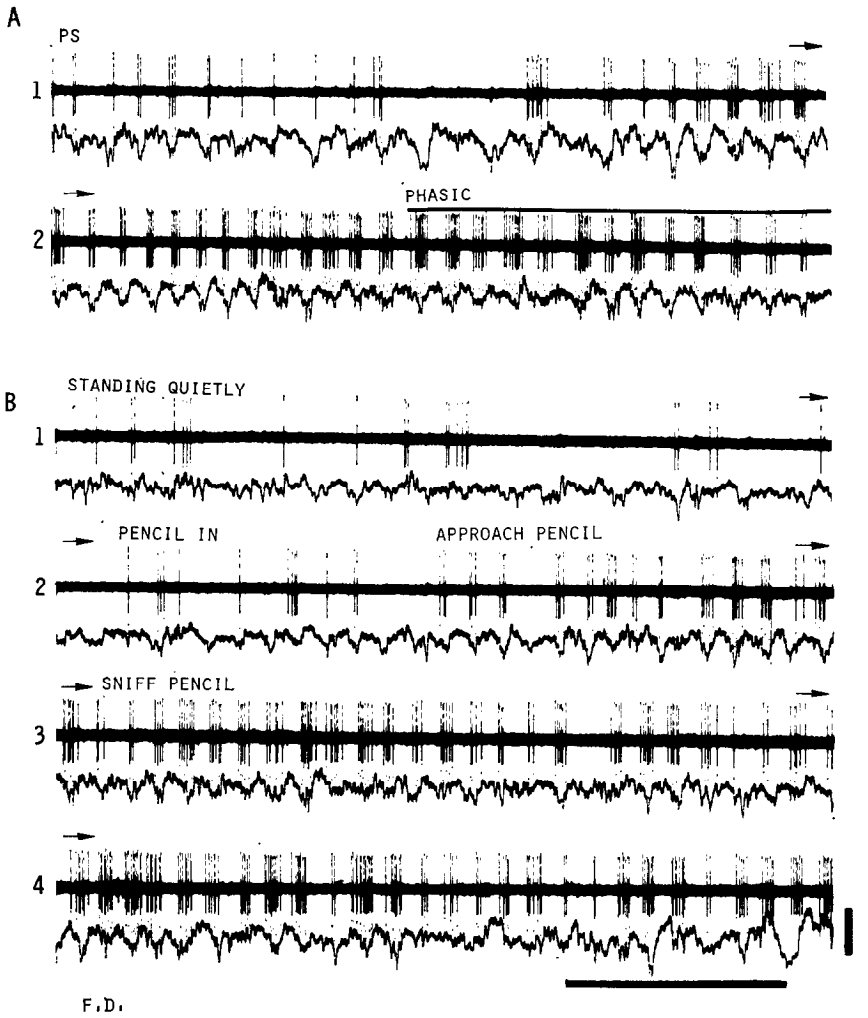


FIG. 3. Theta cell in fascia dentata. This neuron was unusual in that it was off for 10 sec when the rat was awakened from sleep. This neuron has the most striking phase relation to slow waves of any neuron seen.[a] Voltage calibration top trace 310 μv, bottom trace 770 μv; time 1 sec.

[a] In Figs. 3–7 and 11–23, the top trace of each pair of traces is from the narrow band amplifier. The lower trace is of the same input from the broad band amplifier (see Methods). *None of them has been retouched in any way.* Negative is up in all. In each figure all traces are from the same neuron. When lines are continuous there are arrows and the lines are numbered. Letters indicate separate times. PS is paradoxical sleep. SWS is slow-wave sleep. The labeled behavior begins at the beginning of the first letter of the label. Figures 3–7 are theta cells. Figures 11–20 are complex spike cells. Because of the slow sweep speeds the presence of complex spikes can usually not be determined from these figures, but can be determined in the original data.

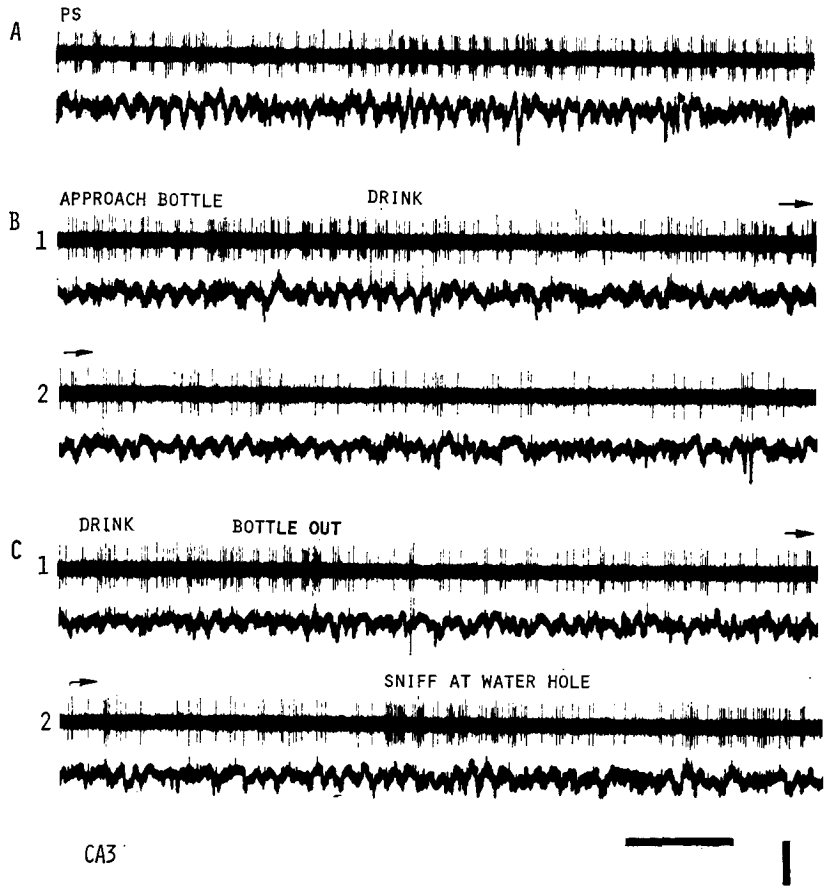


FIG. 4. Theta cell in CA3. This is typical of most theta cells. An artifact (due to touching the spout) is present for the first half second of drinking. Volltage calibration top trace 230 μv, bottom trace 1.5 mv; time 1 sec.

For the same reason the behavioral correlate of rapid firing was identical in all theta cells, although rates of firing and pattern of firing differ between cells. There have been many studies on the behavioral correlates of these slow waves, and there are many interpretations of them which are discussed elsewhere (29). There seem to be important differences between species (104). The most complete general description of hippocampal slow waves in the rat is that of Vanderwolf (97, 98). I have checked the firing of theta cells and slow waves against *all* of the observations in his 1969 paper (97), and have confirmed all his findings. Therefore, the behavioral correlate of these cells in rat will be described largely with Vanderwolf's approach. These cells will be described in general terms in this paper. A much better description of certain behavioral correlates and firing repertoires

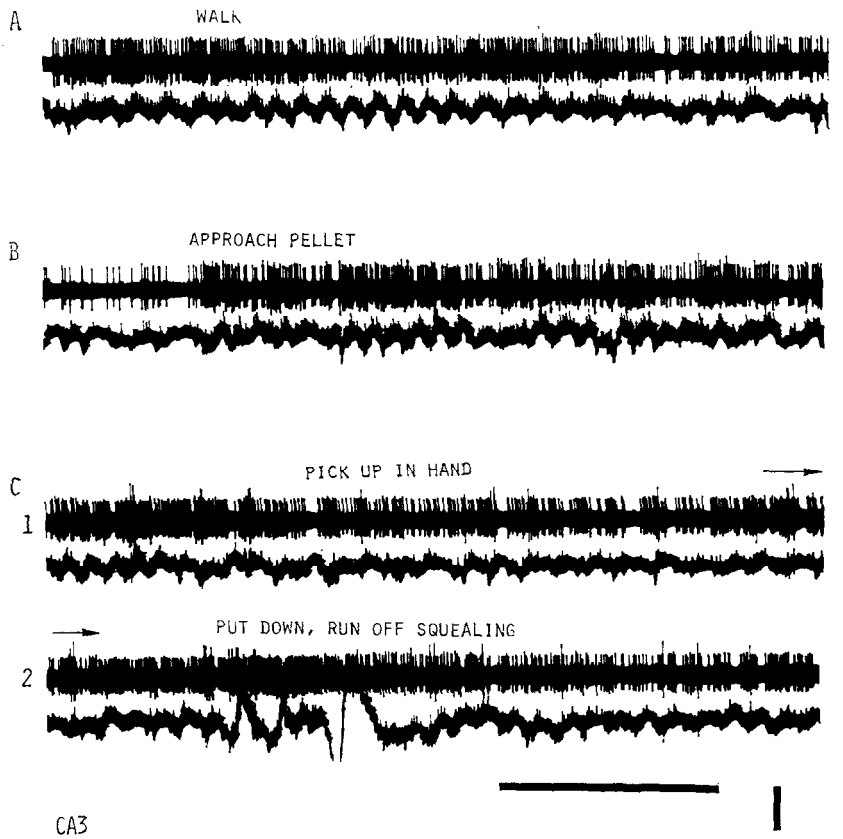


FIG. 5. Theta cell in CA3. (The same cell as in Fig. 6.) During a regular theta rhythm in the slow waves the neuron slows or stops at or soon after the peak slow wave negativity. There is an artifact in the slow waves in C2. A much slower and larger amplitude cell is also present in this and Fig. 6. Voltage calibration top trace 550 μv, bottom trace 2.3 mv; time 1 sec.

is given in another paper (29). Three modes of theta cell firing were recognized: the theta mode (associated with a theta rhythm in the slow waves, or rhythmical slow activity, RSA of Vanderwolf); the automatic mode (associated with large-amplitude irregular activity of the slow waves, LIA of Vanderwolf); and a slow mode (often associated with small-amplitude irregular activity of the slow waves, SIA of Vanderwolf).

Theta Mode. Theta mode firing is the rapid mode of firing. Vanderwolf describes the behavior associated with the theta mode as voluntary behavior—defined and discussed more fully in another paper (29) and paradoxical sleep (97, 98). In the context of this experiment theta mode behavior included the rats' exploration of a novel object, running away from my hand, struggling to escape when in the experimenter's hand but not

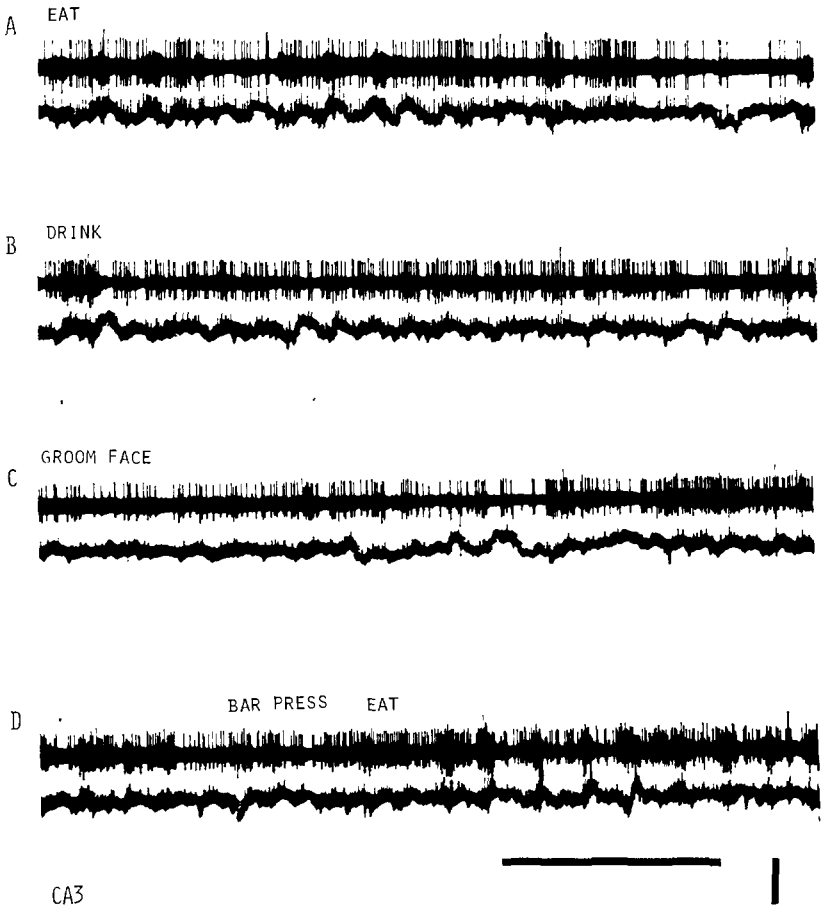


FIG. 6. The same cell as Fig. 5. Firing during eating, drinking, and grooming is all about the same. In A and D an eating artifact, due to the EMG from jaw muscles is present. No relation was apparent between this jaw EMG and the neuronal firing. Voltage calibration top trace 550 μv, bottom trace 2.3 mv; time 1 sec.

lying still there, all walking, no matter what the presumed reason for it, changing positions while grooming, or shifting from grooming one site to another but not grooming itself. It also included turning toward objects, i.e., presumed orienting.[6] There was firing in the theta mode when the rat was almost motionless, but this was either about 1 sec before or after a movement. Usually the theta mode firing stopped if the rat stopped moving

[6] To say "the rat oriented (or turned to) the food pellet" is not behavioristic terminology, as one cannot know what was claiming the rat's attention when he turned. The statement must be an inference largely from the behavior that follows. However, in most cases the inference is so clear that the term "orienting" will be used to mean "presumed orienting."

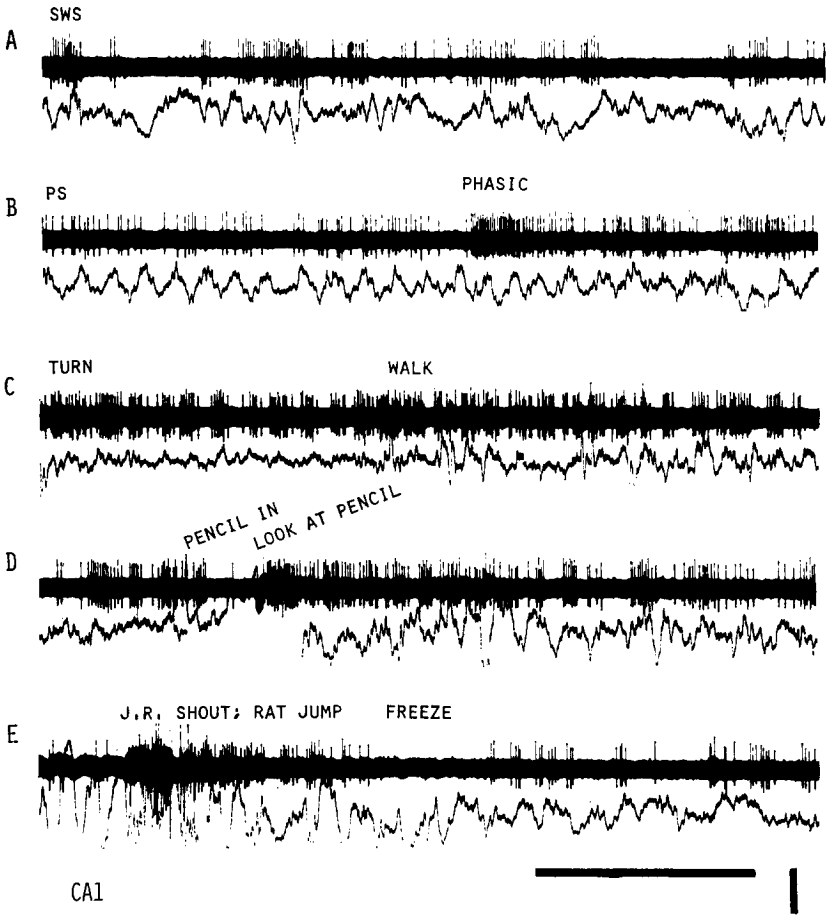


FIG. 7. A theta cell in CA1. This neuron has no obvious phase relation to the slow waves in paradoxical sleep, while the phase relation is obvious when awake. D and E show instances of the neuron stopping during freezing. There is a movement artifact in the slow waves in D for about 250 msec, and in E for about 1 sec. Voltage calibration top trace 400 μv, bottom trace 2 mv; time 1 sec.

even for a second. Sometimes there was theta mode firing when the rat made a 1-cm movement of his foot while lying quietly. A simple generalization, for which there are only a few (but nevertheless important exceptions) is that theta mode firing occurred during any movement which was not a consummatory behavior and in paradoxical sleep.

Komisarak (54) has described an almost one-to-one correlation between vibrissal twitch and a cycle of the theta rhythm. The vibrissae move too rapidly to see this rhythm by simple observation. However, there was a distinctive movement of the vibrissae whenever the rat was in an awake theta mode of behavior which was not seen in other behaviors. It was not

seen in paradoxical sleep where there was also theta mode firing. This was clearly the sniffing behavior analyzed by Welker (101). Some of the rat's sniffing was not associated with a theta rhythm—let us call this automatic sniffing. At this time the theta cells fired in the automatic mode, and the hippocampal slow waves are large amplitude irregular. The vibrissae moved more slowly than during the awake theta mode. The rat was standing still and there was no object or odor apparent toward which the sniffing was directed. His nose may have pointed up or down. This is what Welker (101) described as polypnea and nose movement without head movement or rapid vibrissal movement.

During the most "intense" or vigorous activity some theta cells fired at their most rapid rate, regularly and continuously, losing phase relations to the theta rhythm (Figs. 5 C2, and 7D). This was also seen in paradoxical sleep during some (but not all) phasic episodes (Fig. 7B). I have never seen this for more than 2 sec. Perhaps this should be considered a separate mode of firing, but I have only seen it during a theta mode. When a cell fires in the theta mode it usually maintained that firing for at least several seconds, and the mode could be maintained for many seconds.

There did not appear to be any specificity to the cell firing in a theta mode, i.e., a cell fired in the same way in approach to food, approach to water, or escape from my hand. This is further documented in another paper (29). When a rat changed from one nonautomatic behavior to another, for instance, turning away from exploring an object and going to the water bottle, the theta mode continued with no discernible change and without losing a beat of the rhythm when the behavioral change was made. Sleep and passive avoidance data are given below.

Automatic Mode. This was the slowest mode in which a theta neuron fired for periods of more than a few seconds. This automatic rate was always greater than 10/sec with the exception of two cells, one of which fired at about 0.5 sec during automatic behavior, the other at 1.5/sec. The firing was relatively irregular in this mode.

This, the most common mode of firing, occurred during all automatic behaviors except paradoxical sleep. By automatic is meant consummatory behavior such as eating, drinking, grooming, scratching, automatic sniffing (as defined above), urinating, defecating, and slow-wave sleep. The mode also included almost all motionless behavior, excluding some that are just before or just after a movement, paradoxical sleep and motionless behavior in the slow mode described in the next section. Some behaviors which are well-learned and done in a stereotyped way—for instance, bar pressing—are also included in the automatic mode (29).

The similarity in rates of firing in various consummatory behaviors is documented elsewhere (29). The similarity in rates between slow-wave sleep and other automatic behaviors is documented in the section on sleep of

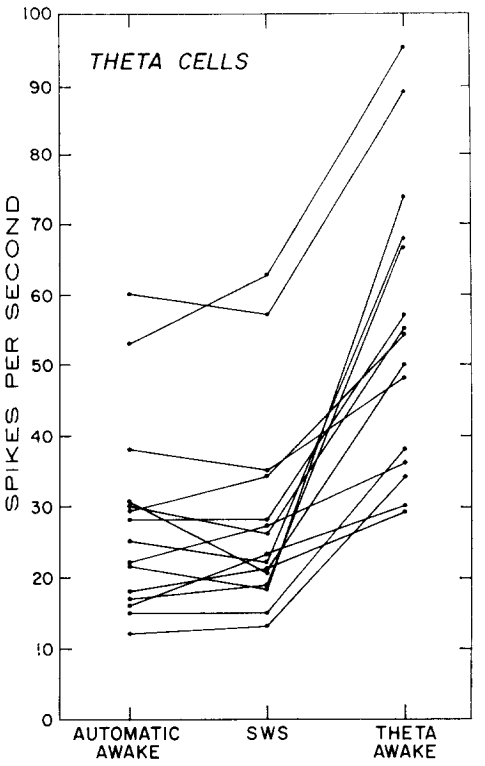


FIG. 8. Rates of firing of theta cells in three states. Rates were counted for at least 5 sec for each data point.

Results. There are some differences in firing within this mode, for instance, in Fig. 8 between slow-wave sleep (B), and standing quietly (D). This was the greatest difference seen. No major differences can be seen between firing during eating, drinking, and grooming, for instance in Fig. 6, which is more typical. By simple observation no phase relation between the firing of theta cells and slow waves in the automatic mode was noted.

Slow Mode. The slow mode is the rate of firing of the cell slowing or most commonly stopping (Fig. 7D, E). This lasted for a maximum of 4 sec. It only occurred immediately after some external stimulus while the rat stood or lay motionless. This often appeared to be "freezing." This mode was especially common when a rat was awakened by an external stimulus (it did not occur if the rat awakened spontaneously). It did not always occur in these situations. It often occurred along with the small amplitude irregular activity of the slow waves, but not always (Fig. 7D, E). The relation of the slow waves and the theta cell slow mode has not been studied systematically.

Passive Avoidance. Seven theta cells were observed during the passive

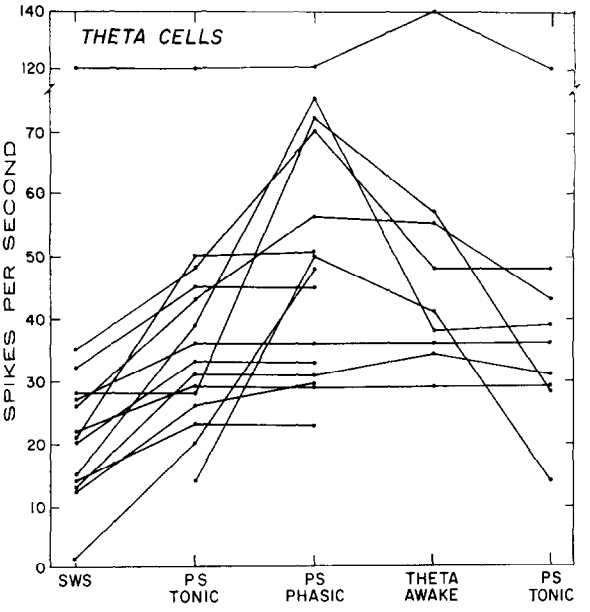


FIG. 9. Rates of firing in theta cells in four states. Note PS tonic is plotted twice to allow several comparisons. All rates were counted for at least 5 sec for each data point. The data for PS phasic were picked to show the *fastest* firing seen in these episodes.

avoidance procedure described in Methods. From simple observation at the time of testing and from simple observation of film of the cells later, no changes in the behavioral correlate or firing repertoire of these cells were seen. There was no suggestion of any special kind of firing during the 3- to 5-min observation of the passive avoidance behavior of each cell.

Sleep. The firing of theta cells in slow-wave sleep was homogenous in time, averaged over a few seconds. Figure 8 shows rates of firing in slow-wave sleep and in some automatic behaviors while the rat is awake, each averaged over at least 5 sec. Elsewhere (29) it will be shown that various automatic-awake behaviors have the same rates of firing averaged over a few seconds. The rates of firing in slow-wave sleep and automatic-awake behaviors were clearly similar. Thus the firing in slow-wave sleep is in the automatic mode. By simple observation I have not been able to find any difference in rate or pattern of the firing of a theta cell in different stages of slow-wave sleep or in slow-wave sleep and other automatic behaviors, with the exception of one cell (Fig. 8).

The firing of theta cells in paradoxical sleep often showed variations which I have not been able to relate to any other parameters. Nevertheless certain generalizations are clear: 12 out of 14 neurons (Fig. 9) fired more rapidly in tonic paradoxical sleep than in slow-wave sleep. The other two

neurons fired at the same rate in these two states. One of these neurons increased its rate in phasic paradoxical sleep; the other did not. Six out of 15 had a more rapid rate of firing in phasic than in tonic paradoxical sleep. However, this increase did not occur in all phasic episodes. The slow waves often changed their amplitude or rhythmicity (or both) in irregular ways during a phasic episode, though not always. The rate of firing in the theta mode while the rat was awake was between the rates of firing in the phasic and tonic phases of paradoxical sleep, with one exception. By simple inspection, the pattern of firing in paradoxical sleep was often identical to that in the theta mode while the rat was awake (Figs. 3, 4), but not always (Fig. 7). Three theta cells stopped firing in paradoxical sleep without relation to anything I could see. Two cells stopped once each for 1 sec and the other stopped once for 15 sec. In these cells the cessation of firing did not occur during other episodes of paradoxical sleep.[7] There were other changes in rate and pattern during paradoxical sleep not related to anything I could see.

If one knows the range of firing over which a given theta cell fires, from the results reported here and in another paper (29) one can predict most of the firing of a theta cell. Predictions are relatively weaker for paradoxical sleep, the slow mode, "well learned" behavior (29), and for the details of firing over times less than about a second.

C. Behavioral Correlates of Complex Spike Cells of Dorsal Ammon's Horn and Dorsal Fascia Dentata

In contrast with the theta cells, each complex spike cell had a behavioral correlate which clearly differed from that of any other cell. Consequently there was no simple relation between the existence of a slow-wave pattern and the firing of a complex spike cell. The behavioral correlates of neurons are different in various parts of dorsal Ammon's horn and dorsal fascia dentata, but each kind of behavioral correlate was seen in more than one part. Therefore, I shall first describe the different behavioral correlates seen, and then describe each of the separate regions.

Motionless Behaviors: Quiet Wakefulness, Slow-Wave Sleep, Paradoxical Sleep. Slow-wave sleep and many other motionless behaviors were part of an unusual behavioral correlate of complex spike cells. Consider the spectrum of motionless behaviors which includes standing quietly awake, sitting or lying quietly awake, drowsiness, light slow-wave sleep, and deep slow-wave sleep. In the rat this spectrum of behaviors includes almost all motionless behaviors which last more than a few seconds, except for paradoxical sleep and freezing. Let us call this spectrum of behaviors "the motionless-

[7] These single episodes in three cells, and the two cells which fired at the same rate in slow-wave sleep and tonic paradoxical sleep were the only exceptions to the relation of increased firing if and only if a theta rhythm was present.

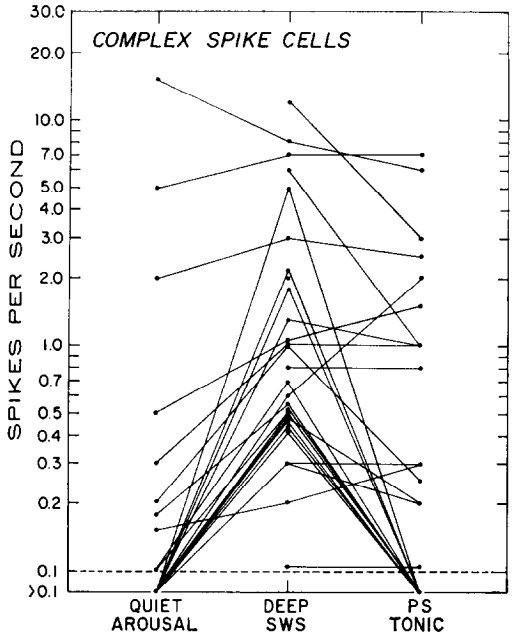


FIG. 10. Rates of firing of complex spike cells in three states. Note the log plot of firing rate.

slow-wave sleep mode." If the neocortical EEG is known, then one can speak of the "depth" of the state of consciousness of the rat within this mode. For each complex spike cell there was a threshold depth. If the state of consciousness of the rat was deeper than this threshold the cell fired more rapidly than once a second, and it fired at the same frequency and pattern at all greater depths. If the state of consciousness of the rat was lighter than this threshold the cell fired less than once every few seconds. The depth of this threshold in this motionless-slow-wave sleep mode varied between cells. Some neurons fired whenever the rat was standing quietly awake and at all deeper stages. Other neurons fired only in the deepest stages of slow-wave sleep. All intermediate stages were seen. However, this threshold depth (i.e., at which the mode becomes a behavioral correlate for the neuron) was constant for a given neuron, and was the same whether the rat was progressively going deeper into the mode or was getting lighter in the mode. Of the cells which were seen at all depths of the mode, only two did not fire in this mode no matter how deep the rat was in this mode.

If a complex spike cell was firing while the rat was in this motionless-slow-wave sleep mode, the cell stopped firing in response to a sensory stimulus if the stimulus caused the rat to go into some lighter stage of the mode at which the cell normally did not fire. This could occur with no overt

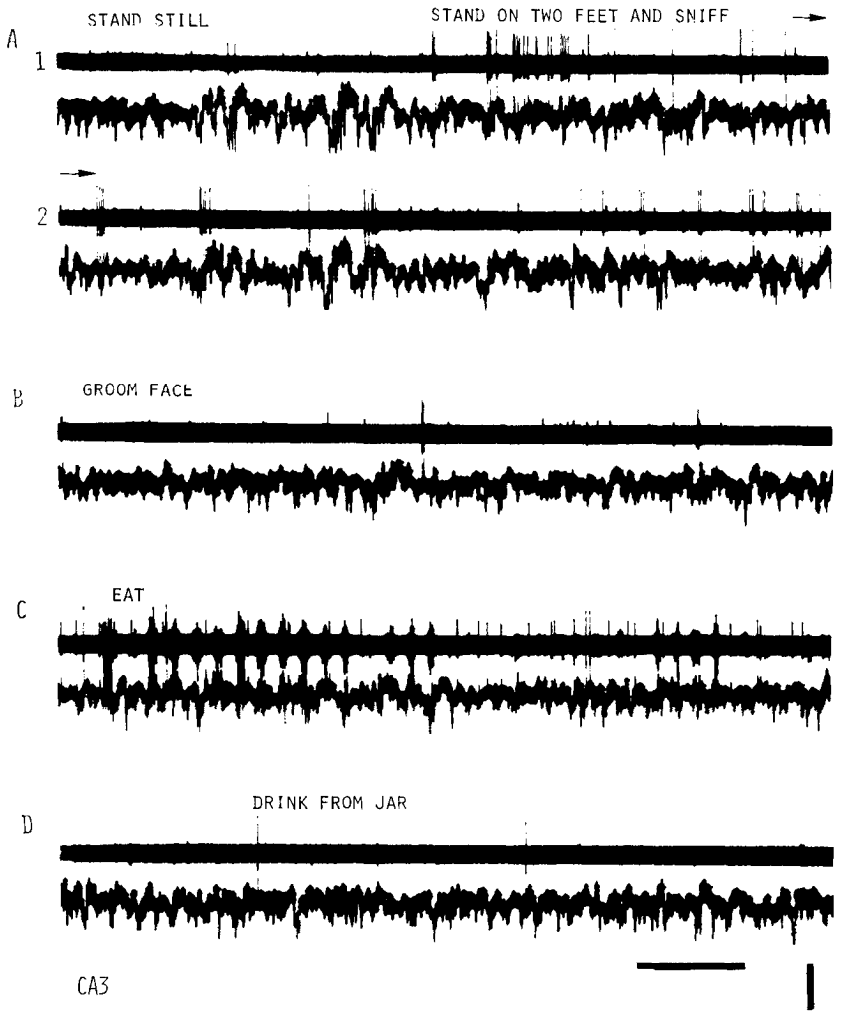


FIG. 11. Complex spike cell from the most posterior part of CA3. Approach-consummate cell. This neuron was completely off most of the time. It fired most rapidly and most commonly in automatic sniffing, with his nose pointed straight ahead with no object of sniffing that I could determine. It usually did not fire during exploratory (theta mode) sniffing. There is some firing during grooming, eating, and drinking, but less than during automatic sniffing. In C there is another smaller cell firing more rapidly and jaw EMG artifact. In the 50 min this cell was observed there were only a few complex action potentials. This cell was one of three complex spike cells with durations of extracellular negativity of less than 0.3 msec (distorted). Voltage calibration top trace 830 μv, bottom trace 4 mv; time 1 sec.

behavior, and the change of depth of the motionless-slow-wave sleep mode was only apparent from changes in the neocortical slow waves. Of course the neuron also stopped firing if the rat woke up, moved, and did not do

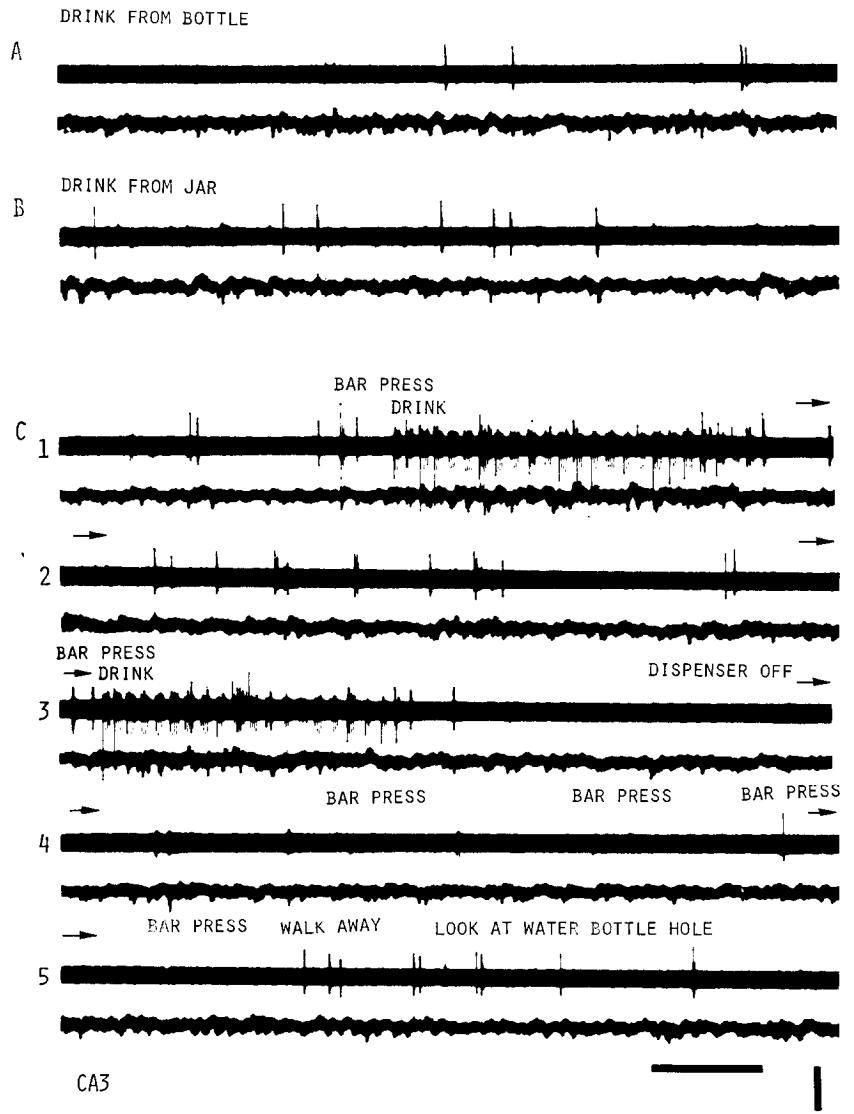


FIG. 12. Complex spike cell in CA3. Approach-consummate cell. This neuron was completely off for 10–30 sec at a time most of the time while awake. It fired mostly during drinking, whether from the water spout of a bottle (A), a jar (B), the water dipper activated by a bar press (C), or licking up water from the floor (not shown). While not apparent from the figure, drinking from a jar was associated with a slower rate than other modes of drinking, and often with drinking from a jar the cell did not fire until he had been drinking for 10 sec. In other drinking the firing started when the drinking started. In C1 and C3 there is an artifact whenever the rat's tongue touches the dipper. This cell also fired when picked up in my hand, during grooming, eating, and some sniffing, but at slower rates than during drinking. Voltage calibration top trace 620 μv, bottom trace 9 mv; time 1 sec.

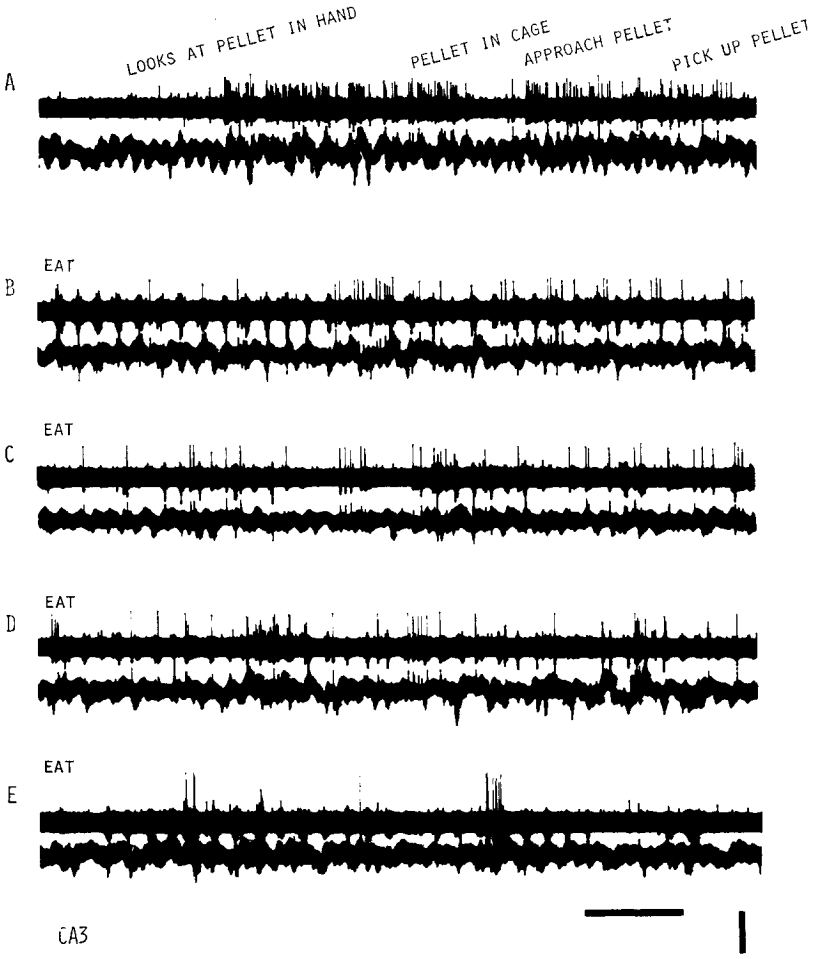


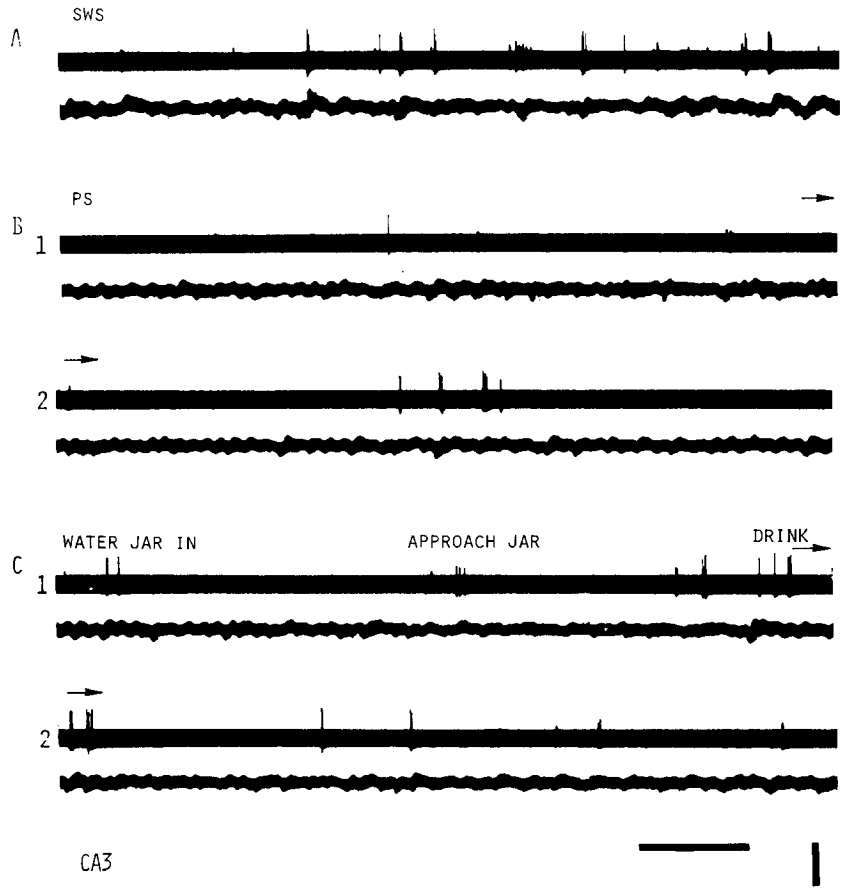
FIG. 13. Complex spike cell in CA3. Approach-consummate cell. The eating of records B–E occurred in sequence. At B the rat had already eaten 4½ pellets (normal ad lib. daily intake 6–7 pellets). C is 9 min later, it has eaten 5½ pellets. E is 56 min after B; it has eaten 5¾. A pellet has been in the cage for 30 min and the rat has not eaten until this time. Jaw EMG artifact is present in B–E. The amplitude of the spike is distinctly larger in E than in any other records. It had increased gradually in the time from D. The firing during the well-learned appetitive behavior for food is unusually rapid for an approach-consummate cell. It is also unusual for it to be so much faster than during the associated consummatory behavior. This cell also fired, but at slower rates, during drinking, automatic sniffing, and lying quietly awake. Smaller action potentials from other cells are also present. Voltage calibration top trace 630 μv, bottom trace 2 mv; time 1 sec.

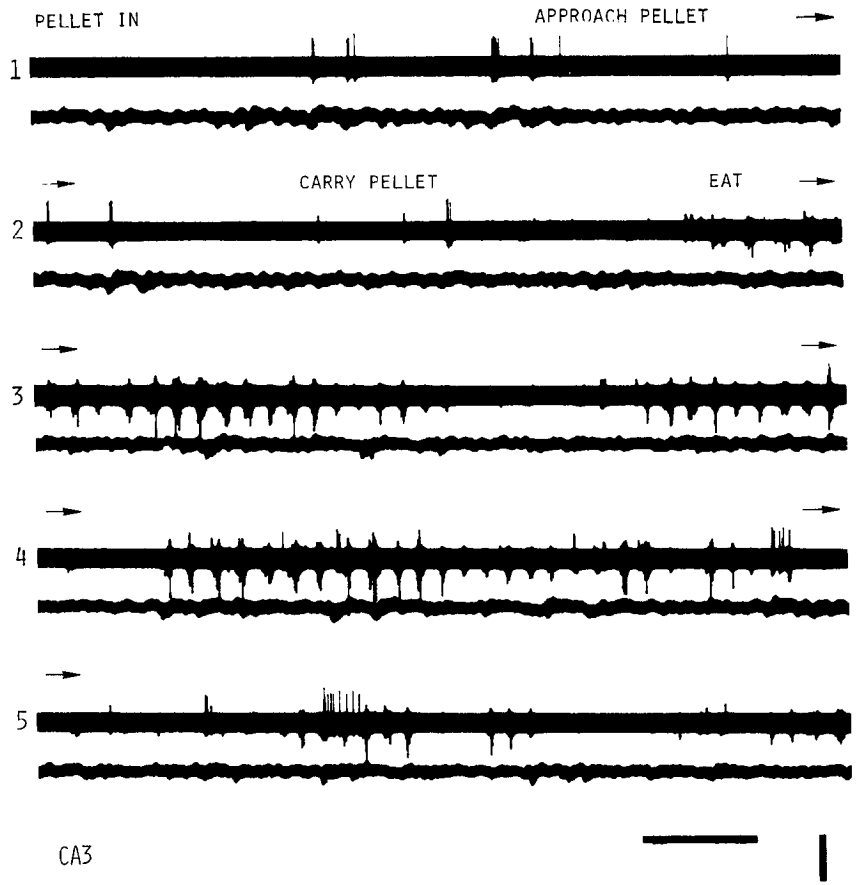
something which was part of other behavioral correlates of the neuron. When a rat changed his posture, even a few millimeters, during slow-wave sleep, there was a low voltage fast neocortical EEG for a few seconds even

if the rat did not open his eyes. A complex spike cell which was firing in slow-wave sleep would stop firing if it normally was off during this lighter stage of the motionless-slow-wave sleep mode. Figure 10 is a conventional plot of the relation of rate of firing and state of consciousness, which quantitatively documents a few aspects of the more general description. Only those neurons for which there is complete data are plotted. Many other complex spike neurons were observed and showed the same general pattern.

In some cells the only behavioral correlate noted was with this motionless-slow-wave sleep mode. Let us call these *simple motionless cells.* Whenever a cell had other behavior correlates the cell was classified on the basis of these other behavioral correlates. Since all but two complex spike cells seen in slow-wave sleep were firing, almost all complex spike cells had a behavioral correlate of some part of this motionless-slow-wave sleep mode.

The firing of complex spike cells in the motionless-slow-wave sleep mode was homogeneous in time in the sense that there was little difference in





FIGS. 14 and 15. These are the same cell. Complex spike cell in CA3. Approach-consummate cell. This cell had been completely off for 30 sec before the recording in paradoxical sleep. There is a phasic episode starting just after the action potential in B1 and ending just before the action potential in B2. This cell fired most during approach to food or water, but the firing seemed to be related to sniffing. (This is theta mode sniffing.) It also often fired during other exploratory (theta mode) sniffing, especially if he licked and sniffed at the floor. Whether this is related to food and water I could, of course, not determine. It did not fire when the rat was clearly attempting to get food or water unsuccessfully. No spatial correlate was noted. It did not fire during most exploratory sniffing. It also fired during eating and drinking, often not until the eating or drinking had been in progress for 5–10 sec, as in 15-2 and 3 where the firing starts after eating eight sec. EMG jaw artifact is present in eating. This cell also fired during some grooming. Smaller action potentials from other cells are also present. Voltage calibration top trace 570 μv, bottom trace 5 mv; time 1 sec.

firing in different periods averaged over a few seconds. This homogeneity in time was also true of the firing of theta cells when the rat was in the motionless-slow-wave sleep mode. Theta cells differ from complex spike

cells in that all theta cells fire in the automatic mode when the rat is at any depth of the motionless-slow-wave sleep mode. Just as for theta cells, most complex spike cells did not fire homogeneously in time during paradoxical sleep, and there were many changes in firing which were not correlated with any other observations. Numerical data are plotted in Fig. 10. Eleven out of 25 complex spike cells were completely off for 10–30 sec at a time during paradoxical sleep, and when firing occurred it was often a group of action potentials for a few seconds, followed by complete silence (Fig. 14B). This firing was sometimes, but not always, associated with phasic episodes. The firing often showed a phase relation to the theta rhythm in the slow waves. Only three complex spike neurons fired more rapidly in tonic paradoxical sleep than in slow-wave sleep.

The firing repertoire and behavioral correlate of a complex spike cell in these various motionless behaviors are not only descriptive but also predictive of much of the behavior of the cell in these behaviors. Predictions are not as good in paradoxical sleep as in other motionless behaviors. No relation has been noted between firing in these motionless behaviors and the different behavioral types or between the different regions studied.

Behavioral Types of Complex Spike Cells. In motionless behavior it is possible to record from a cell in a single behavior for many seconds so that very slow rates of firing can be described. Many awake behaviors cannot be observed continuously for nearly as long. Therefore, in the description of firing of complex spike cells while the rat is awake a cell firing less frequently than once every 5 sec was described as off. Particular attention was paid to the most rapid firing, and behavior associated with all firing at rates greater than 2/sec was described. Behavior associated with rates of firing between 0.2/sec and 2/sec was described less reliably.

(a). Approach-consummate cells (Figs. 11–15). Approach-consummate cells never fired in nonmotionless behaviors at more than 2/sec except during certain consummatory behavior and during some appetitive behaviors associated with the consummatory behavior. Such a cell did not fire during the appetitive behavior unless it was being performed rapidly, smoothly, successfully, and without hesitation, in a familiar situation. The appetitive behavior in the behavioral correlate of these cells was almost always followed by consummatory behavior, i.e., it was successful. If the cell fired during an appetitive behavior it would always fire during the associated consummatory behavior when it occurred.[8]

Many cells fired during more than one kind of performance, for instance, the cell of Fig. 11 fired in slow-wave sleep, automatic sniffing (as defined

[8] There was one exceptional cell. Most of its behavioral correlates met the defining characteristics of this behavioral type and it was specific for food, automatic sniffing, and grooming. However, it also fired during some unrelated orienting and approach behaviors without firing during the associated consummatory behavior.

under B. of results above), grooming, eating, and drinking, but each at a different rate. Because of this multiple specificity, particular care was taken that only one neuron was being described.

The rate of firing during the appetitive behavior was about the same as during the associated consummatory behavior. Some approach-consummate cells did not start to fire until the consummatory behavior had been in progress for some time (Fig. 15). For eating and drinking this delay could be up to 10 sec. All gradations were seen between a cell firing at the beginning of appetitive behavior, to one whose firing was delayed after the beginning of the consummatory behavior, but a given cell maintained the same relation. All cells continued firing throughout the consummatory act without change.

Rats were given water from water bottles, in a water jar, and in a dipper which could be operated by a bar. They also licked water from the floor. Most cells which fired during the rat's drinking fired during all four modes of drinking (Fig. 10), but some fired at distinctly different rates in these different modes. No difference was noticed in the firing of "eating" cells, whether the rat ate a 1–2 g pellet or a 45-mg pellet.

In eating, jaw EMG artifacts appear on all records. In drinking, there are sometimes jaw EMG artifacts and sometimes there is an artifact associated with the tongue touching the spout of the bottle (Figs. 11–13, 15). All records have been examined for any relation between the details of motion and neuron firing. No relations were seen. Furthermore, no relation between neuron firing and details of movement were seen while the rat was being watched. An "eating" cell did not fire when the rat munched without food in his mouth. While none of these observations are compelling, they make it seem unlikely that motor details are the basis of the neuronal firing.

Another possible basis of the firing is some afferent aspect of the behavior. The observations in the paragraph above are relevant and give no evidence for sensory input as a cue. Four "eating" cells were observed while the rat ate a pellet and while he ate a cookie. Although there were differences in taste, texture, and effort of chewing, no difference in firing was noted. By visual observation an attempt was made to see if there was any correlation between firing and sniffing rate or respiratory rate. None was seen, but in view of the irregularity of firing, this is a very weak test. Thus, while there is no evidence to implicate specific sensory inputs as the basis of firing, it is a real possibility which must be considered.

Another possibility is that these cells fire when the rat is attending to a certain kind of thing. This was tested by distracting the rat during the consummatory behavior which was a behavioral correlate of the cell, by the experimenter putting his hand into the experimental box, or snapping his fingers, or touching the rat, or pulling the rat's tail. If the consummatory behavior stopped and the rat was presumably attending to the experi-

menter's hand, the firing of the neuron would sometimes, but not always, stop. The firing was especially likely to continue if the rat stayed in the same location as he changed his focus of attention. I could not clearly define how those cases in which firing continued during distraction differed from those in which it did not. In addition, these cells did not fire during unsuccessful behavior. Therefore, attention does not seem to explain the firing in a simple way.

Another possible basis of firing in these neurons is specific reinforcement, specific drive reduction, etc., i.e., some motivational factor. All rats were run at similar deprivation states for food, water, and sleep and a single neuron usually was not followed over large changes in deprivation. Four "eating" cells were recorded from while the rat ate a third or more of his daily intake (Fig. 13) and three drinking cells were recorded from while the rat drank half or more of his daily intake. In all cases the behavioral correlate of the cell remained the same. In Fig. 13 there does seem to be a change in rate of firing while the deprivation state was changed, but not definitely so. Thus, specific reinforcement or drive reduction, etc., is a possible basis of the firing of these neurons. At least over mild changes in deprivation the behavioral correlate does not change.

Thus, at this stage of investigation we do not know exactly what is signaled by these cells or exactly the nature of a cell's "specificity." Nevertheless, let us speak of the specificity generally as food, water, grooming, etc., without implying exactly what its basis is. Of the 54 approach-consummate cells seen after the behavioral types had been defined, in 31 (57%), only one specificity was noted. The classification to be described on p. 000 can predict almost all the firing averaged over 2 sec of an approach-consummate cell when the rat is awake.

(b). Approach-consummate-mismatch cells (Figs. 16–18). Some cells which had all the characteristics of approach-consummate cells also fired, and often most rapidly, during unsuccessful behavior which had the same specificity as the approach-consummate behavioral correlate of the cell. An example of this was a "drinking cell" which also fired when the rat sniffed at the empty hole where the waterspout was put. This cell also fired if the rat simply stood near the empty water hole, if he licked the floor under the water hole, if he went to the site where the water jar was usually put, if he went to the dipper, or stood near the dipper, if he licked the floor near the dipper, and during extinction of bar-pressing for water. This cell fired at its fastest rate (faster than during drinking) during the more intense sniffing at the water hole. In general the more vigorous the appetitive behavior, the more rapid the firing. Of course, this cell always fired during successful approach to water, and during drinking. Of 27 approach-consummate-mismatch cells seen after the behavioral types had been defined, in 20 (74%), only one specifity was noted.

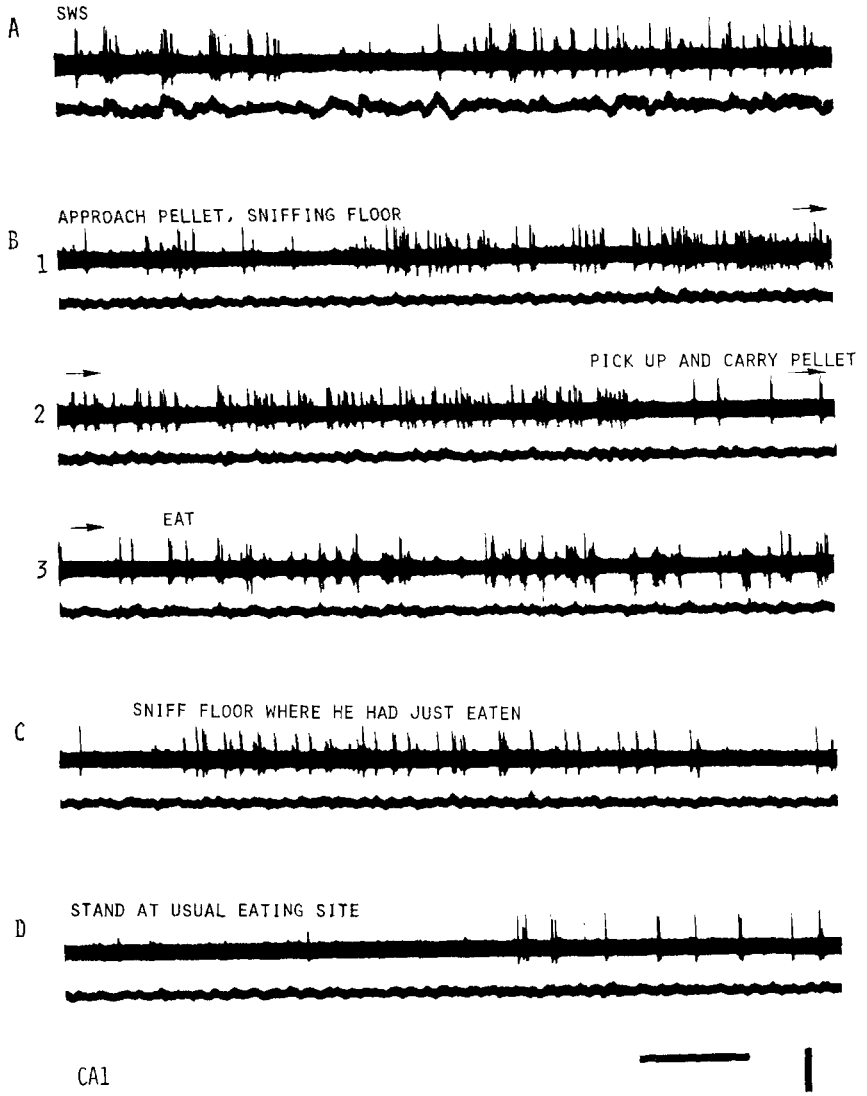


FIG. 16. Complex spike cell in CA1. Approach-consummate-mismatch cell. This neuron was specific for food, firing during eating (B3), and appetitive behavior associated with eating (B1, B2, C) with the most rapid firing during some unrewarded appetitive behavior. It also fired just standing where the rat usually ate (D). The firing rate is less during eating than the appetitive behaviors. It was completely off during avoidance and escape as tested by picking the rat up in my hand and blowing on it. Most of the time awake this cell fired about one burst every 3 sec. During paradoxical sleep this cell fired at about the same rate as in slow wave sleep. Notice in B1, B2, and C the rhythmicity of firing is often at the 8/sec of the accompanying slow-wave theta and in phase. This was also true in paradoxical sleep. Smaller action potentials from other cells are also present. Voltage calibration top trace 440 μv, bottom trace 4.5 mv; time 1 sec.

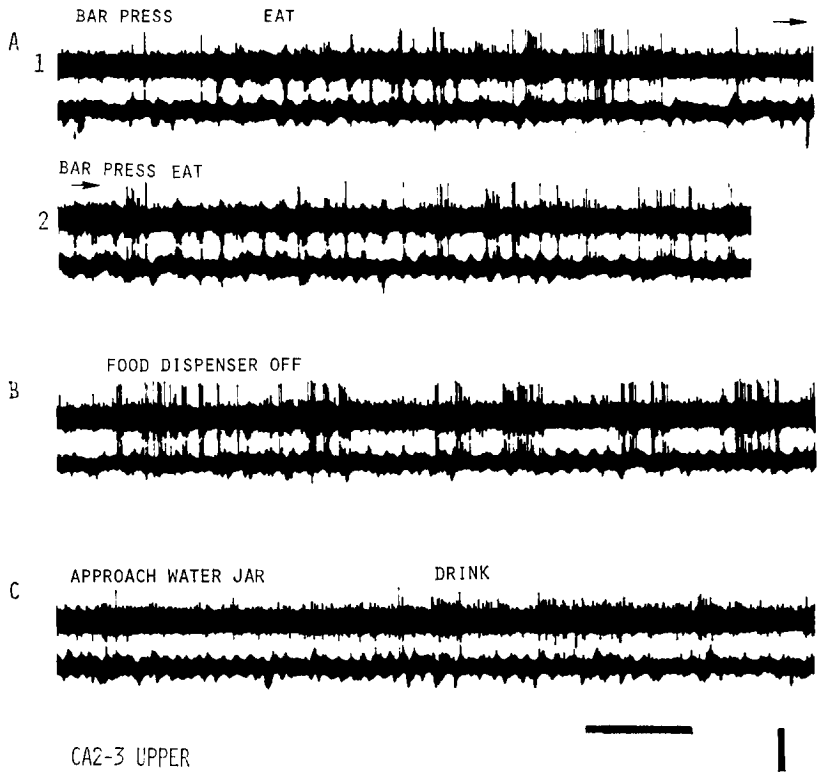


FIG. 17. Complex spike cell in CA3 upper. Approach-consummate–mismatch cell. This cell was completely off most of the time (C). It was specific for food—eating (A) and appetitive behavior associated with eating with the most rapid firing during some unsuccessful appetitive behavior. In B the rat is poking his nose into the pellet dispenser. This cell was recorded from while it ate, after after having eaten 3.5 pellets that day (normal daily ad lib. intake 6–7 pellets) until it ate to satiety with no change in firing.

In B notice a relation of firing to the negative phase of the slow wave theta, which was true in general in this cell. (It was, of course, off during most slow wave theta.) Small action potentials from other cells are also present. Voltage calibration top trace 550 μv, bottom trace 2.3 mv; time 1 sec.

An "eating" cell (Fig. 16) with a mismatch behavioral correlate showed similar behavior, firing after the rat finished eating a pellet and was sniffing and licking at the eating site. Each rat usually carried a pellet to the same site and ate it there. Whenever the rat was near this site the cell fired, especially if he faced that direction. This cell also fired when the rat was near the pellet dispenser. During extinction of bar-pressing for pellets another cell (Fig. 17) fired when the rat searched in the dispenser, but not while he pressed the bar. These cells also fired during the rat's successful approach to food and eating.

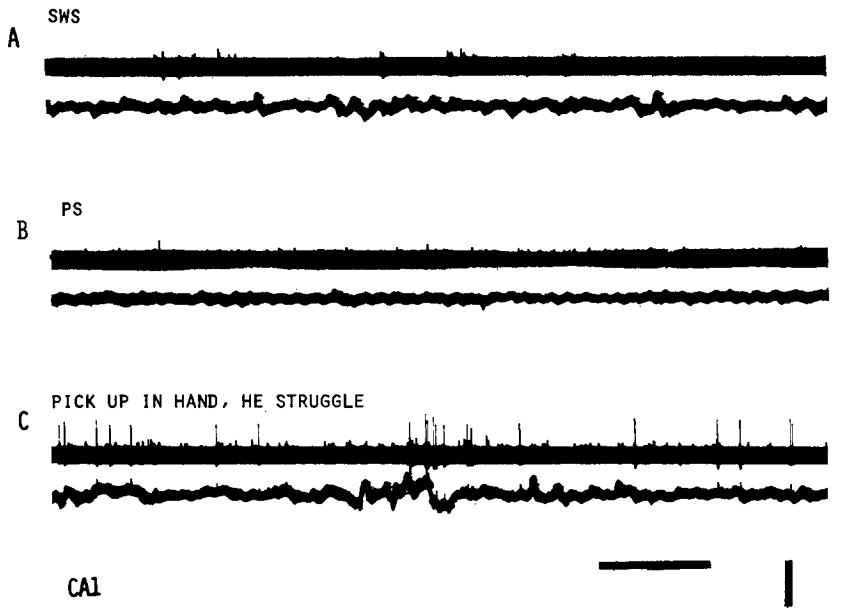


FIG. 18. Complex spike cell in CA1. Approach-consummate–mismatch cell. This was the most specific seen. It was off in slow-wave sleep and paradoxical sleep and all waking. Absolutely no firing for 15 min. It only fired when I picked the rat up in my hand and it was struggling to escape, and for about 2 sec as it escaped. It did not fire if just held in my hand and it did not struggle. If the rat was touched or blown on while it was standing and it escaped the cell did not fire. If the rat was touched while it was eating or drinking (in an attempt to approximate the emotional state of being picked up in a hand), the cell did not fire. The rat was picked up about 20 times over 3 hr and 45 min without change. If a rat is picked up and held in a hand repeatedly it will struggle less and not start to struggle until held for a longer and longer time. Consequently the firing of the cell had a longer and longer latency when picked up. This was not habituation of the cell, because the relation to struggling remained constant. Smaller action potentials from other cells are also present. Voltage calibration top trace 625 μv, bottom trace 4.5 mv; time 1 sec.

With five exceptions, if the cell fired during appetitive behavior, it always fired during an associated consummatory behavior. Four neurons fired when the rat was held in the experimenter's hand and the rat struggled unsuccessfully to escape (Fig. 18). One neuron fired whenever the rat was in a particular location in the running box. An associated consummatory behavior during which the neuron fired could not be discovered in these five cells, but they were classified as approach-consummate–mismatch cells nevertheless, because of the unsuccessful or the spatial aspects of their behavioral correlates.[9]

[9] The use of the term "appetitive behavior" in these four "unsuccessful struggling" cells might be objected to. The term will be used nevertheless, but the objection acknowledged.

Six cells which had approach-consummate–mismatch behavioral correlates for one specificity had approach-consummate behavioral correlates for other specificities. They all fired most rapidly in the mismatch situation and were classified as approach-consummate–mismatch cells. With the classification to be described on p. 000, almost all the firing averaged over 2 sec of an approach-consummate–mismatch cell could be predicted when the rat was awake.

There was no difficulty in distinguishing mismatch (unsuccessful) appetitive behavior from successful appetitive behavior. Figure 12 shows the most borderline case. Approach-consummate–mismatch cells are not cells which fire simply during all behavior relative to a particular consummatory behavior or motive or incentive (even though such a description would describe a lot of the behavioral correlate) for the most rapid firing occurs during unsuccessful behavior, and there are strong spatial aspects to these cells. An "eating cell" of this type fired if the rat was lying near where he usually ate even if no appetitive behavior was manifested. Approach-consummate–mismatch cells were tested for specificity to attention by distraction as described for the approach-consummate cells with similar results. Here too while attention can describe much, it can not explain all of the firing of these cells, at least in a simple way.

Dostrovsky (24) and O'Keefe and Dostrovsky (70) have described single neurons CA1 with a spatial behavior correlate. These cells are almost surely the same as the approach-consummate–mismatch cells. Dostrovsky and O'Keefe found some goal-specific aspects to some of their spatial cells. I had finished our experimental work before I became aware of their findings, and did not consider spatial orientation as the primary determinant of firing when examining these cells. Spatial characteristics were not systematically looked for and were only described when obvious. Perhaps spatial characteristics are the entire basis of firing in these cells. The evidence at present does not allow us to decide.

The approach-consummate behavioral correlate of specific performance can be stated simply in entirely behavioristic terms—what the rat is overtly doing. Whatever the basis of this mismatch aspect, it seems to involve *why* the rat is behaving the way he is behaving. Thus, some may be tempted to use a nonbehavioristic description. For instance something like attention, expectation, error evaluation, and frustration might be the important factor. However, before trying to make inferences of this sort the behavioristic descriptive base should be sounder than it is at present.

(c). Appetitive cells (Fig. 19). An appetitive cell is defined as a cell which never fired during a consummatory behavior except for sleep, and fired during some orienting or approach behaviors. These cells fired only during orienting, approach, escape, avoidance, or motionless behaviors. A cell of this behavioral type fired during less than 10% of all orienting or ap-

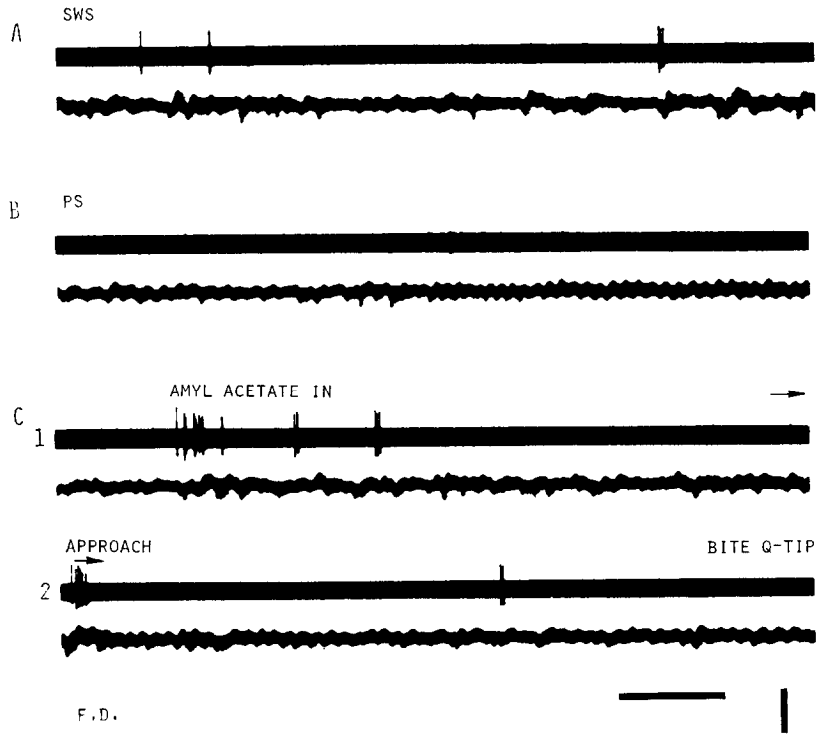


FIG. 19. A complex spike cell in upper limb of dorsal fascia dentata. Appetitive cell. This cell was completely off most of the time while awake. This cell only fired in slow-wave sleep and during sniffing during some orient-approach behavior. It was completely off during all consummatory behaviors other than slow-wave sleep. There were many times when the rat sniffed during orient-approach behavior during which the cell did not fire. I could find no more specific aspect of behavior for when the cell fired except it was more likely to fire if the rat was in the right front corner of the box, or sniffing food, or sniffing some novel objects, or sniffing strong odors, but there were exceptions and it fired in other orient-approach sniffing too. During passive avoidance it was off all the time but fired once with an abortive approach movement toward the water spout and once when the rat turned away from the water spout. It was off during escape from being picked up in my hand, touched, or blown upon. Off during startle. Voltage calibration top trace 570 μv, bottom trace mv; time 1 sec.

proach behaviors. Of the 38 appetitive cells seen after the behavioral types had been defined, a specificity for those orienting and approach behaviors correlated with cell firing could be found in only 16 (42%). Even those for which there does seem to be specificity the relation was weak, i.e., the cell usually fired with approach or orienting to food, but not always, and it fired during some approach and orienting which was not apparently food-related. The appetitive behavioral correlate of approach-consummate cells is a subset of the appetitive behavioral correlate of appetitive cells. In the former case the appetitive behavior is almost always followed by consummatory behav-

TABLE 2

DEFINING CHARACTERISTICS OF THE THREE MAJOR BEHAVIOR TYPES OF COMPLEX SPIKE CELLS[a]

	Consummatory A	Successful appetitive A	Unsuccessful appetitive A	Spatial A	Consummatory B	Any appetitive B
Approach-consummate	+	+ 0	0		May repeat pattern for other specificities	
Approach-consummate-mismatch	+	+	++	+ 0	May repeat pattern for other specificities	
	0	0	+	+ 0		
	0	0	0	+		
Appetitive	0	+ 0	+ 0		May repeat pattern for other specificities	
Combinations never seen	+	0	0	0	0	+
	+	0	+			
	++	+	+			
	+	++	+			
	0	0	0	+	+	+

[a] Although sleep is a consummatory behavior, it is *not* involved in the definition of these behavioral types. (0) indicates a firing rate of less than once every 2 sec; + indicates a firing rate of greater than once every 2 sec; ++ indicates the most rapid rate of firing for that cell (usually about 10/sec). Where two symbols are in the same box, either may be the case. Firing correlates of spatial characteristics is not indicated in all cases, as it was not systematically looked for.

ior. The latter case includes all of the former plus much appetitive behavior not followed by consummatory behavior. Many of these cells sometimes fired when the rat walked across the cage or turned his head toward no apparent object or for no apparent reason. The behavioral correlates of appetitive cells are clearly not as well characterized as the behavioral correlates of the behavioral types above. The description of the behavioral correlate of many

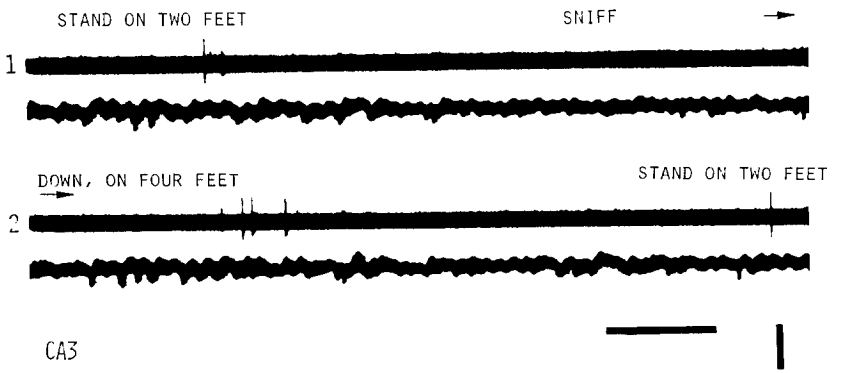


FIG. 20. Complex spike cell in CA3, lower. Motion punctuate cell. Completely off almost all the time. As the rat completed its movement of standing on two feet the cell fired, as it completed the movement of coming down the cell fired again. This cell only fired at the end of an orienting movement, not other movements. It often seemed that when the cell fired at the end of the movement the rat would then start another kind of behavior. However, that is not true for the firing shown in this figure. Voltage calibration top trace 440 μv, bottom trace 2.5 mv; time 1 sec.

appetitive cells is not as good in predicting the firing of the cell as is the case for the behavioral types described above.

Table 2 summarizes the defining characteristics of these three major behavioral types. The only aspect in which there might be any ambiguity is in the distinction between successful and unsuccessful appetitive behavior. In real cases this is always clear. Therefore, these types can be unambiguously distinguished. The fact that certain combinations of behavioral correlates were never seen in any cells is notable.

(d). Motion punctuation firing and motion punctuation cells (Fig. 20). Some neurons fired a few action potentials for about 100 msec at the end of movements which were apparently orienting or approach movements. Another movement often followed immediately. Such a cell fired at the end of only a few movements (less than 10%). However, in a given cell, I was not able to find any characteristic that distinguished those movements associated with firing from the other movements. This description is thus not very good at predicting firing. Many cells which have motion punctuation firing have other behavioral correlates also, and are classified on the basis of these other correlates. There are some pure motion punctuate cells, which fire rarely.

(e) Consummatory cells. Some cells fired during any awake consummatory behavior, fired at the same rate in all these consummatory behaviors, did not fire during appetitive behavior, and showed no sign of any specificity —they were anti-theta cells. They were put in a separate class, rather than included as very general approach-consummate cells, because intermediate stages were not seen.

(f). Instrumental cells. There were some complex spike cells which fired during any instrumental behavior. The behavioral correlate of these cells was similar to that of theta cells, but they were not theta cells by electrophysiological characteristics. I did not find any specificity to these cells. All but one of these cells was found in the early stages of the study, suggesting that this type may be an artifact.

(g). Constant firing cells. Thirteen cells were seen which did not change their rate of firing during observation. This may reflect insensitivity on the part of the observer, or damage to the cell, or both. All these neurons fired at rates of at least 20/sec and with little variation in interspike interval.

(h). Simple motionless cells. Simple motionless cells are defined above (p. 490).

(i). Other cells. After the behavioral types had been identified, six neurons were seen which could not be charatcerized in these terms, or for which no behavioral correlate could be found.

Some Other Behavioral Correlates. Only nine cells fired during active avoidance and escape of the rat as tested by items n, o, and p of the protocol. Any cell which fired during escape of the rat fired during avoidance.[10] Seven of these cells were in fascia dentata. One was an approach-consummate cell, two were approach-consummate–mismatch cells, and four were appetitive cells. The two unsuccessful-struggle-escape cells were in CA1.

Six complex spike cells—three approach-consummate, two appetitive, and one motion punctuate—were observed while the rat was passively avoiding a water spout. In all six cases the cell had the same behavioral correlates and repertoire of firing as it did when the rat was not in passive avoidance. Two of the approach-consummate cells were grooming cells, which fired during grooming, one of the most common behaviors seen during passive avoidance, in the same way as it fired when not passively avoiding. An approach-consummate "drinking" cell with little appetitive behavior in its behavioral correlate was completely off. During this passive avoidance procedure these rats made many one-to-three step approaches to the waterspout, then stopped, often turning away. The motion punctuate cell fired at the end of many of these abortive approaches, and the appetitive cells fired in a few approaches, one firing some of the time when the rat turned away from the direction of the waterspout. All of these cells were off most of the time during passive avoidance with no suggestion of firing specific to passive avoidance. The observation of each of these cells during passive avoidance was only for 3–5 min.

Classification of Complex Spike Cells in Awake Rats. Each neuron was classified by (a) behavioral type and (b) specificities (where applicable,

[10] Two of the four cells which fired while the rat struggled unsuccessfully to get out of the experimenter's hand, mentioned under approach-consummate–mismatch cells, did *not* fire during successful escape, and are not included in these nine cells.

NUMBER OF CELLS OF DIFFERENT TYPES ENCOUNTERED IN FOUR REGIONS

	Anterior CA 1				Dorsal CA3 lower				Dorsal f.d.				Dorsal CA2–3 upper	
	All cells	Late[a] cells	% Late	% late C.S.	All cells	Late cells	% Late	% late C.S.	All cells	Late cells	% Late	% late C.S.	All cells	Late cells
Theta	37	20	31		27	25	27		19	10	26		6	3
Approach-consummate (AC)	16	10	15	22	40	35	38	53*	7	7	18	25	7	2
Approach-consummate–mismatch (ACM)	29	19	29	42*	3	3	3	5	2	2	5	7	3	3
Appetitive (A)	6	6	9	13	18	17	19	26	15	13	34	46*	4	2
Motion punctuate	10	3	5	7	1	1	1	2	5	2	5	7	2	2
Simple motionless	2	2	3	4	6	6	7	9	0	0	0	0	1	1
Constant firing	6	3	5	7	4	1	1	2	2	2	5	7	2	0
Consummatory	1	1	2	2	0	0	0	0	2	2	5	7	0	0
Instrumental	5	0	0	0	2	1	1	2	0	0	0	0	1	0
Other	9	1	2	2	4	2	2	3	3	0	0	0	3	1
Total	121	65			105	91			55	38			29	14
Motionless-awake correlate		3	4	7*		21	23	32		6	16	21		2
Motion punctuate correlate		5	8	11		4	4	6		2	5	7		3
			% of AC, ACM, A				% of AC, ACM, A				% of AC, ACM, A			
Single specificity (of AC, ACM, A cells)		23	64			29	53			9	39			4
Multiple specificity (of AC, ACM, A cells)		13	36			26	47			14	61			3

[a] A late cell is one studied in the second stage of the experiment.

listed in order of rate of firing). These specificities were: any food, food from pellet dispenser only, any water, water from bottle only, water from jar only, water from dipper only, any grooming, grooming scrotum, grooming leg, automatic sniffing, licking floor, behavior related to experimenter's hand, spatial specificity only. (c) The existence of motionless awake or motion punctuate behavioral correlates. Using this classification, 34 different subclasses of approach-consummate cells were seen (out of 55 cells); 14 different subclasses of approach-consummate–mismatch cells were seen (out of 27 cells); and 10 different subclasses of appetitive cells were seen (out of 39 cells). Within a subclass, there were always other differences between cells which were not distinguished by this classification.

D. The Distribution of Behavioral Types in Dorsal Ammon's Horn and Dorsal Fascia Dentata

Table 3 gives the distribution of different types of cells in different regions. Most types of cells occur in all the areas studied. However, the following distributions (marked with an asterisk in the table) are significantly different on the assumption that the frequency of occurrence of each behavioral type follows a binomial distribution: CA3 has the largest proportion of approach-consummate cells (vs CA1 $P = 0.001$; vs f.d. $P = 0.004$); CA1 has the largest proportion of approach-consummate–mismatch cells (vs CA3 $P = 0.0001$; vs f.d. $P = 0.001$); fascia dentata has the largest proportion of appetitive cells (vs CA1 $P = 0.002$; vs CA3 $P = 0.11$). The proportion of cells with single specificity is greater in CA1 than in fascia dentata ($P = 0.063$). The motionless awake correlate is least common in CA1 (vs f.d. $P = 0.047$; vs CA3 $P = 0.0016$).

On a single track through a region there were no striking similarities in the behavioral correlates of neurons—cells of the same behavioral correlate or behavioral type were not grouped together, and the specificity of nearby cells was not always identical. Different tracks through the same region have different mixes of behavioral correlates of cells, so that each track has its own individuality. Blackstadt, Brink, Hem, and Jeune (17) and Andersen, Bliss, and Skrede (6) have shown that Ammon's horn and fascia dentata has a lamellar organization. Inputs from one part of entorhinal cortex project to a single strip (lamella) of fascia dentata, which in turn projects to a single lamella of CA3, which in turn projects to a singe lamella of CA1. These lamella maintain an ordered interrelationship in all three regions. The distance from the most anterior lamella to the most posterior is about 3.5 mm in each region. The electrode tracts in fascia dentata cover 1.4 mm of this distance, in CA3, 2.0 mm, and in CA1, 1.7 mm. Therefore in each region these data cover about half of the range covered by the lamella dorsally. In those sensory and motor systems where topographic

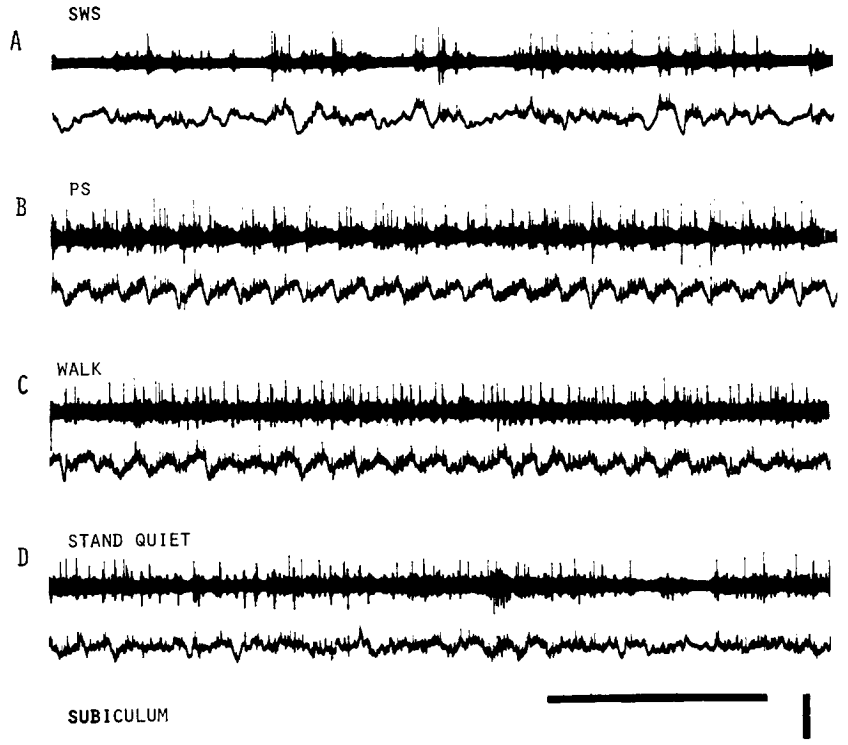


FIG. 21. Neuron in dorsal subiculum which often fires complex action potentials. There may be more than one cell of about the same amplitude here. The cell fired more rapidly during any movement, during a slow-wave theta rhythm or during consummatory movement. The cell often fires with the negative phase of the slow wave, of the theta rhythm and other slow waves. Voltage calibration top trace 500 μv, bottom trace 2 mv; time 1 sec.

order is maintained, we find distinctive receptive fields or motor output at different locations. Therefore we might expect to find some distinctive feature of the behavioral correlates in different lamella. However, no pattern relating to lamellar organization could be found. In many sensory and motor systems many neurons near to each other will share some characteristic. No such relation could be found in these data.

E. Preliminary Results from Some Related Structures

Dorsal Subiculum. Twenty-nine neurons were studied in dorsal subiculum (Fig. 21). Six were theta cells indistinguishable from theta cells elsewhere. Most and perhaps all the other neurons fired complex spikes. However, these complex spike cells fired more rapidly than the complex spike cells of Ammon's horn and fascia dentata. The neurons in subiculum were relatively hard to work with and hence were rather poorly characterized

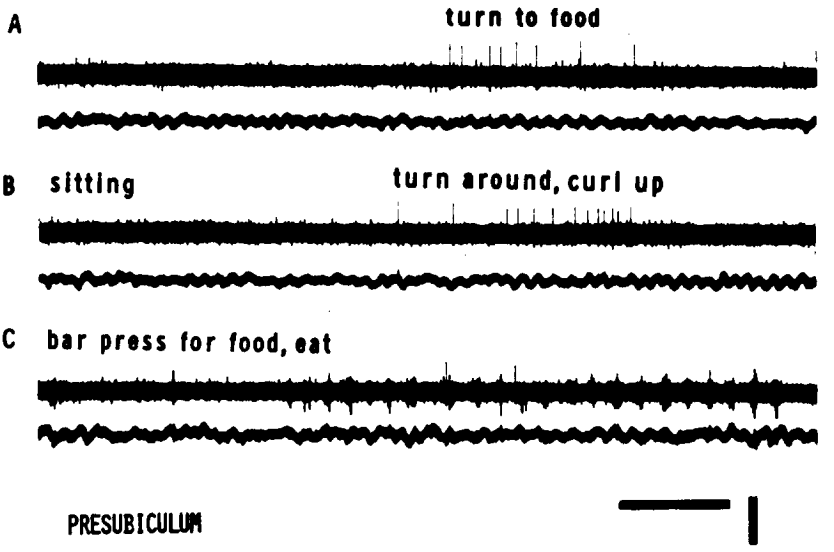


FIG. 22. A specific orienting neuron in presubiculum. A. This neuron fired primarily when the rat oriented to food. It also fired when orienting to my hand if I had been giving it pellets, to a nut about the same size as a pellet (see text), when it finished eating a pellet and when it explored around the site where the pellet had been. The cell fired once when the rat was carrying a pellet, but another time it did not fire when the rat carried a pellet. C. It fired very slowly when bar pressing for food and eating on a well-learned continuous reinforcement schedule. B. It fired sometimes when the rat turned, but I could not tell what it was turning to. It fired when the rat approached water. This neuron was completely off most of the time for minutes at a time. Voltage calibration top trace 250 μv, bottom trace 1.9 mv; time 1 sec.

for five reasons. (a) Good isolation was particularly hard to achieve in subiculum. This was surprising because the cell bodies are much more separated than in Ammon's horn or fascia dentata. (b) Most of the neurons in subiculum, theta, and complex spike cells, increased their firing during most movements of the rat and especially during nonautomatic movements when there was a theta rhythm, so that all neurons had similar behavioral correlates. This meant it was rather difficult to tell one neuron from another unless isolation was excellent. (c) Most complex spike cells fired in the complex spike mode most of the time, so a spike size discrimination is even less useful than in Ammon's horn and fascia dentata. (d) Most neurons fired with clear relations to both regular and irregular slow waves, firing during local negative slow waves, and being off during a positive slow wave. This meant that all neurons fired at about the same time, just the opposite of what is seen in Ammon's horn and fascia dentata. (e) All cells fired fairly rapidly and regularly most of the time so that even theta cells cannot be readily distinguished from complex spike cells by rate and pattern.

Each of these five facts is of some interest in itself, but it makes finding

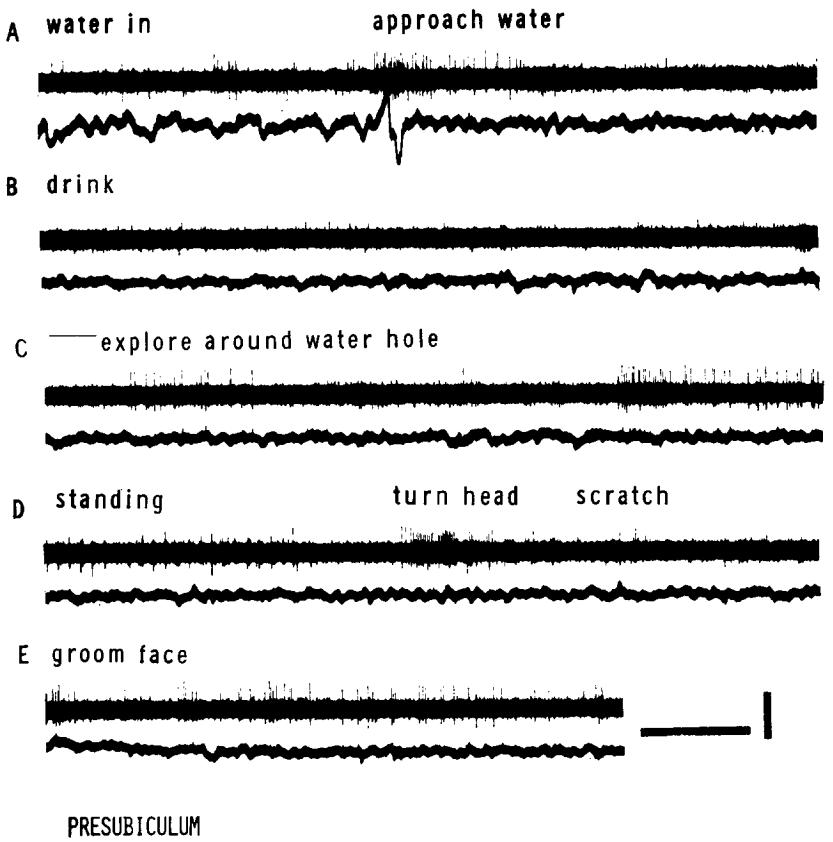


FIG. 23. A specific orienting neuron in presubiculum. A. This neuron fired when the rat turned to or approached water in a water spout, or water in a jar. B. It was off during drinking. When the rat drank from a water jar for the first time (it had *never* done this before) the neuron fired, but not with later drinking. It did not fire with orienting to or approach to a water dipper. C. The neuron fired when the rat explored around the water hole, even though the water spout was not there. It fired when the rat explored around the place where the water jar had recently been. It fired when the rat turned its head away from water while drinking. It fired in the half second before it picked up a food pellet (not for other food orienting or approach). If I had recently been putting the water jar or water bottle or food pellets into the rat's box, the neuron fired when the rat turned to my hand as I put my hand into its box. If I had been recently picking up the rat, the neuron did not fire when the rat turned to my hand as I put my hand into its box. D. The neuron fired a few times when it turned its head, but to nothing that I was aware of. E. The neuron fired during grooming of the face and leg. Smaller action potentials from other cells are also present. Voltage calibration top trace 250 μv, bottom trace 1.9 mv; time 1 sec.

behavioral correlates difficult. These is no question but that most neurons in subiculum increase their rates of firing during *all* movements, automatic and nonautomatic, but especially during nonautomatic ones. I have not been

able to find any difference in behavioral correlate between neurons. They surely all have much in common, but the inability to find any differences may be an artifact for the reasons given above. I also have not been able to find any specificity to movement—all "automatic" movements are about the same, and all nonautomatic about the same.

Dorsal Presubiculum, Parasubiculum, and Medial Entorhinal Cortex. Five neurons have been recorded from in medial entorhinal cortex, and 28 neurons in presubiculum or parasubiculum (Figs. 22, 23). All 33 of these neurons will be discussed together. No complex spikes were seen. Eight (24%) of these neurons were theta cells, which I have not been able to distinguish from theta cells elsewhere. Three (9%) of these cells were approach-consummate cells, similar to such cells in Ammon's horn. Four (12%) of the cells fired constantly and the firing did not seem to change at all.

Nineteen of these neurons called *specific orient cells* had a distinctive behavioral correlate. When they fired it was usually for no more than 3 sec as the animal made a presumed orienting movement and sometimes with an approach movement. Ten of these cells fired only when the rat oriented to specific kinds of things. For instance, one cell fired whenever the rat oriented to water in any form, the waterspout, a jar of water, or drops of water on the floor of the cage. Another fired only when the rat oriented to the waterspout. Most of the firing occurred as the rat turned to the object, which usually meant neck movement. This was such a striking feature that when I first recorded from these neurons I thought that they were related to neck movement, but they fired with other presumed orienting movements not involving neck movement and did not fire with nonorienting movements of the neck. All cells were tested by picking the rat up and moving his neck. At first the rat resisted having his neck moved, but then, after two or three times, allowed his neck to be moved. This then tested for both motor and afferent aspects of neck movement. None of these cells increased their firing during this manipulation.

Four cells were seen which fired when the rat oriented to food, two when the rat oriented to any water, one when the rat oriented to the waterspout, one when the rat turned away from water, and two when the rat oriented to food or water. These cells fired whenever the rat oriented to its specific object.

In addition to these ten cells, nine have been seen which fire only during presumed orienting movements, although during less than about 10% of such movements. For these cells I have not been able to find anything which distinguishes a neck movement during which the cells fire from those during which it does not. However, I tentatively suggest that these cells are also specific orienting cells, though I have not been able to discover the specificity.

One neuron (Fig. 22) fired while the rat was orienting to food and to nothing else tested. The neuron then fired when the experimenter put his empty hand into the cage with the same movement that had been used to put pellets in. A metal nut of about the same size as a food pellet was then put into the cage. The neuron fired as the rat oriented to the nut, as he approached it, and as he picked up the nut and chewed at it for a few seconds. The cell stopped firing when the rat turned away from the nut. Neurons which were specific for water or the waerspout fired when the noise usually associated with putting the water bottle on the cage was made, before the waterspout appeared. A food orienting neuron did not fire during barpressing for food on continuous reinforcement. All of these neurons were tested for time locked visual, auditory, and somatosensory responses as described in Methods. Only one neuron responded—the only neuron in this whole study which gave any indication of a time locked sensory response. This cell was a food orienting cell, which fired when a light was flashed anywhere in the rat's contralateral visual field. These observations suggest that the cells are not responding to some fixed specific sensory details, but rather are involved in some more complicated process such as responding to stimuli conditioned to a given incentive or motive, or perception, or expectancy, or attention, etc. However, these data are far too fragmentary for conclusions to be drawn from them. These neurons fire in many of the same situations as appetitive neurons. However, specific orient neurons are much more specific than appetitive neurons, so they can be described more clearly.

Lateral Septal Nucleus. Sixty-five neurons in lateral septal nucleus have been studied in eleven rats, one tract per rat. Much of the analysis is retrospective, and no sleep data was obtained.

Forty-nine of these 65 neurons (75%) had similar behavioral correlates. They will be called *neck movement neurons.* Whenever one of these neurons increased or changed its rate of firing the rat was moving his neck, apparently orienting, or was approaching something, or had just finished moving. However, no cell increased its firing with all neck movements or with all approaches, but with less than half of these. The duration of the increased firing was usually about 0.25 sec and always less than 1 sec, and there were usually no more than five action potentials. (This contrasts with durations of firing about 1–2 sec for cells firing during orienting movements in medial entorhinal cortex and presubiculum and parasubiculum.) Sometimes the increased firing was at the very beginning of the neck movement, but in most cells the firing occurred during the movement. Some fired at the end of a movement. All cells were tested with neck manipulation as described for specific orienting cells, with no positive results.

I tried unsuccessfully to find any characteristic which would distinguish those neck movements associated with increased firing from those neck

movements which were not. The only suggestive specificity is that some cells fired when I could not determine what the rat was orienting to—i.e., it fired when a rat turned to nothing in particular. This contrasts with the case for specific orient cells.

Of the neurons which were not neck movement neurons, six fired constantly and regularly (constant firing neurons), all of which were in the posterior part of the lateral septal nucleus, at the level of the fornix. Five neurons fired during the rat's sniffing and approach behavior, two were correlated with some motionless behaviors, and one only fired when the rat stood on his two rear feet. Four neurons were seen which fired complex spikes—two were neck movement cells and two were constant firing neurons. All of these were in the posterior lateral septal nucleus at the level of the fornix. Four neurons gave some hint of a theta rhythm at times; all of these neurons were at the level of the fornix.

Medial Septal Nucleus. Thirteen of the 30 neurons recorded here were theta cells, which I cannot distinguish from theta cells elsewhere. There are other neurons there also, which are clearly not theta cells, which I have not been able to characterize yet.

DISCUSSION

A. *Some Generalizations about the Behavioral Correlates Observed.* Perhaps the most remarkable aspect of this whole study is that behavioral correlates could be readily found for almost all neurons. In order to discover a behavioral correlate it must be stable over time, and except in one neuron, there were no indications of changes in behavioral correlate or of changes in the firing repertoire. Considering the methods, about twofold changes in rate would have to occur to be noted. It is noteworthy that many of the changes seen by the Olds' group seem to be less than twofold.

The behavioral correlates found all refer to behavior which is occurring at the moment. Indeed, one need only look at the rat for 1 or 2 sec to know enough about his behavior to describe the behavioral correlates. The behavioral correlates were mostly related to *what* the rat was doing, not *why* he was doing it or *how* he was doing it. This is fortunate for it allows a more behavioristic description of the behavior (or perhaps it is an artifact reflecting a bias toward behavioristic descriptions). The only correlates which might involve *why* are the mismatch and the specific orienting correlates. The observations during passive avoidance are especially pertinent to this point. The cell firing during passive avoidance was related to what the rat was doing in a 1 or 2 sec interval. One did not have to know that the rat was passively avoiding the waterspout to describe the behavioral correlate adequately.

No correlates could be found with details or sensory inputs or motor outputs, except for one cell in medial entorhinal cortex and the qualified

ones in motion punctuation, and the relation of movement of vibrissae to the theta pattern. I could find no correlations with particular movements. This is in marked contrast to cells in neocortex, lateral thalamus, and lateral geniculate, which have been recorded from in the course of doing this study, where there is a strong correlation of almost all firing with details of the motor or sensory changes over a fraction of a second.

Many cells at first appeared to be responding in a time locked way to one or more sensory inputs. However, with further testing, in all but one case it turned out that the firing was correlated with some specific motor behavior or EEG change, which followed the stimulus. Some might argue that these were indeed responses to sensory stimuli and that correlations of firing with subsequent motor behavior or EEG reflected habituation or some other sensory processing. Perhaps this is true, but in this study we can only discover correlations of firing with sensory inputs or motor outputs of the rat. We have no way of determining causal relations. In any event these cells do not show a sensory response in a simple sense. These findings are in agreement with those of MacLean (61) who was not able to find visual, auditory, or somatosensory responses to neurons in hippocampal formation of monkey. He did find responses to these modalities in other parts of limbic cortex. The apparently conflicting results of Vinogradova (99, 100) are discussed below. There are responses in many hippocampal neurons of monkey to electrical stimulation of olfactory tract (61). It is impossible to know from these data how much olfactory input was correlated with neuronal firing. It must be considered an important possibility.

Emotional behavior was barely tested except when the rat was picked up in the experimenter's hand, and in escape tests. In these cases all neuronal firing was related to what the rat was doing rather than some imagined "emotional state." No suggestions of any relations to emotion were ever seen in other less systematic observations. There was little data on "stressful" situations, which is unfortunate in view of the involvement of hippocampus in pituitary–adrenal functions. There were no observations of intraspecific social behavior.

Descriptions of the behavioral correlates given in this paper have usually involved descriptions of motor behavior (or performance), as opposed to more sensory, perceptual, attentional, motivational, intentional, cognitive, or emotional factors. I believe this emphasis on performance is correct, but this emphasis is clearly influenced by both the observer bias and also by the fact that the laboratory rat in familiar surroundings is a very active motoric animal rather than a more passive afferent animal like a rabbit or a cat. It is further biased by the fact that the major sensory input, olfaction, was not well tested. These data do not allow one to decide how much of the individuality of each complex spike cell is genetically determined and how

much learned. Cells in all rats were similar, but all rats had only had very similar grossly abnormal laboratory experience.

B. *Sleep.* Mink, Best, and Olds (67) reported that six out of six neurons in "hippocampus" decreased their rate of firing in paradoxical sleep. Noda, Manohar, and Adey (69) found an increase in rate of firing of "spontaneously firing" hippocampal neurons in paradoxical sleep. Mink's group located units by lowering an electrode until action potentials could be recorded (presumably stratum pyramidale or granulosum), recording many days after the electrode was fixed in position. Almost all neurons in these strata are complex spike cells, which decrease rates of firing in paradoxical sleep. Noda's group lowered a microelectrode in an awake animal until they isolated a "spontaneously firing" cell. It is much easier to locate and isolate theta cells and, depending on one's definition of "spontaneously firing," this may only include theta cells. These are cells which tend to increase their rates of firing in paradoxical sleep. So it seems likely Mink and his colleagues were recording from complex spike cells and Noda and associates were recording from theta cells, and that both groups were correct. Noda's group did not note a relation to phasic episodes as was seen in this study. It is possible that the changing phase relation in paradoxical sleep which they saw and which was not seen in this study was in fact occurring in phasic episodes, when there are substantial and irregular changes in slow waves and unit firing.

Olmstead, Best, and Mays (77) studied neurons in dorsal and ventral Ammon's horn and fascia dentata in the sleeping rat, and at all sites find some neurons increase rates and other decrease rates relative to slow-wave sleep in paradoxical sleep. The relative numbers of cells increasing and decreasing is different from the data reported here. They did not note absolute rates of firing so it is difficult to compare these data.

For theta cells, slow-wave sleep is part of automatic behavior, and for complex spike cells slow-wave sleep is part of a larger motionless-slow-wave sleep mode. Thus slow-wave sleep is not a distinctive behavior for these neurons. On the other hand, paradoxical sleep is a well-defined behavior for both types of neuron.

C. *Other Work on Neurons in Hippocampus and Behavior.* The work of O'Keefe and Dostrovsky (70) on single neurons in hippocampus of freely moving rats uses a strategy very similar to the "microphrenology" part of the strategy I use. The relations between their spatial map cells and the approach-consummate–mismatch cells of this study has been discussed above. They describe "movement" cells which are clearly the same as the "theta" cells here. They have another category of cells inhibited by arousal which seem to include many of the behavioral types of complex spike cells. They were unable to discover the behavioral correlates of 31 of the 76

units they recorded from in CA1, CA4, and fascia dentata. There are no substantial disagreements between their work and the present study.

The work of Olds' group (39, 45, 67, 71–76, 89, 90) recording from neurons in hippocampus of unrestrained rats has many similarities to this work, and indeed was very important in shaping this approach. All of their studies involve careful quantitative analysis of neurons in well-defined behavioral tasks, but usually it is not possible to know which of the types their cells belong to. The study of Ito and Olds (45) is clearly on theta cells and is discussed elsewhere (29). Olds, Mink, and Best (75) showed that some of their cells are especially related to eating and others to drinking just as found in this study. There are other similarities in the results of the Olds' group and my results, but since these are only guesses I will not press the point.

While the present strategy and the Olds' strategy are very different in these initial stages, the use of Olds' type studies on neurons of known behavioral type is an important next step, so the two strategies converge.

Vinogradova (99, 100) studied firing of single neurons in dorsal and ventral hippocampus of awake partially restrained rabbits in response to various sensory inputs. Most neurons were affected, some increasing and some decreasing their rates of firing. Most responded to more than one modality of stimulus. The response to short stimuli usually lasted many seconds. With repeated presentation of stimuli there was habituation of the response which usually took the form of a shorter duration response. Three parallels between her data and mine are strongly suggested. (a) Complex spike cells decreased rates of firing or stopped firing if the depth of the rat in the motionless-slow-wave sleep mode was raised above the threshold for that cell. This could occur in response to sensory stimuli of different modalities. This change in firing long outlasted the duration of the stimulus and the firing remained very slow or the cell remained off until the depth of the rat in the motionless-slow-wave sleep mode had again dropped below the threshold for that neuron. With repeated presentation of the stimulus, the duration of the change in depth of the motionless-slow-wave sleep mode of the rat progressively decreased and the amount of change in depth was not as great. The slowing or stoppage of neuron firing thus became shorter and the firing finally no longer changed with repeated presentation of stimuli. (b) Theta cells often increased their rates of firing in response to sensory stimuli. The response lasted as long as the theta rhythm which, in the rabbit, may long outlast the stimulus even without movement. The response was multimodal and habituates. (c) A theta cell decreased its rate of firing if the rat froze, and freezing to stimuli habituates. Since we cannot tell which of Vinogradova's cells are complex spike cells and which are theta cells, and since she did not meaure hippocampal or neocortical

slow waves, it is impossible to be sure if these suggestions are the basis for her observations.

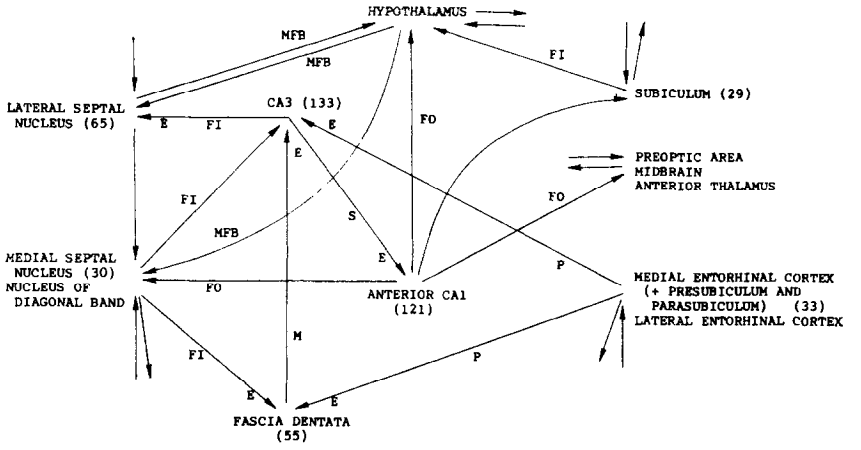
John and Morgades (47), and Fuster and Uyeda (32) also studied hippocampal neurons in behaving animals, but the difference in approach makes comparison impossible. Phillips and Dafny (81), and Pfaff, Silva, and Weiss (80) showed changes in firing in hippocampal neurons in unrestrained rats to cortisol and corticosterone, respectively. Neural inputs are probably not the only unputs to hippocampal neurons.

D. *Identification of Theta and Complex Spike Cells.* The existence of the theta and complex spike cells as two groups of cells clearly distinguishable electrophysiologically, by firing repertoire, and by behavioral correlates, suggests that these cells might be distinguishable as anatomically different types. One possibility is that the theta cells are axons, since they have relatively short duration spikes and are seen ubiquitously. However, only theta cells with 0.2–0.25 msec negative (distorted) spikes are being reported and these can be recorded from over distances of at least 100 μm, and are no more difficult to hold than other cells. These facts make the likelihood of their being axons negligible.

Since complex spike cells are by far the most numerous neurons seen, seem to occur largely in stratum pyramidale or stratum granulosum, and usually occur closely bunched together, there can be little doubt that at least most complex spike cells are pyramidal cells or granule cells and that most pyramidal and granule cells are complex spike cells. The data at present does not allow us to say that the class of complex spike cells is identical with the class of pyramidal cells and granule cells. However, such an identification is certainly suggested.

Perhaps theta cells are short axon (Goli type II) cells, which would include basket cells. The evidence for this is: (a) Theta cells are much less than 25% of the total. (b) Theta cells are in stratum oriens, stratum radiatum, and stratum pyramidale of CA1 and stratum moleculare and stratum granulosum of fascia dentata. (c) Two theta cells have been recorded from simultaneously only rarely. (d) Basket cells inhibit pyramidal cells (see below) and many of the behavioral correlates of theta and many complex spike cells are roughly opposite. In the theta mode (nonautomatic behavior and paradoxical sleep), all theta cells fire near their maximal rates and complex spike cells of Ammon's horn and fascia dentata fire only in special situations and usually for only a few seconds. In the automatic behavior mode, which includes the motionless-slow-wave sleep mode, all theta cells are at their slowest sustained rates and complex spike cells of Ammon's horn and fascia dentata cells are more likely to fire. This is the only time these complex spike cells have sustained firing.[11] Lorente de Nó has de-

[11] Theta cells in septum are almost surely an input to Ammon's horn, and the pyramidal cells are the output of Ammon's horn. Therefore, if theta cells were



MFB= MEDIAL FOREBRAIN BUNDLE
S= SCHAFFER COLLATERAL
P= PERFORANT PATH
M= MOSSY FIBERS
FI= FIMBRIA
FO= DORSAL FORNIX
E= EXCITATORY SYNAPSE

PLUS: COMMISSURAL (E)
$CA3_c \rightarrow$ F.D.
LONGITUDINAL ASSOCIATION BUNDLE
LOCUS COERULEUS
RECURRENT INHIBITION IN AMMON'S HORN, MAYBE F.D. AND LATERAL SEPTUM
RECURRENT FACILITATION IN AMMON'S HORN
CORTICOSTERONE

FIG. 24. The connections of dorsal Ammon's horn, dorsal fascia dentata, medial septum, nucleus of the diagonal band, lateral septum in the rat. An arrow with an unlabled beginning or end indicates other unspecified connections. All connections are indicated in a region with no unlabeled arrows. An arrow without a plus or a minus indicates that it is not known if this connection is excitatory or inhibitory.

scribed many kinds of short axon cells (59), only one group of which might be theta cells. Theta cells of Ammon's horn might be displaced pyramidal cells (59). Some complex spike cells might be short axon cells. These possibilities are all testable, so the issue can be settled in the future. There do not seem to be any obvious candidates for theta cells in subiculum, presubiculum, parasubiculum, and entorhinal cortex at present.

Andersen, Eccles, and Loyning (9, 10) have studied inhibition in Ammon's horn. They showed the extracellular positive field potential during the hyperpolarizing phase of IPSP in pyramidal cells after fornix stimulation was greatest in stratum pyramidale. They infer that these inhibitory synaptic endings are on the pyramidal cell bodies. This is the relation basket cells have to pyramidal cells, therefore they conclude basket cells inhibit pyramidal cells. In addition they have recorded from a group of cells which they suggest are these basket cells because (a) they fire with the appropriate latency after fornix stimulation, (b) their duration of firing

pyramidal cells an output would be the same as one of the inputs, an unattractive conclusion. No matter how motivating this reasoning may be, it is, however, not evidence.

was about as long as the duration of increasing hyperpolarization of the IPSP in pyramidal cells, (c) the latency of firing after fornix stimulation decreases with increasing stimulus strength (consistent with convergence), and (d) the rate of firing of these neurons is the same as a ripple often seen on the IPSP. Kandel (48) has questioned whether this is the only conclusion one can draw from the data. Their conclusion seems even weaker now, for their purported basket cells show spike height changes and interspike intervals which are indistinguishable from the defining characteristics of a complex spike, with the exception that they say the frequency can be from 500/sec to 1000/sec and I have never seen an interspike interval of less than 1.5 msec in a complex spike. Their suggestion is equivalent to the suggestion that inhibitory interneurons are some subgroup of complex spike cells. Extracellular complex spikes can be a millivolt or more in amplitude, so the ripple seen in an IPSP could be a field potential of an adjacent cell. Their conclusion that basket cells inhibit pyramidal cells seems fairly strong. Their suggested electrophysiological identification of basket cells with some kind of complex spike cells is possible, but unlikely.

Andersen, Gross, Lomo, and Sveen (11), continued similar studies. They report presumed "non-pyramidal" cells in stratum oriens responding to electrical stimulation of many pathways with frequencies of 200/sec to 500/sec (much lower than the earlier studies) and their figures do not show the spike height change characteristic of complex spike cells. I have seen interspike intervals of theta cells of as little as 2 msec, but never less. Thus these "non-pyramidal" cells might be either theta cells or complex spike cells. Dichter and Spencer (23) have shown differences between pyramidal cells and "interneurons" but their results do not translate into the terms of this paper.

The issue of exactly which cells are granule and pyramidal cells is important, because these cells are the output of fascia dentata and Ammon's horn. We cannot analyze the "flow of information" unless we know which cells are the output. In the analysis that follows, it will be assumed that complex spike cells are one and the same as granule cells and pyramidal cells. There may be some exceptions to this assumption, but this is surely the case for almost all cells so the possible error introduced by this assumption is small. The issue of which cells are interneurons is much less clear, but this is not a critical point in the following analysis.

E. *Anatomy and Electrophysiology.* All of the data and analysis so far has only involved characterizing the behavioral correlates and firing repertoires of neurons. In preparation for seeing how these cells might interact a review of the anatomy and physiology of the system will be given.

Figure 24 summarizes the connections *in the rat* of the various parts of *dorsal* Ammon's horn, *dorsal* fascia dentata, entorhinal cortex, parasubiculum, presubiculum, medial, and lateral septum. Commissural connections

are omitted, but are in general homotopic or similar to ipsilateral projections (2, 16, 35, 84). This particular figure represents my best judgment of the connectivity from the literature especially with reference to Lorente de Nó (58, 59), Raisman (83), and Raisman, Cowan, and Powell (84, 85), but the following disagreements and, hence, uncertainties should be noted. Raisman, Cowan, and Powell (84) only found septal inputs to fascia dentata and CA3 in the rat and this is given in Fig. 24. In the cat Ibata, Desiraju, and Pappus (44) found septal inputs to fascia dentata, CA3, and also to CA1. Raisman, Cowan, and Powell (84) found perforant path inputs to fascia dentata and CA1 and Lorente de Nó (59) found the perforant path to come from lateral entorhinal cortex. Hjorth-Simonsen and Jeune (43), and Hjorth-Simonsen (41), found there are two perforant paths, one from medial and another from lateral entorhinal cortex, each terminating at a different location on a pyramidal cell of CA3 and a granule cell of fascia dentata. They do not believe there are any fibers from entorhinal cortex ending on neurons in CA1. This is the view given in the figure. There is physiological evidence both for (88) and against (13) a termination of perforant path in CA1. There are connections from CA3c (the part of CA3 closest to CA4) with fascia dentata both ipsilaterally and contralaterally, which are not shown in Fig. 24 (35). The connections of subiculum, presubiculum, and parasubicuum are not well known. In the cat Cragg found septal inputs to presubiculum and entorhinal cortex (18), but these have never been described in the rat. Siegel and Tassoni (91, 92) found different connections to and from septum from ventral and dorsal hippocampus in the cat, but the figure gives the data of Raisman (83) for the rat. There is an input of CA1 to the most medial part of lateral septum (83) not shown in this figure. The ventral hippocampus has different connections which are not given in the figure.

Anderson's group have shown the following inputs to be excitatory by field potential studies and intracellular studies: commissural path to CA1 (3, 5, 14) and CA3 (4, 5, 14); mossy fiber input to CA3 (5, 13, 14); Schaffer collateral input to CA1 (5, 13, 14); perforant path input to fascia dentata (12, 53, 56); and (less well established) septal input to fascia dentata (7) and CA1 (8). These are shown by an E in the Fig. 24. DeFrance, Shimono, and Kitai have shown that hippocampal input to lateral septum is excitatory and there are probably inhibitory interneurons (19–22). Kandel and Spencer (49, 94) have shown that inhibition in Ammon's horn seen after stimulation of the fornix is due to recurrent collaterals. The data of Andersen, Eccles, and Loyning (9, 10) suggest that all or most inhibitory input is by short axon neurons, especially basket cells, but Purpura *et al.* (82) showed that all inhibition is not from basket cells. There are short axon cells which are not basket cells (59), which are likely candi-

dates for this additional inhibition. No inhibition from long axons has been shown. There is recurrent excitation in CA3 (55).

Other inputs probably include corticosterone (34, 80). Noradrenaline is present throughout hippocampus (33). According to Ungerstedt, (96), all these noradrenergic ending have their cell bodies in locus coeruleus. There is also the longitudinal association path from collaterals of pyramidals cells in Ammon's horn, which presumably terminate somewhere within the same field of Ammon's horn (42, 59).

F. *Some Suggested Synaptic Interactions.* (1) If theta cells are short axon inhibitory cells, in the theta mode they maximally inhibit complex spike cells, and in the automatic mode complex spike cells are somewhat released from this inhibition. Careful phase relation studies of these two types of cells could help clarify synaptic relations.[12]

Strong recurrent inhibition is present in pyramidal cells of Ammon's horn. A consequence of this would be that two neighboring complex spike cells with very similar inputs would have somewhat different behavioral correlates. Lateral inhibition in afferent systems functions to bring out contrast in receptive field. This suggested lateral inhibition in Ammon's horn and fascia dentata would function to bring out contrast in behavioral correlate, and it is notable how each complex spike cell has a distinctive behavioral correlate. Two modes of inhibition are thus suggested, a global inhibition during the theta rhythm and a localized lateral inhibition of neighboring complex spike cells.

(2) Theta cells in medial nucleus of the septum, nucleus of the diagonal band, Ammon's horn, fascia dentata, subiculum, presubiculum, parasubiculum, and medial entorhinal cortex all seem to be the same. Since destruction of septum or cutting the fornix eliminates the rhythmical slow waves in Ammon's horn, the theta cells in septum would seem to be driving the others, although other interpretations are possible (79). There are direct connections of medial septal nucleus to fascia dentata and CA3. It is not clear how theta cells in CA1, subiculum, presubiculum, parasubiculum, and entorhinal cortex might be driven. Perhaps the connections from septum to presubiculum and entorhinal cortex with Cragg has seen in cat (18) are present in rat. Perhaps the connections from septum to CA1 which are known in cat (44) also exist in rat. All these theta cells must have very tight synaptic connections. This is the kind of situation in which the presence of an electric synapse should be considered.

[12] We must be careful to remember that the magnitude of slow wave potential changes during a theta rhythm is three or more times the magnitude of slow waves seen most other places in brain. Therefore, there could be a significant direct effect of slow waves on firing without a synapse. However, the large intracellular theta rhythm shown by Fujita and Sato (31) indicates that there is a synaptic effect and the slow waves are no doubt due to synaptic potentials.

(3) The motion punctuate cells fire just at the end of an orienting movement, as if this were an inhibitory rebound when a specific orienting cell or appetitive cell had stopped firing. No specificity to these motion punctuate cells has been found, suggesting convergence of many different specific orienting or appetitive cells of different specificity. Motion punctuate cells of fascia dentata can only project to CA3 or to contralateral fascia dentata of Ammon's horn. It is not clear how these cells affect any others. They fire so rarely that their influence must be in a finer microstructure of behavioral correlates than has been determined so far.

(4) The appetitive cells of fascia dentata may be driven by specific orient cells of entorhinal cortex through the perforant path. Appetitive cells of CA3 may be driven from appetitive cells of fascia dentata through the mossy fibers, or from specific orient cells of entorhinal cortex through the perforant path. Appetitive cells are less specific than specific orienting cells, suggesting a convergence of specific orienting cells of different specificity on a single appetitive cell.

(5) The appetitive behavioral correlate of many neurons in fascia dentata may be the source of the appetitive behavioral correlate of approach-consummate cells in CA3 through the mossy fibers. A possible mechanism for greater specificity of these approach-consummate cells than the appetitive cells is suggested in part (j) below. Appetitive cells fire in all sorts of appetitive behavior, while approach-consummate cells usually fire only during appetitive behavior which is followed by consummatory behavior. The basis of this difference is not clear.

(6) Most of the behavioral correlates of the approach-consummate–mismatch cells, so common in CA1 are the same as those of approach-consummate cells most common in CA3. It seems likely that the behavioral correlates these two groups share is conveyed by the Schaffer collaterals. The mismatch behavioral correlates of approach-consummate–mismatch cells could result from a comparison of appetitive cells of CA3 with approach-consummate cells of CA3 of matched specificity. Appetitive cells fire in all kinds of appetitive behavior, and approach-consummate cells fire usually in appetitive behavior which is followed by consummatory behavior. It is easy to construct models in which the CA1 cell would fire most rapidly, when only its appetitive input cells fired, and less rapidly when both appetitive and approach-consummate inputs fired or only its approach-consummate inputs fired. If there are direct inputs to CA1 from entorhinal cortex (which seems unlikely) a similar comparison could be made between specific orient cells and approach-consummate cells to give the mismatch behavioral correlate. The source of the spatial behavioral correlate is not clear.

(7) Raisman (83) has shown in the rat that the major inputs to lateral septal nucleus are from CA3, CA4, hypothalamus, and probably medial septal nucleus. Siegel and Tassoni (91, 92) have shown a major input

from all parts of ventral hippocampus in the cat. Knowledge is lacking of the behavioral correlates of inputs from hypothalamus and from ventral hippocampus. The neck movement behavioral correlate suggests that theta cells may have an input to lateral septal nucleus, but I have not been able to see or hear any phase relation of the firing of lateral septal nucleus cells with the theta rhythm except for a suggestion in four posterior cells. It seems unlikely that theta cells are an output of CA3, but they are presumably an output of the medial septal nucleus.

The behavioral correlate of neck movement of lateral septal nucleus cells is included in the appetitive behavioral correlates of approach-consummate cells, approach-consummate–mismatch cells, and appetitive cells, which include most of the presumed output of dorsal CA3. The lack of specificity presumably indicates convergence on lateral septal cells from cells in CA3 of different specificities. The difficulty is that the consummatory behavioral correlate which is so common in CA3 output is not notable in lateral septal nucleus. Lateral septal nucleus cells may thus be inhibited during consummatory behaviors, presumably from inputs from the hypothalamus or medial septal nucleus. Any lateral septal nucleus neurons with excitatory inputs from only appetitive cells need have no such inhibition. Perhaps only appetitive cells of CA3 project to the lateral septal nucleus.

(8) The medial septal nucleus receives a major input from anterior CA1. The approach-consummate–mismatch cells fire most rapidly when a behavior is unsuccessful. Theta mode behavior is usually continued when it is unsuccessful, while theta mode behavior usually stops when it has been successful and a consummatory act occurs. This suggests that inputs from approach-consummate–mismatch cells may help maintain the generation of the theta mode in medial septal nucleus as long as the behavior is unsuccessful.

(9) We do not know which neurons are the source of the consummatory behavioral correlates. Medial septal nucleus, nucleus of diagonal band, and entorhinal cortex are candidates and must be studied. Some medial septal nucleus cells seem especially likely, since there are neurons there with endings on pyramidal cells of Ammon's horn and granule cells of fascia dentata (44) and there are neurons in medial septal nucleus with undetermined behavioral correlates. The specificity of the consummatory behavioral correlate must be matched with the specificity of the appetitive behavioral correlates.

(10) Andersen and Lomo (14, 15, 57) have shown that an EPSP in pyramidal and granule cells can be increased manyfold if the afferents fire repetitively, with an optimal rate of about 10/sec, the maximal rate of many complex spike cells. They call this frequency potentiation. Complex spike cells usually fire less than 2/sec, at which frequency there is little frequency potentiation. Therefore, frequency potentiation increases the contrast be-

tween differences in rate, so that only more rapid rates may be transmitted, and low rates are much less effective. As one goes from fascia dentata to CA3, to CA1 in dorsal hippocampus, the behavioral correlates of the complex spike cells become sharper, often narrowing to a single specificity in CA1 (Table 3). In view of divergence and convergence of synaptic relations we might expect less specificity as we progress through these steps of hippocampal processing. Approach-consummate and approach-consummate–mismatch cells with more than one specificity fire at a different rate for each specificity. Frequency potentiation would thus markedly increase the effect of the specificity associated with the greatest frequency of firing.

(11) The two major suggested excitatory inputs to approach-consummate–mismatch cells, those from approach-consummate cells, and those from appetitive cells, usually do not fire at the same time. Similarly the two major suggested excitatory inputs to approach-consummate cells of CA3, those from appetitive cells through mossy fibers and from some cells with consummatory behavioral correlates of unknown source but not by way of mossy fibers, will usually not be firing at the same time. In other words, these suggestions imply that synaptic spatial summation on many of the presumed pyramidal cells of Ammon's horn is not used for summation of synaptic inputs from afferents from different areas and is only used for summation of afferents from the same region. The cell works as an *or* gate, not an *and* gate. Two somewhat unusual features of synaptic organization of hippocampal pyramidal and granule cells make sense in this light. Both the ability to generate dendritic spikes (14, 15, 93) and the grouping together on the same area of the dendrite of excitatory inputs from afferents from the same area (84) will increase the possibilities of spatial summation from excitatory input from afferents from the same area and decrease possibilities of excitatory spatial summation of afferents from different areas. Low levels of simultaneous firing in two groups of inputs will thus be less likely to seem to give an action potential of the pyramidal and granule cell. This effect, like the effect of frequency potentiation above, will tend to maintain the specificity of the behavioral correlate of the cell. Andersen and Lomo (15) have demonstrated that inhibition in pyramidal cells is very powerful. Much of this inhibition is on the cell body, where it can affect all excitatory inputs, fairly nonspecifically. Theta cells, a possible source of this inhibition, have nonspecific behavioral correlates, so nonspecificity of synaptic effect is needed to preserve this behavioral correlate. Andersen and Lomo (15) pointed out how the powerful frequency potentiation can be used to overcome the powerful inhibition. But this frequency potentiation will only work to enhance temporal summation from the same inputs.

(12) The mismatch behavioral correlate is similar to some of the kinds of situations which are associated with the release of ACTH (62). Neurons with the mismatch behavioral correlate are especially common in anterior

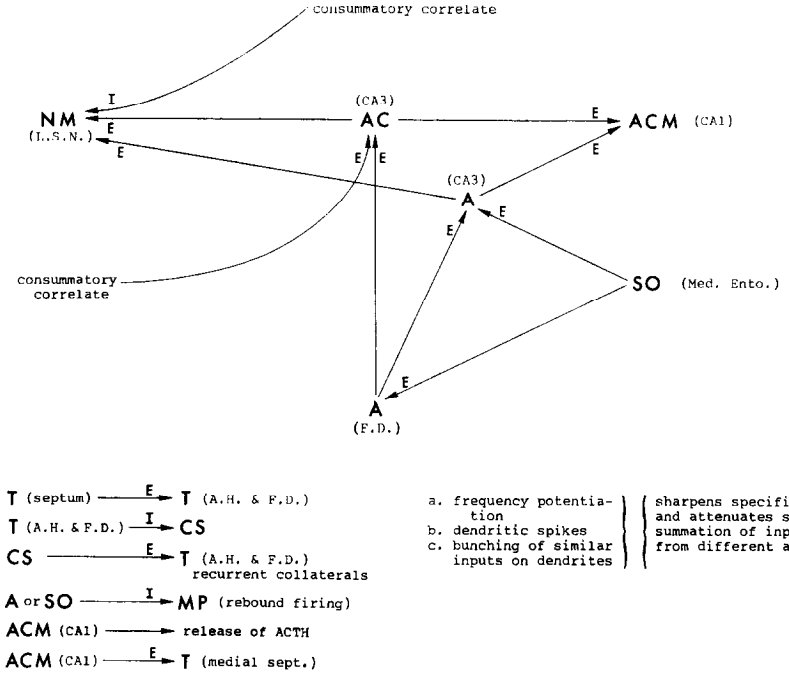


FIG. 25. Summary of suggested synaptic interactions.

CA1 and upper CA2-3. Gerlach and McEwen (34) have shown CA1 and CA2 concentrate cortiocosterone more heavily than any other part of the brain. Pyramidal cells of CA1 project to hypothalamus (85). Many other bits of data suggest relations between hippocampus and the pituitary–adrenal system (34). It seems approach-consummate–mismatch cells may be of particular importance in this relation.

(13) The inability to find a relationship between behavioral correlates and lamellar organization is disappointing. The significance of lamellar organization remains tantalizing.

Figure 25 summarizes these suggestions. These suggested synaptic interactions are testable with stimulation or lesion studies, with more accurate data on timing of firing on behaviorally identified cells, and with more accurate descriptions of the behavioral correlate.

To have found a correlation between the behavior of the rat and the firing of a neuron does not tell us anything about causal relations between the neuron firing and the rat's behavior, nor does it tell us what is signaled by the neuron. For instance, some neurons only fired when the rat ate or was in slow-wave sleep. But we have *not* yet determined whether the firing which occurred when the rat ate was signaling (or was causally related to) some sensory aspect of eating, some motor aspect, some motivational aspect, some attentional aspect, some autonomic aspect, some biochemical change

in blood, etc. *The suggestions of synaptic relationship between neurons above have been developed without making any assumptions about what the firing of a neuron signaled or its causal relation to behavior.* We have simply looked at which neurons fire at the same time along with our knowledge of anatomy and physiology to develop these suggestions. Nevertheless, even at this early stage some intuitive sense of flow of information in hippocampal formation starts to emerge.

G. *Global Function of the Hippocampal Formation.* Even at this first crude level of description our data are incomplete. We lack information from lateral entorhinal cortex, all ventral hippocampus, from about half the cells in medial septal nucleus, and most of the cells in the nucleus of diagonal band. We do not know how behavioral correlates about consummatory behavior gets to hippocampus. Therefore, comments about more global function of the hippocampal formation from these data are perhaps premature, but let us try.

In a sense the function of the hippocampus is the transformation of information from its inputs to its outputs. The major *inputs* to hippocampus are cells with three kinds of behavioral correlates: nonspecific nonautomatic behavior (theta cells of medial septal nucleus); specific orienting behavior (cells of medial entorhinal cortex, presubiculum, and parasubiculum); and specific consummatory behaviors (in some cells not yet discovered). The major *outputs* of hippocampus are neurons with five kinds of behavioral correlates: (a) appetitive behaviors in varying degrees of specificity (appetitive cells); (b) specific successful appetitive behaviors combined with their associated consummatory behavior (approach-consummate cells); (c) specific successful appetitive behaviors combined with their associated consummatory behavior and unsuccessful appetitive behavior (approach-consummate–mismatch cells); (d) motion punctuation; and (e) motionless-slow-wave sleep mode. A given cell of the output may have behavioral correlates of more than one specificity, and d or e along with the a, b, or c. We do not know how the rest of the brain uses these outputs, but let us make a guess. Consider the following general formulation.

A rat has many appetitive and consummatory behaviors which he can perform relatively automatically, with the amounts of genetic prewiring and learning varying in each. Elsewhere (29) it is shown that some voluntary behavior can become automatic (as defined for theta cells) and some not. Programs for these behaviors are stored in nonhippocampal parts of the nervous system since a rat can perform them all with his hippocampus removed. The rat has a nonautomatic extrahippocampal mode since a hippocampectomized rat can learn many new tasks as well as controls. He also has extrahippocampal escape and avoidance modes. Hippocampal transformations would seem to help solve such problems as how to sequence various automatic behaviors appropriately, how to sequence automatic and non-

automatic behaviors appropriately, how to test the appropriateness of an automatic behavior or sequence and stop or change it if needs be, how to shift from one behavior to another, how to combine automatic and nonautomatic behaviors into new patterns, how to use behaviors which are being learned along with older behaviors, or in general how to use these automatic and nonautomatic behaviors in a flexible way and to avoid being too rigid.

The behavioral deficits seen in rats with hippocampal lesions have been analyzed in many ways (25, 51, 63, 65, 95 for reviews) but deficits in inhibiting a prepotent (i.e., automatic) response (25), deficit in Pavlovian internal inhibition (51), deficit in ability to shift attention (27, 52), deficit in selective attention (38), decreased sensitivity to changes in environmental cues (102, 103), deficit in error evaluation (26), lack of variability of behavior (40), hyperreactivity (64), and deficits in spatial maps (70) all have been suggested. Preoperative set (i.e., learned automatic behavior) has been shown to have an abnormally great interference with postoperative learning (30, 105). Sequenced maternal behavior is lost, even though most of the component behaviors remain (53).[13] All of these are clearly related to the general formulation given above. O'Keefe and Nadel (in preparation) see the function of the hippocampus as a spatial (or cognitive) map in the Tolmanian sense. They show how it is especially involved in exploration, and rapid learning of spatial relationships, as opposed to the learning of stimulus–response relationships which they feel occur outside the hippocampus. They interpret many of these behavioral correlates of hippocampal neurons in spatial and cognitive terms and sketch out a neural model of hippocampal function. Their interpretations are consistent with the data of the present study.

Thus an interpretation of the global functions of the hippocampal formation derived from these data on behavioral correlates and firing repertoire of single neurons is consistent with many views derived from animal lesion data. Furthermore, this study yields suggestions of the mechanisms by which these functions are performed. As these studies are improved and made more complete they should help us determine the functions of the hippocampal formation and its mechanisms more precisely.

SUMMARY

Extracellular action potentials of single neurons in dorsal hippocampal formation and medial and lateral nuclei of the septum were recorded in unrestrained rats. The rat was observed during slow-wave sleep, during paradoxical sleep, while eating, drinking, and grooming, while held in the experimenter's hand, when novel objects were introduced, during bar-pressing

[13] The memory deficit seen in human beings after bilateral hippocampal damage is, however, not clearly related to any of these findings in rats (66).

for food and water on continuous reinforcement, in general activity in the cage, and with visual, auditory, and somatosensory stimuli.

It was possible to find a correlation between the firing of a cell and the behavior in almost all neurons. The data include: CA1—121 cells; CA3—134 cells; fascia dentata—55 cells; lateral septal nucleus—65 cells; medial septal nucleus—30 cells; entorhinal cortex, parasubiculum, and presubiculum—33 cells; and subiculum—29 cells.

In Ammon's horn and fascia dentata there were two groups of neurons which could be distinguished on the basis of firing repertoire alone. One group, the "theta cells" (less than 25% of the total) never showed a complex spike, the remaining "complex spike cells" (greater 75% of the total) always did at some time. A complex spike is a series of two to seven spikes with 1.5–6 msec interspike intervals in which the amplitude of the extracellularly recorded spike changes during the series, usually decreasing. Most of the time theta cells fired faster than 5/sec (most are faster than 10/sec) and they had maximal rates of 30–120 sec. Most of the time complex spike cells fired from zero to less than 12/sec (most are less than 2/sec). The duration of the extracellularly recorded action potentials was different in the two groups. Theta cells increased their rate of firing if and only if a regular theta rhythm occurred in the slow waves, whether during paradoxical sleep or wakefulness. Firing in complex spike cells had no simple relation to the presence or absence of a slow-wave theta rhythm. When a cell of either group fired during a theta rhythm, there was usually a phase relation to the slow waves.

The theta cells fired at their fastest rate during paradoxical sleep and during "nonautomatic" behavior, and fired at slower rates during consummatory or some well-learned behavior—relatively "automatic" (eating, drinking, grooming, slow-wave sleeping, standing quietly, or bar-pressing for food or water when well learned). Theta cells also occurred in medial septal nucleus, subiculum, presubiculum, parasubiculum, and entorhinal cortex. (In septum and fascia dentata there may be no theta rhythm in the slow waves.) No differences were observed between theta cells in the various locations. Theta cells were nonspecific in the sense that one fired in the same way during approach to food or to water. All theta cells had the same behavioral correlate, although their firing repertoires differed.

No two complex spike cells had the same behavioral correlate. Almost all fired if the state of consciousness of the rat dropped below a certain threshold, but this threshold was different for each neuron. Most did not fire during paradoxical sleep.

There were four behavioral types of complex spike cells which are most common. (a) *An approach-consummate cell* fired most rapidly during certain consummatory behaviors and the successful appetitive behavior associated with it. For instance, one cell fired during the rat's approach to a

pellet, and while the rat explored it and then ate it. (b) *An approach-consummate–mismatch cell* fired during the same behaviors as an approach-consummate cell, but it also fired during unsuccessful behavior of the same specificity. For instance, the cell fired during the rat's approach to water and during drinking, but also during the rat's exploration of the water hole when the bottle has been removed, or when the rat was lying in front of the water hole. (c) *An appetitive cell* fired during some orienting movements or approach behavior but during no consummatory behavior except sleep. A specificity to objects or places was noted in some, but not all these cells. (d) *A motion punctuate cell* fired one to five action potentials at the end of some presumed orienting movements, or sometimes when the direction of movement was changed. Approach-consummate cells were most common in dorsal CA3. Approach-consummate–mismatch cells were most common in dorsal CA1. Appetitive cells were most common in dorsal fascia dentata. All these types were found in all regions of dorsal Ammon's horn and dorsal fascia dentata. Other less common behavioral types were also found.

Most cells in presubiculum, parasubiculum, and medial entorhinal cortex are *specific orient cells* which fire for about 2 sec when the rat makes an orienting movement to something in particular, for instance food or water. Non-theta cells in subiculum are very poorly characterized, but fire during any movement. Most neurons in lateral septal nucleus fire or increase their rate of firing when the rat makes an orienting or approach movement. A given cell will only fire during certain of these movements of the rat, but no specificity has been found. There are no theta cells in lateral septum. About half the neurons in medial septum are not theta cells, but these have not been characterized yet.

Many testable inferences about the interaction of these neurons can be drawn from known anatomy and physiology. The class of granule cells of fascia dentata and pyramidal cells of Ammon's horn have a very large overlap with the class of complex spike cells. It seems likely that specific orient cells excite appetitive cells; that appetitive cells plus some as yet unidentified sources of consummatory behavioral correlate excite approach-consummate cells; that approach-consummate cells and appetitive cells excite approach-consummate–mismatch cells. The preliminary view of the flow of information in hippocampus which emerges from these data is in general agreement with ideas of the function of the hippocampus derived from lesion experiments.

Note added in proof. In recent studies neurons in the medial septal nucleus have been found which fire predominantly during consummatory behavior. They fire during more than one consummatory behavior. They are off during most but not all theta mode behavior. They fire about five to nine spikes in a group with about 1.5–4 msec interspike intervals. The spikes do *not* change in amplitude during a group, so then are not complex spikes. When the cell is firing a group occurs at a frequency of about 0.5–3 per sec. It seems likely that these neurons are the source of the consummatory behavioral correlate seen in Ammon's horn and fascia dentata.

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