HIPPOCAMPAL SLOW RHYTHMS IN ONGOING BEHAVIOUR AND DURING CLASSICAL CONDITIONING*

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Experiments on the relationships between hippocampal slow (or theta) rhythms and phases of approach learning have used different and complex learning tasks. For example, in the experiment by Grastyan *et al.*[1] the animal had to climb up to the feeding device, whereas Elazar and Adey[2] used a T-maze with an auditory stimulus simultaneous with the opening of a starting box and the brief exhibition of a light signalling the baited arm. Holmes and Adey[3] baited one of two boxes in view of the animal and 5 seconds later lowered a gangway to the goal. And, recently, Lopes da Silva and Kamp[4] used a bar-pressing response to a stimulus by an animal free to move in a large room.

The findings between these (and other) experiments vary, though there are some common observations. The differences may be, in part, due to the different tasks involved; an animal making a T-maze discrimination is overtly behaving differently from one pressing a bar. Furthermore, to equate similar appearing elements of different responses as some workers do as being behaviour of the same kind is not necessarily valid. An animal 'approaching' a bar following a signal moves towards the bar just as an animal moving down an arm of a T-maze 'approaches' the goal. But there is no reason to expect the two behaviours to be accompanied by the same central processes.

The difference between experiments may also be due, in part, to the difficulty of correlating a long, fairly complex behaviour sequence with a long EEG record, both of which show great variability between trials and animals.

To overcome some of these problems, in the following experiment the slow hippocampal rhythm was studied in a simple learned response: the conditioning of eating to a brief signal. Such a classical conditioning situation provides a short behaviour sequence composed of easily distinguishable events (a stimulus, a short period before eating, eating, and cessation of eating) with which electrographic changes may be precisely correlated.

The experiment had another purpose. Animals learning a complex response (e.g. running down the arm of a T-maze and then feeding) are behaving, in part, as they do in many other situations, and Vanderwolf[5] has shown that, in fact, some of the electrographic patterns observed during avoidance learning may indicate only that such kinds of behaviour are occurring, and may not be peculiar to the learning situation. Therefore, in this experiment, a study was also made of the electrographic changes during various free behaviours.

METHOD

The subjects were 10 (5 male, 5 female) tame and well handled (weight approximately 200 g) albino rats. Under pentobarbital anaesthesia, bipolar electrodes were implanted in the dorsal hippocampus at least 6 days before the experiment, with the midpoint of their tips located as shown in Fig. 1.

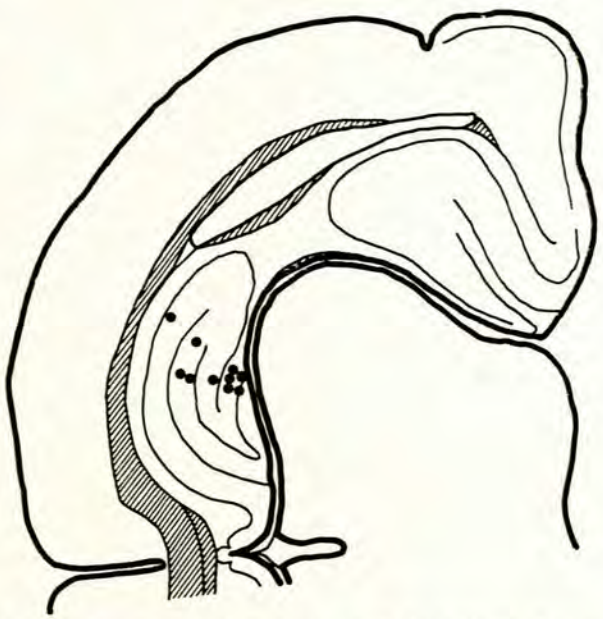

Fig. 1. Electrode locations. The actual electrode track was approximately three times as wide as the dot on the diagram.

The electrodes were glass-coated, stainless steel, 0·01 in in diameter, separated at their tips by 0·02 in, and attached to a miniature male socket anchored by dental acrylic to 3 watch screws inserted into the skull.

The experiments were done in a transparent perspex cage (plan 9 in by 16 in) insulated from earth by paraffin blocks and standing inside a Farady cage. An elastically suspended cable, long enough to permit free movement of the animal, connected the electrodes to the amplifiers via a female socket. With these arrangements the records were virtually free of artefacts.

The EEG was recorded at a paper speed of 1 cm/s and with an amplification of 150 MV/cm. The amplifiers passed frequencies between 1·5 Hz and 15 Hz, with an attenuation of 50% occurring at the limits of the band. The response between 3 Hz and 8 Hz was maximal and relatively flat.

Inspection of unfiltered hippocampal records in freely behaving animals determined the choice of filters and scoring methods. Such records in rats show a continuous series of wave forms varying from a highly synchronized rhythm of approximately 8 Hz to a desynchronized wave with small fast, and irregular high amplitude components occurring at a frequency of approximately 6 Hz. (There is no sharp distinction between the synchronized and desynchronized rhythms.) Thus, a filter which passes in the band 3 Hz - 8 Hz enables a decision to be easily made, by a simple count of the dominant frequency of where the rhythm lies on the series. Furthermore, though the fast, small components of the desynchronized rhythm will be

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attenuated they will, nevertheless, tend to further desynchronize the record. Thus, a high frequency synchronous score indicates pure 'theta', a low frequency asynchronous score a more or less desynchronized rhythm. There also occur, in the desynchronized record, short (approximately 1 s) bursts of low amplitude, fast and asynchronous rhythms, which will tend to further lower both the frequency and synchrony of the record.

Parallel to the EEG record a coded event record of the onset of particular behaviours was traced.

The experiment was conducted identically on each animal. On all recorded trials, the experimenter signalled, on one of a set of keys, the appearance of certain behaviour and a coded record of the event was automatically recorded on the event trace. Nine categories of behaviour were distinguished: grooming, sniffing, climbing, exploring, investigating, alert (eyes open), alert (eyes half open), eating and resting. An exploring animal was distinguished from an investigating animal by the presence of locomotion in addition to active investigation of objects by movement of the snout and forepaws over them. A resting animal was distinguished from an alert animal by closed eyelids, dropped head and a generally relaxed appearance. The other categories are self-explanatory. In general, the categories chosen appeared to be mutually exclusive, although occasionally two kinds of behaviour might occur simultaneously (e.g. sniffing and investigating).

The stimulus on all trials was a triplet of taps, lasting 0·7 s, alternating between opposite sides of the cage from trial to trial. The taps were manually produced by a rod containing an open switch which, when the rod was tapped on the cage, would close and signal the occurrence of the tap on the event trace.

Results are given for 8 days, each of which represents the trials from a particular day selected from the whole training series as described below. On Day 1 of the experiment the fully fed animal was placed for the first time in the cage and its EEG and behaviour recorded for 15 minutes. Stimulus taps were given at least once during each category of behaviour.

On Day 2 the procedure of Day 1 was followed, but with animals deprived of food for the 24 hours following Day 1. Following this, daily training began. Each animal was given 10 training trials, spaced randomly over a 15-min period in the cage, and under 24-hour deprivation. A trial consisted of stimulus taps followed immediately by food being placed manually (with a spatula) in the cage on the side of the stimulus. Daily training continued until the latency between the stimulus and eating remained constant (mean = 1·8 s, σ = 0·3 s) over 10 trials on one day.

The first day of training is designated Day 3. Day 5 is the last day of training on which the latency was constant. Day 4 is a day in the middle of the training period on which the latency was approximately half that observed on Day 3 (mean 4·8 s, standard deviation 3·6 s). On Days 3, 4 and 5 only the recording procedure of Day 1 was followed.

Day 6 was the beginning of extinction and was identical with Day 2. Extinction was then continued daily, without recording, until the latency had returned to the value it had on Day 3 and remained so over 10 trials. The last day of extinction is designated Day 7. The final Day 8 followed Day 7, and replicated Day 1.

The data considered in this paper for Days 1 - 8 consists of that for 4 trials selected randomly from the 10 on each designated day. Three periods of 1 s each of the following phases of a trial were marked: preceding (A) and following the stimulus (B), during eating (C) and following the end of eating (D). The EEG frequency in each one-second period of these phases was counted manually and rated as synchronous or asynchronous. Only a record which appeared sinusoidal in its whole extent was classified as synchronous.

The measurement procedure appeared to be quite reliable, the correlation between frequency counts by a trained and an untrained scorer being 0·89 (N = 100) for frequencies estimated over continuous periods of 10 s and 0·85 (N = 100) for periods of 1 s. Disagreement between the same scorers over judgements of synchrony occurred in 7% of 300 judgements of 1-s periods.

In addition to the above measurements, identical measures were made of EEG activity over 3-s periods in the middle of each epoch of each of the distinguished behaviours (except eating) on Days 1, 2 and 8. The value of the EEG measures during eating was estimated from the mean values in the middle second of the eating phase on Days 3, 4 and 5.

RESULTS

The values of frequency and synchrony used for analysis were the sum of those for the 4 recorded trials on each of the designated days. There is, therefore, no estimate of the between-trial variability on a given day. The frequency data were transformed to logarithms for statistical analysis, but the synchrony-asynchrony ratings were not transformed. All data were treated by analysis of variance.

Response to Stimulus

Non-learning days (1, 2, 7 and 8). On Days 1 and 8 the animal was fully fed, and on 2 and 7 was deprived. It will be seen in Fig. 2 that on all these days the stimulus produces a significant increase in frequency ($p<0·001$).

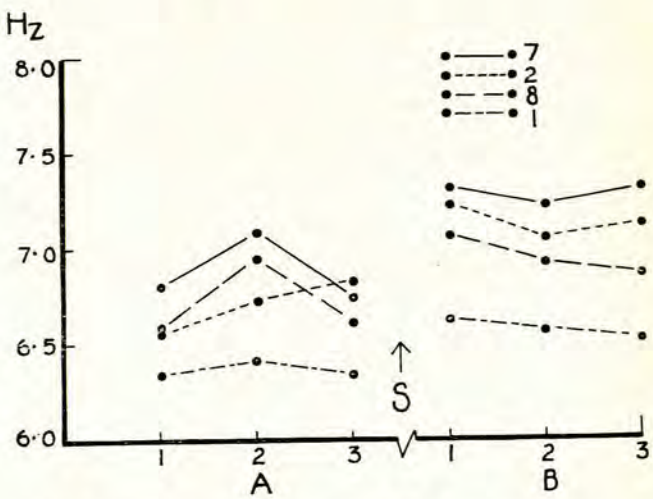

Fig. 2. Frequency in phases A and B before and immediately following stimulus (S) on Days 1, 2, 7 and 8.

TABLE I. MEAN FREQUENCIES OF SLOW RHYTHMS IN ALL PHASES AND PERIODS ON ALL DAYS

	A				*B*				*C*				*D*			
Day	*1*	*2*	*3*	*Mean (n=30)*	*1*	*2*	*3*	*Mean (n=30)*	*1*	*2*	*3*	*Mean (n=30)*	*1*	*2*	*3*	*Mean (n=30)*
1	6·35	6·41	6·35	6·37	6·62	6·59	6·51	6·57								
2	6·53	6·74	6·85	6·71	7·23	7·06	7·13	7·14								
3	6·45	6·26	6·55	6·42	7·38	7·06	7·14	7·19	6·53	6·62	6·14	6·43	7·07	7·06	6·87	7·00
4	6·92	7·23	7·45	7·20	7·92	7·86	7·83	7·87	7·14	6·79	6·57	6·83	7·21	7·31	7·21	7·24
5	7·13	7·44	7·56	7·38	8·13	7·49	7·49	7·70	7·03	6·76	6·68	6·82	7·58	7·09	6·99	7·22
6	6·90	6·90	7·22	7·01	7·96	7·81	7·43	7·73								
7	6·82	7·08	6·77	6·89	7·32	7·23	7·32	7·29								
8	6·56	6·95	6·61	6·51	7·08	6·93	6·87	6·96								

TABLE II. PERCENTAGE OF SYNCHRONY IN ALL PHASES AND PERIODS FOR ALL DAYS

	A				*B*				*C*				*D*			
Day	*1*	*2*	*3*	*Mean (n=30)*	*1*	*2*	*3*	*Mean (n=30)*	*1*	*2*	*3*	*Mean (n=30)*	*1*	*2*	*3*	*Mean (n=30)*
1	30	27	30	29	37	25	10	24								
2	35	40	37	37·3	52	45	37	44·6								
3	50	40	32	40·7	58	55	40	51	22	8	5	11·6	62	70	45	59
4	50	50	38	46	67	65	60	64	22	8	8	12·6	47	52	42	47
5	38	52	52	47·3	55	62	60	59	30	15	20	21·6	50	55	55	50
6	37	37	35	36·3	75	70	60	68·3								
7	15	25	17	19	13	35	32	26·6								
8	20	25	17	20·6	29	20	22	23·6								

Also the separation of the days in both phases A and B is significant ($p<0·001$). As the variance between all one-second periods of both phases is insignificant, it may be assumed that the order of the mean values of the 3 periods in each phase represent the relative elevation of the frequencies from day to day. This order, from lowest to highest, is Days 1, 8, 2, 7 (Table I).

It seems, therefore, that both before the animal has learned and when its learning has been extinguished and whether it is fed or deprived the hippocampus responds to a stimulus by a rise in the frequency of the slow rhythm. Also, food deprivation raises the frequency of the rhythm, for the graphs for the days when the animal was deprived (Days 2 and 7) are more elevated than on the days when it was fed (Days 1 and 8). It is interesting, too, to observe that the frequency is more generally elevated on the last undeprived day (Day 8) of the experiment than at the beginning (Day 1); a change which may be due either to habituation to the apparatus or to the learning procedure.

Table II exhibits the synchrony changes corresponding to the frequency changes in Fig. 1 and Table I. The stimulus leads to an increase in synchrony on all days. These changes in synchrony following the stimulus are significant ($p<0·001$) as also are the over-all differences between the days ($p<0·001$). As in the case of frequency, and for the same reasons, the mean values of the 3 periods in each phase represent the relative elevation of synchrony from day to day. This order, from lowest to highest, is Days 7, 8, 1, 2 for phase A and Days 8, 1, 7, 2 for phase B.

The degree of response to the stimulus, both of frequency and synchrony, is not, however, dependent upon the day, for the interaction of days and phases A and B is insignificant.

The different orders of elevation of frequency as compared with synchrony imply that the change in the EEG from day to day is not only an elevation in frequency and synchrony, that is, a progressive increase in theta. The change is more complex than this, but in what respects cannot be inferred from these data.

The learning days. Fig. 3 exhibits the frequency data (Table I) for the learning days (3, 4 and 5) in all phases (A, B, C, D) of the experiment, and Table II the synchrony data for the same days and phases.

The over-all analysis of variance of frequencies for Days 3, 4 and 5 over all phases showed the only insignificant term to be the periods and days interaction.

It can, therefore, be assumed that during learning there is a rise in frequency following the stimulus, an abrupt drop during eating and then a rise following eating, each of these changes persisting for at least 3 seconds.

Also, it may be inferred that the separation of the frequency curves for each day is significant; a separation which appears most obvious to inspection in phases A and B.

In the case of synchrony the general picture is much the same except that there is less apparent separation between days. Apart from variation between animals ($p<0·001$) the only significant variation is that due to phases ($p<0·001$).

It may, therefore, be assumed that the changes in frequency between phases (neglecting any differences between days) are accompanied by similar changes in synchrony; a higher frequency being associated with a higher degree of synchrony.

The high frequency, synchronous rhythms approximate what is conventionally called theta, and are most marked in phase B following the stimulus. (It should be remarked here that the hippocampal theta of the rat as seen in these experiments seems to have a higher frequency than in

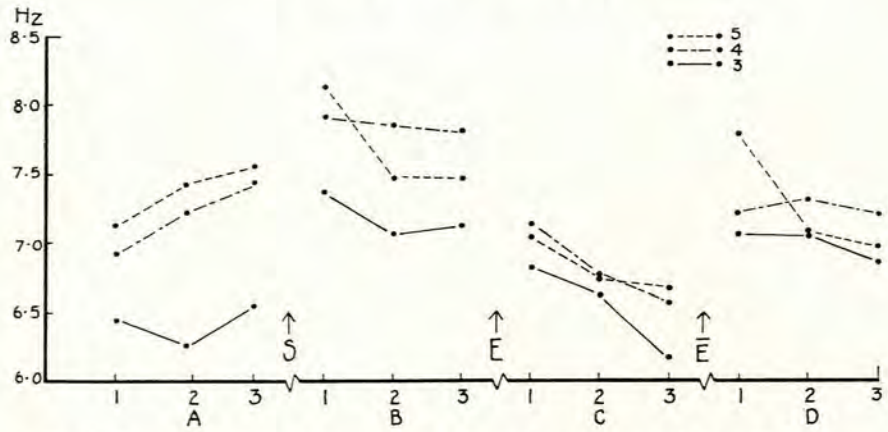

Fig. 3. Frequency in all phases and periods on Days 3, 4 and 5. (See Fig. 5 for key to symbols.)

higher mammals and seems to approximate those observed by Routtenberg.[6])

This over-all analysis gives a general picture of the changes in hippocampal rhythm in learning, but a more detailed analysis of each phase is necessary. From visual inspection of Fig. 3 it seems as if frequency is dependent upon the training day in phases A and B but less so in phases C and D; a relationship which does not appear to obtain for synchrony.

An analysis of variance for frequency and synchrony for days 2, 3, 4 and 5 over phases A and B shows this inference to be correct. The variance due to days and to phases are significant for frequency ($p<0{\cdot}001$ for days, $p<0{\cdot}001$ for phases). But the variation in synchrony is significant between days and also phases A and B ($p<{\cdot}025$ for phases, $p<{\cdot}01$ for days). (Day 2 was included in this analysis to determine whether the elevation of the curves for Days 4 and 5 above Day 2 and Day 3 was significant. The difference between Days 2 and 3 was separately treated and found insignificant.)

Thus, both synchrony and frequency rise, following the stimulus on all days. Furthermore, there is, during training from Days 3 to 5, a progressive elevation in frequency that is present both before and following the stimulus. Synchrony likewise increases from Day 3 to Day 4, but falls on Day 5 to a value between those of Days 3 and 4. As the interaction between days and periods is insignificant for both frequency and synchrony, the mean value for Days 2, 3, 4 and 5 in Tables I and II may be taken to represent the differences between phases and days.

Analysis of phases C and D over Days 3, 4 and 5 shows that the levels of frequency ($p<{\cdot}001$) and of synchrony ($p<{\cdot}001$) are significantly different between the phases. However, these differences may be independent of the day of training as the variance due to days and interaction of days and phases is insignificant. It may, therefore, be inferred that the increasing frequency and synchrony during the learning days in response to the stimulus is confined to phases A and B.

It might be asked whether the drop in frequency and synchrony in phase C occurs on eating. The changes observed in phase C may have begun earlier than the beginning of eating on the earliest learning day (Day 3), as the latency was longer (mean = 27·6 s, σ = 7·5 s) than the 3 seconds of phase B. Thus, there was a period in the second immediately before phase C that was not measured. But it is unlikely to have done so on Days 4 and 5. For on Day 4 the latency occupied little more than the 3 seconds of phase B (mean latency = 4·8 s, σ = 3·6 s) and on Day 5 eating actually began before the end of phase B, for the latency was less than 3 seconds (mean latency = 1·8 s, σ = 0·3 s). These considerations allow the conclusion that the drop in frequency and synchrony does, in fact, occur as the animal begins to eat. (It should be noted that on Day 5 the data for phase B include part of phase C, and those of phase C part of those for B. The fact that the relationship of phases B and C observed on earlier days is preserved on Day 5 in spite of this confounding further supports this conclusion.)

Extinction days. Fig. 4 exhibits the frequency responses to the stimulus on the first and last extinction trials in phases A and B, with the response on Day 1 included for comparison. The synchrony responses present a similar picture (Table II). The differences between Days 1, 7 and 6 are significant for both frequency ($p<0{\cdot}001$) and synchrony ($p<0{\cdot}001$). Also, the changes in frequency following the stimulus are significant ($p<0{\cdot}001$) as are the changes in synchrony ($p<0{\cdot}001$). Also, the interaction between phase and days is significant both for synchrony ($p<0{\cdot}01$) and frequency ($p<0{\cdot}01$), indicating that the greater differences in separation between the days in phase B as compared with those in phase A is a real effect, the response, both in synchrony and frequency, on Day 7 being less than on Day 6. As there is no significant interaction between periods and days the mean values of the 3-s periods in each phase (Tables I and II) may be taken to represent values for the phases A and B.

The Prestimulus Phase

There is a significant rise in frequency and synchrony with learning in phase A preceding the stimulus which requires special explanation. There are two possibilities; either the animal was receiving a cue before the signal from the experimenter's movements, or a general rise

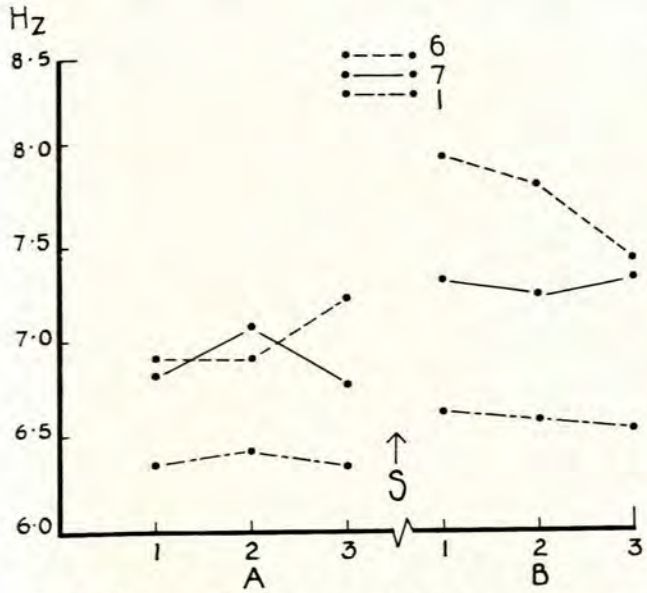

Fig. 4. Frequency in phases A and B before and immediately following the stimulus (S) on Days 1, 6 and 7.

occurred as the experiment proceeded. The former is the most likely, as in phase D the differences between the Days 3, 4 and 5 are insignificant, which could not be true on the latter explanation. This unexpected finding, however, demonstrates that the later parts of a stimulus of long duration have a greater effect than the earlier.

Hippocampal Rhythm During Various Behaviours

Fig. 5 shows the frequency and degree of synchrony during the various recorded categories of behaviour. (The graph has been arranged with behaviour in descending order of frequency from left to right.) The differences are significant both for synchrony ($p<0{\cdot}001$) and frequency ($p<0{\cdot}001$). It will be observed that the general tendency

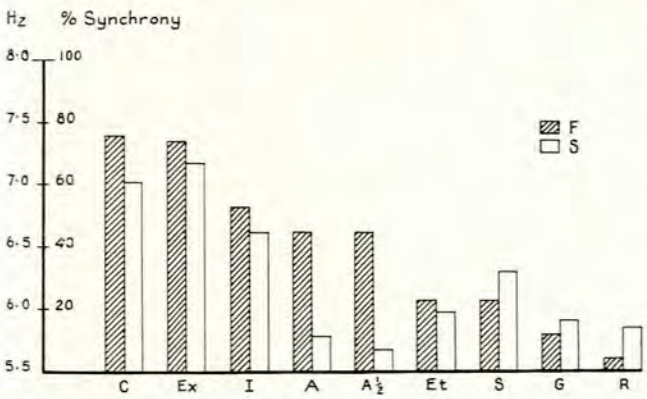

Fig. 5. Percentage synchrony and frequency in various observed behaviours. C = climbing; Ex = exploring; I = investigating; A = alert; $A\frac{1}{2}$ = alert, eyes half open; Et = eating; S = sniffing; G = grooming; R = resting.

is for those behaviours concerned with environmentally directed activities of an information-seeking kind to be associated with high values of frequency and synchrony, while those which represent possibly subcortically subsumed behaviours (grooming, eating, sniffing and resting) are associated with low values. Except for the two alert states, synchrony is correlated with frequency.

DISCUSSION

The experiment generally confirms the findings of Adey *et al.*[7] that theta, which occurred in response to a novel stimulus on Day 1 in this experiment, persists throughout learning, but contradicts that of Grastyan *et al.*[3] showing theta to be marked only at the beginning of learning or during extinction.

These findings suggest that increasing frequency and synchrony or theta are associated with increasing learning —as indicated by response latency—of the significance of a stimulus as a cue for reward in a food-deprived animal. In phase C, when the animal eats, the rhythm is asynchronous and does not change during learning. This fact is significant, for if it is assumed, with Grastyan *et al.*[3] and Douglas,[8] that synchronous hippocampal rhythm indicates 'inactivity' of the hippocampus, then the hippocampal rhythm observed during eating may be regarded as an indication of hippocampal activity. If this is so, then it may be the case that the hippocampus itself has no role in the learning of the significance of a stimulus, but has, rather, some effect in initiating and maintaining the eating response.

The relationship between various behaviours and the observed rhythm is interesting in this respect. For the behaviours associated with synchronous high frequency slow rhythm are of an environmentally directed kind, whereas low frequency asynchronous rhythms are associated with eating, sniffing and grooming, which are hypothalamically, or at least subcortically, subsumed stereotyped behaviours. This finding has been reported also by Routtenberg,[6] who observed much the same range of frequency values and asynchrony in the hippocampus as is described here. Furthermore, that hippocampal seizure activity, not resembling theta but approximating the desynchronized rhythm, does potentiate hypothalamically mediated reflex behaviour is shown in MacLean's experiments on hippocampal stimulation.[9] And Yoshii *et al.*[10] observed desynchronized hippocampal rhythm during urination, defaecation and contact with food.

It could, therefore, be suggested that the hippocampus is concerned in its active state to modulate hypothalamically mediated stereotyped responses, and that the theta—or highly synchronized—rhythms indicate that other systems (probably cortical) are controlling less stereotyped behaviour when theta is present. And that the degree of theta indicates the degree to which such cortical systems are operating. The observations of Roth *et al.*[11] that cortical synchronization occurs during and just before eating and increases as learning proceeds, support this view.

Also, it is known that in man cortical synchrony is associated with inattention to the environment. It seems reasonable in view of the above argument for an inverse relationship between hippocampus and cortex to assume also that hippocampal asynchrony is similarly associated with inattention. And that the eating response implies the execution of an act not dependent upon attention—it is a reflex

not involving higher information processing systems. This is further supported by the fact that cortical synchronization accompanies grooming.[11]

This, in general, coincides with the original view of Grastyan *et al.*,[1] except that it does not attribute to hippocampal theta an inhibitory function on orientation, but rather suggests that a desynchronized hippocampus is associated with the potentiation of hypothalamic reflex systems, and a synchronized one with inactivity of such systems.

Thus, the increase observed in this experiment in slow, synchronous rhythms, as learning proceeds, could be explained as due to an increasing and directed attentiveness (or orientation) to the environment accompanied by a high level of cortical activity and an inhibition of hypothalamically modulated responses.

The findings of Elazar and Adey[2] do, however, suggest a more complex function of the hippocampus than that proposed here. They, in general, observed a gradual increase in dominant frequency as the animal approached the goal in his experimental situation, and this they attributed to changes in attentional activity of the animal. However, the experiment is complex. The animal begins each run by being placed in a starting box which may be, in fact, the first stimulus to induce a set to respond. The animal, then, following a tone, traverses a T-maze. In this period the hippocampal rhythms may change simply because investigating activity has been initiated (which, as the view here proposes, is the accompaniment of theta). However, the lighted box provides a third stimulus (the start-box and tone being the first two stimuli) which will have the effect of further setting the animal to respond by investigation, leading to a further elevation of theta (and cortical desynchronization). Thus, on the present theory the progressive changes in rhythm as the animal moves to the goal may be due to an increase of directed exploratory and investigatory behaviour and a consequent diminution of hippocampal activity. The lack of the 6 Hz peak when the animal turns into the incorrect alley may simply be the result of the lack of a stimulus (learned) to direct investigating and exploratory behaviour.

On such a view the question remains as to what system controls these reciprocal relationships between hippocampus and cortex. For this system must be closely involved in learning to respond to a stimulus with eating, as its activity must be dependent upon the degree to which a stimulus has acquired significance.

Kawamura and Domino[12] have shown that the posterior hypothalamus contains a mechanism for desynchronizing the hippocampus, and that desynchronization of the cortex depends less on this than on the reticular activating system. Also, the septum directly drives the hippocampal theta.[13] Neocortical stimulation does not desynchronize the hippocampus in the rostral midbrain cat. Thus, it seems unlikely that the cortex and hippocampus reciprocally determine each other's state, but rather that the state of each is determined by systems which are in the first place distinct. This implies a complex relationship between cortex and hippocampus which requires investigation.

The view expressed above is similar to that of Vanderwolf[5] and the findings of this experiment, in general, support his conclusions that hippocampal theta is associated with 'voluntary' activities and fast activity with more automatic responses. Vanderwolf, however, did not investigate the precise relation of theta to a conditioned stimulus as was done in this experiment. Nevertheless, he did observe gross changes during an avoidance response similar to those observed in the approach response studied in this paper.

SUMMARY

An experiment is described showing significant changes in the slow rhythms (6 - 8 Hz) of the dorsal hippocampus in animals learning to respond with eating to a brief auditory stimulus. There is a significant rise in both frequency and synchrony of the slow rhythms in response to the stimulus during learning, and this rise is dependent upon the degree of learning. During eating the rhythms drop in frequency and synchrony and remain lowered until eating ceases, when a rise again occurs. However, during eating and immediately following eating the changes are not dependent upon the degree of learning. Further, changes in hippocampal rhythm occur in freely behaving animals which are correlated with various behavioural states. In general, exploration and investigation of the external environment are accompanied by high frequency synchronous rhythms, whereas grooming, eating and resting are accompanied by low frequency asynchronous rhythms.

A theory of hippocampal function is proposed which suggests the hippocampus to be a modulator of hypothalamically mediated behaviour.

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